

18th Summer Academy of Dermatopathology
Graz, July 6 – 10, 2026

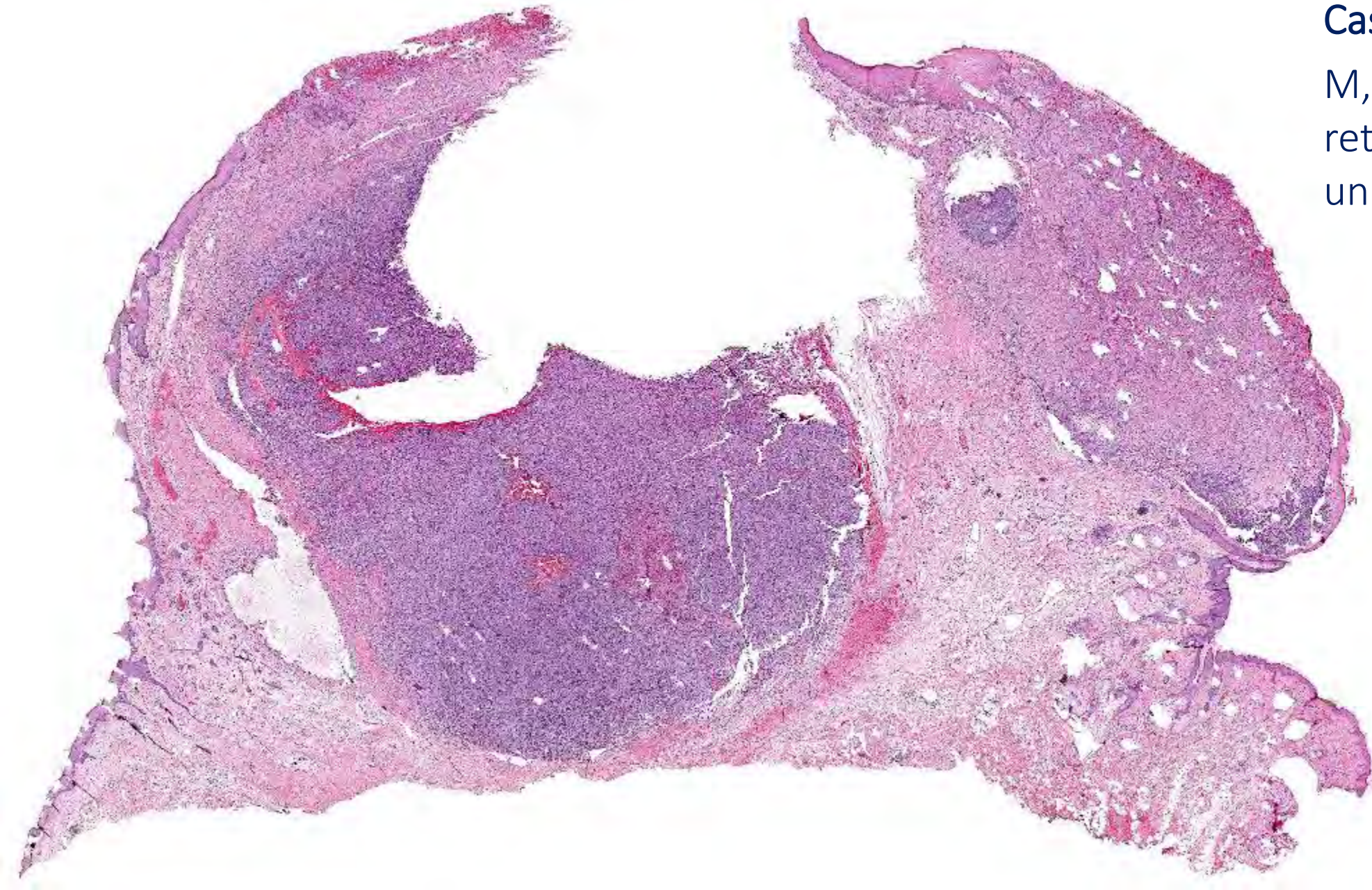


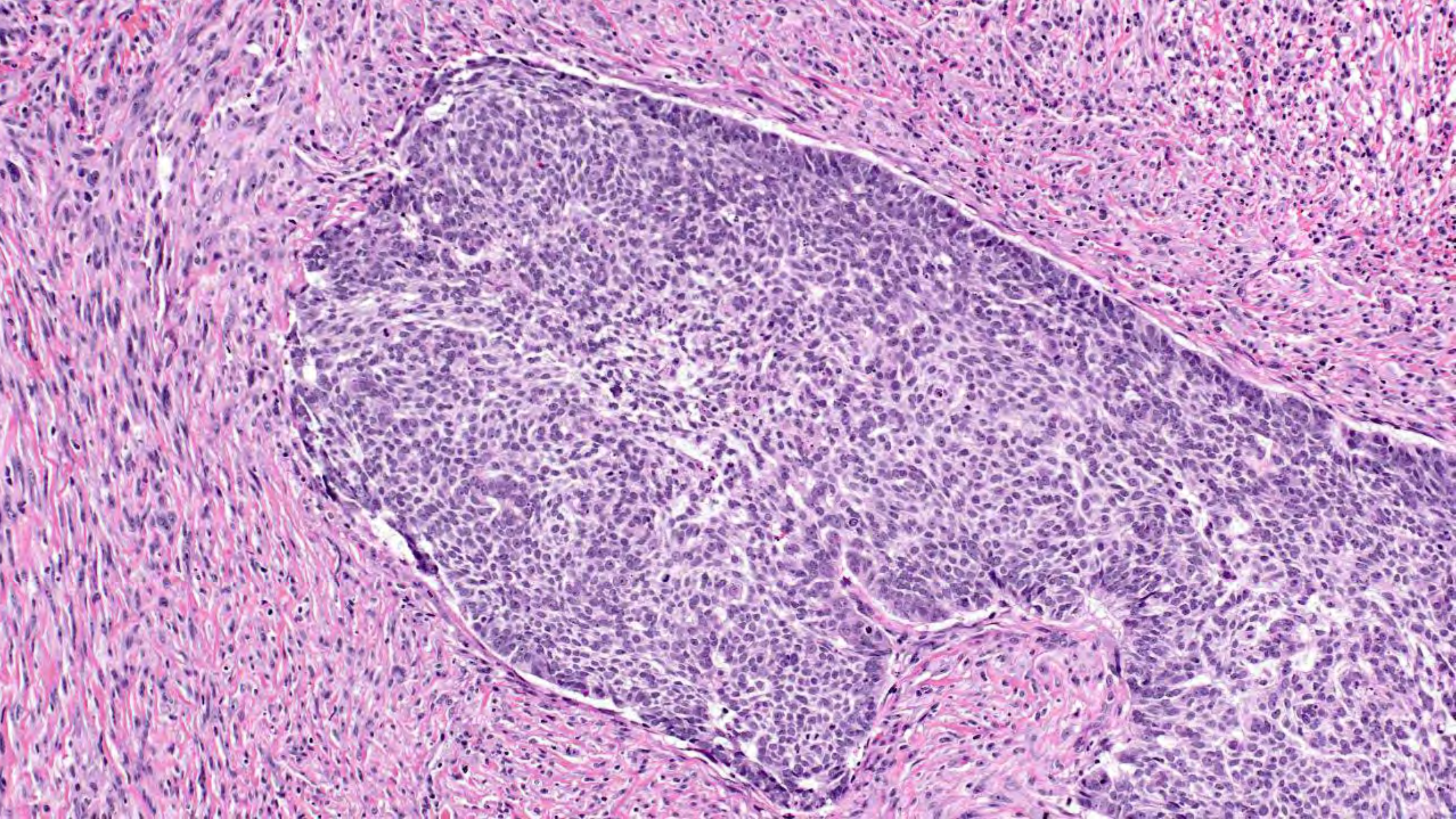
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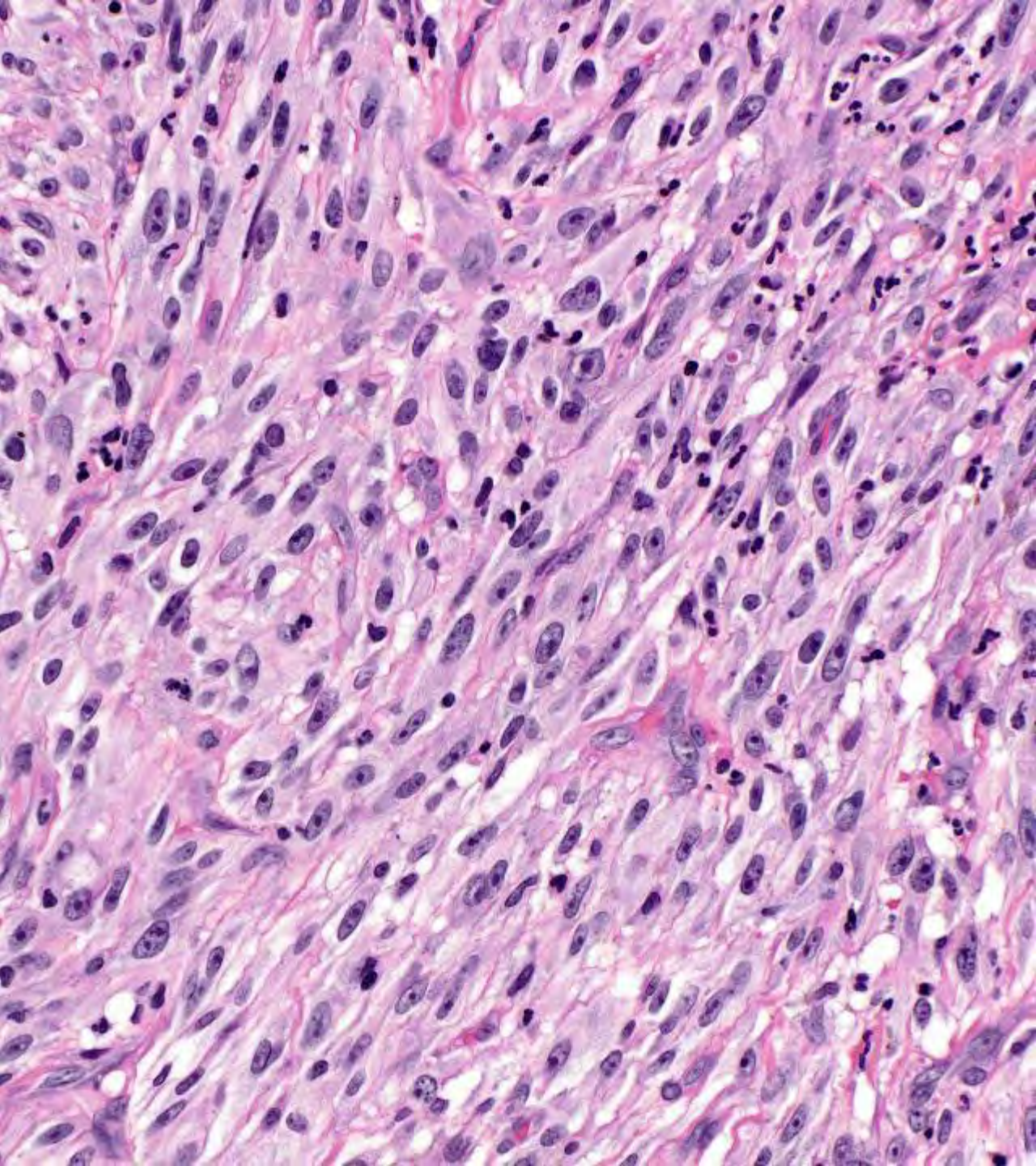
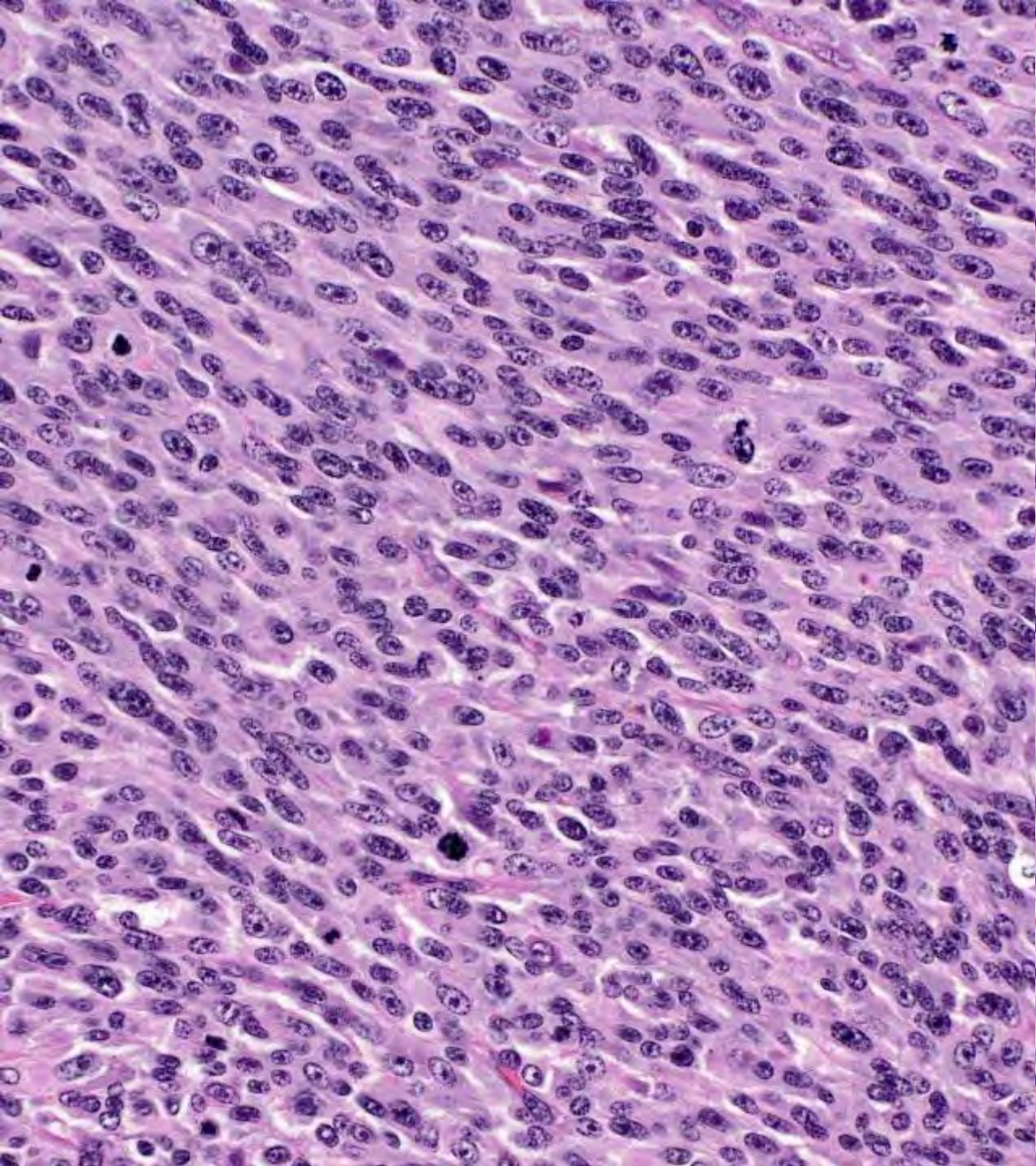
Lorenzo Cerroni

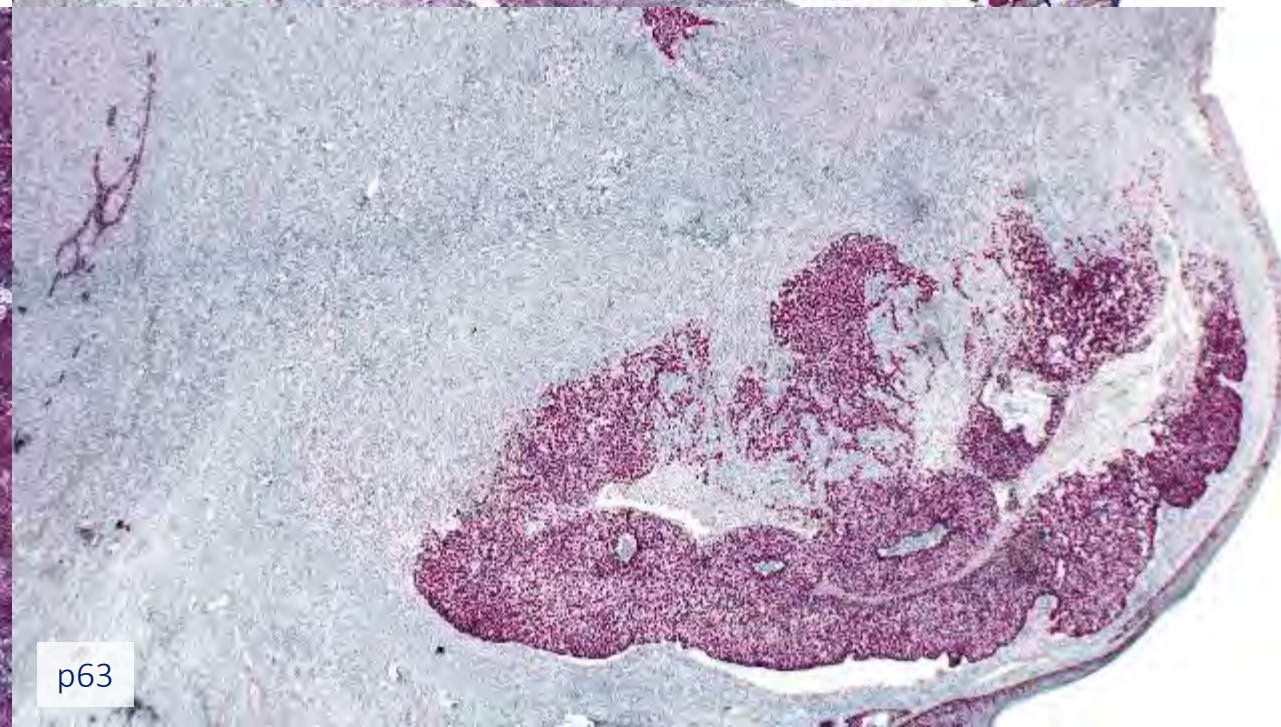
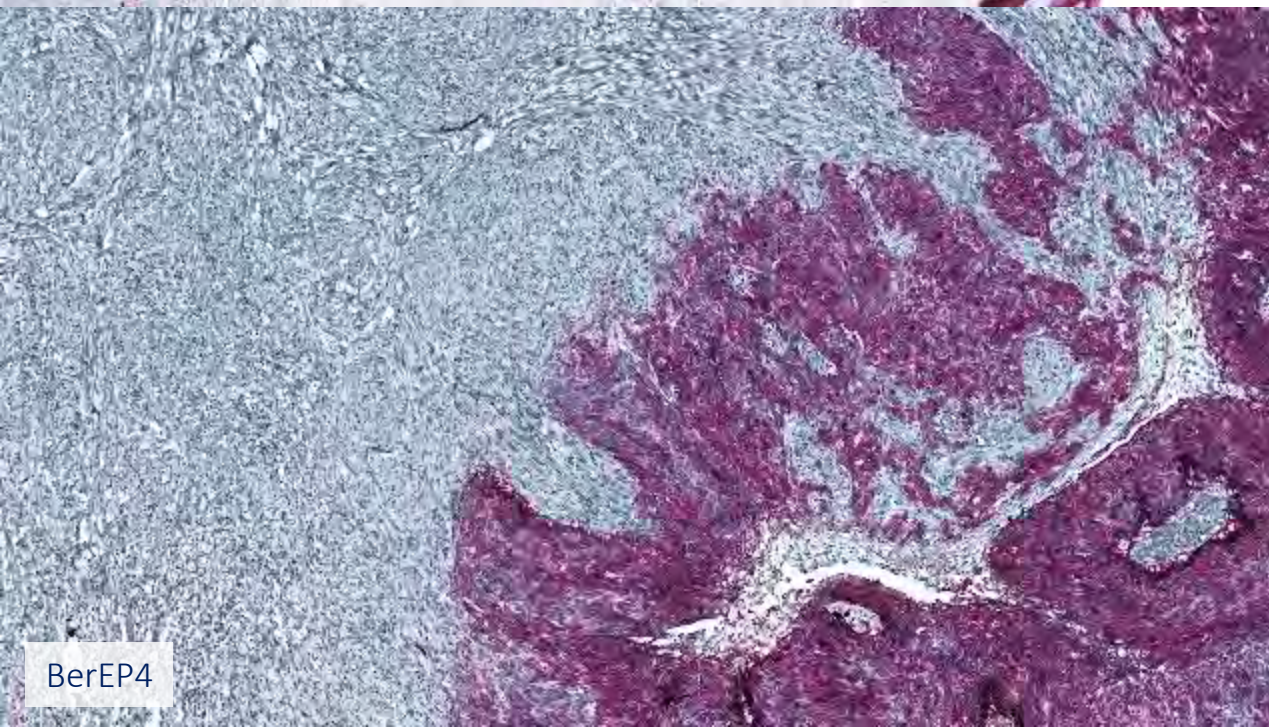
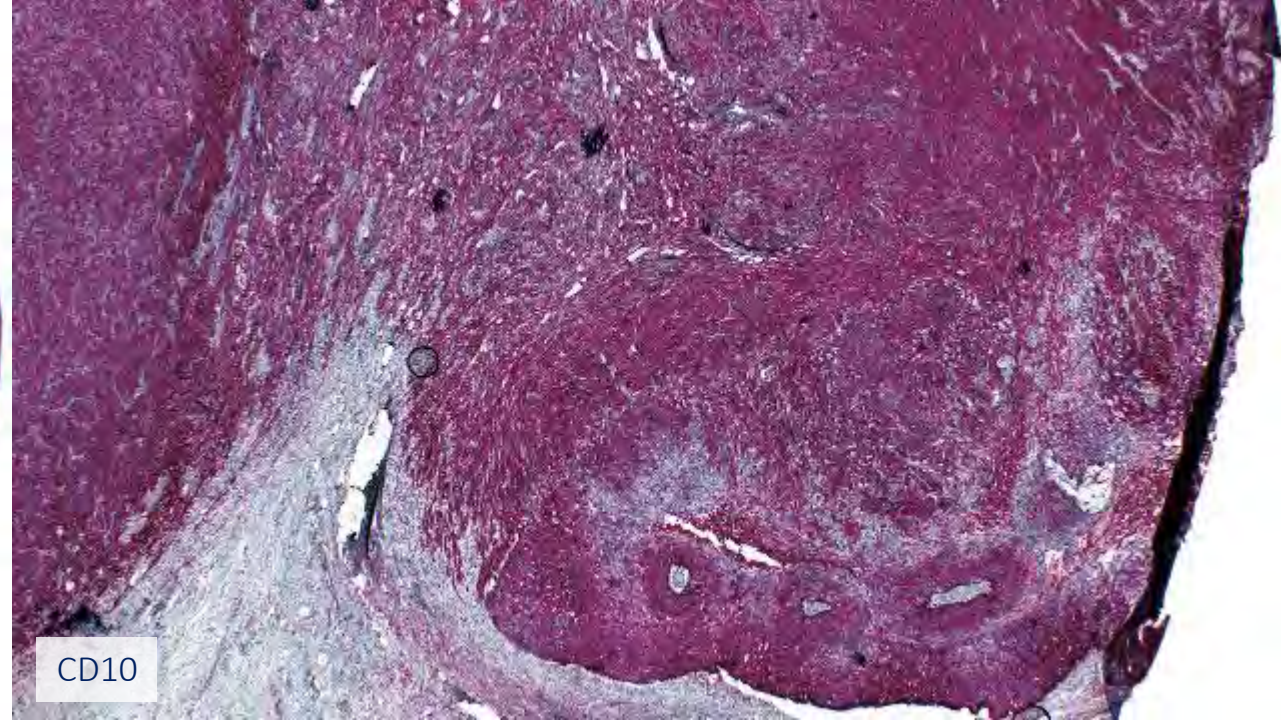
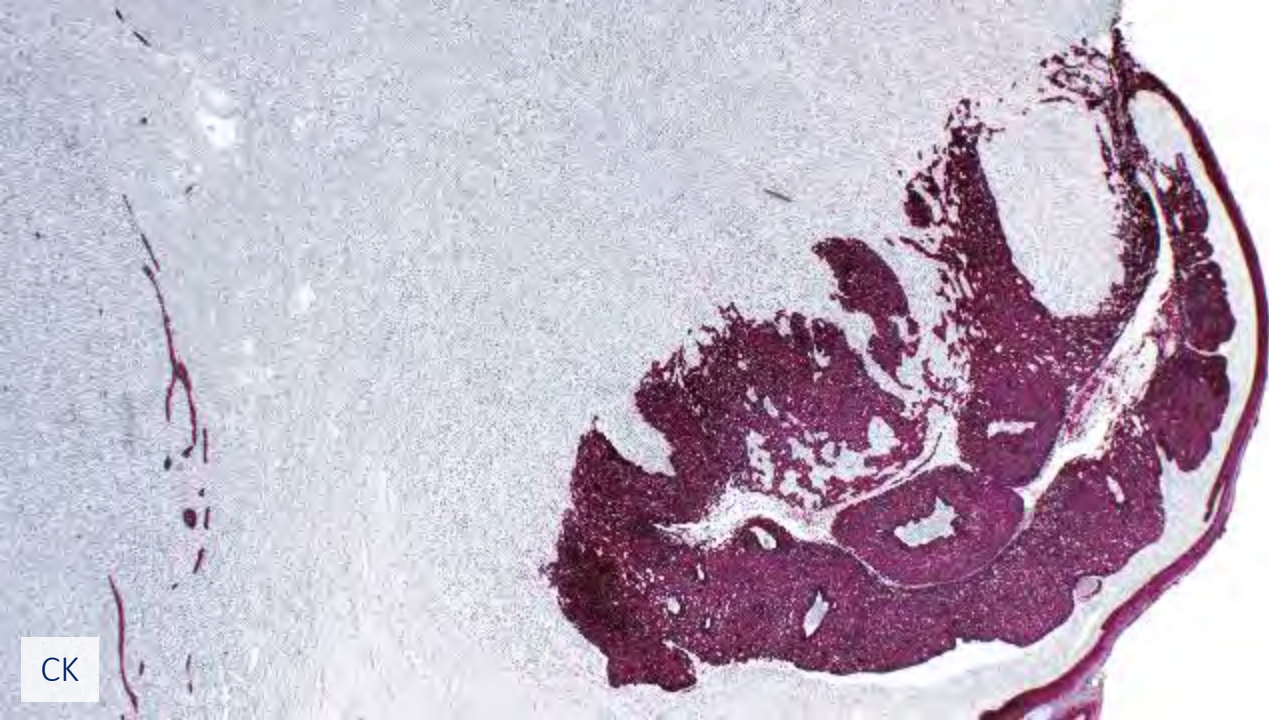
Case 1

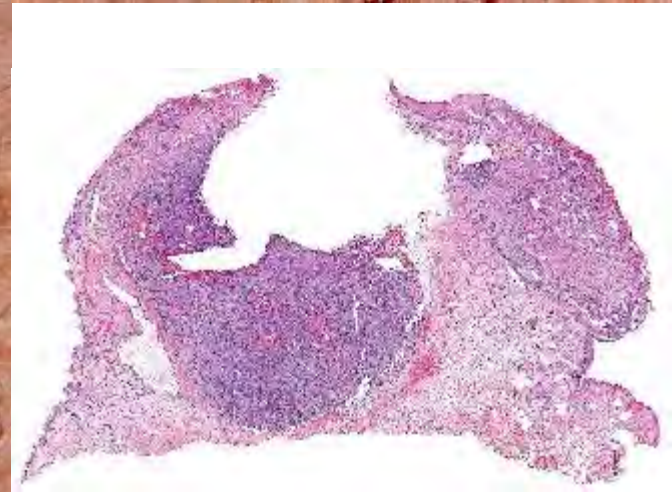
M, 85. Bleeding
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unknown duration.

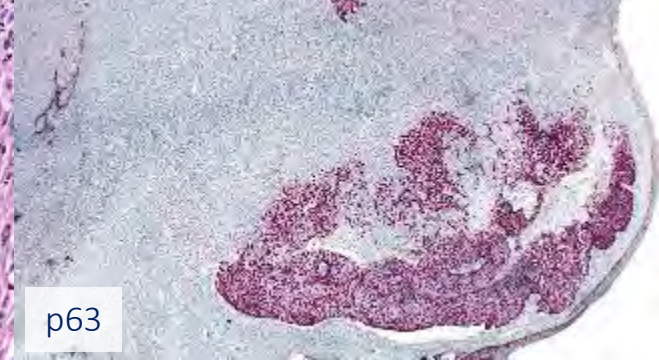
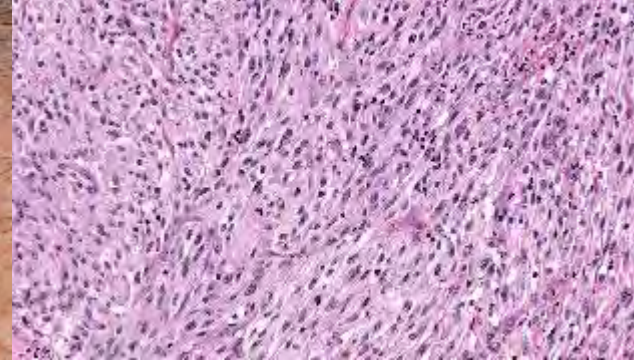
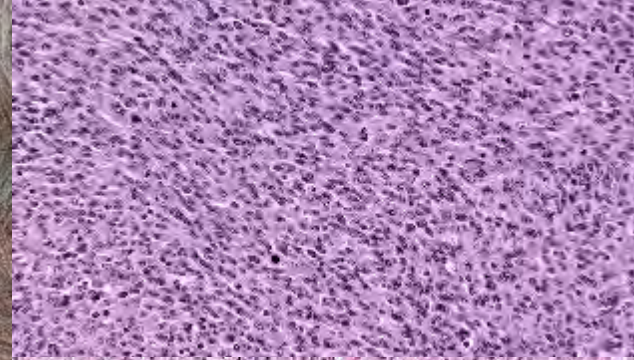
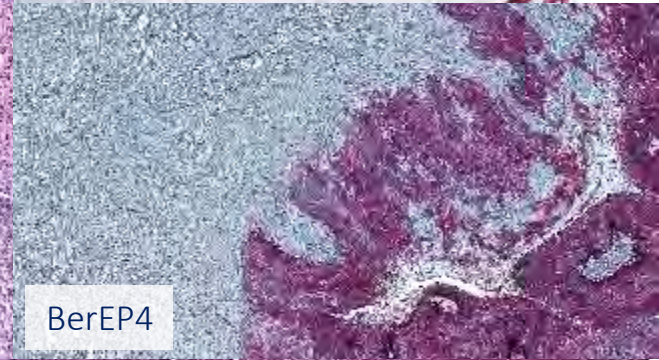
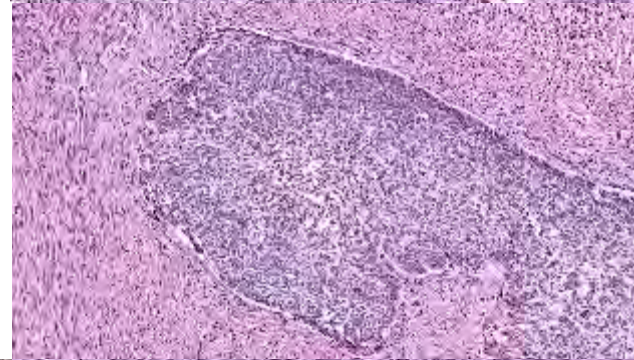
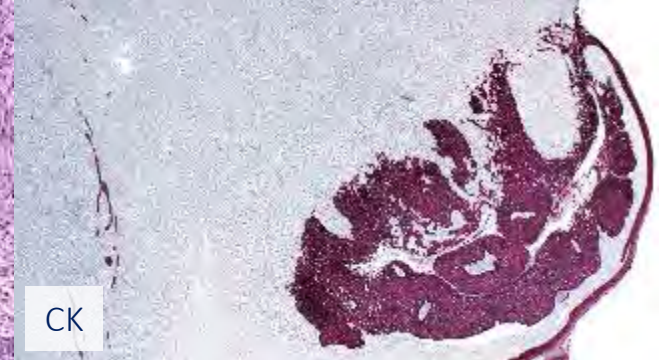
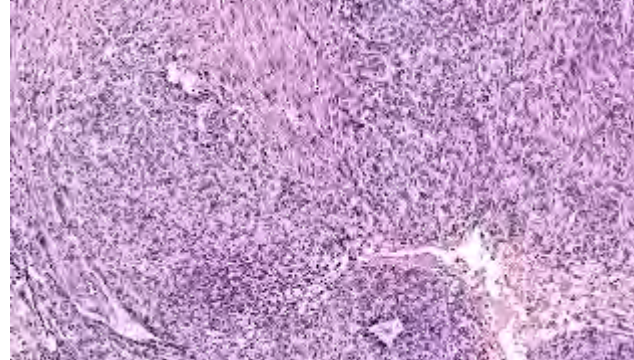












Cutaneous carcinosarcoma: adnexal vs. epidermal types define high- and low-risk tumors. Results of a meta-analysis

Objective: We report four cases of cutaneous carcinosarcoma (CS) and perform a meta-analysis of the cutaneous CS literature.

Results: CS occurred in a derm patients (mean of 40 years) on sun-damaged skin and were keratinocytic of short duration. They did not comprise a distinct CS exhibited basal cell carcinoma mixed with atypical fibrosarcoma cell populations. Immunophenotype revealed vimentin + keratin + spindle cell and vimentin + keratin epithelial cells. Three cases exhibited p53 protein expression of both carcinomas and sarcomatous components. Literature review identified 56 cases of cutaneous CS that could be broadly class into two distinct groups. Epidermal-derived basal or squamous cell carcinoma epithelial component CS arose on the sun-damaged skin of the head and neck of elderly males (mean age 72 years) and had a 70% 5-year disease-free survival. In contrast, adnexal CS (spindle neurofibroma, plexiform neurofibroma, proliferating nodular basal cystic carcinoma, or matrix trichofibroma) occurred in younger patients (mean age 58 years), showed rapid growth, in a long-standing nodule and had a 43% 5-year disease-free survival. Age less than 65 years, recent growth, long-standing skin tumor, and tumor size greater than 2 cm significantly correlated with poor outcome.

Conclusions: Cutaneous CS is an aggressive skin cancer with high risk for advanced disease. Significant risk factors exist whose identification will allow for better management of CS patients.

Tran TA, Mulker S, Chaudhri FJ, Carlson JA. Cutaneous carcinomas: a racial vs. epidermal types define high- and low-risk tumors. Results of a mesoregional.

1. *Conte Pacific* 2001: 32, 2–, 3, 6; Blackwell Munksgaard 2003:

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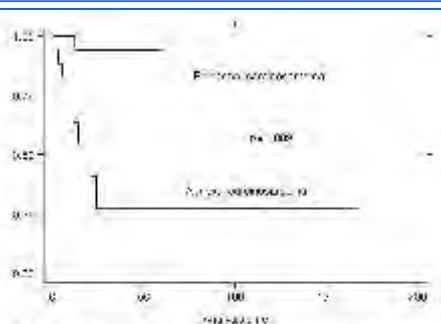
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thesis, in which the tumor is derived from a single progenitor cell that undergoes divergent differentiation into separate epithelial and mesenchymal elements in either a synchronous or metachronous fashion. In fact, most molecular studies examining three translocational origin for GBs with further accumulation of alterations that lead to its biphasic/divergent phenotype.^{1,2,3,13,14,25}

Cutaneous CS is uncommon with only 38 cases reported to date.^{1,2,9,10,12} In this case series and literature review, we delineate and discuss cutaneous CS's clinicopathologic features, differential diagnosis, and treatment options.

Table 1. Clinicopathologic findings of reported cases of cutaneous carcinomas

Number	Reference	Sex	Age	Site	Duration	Symptoms/signs	Size (cm)	Extinctal component	Metastases component	Recurrence	Outcome	Treatment
1	Ref study	Male	75	4th rib	3 months	None	1.8	HRP	APX	None	AWD 10 years	S
2	This study	Female	61	3 week	2 months	Tumor	0.4	BOC	APX, OS	None	AWD 3 years	S
3	This study	Female	75	hand	3 years	Parosteal tumor, 1 year after Rx (PC)	0.6	BOC	APX	None	AWD 3 years	S, EO
4	This study	Male	80	scap	4 months	Ap. in	0.4	HRP	APX	None	AWD 3 months	S
5	Ref	Male	73	2nd rib	1-2 years	Growth, discomfort	1.0	BOC, SCC	APX, OS	None	AWD 1 year	S, R
6	Ref	Female	46	Thorax	12 years	Growth, discomfort	1.0	HRP	APX	None	HR	S
7	Ref	Female	75	Thorax	30 years	Growth, discomfort	2	SAR	APX	Mets lung (C), brain (S), bone	AWD 11 months	S
8	Ref	Female	70	Scap	1 year	Growth, discomfort	2	HRP	APX	None	AWD 15 months	S
9	Ref	Male	72	Ant. ilia	8 weeks	Growth	0	BOC	FS, OS, CC, SO	Mets Lung (C)	AWD 3 years	S
10	Ref	Female	61	Forehead	3 months	Growth	2	EOC	OS	None	AWD 1 year	S
11	Ref	Male	73	Temples	3 years	Ulceration	NR	SCC	APX	None	AWD 1 year	S, R
12	Ref	Male	54	Apex	1 year	Soft mass, irritation	4	SDO	APX	L3, 1 year	AWD 8 years	S
13	Ref	Male	88	Claw	150 years	Growth, ulcer of foot, pain, considerable pain	3	SAR	APX	L3, Mets lung	AWD 2 months	S
14	Ref	Female	59	3 week	2 months	Growth, ulcer, bleeding	5	SCC	APX	Mets LN (C), V9	AWD 4 months	S
15	Ref	Female	52	Wrist (dist)	12 years	Growth, bleeding	6	SAR	OS	Mets (SAR)	AWD 2 years	S, R
16	Ref	Female	46	Arm	1-3 months	Swelling of elbow joint	5	SAR	OS	None	AWD 14 years	S
17	Ref	Female	54	Scalp	10 years	Growth	7	PDCC	APX	L3 (SAR), Mets L3, Lung, pleura	AWD 1 year	S
18	Ref	Female	50	Wrist	1 month	Growth	1.5	BOC	APX, OS	L3 5 years, 5 years (6 years post)	AWD 7 years	S
19	Ref	Male	44	Apex	10 years	Growth	1.6	BOC	APX	L3, arterial invasion	AWD 1 year	S, R, C
20	Ref	Female	86	Scalp	12 years	Growth, ulceration	3.5	PDCC	APX	None	AWD 2 years	S
21	Ref	Male	35	Face	2 months	Growth	4	MC	APX	Mets lung	AWD 14 months	S, R
22	Ref	Male	38	Forehead	14 years	Growth	1.5	SAR	APX, OS	L3, Mets LN, brain	AWD 8 months	S
23	Ref	Male	86	Temples	1 year	Chen'ing	1.0	HRP	OS	None	AWD 4 months	S
24	Ref	Male	74	Ant. ilia	14	Hanging tumor	NR	SCC	APX	L3 (SAR), V9	AWD 5 months	S
25	Ref	Female	69	Arm	2 years	Ulceration	2	SCC	APX	Mets LN (C), C, mouth	AWD 22 months	S, R
26	Ref	Female	68	3 years	30 years	Growth, white discharge	4.9	SAR, SCC	OS, FS	None	AWD 6 months	S
27	Ref	Male	61	Anterior	15 years	Growth	1.7	SAR	APX	Mets, metastases (L3, lung)	AWD 3 months	S
28	Ref	Female	66	Apex	6 months	Growth	2	SAR	APX	None	AWD 8 months	S
29	Ref	Male	71	Scap	14	Ulceration	3	SCC	OS	UK	AWD 15 months	S, R
30	Ref	Male	74	Scalp	14	Ulceration	3	SCC	OS, LS	None	AWD 19 months	S, R
31	Ref	Male	83	Hand	14	Tumor	1.5	SCC	OS, FS	None	AWD 20 months	S
32	Ref	Male	68	Temples	14	Pain, numb	1.5	PDCC	OS	None	AWD 15 months	S, R
33	Ref	Male	68	Temples	14	Transitory mass	4.5	SCC	OS, FS, SAR, LS	None	AWD 3 years	S
34	Ref	Male	62	Shoulder	1-2 years	Growth, discomfort	2.5	BOC	APX	None	AWD 1 year	S
35	Ref	Male	72	Arm	1 month	Growth	2.2	SCC	APX	None	AWD 9 months	S
36	Ref	Male	87	Arm	3 months	Growth, discomfort	2	Adenoca	OS, OS, RS, LS	L3 (SAR), C, 12 months	AWD 12 months	S
37	Ref	Female	37	Ant. ilia	20 years	Growth, tenderness	1	SAR, SCC, Adenoca	OS	Mets LN, lung	AWD 7 months	S, R
38	Ref	Male	41	Scalp	12 years	Growth, discomfort	1.1	SCC, BOC, Adenoca	OS, OS	L3, Mets SC, lung, bone 17 months	AWD 21 months	S, R
39	Ref	Male	51	Scalp	3 years	Growth	2.3	PDCC	APX	None	AWD 1 year	S
40	Ref	Male	84	scap	6 months	Growth, bleeding	1.9	BOC	APX	None	AWD 2 years	S
41	Ref	Female	73	Forehead	6 months	Growth	3.5	BOC	APX	None	AWD 1 year	S
42	Ref	Male	65	Thigh	MF	MF	4	BOC	APX	NR	NR	S

[illegible]

Two Factors with different contributions composed the result - a slower diagnostic rate than the patients with a low baseline of pain has well psychosocial conditions for prognosis. Other factor that appeared on prognosis are history of surgery, mainly the history of pain and changes in the clinical and psychosocial aspects over a longer and shorter time than 50 years.

Sarcomatoid Basal Cell Carcinoma—Predilection for Osteosarcomatous Differentiation

A Series of 11 Cases

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W. Pecklet, MD,‡ B. E. Cosslett, MBBS, FRCPATH,§ A. Robson, MBBS, Dip RCPATH, MRCPath,||
and E. Calonje, MD, Dip RCPATH

Abstract: Primary cutaneous carcinomas rarely show heterologous malignant mesenchymal differentiation. We report 11 cases of sarcomatoid basal cell carcinoma (BCC) with osteosarcomatous differentiation. The patients (7 men and 4 women) ranged in age from 61 to 92 years (median 75 y). The tumors presented as nodules (median 0.5 to 7 cm) on the head (n = 6), upper limbs (n = 3), and lower limbs (n = 2). All lesions were completely excised. Seven patients were alive without evidence of disease (disease-free interval 3 to 24 mo) and 1 patient died of unrelated causes at 7 months without evidence of disease. On microscopy, the tumors were dermal or located with 2 cases showing focal subcutaneous involvement. Ten tumors were well-circumscribed and 1 tumor showed focally infiltrative edges. The tumors consisted predominantly of BCC associated with varying proportions of osteosarcomatous and chondrosarcomatous differentiation. Transient from osteoblastic epithelium to osteosarcomatous cells was seen in 3 cases. One case showed a poorly circumscribed area with disorganized mesenchyme, unrelated to the sarcomatous areas, suggesting an osteosarcomatous transformation. Histologically interpreted as sarcomatoid BCC, no mesenchymal component of either case displayed predominant malignant giant cell areas, two areas and 1 further case displayed areas reminiscent of telangiectatic osteosarcoma. Immunohistochemistry (IHC) and MIB-1 (Ki-67) staining merely identified occasional undifferentiated sarcomatous cells in 3 and 5 cases, respectively. MIB-1 and EMA were mostly positive in osteosarcomatous tumor cells of 3 cases. Although the following analysis is short, our data suggest an excellent prognosis for polypoid and nodular sarcomatoid BCC after complete surgical resection.

Key Words: sarcomatoid carcinoma, sarcomatous, basal cell carcinoma, osteosarcoma, osteosarcomatous skin

(Am J Surg Pathol 2008;32:1299-1308)

TABLE 1. Clinicopathological Features of Previously Reported Cutaneous Sarcomatoid Carcinoma With Heterologous Mesenchymal Differentiation in the English Literature

No	Reference	Sex	Age	Site	Duration	Size (cm)	Epithelial Component	Mesenchymal Component	Recurrence	Outcome	Rx
1	Bigby et al ⁴	M	83	Earlobe	3 mo	1.5	BCC	Os, mf	None	Awod 22 mo	S
2	Bigby et al ⁴	M	86	Upper back	2 y	1.2	BCC	Ls	None	Awod 6 mo	S
3	Velazquez et al ³⁵	Unk	Unk	Penis	Unk	unk	SCC	Os	Unk	Unk	S
4	Tran et al ²¹	F	81	Cheek	2 mo	0.7	BCC	Afx, Cs	None	Awod 3 y	S
5	Dawson et al ¹¹	M	75	Chest	> 2 y	10	BCC, SCC	Afx, Os	None	Dwod 1 y	S, R
6	Quay et al ⁴¹	M	74	Axilla	6 wk	8	BCC	Fs, Os, Cs, Ss	Mets lung (2a)	Awod 5 y	S
7	Tschien et al ³⁷	F	91	Forehead	6 mo	7	BCC	Os	None	Awod 1 y	S
8	McKee et al ³⁴	F	52	Iliac crest	13 y	6	Sac	Os	Mets (sa)	Dwd 2 y	S, R
9	McKee et al ³⁴	F	25	Arm	< 3 mo	1	Sac	Os	None	Awod 11 y	S
10	Parham et al ³⁹	F	54	Vulva	1 mo	1.5	SCC	Os, afx	Tr 3y, 5y, 6y × 2	Awod 7 y	S
11	Leen et al ²⁹	M	86	Tragus	1 y	1.5	BCC	Os	None	Awod 5 mo	S
12	Saboorian et al ⁴²	F	68	Breast	50 y	4.5	Sac, SCC	Os, Rs	None	Awod 9 mo	S
13	Itoh et al ²⁷	F	68	Hip	6 mo	2	Sac	Ls	None	Awod 8 mo	S
14	Patel et al ⁴⁰	M	71	Eyelid	Unk	2	SCC	Os	Unk	Unk	S
15	Patel et al ⁴⁰	M	74	Scalp	Unk	3	SCC	Rs, Ls	None	Awod 19 mo	S, R
16	Patel et al ⁴⁰	M	83	Head	Unk	1.5	SCC	Os, Cs	None	Dwod 20 mo	S
17	Patel et al ⁴⁰	M	64	Nose	Unk	1	Poroc	Os	None	Awod 16 mo	S, R
18	Antonini et al ¹	M	66	Penis	Unk	4.5	SCC	Os, Cs, R ₉ /Ls	None	Awod 5 y	S
19	Islikawa et al ²⁰	F	37	Axilla	20 y	3	Sac, SCC, ad	Cs	Mets Ln lung	Dwd 7 mo	S, C, R
20	Cooper et al ⁸	F	79	Forearm	Unk	Unk	Merkel	Ls (in mets)	Mets LN	Mets 4/12 mo	S

BCC indicates basal cell carcinoma; SCC, squamous cell carcinoma; Sac, spindle sarcoma; Poroc, porocarcinoma; Ade, adenocarcinoma; Os, osteosarcoma; Mf, myofibrosarcoma; Cs, chondrosarcoma; Ls, leiomyosarcoma; Rs, rhabdomyosarcoma; Afx, atypical fibrosarcoma; Tr, local recurrence; Mets, metastasis; Ln, lymph node; Cs, carcinoma; Sac, sarcoma; Awod, alive without disease; Awod, alive with disease; Dwd, dead with disease; Dwod, dead without disease; S, surgery; C, chemotherapy; R, radiotherapy; Unk, unknown.

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Case study

Primary cutaneous carcinosarcoma: insights into its clonal origin and mutational pattern expression analysis through next-generation sequencing ^{☆, ☆, ☆}

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(*Am J Surg Pathol* 2014;38:1358–142)

CASE REPORT

Basal Cell Carcinosarcoma With *PTCH1* Mutations in Both Epithelial and Sarcomatoid Primary Tumor Components and in the Sarcomatoid Metastasis

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Abstract: Basal cell carcinomas are a rare biphenotypic malignant skin tumor, in which one tumor component has light microscopic features of basal cell carcinoma, whereas the other has features of sarcoma. Clinical experience with this tumor is limited, and associated molecular genetic alterations are unknown. Herein, we report a unique case of metastatic basal cell carcinomasarcoma, in which we analyzed the 2 components of the primary tumor as well as the metastasis by next-generation sequencing. The patient was a 72-year-old man who presented with a 7-year history of a large

Cutaneous carcinosarcoma is a rare biphenotypic malignant skin tumor with light microscopic features of carcinoma and sarcoma.¹ It tends to affect sun-damaged skin of elderly individuals.² The epithelial component most commonly has features of basal cell carcinoma or squamous cell carcinoma. Other skin tumors, such as Merkel cell carcinoma, eccrine porocarcinoma, proliferating tricholemmal tumor, or eccrine spiradenocarcinoma may be associated with a second sarcomatous tumor component.³ The spectrum of

ORIGINAL ARTICLE

Cutaneous carcinosarcoma: further insights into its mutational landscape through massive parallel genome sequencing

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A. Hafeez Diwan • Bedia A. Barkoh • Ronald Cason • Yve Hattenbach •
Gustavo Benaim • John Galbreath • Rajyalakshmi Luthra

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Abstract Cutaneous carcinosarcoma (CCS) is an extraordinarily rare neoplasm with a biphasic morphological pattern exhibiting both epithelial and sarcomatous components. Although its histogenesis and biological aspects remain poorly understood, previous studies have postulated that this tumor

indeed share a common clonal origin. Additionally, CCS appears to embrace a heterogeneous spectrum with specific underlying molecular signatures correlating with the defining epithelial morphotype, with those carcinosarcomas exhibiting a squamous cell carcinoma epithelial component exhibiting

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Original contribution

Cutaneous basal cell carcinomasarcomas: evidence of clonality and recurrent chromosomal losses

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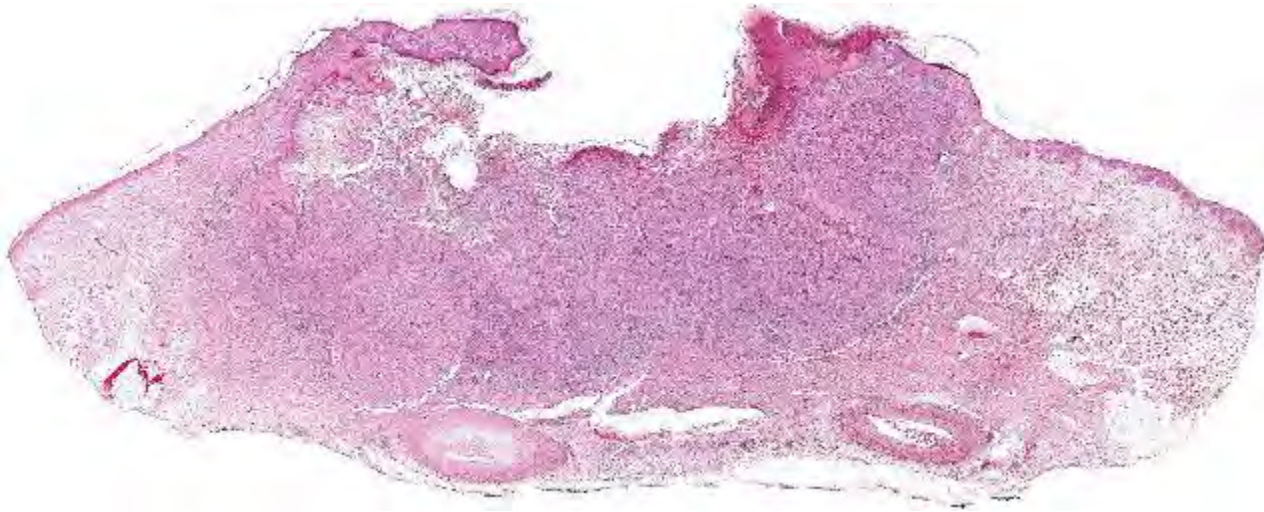
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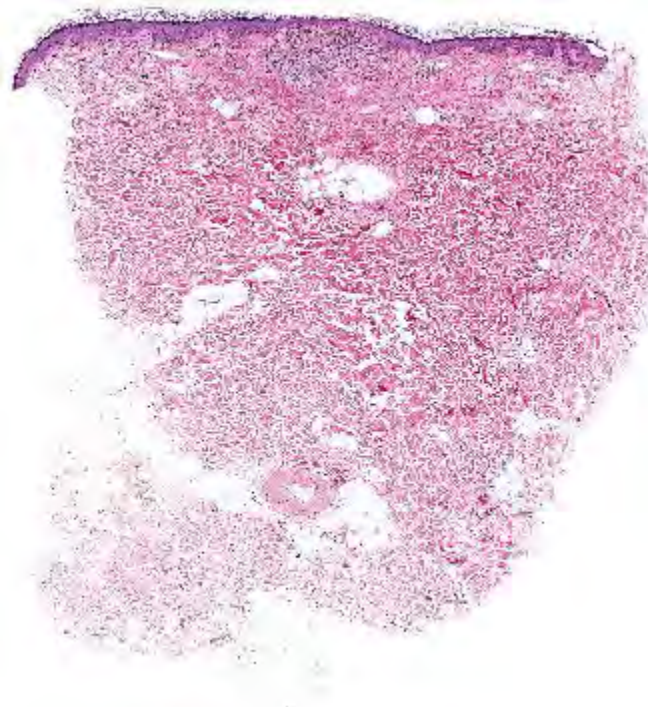
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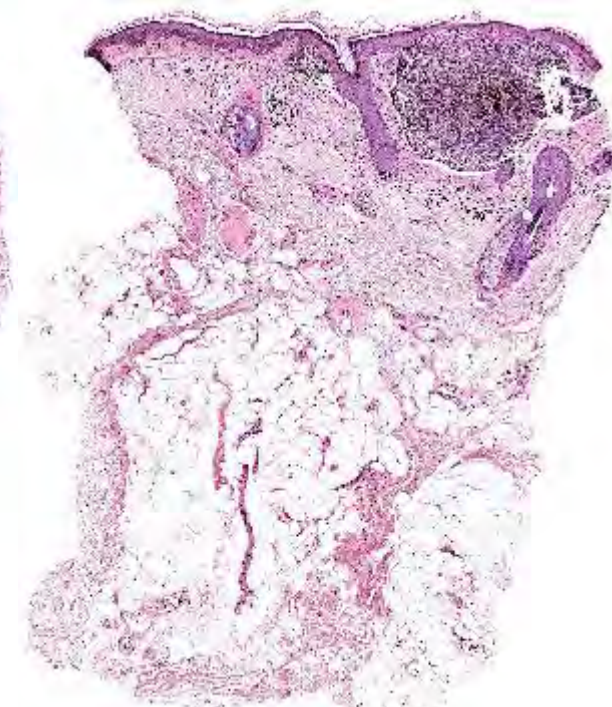
Next 5 cases present a similar problem



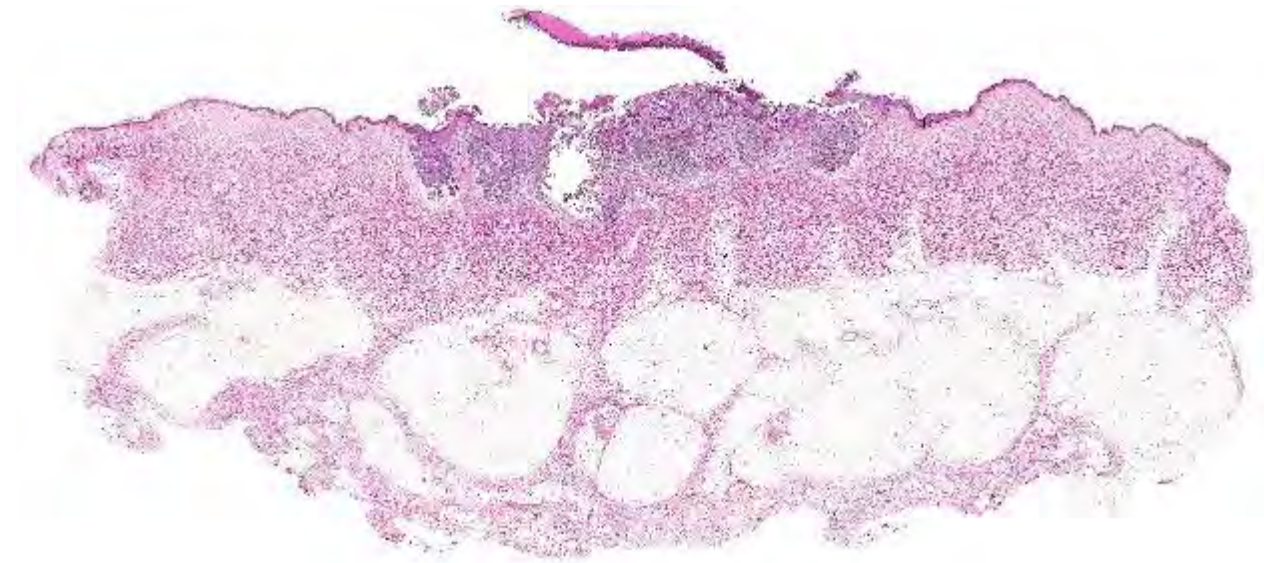
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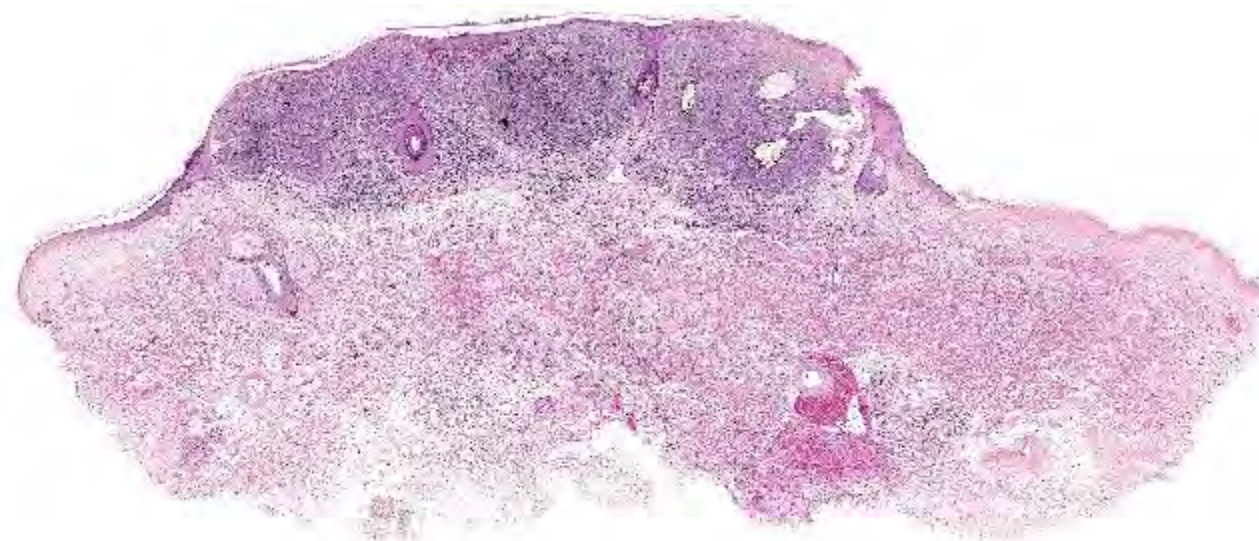
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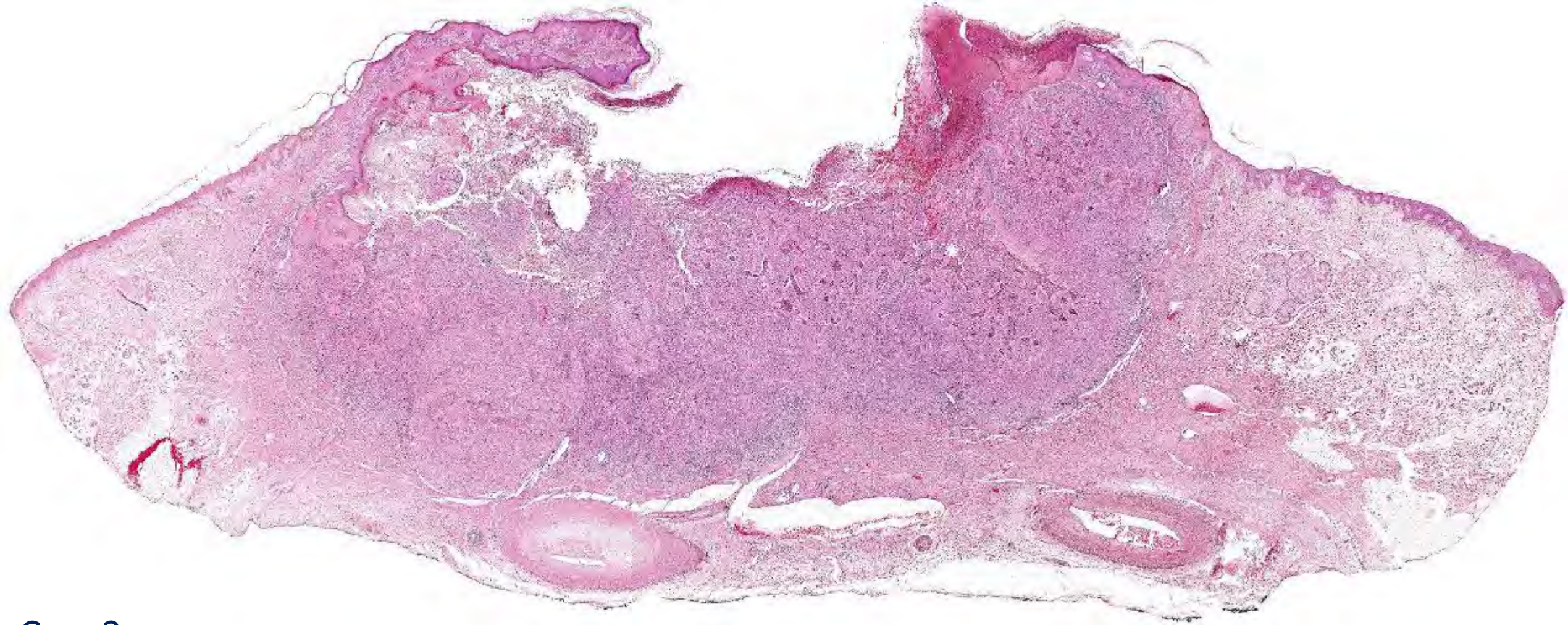
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Case 5



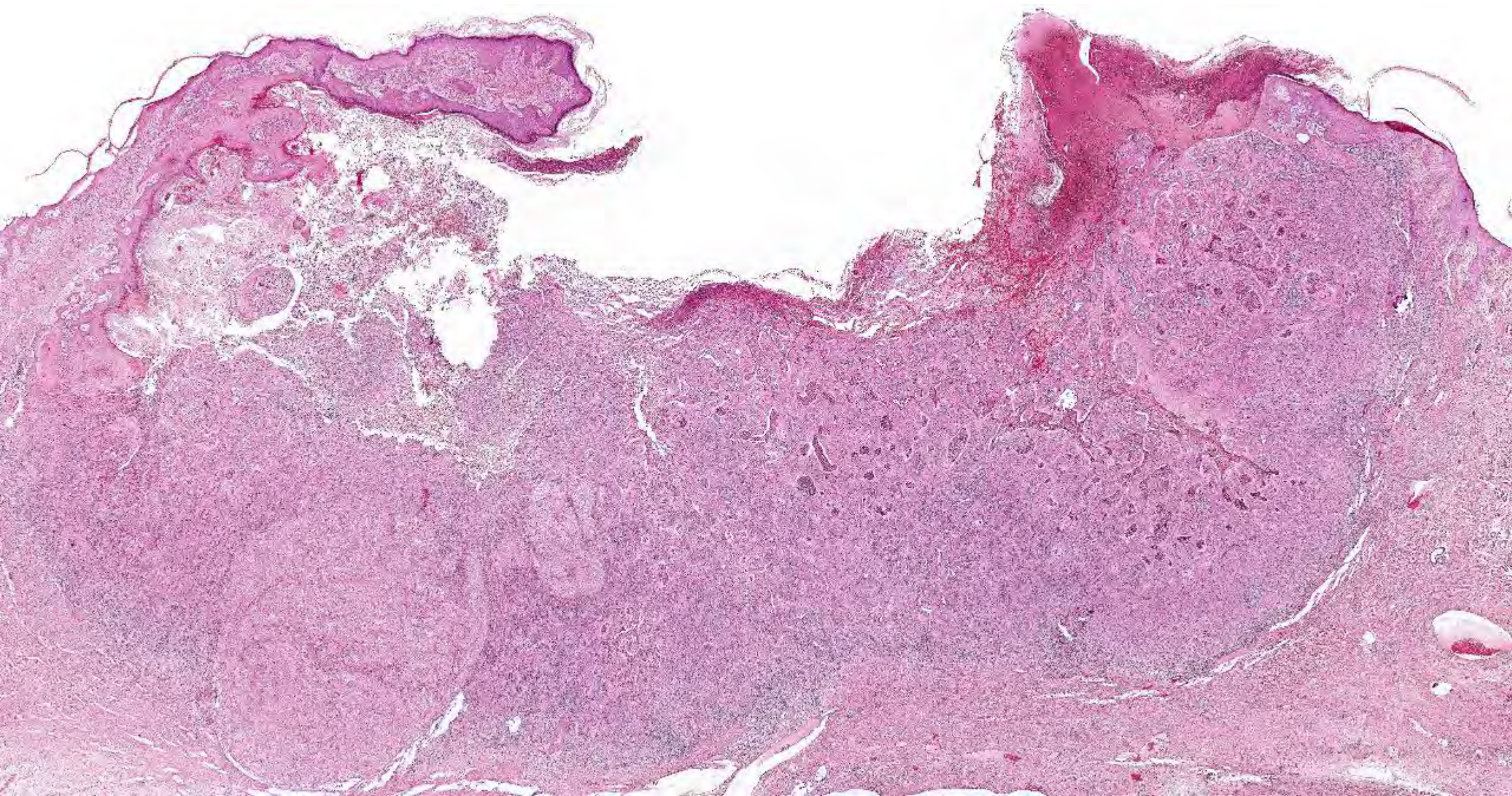
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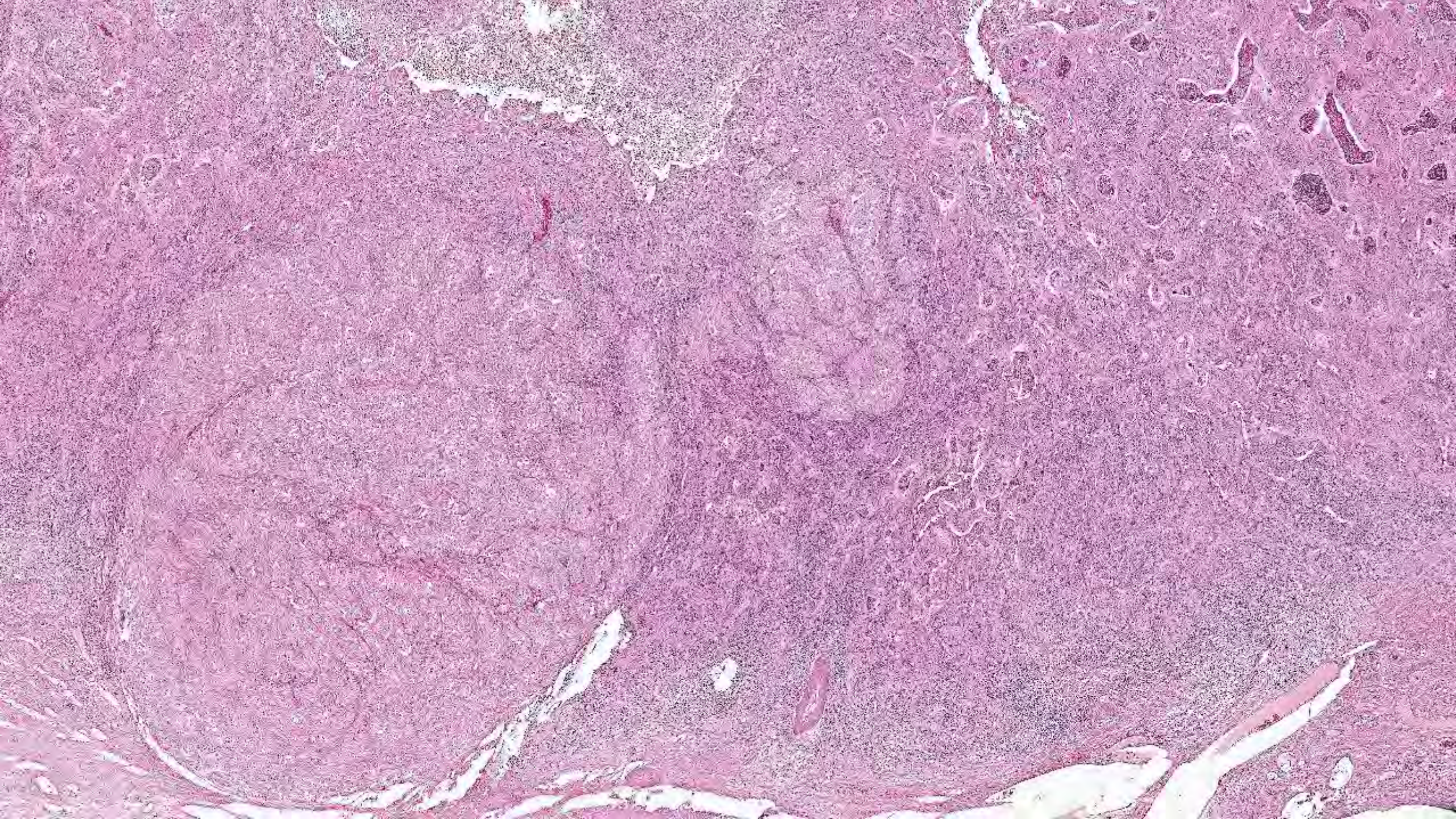


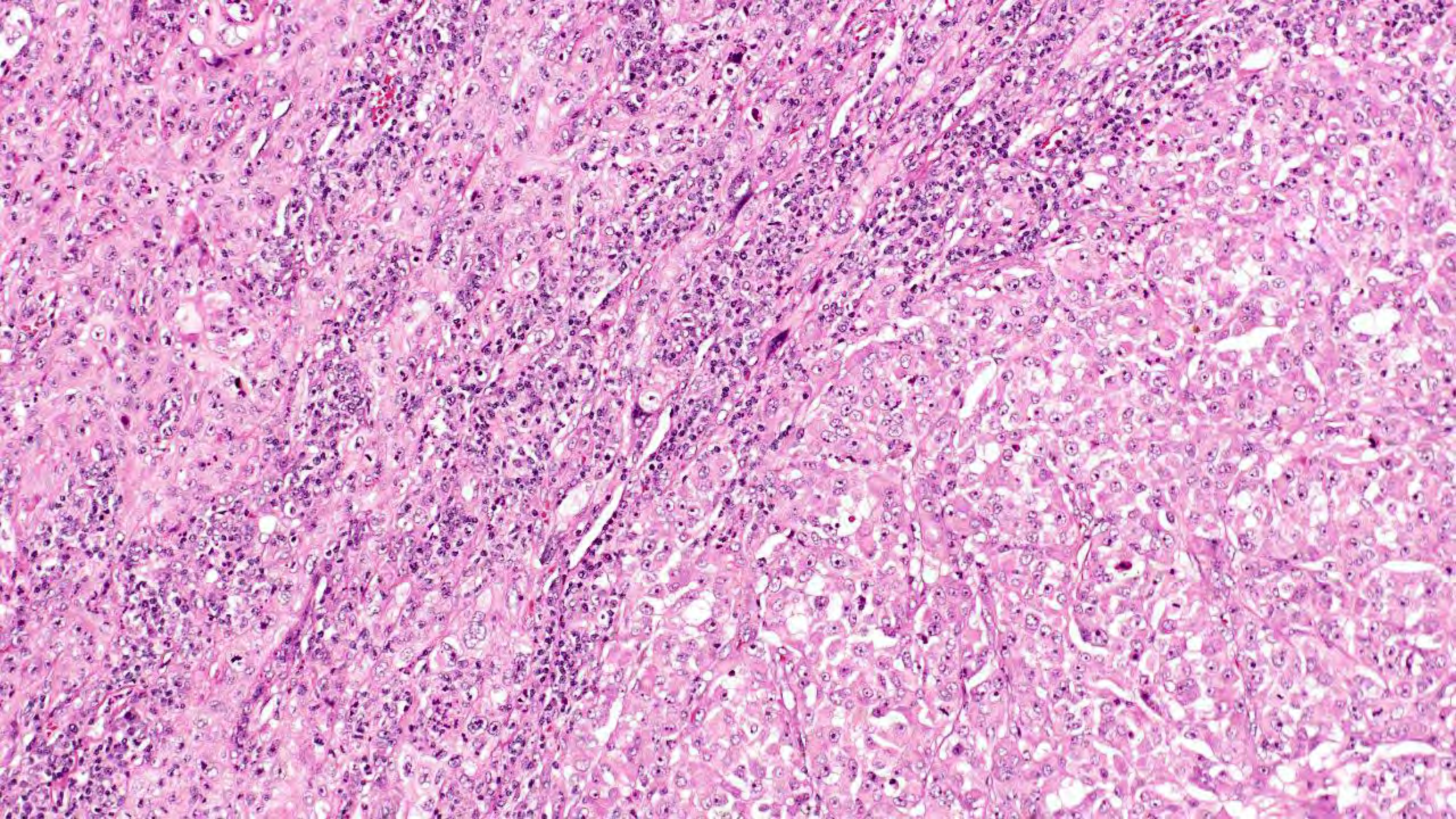
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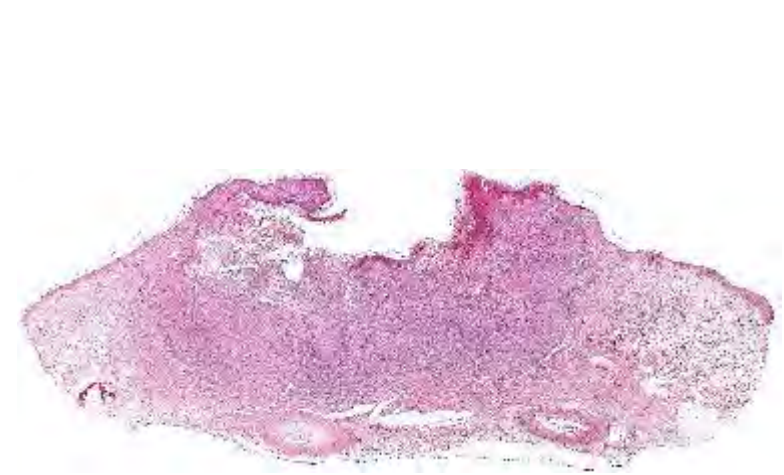
M, 91. History of melanoma in situ on the right temple 2 years before presentation (confirmed by punch biopsy; the planned surgical excision was not performed because of a Covid-19 infection and later on a femoral neck fracture; the patient did not come back afterwards).

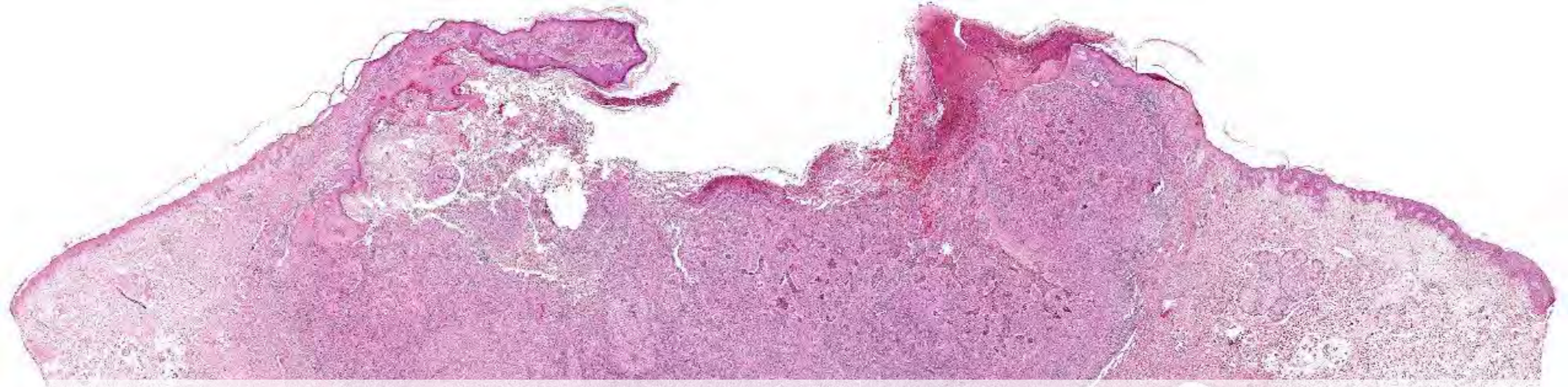
Ulcerated tumor approx. 2 cm. distal from the site of the previous punch biopsy.





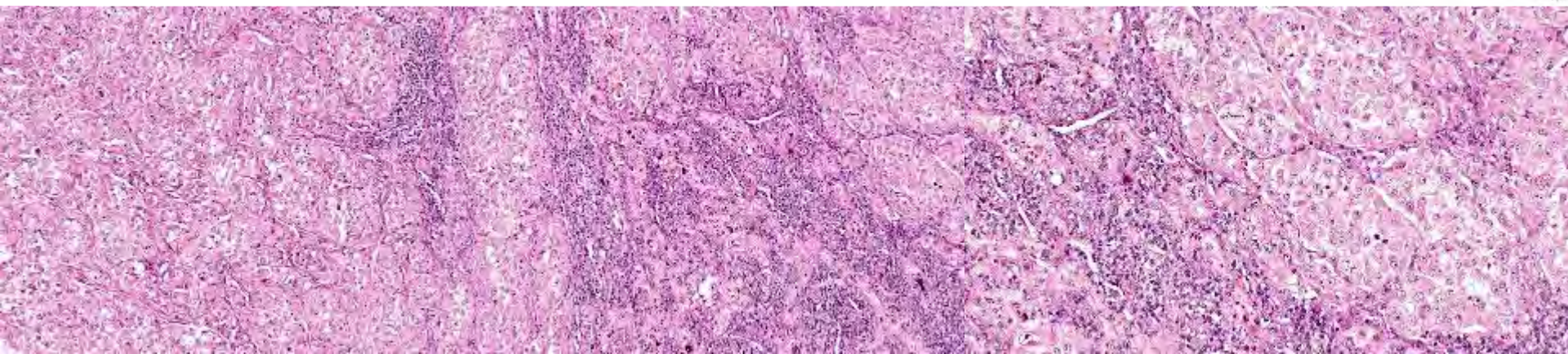






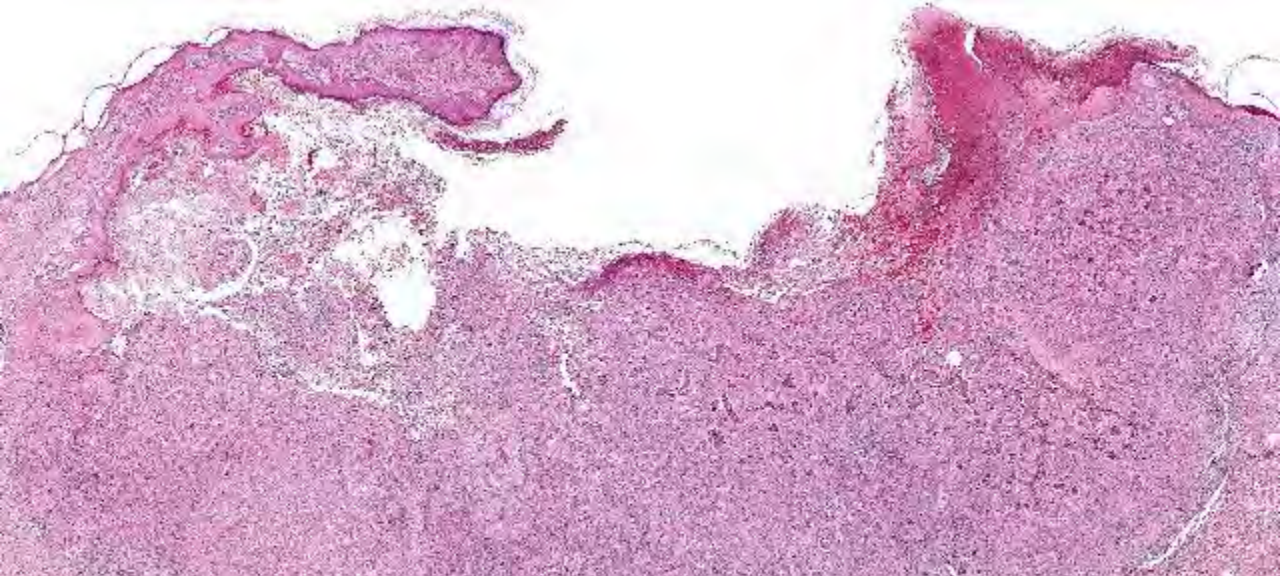
Squamous cell carcinoma, keratoacanthoma type, with focal clear-cell differentiation

Dr. Schadelbauer: should we stain it? Prof. Cerroni: not necessary

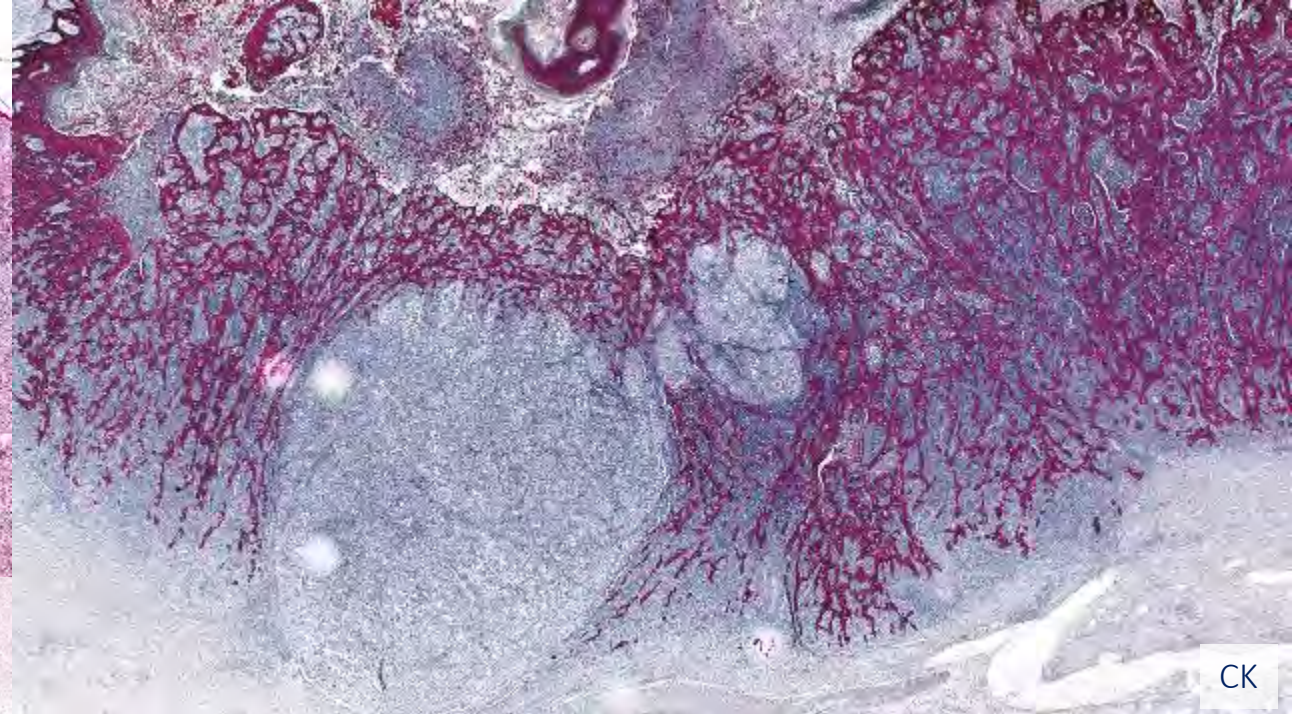


*On Fridays, Prof. Cerroni is not at the Department, and spends his time at his mountain house;
Dr. Fried gets the case, and decides that staining may be worthwhile...*

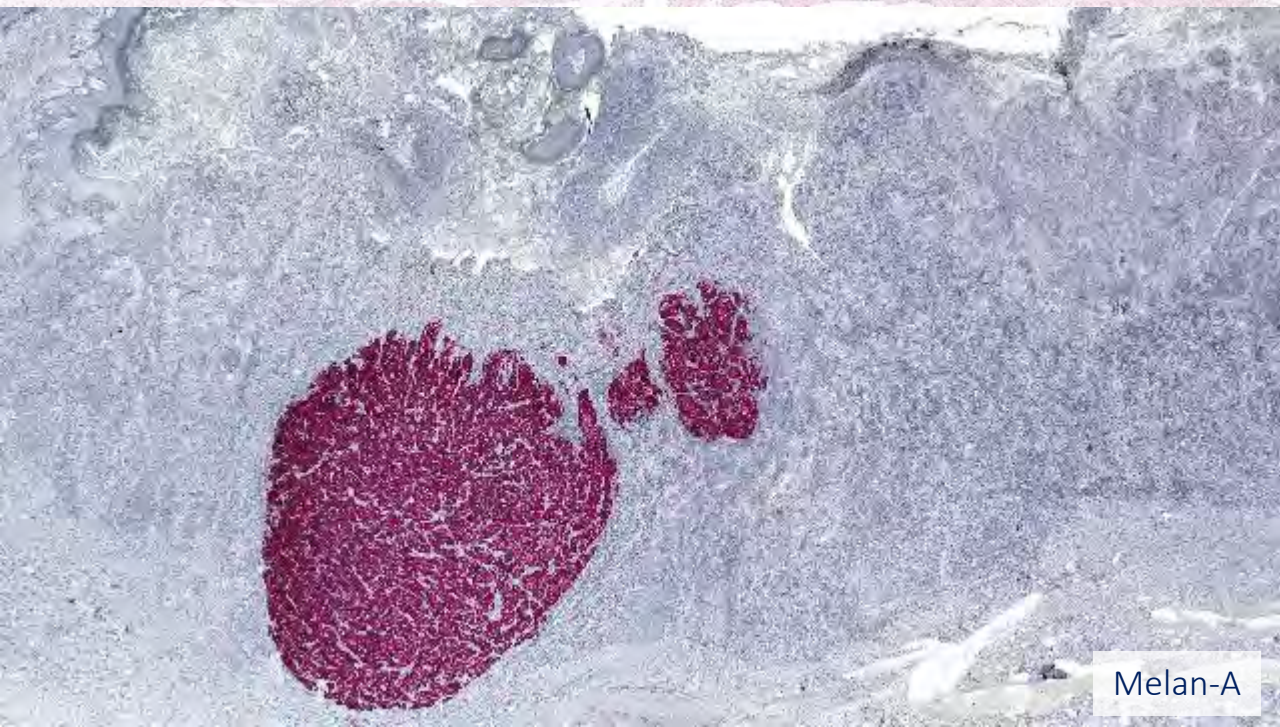




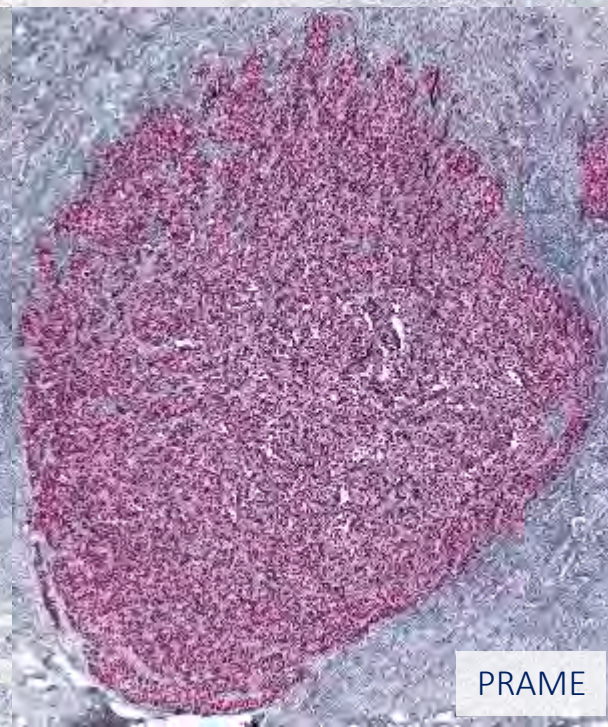
Nodular complexes of a melanoma
within a squamous cell carcinoma, keratoacanthoma type



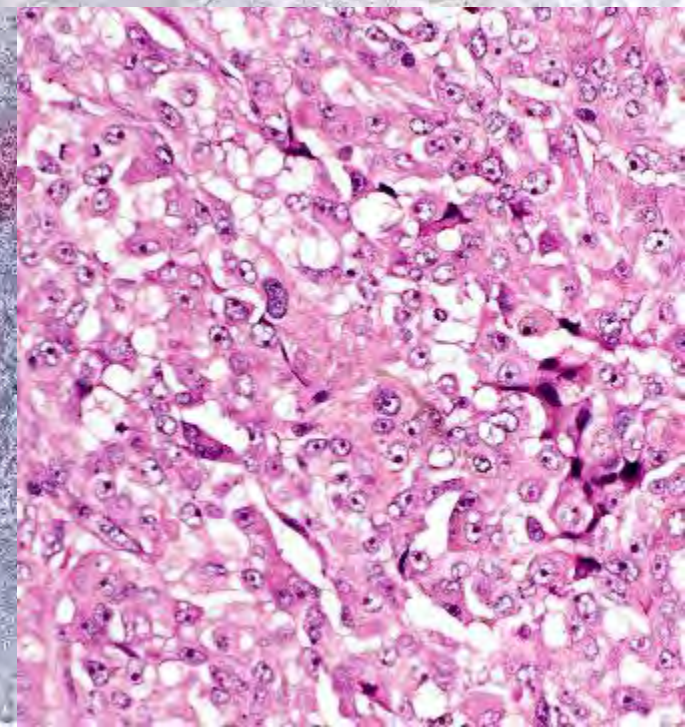
CK

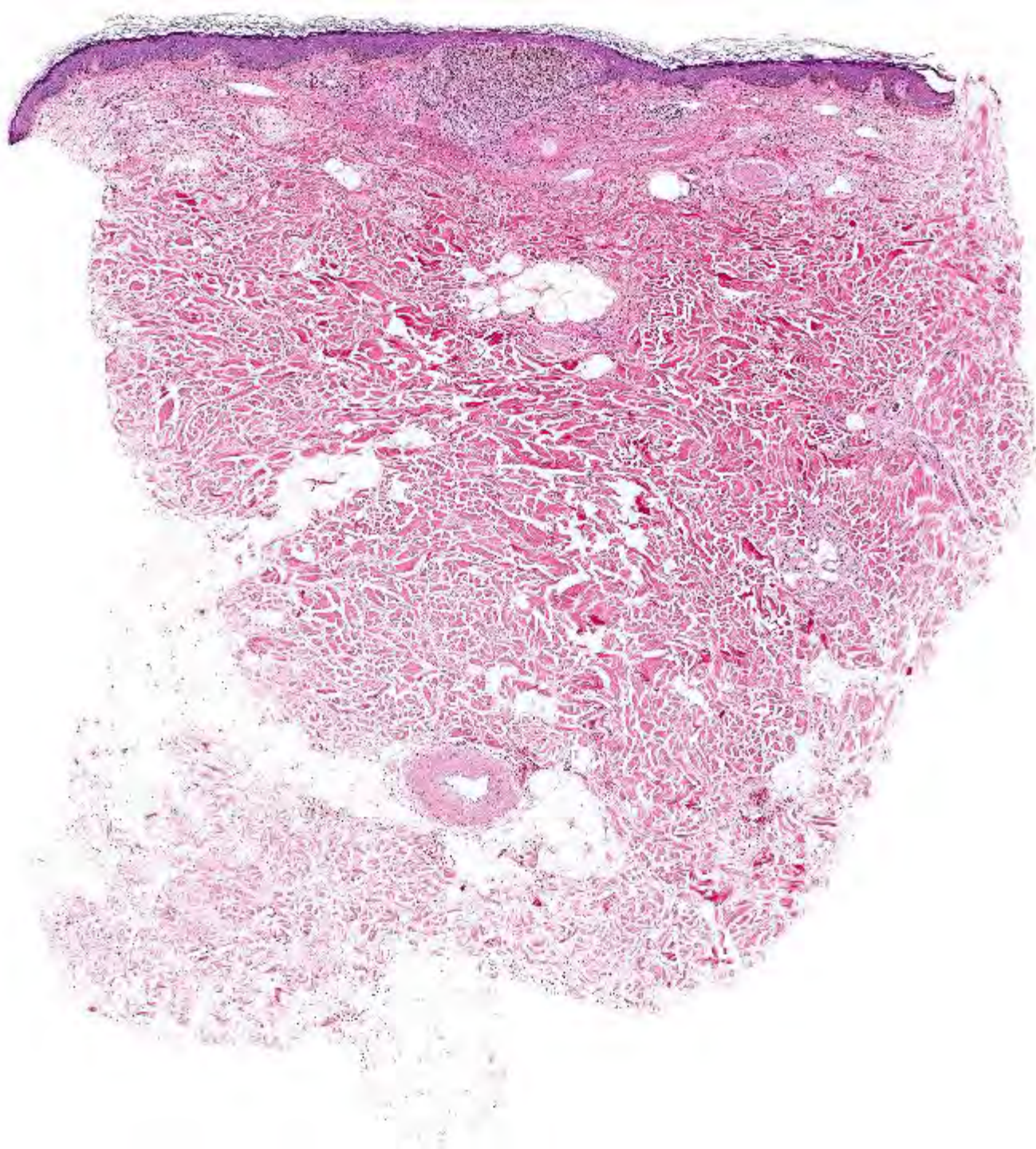


Melan-A



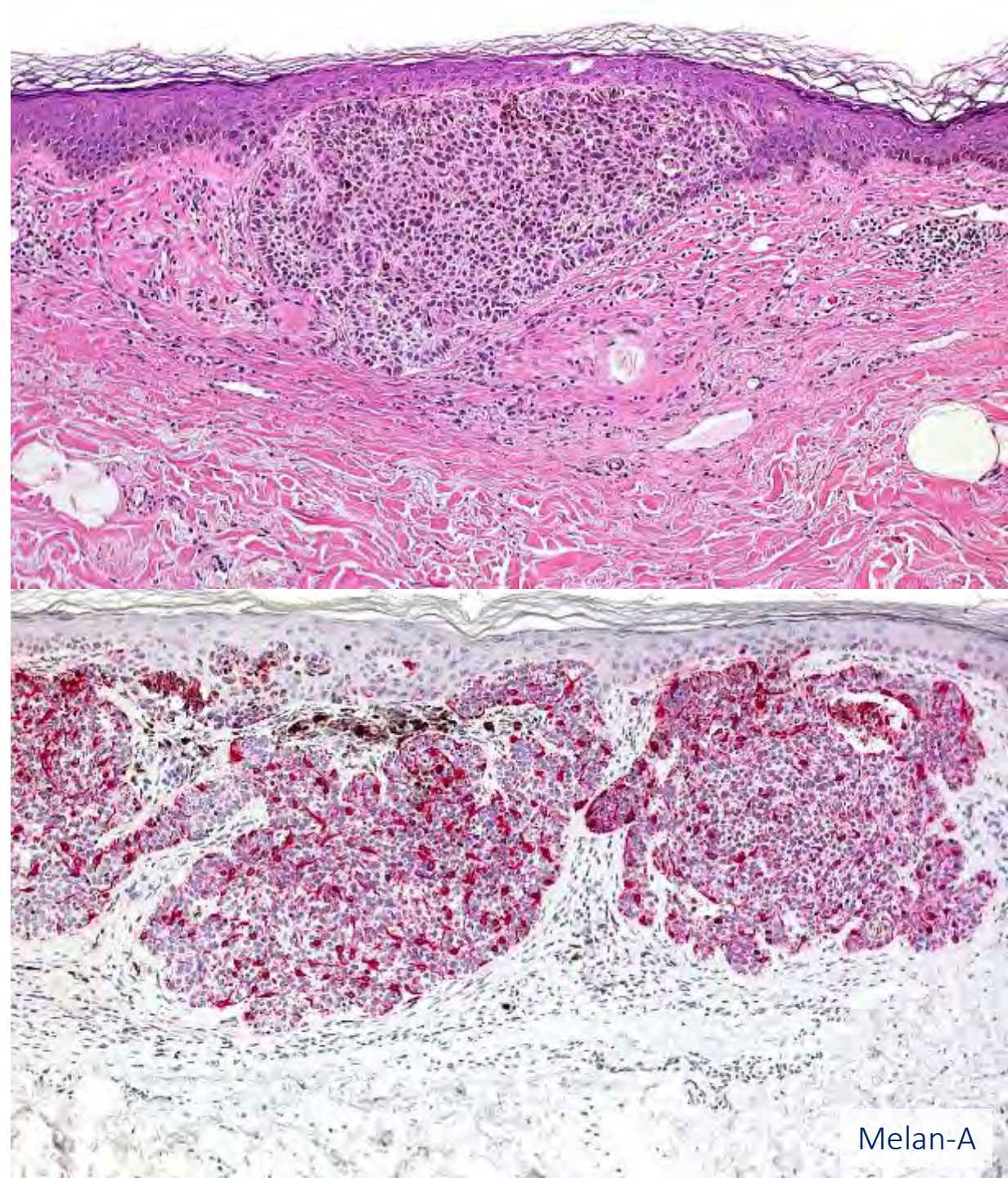
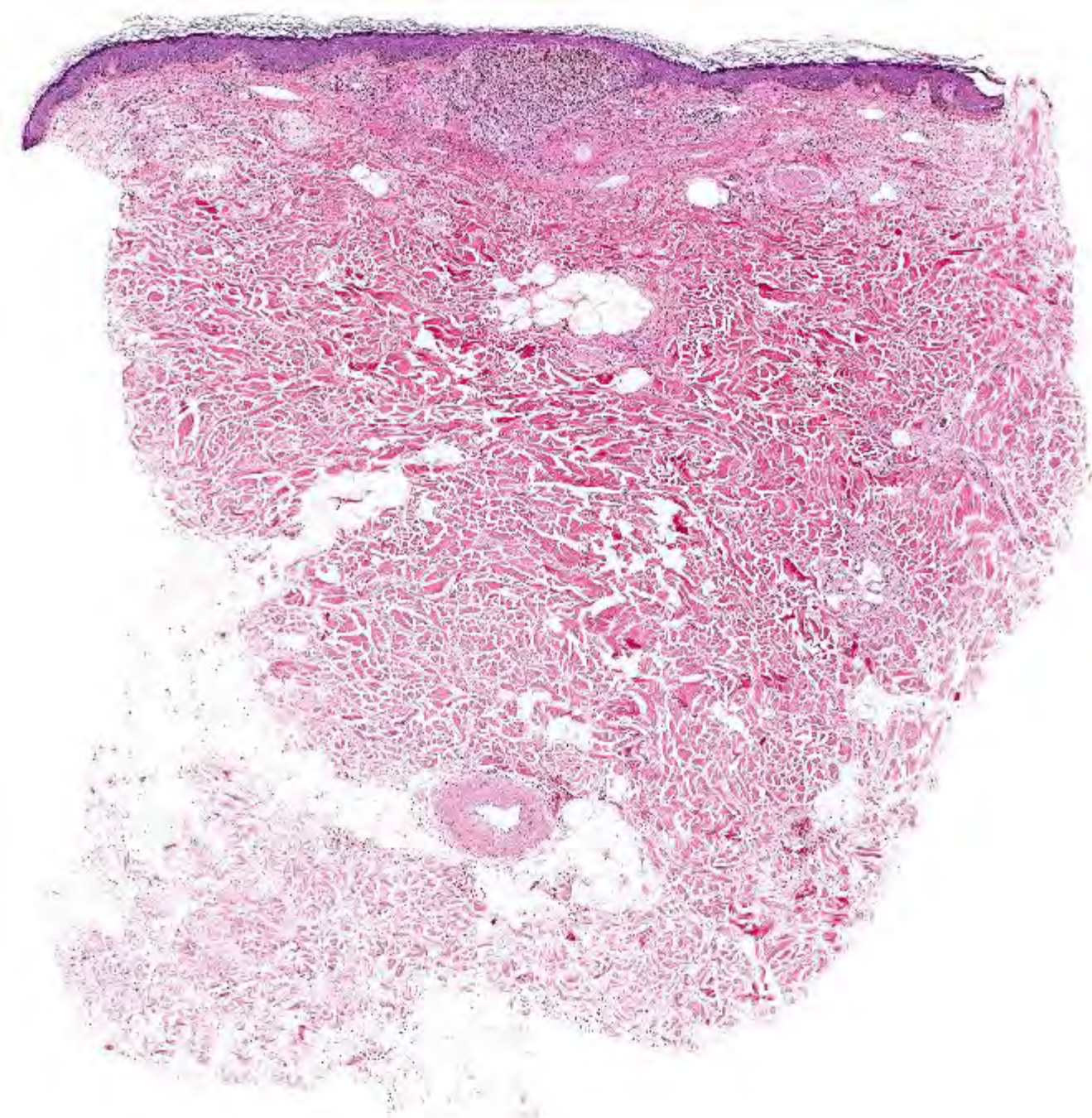
PRAME

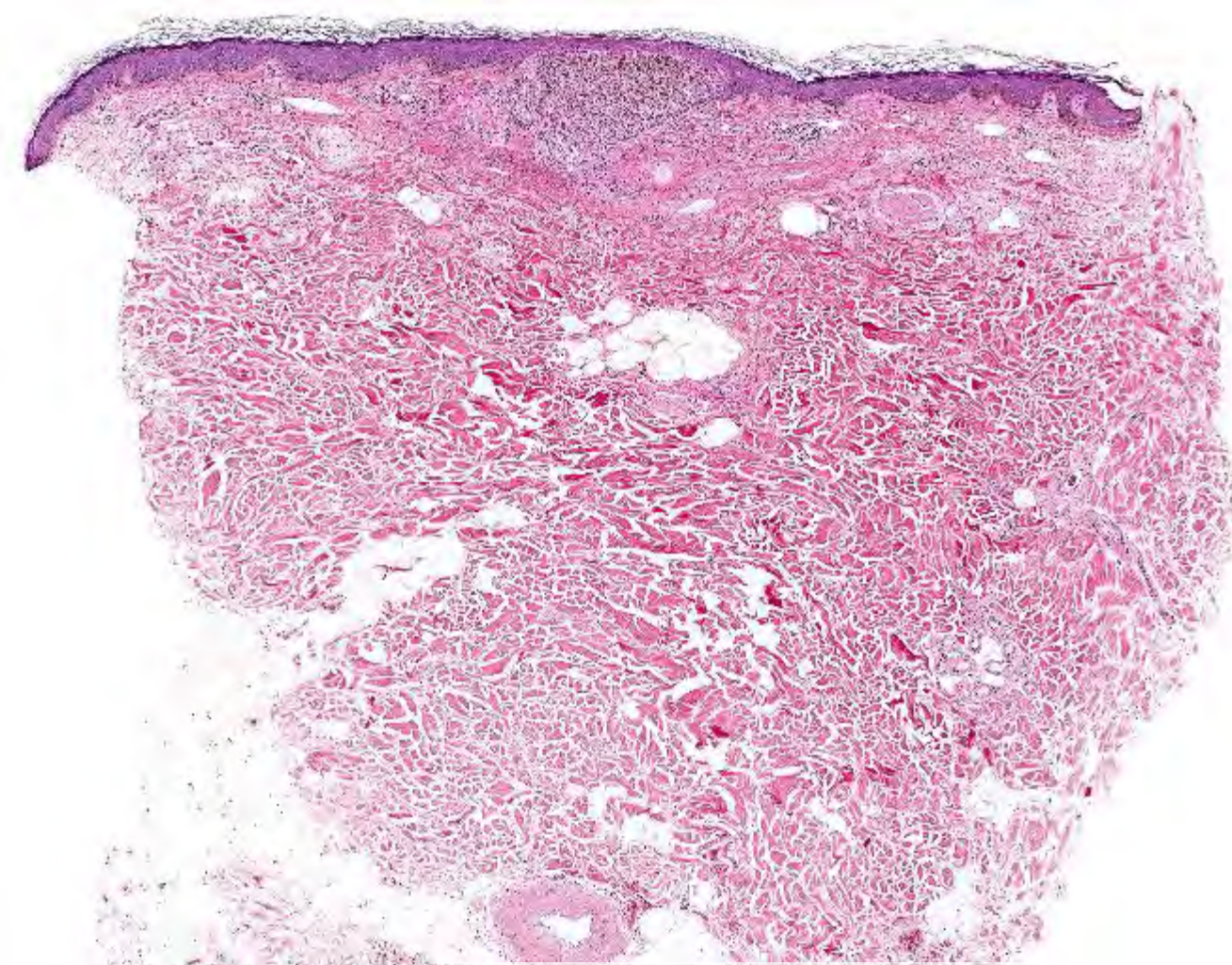




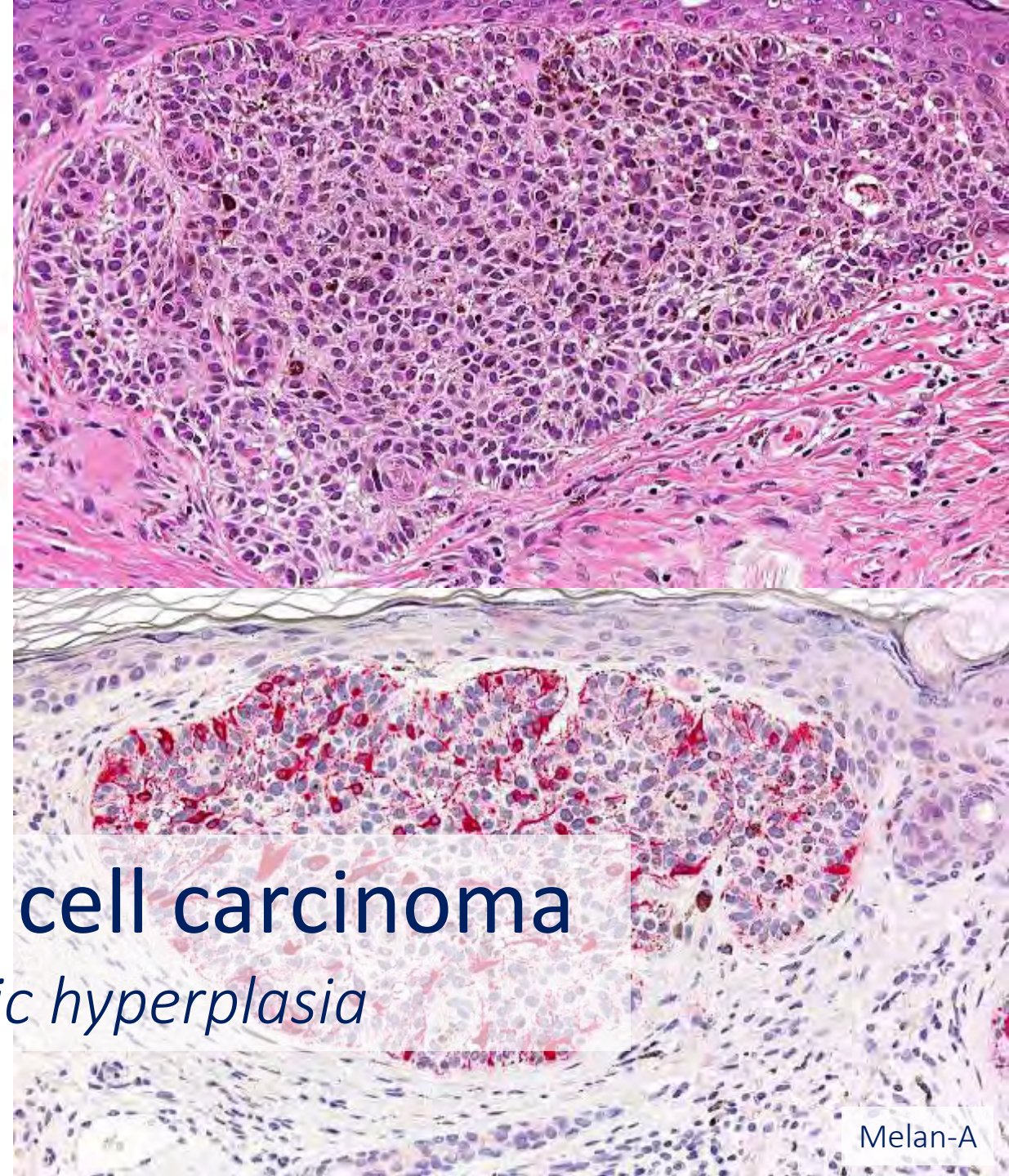
Case 3

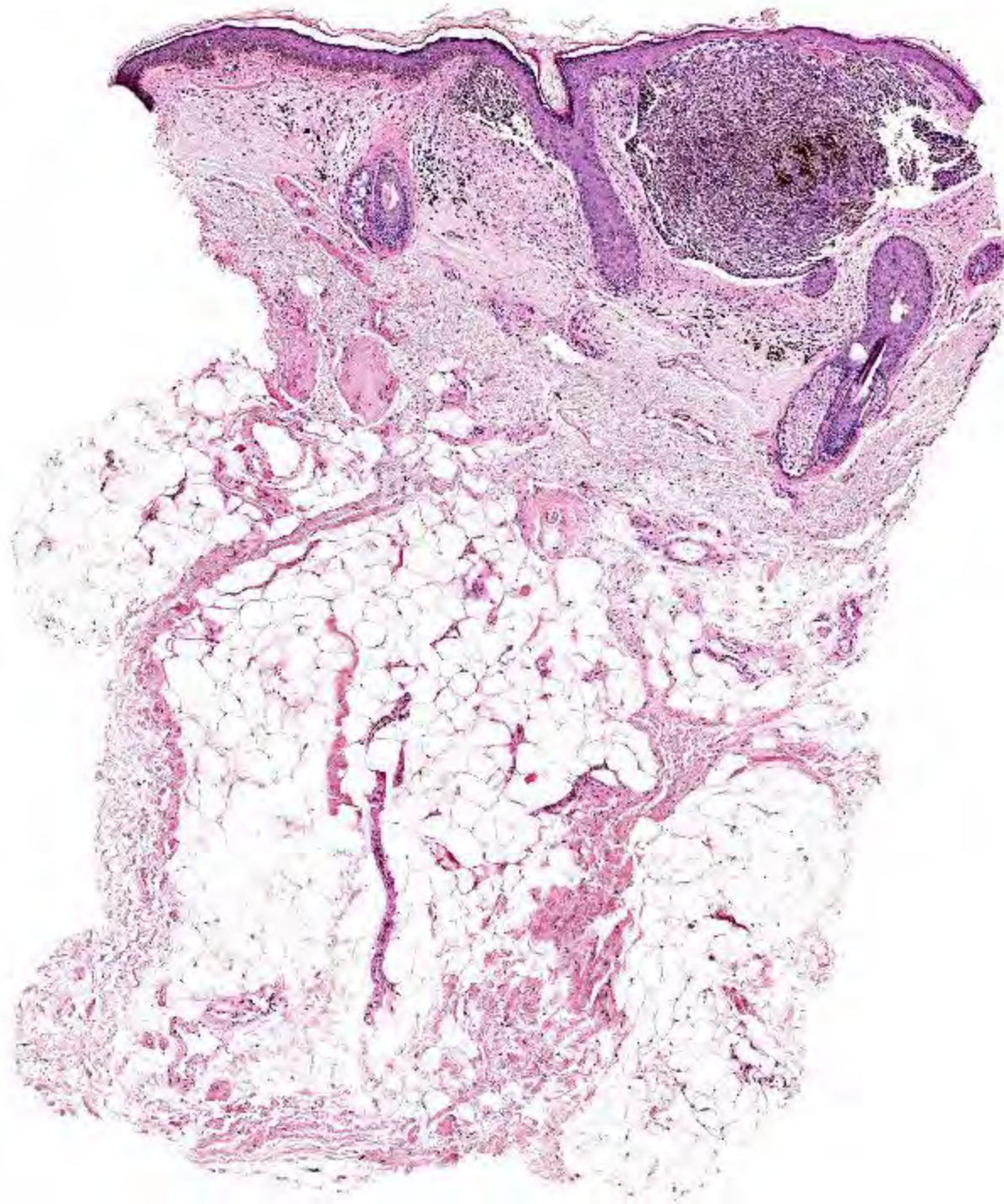
M, 85. Pigmented lesion of unknown duration on the right shoulder.





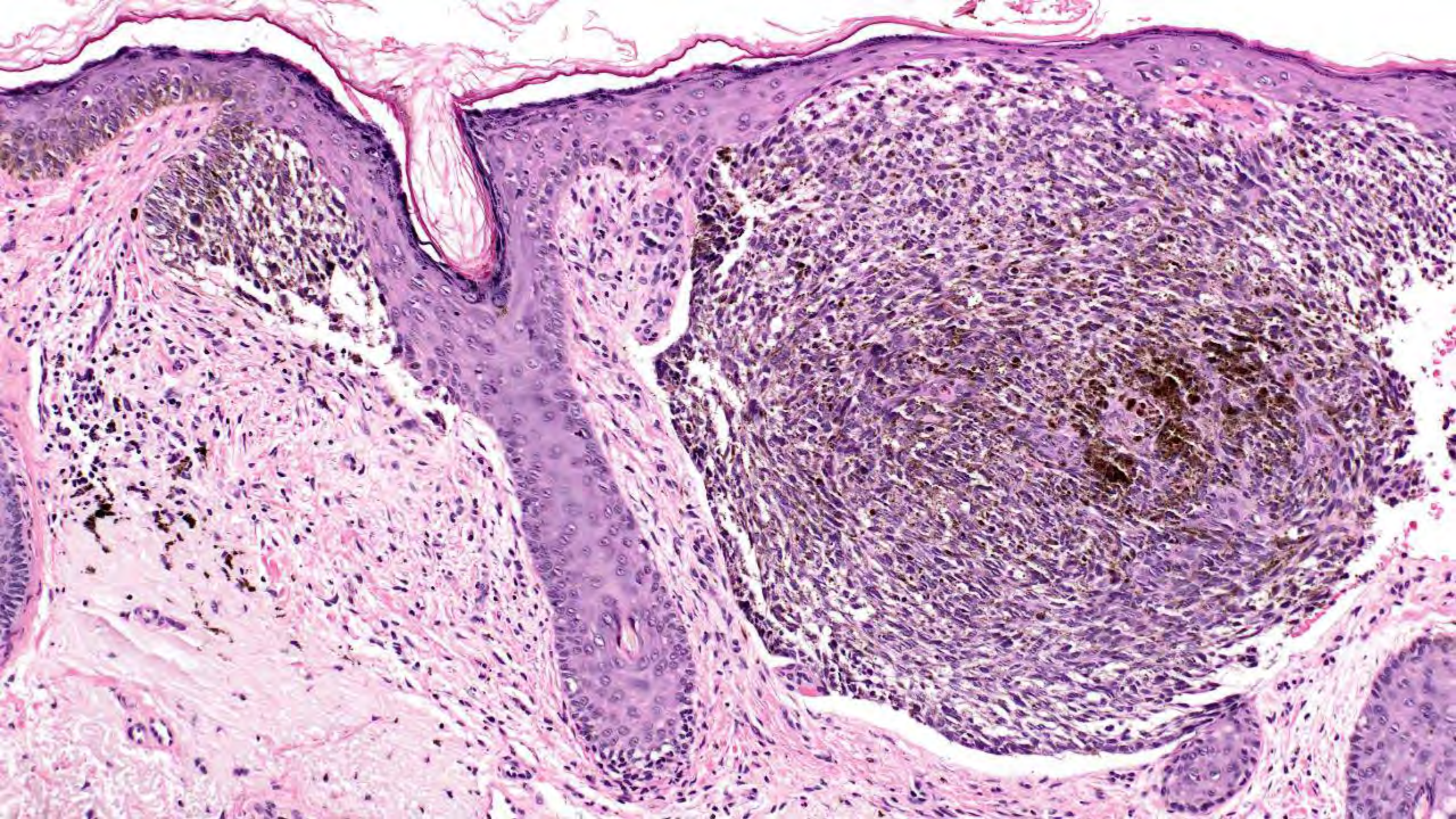
Pigmented basal cell carcinoma
with melanocytic hyperplasia

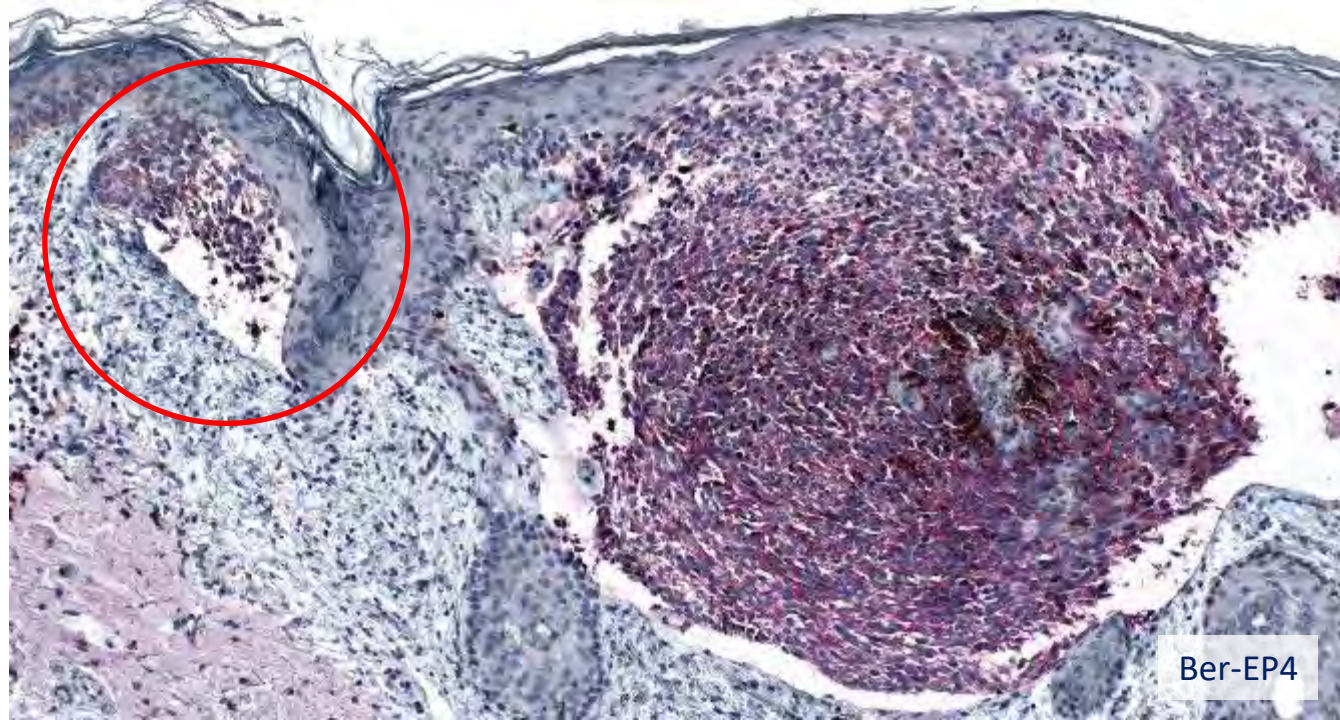
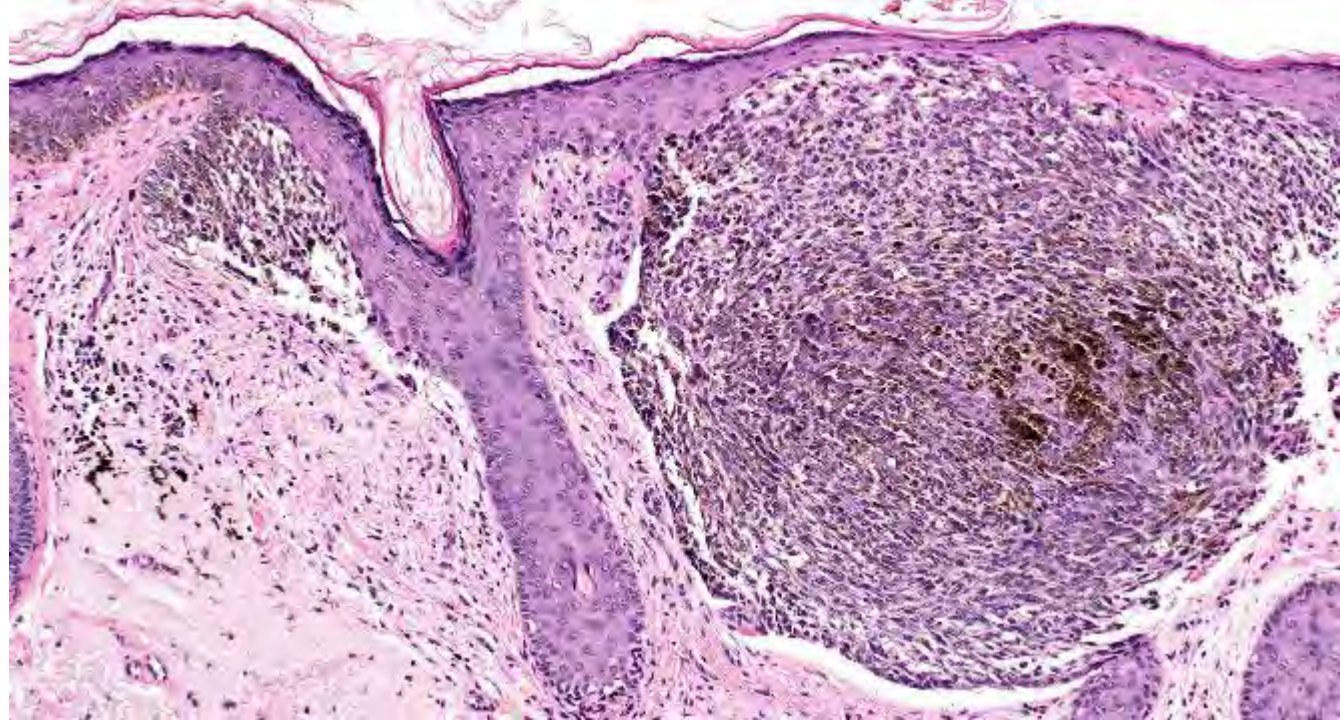
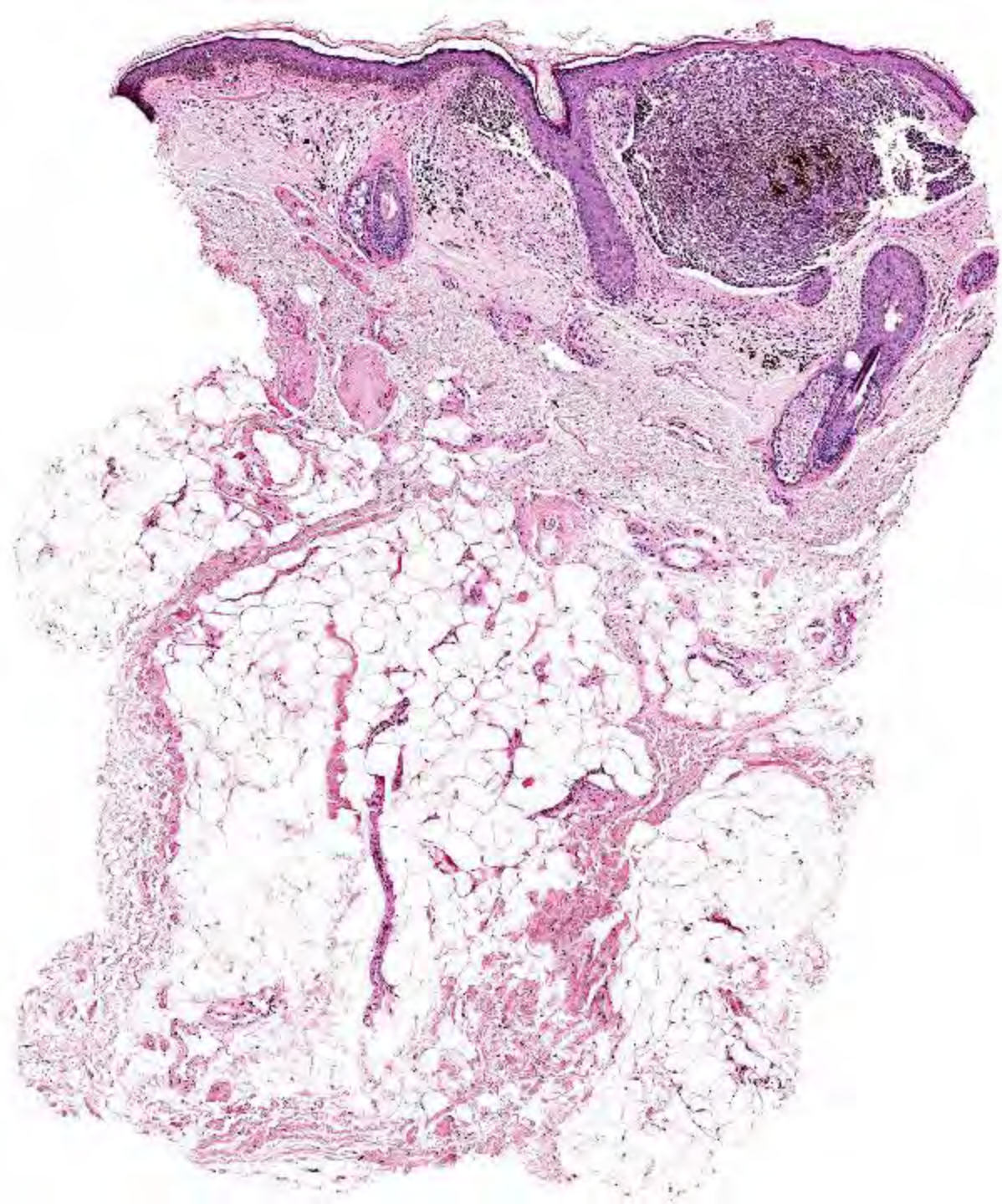


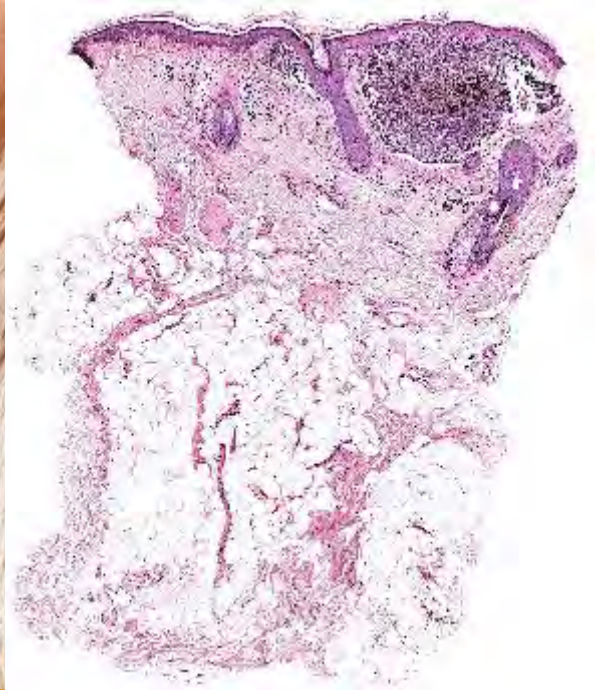


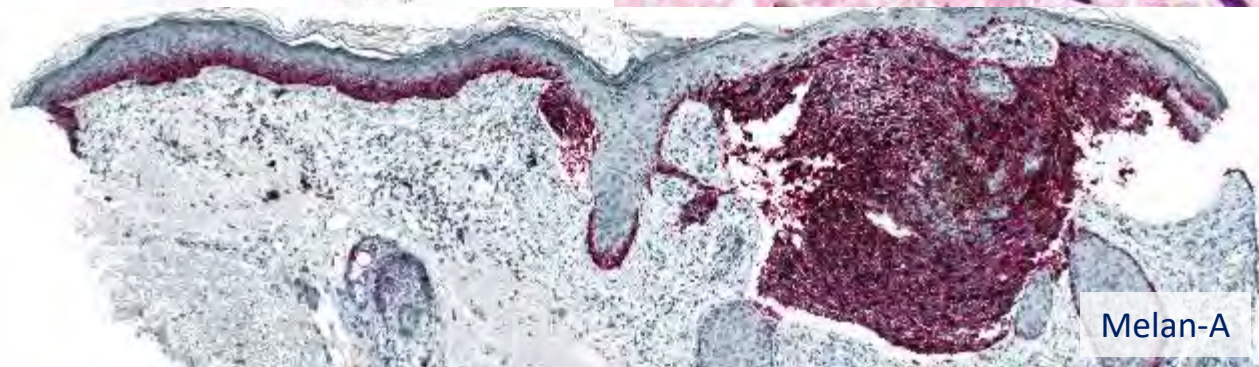
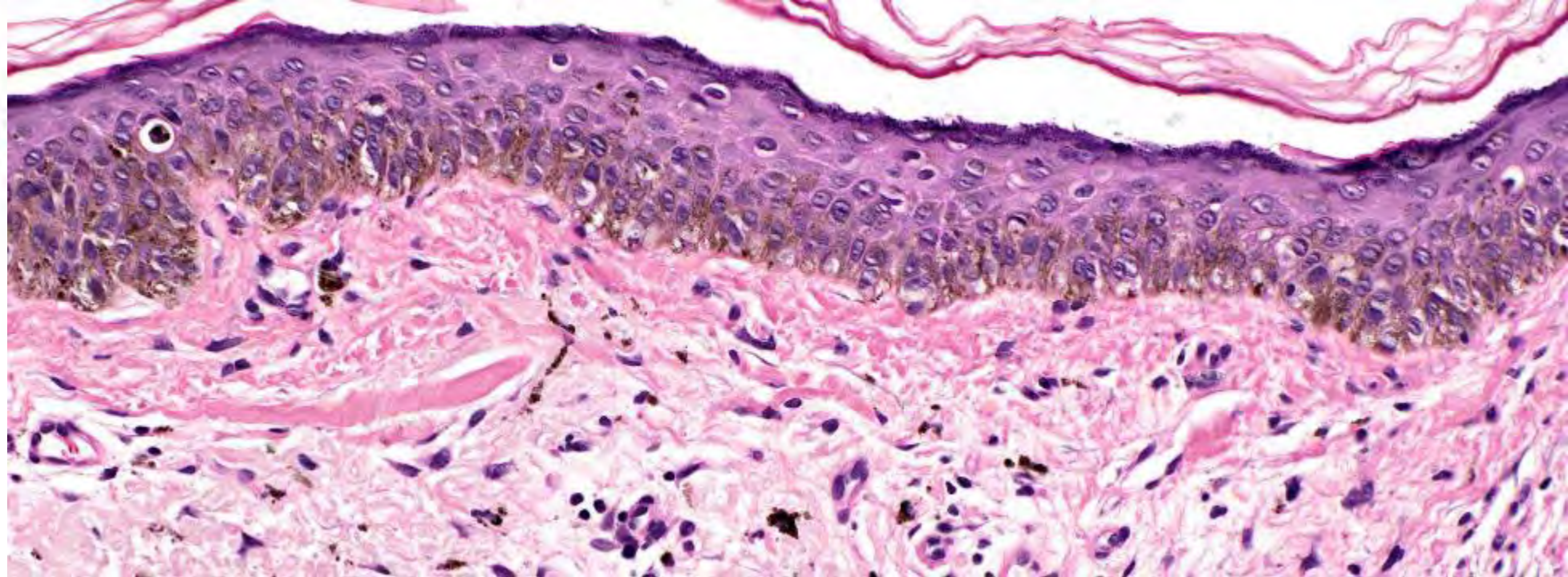
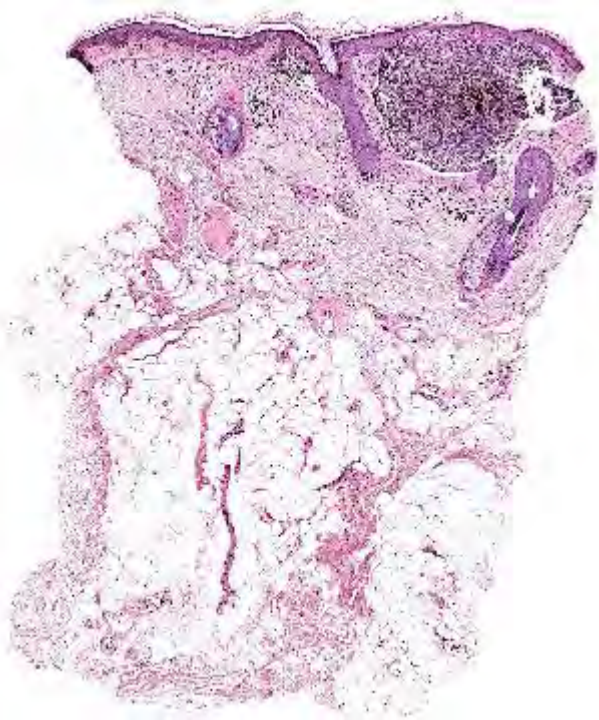
Case 4

F, 89. In-patient at Cardiology.
Sent for evaluation of a pigmented
lesion of unknown duration on the
left ear.

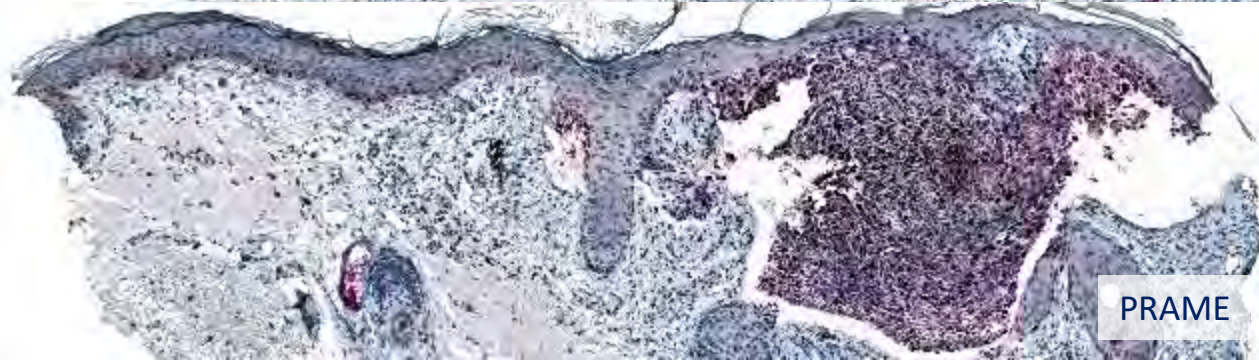




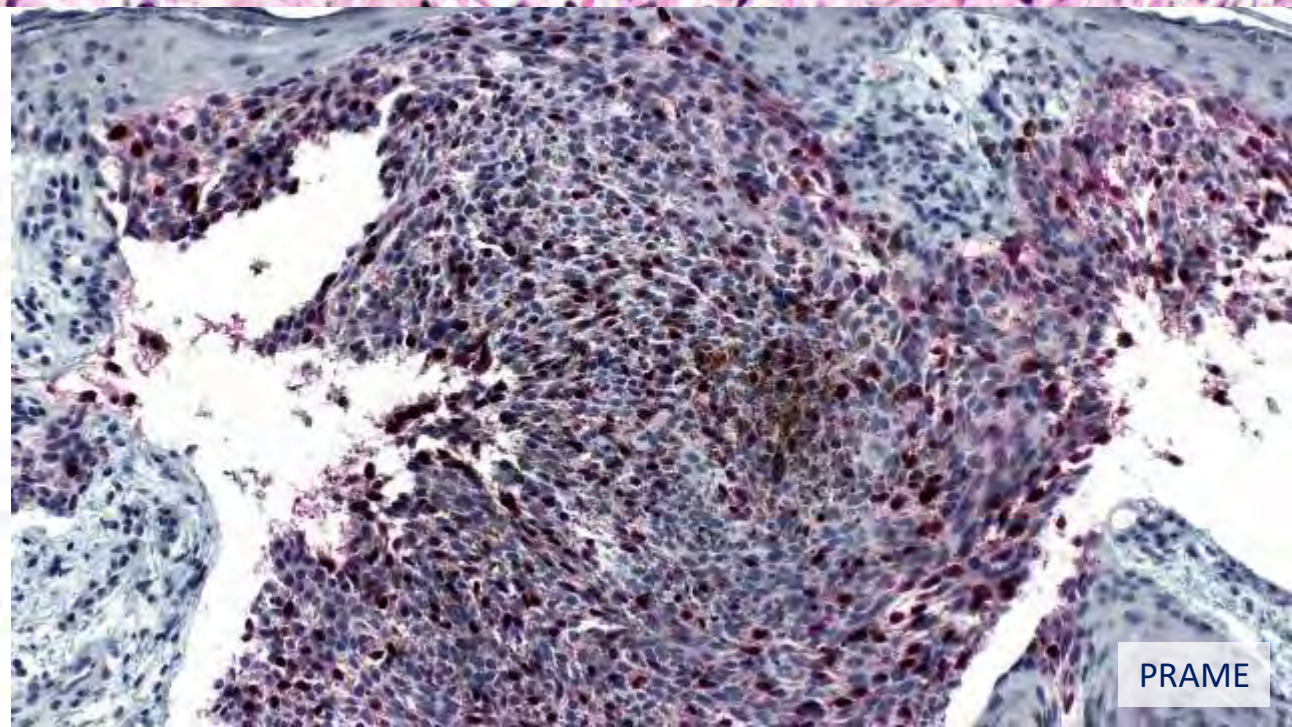




Melan-A



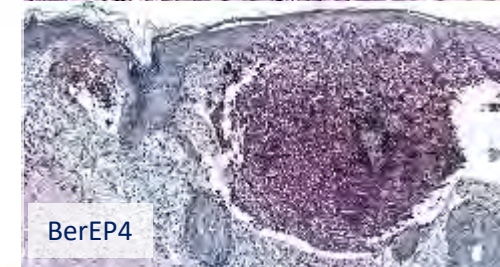
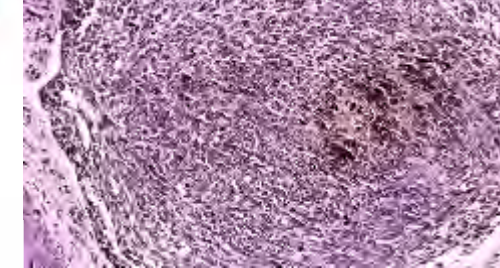
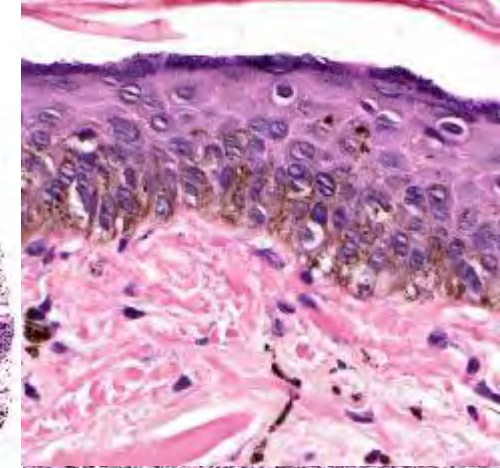
PRAME



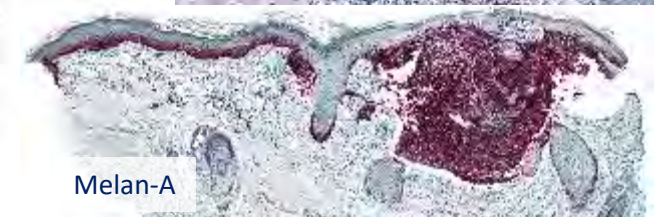
PRAME



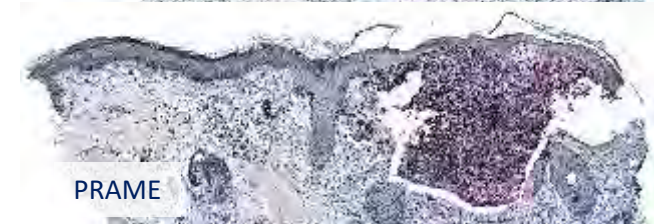
Melanoma in situ & small superficial BCC



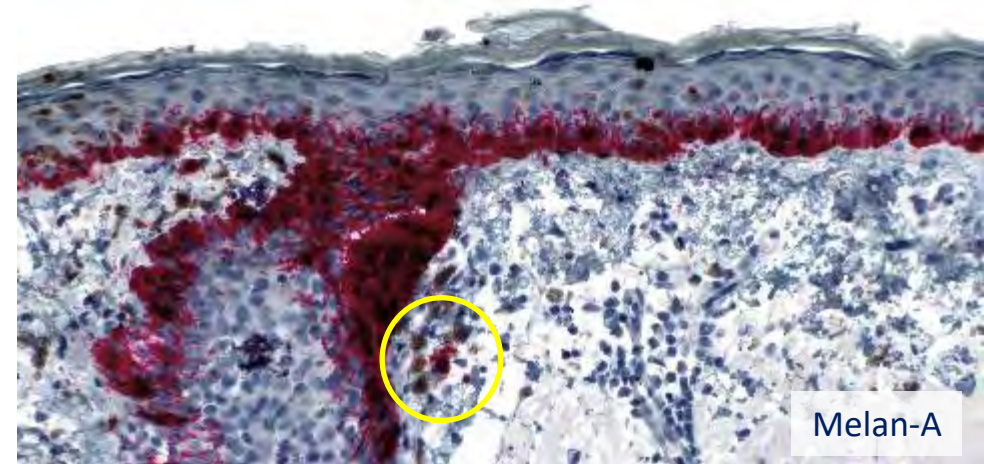
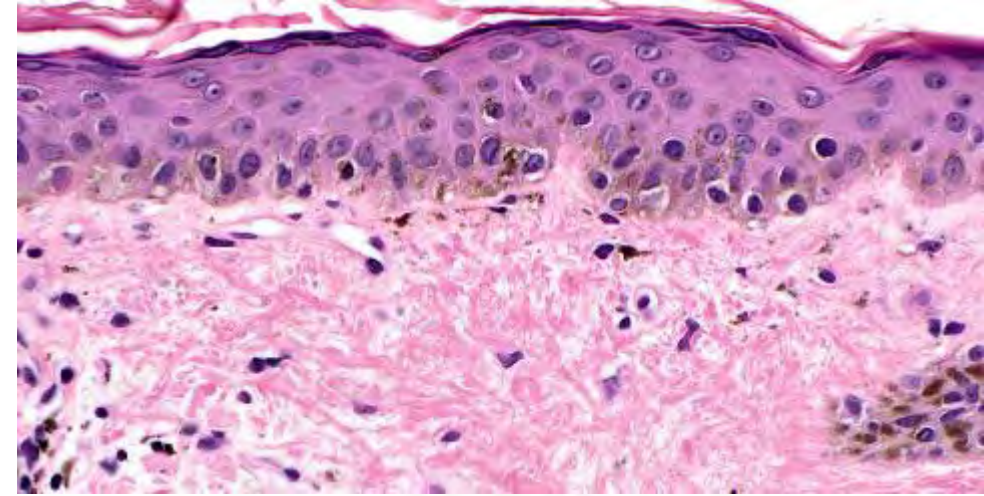
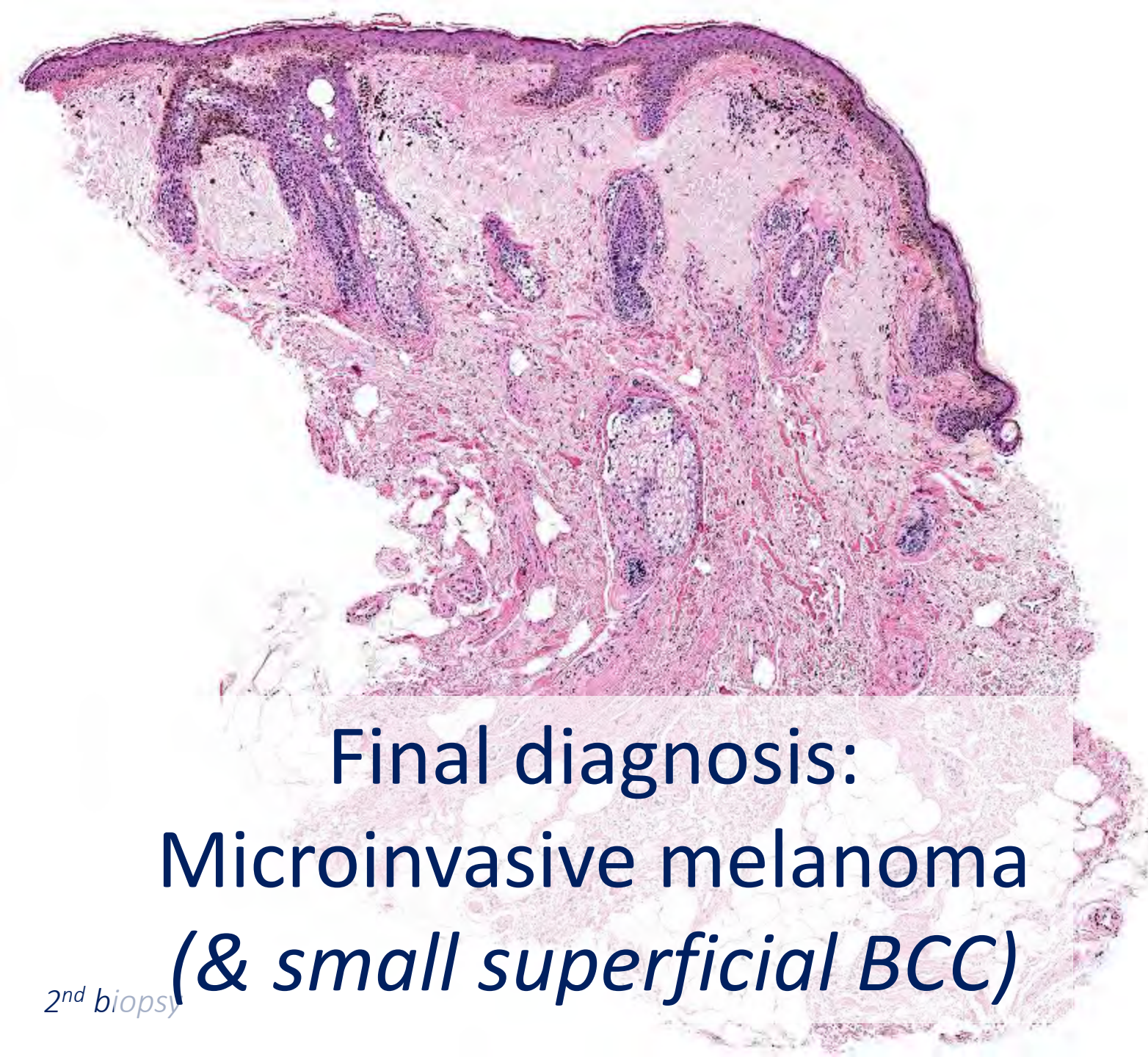
BerEP4



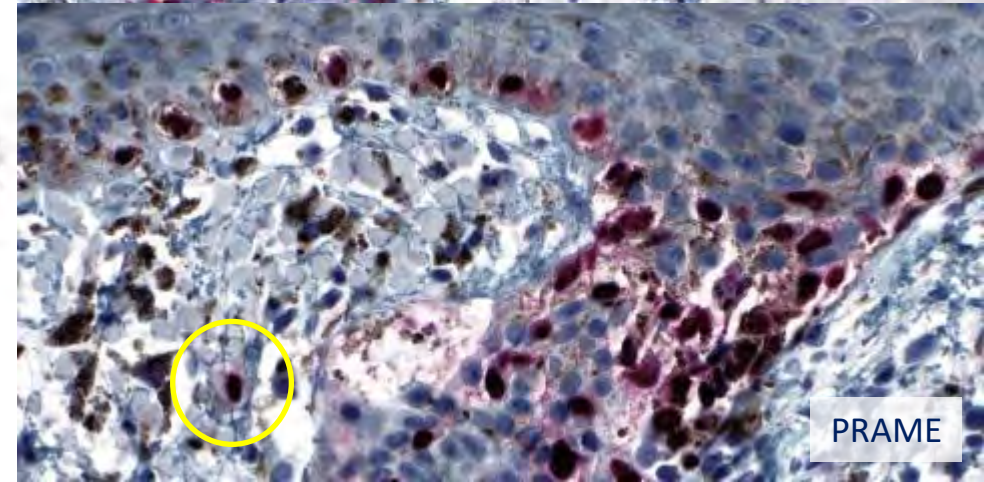
Melan-A



PRAME



Melan-A



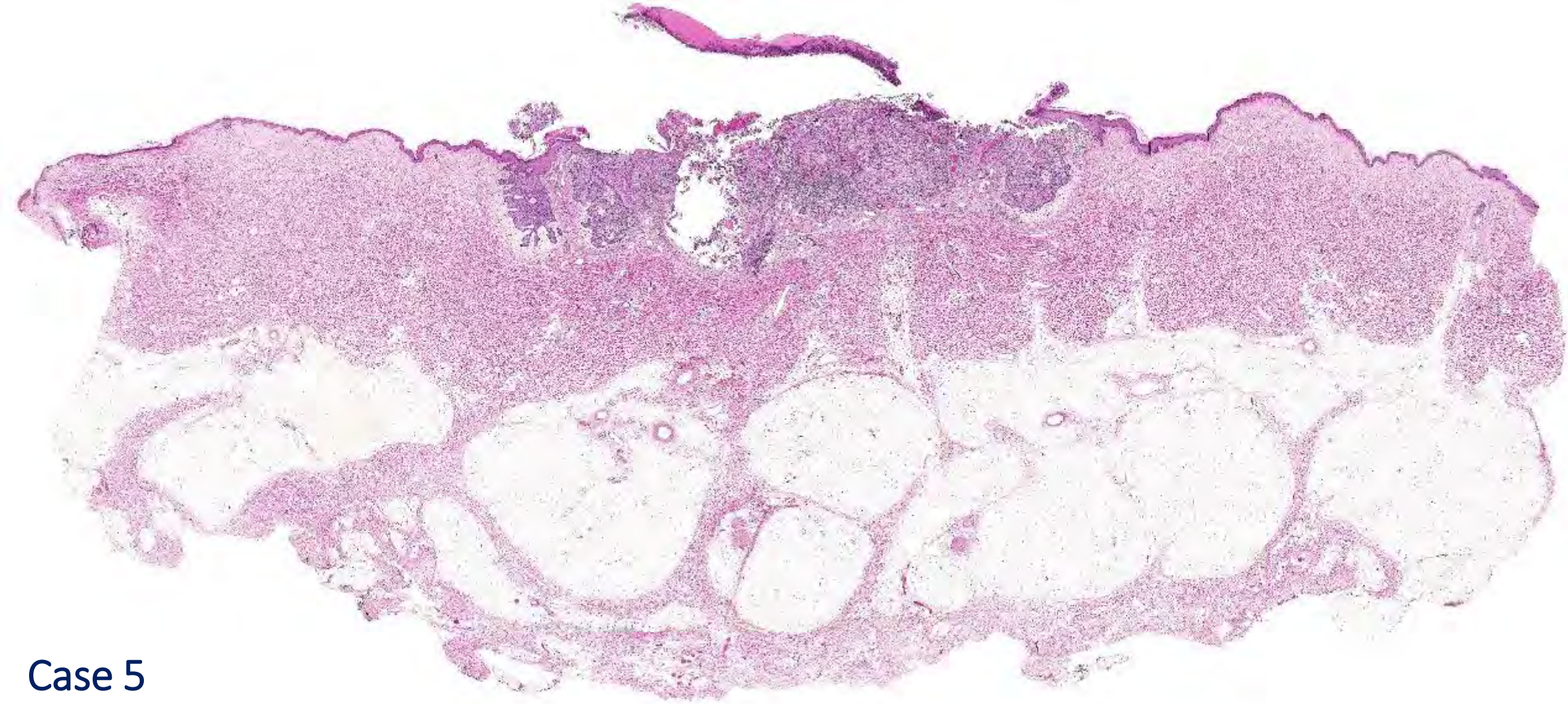
PRAME

Final diagnosis:
Microinvasive melanoma
(*& small superficial BCC*)

2nd biopsy

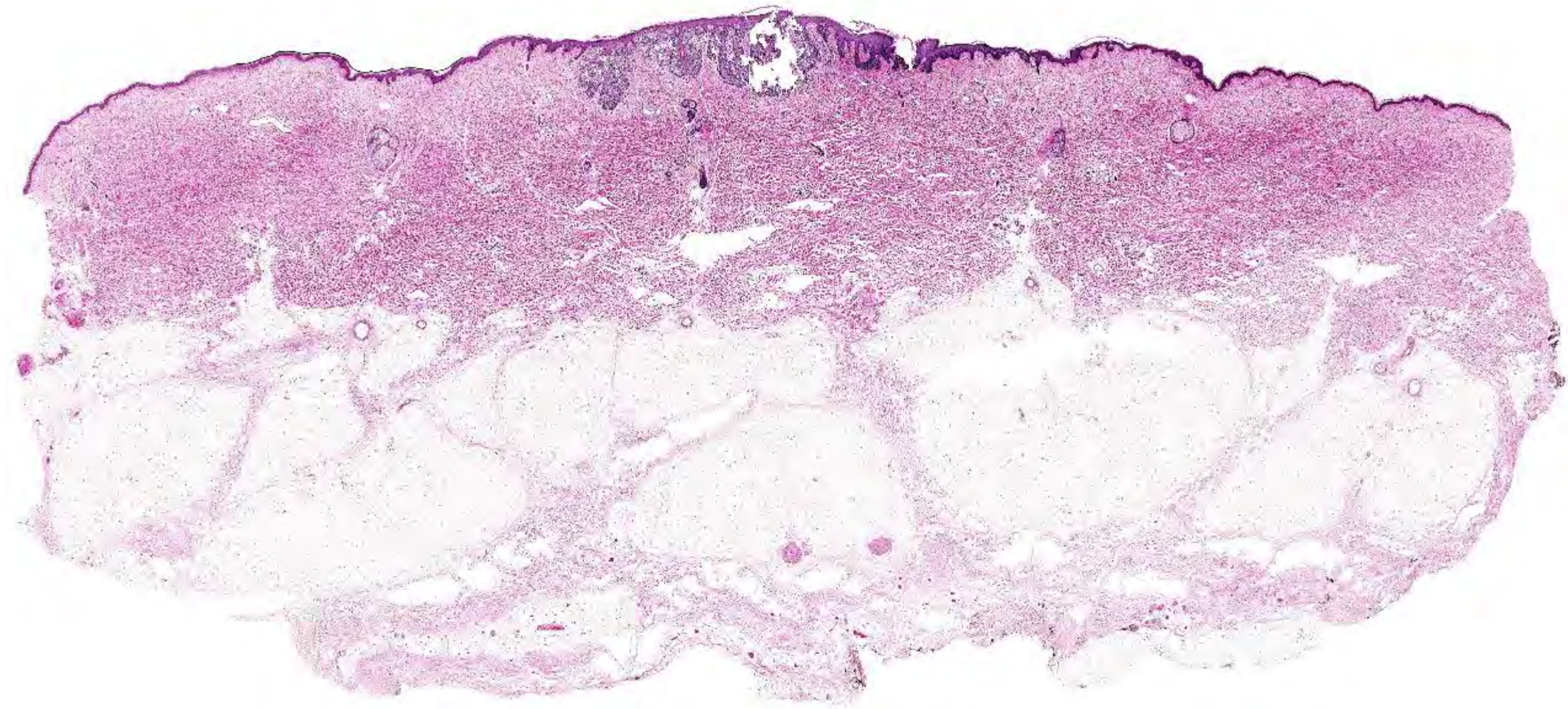


Where is the BCC?...

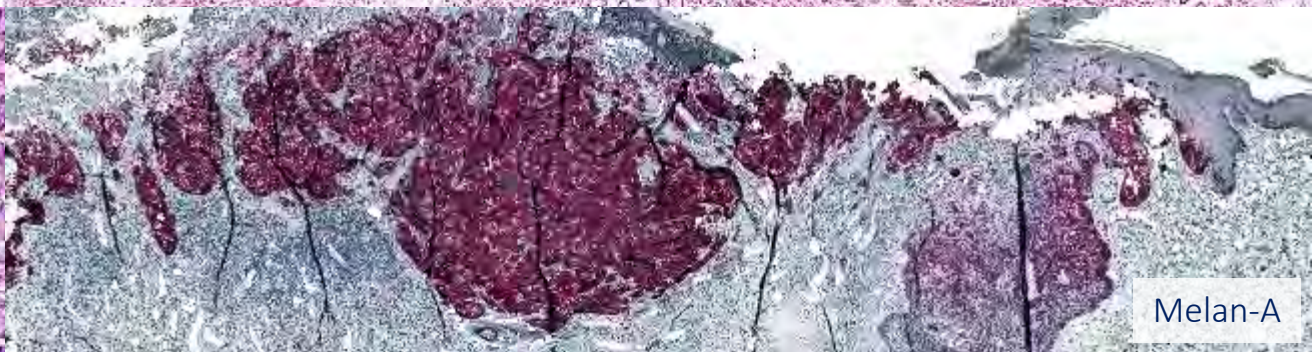
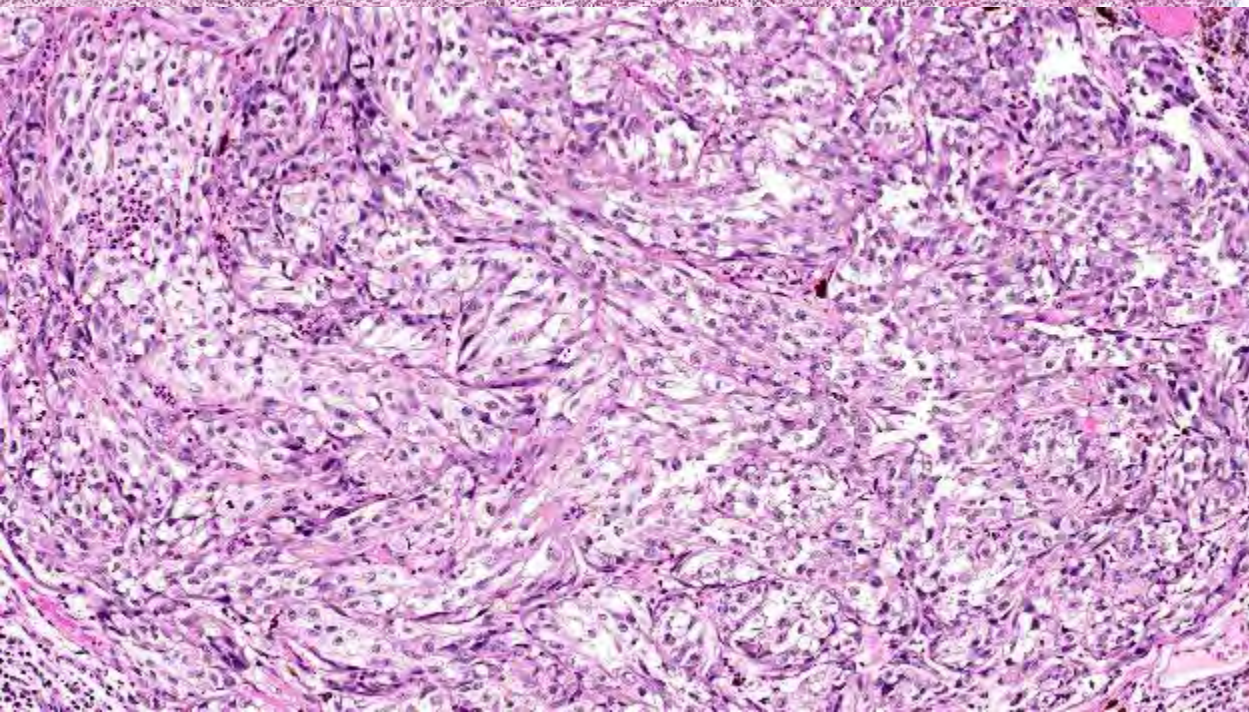
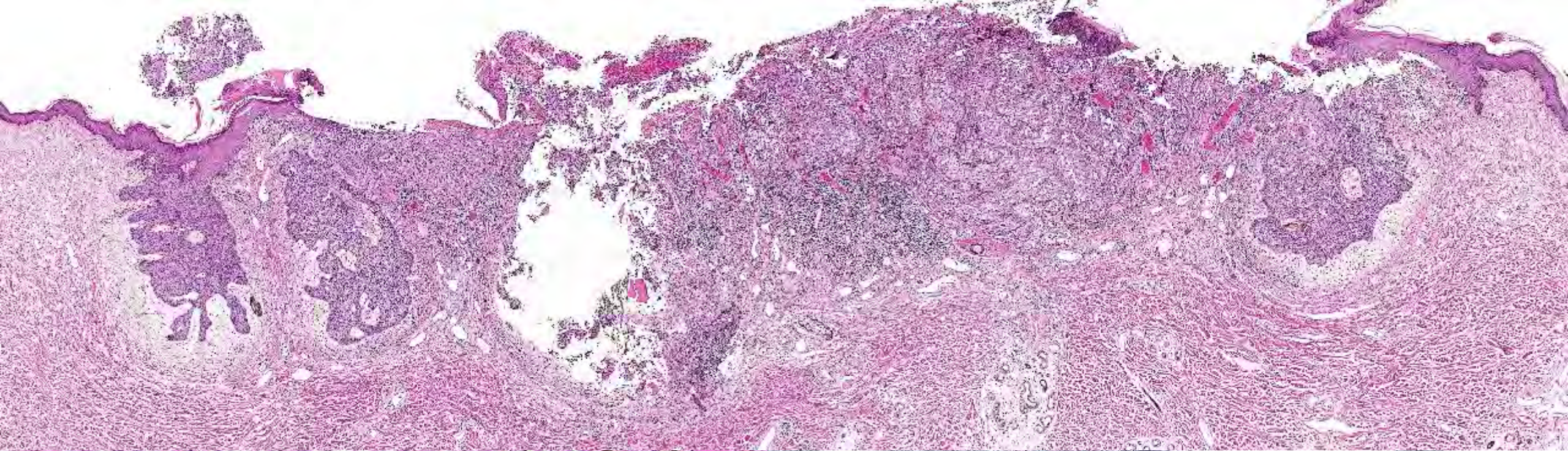


Case 5

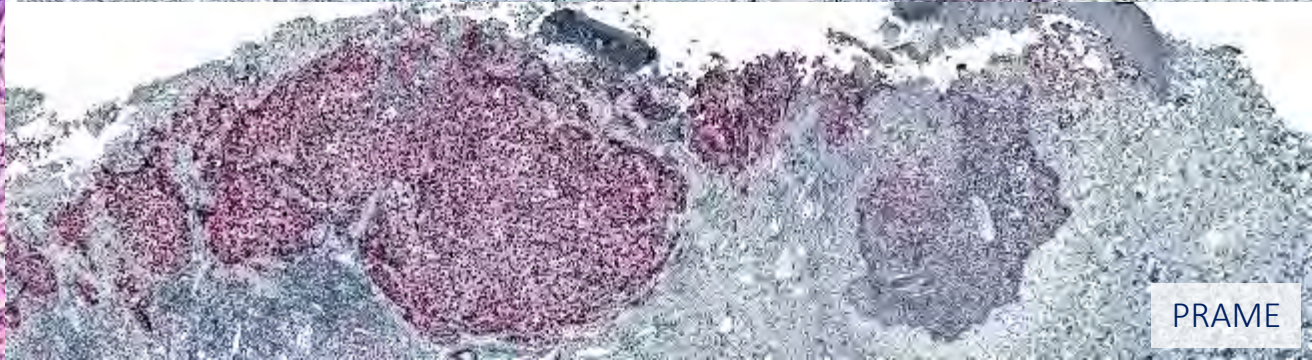
F, 64. 1 week previously excision of a large melanoma on the back (Breslow: 22 mm.). A pigmented lesion in the left submammary area is excised during the visit for re-excision and planning of staging.



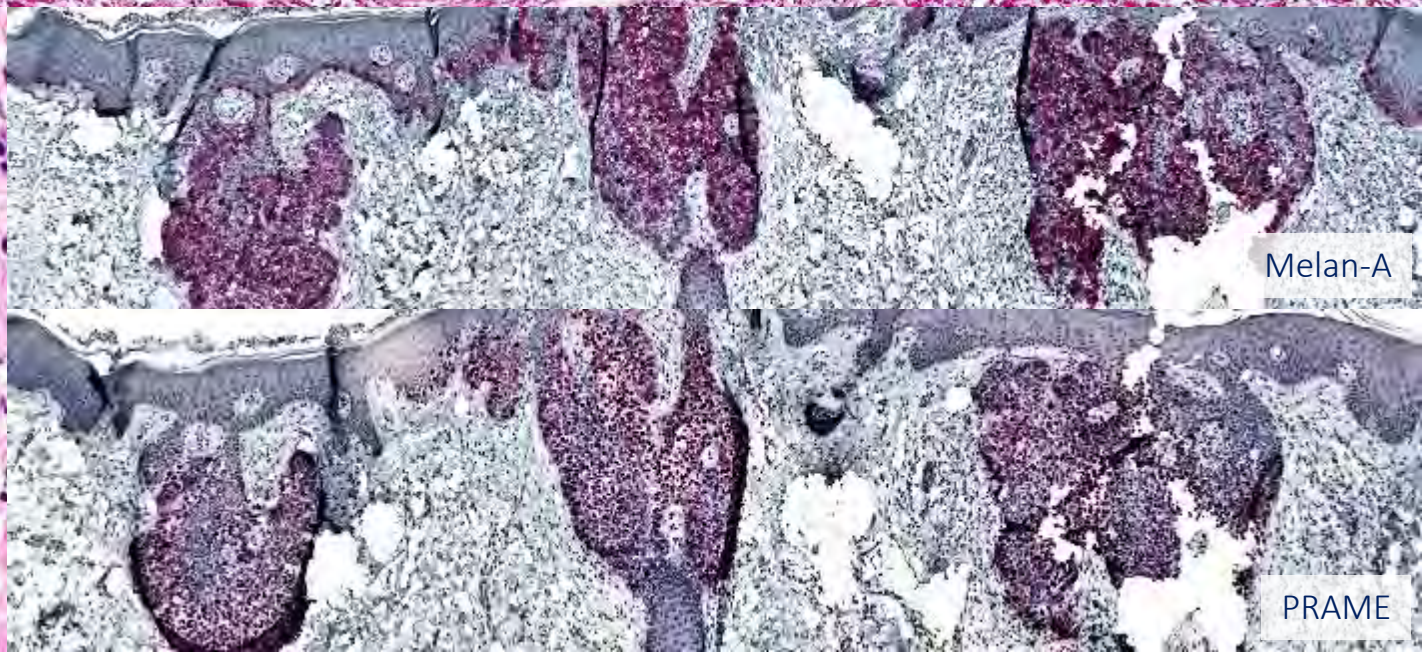
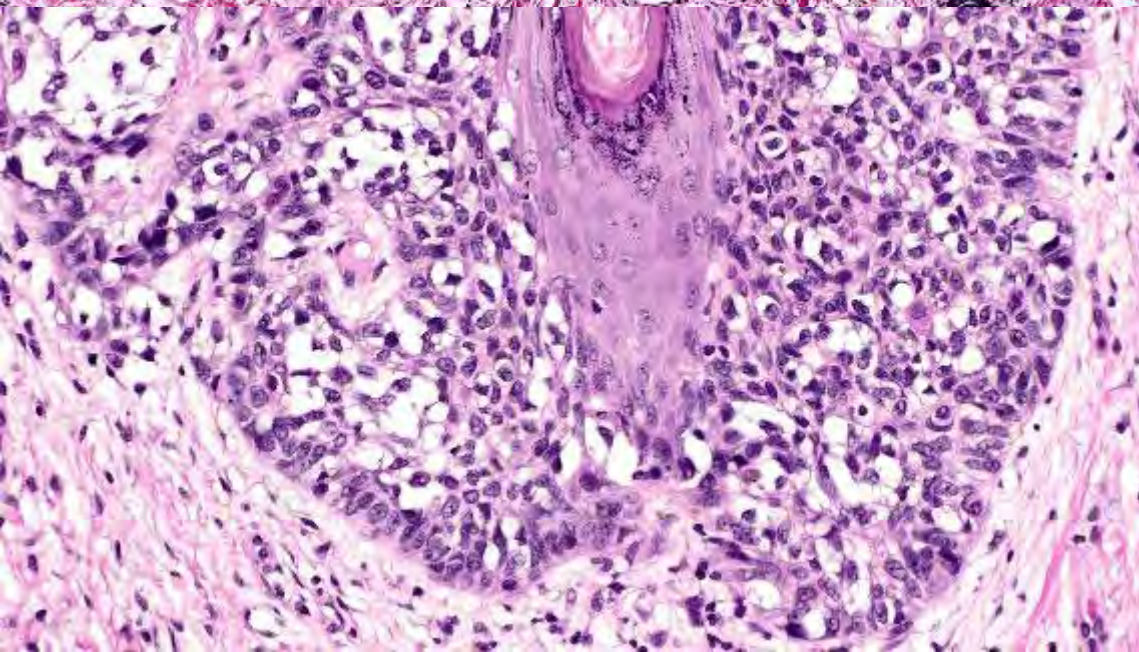
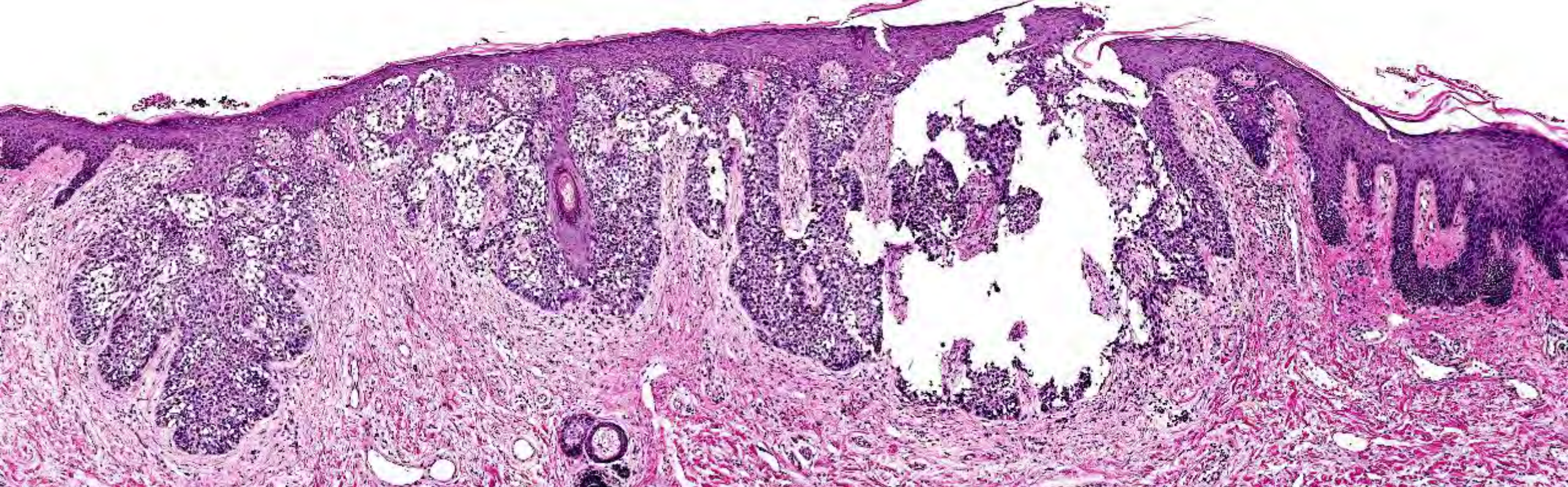
Basal cell carcinoma...

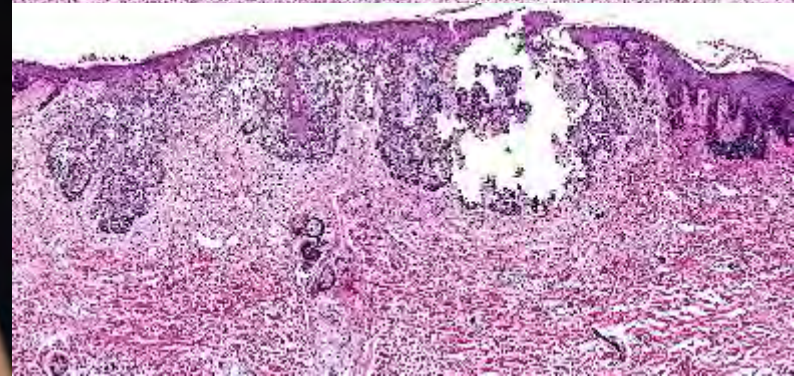
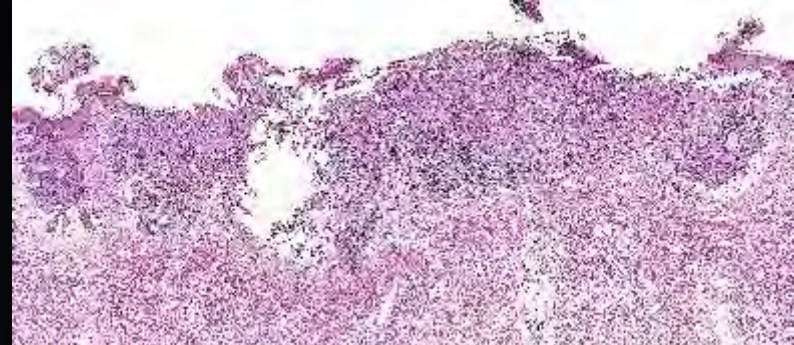


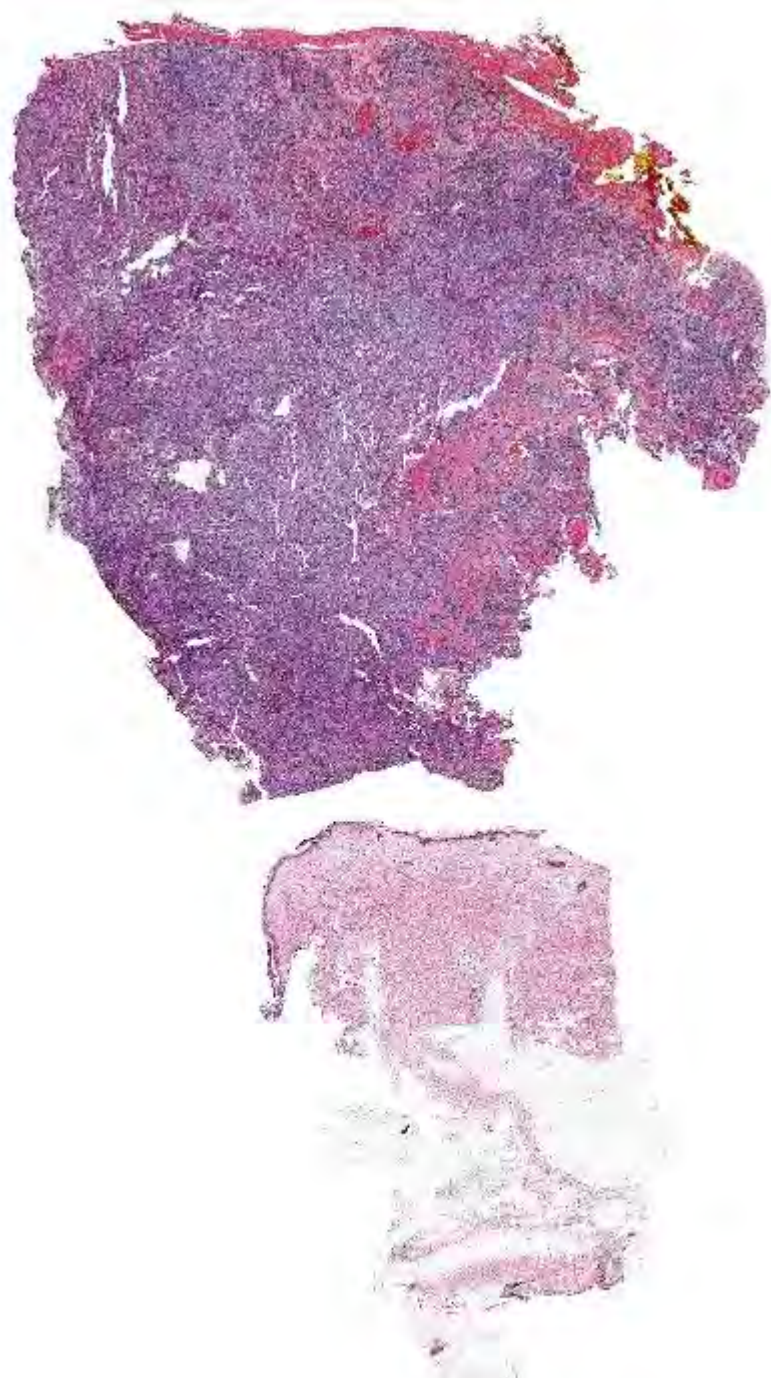
Melan-A



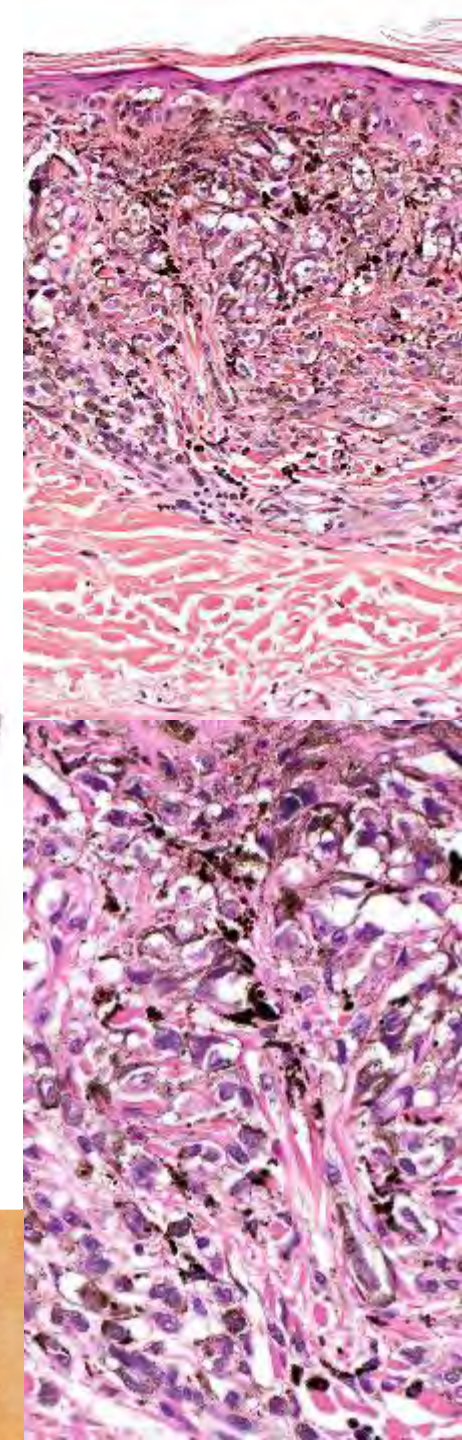
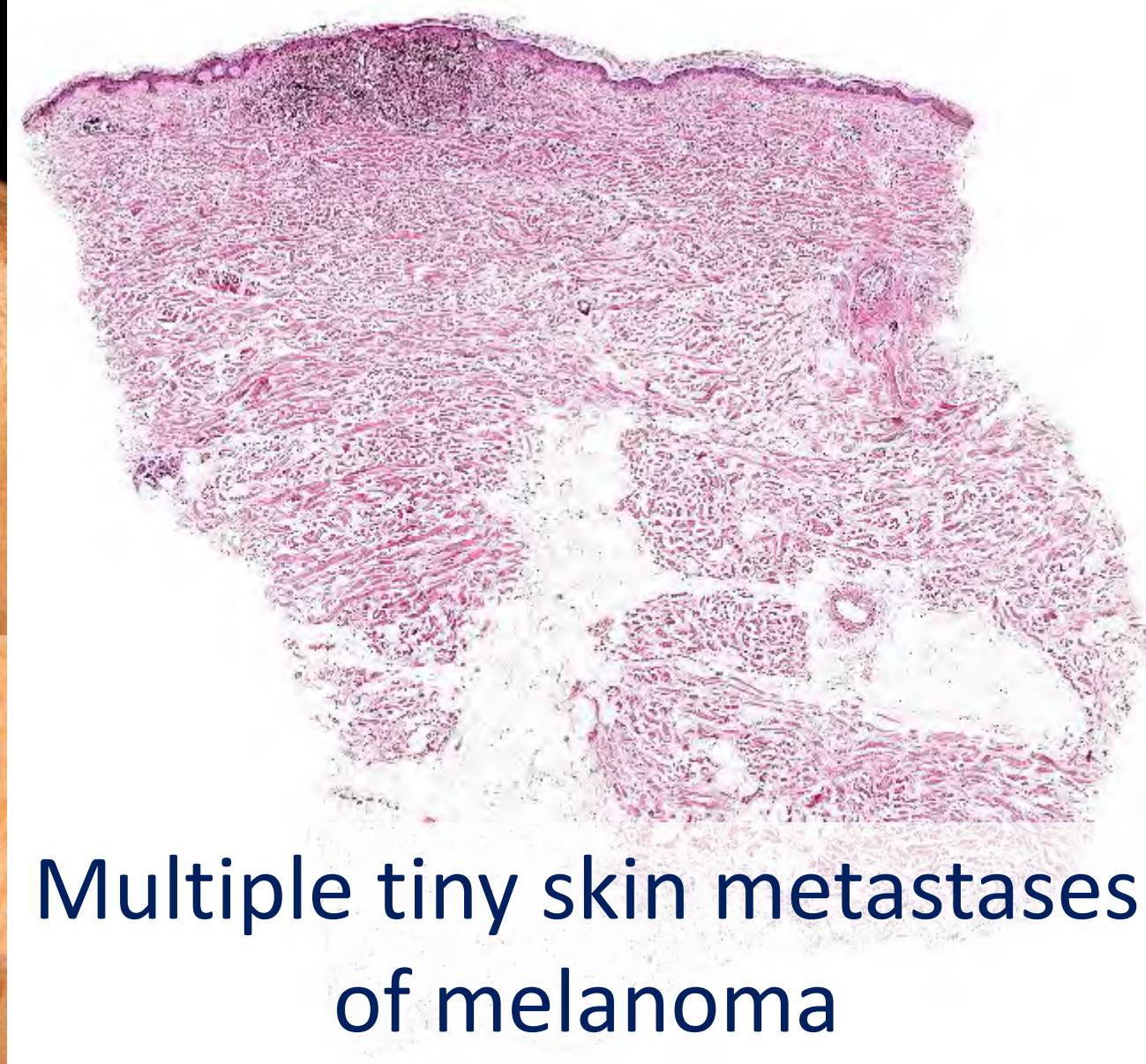
PRAME

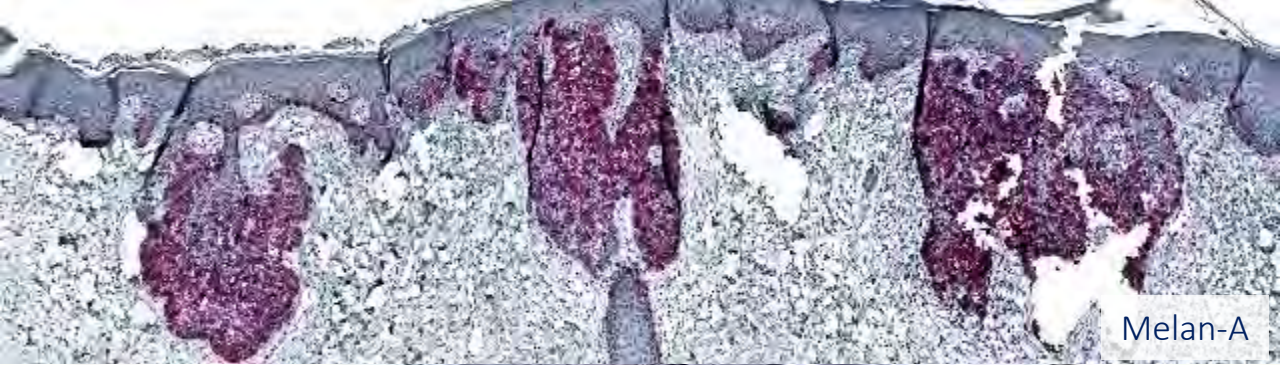
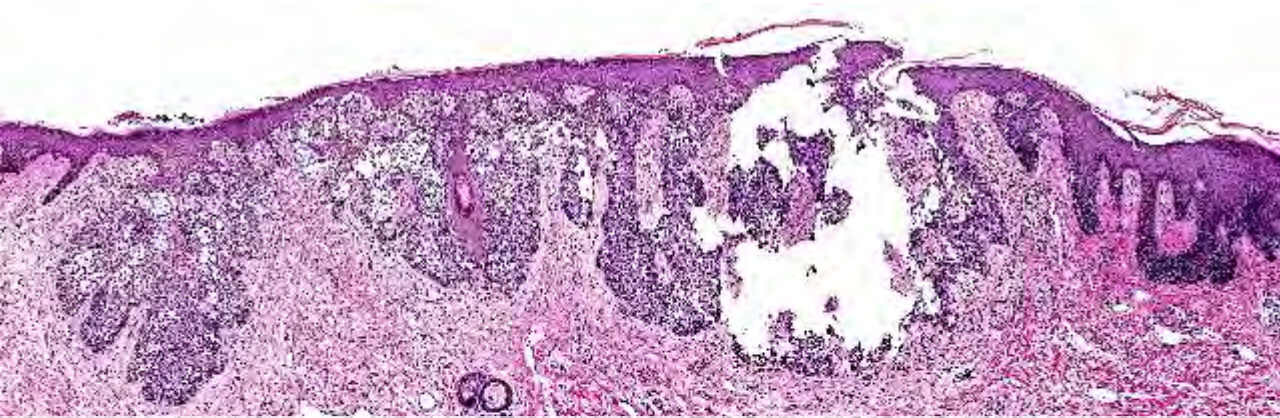
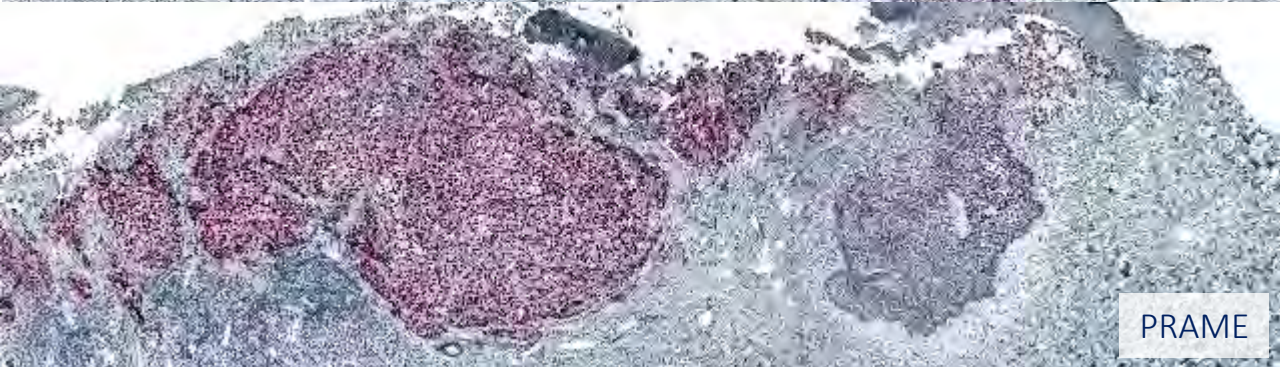
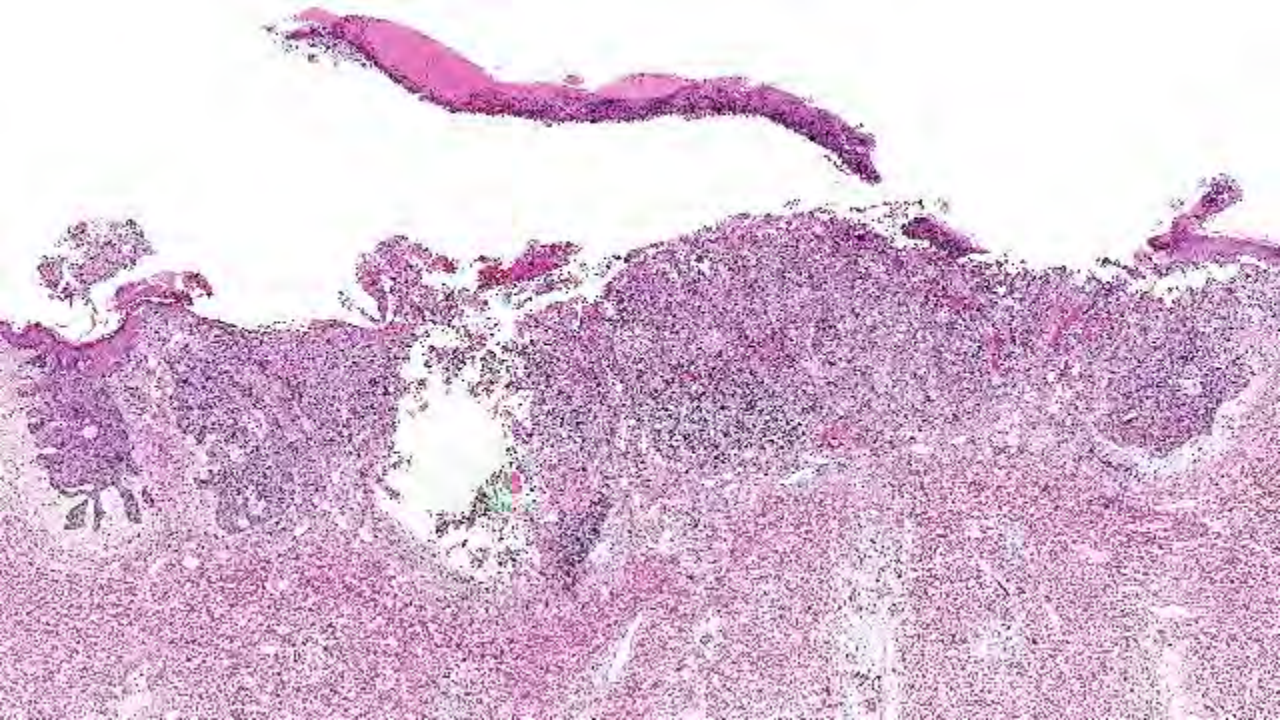




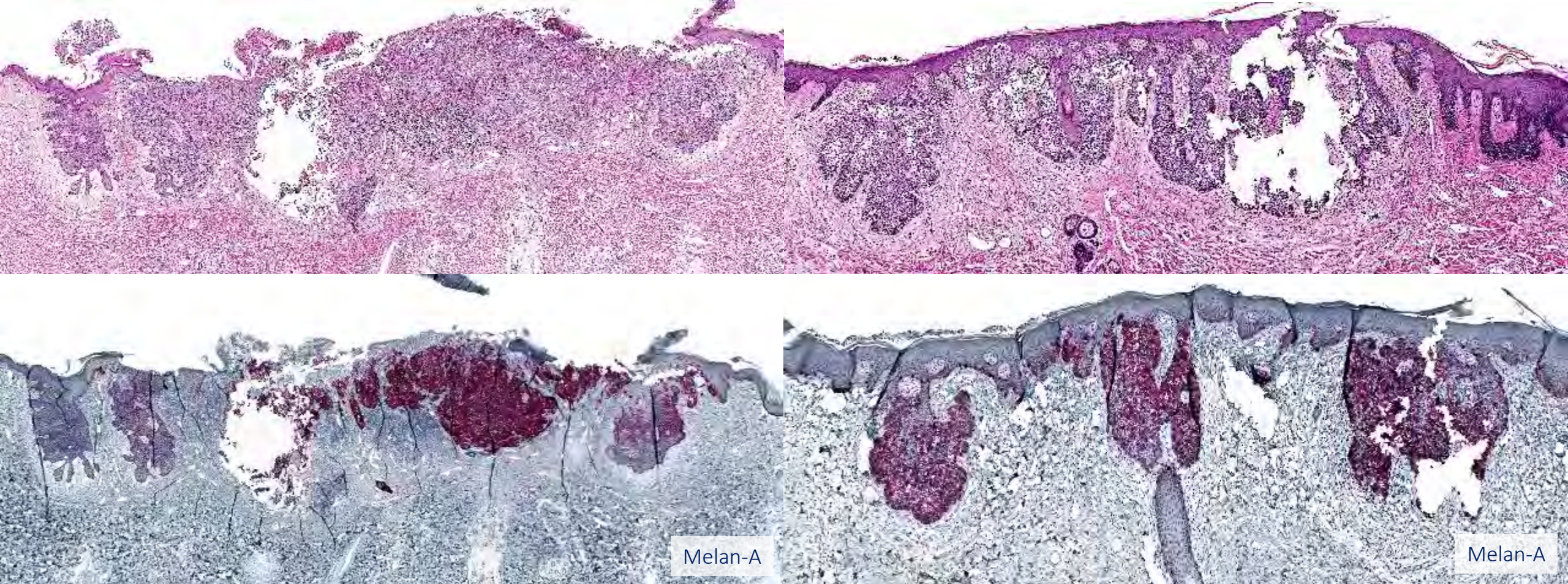


Previous MM (excised one week earlier)





Melanoma metastatic to
a basal cell carcinoma



The exception to the rule

A melanoma metastatic to a basal cell carcinoma mimicking the distribution of melanocytes observed in BCCs with melanocytic hyperplasia
(but with a nodular component outside of the BCC complexes as well)

Malignant Melanoma Metastatic to a Basal Cell Carcinoma Simulating the Pattern of a Basomelanocytic Tumor

Klaus J. Busam, MD,* Allan Halpern, MD,† and Ashfaq A. Marghoob, MD‡

Abstract: We report a case of metastatic melanoma colliding with and colonizing a basal cell carcinoma (BCC) on the head of a 69-year-old man. The man had a prior history of multiple primary BCCs and melanomas. One of his primary melanomas, on the left scalp, occurred locally and resulted in the development of numerous in-transit metastases. A bluish nodule was noted on the postauricular skin which resolved spontaneously with a pigmented BCC. Dermoscopy showed some large gray-blue ovoid structures and blood vessels. Features also consistent with BCC. However, the histologic findings revealed that the nodule consisted of both metastatic melanoma as well as BCC. Melanoma was present adjacent to as well as within the epithelium of the BCC. The intimate association of melanoma cells within the nodules of BCC simulated the pattern of so-called "malignant basomelanocytic tumor," a recently proposed novel entity. To our knowledge, this is the first description of metastatic melanoma colonizing a BCC.

Key Words: melanoma, basal cell carcinoma, basomelanocytic tumor

(*Am J Surg Pathol* 2006;30:133-136)

At times, two independent and different types of tumors may coincidentally involve the same anatomic site and lead to a so-called "collision" tumor. Because of the high frequency of basal cell carcinoma (BCC) among whites, it is not surprising that among cutaneous collision tumors, BCC is commonly represented.¹ BCC has been reported to coexist with a number of benign and malignant epithelial, mesenchymal, and melanocytic tumors.²⁻⁶ In an analysis of 69 cutaneous collision tumors (excluding biphasic tumors of the same cell type),⁴ BCC was part of the two most common combinations, namely, BCC and melanocytic nevus and BCC and sebaceous keratosis.

Melanoma may also collide with various other types of tumors,^{4,7-9} including BCC. An association of BCC with in situ melanoma has been reported for both superficial spreading as well as lentigo maligna types of melanoma.^{4,10} BCC may

coincidentally be surrounded by melanoma or may be colonized by intraepithelial (ie, in situ) melanoma cells and thus simulate invasive melanoma.² We report herein what we believe to be the first documented case in the literature of metastatic melanoma colliding with and colonizing a BCC.

MATERIALS AND METHODS

Clinical information was obtained from the medical records. Routine hematoxylin and eosin-stained sections as well as immunohistochemical stains were examined. For the latter, the monoclonal antibodies A103 (anti-Melan-A) and HMB-45 (anti-gp100) were used as well as 34BE12 (cytokeratin). For immunohistochemistry, charged slides (Superfrost, Fisher Scientific, Pittsburgh, PA) were used and after application of 5- μ m cuts, heated for at least 2 hours at 60°C to ensure proper attachment. The primary antibodies were precluded by the manufacturer (Verana, Tucson, AZ). A fully automated staining system (Benchmark, Ventana) was used in conjunction with the iView detection system (Ventana).

CASE REPORT

Clinical Findings

A 69-year-old man presented with a new pigmented nodule in the right postauricular region. He had a prior history of multiple BCCs as well as three primary melanomas. One melanoma had occurred on the chest, one on the back, and one on the posterior scalp. The scalp melanoma was diagnosed 2 years earlier. It measured 2.2 mm in thickness and extended into the reticular dermis. This melanoma subsequently recurred, resulting in the development of many satellite metastases (Fig. 1).

The new postauricular lesion was a bluish multilobulated nodule with focal ulceration, a shiny surface appearance, and surrounding ectatic blood vessels (Fig. 2). It was clinically and dermoscopically suspected to be a BCC. A shave biopsy was performed.

Histologic Findings

At scanning magnification, the histology revealed a basoid tumor arising from the epidermis and infiltrating the dermis in the form of multiple small nodules (Fig. 3). Thin clefts were seen between the small solid aggregates of the basoid tumor and the dermal stroma (Fig. 4). Melanin pigment was present within sheets of melanophages as well as in a subpopulation of cells within the tumor (Fig. 4). The histologic features were strikingly similar to BCC.

An immunostain for cytokeratin (34BE12) highlighted the epithelial cells (Fig. 1B). They represented the majority of cells within the solid tumor cell aggregate featured in Figure 4. However,



FIGURE 2. A, Clinical image of the postauricular nodule. B, Dermoscopic image: multilobulated bluish nodule is present with a shiny surface. Fine blood vessels and large gray-blue ovoid structures are noted. The findings suggest a basal cell carcinoma.

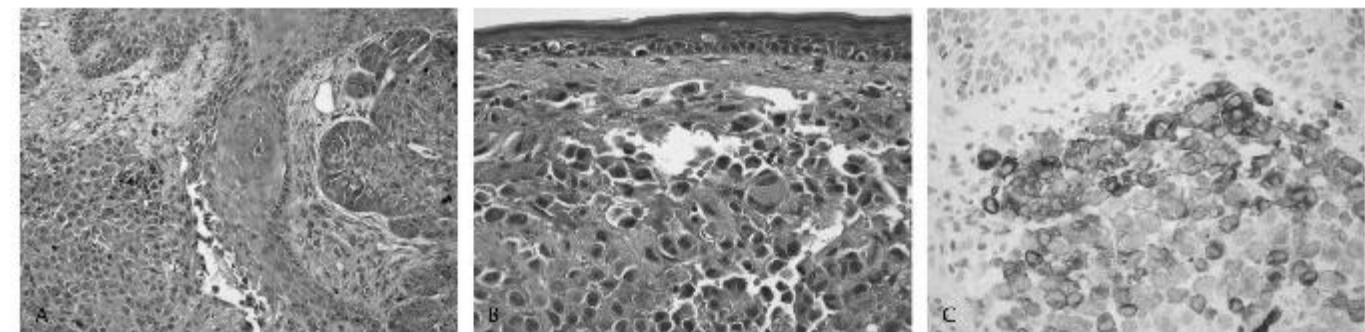
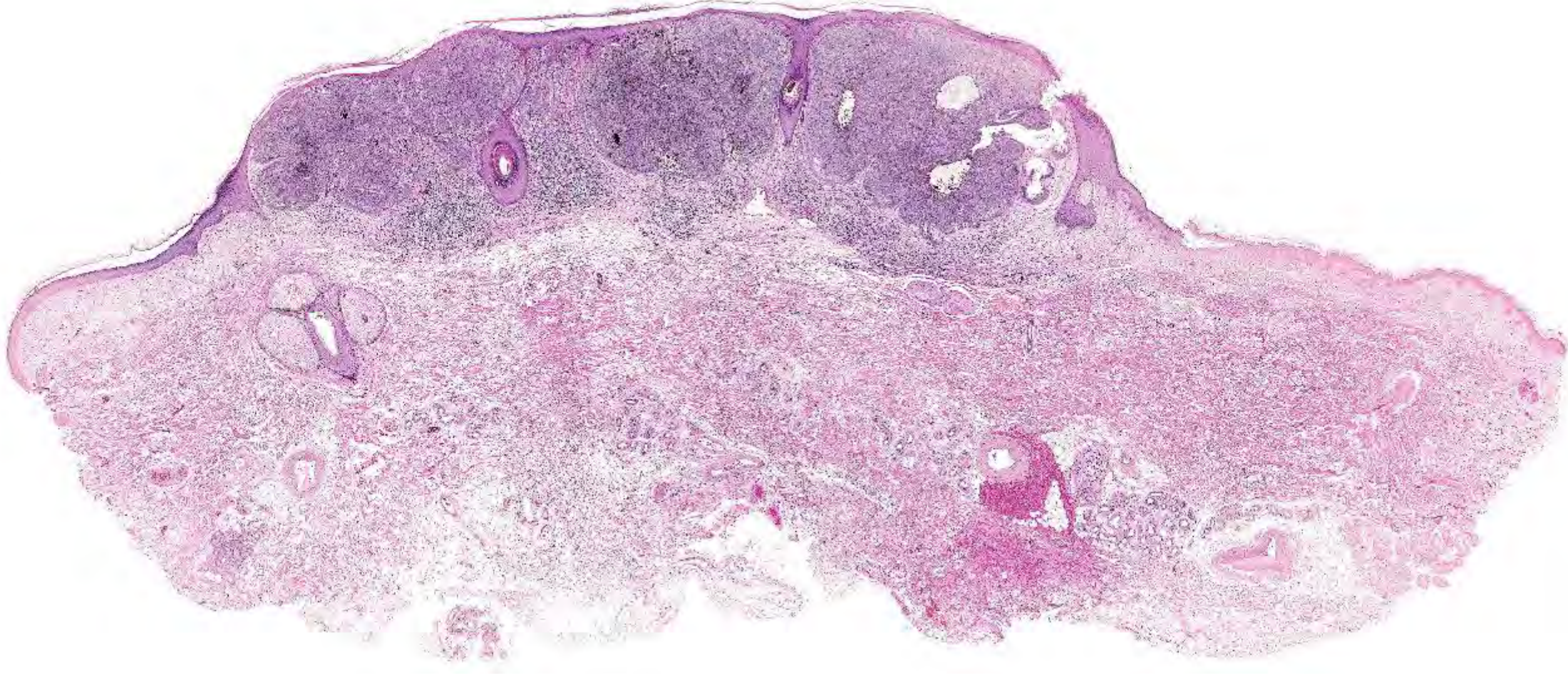


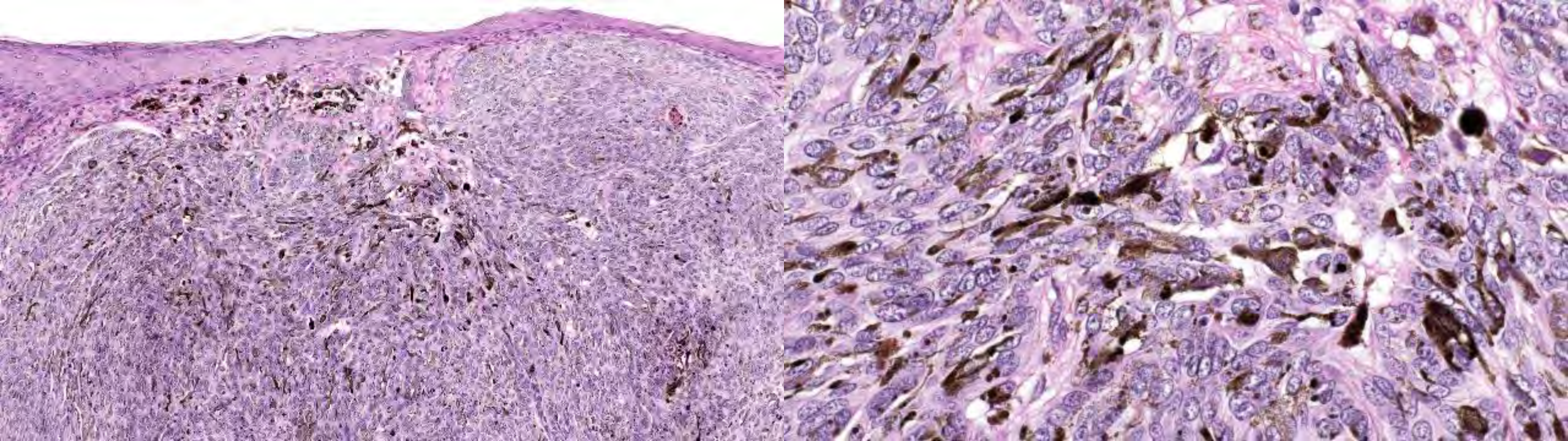
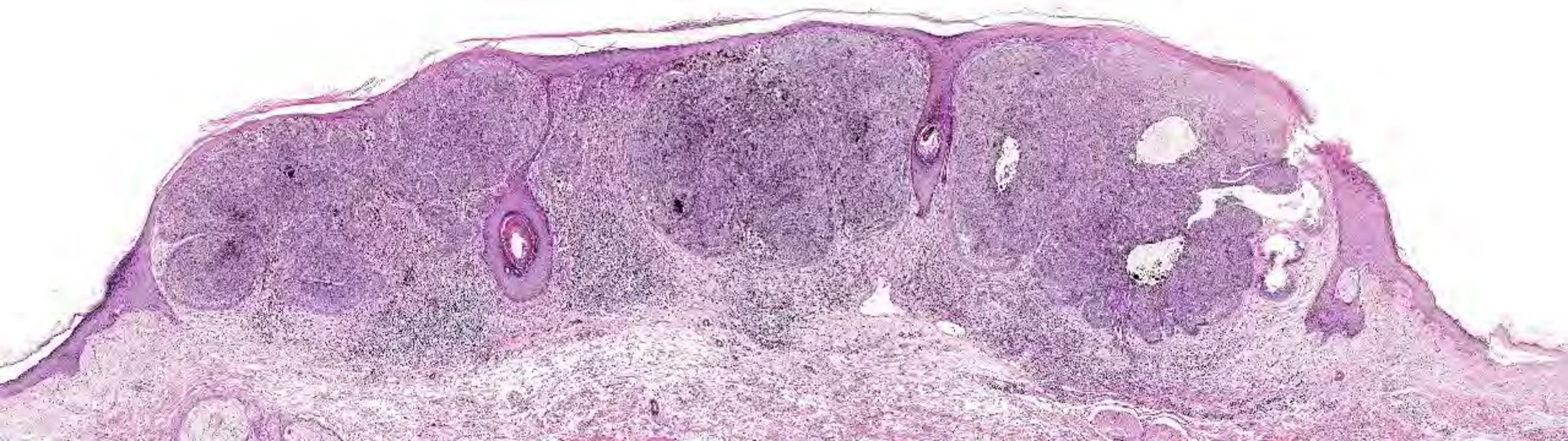
FIGURE 5. A, Melanoma cells are present within and adjacent to a nodule of BCC. B, A melanoma cell aggregate in the superficial dermis is composed of large epithelioid tumor cells. C, The tumor cells are diffusely positive for gp100 (HMB-45).

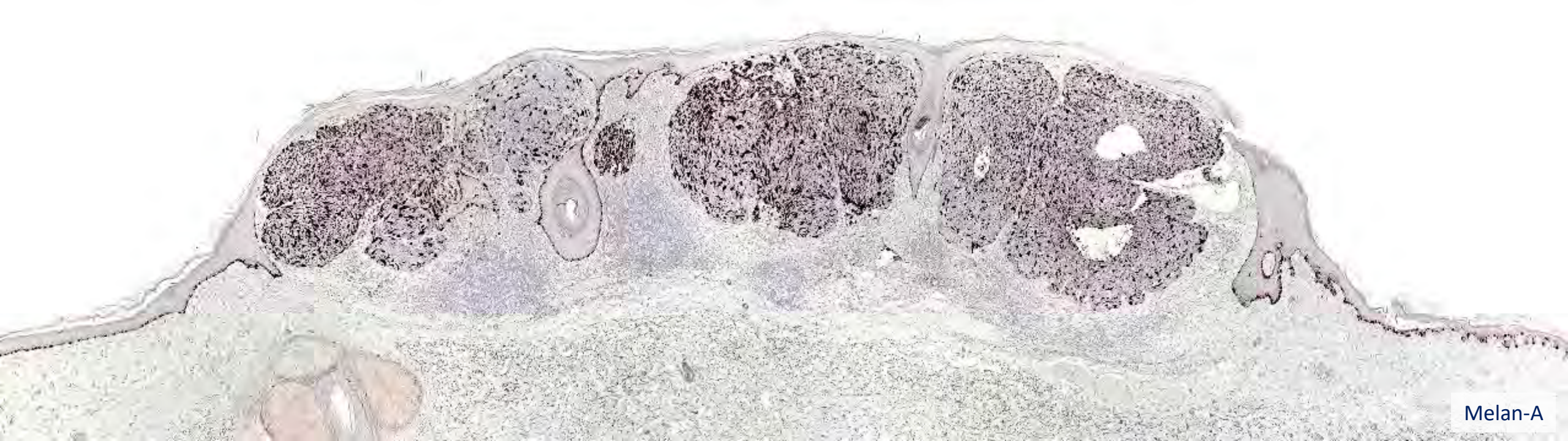
From the Departments of *Pathology and †Medicine, Dermatology Service, Memorial Sloan-Kettering Cancer Center, New York, NY.
Reprints: Klaus J. Busam, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (e-mail: busam@mskcc.org).
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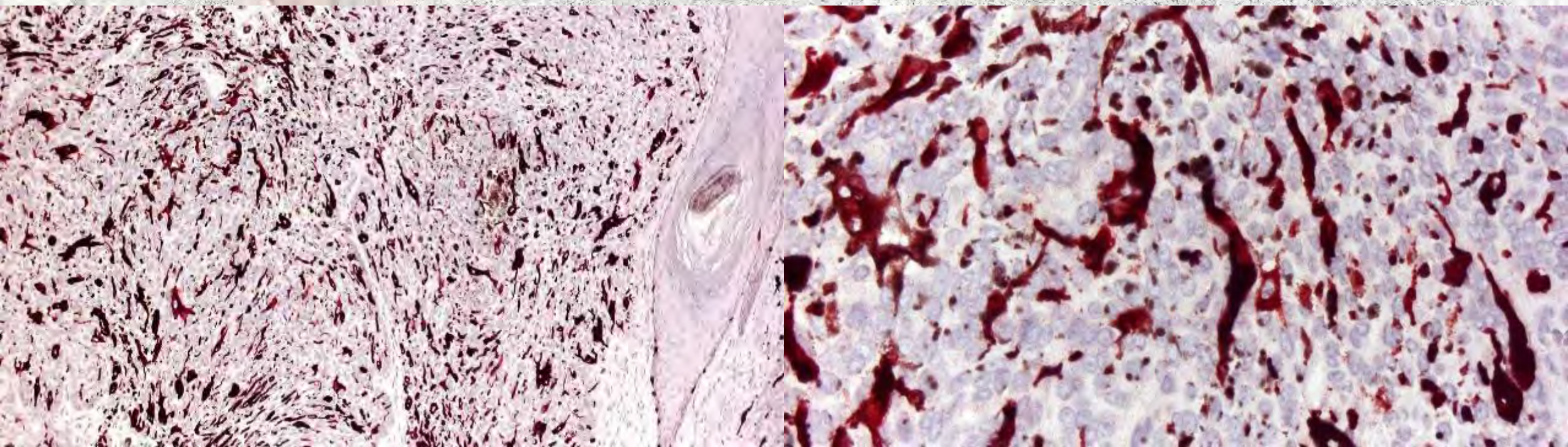
Case 6

M, 81. Pigmented tumor of unknown duration on the pre-sternal area.



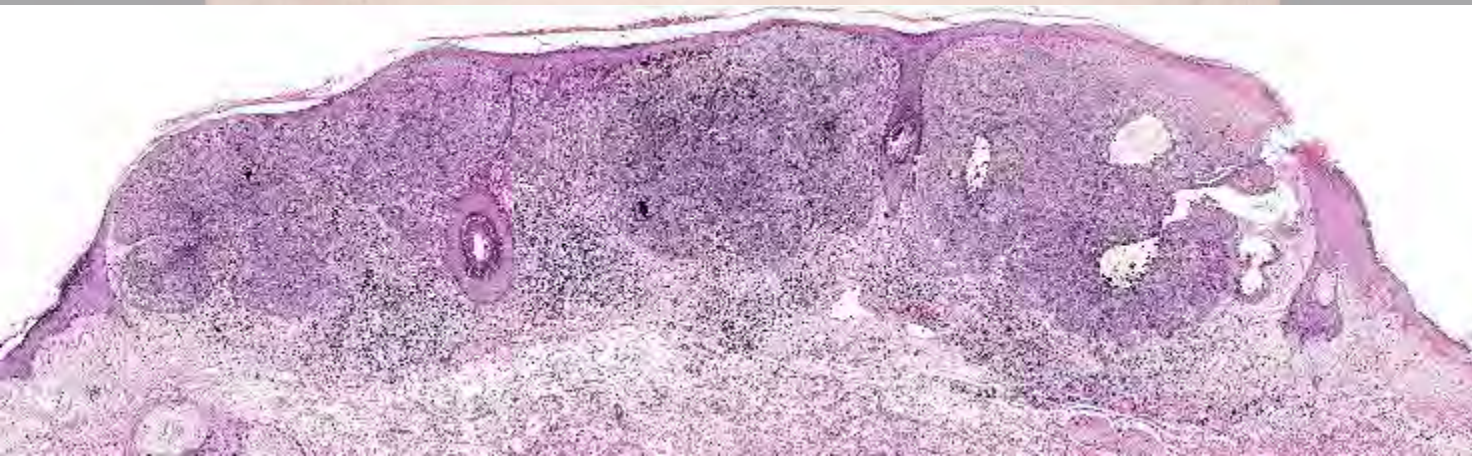


Melan-A

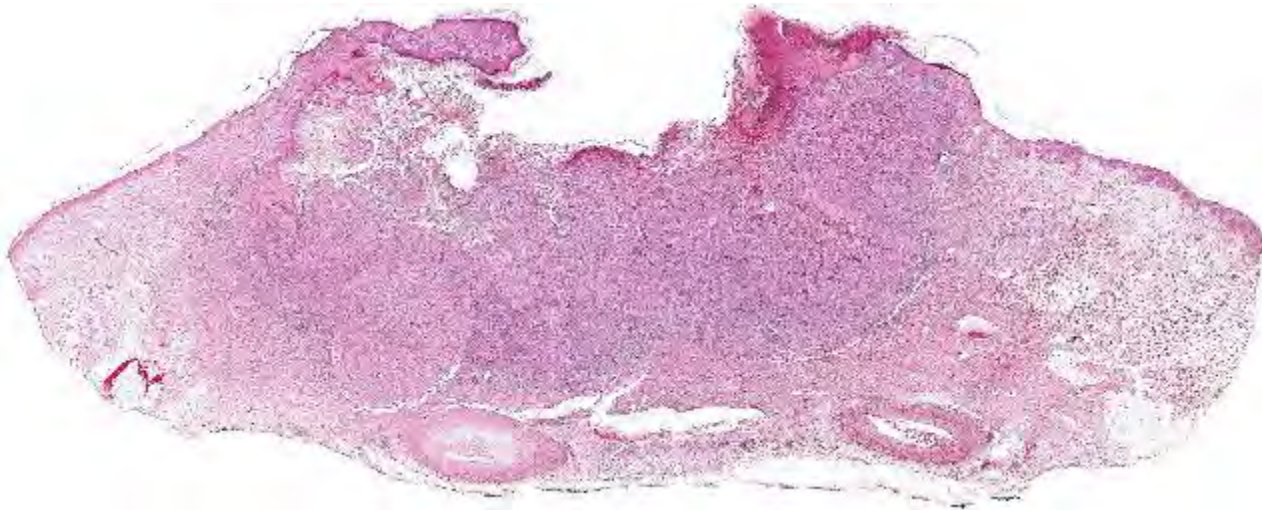




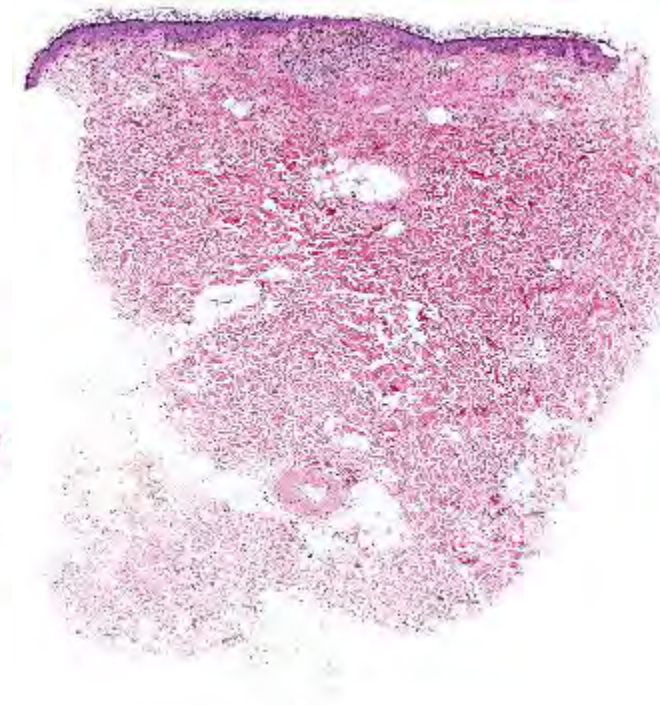
Pigmented basal cell carcinoma
with melanocytic hyperplasia



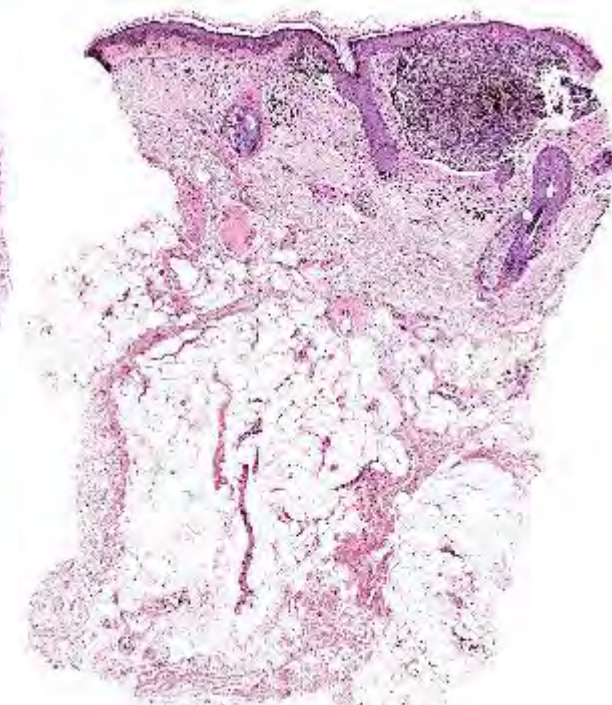
5 cases presenting a similar problem



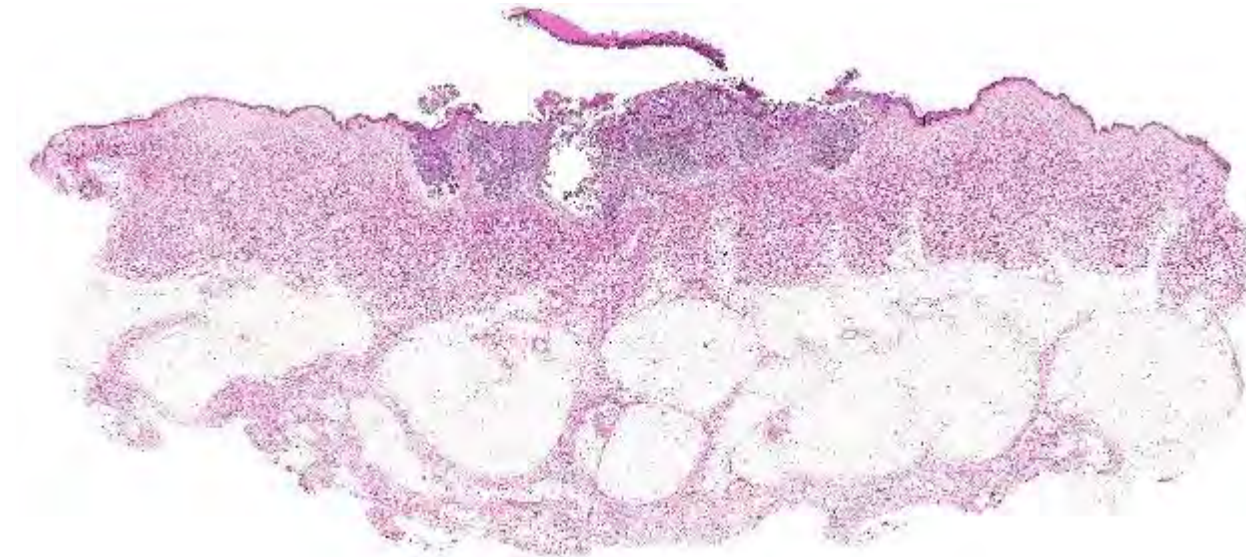
Melanoma metastatic to SCC



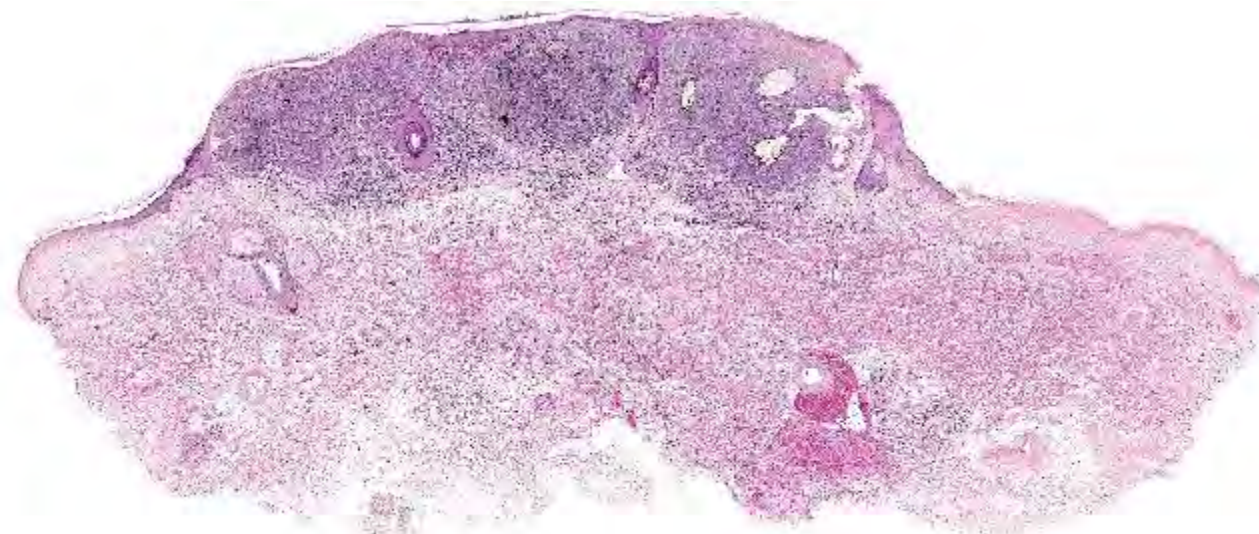
BCC with melanocytic hyperplasia



Collision of MM & BCC



Melanoma metastatic to BCC

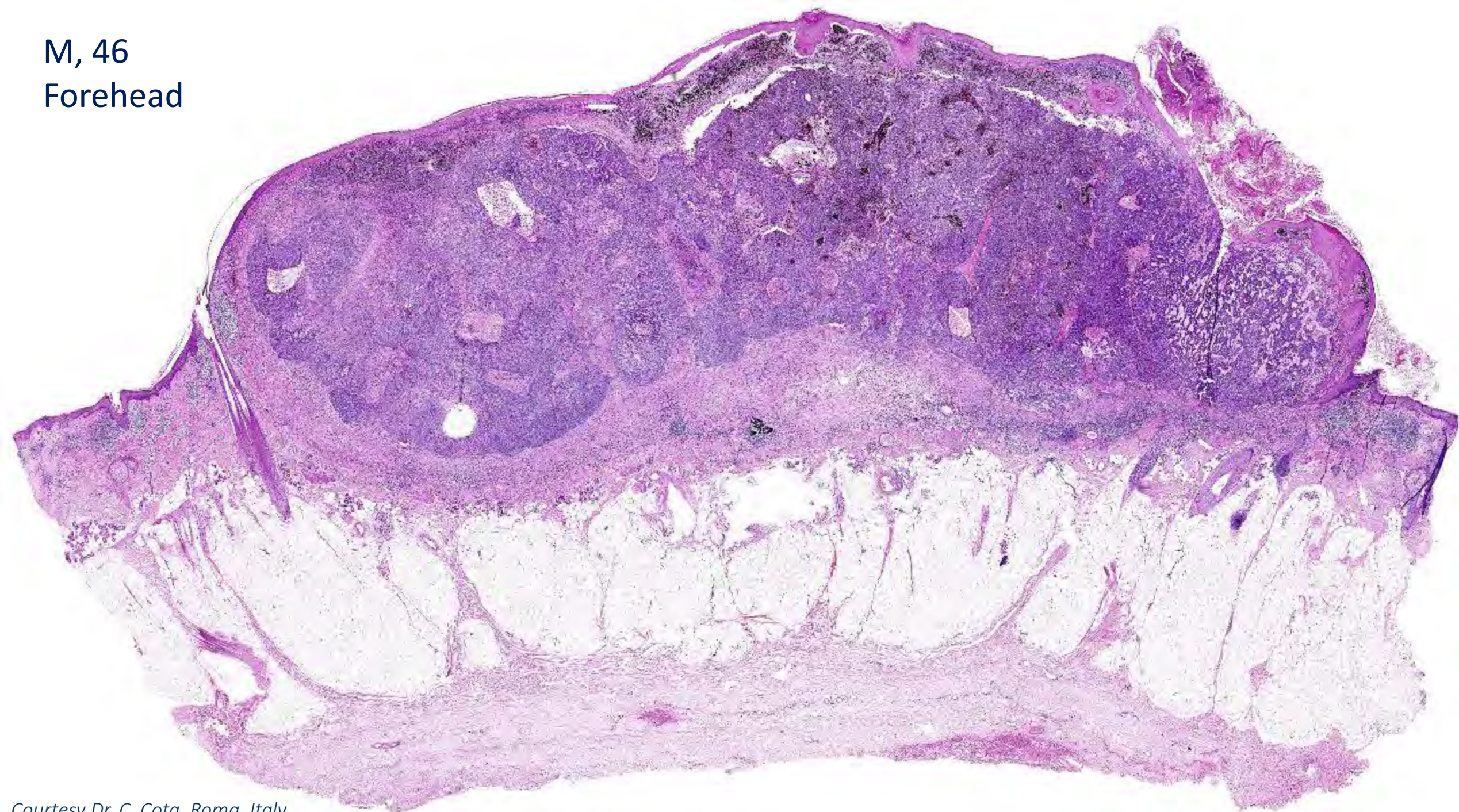


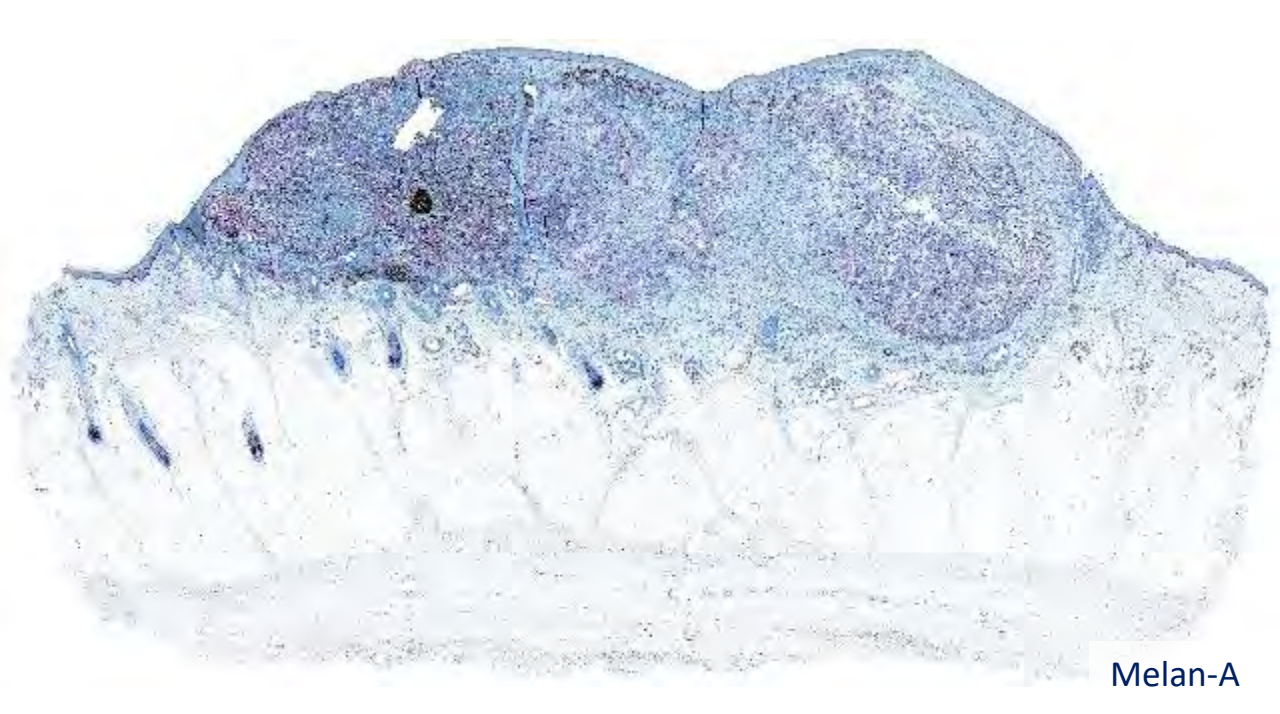
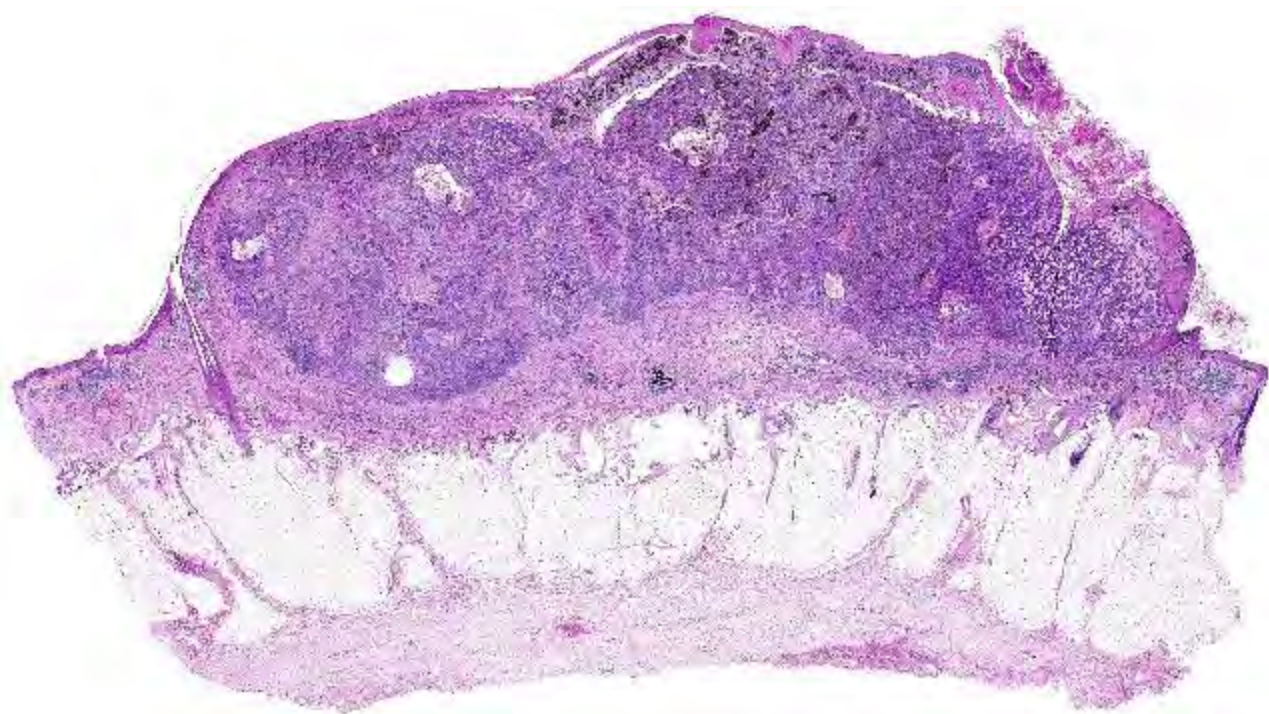
BCC with melanocytic hyperplasia

BCC with melanocytic hyperplasia vs. collision of MM & BCC

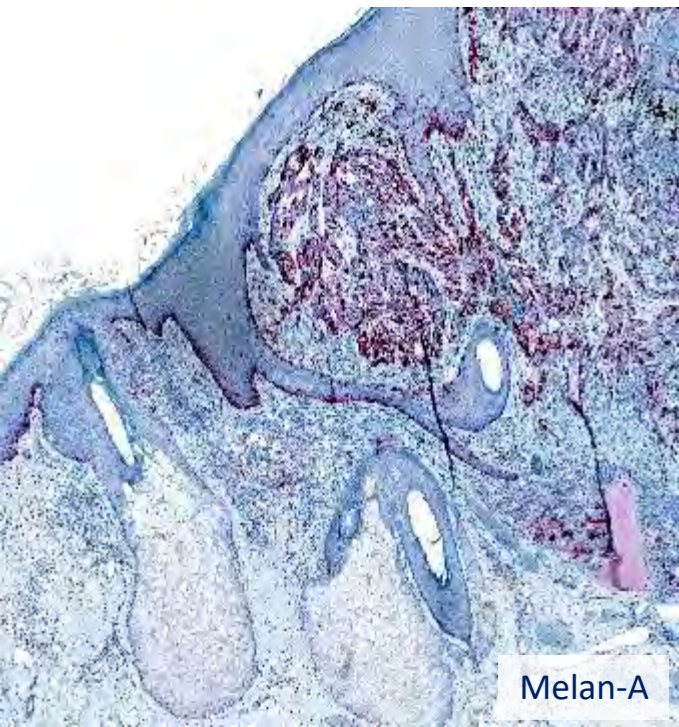
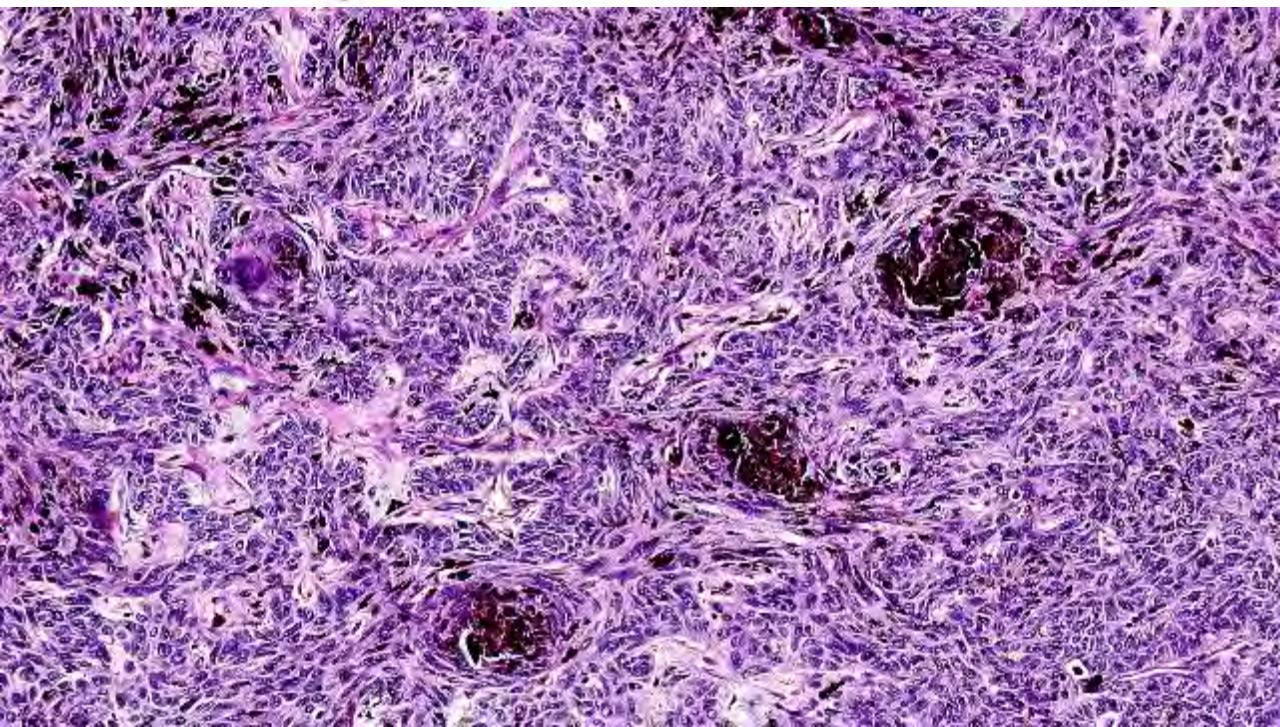
- Confusing literature on "malignant basomelanocytic tumor"
- In BCC with melanocytic hyperplasia dendritic melanocytes in solitary units are dispersed uniformly within the tumor complexes of the BCC; normal number of melanocytes within the skin above and adjacent the BCC
- In collision tumors of MM & BCC neoplastic melanocytes within the tumor complexes of BCC may mimic the pattern observed in hyperplasia; however, an increase of melanocytes with the pattern of MM in situ is invariably observed also in the epidermis above and adjacent to the tumor
- PRAME can be a helpful diagnostic clue (but it is usually not necessary)

M, 46
Forehead

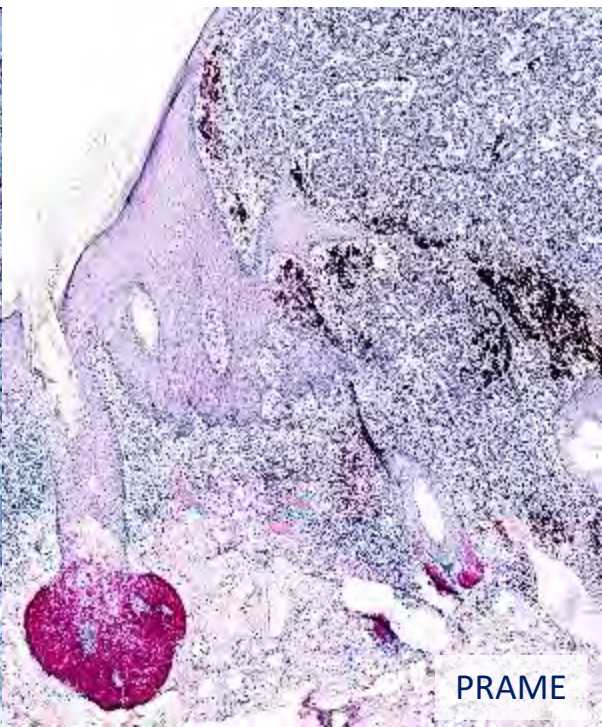




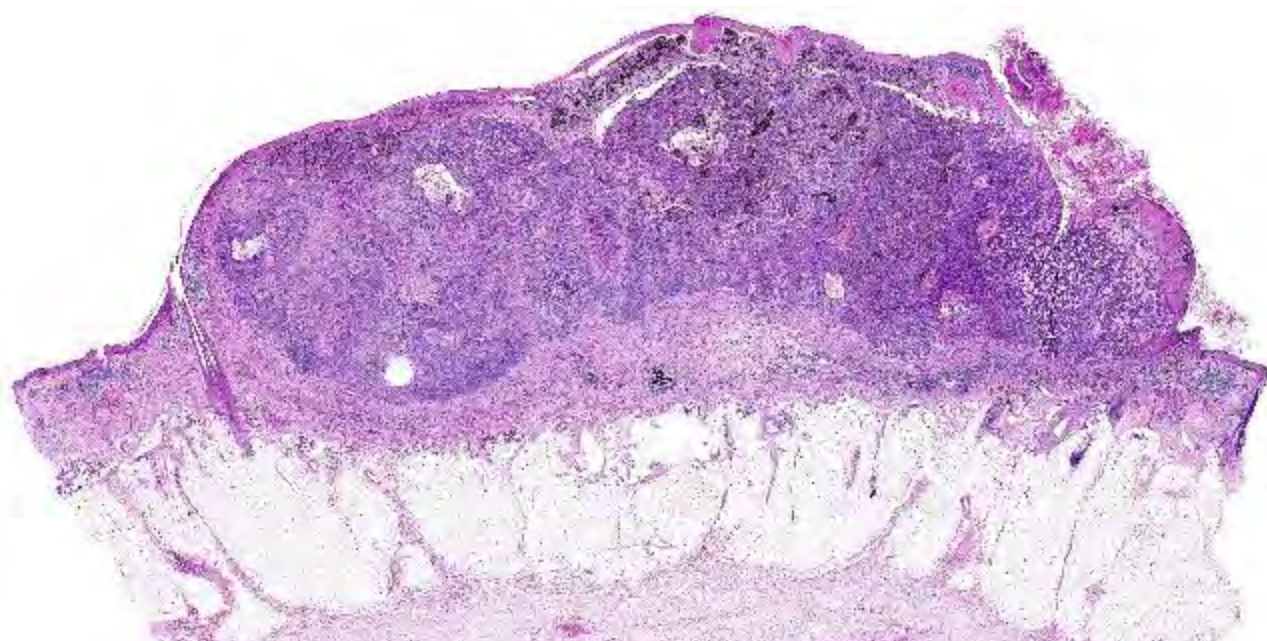
Melan-A



Melan-A

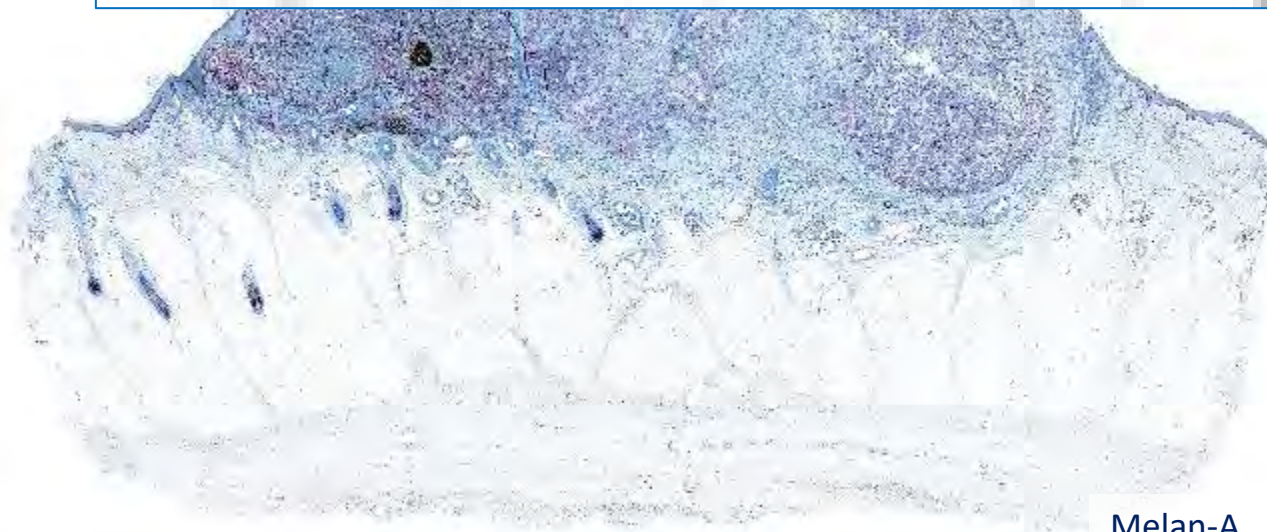


PRAME



reported (not by Dr. Cota...) as high grade BCC with a melanoma

Am J Dermatopathol 27: 314-318, 2005).



Melan-A

Esame 26-1-00424
Cognome e nome:
Sesso: M Data nascita: 26/02/1980

Accettato il: 21/01/2026
Refertato il: 24/02/2026
Richiesto da:

ESAME ISTOLOGICO

Materiale in esame
Neoplasia linfoma

Quesito diagnostico: Basalioma pigmentato

Notizie cliniche

Prelevi:
1 - margine apicale
da 2 a 5 - sezioni ventrali
Il materiale viene completamente incluso ed esaminato

"High grade basal cell carcinoma combined with a strongly pigmented spindle and epithelioid cell melanoma (so-called malignant basomelanocytic tumor)."

Combined High-Grade Basal Cell Carcinoma and Malignant Melanoma of the Skin ("Malignant Basomelanocytic Tumor")

Report of Two Cases and Review of the Literature

Juana Rodriguez, MD,* Daiwake Nomata, MD,* Elisabeth Kahn, MD,*
Martin Reichel, MD,[†] and Juan Rosai, MD[‡]

Abstract: We describe two cases of malignant combined squamocarcinoma with cutaneous plasmacytoid features—high-grade basal cell carcinoma and malignant melanoma. Some tumor cells showed a T-cell-type plasmacytoid morphology, p63 and p16^{ink4a} immunohistochemical phenotype (HMB-45, MART-1, Melan-A, S100-positive). We cover the hypothesis of tumor origin either from a malignant melanocytic differentiation or an epithelial cell event.

Key Words: basal cell carcinoma, histiocytic differentiation, collision tumor, malignant basomelanocytic tumor, malignant melanoma

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Cutaneous collision tumors, defined as the merging of 2 originally separate neoplasms, are very rare but well-established entities. Cutaneous combined tumors (ie, combining 2 or more histiologic differentiations) are also well recognized, most of them being represented by tumors with various types of adnexal and/or neuroectodermal differentiation.¹⁻³ An exceptionally rare form of cutaneous combined tumor is that composed of keratinocytes and melanocytes. We are aware of only a handful of previously recorded cases of this entity in the English literature, some described as combined squamous cell carcinoma and melanoma,⁴ and others as combined basal cell carcinoma and melanoma ("malignant basomelanocytic tumor").^{1,2} We report here 2 additional cases of combined carcinoma and melanoma of skin in which the epithelial component had the features of a high-grade basal cell carcinoma.

MATERIALS AND METHODS

Both cases had been sent to one of the authors (J. Rosai) for consultation. The hematoxylin and eosin slides were reviewed, and immunohistochemical studies using the avidin-biotin complex immunoperoxidase technique were performed. The following antibodies were used: AE1/AE3 (1:800, Dako, Carpinteria, CA), cytokeratin 903 (1:50, Dako), cytokeratin 7 (1:4,000, Dako), cytokeratin 20 (1:1,000, Dako), p63 (1:2,000, Dako), HMB-45 (1:2,000, Enzo, Farmingdale, NY), MART-1 (1:2,000, Novocastra, Fremont, CA), Melan-A (1:100, Dako), S-100 protein (1:8,000, Dako), vimentin (1:70,000, Dako), and chromogranin (1:16,000, Dako). A double immunostaining method was also performed in both cases for p63 and MART-1, detecting the former with a brown chromogen (3,3'-diaminobenzidine, Sigma-Aldrich, St. Louis, MO) and the latter with a blue chromogen (Fast Blue BB, Sigma-Aldrich, St. Louis, MO).

Clinical and follow-up information was obtained through direct contact with the referring pathologists.

RESULTS

Clinical Findings

Case 1

A 90-year-old fisherman with severely sun-damaged skin had a long history of numerous numerous basal cell carcinomas, squamous cell carcinomas, and atypical keratosis. In addition, a malignant melanoma in situ from his forehead skin had been previously excised 5 years previously, with no evidence of recurrence or metastasis. The current lesion presented as a solitary, firm, plaque on the skin of the left nasal cheek. The clinical differential diagnosis included atypical keratosis, squamous cell carcinoma, and basal cell carcinoma. A skin shave biopsy was performed, followed by a re-excision. The patient is well without evidence of recurrence or metastasis 12 months after the initial diagnosis.

Case 2

A 70-year-old man with a long history of basal cell carcinomas, squamous cell carcinomas, and atypical keratosis of the skin of the face presented with a 2 × 4-cm left forehead non-healing skin lesion in the left preauricular region, clinically

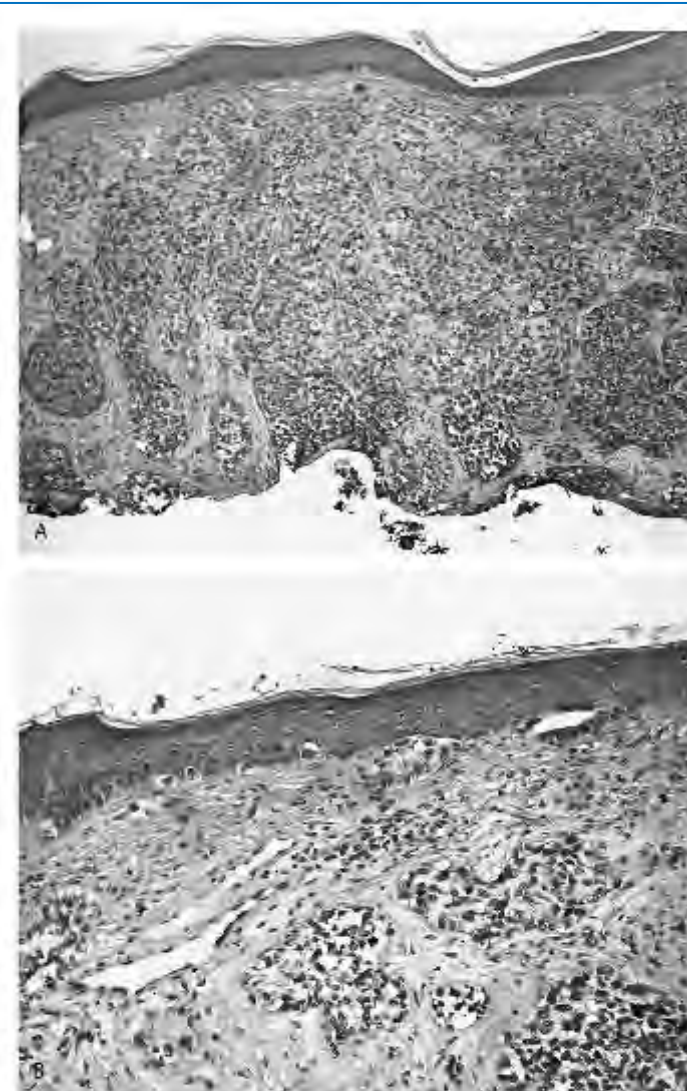


FIGURE 1. (Case 1) A, Low-power view of the tumor showing basaloid pattern of growth in the dermis, beneath an attenuated epithelium. B, Higher-power view, showing basaloid tumor nests in the dermis and atypical cells in a junctional location, the latter arranged as strips, nests, or isolated elements.

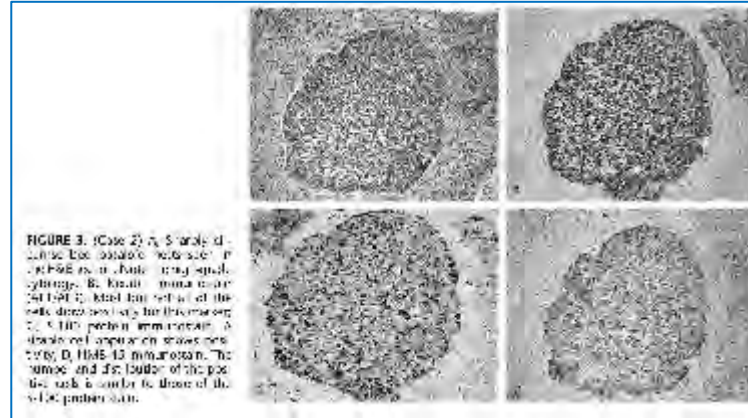


FIGURE 2. (Case 2) A, 5-μm slide of tumor. B, 5-μm slide of tumor. C, 5-μm slide of tumor. D, 5-μm slide of tumor. E, 5-μm slide of tumor. F, 5-μm slide of tumor. G, 5-μm slide of tumor. H, 5-μm slide of tumor. I, 5-μm slide of tumor. J, 5-μm slide of tumor. K, 5-μm slide of tumor. L, 5-μm slide of tumor. M, 5-μm slide of tumor. N, 5-μm slide of tumor. O, 5-μm slide of tumor. P, 5-μm slide of tumor. Q, 5-μm slide of tumor. R, 5-μm slide of tumor. S, 5-μm slide of tumor. T, 5-μm slide of tumor. U, 5-μm slide of tumor. V, 5-μm slide of tumor. W, 5-μm slide of tumor. X, 5-μm slide of tumor. Y, 5-μm slide of tumor. Z, 5-μm slide of tumor.

Case 1 most likely represents collision of MM & BCC

Case 2 to my eyes represents a classical example of BCC & melanocytic hyperplasia

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TEACHING CASE

Collision tumor of malignant skin cancers: A case of melanoma in basal cell carcinoma

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Abstract

The coexistence of two malignant skin tumors intermingling in the same histologic specimen is rare. We report a case of melanoma in a basal cell carcinoma collision tumor. The presence of two intermingled neoplasms was confirmed by immunohistochemistry, which showed strong positivity for S-100 and HMB-45. A review of the literature and a case analysis allow for some pathogenetic and prognostic considerations.

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Keywords: Collision skin tumor; Basal cell carcinoma; Melanoma

Introduction

Although rare, the association of two different skin tumors in the same anatomic specimen has been described by many authors [14]. In most cases, the lesions are found to be contiguous, up to 1 mm apart [3]. Far less frequent is the collision of two tumors. Collision refers to the coexistence of two tumors intermingling within the same lesion [13].

The collision of malignancies originating from different cell lines in a single skin lesion is a rare occurrence.

In particular, the collision of basal cell carcinoma and malignant melanoma (MM) is very rare, although both lesions may develop in skin damaged by chronic exposure to sunlight [1].

The pathogenesis of coexisting skin tumors remains a matter of speculation [5].

Some authors consider the various combinations to be merely coincidental [2,12], whereas others hypothesize that the presence of one tumor may induce epithelial or stromal changes responsible for the development of a second tumor [4,12,19].

Basal cell carcinomas (BCC) are considered tumors of trichogenic origin in most cases, i.e., they derive from the hair follicle of the skin [10]. Hair follicles as well as BCC are known to contain HMB45-positive melanocytes [2], which may give rise to chaotically pigmented lesions [8].

Therefore, an abnormal stimulation of such melanocytes could lead to the development of MM within BCC [7].

This is most possibly the reason for the rarity of a “basal cell carcinoma-associated MM”.

A review of the literature revealed a dearth of reports on MM arising in basal cell carcinoma (Table 1).

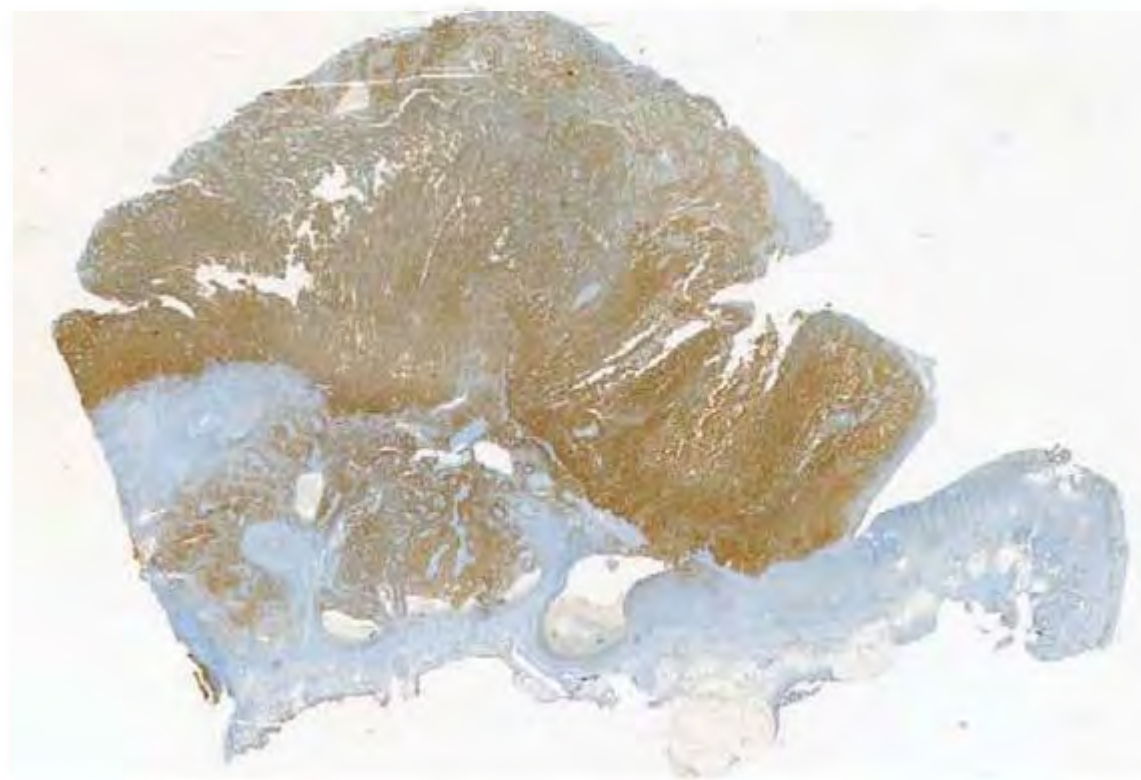


Fig. 1. Original magnification ($\times 1$); immunocytochemical staining (HMB-45) shows a basal cell carcinoma at the base of the lesion and a pigmented epithelioid melanoma on its exophytic portion.

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A Rare Case of a Cutaneous Squamomelanocytic Tumor: Revisiting the Histogenesis of Combined Neoplasms

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Abstract: We describe what we believe to be the seventh report of a combined tumor with histologic features of both malignant melanoma and a squamous cell carcinoma, a squamomelanocytic tumor. An 82-year-old woman presented with a nondescript, skin-colored, firm papule on her nose. Histology showed 2 different neoplastic cell proliferations: atypical squamoid cells and irregularly shaped nests of atypical pigmented epithelioid cells (melanocytes) arranged in small to large nests at the dermal-epidermal junction and within the epidermis. Both components were closely admixed and restricted to the epidermis. Immunohistochemistry showed diffuse cytoplasmic reactivity for p40/p63 that most closely supported the histopathologic features of a squamous cell carcinoma. S-100 and melanoma antigen recognized by T cells 1 did not stain these areas and showed strong selective positivity for the atypical melanocytic component. A true simultaneous proliferation of 2 distinct cell phenotypes due to clonal genetic interactions is our favored interpretation because of the intimate admixture, distinct immunohistochemical pattern, and unique histologic features. Perhaps, chronic sun damage (facial location and advanced age) and reduced immunity (history of other malignancies, particularly recent history of a basal cell carcinoma) played a complementary role for the development of the squamomelanocytic tumor.

Key Words: SMT, collision, squamous cell carcinoma, SCC, malignant melanoma, MM, cytokeratin, MART-1, S-100, biphasic tumor, intermingled tumor, skin.

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INTRODUCTION

The coexistence of 2 malignant neoplasms within a single cutaneous lesion is a rather unusual manifestation. Although a well-established entity, such a combination of neoplasms originating from different cell lines has been given various names, that is, combined, colliding, biphasic, contiguous, colocalizing, or even parasitic.¹ The proper designation of these tumors in the literature and their classification, pathogenesis, and prognosis are still a matter of speculation.

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According to Boyd and Rapini,² who have published one of the 2 most thorough evaluations on cutaneous collision tumors so far, a tumor is considered contiguous or "collision" if it consists of 2 or more neoplasms identifiable within a millimeter of each other. Some authors refer *collision* tumors to the meeting of 2 separate adjacent neoplasms originating from different cell lines,^{1,2} whereas *biphasic* tumors to an intimate admixture of 2 or more neoplastic proliferations intermingling closely within the same lesion.³ However, others suggest that collision tumors per se represent coexistence of 2 neoplasms intermingling together.⁴

On one hand, the lack of consensus in the literature about the proper terminology of these tumors is probably related to the fact that they are unusual and many times are falsely diagnosed as a solitary neoplasm, particularly if only a single punch biopsy or a superficial shave biopsy is obtained. On the other hand, the interpretation of the existing terminology adds further confusion, namely: if 2 or more neoplastic portions coexist within more than a millimeter of one another but, yet in 1 specimen, should they still be referred to as collision tumors or rather called a chance happening? Moreover, identifying collision tumors with biphasic pattern might be another pitfall because this pattern signifies that tumor cells arise concurrently from a common precursor and undergo subsequent divergent immunohistochemical differentiation. This is true for neoplasms in which a single cell is biphasic, such as basal-squamous carcinomas and combined nevi (ie, blue nevi with an ordinary dermal nevus).² However, if sticking to this approach, the very rare tumors composed of a malignant melanoma (MM) (cutaneous melanocytes have neural crest derivation) and a squamous cell carcinoma (SCC) (keratinocytes have ectodermal origin) could not be referred to as biphasic although present in the same lesion. We would therefore support the use of the term *combined* tumors for all neoplasms showing biphasic and/or dual differentiation patterns: a *collision* for those with clear demarcation between the 2 components and *intermingled* for those with both cell types growing intimately together almost on a single-cell level.¹

We present a new case of an intermingled tumor with histologic features combining a MM and a SCC, squamomelanocytic tumor (SMT). Such combination is believed to be very rare. Boyd and Rapini² found 0 SMTs of 69 collisions in their study on cutaneous collision tumors. Picard et al⁵ identified among a series of 78,000 primary cutaneous cancers, 105 basal-squamous carcinomas and 0 SMTs. To our knowledge, this is the seventh reported case in the world literature.^{1–5,7–11}

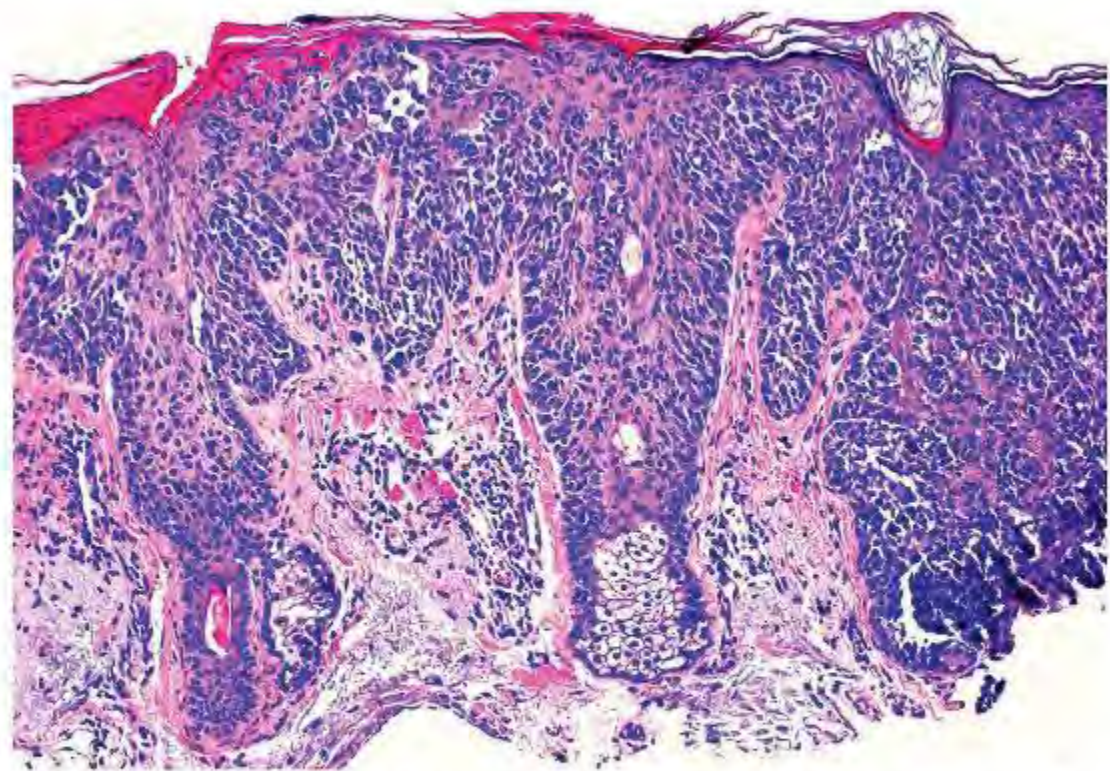


FIGURE 1. H&E, original magnification $\times 10$: focally eroded hyperplastic epidermis showing atypical squamoid component intermingled with nests of atypical melanocytes at the periphery. H&E, hematoxylin and eosin.

Malignant Melanoma Within Squamous Cell Carcinoma and Basal Cell Carcinoma: Is it a Combined or Collision Tumor?—A Case Report and Review of the Literature

Kristine M. Cornejo, MD and April C. Deng, MD, PhD

Abstract: We report a case of a very unusual combined and collision basosquamous melanocytic malignant tumor on the chest of an 84-year-old man. To our knowledge, this is the first case report describing this entity. We attempt to address the diagnostic challenge and the clinical and histological characteristics of these rare neoplasms with a review of the English literature to further categorize and summarize what has been previously reported about these exceptional tumors.

Key Words: combined tumor, collision tumor, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, biphasic tumor

(*Am J Dermatopathol* 2013;35:226–234)

INTRODUCTION

Malignant cutaneous tumors comprising melanocytes and keratinocytes are rare but well documented. These cutaneous neoplasms have been described as malignant melanoma (MM) with either a basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), but it has not been described in both. The terminology used to define these tumors was confusing, until they were recently clarified to include combined, collision, biphenotypic, and colonized tumors.¹ We herein report the first case of a malignant tumor with all 3 components, with a review of the literature.

CASE REPORT

An 84-year-old man with a history of multiple actinic keratoses and BCCs presented with an 8.0-mm nonpigmented, poorly papule on the chest present for several months. Clinically, the lesion was suspicious for a BCC. The patient had no personal or family history of melanoma. A shave biopsy was obtained, and microscopic examination revealed a malignant neoplasm consisting of multiple distinct tumor cell populations that were intimately admixed to form large, well-demarcated lobules in the dermis, compressing the overlying atrophic epidermis with minimal epidermal involvement (Fig. 1A). One population of tumor cells within the main tumor lobules were epithelioid with eosinophilic cytoplasm and high-grade nuclear atypia characterized by pleomorphism, hyperchromasia, multinucleation,

prominent nucleoli, and brisk apoptotic/necrotic activity (Fig. 2). These tumor cells also involved the hair follicles (Fig. 1B). Two tumor cells at the periphery of the main tumor lobules were basoid with peripheral palisading. These basoid cells also formed islands and cords adjacent to the main tumor lobules (Fig. 1C). Melanin pigment was evident lobules within both the rimmed and epidermal components on routinely stained sections. No overt melanocytic proliferation was observed.

The immunohistochemical profile revealed strong immunoreactivity for cytokeratins (AE1/AE3 and cytokeratin 903) and p63 in all the tumor lobules but did not stain all tumor cells (Fig. 2). Her-2/3 and CD10 highlighted one subset of cytokeratin-positive tumor cells at the periphery of the main tumor lobules and adjacent islands and cords, classic for BCC (Fig. 3). However, another subset of cytokeratin-positive cells were negative for Her-2/3 and CD10, thus revealing a second population. These tumor cells contained eosinophilic cytoplasm and marked nuclear atypia consistent with features of SCC. Interestingly, the melanocytic markers (S-100 protein, MART-1, Melan-A, HMB-45) showed strong immunoreactivity in a third subset of high-grade atypical tumor cells that were negative for cytokeratin and p63, intimately admixed with the cytokeratin-positive cells within the tumor lobules as both individual cells and in clusters (Fig. 4). Dual staining with p63 and Mart-1 revealed that the main tumor lobules consisted of an admixture of at least 2 distinct populations without dual labeling (Fig. 5).

Based on the above-described morphological features and the results of the immunohistochemistry studies, this unusual neoplasm was interpreted as a combined and collision basosquamous melanocytic malignant tumor. The patient was treated with wide local excision and remains free of disease 6 months after diagnosis and treatment.

DISCUSSION

The first report of a case consisting of a malignant neoplasm comprising keratinocytes and melanocytes was described by Novick et al² in 1977. In this study, a patient with a prior burn scar developed a combination of an SCC with MM. In 1999, a similar biphasic neoplasm was coined by Pool et al³ as a squamomelanocytic tumor and reported 4 cases exhibiting combined features of both SCC and MM with true malignant proliferation of both phenotypes. In 1984, Bhawan et al⁴ reported the first collision neoplasm consisting of an MM and BCC. Twenty years later, the term basomelanocytic tumor was reported by Erickson et al⁵ in a patient who died of metastatic MM. The primary lesion of this patient was initially diagnosed as a BCC on the scalp. However, a subsequent biopsy was performed after the patient was noted to have metastasis revealing invasive MM. Retrospectively, the initial biopsy was discovered to be a triphasic neoplasm consisting of

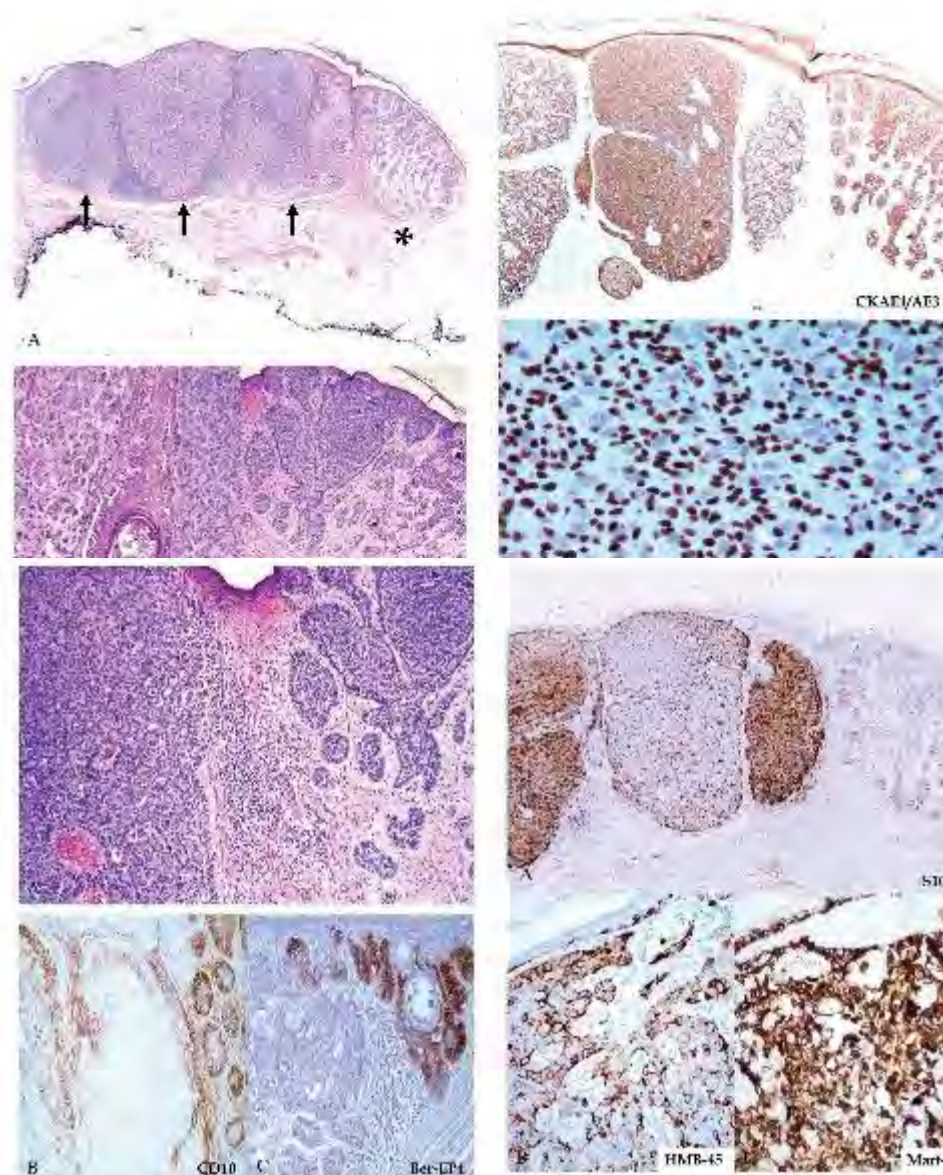


FIGURE 3. A, Medium-power view of a tumor lobule with adjacent basaloid islands and cords. The periphery of the tumor lobules are lined by basaloid cells with intimate admixing of at least 2 distinct tumor cell populations within the center. B, CD10 and C, Her-2/3 immunostains highlight the basal cell carcinoma component within the periphery of the main tumor lobules and the adjacent basaloid tumor islands and cords.

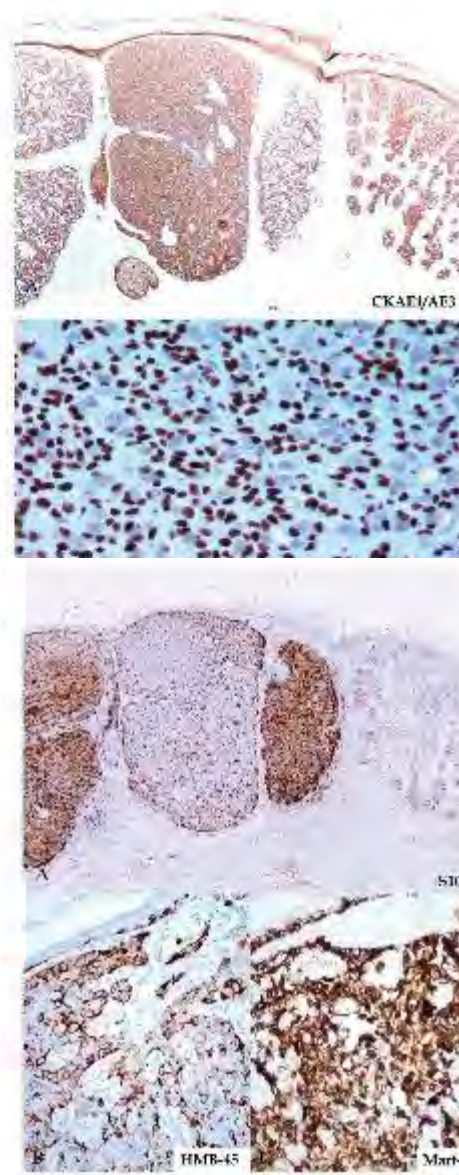


FIGURE 4. A, S-100 protein; B, HMB-45; and C, Mart-1 immunostains. Many cells show strong positivity within the main tumor lobules as single cells and clusters with scant, scattered staining in the adjacent basaloid islands and cords.

of the BCC, it appears to be consistent with a colonized tumor as the MM component grew within and into an underlying

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Malignant Basomelanocytic Tumor Manifesting as Metastatic Melanoma

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Svetomir N. Markovic, MD, PhD,† and Mark R. Pittelkow, MD,‡

Abstract: We report a case of an unusual basomelanocytic tumor from the scalp of a 56-year-old man. A 56-year-old white man presented with a scalp lesion that was biopsied and interpreted as a basal cell carcinoma. On histologic review, melanocytic melanoma was also present in a dermal lymph node and the lymph node biopsy from the area of the previously biopsied basal cell carcinoma of the scalp showed an invasive malignant melanoma. Immunohistochemical staining performed on the original scalp specimen showed positive immunohistochemical profile. A population of neoplastic cells was strongly positive for the melanocytic markers Melan-A, HMB-45, and tyrosinase and showed weak to moderate reactivity for S-100. A second population of cells was strongly immunoreactive for MART-1, a melanoma cocktail, HMB-45, tyrosinase, S-100 protein, Bcl-2, and cytokeratin. There was a distinct population of neoplastic cells within the epithelial islands that were strongly and diffusely immunoreactive for MART-1, HMB-45, and tyrosinase and weakly immunoreactive for S-100 (Fig. 1). A second population of cells failed to stain for the melanoma-associated antigens and were instead strongly immunoreactive for cytokeratin and Bcl-2 (Fig. 1). Tumor cells in subsequent liver and lymph node biopsies were positive for Melan-A and S-100 protein.

Key Words: basomelanocytic, basal cell carcinoma, malignant melanoma

J Am Acad Surg 2004;28:1393-1396

CASE REPORT

Clinical Findings

A 56-year-old man with a long-standing history of sarcoidosis presented with a scalp lesion. Clinical examinations included entonox, steroids, and 5-fluorouracil. A biopsy showed a tumor in the dermis characterized by islands of basaloid cells surrounded by fibrous stroma with no connection to the overlying epidermis and no intraepithelial component (Fig. 1A-D). The tumor cells composing the islands in the dermis were basoid and showed prominent peripheral palisading. Retraction spaces between the tumor islands and the surrounding stroma were present.

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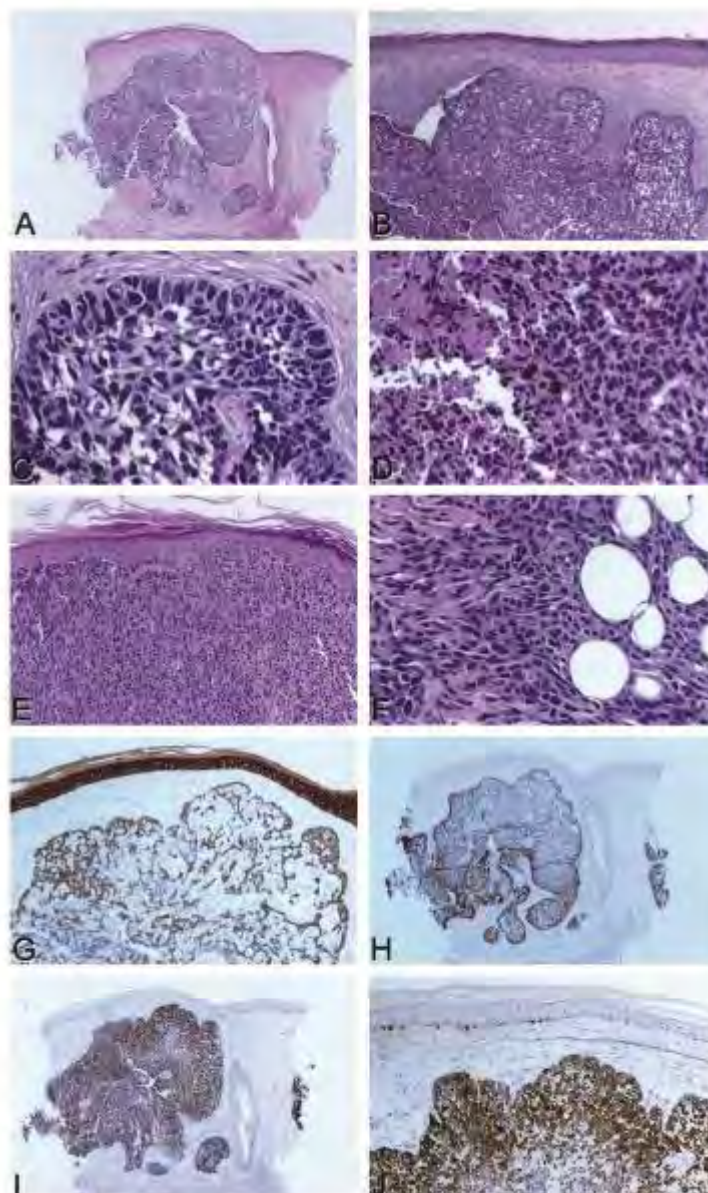
A biopsy was performed 1 year later for surveillance, showing that the tumor had multiple liver nodules. A needle biopsy showed metastatic malignant melanoma. Three lymph nodes were palpated in the left supraclavicular and lower cervical region, one of which measured 2 cm in largest dimension. A needle biopsy of the largest lymph node also revealed metastatic malignant melanoma. The patient died of metastatic malignant melanoma 5 months later.

A workup was initiated to look for a potential primary site. A scalp lesion was identified in the same region as the previously diagnosed basal cell carcinoma. Biopsies revealed a conventional vertical growth phase malignant melanoma with an intraepithelial component and an invasion to Clark level V, Breslow depth 3.0 mm (Fig. 1E). Immunohistochemical studies were performed on the originally biopsied scalp tumor using a standard ABC technique and the following commercially available antibodies: MART-1, melanoma cocktail, HMB-45, tyrosinase, S-100 protein, Bcl-2, and cytokeratin. There was a distinct population of neoplastic cells within the epithelial islands that were strongly and diffusely immunoreactive for MART-1, HMB-45, and tyrosinase and weakly immunoreactive for S-100 (Fig. 1). A second population of cells failed to stain for the melanoma-associated antigens and were instead strongly immunoreactive for cytokeratin and Bcl-2 (Fig. 1). Tumor cells in subsequent liver and lymph node biopsies were positive for Melan-A and S-100 protein.

DISCUSSION

Biphasic tumors with epithelial and melanocytic components are rare. This is the first description of a biphasic melanocytic tumor in a patient who died of metastatic malignant melanoma. Patel et al described four examples of squamomelanocytic tumors; the case of the patient was reported to be a metastatic melanoma or metastatic squamous cell carcinoma.¹ One purported example of a basomelanocytic tumor similar to that described in our patient was published by the presence of metastatic lung carcinoma, and no immunostains were performed.²

Biphasic tumors show an intricate architecture of melanocytic cells and basaloid cells or squamous cells in contrast to



A scalp lesion was identified in the same region as the previously diagnosed basal cell carcinoma. Biopsies revealed a conventional vertical growth phase malignant melanoma with an intraepithelial component and an invasion to Clark level V, Breslow depth 3.0 mm. Immunohistochemical studies were performed on the originally biopsied scalp tumor (...). There was a distinct population of neoplastic cells within the epithelial islands that were strongly and diffusely immunoreactive for MART-1, HMB-45, and tyrosinase and weakly immunoreactive for S-100.

Tumors composed of malignant epithelial and melanocytic populations: a case series and review of the literature

Over the last 30 years, there have been approximately 49 case reports of tumors composed of both malignant epithelial and melanocytic melanocytic populations. Herein, we present four additional cases of combined tumors that consist of two phenotypically distinct but intermingled populations of malignant cells. Each tumor was composed of an invasive melanoma closely associated with either a basal cell carcinoma or a squamous cell carcinoma. We review all previous case reports in the English literature and attempt to clarify the terminology and summarize what is currently known about these unique tumors.

Sattler RS, Metcalf JJ, Lountzis N, Elston D. Tumors composed of malignant epithelial and melanocytic populations: a case series and review of the literature.

J Cutan Med Surg. 2002;38:211-219. © 2002 Blackwell Munksgaard

Despite the fact that melanocytes and keratinocytes normally exist in close association in the basal layer of the epidermis and in hair follicles, the simultaneous malignant transformation of both populations is a rare event.¹⁻³ Upon retrospectively examining 78,000 sections of primary cutaneous tumors, Picard et al.⁴ found only 11 cases of malignant melanoma (MM) that were contiguous with a basal cell carcinoma (BCC) (0.0004% of specimens) and no cases of squamous cell carcinoma (SCC) associated with MM. Currently, in the English literature, there are approximately 19 cases of tumors that contain both BCC or SCC associated with MM.

Perhaps, because of the rarity of these tumors, no consensus has been reached as to how to classify these

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namings, and therefore the nomenclature is confusing. Over the years, a plethora of descriptive modifiers have been used to depict these tumors; however, no one term encompasses all tumors. Although the term "melanocarcinoma" seems intuitive, as it refers to a MM combined with a carcinoma, the term is problematic because it was a term once used to describe melanomas in general. Currently, at least a dozen names have been given to these tumors; yet, in most case reports, there is no clear sense as to what the term actually means. Moreover, many terms have been used interchangeably, even though they have different meanings.

Herein, we present four additional cases of combined tumors that consist of two phenotypically distinct but intermingled populations of malignant cells. Each tumor was composed of an invasive melanoma closely associated with either a BCC or a SCC. We review all previous case reports in the English literature and

1. Collision tumor: two independent neoplasms that occur in close proximity to one another, yet maintain sharp distinct boundaries.

2. Colonization: a MIS that permeates an underlying BCC, with the proviso that the atypical melanocytes must remain within the confines of the BCC. Prudence must be employed when this term is used because the term "colonization" widely pervades the literature to describe a situation where large dendritic non-neoplastic melanocytes populate various neoplasms. In this latter situation, the melanocytes are hypothesized to be reactive bystanders and non-neoplastic, yet this is not the case with colonization of a BCC by a melanoma where both populations of cells are malignant.

3. Combined tumor: a neoplasm composed of two distinct yet intertwined populations of malignant cells. Often, the epithelial and melanocytic populations merge imperceptibly when viewed with routine stains, but are better appreciated when immunohistochemical stains are utilized.

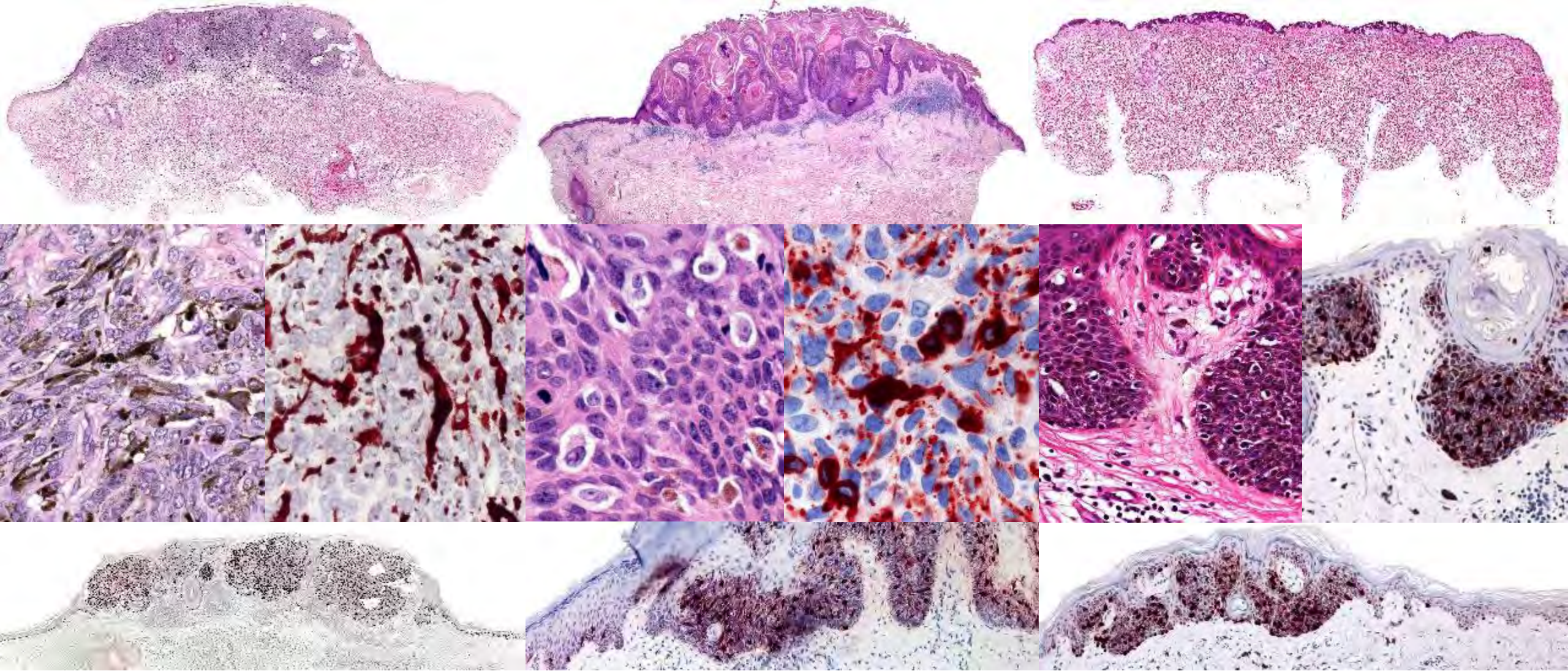
4. Biphenotypic tumor: a tumor that arises from a common stem cell precursor that undergoes divergent differentiation with the two tumor populations exhibiting overlapping immunohistochemical and molecular properties.

My own classification of "combined" melanocytic tumors

1. Collision tumors: two independent neoplasms that occur in close proximity to one another *and show areas of overlap.*

The melanocytic component may be a primary or metastatic melanoma.

2. Epithelial tumor with melanocytic hyperplasia: a population of dendritic, non-neoplastic melanocytes arranged as solitary units, that populate various epithelial neoplasms including particularly BCCs, SCCs and seborrheic keratoses.

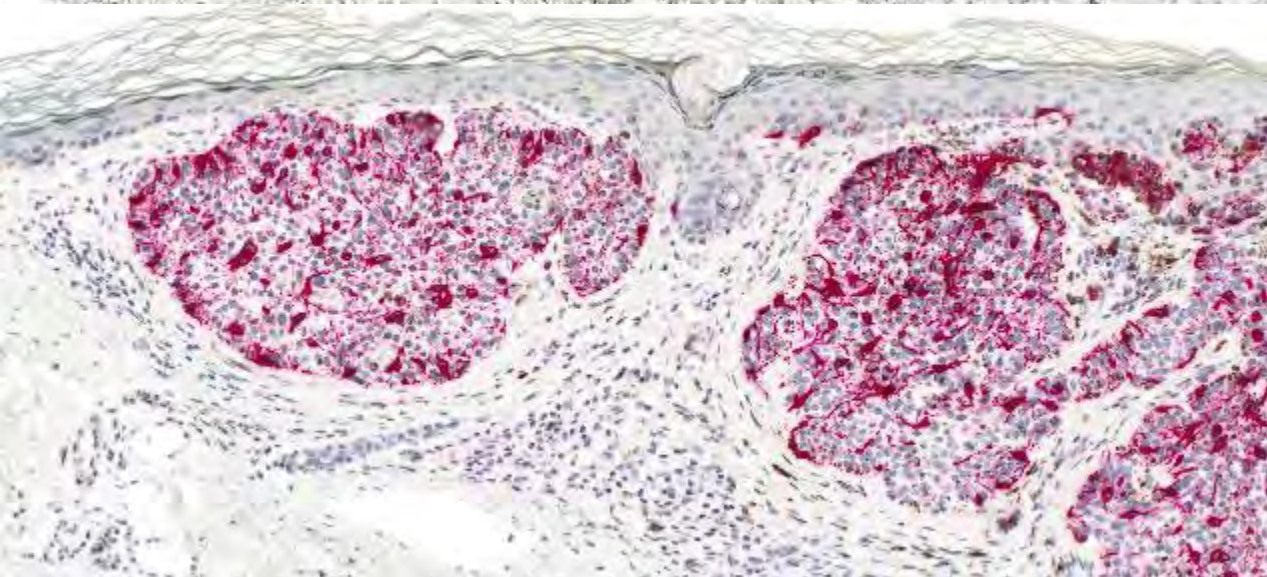
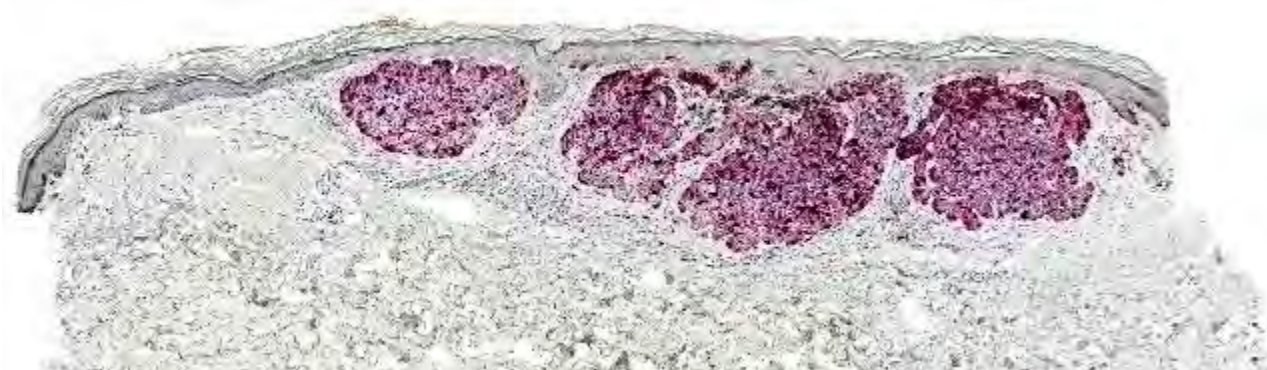
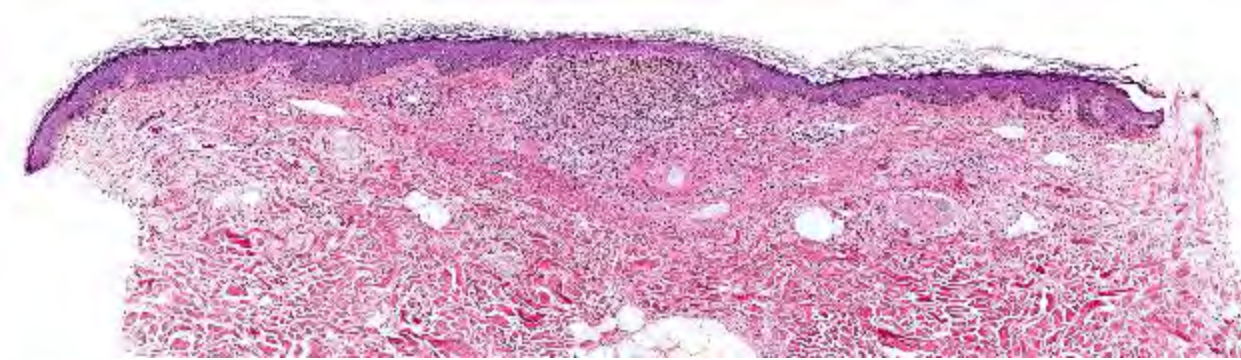


Basal cell carcinoma

Squamous cell carcinoma

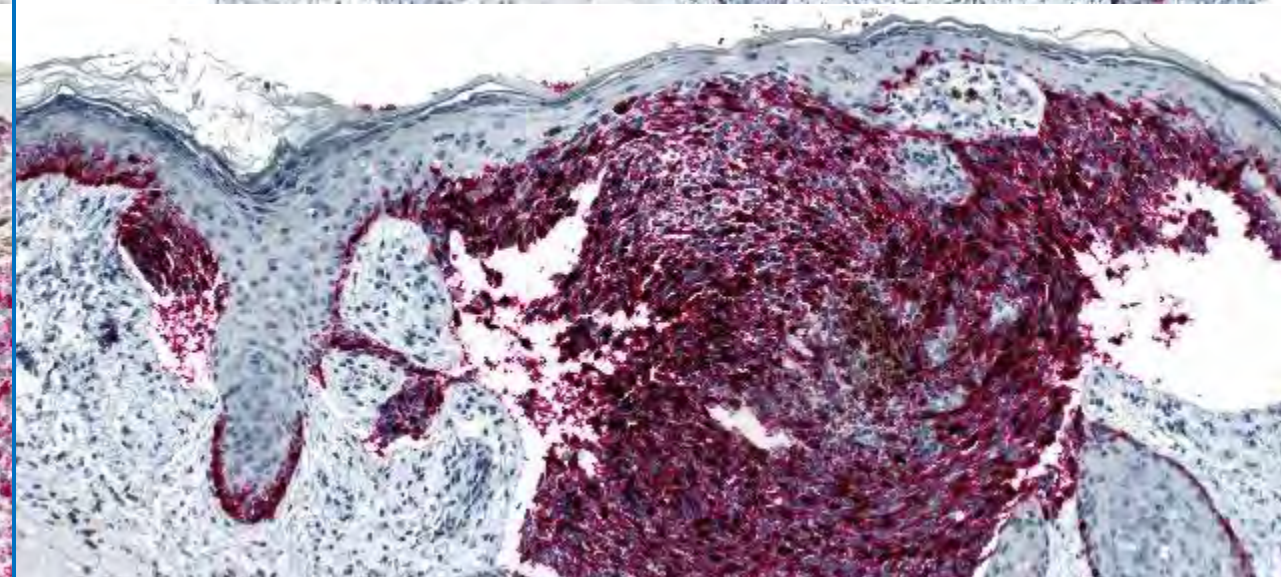
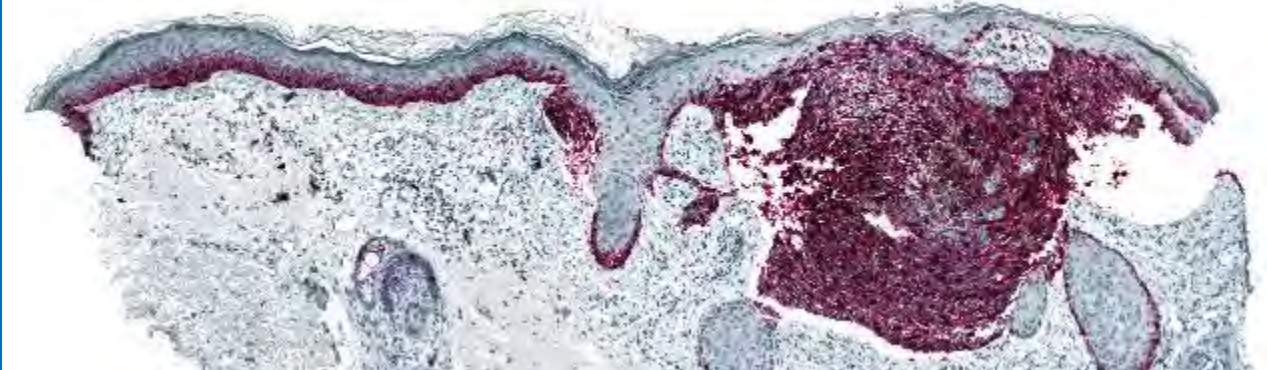
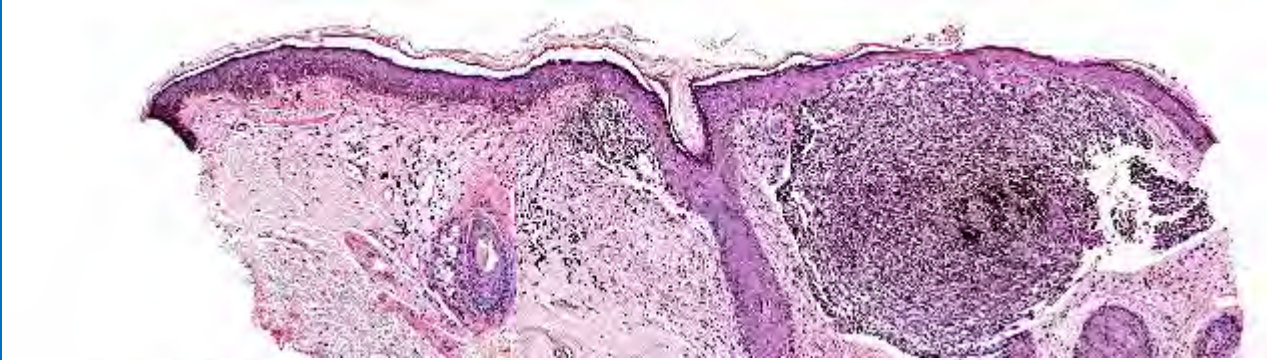
Seborrheic keratosis

In colonization, melanocytes are confined to the epithelial tumor, are uniformly distributed, do not form nests, and have a dendritic shape



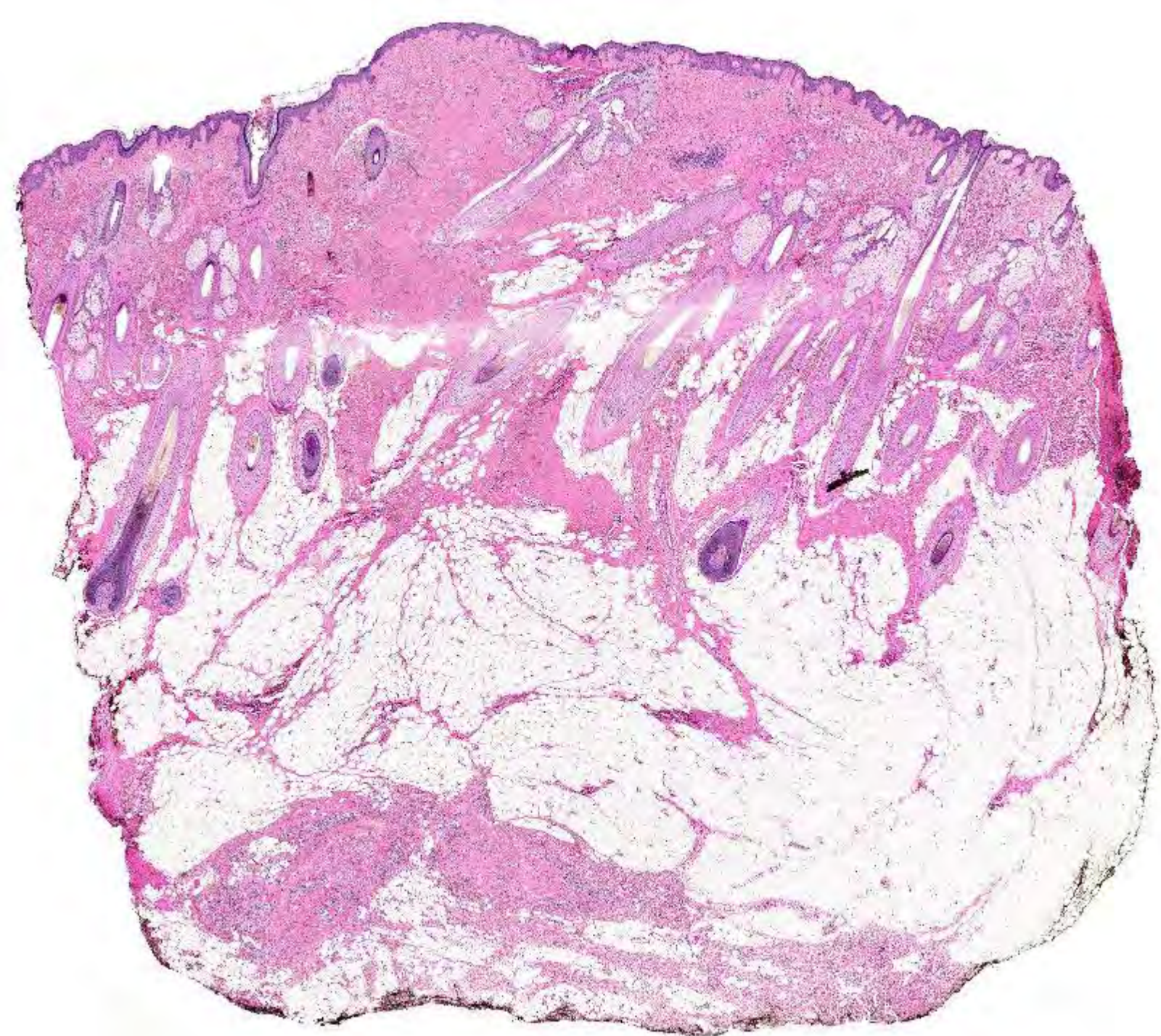
Basal cell carcinoma with melanocytic hyperplasia

Melanocytic proliferation restricted to complexes of the basal cell carcinoma



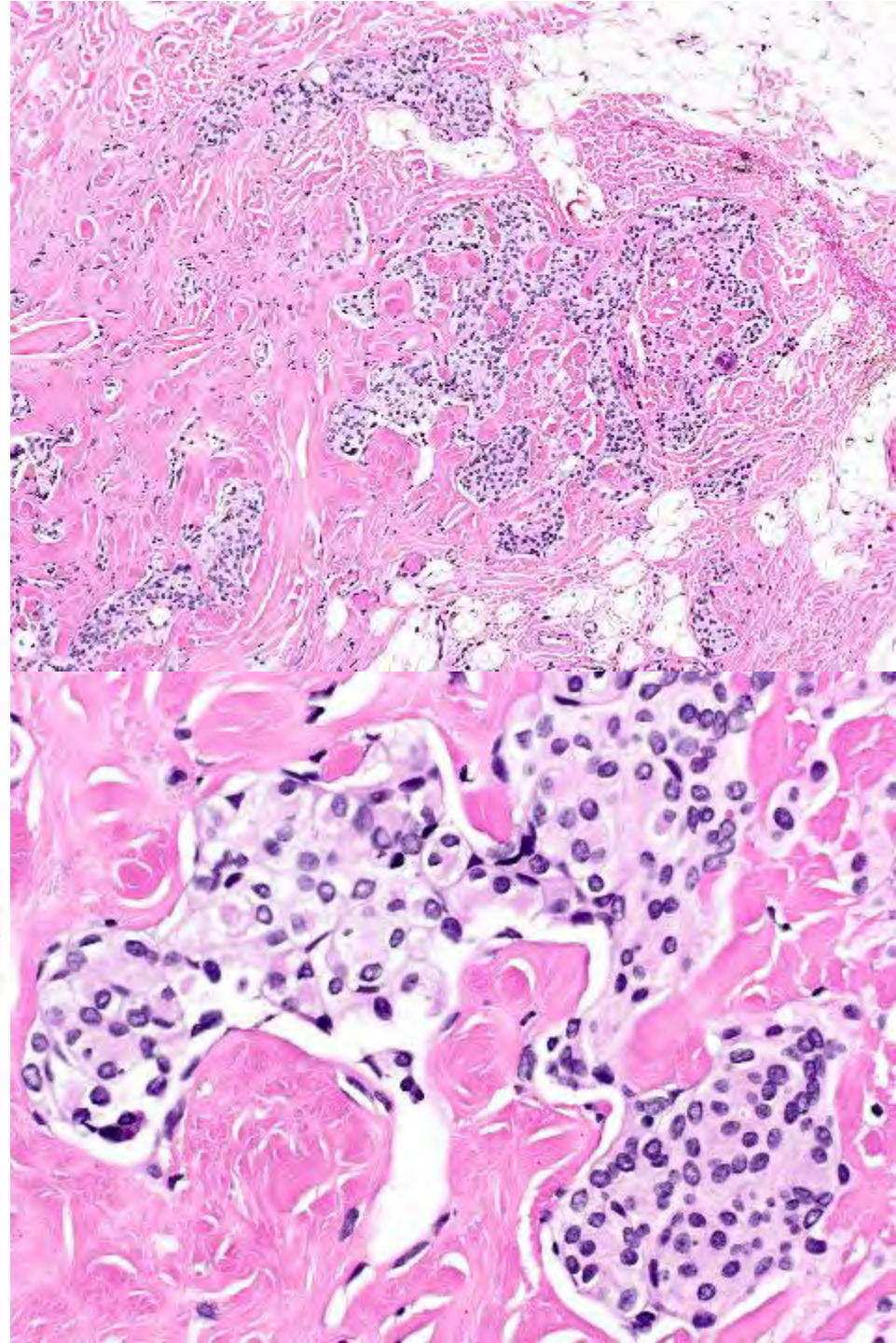
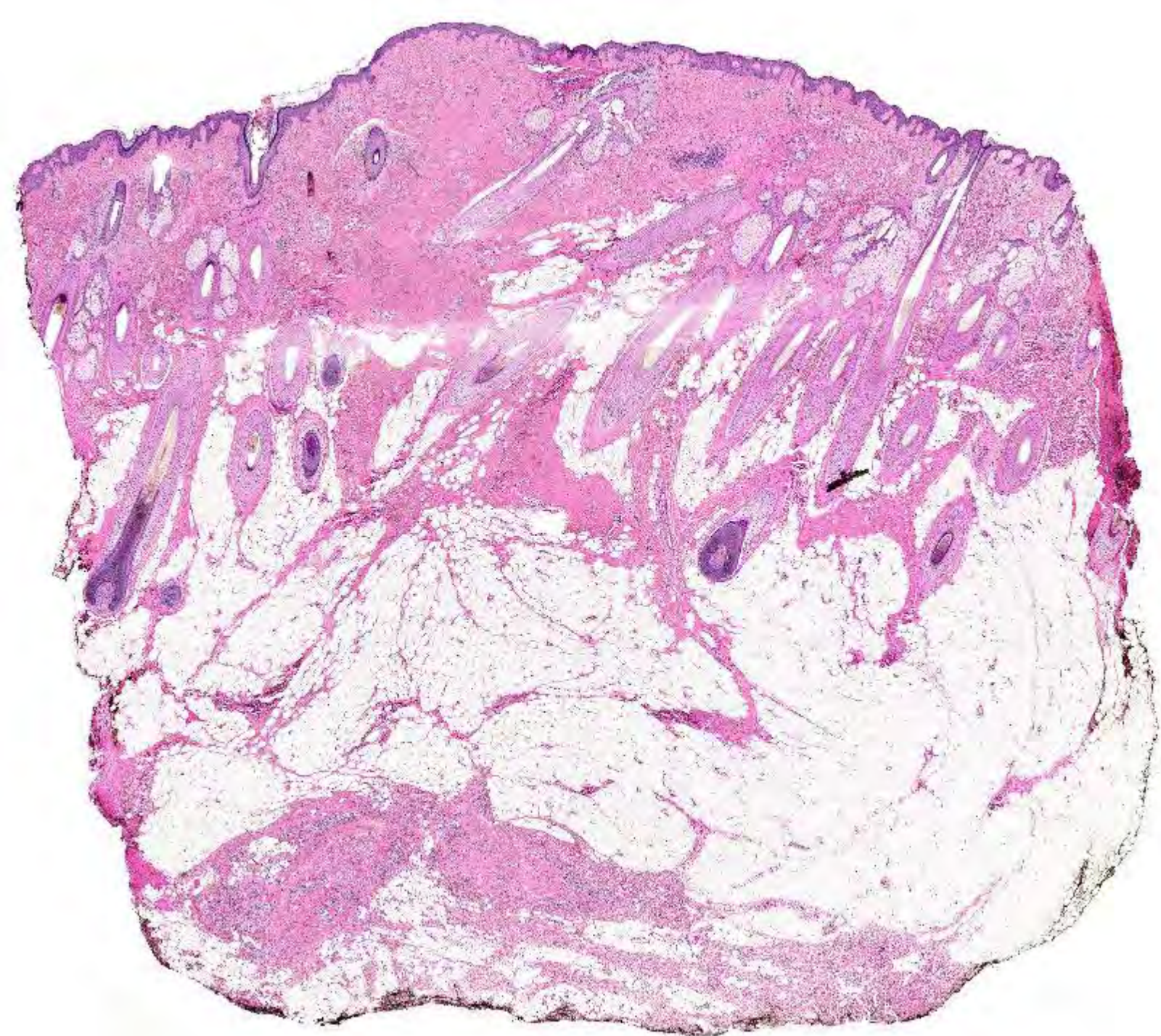
Collision of melanoma and basal cell carcinoma

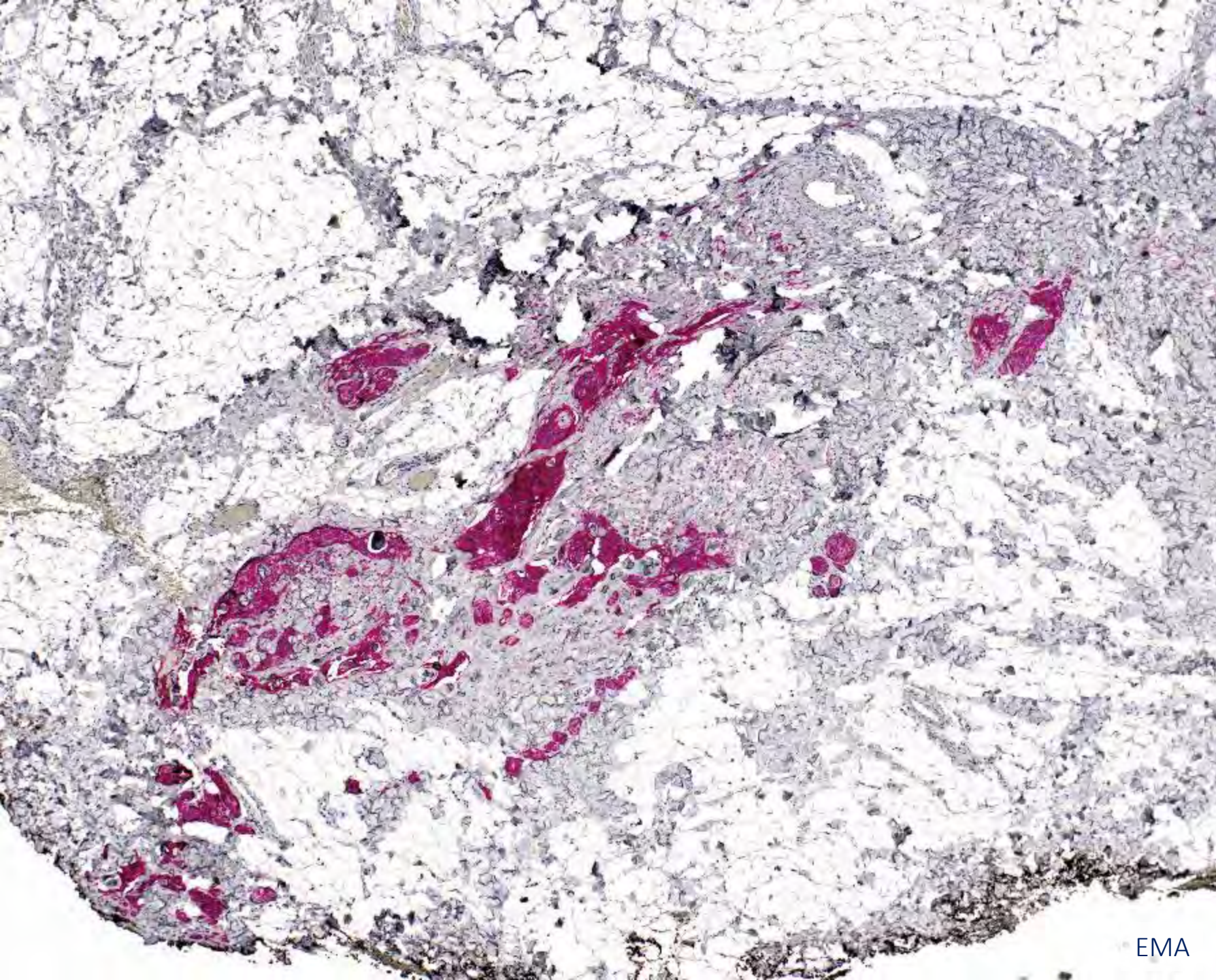
Melanocytic proliferation beyond the complexes of the basal cell carcinoma



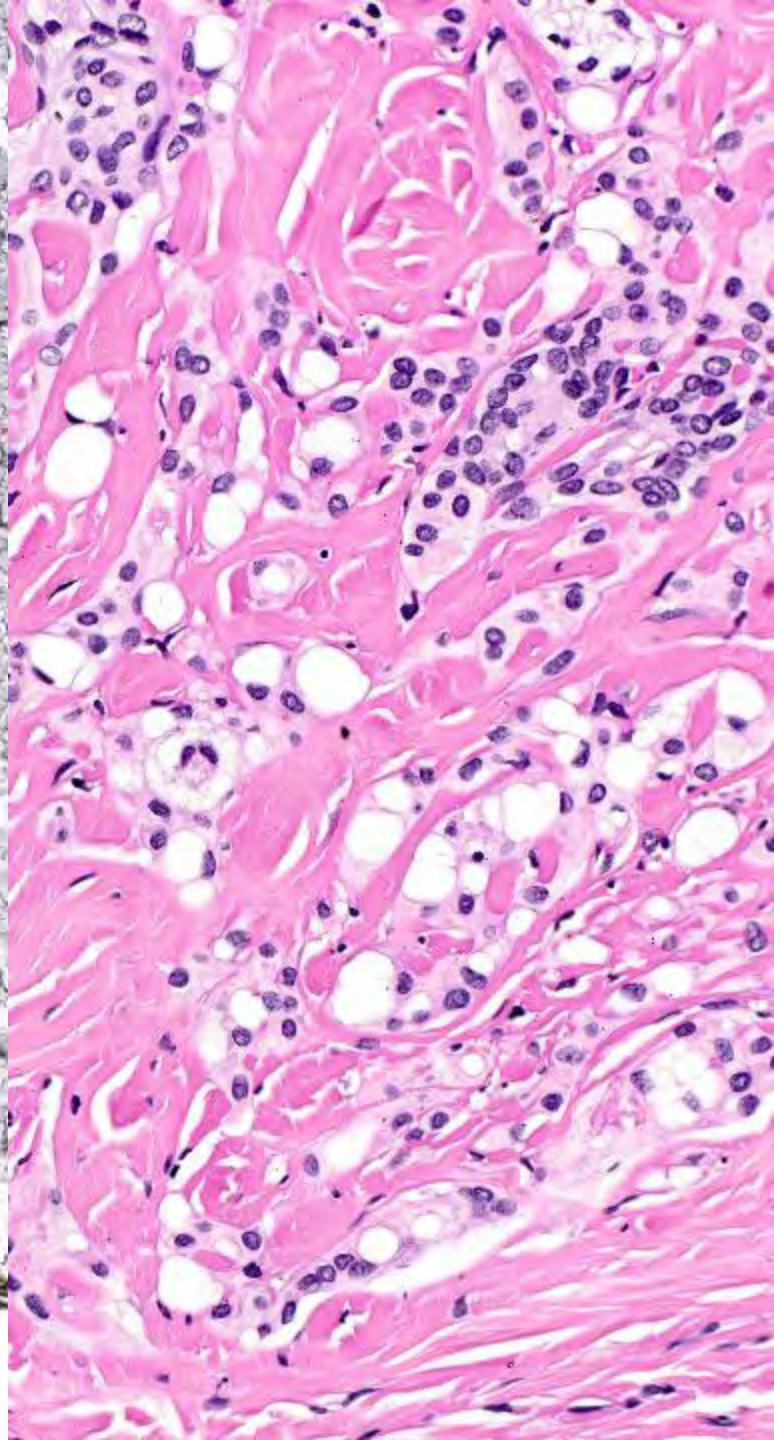
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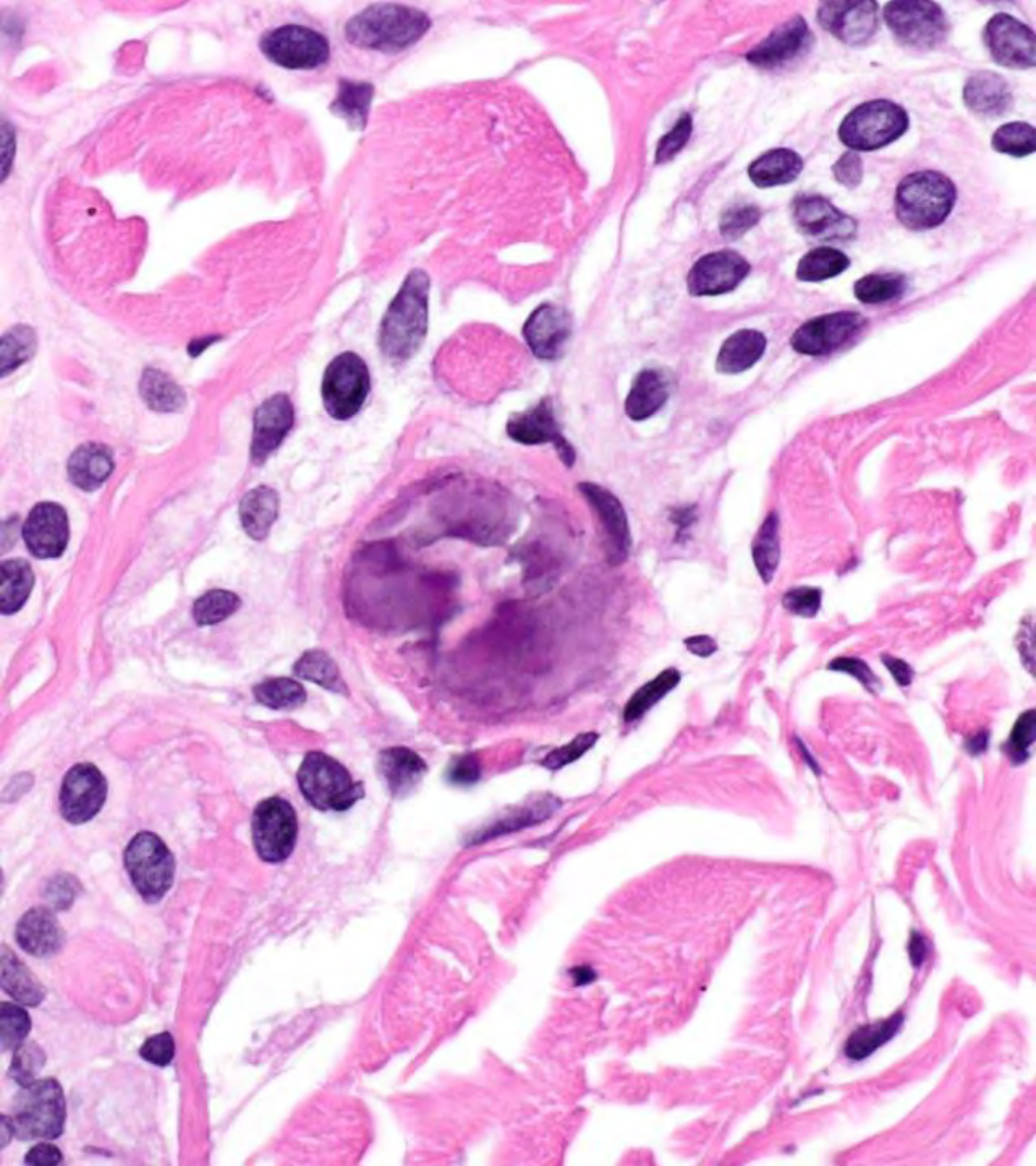
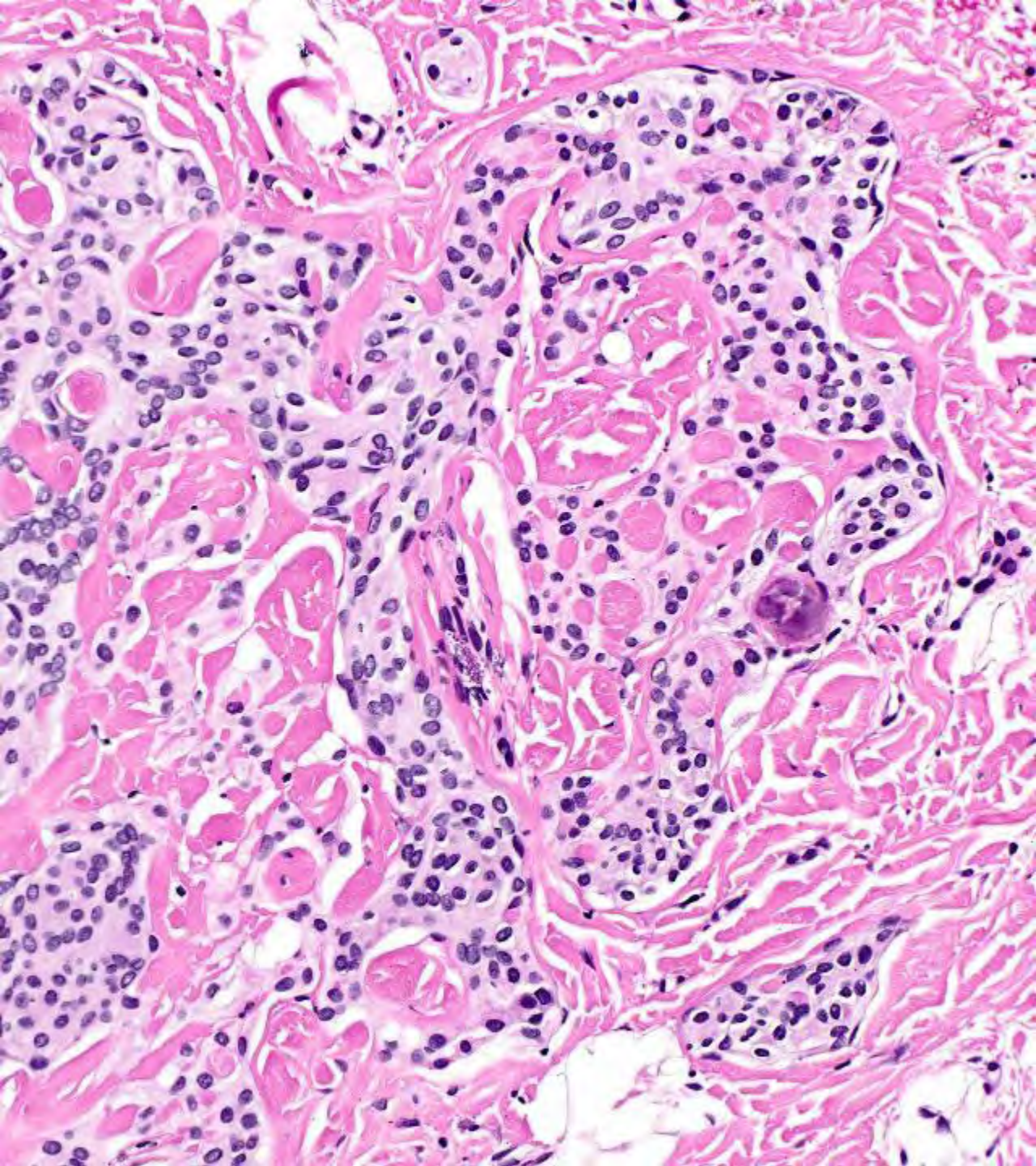
F, 19. Recurrent tumor on the scalp. A previous biopsy was diagnosed as desmoplastic trichoepithelioma.

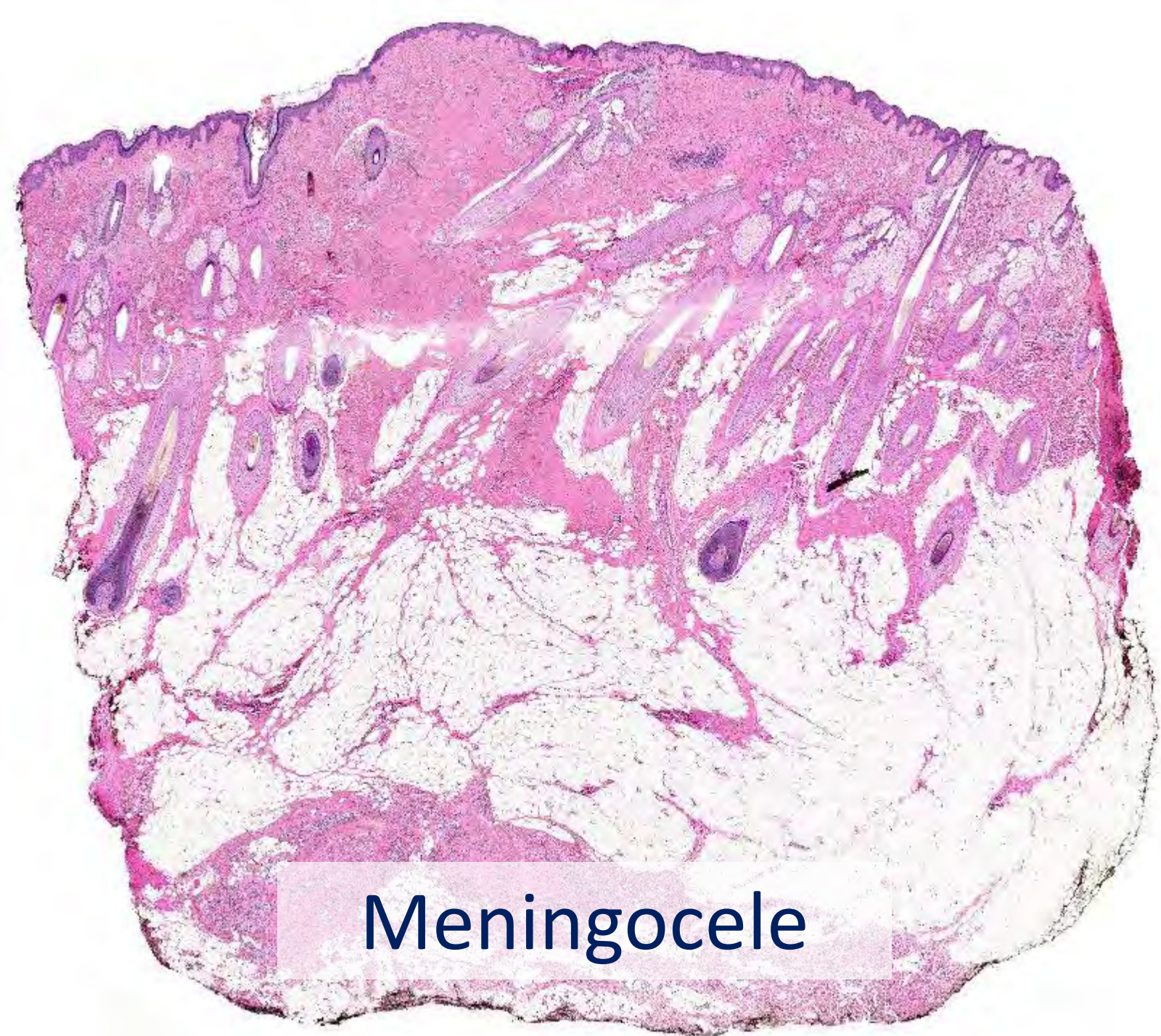




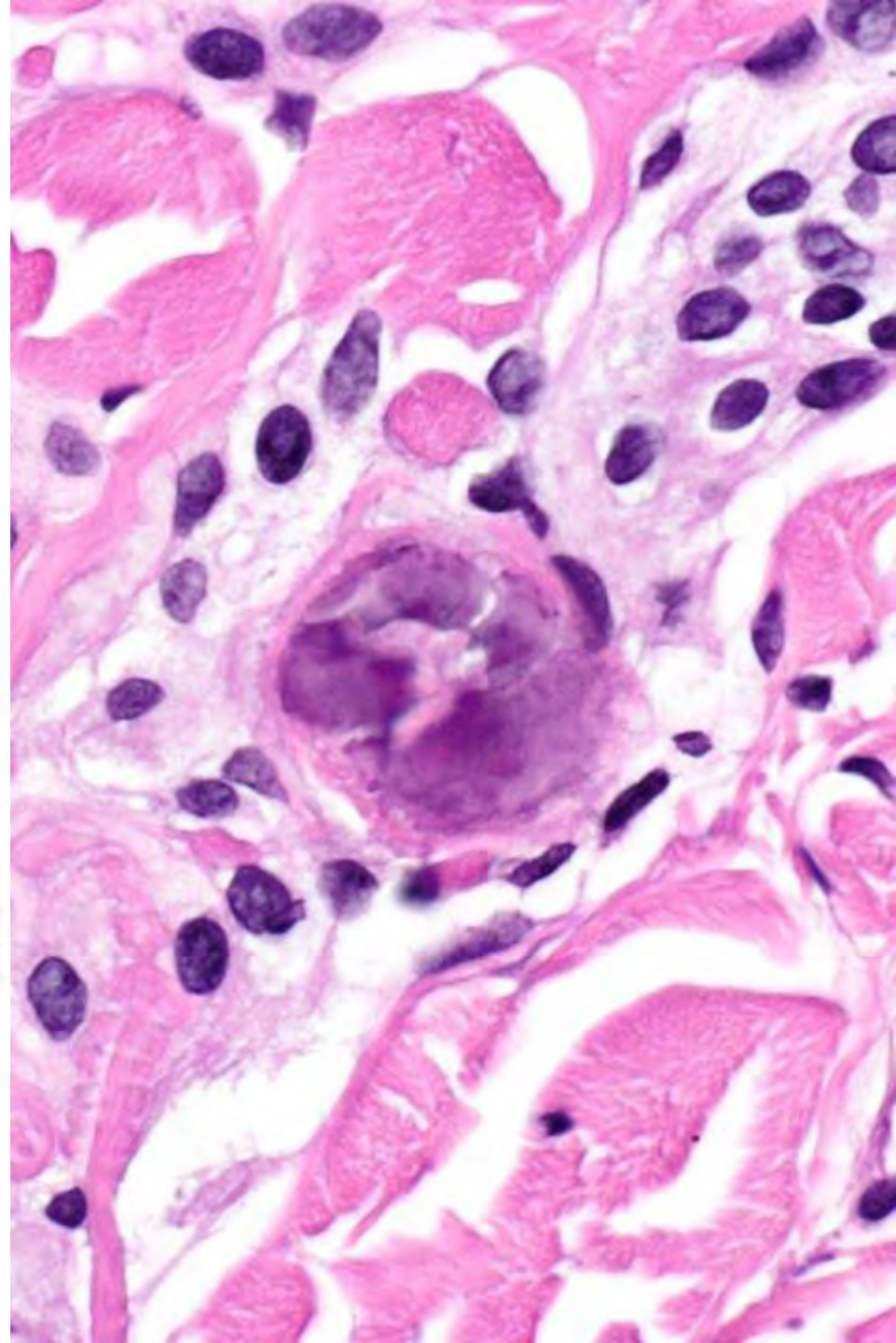
EMA







Meningocele



Neural heterotopias & related tumors

Abnormalities of the cerebrospinal axis, mostly due to abnormal closure of the neural tube and its associated components

Three major histopathological manifestations of neural heterotopia to the skin: meningeal, neuroglial, neuroblastic / ganglionic

Heterotopic meningeal tissue:

- **Meningocele** (herniation of the meningeal linings) (*described in the past as cutaneous meningioma, hamartoma of the scalp with ectopic meningotheelial elements, sequestered meningocele, acolic meningeal hamartoma, cutaneous heterotopic meningeal nodules*)
- Meningiomas (autonomous proliferations of displaced meningotheelial cells)
 - Meningiomas of type I: arachnoid lining cells displaced during embryogenesis
 - Meningiomas of type II: along the course of cranial nerves
 - Meningiomas of type III: cutaneous metastasis or direct extension of primary meningiomas of the arachnoid lining

Meningoceles, meningocele, and encephaloceles: a neuro-dermatopathologic study of 132 cases

Because there have been few comprehensive histopathologic studies of meningocele and related malformations, we undertook a systematic study of these lesions. One hundred and thirty-two cases were obtained from our surgical pathology files; these included 38 meningoceles, 71 meningocele, and 23 encephaloceles. Tissue sections were stained with hematoxylin and eosin; special stains included trichrome, alcian blue, Fontana-Masson, Nissl, Holzer, and immunoperoxidase for glial fibrillary acidic protein. Epithelial changes included ulceration, atrophy, or nevoid hyperplasia of the epidermis, and loss of appendages. Mesodermal features included fibrous zones resembling dura, subarachnoid tissue or scar (99% of cases), increased numbers of blood vessels (83%), hypertrophy of arrector pili muscle (42%), lipoma formation (38%), and immature skeletal muscle fibers (5%) that rarely intermingled with neuropil-like matrix. The latter tissue was identified in 71% of cases and included neurons, astrocytes, oligodendroglia, and ependyma. Forty-eight percent of cases included peripheral nerve fibers or roots, and some fibers formed onion bulb or Pacinian corpuscle-like structures. Meningothelial cells were observed in 26% of cases and sometimes formed recognizable whorls. Choroid plexus was noted in 3 cases, one example showing an unusual dystrophic calcification that formed long parallel spicules. Pigmented dendritic cells were observed within zones of fibrous tissue in 10% of cases. These malformations involve complex arrangements of ectodermal, neuroectodermal, and mesodermal elements. Because they may be encountered by dermatopathologists, familiarity with the microscopic features of dysraphic lesions is essential.

Berry AD, Patterson W. Meningocele, meningocele, and encephalocele: a neuro-dermatopathologic study of 132 cases. *J Cutan Pathol* 1990; 18: 164-177.

Dysraphic conditions of the spine and calvarium resulting from non-closure of the neural groove consist of several different types of malformations ranging in severity from incidental findings of no clinical significance to severe defects that are incompatible with life. Such lesions, when they involve the spinal cord, are called *spina bifida* and consist of a combination of malformations involving ectoderm and mesoderm (Fig. 1). They have been divided into several types. 1) *Spina bifida occulta* consists of nonclosure of the vertebral arches without any visible external

defect, and most frequently affects the 5th lumbar and 1st and 5th sacral segments (1-3). In this malformation, the spinal cord remains completely within the spinal canal and may be otherwise normal or abnormal. 2) *Spina bifida cystica* is a defect usually characterized by a cystic lesion (4). There are two subtypes of *spina bifida cystica*. The first, designated *meningocele*, involves herniation of the dura and arachnoid through a defect in the vertebral lamina, with the spinal cord remaining within the spinal canal. In the second type of *spina bifida*

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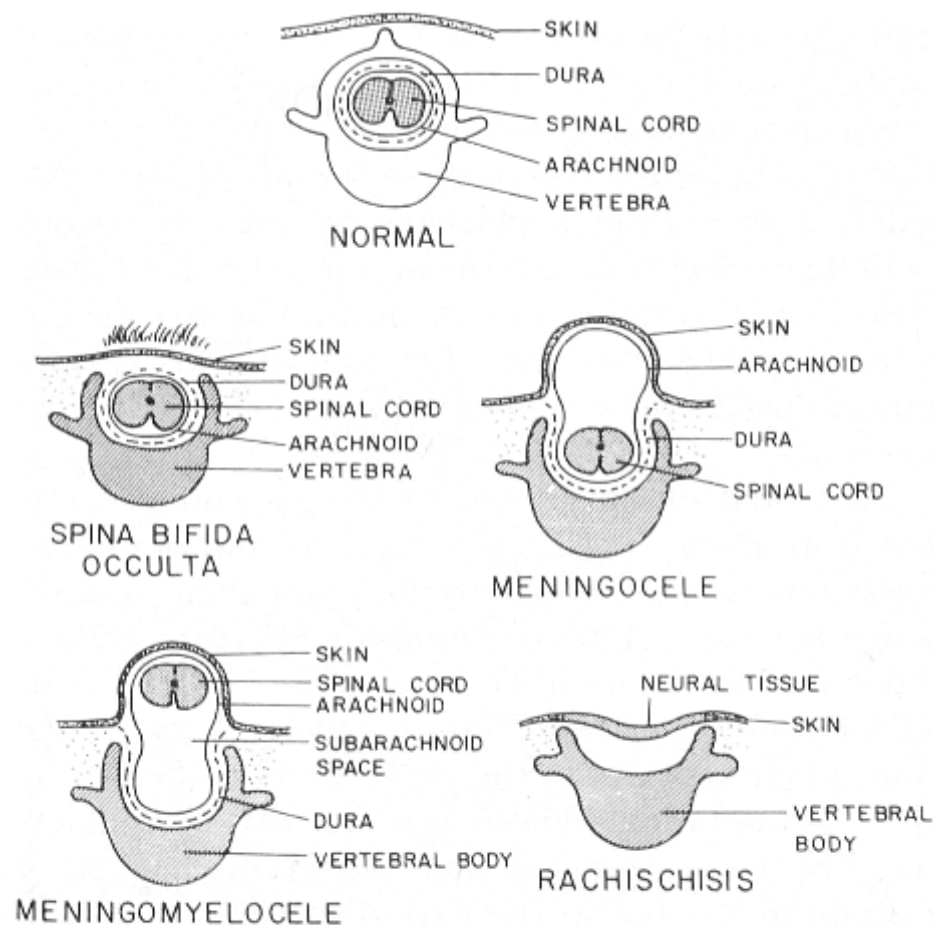


Fig. 1. Cross sectional diagram of spinal dysraphic conditions (modified from Sadler T (ed), *Langman's Medical Embryology*, 3rd ed, Williams and Wilkins Co, Baltimore, 1975, p. 345, with permission of the editor and publisher).

Neural Tube Dysraphism: Review of Cutaneous Markers and Imaging

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Abstract: Neural tube dysraphisms are congenital anomalies resulting from impaired formation of structures along the craniospinal axis during central nervous system development. When these malformations are large or lack a skin covering, they are easily recognized, whereas smaller or skin-covered malformations may not be readily apparent. Due to the intimate embryologic origin of the skin and nervous system, these occult malformations are often heralded by associated cutaneous abnormalities. In this article, the common clinical presentations and cutaneous markers of craniospinal dysraphism are reviewed, along with the recommended imaging modalities.

Neural tube dysraphisms (NTDs) represent a broad spectrum of congenital anomalies resulting from impaired formation of structures along the craniospinal axis during development of the brain and spinal cord. Their multifactorial etiology includes genetic and environmental factors, and they may occur in isolation or as part of a syndrome or chromosomal disorder. The nomenclature and classification of NTDs is variable and often confusing. Broadly, they may be classified as open when neural tissue is exposed, without a skin covering (e.g., anencephaly, myelomeningocele) or closed when there is skin covering the neural defect. These malformations range in severity from clinically insignificant minimally lethal. Open or severe hemiation defects are readily diagnosed and within the purview

of pediatric neurosurgeons. This discussion is limited to the closed or smaller herniation defects that may present to dermatologists and are often heralded by associated cutaneous stigmata.

EMBRYOLOGICAL REVIEW

Neural tube development occurs during weeks 2 to 6 of gestation and proceeds through a complex, multi-step process (1–4). There is still a great deal unknown about the formation of the neural tube and the mechanism of associated defects. Craniospinal dysraphism results from defects in this process that lead to impaired formation of paraxial mesodermal, neuroectodermal, or neuroectodermal structures. A general knowledge of this process allows for a better understanding

TABLE 1. Cranial Dysraphism

	Cephalocele	Meningeal heterotopia	Neuroglial heterotopia	Dermoid cyst
Location	Occipital,* parietal, temporal, anterior	Occipital,* parietal,* anterior	Anterior (nasal),* occipital, parietal	Embryonic fusion lines (lateral eyebrow*), neural axis
Appearance	Soft, compressible nodule; skin-colored or blue, glistening	Firm, noncompressible nodule; skin-colored or blue, glistening	Firm, noncompressible nodule; skin-colored or red-blue	Very firm nodule; skin-colored or bluish; may have associated sinus with protrusion of hair tuft
Skull defect	+	— (May have fibrous stalk)	— (May have fibrous stalk)	+/— (if intracranial connection or bony erosion)
Patent intracranial connection	+	—	—	+/— (possible if along neural axis)
Enlarges with intracranial pressure	+	—	—	—

*Most common location.

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Rudimentary meningocele: a variant of "primary cutaneous meningioma"

Sibley DA, Cooper PH. Rudimentary meningocele: a variant of "primary cutaneous meningioma". J Cutan Med Biol 1989; 16: 72-80.

We studied 5 primary cutaneous meningiomas. All were congenital. Four were nodules or plaques on the scalp, and one was a lumbar polyp. Two were alopecic. A skull defect was present deep to one lesion, and the lumbar polyp was attached to dura. The tumors were concentrated in the subcutis, where strands of meningocytes were embedded in dense collagenous tissue. Meningocytes wrapped around collagenous fibers, producing "collagen bodies". These formed the nidus for calcification that included psammoma bodies. Meningocytes also dissected between collagenous fibers, creating anastomosing spaces that mimicked a vascular tumor. Meningothelial-lined clefts, several millimeters in length, were present in 4 cases. Two lesions extended through dermal defects into the superficial dermis, where adnexa were reduced or absent. The meningocytes contained vimentin and epithelial membrane antigen. They lacked cytokeratin, S100 protein, and endothelial markers. The meningothelial lesions described herein lack the nodular and sheet-like growth patterns that typify meningiomas of the central nervous system and most primary ectopic meningiomas, including some that develop within the skin. They appear closely related to meningoceles and should be viewed as developmental abnormalities rather than neoplasms. The term "rudimentary meningocele" seems appropriate for these lesions.

Meningiomas account for 15% of surgically treated neoplasms of the central nervous system (CNS) (1). They typically occur during the middle decades of life. Meningiomas are rare in childhood, and congenital meningiomas are exceptional (1). A cellular proliferation with the cytologic features of arachnoid cap cells is fundamental to the diagnosis. The usual growth patterns include multinodular masses and sheets of cells. An additional distinctive feature is the tendency of the meningocytes to wrap themselves about one another, forming nests of concentrically arranged cells known as meningothelial whorls. They also wrap about and isolate virtually any other structure they encounter (1). Ultrastructurally, meningocytes exhibit interdigitating cell membranes, desmosomes, and intermediate cytoplasmic filaments. Immunohistochemical studies indicate that the cells contain vimentin (2-4) and epithelial membrane antigen (2-3). Cytokeratin is

also present in some (2, 3, 5), and possibly most (4), meningiomas.

There are a number of settings in which meningioma occurs outside the CNS (ectopic meningioma) (1, 6-11). These can be divided into 3 categories: (1) *direct extension* of a CNS meningioma into adjacent soft tissue, often through bone or bony foramina; (2) *metastatic* meningioma; and (3) *primary ectopic* meningioma. Primary ectopic meningiomas can arise from arachnoid cells that accompany cranial nerves as they exit the CNS; such tumors have a predilection for soft tissues of the orbit, ear, and neck. Other primary ectopic meningiomas, of less certain origin, develop in the soft tissues of the head and rarely at sites more remote from the CNS. Each of the 3 categories of ectopic meningioma can involve the skin (1, 12-16). Such cutaneous involvement is invariably acquired and has the microscopic appearances of conventional meningioma.

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"The meningothelial lesions described herein lack the nodular and sheet-like growth patterns that typify meningiomas of the central nervous system and most primary ectopic meningiomas, including some that develop within the skin. They appear closely related to meningoceles and should be viewed as developmental abnormalities rather than neoplasms. The term "rudimentary meningocele" seems appropriate for these lesions."

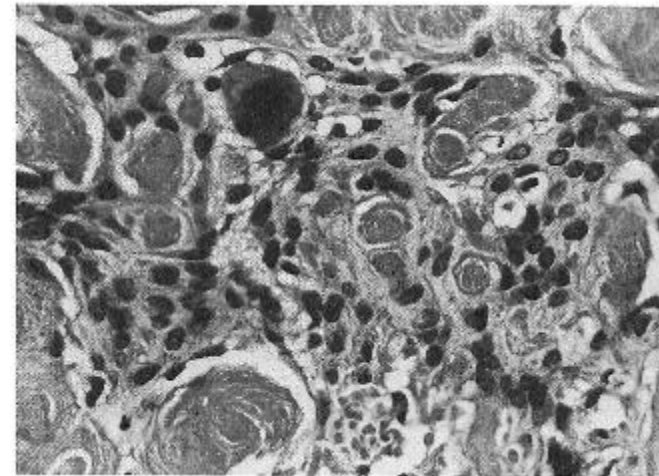


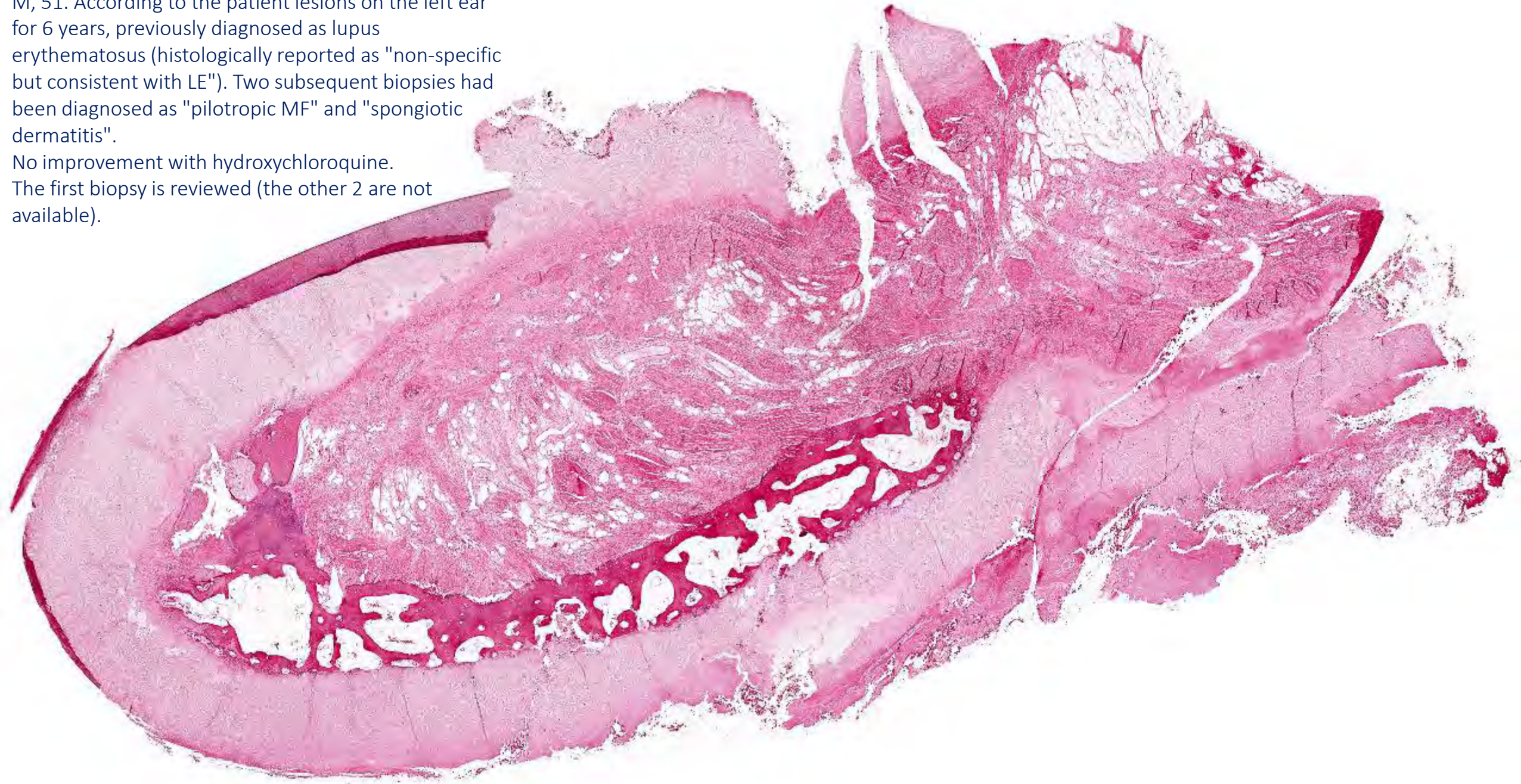
Fig. 3. Meningocytes have light eosinophilic cytoplasm, indistinct cell borders, and numerous ovoid nuclei. Note the presence of collagen bodies, one of which is calcified (H&E, ×500).

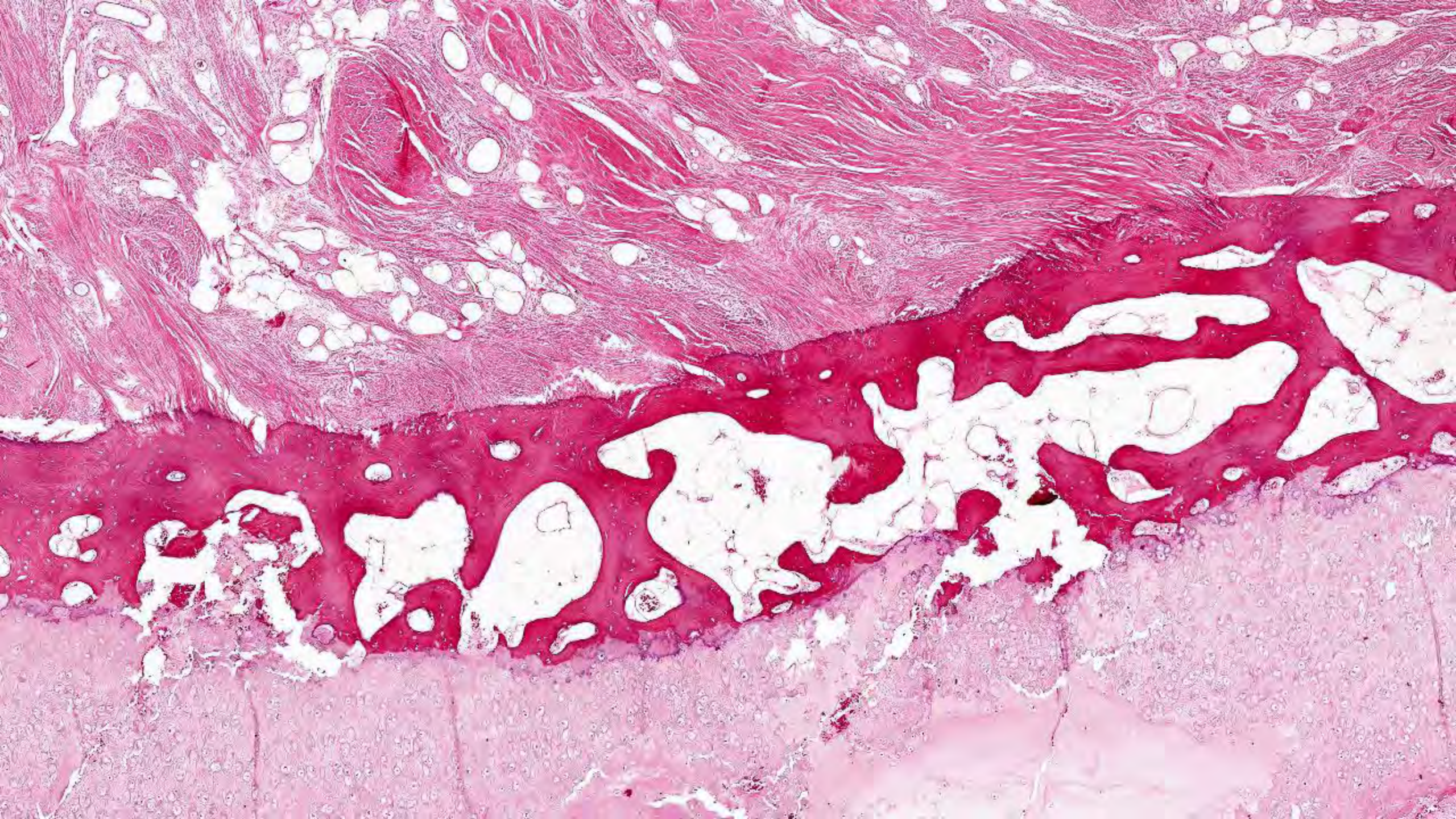
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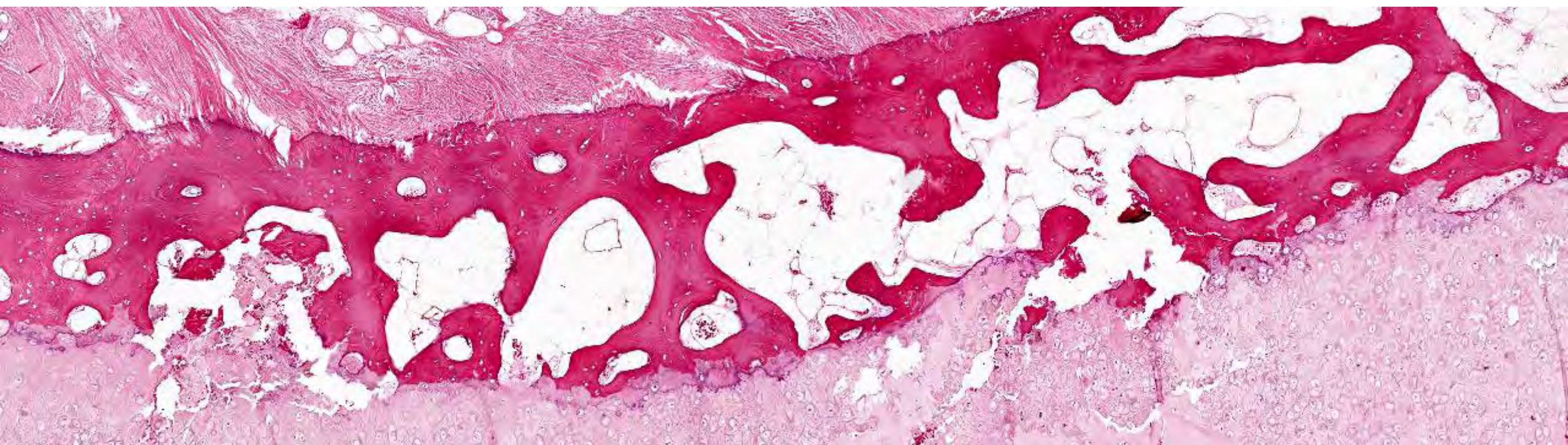
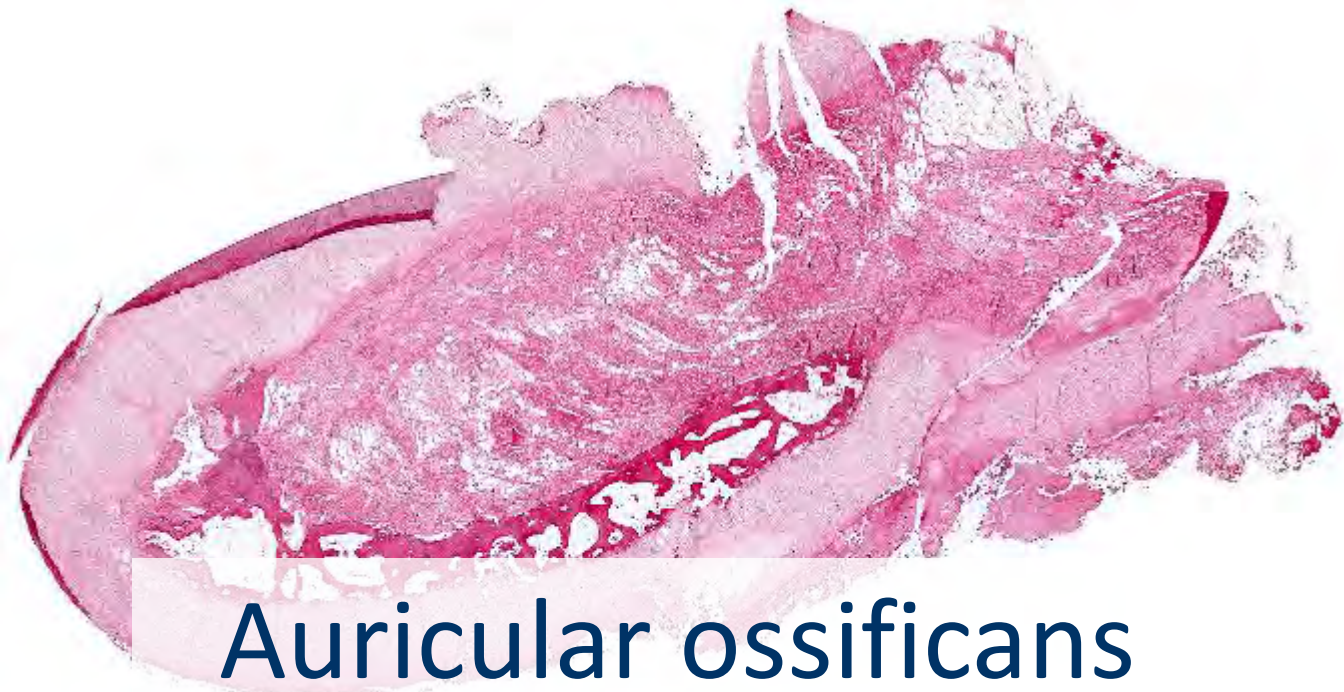
M, 51. According to the patient lesions on the left ear for 6 years, previously diagnosed as lupus erythematosus (histologically reported as "non-specific but consistent with LE"). Two subsequent biopsies had been diagnosed as "pilomatricoma" and "spongiotic dermatitis".

No improvement with hydroxychloroquine.

The first biopsy is reviewed (the other 2 are not available).







Auricular ossificans (ectopic ossification of the auricle)

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The petrified auricle is an unusual clinical entity in which the ear becomes partially or totally rigid, which may result from local trauma, inflammation, or systemic diseases. This process is most commonly associated with ectopic calcification, but rarely, ossification is responsible. Severe hypothermia (frostbite) is the most common cause of auricular ossification. Only 9 cases of histologically proven ossification of the ear have been reported in the English-language literature. Because of its rarity, there is a paucity of articles addressing its treatment. We report a case of unilateral auricular ossificans related to or secondary to cold injury. Ectopic ossification was detected on both radiologic and histologic examinations. The previously reported cases are reviewed and possible causative factors are discussed. (*J Am Acad Dermatol* 2003;49:142-4.)

The petrified auricle is an uncommon clinical entity in which the ear becomes rigid, usually from ectopic calcification and, rarely, ossification. This may result from injurious processes including frostbite, physical trauma, and inflammatory conditions. It is also associated with various endocrinopathies.

Auricular ossificans (ectopic ossification) is a rare phenomenon in which the rigidity of the petrified ear is a result of replacement of the cartilage by bone. Since the first description of petrified auricles by Boeck-Welch in 1905, fewer than 160 cases have been reported. Of these, only 9 were shown histologically to represent ectopic bone formation.

We report a case of unilateral auricular ossificans secondary to severe hypothermia along with a review of the literature.

CASE REPORT

A 65-year-old man presented with a 10-year history of gradual stiffening of the left ear. He had difficulty sleeping on the affected side, but was otherwise asymptomatic. While serving in the armed forces in the 1950s, he experienced several episodes of frostbite affecting his ears. He denied any history of boxing, wrestling, or other direct trauma. His medical



Fig 1. Technically damaged left ear with normal configuration.

and history was significant for hypertension, hypercholesterolemia, and diet-controlled diabetes mellitus.

On examination, the external ear was of normal configuration, and sensation to pinprick was appa-

Idiopathic Bilateral Auricular Ossificans

A Case Report and Review of the Literature

Brinley A. Lipp, MD, Matthew J. Lissner, MD, and E. Liang, MD

Petrification of the auricle results in a rigid and unmovable ear. The etiology of such a finding is usually ectopic calcification. The condition has been associated with injurious processes, such as cold injury, and with various endocrinopathies, including Addison disease. In a significant number of cases, ossification occurs without knowledge of the precipitating cause or event. True auricular ossification is a rare occurrence, with only 12 histologically confirmed cases in the literature. We herein present the clinical and pathologic findings of another case. A 60-year-old man with diet-controlled diabetes presented with a 10-year history of slowly and insidiously stiffened auricles. He denied any precipitating historical events. Routine testing did not demonstrate systemic abnormalities. Radiographic examination revealed opacities consistent with bony structure in the auricles of the ears, with the right more prominent than the left. Histologic sampling demonstrated ossification with deposition of trabecular bone in proximity to normal elastic cartilage.

(*Arch Pathol Lab Med*. 2004;128:1432-1434)

Petrification of the auricle, resulting in a rigid ear, is a uncommon occurrence. When observed, the etiology of such a finding is usually ectopic calcification, from auricular ossification, in which the normal cartilaginous structures of the ear are replaced by bone, as decidedly rare with only 12 histologically confirmed cases in the literature.^{1,2} Injurious processes, such as frostbite,^{3,4} physical trauma,⁵ and inflammation conditions,^{6,7} are known to precipitate such an event. The condition has

REPORT OF A CASE

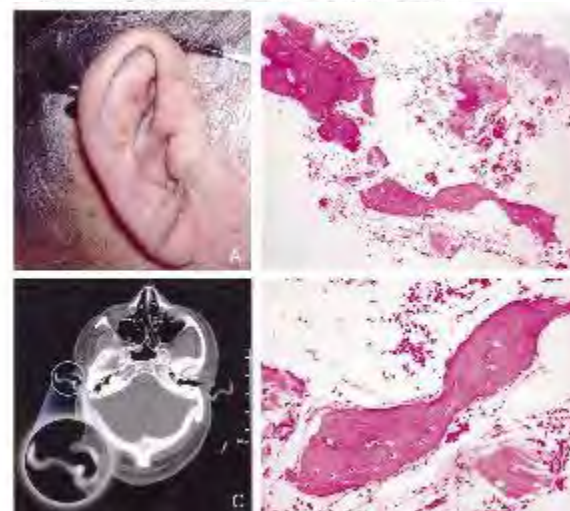


Fig 2. Left auricle is stiff (A). A computed tomography scan of the patient reveals opacities of the auricles and secondary ossification that is consistent with bony structure (B). The histologic specimen shows trabecular bone deposition in proximity to elastic cartilage (C).

Demographic Data of 13 Cases of Auricular Ossification

Source, y	Age, y/Sex	Bilateral Versus Unilateral*	Cause
Current case, 2004	60/M	R and L	Unknown
Stiles et al, ¹ 2003	65/M	L	Cold injury
Yearman and Varigos, ¹¹ 1998	66/M	R	Cold injury
Lautenschlager et al, ² 1994	66/M	R and L	Recurrent cold injury
Cohen et al, ³ 1991	46/M	R and L	Addison disease
Lari et al, ⁴ 1989	17/M	R and L	Trauma
Cohen et al, ⁵ 1989	70/M	R and L	Addison disease
DiBartolomeo, ⁶ 1985	77/M	R and L	Cold injury
	72/M	R and L	Cold injury
Lister, ⁷ 1969	58/M	R and L	Unknown
Gordon, ⁸ 1964	34/F	R and L	Perichondritis
Scherrer, ⁹ 1932	53/F	R and L	Unknown
Knapp, ¹⁰ 1890	24/M	Unilateral	Perichondritis

* R indicates right side; L, left side.

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Ulcerative colitis with autoimmune thyroid disease results in bilateral auricular ossification: a case

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ABSTRACT

Background: Patients with ulcerative colitis (UC) often exhibit comorbidities to autoimmune diseases such as Sjögren's syndrome, primary biliary cirrhosis, systemic lupus erythematosus, and rheumatoid arthritis. This case reports a patient from eastern polygenic autochthonous ancestry from the northern province. This paper highlights the occurrence of autoimmune thyroid disease during UC exacerbations. Finally, the present clinical practical analysis.

Case Summary

A 57-year-old male complained of recurrent diarrhea, pain, fatigue, hematochezia, and recurrent infection of 20 days. The diagnosis of UC was confirmed through sigmoidoscopy, histopathological examination, and stool flora. UC clinical conditions resulted bilateral osteopetrosis in his ears, which appeared to develop over an extended time frame. Imaging and histological examination substantiated the complex coexisting diagnosis while eliminating the possibility of other conditions. The present clinical case suggests a link between ulcerative colitis and ossification, which is hypothesized to result from local osteoclasts.

Conclusion: Our case report underscores the necessity of considering occurrence of the case (complications associated with UC) and the role of local osteoclasts in the pathogenesis of the disease. In addition, thyroid diseases in UC patients. It is imperative to test for thyroid-related antibodies locally and identify causes of local thyroid dysfunction.

1. Introduction

The etiology of ulcerative colitis remains elusive, yet emerging research posits that individuals with a genetic predisposition might exhibit an dysregulated immune response to commensal gut bacteria, precipitating mucosal inflammation [1]. Existing studies corroborate that genetic disposition, with numerous variants, confer a high risk of predisposition to coexistent immune-mediated disorders, encompassing autoimmune hepatitis, autoimmune thyroiditis, primary biliary cirrhosis, polymyositis, rheumatoid, and temporal arteritis. Our understanding of plausible epidemiological linkage among these ailments, perhaps attributable to a shared immunopathogenic mechanism. These conditions can either manifest simultaneously or occur in a sequential manner. The coexistence or sequential onset of multiple diseases might

reflect a common overlapping syndrome.

The coexistence of ulcerative colitis (UC) with autoimmune thyroid disease (AITD) is relatively rare in clinical practice. Autoimmune thyroid diseases (AITD) encompass Graves' disease (GD) and Hashimoto's thyroiditis (HT), posing significant clinical consequences (hyperthyroidism and hypothyroidism). AITD results from the interplay between multiple environmental factors, genetic predisposition, and epigenetic mechanisms. Immune dysfunction, leading to thyroid tissue damage, involves B lymphocytes, T lymphocytes, and regulatory T cells [2].

The concurrent coexistence of UC with GD or the exacerbation phase of Hashimoto's thyroiditis might exacerbate the incidence of osteoporosis, result in accelerated osteoporosis in affected individuals. The clinical course of both UC and AITD is closely linked, in which humoral immunity, with cell-mediated immune processes playing a



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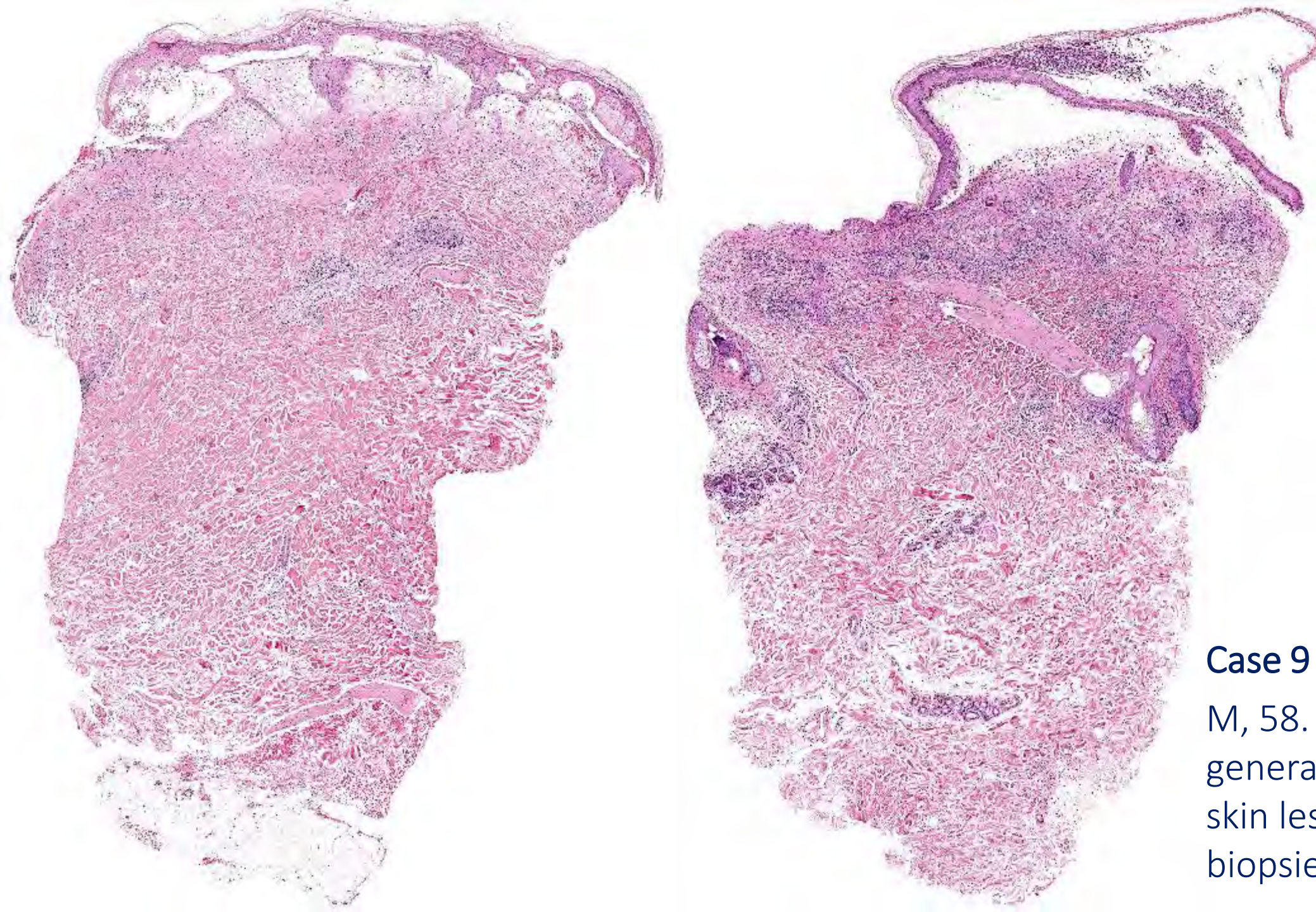
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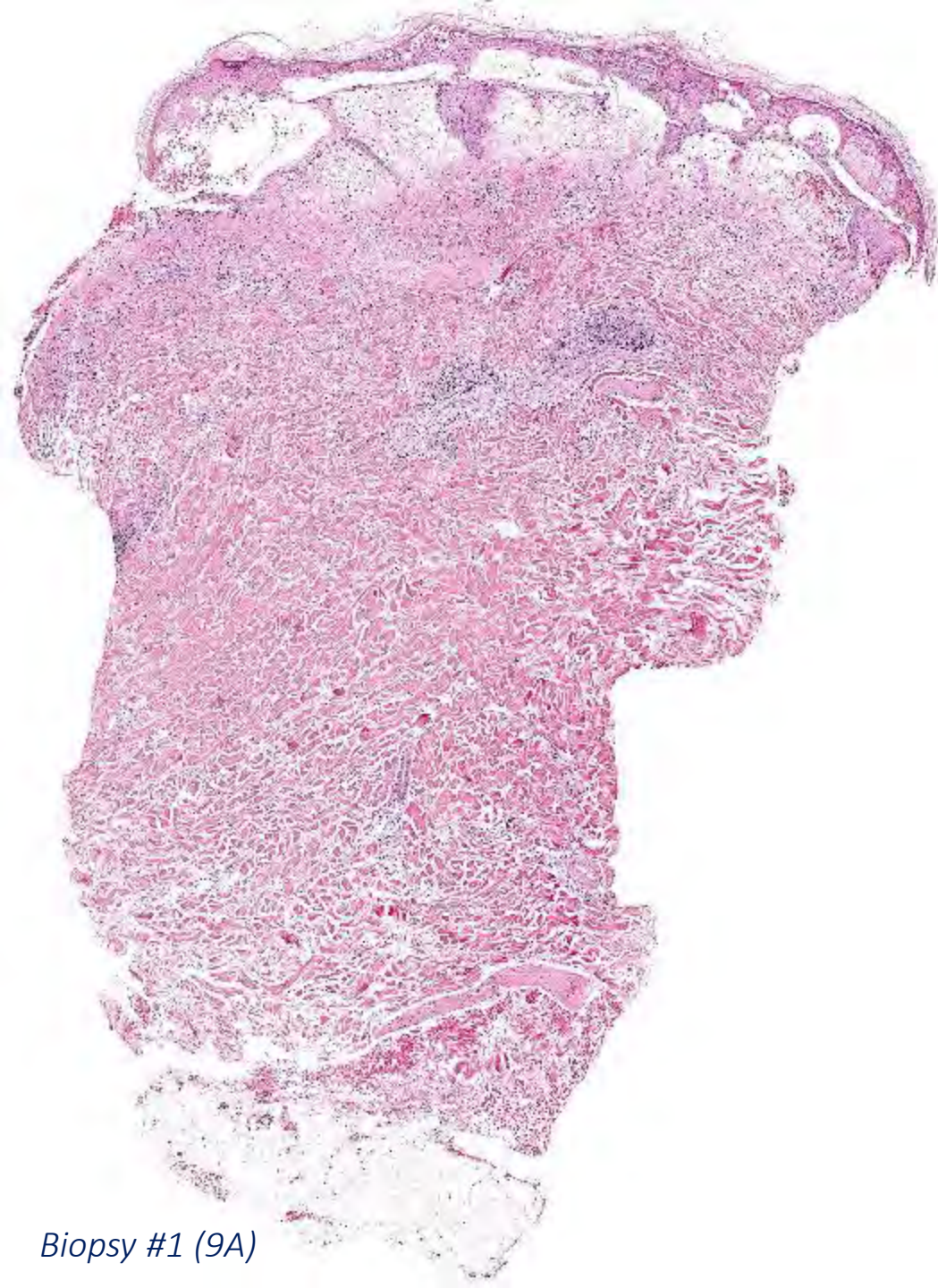
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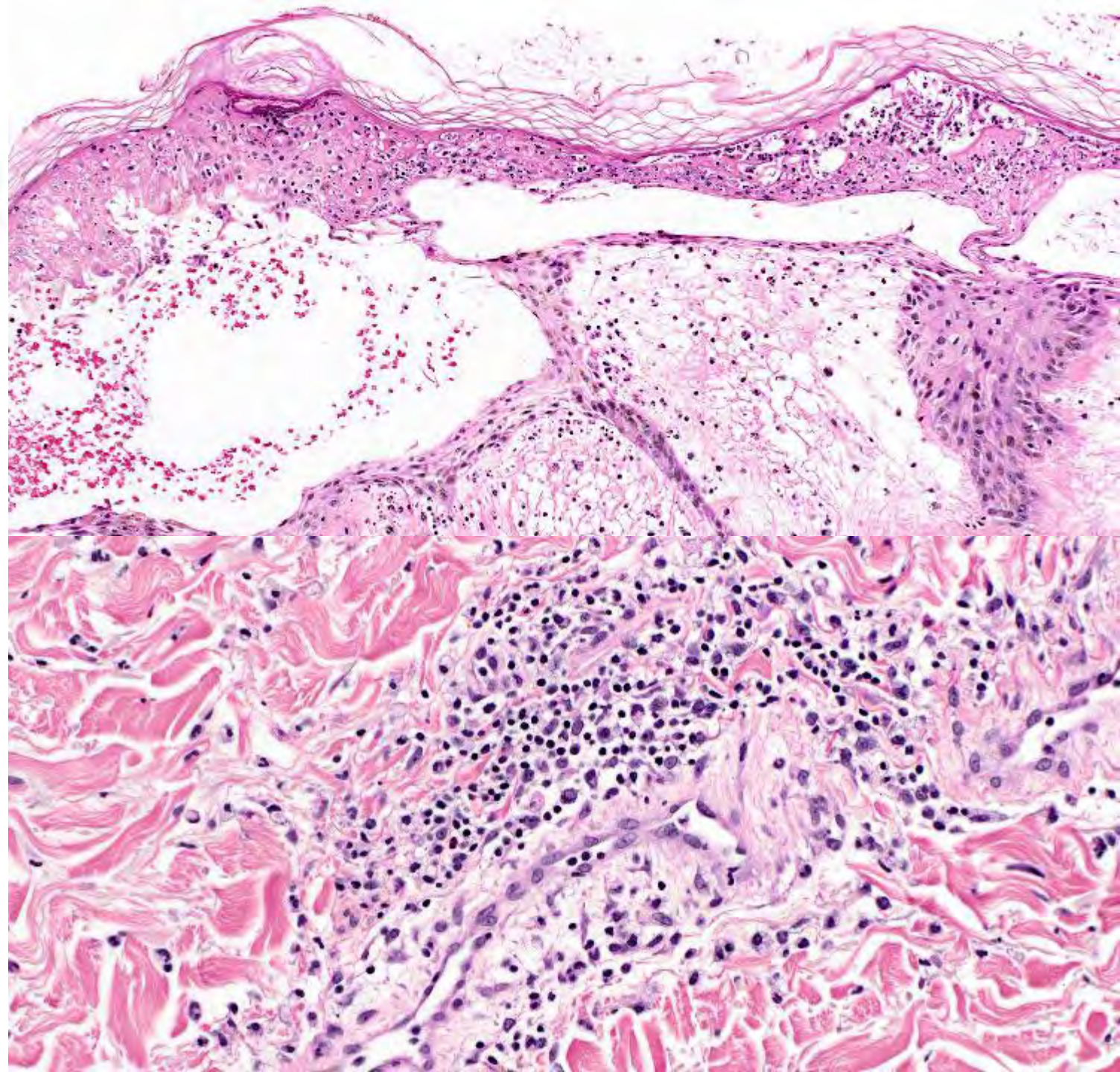


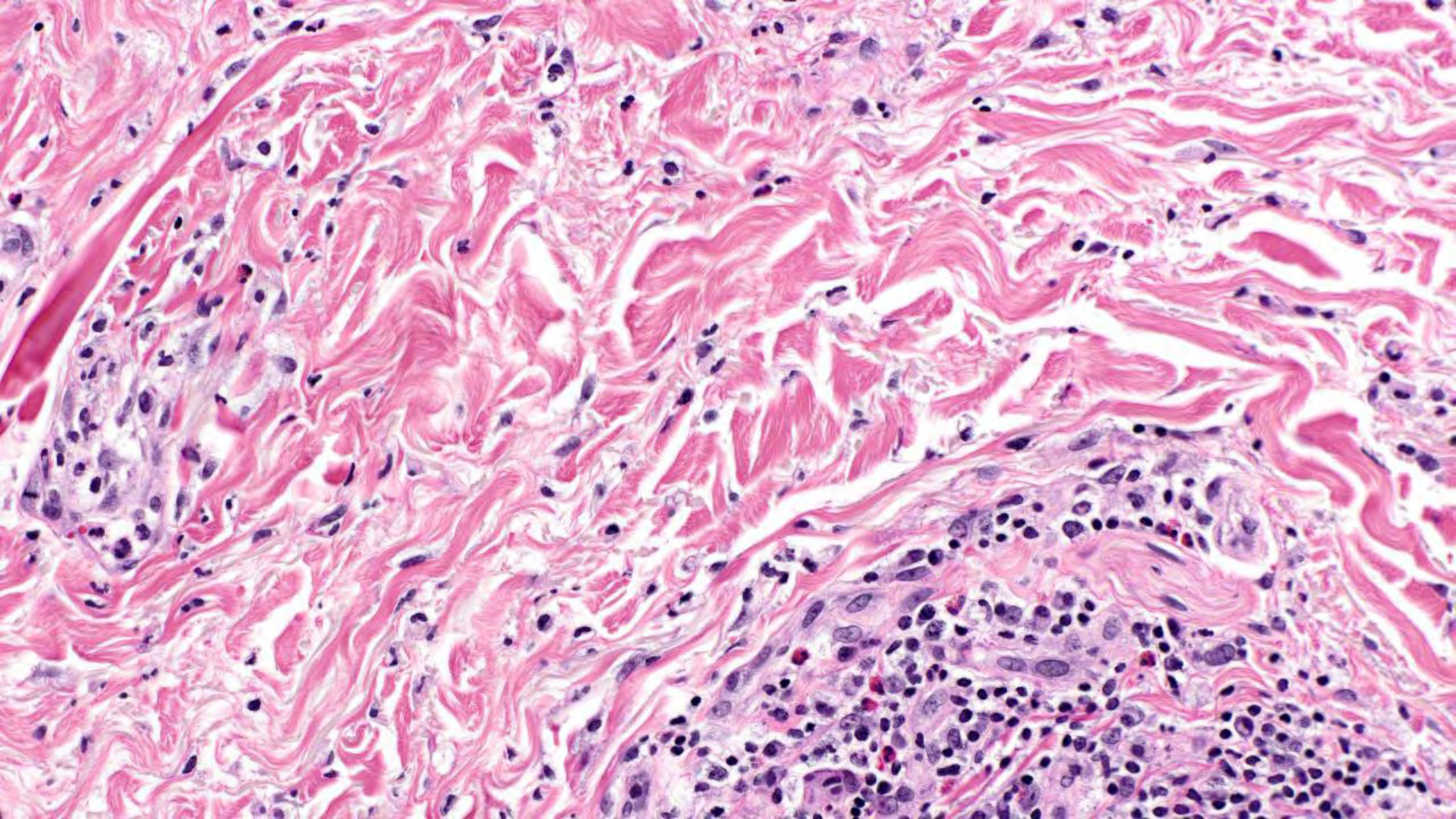
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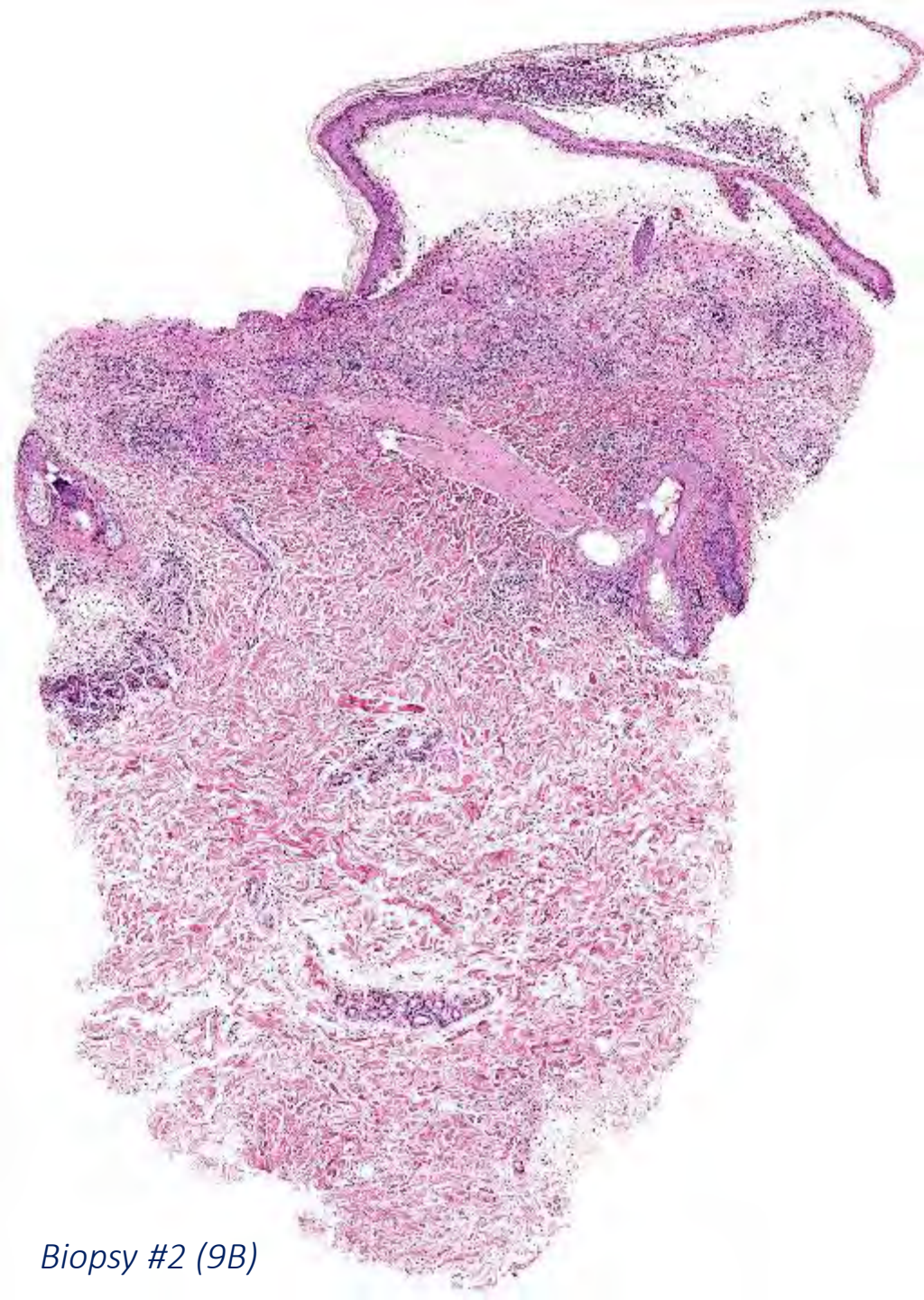
M, 58. Recent onset of generalized "Sweet-like" skin lesions (two biopsies).



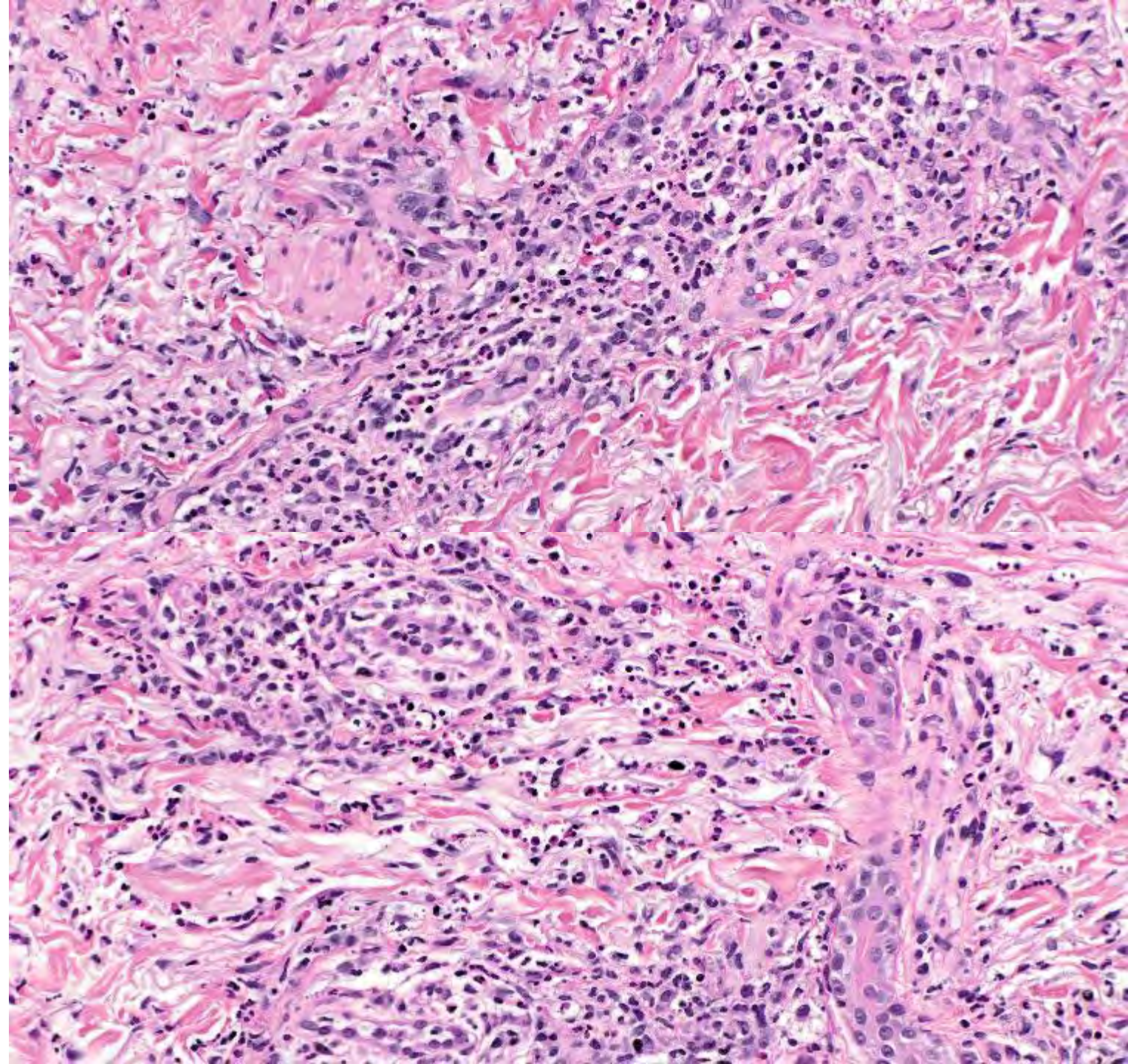
Biopsy #1 (9A)

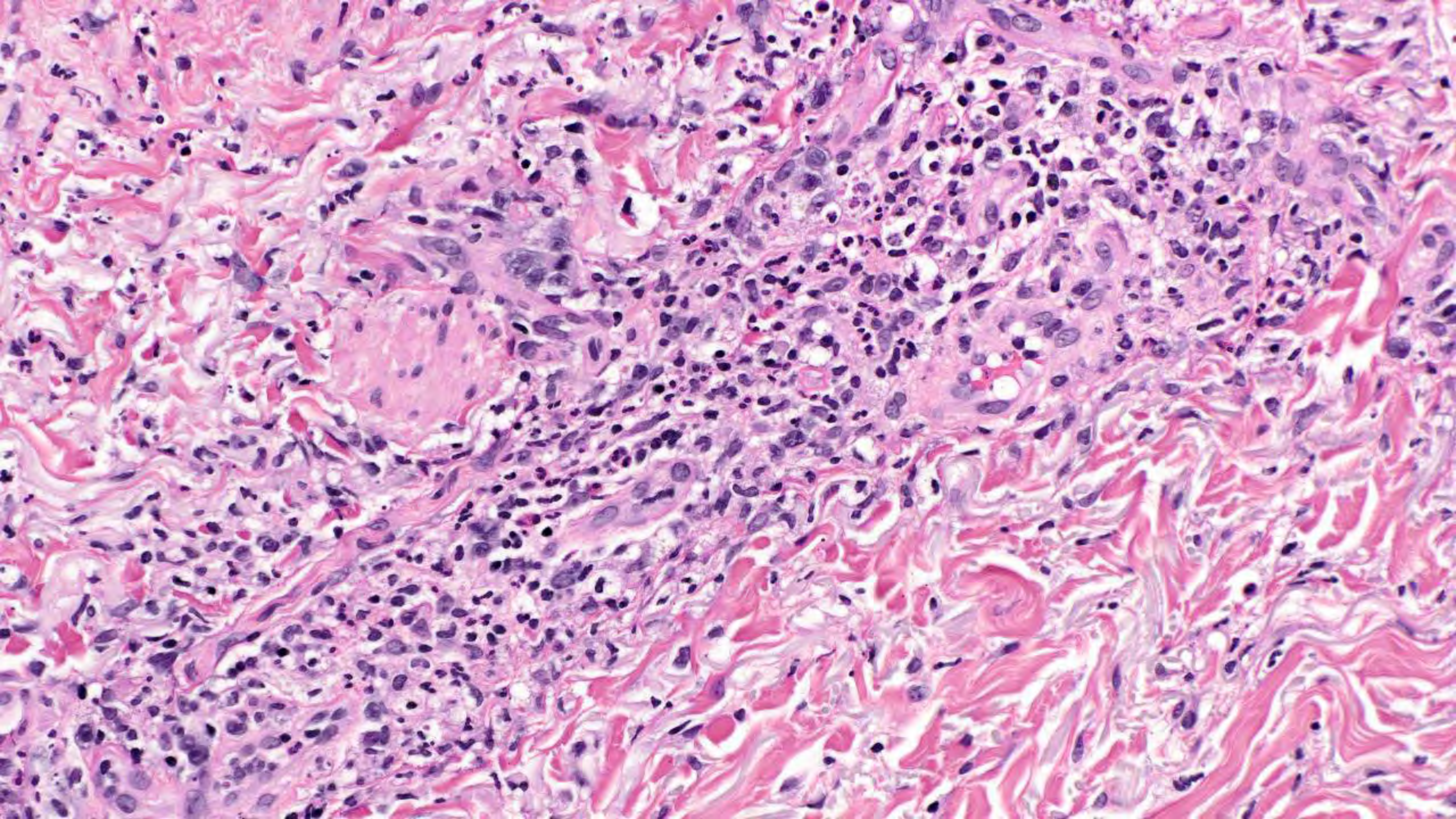


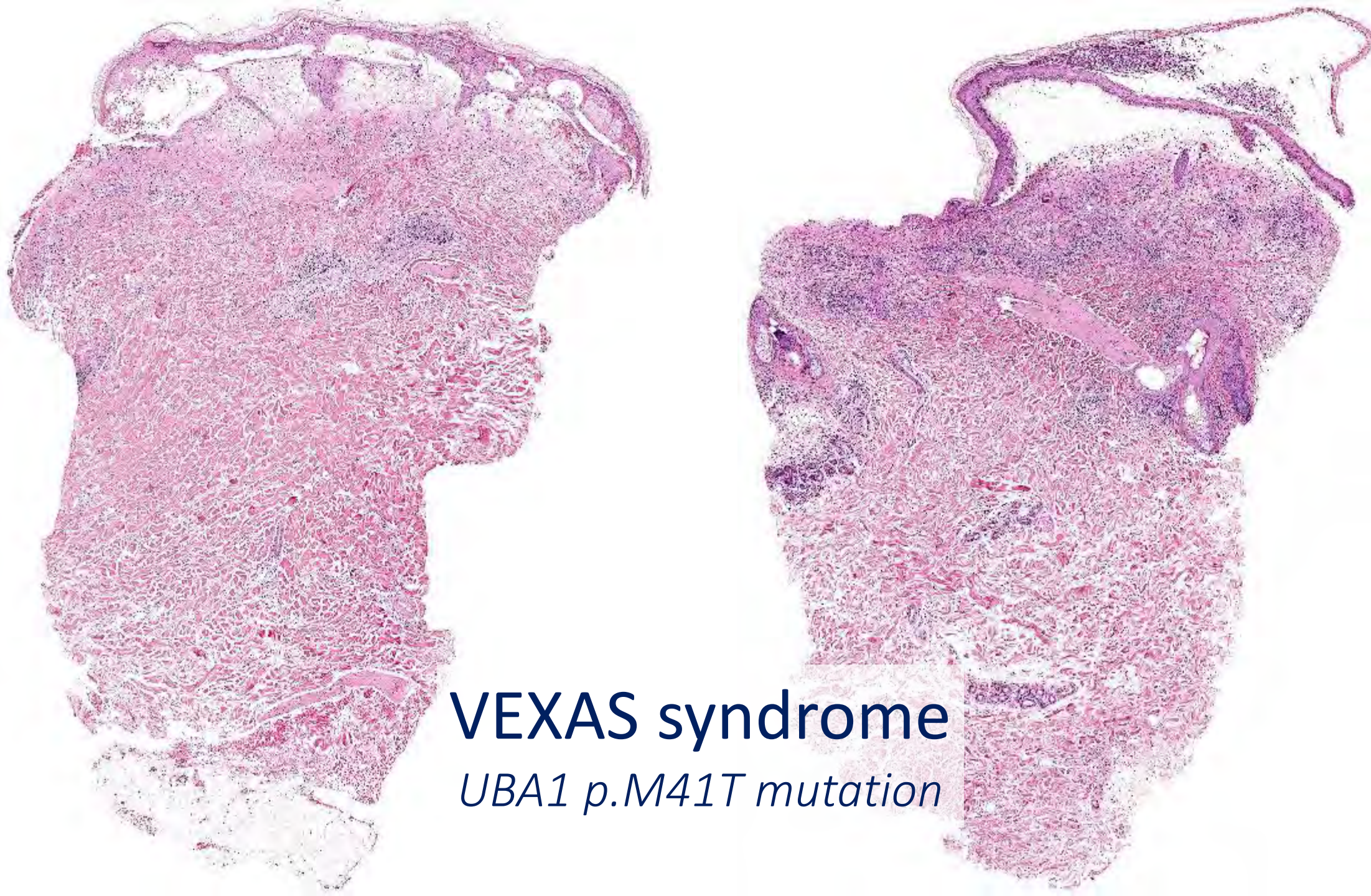




Biopsy #2 (9B)







VEXAS syndrome

UBA1 p.M41T mutation

VEXAS syndrome

- V** *acuoles*, in myeloid and erythroid progenitor cells within the bone marrow.
- E** *1 enzyme*, alterations of the ubiquitin-activating enzyme.
- X** *-linked*, *UBA1* gene is found on the X chromosome at Xp11.23.
- A** *utoinflammation*, as the resulting pathological process.
- S** *omatic*, i.e. mutations of the *UBA1* gene are not germline.

Mostly in males >50 presenting with glucocorticoid-dependent inflammation, neutrophilic dermatoses, chondritis and myelodysplastic features.

Considered as an autoinflammatory disorder.

Skin manifestations are common and an early feature of the disease (leukocytoclastic vasculitis, neutrophilic dermatoses including Sweet syndrome).

"Histiocytoid" cells frequently found in skin biopsies (e.g., histiocytoid Sweet syndrome).

Poor prognosis.

HEMATOPOIESIS AND STEM CELLS

CME Article

Spectrum of clonal hematopoiesis in VEXAS syndrome

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KEY POINTS

UBA1 mutations are primarily responsible for myeloid clonal expansion and both the inflammatory and hematologic phenotype in VEXAS.

Patients with VEXAS have an enrichment of typical CH mutations, particularly in DNMT3A and TET2.

Vasculitis, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is caused by somatic mutations in UBA1 (*UBA1*^{mut}) and characterized by heterogeneous systemic autoinflammation and progressive hematologic manifestations, meeting criteria for myelodysplastic syndrome (MDS) and plasma cell dyscrasias. The landscape of myeloid-related gene mutations leading to typical clonal hematopoiesis (CH) in these patients is unknown. Retrospectively, we screened 80 patients with VEXAS for CH in their peripheral blood (PB) and correlated the findings with clinical outcomes in 77 of them. *UBA1*^{mut} were most common at hot spot p.M41 (median variant allele frequency [VAF] = 75%). Typical CH mutations cooccurred with *UBA1*^{mut} in 60% of patients, mostly in *DNMT3A* and *TET2*, and were not associated with inflammatory or hematologic manifestations. In prospective single-cell proteogenomic sequencing (scDNA), *UBA1*^{mut} was the dominant clone, present mostly in branched clonal trajectories. Based on integrated bulk and scDNA analyses, clonality in VEXAS followed 2 major patterns: with either typical CH preceding *UBA1*^{mut}

selection in a clone (pattern 1) or occurring as an *UBA1*^{mut} subclone or in independent clones (pattern 2). VAF in the PB differed markedly between *DNMT3A* and *TET2* clones (median VAF of 25% vs 1%). *DNMT3A* and *TET2* clones associated with hierarchies representing patterns 1 and 2, respectively. Overall survival for all patients was 60% at 10 years. Transfusion-dependent anemia, moderate thrombocytopenia, and typical CH mutations, each correlated with poor outcome. In VEXAS, *UBA1*^{mut} cells are the primary cause of systemic inflammation and marrow failure, being a new molecularly defined somatic entity associated with MDS. VEXAS-associated MDS is distinct from classical MDS in its presentation and clinical course.



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KEY POINTS

- **UBA1 mutations are primarily responsible for myeloid clonal expansion and both the inflammatory and hematologic phenotype in VEXAS.**
- **Patients with VEXAS have an enrichment of typical CH mutations, particularly in DNMT3A and TET2.**

HEMATOPOIESIS AND STEM CELLS

Gutierrez-Rodriguez et al | *Blood* 2023;141:214-224

VEXAS: walking on the edge of malignancy

Luisa Malcovati, University of Pavia

In this issue of *Blood*, Gutierrez-Rodriguez et al analyze a large cohort of 80 patients with VEXAS syndrome for additional somatic mutations. Based on these findings, they reconstruct major patterns of clonal hierarchy and correlate the findings with clinical outcomes.¹

VEXAS (VEXAS: Systemic Inflammation and bone marrow failure) is a systemic autoinflammatory disease associated with acquired somatic mutations affecting the hematopoietic stem/progenitor cells in the gene *UBA1*, an X-linked gene encoding an enzyme involved in ubiquitination.² *UBA1* mutations are propagated in the myeloid lineage and trigger the activation of inflammatory pathways, resulting in systemic inflammatory symptoms.³ Patients with the VEXAS syndrome have a predisposition for hematologic malignancies, including myelodysplastic syndrome (MDS) and plasma cell dyscrasias (浆细胞病). Notably, although MDS has been reported at a high frequency in VEXAS syndrome, most cases are classified as relatively juvenile MDS, while increased clonal progression to acute myeloid leukemia (AML) has been reported occasionally.

Concomitant somatic mutations in genes within the spectrum of myeloid clonal evolution have been reported occurring with *UBA1* mutation in VEXAS syndrome.⁴ However, the true prevalence and the biological and clinical implications of these mutations have not been so far fully elucidated. The study by Gutierrez-Rodriguez et al¹ found typical myeloid mutations occurring with *UBA1* mutations in 67% of patients (total *n* = 53), approximately half of these patients showed second mutations in 2

or more myeloid genes, consistent with an increased propensity to hematopoietic clonal expansion of mutant clones. The observed mutations largely involved *DNMT3A* and *TET2*, detectable in approximately 50% of patients, although somatic mutations in classical MDS-associated genes, including *TP53*, *NRAS* and *NRAS*, *STX11*, *STAG2*, and *DNMT3A*, were also observed.

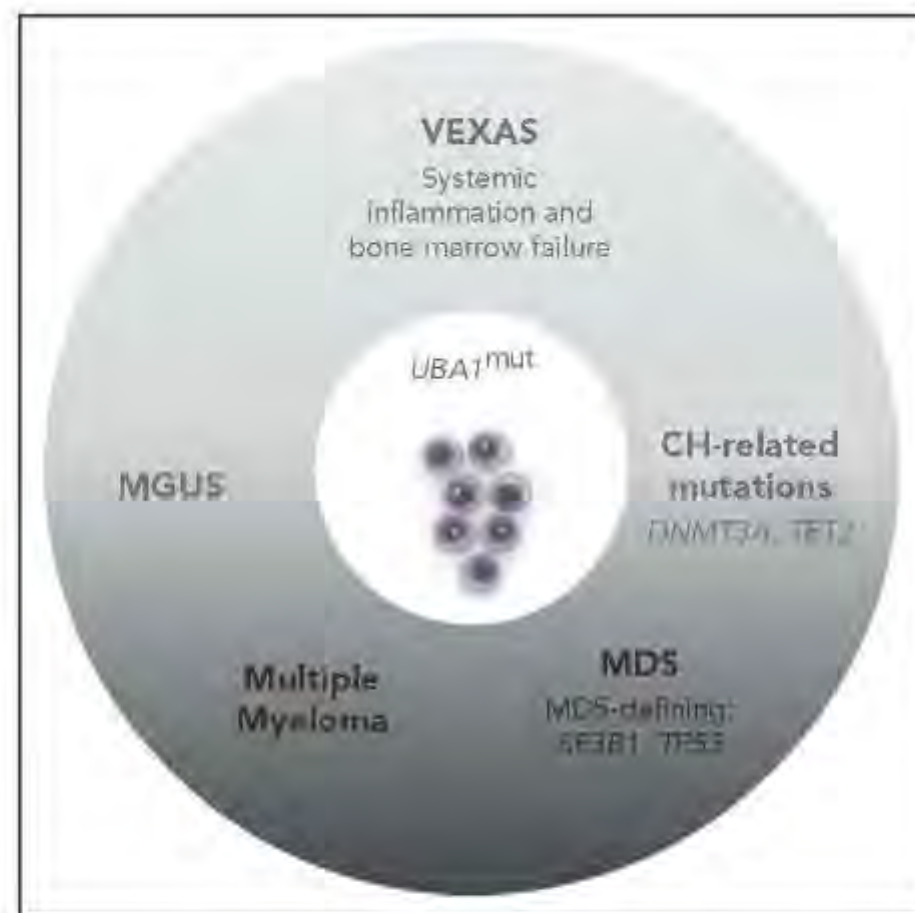
Although the variant allele frequency (VAF) of *UBA1* mutations was almost invariably consistent with being the dominant hematopoietic clone, the VAF of other mutated myeloid genes ranged from 21% for *DNMT3A* to <0.5% for *TET2*, clearly defining clonal architecture. Accordingly, single-cell DNA analysis revealed distinct patterns of clonality. *DNMT3A* mutations mostly preceded *UBA1* mutations, consistent with the occurrence of the latter on the background of a *DNMT3A*-driven clonal hematopoiesis. Conversely, *TET2* and other genes mainly occurred as *UBA1* mutation subclones or independent clones. Although hematologic phenotype apparently did not differ between patients with or without additional myeloid mutations, survival was significantly affected by co-occurring mutations and bone marrow suppression, whereas somatocytopenia/transfusion dependence and thrombocytopenia strongly associated with a diagnosis of MDS, additional somatic mutations apparently did not.

The study by Gutierrez-Rodriguez et al sheds light on the spectrum of mutations and their clonal trajectories in patients with VEXAS syndrome. The results further corroborate the association



Figure 1. Spectrum of clonal trajectories of *UBA1* mutant clones. Data are derived from 53 patients with VEXAS syndrome. The central circle represents the *UBA1* mutation. The surrounding segments represent the clonal trajectories of the *UBA1* mutant clones. The outer ring represents the clonal trajectories of the *UBA1* mutant clones. The inner ring represents the clonal trajectories of the *UBA1* mutant clones. The outer ring represents the clonal trajectories of the *UBA1* mutant clones. The inner ring represents the clonal trajectories of the *UBA1* mutant clones.

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Spectrum of clonal trajectories of *UBA1* mutant clones. Patients with the VEXAS syndrome have increased risk of MDS and plasma cell dyscrasias (monoclonal gammopathy of undetermined significance [MGUS] and multiple myeloma). Additional somatic mutations in typical drivers of clonal hematopoiesis (*DNMT3A* and *TET2*) and/or other genes enriched/specific for MDS contribute to clonal progression toward overt malignancy. A staging based on conventional clinical parameters (cytopenia and bone marrow dysplasia) is complicated by the inflammatory environment. CH, clonal hematopoiesis.

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Section 9

Sections
Introduction
Epidemiology
Mechanisms/pathophysiology
Diagnosis, screening and prevention
Management
Quality of life
Outlook

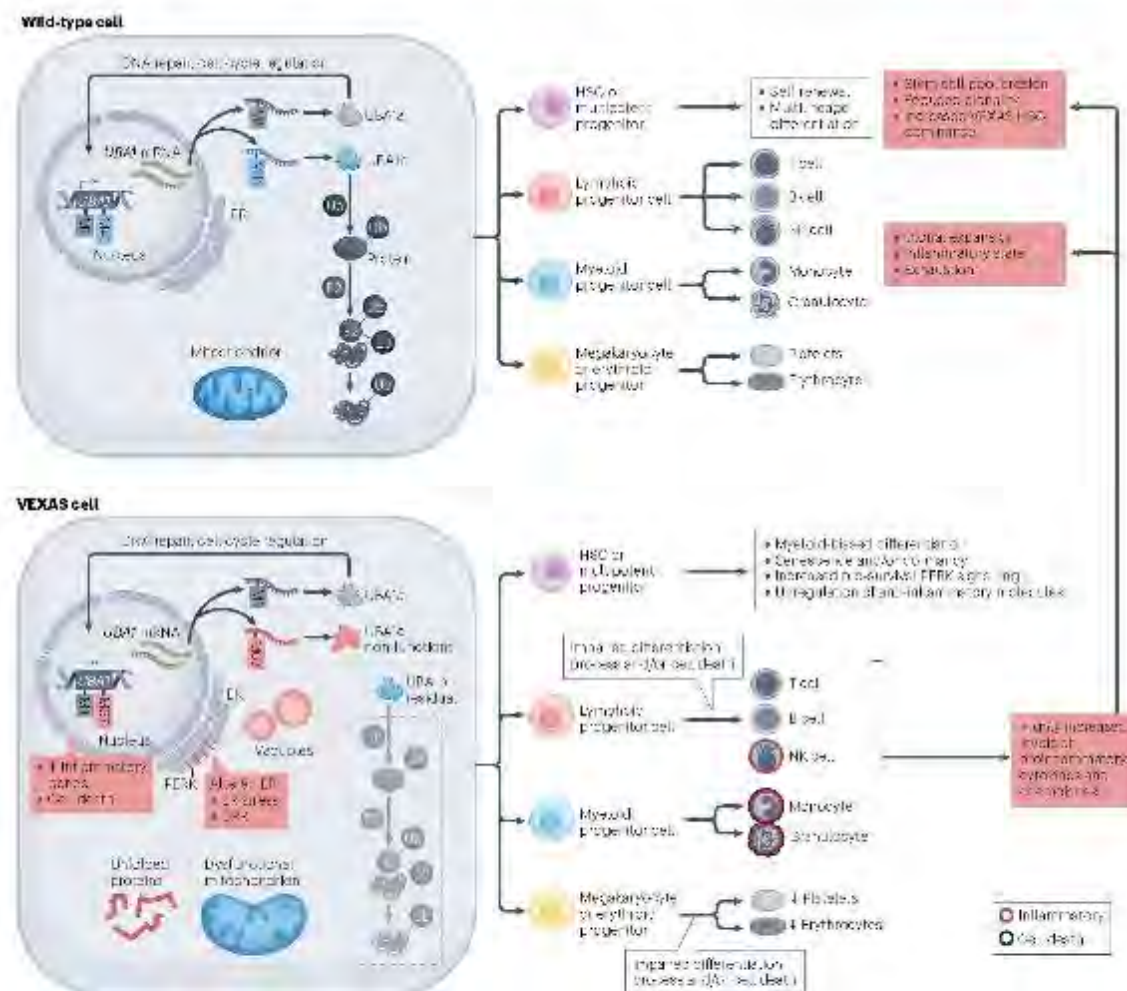


Fig. 2 | Cell-intrinsic and cell-extrinsic mechanisms of VEXAS syndrome pathophysiology. VEXAS (vacuoles, L1 enzyme, X-linked, a autoinflammatory, somatic) syndrome pathophysiology is the result of cell-intrinsic effects within cells with pathogenic UBA1 mutations (VEXAS cells) and cell-extrinsic effects of these cells on wild-type cells. In VEXAS cells, impaired UBA1b production leads to defective ubiquitin (Ub) charging, disrupted endoplasmic reticulum (ER) associated degradation, chronic unfolded protein response (UPR) activation, abnormal endolysosomal and mitochondrial morphology and increased vacuolization. These intrinsic stress programmes drive premature ageing signatures in haematopoietic stem and progenitor cells

(HISPCs), myeloid-biased differentiation, ineffective erythropoiesis, impaired megakaryopoiesis and counterselection along myeloid trajectories. Cell-extrinsic effects lead to inflammatory amplification. Mutant myeloid cells exhibit exaggerated inflammatory activation, dysregulated cytokine secretion and impaired efficiency, generating a pro-inflammatory milieu. This toxic microenvironment promotes functional decline of wild-type HISPCs while mutant HISPCs persist through stress adaptive pathways, collectively driving clonal dominance, immune dysregulation and progressive haematopoietic failure. HSC, haematopoietic stem cell; NK cell, natural killer cell; PERK, protein kinase R-like ER kinase.

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ORIGINAL ARTICLE

VEXAS syndrome: Focus on dermatological manifestations and their histopathological correlate

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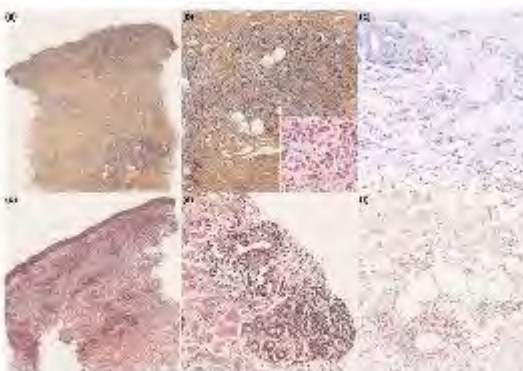
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Abstract

Background: VEXAS (Vasculitis, Erythema, X-Linked, Autoinflammatory, Somatic syndrome) is a rare autoinflammatory syndrome, first described in October 2020 by Beck et al. It is caused by somatic mutations in the UBA1 gene, coding for the E1 enzyme, responsible for ubiquitination. It manifests in adulthood, mainly in men, with constitutional symptoms, haematological abnormalities and often skin lesions with neutrophilic dermatoses most frequently reported. Since skin lesions are a frequent and early manifestation,



Atypical extensive lupus tumidus-like eruption as an early presentation of VEXAS syndrome

Dear Editor,
VEXAS syndrome (vasculitis, E1 enzyme, X-linked, autoinflammatory, somatic) has recently been described as the

association of severe adulthood inflammatory manifestations (including cutaneous features, mainly Sweet's syndrome, vasculitis, and rheumatism) and hematologic disease (myelodysplastic syndrome or multiple myeloma) typically with vacuolated myeloid and erythroid progenitor cells on bone marrow biopsy, caused by somatic mutations in ubiquitin-like modifier activating enzyme 1 (UBA1) gene.

We report two very similar cases of VEXAS syndrome patients presenting with predominant cutaneous clinical features with only very subtle blood cell count disorders.

Case 1. A 58-year-old Caucasian male was referred in October 2018 for a 1-year lasting recurrent eruption. Physical examination showed multiple erythematous plaques with annular and arciform distribution, infiltrated borders, central clearing, and slight desquamation (Fig. 1). He had neither fever nor systemic symptoms. Laboratory analysis revealed a moderate inflammatory reaction (C-reactive protein: 39 mg/L; normal: 0–6.0 mg/L), lymphopenia (590 mm³; normal: 1000–4000 mm³), anemia (12.0 g/dL; normal: 11.8–15.0 g/dL) with normal mean corpuscular volume (98 fL; normal: 80–105 fL), and normal platelets. Bone marrow assessment showed no concomitant myelodysplastic syndrome or other lymphoproliferative disorder. Antinuclear and anti-SSA antibodies were negative. Histopathologic examination showed dermal edema associated with perivascular and periarterial infiltrates of small lymphocytes.



Figure 1 Multiple erythematous plaques with edematous borders, annular or arciform configuration (a, b: case 1; c, d: case 2)

TABLE 1 Patient characteristics, initial diagnoses and confirmed UBA1 mutation

Patients	1	2	3	4	5	6	7	8	9
Sex, age	Male, 75 y	Male, 75 y	Male, 84 y	Male, 74 y ^a	Male, 77 y	Male, 62 y	Male, 70 y	Male, 67 y	Male, 79 y ^a
Age of onset (y)	71 y	69 y	79 y	58 y	71 y	50 y	68 y	58 y	71 y
Diagnostic delay (y)	1 y	5 y	5 y	5 y	3 y	13 y	2 y	8 y	9 y
Age of death (y)	–	–	–	74 y	–	–	–	–	79 y
Initial diagnoses	UD CTD HUVS	Sweet's Sy Atypical Behçet Systemic vasculitis	IgG4 RD TIPIC Sy	SCLE RP	Schnitzler's Sy RP	SCLE RP	Idiopathic antineutrophil cytoplasmic antibodies Osteoarthritis Kasai-Dreifuss Sy IgG4 RD	RP	UD CTD ANCA neg IgG4 SS3PE
UBA1 mutation	c.122T>C (p.Met41Thr)	c.118-1C>G (p.Splice)	c.132T>C (p.Met41Thr)	c.132T>C (p.Met41Thr)	c.121A>C (p.Met41Leu)	c.121A>C (p.Met41Leu)	c.122T>C (p.Met41Thr)	c.132T>C (p.Met41Thr)	c.121A>C (p.Met41Leu)

Note: This table describes the patient characteristics, including current sex, age, age of onset, diagnostic delay and age of death (if applicable), and initial diagnoses and UBA1 mutations confirmed by Sanger sequencing of our VEXAS patient population.

Abbreviations: A, adenine; ANCA, antineutrophil cytoplasmic antibodies; C, cytosine; CTD, connective tissue disease; E3PA, eosinophilic granulomatosis with polyangiitis; G, guanine; HUVS, hypocomplementemic urticarial vasculitis syndrome; IgG4 RD, immunoglobulin G4-related disease; Leu, leucine; Met, methionine; neg, negative; RP, relapsing polychondritis; SS3PE, Sjögren's syndrome with pitting keratoconjunctivitis; SCLE, subacute cutaneous lupus erythematosus; Splice, splice mutation; Sy, syndrome; T, thymine; Thr, threonine; TIPIC, transient perivascular inflammation of the intimal artery; UD, undifferentiated; y, years.

^a Died.

Skin Manifestations of VEXAS Syndrome and Associated Genotypes

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IMPORTANCE VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a newly defined genetic disease with an estimated prevalence of 1 in 4229 men older than 50 years and is marked by systemic inflammation, progressive bone marrow failure, and inflammatory cutaneous manifestations.

OBJECTIVE To define the spectrum of cutaneous manifestations in VEXAS syndrome and the association of these findings with clinical, genetic, and histological features.

DESIGN, SETTING, AND PARTICIPANTS This observational cohort study included data from 112 patients who were diagnosed with VEXAS-defining genetic variants in USA between 2019 and 2023. Data were collected from medical record review or from patients with VEXAS directly post listed to the National Institutes of Health in Bethesda, Maryland.

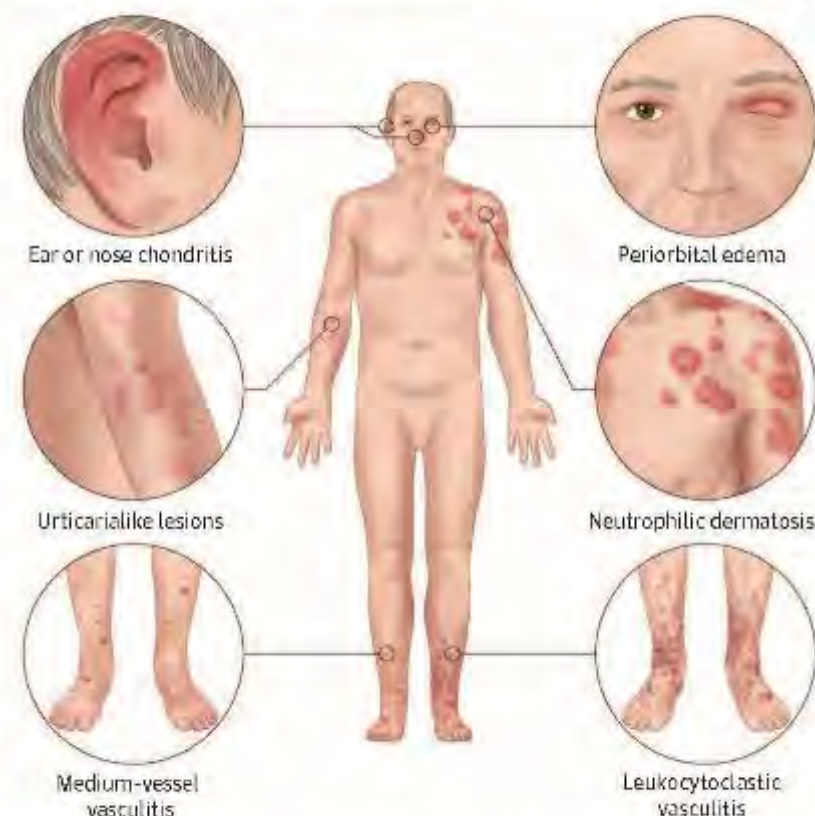
MAIN RESULTS AND MEASURES To define the spectrum of cutaneous manifestations in VEXAS in association with genetic, histological, and other clinical findings. A secondary outcome was cutaneous response to treatment in VEXAS.

RESULTS Among the 112 patients (median [range] age, 69 [29–99] years; 111 [99%] male), syndromic arthritis was common (80 [89%]), arthritis was frequent, preceding features of disease (68 [61%]). Of 64 histopathologic reports available from 60 patients, predominant skin histopathologic findings were leukocytoclastic vasculitis (20 [36%]), neutrophilic dermatosis (22 [34%]), and perivascular dermatitis (16 [30%]). Distinct pathogenic genetic variants were associated with specific cutaneous manifestations. The p.Met41Leu variant was most frequently associated with neutrophilic dermal infiltrates (14 of 7 patients [52%]), often resembling histiocytoid Sweet syndrome. In contrast, the p.Met419Val variant was associated with vasculitic lesions (11 of 20 patients [55%]) with a mixed leukocytic infiltrate (17 of 20 patients [85%]). Clinical presentation improved skin manifestations in 67 of 73 patients (92%). Patients with VEXAS treated with systemic corticosteroids developed severe injection site reactions (12 of 16 [75%]), including ulceration (2 of 12 [17%]) and abscess formation (1 of 12 [8%]).

CONCLUSIONS AND RELEVANCE Results of this cohort study show that skin manifestations are a common and frequent manifestation of VEXAS syndrome. Genetic evaluation for VEXAS should be considered in older male patients with cutaneous vasculitis, neutrophilic dermatosis, or chondritis. Awareness of VEXAS among dermatologists is critical to facilitate early diagnosis.

Supplemental content

Figure 1. Cutaneous Signs of VEXAS Syndrome



The most common cutaneous features of VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome are graphically depicted. Nondestructive inflammation of ear and nose cartilage can lead to a clinical diagnosis of relapsing polychondritis. Periorbital edema with inflammation is relatively specific for VEXAS syndrome. Urticarial-like lesions and neutrophilic dermatosis can invoke a diagnosis of urticarial vasculitis or Sweet syndrome, respectively. Livedo reticularis and nodular skin lesions with associated medium-vessel vasculitis can lead to a clinical diagnosis of polyarteritis nodosa. Purpuric lesions with leukocytoclastic vasculitis or leukocytoclasia without overt vasculitis have been described.

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CASE STUDY

VEXAS Syndrome: Histiocytoid Cells With Feathery Cytoplasm as a Clue to the Diagnosis

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Keywords: autoinflammation; histiocytoid cells; dermatosis; Sweet's syndrome; VEXAS syndrome

ABSTRACT

VEXAS (Vasculitis, Erythrocytosis, activating enzyme UBA1 variant, X-linked, Autoinflammatory, Syndrome) syndrome was initially described as having mature neutrophil-predominant infiltrates. More recent reports suggest that infiltrates can be composed of erythrocytoid types. We report three cases of VEXAS syndrome with skin biopsies revealing a mature histiocytoid cells with feathery cytoplasm. These cells may be a potential clue to the diagnosis.

1 | Introduction

VEXAS (Vasculitis, Erythrocytosis, activating enzyme UBA1 variant, X-linked, Autoinflammatory, Syndrome) syndrome was first described in 2010 with cutaneous histopathologic findings, including neutrophilic infiltrates and vasculitis [1]. UBA1 variants associated secondarily associated, complex findings with variable clinical presentations (reviewed in Table 1). While the true prevalence of the disease is unknown, in one US health care, the estimated UBA1 pathogenic variant prevalence was 1 in 14 000 [2]. The majority of individuals have symptoms and signs of autoinflammation, exclusive of fever, fatigue, weight loss, lymphadenopathy, arthritis, vasculitis, pulmonary involvement, and renal or skeletal inflammation [3–10].

Initial detailed description of VEXAS syndrome clinical and histopathologic findings from papulonodules and plaques included: acute localized mature neutrophils, immature neutrophils, lymphocytes, and leukocytoclasts; these cases were categorized as Sweet syndrome-like neutrophilic dermatoses [5]. Subsequent reports confirmed that cutaneous findings are common [11–14] but polymorphic; the color may be pink

or red in color, size can range from <1 cm raised macules to >1 cm larger patches; morphology is variably round or elliptical, oval, or irregular, papular, plaque, or annular [15]. Chondritis, periorbital edema (unilateral or bilateral), and angiodomas may also be significant features on cutaneous examination [3, 4]. Therefore, histopathologic evaluation of affected patient skin can be a critical component to the diagnosis of VEXAS syndrome.

The most commonly reported microscopic pattern of VEXAS syndrome is a neutrophilic dermatosis [1, 2, 7], associated with rare UBA1 p.Met41Leu variant [15], but inflammatory infiltrates have also been reported as neutrophilic and histiocytoid [11], mixed [13, 16], leukocytoclastic [17], or lymphocyte-predominant [13, 18–20]. Thus, cutaneous lesions of VEXAS syndrome are not defined by a single histopathologic pattern, and a unifying clue would facilitate accurate diagnosis. While vacuolization of erythroid and myeloid precursors in the bone marrow [21] is seen in the majority of patients, these cells are not present in skin infiltrates. We report three cases of VEXAS syndrome infiltrated with histiocytoid cells with feathery cytoplasm on skin biopsy and suggest these cells may be a histologic clue to the diagnosis.

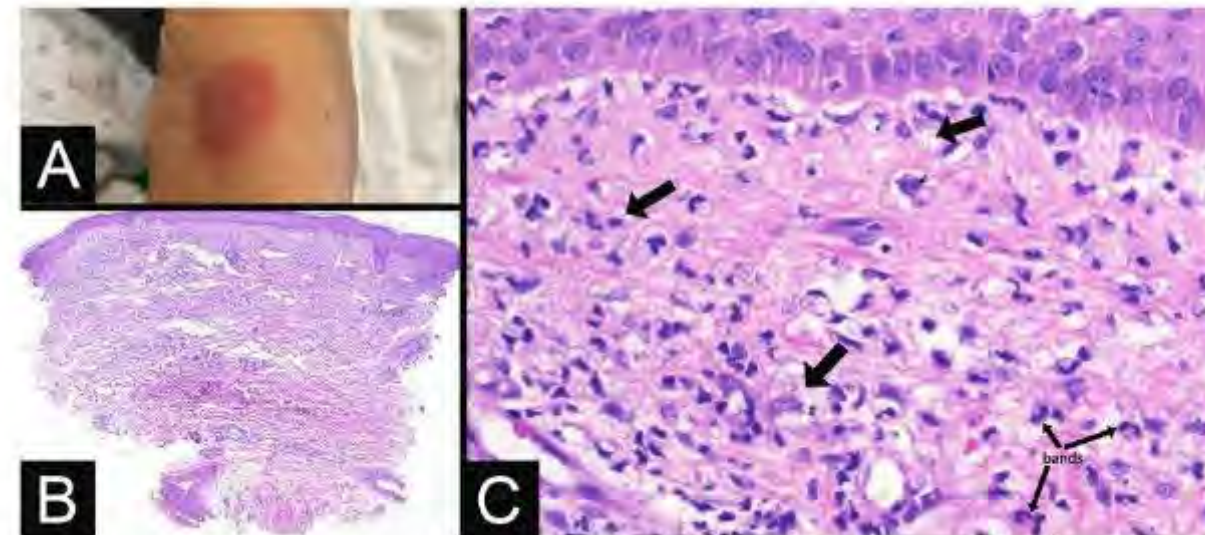
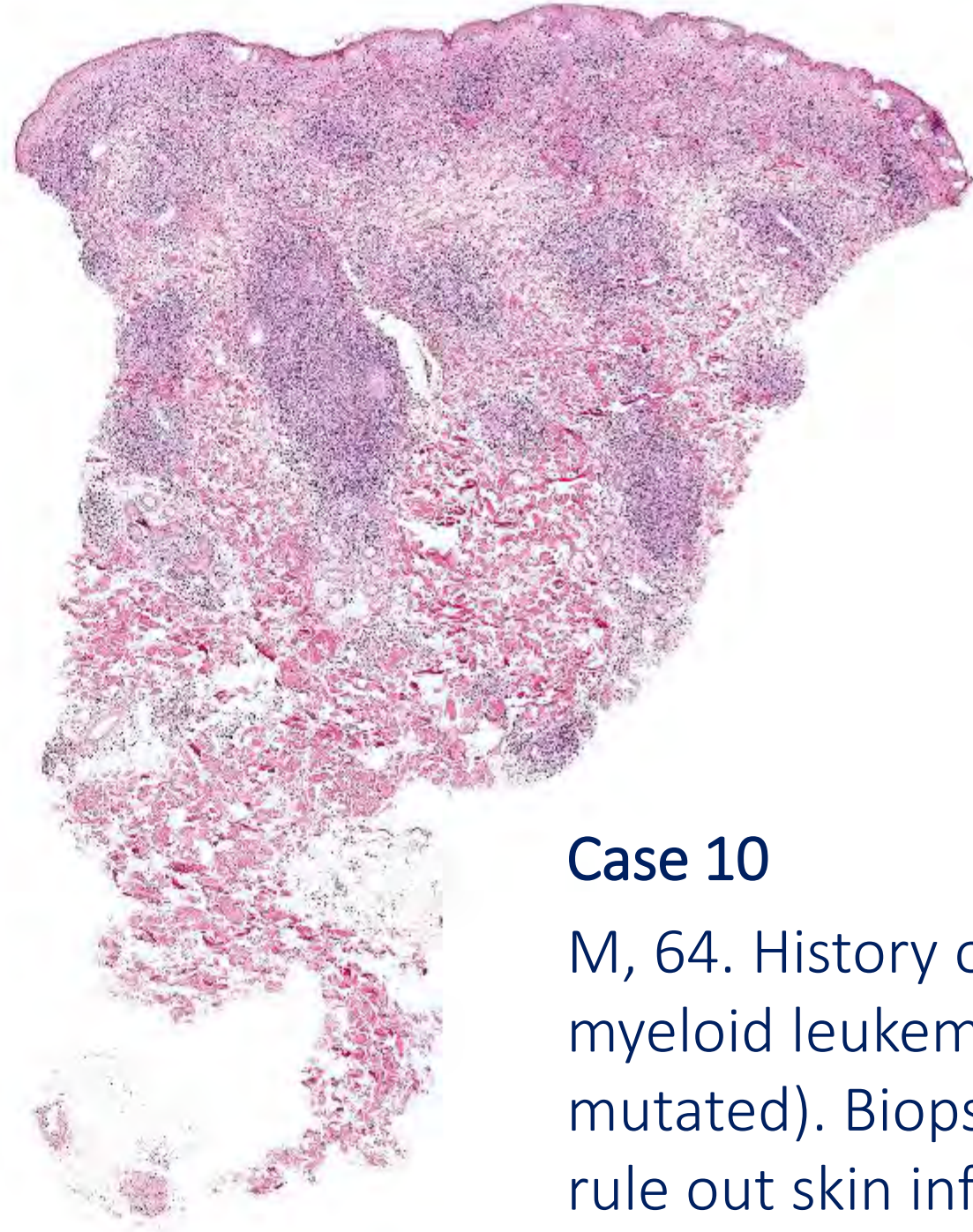
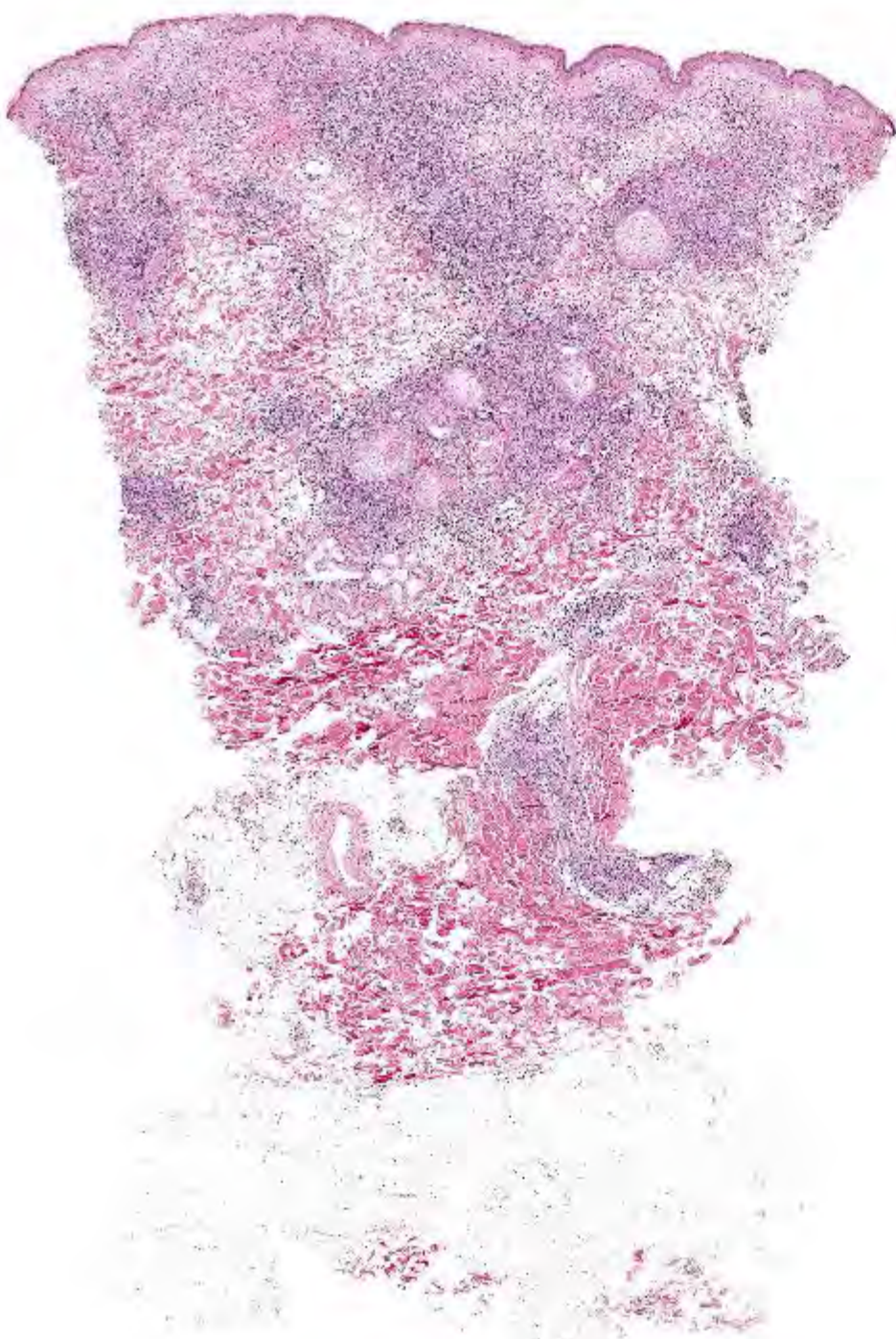
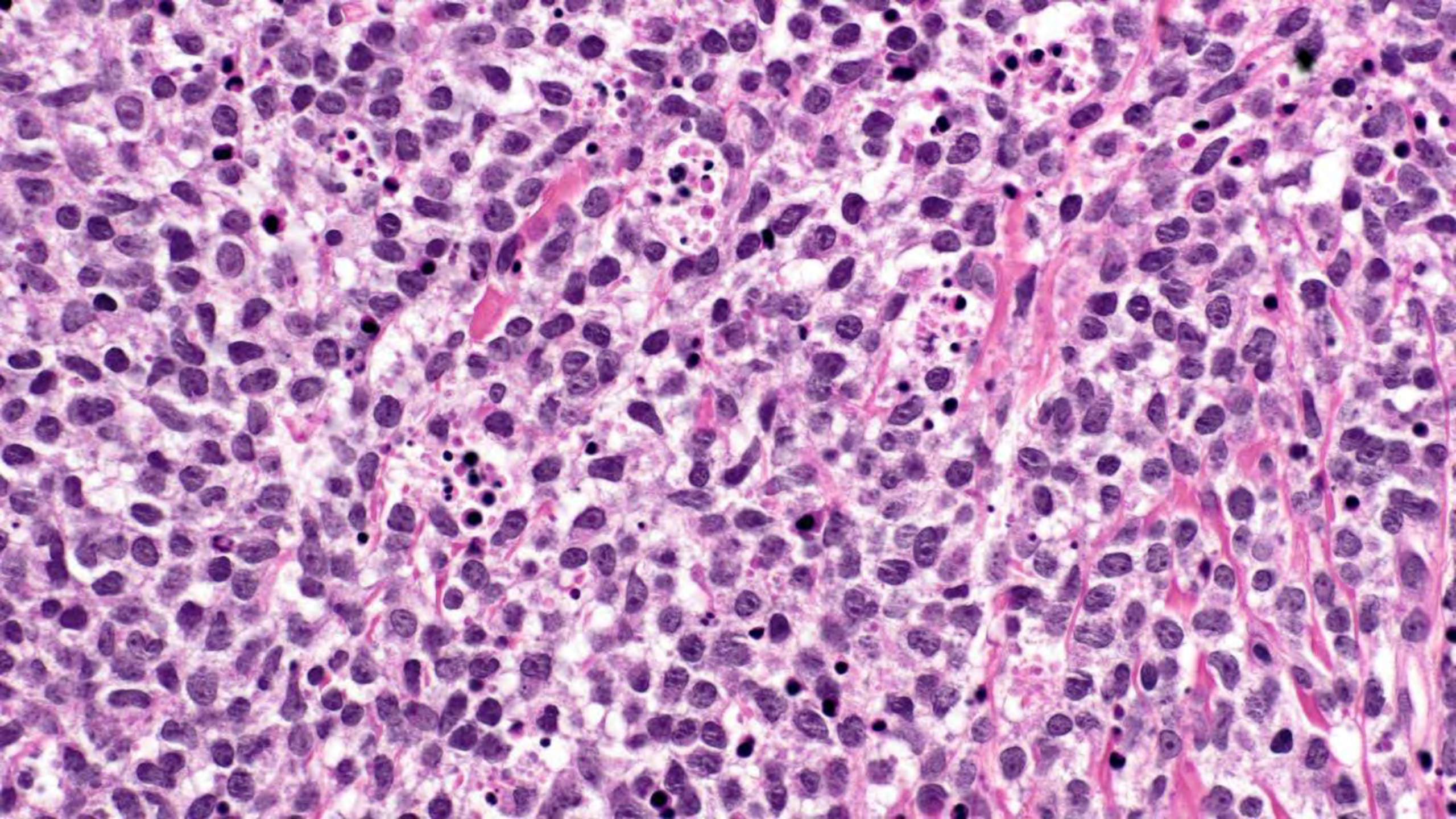


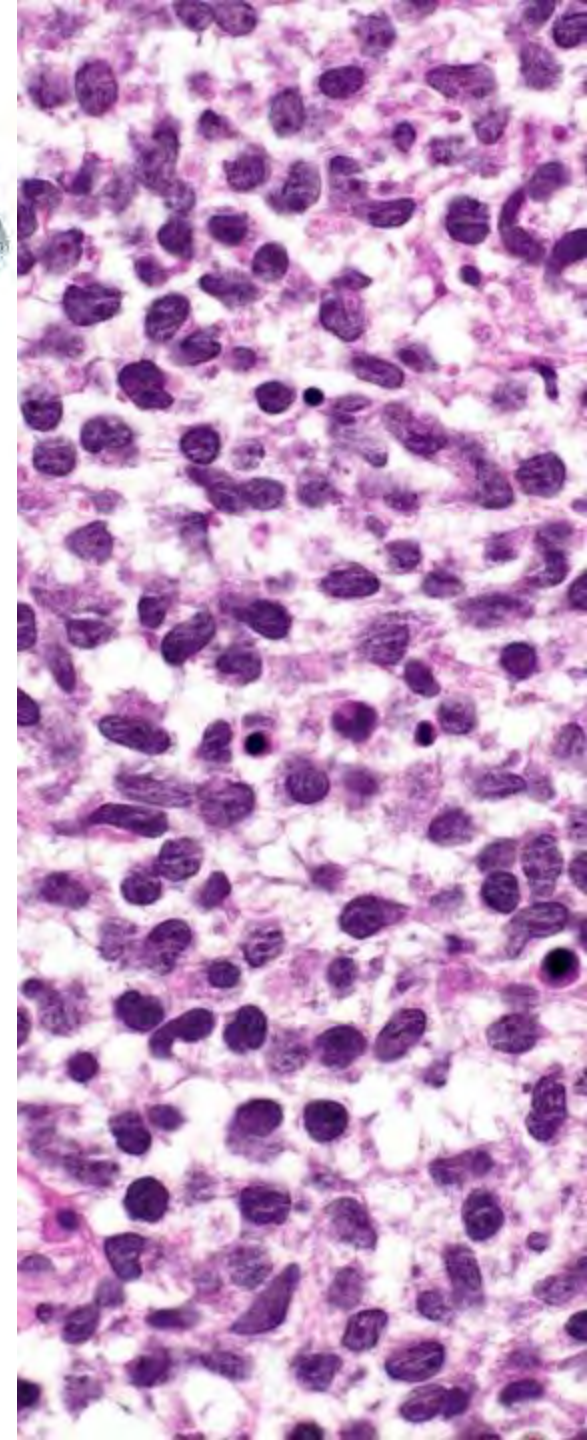
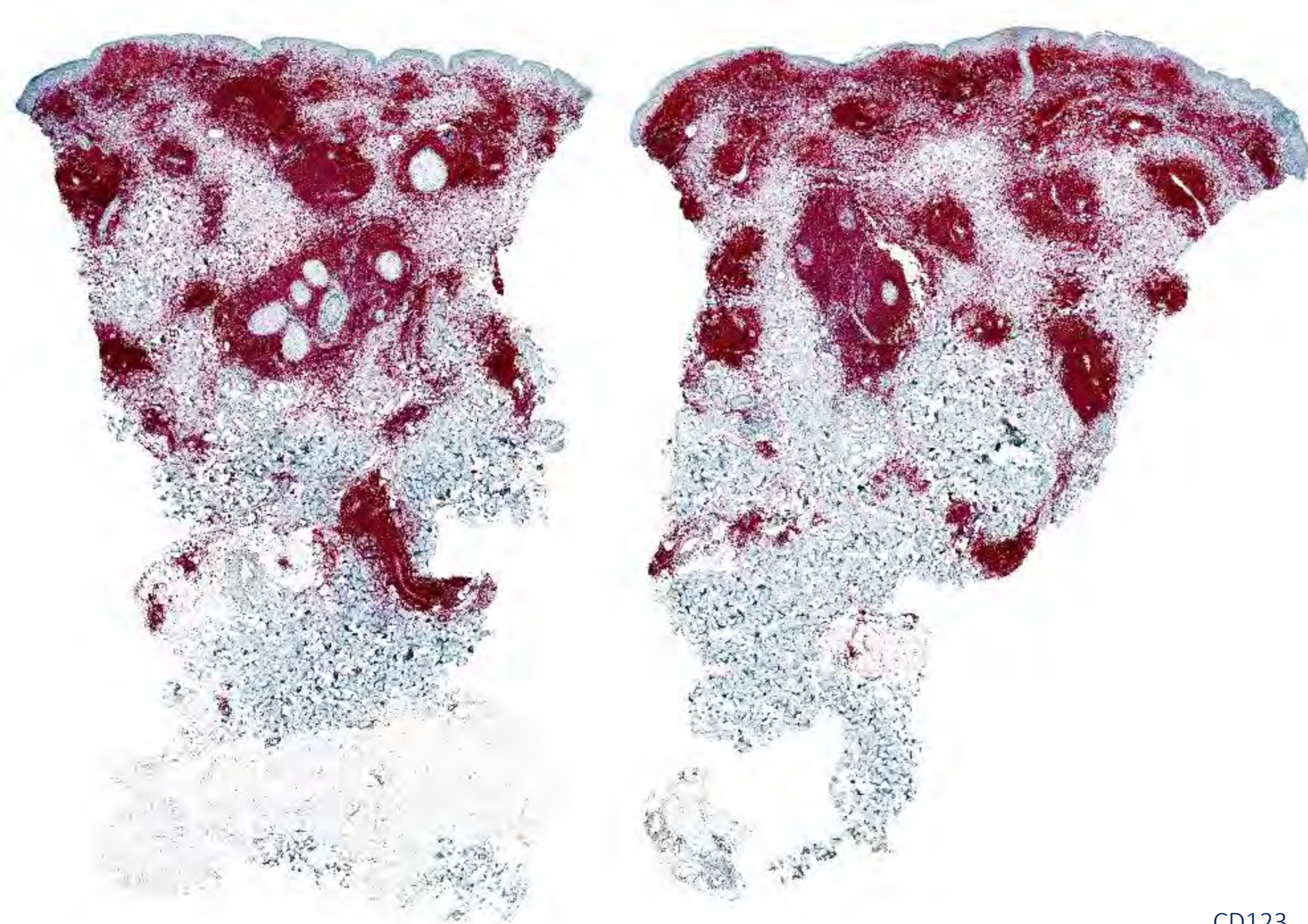
FIGURE 3 | VEXAS syndrome. Case 1, 2 months after diagnosis of VEXAS syndrome. A solitary, circular, red plaque (A) was the only cutaneous manifestation during this episode. Recurrent flares of skin disease, with polymorphous presentations and variable microscopic infiltrates, are a feature of VEXAS syndrome. Histopathologic findings include a mixed infiltrate of histiocytoid cells with clear to feathery cytoplasm (thick arrows), immature neutrophils (thin arrows), and lymphocytes (B and C). At the time of this biopsy, the patient was known to have a p.Met41Leu UBA1 variant. (Hematoxylin and eosin; (B) 40×; (C) 400×).



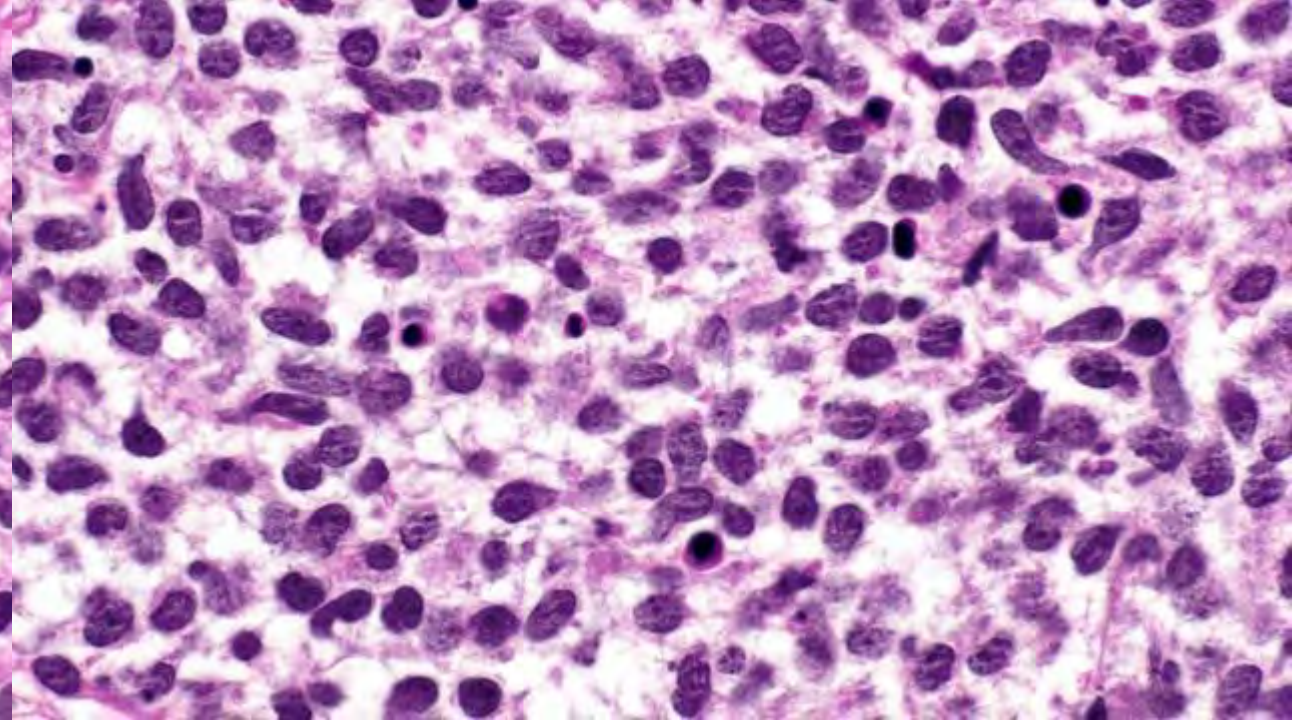
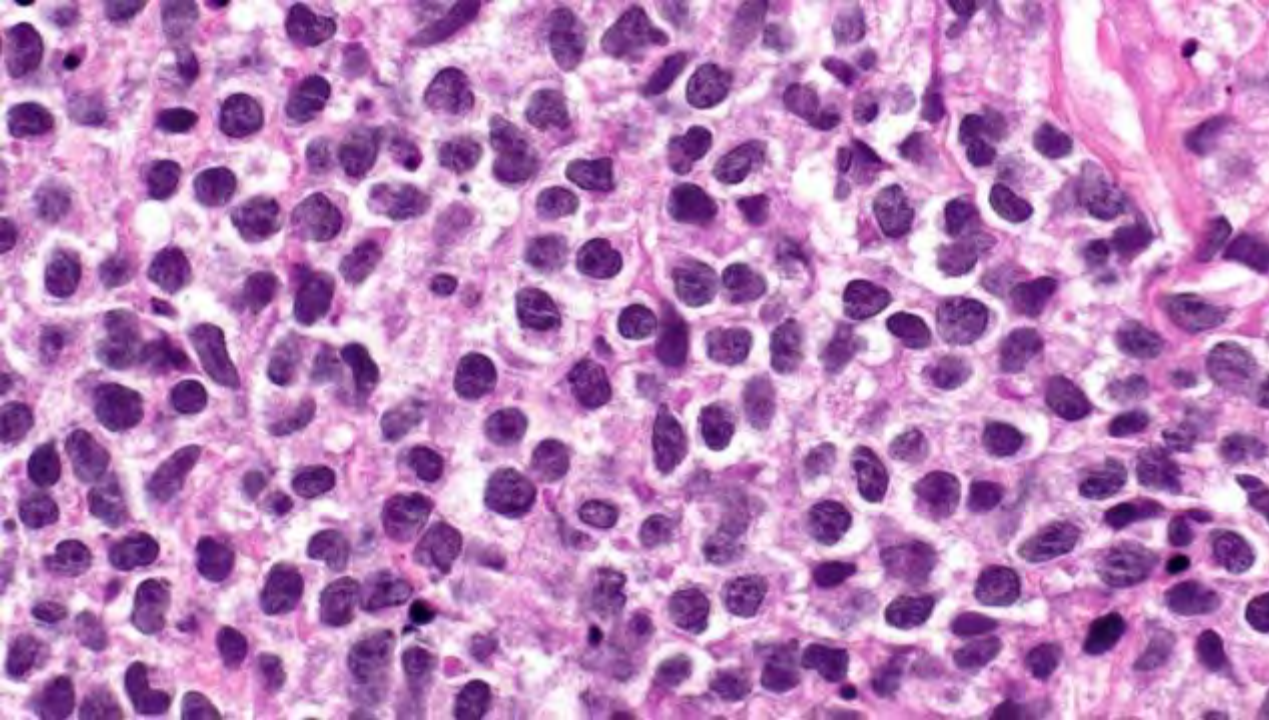
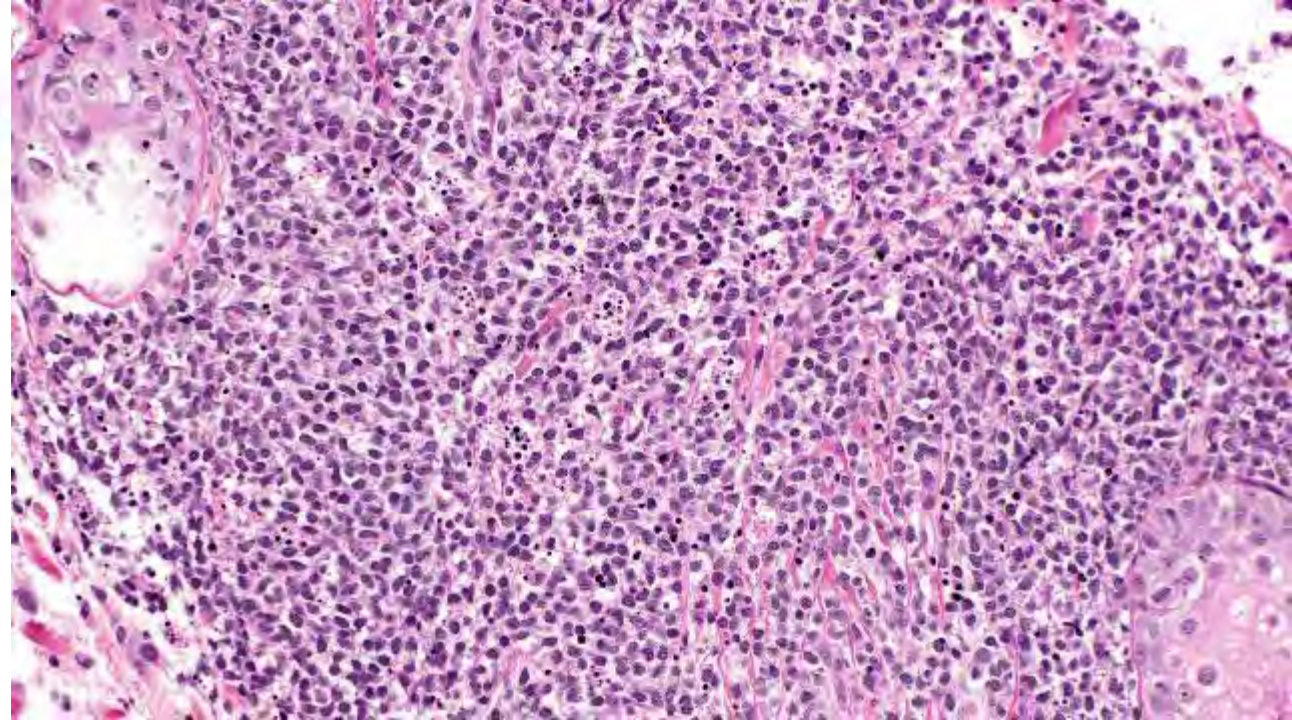
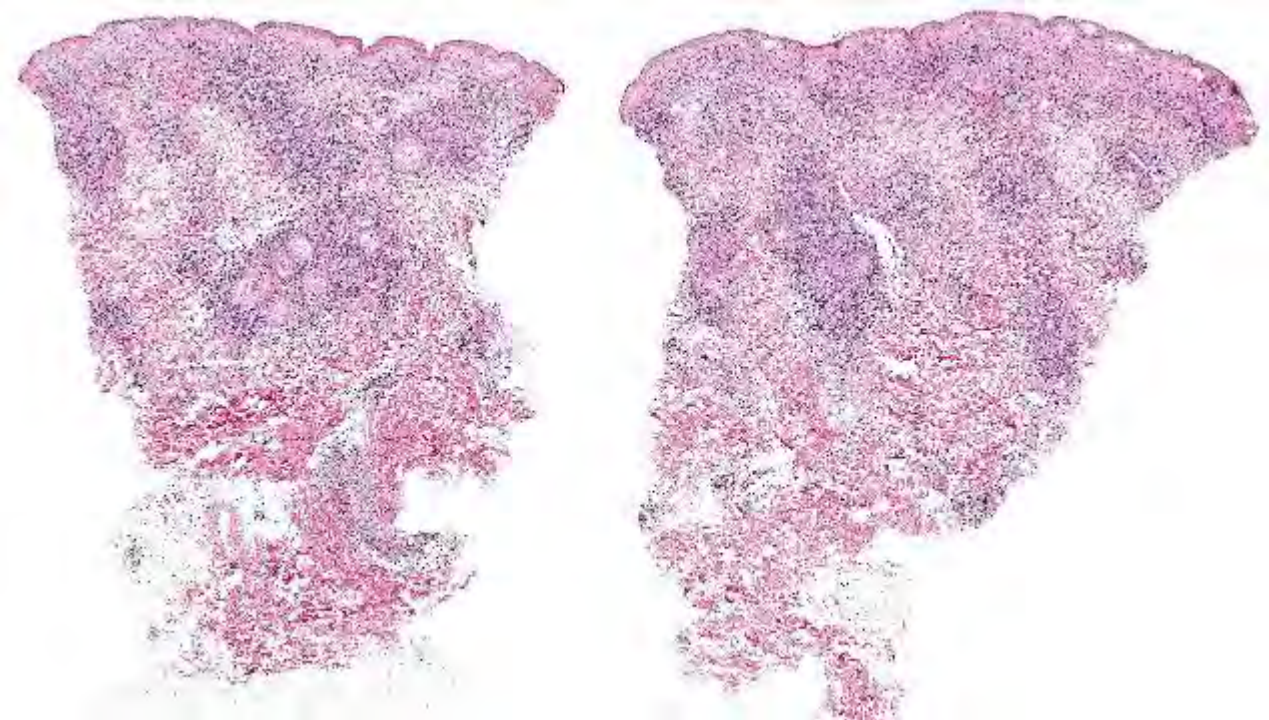
Case 10

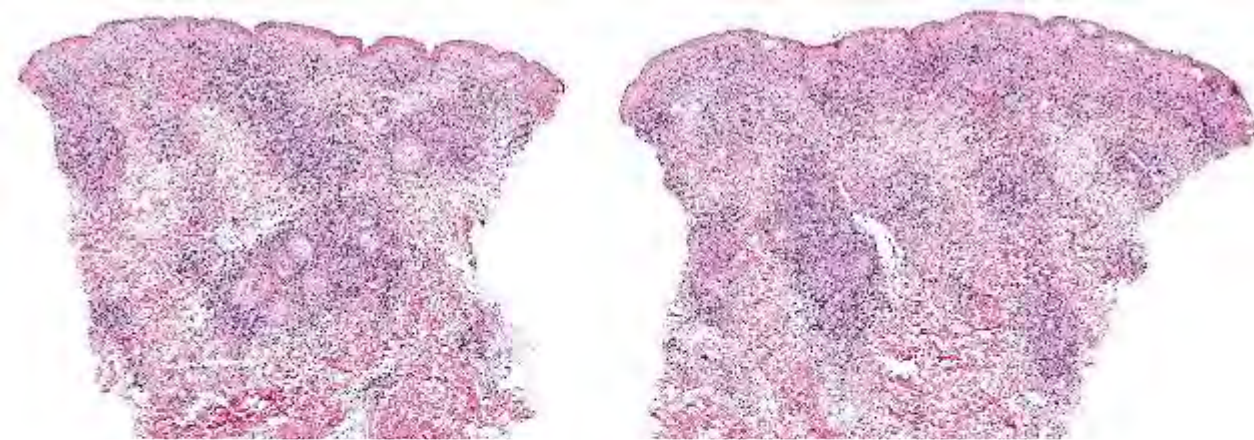
M, 64. History of acute myeloid leukemia (*RUNX1* mutated). Biopsy taken to rule out skin infiltration.



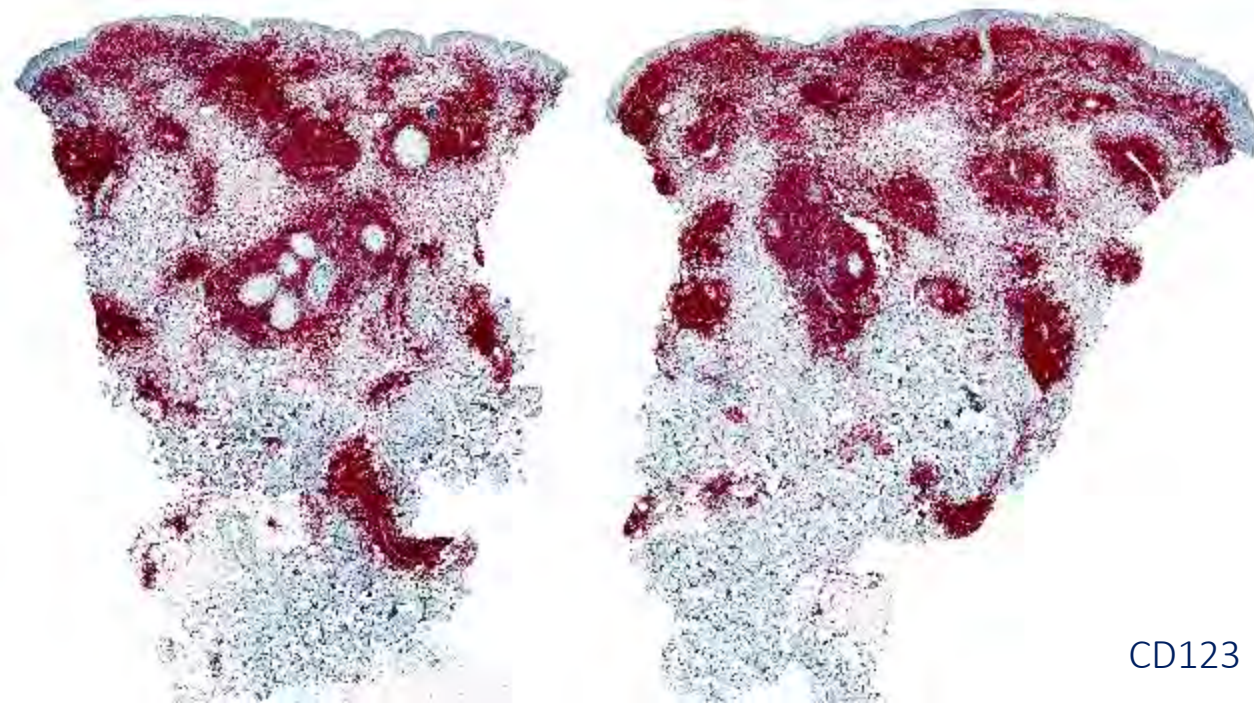


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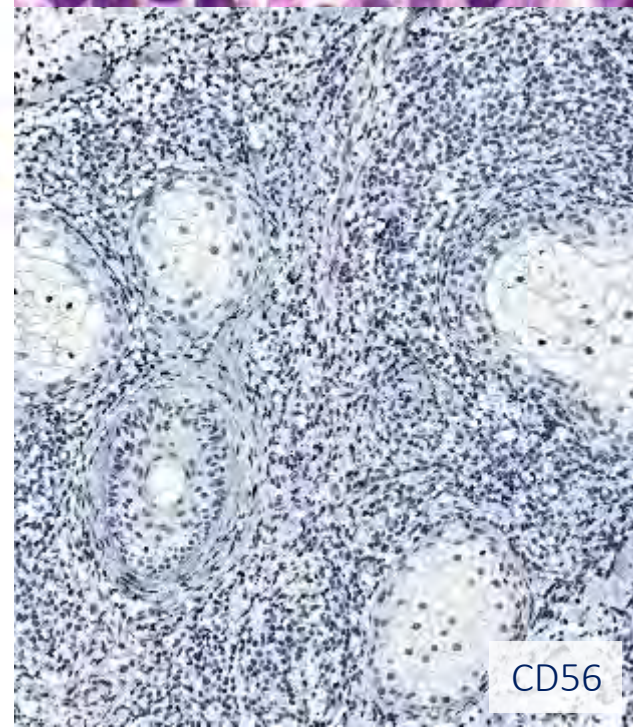
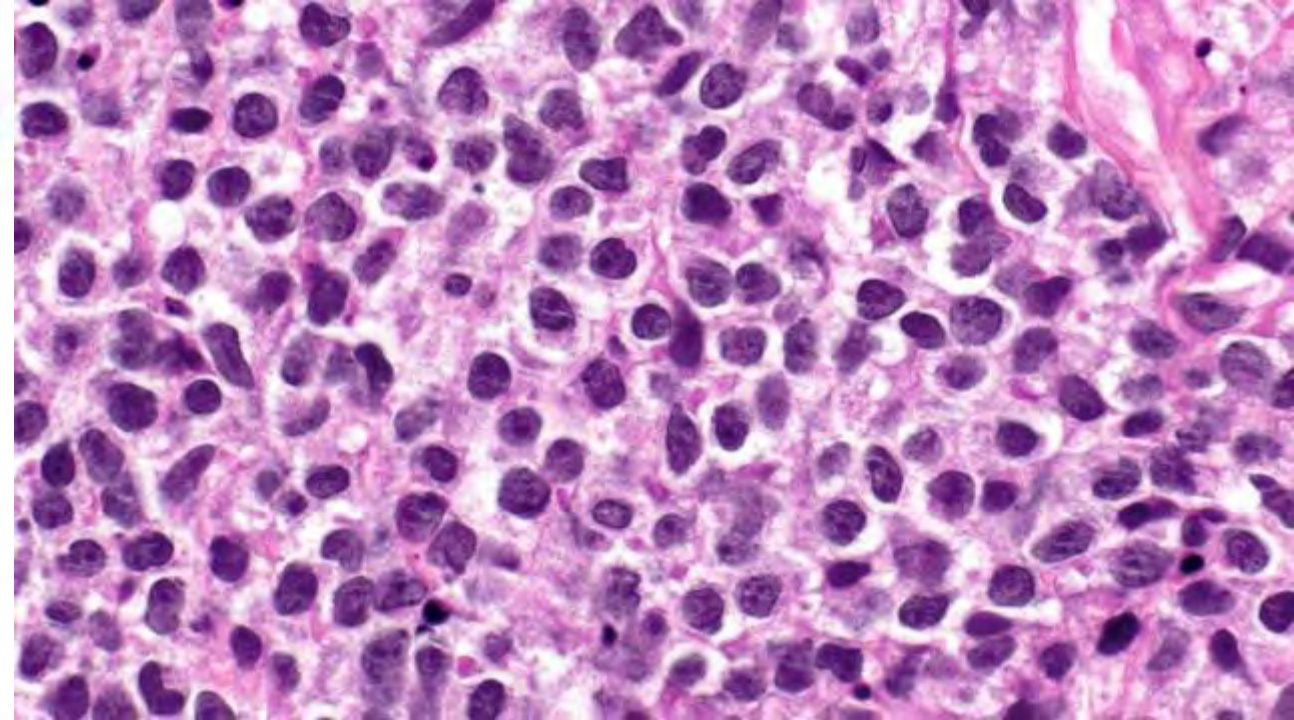




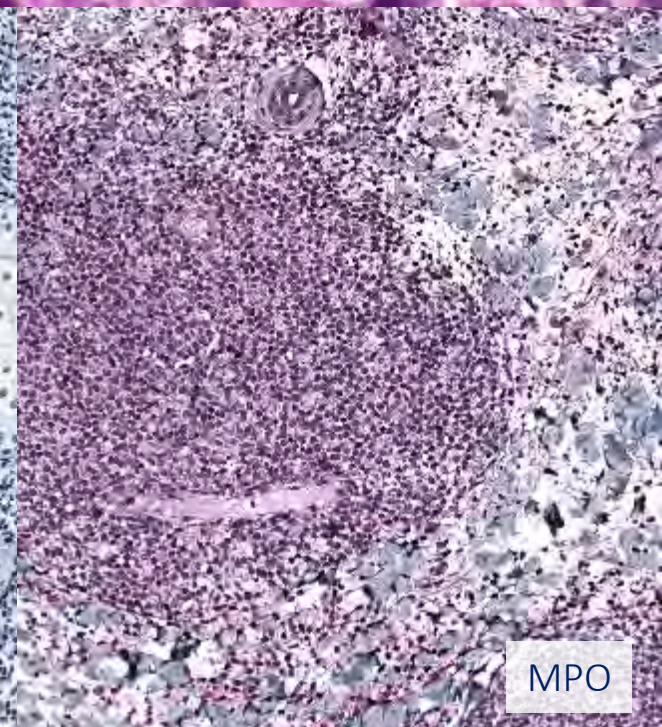
Mature plasmacytoid dendritic cell proliferation



CD123



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3. Histiocytic/Dendritic cell neoplasms

[Introduction](#)

[Plasmacytoid dendritic cell neoplasms](#)

[Plasmacytoid dendritic cell neoplasms](#)

[Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm](#)

[Blastic plasmacytoid dendritic cell neoplasm](#)

[Langerhans cell and other dendritic cell neoplasms](#)

[Langerhans cells neoplasms](#)

[Langerhans cell histiocytosis](#)

[Langerhans cell sarcoma](#)

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[Histiocyte/macrophage neoplasms](#)

[Histiocytic neoplasms](#)

[Juvenile xanthogranuloma](#)

[Erdheim-Chester disease](#)

[Rosai-Dorfman Disease](#)

[ALK-positive histiocytosis](#)

[Histiocytic sarcoma](#)

Localization

Most cases have been described in the skin and bone marrow, and very rarely, in lymph nodes.

Essential and desirable diagnostic criteria

Essential:

Accumulation of mature cells with plasmacytoid morphology and expression of CD123 and/or other pDC markers in the context of a defined myeloid neoplasm.

Desirable:

Aberrant pDC immunophenotype

Absence or low/partial expression of CD56.



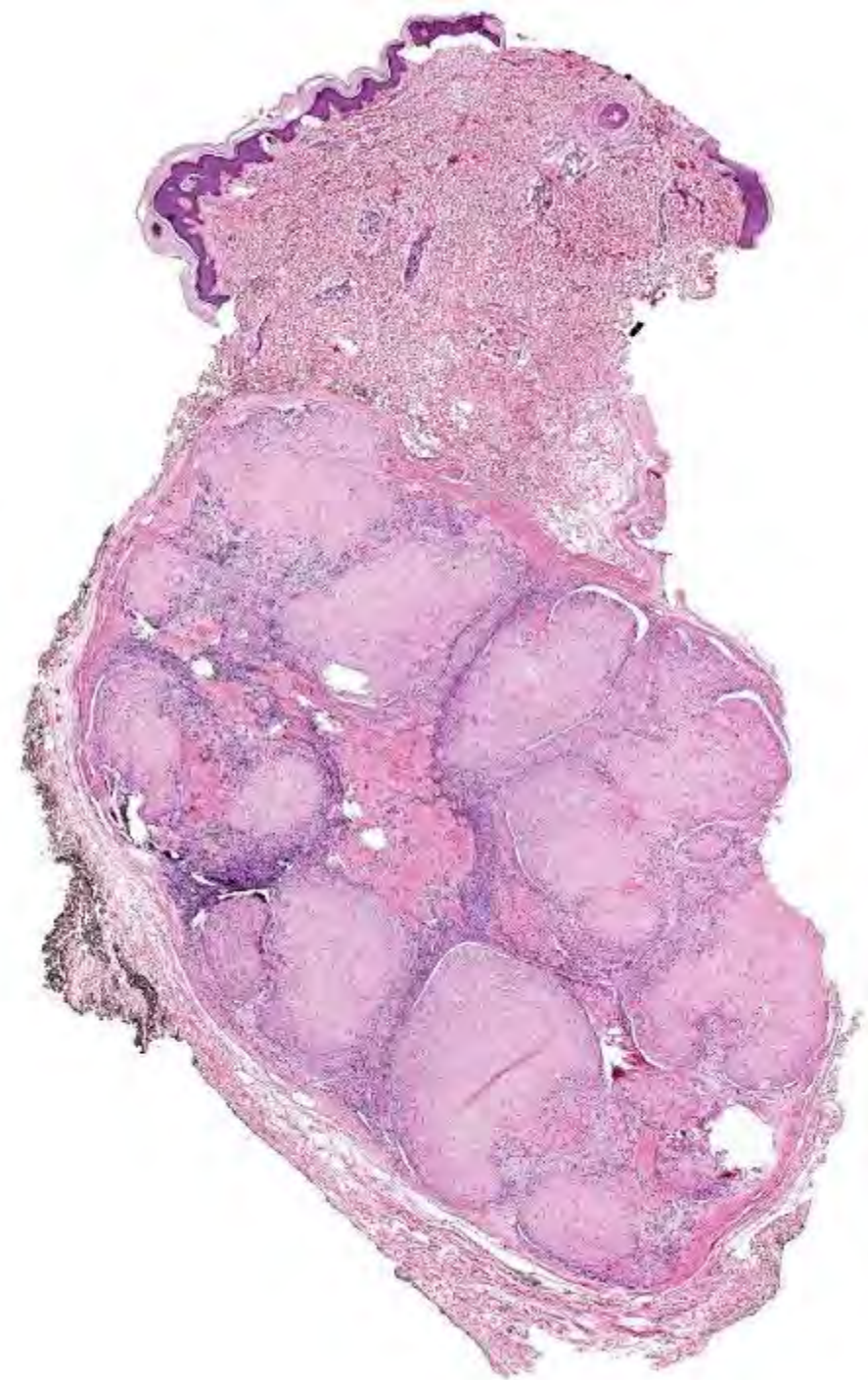
CASES 11-20

Iva Brcic
Department of Dermatology und Venerology
Medical University of Graz

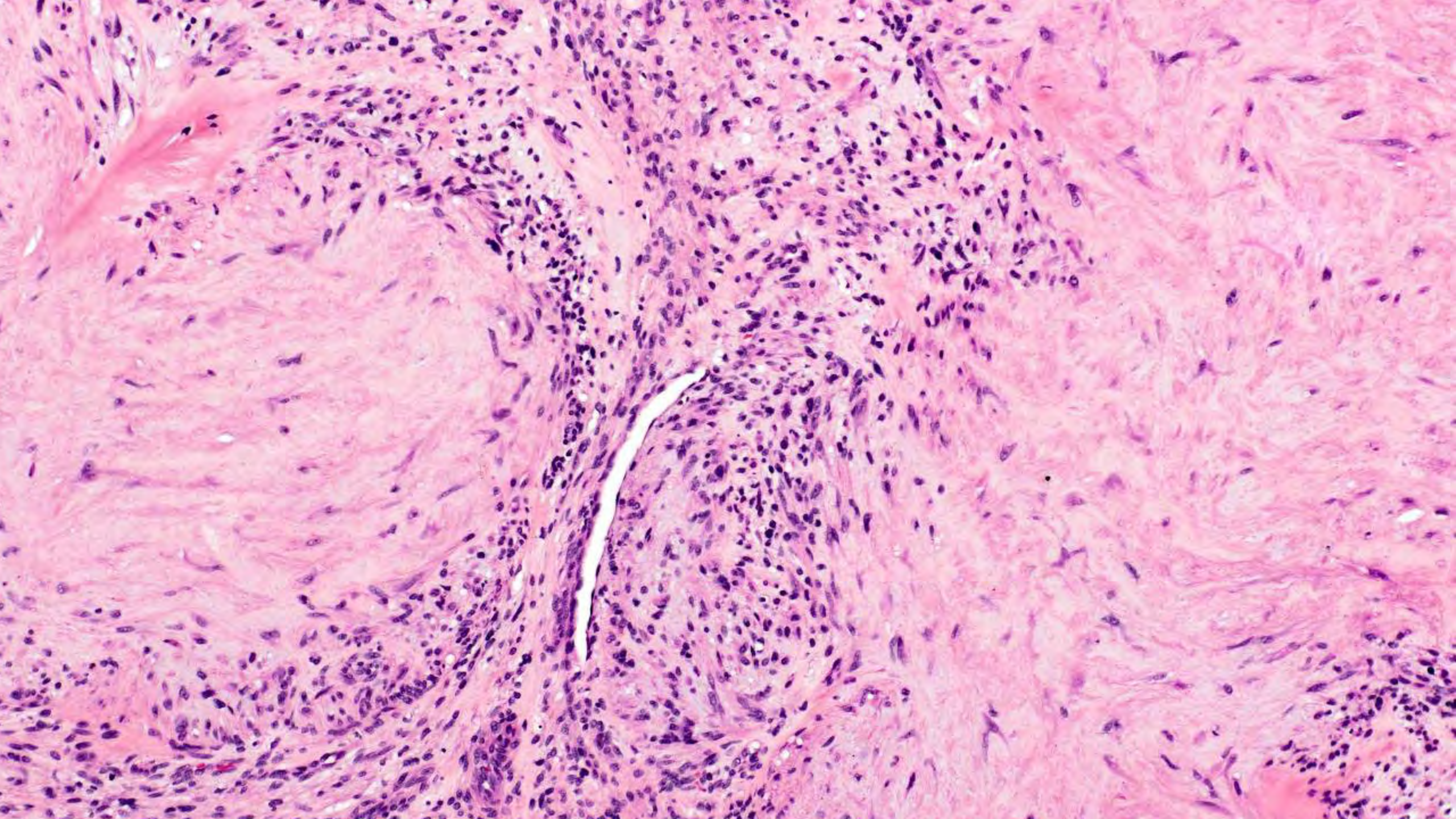


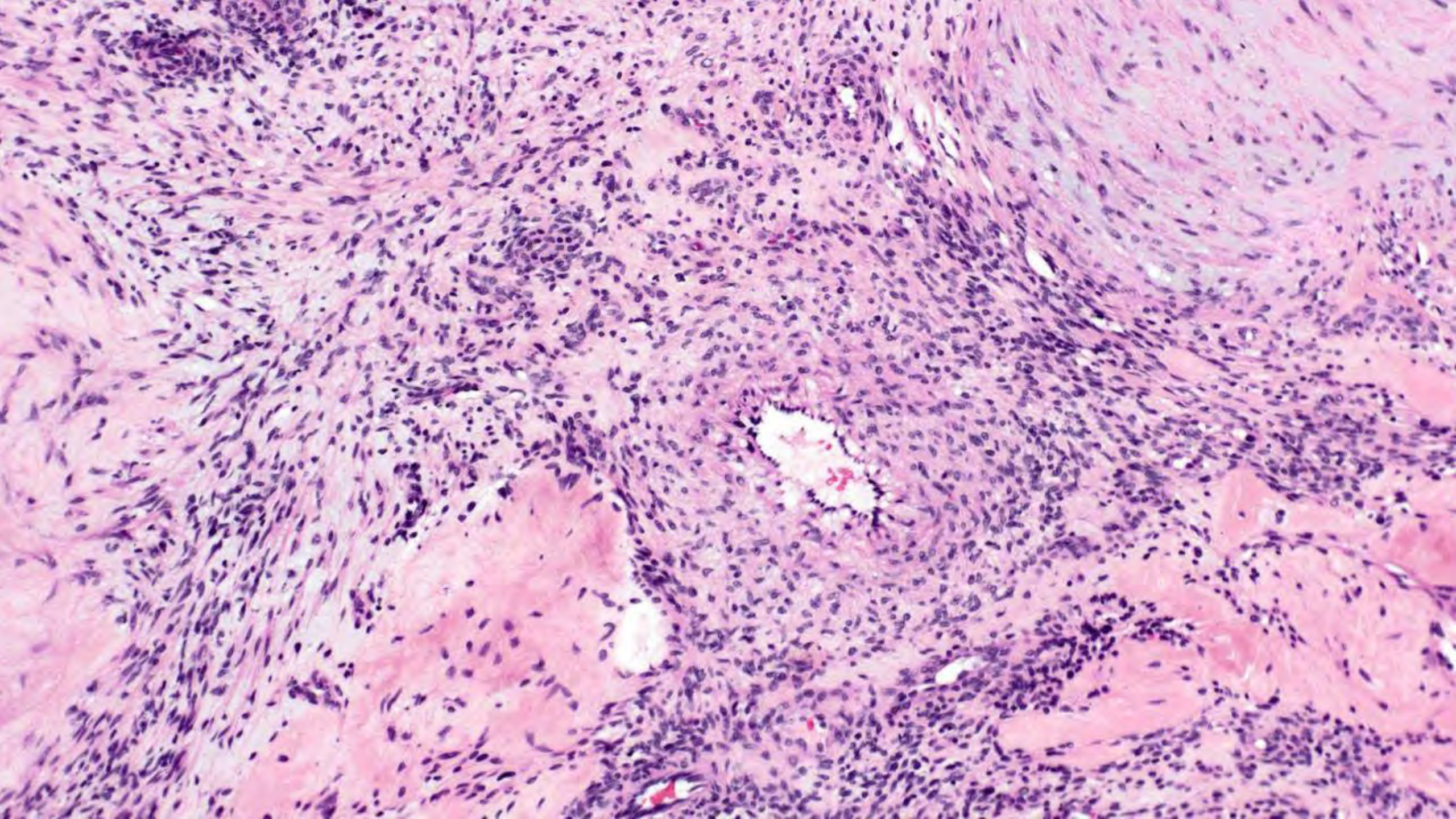
Case 11

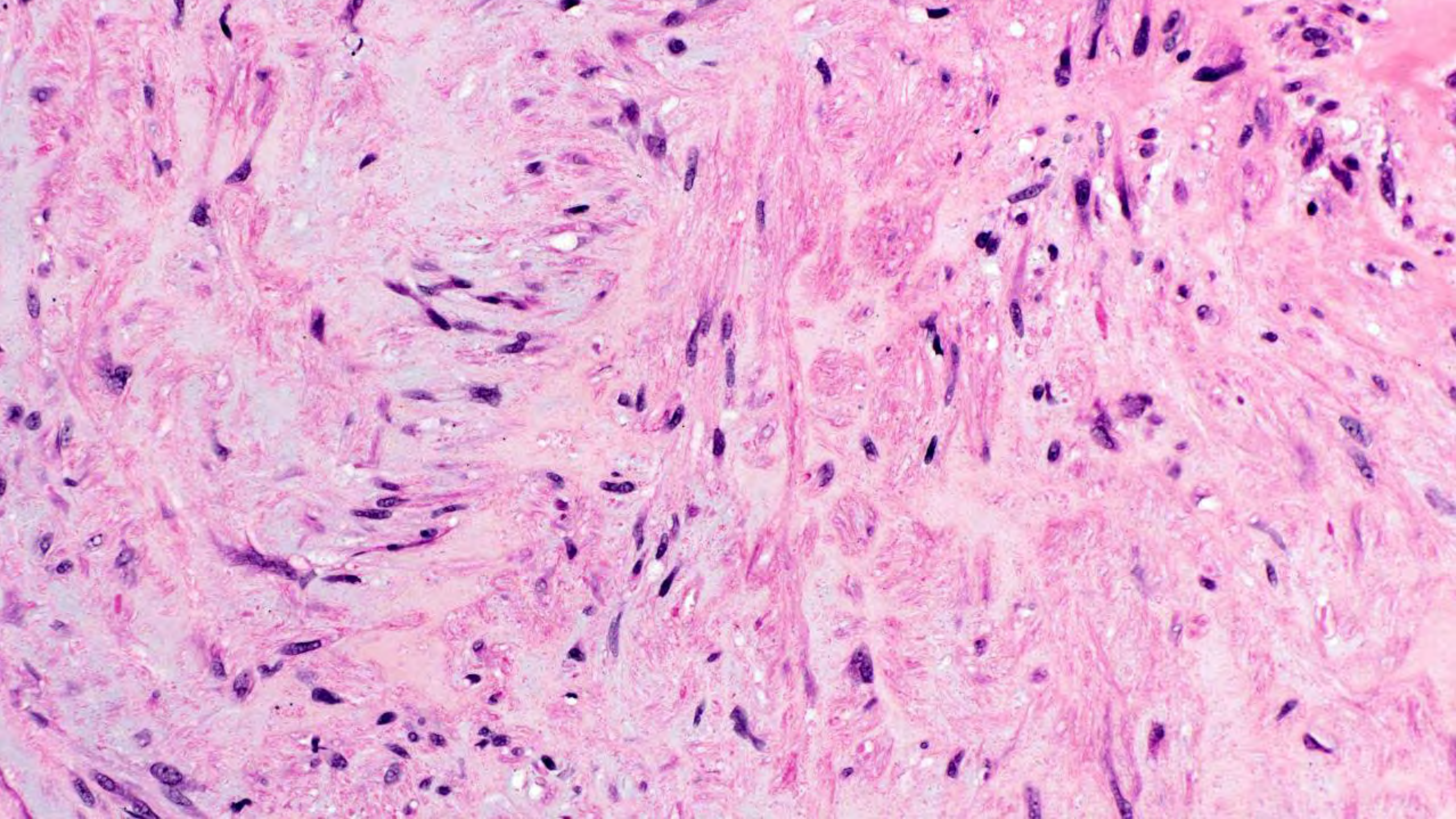
- ▶ 56y, M
- ▶ 1,1 cm large nodule suprapatellar
- ▶ DD: chondrom?

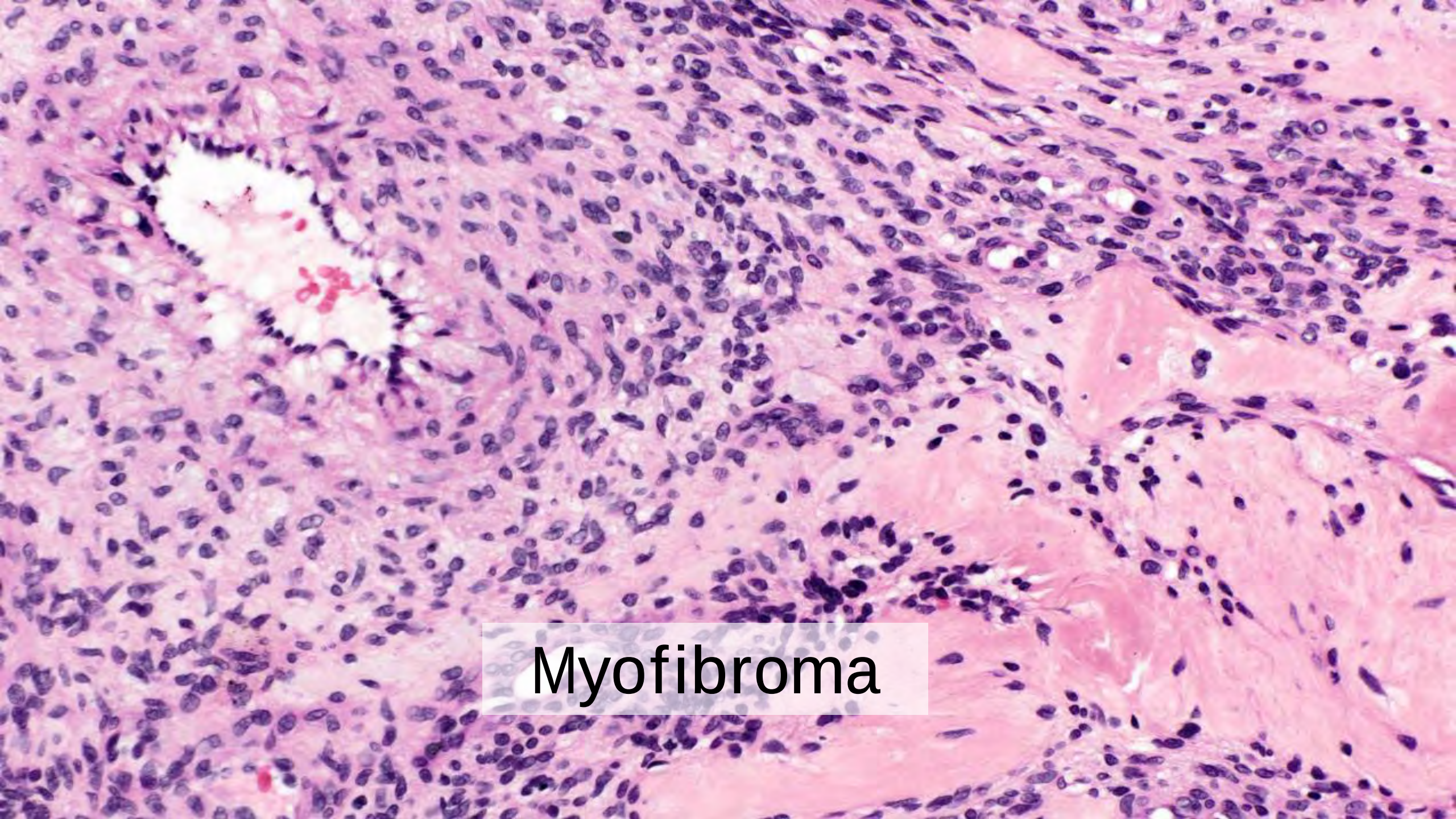












Myofibroma

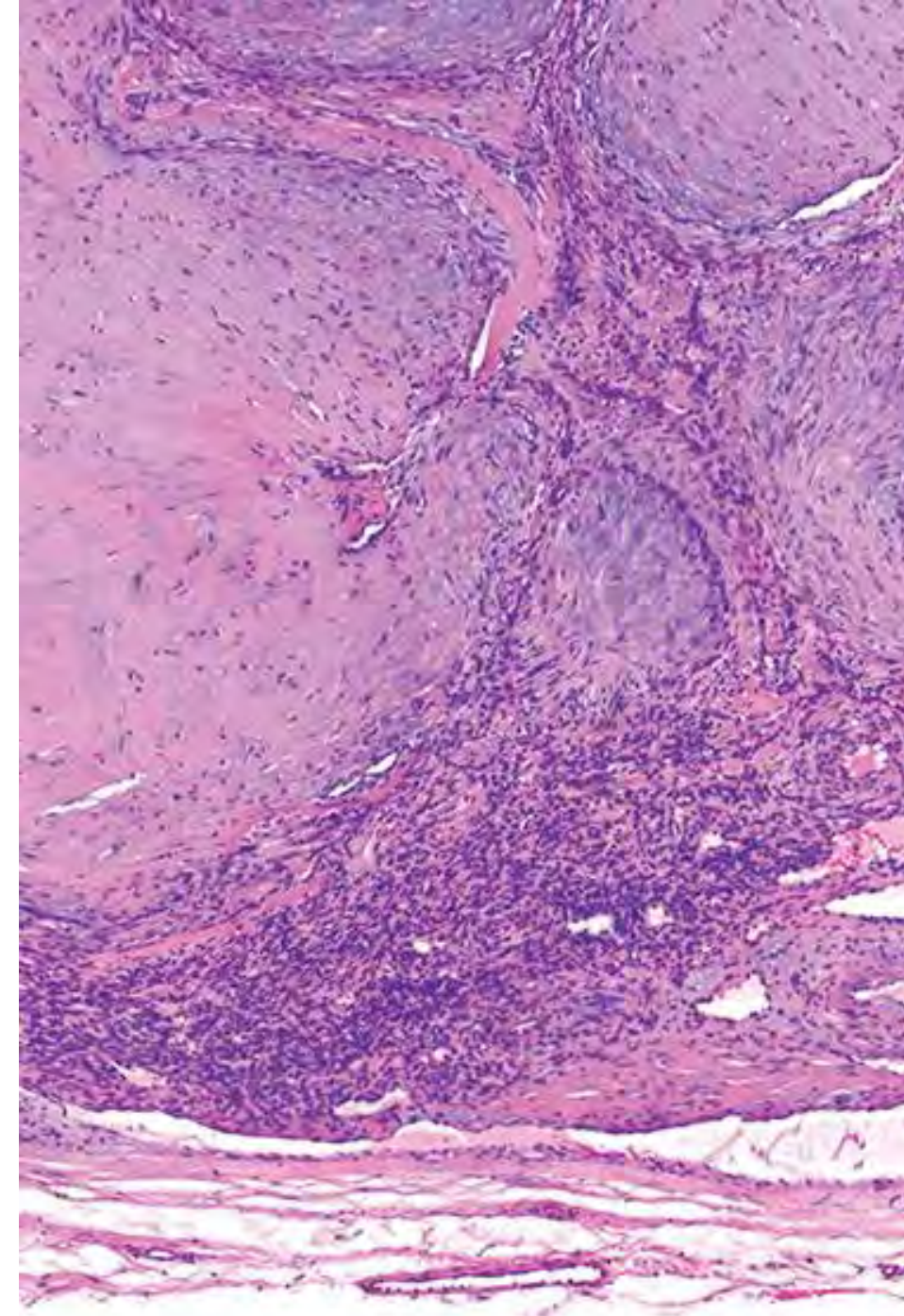
Myofibroma (Myofibromatosis)

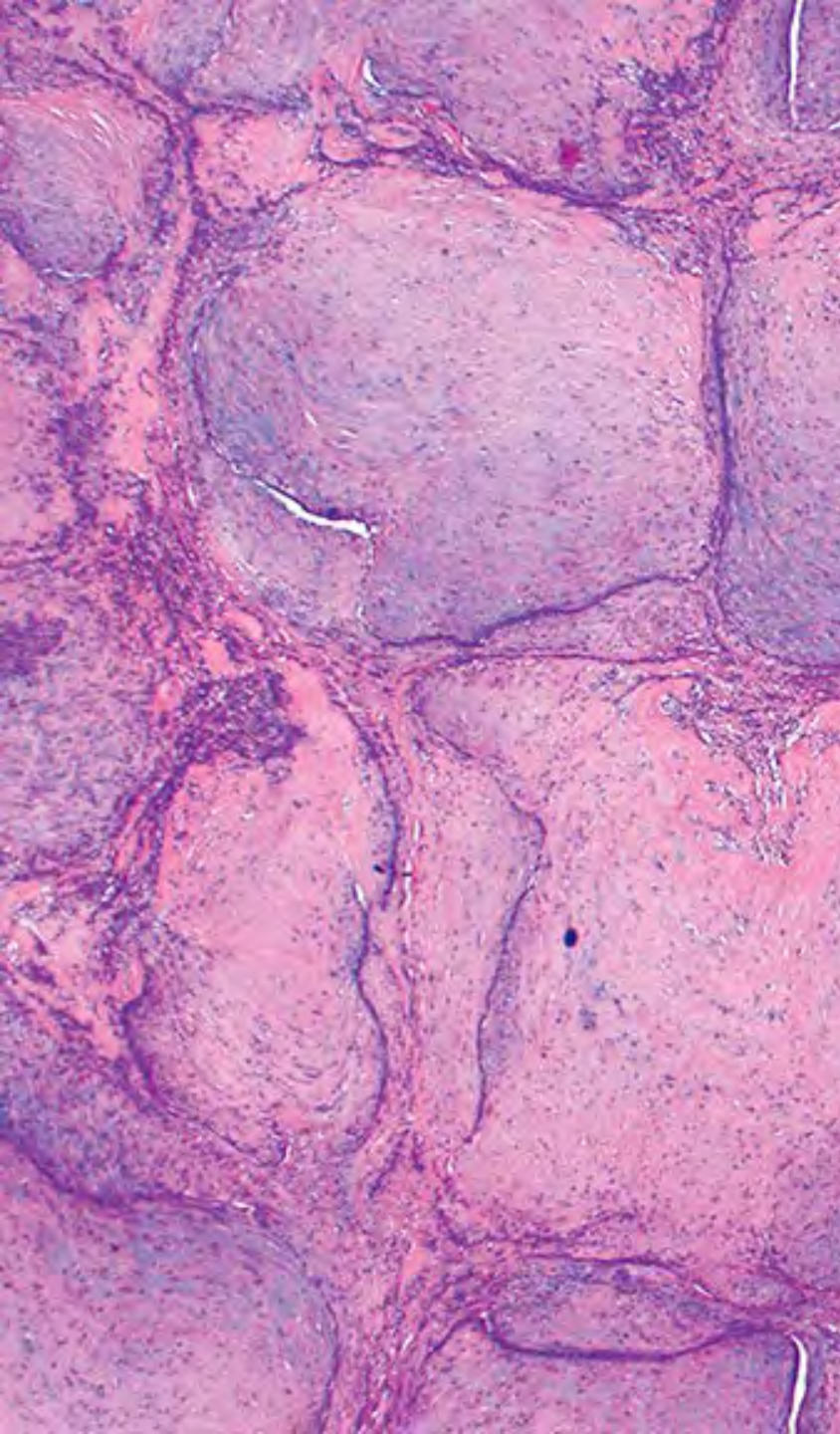
- ▶ 90% of cases are paediatric (65% occur by the age of 2 years)
- ▶ 3 forms:
 - ▶ **solitary:** skin/subcutis of the head & neck, upper extremities, trunk (>M)
 - ▶ frequent somatic *PDGFRB* mutations
 - ▶ **multicentric** (>F, pediatric cases)
 - ▶ **generalized** - visceral involvement
 - ▶ Germline mutations in *PDGFRB* (89%) and *NOTCH3* (11%) in the familial disease

► biphasic growth:

- 1) primitive, small rounded cells and plump spindled mesenchymal cells
 - associated with numerous thin-walled haemangiopericytoma-like vessels
- 2) mature eosinophilic plump spindled myoid cells
 - frequent myointimal-like nodular proliferations (vascular balls)

- **IHC:** SMA+, (h-caldesmon absent or focally +)
- usually desmin-negative

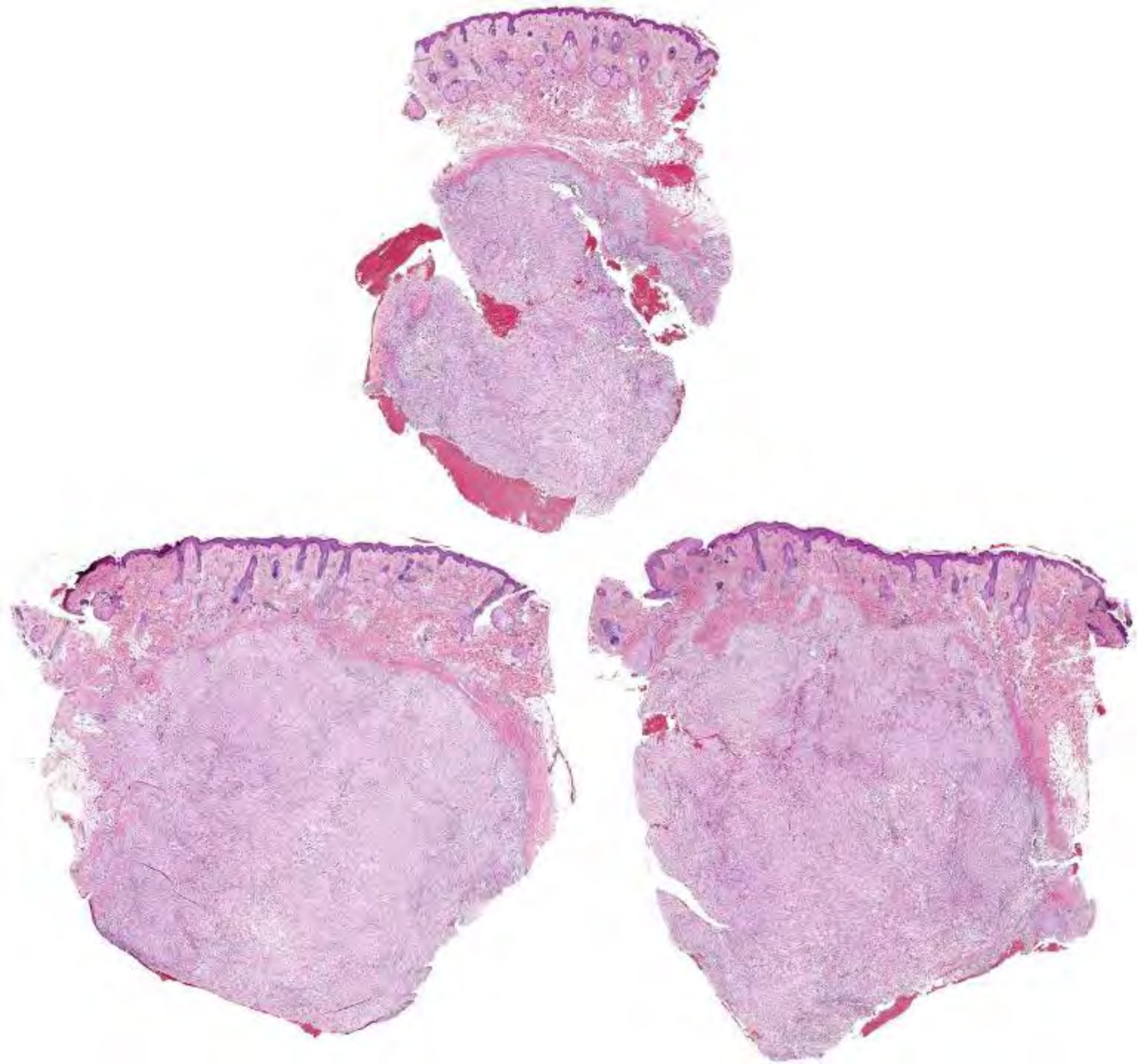


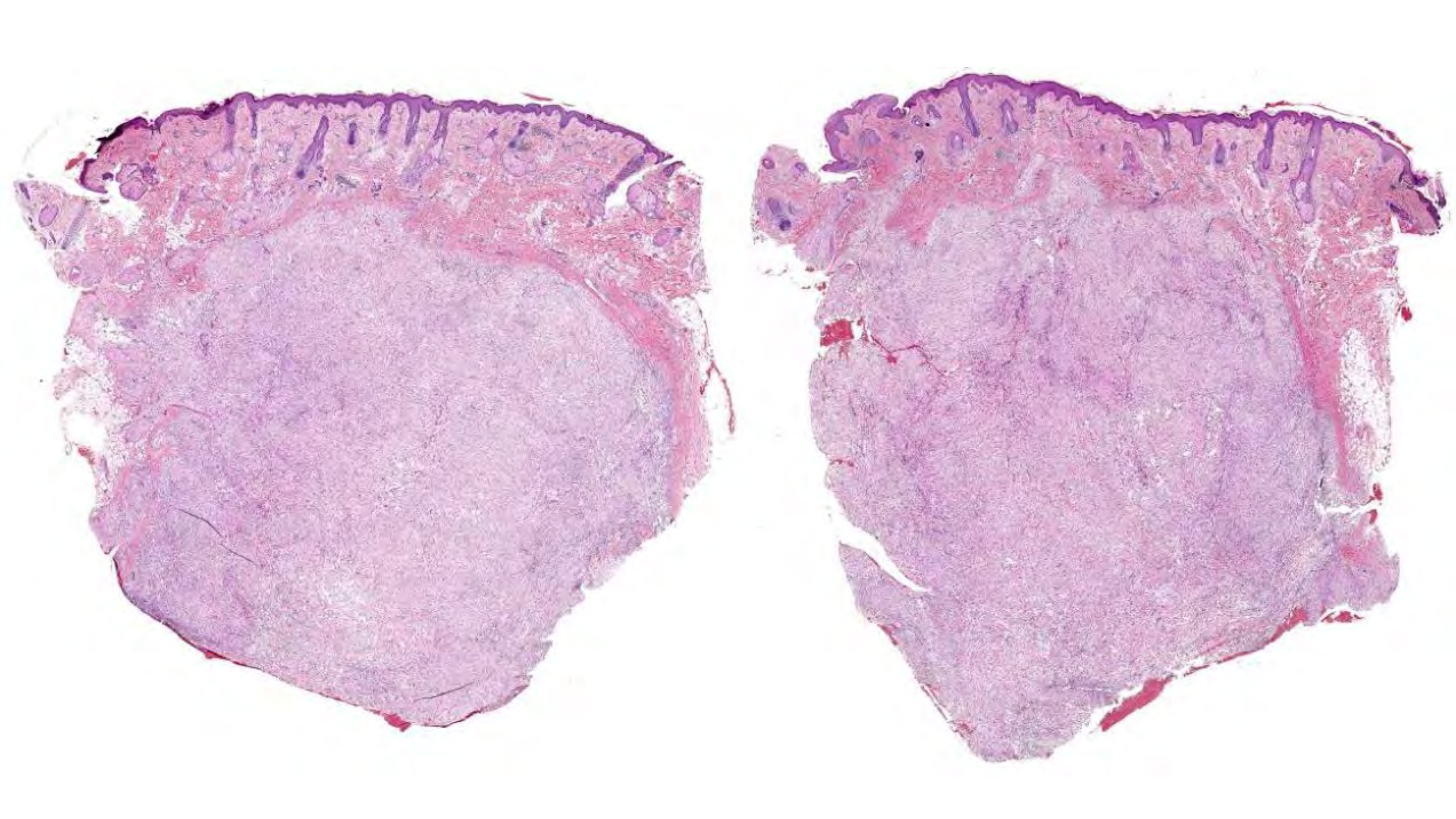


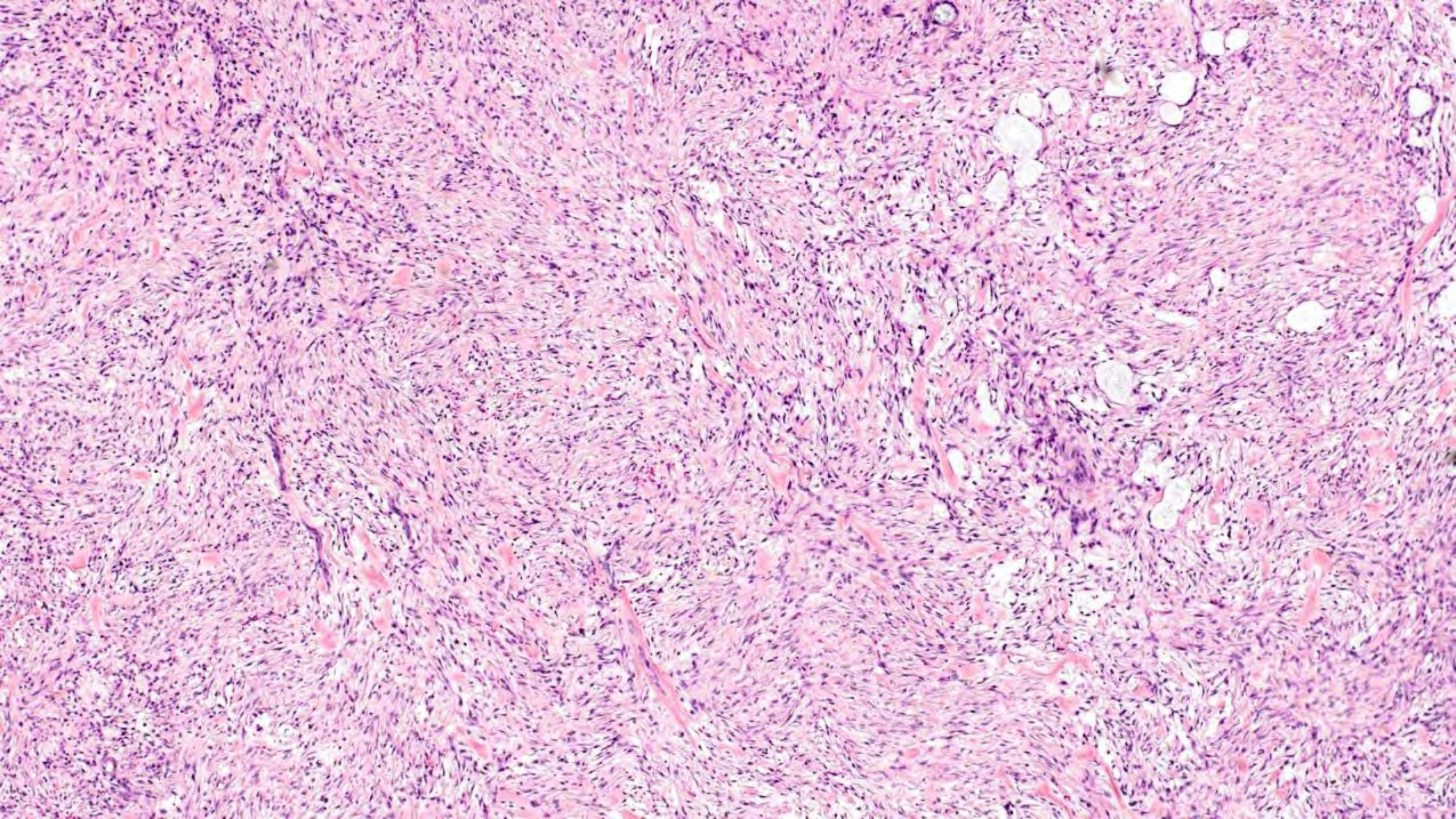
SMA

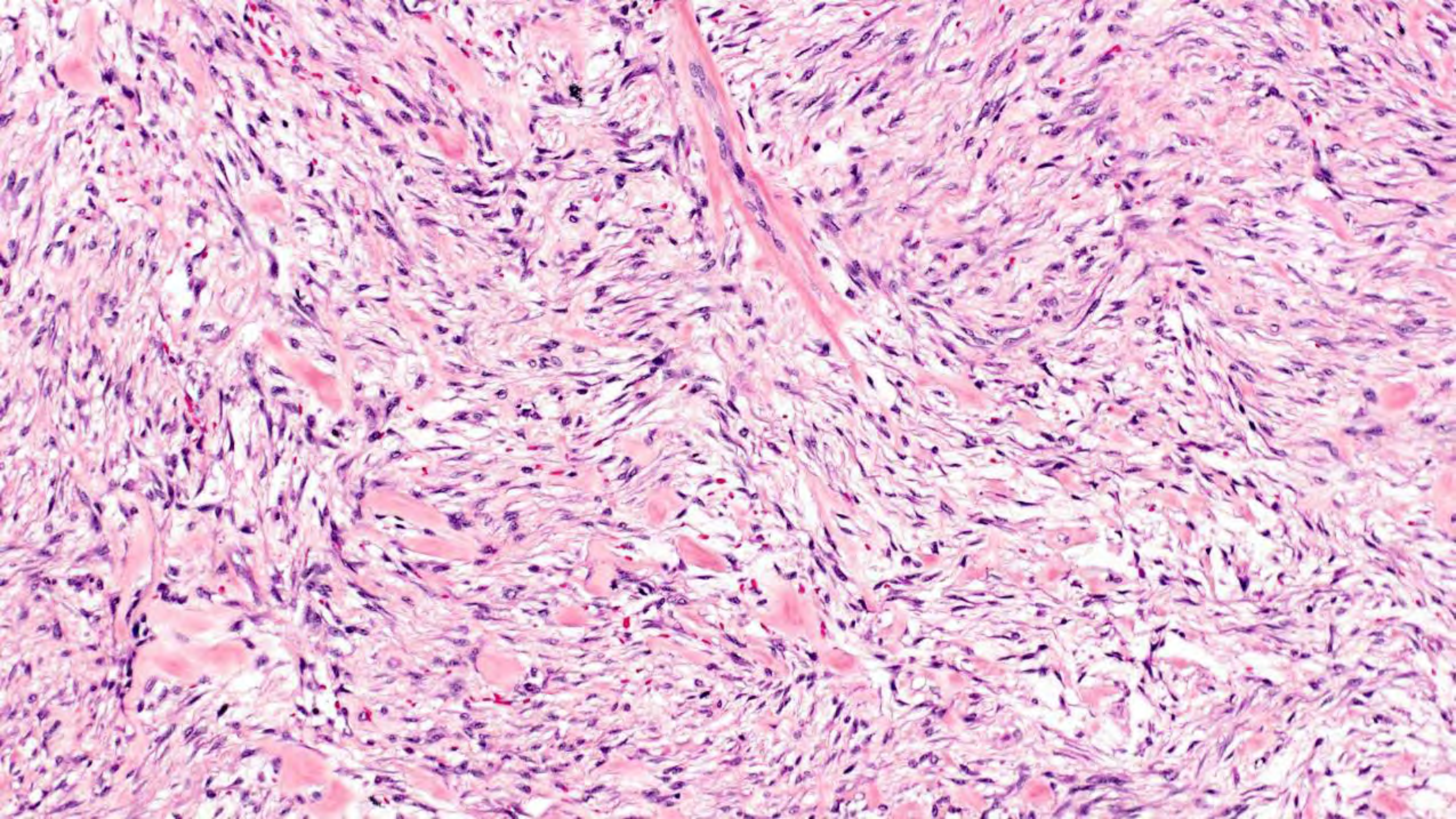
Case 12

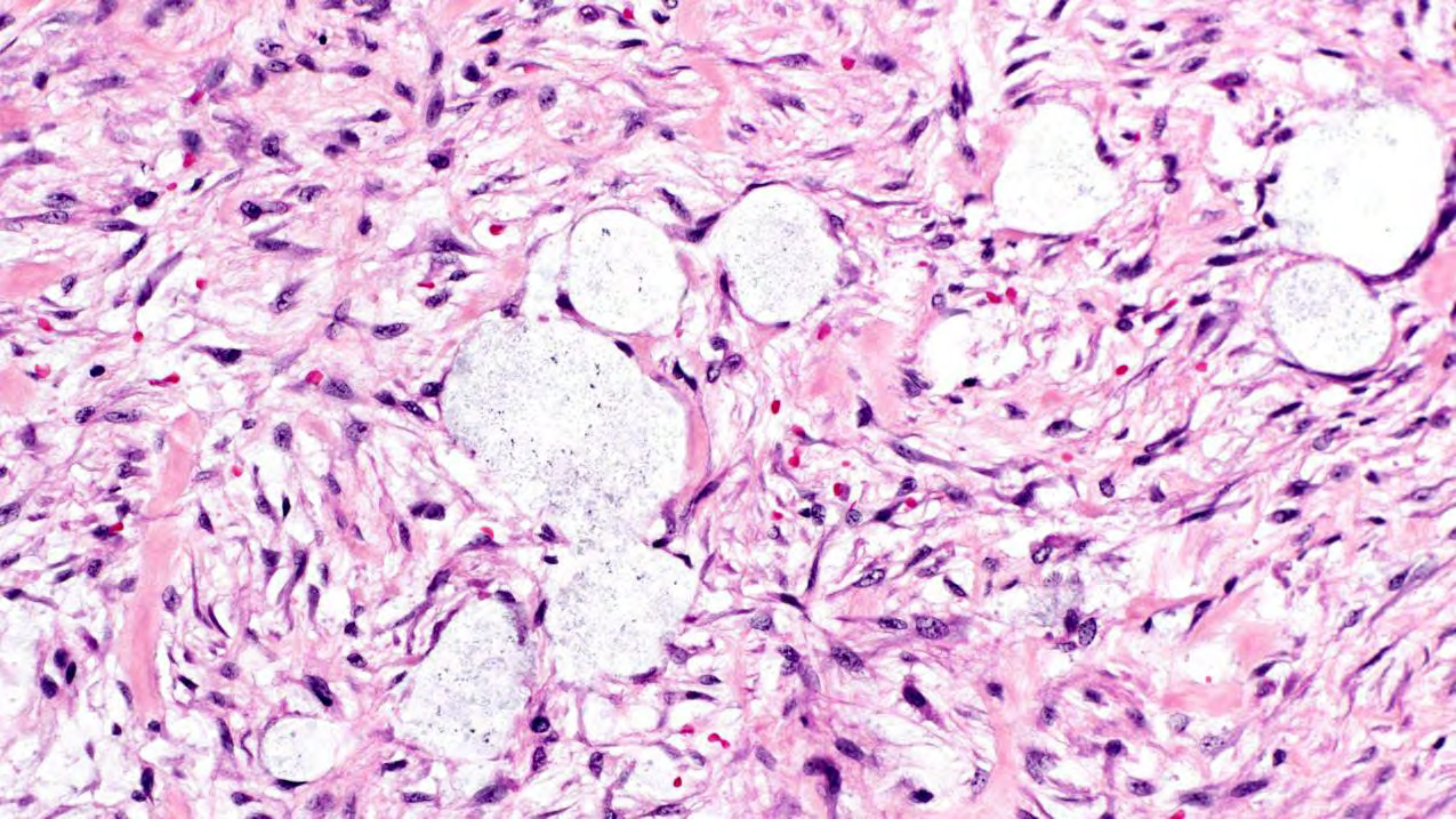
- ▶ 31y, F
- ▶ 0,8 cm large elevated lesion on the chin

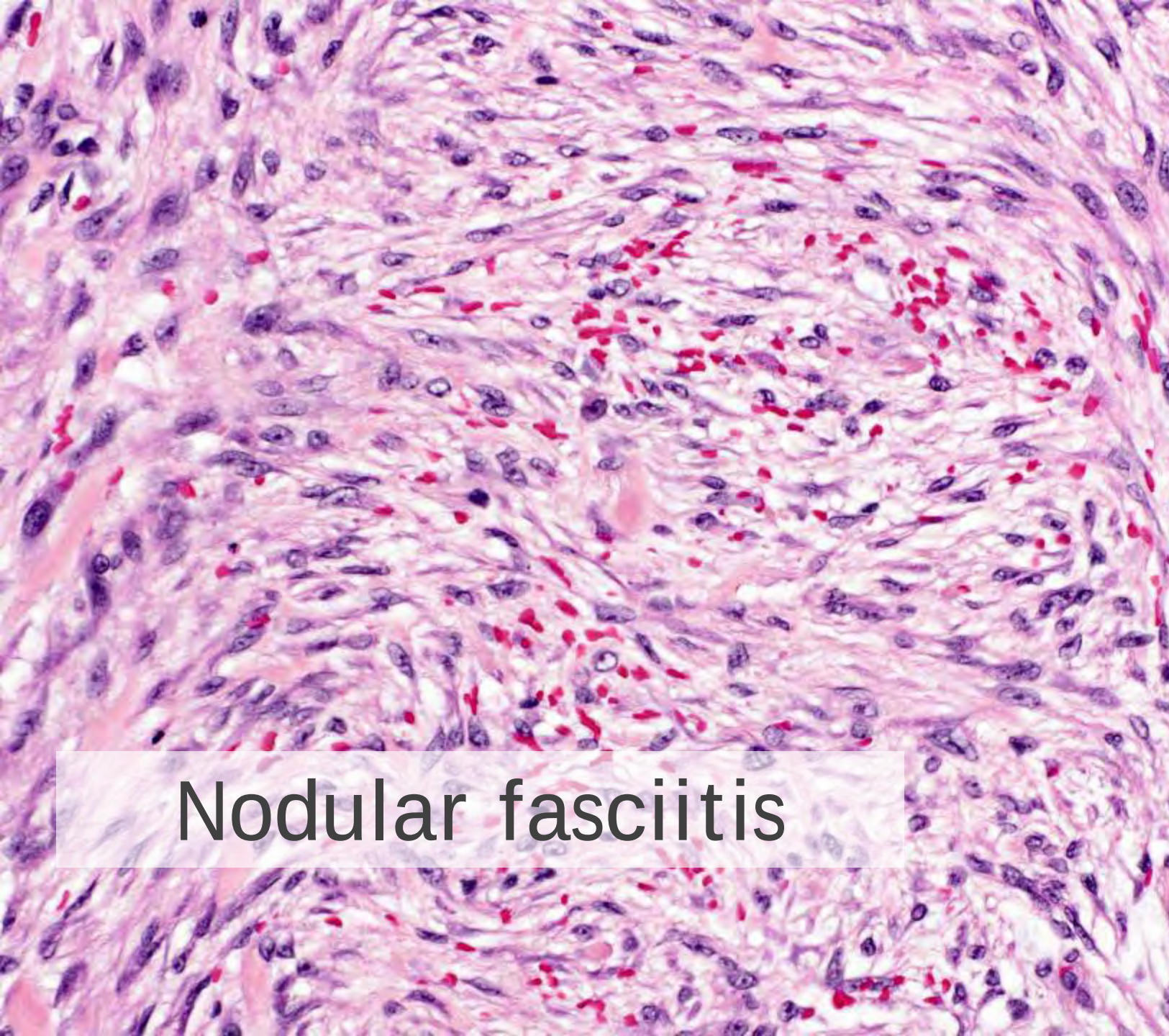




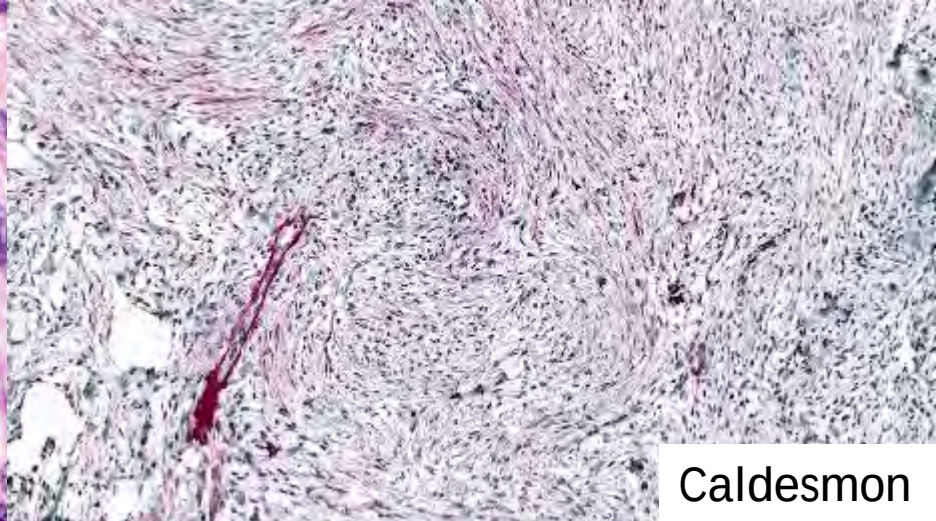




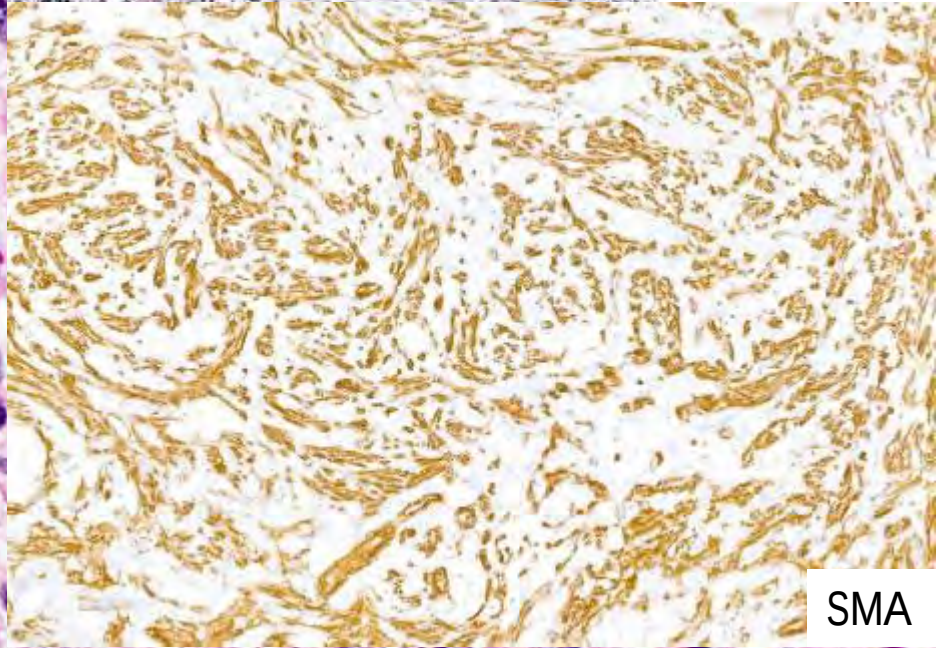




Nodular fasciitis



Caldesmon



SMA

Nodular fasciitis

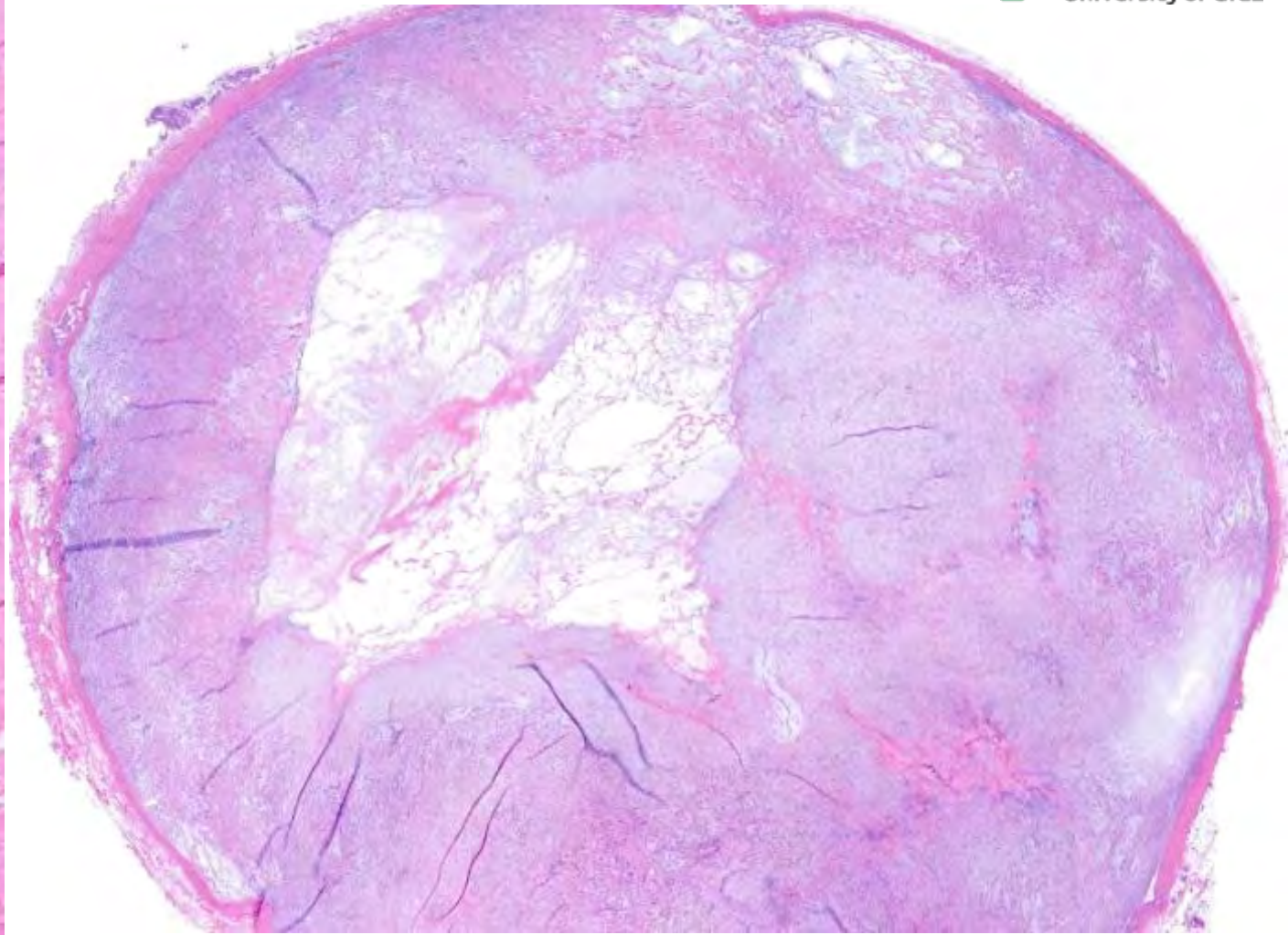
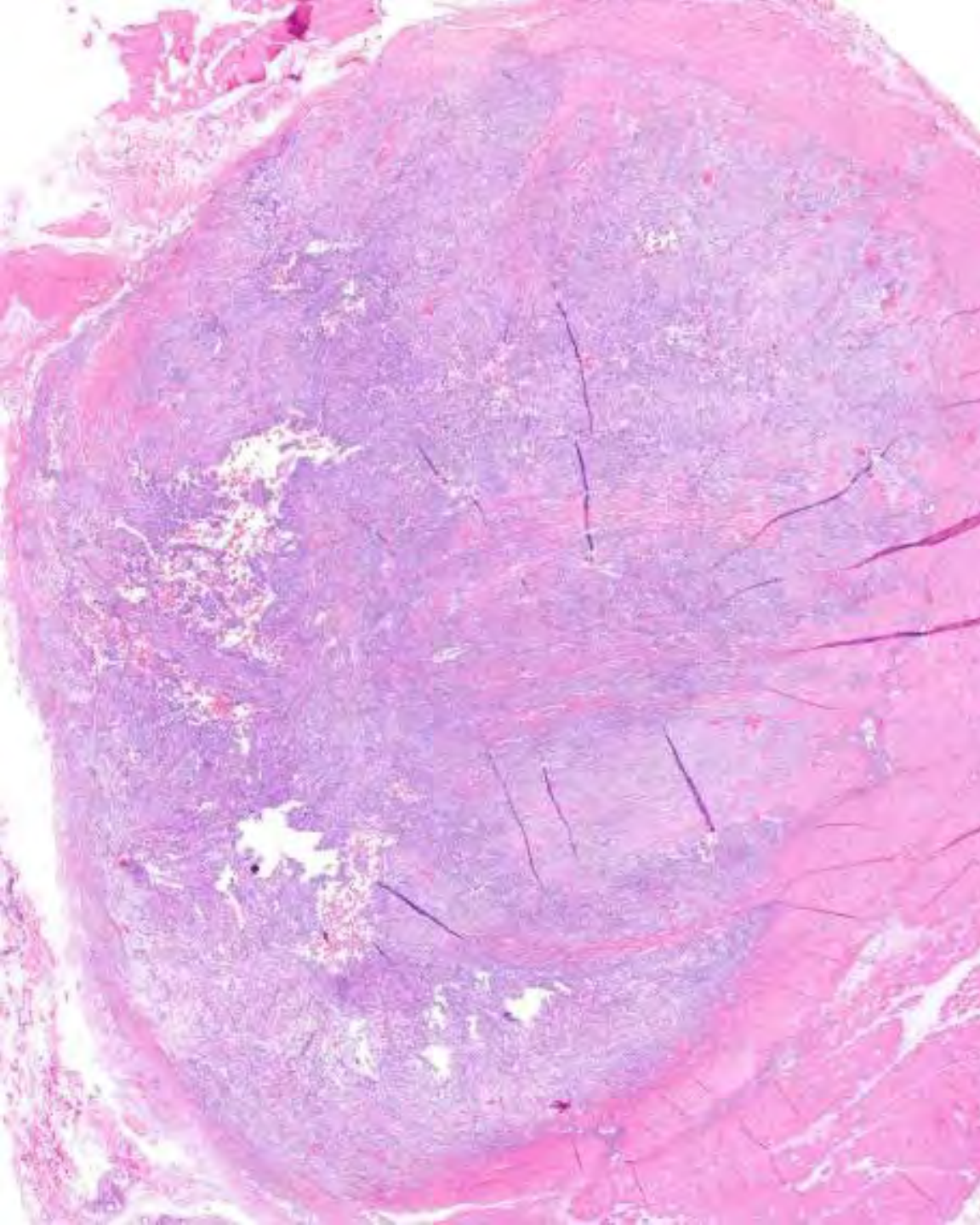
- ▶ Involve surface of fascia and extend into subcutis (also intramuscular)
- ▶ Any anatomic site can be involved
- ▶ **Variants:**
 - ▶ Intravascular fasciitis
 - ▶ Cranial fasciitis
 - ▶ Tenosynovial fasciitis
- ▶ Cellularity can vary
 - ▶ Degenerative changes – myxoid, cystic
- ▶ *USP6* fusion partners:
 - ▶ *MYH9*, *COL1A1*, *COL3A1*, *COL1A2*, *RRBP1*, *CALU*, *CTNNB1*, *MIR22HG*, *SERPINH1*,

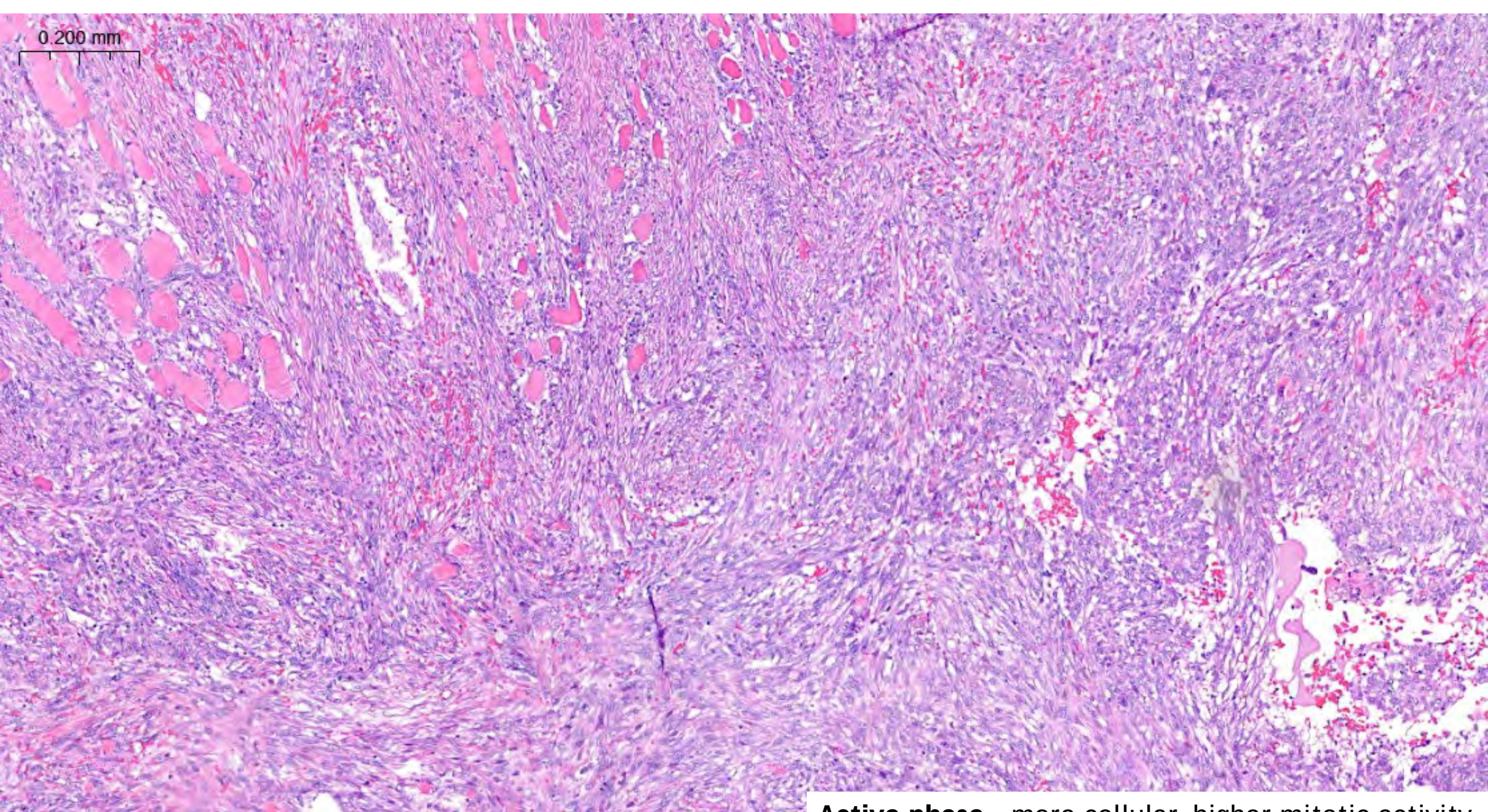
USP6 rearranged neoplasms (soft tissue)

- ▶ **Nodular fasciitis** (*MYH9*, ...)
- ▶ (Cellular) Fibroma of tendon sheath (*MYH9*, *COL1A1*, ...)
- ▶ **Myositis ossificans** (*COL1A1*)
- ▶ Fibro-osseous pseudotumor of digits (*COL1A1*)

Without bone
formation

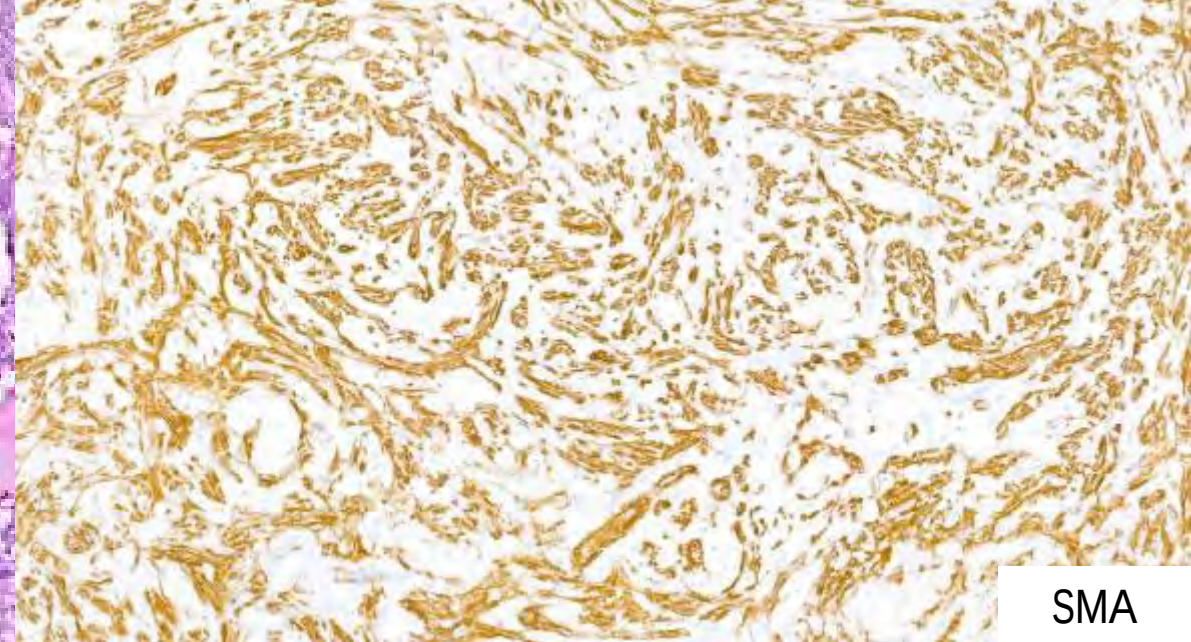
With bone
formation





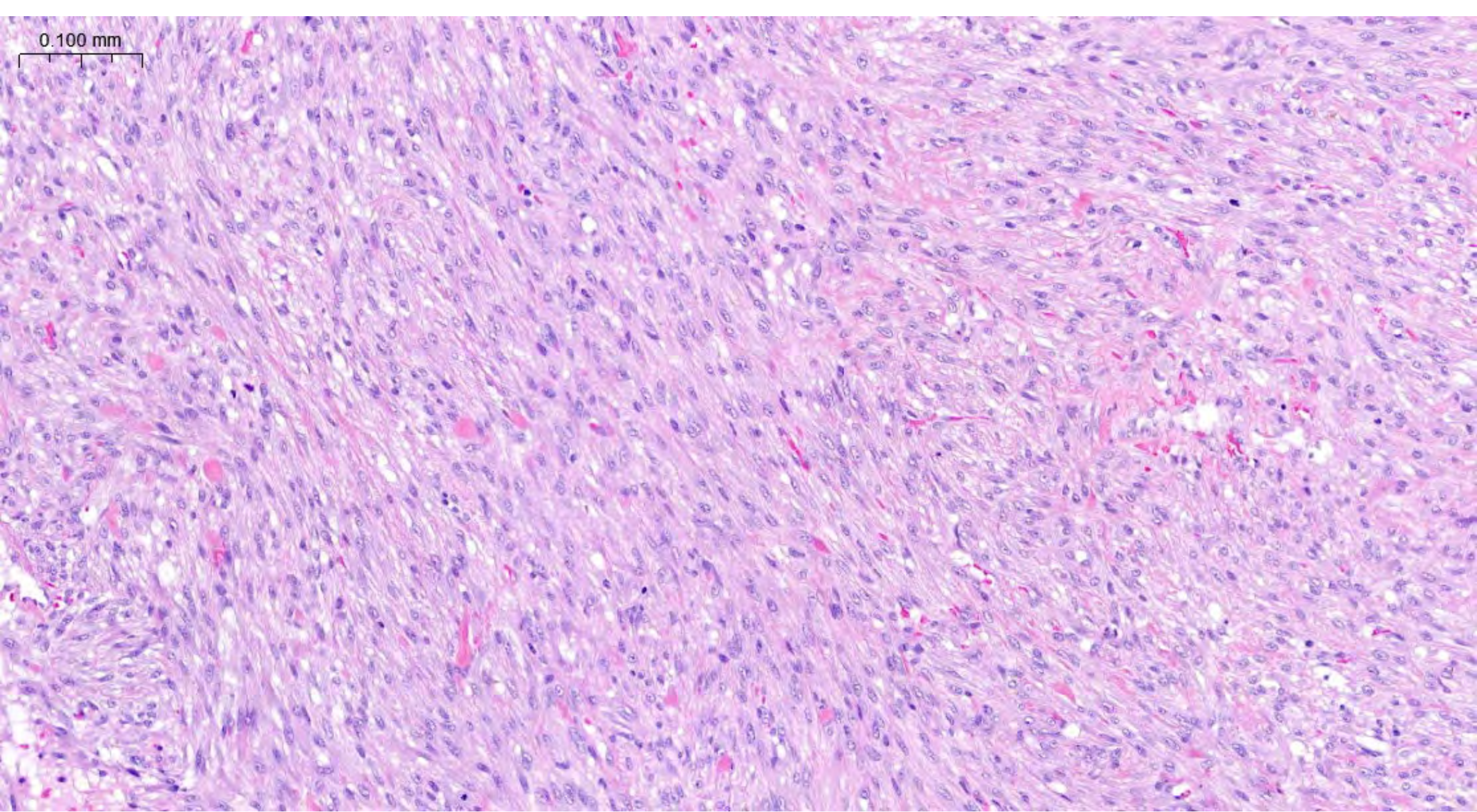
Active phase – more cellular, higher mitotic activity

0.500 mm

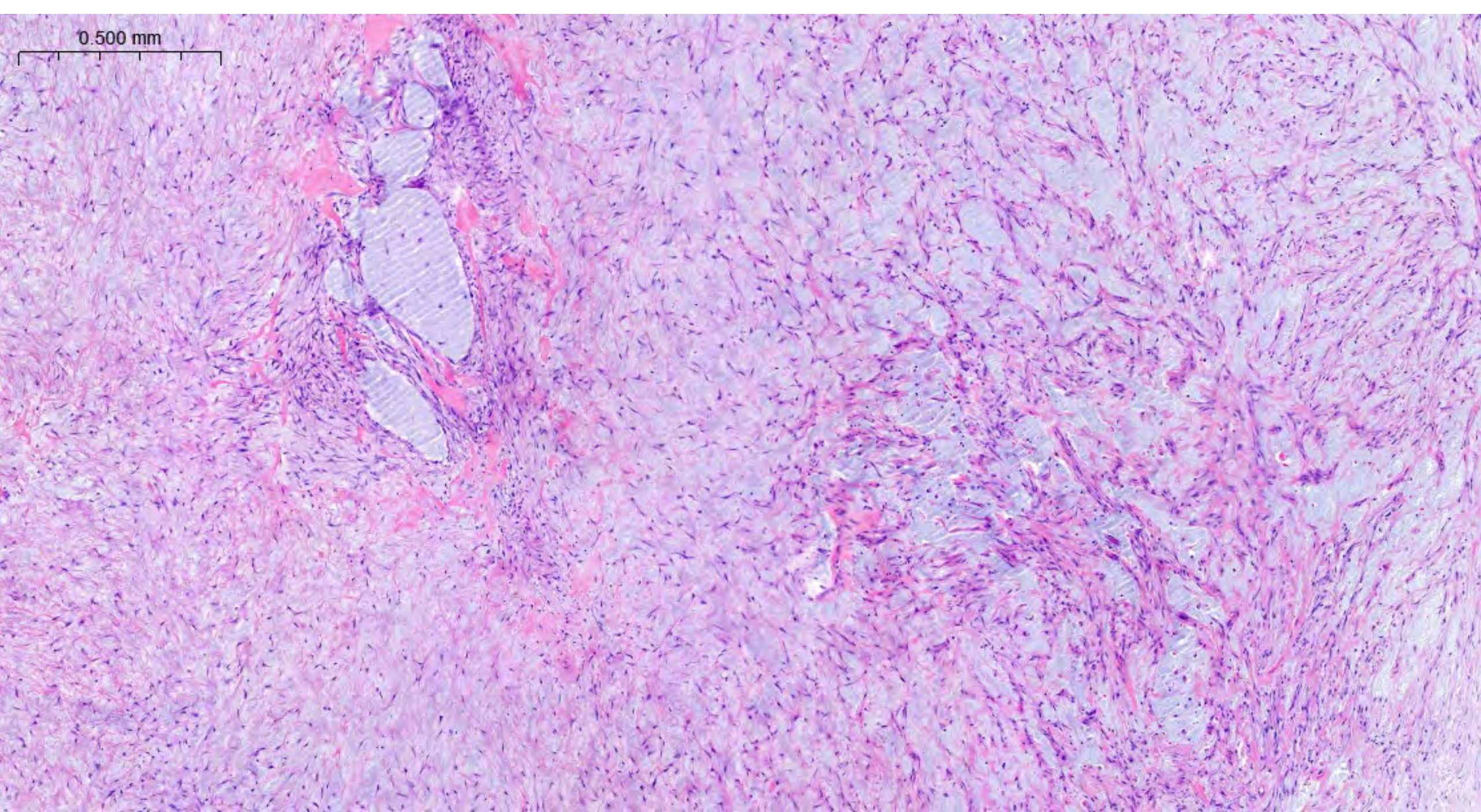


SMA

0.100 mm

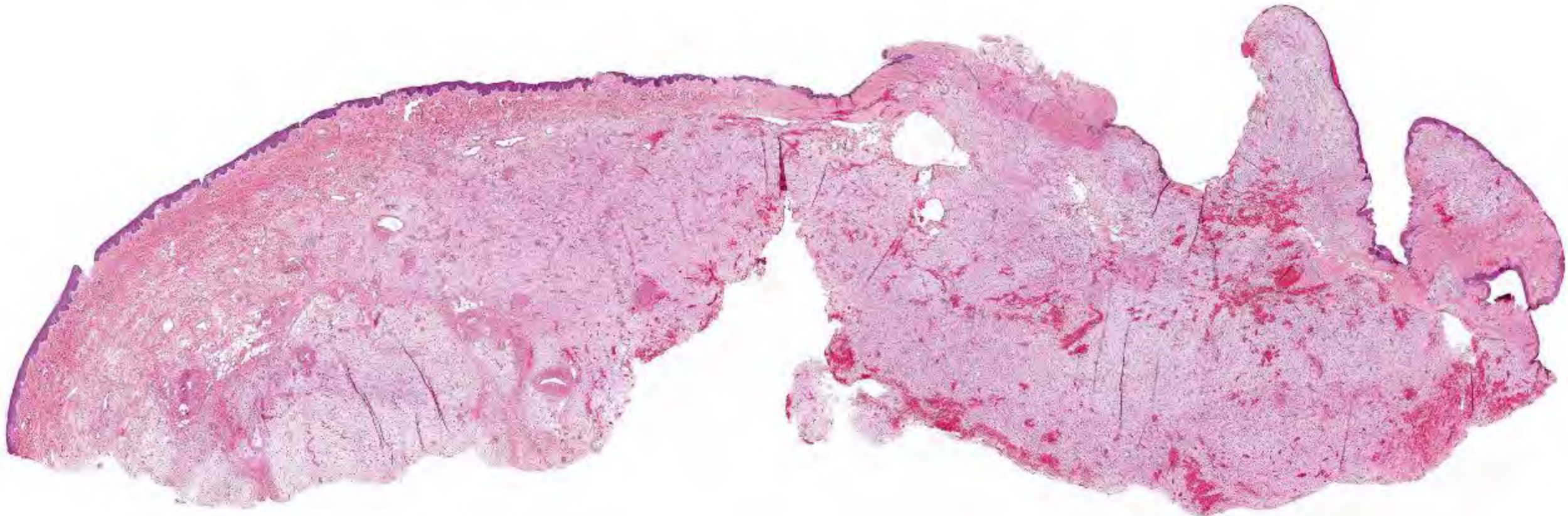


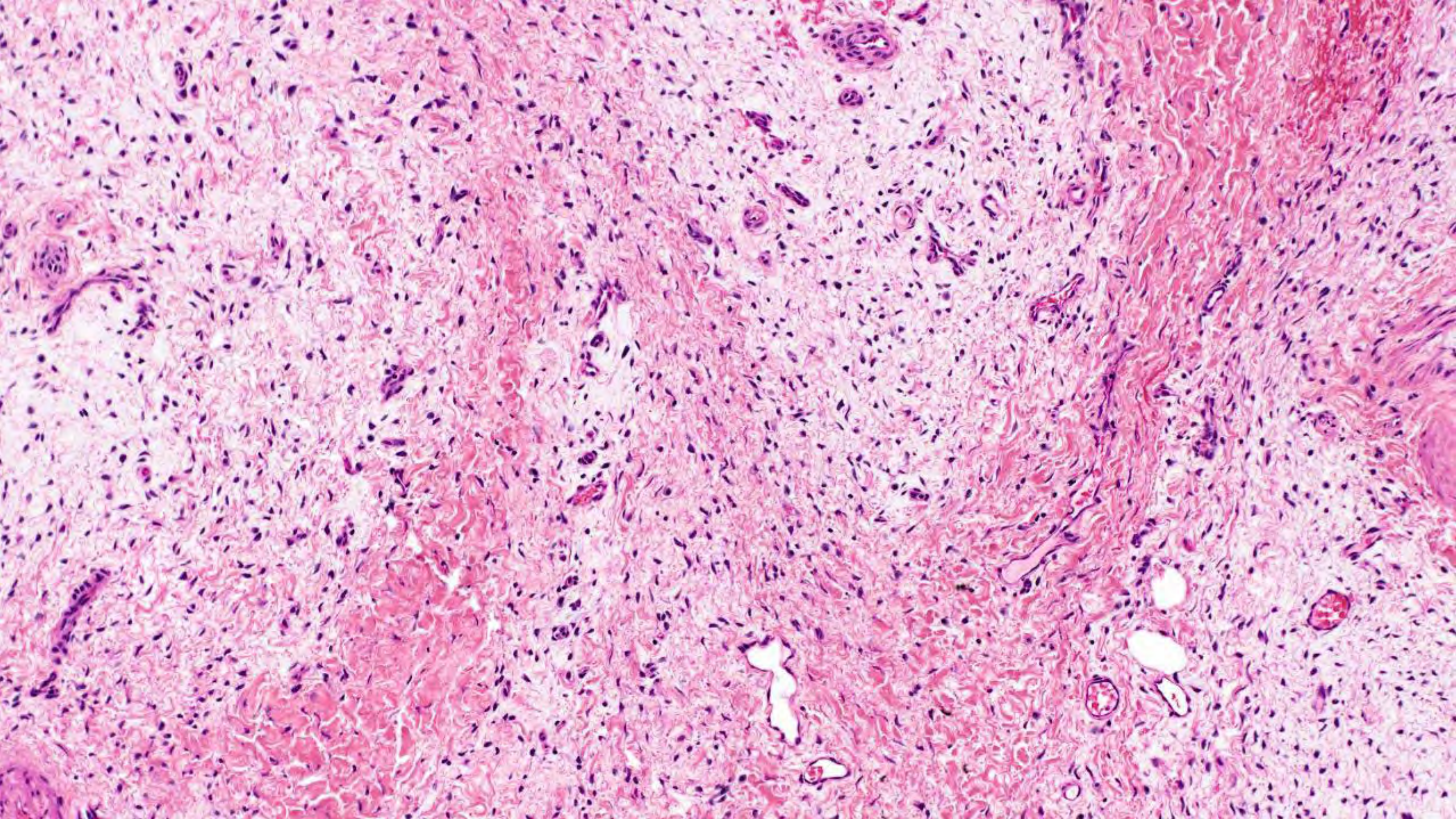
0.500 mm

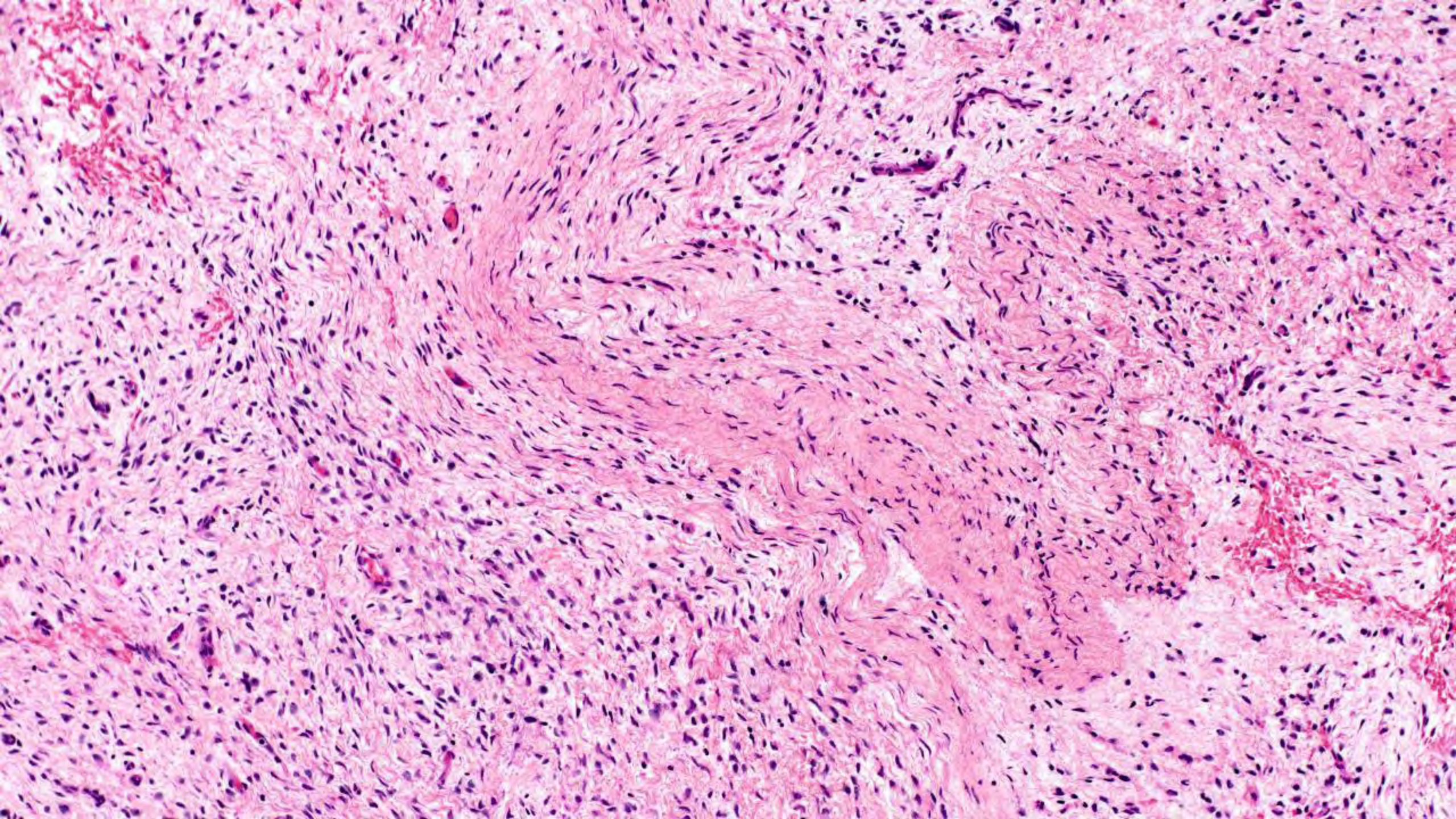


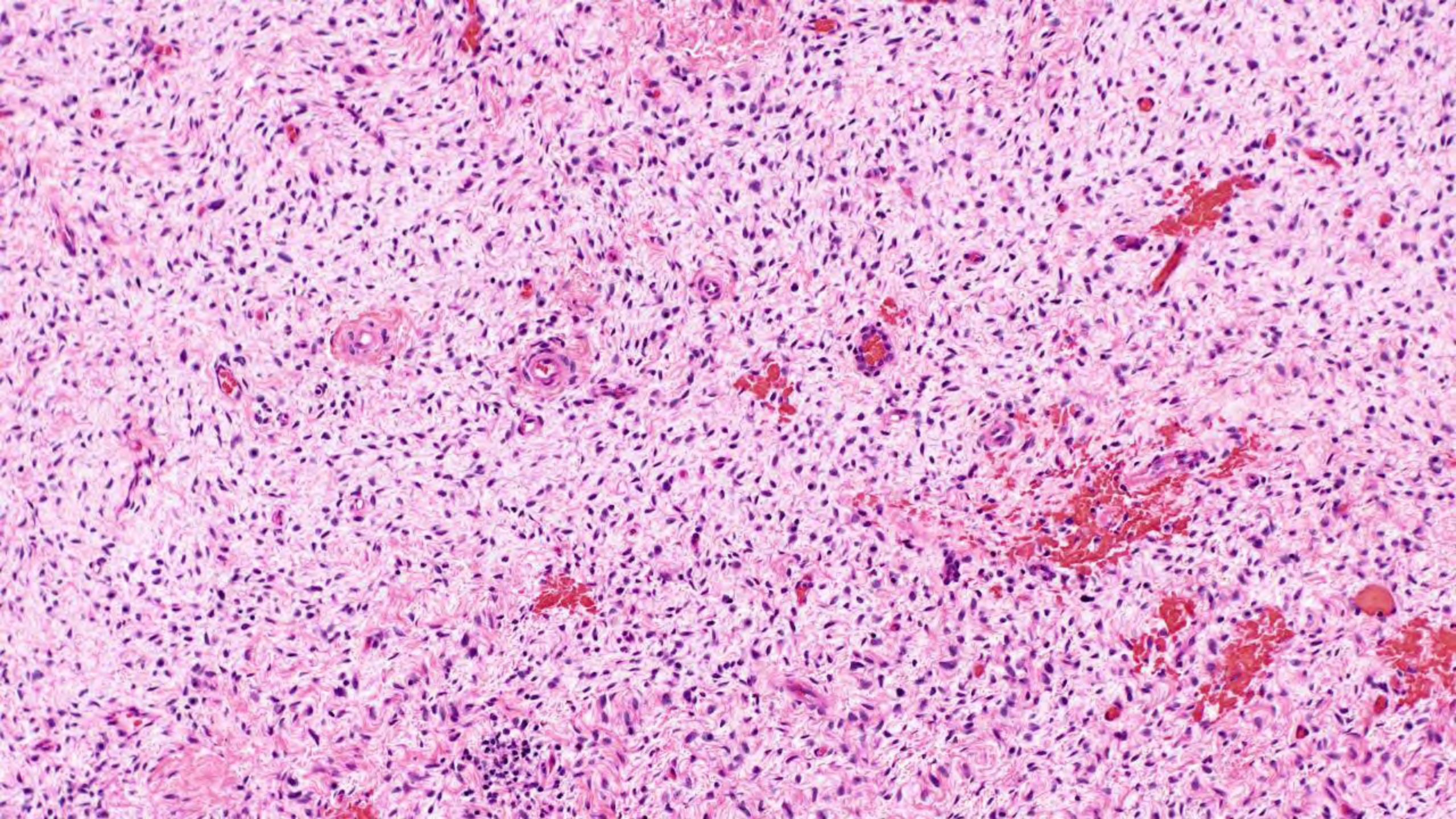
Case 13

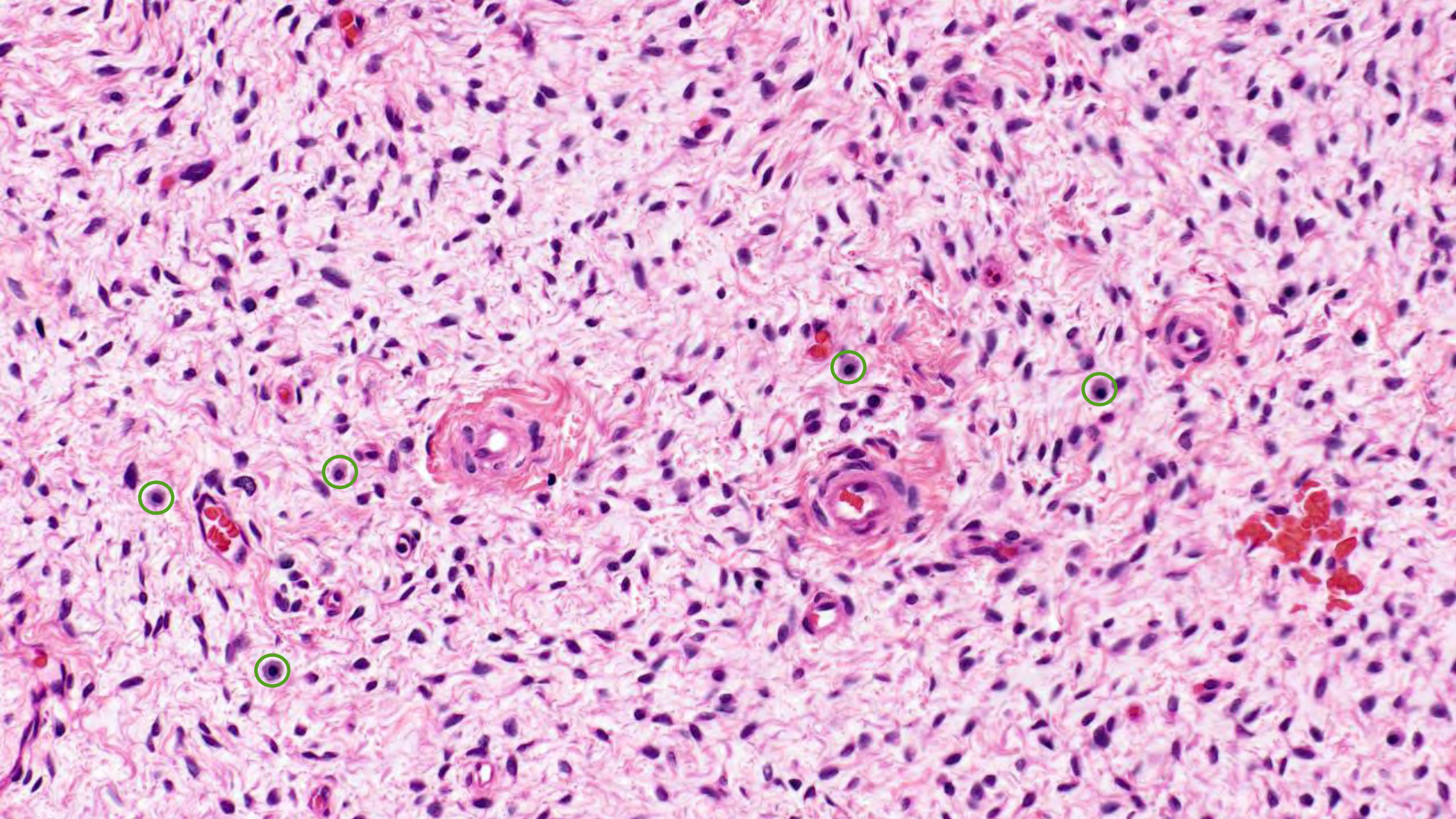
- ▶ 60y, F
- ▶ nodule in the peri-/subungual region

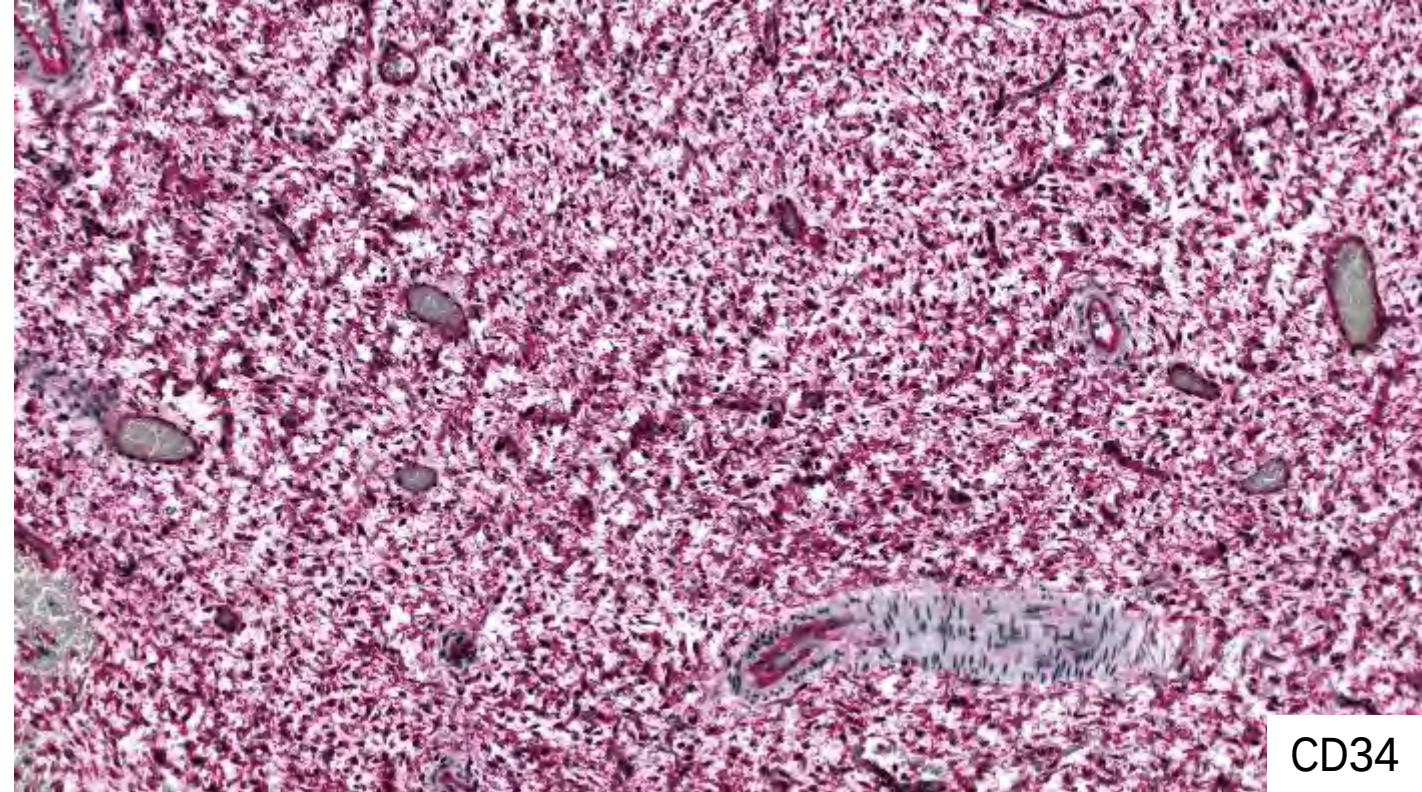
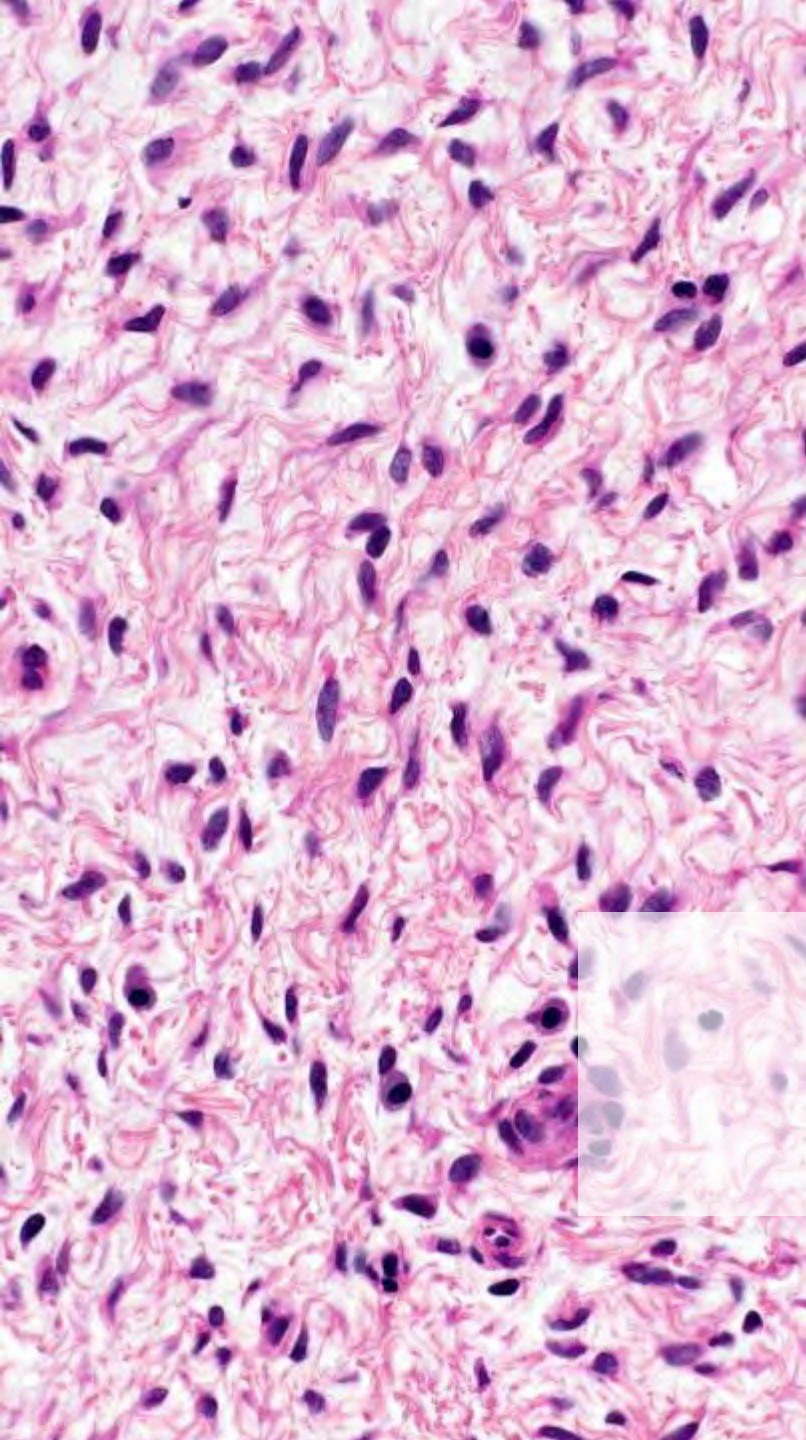






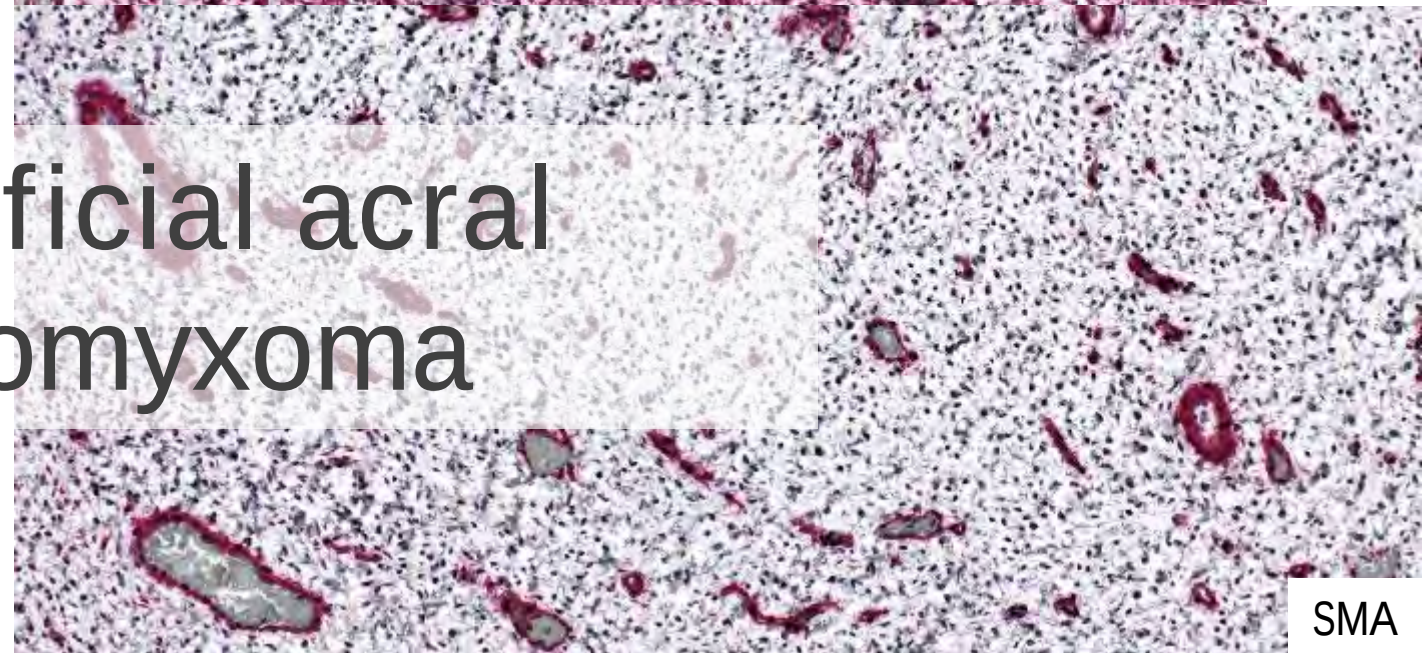






CD34

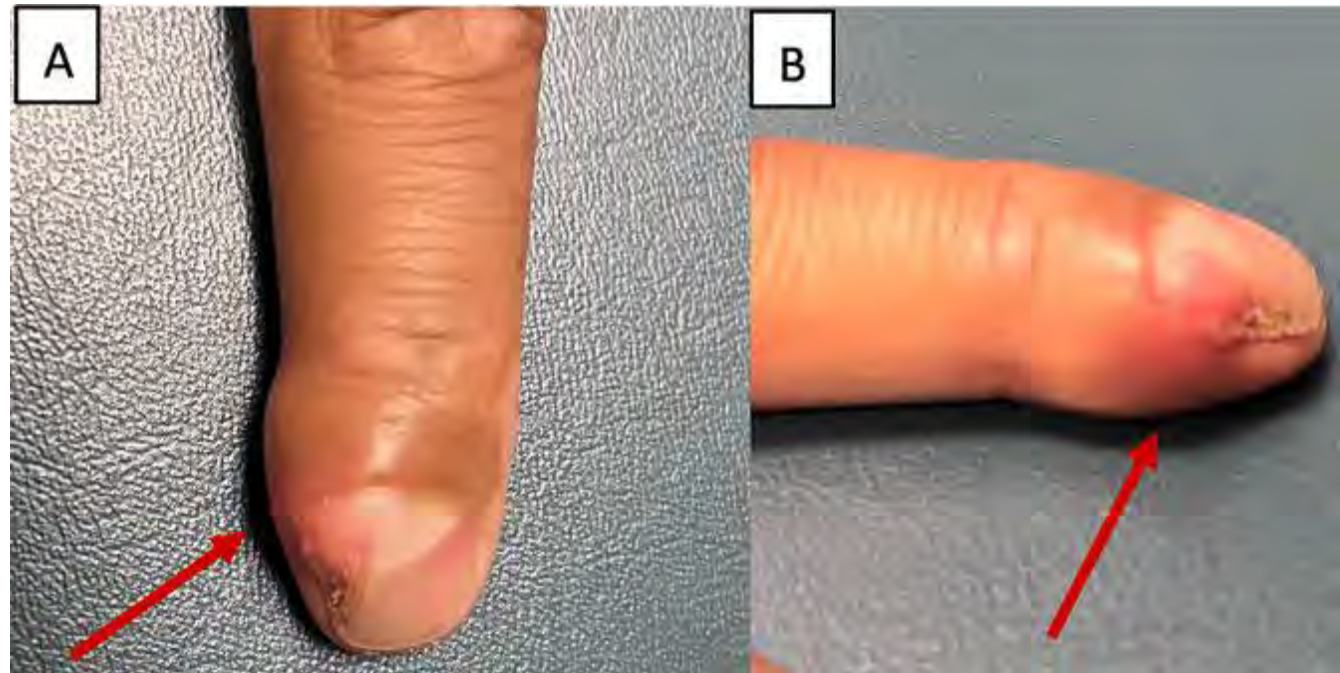
Superficial acral fibromyxoma



SMA

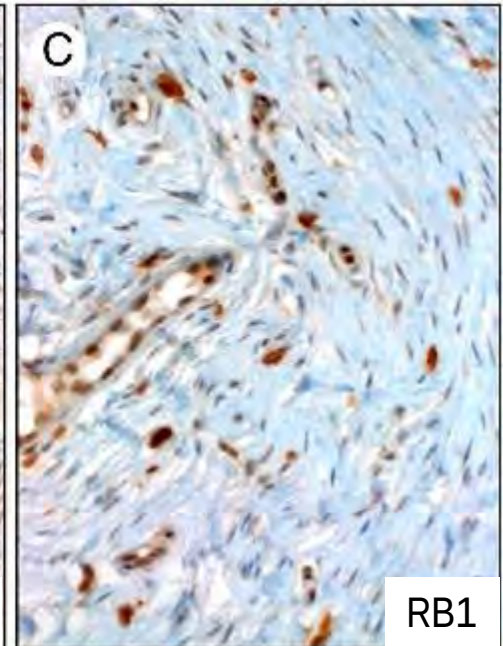
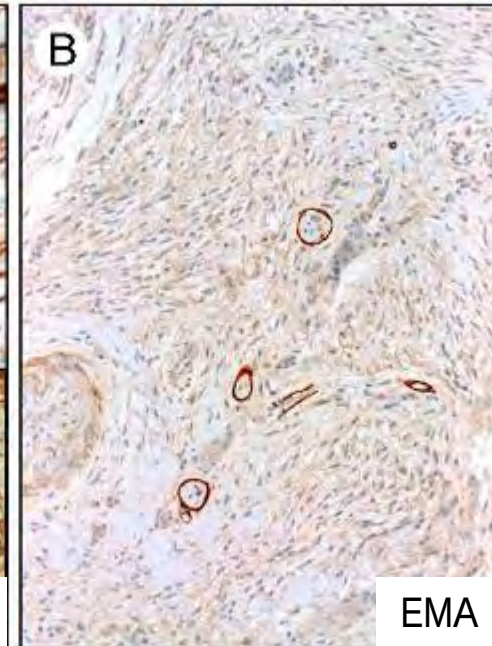
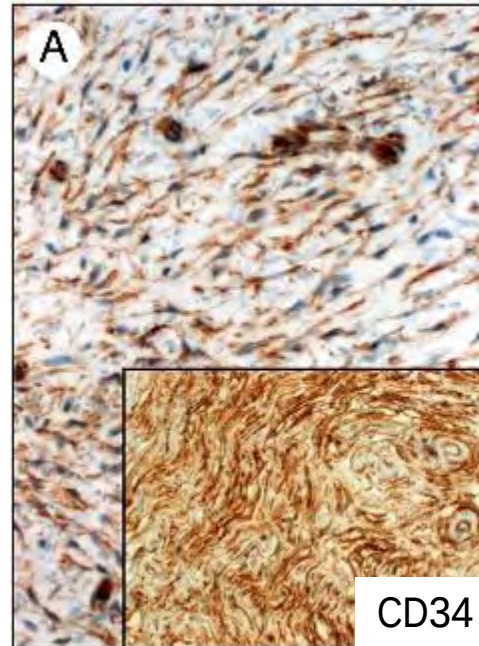
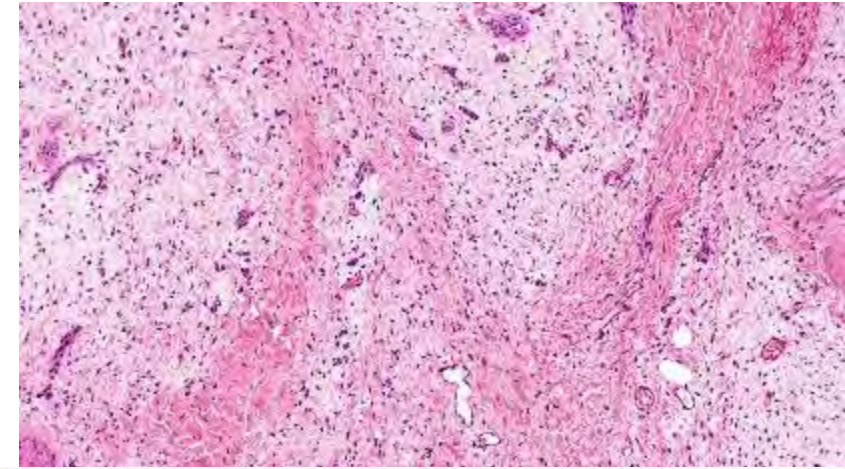
Superficial acral fibromyxoma

- ▶ benign fibroblastic neoplasm
- ▶ restricted to acral sites
 - ▶ marked predilection for the **periungual (subungual) region of the digits**
 - ▶ potential for local recurrence
- ▶ solitary, slowly growing
- ▶ often painful



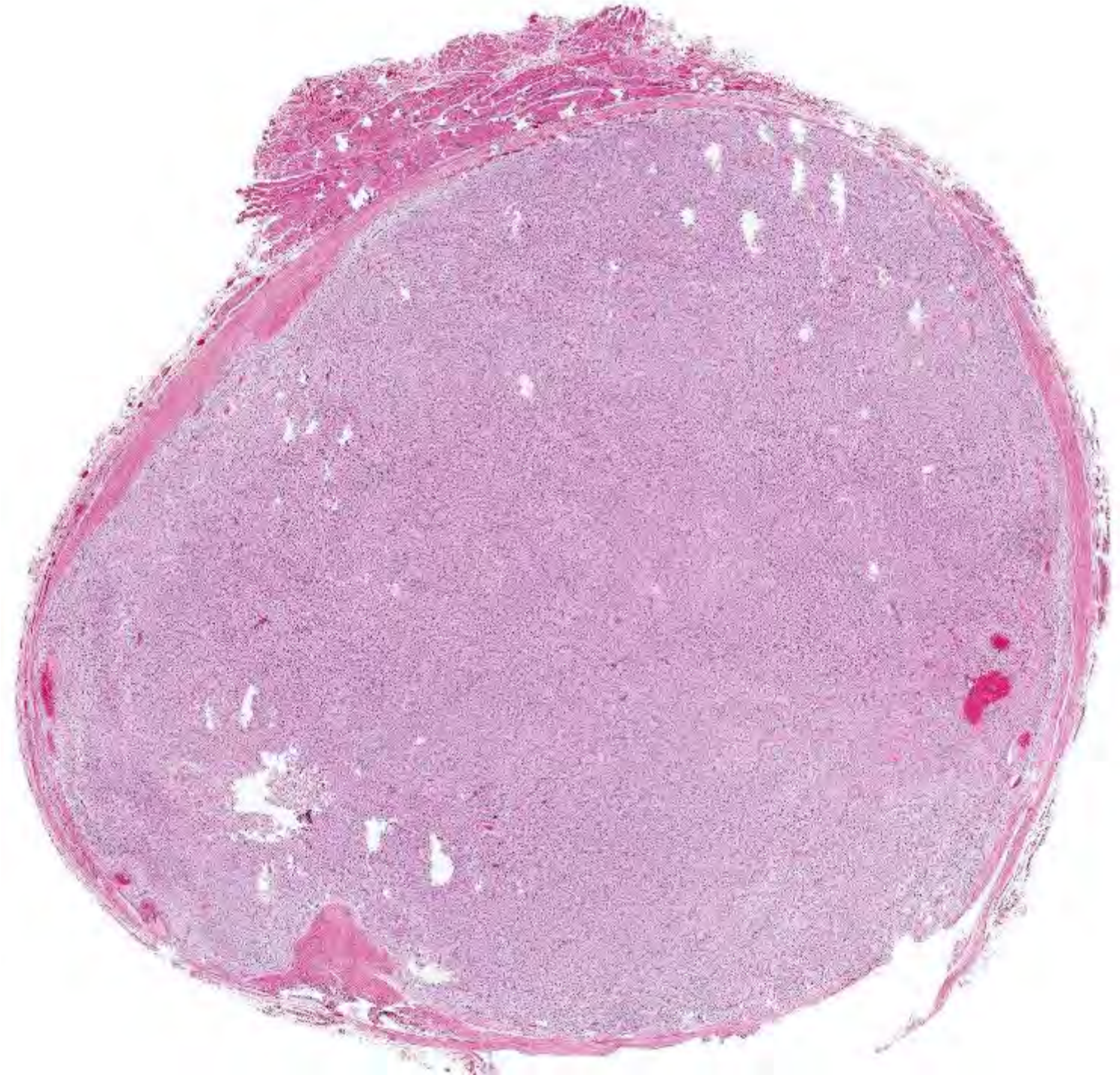
Superficial acral fibromyxoma

- ▶ *RB1* gene deletions at chromosome 13q14.2
 - ▶ RB1 loss
- ▶ DD (CD34+):
 - ▶ **DFSP** myxoid variant
 - ▶ superficial angiomyxoma
 - ▶ myxoid neurofibroma

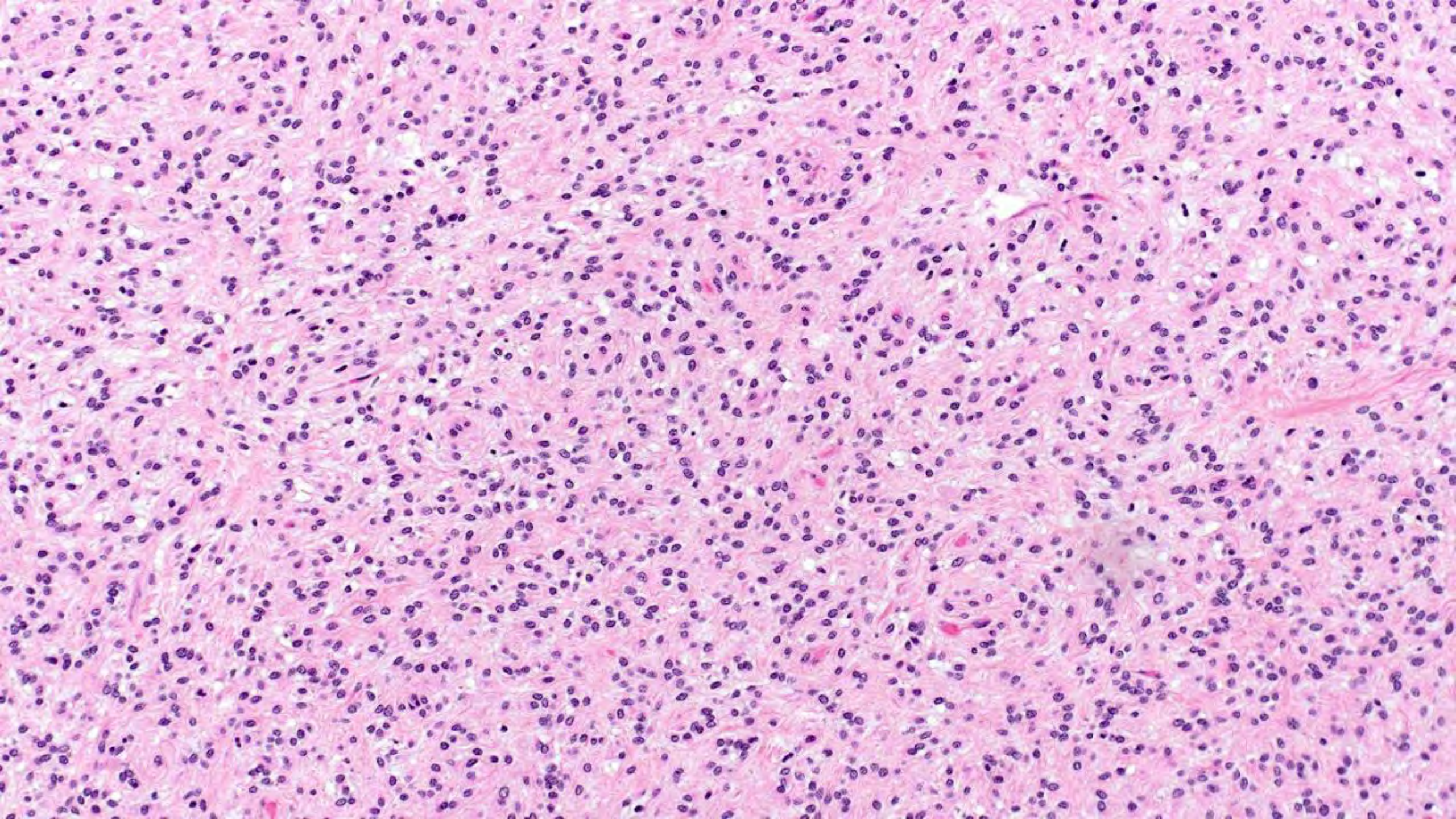


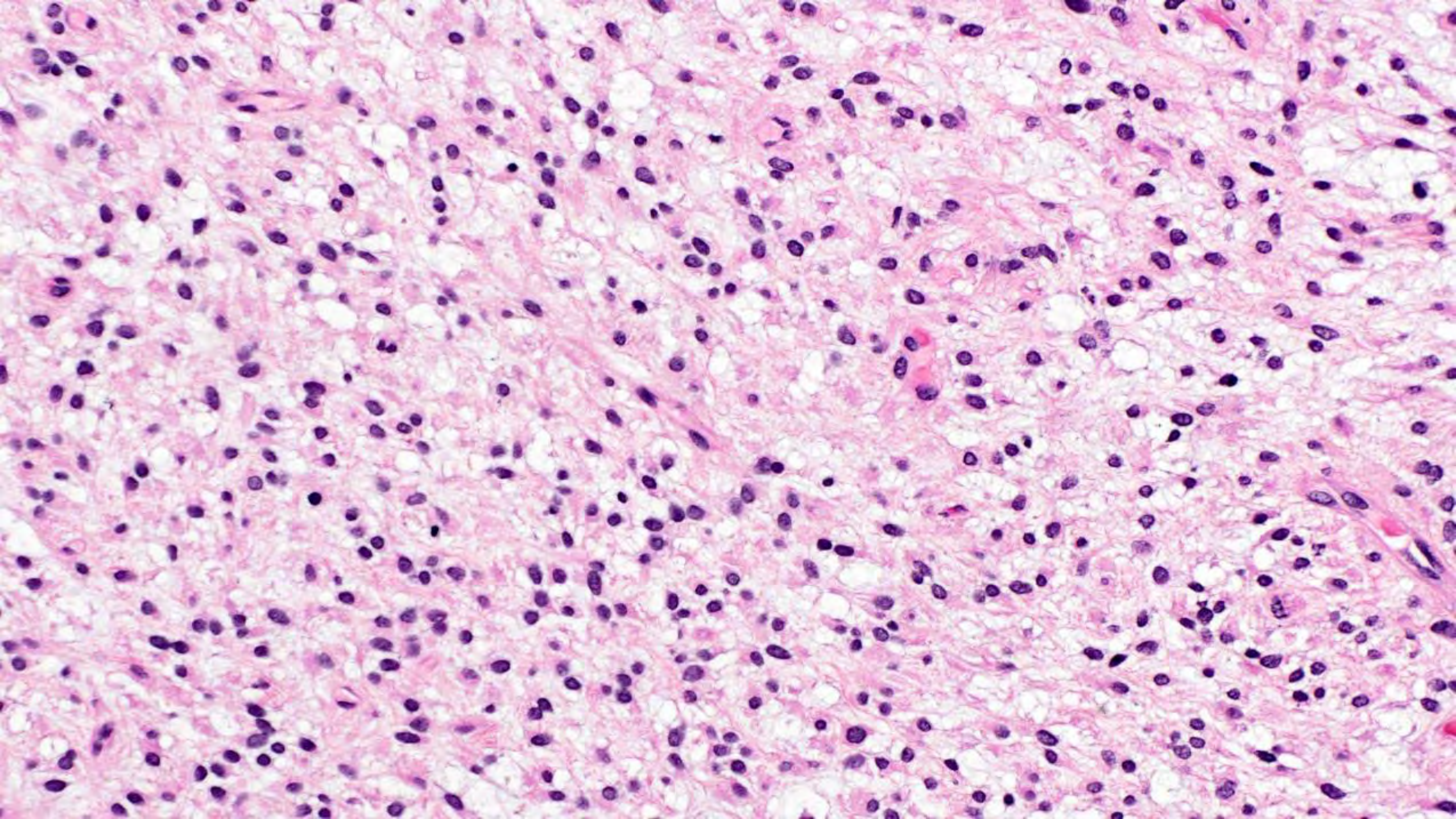
Case 14

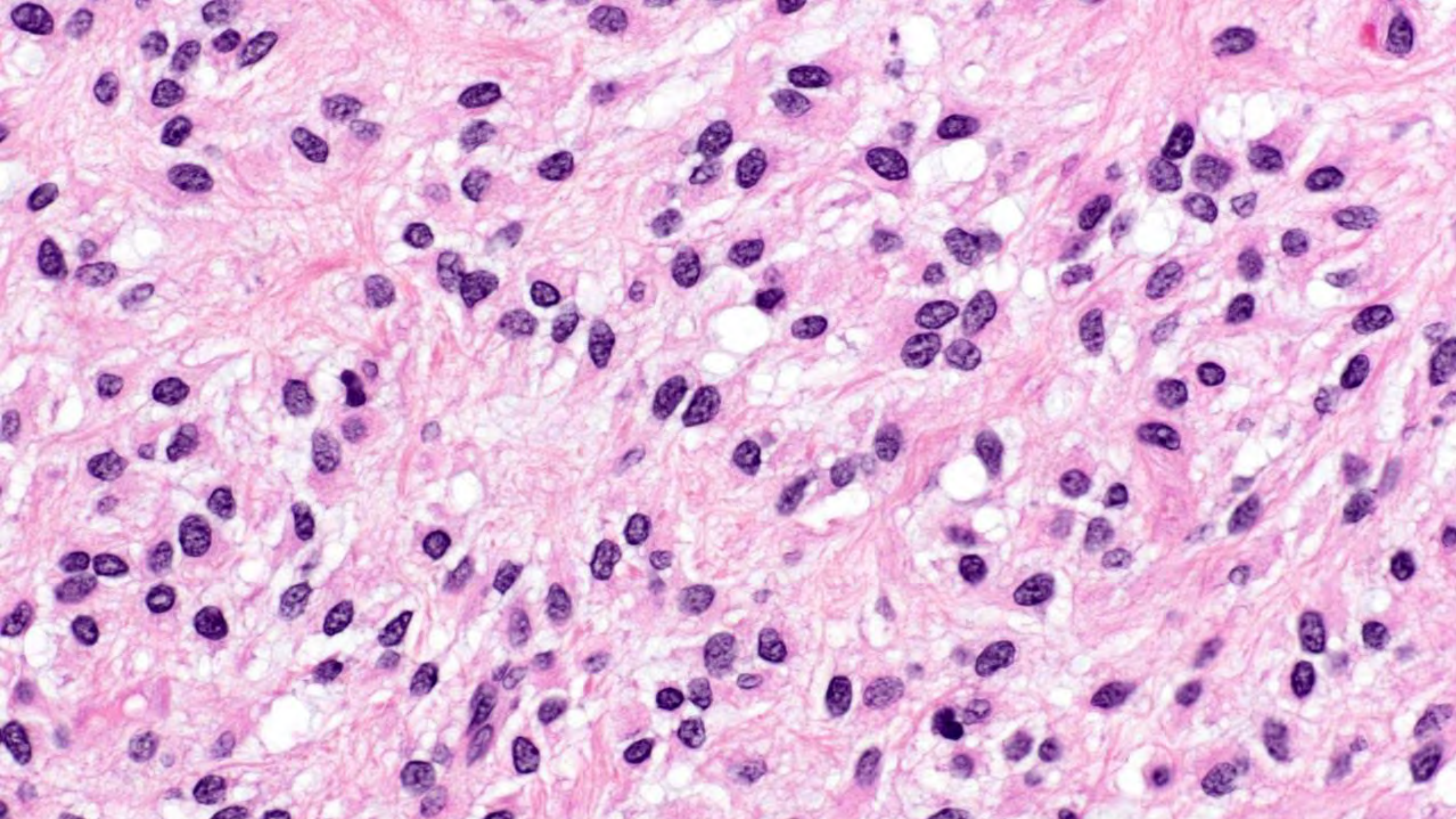
- ▶ 63y, F
- ▶ Upper lip; inner side
- ▶ 1,7 cm soft nodular lesion

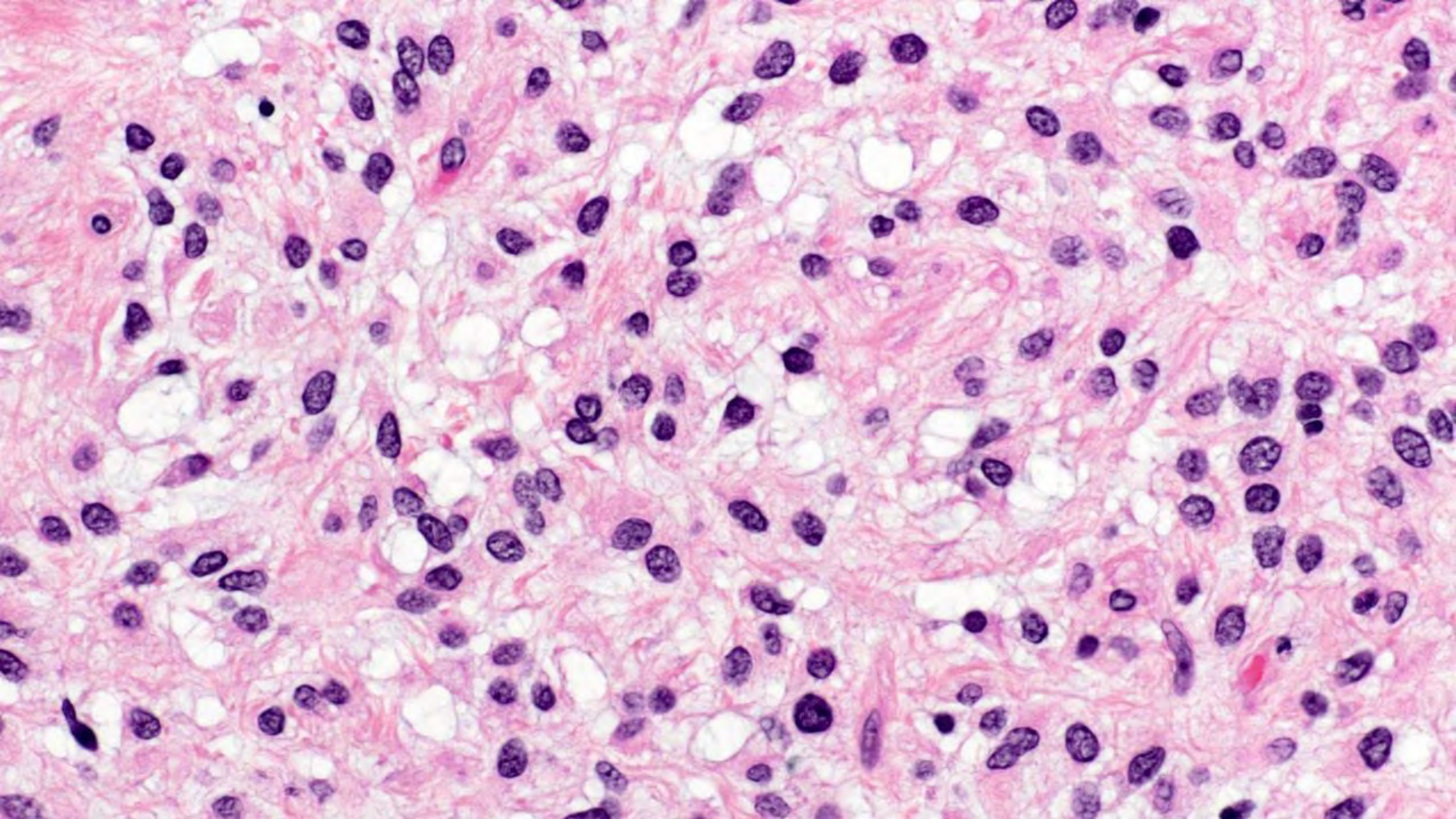


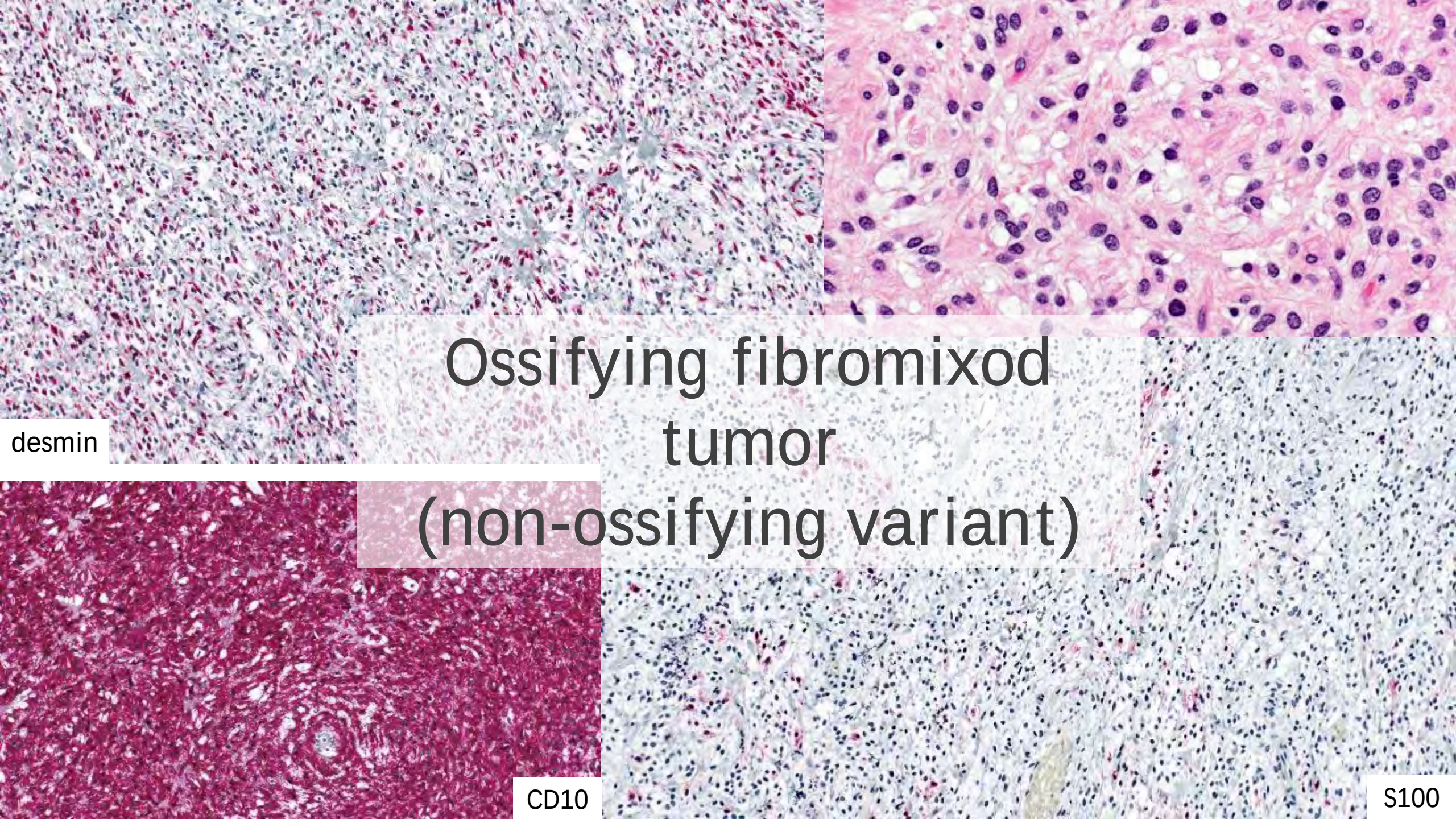












Ossifying fibromyxoid
tumor
(non-ossifying variant)

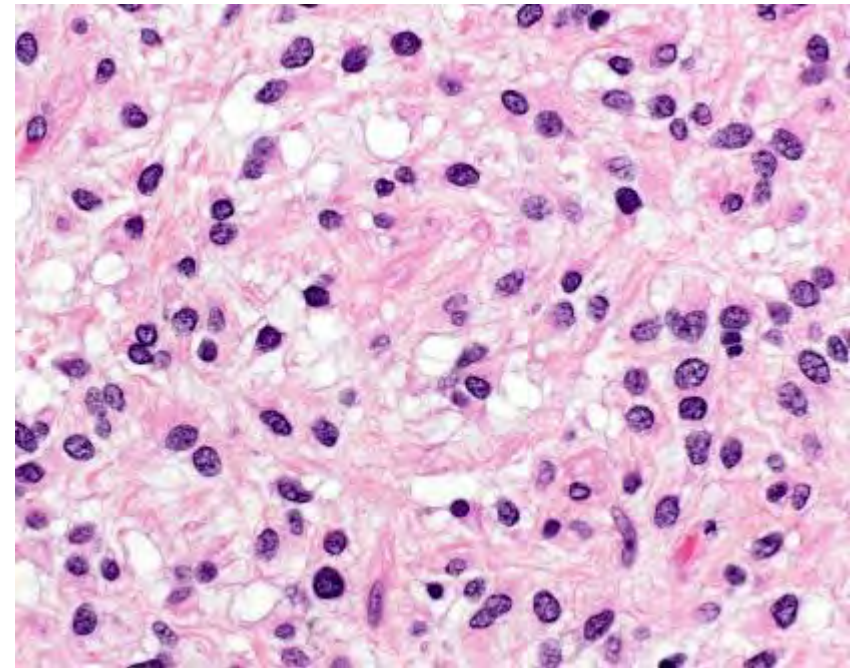
desmin

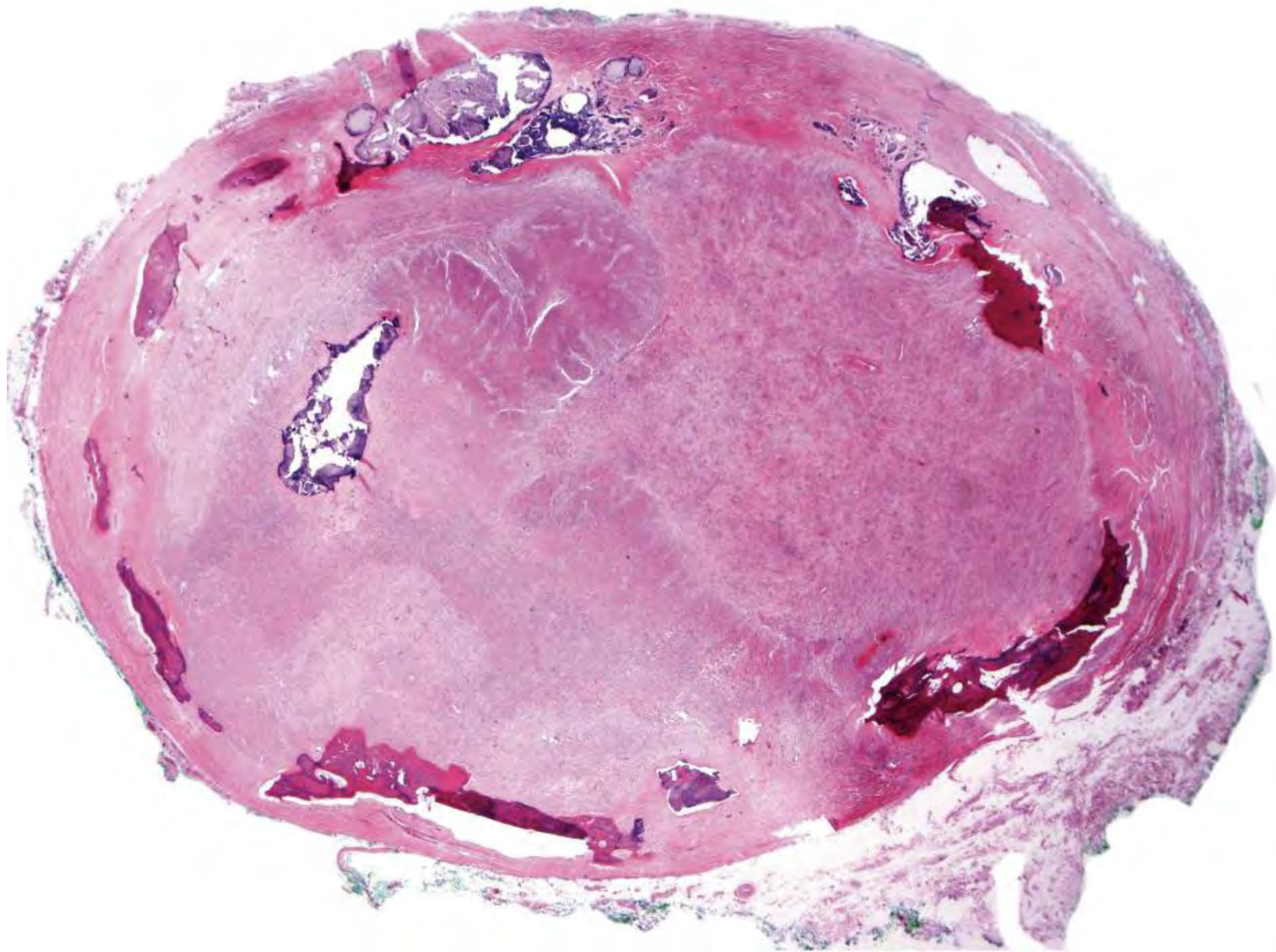
CD10

S100

Ossifying fibromyxoid tumor (OFT)

- ▶ a rare mesenchymal neoplasm of uncertain differentiation
- ▶ often surrounded by a complete or incomplete peripheral shell of lamellar bone
- ▶ cords and trabeculae of ovoid cells embedded in a fibromyxoid matrix
- ▶ *PHF1* gene rearrangement (80%)
 - ▶ with fusion to *EP400* (44%), *MEAF6*, *TFE3*
- ▶ potential for local recurrence and metastasis
 - ▶ especially when showing malignant features





Head & neck

Systematic Review

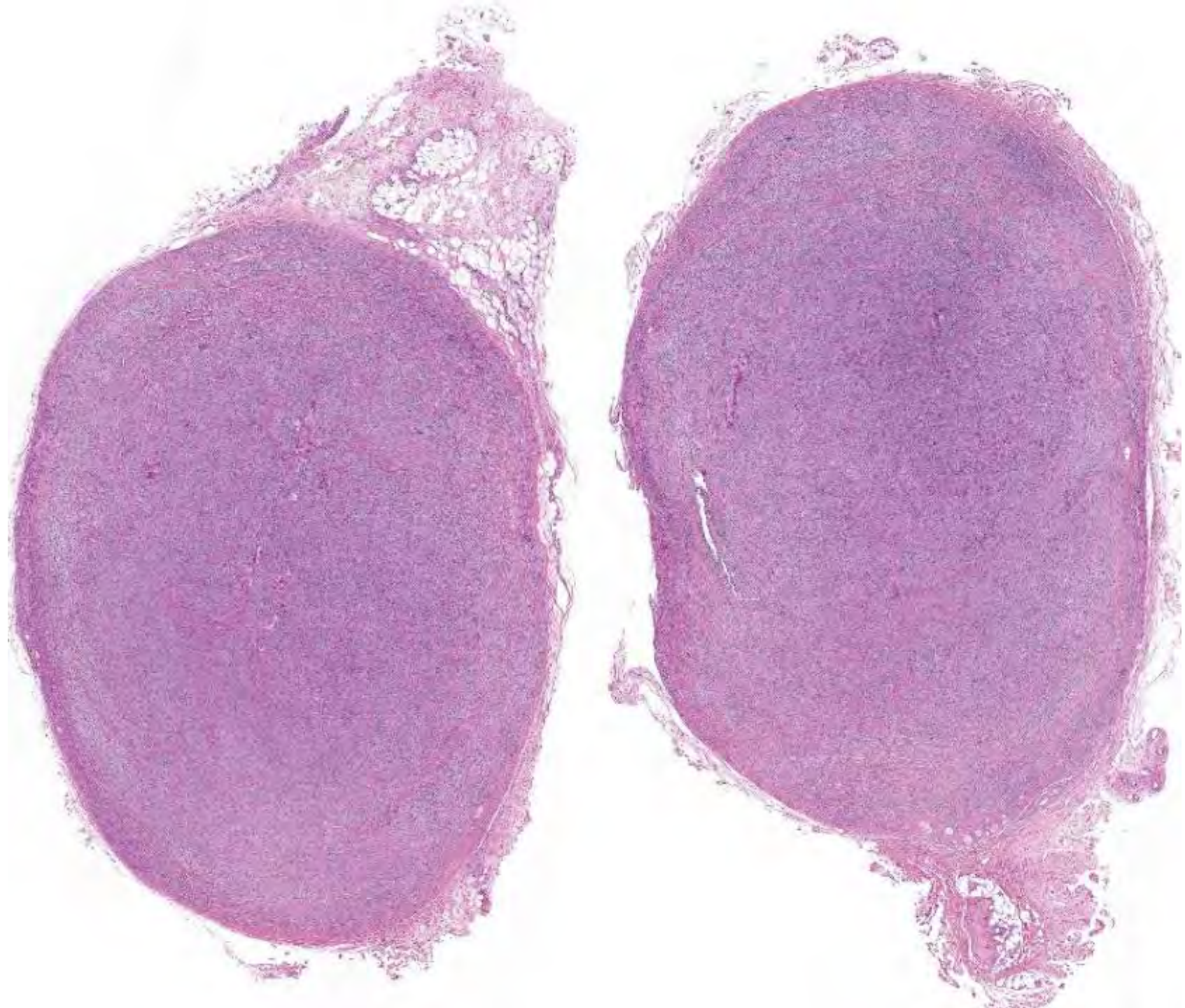
Ossifying Fibromyxoid Tumor of Soft Parts in the Head and Neck: A Systematic Review Addressing Surgical Management and Adjuvant Therapies

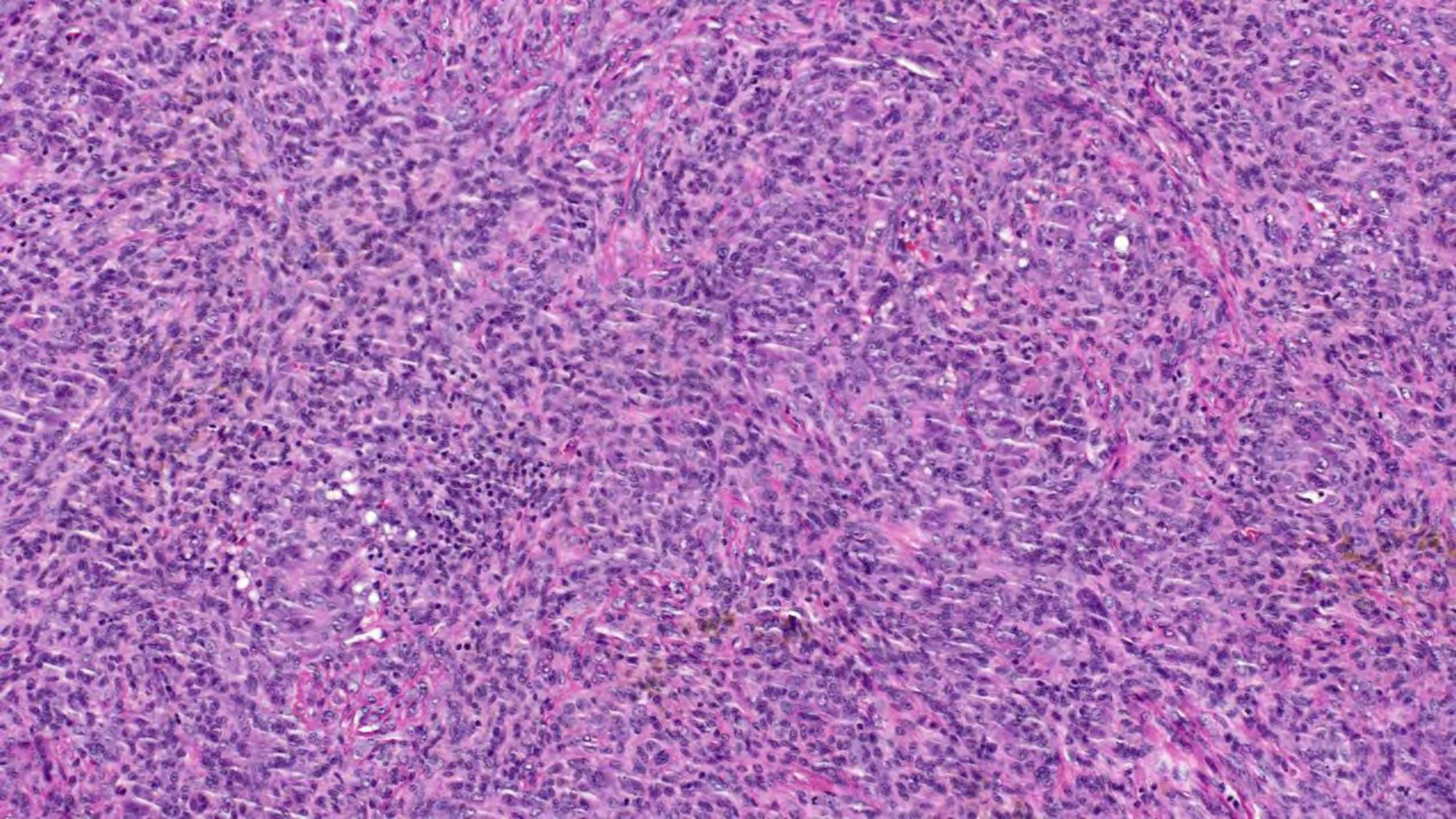
Gianluca Scalia ^{1,2}, Valentina Zagardo ³, Zubayer Shams ⁴, Gianluca Ferini ^{2,3,*}, Salvatore Marrone ⁵, Eliana Giurato ⁶, Francesca Graziano ¹, Giancarlo Ponzio ¹, Massimiliano Giuffrida ¹, Massimo Furnari ¹, Giuseppe Emmanuele Umana ^{2,7} and Giovanni Federico Nicoletti ¹

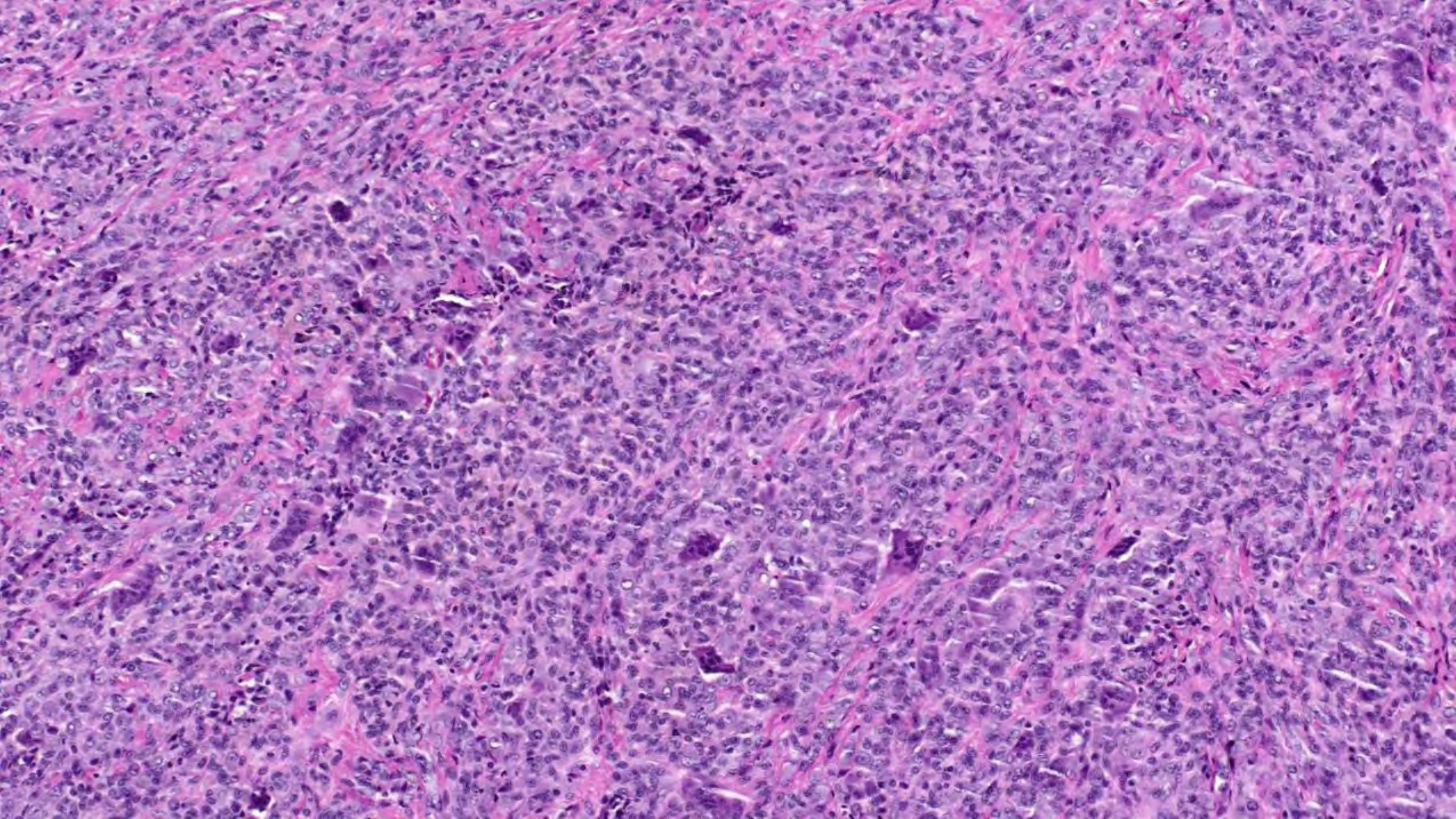
Variable	Description
Total Number of Patients	99
Age (years)	Range: 3 weeks–88 years; median: 47; mean: 46.75; SD: 12.23; IQR: 39–52.
Sex	Male: 63 (63.64%); female: 36 (36.36%).
Location of Lesions	Neck (18, 18.18%); scalp (6, 6.06%); calvarium/Skull (2, 2.02%); inner cheek (4, 4.04%); lip (2, 2.02%); pretracheal region (1, 1.01%); posterior neck (1, 1.01%); submental area (1, 1.01%); chin (1, 1.01%); mandibular vestibule (1, 1.01%); maxilla/nasal bone (1, 1.01%); soft palate (1, 1.01%); parapharynx (1, 1.01%); parotid/zygomatic arch (1, 1.01%); nasal cavity and sinuses (5, 5.05%); thyroid region (1, 1.01%); mandible (4, 4.04%); orbit (1, 1.01%); tongue (1, 1.01%); buccal mucosa (3, 3.03%); submandibular region (1, 1.01%); paralaryngeal region (1, 1.01%); retromolar triangle (1, 1.01%); supraclavicular region (2, 2.02%); infratemporal fossa (1, 1.01%); brain lobe (1, 1.01%); maxillary bone (1, 1.01%); gingiva (2, 2.02%); site not specified (28, 28.28%).
Clinical Presentation	<u>Slow-growing mass</u> (typical feature): 14 cases (14.14%); other presentations (<u>painless swelling</u> , <u>subcutaneous masses</u> , <u>congestion</u> , <u>indurated mass</u> , etc.): 85 cases (85.86%).
Surgical Treatment	Local excision/excisional biopsy: 28 cases (28.28%); wide local excision, subtotal resections, or craniectomy as required in other cases.
Mitotic Activity	No mitotic activity detected in 23 cases (23.23%); low mitotic index (≤ 2 mitoses/10 HPFs) in 26 cases (26.26%); mitotic data not reported in 50 cases (50.51%).
Atypia	Atypia absent in 31 cases (31.31%); atypia present (mild to moderate) in 20 cases (20.20%); atypia not reported in 48 cases (48.48%).
Recurrence	No recurrence documented in 31 cases (31.31%); <u>recurrence documented in 9 cases (9.09%)</u> ; recurrence status not reported in 59 cases (59.60%).
Metastasis	No metastasis observed in 40 cases (40.40%); <u>metastasis documented in 2 cases (2.02%)</u> ; metastasis status not reported in 57 cases (57.58%).
Follow-up Duration (years)	Range: 6 months to 33 years; mean: 6.21; SD: 3.50
Adjuvant Therapy	Adjuvant therapy used in 15 cases (15.15%); no adjuvant therapy in 84 cases (84.85%).

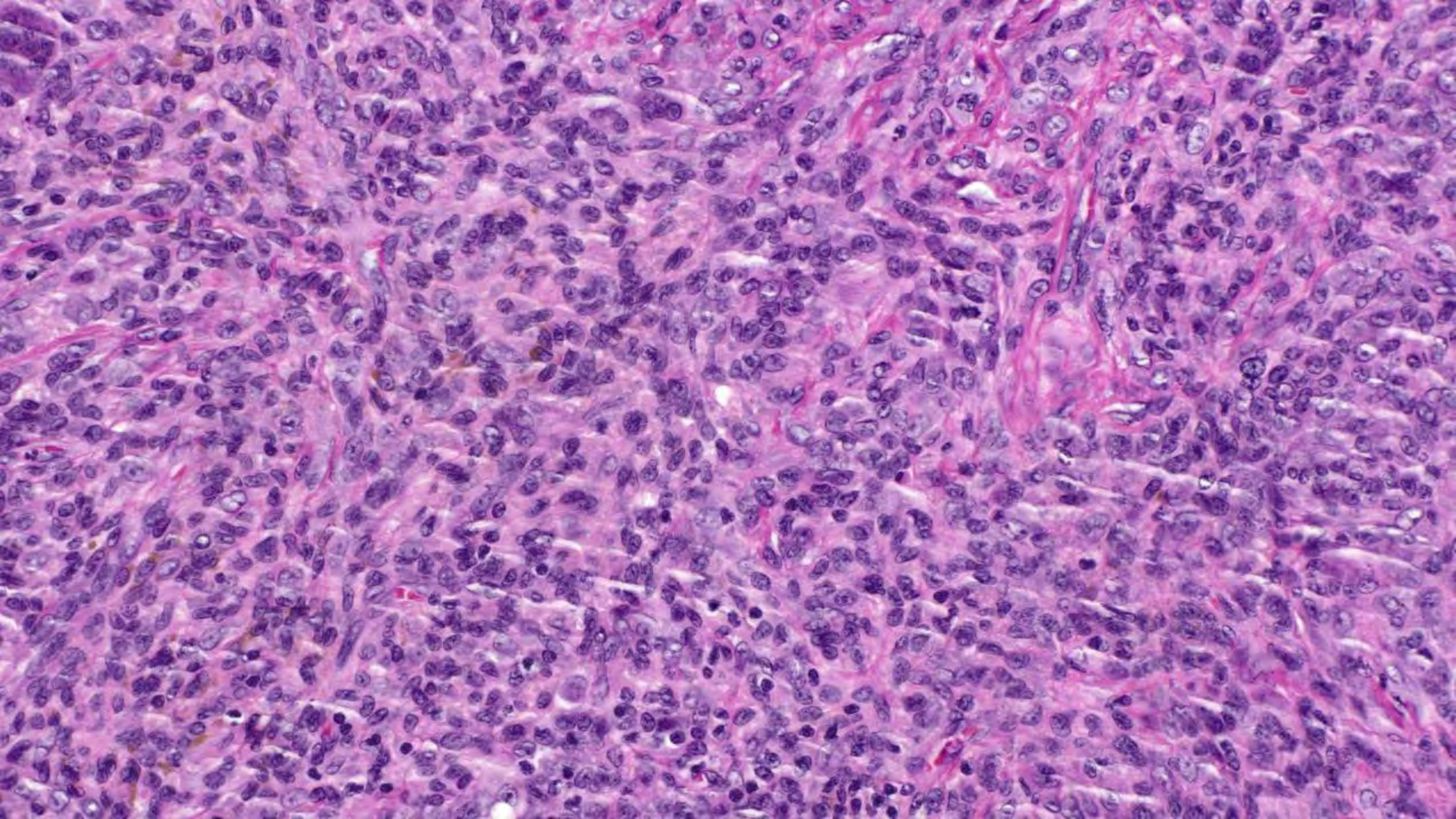
Case 15

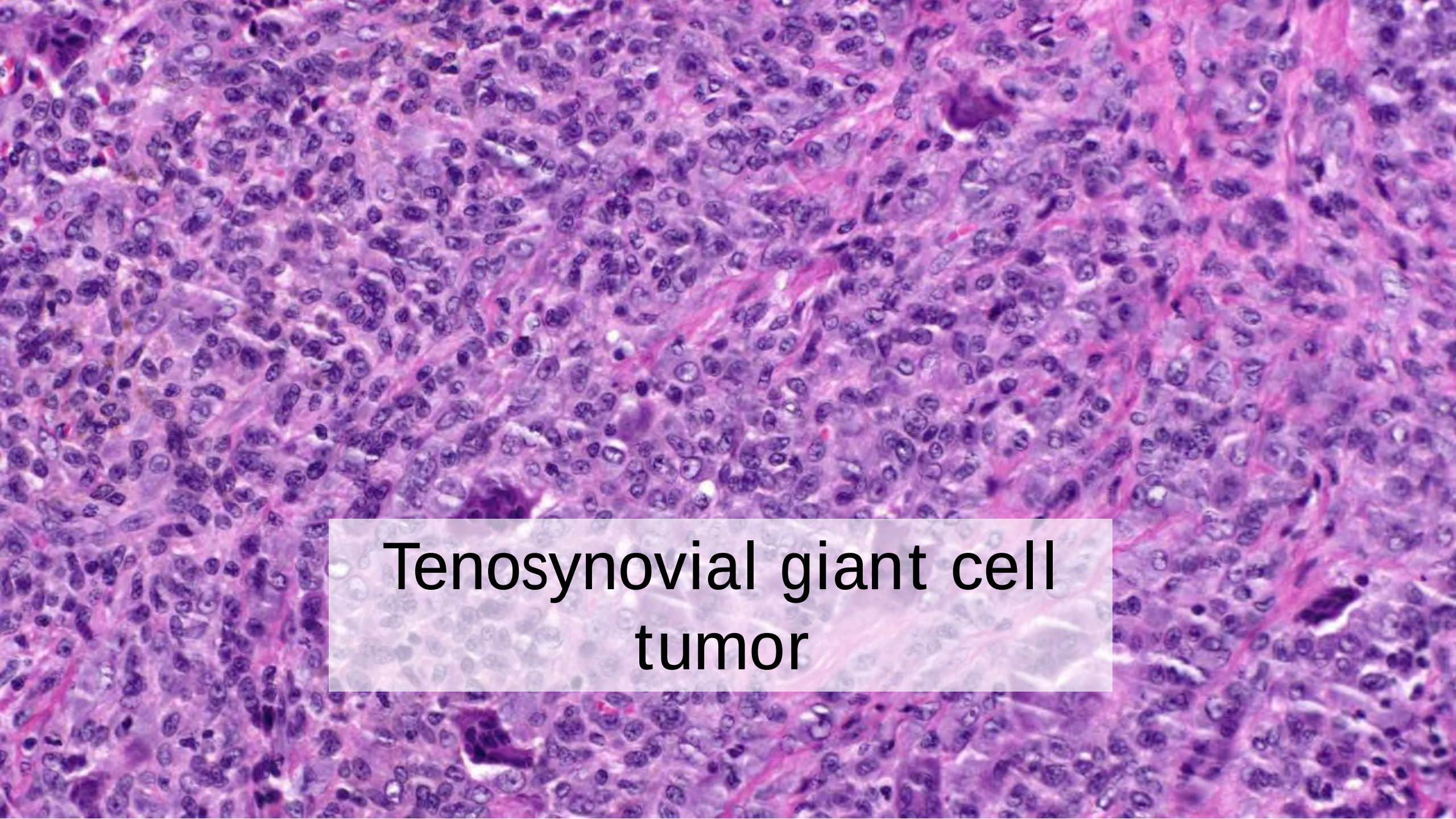
- ▶ 35y, M
- ▶ II-III Dig. man. sin
- subcutaneous
tumor
- ▶ duration 2
months
- ▶ DD: hematoma
after trauma?











A high-magnification histological image of a Tenosynovial giant cell tumor. The tissue is stained with hematoxylin and eosin (H&E), showing a dense population of cells with dark purple nuclei and pink cytoplasm/extracellular matrix. The cells are arranged in a disorganized, infiltrative pattern, characteristic of this type of tumor. The nuclei are generally round to oval, and the overall architecture lacks the normal organization of a synovium.

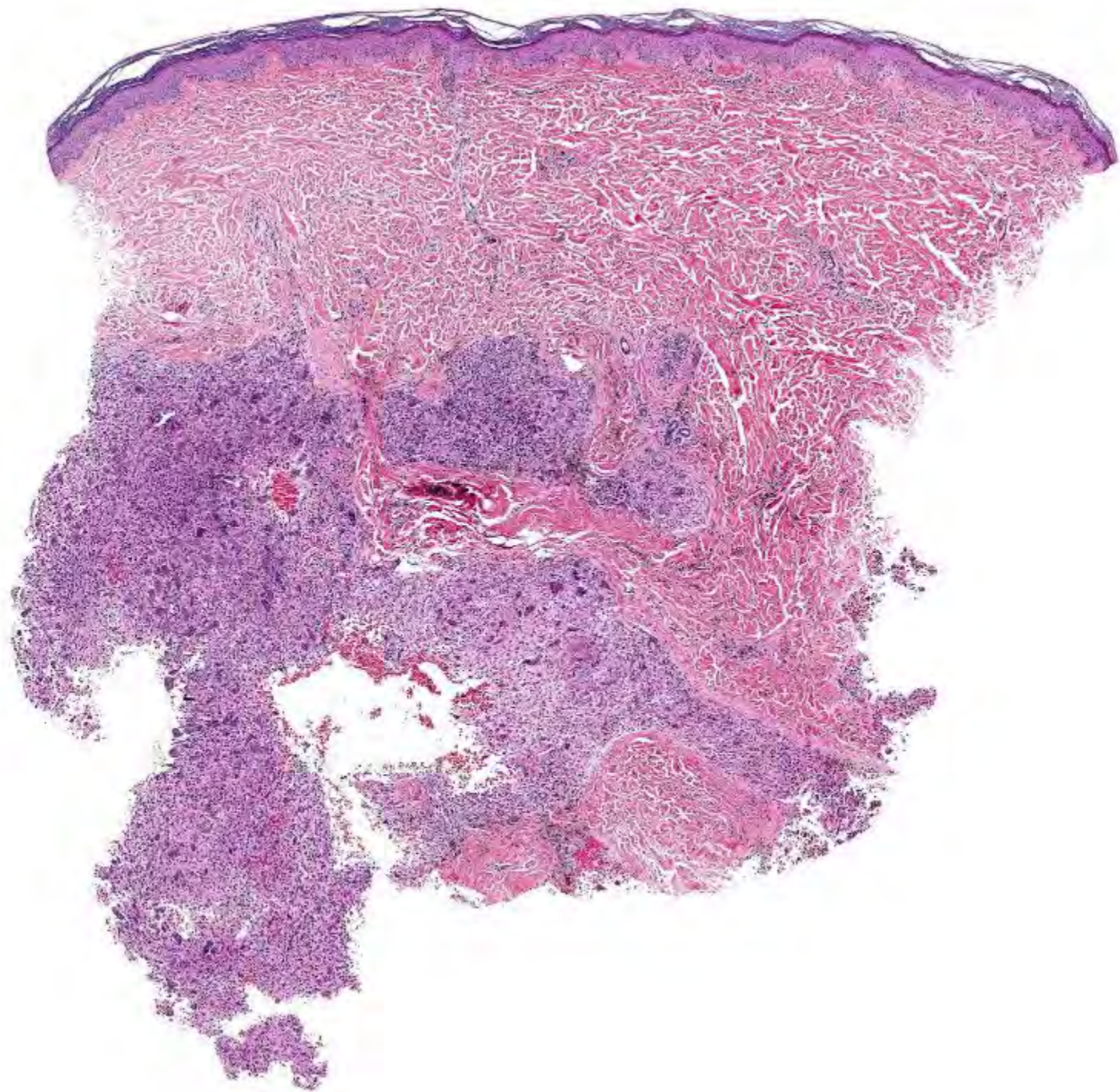
Tenosynovial giant cell
tumor

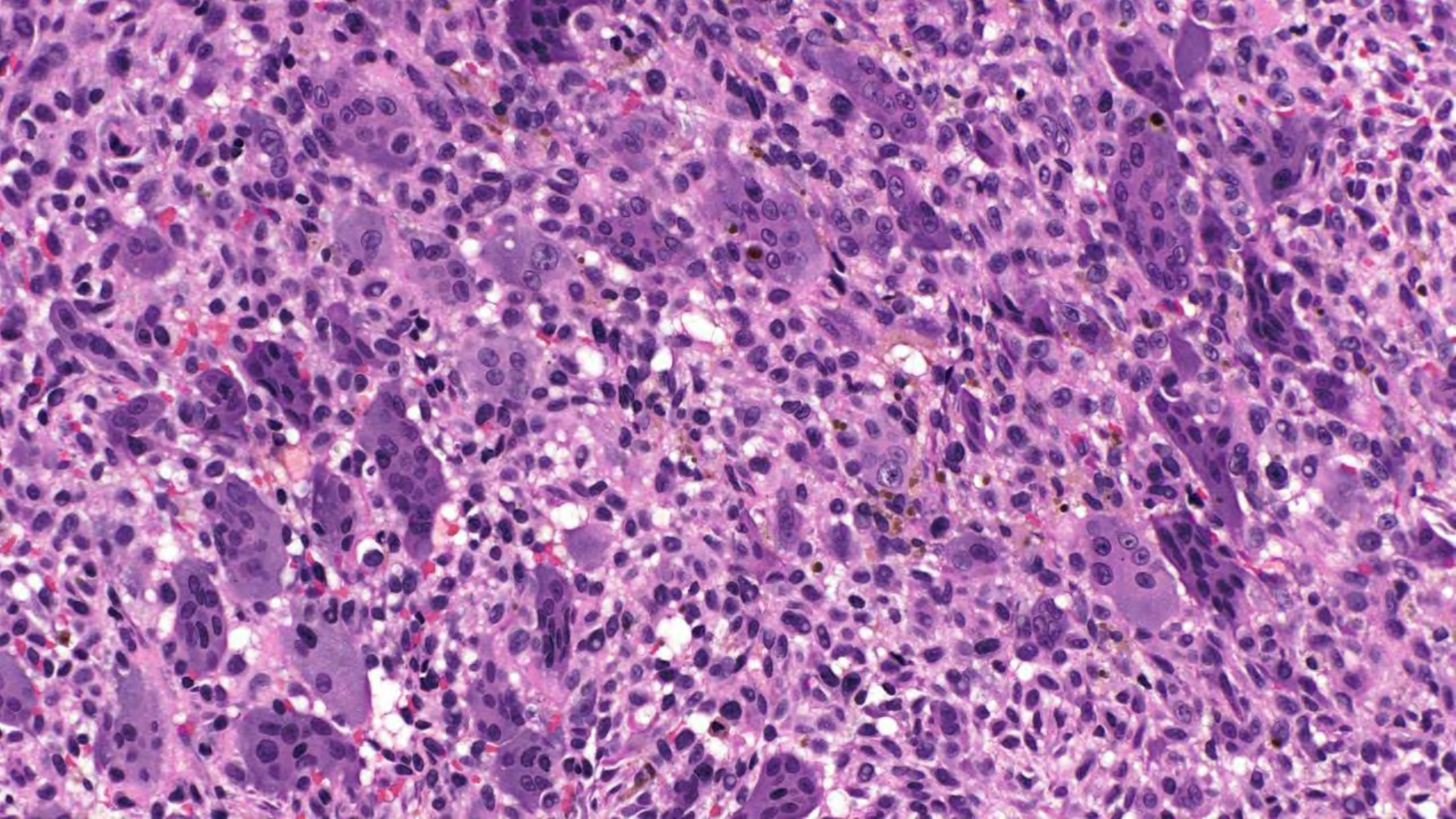
Tenosynovial giant cell tumor

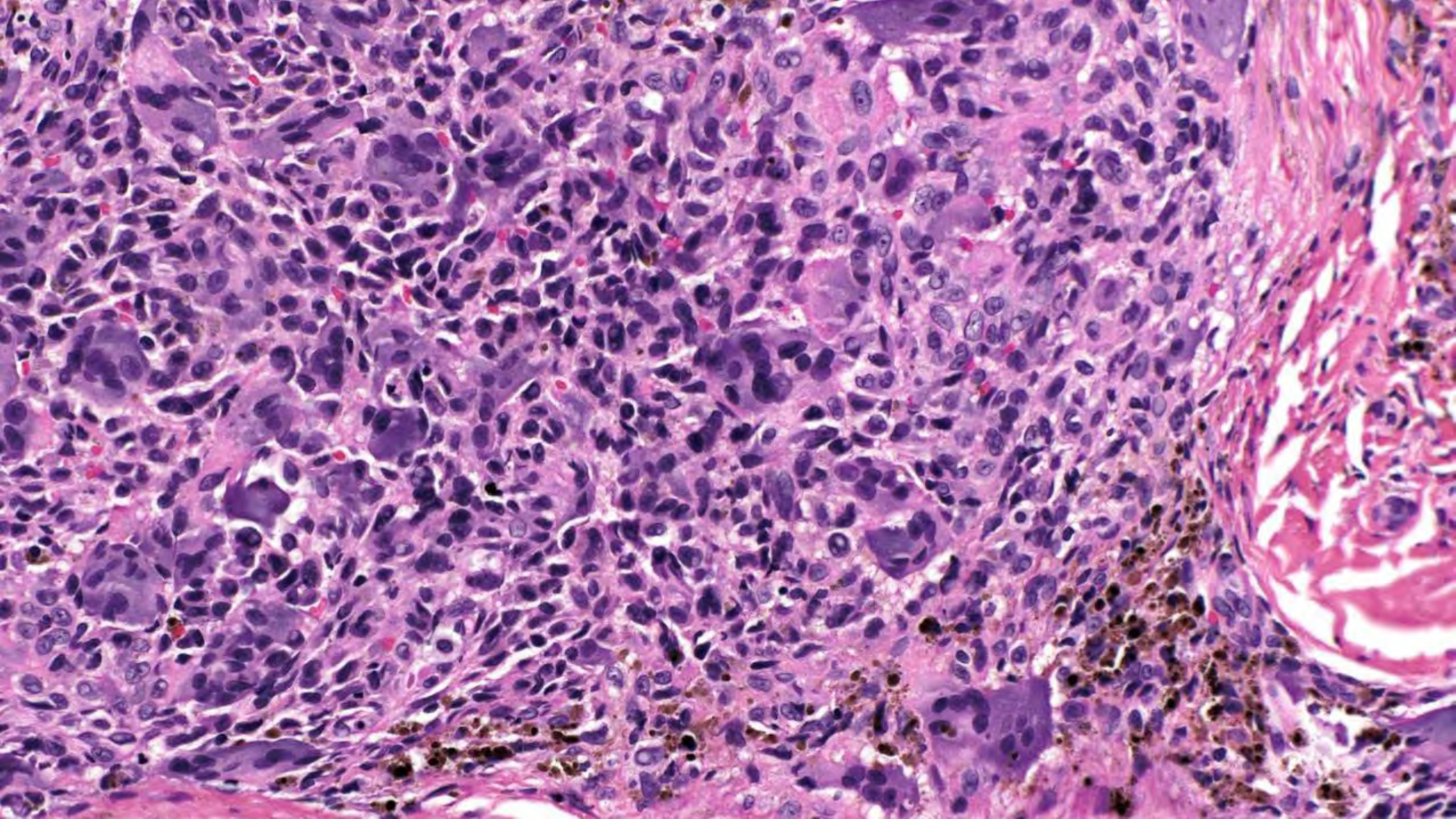
- ▶ most often arising from the synovium of joints, bursae, and tendon sheaths
- ▶ 2 Subtypes:
 - ▶ **Localized:** predominantly in the hand
 - ▶ **Diffuse:** knee

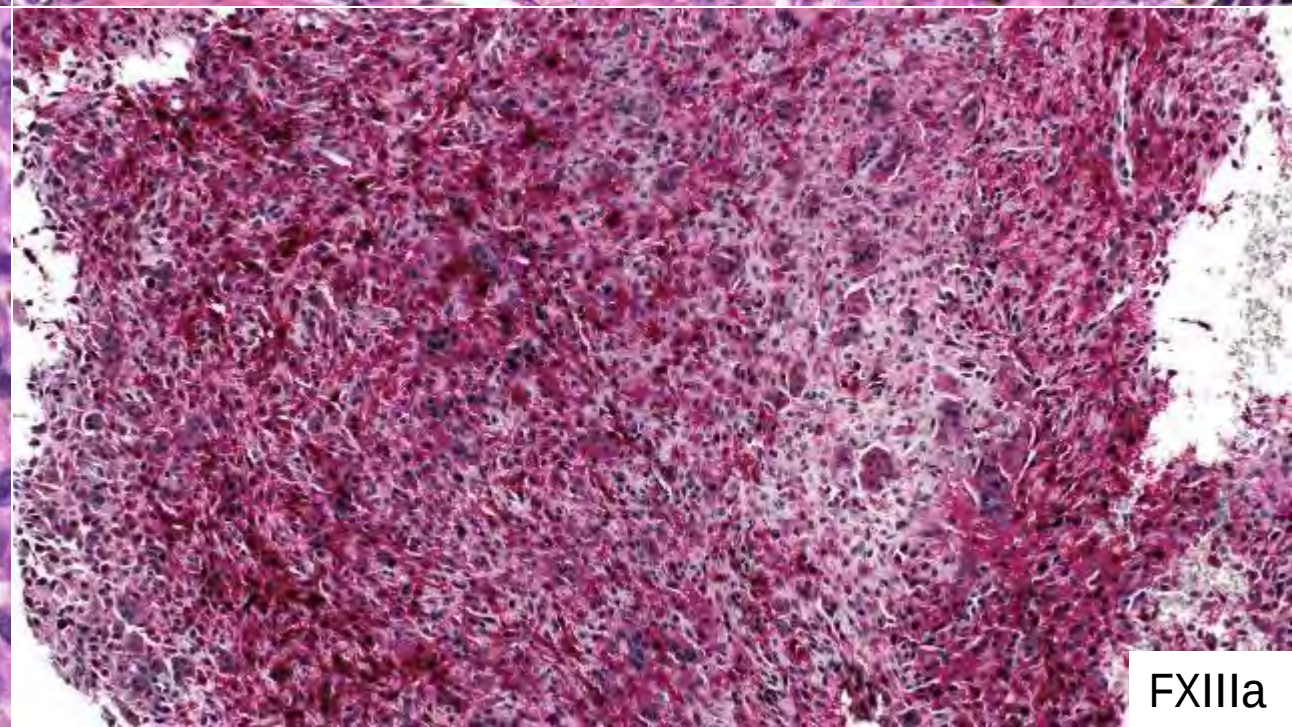
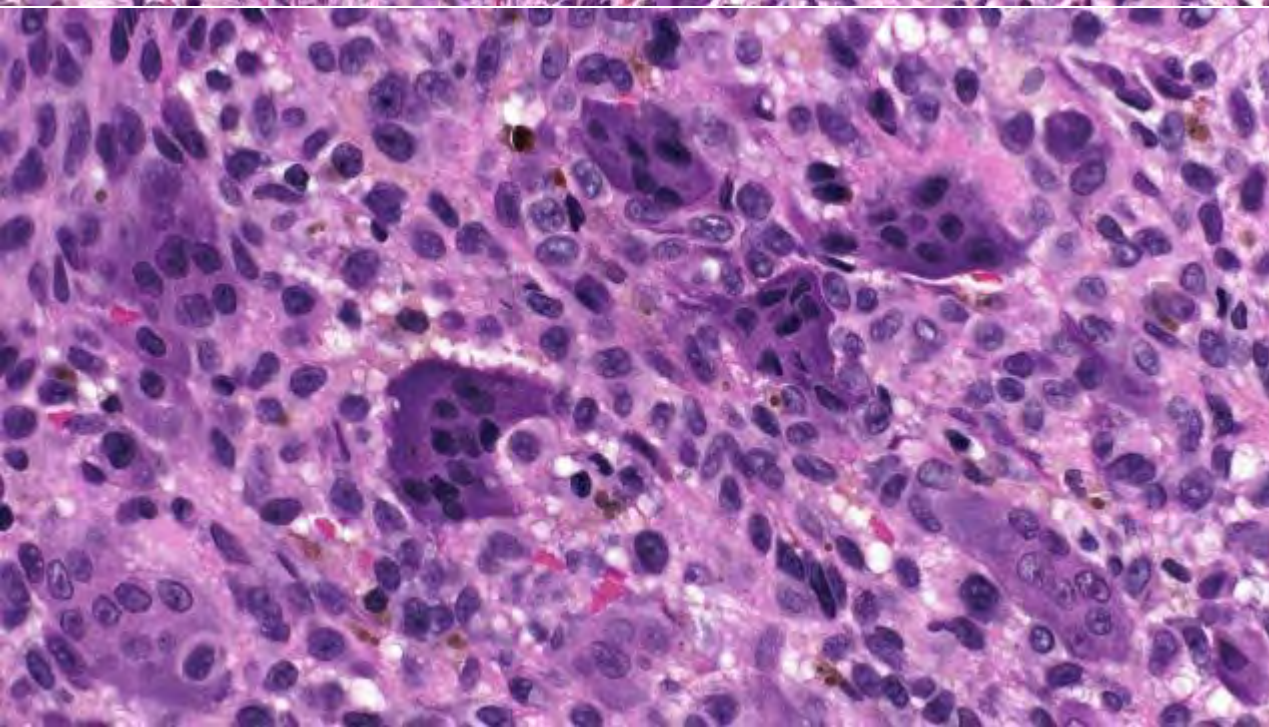
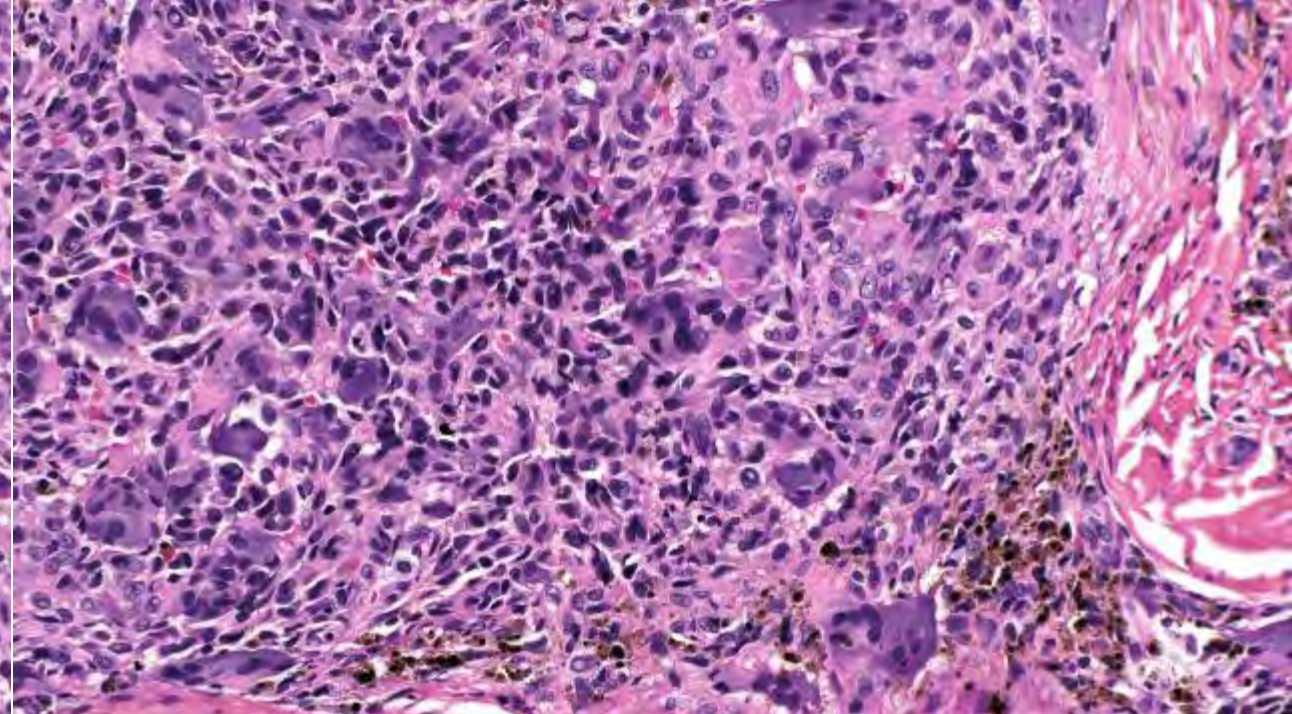
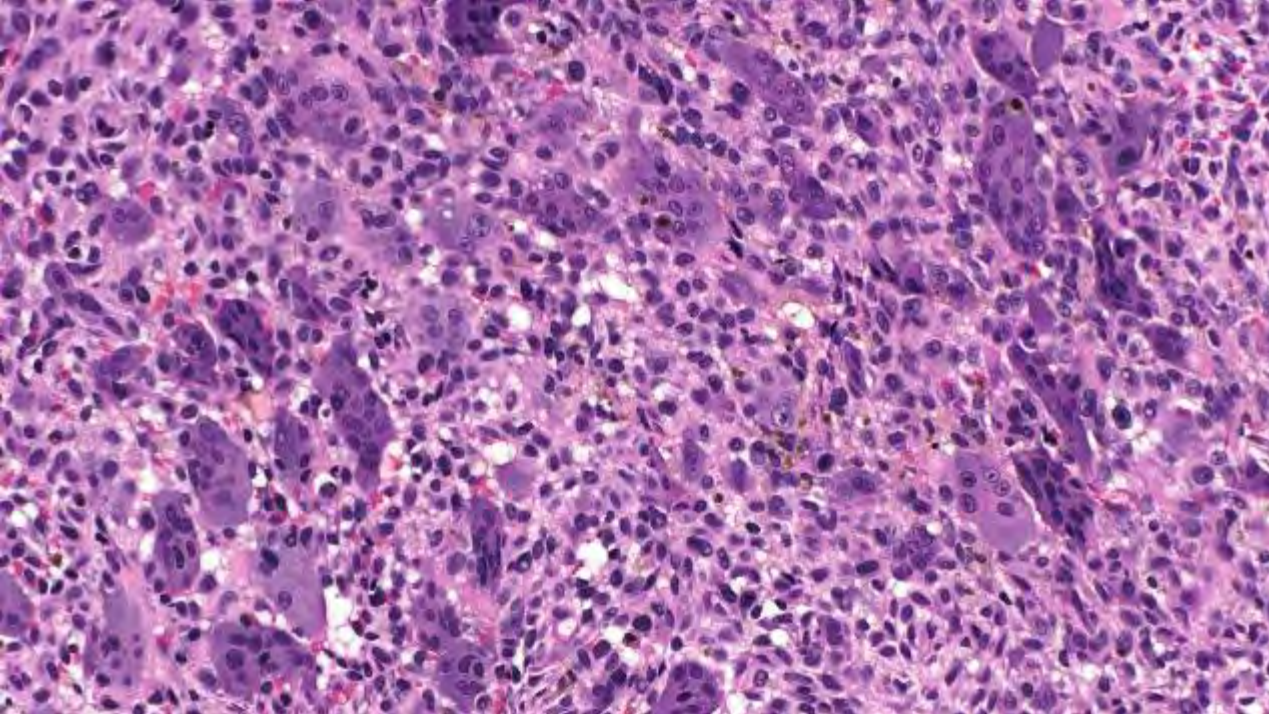
Translocations involving *CSF1* gene

Correlation with
radiology!

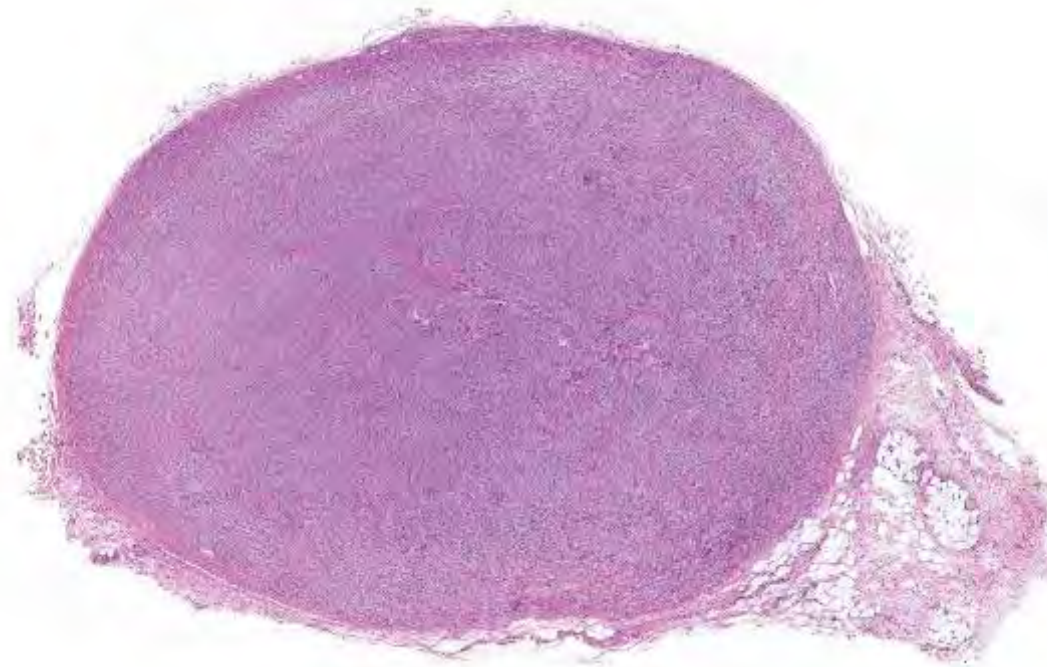








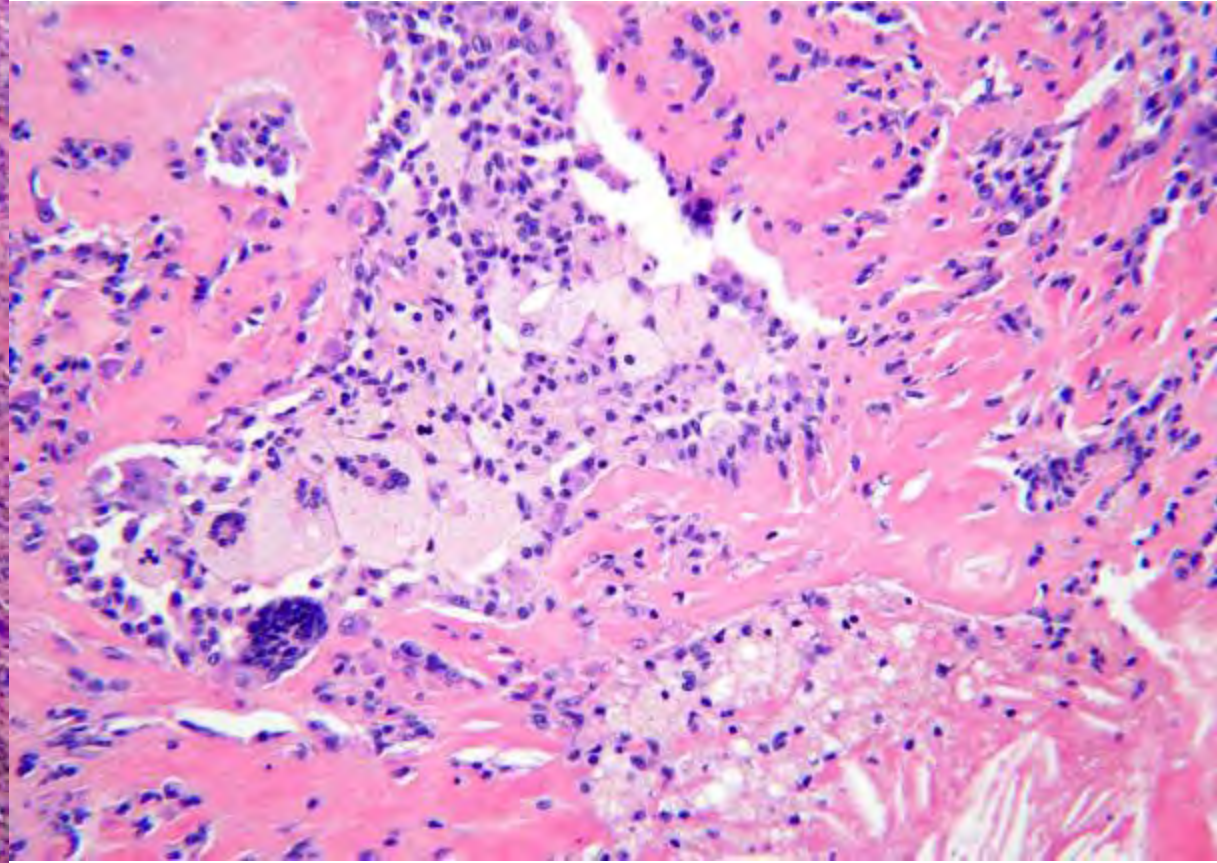
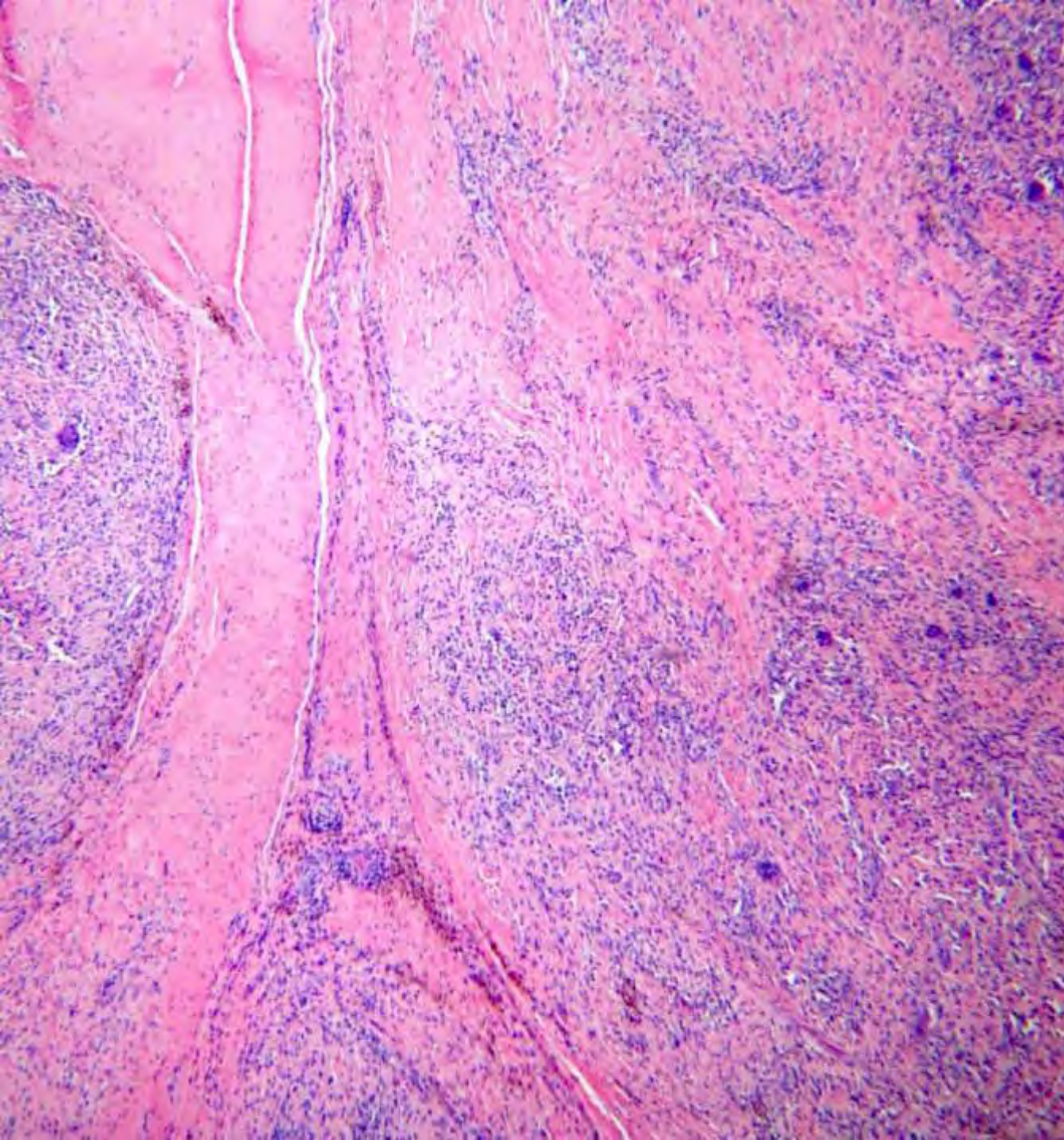
FXIIIa



localized



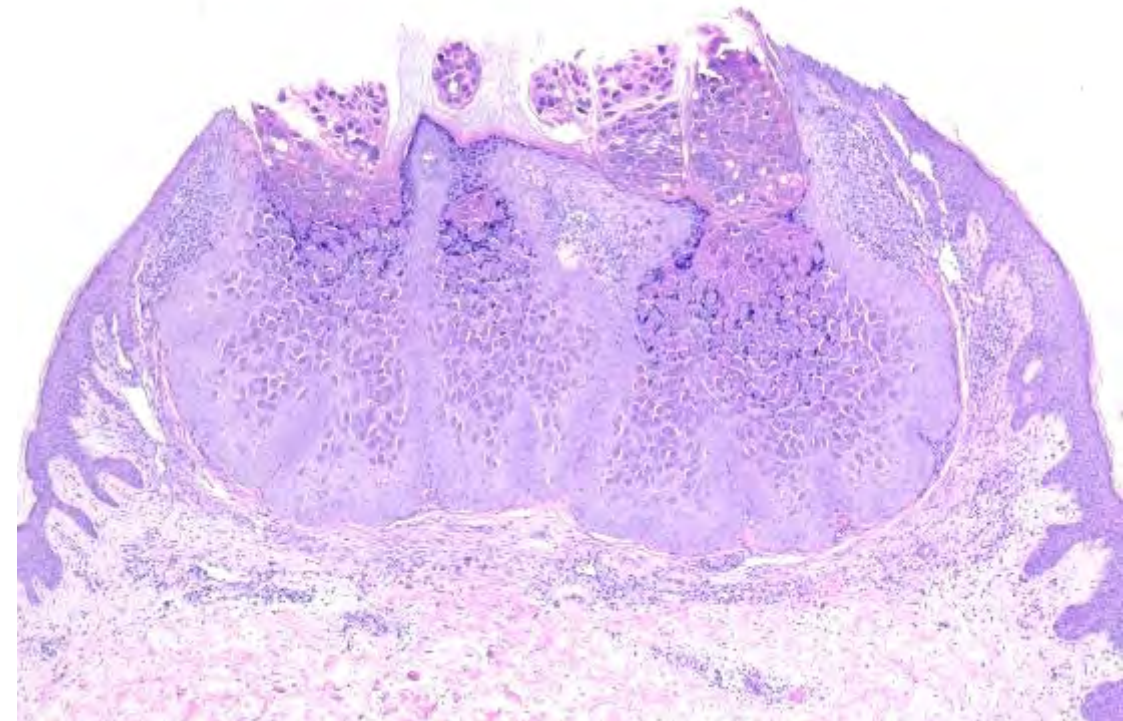
diffuse

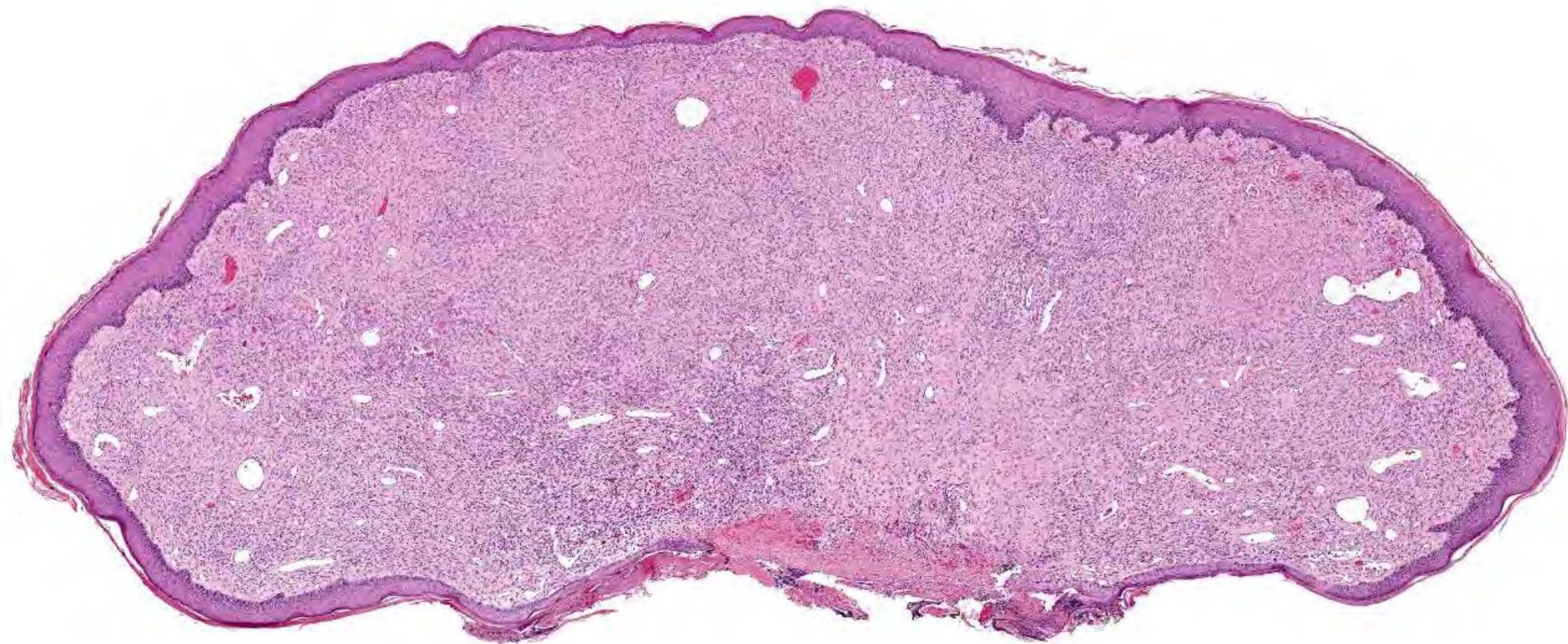


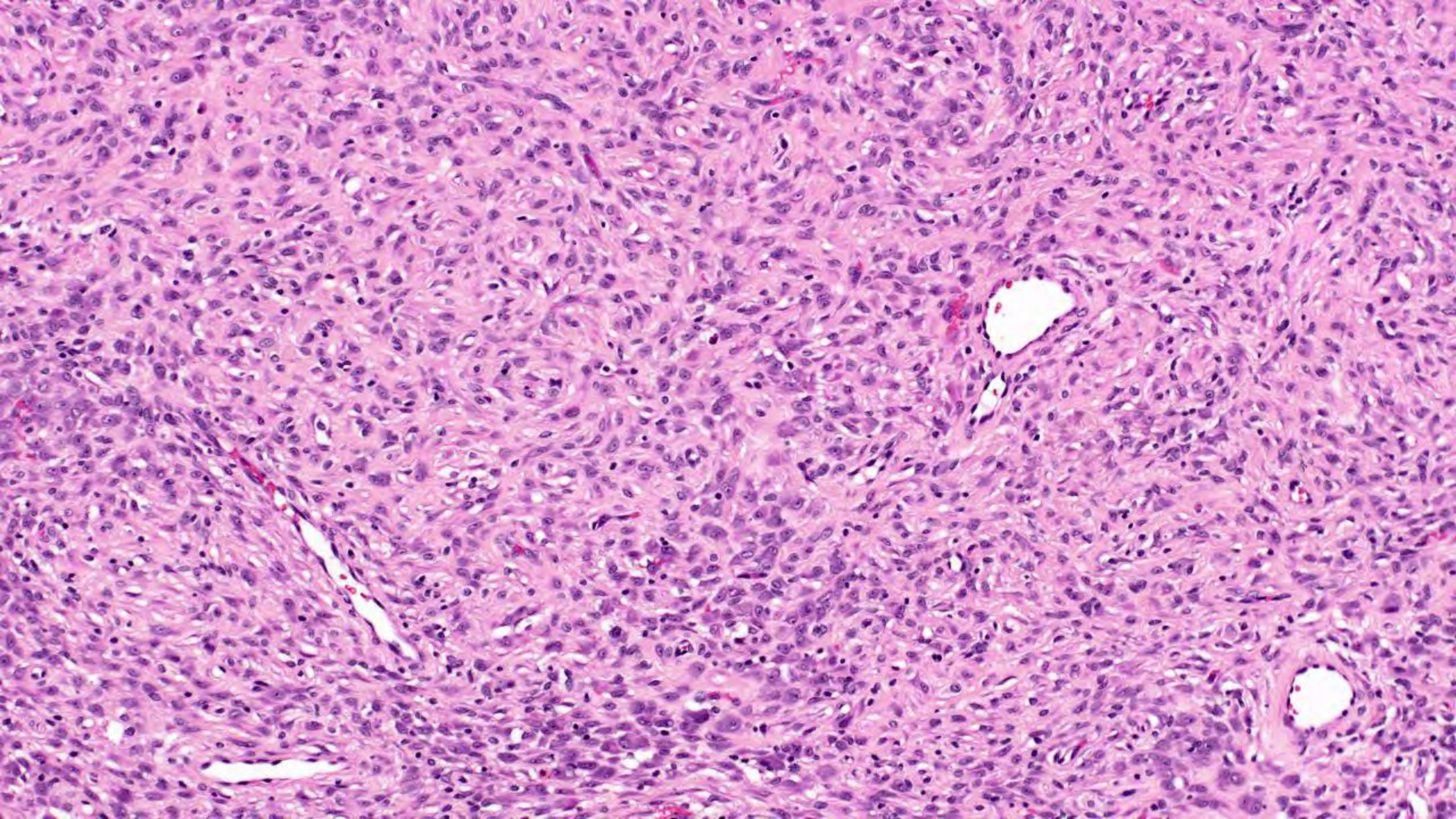
Case 16

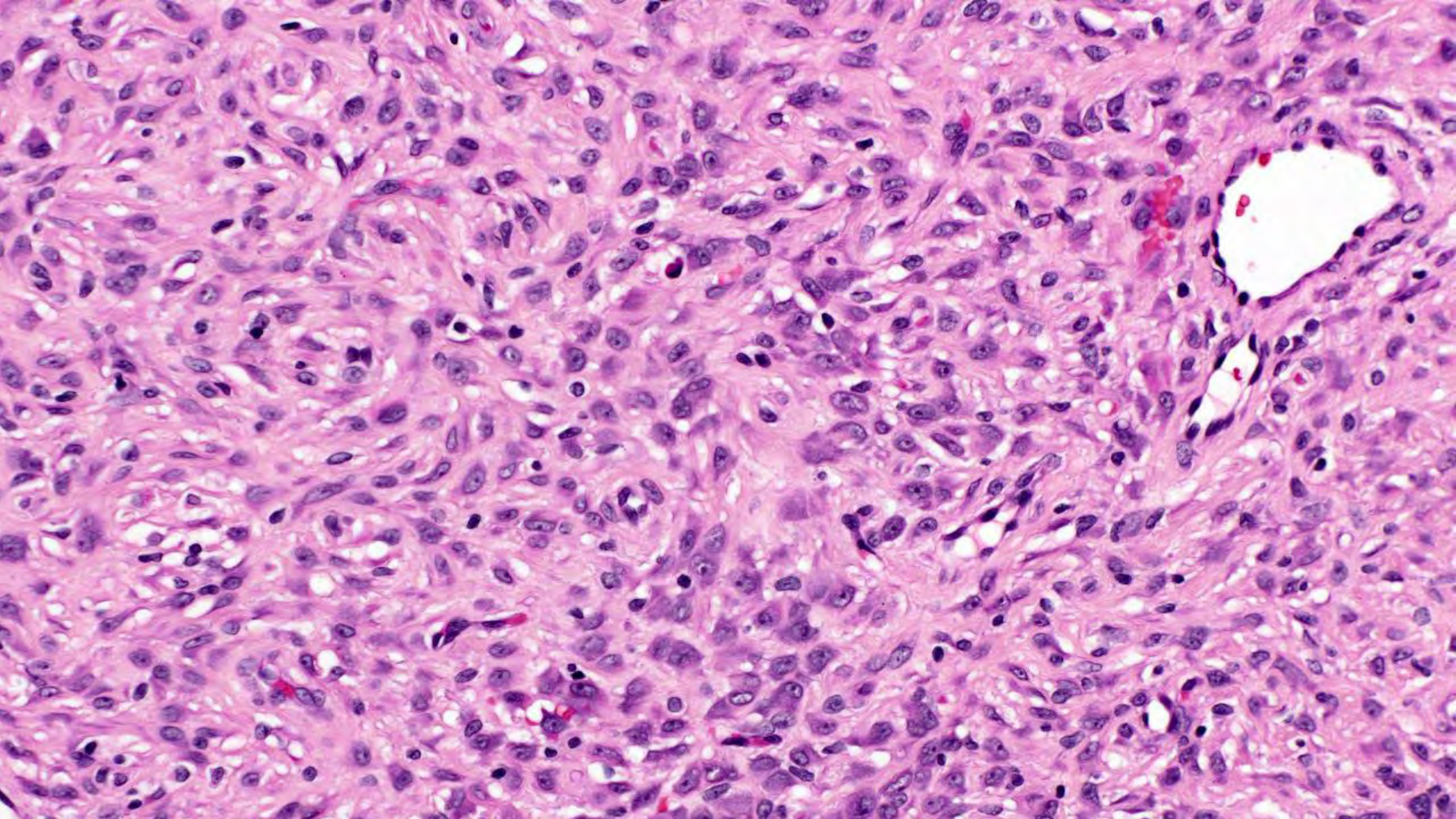
- ▶ 44y, M
- ▶ Fosa poplitea, 0,4 cm large papule
- ▶ DD: Molluscum contagiosum

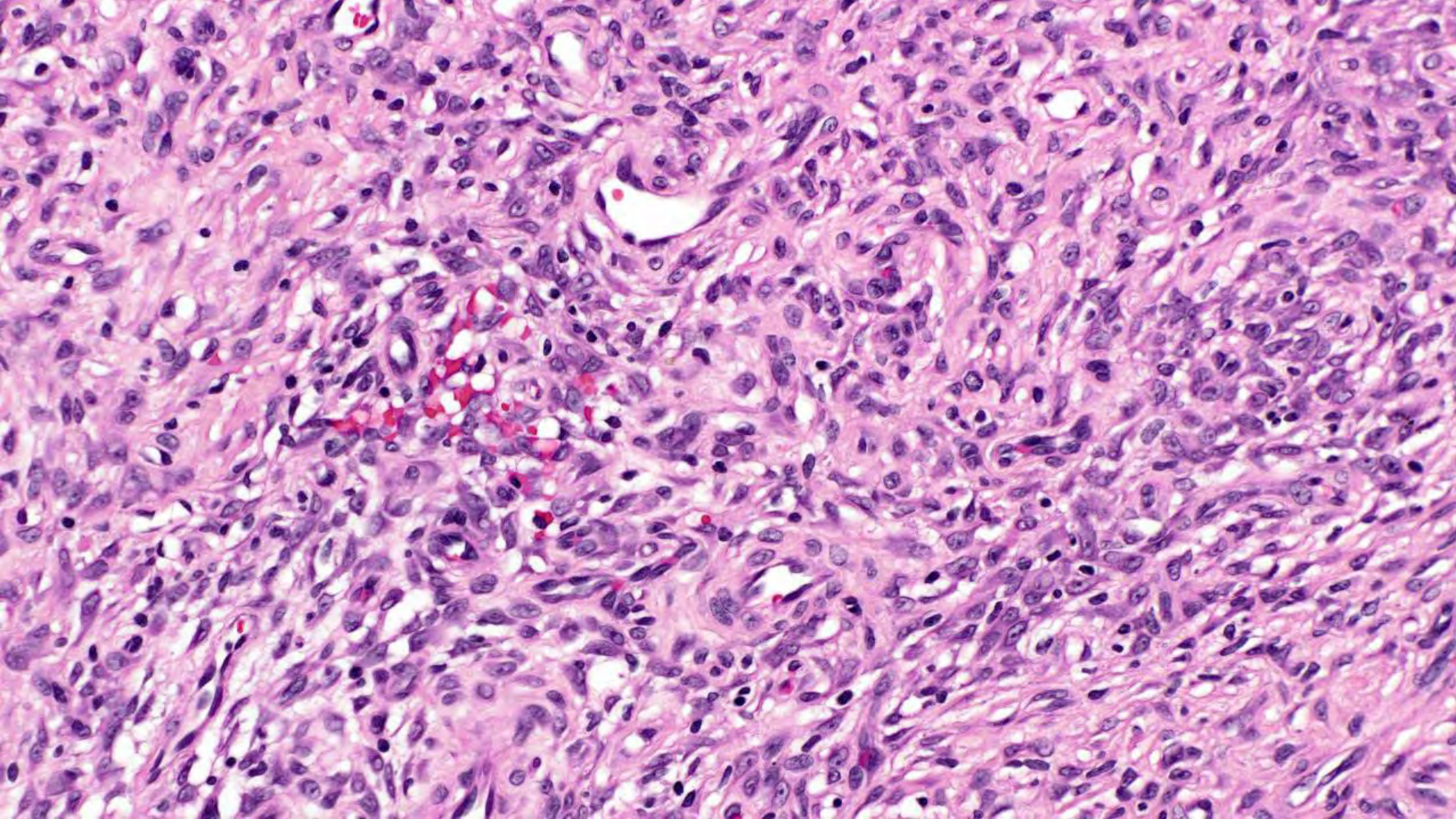
External report:
Epithelioid sarcoma

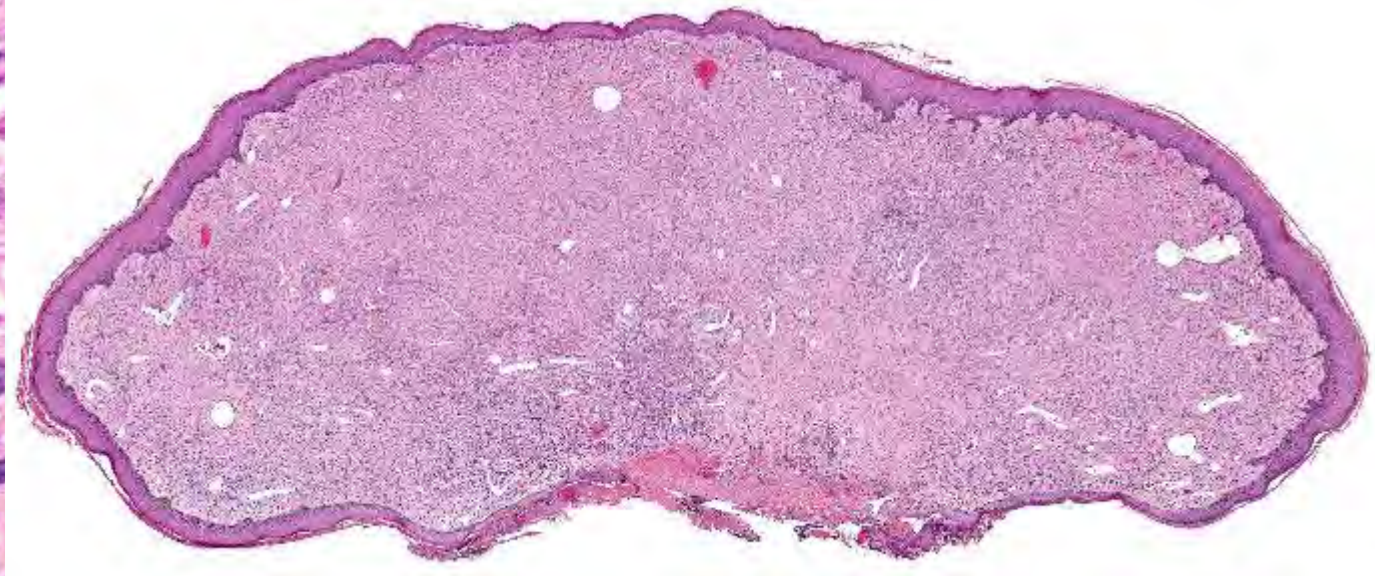
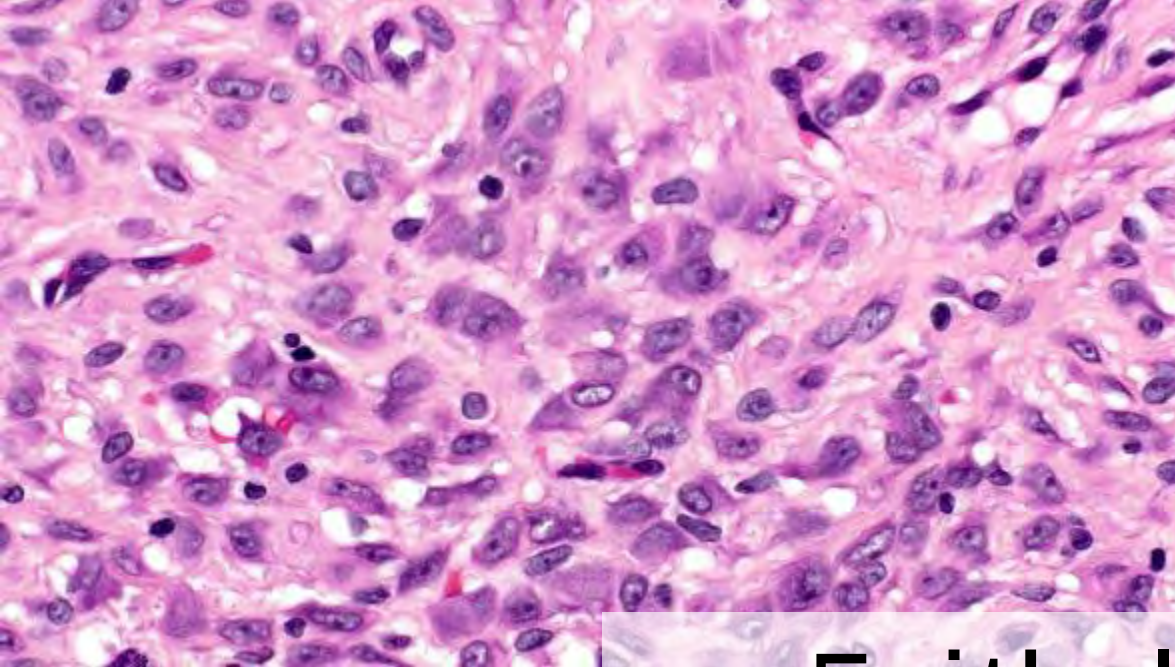




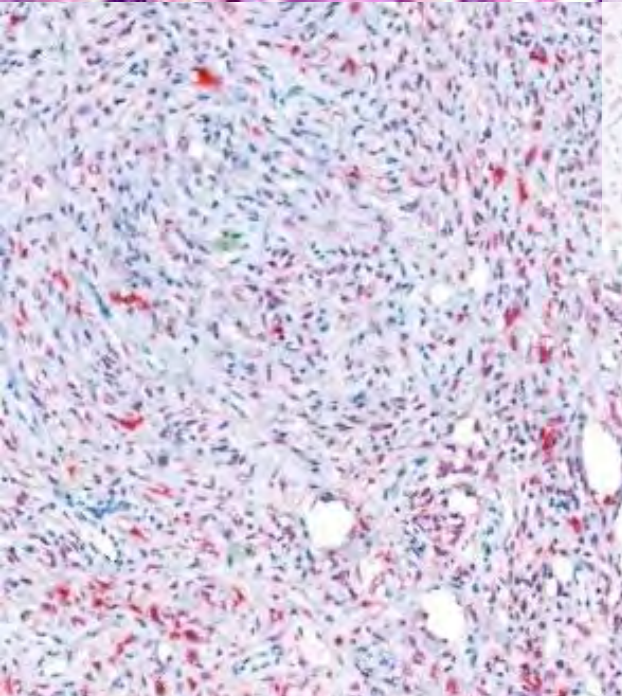








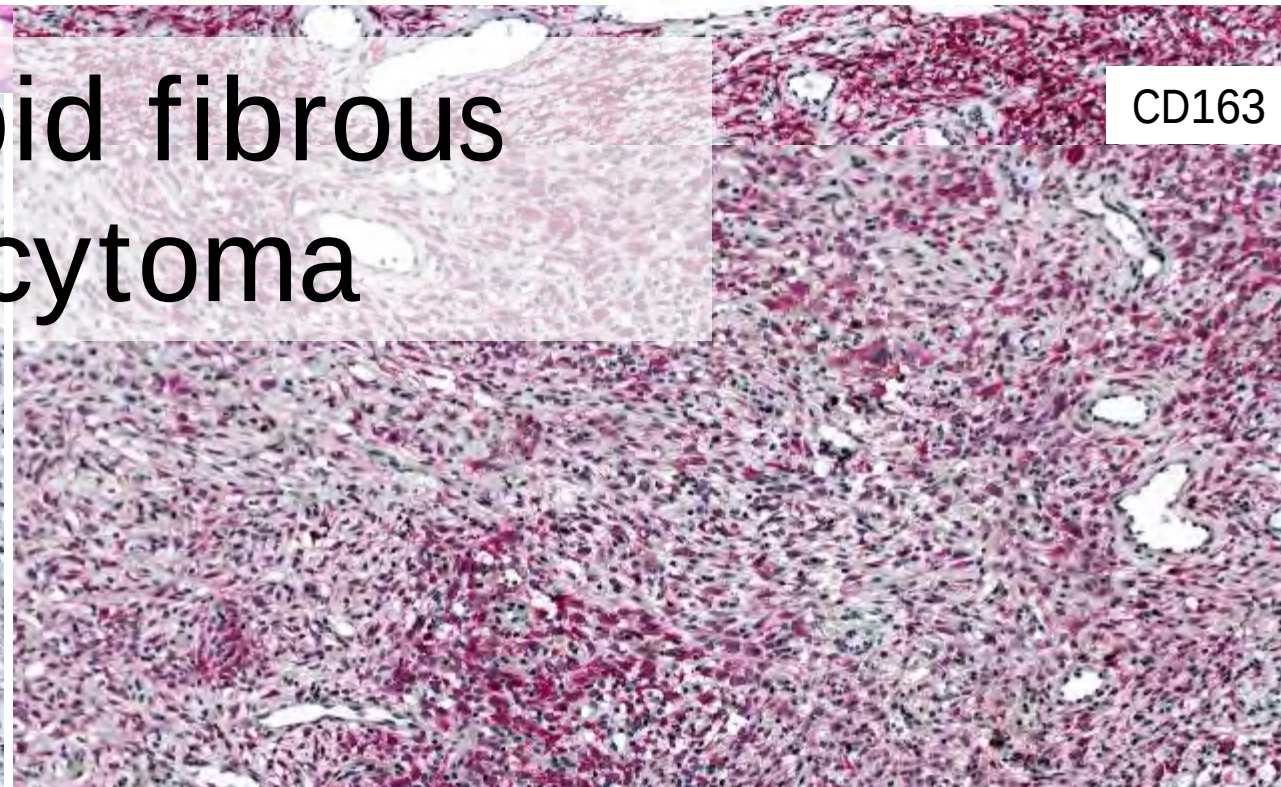
Epithelioid fibrous histiocytoma



S100



CK/SOX10



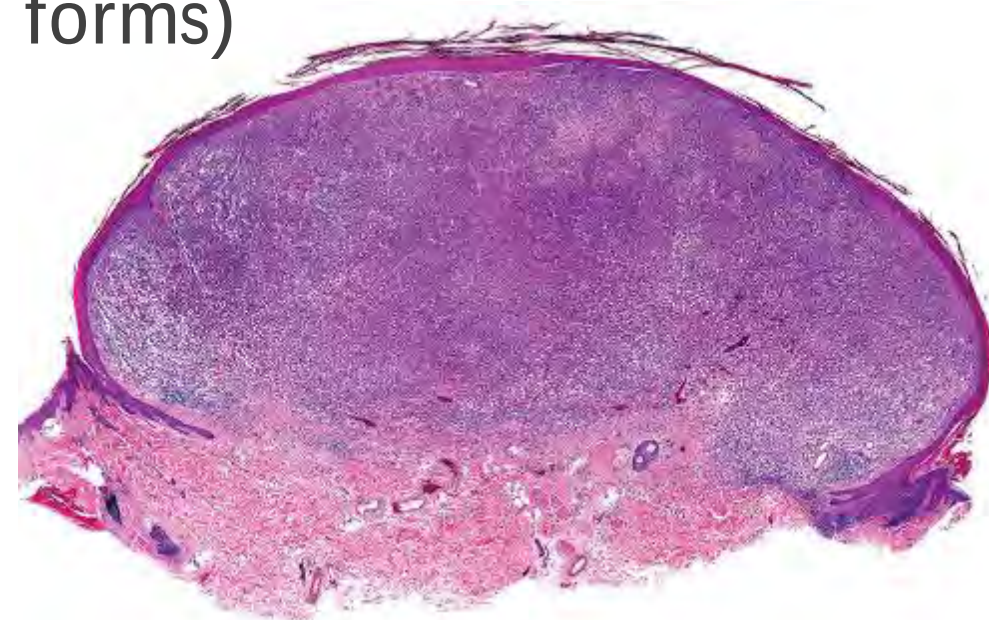
CD163



ALK

Epithelioid fibrous histiocytoma

- ▶ usually exophytic and well-circumscribed benign cutaneous neoplasm of uncertain differentiation
- ▶ lower extremities, upper extremities
 - ▶ Uncommon: trunk, head and neck region
- ▶ epithelioid cells (including binucleated forms)
- ▶ **ALK rearrangement**
 - ▶ *Subset: PRKCB & PRKCD fusion*



Dermal/superficial neoplasms with *ALK* rearrangement

- ▶ Epithelioid fibrous histiocytoma
- ▶ Nonneural granular cell tumor
- ▶ Spitz nevus/melanocytoma/melanoma
- ▶ Plaque-like *ALK* fusion dermal neoplasm
 - ▶ plaque-like CD34+ dermal fibroma
 - ▶ plaque-like DFSP
- ▶ Superficial *ALK*-rearranged myxoid spindle cell neoplasm
- ▶ *TPM4::ALK* rearranged cutaneous epithelioid vascular tumor/hemangioma
- ▶

Table 3
 Reported distinct ALK immunoreactivity patterns and their molecular correlates in certain ALK fusion neoplasms.

Entity	ALK staining pattern	Fusion partner	Reference
Epithelioid fibrous histiocytoma	Nuclear only	ETV6	36]
Epithelioid fibrous histiocytoma	Perinuclear dots	PRKAR2A	40
Epithelioid fibrous histiocytoma	Nuclear dots	SP100	41
Epithelioid fibrous histiocytoma	Diffuse cytoplasmic (-/+ nuclear)	All other reported ALK partners	35, 36
Epithelioid inflammatory myofibroblastic sarcoma	Nuclear membrane/perinuclear	RANBP2	26
IMT, classical	Diffuse cytoplasmic only	All reported ALK partners	27,-29
ALK+ with non-ALK fusions	Diffuse cytoplasmic only	Non-ALK fusions: FET::CREB fusions, FET::TFCP fusions, EWSR1::PBX3	42_43

Seminars in Diagnostic Pathology 42 (2025) 150947

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Review article

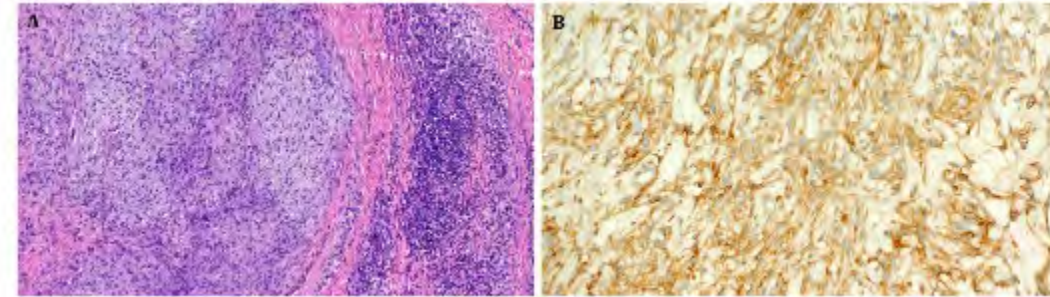
The expanding family of ALK-rearranged Mesenchymal Neoplasms

Abbas Agaimy^{a,b,*}

CAVE!!!!

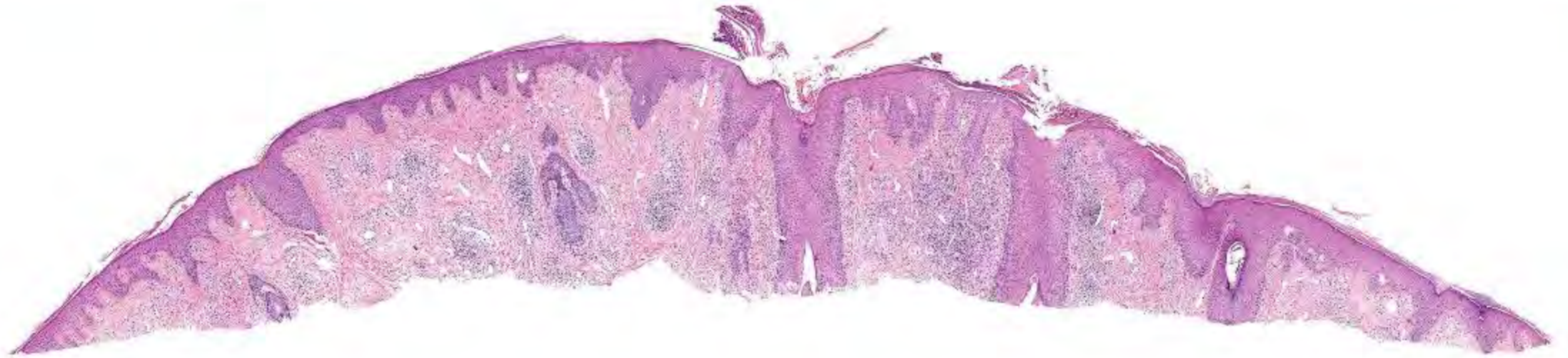
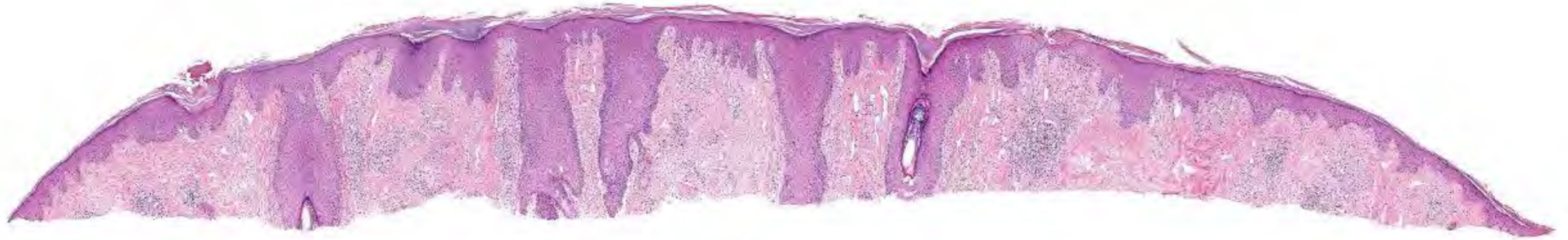
Table 4
Main ALK-immunoreactive mesenchymal entities that harbor non-ALK fusions.

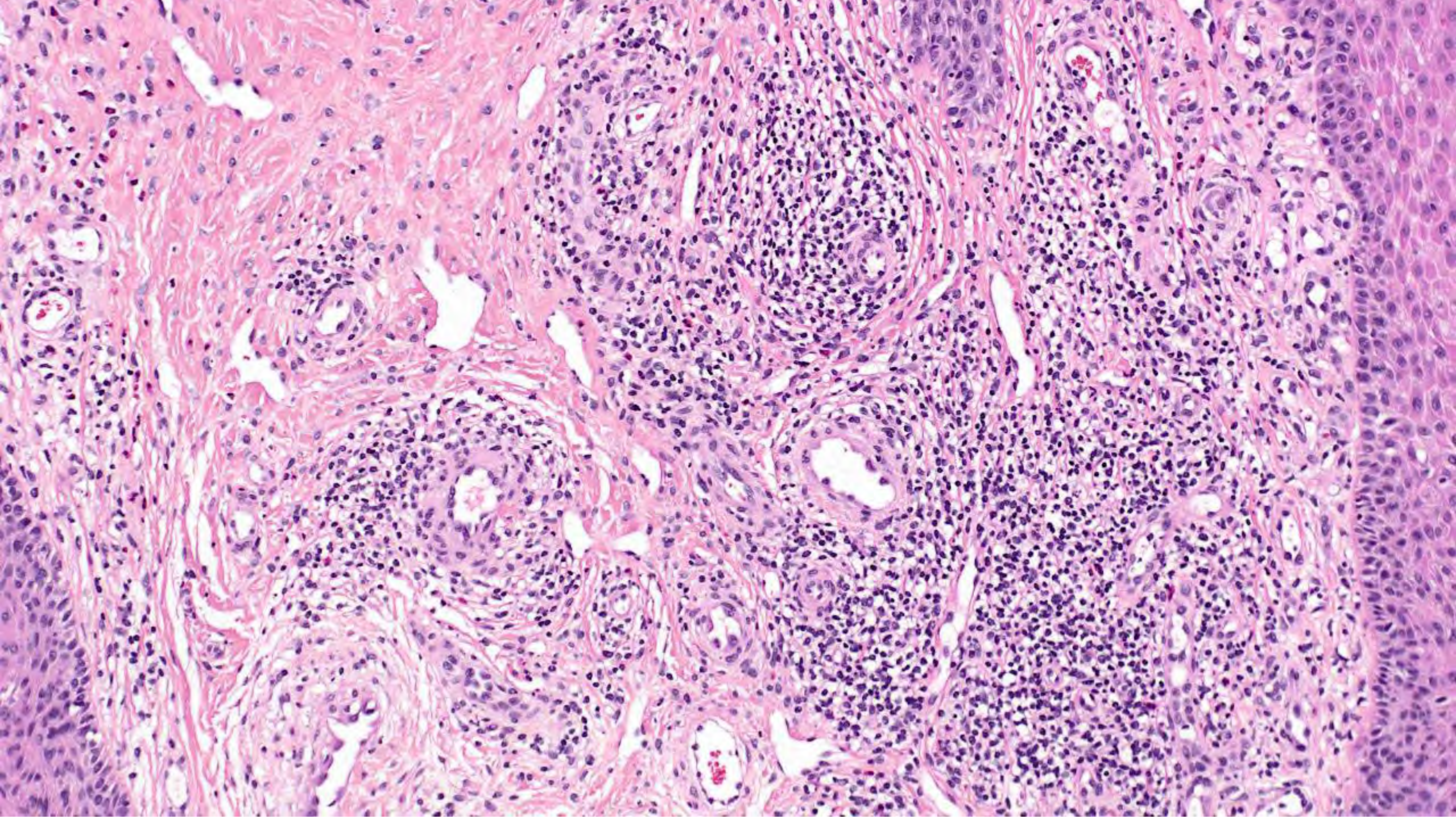
Entity	% ALK positive	Main + IHC	Genotype
Alveolar rhabdomyosarcoma	50 %	Desmin, myogenin	<i>FOXO1::PAX3</i> , <i>FOXO1::PAX7</i>
Angiomatoid fibrous histiocytoma	80–90 %	Desmin, EMA	<i>EWSR1/</i> <i>FUS::ATF1/</i> <i>CREM/</i> <i>CREB1</i> fusions
Spindel cell/epithelioid rhabdomyosarcoma	>90 %	Desmin, pankeratin, MyoD1, Myogenin	<i>FUS/</i> <i>EWSR1::</i> <i>TFCP2</i> fusions
Unclassified <i>FET::CREB</i> sarcomas	30–50 %	Frequently pankeratin & EMA, variably MUC4, synaptophysin, WT1, desmin & others	<i>EWSR1/</i> <i>FUS::ATF1/</i> <i>CREM/</i> <i>CREB1</i> fusions
Syncytial myoepithelioma	Insufficient data	S100, EMA	<i>EWSR1::</i> <i>PBX3/1</i> fusions

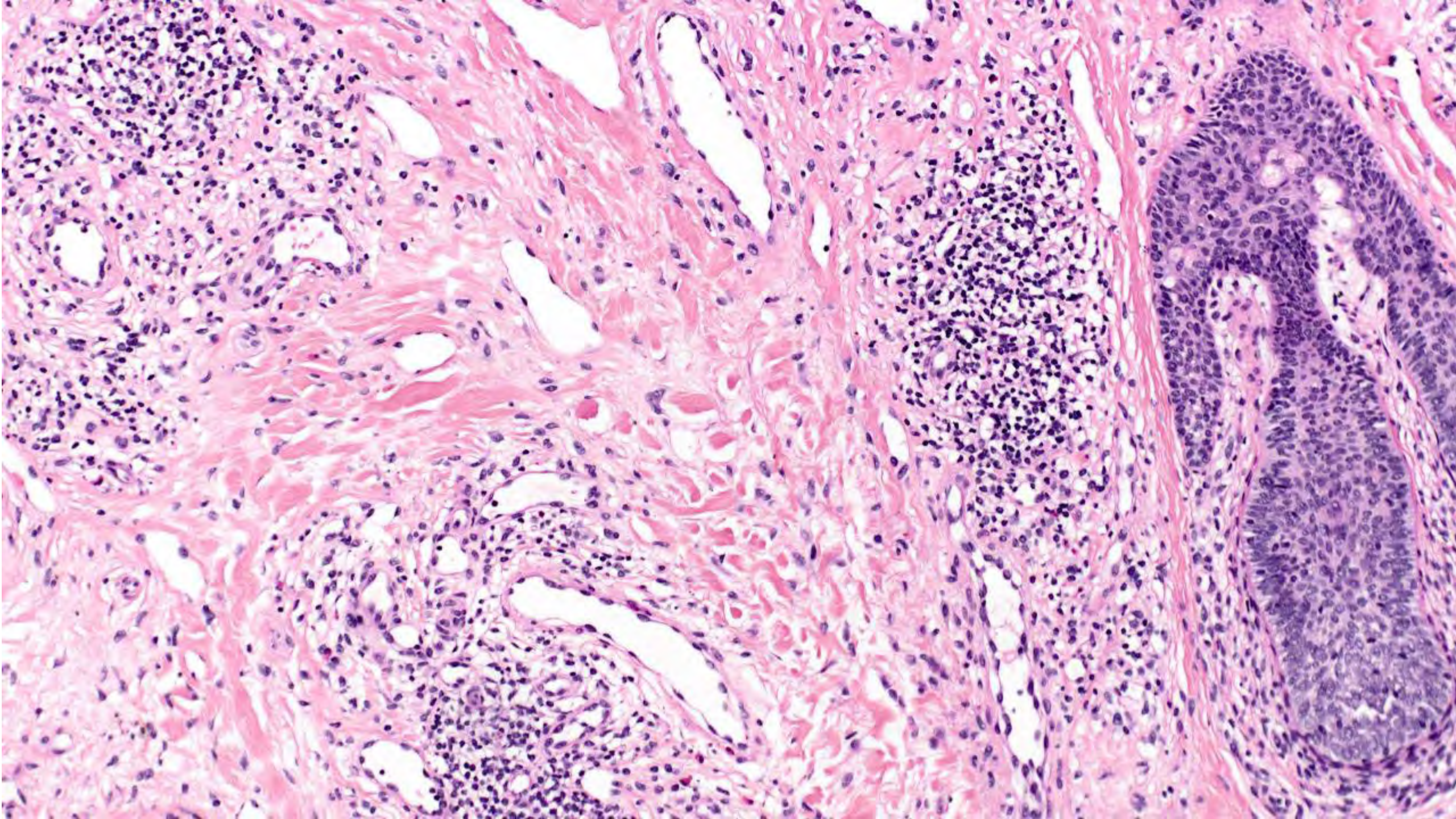


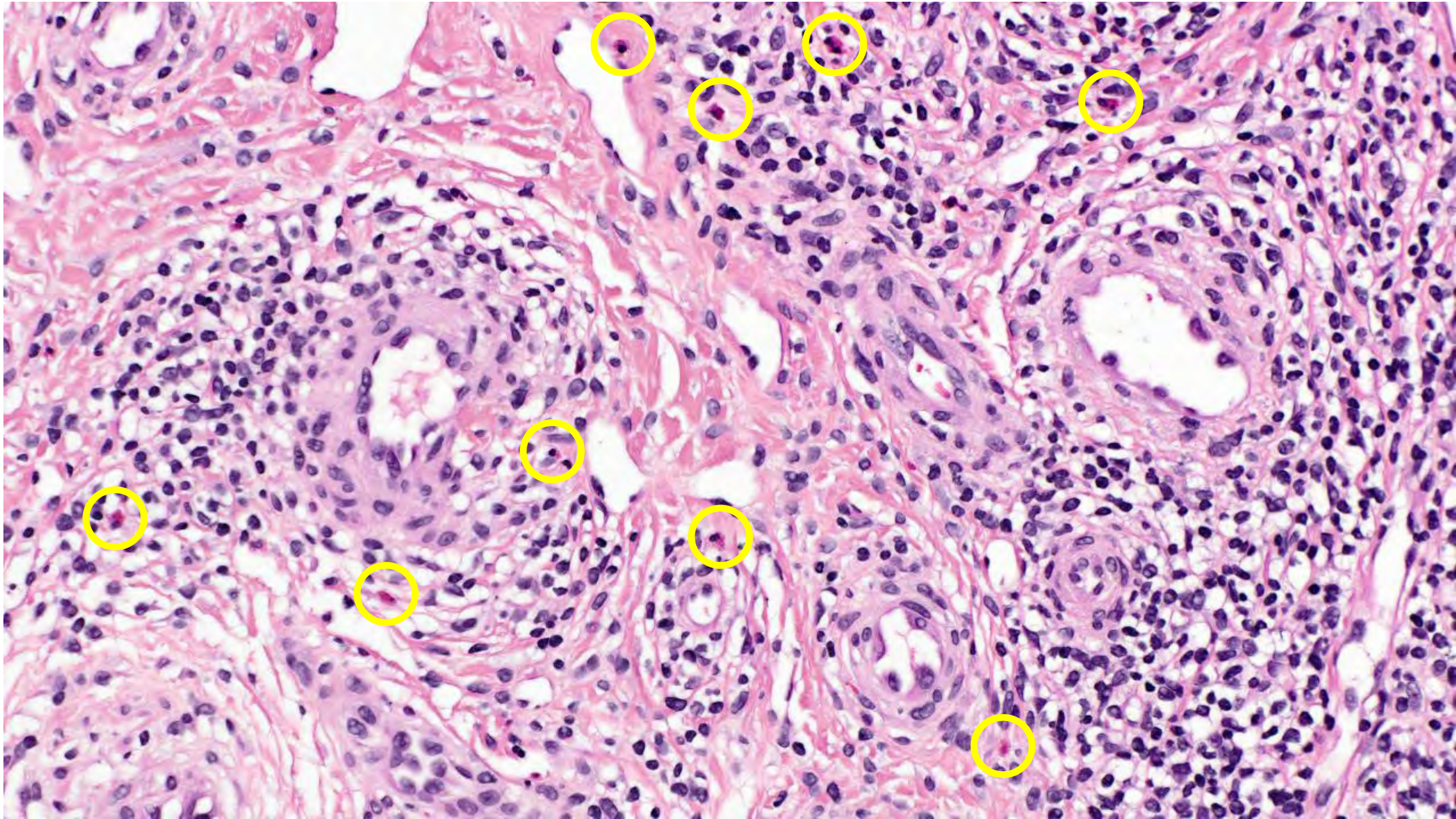
Case 17

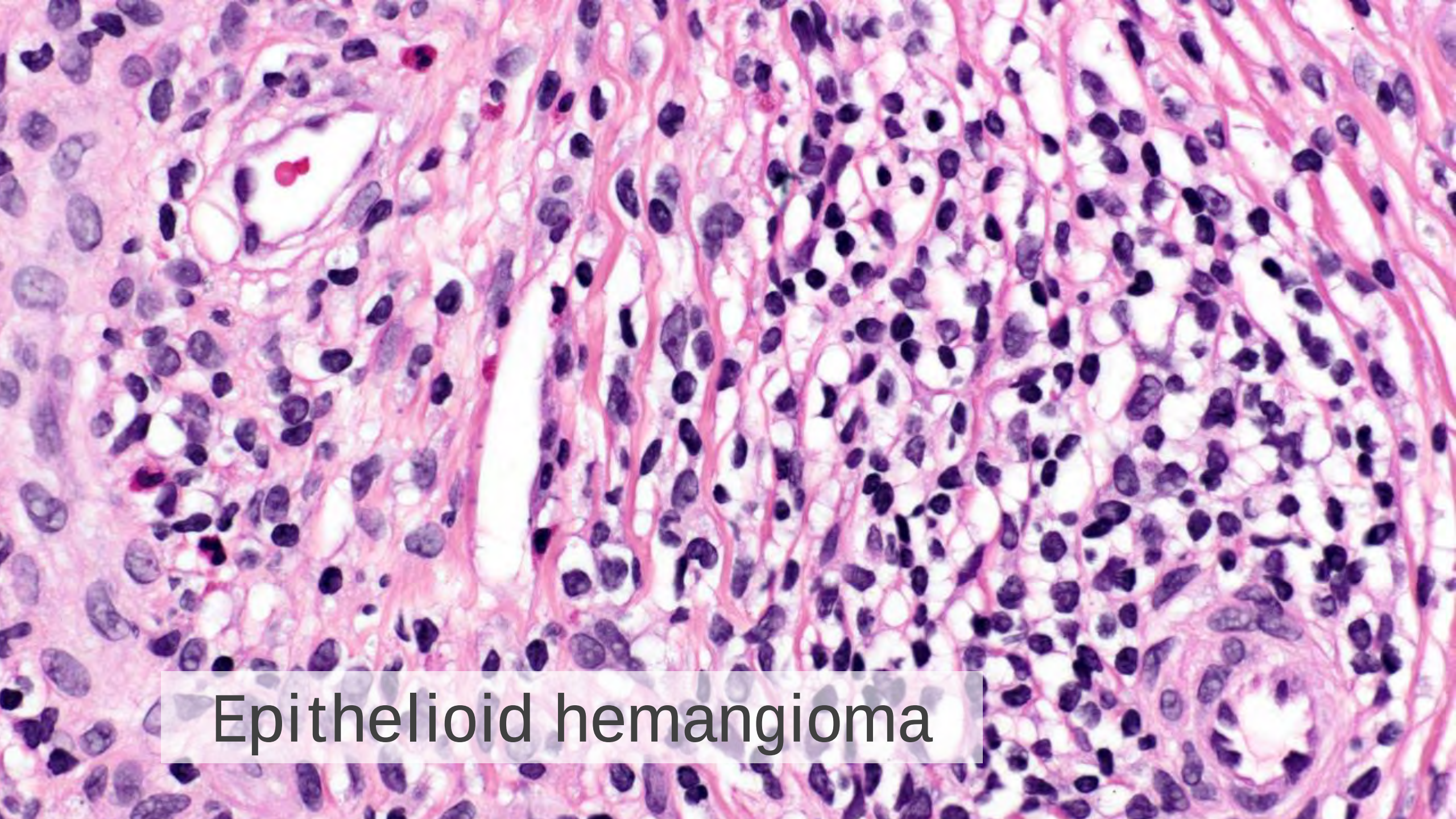
- ▶ 35 y, F
- ▶ occipital
- ▶ DD: dermal naevus?







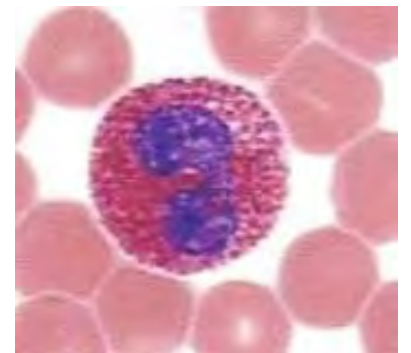


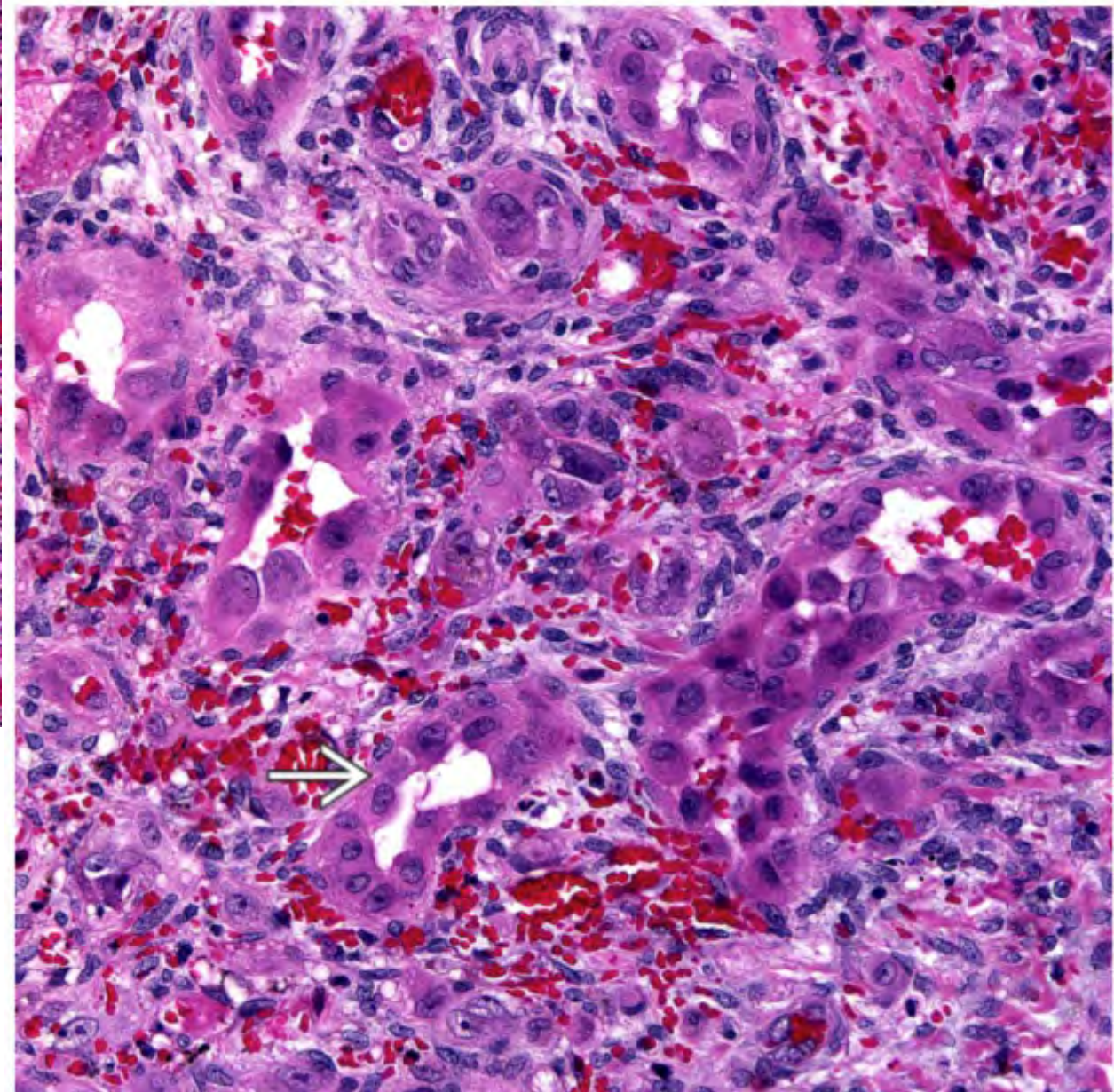
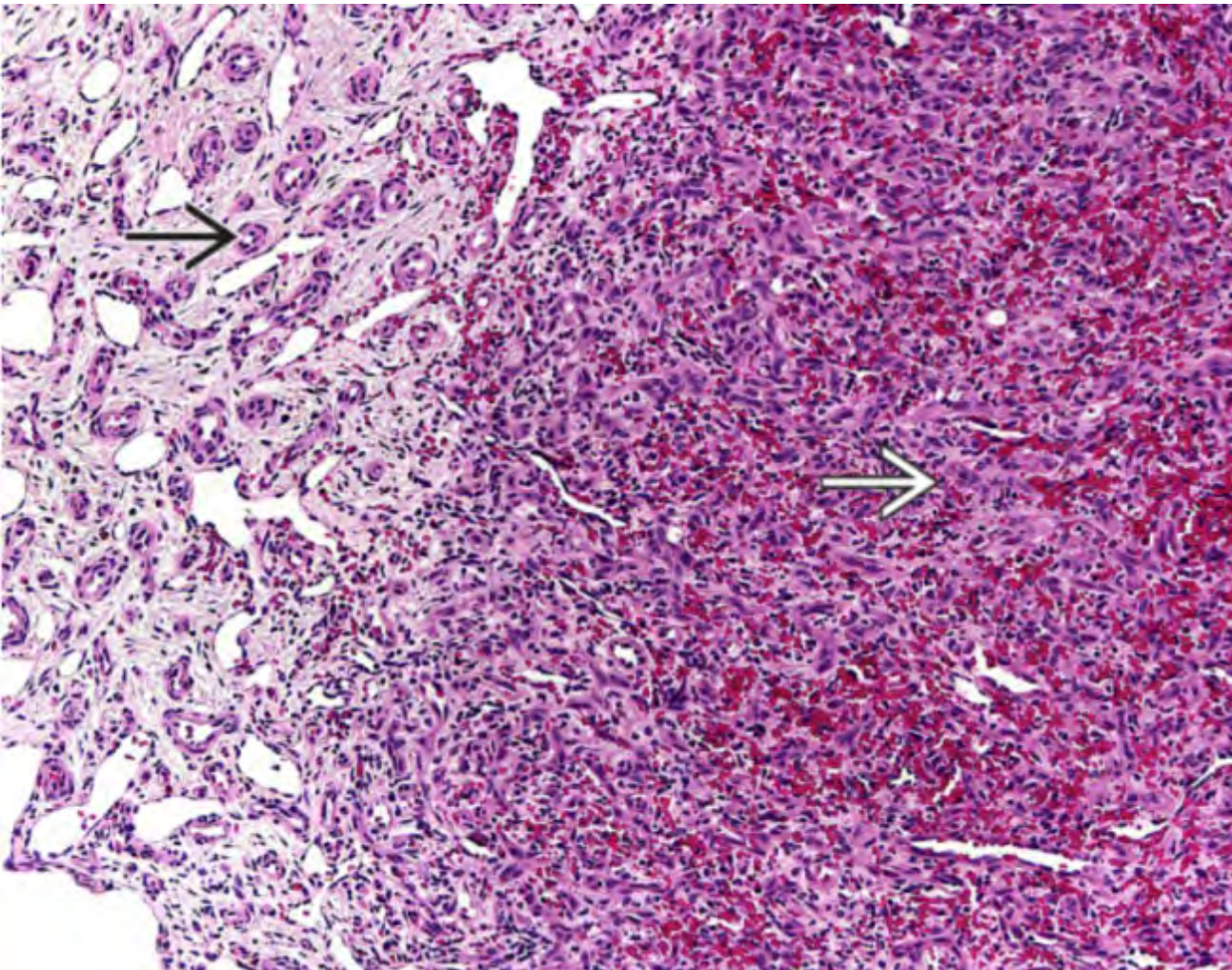


Epithelioid hemangioma

Epithelioid hemangioma

- ▶ benign vascular proliferation (vessels lined by epithelioid endothelial cells)
 - ▶ often an associated inflammatory component
- ▶ Not recommended: angiolymphoid hyperplasia with eosinophilia; histiocytoid haemangioma; pseudopyogenic granuloma
- ▶ Cutaneous lesions: head & neck and trunk
 - ▶ occur also in deeper soft tissue, internal organs, and bone
- ▶ single or multiple, persistent, skin-coloured to erythematous papules and nodules
- ▶ peripheral eosinophilia (15%)
- ▶ *FOS* or *FOSB* gene rearrangements (in BST lesions)
 - ▶ rare in cutaneous lesions (FOSB IHC can be positive!)

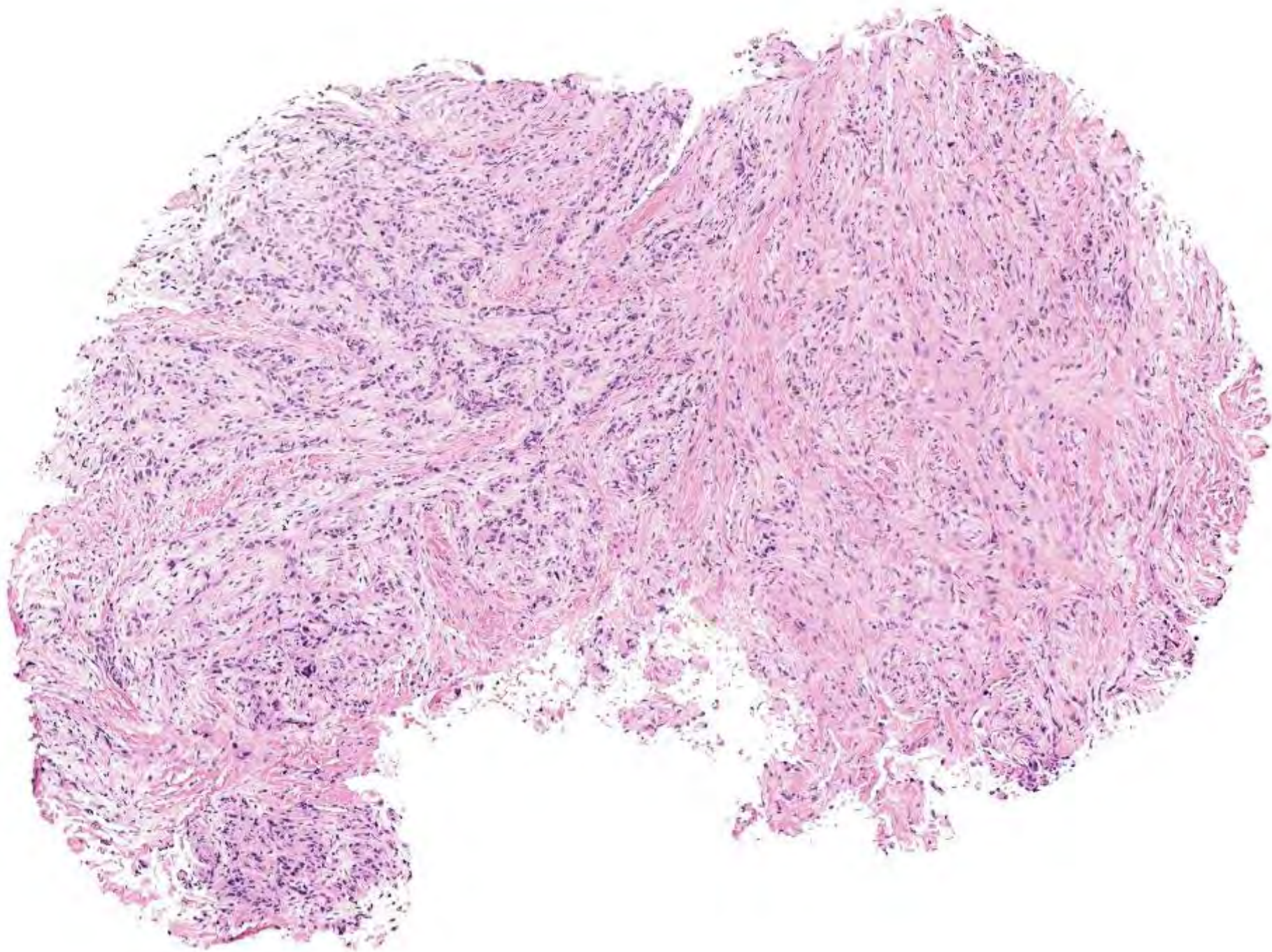


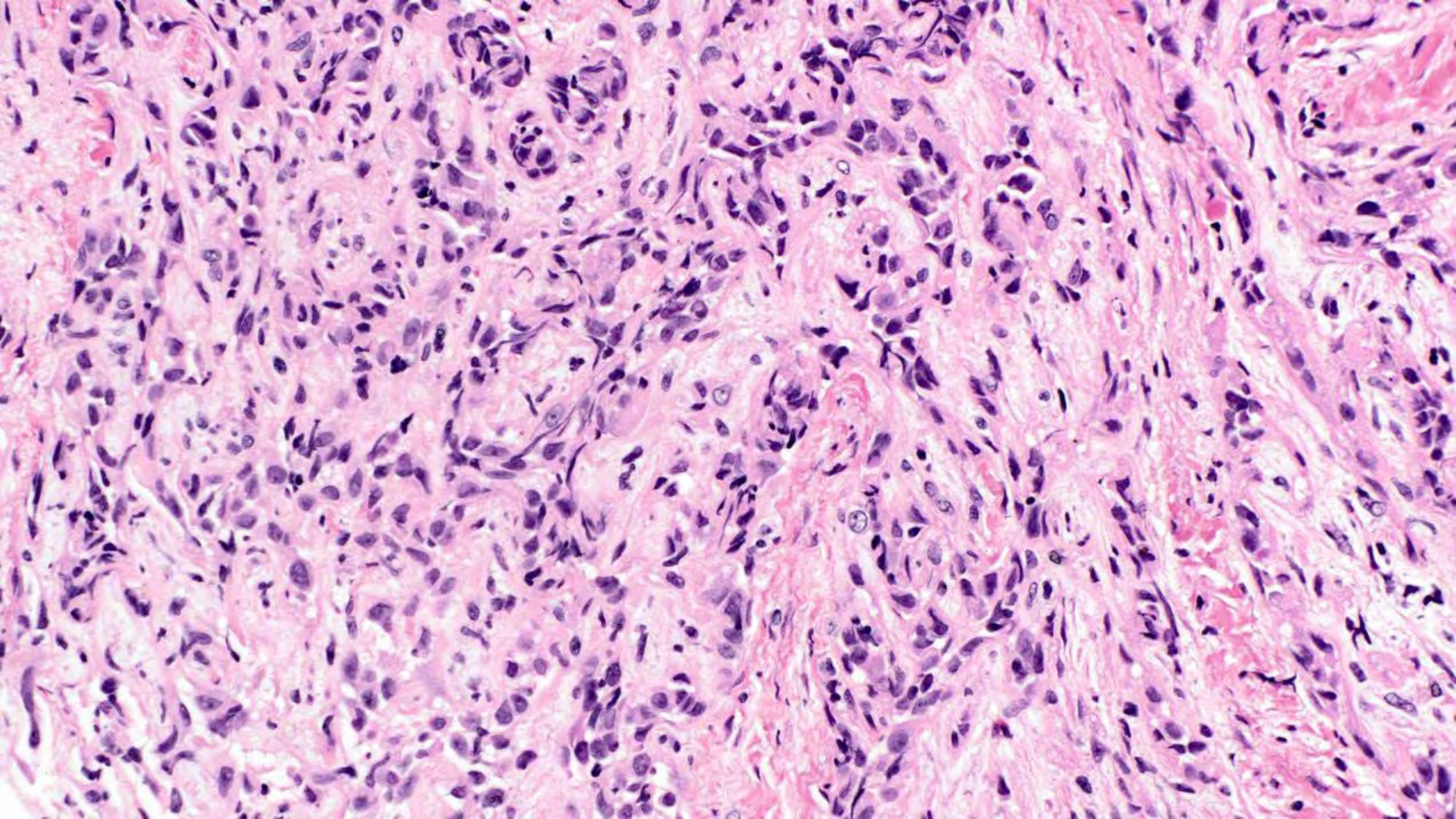


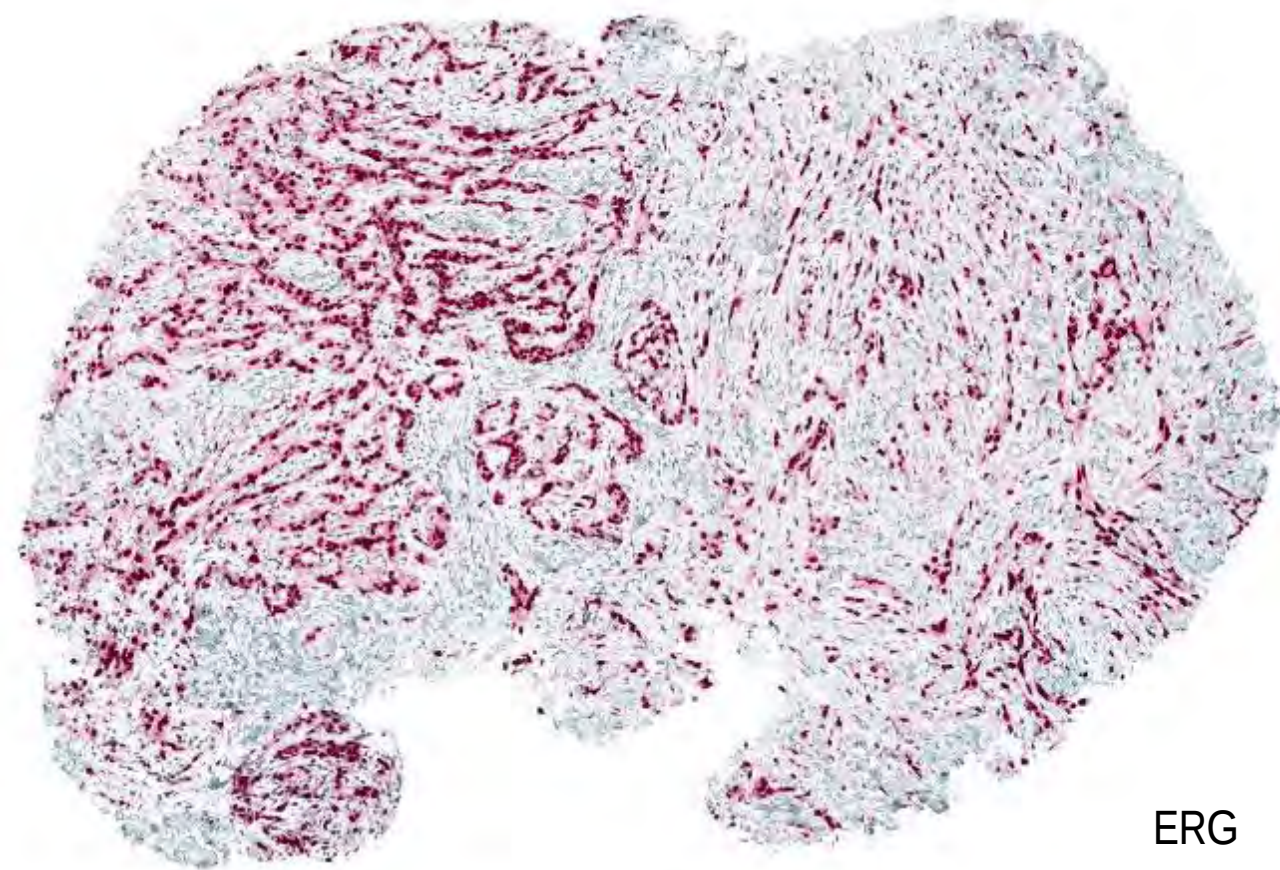
Case 18

- ▶ 73y, F
- ▶ Upper leg 1,5x1,5 cm subcutaneous nodule
- ▶ Overlying skin red
- ▶ DD: inflamed epidermal cyst
- ▶ Ultrasound: 9x8mm hypoechogenic lesion in the dermis und subcutis



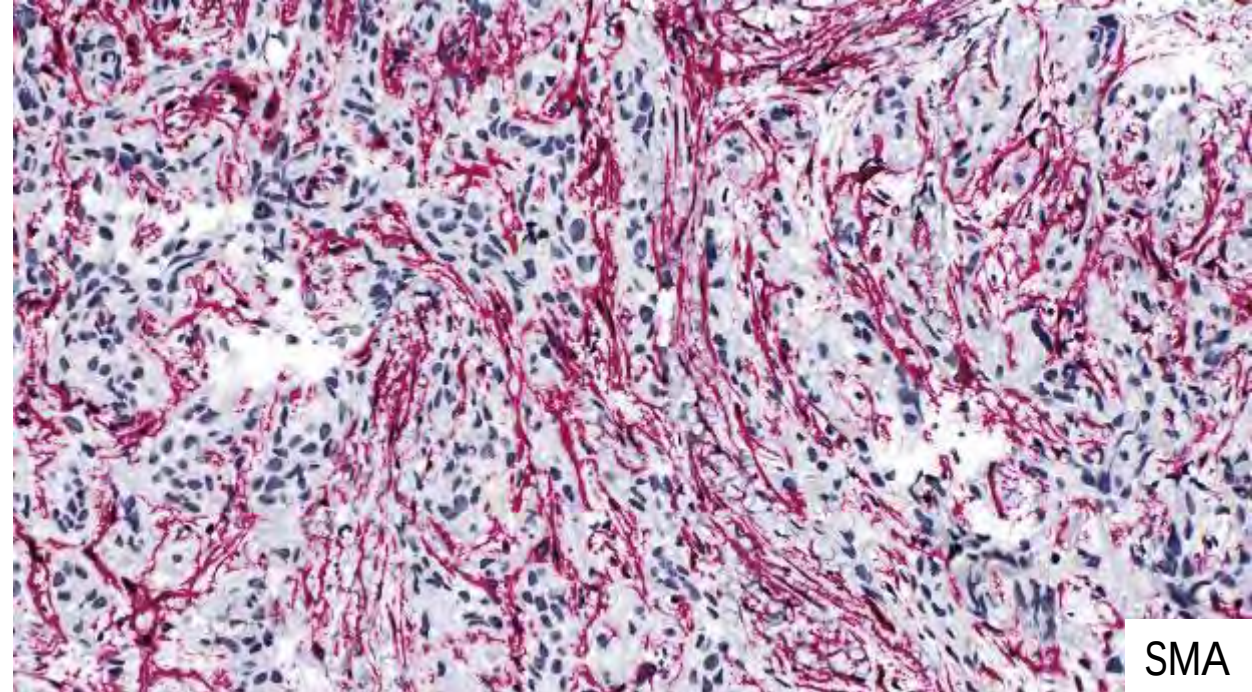




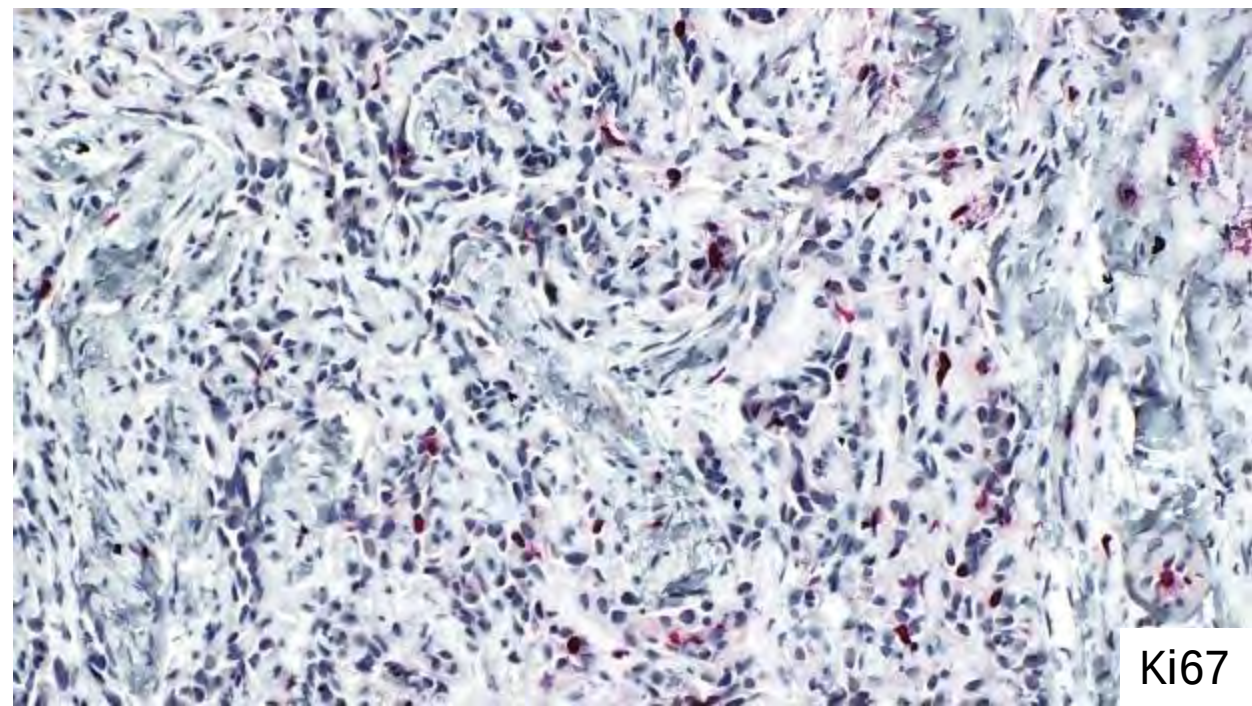


ERG

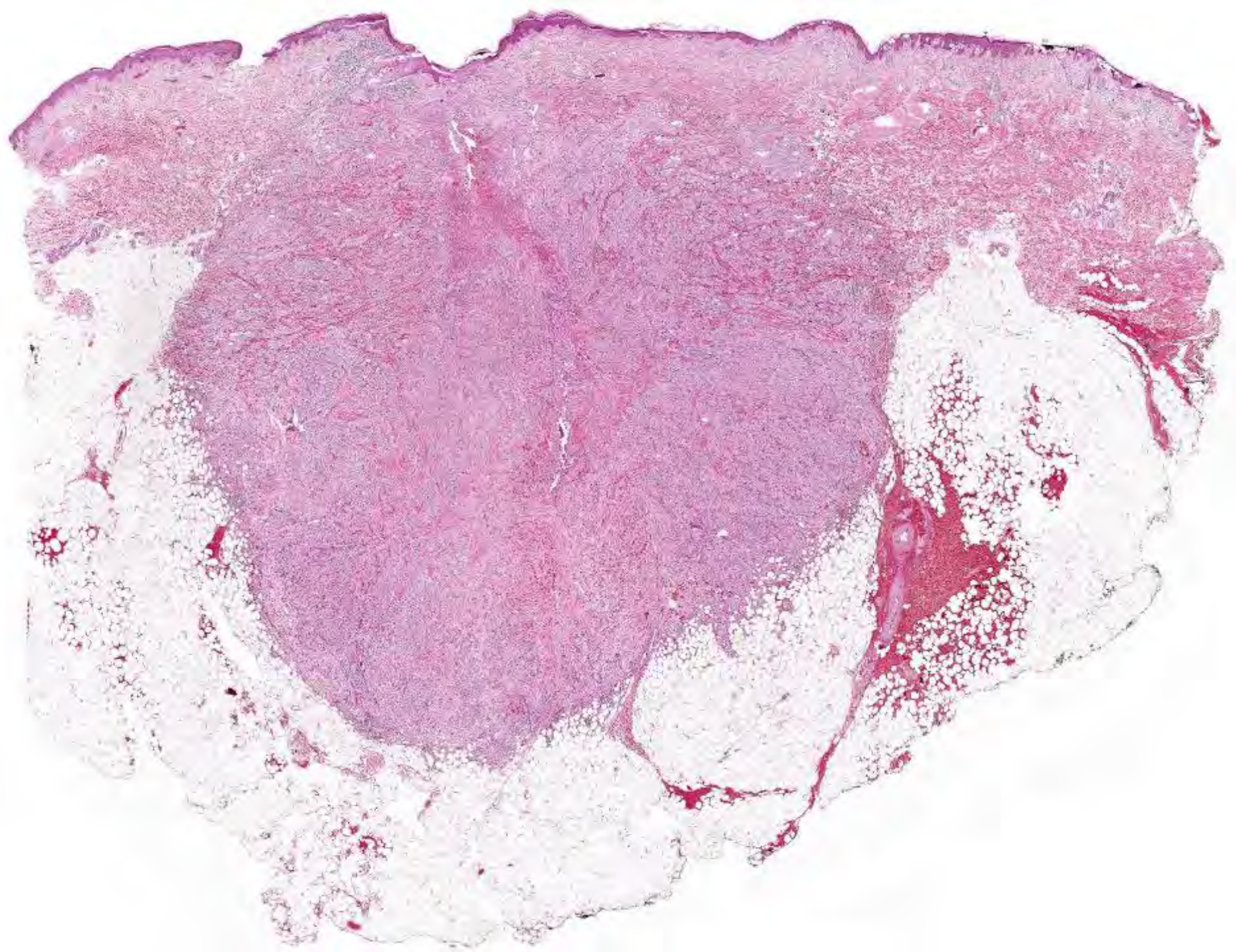
Vascular lesion: Resection

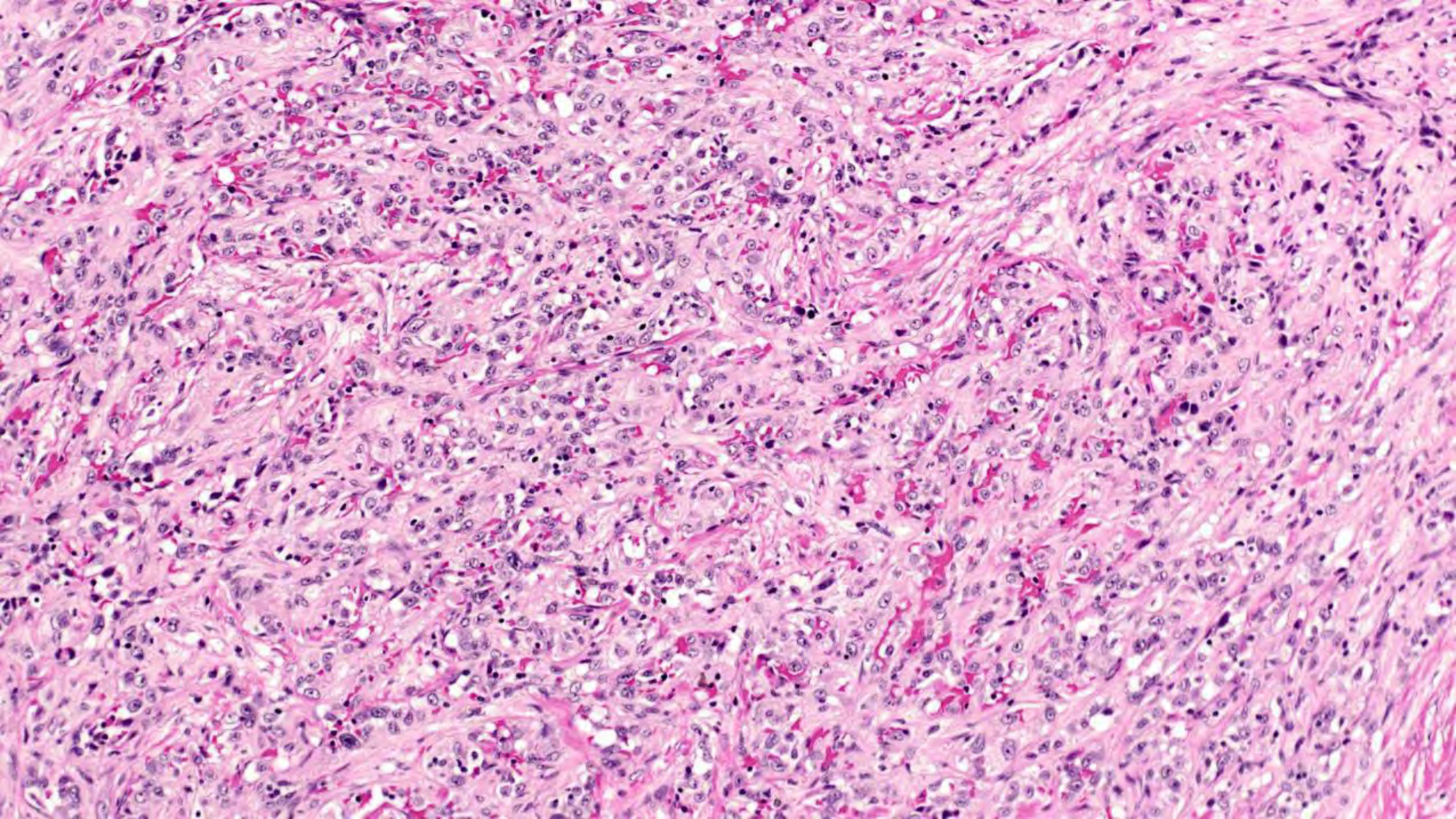


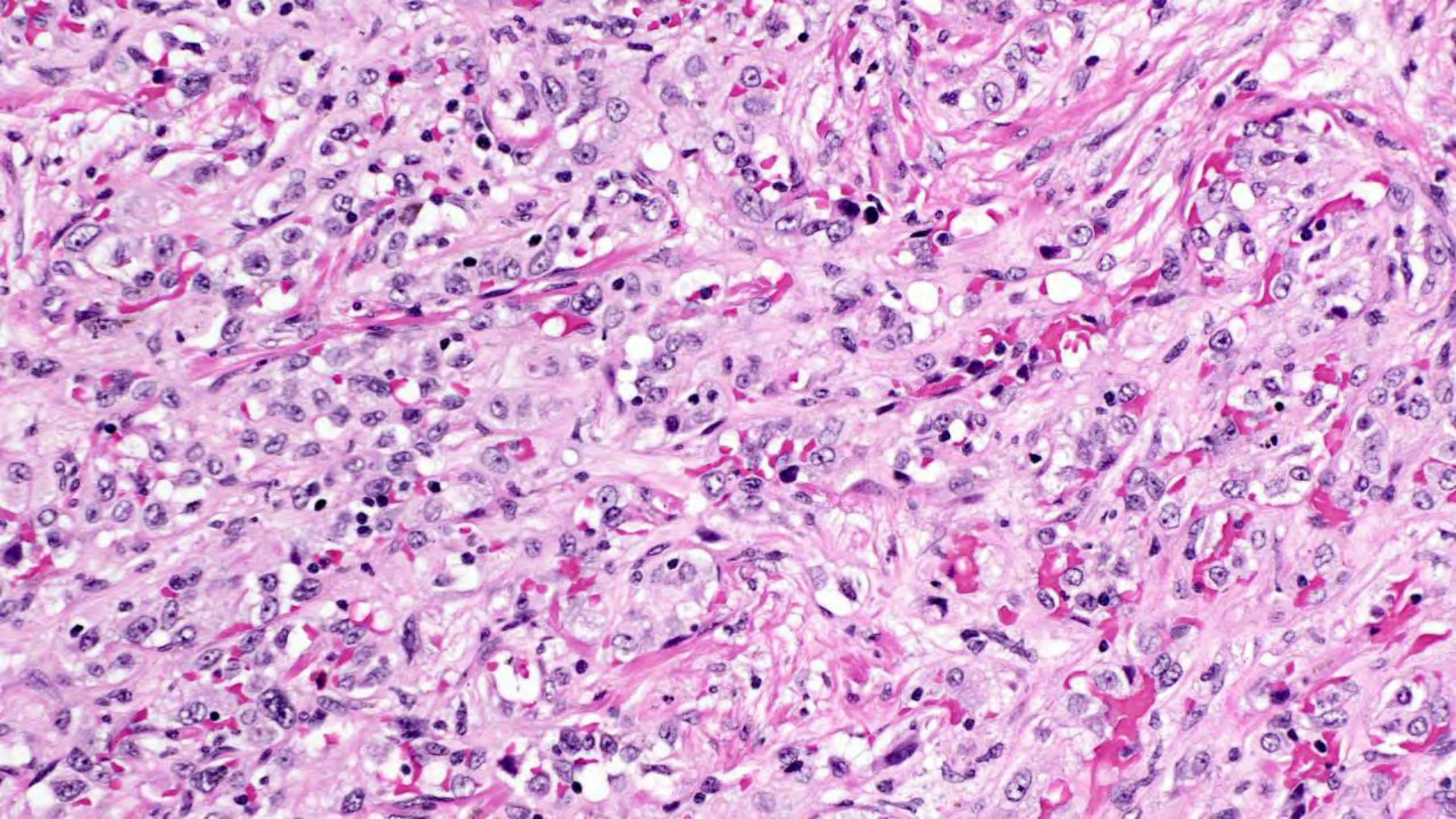
SMA

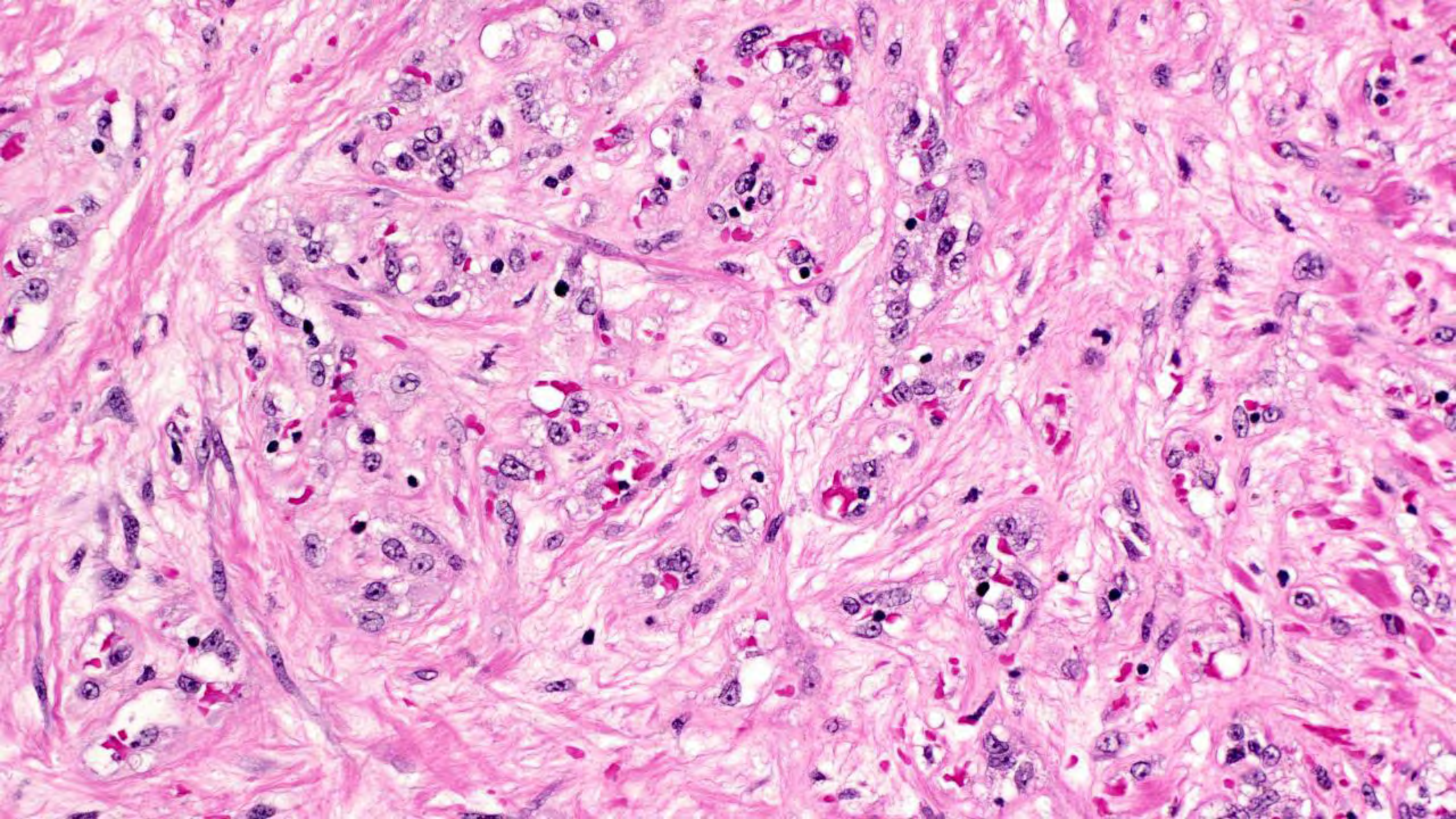


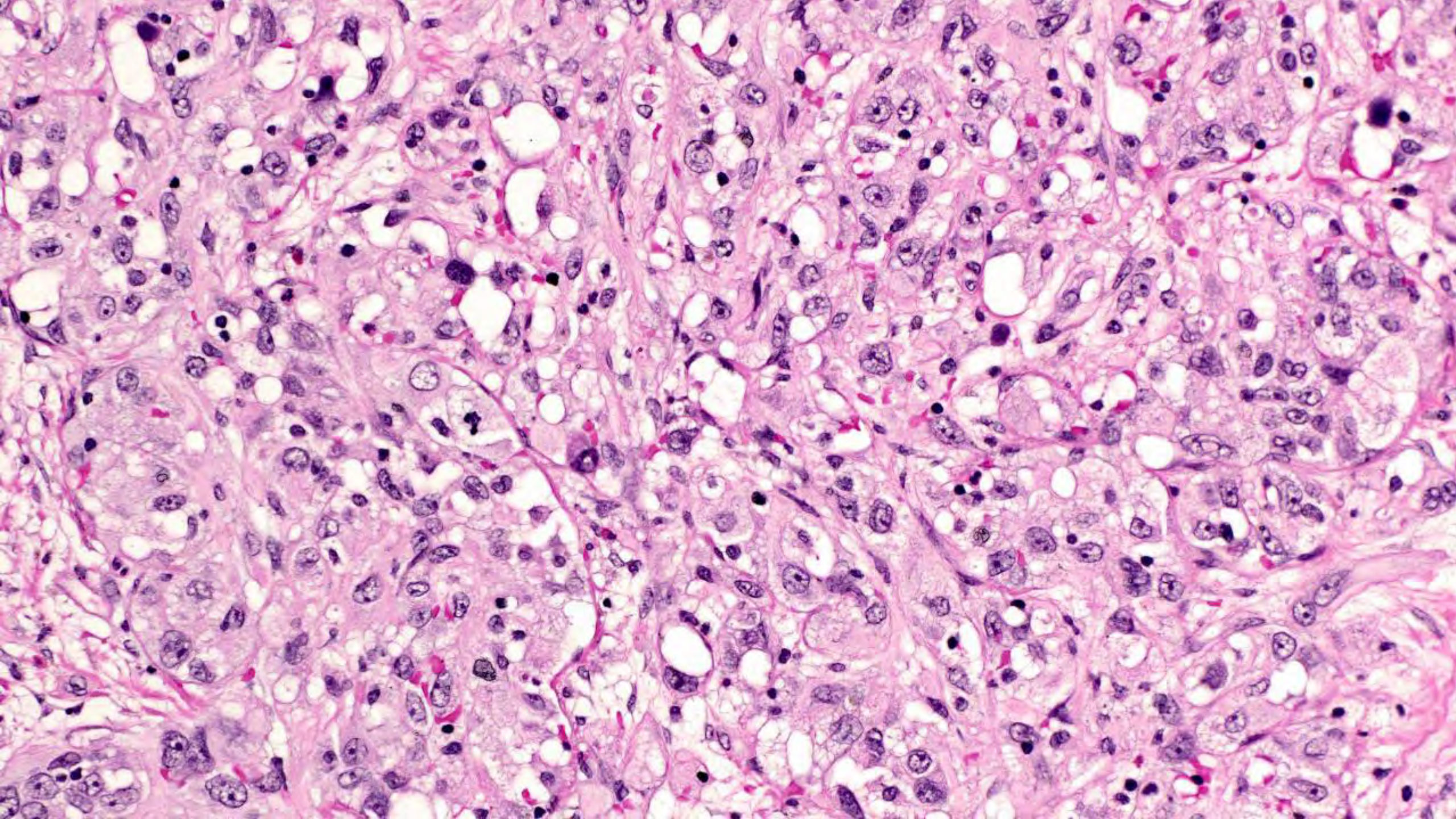
Ki67

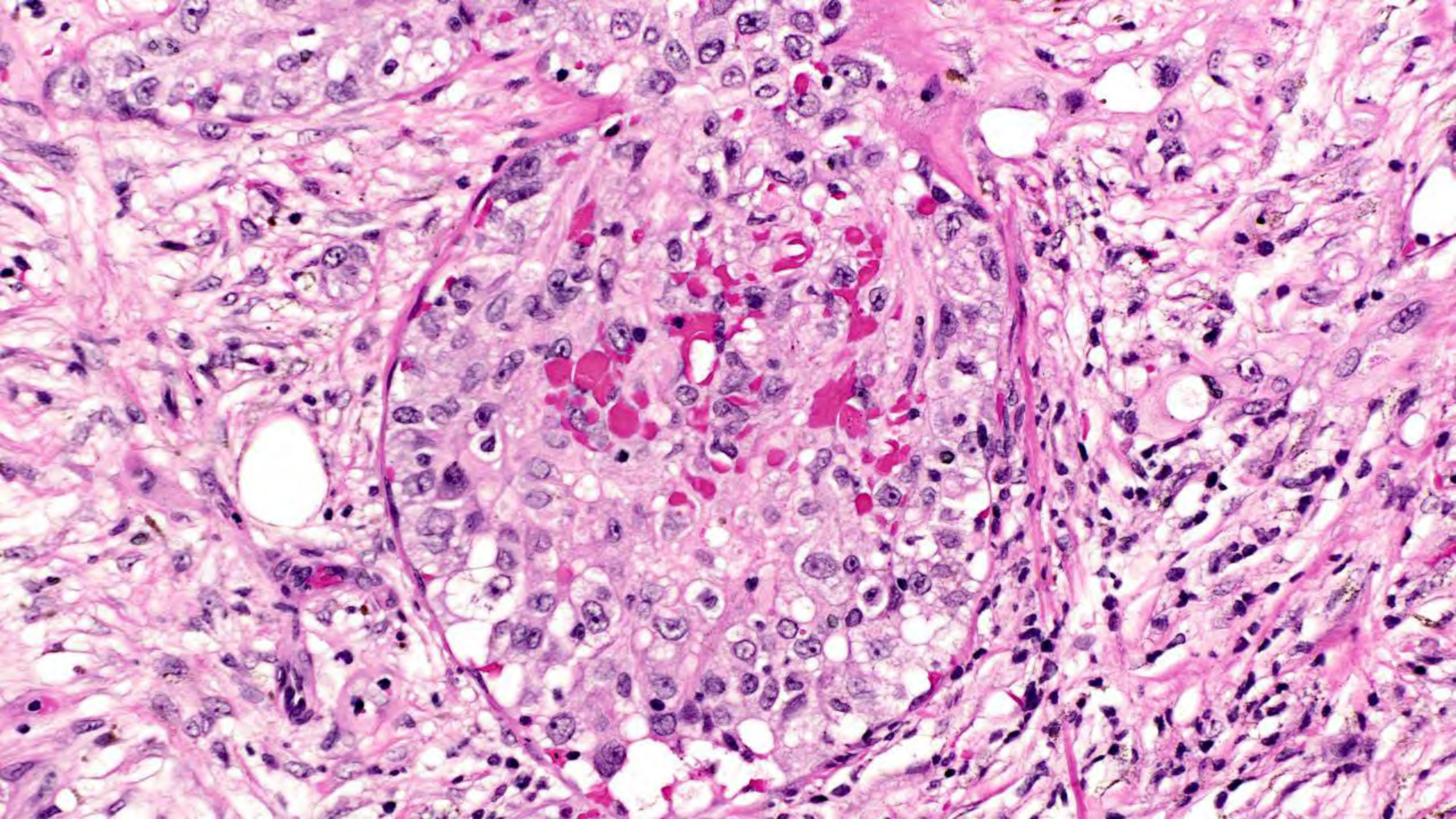


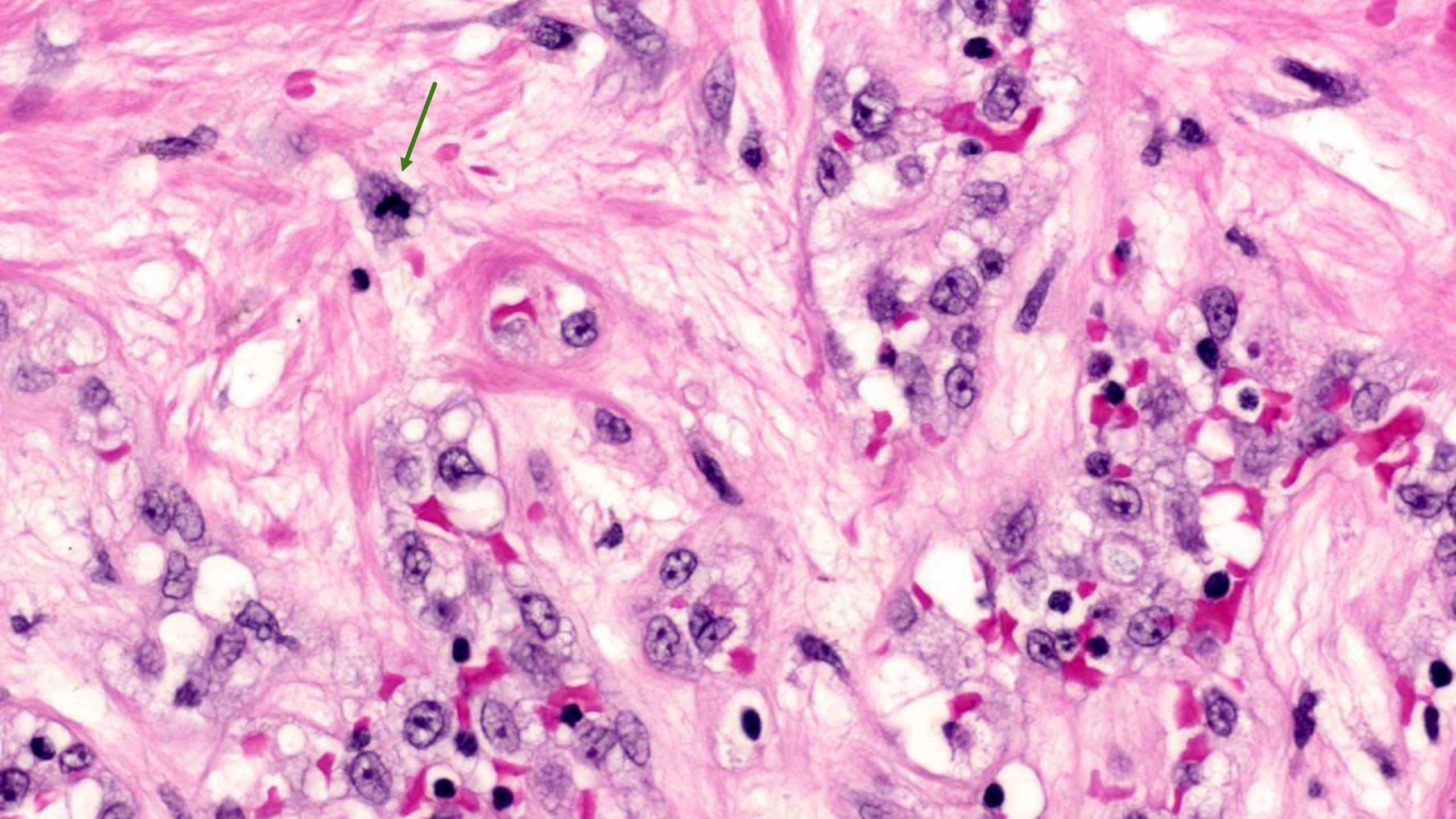


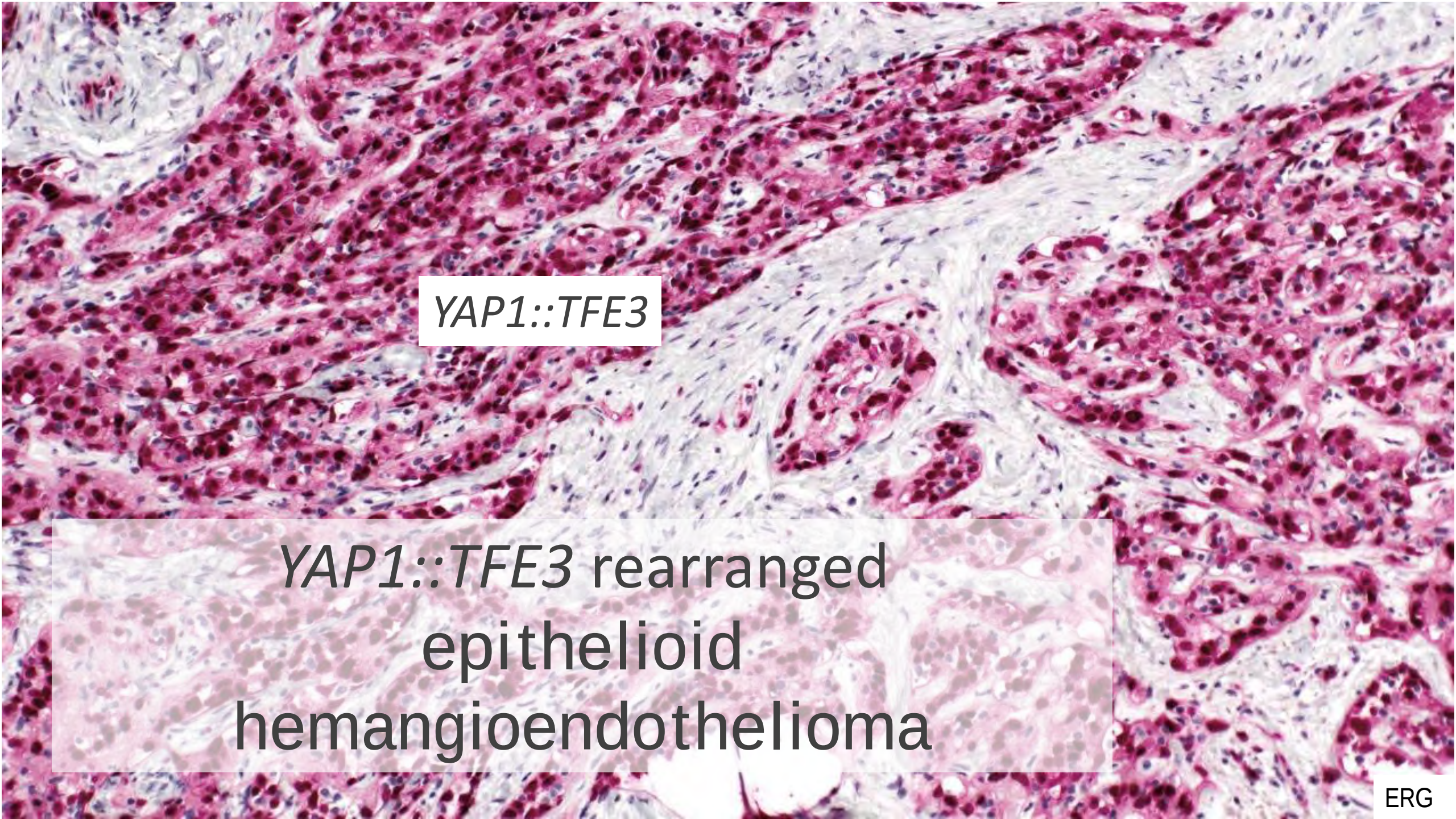












YAP1::TFE3

YAP1::TFE3 rearranged
epithelioid
hemangioendothelioma

Epithelioid hemangioendothelioma

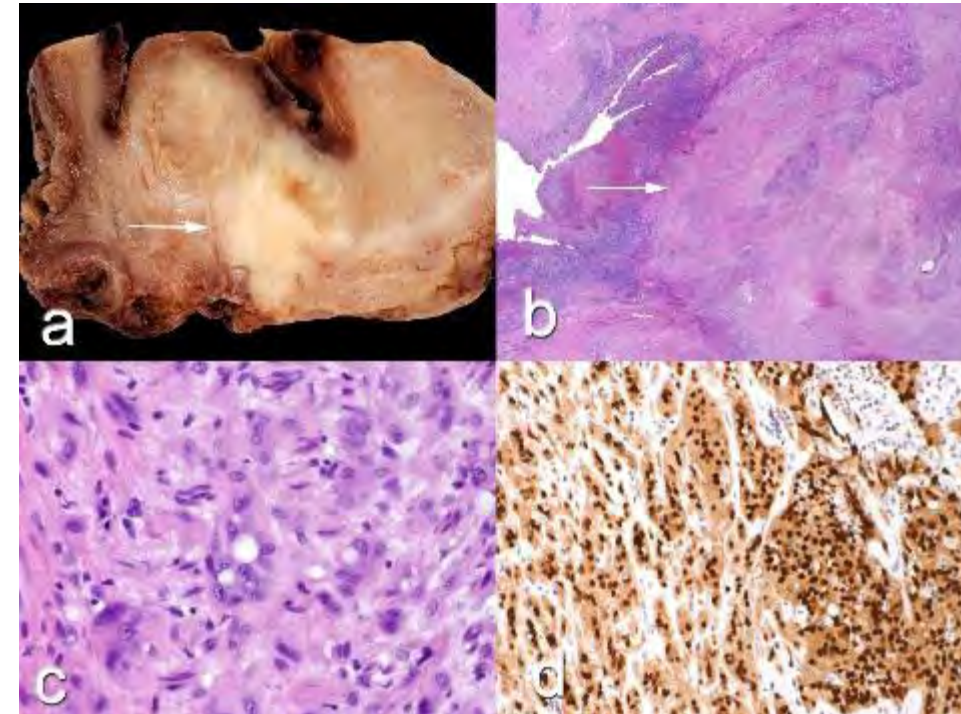
- **malignant** endothelial neoplasm
- can be locally aggressive
- has metastatic potential

Age & Gender:

- ▶ Peak: 2nd-3rd decades of life

Location:

- ▶ soft tissue, bone, lung, skin and liver
- ▶ often multifocal: bone and visceral lesions



Epithelioid Hemangioendothelioma of the Bowel in Crohn's Disease: The First Reported Case

Smiljana Seask, MD, Iva Brčić, MD, PhD, and Andrew E. Rosenberg, MD

Volume 27, Issue 4 | <https://doi.org/10.1177/1066896918801527>

EHE - Molecular analysis

2 Subtypes:

- ▶ *WWTR1::CAMTA1* rearrangement
- ▶ *YAP1::TFE3* rearrangement

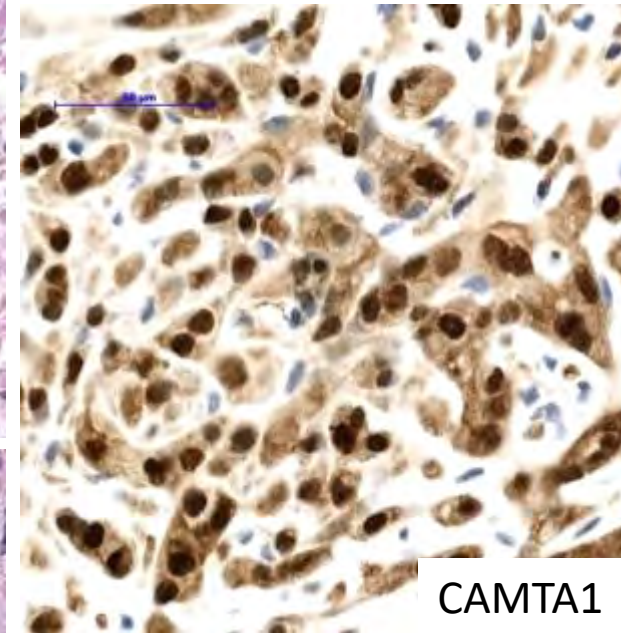
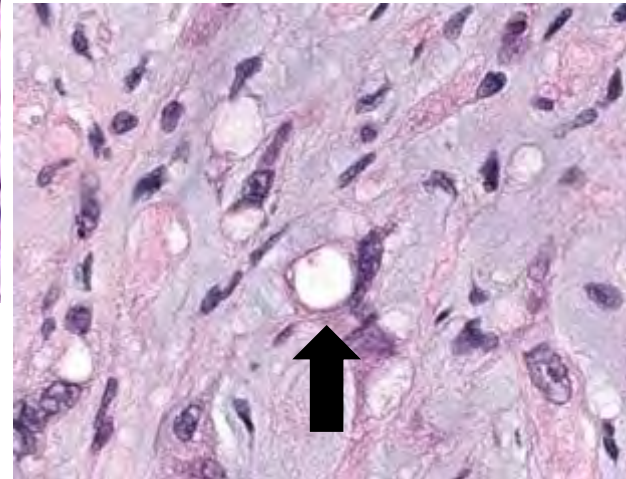
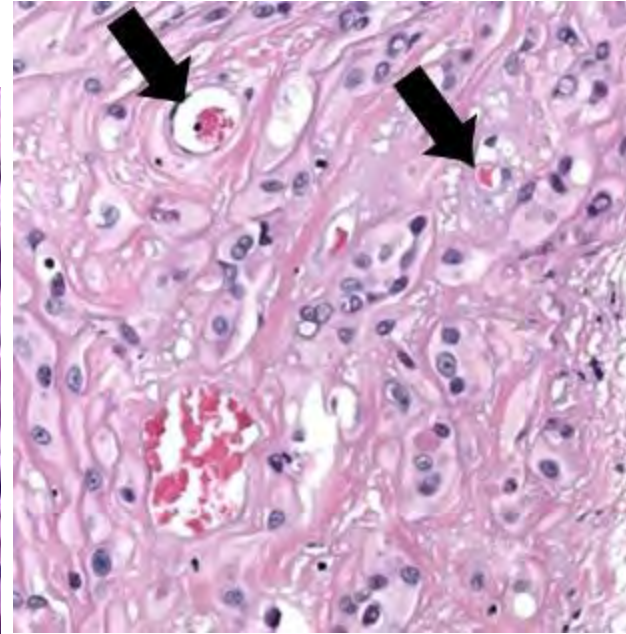
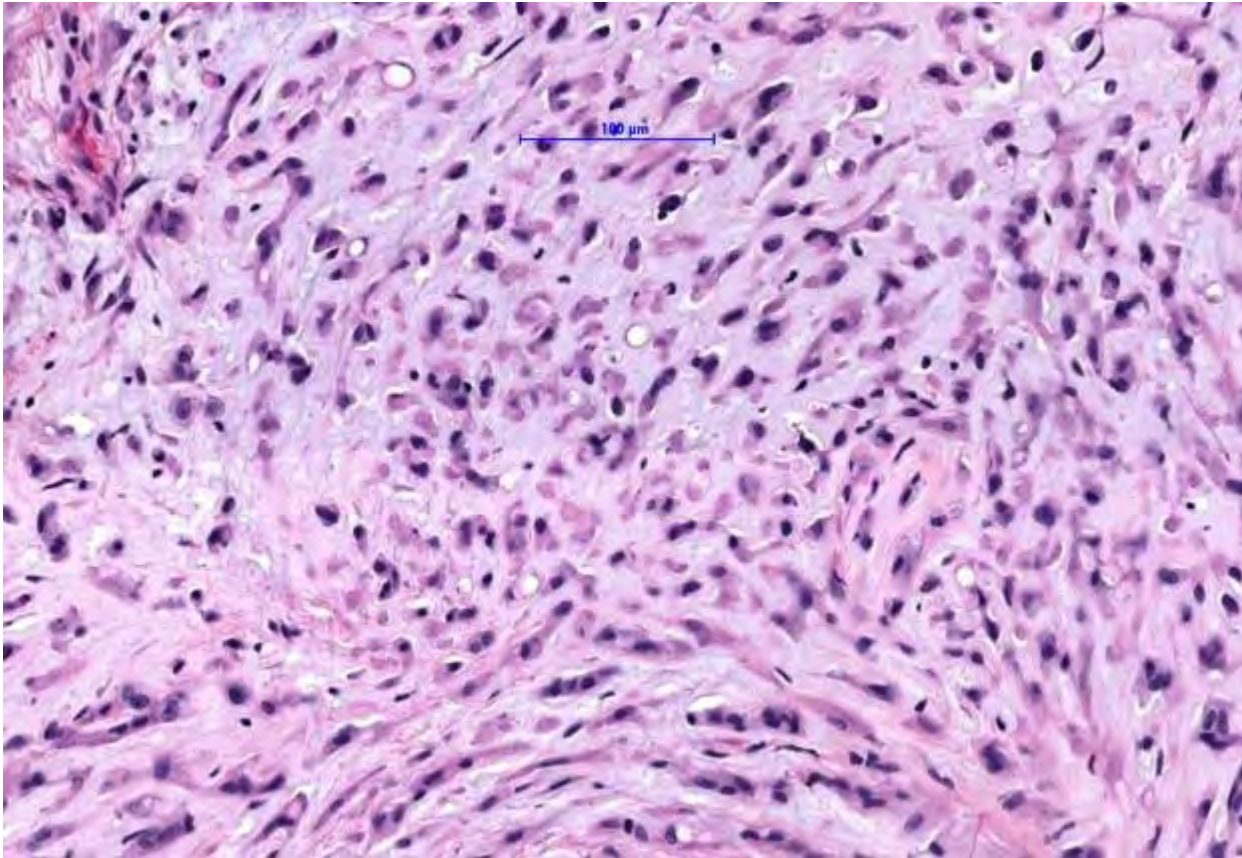


IHC:

CAMTA1

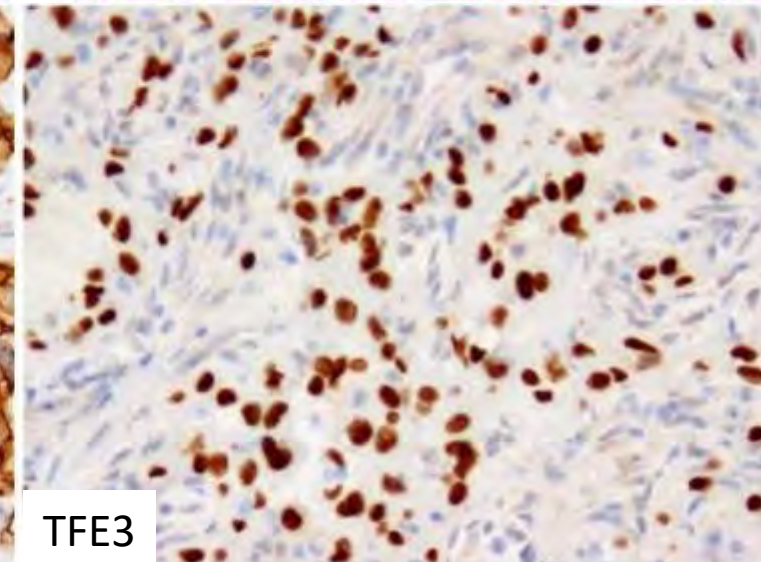
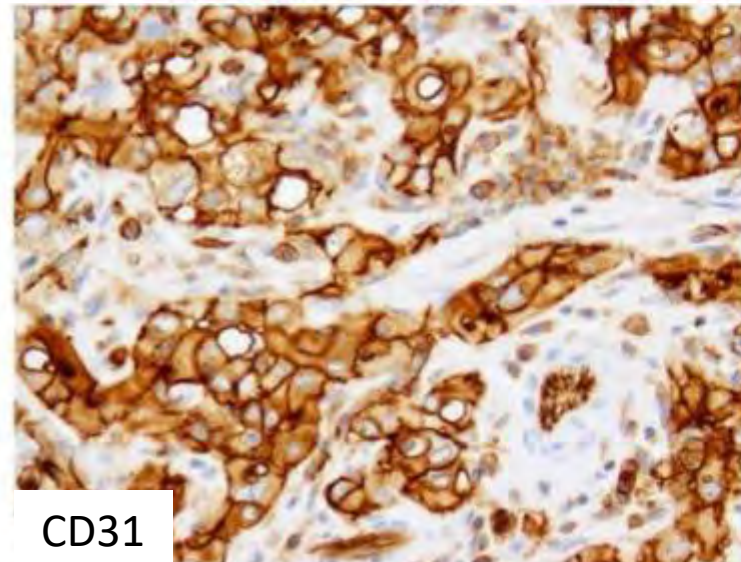
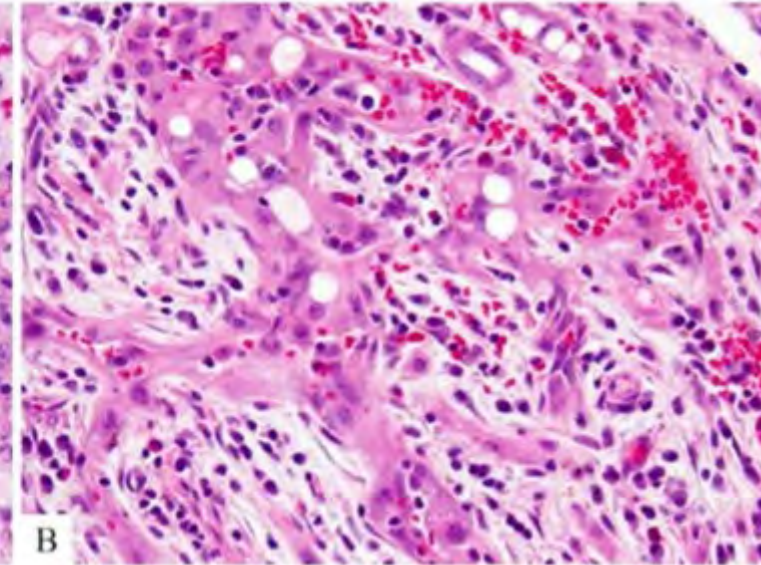
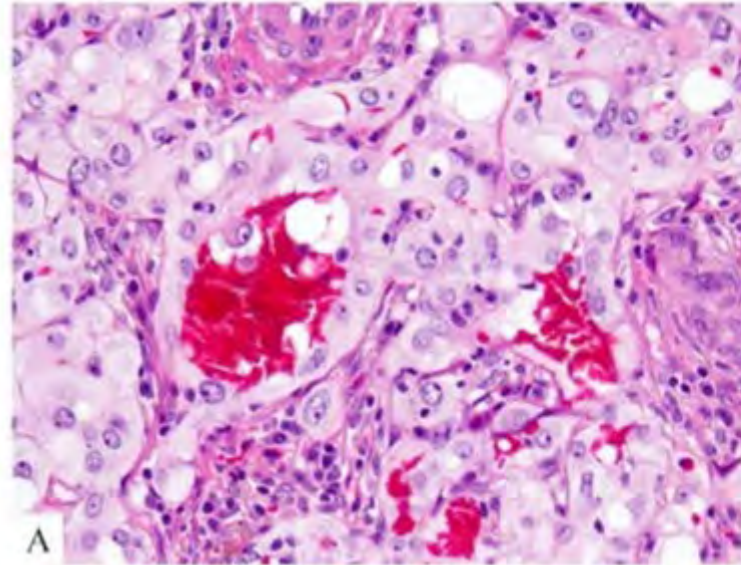
TFE3

WWTR1::CAMTA1

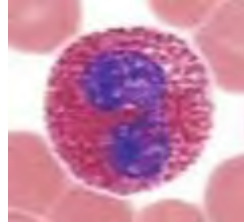


YAP1::TFE3

- ▶ Solid nests or pseudo-alveolar structures of epithelioid cells
- ▶ Fibrous stroma



DD:

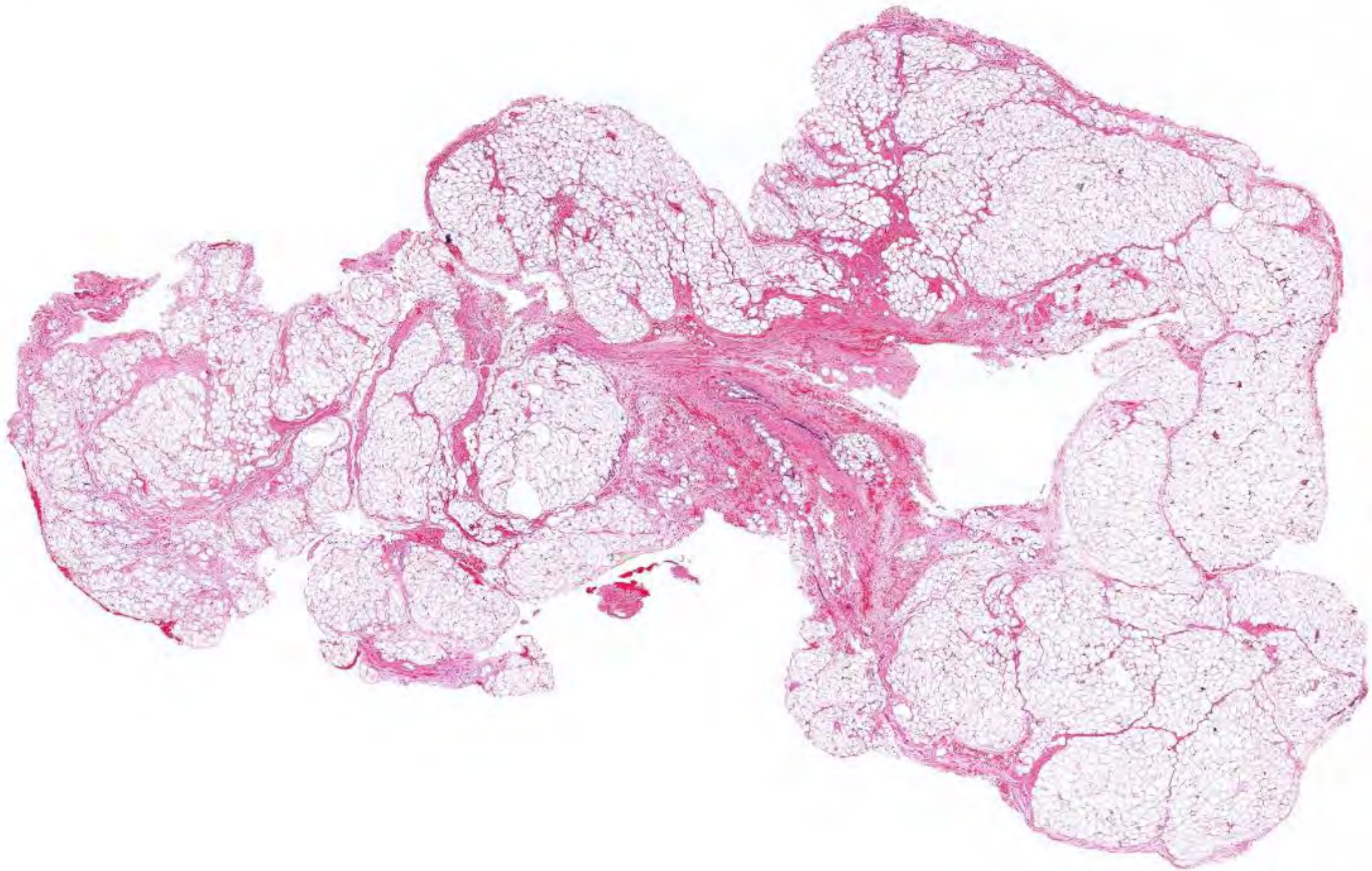


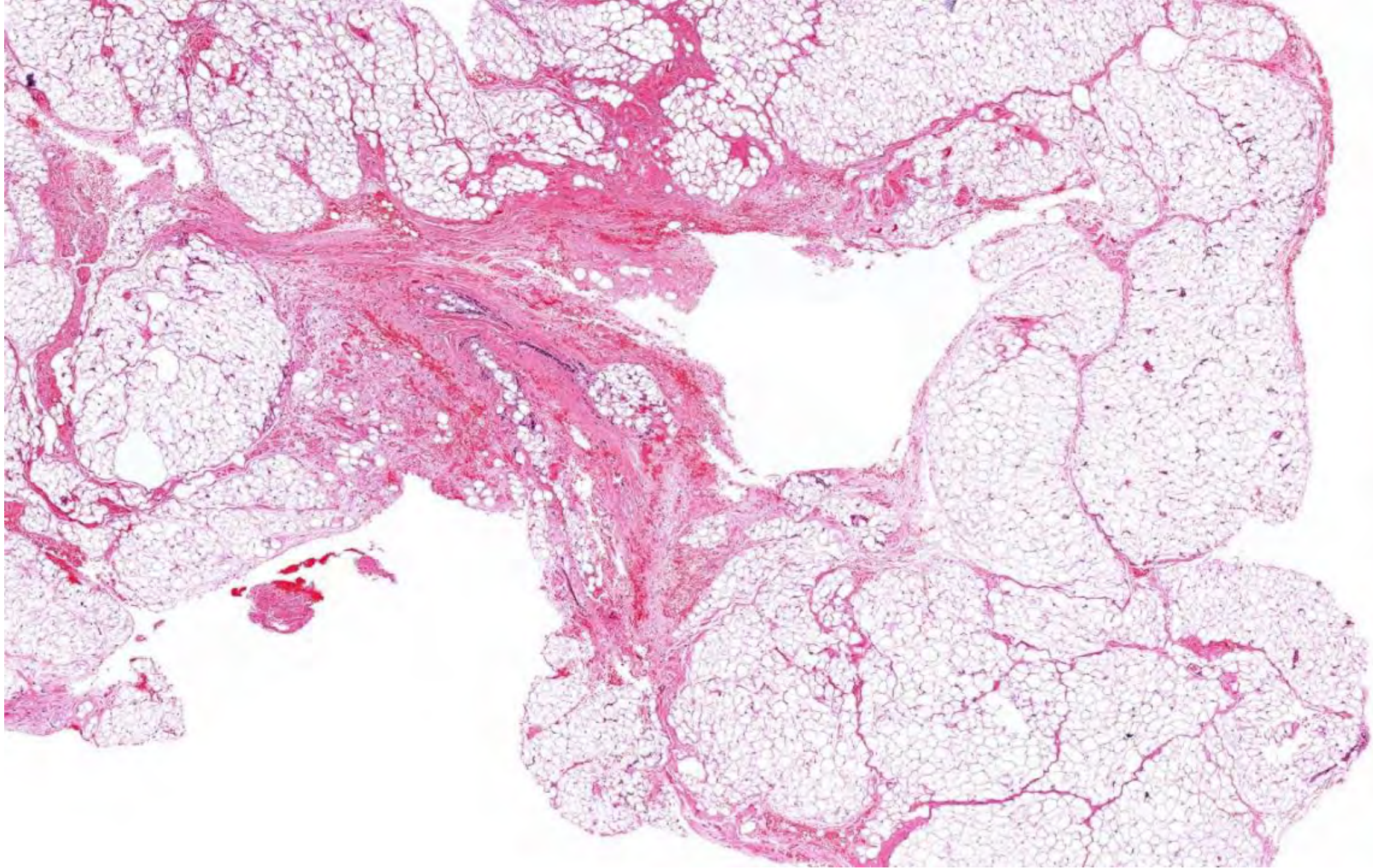
- ▶ **Epithelioid hemangioma**
- ▶ **Epithelioid angiosarcoma:**
 - ▶ **IHC:** CAMTA1/TFE3 negativ
- ▶ **Epithelioid sarcoma:**
 - ▶ **IHC:** keratin+ (strong), CD31-, CD34-, ERG-, INI1 lost
- ▶ **Melanoma: IHC:** S100+, SOX10+, HMB45+, Melan A+, CD31-
- ▶ **Carcinoma/Carcinoma-metastasis**
 - ▶ **IHC:** keratin+, CD31-, CD34-, ERG-

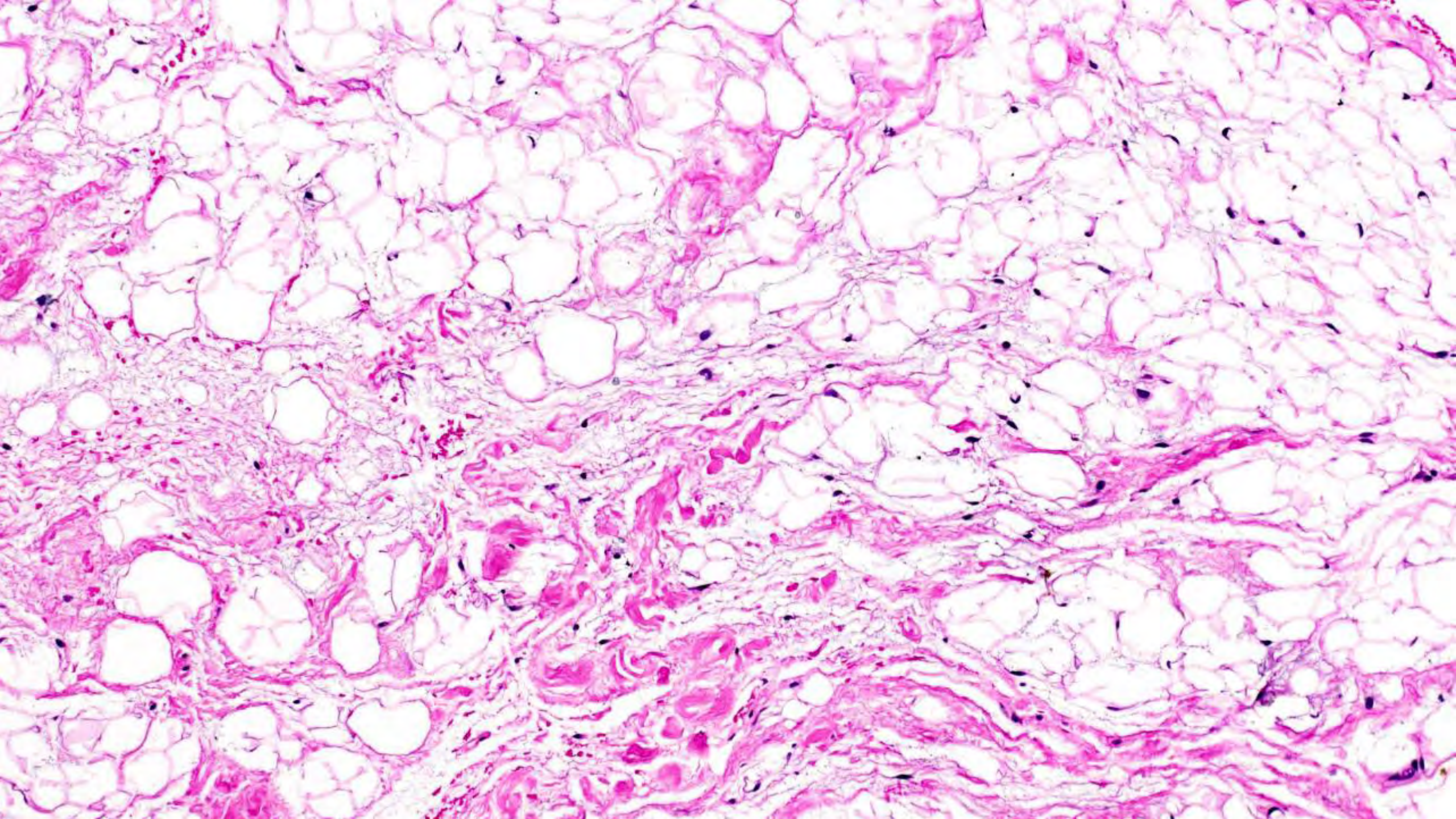
Case 19

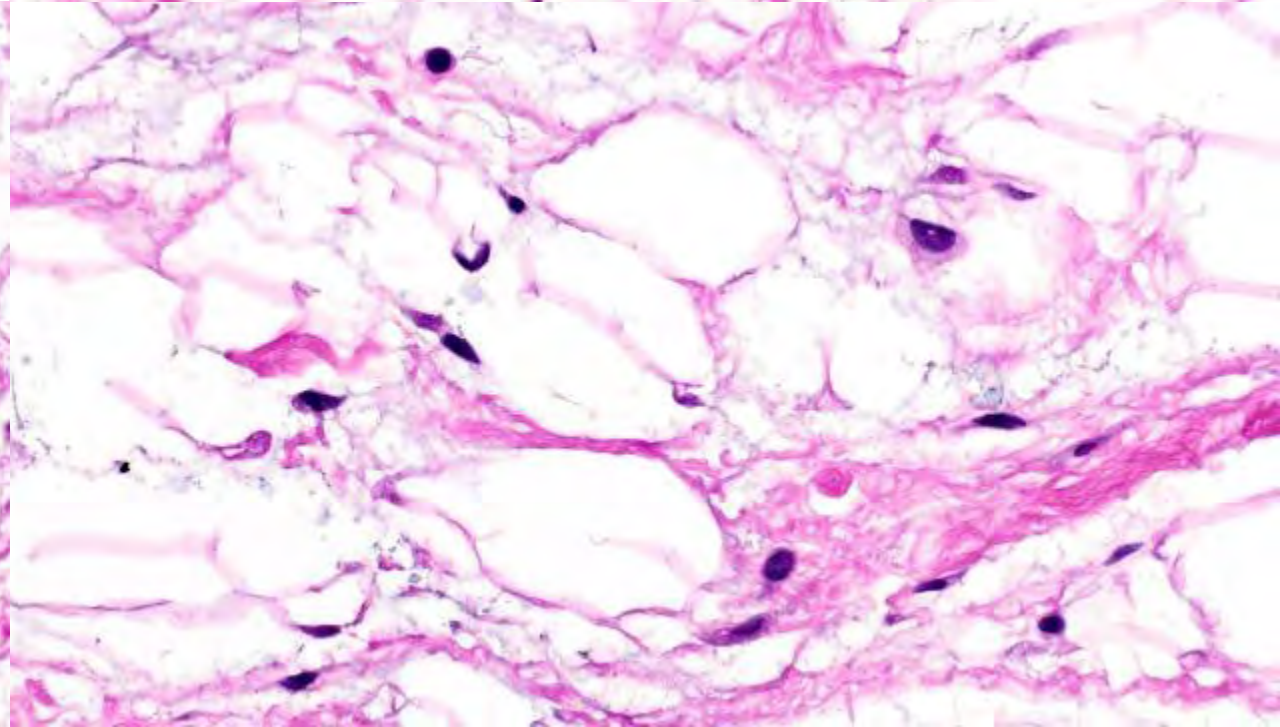
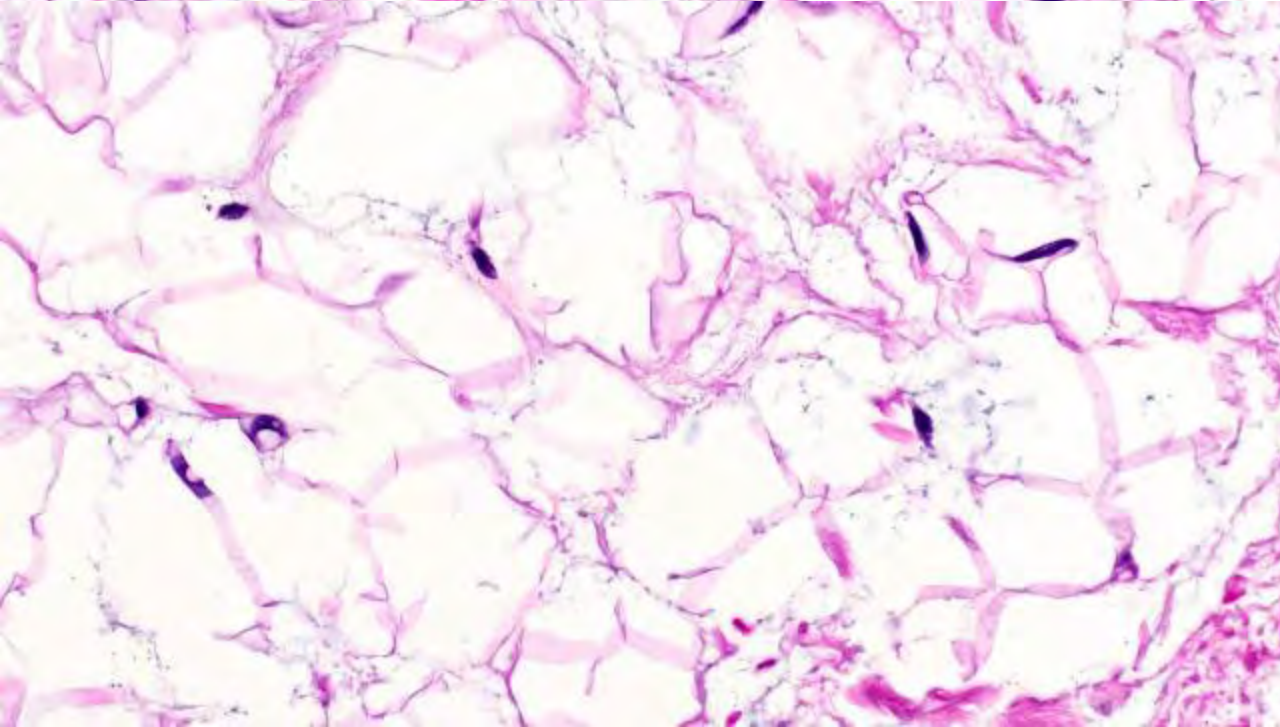
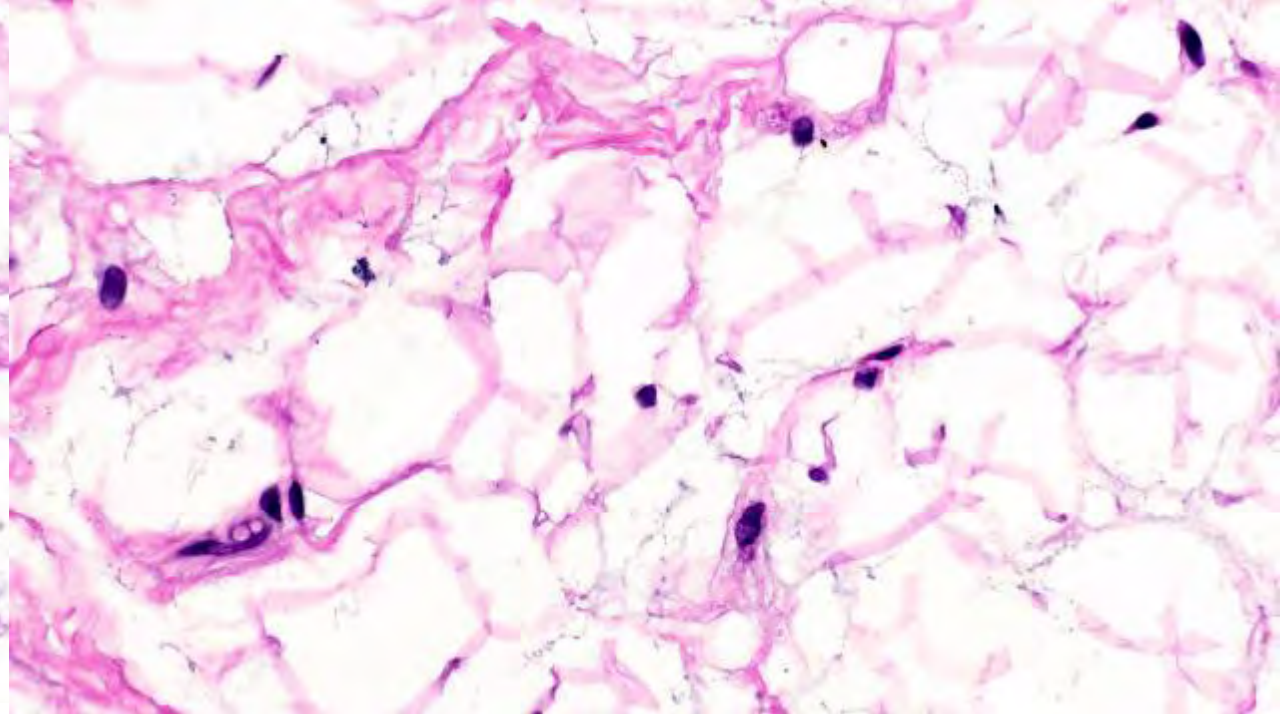
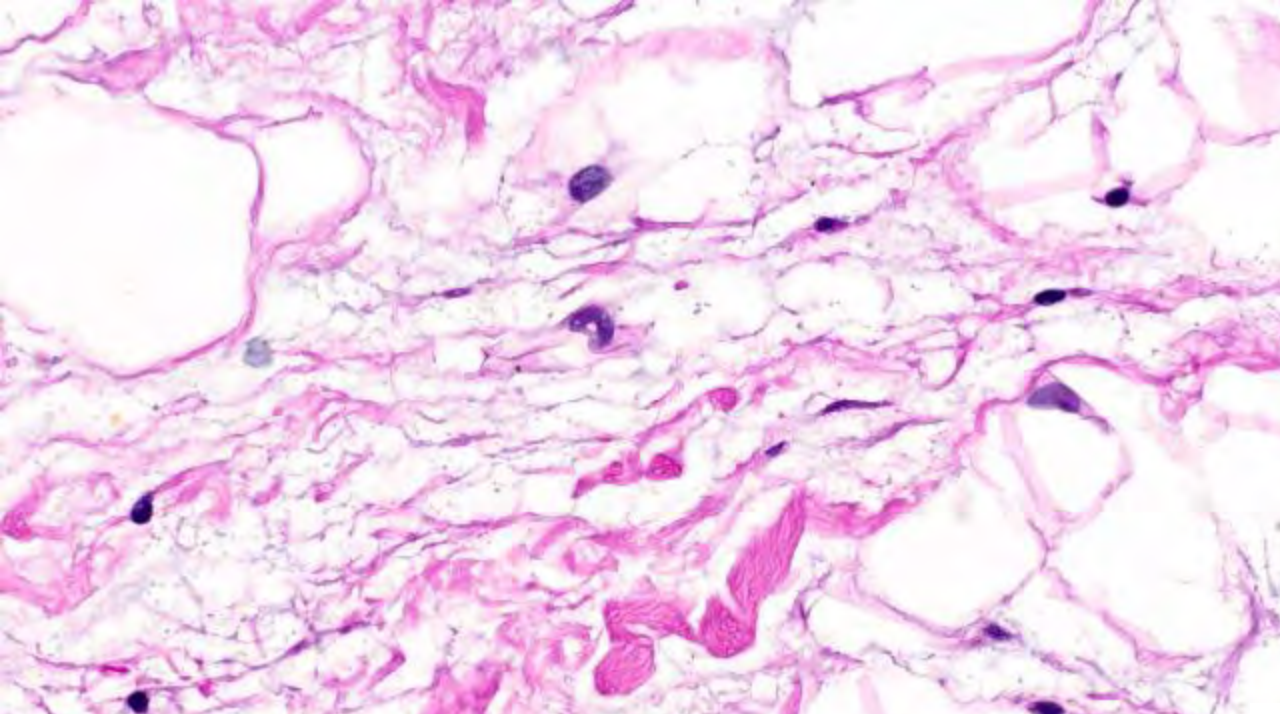
- ▶ 31y, F
- ▶ swelling of the finger with slow growth for the last 2 years
- ▶ Private dermatologist: ganglion
- ▶ Pt came for surgical excision

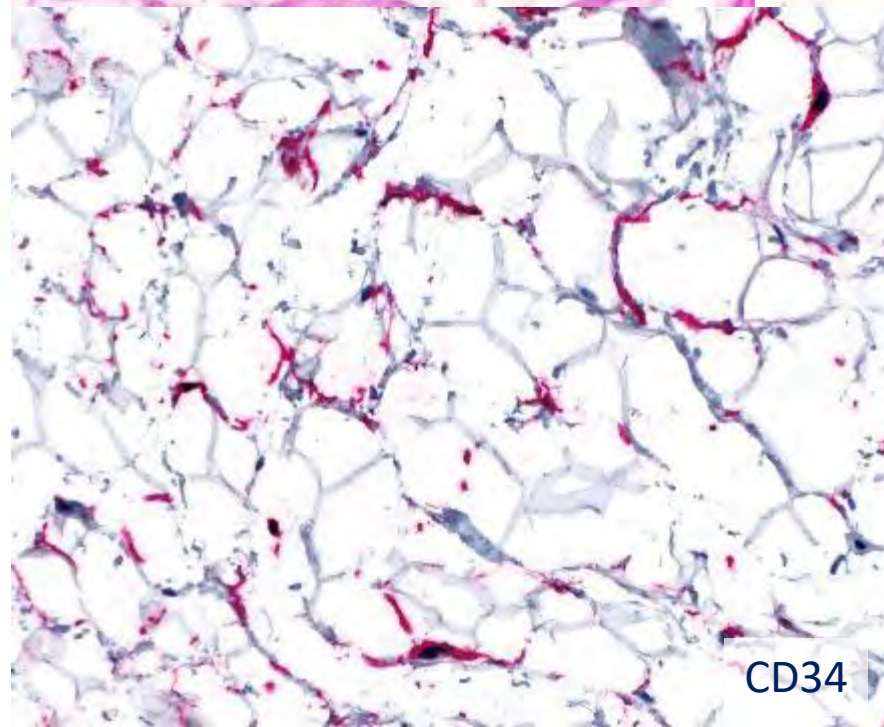
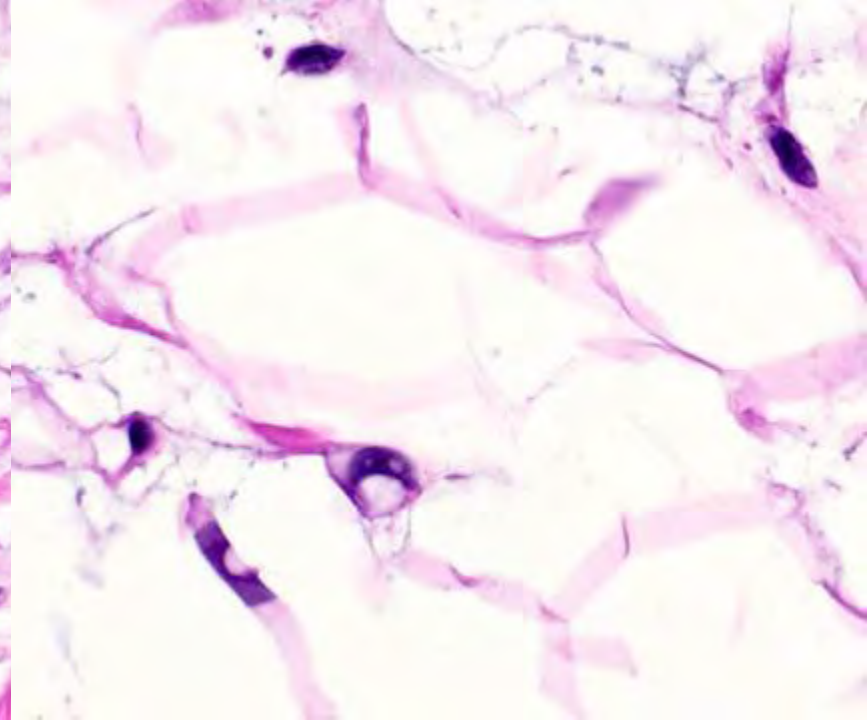
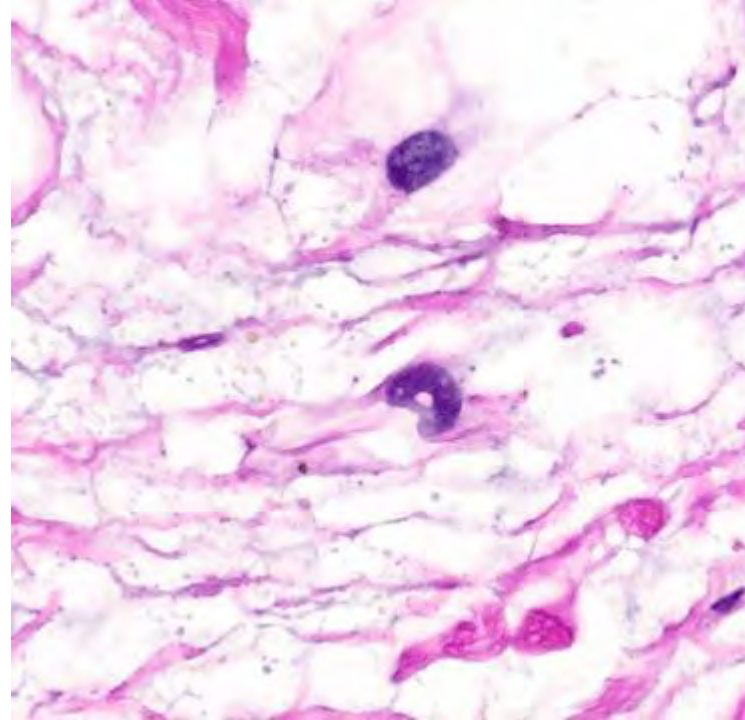
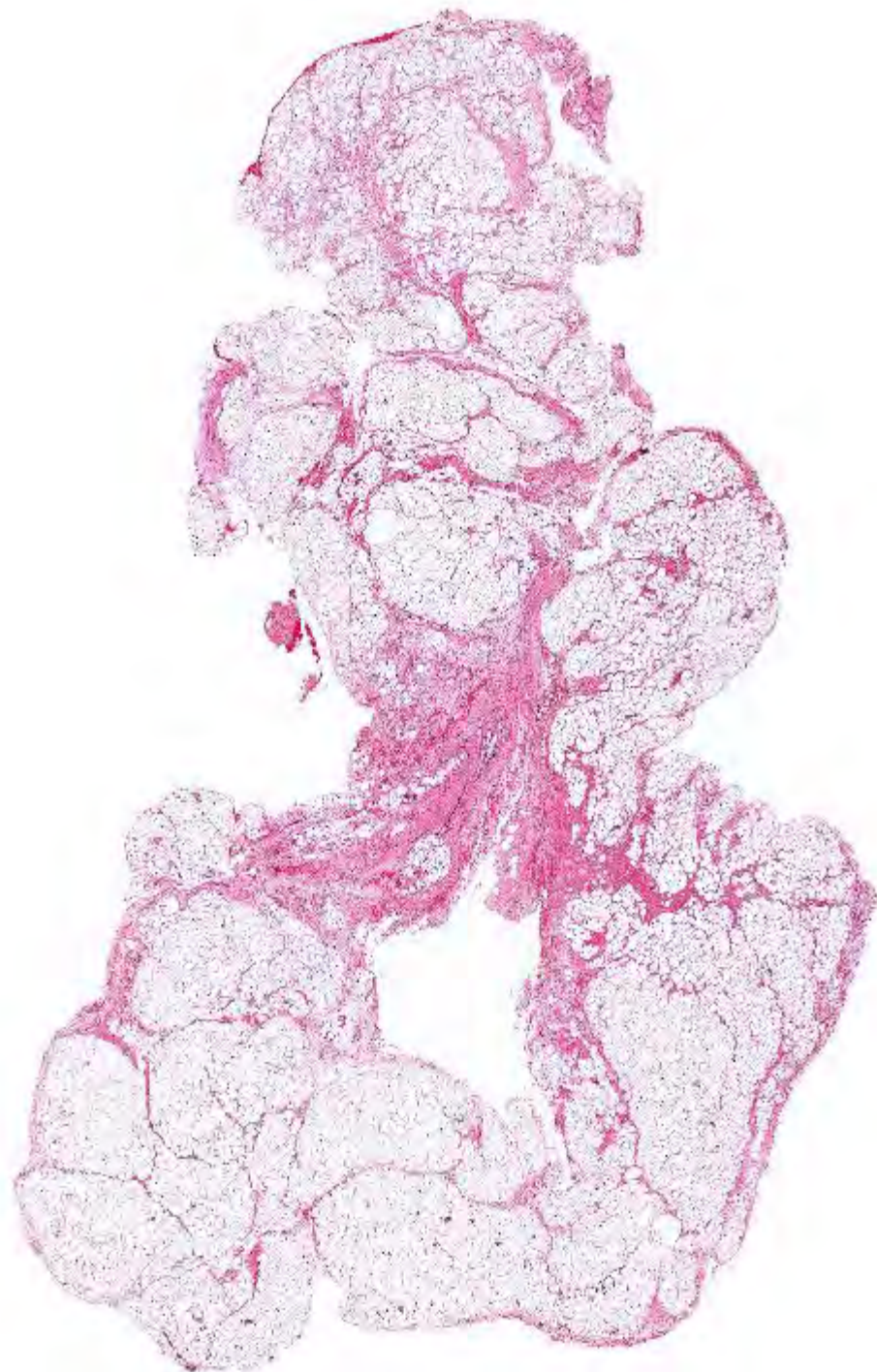




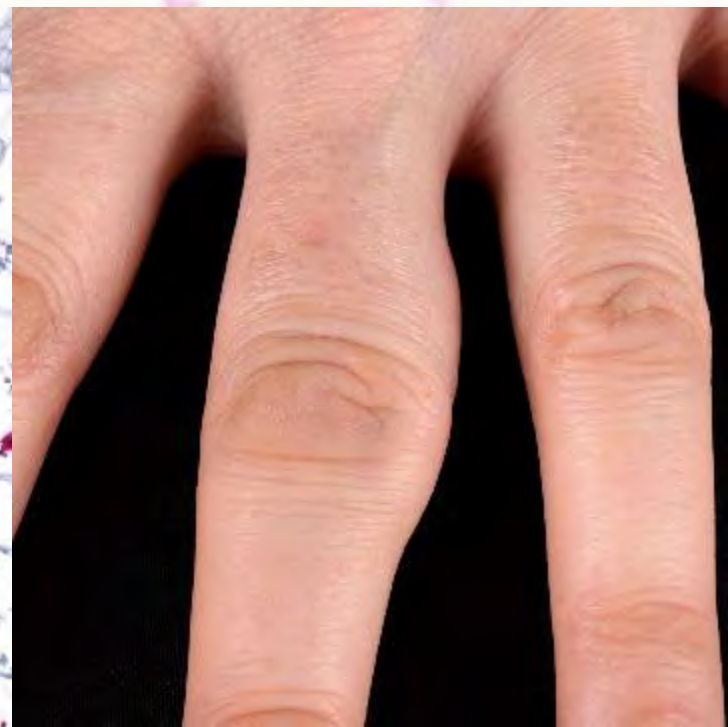








CD34



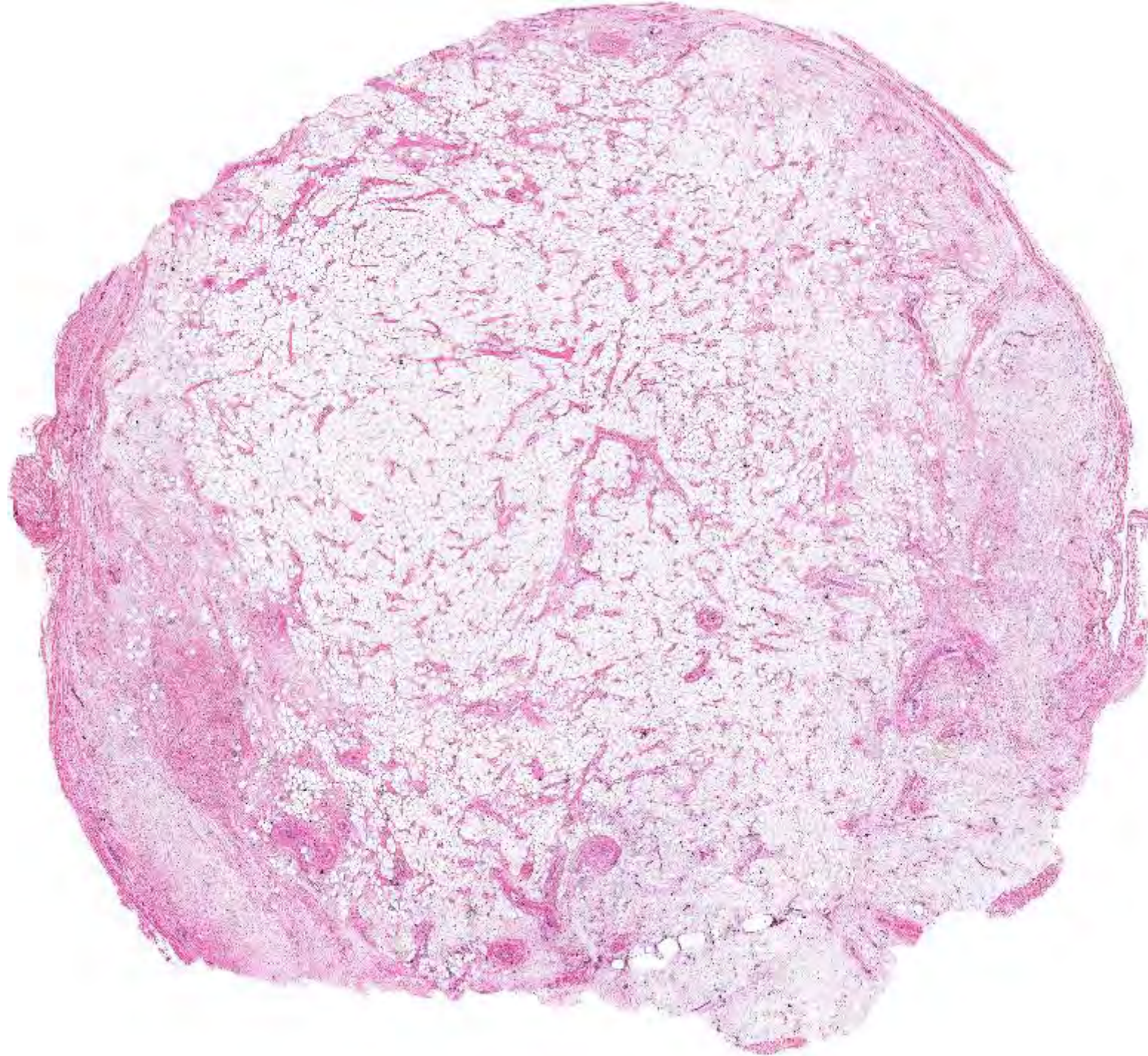
Case 19b

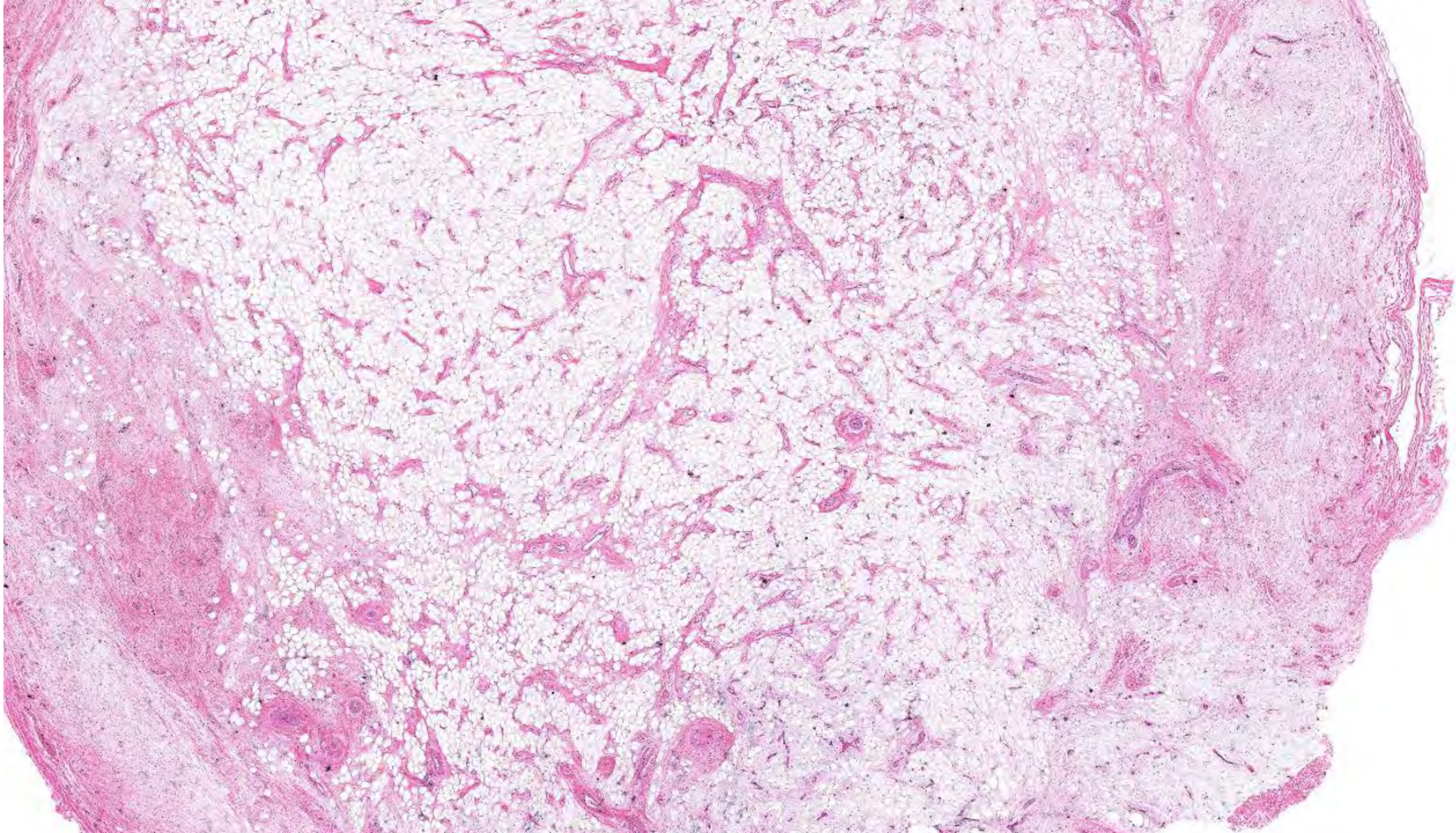
- ▶ 80y, M
- ▶ tumor on the foot present for >20 years, "stable or slowly enlarging"

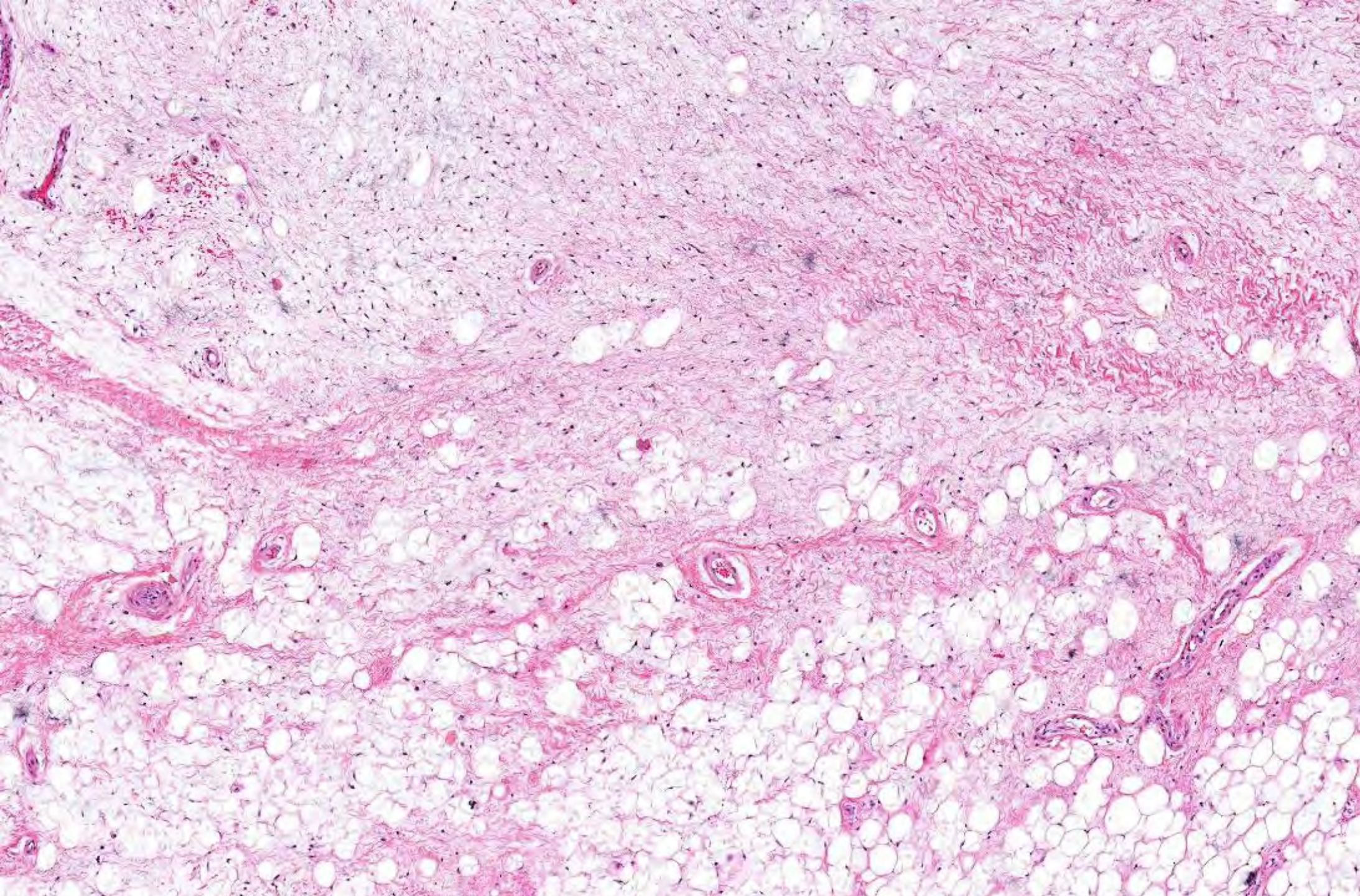
Other skin changes:

- ▶ chronic venous insufficiency
 - ▶ stasis dermatitis
 - ▶ lipodermatosclerosis
 - ▶ small ulcerations on both lower limbs
-
- ▶ Tumor: excised under the clinical diagnosis of lipoma



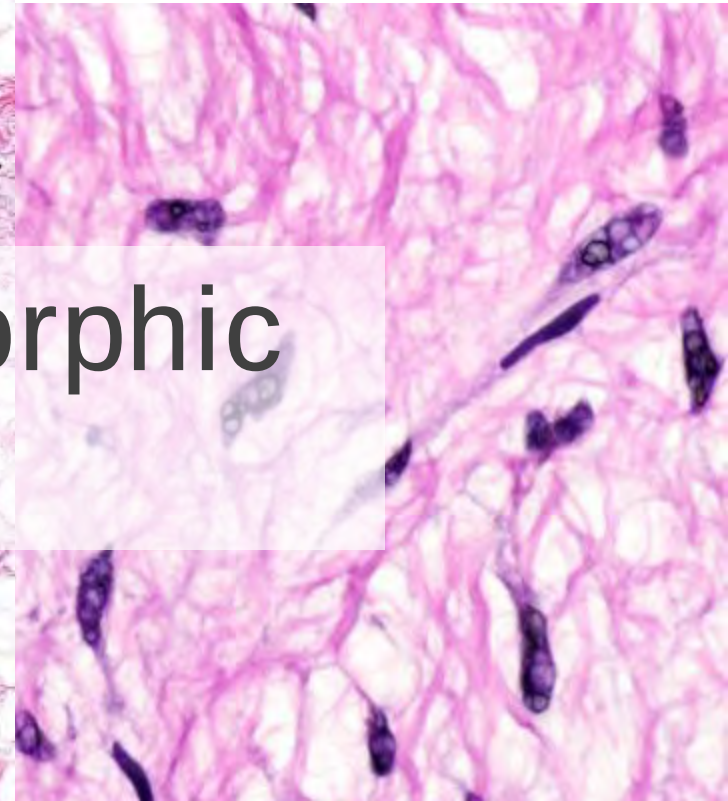






CD34+, Rb1 loss
MDM2 -

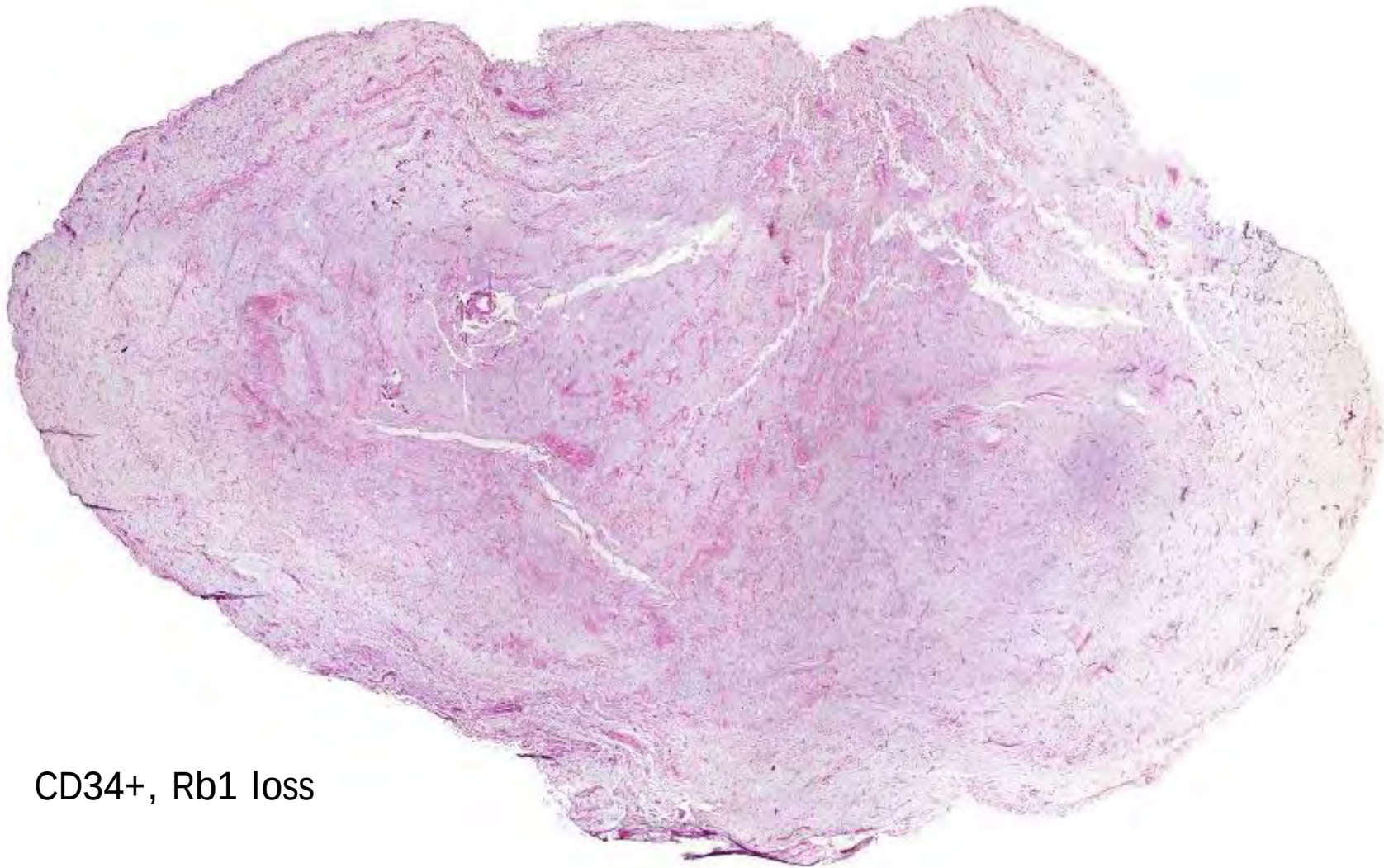
Atypical spindle cell/pleomorphic
lipomatous tumor



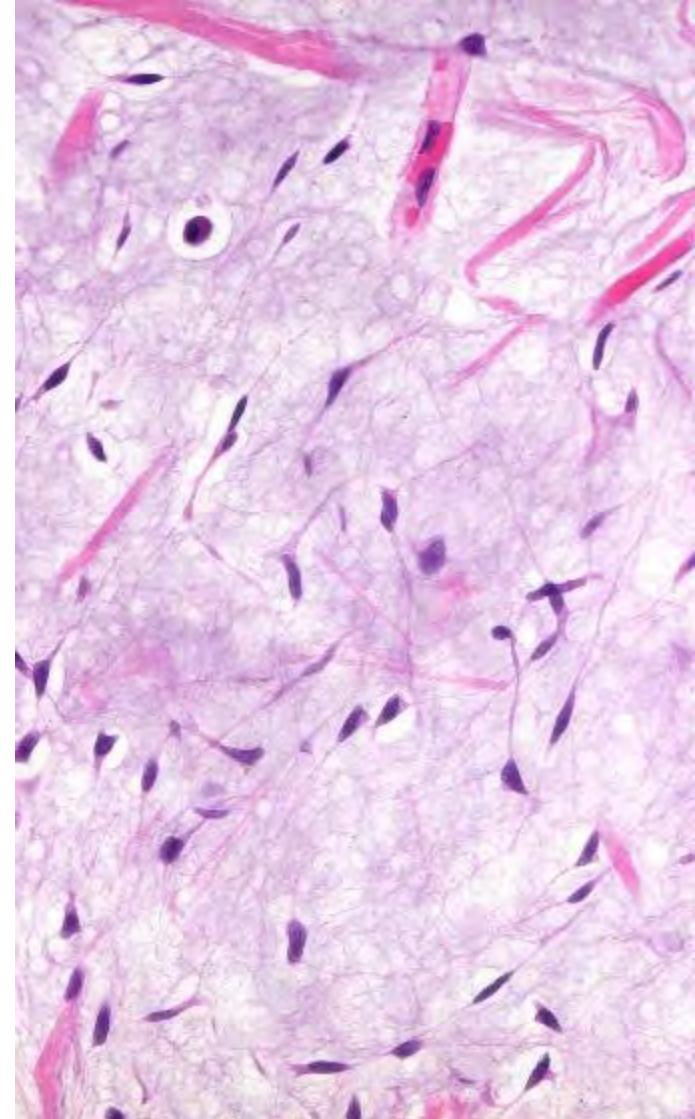
Atypical spindle cell/pleomorphic lipomatous tumor

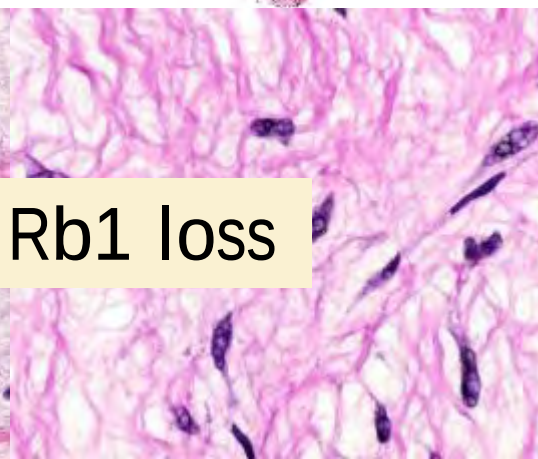
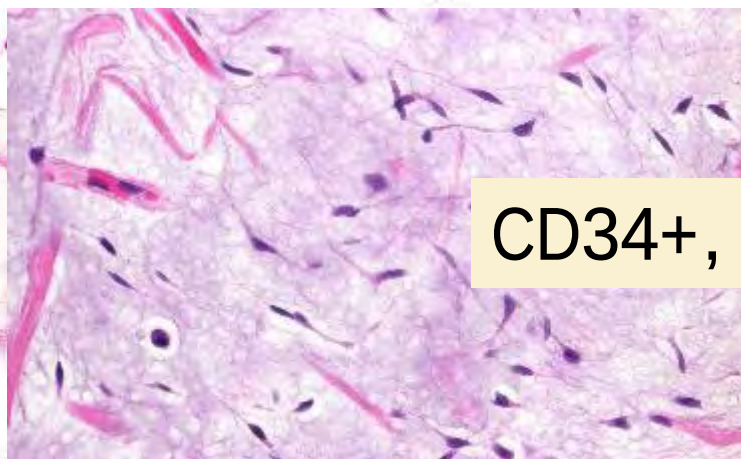
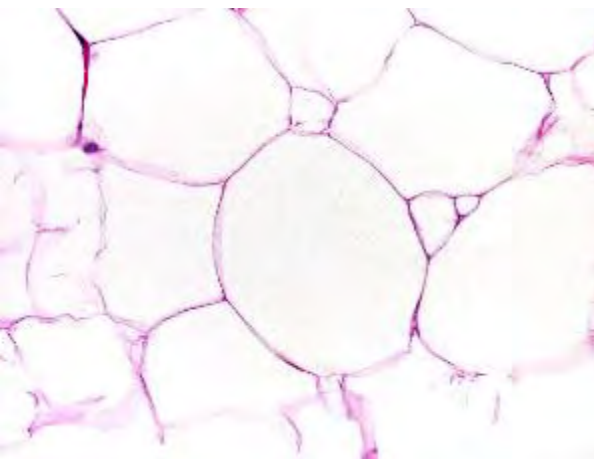
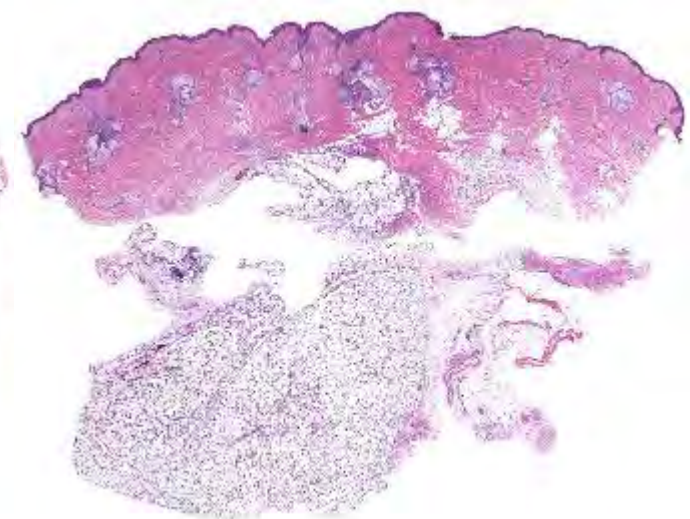
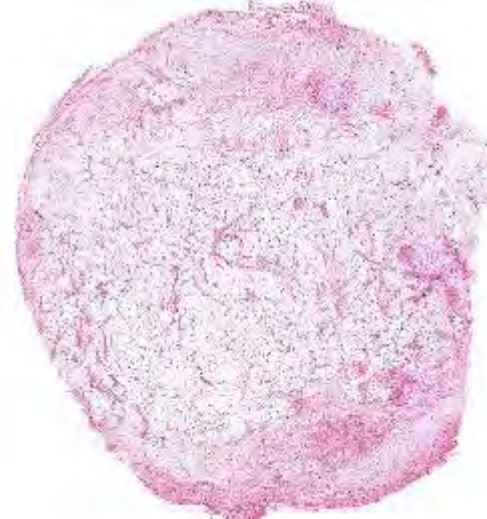
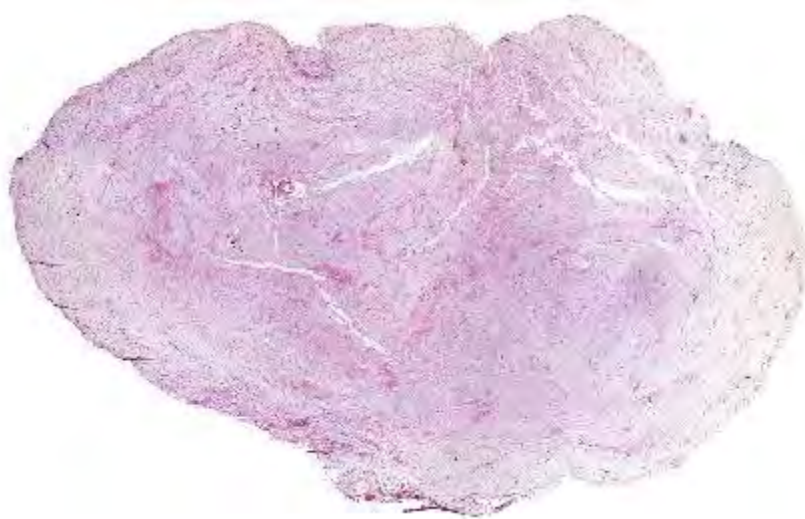
- ▶ a benign adipocytic neoplasm
- ▶ characterized by:
 - ▶ ill-defined tumour margins
 - ▶ variable proportions of mild to moderately atypical spindle cells, adipocytes, lipoblasts, pleomorphic cells, multinucleated giant cells
 - ▶ myxoid or collagenous extracellular matrix
- ▶ CD34+, Rb1 loss
- ▶ a low tendency for local recurrence if incompletely excised

DD: Spindle cell/pleomorphic lipoma



CD34+, Rb1 loss





CD34+, Rb1 loss

MDM2
amplification

Lipoma

Neck
Shoulders
Back
Abdomen
Arms
Thighs

Spindle cell/pleom. lipoma

Posterior neck
Shoulders
Back

Atypical spindle cell / pleomorphic lip. tumor

Hands
Feet

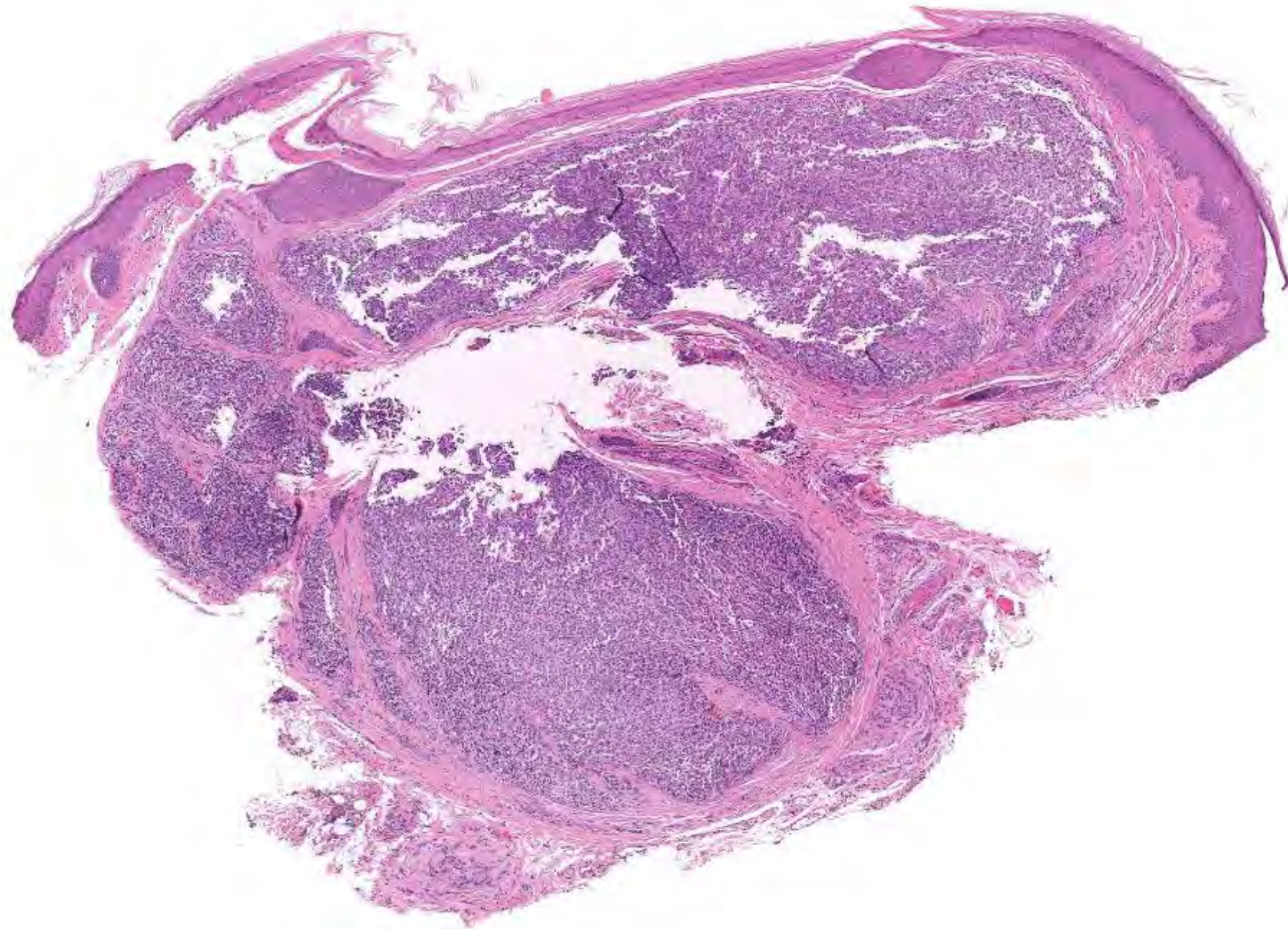
Atypical lipomatous tumor ("cutaneous liposarcoma")

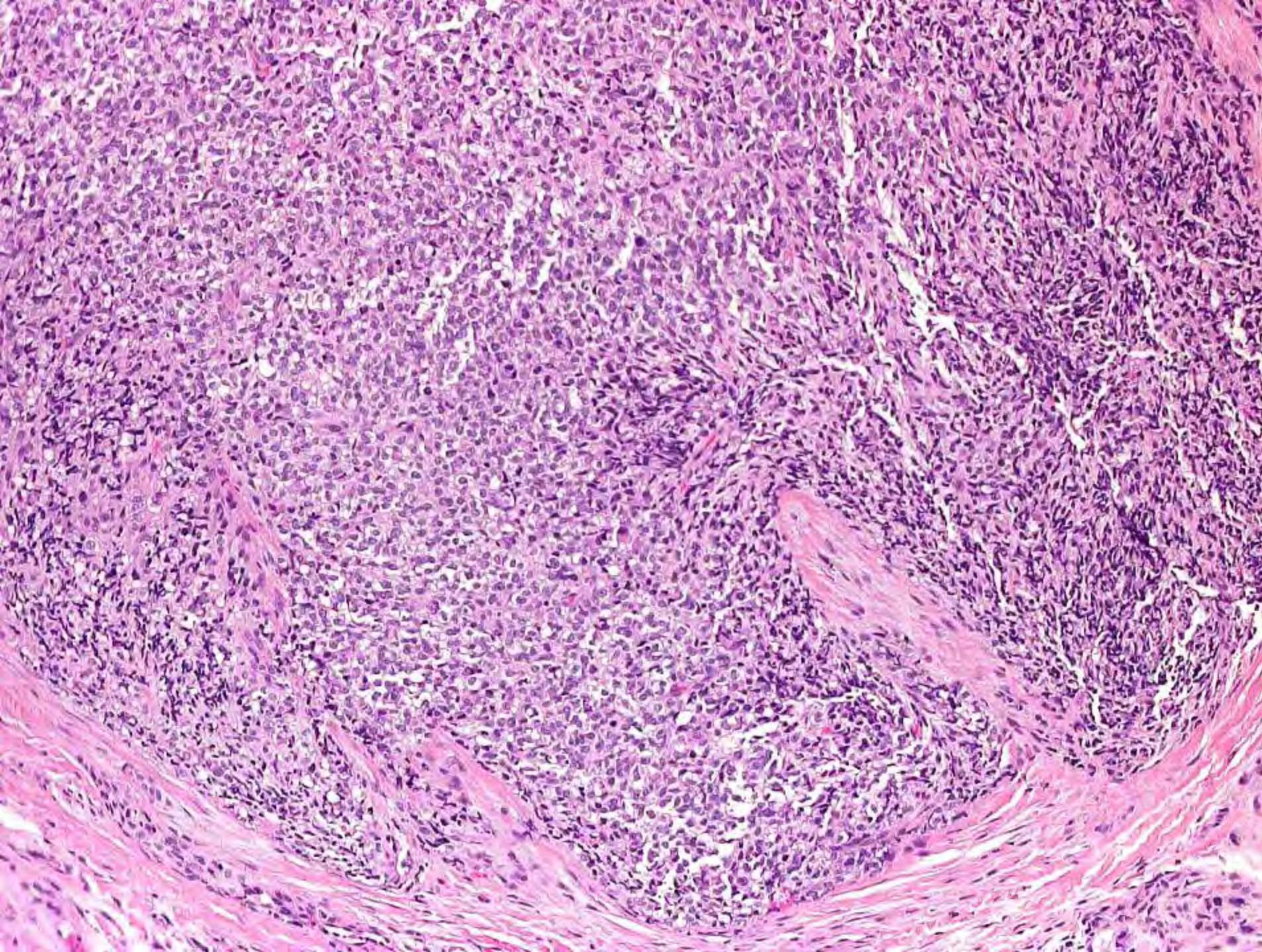
Thighs
Buttocks

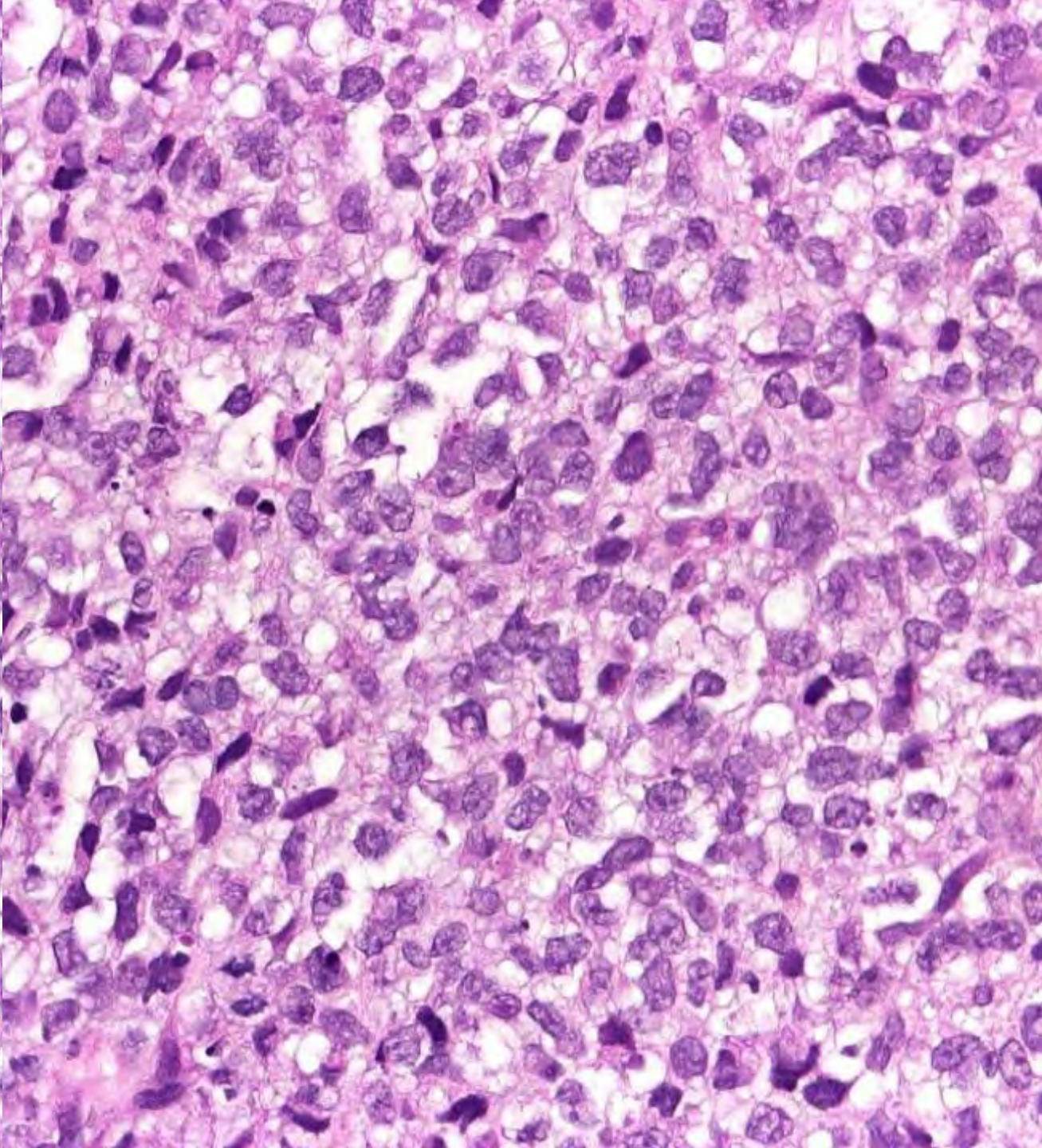
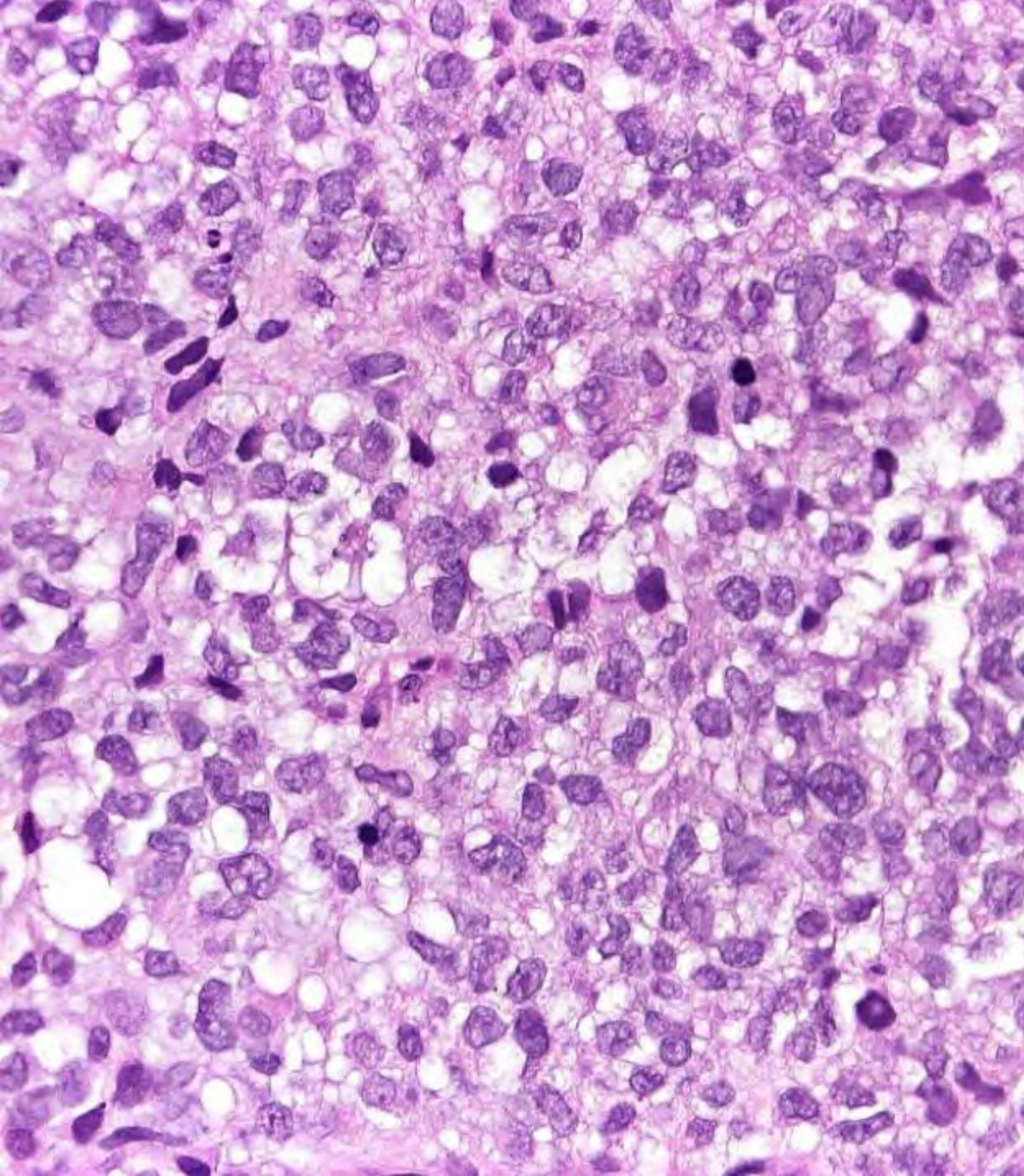
Location matters – Site is important in "lipomas"

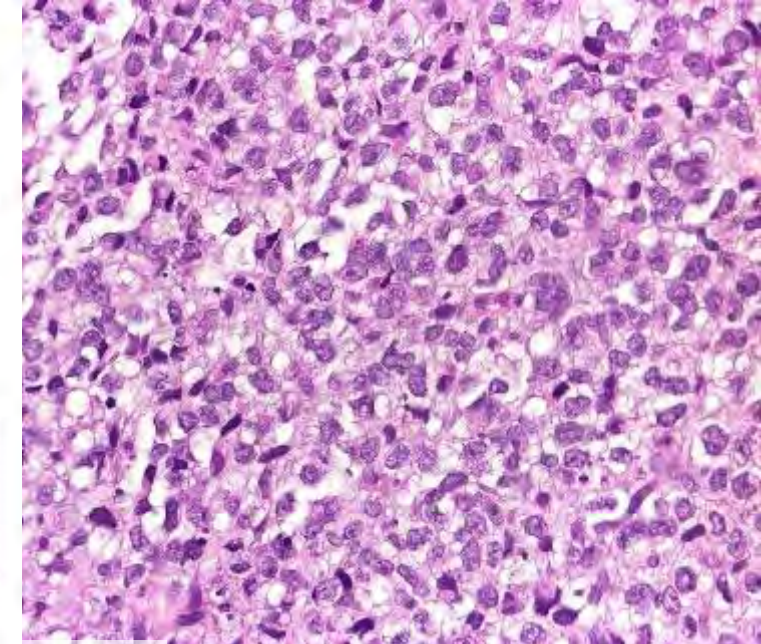
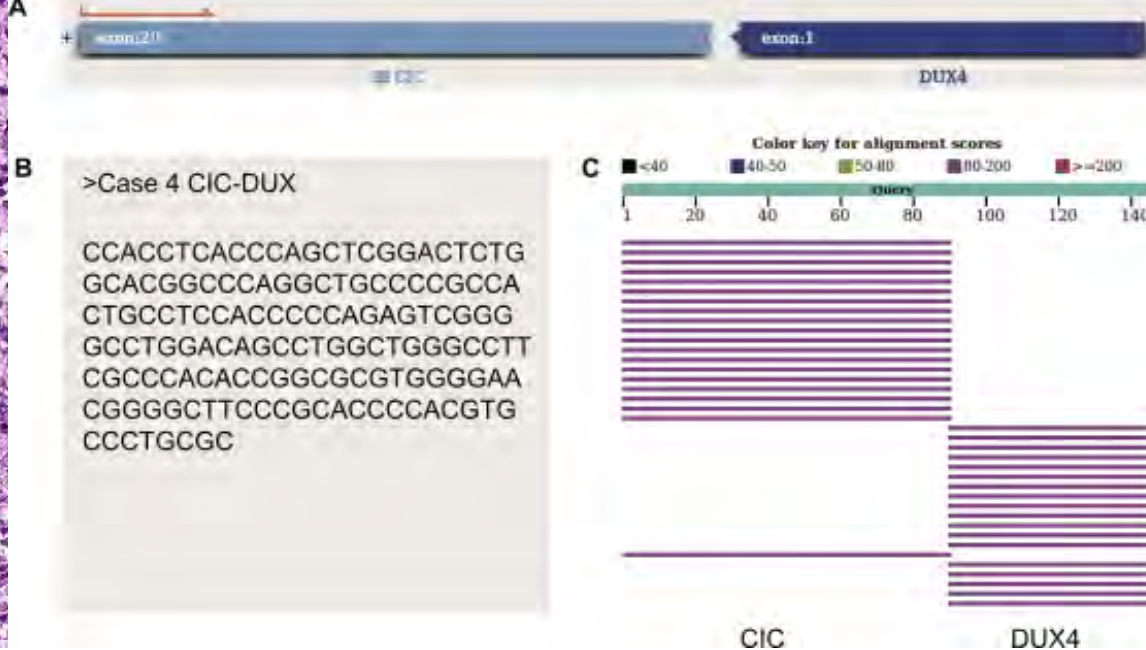
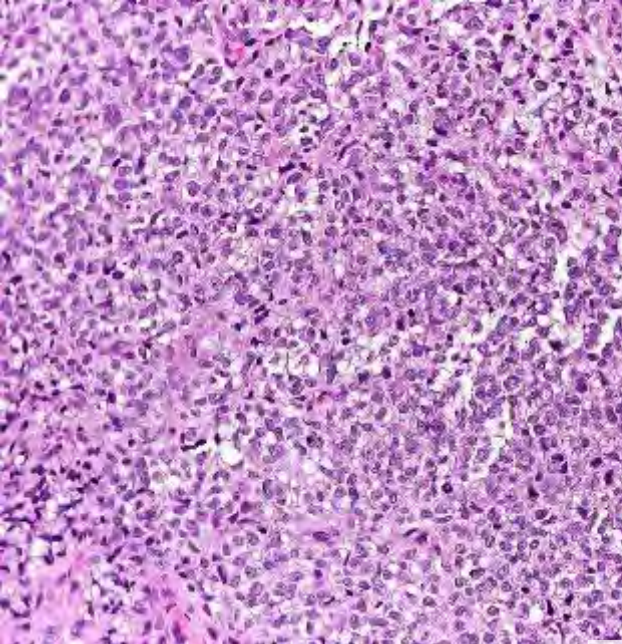
Case 20

- ▶ 32y, F
- ▶ 1cm lesion on the left ear

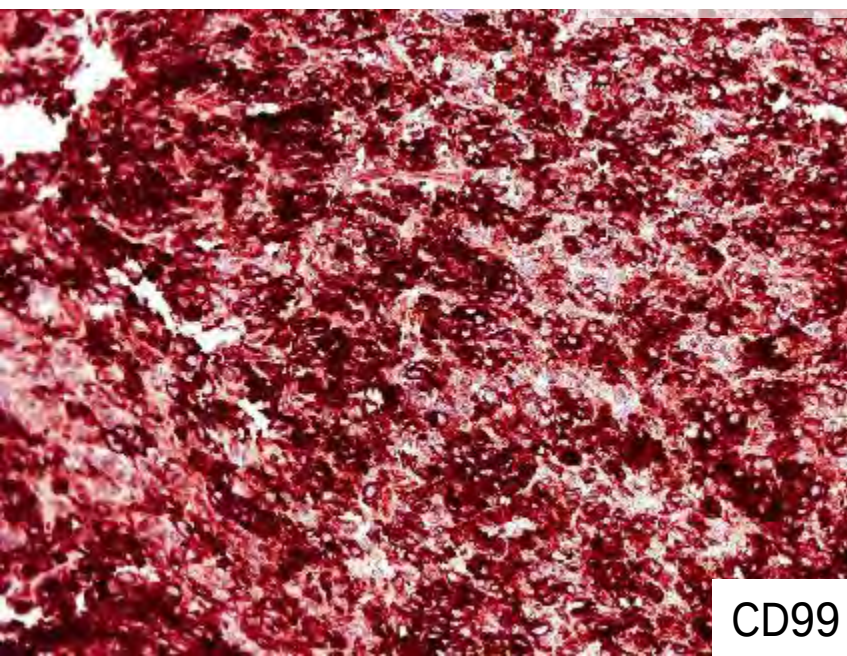




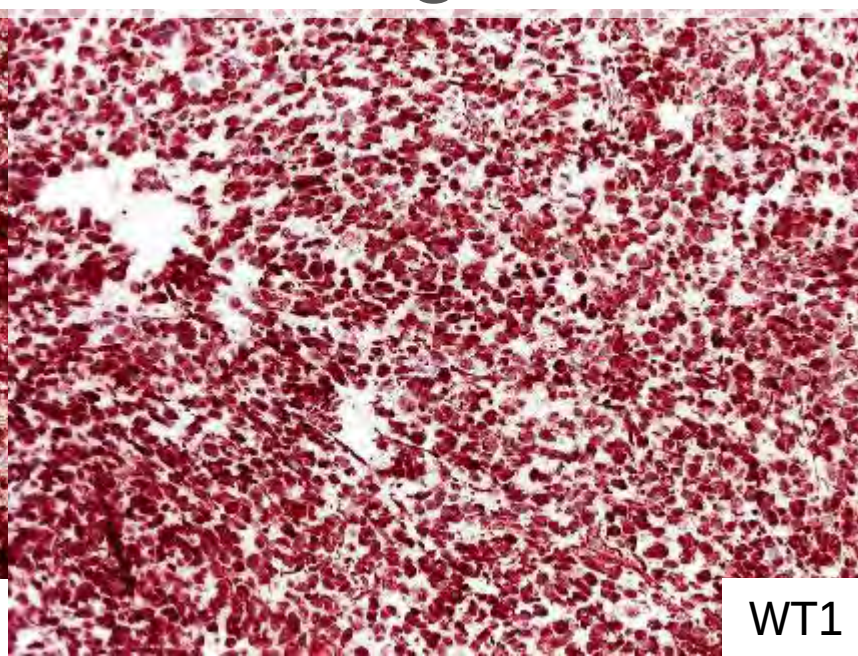




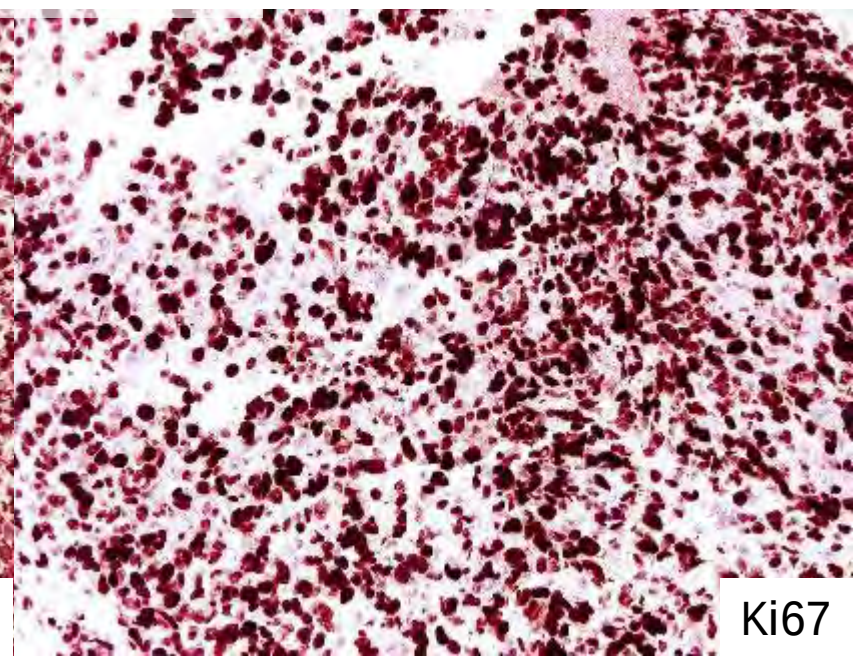
C/C-rearranged sarcoma



CD99



WT1



Ki67

C/C-rearranged sarcoma

- ▶ high-grade round cell undifferentiated sarcoma defined by C/C-related gene fusions (***DUX4***; *FOXO4*, *LEUTX*, *NUTM1*, *NUTM2A*)
- ▶ young adults
- ▶ deep soft tissues of the limbs or trunk
 - ▶ head and neck, retroperitoneum, pelvis, visceral organs

Superficial sarcomas with *CIC* rearrangement are aggressive neoplasms: A series of eight cases

Jennifer S. Ko MD, PhD¹  | Zlatko Marusic MD, PhD² |
 Elizabeth M. Azzato MD, PhD¹ | Daniel H. Farkas PhD¹ | John Van Arnam MD³ |
 Sven Seiwerth MD, PhD^{2,4} | Karen Fritchie³ | Rajiv M. Patel MD⁵  |
 Brian P. Rubin MD, PhD¹ | Steven D. Billings MD¹ 

TABLE 1 Clinical data

Case	Age	Sex	Site	Size (cm)	Ulcerated	Original excision	Re-excision margins	Adjuvant Rx	Recurrence/metastasize	Status	Follow-up/death (mos)
1	65	M	Forearm	3	Y	Incomplete	Y	Radiation	Recur.	AWD	48
2	55	F	Hand	8	U	Incomplete	Y, Amputation	No	N/Y- Lungs and LN	DOD	24
3	32	F	Foot	U	Y	Incomplete	Y	No	N/Y- LN	DOD	22
4	14	F	Vulvar	4	Y	Incomplete	Y	No	N/Y- Lungs	DOD	23
5	58	F	Labium	0.5	N	Incomplete	Y	No	No	ANED	12
6	26	F	Flank	2	N	Incomplete	Y	Chemo	No	ANED	2
7	35	F	Lower Flank	1	N	Incomplete(Punch)	Y				
8	55	M	Lower Leg	2	Y	Complete, narrow	Y				
Total	45 y/o 14–65 y/o range	6F:2M	–4 distal extr –2 flank –2 labia/vulva	2 cm 0.5–8 cm	4/8 ulcerated	7/8 incomplete excisions	8/8 re-excised with negative margins	1/6 adj chemo 1/6 adj radiation	4/5 recur. 3/5 metastasize	3/5 DOD 1/5 AWD 1/5 ANED	22.5 mos 2–48 mos



gettyimages
Credit: Juanmonino



CK, SMA,
CD34, SOX10,
desmin,
ERG/EMA



18th Summer Academy of Dermatopathology
Graz, July 6 – 10, 2026



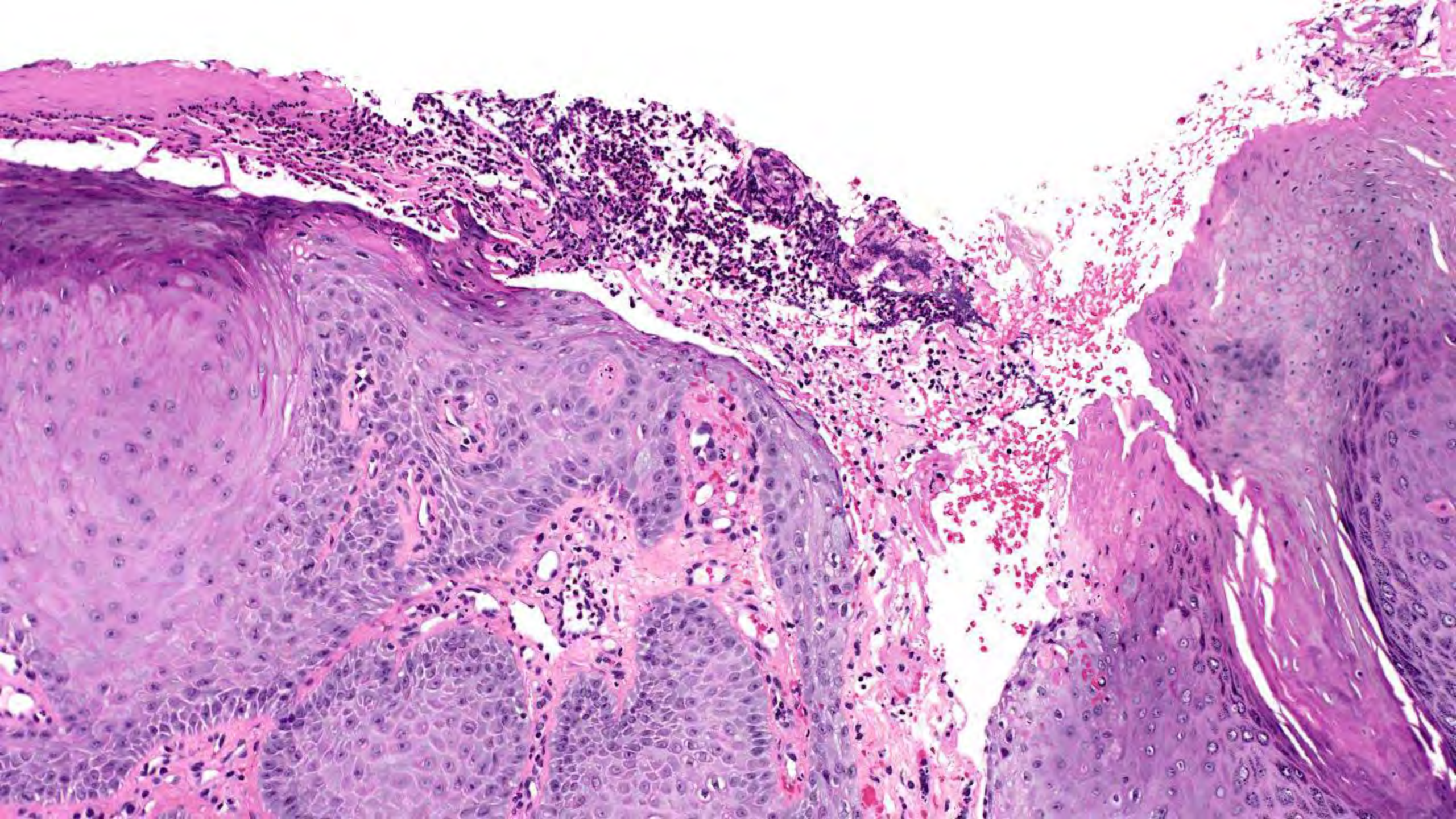
Self-assessment (cases 21-30)

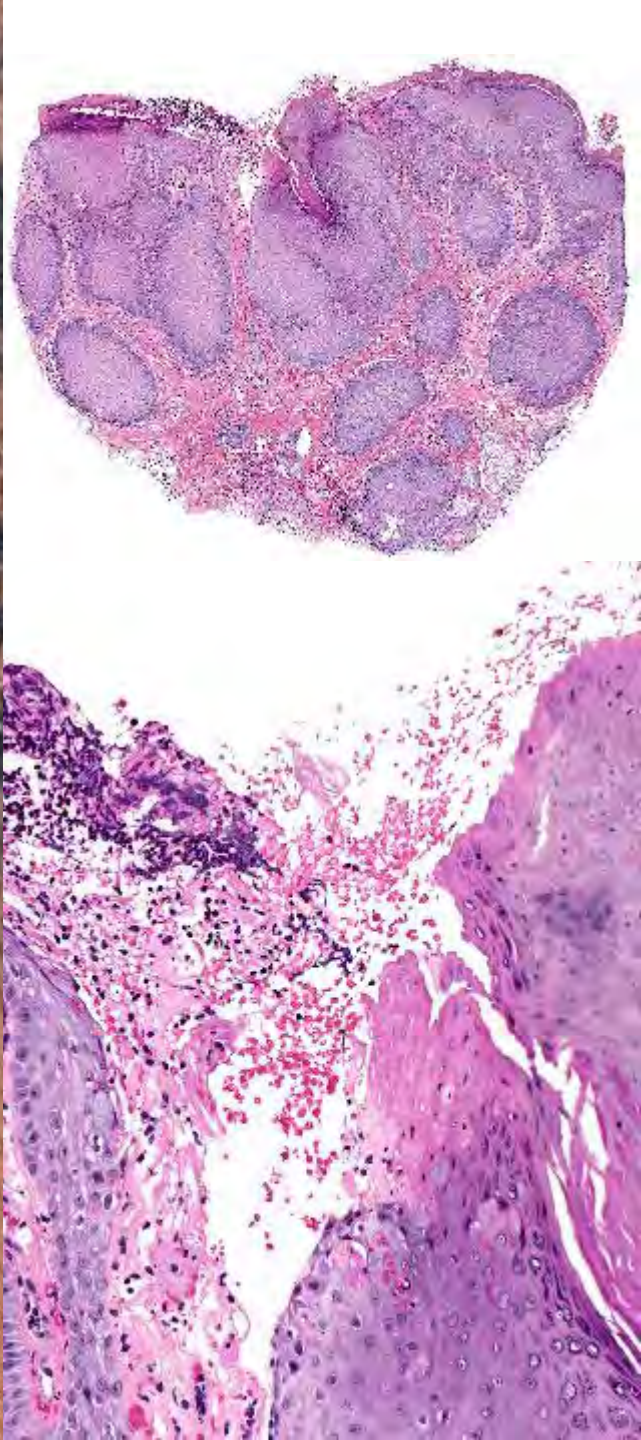
Lorenzo Cerroni

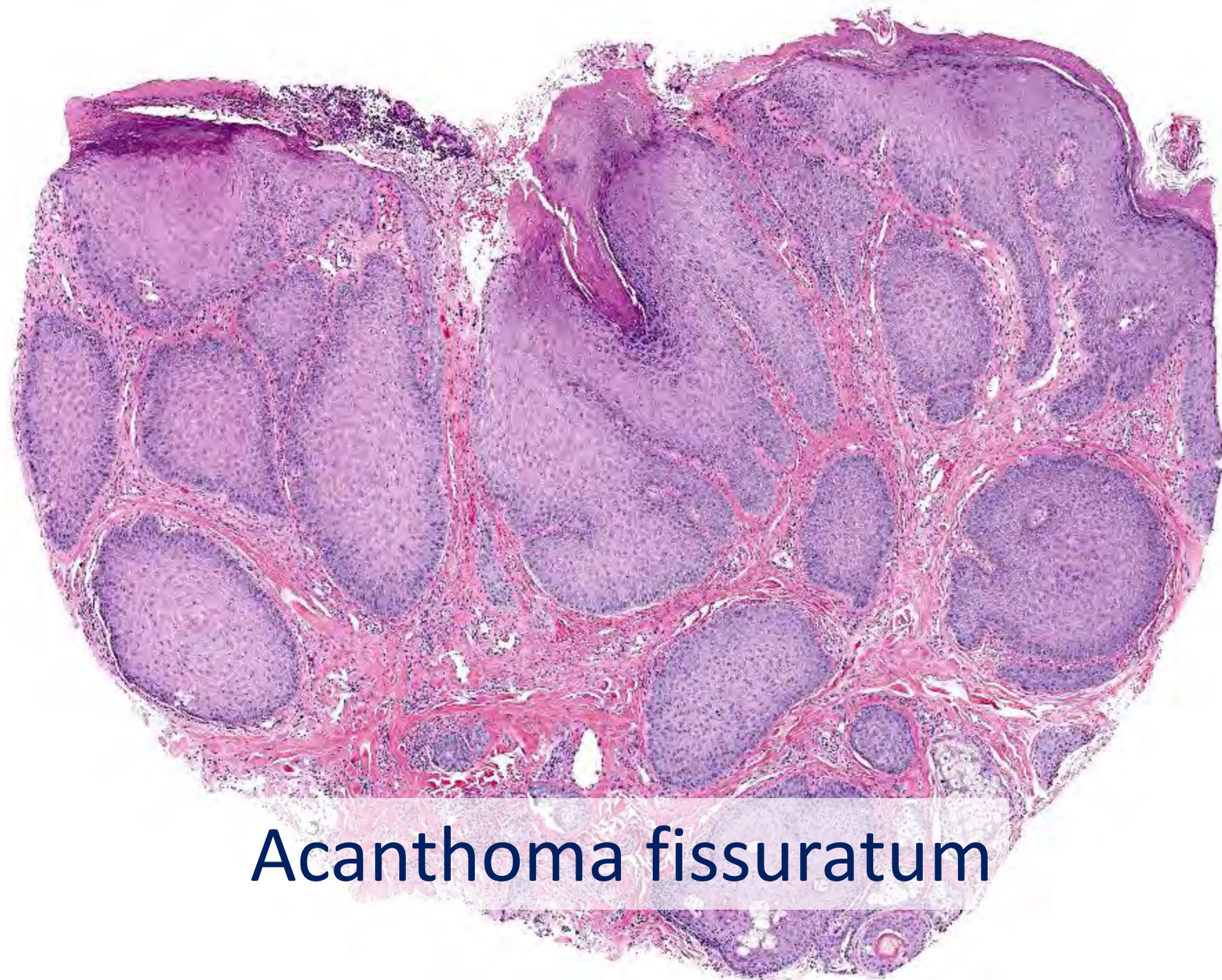


Case 21

M, 36. Painful lesions on the nose and left retroauricular region for several months.







Acanthoma fissuratum

8th INTERNATIONAL DERMATOPATHOLOGY COLLOQUIUM



October 8-10, 1987
BARCELONA (Spain)

8th - 9th - Palácio de Congressos
Feria de Barcelona
10th - Princessa Sofia Hotel

PROGRAMME - ABSTRACTS

8th-9th - A Spanish Translation will be provided
Traducción simultánea

CONGRESS SECRETARIAT
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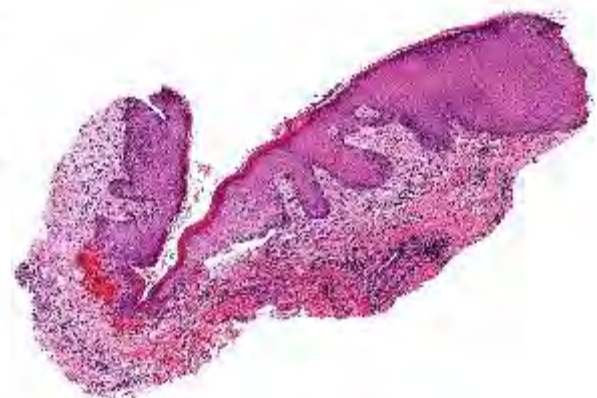
SESSION V: INFLAMMATORY SKIN DISEASES

AFTERNOON:

ROOM N.º 8:

Chairmen: J. L. Diaz, J. M. Moragas, G. E. Pierard,

- 17:10 - 17:20** (33) **LIPID - MEMBRANOCYSTIC CHANGES IN INFLAMMATORY NODULES OF THE LEGS**
V. Alegre R. K. Winkelmann.
- 17:20 - 17:30** (34) **CLINICAL AND HISTOPATHOLOGICAL CORRELATION OF KERATOTIC LESIONS OCCURING IN RENAL TRANSPLANT RECIPIENTS (RTR)**
G. W. Beveridge M. H. Bunney, K. McLaren, J. A. A. Hunter and: I. Umbert.
- 17:30 - 17:40** (35) **TWO CASES OF DISSEMINATED EPIDERMOLYTIC ACANTHOMA**
I. Mihara, S. Sawada, Y. Yada, T. Tozawa, M. Nimura.
- 17:40 - 17:50** (36) **OCCLUSIVE HYPOHIDROSIS**
J. L. Diaz Perez, A. Aguirre, J. Goday, J. Gardezabal, J. Burgos.
- 17:50 - 18:00** (37) **ELASTIC TISSUE IN GRANULOMA ANNULARE LESIONS FROM EXPOSED AND UNEXPOSED SKIN**
R. Friedman - Birnbaum, S. Wellfriend, H. Kerner, C. Lichtig.
- 18:00 - 18:20** COFFEE BREAK
- 18:20 - 18:30** (38) **COLLOID KERATOSIS ULTRASTRUCTURAL AND IMMUNOHISTOCHEMICAL STUDIES**
J. González.
- 18:30 - 18:40** (39) **HYPERKERATOSIS LENTICULARIS PERSTANS (FLEGEL)**
Ch. Kuehn-Petzoldt, R. Laurier, J. Kunze.
- 18:40 - 18:50** (40) **ACANTHOMA FISSURATUM OF THE SKIN**
I. Cerroni, H. P. Söyer.
- 18:50 - 19:00** (41) **LINEAR POROKERATOSIS OF MIBELLI AND MULTIPLE SQUAMOUS-CELL CARCINOMAS**
G. Borrani, R. Rosso, V. Brazzelli, G. Vignati, G. Rabbiosi.
- 19:00 - 19:10** (42) **OFUJI'S SYNDROME**
P. Sánchez-Pedreño, J. Mazuecos, A. Rodríguez Pichardo, B. García Bravo, J. C. Moreno, F. Camacho Martínez.
- 19:10 - 19:20** (43) **HISTOLOGICAL ASPECTS OF CLARKE - HOWEL EVANS - MCCONNELL - SHEPPARD - SYNDROME**
M. Hagedorn.



Acanthoma Fissuratum

LORENZO CERRONI, M.D.
HANS PETER SOYER, M.D.
SERGIO CHIMENTI, M.D.

ARTICLE

Abstract. Five cases of acanthoma fissuratum observed in the last years are reported. These lesions, located along the retroauricular fold and on the nasal bridge, are caused by ill-fitting eyeglasses. Clinically, acanthoma fissuratum is often mistaken for a basal cell epithelioma. The definitive diagnosis can be confirmed by characteristic histologic features in association with clinical and anamnestic data. Acanthoma fissuratum needs recognition as a distinctive lesion of importance for dermatologists and surgeons. *J Dermatol Surg Oncol* 1988; 14: 1003-1005.

INTRODUCTION

The term "granuloma fissuratum" was first mentioned by Sutton¹ in 1932 to describe a lesion located in the buccal mucosa characterized by a granulomatous reaction caused by lodged food particles. In 1965, Epstein² described a case of "granuloma fissuratum of the ears" occurring at the site of friction from ill-fitting eyeglasses with analogous histopathologic appearance. The terms "spectacle-frame acanthoma" and "acanthoma fissuratum"—histologically more accurate terms—were introduced for the first time by Barnes in 1974 and by MacDonald in 1975.^{3,7}

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J Dermatol Surg Oncol 14:8 September 1988

In an attempt to delineate the clinical and histopathological aspects of acanthoma fissuratum of the skin in detail, we studied five cases of this lesion observed in the last years.

CASE REPORTS

Case 1

A 74-year-old female presented with a 3-month-old firm, nonpainful, flesh-colored retroauricular nodule with a central fissure corresponding to the site of friction from the spectacle frame. The clinical diagnosis was basal cell epithelioma.

Case 2

A 58-year-old female presented with a deep-red, nonpainful retroauricular lesion with a central furrow that she developed 3 months after switching to a different pair of spectacles. The clinical diagnosis was basal cell epithelioma.

Case 3

A 62-year-old male patient had noticed at the retroauricular friction point from the spectacle frame the presence of a firm, deep-red nodule with a central fissure (Fig. 1). The lesion was asymptomatic. The clinical diagnosis was acanthoma fissuratum.

Case 4

In recent months an 81-year-old male had developed a small, asymptomatic, flesh-colored nodule



FIGURE 1. A 42-year-old male with a solitary nodular lesion along the retroauricular fold (Case 3).

with central hyperkeratosis on the left side of the nasal bridge. The lesion was located at the pressure point from ill-fitting new frames. The clinical diagnosis was basal cell epithelioma.

Case 5

A 42-year-old male presented with a lesion located along the retroauricular fold. With the exception of the clinical diagnosis of acanthoma fissuratum, no other clinical data were available.

HISTOPATHOLOGY

All five lesions showed the same histologic features. The epidermis exhibits irregular acanthosis, accentuated at the edge of the lesion, with a central depression where the epidermis is thinned (Fig. 2). The horny layer shows compact orthokeratosis with focal parakeratosis in the zone of the central depression, which is filled with keratin masses and debris of inflammatory cells (Fig. 3). In the upper dermal layer, blood vessels are dilated with a moderately dense perivascular inflammatory infiltrate, mainly constituted of plasma cells, histiocytes, and lymphocytes. Variable degrees of edema in the papillary dermis and slight fibrosis in the superficial and mid dermis are detectable.

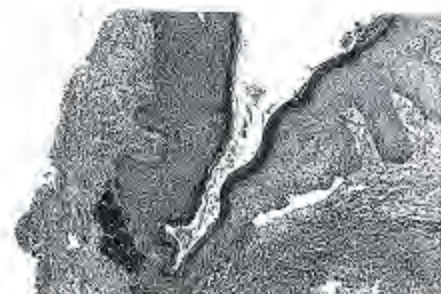


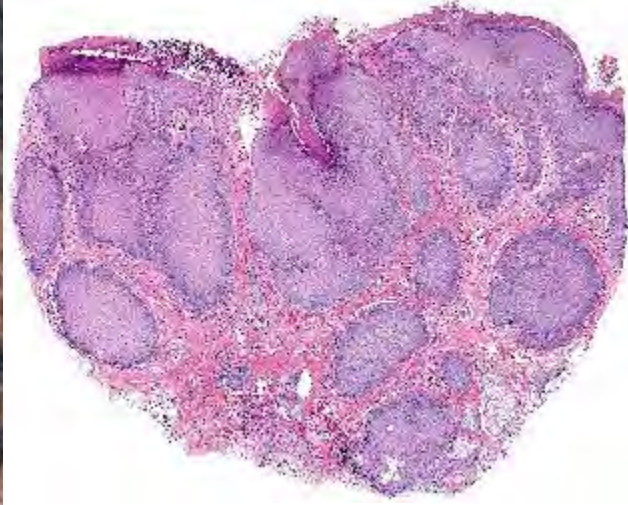
FIGURE 2. Scanning magnification of acanthoma fissuratum showing a central furrow with irregular acanthosis accentuated at the edge (H&E, $\times 100$).

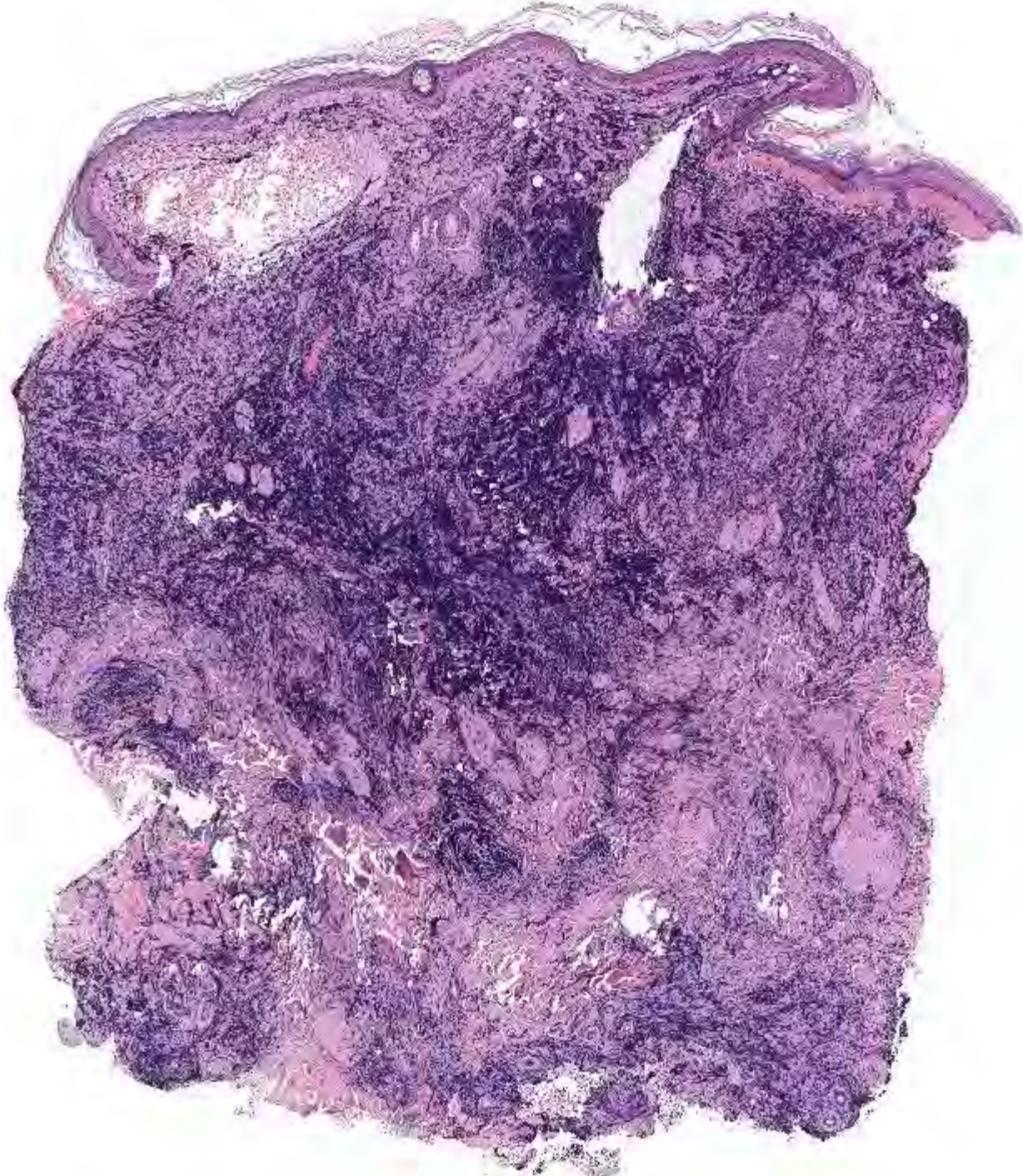
COMMENT

Acanthoma fissuratum is an unusual lesion caused by ill-fitting spectacle frames, which by some authors has been designated as a variety of prurigo nodularis.^{3,8} Acanthoma fissuratum has a clinically distinctive appearance allowing the diagnosis in many cases. Nevertheless, this benign acanthoma is often misinterpreted as basal cell epithelioma, as it was in three of our cases.^{3,4,7,8} The lesion usually occurs at any location along the retroauricular



FIGURE 3. Higher magnification with keratin masses and cellular debris in the central depression. Note orthohyperkeratosis with focal parakeratosis (H&E, $\times 250$).



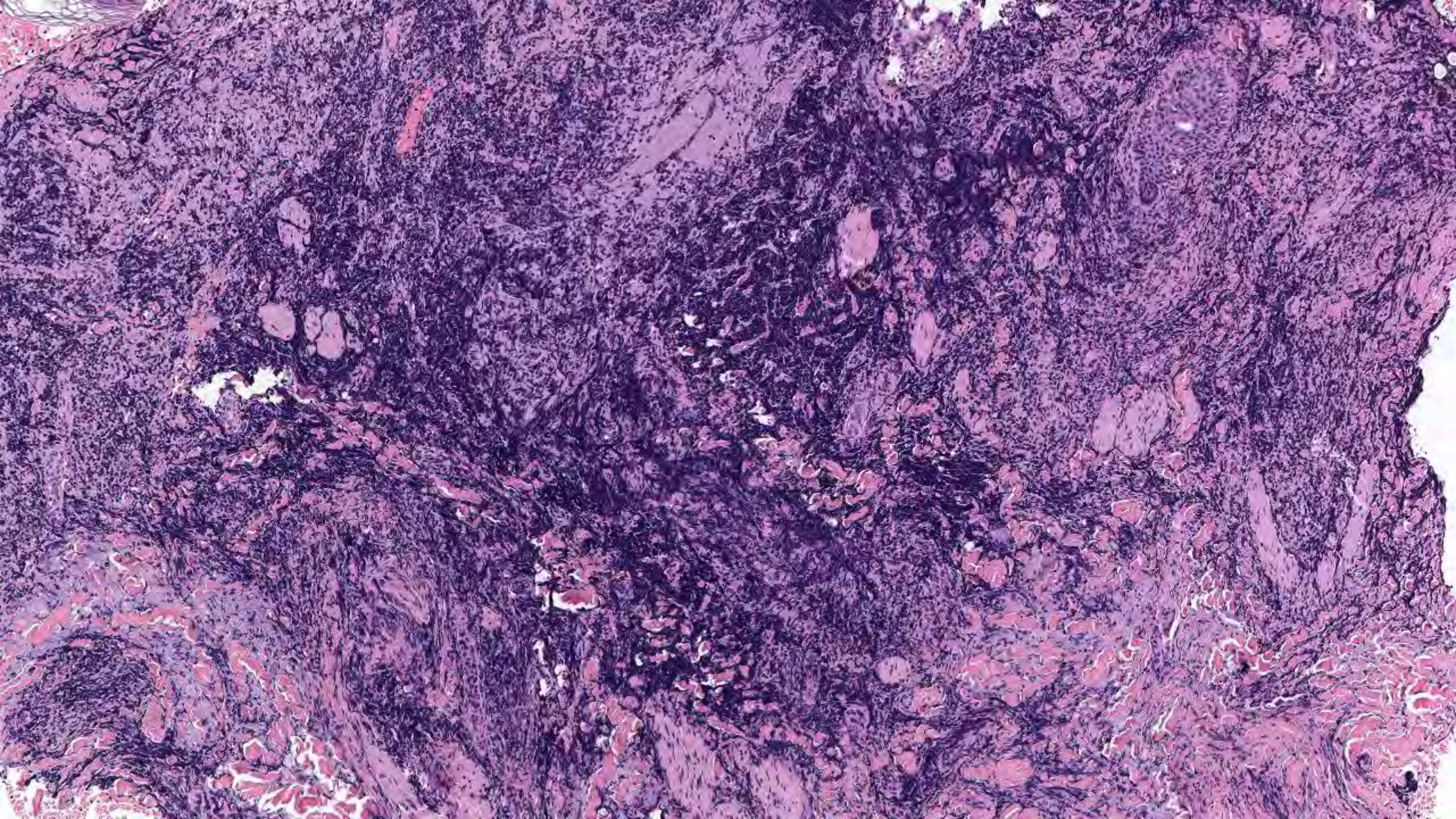


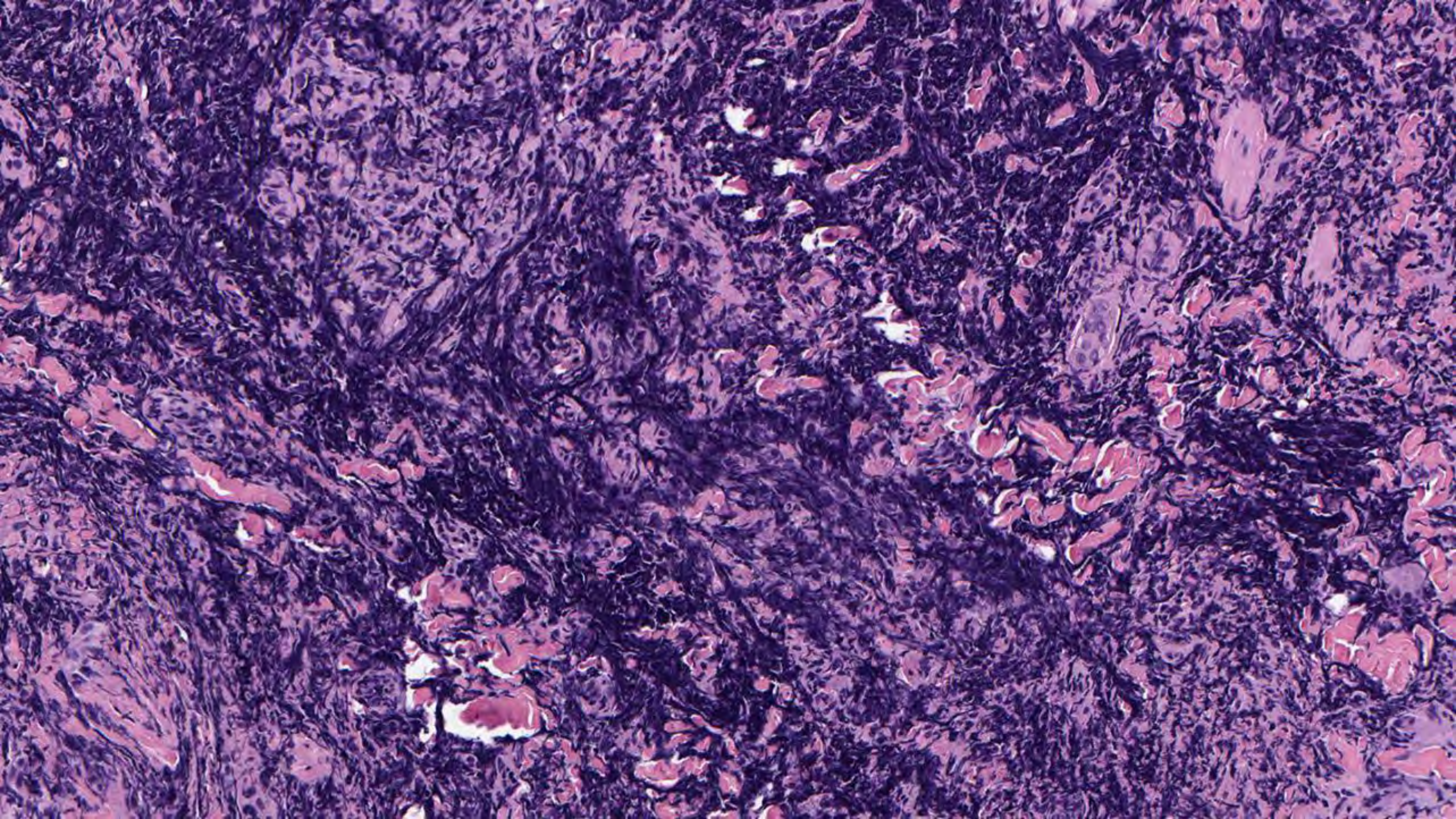
Case 22

M, 78. History of MF (1st diagnosis at the age of 56; according to the patient 1st manifestation at the age of 40).

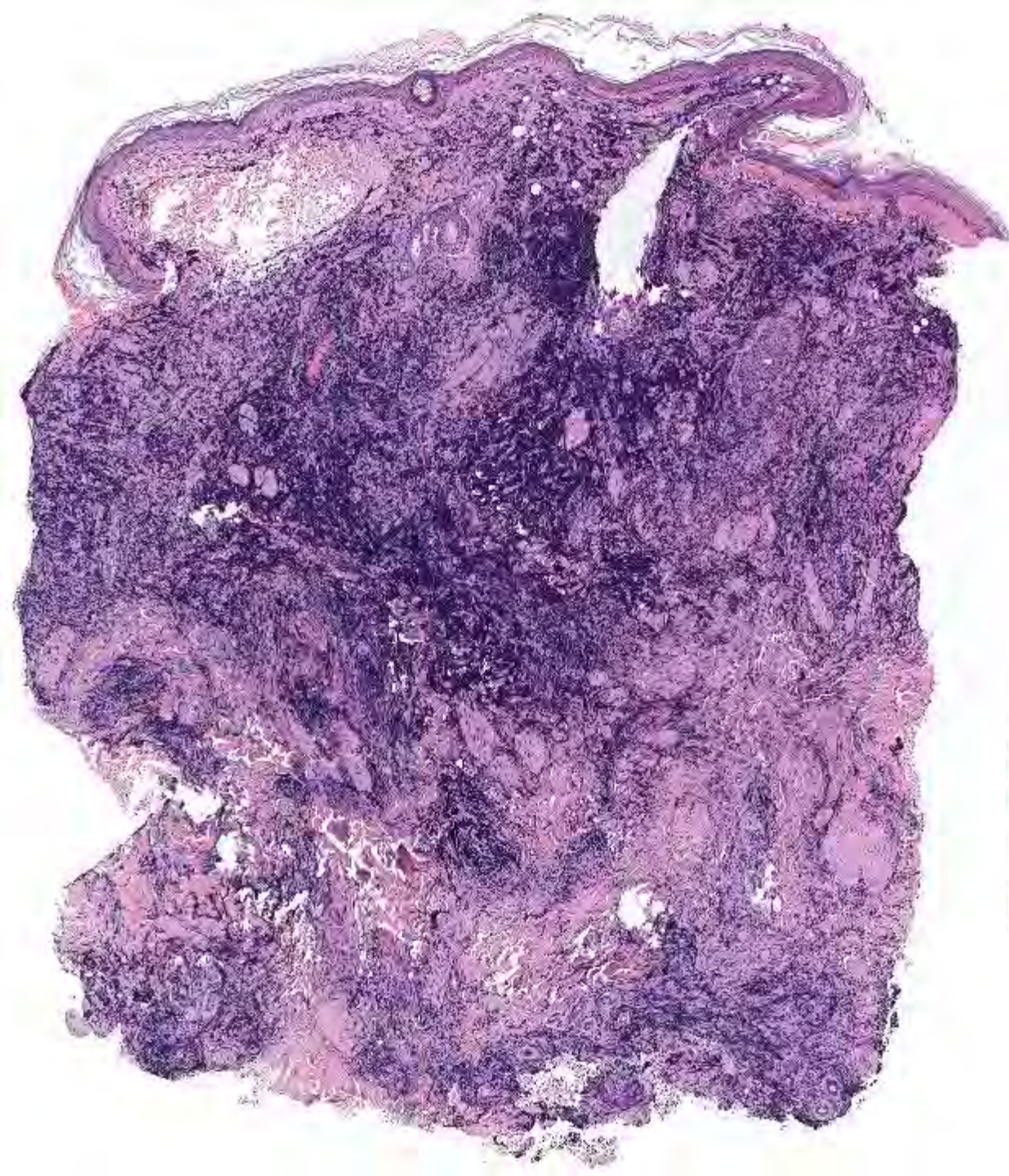
Actual presentation: confluent papules and small nodules on the forehead for the last 3 months.

Biopsy taken with a suspect clinical diagnosis of progression of MF.

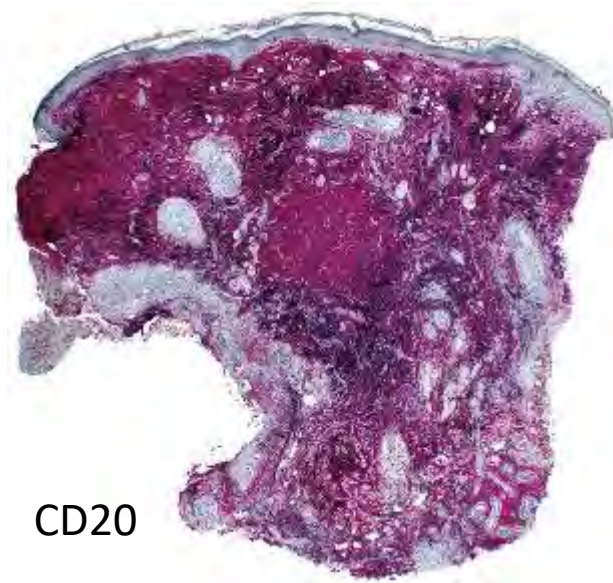




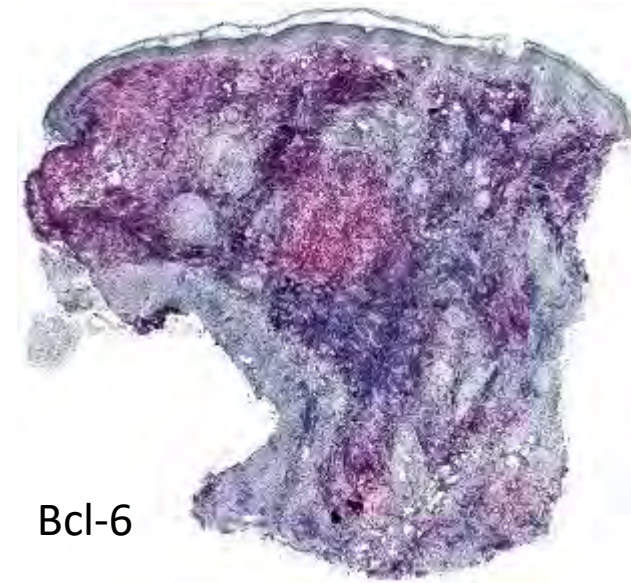




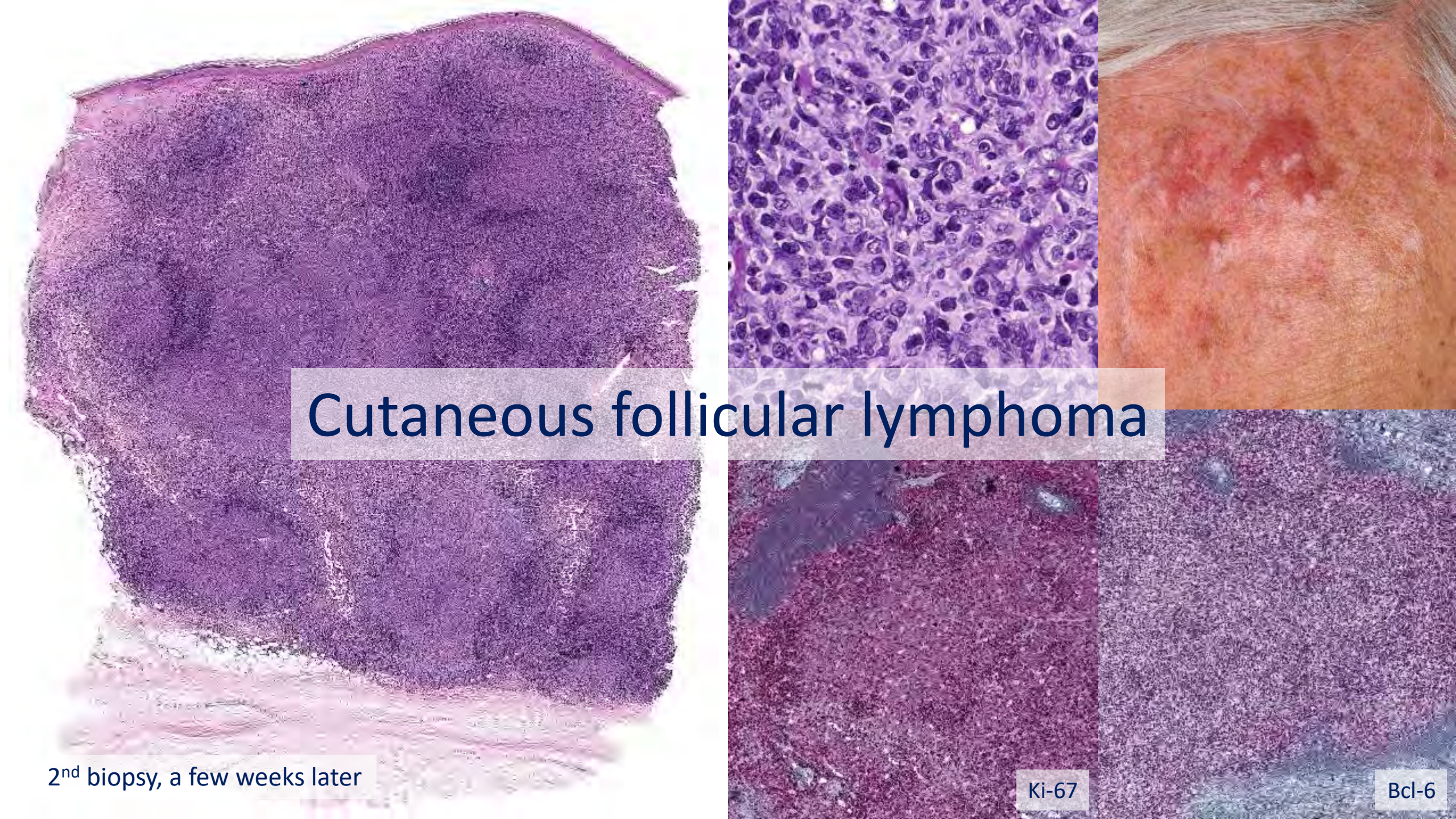
Inadequate biopsy showing severe drying artifacts, reported as atypical lymphoid proliferation with suspicion of follicular lymphoma and with request of a new, proper biopsy



CD20



Bcl-6



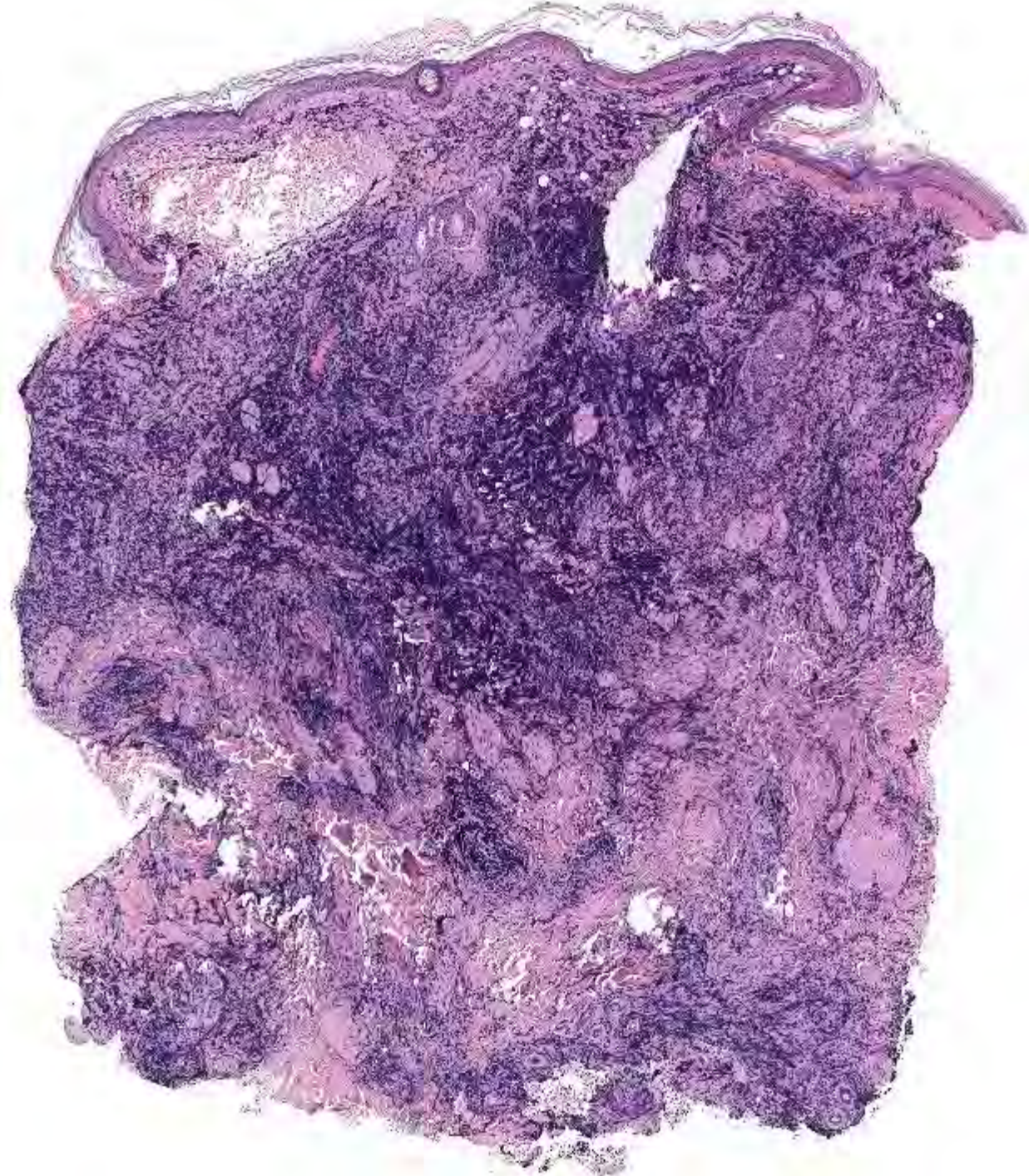
The image is a composite of five panels. The largest panel on the left is a low-magnification H&E stained histological section of a skin biopsy, showing a dense, dark purple infiltrate of lymphocytes in the dermis. To its right is a high-magnification H&E stained section showing individual lymphocytes with large, cleaved nuclei. Above this high-magnification section is a clinical photograph of a skin lesion, which appears as a large, irregular, reddish-brown plaque. Below the high-magnification H&E section are two immunohistochemical (IHC) stained sections. The bottom-left IHC section is labeled 'Ki-67' and shows brown nuclear staining, indicating proliferating cells. The bottom-right IHC section is labeled 'Bcl-6' and shows blue nuclear staining, indicating B-cell lineage.

Cutaneous follicular lymphoma

2nd biopsy, a few weeks later

Ki-67

Bcl-6



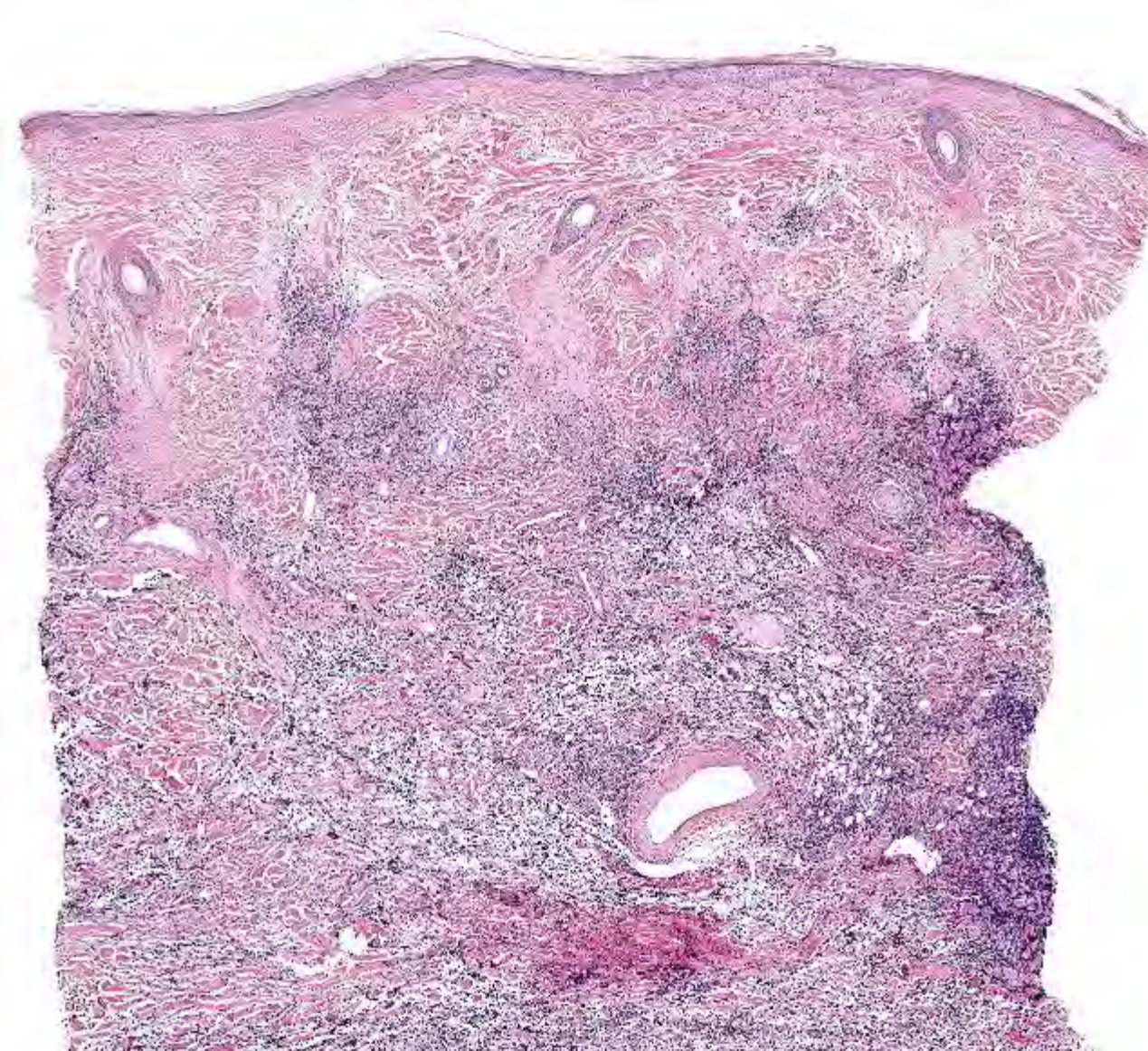




F, 65

History of primary cutaneous follicular lymphoma of the scalp (1st diagnosis 3 years before presentation; managed with 18x 2Gy irradiations). Alopecia and light erythema in the irradiated area.

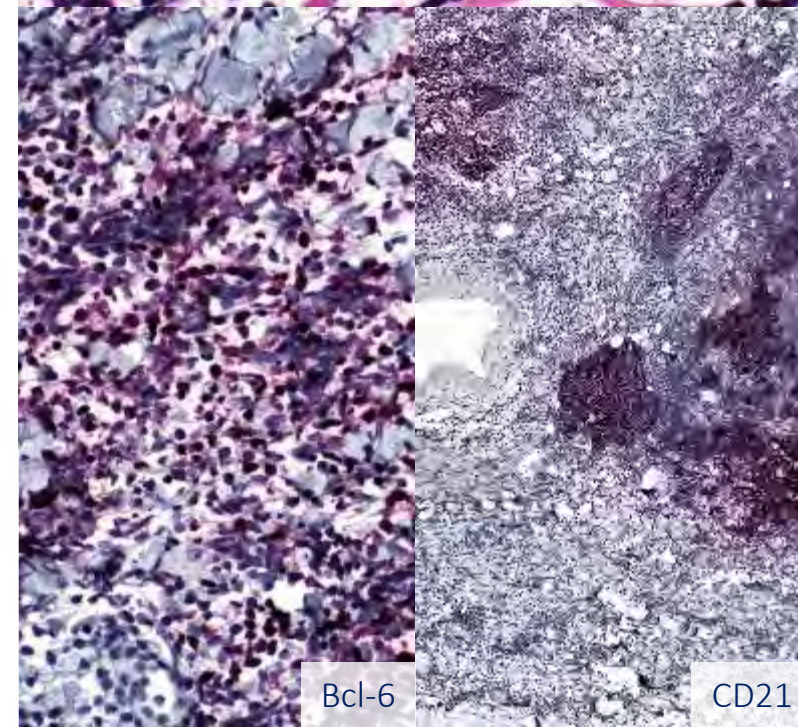
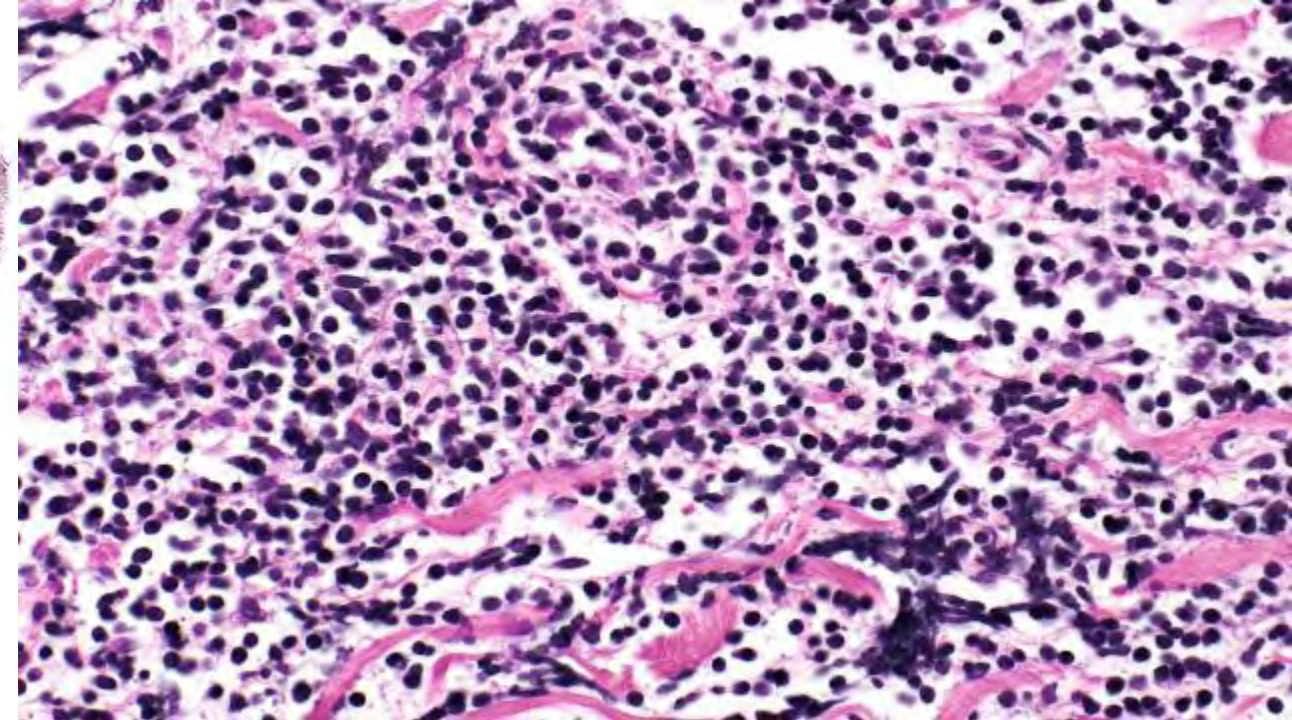
A biopsy is taken.



Cutaneous follicle center lymphoma

"Small" neoplastic cells

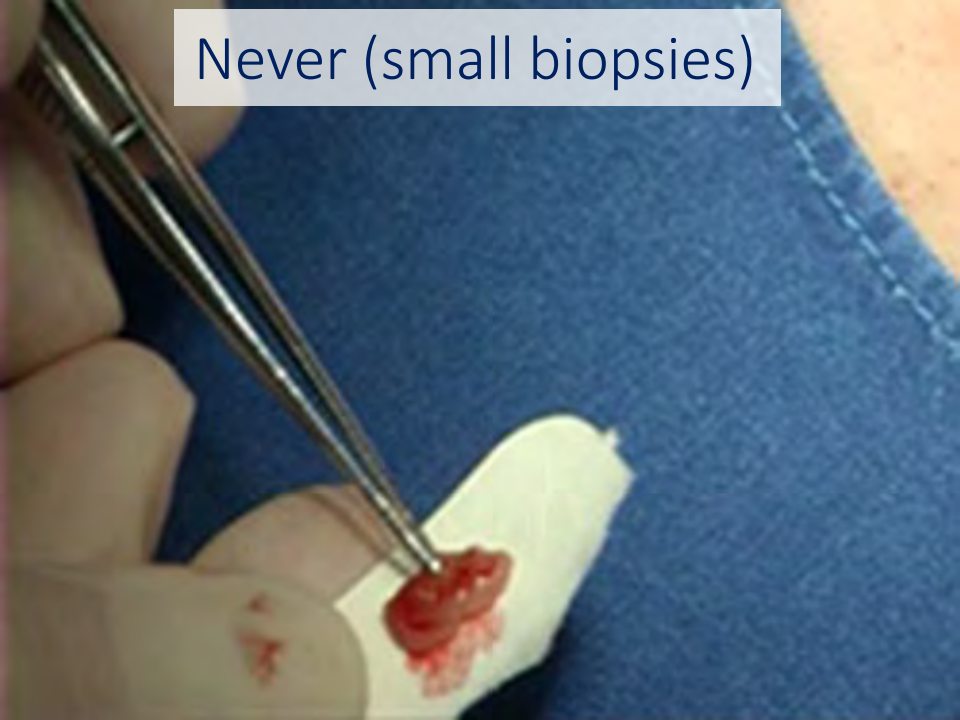
(morphology altered by surgical drying artifacts)



Bcl-6

CD21

Never (small biopsies)



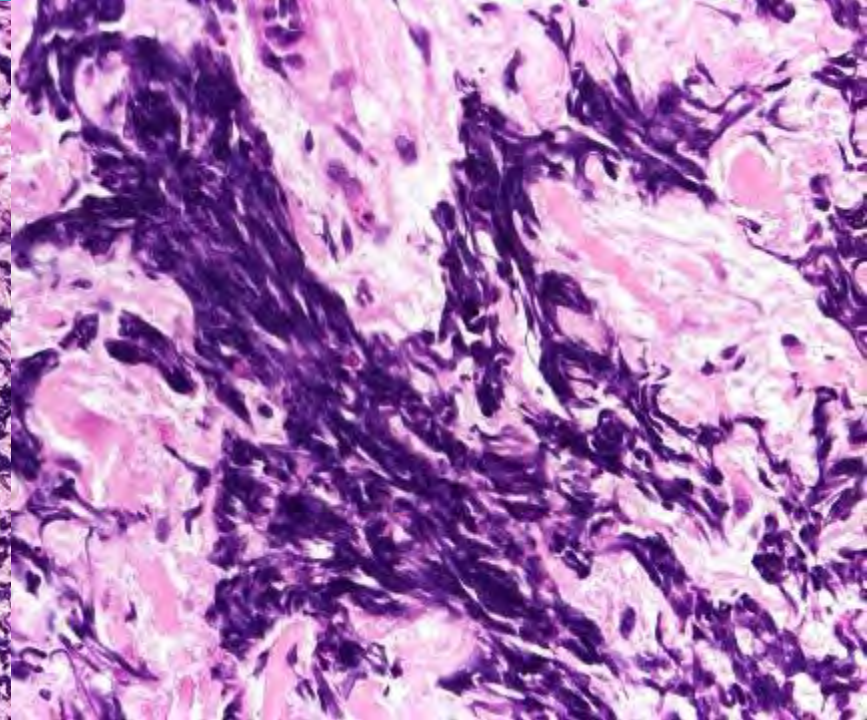
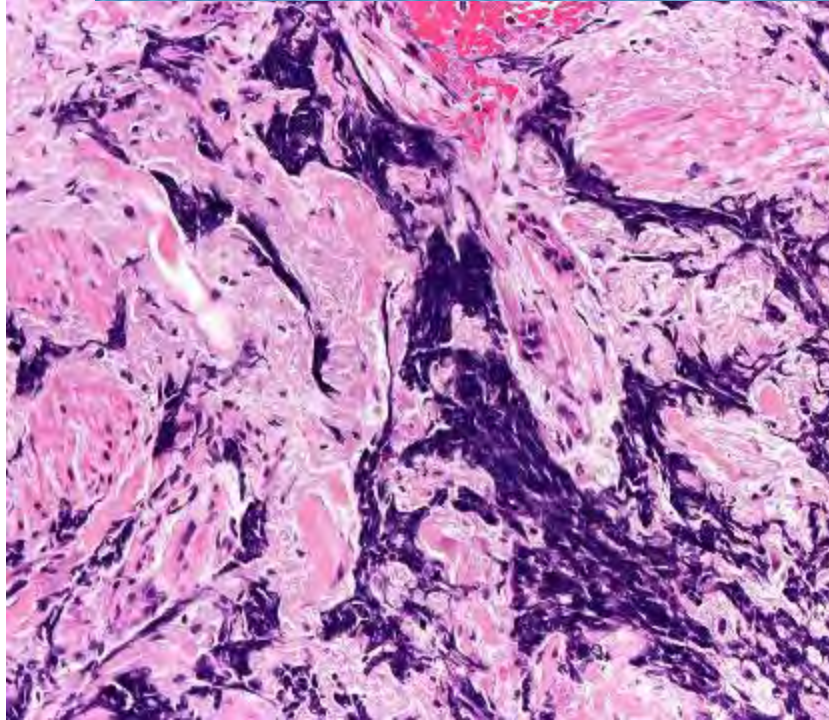
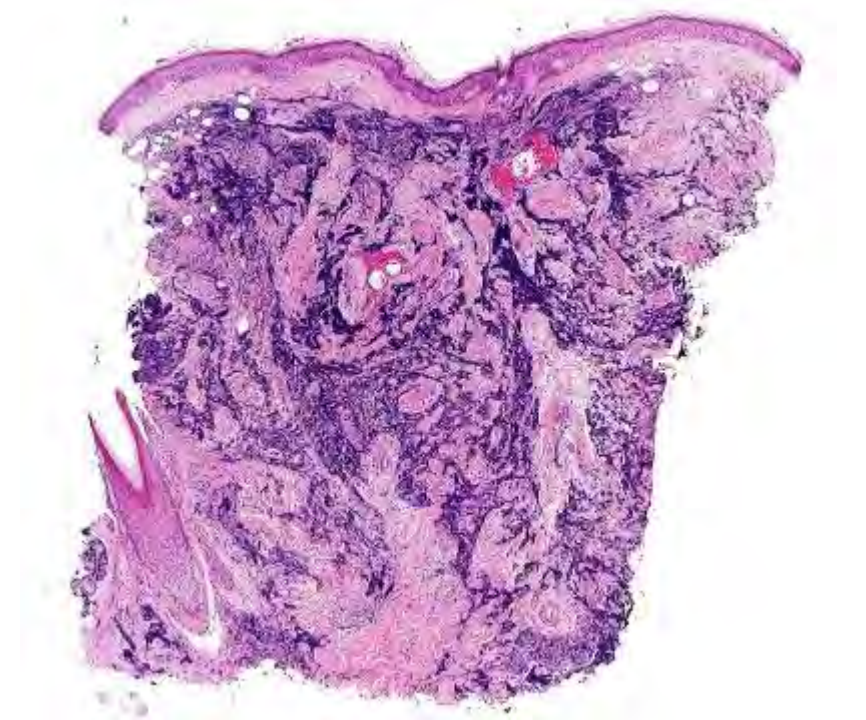
Yes (large biopsies)



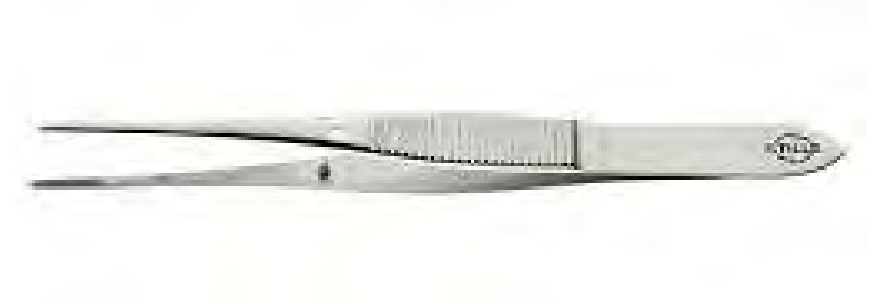
"Drying" artifacts

Most sensible cells:

- * Large lymphocytes (e.g., follicular lymphoma, other lymphomas)
- * Neoplastic cells of Merkel cell carcinoma

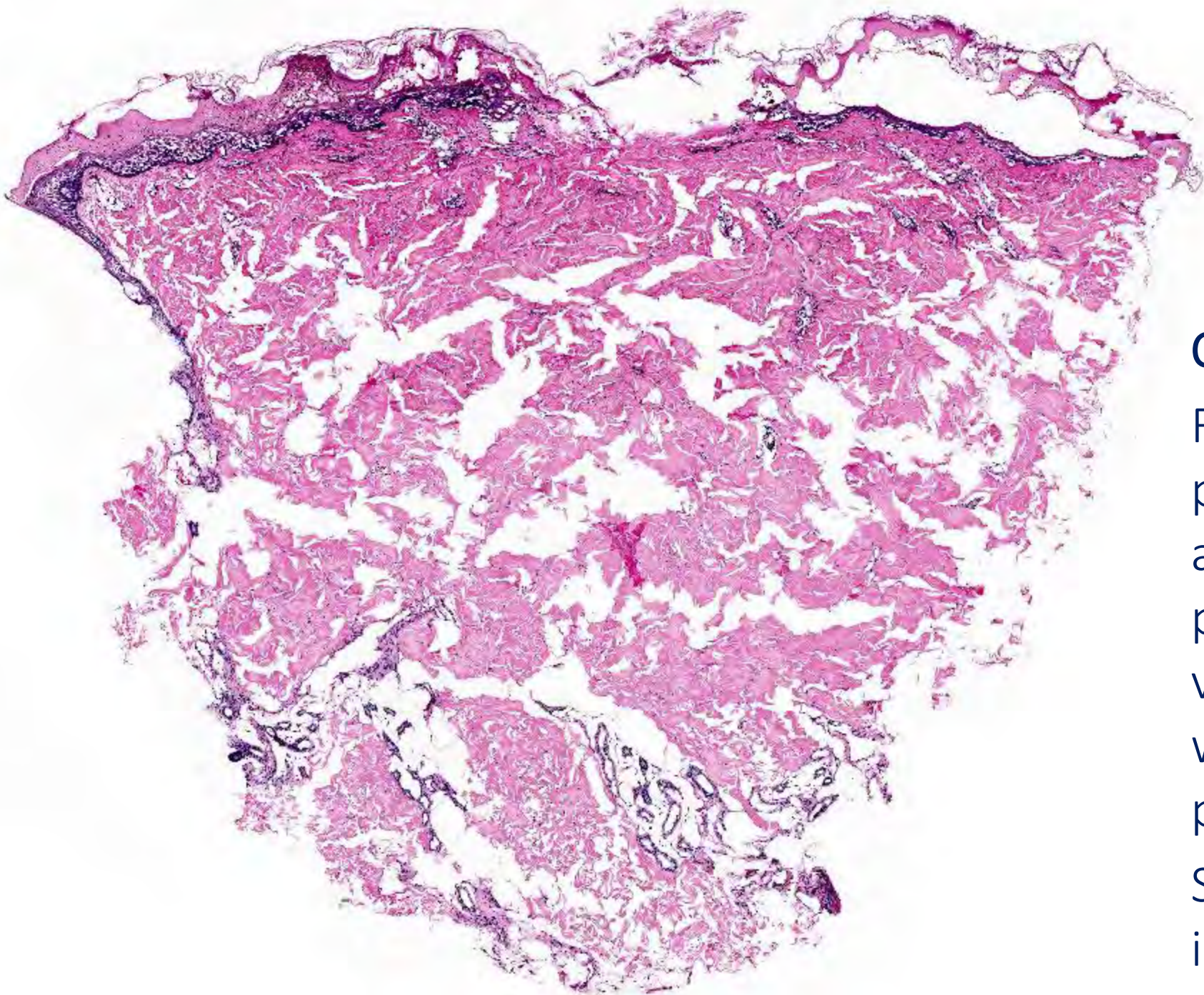


Forceps should never be used in punch or shaving biopsies !



A small biopsy (e.g., punch or shaving biopsy) should never be put on a gauze !

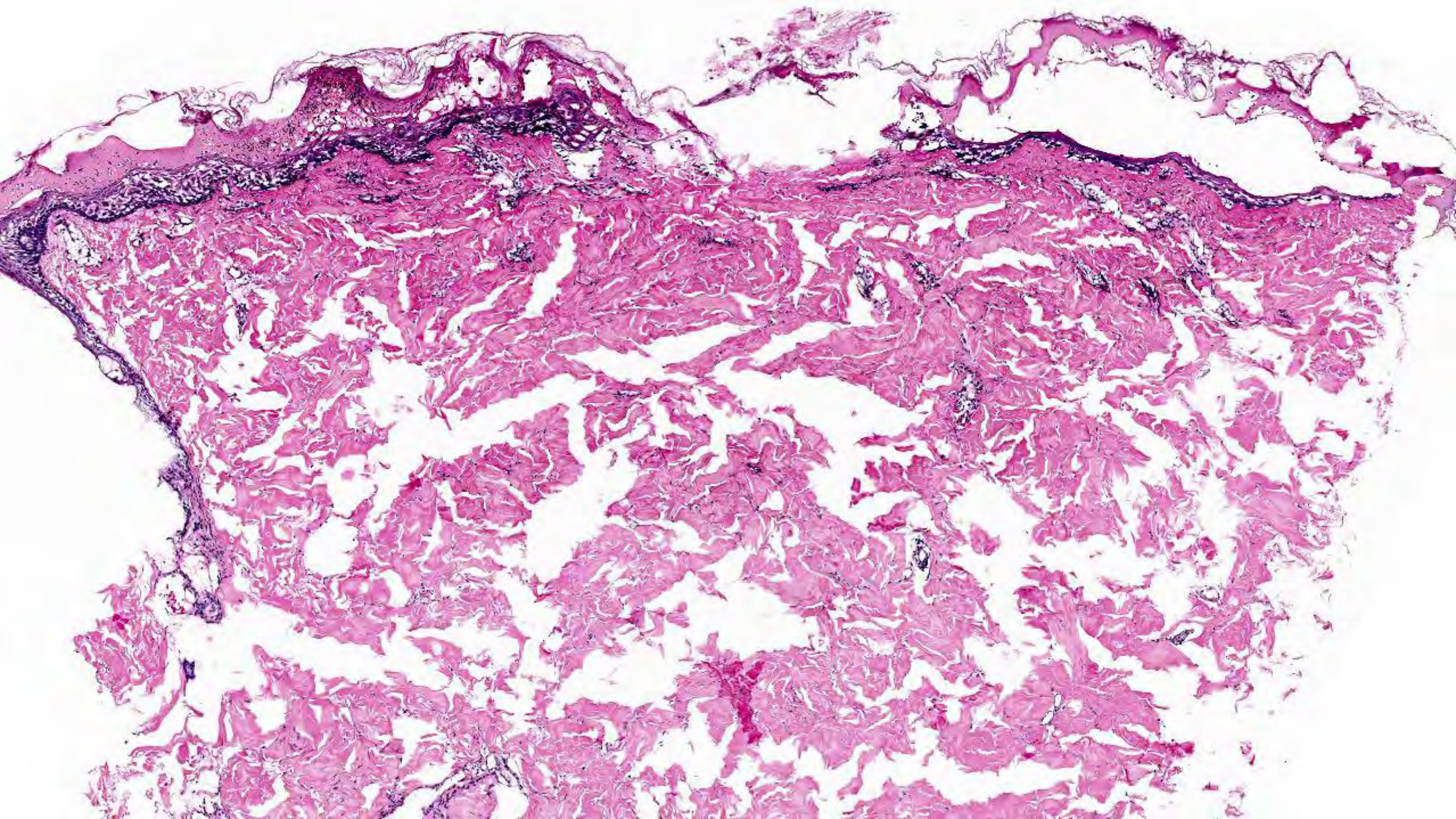


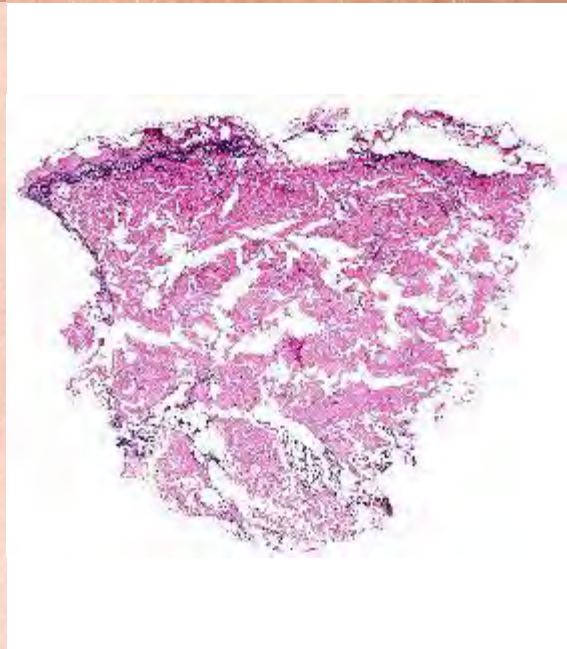


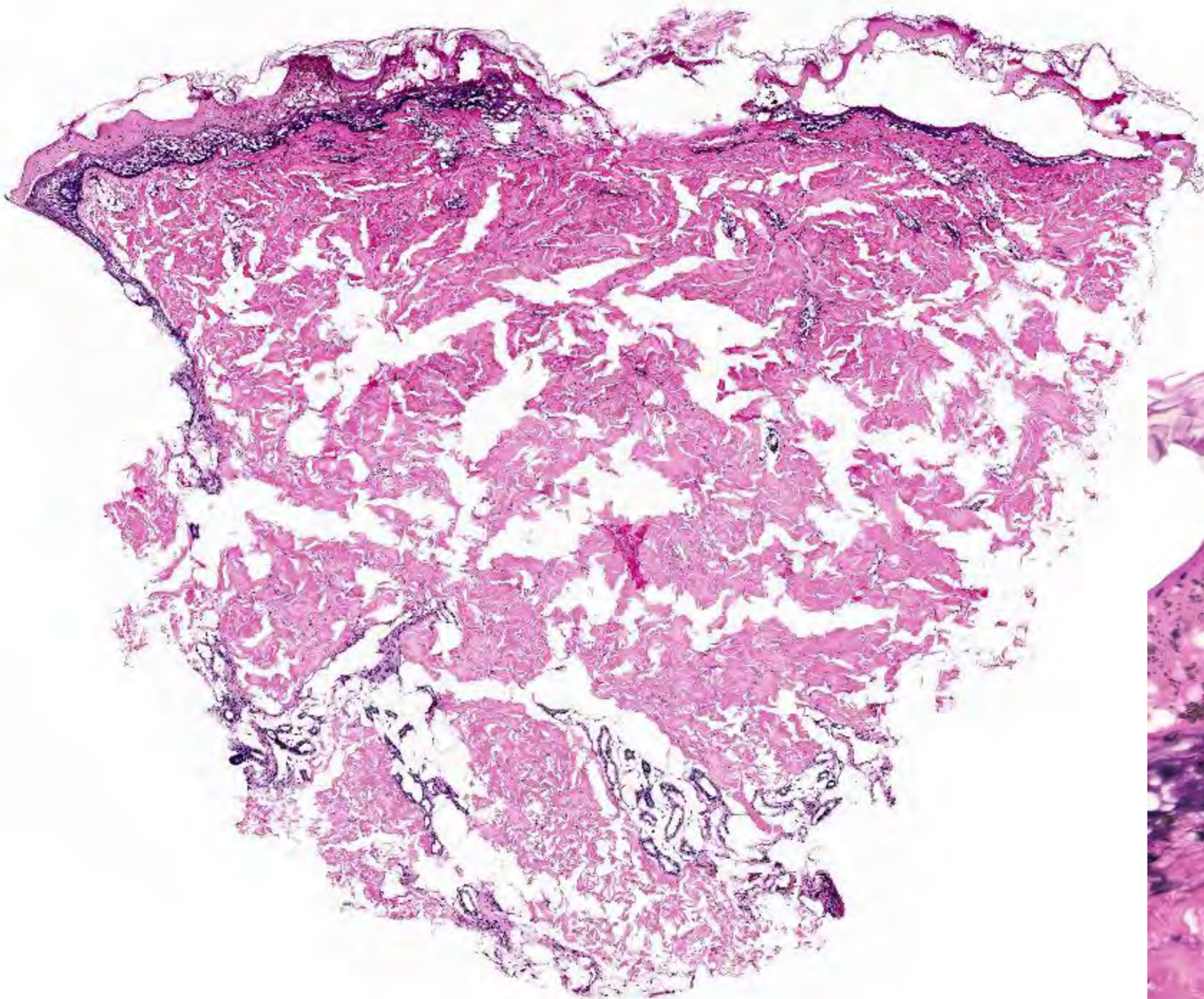
Case 23

F, 15. According to the patient 3 lesions on both arms for 3 days. The patient works by a veterinary and had contact with a cow few days previously.

Sent by GP for mycological investigation.

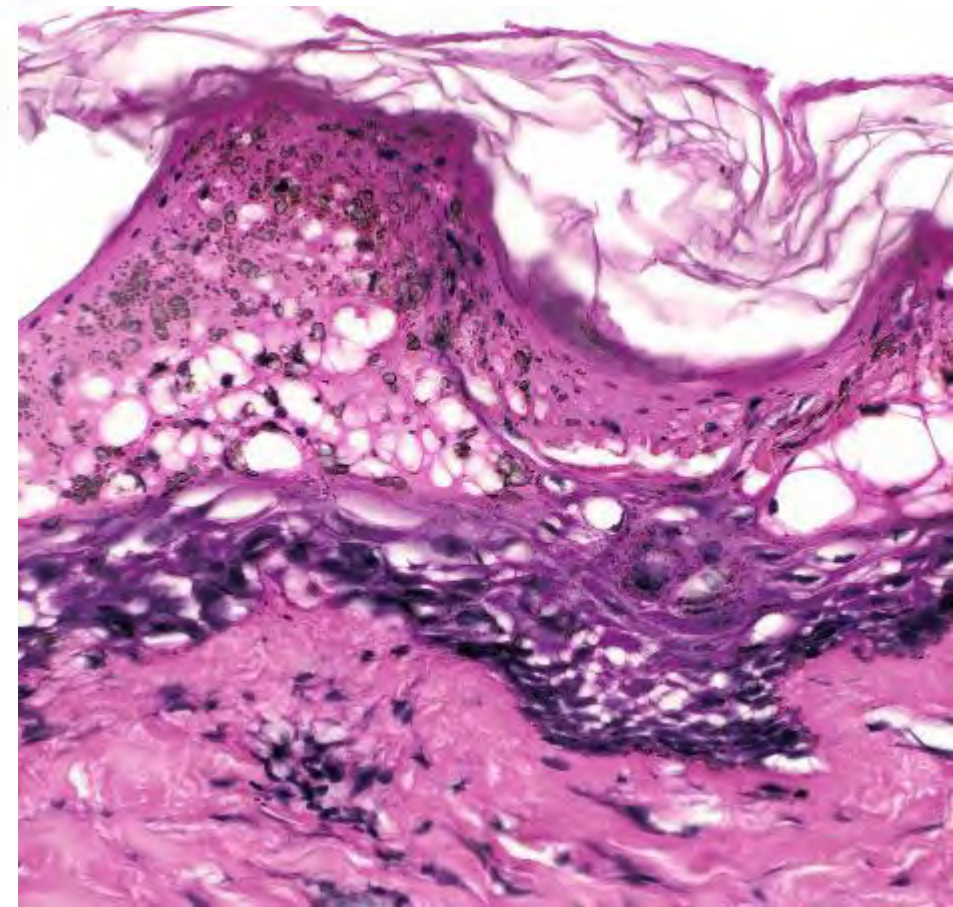


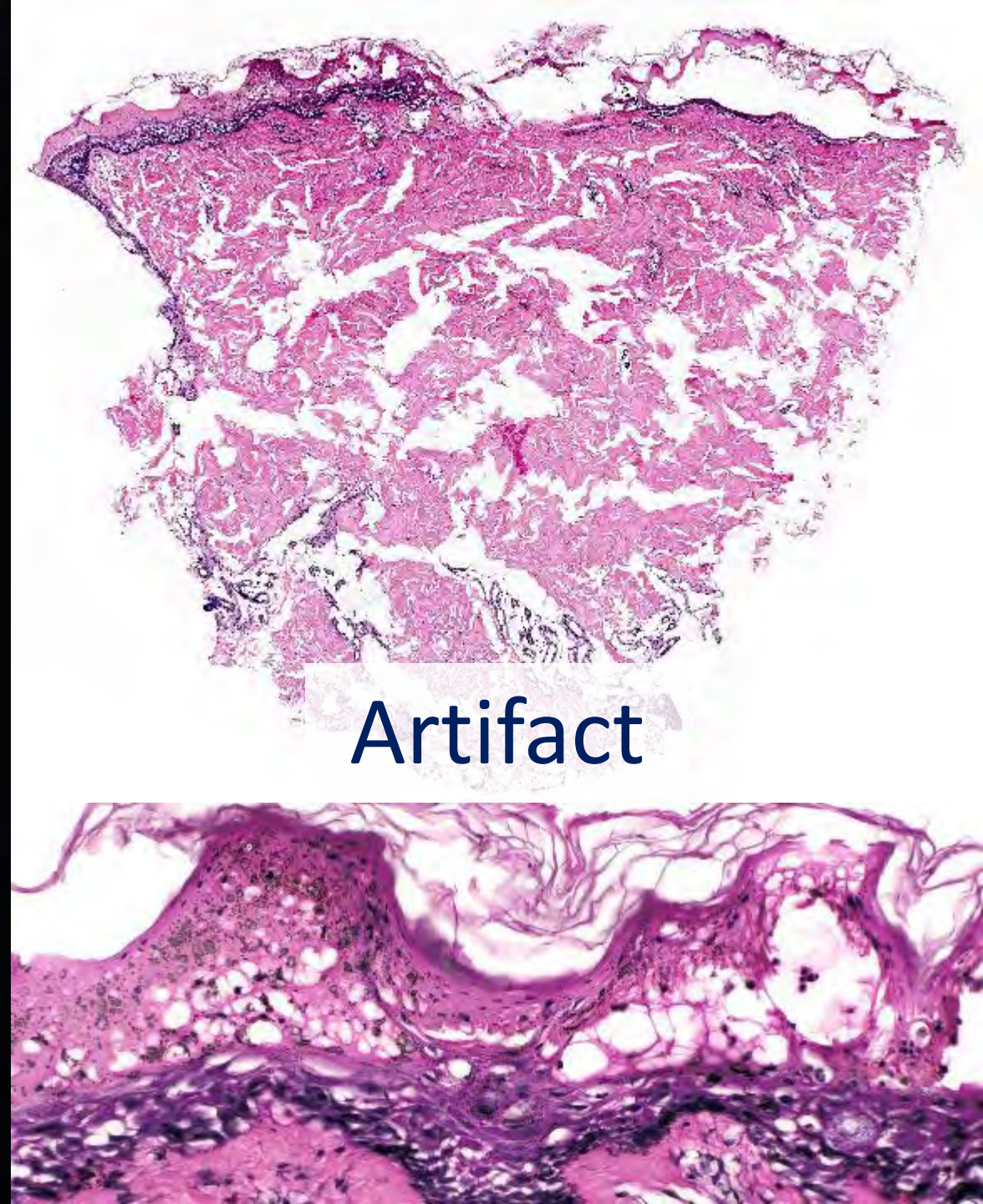




A biopsy showing severe fixation artifacts – can some information still be retrieved?

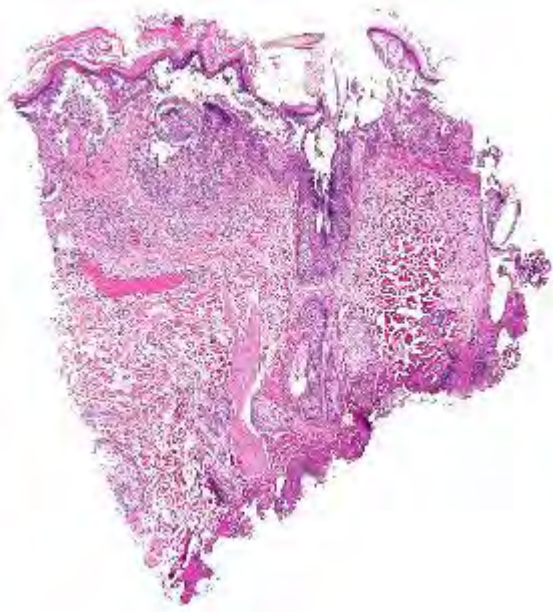
1. Absence of inflammation
2. Epidermal necrosis with normal horny layer above regenerating epidermis



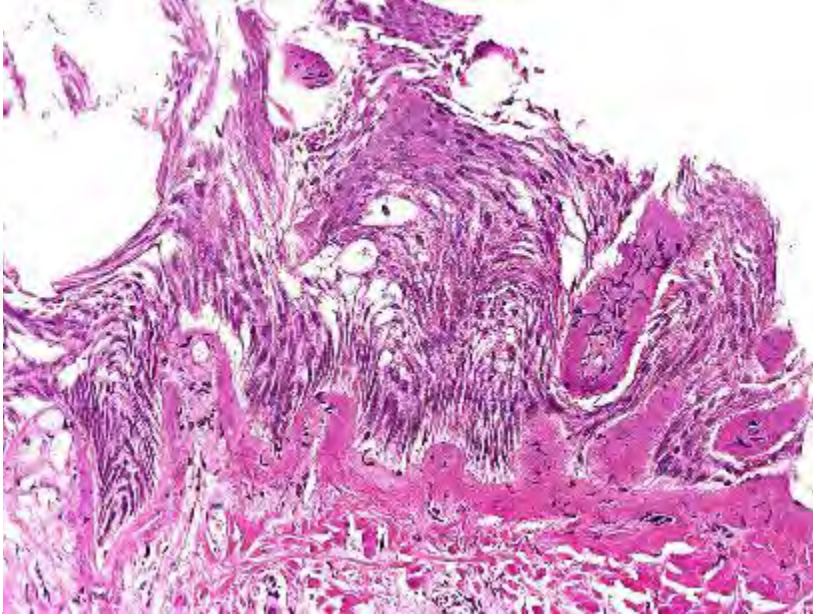


Artifact

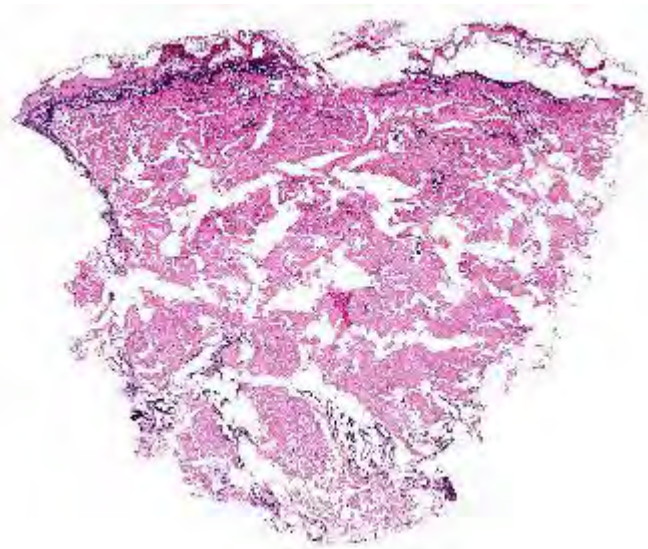
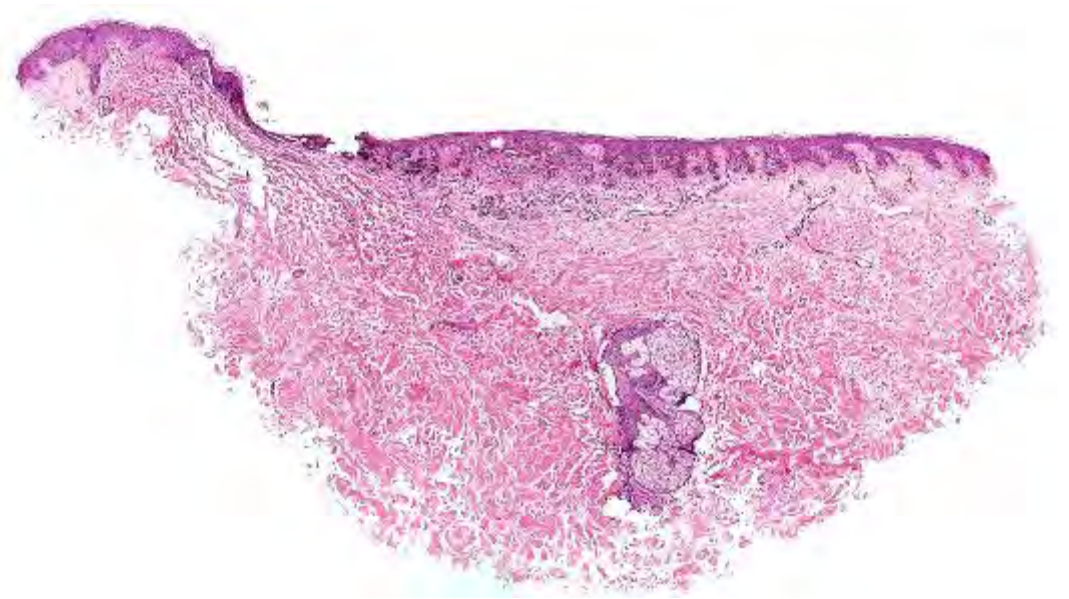
Recognizing surgical artifacts in dermatopathology



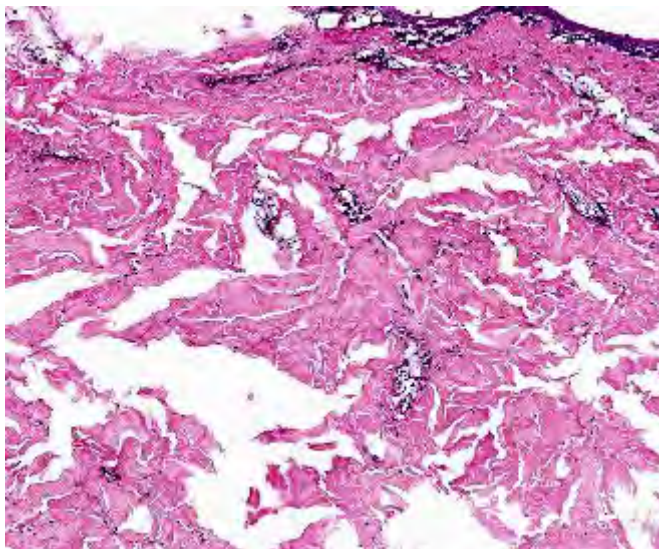
Cauterization artifact (electro cautery-knife)



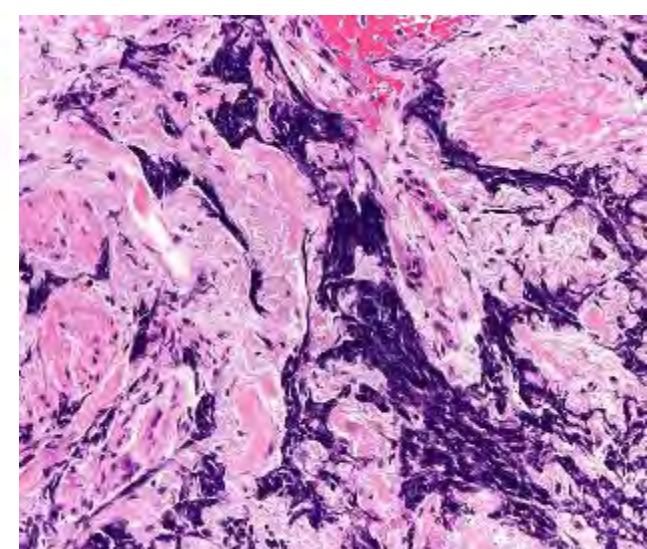
Squeeze (crash) artifact (squeezing the specimen with the forceps)

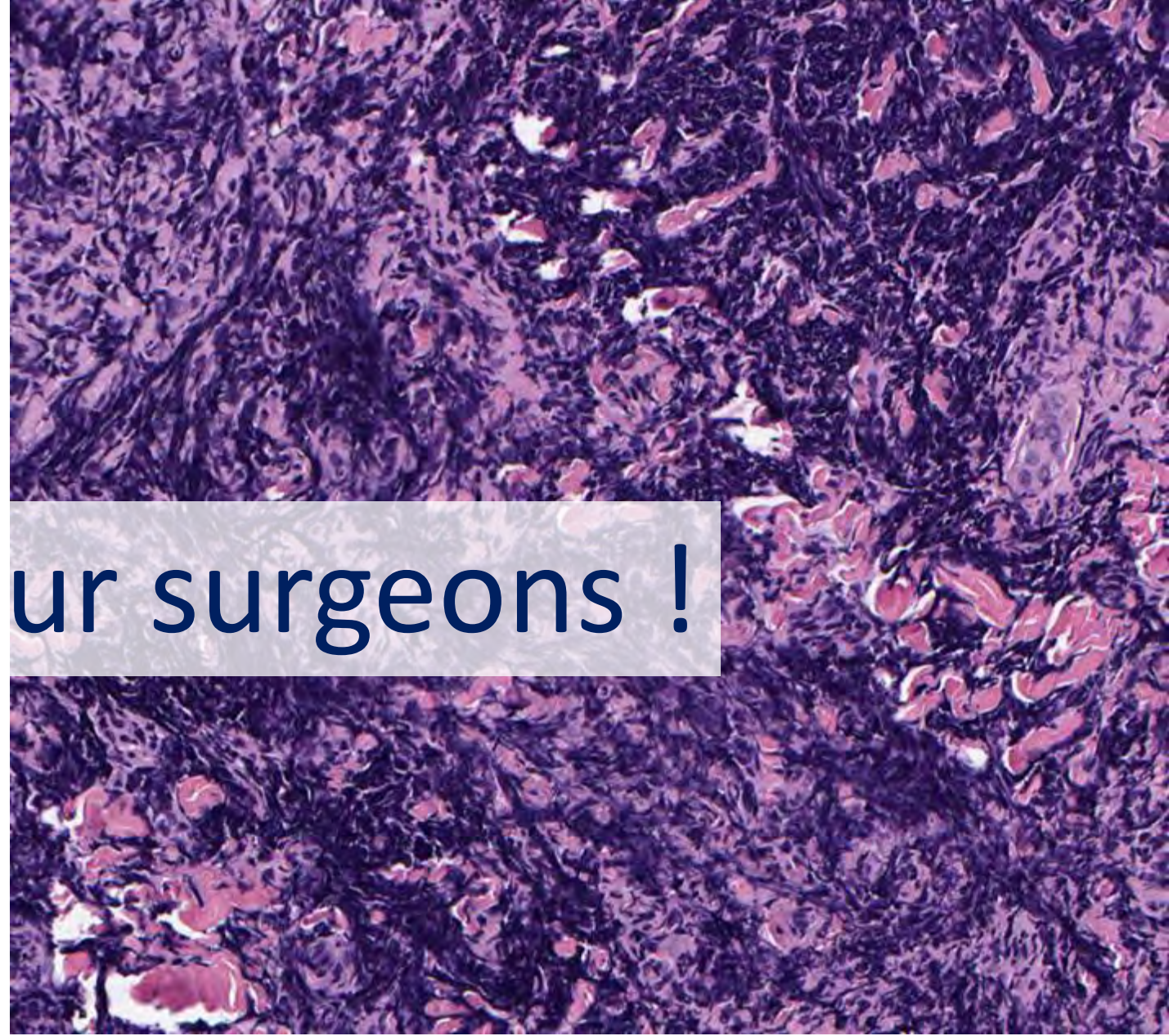


Poor fixation (usually too little or no formalin in the vessel)



Drying artifact (putting a small biopsy specimen, like a punch, on a gauze)





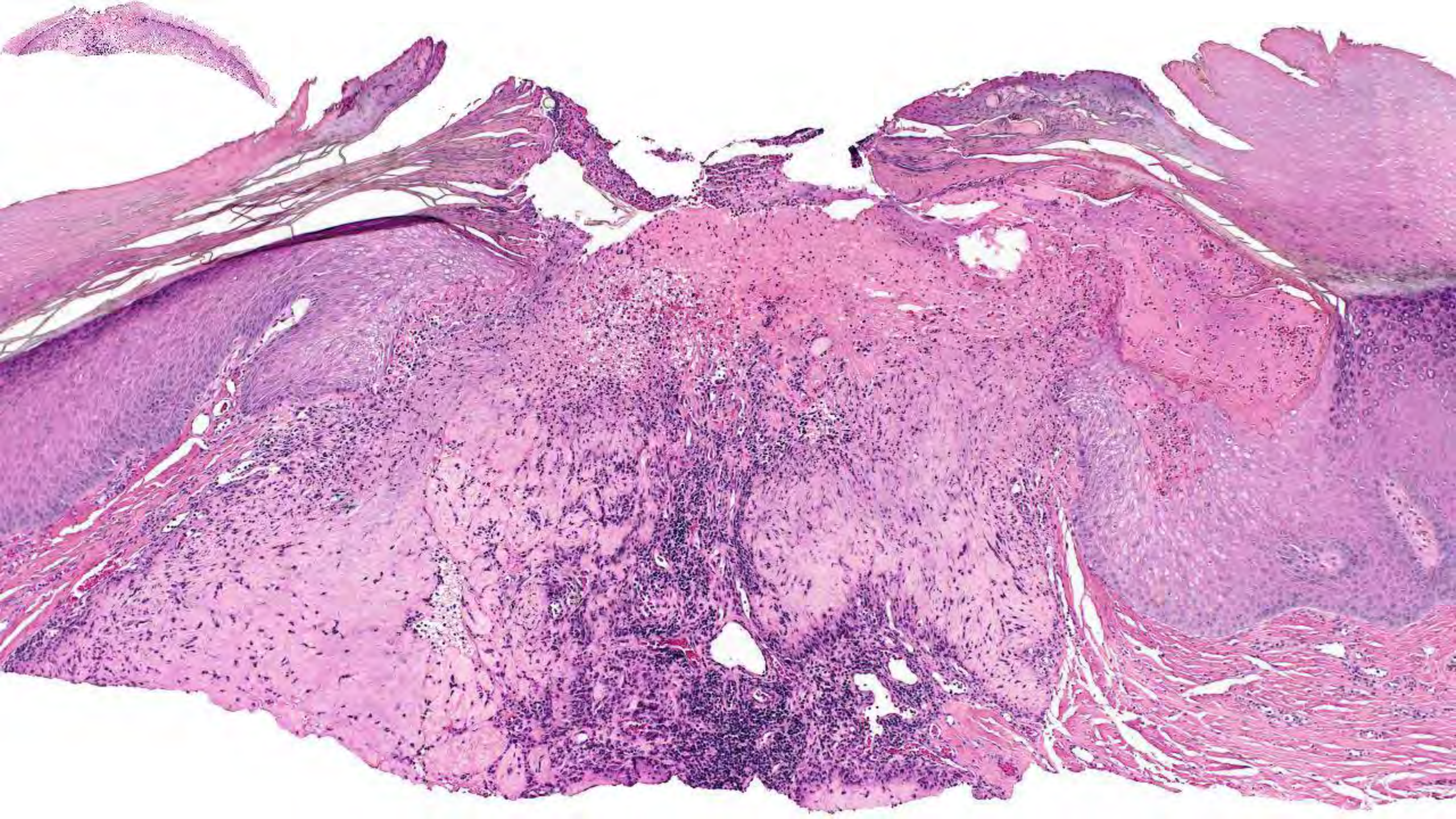
Teach your surgeons !

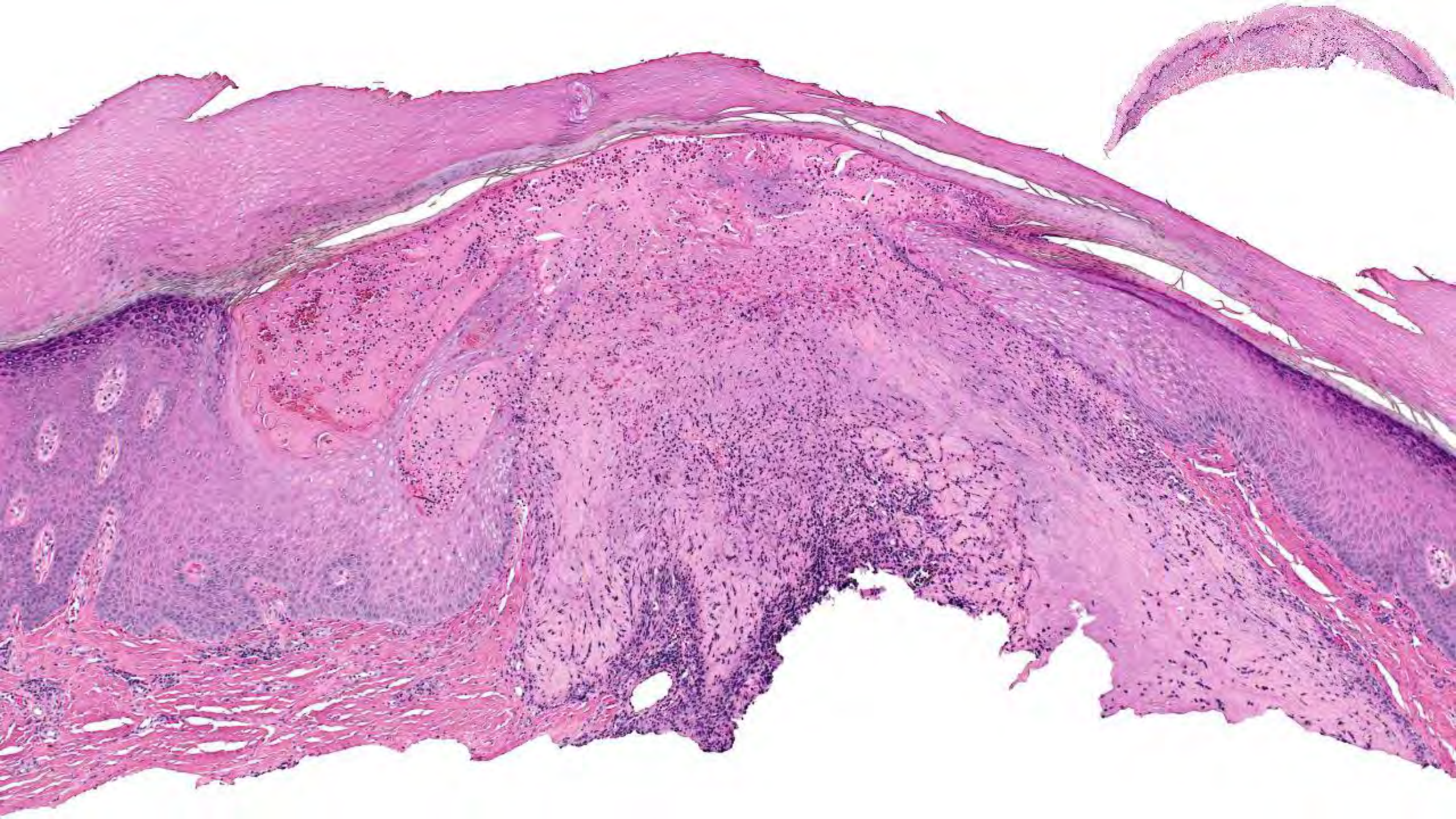
Drying artifact – not a squeezing artifact, not a fixation artifact

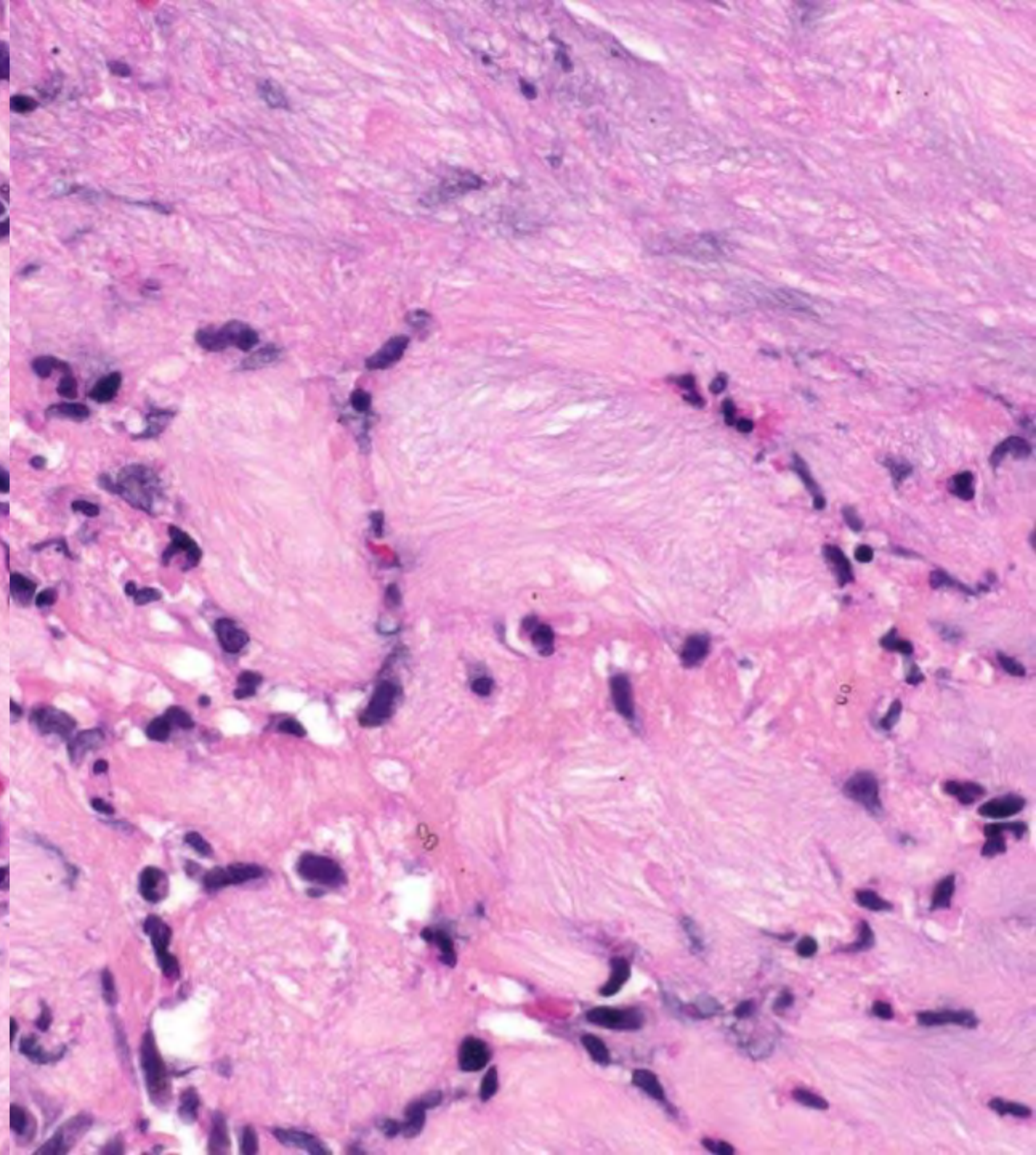
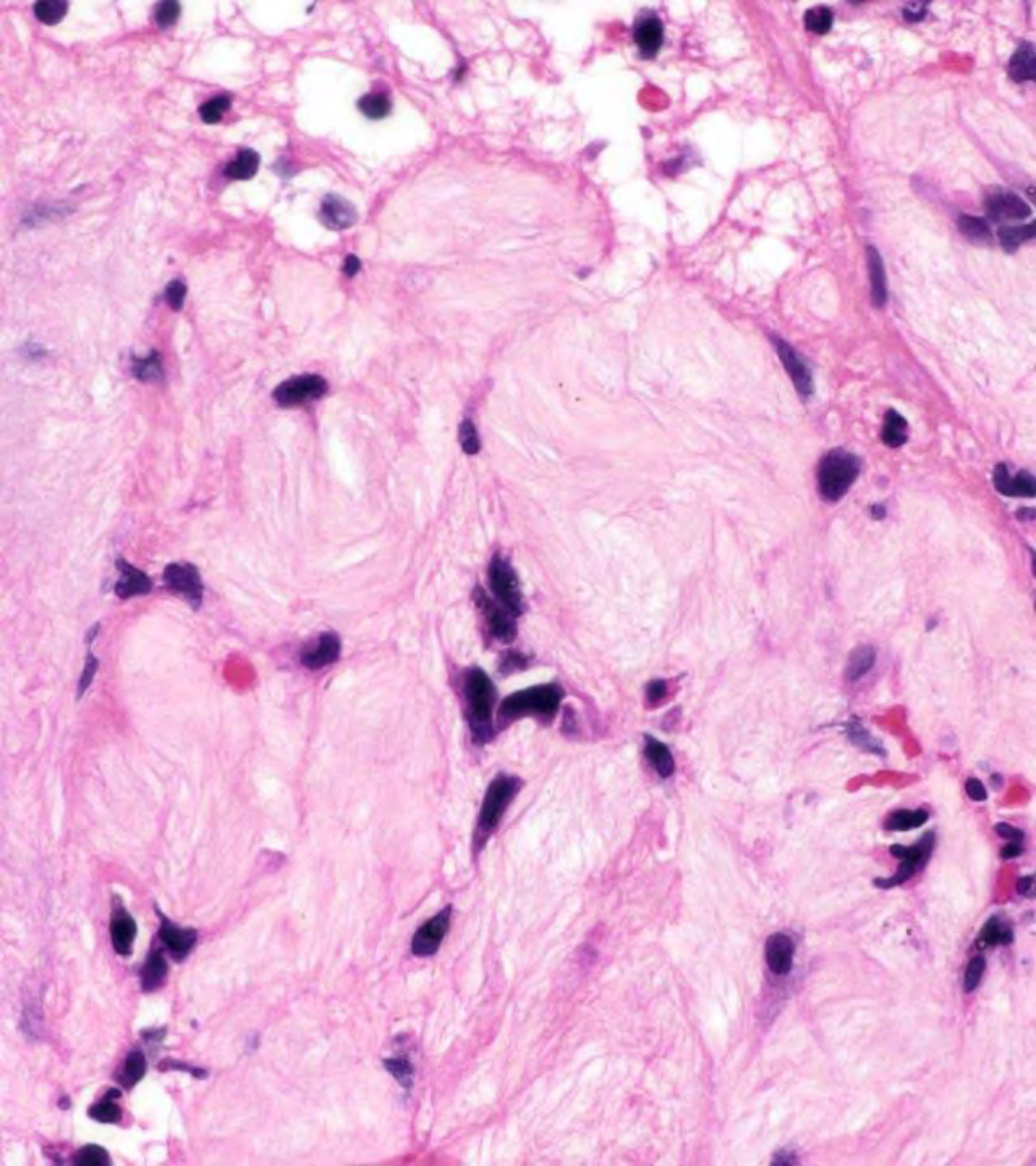


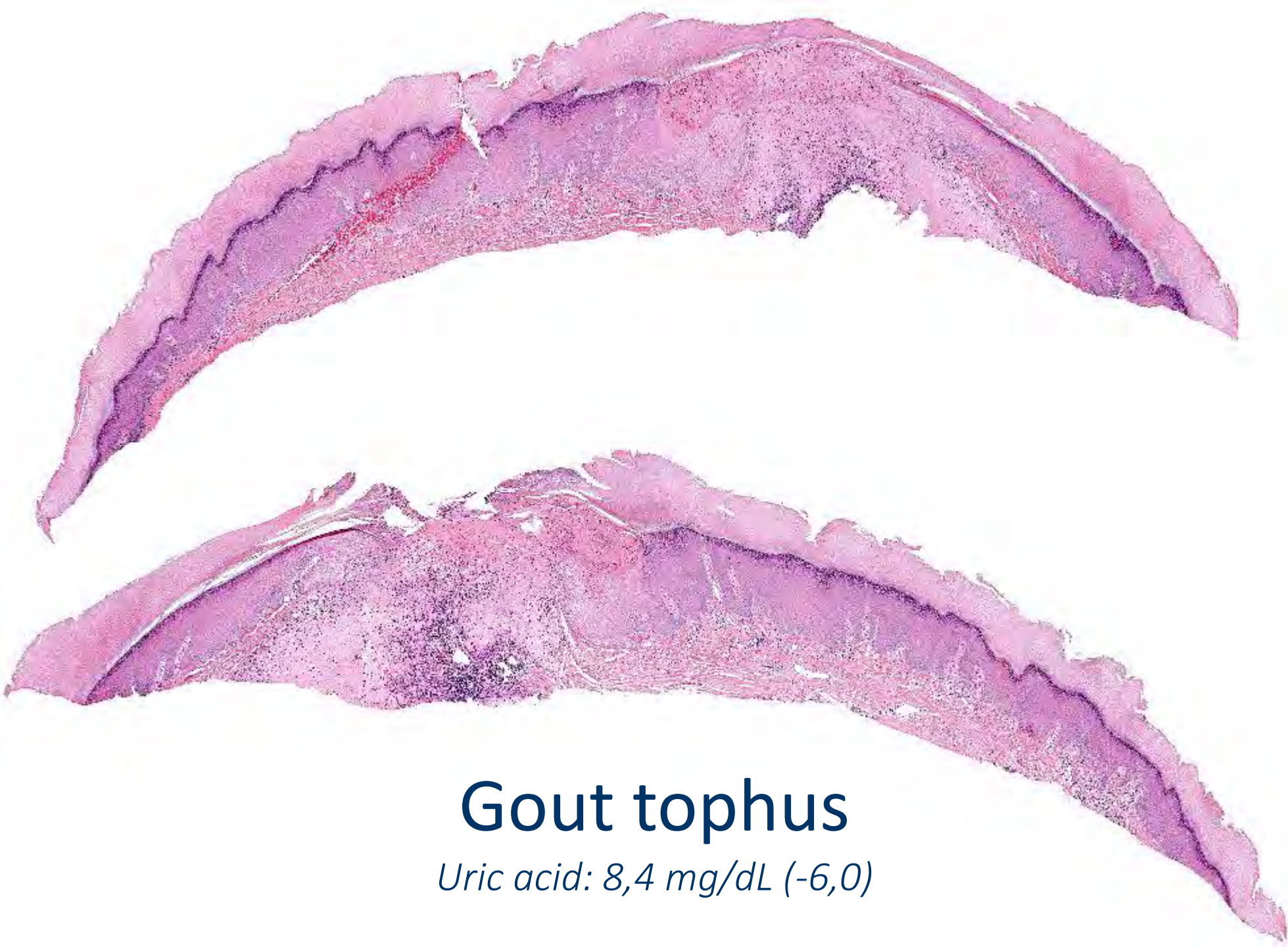
Case 24

M, 86. An ulcerated lesion on the 2nd finger of the left hand is removed by shaving under the clinical diagnosis of SCC vs. mucoid cyst.



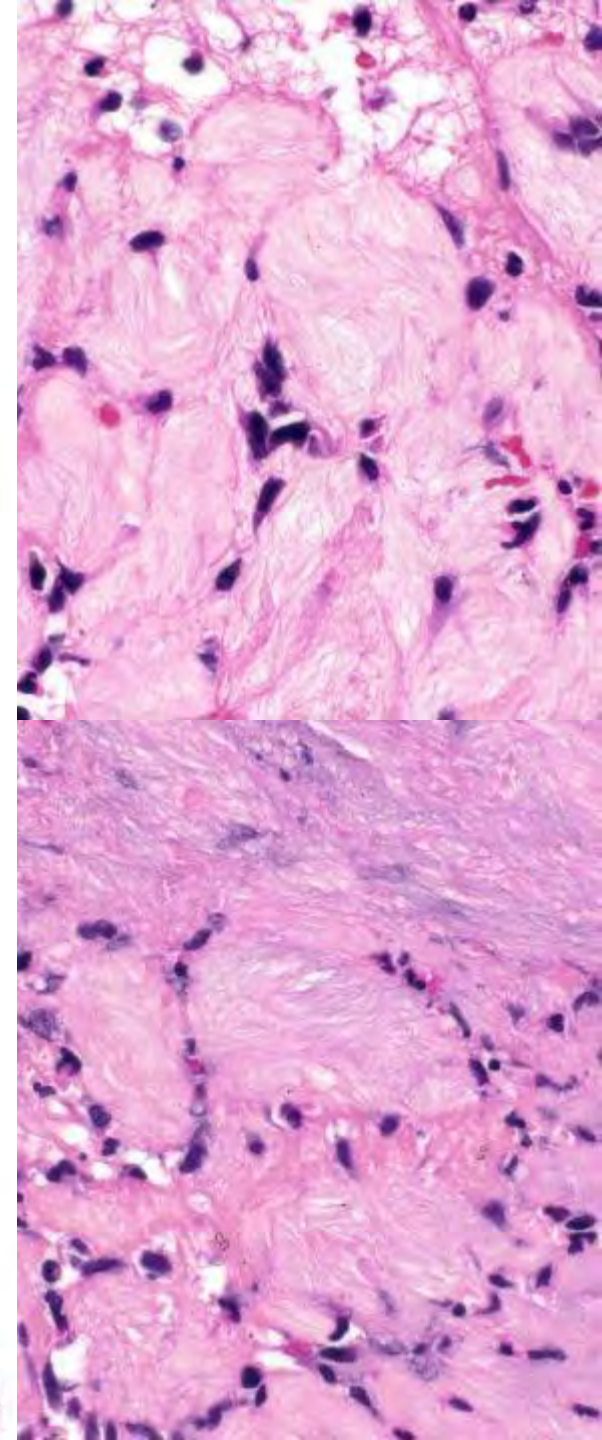




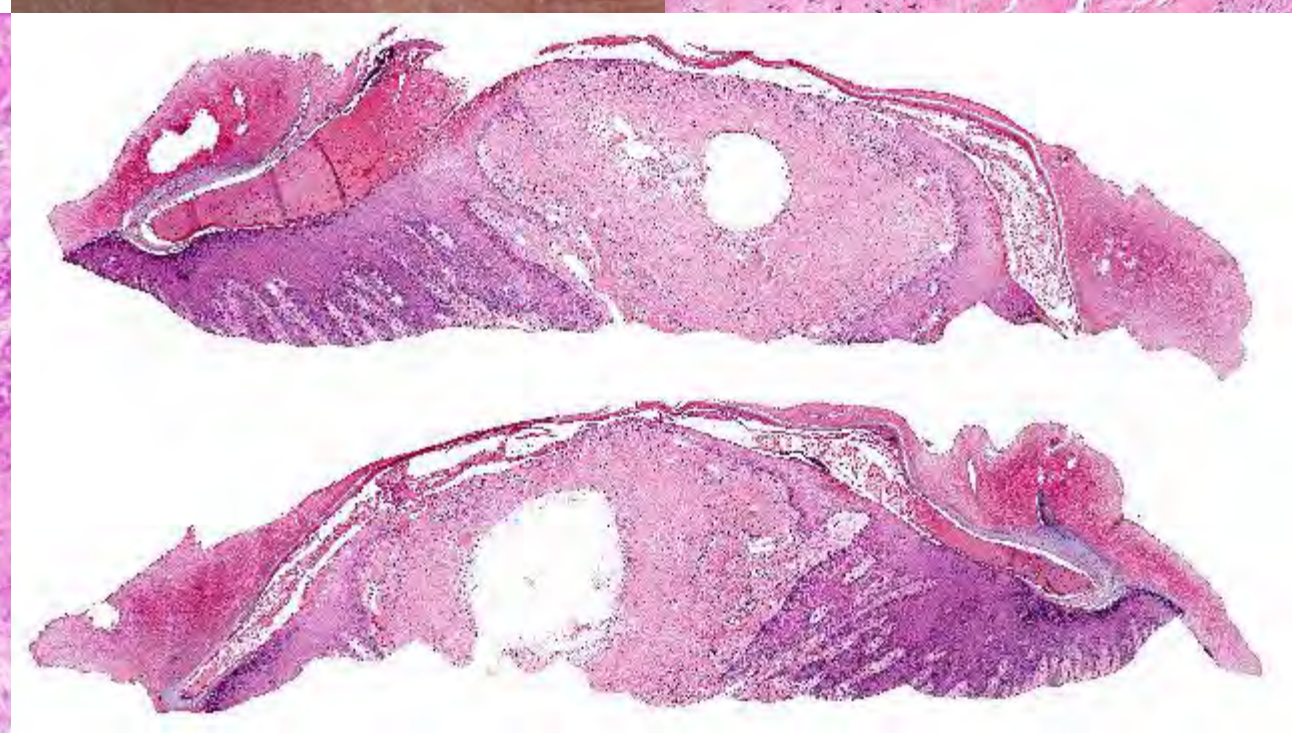
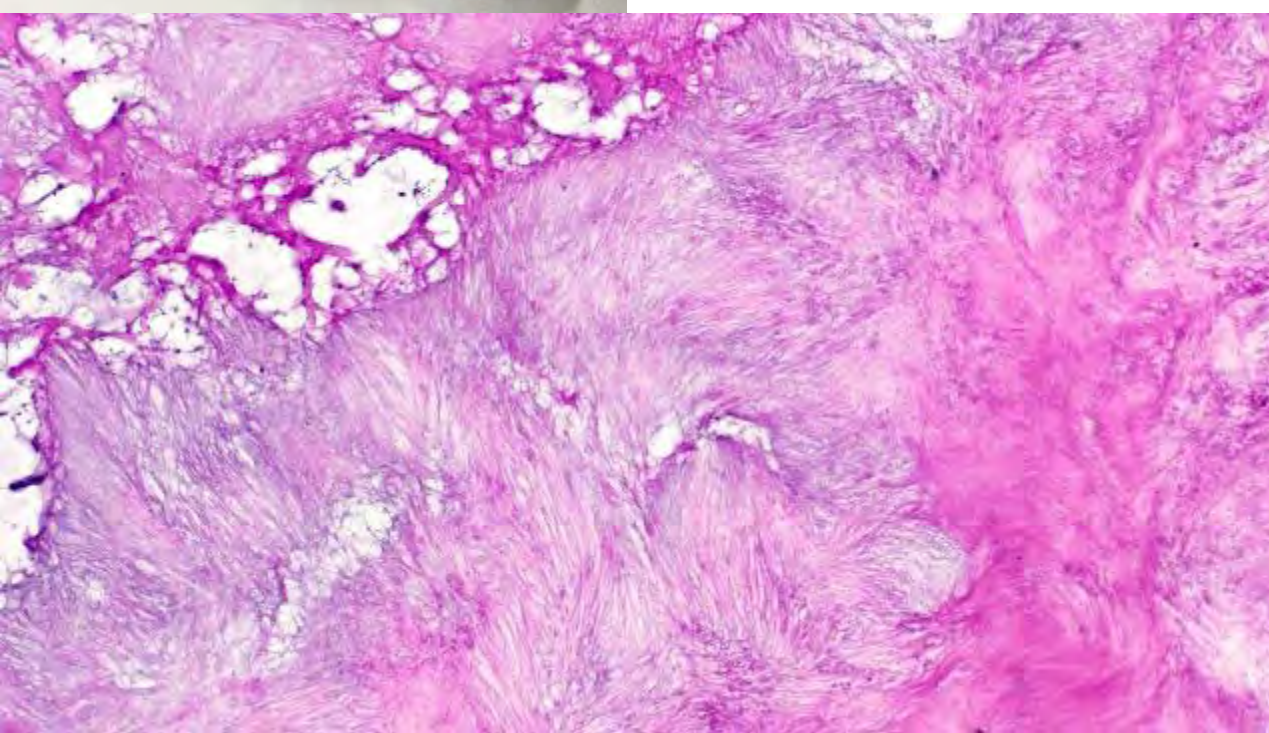
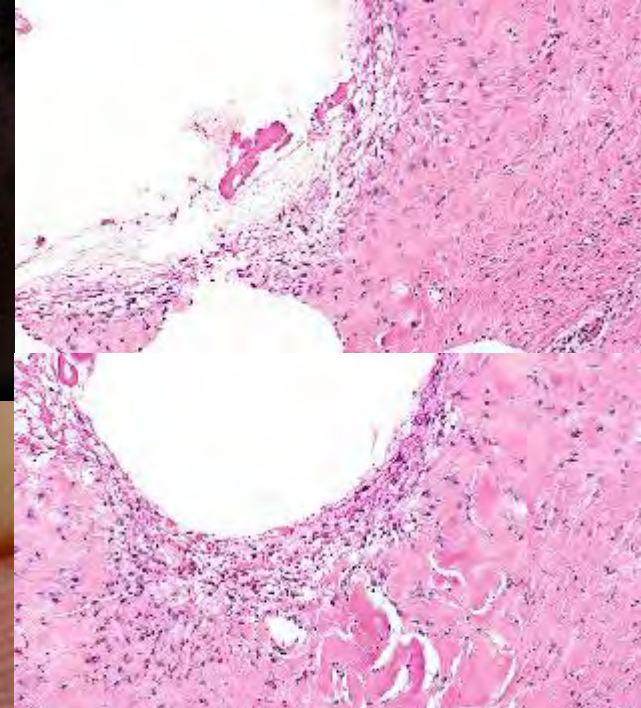
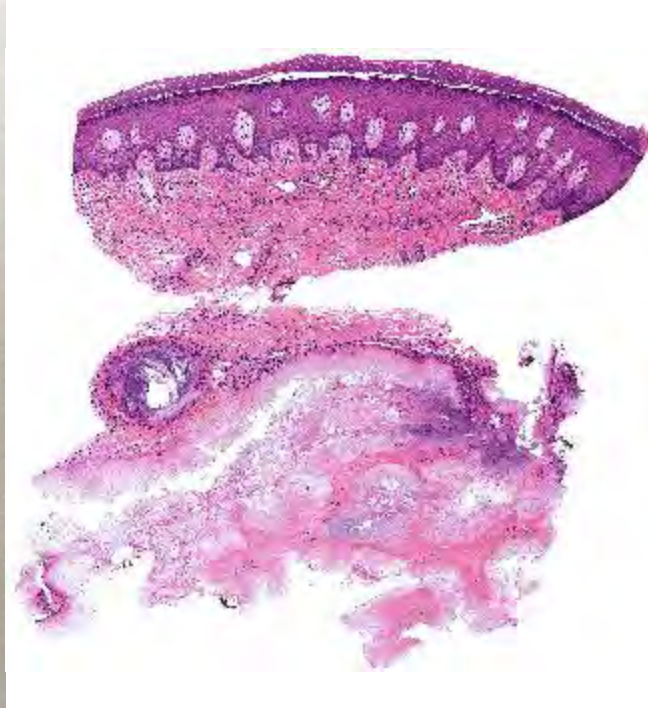


Gout tophus

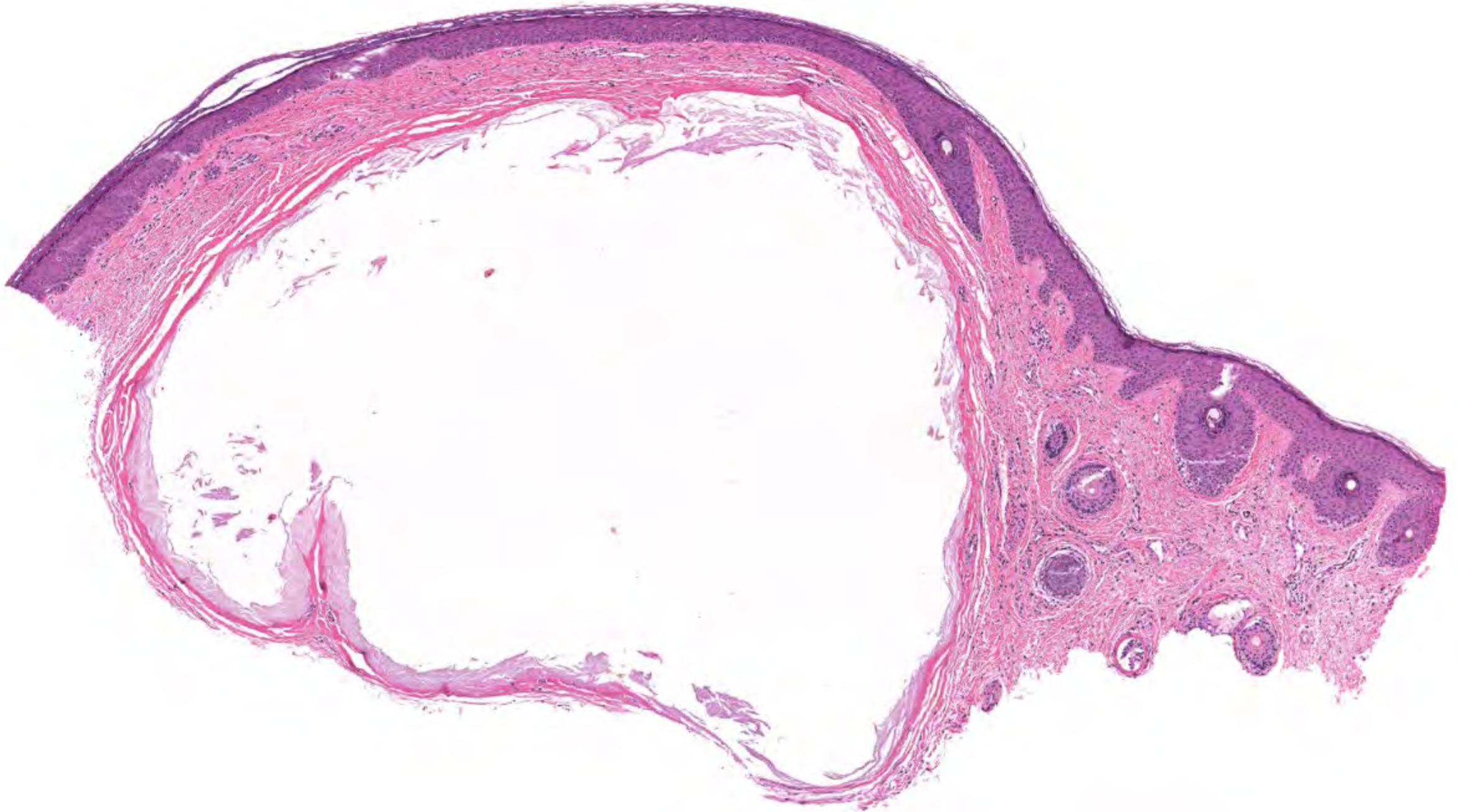
Uric acid: 8,4 mg/dL (-6,0)



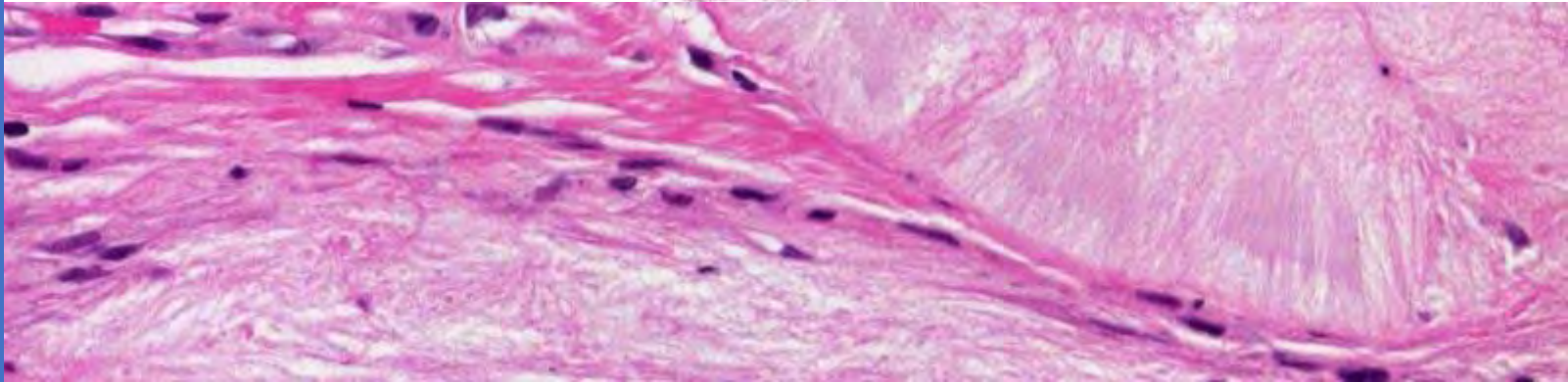
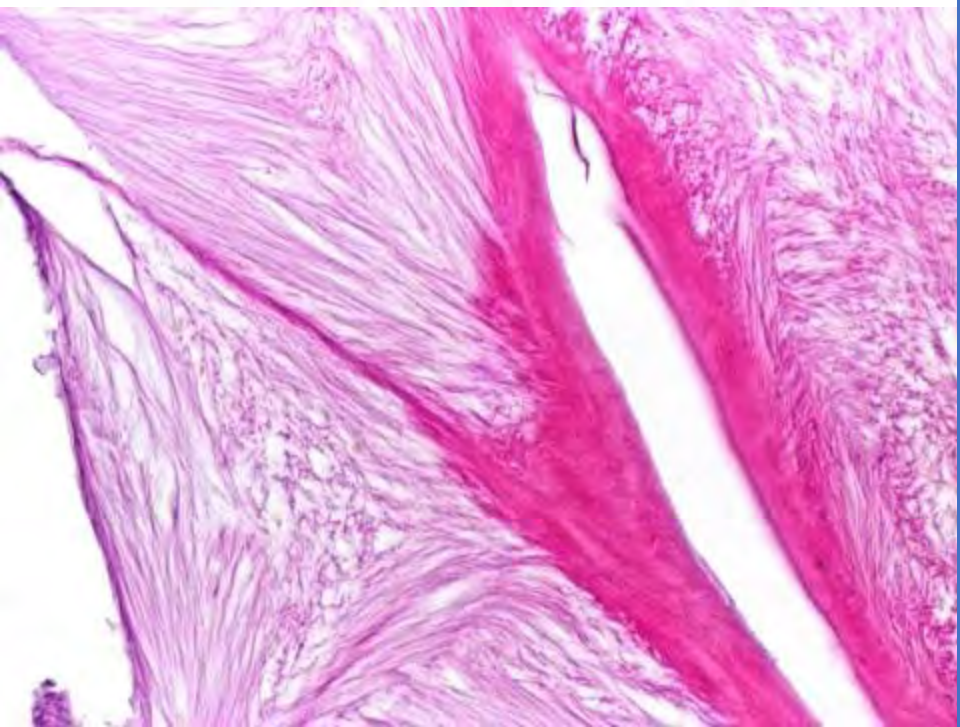
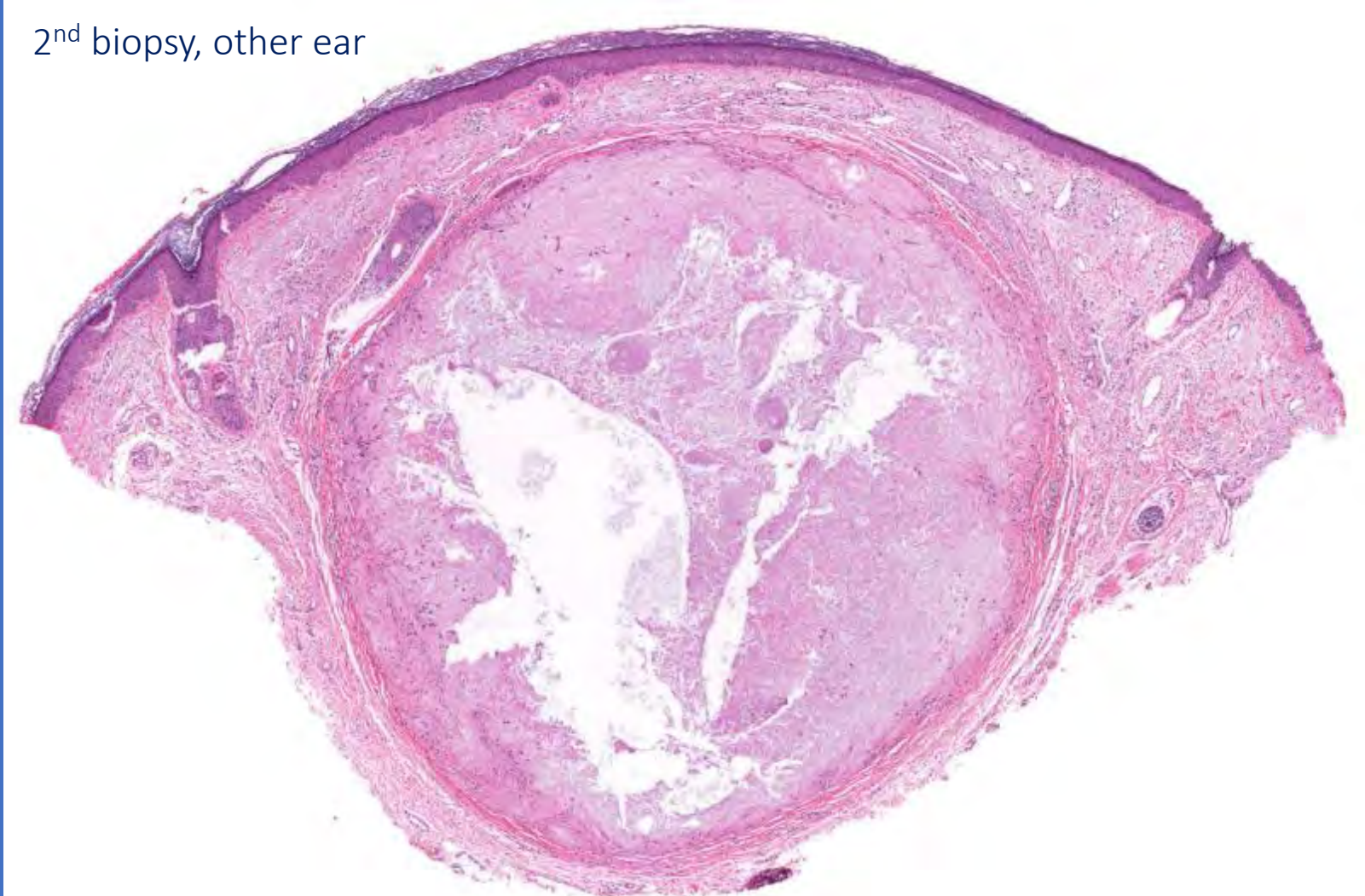
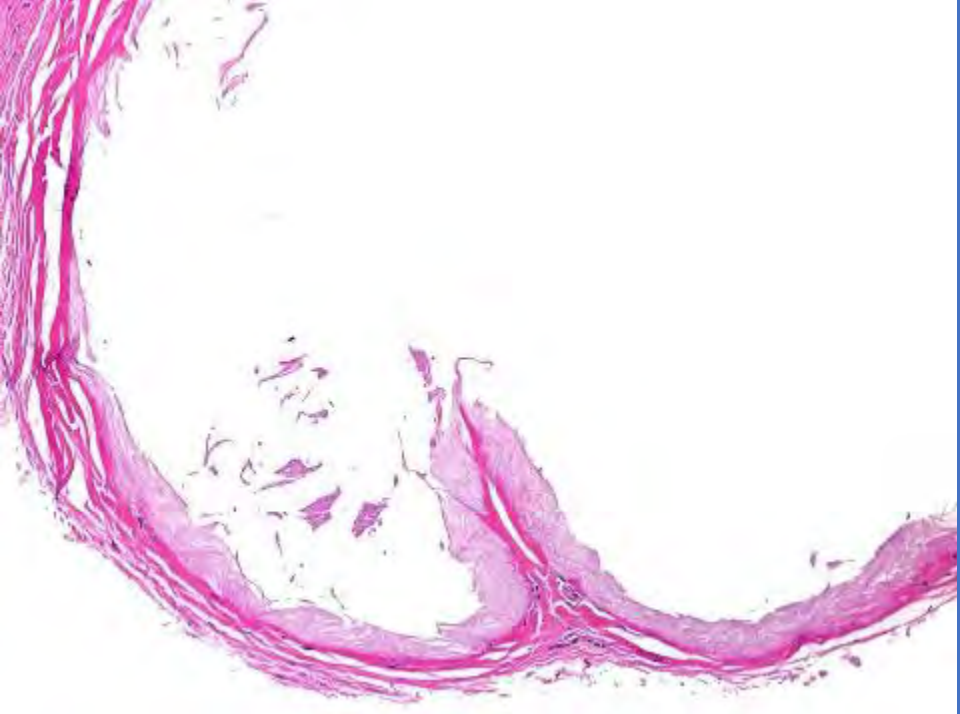


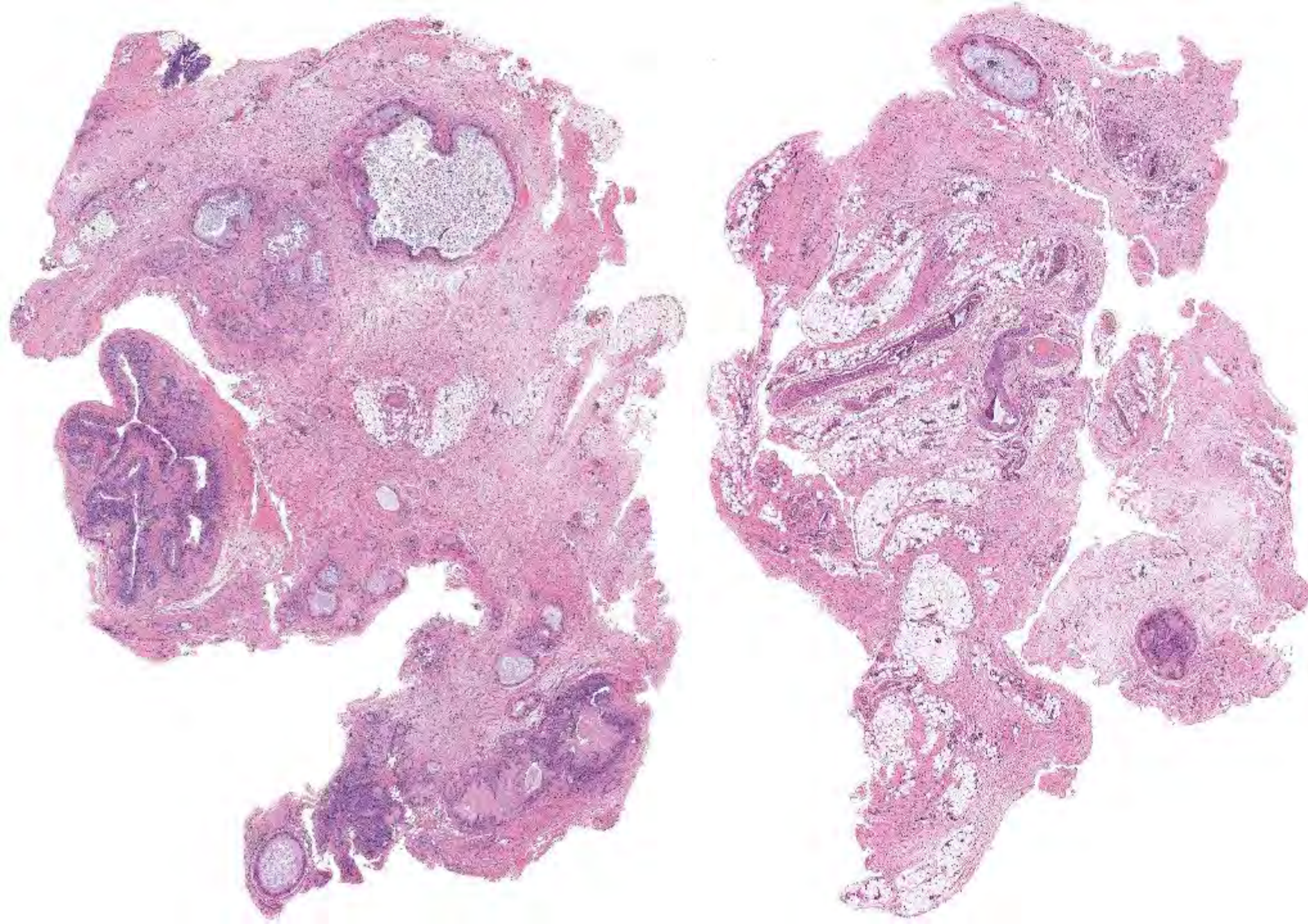


M, 71. Cysts on both ears. *Clinical diagnosis:* Cyst, pseudocyst of ear?



2nd biopsy, other ear





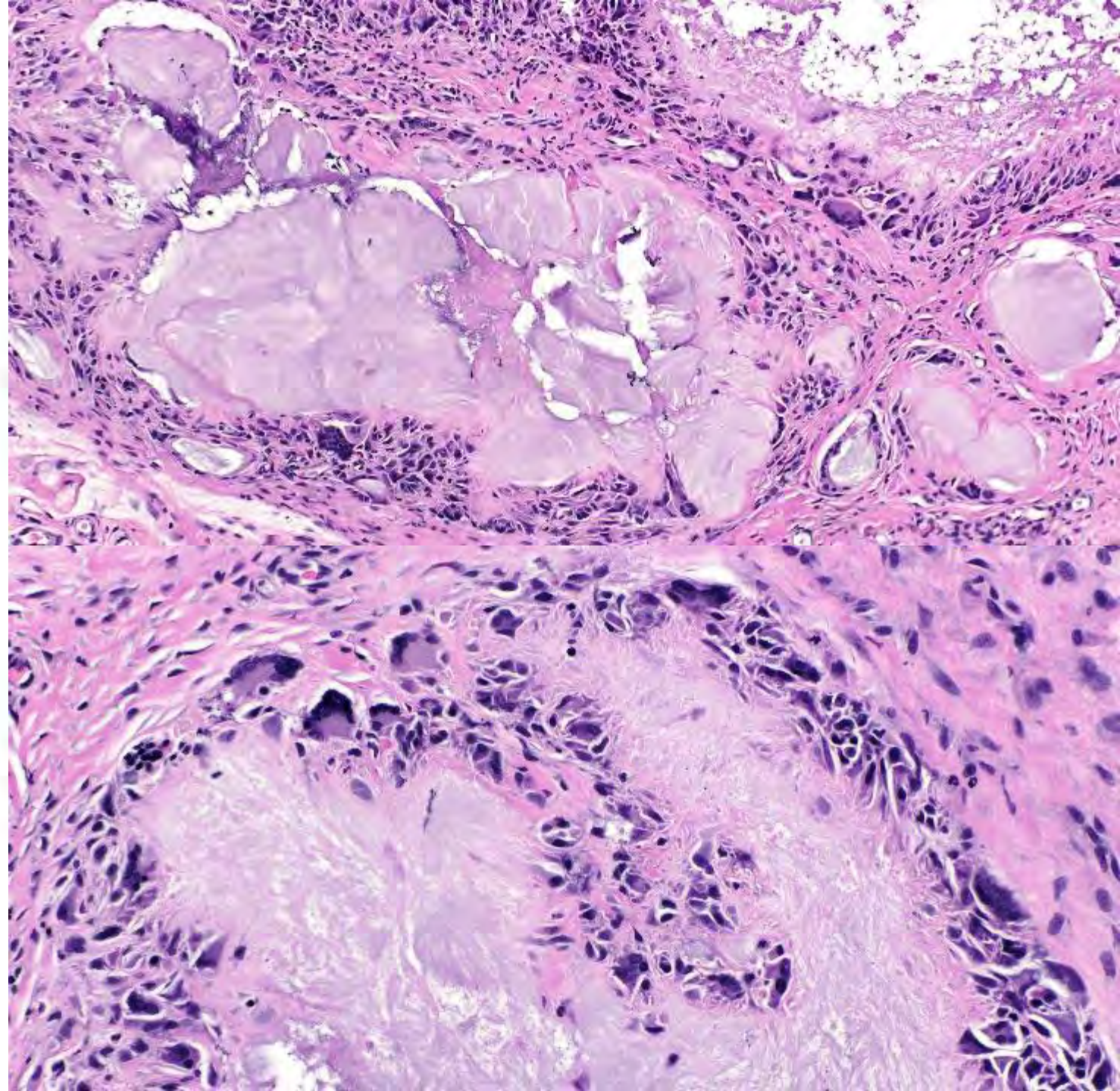
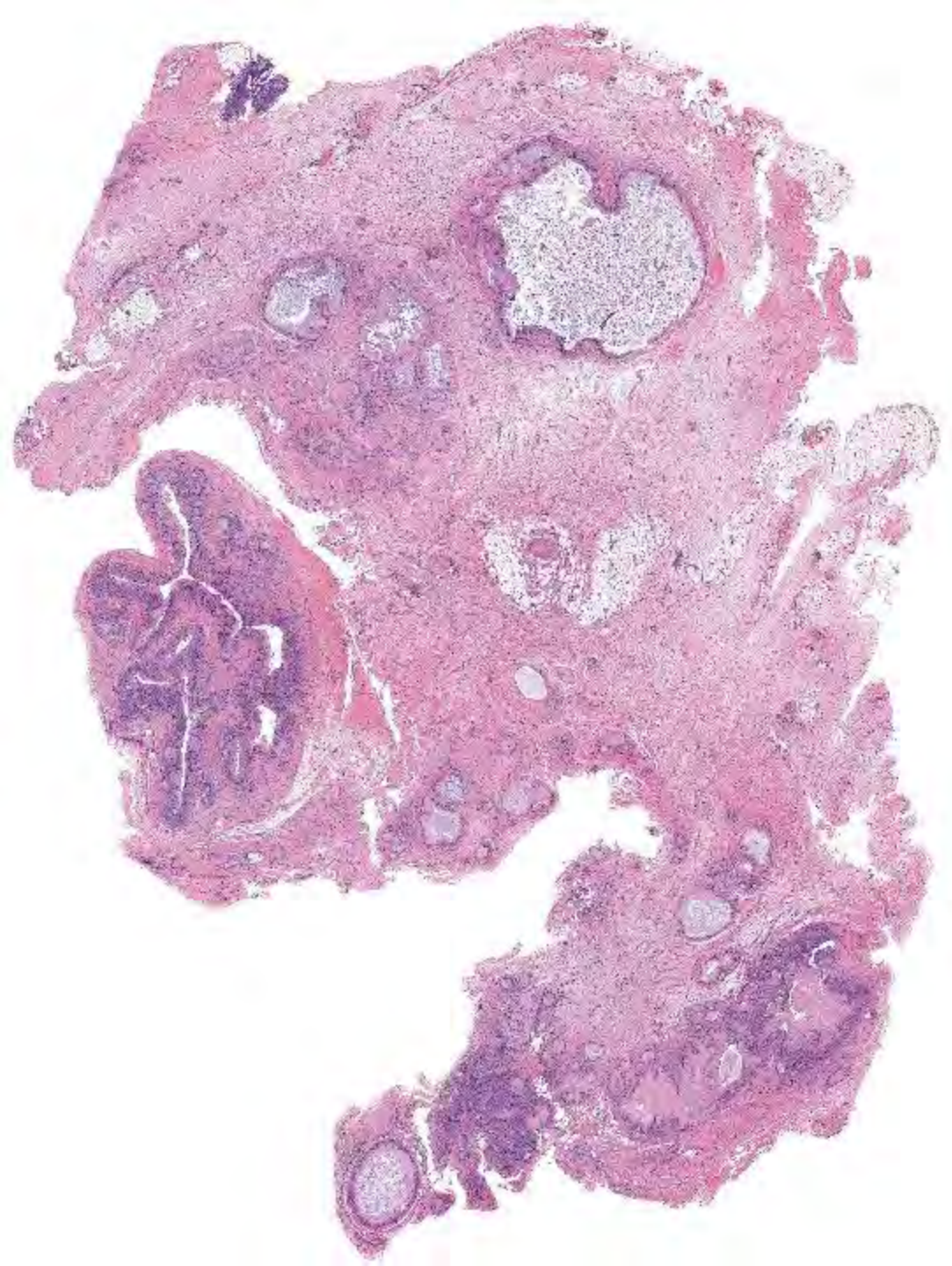
M, 54.

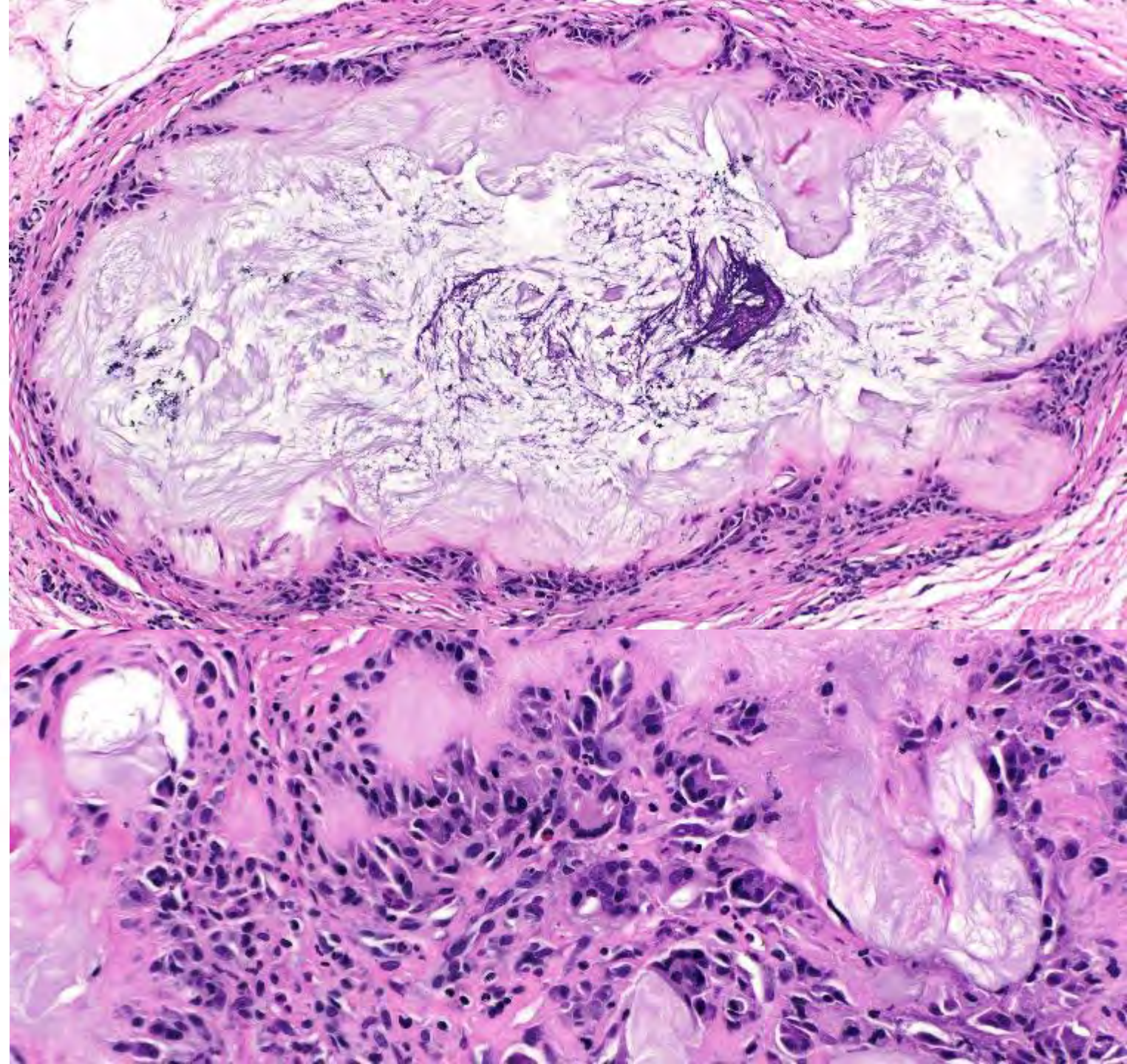
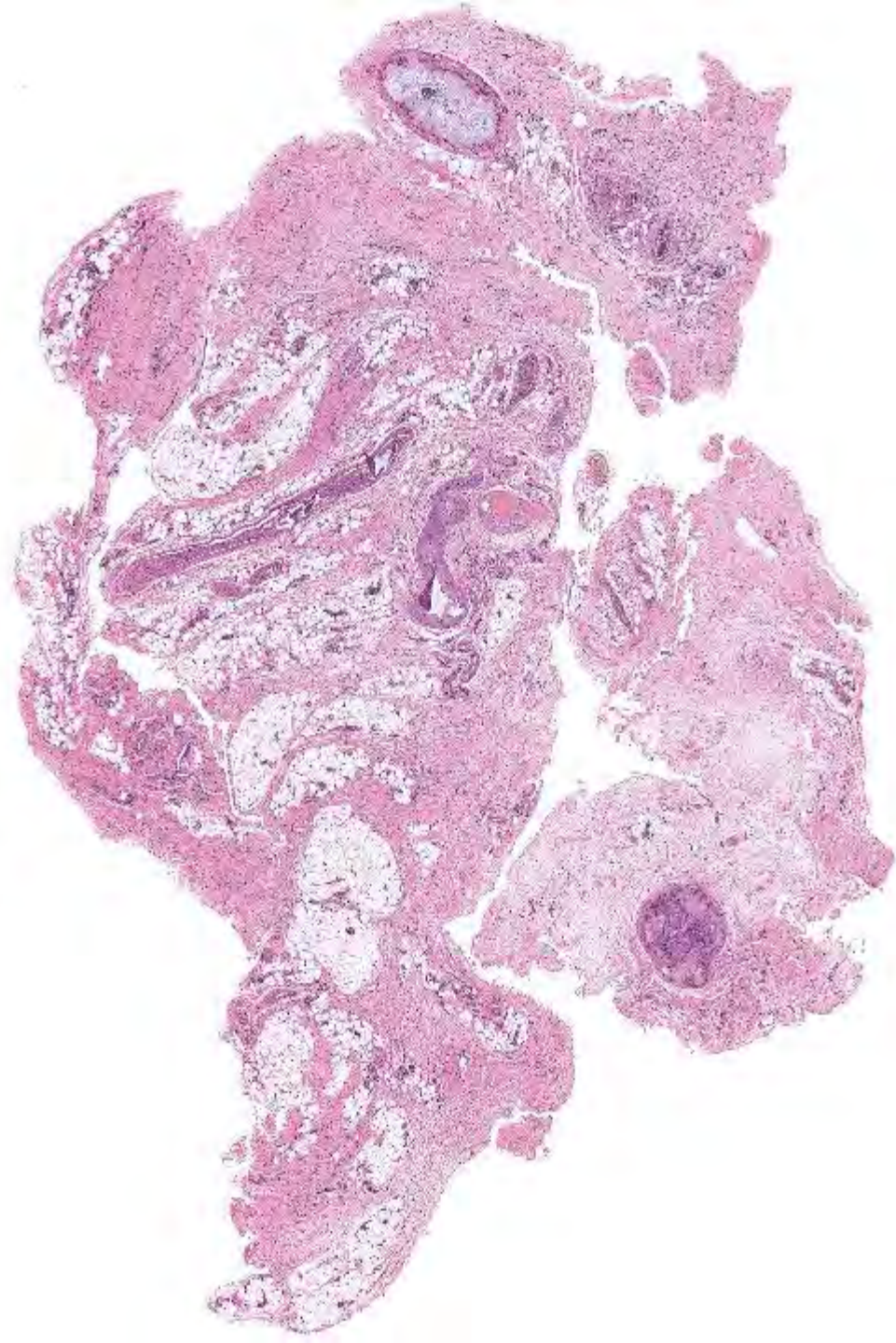
History of factor V Leiden mutation with recurrent thrombosis of the deep veins of both lower extremities.

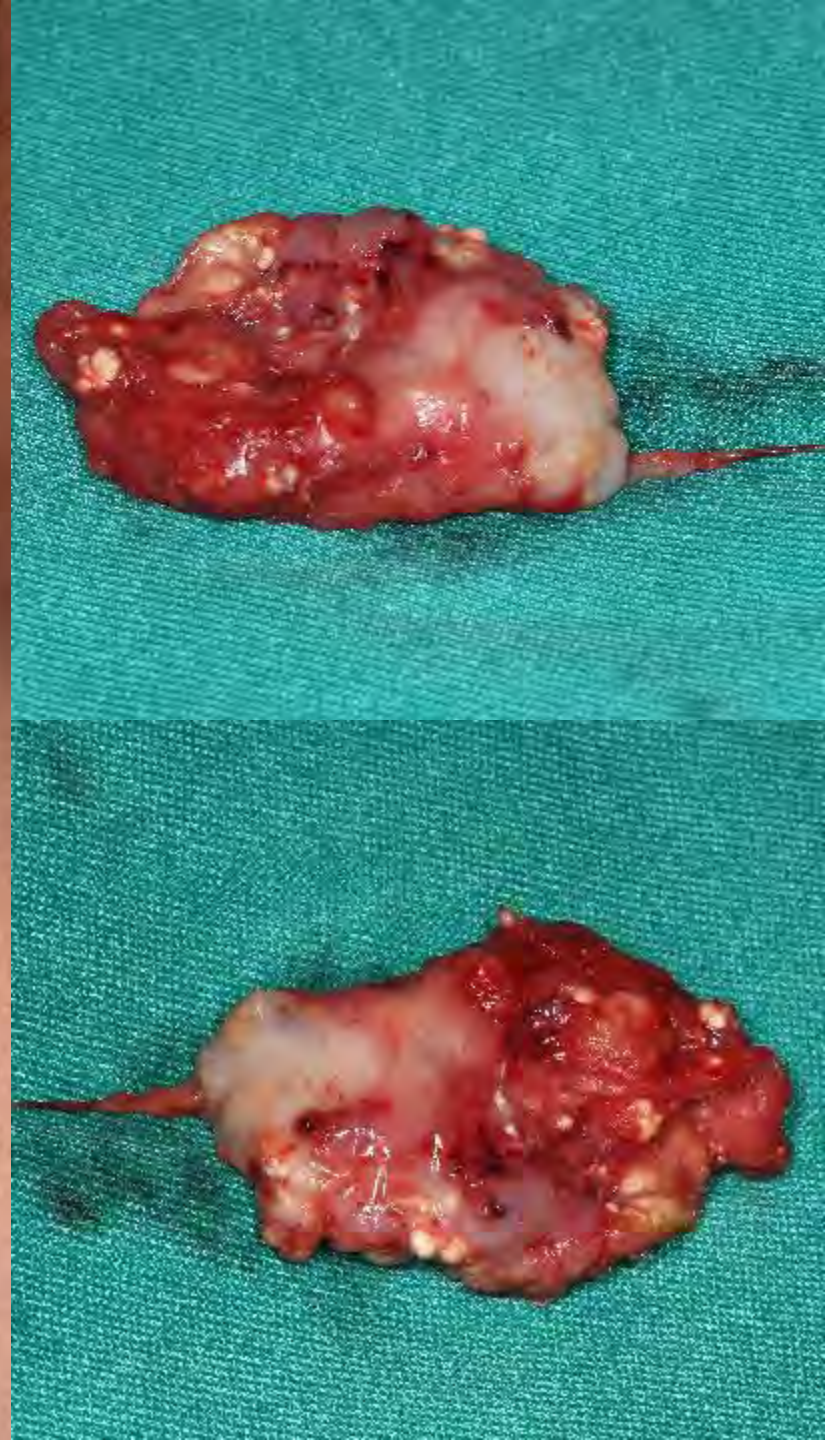
Sepsis (*E. coli*) 3 months before presentation.

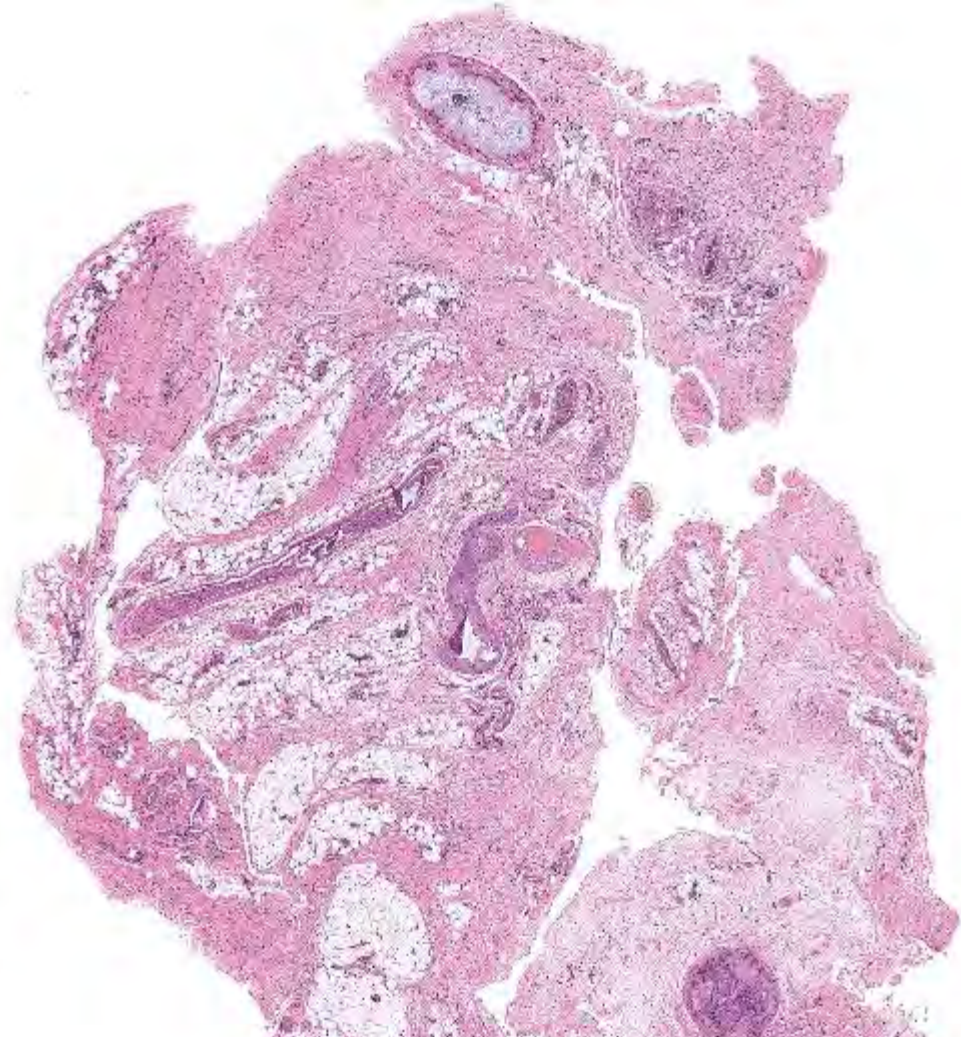
New, painful subcutaneous nodule on the right arm; soft tissue sonography showed an encapsulated thickening of the fat tissue.

The lesion is excised surgically (the surgeon reports presence of "calcifications").



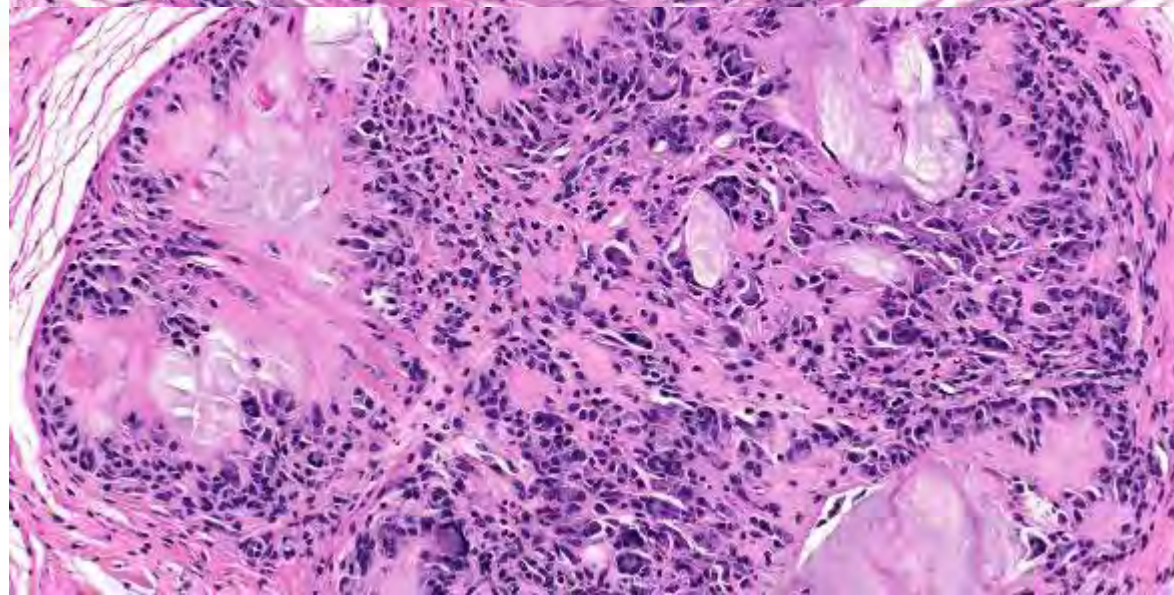
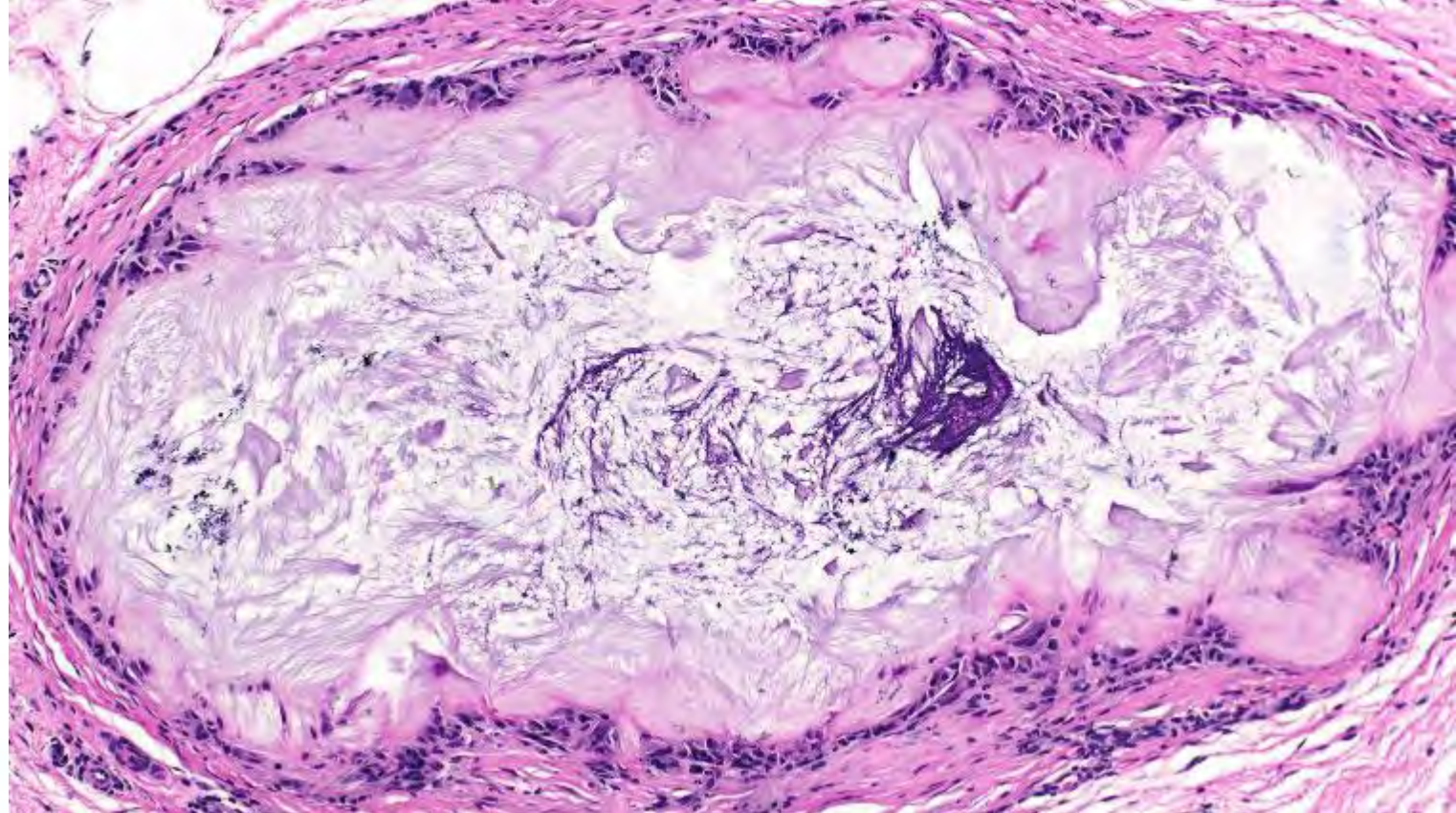






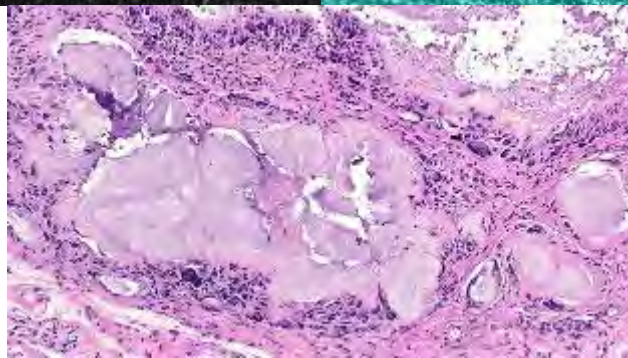
Subcutaneous gout tophus

Urea: 69 mg/dL (10-45)





"Conventional" gout tophus



Subcutaneous gout tophus

Gout Nodulosis: Widespread Subcutaneous Deposits without Gout

Antonio Iglesias G, Juan C. Loidlou, Diego L. Sorribi, Maria Peña, Humberto Lizarazo, and Emilio R. Gonzalez

Subcutaneous tophaceous deposits of monosodium urate, in the absence of arthritis, may occasionally occur as the initial manifestation of gout. In this report, we describe a 35-year-old man who presented with a 6-year history of multiple subcutaneous nodules and no history of previous articular complaints. Needle aspirations of the nodules proved them to be deposits of monosodium urate. A literature search revealed 28 other cases with a similar presentation. We propose the term "gout nodulosis" as a clinical entity at one end of the spectrum of gout to describe this group of patients.

INTRODUCTION

A number of nodular lesions have been associated with systemic illnesses, and several bear the name of illustrious individuals: Heberden's nodes in osteoarthritis (1), Osler's infectious endocarditis (2), Weiss (3) and Maynard (4) in rheumatic fever, the nodes in Parry's disease (5), and Kussmaul's in polyarteritis nodosa (6). Rheumatoid nodules were investigated by

Storages in 1763 (7), Chomel in 1813 (8), Protop in 1843 (9), and Jaccoud in 1870 (10).

In 1862, William Osler (11) noted the clinical characteristics that distinguish the acute rheumatism associated with rheumatic fever from chronic rheumatism. Subsequently, Haysorth (12) classified "rheumatism" into 2 different entities: acute rheumatism or rheumatic fever, gout, chronic rheumatism, and "nodulosis of the joints." In 1975, Girschberg et al (13) first used the term "rheumatoid nodulosis" to describe a group of patients with rheumatoid arthritis, minimal synovitis, positive rheumatoid factor, a benign clinical course, and subcutaneous nodules pathologically characteristic of rheumatoid nodules.

In the present report, we call attention to the clinical presentation of a 35-year-old male with a 6-year history of arthralgias and multiple subcutaneous tophaceous deposits, and who apparently had never experienced episodes of acute arthritis. We propose the term "gout nodulosis" to describe this clinical presentation at one end of the spectrum of hyperuricemia and gout.

A review of the literature revealed 28 previously described cases of gout with tophaceous deposits as the initial manifestation of the disease (14-27).

Case report. A 35-year-old man presented with a 6-year history of gradually developing, multiple, painless, subcutaneous nodules over the knees, elbows, wrists, small joints of the hands, and ankle joints. He had also experienced occasional arthralgias. However, he denied having any episodes of acute articular inflammation. There was no history of first metatarsophalangeal (MTP) joint involvement or podagra. The patient's personal and family histories were unremarkable; in particular, there was no family history of gout.

Table 1. Tophaceous deposits as the initial manifestation of gout*

Case	Ref./Year	Age	Sex	Localization
1	14/1965	NA	NA	NA
2	15/1977	72	F	NA
3	16/1977	69	F	Legs
4	17/1980	63	F	Fingers, elbows, feet
5	18/1981	67	F	Fingers
6	19/1982	37	F	Breast
7	20/1983	46	M	Ears
8	20/1983	69	M	Fingers
9	20/1983	70	M	Fingers, elbows, feet
10	20/1983	75	M	Fingers
11	20/1983	72	F	Fingers
12	21/1985	89	F	Fingers
13	21/1985	NA	F	Fingers
14	21/1985	NA	M	Fingers
15	22/1985	74	F	Fingers
16	23/1985	NA	NA	Prepatellar
17	24/1988	38	M	Toes
18	25/1988	81	F	Fingers
19	25/1988	80	F	Fingers
20	25/1988	76	F	Fingers
21	25/1988	86	F	Fingers
22	26/1990	76	F	Fingers
23	27/1992	77	M	Toes
24	27/1992	78	F	Fingers
25	27/1992	68	M	Fingers
26	27/1992	74	M	Elbow
27	27/1992	91	M	Toes
28	27/1992	73	M	Elbows/toes
29	Present report	35	M	Fingers, hands, wrists, elbows, knees, ankles

* F = female; M = male; NA = not available.

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Address correspondence to Dr. Sorribi at: 3415 Blvd. Elbow, number 2600, Gregorio Marañón Hospital, Calle Padre Sison, CP Atlanta, GA 30303.

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IMAGES IN CLINICAL MEDICINE

Gout Nodulosis



A 70-YEAR-OLD MAN PRESENTED FOR EVALUATION OF TENDER MASSES over each elbow that had been gradually enlarging for several years. There was no history of joint pain. Physical examination revealed a large, erythematous, fluctuant, subcutaneous mass covering each olecranon process (Panel A, lateral view of the right arm). On laboratory examination, the serum uric acid level was normal (3.4 mg per deciliter [202 mmol per liter]; reference range, 2.0 to 7.0 [120 to 420]), but the serum C-reactive protein level was elevated (105 mg per liter; reference range, 0 to 5). There was no evidence of erosive arthritis on plain radiographs of the elbows. Biopsy of each mass revealed fibrovascular tissue with multinucleated giant cells and calcifications. Monosodium urate crystals were identified on polarized microscopical examination of the biopsy specimen (Panel B, without red compensator; and Panel C, with red compensator). The patient received a diagnosis of gout nodulosis, a rare presentation of gout in which nodular tophi form in the absence of gouty arthritis. Treatment with allopurinol did not result in any clinically significant reduction in symptoms on repeat examination 6 months later. The patient declined to undergo surgical excision of the lesions.

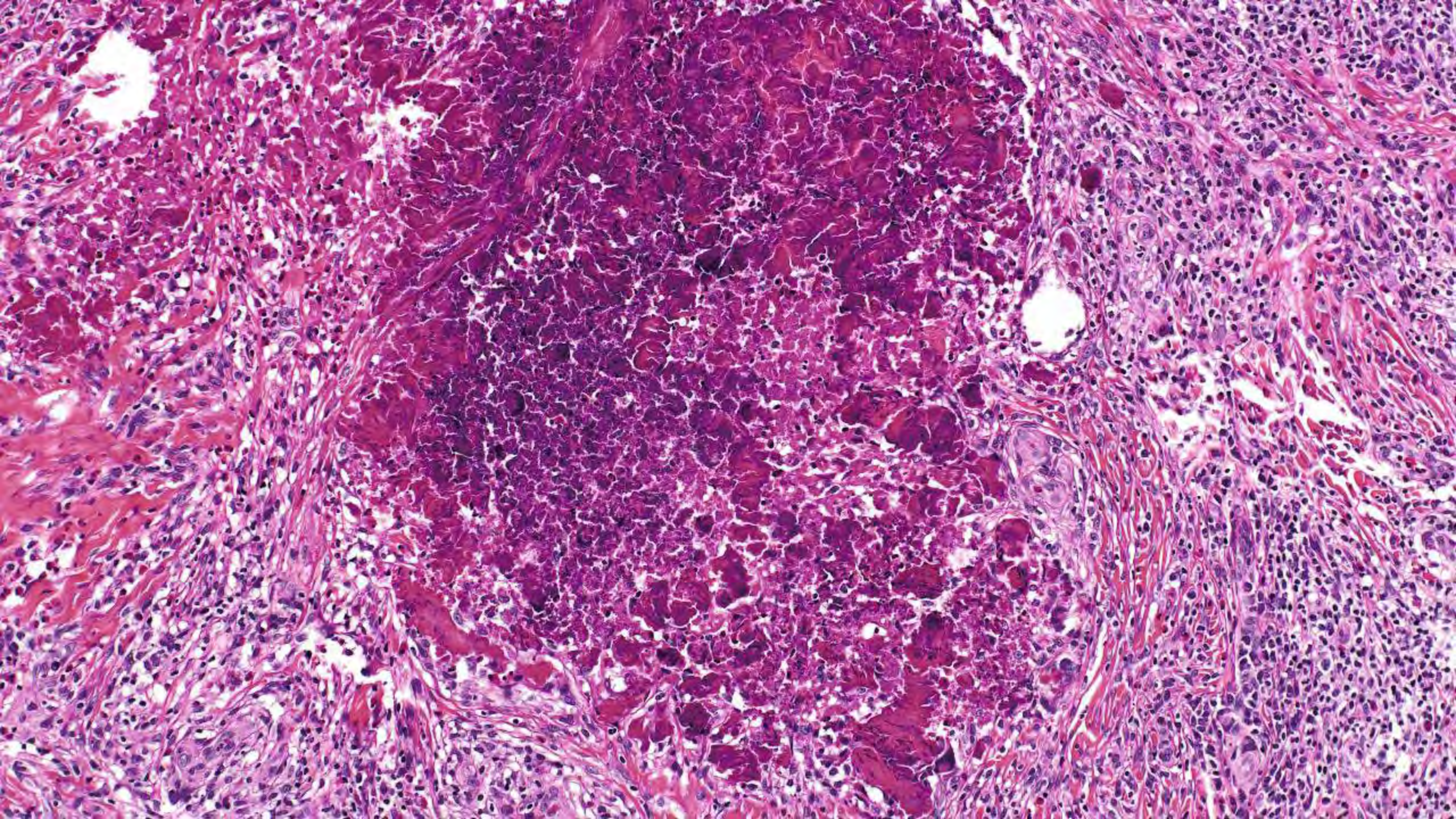
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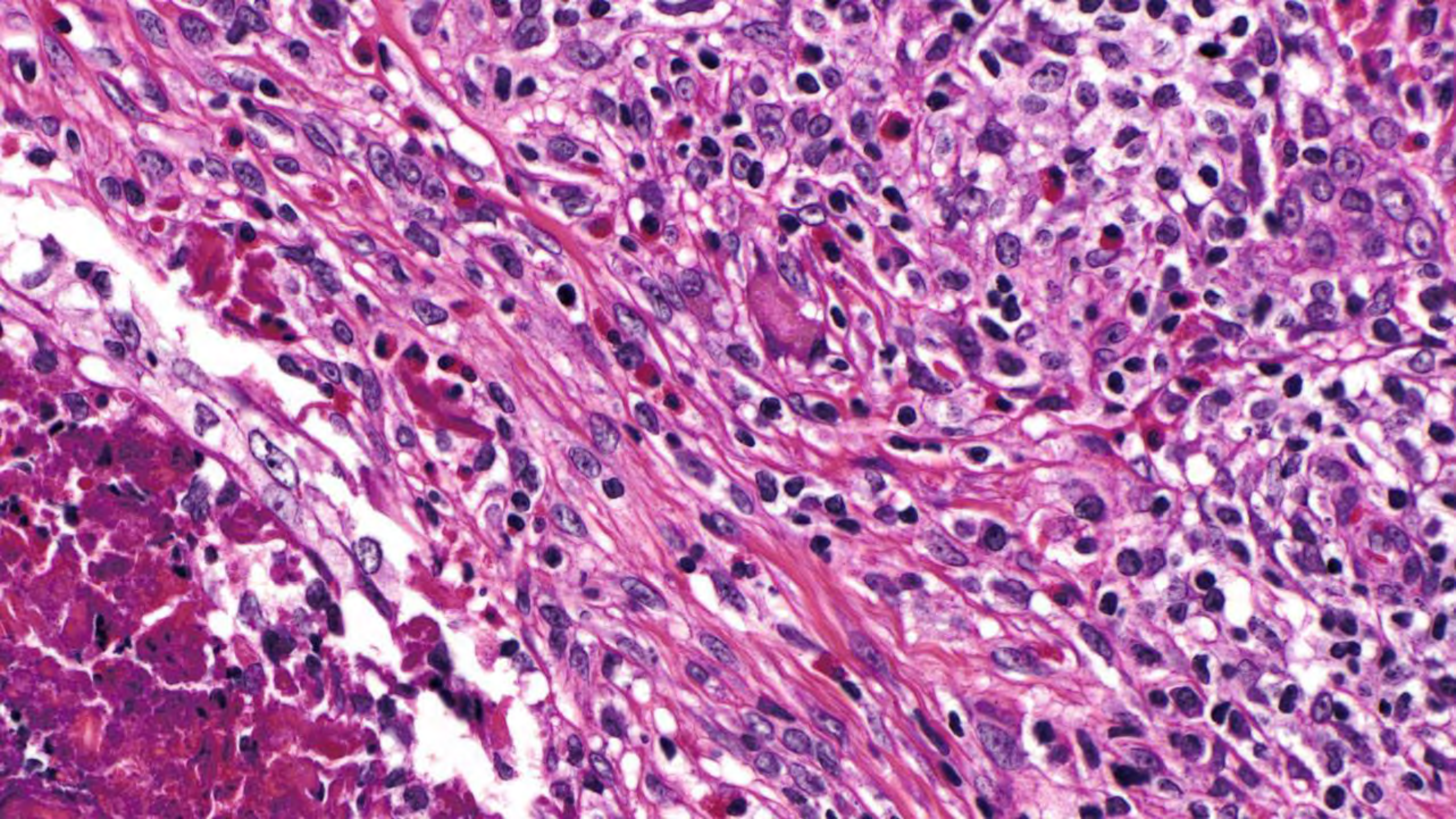
Southern Illinois University School
of Medicine
Springfield, IL

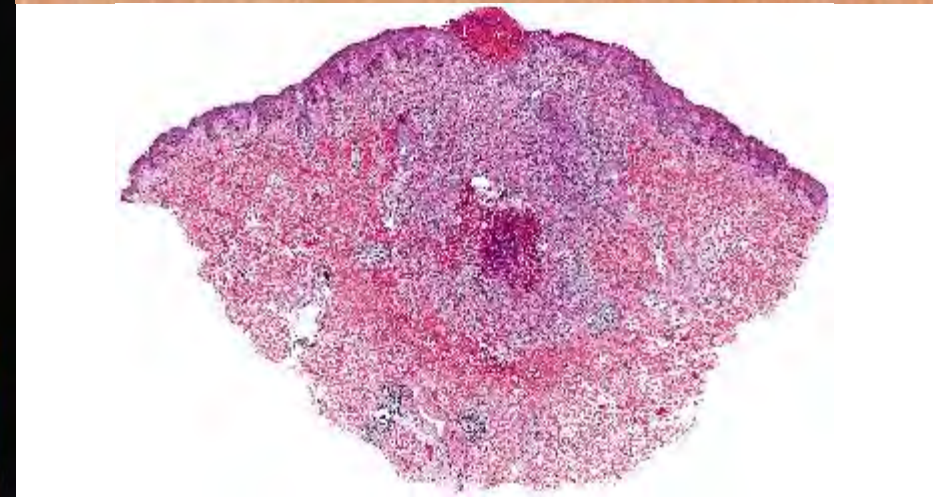


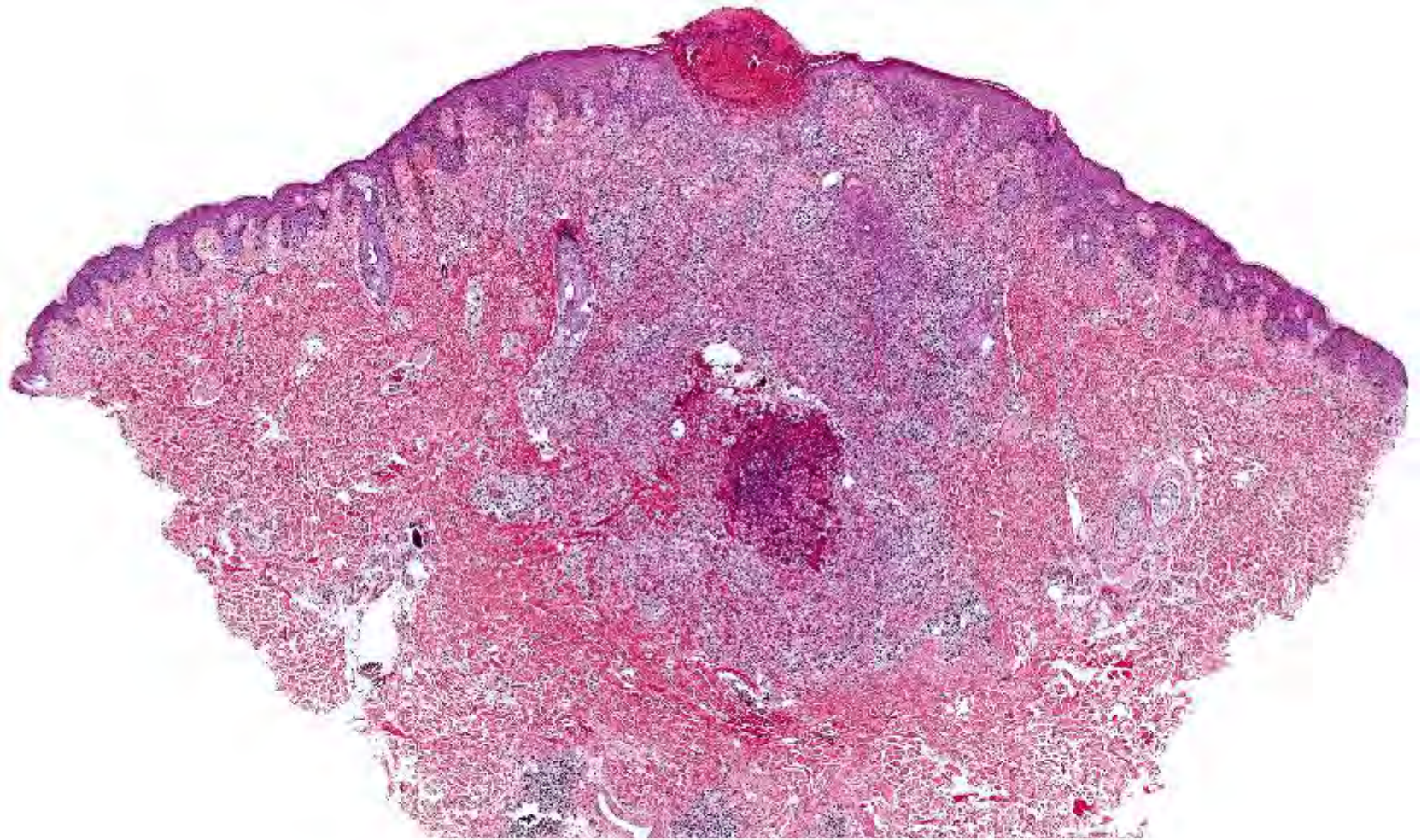
Case 25

M, 6. Solitary small nodule on the back for 3 months, according to the mother starting after an insect bite at the same site.

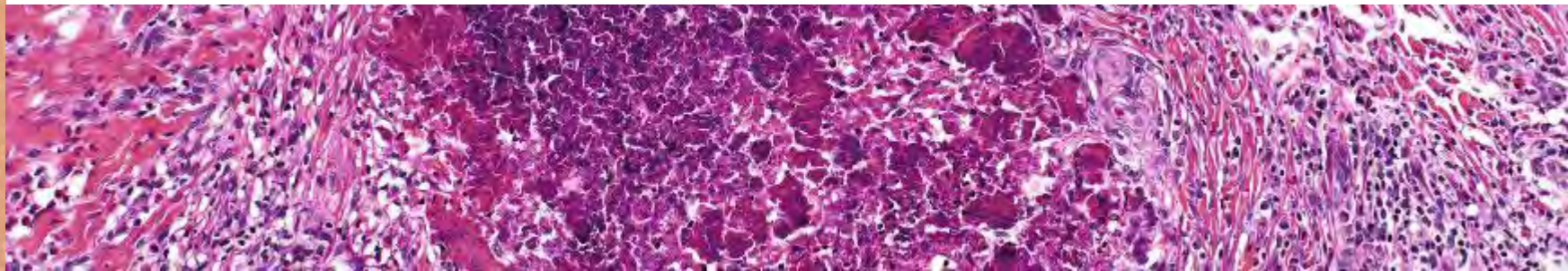


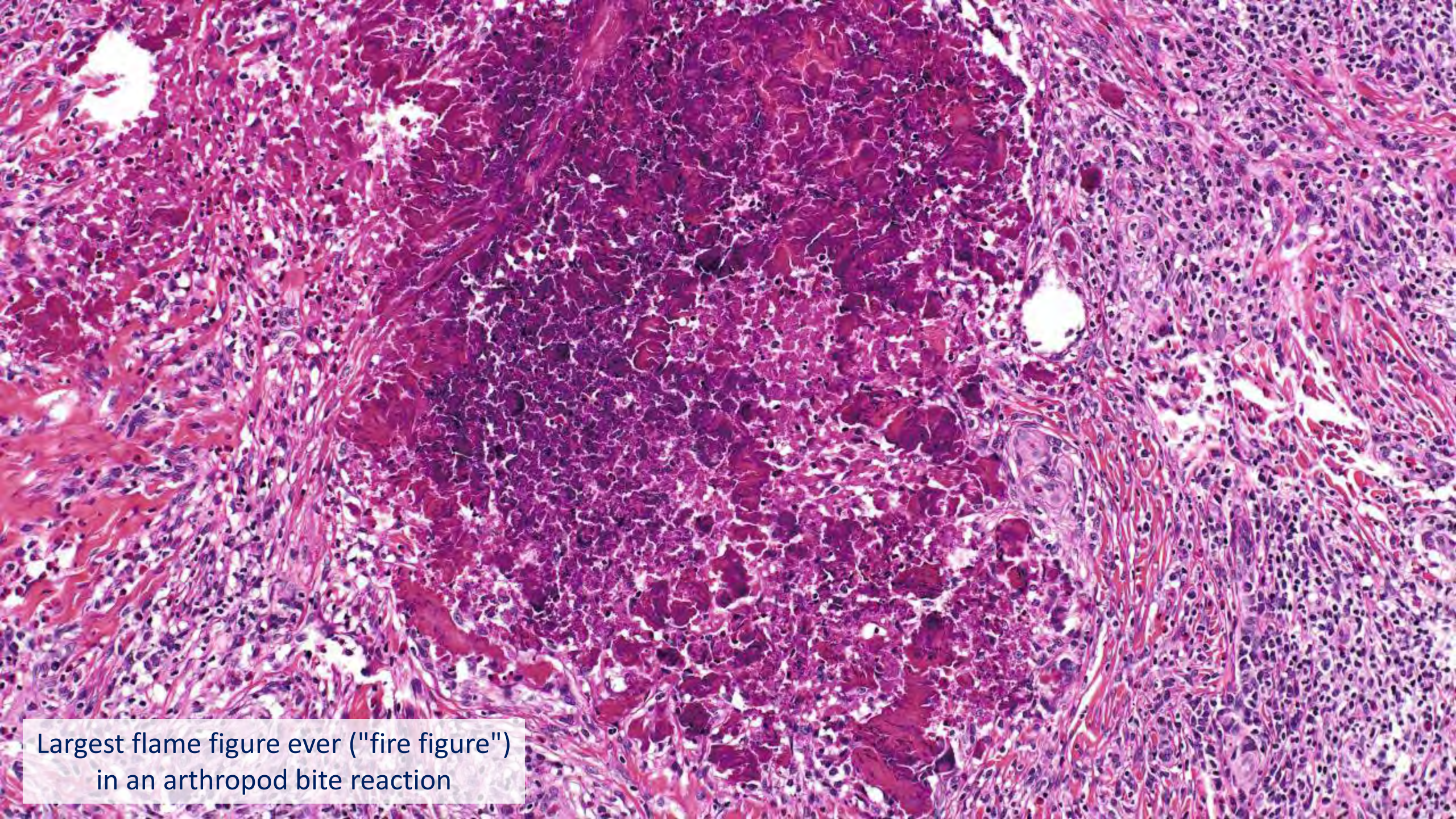






Arthropod bite reaction





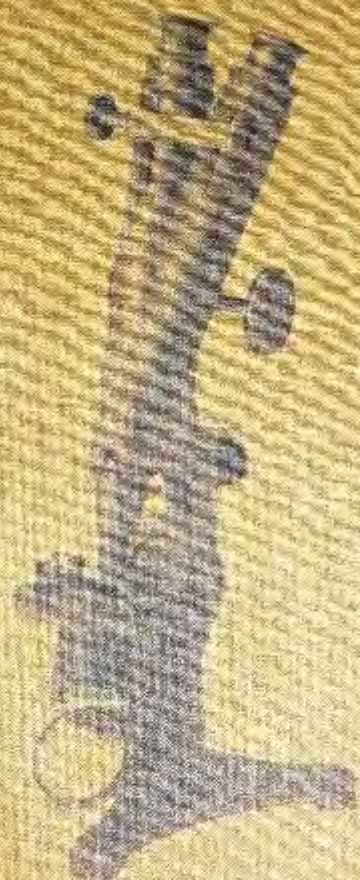
Largest flame figure ever ("fire figure")
in an arthropod bite reaction

HISTOLOGIC DIAGNOSIS OF INFLAMMATORY SKIN DISEASES

An Algorithmic Method Based On Pattern Analysis

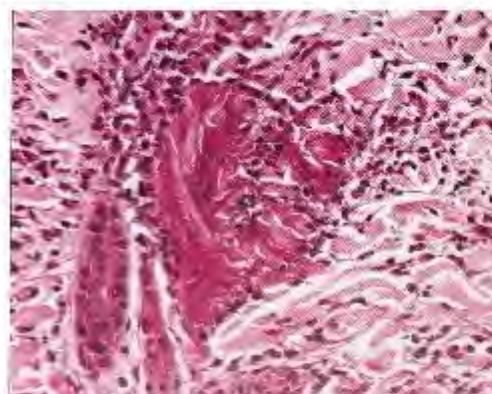
THIRD EDITION

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ALMUT BOER, M.D.
BRUCE BENNIN, M.D.
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2005

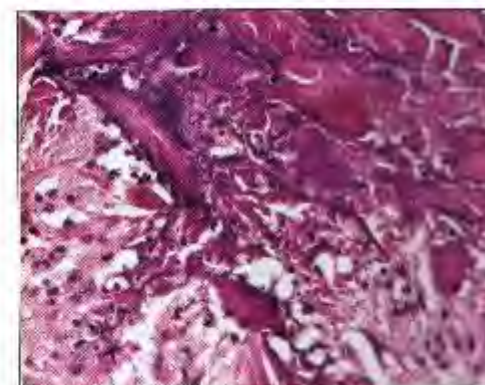
"FLAME FIGURE(S)"



Granules of eosinophils disposed in clusters around one or more collagen bundles (this may show signs of degeneration (basophilic), the clusters being surrounded by histiocytocentrically. Flame figures may come into being, because eosinophils are present in a perivascular infiltrate.

- Edema of the papillary dermis, lymphocytes in a perivascular infiltrate, and many eosinophils in the interstitium
 - Lymphocytes, eosinophils, and sometimes plasma cells in a nodular and interstitial infiltrate
 - Worms or larvae in the dermis and/or subcutaneous fat
 - Epithelioid histiocytes, in company with eosinophils and neutrophils, in interstitial and palisaded array in the lower two thirds of the reticular dermis and sometimes in septa of the subcutaneous fat
 - Subepidermal blister, eosinophils in an edematous papillary dermis, and eosinophils and lymphocytes in at least the upper half of the reticular dermis
 - + Neutrophils and nuclear "dust" of neutrophils in a perivascular and interstitial infiltrate; fibrin in wall of venules
 - + Widely dilated muscle- and mucin-containing vessels in the dermis and/or subcutaneous fat with prominent endothelial cells that protrude strikingly into lumina and that house a vacuole in their cytoplasm
 - + Lymphoid follicles throughout the dermis and subcutis
- Insect "bite" (including "Wells' syndrome")
 - Nodular scabies
 - Helminthiasis
 - Interstitial granulomatous dermatitis with arthritis
 - Bullous pemphigoid/Herpes gestationis
 - Leukocytoclastic vasculitis
 - Angiolymphoid hyperplasia with eosinophilia
 - Kimura's disease

"CHURG STRAUSS GRANULOMA": Neutrophils, nuclear "dust" of neutrophils, and, sometimes, eosinophils in a discrete locus of degenerated collagen in the reticular dermis, histiocytes in palisaded array at the periphery tending to join later, a constellation of findings found especially in patients with rheumatoid arthritis or lupus erythematosus. Small infarcts consequent to the effects of anti-cardiolipin antibody may be responsible for the distinctive changes.



CHURG-STRAUSS SYNDROME: DIAGNOSIS SUSPECTED BY CUTANEOUS BIOPSY

Luis Requena, MD, José Luis Sarasa, MD,* Lucía Martín, MD, M^a Carmen Fariña, MD,
Enric Piqué, MD, and Mercedes Olivares, MD

A 47-year-old woman with a long history of asthma and allergic rhinitis developed erythematous papules, some of them with a central crust or ulcer, on the extensor aspects of the fingers, elbows, knees, palms, and buttocks. Histopathologic examination of sections of a biopsy specimen taken from a papule on a buttock revealed "necrotizing extravascular granulomas," marked infiltration of the dermis with eosinophils, and no vasculitis. These findings, in conjunction with laboratory studies and meningiographic exploration, led us to a diagnosis of allergic granulomatosis of Churg and Strauss. Skin manifestations of Churg-Strauss syndrome often are not specific for that condition, but at times, such as in the lesion of this patient, they are.

Allergic granulomatosis, known also as Churg-Strauss syndrome, is a systemic disorder characterized by asthma, transient pulmonary infiltrates, eosinophilia, and systemic vasculitis. The original description by Churg and Strauss in 1951 was based on study by them of material derived mostly from autopsies.¹ The authors considered the condition to be distinct from periarthritis nodosa and termed it "allergic granulomatosis" because of what they deemed to be characteristic histopathologic findings of an "allergic granuloma" in different organs. They described an "allergic granuloma" in these words: "a central, eosinophilic core surrounded by radially arranged macrophages and giant cells. The eosinophilic core consisted of two elements: necrotic cells and severely altered collagen fibers."¹

Churg-Strauss syndrome is rare and the diagnosis may be difficult to make because the four cardinal clinical criteria for it may not be present together at the same time in a particular patient. Furthermore, the typical histopathologic features of an "allergic granuloma" also can be found in disparate conditions that are unrelated to Churg-Strauss syndrome.²

CASE REPORT

A 47-year-old woman with asthma for 11 years and allergic rhinitis for 5 years was admitted to the hospital for pain in the left ankle and widespread cu-

taneous lesions. Her major complaints were pain, numbness, paresthesia, and weakness in her lower limbs that caused difficulty in walking. Synovitis was diagnosed by rheumatologists. The patient was sent to the Dermatology Department because of her cutaneous lesions.

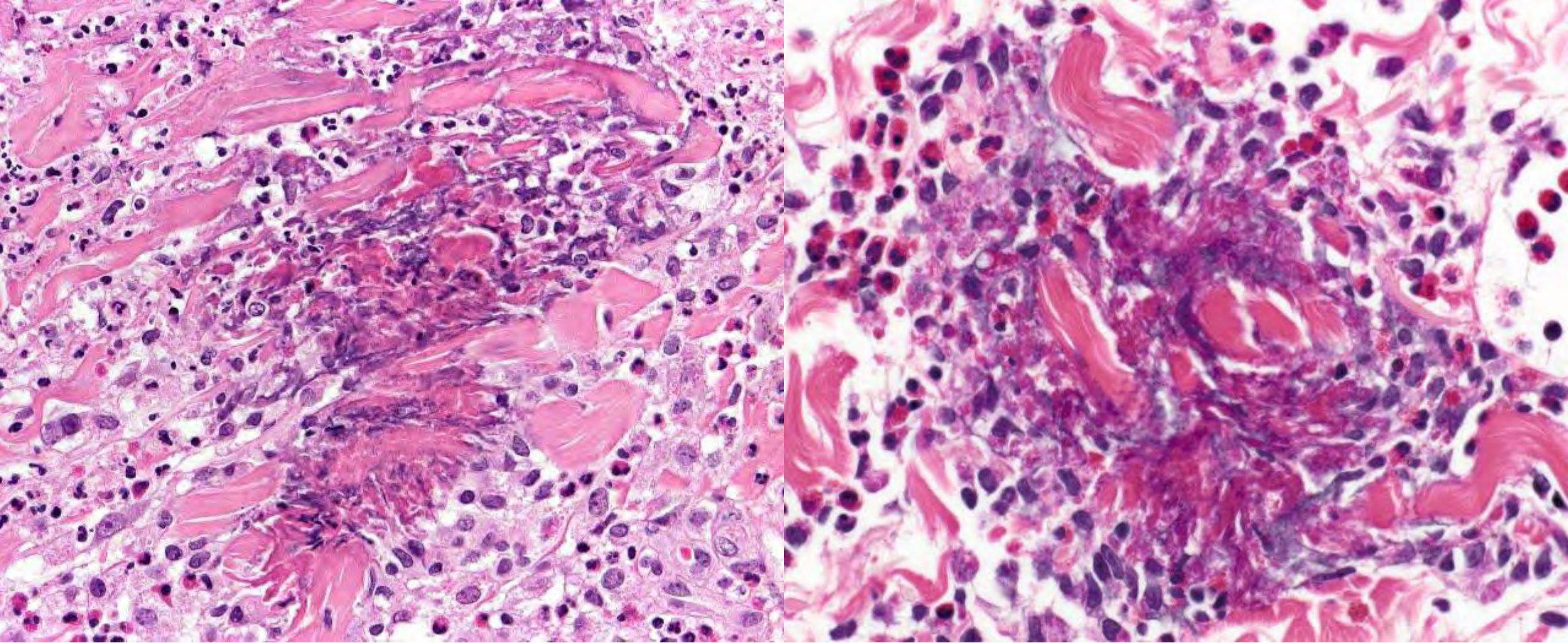
Erythematous, slightly tender, firm papules were distributed on finger pads (Fig. 1), and on palms and elbows, and vesiculobullous lesions were on the buttocks. Some of the lesions, especially those on the elbows, showed central crusts or ulcers, imparting to them an umbilicated contour (Fig. 2). The lesions varied in color from red to violaceous, and in size from 3 mm to 1 cm in diameter. Urticarial lesions on the inner aspect of both thighs (Fig. 3) resolved with hyperpigmentation. Petechiae were present on the shins and dorsal aspect of the feet (Fig. 4).

The patient was afebrile and normotensive, and her chest was clear upon auscultation. Neurologic and electromyographic examinations demonstrated features of mononeuritis multiplex in the left lower limb with asymmetric sensory and motor nerve impairment.



Figure 1 Erythematous papules on the right thumb.

"We believe that "flame figures" seen in sections of specimens from some lesions of insect bites and Wells syndrome are examples of Churg-Strauss granulomas in miniature."



Churg-Strauss granuloma

Flame figure

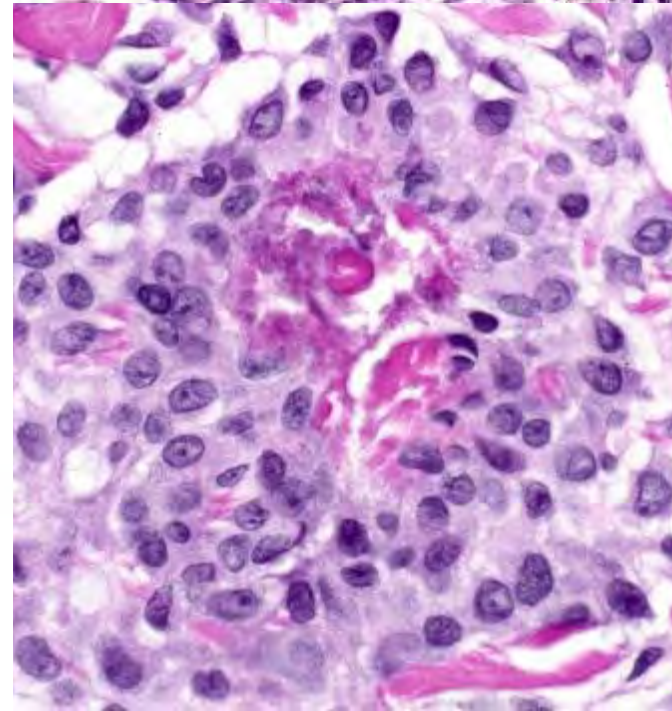
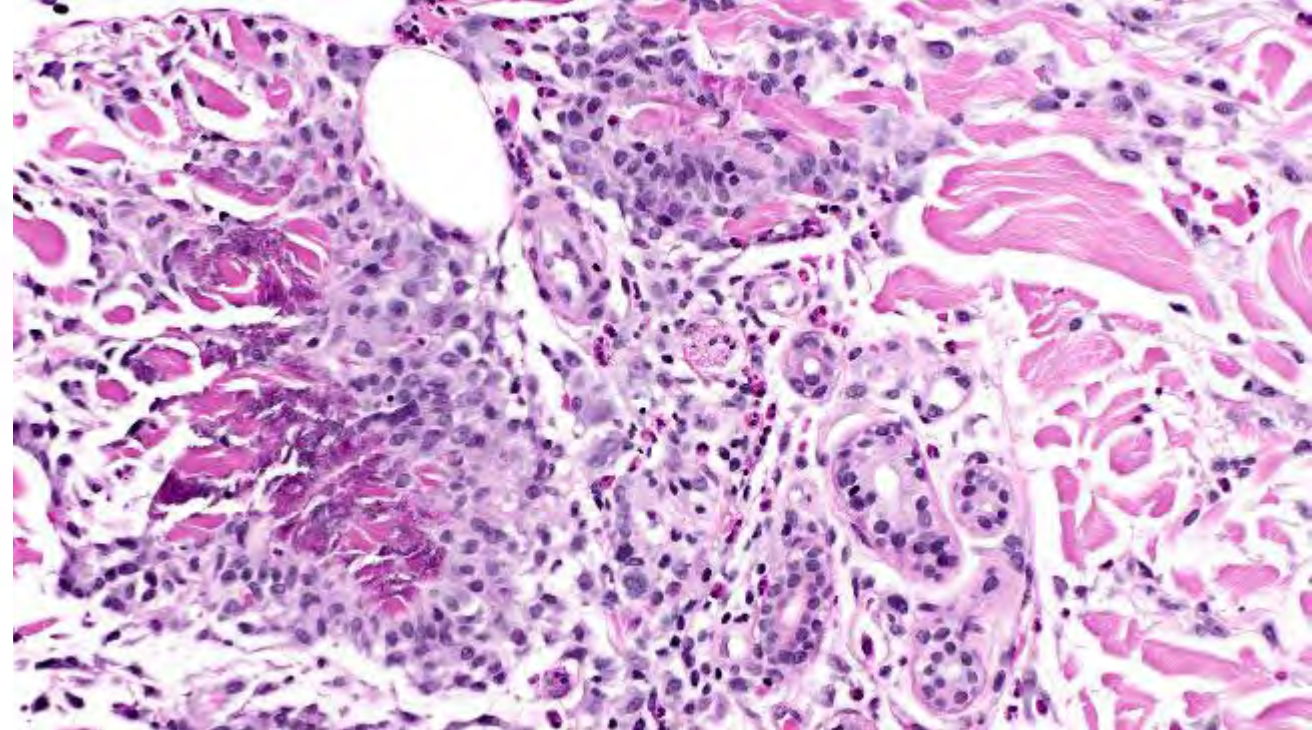
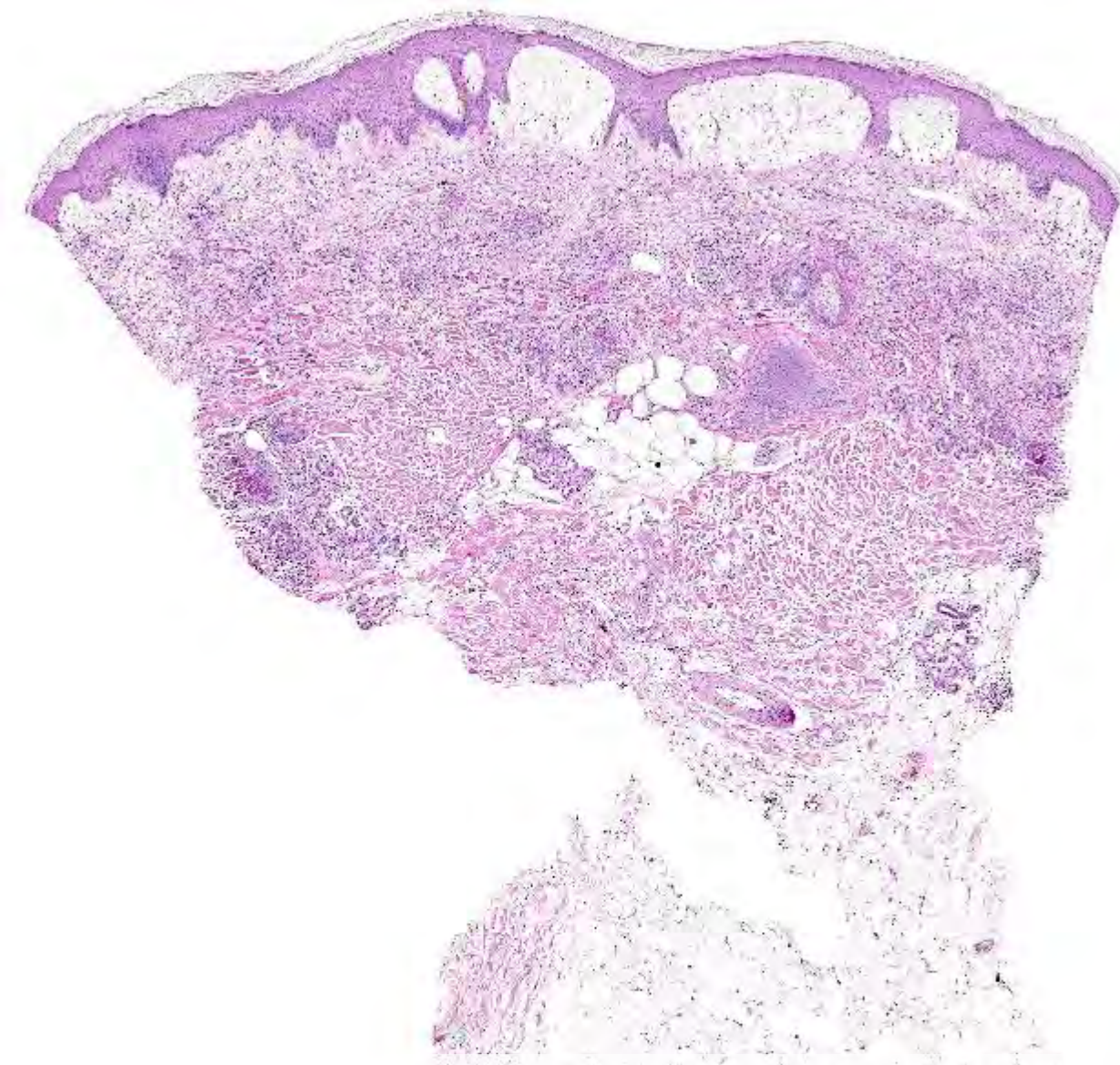
To my eyes, parts of a histopathological spectrum, characterized by abundant neutrophils (Churg-Strauss) or eosinophils (flame figure) with subsequent, variable basophilic degeneration of collagen fibers. Histiocytes may be absent and eosinophils are often present in Churg-Strauss "granulomas"; granulomas are often present in late stages of flame figures.



F, 55

According to the patient very itchy skin lesions for the last 2 months. She reports a constant enlargement of the affected area without remissions. No systemic symptoms, no other complaints. No improvement with local steroids or with oral steroids and anti-histamines taken for a few days.

A biopsy is taken.



Hypersensitivity reaction
With Churg-Strauss granulomas (flame figures)



1st presentation

18 days later

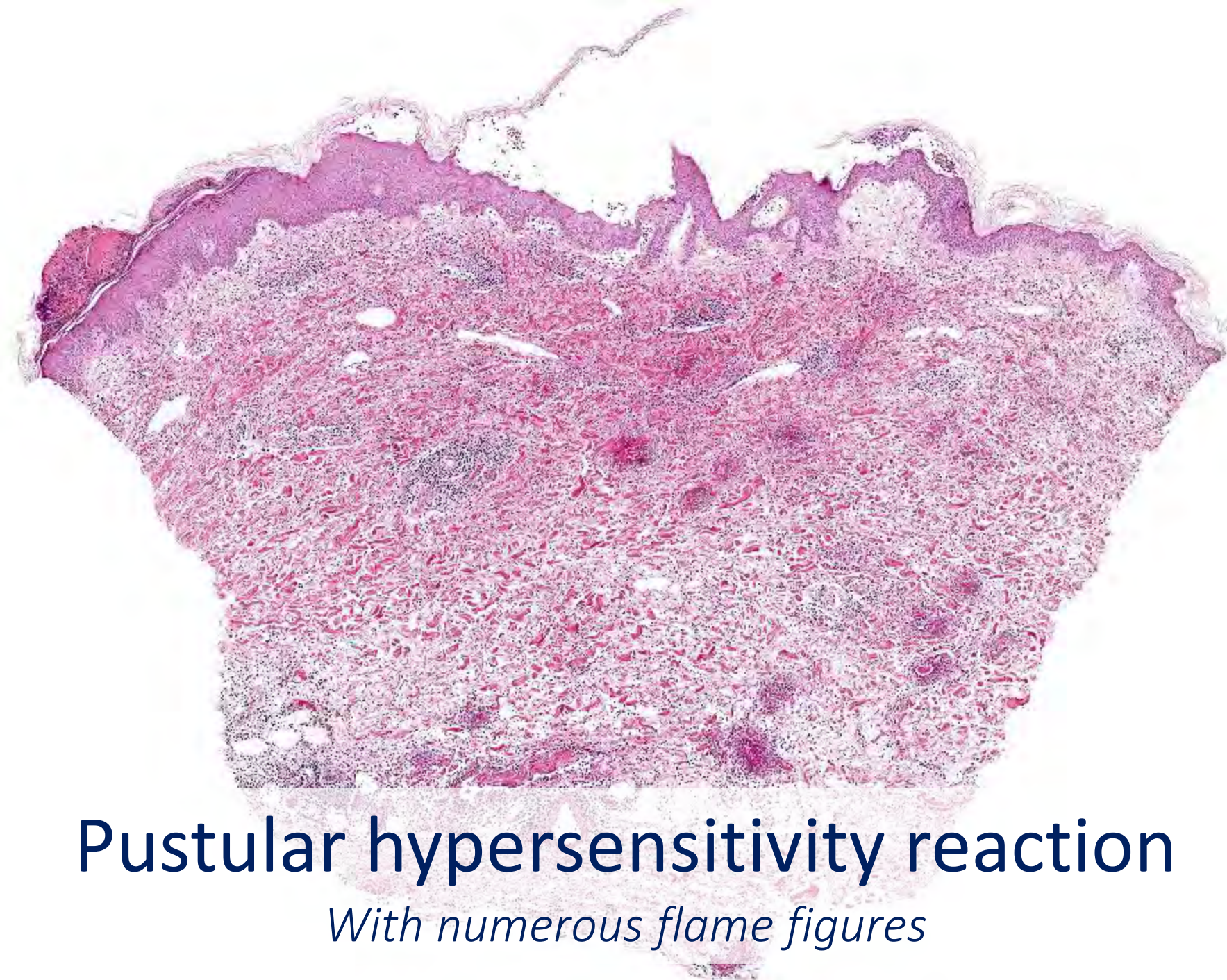
Local steroids; systemic steroids for the last 3 days (50 mg prednisolone)



F, 67

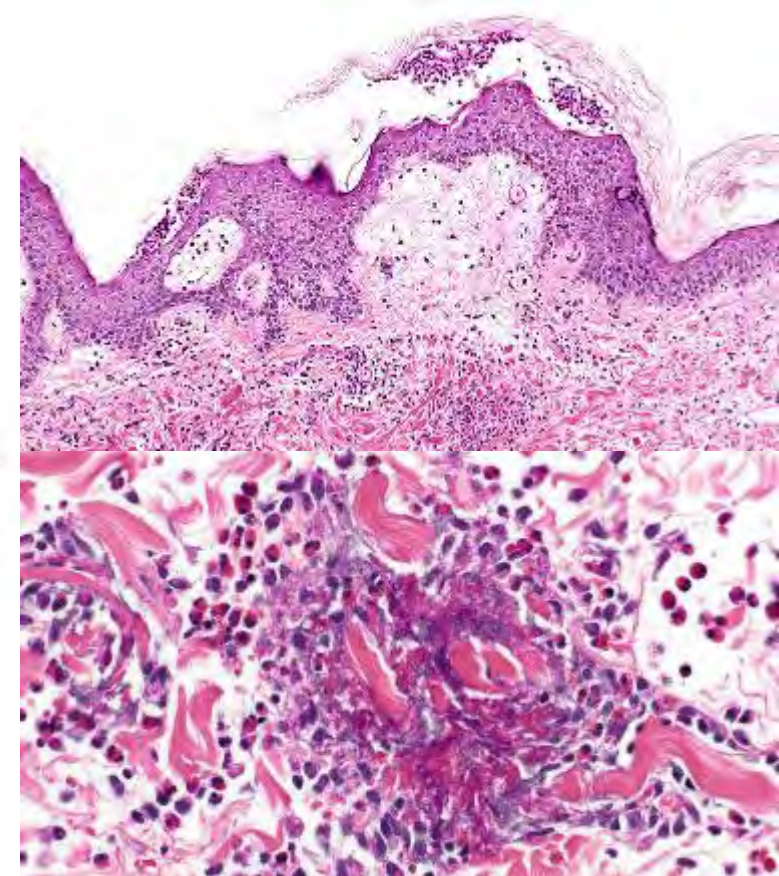
According to the patient
generalized skin
lesions for 1,5
years.

A biopsy is taken.



Pustular hypersensitivity reaction

With numerous flame figures





Contact dermatitis



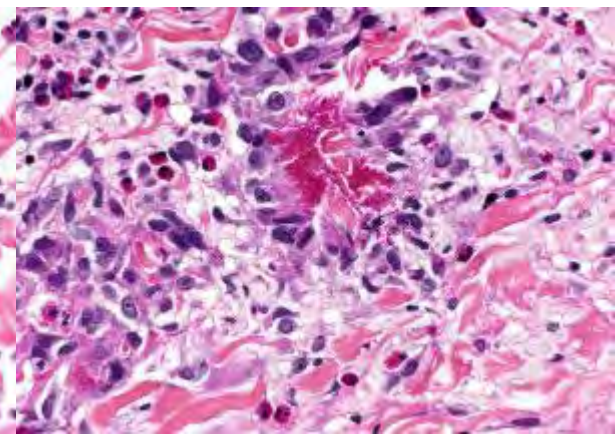
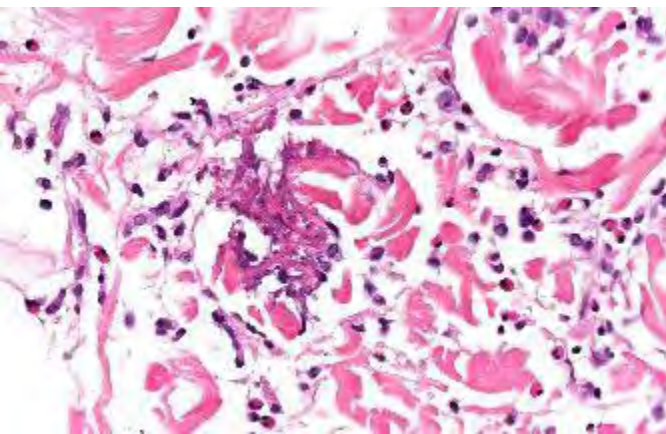
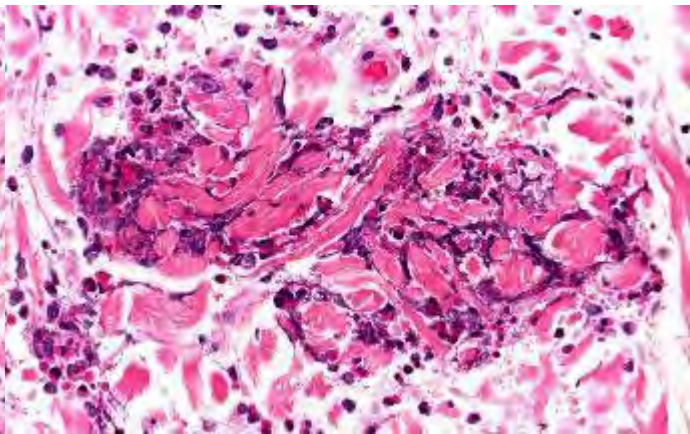
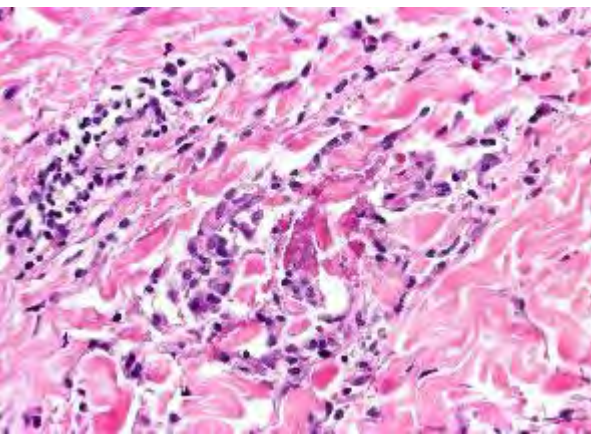
Wells syndrome

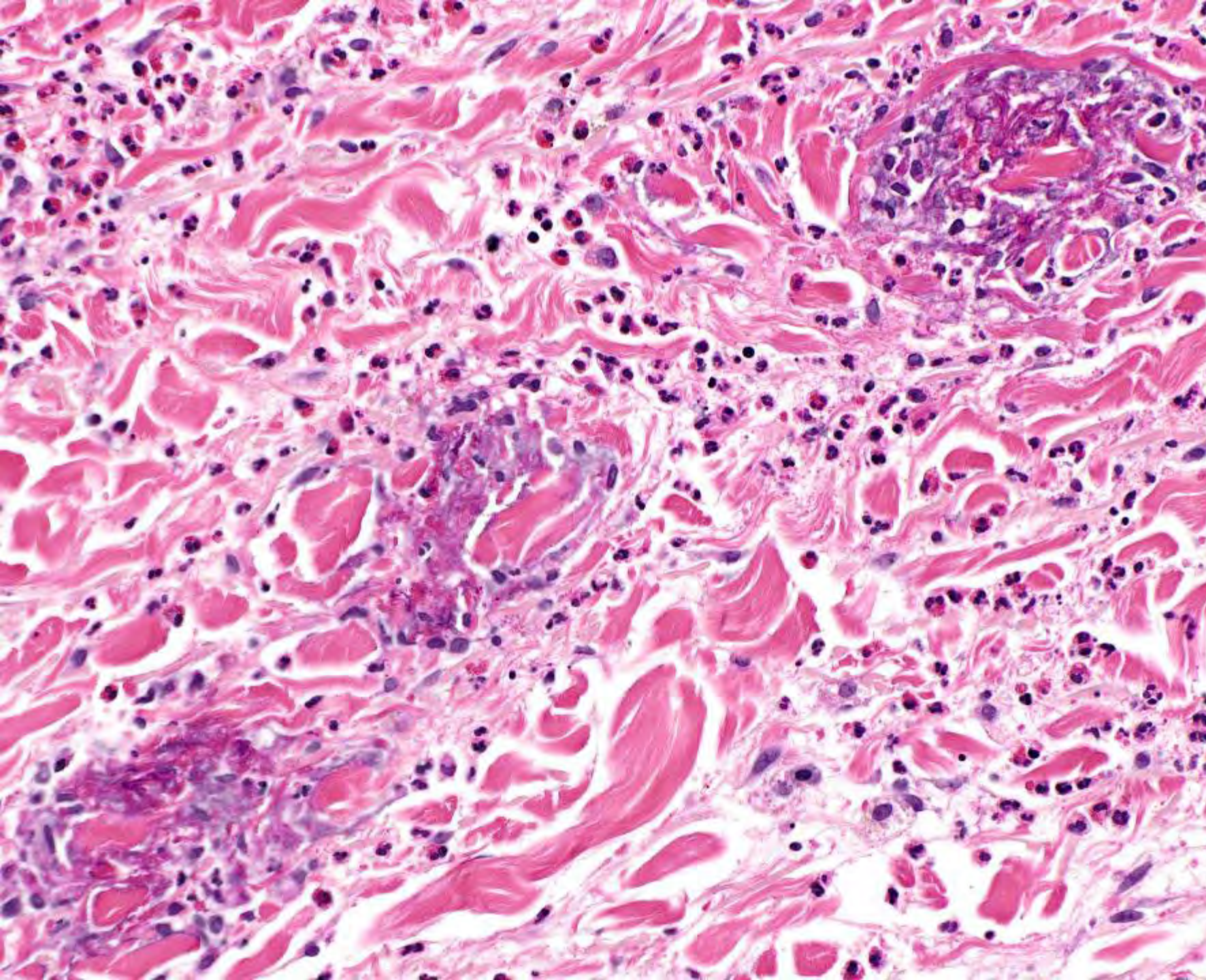


Polymorphous light eruption



Phototoxic dermatitis





Flame Figures

Granules of eosinophils disposed in clusters around one or more collagen bundles that may show signs of degeneration (basophilia).

AB Ackerman, Histologic diagnosis of inflammatory skin diseases, 3rd ed., 2005

Wells syndrome

Arthropod bite reactions (including scabies)

Parasitic disorders (e.g., gnathostomiasis, helminthiasis)

Bullous pemphigoid

Dermatitis herpetiformis

Tr. rubrum infection

Drug eruptions

Leukocytoclastic vasculitis

Hypereosinophilic syndrome

Interstitial granulomatous dermatitis

Kimura disease

AHWE

My experience

Phototoxic dermatitis

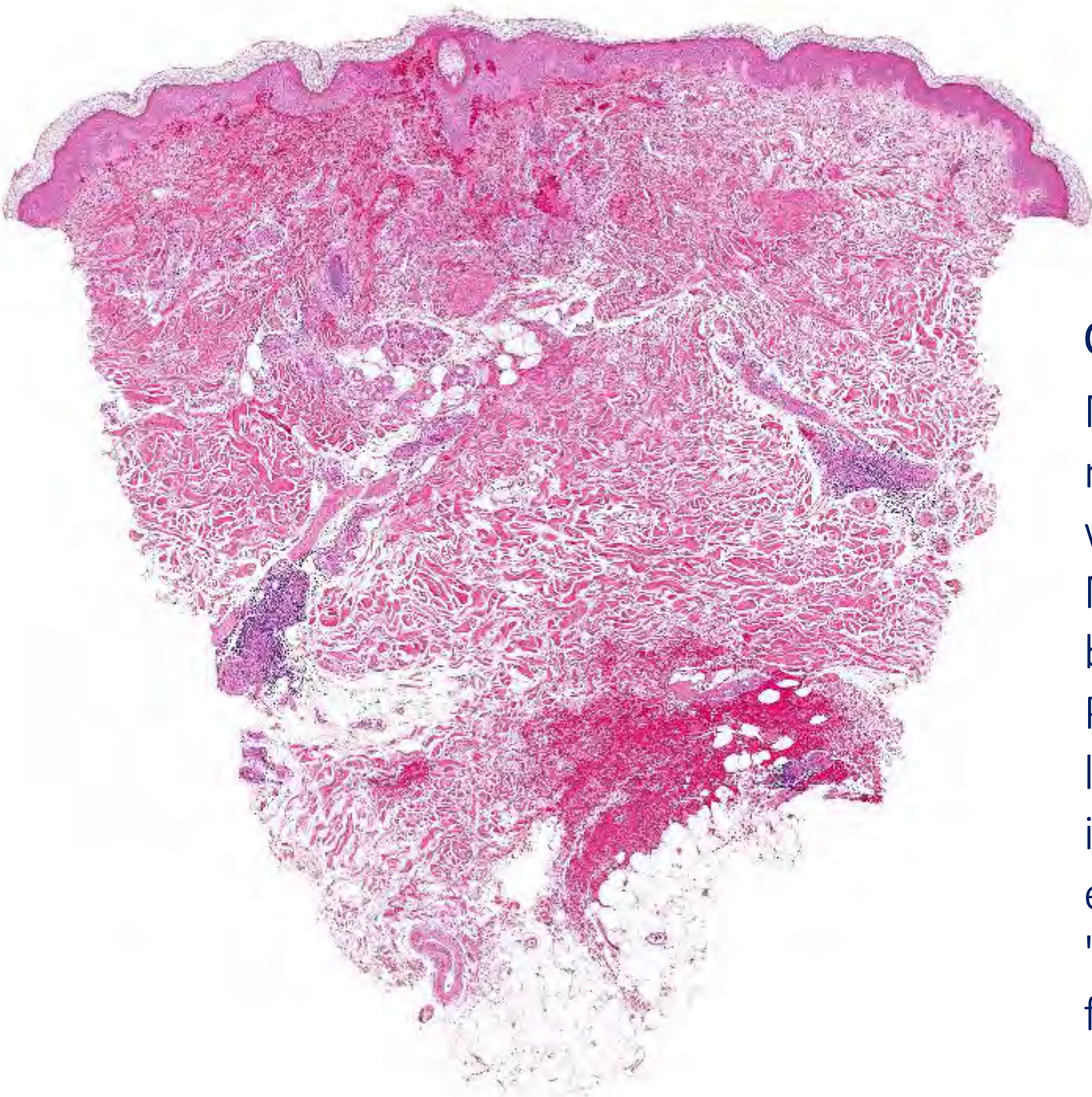
Contact dermatitis

Polymorphous light eruption

Requena et al., DPP&C 1996;2:21-24

Sweet syndrome

Erythema elevatum et diutinum

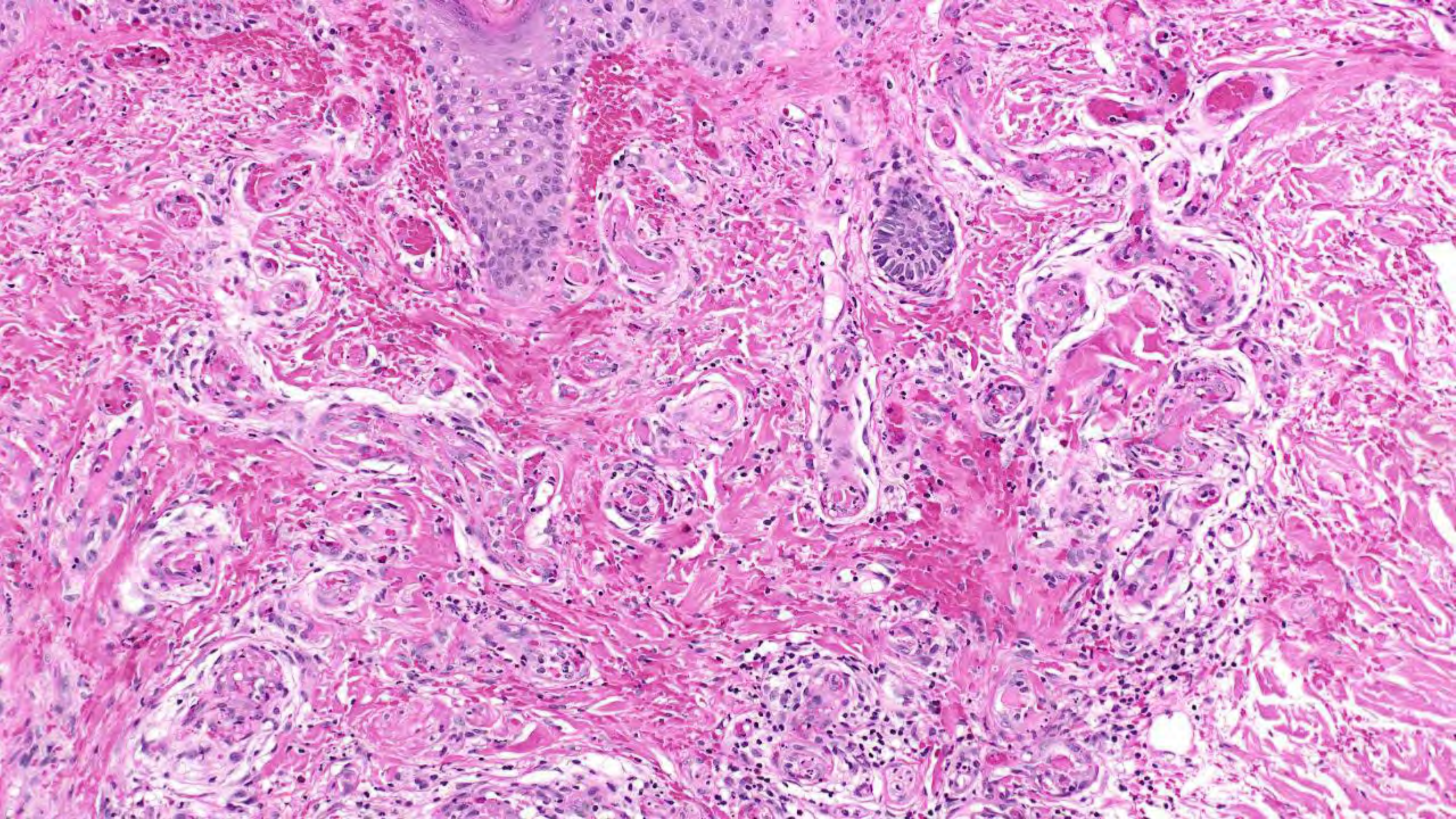


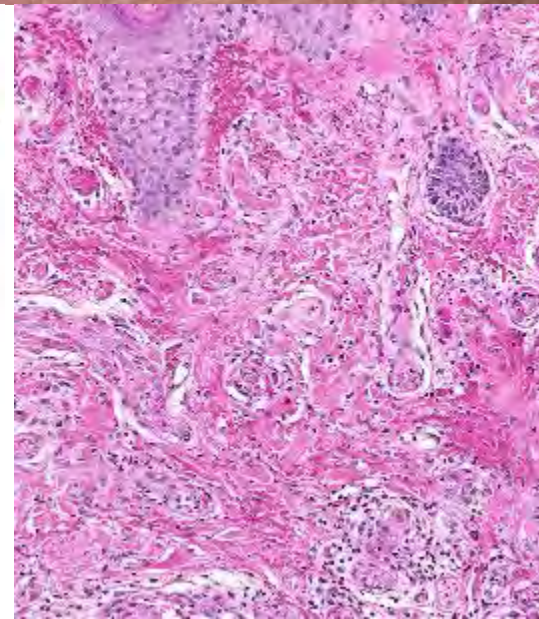
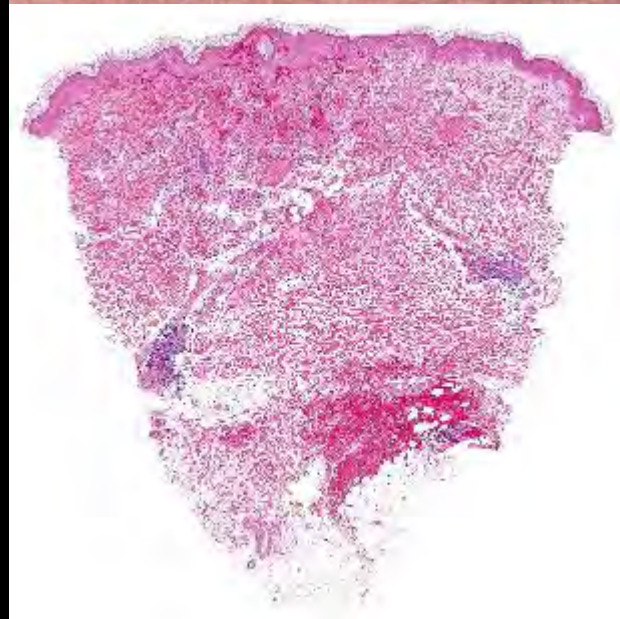
Case 26

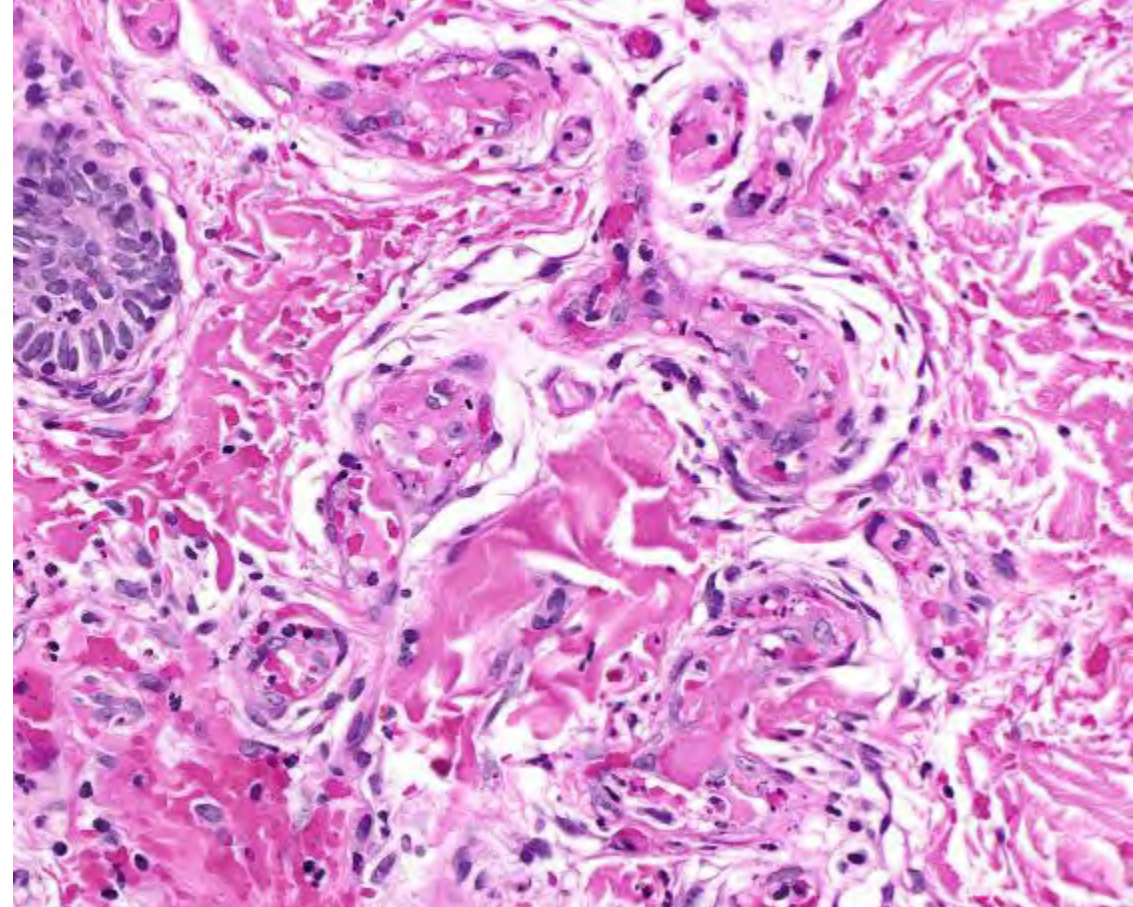
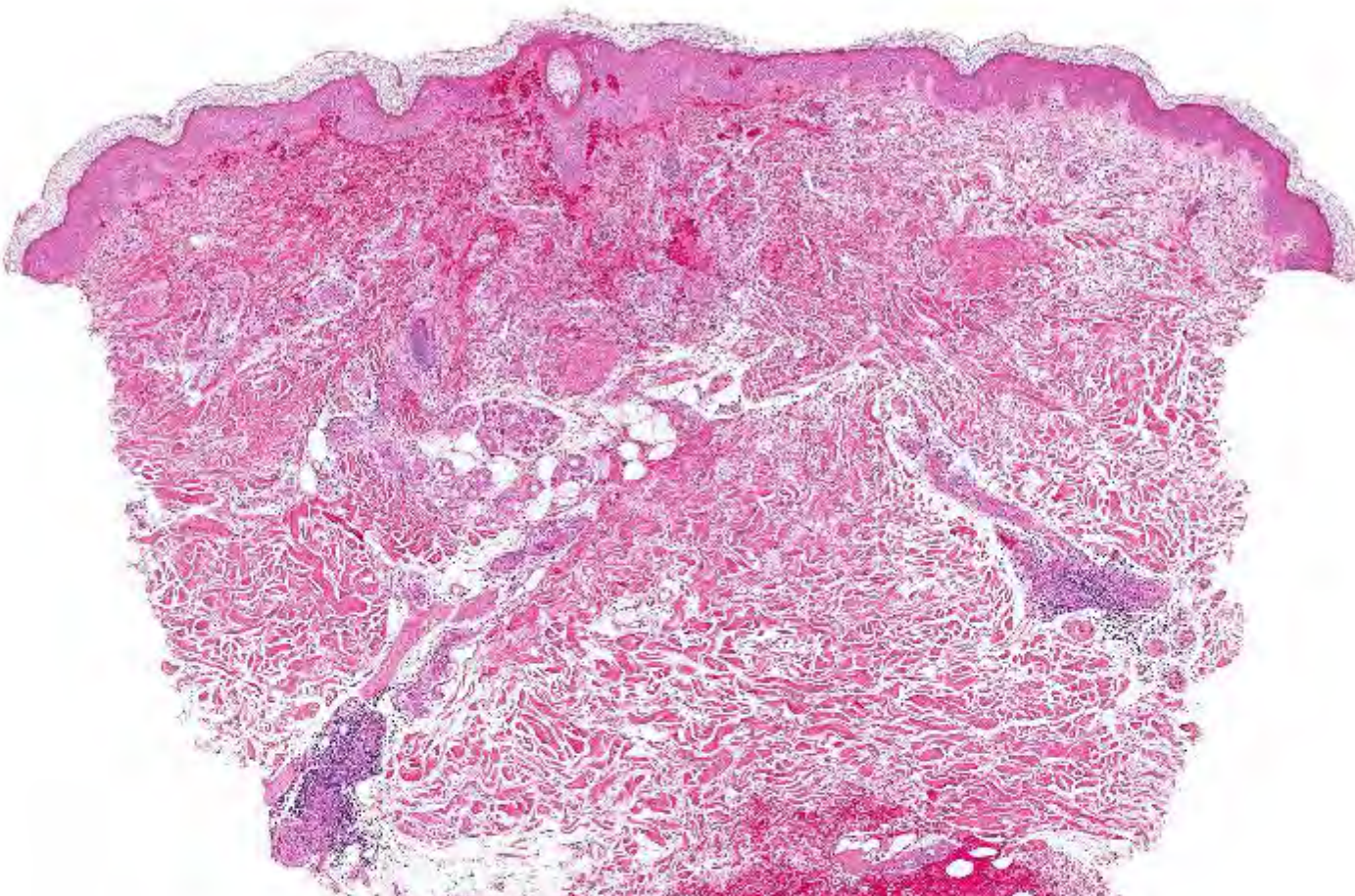
M, 79. History of B-CLL (1st diagnosis 15 months before presentation); managed with watchful waiting.

Monoclonal IgG/lambda peak in peripheral blood.

Partly necrotic, hemorrhagic lesions on the lower extremities for the last 4 months, not improving on local steroid treatment; an external biopsy was reported as "leukocytoclastic vasculitis" (not available for review).







Vasculitis with occlusive vasculopathy in B-CLL

DIF: IgM in 2 vessel walls, C3 in some vessel walls. Discharged as vasculitis; Two new similar crops 4 and 19 months later, respectively (in winter- and summertime; still diagnosed as "vasculitis" and managed with systemic steroids & rituximab)

Occlusive Nonvasculitic Vasculopathy

Mar Llanas-Velasco, MD,* Victoria Alegría, MD,† Ángel Santos-Briz, MD,‡ Lorenzo Cerroni, MD,§
Heber Kutner, MD,¶ and Luis Requena, MD||

Abstract: We review the most characteristic clinical and histopathologic findings of the cutaneous manifestations of the occlusive nonvasculitic vasculopathic disorders. Clinically, most of these conditions are characterized by cutaneous purpura. Histopathologic findings consist of occlusion of the vessel lumen with no vasculitis. Different disorders may produce nonvasculitic occlusive vasculopathy in cutaneous blood and lymphatic vessels, including embolization due to cholesterol and oxalate emboli, cutaneous intravascular metastasis from visceral malignancies, atrial myxomas, intravascular angiosarcoma, intralymphatic histiocytosis, intravascular lymphomas, endocarditis, crystal globulin vasculopathy, hyperesophilic syndrome, and foreign material. Other times, the occlusive disorder is due to platelet plugging, including heparin necrosis, thrombocytosis secondary to myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, and thrombotic thrombocytopenic purpura. Occlusive vasculopathy may also appear in cutaneous pitting apoplexias, the last occurring in cryofibrinogenemia, cryoglobulinemia, cold agglutinin syndrome, and crystalglobulinemia. Microorganisms may also occlude the vessels lumen and this is especially frequent in ecthyma gangrenosum, opportunistic fungi as aspergillosis or fusariosis, Listeria phenomenon of lepromatous leprosy and disseminated strongyloidosis. Systemic coagulopathies due to defects of C and S proteins, coumarin/warfarin-induced skin necrosis, disseminated intravascular coagulation, and antiphospholipid antibody/human anticoagulant syndrome may also result in occlusive nonvasculitic vascularities. Finally, vascular coagulopathies such as Scurdman syndrome, livedoid vasculopathy, and atrophic purpura may also cause occlusion of the vessels of the dermis and/or subcutis. Histopathologic study of occlusive vasculopathic lesions is the first step to achieve an accurate diagnosis, and they should be correlated with clinical history, physical examination, and laboratory findings to reach a final diagnosis.

Key Words: occlusive vasculopathy, nonvasculitic occlusive vasculopathy, vascular occlusion, cholesterol embolization, cutaneous intravascular metastasis, intravascular angiosarcoma, intralymphatic histiocytosis, intravascular lymphoma, endocarditis, crystal globulin vasculopathy, hyperesophilic syndrome, heparin necrosis, thrombocytosis secondary to myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, cryoglobulinemia, cryofibrinogenemia, cold agglutinin syndrome, crystalglobulinemia, septic emboli or vasculopathy, C and S protein defects, coumarin/warfarin-induced skin necrosis, disseminated intravascular coagulation, antiphospholipid antibody/human anticoagulant syndrome, livedoid vasculopathy, atrophic purpura

(*Am J Dermatopathol* 2017;39:647-662)

LEARNING OBJECTIVES

Upon completion of this learning activity, participants should be better able to:

1. Evaluate the clinical-pathologic features of the non-vasculitic occlusive vasculopathies with cutaneous manifestations.
2. Establish the histopathologic differential diagnosis among the different disorders that may cause non-vasculitic occlusive vasculopathy in the skin.

INTRODUCTION

Diverse stimuli may produce identical responses in the vessel wall making etiologic diagnoses of vascular injury a challenge. Some nonvasculitic vascular disorders may mimic vasculitis as the result of dermal hemorrhage because of blood vessel wall incompetence or infarction secondary to luminal obstruction.¹ In this review, we will focus only on the occlusive nonvasculitic vasculopathies, which are clinically characterized by the presence of reform lesions, but may also produce ulcers, ulcers, infarcts, and "purple toe syndrome."²

Clinically, the most characteristic finding in most occlusive nonvasculitic vasculopathic disorders is reform purpura. We shall include the livedo lesions within the spectrum of the reform lesions. Most authors differentiate livedo reticularis, characterized by a regular network of blue bands and streaks forming symmetric dynamic figures, from livedo racemosa, presenting with a static network of noncircular lived streaks and bands.² Livedo reticularis is considered a benign condition caused by vasospasm or vascular occlusion of arterial vessels and secondary venous congestion, always showing a dynamic clinical course with a rapidly changing pattern and therefore will not be discussed in this article. The

TABLE 1. Occlusive Nonvasculitic Vasculopathies

Type of Occlusive Vasculopathy	Entities
Embolization	Cholesterol embolus Oxalate embolus Cutaneous intravascular metastasis from visceral malignancies Atrial myxoma Angiosarcoma ILH IL Lüman-Sacks endocarditis in systemic lupus erythematosus Infective endocarditis Crystal globulin vasculopathy IDS Foreign material Heparin necrosis Thrombocytosis secondary to myeloproliferative disorders PNH RAI TTP
Platelet plugging	Cryofibrinogenemia Cryoglobulinemia CAS Crystalglobulinemia
Cold-related pitting or agglutination	EG Opportunistic fungi: aspergillosis, fusariosis Lucio phenomenon of lepromatous leprosy Disseminated strongyloidosis Defects of C and S proteins Coumarin/warfarin-induced skin necrosis Disseminated intravascular coagulation Antiphospholipid antibody/LA syndrome
Vessel-invasive microorganisms	SS LV (atrophic blanche) Atrophic psoriasis (DD) Cutaneous collagenous vasculopathy RAE
Systemic coagulopathies	Stress reticulocyte adhesion Cutaneous calciphylaxis HCU-induced ulcers Occlusive vasculopathy induced by CI Contact dermatitis from lepraxinol
Vascular coagulopathies	
Red cell occlusion syndromes	
Miscellaneous	

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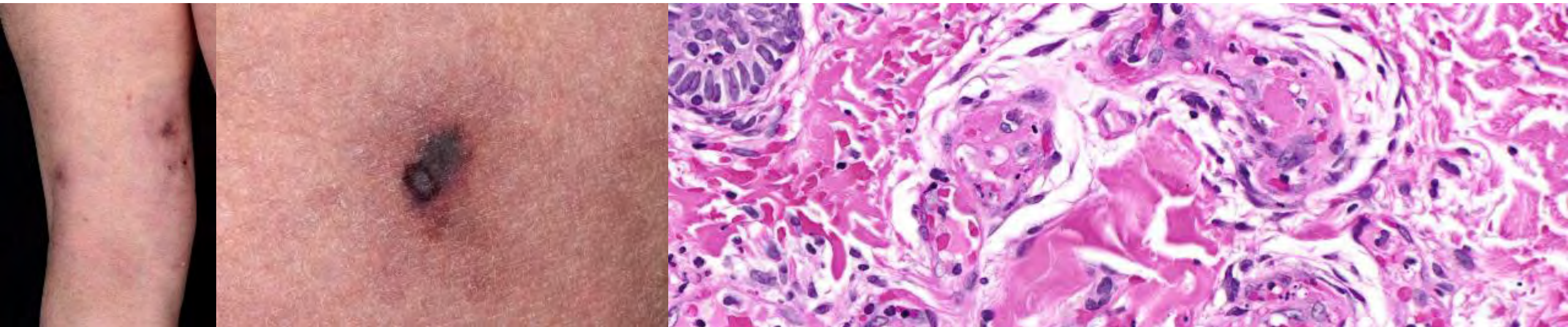
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In the setting of leukemia / lymphoma think of:
Cold-agglutinin syndromes
Cryoglobulinemia (monoclonal)
Crystalglobulinemia

Cryoglobulinemia

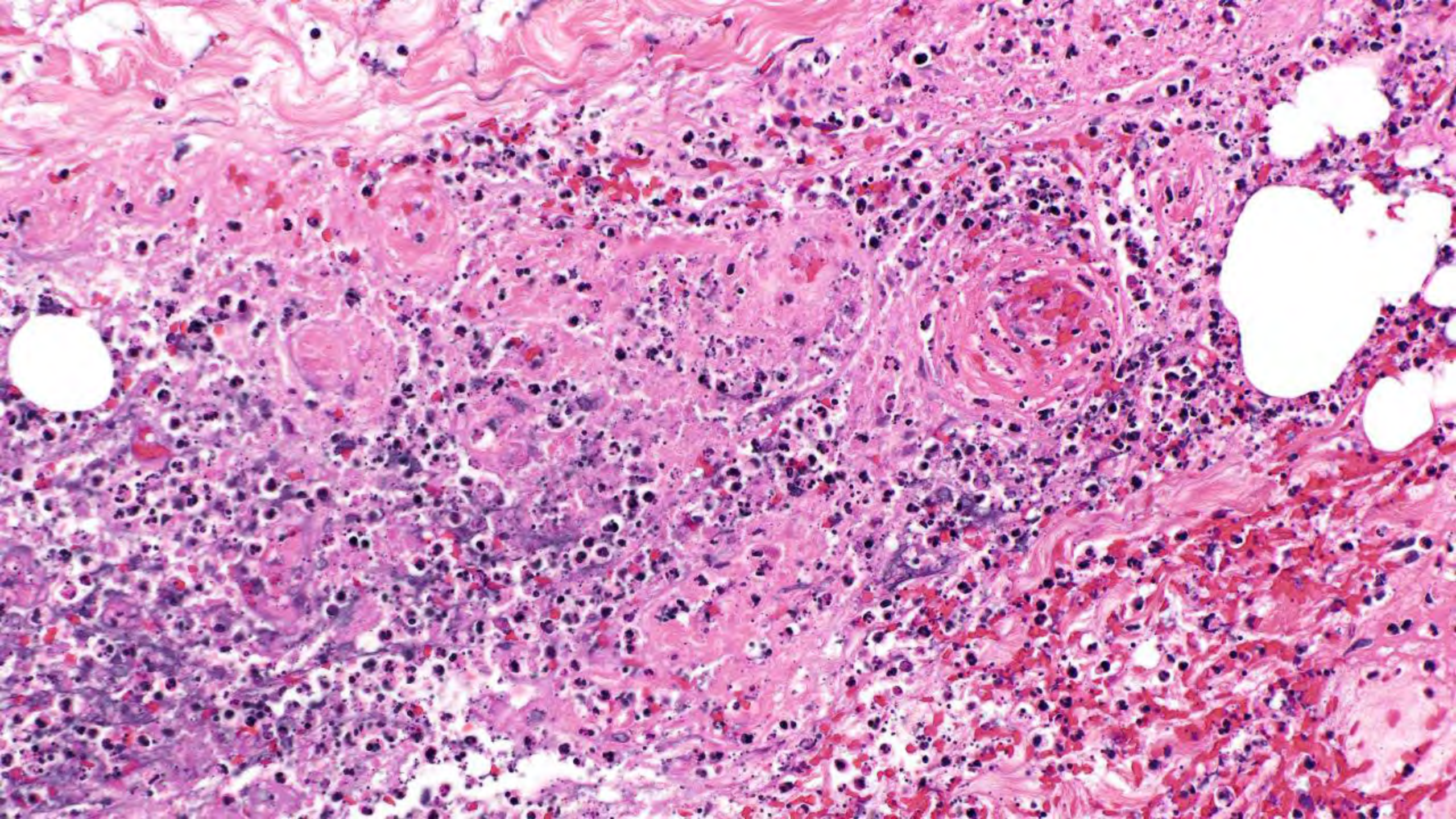
- Monoclonal (usually in the setting of hematological disorders; intravascular deposits)
- Mixed (often in association with hepatitis C; acute vasculitis with variable leucocytoclasia)
- Immunoglobulin and complement found often within the vessel walls in mixed cryoglobulinemia

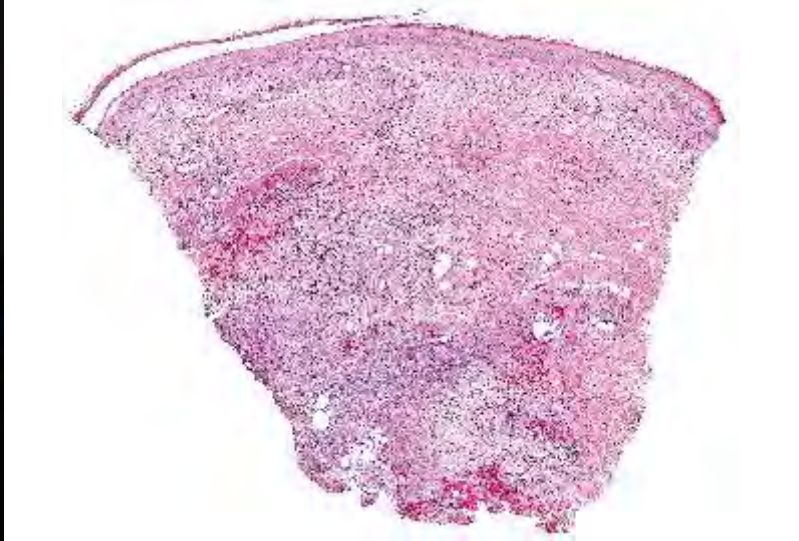
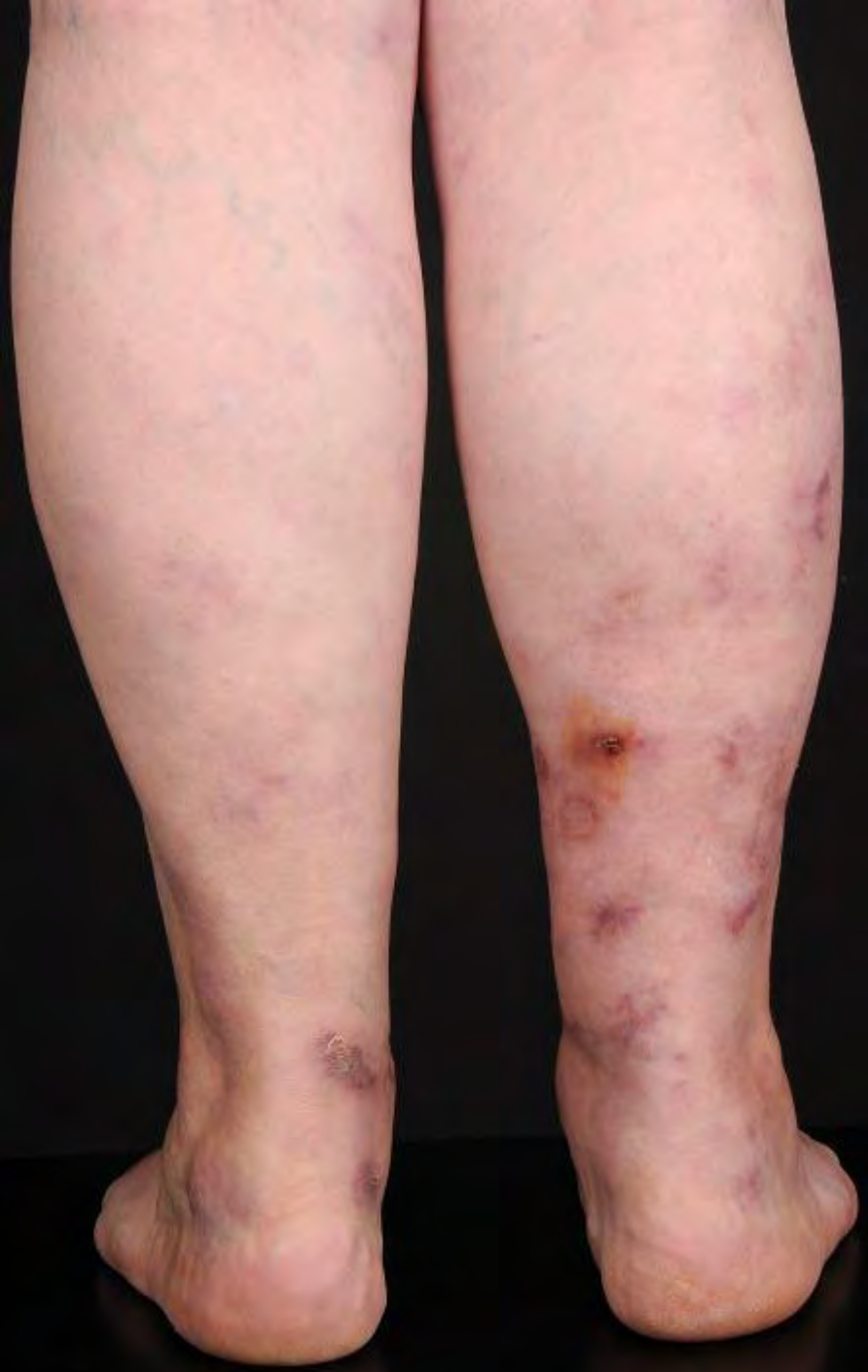


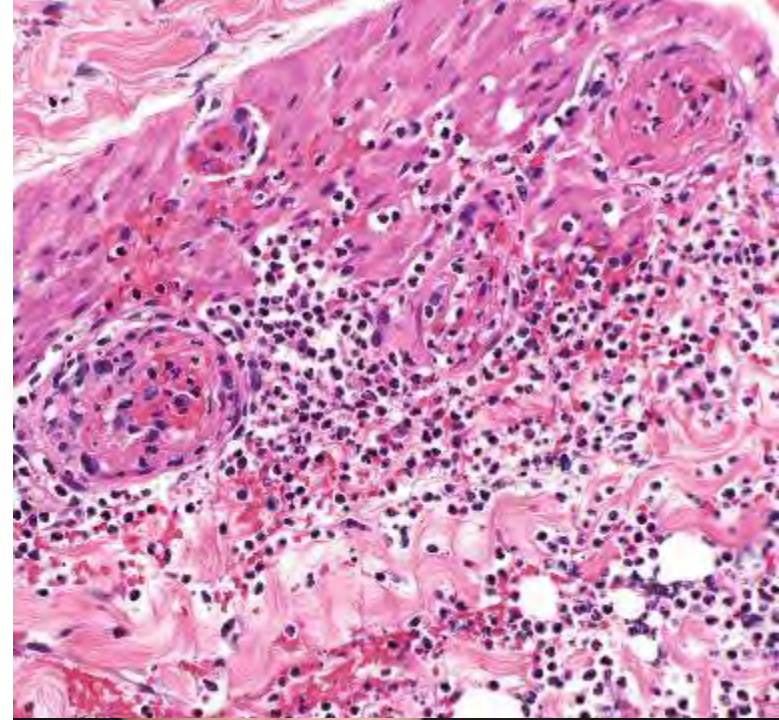
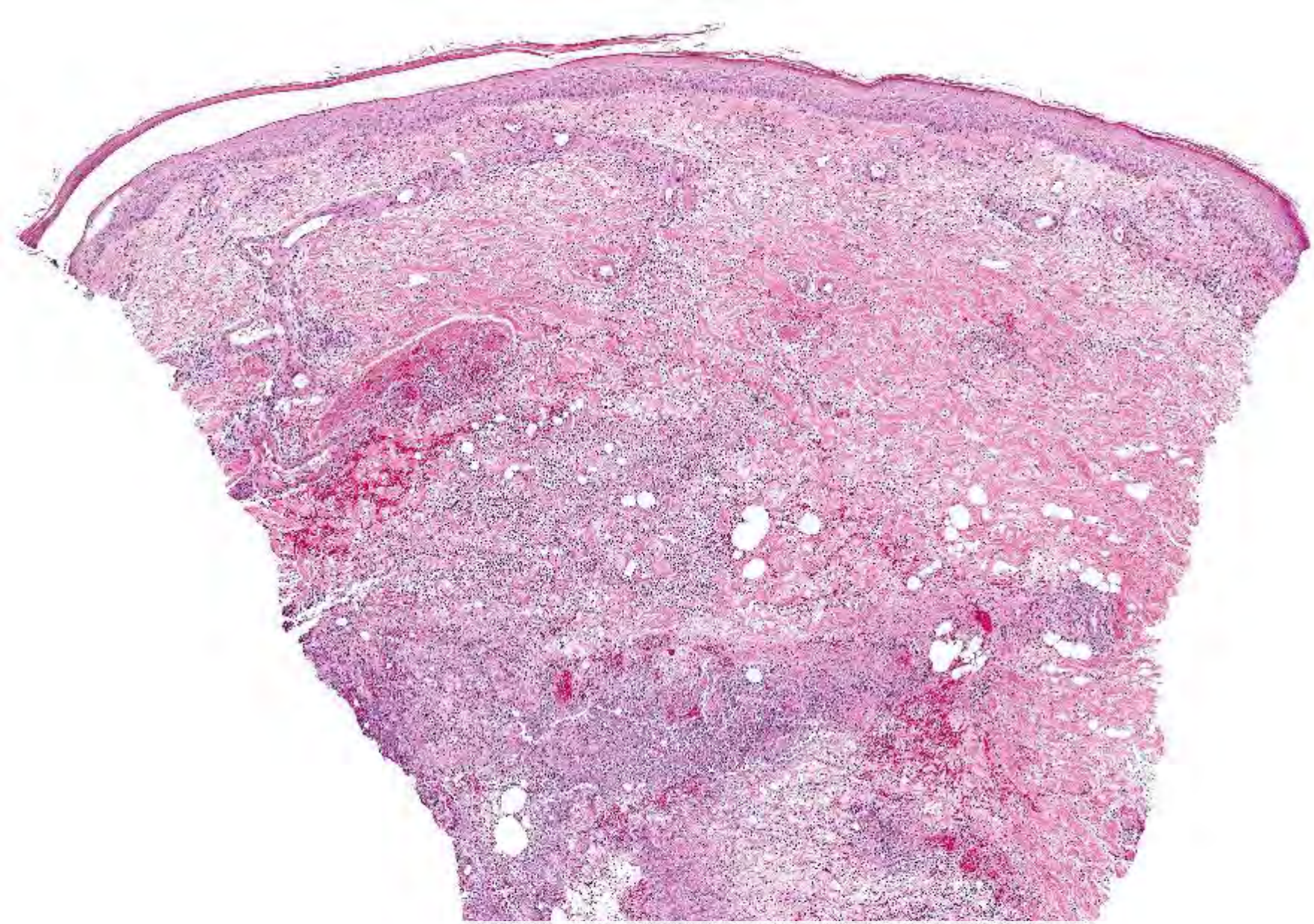


Case 27

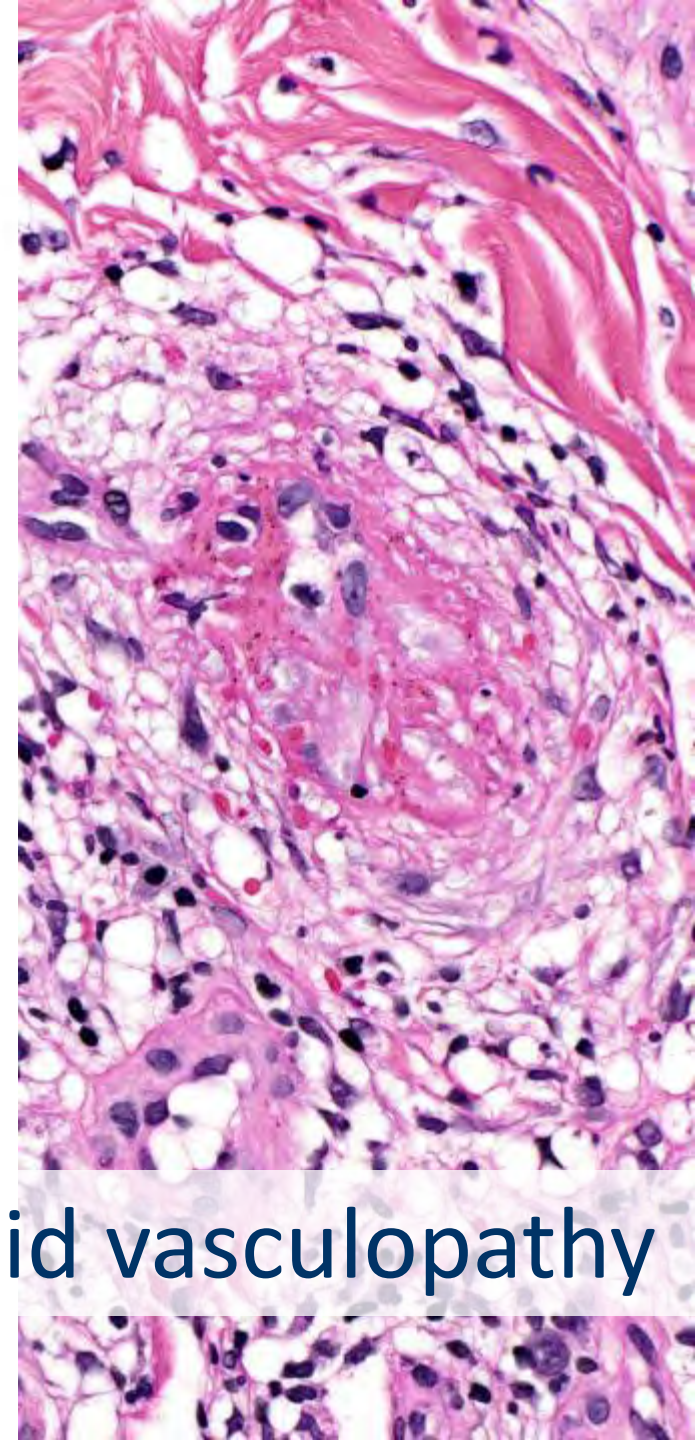
F, 41. Recurrent "erythema nodosum" for 6 years. A previous external biopsy was interpreted as "erythema nodosum" (not available for review).







reported as livedoid vasculopathy



reported again as livedoid vasculopathy

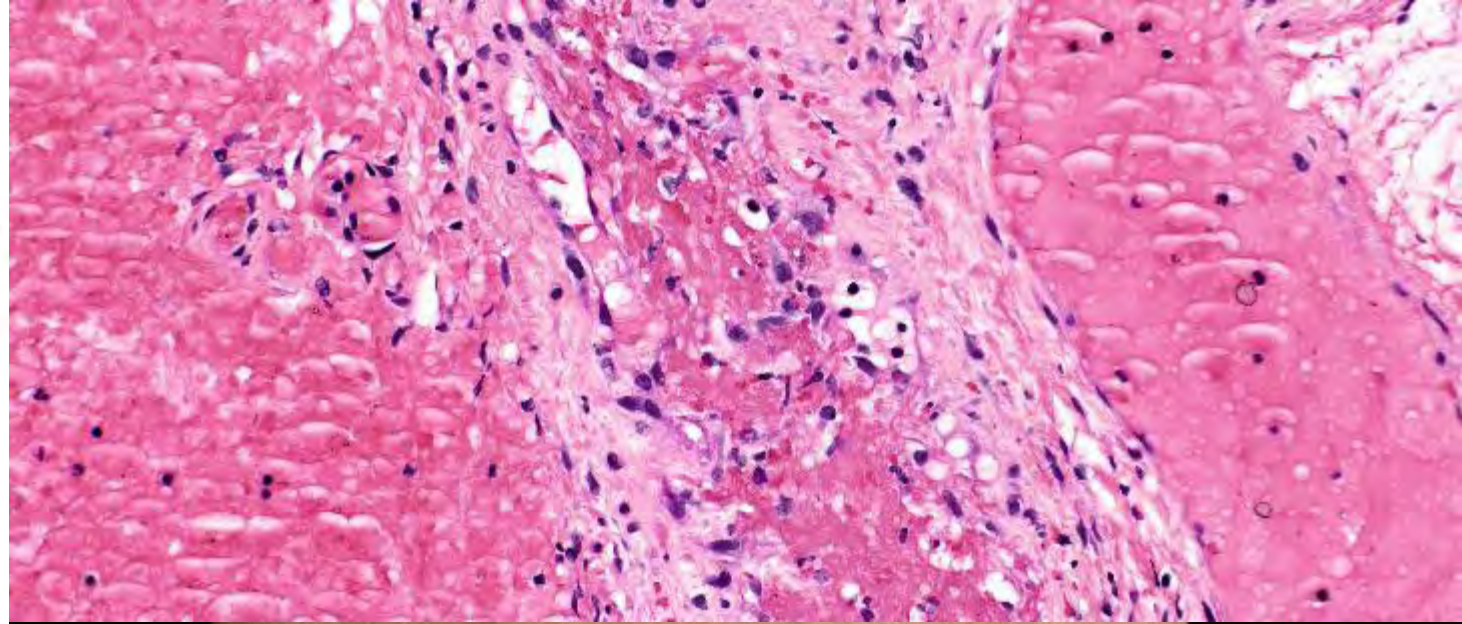
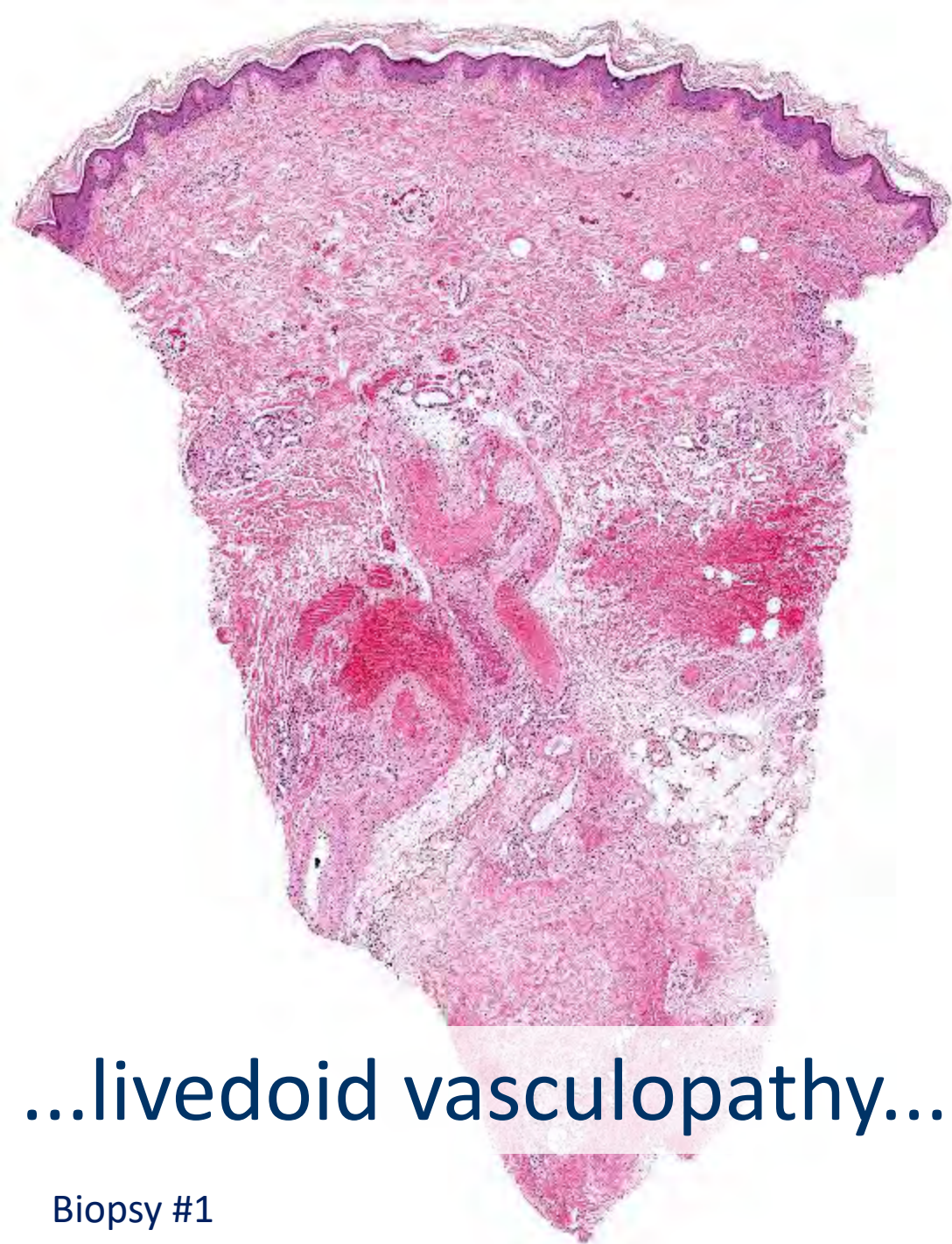
6 years later



16 years later (now age 57). Managed over the years with systemic steroids, alprostadil, chloroquine.

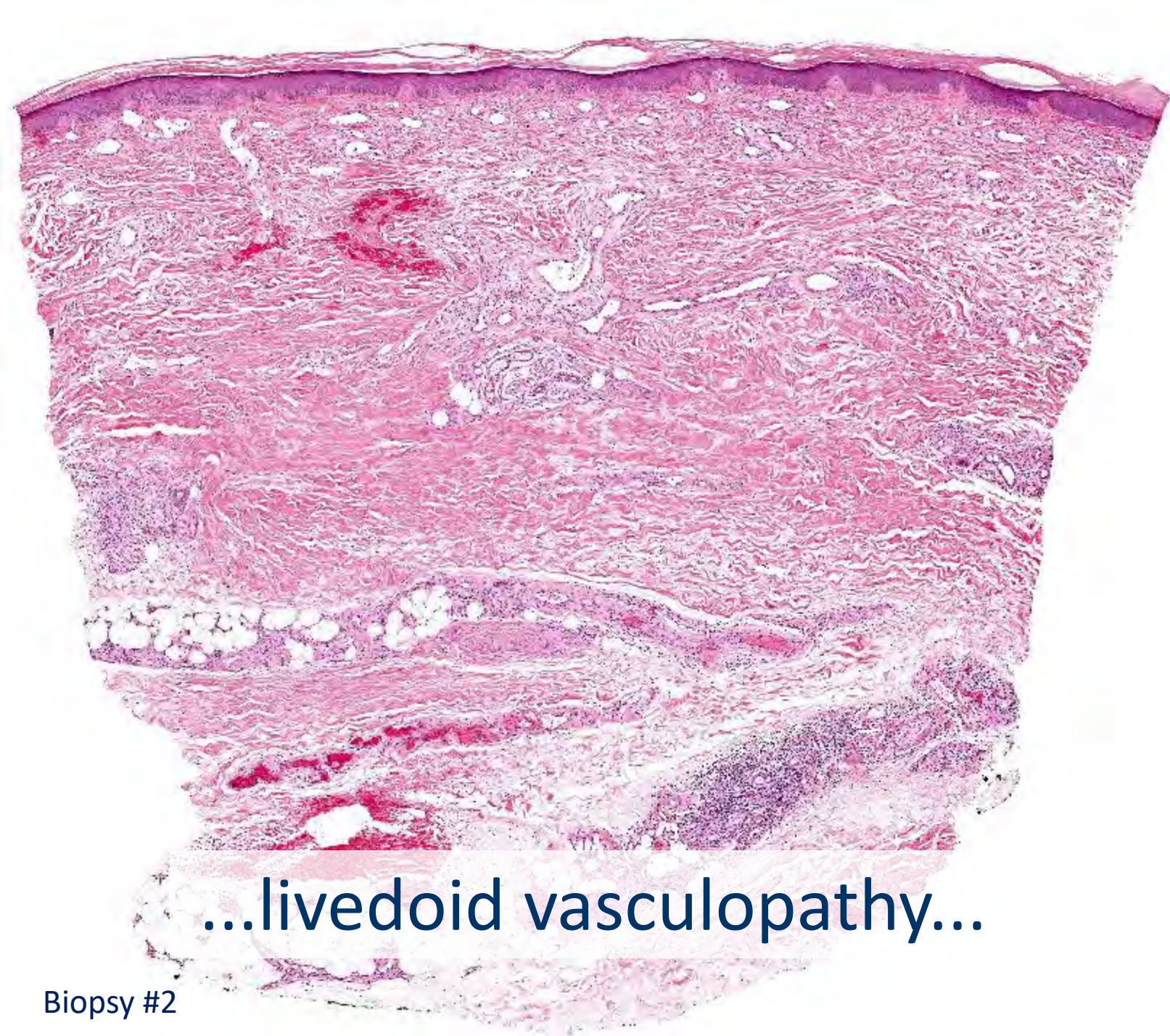
Two new biopsies and a few days later a third one are taken.





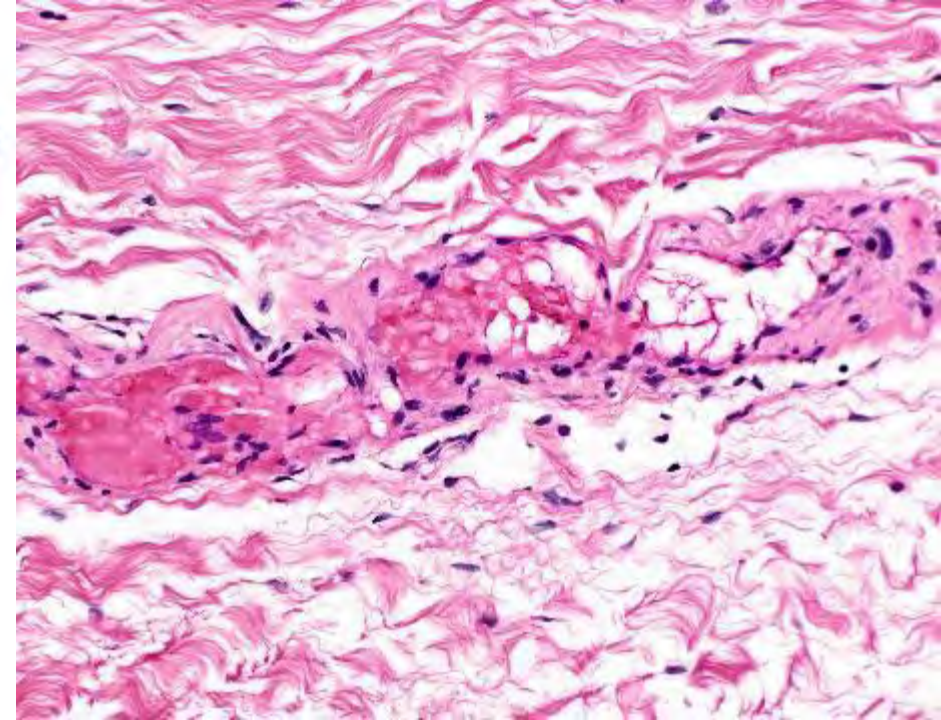
...livedoid vasculopathy...

Biopsy #1



...livedoid vasculopathy...

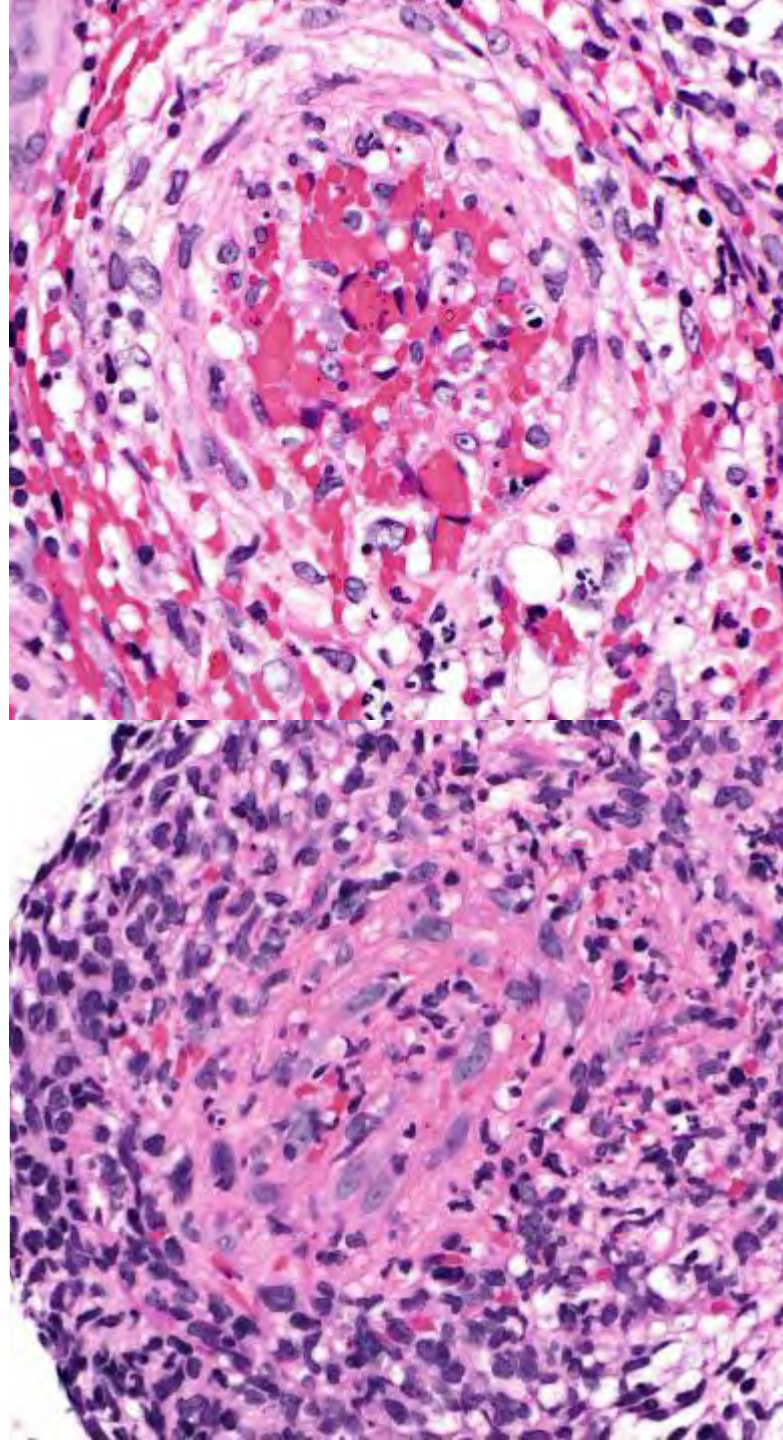
Biopsy #2



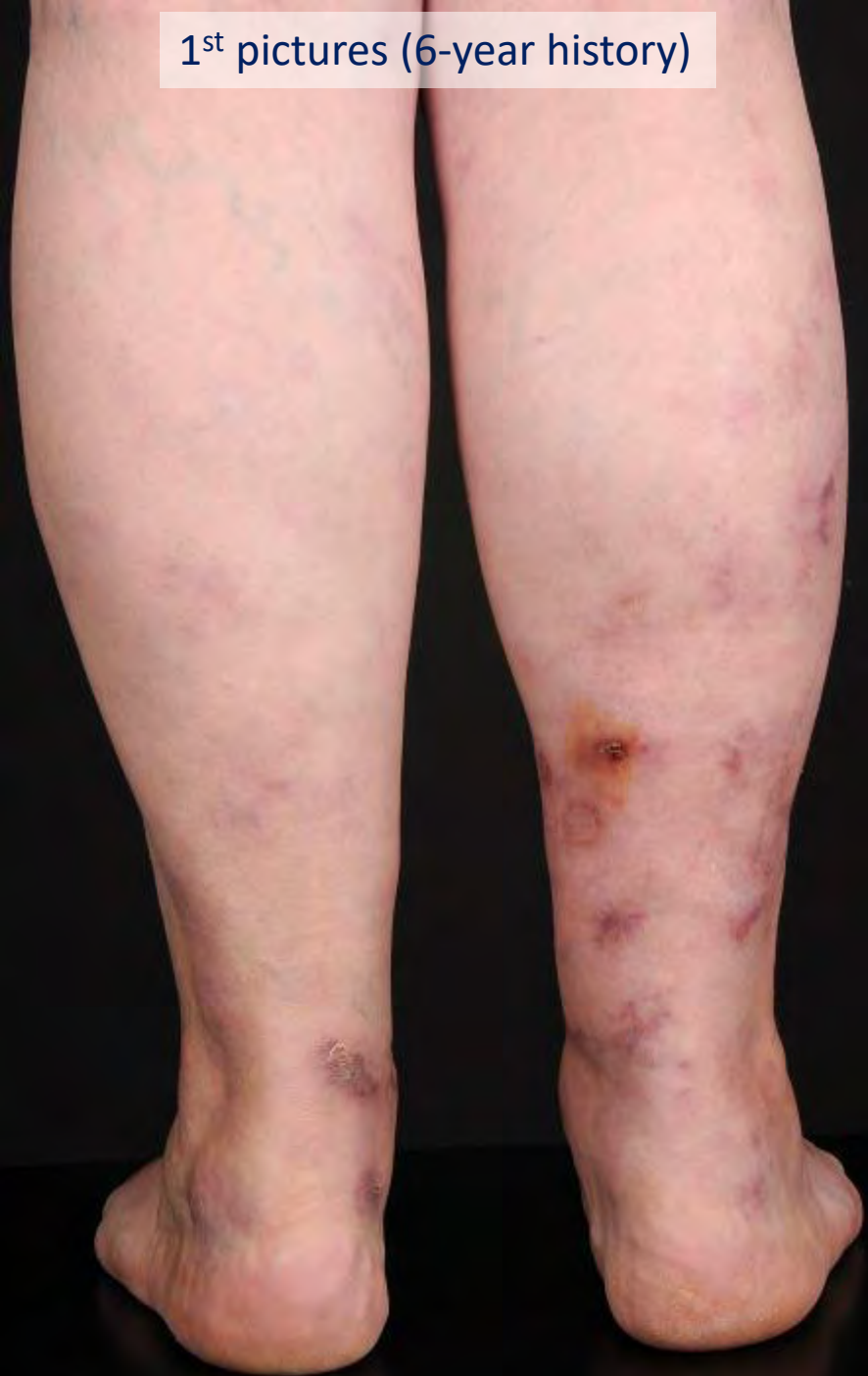


...livedoid vasculopathy
& cutaneous arteritis

Biopsy #3



1st pictures (6-year history)



16 years later



Clinical presentation remarkably similar 16 years after first presentation; several biopsies over the years showing livedoid vasculopathy, and focal features of cutaneous arteritis only in one specimen.

CONCISE COMMUNICATION

Cutaneous polyarteritis nodosa in patients presenting with atrophic blanche

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Accepted for publication 23 August 2002

Summary

Background: The term 'atrophic blanche' is used both as a descriptive term denoting ivory-white stellate scars on the lower limbs as well as a diagnostic label synonymous with livedoid vasculitis, an ill-defined entity. Medium-sized vasculitides, such as polyarteritis nodosa (PAN), occasionally present with ulceration resulting in ivory white stellate scarring on the lower limbs and may potentially be misdiagnosed as livedoid vasculitis.

Objectives: To assess the occurrence, clinical and immunopathological features of medium-sized vasculitis in patients presenting with atrophic blanche without clinical and/or compression duplex ultrasonographic evidence of venous insufficiency.

Methods: We retrospectively evaluated patients presenting with atrophic blanche at the Department of Dermatology of Johns Hopkins Medical Institutions, from April 1996 until April

2002, following the diagnostic guideline for leg ulcers of the Division of Immunodermatology. All patients underwent skin biopsy, nerve conduction studies and compression duplex ultrasonography of the lower extremities.

Results: Six patients were identified with atrophic blanche, all of whom had underlying medium-sized vasculitis consistent with PAN. Three of them had previously been diagnosed to have segmental (affecting vasculitis/vasculopathy [livedoid vasculitis/vasculopathy]) on superficial biopsies. All six patients had evidence of venous insufficiency on duplex ultrasonography.

Conclusions: In patients with atrophic blanche, the characteristic histological features of segmental hyalinizing vasculopathy were identified on the superficial dermal vessels underlying areas of ulceration in all patients.

Key words: atrophic blanche, livedoid vasculitis, polyarteritis nodosa.

Atrophic blanche is a clinical entity characterized by ivory-white stellate scars on the lower limbs. It is often associated with livedoid vasculitis, a form of segmental hyalinizing vasculopathy (SV) affecting the superficial dermal vessels.

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Figure 1. Stellate white scars are evident around the sides of patients with atrophic blanche-like cutaneous polyarteritis nodosa after prednisone and azathioprine treatment. (A) Patient 1; (B) patient 2.

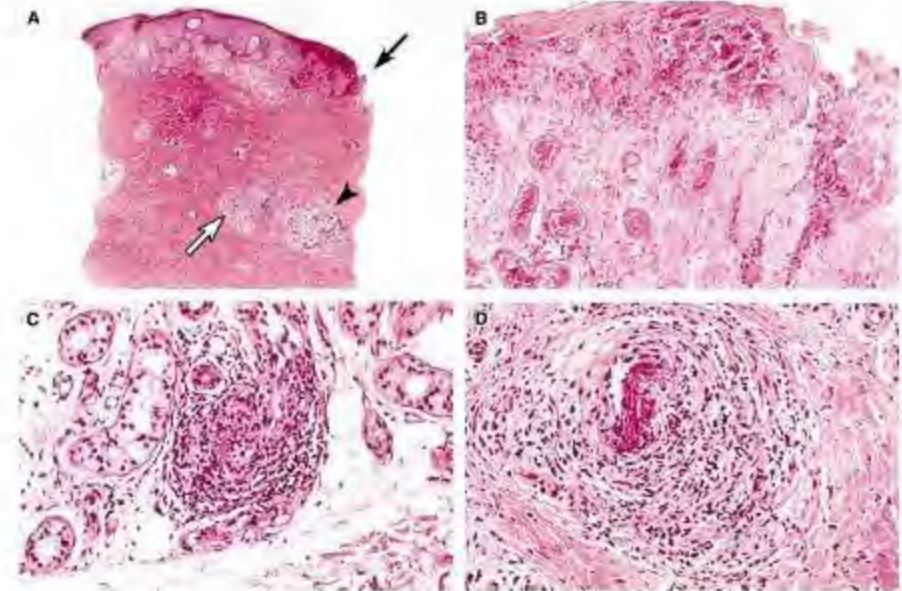


Figure 2. A skin biopsy from patient 2 shown at different magnifications. (A) Superficial and deep (white arrow and black arrowhead) dermal necrosis and/or vascular inflammation associated with significant dermal fibrosis and localized epidermal/dermal necrosis (black arrow). (B) Higher magnification of epidermal/dermal necrosis area (A, black arrow) showing the typical 'vasculopathic' changes (non-inflammatory dilation, congestion and hyaline necrosis) previously reported in atrophic blanche. (C) Magnified area of black arrowhead (A), showing vasculitic changes (necrotizing and leucocytoclastic features) of muscular blood vessel located around sweat glands in a subcutaneous/dermal junction area affected with significant fibrosis. (D) Magnified area of white arrow (A) showing vasculitic changes (necrotizing and leucocytoclastic features) of muscular blood vessel located at the deep dermis or at what may previously have been the dermal/subcutaneous junction, now affected by significant fibrosis. Haematoxylin and eosin; original magnification: (A) $\times 20$; (B) $\times 80$; (C) $\times 100$; (D) $\times 200$.

Focal vascular occlusion: A link between livedoid vasculopathy and cutaneous arteritis?

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Erika Varga¹ | Irma Korom¹ | Lajos Kemény¹ | Zsuzsanna Bata-Csörgő¹

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Funding information:
None

Abstract

Background: Livedoid vasculopathy (LV) and cutaneous arteritis (CA) are rare cutaneous diseases. A consideration of these two conditions as different entities is debatable, because thrombosis and inflammation are closely related in their pathogenesis mechanisms. Varying reports on the effectiveness of anticoagulant and immunosuppressant therapies in LV and CA also point to diagnostic challenge and overlap in these conditions.

Objectives: We sought to assess the therapeutic effect of anticoagulation therapy in adult patients with CA, who were recalcitrant to immunosuppressive modalities.

Methods: A monocentric retrospective analysis of adult patients who were diagnosed with CA between 2010 and 2018, was carried out.

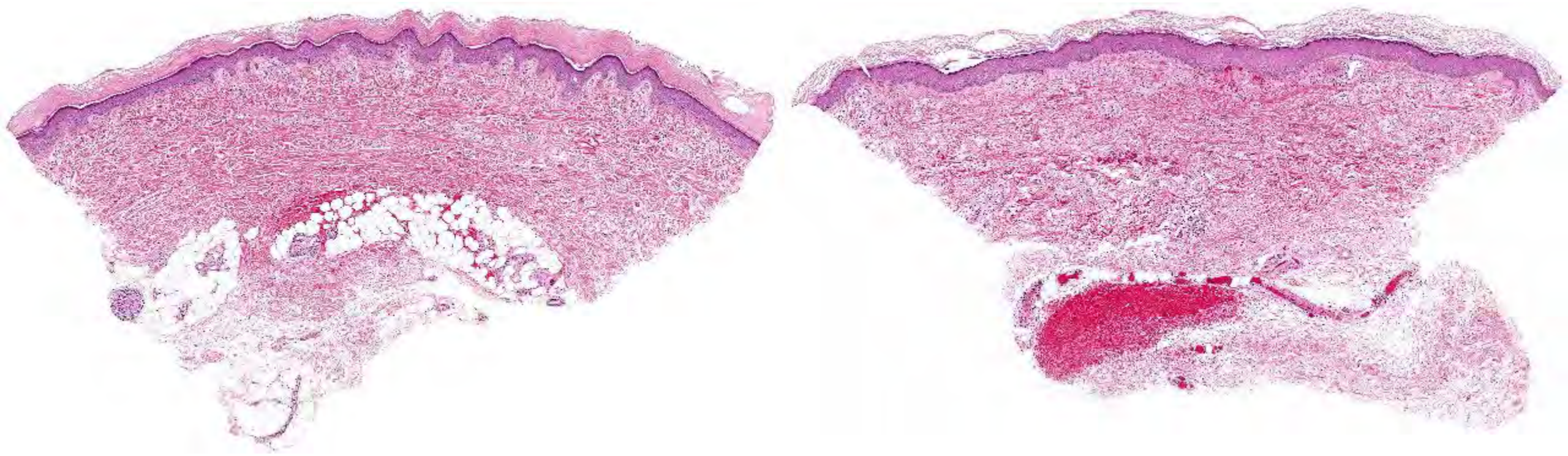
Results: We describe 8 cases of long-term recalcitrant CA, in whom anticoagulation therapy significantly reduced the pain and cutaneous symptoms. All patients had cutaneous symptoms compatible with CA along with clinical features also characteristic of LV, including underlying prothrombotic disorders in the majority (87.5%), as confirmed by screening for thrombophilia. We also review current concepts regarding LV and CA, and suggest vascular occlusion is a common link between these two entities.

Conclusions: Although current knowledge advocates segregating vasculopathy from vasculitis by means of histopathological examination in LV and CA, clinical experience suggests some overlap and common complex underlying pathomechanisms.

KEYWORDS

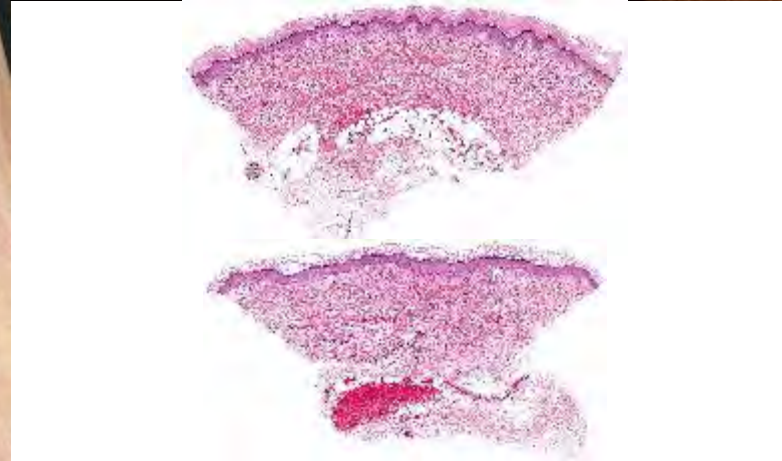
cutaneous arteritis, cutaneous polyarteritis nodosa, livedoid vasculopathy, vasculitis, eosinophilia

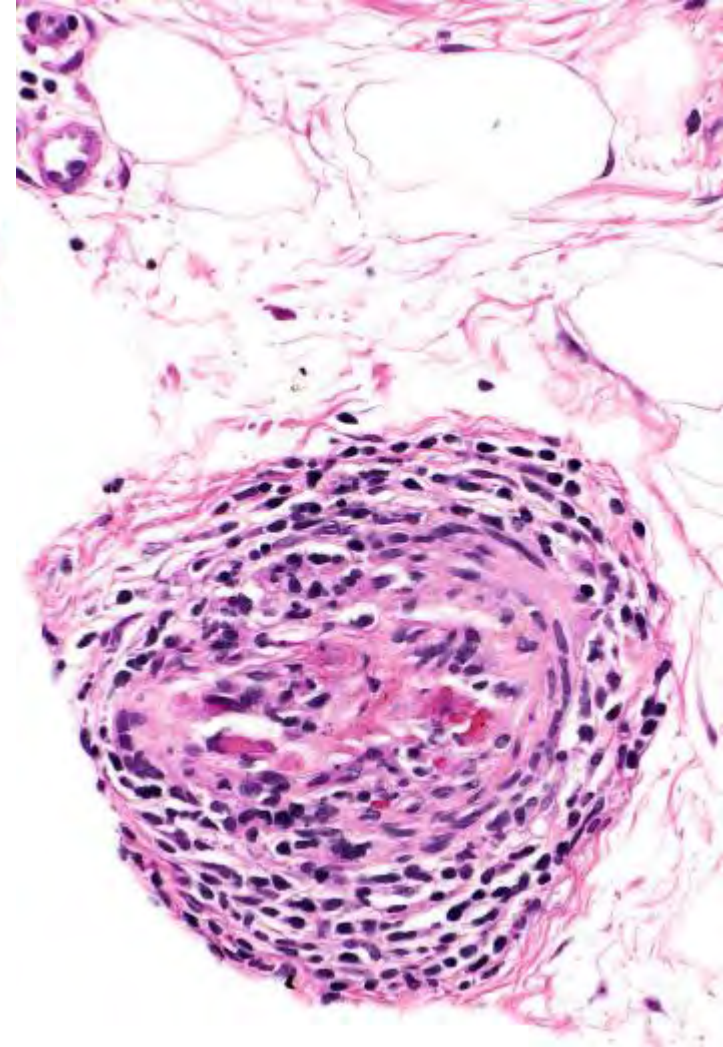
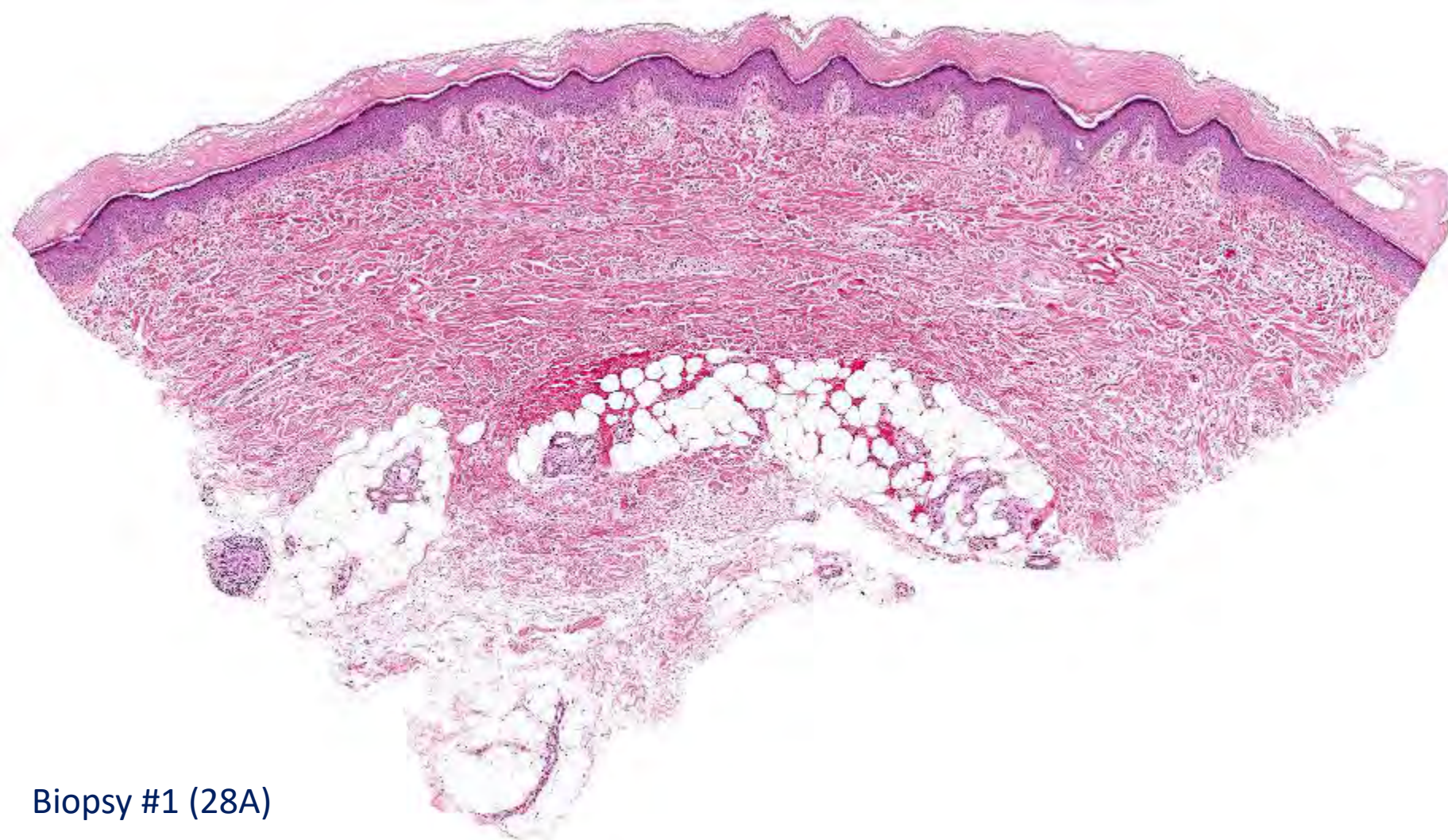
Conclusions: Although current knowledge advocates segregating vasculopathy from vasculitis by means of histopathological examination in LV and CA, clinical experience suggests some overlap and common complex underlying pathomechanisms.



Case 28

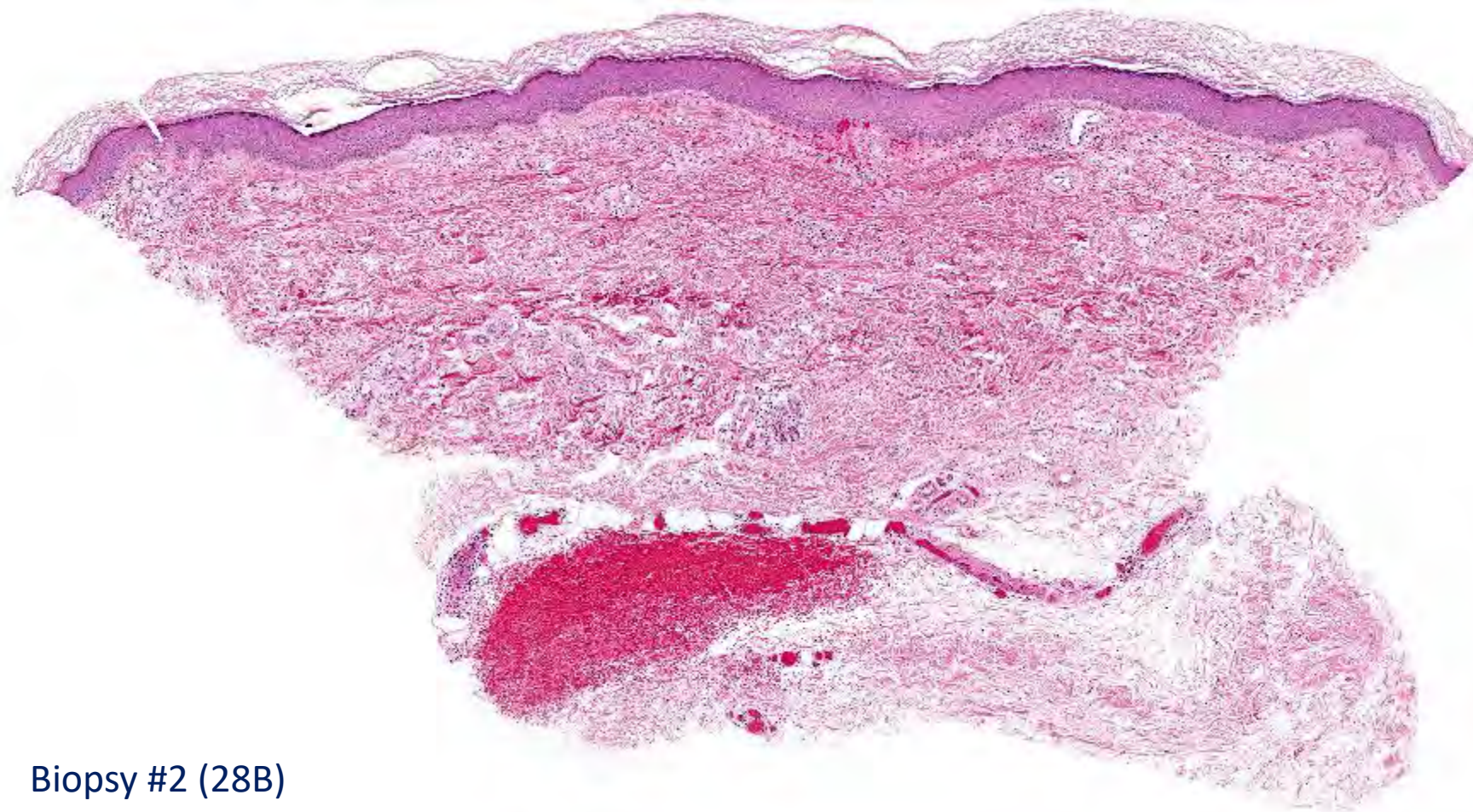
F, 39. History of recurrent "leukocytoclastic vasculitis" on both lower extremities for 2 years (external biopsy not available for review). Comes because of exacerbation of the lesions. Two biopsies.



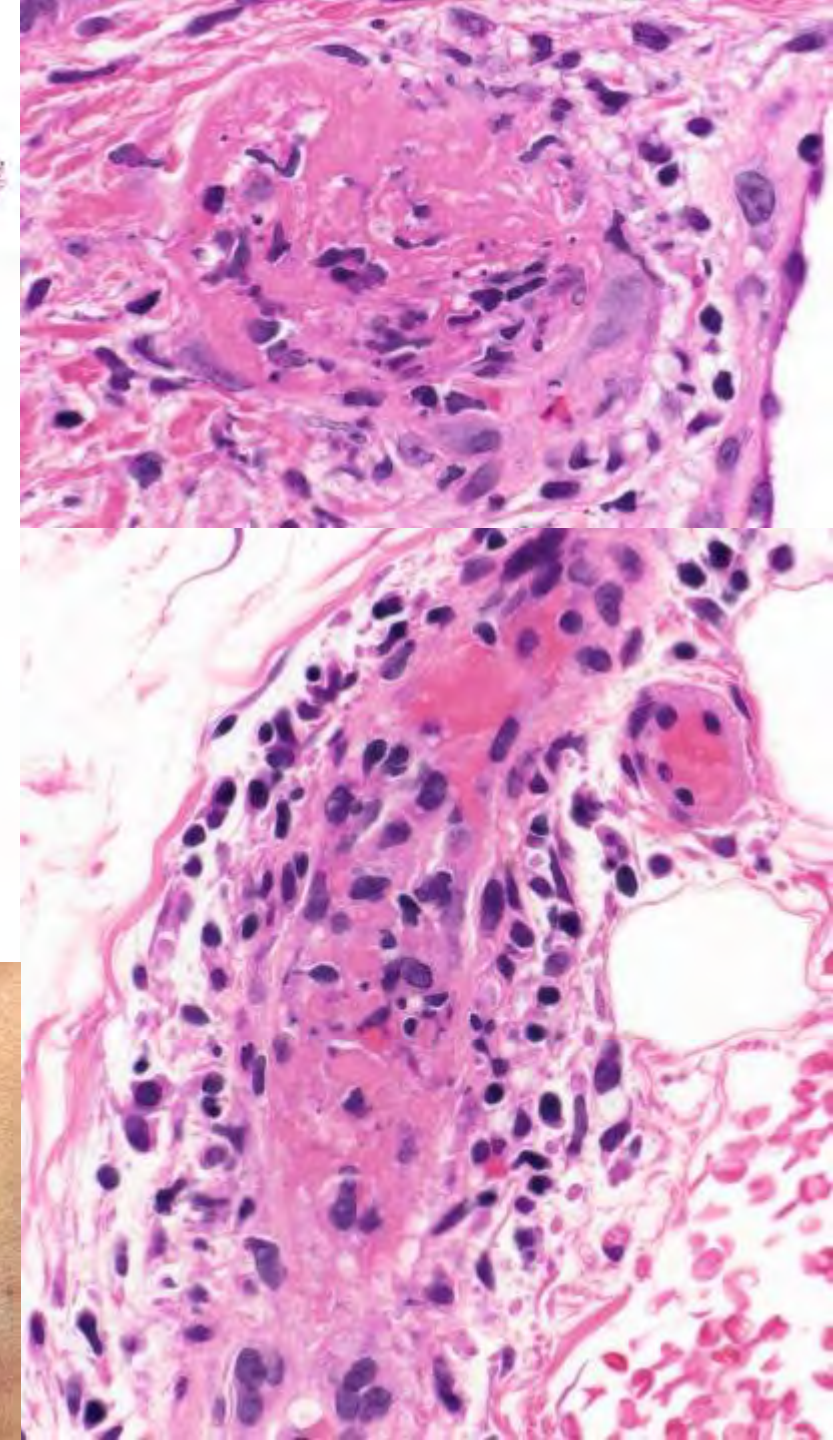


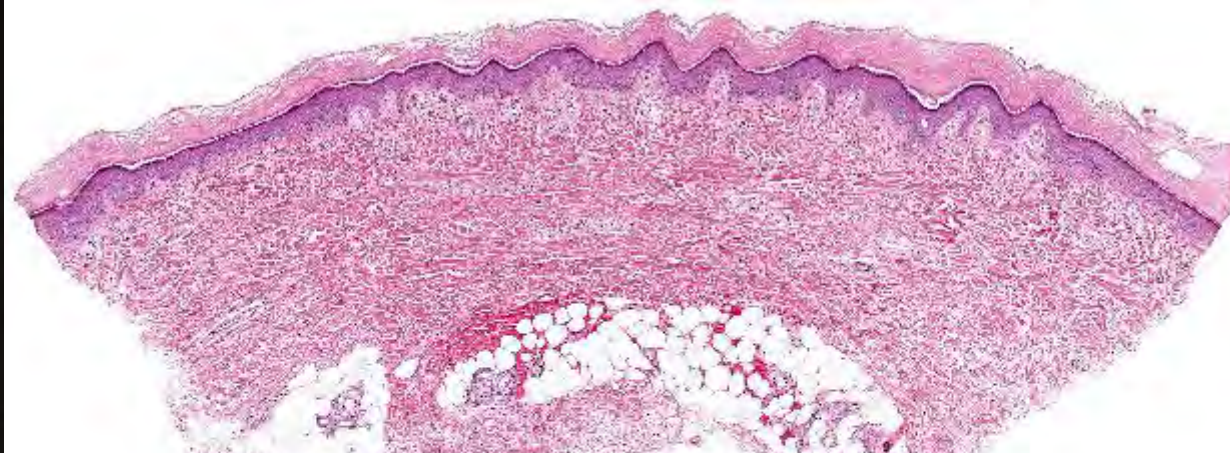
Biopsy #1 (28A)



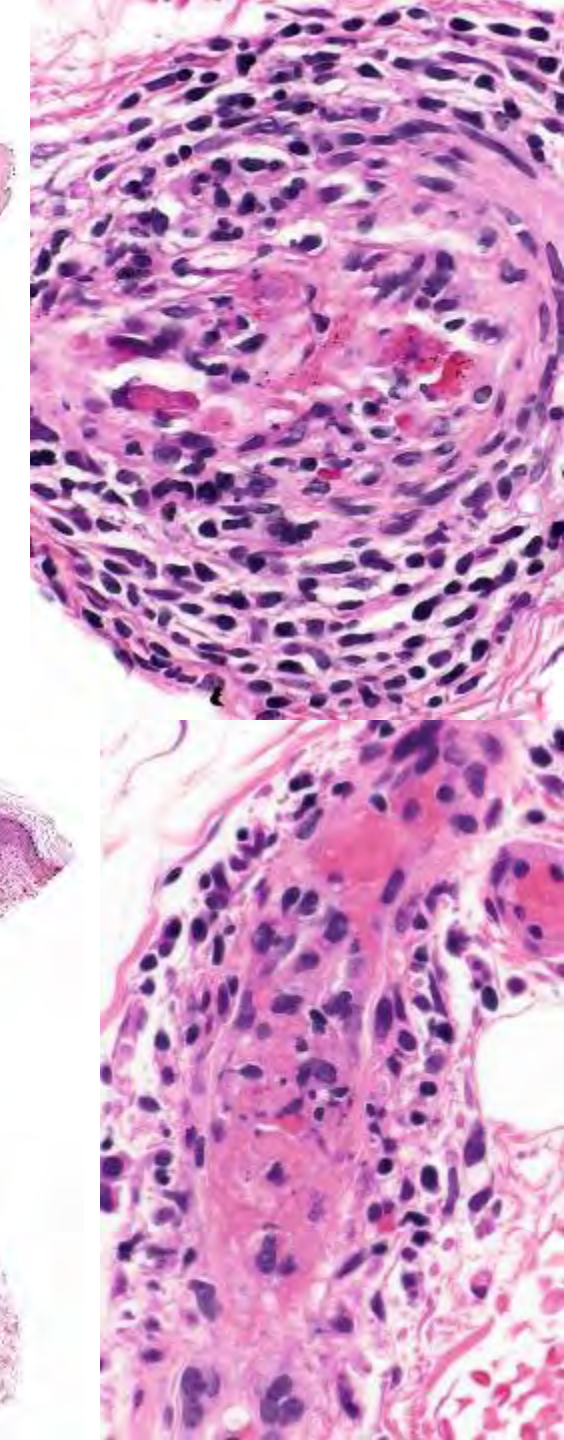
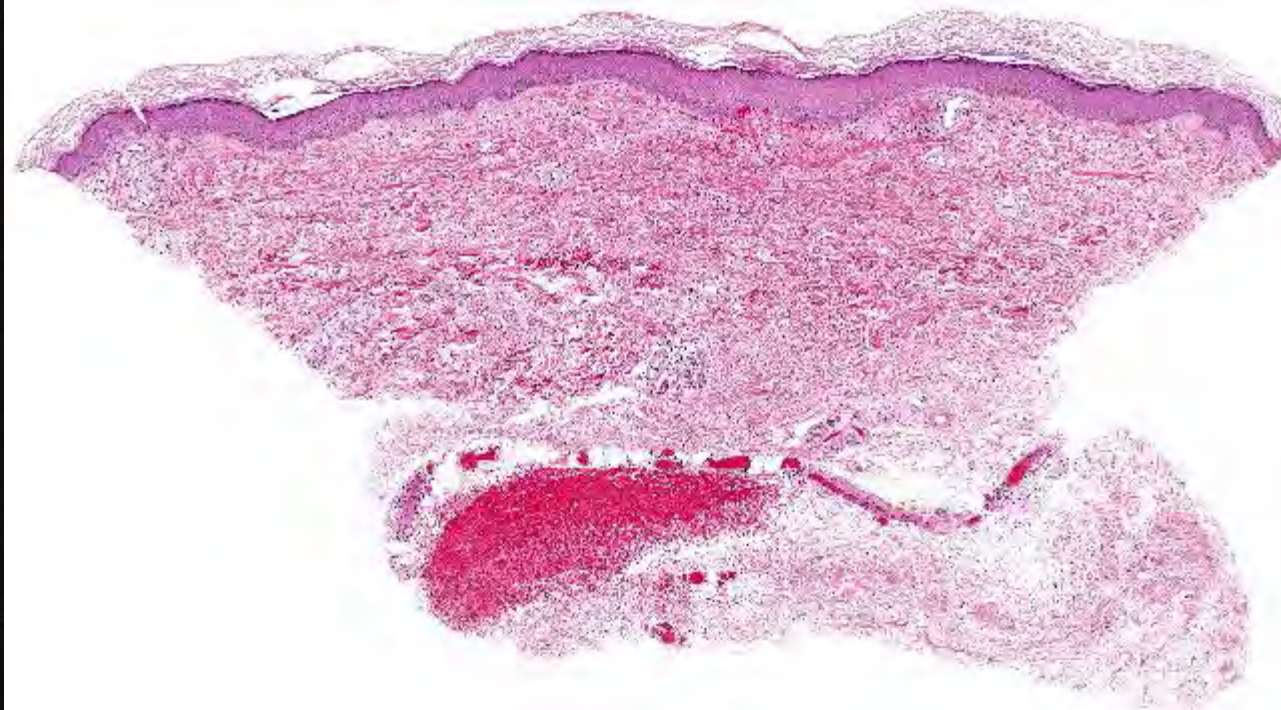


Biopsy #2 (28B)





Livedoid vasculopathy (*atrophie blanche*)



Occlusive Nonvasculitic Vasculopathy

Mar Llanas-Velasco, MD,* Victoria Alegria, MD,† Ángel Santos-Briz, MD,‡ Lorenzo Cerroni, MD,§
Heinz Kutzner, MD,¶ and Luis Requena, MD||

Abstract: We review the most characteristic clinical and histopathologic findings of the cutaneous manifestations of the occlusive nonvasculitic vasculopathic disorders. Clinically, most of these conditions are characterized by cutaneous purpura. Histopathologic findings consist of occlusion of the vessel lumen with no vasculitis. Different disorders may produce nonvasculitic occlusive vasculopathy in cutaneous blood and lymphatic vessels, including embolization due to cholesterol and oxalate emboli, cutaneous intravascular metastasis from visceral malignancies, atrial myxomas, intravascular angiosarcoma, intralymphatic histiocytosis, intravascular lymphomas, endocarditis, crystal globulin vasculopathy, hyperimmunophilic syndrome, and foreign material. Other times, the occlusive disorder is due to platelet plugging, including heparin necrosis, thrombocytosis secondary to myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, and thrombotic thrombocytopenic purpura. Occlusive vasculopathy may also appear in subcutaneous pitting apoplexiform, the last occurring in cryofibrinogenemia, cryoglobulinemia, cold agglutinin syndrome, and cryoglobulinemia. Microorganisms may also occlude the vessels lumen and this is especially frequent in ecthyma gangrenosum, opportunistic fungi as aspergillosis or fusariosis, Listeria phenomenon of lepromatous leprosy and disseminated strongyloidiasis. Systemic coagulopathies due to defects of C and S proteins, coumarin/warfarin induced skin necrosis, disseminated intravascular coagulation, and antiphospholipid antibody/anticoagulant syndrome may also result in occlusive nonvasculitic vasculopathy. Finally, vascular coagulopathies such as Sneddon syndrome, livedoid vasculopathy, and atrophic papulosis may also cause occlusion of the vessels of the dermis and/or subcutis. Histopathologic study of occlusive vasculopathic lesions is the last step to achieve an accurate diagnosis, and they should be correlated with clinical history, physical examination, and laboratory findings to reach a final diagnosis.

Key Words: occlusive vasculopathy, nonvasculitic occlusive vasculopathy, vascular occlusion, cholesterol embolization, cutaneous intravascular metastasis, intravascular angiosarcoma, intralymphatic histiocytosis, intravascular lymphoma, endocarditis, crystal globulin vasculopathy, hyperimmunophilic syndrome, heparin necrosis, thrombocytosis secondary to myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, cryofibrinogenemia, cryoglobulinemia, cold agglutinin syndrome, cryoglobulinemia, septic emboli, coagulopathy, C and S protein defects, coumarin/warfarin-induced skin necrosis, disseminated intravascular coagulation, antiphospholipid antibody/Lewis anti-coagulant, Sneddon syndrome, livedoid vasculopathy, atrophic papulosis

(*Am J Dermatopathol* 2017;39:647-662)

LEARNING OBJECTIVES

Upon completion of this learning activity, participants should be better able to:

1. Evaluate the clinical-pathologic features of the non-vasculitic occlusive vasculopathies with cutaneous manifestations.
2. Establish the histopathologic differential diagnosis among the different disorders that may cause non-vasculitic occlusive vasculopathy in the skin.

INTRODUCTION

Diverse stimuli may produce identical responses in the vessel wall making etiologic diagnoses of vascular injury a challenge. Some nonvasculitic vascular disorders may mimic vasculitis as the result of dermal hemorrhage because of blood vessel wall incompetence or infarction secondary to luminal obstruction.¹ In this review, we will focus only on the occlusive nonvasculitic vasculopathies, which are clinically characterized by the presence of reiform lesions, but may also produce ulcers, ulcers, infarcts, and "purple toe syndrome."²

Clinically, the most characteristic finding in most occlusive nonvasculitic vasculopathic disorders is reiform purpura. We shall include the livedo lesions within the spectrum of the reiform lesions. Most authors differentiate livedo reticularis, characterized by a regular network of blue bands and streaks forming asymmetric gyrate figures, from livedo racemosa, presenting with a static network of racemoid livedo streaks and bands.² Livedo reticularis is considered a benign condition caused by vasospasm or vascular occlusion of arterial vessels and secondary venous ones, always showing a dynamic clinical course with a rapidly changing pattern and therefore will not be discussed in this article. The

TABLE 1. Occlusive Nonvasculitic Vasculopathies

Type of Occlusive Vasculopathy	Entities
Embolization	Cholesterol embolus Oxalate embolus Cutaneous intravascular metastasis from visceral malignancies Atrial myxoma Angiosarcoma ILH IL Libman-Sacks endocarditis in systemic lupus erythematosus Infective endocarditis Crystal globulin vasculopathy HES Foreign material Heparin necrosis Thrombocytosis secondary to myeloproliferative disorders PNH RAI TTP Cryofibrinogenemia Cryoglobulinemia CAS Crystalglobulinemia EG Opportunistic fungi: aspergillosis, fusariosis Listeria phenomenon of lepromatous leprosy Disseminated strongyloidiasis Defects of C and S proteins Coumarin/warfarin-induced skin necrosis Disseminated intravascular coagulation Antiphospholipid antibody/LA syndrome SS LV (atrophic blanche) Atrophic papulosis (DD) Cutaneous collagenous vasculopathy RAE Stress reticulocyte adhesion Cutaneous calciphylaxis HCU-induced ulcers Occlusive vasculopathy induced by CI Contact dermatitis from leprazolol
Platelet plugging	
Cold-related gelling or agglutination	
Vessel-invasive microorganisms	
Systemic coagulopathies	
Vascular coagulopathies	
Red cell occlusion syndromes	
Miscellaneous	

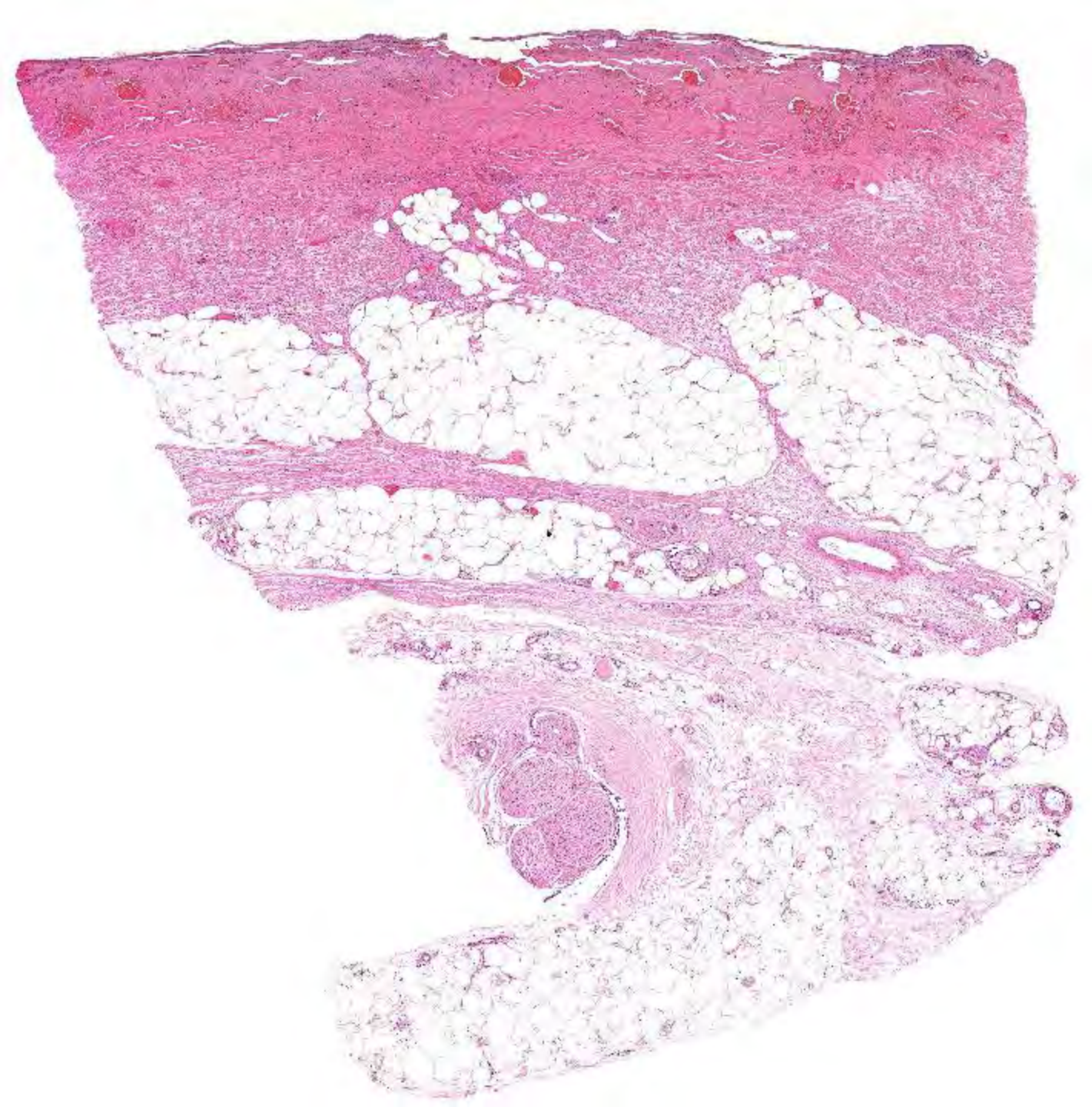
Although all aspects of pathogenesis have not yet been clearly delineated, LV often is associated with several hypercoagulable states, including Factor V Leiden mutation, prothrombin gene mutation, antithrombin III deficiency, protein C deficiency, APS, and hyperhomocysteinemia. (...) LV may coexist with cutaneous polyarteritis nodosa within the same skin biopsy; remarkably cutaneous polyarteritis nodosa may clinically mimic atrophie blanche, thereby underlining the importance of performing deep biopsies in these patients, especially when they present with peripheral neuropathy or other signs suspicious of an underlying vasculitis, to demonstrate the segmental involvement of a muscular vessel.

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All authors, faculty, and staff in a position to control the content of this CME activity and their immediate superiors (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organization pertaining to this educational activity.

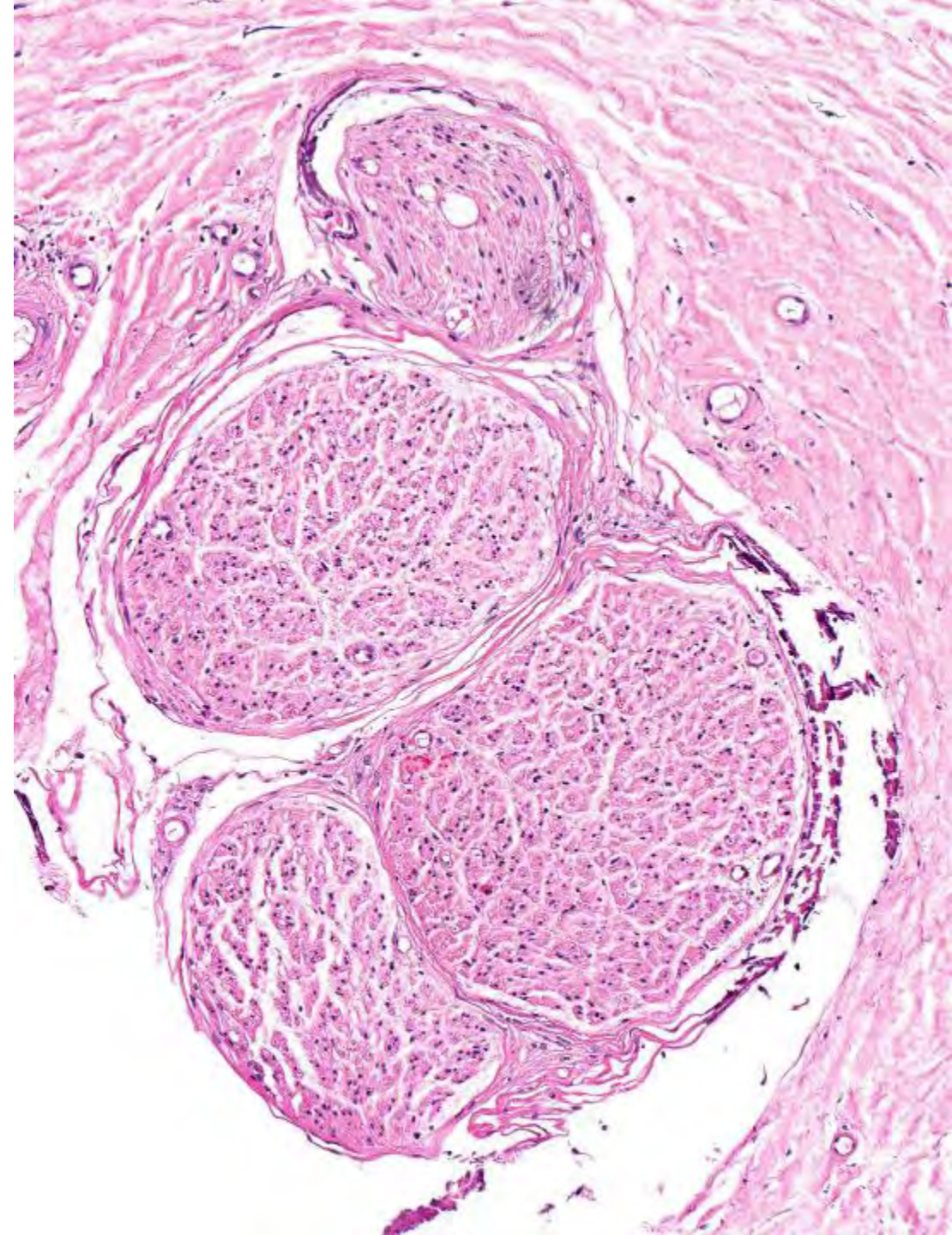
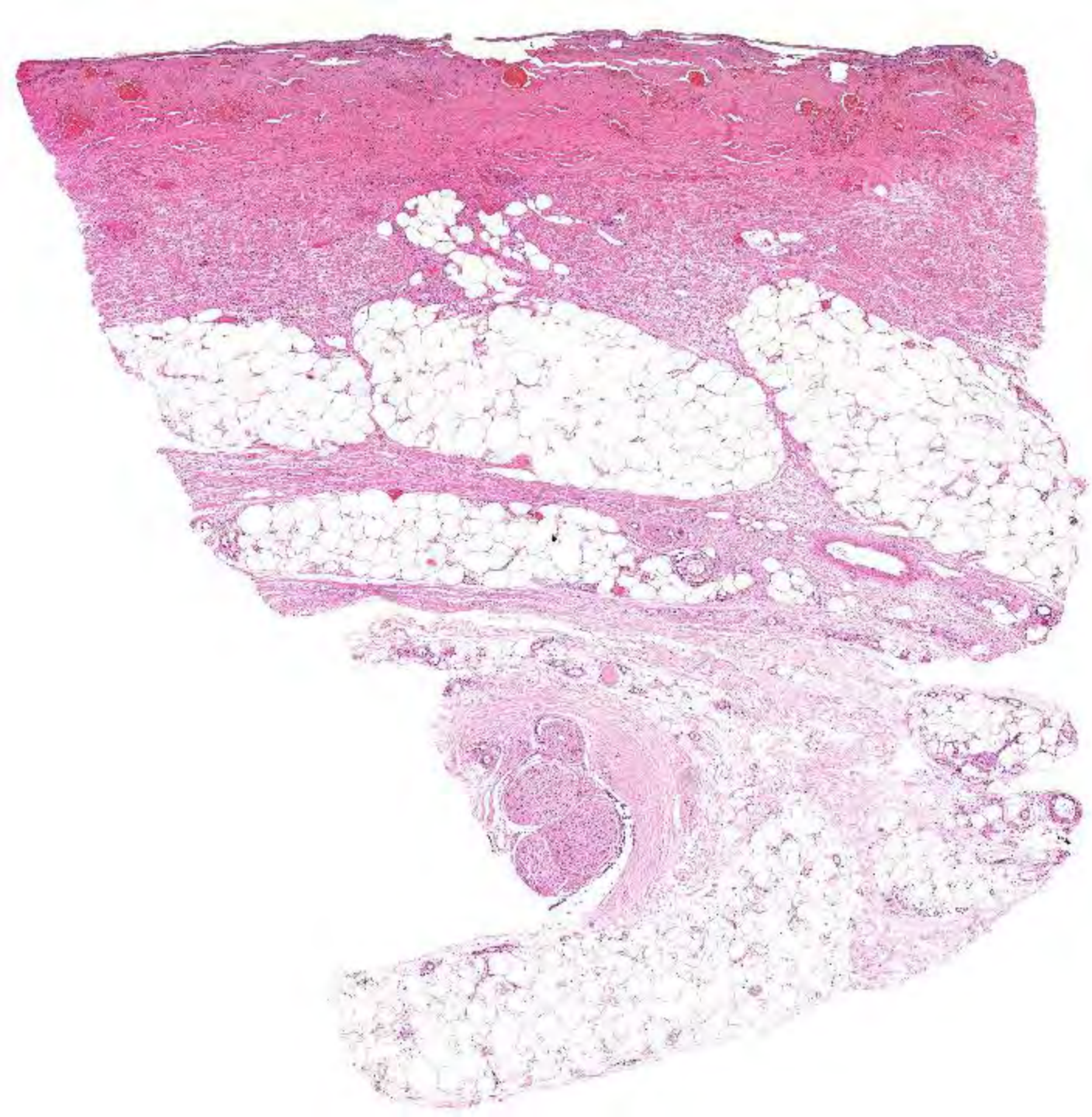
Reprints: Luis Requena, MD, Department of Dermatology, Fundación Hospital Díaz Vialer, Reyes Católicos 2, 28019 Madrid, Spain (e-mail: lrequena@fjv.es).

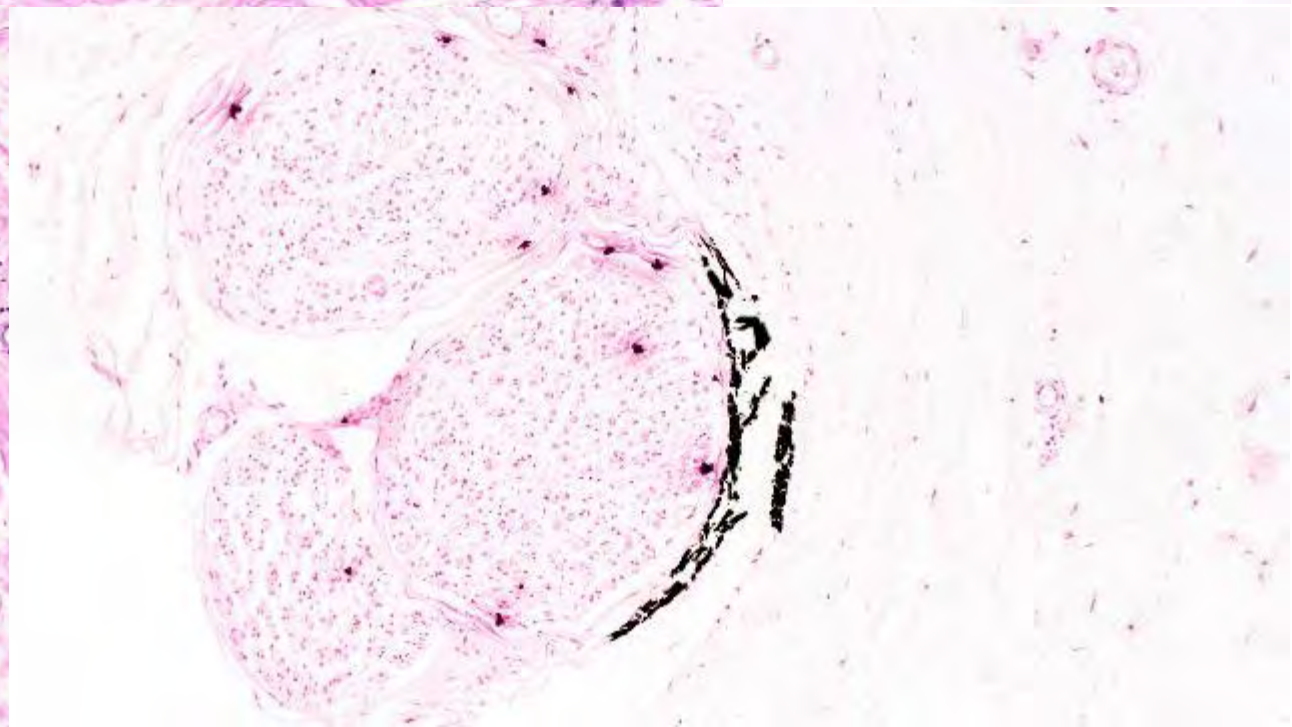
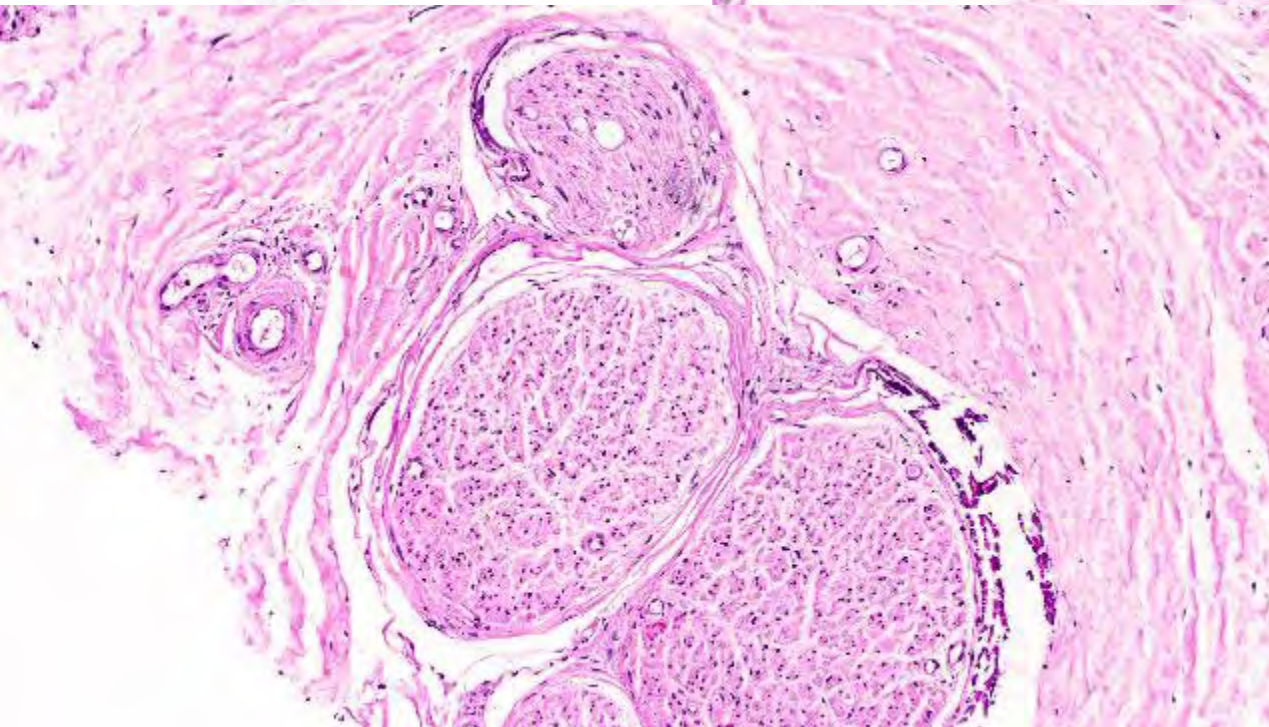
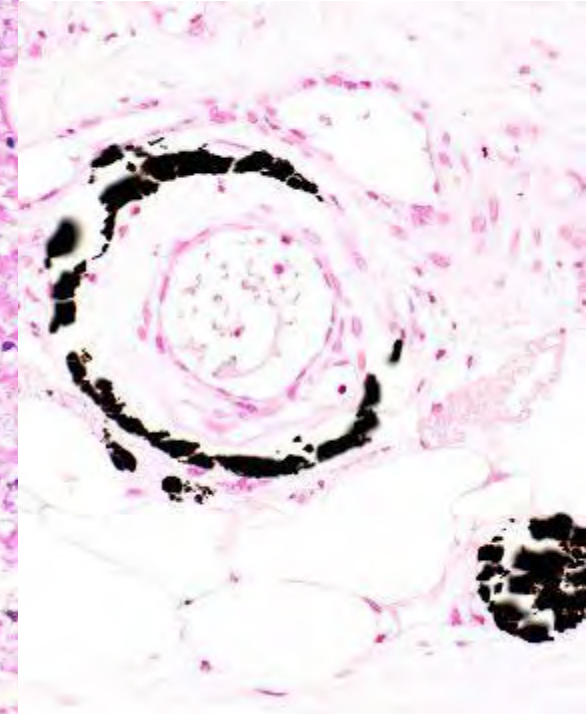
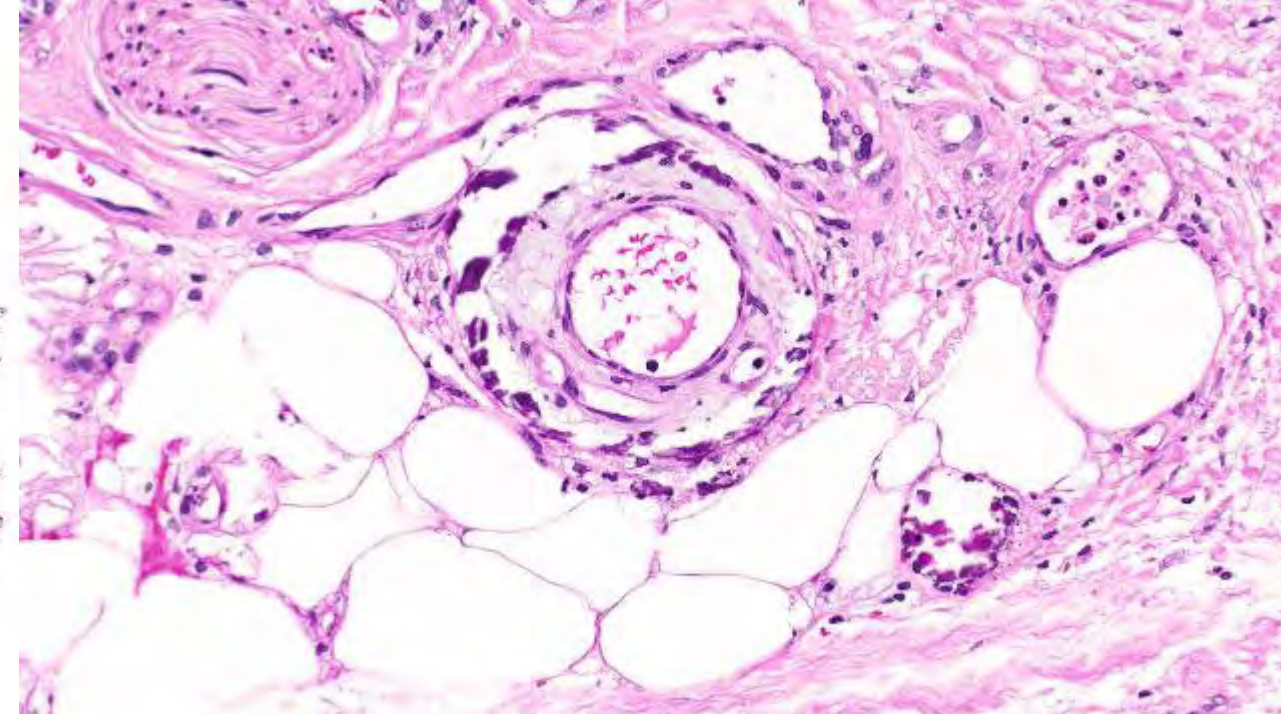
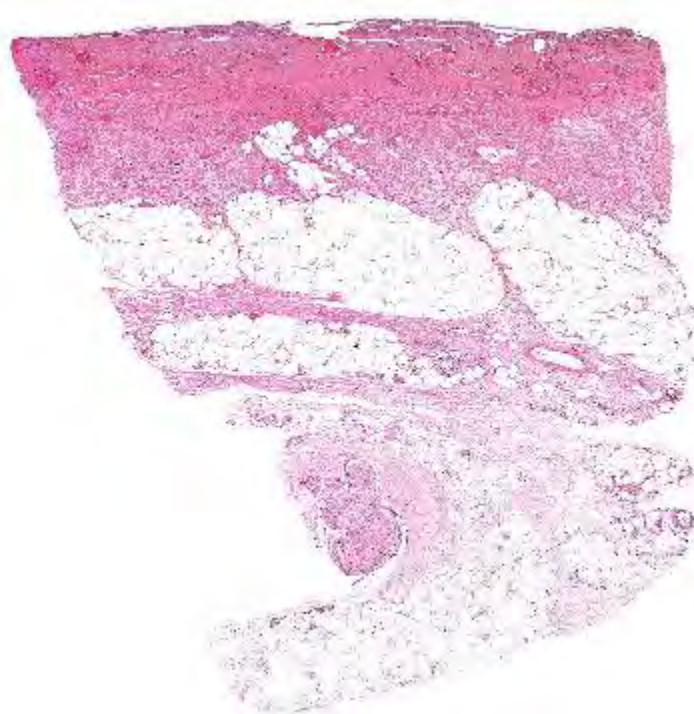
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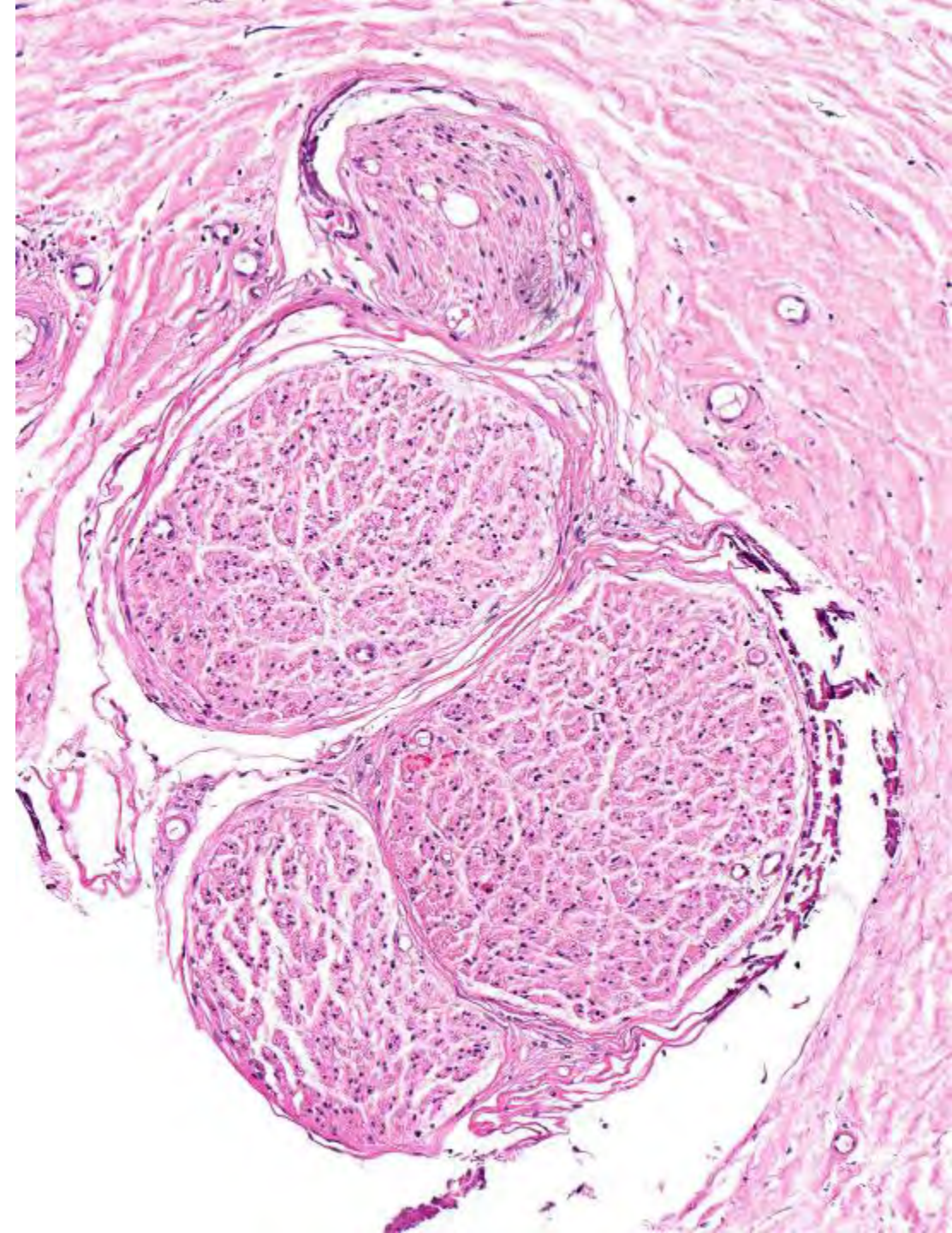
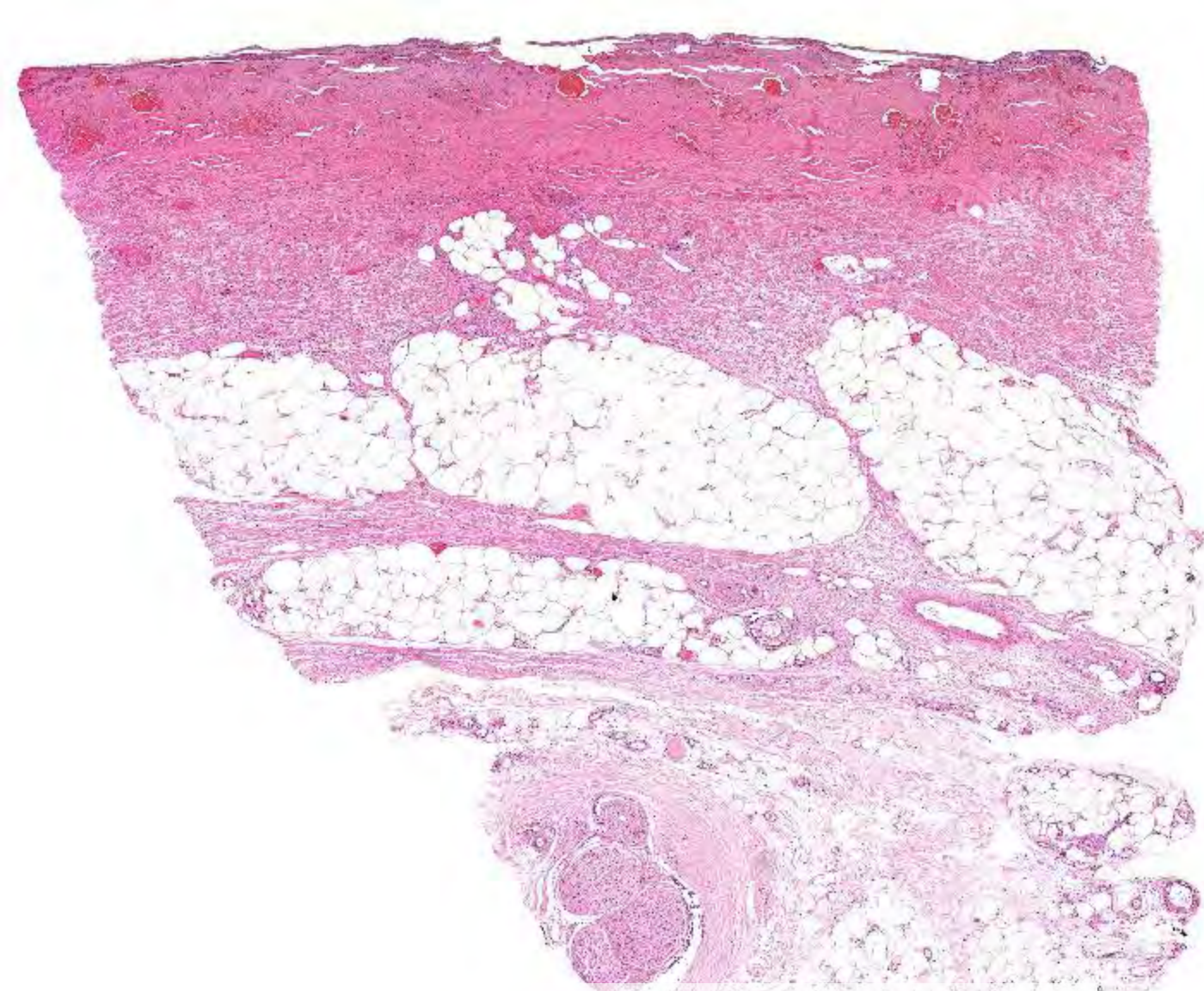


Case 29

M, 84. Chronic renal insufficiency. Ulcerations on the distal lower extremities.







Calciophylaxis
with perineural calcification

Perineurial and Vascular Calcification in a Patient with Chronic Renal Failure

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Received April 13, 2016

Sir,

The term calciphylaxis, coined by Seyle in 1962 (1), traditionally describes an uncommon entity that usually presents with cutaneous necrosis due to small vessel calcification. As the original concept regarding risk factors for the disease has changed considerably in the past few years, we have recently suggested the term 'cutaneous vascular calcification' for this pathology, based on the study of associated diseases and chronic pathological features of > 2 patients with calcification within the walls of cutaneous vessels (2). To date, however, calcanea deposits in the perineurium have never been described in the setting of cutaneous vascular calcification.

We report here the finding of cutaneous vascular and perineurial calcification in skin samples from a diabetic patient with chronic renal failure who developed extremely painful erythematous and violaceous lesions in the abdomen, thighs and foot.

CASE REPORT

A 67-year-old woman with a history of chronic renal failure due to diabetic nephropathy who was undergoing peritoneal dialysis was admitted for evaluation of an episode of dialysis fluid leak. She developed an erythematous plaque located in the infraumbilical region. This lesion was extremely painful and progressively increased in size. Physical examination revealed a firm plaque of this (10 cm in size) with violaceous calcification (Fig. 1). Similar painful lesions subsequently appeared on both thighs and purpuric reticulated macular lesions developed on the dorsal and lateral sides of the left foot. During the following days, necrotic areas appeared on the abdominal plaque, evolving into ulcerated lesions. Morphine did not achieve good control of the intense pain.

Blood count revealed leukocytosis, neutrophilia and leucocytosis (15,420 leucocytes/mm³), mild activated neutrophilia (11%), and monocytosis (10%). Hemoglobin was 10.9 g/dL. The blood film showed marked monocytosis, poikilocytes and abnormal nucleocytization. Biochemical tests disclosed elevated parathyroid hormone levels (144 pg/mL; normal 10–35 pg/mL), with normal calcium and phosphate levels, low albumin (2.4 g/dL; normal 3.4–4.8 g/dL) and protein levels (6 g/dL; normal 6.6–8.7 g/dL) and elevated creatinine (3.5 mg/dL; normal 0.5–1.3 mg/dL), urea (58 mg/dL; normal 14–20 mg/dL), alkaline phosphatase (419 U/L; normal 31–236 U/L) and erythrocytase levels (157 U/L; normal 7–52 U/L). Erythrocytase levels were within normal range. Coagulation tests disclosed a shortened thromboplastin time (62.9%). Radiological studies of lower extremities and abdomen revealed arterial calcifications of the abdominal aorta and its branches, both iliac arteries and left femoropopliteal territory. An abdominal ultrasound study showed calcifications of the subcutaneous tissue.

Four biopsies were performed, two from the abdomen, one from the right thigh and one from the left foot. Parietal calcification of small vessels located in the dermis and/or subcutaneous tissue was observed in all samples. The skin from abdomen and thigh also showed continuous circumferential calcium deposits in the perineurial sheaths of small dermal nerve twigs (Fig. 2 and 3). The staining pattern of the perineurial sheaths was continuous. No alteration of the nerve fibres was observed. No extravascular calcifications were observed in any of the samples. Different grades of calcifications and eccrine gland necrosis could also be observed, without an inflammatory infiltrate.

The patient died 1 month after the onset of the cutaneous lesions due to massive gastrointestinal bleedings.

DISCUSSION

The presence of vascular calcification in patients with chronic renal failure is a well-known phenomenon. Clinically these patients usually develop extremely painful indurated areas and cutaneous purpura located on the medial thighs, buttocks and the lower part of the abdomen. Progression results in the development of central necrosis and ulceration (3). Our patient could be included in this group of patients. Histologically, they are characterized by the presence of calcium deposition in the walls of small-to-medium diameter blood vessels of the dermis and subcutaneous fat followed by fibroblast proliferation and giant cell formation (3). Fibrosis, luminal hyperplasia and occasionally thrombosis of the vessel result (3).

Reports on calcification in human peripheral nerves are scarce. Pietari & Halla (4) reported selective calcification of the perineurial sheaths in the sciatic nerve found in a necropsy of a 32-year-old woman who died from uremia complicating juvenile diabetes. Histological studies showed that the outer layers of the perineurium were more heavily calcified, while the innermost layers often were free. In a later report (5) they concluded that the mineral deposits were definitely represented in the outer perineurium and composed mainly of calcium hydroxyapatite. Perineurial calcification has been verified in diabetes by Johnson et al. (6). Vadas et al. (7) studied sural nerve biopsies from 25 patients with different pathologies, mostly neurovascular diseases. Calcium deposits were found in the perineurial sheaths of 20 individuals > 16 years of age, irrespective of the presence or absence of nerve fibre pathology. Fifteen of these patients suffered from normal pathology. The staining pattern of the perineurial sheaths was, most and deposits were located in the middle and outer layers of the

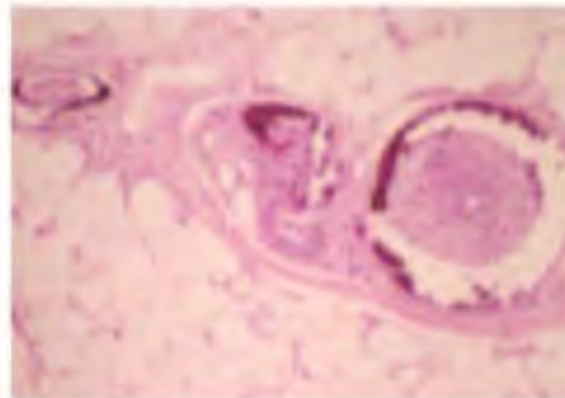


Fig. 2 Parietal vascular calcification and intimal proliferation can be observed on the right side of the biopsy. Concentric calcification around a small nerve twig is present on the left side. H&E $\times 10$.

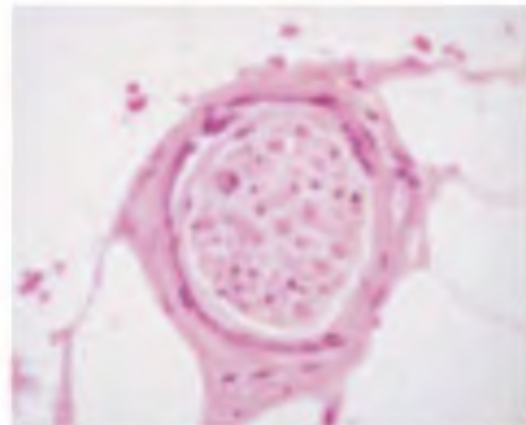


Fig. 3 Transverse section of a dermal nerve. Detail of the calcified perineurial sheath surrounding the nerve. H&E $\times 25$.

Cutaneous vascular calcification. Perieccrine calcification as a diagnostic key for calciphylaxis

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Abstract

Background: Attempts have been made to establish discriminative criteria between classic calciphylaxis (CPX) and those cases in which cutaneous vascular calcification (CVC) represents an incidental finding (epiphenomenon).

Methods: Retrospective, observational cohort study of patients with CVC to distinguish clinicopathological features between CVC as classic CPX (CVC in cutaneous lesions with erythematous–violaceous plaques with or without ulceration) or as an epiphenomenon (CVC in cutaneous lesions with known diagnosis). Different clinicopathological parameters and the presence of perieccrine calcification and psoriasisiform vasculopathy (PXV) lesions were evaluated.

Results: Sixty-six patients were studied. The CPX group showed a significantly higher percentage of renal failure, hypertension, altered laboratory parameters, painful lesions, and mortality rate. Histopathologically, the CPX group was associated with more than one vessel per field involved with subintimal concentric calcification and perieccrine calcification (observed exclusively in the CPX group) while PXV lesions, although more frequent in the CPX group, were also observed in the epiphenomenon group.

Conclusion: Perieccrine calcification and the presence of more than one vessel per field involved by concentric pattern calcification could be used as a diagnostic marker of CPX. Although PXV lesions are not an exclusive marker, they could suggest CPX diagnosis.

KEYWORDS

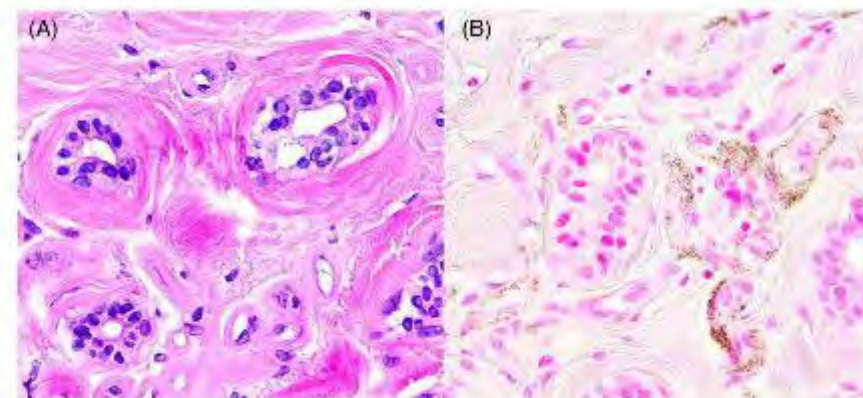
calcification, cutaneous calciphylaxis, epiphenomenon, perieccrine calcification

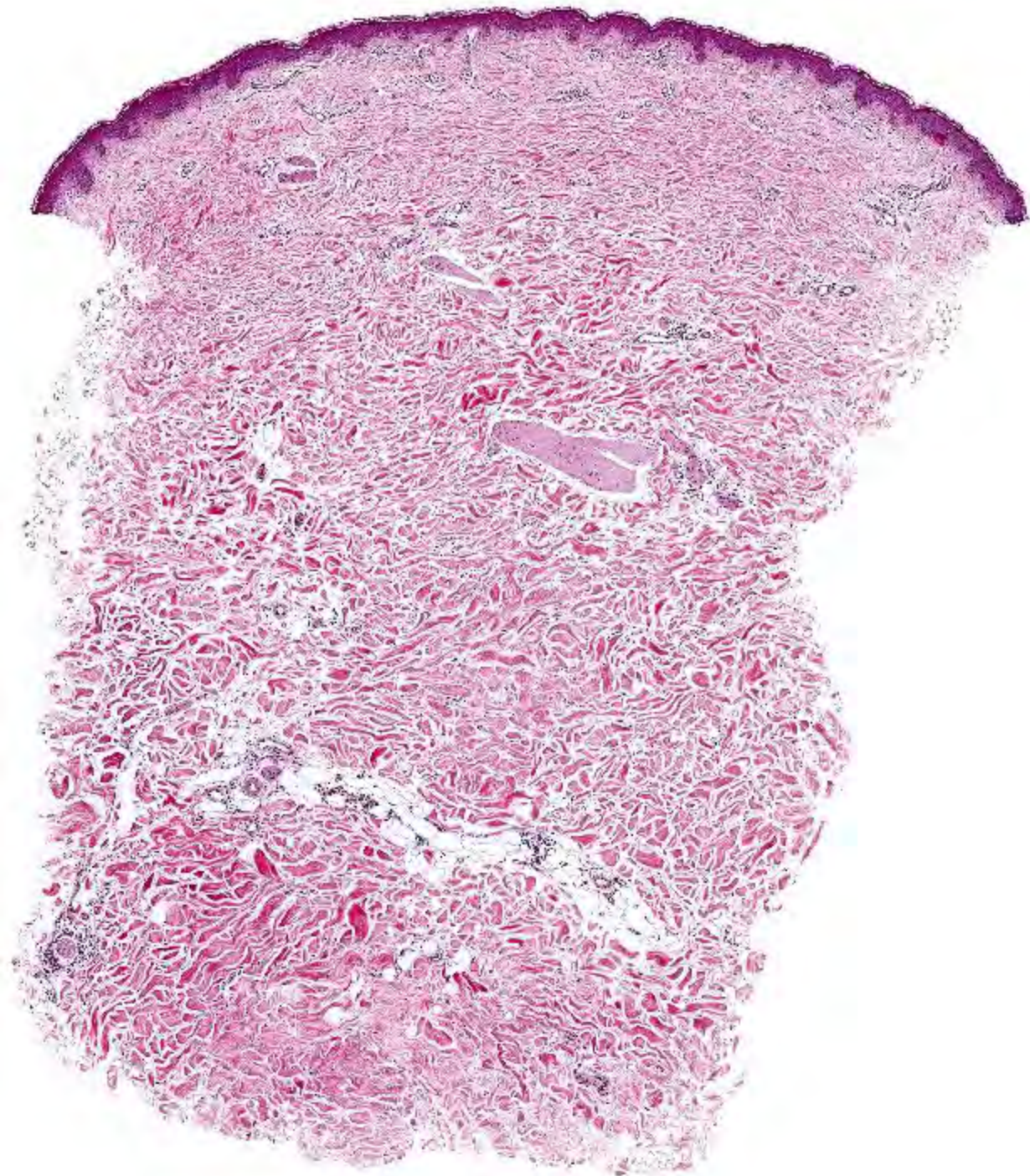
1 INTRODUCTION

Since Selig et al first coined the term calciphylaxis (CPX),¹ there has been much controversy about its meaning. There is no unanimity, and cases considered as CPX have been reported using many different terms.^{2–7} Classically, CPX has been characterized by a clinical picture consisting of painful, ulcerated necrotic lesions, generally in the lower limbs, with a high degree of morbidity and fatal outcome. These lesions were associated with accumulation of calcium deposits

metabolism with hyperparathyroidism and renal failure (PTHrP⁸ which has) some authors as refer to these situations as calcific uremic arteriopathy.^{9–11} However, the histopathological presence of calcification in small and medium to large vessels was necessary to confirm CPX diagnosis. Nevertheless, these findings were very different from those observed by Selig et al in the study in which they termed “calcified” leukine deposits in the skin and other organs of CPX patients.¹ Moreover, CPX pathogenesis is not well understood. Current data from numerous studies, possible presence of calciphylaxis

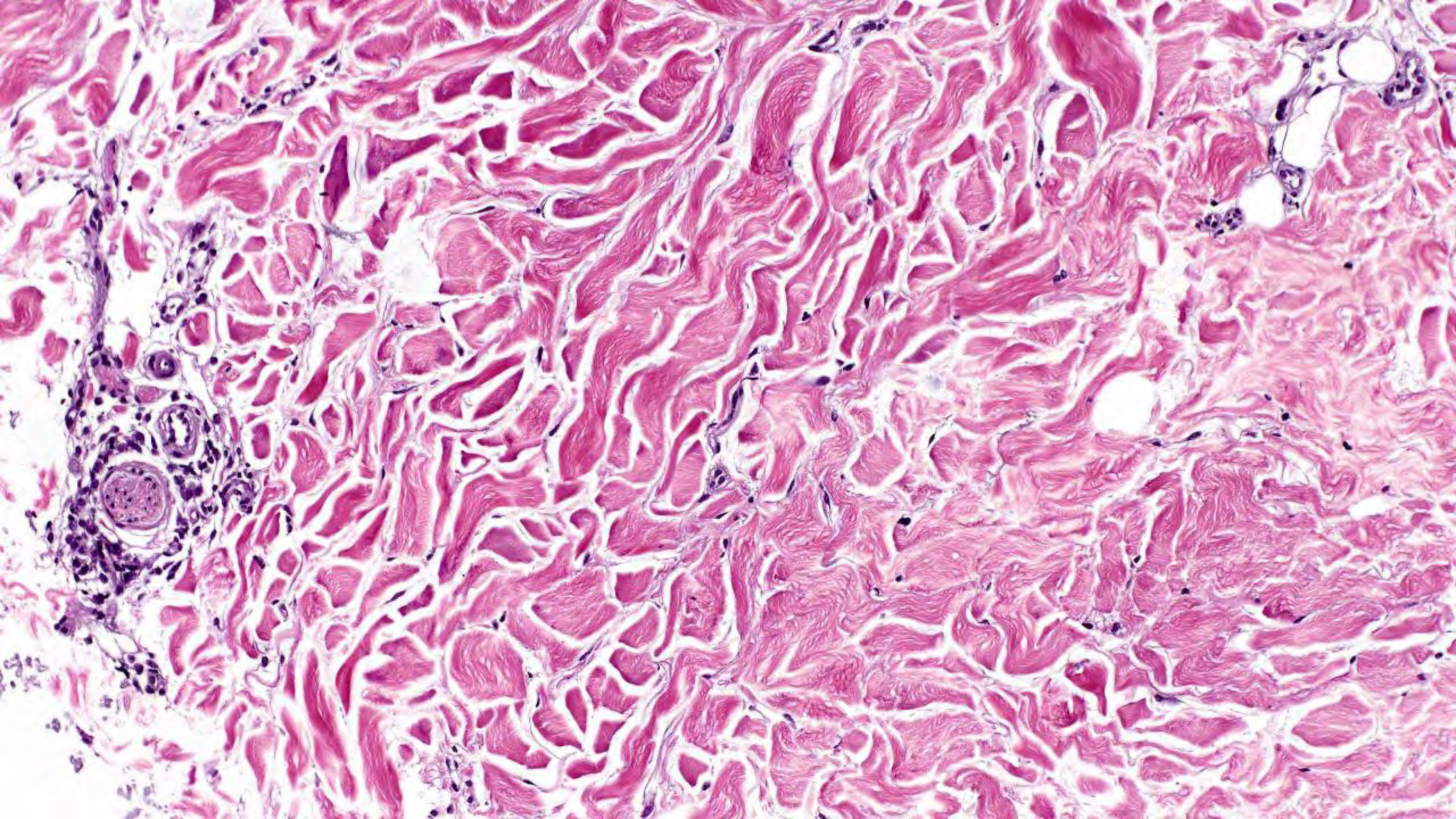
FIGURE 6 (A) Detail of eccrine glands surrounded by dense collagenous tissue where basophilic areas suggest the presence of calcium deposits surrounding them. Hematoxylin–eosin staining $\times 400$. (B) von Kossa $\times 400$ highlighting the calcium deposits surrounding the eccrine glands

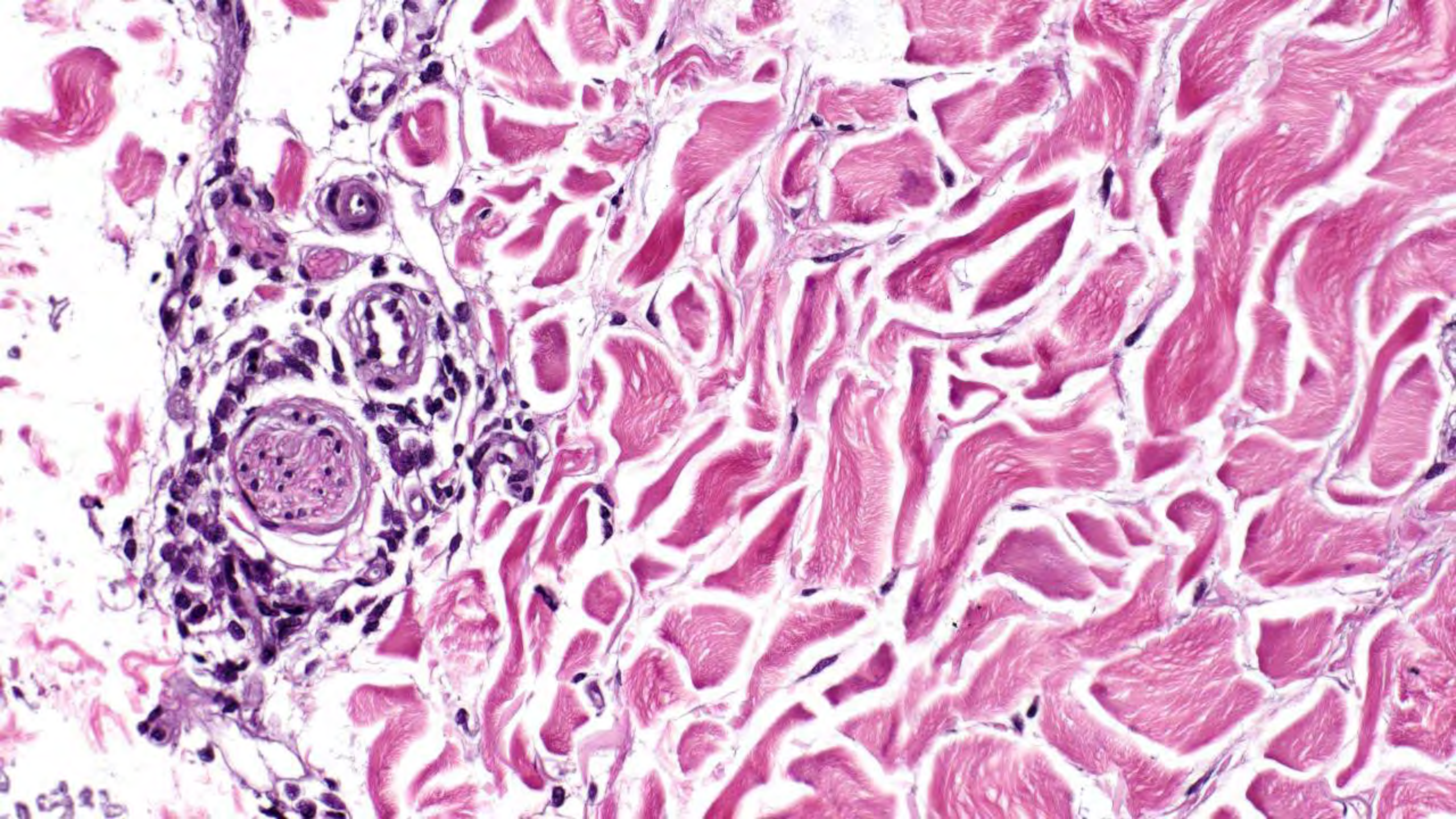


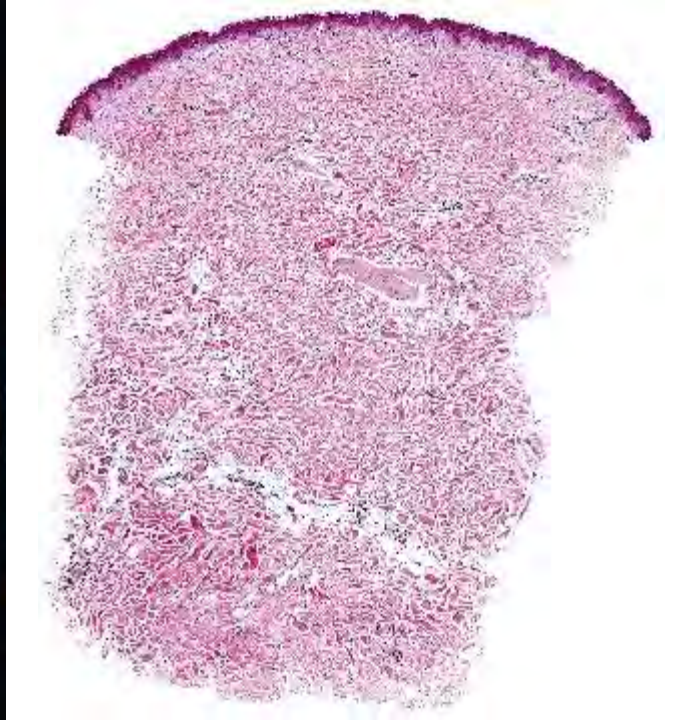


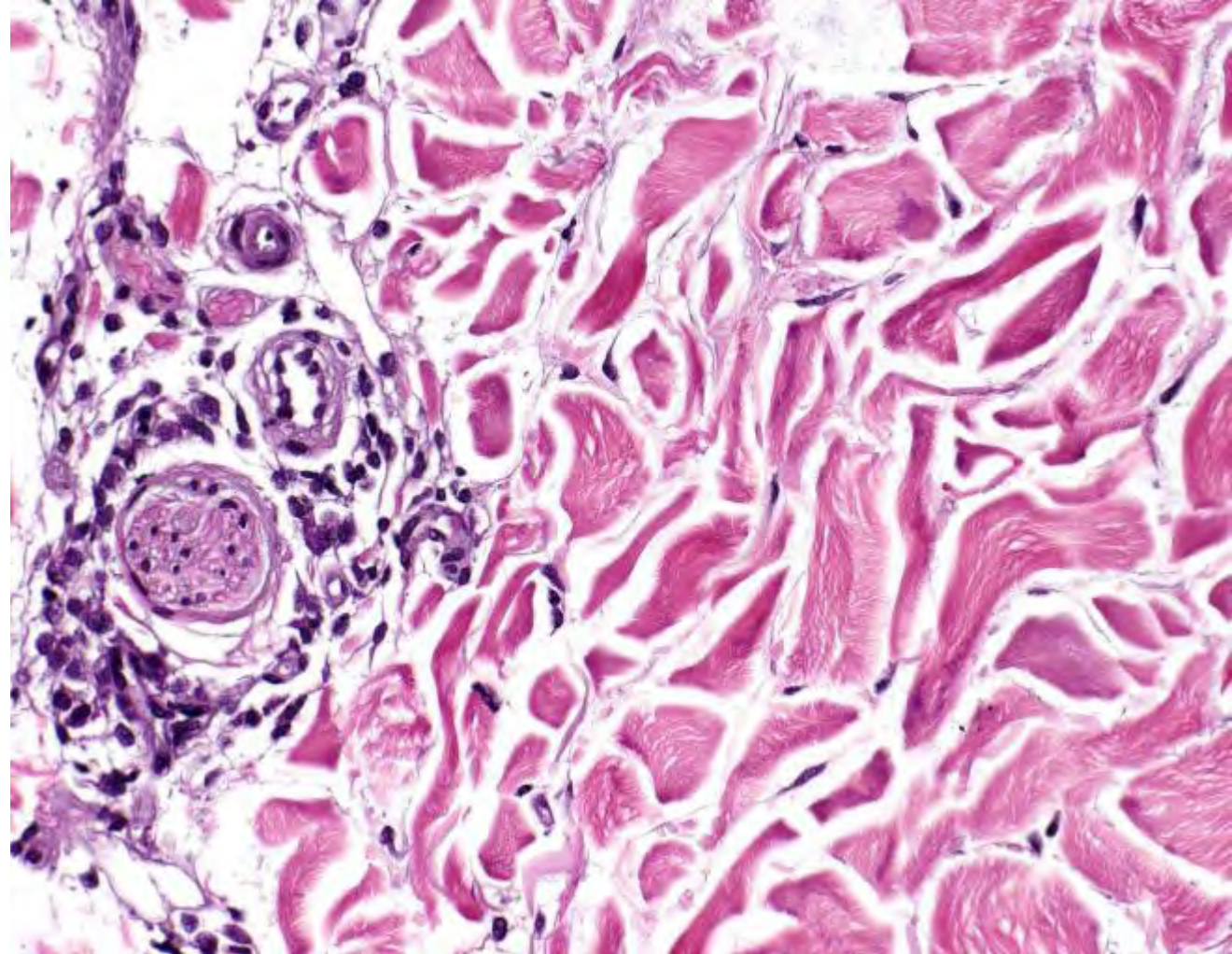
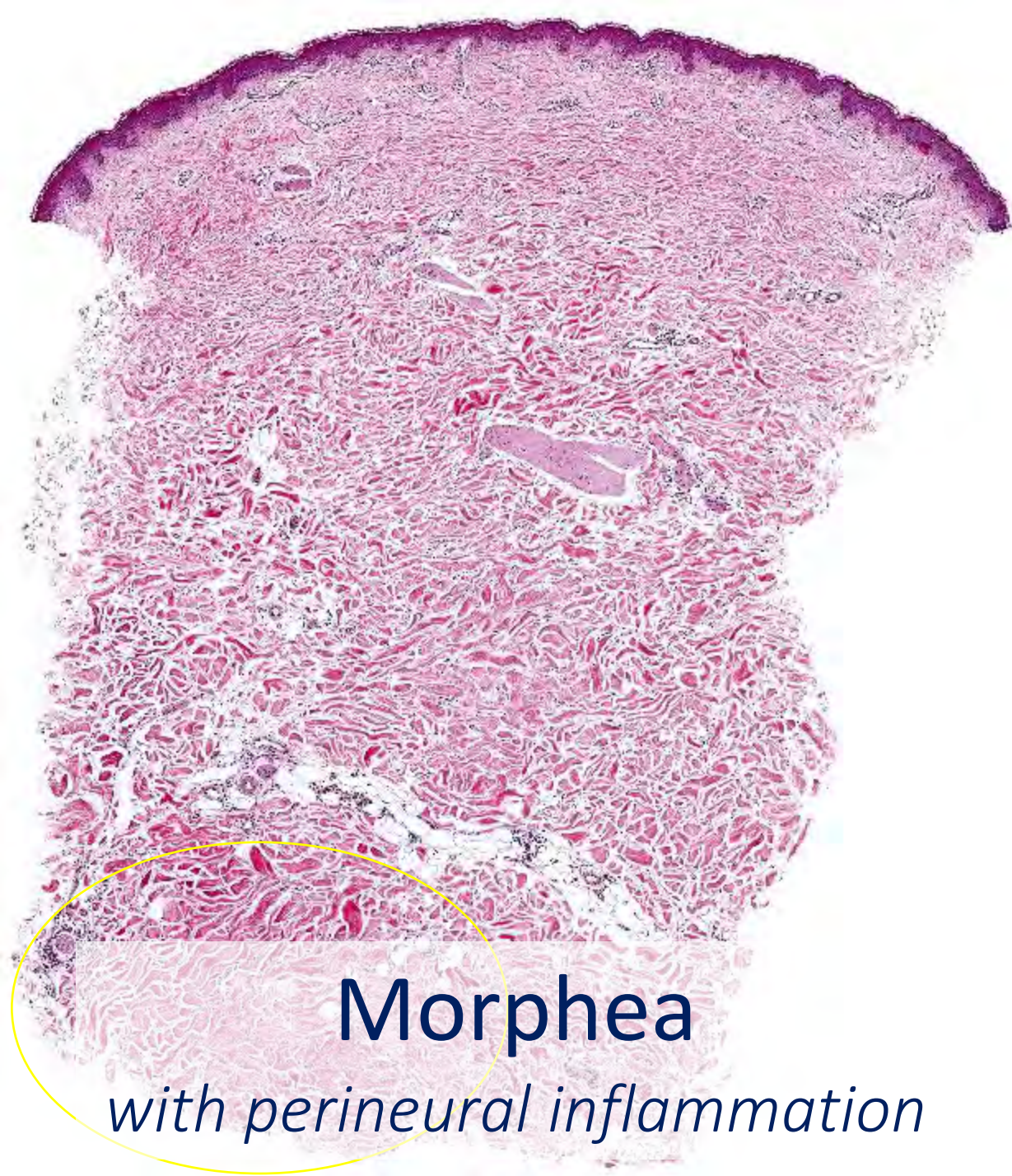
Case 30

F, 59. According to the patient lesions on both flanks for approximately 8 months.









Perineural inflammation in morphea (localized scleroderma): systematic characterization of a poorly recognized but potentially useful histopathological feature†

The association between morphea and perineural inflammation has been reported sporadically but never studied systematically. To assess the prevalence and nature of perineural inflammation in various clinicopathologic stages of morphea and a group of other inflammatory dermatoses, 60 morphea and 30 control skin biopsies were studied using hematoxylin/eosin and S100 stains. Perineural inflammation was semiquantitatively analyzed (scored), which along with the pattern (concentric vs. marginal) and cellular composition was compared in the two groups. Perineural inflammation was identified in 81% and 61% of morphea and control cases, respectively. Identification of only concentric stained sections could still detect this feature in 58% of morphea and 33% of control biopsies. Mean perineural inflammation score in morphea (3.55) was significantly higher than in the control group (0.23) ($p < 0.0001$), and the inflammation tended to show a concentric pattern with plasma cell neurotropism. Intra-neural inflammation was limited to four morphea cases. Although perineural inflammation is common in morphea, it is not unusual to find this feature in other inflammatory conditions. Nevertheless, perineural inflammation can serve as an important diagnostic adjunct in difficult cases of morphea if one considers its greater intensity, predominantly concentric pattern and the tendency to show plasma cell neurotropism.

Keywords: inflammatory disorders, morphea, perineural inflammation, scleroderma

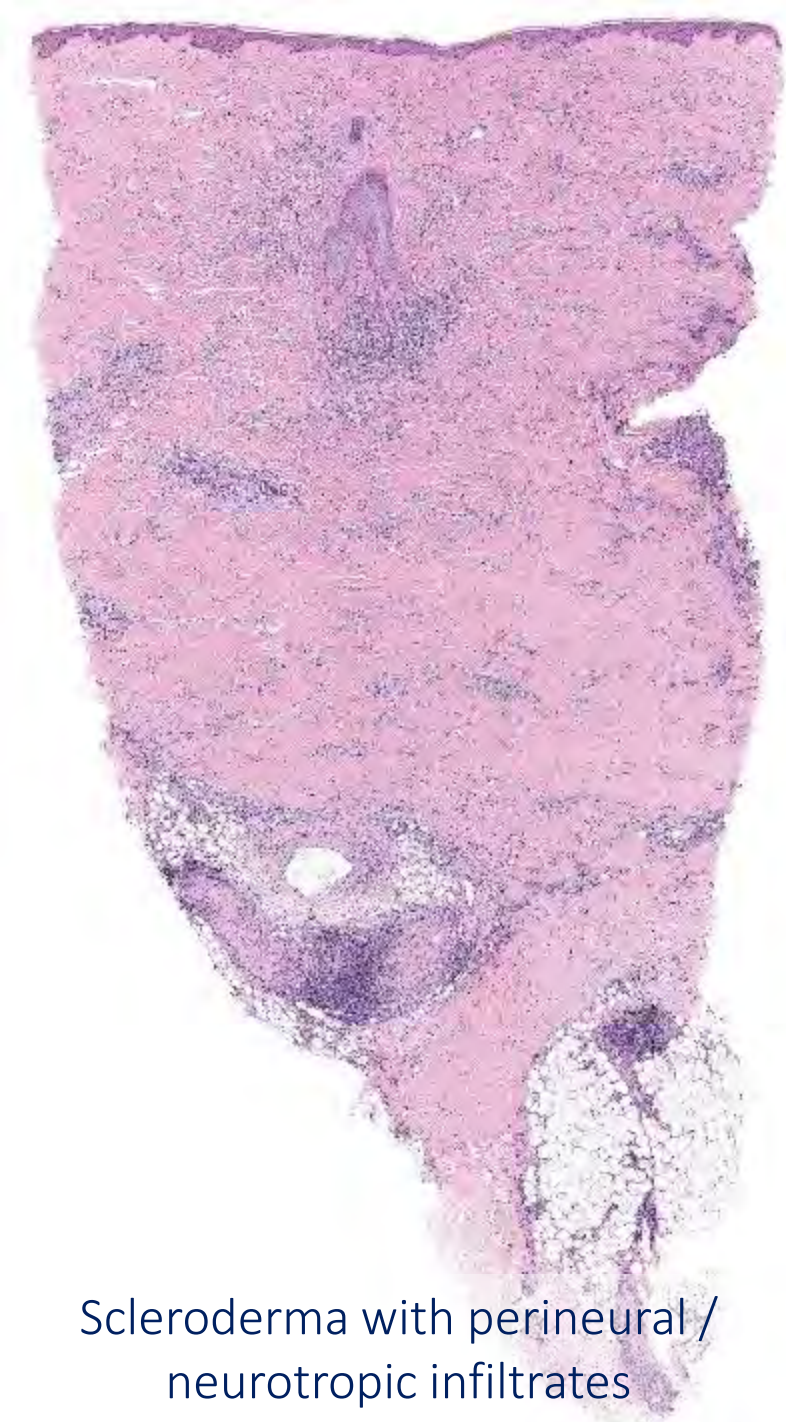
Dhaliwal GA, MacKenzie AL, Biswas A. Perineural inflammation in morphea (localized scleroderma): systematic characterization of a poorly recognized but potentially useful histopathological feature. *J Clin Pathol* 2014; 41: 26–35. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

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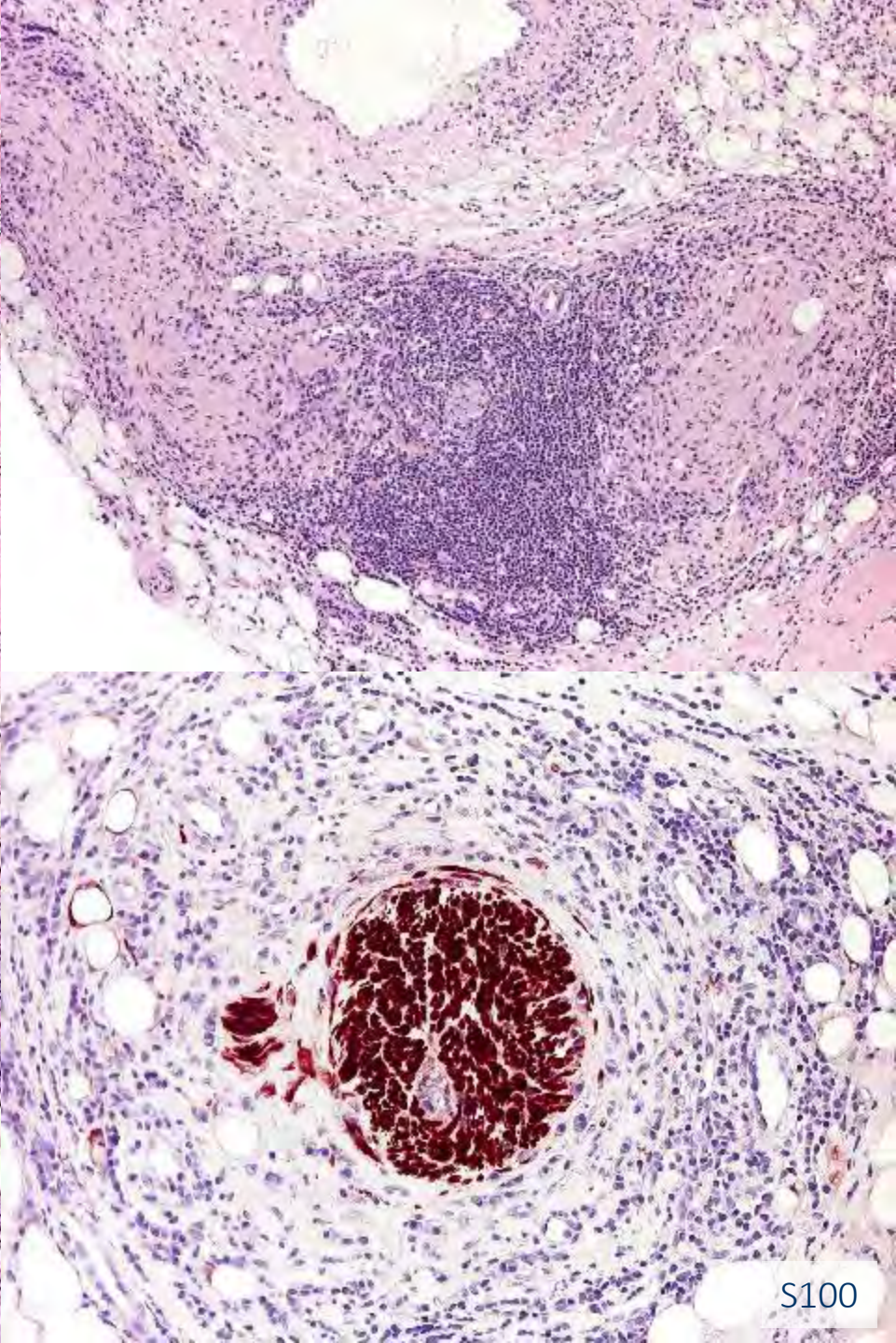
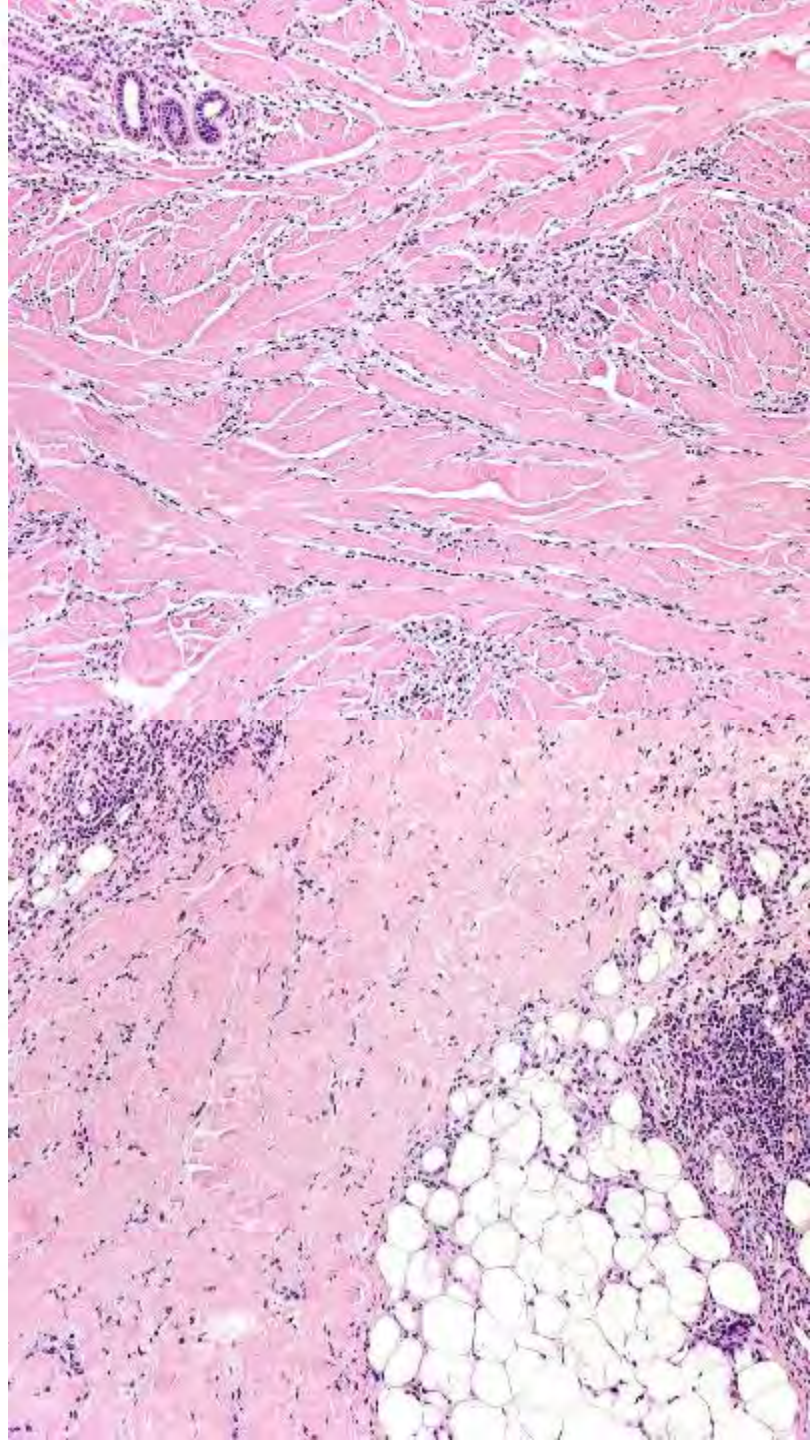
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Scleroderma with perineural /
neurotropic infiltrates





Journal Review

Cutaneous perineural inflammation: a review

As a sensory organ, the skin is supplied by a rich network of nerve fibers, nerve endings and specialized receptors.^{1–3} This network, which primarily consists of sensory and autonomic nerves, usually permeates the entire dermis, especially around skin appendages and blood vessels, and some of its components even reach the epidermis. While sensory nerves are surrounded by a myelin sheath up to their terminal ramifications, autonomic nerves are not. The autonomic nerves, which are mostly sympathetic, and in finely arborized fashion and supply blood vessels, the arrector pili muscle and the eccrine and apocrine glands. Sensory nerves terminate in finely arborized fashion or in specialized nerve end-organs. In addition to its sensory function, this network is also involved in the control of the vascular tone, thermoregulation and modulation of the immune response.^{4–8}

Perineural (and, at times, intraneural) inflammation represents an uncommon finding in cutaneous biopsies. This feature of cutaneous inflammation has been classically described in association with tuberculous leprosy where it is usually associated with clinical symptoms of decreased sensation and enlargement of peripheral nerves.^{9–12} However, this feature can also be seen with other infections such as syphilis and herpetic viral infections, inflammatory conditions such as scleroderma and as an indicator of perineural invasion in the context of cutaneous malignancies (Tables 1–3).^{9–14} While perineural inflammation may be paralleled by clinical neurological symptoms in several entities such as leprosy and herpetic infections, this feature may not be associated with any clinical symptoms in others.

In this review, we aim to discuss the entities that may exhibit cutaneous perineural inflammation on histopathology. This, in turn, may increase the awareness among dermatopathologists and pathologists of this distinctive and incompletely understood attribute, which may serve as a clue for more specific diagnosis.

A section regarding diagnostic approach is included in this review. As we believe this section will be most meaningful to the reader after evaluation of the points that are specific to individual diseases, the approach segment has been placed at the end of this article.

Infections

Leprosy

Leprosy, a chronic slowly progressive infectious disease caused by the bacillus *Mycobacterium leprae* which is an intracytoplasmic parasite of macrophages and Schwann cells, primarily affects the skin and peripheral nerves.^{4,5}

Perineural inflammation is considered to be the morphological hallmark of this disease with tuberculous leprosy representing the prototype of cutaneous disease that may show perineural inflammation on histopathology.^{4–6} However, other forms such as borderline tuberculous leprosy and the earliest lesions of indeterminate leprosy, although less commonly, may also show perineural inflammation.^{4–6} Clinically, this perineural and, occasionally, intraneural inflammation results in different neurological manifestations including anesthesia or hypoaesthesia of individual cutaneous lesions with decreased sensation to pain, temperature and/or touch and enlargement of peripheral nerves.

Tuberculous leprosy is characterized by one to five well-defined erythematous, hypopigmented papules or plaques with associated anesthesia and occasionally thickened local peripheral nerves.^{4,5} Microscopically, there is a dermal granulomatous inflammation that may exhibit a linear pattern as it follows the course of a nerve. Epithelioid cells are usually surrounded by lymphocytes. Cutaneous nerves are commonly edematous and may appear altered or fragmented by the perineural infiltrate (Fig. 1). Acid-fast bacilli are usually absent even with special stains.

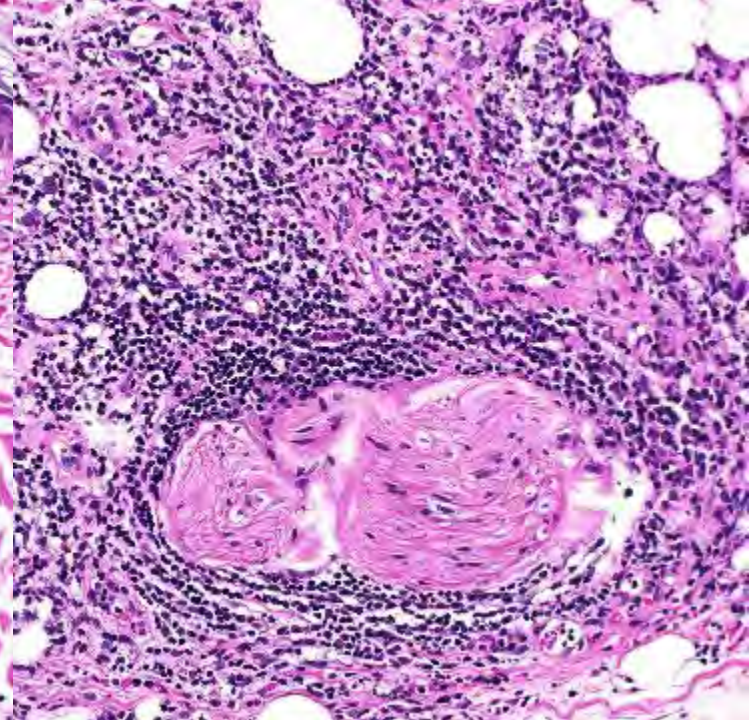
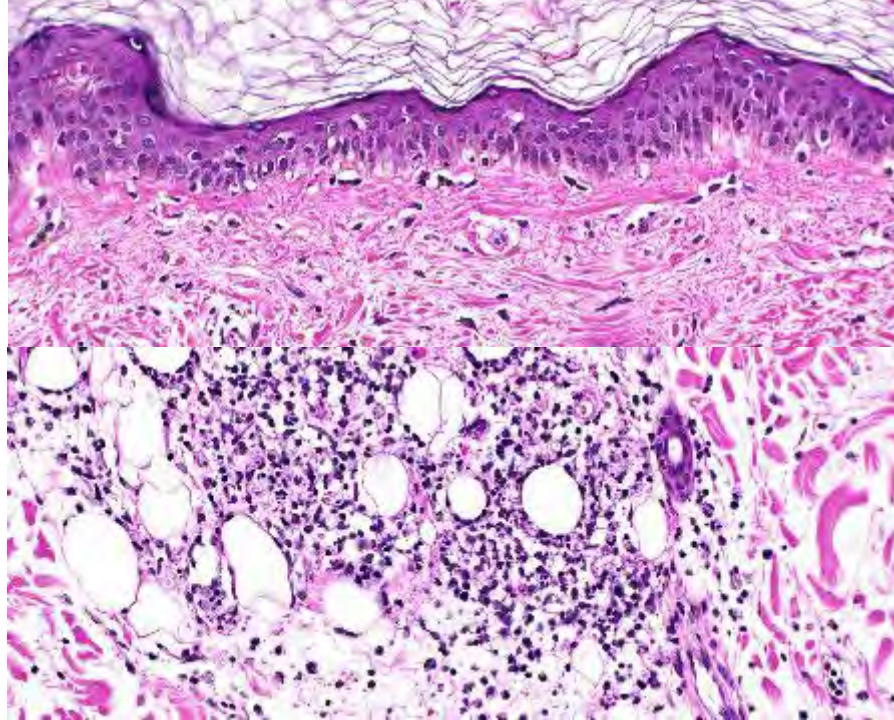
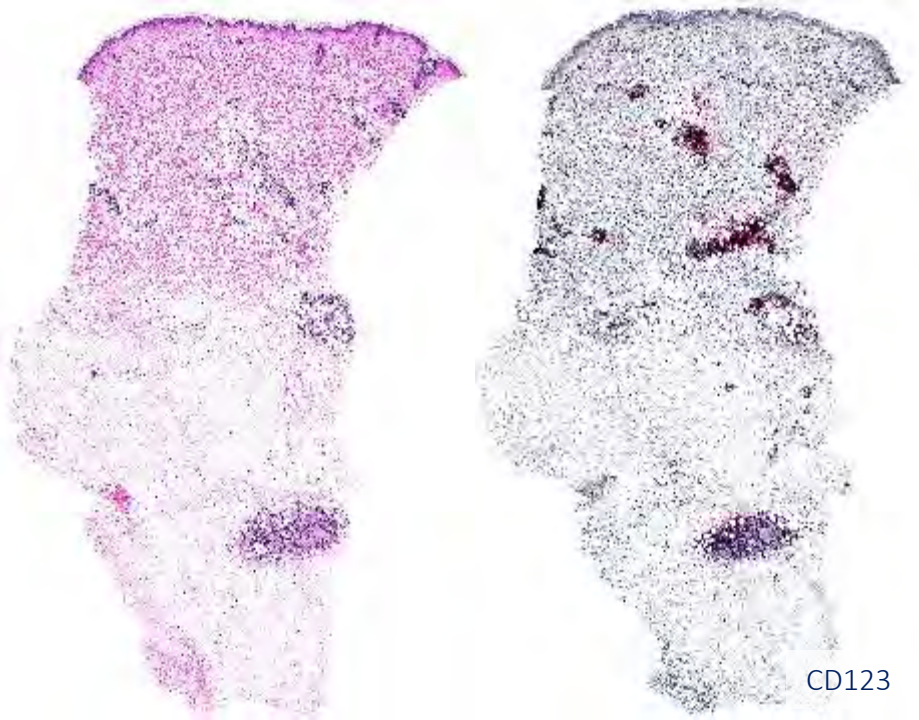
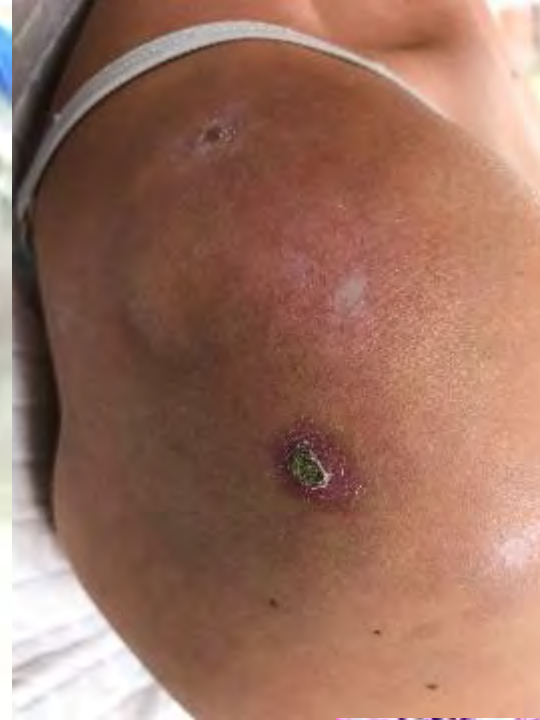
Table 1. Differential diagnosis of entities exhibiting perineural inflammation in cutaneous biopsies

Cutaneous entities exhibiting perineural inflammation		
Infections	Inflammatory conditions	Malignant conditions
Leprosy	Scleroderma	Marker of perineural invasion in cutaneous malignancies
Atypical mycobacterial infections	Eosinophilia–myalgia syndrome	Lymphoproliferative disorders
Syphilis	Shulman's syndrome	(especially chronic lymphocytic leukemia)
Herpetic viral infections	Sarcoidosis	
Acrodermatitis chronica atrophicans	Behçet disease	
Leishmania	Degos' disease	
Parvovirus B19 infection		

*LE with perineural
inflammation*

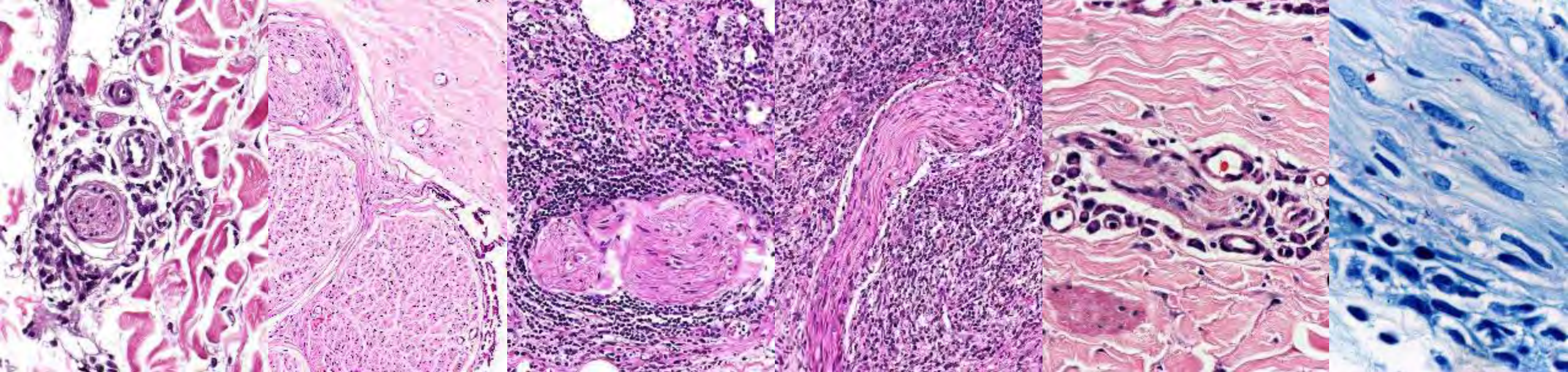
F, 33. Photosensitivity, Ro-
abs+.

Excellent response to
hydroxychloroquine.



CD123

Perineural alterations in non-neoplastic conditions



Morphea

Calciophylaxis

Lupus erythematosus

Syphilis

Borreliosis (ACA)

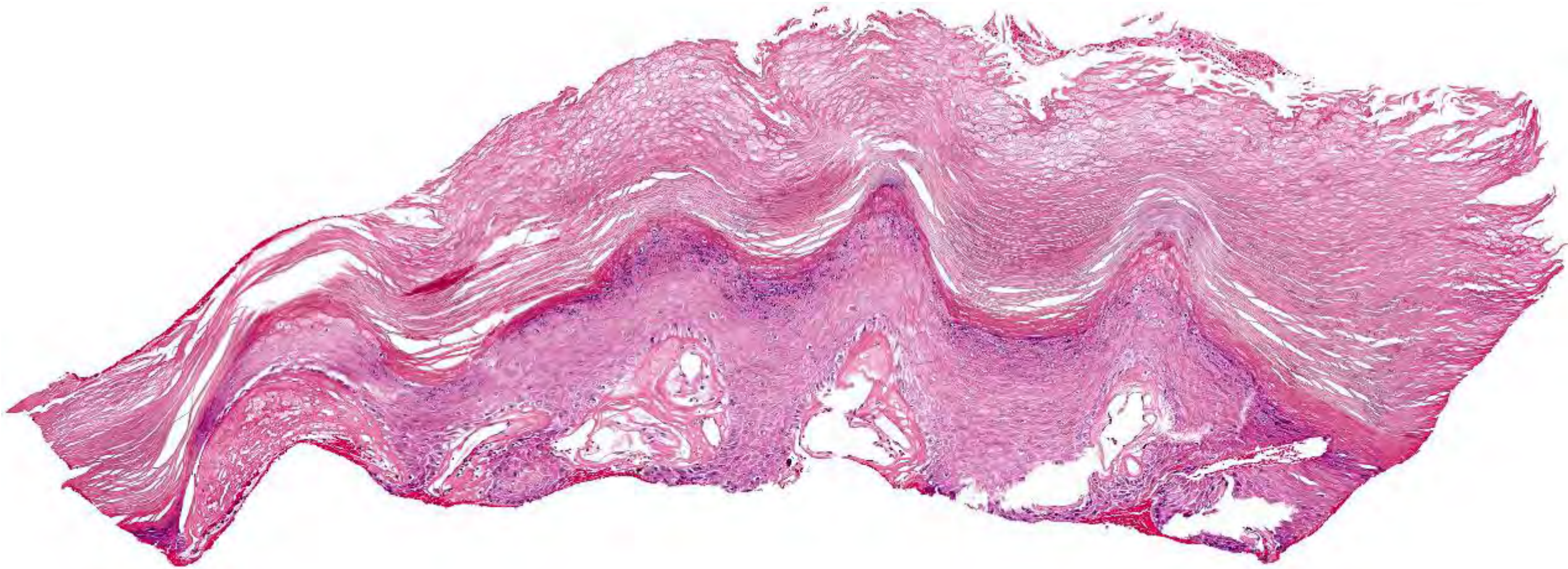
Leprosy

18th Summer Academy of Dermatopathology
Graz, July 6 – 10, 2026



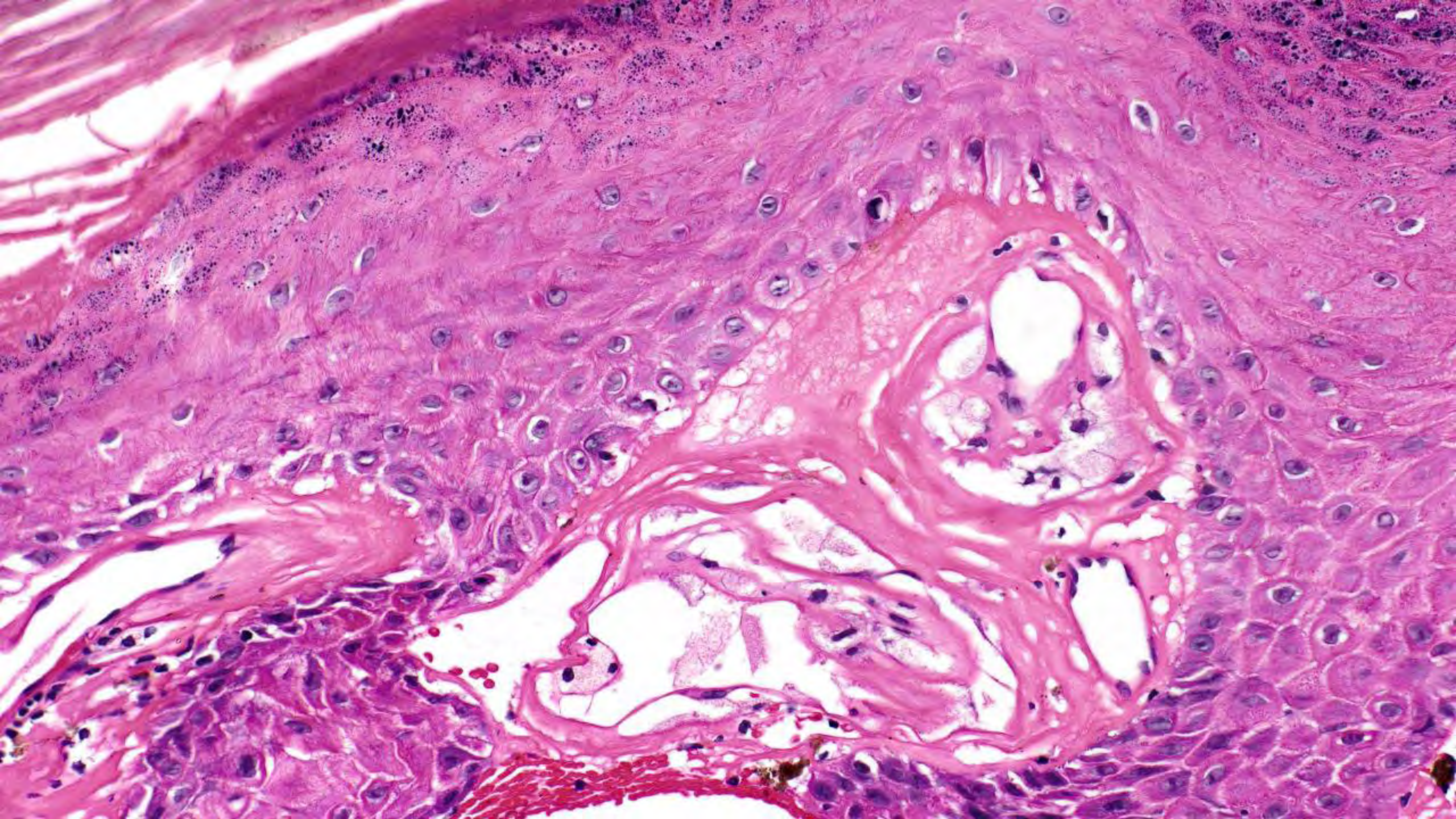
Self-assessment (cases 31-40)

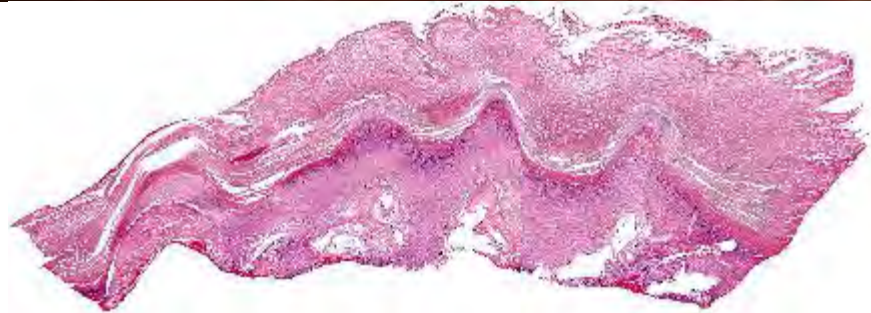
Lorenzo Cerroni

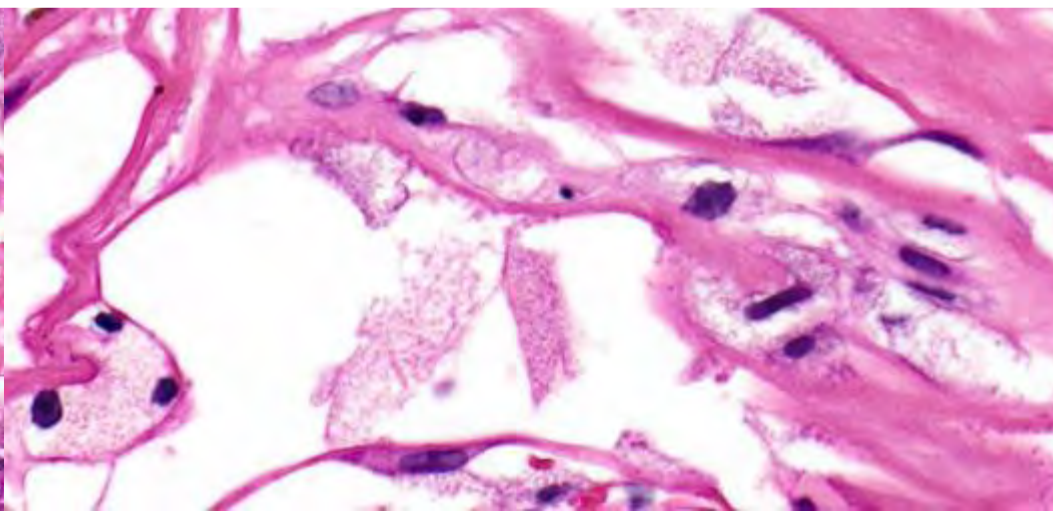
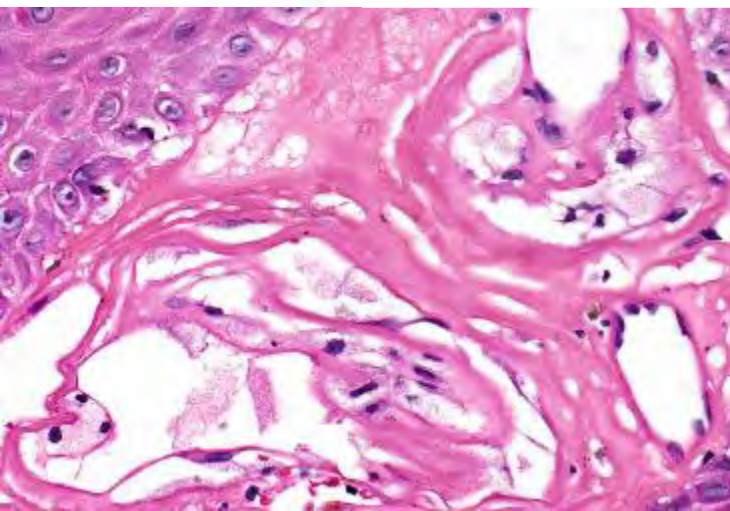


Case 31

M, 65. History of "lichen sclerosus" on the glans for 5 years (verified histologically 4 years before this presentation).







Case Reports

Verruciform Xanthoma of the Vulva

Report of Two Cases

DANIEL J. SANTA CRUZ, M.D., AND SCOTT A. MARTIN, M.D.

Santa Cruz, Daniel J., and Martin, Scott A.: Verruciform xanthoma of the vulva. Report of two cases. *Am J Clin Pathol* 71: 224-228, 1979. Two cases of verruciform xanthoma of the vulva are described. This rare lesion, previously reported to occur only in the oral cavity, is characterized by a verrucous epithelial proliferation accompanied by xanthoma cells distributed exclusively in the papillary dermis. The histologic features of the lesion are diagnostic and include (1) regular acanthosis in which the rete pegs extend to a uniform level into the dermis; (2) hyperkeratosis with parakeratosis often extending deep into the rete pegs and manifesting a massive neutrophilic infiltrate; (3) hyalinization of the collagen and infiltrates of xanthoma cells that are restricted to the papillary dermis between the rete pegs. Additionally, a lichenoid inflammatory infiltrate is seen at the periphery of the verrucous lesions, and in one case this has the pattern of classic lichen sclerosus. Verruciform xanthoma must be differentiated from verruca vulgaris, condyloma acuminatum, granular cell tumor with pseudoepitheliomatous hyperplasia, and verrucous carcinoma. (Key words: Vulva; Skin; Xanthoma; Verruciform xanthoma.)

VERRUCIFORM XANTHOMA is a rare entity, first described by Shafer in 1971.¹ Twenty-four cases of this lesion have been previously published; all have occurred in the oral cavity.¹⁻⁴ The histologic features are characteristic: (1) uniform acanthosis without atypia, (2) parakeratosis, and (3) xanthoma cells located within the papillary dermis between, but not beneath, the acanthotic rete pegs. We have examined vulvar lesions from two patients that are histologically identical to verruciform xanthoma of the oral cavity.

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Supported in part by training grant CF3901 from the American Cancer Society awarded to Dr. Martin, presented to the Dermatopathology Club at the meeting of the International Academy of Pathology in Atlanta, Georgia, on March 5, 1978.

Address reprint requests to Dr. Santa Cruz: Division of Surgical Pathology, Department of Pathology, Washington University School of Medicine, St. Louis, Missouri 63110.

Division of Surgical Pathology, Department of Pathology, Washington University School of Medicine, St. Louis, Missouri

This report constitutes the first description of this entity in an extraoral site. In one case the clinical impression was epidermoid carcinoma, which illustrates the importance of the clinical and pathological recognition of this lesion.

Report of Two Cases

Case 1. A 29-year-old black woman was found to have numerous verrucous lesions of the vulva during a routine prenatal examination. The initial clinical impression was condylomata acuminata. The patient stated, however, that the lesions had been present since the age of 12 years, had produced no symptoms, and had not changed in appearance.

One of the lesions was biopsied and found on histologic examination to contain two craterlike structures with a regular acanthosis, parakeratotic hyperkeratosis and a neutrophilic infiltrate (Figs. 1 and 2) in the upper portion of stratum malpighii. Atypia of epithelial cells was not present. Between the acanthotic rete pegs, the papillary dermis comprised a vascular, hyalinized stroma and an infiltrate of histiocytic-like cells, singly or in clusters, with abundant foamy cytoplasm (xanthoma cells), as shown in Figure 3. Moreover, the xanthoma cells were confined to that portion of the papillary dermis between the acanthotic rete pegs. The foamy histiocytes were observed occasionally between the basal epithelial cells and rarely among the epithelial cells at higher levels in the epidermis. In the papillary dermis at the base of the verrucous lesion and at the periphery was an infiltrate of lymphocytes and plasma cells. The inflammatory infiltrate at the periphery of the lesion manifested a particularly lichenoid quality, which was characterized by a close approximation of the inflammatory cells to the epithelium, prominent dendritic melanocytes in the epidermis, and pigmentary incontinence. Vessels in the dermis beneath the lesion were dilated. Since all the tissue had been paraffin-embedded, stains for lipids were not performed.

Case 2. A 43-year-old white woman was found on routine gynecologic examination to have a polypoid, sessile mass near the clitoris. The

OBSERVATION

Observation

Vulvar Verruciform Xanthoma

Ten Cases Associated With Lichen Sclerosus, Lichen Planus, or Other Conditions

Choumou Rite, MD; Emigdio Plummer, MD; Nicolas Dupla, MD; Eric Marie-Syngosse Avil, MD; Michelle Magal-Bernard, MD

Background: Verruciform xanthoma (VX) is a craterlike lesion that usually involves the oral cavity since the first report of this tumor in 1971, only 9 cases have been reported on the vulva, and 3 of these were associated with epithelioid melanocytosis. We describe the clinical-pathologic features of 10 patients with vulvar VX and focus on their associated conditions.

Observation: The average age of the patients was 48 years (range 31-60 years). The VX lesions were asymptomatic, yellowish-orange verrucous papules. The diagnosis was clinically suspected in 7 cases; other suggested diagnoses were condyloma or squamous cell carcinoma. All of the patients had an associated vulvar condition: lichen sclerosus (6 patients), lichen planus (2 patients), Paget disease, or melanocytosis. Under microscopy, the VX lesions displayed characteristic

acanthosis without atypia, and elongated rete pegs. Xanthomatous cells were aggregated in the papillary dermis.

Conclusions: Vulvar VX is a benign tumor with distinctive clinical features. A lichenoid reaction associated with a vulvar condition, usually a lichen sclerosus. Therefore, VX might represent a reaction pattern induced by different conditions, usually characterized by damage to the dermoepithelial junction. When confronted with the diagnosis of vulvar VX, clinicians may look for an associated vulvar condition.

Arch Dermatol 2011;147:1097-1098.

Published online May 24, 2011.

doi:10.1001/archdermatol.2011.111

V

ERRUCIFORM XANTHOMA (VX) is a rare benign tumor, which was first described in the oral cavity by Shafer in 1971.¹

It is characterized by a regular acanthosis, parakeratotic hyperkeratosis, and a neutrophilic infiltrate, which is usually associated with lichenoid conditions.

RESULTS

Table 1. Characteristics of the Vulvar Verruciform Xanthoma (VX) of the Present Series

Patient No./Age, y	Vulvar Associated Condition ^a	Clinical Description or Hypothesis	Diameter, mm	Location	No.	History of Dyslipidemia	Recurrence/Follow-up, mo
1/75	LS clinically obvious	Condyloma	10	Fourchette	Unique	No	NA
2/90	Vulvar Paget disease	None	2	Labia majora	Unique	Yes	No/14
3/77	LS	"Keratotic papule" ^b	2	Clitoris	Unique	Yes	NA
4/83	LS	Condyloma, SCC, VX	5	Labia minora	Unique	No	No/17
5/51	LP	"Verrucous lesion" ^b	NA	Labia minora	Unique	No	No/108
6/51	LS	VX	4	Clitoris	Unique	No	No/80
7/57	LS	SCC	20	Labia minora	Multiple	Yes	NA/died
8/77	LP	Condyloma	15	Labia majora	Unique	No	Yes/95
9/79	Radiodermatitis	None	3	Fourchette	Unique	Yes	NA
10/73	LS	"Leucoplasia" ^b	4	Labia majora	Unique	No	NA

Abbreviations: LP, lichen planus; LS, lichen sclerosus; NA, not available; SCC, squamous cell carcinoma.

^aThere was histologic confirmation in all patients listed except patient 1.

^bClinical description is given rather than diagnosis.

1st description of verruciform xanthoma in the genital area; 2 cases, 1 associated with LSA

Verruciform xanthoma of the glans penis in a male with undiagnosed genital lichen sclerosus

Dear Editor, A 39-year-old male presented with a 4-week history of an asymptomatic lesion on the glans penis. A superficial shave biopsy performed 2 weeks earlier had shown a hyperplastic epidermis with prominent parakeratosis suggestive of condyloma acuminatum.

His medical history was significant for asthma, previous episodes of otitis cystitis and prostatic sinus. There was no past history of skin disease or sexually transmitted infection and he denied any genitourinary symptoms. His regular medications included montelukast sodium and inhaled budesonide/formoterol (DuoResp Spiromax).

Examination revealed a 1-cm whitish yellow warty plaque on the glans penis (Figure 1). Chronic changes of lichen sclerosus were also noted. These included atrophy of the glans penis, loss of architectural definition posteriorly with complete loss of the frenulum, and constrictive lichenoid prosthesis, although he was able to fully retract the foreskin. The patient reported being aware of some of these changes since childhood, however he was unaware that they were abnormal. There were no palpable lymph nodes.

Clotrimazole cream was commenced once daily, however after 4 weeks there was no significant improvement in the lesion and a punch biopsy was performed. This revealed a slightly acanthotic epidermis with superficial erosions and associated neutrophils (Figure 2a). Within the papillary dermis, large foamy histiocytes were seen with associated lymphoplasmacytic inflammation (Figure 2a,b). There was no dysplasia or malignancy, and no fungal organisms were identified.

The clinical and histological features together confirmed the diagnosis of verruciform xanthoma.

Verruciform xanthoma is a benign warty lesion most commonly arising on the oral cavity. Lesions are usually asymptomatic and have variable morphology ranging from flat to papillary and verrucous. Extraoral lesions are uncommon but have been described affecting both male and female genitalia where they are referred to as

verruciform genital-associated (VEGAS) xanthomas. Other extraoral sites include the face, limbs, and acral skin. Lesions can be multiple.

Verruciform xanthoma of the penis is rare. The first case was reported by Kraemer et al in 1981¹ and to date a total of 41 cases have been reported in the literature. The age of onset ranges from 2 to 86 years, and the average duration of symptoms prior to diagnosis is 5.7 years.² Lesions are typically solitary and enlarge slowly. The most common location is the glans followed by the prepuce/coronal sulcus and shaft of the penis.² Lesions vary from sessile to pedunculated, and are often pink or skin-coloured to yellow. Some lesions show porokeratosis-like features clinically and histologically.

Verruciform xanthoma may resemble condyloma acuminatum, however the latter frequently presents with multiple lesions whilst verruciform xanthoma is usually solitary. Squamous cell carcinoma and verrucous carcinoma must be excluded. Other differential diagnoses to consider include Bowenoid papulosis, verruca vulgaris, granular cell tumour, giant molluscum contagiosum, condyloma latum, and seborrheic keratosis. A biopsy is essential to confirm the diagnosis. The histological features of verruciform xanthoma include acanthosis with parakeratosis, uniformly elongated rete ridges, neutrophilic dermal infiltrate, and the presence of foamy histiocytes within the derma papillae. Foam cells stain positive for Periodic Acid-Schiff and CD68.

Treatment of verruciform xanthoma may not be required beyond reassurance. Surgical excision is curative. Other treatment modalities which have been successful include carbon dioxide laser, superficial electrocoagulation, cryotherapy, trichloroacetic acid, and radiotherapy.³

The aetiology of verruciform xanthoma is poorly understood. An association with human papilloma virus (HPV) infection has been suggested, however the absence of histological features of HPV infection and the failure to detect HPV DNA in numerous cases of verruciform xanthoma is not in favour of this. One hypothesis is that verruciform xanthoma represents a



FIGURE 1 Clinical appearance of verruciform xanthoma. A yellowish cerebiform plaque on the glans penis.

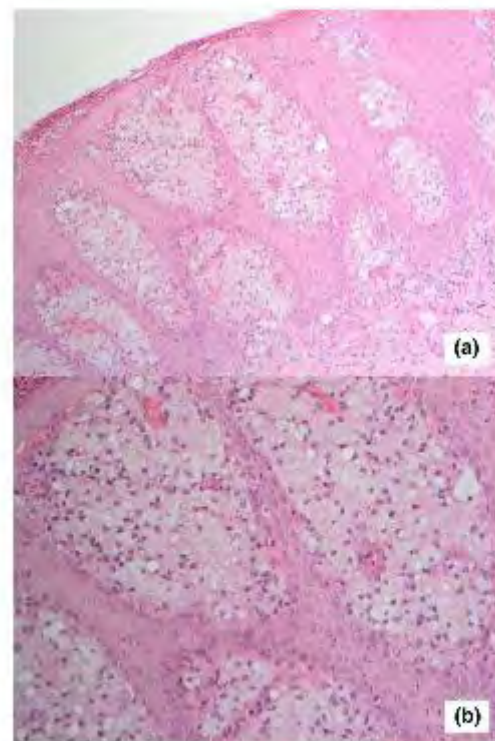
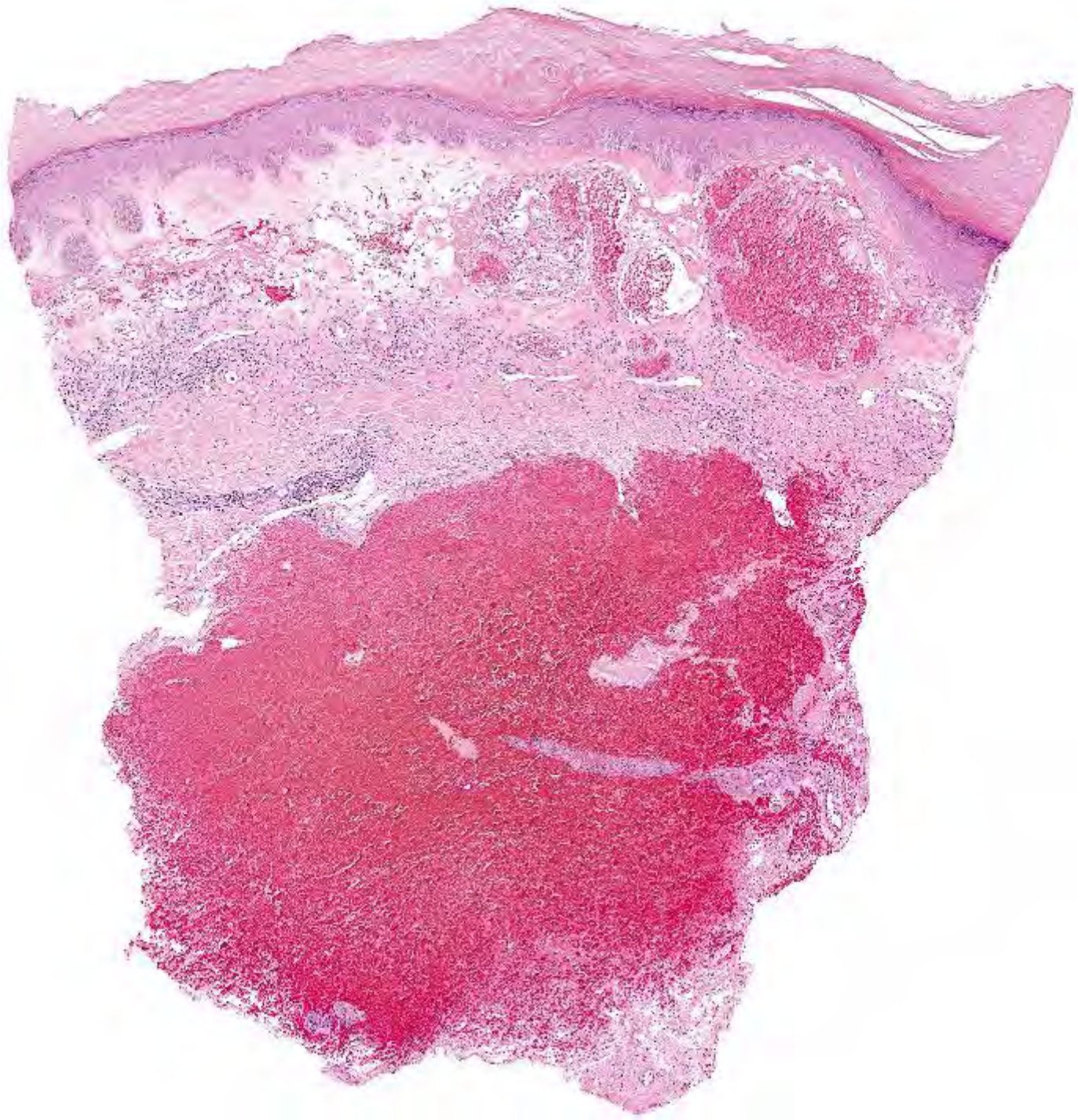


FIGURE 2 (a and b) Histological appearance of verruciform xanthoma. Large foamy histiocytes are seen within the papillary dermis.

The authors declare that they have no potential conflicts of interest with respect to this article. All authors contributed equally and significantly to writing this article. All authors read and approved the final manuscript.

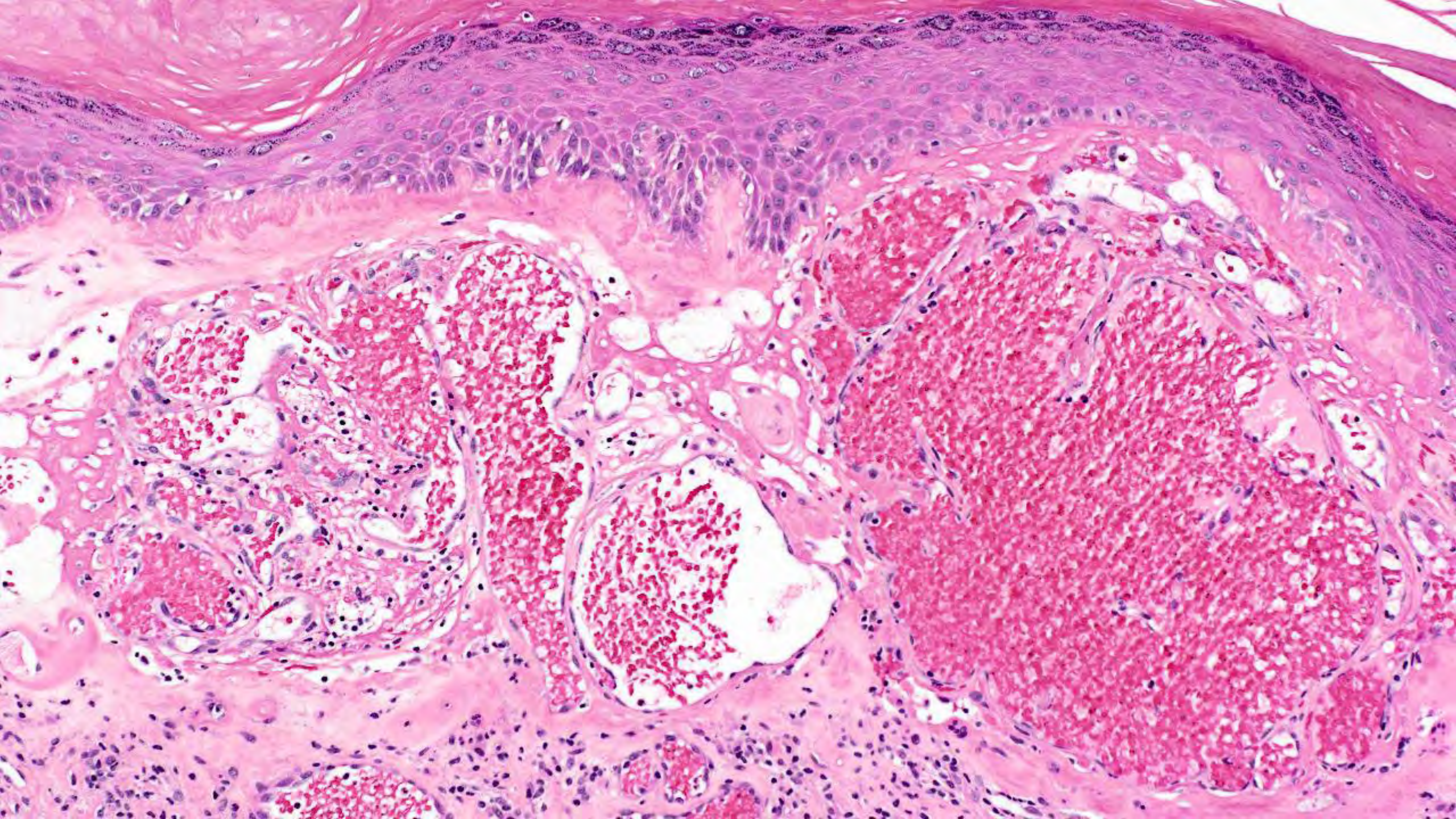
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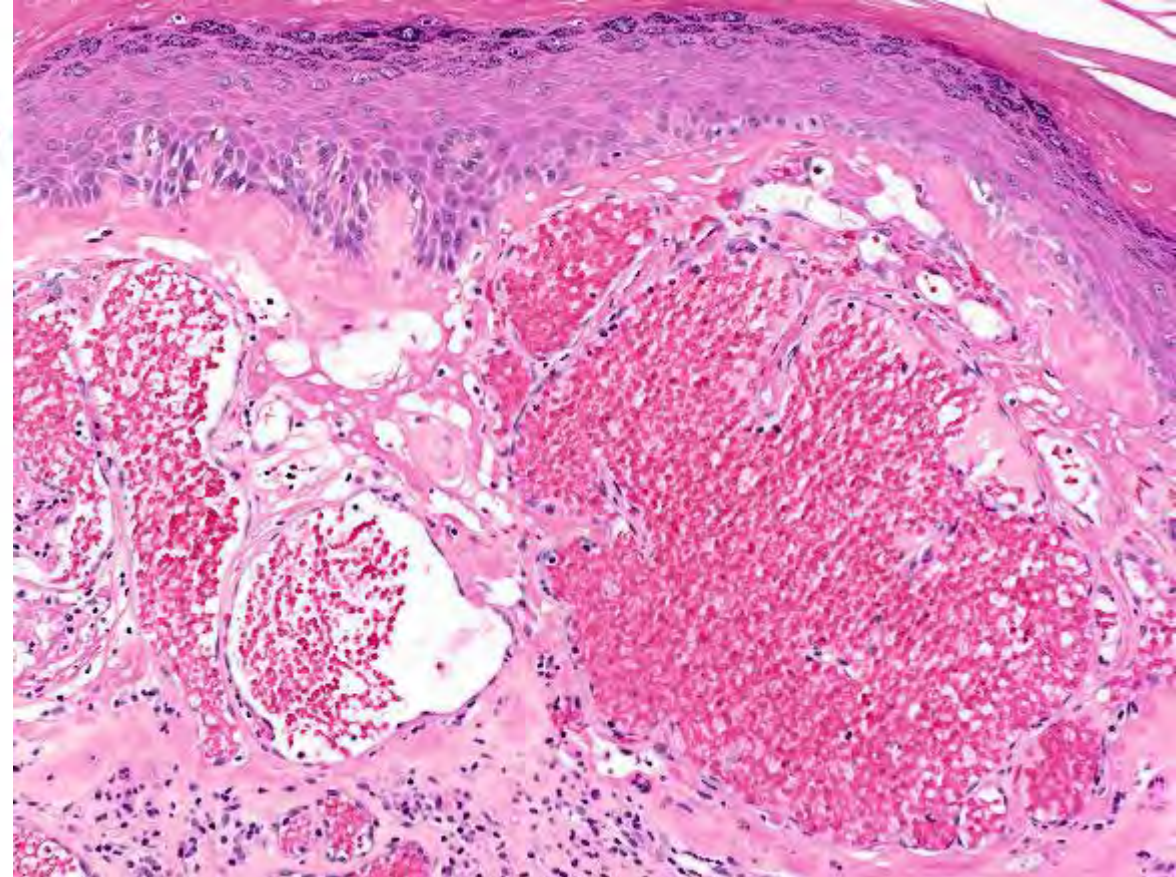
Case 32

F, 14. According to the patient itchy lesion on the left labium minus for approximately 6-7 weeks.

Reported as a "hematoma" at the first visit in the department of dermatology.







Lichen sclerosus

with vascular malformation-like blood vessels



Angiokeratoma-like changes in extragenital and genital lichen sclerosis

Hemorrhagic blains have rarely been described developing in the background of either genital or extragenital lichen sclerosis and have invariably been designated clinically as telangiectatic, hemorrhagic or bullous lichen sclerosis. We describe three patients with extragenital and genital lichen sclerosis who presented clinically with hemorrhagic plaques and/or papules. In addition to the classical histology of lichen sclerosis, dilated, congested and locally thrombosed vascular channels lined by flat endothelium were seen within the sclerotic dermal collagen. They were in close proximity to and even incising into the overlying epidermis and thus mimicked an angiokeratoma. Angiokeratoma-like changes in lichen sclerosis represent secondary features because of damage to the dermis by lichen sclerosis and are characterized histologically by reticulate thin-walled vascular spaces in the papillary dermis immediately associated with the epidermis. Increased venous pressure, local trauma, degenerative changes in the elastic tissue of the vessel wall, and/or surrounding supportive tissues as well as abnormalities in the extracellular protein matrix appear to be implicated in the pathogenesis.

Luzar B, Neil SM, Calonje E. Angiokeratoma-like changes in extragenital and genital lichen sclerosis.
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Lichen sclerosis is an acquired chronic inflammatory disorder of the skin and mucous membranes of unknown etiology, which occurs predominantly in the genital region of adult women.¹ Lesions are present in 15–20% of patients.² A characteristic histological feature of lichen sclerosis is thinning out of the dermal collagen beneath the squamous epithelium with a dermal infiltrate of chronic inflammatory squamous epithelium is usually atrophic. The overall histological pattern may also be hyperplastic.³ Other common histological features of lichen sclerosis are hyperkeratosis, plugging and vascular degeneration (telangiectases).⁴

The aim of this paper was to present three patients with angiokeratoma-like changes developing in the background of extragenital and genital lichen sclerosis.

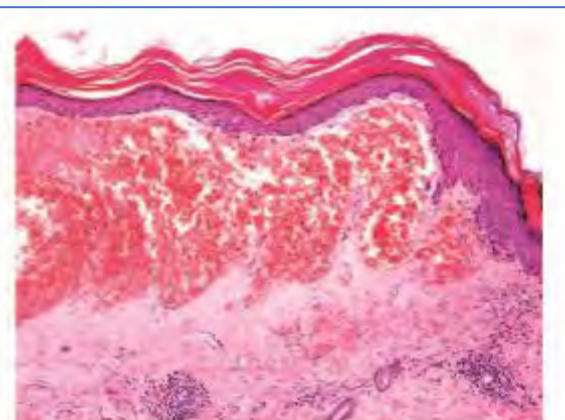


Fig. 2. Angiokeratoma-like changes in extragenital lichen sclerosis. Note dilated and congested vascular spaces in close proximity to the epidermis.

Lichen Sclerosis or Vulvar Angiokeratoma: A Diagnosis That is not always so easy

Vincenzo De Giorgi^{1,2}, Gabriella Perilli¹, Pietro Antonini³, Giovanni Macchi⁴,
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Key words: lichen sclerosis, vulvar angiokeratoma, histopathology, diagnosis.

Calonje E, Luzar B, Perilli G, Antonini P, et al. Lichen sclerosis or vulvar angiokeratoma: diagnosis that is not always so easy.
Dermatol Pract Concept. 2014;18(1):46-50. DOI: 10.1097/JCME.0b013e3182a1a1a1

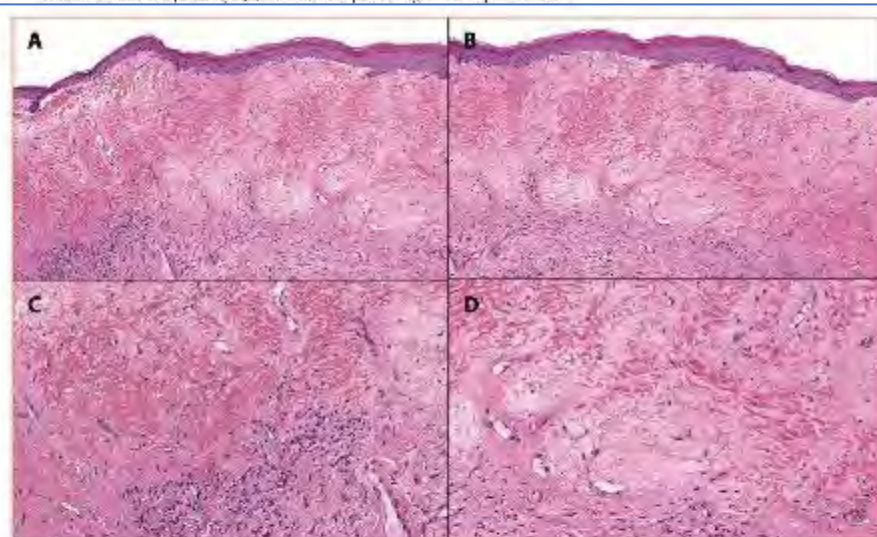
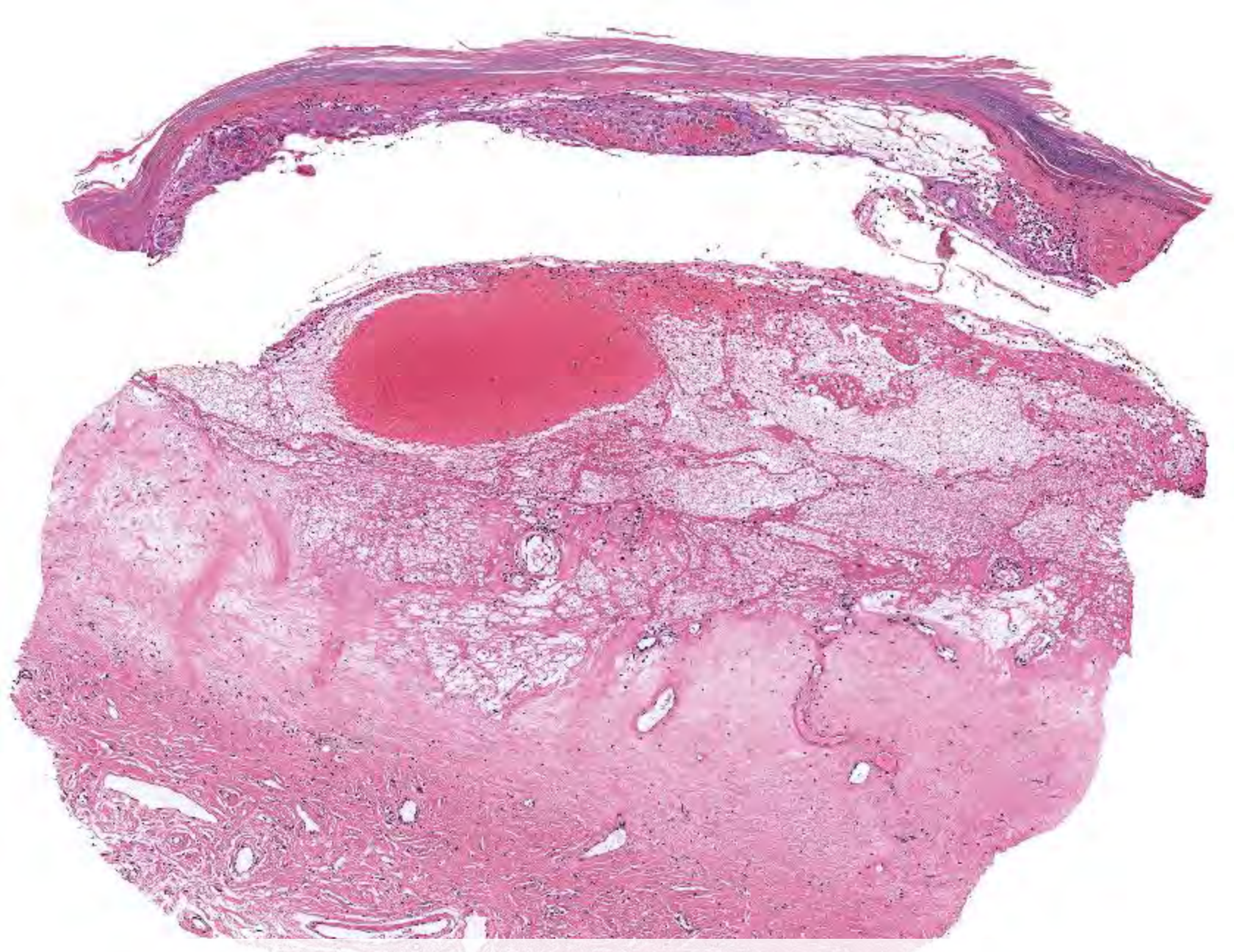
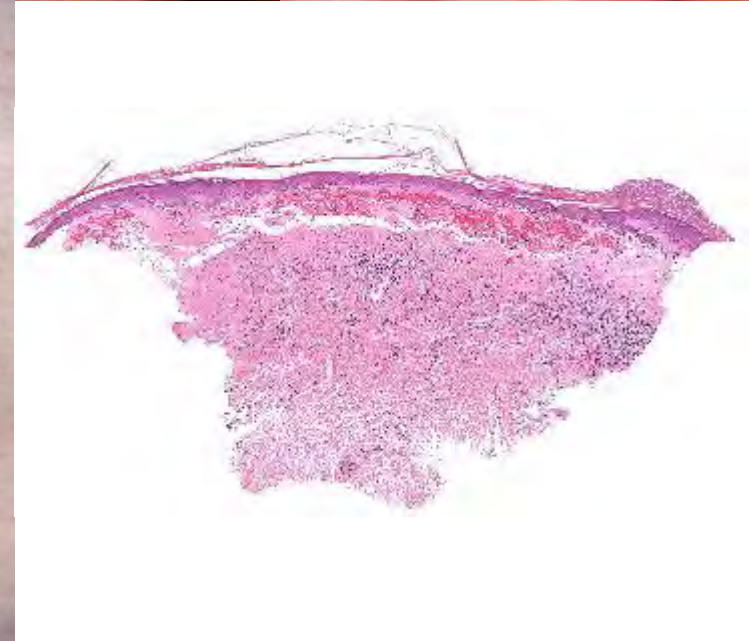


Figure 2. (A–D) Histopathological examination shows epidermal thinning with loss of rete ridges, hyperkeratosis and dermal sclerosis. Notable is the presence of superficial dermal hemorrhage with extravasated red blood cells. (A) H&E, original magnification X10. (B) H&E, original magnification X10. (C) H&E, original magnification X20. (D) H&E, original magnification X20.



Hemorrhagic lichen sclerosus

Lichen sclerosus presenting with a single hemorrhagic lesion



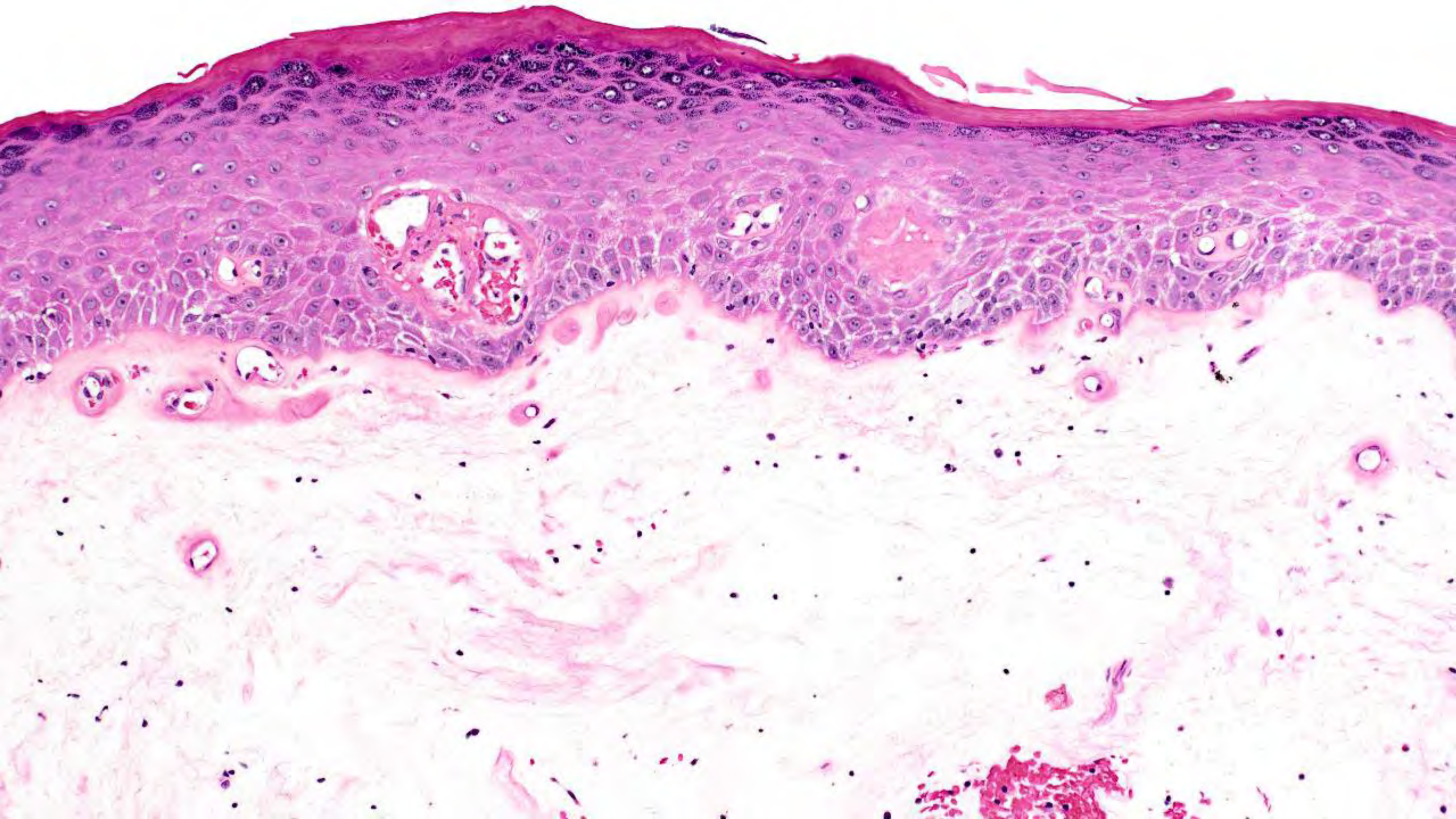
Hemorrhagic lichen sclerosus & morphea

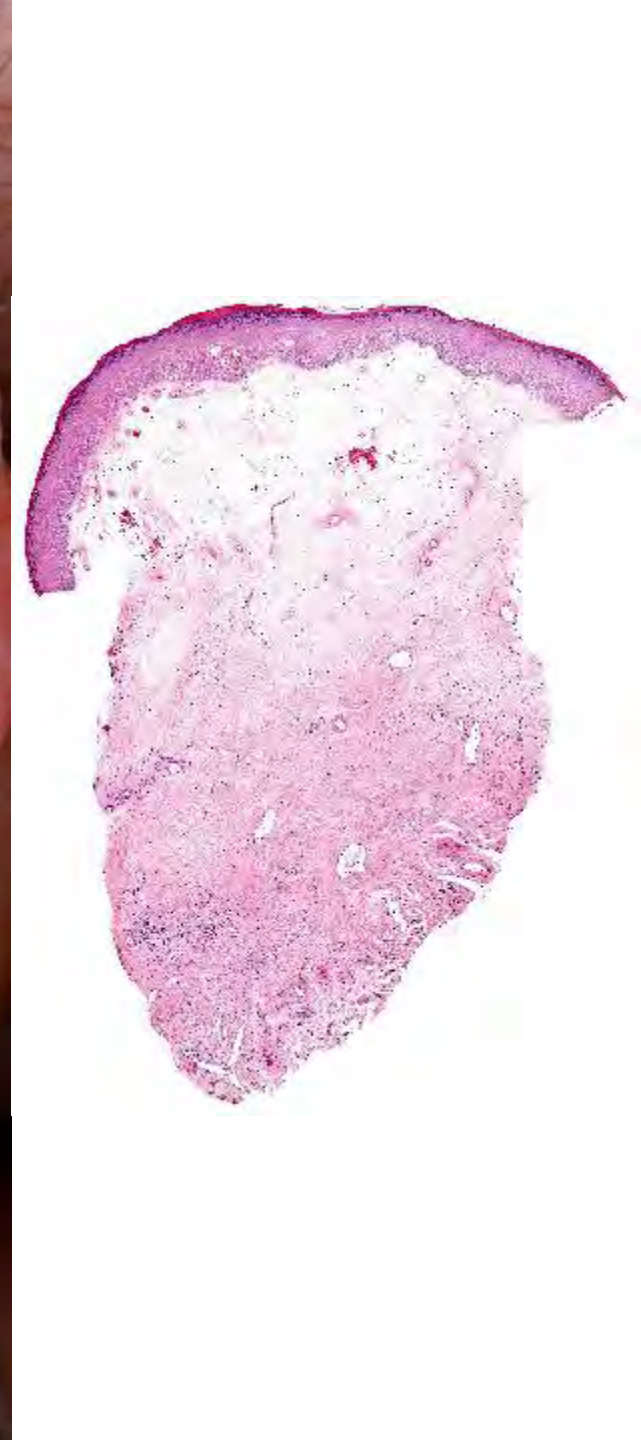


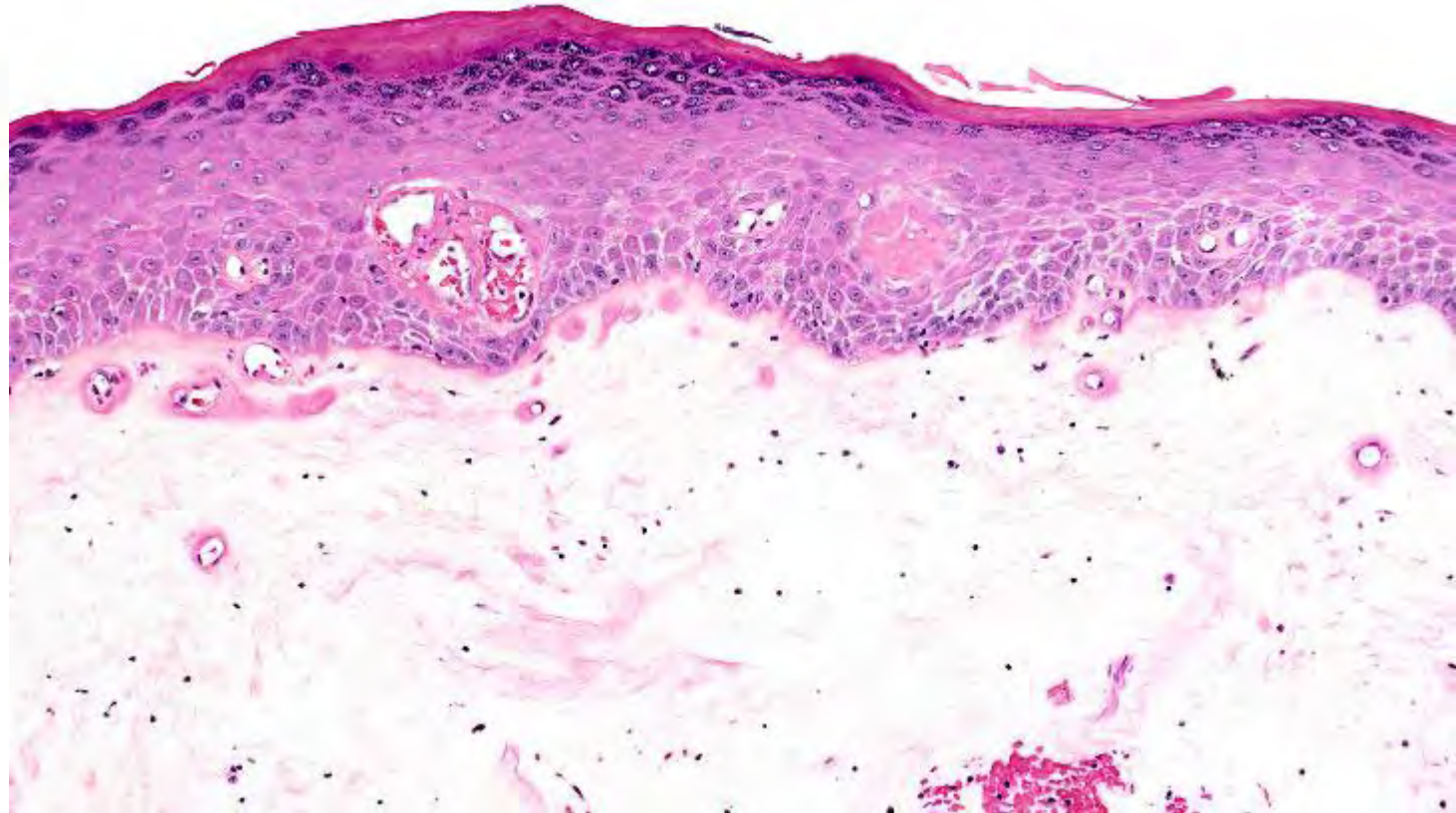
Case 33

M, 61. History of genital lichen sclerosus (1st diagnosis 15 years previously; meatoplasty 19 years previously; circumcision 2 years before presentation).

Partly purulent lesions for 2 months.







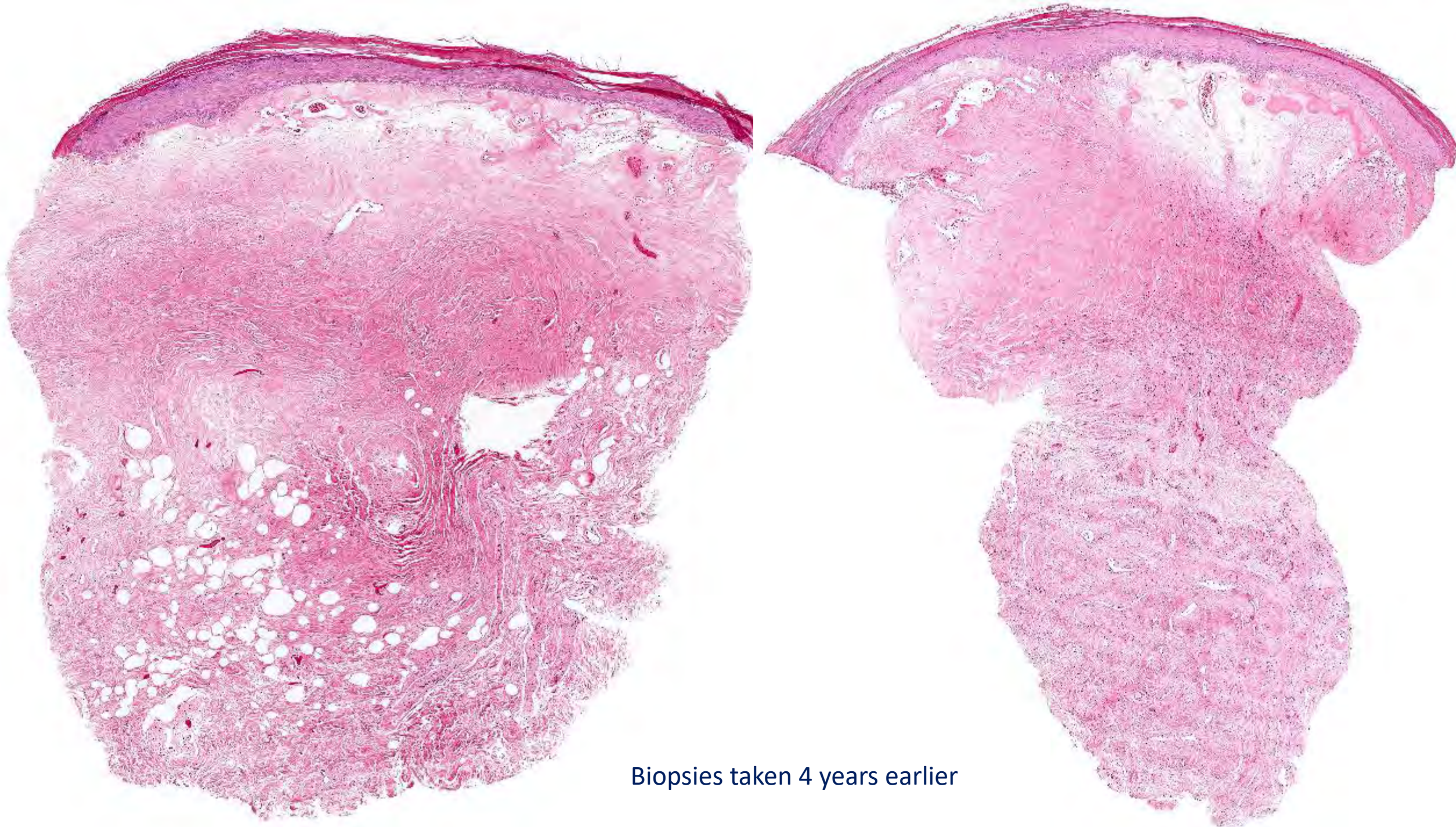
Lichen sclerosus

*bullous-hemorrhagic, complicated by
Streptococcus pyogenes group A infection*



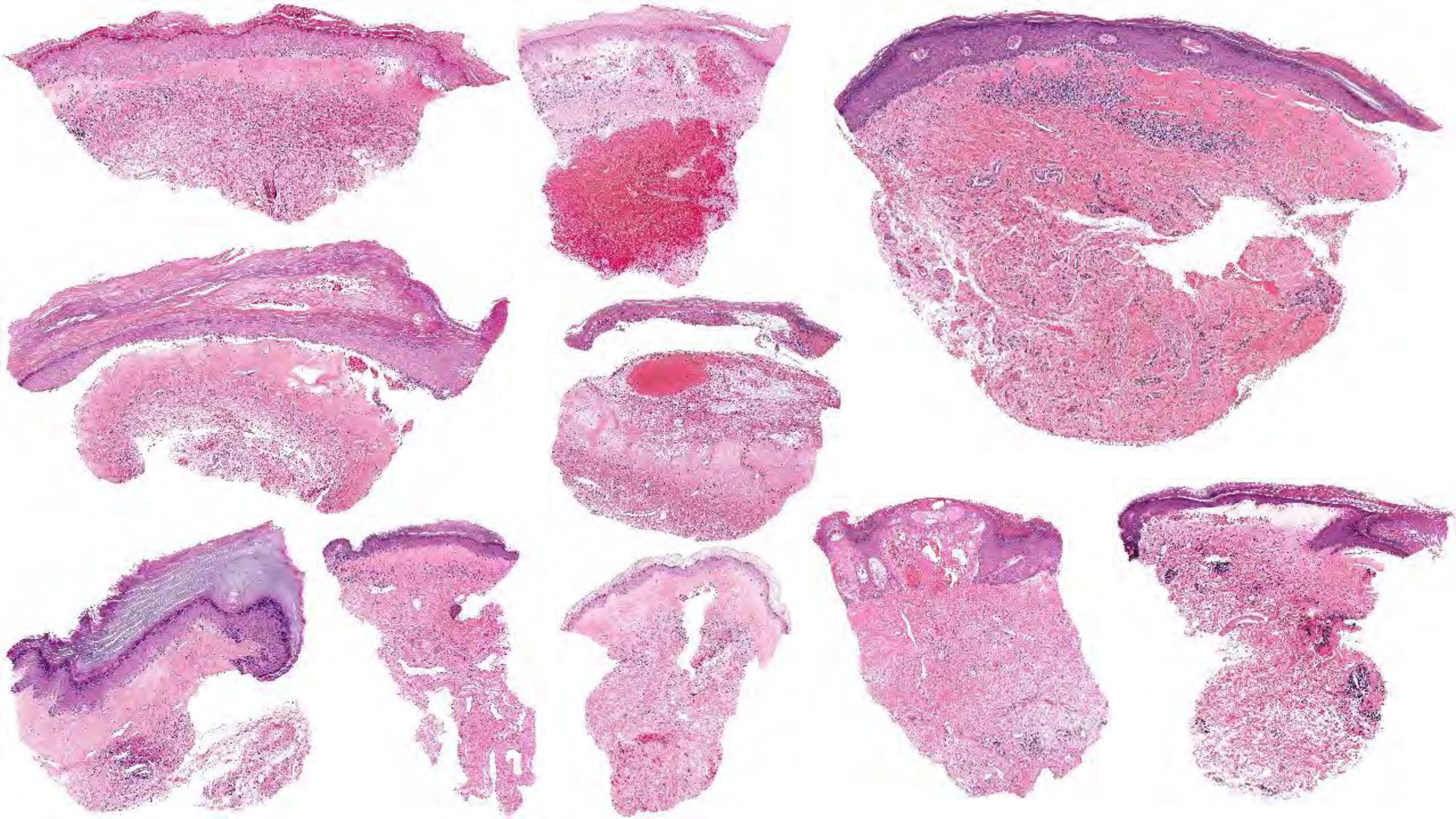
4 years earlier



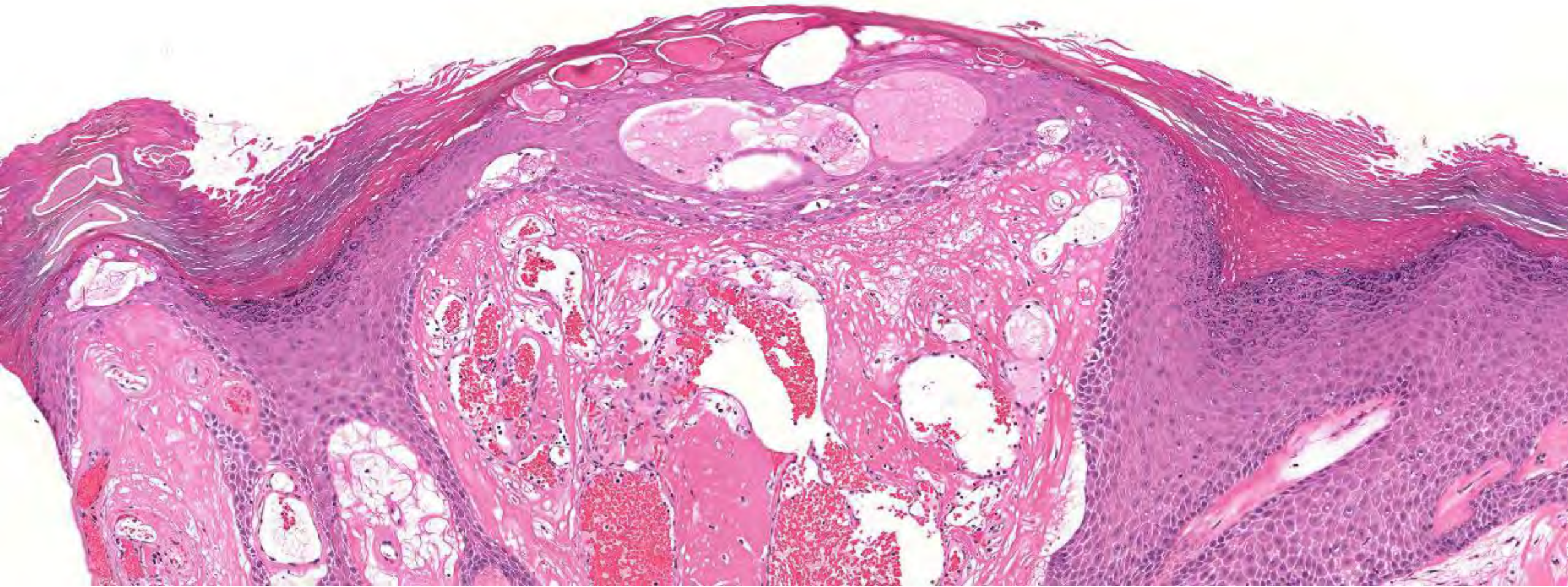


Biopsies taken 4 years earlier

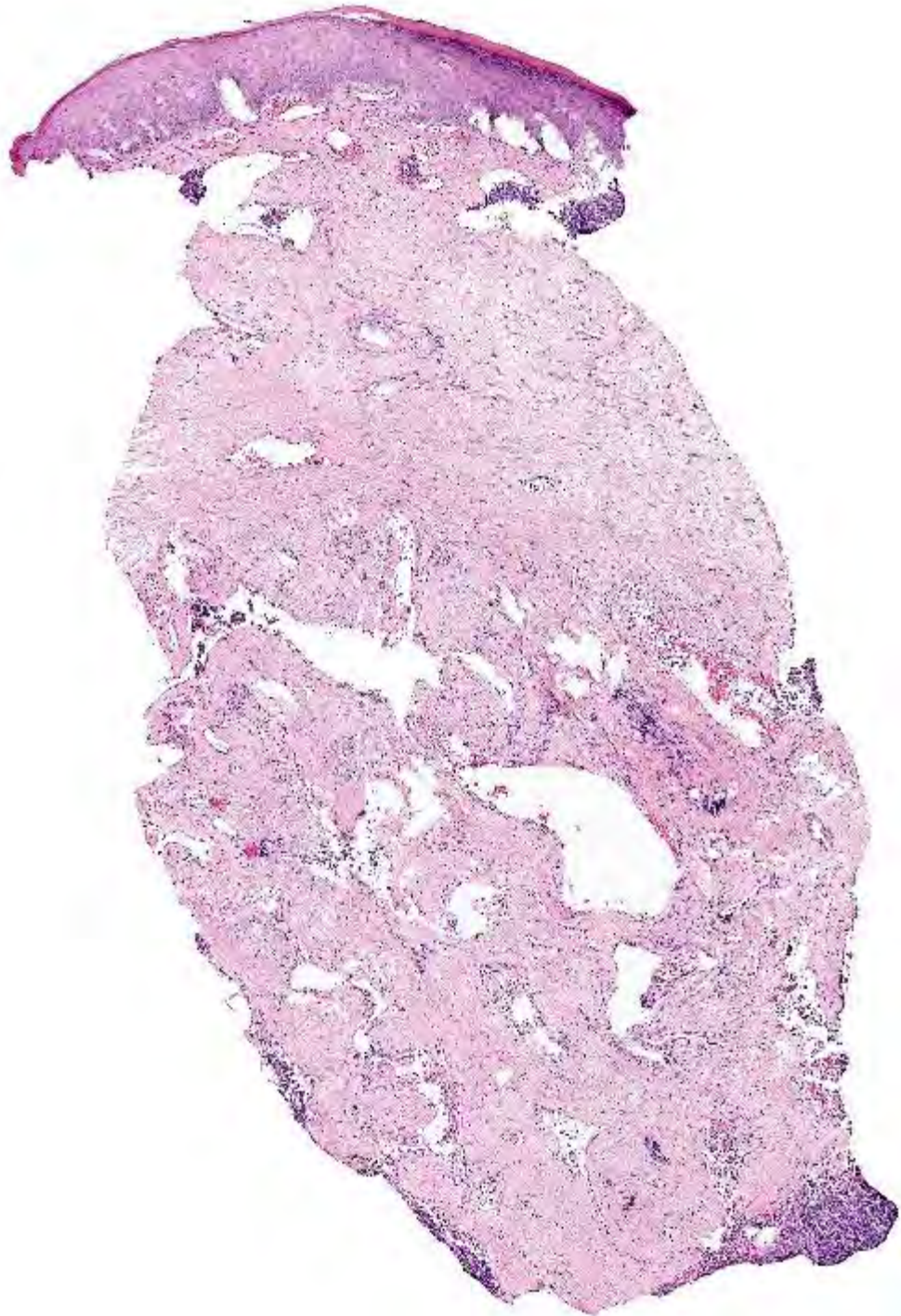




Least common denominator



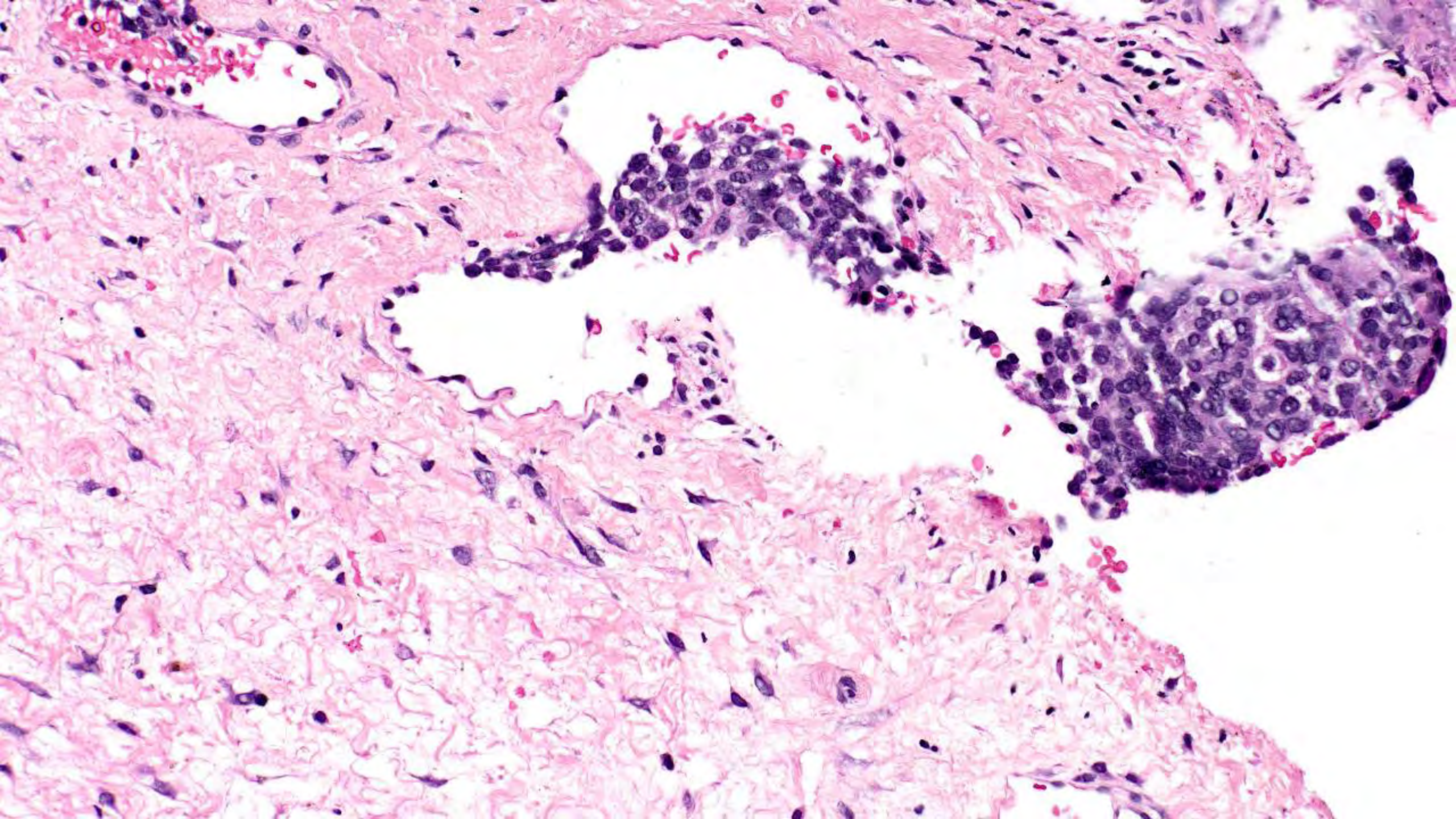
Compact orthohyperkeratosis

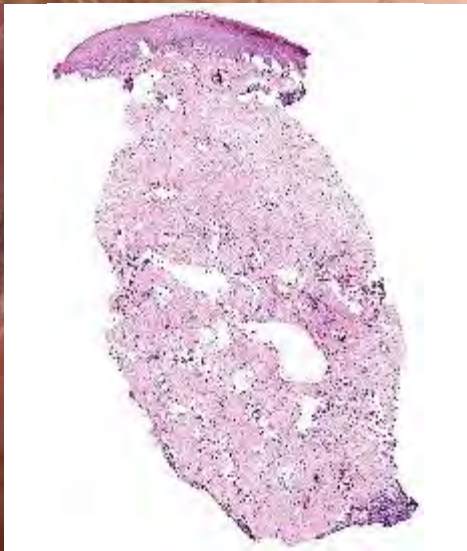


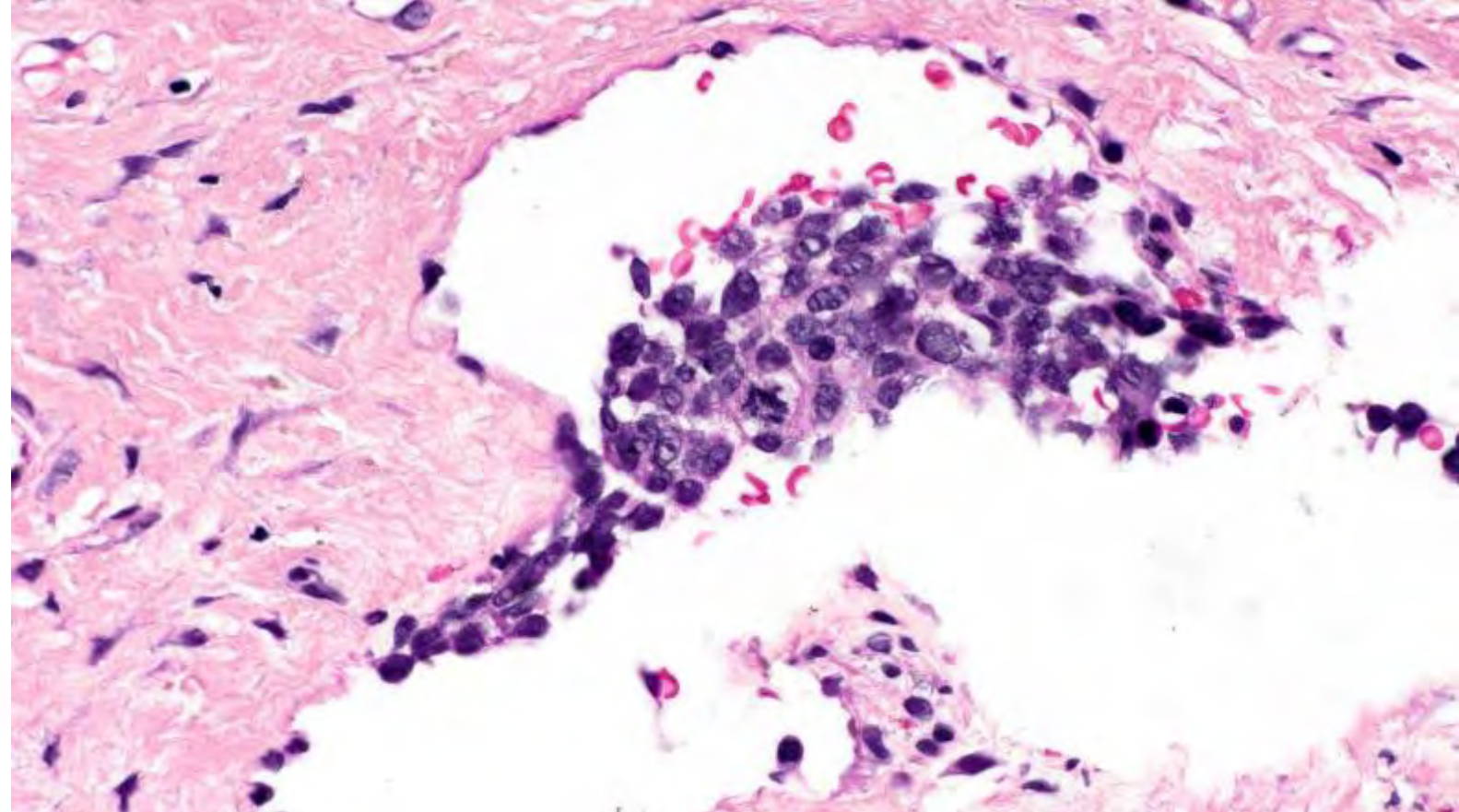
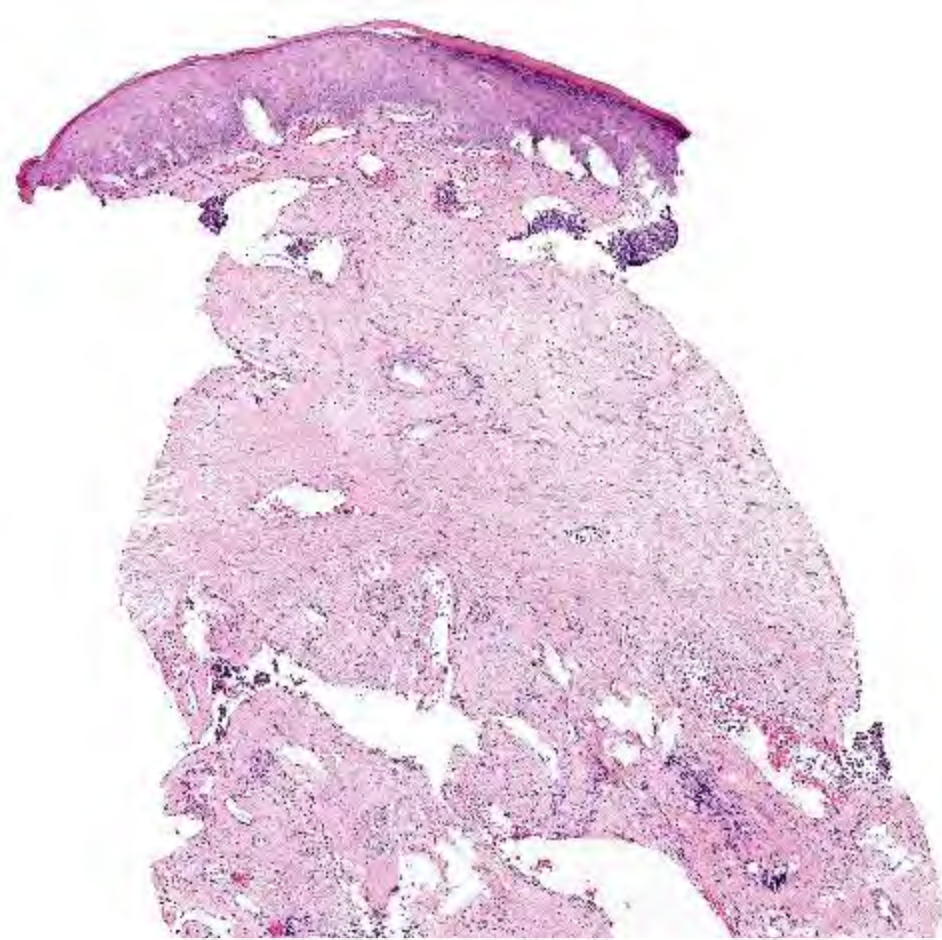
Case 34

M, 67. According to the patient itchy lesions on the glans penis for a few days. Started on valaciclovir for suspicion of herpes simplex infection.

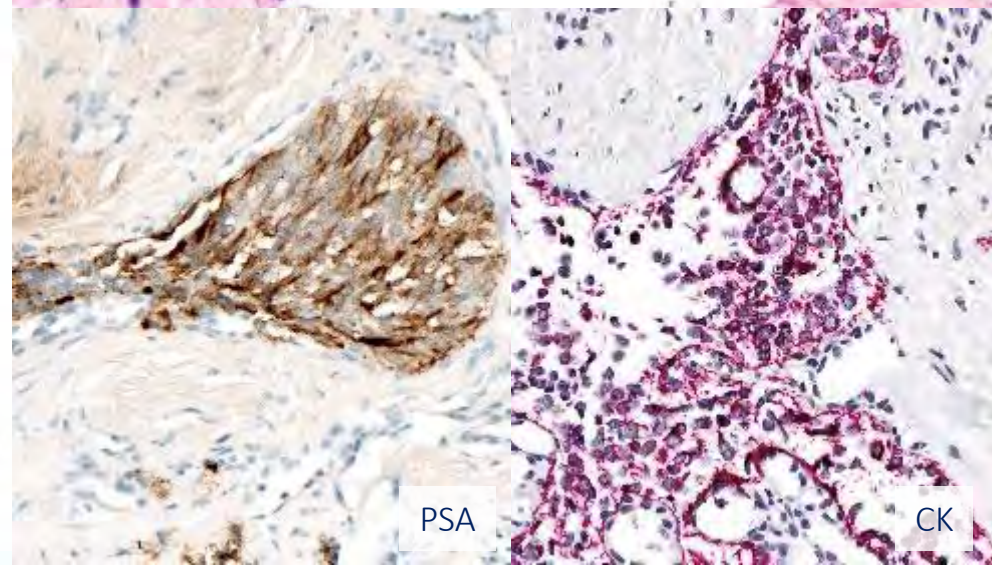
Clinical signs of minimal regression are described 2 days later, yet a biopsy is planned and taken 5 days after the first presentation.







Penile metastasis of prostatic carcinoma



Prostatic carcinoma diagnosed 10 years previously but not mentioned in the chart; liver metastases detected 3 months previously

Prostate Carcinoma with Testicular or Penile Metastases

Clinical, Pathologic, and Immunohistochemical Features

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April Mao, MD,³
Deb Bhowmick, MD,³
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BACKGROUND. Despite the proximity, prostate carcinoma seldom metastasizes to the penis or testis.

METHODS. In this retrospective study, 10 patients who developed testicular or penile metastases from prostate carcinoma were identified by examination of the medical history of 12 patients with prostate carcinoma and metastatic origin, respectively. Pathologic review and immunohistochemical staining were performed on tumors from a subset of these patients.

RESULTS. Patients with prostate carcinoma and metastases to penis or testis responded to androgen ablation therapy median duration, 34 months. They were perisected from developing post-hormone, recurrent urinary symptoms and elevated alkaline phosphatase. Six of 10 evaluable patients had elevated serum carcinoembryonic antigen levels (mean, 10 ng/mL), whereas 2 of 10 patients had low or undetectable serum prostate-specific antigen levels (mean, 4 ng/mL). In seven of the eight patients for whom appropriate penis and/or testis biopsies were obtained, no common histologic features that were compatible with a diagnosis of ductal or endocervical adenocarcinoma of the prostate.

CONCLUSIONS. Patients with prostate carcinoma and testicular or penile metastases have unique clinical and pathologic characteristics. Many of these patients' tumors are compatible with a subtype of prostate carcinoma known as ductal adenocarcinoma. Further studies need to be performed to elucidate the biologic basis of the various histologic subtypes of prostate carcinoma. *Cancer* 2002;94:2619-27. © 2002 American Cancer Society. DOI: 10.1002/cncr.10346

KEYWORDS: prostate carcinoma, testicular metastases, penile metastases, ductal adenocarcinoma.

Despite the proximity, prostate carcinoma seldom metastasizes to the penis or testis. Testicular metastases generally are painless and are, in up to 48% of cases, discovered incidentally during orchiectomy for advanced prostate carcinoma.¹ Even though they are uncommon, secondary testicular tumors tend to originate primarily in the lung or the prostate.² Similarly rare are penile metastases from prostate carcinoma (0.33%), which may present as painless nodules in the glans of the penis.^{3,4} Apart from the prostate, other primary tumors that may metastasize to the penis arise from the bladder, rectum, kidney, or testis.⁵

We hypothesized that prostate carcinoma with such unusual metastatic patterns could be a diagnostic clue with regard to its basic biology and origins of certain types of prostate carcinoma. It might represent an extreme spectrum and a pure variant of prostate carcinoma. In the study reported herein, we investigated the clinical

TABLE 2
Type and Duration of Response in 6 Patients Who Benefited from Chemotherapy

Patient	Treatment	PSA/CEA response	Objective response/clinical benefit	Time to disease progression (mos)
3	Ketocconazole/doxorubicin and estramustine/vinblastine	6.3 to 2.2	Decreased bladder tumor, resolution of hematuria and hydronephrosis, improved performance status	9
4	Estramustine/docetaxel	1747 to 850	Improved bone scan, bone pain, and performance status	4
5	Ketocconazole/doxorubicin and estramustine/vinblastine	250 to 16	Decreased lung metastases, improved dyspnea on exertion, and performance status	19
6	Estramustine/docetaxel/toposide	173 to 57		3
9	Ketocconazole/doxorubicin and estramustine/vinblastine	22 to 2.9*	Decreased liver and penile metastases, decreased penile and perineal pain	8
10	Ketocconazole/doxorubicin and estramustine/etoposide	13.7 to 0.5 484 to 12.6*	Decreased lung and liver metastases, improved dyspnea on exertion and performance status, Foley/suprapubic catheters removed, hypercalcemia resolved	7

PSA, prostate-specific antigen; CEA, carcinoembryonic antigen.

*Carcinoembryonic antigen levels.

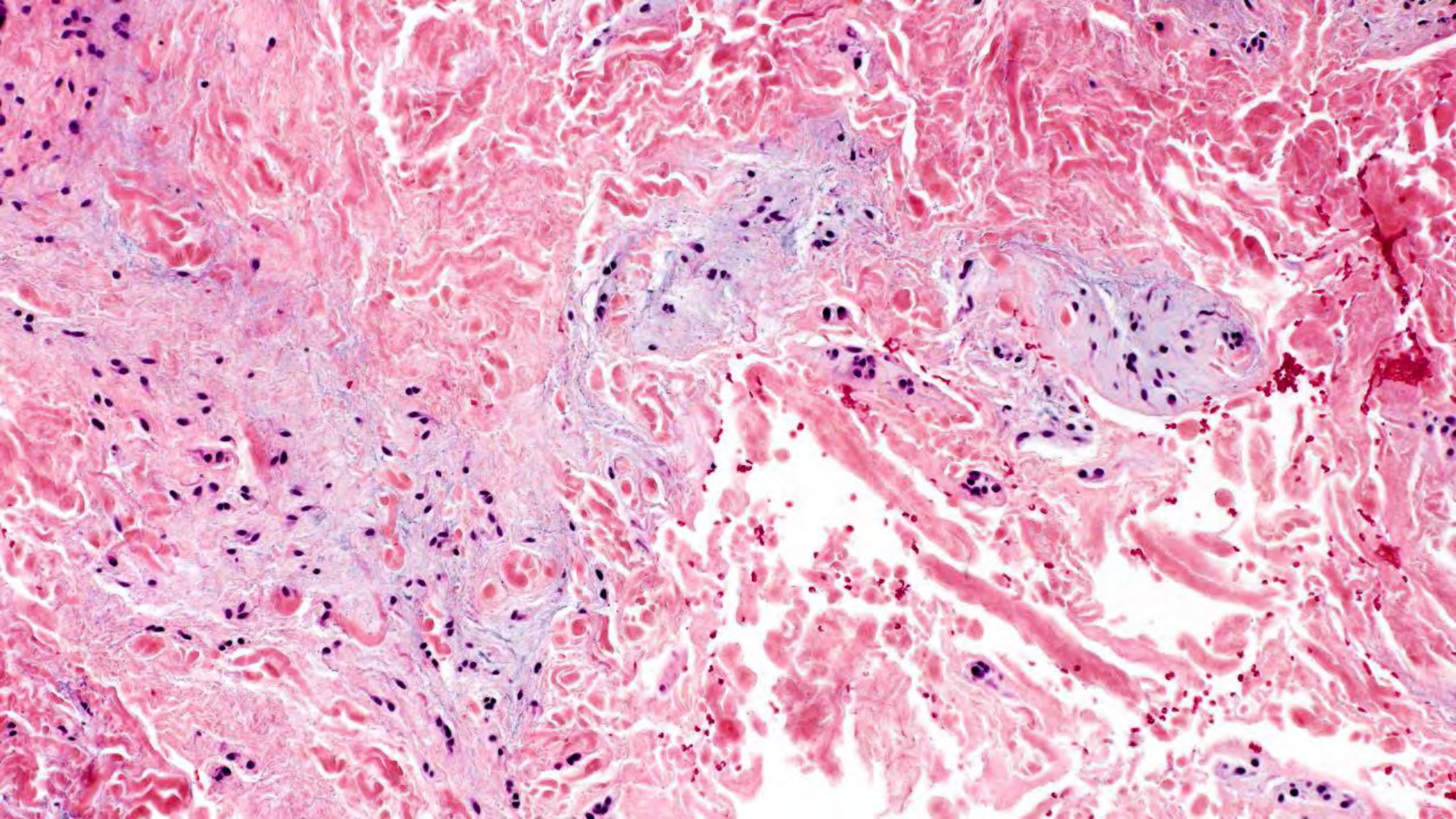


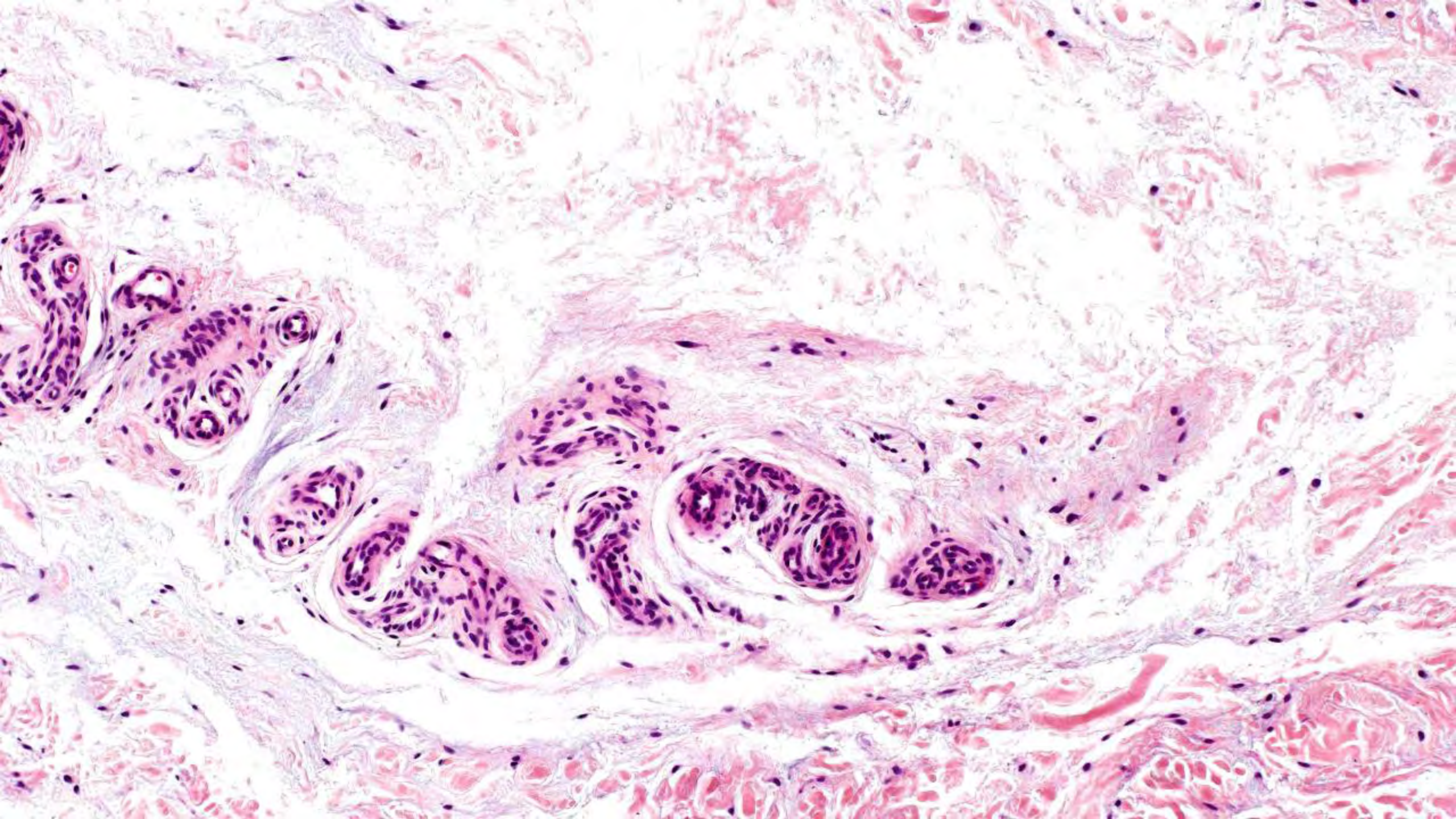
Case 35

F, 11. According to the patient and her mother lesions on both feet for approximately 4 years. An MR examination showed "symmetrical signal modification in the subcutaneous tissue, not clearly explainable".

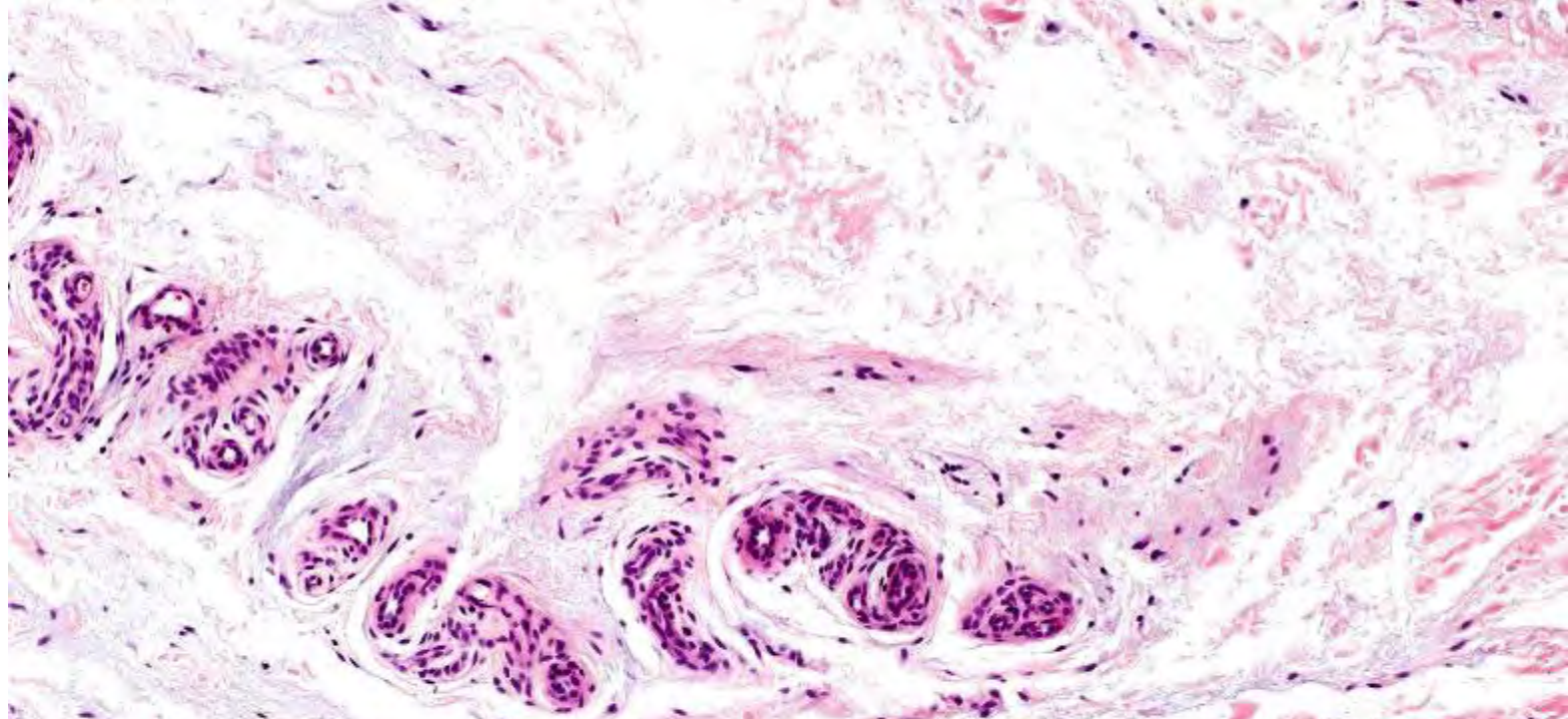
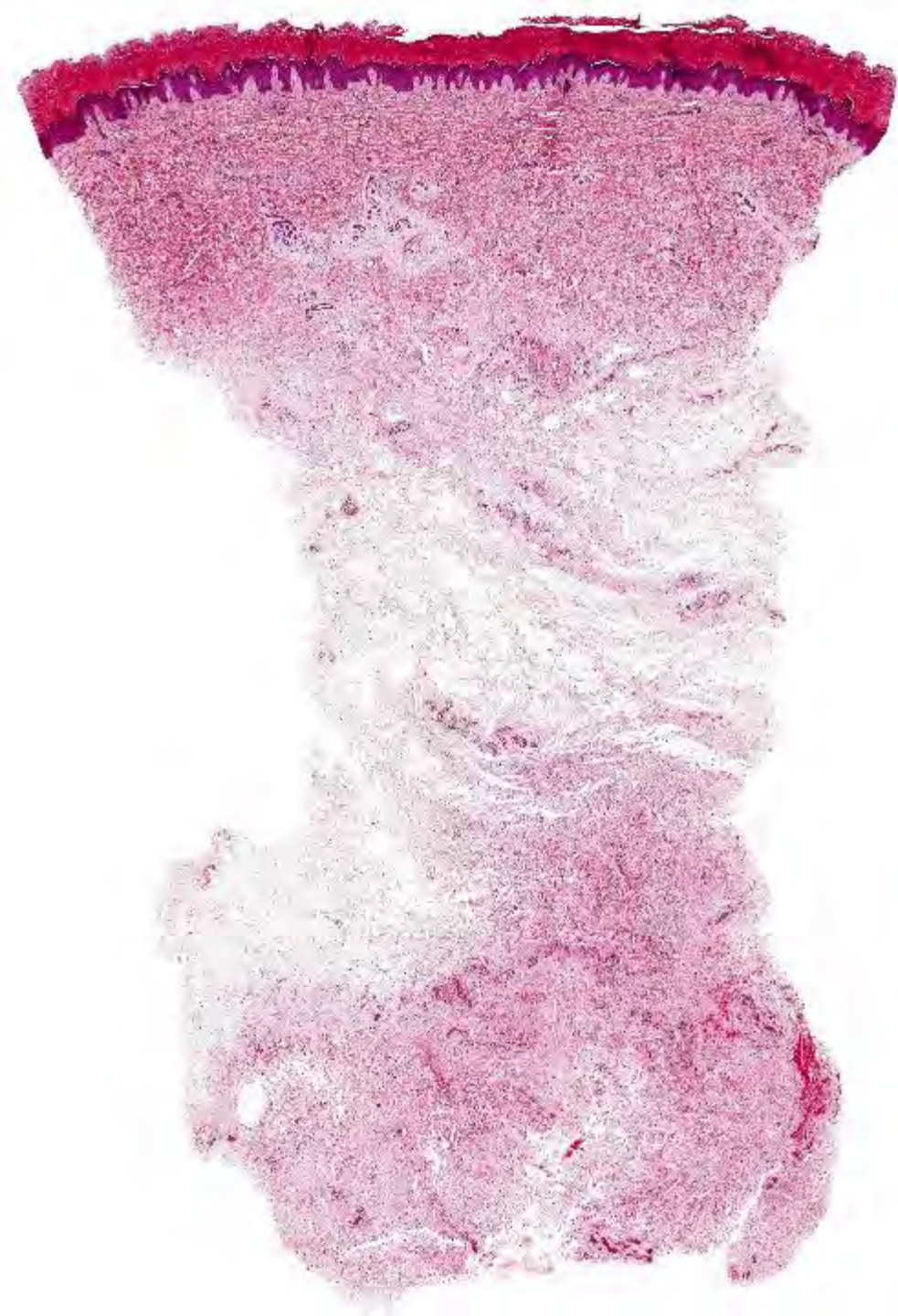
A previous external biopsy was reported (by me, without access to any clinical documentation but for the clinical diagnosis of "skin nodule") as subcutaneous mucin deposition.

The biopsy is re-evaluated in the light of the clinical correlation.









Piezogenic nodule-like herniation



September 5, 2025

Dearest Vertico-Drático,

Once more, thank you very much for your masterclass yesterday

I was most interested in your case of the lesion in the ankle with a nodule filled with mucin. I've seen many cases of lesions like that, due to prolonged friction with a prominent astragalus bone; I have biopsied a few (2 that I can remember, the patients in the pictures attached). One had a huge mucin deposition and the other a more modest one. I think these are just friction collagenomas with mucinous degeneration. Do you agree with my theory? The cases with huge mucin deposition can be doubtful, but the cases with collagen deposition and incipient mucin deposition I think support my view. What do you think? Do you want us to gather our 3 cases (and possibly more cases if I find them) and do a paper on it? It is not an uncommon condition, but the presence of mucin could be misleading, and our paper would clarify and help clinicians worldwide.

All best wishes, and wish you a great time in the weekend,

Toni

September 5, 2025

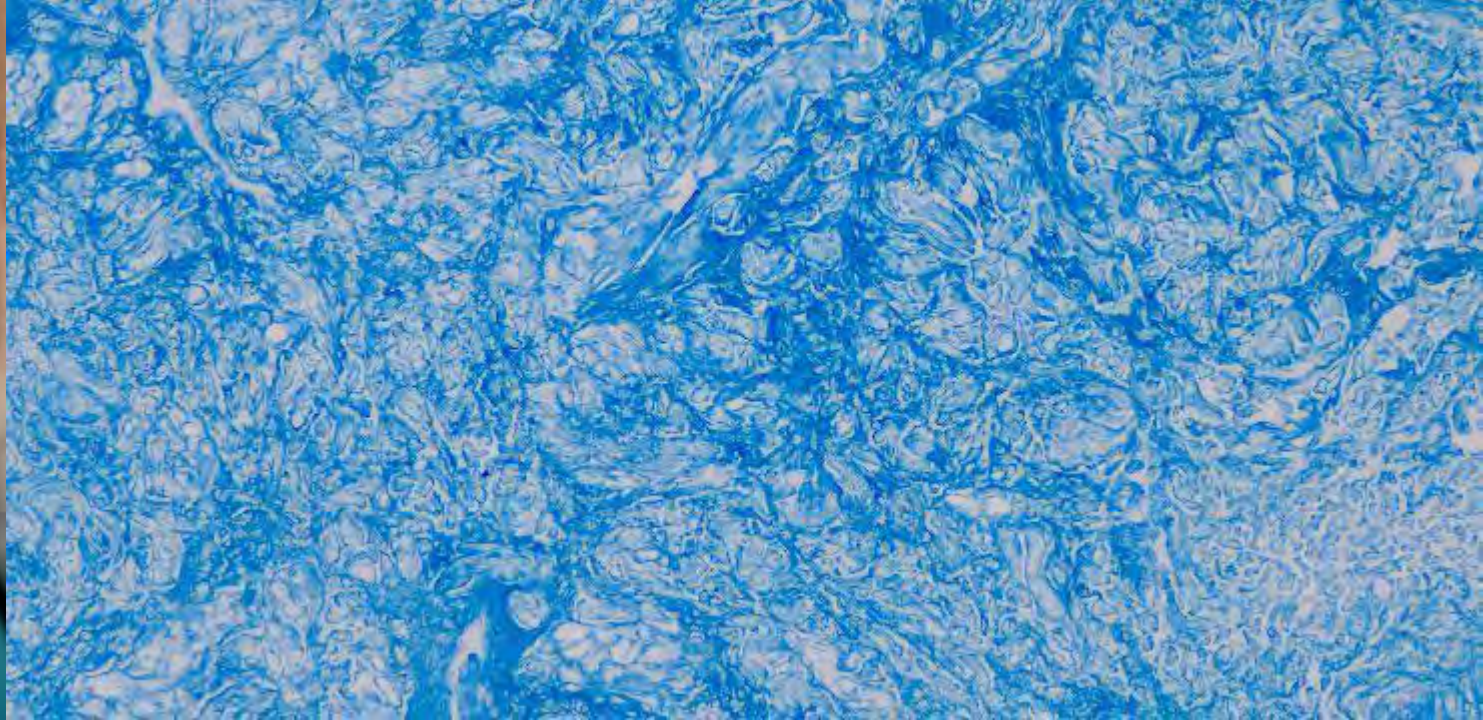
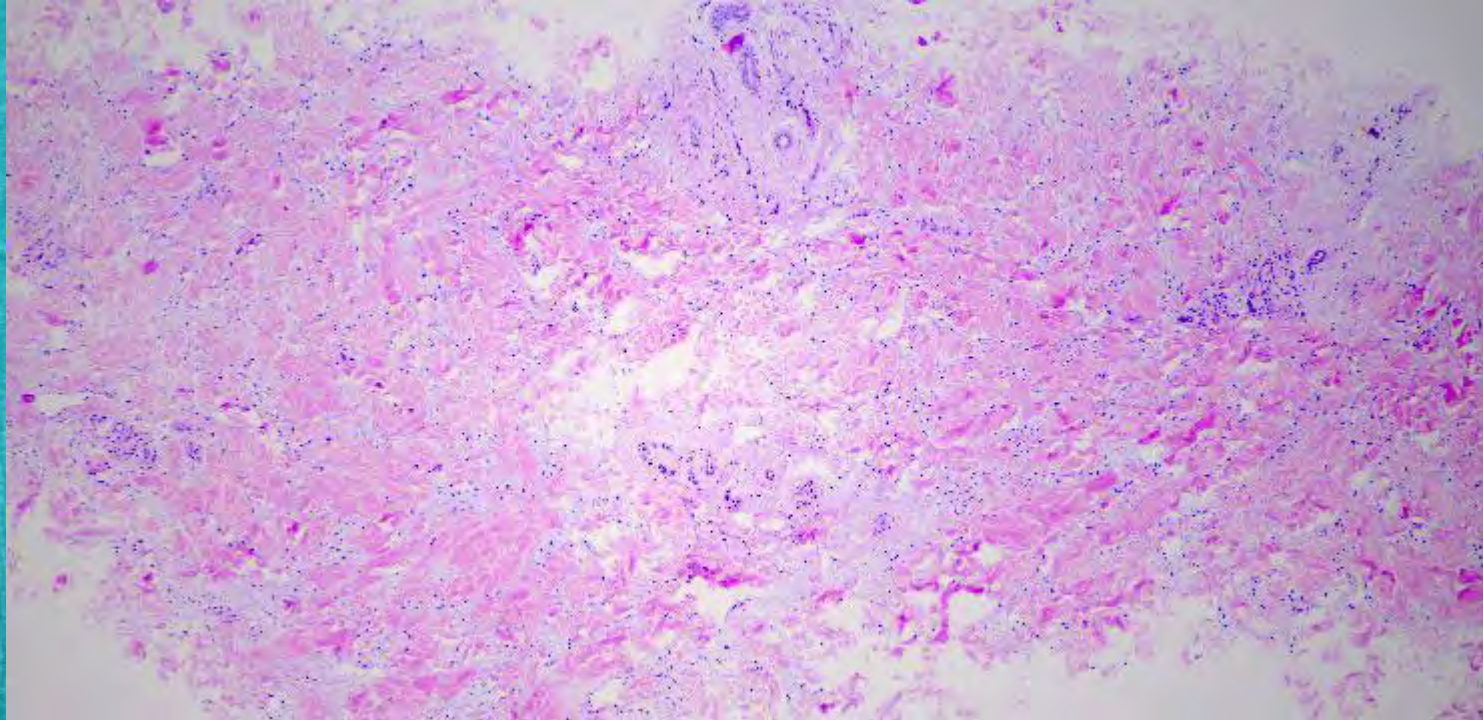
Dear Toni,

Incredible pictures, as always... I don't know how my patient did look like before the biopsy, but cannot imagine that she had such a large lesion, as the biopsy was relatively small, and only a scar was visible at the end. I think that mucin deposition is a secondary phenomenon due to stress situations (one could be piezogenic nodule, the other compression / friction with an underlying bone). Thus I think that your theory may be correct and perhaps the proper way would be to put these cases together (the histology of my case is identical to piezogenic nodule) and propose "mechanic" factors as the reason for the histopathological (and clinical) changes in both conditions.

Be that as it may, of course you can get all material from me, including biopsied case (or cases? I must check) of piezogenic nodule. To have a paper with the master of masters would be the cherry on the cake of my academic life...

Un abrazo,

Lorenzo



September 9, 2025

Dear Professor,

Please correct me if I'm wrong; in my mind, piezogenic papules are small papules appearing on the lateral sides of the feet and heel on standing position, that disappear when pressure from body weight is relieved. In my mind, they represent small fat herniations, and the histology will show normal tissue, because certainly there is no anatomical substrate. Piezogenic papules of the heels are unusual in children. I wonder if you have the same concept, or if you consider in the same group nodules on the side of the ankles over bony prominences as a result of friction rather than true pressure. In these cases, a collagenoma-like changes and sometimes mucinous changes are seen.

Can you please share the clinical pictures of your 2 conventional piezogenic nodules? I am sharing a number of cases I've seen, all of which I diagnosed as 'friction collagenoma' or 'friction nodules', but had not thought of as piezogenic or piezogenic-like nodules. I do not biopsy these lesions regularly.

Yes, my histopics were very primitive; I can do much better or if unsuccessful I can send the slides to el Catedrático.

Please feel free to lead the article writing as first author or if you prefer we can do it here with same pleasure. In my view, only those cases with mucinous changes deserve publication. What do you think?

All best wishes,

Toni

September 10, 2025

Dear Maestrissimo,

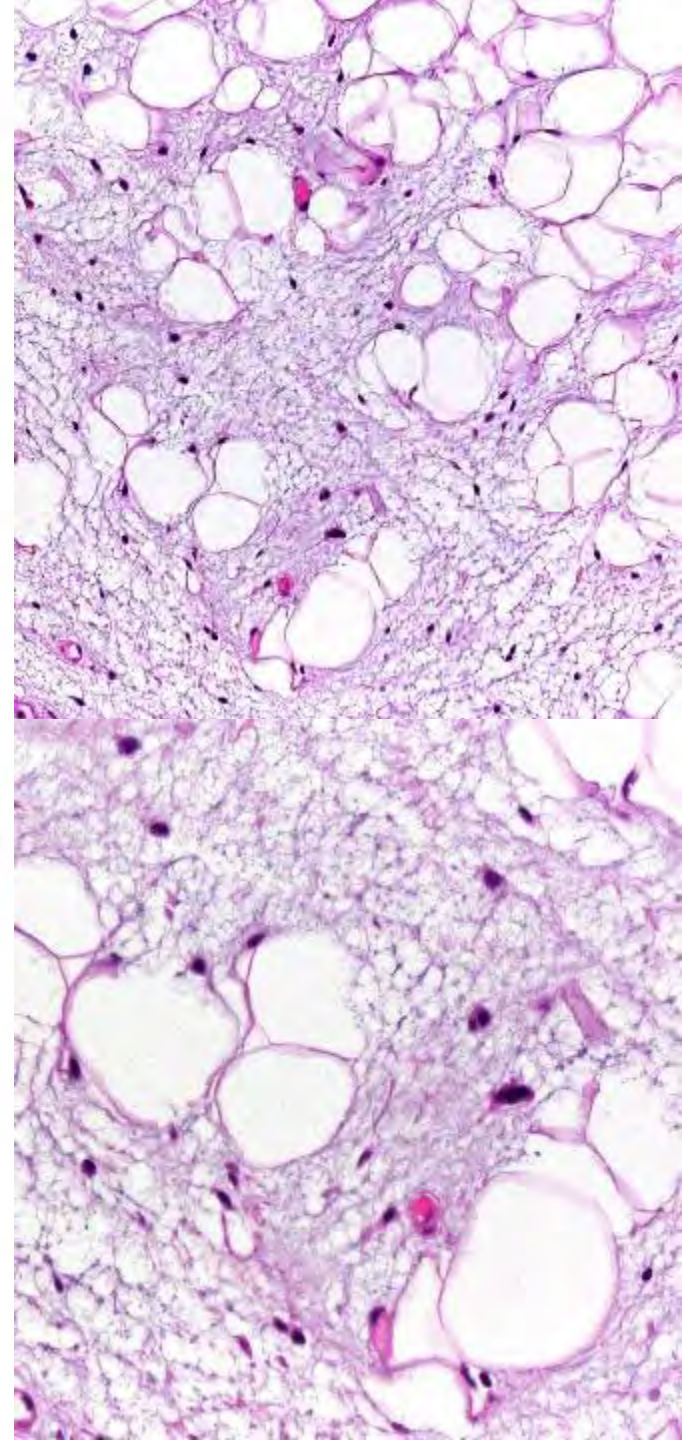
you are right, but not completely. For me the histology of piezogenic papules is almost identical to that of your patient. I send you 2 cases (one with 1 biopsy, the other with several biopsies) and my "piezogenic-like" case that you saw in the last dia-klinik.

To my eyes, this peculiar histology is due to repeated "trauma" (e.g., repeated herniation or compression against a bony structure), thus I would put the two conditions together because I think that the mechanism is similar, and for diagnosis it is important to know that the correlation with the clinical picture is essential. But as you are much better than me (no joke), of course you decide. Just take a look at the cases that I sent you and let me know.

Greetings from Vienna (I am a foreign body at the European Congress of Pathology...)

The Nondratico

F, 21



Painful Piezogenic Pedal Papules in a Female Babysitter: A Case-Based Review

To the Editor:

Piezogenic pedal papules (PPP) are featured by skin-colored hidden lesions and visible only on weight bearing or pressure application. PPP often presents on both heels. Here, we report a case of PPP, which only involved the right heel.

A 40-year-old Chinese woman presented multiple painful papules for 2 years on her right heel. The pain was more pronounced after prolonged standing. Physical examination identified multiple, 0.5–1.0-cm sized, soft, relatively well-demarcated, and skin-colored papules on the medial aspect of her right heel (Fig. 1A). These papules were more prominent by pressing the heel side (Fig. 1B). Her medical and family history was not significant. She worked as a babysitter for years, was never overweight and denied any traumatic events related to the lesions. Histopathological examination revealed normal epidermis with several fat

lobules protruding into the dermis. The prevalence of pedal papules varied widely in literature: 1.4%, 62%, and 100%.^{1–3} The discrepancy may be attributed to the selectiveness of the disease. It appears in children and adults without apparent sexual bias. The pathogenesis of PPP is unclear. Most scholars believe it is a herniation of fat through the dermis. Repetitive stress, trauma, and connective tissue defect are the major factors contributing to the development of PPP because most of the published cases were athletes, obese subjects, or patients with Ehlers-Danlos syndrome. Our patient was a babysitter, a job requiring long-time standing and walking. In addition, she might have



FIGURE 1. Clinical and histological manifestations of piezogenic pedal papules. Yellowish papules and nodules on the right heel without (A) and with pressure (B). C, Several fat lobules in dermis (indicated by arrows; HE, $\times 20$). Inset image shows the adipose tissue surrounded by thick collagen fibers (hematoxylin and eosin (H&E), $\times 200$).

Supported by the National Natural Science Foundation of China (Grant numbers: 81673063, 81673063), Natural Science Foundation of Guangdong Province (Grant numbers: 82011A030113765, 82011A030113759). The authors declare no conflict of interest.

lobules surrounded by dense collagen fibers in deep dermis (Fig. 1C). Together with the clinical manifestation, she was diagnosed with PPP and advised to use compression stockings and to avoid long-time standing.

some hand-to-hand gesture that makes her right heel handle more stress of her body weight than her left heel, eventually resulting in the unilateral lesions.

Piezogenic papules generally present as multiple, 0.2–1.0-cm sized,

A Piezogenic Papule With Histopathologic Features Simulating Angiomyxolipoma

Woo Jin Lee, MD,* Sang Min Lee, MD,† Chang Hyun Won, MD, PhD,† Sung Eun Chung, MD, PhD,†
Mi Won Lee, MD, PhD,† Jee Ho Choi, MD, PhD,† and Kee Chun Moon, MD, PhD†

Abstract: Piezogenic papules are lesions that occur on the feet and arise because of the herniation of fat through the dermis. These papules can be painful or completely asymptomatic. Even compartmentalization of fat occurs because of thinner than normal fibrous trabeculae and contributes to the formation of piezogenic papules. On histological examination, fat is evident extending through the dermis. We report a case of a piezogenic papule simulating angiomyxolipoma on histological examination. The presented case suggests the possibility of an association between herniated fat tissue and fibrous deposition with vascular proliferation.

Key Words: piezogenic papule; angiomyxolipoma

J Am Acad Dermatol 2019;81:463–464 (19)

INTRODUCTION

Piezogenic papules occur from the herniation of fat through the basal layer of the weight-bearing parts of the feet and can create pain in this area.¹ These papules are most apparent when weight is placed on the heel and disappear with the removal of pressure. Although no hereditary diseases or syndromes have been definitively associated with piezogenic papules, they have been reported in some patients with Ehlers-Danlos syndrome.² On histological examination, the normally small fat compartments in the lower dermis and subcutis coalesce because of the loss of the thin fibrous septations.³ Angiomyxolipoma is a rare variant of lipoma first described by Ma et al.⁴ The histopathologic features of angiomyxolipoma include an admixture of myxoid areas with rela-

tively scanty well-circumscribed nodules of lipoma on the medial aspect of both heels (Fig. 1). The papules became prominent when the stood with full weight on the heels and resolved when the sat down. He denied any traumatic event related to the appearance of the lesions. A punch biopsy from one lesion was subsequently performed. Histopathology showed an admixture of paucicellular myxoid tissue and nests of mature adipose tissue (Fig. 2A). The myxoid area was stained with Alcian blue (pH 2.5). The myxoid area contained irregularly distributed sparse spindle cells with bland nuclei (Fig. 2B). Mitotic figures were absent. Spindle cells were not distributed along collagen bundles nor embedded among collagen bundles. No lipoblasts were identified. Additionally, numerous large and small vascular structures within the myxoid and adipose areas were noted (Fig. 2C). Immunohistochemical studies found that spindle cells in the myxoid area were positive for CD34 (Fig. 2A) but were negative for S-100 protein, smooth muscle actin (SMA), and desmin. Mature adipocytes were reactive for S-100 protein. The vascular endothelium expressed CD31 and SMA (Fig. 2D). The histopathologic and immunohistochemical findings were consistent with angiomyxolipoma; however, clinical features were more consistent with a diagnosis of piezogenic papule. The patient declined further surgical interventions.

DISCUSSION

Piezogenic papules form because of the herniation of fat into the dermis and generally present as multiple small papulonodules on the feet or wrist.¹ Piezogenic papules may be more common in obese individuals and in patients with various hereditary problems (eg, flat feet). However, they also can occur occasionally with no clear predisposition.⁵ In

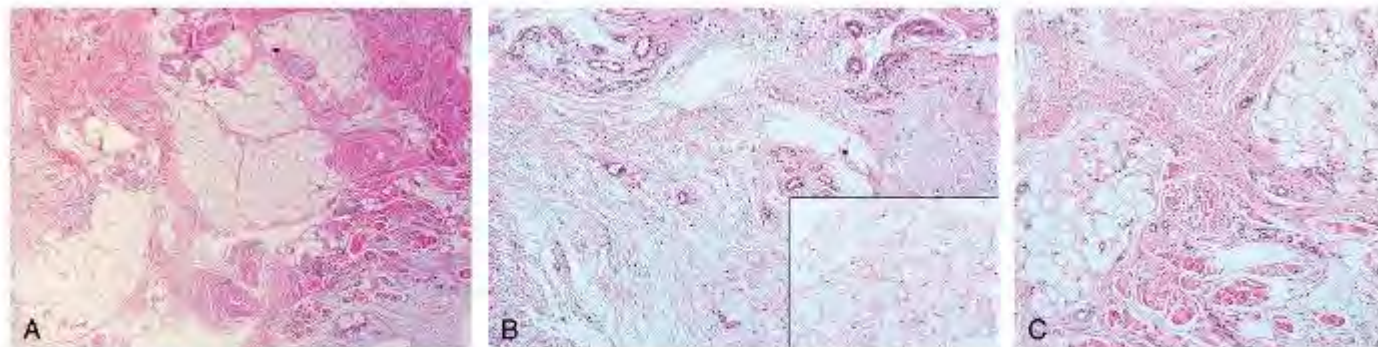
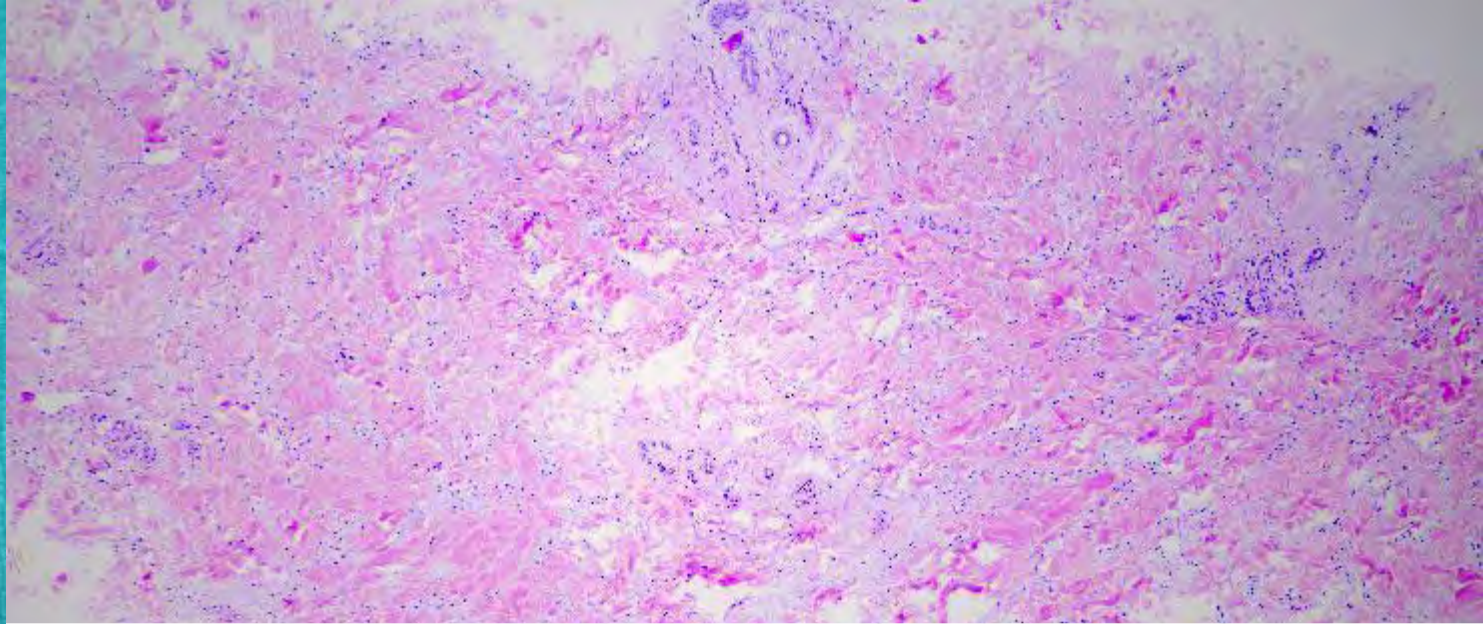
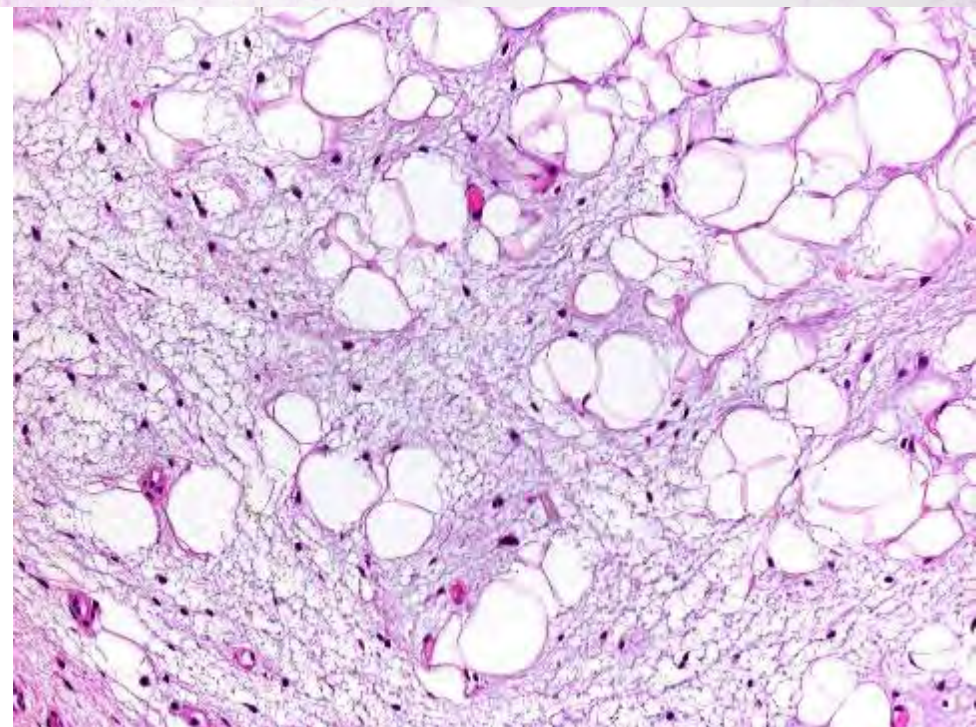
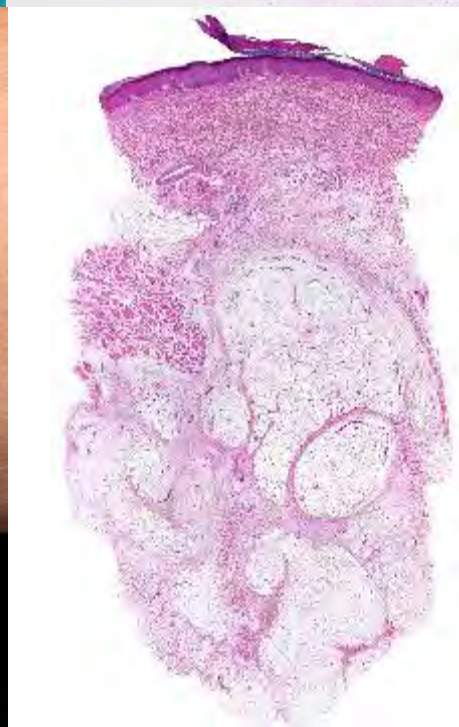
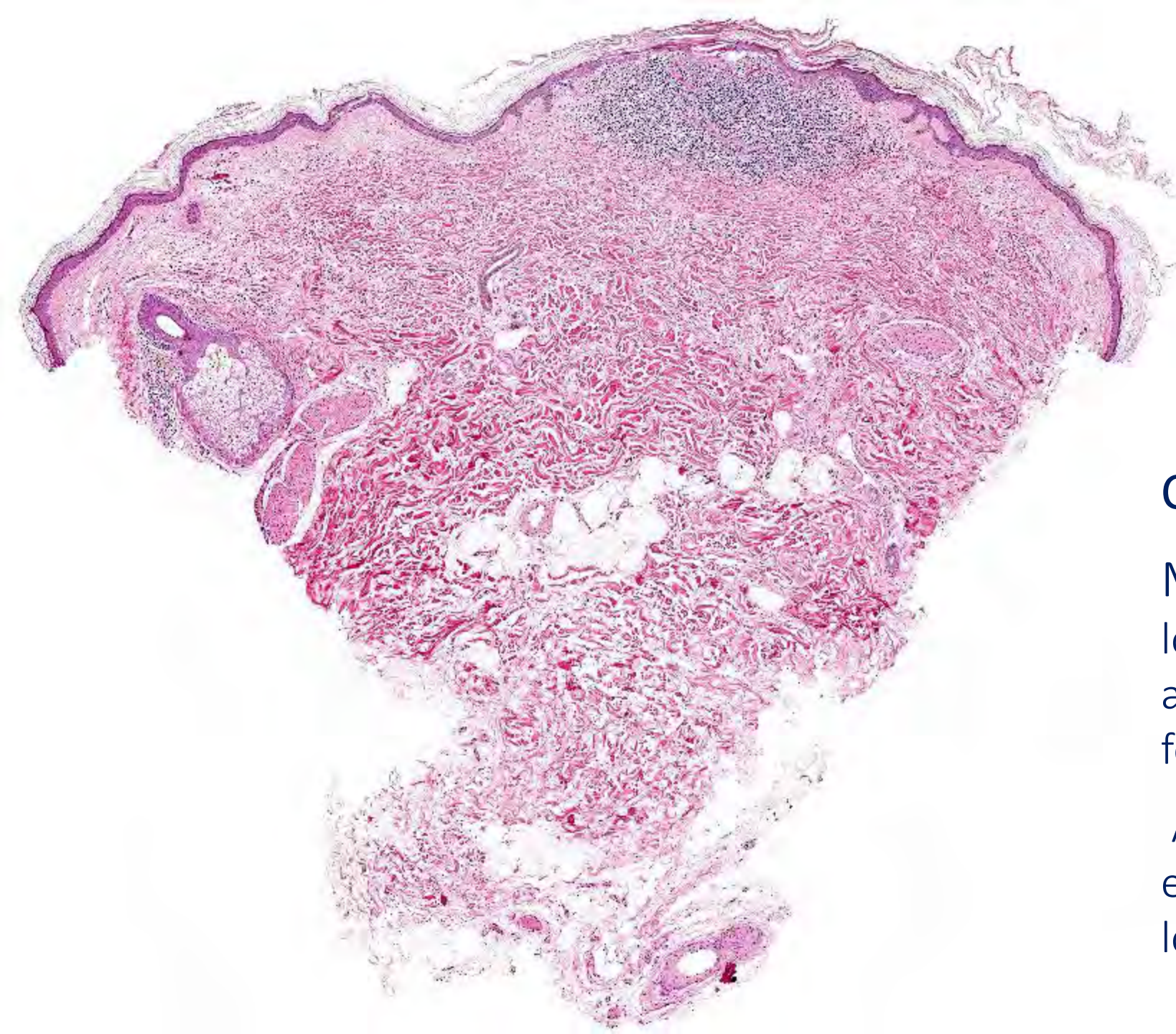


FIGURE 2. A, Histopathologic findings showing both paucicellular myxoid tissue and lipomatous areas (hematoxylin and eosin staining, $\times 40$). B, Randomly distributed, sparse spindle cells in the myxoid area. C, Proliferative vascular structures in both the myxoid and the fat tissue (B and C: hematoxylin and eosin staining, $\times 100$).



Acral mechanic subcutaneous mucinous degeneration

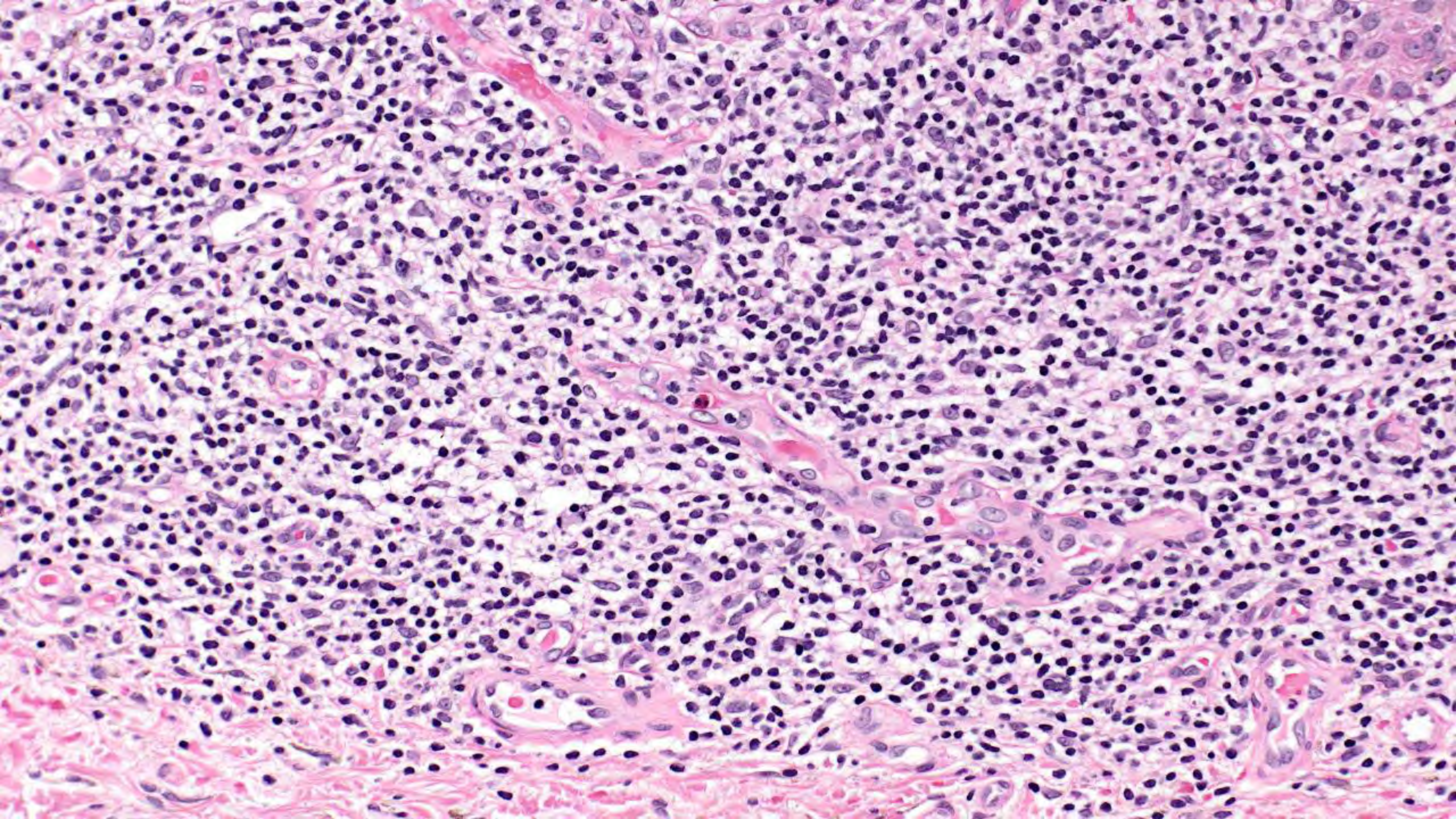


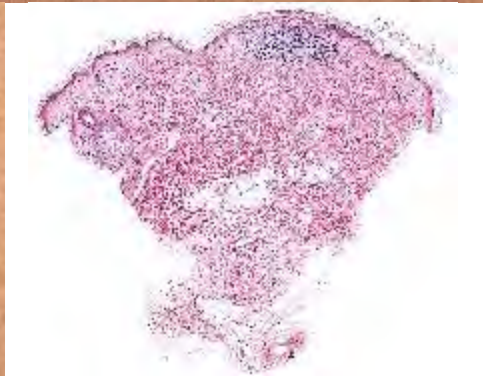


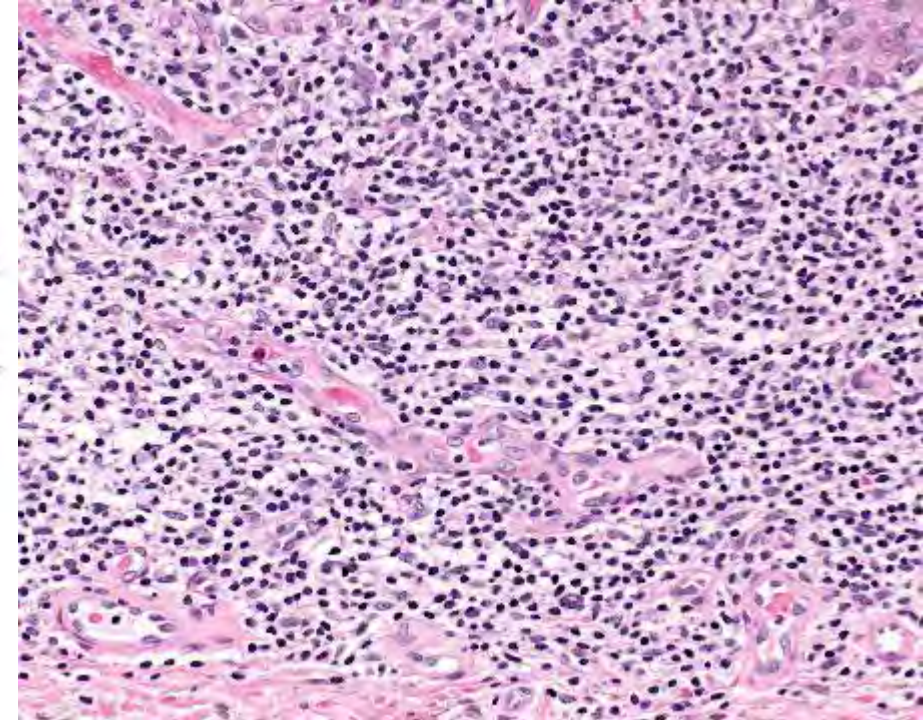
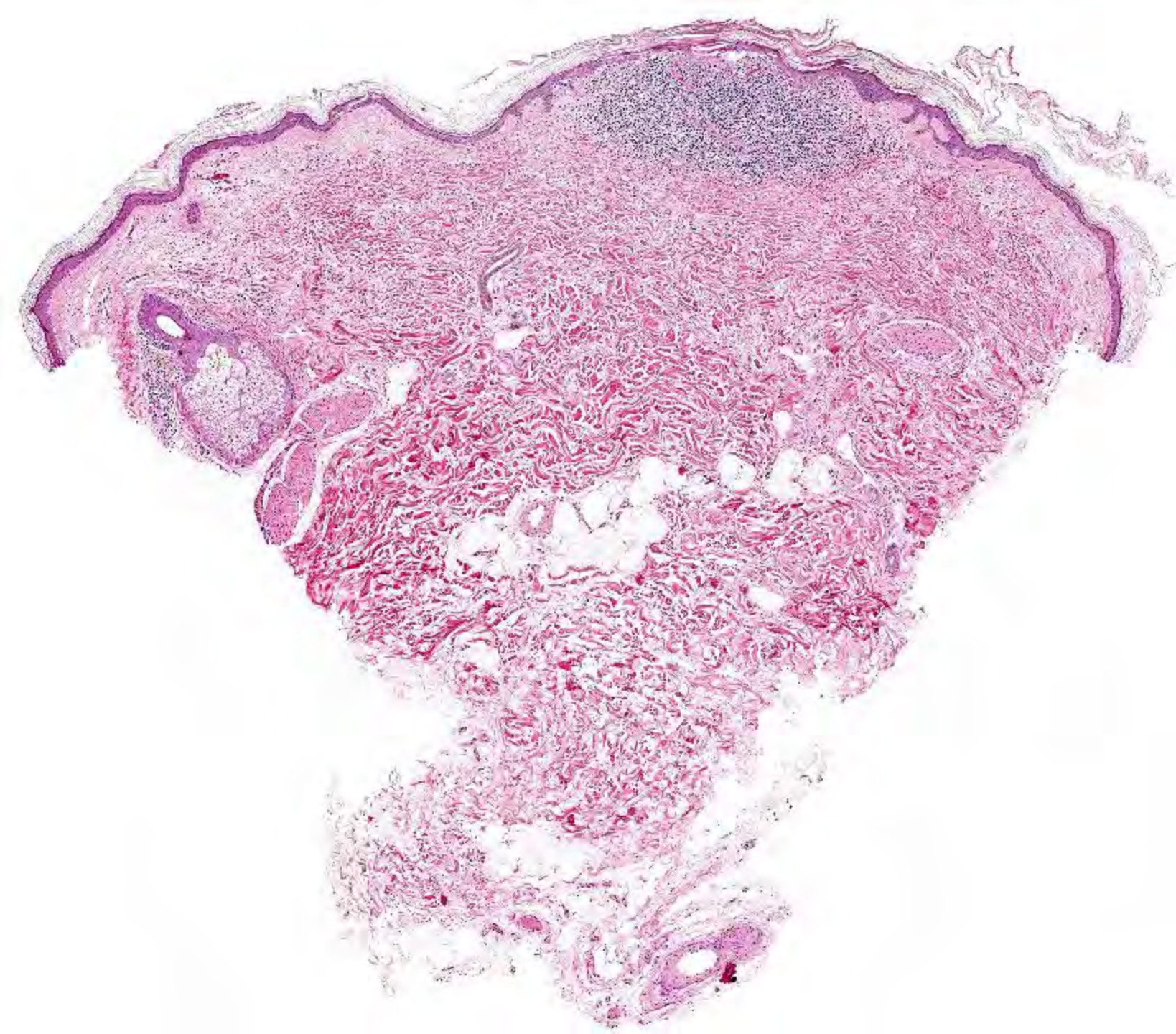
Case 36

M, 60. Hematoma on the right lower leg for one week. Oral antibiotics and diuretic for a few days, prescribed by the GP.

According to the patient small erythematous lesions on both lower extremities for one year.

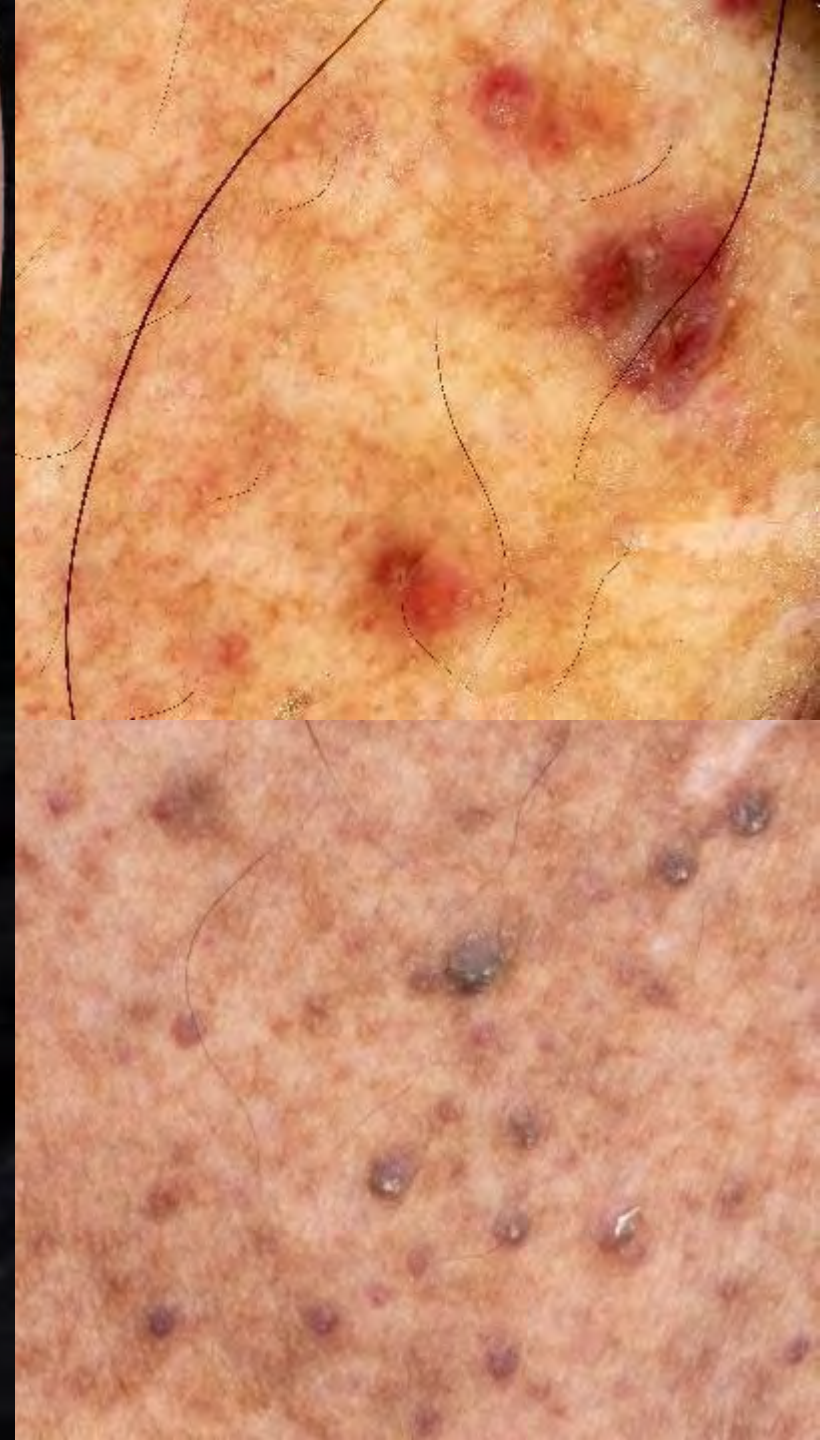


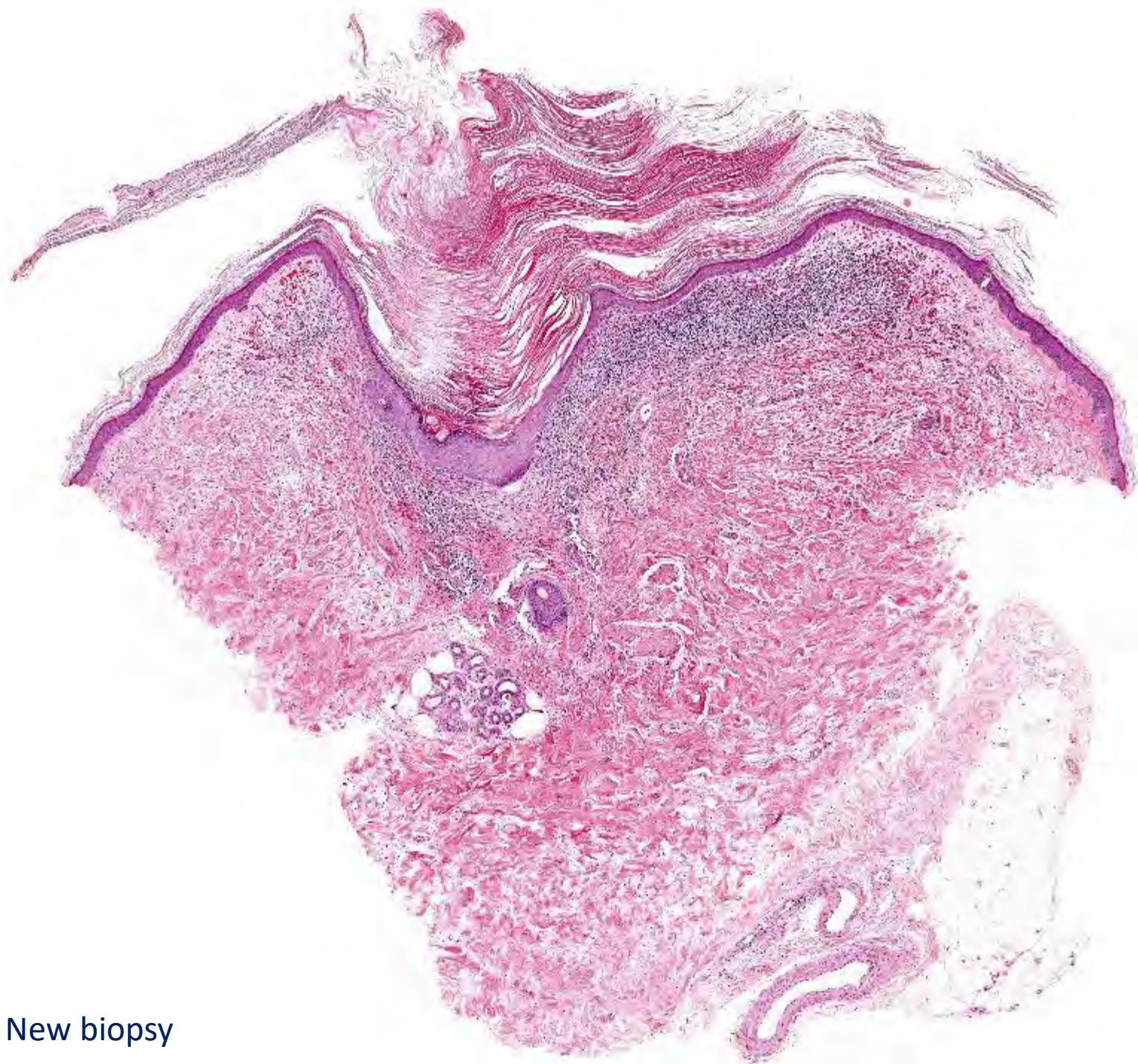






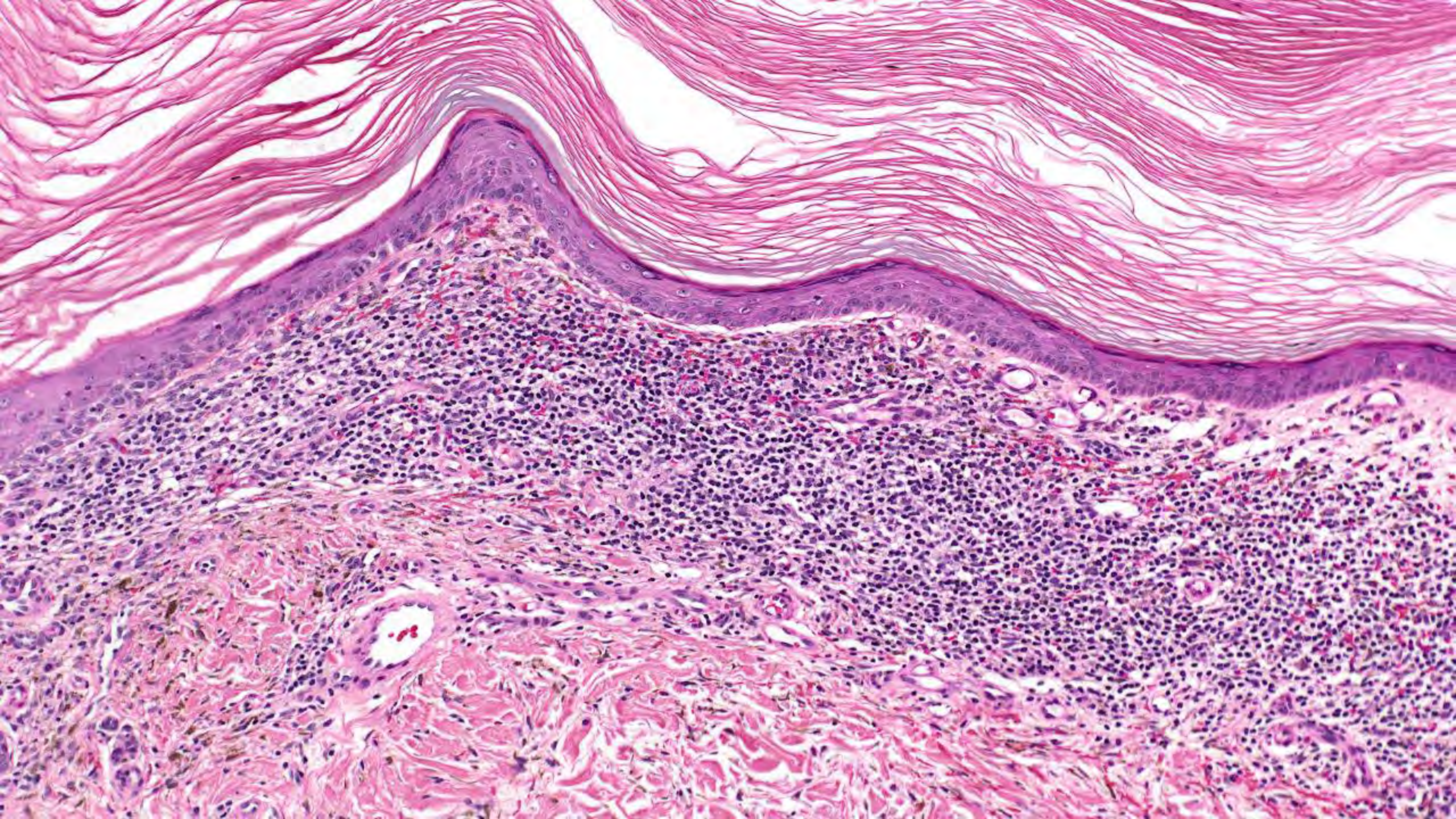
2 weeks later

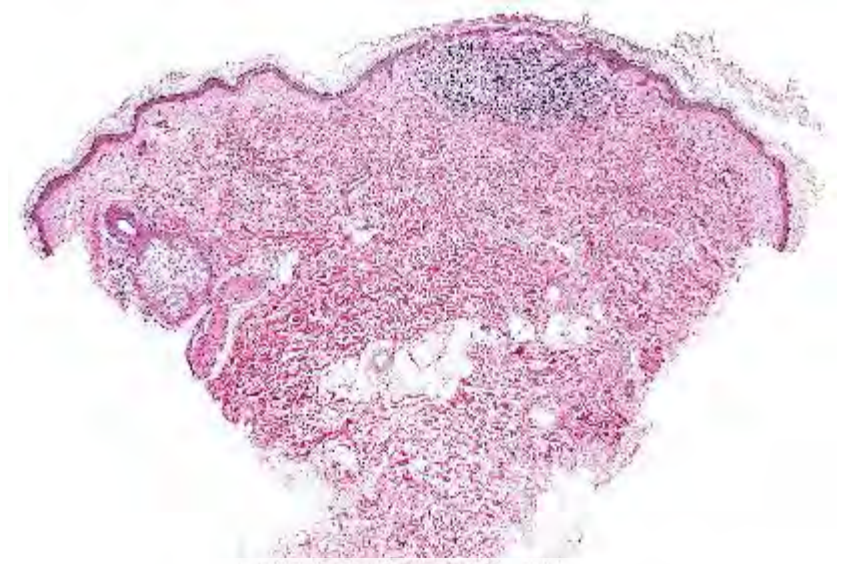




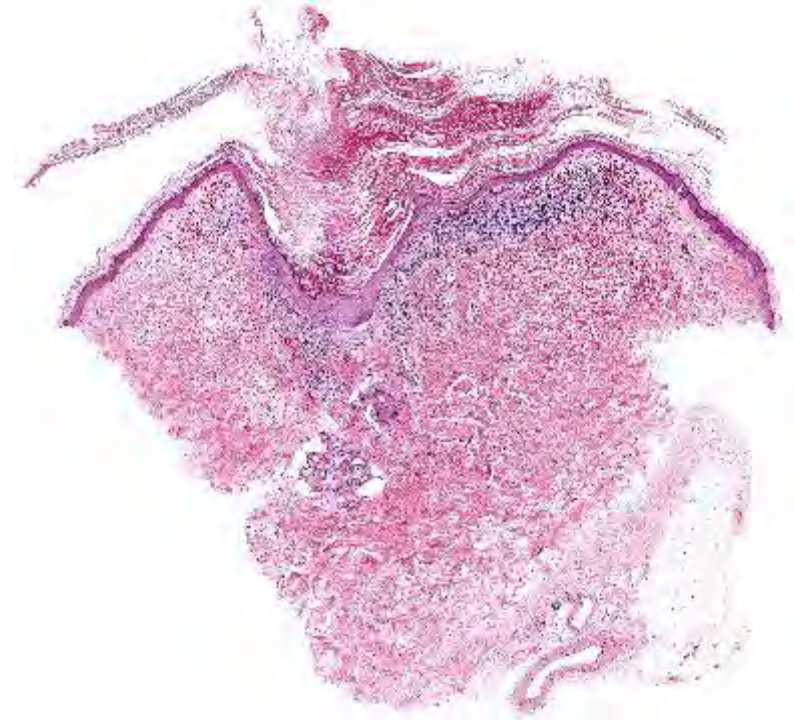
New biopsy







Flegel disease



Histopathological Differences Between Early and Old Lesions of Hyperkeratosis Lenticularis Perstans (Flegel's Disease)

Ko-ichi Ando, MD, Hisao Hattori, MD, and Yohel Yamaguchi, MD

Abstract: A case of hyperkeratosis lenticularis perstans (Flegel's disease) was studied histopathologically comparing early and old lesions. The age of the lesions were judged by both the patient's history and clinical observation. The histopathologic and immunohistochemical features of early lesions were essentially in accordance with previous findings. However, the old lesion had obviously different histologic features. These included the absence of epidermal atrophy and infiltration of the upper dermis by mononuclear lesions. These findings suggest that the process of early hyperkeratosis lenticularis perstans involves the keratinocytes of the epidermis, whereas the granuloma was not found in the histopathology of the early lesion.

Key Words: Flegel's disease, hyperkeratosis lenticularis perstans, keratinization, membrane-coating granules, Golliard bodies

(*Am J Dermatopathol* 2006;28:122-126)

Hyperkeratosis lenticularis perstans (Flegel's disease) (HLP) is a rare dermatosis first described in 1958 by Flegel.¹ This entity is characterized by asymptomatic hyperkeratotic papules from 1 to 5 mm in diameter and is found predominantly on the dorsa of the feet and lower legs.¹⁻² The lesions of HLP last indefinitely.² Removal of the spiny scale above each papule causes slight bleeding.²⁻¹³ Although HLP has been considered an autosomal dominant condition,⁴⁻¹⁵ most cases seem to occur sporadically and usually start in late adult life.^{4-7,9,16} HLP can be clearly distinguished from clinically similar disorders such as Kyle's disease, porokeratosis, and squamous keratosis by its characteristic histologic features.¹⁷ The eruption is characterized by foci of compact hyperkeratosis overlying a thinner stratum corneum and a well-circumscribed, band-like lymphoid infiltrate in the underlying papillary dermis.² Previous immunohistochemical features suggested that the composition of the dermal infiltrate contains more CD4-positive T lymphocytes than CD8-positive T lymphocytes.^{18,19}

Ultrastructural studies suggested that HLP is a disorder of keratinocyte proliferation with quantitative and/or qualitative alterations in the membrane-coating granules (MCGs) [lamellar granules, Golliard bodies] of the keratinocytes.²⁰⁻²³ But other authors have reported no abnormalities.^{24,25} The importance of MCGs in the formation of the epidermal permeability barrier is established.²⁶ Abnormalities in MCGs structure and function may result in a decreased desquamation of the stratum corneum and in retention hyperkeratosis, because MCG-derived lipids are involved in the regulation of corneocyte desquamation.²⁷ The ultrastructure of the inflammatory cell in HLP has been studied by only a few authors. The presence of cerebriform lymphocytes is noted.^{4,5,17-19}

Recently, applying the term "version pattern" to bundles of filaments embedded in an amorphous inter-filamentous substance within the corneocyte. In a recent report,²⁸ of corneocyte ultrastructural investigation of HLP both the version pattern in corneocytes and the corneal envelope under the cell membrane of the corneocyte decreased.²⁸

We found differences in the histologic and electron microscopic features between an early and an old lesion of HLP.

CASE REPORT

A 54-year-old Japanese woman developed keratotic papules of less than 5 mm in diameter on the legs and forearms over three years. She was seen primarily because of a recent increase in the number of these lesions (Fig. 1). The eruption first appeared on the dorsal aspect of the feet extending gradually to the upper part of the legs, thighs and forearms. The patient's palms and soles were not affected. Her hair, nails and mucous membranes were normal. Hard and spiny lesions could be palpated, and were asymptomatic except for localized pruritus with the appearance of early lesions. It was comparatively easy to decide whether one lesion was early or old. The differences in appearance between the new, according with the patient's history. The early lesions were reddish-brown whereas the old lesions were brown and there appeared to be desquamation at the edges of lesions (Fig. 1). The hard scales could be removed, leaving tiny craters with foci of bleeding.

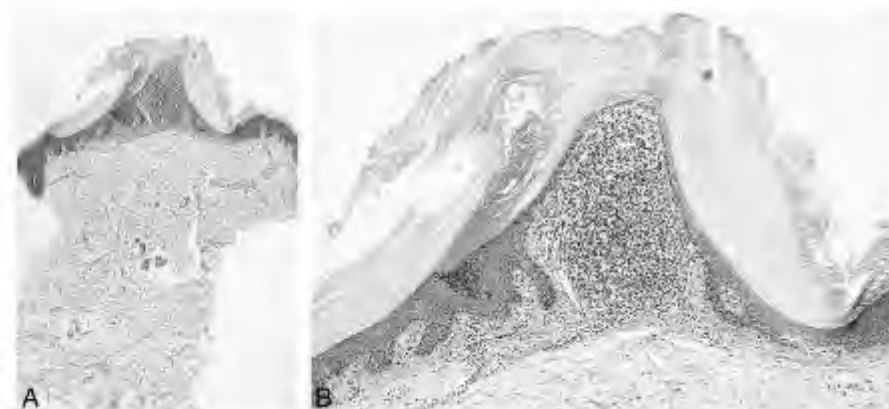


FIGURE 2. Histology of the early lesion. A, A hyperkeratotic papule with atrophic epidermis and dense, tent-like lymphocytic dermal infiltrate. B, The center of the lesion.

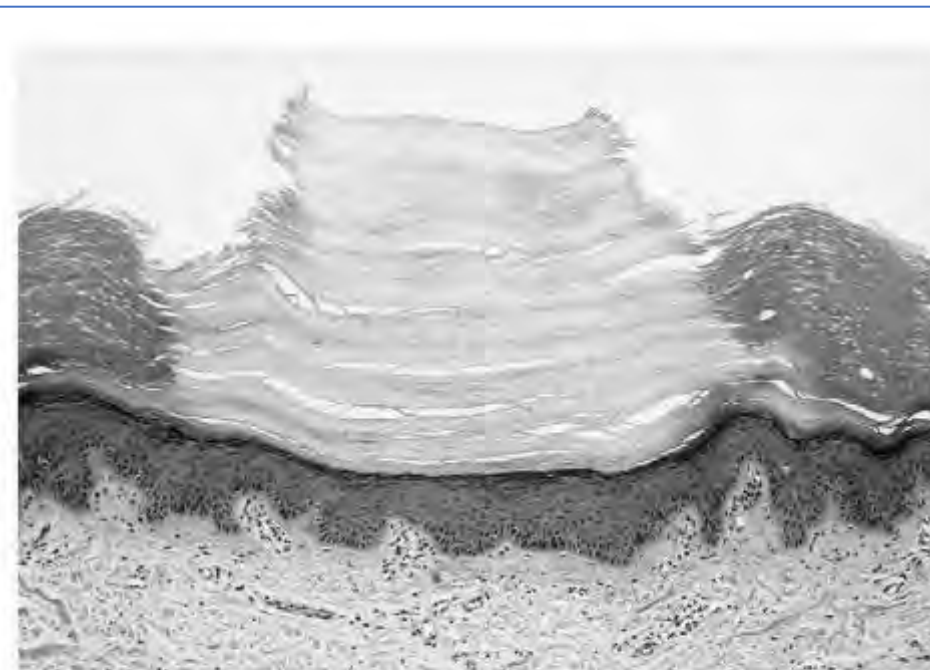
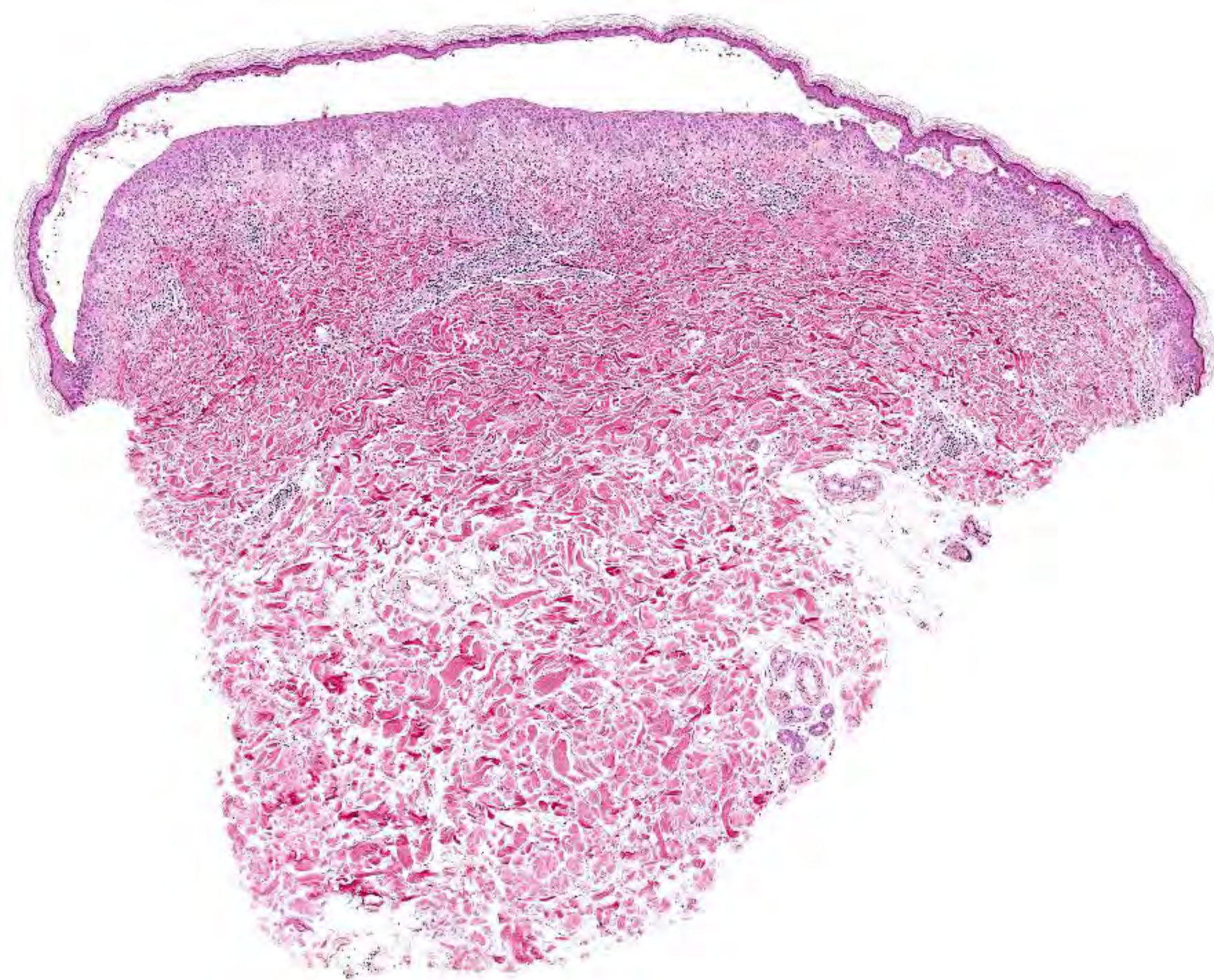


FIGURE 6. Histologic features of the old lesion. A hyperkeratotic papule with a flattened epidermis with a thickened granular layer and no infiltration in the dermis.

From the Department of Dermatology, Aomori Red Cross Hospital, Aomori, Japan.

No sources of support that require acknowledgment.

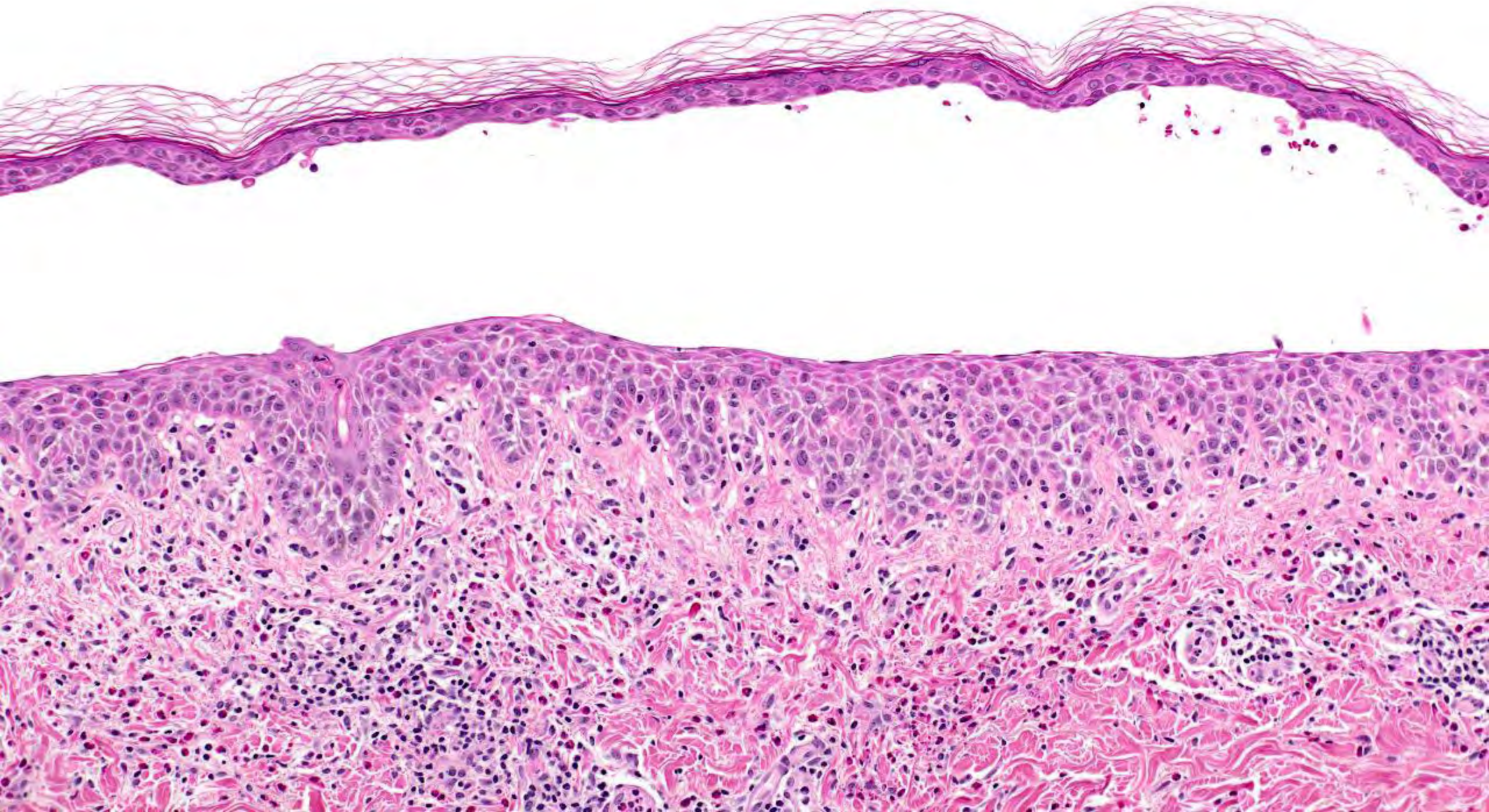
Reprints: Ko-ichi Ando, Department of Dermatology, Japanese Red Cross Aomori East Hospital, 1-15, Minamishinjo, Nishiku, Aomori 981-8511, Japan (e-mail: ando@redcross-aomori.jp). Copyright © 2006 by Lippincott Williams & Wilkins

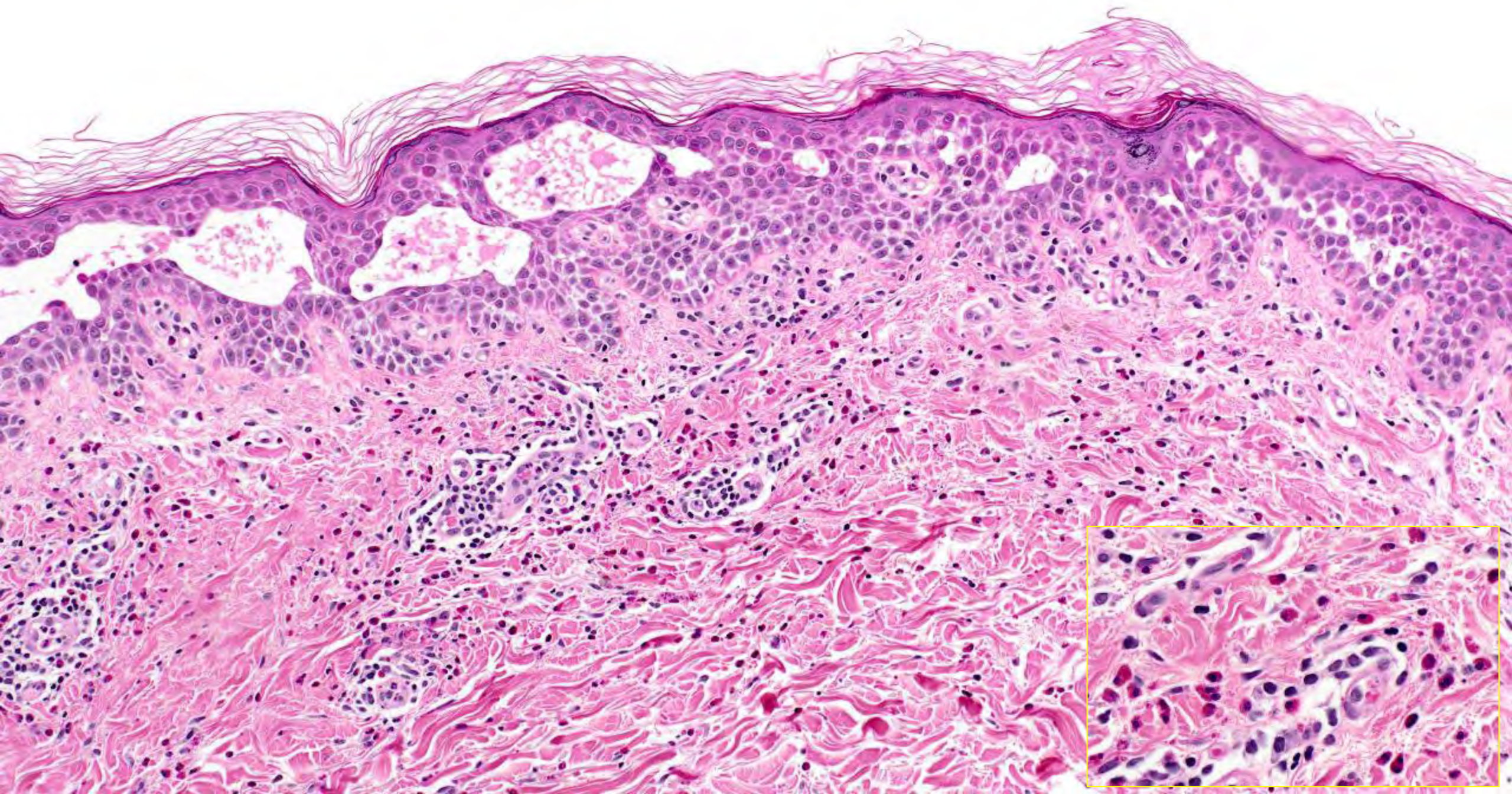


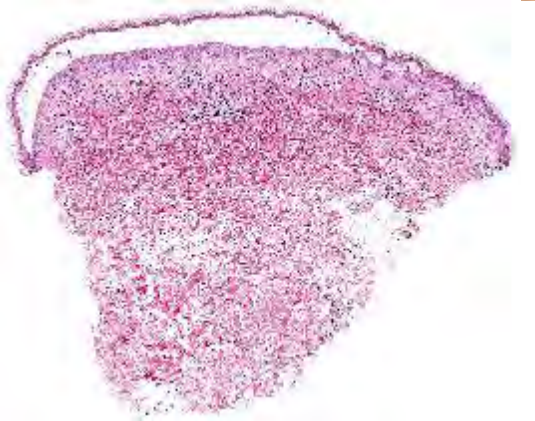
Case 37

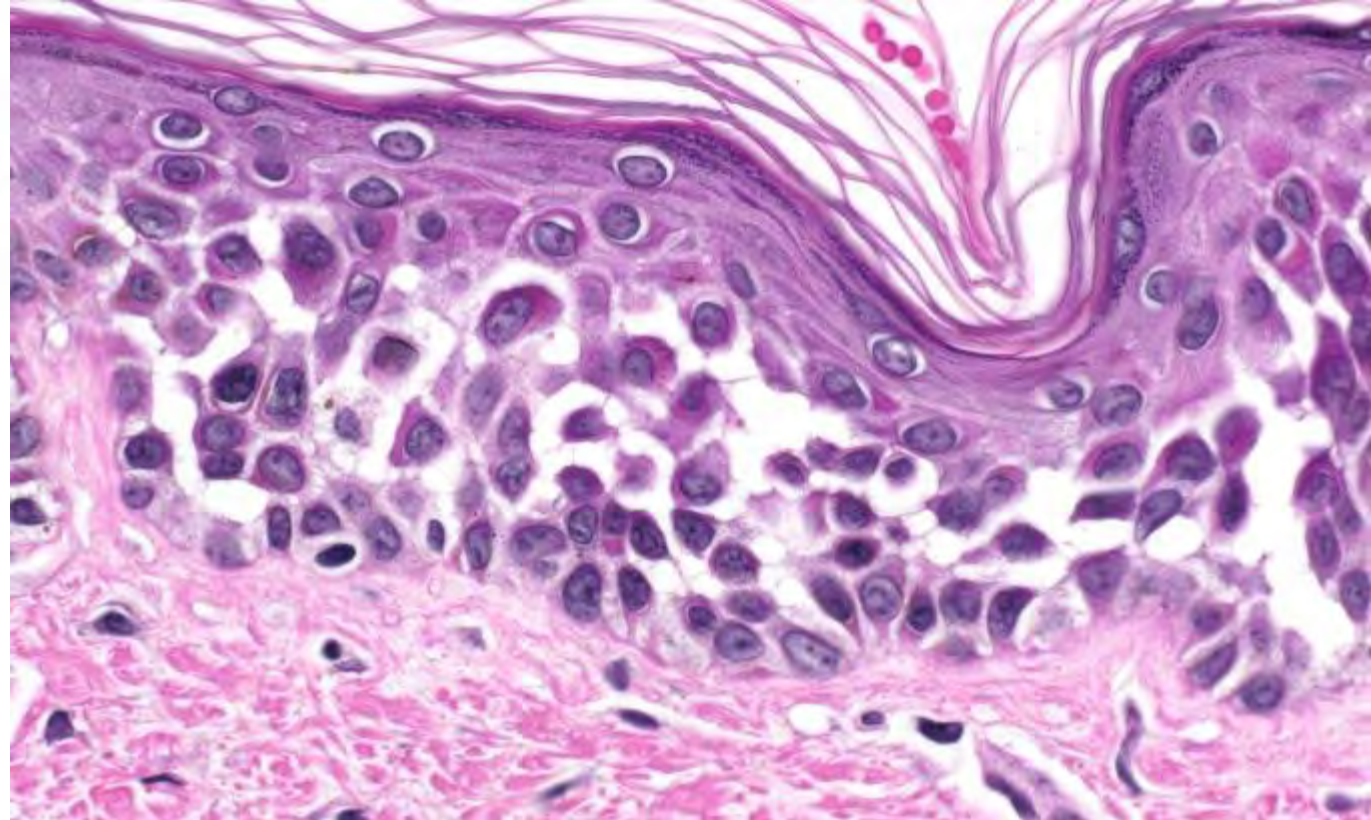
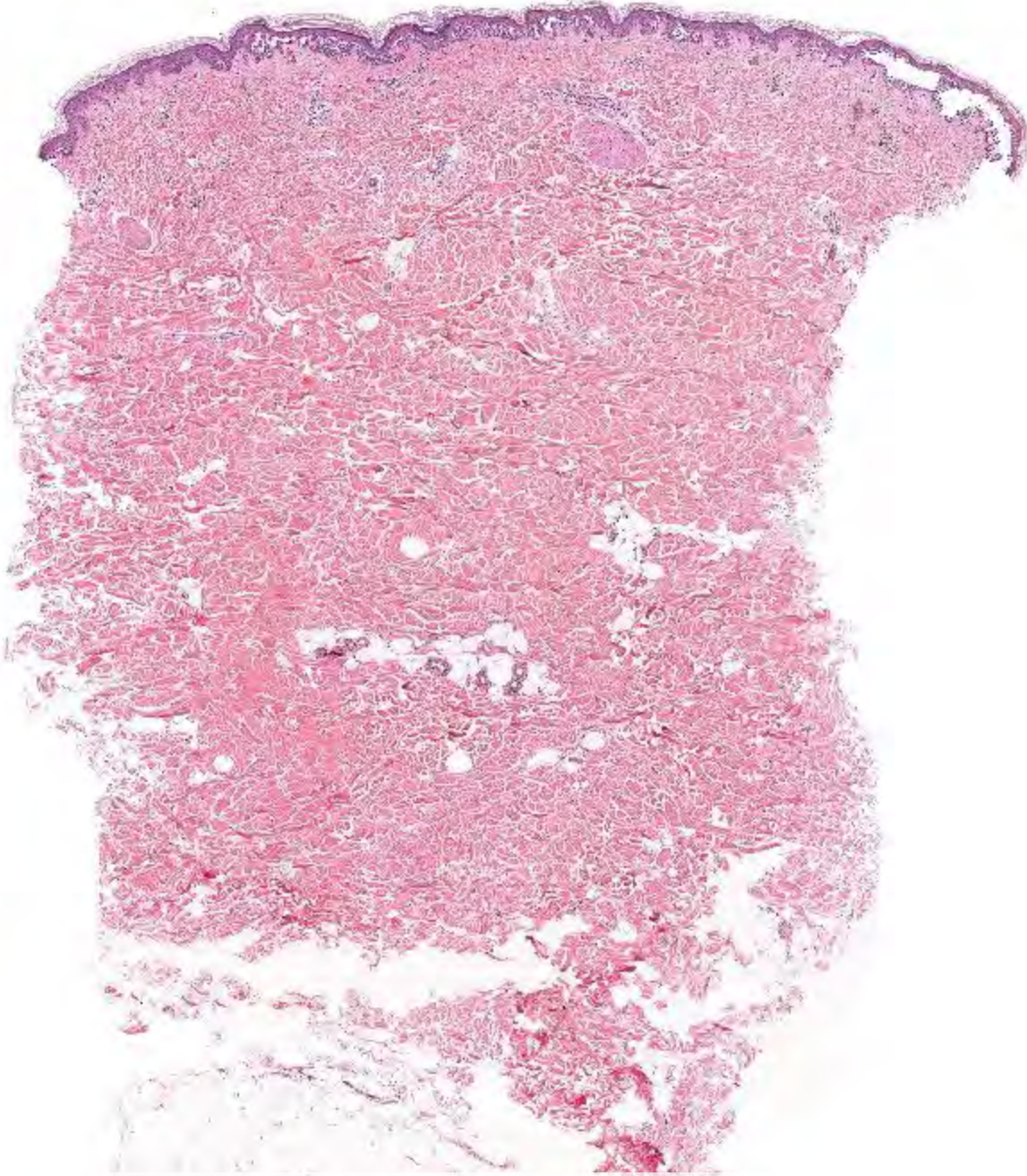
F, 55. History of "pemphigus vulgaris" (1st diagnosis 13 years before presentation, confirmed by biopsy; symptoms present for >20 years; DIF & IIF negative). Improvements and relapses under dapsone therapy.

According to the patient recent worsening after a respiratory infection.

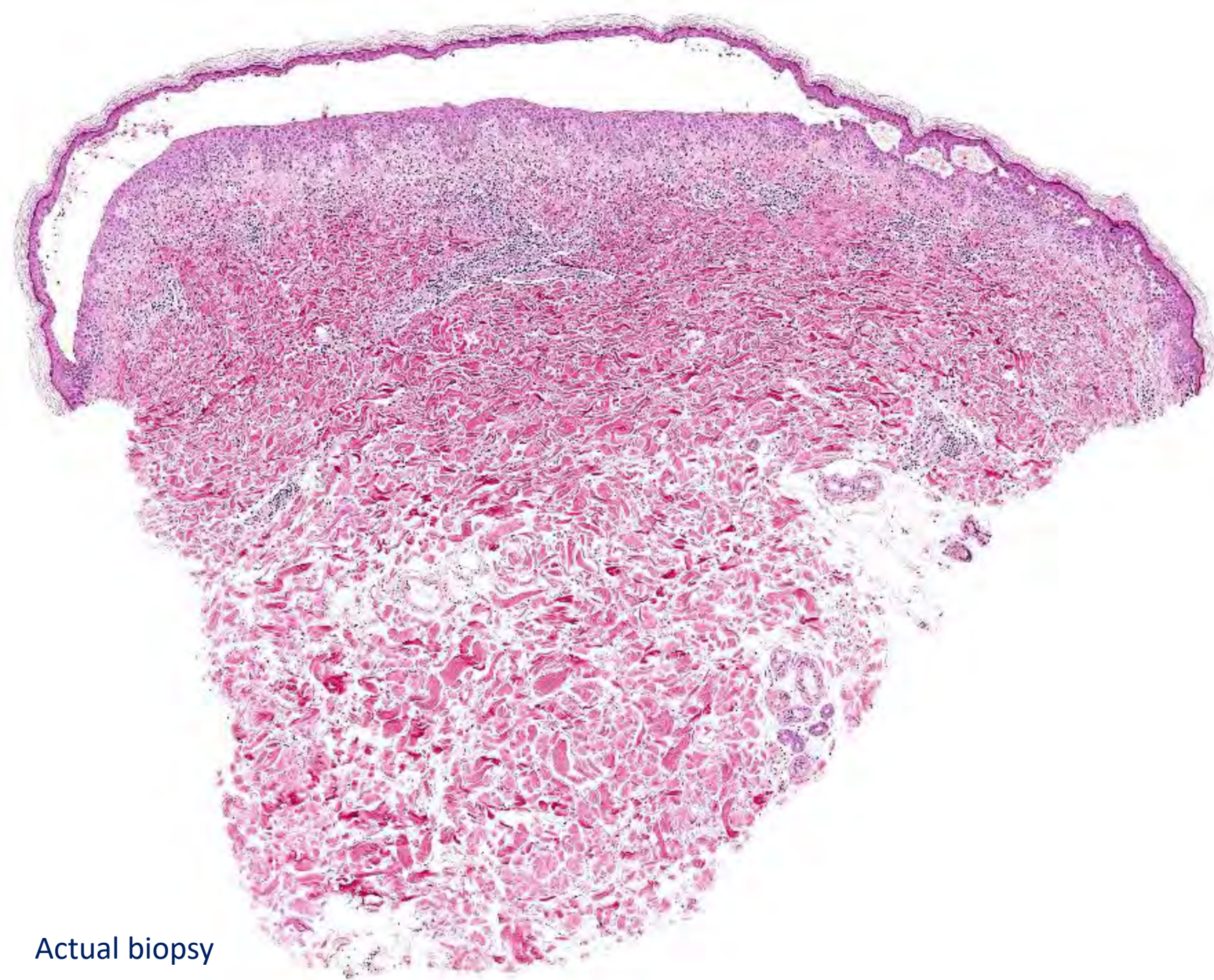




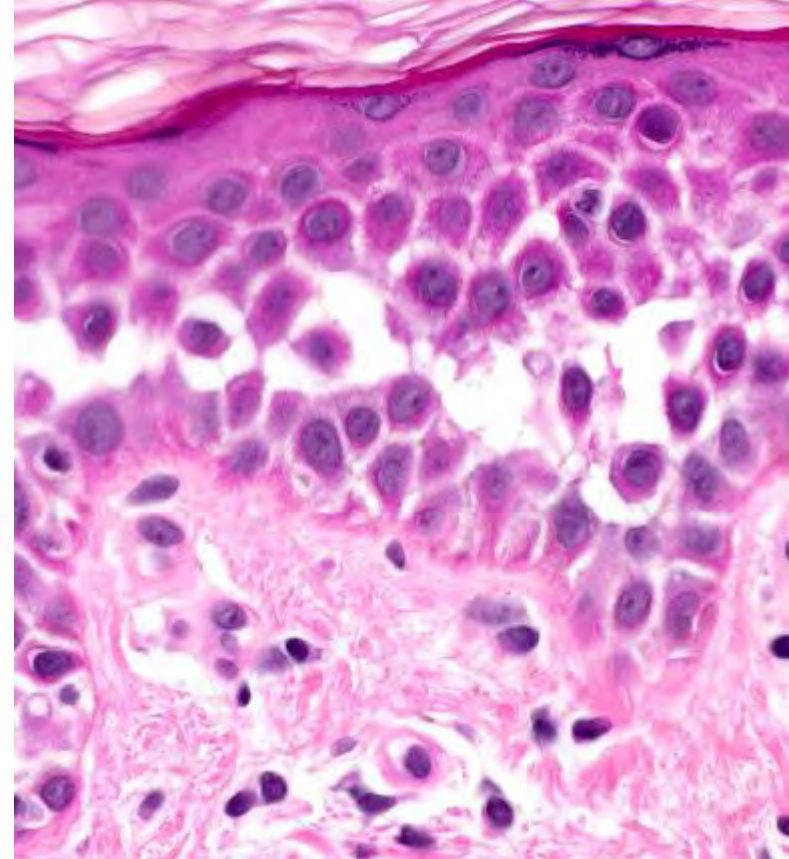




Biopsy taken 13 years earlier & old clinical picture



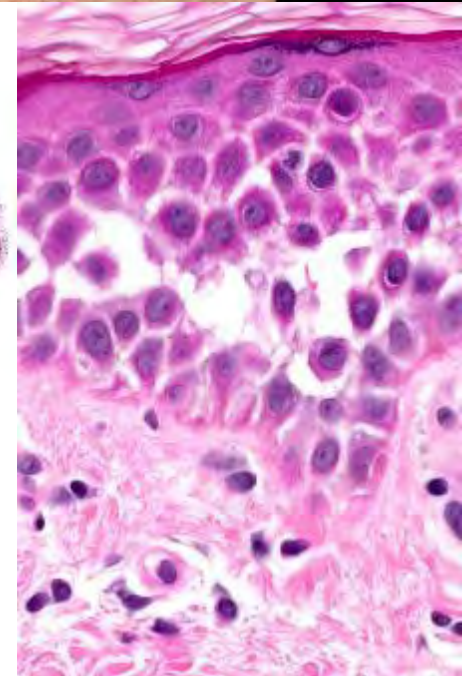
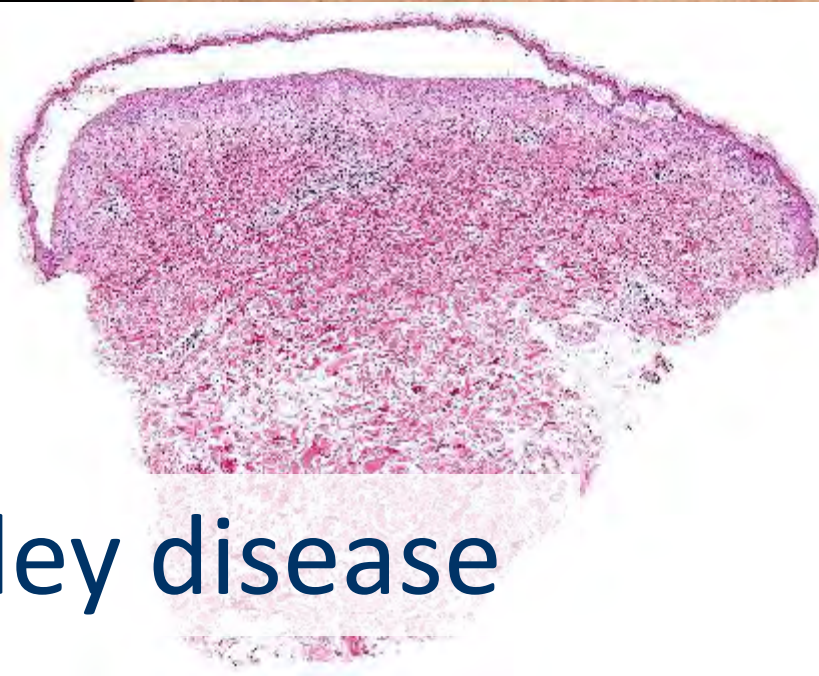
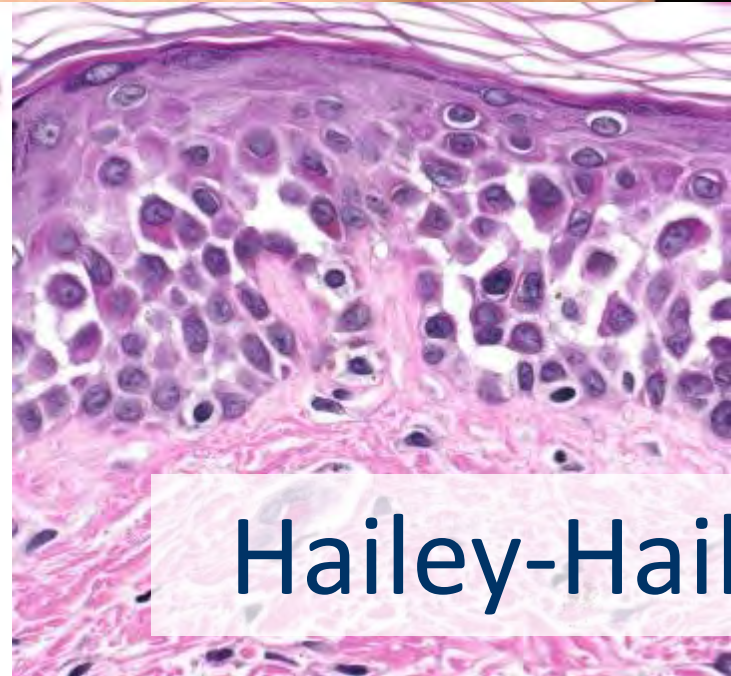
Actual biopsy



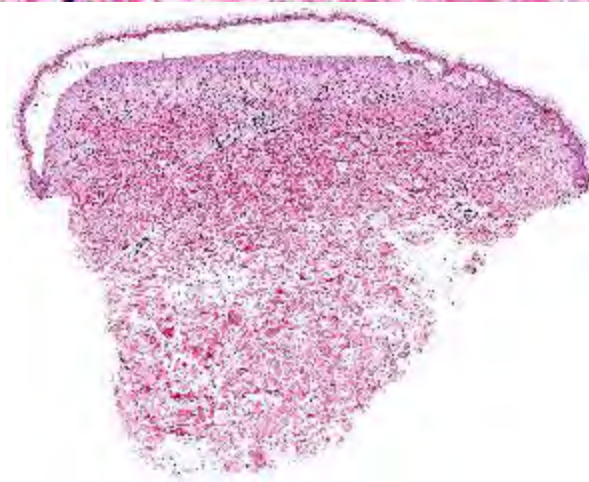
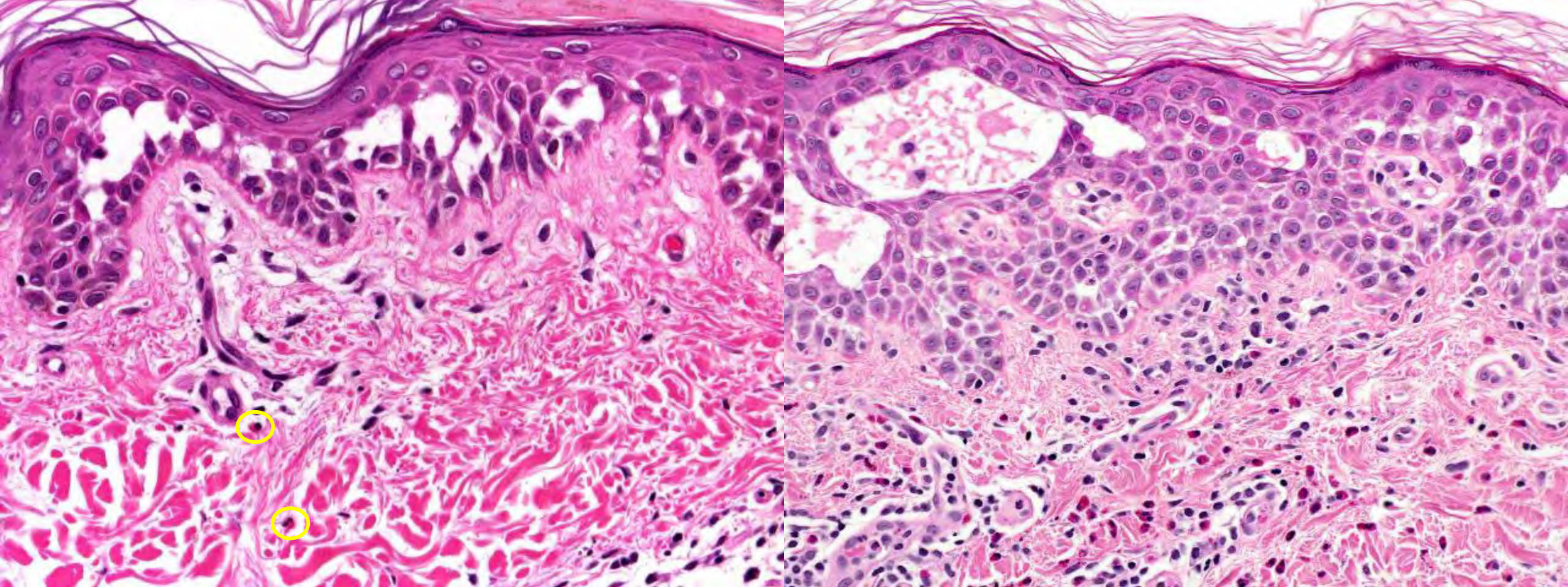
1st presentation



13 years later

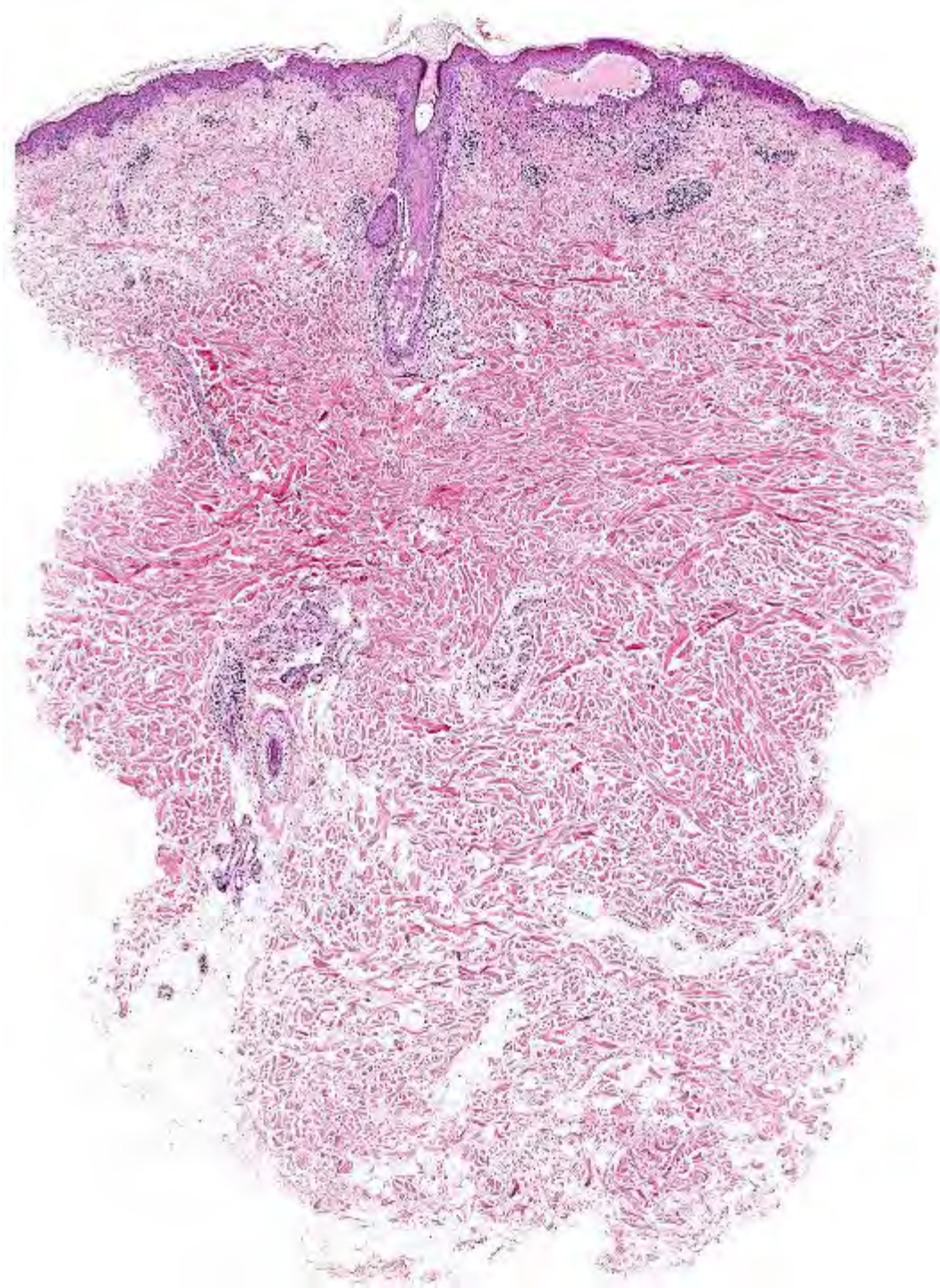


Hailey-Hailey disease



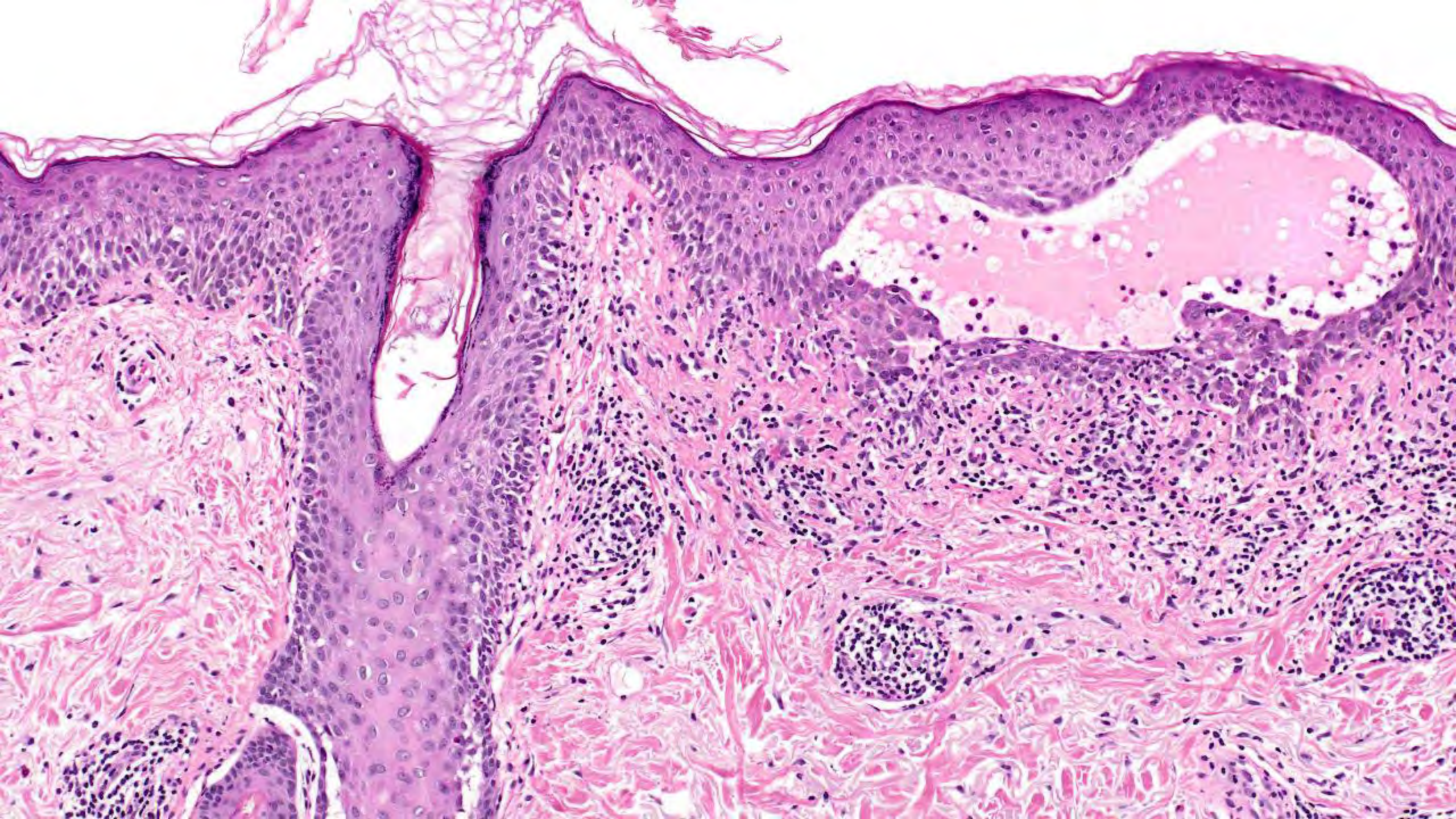
In an acantholytic skin disorder, the presence of eosinophils, even in large numbers, is not a clue to a histopathological diagnosis of pemphigus

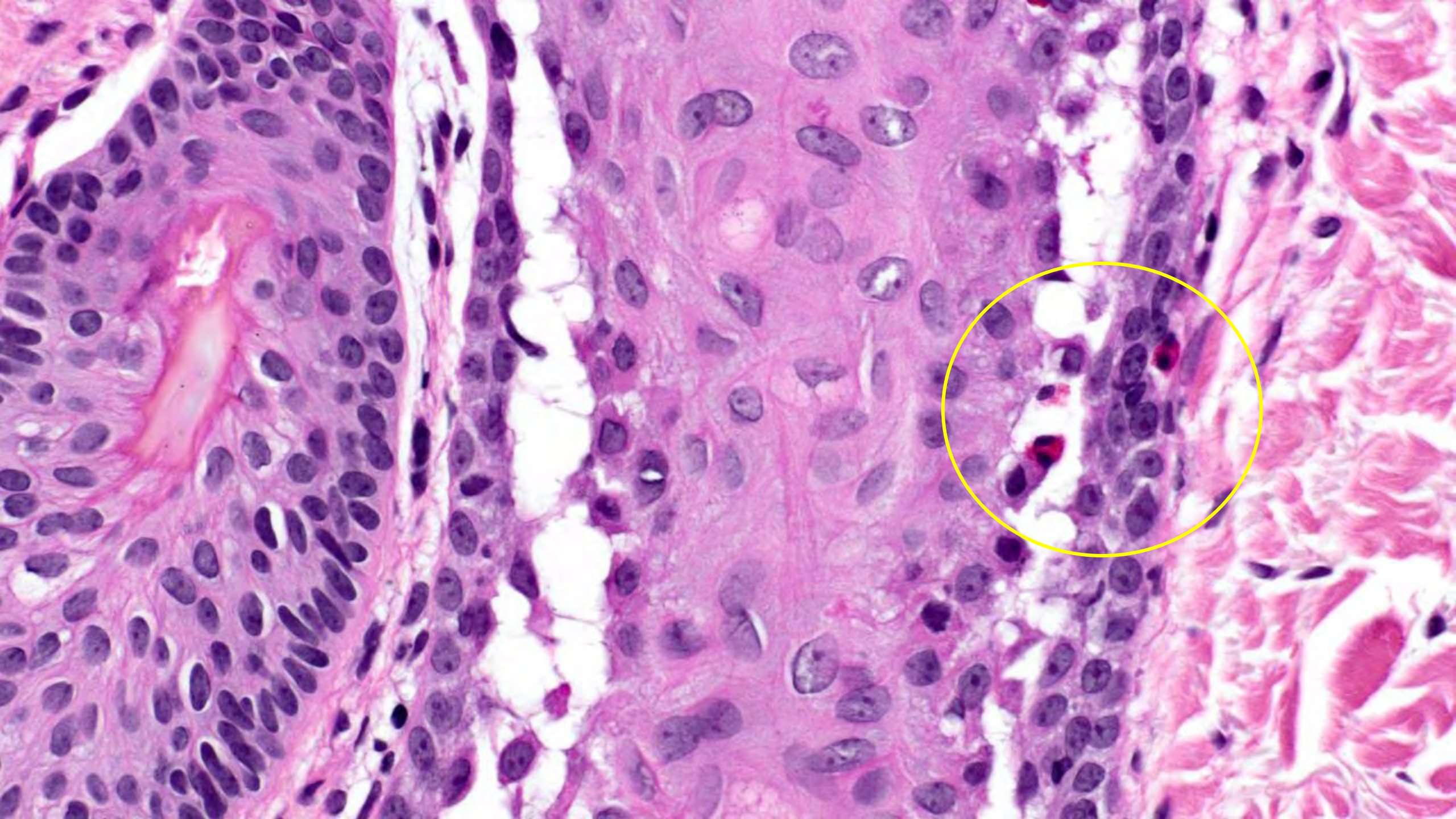
Acantholytic keratinocytes with a reddish or purple cytoplasm are a clue to the histopathological diagnosis of Hailey-Hailey disease

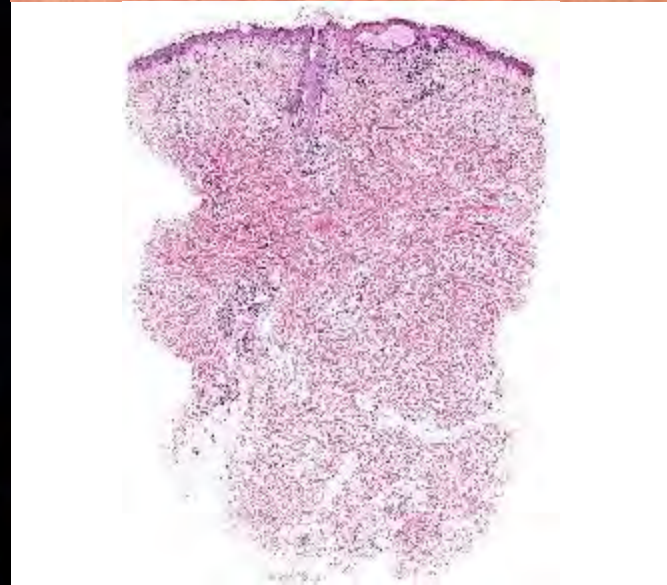


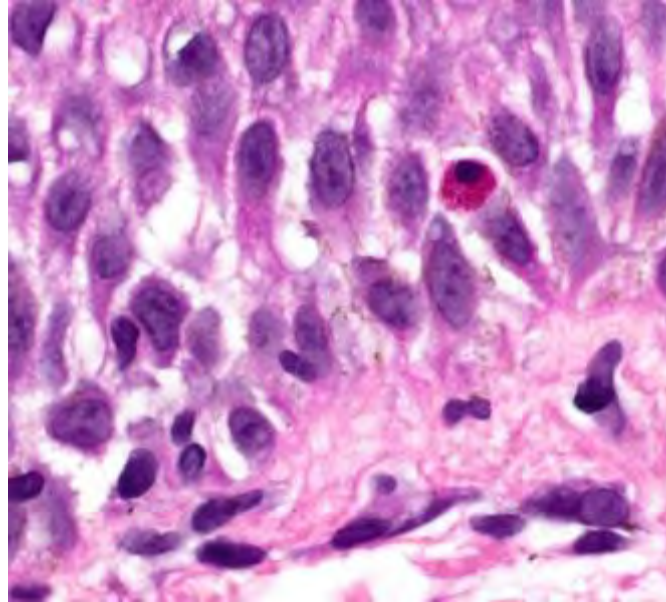
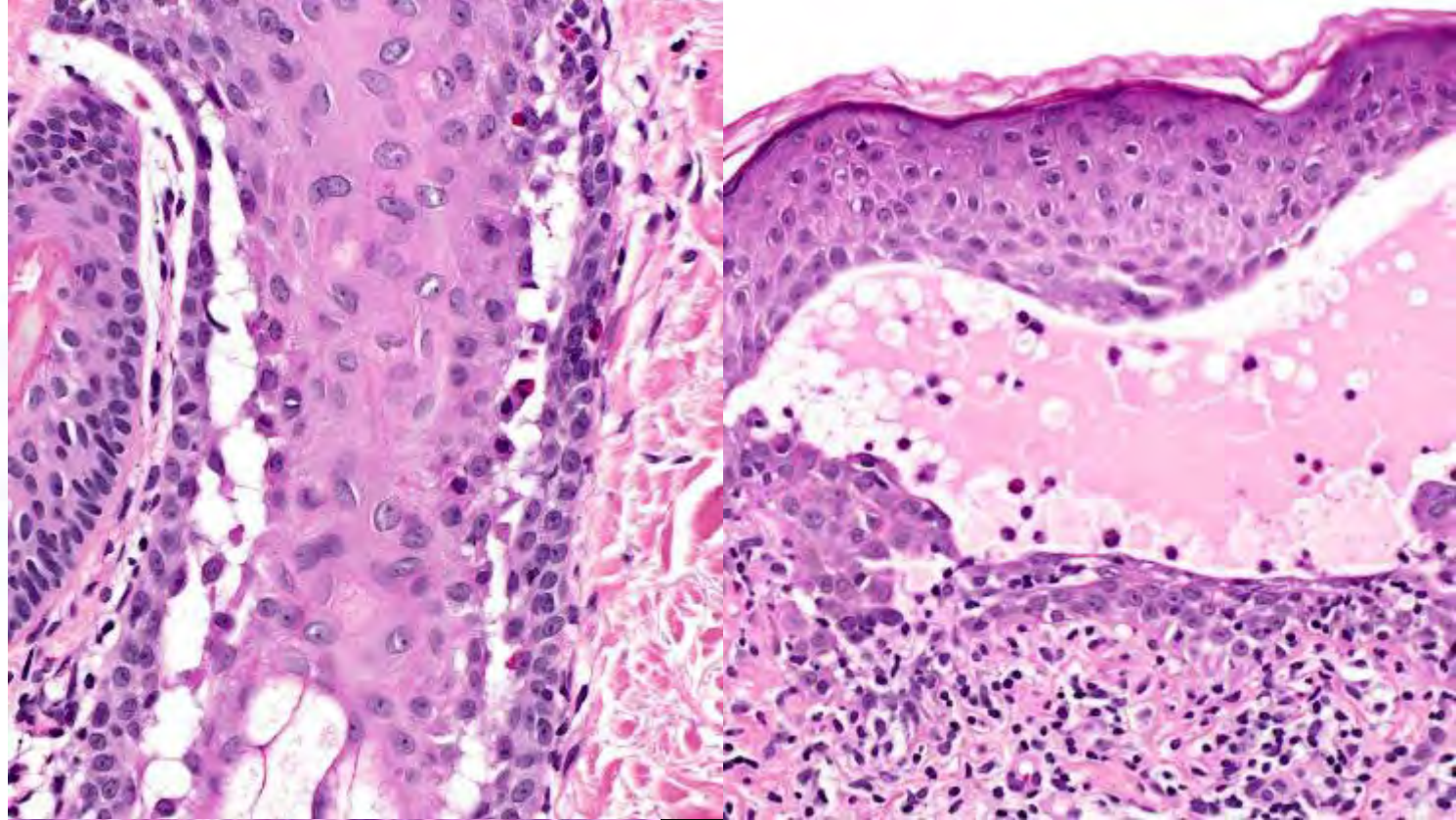
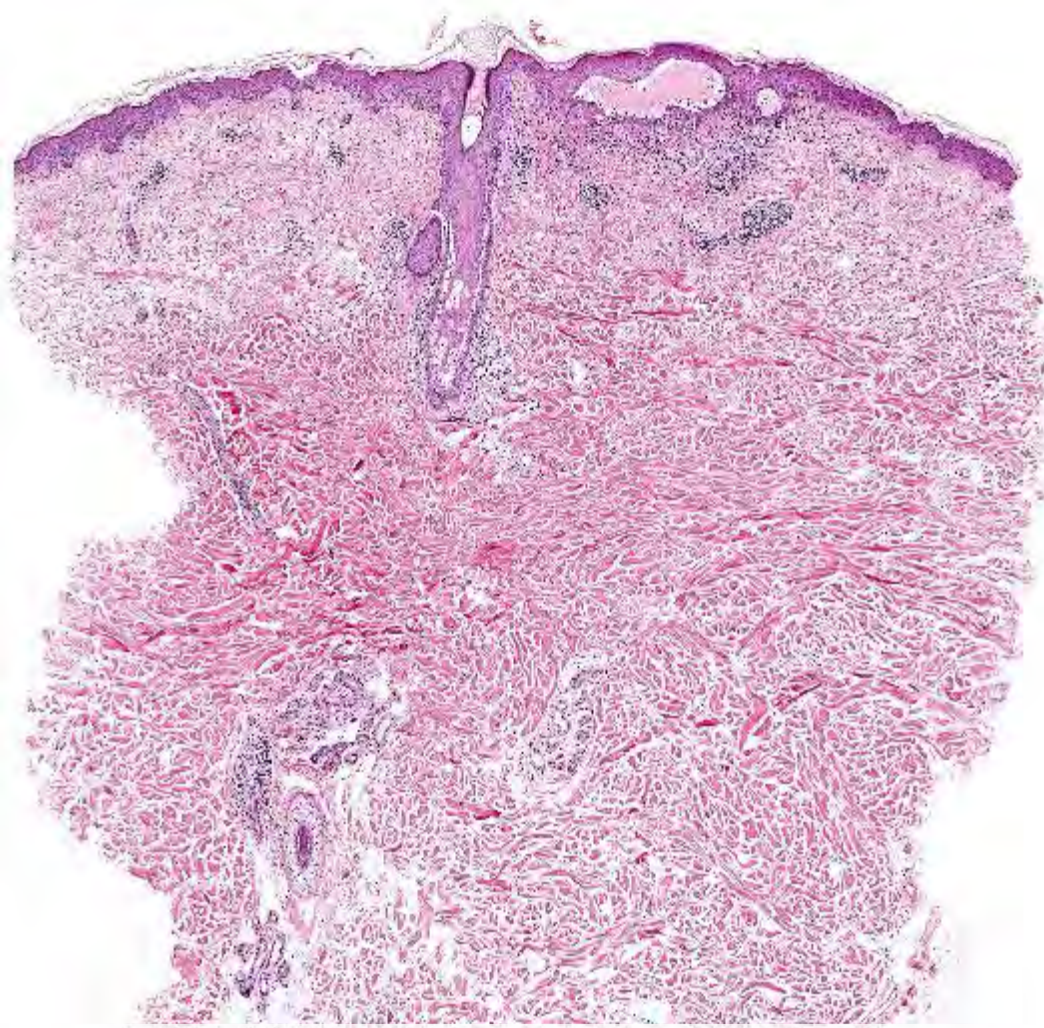
Case 38

F, 57. According to the patient itchy skin lesions for 8 months; in the last days "burning" in the mouth and sore throat.









Pemphigus vulgaris

DIF: Granular intercellular IgG deposition within the mid- and lower epidermal layers; C3 deposition within the lower epidermal layers.

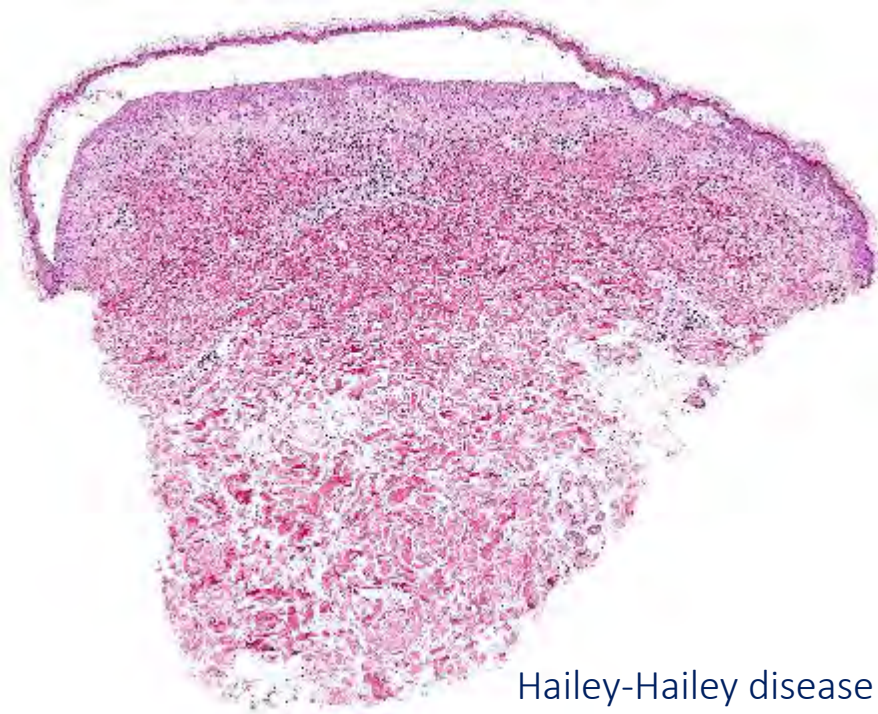
Desmoglein 1: 80+; Desmoglein 3: 228+



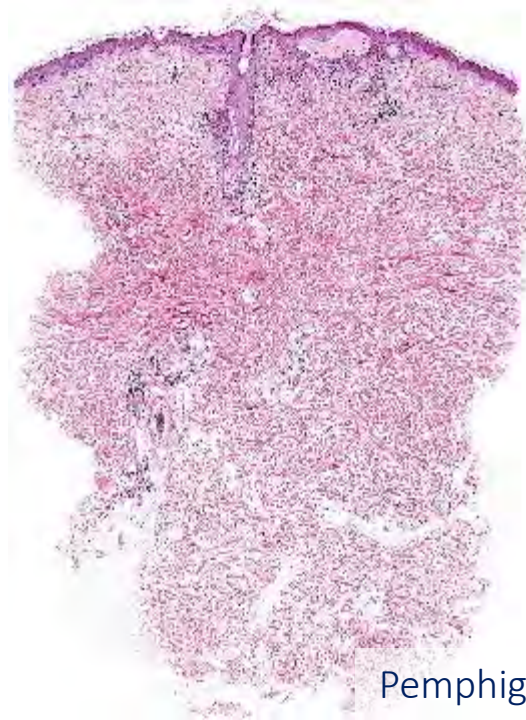
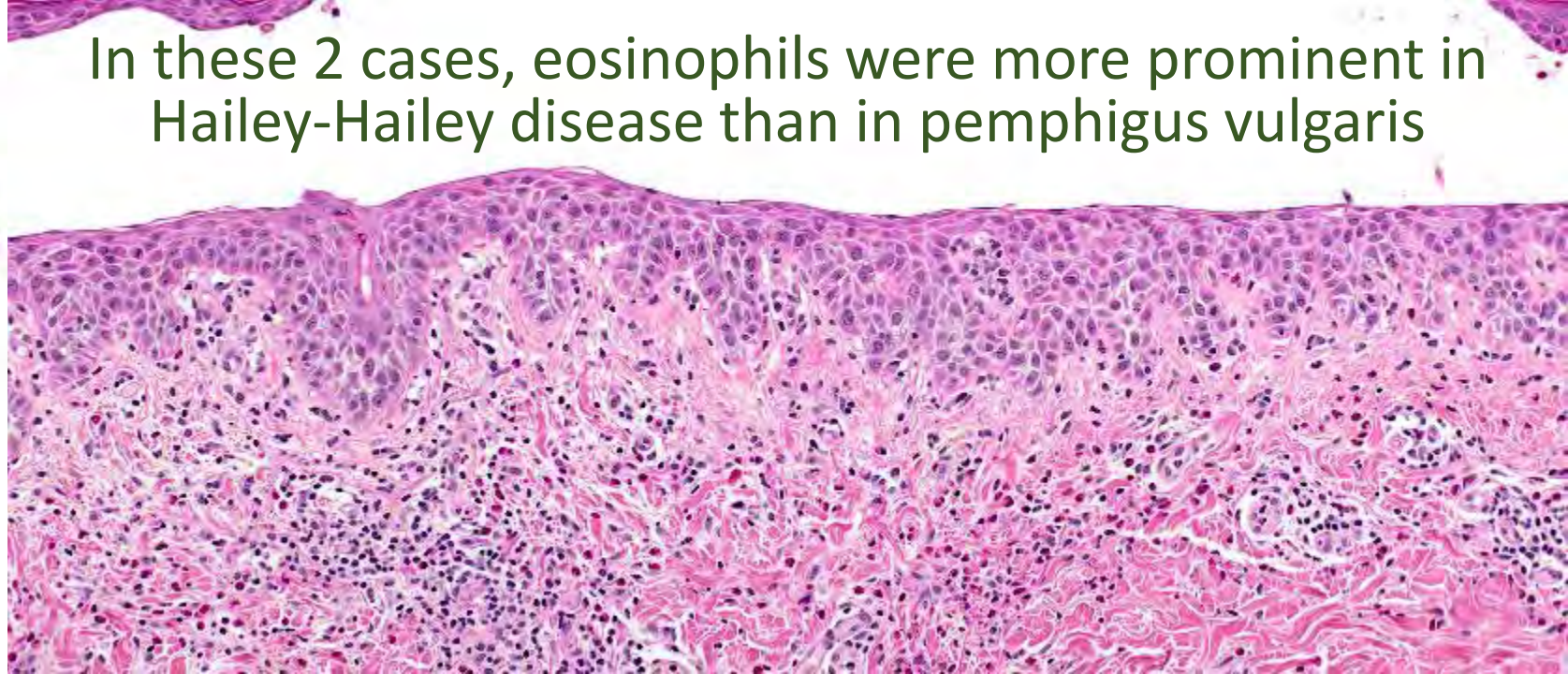
2 weeks later



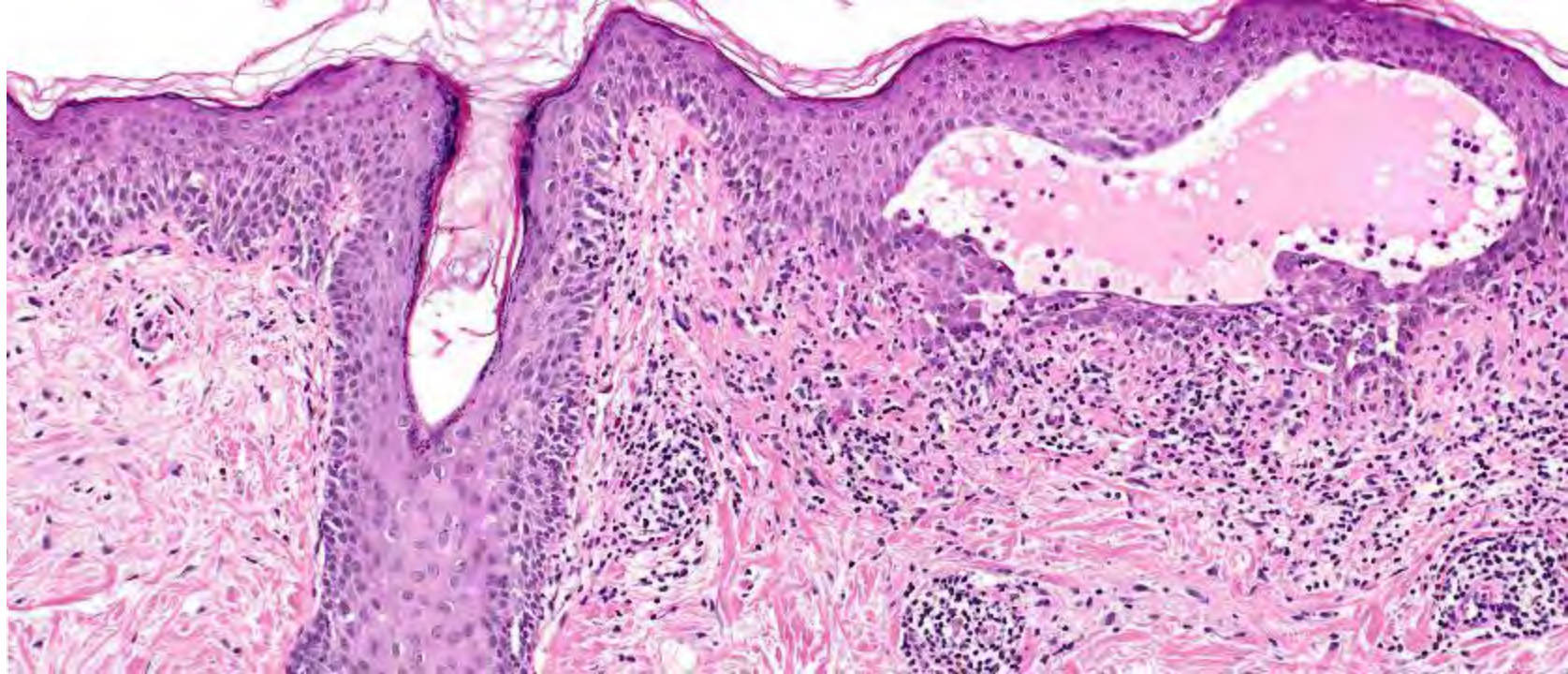
In these 2 cases, eosinophils were more prominent in Hailey-Hailey disease than in pemphigus vulgaris

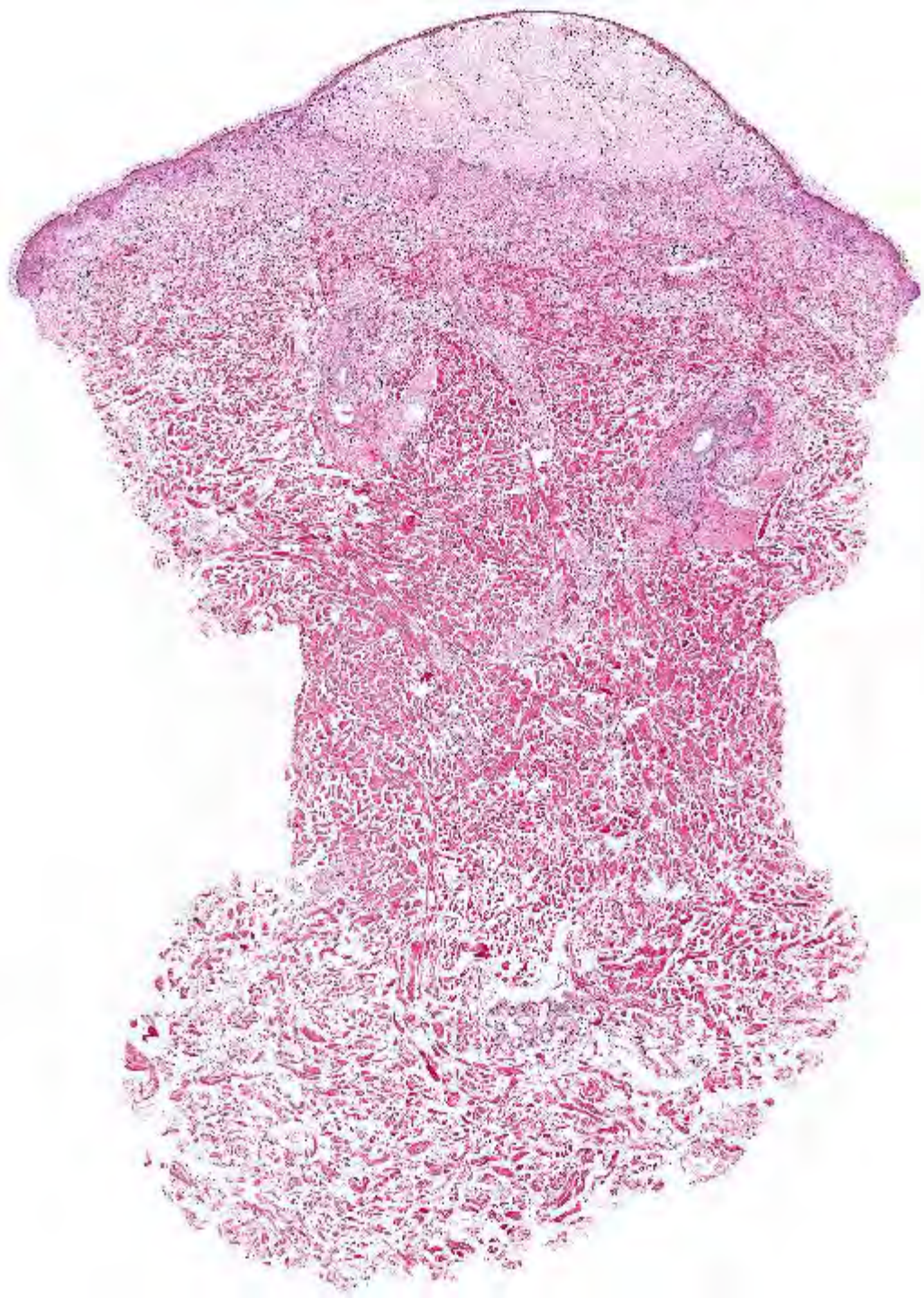


Hailey-Hailey disease



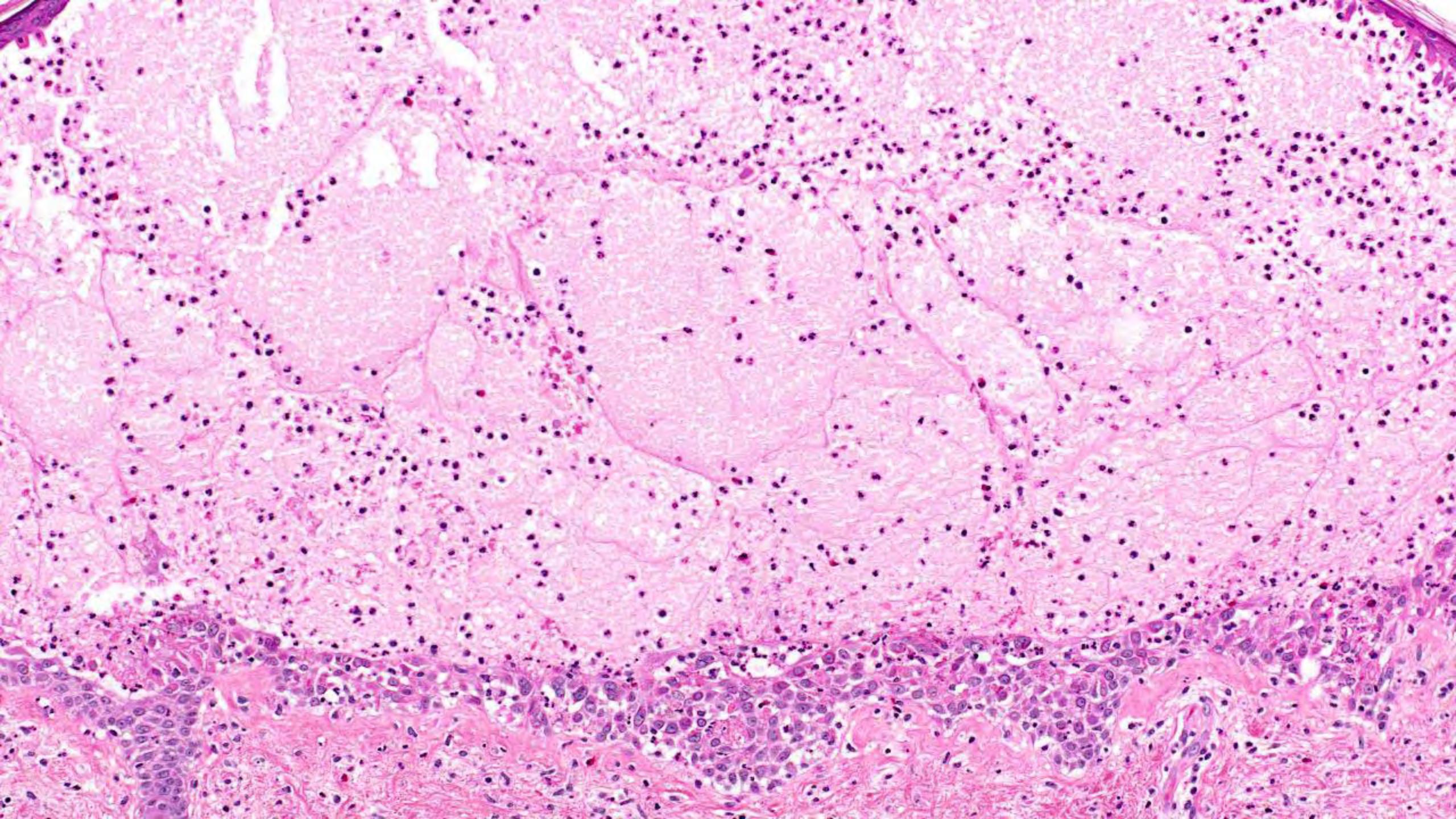
Pemphigus vulgaris

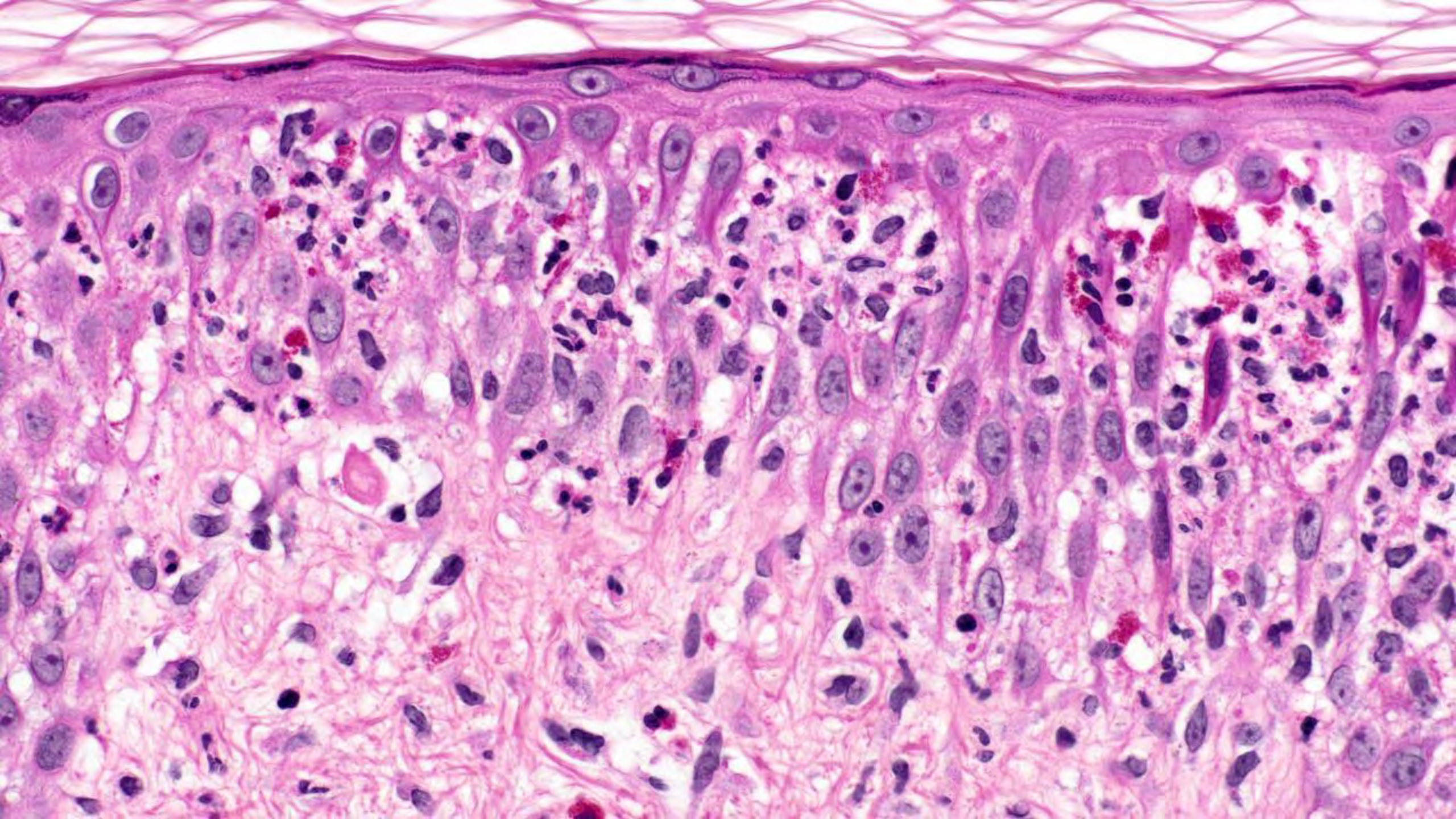




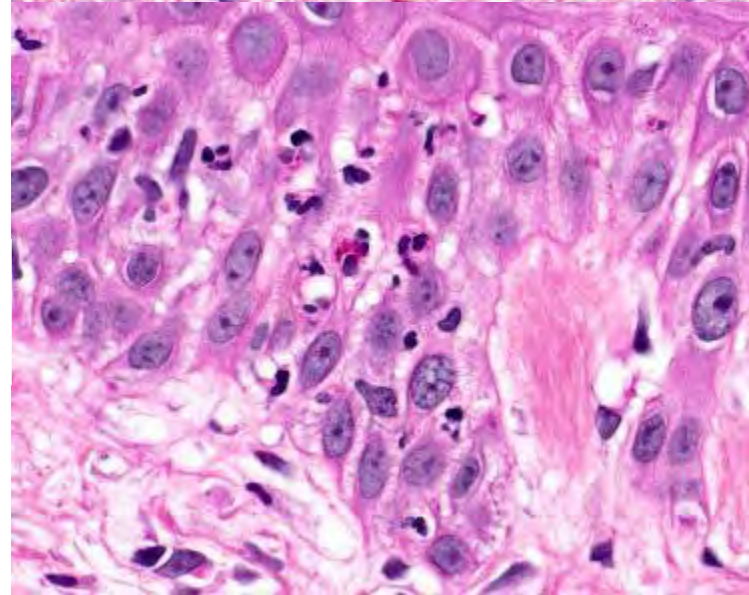
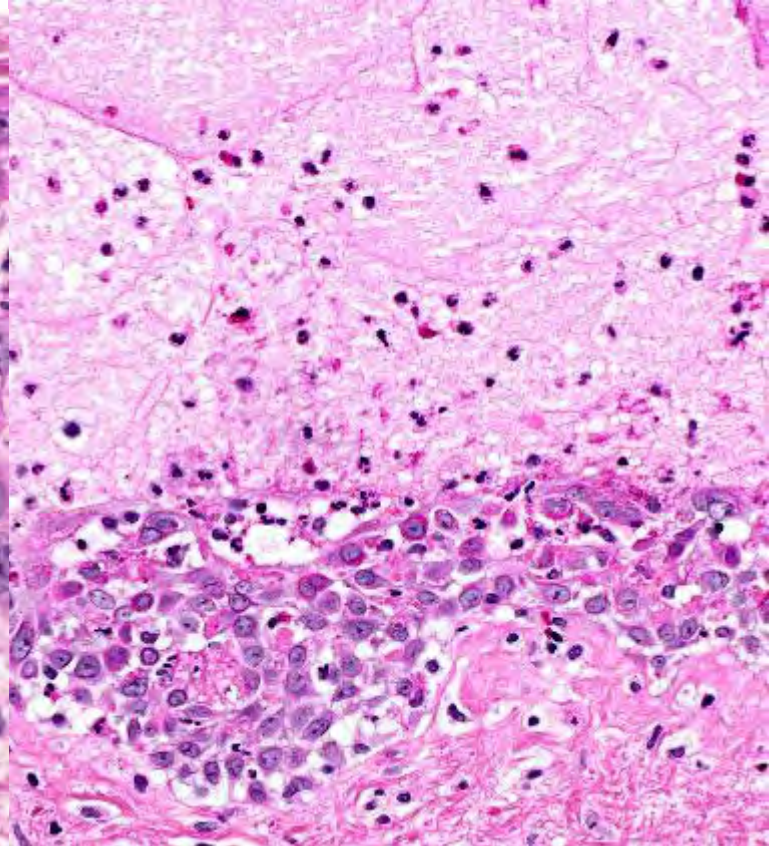
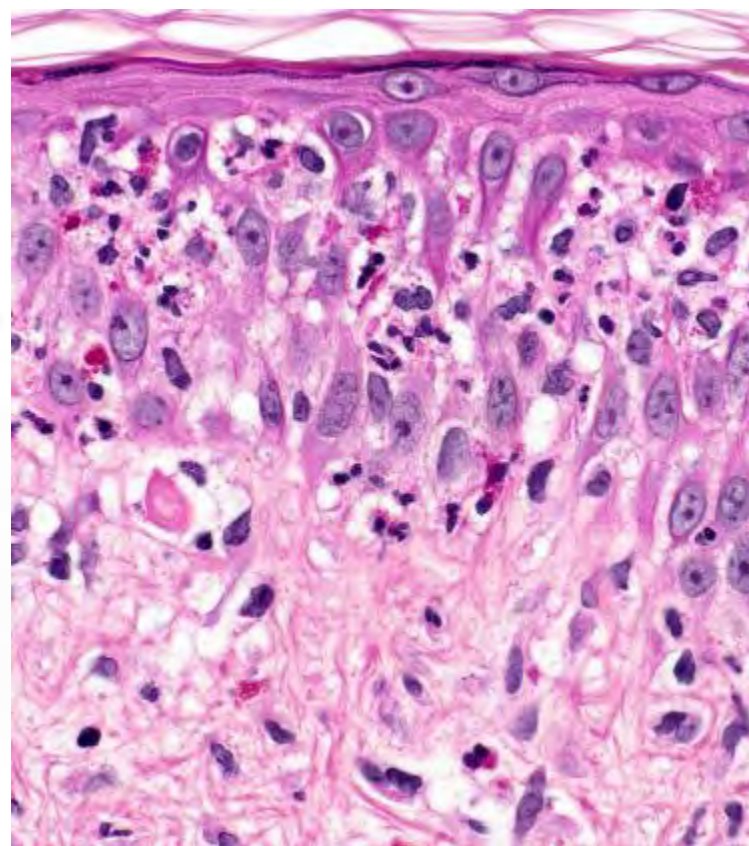
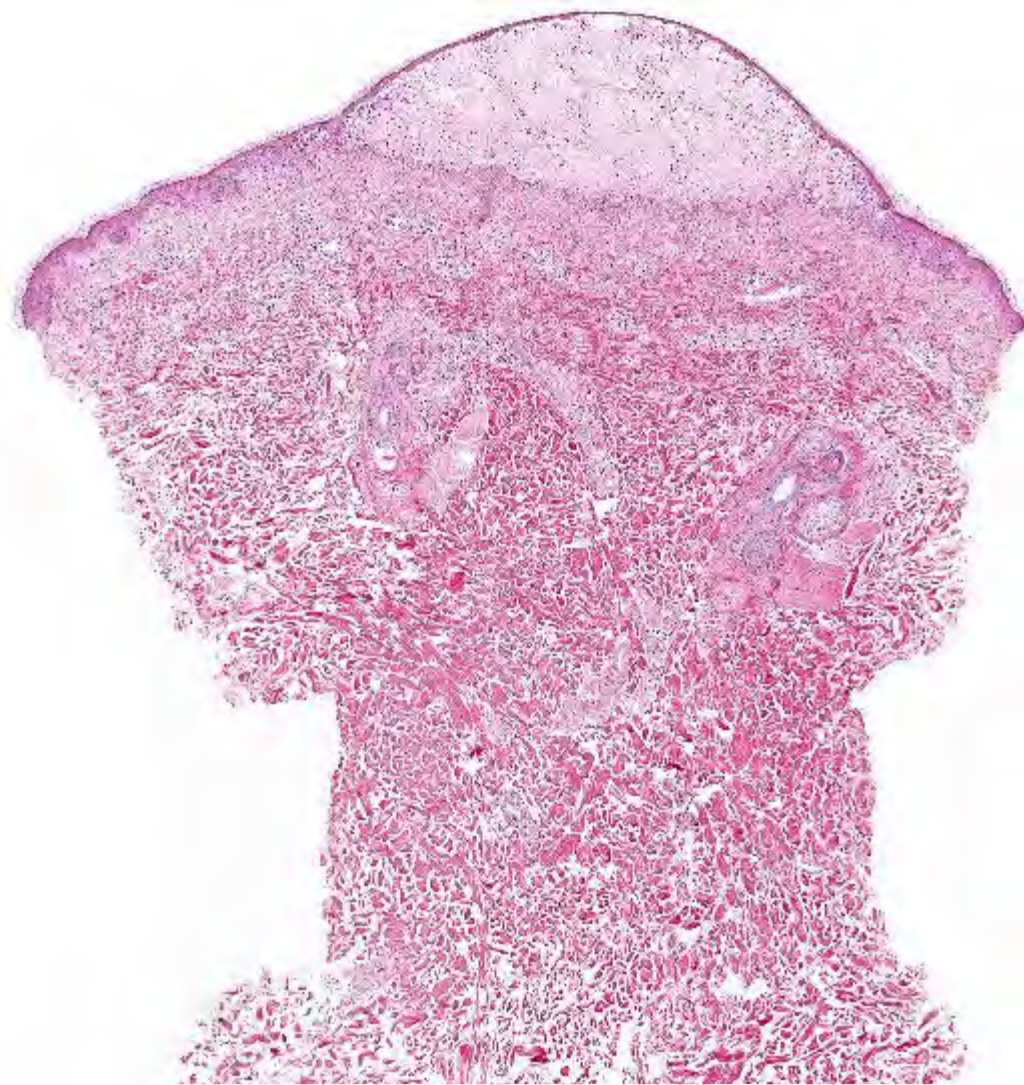
Case 39

M, 75. According to the patient generalized, itchy lesions for 2 months.









Herpetiform pemphigus

*DIF: Intraepidermal intercellular IgG deposition;
C3 weak.*

Desmoglein 1: 136+; Desmoglein 3: 2-

Neutrophilic spongiosis in pemphigus herpetiformis

Pemphigus herpetiformis is a rare pemphigus variant with light microscopic features that have historically been described as either "acantholytic dermatitis herpetiformis" or as "eosinophilic spongiosis in pemphigus". The clinical features of this form of pemphigus are reminiscent of dermatitis herpetiformis; however, the direct immunofluorescence finding of epidermal intercellular IgG deposition is that of the pemphigus group. We report two patients with clinical presentations suggestive of dermatitis herpetiformis in whom the histopathologic features were those of a neutrophilic intraepidermal blistering disorder. Biopsies showed marked epidermal spongiosis with midepidermal acantholytic vesicles containing predominantly neutrophils and a few eosinophils. Direct immunofluorescence was positive for epidermal intercellular IgG; IgA deposition was not present. Neutrophilic spongiosis, in the absence of a prominent eosinophilic infiltrate, should be recognized as an early finding in some cases of pemphigus, and immunofluorescence studies are justified when this histologic feature is encountered in a skin biopsy.

Huhn KM, Tron VA, Nguyen N, Trotter MJ. Neutrophilic spongiosis in pemphigus herpetiformis. *J Cutan Pathol* 1996; 23: 264-269. © Munksgaard 1996.

The term pemphigus herpetiformis (PH) was first coined by Jablonska et al. (1) to describe a condition clinically resembling dermatitis herpetiformis, in which epidermal acantholysis was noted on skin biopsy and cutaneous immunofluorescence findings supported a diagnosis of pemphigus. Many other diagnostic terms had been proposed prior to this including "dermatitis herpetiformis with acantholysis" (2-5), "pemphigus foliaceus presenting as dermatitis herpetiformis" (6), "eosinophilic spongiosis in pemphigus" (7, 8), "pemphigus controlled by sulphapyridine" (9), and "mixed bullous disease" (10). The application of immunofluorescence methods with the finding of positive intercellular IgG on direct immunofluorescence (DIF) helped define this disease entity; two series of pemphigus herpetiformis have been published (11, 12) and there are numerous case reports, especially in the German literature (13-22).

PH is one of the less common forms of the IgG class of pemphigus, accounting for 7.3% of cases (11). While the early clinical findings are sugges-

tive of dermatitis herpetiformis, the histopathologic appearance is variable and includes epidermal acantholysis, eosinophilic spongiosis, and blisters containing predominantly eosinophils and acantholytic cells. Less commonly mentioned is the presence of neutrophils within the epidermis. This finding has not been included in the diagnostic criteria outlined by Ingher and Feuerstein (12). In this paper we report two cases of PH in which neutrophilic spongiosis was a prominent histologic feature.

Case reports

Case 1

A 14-year-old Caucasian female presented with a widespread pruritic skin eruption which began on her legs and later expanded to involve her abdomen, back, wrists and forearms. The eruption did not respond to a course of oral penicillin; it temporarily subsided with topical corticosteroid applications. There were no accompanying consti-

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Nhien Nguyen² and
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Accepted: November 18, 1996

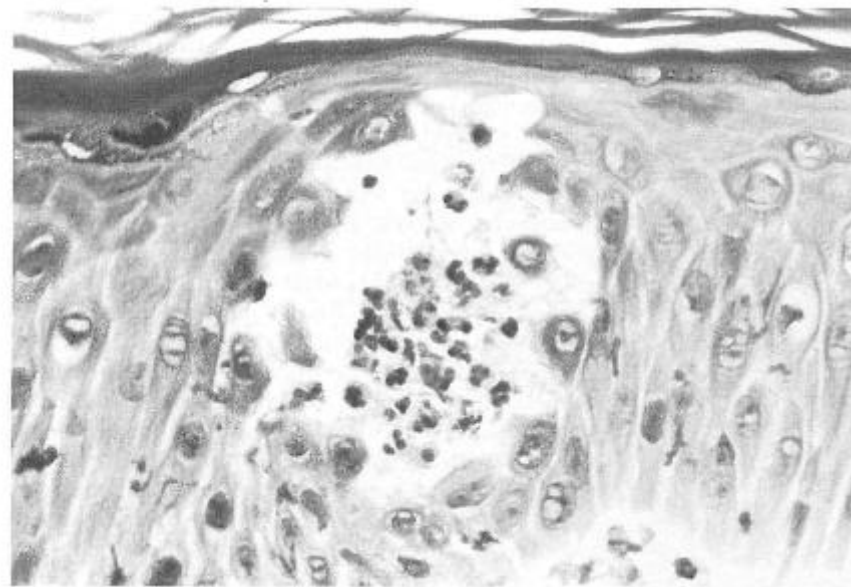


Fig. 4. Skin biopsy of a small vesicular lesion from patient 2 showed intraepidermal vesicles containing neutrophils (H&E, $\times 312$).

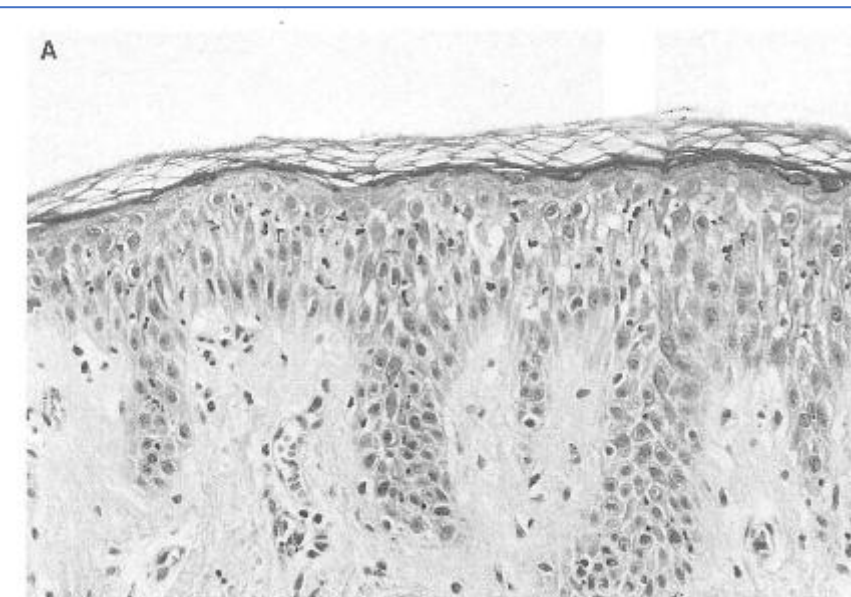


Fig. 2. Initial biopsy from patient 1 showed spongiosis with some intraepidermal neutrophils and eosinophils (A, H&E, $\times 125$). A later biopsy showed a mid-epidermal vesicle with acantholysis and numerous neutrophils both within the epidermis and the blister cavity (B, H&E, $\times 125$, inset $\times 250$).

Pemphigus herpetiformis: From first description until now

Michael Kasperkiewicz, MD,* Cezary Kowalewski, MD, PhD,¹ and Stefania Jabłońska, MD, PhD¹
 Lübeck, Germany, and Warsaw, Poland

Pemphigus herpetiformis is one of the less common forms of pemphigus, first introduced by Jabłońska and colleagues in 1975. This autoimmune bullous disease combines the clinical features of dermatitis herpetiformis and the immunologic characteristics of pemphigus. The target autoantigen is usually desmoglein 1 (or less frequently desmoglein 3), although recently it has become increasingly obvious that patients with pemphigus herpetiformis also demonstrate autoantibodies against desmocollin. Here, we summarize reported cases of pemphigus herpetiformis and describe current knowledge considering epidemiology, clinical manifestations, histologic findings, immunopathology, pathophysiologic concepts, associated diseases, and treatment of this rare disorder (*J Am Acad Dermatol* 2014;70:780-7).

Key words: autoantibody; autoantigen; autoimmunity; bullous disease; desmoglein; pemphigus.

Pemphigus diseases are potentially life-threatening autoimmune bullous disorders affecting the skin and mucosa and characterized by intraepithelial blisters because of autoantibody-induced disruption of the components of the cell-cell anchoring complex, the desmosomes. Pemphigus is divided into 2 major types: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is characterized by a predominance of mucosal lesions, a split formation in the basal layer of the epithelium, and autoantibodies against desmoglein (Dsg) 3 and 1. PF is typically characterized by skin lesions without mucous membrane involvement, a split formation in the upper epidermis, and autoantibodies against Dsg1. Their incidence has been reported as 0.6 to 6.8 new cases per 1 million inhabitants annually in central Europe.^{1,2}

In addition to classic pemphigus, some rare forms are recognized: pemphigus herpetiformis (PH), pemphigus vegetans, pemphigus seborrheicus, fogo selvagem, pemphigus erythematous (Senear-Usher syndrome), paraneoplastic pemphigus, IgA pemphigus, and IgA/IgG pemphigus.³ In this review, we give an up-to-date overview on PH, a disease entity that was originally

Abbreviations used:
 Dsc: desmocollin
 Dsg: desmoglein
 PF: pemphigus foliaceus
 PH: pemphigus herpetiformis
 PV: pemphigus vulgaris

named by our coauthor Professor Stefania Jabłońska and colleagues.³

EPIDEMIOLOGY

The diagnostic criteria of PH were first established by Jabłońska et al in 1975,³ although similar clinical phenotypes were reported as early as 1955 by Roden and Gentile⁴ under the name "dermatitis herpetiformis with acantholysis." Since then roughly 100 additional patients have been reported in the literature. Its incidence among patients with pemphigus has been reported to be 6% to 7.3%.^{2,5} Based on the cases published so far, the age range of onset varies from 5 to 92 years,^{3,10} although only 4 pediatric patients have been reported.^{3,11-13} There is no clear male or female predilection. PH has been reported from different countries including the

Table 1. Differential diagnosis of pemphigus herpetiformis and their diagnostic characteristics

Diagnosis	Clinical presentation	Histopathology	DIF	IF	Autoantigen
Dermatitis herpetiformis	Pruritic, excoriated papulovesicles often in a grouped pattern	Subepidermal blister, dermal papillary abscesses with neutrophils	Granular IgA and C3 in tips of dermal papillae or BMS	IgA against endomysium	Epidermal transglutaminases
Pemphigus foliaceus	Fragile blisters and pustulobasilar-like scale, typically no mucous membrane involvement	Subcorneal acantholysis	IgG and C3 ICS	IgG ICS	Dsg 1
Pemphigus vulgaris	Mucous membrane erosions, fragile blisters, erosions, and crusts	Suprabasal acantholysis	IgG and C3 ICS	IgG ICS	Dsg3, Dsg1
IgA pemphigus	Fragile blisters and pustules, annular plaques with collarette-like scaling	Intraepidermal neutrophilic dermatosis type: intraepidermal neutrophilic infiltrate, often without acantholysis Subcorneal pustular dermatosis type: subcorneal neutrophilic infiltrate, often without acantholysis	IgA and C3 ICS	IgA ICS	Intraepidermal neutrophilic dermatosis type: unknown, possibly nondesmosomal cell surface protein Subcorneal pustular dermatosis type: Dsc 1
Bullous pemphigoid	Pruritic, tense blisters; erosions and crusts; urticarial, prurigo-like, or eczematous plaques	Subepidermal blister, dermal, predominantly eosinophilic infiltrate	C3 and IgG BMS	IgG BMS, epidermal IgG BMS (human salt-split skin)	BP180, BP230
Linear IgA dermatosis	Vesicle-bullous and/or formations, typically in a "cluster of jewels" configuration	Subepidermal blister, dermal, predominantly neutrophilic infiltrate	IgA and C3 BMS	IgA BMS, epidermal and/or dermal IgA BMS (human salt-split skin)	LAD-1, BP180

BMS, basal membrane zone staining; BP, bullous pemphigoid; DIF, direct immunofluorescence microscopy; Dsc, desmocollin; Dsg, desmoglein; ICS, intracellular staining; IF, indirect immunofluorescence microscopy; LAD-1, linear IgA dermatosis.

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Conflicts of interest: None declared.

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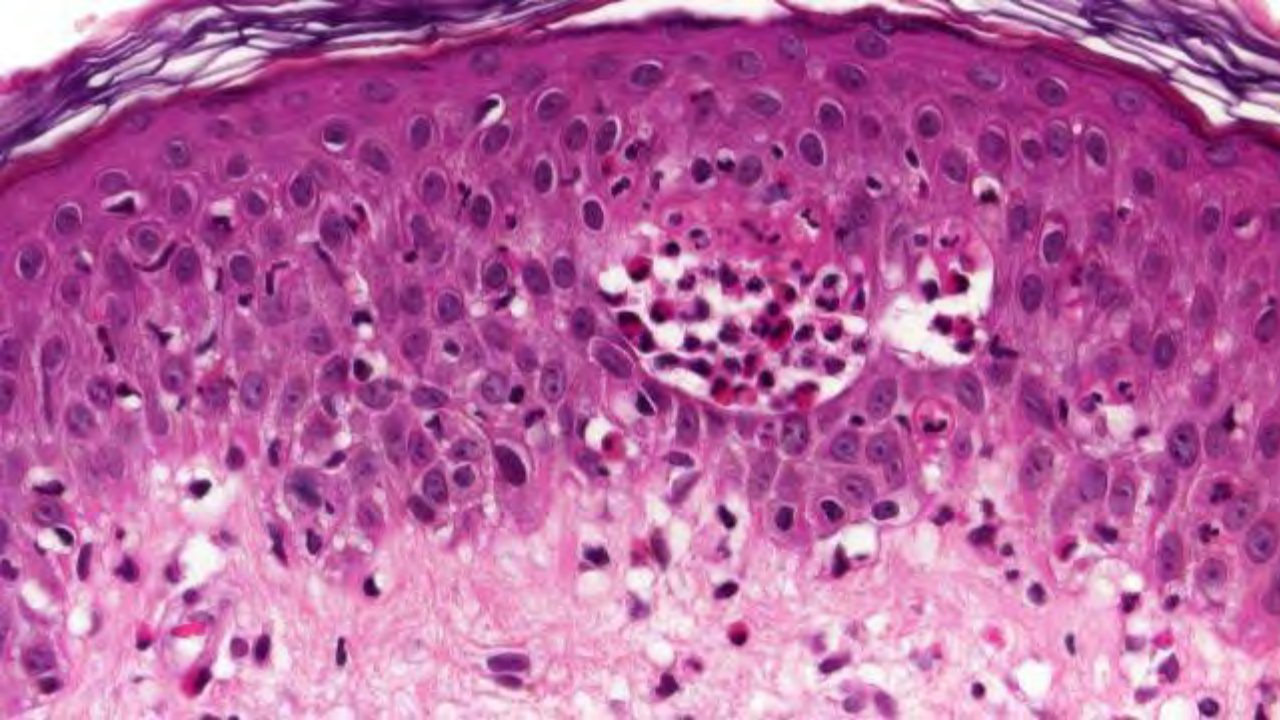
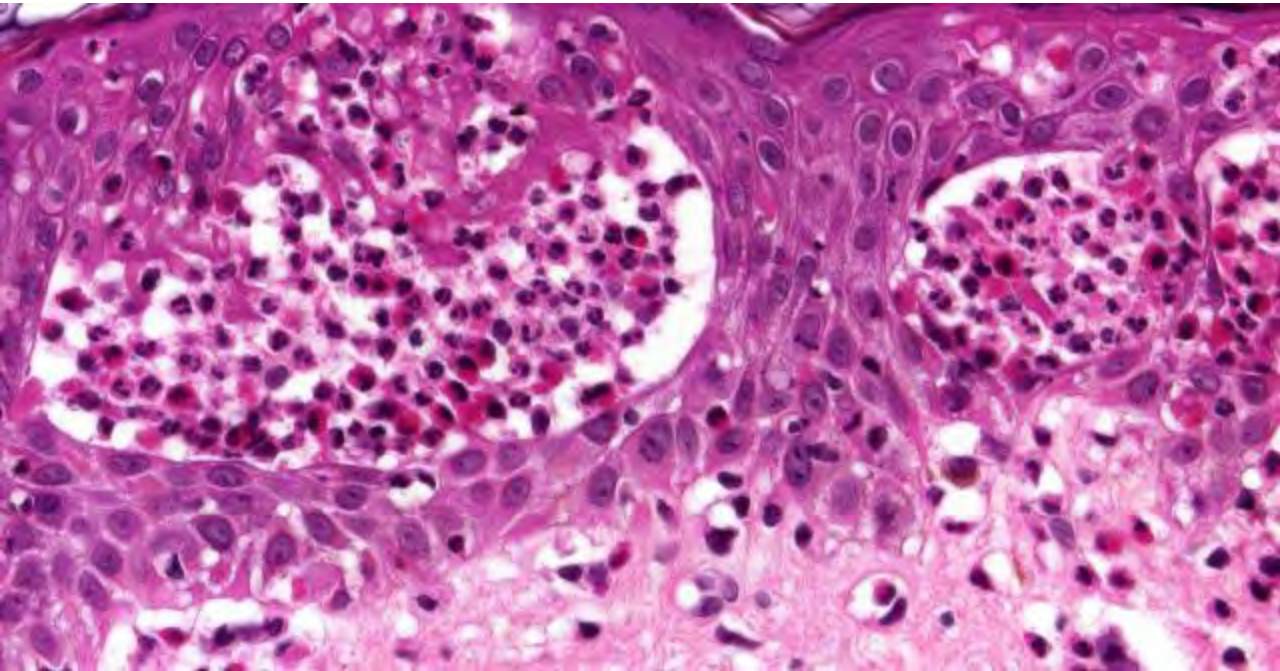
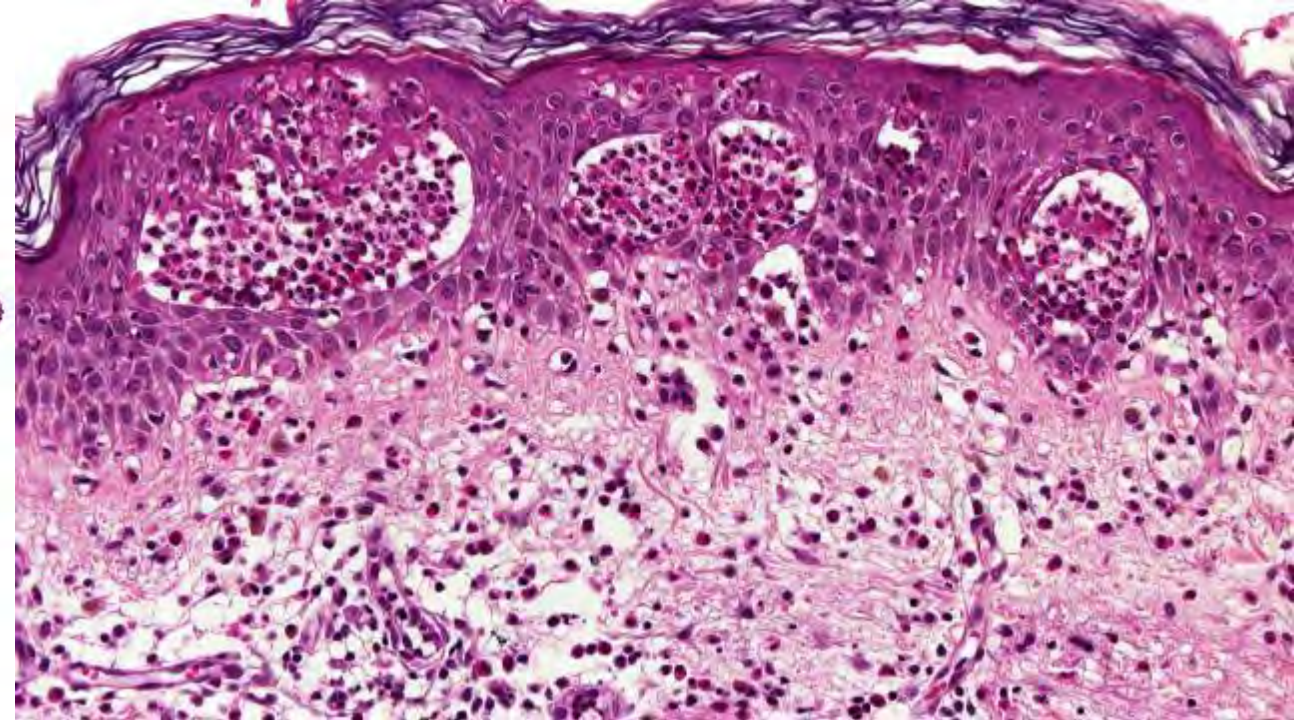
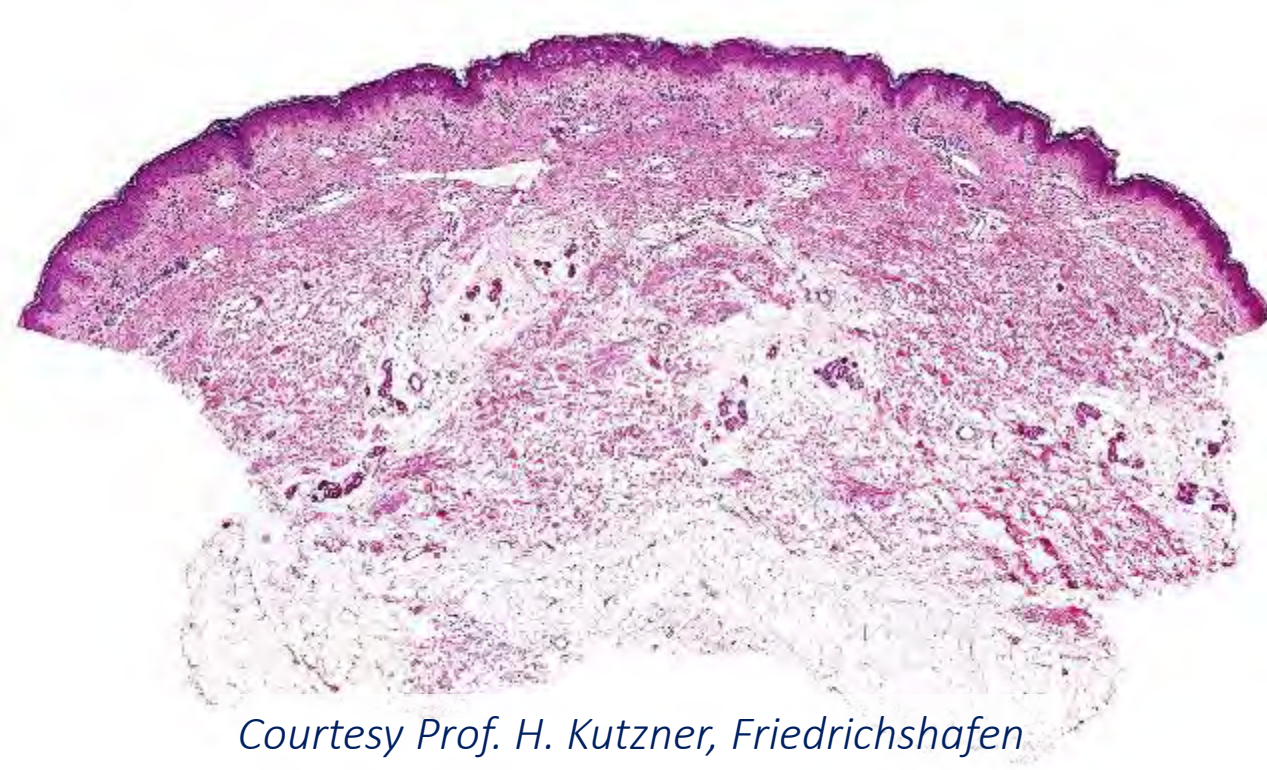
160, 23538 Lübeck, Germany. E-mail: Michael.Kasperkiewicz@uk-luebeck.de.

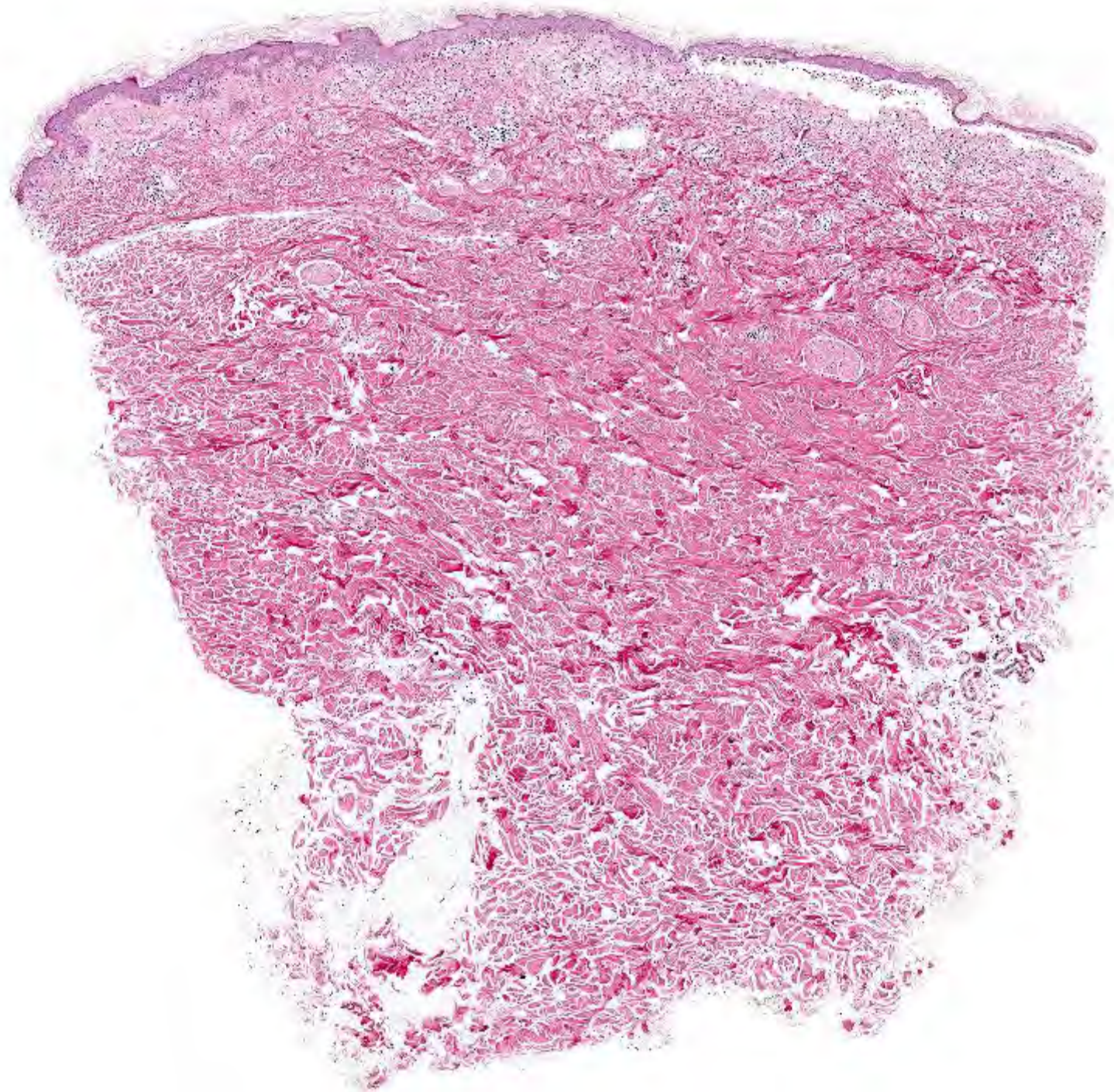
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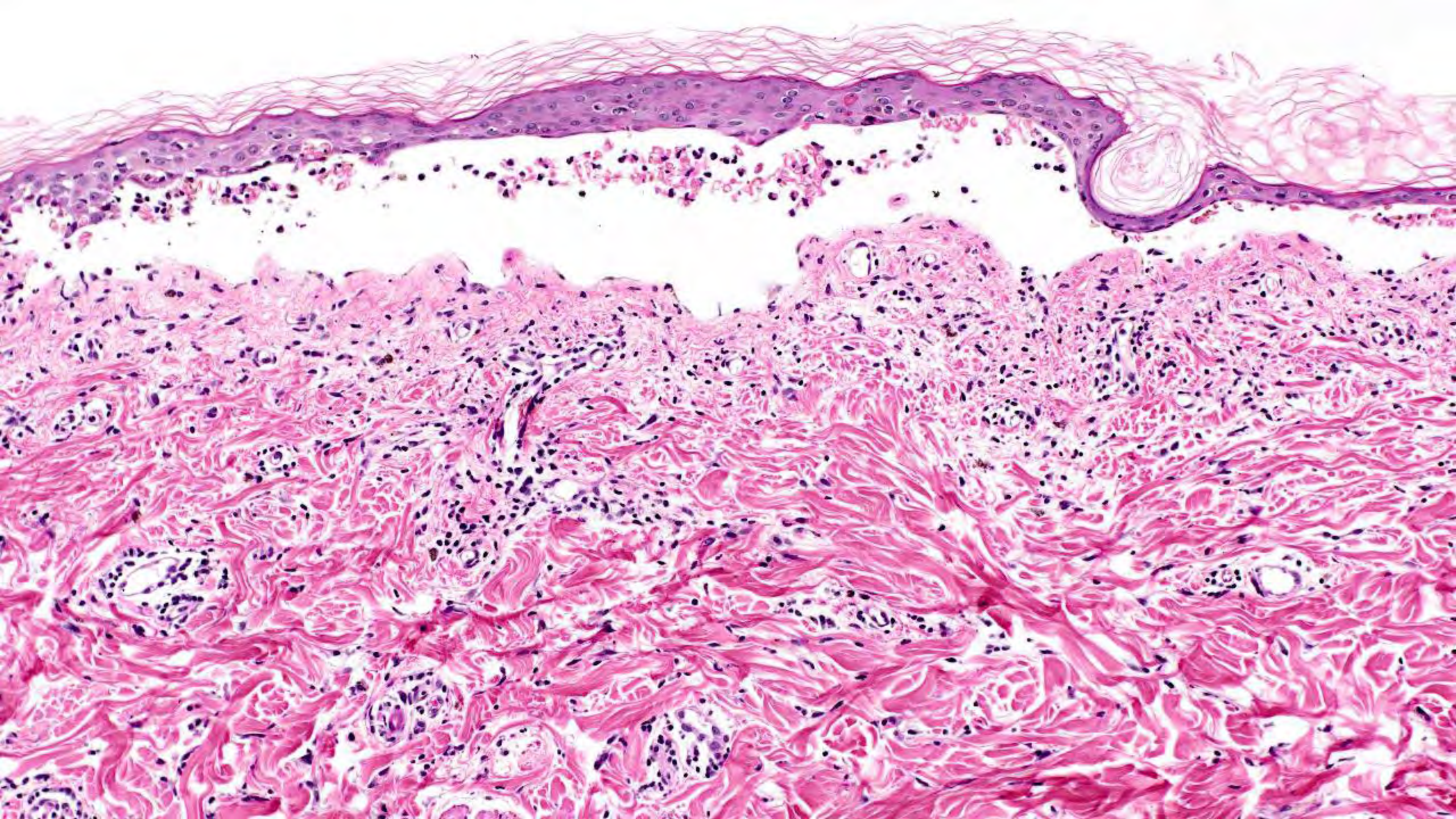
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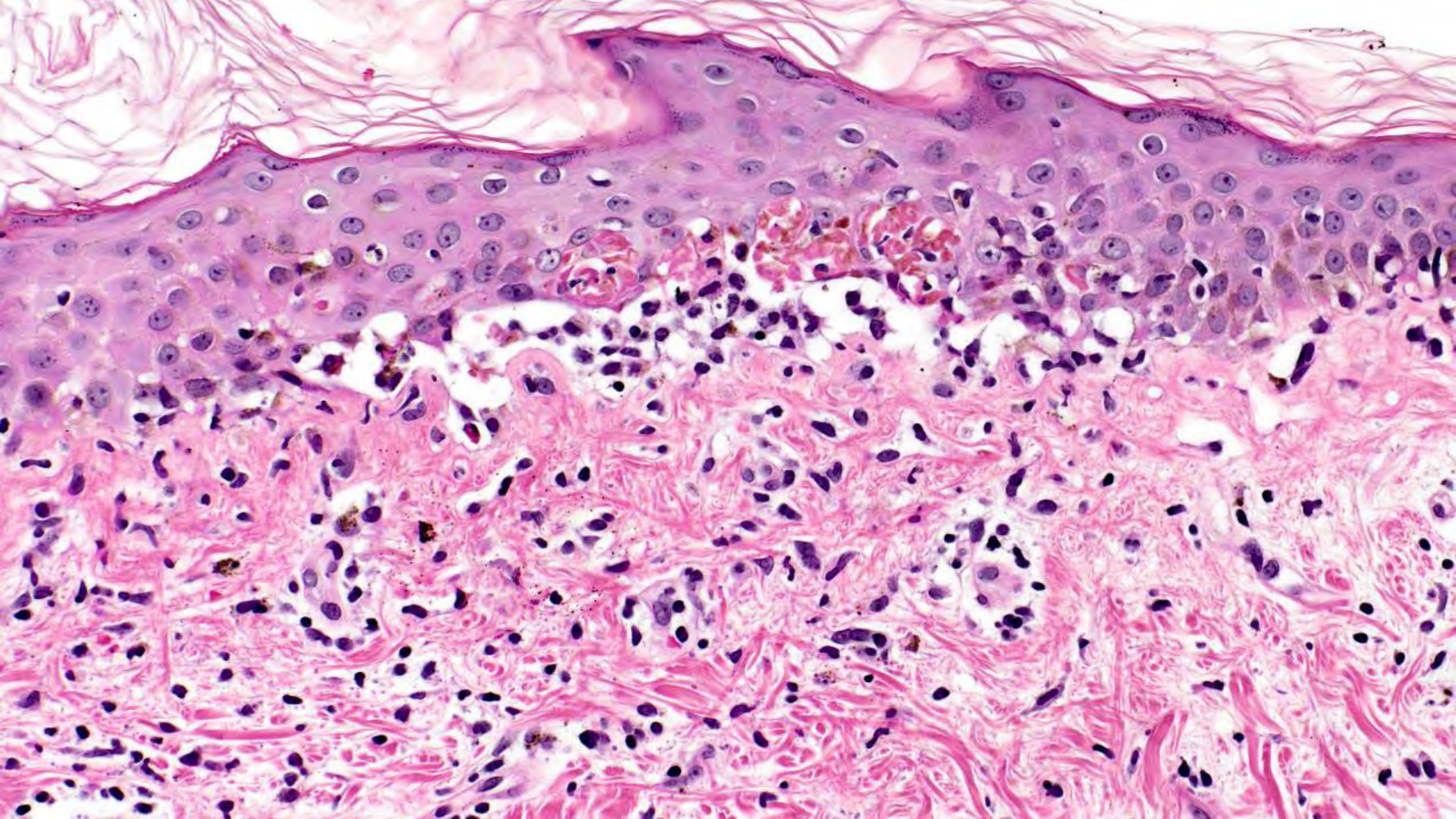


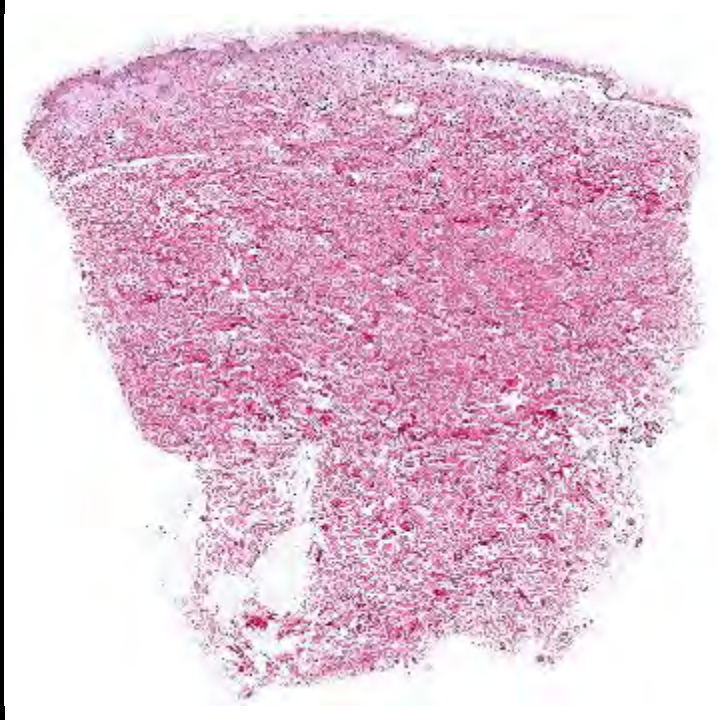


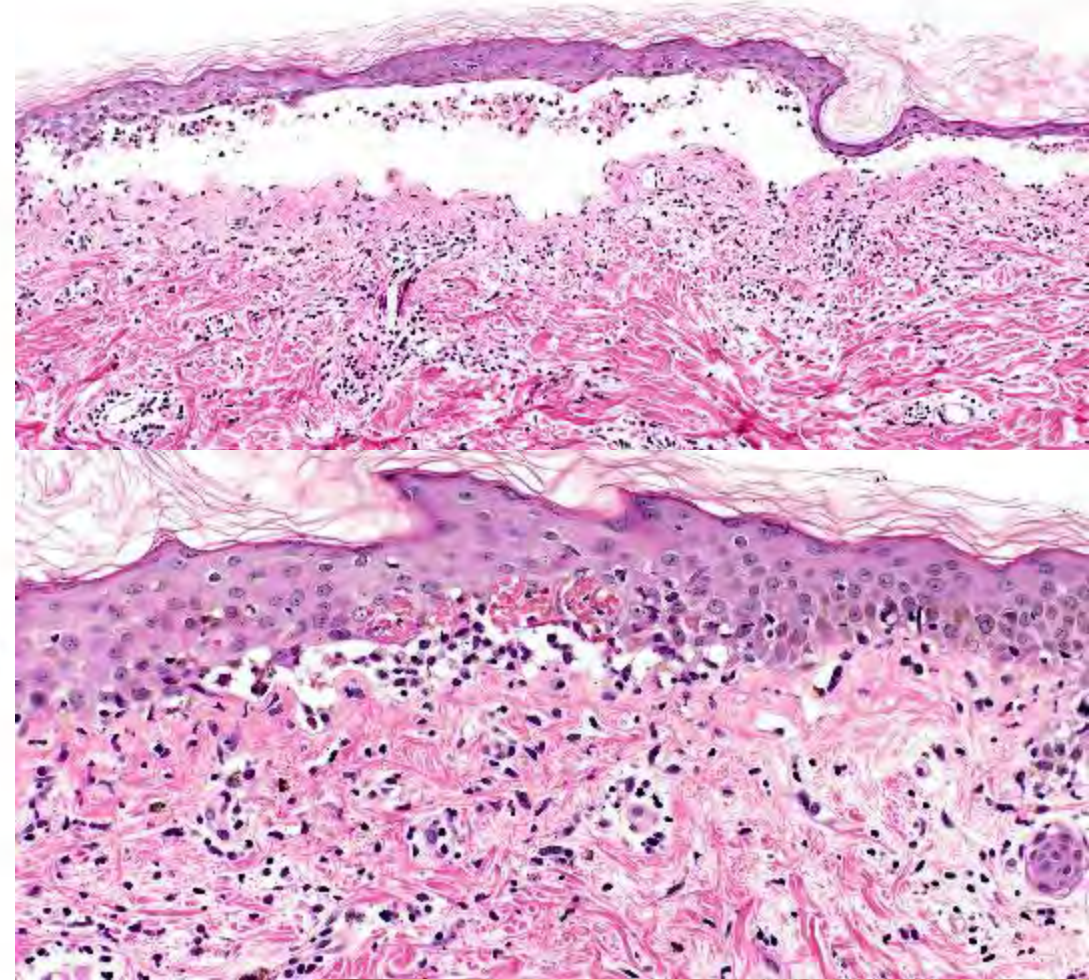
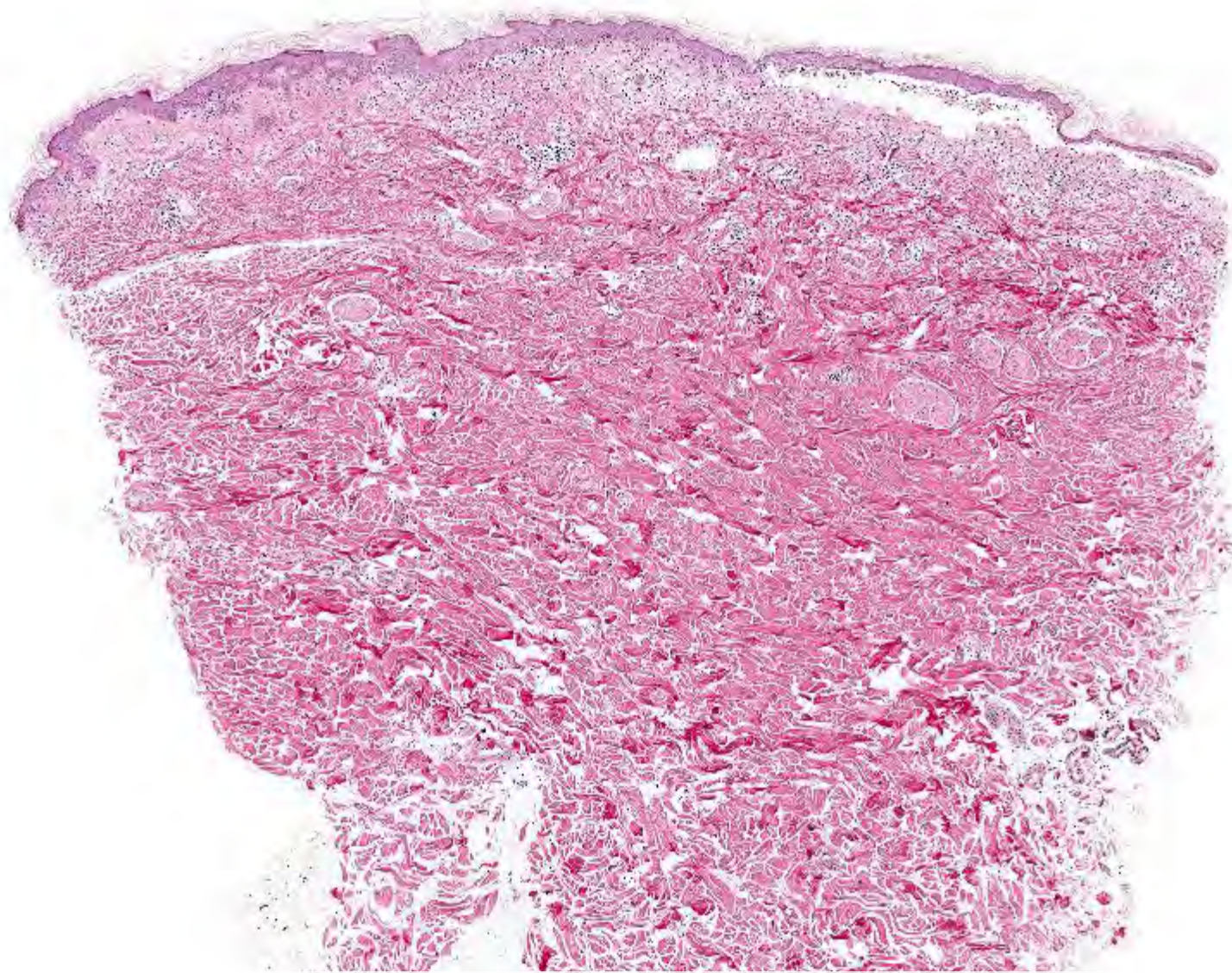
Case 40

F, 45. History of metastatic breast carcinoma (at present managed with datopotamab deruxtecan; last treatment 14 days before presentation). Some erosions on the mouth after each treatment, now partly bullous, generalized skin lesions.





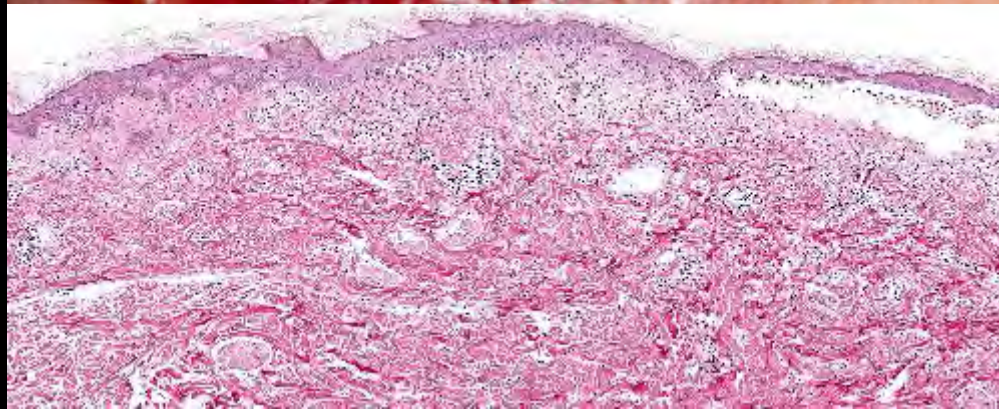




My histological diagnosis:

Stevens-Johnson syndrome





Metastatic breast carcinoma.

Stomatitis is a common side-effect of datopotamab deruxtecan treatment.

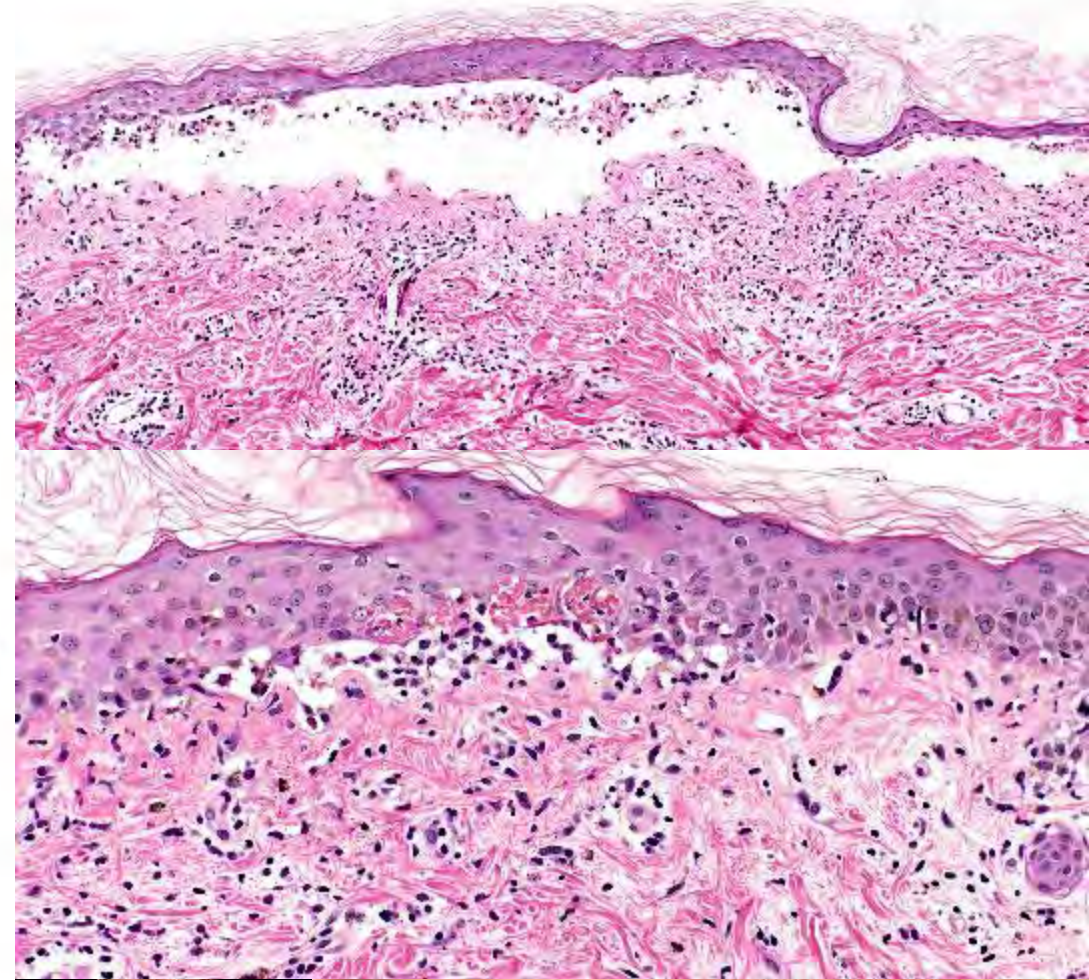
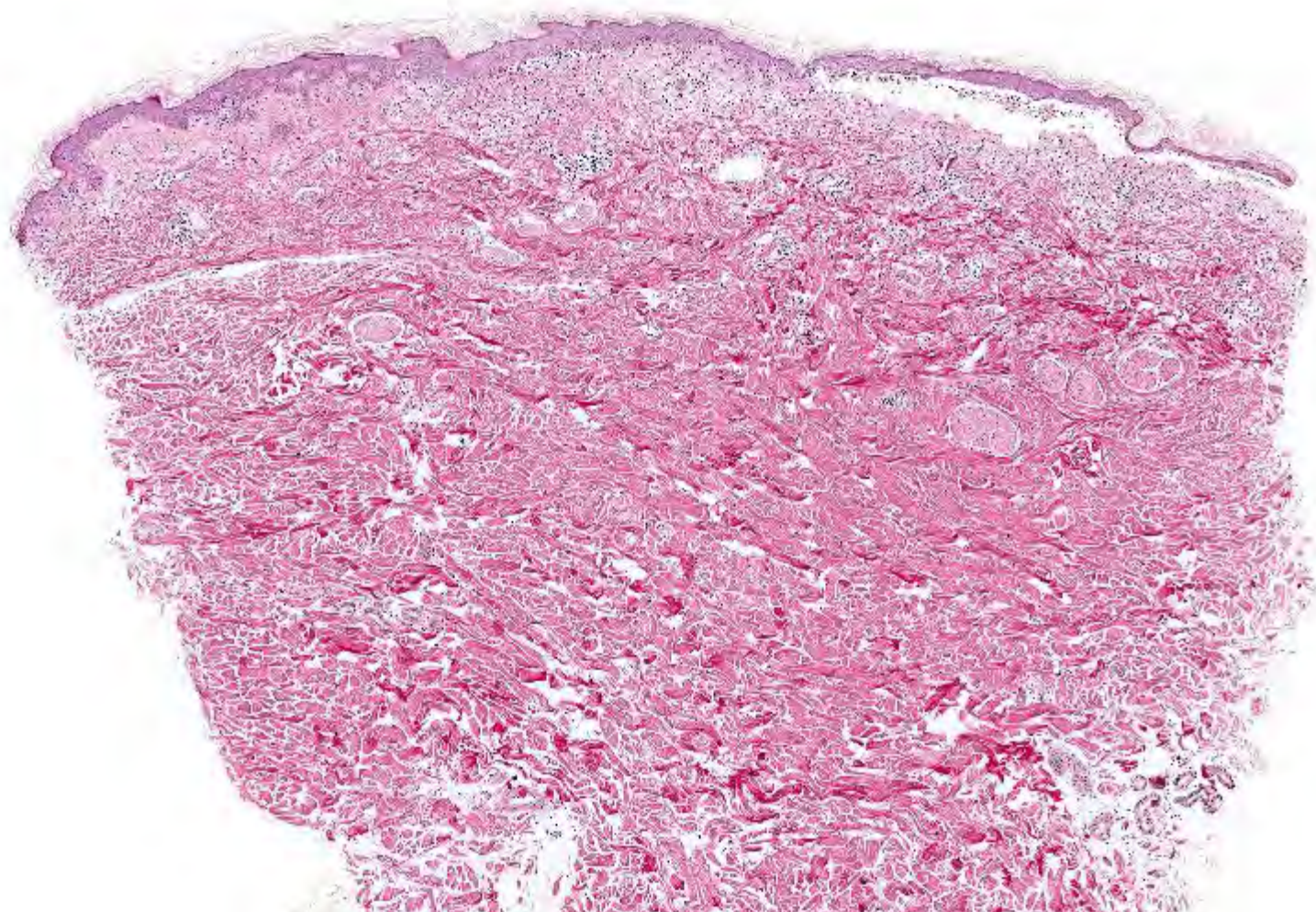
Minimal involvement of the palms.

Multiforme-like histological pattern with subepidermal cleft.

DIF: Intraepidermal intercellular IgG deposition; C3 cytooid bodies.

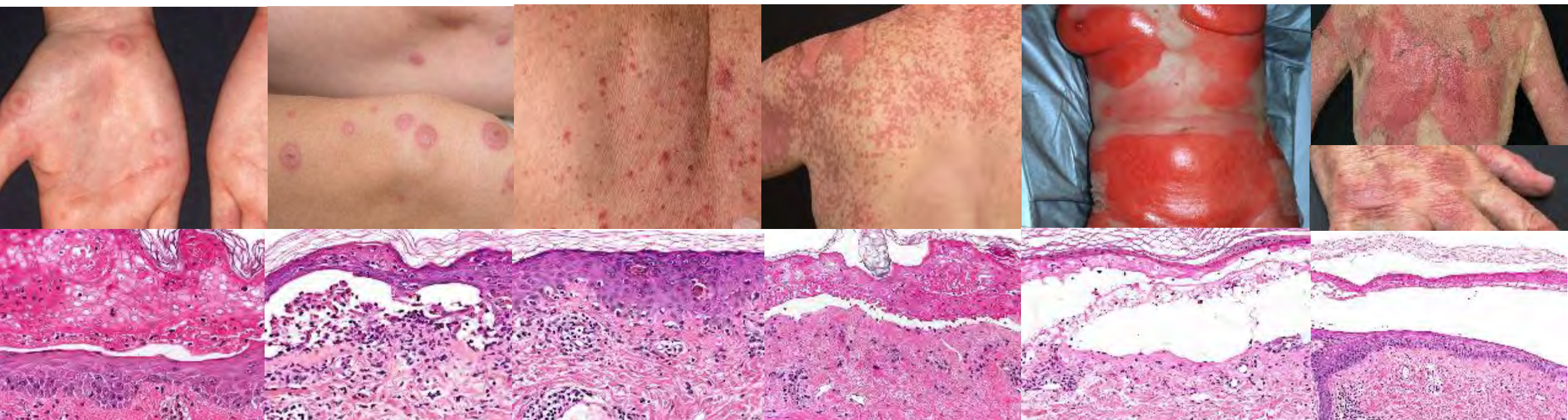
Desmoglein 1: 2-; Desmoglein 3: 14-/+

Managed with systemic steroids (initial dose 100 mg prednisolone); improvement of cutaneous and oral lesions.



Revised diagnosis:
**Drug-induced
paraneoplastic pemphigus**





**Erythema multiforme
minor**

No involvement of
mucosae
Target lesions
No progression to TEN

**Erythema multiforme
major**

Involvement of mucosae
(may be severe)
Lesions mostly on face
and distal extremities
Target lesions
No progression to TEN

**Stevens-Johnson
syndrome (SJS)**

Involvement of mucosae
Lesions mostly on trunk
No target lesions
Skin detachment <10%
Progression to TEN
possible and unpredictable

SJS / TEN overlap

Involvement of mucosae
No target lesions
Skin detachment 10-30%
Progression to TEN likely

**Toxic epidermal
necrolysis (TEN)**

Involvement of mucosae
No target lesions
Large areas of skin
exfoliation (>30%)

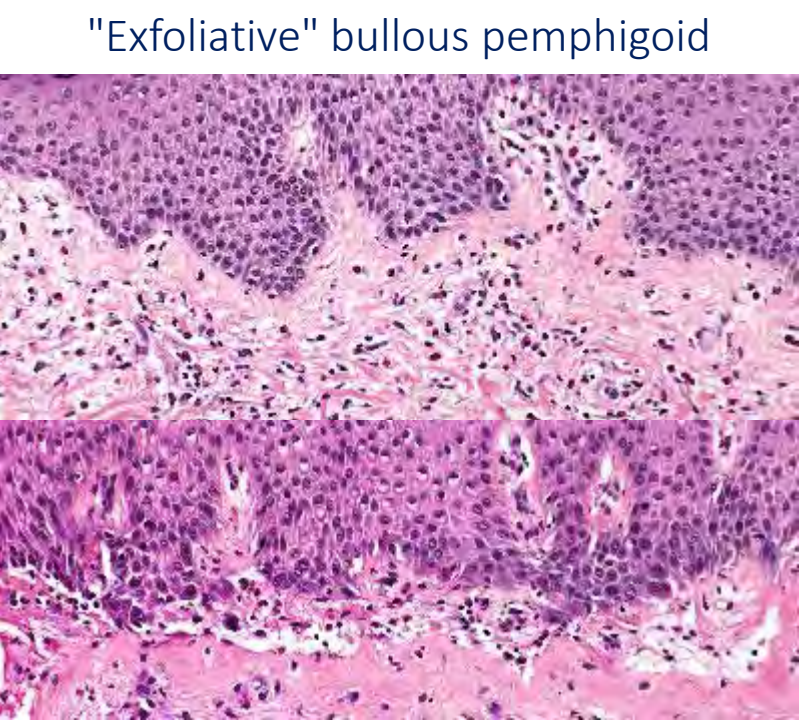
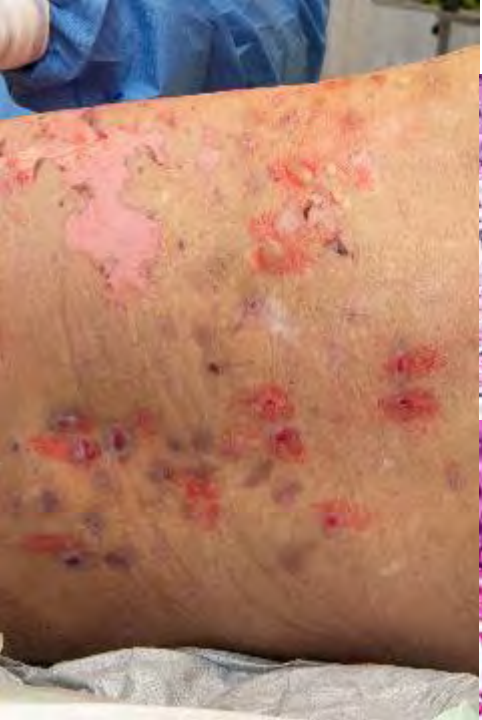
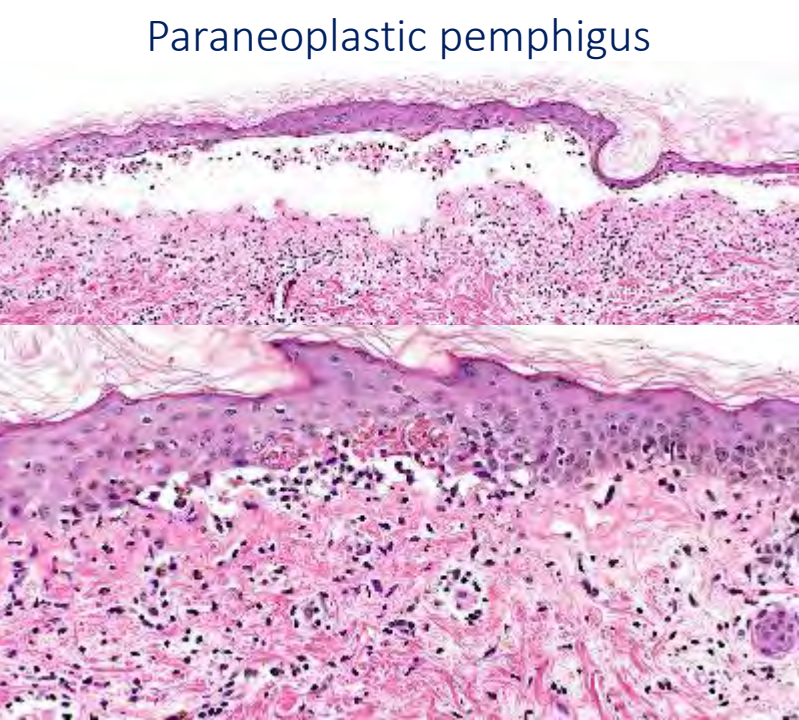
**Generalized bullous
fixed DE**

Involvement of mucosae
in severe cases
No target lesions
Lesions of fixed DE focally
Mortality rate 0-22%



Paraneoplastic pemphigus

"Exfoliative" bullous pemphigoid

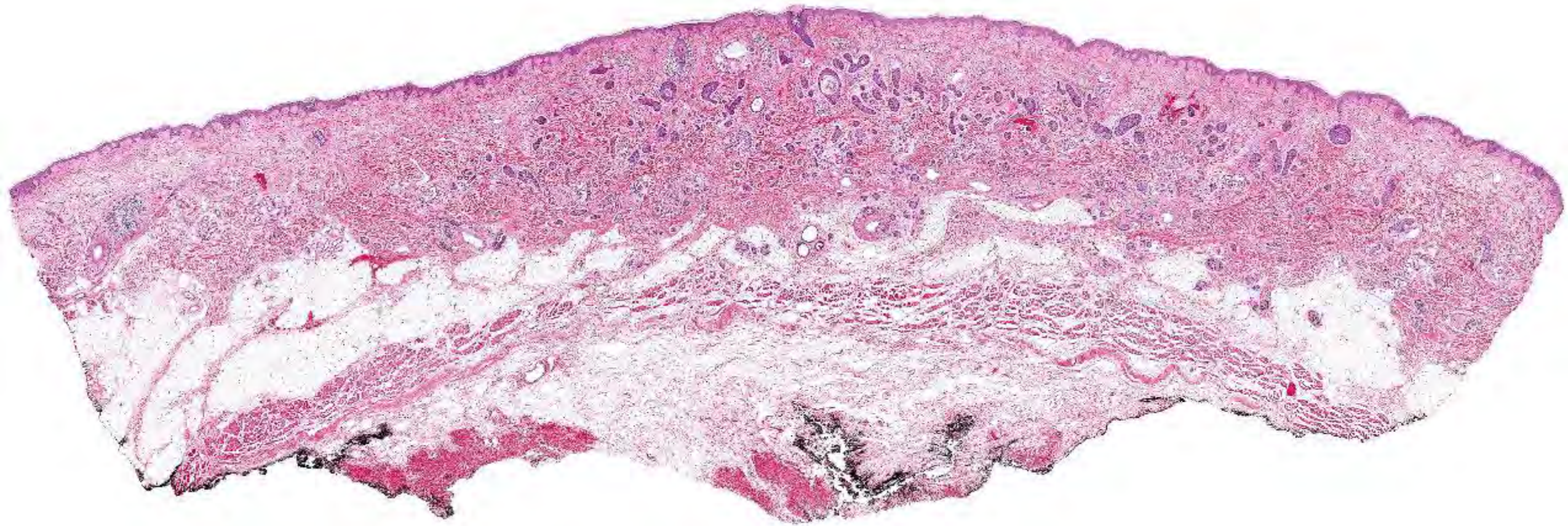


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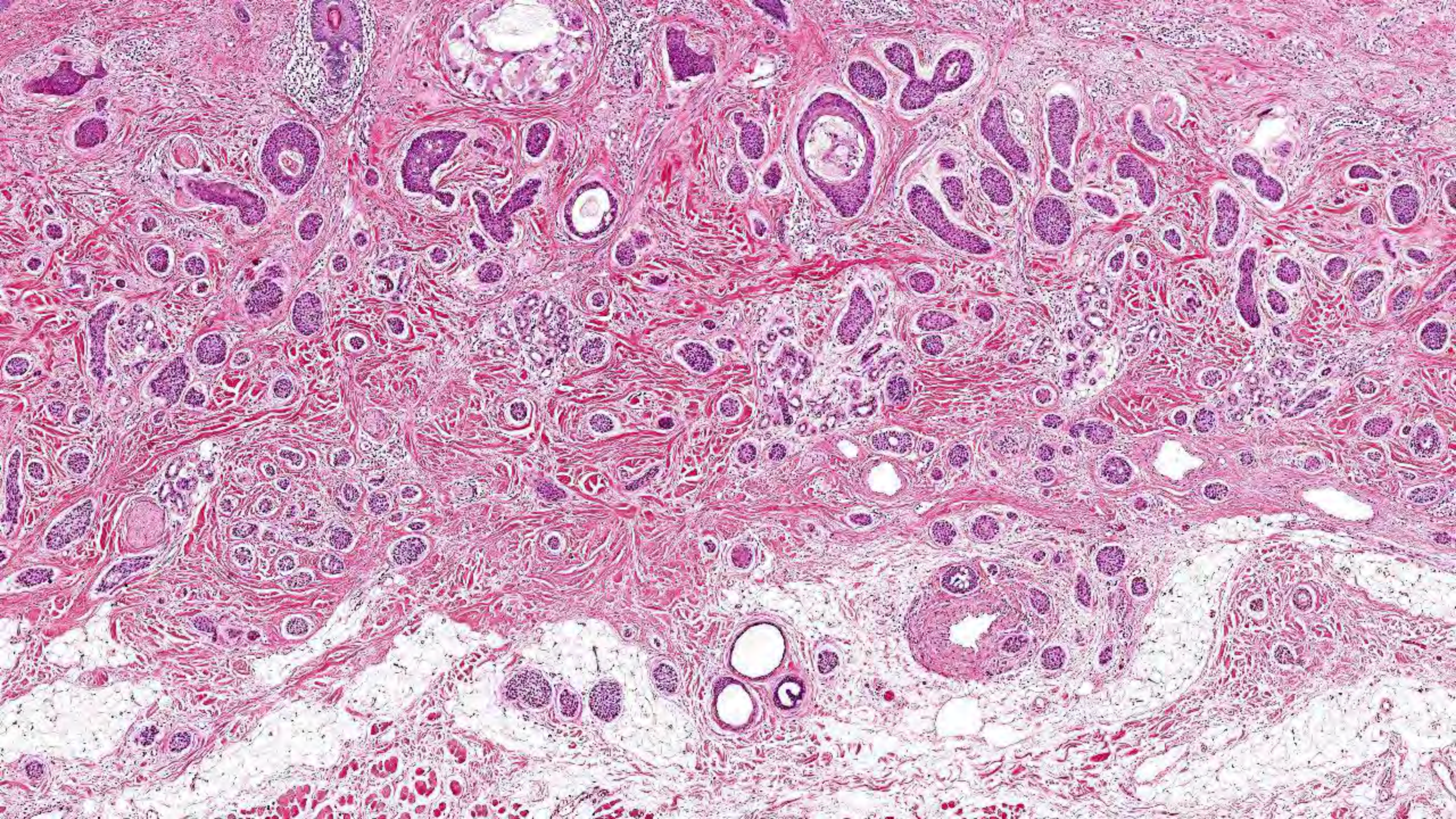
Self-assessment (cases 41-50)

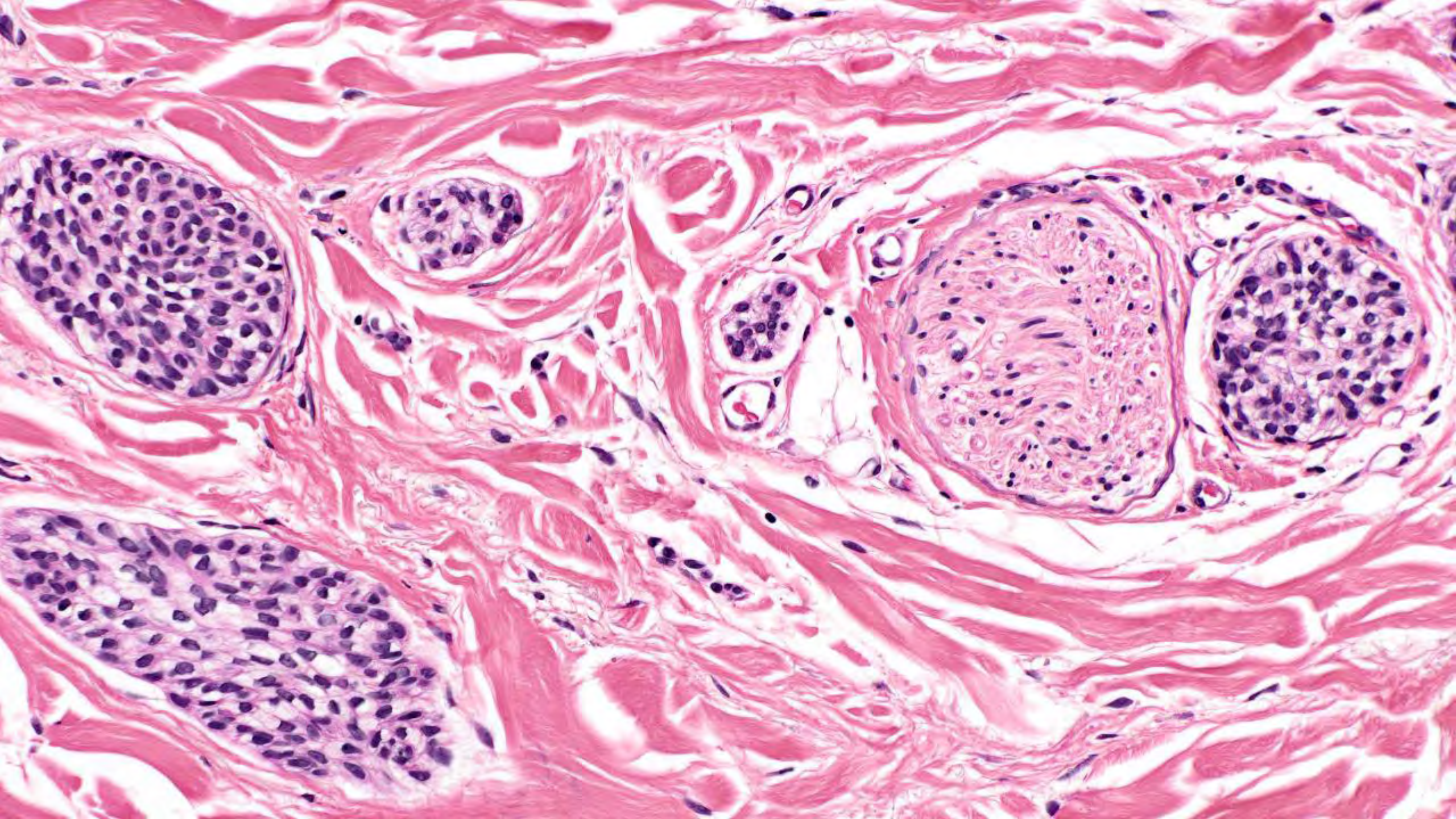
Lorenzo Cerroni

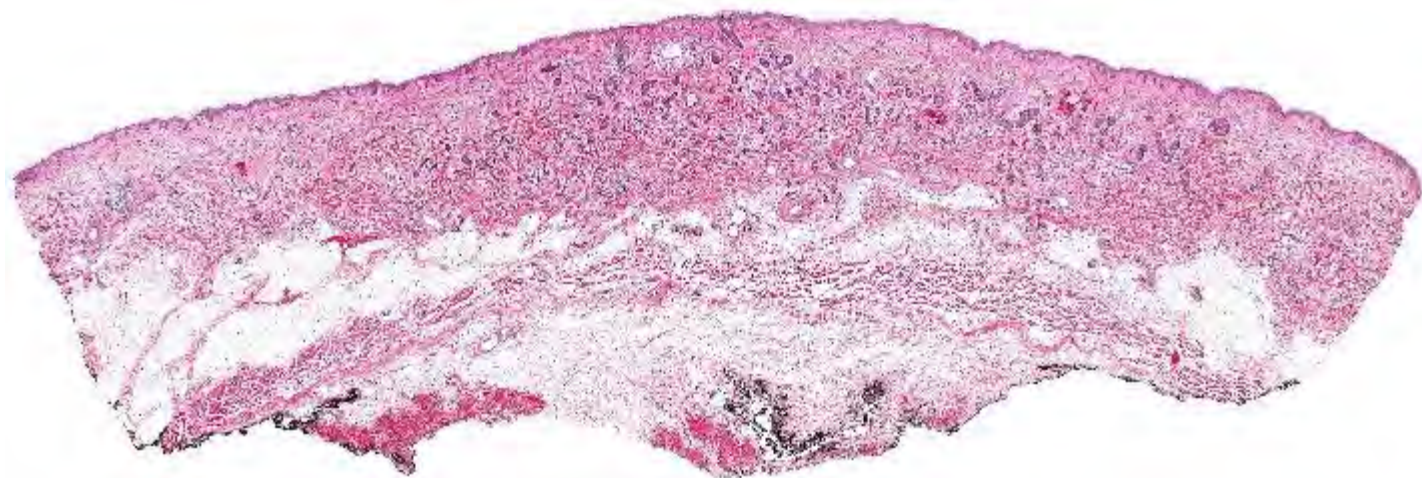


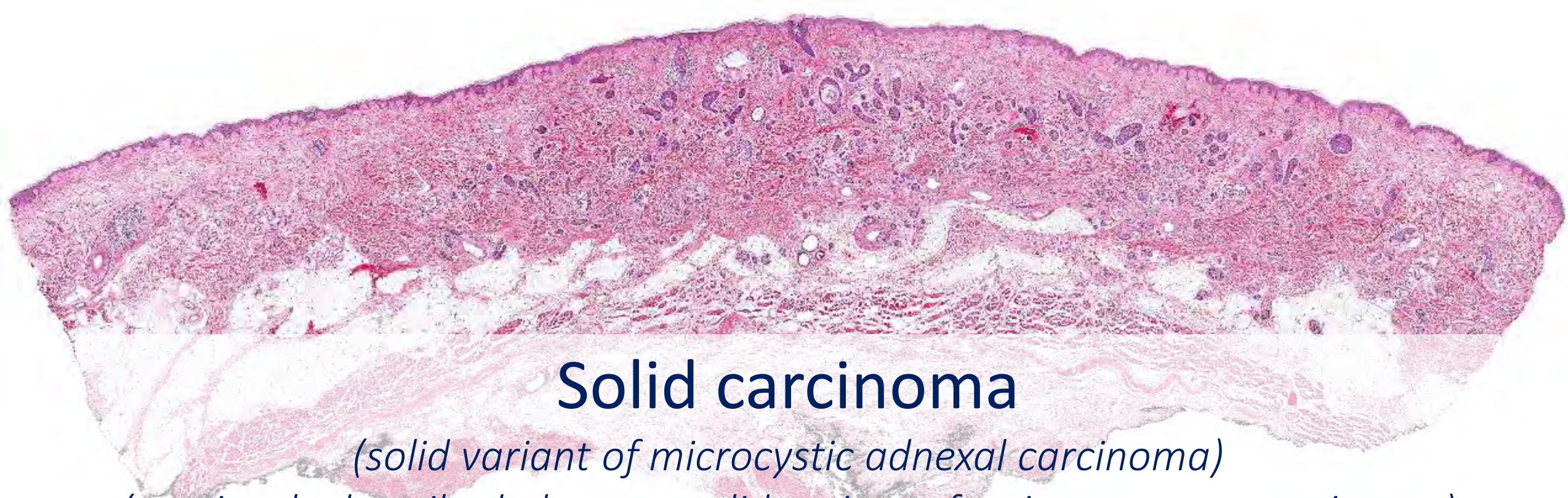
Case 41

F, 57. An external biopsy was reported by a private dermatopathologist as "part of a poroma", with a recommendation to perform a complete excision. According to the patient the lesion is present for approximately one year.





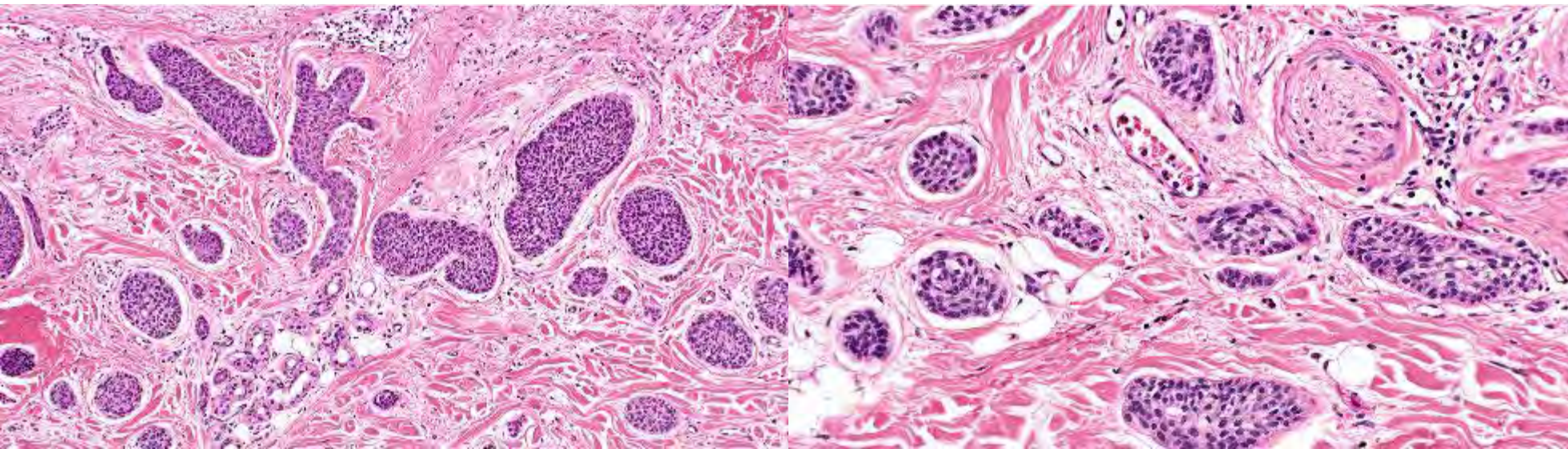




Solid carcinoma

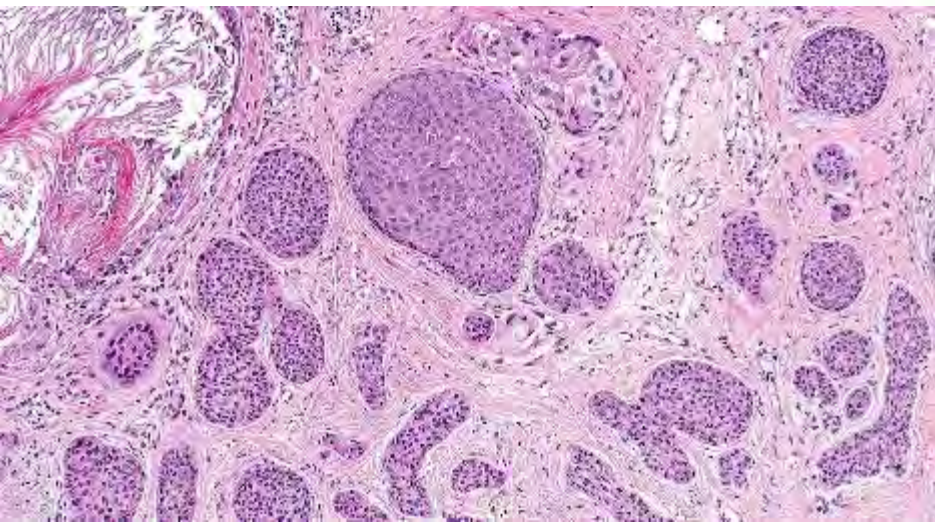
(solid variant of microcystic adnexal carcinoma)

(previously described also as a solid variant of syringomatous carcinoma)





Previous biopsy



Cutaneous Adnexal Neoplasms

Second Edition

- Solid carcinoma probably is the solid variant of microcystic adnexal carcinoma (MAC), with predilection for the scalp of elderly patients.

460

26 Solid Carcinoma

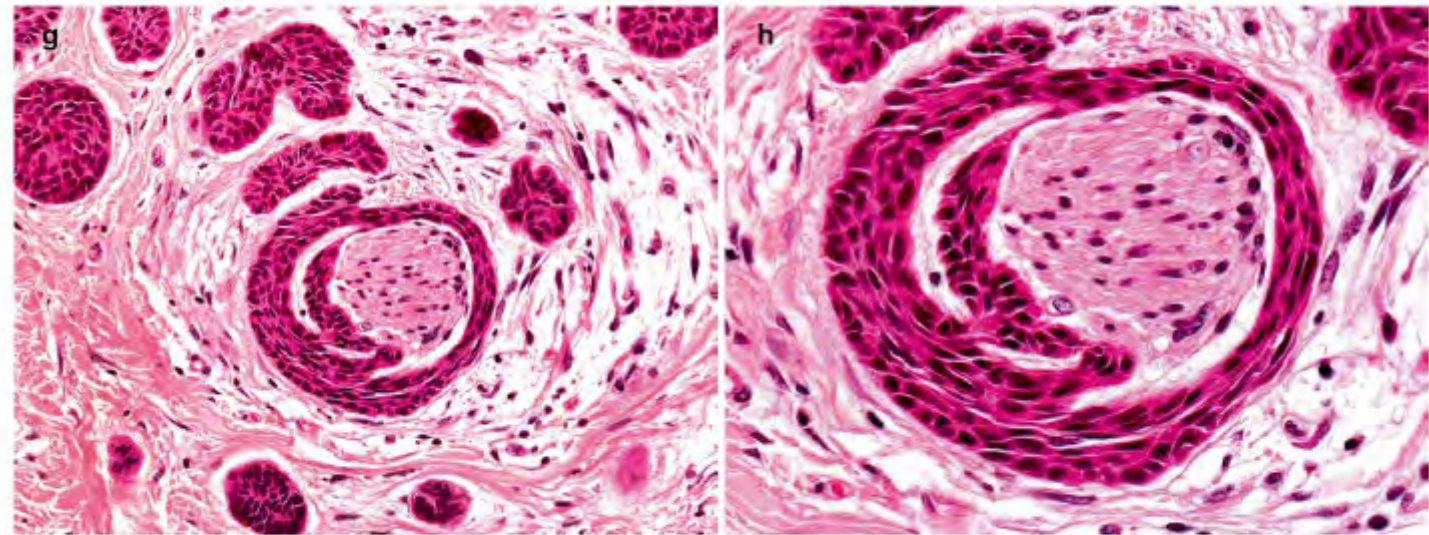
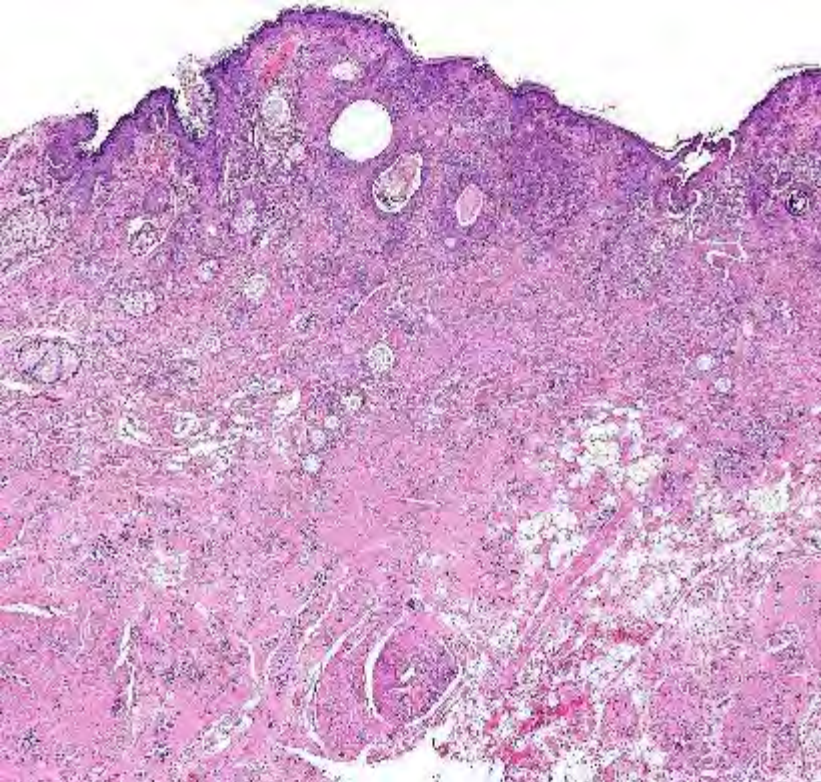
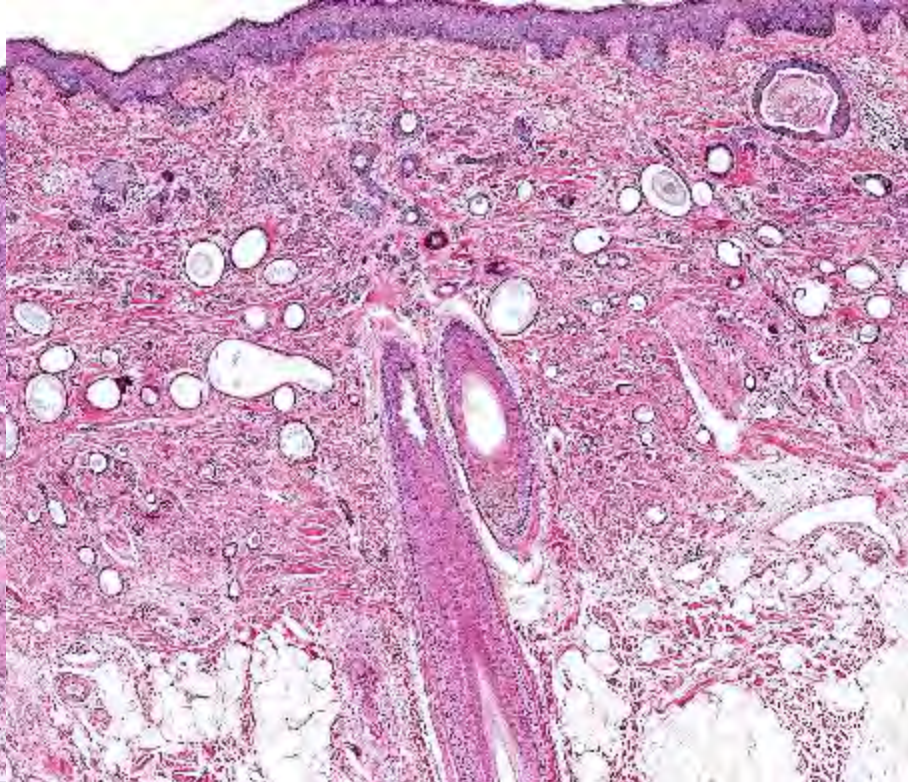


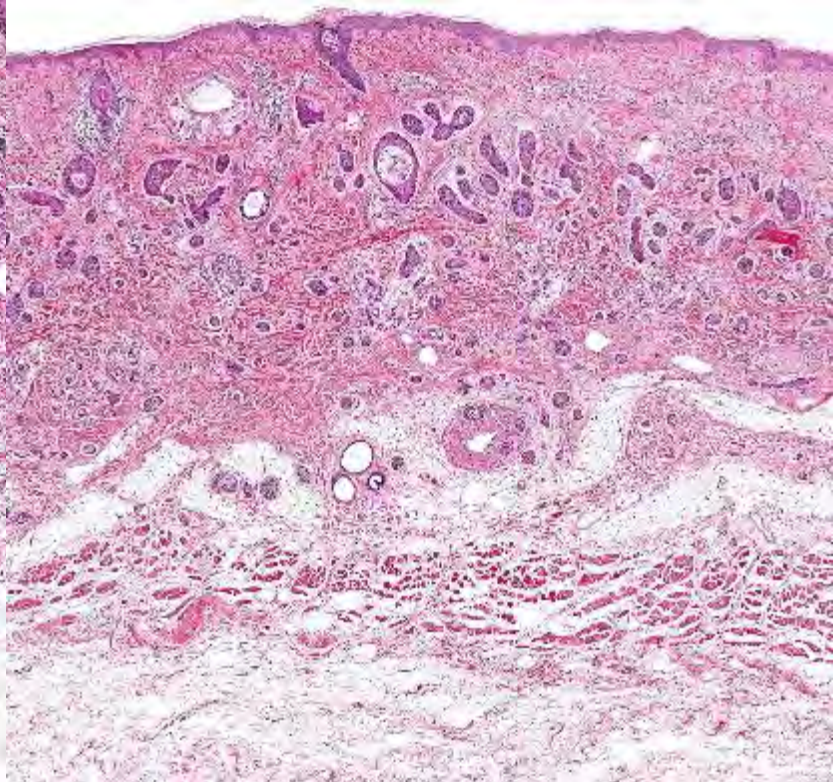
Fig. 26.4 (continued)



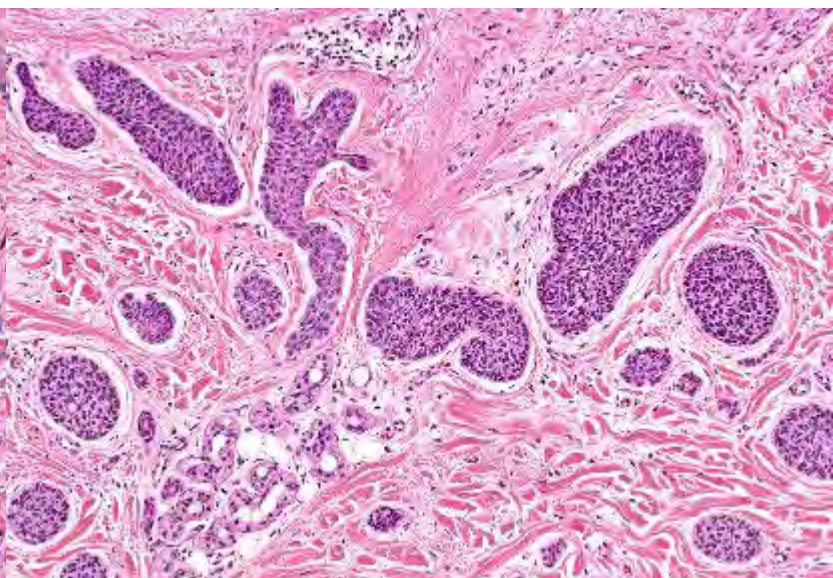
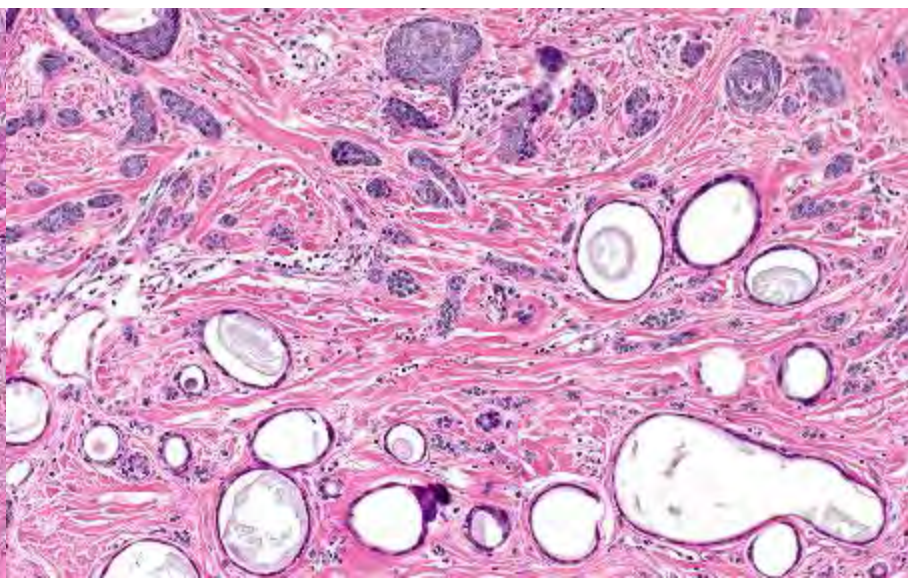
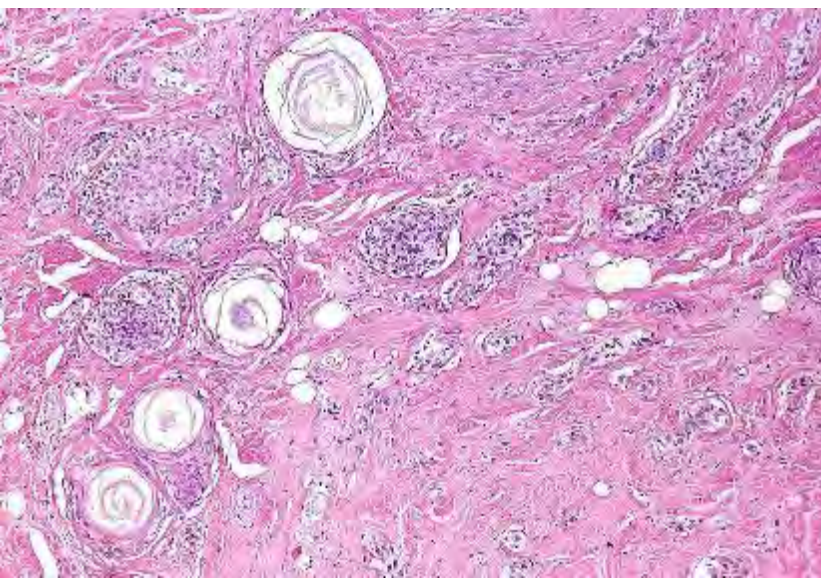
Microcystic adnexal carcinoma

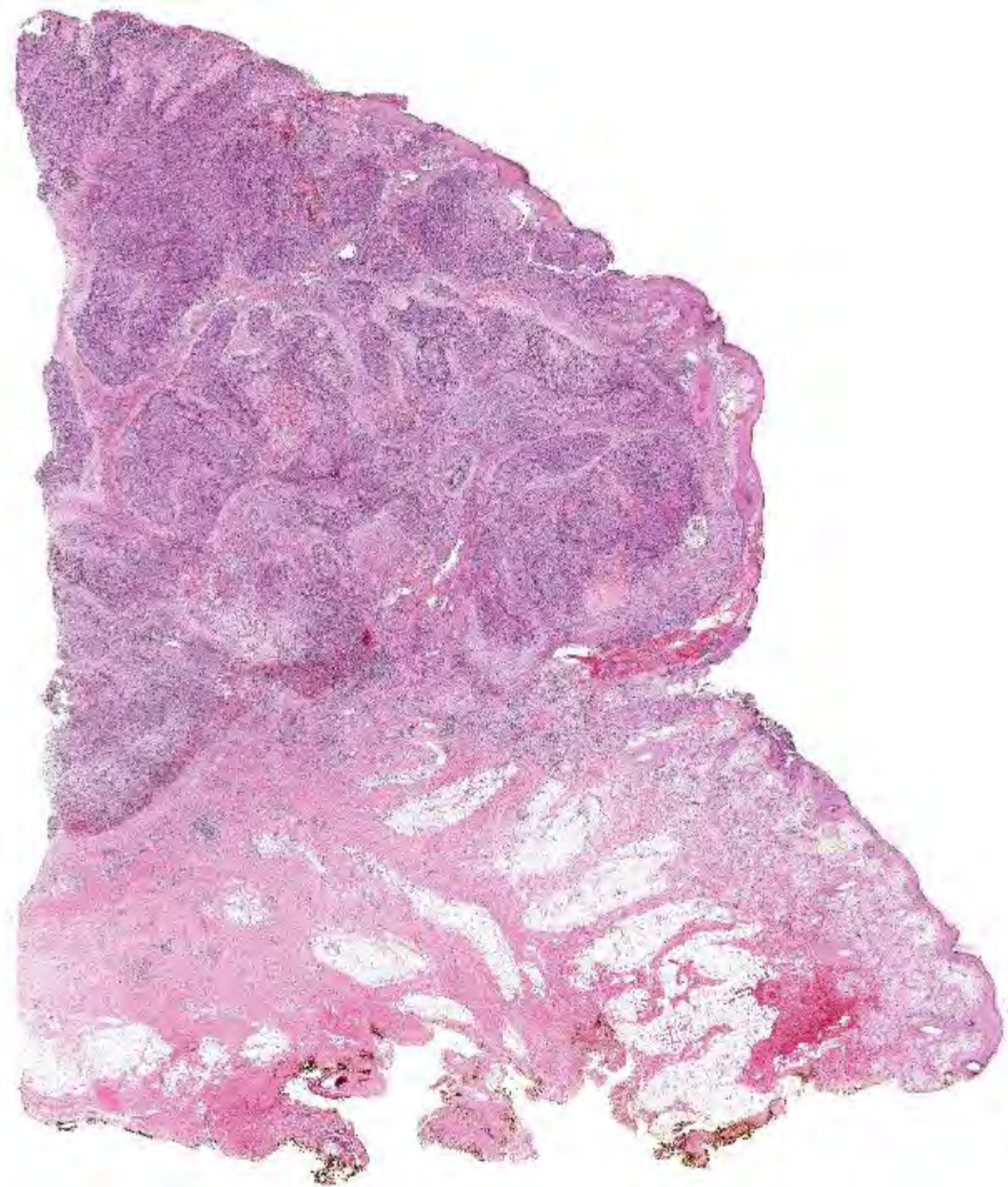


Syringomatous carcinoma



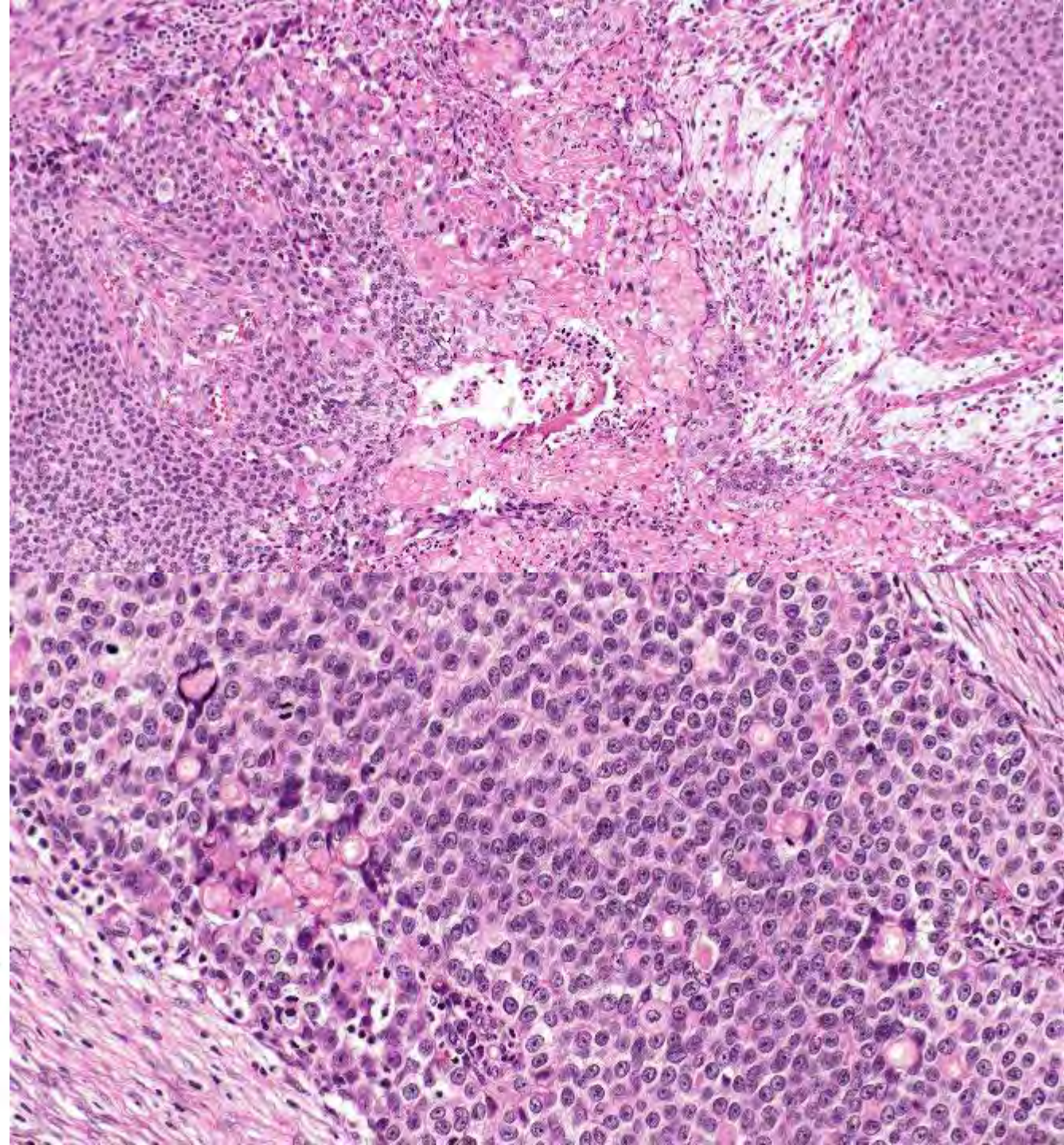
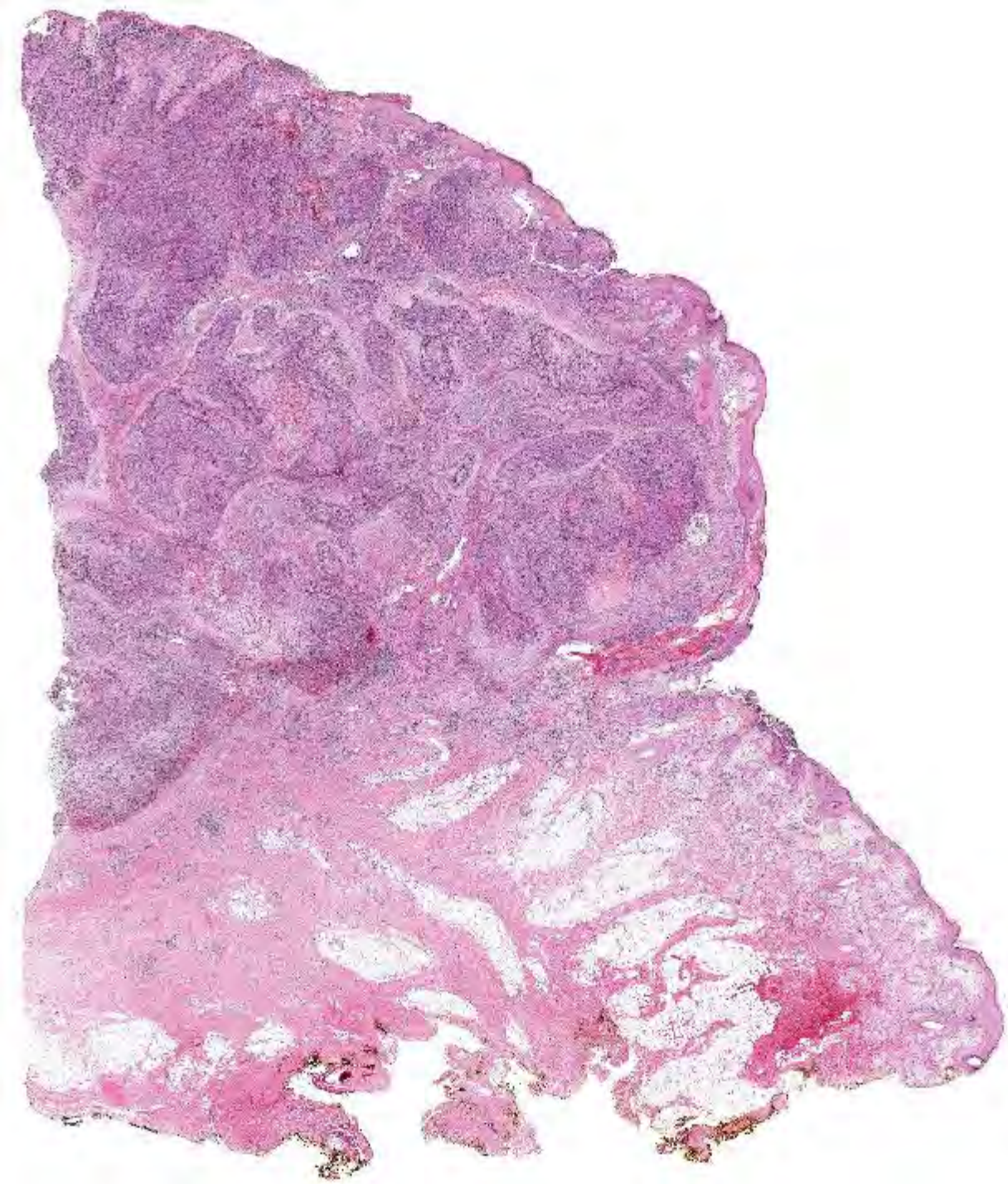
Solid carcinoma

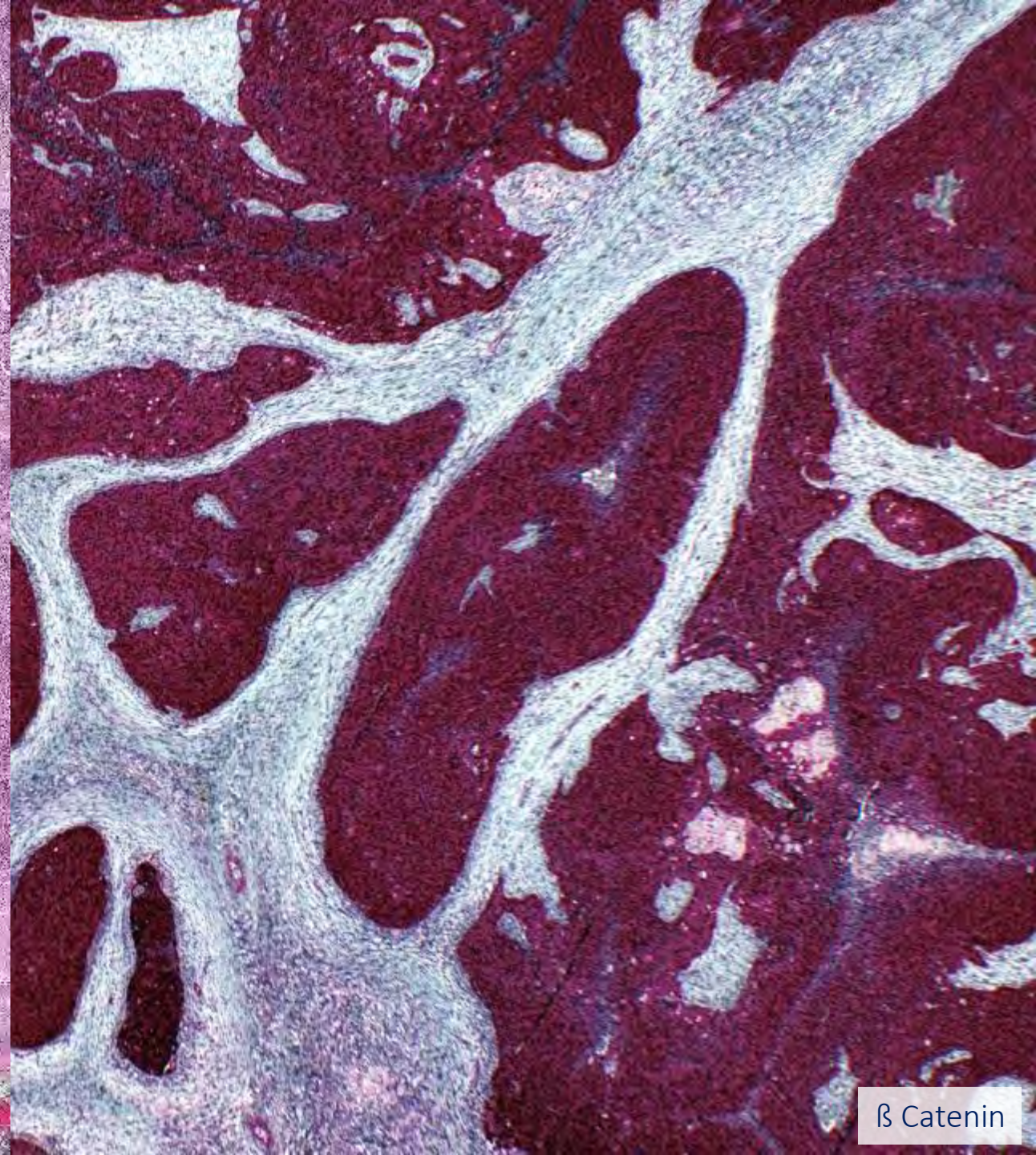
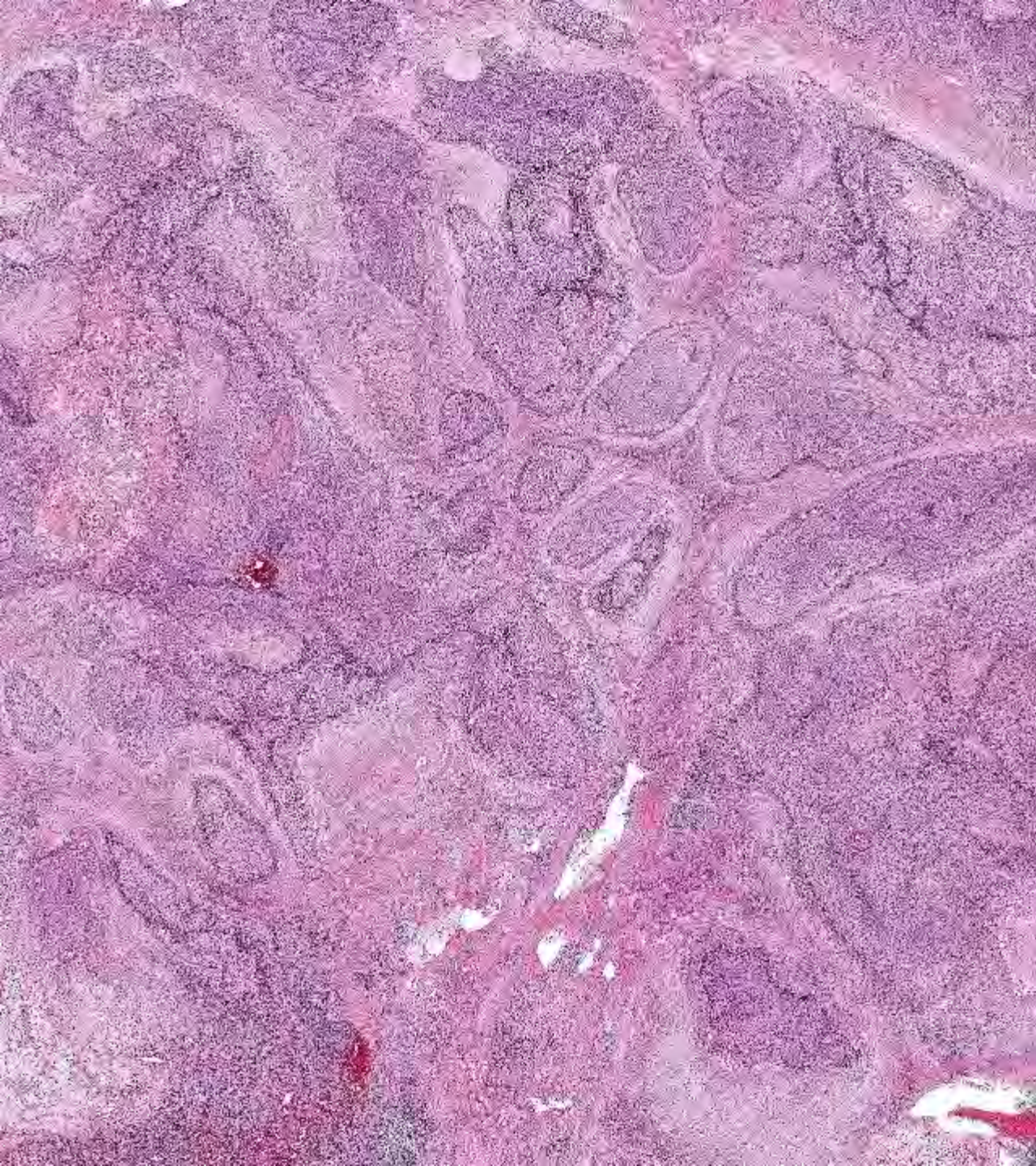


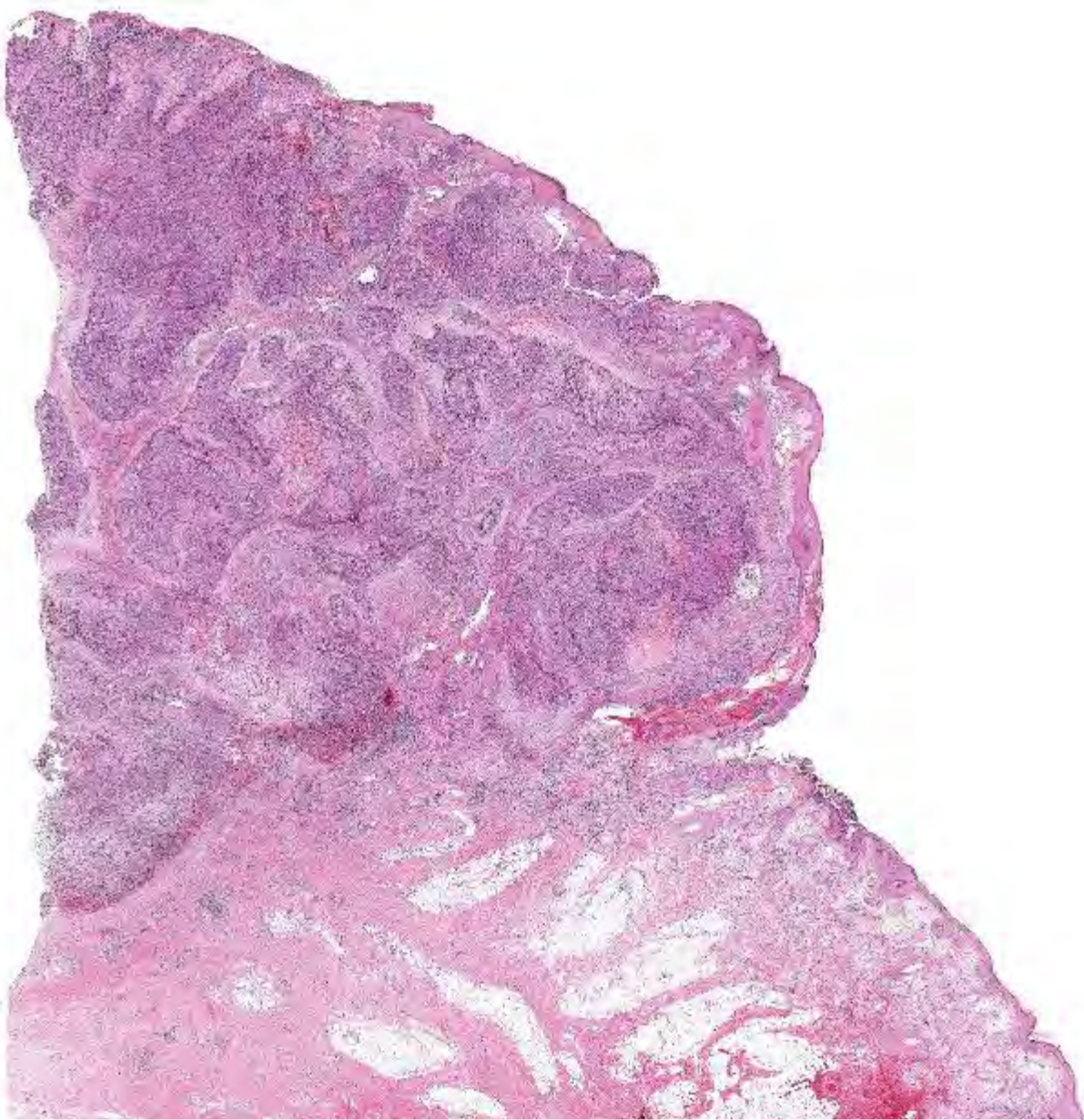


Case 42

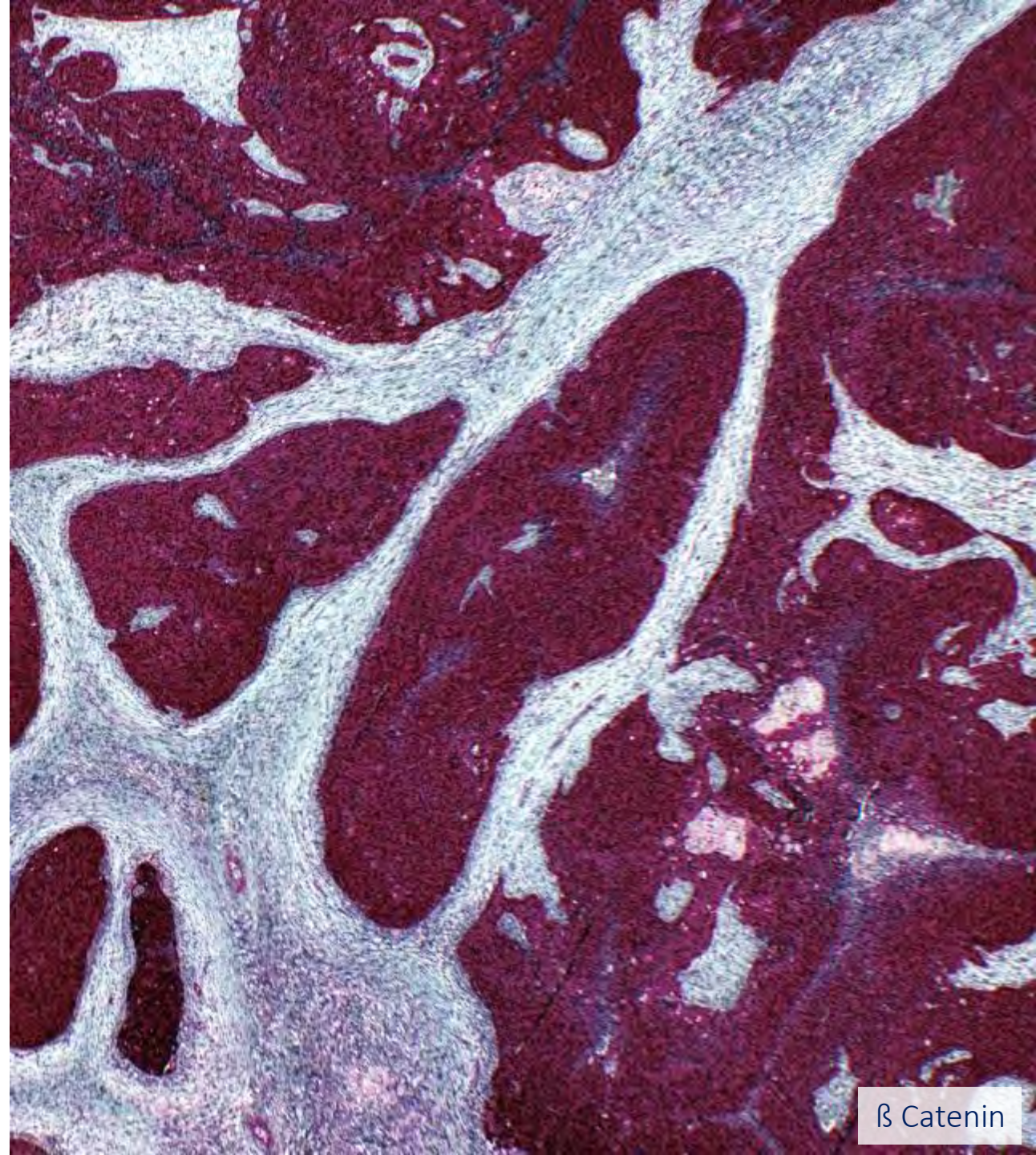
M, 83. Exophytic
preauricular tumor of
unknown duration.



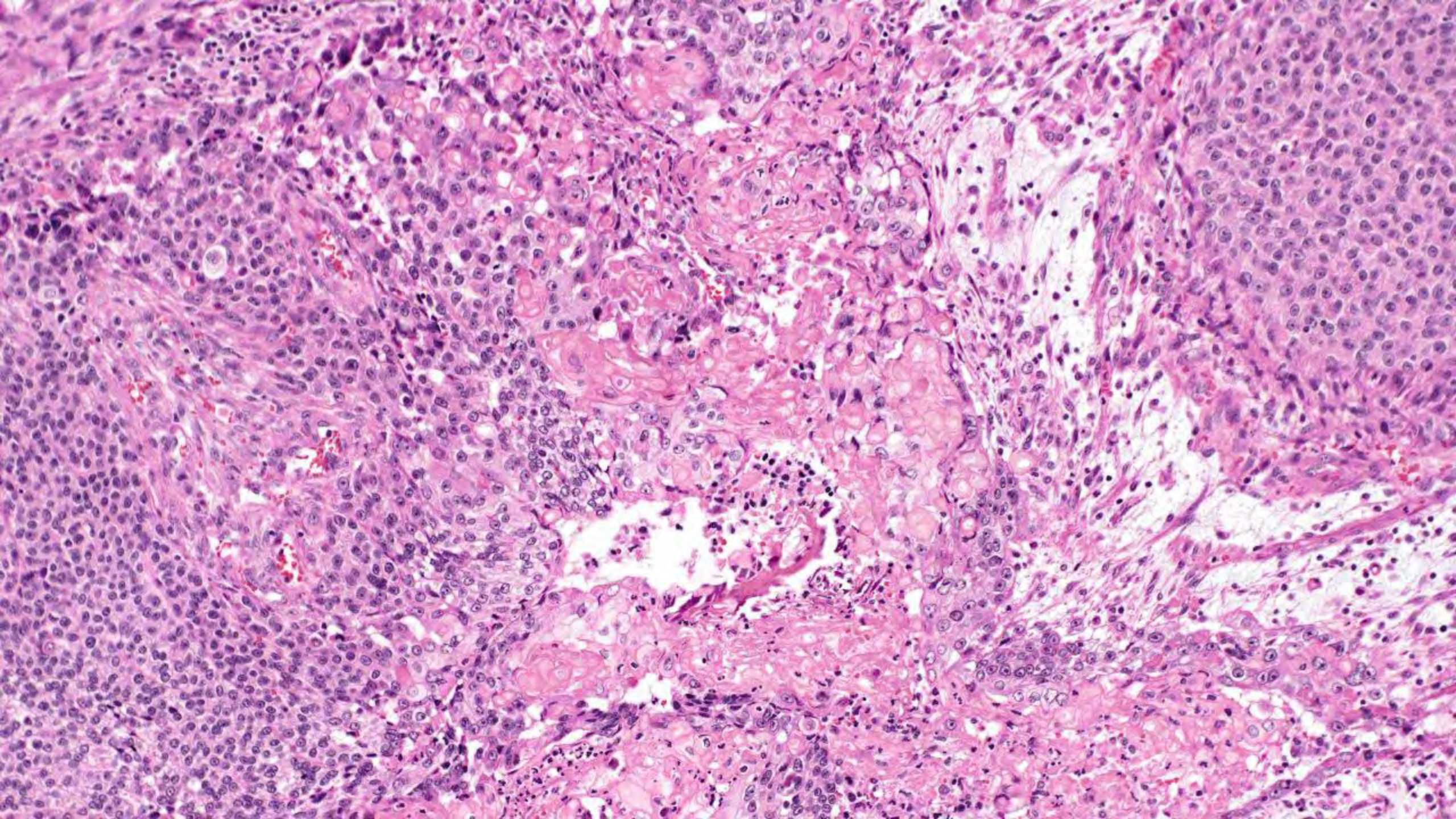




Pilomatrical carcinoma



β Catenin



Cutaneous Adnexal Neoplasms

Second Edition

- In few cases of pilomatrix carcinoma studied by molecular biology, mutations in the beta-catenin gene *CTNNB1* have been found.

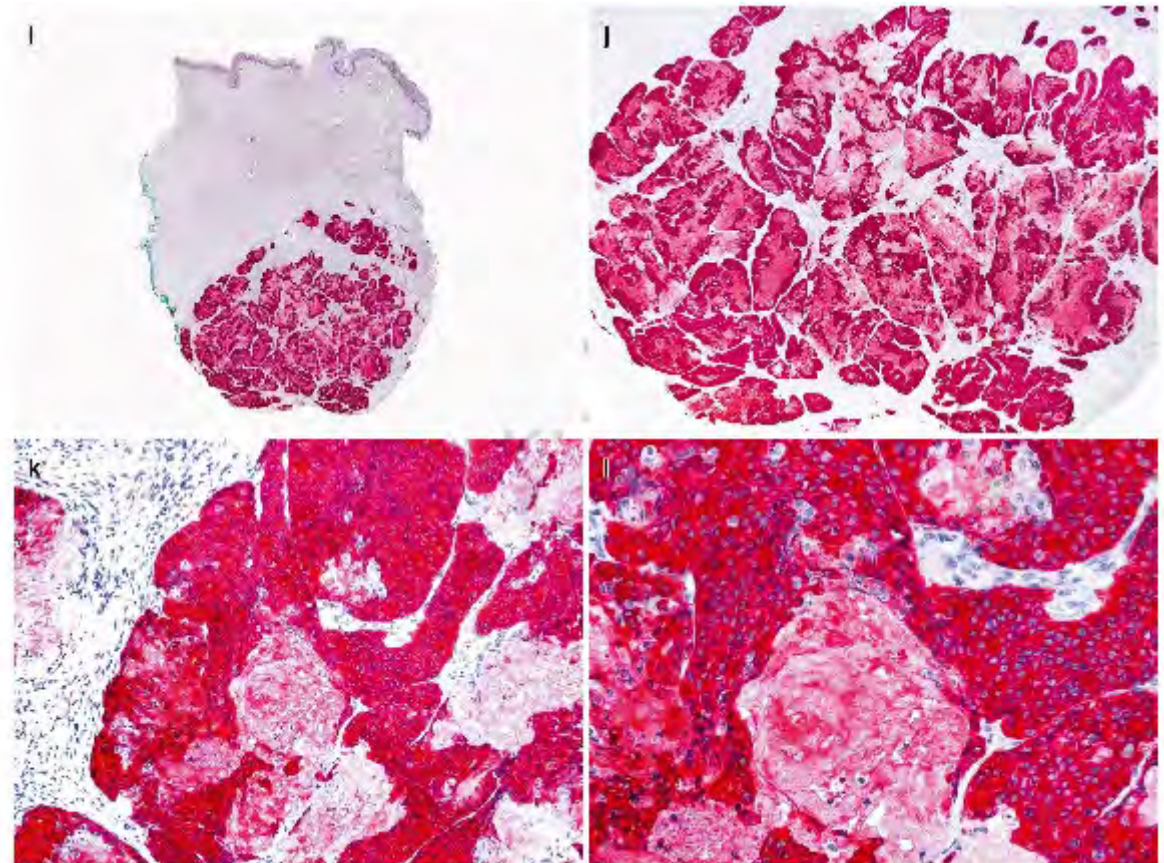
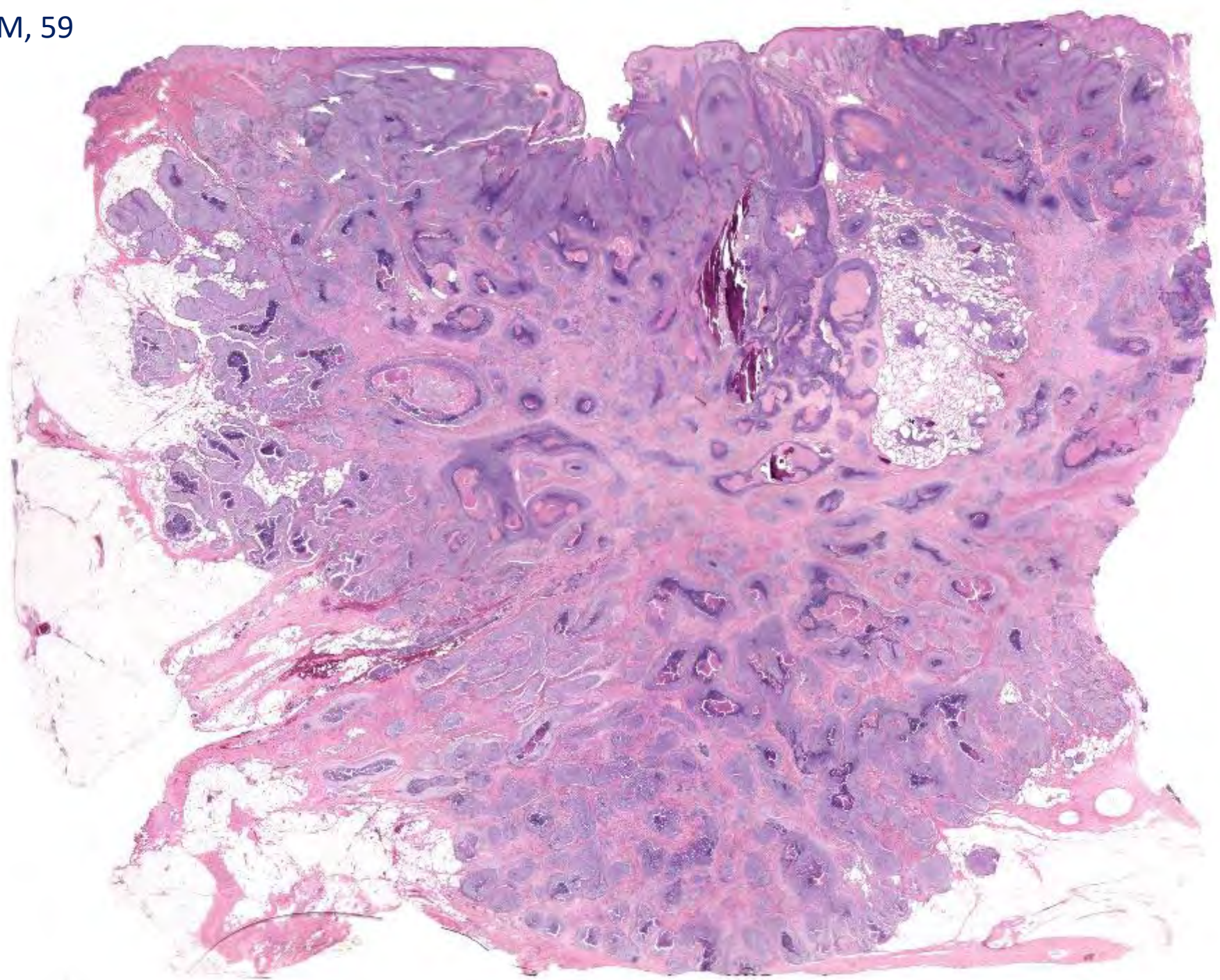
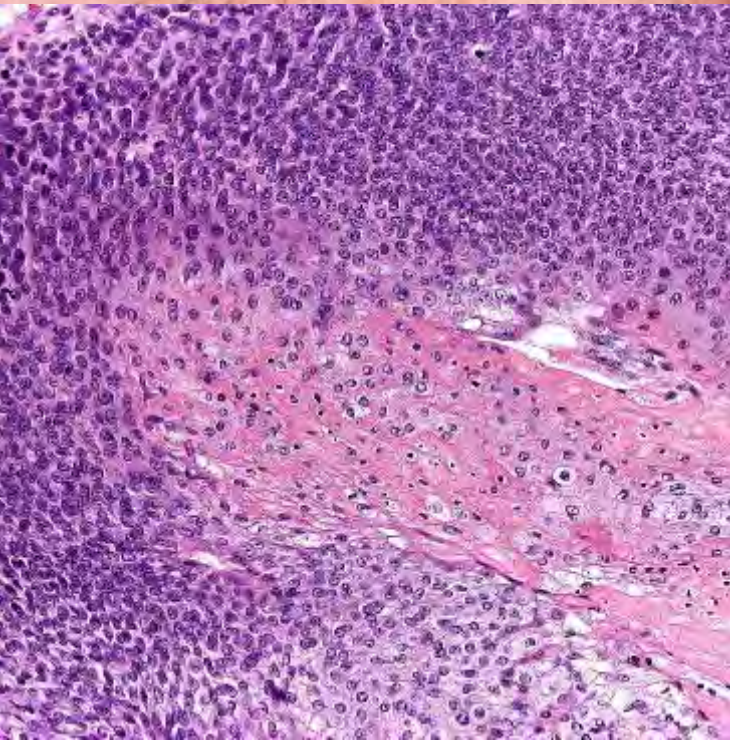
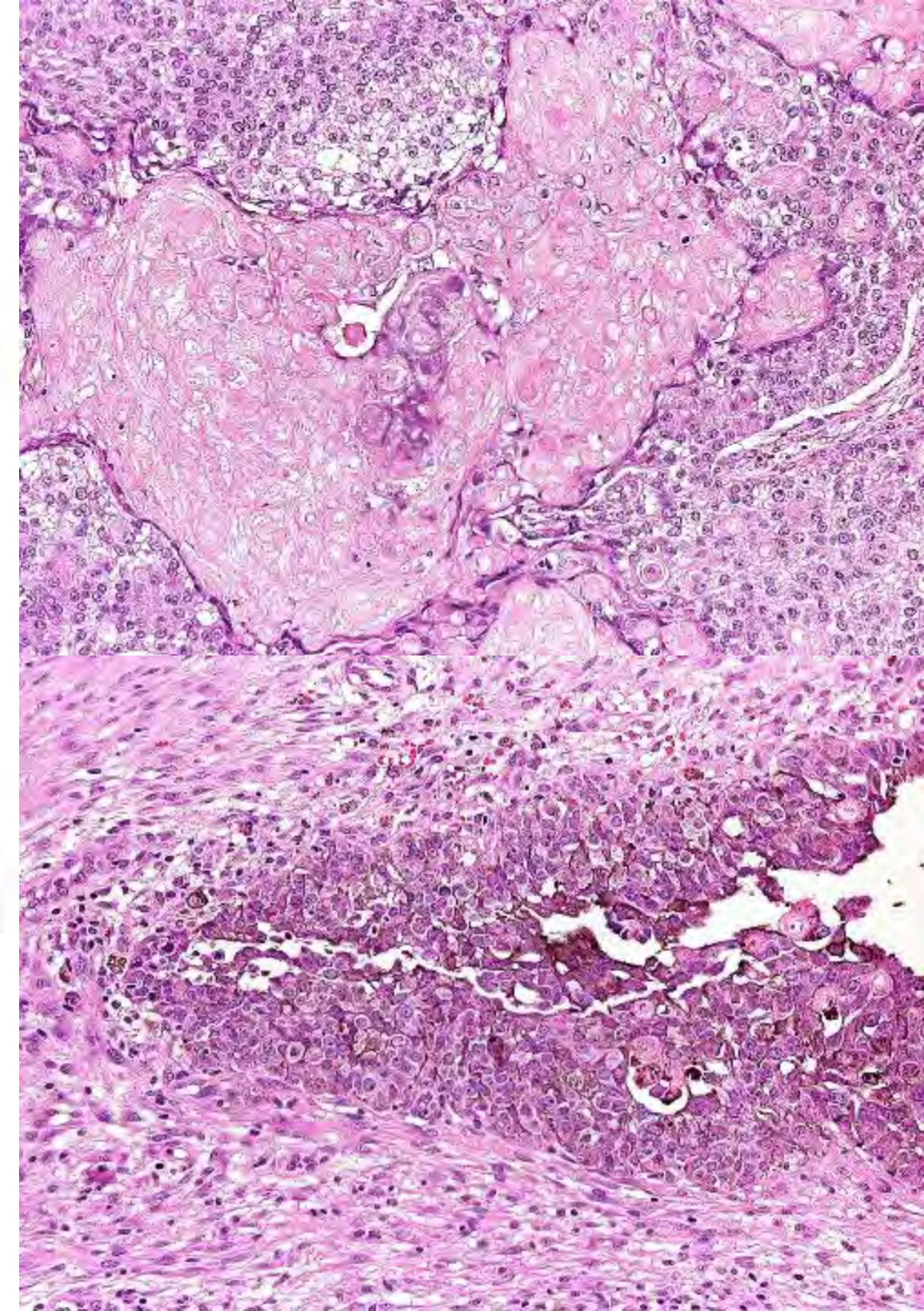
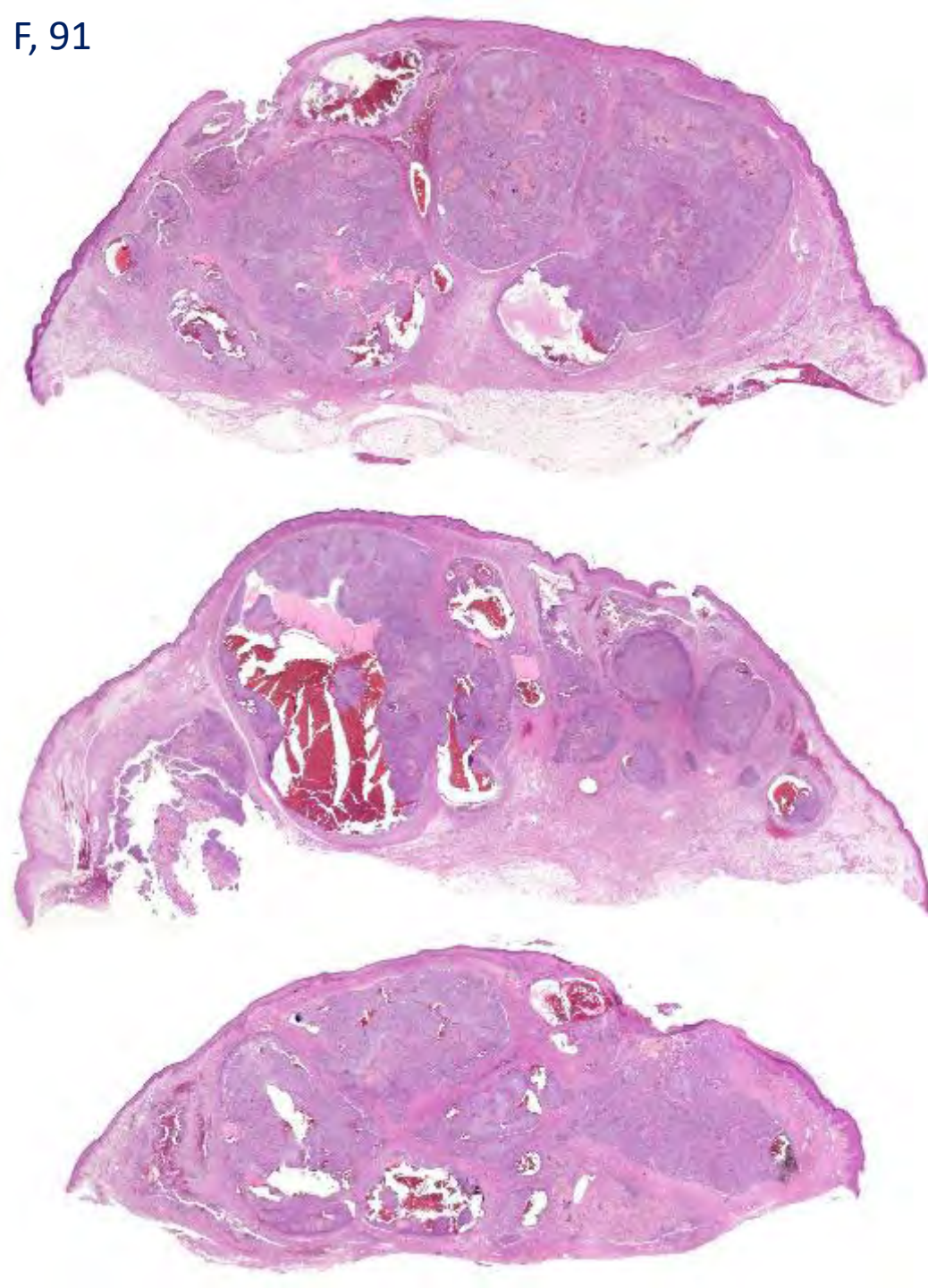


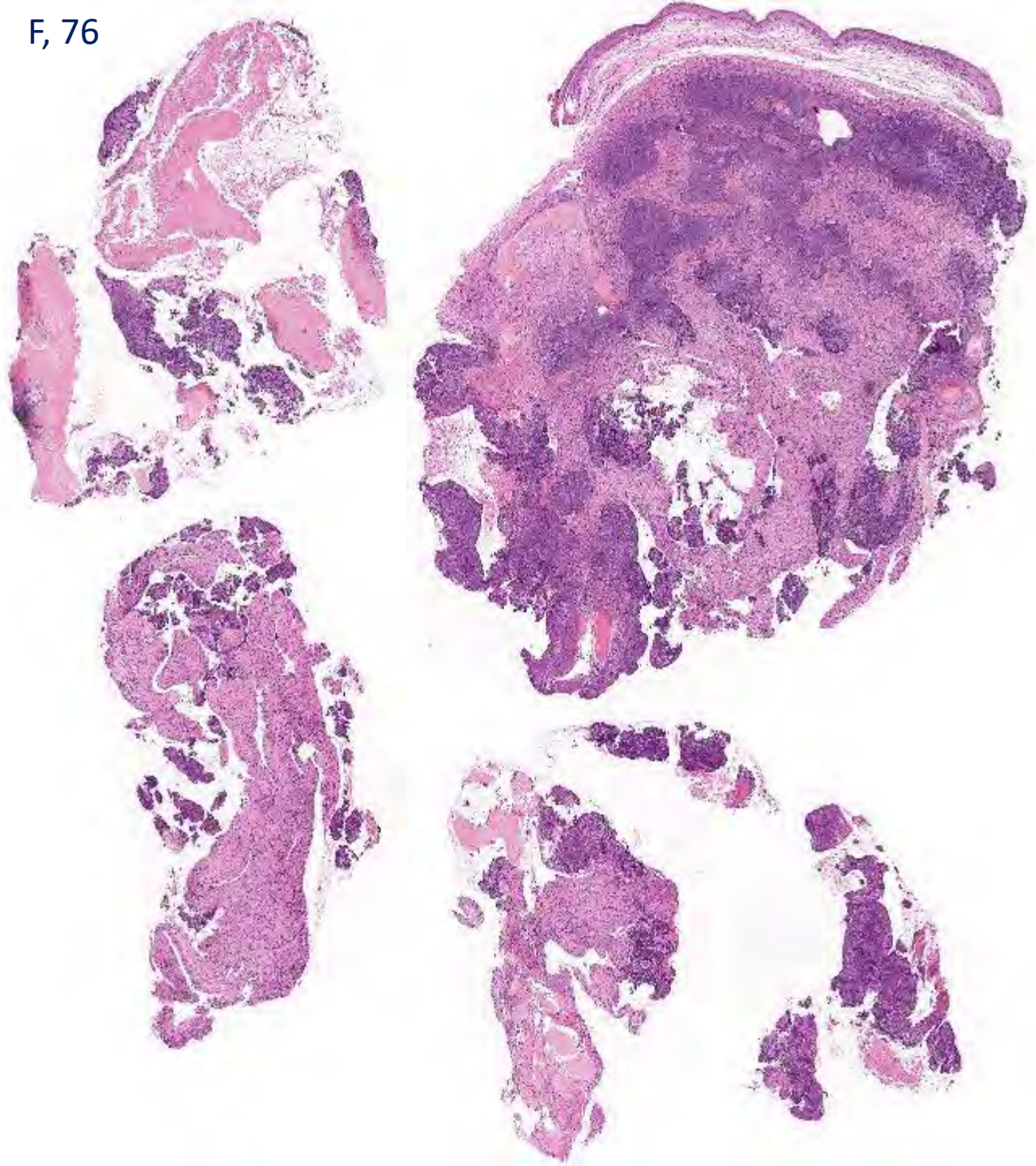
Fig. 61.4 (continued)

M, 59

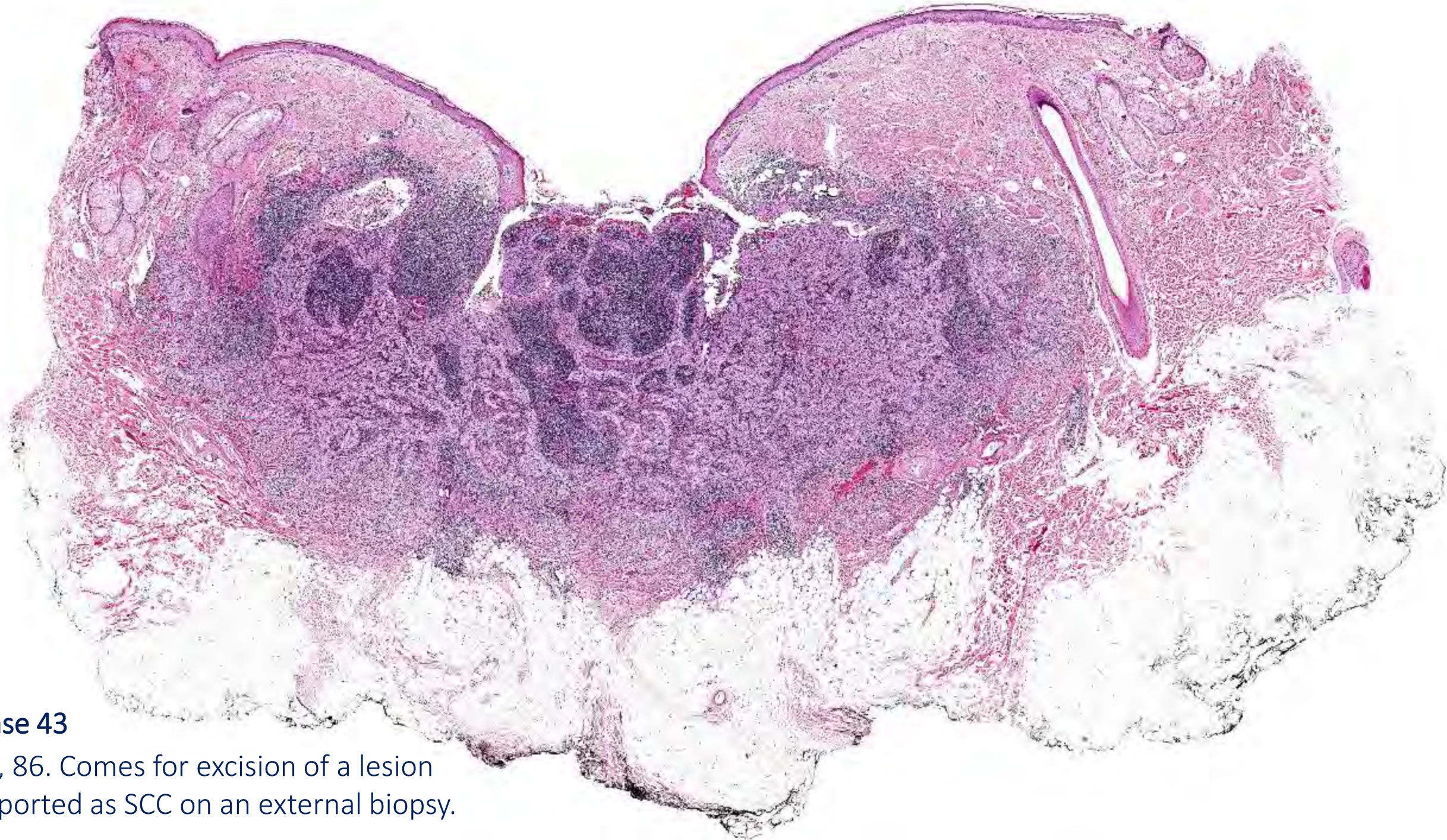


F, 91



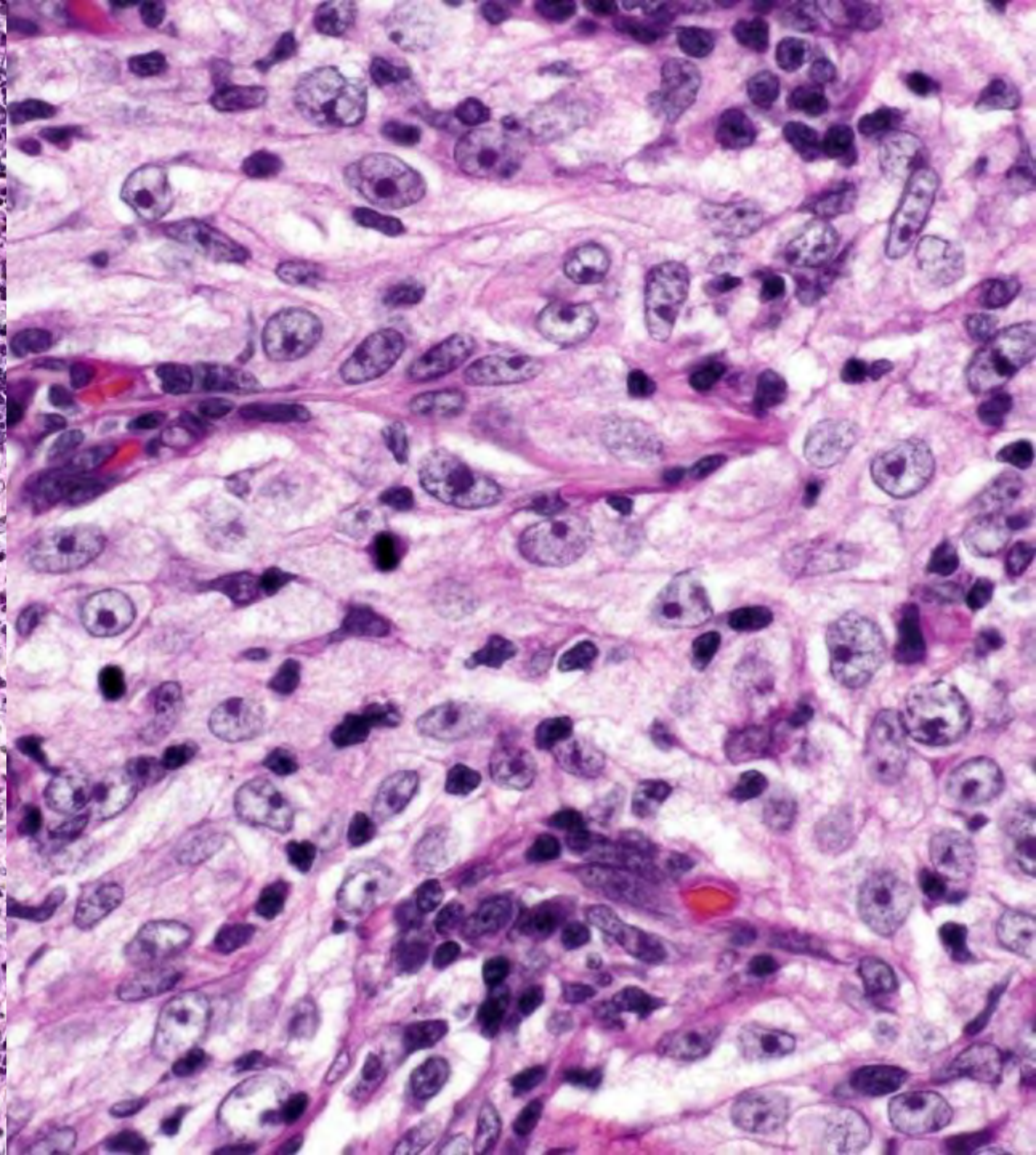
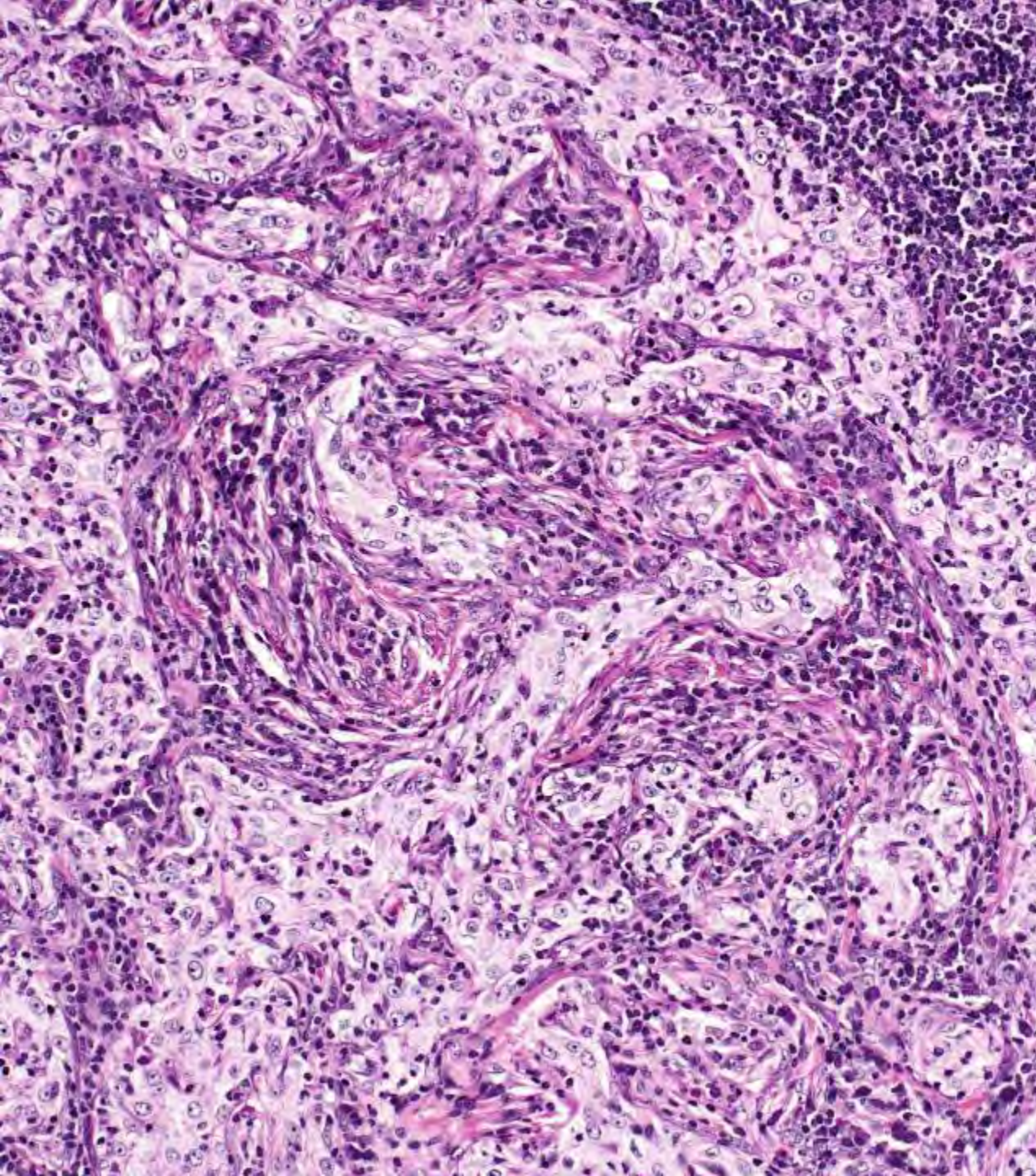


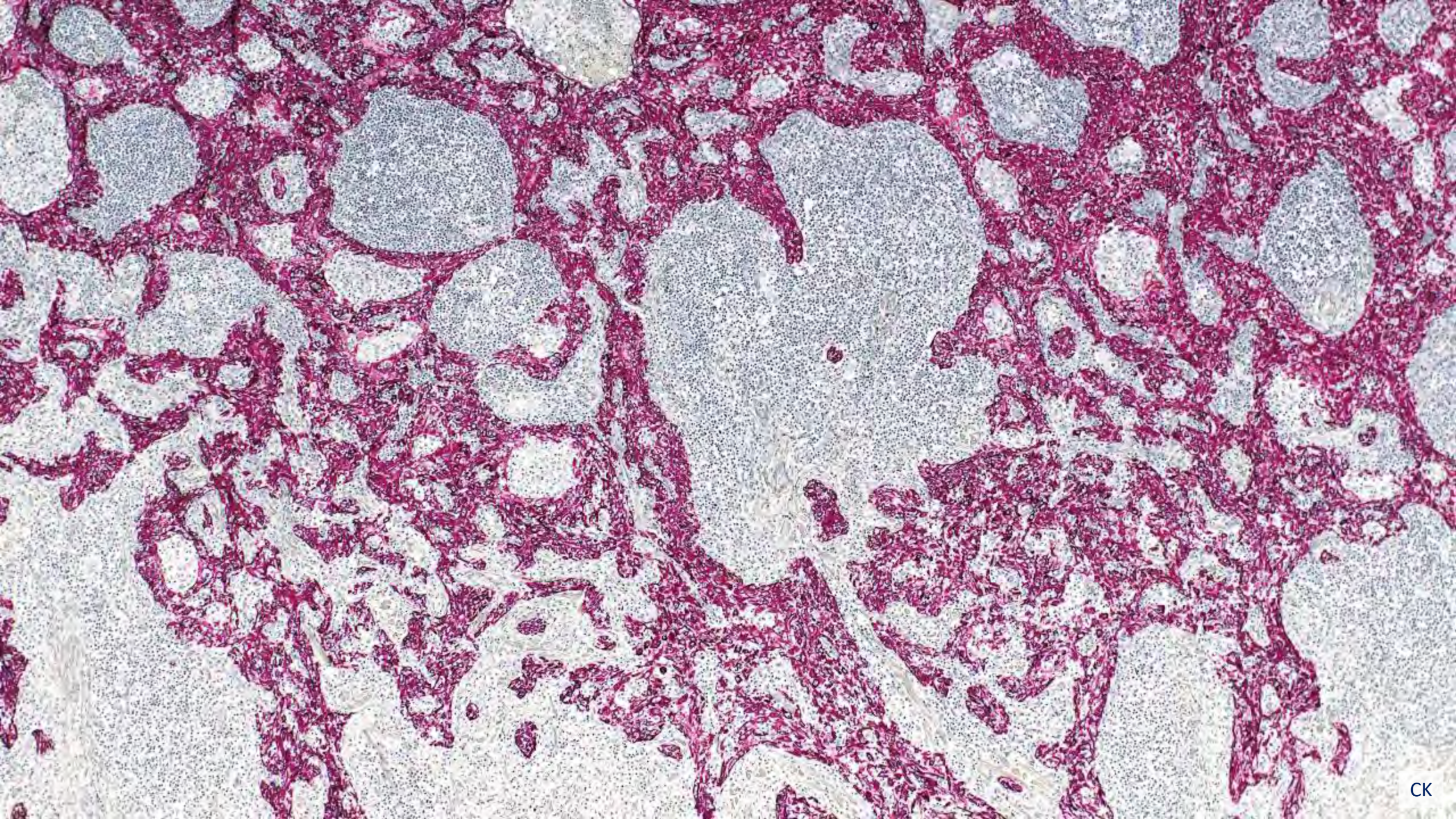
The diagnosis of pilomatrical carcinoma relies on architectural features (asymmetry, poor circumscription) more than on cytological ones; fragmented, incomplete biopsies may be impossible to classify precisely (*in this particular case I favor pilomatricoma; patient alive and well 6 years after the biopsy*). Necrosis en masse, prominent atypia, low proportion of shadow cells, scant stroma represent useful criteria for malignancy. Presence of numerous, scattered dendritic melanocytes maybe observed in pilomatrical carcinoma (it should be underlined that "melanocytic matricoma" represents a variant of pilomatricoma).

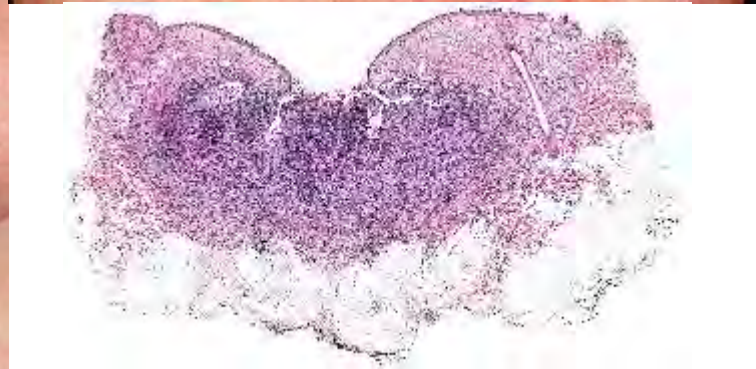


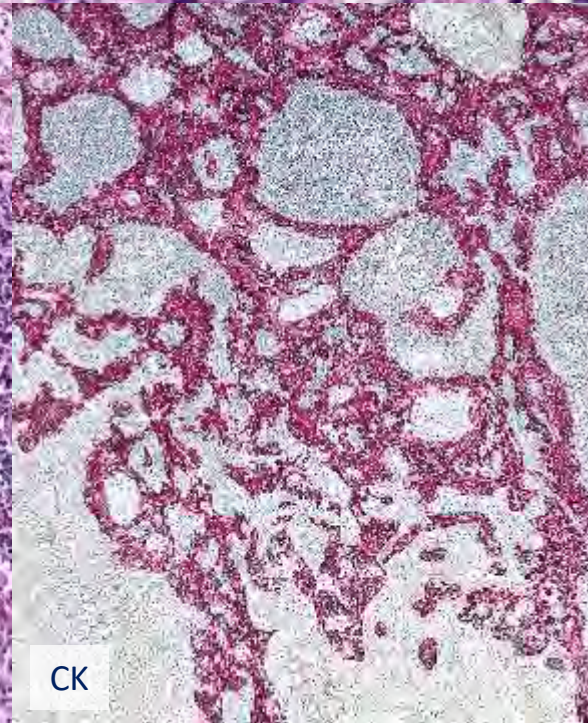
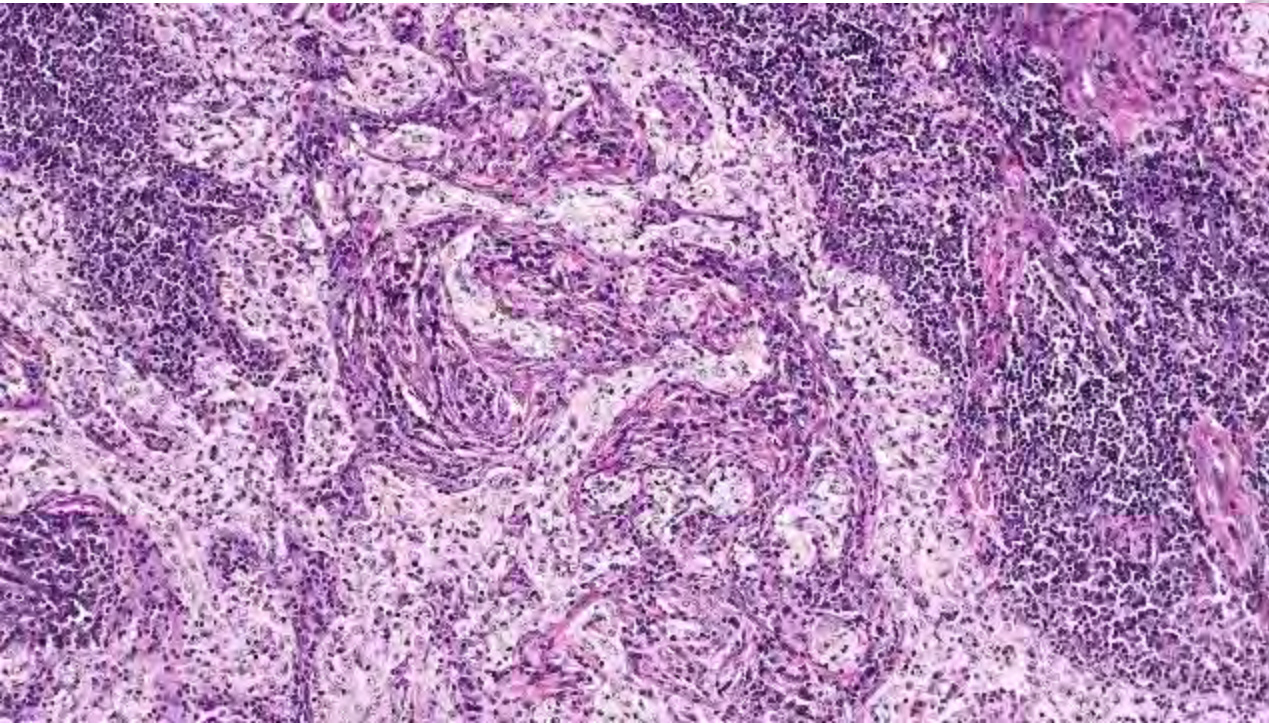
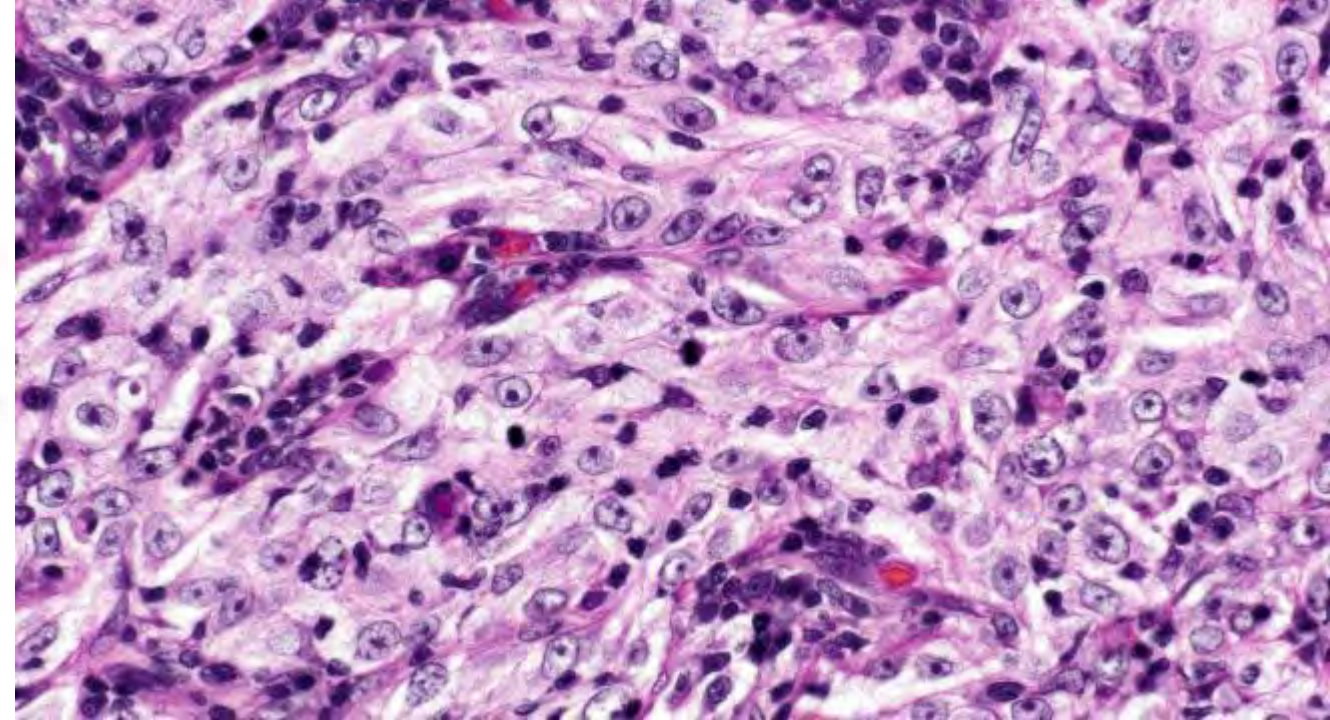
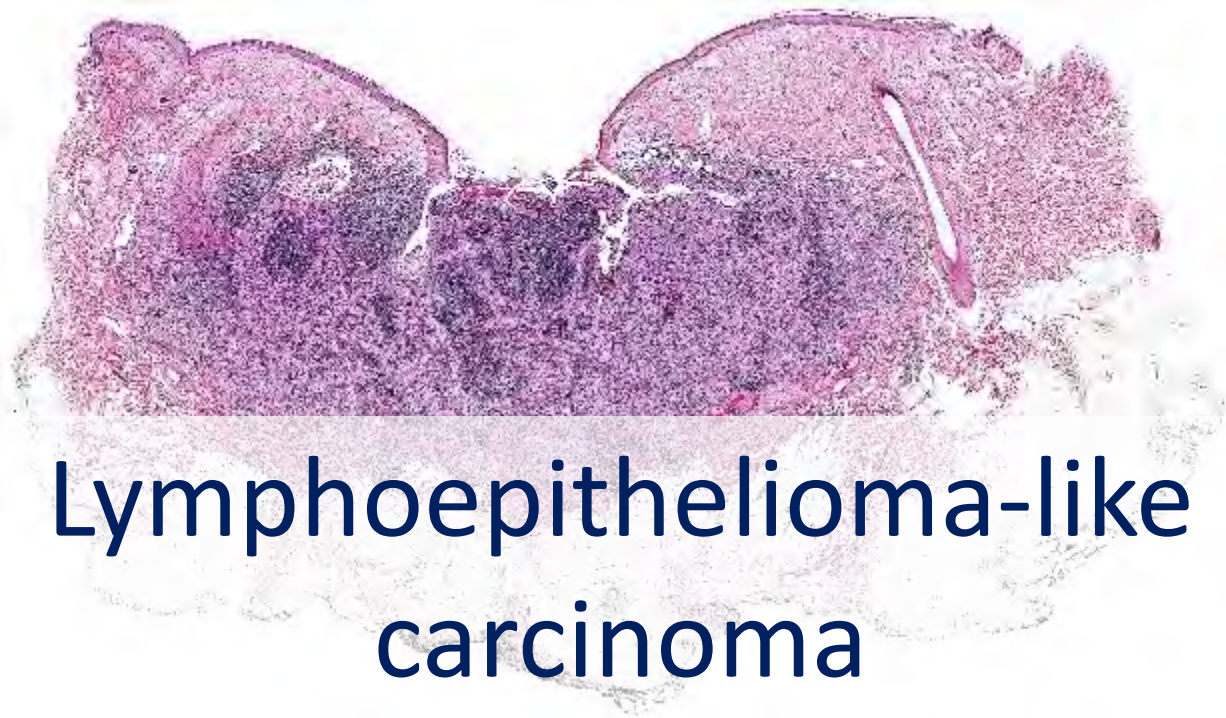
Case 43

M, 86. Comes for excision of a lesion
reported as SCC on an external biopsy.









Lymphoepithelioma-like carcinoma

- Head & neck, elderly; very rare
- Local spread, very rarely metastases
- Lymphoid infiltrate mixed (B- and T-lymphocytes); may mask the epithelial component
- EMA+, CK+, EBV—
- No squamous differentiation
- Unknown origin

Lymphoepithelioma-like carcinoma of the skin: A light-microscopic and immunohistochemical study

Cutaneous carcinoma histopathologically resembling nasopharyngeal carcinoma has been termed lymphoepithelioma-like carcinoma of the skin. We present an additional example of this rare cutaneous neoplasm that was located on the left temple of an 83-year-old woman. Serology for Epstein-Barr virus was negative, and exploration of the nasopharyngeal region disclosed no abnormalities. Histopathologically, the neoplasm consisted of a relatively well-circumscribed, dermal-hypodermal nodule composed of irregular aggregates of epithelial cells with vesicular nuclei, some of them in mitosis, and scant cytoplasm. A dense lymphocytic infiltrate was present within the neoplastic aggregates, obscuring the epithelial component, and at scanning magnification, the lesion closely resembled cutaneous lymphoma or pseudolymphoma. There was focal sebaceous differentiation. Immunohistochemistry showed positivity in the epithelial component for AE1/AE3 and AEB 903 cytokeratins and negativity for 8–18 cytokeratins. The inflammatory infiltrate was positive for leukocyte common antigen, UCHL-1, L26, Leu-22, and OPD-4 in variable proportions. Scattered cells within this inflammatory infiltrate were also positive for S-100 protein, vimentin, HAM-56, and MAC-387. *In situ* hybridization investigations for the presence of Epstein-Barr virus genomic DNA yielded negative results. Lymphoepithelioma-like carcinoma of the skin is a distinct cutaneous neoplasm of unknown histogenesis, although some foci of adnexal differentiation have been found in some specimens. The possibility of cutaneous metastasis from occult nasopharyngeal carcinoma should be ruled out.

Requena I, Sánchez Yus E, Jiménez E, Roo E. Lymphoepithelioma-like carcinoma of the skin: A light-microscopic and immunohistochemical study. *J Cutan Pathol* 1994; 21: 541–548. © Munksgaard, 1994.

Luis Requena¹,
Evaristo Sánchez Yus²,
Esther Jiménez³ and Elia Roo²

Departments of Dermatology ¹Hospital de Jiménez Díaz, Clínica de la Concepción, Universidad Autónoma, ²Hospital Universitario San Carlos, Universidad Complutense, Madrid, Spain.

Luis Requena, c/o Leopoldo Mes, Clam 4 194,
28035-Madrid, Spain

Accepted June 10, 1994

"Lymphoepithelioma-like carcinoma of the skin is a distinct cutaneous neoplasm of unknown histogenesis, although some foci of adnexal differentiation have been found in some specimens."

In 1958, Swanson et al. published findings on five examples of an uncommon cutaneous carcinoma. The lesions were situated on sun-exposed areas of elderly patients. Histopathologically, the neoplasms consisted of irregular dermal aggregates of neoplastic cells with no connections to the epidermis. Neoplastic cells showed vesicular nuclei with prominent nucleoli and moderate amounts of eosi-

nophilic cytoplasm. Some of these cells exhibited atypical mitotic figures. A dense lymphoid infiltrate involved aggregates of neoplastic cells, obscuring their epithelial appearance and, at first glance, the neoplasm could be misinterpreted as cutaneous lymphoma or pseudolymphoma. The histopathologic appearance of these carcinomas closely resembled nasopharyngeal lymphoepithe-

Absence of Epstein–Barr Virus, Human Papillomavirus, and Simian Virus 40 in Patients of Central European Origin With Lymphoepithelioma-like Carcinoma of the Skin

Dmitry V. Kazakov, MD, Jana Nemcova, MSc, Iva Mikyskova, MSc, and Michal Michal, MD

Abstract: The authors report 10 cases of lymphoepithelioma-like carcinoma (LELC) of the skin and the results of a molecular biological study for HPV, EBV, and SV40 in lesional tissues. All patients originated from Central Europe. There were seven men and three women, ranging in age from 57 to 86 years. Locations included the face (n = 4), scalp (n = 2), penis (n = 2), and retroauricular area (n = 1); location was unknown for one subject. All but two patients presented with a tumor confined to the skin; in both patients with the penile carcinoma, the tumors had metastasized to an inguinal lymph node. Six patients with available follow-up included four individuals with no evidence of tumor metastasis or recurrences at 2, 3, 4, and 5 years, one patient who died with metastatic disease 7 years after diagnosis, and one patient who died of an unrelated course. Microscopically, all cases showed distinctive features of LELC characterized by variably sized and shaped nodules or syncytial sheets of epithelial cells that contained vesicular chromatic and prominent nucleoli and that were permeated and surrounded by small, well-differentiated lymphocytes and plasma cells. Because all 10 cases studied proved negative for EBV, HPV, and SV40, these viruses seem to play no causal role in LELC of the skin in patients from Central Europe.

Key Words: lymphoepithelioma-like carcinoma, Epstein–Barr virus, human papillomavirus, simian virus 40, squamous-cell carcinoma, adnexal tumors

(*Am J Dermatopathol* 2007;29:365–369)

Lymphoepithelioma-like carcinoma (LELC) of the skin is a rare, cutaneous neoplasm with a microscopic resemblance to undifferentiated carcinoma of the nasopharynx. A recent review of the literature performed by Fenniche et al¹ disclosed only 36 cases of LELC reported to have occurred in the skin^{2–21}; an additional case was reported afterwards.²² The histogenesis of the neoplasm is uncertain. It has been suggested that in the skin, this tumor may represent a morphological pattern rather than a distinct clinicopathological entity, but some authors have speculated on the relationship between LELC and adnexal neoplasms.^{5,8,20} Tumors with

morphological features identical to undifferentiated carcinoma of the nasopharynx may occur in other organs, including the salivary glands, thyroid, thymus, trachea, lungs, uterine cervix, vulva, vagina, breasts, stomach, biliary tree, intestine, prostate, and urinary bladder. In some anatomic sites—namely, the stomach, salivary gland, lung, and thymus—they seem to be associated with Epstein–Barr virus (EBV) infection.^{23–26} Racial and/or geographic factors seem to influence the association of EBV with LELC in some of these organs. Previous studies from different geographic regions have demonstrated repeatedly that LELC of the skin is not associated with EBV.^{1,14,21} The role of other oncogenic viruses has not been studied. Our aim was to investigate a potential causal role of human papillomavirus (HPV) and simian virus 40 (SV40) in the origins of cutaneous LELC. We also aimed to check for EBV in our patients who were of Central European origin—the population that has not been well studied previously for EBV DNA presence in cutaneous LELC.

MATERIAL AND METHODS

Among 19 cases of LELC of the skin stored in our consultation files between 1996 and 2004, 10 cases were available with paraffin blocks. The original hematoxylin- and eosin-stained and immunohistochemical slides from all patients were retrieved and reexamined to confirm the diagnosis. In seven cases, only a single paraffin block was available for molecular genetics studies; in the remaining three cases, tissues from two blocks for each case were studied. In addition, two patients had metastatic carcinoma to regional lymph nodes, and the tissue from the lymph node metastasis was investigated in one of them.

DNA Extraction and Control Gene Amplification

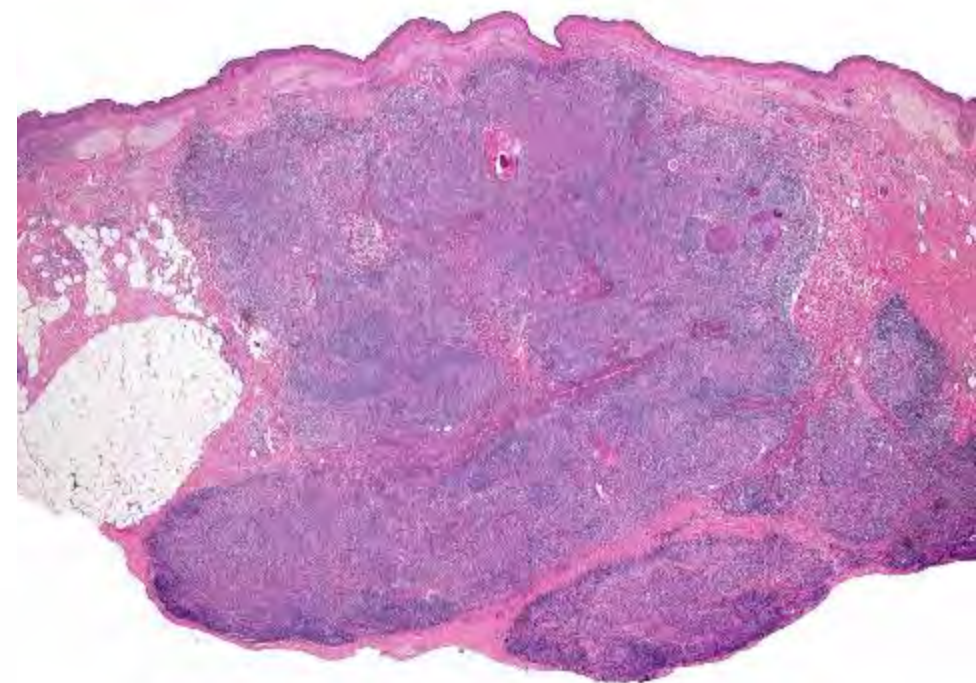
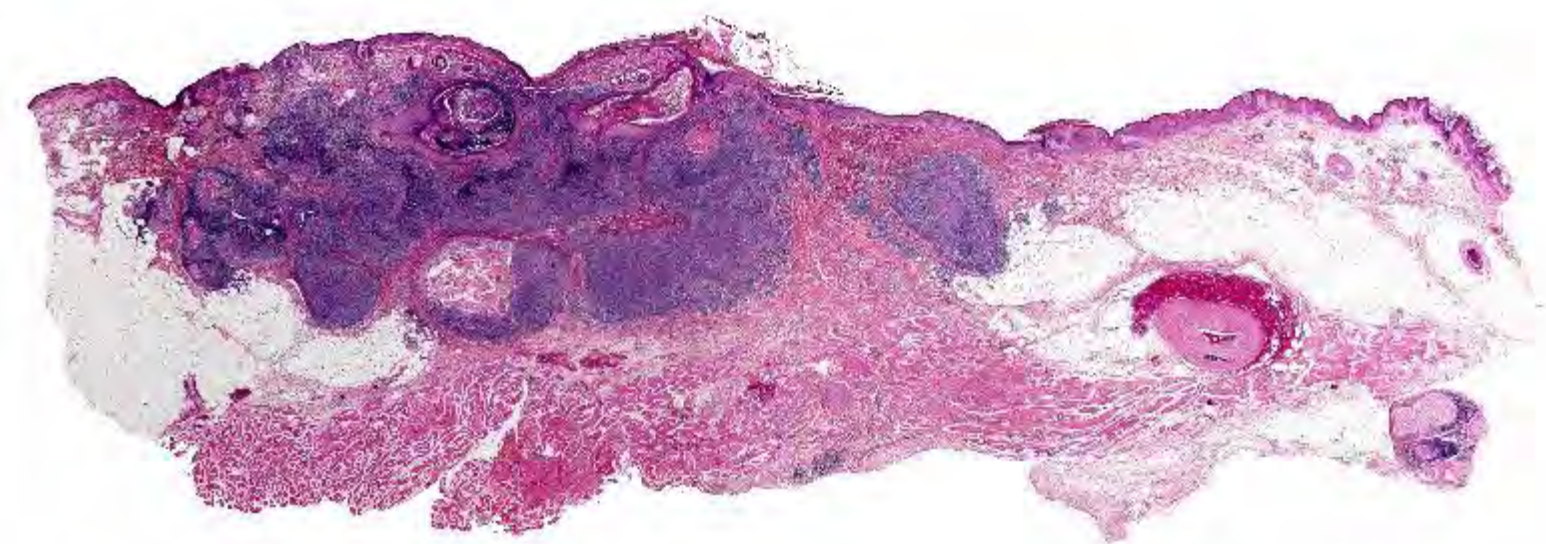
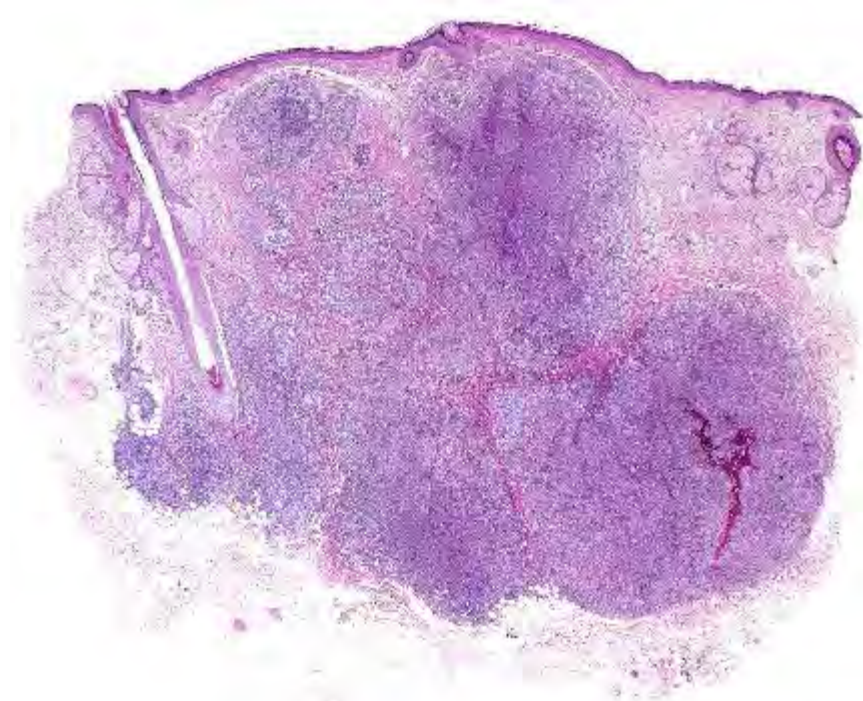
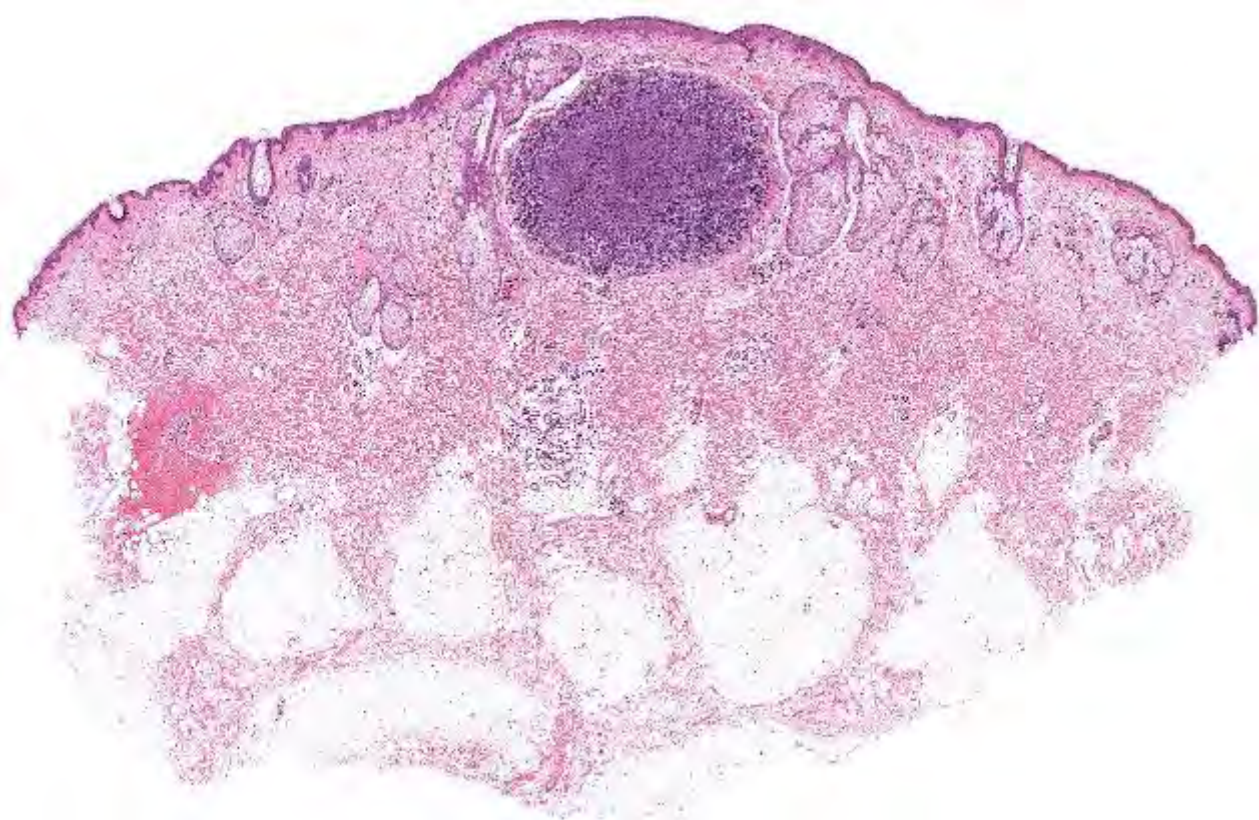
From the blocks, two 20 μ m sections were taken. Before cutting each sample, the microtome knife was cleaned by xylene and ethanol to prevent cross-contamination. Paraffin with no histological tissue was included as a control for contamination. All samples and controls were deparaffinized with xylene and washed with ethanol. Genomic DNA was isolated using a QIAamp Tissue kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. A polymerase chain reaction (PCR) with primers amplifying a 150-bp-long region of the human β -globin gene was performed to check the quality of the extracted DNA and the absence of PCR inhibitors, as described previously.^{27,28}

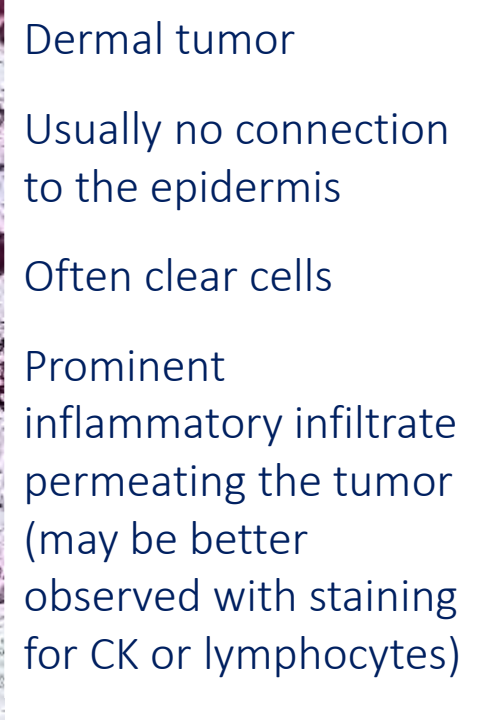
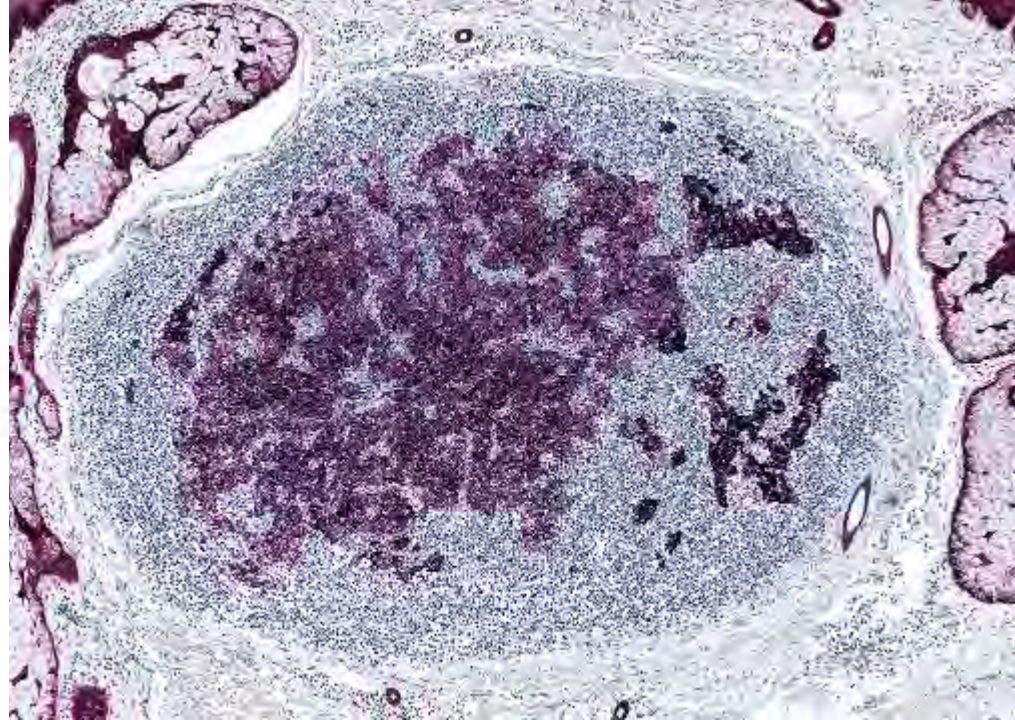
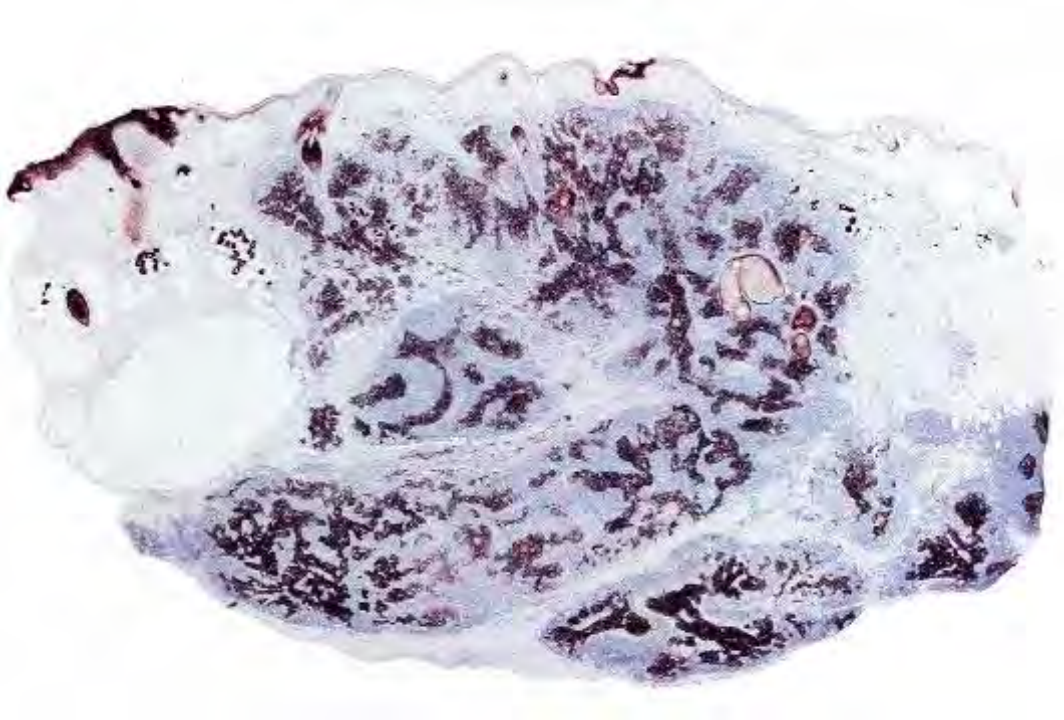
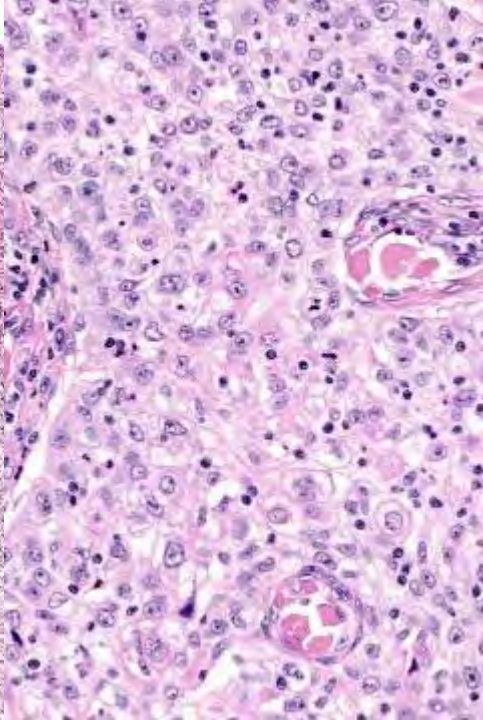
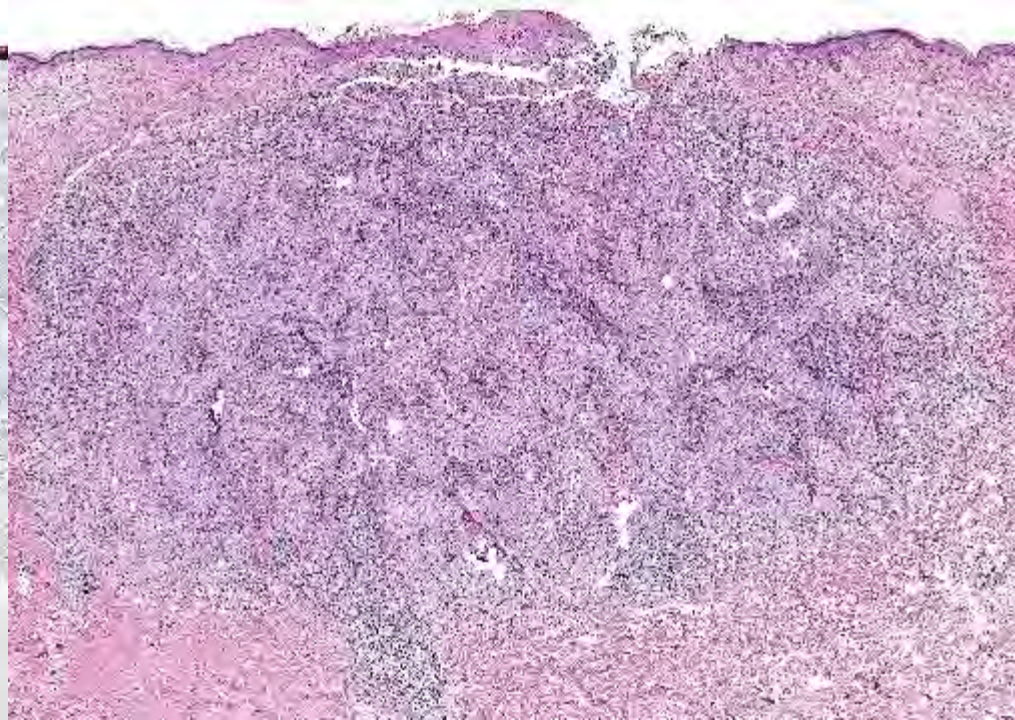
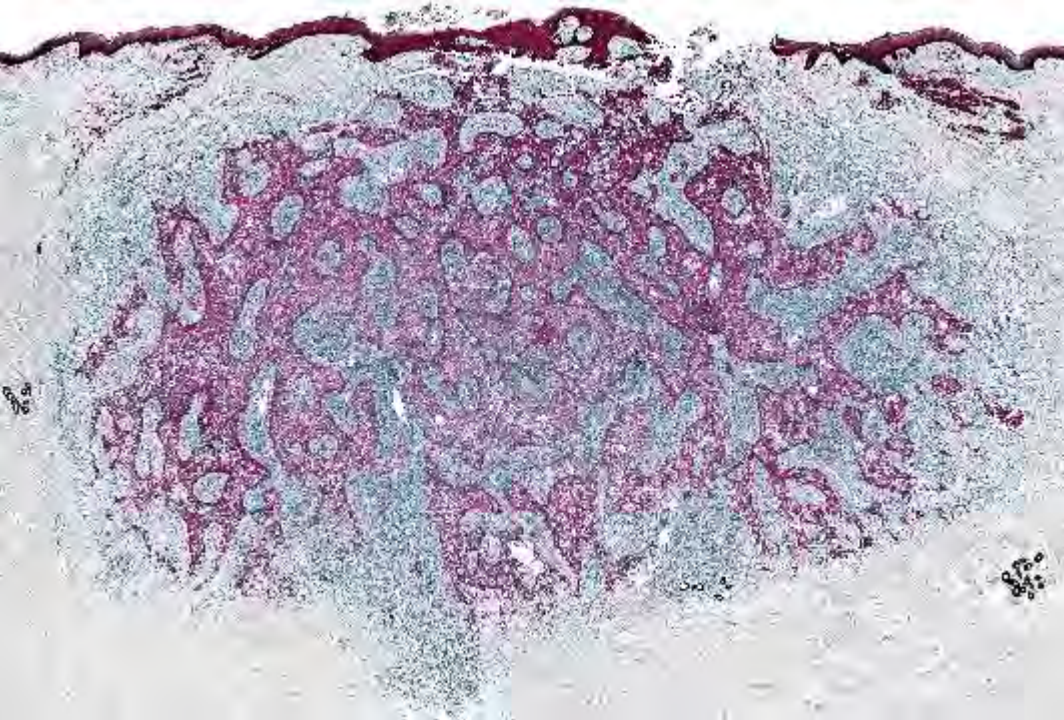
"We agree with those who view LELC of the skin as a morphological pattern rather than a distinct clinicopathological entity, and we think that this tumor in the skin likely represents a variation of squamous-cell carcinoma."

From the Siki's Department of Pathology, Charles University, Medical Faculty Hospital, Pilsen, Czech Republic.

Reprints: Dmitry V. Kazakov, MD, Siki's Department of Pathology, Charles University Medical Faculty Hospital, Alej Svobody 80, 304 60, Pilsen, Czech Republic (e-mail: kazakov@medima.cz).

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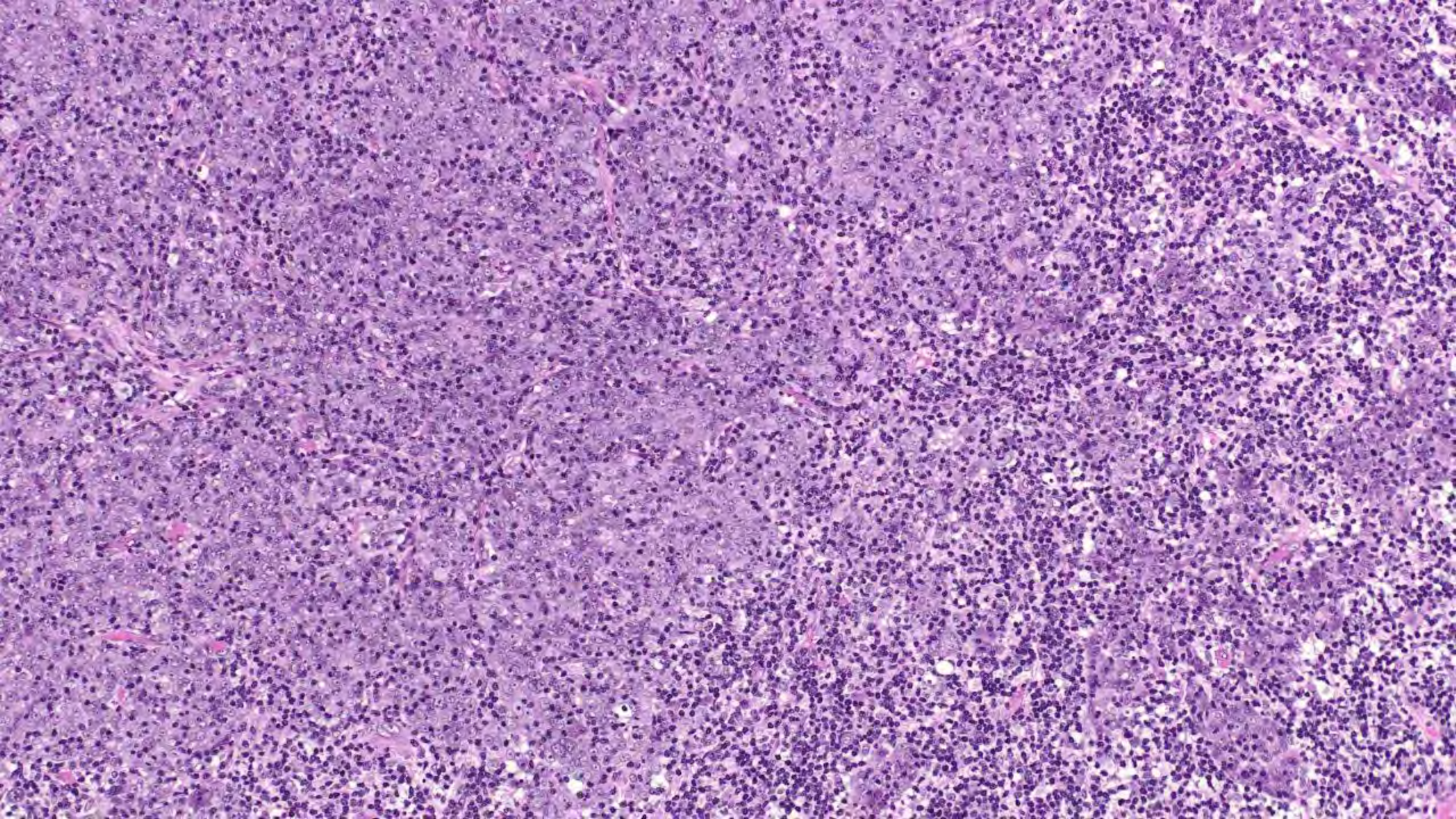


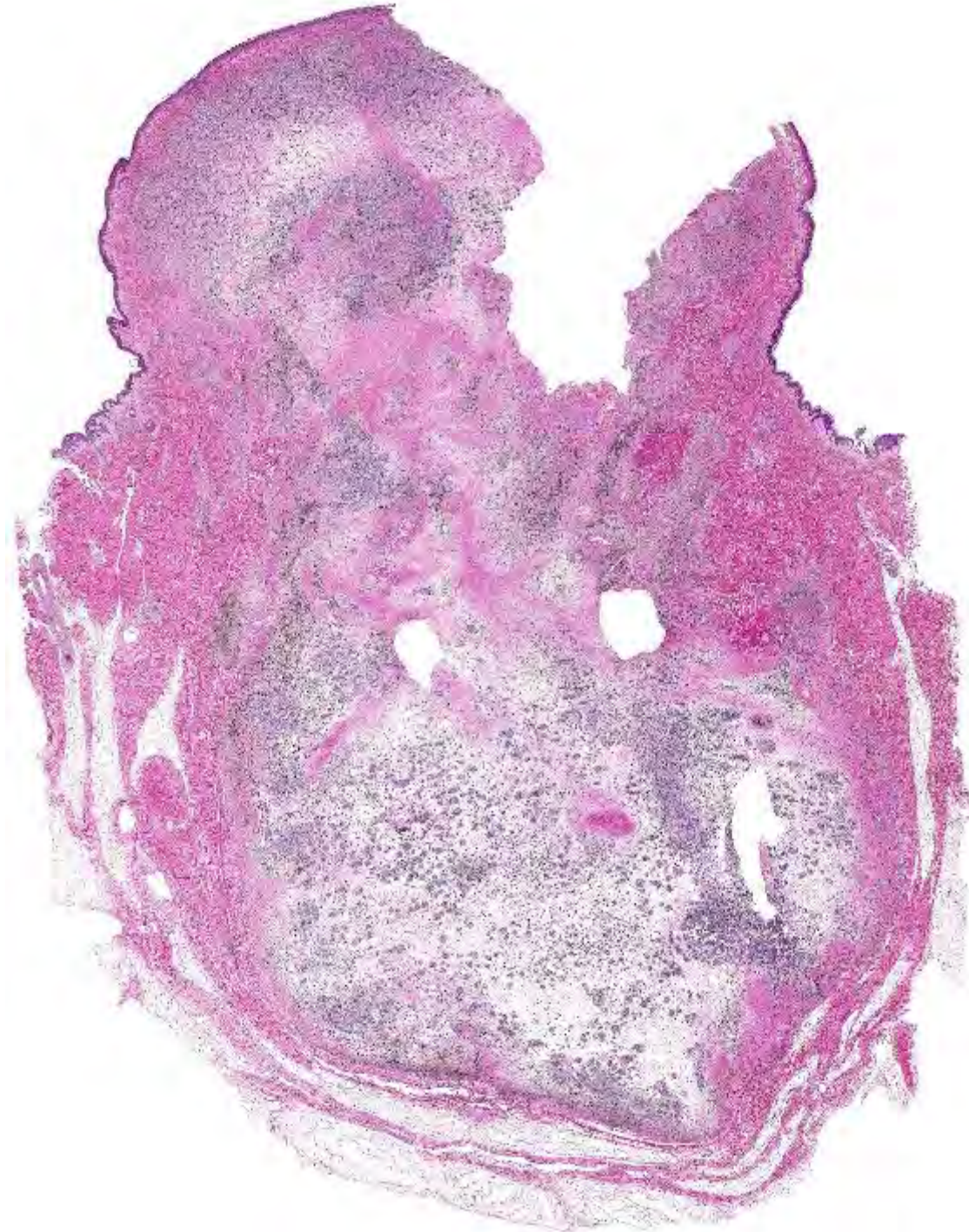
Dermal tumor

Usually no connection to the epidermis

Often clear cells

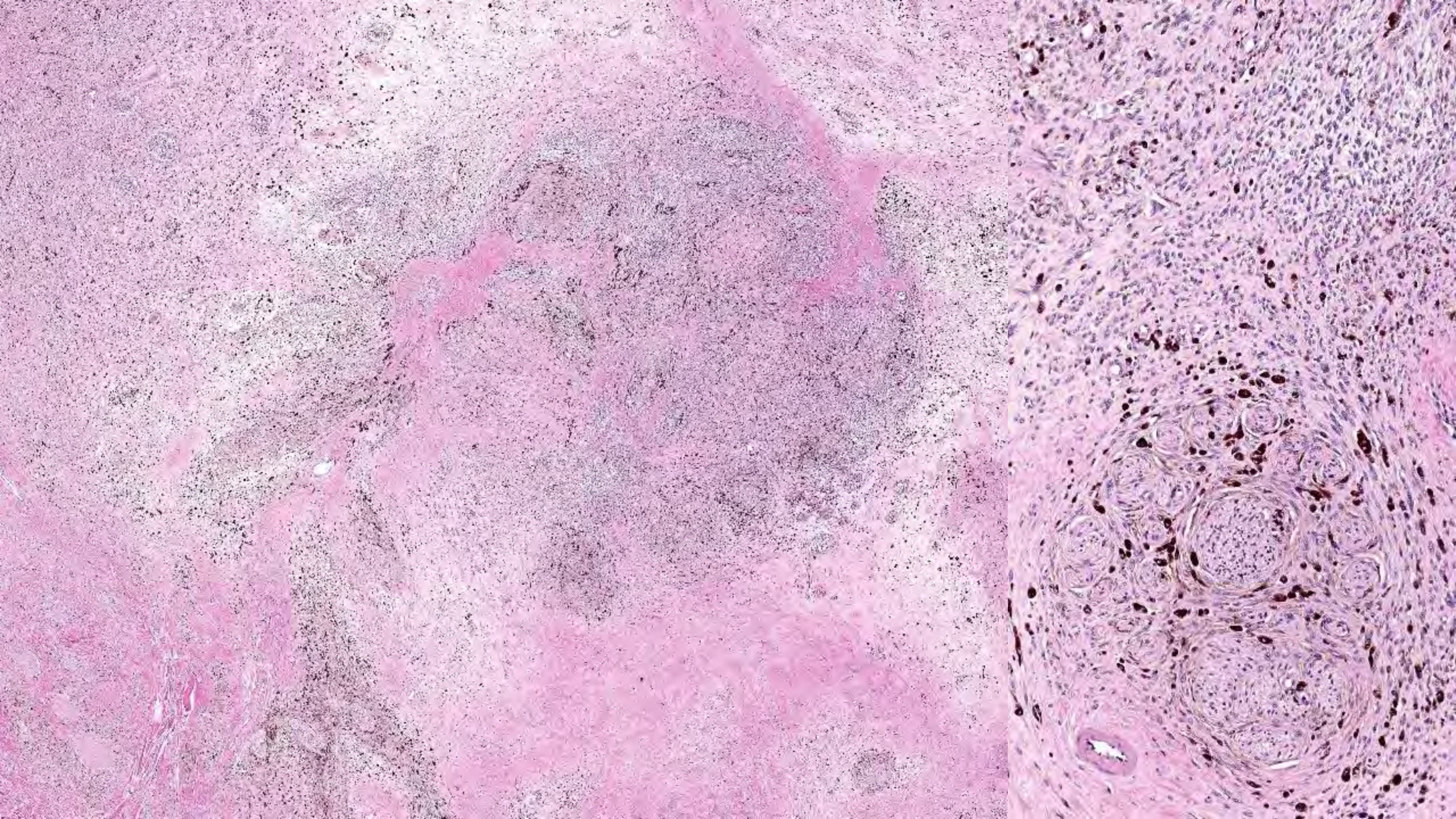
Prominent inflammatory infiltrate permeating the tumor (may be better observed with staining for CK or lymphocytes)

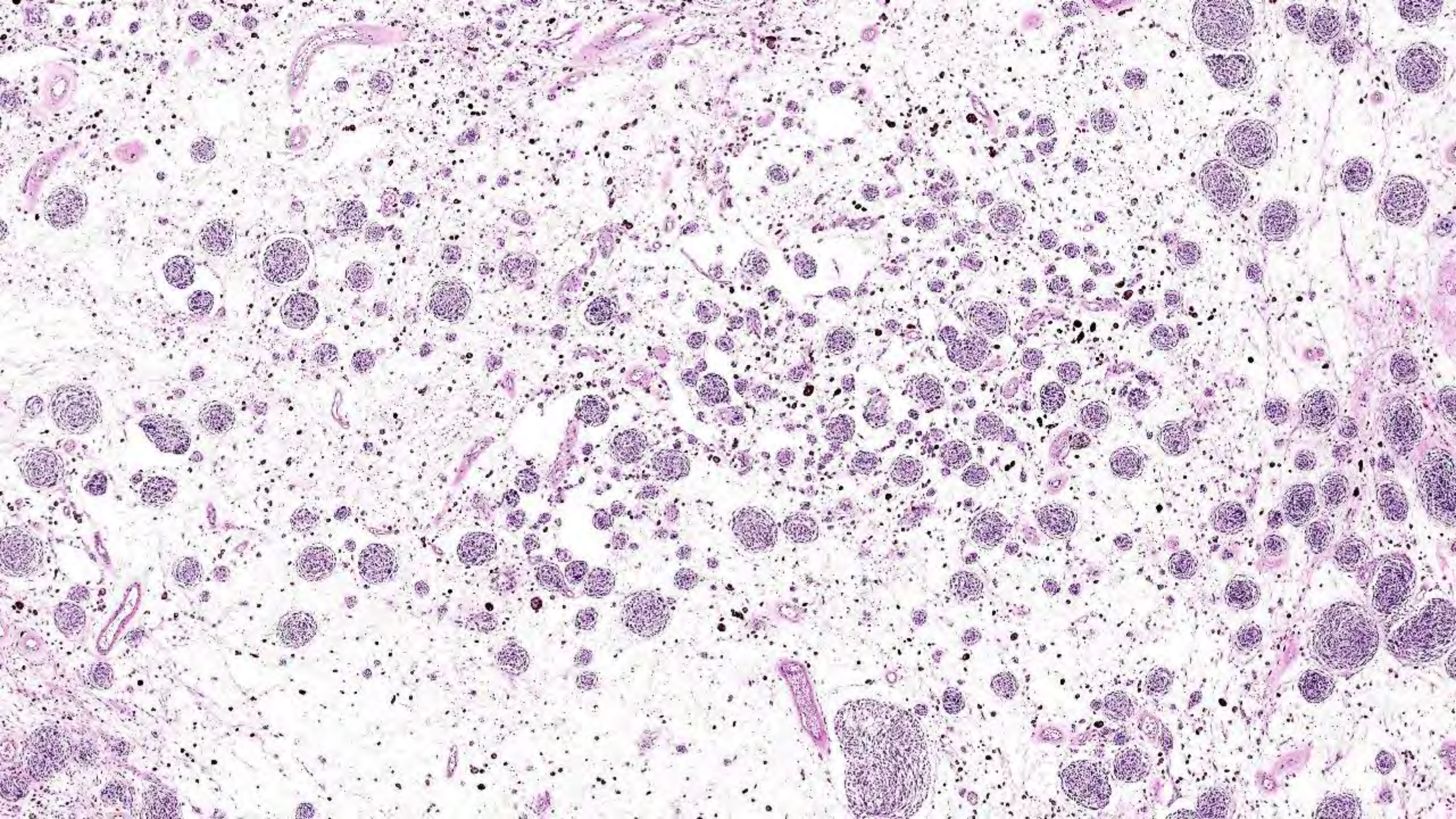


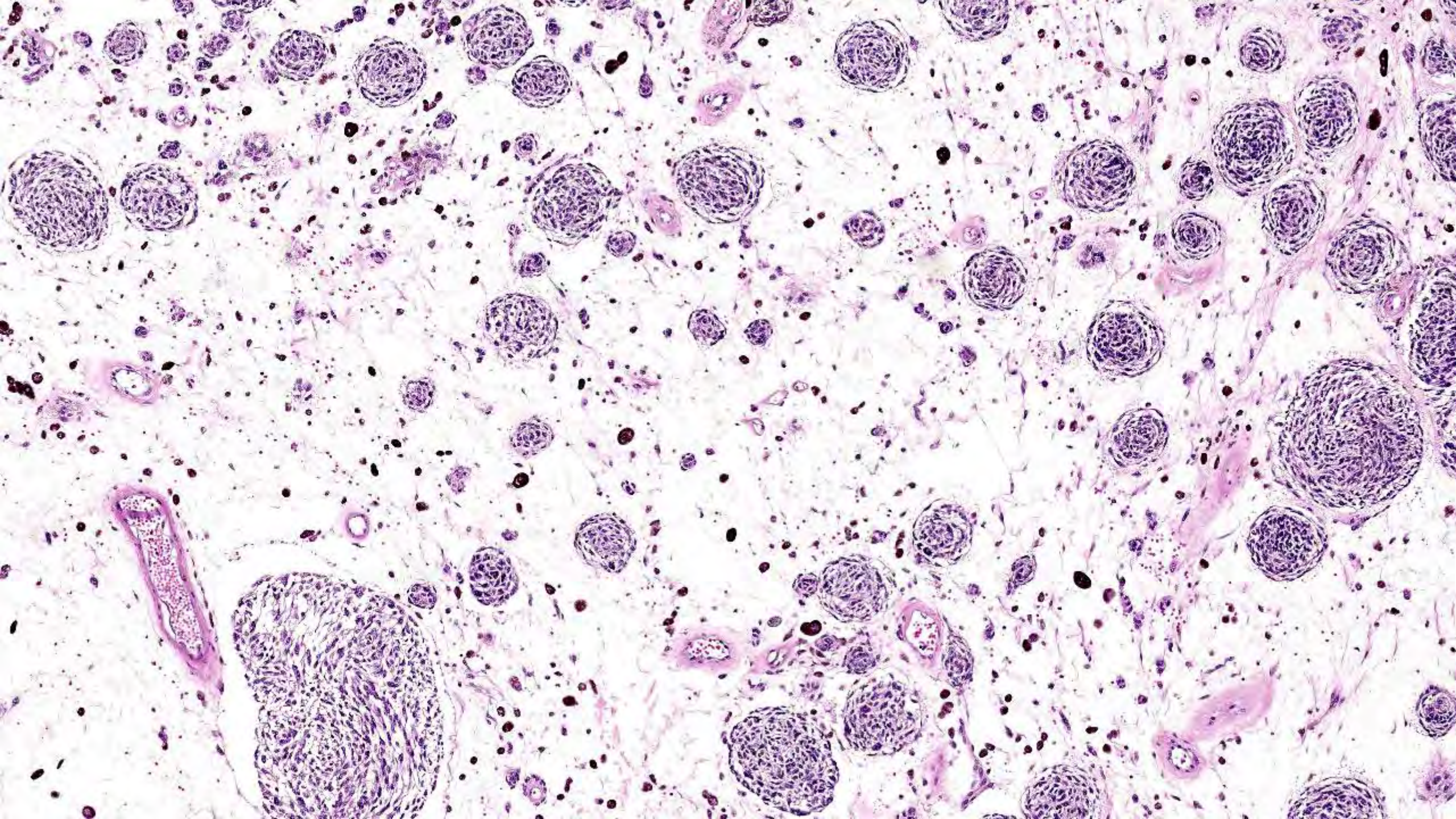


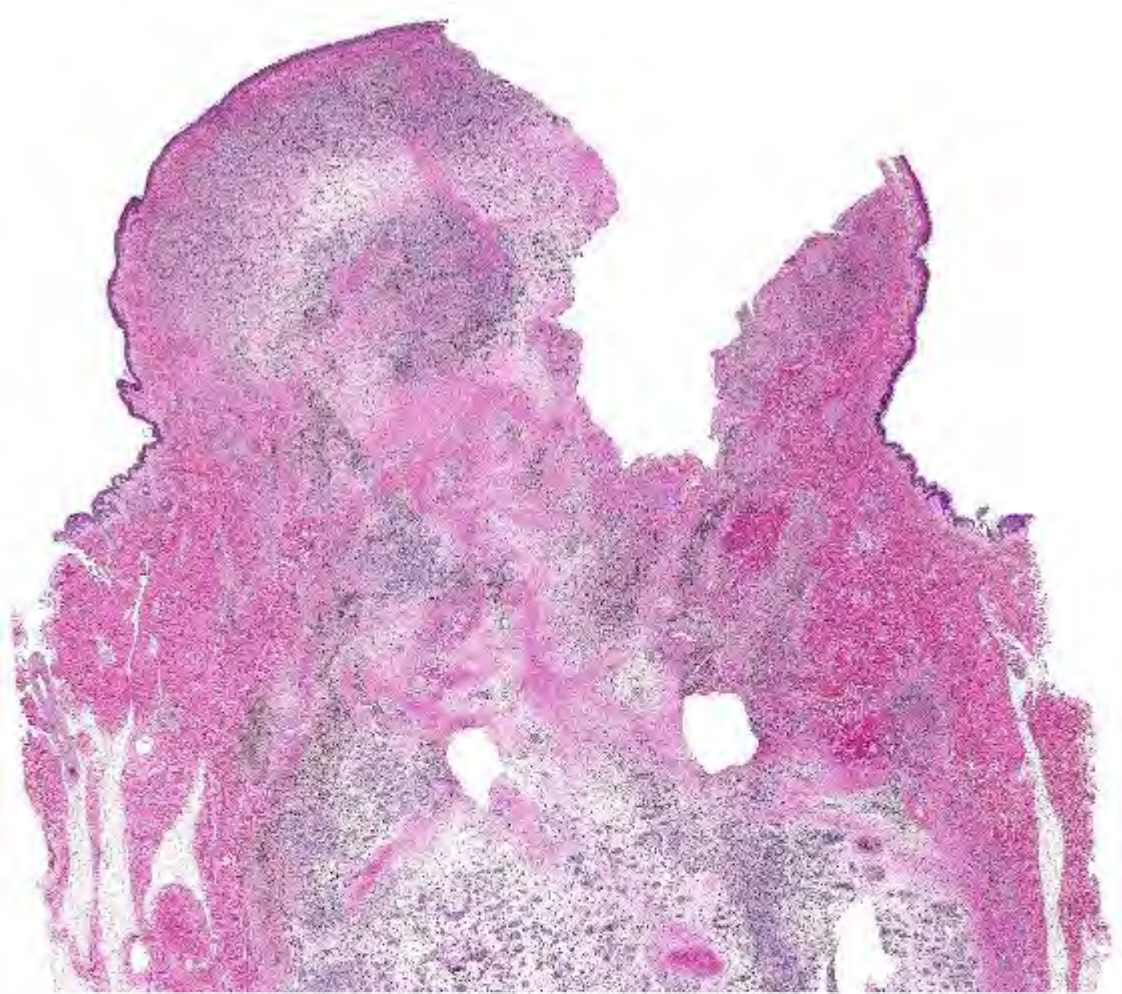
Case 44

F, 40. Large pigmented tumor (>5 cm) on the buttocks.



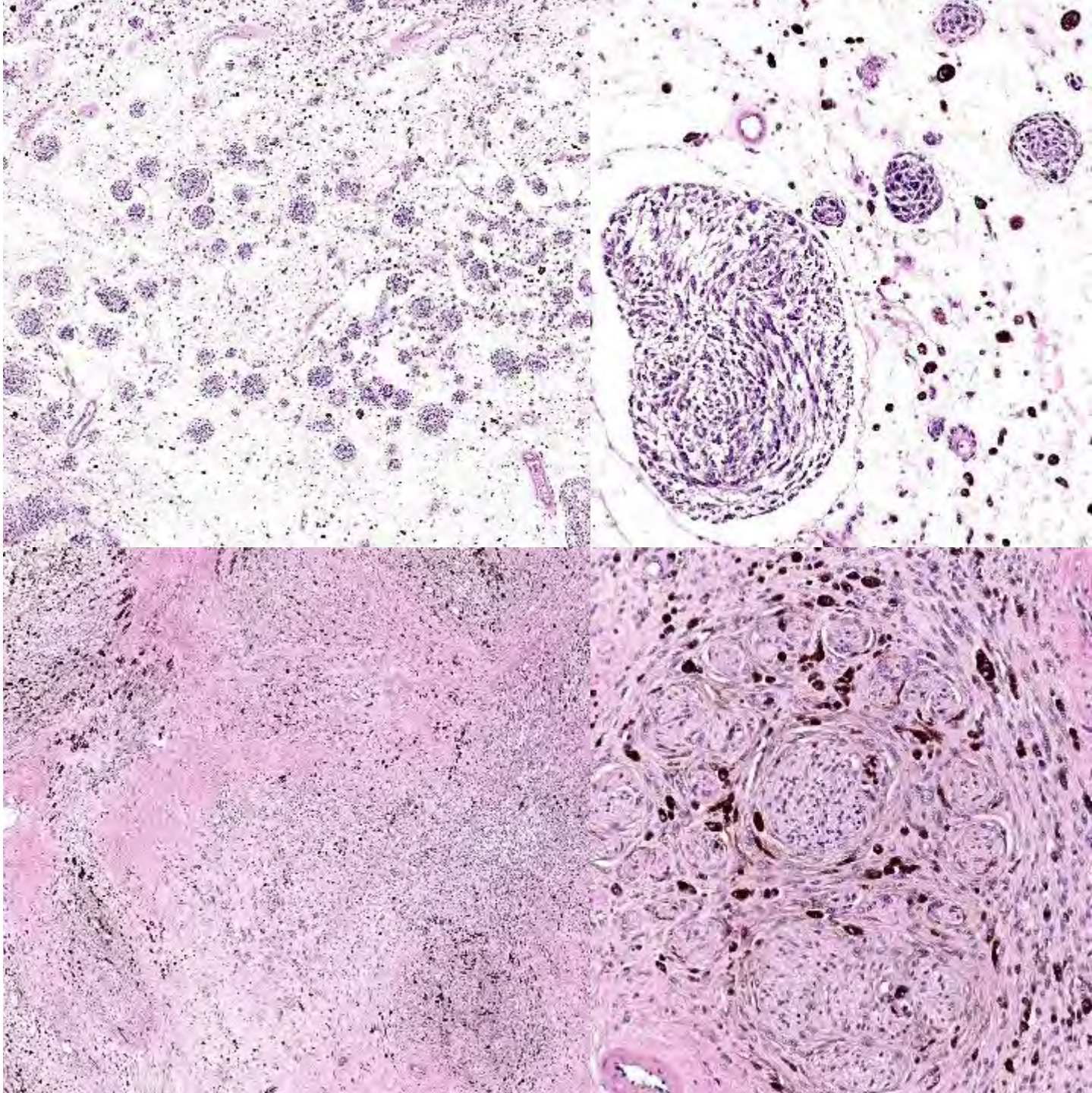






Ancient cellular blue nevus

(ancient neuronevus of Masson)



"Ancient" Blue Nevus (Cellular Blue Nevus With Degenerative Stromal Changes)

Lorenzo Correia, MD,* Riccardo G. Borroni, MD,** Cesare Massone, MD,* and Hebaoui Karl, MD*

Abstract: Ancient melanocytic nevi are benign melanocytic neoplasms that show degenerative and atypical changes sometimes leading to a misdiagnosis of melanoma. We describe 6 patients (M:F ratio 4:2; age range, 15–84 years; median, 50 years) who presented with cellular blue nevus with stromal changes resembling those of ancient melanocytic nevi. The lesions were located on the buttocks (4 patients) and on the trunk (2 patients), and consisted of heavily pigmented nodules. Histology revealed the architectural and cytologic features of blue nevus. However, the architecture was strikingly altered by stromal changes like those seen in ancient melanocytic nevi, including a mixed number of large dilated vessels with pseudothrombotic features in 4 cases, hyaline angiodysplasia in 4 cases, necrotic changes, sclerosis or hyalinization of the stroma in all cases, and variable amounts of edema in 4 cases. In 2 cases, a large edematous area was present in the center of the lesion, and nests of ovaloid melanocytes and single dendritic melanocytes appeared in "islets" in the stroma. Pleomorphic melanocytes were observed in all cases. Ancient blue nevi represent a morphologic variation of cellular blue nevus. Major nevi with degenerative stromal changes. Recognition of these lesions can help prevent overdiagnosis of melanoma.

Key Words: ancient melanocytic nevi, blue nevus, and cellular blue nevus, cutaneous melanoma

(Am J Dermatopathol 2008;30:1–5)

Ancient melanocytic nevi are benign melanocytic neoplasms that show degenerative and atypical changes, thus being sometimes misdiagnosed as melanoma.^{1,2} They are characterized by the presence of different populations of melanocytes, including small dendritic melanocytes and larger pleomorphic cells with a hyperchromatic nucleus, coarse chromatin, and an indistinct nucleolar nucleolus.³ Pseudo-

features with ancient schwannoma.⁴ A list of cutaneous findings with ancient changes is summarized in Table 1.

In this study we describe 6 patients who presented with cellular blue nevus showing stromal changes resembling those of ancient melanocytic nevi.

PATIENTS AND METHODS

Histopathologic specimens of 6 patients with ancient blue nevi were retrieved from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Göttingen. Four of the specimens had been sent for consultation to 2 of the authors (L.C., H.K.). Data of all patients are reported in Table 2.

Paraffin-fixed, paraffin-embedded specimens were available in all cases. Sections of tissue were cut and stained with hematoxylin and eosin. All histopathologic sections were reviewed by 2 of the authors (L.C., R.G.B.) and analyzed for presence or absence of the following features: pseudothrombotic changes, hemorrhage, hyaline angiodysplasia, sclerosis or hyalinization, edema, tumor deposition, and atypical melanocytes.

RESULTS

Clinical findings are summarized in Table 2. Patients consisted of 4 males and 2 females. Their ages ranged from 15 to 84 years (median, 50 years). The lesions were located on the buttocks (4 patients) and the trunk (2 patients) and clinically consisted of heavily pigmented nodules.

The histopathologic findings are summarized in Table 3. On histologic examination, the architecture pattern observed in all cases was that of cellular blue nevi, namely of the so-called Masson's melanocytoma (Fig. 1). However, the architecture was strikingly altered by stromal changes like those seen in ancient melanocytic nevi. The lesions occupied the entire thickness of the dermis and extended to the subcutaneous fat.

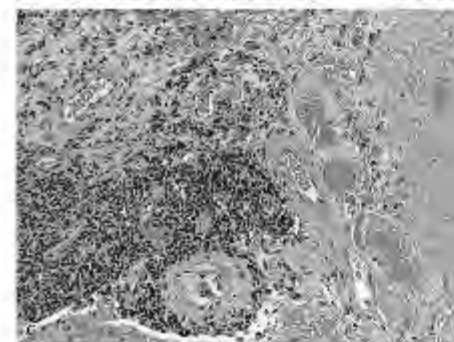
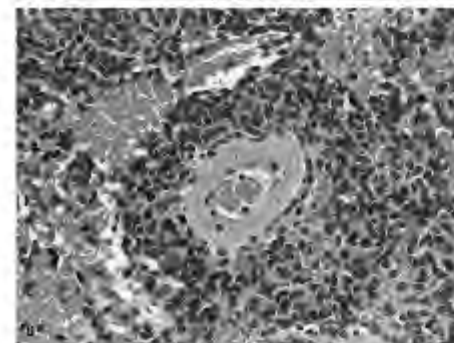
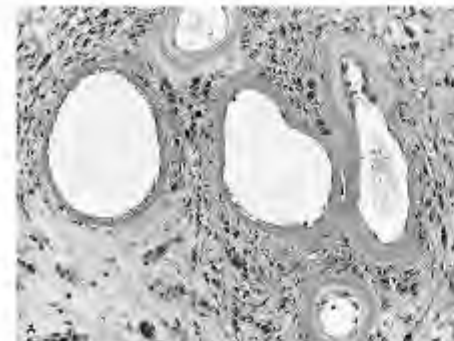


FIGURE 5. A, Hyaline angiodysplasia in case 1. B, Blood vessel with hyaline angiodysplasia surrounded by melanocytes and hemorrhage. C, Marked necrosis with necrotic vessels in the vicinity of vessels with hyaline angiodysplasia (case 5).

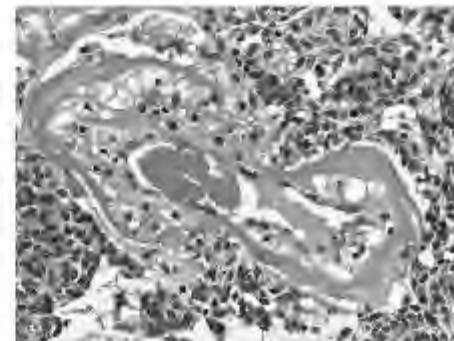


FIGURE 6. Foamy histiocytes with hyalinized vessel walls (case 5).

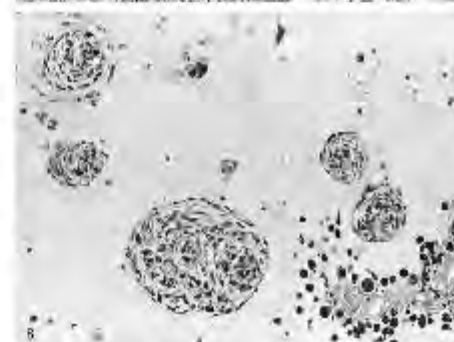
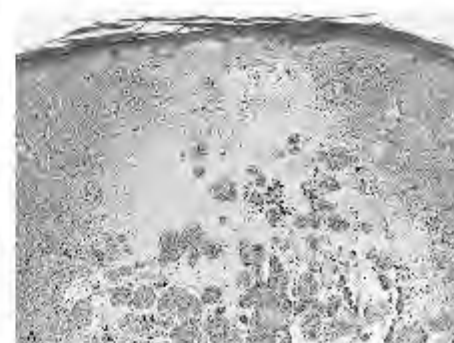
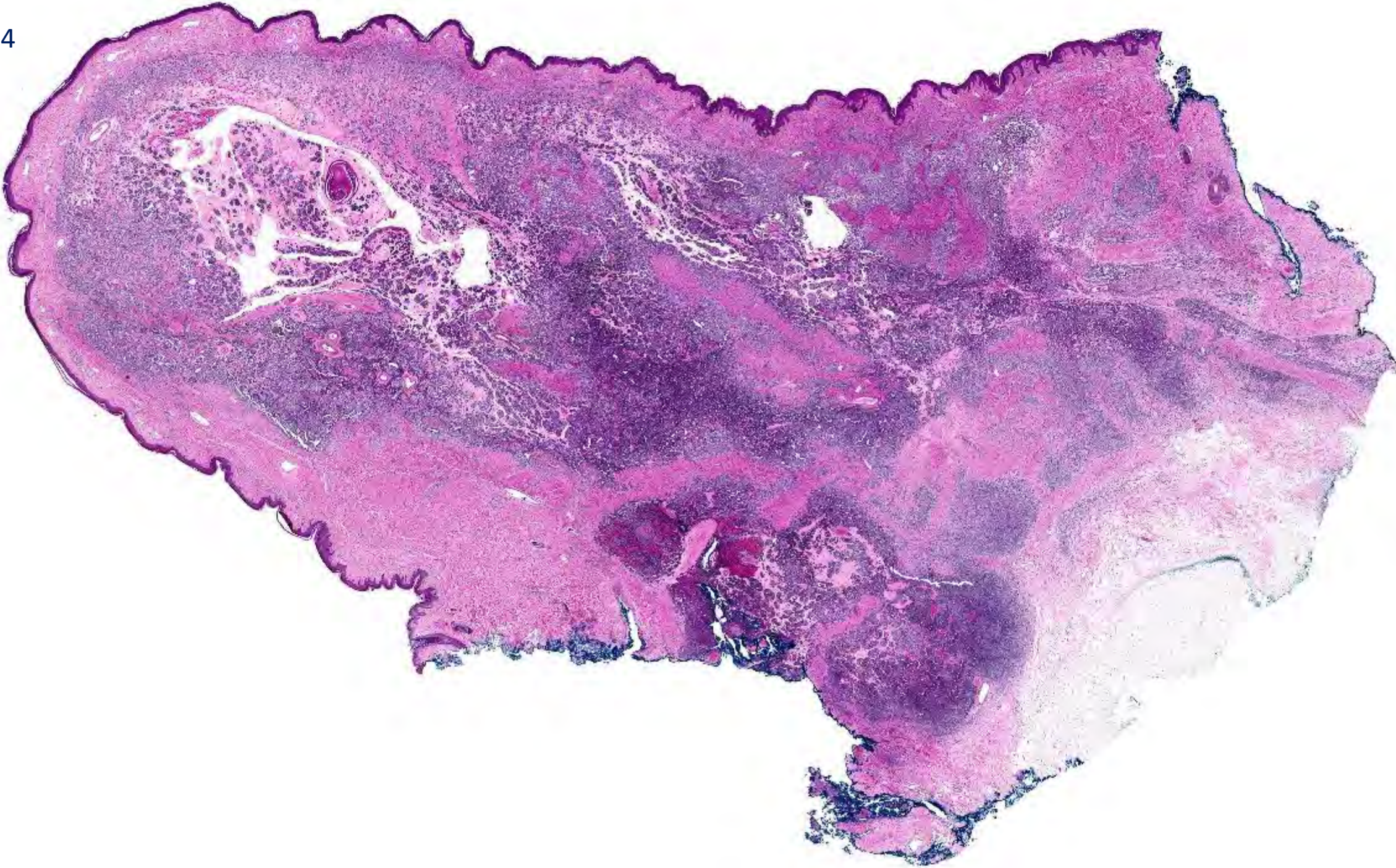


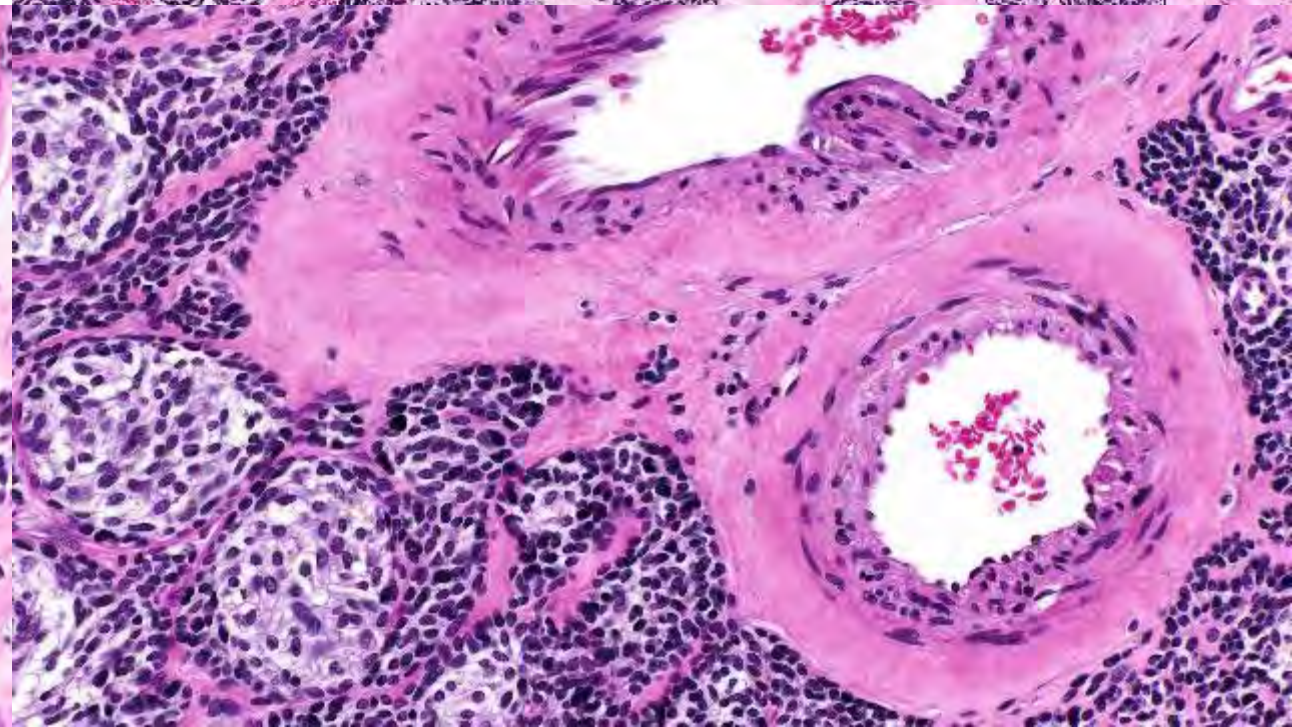
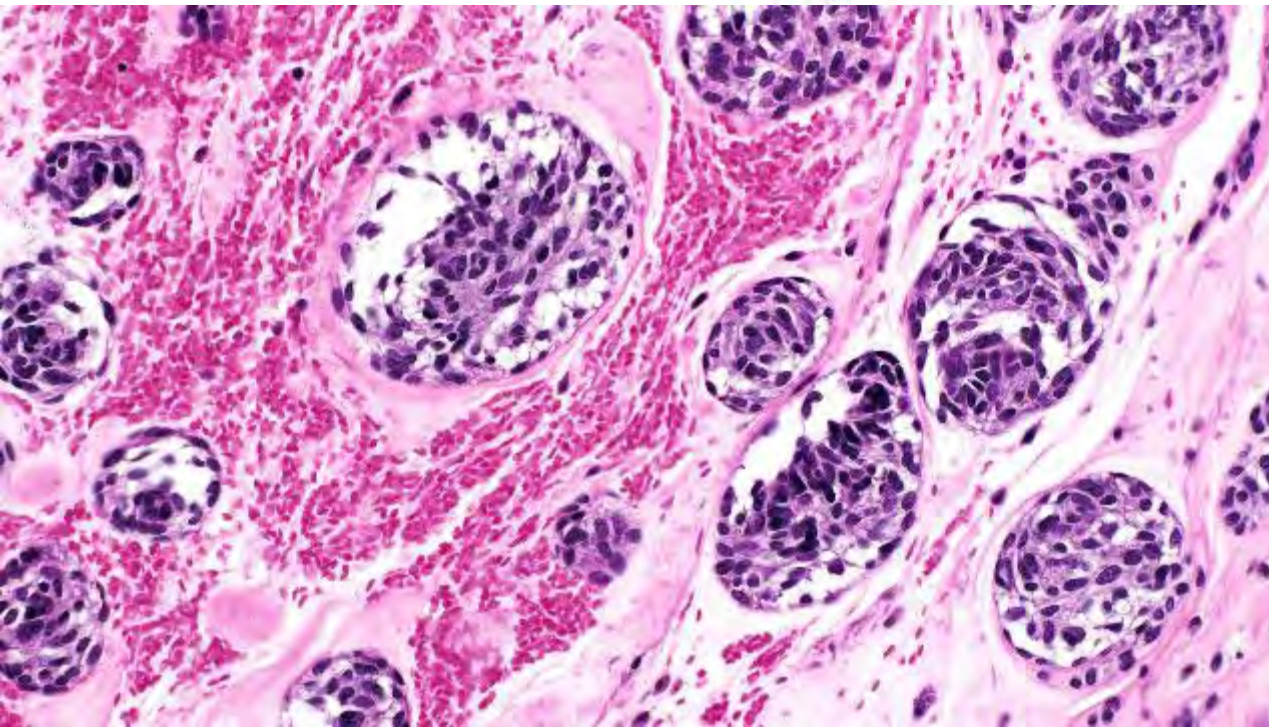
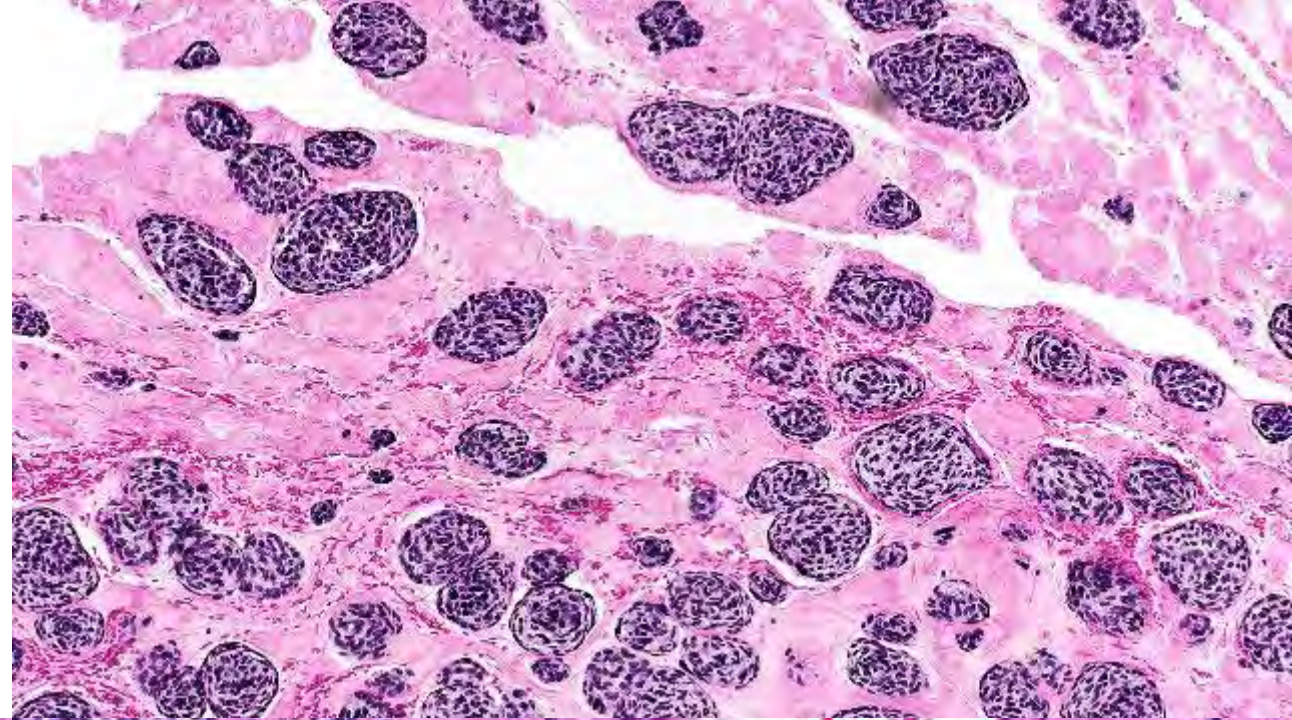
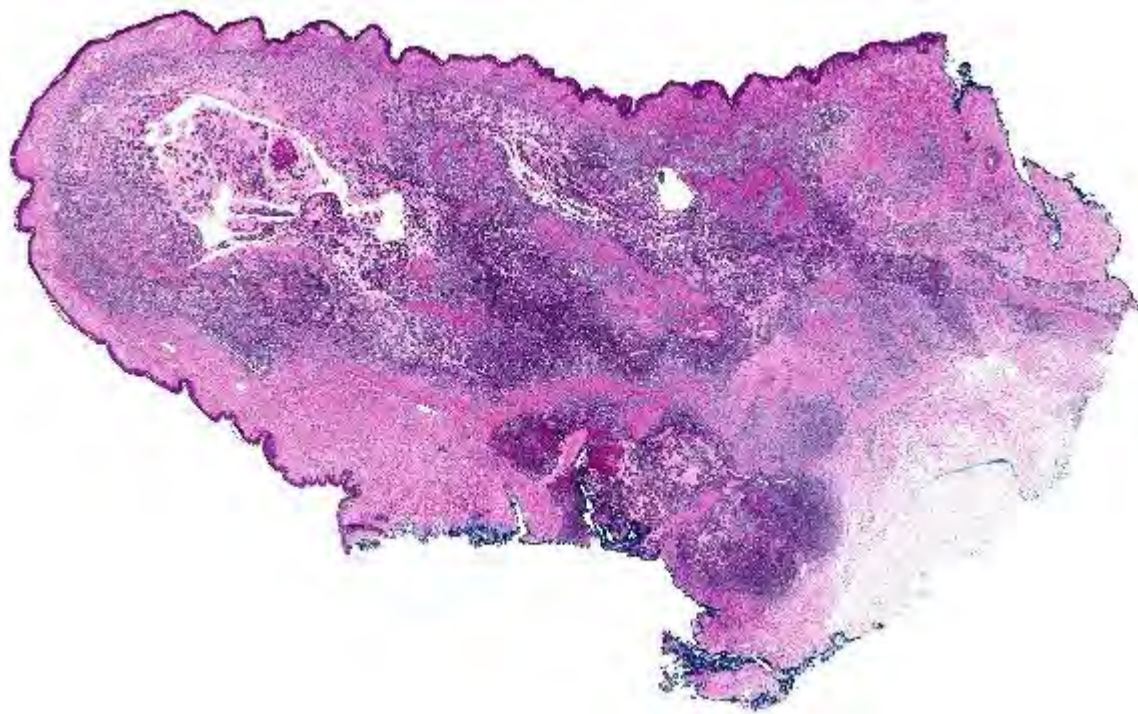
FIGURE 7. Large edematous area (A), with nests of melanocytes floating within abundant edema (B) (case 2).

TABLE 2. Clinical and Histopathologic Features of Ancient Blue Nevus

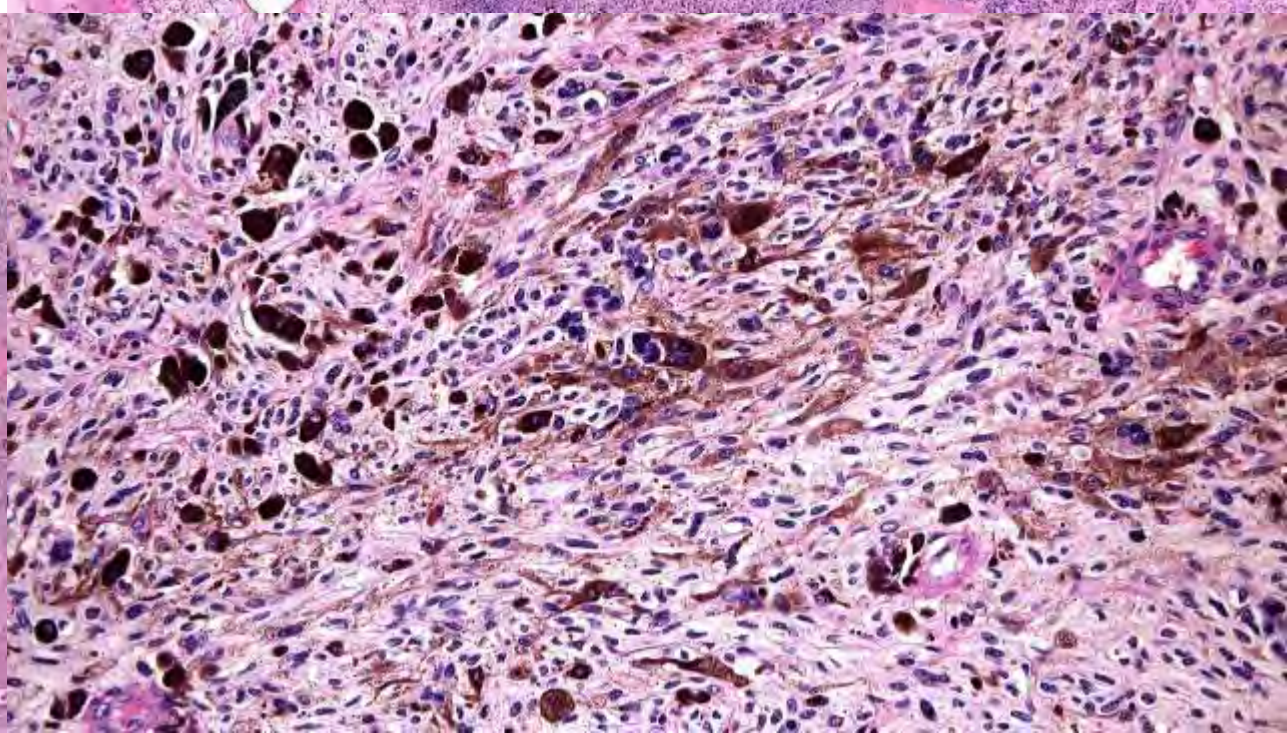
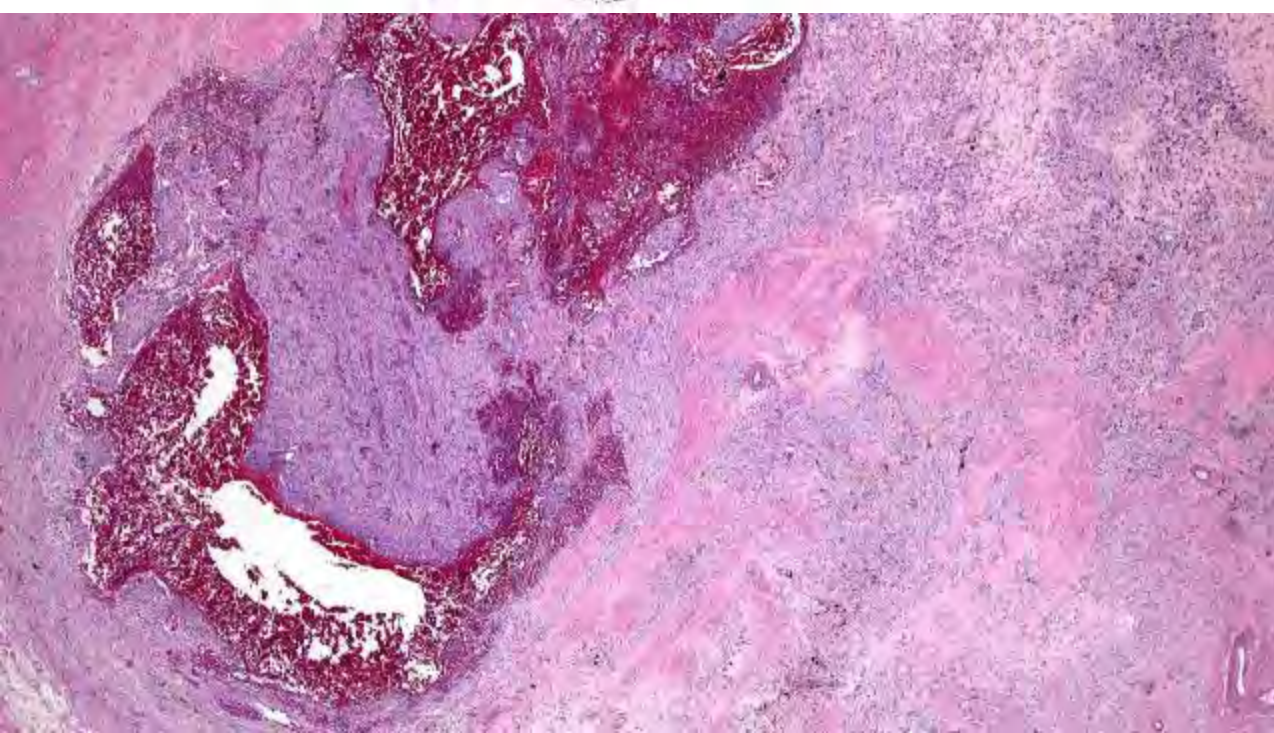
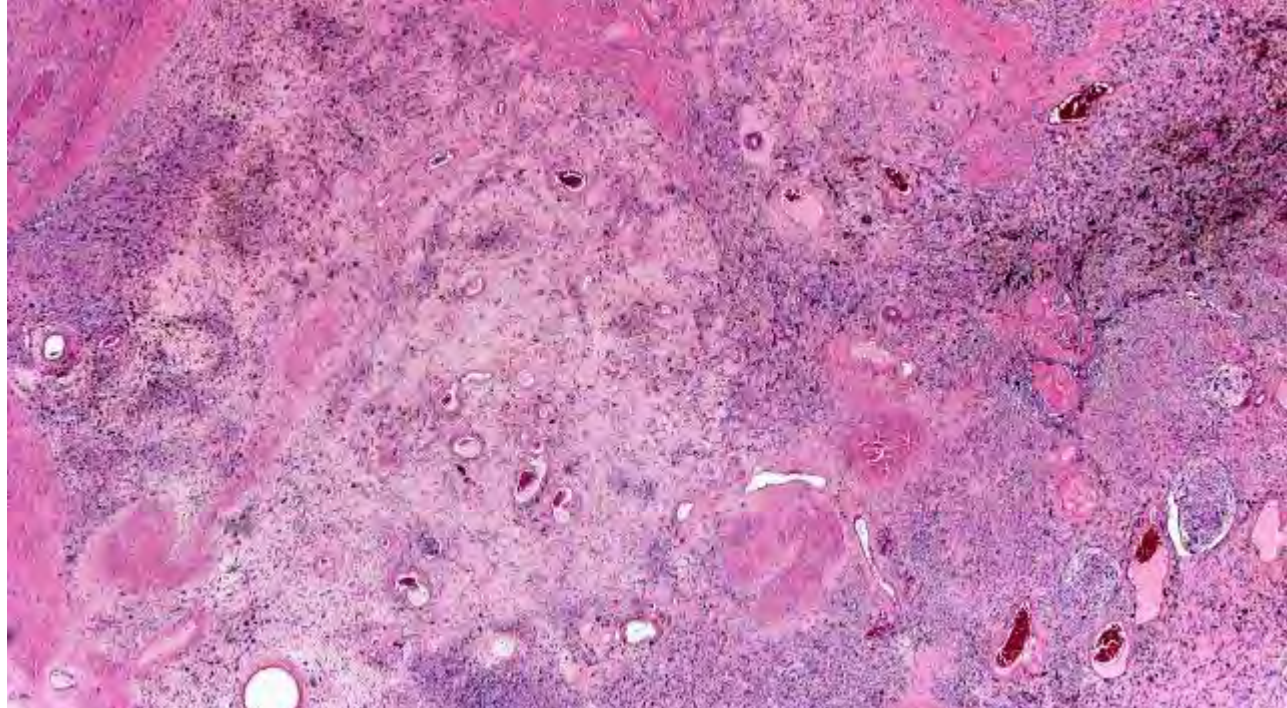
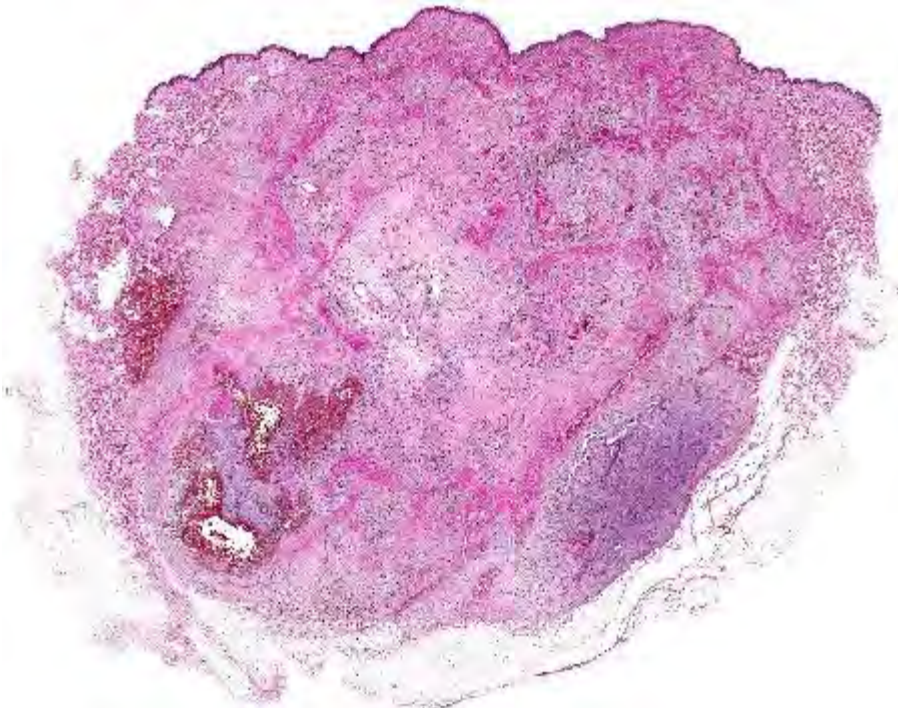
Patient Number	Sex	Age	Site	Pseudothrombotic Changes	Hemorrhage	Hyaline Angiodysplasia	Sclerosis or Hyalinization	Edema	Mucin Deposition	Atypical Melanocytes	Follow-up (Months)
1	F	61	Buttock	+	—	—	—	—	—	+	NA
2	M	39	Buttock	—	—	—	—	—	—	+	120, A
3	F	84	Buttock	—	—	—	—	—	—	+	12, A
4	M	37	Back	+	—	—	—	—	—	+	NA
5	M	69	Back	+	—	+	—	—	—	+	NA
6	M	15	Buttock	Small	—	—	—	—	—	+	2, A

NA, not available; A, follow-up.

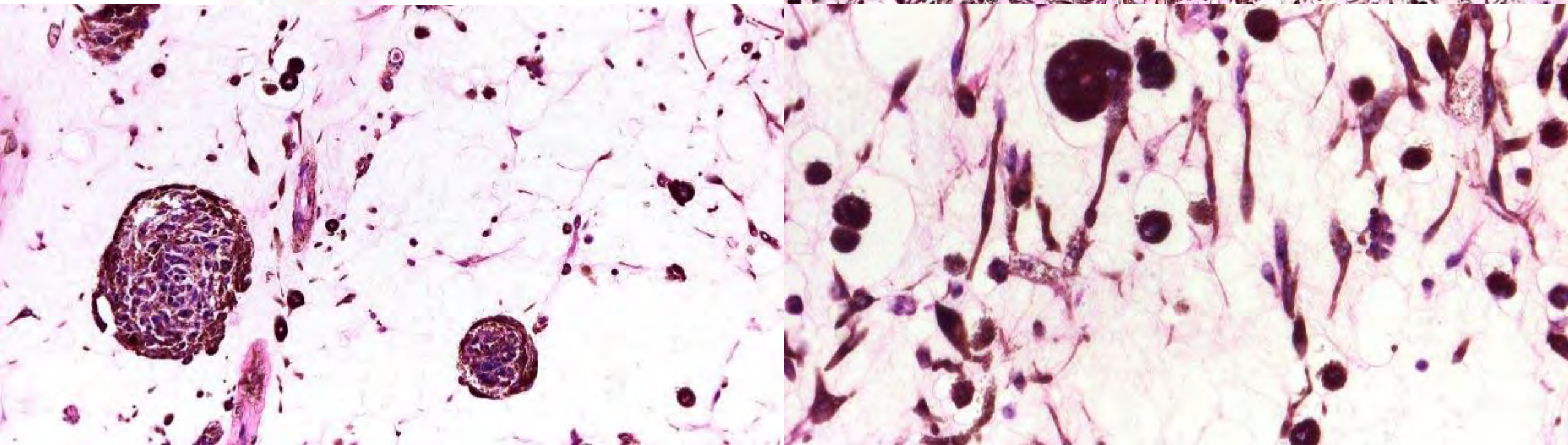
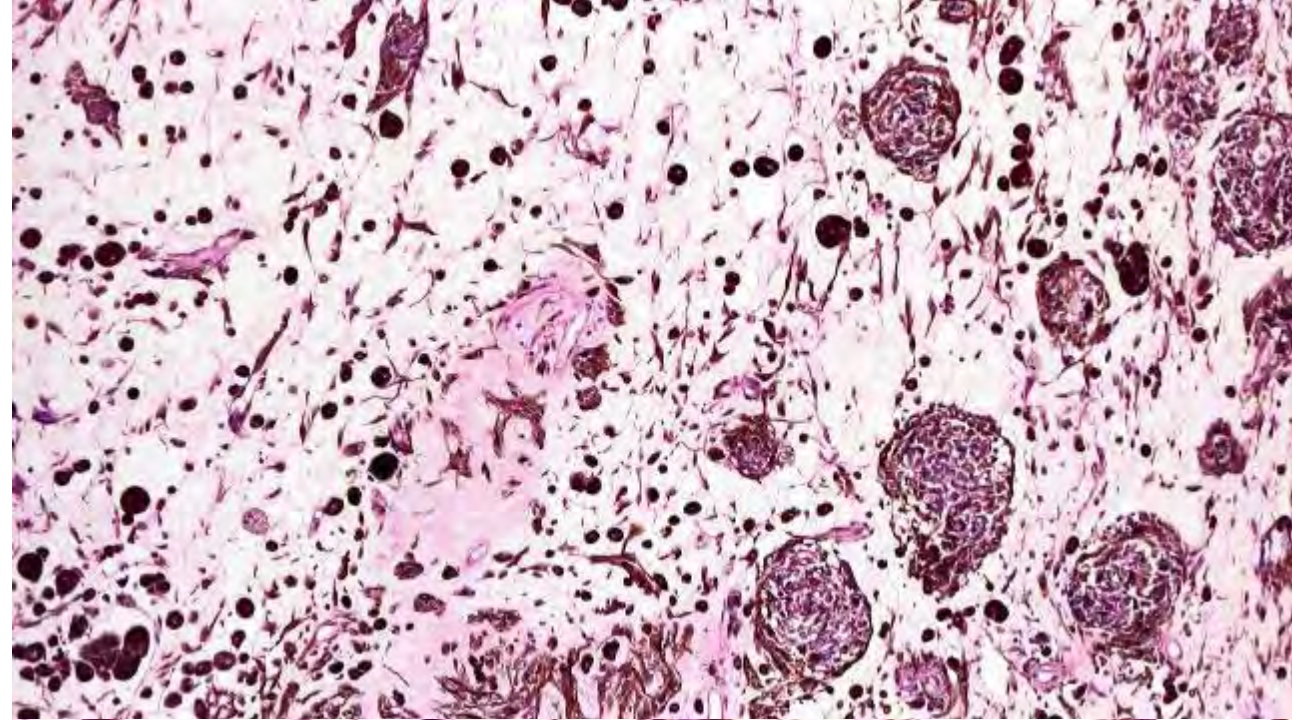
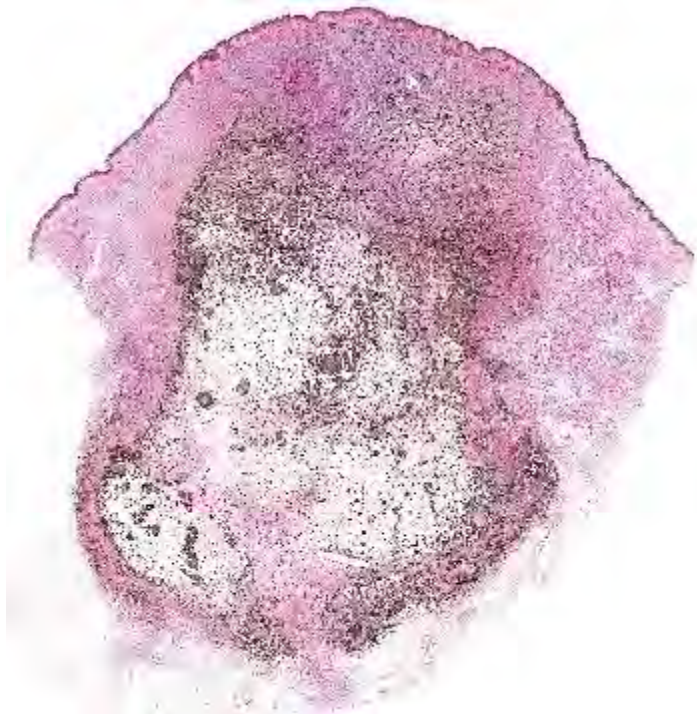


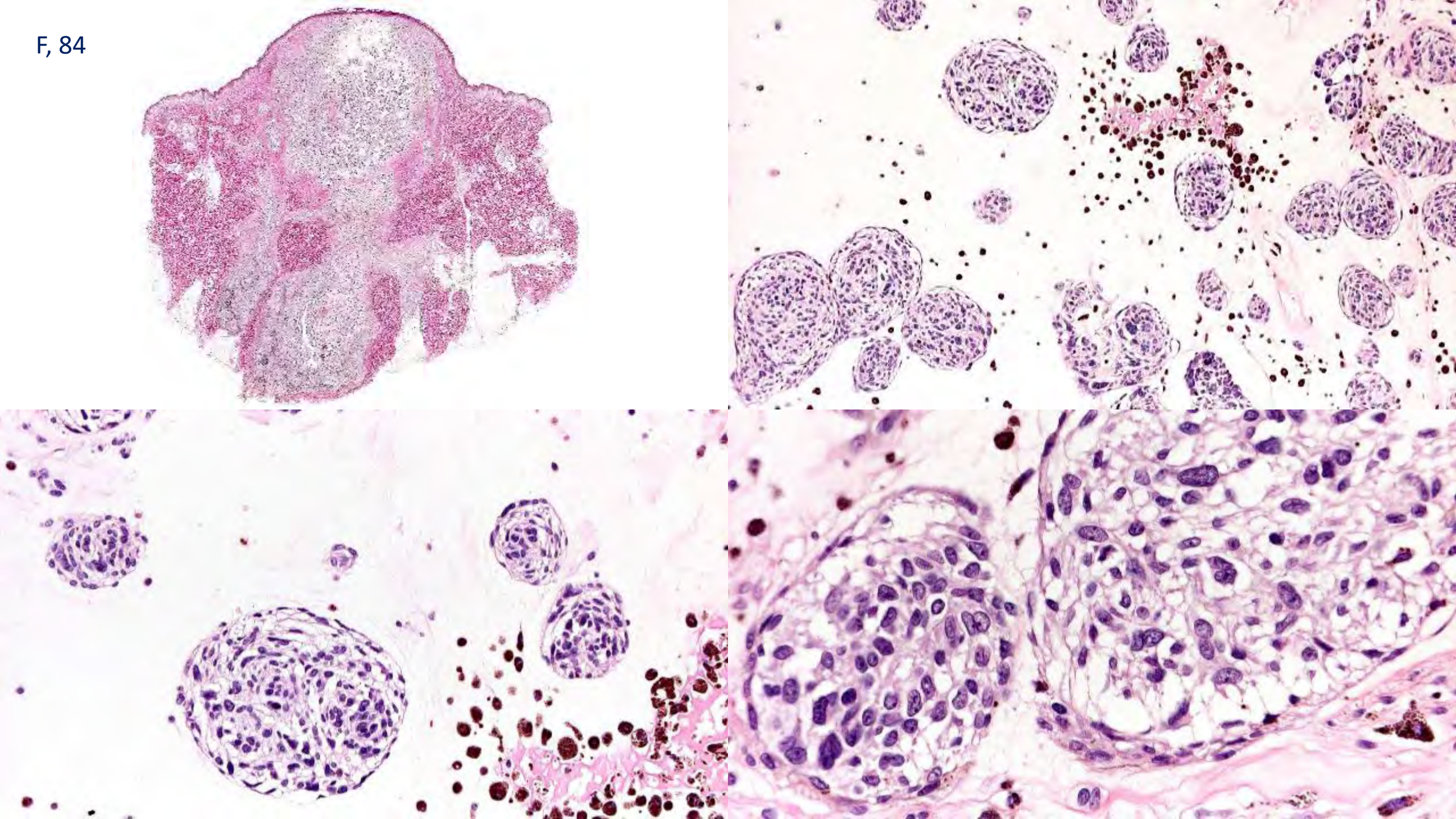


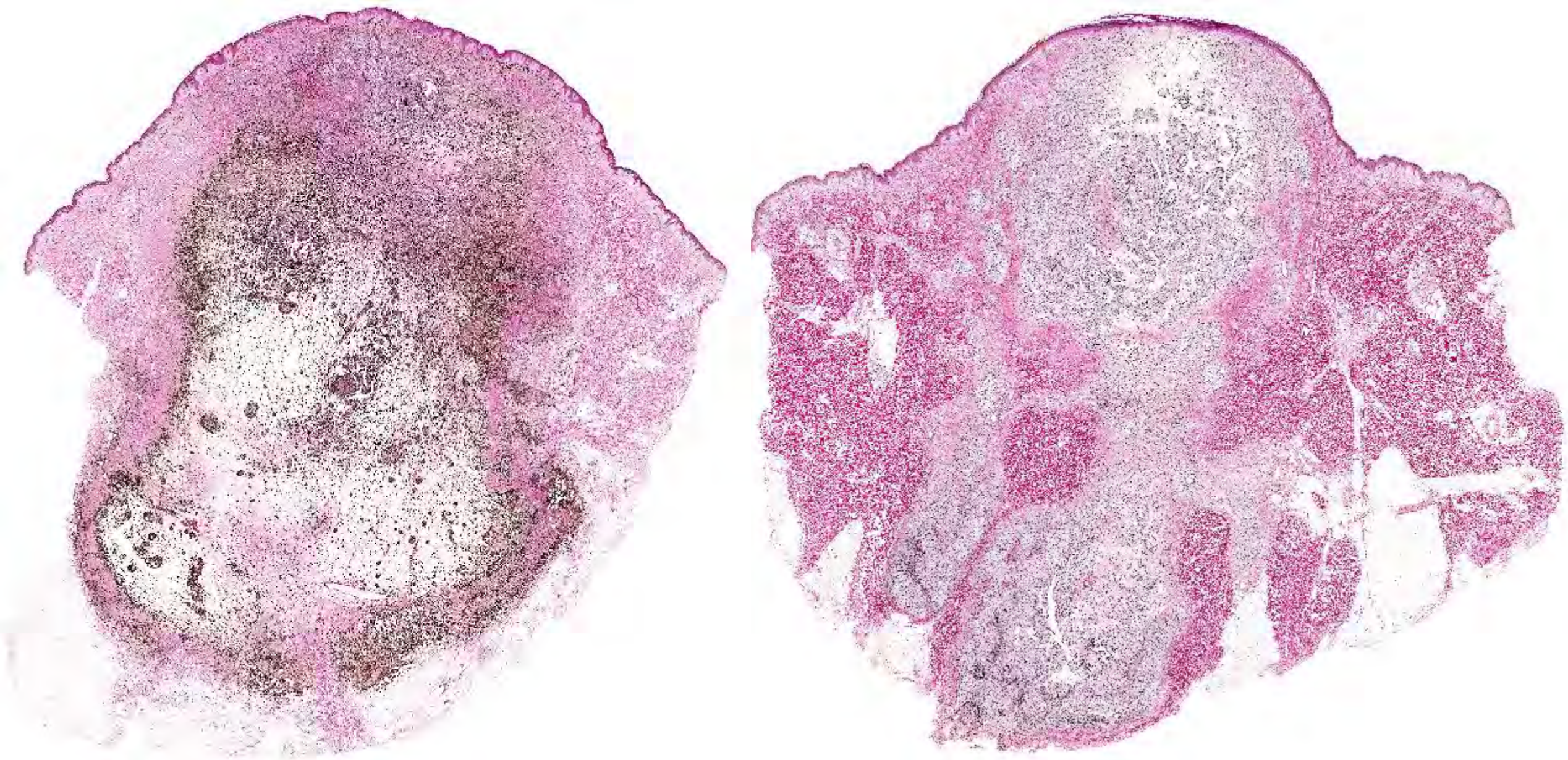
F, 61



M, 39



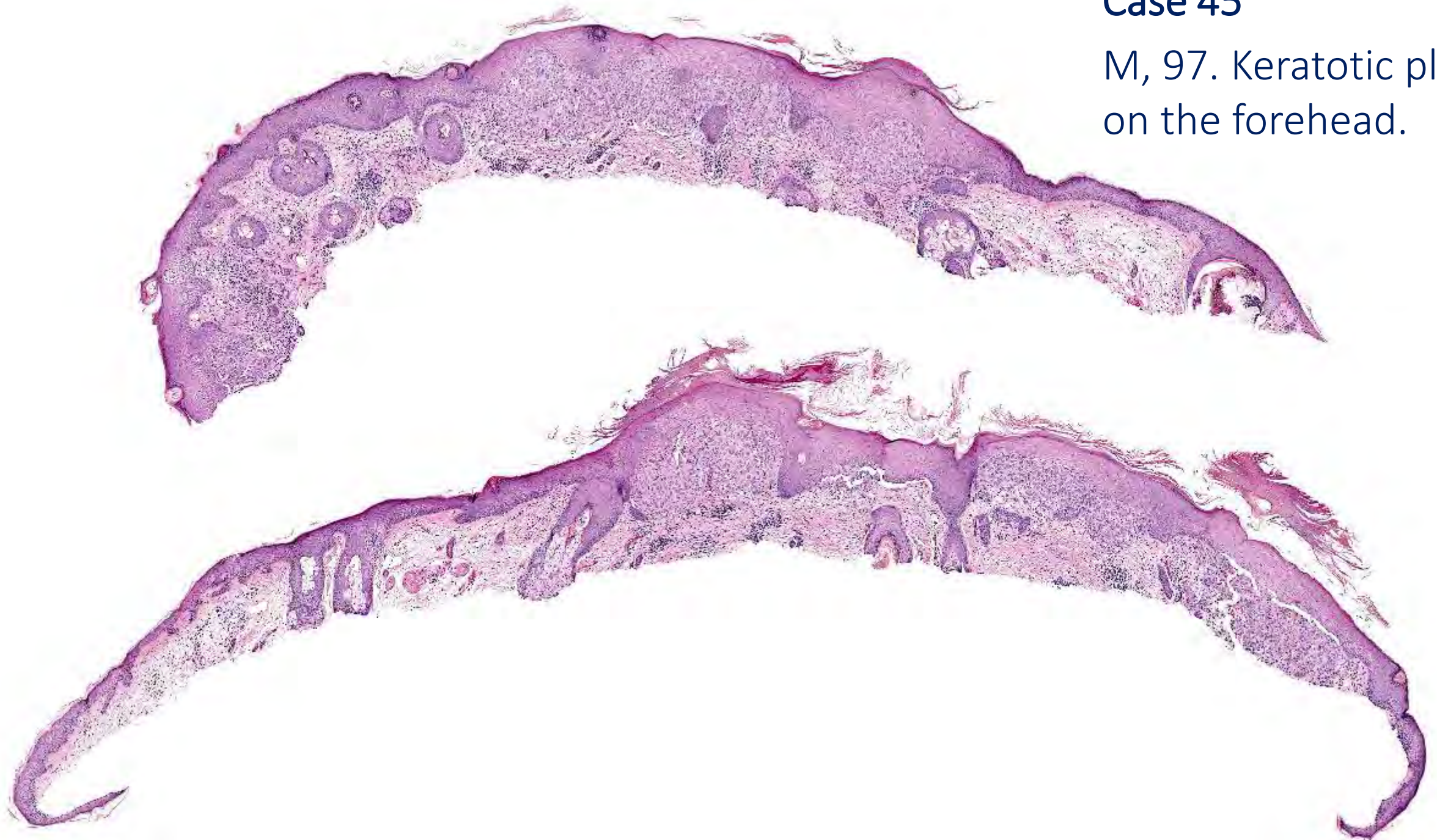


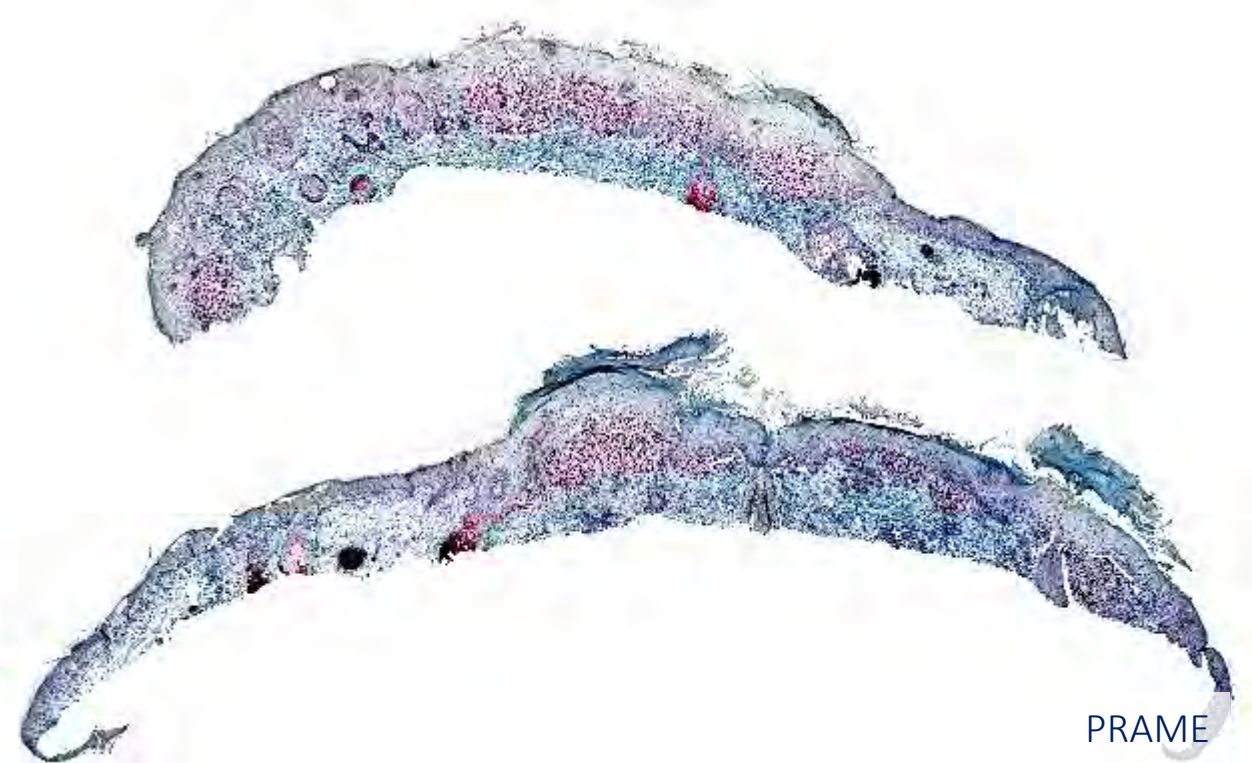
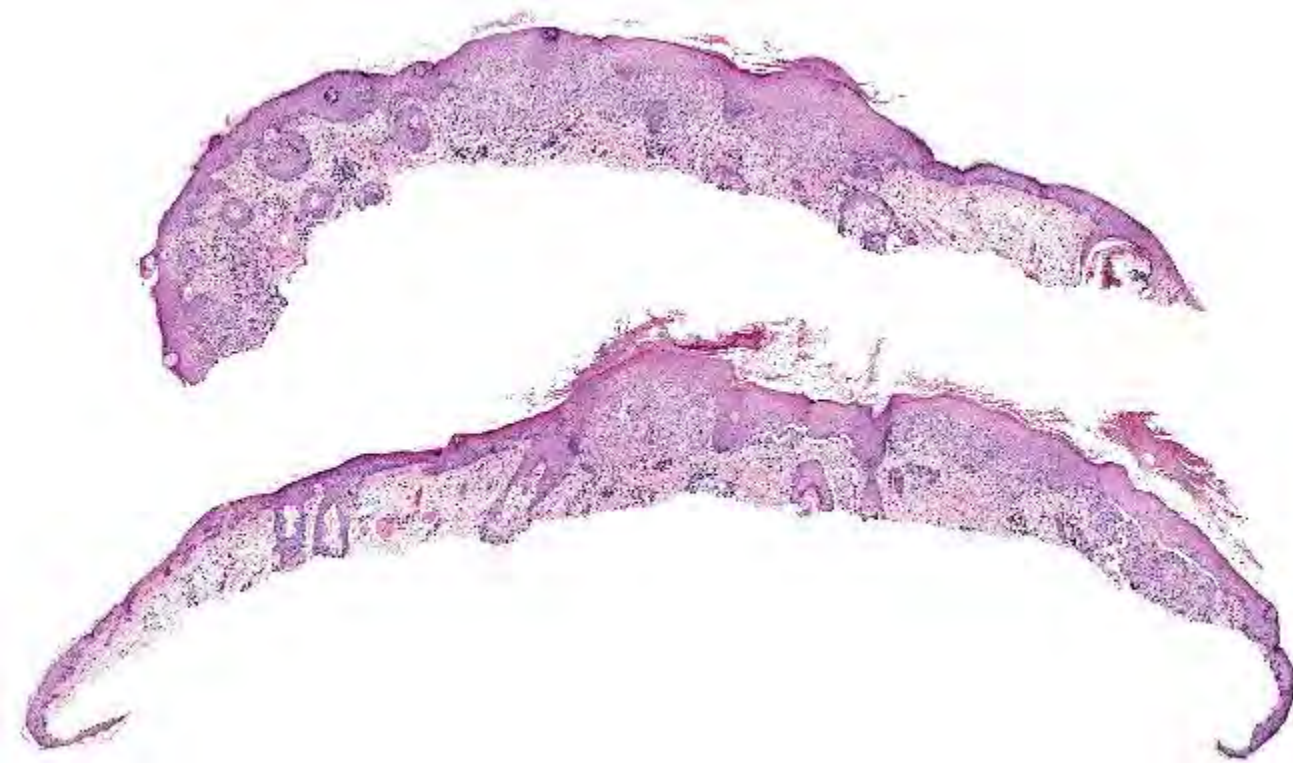


Ancient blue nevus

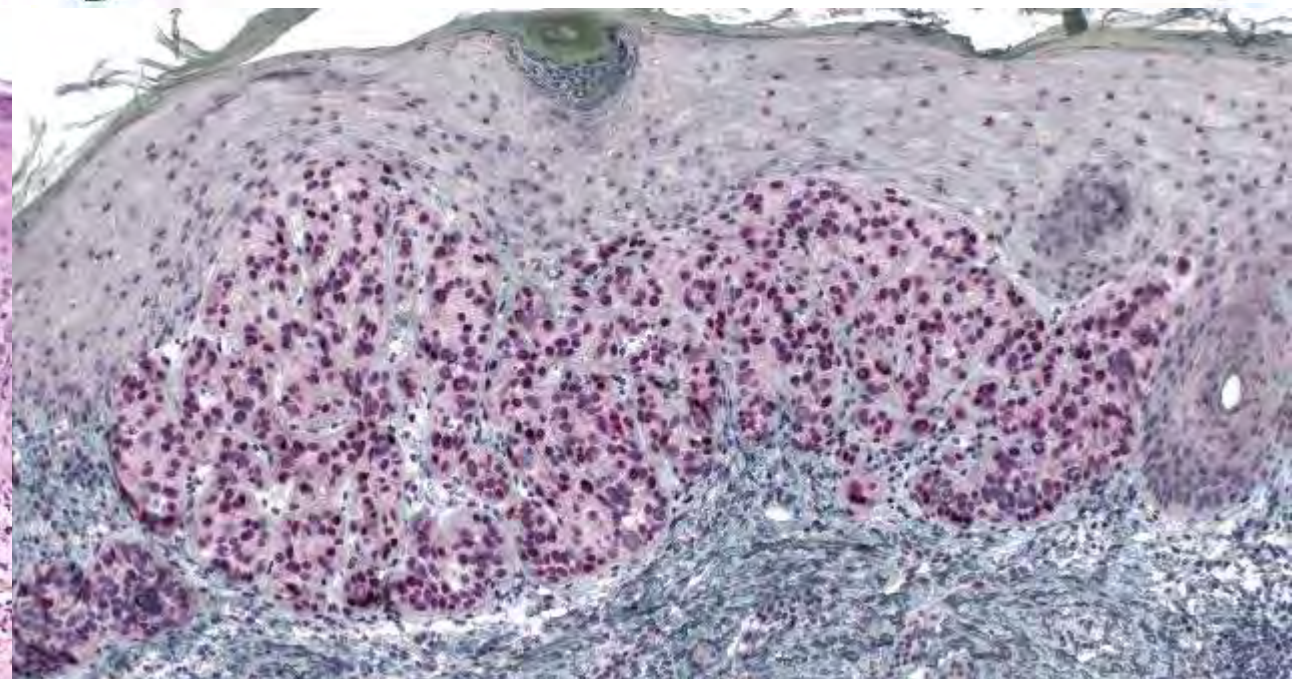
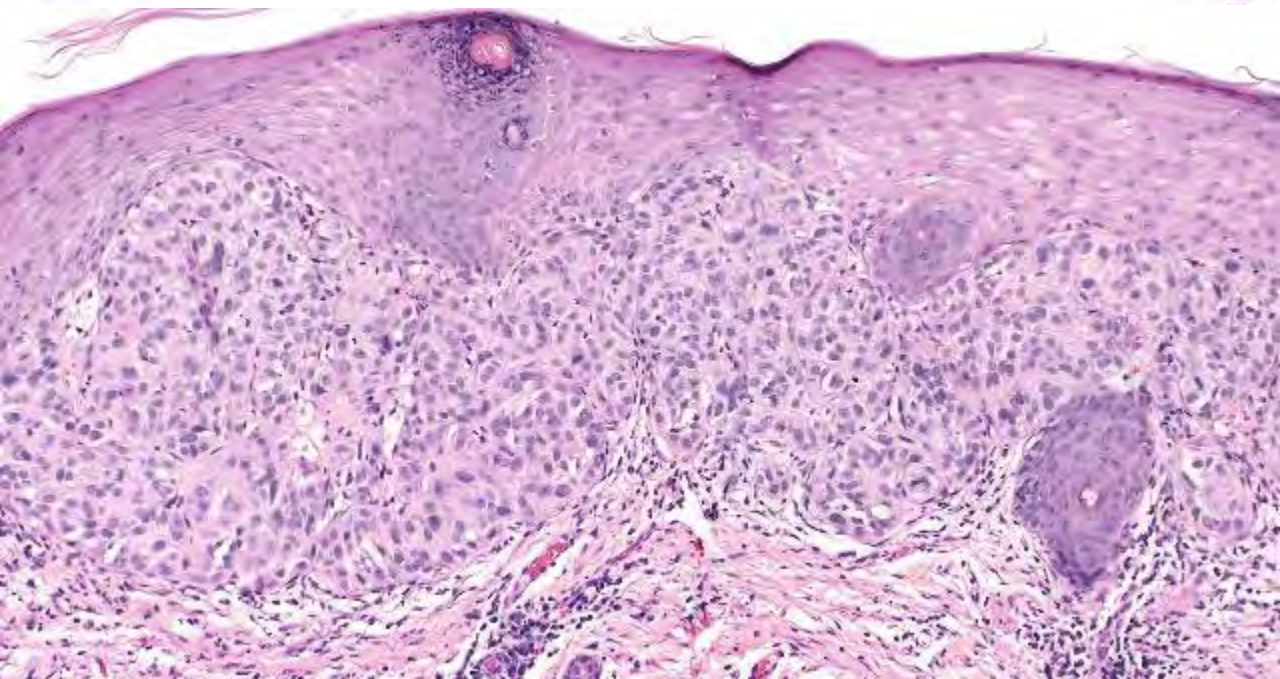
Case 45

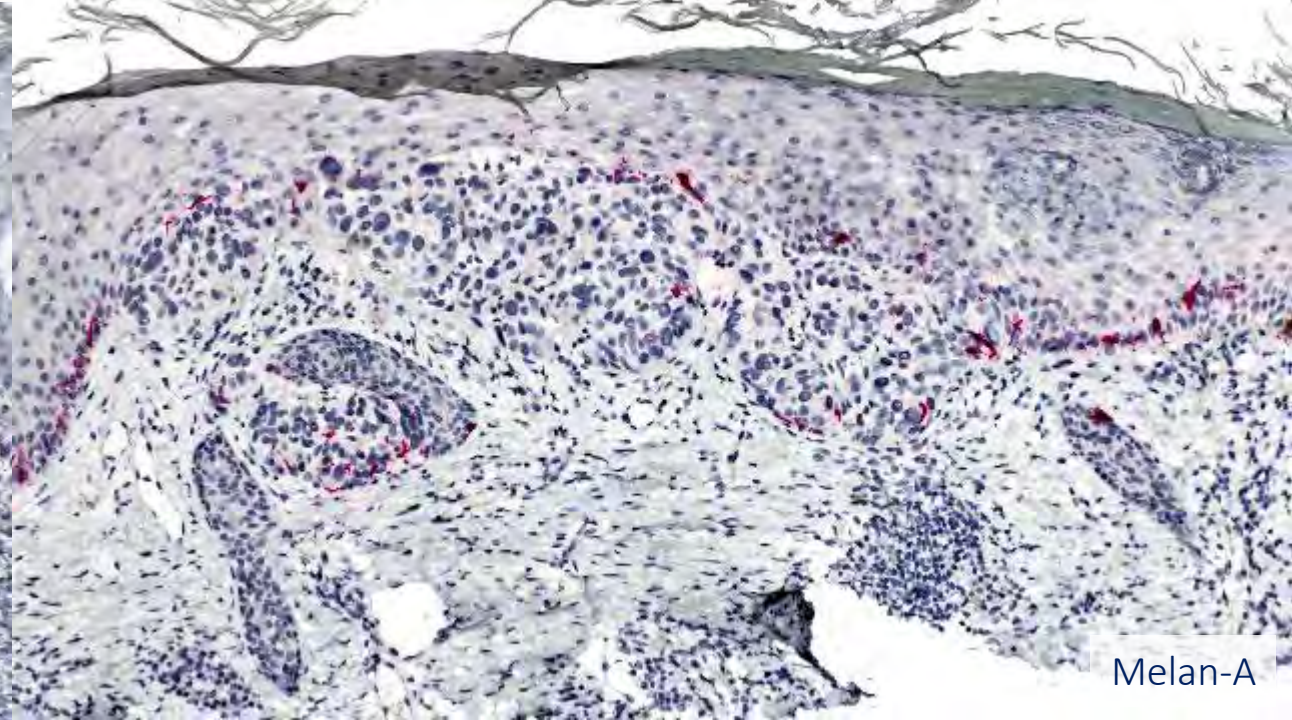
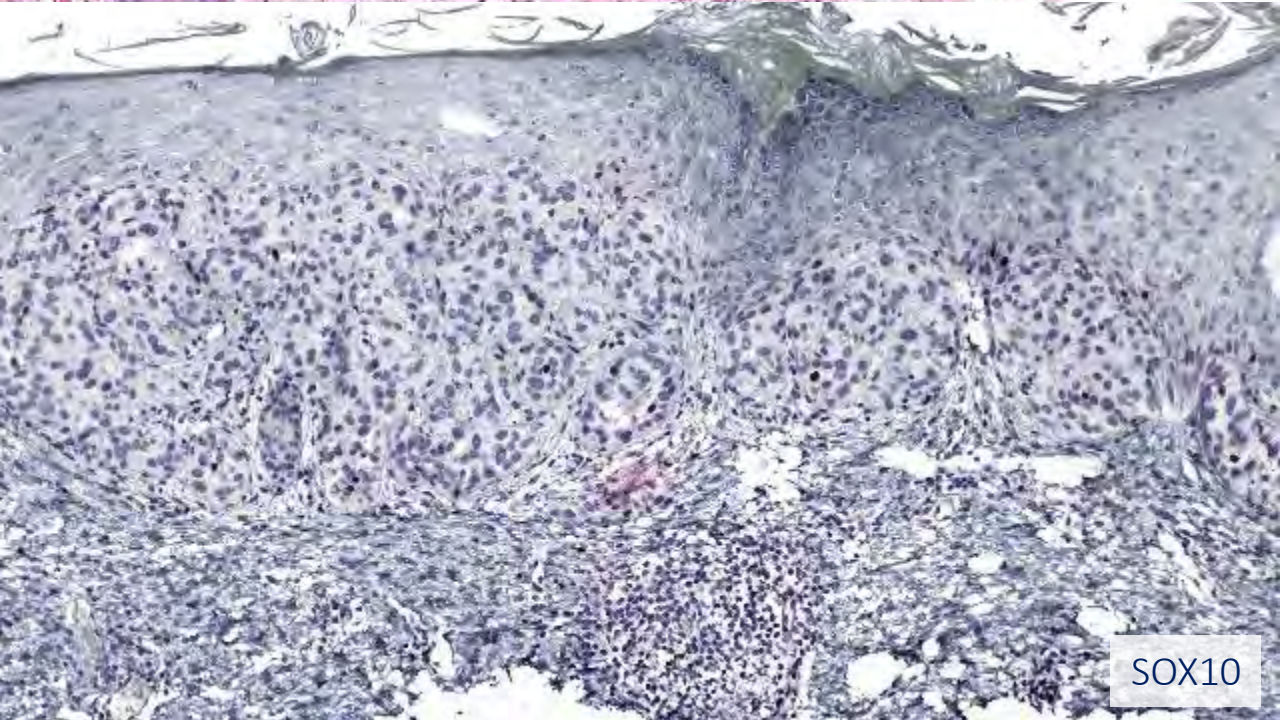
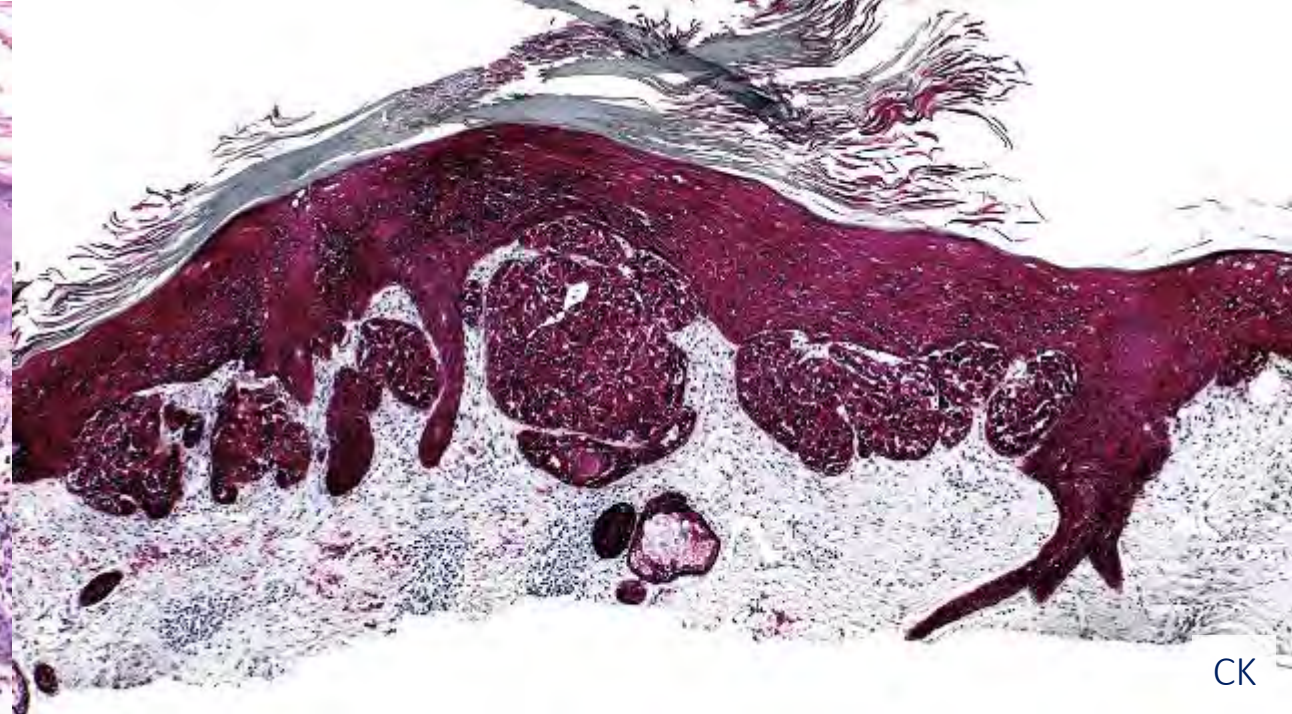
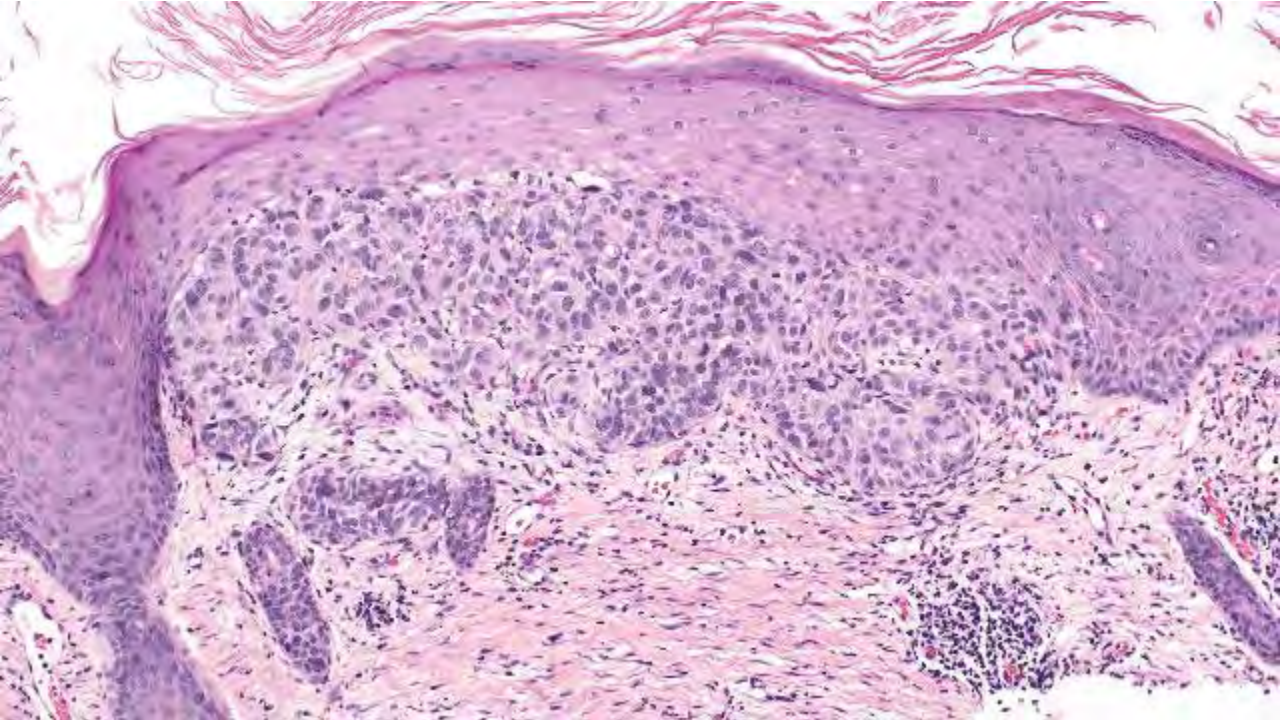
M, 97. Keratotic plaque
on the forehead.

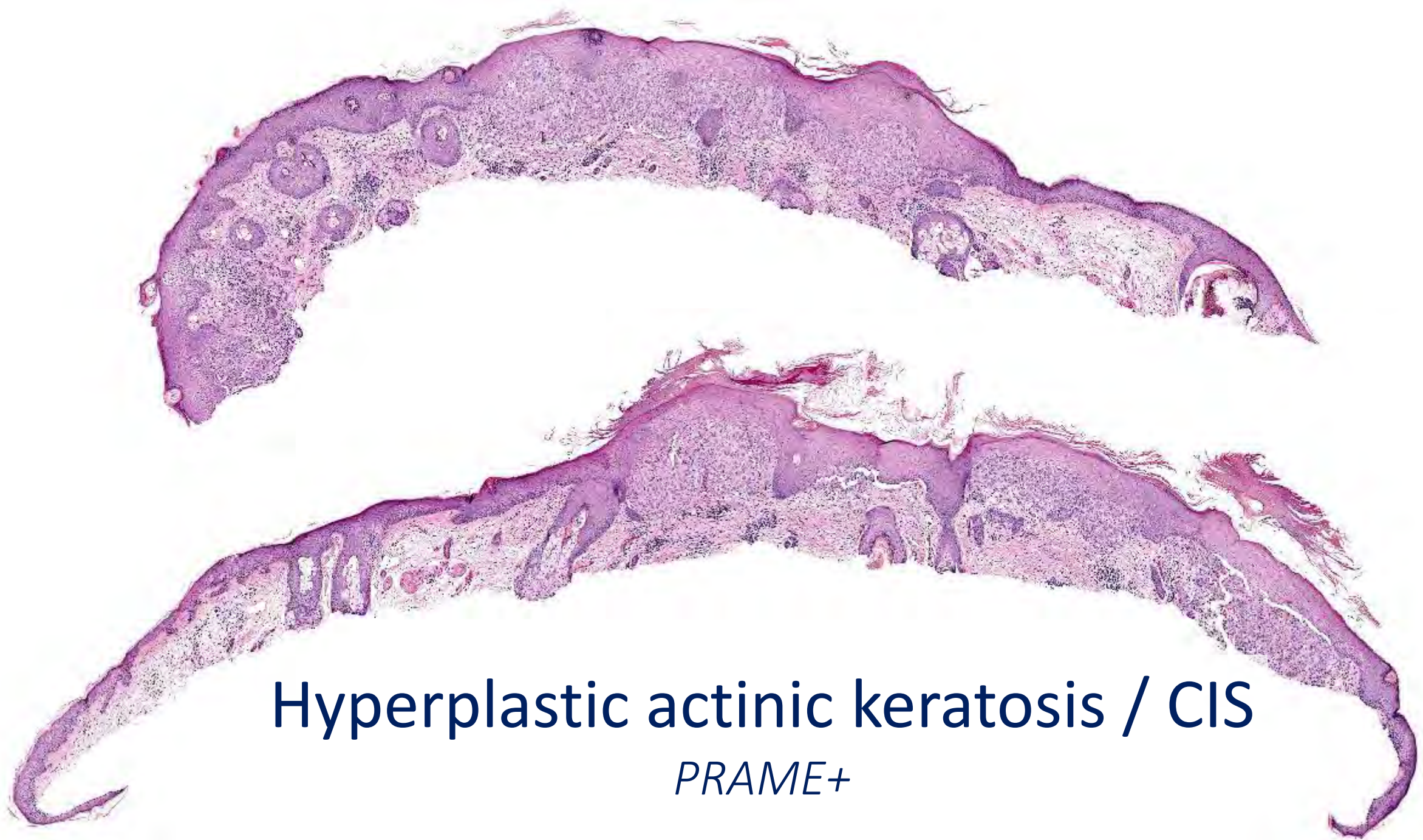




PRAME







Hyperplastic actinic keratosis / CIS

PRAME+

PRAME Staining of Adnexal Lesions and Common Skin Cancer Types: Biomarker with Potential Diagnostic Utility

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Abstract: PRAME (Preferentially Expressed Antigen in Malignant Melanoma) is a cell-surface antigen first identified in amelanotic (cell-line) derived from a patient with malignant melanoma. Immunohistochemistry (IHC) for PRAME is useful for diagnostic purposes to support a suspected diagnosis of melanoma. Immunohistochemical (PRAME) expression is observed in various cutaneous malignancies including melanoma, basaloid, and squamous. In this study, we performed PRAME IHC on adnexal lesions and common skin cancers to determine whether it could potentially distinguish different types of lesions. The differential expression patterns in various lesions and cancers were analyzed. IHC performed on Mount Sinai Medical Center (MSMC) was obtained. It is a retrospective study of 100 cases over a 10-year period (1 January 2012, and 31 December 2023). We used the immunohistochemical (IHC) staining, including squamous, sebaceous, and follicular lesions, in addition to basaloid melanoma (BCC) and squamous cell carcinoma (SCC), from 81 patients who underwent shave/punch biopsy or surgical excision. We evaluated the IHC staining percentage positivity and intensity for PRAME. Staining intensity was subcategorized into negative, weak, moderate, and strong, whereas expression percentage positivity was subcategorized into 0%, 1–25%, 26–50%, 51–75%, and 76–100%. Most sebaceous versus non-sebaceous lesions demonstrated cytoplasmic staining of moderate to strong intensity (50–75% of cells). PRAME has sensitivity and specificity of 100% and 86.7%, respectively, in distinguishing between sebaceous and non-sebaceous lesions. Lesions of pigmented melanoma, including basaloid, BCC, and SCC, showed weak to moderate cytoplasmic staining for PRAME in >75% of cells. None of the 13 lesions of basaloid, benign, showed any staining. A total of 75 of the 81 lesions of sweat gland origin were negative while 6 (8.75%) showed positive staining. In conclusion, we confirm the potential utility of PRAME in supporting the distinction between sebaceous and non-sebaceous adnexal lesions on one hand, and on the other, distinguishing BCC and SCC that may show nuclear staining from melanocytic carcinoma that shows cytoplasmic staining.

Keywords: PRAME; adnexal lesions; melanoma; BCC; SCC; staining; immunohistochemistry

1. Introduction

Cutaneous neoplasms encompass a diverse array of tumors arising from various components of the skin, including the epidermis, adnexal structures, and dermis. Accurate diagnosis and classification of these lesions are essential for guiding appropriate management and prognostication. While traditional histopathological examination and morphology remains the cornerstone of diagnosis, ancillary techniques such as immunohistochemistry (IHC) have emerged as valuable adjuncts in facilitating the characterization of tumors, especially when biopsy contains only a small portion of the lesion.

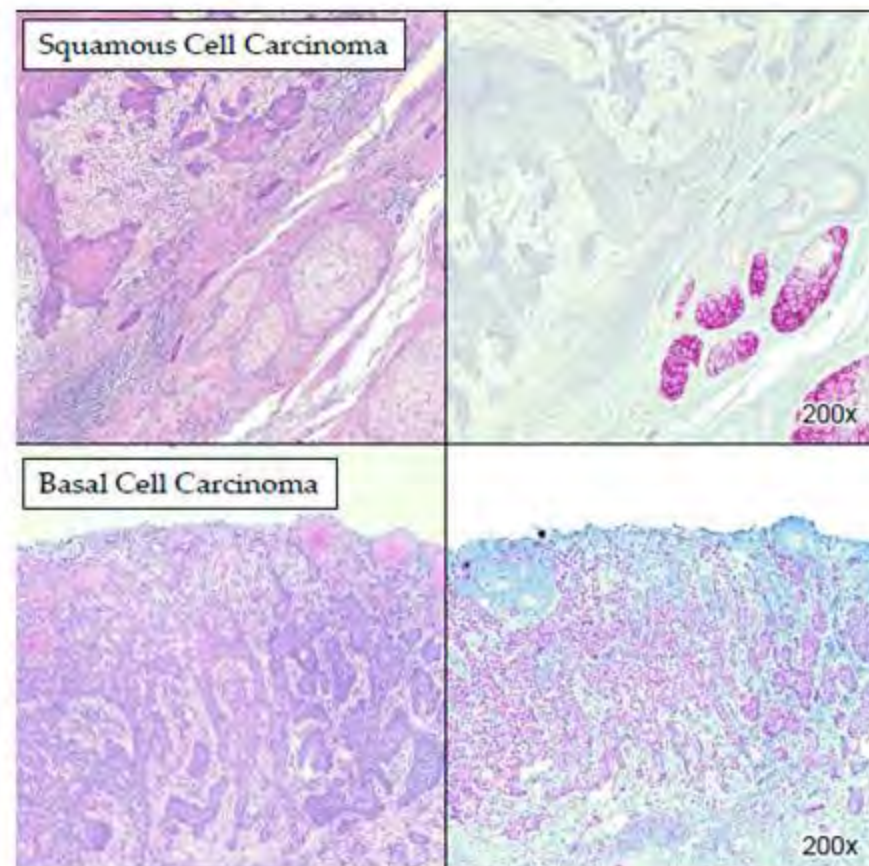


Figure 4. PRAME IHC staining in SCC and BCC. In the upper panel (squamous cell carcinoma), the neoplastic cells demonstrated weak nuclear staining for PRAME while the internal control sebaceous glands stained strongly positive for PRAME (cytoplasmic staining pattern). In the lower panel (basal cell carcinoma), the neoplastic cells demonstrated moderate nuclear staining for PRAME in >75% of cells.

Table 4. PRAME nuclear positivity in BCC and SCC.

	BCC (n = 10)	SCC (n = 9)
PRAME Positivity		
Negative	0 (0.0%)	2 (22.2%)
Positive	10 (100.0%)	7 (77.8%)



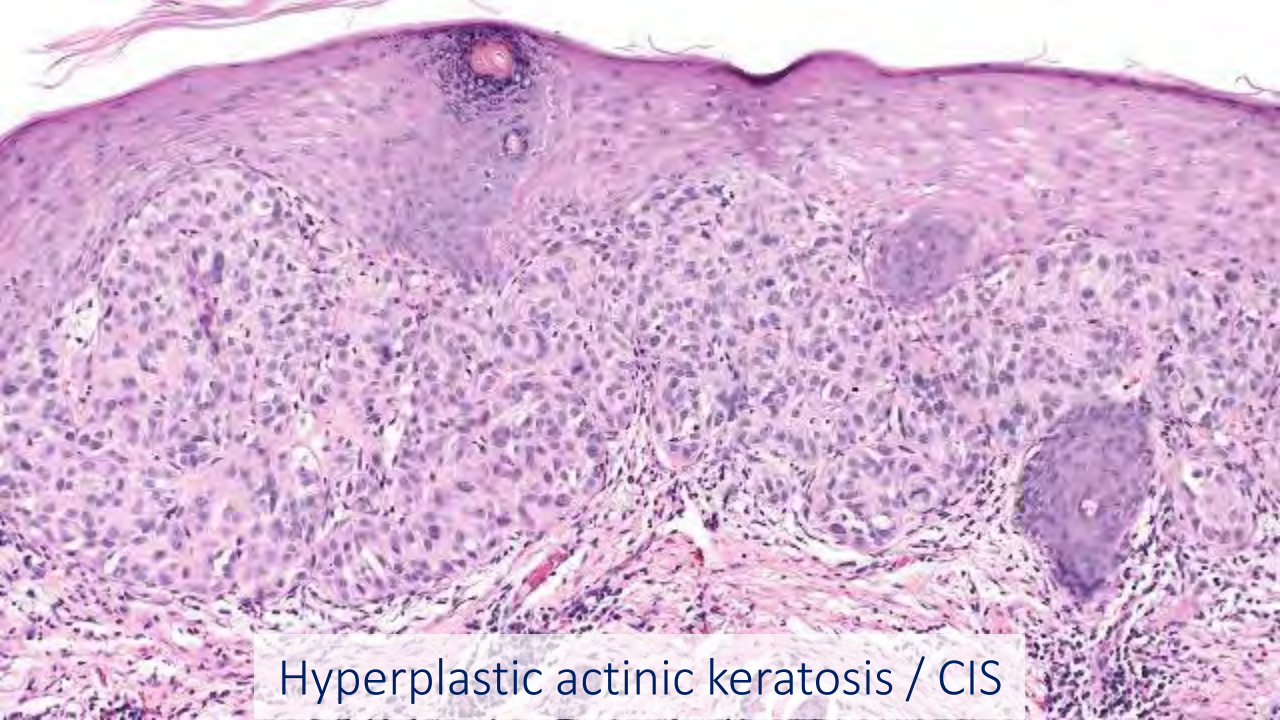
Check for updates
PRAME Staining of Adnexal Lesions and Common Skin Cancer Types: Biomarker with Potential Diagnostic Utility
Hisham E. Bahmed, John Alexis, and John Alexis
Dermatopathology 2024, 7(1), 34–37
doi:10.3390/dermatopathology7010034

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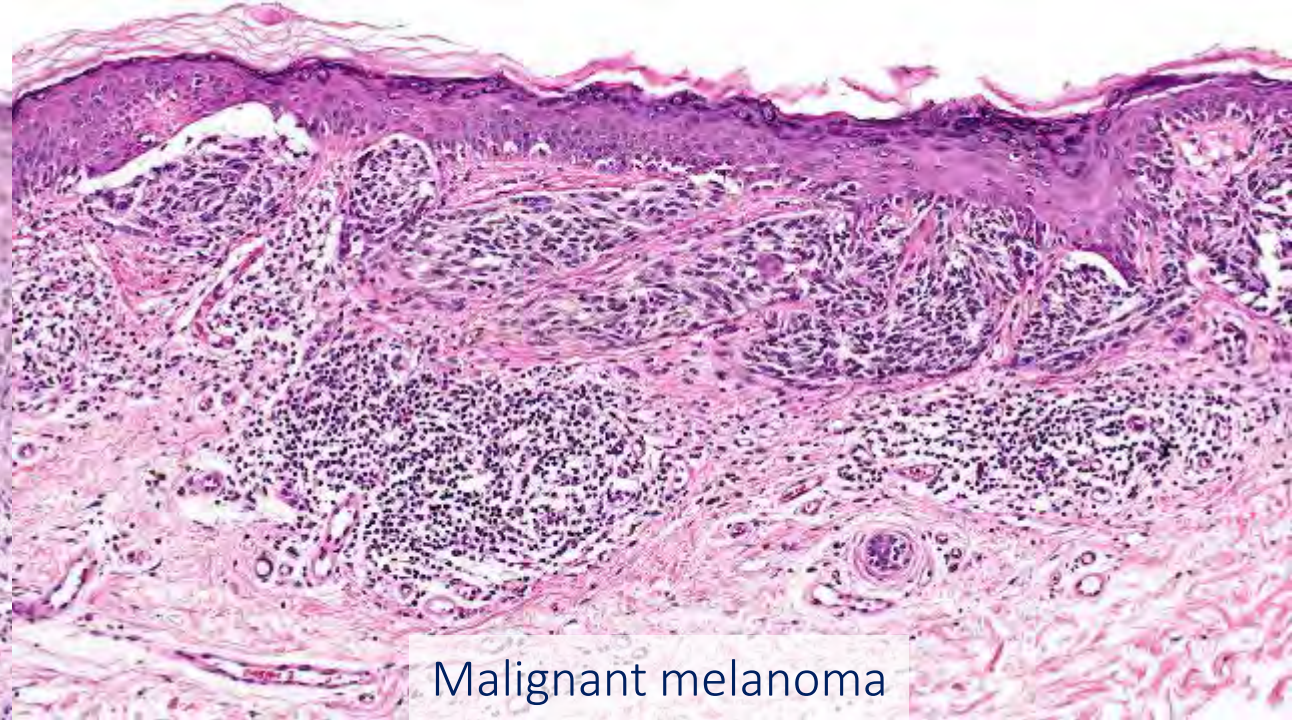
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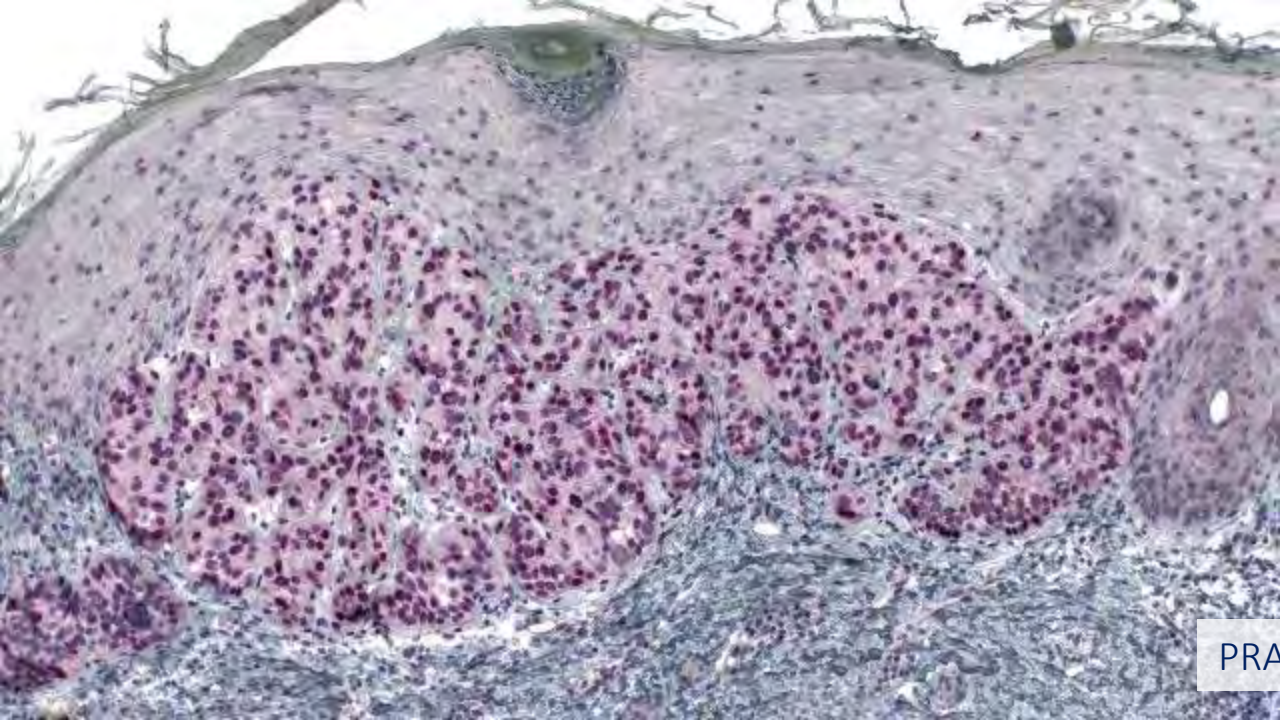
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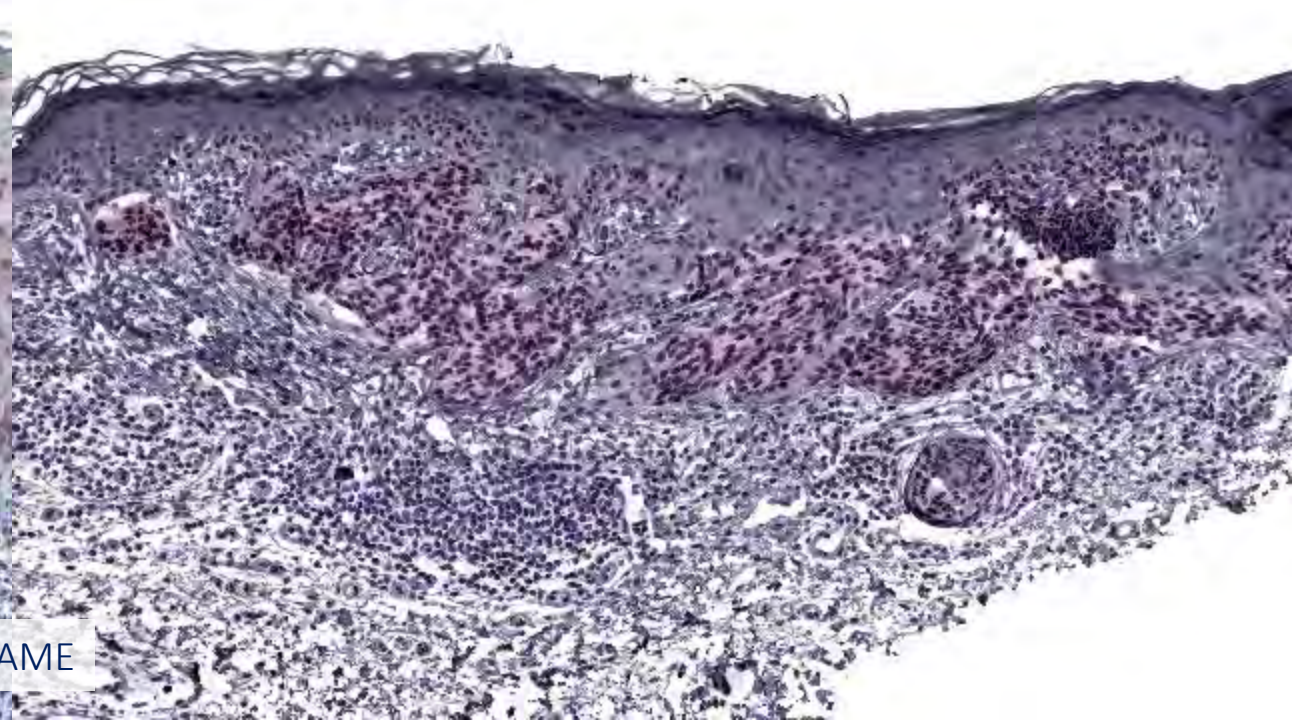
Hyperplastic actinic keratosis / CIS

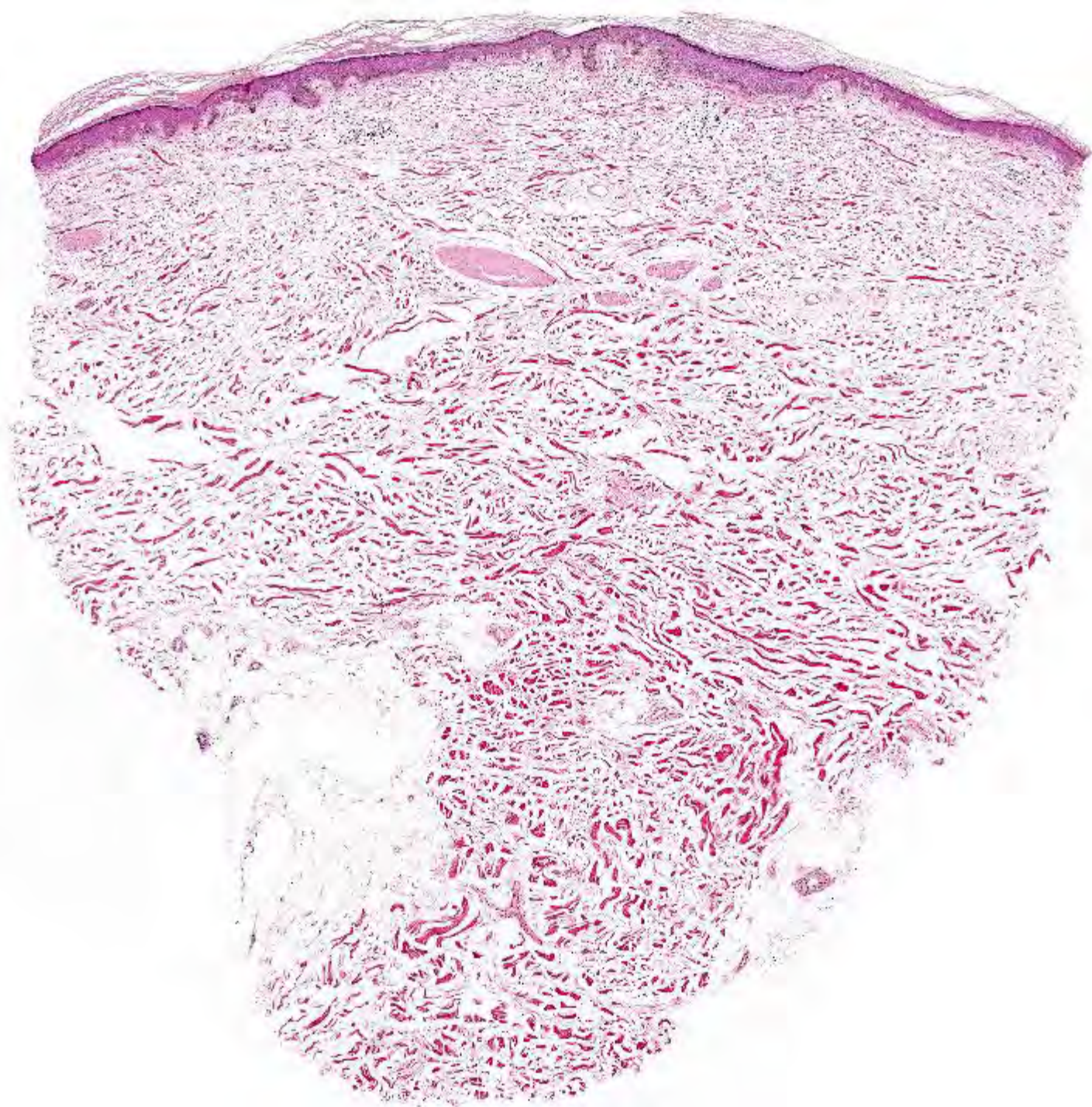


Malignant melanoma



PRAME

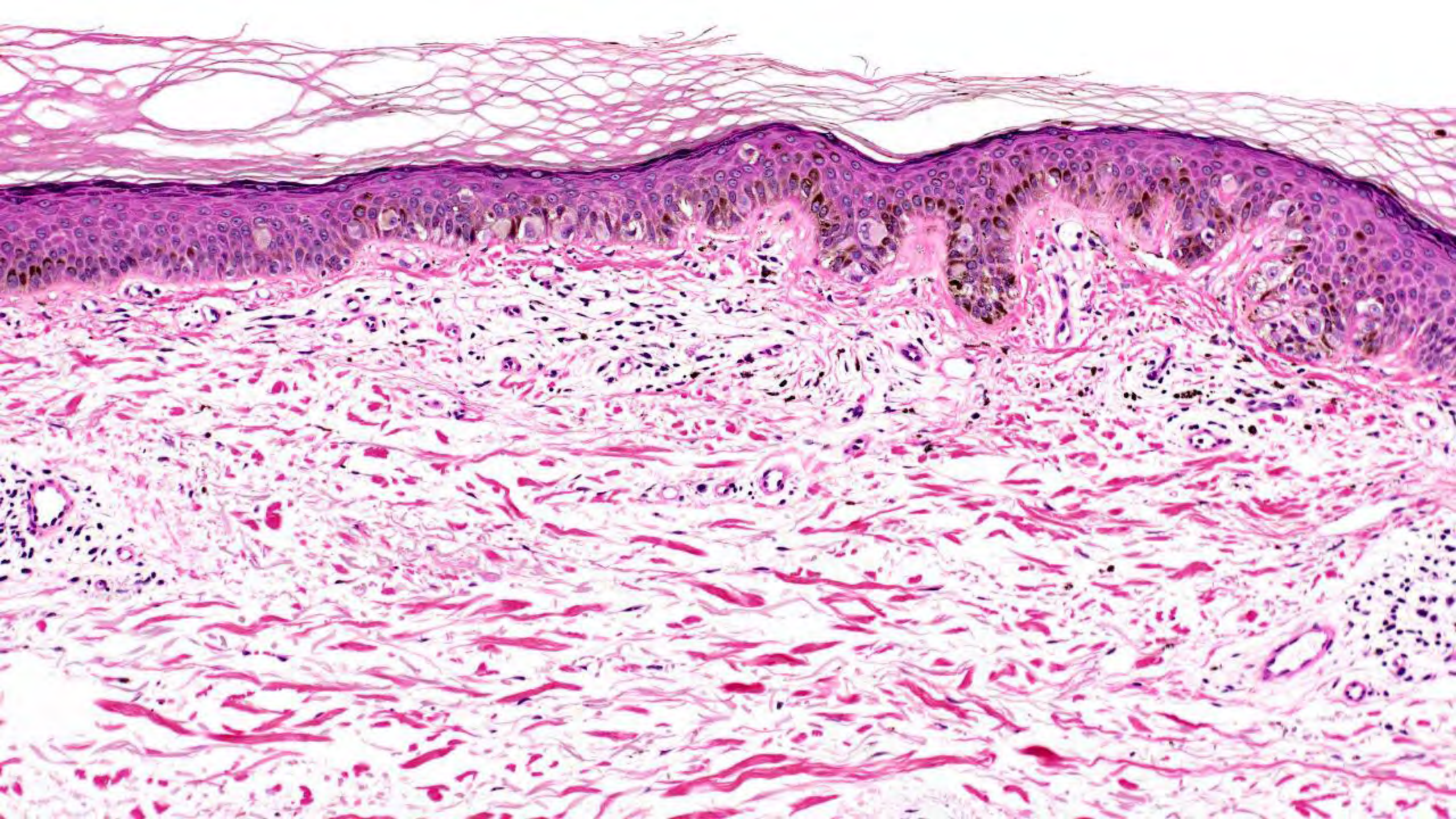


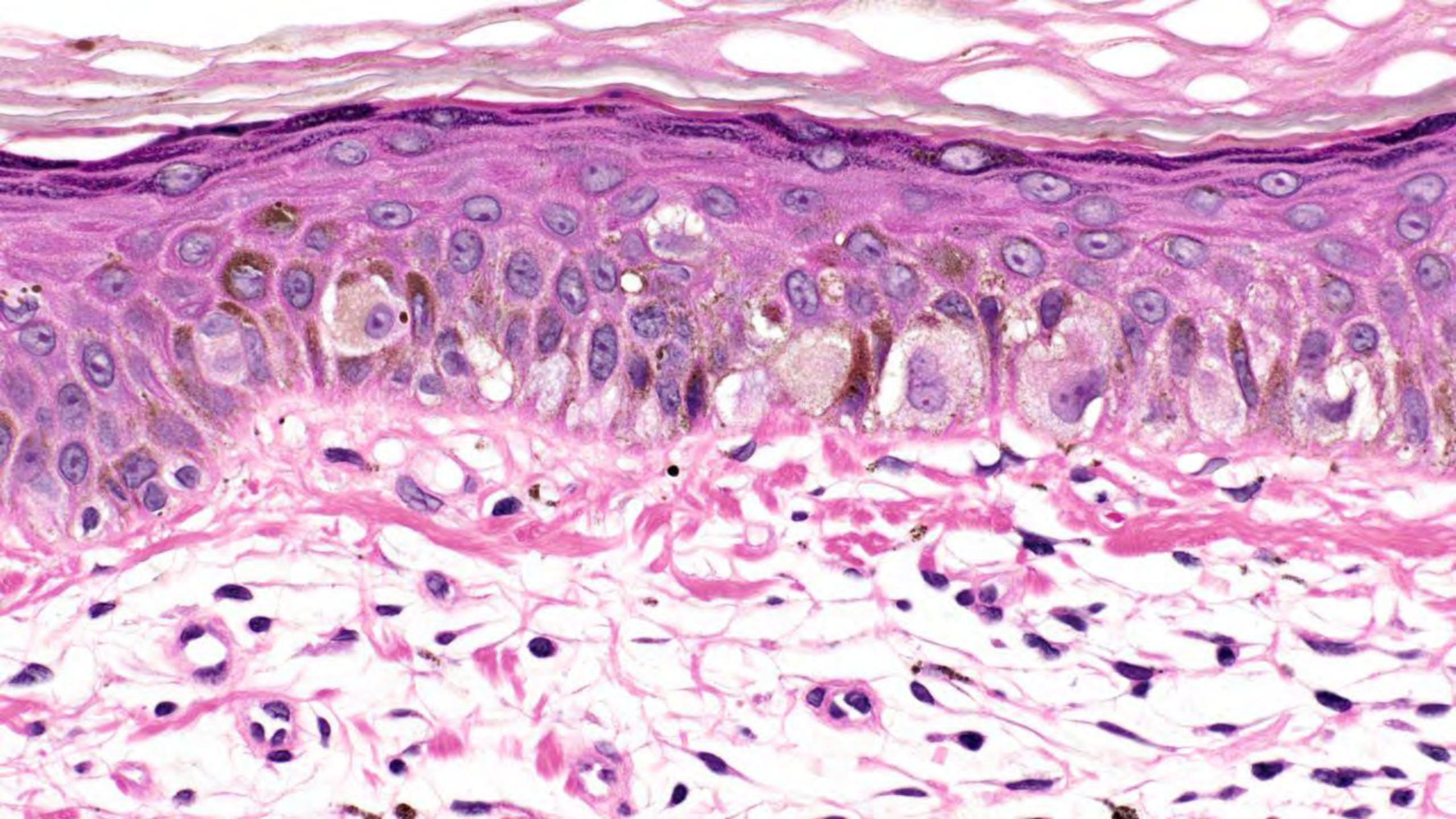


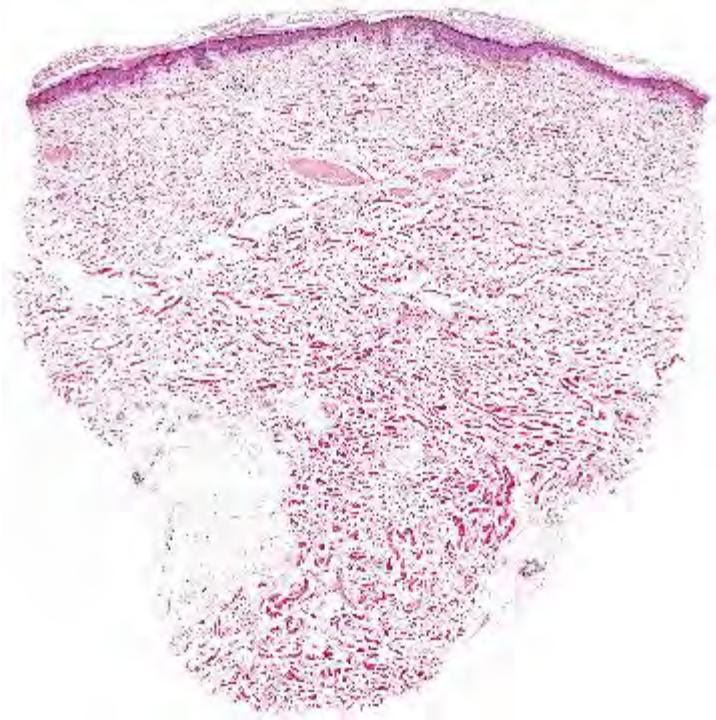
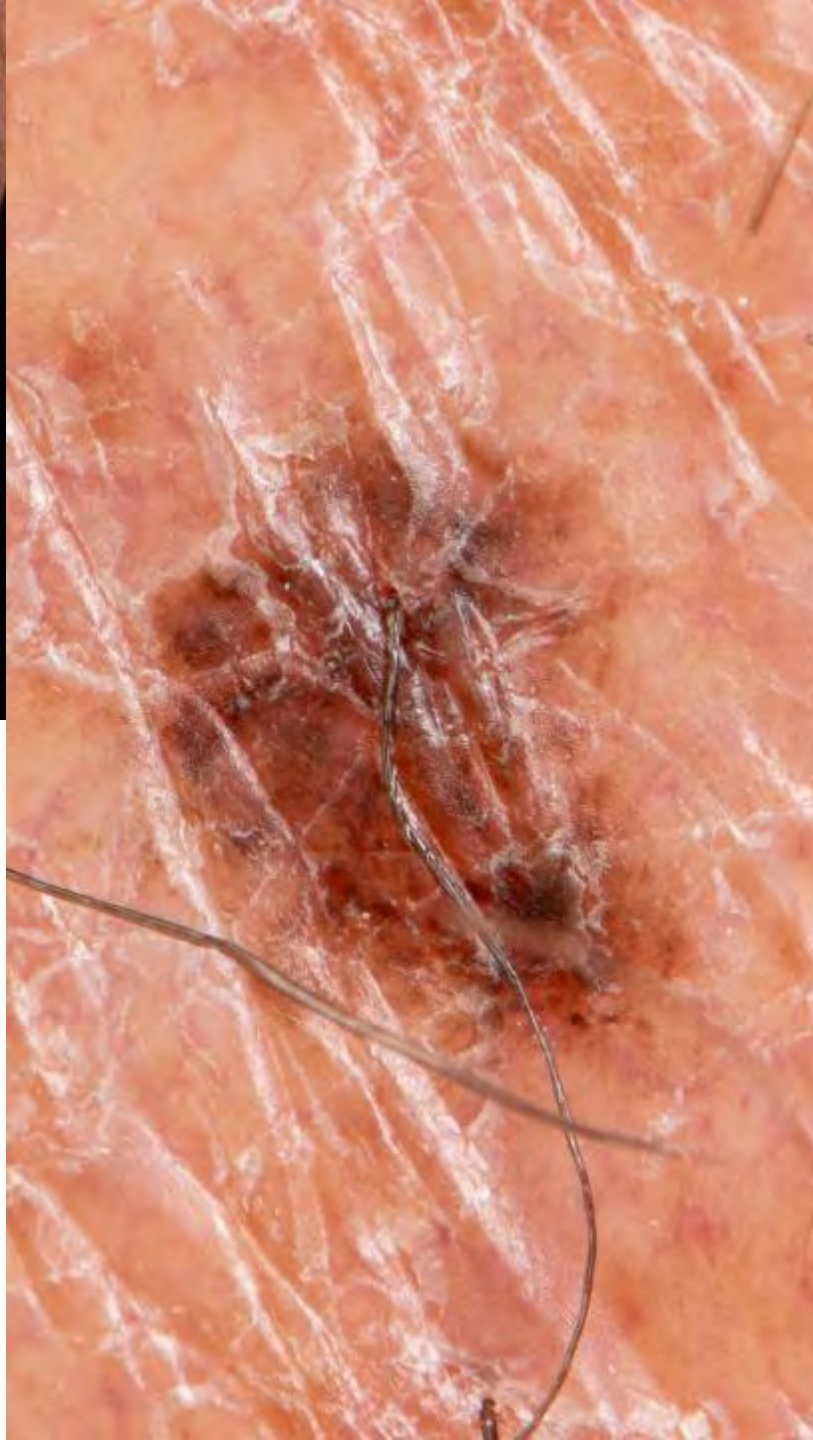
Case 46

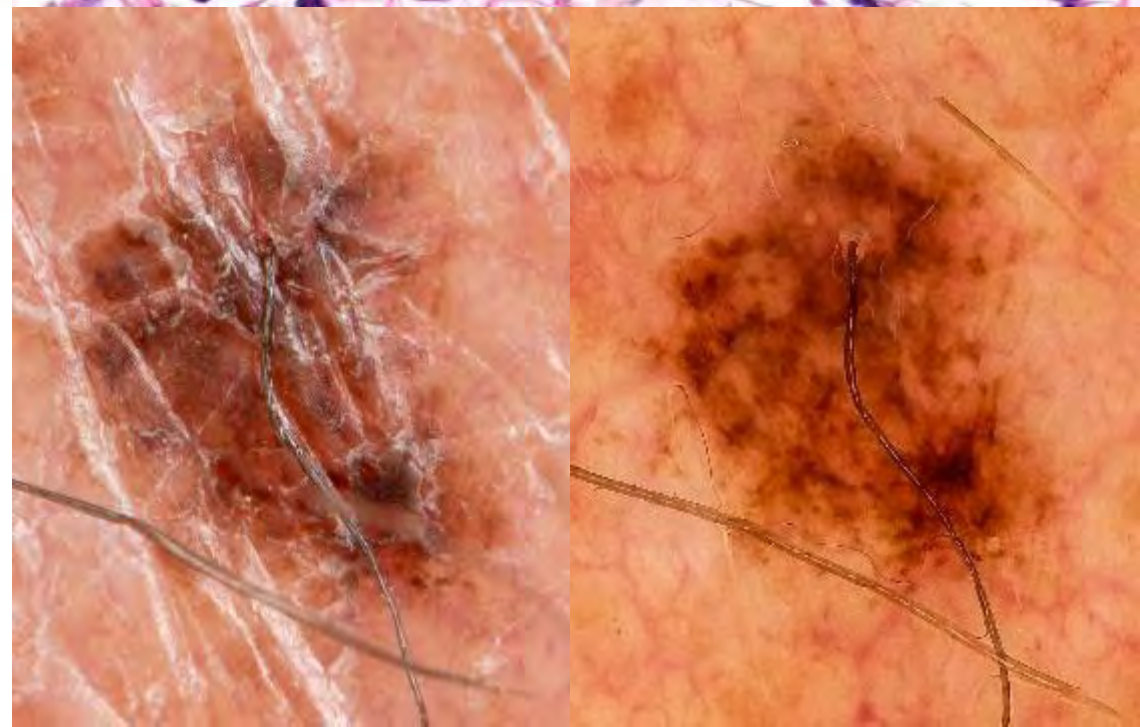
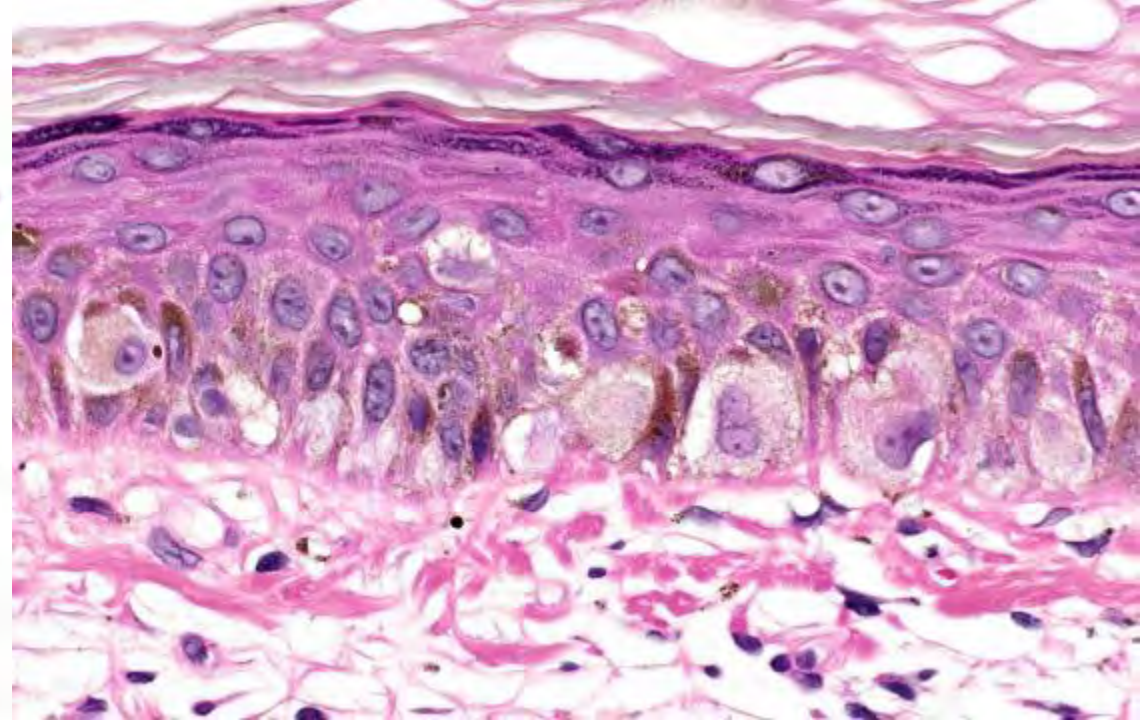
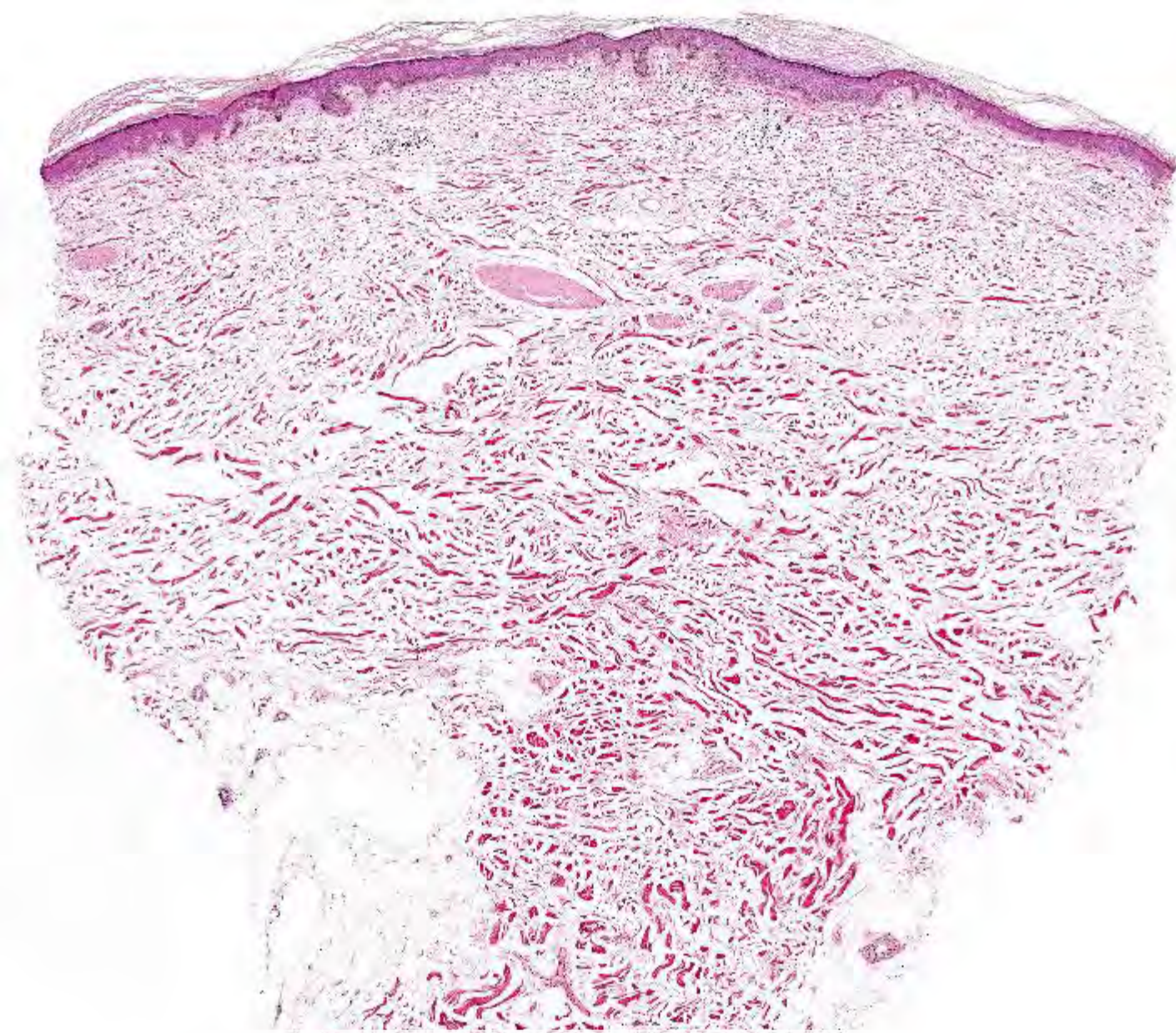
M, 62. History of 3 melanomas.

During a follow-up visit an "atypical pigmented lesion" on the right thigh is noticed.

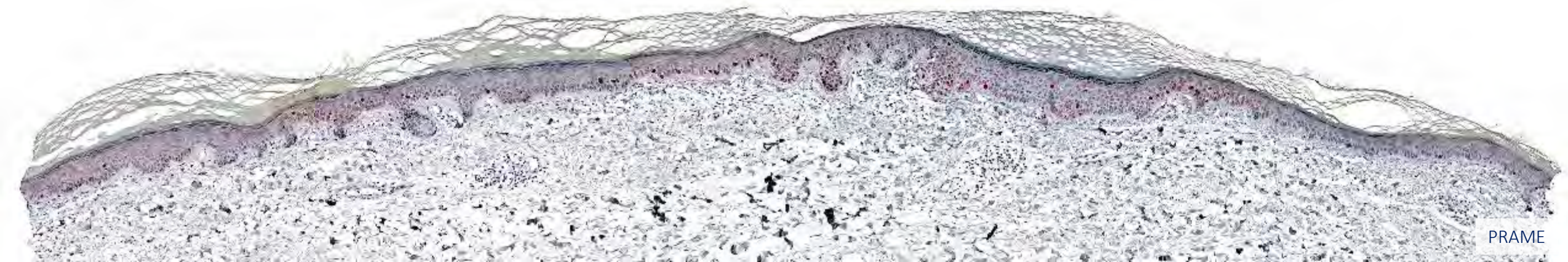
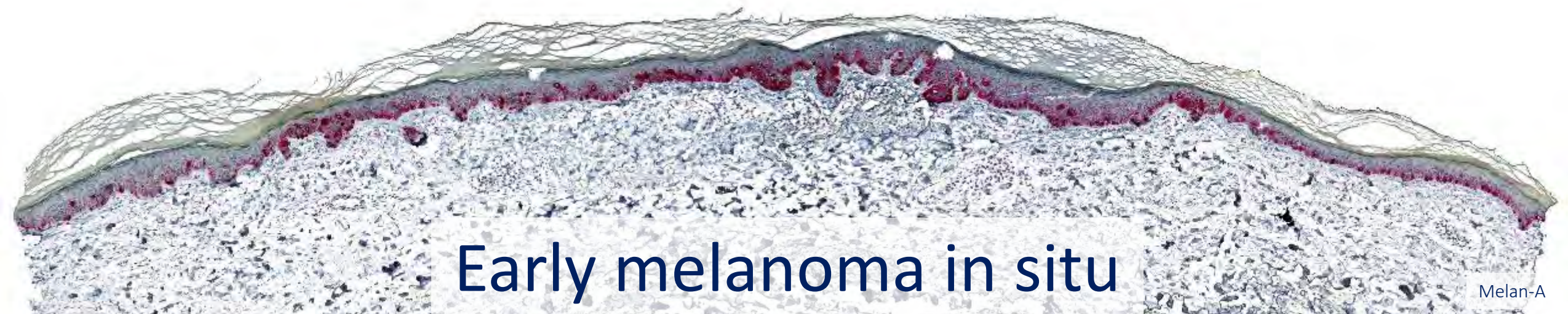
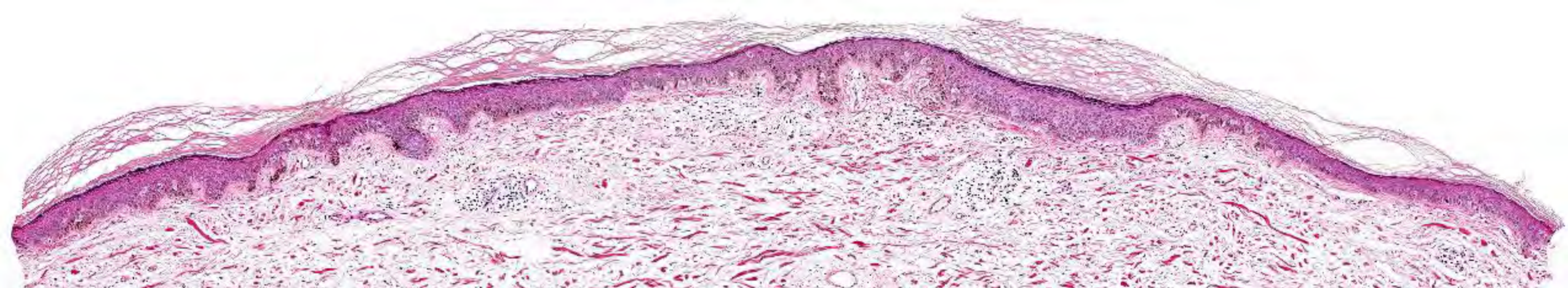








"Baby" (early) Spitz nevus?



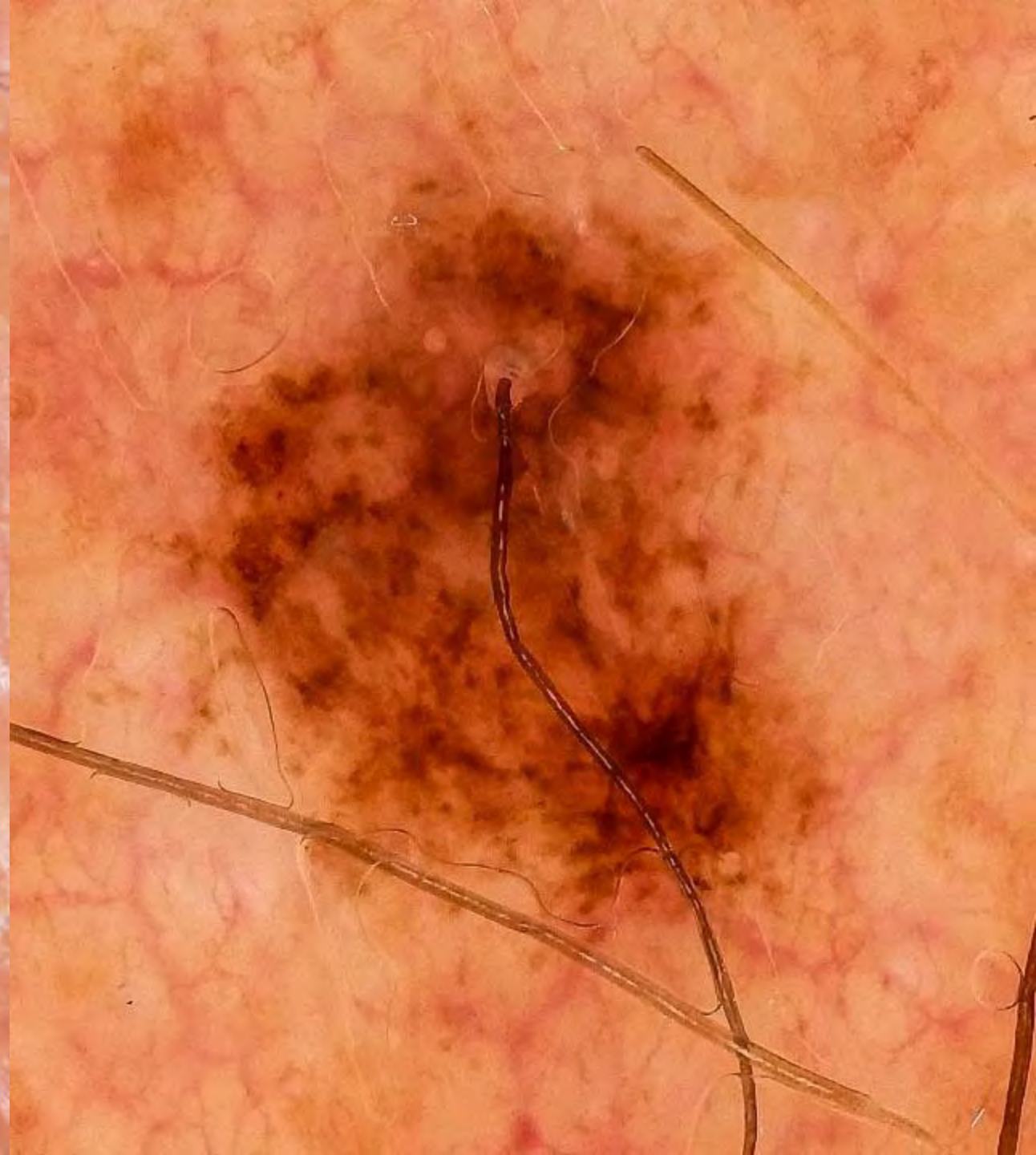


Fig. 12.1

Spitz nevus, intraepidermal

This lesion has two important details indicating a Spitz nevus:

- Cells are epithelioid and have very monomorphic features.

The lesional epidermis is uniformly hyperplastic, with elongated rete ridges (a), with this alteration suddenly ending at the edges of the melanocytic proliferation.

Immunohistochemical studies and clinical history can be useful if there is a concern about Paget disease or an in situ epidermal or adnexal neoplasm.

Cells have, just as in Paget disease, a scattered pattern, being situated mostly in the spinous layer. Only few elements are in the basal layer (b).

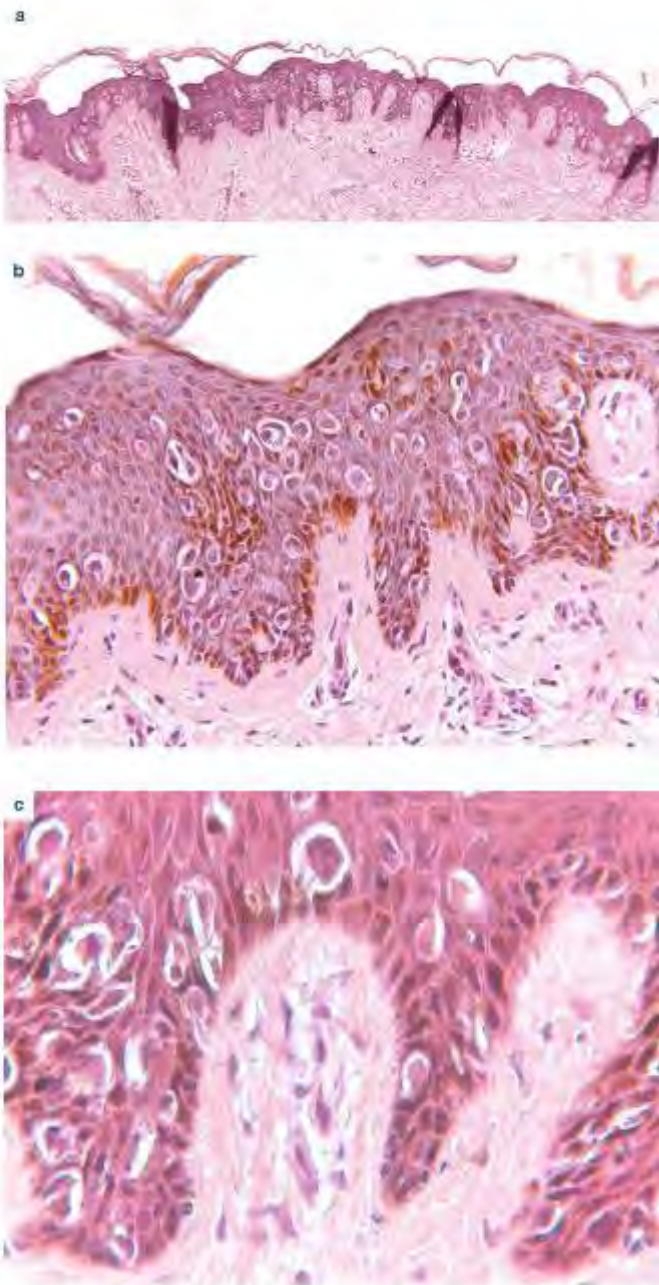
The cells are large and atypical (c) and a melanoma in situ must be ruled out. Clues for a benign lesion are:

- The uniform cell density and morphology.

There is even epidermal hyperplasia with rete ridges of roughly the same lengths.

- The absence of a significant inflammatory infiltrate in the dermis.

In incipient Spitz nevi of this type, clefts uniformly delineate the atypical melanocytes from the adjacent epidermis. Frequently, one finds more multinucleated melanocytes in an intraepidermal Spitz nevus than in an early melanoma in situ. The finding of tiny Kamano bodies can also be helpful.



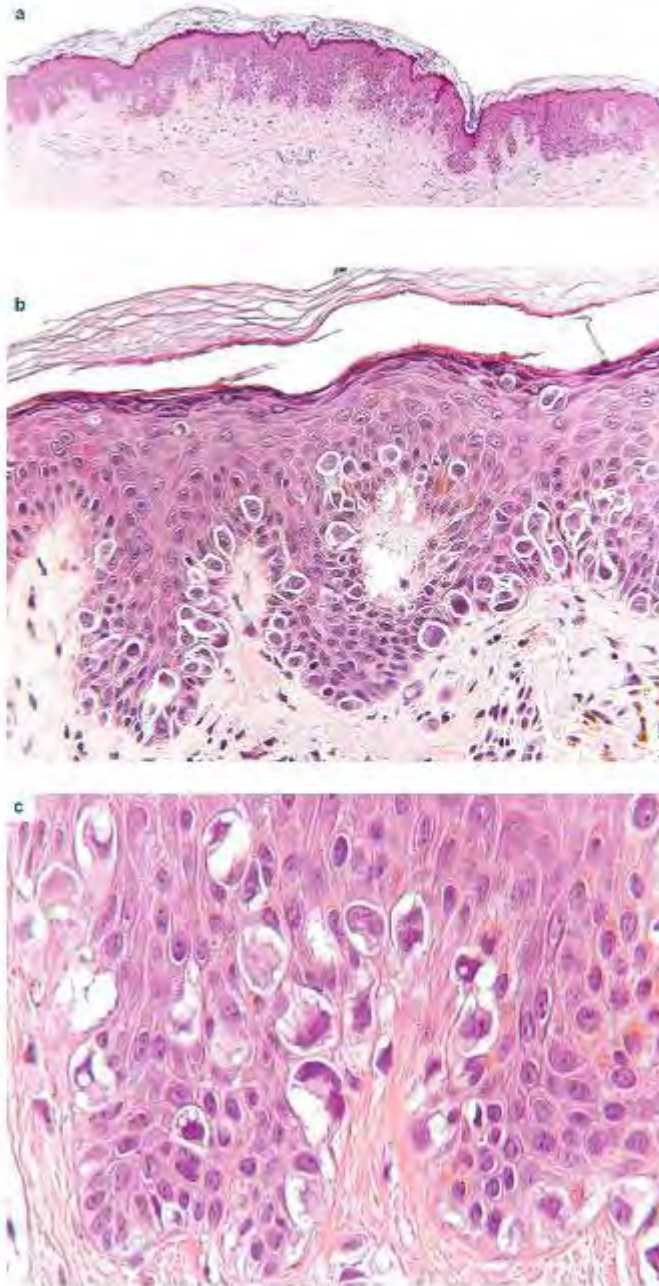
12.5.1 Intraepidermal, Sometimes Pagetoid Spitz Nevus

In some cases of early stage Spitz nevus, only single melanocytes are present and sometimes in a pagetoid pattern (Fig. 12.1). This variant seems to occur disproportionately on the legs of women. The cells are in single units inside the epidermal spinous layer or are gathered in intraepidermal nests. The most typical cells are large, with abundant homogeneous-appearing ground glass cytoplasm and sharp cytoplasmic borders. These result in prominent clefts that outline the cells in a uniform manner. Their nuclei are vesicular, with “open” chromatin and distinct nucleoli. The lesions are small (4 mm) and sharply circumscribed, both clinically and histologically. Epidermis is uniformly altered (slight hyperplasia) and the melanocytes and nests are uniformly scattered throughout the lesion. At the edge of the lesion, the melanocytes and the epidermal hyperplasia “stop” at exactly the same point. The differential diagnosis is with melanoma in situ. The age of the patient (20s on average for this form of Spitz nevus vs. 50s for melanoma in situ) can be helpful in determining how likely one’s diagnosis is. The even distribution and lateral demarcation noted above are useful diagnostic clues. Also, multinucleated melanocytes seem disproportionately common in these lesions. In difficult cases, fluorescence in situ hybridization can distinguish many melanomas in situ from pagetoid Spitz nevi, but the cost of this technique and its limited sensitivity make it impractical, especially as re-excision will usually be done for cases in which there is any doubt.

Fig. 12.2
Spitz nevus, intraepidermal

This lesion has a few cells in the papillary dermis but is largely intraepidermal (a). As in Fig. 12.1, large epithelioid melanocytes predominate. The epidermis overlying the lesion is thickened, with an accentuated granular layer and slight hyperkeratosis.

Unlike the case in melanoma *in situ*, this epidermal hyperplasia tends to be uniform into "end" at the limits of the melanocytic proliferation that define the end of the lesion. Again, clefts uniformly separate melanocytes from one another (b, c) and from epidermal keratinocytes. Multinucleated cells are present in some foci.



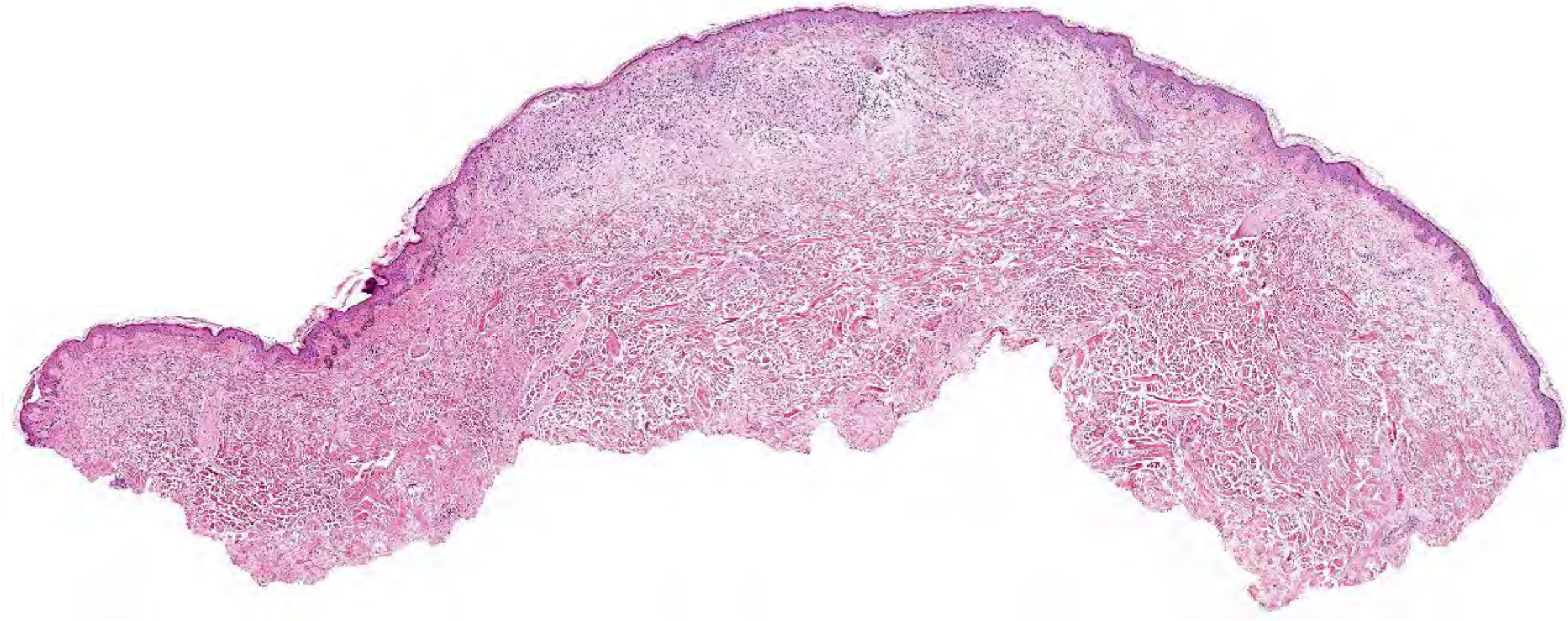
12.5.2 Lentiginous Spitz Nevus

The earliest phase of a Spitz nevus sometimes features single melanocytes evenly distributed along the junction in a lentiginous pattern (Fig. 12.2). The cells can sometimes be present up to the middle of the spinous layer. Single melanocytes are distributed preferentially along the sides and bases of elongated rete ridges in a variant termed as "spitzoid lentigo." Junctional nests are inconspicuous or small. The cells, while large, are monomorphous, with features similar to those described above for pagetoid Spitz nevus. Occasionally, there are long dendrites that extend into the spinous layer. Such cases often feature hyperpigmentation of the spinous layer and melanin in the cornified layer as well. A cleft frequently separates them from the surrounding keratinocytes. As a rule, however, pigmentation is scarce. The epidermis overlying the proliferation is unaffected in the very earliest lesions but later becomes slightly hyperplastic with jagged acanthosis, hypergranulosis, and compact hyperkeratosis. The epidermal hyperplasia may be slight but is remarkable enough to contrast sharply with the surrounding normal epidermis. In lesions with a lentiginous pattern, there can be several exceptional findings. If the lesion is hyperpigmented, globules of melanin may be present in the cornified layer, and single melanocytes may trail off at the edge of the lesion. As with pagetoid Spitz nevus, any doubt usually triggers re-excision with margins used for melanoma *in situ*.

Intraepidermal, Sometimes Pagetoid Spitz Nevus & Lentiginous Spitz Nevus

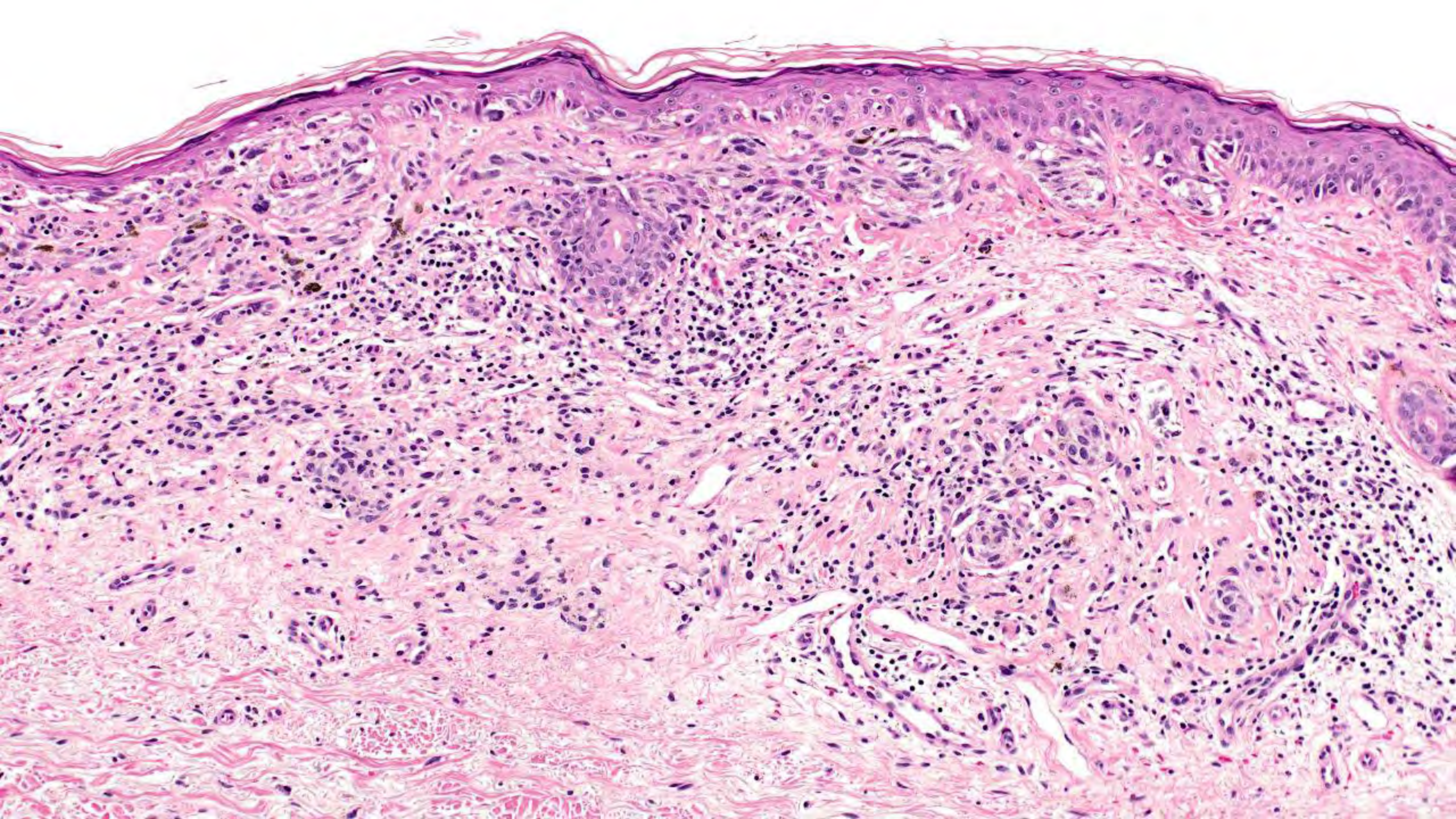
(colloquially often referred to as "baby Spitz")

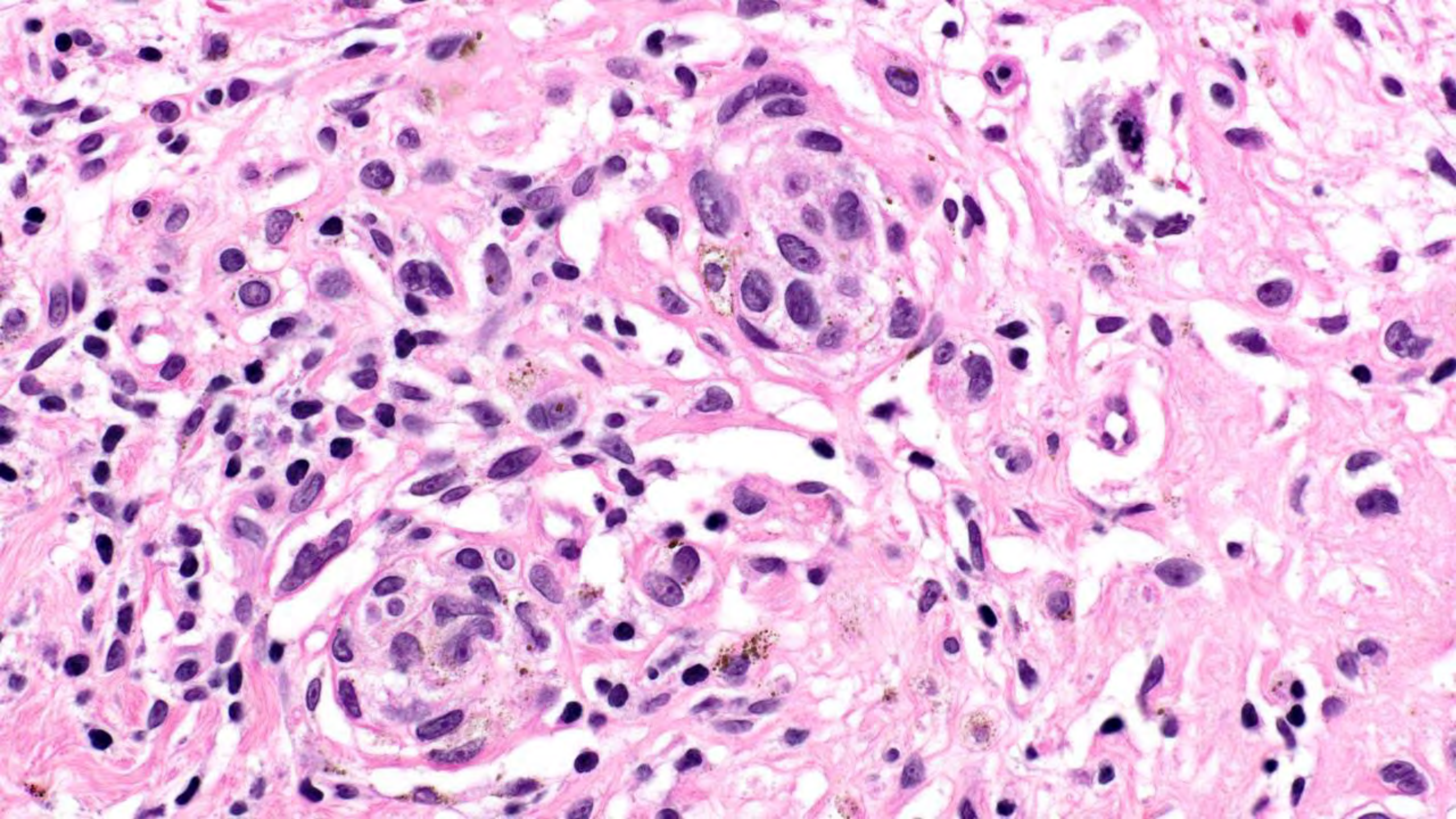
- Should represent an early stage of Spitz nevus, yet is observed almost exclusively in adults, never in children
- Characterized by melanocytes arranged in solitary units predominating over melanocytes arranged in nests – one of the histopathological criteria of melanoma
- Often presence of an intraepidermal pagetoid pattern – another histopathological criterion of melanoma
- "Baby Spitz nevus" or "baby melanoma in situ"?
- Beware a diagnosis of "early Spitz nevus" in middle-aged adults and elderly patients...

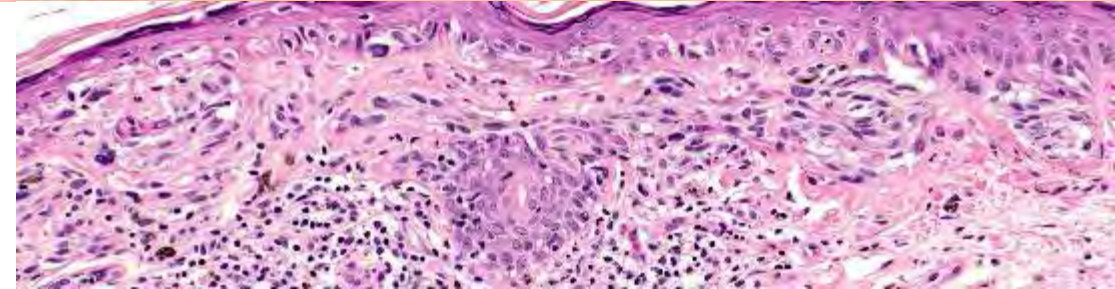
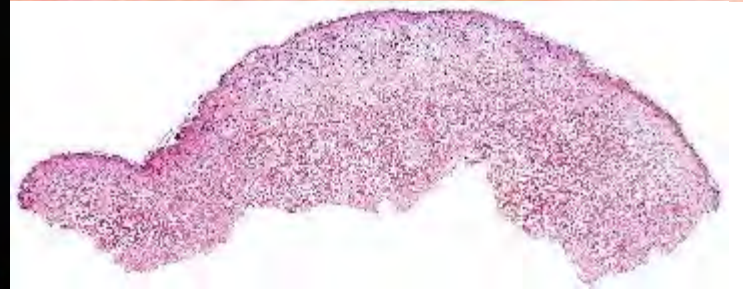


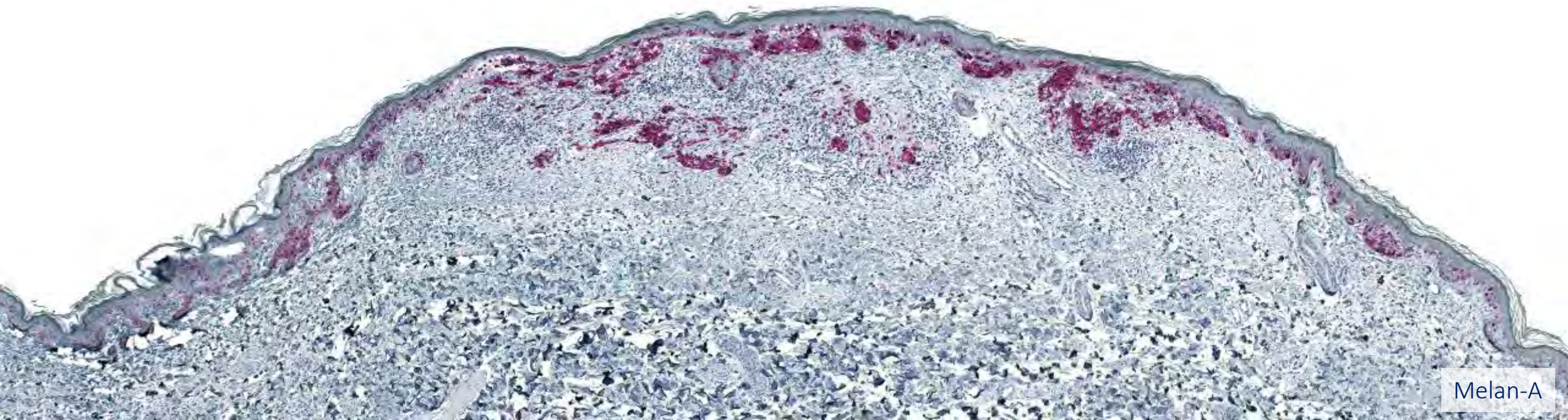
Case 47

M, 68. Sent by a private dermatologist for evaluation of a pigmented lesion on the right arm (duration unknown).

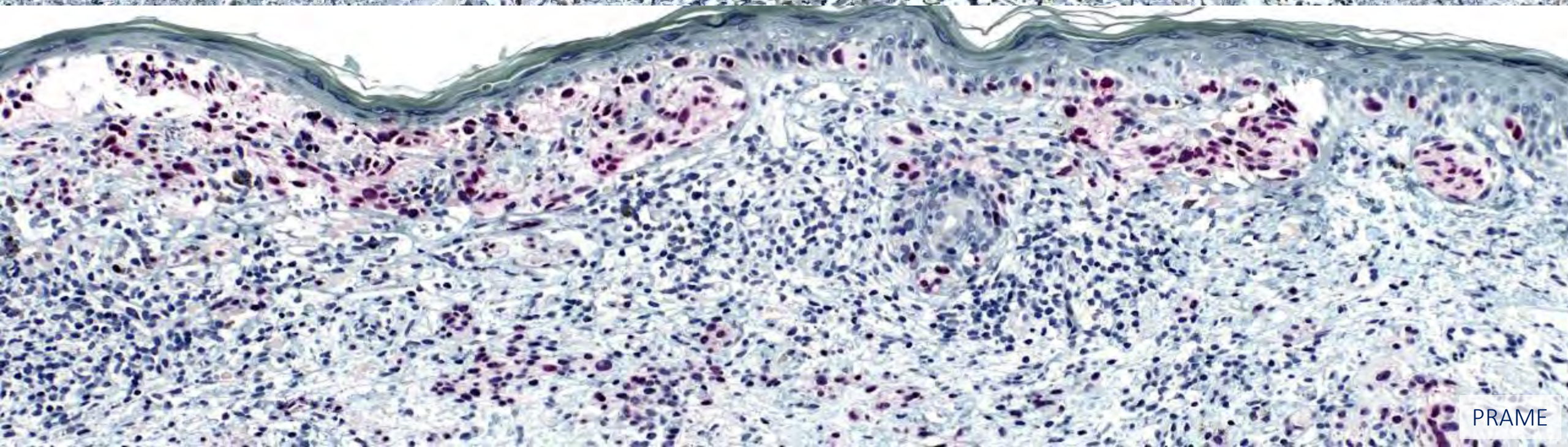




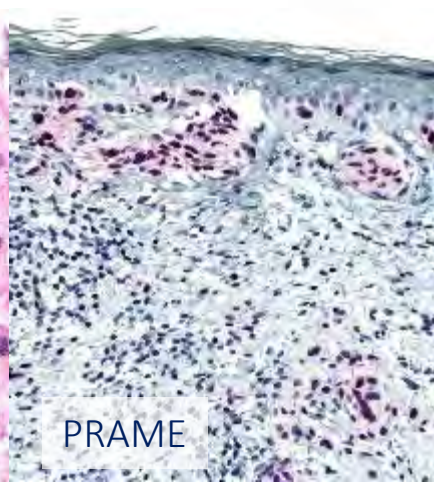
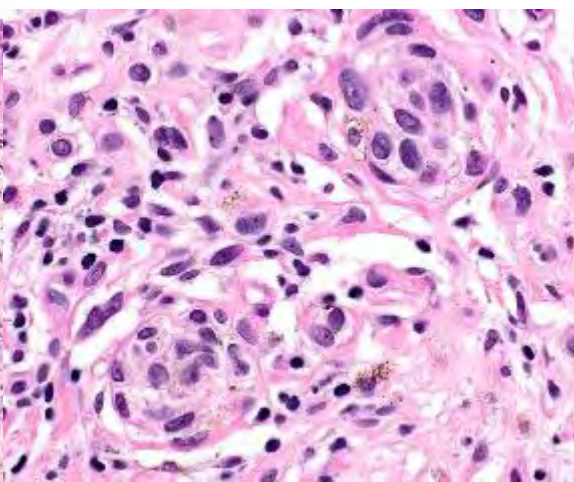
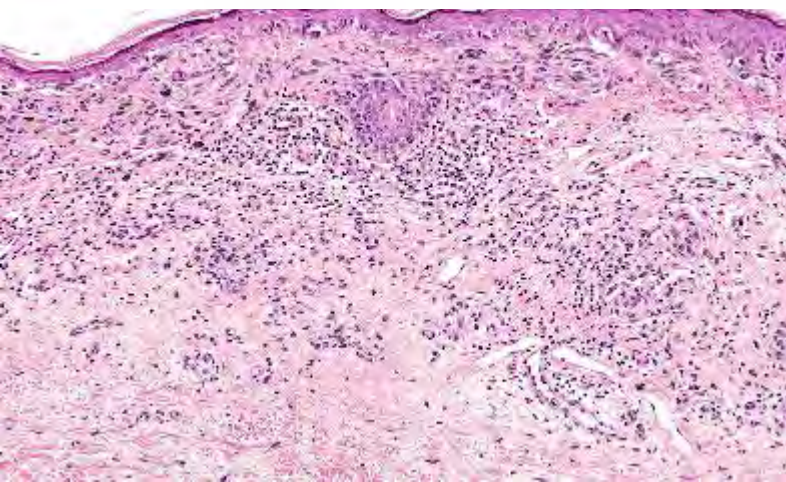
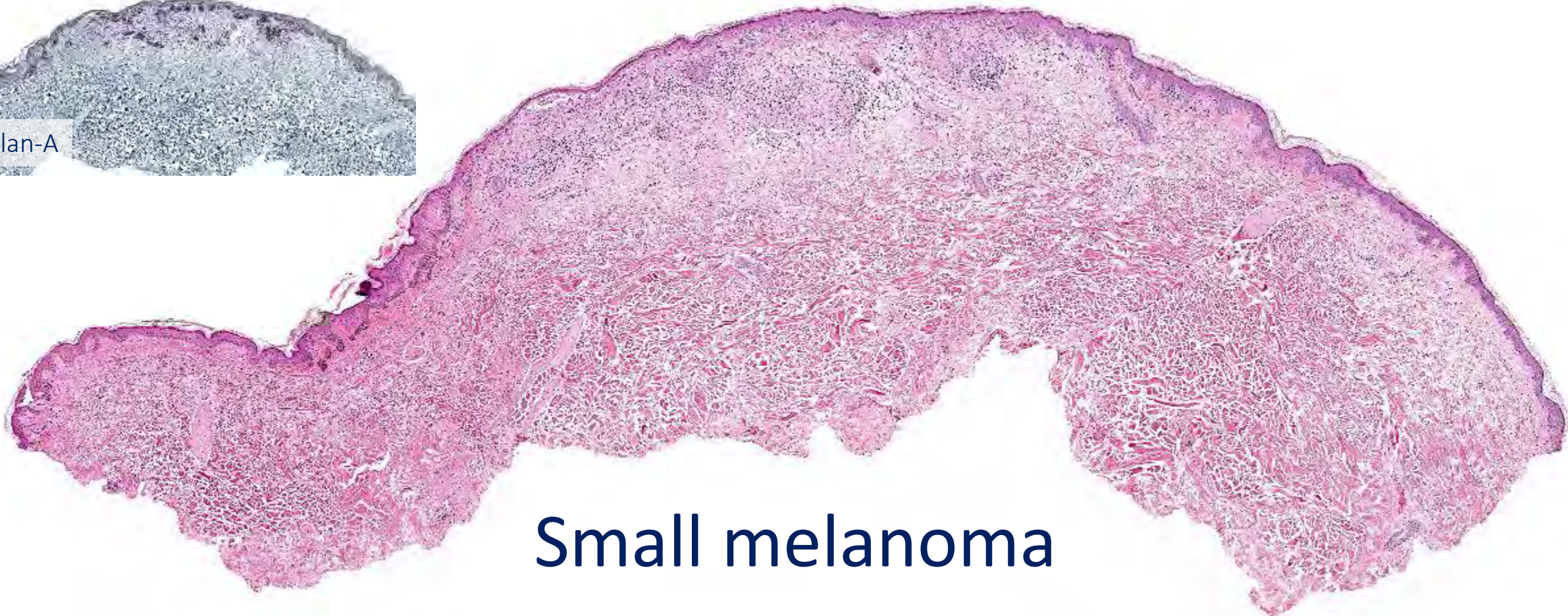
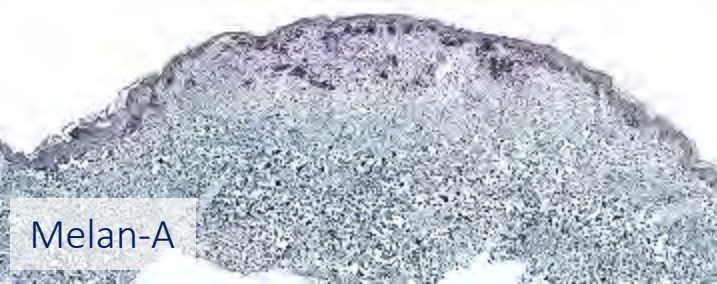


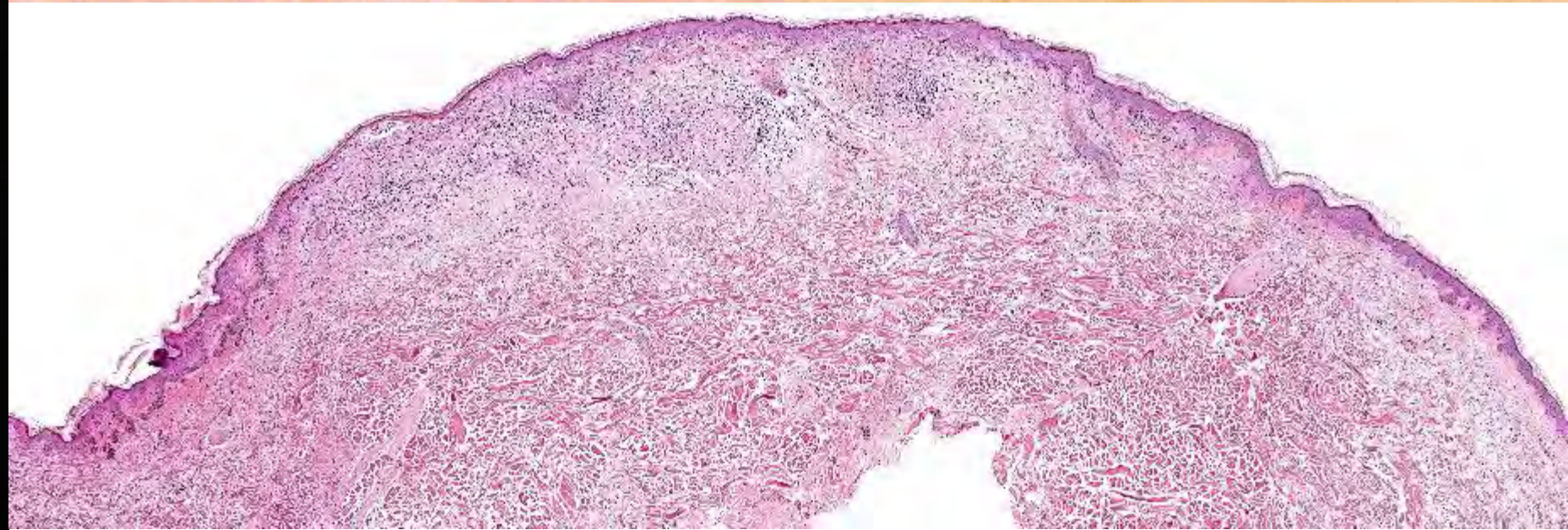


Melan-A



PRAME







Diagnostic criteria

Age

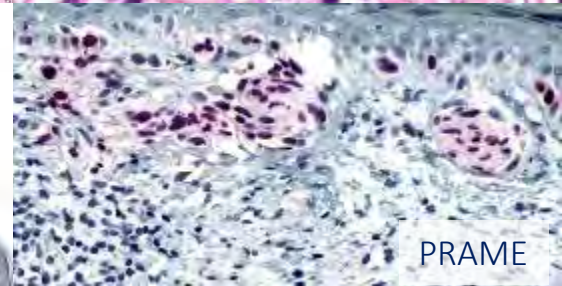
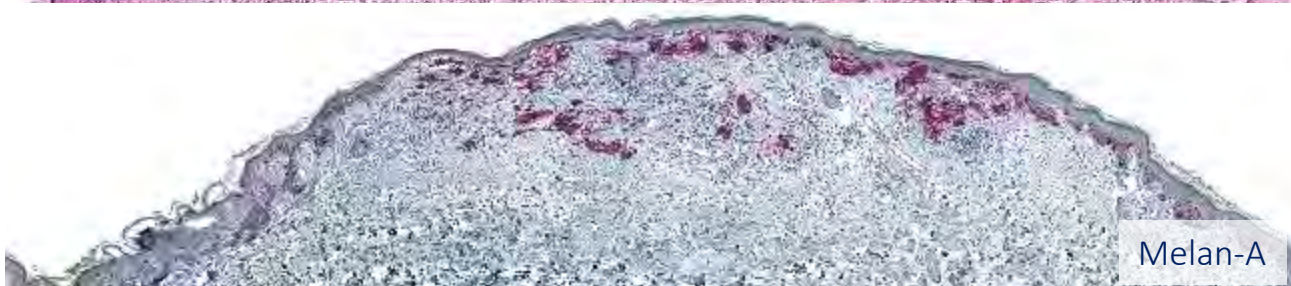
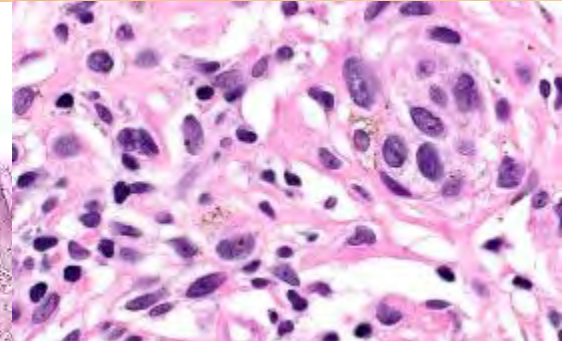
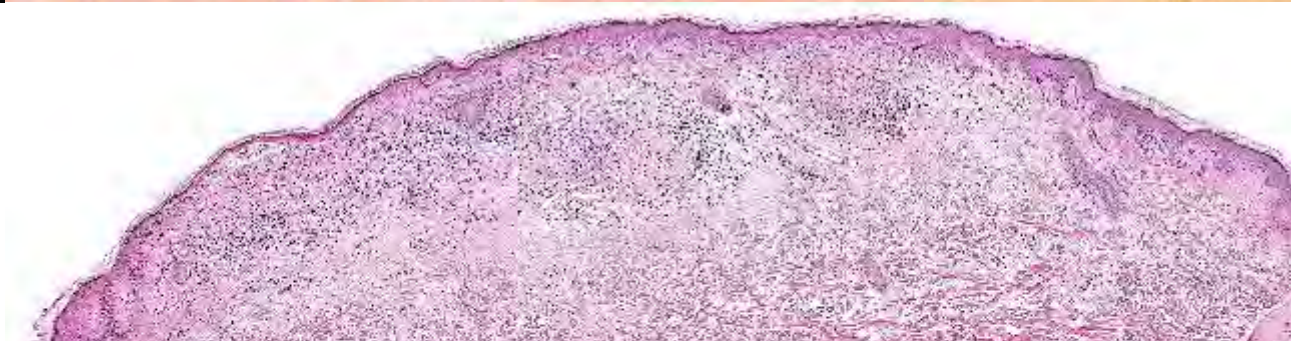
Asymmetry (clinical and H&E)

Unsharp circumscription (clinical and H&E)

Atypical melanocytes (H&E)

PRAME+ (IHC)

In spite of the clinical picture, no remnants of a previous melanocytic nevus on H&E or IHC



Melan-A

PRAME

REVIEW

Overdiagnosis in Cancer

H. Gilbert Welch, William C. Black

Manuscript received September 1, 2018; revised March 1, 2019; accepted March 1, 2019

Correspondence to: H. Gilbert Welch, MD, Veterans Affairs Outpatient Clinic, 116A, 16801, Veterans Affairs Medical Center, White River, VT 05370 (e-mail: g.welch@va.gov).

This article summarizes the phenomenon of cancer overdiagnosis—the diagnosis of a “cancer” that would otherwise not go on to cause symptoms or death. We describe the two prerequisites for cancer overdiagnosis to occur: the existence of a silent disease reservoir and activities leading to its detection (particularly cancer screening). We estimated the magnitude of overdiagnosis from randomized trials about 25% of mammographically detected breast cancers, 50% of chest x-ray and/or sputum-detected lung cancers, and 60% of prostate-specific antigen-detected prostate cancers. We also review data from observational studies and population-based cancer statistics suggesting overdiagnosis in computed tomography-detected lung cancer, melanomas, thyroid cancer, meningioma, and kidney cancer. To address the problem, patients must be adequately informed of the nature and the magnitude of the tradeoff involved with early cancer detection. Equally important, researchers need to work to develop better estimates of the magnitude of overdiagnosis and develop clinical strategies to help minimize it.

J. Natl. Cancer Inst. 2019;111(2):105–113

Early detection has forced clinicians and researchers to recon-

sider the interplay of three variables: the cancer size at diagnosis, the growth rate, and the patient’s remaining time for mortality.

Overdiagnosis is the term used when a condition is diagnosed that would otherwise not go on to cause symptoms or death. (...) Overdiagnosis should not be confused with false-positive results, that is, a positive test in an individual who is subsequently recognized not to have cancer. By contrast, an overdiagnosed patient has a tumor that fulfills the pathological criteria for cancer.

What Is Cancer Overdiagnosis?

Overdiagnosis is the term used when a condition is diagnosed that would otherwise not go on to cause symptoms or death. Cancer overdiagnosis may have one of two explanations: (1) the cancer never progresses or (2) the cancer progresses slowly enough that the patient dies of other causes before the cancer becomes symptomatic. Note that this second explanation under-

lies the importance of the timing of cancer diagnosis. The cancer may never progress, or it may progress so slowly that the patient dies of other causes before the cancer becomes symptomatic. Note that this second explanation under-

Overdiagnosis occurs when either: nonprogressive cancers at very slow-growing cancers (more precisely, at a slow enough pace that individuals die of other causes) die before the cancer ever

Downloaded from https://academic.oup.com/jnci/advance-article-abstract/doi/10.1093/jnci/dkz099/5400000 by University of Oxford user on October 23, 2019

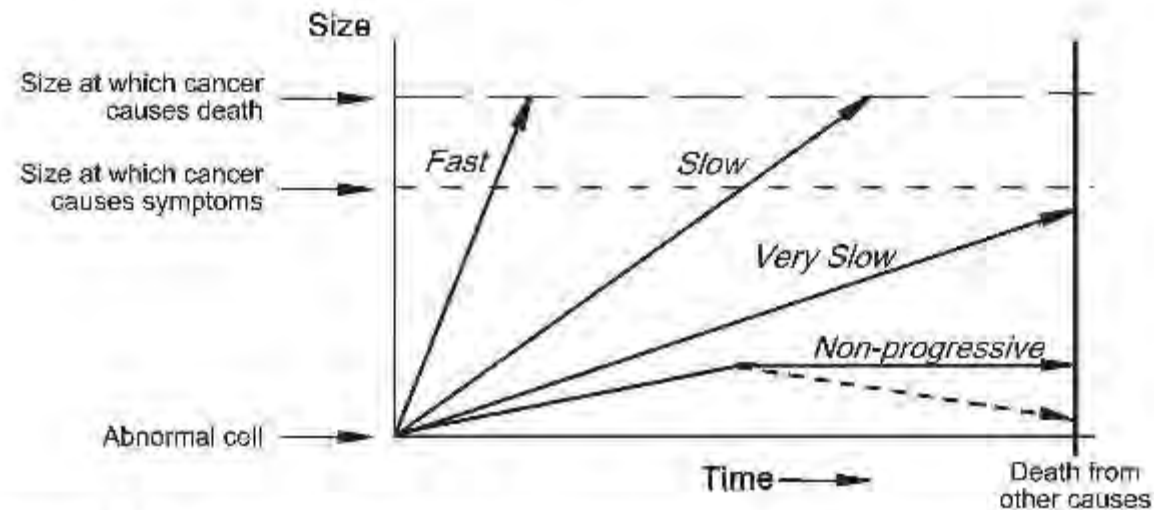


Figure 1. Heterogeneity of cancer progression. The arrow labeled “fast” represents a fast-growing cancer, one that quickly leads to symptoms and to death. The arrow labeled “slow” represents a slow-growing cancer, one that leads to symptoms and death but only after many years. The arrow labeled “very slow” represents a cancer that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms. The arrow labeled “nonprogressive” represents cellular abnormalities that meet the pathological definition of cancer but never grow to cause symptoms—Alternatively, they may grow and then regress (dotted line). (Figure 1 was previously supplied by the authors to Wikipedia.)

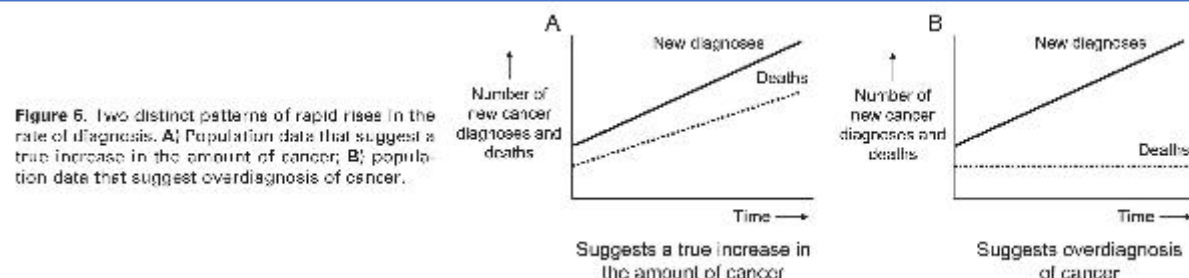


Figure 6. Two distinct patterns of rapid rises in the rate of diagnosis. A) Population data that suggest a true increase in the amount of cancer; B) population data that suggest overdiagnosis of cancer.

Cancer Stat Facts: Melanoma of the Skin

Expand All Collapse All

Reports on Cancer

Annual Report to the Nation

Cancer Stat Facts

Cancer Statistics Review +

Preliminary Cancer Incidence Rates and Trends +

SEER Publications +

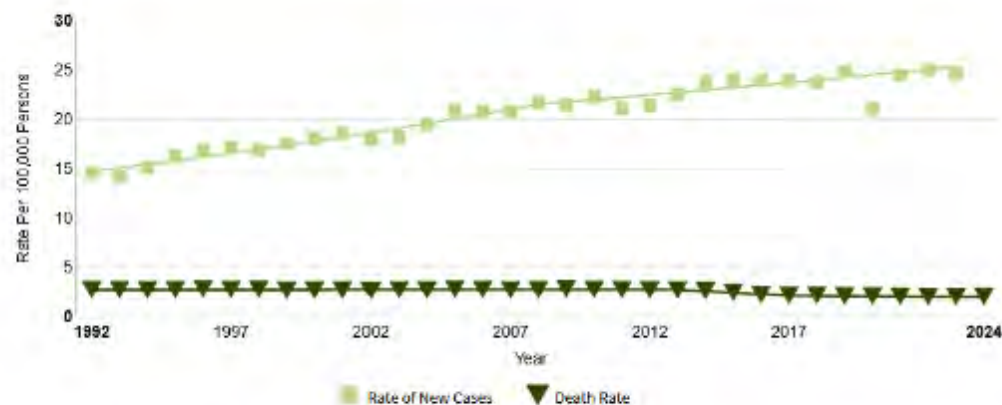
Statistics at a Glance

At a Glance

Estimated New Cases in 2026	112,000
% of All New Cancer Cases	5.3%
Estimated Deaths in 2026	8,510
% of All Cancer Deaths	1.4%

5-Year
Relative Survival
94.7%

2016-2022



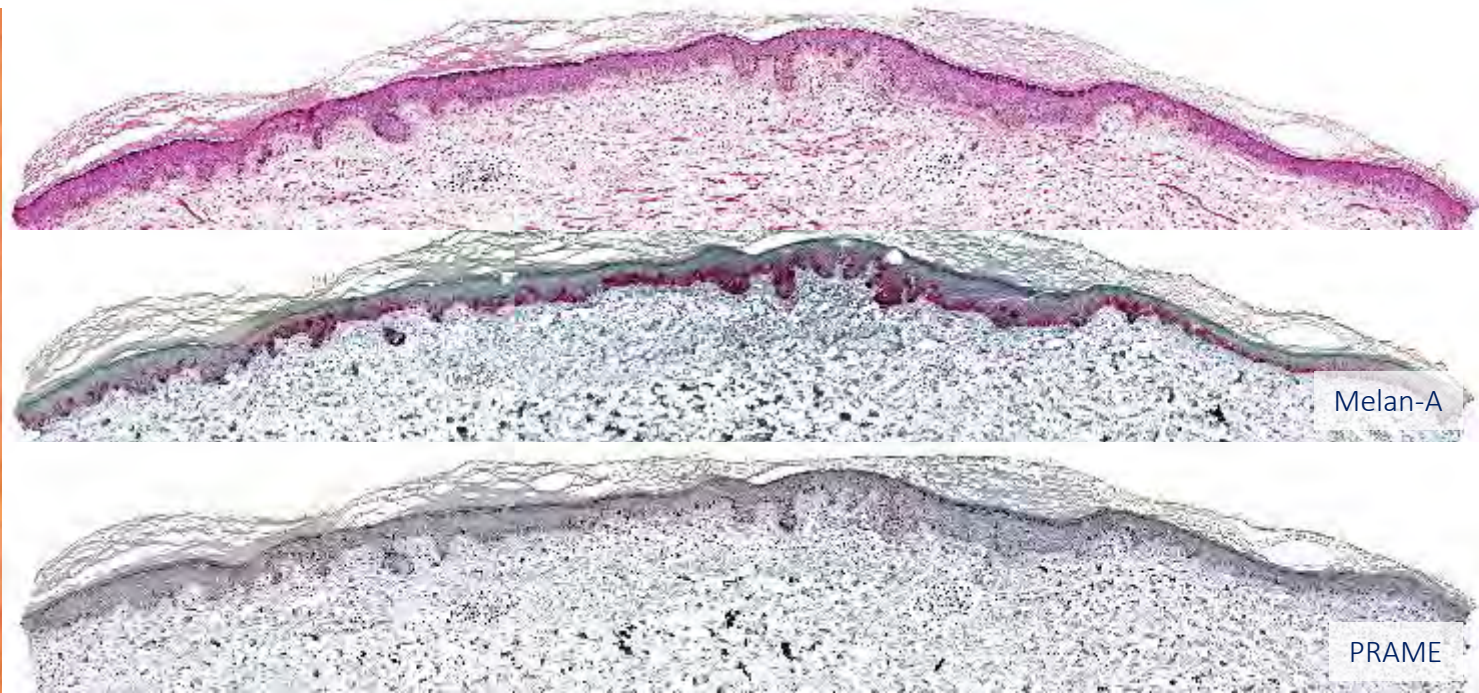
New cases come from SEER 12. Deaths come from U.S. Mortality.

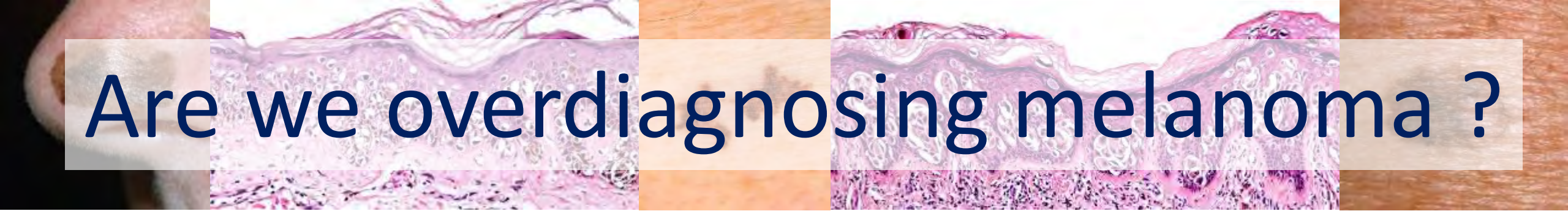
All Races, Both Sexes. Rates are Age-Adjusted.

Modeled trend lines were calculated from the underlying rates using the [Joinpoint Trend Analysis Software](#).

The 2020 incidence rate is displayed but not used in the fit of the trend line(s). [Impact of COVID on SEER Cancer Incidence 2020 data](#)

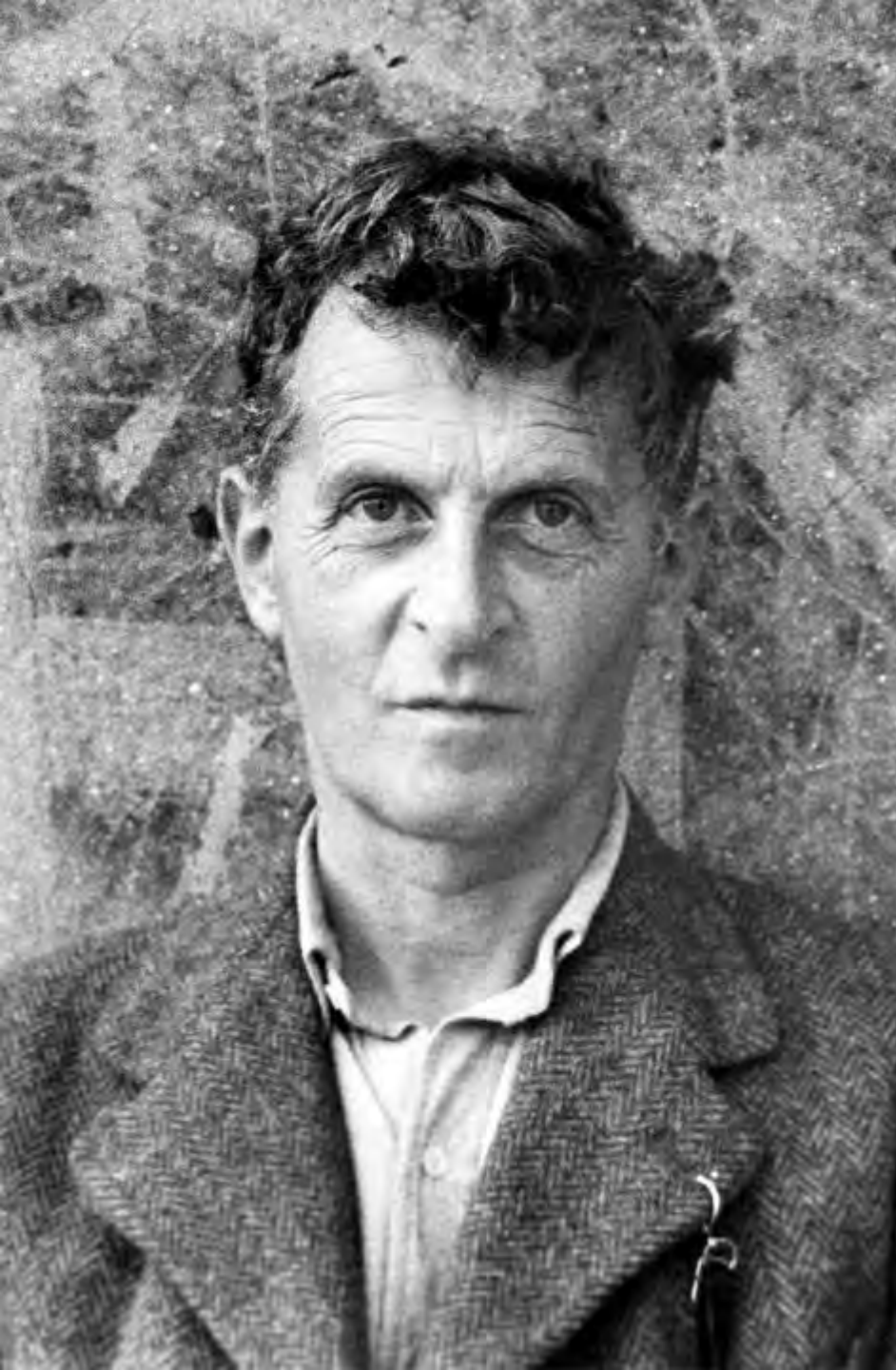
New cases are also referred to as incident cases in other publications. Rates of new cases are also referred to as incidence rates.





Are we overdiagnosing melanoma ?

- In situ cancer doesn't kill a patient
- The term "cancer" should be used only for advanced disease likely to be fatal
- A diagnosis of "cancer" is bound with considerable distress by patients
- Patients diagnosed with cancer may lose their health insurance
- Invasive cancer may not kill a patient either; even metastatic cancer may be cured
- The term "lion" is used irrespective of the age of the animal, although a baby lion will never kill; we don't call baby lions "dysplastic cats"
- A diagnosis of diabetes is bound with distress as well (and diabetes may be life-threatening if unmanaged), but in 1997 the diagnostic threshold has been lowered according to medical knowledge from 140 mg/dL to 126 mg/dL (with the new threshold, only in the US >1.500.000 persons became diabetic overnight)
- The health insurance systems should be reformed, not the classification of diseases



Die Grenzen meiner Sprache bedeuten
die Grenzen meiner Welt.

(The limits of my language define the
limits of my world).

Ludwig Wittgenstein.

Tractatus Logico-Philosophicus, 1922

Dermatopathologisches Laboratorium

Leiter: Univ.-Prof. Dr. Lorenzo Cerroni

A-8036 Graz, Auenbruggerplatz 8

Sekretariat: Tel. (0316) 385-3235; Fax (0316) 385-4957; Labor: Tel. (0316) 385-2344

08.10.2010



H2010046371

Zuweisung:

- ☐ Extern
- ☐ OP
- ☐ Station
- ☐ Ambulanz
- ☐ Eingriffsraum

ANGELANGT AM

06. Okt. 2010

Geburtsdatum:

19.02.1936

Datum:

04.10.2010

Tel.: 0316/77 18 02

Art des Eingriffes:

- ☐ Stanze / Probenexzision
- ☒ Abtragung / Shaving
- ☐ Totalexzision (auch mittels Stanze)

KLINISCHE DATEN (hausinterne PatientInnen: BITTE KÖPIE DES ARZTBRIEFES BEILEGEN!):

Lokalisation: Nasenspitze

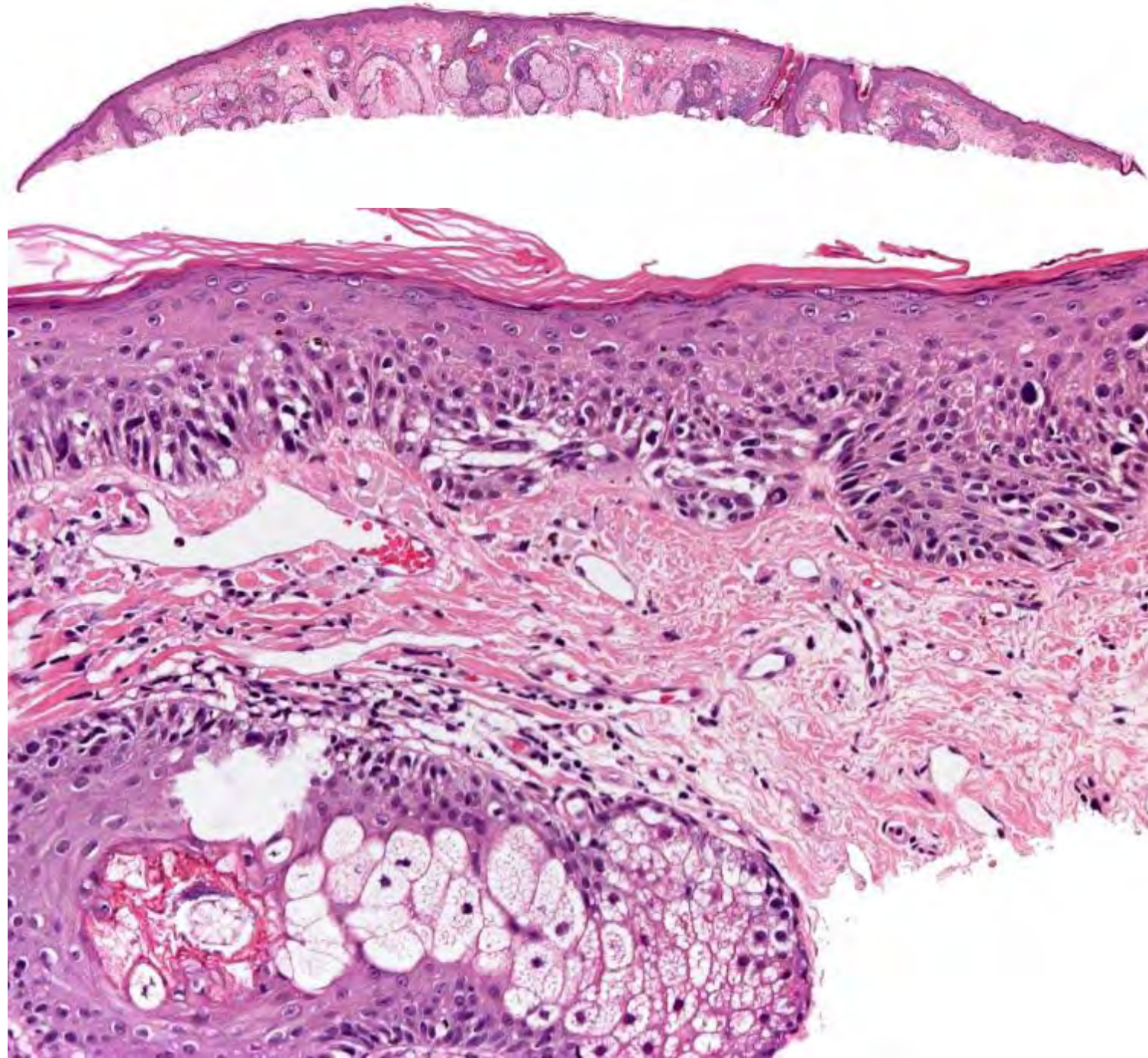
Anamnese und klinische Beschreibung:

Klinische Diagnose: susp. Lentigo maligna

Differentialdiagnose:

Vorbefunde:

October 4, 2010



Landeskrankenhaus - Universitätsklinikum Graz

Universitätsklinik für Dermatologie und Venerologie

Klinikversand: Univ.-Prof. Dr. Werner Aberer

A-8036 Graz, Auenbruggerplatz 8, Telefon: +43 (316) 385-2423, Fax: +43 (316) 385-2466

E-Mail: dermatologie@meduni-graz.at, Internet: http://www.meduni-graz.at/dermatologie/

GRATIS: Telefon: Servicecenter 1016 (170 von 25.06.2011)

Stellenärztliche Krankenkassengemeinschaft mbH



Medizinische Universität Graz

Dermatopathologisches Laboratorium

Leiter: Univ.-Prof. Dr. Lorenzo Cerroni

A-8036 Graz, Auenbruggerplatz 8

Sekretariat: Tel. (0316) 385-3233; Fax (0316) 385-4957; Labor: Tel. (0316) 385-2341

08.06.2011



H2011028877

Zuweisung:

- ☐ Extern
- ☐ OP
- ☐ Station
- ☐ Ambulanz
- ☐ Eingriffsraum

EINGELANGT AM

08. Juni 2011

10:00 Uhr

Geburtsdatum: 19.02.1936

Datum: 08.06.2011

Tel.: 0316/77 18 03

Art des Eingriffes:

- ☐ Stanze / Probeexzision
- ☒ Abtragung / Shaving
- ☐ Totalexzision (auch mittels Stanze)

KLINISCHE DATEN (hausinterne PatientInnen: BITTE KOPIE DES ARZTBRIEFES BEILEGEN!):

Lokalisation: re Nasenspitze

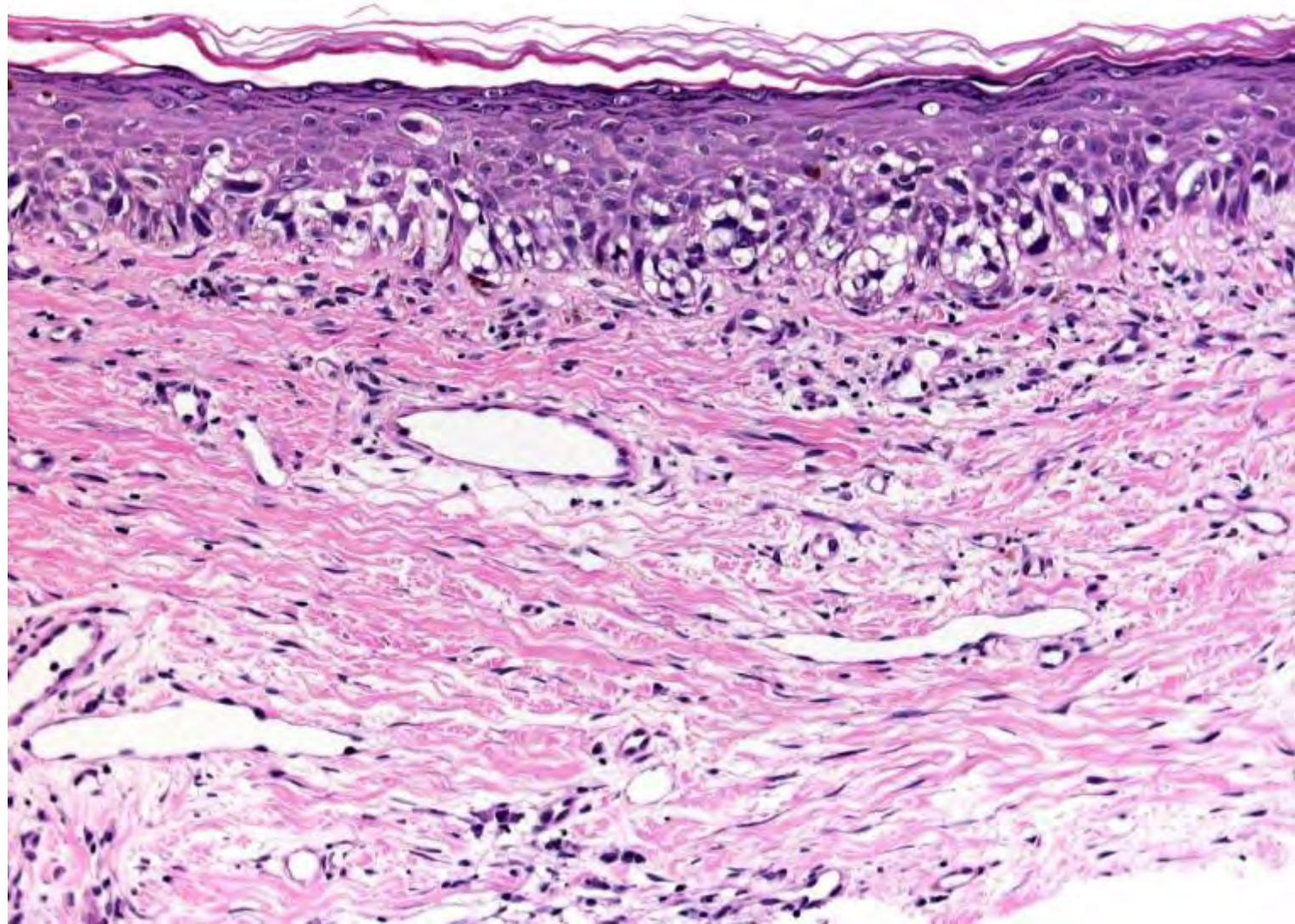
Anamnese und klinische Beschreibung:

Klinische Diagnose: antigo mal.

Differentialdiagnose:

Vorbefunde:

June 8, 2011
(9 months later)





Dermatopathologisches Laboratorium

Leiter: ao Univ.-Prof. Dr. Lorenzo Cerroni

A-8036 Graz, Auenbruggerplatz 8

Sekretariat: Tel. (0316) 385-3235; Fax (0316) 385-4957; Labor: Tel. (0316) 385-2341

22.03.2012



H2012012858

Zuweisung:

- ☐ Extern
- ☐ OP
- ☐ Station
- ☐ Ambulanz
- ☐ Eingriffsraum

Eingelangt am
22. März 2012

PATIENTENDATEN:

EINSENDER:

Geburtsdatum: 19.02.1936

Datum: 20.03.2012

Tel.: 0316/77 18 03

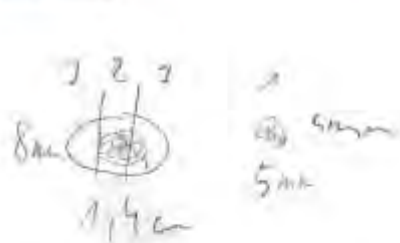
Art des Eingriffes:

- ☐ Stanze / Probeexzision
- ☐ Abtragung / Shaving
- ☐ Totalexzision (auch mittels Stanze)

KLINISCHE DATEN (hausinterne PatientInnen: BITTE KOPIE DES ARZTBRIEFES BEILEGEN !):

Lokalisation: Nasenspitze re

Anamnese und klinische Beschreibung:



Lentigo mal. Rezidiv

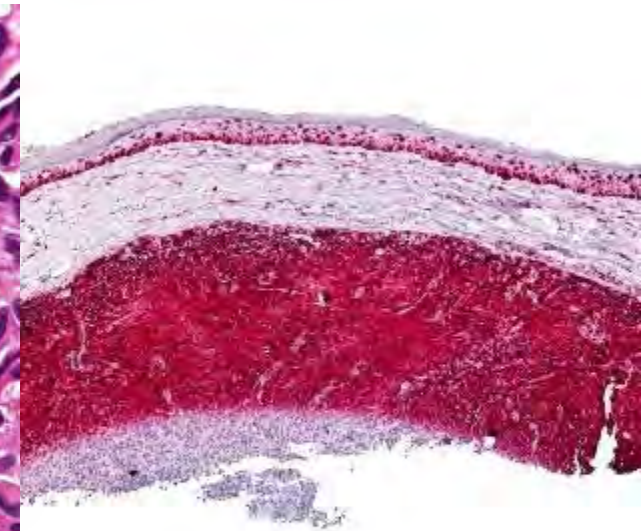
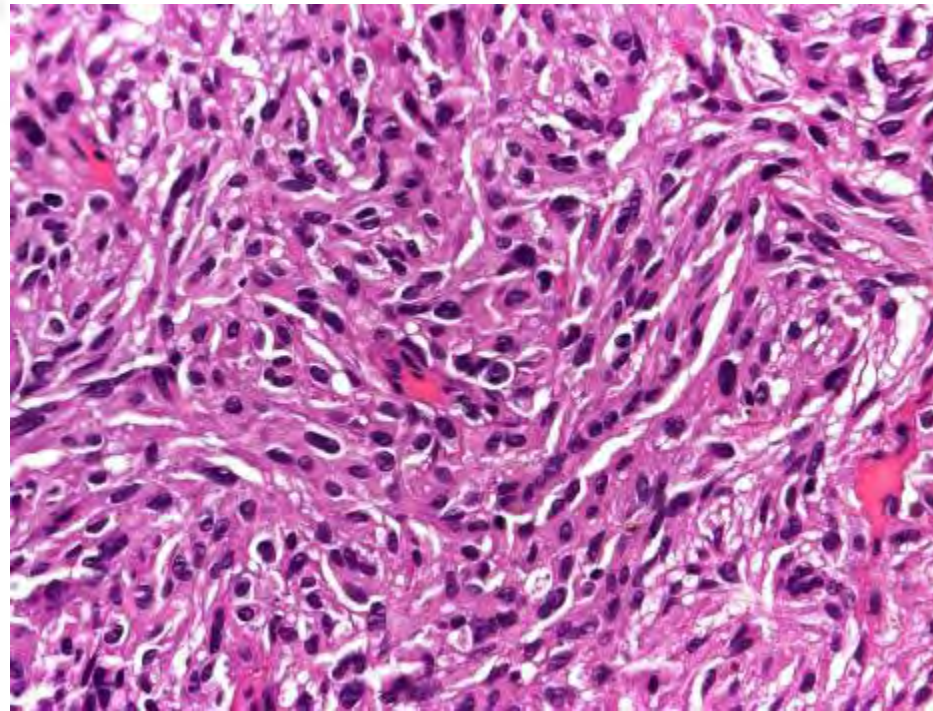
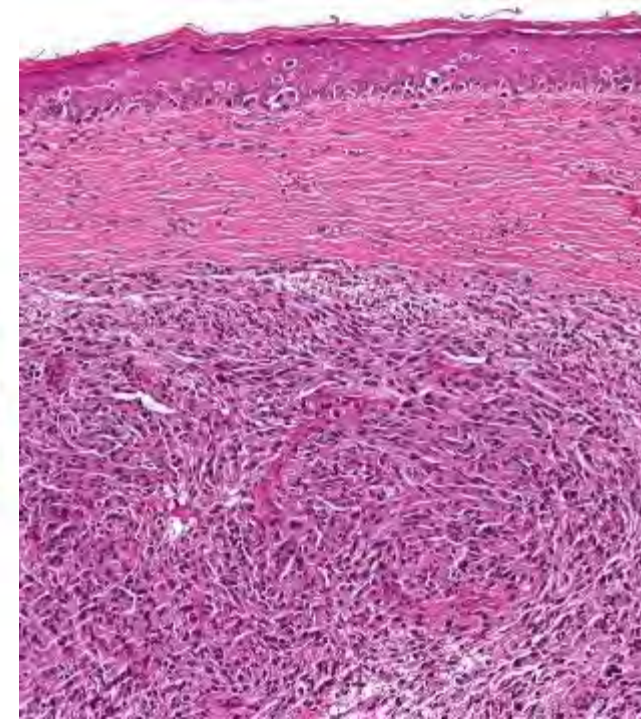
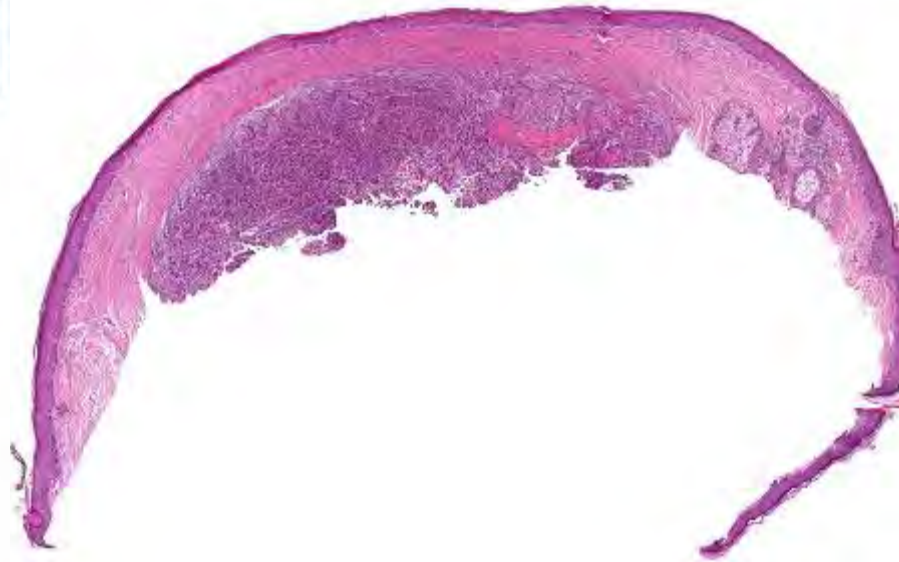
Klinische Diagnose:

Differentialdiagnose:

Vorbefunde:

March 20, 2012

(9 more months later)



Melan-A

1st presentation



35 days later

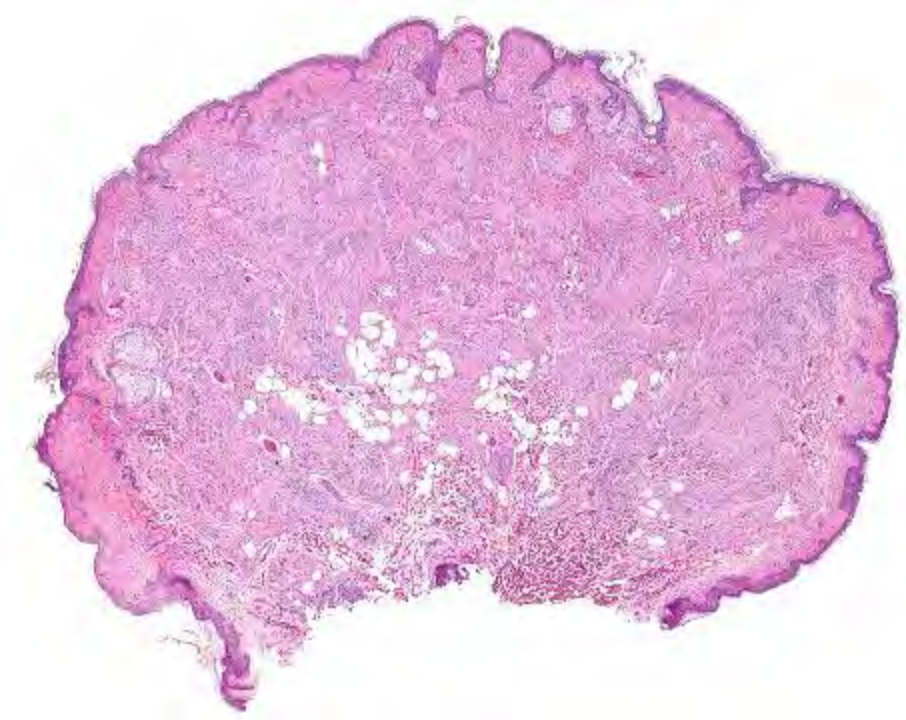


Every "indolent" or "slow growing" cancer will get speed,
sometime...

An "indolent" or "slow-growing" cancer is not a turtle;
rather a cheetah that doesn't (yet) run...



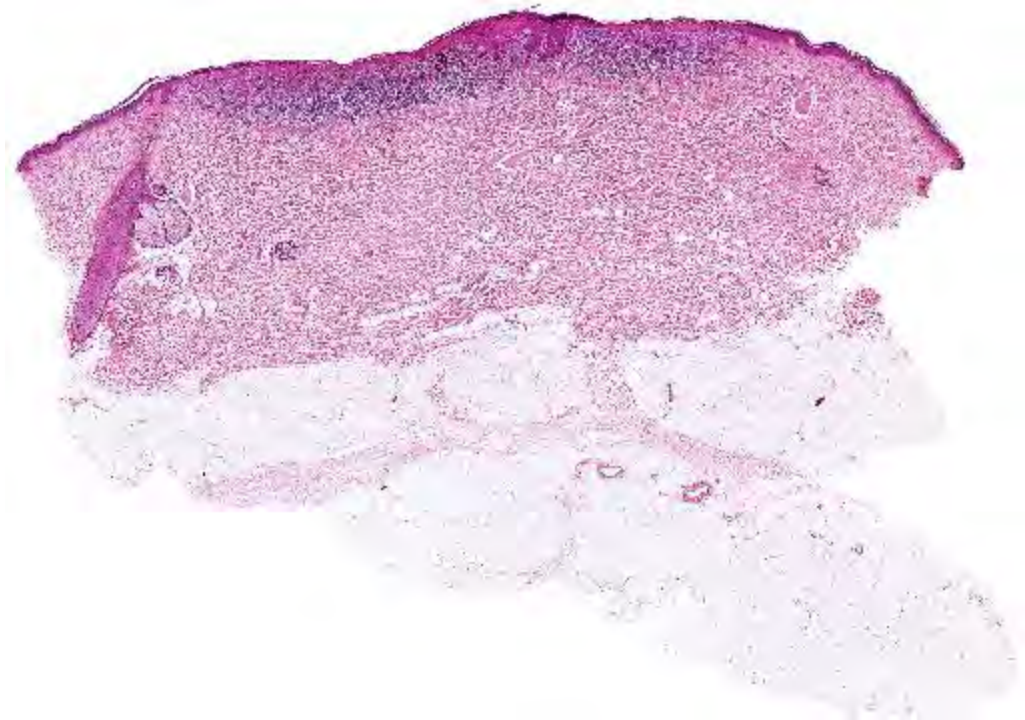
What is the biological difference between a melanocytic nevus and a melanoma ?

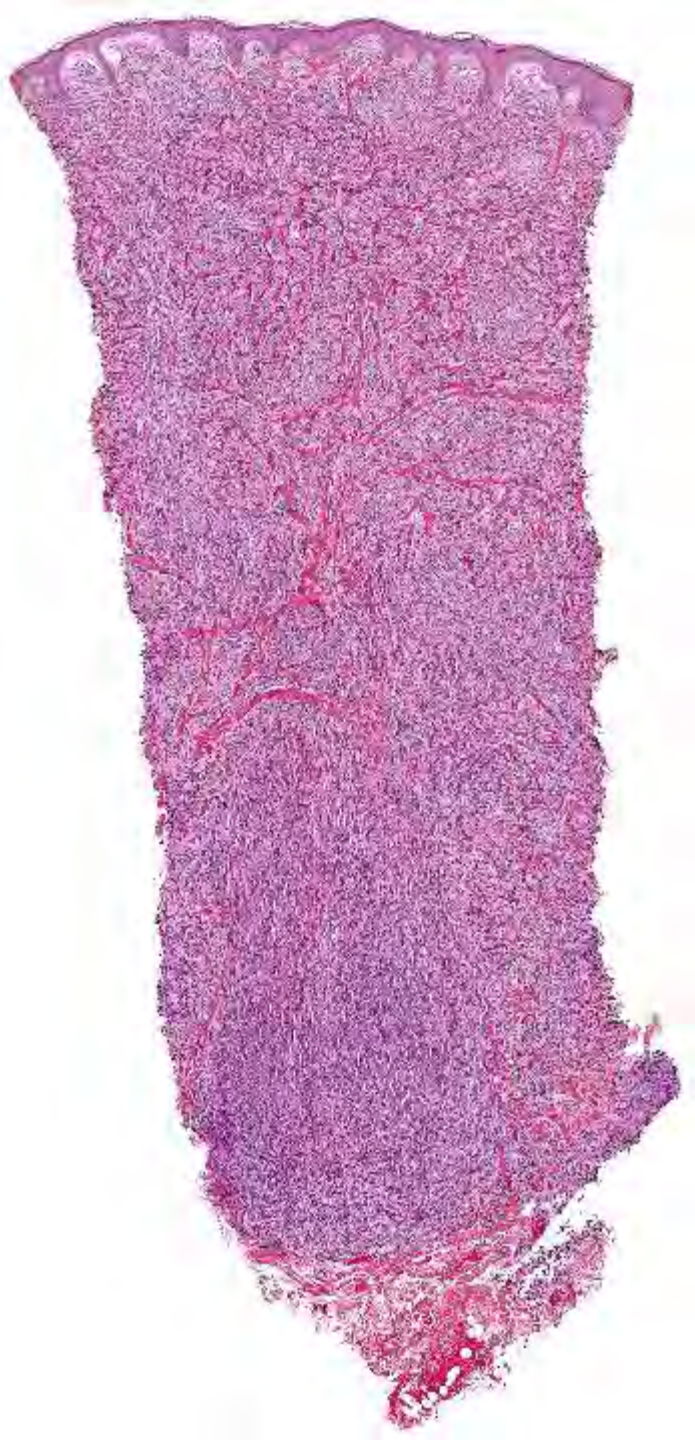


Both are caused by a molecular mechanism

Melanocytic nevi start growing and then stop and remain stable or involute

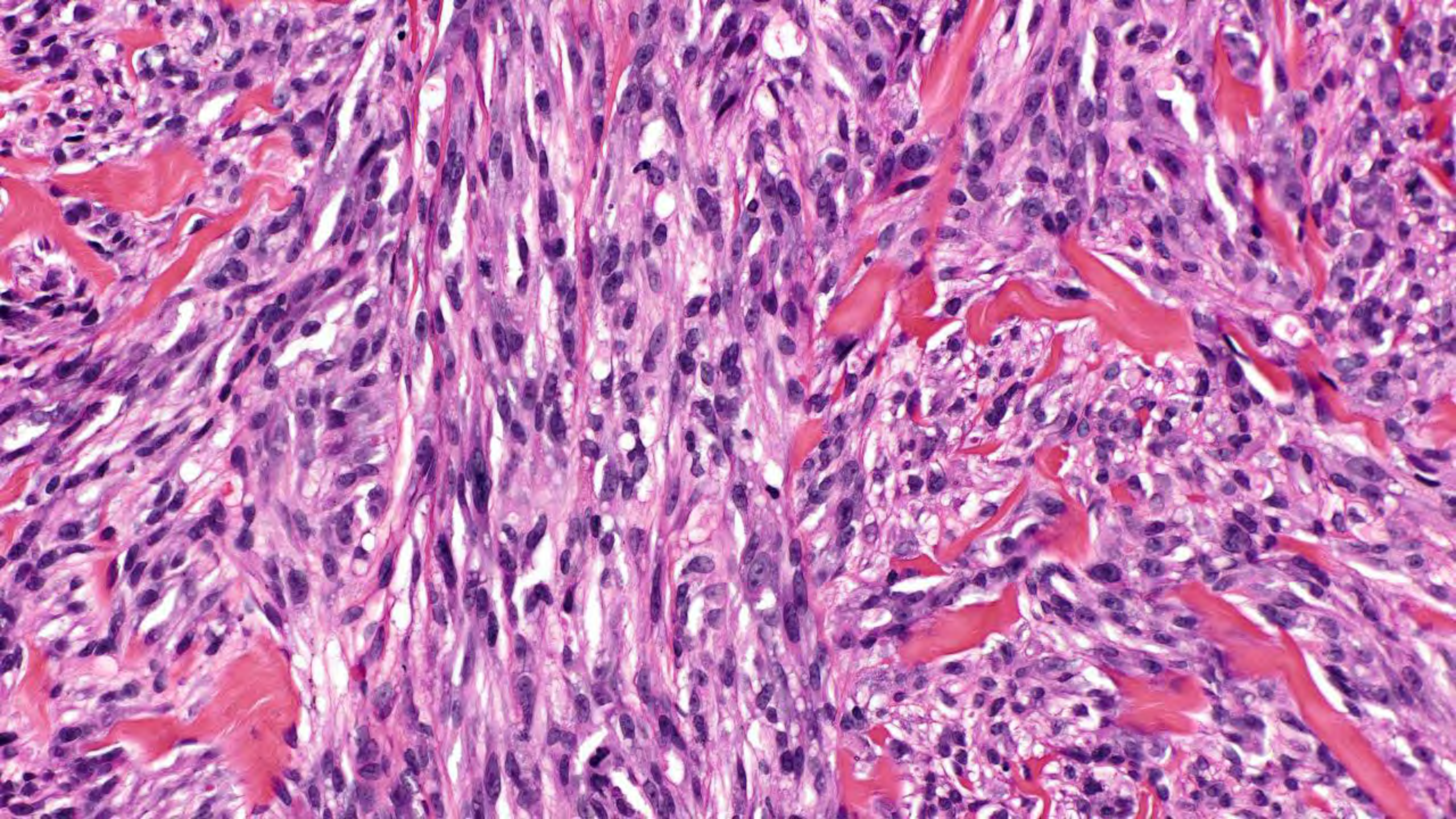
Melanomas start growing and continue to grow indefinitely – yet at variable pace

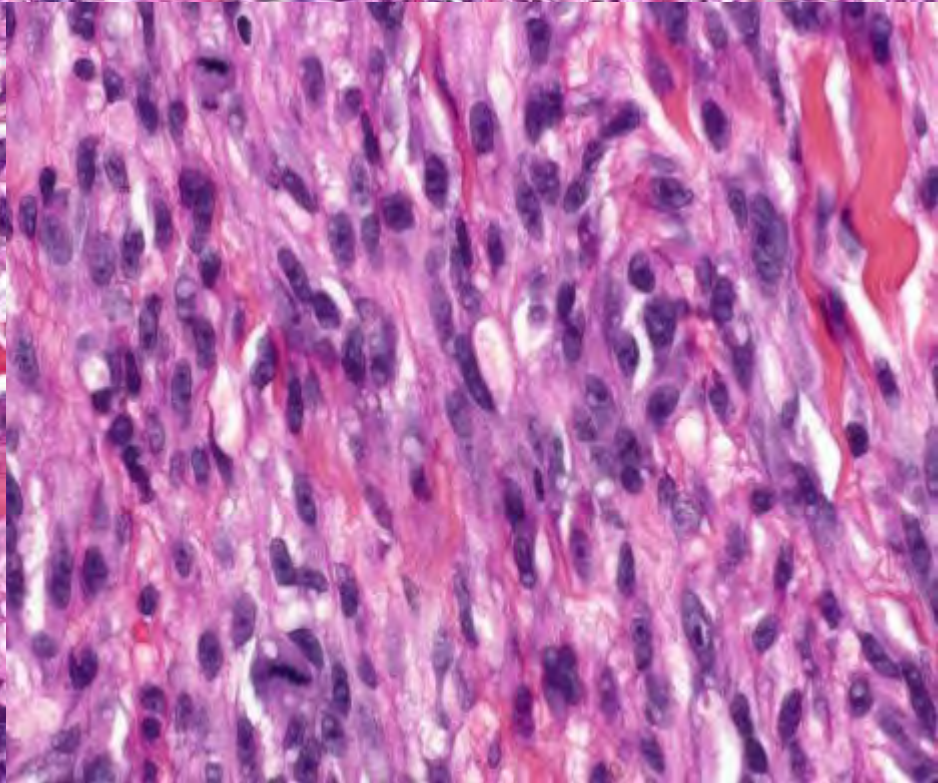
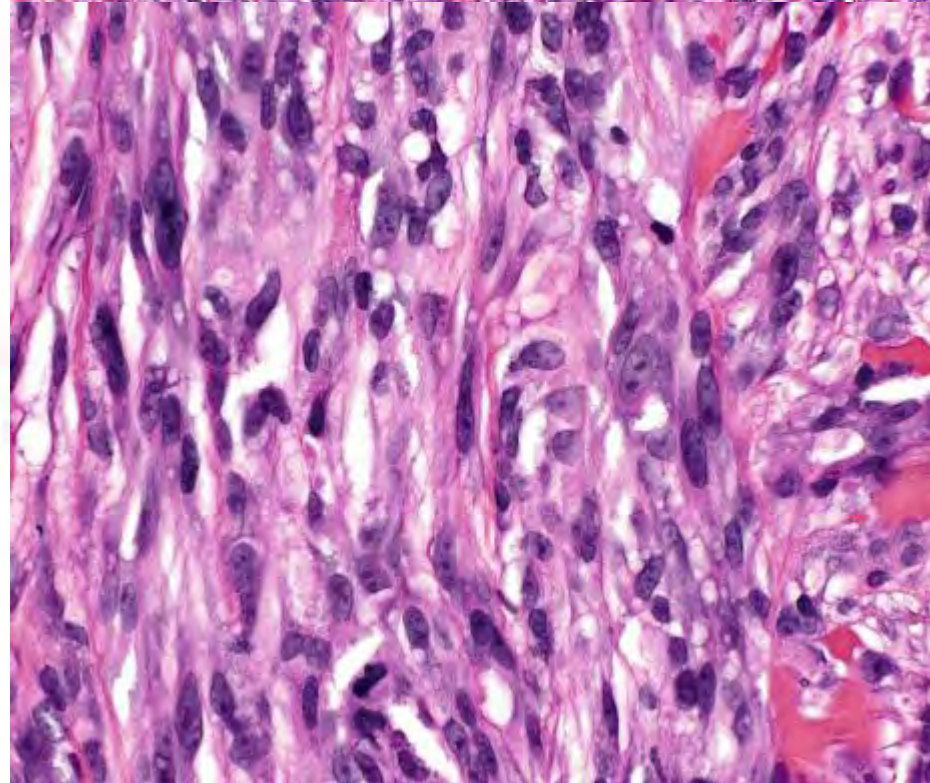
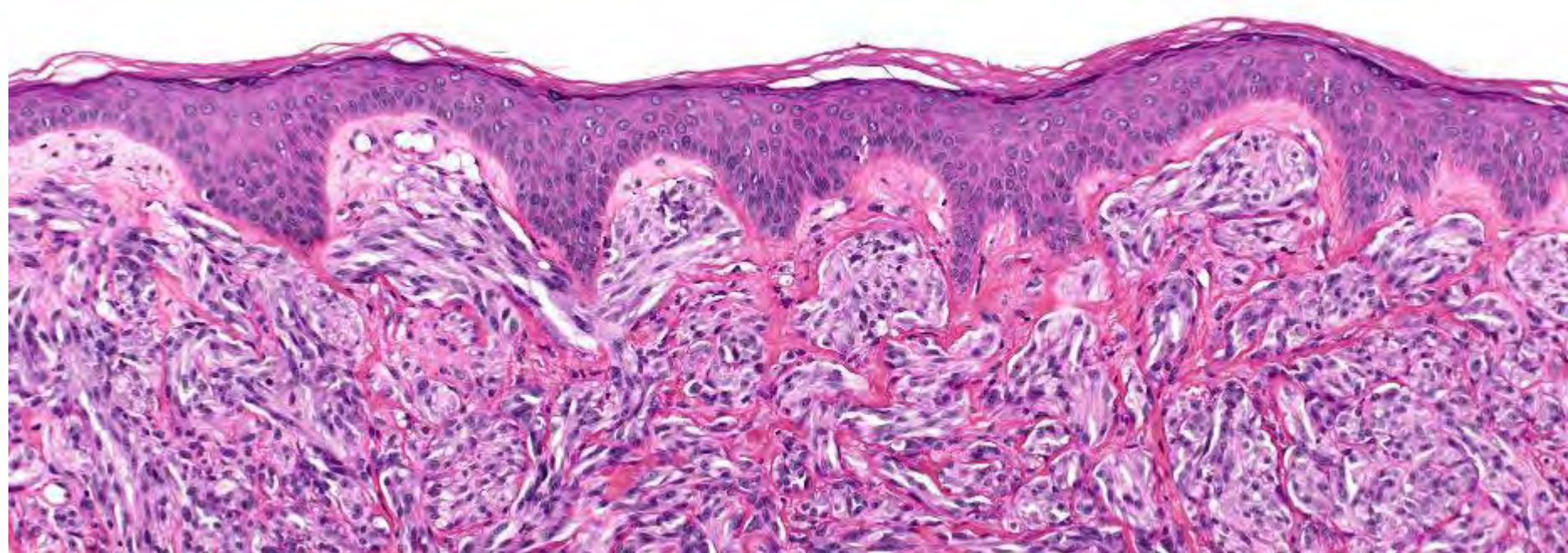


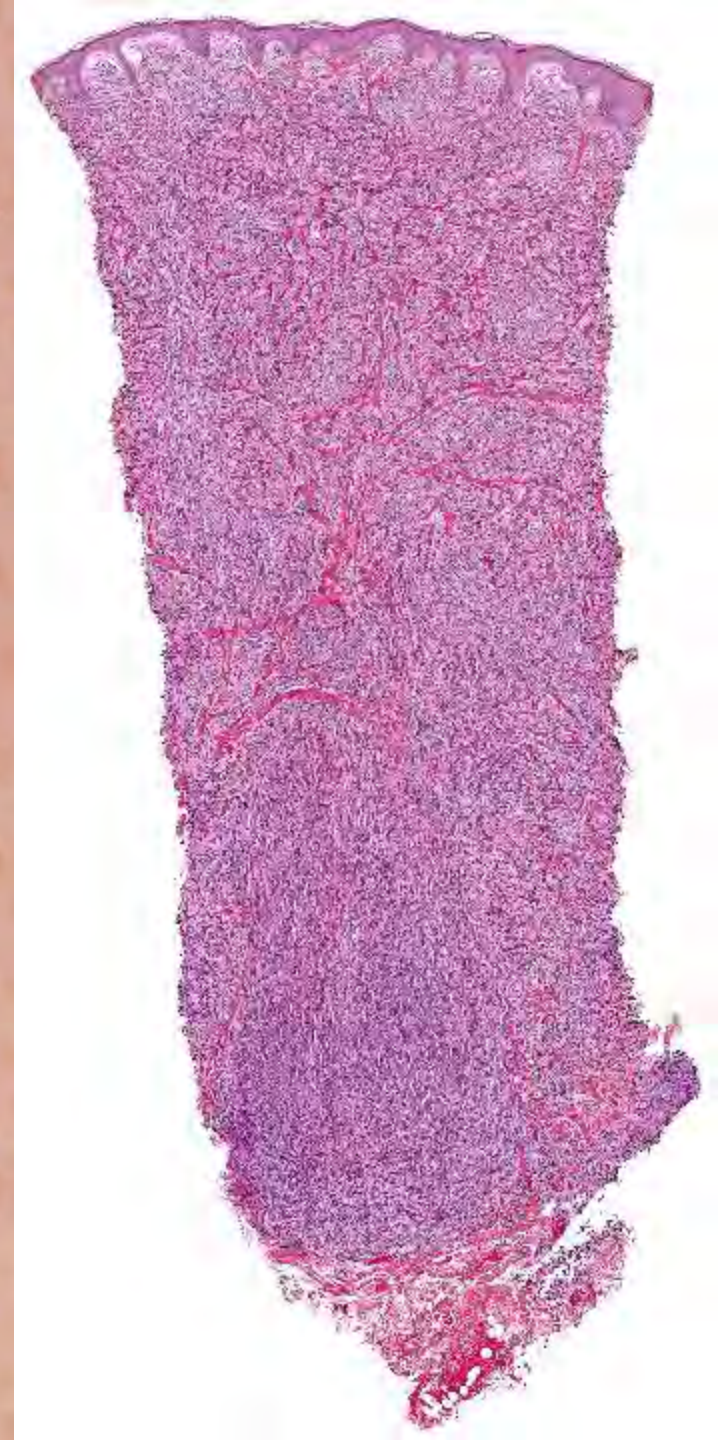


Case 48

F, 18. Reddish small plaque / flat nodule of recent onset on the right breast.

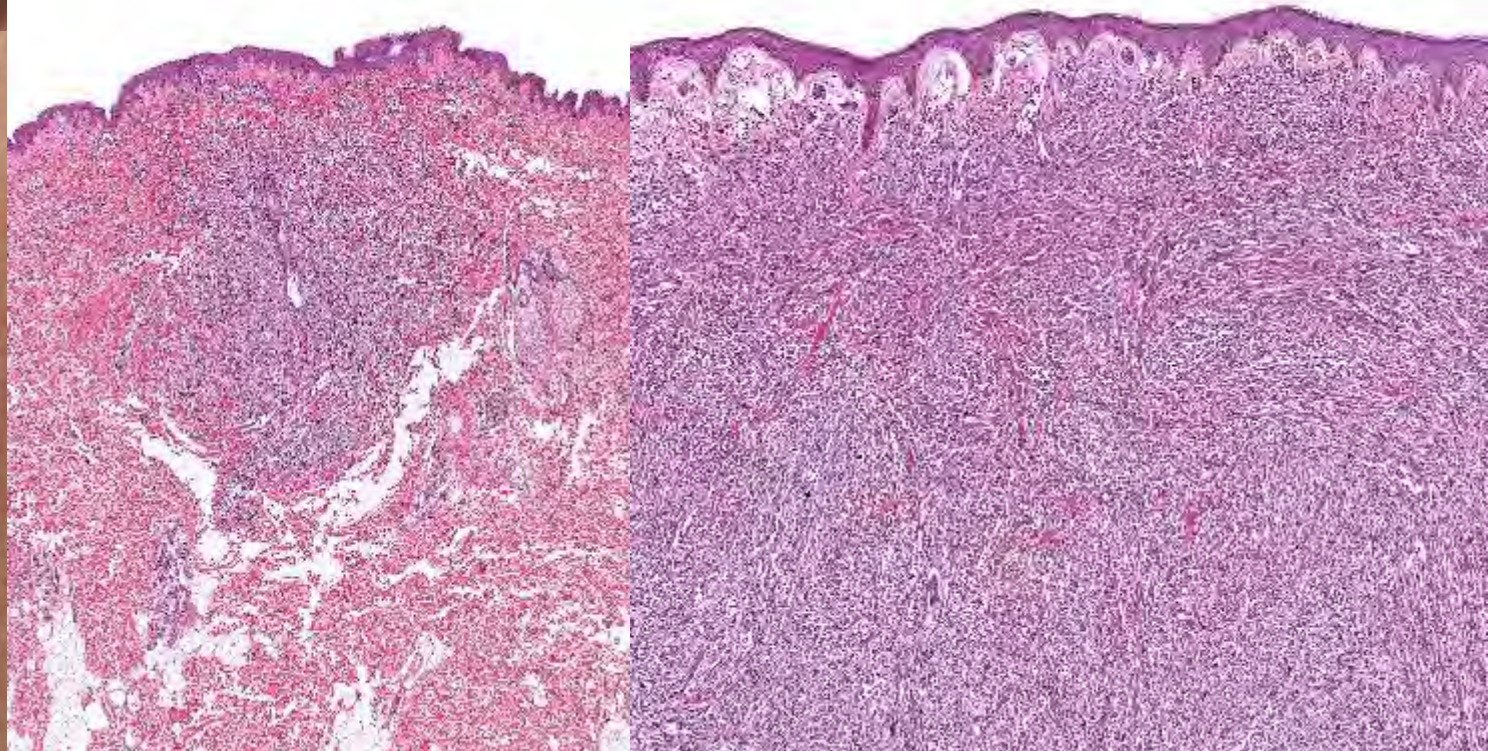
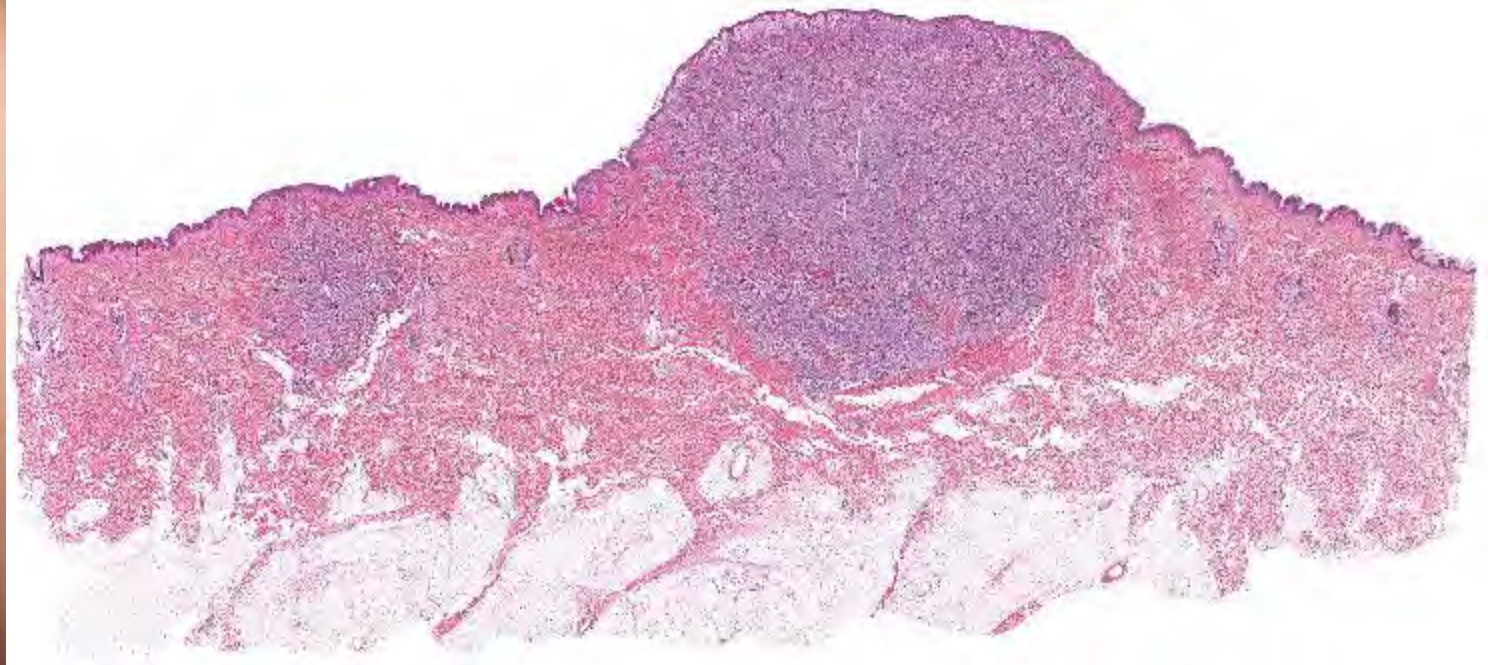
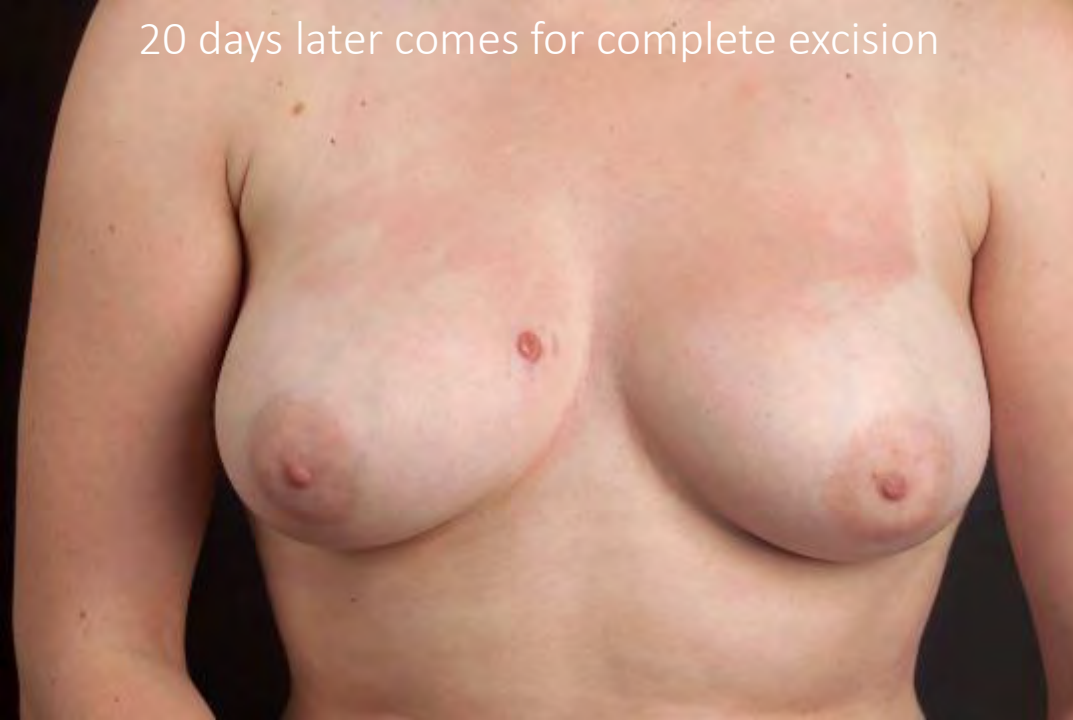


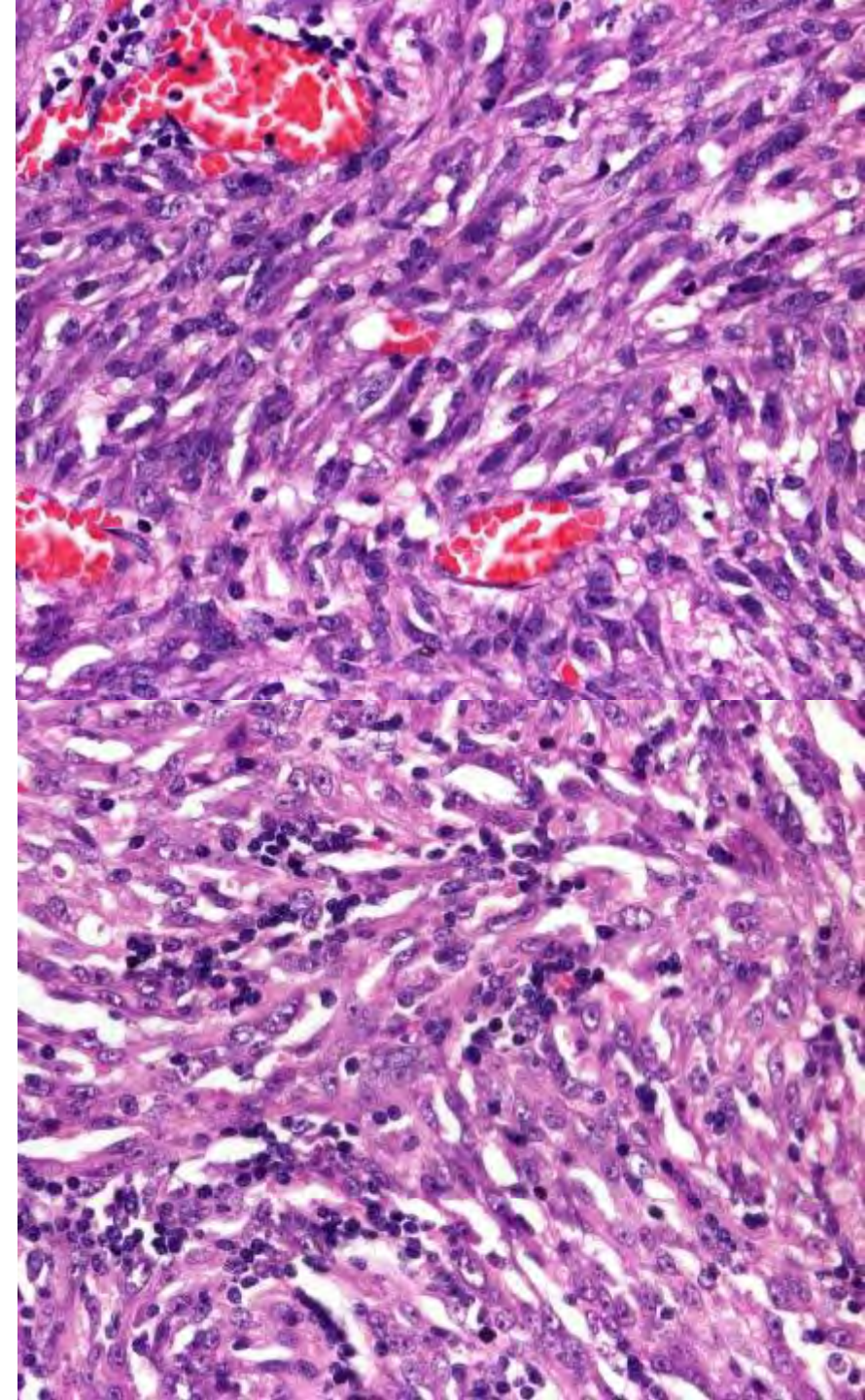
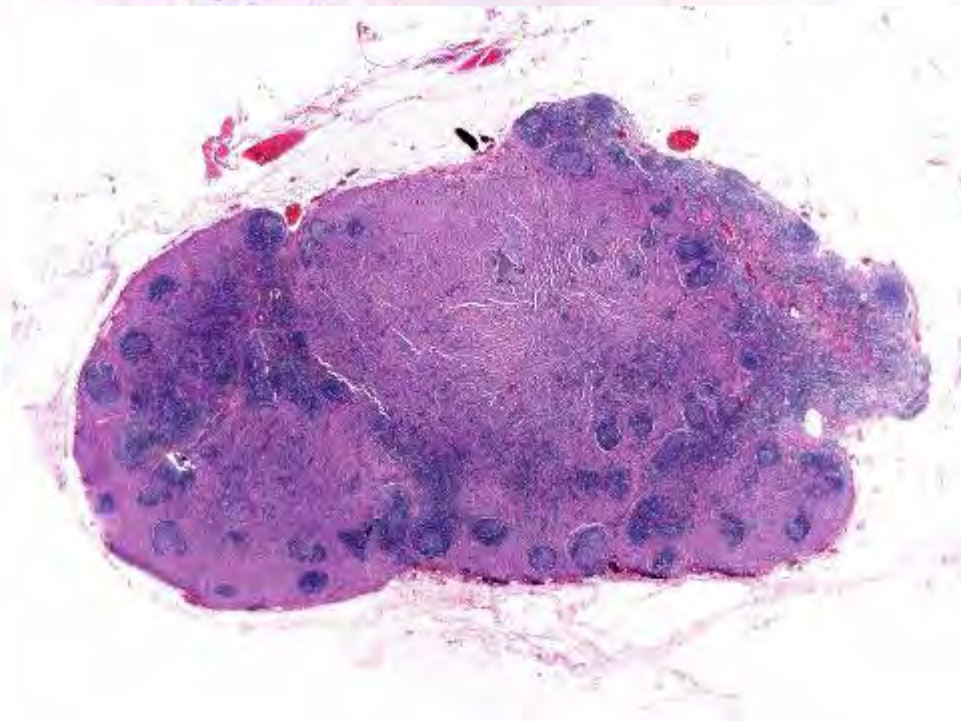
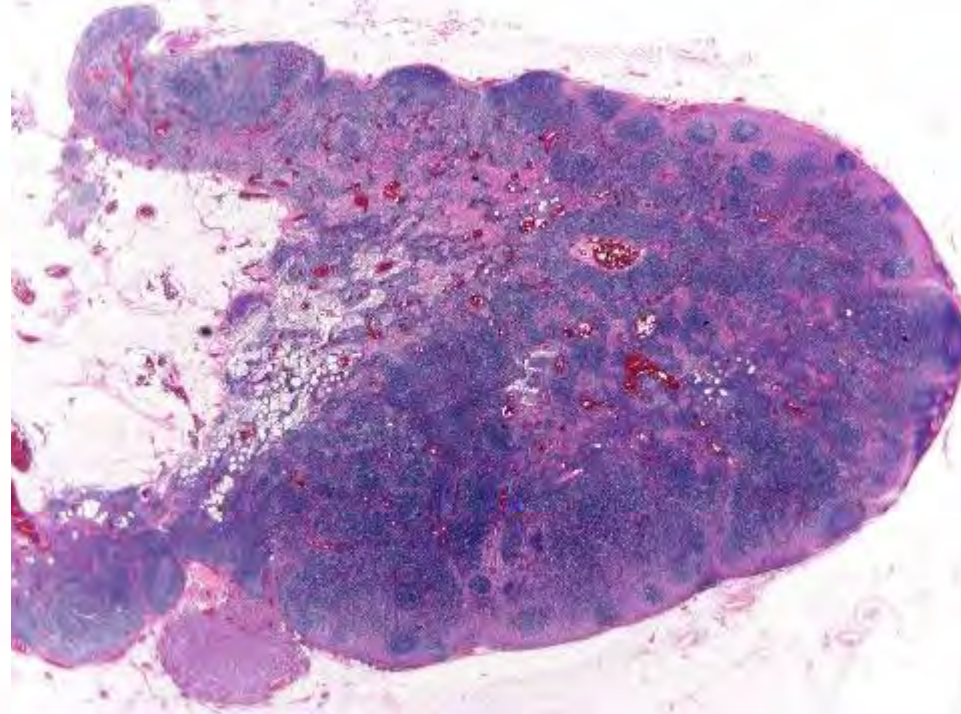
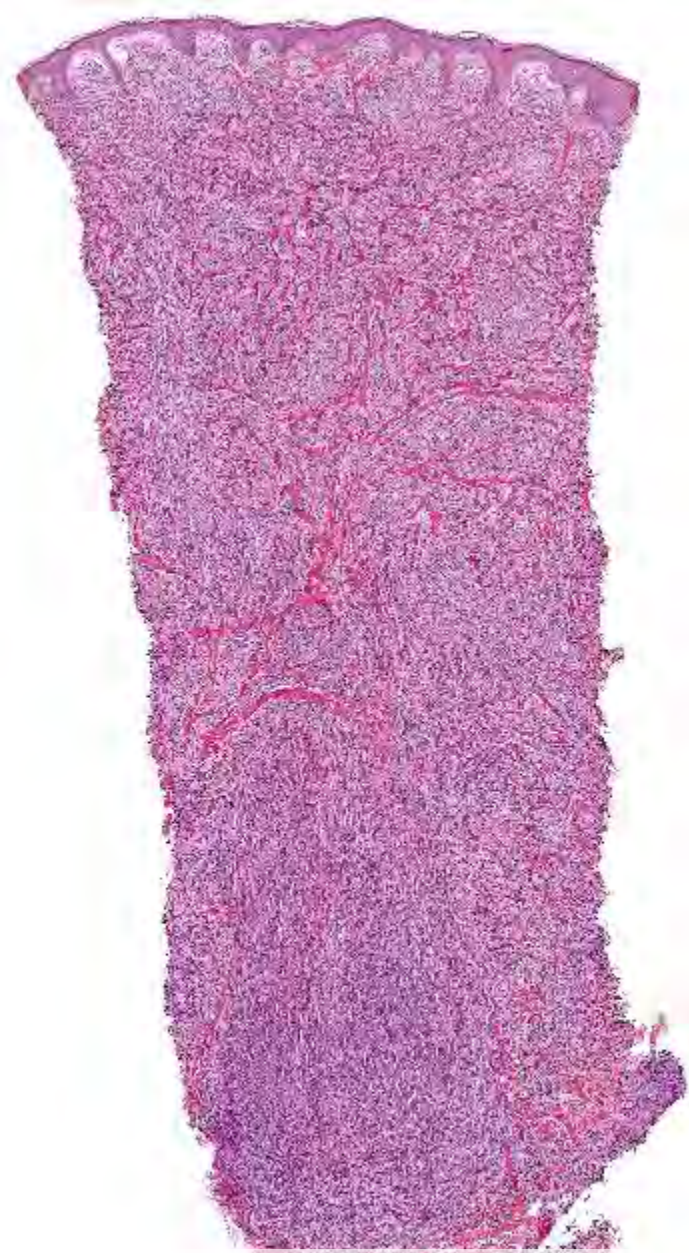




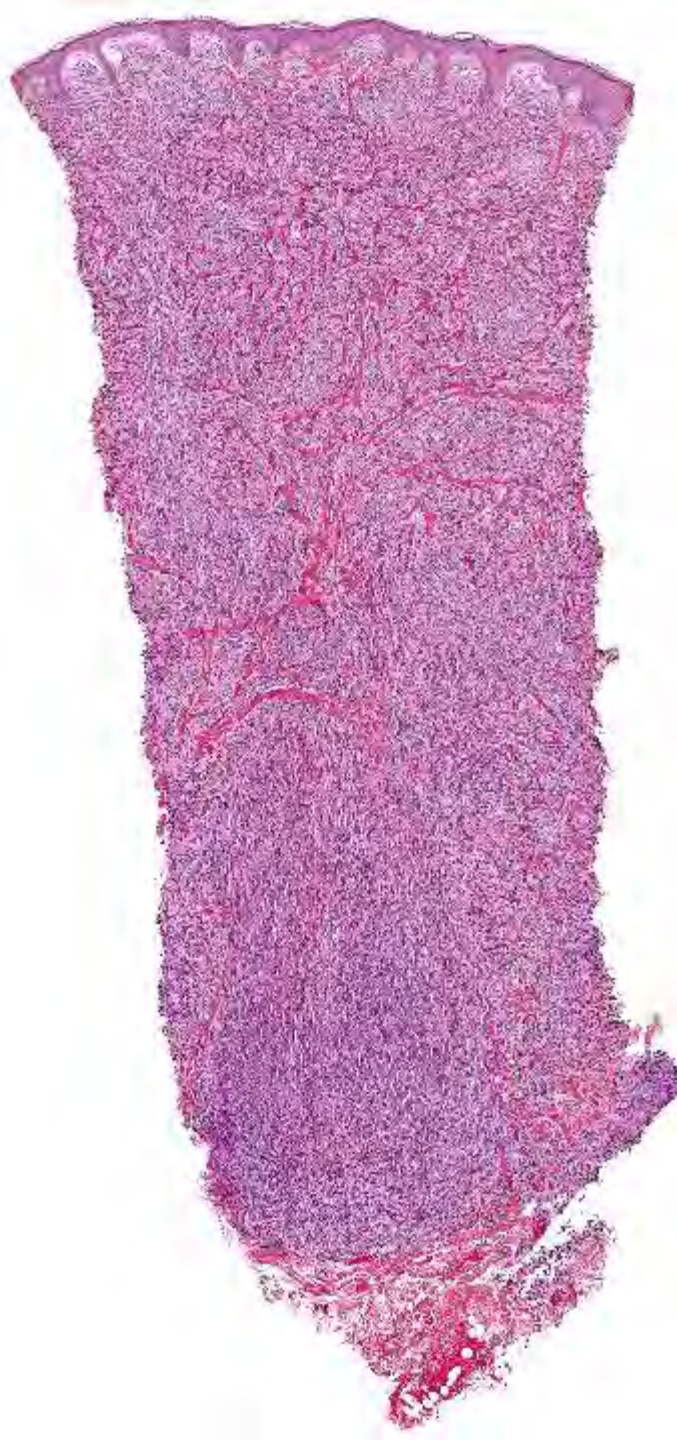
Atypical Spitz nevus/tumor...

20 days later comes for complete excision





Melanoma



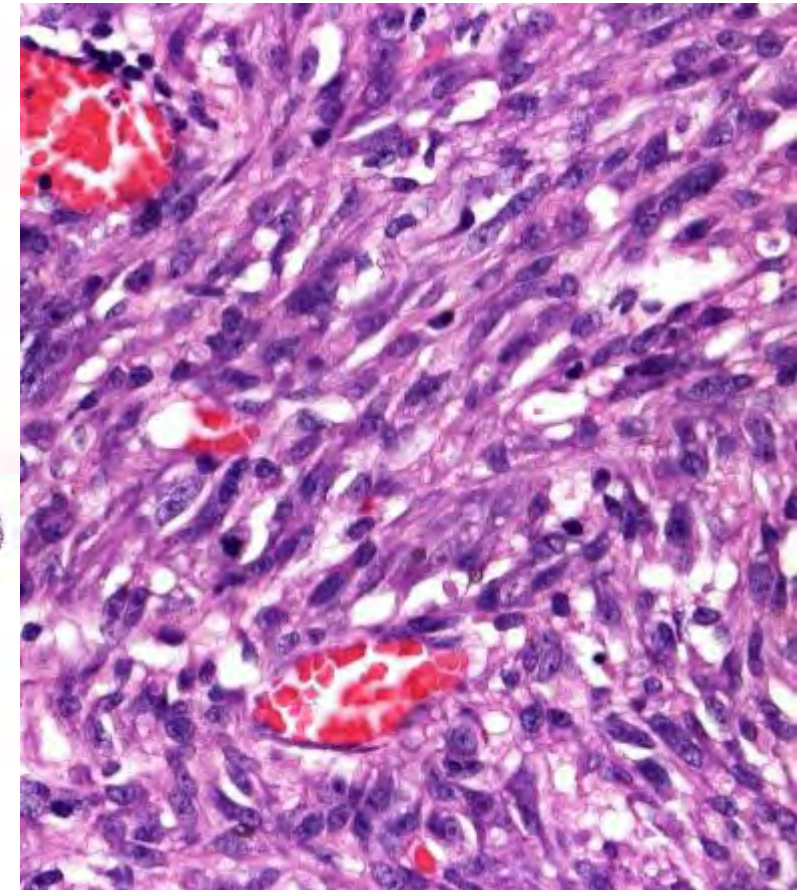
Satellite skin metastases

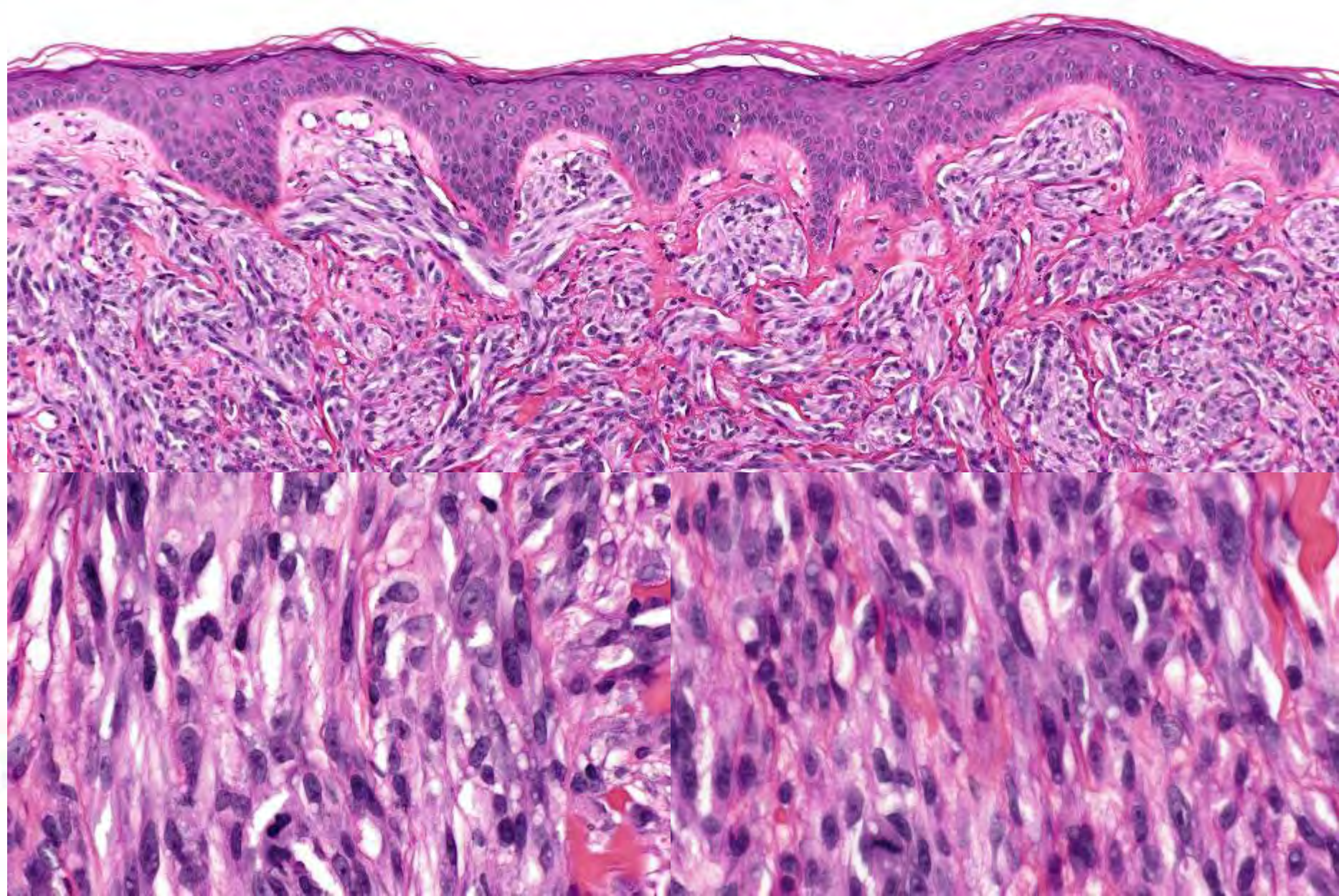
Lymph nodes metastases

Subcutaneous metastases

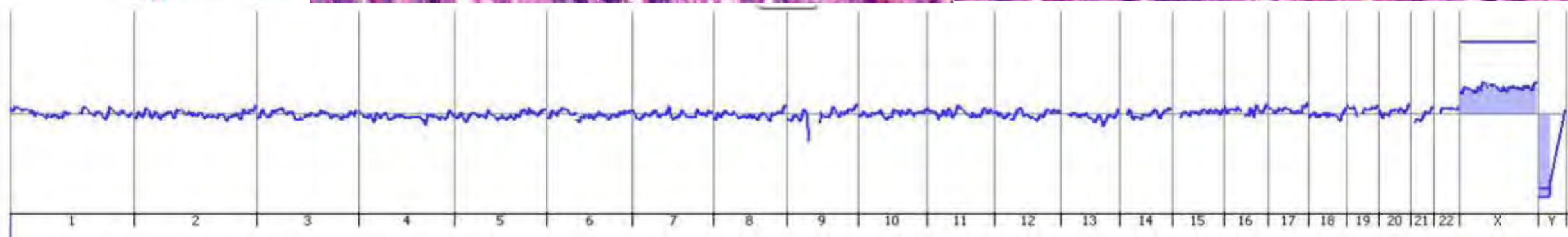
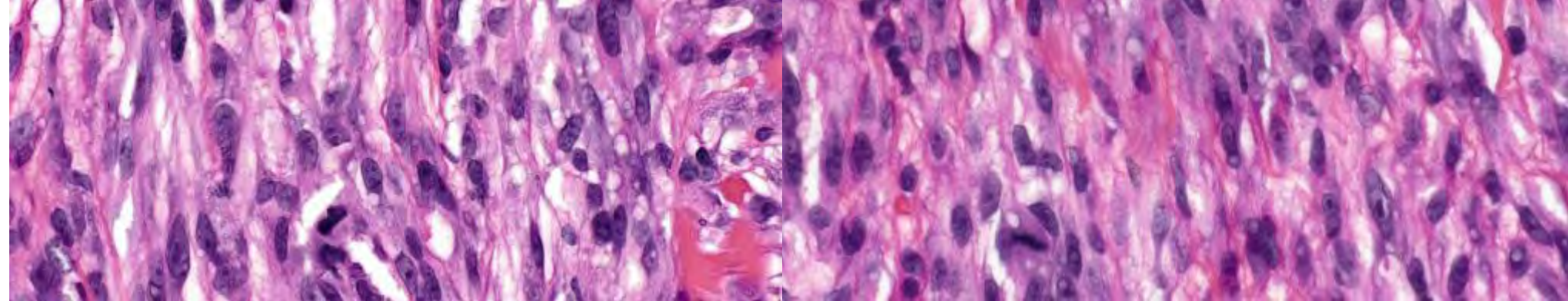
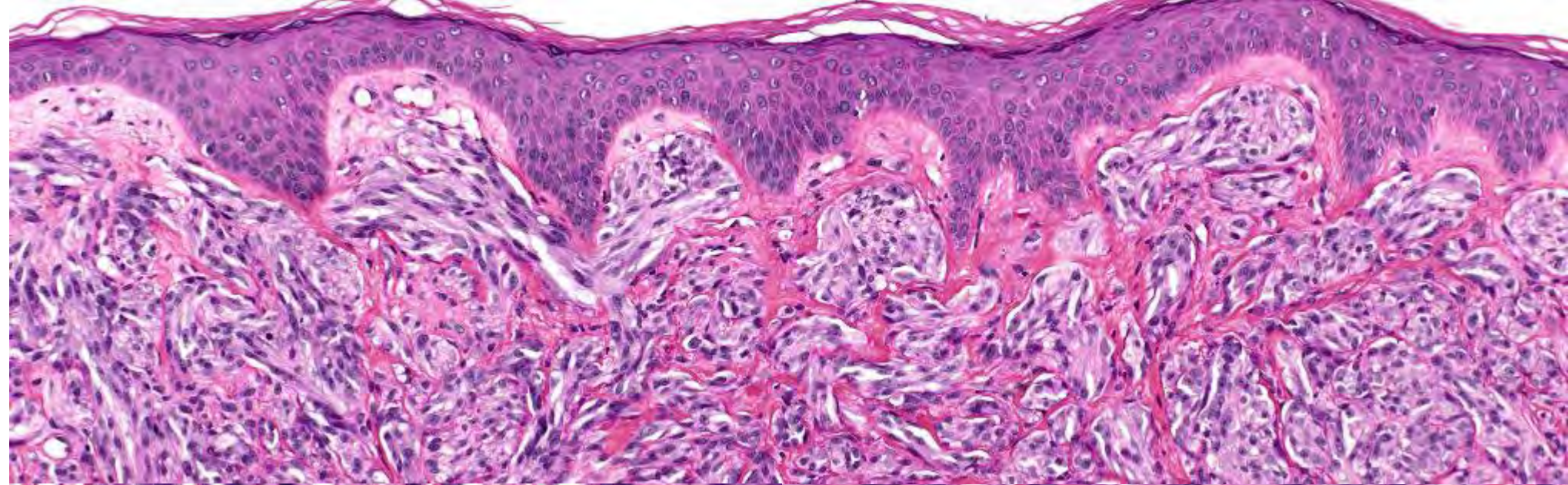
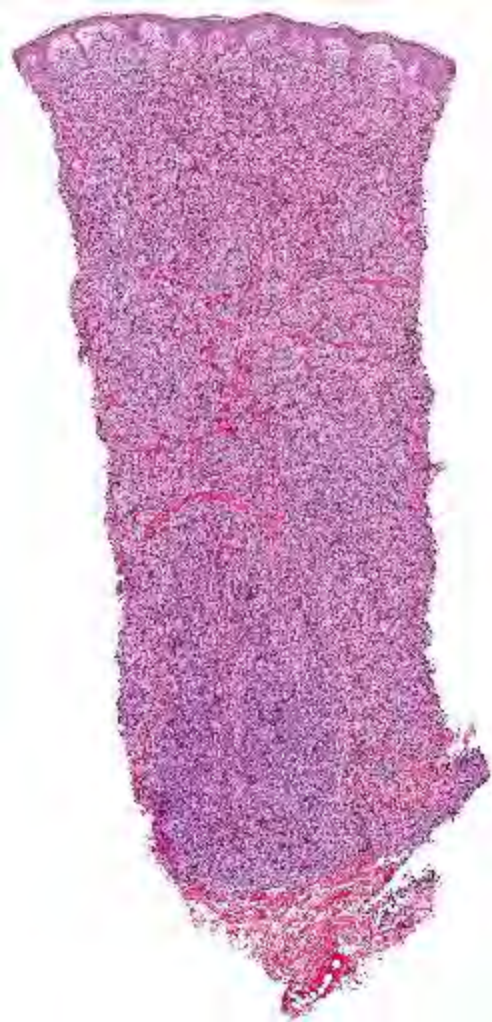
19 months later: lung, liver metastases

Died of progressive disease 6 years after presentation





No epidermal involvement but confluence of dermal complexes, high cellularity, absence of maturation, predominance of spindle cells, mitoses also near the base of the tumor





The International Society of Dermatopathology

XXIX Symposium

Graz, Austria
October 2-4, 2008

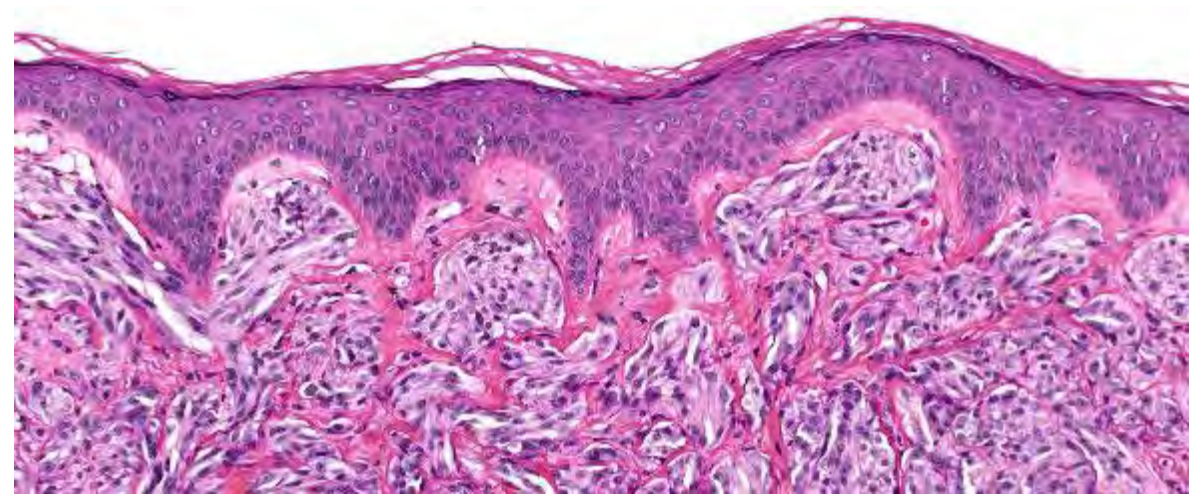
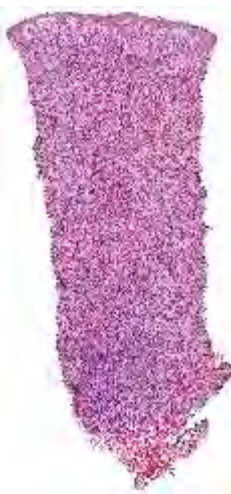
Convention Center, Sparkassenplatz, Graz

Panel of experts

Ray Barnhill, David Elder, Geoffrey Gottlieb, Peter Heenan, Heinz Kutzner, Phil LeBoit, Martin Mihm, Jr., Juan Rosai.

Tutorial 2008

Panelist A	Borderline
Panelist B	Melanoma
Panelist C	Melanoma
Panelist D	Melanoma
Panelist E	Melanoma
Panelist F	Melanoma
Panelist G	Melanoma
Panelist H	Melanoma



Melanocytic Tumors of Uncertain Malignant Potential

Results of a Tutorial Held at the XXIX Symposium of the
International Society of Dermatopathology in Graz,
October 2008

Lorenzo Cerroni, MD,* Raymond Barnhill, MD,† David Elder, MD,‡
Geoffrey Gottlieb, MD,§ Peter Heenan, MD,¶ Heinz Kutzner, MD,¶
Philip E. LeBoit, MD,‡ Martin Mihm, Jr., MD,**
Juan Rosai, MD,†† and Helmut Kerl, MD*

Abstract: Several reports demonstrated the difficulties and lack of agreement in the histopathologic diagnosis of particular melanocytic tumors (atypical Spitz tumors, atypical blue nevi, deep penetrating nevi). These lesions are often referred to as "melanocytic tumors of uncertain malignant potential" (MELTUMPs). We studied a large number of such tumors to find out whether repeatable histopathologic criteria for distinction of benign from malignant cases exist. Fifty-seven cases of MELTUMPs were classified within 3 groups according to behavior as follows: (a) favorable (no evidence of metastatic disease after a follow-up of ≥ 5 y), (b) unfavorable (tumor-related death and/or large metastatic deposits in the lymph nodes and/or visceral metastases), (c) borderline (small nodal deposits of tumor cells ≤ 0.2 mm). There were no significant differences in tumor thickness and presence or absence of ulceration between the different groups. The only 3 histopathologic criteria that were statistically different between the groups of favorable and unfavorable cases were presence of mitoses, mitoses near the base, and an inflammatory reaction; all of them found more frequently in cases with unfavorable behavior. The major outcome of this study of a series of "MELTUMPs" suggests as a preliminary observation that these lesions as a group exist and that they may be biologically different from conventional melanoma and benign melanocytic nevi. The terminology remains highly controversial, reflecting

the uncertainty in classification and interpretation of these atypical melanocytic tumors.

Key Words: atypical Spitz tumor, malignant melanoma, melanocytic tumor of uncertain malignant potential, atypical blue nevi, deep penetrating nevi

Am J Surg Pathol 2010;34:314–326

Melanocytic lesions continue to pose significant interpretative problems to histopathologists. Cases that were difficult to distinguish from benign melanocytic nevi have been designated by some authors as "minimal deviation melanoma" or "nevroid melanoma."^{23,25–27,28} Among the most challenging problems encountered are a spectrum of relatively thick, mainly dermal tumors that are often quite difficult or impossible to distinguish from melanoma, including particularly neoplasms with spindle and/or epithelioid cells suggesting Spitz tumors, cellular and/or epithelioid blue nevi, and so-called "deep penetrating nevi."^{16,17} In the last years, several reports clearly demonstrated the difficulties and lack of agreement in the histopathologic diagnosis and differential diagnosis of these particular lesions.^{2–5,9,10,31,32} Two of us have previously proposed the terms "melanocytic tumor of uncertain malignant potential (MELTUMP)" or "melanocytic proliferation with indeterminate biologic potential," respectively, to reflect the uncertainty of the precise classification of such tumors.^{3,14} The malignant behavior of some melanocytic tumors that had been previously classified as Spitz nevi has been described,³³ and one of us suggested that these neoplasms may represent a distinct subtype of malignant melanocytic tumors with low-grade behavior.^{16,17} Finally, at several dermatopathologic meetings many anecdotal cases of otherwise typical "Spitzoid tumors" or "deep penetrating nevi" with lymph node and/or visceral metastases have been presented.

In October 2008 we organized a Tutorial on melanocytic tumors in the course of the XXIX Symposium of the International Society of Dermatopathology

Cases with favourable behaviour (n=17)

(no metastases, follow-up of 5 years or longer; median FU: 10y)

Unanimously diagnosed as benign:	0	
Majority favoured benign:	8	(cum. benign dg.: 47,1%)
Majority favoured malignant:	6	
Unanimously classified as malignant:	1	
No clear-cut majority:	2	

Cases with unfavourable behaviour (n=26)

(large LN metastases, or visceral metastases, or DoD)

Unanimously diagnosed as malignant:	4	(15,4%)
Majority favoured malignant:	15	(cum. malignant dg.: 73,1%)
Majority favoured benign:	6	
No clear-cut majority:	1	

14 cases were considered biologically "borderline" (lymph nodes involved by small parenchymal clusters of melanocytes, no other evidence of disease progression)

Digital slides; Panelists: R. Barnhill, D. Elder, G. Gottlieb, P. Heenan, H. Kutzner, P.E. LeBoit, M. Mihm, Jr., J. Rosai

From the *Department of Dermatology, Medical University of Graz, Austria; †Departments of Dermatology and Pathology, Hôpital Saint Louis, University of Paris VII, Paris, France; ‡Department of Pathology and Laboratory Medicine, University of Pennsylvania Health System, Philadelphia, PA; §Academy of Dermatology, New York, NY; ¶Departments of Pathology and Dermatology, University of California San Francisco, San Francisco, CA; **Department of Pathology, Massachusetts General Hospital, Boston, MA; ††Centro Patologia, Nodulari, Western Australia; ††Dermatopathologische Gemeinschaftslabor, Friedrich-Alexander-Universität Erlangen-Nürnberg, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany; and ††Centro Consultorio Anatomico Patologico, Centro Diagnostico Italiano, Milano, Italy.

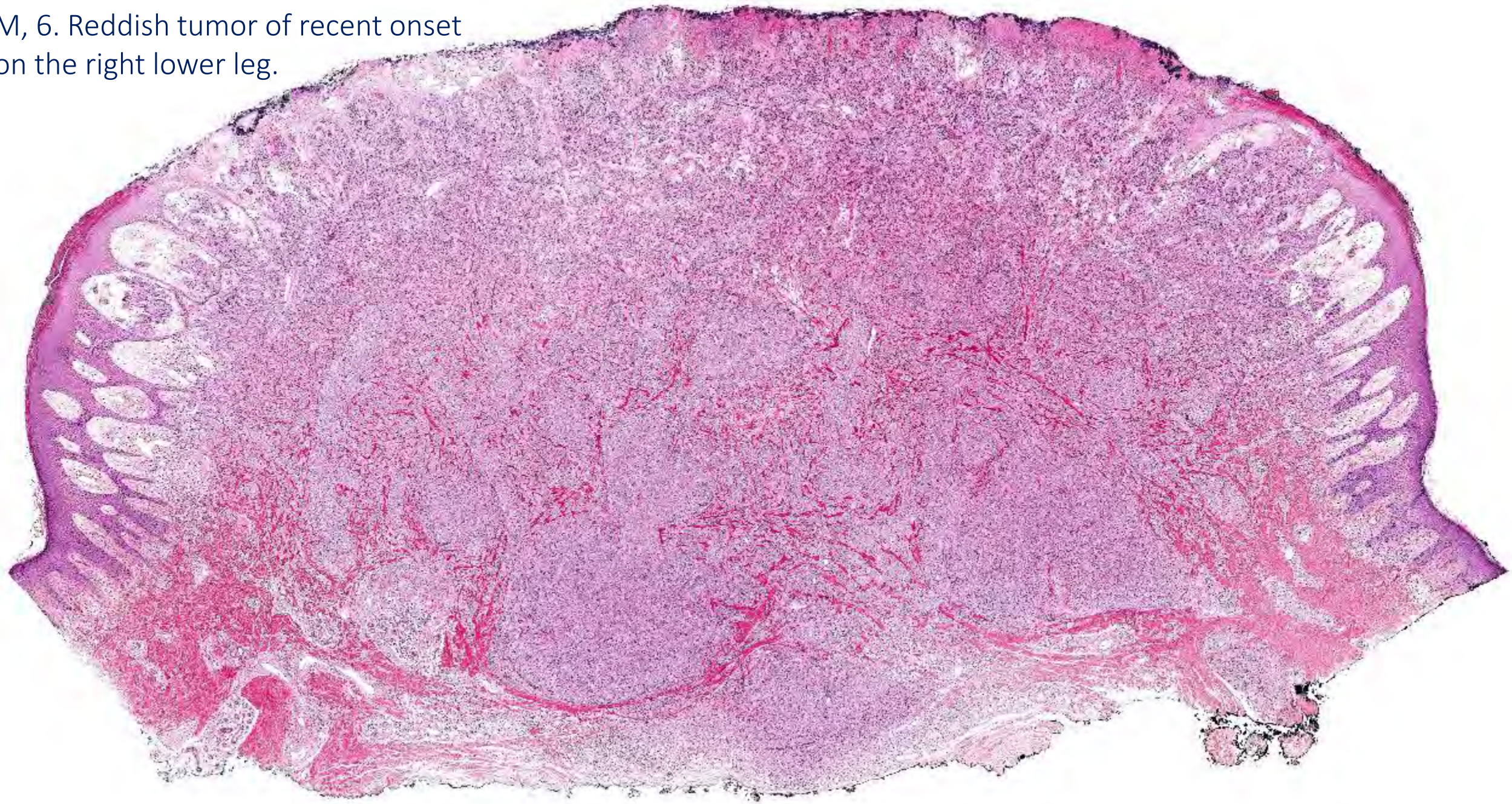
Funding Sources: None.

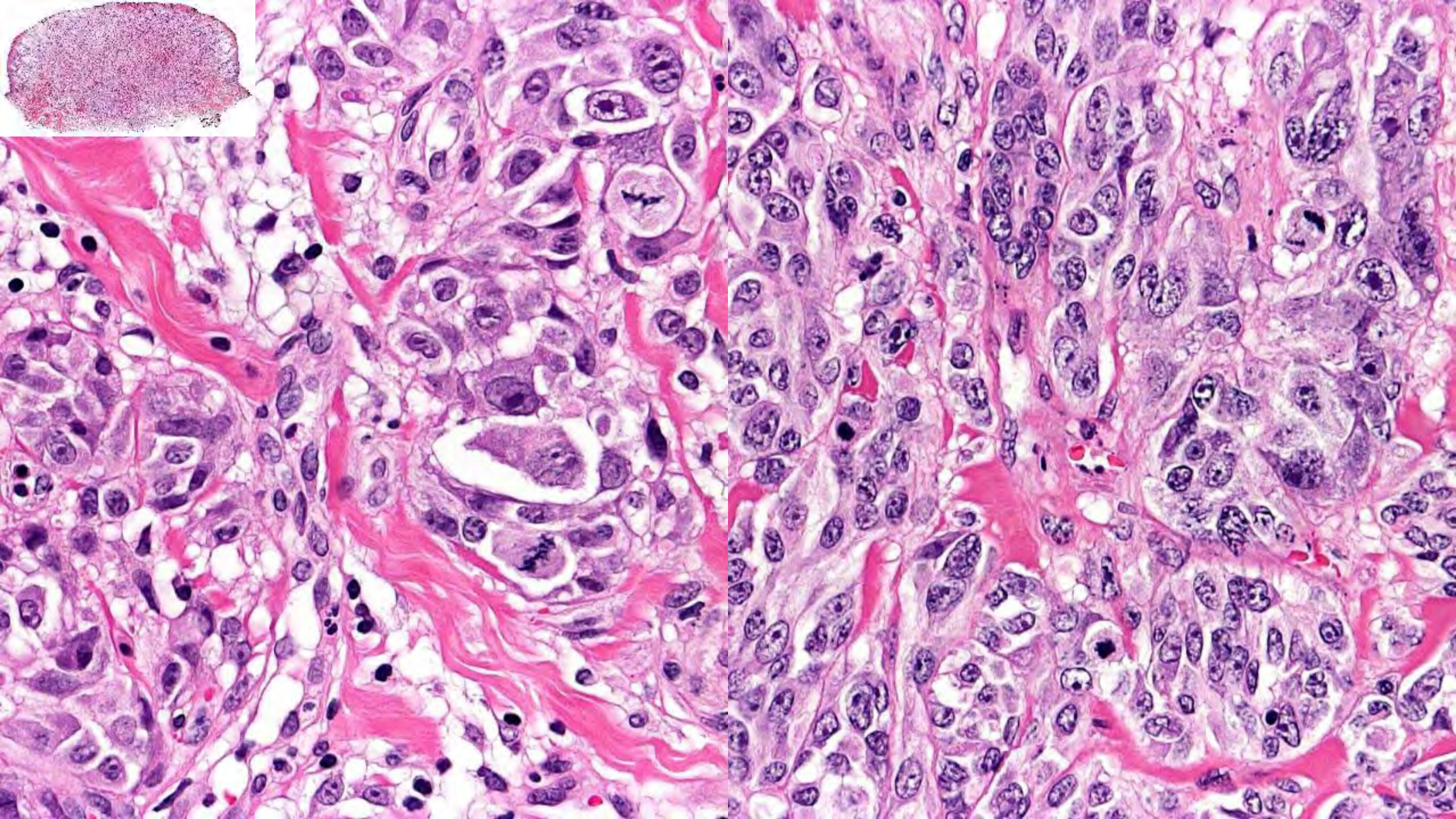
Correspondence: Lorenzo Cerroni, MD, Department of Dermatology, Medical University of Graz, Ausberggasse 8, A-8036 Graz, Austria (e-mail: lorenzo.cerroni@meduni-graz.at).

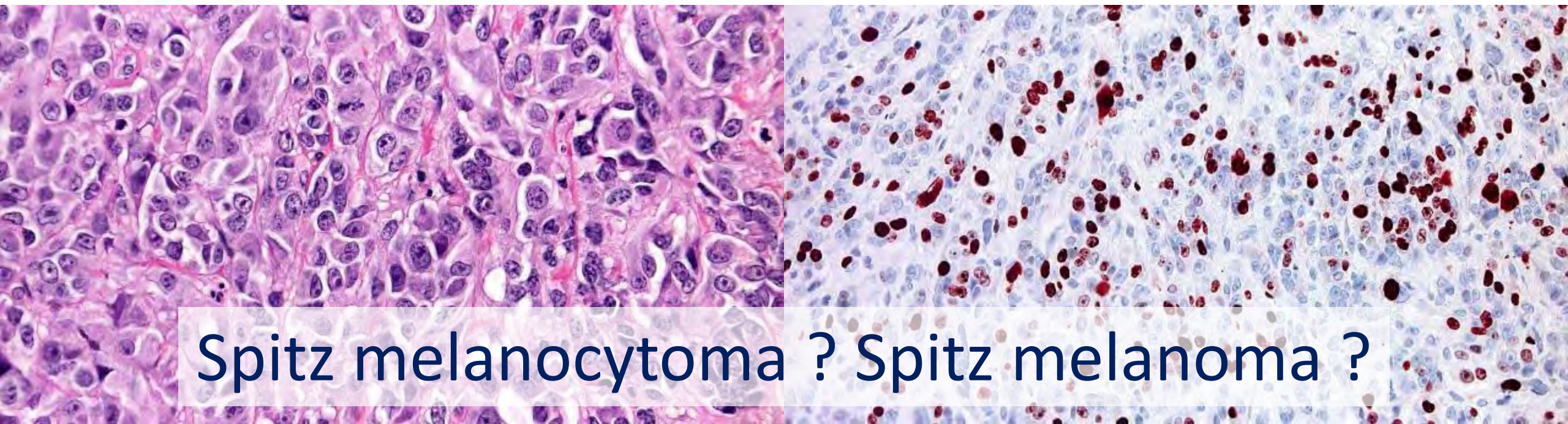
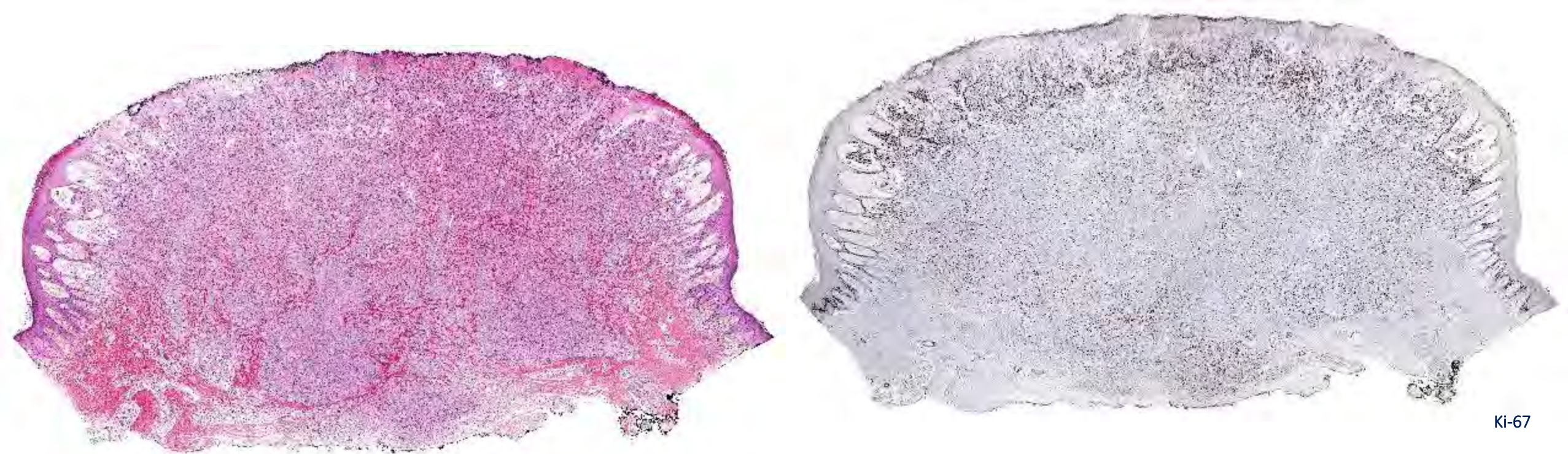
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Case 49

M, 6. Reddish tumor of recent onset
on the right lower leg.



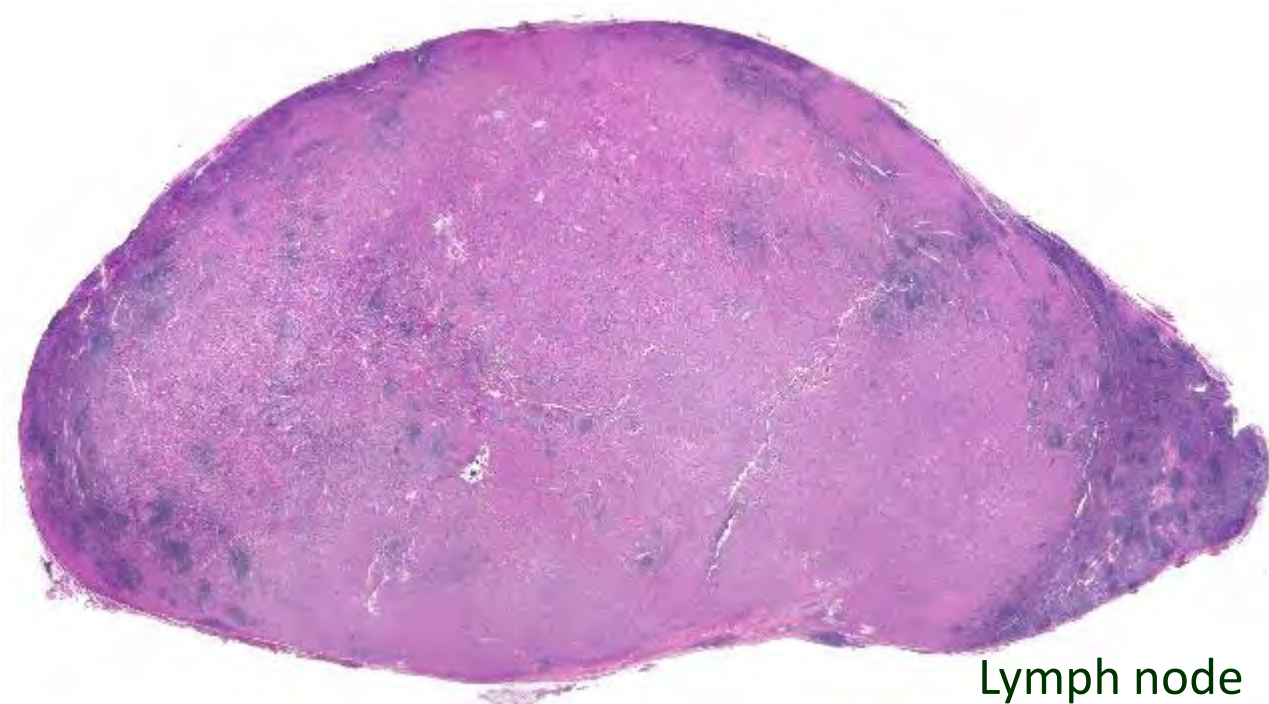




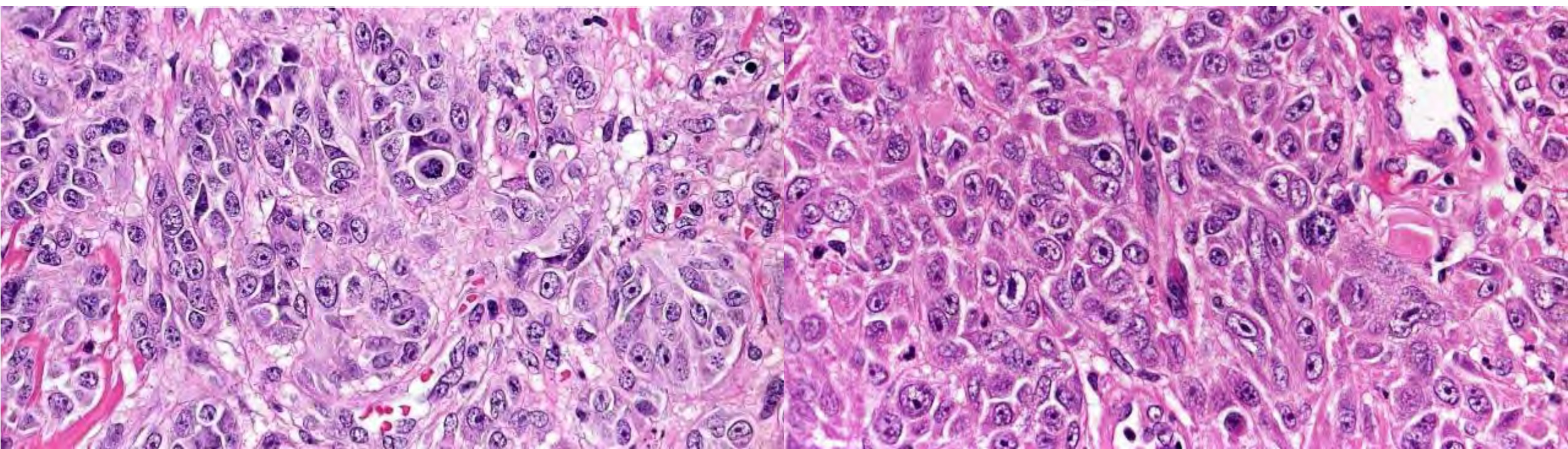


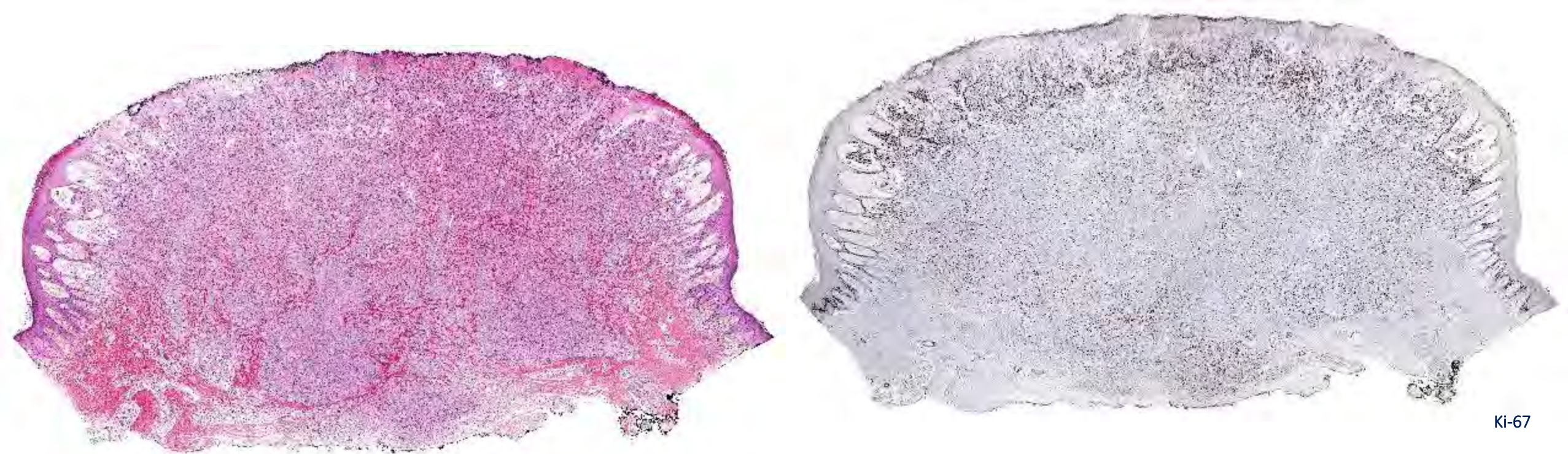
Spitz melanoma

Skin

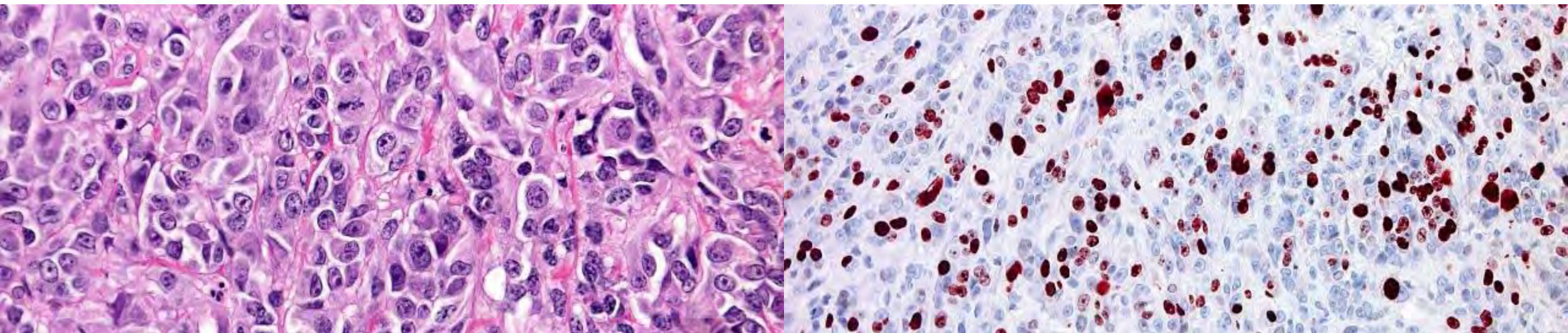


Lymph node





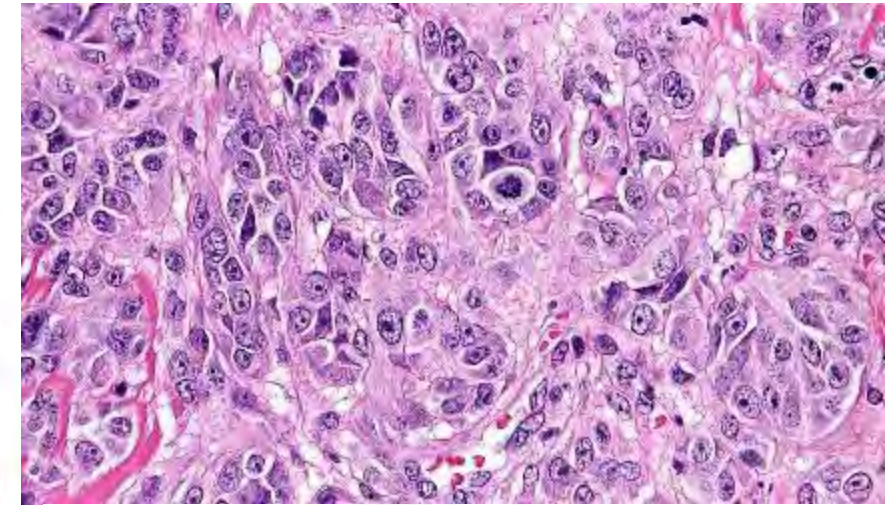
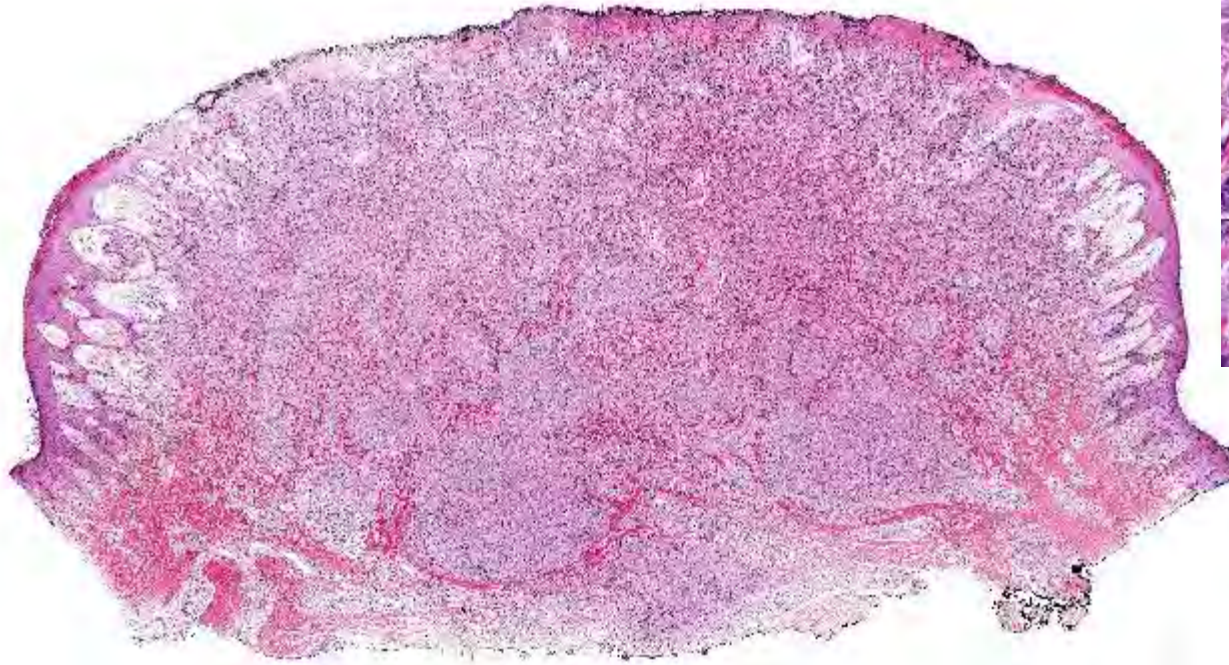
Ki-67



Symmetrical and mainly dermal, but large ulceration (in children may be traumatic), confluence of dermal complexes, high cellularity, absence of maturation, several mitoses, high Ki-67 index also near the base of the tumor

Spitz melanoma

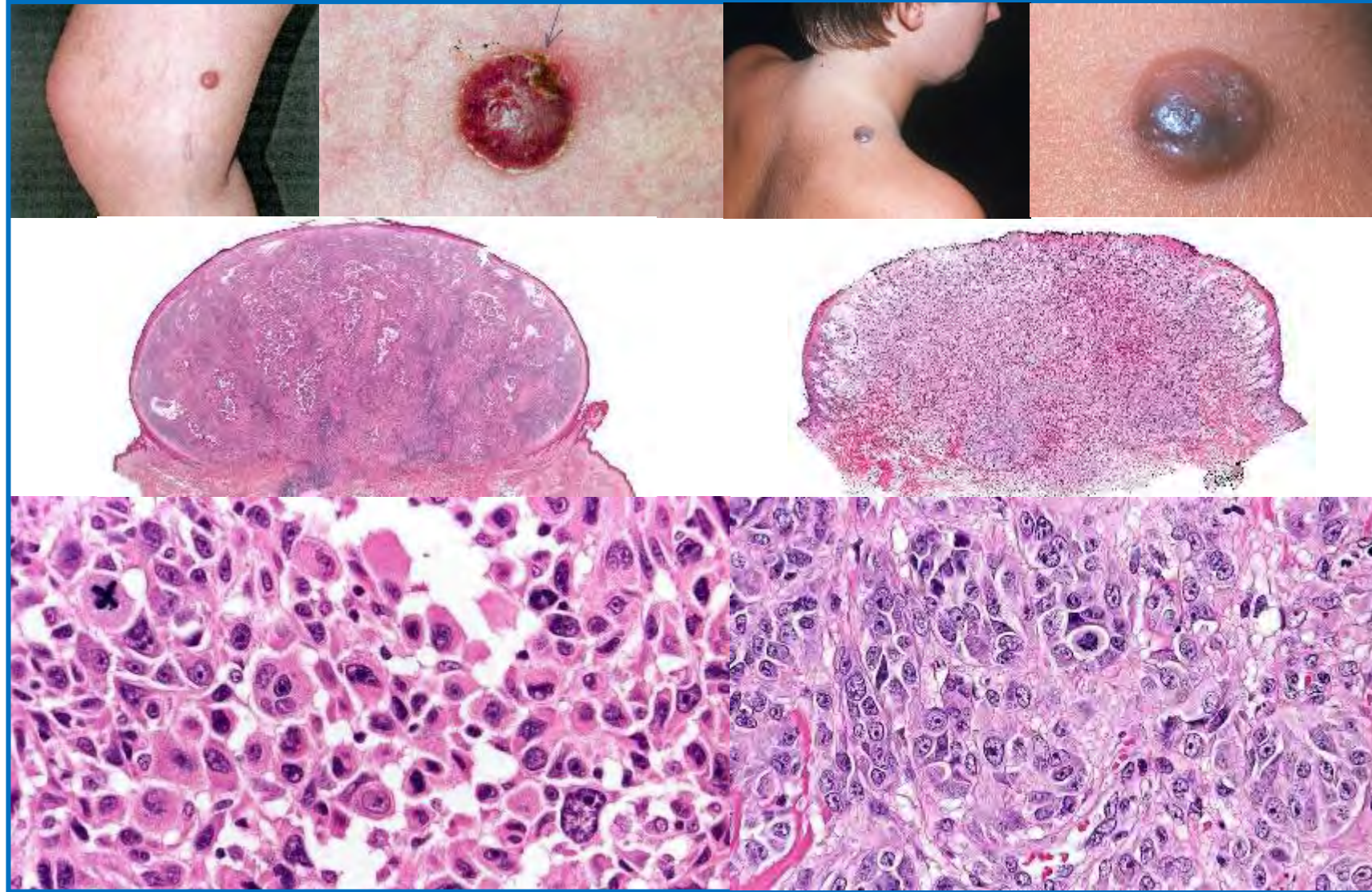
A rare type of melanoma showing molecular features of the so-called Spitz lineage (i.e., molecular features found in Spitz nevi and atypical Spitz tumors, including *HRAS* mutations; tyrosine kinase fusions (*MET*, *ALK*, *ROS1*, *NTRK1*, *NTRK2*, *NTRK3*, *RET*, *MERTK*, *LCK*), serine-threonine kinase fusions (*MAP3K3*, *MAP3K8*, *BRAF*), or other rare molecular events. Conventional melanomas with spitzoid morphology and *BRAF* or *NRAS* mutations, or other non-Spitz molecular features, are not classified as Spitz melanoma.



Spitz nevus, Spitz melanocytoma, Spitz melanoma

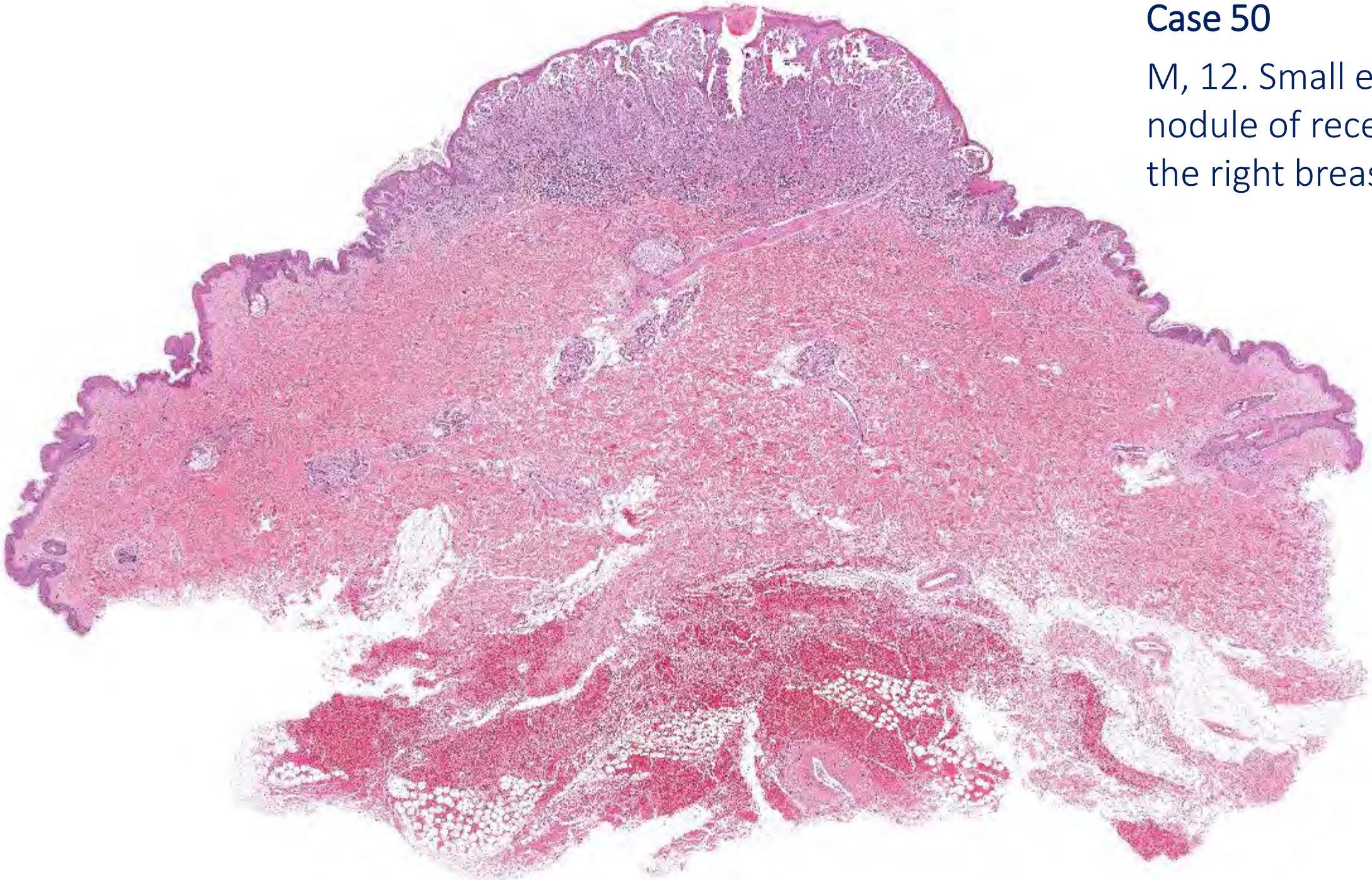
Tumors characterized by the so-called Spitz lineage: *HRAS* mutations; tyrosine kinase fusions (*MET*, *ALK*, *ROS1*, *NTRK1*, *NTRK2*, *NTRK3*, *RET*, *MERTK*, *LCK*), serine-threonine kinase fusions (*MAP3K3*, *MAP3K8*, *BRAF*).

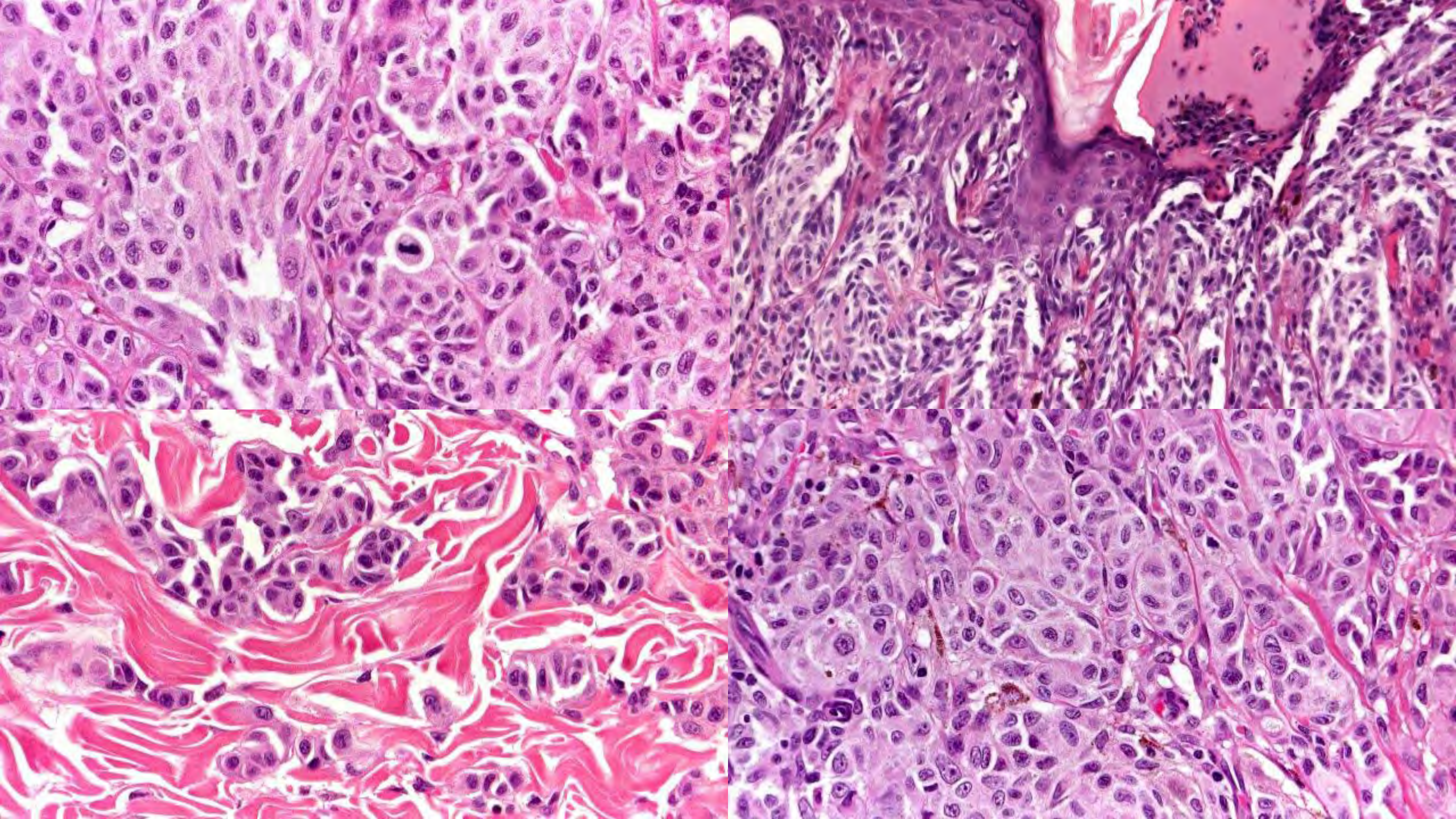
WHO 5ed: "*The distinction (of Spitz melanoma) from Spitz melanocytoma is best made by using a constellation of clinical, morphologic and molecular findings and no single data point can completely distinguish Spitz melanoma from Spitz melanocytoma.*"

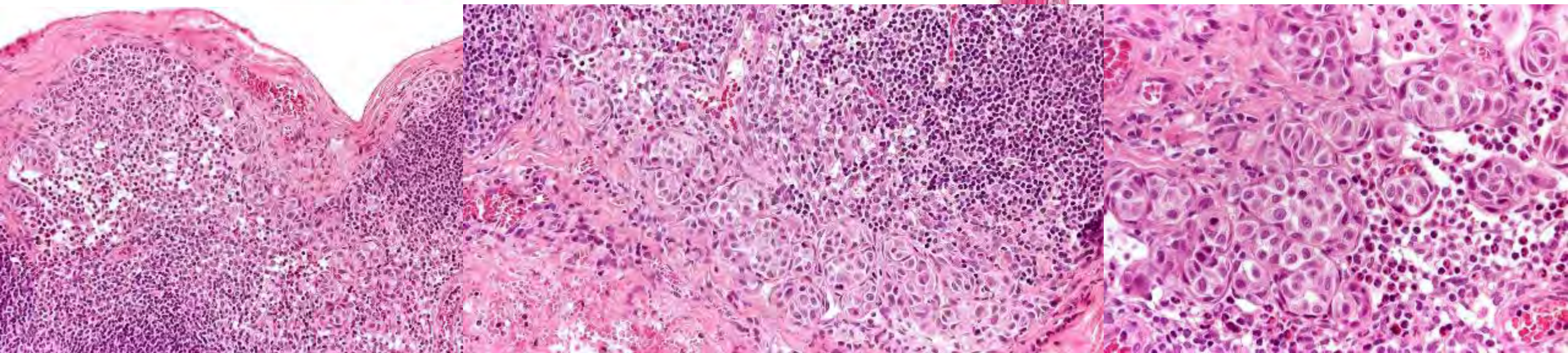
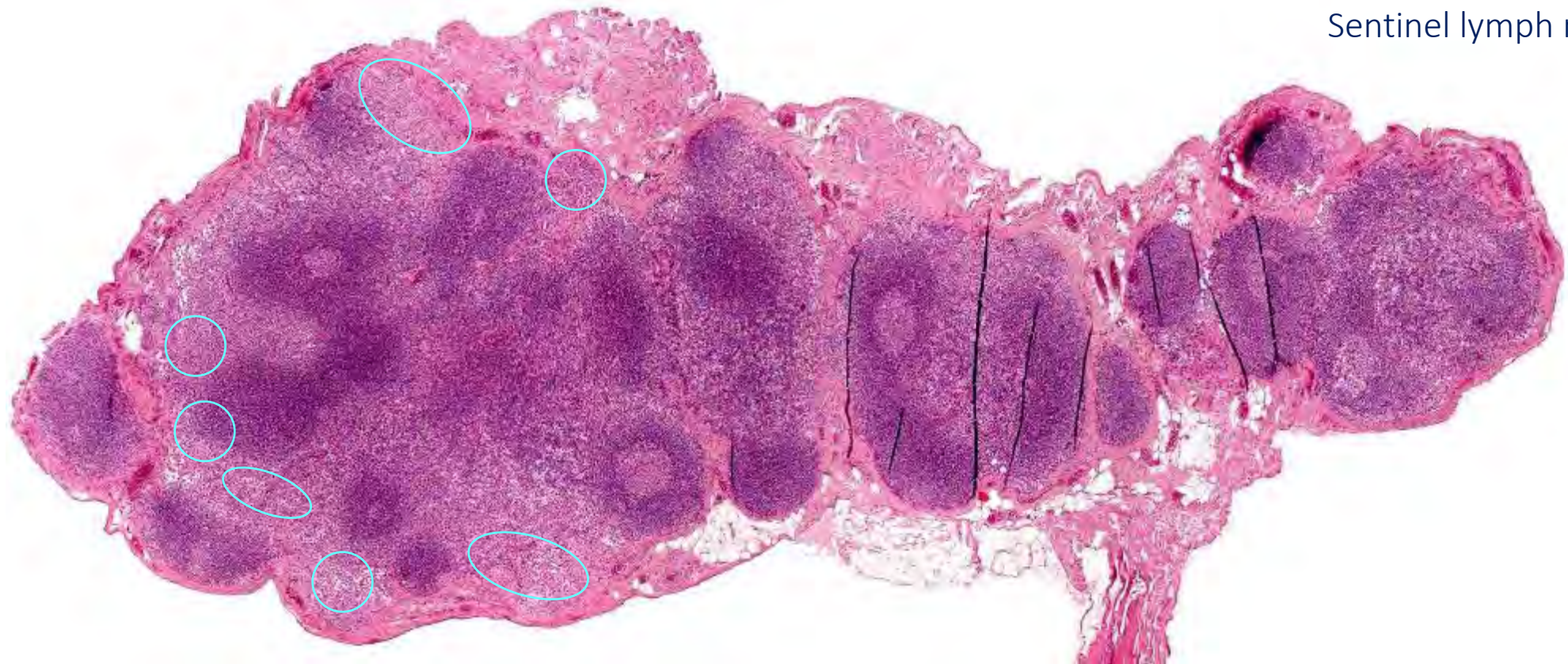


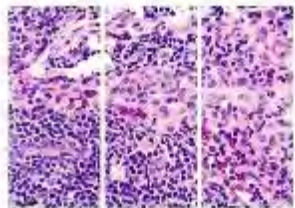
Case 50

M, 12. Small erythematous
nodule of recent onset on
the right breast.









On the Cover

What Do These Cells Prove?

Philip E. LeBoit, MD

Key Words: melanoma, metastasis, sentinel node biopsy, Spitz nevus

A patient has an unusual melanocytic proliferation. Skilled observers are puzzled—is it a Spitz's nevus or a melanoma? The patient and the dermatologist want to know, and with certainty. Why not do a sentinel node biopsy to find out?

Certainly, this question has been asked and answered before. Several reports now tell of cases in which diagnostic uncertainty was settled by means of a sentinel node biopsy.^{1–3} But is this an accurate approach?

From the Departments of Pathology and Dermatology, University of California, San Francisco, California.

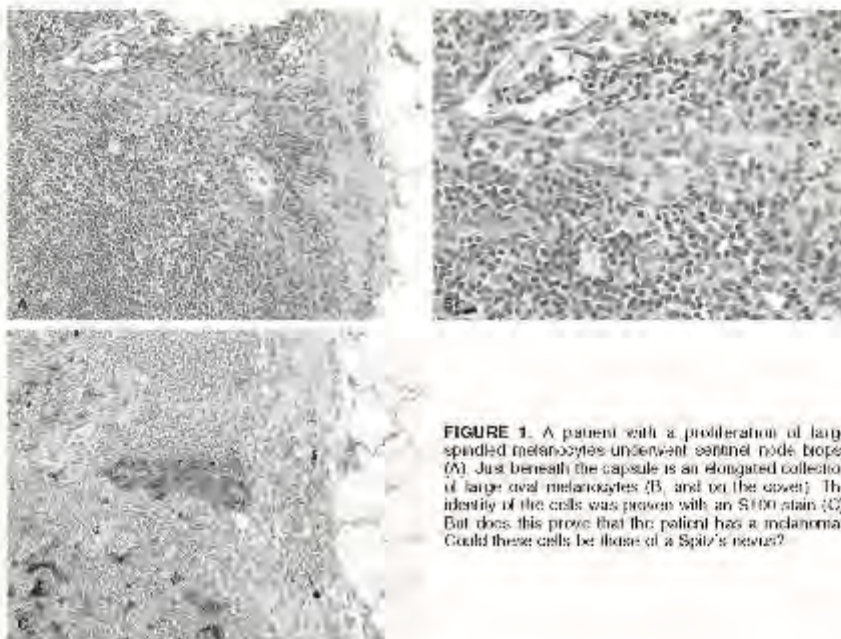
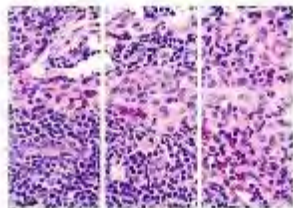


FIGURE 1. A patient with a proliferation of large spindle melanocytes underwent sentinel node biopsy (A). Just beneath the capsule is an elongated collection of large oval melanocytes (B, and on the cover). The identity of the cells was proven with an S100 stain (C). But does this prove that the patient has a melanoma? Could these cells be those of a Spitz's nevus?

Certainly, if a patient with an ambiguous neoplasm has a sentinel lymph node packed with anaplastic-appearing melanocytes, with many mitotic figures and zones of necrosis, you will get no argument from me (although such a node is usually palpable). On the other hand, what if the node shows only a small cluster of large melanocytes (on the cover, and Fig. 1)? What then?

So what do the melanocytes in the lymph node on the cover prove? To some, everything—a sure diagnosis of melanoma. To me, nothing.



On the Cover

What Do These Cells Prove?

Philip E. LeBoit, MD

Key Words: melanoma, metastasis, sentinel node biopsy, Spitz nevus

A patient has an unusual melanocytic proliferation. Skilled observers are puzzled—is it a Spitz's nevus or a melanoma? The patient and the dermatologist want to know, and with certainty. Why not do a sentinel node biopsy to find out?

Certainly, this question has been asked and answered before. Several reports now tell of cases in which diagnostic uncertainty was settled by means of a sentinel node biopsy.¹⁻³ But is this an accurate approach?

From the Departments of Pathology and Dermatology, University of California, San Francisco, California.

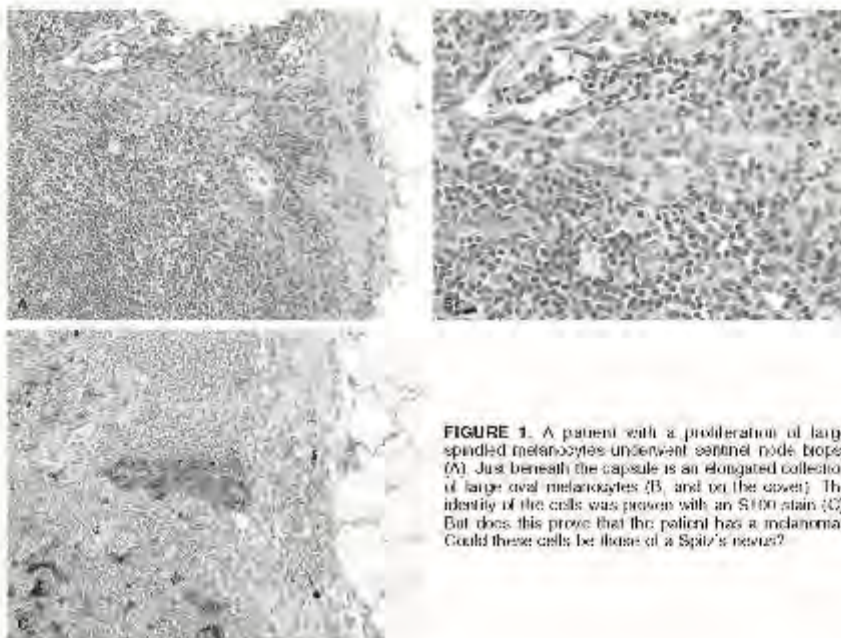


FIGURE 1. A patient with a proliferation of large spindled melanocytes underwent sentinel node biopsy (A). Just beneath the capsule is an elongated collection of large oval melanocytes (B, and on the cover). The identity of the cells was proven with an S100 stain (C). But does this prove that the patient has a melanoma? Could these cells be those of a Spitz's nevus?

BUT REMEMBER:

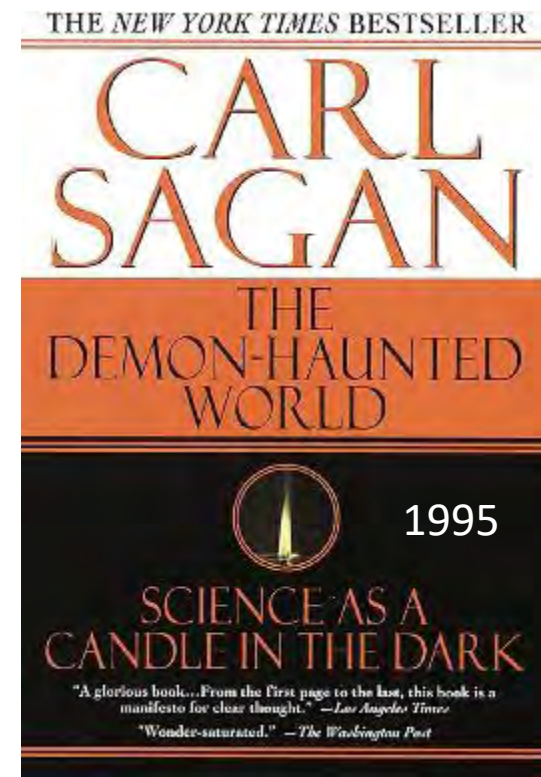
The melanocytes in the lymph node on the cover do not prove that the primary lesion was a melanoma – but also do not prove that it was *not* a melanoma...

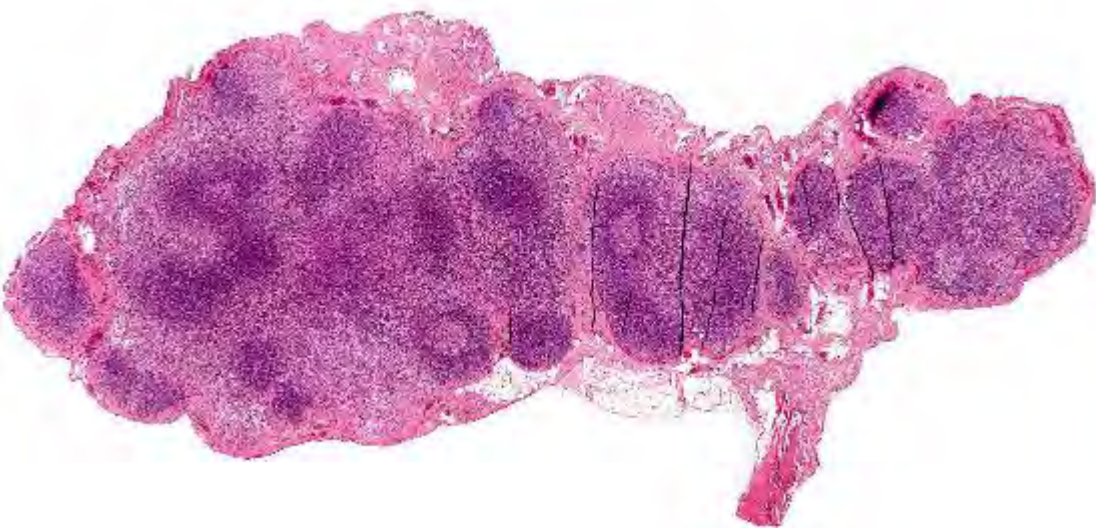
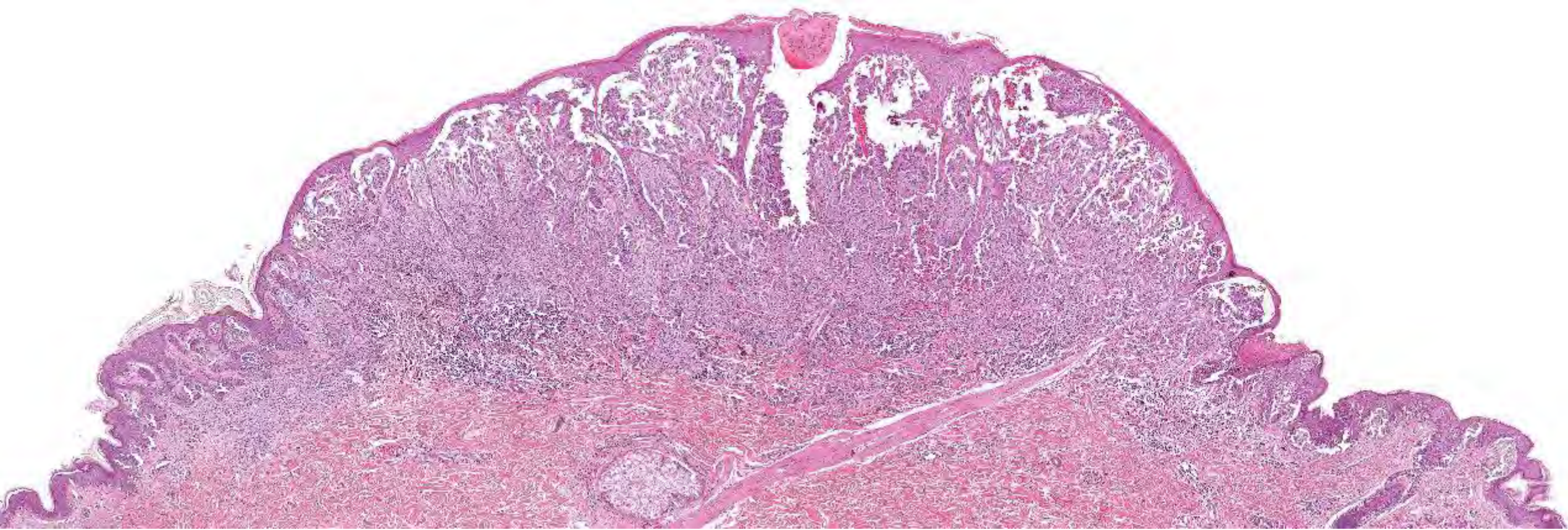
A small cluster of large melanocytes in a lymph node does not have any diagnostic meaning



Absence of evidence
is not evidence of absence.

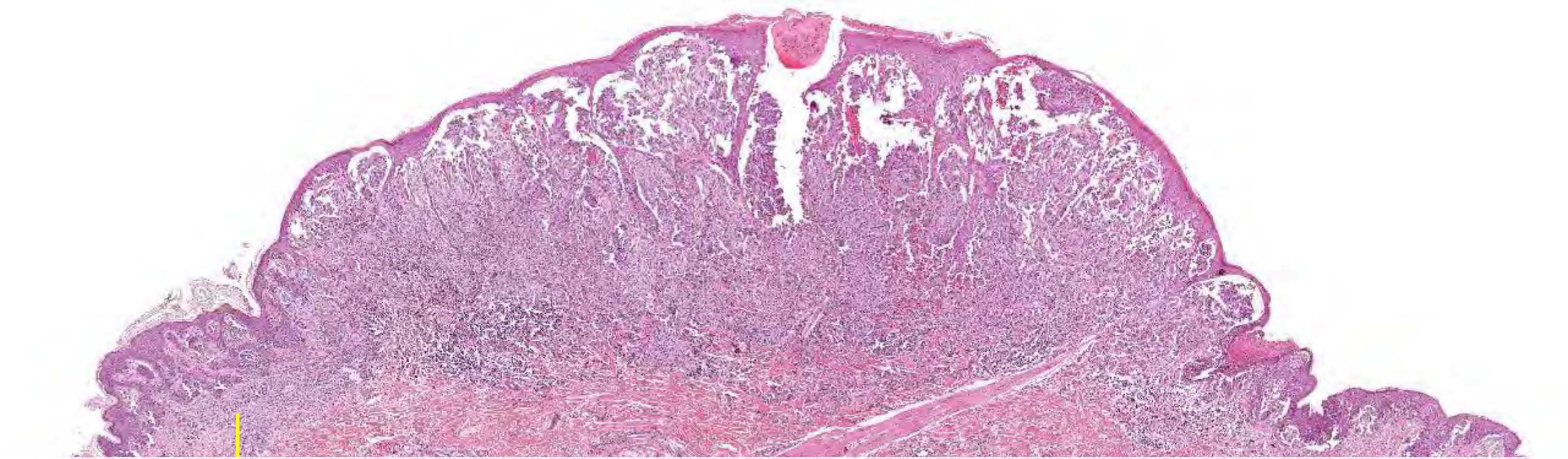
Carl Sagan (1934-1996)



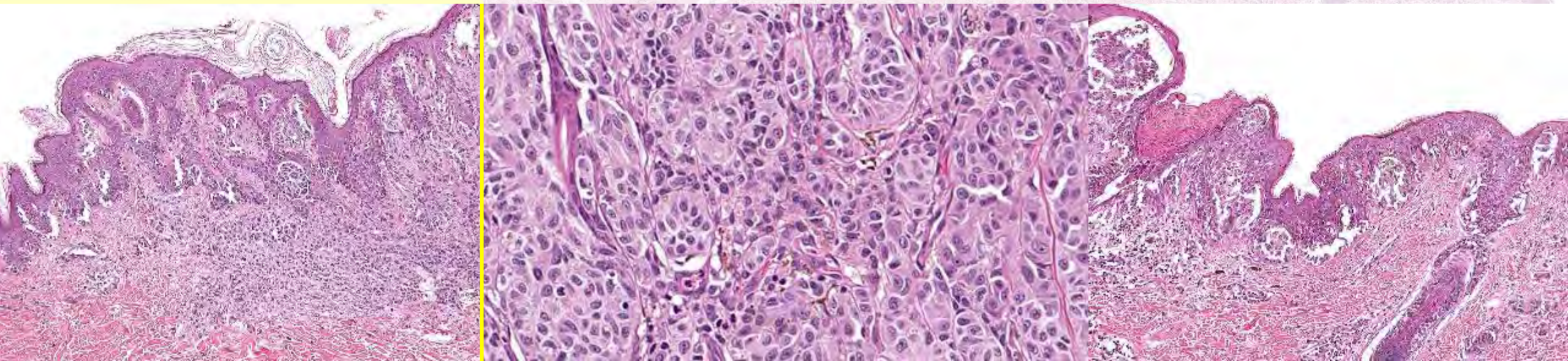


- Primary tumor
- Sentinel LN positive (1 month later)
- Multiple metastases in lungs, kidneys, liver, spleen, orbita, brain (7 years later)
- Death of progressive disease (8,5 years later)

Spitz melanoma ?



"Conventional" (spitzoid) melanoma arising in a nevus – not a "Spitz melanoma"





**21st Symposium of the International Society of
Dermatopathology**

Neoplasms of the Skin: "Benign" vs. "Malignant"

A New Kind of Meeting in Dermatopathology for the New Millennium

September 14 - 16, 2000

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Programme



The International Society of Dermatopathology

XXIX Symposium

**Graz, Austria
October 2-4, 2008**



Convention Center, Sparkassenplatz, Graz

Tutorial on Melanocytic Lesions

Lorenzo Cerroni, MD,† and Helmut Kerl, MD

During the 29th Symposium of the International Society of Dermatopathology, which was held in Graz, Austria, September 2008, an entire session was devoted to a Tutorial on melanocytic lesions. A panel of 6 experts in histopathologic diagnoses of melanocytic tumors (A. Bernard Ackerman, New York; David E. Elder, Philadelphia; Peter Heenan, Perth; Helmut Kerl, Graz; Philip C. LeBoit, San Francisco; and Juan Rosai, Milan) had the opportunity of studying 71 cases submitted by participants in the Symposium before the beginning of the meeting. All cases were then presented during the session, and both audience and experts had the opportunity to review histopathologic features and discuss criteria for diagnosis. This session was instructive for several reasons. First, it is uncommon to have the opportunity to discuss difficult melanocytic lesions with 6 among the best dermatopathologists of the world. Second, it gave the opportunity to compare and contrast different approaches to the diagnosis of these lesions. Last, it gave a kind of "current status" about the degree of agreement among experts on diagnoses of difficult melanocytic lesions. The discussion was open, but, and constructive. A brief analysis of data concerning this session shows many positive aspects, but it also shows some concerns.

Table 1 summarizes the level of agreement in 67 out of 71 cases where diagnoses could be compared. The other 4 cases represented examples of non-melanocytic lesions (not of epithelioid tumors), or were not interpretable because of technical problems. Cases are grouped in the table according to the majority diagnosis. Of course, inclusion of cases with discordant diagnoses at one or the other group is subjective (ie, Spitz's nevus versus "Spitzoid" melanoma), but it does not affect in any way the interpretation of the results. Agreement in diagnosis was analyzed at the level of benignity versus malignancy, irrespective of possible differences in terminology (for example, deep penetrating nevus, Spitz's nevus, or compound nevus were considered equivalent diagnoses). The level of agreement was scored from 0-0 (all experts scored 0-5) (3 experts favor benignity and 3 malignancy, or vice versa).

All in all, a complete agreement was observed in 53/67 cases (49.3%), and a 5-0 score in 21 (31.3%). These figures, in our opinion, are particularly good, especially in view of the difficulties that many of the cases presented. Remarkably, uncertainty in diagnosis could be observed for all lesions classified as either desmoplastic melanoma or desmoplastic nevus (8 cases, all 0-0). These results clearly show that these problematic lesions can be agreed upon by all experts, in fact, consensus on the diagnosis of desmoplastic melanoma was reached even in cases without clear-cut changes of melanoma *in situ* in the epidermis (Fig. 1). A very good agreement was observed also in 3 cases of melanoma *in situ* and in 7 of histologic variants of melanoma, excluding "nevoid" melanoma. Of particular interest is also the remarkable agreement in the diagnosis of recurrent nevus and recurrent melanoma observed in the 5 lesions presented in the tutorial. In fact, although the primary lesions could not be reviewed by the experts before the meeting, a unanimous diagnosis was observed in 5 cases, and a 5-0 score in 3. More important, diagnoses in this group of lesions

TABLE 1. Diagnostic categories and level of agreement

Diagnostic category	0-0	5-0	4-1	3-2
Desmoplastic nevus (n = 5)	1	—	—	—
Recurrent (persistent) nevus (n = 2)	2	—	—	—
Pseudomelanoma in children (n = 6)	3	1	—	—
Spitz nevus and variants (n = 6)	4	1	—	—
Other variants of melanocytic nevi (n = 12)	4	4	1	3
Total melanocytic nevi (n = 35)	14	10	1	4
Melanoma <i>in situ</i> (n = 3)	2	1	—	—
Desmoplastic melanoma (n = 8)	0	—	—	—
Recurrent (persistent) melanoma (n = 5)	1	3	—	—
Variants of melanoma (non-nevoid) (n = 7)	3	1	—	—
Nevo (Spitzoid) melanoma (n = 10)	3	4	2	1
Total (malignant) melanoma (n = 28)	15	9	2	1
Total	33	21	1	5

From the *Department of Dermatology, University of Graz, Graz, Austria.

†Correspondence to: Lorenzo Cerroni, MD, Department of Dermatology, Medical University of Graz, Inbaurgplatz 8, A-8036 Graz, Austria (e-mail: lorenzocerroni@meduni-graz.at).

Melanocytic Tumors of Uncertain Malignant Potential

Results of a Tutorial Held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008

Lorenzo Cerroni, MD,* Raymond Barnhill, MD,† David Elder, MD,‡
Geoffrey Gottlieb, MD,§ Peter Heenan, MD,¶ Heinz Kutzner, MD,*
Philip E. LeBoit, MD,‡ Martin Mihm, Jr., MD,**
Juan Rosai, MD,†† and Helmut Kerl, MD*

Abstract: Several reports demonstrated the difficulties and lack of agreement in the histopathologic diagnosis of particular melanocytic tumors (atypical Spitz tumors, atypical blue nevi, deep penetrating nevi). These lesions are often referred to as "melanocytic tumors of uncertain malignant potential" (MELTUMPs). We studied a large number of such tumors to find out whether repeatable histopathologic criteria for distinction of benign from malignant cases exist. Fifty-seven cases of MELTUMPs were classified within 3 groups according to behavior as follows: (a) favorable (no evidence of metastatic disease after a follow-up of >5 y), (b) unfavorable (tumor-related death and/or large metastatic deposits in the lymph nodes and/or visceral metastases), (c) borderline (small nodal deposits of tumor cells ≤ 0.2 mm). There were no significant differences in tumor thickness and presence or absence of ulceration between the different groups. The only 3 histopathologic criteria that were statistically different between the groups of favorable and unfavorable cases were presence of mitoses, mitoses near the base, and an inflammatory reaction; all of them found more frequently in cases with unfavorable behavior. The major outcome of this study of a series of "MELTUMPs" suggests as a preliminary observation that these lesions as a group exist and that they may be biologically different from conventional melanoma and benign melanocytic nevi. The terminology remains highly controversial, reflecting

the uncertainty in classification and interpretation of these atypical melanocytic tumors.

Key Words: atypical Spitz tumor, malignant melanoma, melanocytic tumor of uncertain malignant potential, atypical blue nevus, deep penetrating nevus

Am J Surg Pathol 2010;34:314-326

Melanocytic lesions continue to pose significant interpretative problems to histopathologists. Cases that were difficult to distinguish from benign melanocytic nevi have been designated by some authors as "minimal deviation melanoma" or "nevoid melanoma."^{23,25-27,28} Among the most challenging problems encountered are a spectrum of relatively thick, mainly dermal tumors that are often quite difficult or impossible to distinguish from melanoma, including particularly neoplasms with spindle and/or epithelioid cells suggesting Spitz tumors, cellular and/or epithelioid blue nevi, and so-called "deep penetrating nevi."^{6,13} In the last years, several reports clearly demonstrated the difficulties and lack of agreement in the histopathologic diagnosis and differential diagnosis of these particular lesions.^{2,29,30,31,32} Two of us have previously proposed the terms "melanocytic tumor of uncertain malignant potential (MELTUMP)" or "melanocytic proliferation with intermediate biologic potential," respectively, to reflect the uncertainty of the precise classification of such tumors.^{3,34} The malignant behavior of some melanocytic tumors that had been previously classified as Spitz nevus has been described,³³ and one of us suggested that these neoplasms may represent a distinct subtype of malignant melanocytic tumors with low-grade behavior.³⁵⁻³⁷ Finally, at several dermatopathologic meetings many anecdotal cases of otherwise typical "Spitzoid tumors" or "deep penetrating nevi" with lymph node and/or visceral metastases have been presented.

In October 2008 we organized a Tutorial on melanocytic tumors in the course of the XXIX Symposium of the International Society of Dermatopathology

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Funding Sources: None.

Correspondence: Lorenzo Cerroni, MD, Department of Dermatology, Medical University of Graz, Inbaurgplatz 8, A-8036 Graz, Austria (e-mail: lorenzocerroni@meduni-graz.at).

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Tutorial on Melanocytic Lesions

Lorenzo Cerroni, MD, and Helmut Kerl, MD

During the 2nd Symposium of the International Society of Dermatopathology, which was held in Graz, Austria, September 2000, an entire session was devoted to a Tutorial on melanocytic lesions. A panel of 6 experts in histopathologic diagnosis of melanocytic tumors (A. Bernard, Amsterdam, New York; David E. Elston, Philadelphia; Peter Hohen, Perth; Helmut Kerl, Graz; Paolo C. Leifery, San Francisco; and Juan Rosai, Milan) had the opportunity of studying 71 cases submitted by participants in the Symposium before the beginning of the meeting. All cases were then presented during the session, and both audience and experts had the opportunity to review histopathologic features and discuss criteria for diagnosis. This session was instructive for several reasons. First, it is uncommon to have the opportunity to discuss different melanocytic lesions with 6 among the best dermatopathologists of the world. Second, it gave the opportunity to compare and contrast different approaches to the diagnosis of these lesions. Last, it gave a kind of "current status" about the degree of agreement among experts on diagnosis of difficult melanocytic lesions. The discussion was open, but, and constructive. A brief analysis of data concerning this session shows many positive aspects, but indicates also some more subtle remarks.

Table 1 summarizes the level of agreement in 67 out of 71 cases where diagnosis could be compared. The other 4 cases represented examples of non-melanocytic lesions, not of melanocytic tumors, or were not interpretable because of technical problems. Cases are grouped in the table according to the majority diagnosis. Of course, inclusion of cases with discordant diagnoses at one or the other group is subjective (i.e., Spitz's nevus versus "Spitzoid" melanoma), but it does not affect in any way the interpretation of the results. Agreement in diagnosis was analyzed at the level of benignity versus malignancy, irrespective of possible differences in no-

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All in all, a complete agreement was observed in 53/67 cases (49.3%), and a 5-5 score in 21 (31.3%). These figures, in our opinion, are particularly good, especially in view of the difficulties that many of the cases presented. Remarkably, uncertainty in diagnosis could be observed for all lesions classified as either desmoplastic melanoma or desmoplastic nevus (8 cases, all 6-0). These results clearly show that these problematic lesions can be agreed upon by all experts, in fact, consensus on the diagnosis of desmoplastic melanoma was reached even in cases without clear-cut changes of melanoma *in situ* in the epidermis (Fig. 1). A very good agreement was observed also in 3 cases of melanoma *in situ* and in 7 of histologic variants of melanoma, excluding "nevoid" melanoma. Of particular interest is also the remarkable agreement in the diagnosis of recurrent nevus and recurrent melanoma observed in the 5 lesions presented in the tutorial. In fact, although the primary lesions could not be reviewed by the experts before the meeting, a unanimous diagnosis was observed in 5 cases, and a 5-4 score in 3. More important, diagnoses in this group of lesions

TABLE 1. Diagnostic categories and level of agreement

Diagnostic category	6-0	5-1	4-2	3-3
Desmoplastic nevus (n = 3)	3	—	—	—
Recurrent (persistent) nevus (n = 2)	2	—	—	—
Pseudomelanoma in children (n = 6)	5	1	—	—
Spitz nevus and variants (n = 16)	4	7	—	1
Other variants of melanocytic nevi (n = 12)	4	4	1	3
Total (melanocytic nevi, n = 39)	18	12	5	4
Melanoma <i>in situ</i> (n = 3)	2	1	—	—
Desmoplastic melanoma (n = 5)	5	—	—	—
Recurrent (persistent) melanoma (n = 3)	1	2	—	—
Variants of melanoma (non-nevoid) (n = 7)	4	3	—	—
Nevoid/spitzoid melanoma (n = 10)	3	3	2	2
Total (malignant melanoma, n = 28)	15	9	2	2
Total	33	21	7	6

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Melanoma <i>in situ</i> (n = 3)	2	1	—	—
Desmoplastic melanoma (n = 5)	5	—	—	—
Recurrent (persistent) melanoma (n = 3)	1	2	—	—
Variants of melanoma (non-nevoid) (n = 7)	4	3	—	—
Nevoid/spitzoid melanoma (n = 10)	3	3	2	2
Total (malignant melanoma, n = 28)	15	9	2	2
Total	33	21	7	6

TABLE 2. Level of agreement according to age of patients

Age (years)	6-0	5-1	4-2	3-3
0-12	10	5	—	—
13-20	2	2	1	2
21-30	4	5	1	2
31-40	4	3	1	—
41-50	3	3	1	—
51-60	1	1	1	—
61-70	3	1	2	1
>70	6	1	—	1



Tutorial 2000

Panelist A	Melanoma
Panelist B	Melanoma
Panelist C	--
Panelist D	--
Panelist E	--
Panelist F	--
Panelist G	Malignant melanoma, ? associated nevus
Panelist H	Spitz nevus
Panelist I	Melanoma and nevus
Panelist J	Melanoma vs. Spitz nevus, favor melanoma



Tutorial 2008

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Nevus

Melanoma

Melanoma

Nevus

Nevus

Nevus

Borderline

Melanoma

Panels of experts

A.B. Ackerman (2000), R. Barnhill (2008), David Elder (2000, 2008), Geoffrey Gottlieb (2008), Peter Heenan (2000, 2008), Heinz Kutzner (2008), Phil LeBoit (2000, 2008), Martin Mihm, Jr. (2008), Juan Rosai (2000, 2008).

