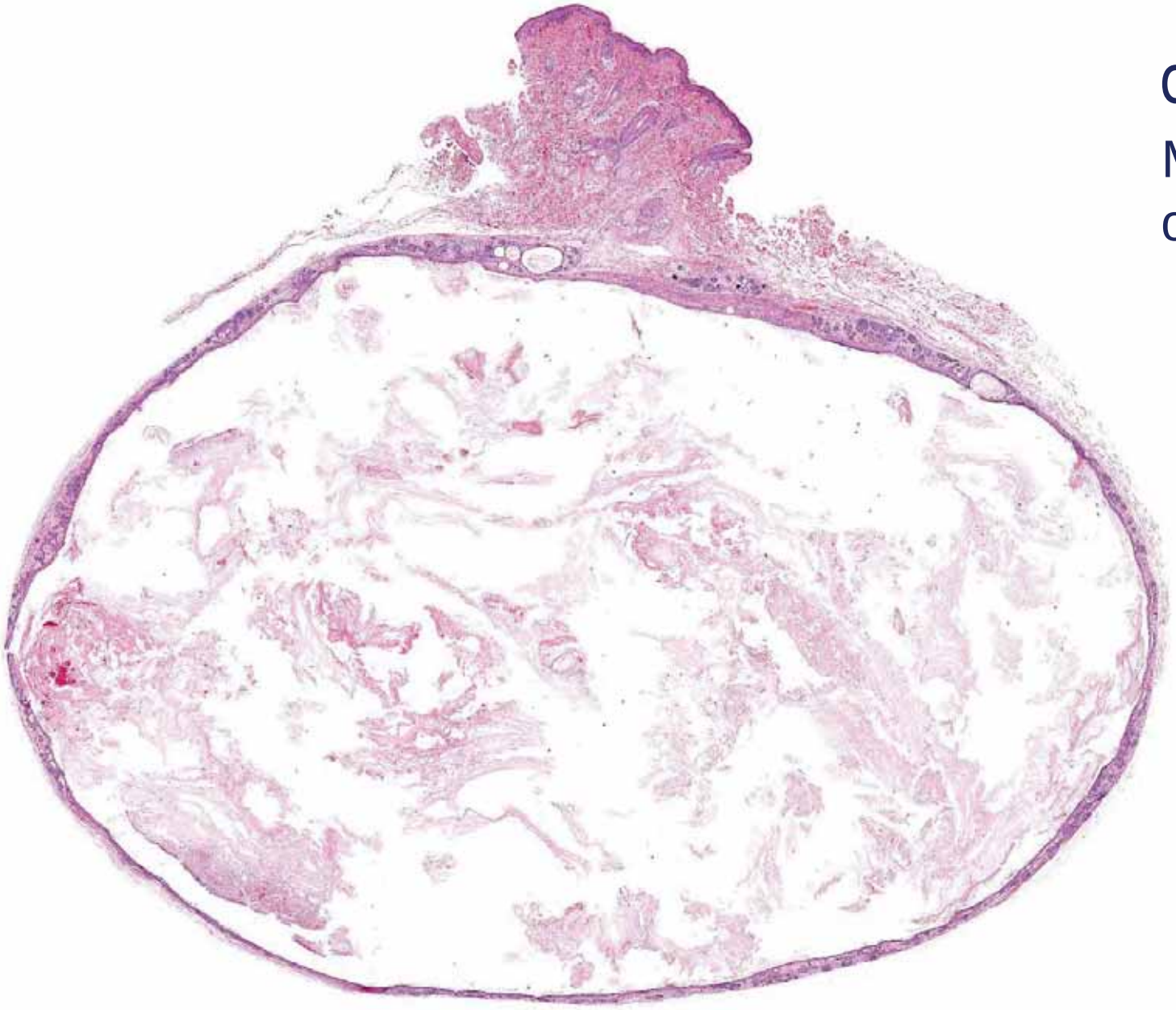
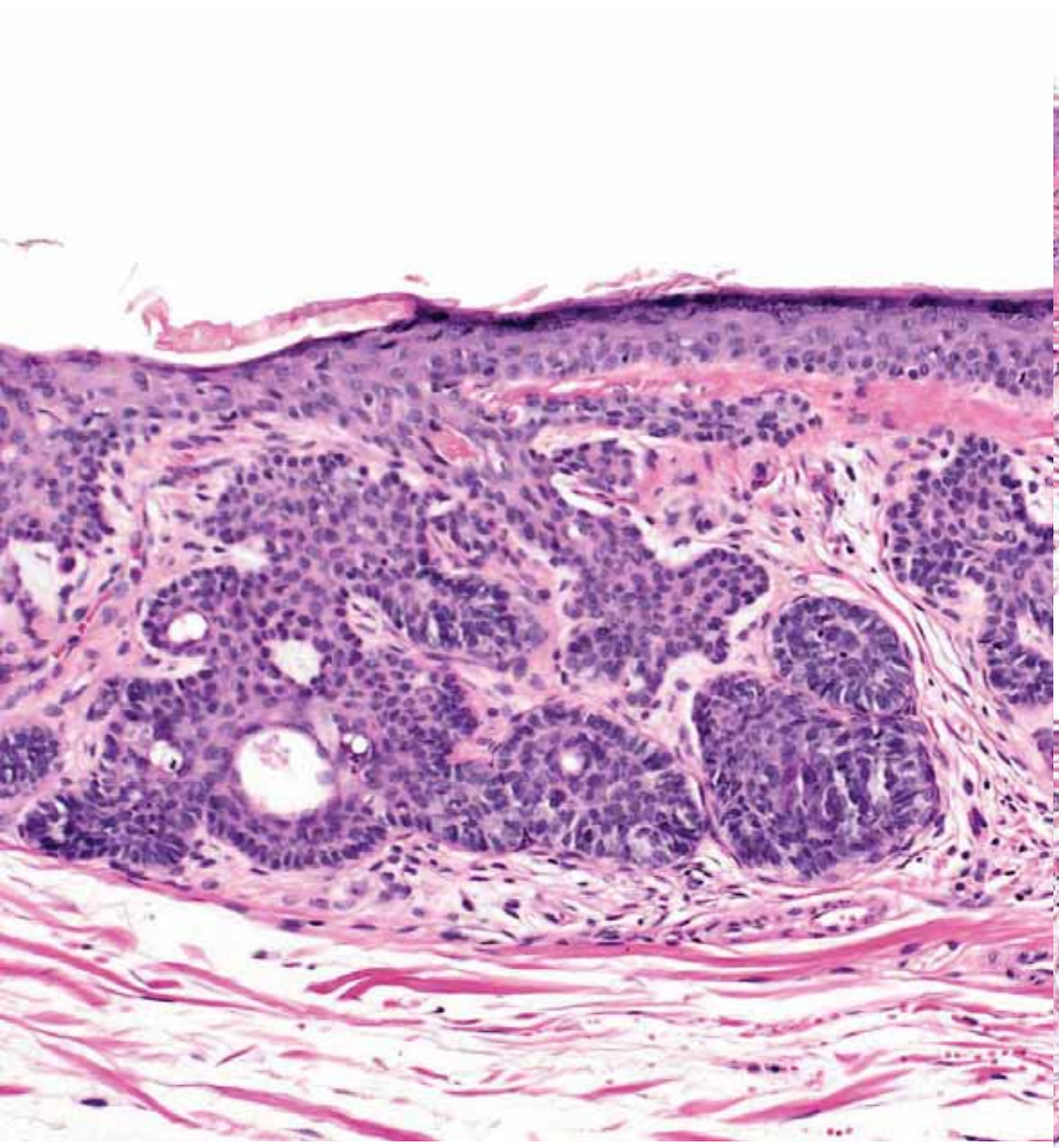
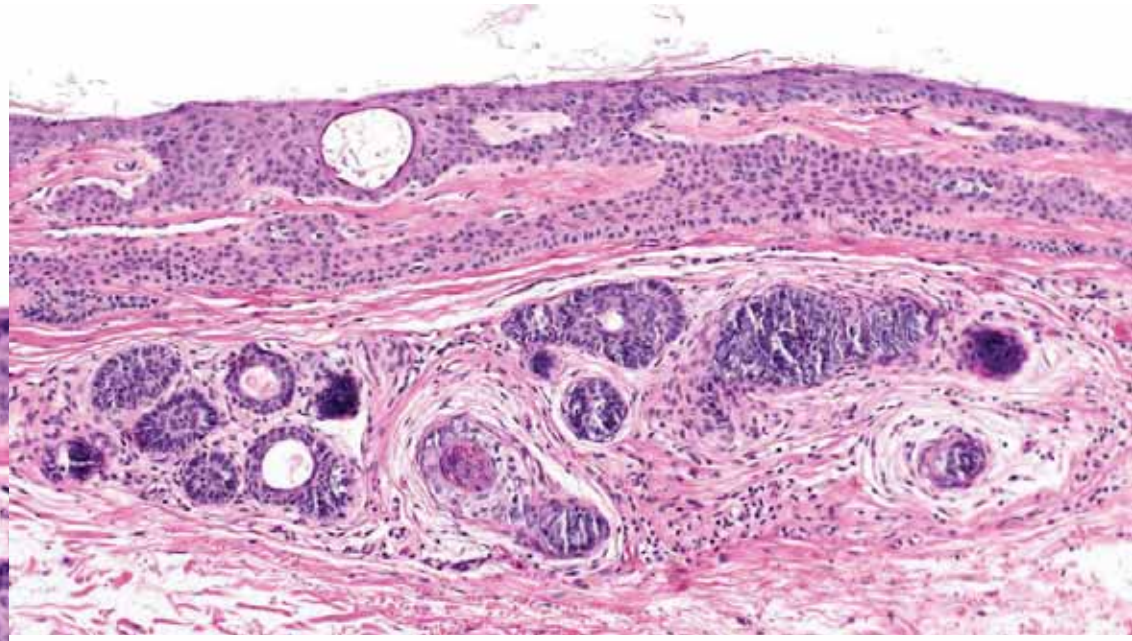
17th Summer Academy of Dermatopathology
Graz, June 30 – July 4, 2025
Self-assessment cases

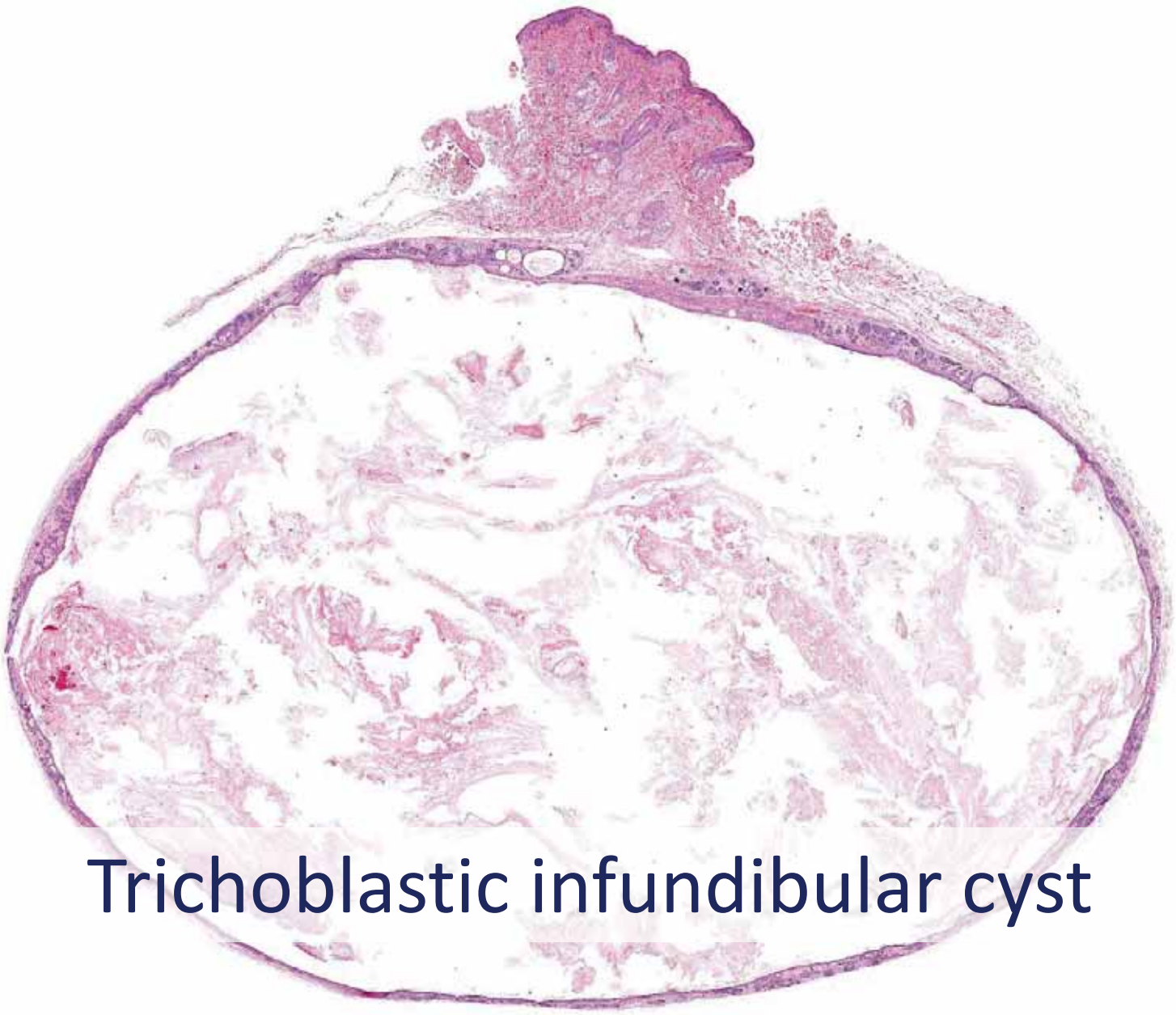


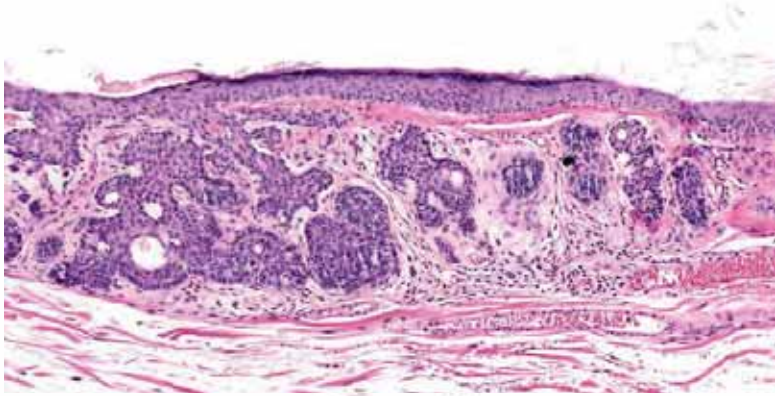
Case 1

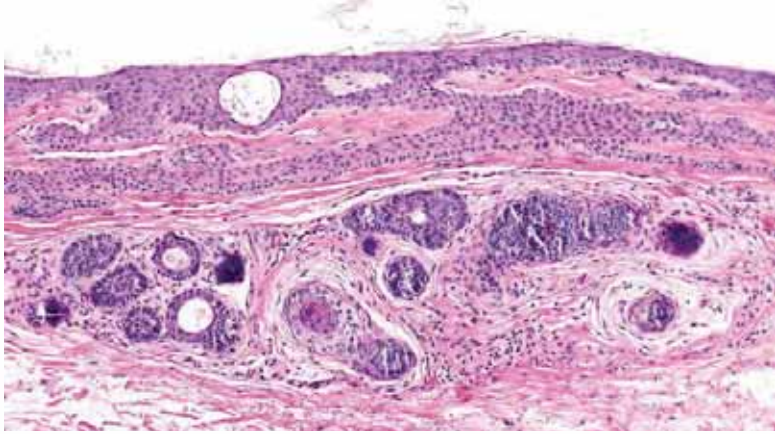
M, 22. Cyst on the forehead of unknown duration.

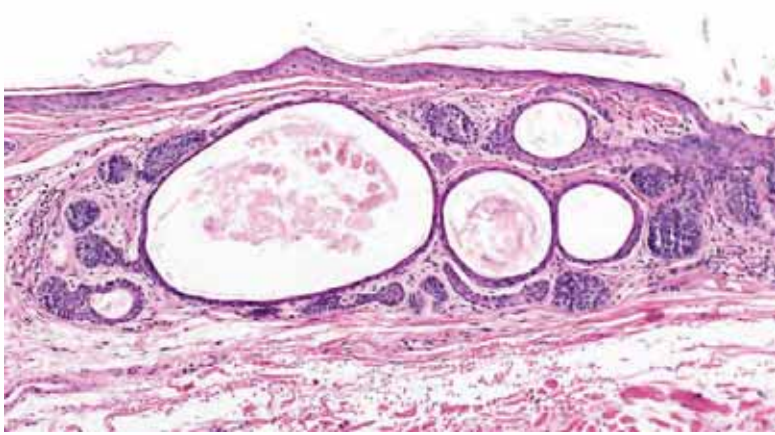




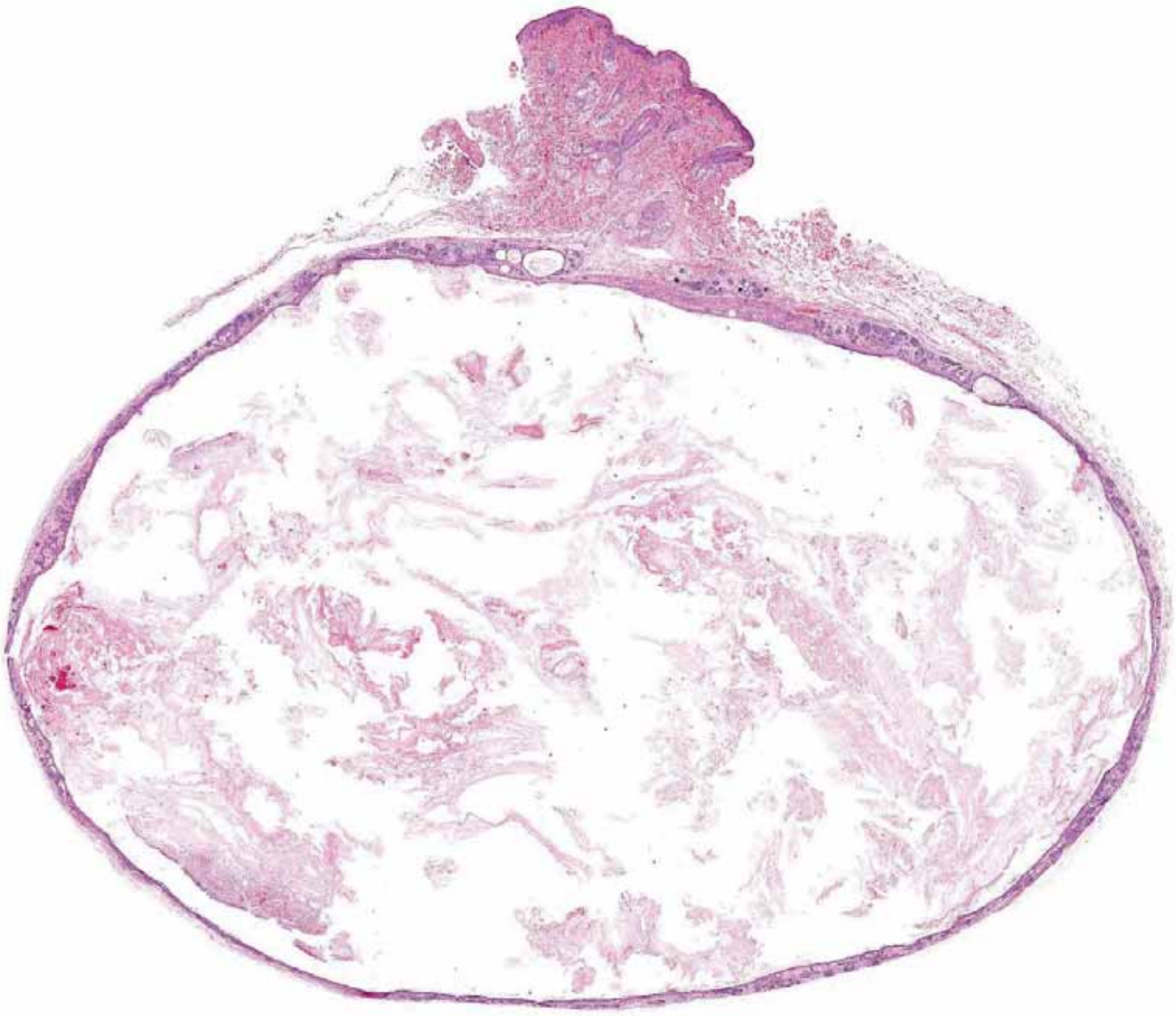


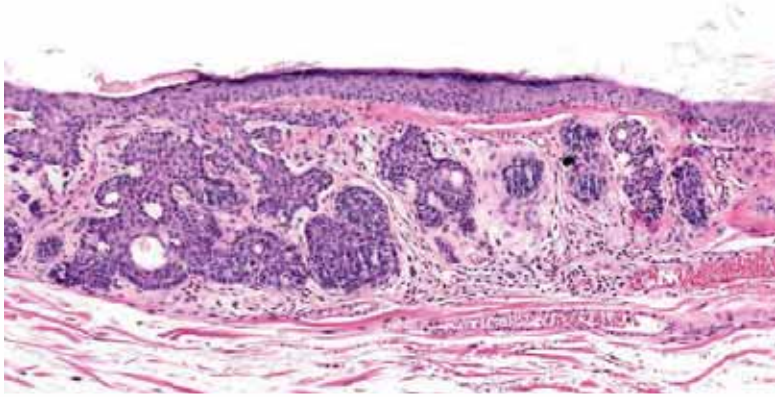


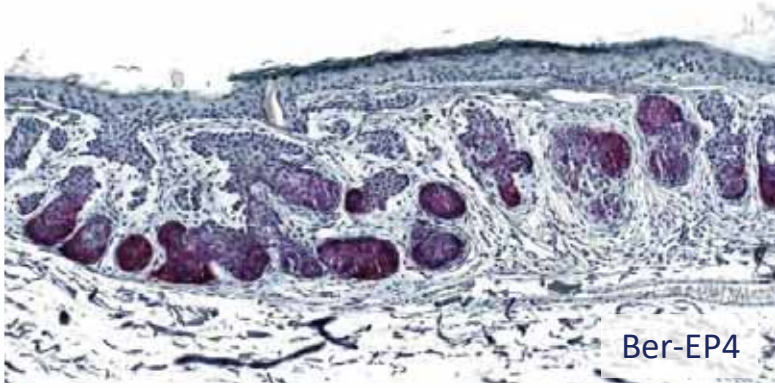




Trichoblastic infundibular cyst



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Trichoblastic Infundibular Cyst

Shin-ichi Ansai,† Masaaki Tsuda,* Hajime Nagato,* Keiko Nishimaki,* Masahiko Wako,* Motomu Manabe,* Takaya Fukumoto,† and Tetsunori Kimura†*

Abstract: We report 4 cases of an infundibular cyst that histopathologically showed small papillary projections of follicular germinative cells emanating from the basal layer of the cyst wall. Some of these projections branched and formed a reticulated pattern. This cystic lesion is histopathologically distinctive. We propose to designate it as a trichoblastic infundibular cyst because its lining resembles that of an infundibular cyst, yet it has cells that resemble those of the follicular germ in its wall.

Key Words: infundibular type follicular cyst, epidermal cyst, epidermoid cyst, follicular germinative cell, trichoblastoma, trichofolliculoma

(*Am J Dermatopathol* 2006;28:507–509)

INTRODUCTION

The infundibular type of follicular cyst, also referred to as "epidermal inclusion cyst" or "epidermoid cyst," is one of the most common epithelial cysts of the skin.[1–4] We report 4 cases of an infundibular type of follicular cyst with distinctive histopathological features, namely foci of cells resembling follicular germ. This cyst is to be differentiated from other infundibular cystic lesions, including neoplasms comprised of follicular germinative cells.

CASE REPORTS

A summary of the clinical data of our 4 cases is shown in the table. Briefly, 4 males ranging in age from 32 to 83 years (the other patients were 56 and 57 years old, respectively) presented to their dermatologists with either an intracutaneous or subcutaneous nodule or tumor in all patients, and in 3 of the 4 cases the lesions were located on the head or neck (Figure 1). Two of the lesions had surrounding erythema. The clinical duration was known in 2 of the cases; the 83-year-old patient said the lesion was present for more than 35 years and the 32-year-old patient noted it had been present since childhood.

Histopathologically, each lesion showed similar findings (Figure 2). These unilocular cysts cornified in a fashion identical to that of infundibular epithelium (Figure 2A). The cyst walls ranged in thickness from 3 to 4 up to 6 to 7 layers of squamous epithelium (Figure 2B), and the innermost cells contained keratohyaline granules. Emanating from the basal layer of the cyst walls were papillary projections of cells with large nuclei and scant cytoplasm arranged in a peripheral palisade (Figure 2C). Some of the projections of cells branched and formed reticular structures (Figure 2C). None of the cysts contained sebaceous glands, follicular bulbs or papillae, cytologic atypia, or mitoses. One of the cysts (case 4) was ruptured in its lower half and was accompanied by suppurative and granulomatous inflammation.

Immunohistochemical staining using antikeratin 17 (E3), antikeratin 20 (Ks20.8), and anti-Ki67 (MIB1) antibodies showed no positive reactions in cells of the cyst wall and papillary projections in case 1.

DISCUSSION

The basic structure of our 4 cases is similar to that of the infundibular type of follicular cyst, also designated "epidermal inclusion cyst" or "epidermoid cyst." The cyst wall of this lesion is composed of squamous epithelial cells with a granular cell layer, resembling the infundibulum of a hair follicle. These cysts, however, differ from conventional infundibular cysts by containing papillary and reticular projections of cells with large nuclei emanating from the basal layer of the cyst wall. Although we failed to prove the differentiation of these cells toward follicular germinative cells immunohistochemically, these cells are morphologically similar to follicular germinative cells (ie, they have small, dark nuclei and scant cytoplasm)[5] and the outermost cells are columnar and arrayed in palisades.[5] Last, these cells lack cytological atypia and mitoses, suggesting the benignity of these lesions. For these reasons, we designated these lesions as trichoblastic infundibular cysts.

First, we should consider the possibility that these projections were a sign of induction of follicular germs by the fibrohistiocytic stroma.[6] It has been well known that hyperplasia of the cyst wall in infundibular-type follicular cysts occurs with surrounding inflammation or fibrosis. In our 4 cases, inflammatory changes or fibrosis were observed in only 2 cases and in which projections of cells resembling follicular germ were observed in the portions without inflammatory changes or fibrosis. Induction of follicular germinative cells in the epidermis has been noted in dermatofibroma, neurofibroma, and other neoplasms.[6] In sum, we consider that the projections from cyst walls observed in our cases were primary findings of the lesion.

Trichoblastic infundibular cyst is to be differentiated from other lesions with follicular germinative cells and other infundibular cystic lesions. A benign neoplastic proliferation of follicular germinative cells is classified as trichoblastoma.[7,8] Although trichoblastoma may contain a cystic component, in contrast to trichoblastic infundibular cysts, those infundibular cysts are small, do not predominate, and, when present, are

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TABLE 1. Table Summary of the Cases in This Study

Case	Age	Sex	Location	Size of the Lesion	Duration of the Lesion	Clinical Symptom
1	83	Male	Right Neck	5 × 6 × 3 cm	Over 35 years	Intracutaneous tumor with erythema on overlying skin
2	56	Male	Occipital Scalp	About 2 cm	Not apparent	Subcutaneous tumor
3	57	Male	Ear	About 1 cm	Not apparent	Intracutaneous tumor
4	32	Male	Nache	About 8 mm	Since his childhood	Subcutaneous tumor

FIGURE 1. Clinical findings of case 1. This 83-year-old healthy man presented himself to the Department of Dermatology and Plastic Surgery at Akita University Hospital with a history of this cystic tumor on his right neck for more than 35 years. The patient noted that several days before his visit, the lesion had become inflamed. Clinical examination revealed a dome-shaped and cystic tumor measuring 5 × 6 × 3 cm in diameter with overlying telangiectasia and erythema. No recurrence has been noted 1 year after excision of this lesion.

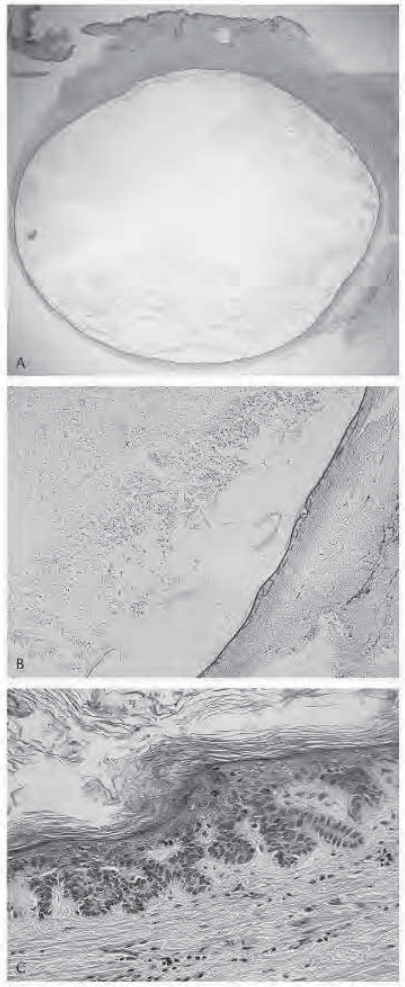

FIGURE 2A–C. Histopathological findings of case 1. A, Within the dermisis a large unilobular cyst with a thin wall. B, Intermediate magnification shows the cyst wall contains radial projections of epithelium and is filled with basket-weave corneocytes. C, Higher magnification reveals the cyst wall is composed of 3 to 4 layers of squamous epithelium and the inner-most layer of cells contains keratohyaline granules. The papillary projections from the basal layer of the cyst wall are composed of cells with small nuclei and scant cytoplasm in palisaded array at their periphery. Some projections branch and form reticular structures. No follicular bulbs or follicular papillae are present.

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Journal of
Cutaneous Pathology

Cystic trichoblastoma (so-called trichoblastic infundibular cyst): a report of three new cases

Three cases of so-called trichoblastic infundibular cyst are reported. The lesions showed a configuration similar to infundibular cysts, including basophilic orthokeratotic corneocytes arranged in basket-weave pattern and intermingled with eosinophilic sebum. The cyst wall was mainly composed of stratified squamous epithelium showing infundibular keratinization throughout a granular layer. However, in some areas, epithelial cords, buds and reticulated proliferations of follicular germinative cells surrounded by a densely cellular stroma emanated radially from the cyst wall. In one case, in addition to the presence of follicular germinative cells, there were also aggregations of matrical cells with evidences of inner sheath and matrical differentiation. In our opinion, these findings support a neoplastic rather than a cystic nature for this lesion. We discuss the histopathologic differential diagnosis with other follicular cystic lesions

África Juárez[1], Arno Rütten[2], Heinz Kutzner[2] and Luis Requena[1]

[1]Department of Dermatology, Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain, and
[2]Dermatohistopathologische Gemeinschaftspraxis, Friedrichshafen, Germany

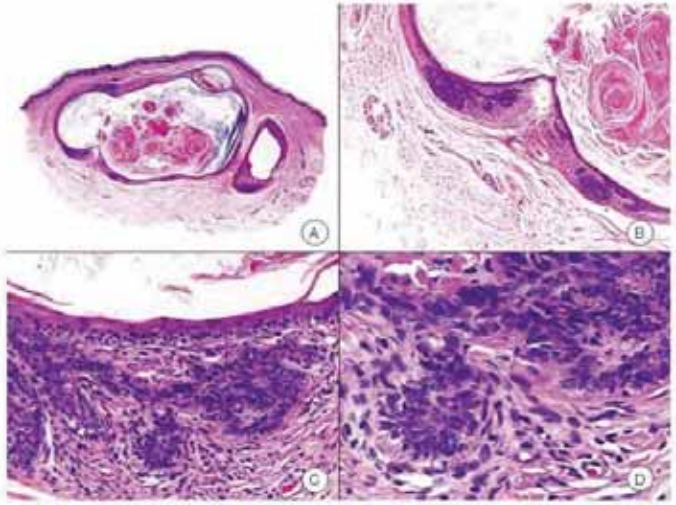

Fig. 1. Case 1: A) Scanning power showing two cystic structures involving the dermis. B) Buds of basaloid epithelium emanating from the cyst wall. C) The buds and cords are composed of follicular germinative cells and surrounded by a stroma containing numerous fibrocytes. D) Evidence of primitive differentiation toward follicular bulbs and papillae.

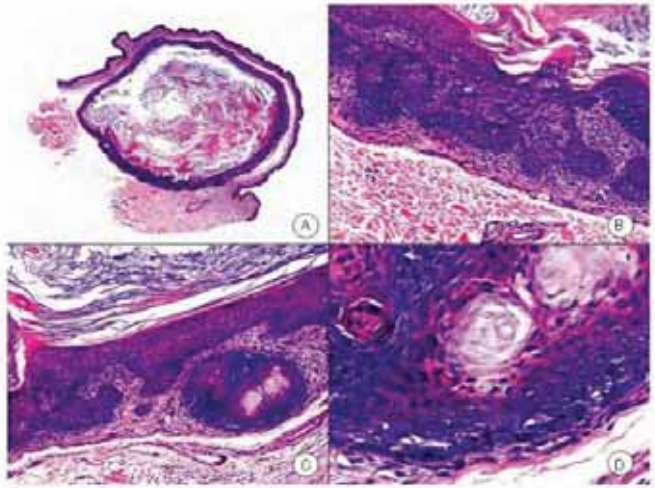

Fig. 3. Case 3: A) Scanning power showing a cystic lesion in the dermis. B) Buds of primitive follicular germinative cells, some of them showing peripheral palisading, emanated from the cyst wall. Note the densely cellular stroma. C) In some areas, there were also aggregations of matrical cells. D) These aggregations of matrical cells showed evidence of matrical keratinization with trichohyaline granules and hints of formation of shadow corneocytes.

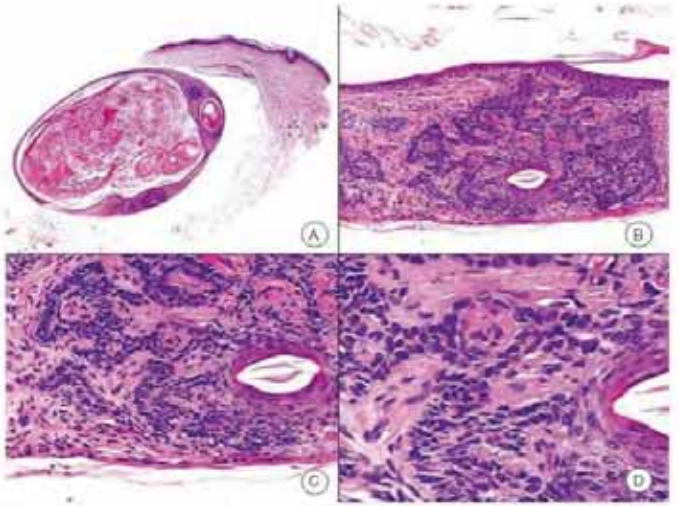

Fig. 2. Case 2: A) Scanning power showing a cystic lesion involving the dermis. B) Basophilic cords of follicular germinative cells arranged in reticulated pattern emanating from the cyst wall. C) In some areas, these basophilic cords contained tiny infundibular cystic foci. D) The stroma surrounding the cords of follicular germinative cells contained numerous fibrocytes.

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CASE REPORT

WILEY

Trichoblastic infundibular cyst should be renamed infundibular cyst with unique papillary projections

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Abstract

Trichoblastic infundibular cyst (TBIC) was previously reported as a unique keratinous cystic lesion, which was characterized by the papillary projections of follicular germinative-like cells emanating from the cyst wall. Here, we report three additional cases of this cyst and discuss the pathogenesis of this unique entity. In all cases, a unilocular cyst contained keratin, and the cyst wall was composed of squamous epithelium. A number of cords and papillary projections emanated from the basal layer of the cyst wall. They were composed of cells with large nuclei and scant cytoplasm arranged in a peripheral palisade. Immunohistochemically, anti-cytokeratin 15, anti-cytokeratin 20, and anti-epithelial cell adhesion molecule antibodies were negative. Thus, these cells resembled follicular germinative cells or sebaceous mantle morphologically, but we failed to prove the differentiation immunohistochemically. The cyst was surrounded by fibrotic stroma and inflammatory cells, suggesting previous rupture of the cyst. We speculate that the cells of the projections possibly differentiate into the mantle rather than follicular germinative cells, even though we could not provide sufficient immunohistochemical evidence. We also suggest that they may be induced by special reaction to fibrohistiocytic stroma surrounding the infundibular cyst. Therefore, TBIC should be renamed infundibular cyst with unique papillary projections.

KEYWORDS
cystic trichoblastoma, follicular germinative differentiation, infundibular cyst, mantle, trichoblastic infundibular cyst

1 | INTRODUCTION

Ansai et al previously reported four cases of unique keratinous cystic lesions, designated as trichoblastic infundibular cyst (TBIC).[1] TBIC is a distinct variant of infundibular cyst characterized by papillary projections of epithelial cells with large nuclei from the cyst wall. Juárez et al reported similar cystic lesions with evidence of inner sheath and matrical differentiation in the epithelium of the cyst wall.[2] In the report, TBIC was renamed as cystic trichoblastoma (CTB) because of the neoplastic, rather than cystic, nature of this entity. However, we think that TBIC should be distinguished from CTB in terms of differentiation of the cells, that compose the papillary projections. Here, we report three additional cases of this cyst and discuss the pathogenesis of this unique cystic lesion.

2 | CASE REPORTS

2.1 | Case 1

A 52-year-old Japanese man exhibited a skin-colored to slightly reddish nodule with a central pore on his neck (Figure 1A). A clinical diagnosis of infundibular cyst was made. After the redness

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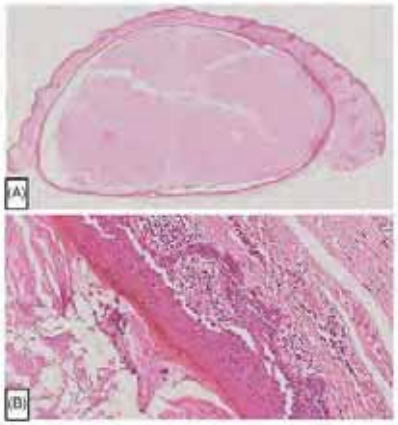

FIGURE 2 Case2: A, Histopathologically, scanning magnification showed a unilocular cyst in the dermis (H&E, 20×). B, Higher magnification showed that cords emanated from the basal layer of the cyst walls and formed a reticular structure. They were composed of cells with large nuclei and scant cytoplasm. Fibrotic stroma with infiltration of lymphocytes surrounded the cyst (H&E, 200×)

FIGURE 1 Case1: A, Clinical findings of the lesion. A skin-colored nodule with a central pore on the neck. B, Histopathological findings: scanning magnification showed a unilocular cyst in the dermis (H&E, 20×). C, Higher magnification showed the cyst wall to be composed of squamous epithelium and the innermost layer of cells containing keratohyalin granules (H&E, 200×). D, The papillary projections emanated from the basal layer of the cyst wall and formed reticular structures. The projections were composed of cells with large nuclei and scant cytoplasm, resembling follicular germinative cells. Fibrotic stroma with infiltration of lymphocytes surrounded the cyst (H&E, 200×)

EXTRAORDINARY CASE REPORT

Trichoblastic Infundibular Cyst

Shin-ichi Ansai,† Masaaki Tsuda,* Hajime Nagato,* Keiko Nishimaki,* Masahiko Wako,* Motomu Manabe,* Takaya Fukumoto,† and Tetsunori Kimura†*

Abstract: We report 4 cases of an infundibular cyst that histopathologically showed small papillary projections of follicular germinative cells emanating from the basal layer of the cyst wall. Some of these projections branched and formed a reticulated pattern. This cystic lesion is histopathologically distinctive. We propose to designate it as a trichoblastic infundibular cyst because its lining resembles that of an infundibular cyst, yet it has cells that resemble those of the follicular germ in its wall.

Key Words: infundibular type follicular cyst, epidermal cyst, epidermoid cyst, follicular germinative cell, trichilemmoma, trichofolliculoma

(*Am J Dermatopathol* 2006;28:507–509)

INTRODUCTION

The infundibular type of follicular cyst, also referred to as "epidermal inclusion cyst" or "epidermoid cyst," is one of the most common epithelial cysts of the skin.[1,2] We report 4 cases of an infundibular type of follicular cyst with distinctive histopathological features, namely foci of cells resembling follicular germ. This cyst is to be differentiated from other infundibular cystic lesions, including neoplasms comprised of follicular germinative cells.

CASE REPORTS

A summary of the clinical data of our 4 cases is shown in the table. Briefly, 4 males ranging in age from 32 to 93 years (the other patients were 56 and 57 years old, respectively) presented to their dermatologists with either an intracutaneous or subcutaneous nodule of firmer to soft consistency, and in 3 of these cases the lesions were located on the head or neck (Figure 1). Two of the lesions had surrounding erythema. The clinical duration was known in 2 of the cases; the 83-year-old patient said the lesion was present for more than 35 years and the 32-year-old patient noted it had been present since childhood.

Histopathologically, each lesion showed similar findings (Figure 2). These unilocular cysts consisted in a fashion identical to that of infundibular epithelium (Figure 2A). The cyst walls ranged in thickness from 3 to 4 up to 6 to 7 layers of squamous epithelium (Figure 2B), and the innermost cells contained keratohyaline granules. Emanating from the basal layer of the cyst walls were papillary projections of cells with large nuclei and scant cytoplasm arranged in a peripheral palisade (Figure 2C). Some of the projections of cells branched and formed reticular structures (Figure 2C). None of the cysts contained sebaceous glands, follicular bulbs or papillae, cytologic atypia, or mitoses. One of the cysts (case 4) was ruptured in its lower half and was accompanied by suppurative and granulomatous inflammation.

Immunohistochemical staining using antikeratin 17 (K33), antikeratin 20 (Ks20.8), and anti-Ki67 (MIB1) antibodies showed no positive reactions in cells of the cyst wall and papillary projections in case 1.

DISCUSSION

The basic structure of our 4 cases is similar to that of the infundibular type of follicular cyst, also designated "epidermal inclusion cyst" or "epidermoid cyst." The cyst wall of this lesion is composed of squamous epithelial cells with a granular cell layer, resembling the infundibulum of a hair follicle. These cysts, however, differ from conventional infundibular cysts by containing papillary and reticular projections of cells with large nuclei emanating from the basal layer of the cyst wall. Although we failed to prove the differentiation of these cells toward follicular germinative cells immunohistochemically, these cells are morphologically similar to follicular germinative cells (ie, they have small, dark nuclei and scant cytoplasm)[3] and the outermost cells are columnar and arrayed in palisades.[4] Last, those cells lack cytological atypia and mitoses, suggesting the benignity of these lesions. For these reasons, we designated these lesions as trichoblastic infundibular cysts.

First, we should consider the possibility that these projections were a sign of induction of follicular germs by the fibrohistiocytic stroma.[5] It has been well known that hyperplasia of the cyst wall in infundibular-type follicular cysts occurs with surrounding inflammation or fibrosis. In our 4 cases, inflammatory changes or fibrosis were observed in only 2 cases and in which projections of cells resembling follicular germ were observed in the portions without inflammatory changes or fibrosis. Induction of follicular germinative cells in the epidermis has been noted in dermatofibroma, neurofibroma, and other neoplasms.[6] In sum, we consider that the projections from cyst walls observed in our cases were primary findings of the lesion.

Trichoblastic infundibular cyst is to be differentiated from other lesions with follicular germinative cells and other infundibular cystic lesions. A benign neoplastic proliferation of follicular germinative cells is classified as trichoblastoma.[7] Although trichoblastoma may contain a cystic component, in contrast to trichoblastic infundibular cysts, those infundibular cysts are small; do not predominate; and, when present, are

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Journal of Cutaneous Pathology

Cystic trichoblastoma (so-called trichoblastic infundibular cyst): a report of three new cases

África Juárez[1], Arno Rütten[2], Heinz Kutzner[2] and Luis Requena[1]

Three cases of so-called trichoblastic infundibular cyst are reported. The lesions showed a configuration similar to infundibular cysts, including basophilic orthokeratotic cornecytes arranged in basket-weave pattern and intermingled with eosinophilic sebum. The cyst wall was mainly composed of stratified squamous epithelium showing infundibular keratinization throughout a granular layer. However, in some areas, epithelial cords, buds and reticulated proliferations of follicular germinative cells surrounded by a densely cellular stroma emanated radially from the cyst wall. In one case, in addition to the presence of follicular germinative cells, there were also aggregations of matrical cells with evidences of inner sheath and medical differentiation. In our opinion, these findings support a neoplastic rather than a cystic nature for this lesion. We discuss the histopathologic differential diagnosis with other follicular cystic lesions showing similar keratinization.

Keywords: cyst, cystic trichoblastoma, follicular cyst, infundibular cyst, trichoblastic cyst

Juárez A, Rütten A, Kutzner H, Requena L. Cystic trichoblastoma (so-called trichoblastic infundibular cyst): a report of three new cases. J Cutan Pathol 2012; 39: 631–636. © 2012 John Wiley & Sons A/S

A cyst is an abnormal sac within tissue that contains fluid or semifluid matter and that is lined by epithelium. In the skin, each of the three parts of the hair follicle (infundibulum, isthmus and inferior segment) produces different types of cutaneous cysts. Thus, follicular cysts include infundibular, tricholemmal and matrical cysts, and different combinations of them result in the so-called hybrid follicular cysts.[1,2]

Recently, trichoblastic infundibular cyst has been reported as a distinctive variant of infundibular cyst.[3] This cystic lesion consisted mostly of an infundibular cyst that histopathologically showed features of germinative follicular differentiation in its cyst wall. We report on the clinico-pathologic features of three cases of this new variant of infundibular cyst, which showed additional histopathologic features of germinative and matrical differentiation in the epithelium of the cyst wall. In our opinion, these findings support a neoplastic rather than a cystic nature for this lesion. Thus, we believe that so-called trichoblastic infundibular cysts should be interpreted as cystic trichoblastomas. We also discuss the histopathologic differential diagnosis with other follicular cystic lesions that may exhibit similar features.

Case reports

Patient 1

A 32-year-old man presented with a subcutaneous nodule of the left lateral aspect of the neck. The patient had history of acne vulgaris that had been treated with oral isotretinoin 10 years ago.

CASE REPORT

WILEY

Trichoblastic infundibular cyst should be renamed infundibular cyst with unique papillary projections

Kenta Kobayashi[1] | Tomoaki Yokoyama[1] | Yoko Masuda[1] | Ichiro Hashimoto[2] | Shin-ichi Ansai[3]

Abstract

Trichoblastic infundibular cyst (TIBC) was previously reported as a unique keratinous cyst, which was characterized by the papillary projections of follicular germinative like cells emanating from the cyst wall. Here, we report three additional cases of this cyst and discuss the pathogenesis of this unique entity. In all cases, a unilocular cyst contained keratin, and the cyst wall was composed of squamous epithelium. A number of cords and papillary projections emanated from the basal layer of the cyst wall. They were composed of cells with large nuclei and scant cytoplasm arranged in a palisade. Immunostained basally, anti-cytokeratin 15, anti-cytokeratin 20, and anti-adhesion molecule antibodies were negative. Thus, these cells resembled follicular germinative cells or sebaceous mantle morphologically, but we failed to prove the differentiation immunohistochemically. The cyst was surrounded by fibrotic stroma and inflammatory cells, suggesting previous rupture of the cyst. We speculate that the cells of the projections partially differentiate into the matrix rather than follicular germinative cells, even though we could not provide sufficient immunohistochemical evidence. We also suggest that they may be induced by steroid reaction of the fibrohistiocytic stroma surrounding the infundibular cyst. Therefore, TIBC should be renamed infundibular cyst with unique papillary projections.

KEYWORDS

cystic trichoblastoma, follicular germinative cell, hamartoma, infundibular cyst, keratin, trichoblastic infundibular cyst

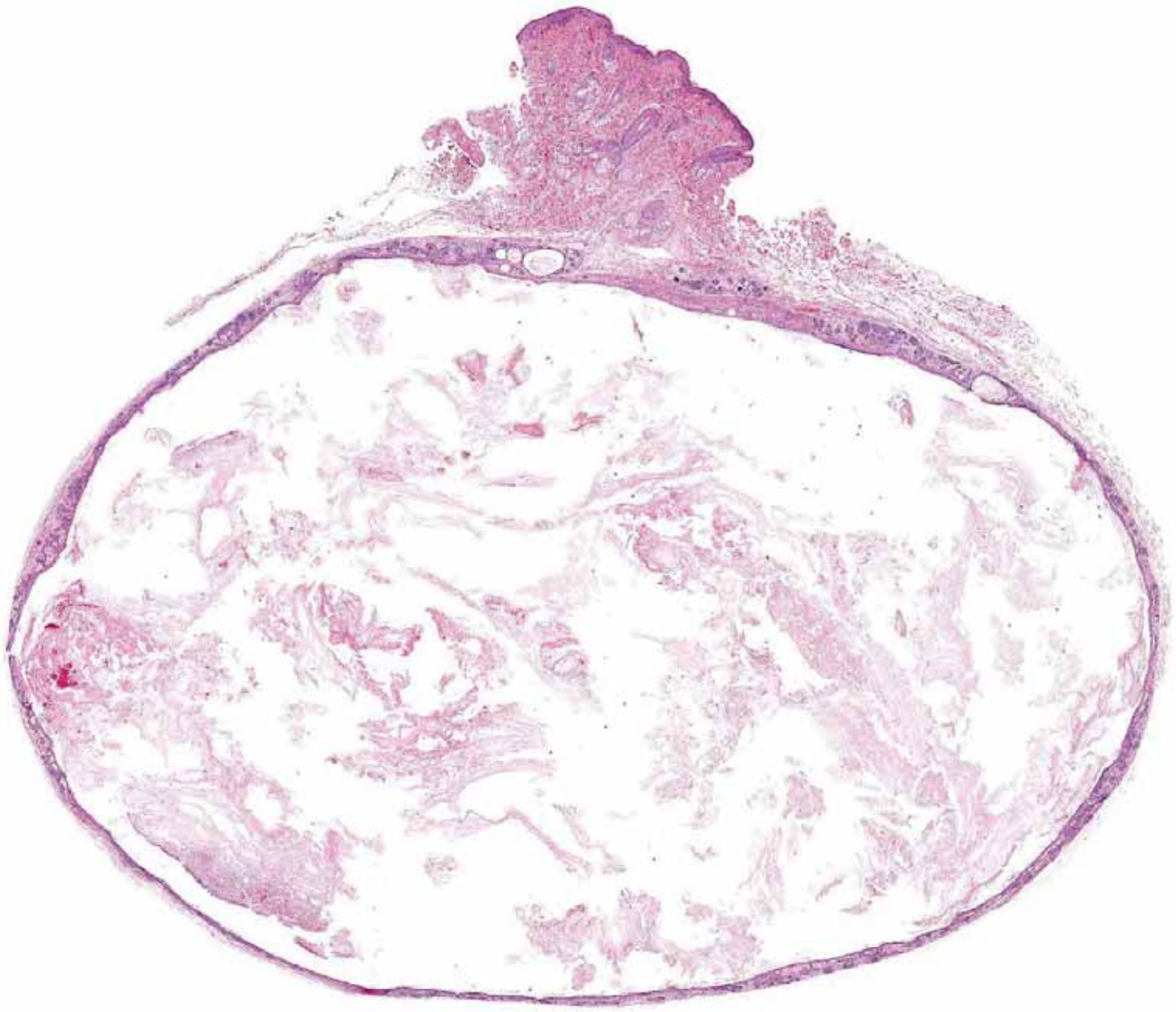
1 | INTRODUCTION

2 | CASE REPORTS

2.1 | Case 1

A 32-year-old Japanese man exhibited a 40-year-old slightly reddish nodule with a central pore on his neck (Figure 1A). A clinical diagnosis of a hamartoma cyst was made. After the nodule

A rare cyst, 3 publications, 3 different names…



EXTRAORDINARY CASE REPORT

Trichoblastic Infundibular Cyst

Shin-ichi Ansai,† Masaaki Tsuda,* Hajime Nagato,* Keiko Nishimaki,* Masahiko Wako,* Motomu Manabe,* Takaya Fukumoto,† and Teisunori Kimura†*

CASE REPORT

WILEY

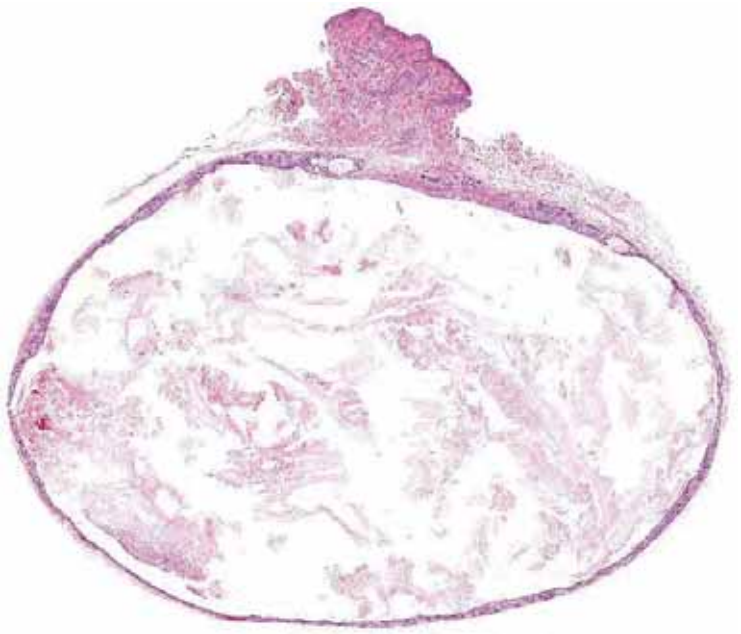
Trichoblastic infundibular cyst should be renamed infundibular cyst with unique papillary projections

Kenta Kobayashi[1] | Tomoaki Yokoyama[1] | Yoko Masuda[1] | Ichiro Hashimoto[2] | Shin-ichi Ansai[3]

Journal of Cutaneous Pathology

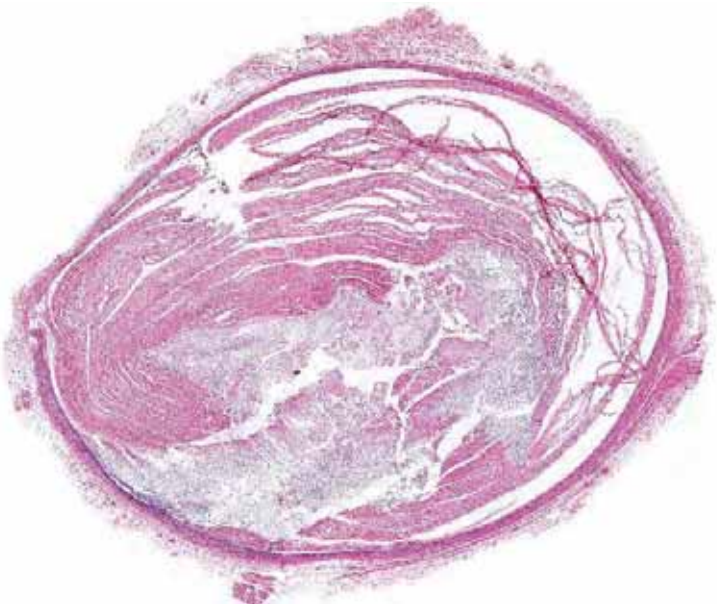
Cystic trichoblastoma (so-called trichoblastic infundibular cyst): a report of three new cases

África Juárez[1], Arno Rütten[2], Heinz Kutzner[2] and Luis Requena[1]

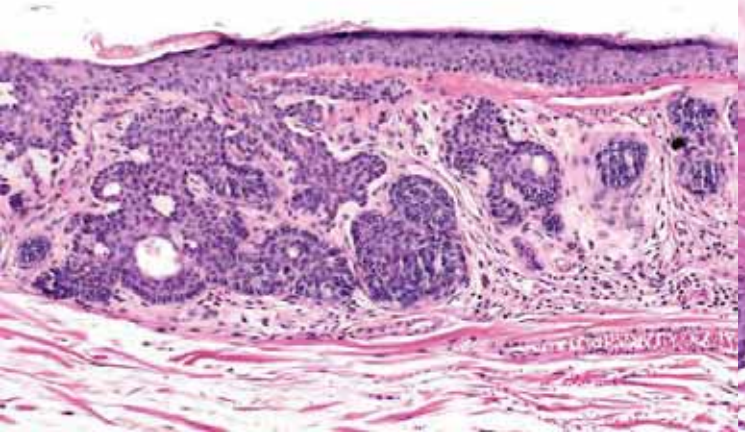


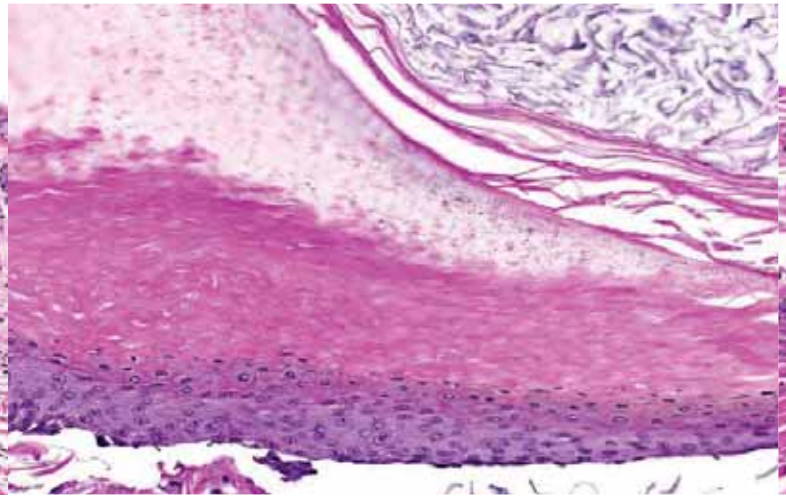
Trichoblastic infundibular cyst

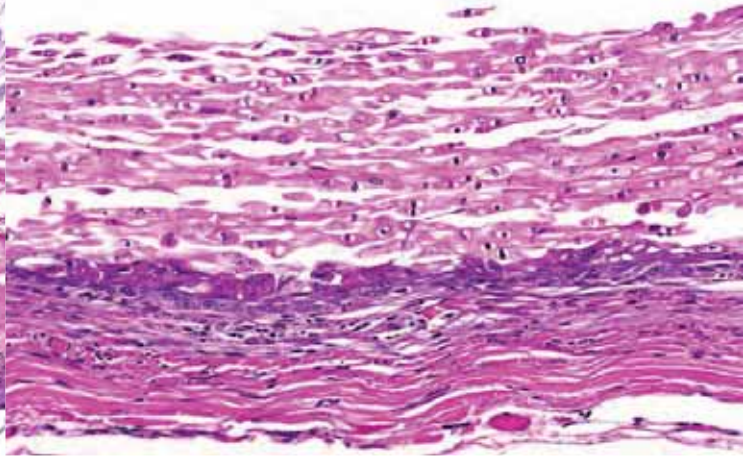
Infundibular cyst with matrical differentiation

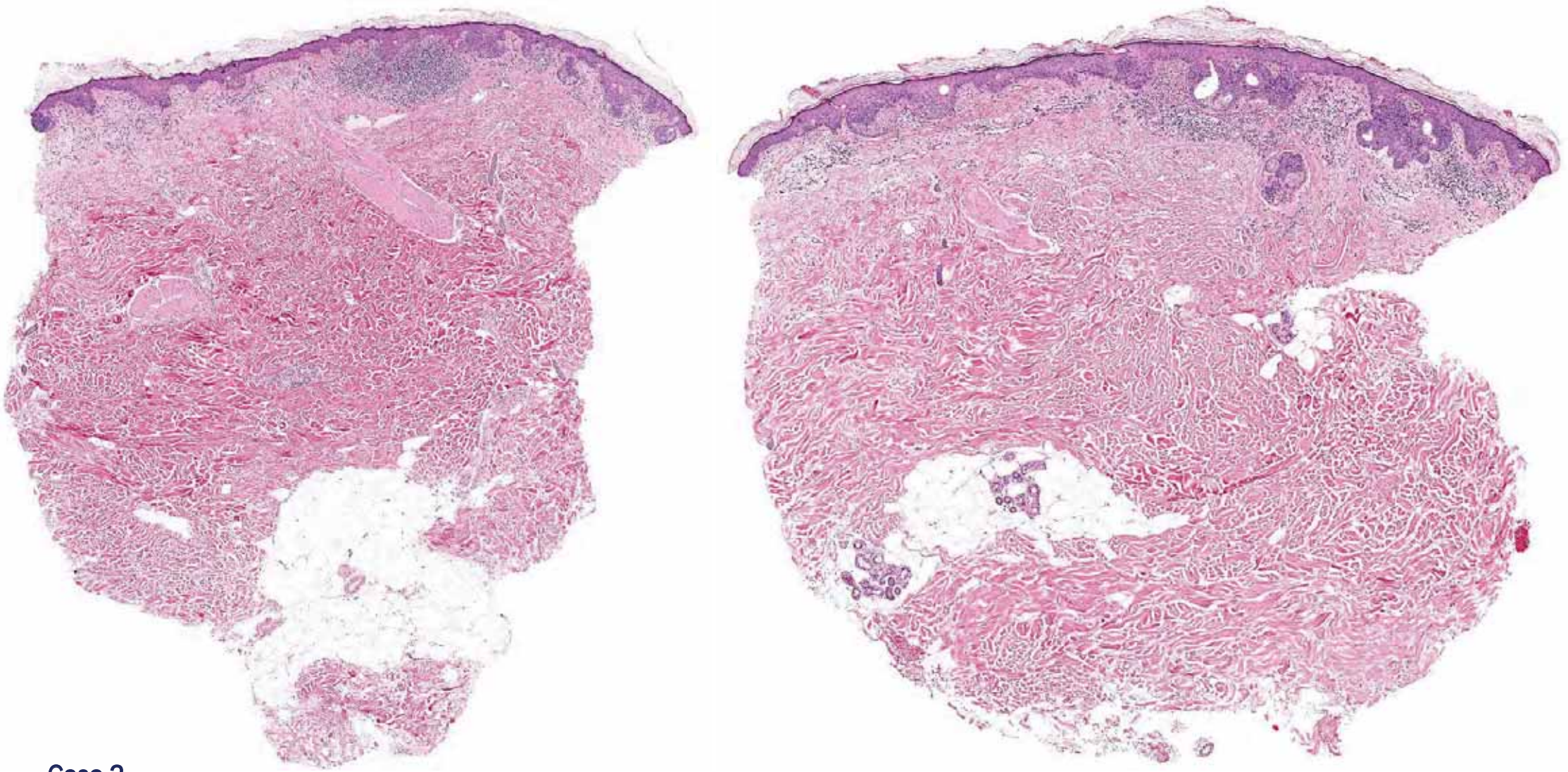


Infundibular cyst with focal acantholytic dyskeratosis



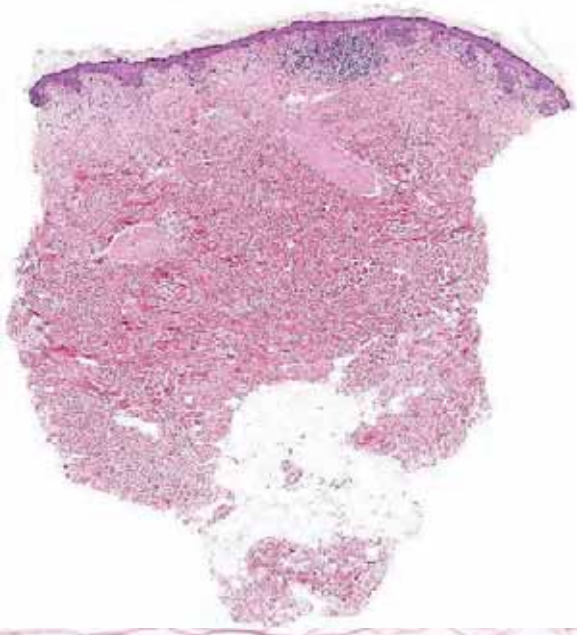


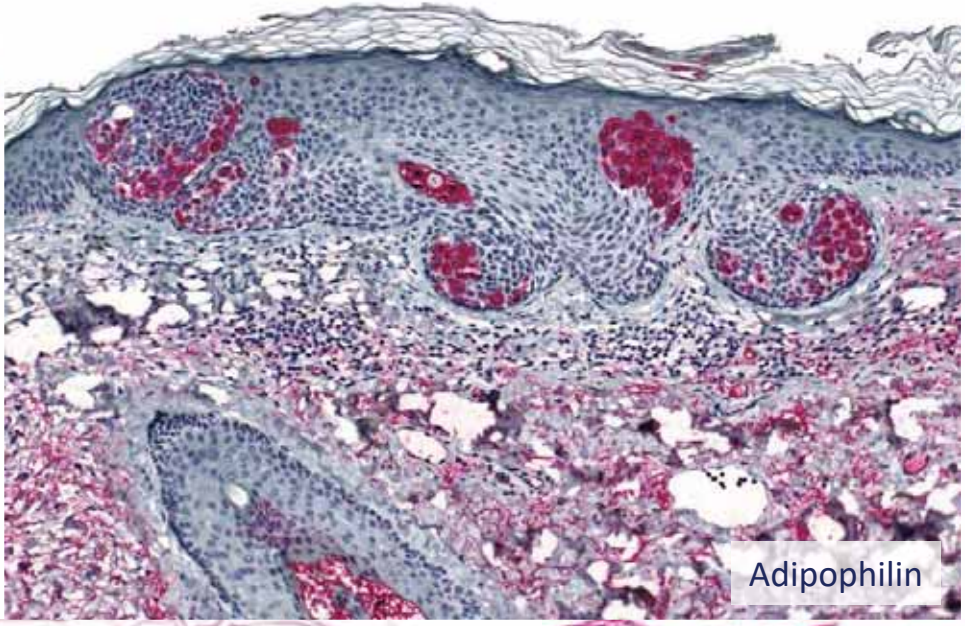


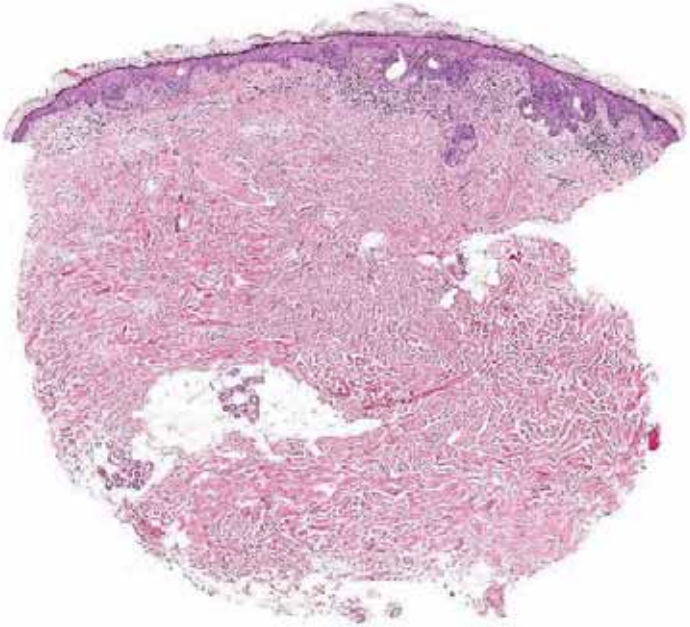


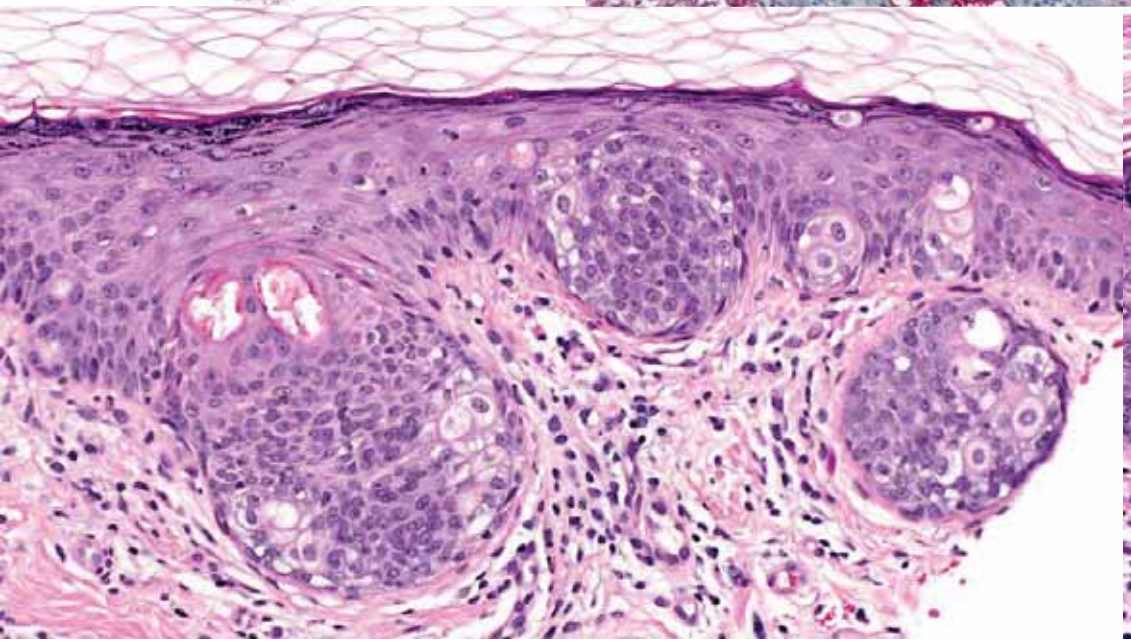
Case 2

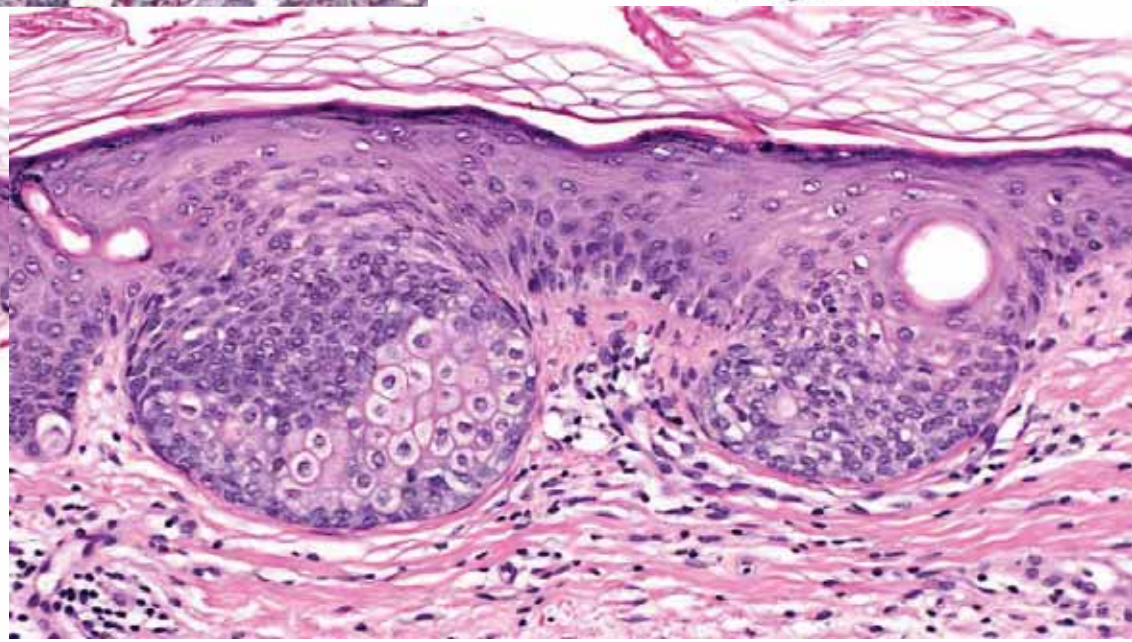
F, 70. History of melanoma on the left shoulder. During a follow-up visit a flat lesion on the right thoracal area is noticed and excised by shaving under a clinical diagnosis of basal cell carcinoma vs. carcinoma in situ.

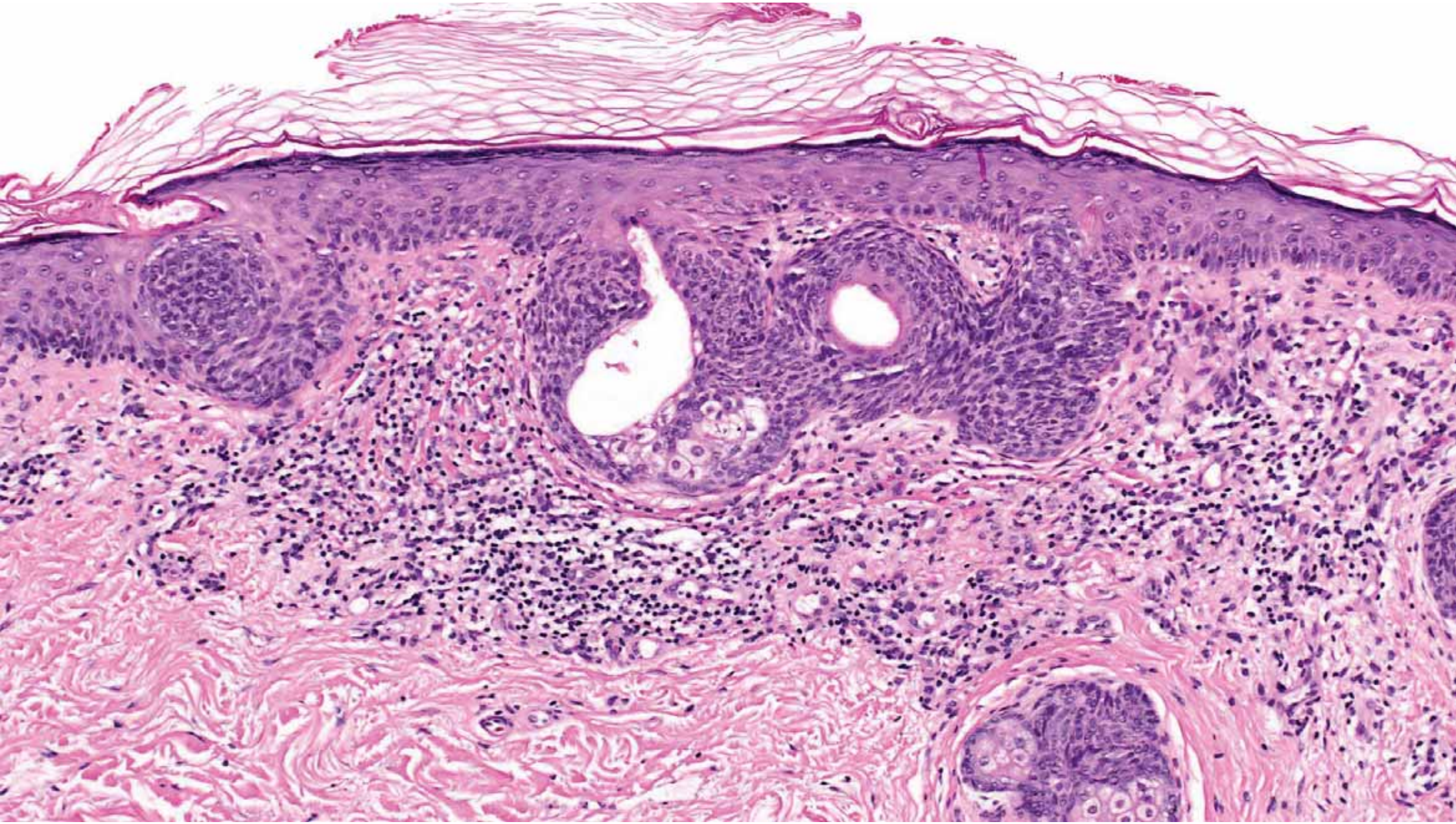


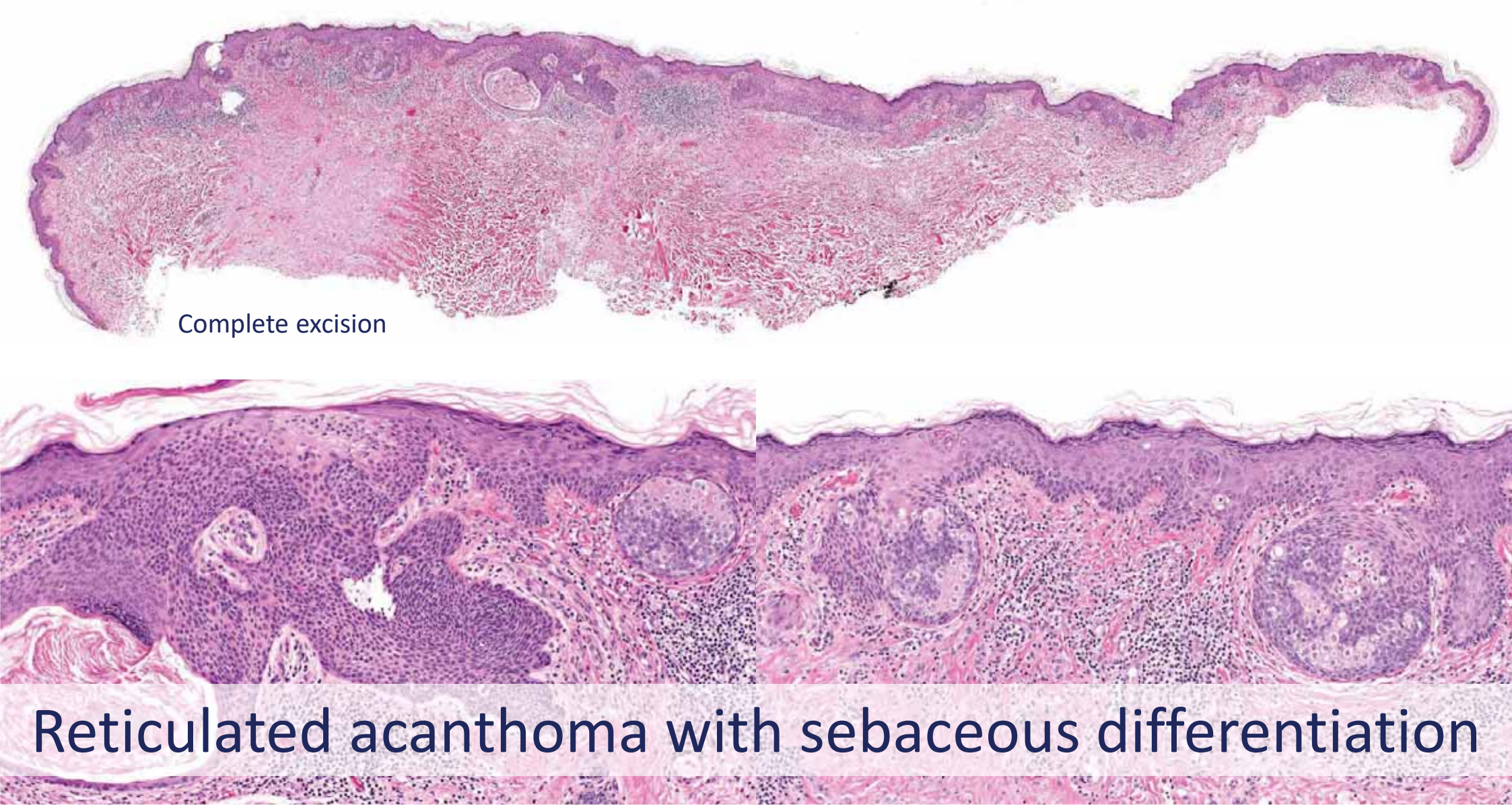

Adipophilin











Reticulated acanthoma with sebaceous differentiation

Ackerman's Histologic Diagnosis of Neoplastic Skin Diseases:
A Method by Pattern Analysis

Neoplasms with Sebaceous Differentiation

CHARLES STEFFEN / A. BERNARD ACKERMAN

1994

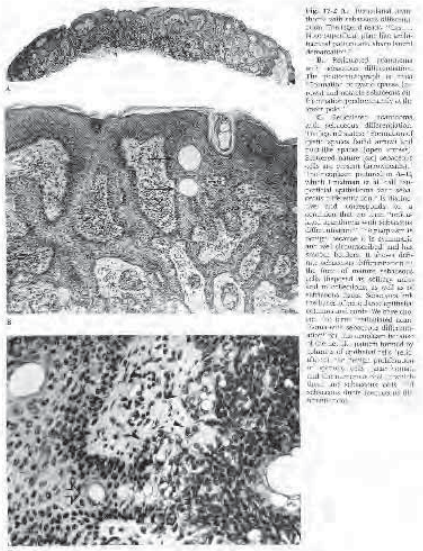
17

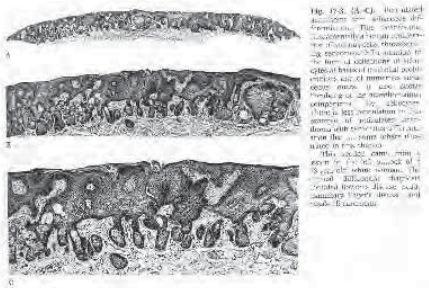
Reticulated Acanthoma with Sebaceous Differentiation

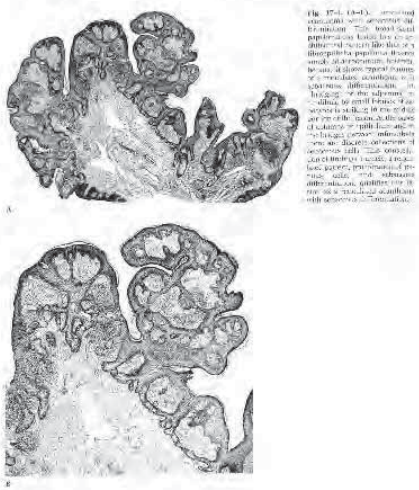
Historical Perspective

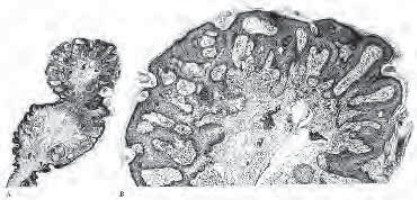
In 1980, under the tide "Superficial epithelioma with sebaceous differentiation", Rothko et al.[1] reported on the case of a 48-year-old man who, over a period of 8 years, developed six papules, 3 to 15 mm in diameter, in the center of the face, on a thigh, and in the axillae. The clinical diagnoses were fibrous papule of the nose, basal-cell carcinoma, sebaceous hyperplasia, actinic keratosis, fibroepithelioma, and seborrheic keratosis. Lesions were of two types. The first (two lesions) was characterized by "multilobular, superficial dermal tumors with numerous broad attachments to the overlying epidermis (Fig. 17-1A). The tumor cells had pale, basophilic nuclei, visible but not prominent nucleoli, eosinophilic cytoplasm, and poorly defined borders without apparent intercellular bridges. At the epidermal-tumor junction, the transition between tumor cells and epidermal cells was gradual. No mitoses were noted. The cellular pattern was disorganized with many whorled areas and only minimal peripheral palisading (Fig. 17-1B). Randomly scattered within the tumor mass were keratin-filled cysts of varying size . . . Clusters of mature sebaceous cells were also present in two of the three lesions (Fig. 17-1C). Occasional sebaceous cell clusters appeared to open to the skin surface . . . The papillary dermis closely surrounded the tumor and was somewhat sclerotic."

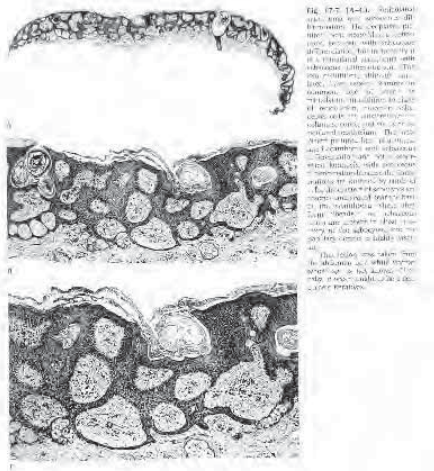
The second type, manifested in the other lesions, "did not show the superficial plate-like configuration of the first two tumors, but did share certain features with them. All were multilobular and showed attachments to the overlying epidermis (Fig. 17-1D). The paranasal and nasal tumors











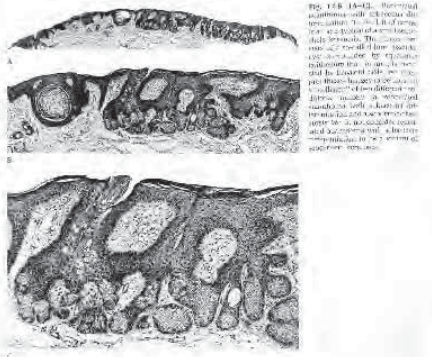
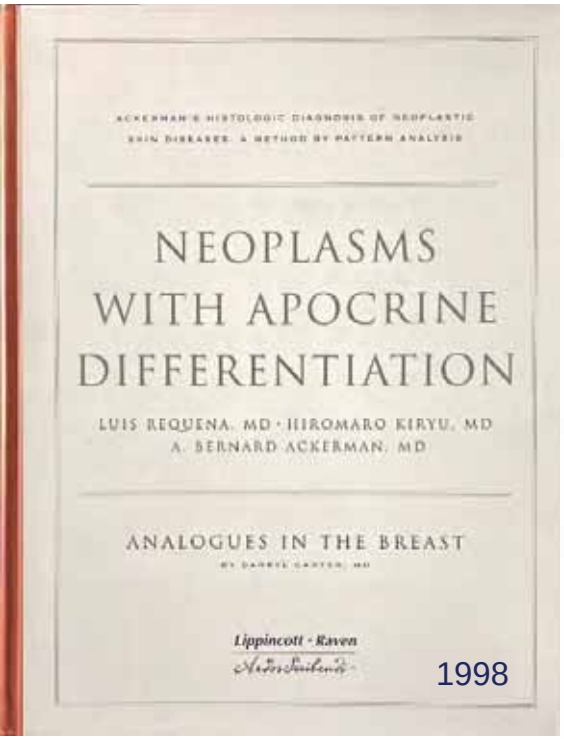


TABLE 17-1. *Histopathologic Differential Diagnosis of Reticulated Acanthoma with Sebaceous Differentiation, Seborrheic Keratosis with Sebaceous Differentiation, and Verruca Vulgaris with Sebaceous Differentiation*

RETICULATED ACANTHOMA WITH SEBACEOUS DIFFERENTIATION	SEBORRHEIC KERATOSIS WITH SEBACEOUS DIFFERENTIATION	VERRUCA VULGARIS WITH SEBACEOUS DIFFERENTIATION
1. Broad, symmetric, exo-endophytic, well-circumscribed, and confined to surface epithelium and papillary dermis	1. Broad, symmetric, exo-endophytic, well-circumscribed, and confined to surface epithelium and papillary dermis	1. Narrow, mainly endophytic, well-circumscribed, and confined to surface epithelium and papillary dermis
2. May be polypoid like an acrochordon	2. Rarely polypoid	2. Rarely polypoid
3. Not markedly keratotic	3. May be markedly hyperkeratotic	3. Usually hyperkeratotic
4. Few if any infundibular tunnels ("horn pseudocysts")	4. Infundibular tunnels ("horn pseudocysts") frequent	4. No infundibular tunnels ("horn pseudocysts")
5. Surface epithelium reticulated	5. Surface epithelium usually solid, but may be reticulated	5. Surface epithelium not reticulated
6. Compact orthokeratosis	6. Basket-woven and laminated orthokeratosis	6. Compact orthokeratosis with focal parakeratosis at tips of digitations
7. Granular layer normal	7. Granular layer normal or thinned	7. Focal hypergranulosis
8. Sebaceous cells in aggregations at bases of rete ridges; none in upper reaches of epithelium	8. Sebaceous cells scattered, often as solitary units throughout the epithelium	8. Sebaceous cells scattered as solitary units and in small clusters at a few foci throughout the epithelium
9. Sebocytes link rete ridges like a "string of pearls"	9. Sebocytes never link rete ridges like a "string of pearls"	9. Sebocytes never link rete ridges like a "string of pearls"
10. Sebaceous ductal structures nearly always present	10. Sebaceous ductal structures usually present	10. Sebaceous ductal structures unusual
11. Cells of neoplasm squamoid	11. Cells of neoplasm basaloid and squamoid	11. Cells of hyperplasia squamoid
12. Dilated blood vessels in the thickened papillary dermis	12. No dilated blood vessels in the thickened papillary dermis, unless lesion has been traumatized	12. Markedly dilated, tortuous capillaries apical to tips of dermal papillae



RETICULATED ACANTHOMA WITH APOCRINE DIFFERENTIATION

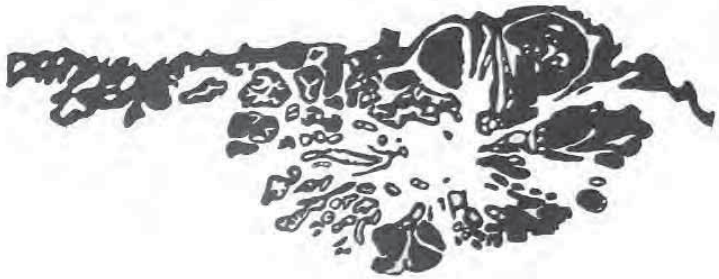
In an embryo, follicular, sebaceous, and apocrine units originate from crescentic clusters of germinative cells that emanate from surface epithelium. As a consequence of this common ancestry, follicular, sebaceous, and apocrine elements remain in intimate association throughout the course of intrauterine and postuterine life. It is not surprising, therefore, that a neoplasm may differentiate toward all three components of the follicular-sebaceous-apocrine unit. And that is what happens in such neoplasms as apocrine mixed tumor, apocrine poroma, and reticulated acanthoma with apocrine differentiation.

HISTORICAL PERSPECTIVE

Although reticulated acanthoma with apocrine differentiation is described for the first time in this monograph, a brief review of the literature about adnexal proliferations in which there is more than one type of differentiation may be helpful in understanding the nosologic position of the lesion. Some of these papers have been discussed in the "Historical Perspective" section of the chapter on apocrine poroma (Chapter 19), and readers are referred to that chapter for a more detailed review of the pertinent literature.

In 1965, Wechsler and Fisher reported on a condition that they named "a combined polymorphic epidermal and adnexal tumor in nevus unius lateris."[1] Clinically, the lesion was a linear keratotic growth on the right ear. Histopathologically, the epidermis was hyperplastic and, in fact, showed changes that the authors considered to be those of basal cell carcinoma. In our opinion, based on findings in photomicrographs, the foci of basaloid cells corresponds to follicular germ-like structures comparable to those seen in nevus sebaceus and in some dermatofibromas. Within the lesion, there were also many tubular structures lined by apocrine glandular epithelium. Papillations whose lining cells displayed apocrine secretion were connected to the epidermis, just as they are in syringocystadenoma papilliferum. The dermis was dotted by "many mature sebaceous glands that were unassociated with hair follicles, similar to the situation in nevus sebaceus" and by foci that the authors designated myoepithelioma but that we consider, on the evidence offered by photomicrographs, to be an apocrine mixed tumor.

Last, Wechsler and Fisher described aggregations of basophilic neoplastic cells surrounded by a thick eosinophilic basement membrane, like those of cylindroma, and nests of a melanocytic nevus. They concluded, "There is little doubt that these growths are primary epithelial germ tumors exhibiting degrees of differentiation toward organoid nevi, adenomas, and epithelioma. The most compatible explanation is that they arise from pluripotential cells as contended by Pinkus." In our judgment, the lesion described by Wechsler and Fisher seems to be the first authentic example of a neoplasm that combined follicular, sebaceous, and apocrine elements. An alternative explanation is that the lesion was simply an unusual example of nevus sebaceus with follicular and apocrine differentiation.



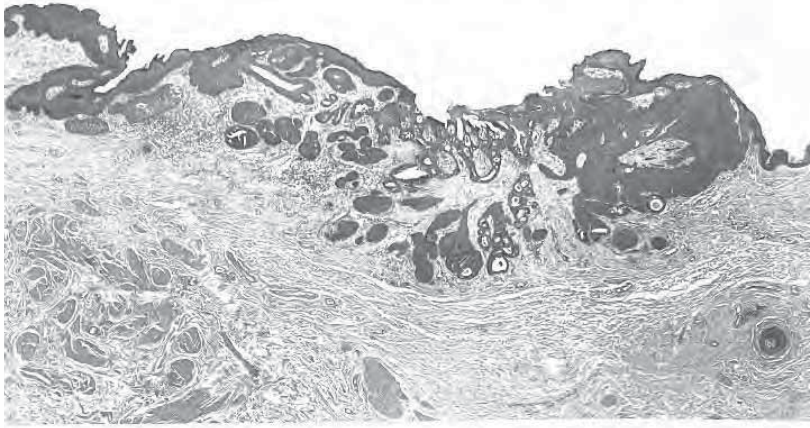
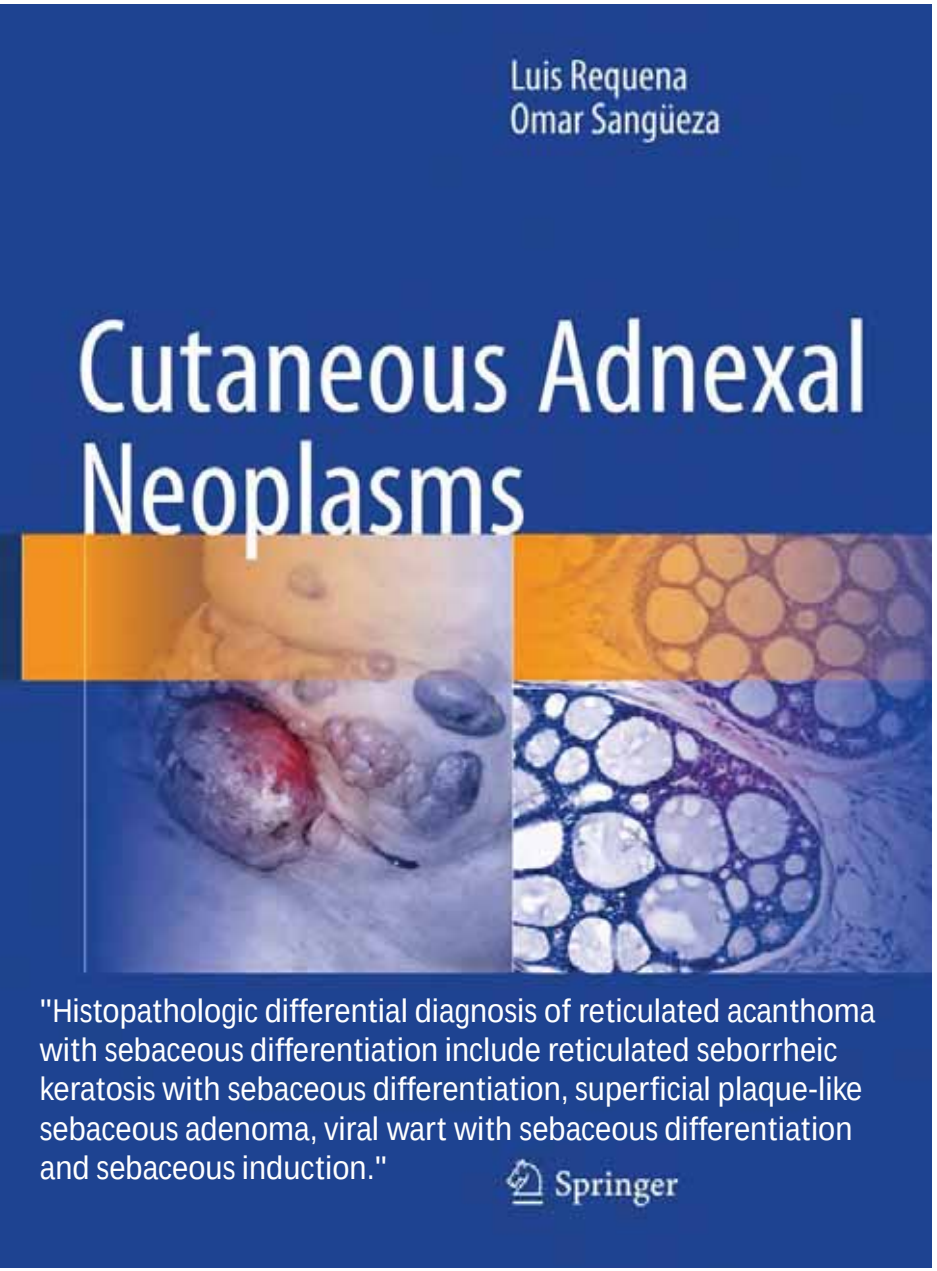


FIG. 20.5 RETICULATED ACANTHOMA WITH APOCRINE AND SEBACEOUS DIFFERENTIATION
This neoplasm, benign by silhouette, displays both solid and tubular features. The solid component consists of two different types of cells, sebocytes (in aggregations on the upper left at scanning magnification) and poroid (in aggregations in the center and on the right). Within conglomerations of poroid cells, discrete tubules are apparent. Because some tubules seem to enter infundibula, the poroid cells and tubules associated with them may be inferred to be apocrine in character. The sebocytes, although immature, can be identified because of their distinctly vacuolated cytoplasm. The presence in this neoplasm of cells with sebaceous differentiation also adds legitimacy to the notion that the noncornifying tubular structures associated with poroid cells have apocrine differentiation.
(figure continues on next two pages)



"Histopathologic differential diagnosis of reticulated acanthoma with sebaceous differentiation include reticulated seborrheic keratosis with sebaceous differentiation, superficial plaque-like sebaceous adenoma, viral wart with sebaceous differentiation and sebaceous induction."

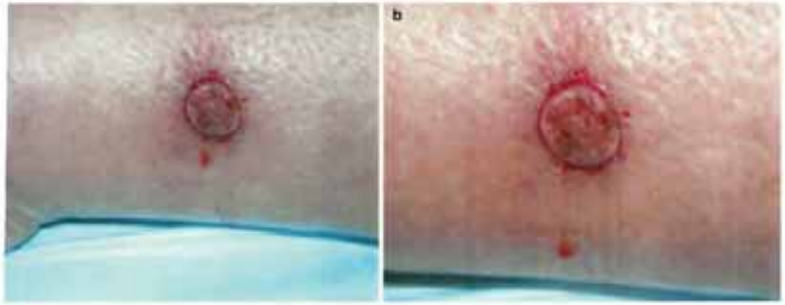
Reticulated Acanthoma with Sebaceous Differentiation 70

Summary

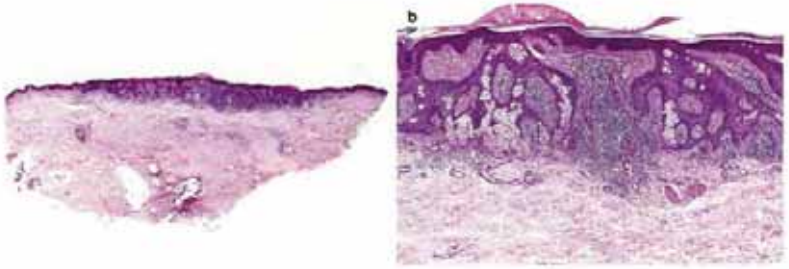
- Reticulated acanthoma with sebaceous differentiation seems to be more common in adults and is mostly located on the face and neck. The lesions consist of papules, nodules, or plaques, with a smooth or slightly papillomatous surface.
- Histopathologically, at scanning magnification, the lesion appears as a plaque and more endophytic than exophytic and consists of epithelial cords that emanate from the lower border of the epidermis, involve an expanded papillary dermis, and anastomose each other in a reticulated pattern. At first glance, the lesion resembles a reticulated seborrheic keratosis, but the most striking finding is seen at the lower end of many of the epithelial cords, which are connected with small groups of fully mature sebocytes. Furthermore, the anastomosing epithelial cords are not composed of basaloid cells like in a seborrheic keratosis but rather of squamous keratinocytes.
- Reticulated acanthoma with sebaceous differentiation is a benign lesion, and its association with Muir-Torre syndrome is controversial.

.1 History

1980, Rothko et al. described a 48-year-old male patient th six lesions showing sebaceous differentiation [1]. At the te of publication, neither the patient nor his relatives showed dence of Muir–Torre syndrome. Histopathologically, the thors described two types of lesions. Some consisted of ilinodular neoplasms occupying the superficial dermis, th multiple connections to the epidermis. The tumor cells



70.1 (a) Clinical appearance of reticulated acanthoma with sceous differentiation on the lower leg of an adult woman. Close-up view of the lesion. It was clinically interpreted as basal cell carcinoma or keratoacanthoma, but the histopathologic study established the right diagnosis



70.2 Histopathologic features of reticulated acanthoma with sceous differentiation. (a) Scanning power showing a superficial pac-like lesion with areas of reticulated pattern. (b) Cords of sloid cells and aggregates of mature sebocytes emanating from the undersurface of the epidermis. (c) Entirely matured sebocytes with scalloped nuclei and multivacuolated cytoplasms. (d) Higher magnification of the entirely mature sebocytes

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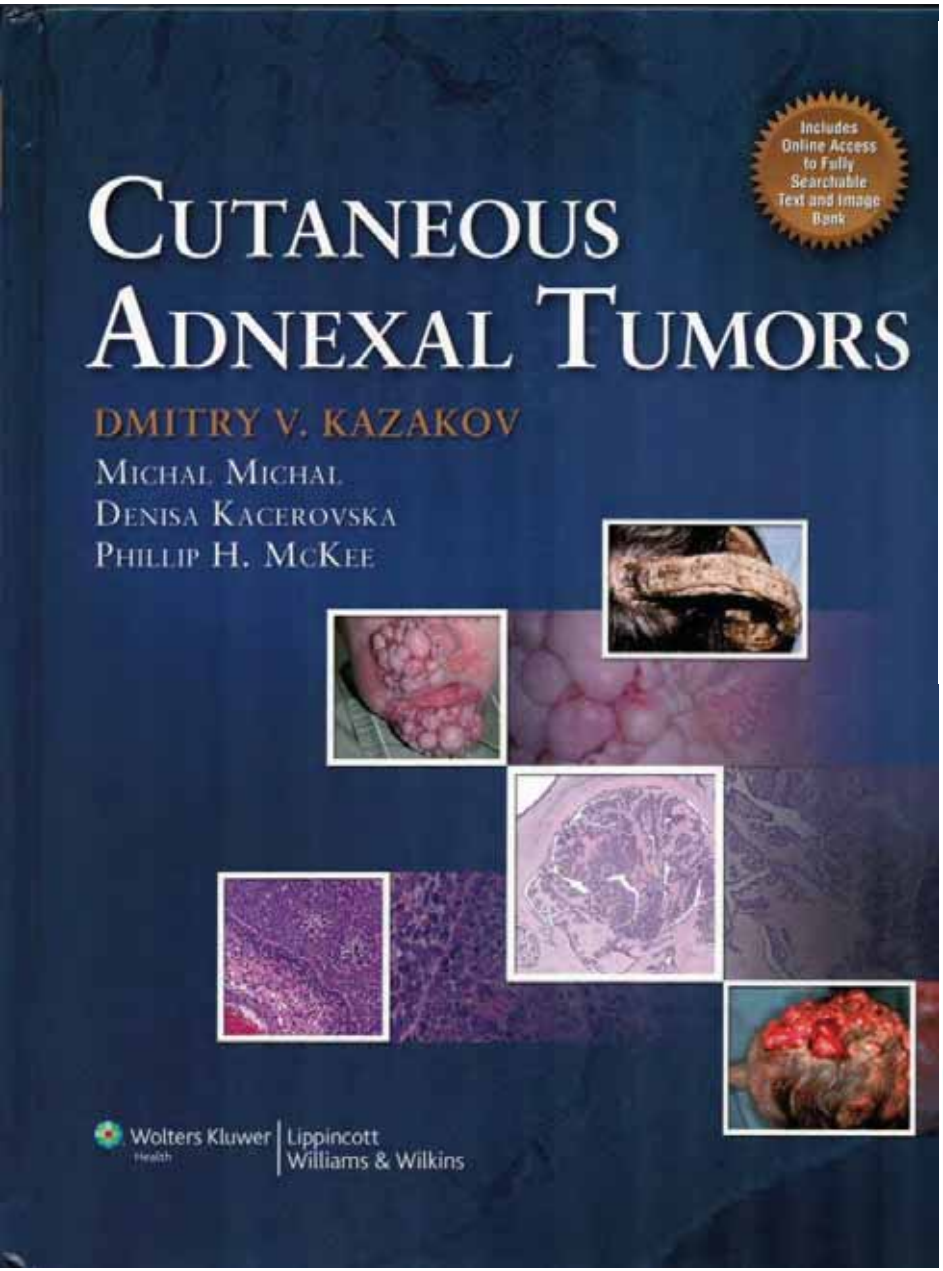
Requena, O. Sangüeza, *Cutaneous Adnexal Neoplasms*, DOI 10.1007/978-3-319-45704-8_70

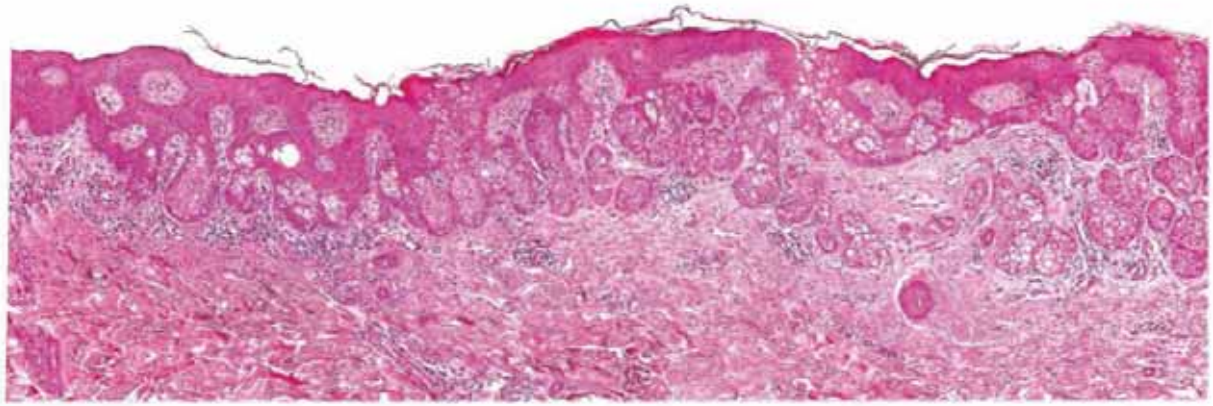


RETICULATED ACANTHOMA WITH SEBACEOUS DIFFERENTIATION

Reticulated acanthoma with sebaceous differentiation is a rare benign sebaceous neoplasm, with less than 20 reported cases.[24,77,78,83,91b] The term was introduced by Steffen and Ackerman[23,65] to replace the previously used designation "superficial epithelioma with sebaceous differentiation." According to Steffen and Ackerman, the latter had likely been applied to two different conditions, namely reticulated acanthoma with sebaceous differentiation and seborrheic keratosis with sebaceous differentiation.[77,122,126] At present, no definite association of the tumor with MTS has been established, although one of the five patients reported by Friedman et al.[77] developed an esophageal and colon carcinoma, suggesting a possible link.

Reticulated acanthoma with sebaceous differentiation vs. seborrheic keratosis with sebaceous differentiation:
* Small basaloid cells in seborrheic keratosis
* Scattering of individual sebocytes in seborrheic keratosis rather than clusters at the base of rete ridges.
* Ductal sebaceous differentiation rare in seborrheic keratosis.

Other differential diagnoses: poroma with sebaceous differentiation, verruca vulgaris with sebaceous differentiation, nevus sebaceous of Jadassohn, tumor of the follicular infundibulum, rarely sebaceoma or sebaceous adenoma.



JRE 3.55 Reticulated acanthoma with sebaceous differentiation: there is a relatively broad and superficial zone of thosis with a reticulated pattern and clusters of mature sebocytes attached to the bases of the anastomosing rete s. Focal coalescence of sebaceous lobules can be seen

Dermatology

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BRIEF REPORT

Reticulated acanthoma with sebaceous differentiation: another sebaceous neoplasm associated with Muir–Torre syndrome?

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ABSTRACT

Reticulated acanthoma with sebaceous differentiation (RASD) represents a rare benign cutaneous epithelial neoplasm with sebaceous differentiation. There has been much speculation about the relationship between RASD and Muir–Torre syndrome (MTS). We report a 55 year old man who presented with RASD in addition to a prior history of sebaceous adenomas. Immunohistochemically, the tumour cells in the RASD and sebaceous adenomas showed a significantly reduced MSH6 protein expression, whereas there was no loss of MLH1, MSH2 and PMS2. This benign neoplasm, which can be mistaken for various other cutaneous lesions with sebaceous differentiation, deserves wider recognition for its possible association with MTS.

Key words: Muir–Torre syndrome, reticulated acanthoma with sebaceous differentiation, sebaceous neoplasm.

INTRODUCTION

Muir–Torre syndrome (MTS) is an autosomal dominant subset of the genodermatosis known as hereditary nonpolyposis colorectal cancer syndrome or Lynch syndrome. On a molecular level MTS typically results from mutations in DNA mismatch repair genes, particularly *MLH1*, *MSH2* and *MSH6*.[1,2] Clinically, the diagnosis of MTS is commonly based on the presence of at least one sebaceous tumour and one visceral malignancy without other known predisposing factors. The sebaceous tumours usually associated with MTS include sebaceous adenomas, epitheliomas and carcinomas, although keratoacanthoma like squamous cell carcinoma with sebaceous differentiation may also be an associated neoplasm in this syndrome. Moreover, these tumours arising in the non-head and neck region have an increased risk of MTS.

Steffen and Ackerman in 1995 coined the term 'reticulated acanthoma with sebaceous differentiation' (RASD) to describe histopathologically a distinct benign sebaceous neoplasm that was first designated a superficial epithelioma with sebaceous differentiation (SESD). Clinically, it appears as a smooth or scaly papule, plaque or nodule that is usually located on the head and neck area.[3] RASD occurring in association with MTS has only rarely been reported.[3,4] However, whether RASD can point toward a diagnosis of MTS is controversial. We report herein a case of MTS-associated RASD and postulate that RASD may be part of this genetic syndrome.

CASE REPORT

A 55 year old man presented with a 1.0 cm yellow to skin-colored plaque on his lower back. Notably, the patient's family history was significant for visceral malignancies. His father and mother both had colorectal cancers and three siblings had abnormal colonoscopies with polyps. The patient also had a history of biopsy-proven sebaceous adenomas; however, subsequent colonoscopies were unremarkable. Although the patient did not fulfill the Amsterdam criteria for MTS, because of his distinctive clinical presentation with respect to multiple previous sebaceous adenomas and his strong family history, the diagnosis of MTS was suggested.

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Authors' suggestion based on a single case…

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Reticulated acanthoma with sebaceous differentiation mimicking melanoma

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Figure 1. A 10 x 15 mm asymmetric brown macule on the hip of a 65-year-old male. [Copyright: ©2017 Ribeiro et al.]

Figure 2. Dermatoscopic findings in an RASD mimicking melanoma. Pigmented reticular lines in the periphery. White reticular lines in the center extending into an eccentric white structureless zone. Gray structures. No yellow structures indicating sebaceous differentiation can be seen. [Copyright: ©2017 Ribeiro et al.]

Discussion

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CARTA CIENTÍFICO-CLÍNICA

Acantoma reticulado con diferenciación sebácea

Reticulated Acanthoma with Sebaceous Differentiation

Sr. Director:

El acantoma reticulado con diferenciación sebácea (RASD) es un tumor anexial benigno descrito por primera vez por Ackerman et al. en 1998[1]. La frecuencia de aparición se desconoce y suele presentarse en la séptima década de la vida, con un leve predominio masculino y una localización preferente en el tronco, la cabeza y el cuello[2]. Clínicamente se presenta como unas pápulas o unas placas amarillentas, parduzcas o rojizas[3,4]. A la dermatoscopia suele observarse un patrón multicomponente con unas estructuras curvilíneas amarillentas y brillantes que se anastomosan, o unas estructuras amarillentas bien delimitadas, con o sin líneas reticulares de pigmento, líneas reticulares blanquecinas y vasos atípicos[4,5]. Histológicamente se observa una lesión tumoral epitelial benigna caracterizada por una proliferación de queratinocitos con un aspecto de predominio escamoso o con focos más basaloides, que hacen fusión de la red de crestas asociadas a sebocitos maduros[2,4].

Es discutida la asociación de las lesiones tumorales cutáneas sebáceas con el cáncer colorrectal hereditario conocido como síndrome de Muir Torre (SMT), sin embargo, los tumores sebáceos se desarrollan en el 5% de los pacientes con un síndrome de Lynch (SL)[2,6].

Una mujer de 83 años presentó un RASD de localización glútea y sin relación con SMT, que fue detectado durante un seguimiento rutinario por otro motivo. La lesión fue descrita como una placa eritematosa descamativa de bordes bien definidos (fig. 1 A y B), con vasos glomeruloides a la dermatoscopia y una impresión diagnóstica de enfermedad de Bowen (fig. 1C).

En el estudio histológico de una biopsia se observó una lesión tumoral epitelial anexial, caracterizada por una proliferación de queratinocitos eosinofílicos con algunos focos de aspecto basaloide (fig. 2A), asociados con grupos de sebocitos en la base de los cordones epiteliales anastomosados (fig. 2 B y C). Este último hallazgo se observaba mucho mejor con la tinción inmunohistoquímica para receptores de andrógenos (fig. 2D). En la dermis papilar se apreciaban algunos vasos de apariencia reactiva sin atipia, con un escaso infiltrado inflamatorio mononuclear perivascular superficial. No se observaron criterios de malignidad. Se realizaron estudios de inmunohistoquímica para las proteínas relacionadas con la reparación del ADN con una expresión nuclear intacta para MLH1, MSH2, MSH6 y PMS2 (fig. 2 E-H).

Los RASD son unos tumores benignos originados de los anejos cutáneos, de un crecimiento lento, de carácter esporádico y, en general, solitarios[2,3,7].

Su sospecha es infrecuente en la clínica, por lo que el diagnóstico suele hacerse de forma tardía[2]. Por su manifestación clínica se asemejan a lesiones cutáneas benignas y malignas y los principales diagnósticos diferenciales clínicos incluyen la queratosis seborreica, el adenoma sebáceo, la enfermedad de Bowen y el carcinoma basocelular, entre otros[3,4]. Los síntomas están en relación con el tamaño aunque suelen ser asintomáticos. La correlación clínica y los hallazgos en la dermatoscopia pueden orientar el diagnóstico, sin embargo, el estudio histopatológico lo confirma[3,7].

El hallazgo dermatoscópico más característico es la presencia de zonas amarillentas bien delimitadas, o de haces amarillentos anastomosados que corresponden, desde el punto de vista histológico, al acúmulo de sebocitos en la parte inferior de los lóbulos tumorales y las hiperpigmentaciones reticulares, que, también en lo histológico, son unos queratinocitos cargados de melanina[4,7].

Histológicamente consiste en una lesión epitelial caracterizada por la proliferación de queratinocitos con elongación de la red de crestas epidérmicas con un patrón anastomótico, asociado con glándulas sebáceas y unas estructuras ductales sebáceas maduras en la capa basal[2,4]. Dentro de la dermis papilar se identificaban vasos capilares poco dilatados asociados a infiltrado mononuclear leve[2,4]. Dentro de los diagnósticos diferenciales histológicos se encuentran los siguientes: la queratosis seborreica, que se distingue del RASD por la ausencia de componente sebáceo en los cordones reticulares; el poroma ecrino, el cual presenta una proliferación de células poroides y cuticulares y se diferencia del RASD por la presencia ductos, además la diferenciación sebácea es focal y poco frecuente en los poromas; la verruga vulgar contrasta con el RASD por la presencia de los cambios citopáticos virales y la ausencia de componente sebáceo; por último, se ha de tener en cuenta el diagnóstico de nevus sebáceo, que difiere del RASD por la proliferación epitelial papilomatosa, además del incremento en el componente sebáceo.

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Figura 1 **A y B)** Placa amarillenta eritematosa levemente descamativa, con zona hiperpigmentada en su segmento inferior, bordes bien definidos, de 9 × 8mm en la región glútea derecha. **C)** Dermatoscopia. Se observa una lesión de fondo rosa, con algunos vasos puntiformes y glomeruloides, haces amarillos brillantes anastomosados, puntos blancos y amarillos y glóbulos azul-grisáceos.

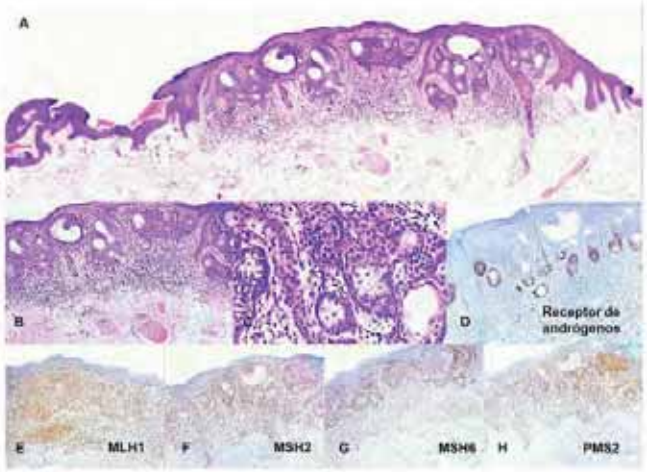
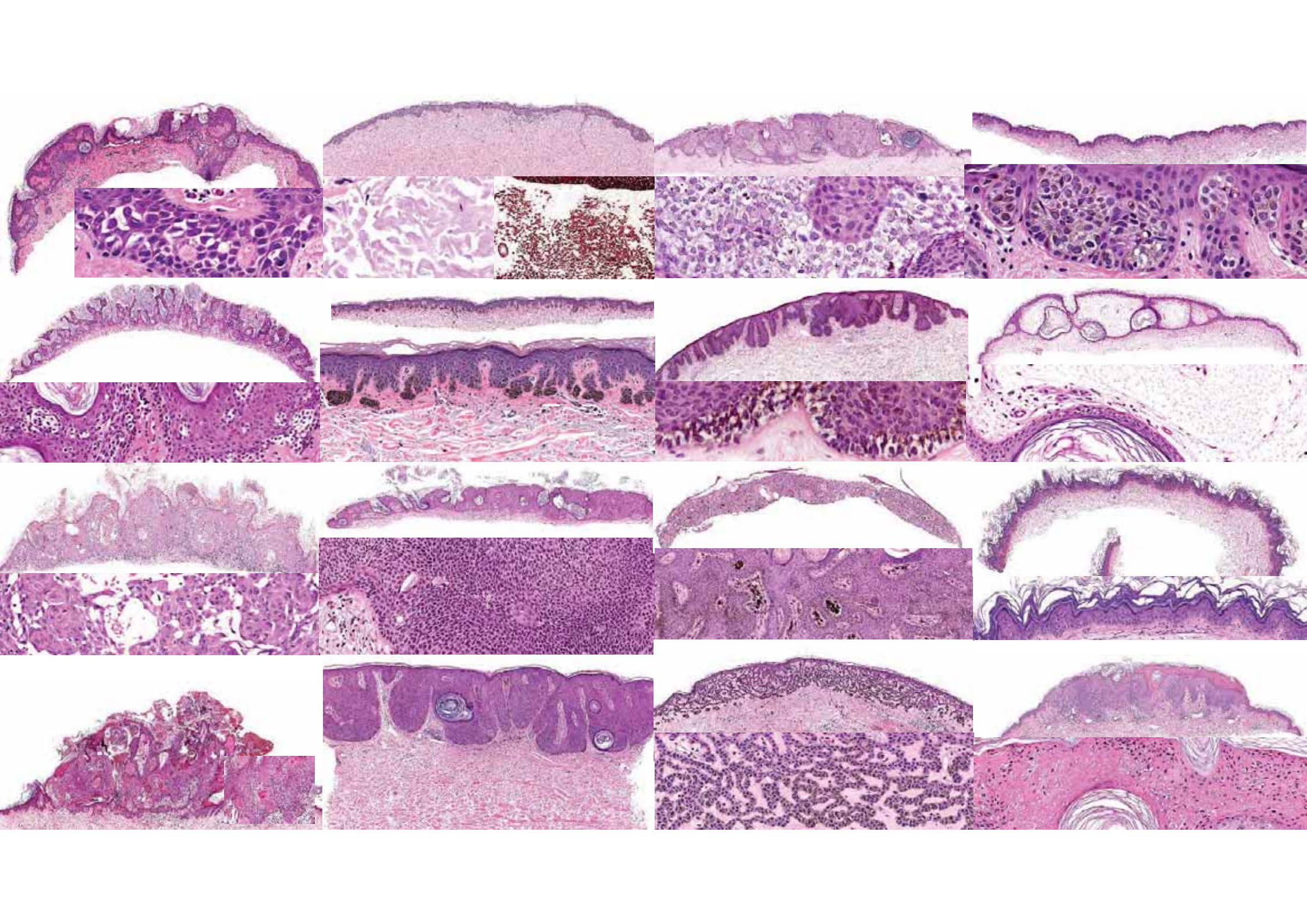
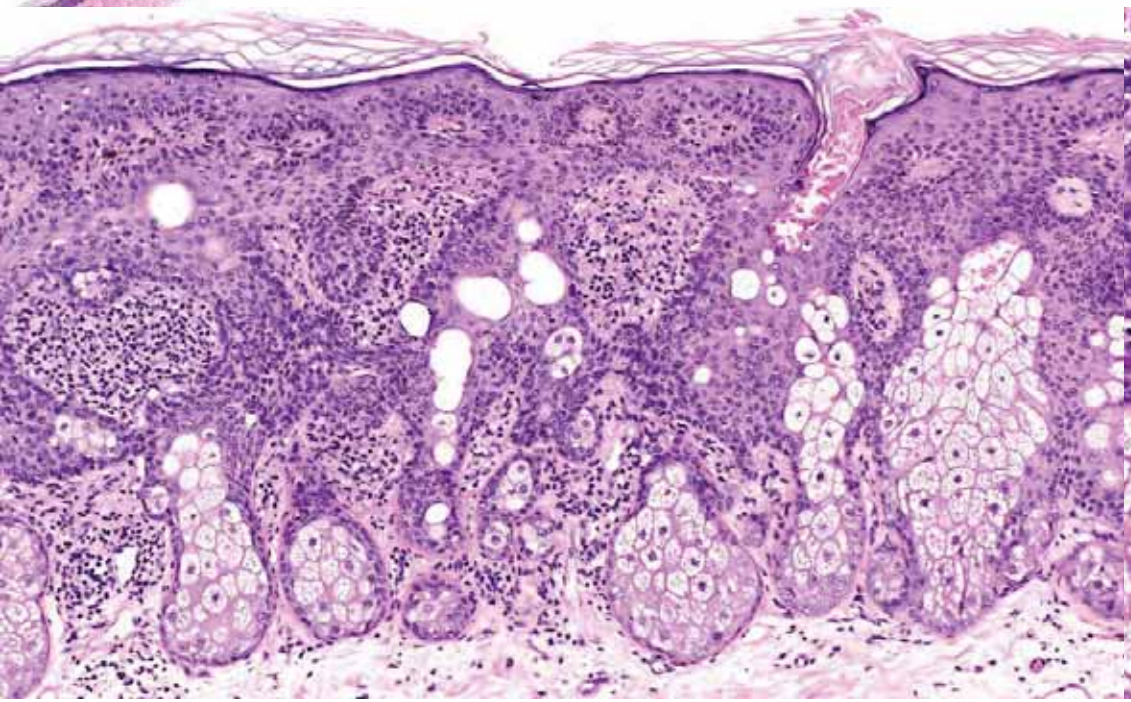


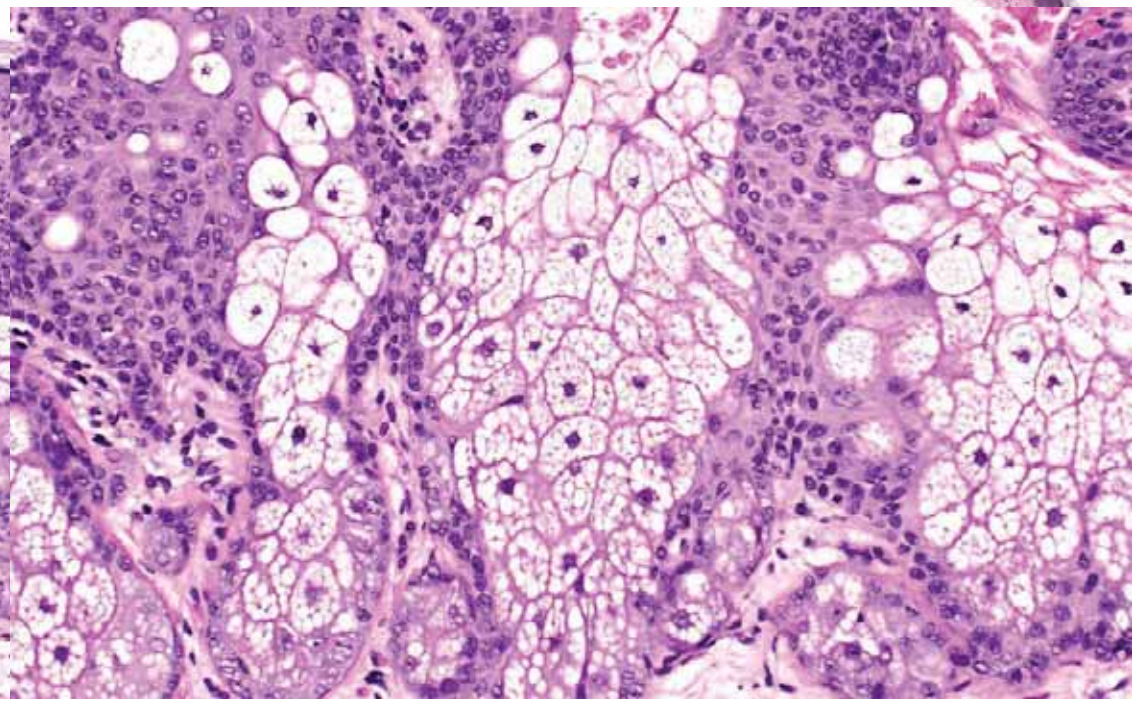
Figura 2 Acantoma reticulado con diferenciación sebácea. **A)** Microfotografía (H-E 4X). Lesión neoplásica de aspecto epitelial anexial caracterizada por una proliferación de queratinocitos eosinofílicos predominantes. **B)** Microfotografía (H-E 10X). Pequeños focos de aspecto más basaloides anastomosados. **C)** Microfotografía (H-E 40X). Presencia de grupos de sebocitos en la base de los cordones epiteliales anastomosados. **D)** Microfotografía (10X). Inmunohistoquímica para receptores de andrógenos en la que resalta el componente sebáceo. **E)** Microfotografía (10X). Inmunohistoquímica para MLH1 con patrón nuclear intacto. **F)** Microfotografía (10X). Inmunohistoquímica para MSH2 con patrón nuclear intacto. **G)** Microfotografía (10X). Inmunohistoquímica para MSH6 conpatrón nuclear intacto. **H)** Microfotografía (10X). Inmunohistoquímica para PMS2 con patrón nuclear intacto.

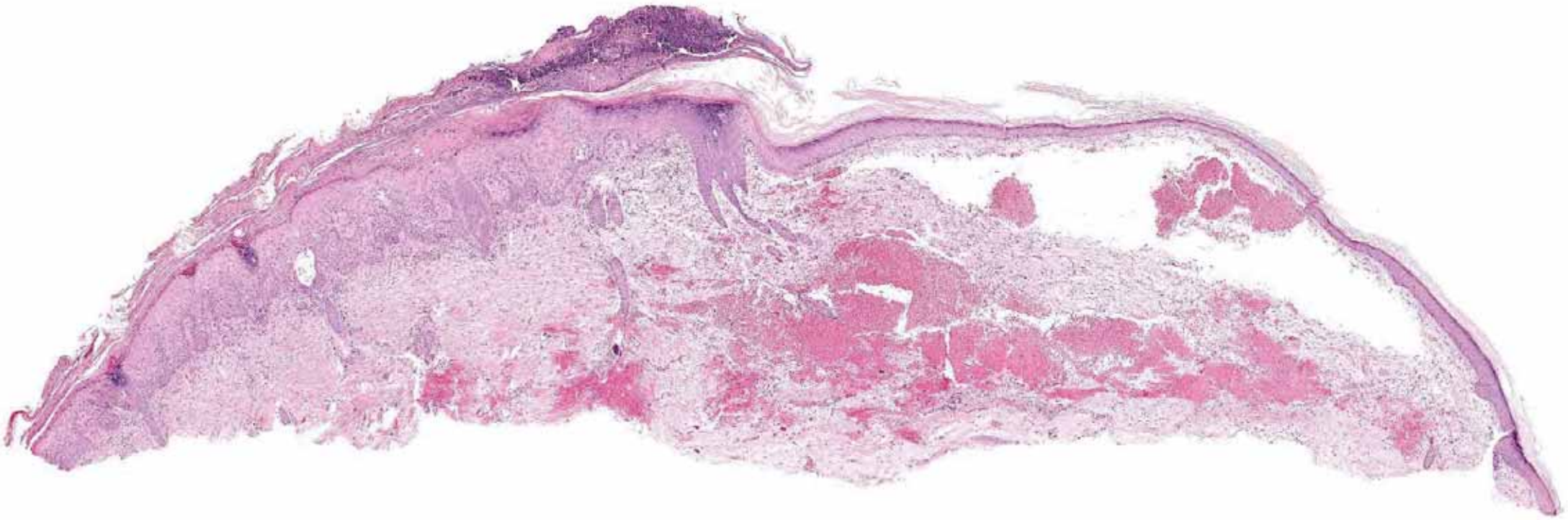


F, 68. Back.

Seborrheic keratosis with sebaceous differentiation

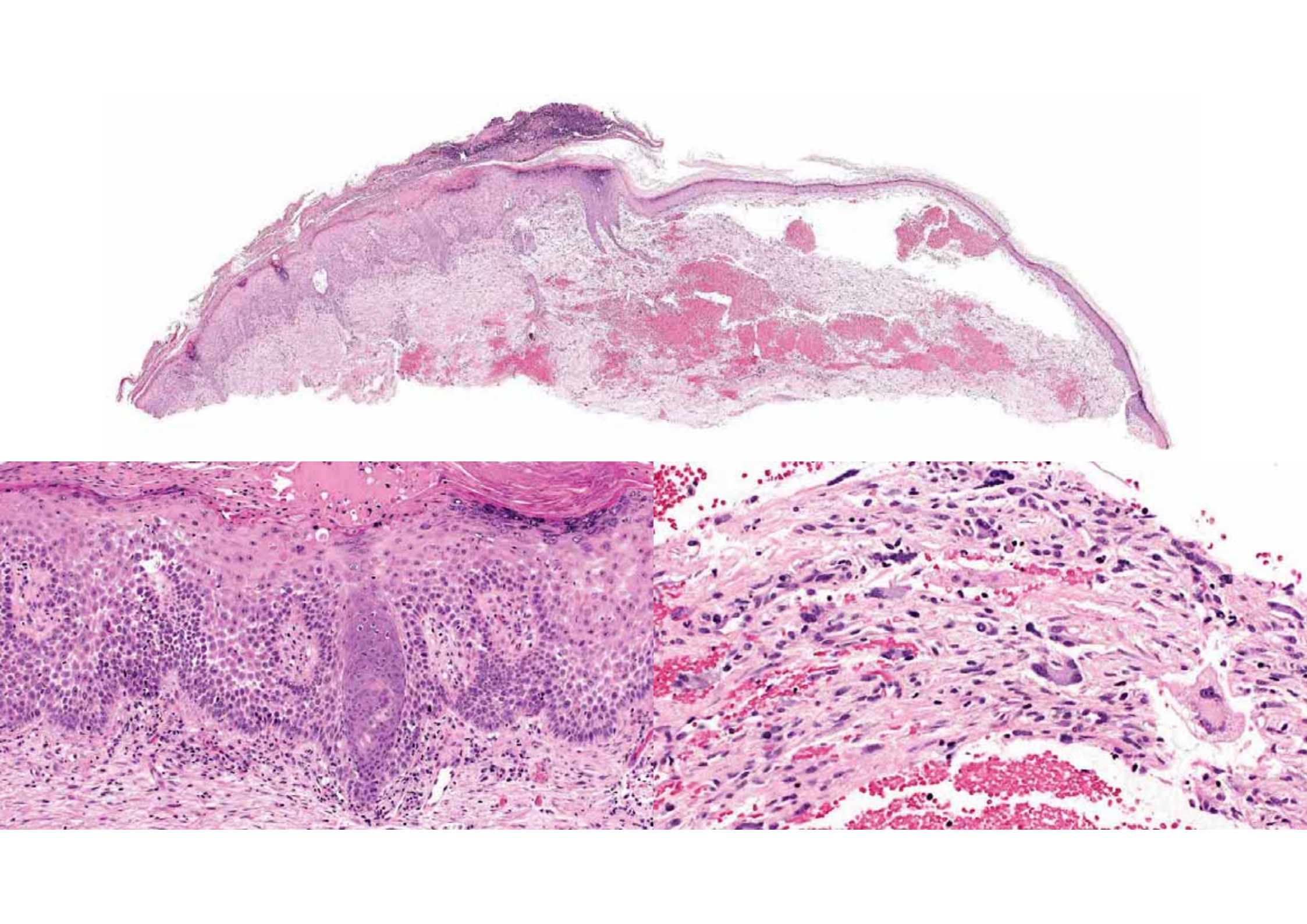




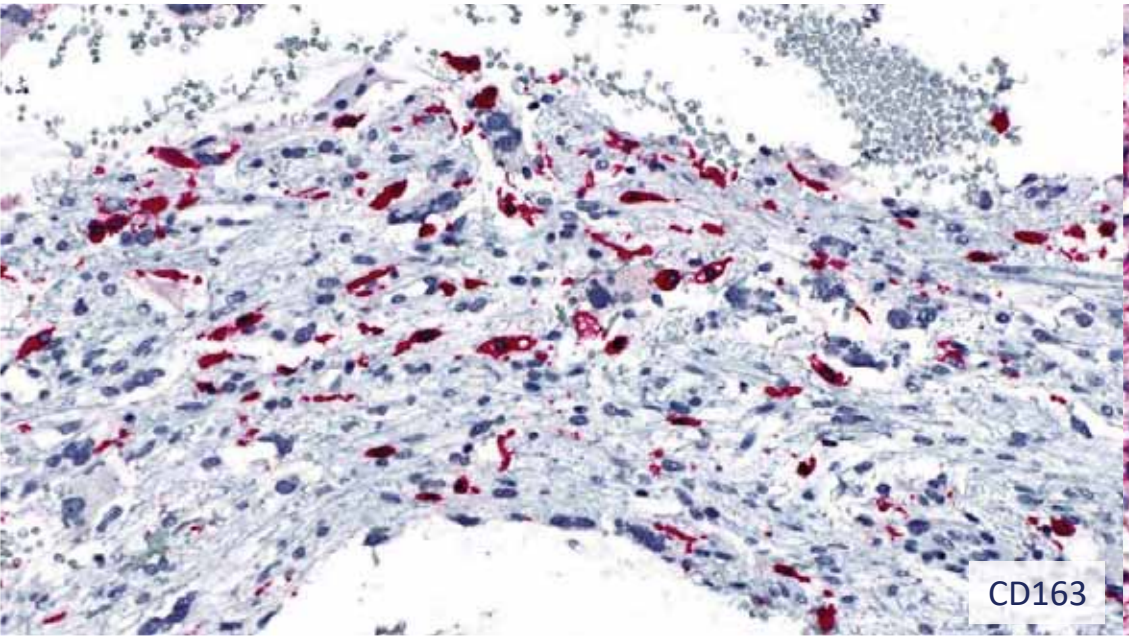


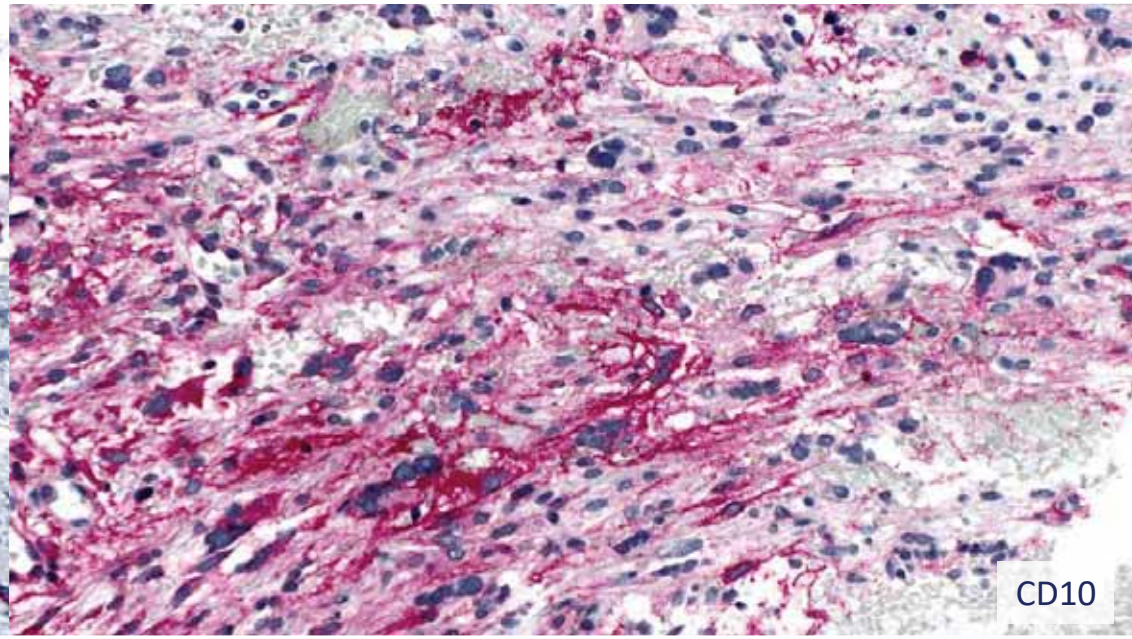
Case 3

M, 88. History of multiple non-melanoma skin cancers. A lesion on the right forehead is excised under a clinical diagnosis of hyperplastic actinic keratosis.



Early atypical fibroxanthoma near carcinoma in situ





Bernhard Zelger, M.D. and H. Peter Soyer, M.D.

BETWEEN SCYLLA AND CHARYBDIS: MYTHOLOGY IN DERMATOPATHOLOGY

"A myth is a story, handed down from olden times, containing the early beliefs of a race and especially explanations of natural events; a false belief, non-existing person, thing, etc."[1]

There are numerous myths in dermatopathology and pathology, chief among them the concepts of eczema, parapsoriasis, and hemangioendothelioma, to mention but three flagrant examples. In the ultimate analysis, myths, including those in medical science, do not survive. For example, the so-called parapsoriasis group has been reduced to two basic conditions, namely, Mucha-Habermann disease and mycosis fungoides, the former consisting of parapsoriasis lichenoides et variioliformis acuta and parapsoriasis lichenoides chronica, and the latter of small-plaque parapsoriasis (guttate parapsoriasis, chronic superficial scaly dermatitis, digitate dermatosis), large

Myths, once created, have many "believers," and many of them are devout. Opposing such myths is hard work. The "believers" resist, thwart, and all too often denigrate rational arguments to the contrary. Nobody likes to admit being wrong.

In order to help explode the myth that follows, I have invited H. Peter Soyer, a fellow sailor for many years in the turbulent seas between Scylla and Charybdis,* to join me aboard the cruiser, "Dermatopathology."

This article is dedicated to Prof. Peter O. Fritsch, Head of the Department of Dermatology, University of Innsbruck, Innsbruck, Austria on the occasion of his

Editor's note: The pages of *Dermatopathology: Practical and Conceptual* are open to a contrary point of view such as the one expressed about malignant fibrous histiocytoma (atypical fibroxanthoma) by Drs. Zelger and Soyer, whether or not the editor shares that particular point of view. What matters is that the case for the point of view be made in a logical, incisive, lucid, dispassionate manner.

Of the many morphologic expressions of squamous-cell carcinoma there are the solar keratotic (as well as radiation keratotic, X-irradiation keratotic, and arsenical keratotic), Bowen's, bowenoid papulotic, verrucous, keratoacanthomatous, and proliferating tricholemmal cystic.[2] In our view, what is diagnosed as atypical fibroxanthoma often is a squamous-cell carcinoma (solar keratotic type) that characteristically affects skin damaged chronically either by ultraviolet light or X-irradiation. In favor of this thesis are the following:

1. The clinical diagnosis usually is squamous-cell carcinoma.
2. The surrounding skin often shows severe solar damage and the patient has solar keratoses or a history of having had them.
3. Histopathologically, there are dyskeratotic cells and hints of intercellular bridges. A solar keratosis often is contiguous or continuous; serial sections often revealing a merging of the solar keratosis and the purported atypical fibroxanthoma. Another morphologic expression of squamous-cell carcinoma, *e.g.*, the keratoacanthomatous, may blend imperceptibly into what is thought to be an atypical fibroxanthoma (Figure 4).
4. Immunohistochemically, there is reactivity for vimentin, whereas other markers, such as S100 protein, smooth muscle actin, desmin, CD31, and CD34 are negative. A variety of keratin markers, like AE1/AE3, KL1, or CAM5.2, often are completely negative or show only a few solitary keratocytes or clusters of them. Negativity for keratin, however, does not exclude differentiation toward keratin.[3] In contrast to better differentiated squamous-cell carcinomas that often are keratin positive/vimentin negative, dedifferentiated variants, including those thought to be an atypical fibroxanthoma, are keratin negative/vimentin positive. The latter immunoprofile also is observed often in the basal layer of solar keratoses. A switch from a keratin posi-

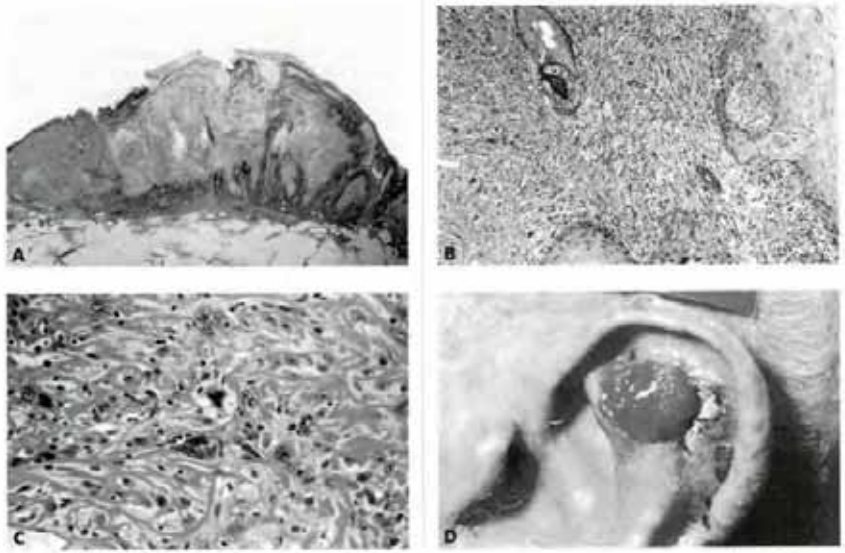


FIGURE 4A: *Keratoacanthomatous squamous-cell carcinoma beside* **B:** *atypical fibroxanthomatous squamous-cell carcinoma.* **C:** *Zone of collision of two different patterns of squamous-cell carcinoma, to wit, the atypical fibroxanthomatous and the keratoacanthomatous.* **D:** *Classic ivroide reddish-crusted lesion of "atypical fibroxanthoma" (in fact a squamous-cell carcinoma) on an ear. Note solar keratoses on the inner and lateral side of the helix.*

Australasian Journal of Dermatology (2005) **46**, 235–238

RESEARCH PAPER

Atypical fibroxanthoma: A clinicopathological study of 89 cases

Basit Mirza[1] and David Weedon[2]

[1]Mater Adult Hospital and [2]Sullivan Nicolaides Pathology, Brisbane, Queensland, Australia

SUMMARY

Atypical fibroxanthoma is a controversial entity with a disputed histogenesis. It has recently been suggested that most atypical fibroxanthoma are actually variants of squamous cell carcinoma. We reviewed 100 purported cases of atypical fibroxanthoma received over 4 years to perform clinical follow up and immunohistochemical markers. In particular, we focused on the detection of any recurrence or metastasis. Ten cases were subsequently excluded on the basis of either incorrect coding, or insufficient or absent paraffin blocks on file. A further case was interpreted as a malignant fibrous histiocytoma. Additional new markers, such as CD10 and CD99, were employed in a proportion of cases. Our cases were typical of the usual clinical presentation of atypical fibroxanthoma on the skin of the sun-damaged elderly. We found no cases of recurrent or metastatic atypical fibroxanthoma. Two patients developed a second primary atypical fibroxanthoma. CD10 proved to be a useful marker for atypical fibroxanthoma when used on 20 cases in the present study, as was CD99 in seven cases. The only case demonstrating positive staining for keratin also stained for CD10. It had dual features of atypical fibroxanthoma and squamous cell carcinoma. However, as the majority of atypical fibroxanthoma had no adjacent solar keratosis, our data suggest it is unlikely that atypical fibroxanthoma is a variant of squamous cell carcinoma.

Key words: CD10, CD99, malignant fibrous histiocytoma, metastasis, recurrence, skin cancer, squamous cell carcinoma.

INTRODUCTION

Atypical fibroxanthoma is a controversial entity whose histogenesis remains an enigma, despite the availability of various immunoperoxidase markers. The term was coined in 1963.[1] In the same year, Bourne, from the Queensland Radium Institute, reported 13 similar cases as 'paradoxical fibrosarcoma' (pseudosarcoma) of the skin, in recognition of the tumour's marked cellular pleomorphism yet benign behaviour.[2] Rare cases of metastases have been reported, but the diagnosis of some of these cases has been disputed subsequently.

Recently, it has been suggested that most AFX are actually variants of SCC.[3] In view of the controversy surrounding this entity we reviewed 100 purported cases of AFX from the files of a private pathology practice in Brisbane, to perform clinical follow up and various immunohistochemical markers on these cases.

METHODS

We searched the histopathology database of a private pathology practice for specimens with the diagnosis of AFX received during the years 1996–1999. This allowed completion of a minimum of 3 years follow up from the time of the procedure. A total of 100 cases were obtained. Ten cases were subsequently excluded on the basis of either incorrect SNOMED coding, insufficient material for subsequent immunohistochemical stains, or absence of paraffin blocks from the files. A further case was excluded after review of the histology. It was interpreted as an MFH. One patient had two simultaneous AFX.

Follow up letters were mailed to the treating practitioners to determine if the patients had been assessed in the previous 3 months, and whether recurrence had occurred. If a patient had not attended in the previous 3 months, we

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Basil Mirza, MB BS. David Weedon, FRCPA.

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Abbreviations:

AFX	atypical fibroxanthoma
MFH	malignant fibrous histiocytoma
SCC	squamous cell carcinoma

"The only case demonstrating positive staining for keratin also stained for CD10. It had dual features of atypical fibroxanthoma and squamous cell carcinoma. However, as the majority of atypical fibroxanthoma had no adjacent solar keratosis, our data suggest it is unlikely that atypical fibroxanthoma is a variant of squamous cell carcinoma."

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Collision of Atypical Fibroxanthoma and Acantholytic Squamous Cell Carcinoma In Situ

To the Editor:

A previous case of atypical fibroxanthoma (AFX) surrounding a trichilemmal cyst with squamous cell carcinoma in situ (SCCis) arising within its wall has been reported.[1] We report a collision tumor of SCCis occurring in the epidermis overlying an AFX.

The authors have no funding or conflicts of interest to declare.

FIGURE 1. Full thickness atypia and acantholysis of keratinocytes and a proliferation of pleomorphic plump spindle and epithelioid cells in the papillary dermis (hematoxylin and eosin, ×10).

A 60-year-old white male presented with a several year history of a tender lesion on the left cheek. Clinical examination revealed a 7-mm firm pink papule on his left preauricular cheek. He had no palpable lymphadenopathy. Shave biopsy revealed full-thickness atypia and acantholysis of keratinocytes. Within the papillary dermis, unconnected to the overlying atypical epidermis, was a proliferation of plump spindle and epithelioid cells with marked pleomorphism, multinucleation, vesicular nuclei, markedly abundant cytoplasm, and bizarre mitotic figures (Fig. 1). Antibodies to pan-keratin (AE1/AE3) and high molecular weight keratin (HMWK; 34betaE12) labeled atypical epidermal cells, characteristic of SCCis, but did not label the pleomorphic dermal cells (Fig. 2A). In contrast, the pleomorphic dermal cells were strongly and diffusely labeled by antibodies to CD10 (Fig. 2B) but not by antibodies to pankeratin or HMWK, characteristic of AFX. Thus, the histopathologic and immunohistochemical findings were characteristic of a collision tumor of acantholytic SCCis and AFX.

AFX is a superficial fibrohistiocytic tumor that presents on the head and neck of elderly patients and is usually a pink or red, solitary, firm, asymptomatic papule or nodule.[2,3] Histologically, AFX reveals a dermal proliferation of spindle and epithelioid cells with (often marked) pleomorphism, bizarre mitotic figures, and multinucleated cells.[3] There are many variants of AFX, including spindle cell anaplasmorphic, clear cell, osteoclastic, and granular cell.[3] Cutaneous squamous cell carcinoma (SCC) has a very diverse range of clinical and pathological subtypes including, but not limited to, acantholytic, poorly differentiated and spindle cell.[4]

A patient with a forehead lesion containing both an SCCis arising within the wall of a trichilemmal cyst and surrounding AFX has been previously reported.[1] AFX and SCC occurring together on the conjunctiva[5] and face[6] of patients with xeroderma pigmentosum have also been reported. It is not surprising to observe a collision of SCCis (or SCC) and AFX because both tumors occur in photoexposed skin.[1] In the present case, full thickness epidermal atypia was observed immediately overlying undifferentiated pleomorphic dermal cells, making it necessary to exclude invasive poorly differentiated SCC arising from SCCis by staining with antibodies to pankeratin. Furthermore, because keratinocytes in spindle[4] and poorly differentiated[3] SCC may lose expression of low molecular weight keratin, we used antibodies to HMWK (34betaE12) to exclude poorly differentiated SCC. Finally, strong and diffuse labeling of pleomorphic dermal cells with antibodies to CD10 confirmed the diagnosis of AFX.[3]

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LETTER TO THE EDITOR

Spindle cell squamous cell carcinoma exhibiting a metaplasia to atypical fibroxanthoma

Dear Editor,

An 82-year-old Japanese man presented with an ulcerated, pedunculated, fresh-red nodule measuring 20 × 15 mm on the left cheek (Figure 1a). A hematoxylin-eosin (HE) specimen demonstrated a pedunculated nodule contiguous with acanthotic epidermis (Figure 1b), lower layers of which were composed of atypical keratinocytes (Figure 1c). Solar degeneration was obvious (Figure 1c). The atypical keratinocytes of the acanthotic epidermis were transitioned to atypical spindle cells of the pedunculated nodule (Figure 1d). A continuum between the two types of cells was evident. Fascicles of atypical spindle cells were observed primarily in the periphery of the nodule, closer to the contiguous epidermis. The cellular component in the center of the nodule was arranged in sheets of atypical epithelioid cells with occasional osteoclast-like giant cells (Figure 1e).

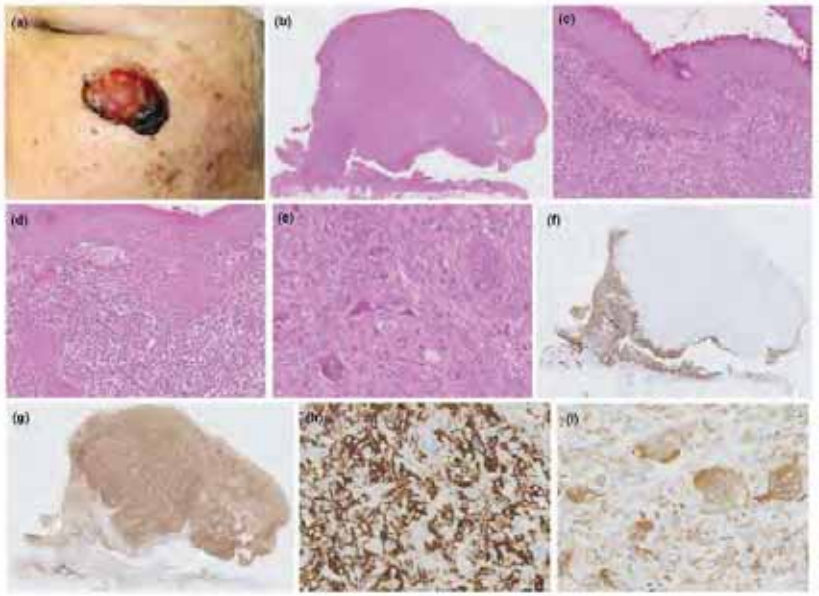
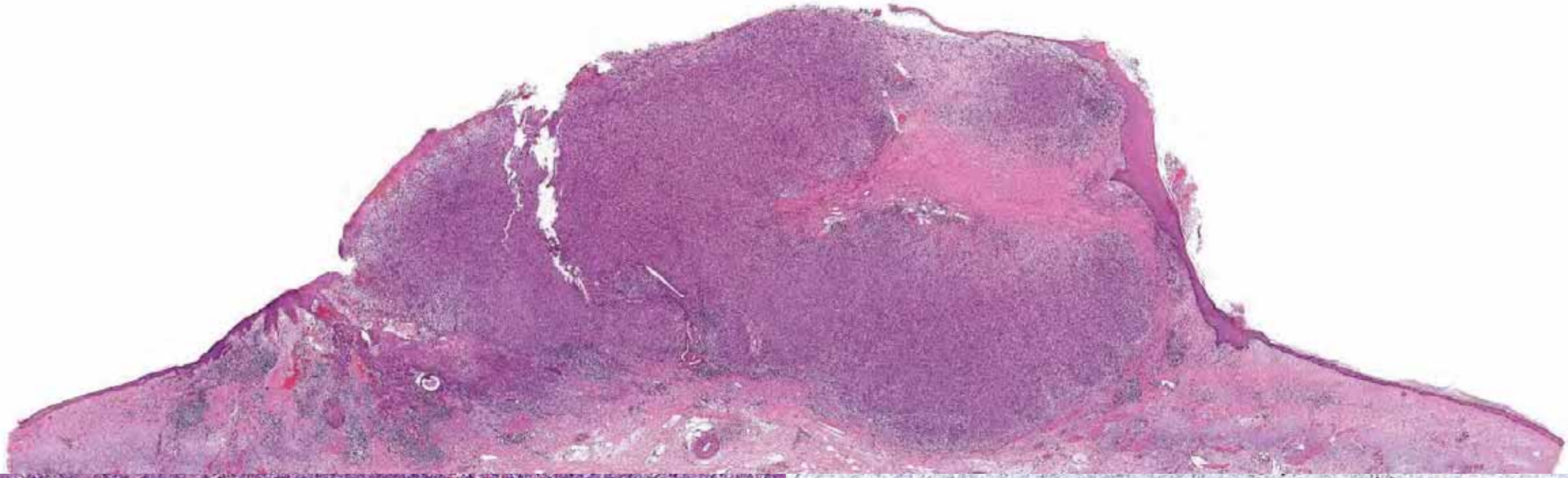
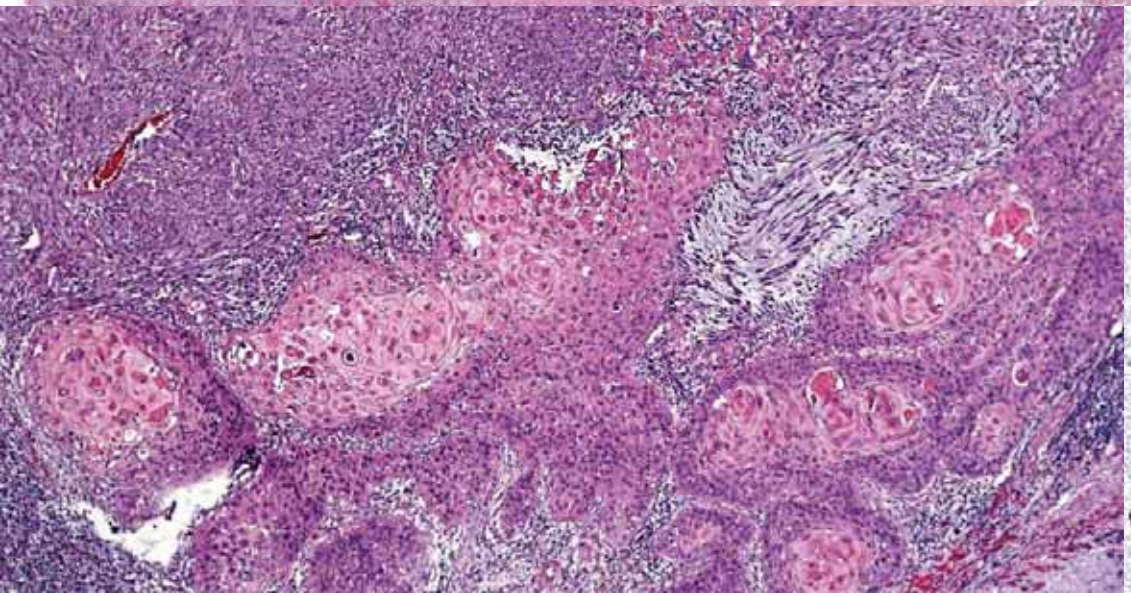
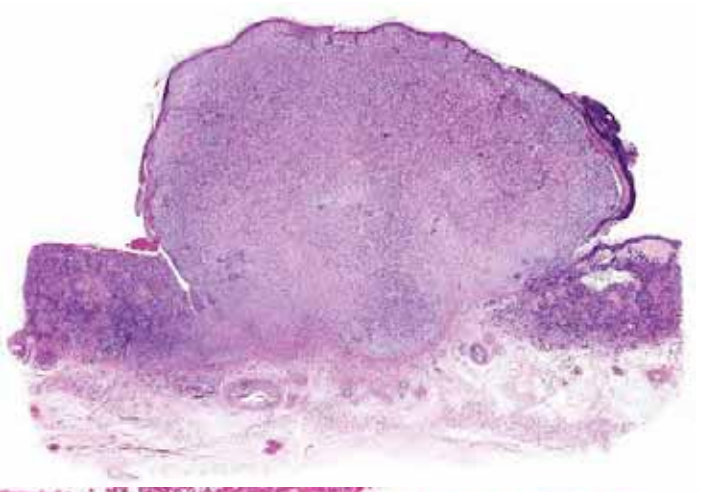


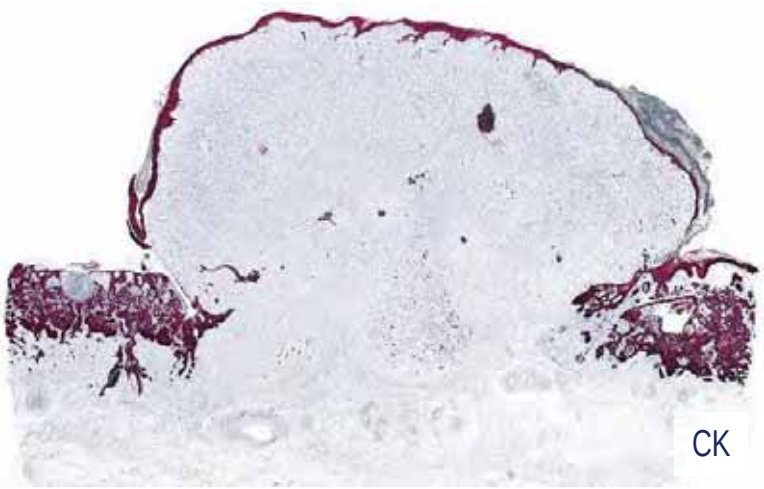
FIGURE 1 (a) A 20 × 15-mm, ulcerated, pedunculated, fresh-red nodule on the left cheek of an 82-year-old Japanese man (clinical view). (b) A pedunculated nodule contiguous with the acanthotic epidermis (HE, ×10). (c) Actinic keratosis with atypical keratinocytes in the lower epidermis, underlying solar degeneration (HE, ×200). (d) Atypical keratinocytes of the acanthotic epidermis transitioned to atypical spindle cells of the pedunculated nodule (HE, ×200). (e) Sheets of atypical epithelioid cells with occasional osteoclast-like giant cells (HE, ×400). (f) CK5/6 expression in spindle cells in the periphery of the nodule (immunohistochemistry (IHC), × 10). (g) CD10 expression in epithelioid cells (IHC, ×10). (h) CD163 expression in epithelioid cells (IHC, ×400). (i) CD68 expression in multinucleated giant cells (IHC, ×400)

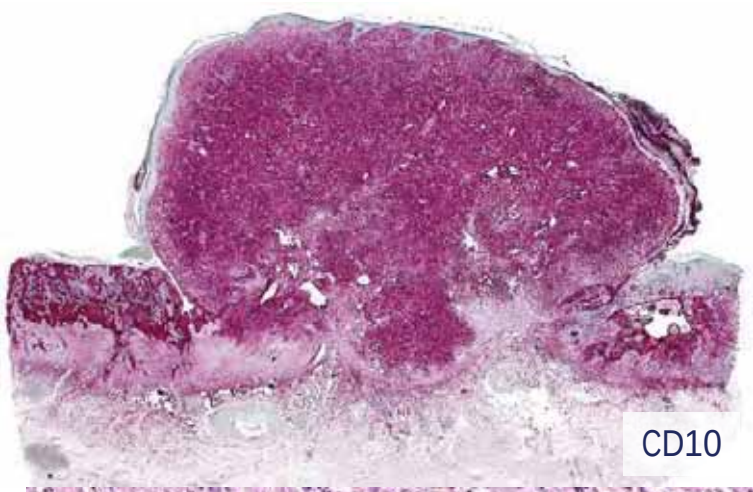


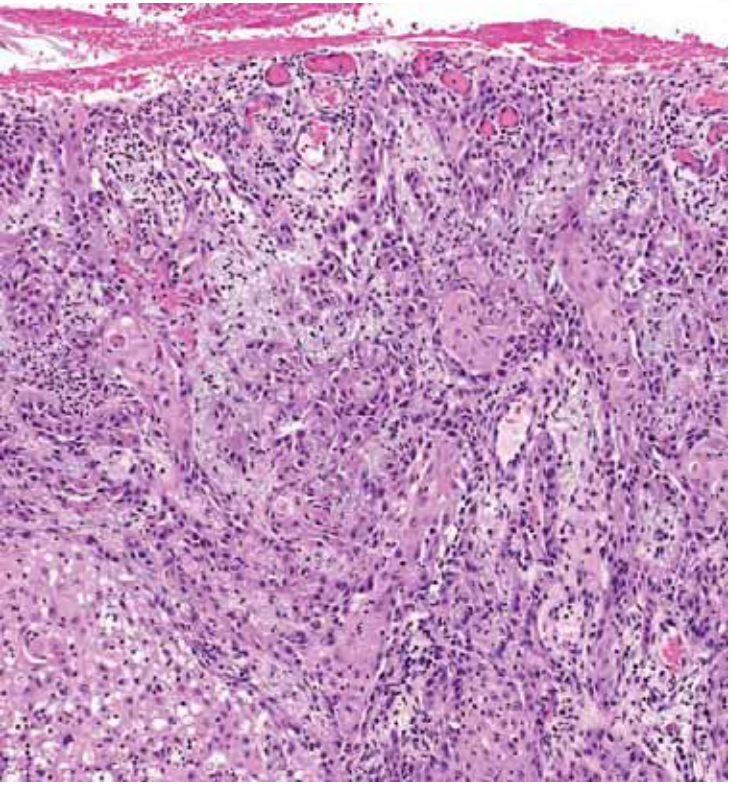


CK







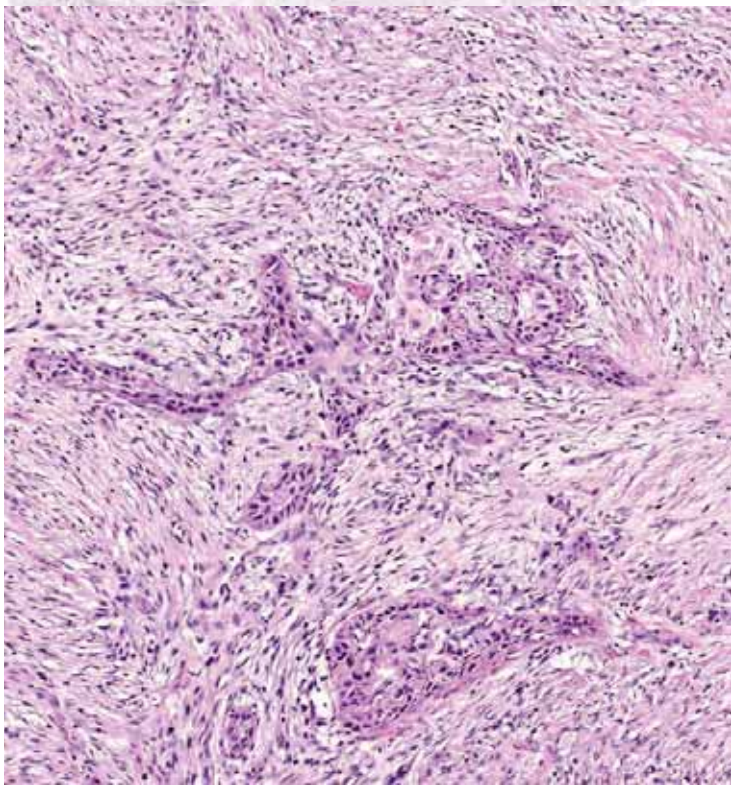


Atypical fibroxanthoma

Distinct entity ("fibrohistiocytic" tumor) ?
Dedifferentiated squamous cell carcinoma ?

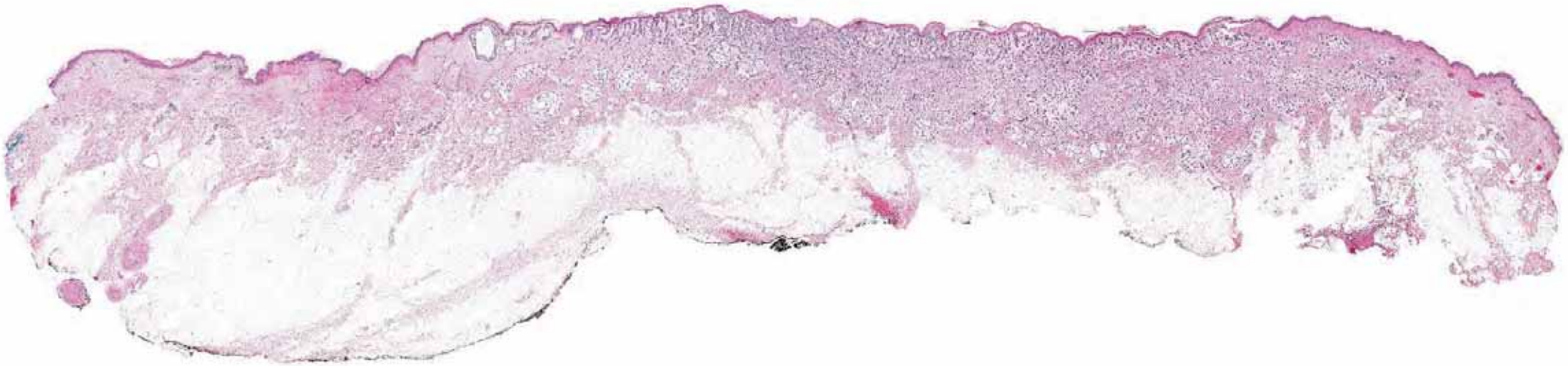
A diagnosis of exclusion (r/o mostly SCC, melanoma, leiomyosarcoma, angiosarcoma)
CD10 (and vimentin) completely non-specific (made mostly to have a positive staining…)
SCC or not: an academic discussion without relevance for the management of patients

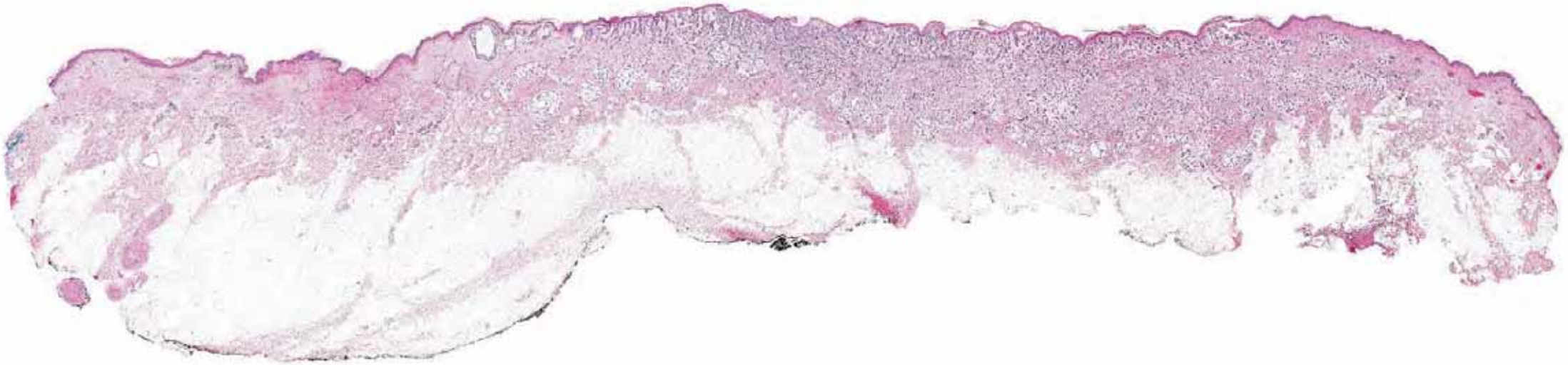
My opinion: dedifferentiated SCC

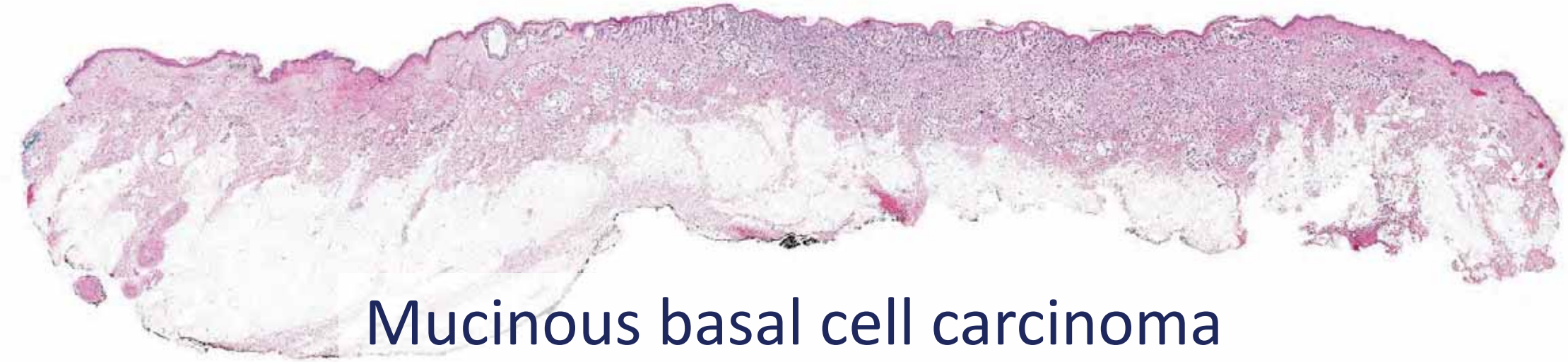


Case 4

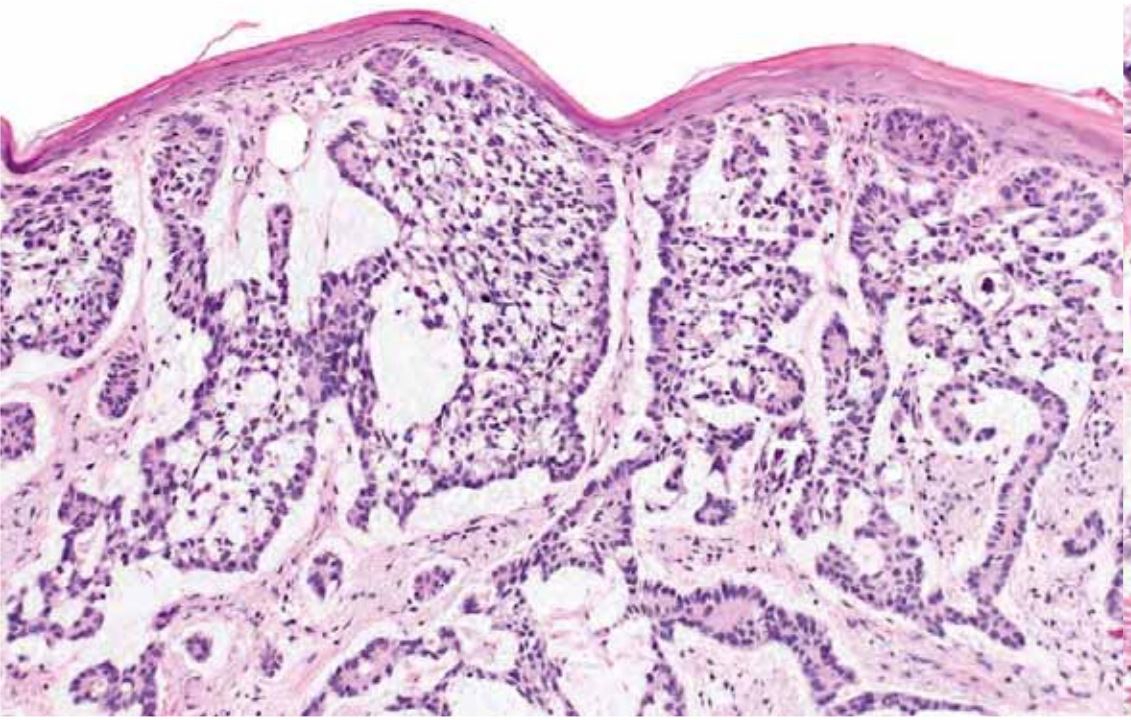
F, 94. Skin tumor on the left temporal region of unknown duration.

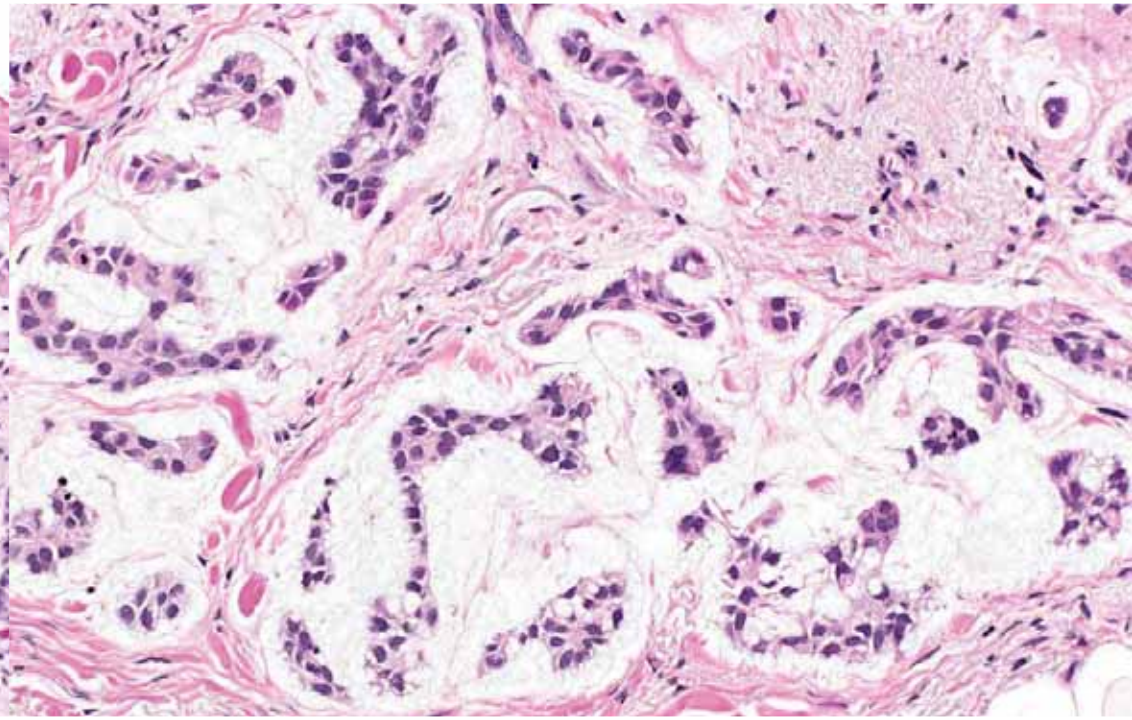




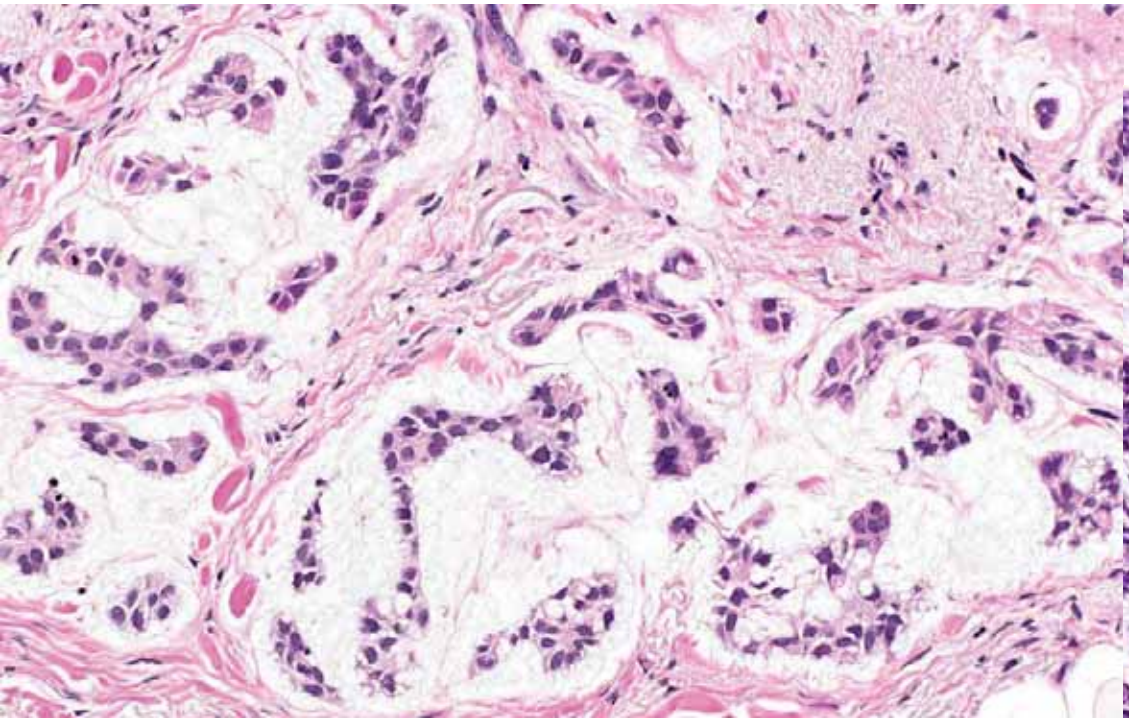


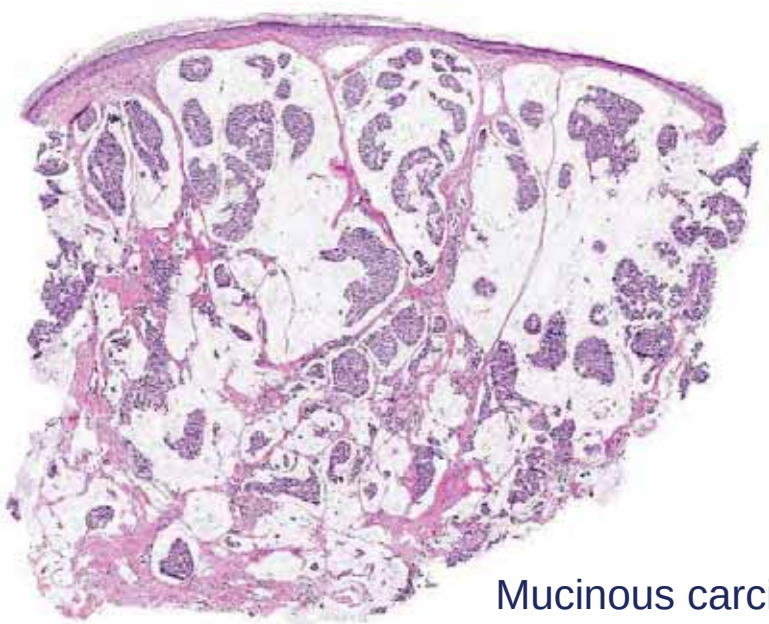
Mucinous basal cell carcinoma



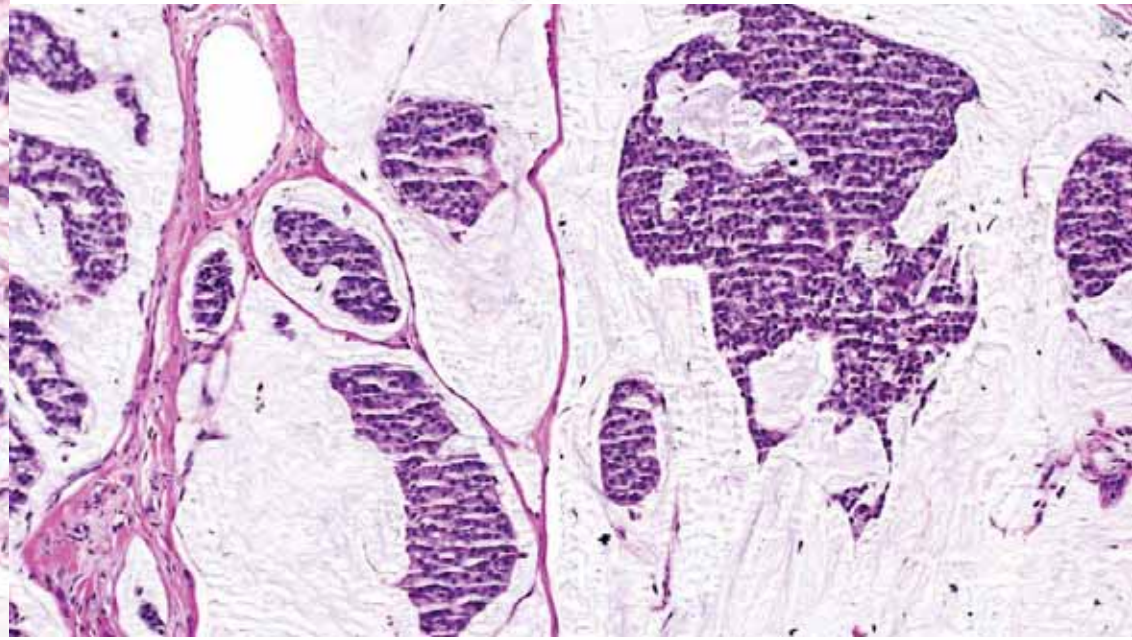


Mucinous BCC



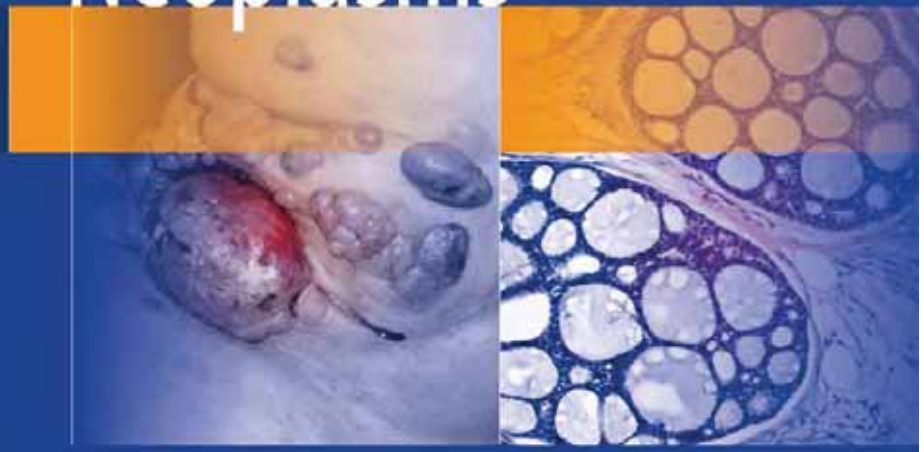


Mucinous carcinoma



Luis Requena
Omar Sangüeza

Cutaneous Adnexal Neoplasms



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Summary

- Most primary cutaneous mucinous carcinomas appear on the head, the majority of which were settled on the eyelid.
- Mucinous carcinoma is made up of small groups of neoplastic cells embedded in lakes of mucin and separated from each other by thin septa of connective tissue, compartmentalizing the tumor. Neoplastic cells are round, oval, or polygonal, with small hyperchromatic nuclei and abundant cytoplasm.
- The so-called endocrine mucin-producing sweat gland carcinoma of the skin may be a precursor or an early stage in the evolution of cutaneous mucinous carcinoma with neuroendocrine differentiation.
- Immunohistochemically, neoplastic cells of mucinous carcinoma show positivity for CEA, S-100 protein, EMA, GCDFP-15, CK7, alpha-lactalbumin, salivary amylase, beta-2-microglobulin, antigen Leu-M1, TFF1, TFF3, estrogen and progesterone receptors [54]. A peripheral layer of myoepithelial cells expressing smooth muscle markers, such as smooth muscle actin, p63, and calponin, favors a primary cutaneous origin and militates against a cutaneous metastasis from a visceral mucinous carcinoma.
- Primary cutaneous mucinous carcinoma is a low-grade carcinoma, and few cases have developed lymph node or visceral metastases

29.1 History

The first published case of primary cutaneous mucinous carcinoma is probable due to Lennox et al. who, in 1952, described 11 cases of mucin-secreting neoplasms. One of those cases corresponded to a nodule located on the scalp of a 67-year-old woman, which, after a 7-year follow-up, was found to have a similar tumor in the internal organs. The

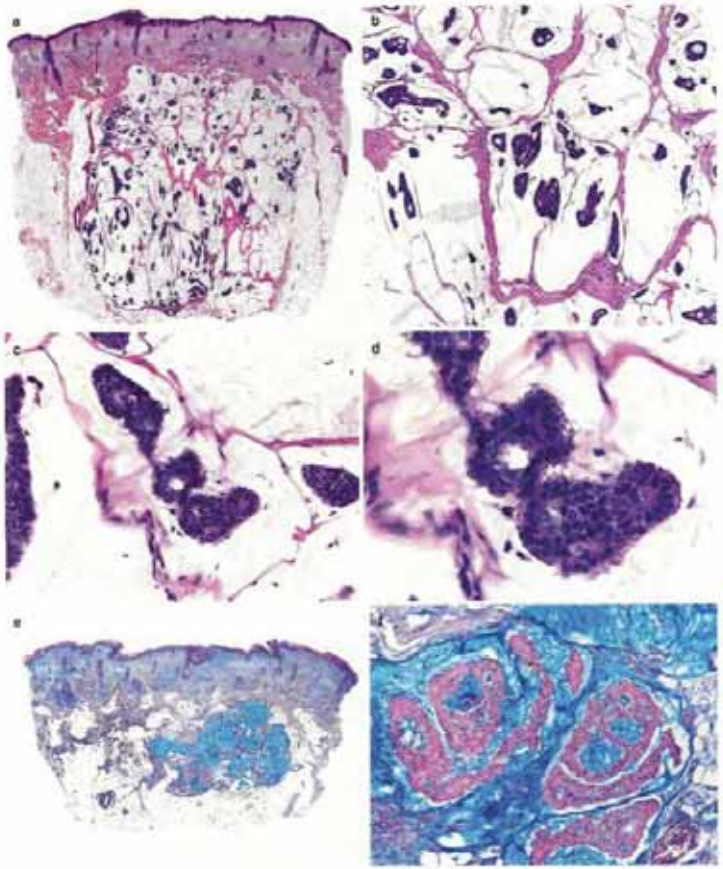

Fig. 29.2 Histopathologic features of mucinous carcinoma of the skin. (a) Scanning view showing a relative well-circumscribed nodule involving the deep dermis and subcutis. (b) The neoplasm shows a fenestrated pattern with thin septa of connective tissue delimiting lakes of mucin, which contain epithelial aggregates of basophilic cells. (c) Neoplastic epithelial cells have round nuclei and eosinophilic cytoplasm. (d) Higher magnification of neoplastic aggregates of epithelial cells, some of them showing central ductal differentiation. (e) The same case stained with Alcian Blue. (f) Abundant mucin around neoplastic aggregates of epithelial cells. (g) There is also mucin among neoplastic epithelial cells. (h) Higher magnification of neoplastic cells

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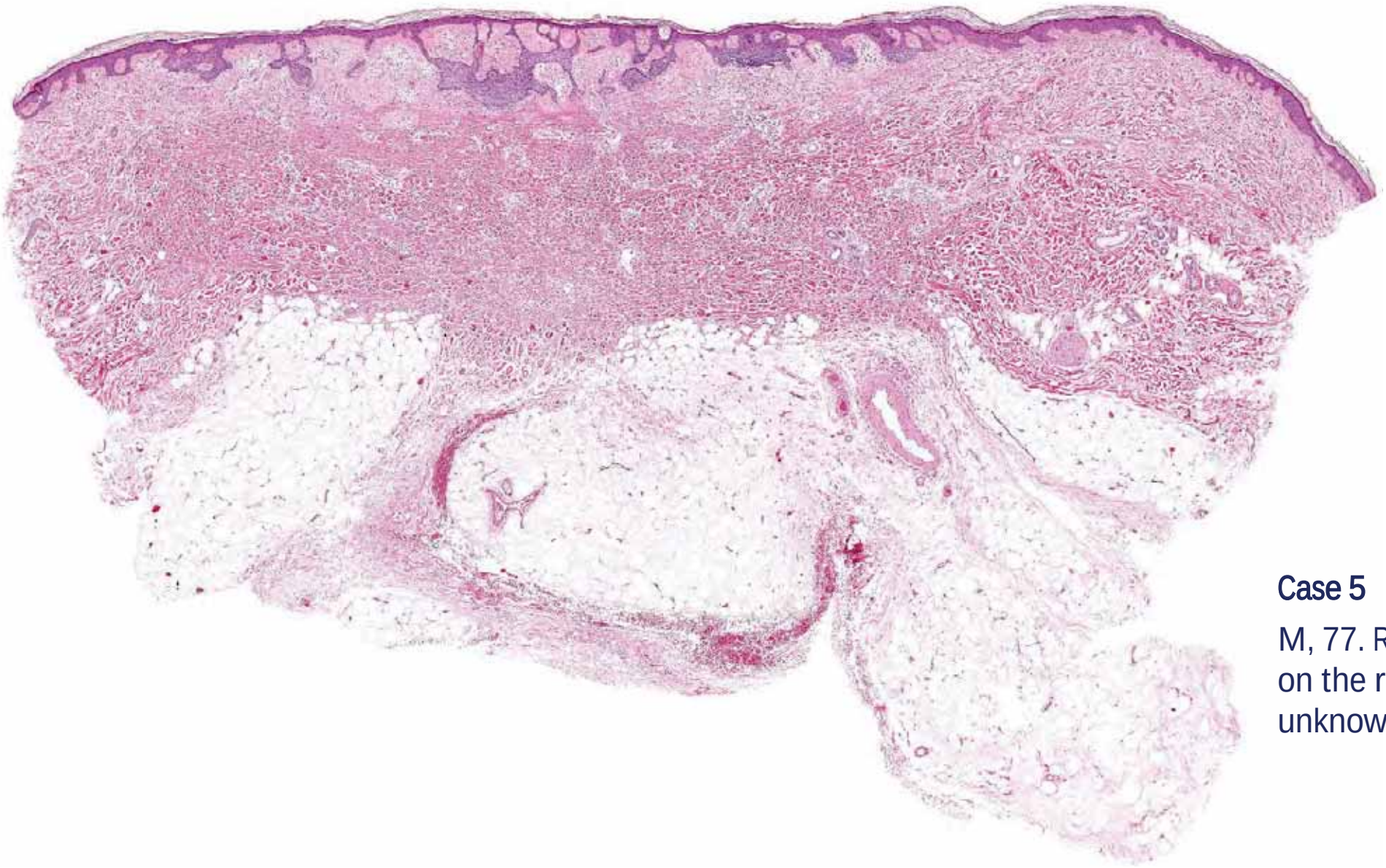
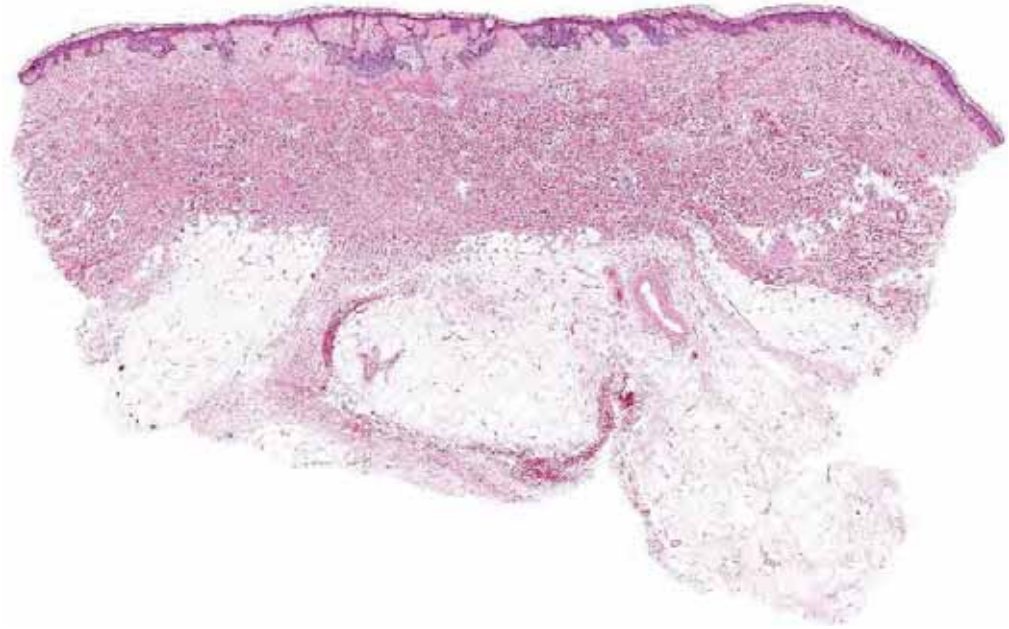
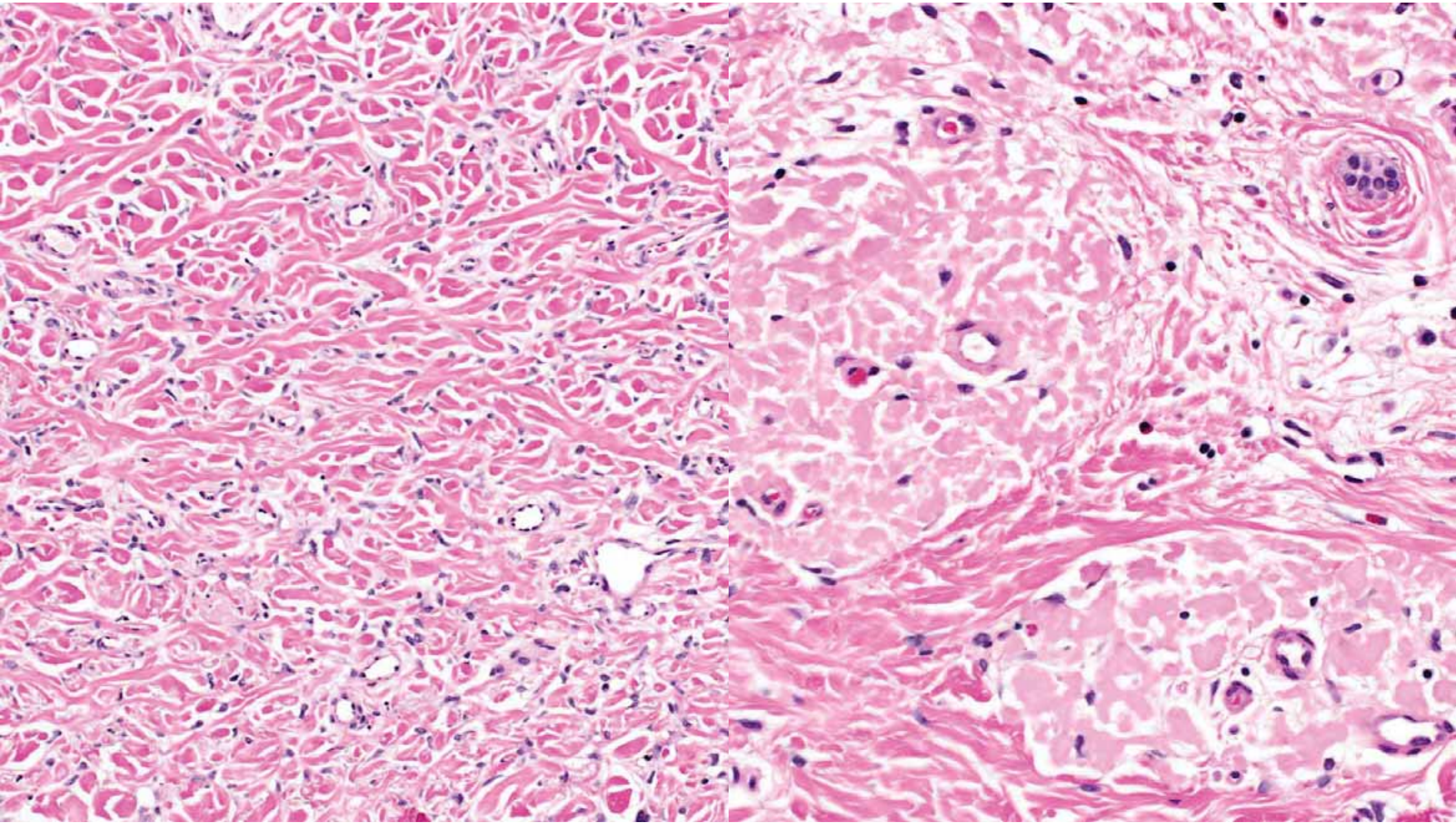
L. Requena, O. Sangüeza, *Cutaneous Adnexal Neoplasms*, DOI 10.1007/978-3-319-45704-8_29

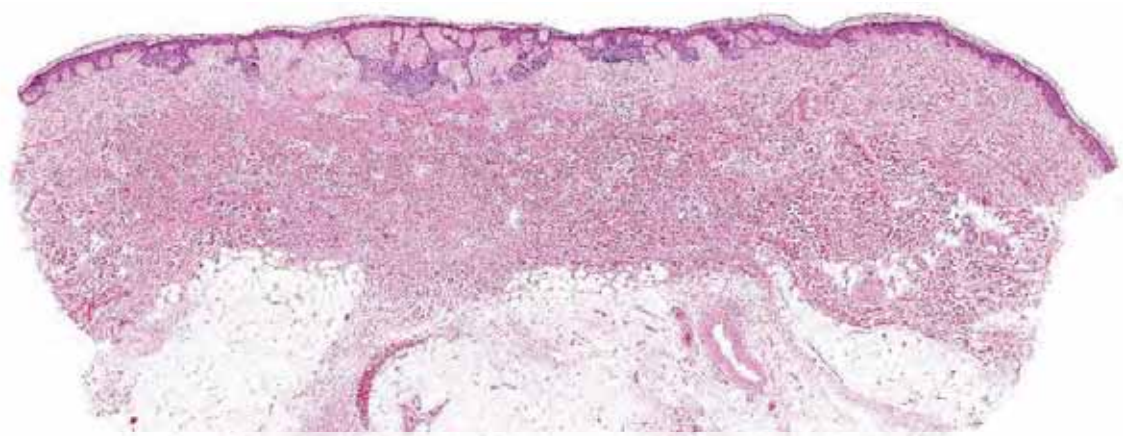


Case 5

M, 77. Red-livid lesion on the right leg of unknown duration.

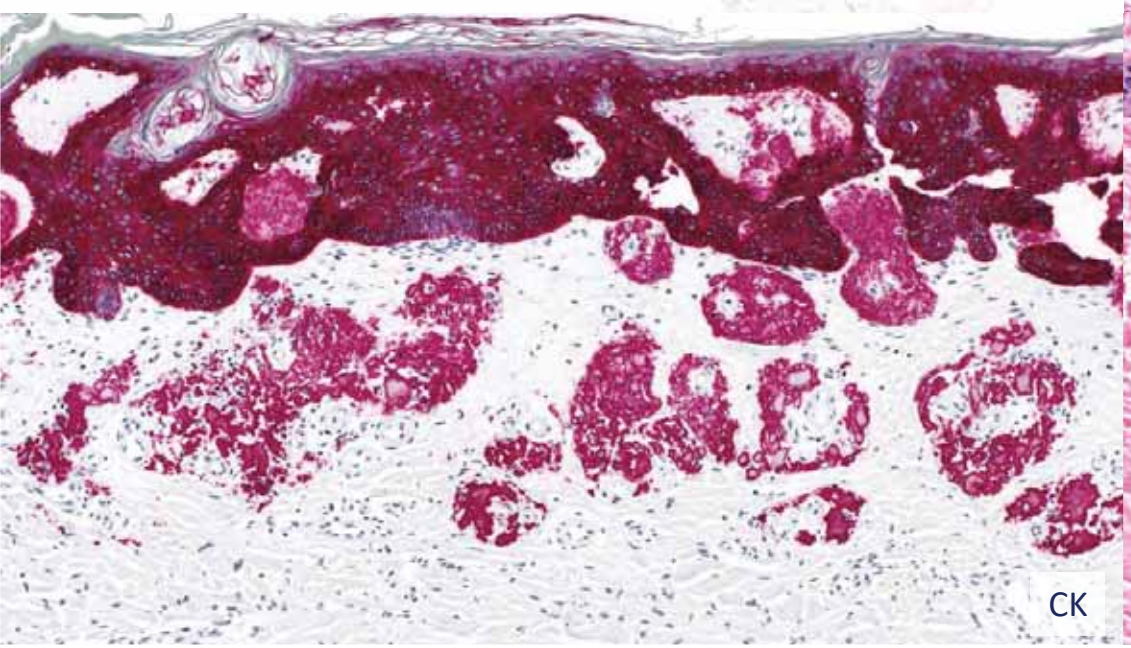


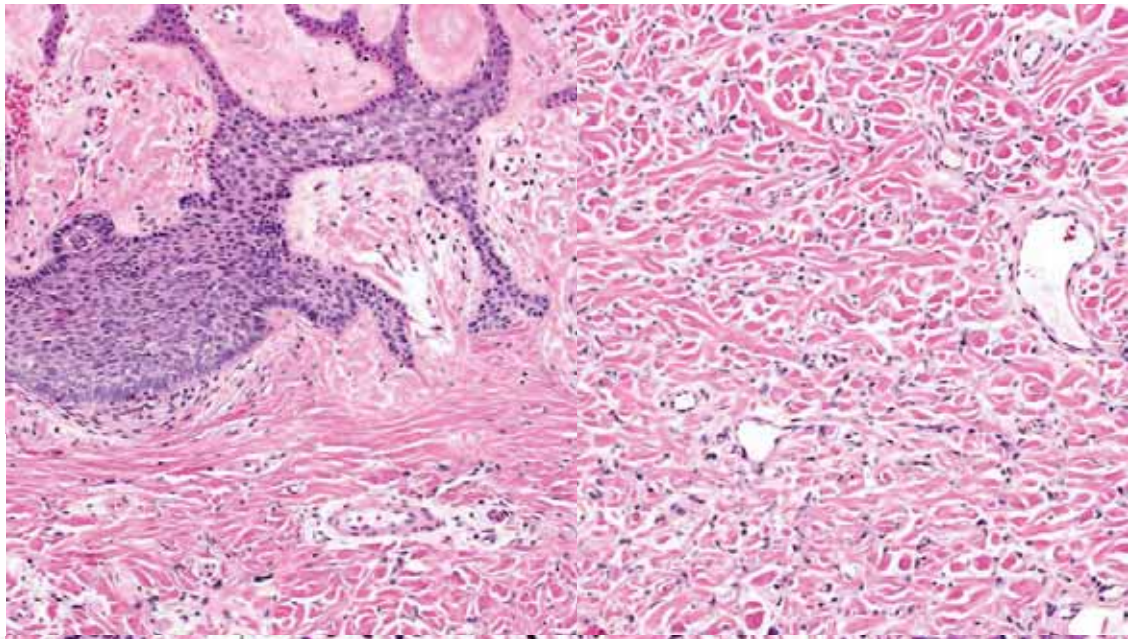


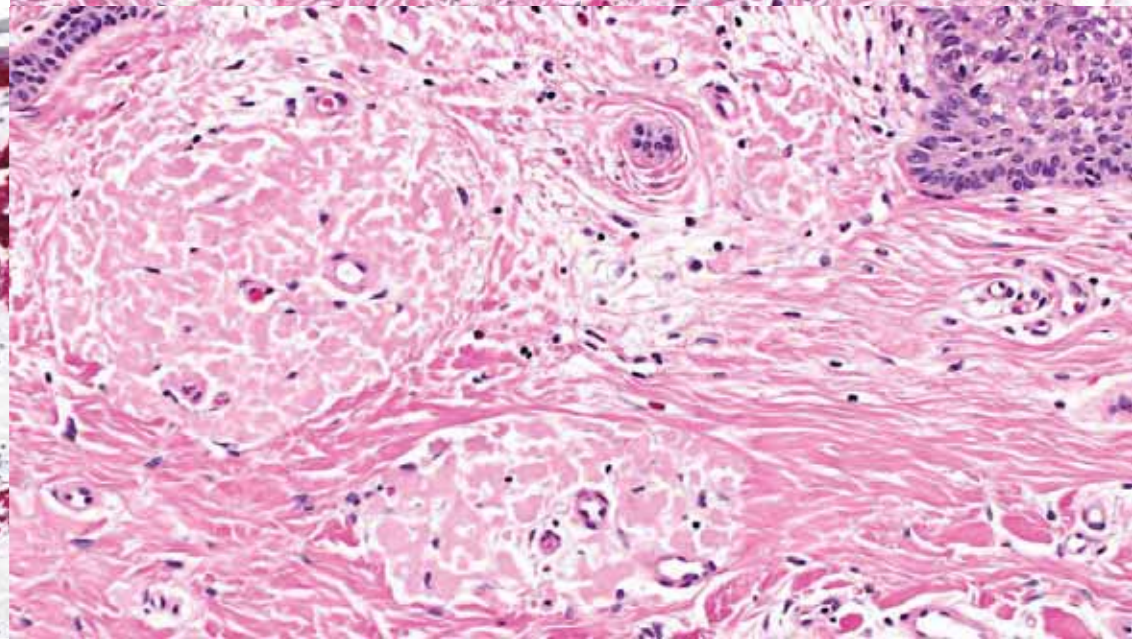


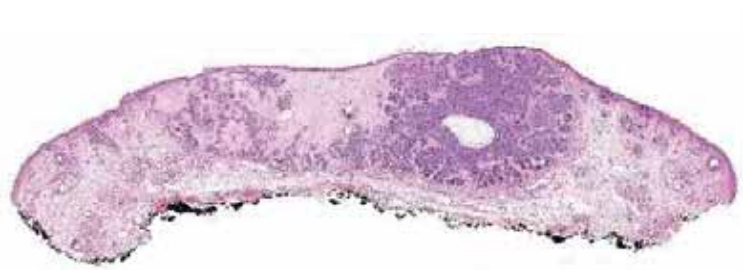
Dermatofibroma

with basaloid induction and amyloid K deposition

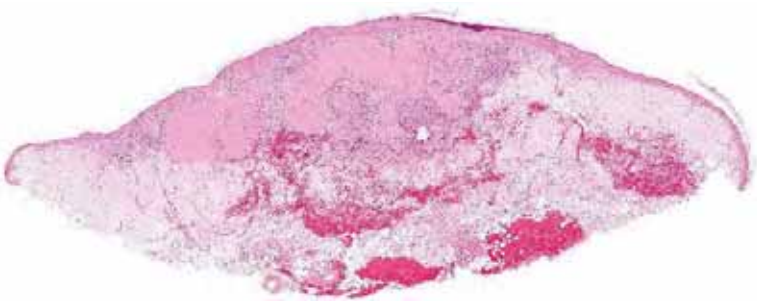




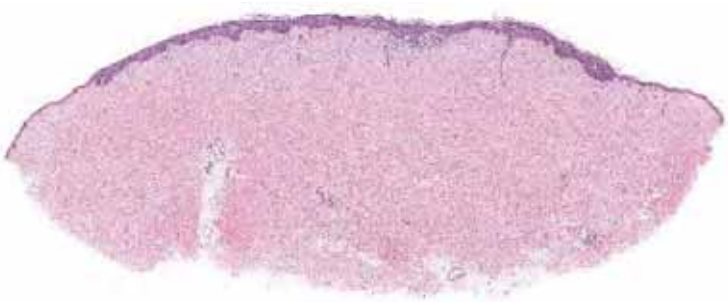




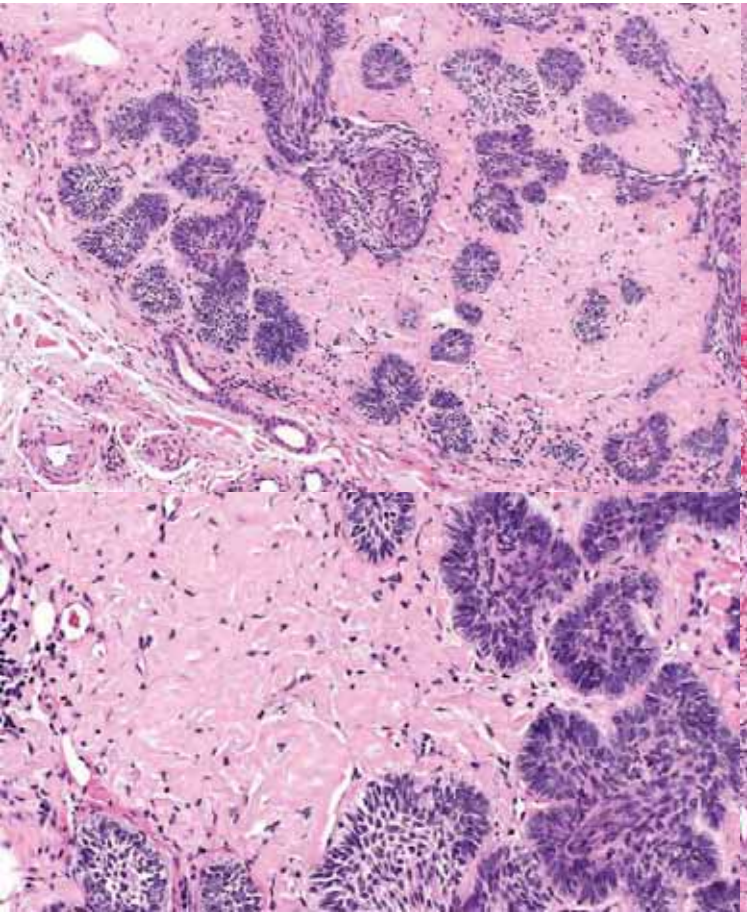
Basal cell carcinoma

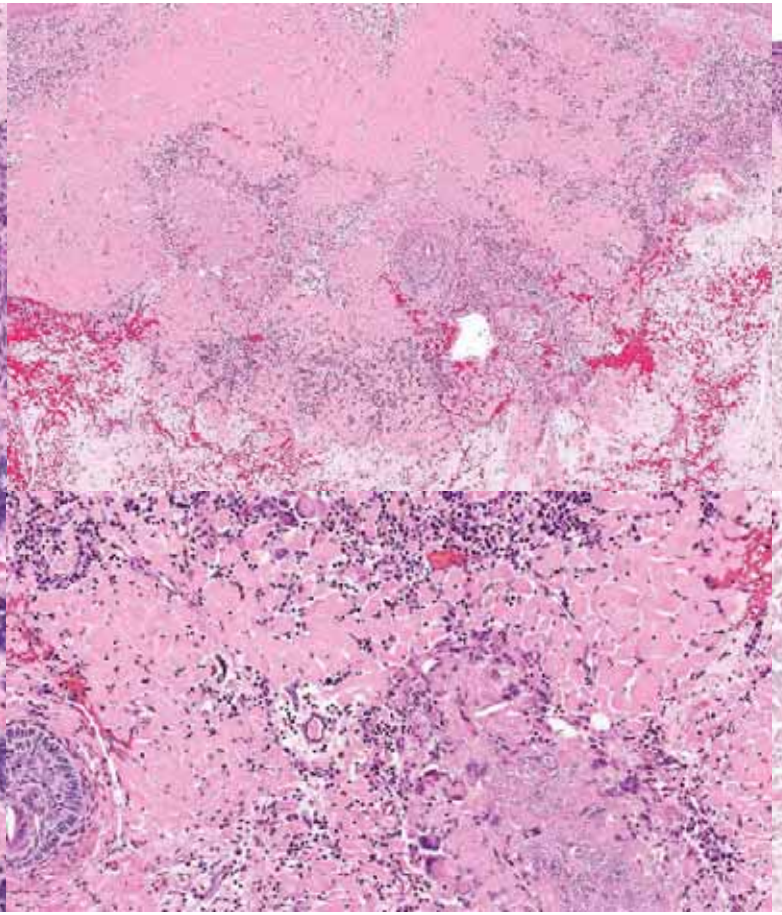


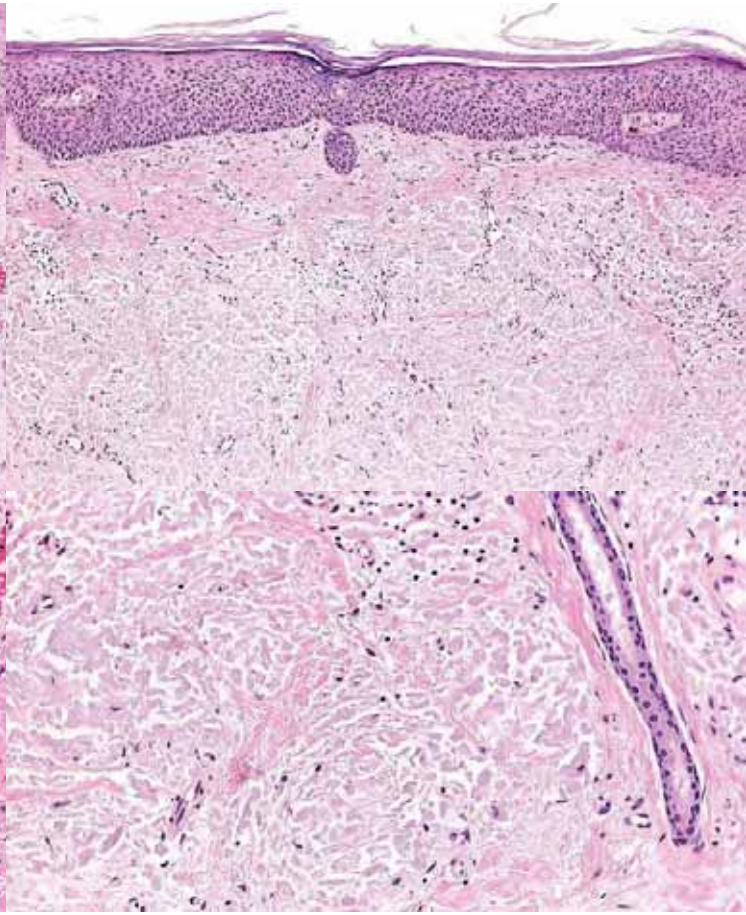
Squamous cell carcinoma



Seborrheic keratosis







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Histogenesis of Primary Localized Cutaneous Amyloidosis: Sequential Change of Epidermal Keratinocytes to Amyloid via Filamentous Degeneration

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The Veterans Administration Center and Wright State University School of Medicine, Dayton, Ohio, U.S.A.

Two cases of lichen amyloidosus and 8 cases of macular amyloidosis were examined by electron microscopy. Epidermal keratinocytes showed variable degrees of focal degeneration in the basal or lower Malpighian layer. The primary change was seen in cells which contain fibrillar (30 nm in thickness) cytoplasmic inclusion. The following developments seemed to lead to filamentous degeneration (colloid bodies): (1) aggregation of tonofilaments within the granular or fibrillar cytoplasm, (2) filamentous cells, which are composed of bundles of 7-nm thick filaments surrounded by cell membrane and desmosomes, and (3) filamentous masses composed of bundles or whorls of tightly packed 7-nm thick filaments in the intercellular spaces. At the dermo-epidermal junction, some of the filamentous masses were surrounded by the basal lamina of the epidermis and others were dropping into the dermis. Occasionally, loosened filaments (similar to amyloid filaments) were about to drop into the dermis. Early formation of amyloid islands consisted of electron-dense and electron-light parts. They were located directly beneath the epidermis. In the deeper portion of the papillary dermis and in the upper reticular dermis, the majority were electron-light masses. Electron dense parts were the densely packed 7-nm thick filaments, whereas electron-light parts were the typical straight amyloid filaments. Small tubular filaments were seen in common in the *filamentous cells, filamentous masses,* and *amyloid islands.*

It is concluded that some of the amyloid substance in primary localized forms of cutaneous amyloidoses derive from the epidermal cells through filamentous degeneration.

A different pathogenesis seems to exist between systemic amyloidosis and primary localized cutaneous amyloidosis [1–3]. Although amyloid deposits in both are composed of 6 to 10-nm thick straight filaments [4–11], primary localized cutaneous amyloidoses show some biological peculiarities [1]: (1) the deposition of amyloid is limited to the papillary dermis in lichen amyloidosus [5,6] and macular amyloidosis [7,8], (2) the amyloid formation is seen only in the immediate surroundings of epithelial tumors [10,11], (3) in wound healing experiments in the lesions of lichenoid and macular amyloidoses and in actinic keratosis, amyloid does not accumulate until the wound is re-epithelialized [8,11], and (iv) no plasma cells are found in the lesion [5–11].

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Ultrastructural studies have not clearly demonstrated the precursor of amyloid filaments in the epidermis [5–21]. Some investigators, however, found the filamentous masses (colloid or hyalin bodies) [6,19], which were similar to the Civatte bodies in lichen planus [19,22], but distinctly different from amyloid. The relationship between Civatte bodies and amyloid islands was therefore an interesting subject to study.

Studying PUVA (psoralen and ultraviolet A) treated skin [23] and ultraviolet (UV) irradiated skin [24], we found that repeated irradiation of UVA is amyloidogenic. Filamentous masses and/or amyloid islands were in the dermo-epidermal junction or in the papillary dermis. Particularly some deposits shared characteristics of both filamentous mass (whorls of filaments) and amyloid (randomly oriented straight filaments). These filamentous masses were often surrounded by the basal lamina of the epidermis. Thus, the conversion from epidermal keratinocytes to amyloid islands was dramatically demonstrated [23]. Encouraged by this finding, we carefully re-examined the specimens of lichen amyloidosus and macular amyloidosis, which had been studied previously for other aspects of diseases [6–8].

MATERIALS AND METHODS

Two cases of lichen amyloidosus and 8 cases of macular amyloidosis were re-examined. Case histories were fully documented previously [6–8]. Briefly, 2 cases of lichen amyloidosus were a 45 yr-old Chinese man and a 36 yr-old Puerto Rican woman. The clinical diagnosis was confirmed by histological examination [6,8]. Eight cases of macular amyloidosis were comprised of 6 Puerto Ricans, an Equadorian woman, and a Caucasian woman. The hyperpigmented macules were biopsied and amyloid deposits in the papillary dermis were confirmed [7,8].

The diced skin samples were fixed for 72 hr in chilled 5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4). After an overnight rinse, specimens were postfixed with 1% osmic acid in barbital (veronal) buffered to pH 7.4 or in 0.1 M cacodylate buffered to pH 7.4 for 3 hr. All specimens were dehydrated with ethanol, 50% through absolute, and propylene oxide. Araldite was used for embedding. Thin sections were cut in an ultramicrotome (Porter-Blum MT-2 or MT-2B). The sections were stained with uranyl acetate and lead citrate, and examined with an electron microscope (Phillips 400). To study the thickness of filamentous structure, electron micrographs were taken at a high magnification (× 60,000) with an accelerating voltage of 100 kv, and were enlarged to × 150,000.

RESULTS

Histological findings reported [6–8] previously were confirmed. No significant differences were noted between lichen amyloidosus and macular amyloidosis regarding the ultrastructure of amyloid deposit [6–8]. Therefore, the following is the summary of both types of specimens.

Epidermal Changes

Frequently, there were degenerating foci in the basal or lower Malpighian layer (Fig 1). Affected keratinocytes had a pyknotic nucleus, abnormally aggregated tonofilaments, vacuoles, and fragmented cell organelles among condensed cytoplasm. Huge vacuoles up to 5 μm in diameter were sometimes observed in

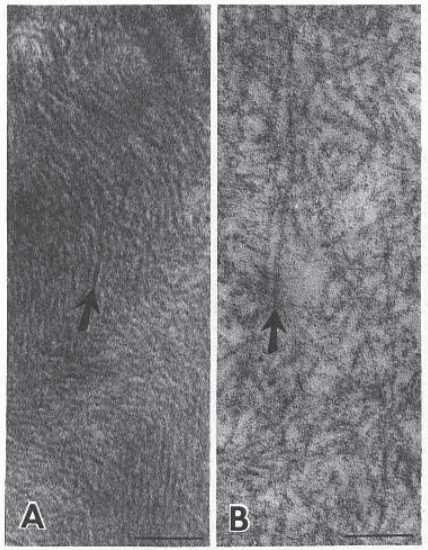


FIG. 4. The filaments in the filamentous cell (*A*) and typical amyloid island (*B*) are compared at the same magnification. No difference is noticed between the thickness of individual tubular structures (→). *A*: The filamentous cell shown by the *asterisk* in Fig 3 is enlarged. Tightly packed filaments are resolved into 7-nm thick tubules (→). (Lichen amyloidosus). *Scale* = 100 nm (× 150,000). *B*: typical amyloid filaments are tubules of about 7 nm in diameter (→). Low magnification of this area will be shown in Fig 12. (Macular amyloidosis). *Scale* = 100 nm (× 150,000).

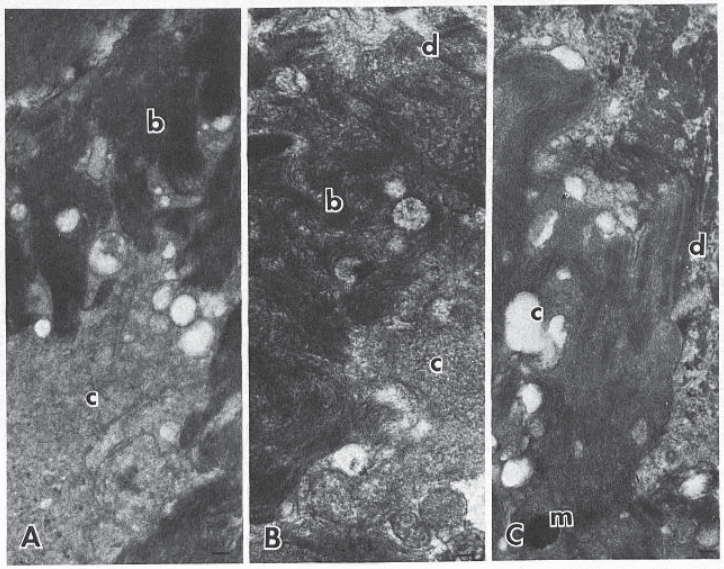
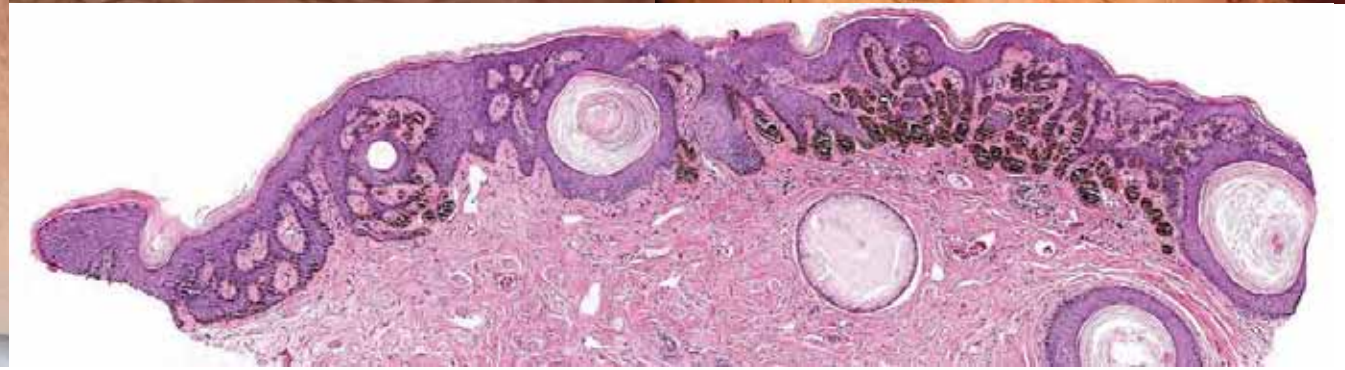
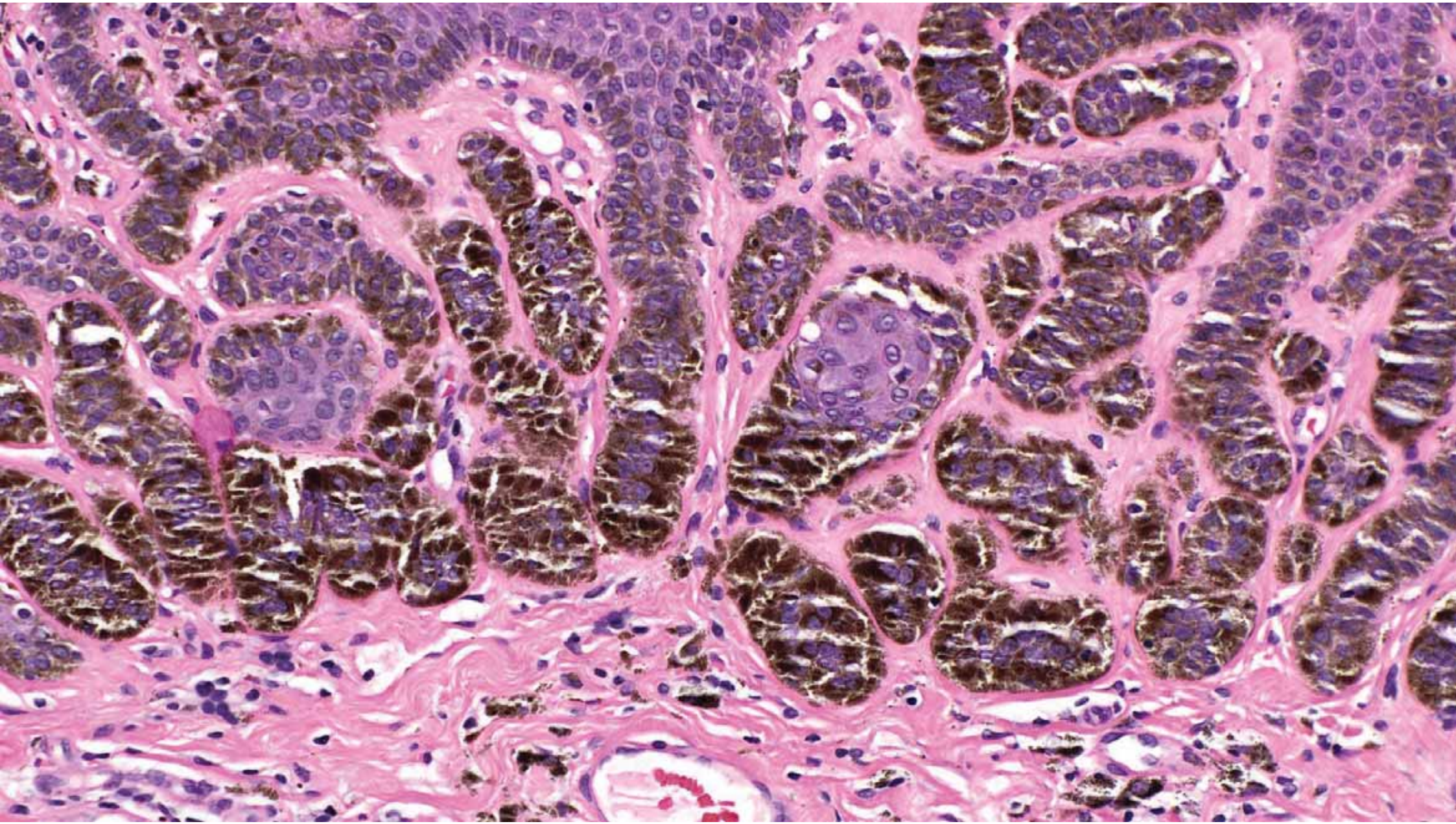


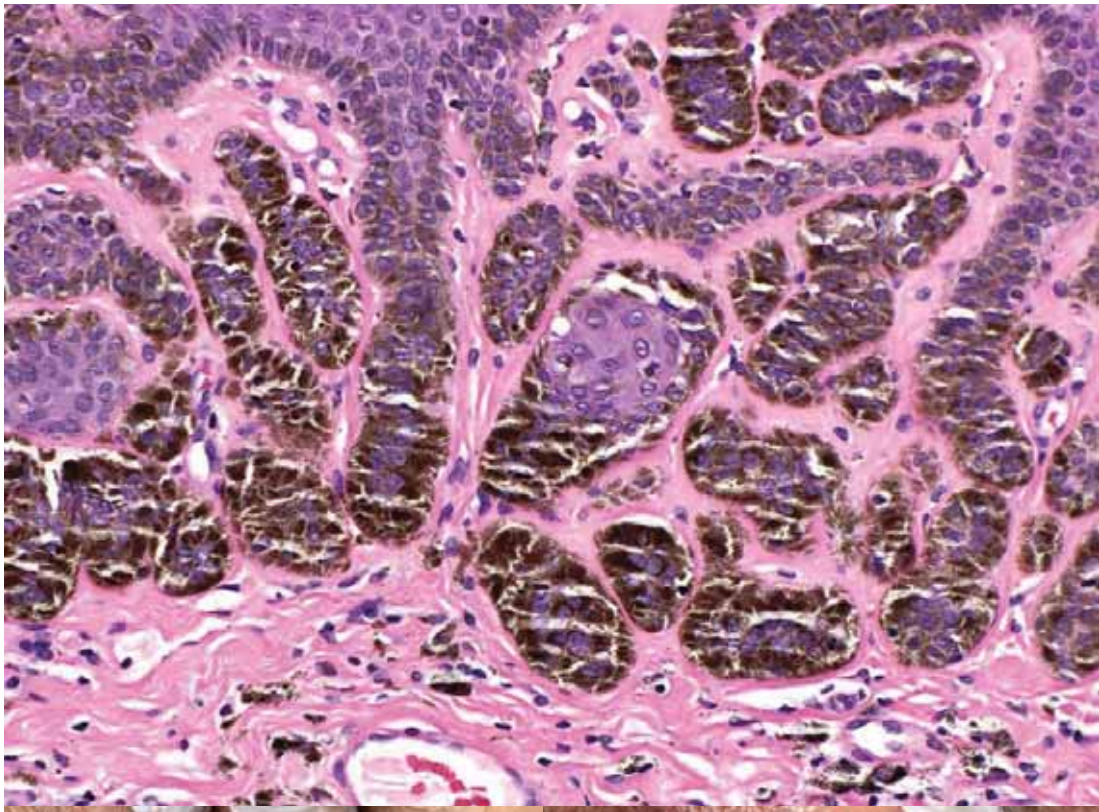
FIG. 5. Sequential changes from keratinocytes to filamentous cells are displayed (lichen amyloidosus). *A*, Early change is bundle formation of the tonofilaments (*b*) and granular or fibrillar cytoplasm (*c*). *B*, Desmosomes (*d*) are still seen; however, filaments (*b*) begin to have a wavy nature within the cytoplasm (*c*). *C*, Filamentous cells have desmosomes (*d*) and cell membrane. Density in the bundles of filaments is diminished. Condensed cytoplasm (*c*) are vacuolated. *M*, Melanosome. *Scale* = 100 nm each (× 44,000 each).

Case 6

F, 83. According to the patient pigmented lesion on the right labium for approximately 6 months.

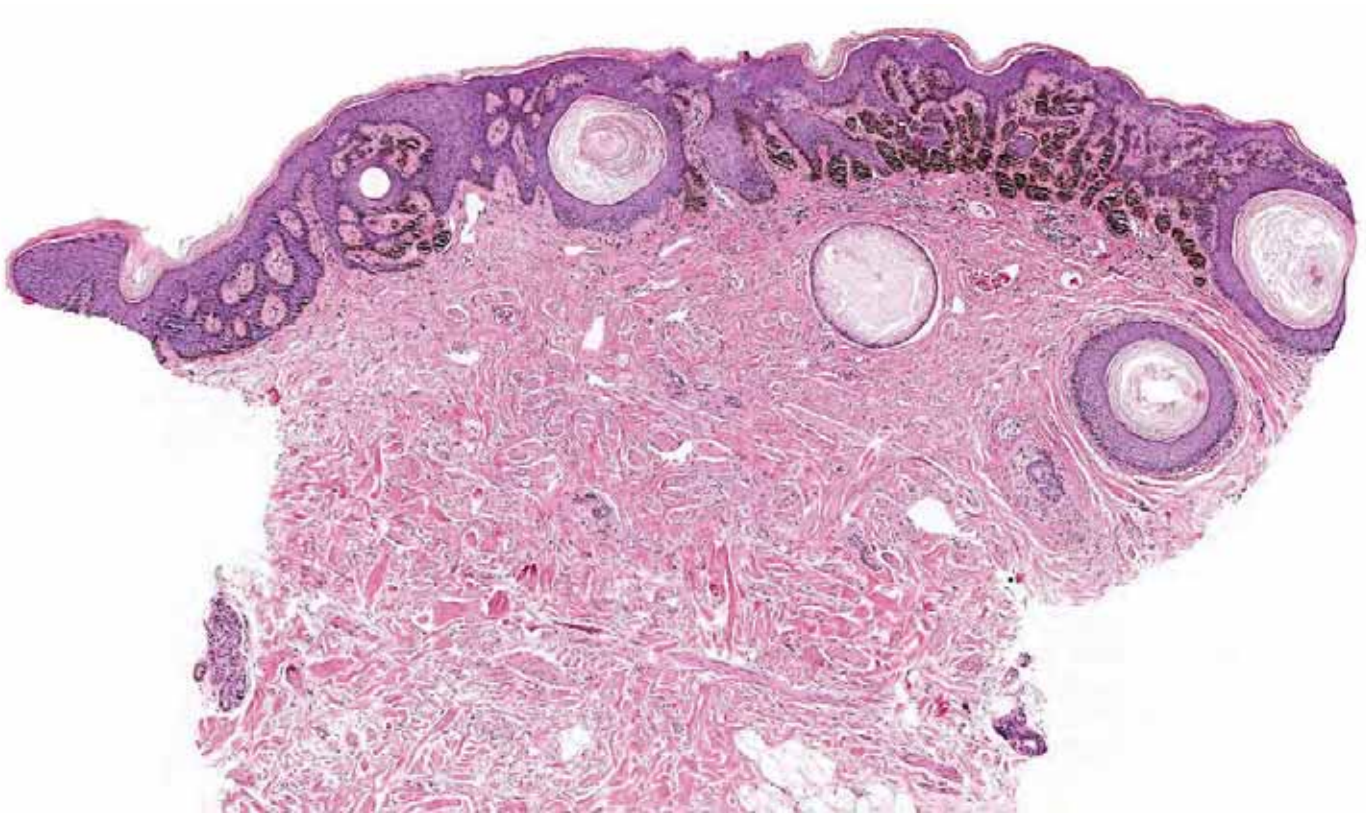






Dowling-Degos disease

HPV-PCR: negative



Features supporting the diagnosis of Dowling-Degos disease:
Pigmentation not restricted to the main area, with small spots around it.
Histopathological features.

Features militating against the diagnosis of Dowling-Degos disease:
Age of onset (if history correct...).
Unilateral distribution with "patchy" pigmentation.

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doi: 10.4103/ijd.IJD_10_18 10.4103/ijd.IJD_10_18

PMCID: PMC6233035
PMID: 30504985

Dowling-Degos Disease Localized on Vulva Mimicking Condyloma Acuminata

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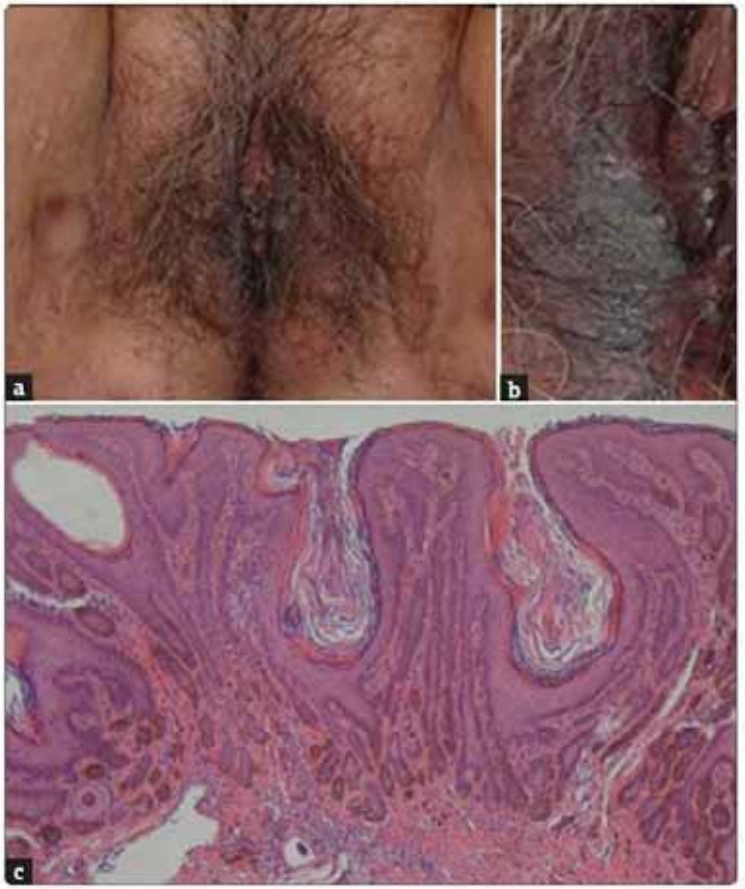
Sir,

A 66-year-old female presented with multiple brown reticulate pigmentary plaques on perineum for decades [Figures 1a and b]. A biopsy specimen showed irregular, filiform epidermal elongations of hyperpigmented rete ridges [Figure 1c]. Multiple subcutaneous nodules on groins were also noted [Figure 1a] and the biopsy proved that those were epidermal inclusion cysts. According to the above findings, Dowling-Degos disease (DDD) associated with multiple epidermal inclusion cysts were diagnosed. Her younger sister also had the same lesions. On the other hand, her brothers and nieces had multiple epidermal inclusion cysts on the trunk. Because of the benign prognosis of DDD, the patient preferred long-term observation.

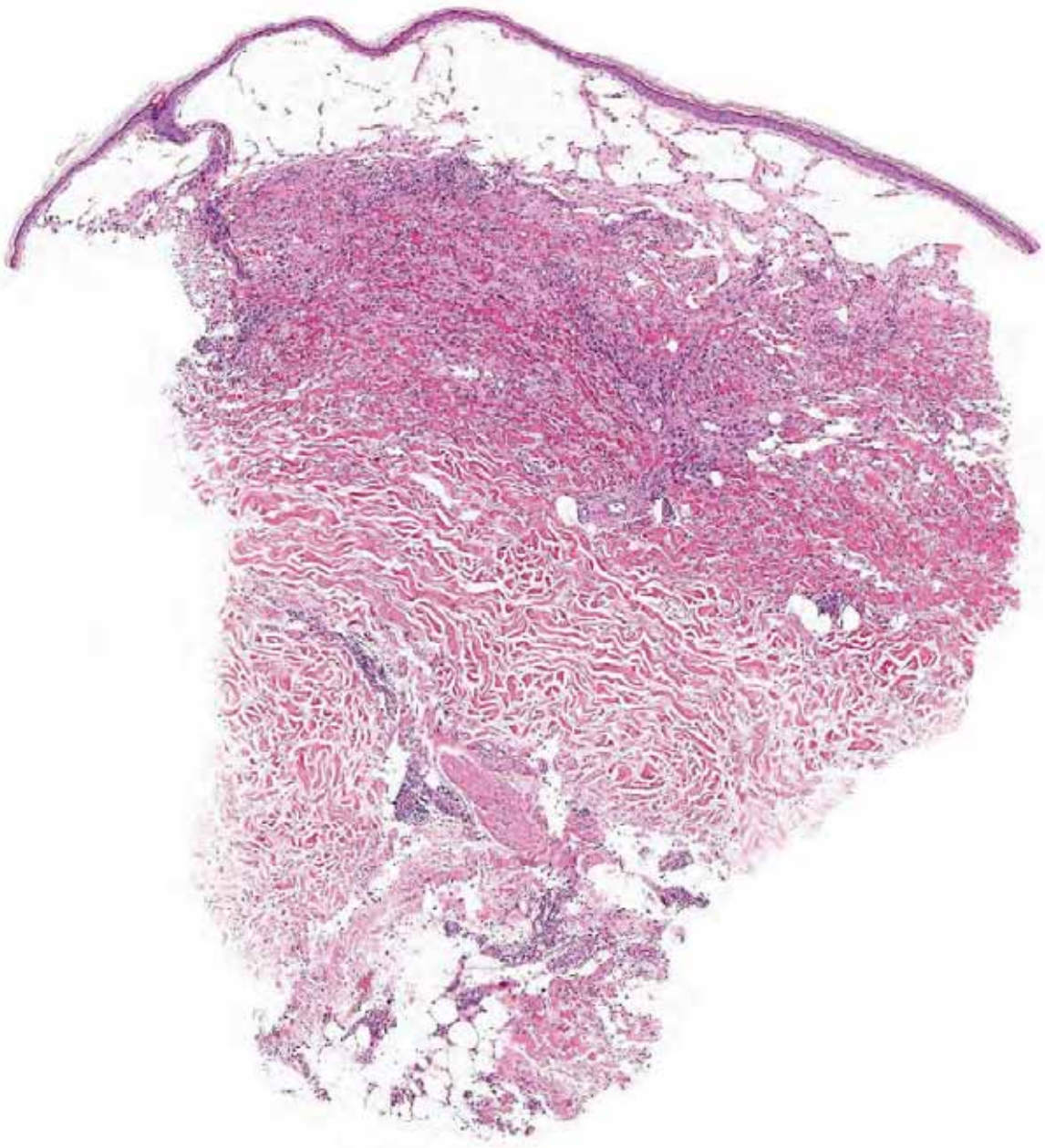
As the genetic basis of DDD was recently reported, we focused our genetic analysis on exon 1 of the *KRT5* gene. Direct DNA sequencing of PCR products derived from the patient did not reveal any mutation compared to the control sequence. We identified c-73 T>C (negative strand), which was a single-nucleotide polymorphism (SNP) 4rs371725 of keratin 5 (K5) located in chromosome 12 52914153 [Figure 2]. This SNP was located at 5′ end of exon 1 but not translated.

DDD is characterized by acquired, progressive pigmented lesions that primarily involve the large flexural areas. It is common that DDD involved the genitalia;[1] however, DDD resulted from SNP and associated with family members had not been reported. In addition, the distinct clinical presentation might be due to long-standing lesions with local stimuli by me-

Figure 1



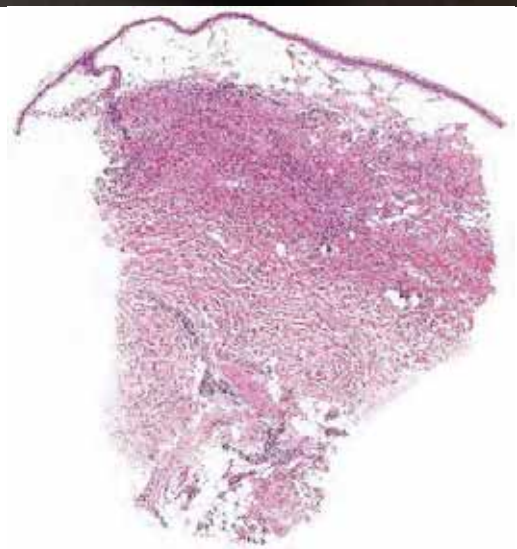
(a and b) Multiple brown reticulate pigmentary macules on labia minora and confluent brown plaques on labia majora with multiple epidermal inclusion cysts on inguinal area. (c) Typical filiform epidermal elongations of hyperpigmented rete ridges with a concentration of melanin at the tips (H and E, ×100)

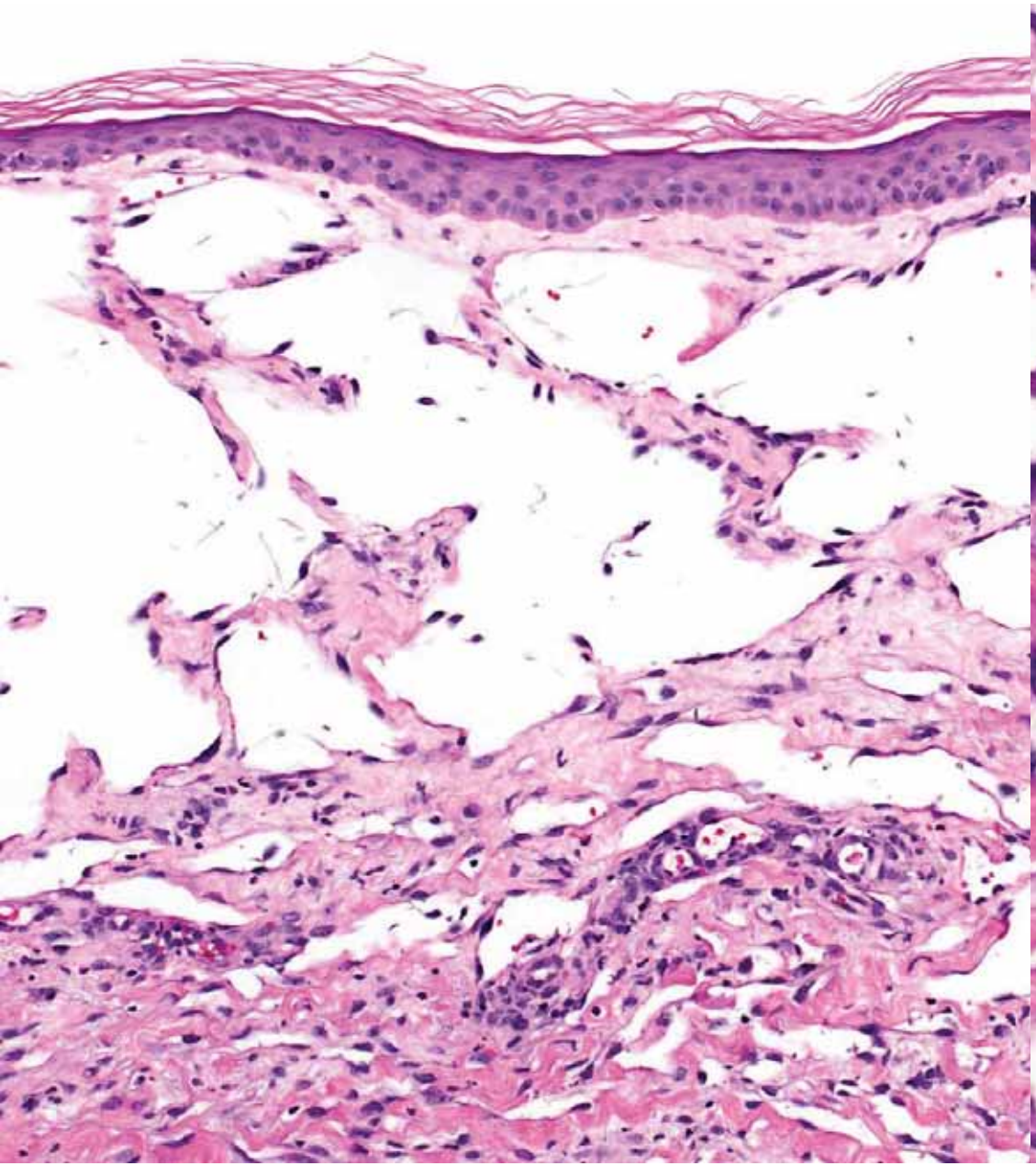


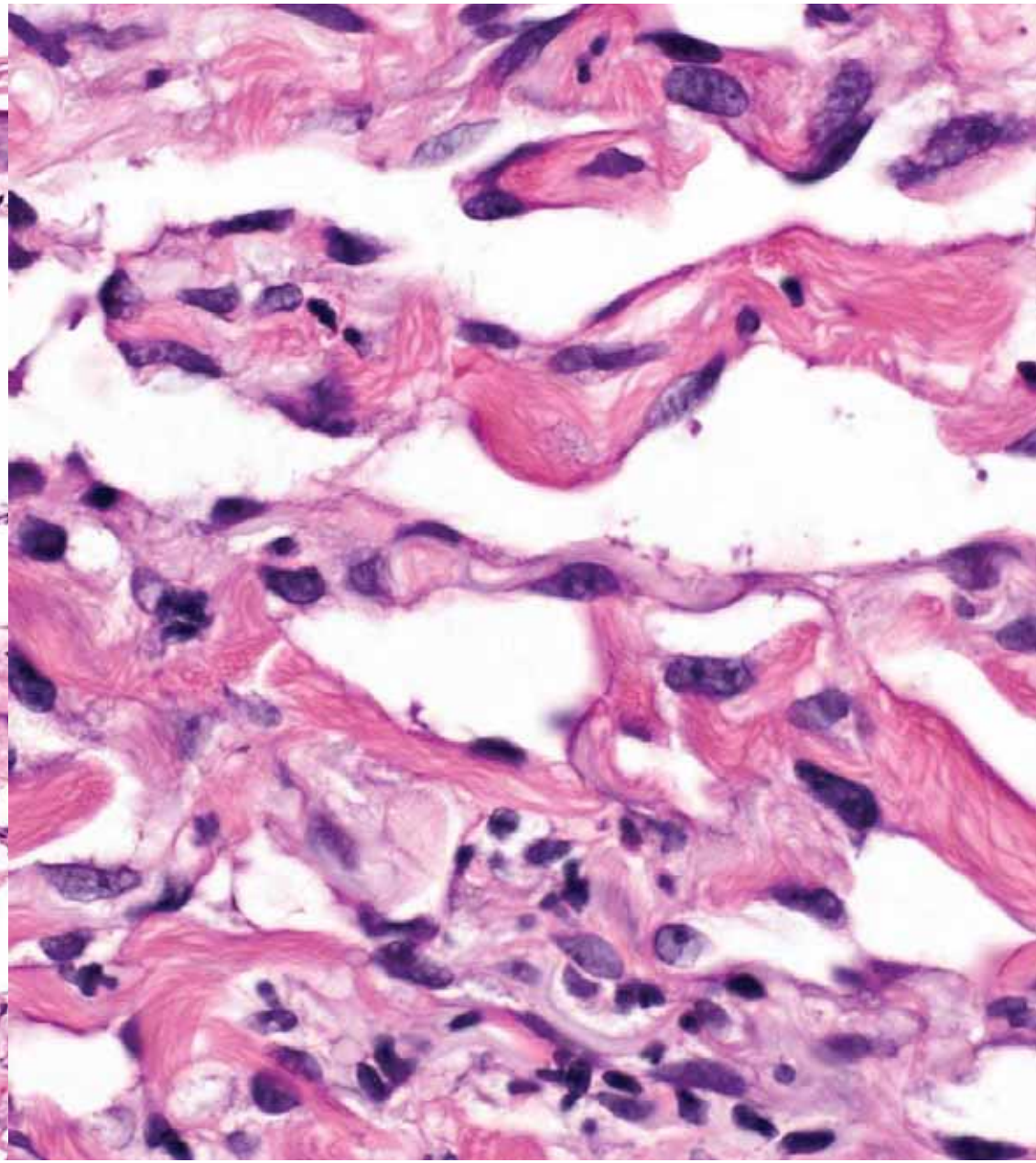
Case 7

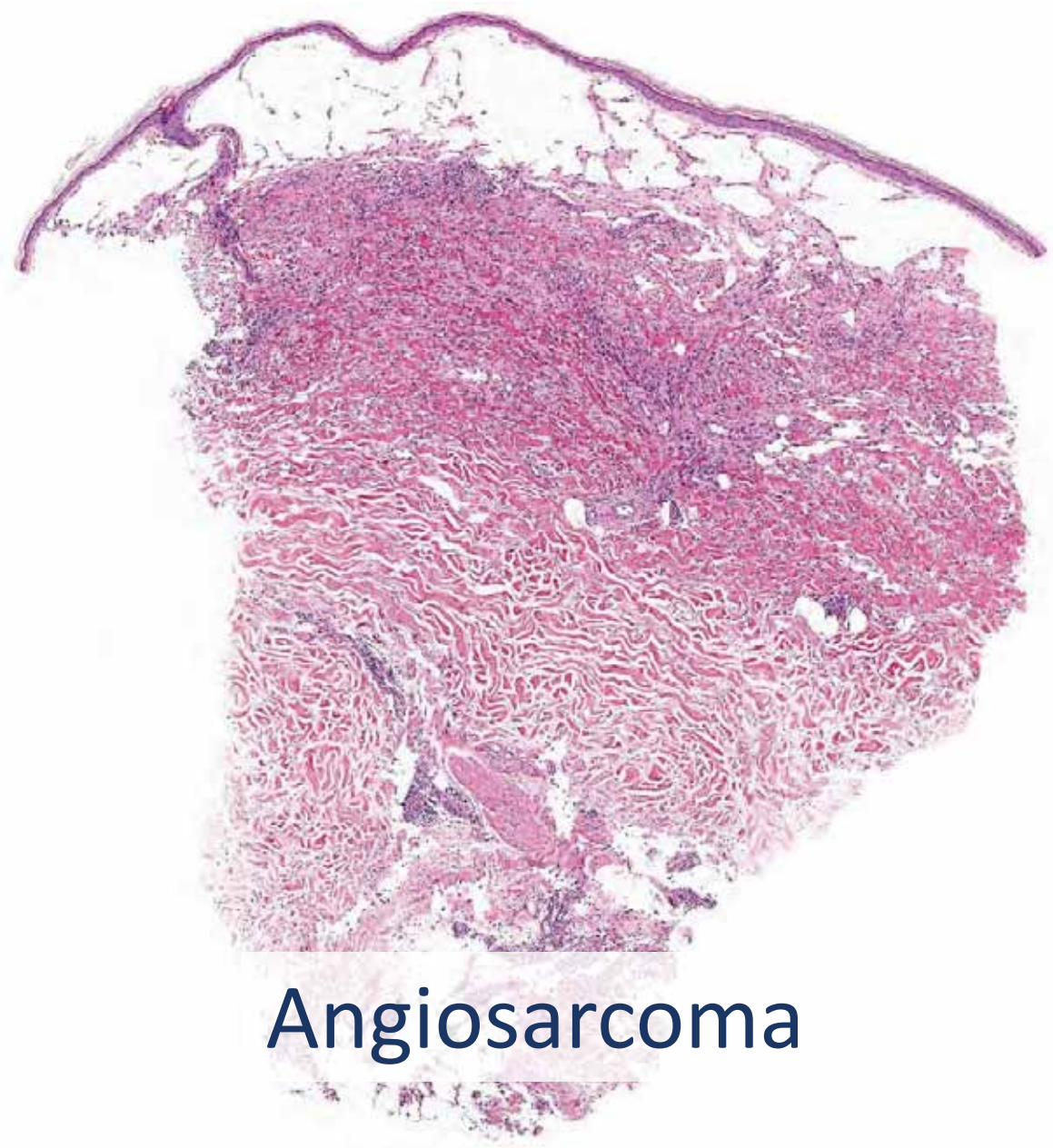
F, 89. Sent by a private dermatologist for evaluation of hemorrhagic, partly erosive lesions on the left lower leg and foot (unknown duration).

Admitted as in-patient and started on oral prednisone under a clinical diagnosis of bullous pemphigoid.

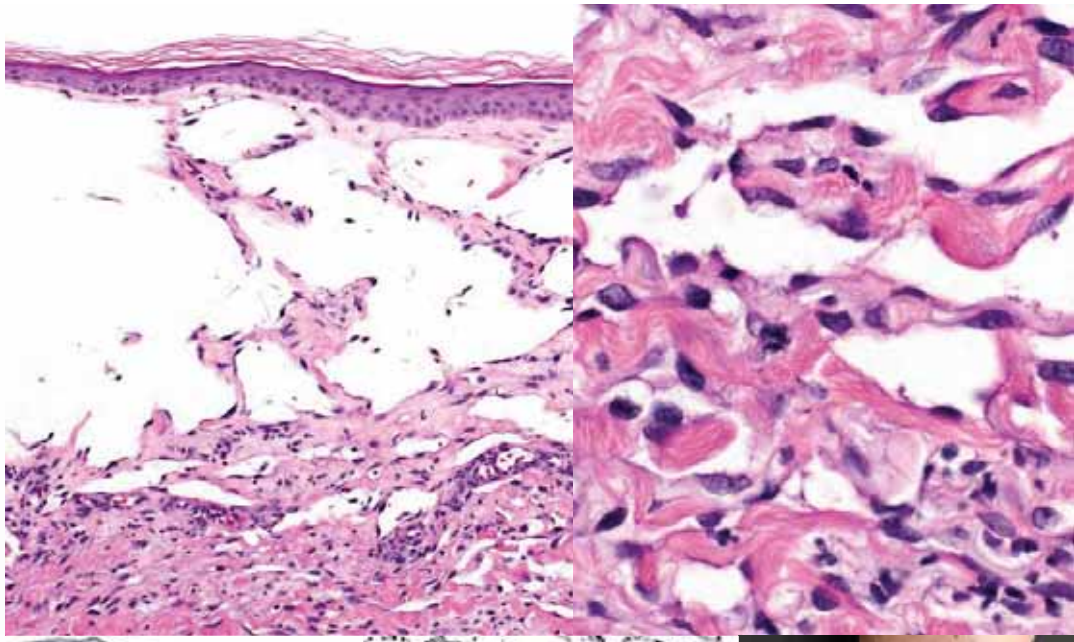


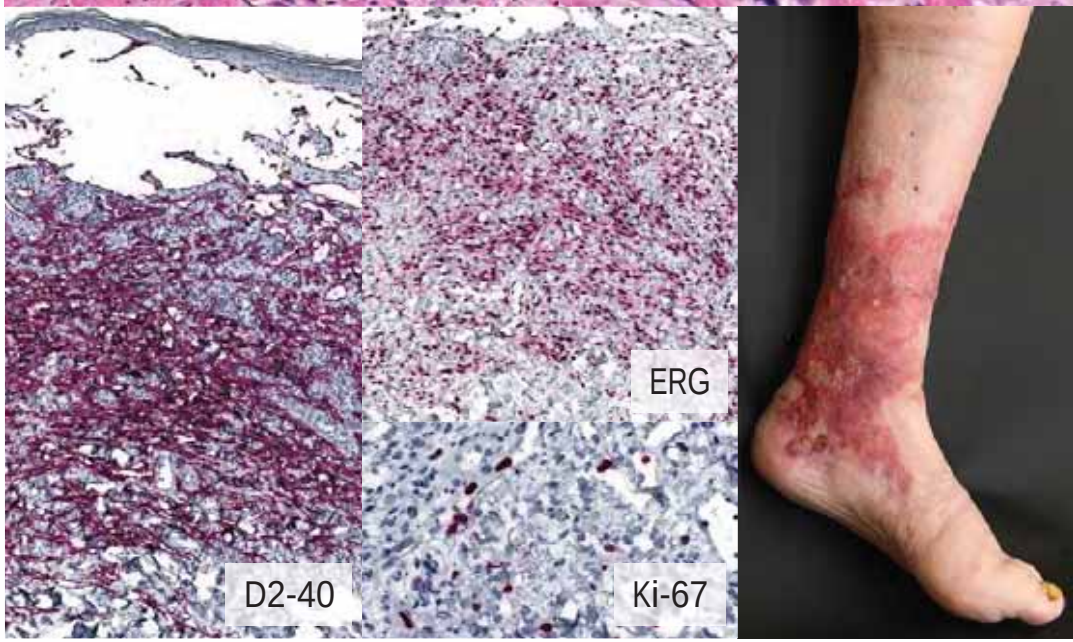




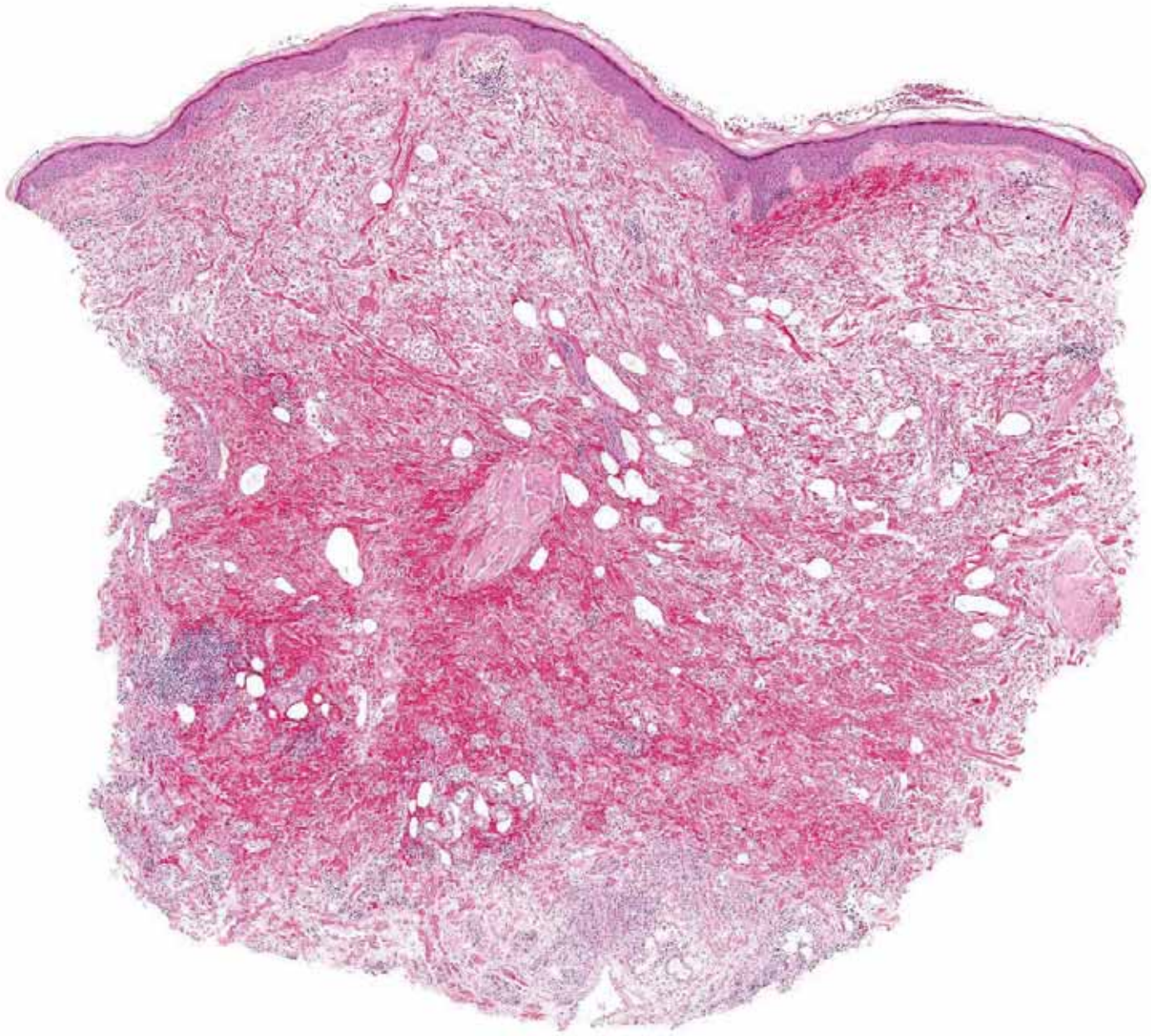


Angiosarcoma





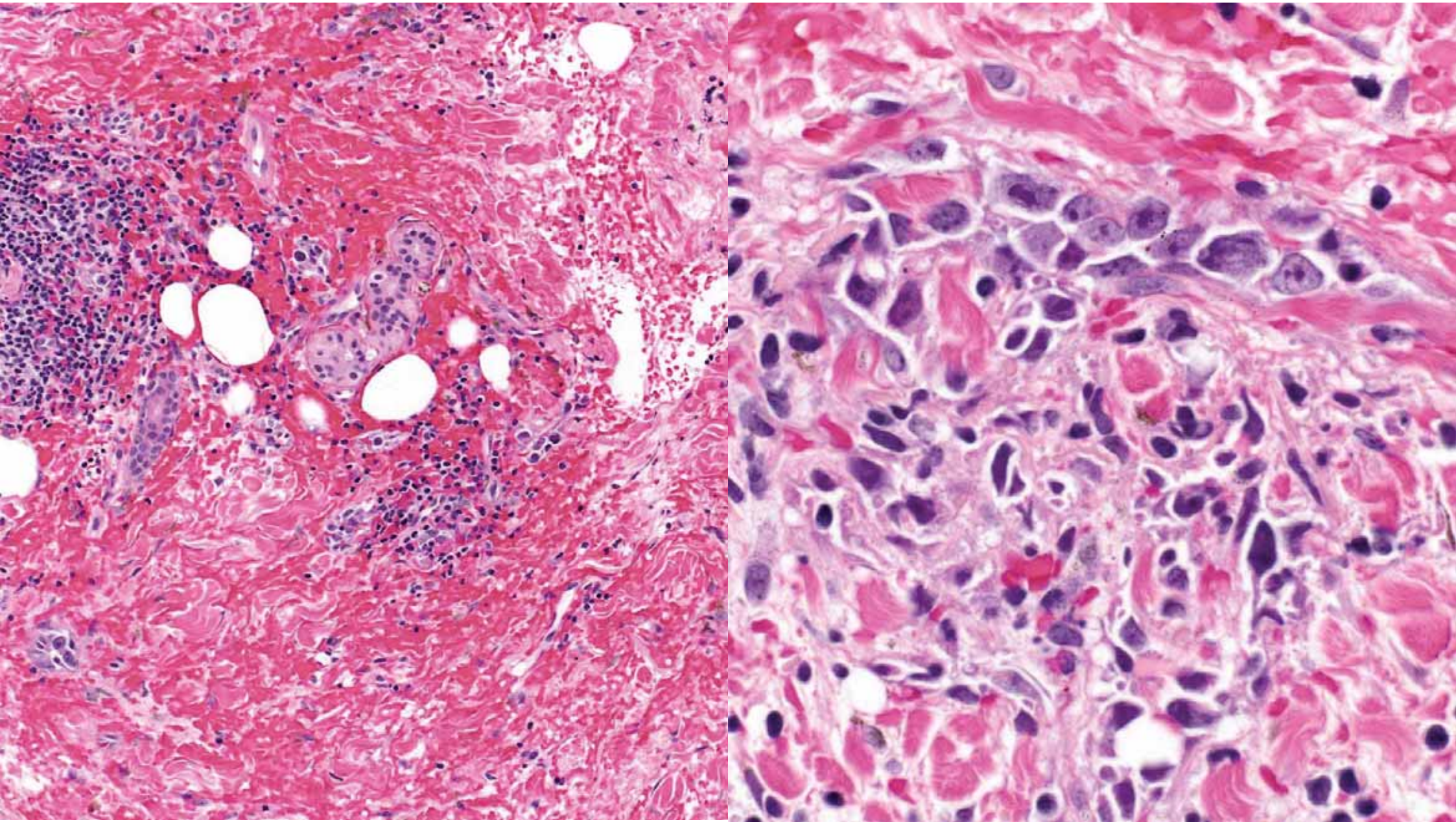
Erysipelas
Angiosarcoma
Bullous pemphigoid
Herpes zoster
DLBCL, leg-type



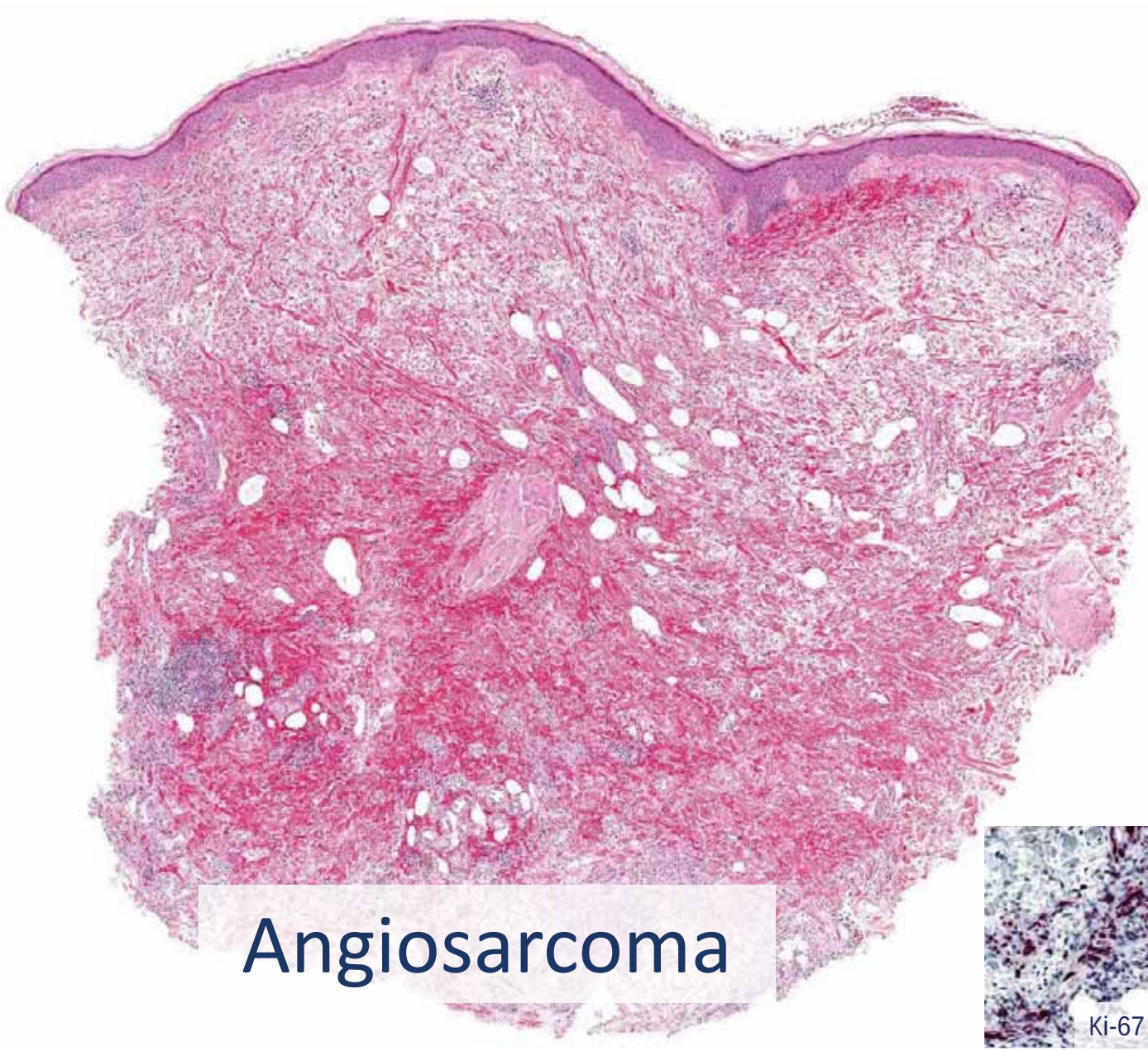
Case 8

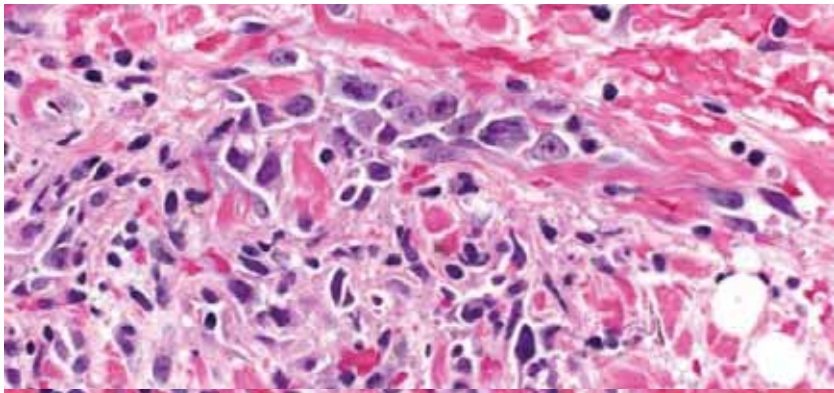
F, 71. Hemorrhagic skin lesion on the right arm for one month, not improving with compression; according to the patient similar hemorrhagic lesions also 1 year previously.

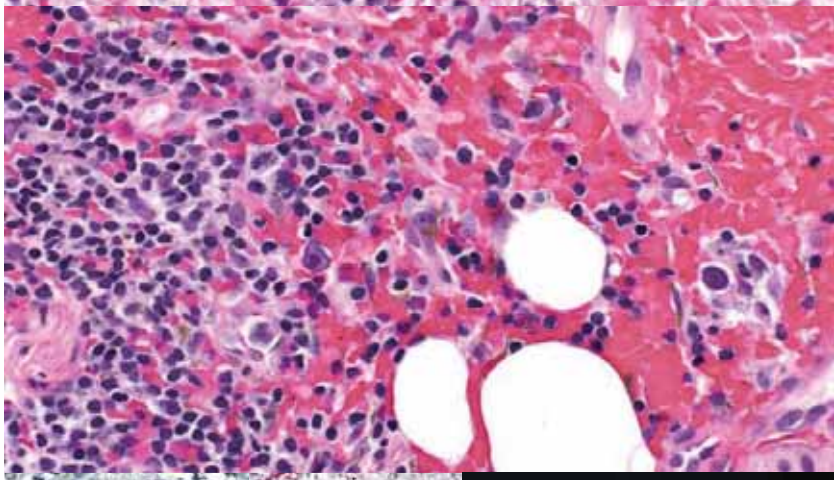
History of breast carcinoma 21 years before presentation.

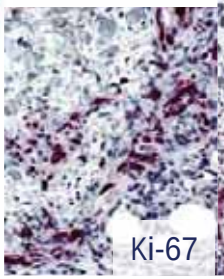


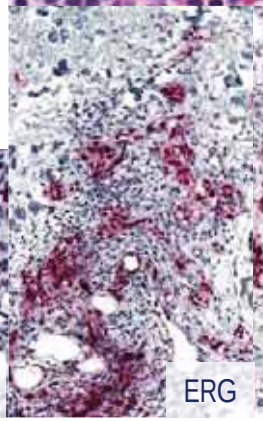
Angiosarcoma

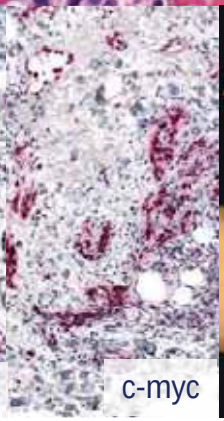


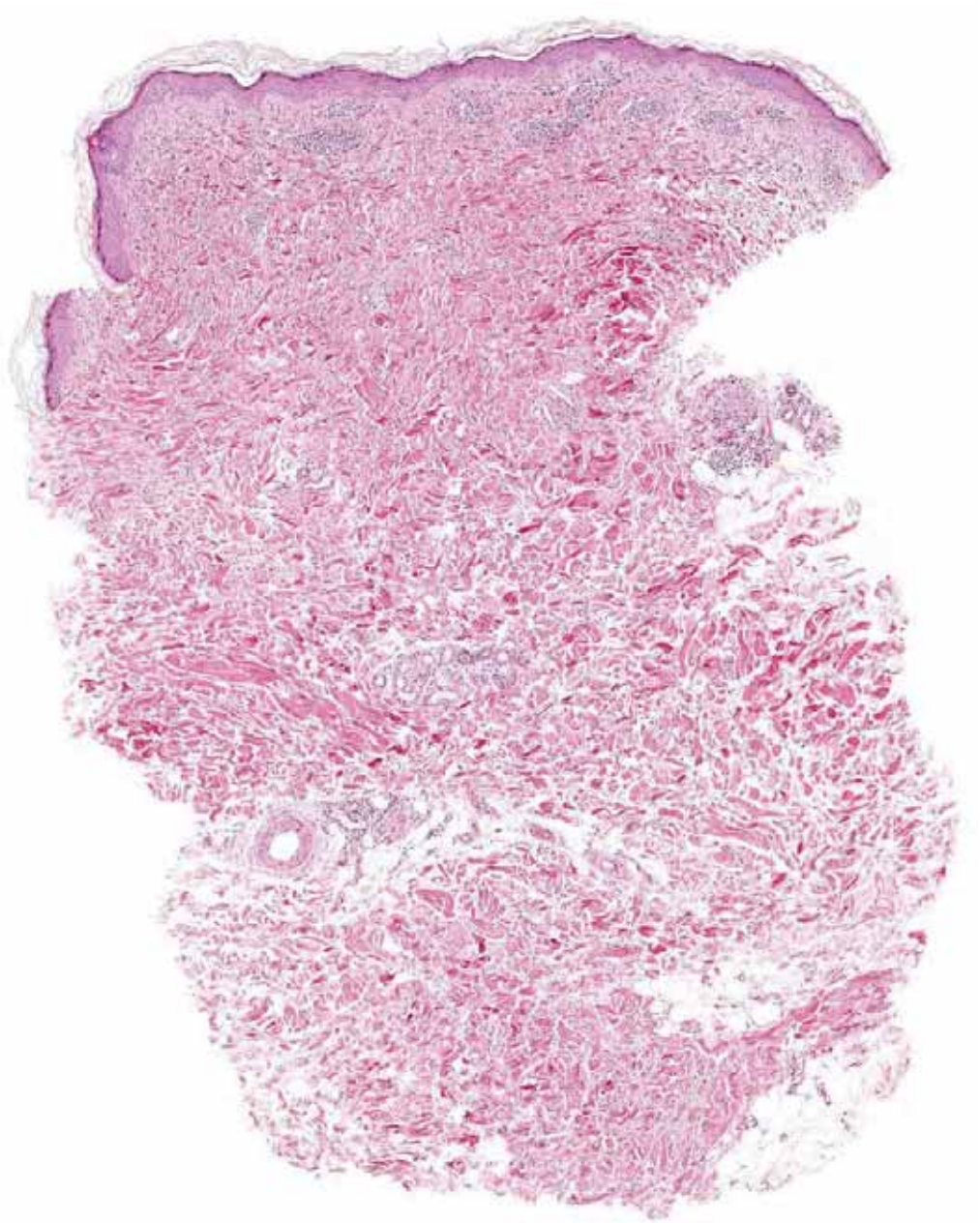










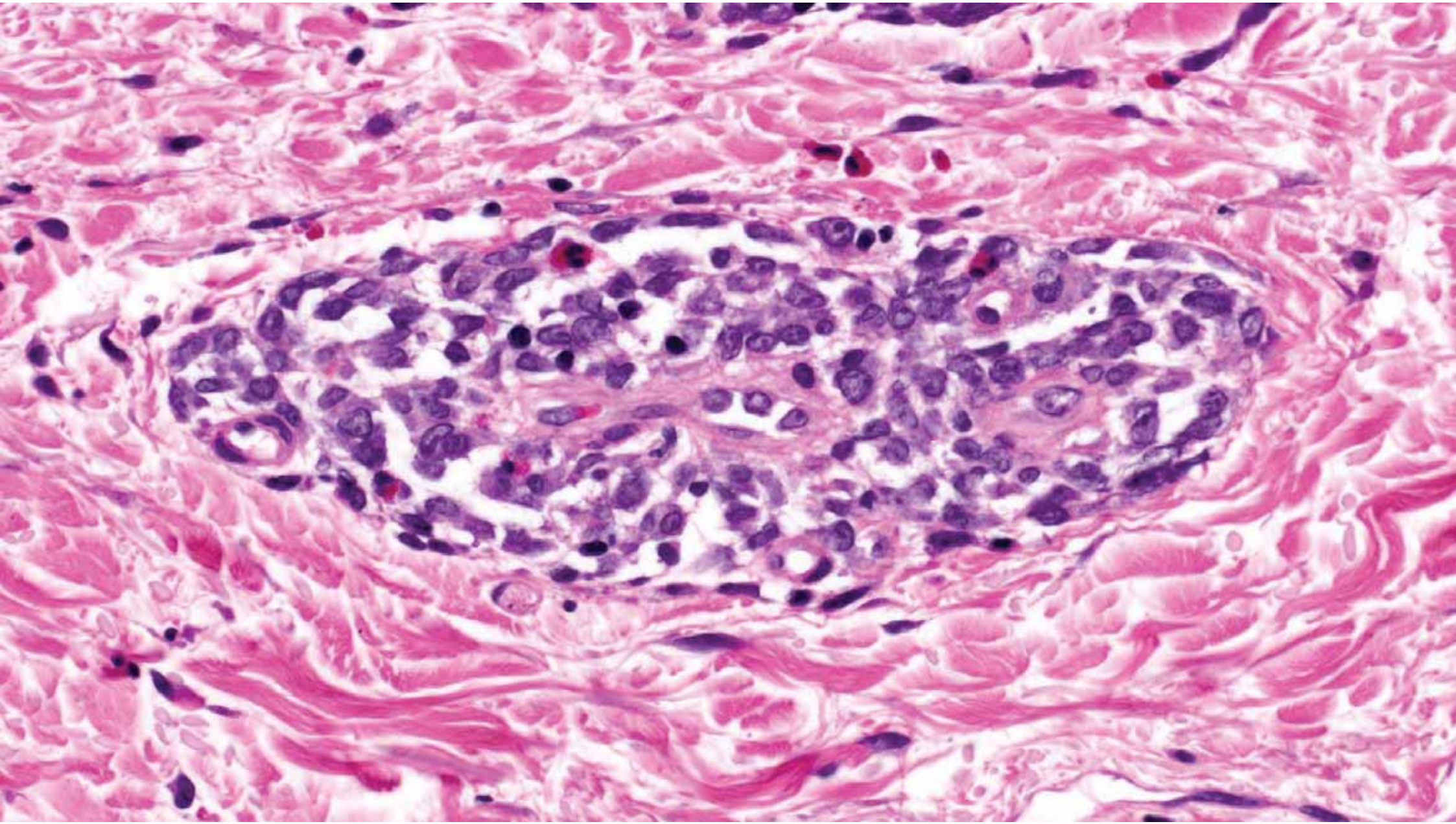


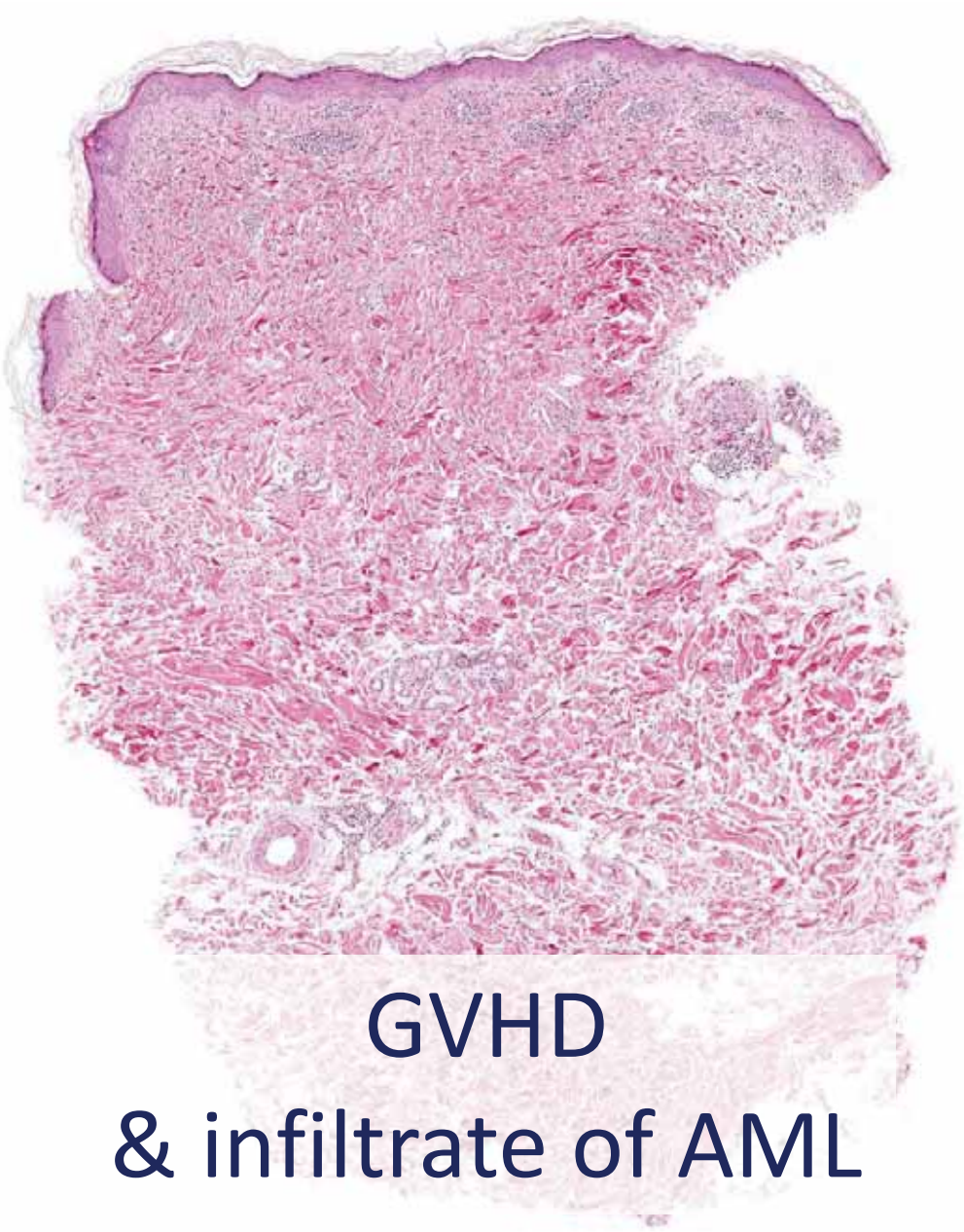
Case 9

M, 48. History of AML (myelodysplasia-associated; 1st diagnosis 6 months previously). Allogeneic stem cell Tx (day +53).

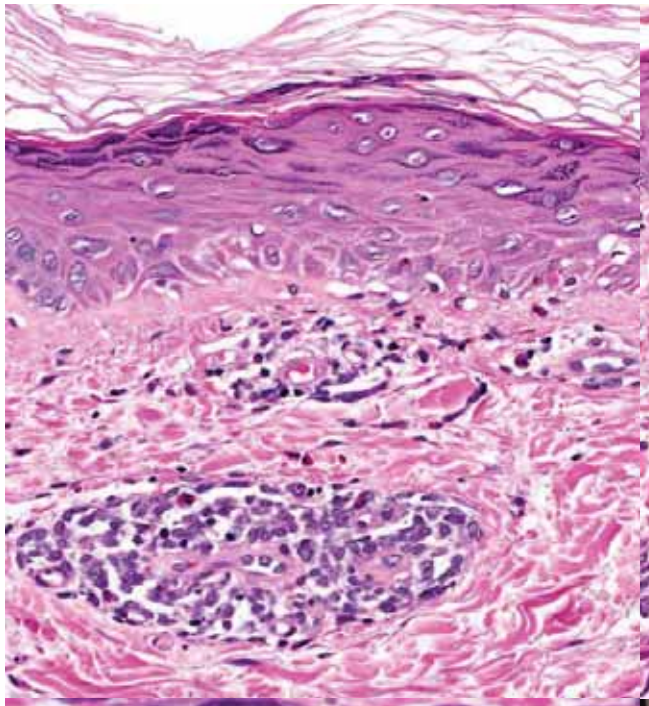
Itchy skin lesions for 7 days.

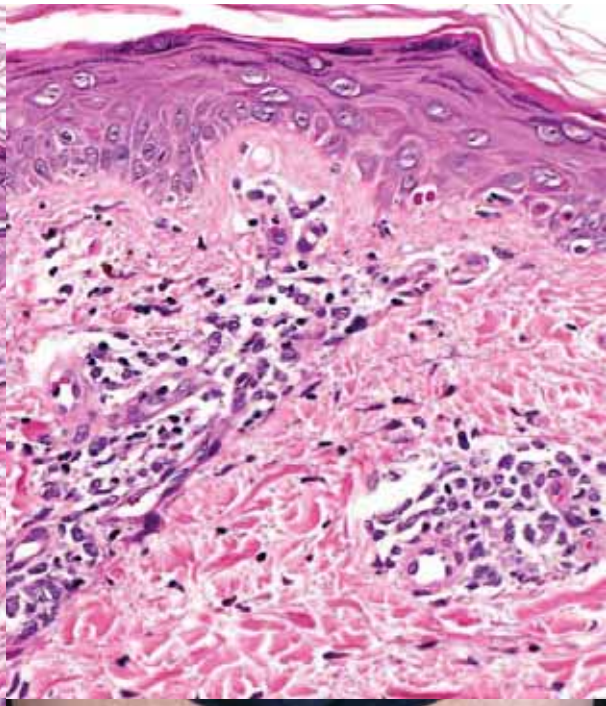
MR. BIG

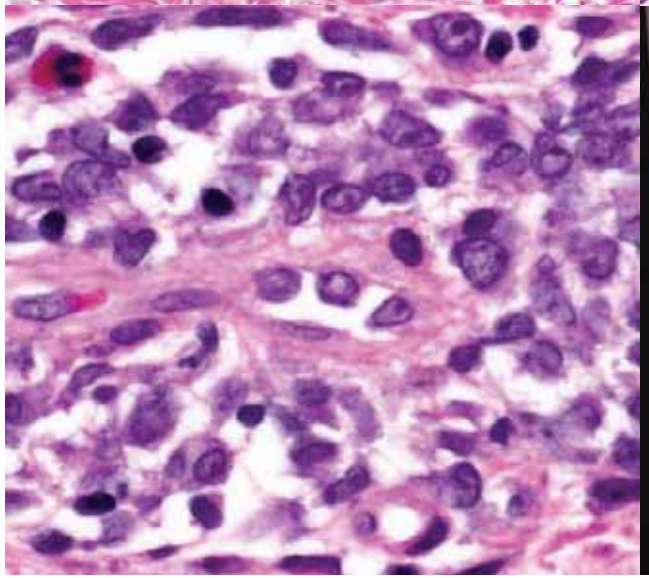




GVHD
& infiltrate of AML







J Cutan Pathol 1997: 24: 445–448
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Journal of
Cutaneous Pathology

Leukemic cells within skin lesions of psoriasis in a patient with acute myelogenous leukemia

Gisela Metzler[1], Lorenzo Cerroni[2], Helmut Schmidt[2], H. Peter Soyer[2], Heinz Sill[3] and Helmut Kerl[2]

[1]Department of Dermatology, University of Tübingen, Germany, and Department of [2]Dermatology and [3]Internal Medicine, University of Graz, Austria

We report on an 81-year-old man with acute myelo-monocytic leukemia (FAB M4) and a long-standing history of psoriasis. Biopsy of psoriatic plaques revealed the coexistence of characteristic histopathologic aspects of psoriasis together with an infiltrate of blasts with features of myelo-monocytes, suggestive of a specific leukemic infiltrate within plaques of psoriasis. Immunohistologic stainings showed positivity of blasts for LN2 (CD74), MT1 (CD43), and lysozyme, consistent with a myeloid lineage of these cells. To the best of our knowledge, this is the first report on the association of psoriasis with myelogenous leukemia. The presence of leukemic cells within psoriatic skin plaques may be explained by non-specific recruitment of recirculating malignant cells to the skin. Alternatively, as psoriasis is an inflammatory disease involving granulocytes among other cell types, it may be hypothesized that leukemic cells retain to some extent their capability to respond to physiologic stimuli and enter the skin in response to specific chemotactic factors.

Metzler G, Cerroni L, Schmidt H, Soyer HP, Sill H, Kerl H. Leukemic cells within skin lesions of psoriasis in a patient with acute myelogenous leukemia
J Cutan Pathol 1997: 24: 445–448. © Munksgaard 1997.

Lorenzo Cerroni, M. D., Department of Dermatology, University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria

Accepted February 21, 1997

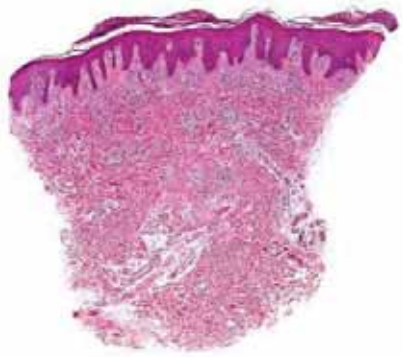
Specific skin involvement can be observed in more than 10% of patients with acute myelogenous leukemia (AML) (1). Clinical manifestations are usually characterized by generalized erythematous papules, plaques or nodules. Skin infiltrates may precede, be concomitant with or arise after leukemic blood involvement. We describe a patient with acute myelo-monocytic leukemia presenting with infiltrates of leukemic cells within skin lesions of psoriasis.

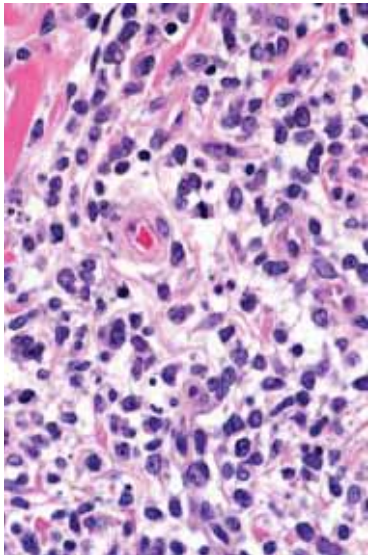
Case report

An 81-year-old man with a long-standing history of psoriasis localized to the elbows presented with increasing fatigue, anemia and leucocytopenia. Bone marrow examination showed diffuse infiltration of myelomonocytic blast cells positive for CD13, CD14, CD15 and CD33. According to these findings, a diagnosis of AML (FAB-M4) was made. Due to the advanced age no chemotherapy was administered, and the patient was followed-up at short intervals.

At the same time, the patient experienced a sudden generalization of psoriasis with manifestations on previously uninvolved skin such as the trunk and both lower extremities (Fig. 1). In order to rule out uncommon skin infiltrates of myelo-monocytic leukemia, three 4-mm punch biopsies were obtained from lesions on both lower legs. Specimens were fixed in 4% buffered formalin and embedded in paraffin for routine histopathologic and immunohistochemical studies.

Histopathology. All three skin biopsies revealed similar histopathologic features. The epidermis showed a marked psoriasiform acanthosis (Fig. 2). Neutrophils could be observed within both the epidermis and a parakeratotic horny layer. Dermal papillae were elongated and characterized by the presence of dilated, tortuous blood vessels (Fig. 2). In the upper dermis there was a relatively dense infiltrate composed of lymphocytes and histiocytes mingled with numerous medium-sized and large atypical mononuclear cells (Fig. 3). Cytomorphology of atypical cells was characterized by irregular nuclei with prominent nucleoli and





Case report

Sweet dermatitis-like leukaemic infiltration in a patient with myelodysplastic syndrome

E. Papadaki, I. Panayiotidis,* A. Katsalis, V. Papas, I. Vermeulen† and S. Stavrianos

Summary We report a case of leukaemia cutis presenting as sweet dermatosis-like eruption in a patient with myelodysplastic syndrome progressing to acute undifferentiated leukaemia.

Cutaneous lesions in leukaemia are classified into specific and non-specific, based on their histopathological characteristics. Specific lesions are considered to be those directly caused by the presence of neoplastic cells in the skin and termed leukaemia cutis. These lesions are indicative of an unfavourable prognosis of leukaemia and carry a poor prognosis. Leukaemia cutis may mimic inflammatory skin disorders. These diagnostic difficulties are considered in patients with haematological malignancies and unusual cutaneous lesions.

[...] types of leukaemias are investigated in the skin-producing cutaneous infiltrate known as leukaemia cutis. Leukaemia cutis is found in 10–30% of patients with acute myelogenous leukaemia (AML). Leukaemia cutis is associated with poor survival in myelodysplastic syndrome (MDS).

Report

[...]-year-old Greek man was referred to our dermatology department with a multifocal proliferation of several violet skin[...]

Figure 1 Leukaemic infiltration in the forearm (e.g. resembling sweet syndrome).

[...] Correspondence: S. Stavrianos. Address: Medical Department of Haematology and Haematology Laboratory of Athens General Hospital, Athens, Greece. E-mail: [...]

[...] Accepted for publication [...] July 2003

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Clinical and Experimental Dermatology

LETTER TO THE EDITOR

Leukaemia cutis limited to the needle puncture sites

Dear Editor,

Leukaemia cutis is a localized or disseminated skin infiltration by leukaemic cells. An early and accurate identification of leukaemia cutis is important as it implies poor prognosis.[1] Although the incidence of leukaemia cutis in sweet-[...]

Figure 1 Multiple painless, 1–2.5 cm, violaceous plaques localized with cutaneous lymphoma arranged in a linear fashion.

Aggressive presentations, following a rapidly fatal clinical course, be [...] as a result of disease progression and associated complications such as acute renal failure and post-[...] haemorrhage.

Patient [...] have manifested first leukaemic infiltration one week or more from mechanical or surgical trauma and from [...] injection points. The mechanism of tumour cell implantation and proliferation at the needle puncture site is not clear. The release of chemotaxis factors such as interleukin (IL)-1 and [...] activating factors including IL-3, IL-6, granulocyte-macrophage colony-stimulating factor from the injured and activated keratinocytes has been suggested to enhance adherence and chemotaxis as well as malignancy of the leukaemic cells at the traumatized site.[2]

Correspondence: Young Mee Kim, M.D., Department of Dermatology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea. E-mail: [...]

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Acta Dermato-Venereologica

CLINICAL REPORT

Myeloid Sarcoma Developing in Pre-existing Pyoderma Gangrenosum

[...] Department of Dermatology, Ohara Hospital, Fukuoka, Japan

We report here a case of pyoderma gangrenosum in a patient with acute myelogenous leukemia (AML) who developed myeloid sarcoma in a site of keratinocytic lesion during chemotherapy. The patient was treated successfully with intensive chemotherapy and achieved complete remission, and her extensive pyoderma lesions improved to scar. This is the first reported case of myeloid sarcoma [...] in pyoderma gangrenosum, and it [...] the [...] of pyoderma gangrenosum, and it [...] in [...] of [...] myeloid sarcoma. Key words: myeloid sarcoma; pyoderma gangrenosum; myelogenous leukemia.

(Accepted September 27, 2000.)

Acta Derm Venereol 2001; 81: 374–375

[...] Department of Dermatology, Ohara Hospital, Fukuoka, Japan. E-mail: [...]

Myeloid sarcoma (MS) is an extramedullary tumour consisting of [...] immature myeloid cells, also used as synonyms granulocytic sarcoma and chloroma. Clinically it presents either as [...] or [...] tumour in young adults and children and rarely frequent in men.[1]

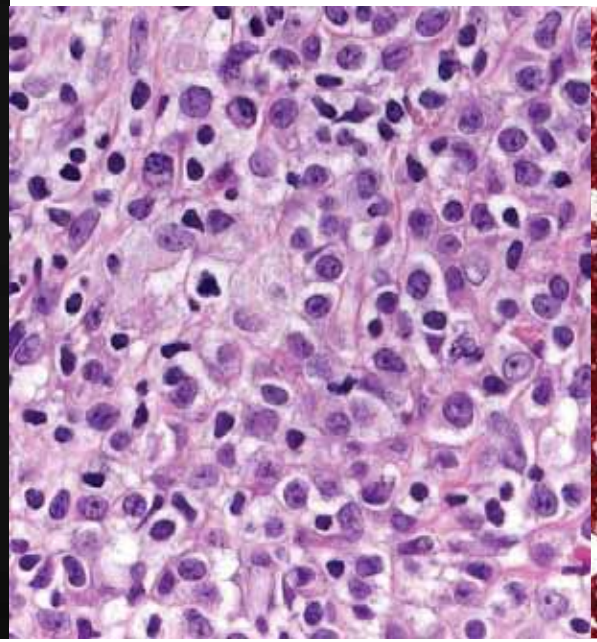
We describe here a patient with pyoderma gangrenosum (PG) [...] in MS at the time of [...] transformation of myelodysplastic syndrome (MDS) into acute myeloid leukaemia (AML).

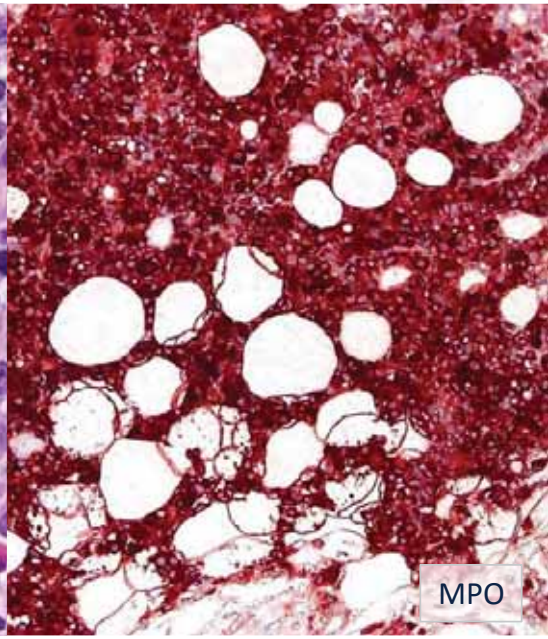
CASE REPORT

A 63-year-old woman with a history of rheumatoid arthritis, secondary to [...] was referred to the department of dermatology due to several round ulcers [...] in the forearm (Fig. 1). The ulcers had developed in [...] during the previous 6 months, and PG was suspected [...]. A biopsy showed [...] with a mixed cell infiltration [...] neutrophils, lymphocytes, histiocytes, but also including [...] cells with [...] nucleoli with an [...] of myeloblast (Fig. 2). These histopathological findings were compatible with the diagnosis of MS. The [...] were treated with [...] and topical steroids. Treatment of concomitant anaemia [...] with [...] [...] and the patient was diagnosed with [...] cells 36.1%, blasts [...] myeloid [...] with [...] blasts, FAB [...] positive for CD117 and negative for CD34.

Due to progression of the ulcers after an initial response, she was transferred to the [...] for [...] 3 months later. The ulcers were described as [...] skin lesions with a border [...] the [...] had [...] [...] (Fig. 3). The ulcers were very painful and [...] under general [...] Bone marrow biopsies showed granulocytic [...] with [...] [...] (20/417, 4.8%), [...] and myelocytes [...] (20/417, 4.8%), [...] (20/417, 4.8%), [...] (20/417, 4.8%), [...] and CD117, respectively (Fig. 4). A second bone marrow [...] showed [...] [...] with [...] AML with 16% myeloblasts with a [...] karyotype. The [...] [...] Wilms' Tumour Antigen 1 (WT1) [...] by polymerase chain reaction in both [...] at [...] [...] [...]

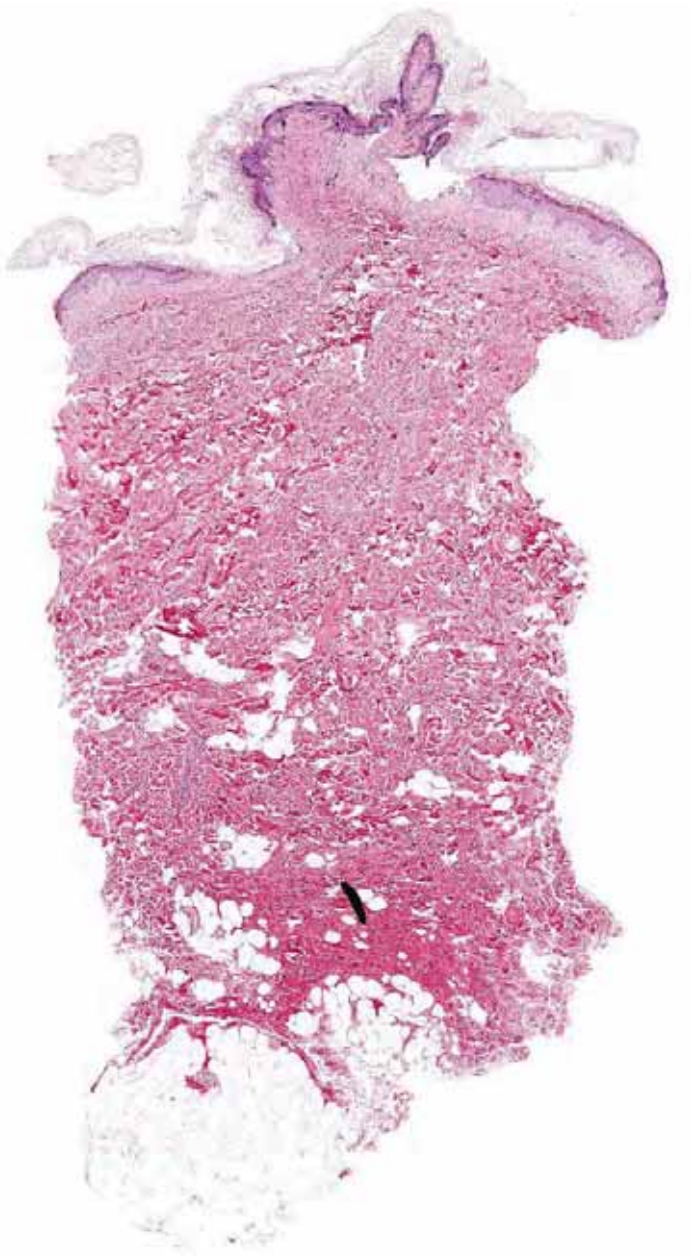
M, 67.
History of nodal FCL (1999) with progression (2003), treated with R-CHOP. MDS (2014), evolution into AML (2015). Best supportive care.
Herpes zoster cervico-thoracal dx (2015).
No improvement under anti-viral treatment (lesions become more infiltrated).





AML & other skin disorders

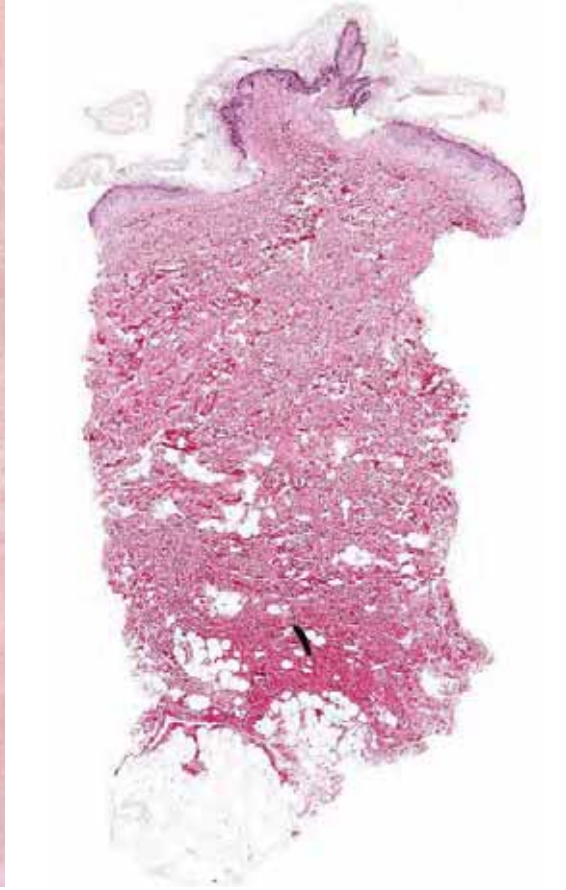
- In contrast to B-CLL, skin infiltrates of myelogeneous leukemia are seen uncommonly at the site of skin inflammation
- Relationship between Sweet syndrome (particularly "histiocytoid" Sweet syndrome) and myeloid leukemia likely; specific cells demonstrated in a number of cases
- In some cases, Sweet syndrome-like infiltrates may represent a mimicker rather than a colonization of genuine Sweet syndrome by leukemic cells

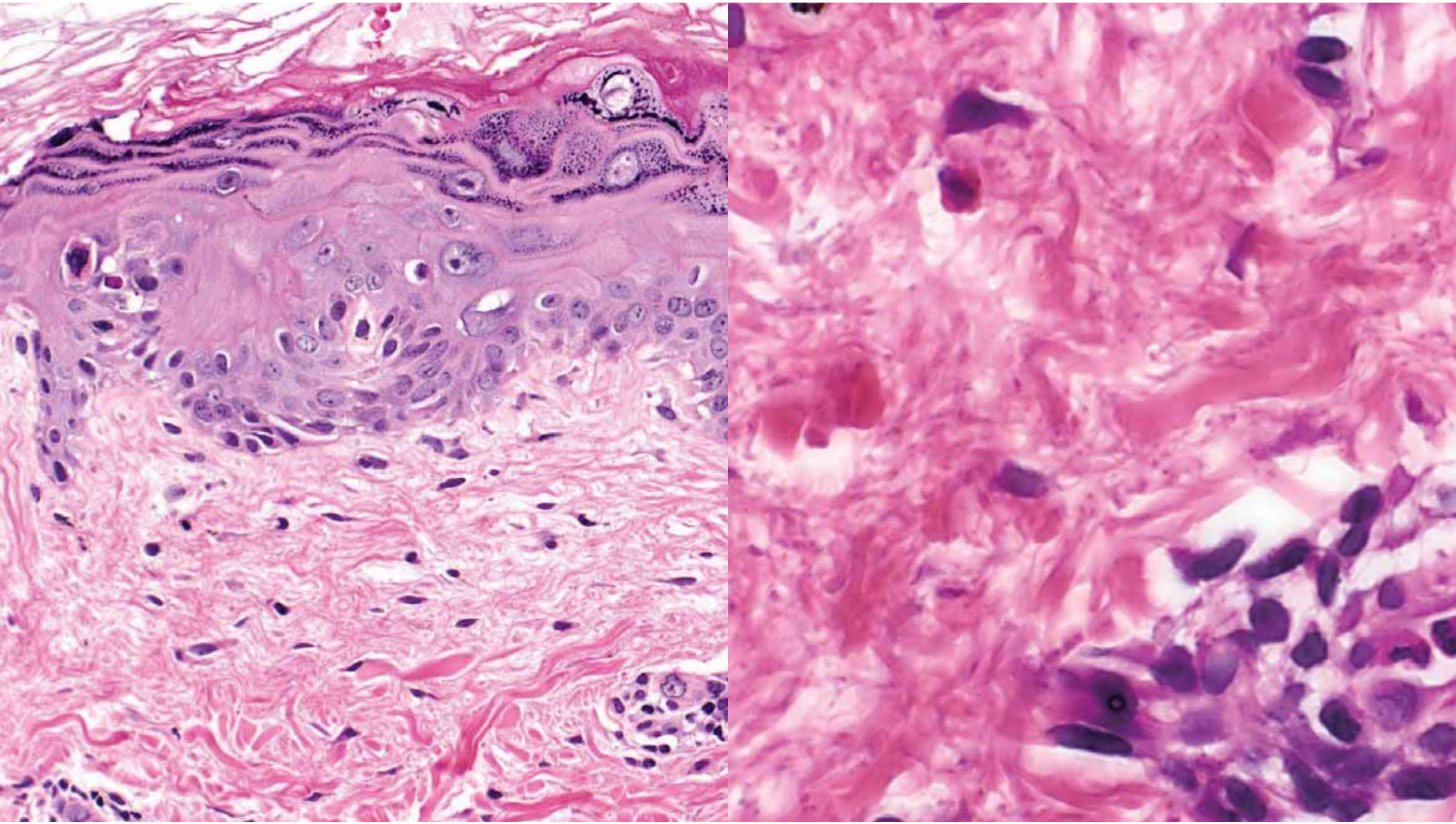


Case 10

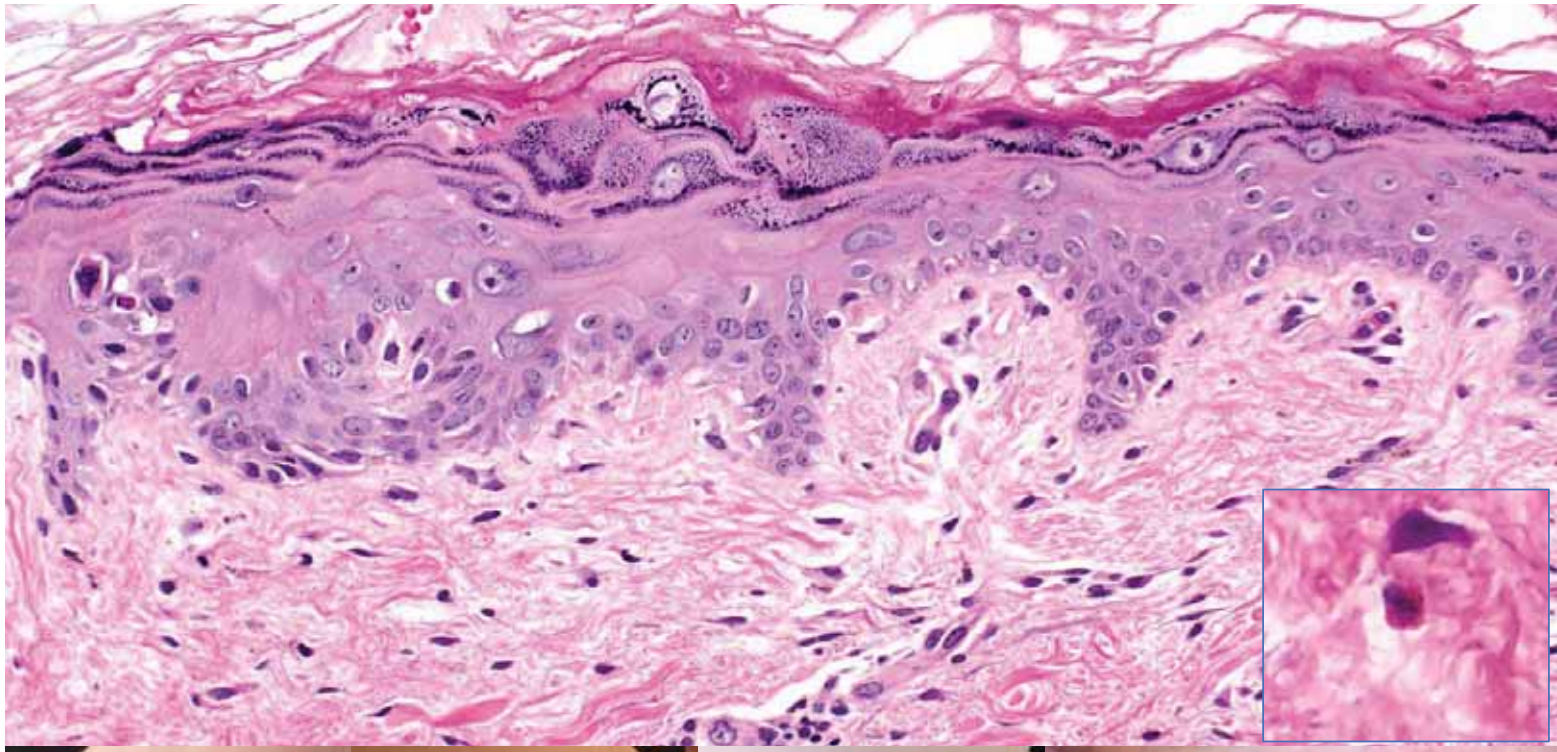
F, 54. History of AML with *NPM1* mutation 18 months before presentation; allogeneic stem cell transplantation (day +43).

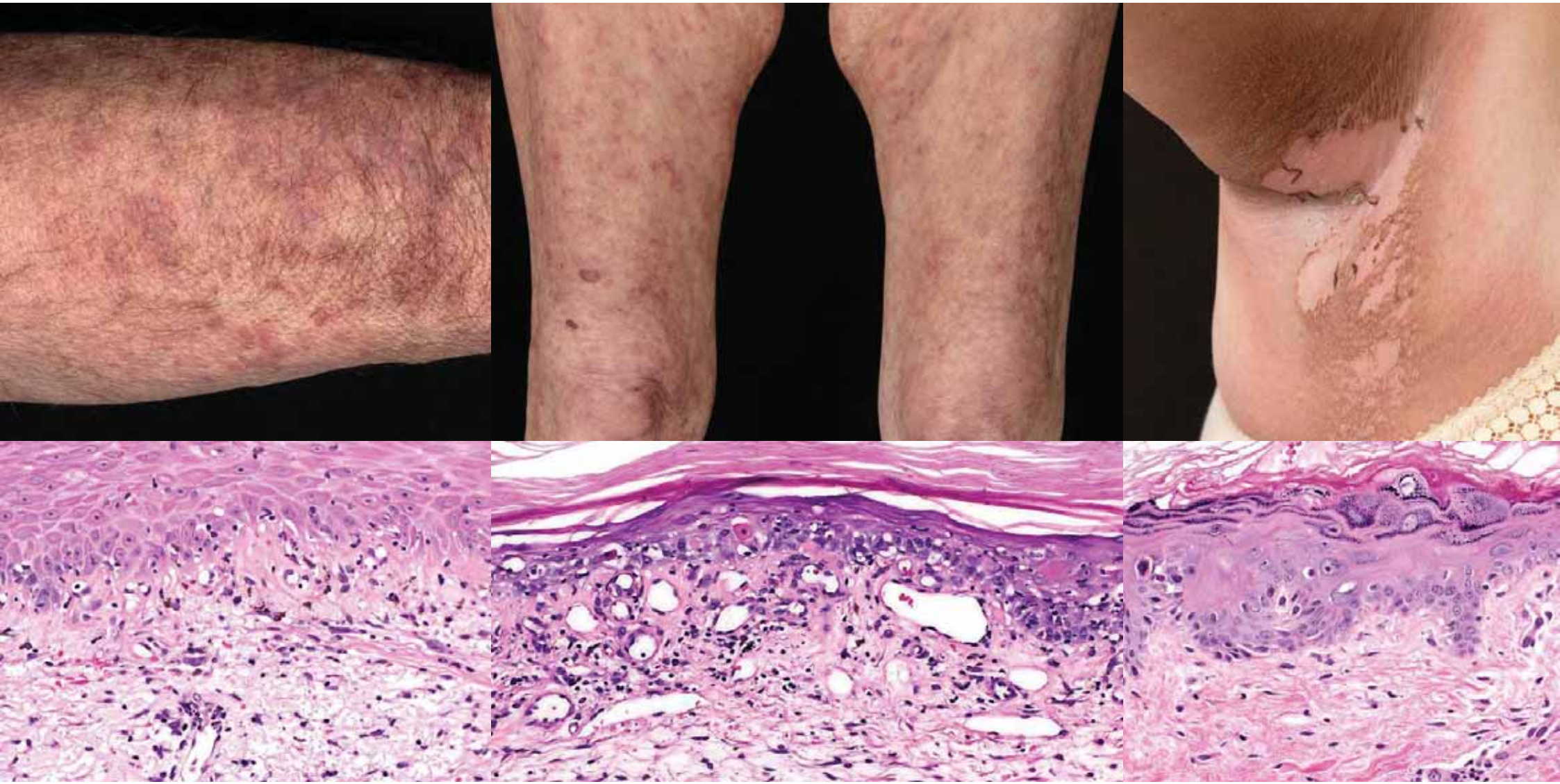
Suspicion of cutaneous and gastrointestinal GVHD (grade 1); skin lesions present for approximately 2 weeks.





SDRIFE
(& GVHD)

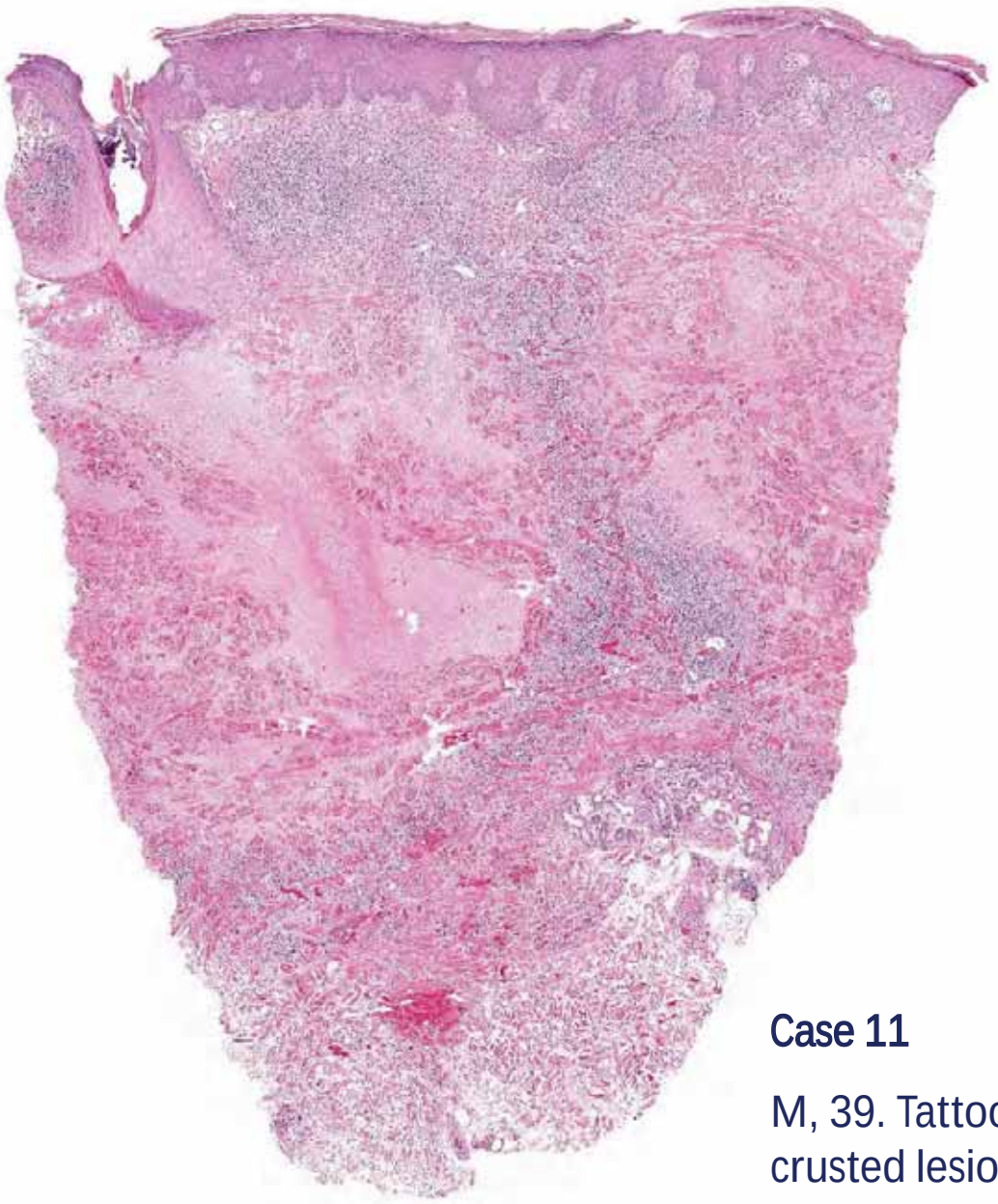




GVHD, LE-like

GVHD, erythema multiforme-like

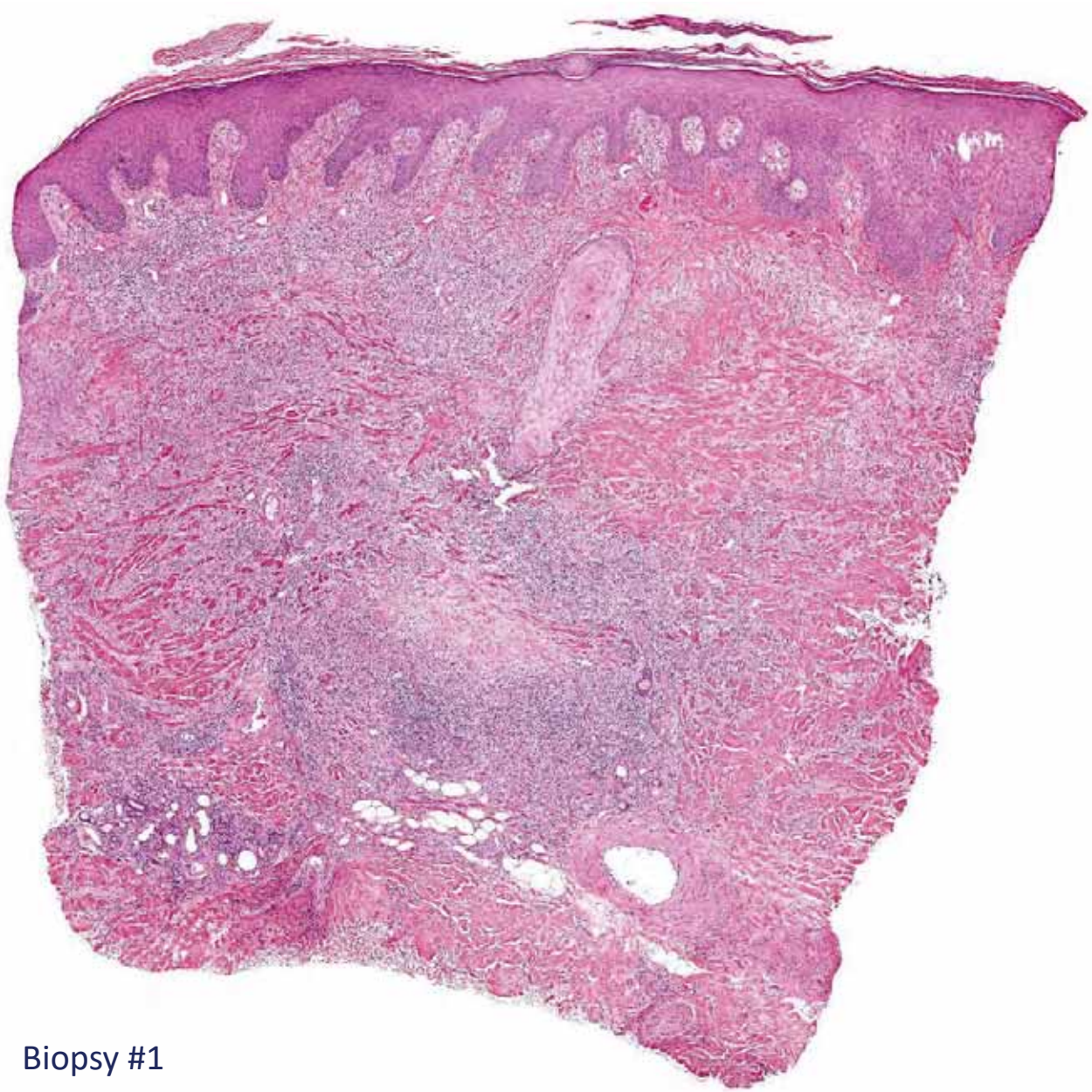
GVHD & SDRIFE



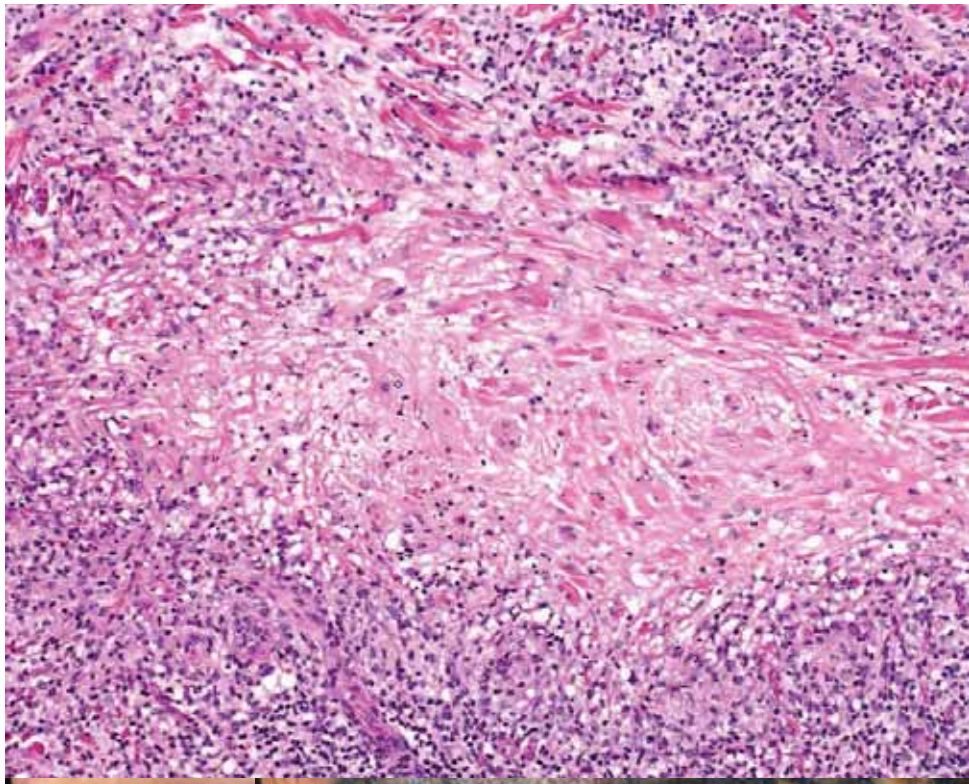
Case 11

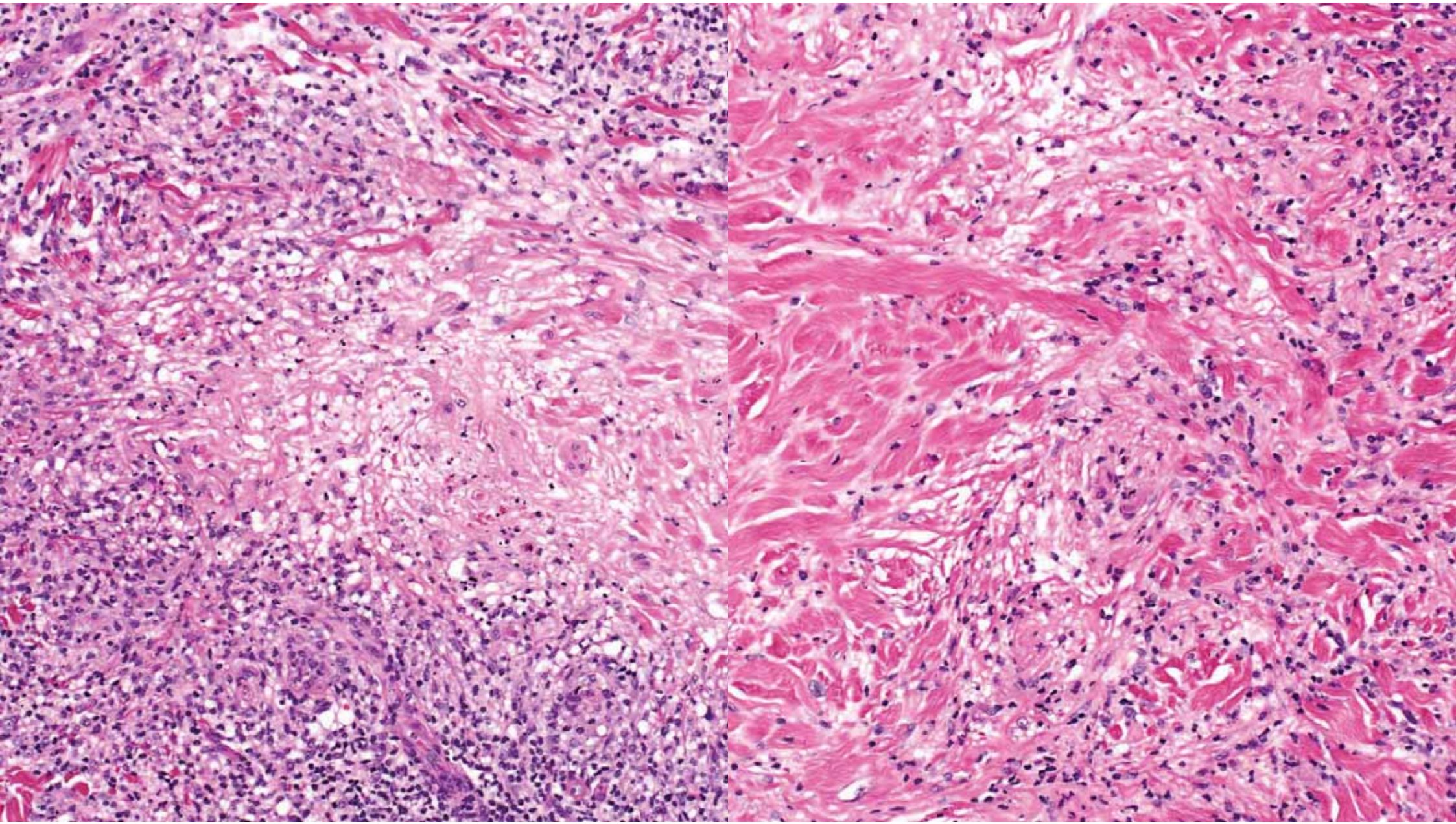
M, 39. Tattoo done >10 years previously. According to the patient partly crusted lesions for the last months, arising in areas tattooed with red color.

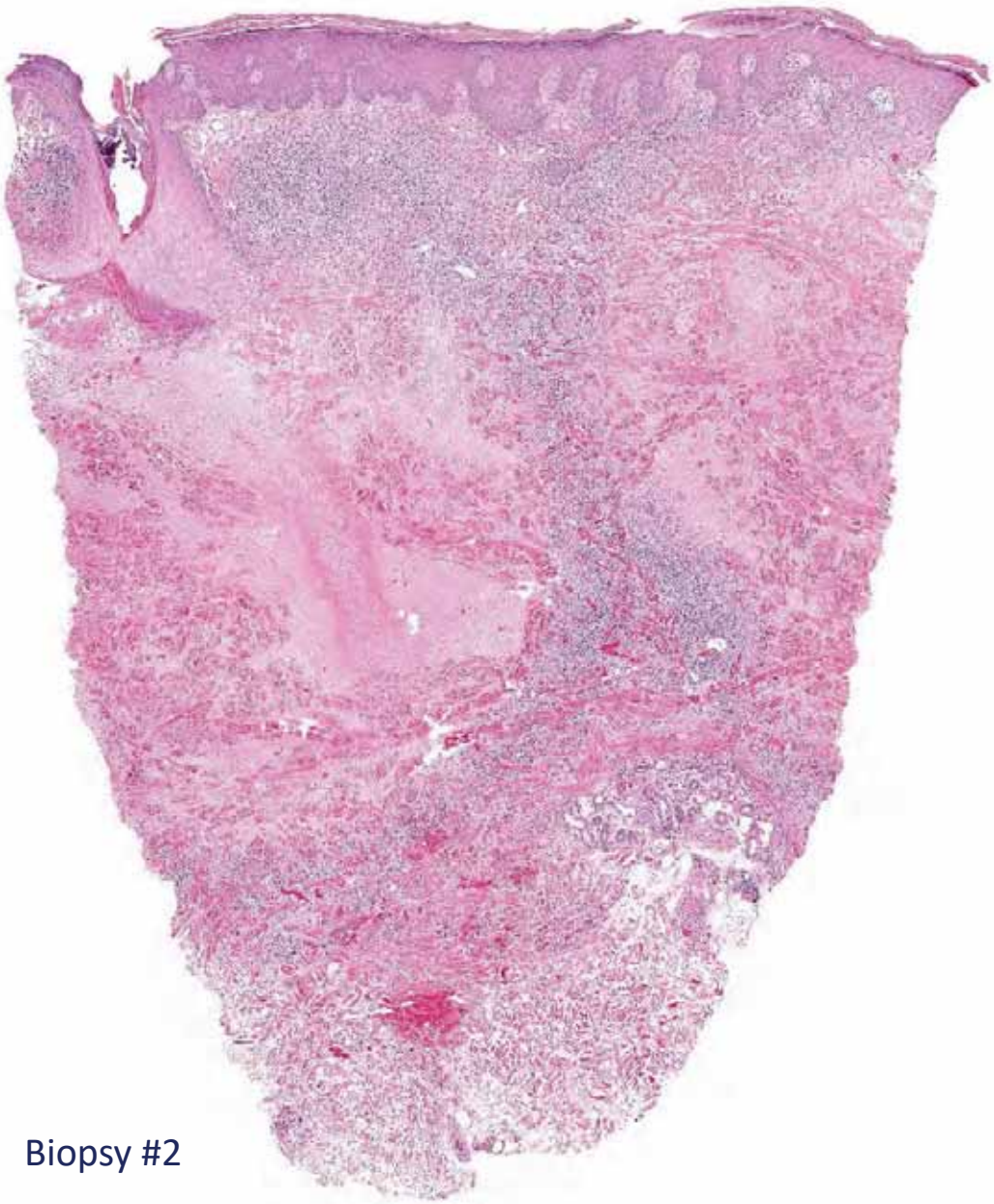
FEUERWEH



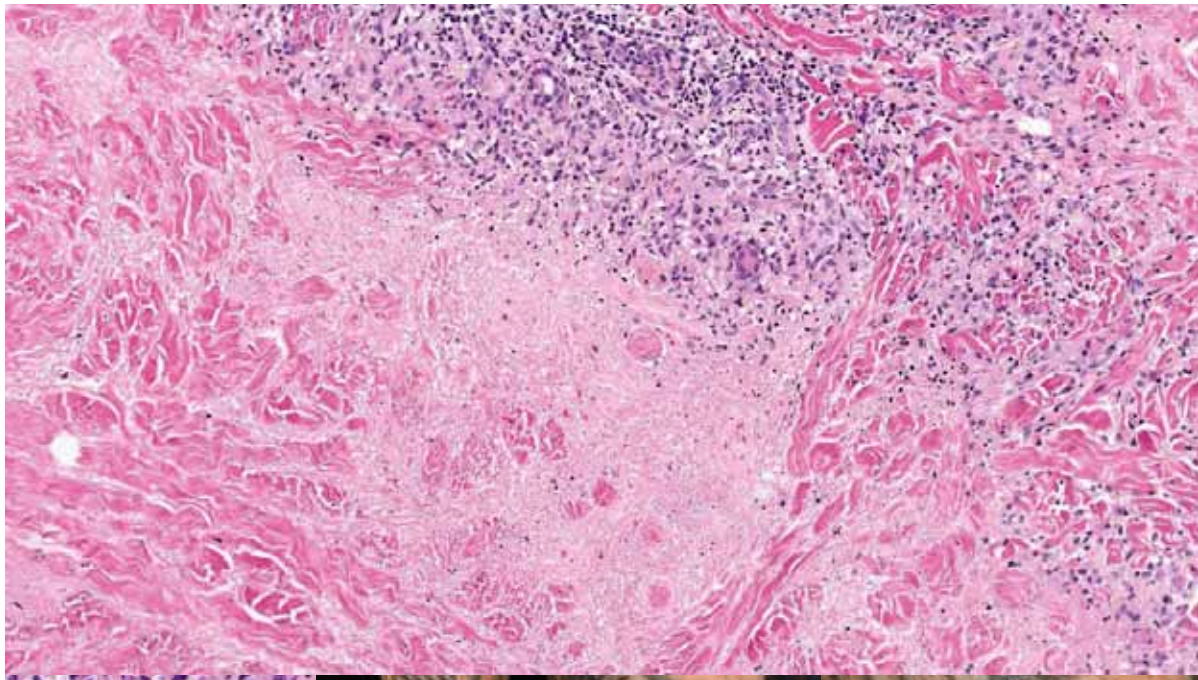
Biopsy #1

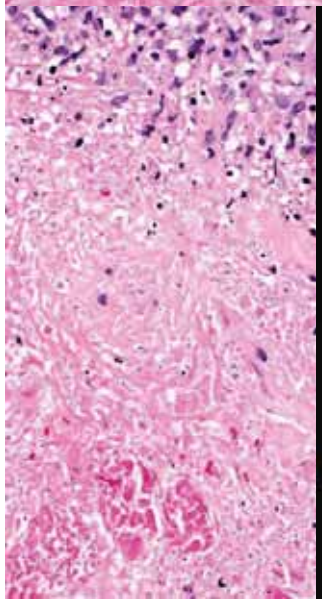


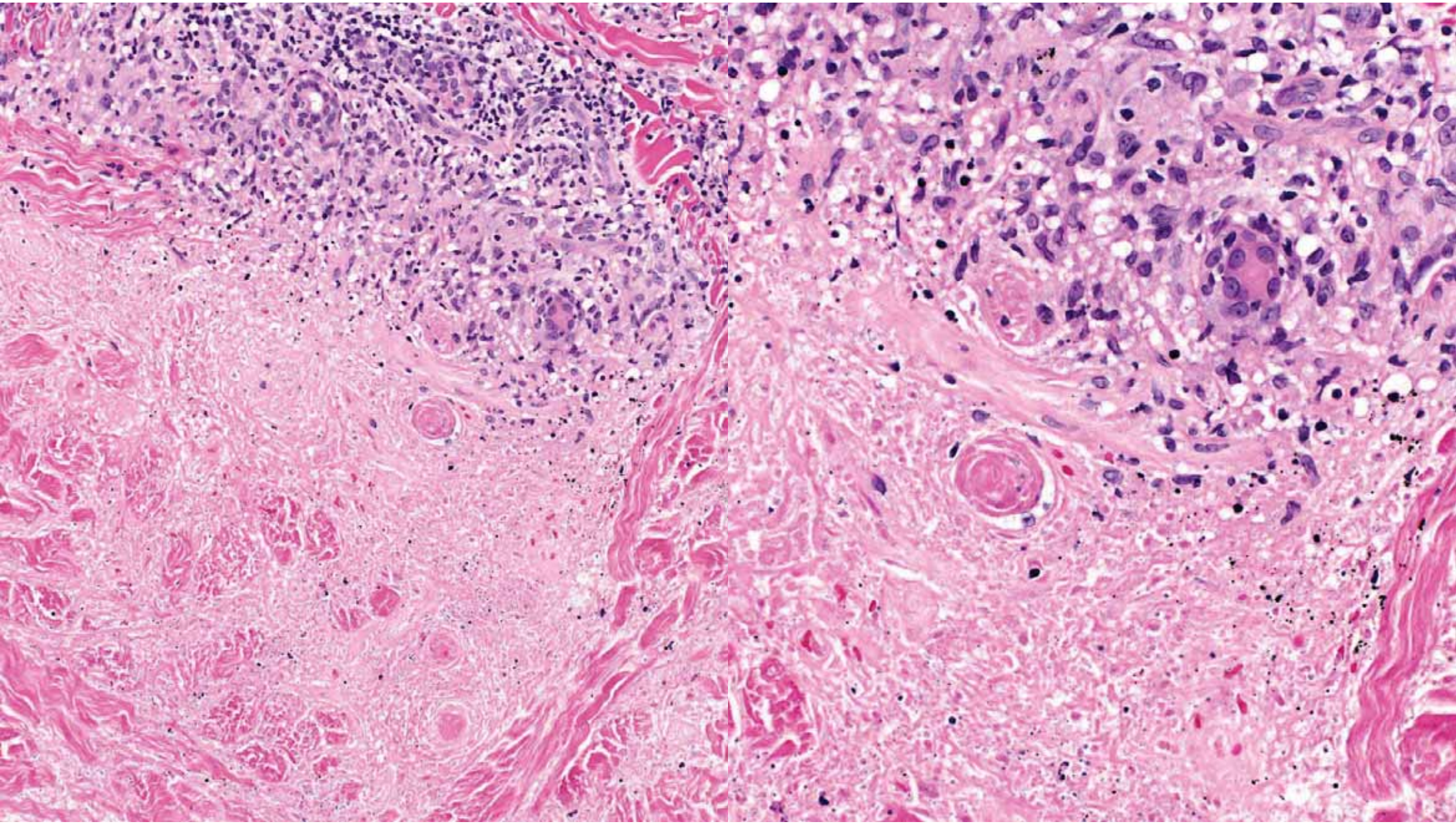


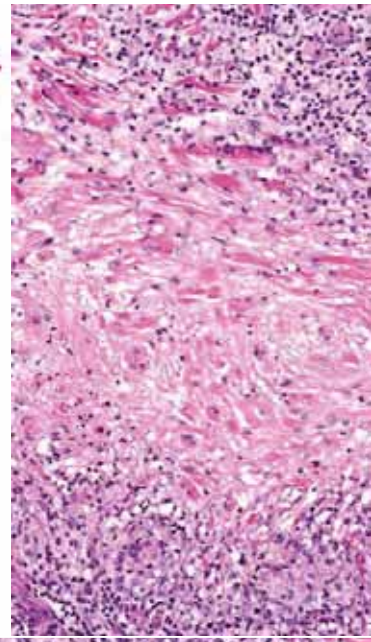


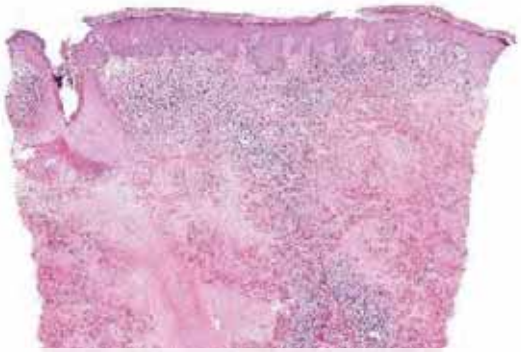
Biopsy #2

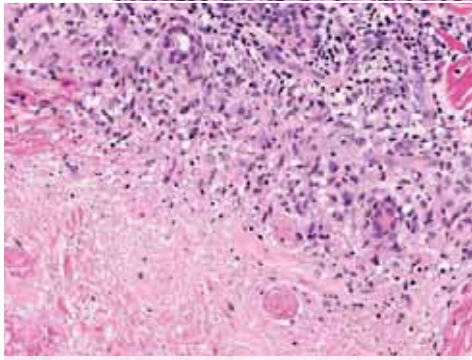






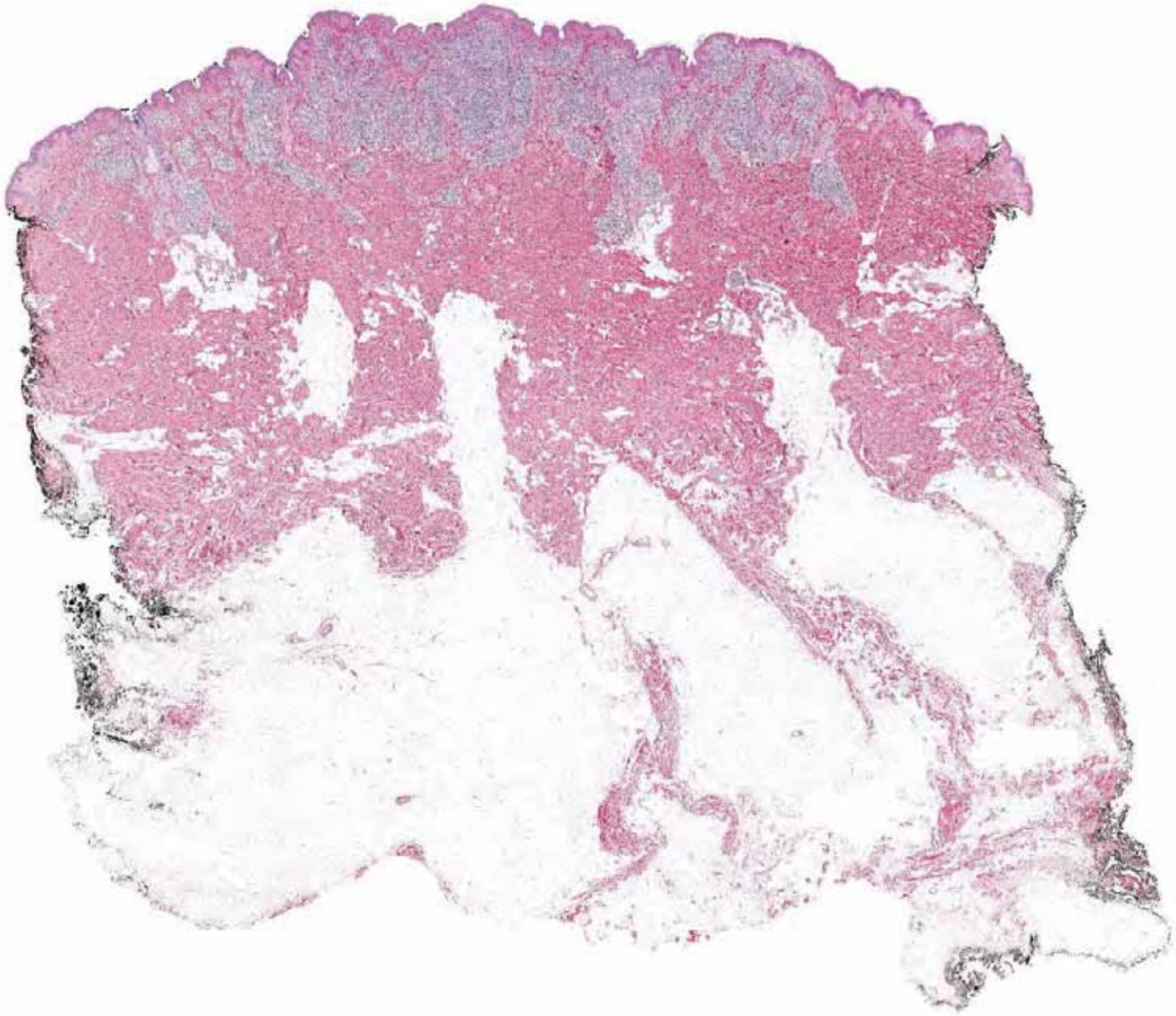






Necrotizing granulomatous reaction to tattoo pigment

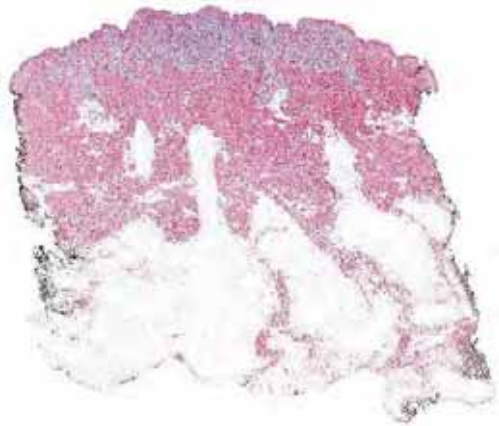
PCR for TBC and MOTT: negative

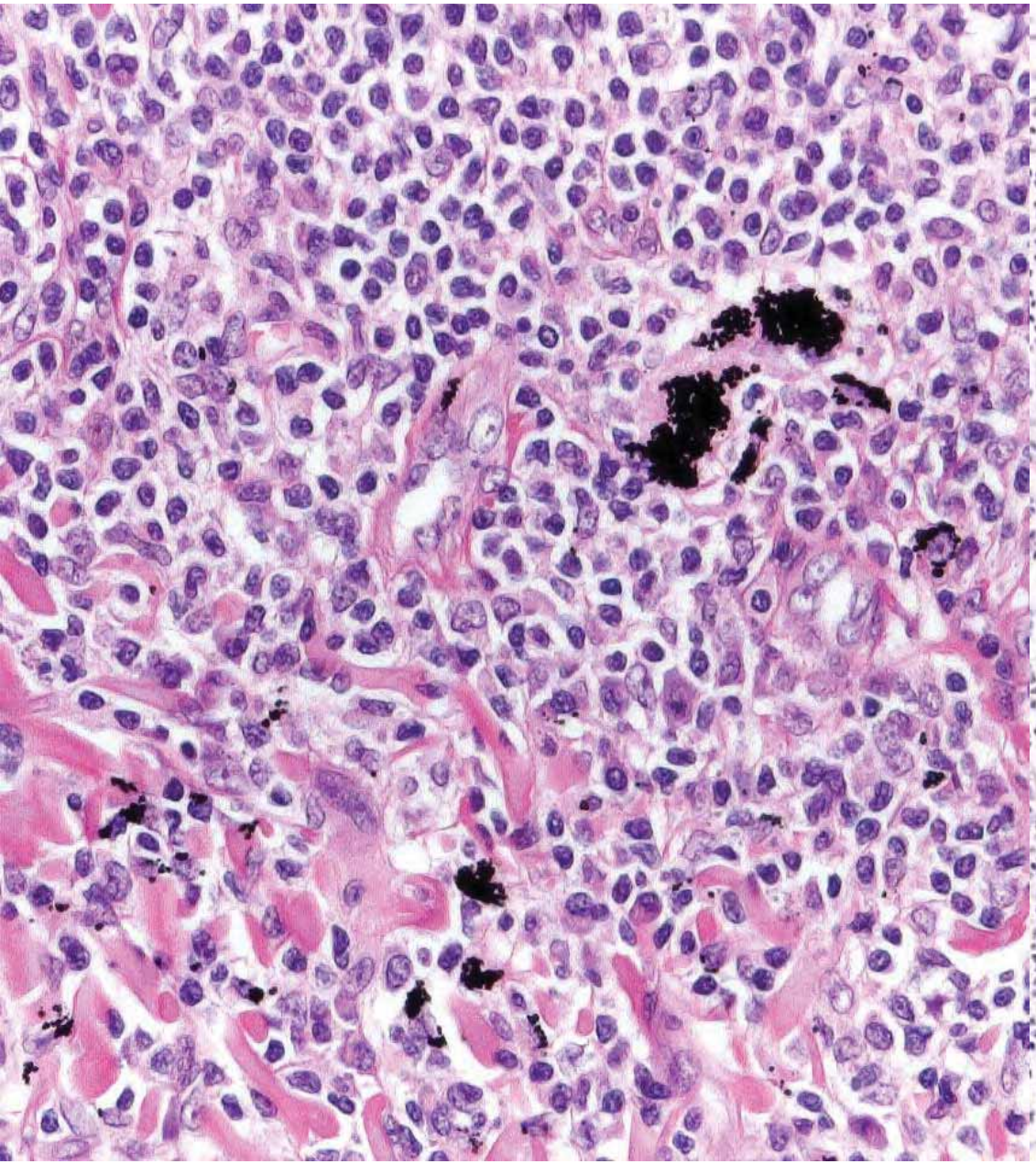


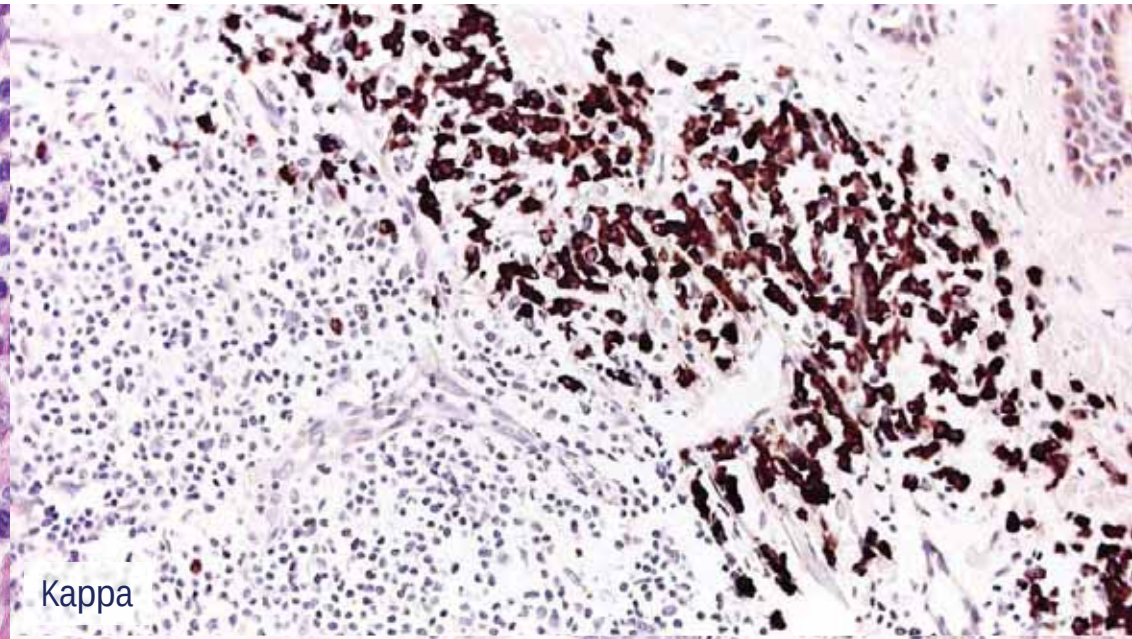
Case 12

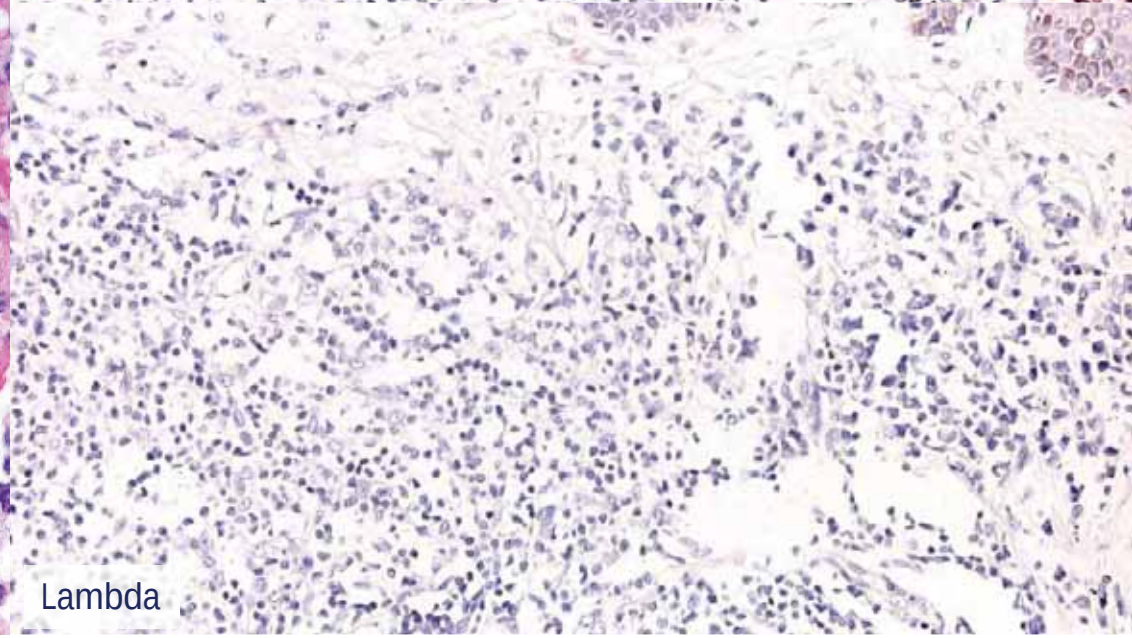
M, 61. Several, irregular papulo-nodular lesions arising within a large tattoo on the left shoulder.

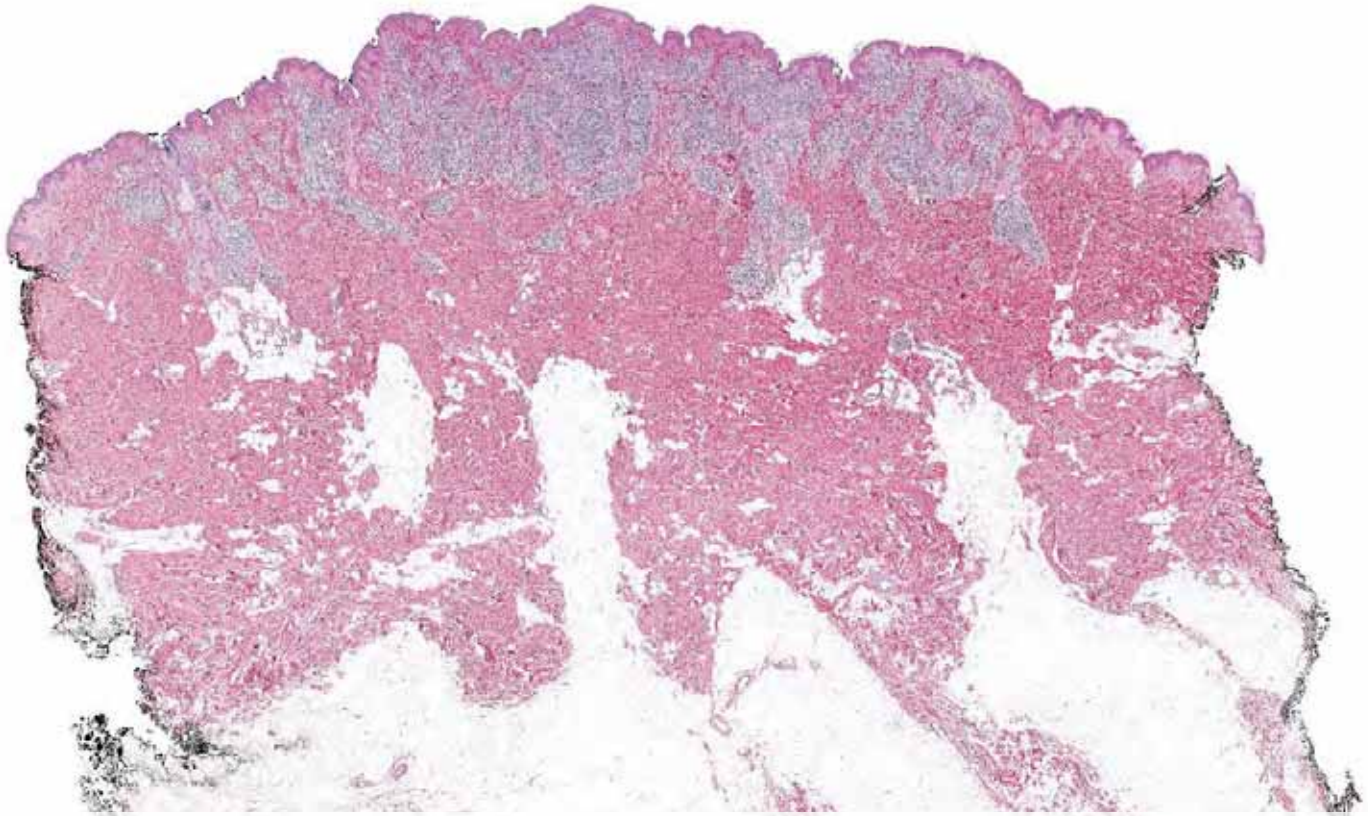
(Consultation Prof. C. Massone, Genova)

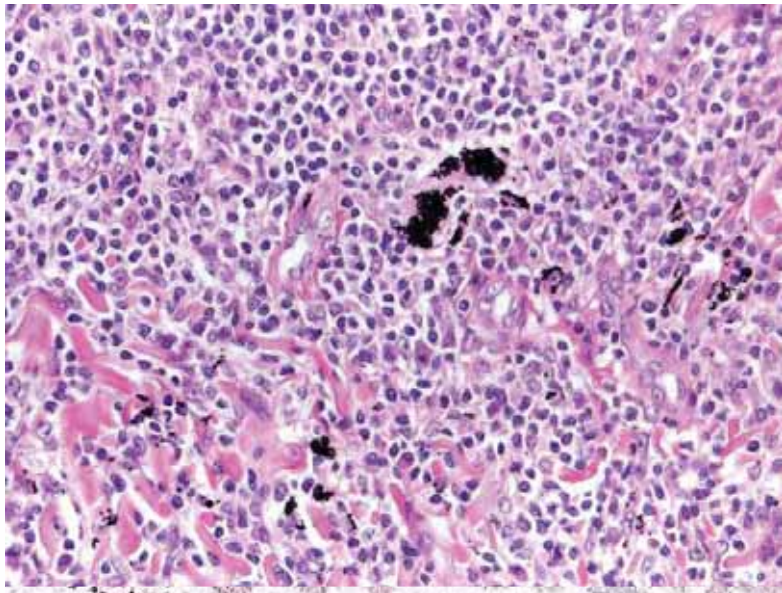


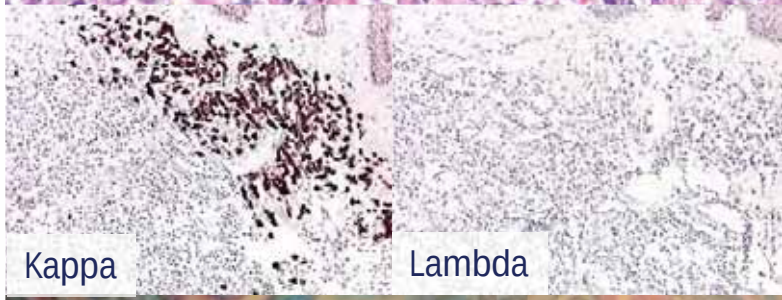



Kappa


Lambda







Cutaneous marginal zone lymphoproliferative disorder associated to tattoo

Reactions to tattoo pigment vs. chance associations

EARLY

- Acute inflammatory reaction after injection of tattoo pigment(s); rarely anaphylactic shock *(may be delayed!)*
- Koebnerization of dermatoses (e.g., psoriasis, lichen planus)
- Infections, rarely progressing to gangrene, sepsis

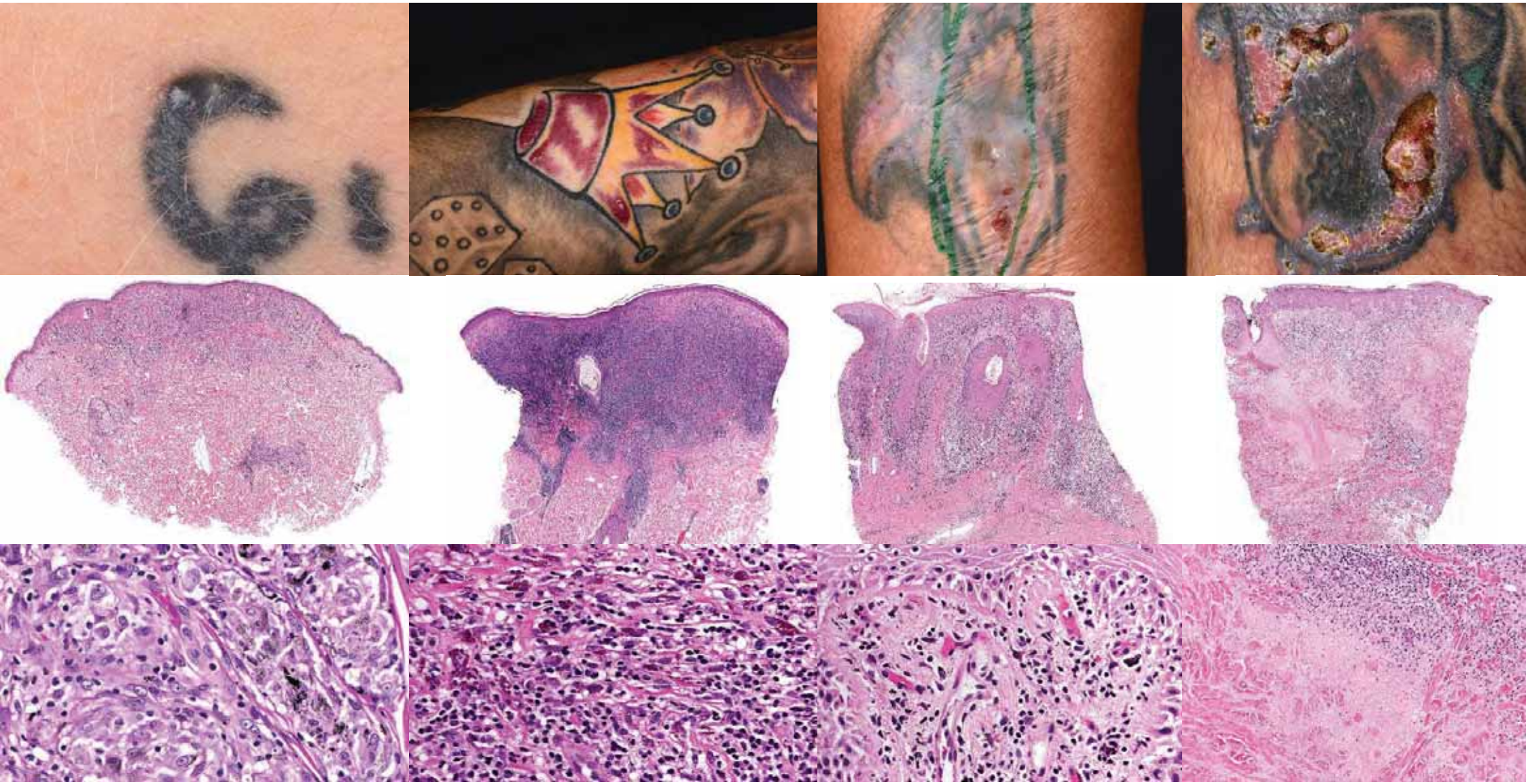
LATE

- Hypersensitivity reactions including allergic contact dermatitis
- Photo-aggravated reactions
- Granulomatous reactions, including sarcoidosis
- Lichenoid reactions
- Pseudolymphomatous reactions, marginal zone "lymphoma"
- Pseudoepitheliomatous epithelial hyperplasia, keratoacanthoma, squamous cell carcinoma
- Hypertrophic scars & keloids

OTHERS

- Swelling and burning after magnetic resonance imaging
- Reactions to tattoo removal (several types)

- Any skin disease can occur by chance at the site of a tattoo, without a pathogenetic link
- Melanocytic tumors located within a tattoo should be judged with caution (a professional tattoo will never be done on a preexisting mole, but pigment injected in the surrounding skin may "leak" into the mole)
- Many tumors reported as "caused" by tattoos are probably only chance associations



Sarcoidosis | Pseudolymphoma | Lichenoid reaction | Necrotizing non-sarcoidal granuloma

Tattoos as a risk factor for malignant lymphoma: a population-based case–control study

Christel Nielsen,[1,2] Hans Jerkeman,[3] and Anna Porwit[1,4]

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[3]Department of Oncology, Skåne University Hospital, Lund, Sweden
[4]Division of Orthopaedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden

Summary

Background The popularity of tattoos has increased dramatically over the last few decades. Tattoo ink often contains carcinogenic chemicals, e.g., primary aromatic amines, polycyclic aromatic hydrocarbons, and metals. The tattooing process invokes an immunologic response that causes translocation of tattoo ink from the injection site. Deposition of tattoo pigment in lymph nodes has been confirmed but the long-term health effects remain unexplored. We used Swedish National Authority Registers with full population coverage to investigate the association between tattoo exposure and overall malignant lymphoma as well as lymphoma subtypes.

Methods We performed a case–control study where we identified all incident cases of malignant lymphoma diagnosed between 2007 and 2017 in individuals aged 20–60 years in the Swedish National Cancer Register. Three random age- and sex-matched controls per case were sampled from the Total Population Register using incidence density sampling. We assessed exposure through a questionnaire in 2021, and data on potential confounders were retrieved from registers. We used multivariable logistic regression to estimate the incidence rate ratio (IRR) of malignant lymphoma in tattooed individuals.

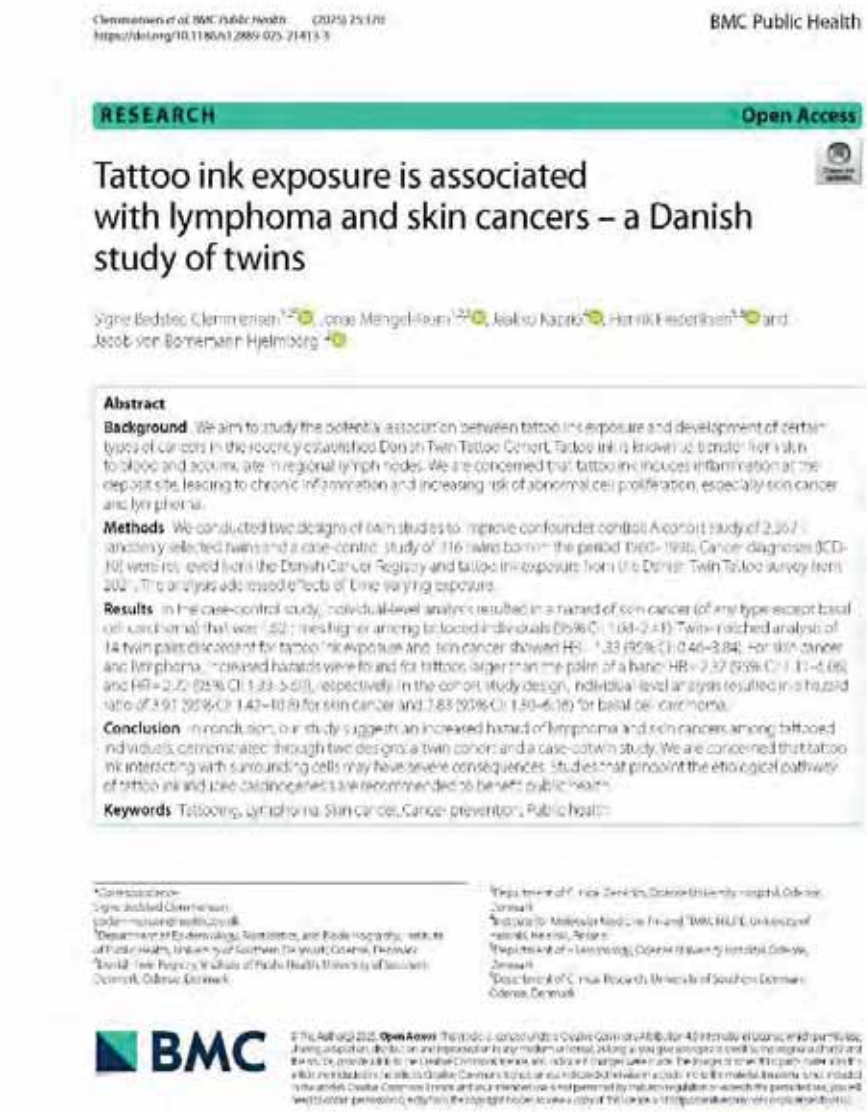
Findings The study population consisted of 11,905 individuals, and the response rate was 54% among cases (n = 1595) and 47% among controls (n = 4193). The tattoo prevalence was 21% among cases and 18% among controls. Tattooed individuals had a higher adjusted risk of overall lymphoma (IRR = 1.21; 95% CI 0.99–1.48). The risk of lymphoma was highest in individuals with less than two years between their first tattoo and the index year (IRR = 1.81; 95% CI 1.03–3.20). The risk decreased with intermediate exposure duration (three to ten years) but increased again in in-

We found that tattooed individuals had a 21% higher risk of overall malignant lymphoma compared with non-tattooed individuals, and that the association was strongest for diffuse large B-cell lymphoma and follicular lymphoma.

Lymphoma subgroup*	Subtype	ICD-O-3.2	ICD-O-3 morphology code	ICD-O-2	ICD-O-2 morphology code
Hodgkin	Lymphocyte-rich classic Hodgkin lymphoma	site	9651/3	C81.6	9651/3
	Nodular lymphocyte predominant Hodgkin lymphoma	site	9659/3	C81.6	9659/3
	Nodular sclerosis classic Hodgkin lymphoma	site	9663/3	C81.1	9663/3
	Mixed cellularity classic Hodgkin lymphoma	site	9652/3	C81.2	9652/3
	Lymphocyte-depleted classic Hodgkin lymphoma	site	9653/3	C81.3	9653/3
	Classic Hodgkin lymphoma, NOS	site	9650/3	C81.9	9650/3
Follicular	In situ follicular neoplasia		9695/3		
	Follicular lymphoma, grade 1	site	9695/3	C82.0	9690/3
	Follicular lymphoma, grade 2	site	9633/3	C82.0	9690/3
	Follicular lymphoma, grade 3	site	9698/3	C82.0	9690/3
	Follicular lymphoma, NOS	site	9690/3	C82.0	9690/3
	Primary cutaneous follicle centre lymphoma	C44	9597/3	C82.0	9690/3
Diffuse large B-cell	Diffuse large B-cell lymphoma (mesothelioma, immunoblastic lymphoma, anaplastic)	site	9680/3	C83.8	9680/3
	Primary cutaneous lymphoma	site	9679/3	C83.8	9680/3
	Thymic large B-cell lymphoma	C37.9	9679/3	C83.8	9680/3
	Mediastinal large B-cell lymphoma	C38.3	9679/3	C83.8	9680/3
	T-cell/histiocyte-rich large B-cell lymphoma	site	9688/3	C83.8	9680/3
	Haematologic lymphoma	site	9745/3	C83.8	9680/3
	ALK-positive large B-cell lymphoma	site	9737/3	C83.8	9680/3
	Large B-cell lymphoma in HHV8-associated multicentric Castleman disease	site	9738/3	C83.8	9680/3
	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma	site	9596/3	C83.8	9680/3
	Intravascular large B-cell lymphoma	C49.9	9712/3	C84.4	9712/3
Non-follicular indolent B-cell	Extranodal marginal zone lymphoma	site	9699/3	C83.9	9699/3
	Nodal marginal zone lymphoma	C77	9699/3	C83.0	9724/3
	Splenic marginal zone lymphoma	C42.2	9689/3	C83.0	9724/3
	Other non-follicular lymphoma	site	9679/3	C83.8	9670/3
	Lymphoplasmacytic lymphoma	site	9671/3	C83.8	9671/3
	Splenic B-cell lymphoma, unclassifiable	C42.2	9591/3	C85.9	9591/3
Mantle cell	In situ mantle cell neoplasia		9673/3		
	Mantle cell lymphoma	site	9673/3	C83.5	9674/3
Aggressive T-cell	Blastic plasmacytoid dendritic cell neoplasm/blastic NK cell lymphoma	site	9727/3	C83.8	9686/3
	Extranodal NK/T cell lymphoma, nasal-type	site	9719/3	C44.4	9719/3
	Enteropathy-associated T-cell lymphoma	site	9717/3	C44.4	9717/3
	Hepatosplenic T-cell lymphoma	site	9716/3	C44.4	9716/3
	Angioimmunoblastic T-cell lymphoma	site	9705/3	C44.4	9705/3
	Subcutaneous panniculitis-like T-cell lymphoma	site	9708/3	C44.4	9708/3
	Peripheral T-cell lymphoma, NOS	site	9702/3	C44.4	9702/3
	Primary cutaneous gammadelta T-cell lymphoma	C44	9726/3	C44.4	9702/3
	Anaplastic large cell lymphoma, ALK-positive	site	9714/3	C84.5	9714/3
	Anaplastic large cell lymphoma, ALK-negative	site	9715/3	C84.5	9714/3
	Early T-cell precursor lymphoblastic leukaemia/lymphoma	site	9729/3	C84.5	9835/3
	Primary cutaneous anaplastic large cell lymphoma	C44	9718/3	C84.5	9714/3
	Lymphomatoid papulosis	C44	9718/3	C81.9	9718/3
Other	Precursor B-cell lymphoblastic lymphoma	site	9728/3	C85.5	9835/3
	Rosai lymphoma	site	9687/3	C81.7	9687/3
	Blastic aggressive non-Hodgkin lymphoma	site	9591/3/3	C81.4	9686/3
	Nycrin lymphoma	C44	9700/3	C84.0	9700/3
	Sézary syndrome	C44	9701/3	C84.1	9701/3
	Cutaneous T-cell lymphoma	C44	9709/3	C84.4	9709/3
	Small cell/indolent non-Hodgkin lymphoma	site	9591/3/3	C85.9	9591/3
	B-cell lymphoma, NOS	site	9591/3/3	C85.1	9591/3/3
	Malignant lymphoma, unspecified	site	9590/3/3	C85.9	9590/3/3
	Malignant lymphoma, NOS	site	9590/3	C85.9	9590/3
	Non-Hodgkin lymphoma, NOS	site	9591/3	C85.9	9591/3
	T-cell lymphoma, NOS	site	9591/3/3	C85.9	9591/3/3

*Diagnostic groups defined according to the National Quality Register for Lymphoma. †International Classification of Diseases for Oncology. ‡NOS, not otherwise specified.

Table 2: Included subtypes of malignant lymphoma and their aggregation into broader diagnostic groups.



BMC Public Health

RESEARCH Open Access

Tattoo ink exposure is associated with lymphoma and skin cancers – a Danish study of twins

Abstract

Background We aim to study the potential association between tattoo ink exposure and development of certain types of cancers in the recently established Danish Twin Tattoo Cohort. Tattoo ink is known to translocate from skin to blood and accumulate in regional lymph nodes. We are concerned that tattoo ink induces inflammation at the deposit site, leading to chronic inflammation and increasing risk of abnormal cell proliferation, especially skin cancer and lymphoma.

Methods We conducted two designs of twin studies to improve confounder control. A cohort study of 2,367 randomly selected twins and a case-control study of 316 twins born in the period 1960–1996. Cancer diagnoses (ICD-10) were retrieved from the Danish Cancer Registry and tattoo ink exposure from the Danish Twin Tattoo survey from 2021. The analyses addressed effects of time-varying exposure.

Results In the case-control study, individual-level analysis resulted in a hazard of skin cancer (of any type except basal cell carcinoma) that was 1.62 times higher among tattooed individuals (95% CI: 1.08–2.41). Twin-matched analysis of 14 twin pairs discordant for tattoo ink exposure and skin cancer showed HR = 1.33 (95% CI: 0.46–3.84). For skin cancer and lymphoma, increased hazards were found for tattoos larger than the palm of a hand: HR = 2.37 (95% CI: 1.11–5.06) and HR = 2.73 (95% CI: 1.33–5.60), respectively. In the cohort study design, individual-level analysis resulted in a hazard ratio of 3.91 (95% CI: 1.42–10.8) for skin cancer and 2.83 (95% CI: 1.30–6.16) for basal cell carcinoma.

Conclusion In conclusion, our study suggests an increased hazard of lymphoma and skin cancers among tattooed individuals demonstrated through two designs: a twin cohort and a case-cotwin study. We are concerned that tattoo ink interacting with surrounding cells may have severe consequences. Studies that pinpoint the etiological pathway of tattoo ink and cave carcinogenesis are recommended to benefit public health.

Keywords Tattooing, Lymphoma, Skin cancer, Cancer prevention, Public health

Cohort study of 2,367 randomly selected twins and a case-control study of 316 twins born in the period 1960–1996. Cancer diagnoses retrieved from the Danish Cancer Registry and tattoo ink exposure from the Danish Twin Tattoo survey from 2021.

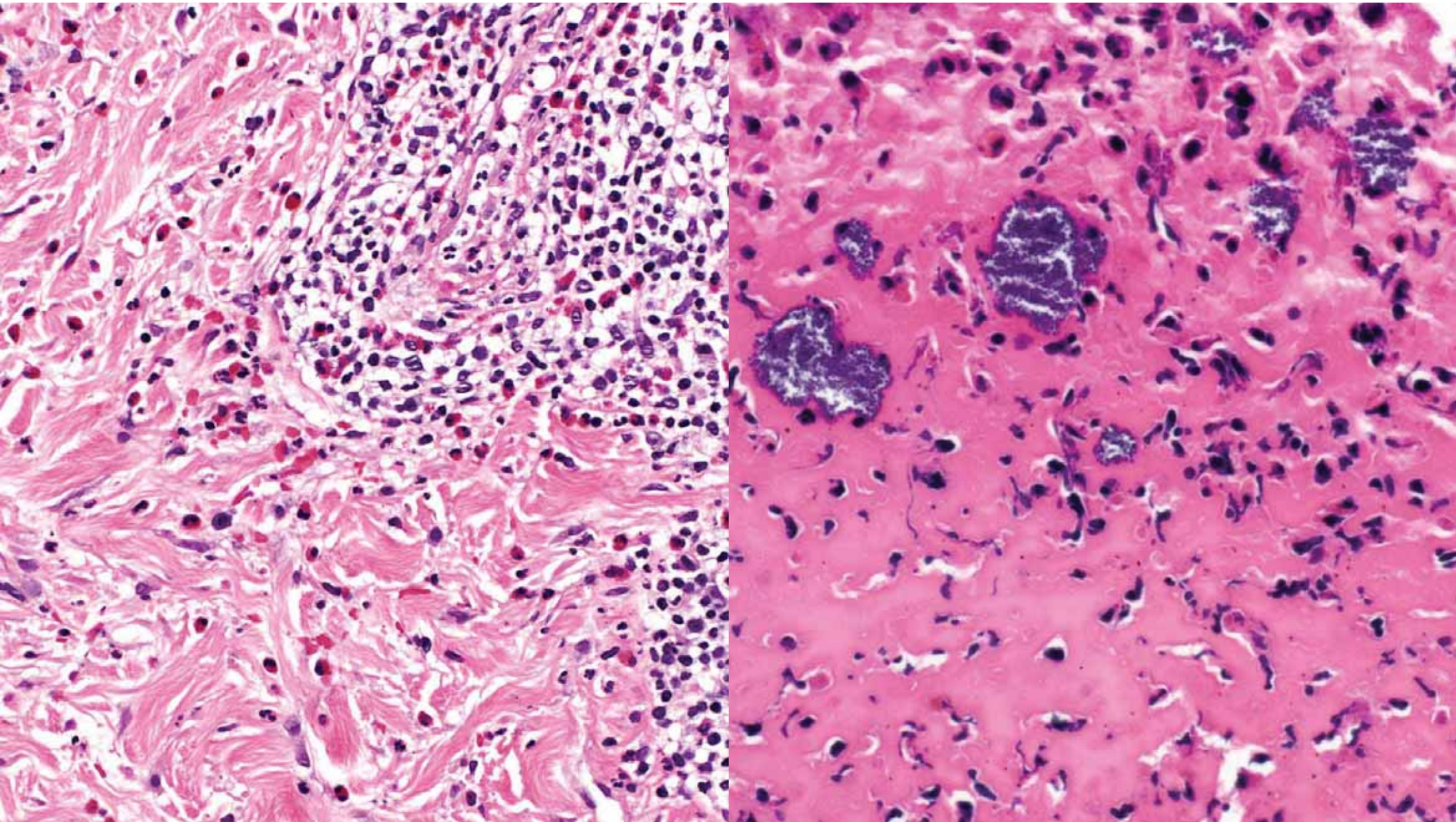
Individual-level analysis resulted in a hazard of skin cancer (of any type except basal cell carcinoma) that was 1.62 times higher among tattooed individuals (95% CI: 1.08–2.41). Twin-matched analysis of 14 twin pairs discordant for tattoo ink exposure and skin cancer showed HR = 1.33 (95% CI: 0.46–3.84). For skin cancer and lymphoma, increased hazards were found for tattoos larger than the palm of a hand: HR = 2.37 (95% CI: 1.11–5.06) and HR = 2.73 (95% CI: 1.33–5.60), respectively. In the cohort study design, individual-level analysis resulted in a hazard ratio of 3.91 (95% CI: 1.42–10.8) for skin cancer and 2.83 (95% CI: 1.30–6.16) for basal cell carcinoma.

SICK

SICK

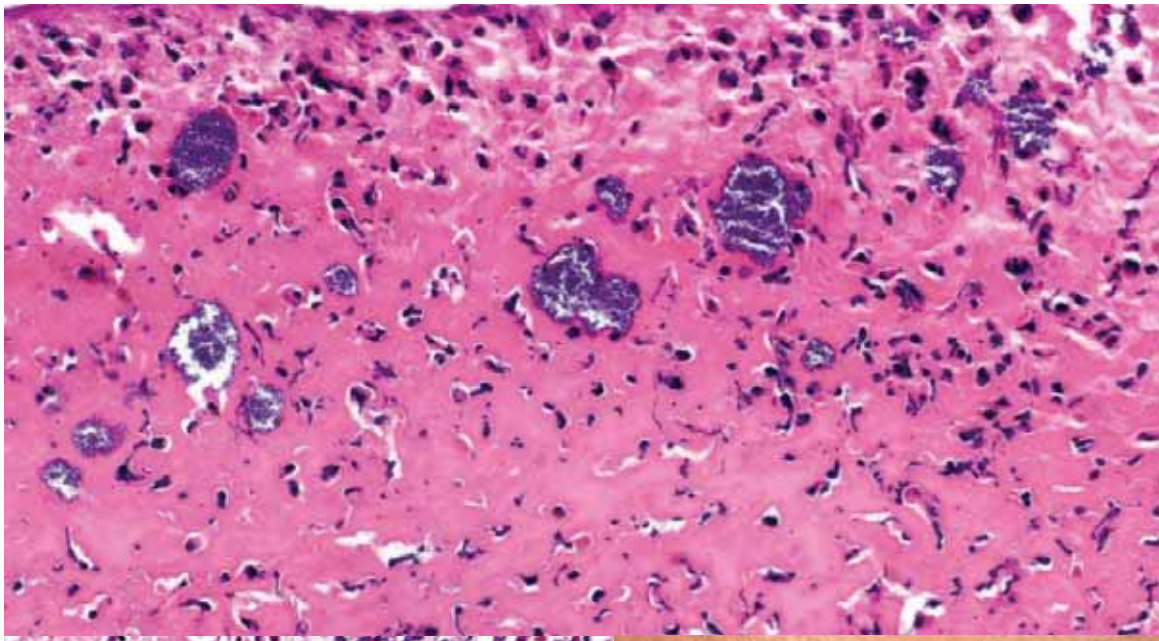
Case 13

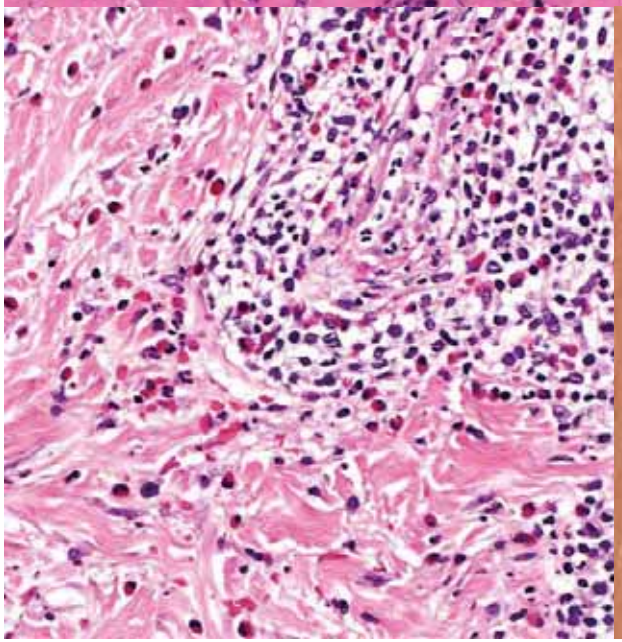
F, 36. According to the patient skin lesions for approximately 2 weeks. A private dermatologist suspected LE or atopic dermatitis (ANA 1:80; IgE 256+).

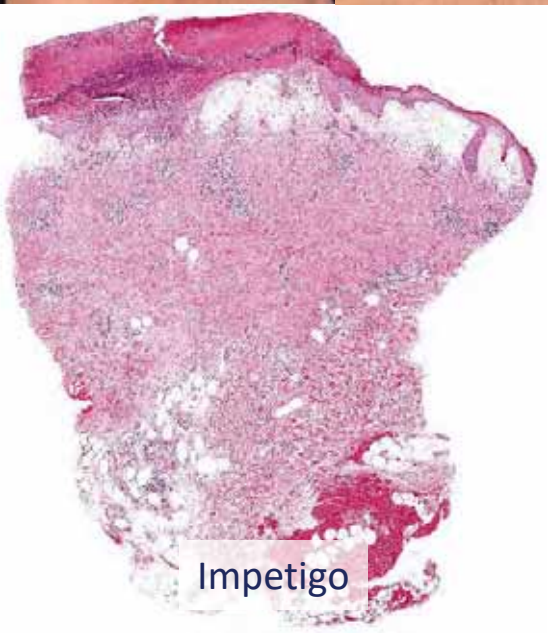


Impetigo

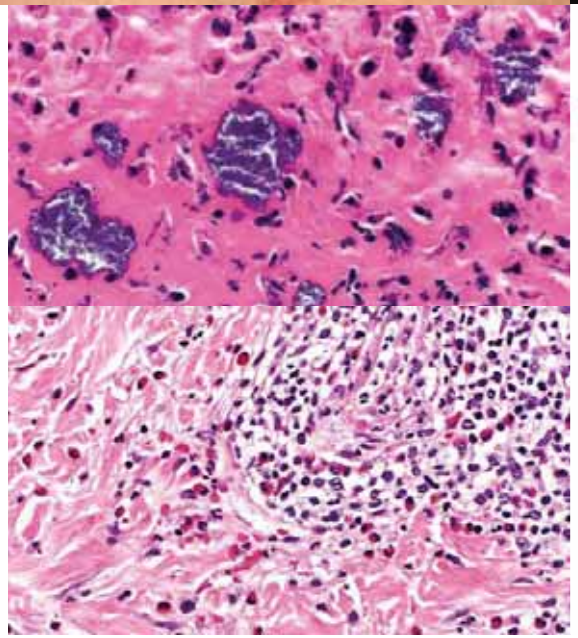
St. aureus+; DIF & IIF: negative

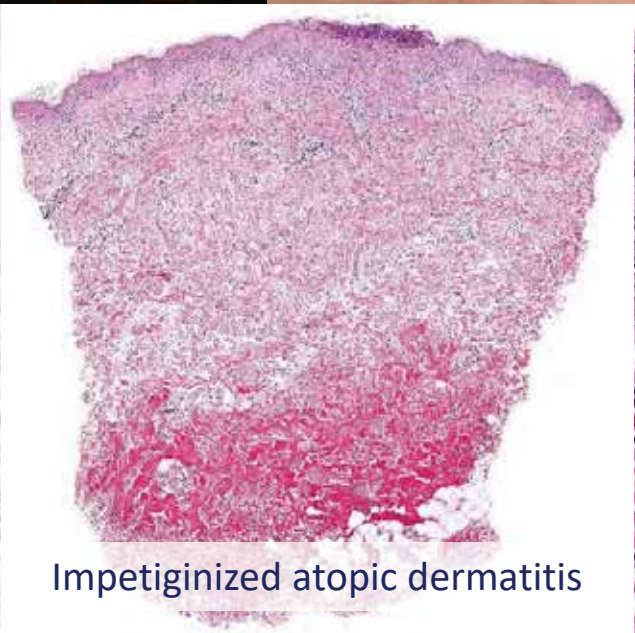




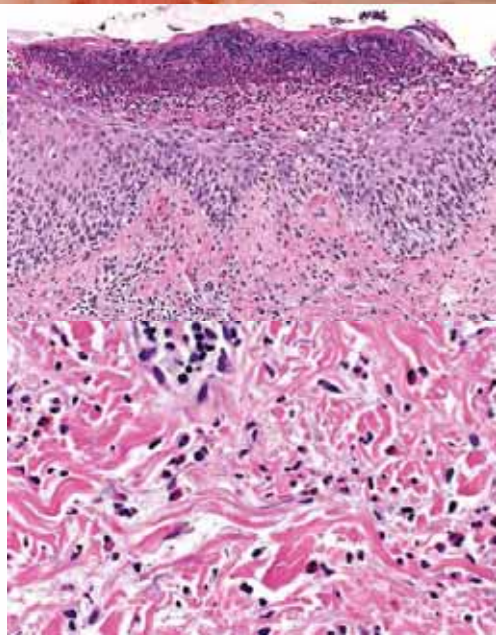


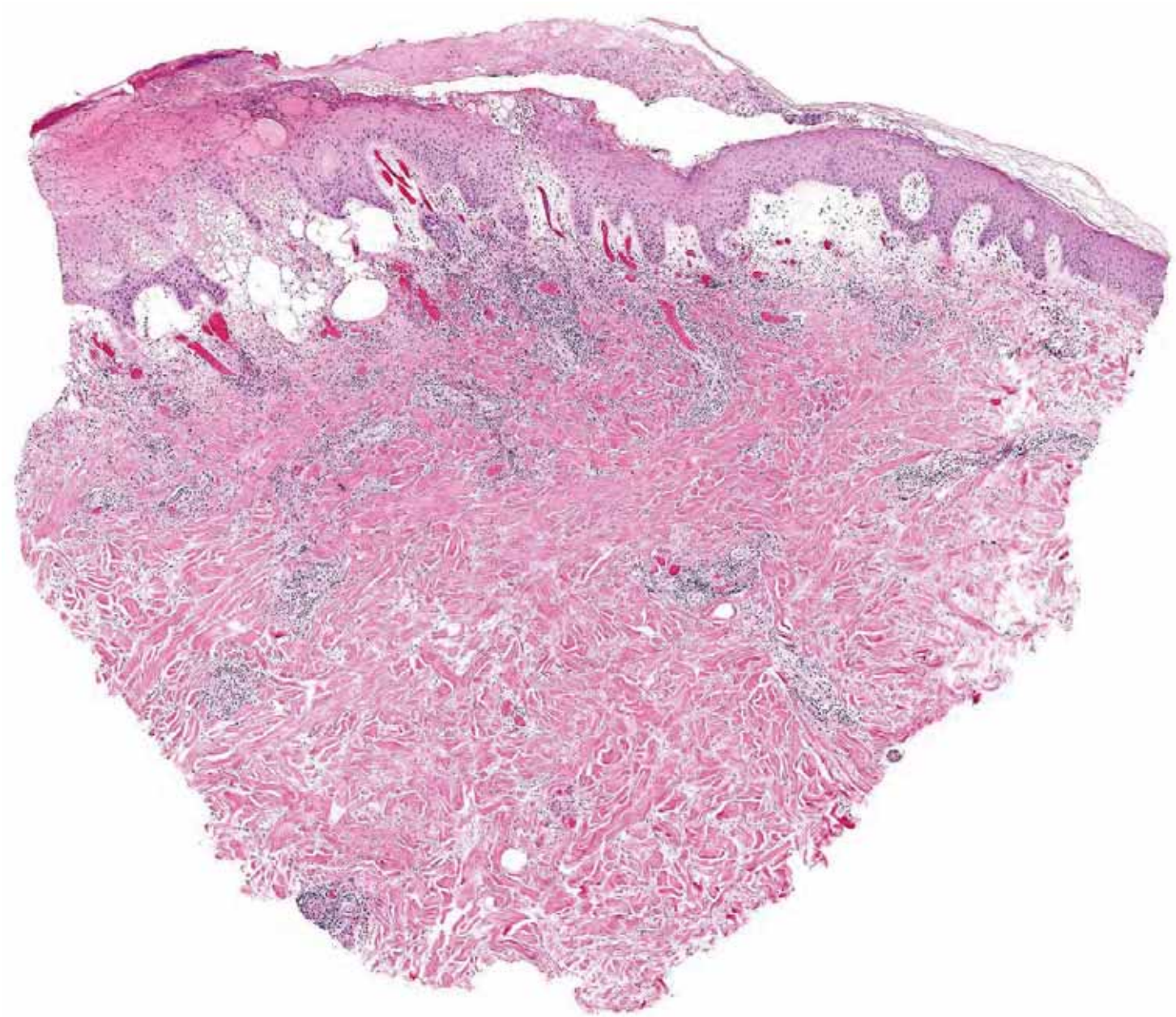
Impetigo





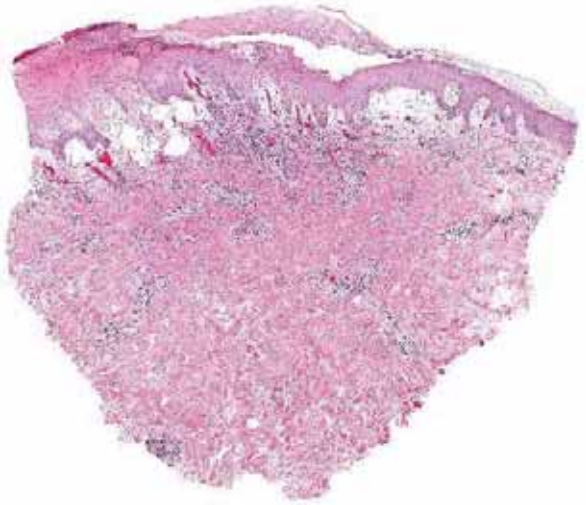
Impetiginized atopic dermatitis

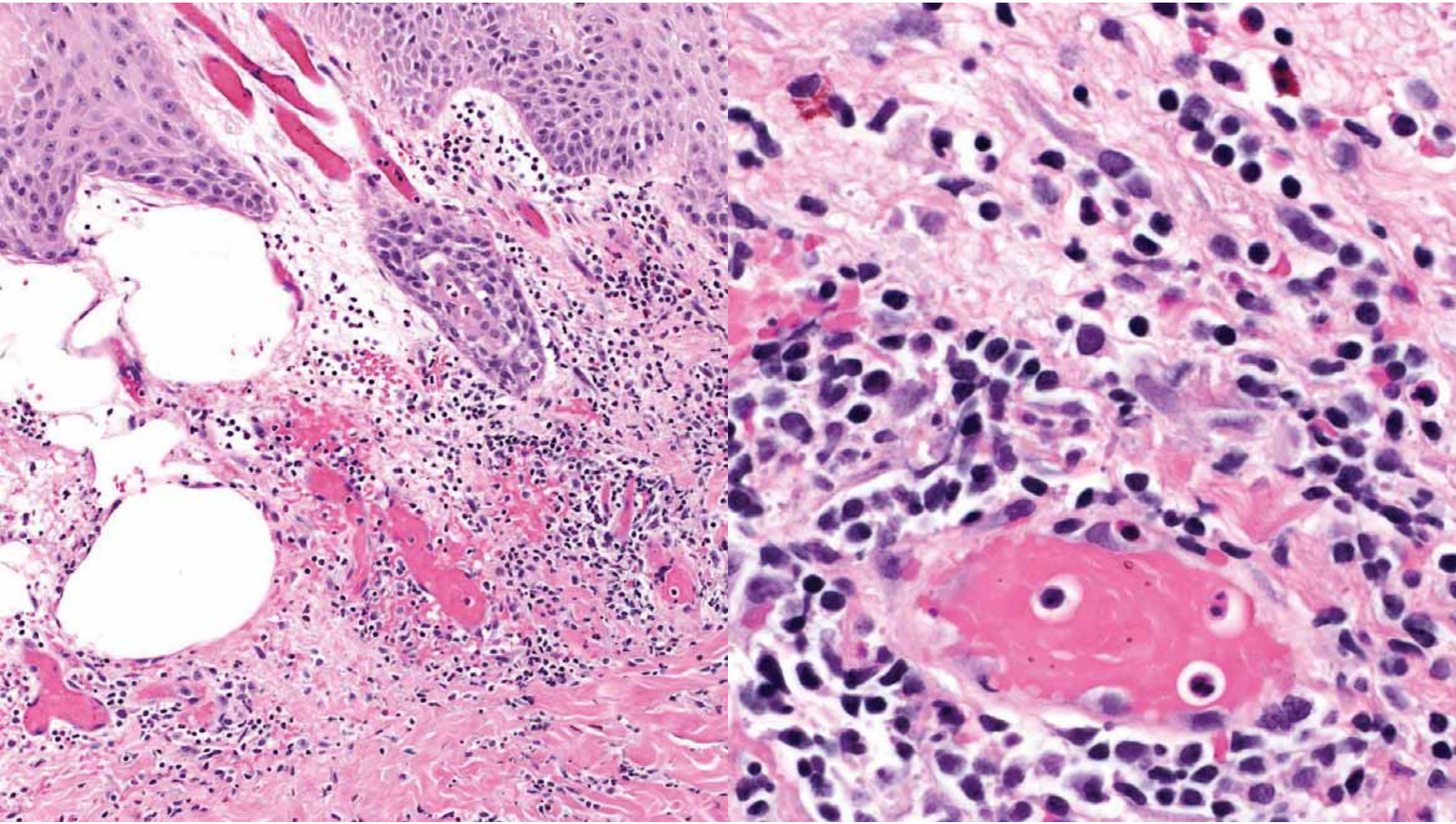


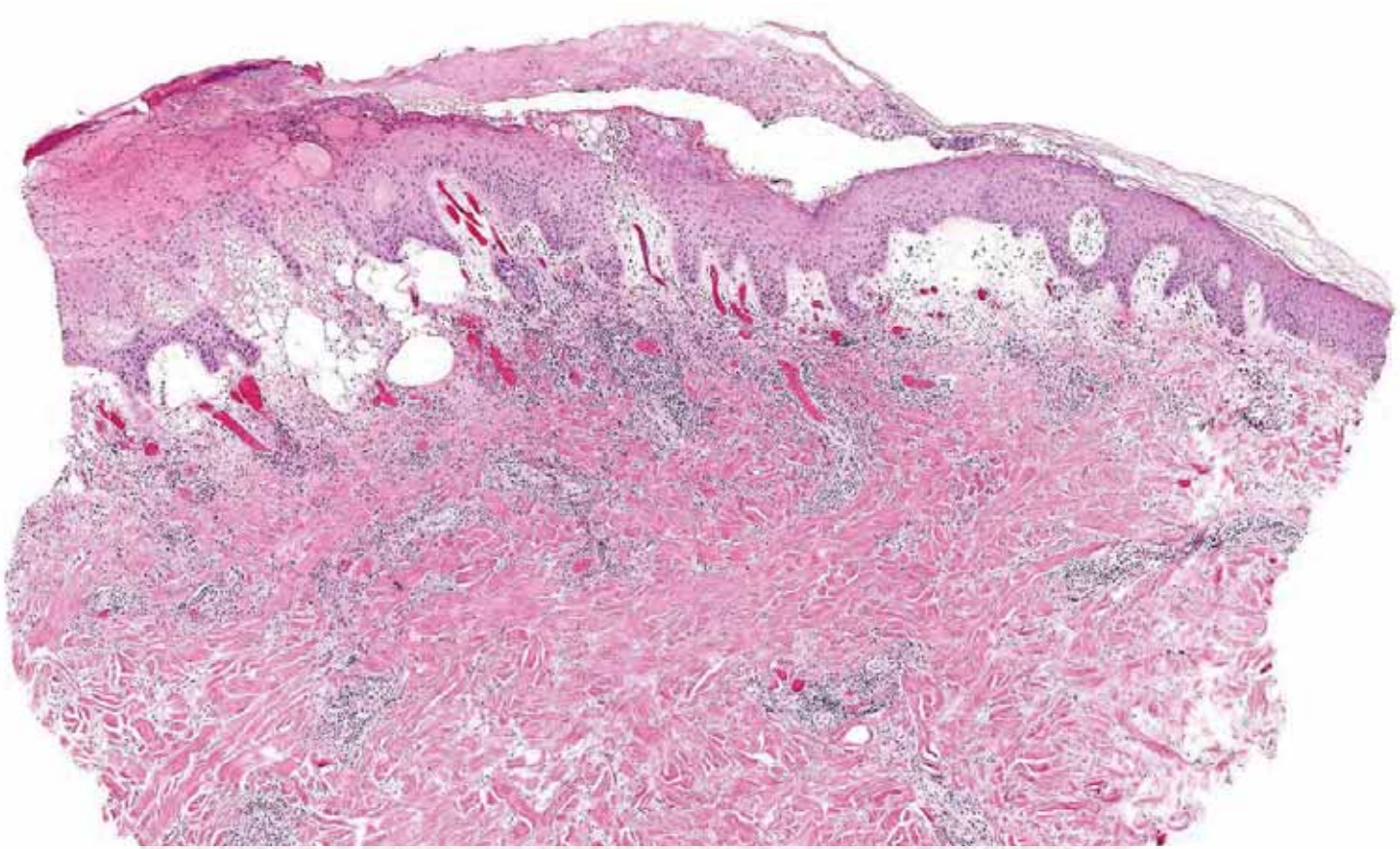


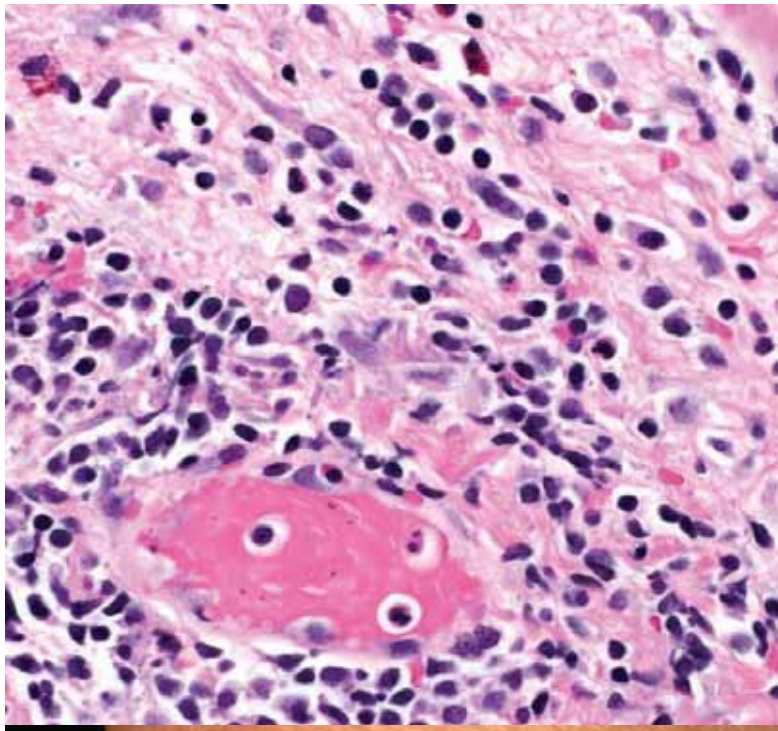
Case 14

F, 52. According to the patient rapidly growing lesion on the left ankle for a few days.



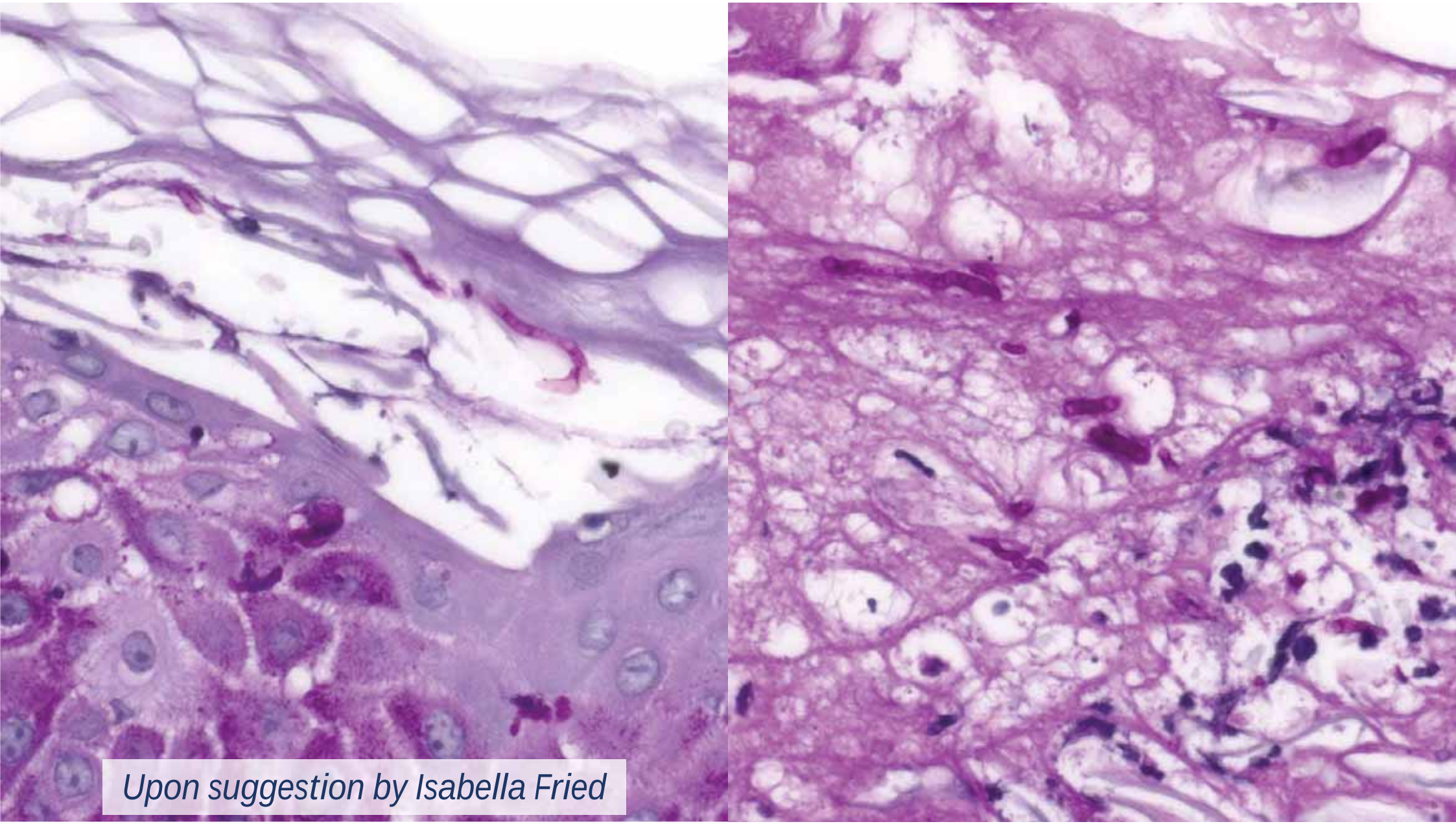




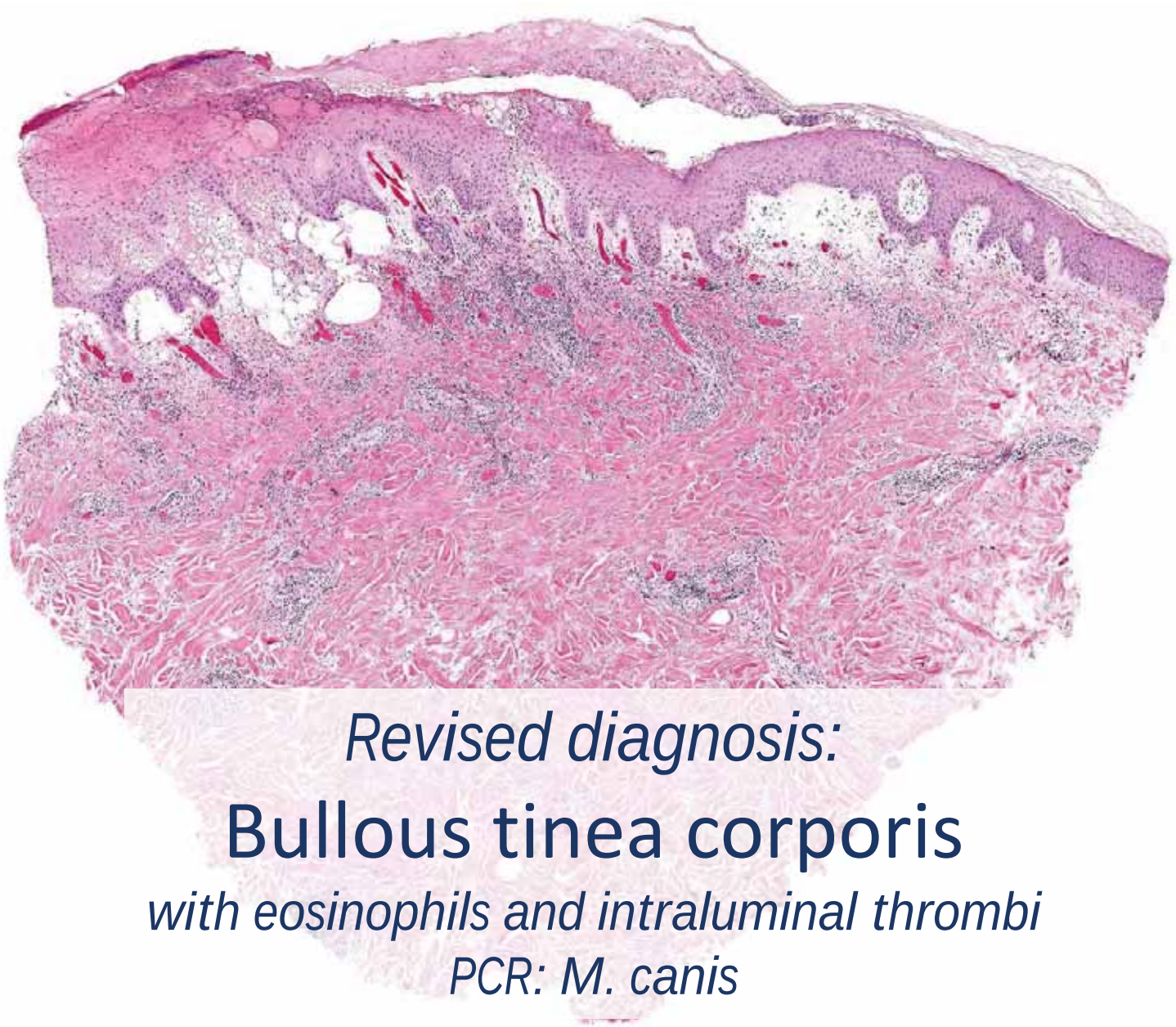


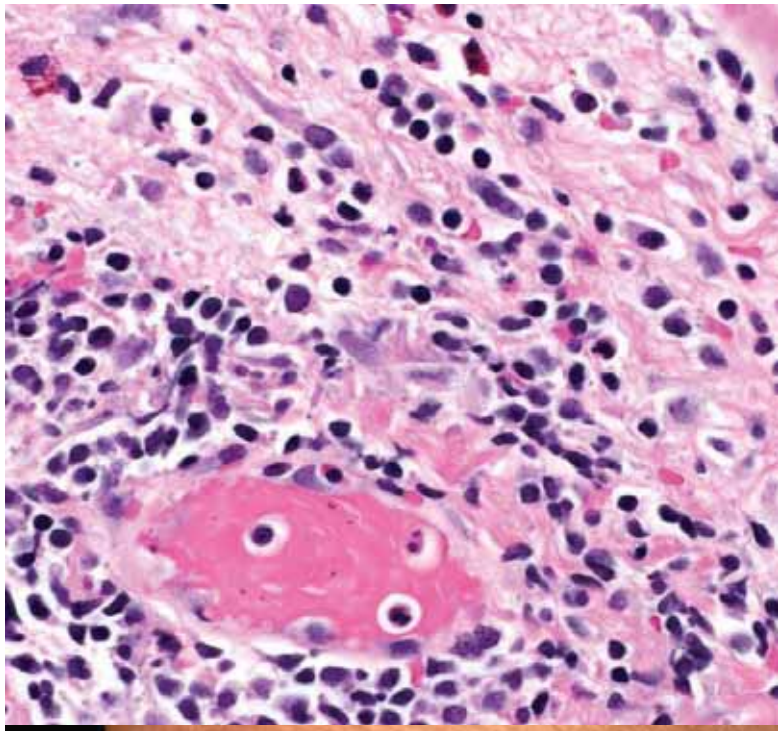
My initial diagnosis:

Bullous arthropod bite reaction with intraluminal thrombi



Upon suggestion by Isabella Fried



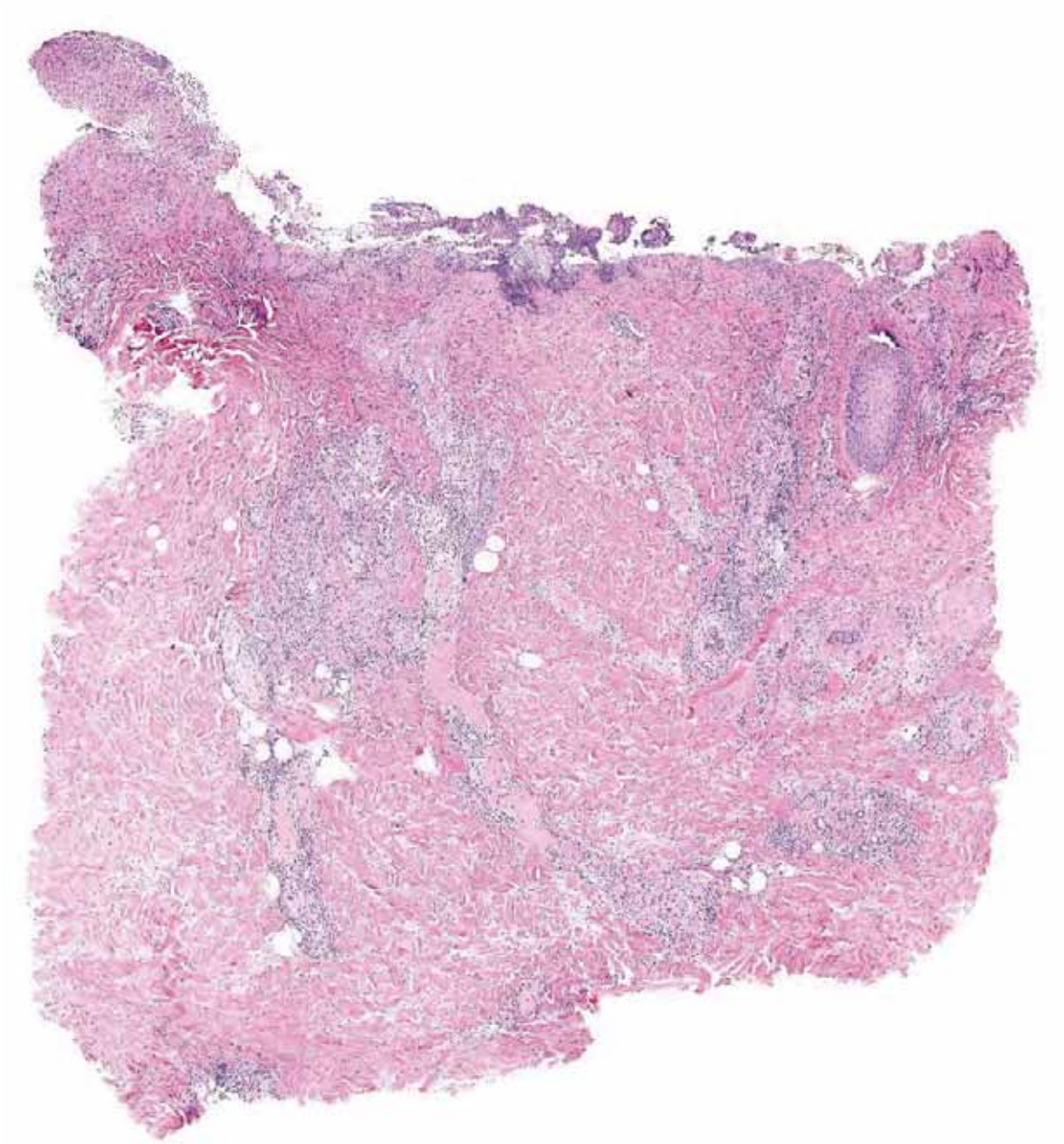


Revised diagnosis:

Bullous tinea corporis

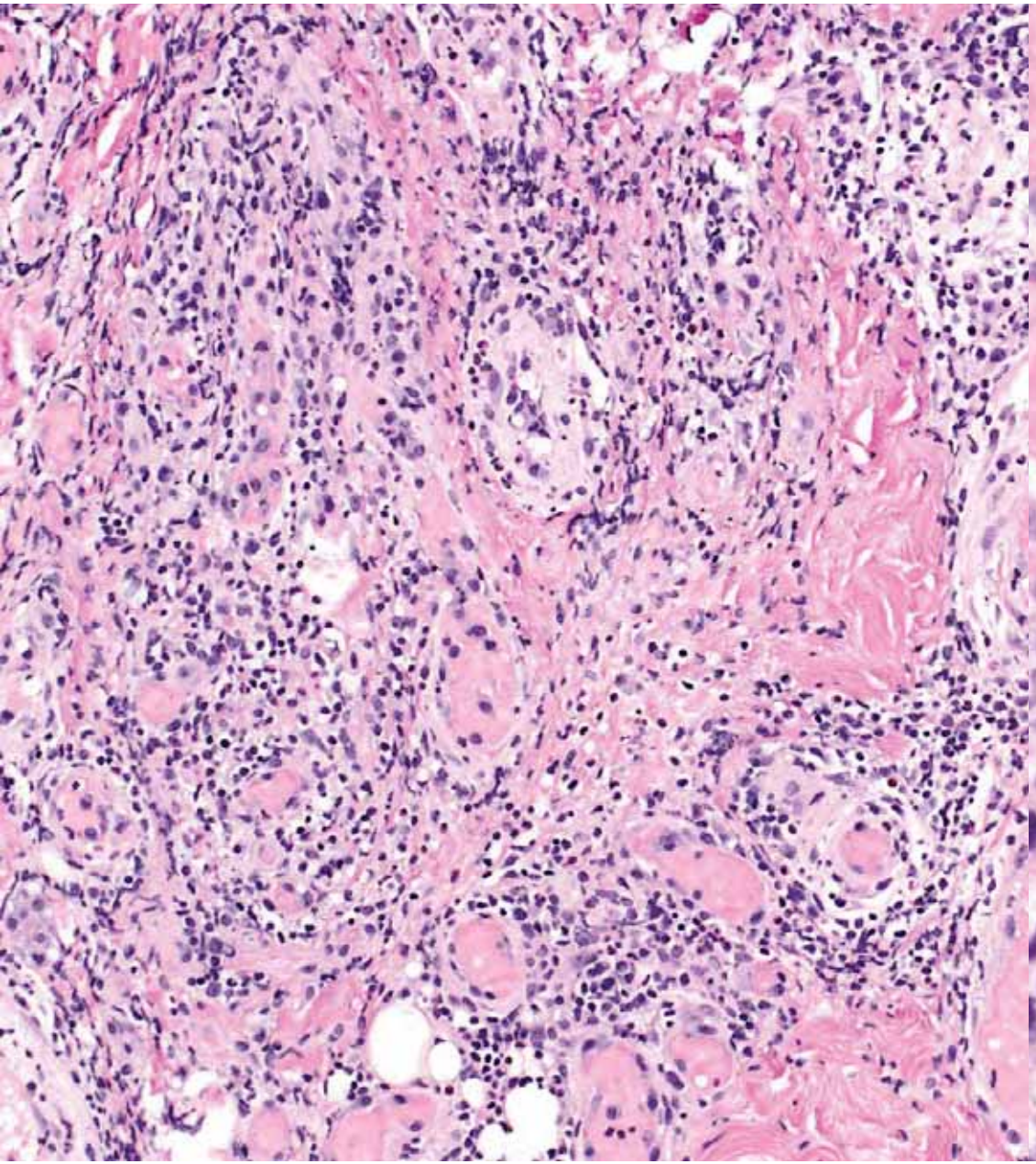
with eosinophils and intraluminal thrombi

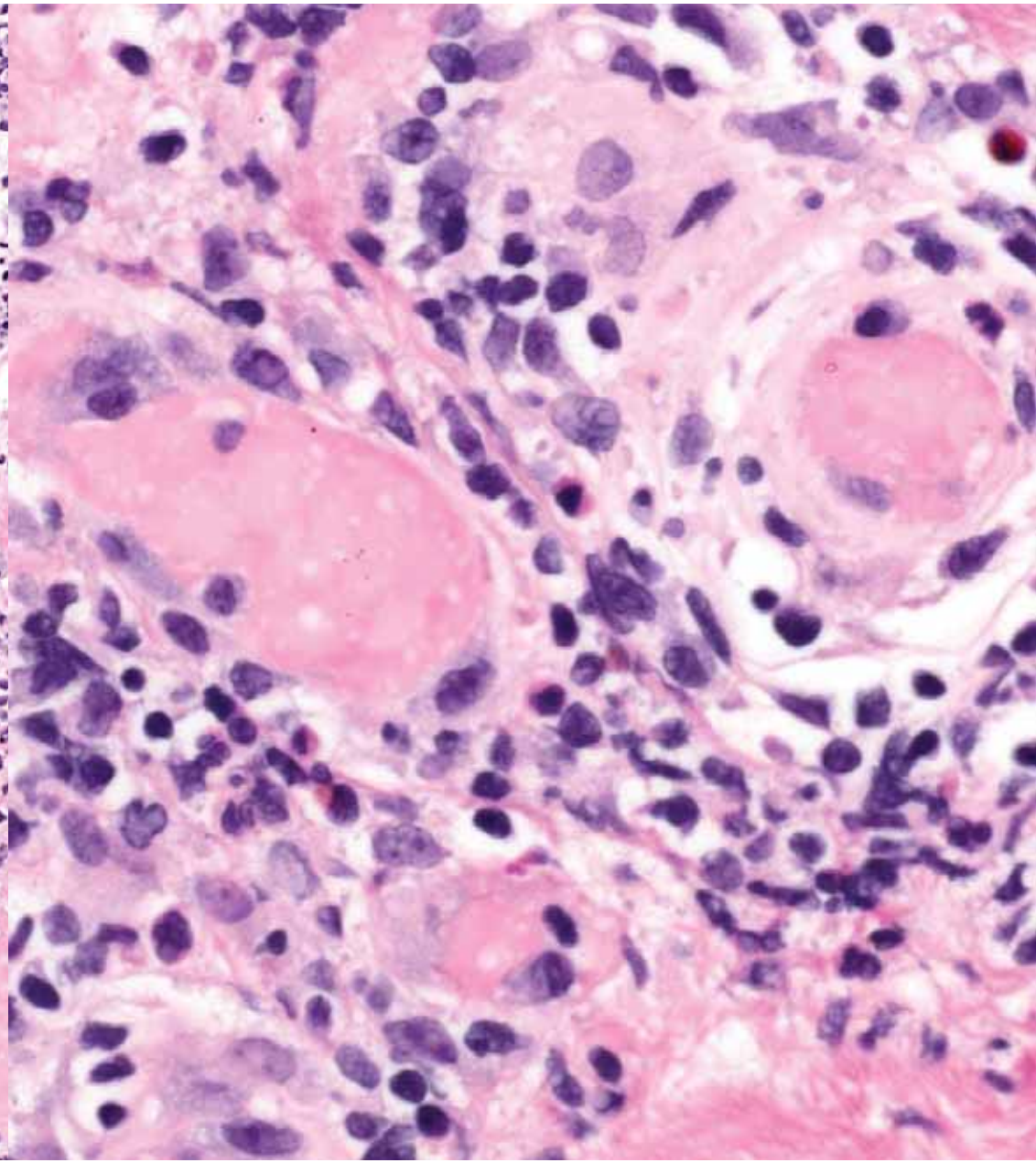
PCR: M. canis

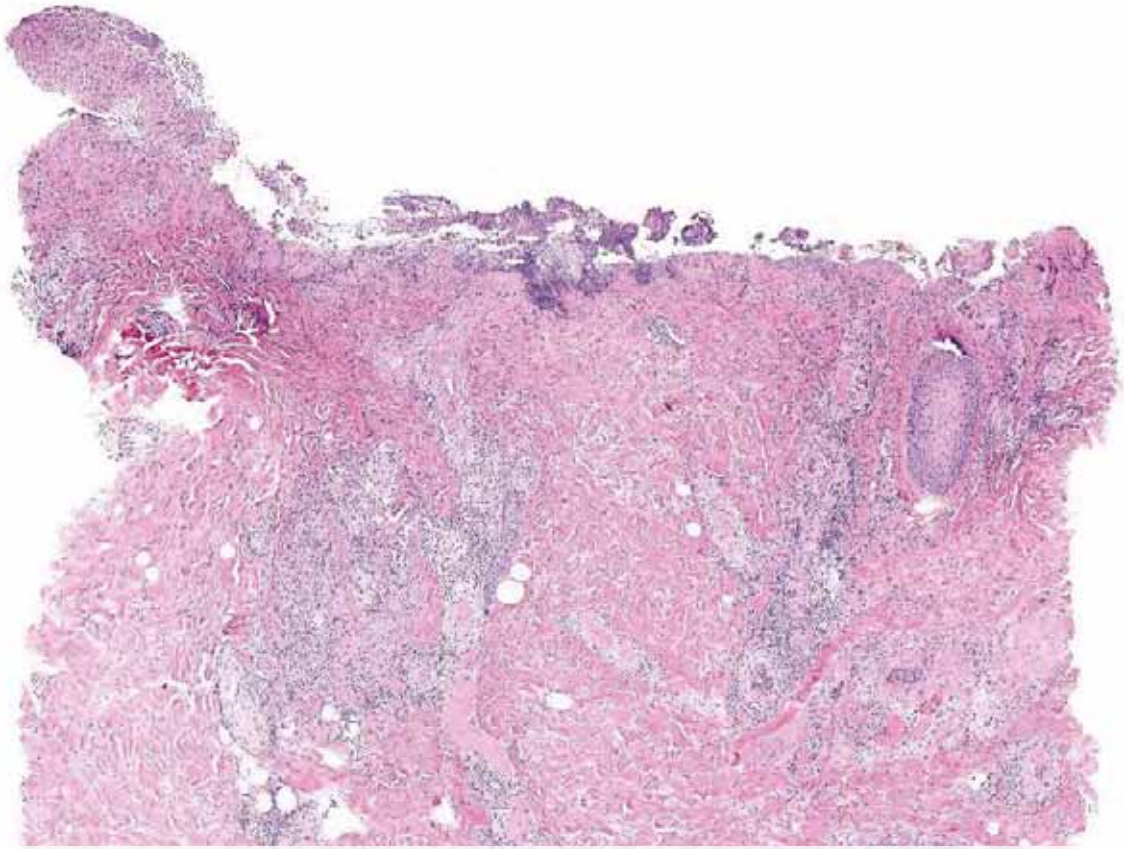


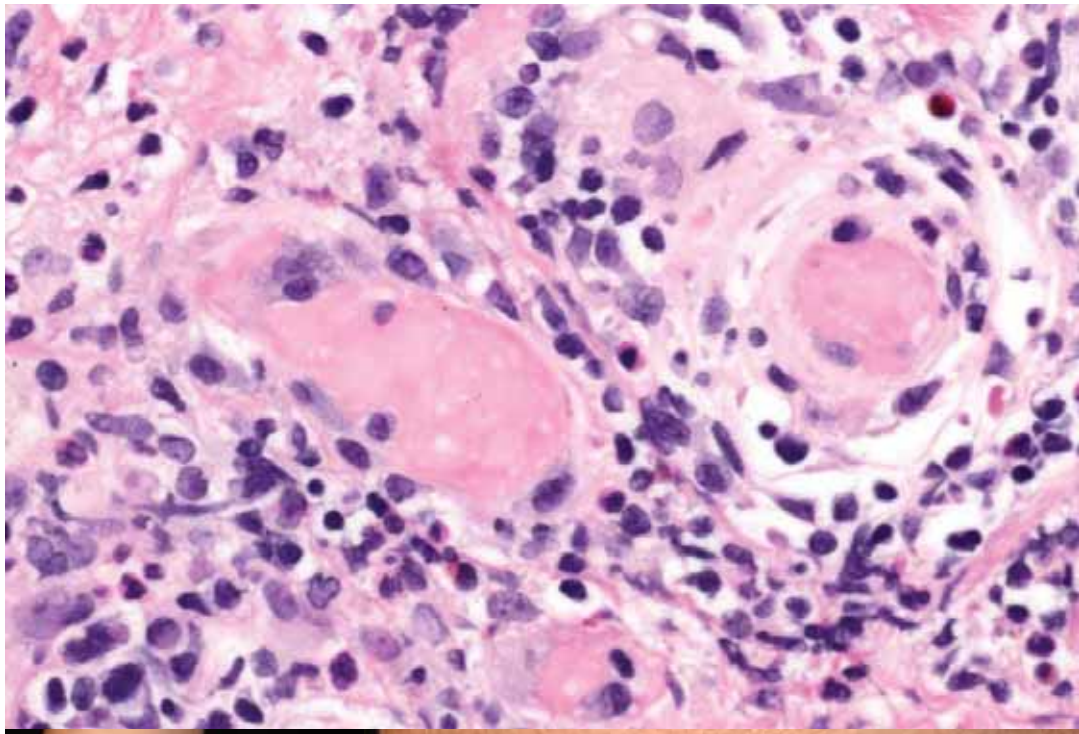
Case 15

F, 42. According to the patient rapidly growing, painful lesion on the left lower leg for 1 week.









Necrotic arthropod bite reaction with intraluminal thrombi

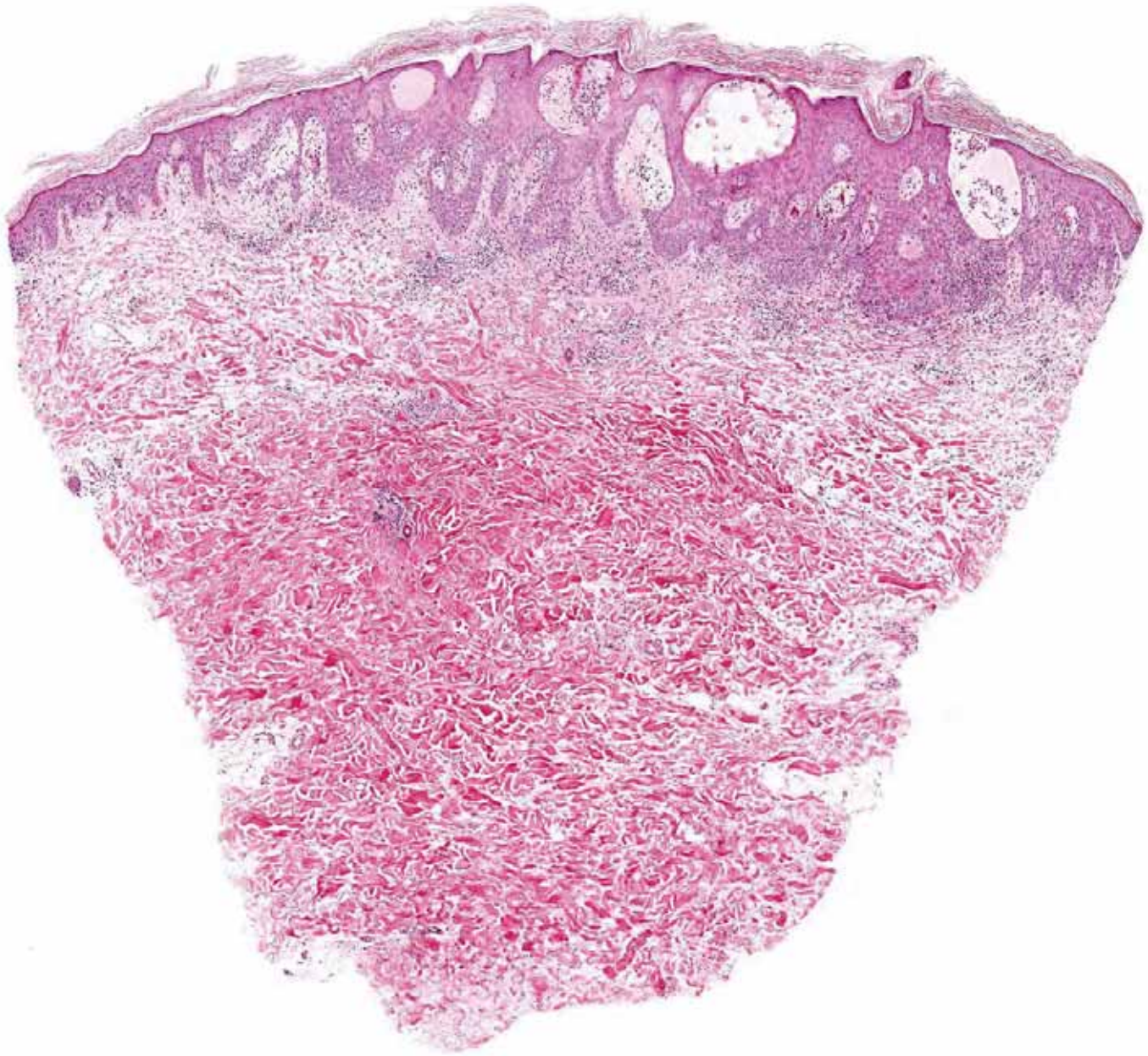
Vascular occlusive diseases

MORE COMMON

- Arthropod bite reactions
- Atrophie blanche (livedo vasculitis)
- Antiphospholipid syndrome
- Protein C and S deficiency
- Covid-19 / Covid-19 vaccination
- Cryoglobulinemia
- DIC / Purpura fulminans
- Cholesterol emboli
- Sneddon's syndrome

LESS COMMON

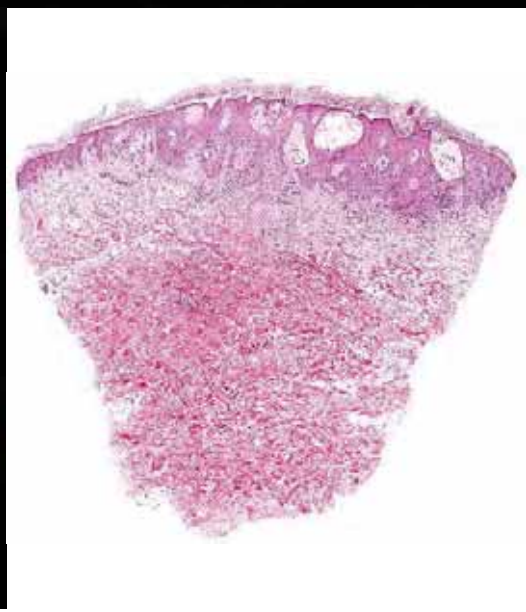
- Warfarin necrosis
- Embolia cutis medicamentosa
- Prothrombin gene mutations
- Thrombotic thrombocytopenic purpura
- Thrombocythemia
- Factor V Leiden mutations
- CADASIL
- Levamisole adulterated cocaine
- Others

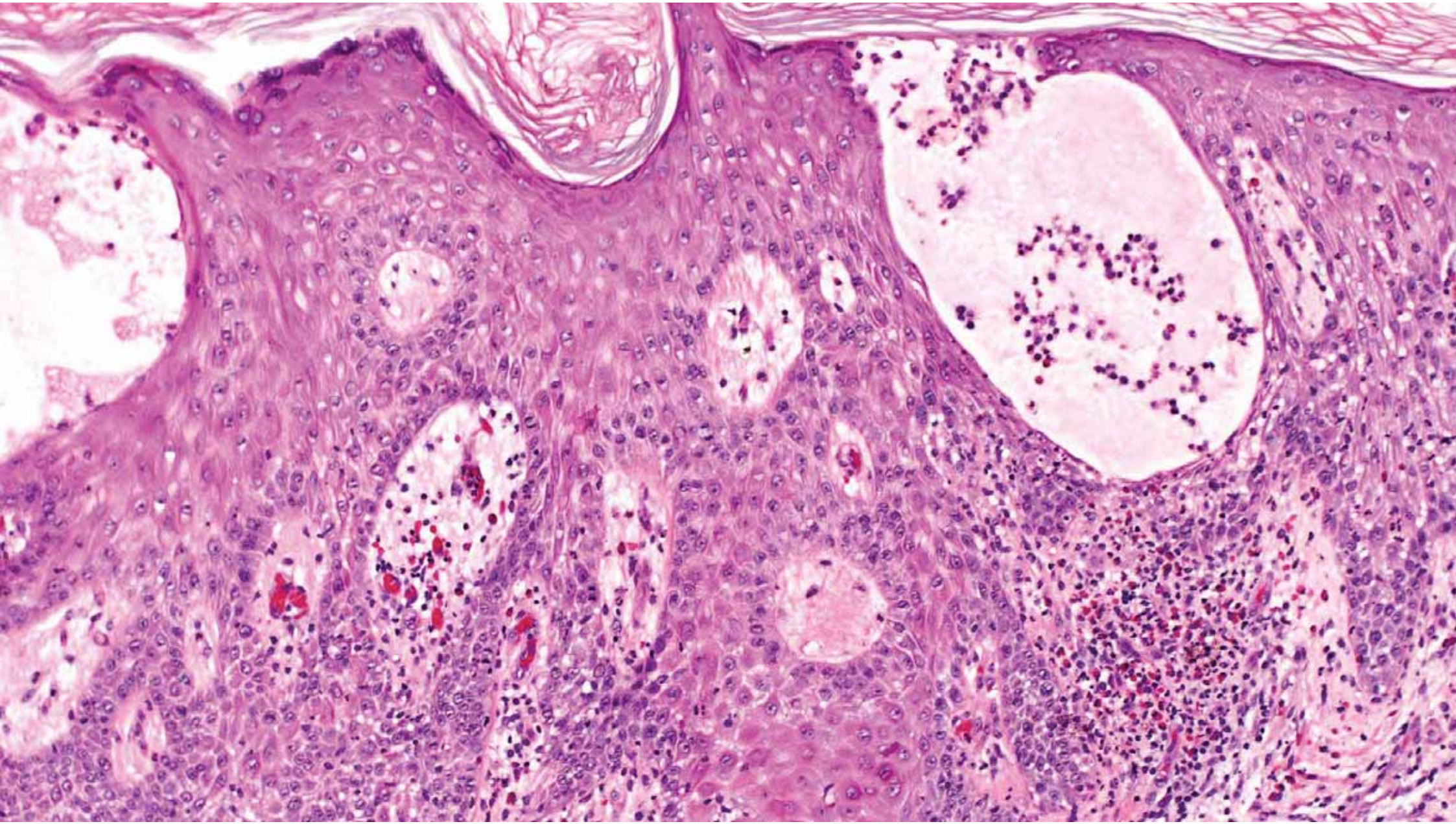


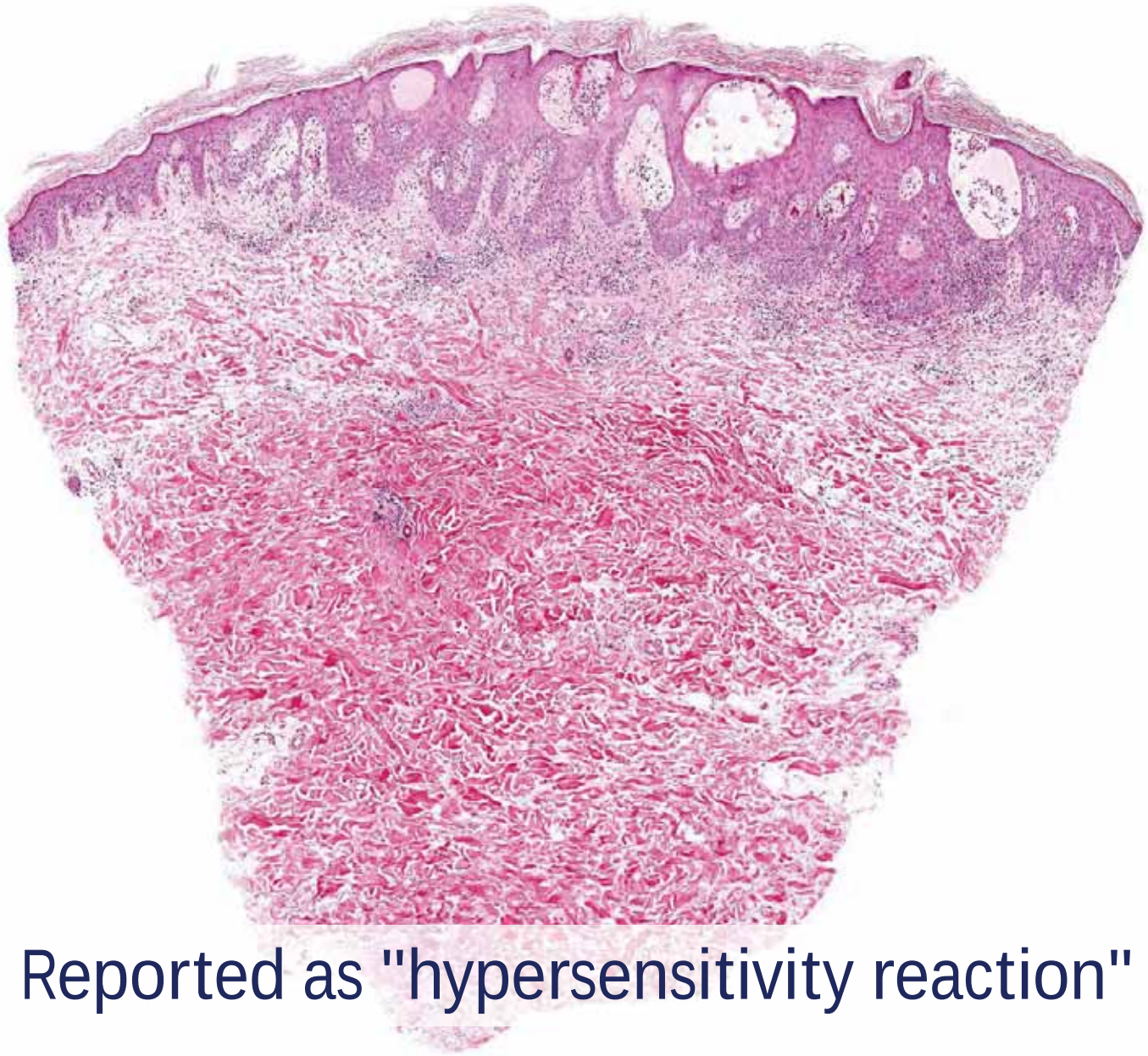
Case 16

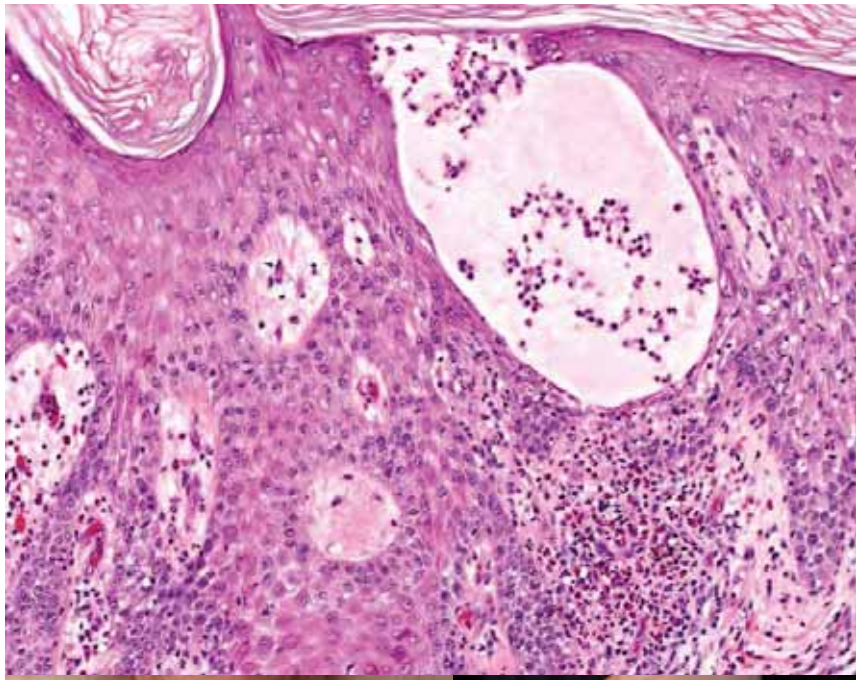
M, 63. A few days after an upper respiratory tract infection onset of generalized papulo-vesicular lesions, becoming confluent and hemorrhagic on the hands.

No fever, no systemic symptoms.



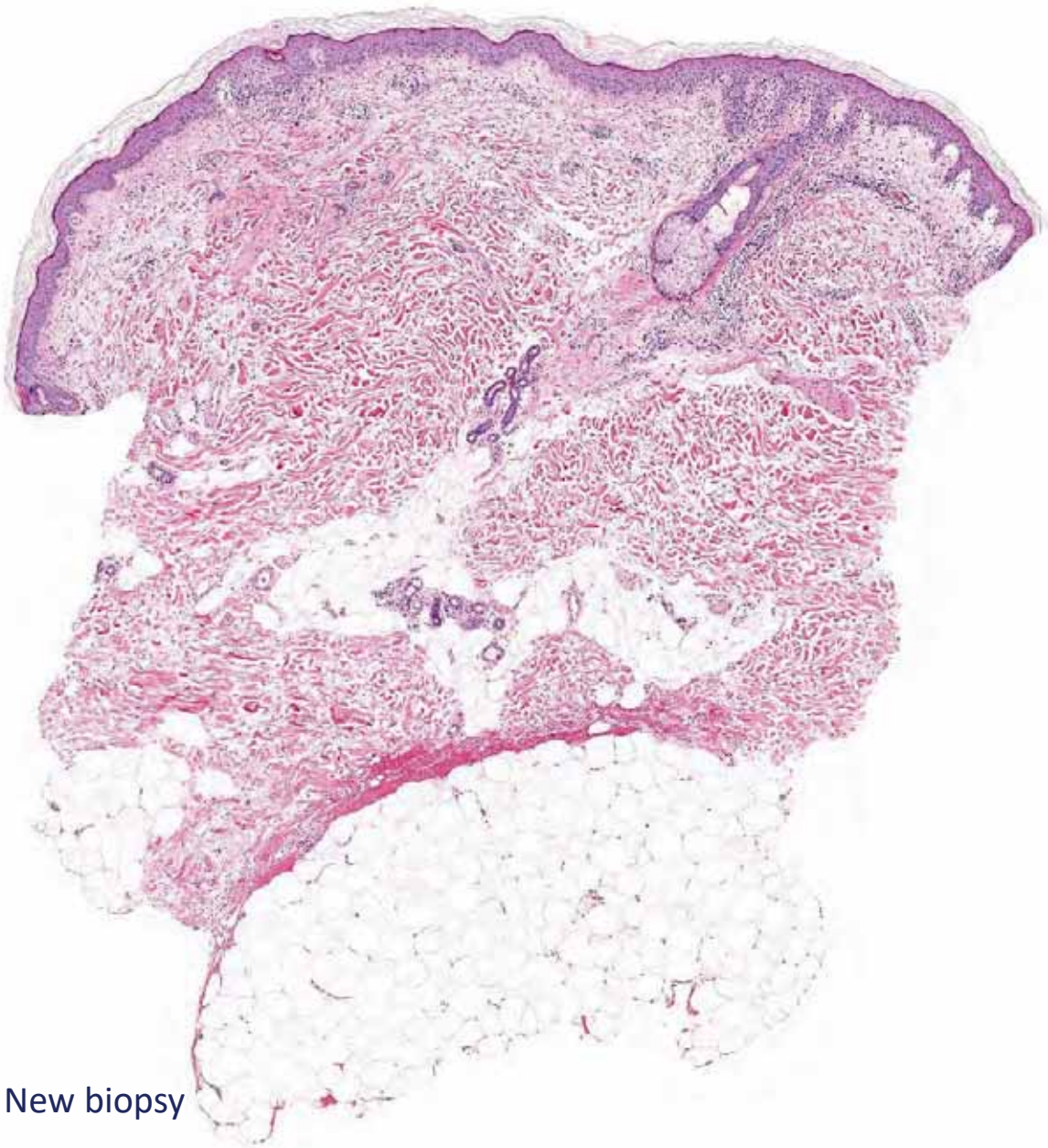




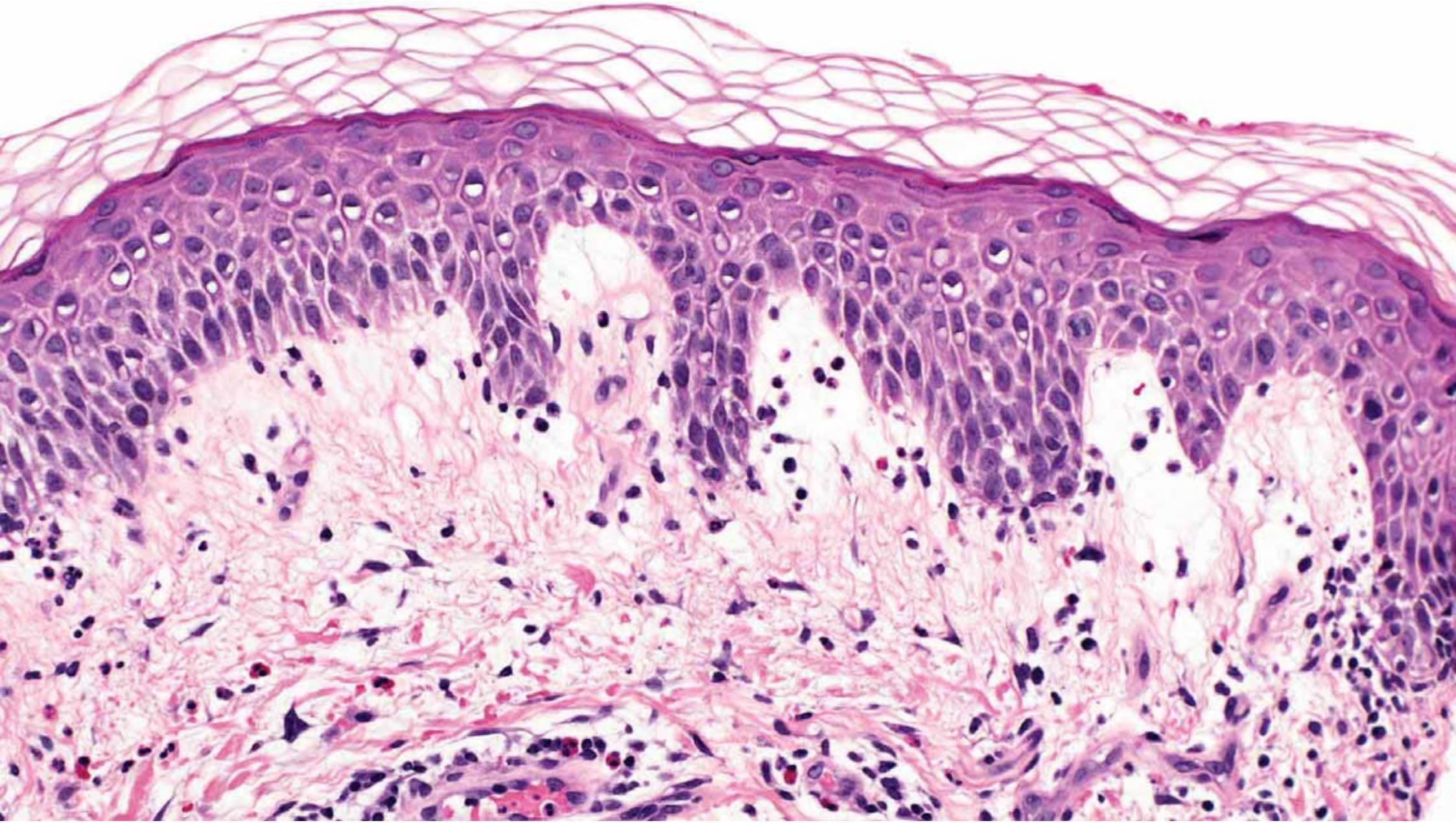


Reported as "hypersensitivity reaction"

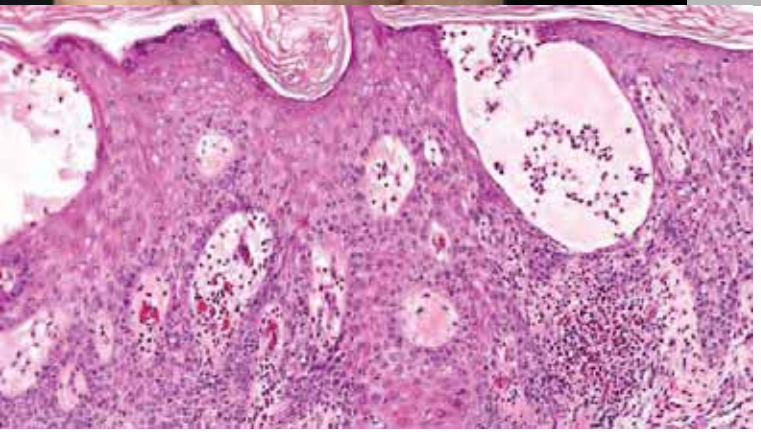
2 months later



New biopsy



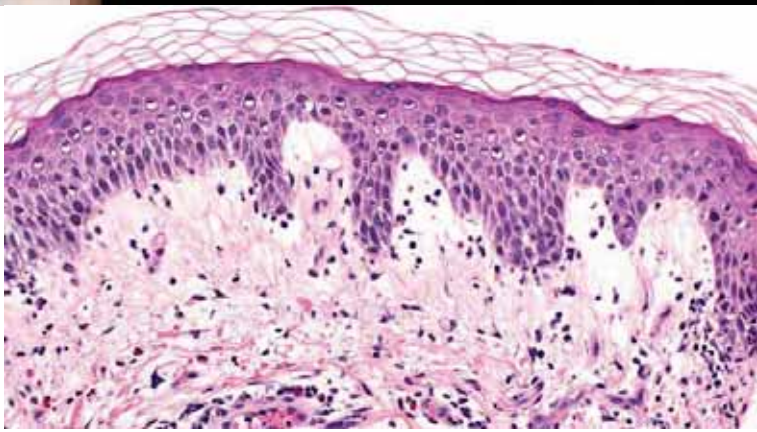
Bullous pemphigoid



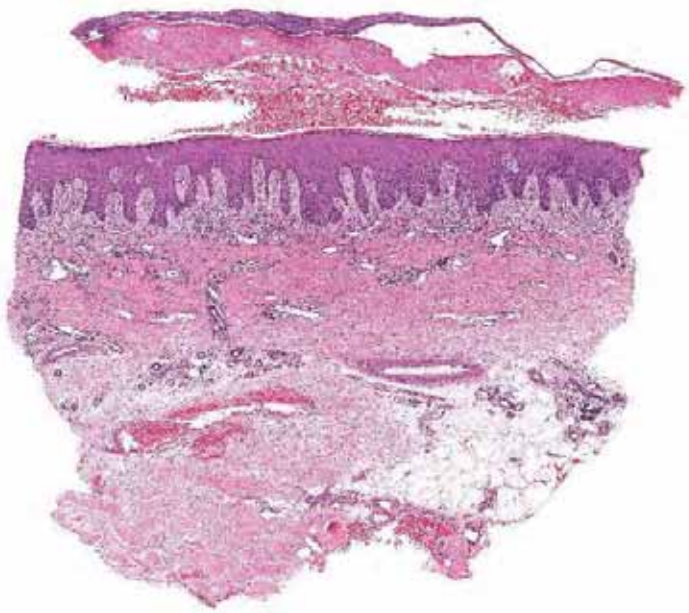
DIF: linear deposition of IgG and C3 with"n-serrated" pattern along the dermoepidermal junction

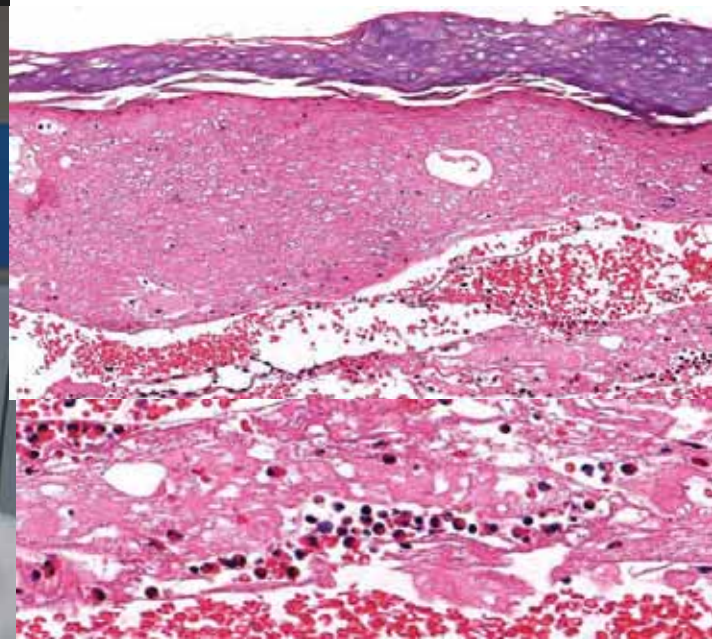
IIF:

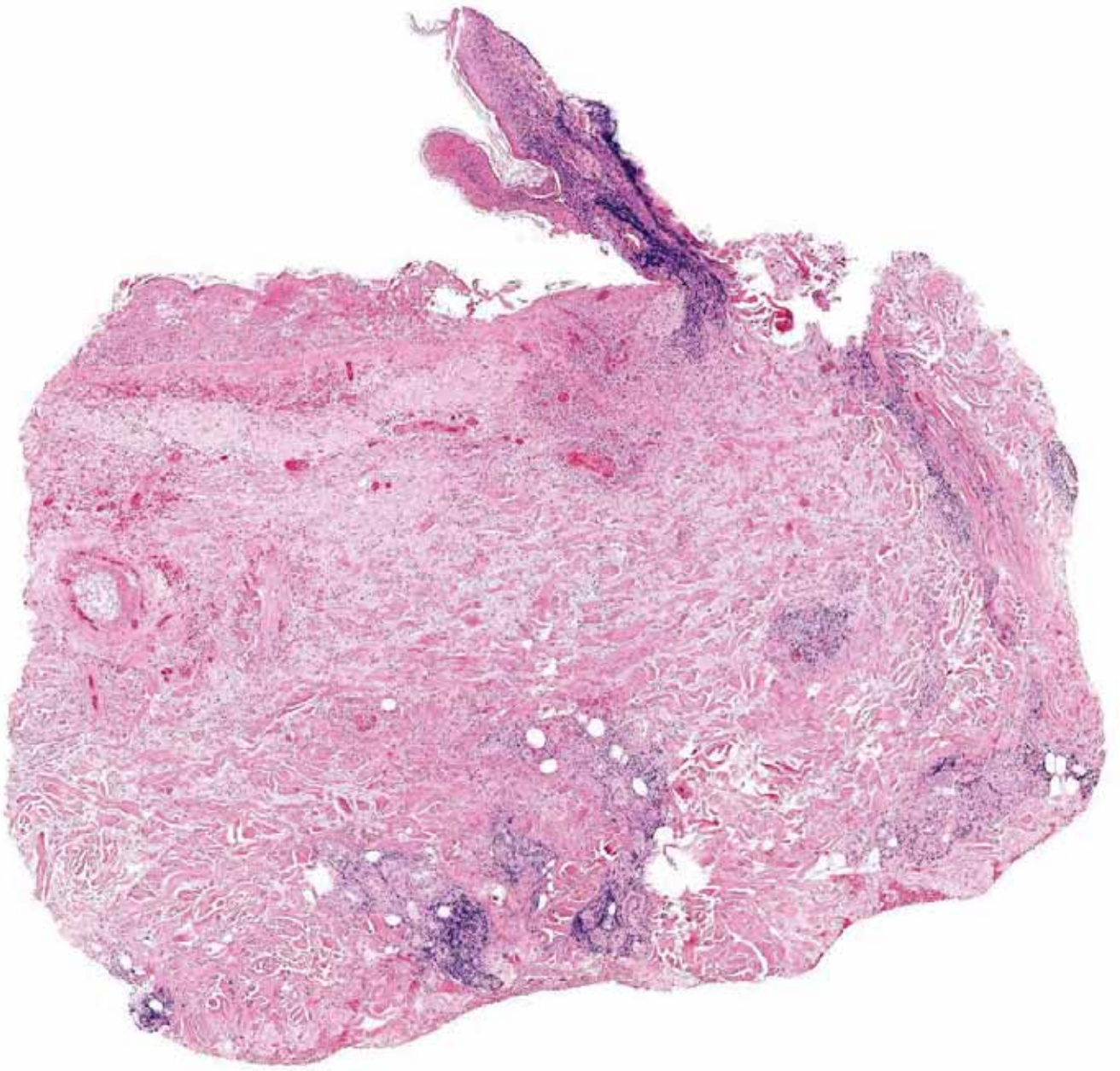
BP180	69+ U/mL (0-14)
BP230	57+ U/mL (0-8)



Bullous pemphigoid on the hands and feet

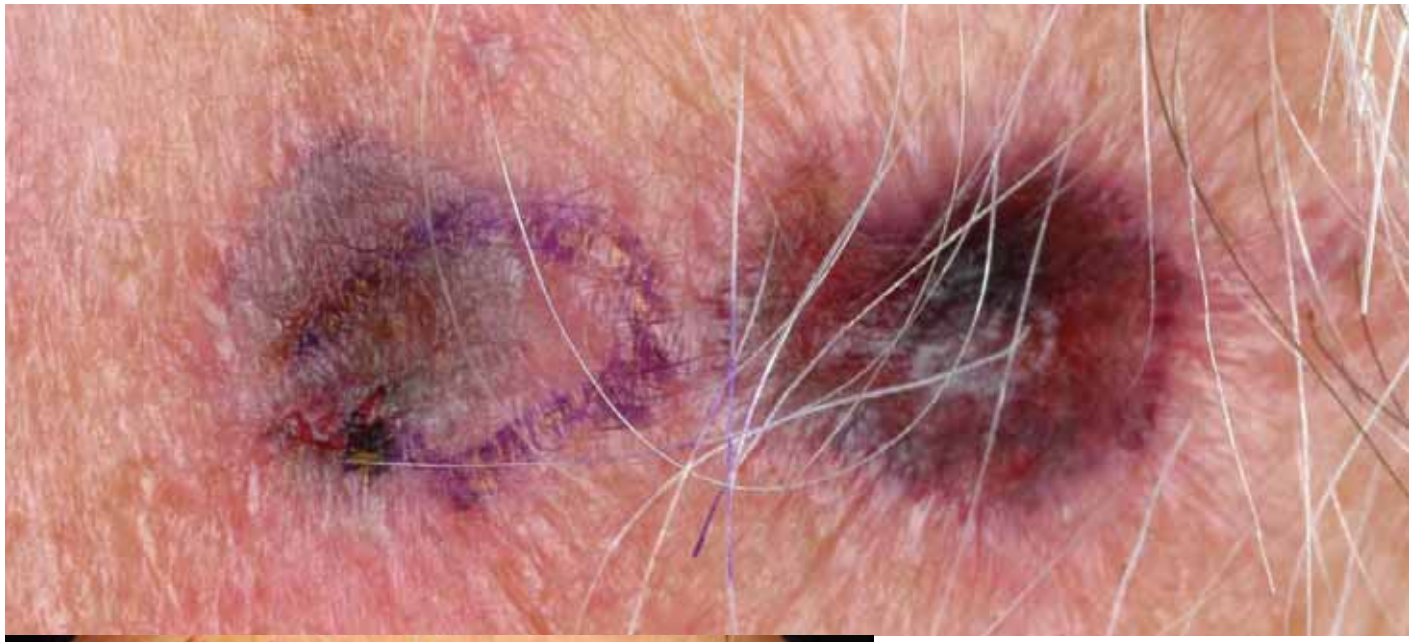


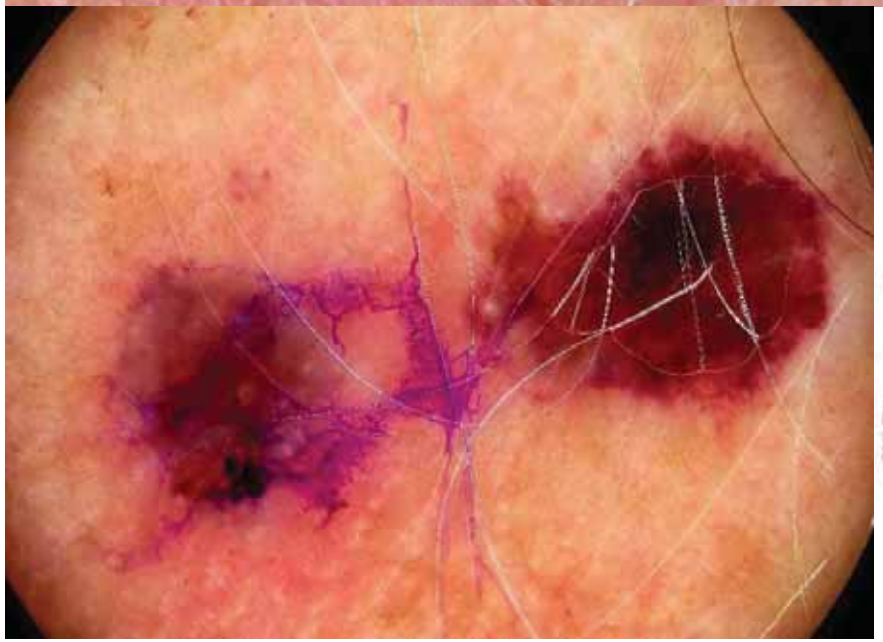


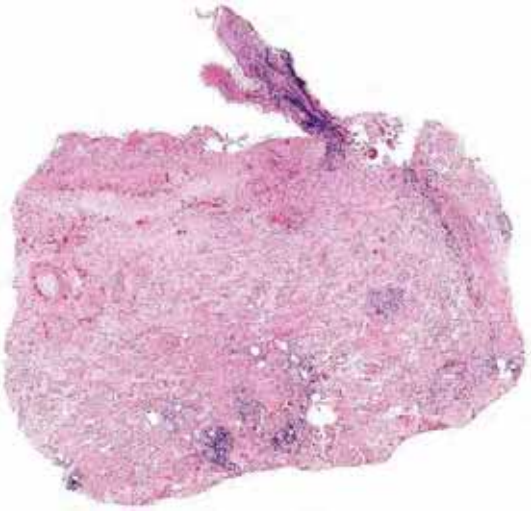


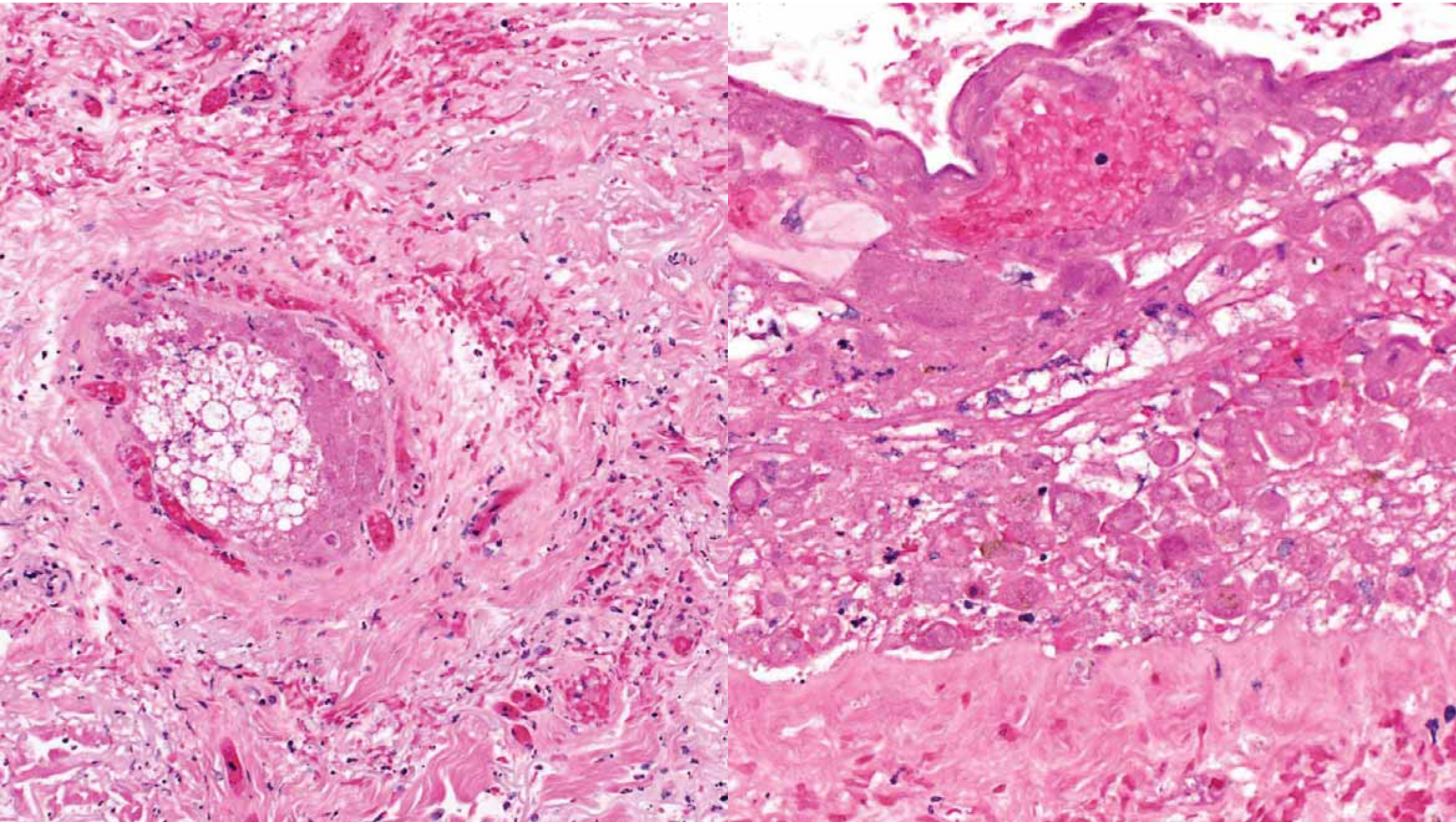
Case 17

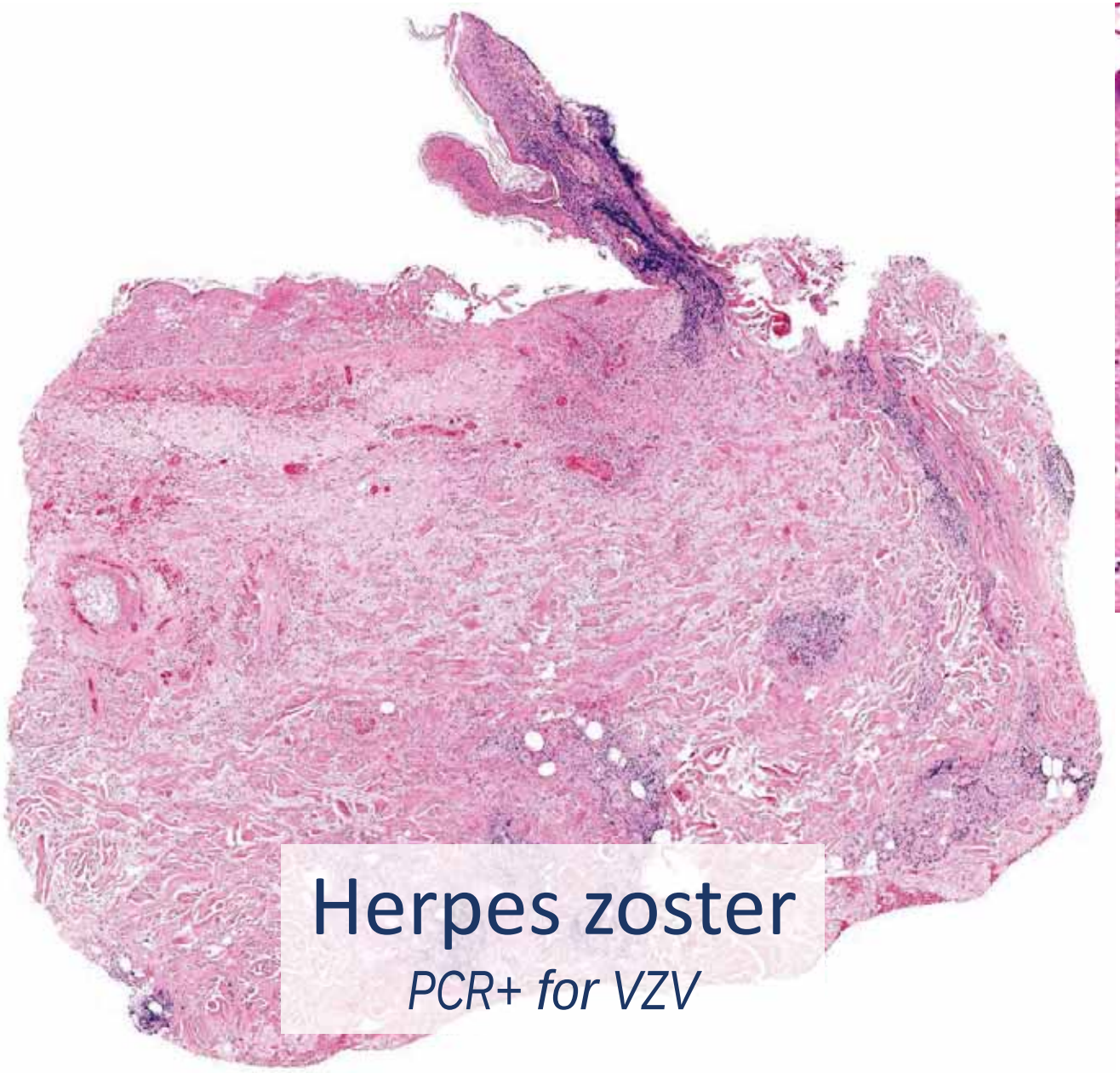
M, 90. According to the patient asymptomatic skin lesion on the left temple for 14 days. Sent by a private dermatologist because of suspicion of basal cell carcinoma.





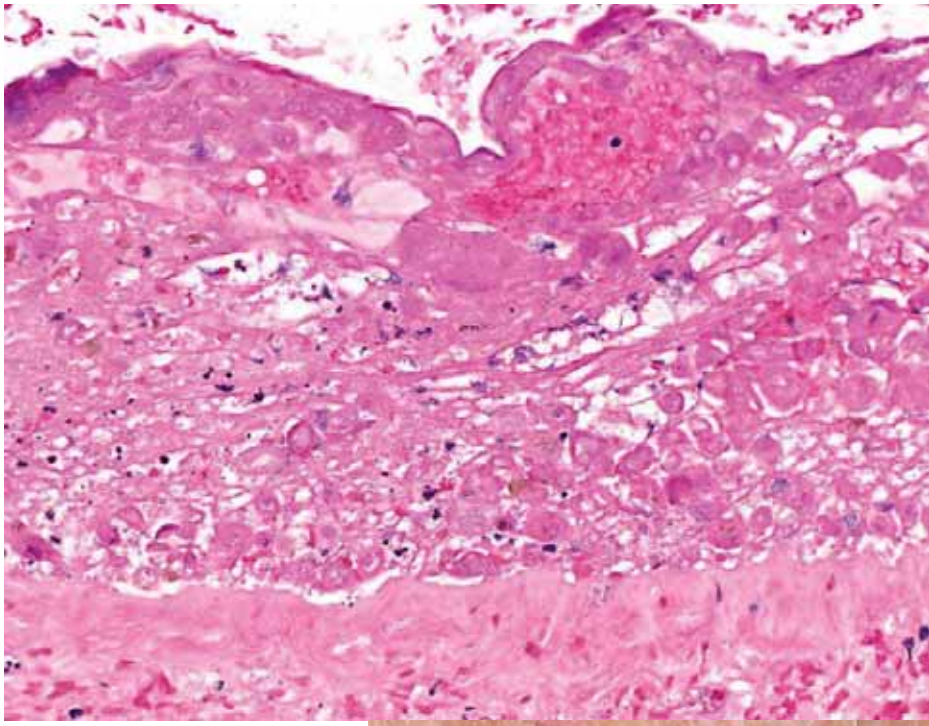




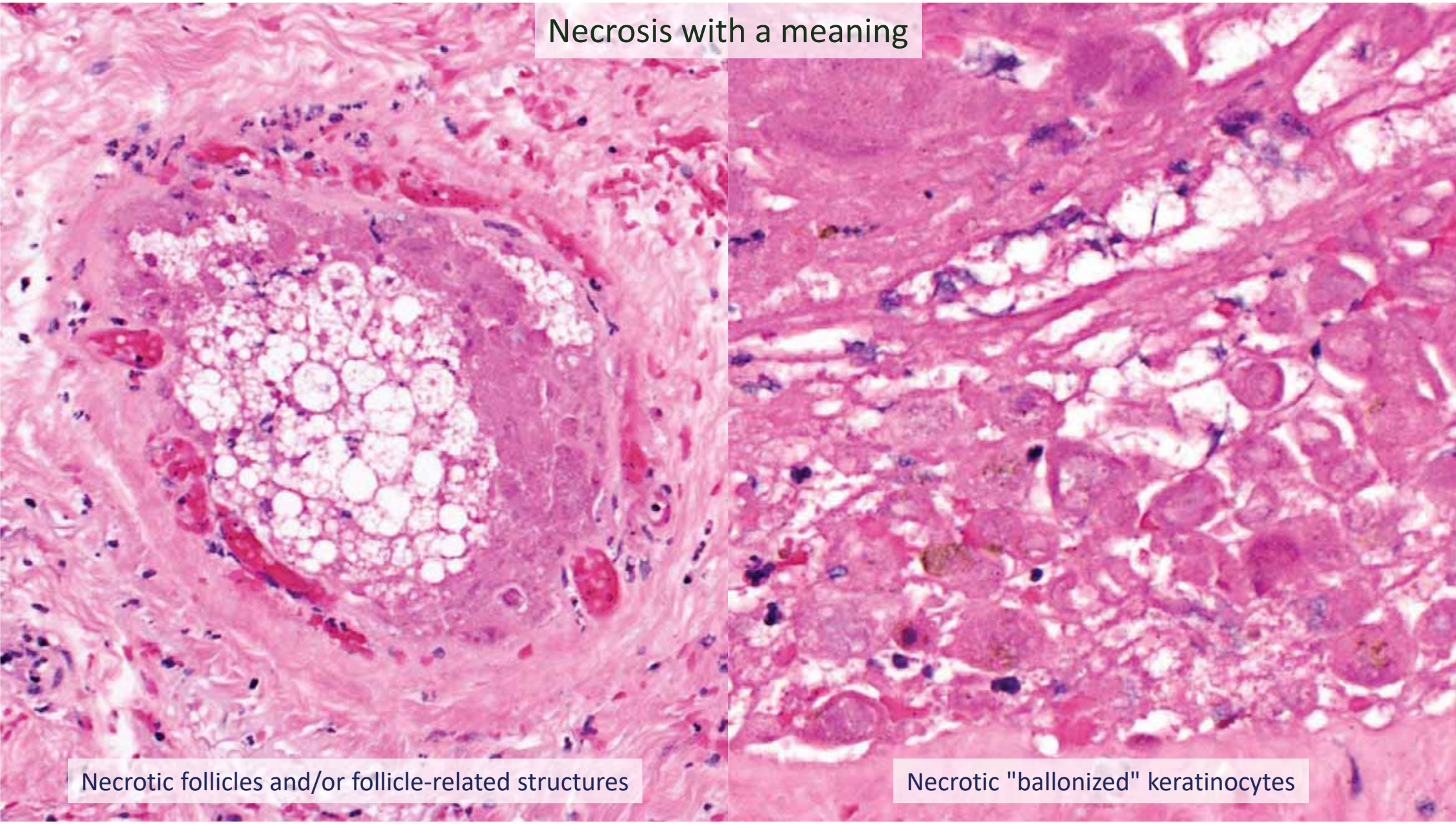


Herpes zoster

PCR+ for VZV

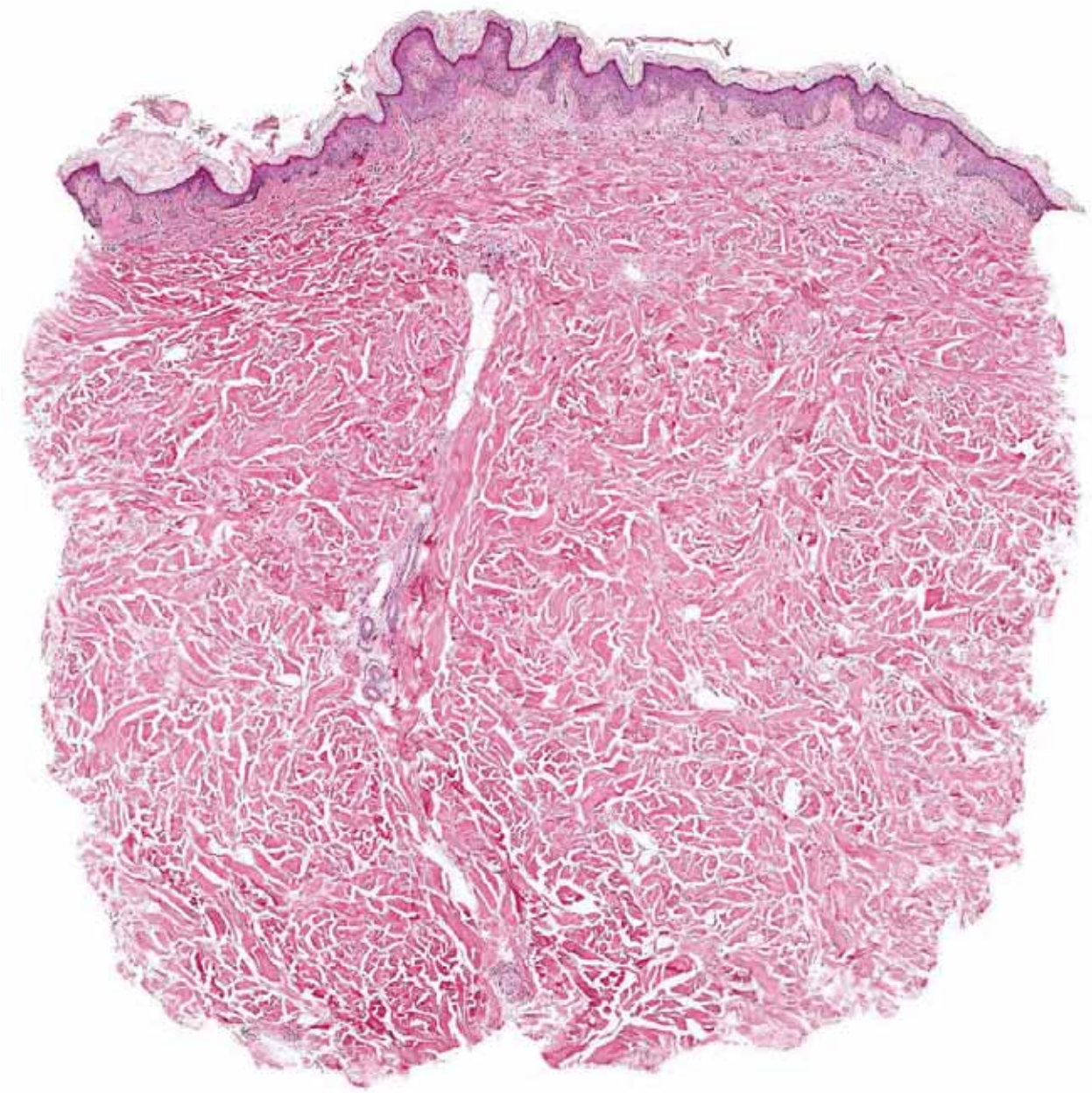


Necrosis with a meaning



Necrotic follicles and/or follicle-related structures

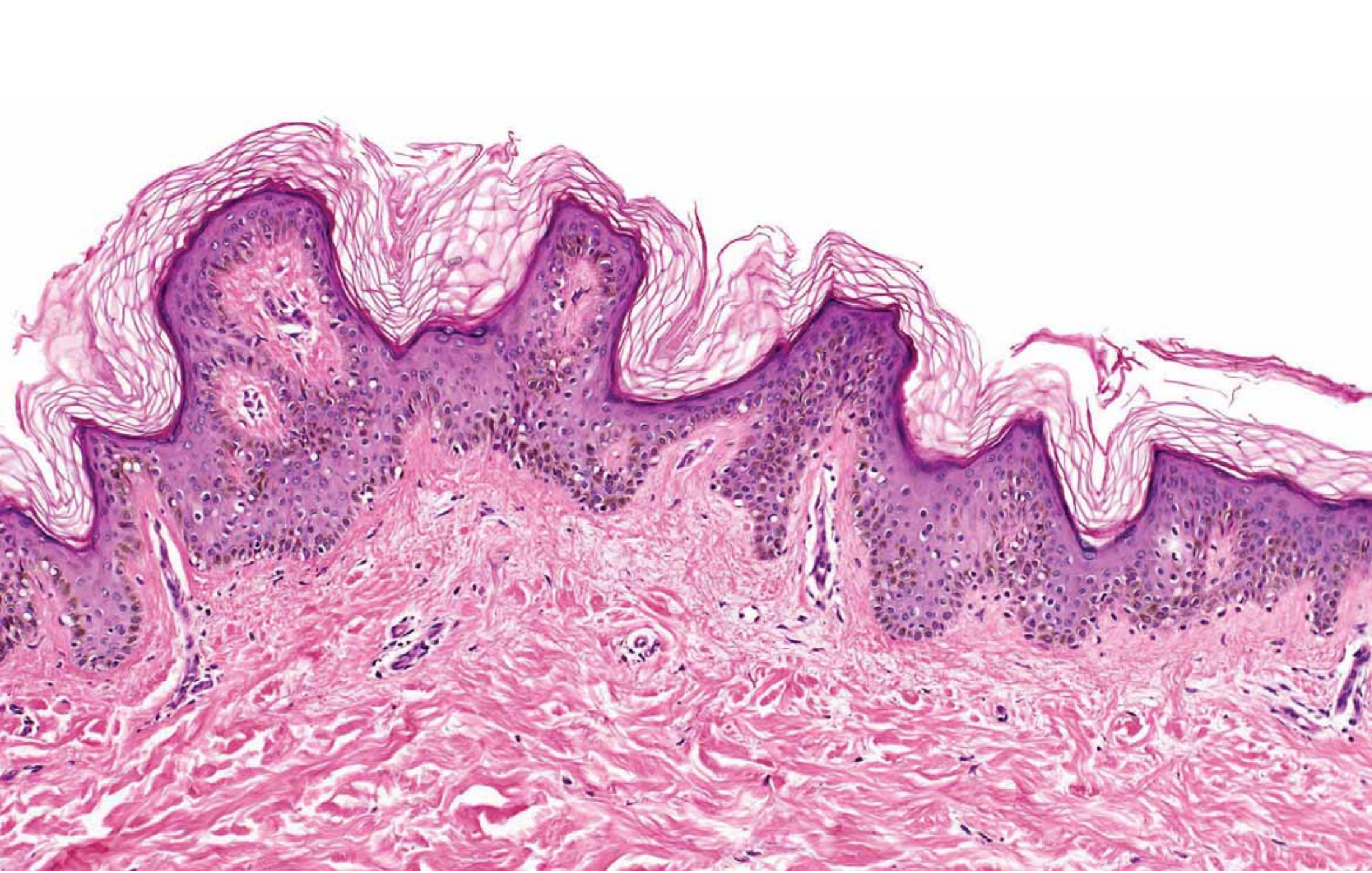
Necrotic "ballonized" keratinocytes

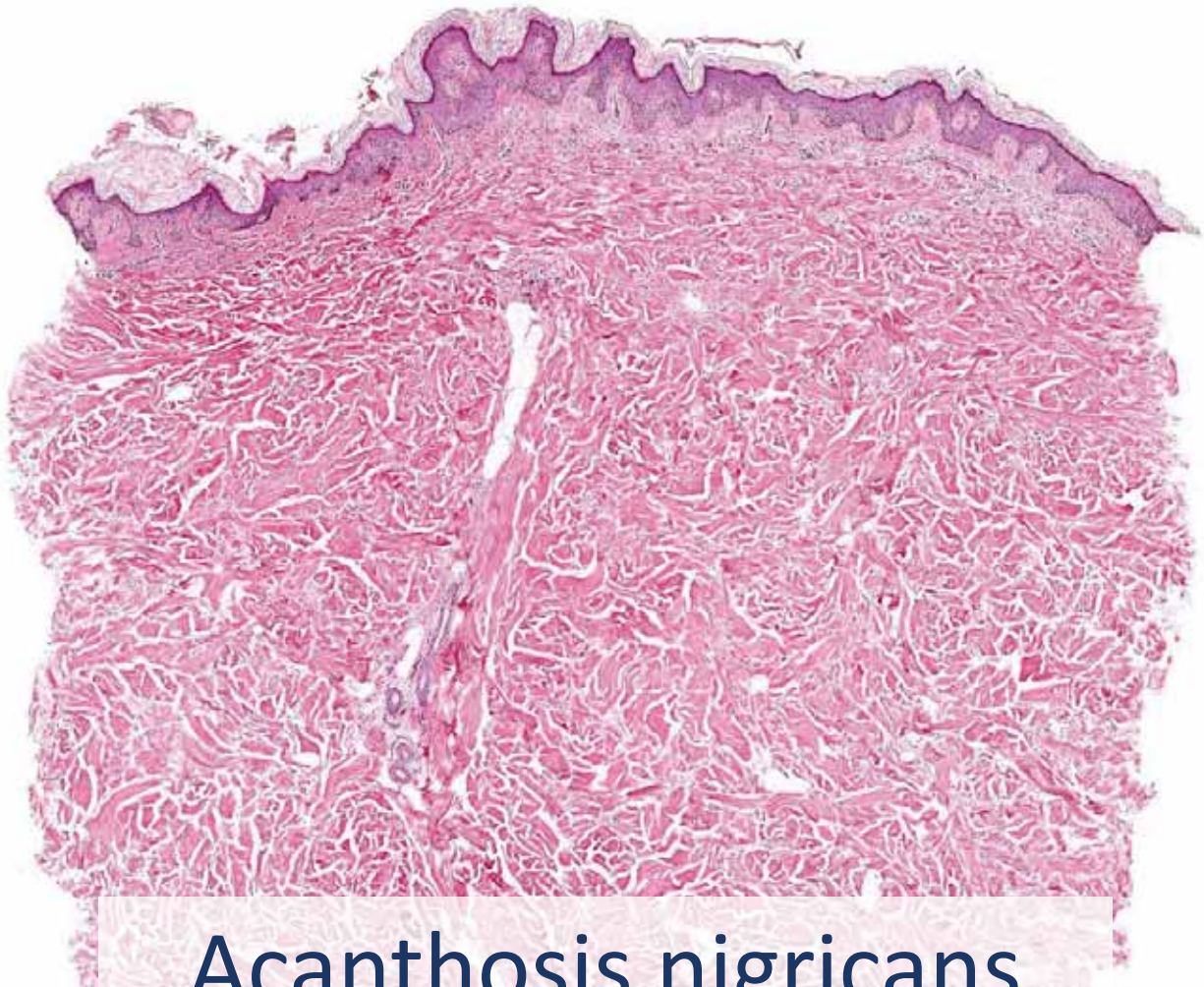


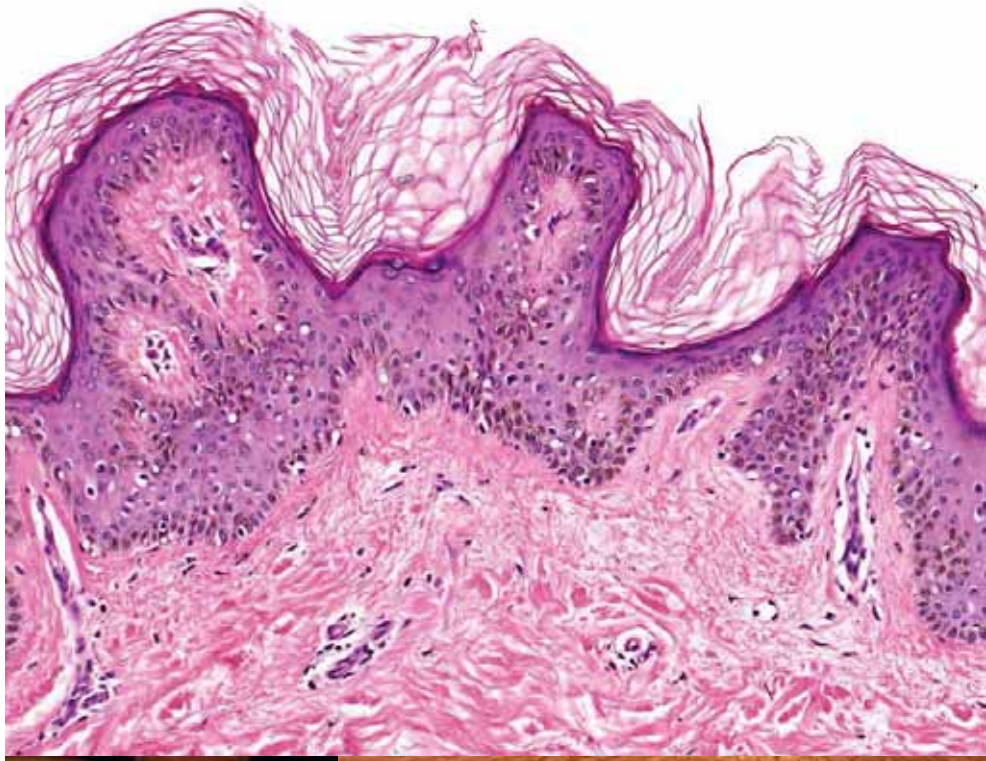
Case 18

M, 50. History of psoriasis for 26 years (at present managed with guselkumab).

According to the patient hyperpigmentation, particularly on the trunk, "for some years".

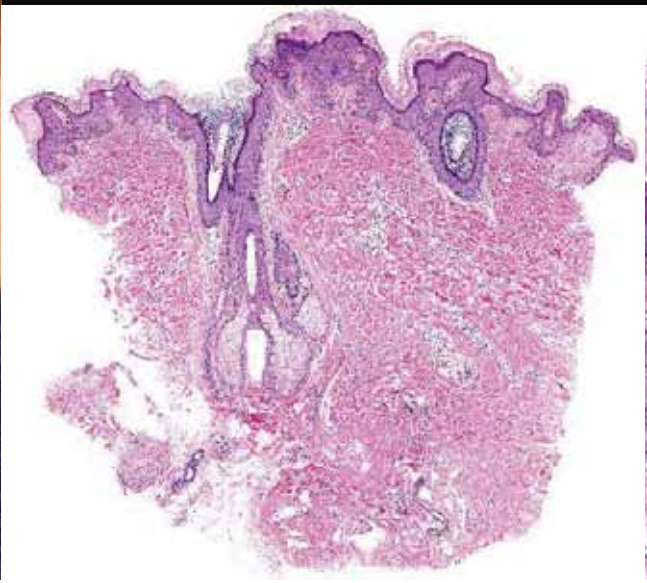


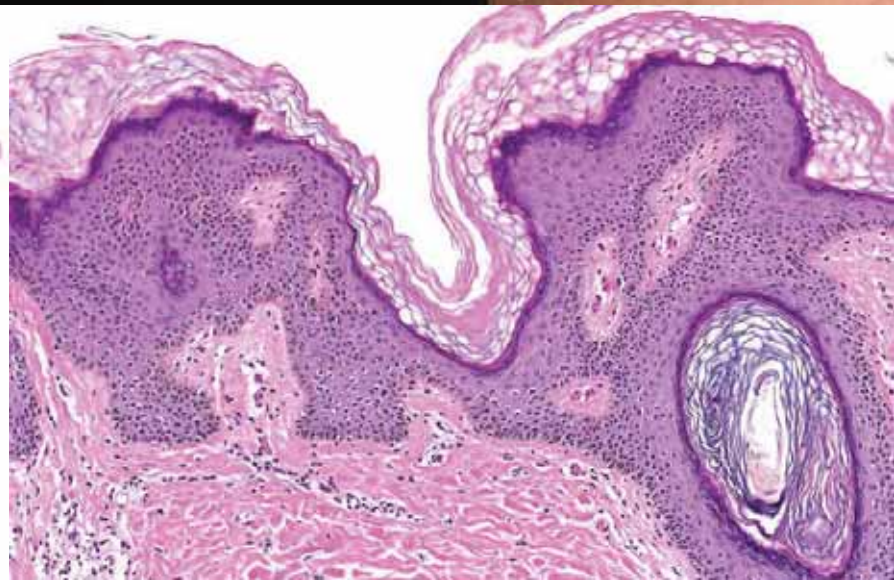


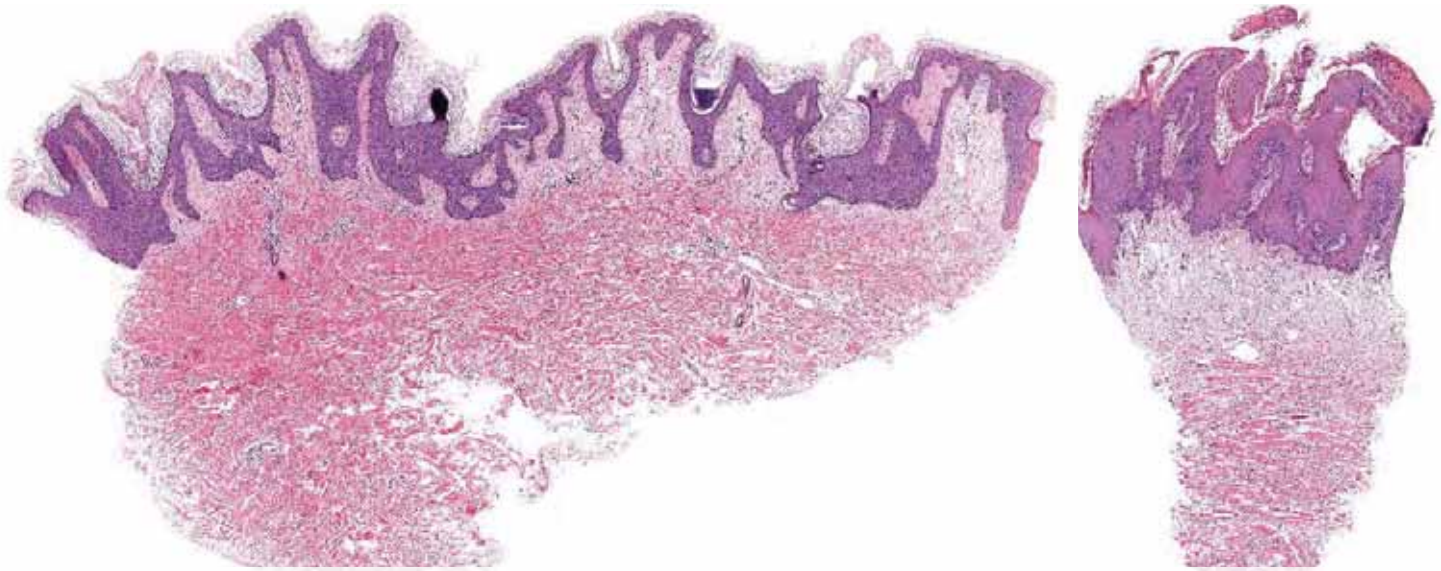


Acanthosis nigricans

(obesity-associated – "pseudoacanthosis nigricans")



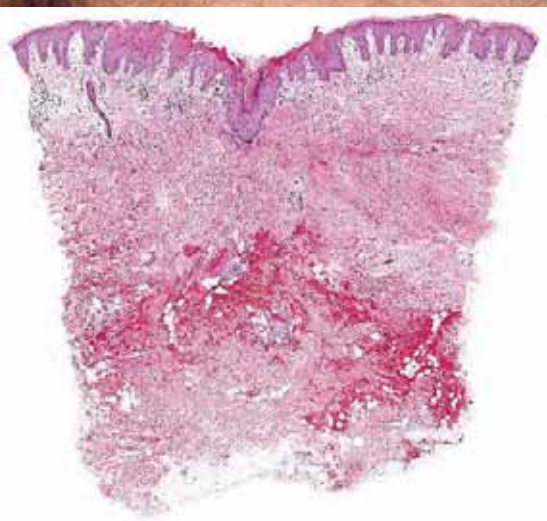


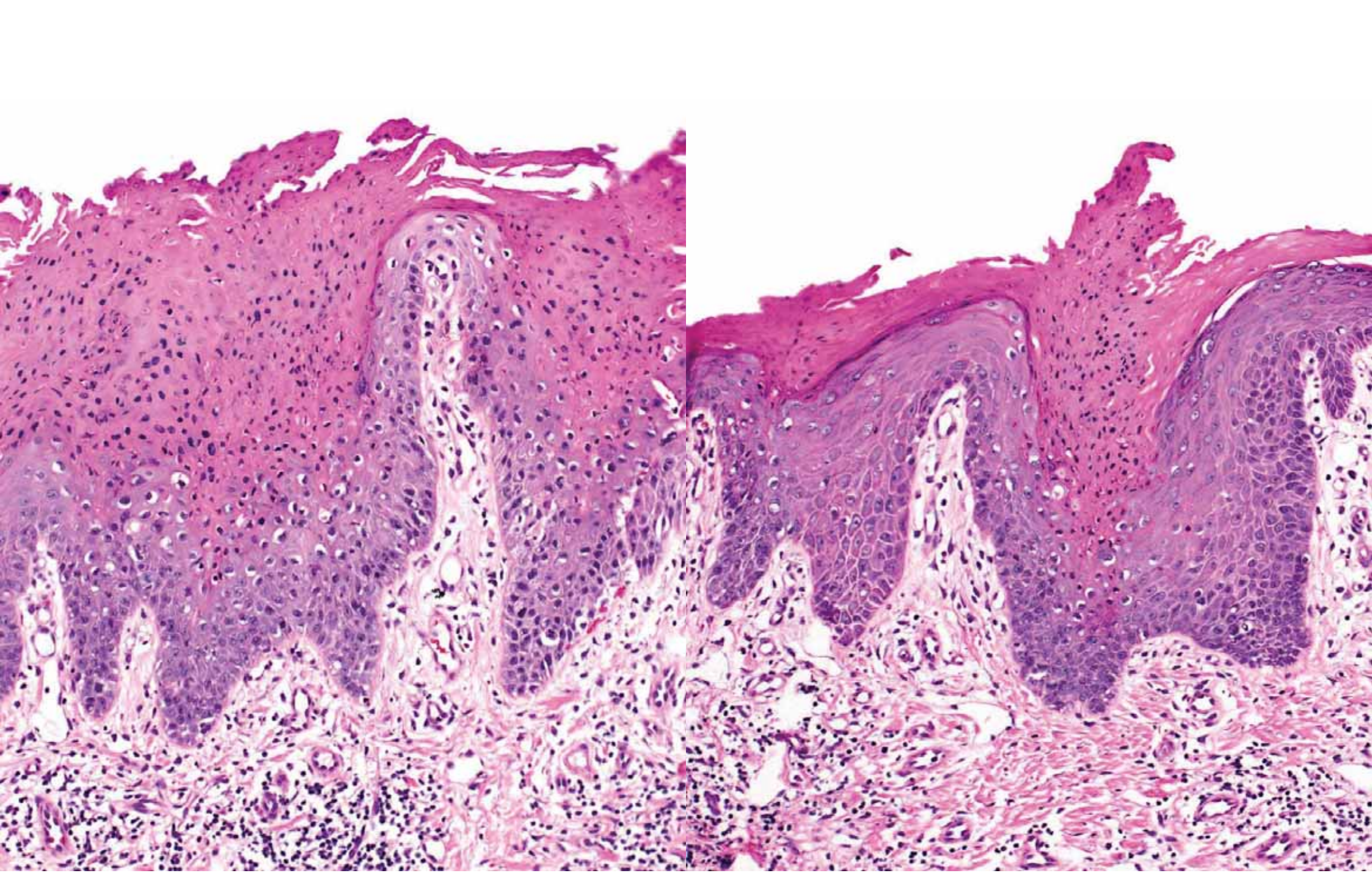


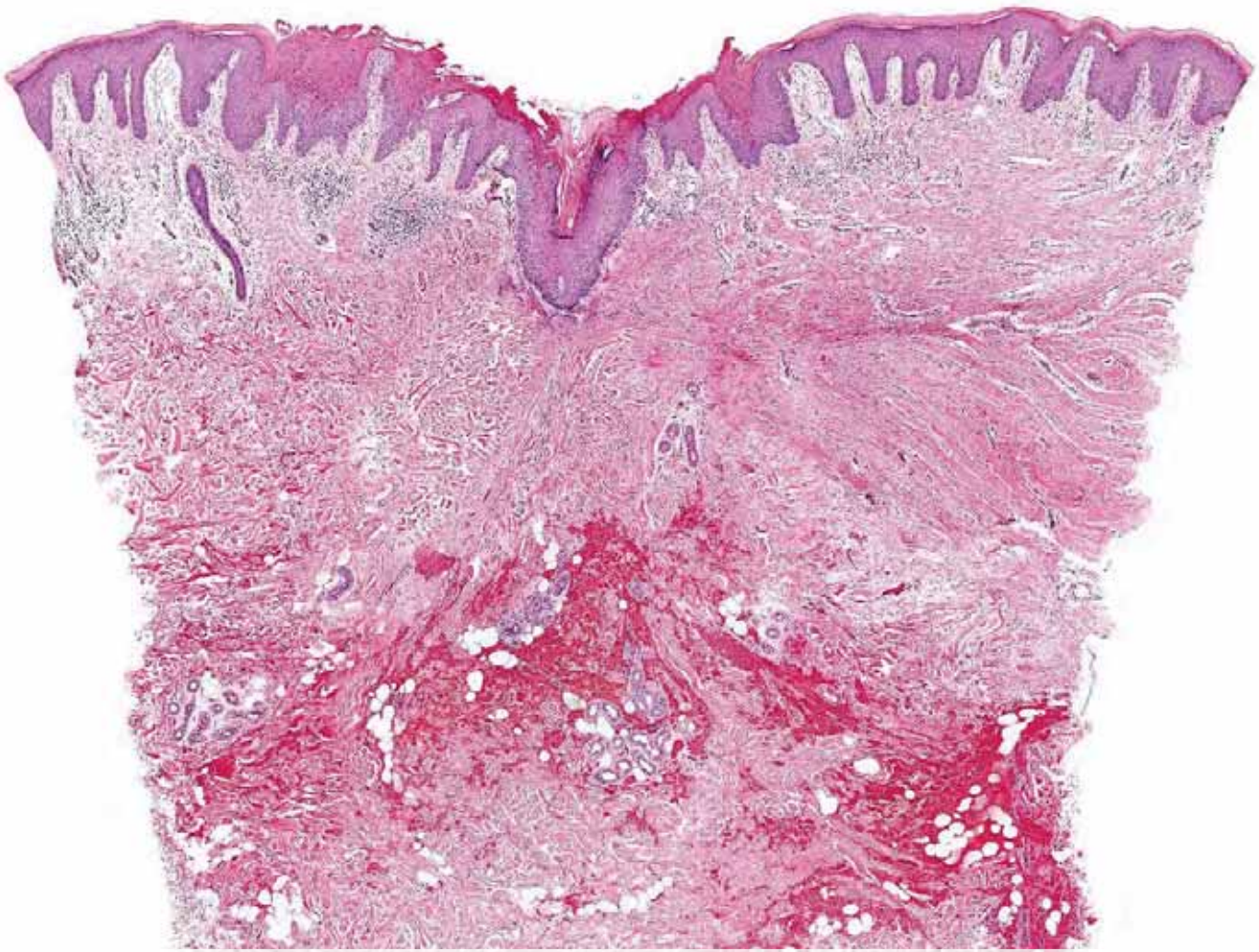
Involvement of lips and oral mucosa is a clue to paraneoplastic acanthosis nigricans

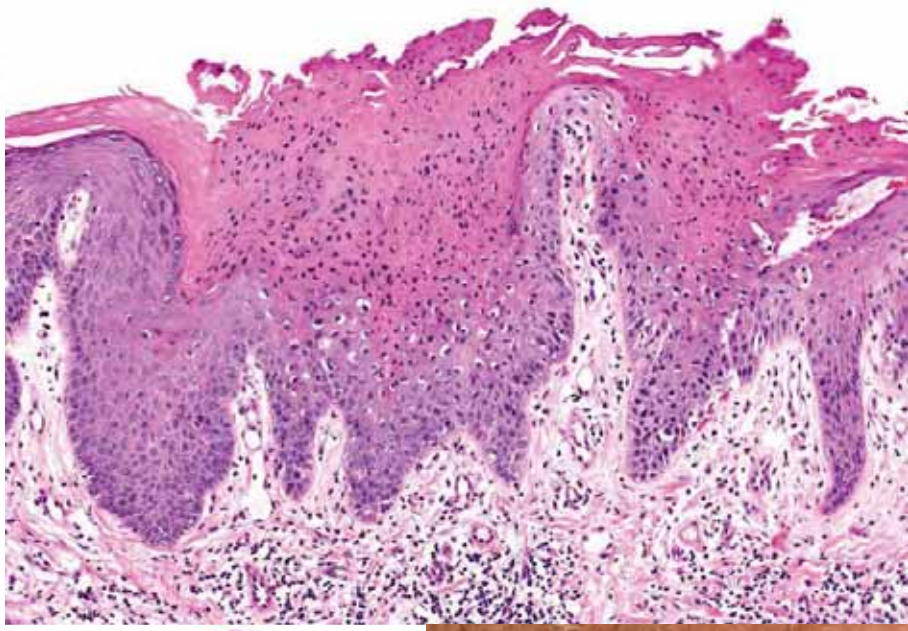
Case 19

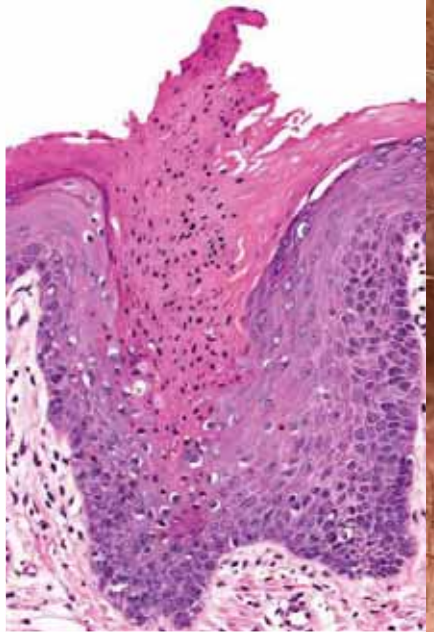
M, 61. According to the patient perianal "eczema" for 4 years; a private dermatologist found several "fungi"; no improvement after 2 weeks of systemic antimycotic treatment.











Porokeratosis ptychotropica & chronic eczema

Clinical and Experimental Dermatology

Porokeratosis ptychotropica: a lesser-known variant

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Summary

We report a case of the rare porokeratosis variant porokeratosis ptychotropica (PP). A circumferential perianal plaque and the characteristic histology of multiple cornoid lamellae with underlying dermal amyloid deposition were seen. Amyloid deposition was seen in the biopsied intertriginous area of the plaque only, which, in concordance with other cutaneous amyloid deposition disorders, may suggest a role for friction in the pathogenesis of this histological finding. We review the literature on PP and summarize the poor response seen to treatments.

Porokeratosis comprises a spectrum of five well-known clinically distinct variants: (i) porokeratosis of Mibelli; (ii) disseminated superficial actinic porokeratosis (DSAP); (iii) punctate porokeratosis; (iv) linear porokeratosis; and (iv) porokeratosis plantaris, palmaris et disseminata. A rare lesser-known variant, porokeratosis ptychotropica (PP), affects the gluteal cleft, with the histology showing multiple cornoid lamellae and dermal amyloid deposition.

We report a patient with PP, review the literature on PP and summarize the poor response seen to treatments.

Report

A 61-year-old man presented with a 6-year history of an itchy perianal rash. It had first appeared as discrete red scaly macules that became confluent centrally while spreading outwards by formation of satellite lesions. There was no history of any previous skin or general medical disorder, and no family history of a persistent skin rash. The patient did not report any excessive activity that might have been contributing to increased intertriginous friction.

On physical examination, an erythematous coalescing circumferential perianal plaque was seen, with peripheral small, mildly scaling, erythematous macules (Fig. 1).

An initial shave biopsy was taken from the intertriginous zone of the plaque, with a further punch biopsy 19 months later taken from a peripheral margin. For both biopsies, histological examination found mild hyperkeratosis with formation of multiple columns of parakeratosis overlying focal hypogranulosis and small numbers of dyskeratotic cells, consistent with cornoid lamellae (Figs 2a–c). The initial biopsy had prominent papillary dermal amyloid deposition, which was confirmed with positive staining to Congo red, crystal violet and high molecular weight cytokeratin, although it was absent in the subsequent biopsy. Treatment with

Figure 1 Perianal plaque of porokeratosis ptychotropica.

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Conflict of interest: none declared.

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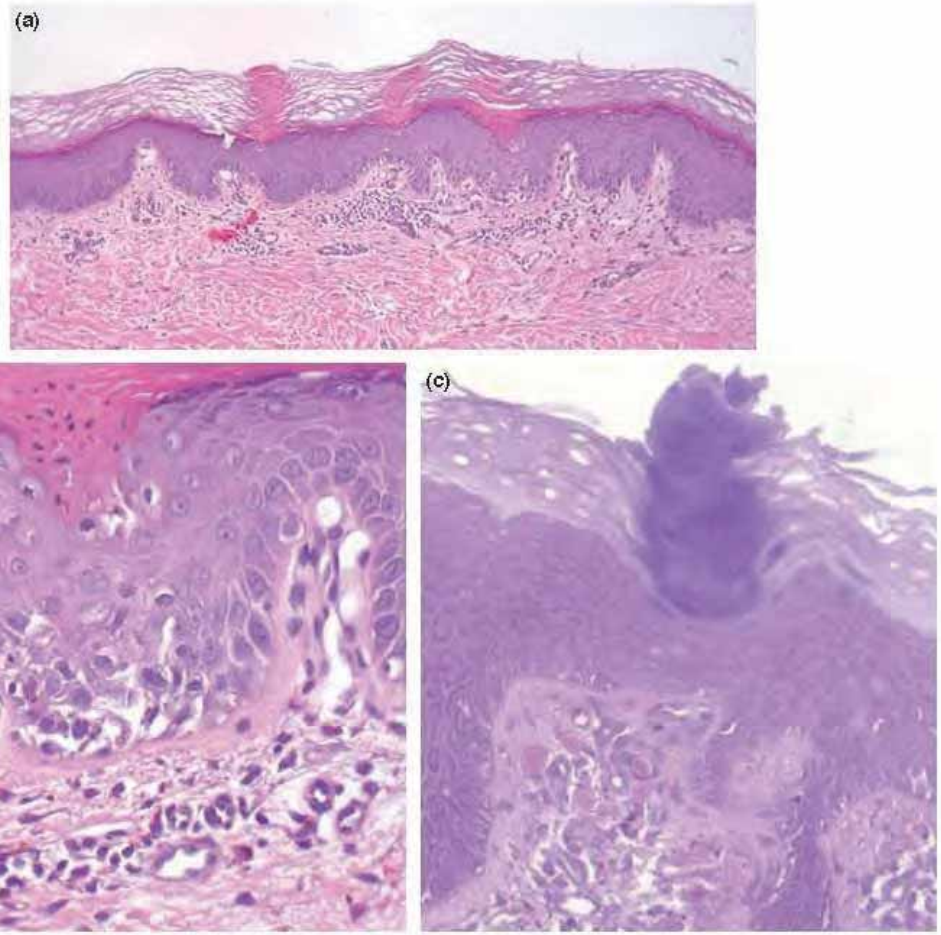
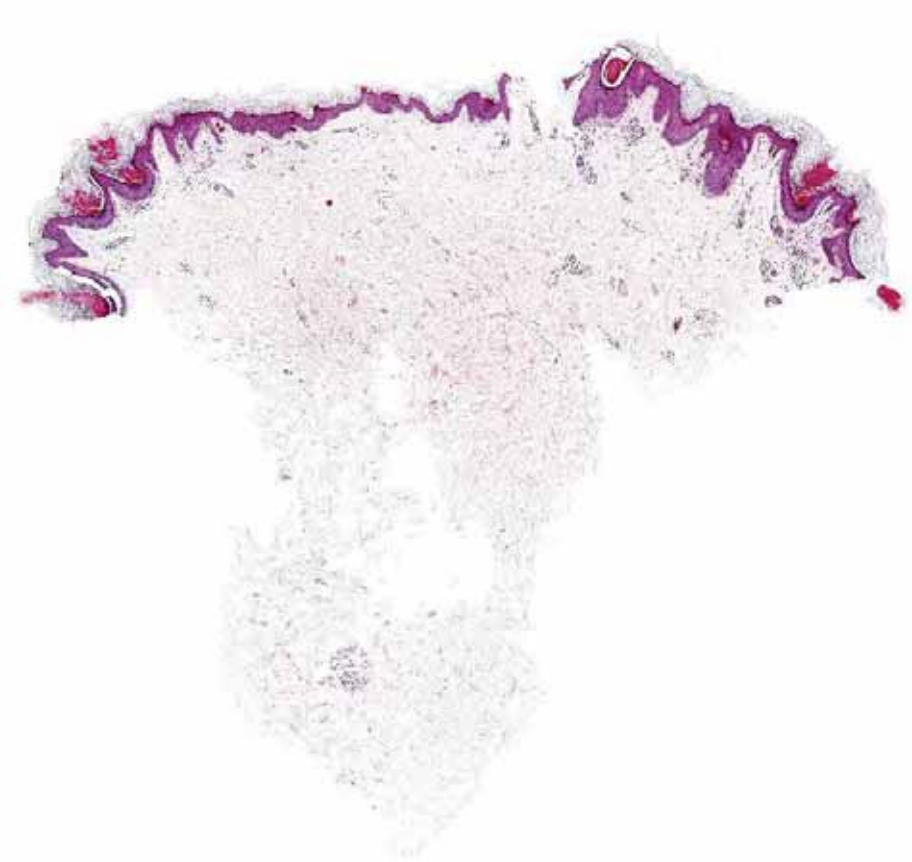
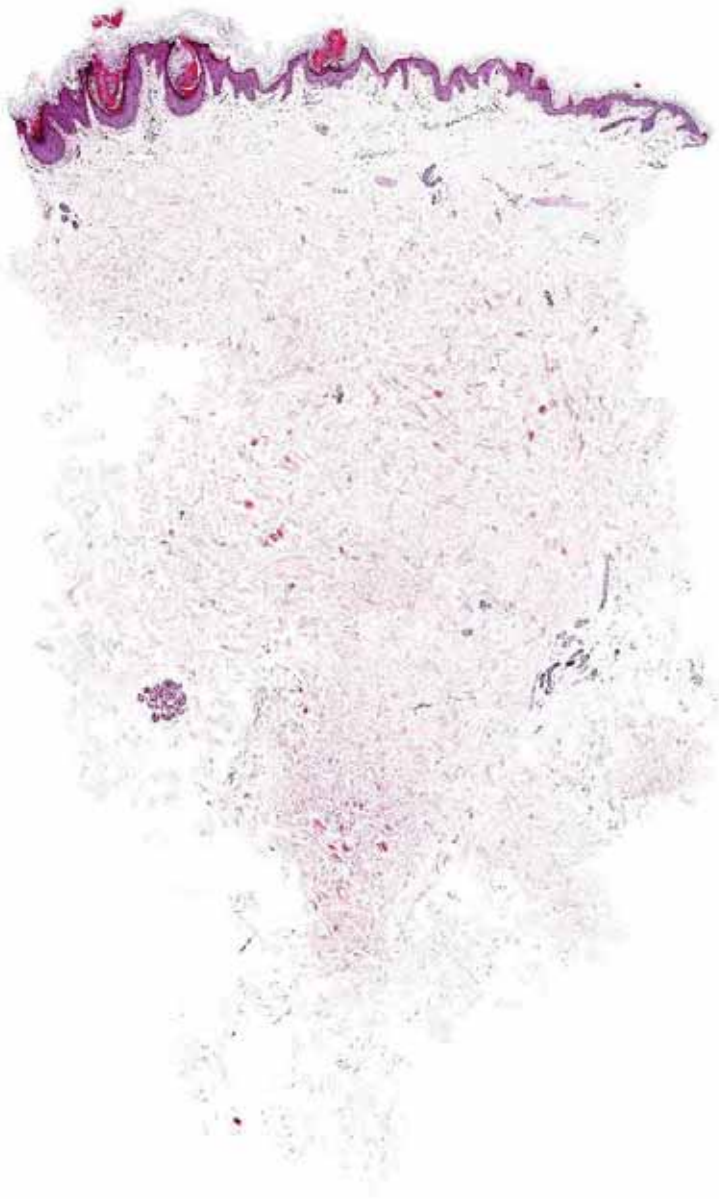


Figure 2 Skin biopsy taken from (a,b) the peripheral margin and (c) the proximal intertriginous area of the buttock plaque, showing (a) mild hyperkeratosis and the characteristic presence of multiple cornoid lamellae (haematoxylin and eosin, original magnification × 10). (b) The base of a parakeratotic column, showing focal hypogranulosis and acantholysis at the basal and upper malphigian layers with no underlying amyloid deposition (haematoxylin and eosin, original magnification × 40). (c) Amyloid deposits (pink) underlying a cornoid lamella (crystal violet, original magnification × 40).

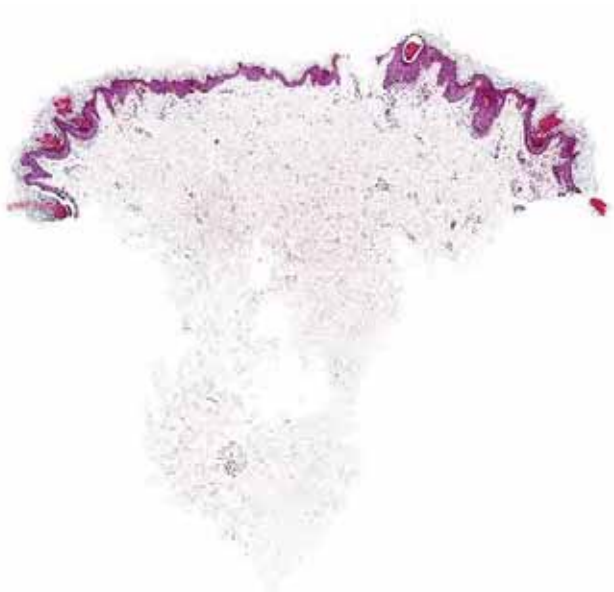
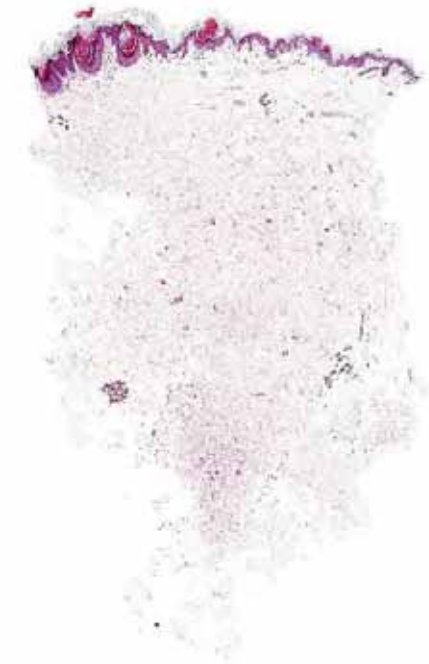


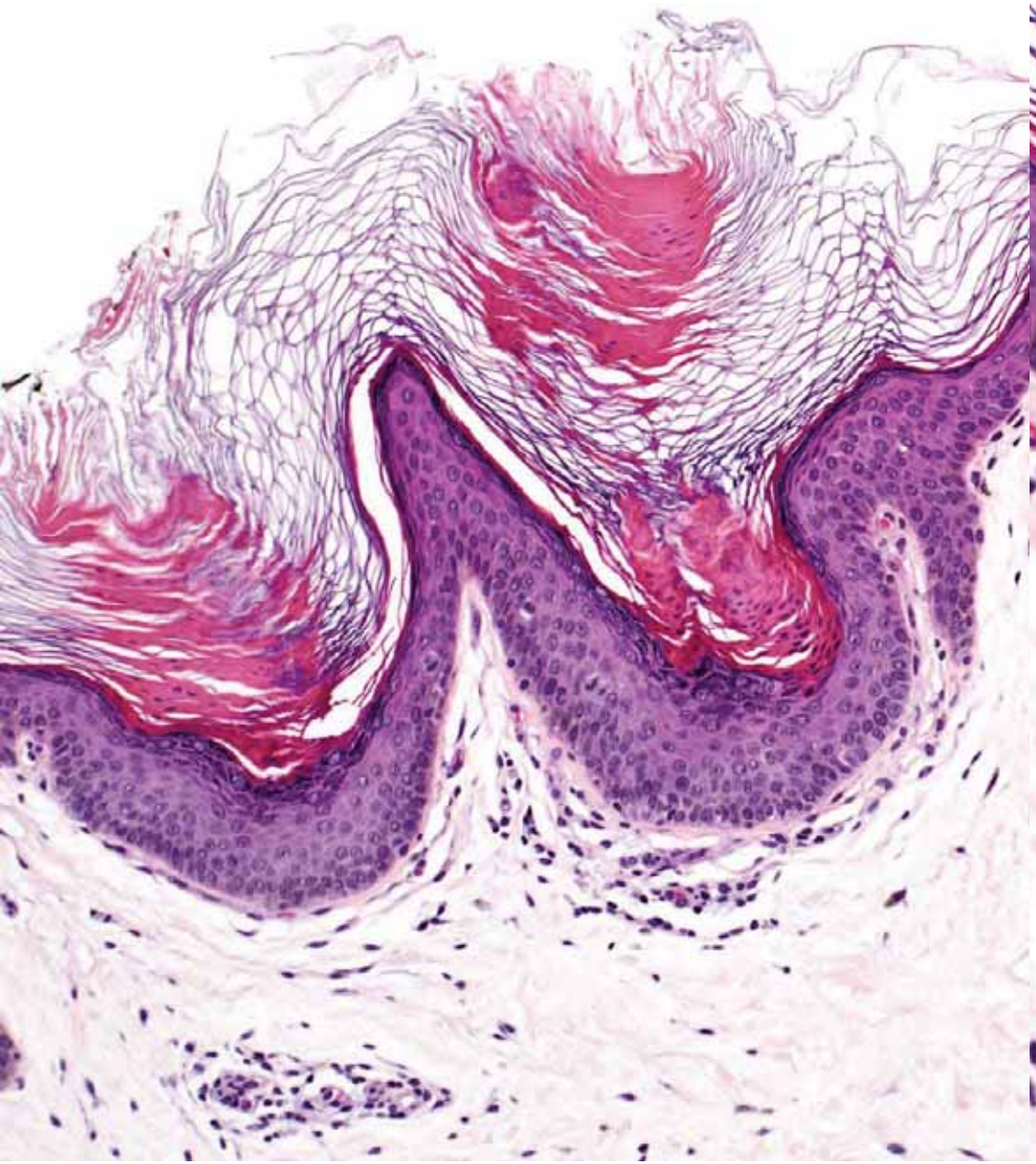


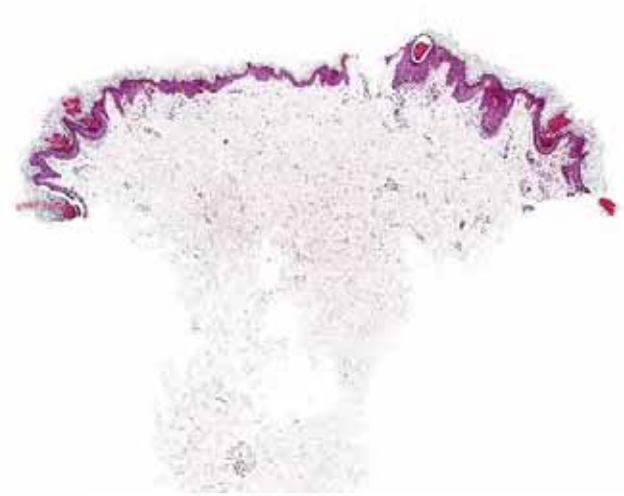
Case 20

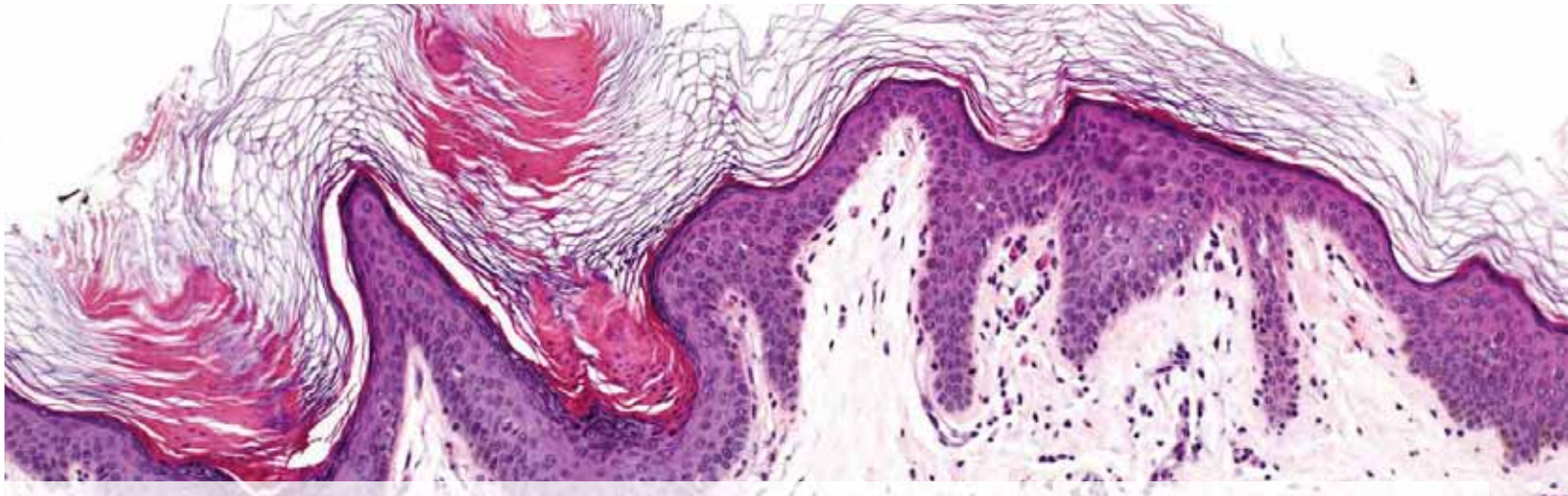
F, 45. Asymptomatic skin lesions mostly on the upper trunk and axillary and antecubital folds present for 1 year. No involvement of the face. Previous diagnosis of "Darier disease".

(Consultation of Dr. Berta Ferrer, Barcelona. Clinical pictures courtesy of Dr. Ferrer).

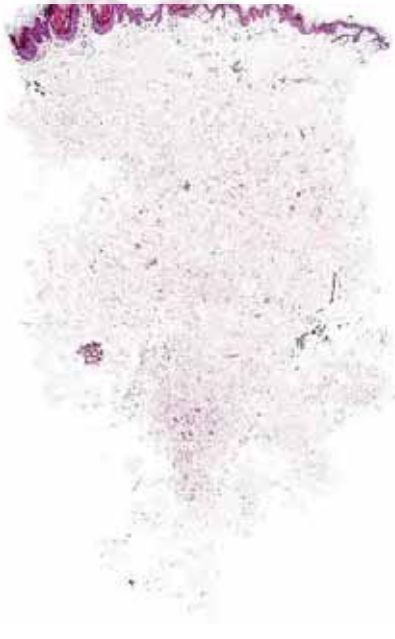



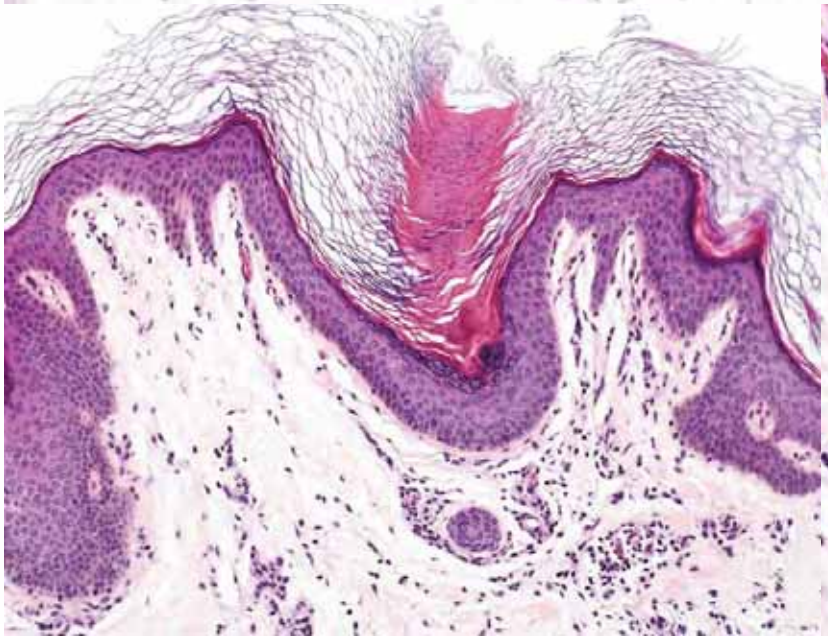


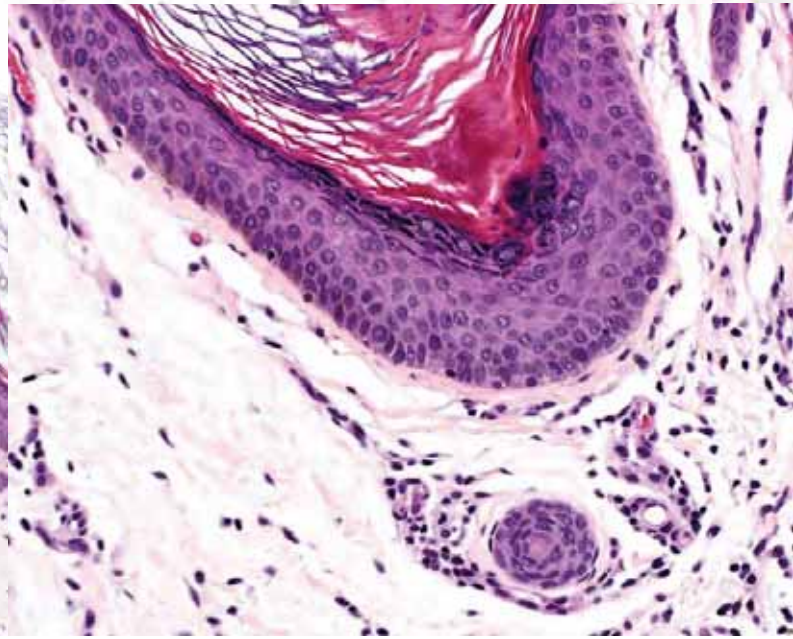


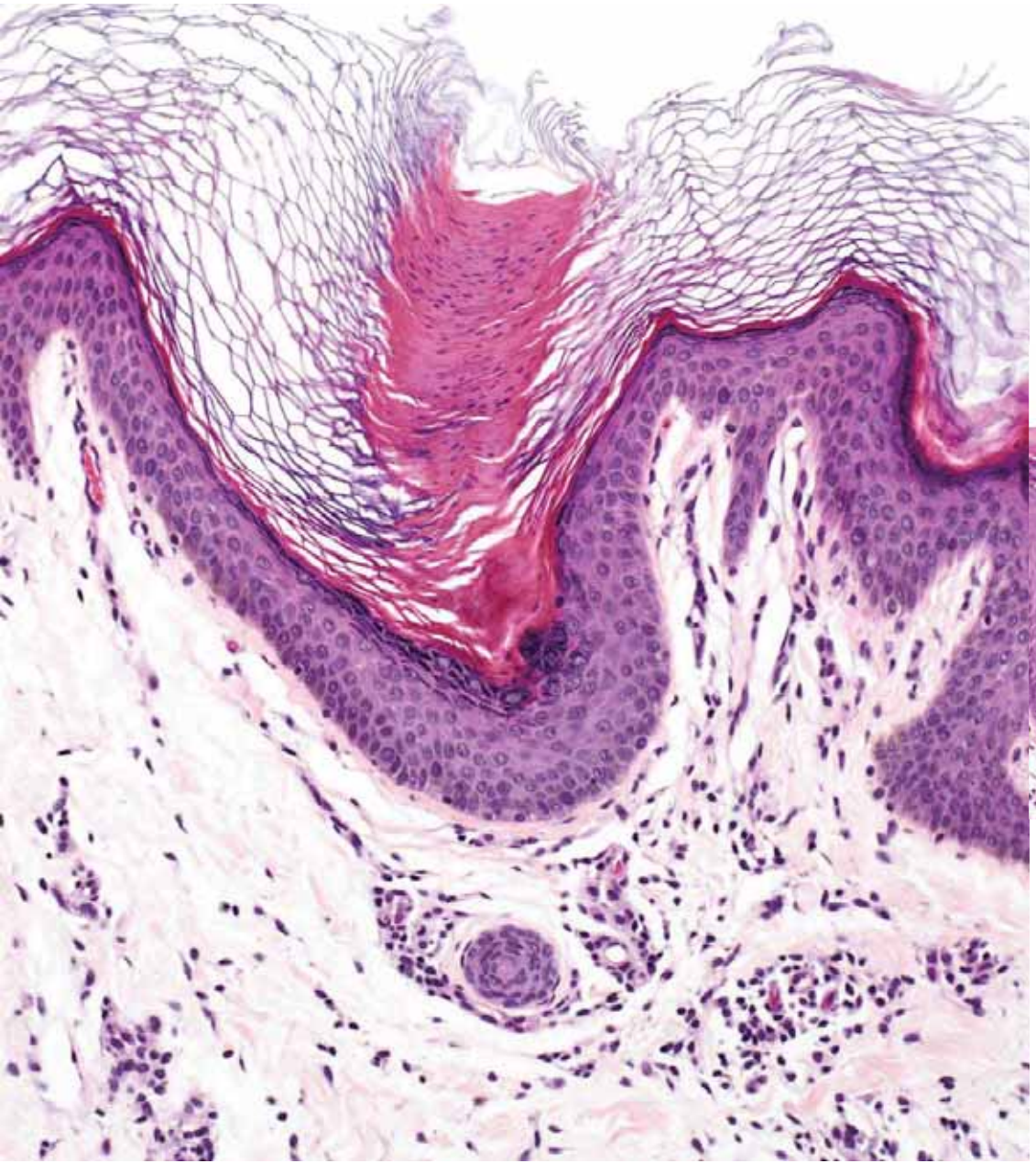


Porokeratotic eccrine ostial & dermal duct nevus





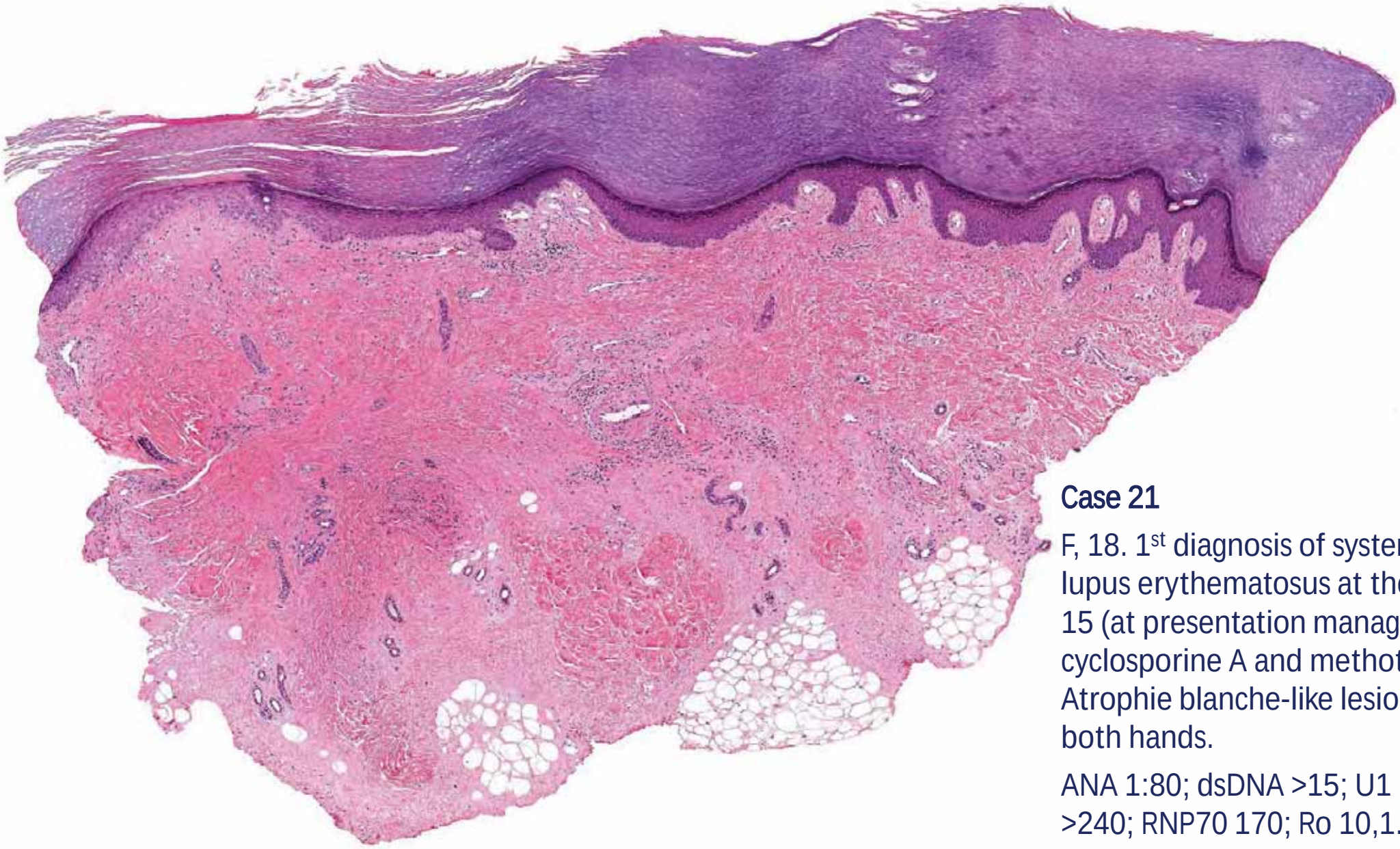




The clinical presentation is not consistent with porokeratosis ptychotropica, a histopathological differential diagnosis.
Not true cornoid lamellae (no absence of granular layer and no dyskeratotic cells in the epidermis); parakeratotic columns over eccrine ducts.

Porokeratosis ptychotropica

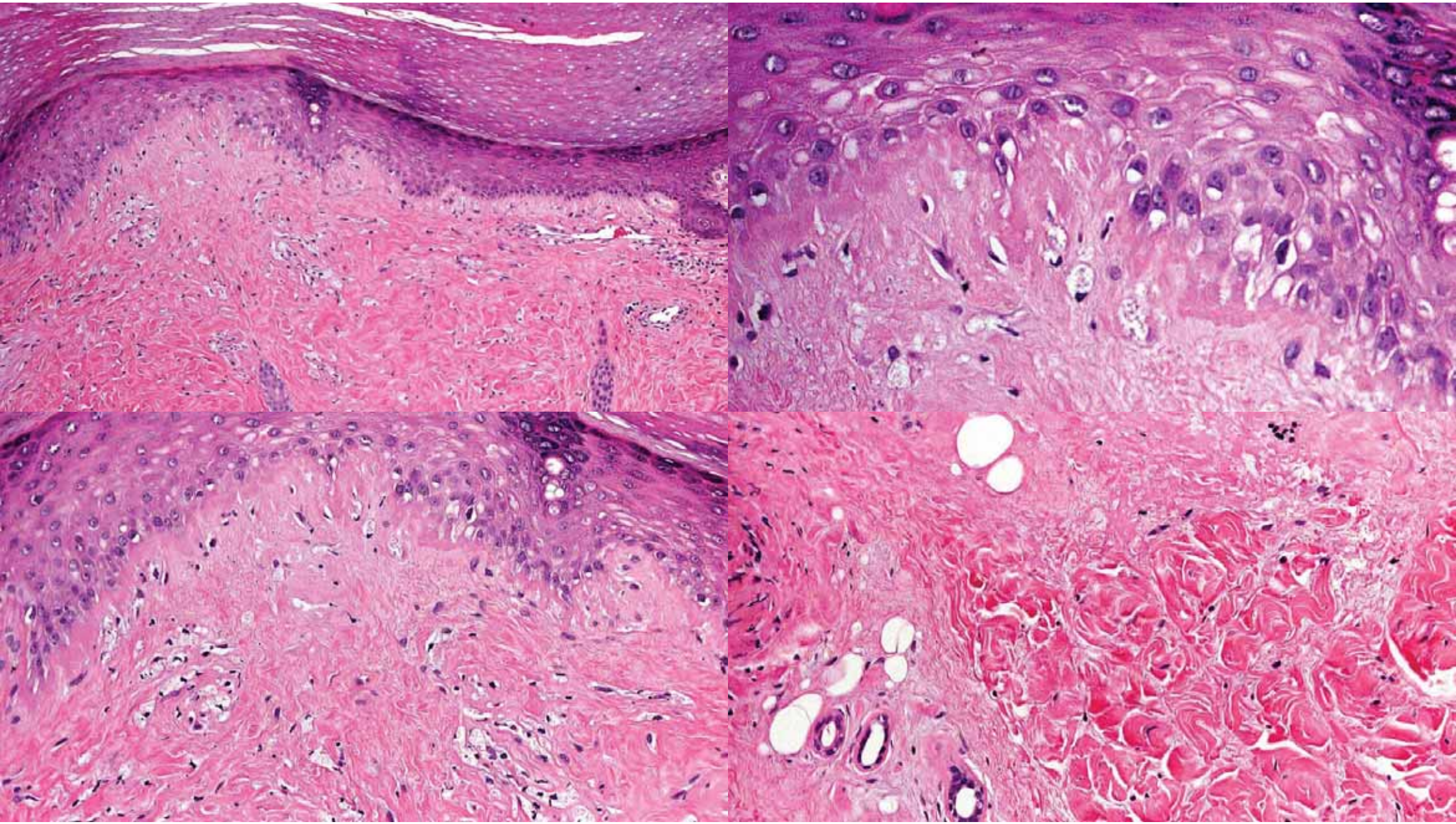
Parakeratotic column & hyperplastic epidermis with invagination & abscence of granular layer & dysmaturation: vacuolated, larger keratocytes with pyknotic nuclei, dyskeratotic cells & variable lymphoid infiltrate, interface dermatitis possible
(Dieter Metze, Summer Academy of Dermatopathology 2024)

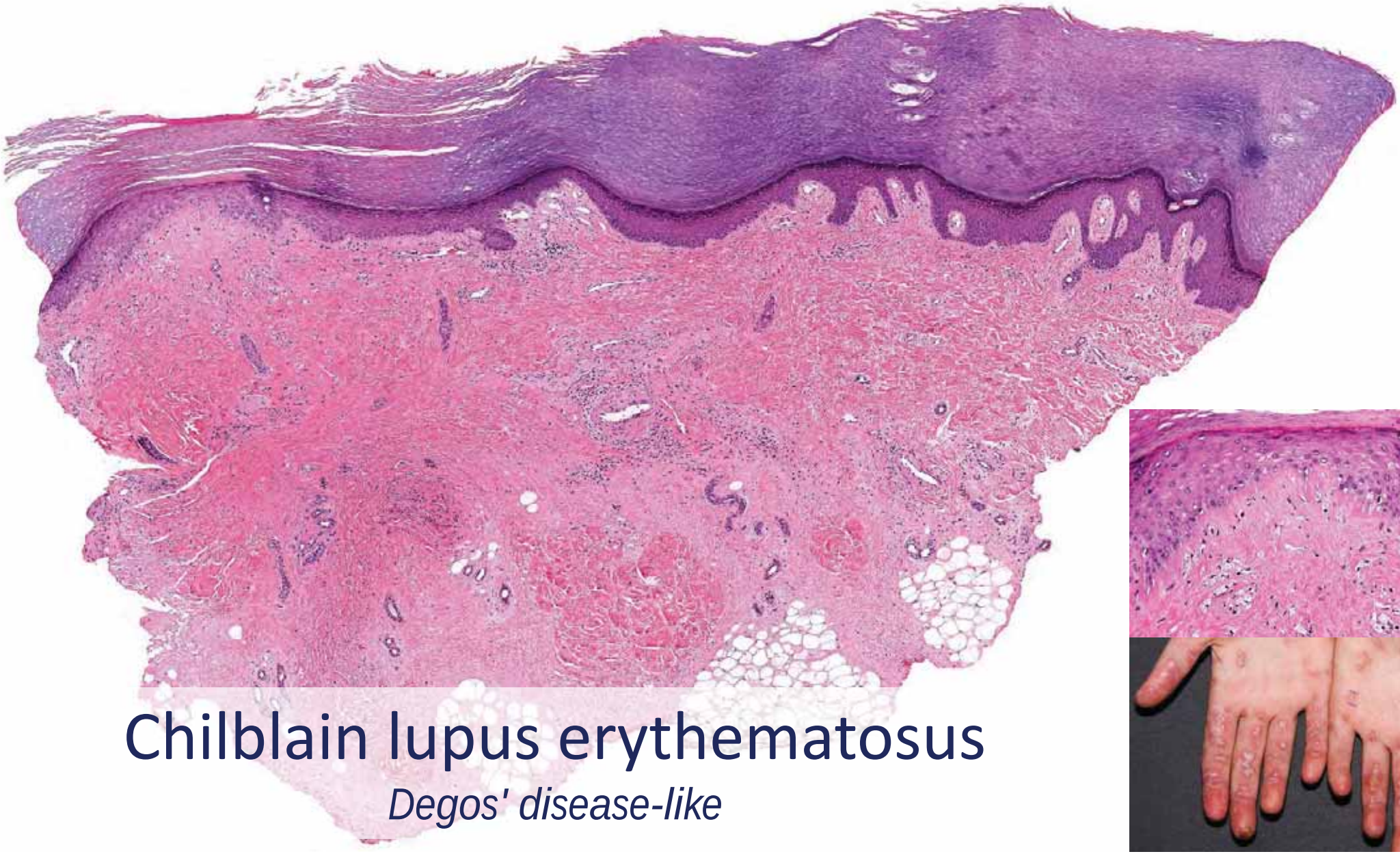


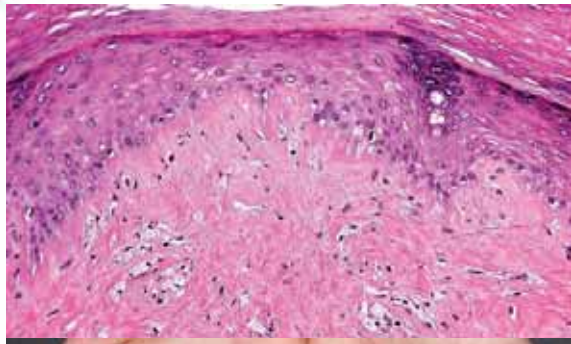
Case 21

F, 18. 1st diagnosis of systemic lupus erythematosus at the age of 15 (at presentation managed with cyclosporine A and methotrexate). Atrophie blanche-like lesions on both hands.

ANA 1:80; dsDNA >15; U1 RNP >240; RNP70 170; Ro 10,1.



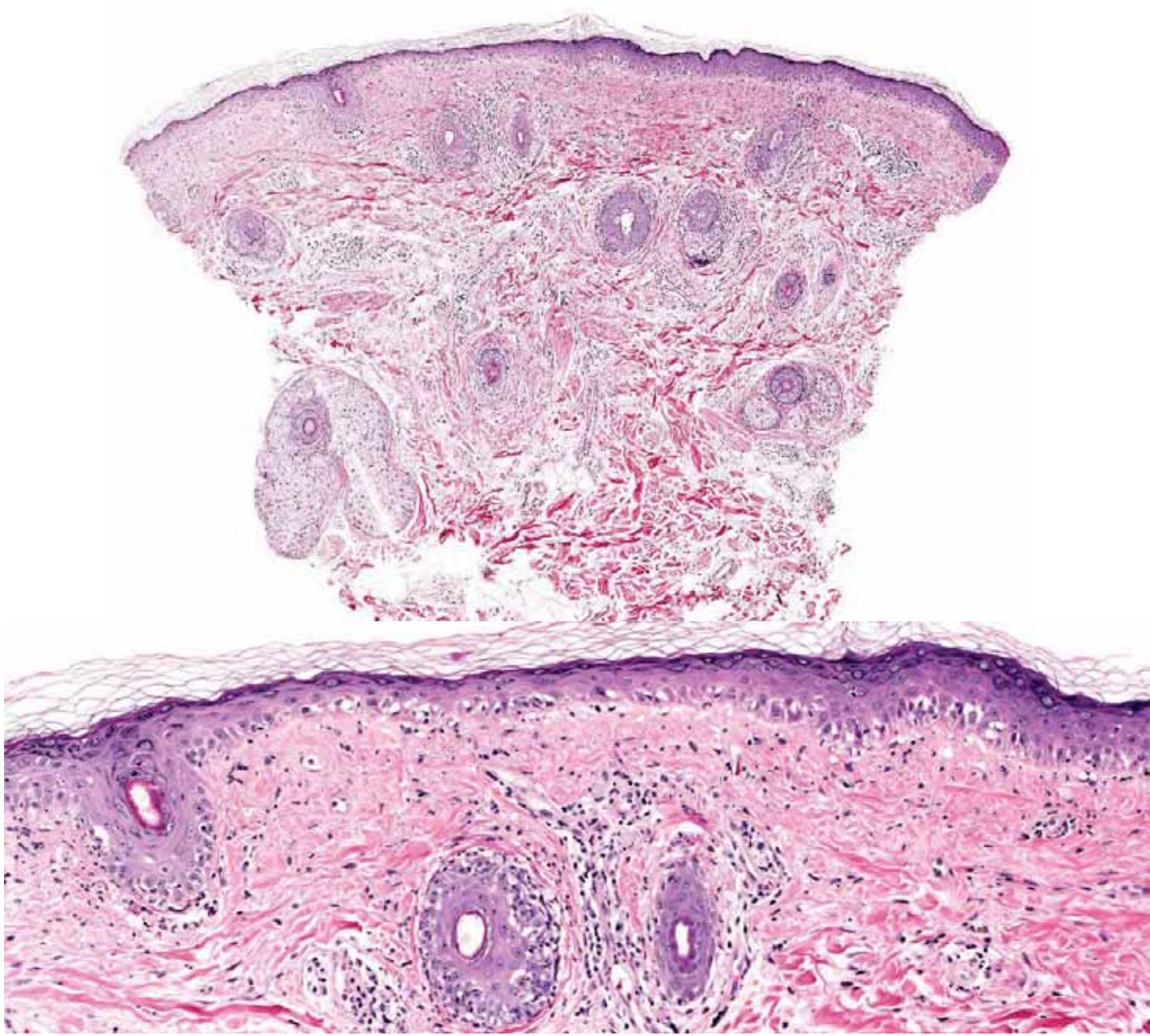




Chilblain lupus erythematosus

Degos' disease-like

+3 years



+3 years

+4 years

+21 years

+21 years

New crop of lesions for the last 2 weeks (according to the patient previously no skin lesions).

History of renal, myocardial and lung involvement; osteopenia and aseptic bone necrosis; IgA deficiency.

Previously managed with systemic steroids, cyclosporin A, methotrexate, cyclophosphamide, rituximab, azathioprine, dapsone, mepacrine, prostacyclin, belimumab; 7 years before last observation bone marrow transplantation.

ANA 1:1280; U1RNP 12+; smD(p)-S 16+

증례 보고

Degos병이 합병된 전신홍반루푸스 1예

서울대학교 의과대학 내과학교실

이정화 · 류희정 · 박영배 · 최병용 · 이은영 · 이윤종 · 이은봉 · 송영욱

= Abstract =

A Case of Systemic Lupus Erythematosus with Degos' Disease

Jung Hwa Lee, M.D., Hee Jung Ryu, M.D., Young Bae Park, M.D., Byoung Yong Choi, M.D., Eun Young Lee, M.D., Yun Jong Lee, M.D., Eun Bong Lee, M.D., Yeong Wook Song, M.D.

Fig. 1. Photographs of skin lesion. Multiple discrete papules are seen on both legs (A) and papules have white atrophic center with thin erythematous rim (B).

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CASE REPORT

Degos-Like Lesions Associated with Systemic Lupus Erythematosus

Min Soo Jang, Jong Ilin Park, Myeong Hyeon Yang, Ji Yun Jang, Joon Hee Kim, Kang Hoon Lee, Geun Tae Kim[1], Hyun Hwangbo, Kee Suck Suh

Departments of Dermatology and [1]Internal Medicine, Kosin University College of Medicine, Busan, Korea

Degos disease, also referred to as malignant atrophic papulosis, was first described in 1941 by Köhlmeier and was independently described by Degos in 1942. Degos disease is characterized by diffuse, papular skin eruptions with porcelain-white centers and slightly raised erythematous telangiectatic rims associated with bowel infarction. Although the etiology of Degos disease is unknown, autoimmune diseases, coagulation disorders, and vasculitis have all been considered as underlying pathogenic mechanisms. Approx-

29(2) 215~218, 2017

-Keywords-
Degos disease, Degos-like lesions, Systemic lupus erythematosus

INTRODUCTION

Fig. 1. (A~C) Multiple erythematous papules with porcelain-white scales surrounded by an erythematous rim were seen on dorsum of all fingers and both knees.

From *Dermatopathology: Practical & Conceptual*

A. Bernard Ackerman, Editor

Degos' Disease: A Distinctive Pattern of Disease, Chiefly of Lupus Erythematosus, And Not a Specific Disease per se

Elizabeth Ball, MD, Amy Newburger, MD, and A. Bernard Ackerman, MD

Degos' disease, known confusingly as malignant atrophic papulosis, is an uncommon condition of unknown cause characterized by distinctive infarctive lesions in the skin, gastrointestinal tract, and central nervous system; the lesions in the two latter sites often result in death. We deem Degos' disease to be analogous to lupus erythematosus in the sense that each is fundamentally a systemic pathologic process involving several organs, among them the skin, but, moreover, we regard Degos' disease, in most instances, to be an actual manifestation of lupus erythematosus. Histopathologically, the findings in sections of tissue of skin lesions of Degos' disease are indistinguishable from those of one expression of cutaneous lupus erythematosus; immunopathologically, some patients with histopathologic findings stereotypical of Degos' disease display signs characteristic of lupus erythematosus. For these reasons, we consider Degos' disease to be a distinctive pattern of disease, rather than a specific disease per se, just as are erythema multiforme, erythema nodosum, leukocytoclastic vasculitis, Sweet's syndrome, and pyoderma gangrenosum, to name but five of scores of them. The singular pattern that is designated Degos' disease usually is an expression of lupus erythematosus, but, episodically, of conditions like dermatomyositis and rheumatoid arthritis.

THE PATIENT WHO SPARKED OUR INTEREST

Our interest in this subject derived from an opportunity to study sections of tissue from a biopsy specimen taken from a 35-year-old man who had skin lesions stereotypical clinically of Degos' disease (Fig. 1). The findings by conventional microscopy, however, were indistinguishable from those of lupus erythematosus (Figs. 2A, 2B and 2C). The patient was asymptomatic and, except for slight increase in SGOT, his laboratory values and immunologic profile were normal or negative. The twin brother and the father of the patient had skin lesions similar to his. A biopsy specimen was taken from a lesion in the skin of the twin brother, the histopathologic features of which also were consonant with lupus erythematosus. The more we read about Degos' disease, the more enigmatic it became, thereby prompting us to review all that has been written about it. Having done that, we now set forth a view of the subject different from any account given before.

HISTORICAL PERSPECTIVE

Although the disease under consideration here bears the name "Degos," it actually was described first in 1941 by Köhlmeier, an Austrian. He observed peculiar atrophic skin lesions in a 22-year-old male who died as a complication of ulcers of the intestine. The process was thought by Köhlmeier to be "*thromboangiitis obliterans* of the intestine with multiple skin lesions" (Figs. 3A and 3B).[2] In 1942, Degos, Delort, and Tricot reported on a 49-year-old plumber with a condition they initially called "*dermatite papulo-squameuse atrophiante.*" The patient sought consultation for an eruption that was characterized by Degos et al[1] (Fig. 4) as follows:

From the Ackerman Academy of Dermatopathology, New York, New York (A.B.A.); Laboratory of Dermatopathology, Department of Dermatology, University Hospital of Caracas, Central University of Venezuela (E.B.); Dermatology Consultants of Westchester, Scarsdale, New York (A.N.).

Dr. Ball did this work during a Visiting Fellowship at the Academy where Dr. Ackerman is the Director.

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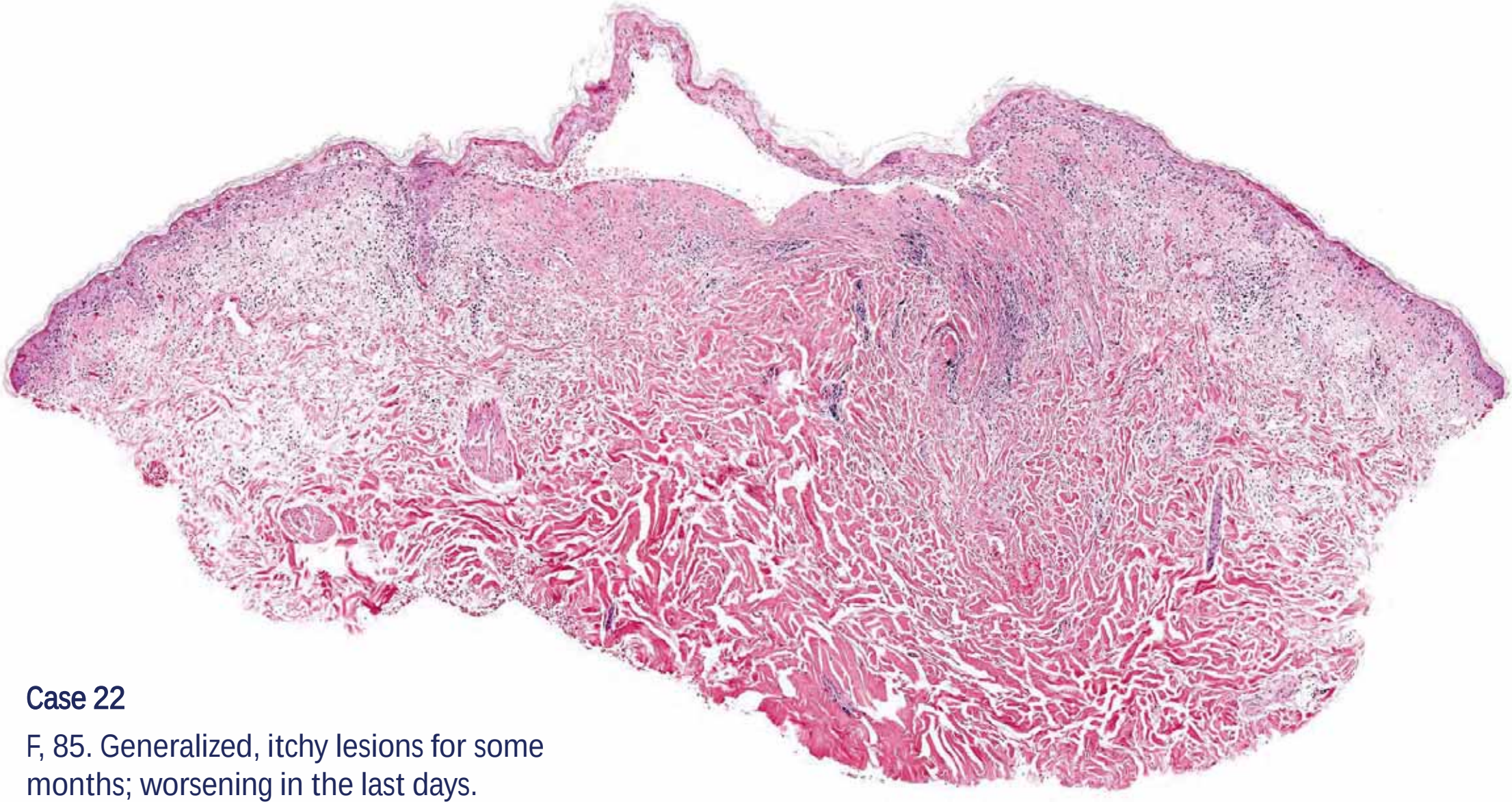
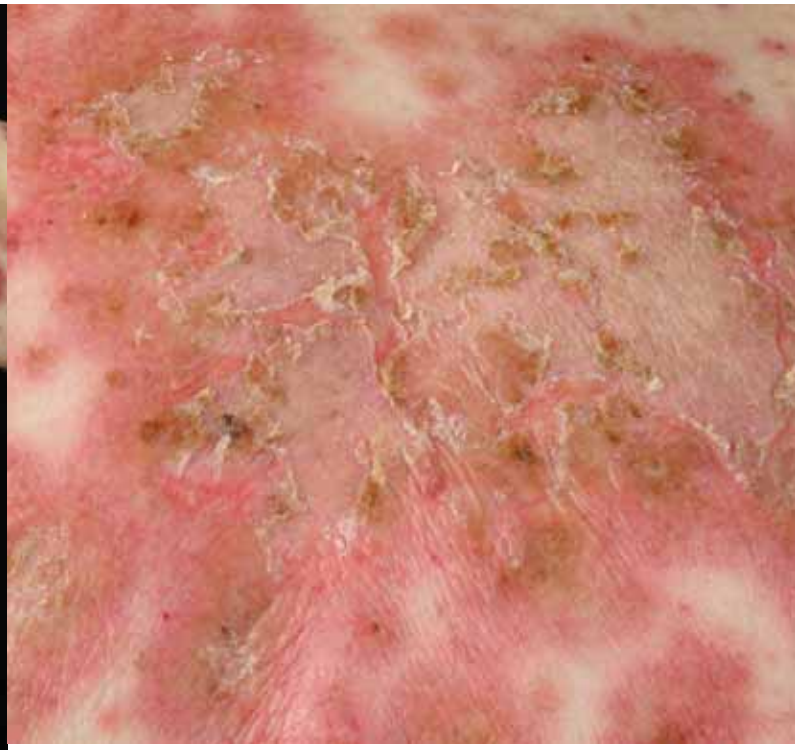
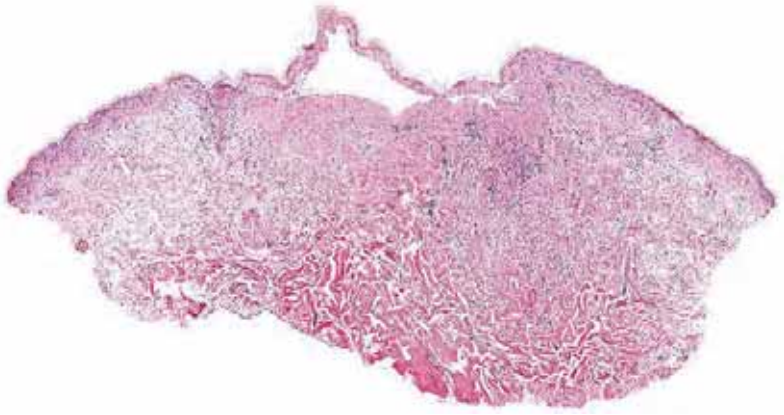
"In short, we do not conceive of Degos' disease as a specific disease, but as a distinctive pattern expressive of different pathologic processes, chief among them lupus erythematosus. Patients with skin lesions typical of Degos' disease should be assessed for evidences of lupus erythematosus and other collagen vascular diseases, and for the presence of antiphospholipid antibodies. It is likely that many patients thought to have Degos' disease will prove to have lupus erythematosus."

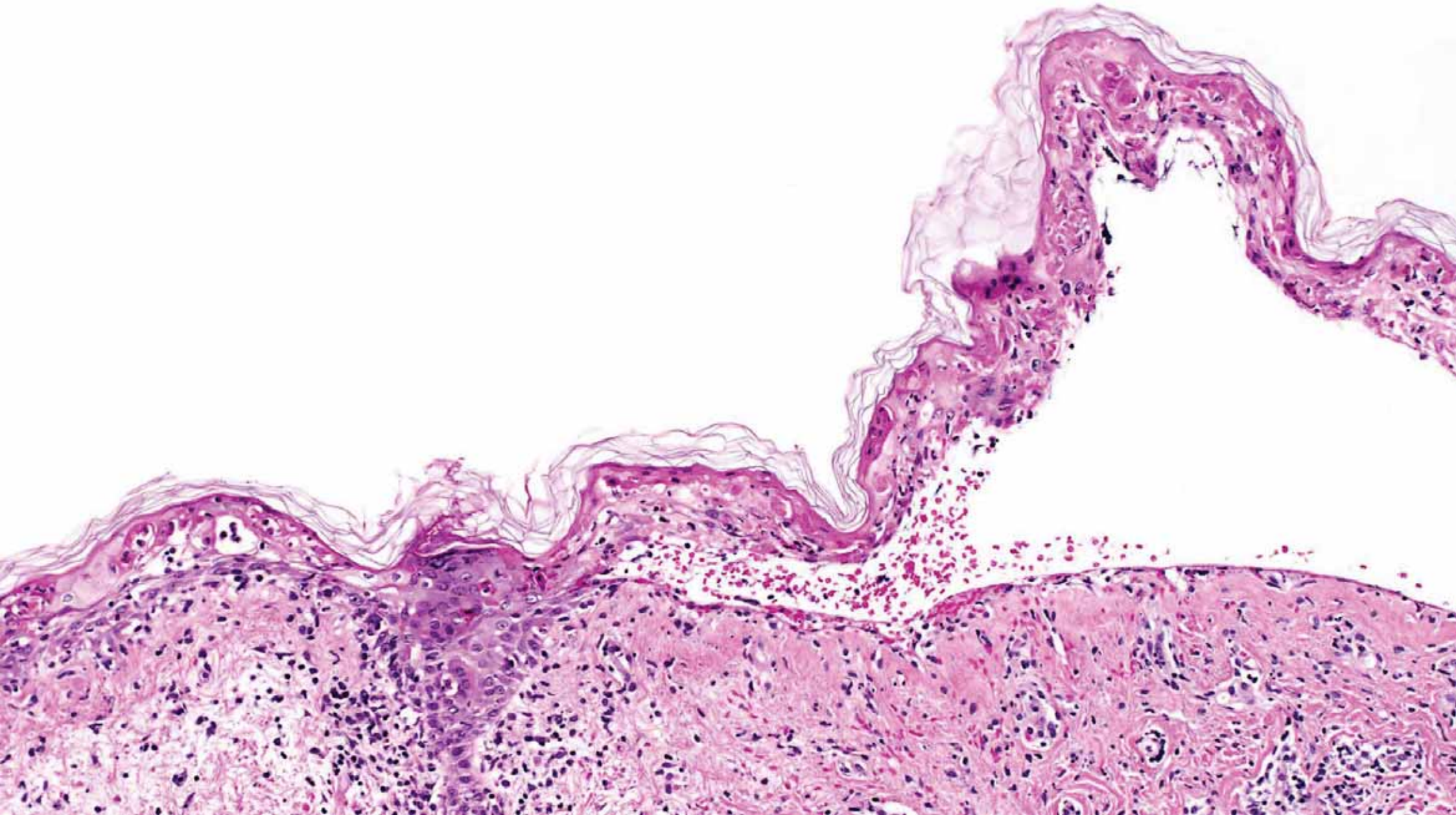


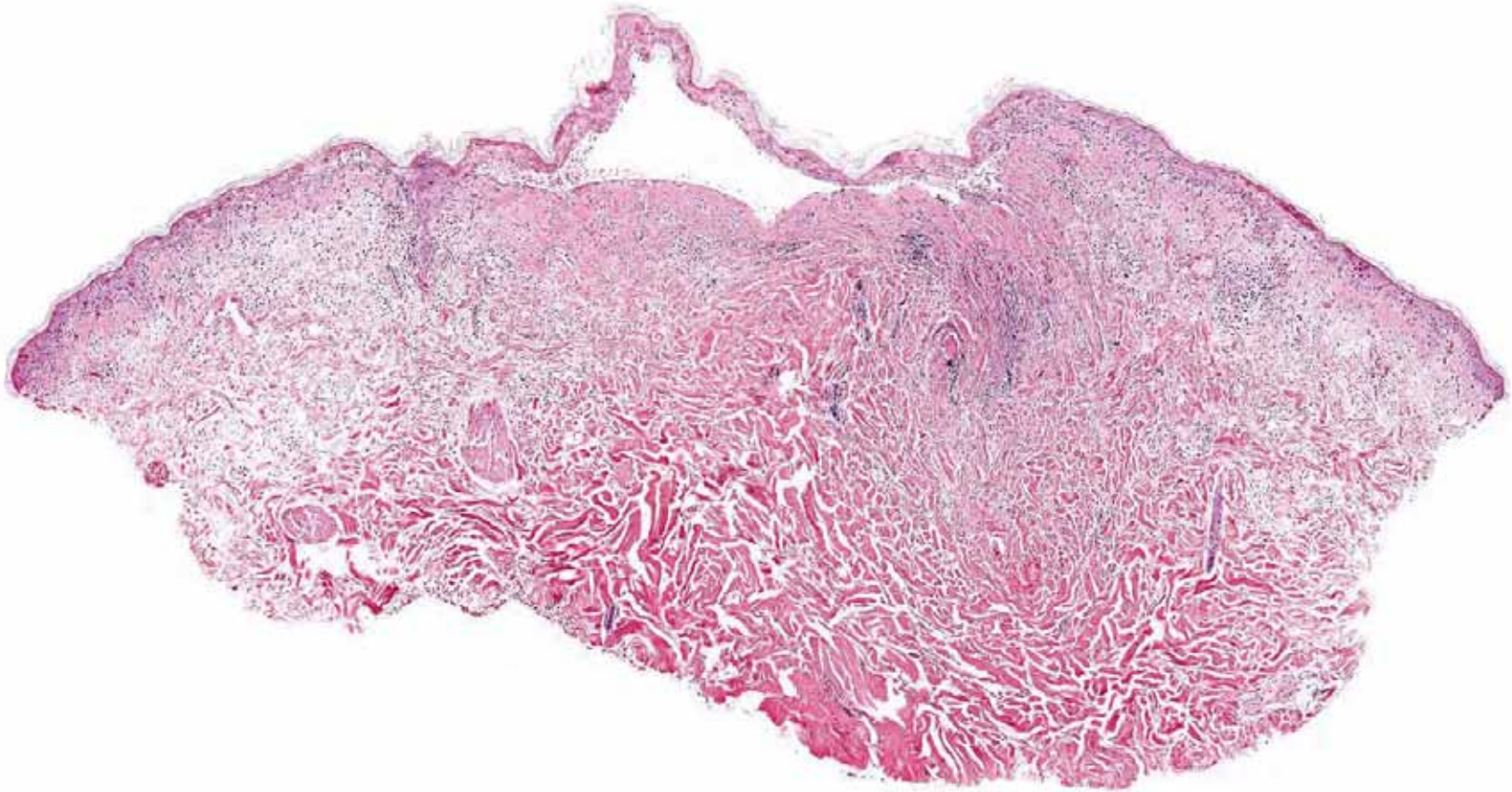
Case 22

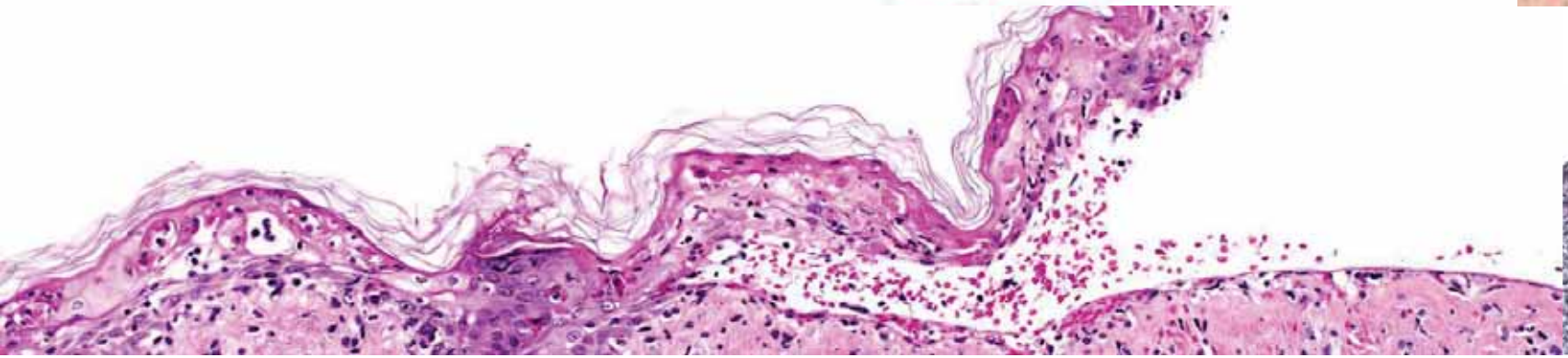
F, 85. Generalized, itchy lesions for some months; worsening in the last days.

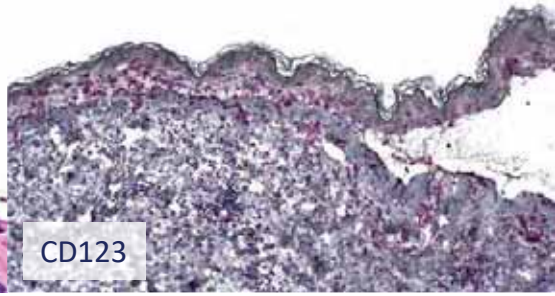








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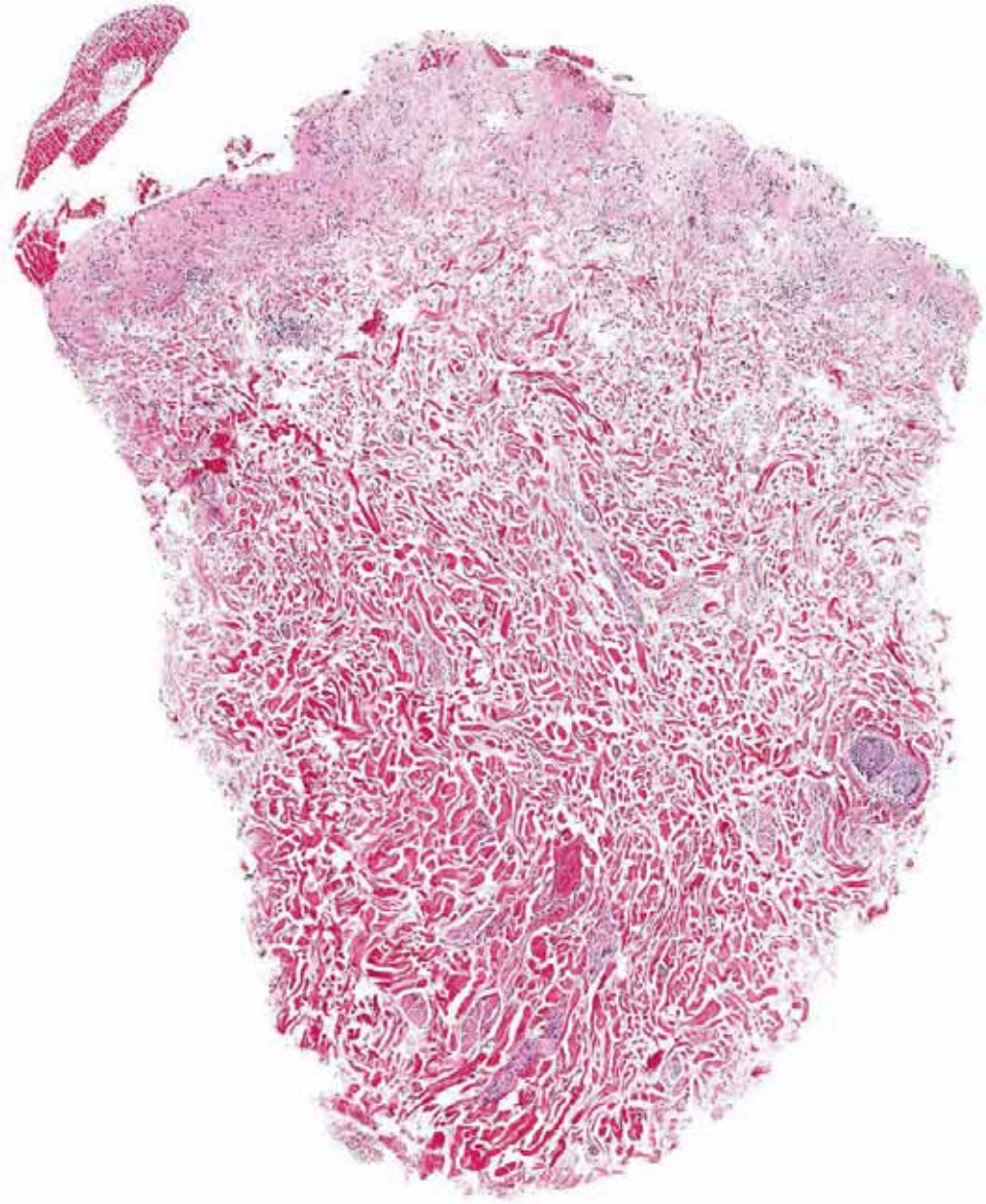
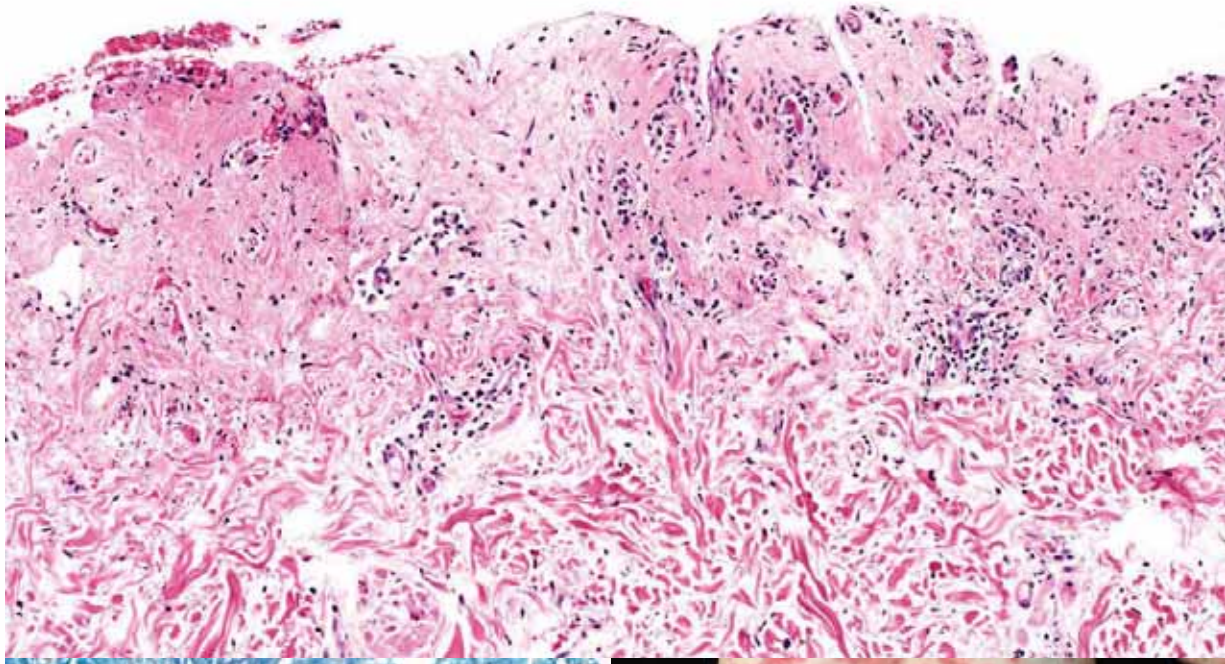
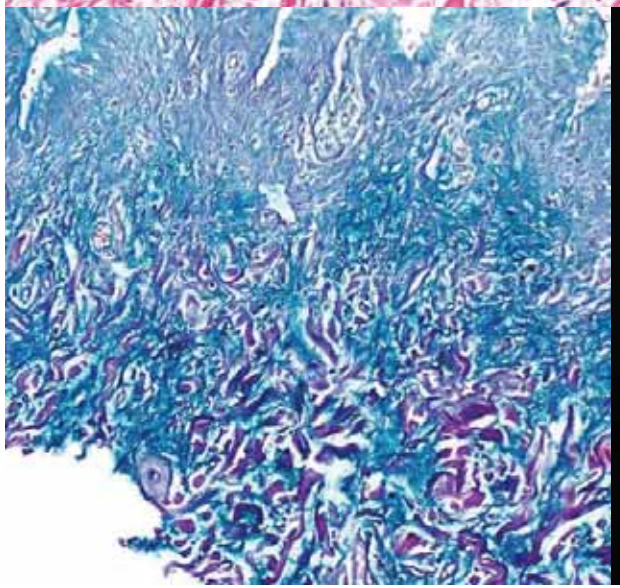
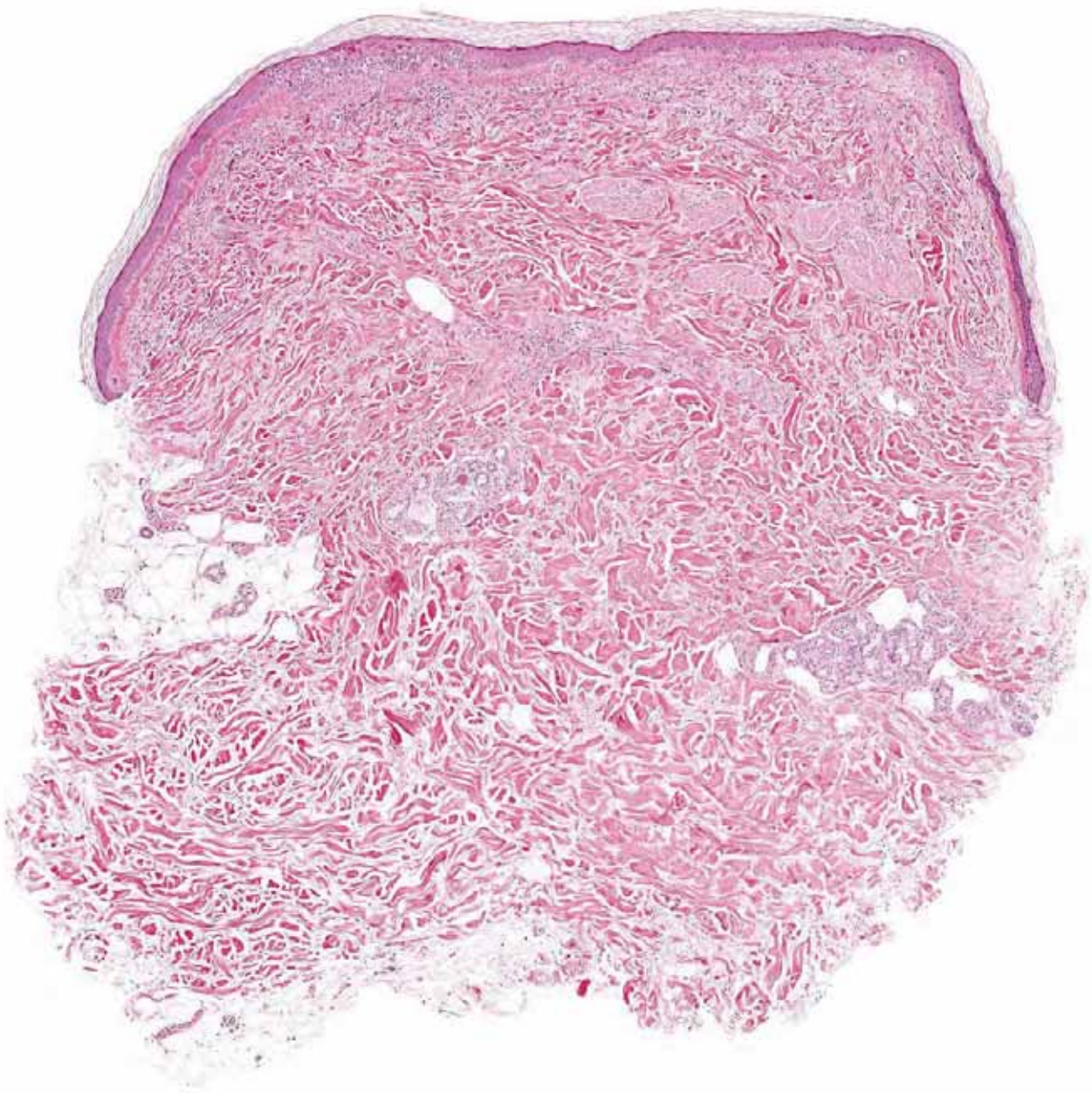
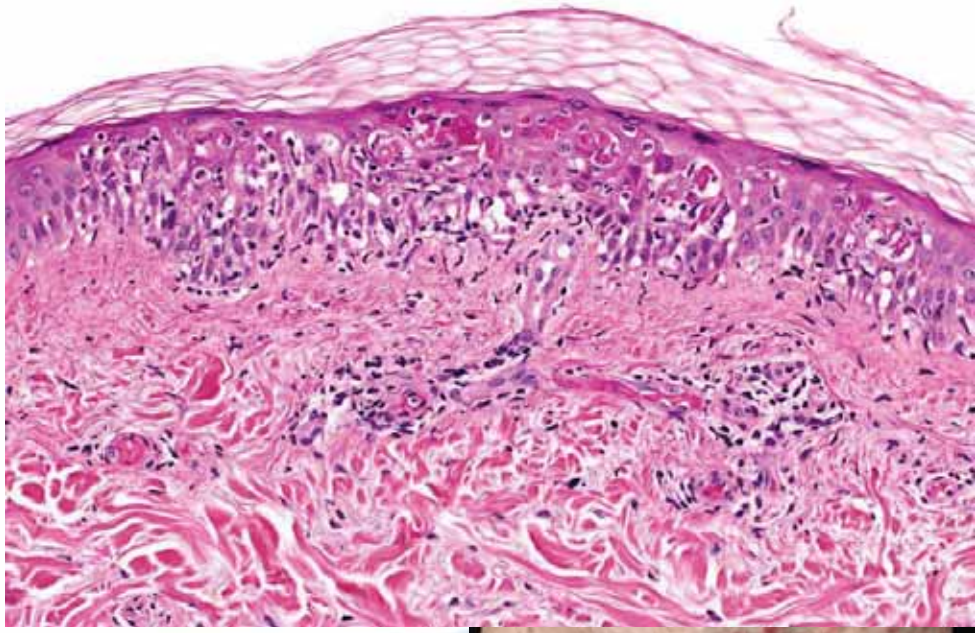
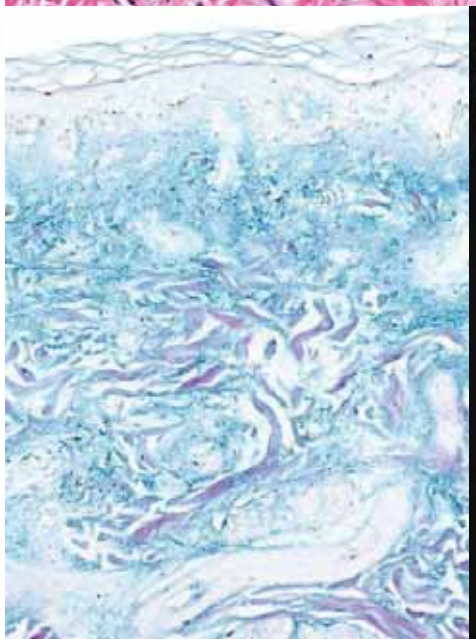


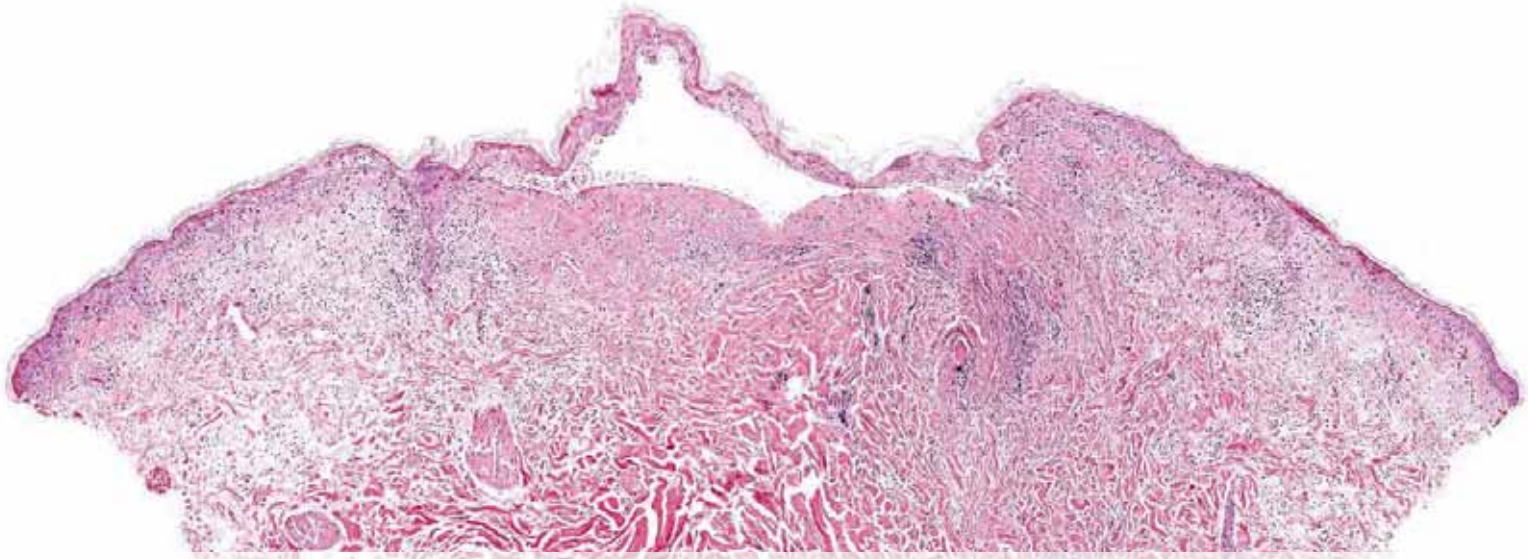








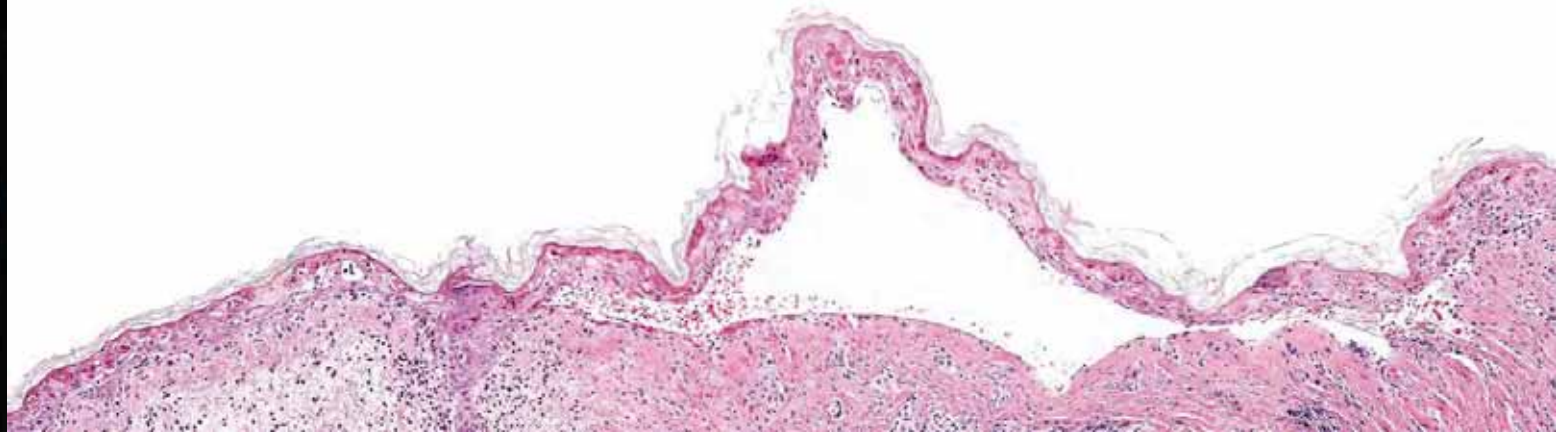




Lupus erythematosus ("Rowell syndrome")

ANA: 1:5120

Ro-abs.: >240; Ro52 abs: >240; Ro60 abs.: >282



Lupus Erythematosus and Erythema Multiforme-like Lesions

A Syndrome With Characteristic Immunological Abnormalities

NEVILLE R. ROWELL, MB, MRCP, DCH
LEEDS, ENGLAND
J. SWANSON BECK, MB, BSc, FRFPS, MRCPE
AND
JOHN R. ANDERSON, MD, BSc, FRFPS, MRCP
GLASGOW, SCOTLAND

Four patients with erythema multiforme-like lesions in association with apparent discoid lupus erythematosus have been described. In each a characteristic immunological pattern was found in the serum consisting of the presence of speckled type of antinuclear factor, the same precipitating antibody to saline extract of human tissues, and rheumatoid factor.

This is considered to be a new syndrome, and the first in the connective tissue diseases to be described in which a distinctive clinical picture is associated with a characteristic pattern of immunological abnormality.

In a recent study of 120 patients with chronic discoid lupus erythematosus (to be published), four patients also had lesions resembling erythema multiforme and showed a similar pattern of immunological abnormality. This consists of the presence in the serum of "speckled" type of antinuclear factor (Beck, 1961), a precipitating antibody to saline extract of human tissues, and rheumatoid factor. These associations have not been described previously, and we regard this group of cases as a distinct entity.

Department of Dermatology, General Infirmary at Leeds (Dr. Rowell); University Department of Pathology, Western Infirmary, Glasgow (Dr. Beck, Dr. Anderson).

Report of Cases

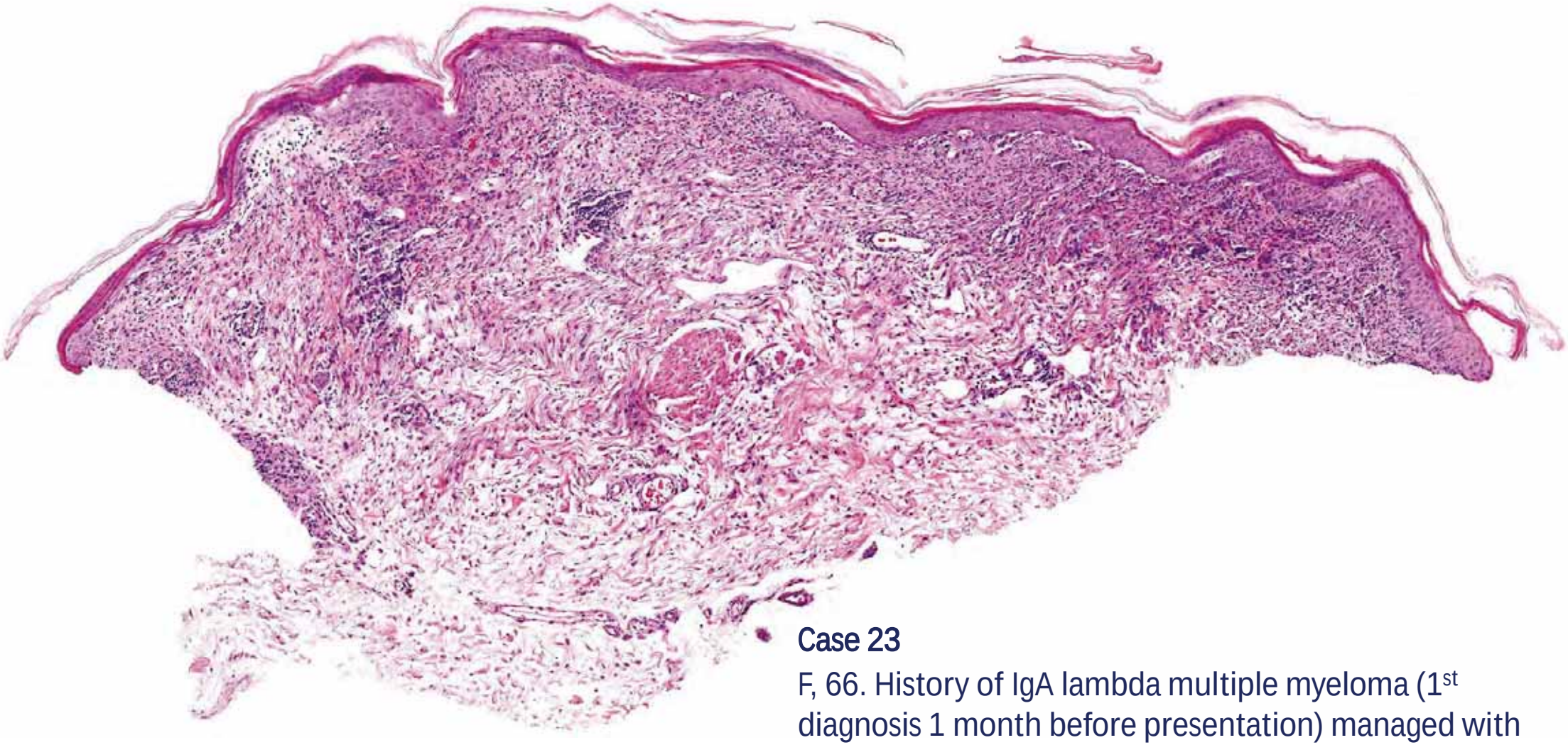
CASE 1.—This woman, now aged 48 years, has had lupus vulgaris of the lateral aspect of the right calf since the age of eight. At the age of 28 years, this was treated with carbon dioxide snow, and two weeks later she developed two raised painful areas on the right leg above the lateral malleolus. These were diagnosed as discoid lupus erythematosus. These lesions have since subsided and reappeared intermittently. At the age of 35 years, the lateral aspect of the feet began to show bluish-red erythema also considered to be lupus erythematosus. Biopsy when she was 40 years of age confirmed the diagnoses of lupus vulgaris and discoid lupus erythematosus in the lesions. The ESR was 49 mm in one hour, hemoglobin 98%, and the white cells 5,400/cu mm. LE cells were not demonstrated, and x-ray of the chest was normal. Treatment with vitamin D in oil (Sterogyl) 600,000 units by mouth twice a week was started, and the lupus vulgaris slowly improved. Over the next few years she had some discoid lesions on the face and right thumb

TABLE 1.—*Clinical Features of Four Patients With Lupus Erythematosus and Erythema Multiforme-like Lesions*

	Case			
	1	2	3	4
Sex	F	F	F	F
Age	48	72	32	31
Raynaud's phenomenon	—	—	+	—
Erythrocyanosis & chilblains	+	+	+	+
LE	Legs, face, hands	Face, hands	Face	Face
Duration of LE, (yr)	13	16	4	5
Duration of toxic lesions, (yr)	20	11	1	4
Site of toxic lesions	Legs, chest	Arms, legs, face, neck	Arms, legs	Arms, legs

Erythema multiforme-like lesions on the right upper arm (case 2).

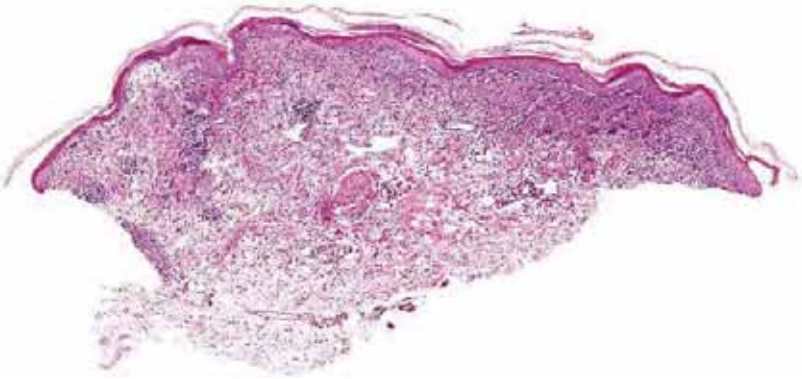
"At the margins of the vesicle the uninvolved epidermis showed infiltration by degenerate leukocytes, **and in other areas the whole thickness of the epidermis was necrotic."**

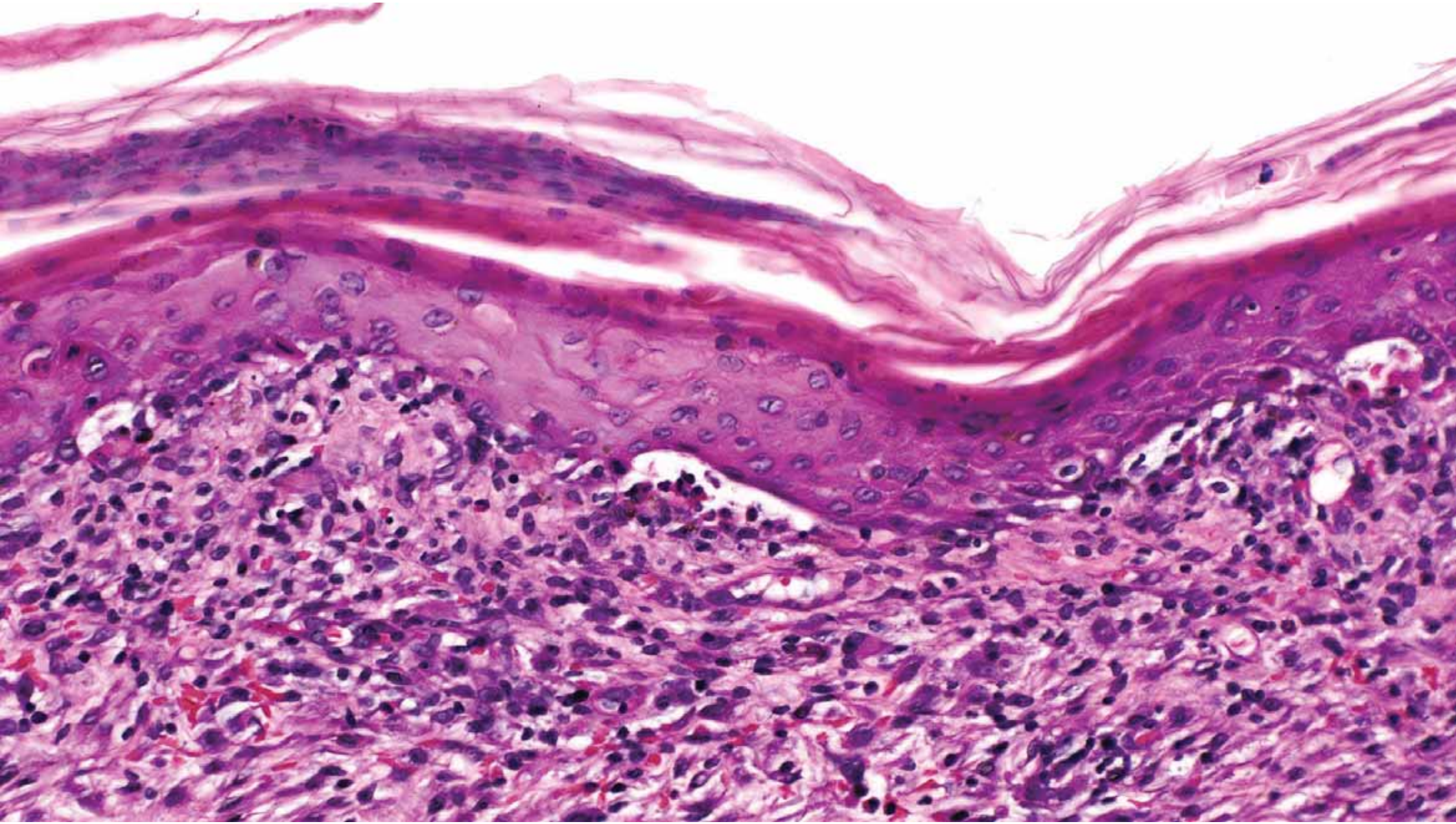


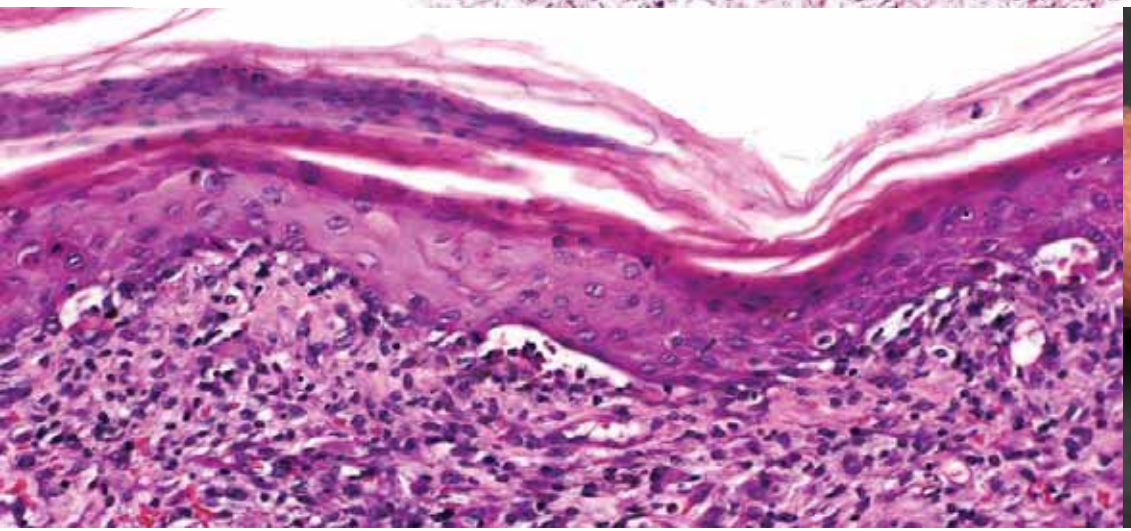
Case 23

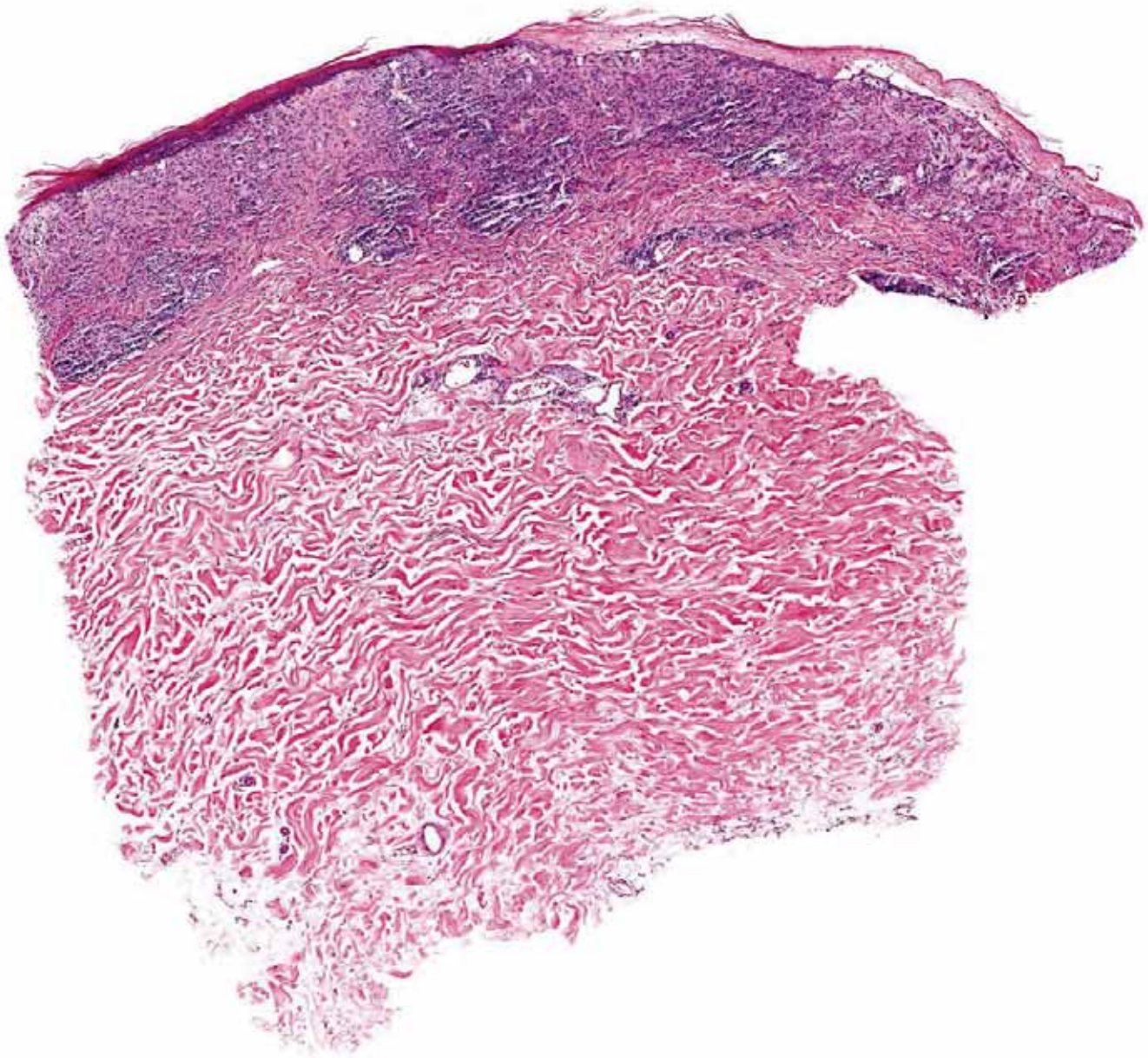
F, 66. History of IgA lambda multiple myeloma (1st diagnosis 1 month before presentation) managed with daratumumab (1st cycle).

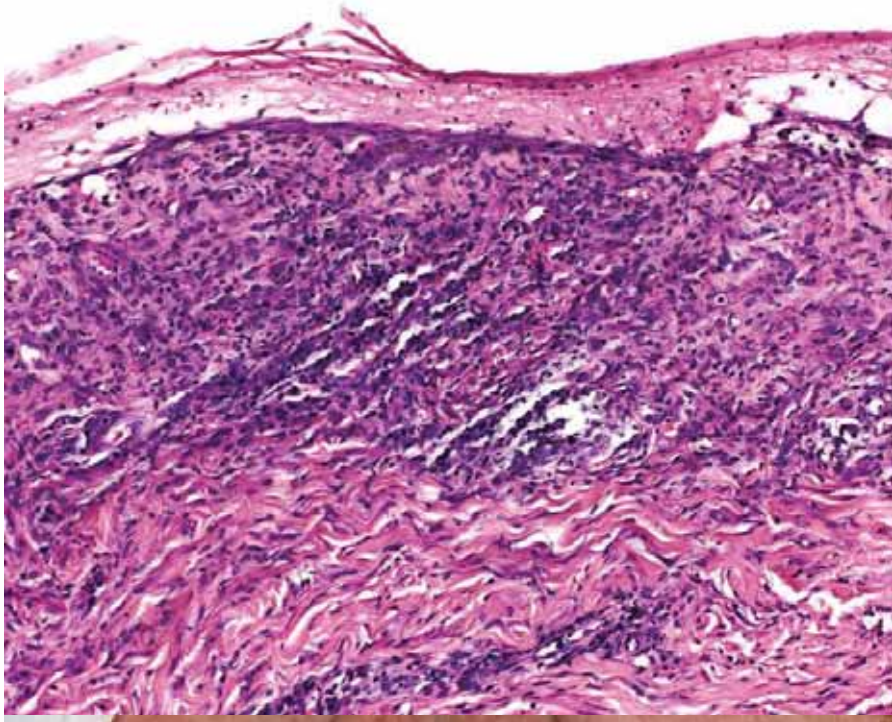
Recent onset of generalized skin lesions (exact timing unknown). Positive Nikolsky sign. Severe leukopenia.

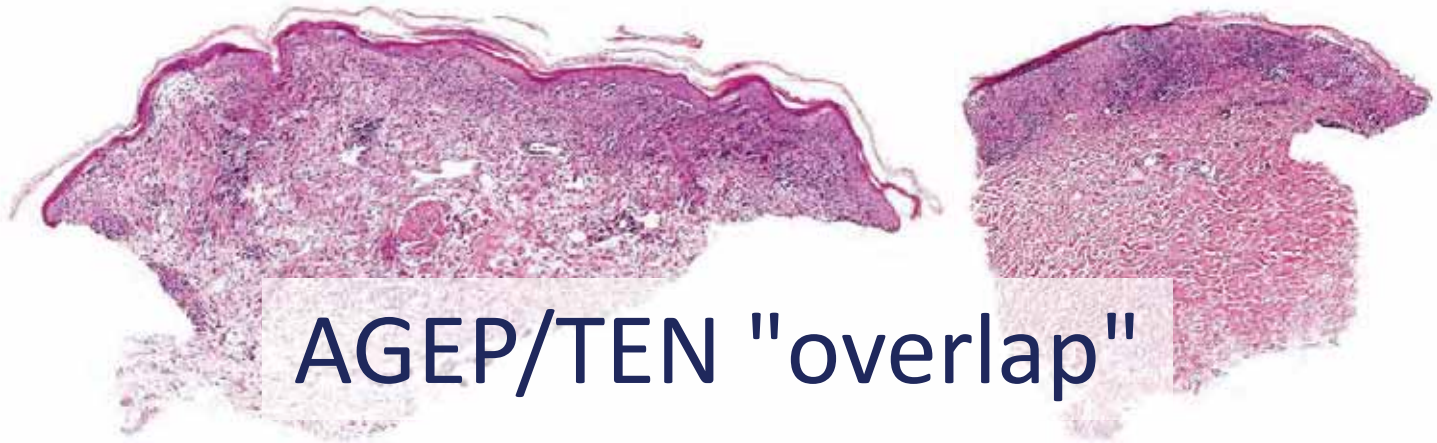




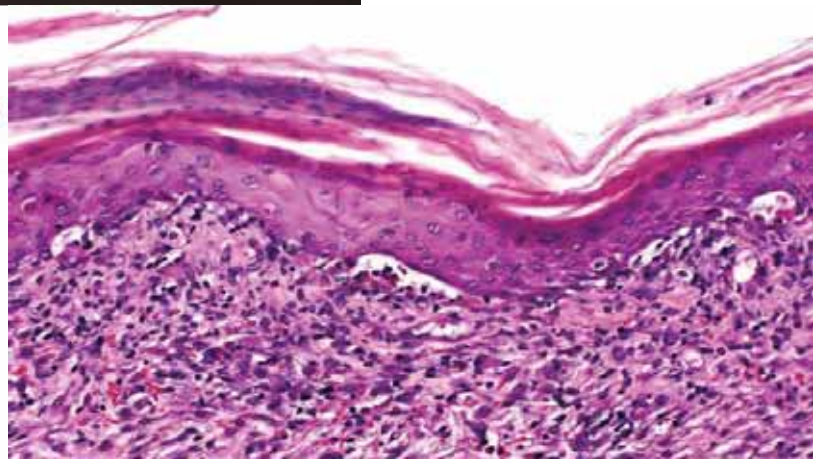




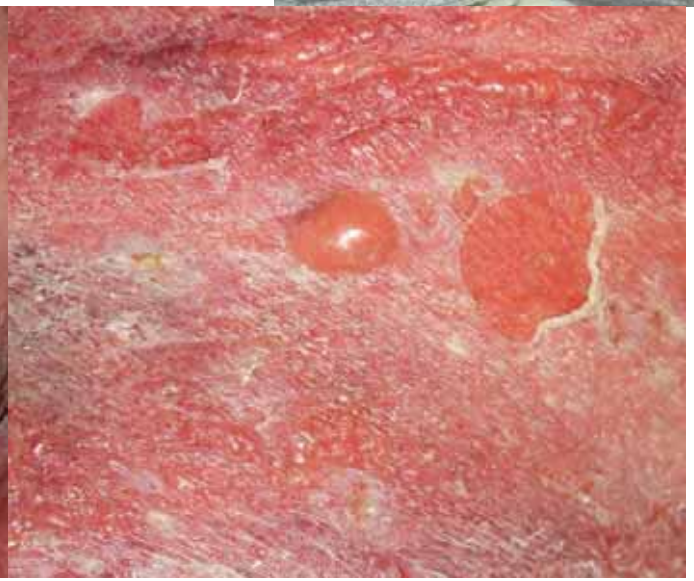




AGEP/TEN "overlap"



Slow improvement (residual skin lesions still present 23 days after presentation; more in keeping with TEN); No atypical target lesions (more in keeping with AGEP); Epidermal exfoliation focally on the shoulder but more pronounced on the back (more in keeping with TEN); No involvement of mucosal surfaces (more in keeping with AGEP); Leukopenia (more in keeping with TEN); Two biopsies (overlapping features AGEP/TEN).

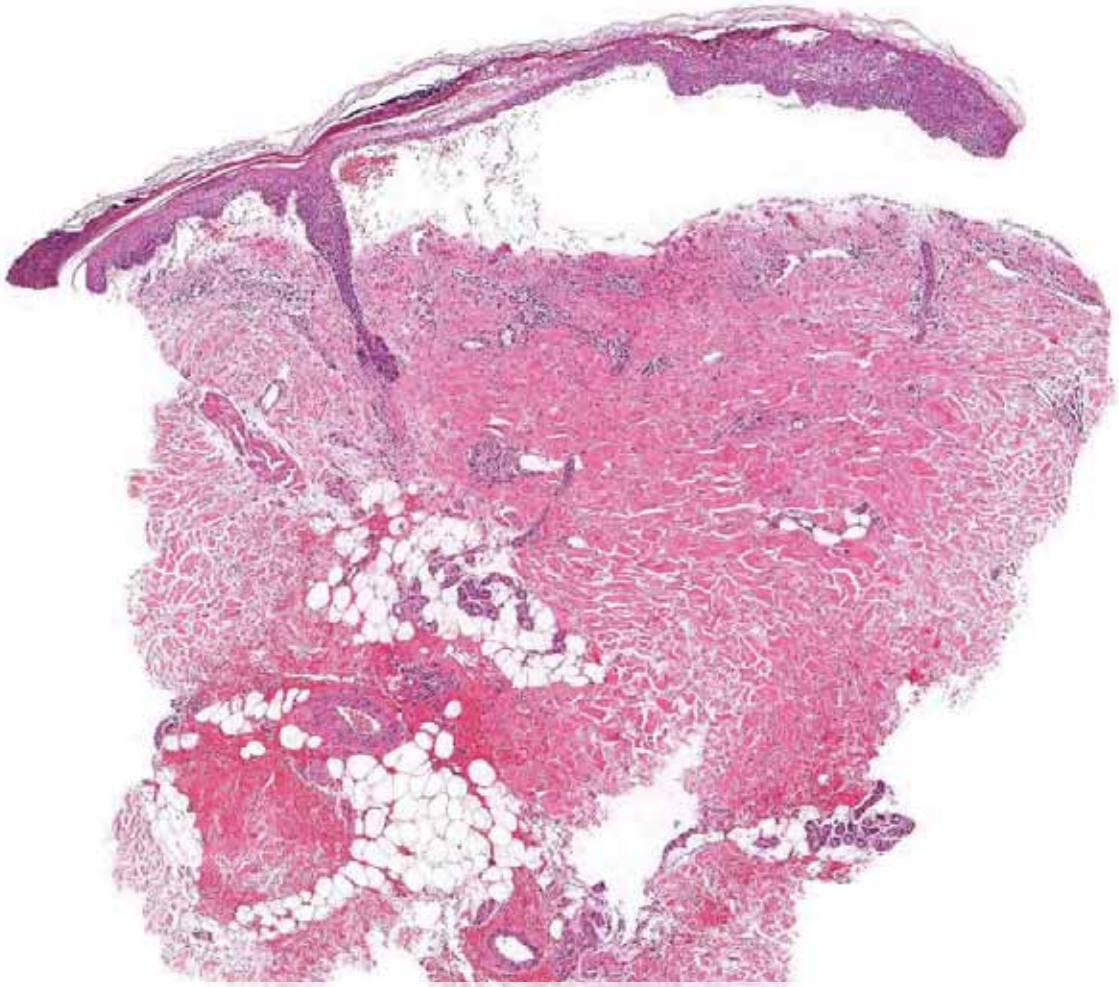


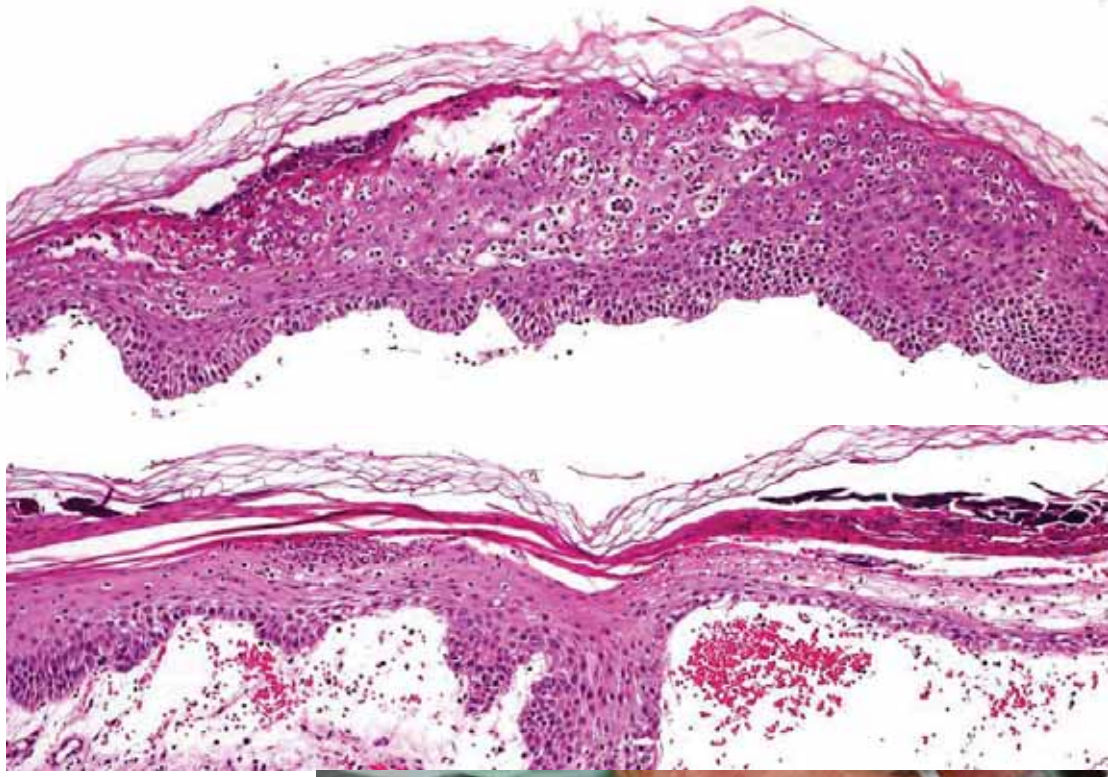
F, 77

Reduced general conditions. Onset of skin lesions 5 days after intake of amoxicillin for eradication of *Helicobacter pylori*. Leukocytosis (>37.000), mild anemia.

Culture negative. Acute renal insufficiency, hypocalcemia hyperkalemia.

A biopsy is taken.





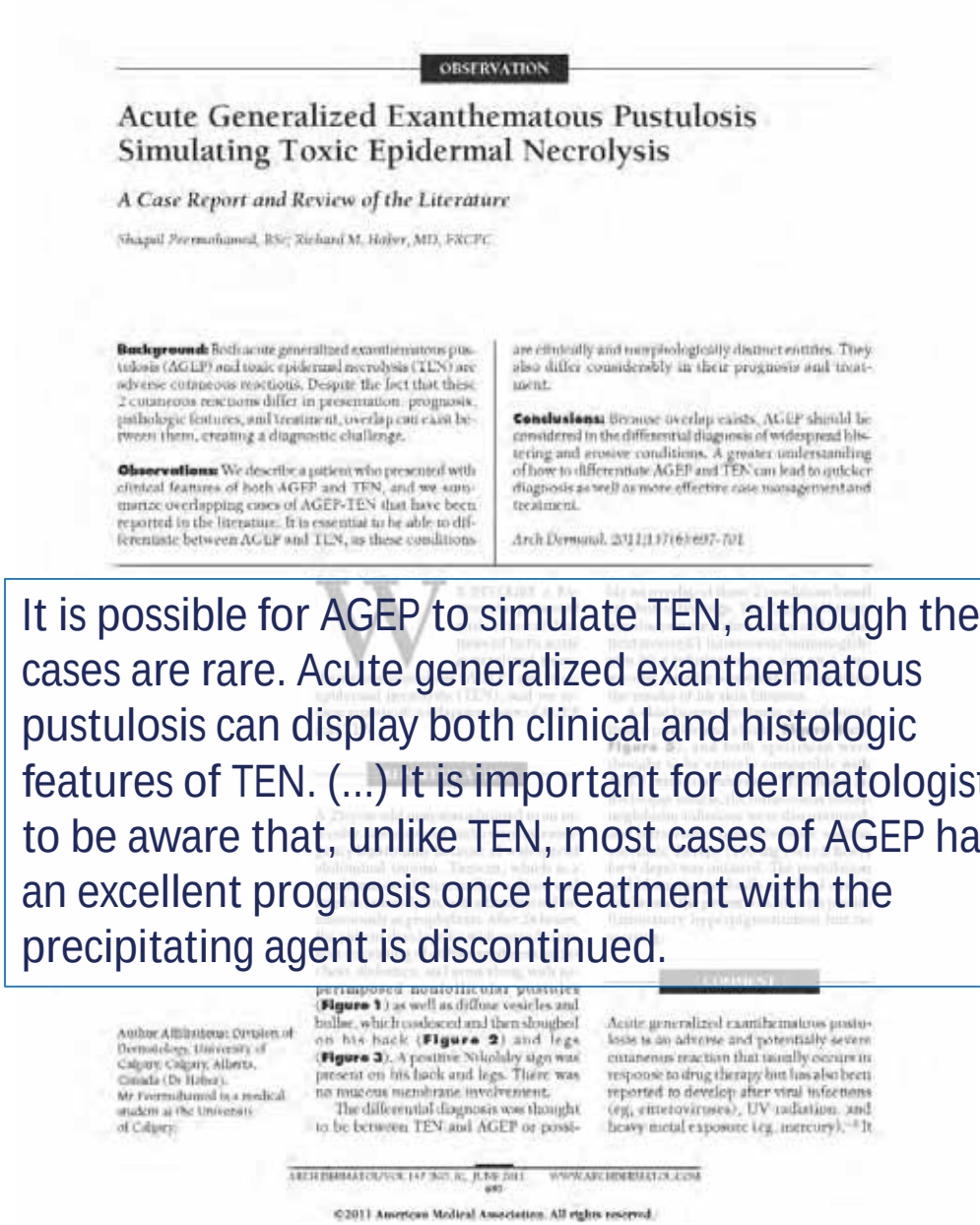
AGEP / TEN "overlap"

Resolved within a few days under systemic steroids (50 mg prednisolone)

1st presentation

8 days later

Course relatively short (more in keeping with AGEP); Atypical target lesions (more in keeping with TEN); Pronounced epidermal exfoliation (more in keeping with TEN); No involvement of mucosal surfaces (more in keeping with AGEP); High white cell count (more in keeping with AGEP); Two biopsies (one consistent with AGEP, the other with TEN).



OBSERVATION

Acute Generalized Exanthematous Pustulosis Simulating Toxic Epidermal Necrolysis

A Case Report and Review of the Literature

Shapil Peermohamed, BSc; Richard M. Haber, MD, FRCPC

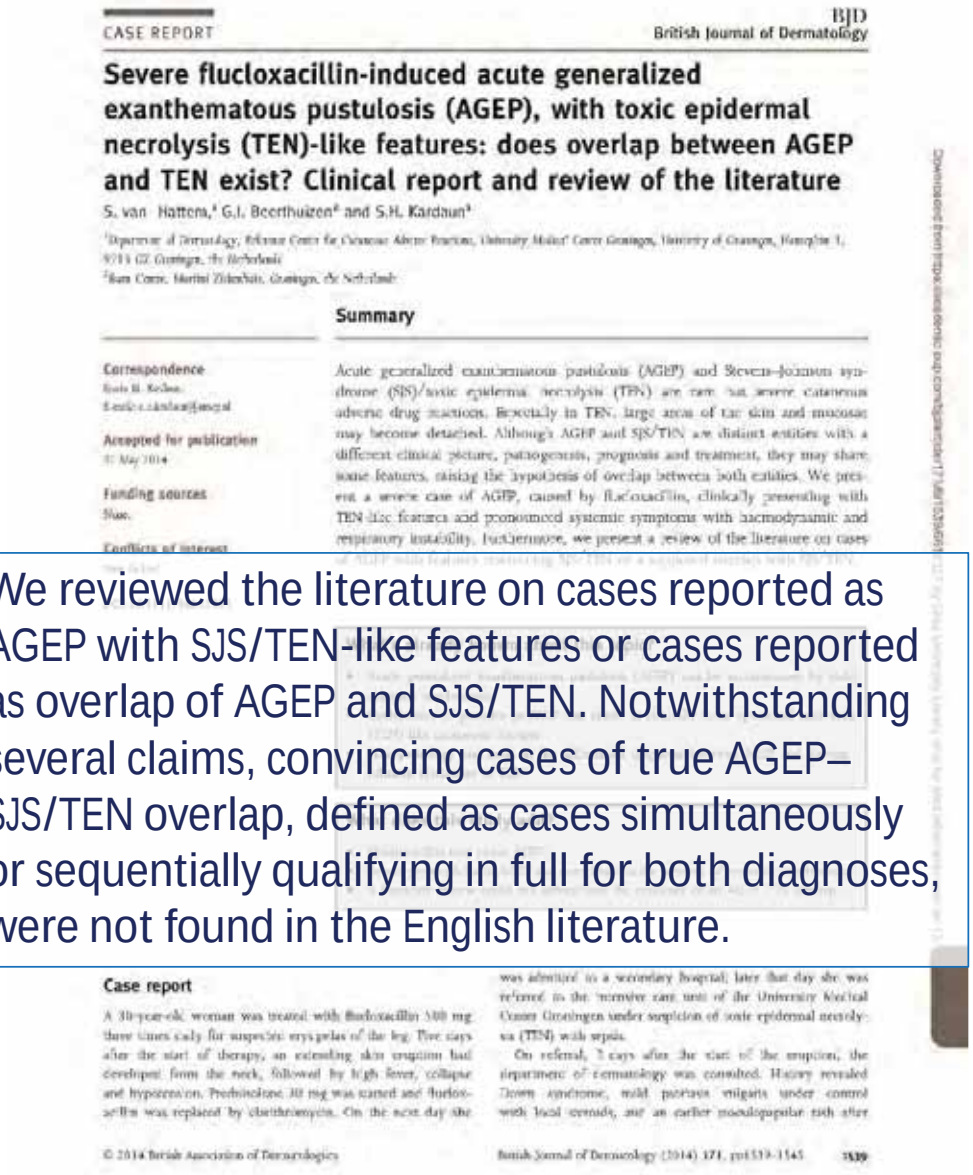
Background: Both acute generalized exanthematous pustulosis (AGEP) and toxic epidermal necrolysis (TEN) are adverse cutaneous reactions. Despite the fact that these 2 cutaneous reactions differ in presentation, prognosis, pathologic features, and treatment, overlap can exist between them, creating a diagnostic challenge.

Observations: We describe a patient who presented with clinical features of both AGEP and TEN, and we summarize overlapping cases of AGEP-TEN that have been reported in the literature. It is essential to be able to differentiate between AGEP and TEN, as these conditions are clinically and histologically distinct entities. They also differ considerably in their prognosis and treatment.

Conclusions: Because overlap exists, AGEP should be considered in the differential diagnosis of widespread blistering and erosive conditions. A greater understanding of how to differentiate AGEP and TEN can lead to quicker diagnosis as well as more effective case management and treatment.

Arch Dermatol. 2011;147(6):697-701

It is possible for AGEP to simulate TEN, although these cases are rare. Acute generalized exanthematous pustulosis can display both clinical and histologic features of TEN. (...) It is important for dermatologists to be aware that, unlike TEN, most cases of AGEP have an excellent prognosis once treatment with the precipitating agent is discontinued.



CASE REPORT

BJD
British Journal of Dermatology

Severe flucloxacillin-induced acute generalized exanthematous pustulosis (AGEP), with toxic epidermal necrolysis (TEN)-like features: does overlap between AGEP and TEN exist? Clinical report and review of the literature

S. van Hattem,[1] G.J. Bruckers[2] and S.H. Kardaun[3]

[1]Department of Dermatology, Referral Center for Cutaneous Adverse Reactions, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
[2]Rein Centre, Martini Ziekenhuis, Groningen, the Netherlands

Summary

Acute generalized exanthematous pustulosis (AGEP) and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) are rare but severe cutaneous adverse drug reactions. Especially in TEN, large areas of the skin and mucosae may become detached. Although AGEP and SJS/TEN are distinct entities with a different clinical picture, pathogenesis, prognosis and treatment, they may share some features, raising the hypothesis of overlap between both entities. We present a severe case of AGEP, caused by flucloxacillin, clinically presenting with TEN-like features and pronounced systemic symptoms with haemodynamic and respiratory instability. Furthermore, we present a review of the literature on cases

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31 May 2014

Funding sources
None.

Conflicts of interest

We reviewed the literature on cases reported as AGEP with SJS/TEN-like features or cases reported as overlap of AGEP and SJS/TEN. Notwithstanding several claims, convincing cases of true AGEP–SJS/TEN overlap, defined as cases simultaneously or sequentially qualifying in full for both diagnoses, were not found in the English literature.

Case report

A 38-year-old woman was treated with flucloxacillin 500 mg three times daily for suspected erysipelas of the leg. Five days after the start of therapy, an extending skin eruption had developed from the neck, followed by high fever, collapse and hypotension. Prednisolone 30 mg was started and flucloxacillin was replaced by clarithromycin. On the next day she was admitted to a secondary hospital; later that day she was referred to the intensive care unit of the University Medical Center Groningen under suspicion of toxic epidermal necrolysis (TEN) with sepsis.

On referral, 2 days after the start of the eruption, the department of dermatology was consulted. History revealed Down syndrome, mild psoriasis vulgaris under control with local steroids, and an earlier mucolagopular rash after

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ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Toxic epidermal necrolysis, DRESS, AGEP: Do overlap cases exist?

Sophie Bouvresse[1], Laurence Valeyrie-Allanore[1,2*], Nicolas Orsonne[2], Marie Pauline Konstantinou[1], Sylvie H Kanzaun[1], Martine Bagot[1], Pierre Wolkenstein[1,3] and Jean-Claude Roujeau[1]

Abstract

Background: Severe cutaneous adverse reactions to drugs (SCARs) include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and epidermal necrolysis (Stevens-Johnson syndrome-toxic epidermal necrolysis: SJS-TEN). Because of the varied initial presentation of such adverse drug reactions, diagnosis may be difficult and suggests overlap among SCARs. Overlapping SCARs are defined as cases fulfilling the criteria for definite or probable diagnosis of at least 2 ADRs according to scoring systems for AGEP, DRESS and SJS-TEN. We aimed to evaluate the prevalence of overlap among SCARs among cases in the referral hospital in France.

Methods: We retrospectively analyzed data for 216 patients hospitalized in the referral centre over 7 years with a discharge diagnosis of AGEP (n = 45), DRESS (n = 47), SJS-TEN (n = 68) or "drug rash" (n = 44). Each case with available clinical data and a skin biopsy specimen was scored for AGEP, DRESS and SJS-TEN by use of diagnostic scores elaborated by the RegiSCAR group.

Results: In total, 45 of 216 cases (21%) had at least 2 possible diagnoses: 35 had a single predominant diagnosis (definite or probable), 7 had several possible diagnoses and 3 (2.1% of 145 confirmed SCARs) were overlap SCARs.

Conclusions: Despite ambiguities among SCARs, confirmed overlap cases are rare. This study did not avoid pitfalls linked to its retrospective nature and selection bias to the acute stage of disease. Early identification of severe ADRs can be difficult because of clinical or biologic overlapping features and missing data on histology, biology and evolution. Retrospectively analyzing cases by use of diagnostic algorithms can lead to reliable discrimination among AGEP, DRESS and SJS-TEN.

Keywords: Toxic epidermal necrolysis, DRESS, AGEP, Severe cutaneous adverse reactions, Overlap

Background

Adverse cutaneous reactions to drugs are frequent, affecting 2% to 3% of all hospitalized patients [1]. Only about 2% of these adverse cutaneous reactions are considered severe [1]. The spectrum of severe cutaneous adverse reactions to drugs (SCARs) include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and epidermal necrolysis (Stevens-Johnson syndrome-SJS, toxic epidermal necrolysis -TEN). These conditions are defined by clinical features associated more or less with specific biological and histological findings [2,3].

AGEP is characterized by a pustular eruption arising quickly after administration of the causative drug (usually aminopenicillin, pristinamycin, diltiazem) [4,5]. DRESS, also known as drug-induced hypersensitivity syndrome, is a severe, systemic drug reaction most commonly associated with aromatic anticonvulsants, allopurinol and sulfonamides [6-8]. Patients typically present fever, facial oedema, lymphadenopathy and morbilliform eruption, which may progress to erythematous rash and exfoliative dermatitis. Hematologic abnormalities, including eosinophilia and atypical lymphocytosis, are a hallmark of the condition. Visceral organ involvement typically manifests as hepatitis but may include nephritis, interstitial

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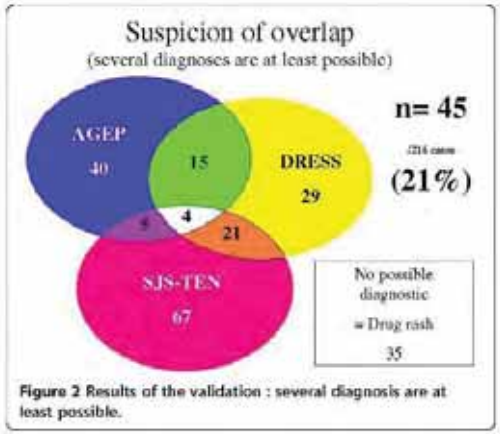


Figure 2 Results of the validation : several diagnosis are at least possible.

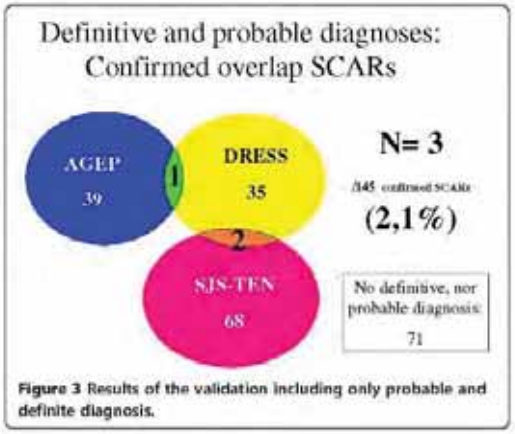
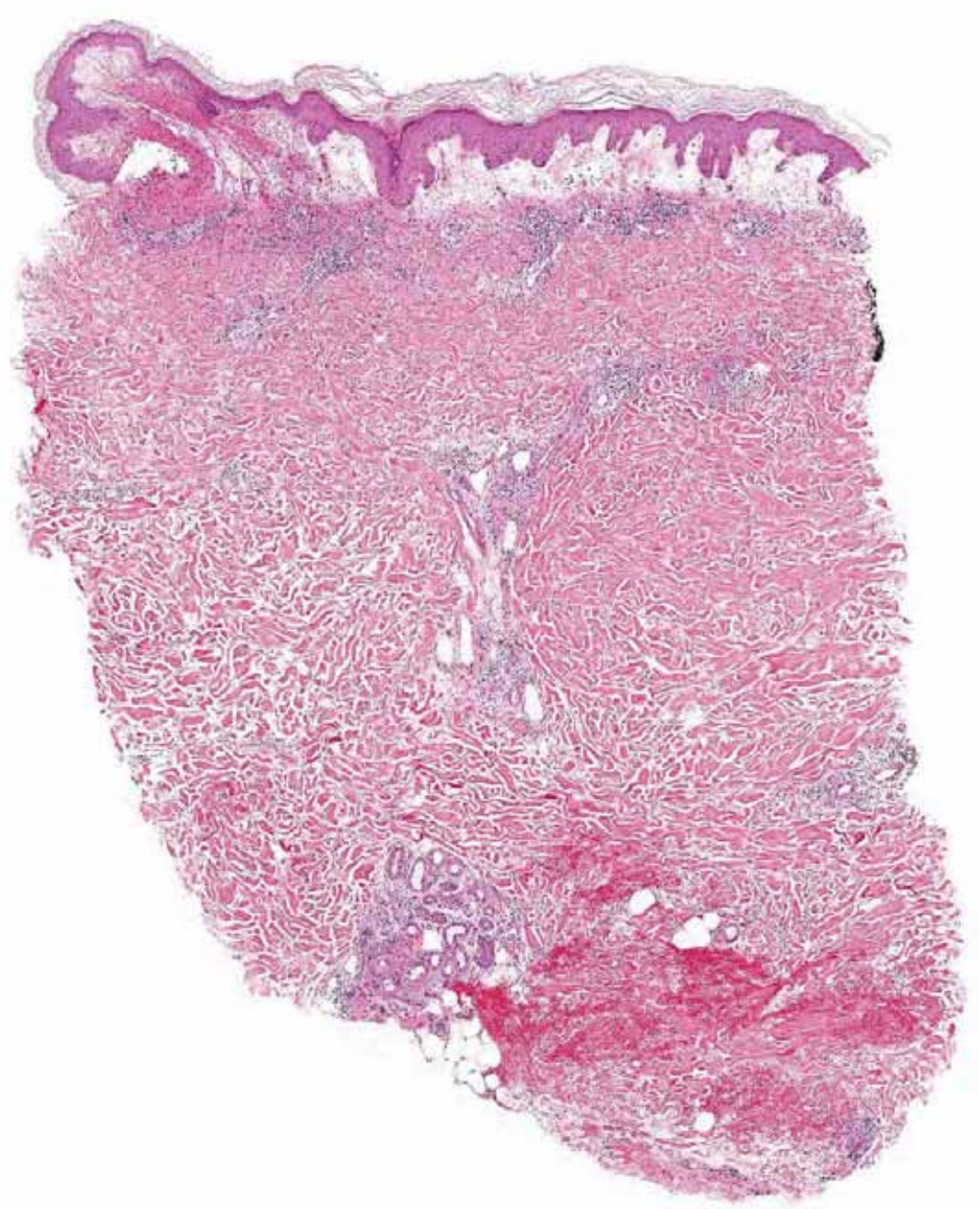
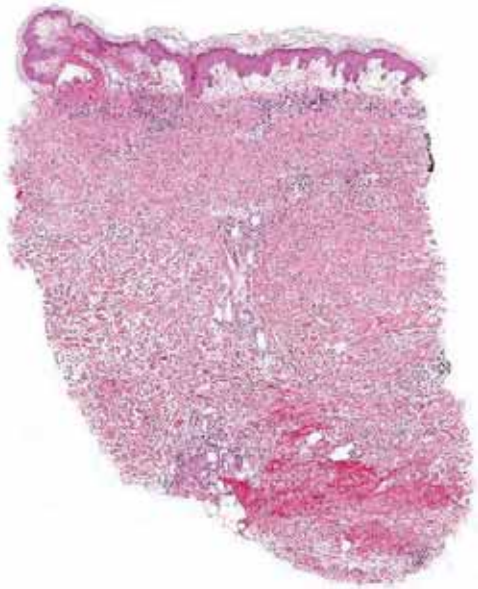


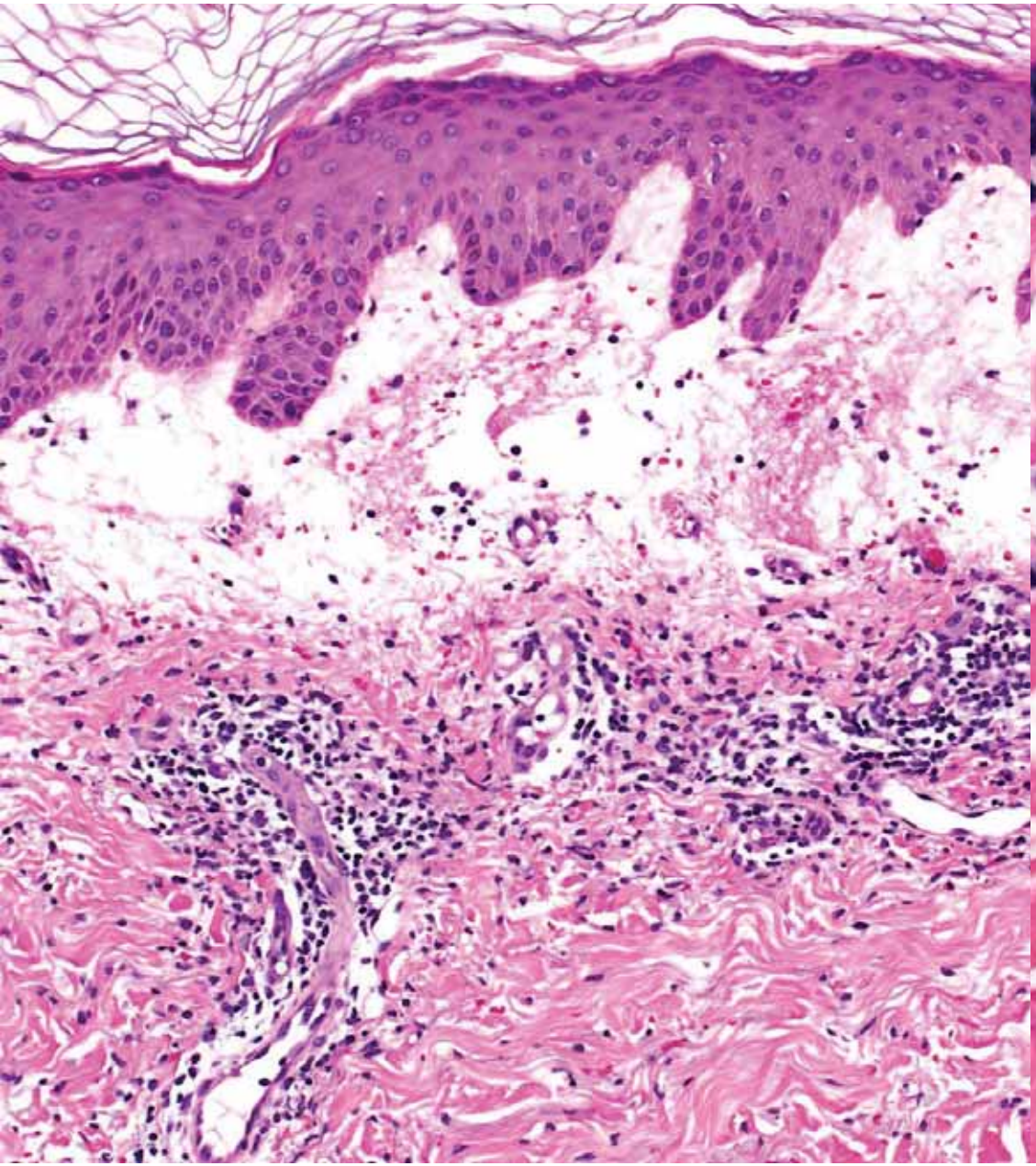
Figure 3 Results of the validation including only probable and definite diagnosis.

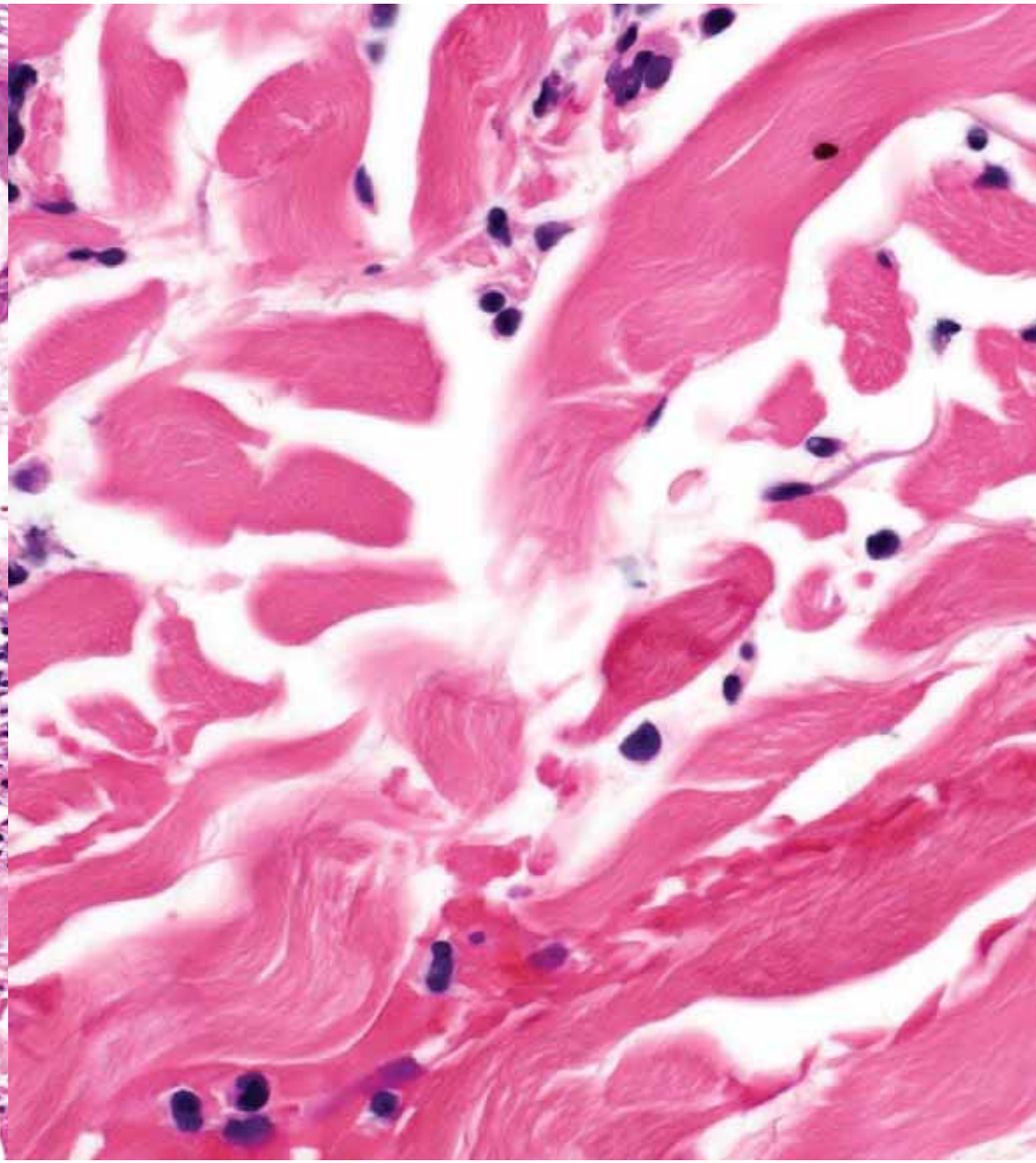


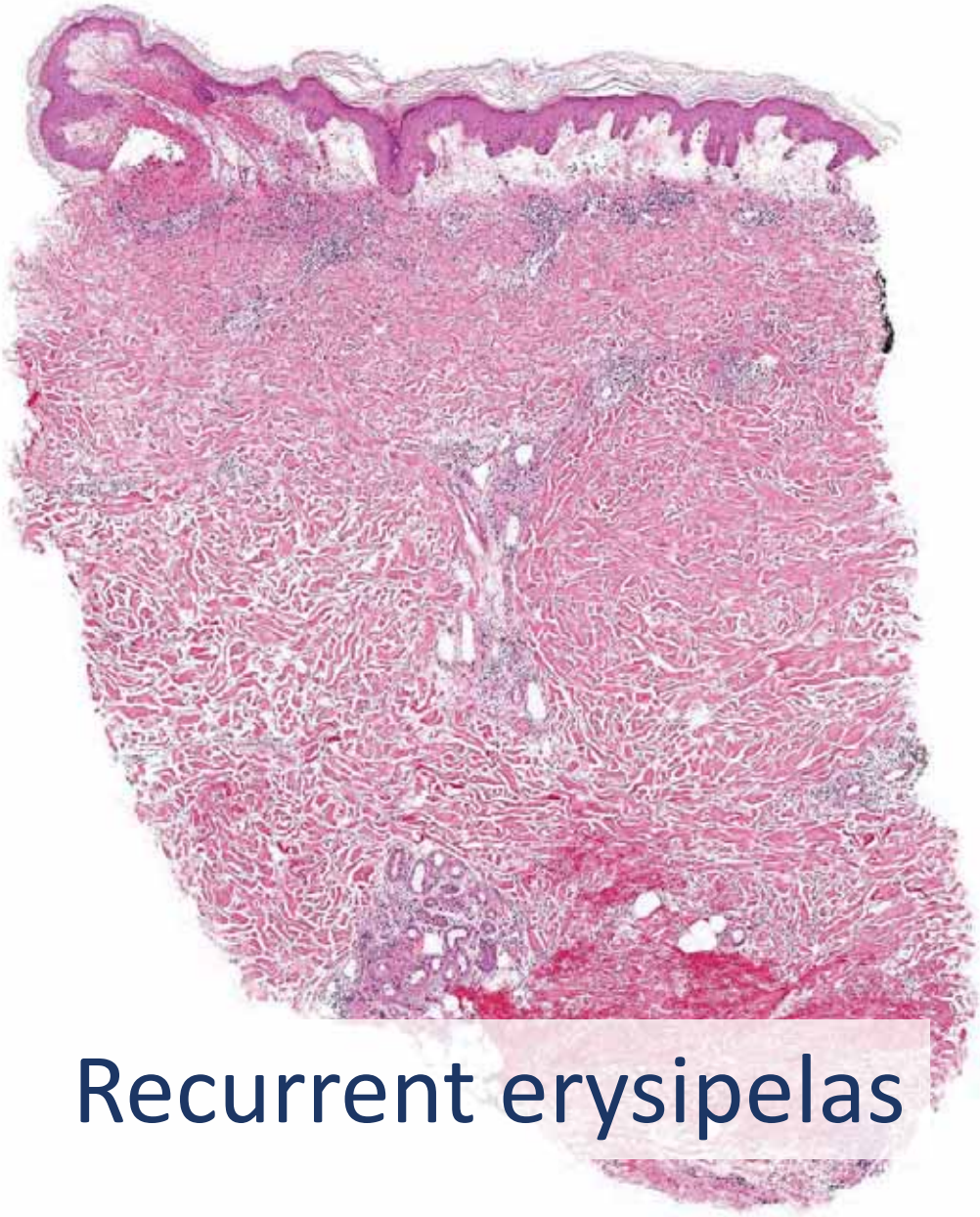
Case 24

M, 63. According to the patient recurrent skin lesions on the right leg for approximately 10 years (3x/year), accompanied by fever, diarrhea and malaise.

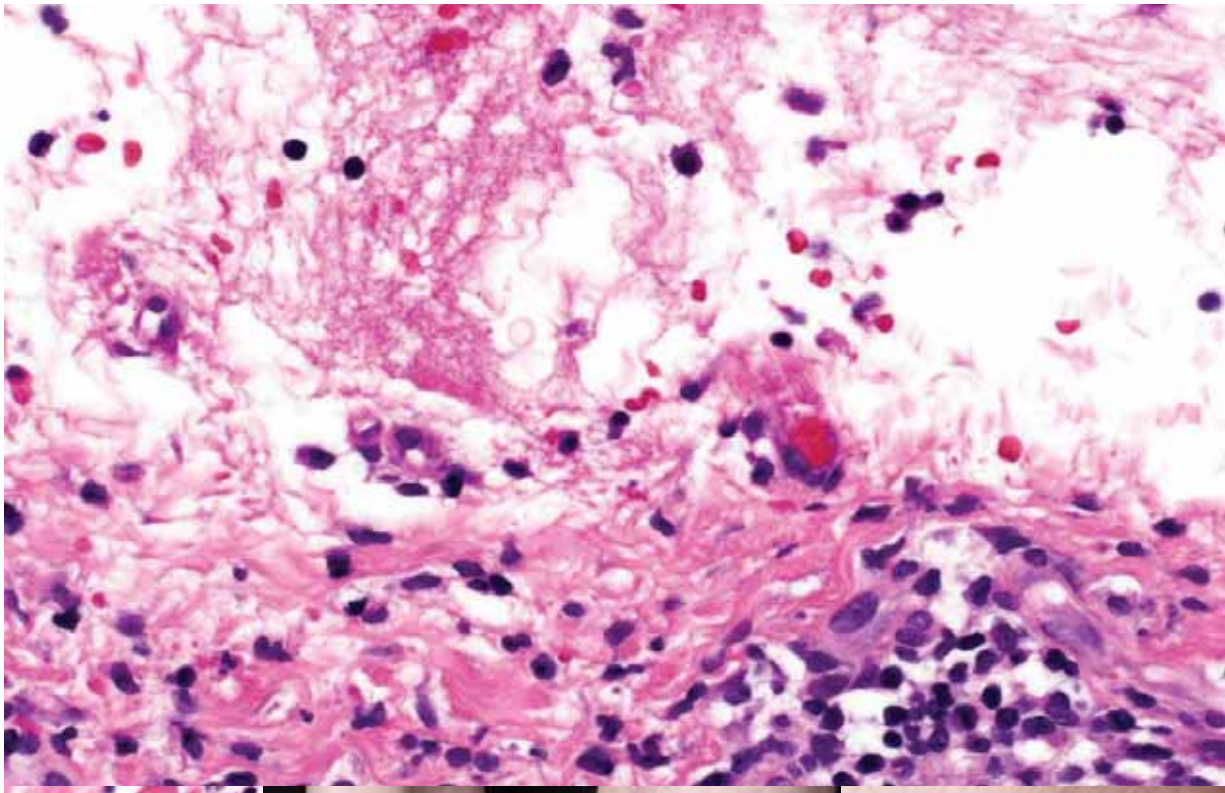


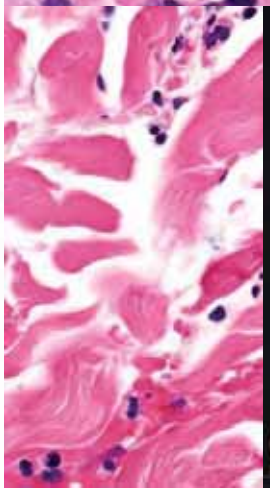


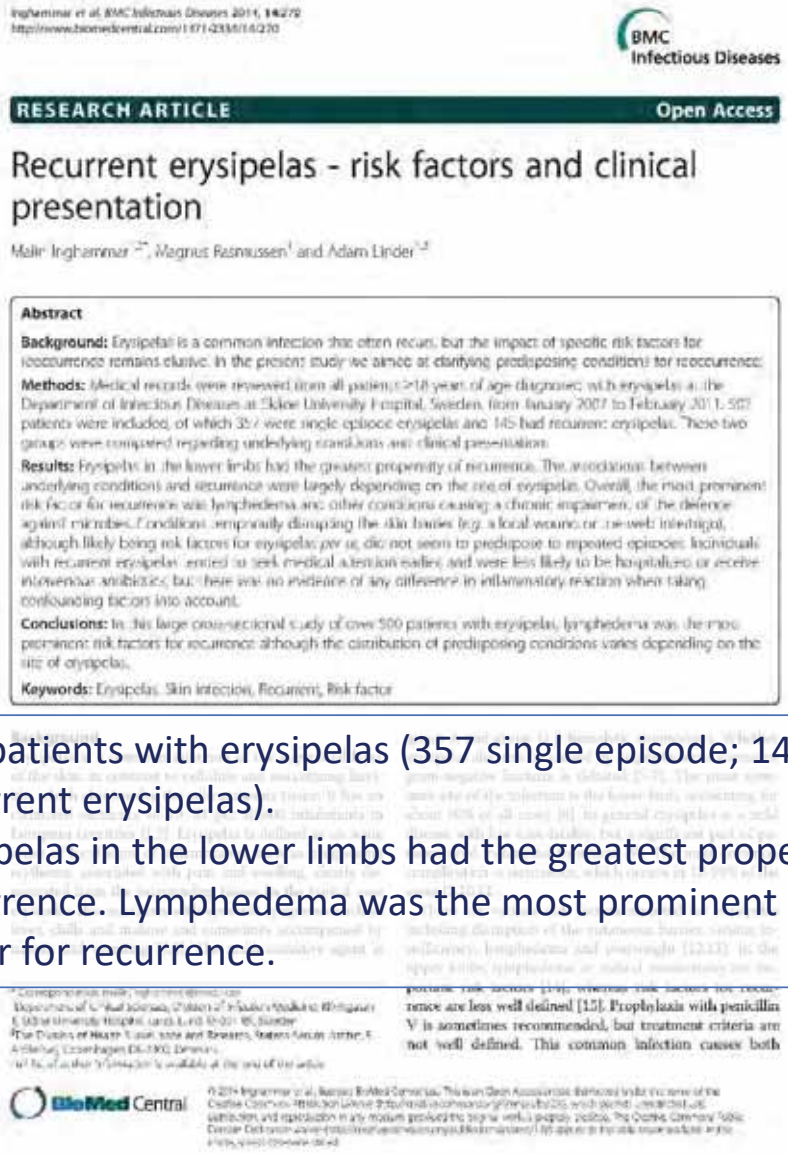




Recurrent erysipelas







BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Recurrent erysipelas - risk factors and clinical presentation

Malin Inghammar*, Magnus Rasmussen and Adam Linder

Abstract

Background: Erysipelas is a common infection that often recurs, but the impact of specific risk factors for recurrence remains elusive. In the present study we aimed at clarifying predisposing conditions for recurrence.

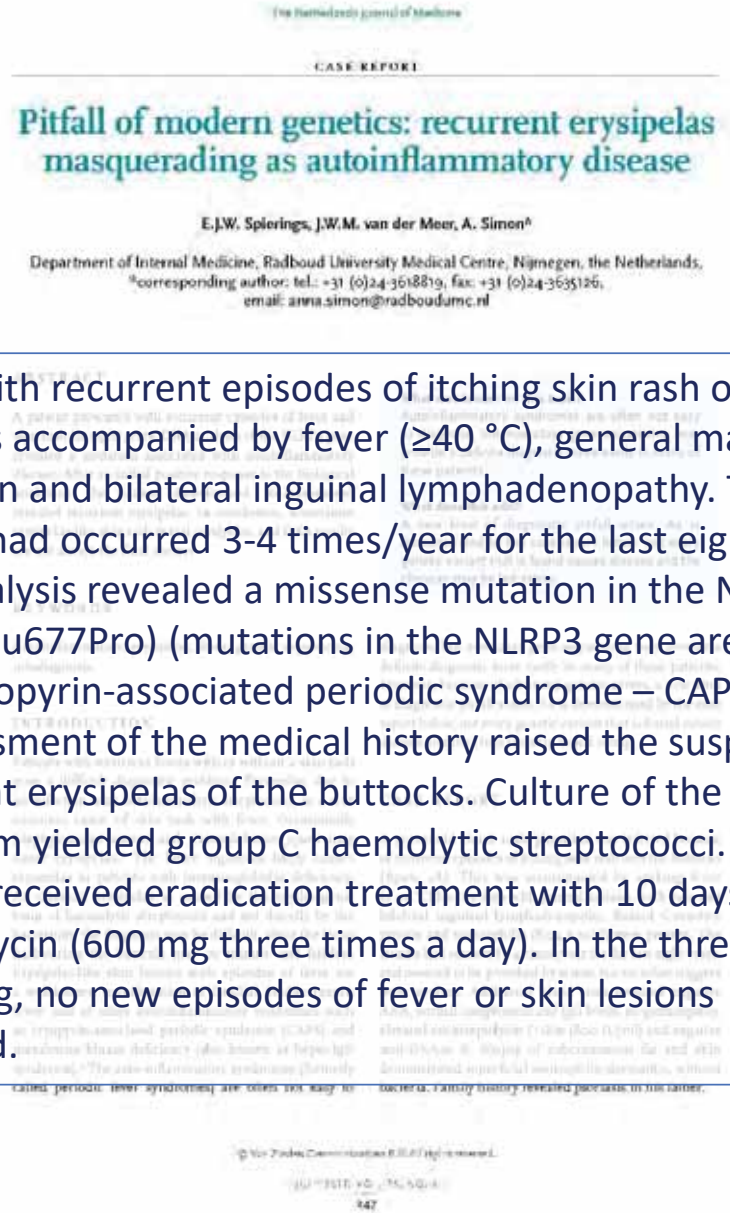
Methods: Medical records were reviewed from all patients >18 years of age diagnosed with erysipelas at the Department of Infectious Diseases at Skåne University Hospital, Sweden, from January 2007 to February 2011. 502 patients were included, of which 357 were single episode erysipelas and 145 had recurrent erysipelas. These two groups were compared regarding underlying conditions and clinical presentation.

Results: Erysipelas in the lower limbs had the greatest propensity of recurrence. The association between underlying conditions and recurrence were largely depending on the site of erysipelas. Overall, the most prominent risk factor for recurrence was lymphedema and other conditions causing a chronic impairment of the defence against microbes. Conditions temporally disrupting the skin barrier (e.g. a focal wound or "cat-web" interdigital), although likely being risk factors for erysipelas per se, did not seem to predispose to repeated episodes. Individuals with recurrent erysipelas tended to seek medical attention earlier and were less likely to be hospitalized or receive intravenous antibiotics, but there was no evidence of any difference in inflammatory reaction when taking confounding factors into account.

Conclusions: In this large cross-sectional study of over 500 patients with erysipelas, lymphedema was the most prominent risk factors for recurrence although the distribution of predisposing conditions varies depending on the site of erysipelas.

Keywords: Erysipelas, Skin infection, Recurrent, Risk factor

502 patients with erysipelas (357 single episode; 145 recurrent erysipelas).
Erysipelas in the lower limbs had the greatest propensity of recurrence. Lymphedema was the most prominent risk factor for recurrence.



CASE REPORT

Pitfall of modern genetics: recurrent erysipelas masquerading as autoinflammatory disease

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M, 35 with recurrent episodes of itching skin rash over the buttocks accompanied by fever (≥40 °C), general malaise, back pain and bilateral inguinal lymphadenopathy. The attacks had occurred 3-4 times/year for the last eight years. DNA analysis revealed a missense mutation in the NLRP3 gene (Leu677Pro) (mutations in the NLRP3 gene are linked with cryopyrin-associated periodic syndrome – CAPS). Reassessment of the medical history raised the suspicion of recurrent erysipelas of the buttocks. Culture of the perineum yielded group C haemolytic streptococci. The patient received eradication treatment with 10 days of clindamycin (600 mg three times a day). In the three years following, no new episodes of fever or skin lesions occurred.

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Original article

Erysipelas of the leg: A cross-sectional study of risk factors for recurrence

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ABSTRACT

Background: Erysipelas is a common infection of the superficial layer of skin. The main causative agent is group A β-hemolytic streptococci. One of the most challenging aspects of this disease is its high rate of recurrence.

Objectives: To identify risk factors for recurrence of erysipelas of the leg.

Patients and methods: We included in a cross-sectional study all patients hospitalized for erysipelas of the leg seen at the dermatology department of the Ibn Rochd University Hospital in Casablanca, Morocco, from January 2015 to April 2020. Patients were divided into two groups: those with a single episode (SE) and those with recurrent erysipelas (RE). These two groups were compared for clinical and laboratory characteristics, with particular focus on systemic and local risk factors.

Results: The study included 270 patients, of whom 132 had SE and 138 had RE. Age, gender, hospital stay as well as laboratory finding- did not differ significantly between the two groups. In multivariable analysis, cutaneous disruption [adjusted odds ratio [aOR]= 1.9; 95% confidence interval (95% CI): 1.0–3.7] lymphedema [aOR= 19.6; 95% CI: 8.0–57.2] and obesity [aOR= 2.3; 95% CI: 1.1–6.2] were significantly associated with RE. Venous insufficiency and diabetes were not found to be associated with risk of recurrence.

Conclusion: Our results suggest that erysipelas is a potentially chronic disease and patients with identified local risk factors or obesity should be considered as exposed to recurrence and considered as targets for antibiotic prophylaxis and other preventive methods.

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1. Introduction

Erysipelas is an acute superficial dermal hypodermal infection usually affecting the leg and chiefly caused by group A β- hemolytic *Streptococcus* [1,2]. The terms erysipelas and cellulitis are often used interchangeably, although cellulitis is considered a deeper skin infection by many authors [2]. Recurrence is one of the most common complications of erysipelas, which occurs in 12–29% of cases [1–3]. However, only very few studies have assessed the implication of general and local factors in erysipelas relapse. Identifying risk factors for recurrence of erysipelas is a medical priority to reduce the social and financial burden of this disease. There are only a few outdated studies regarding risk factors, most of which were not powerful enough to allow a multivariable analysis of risk factors for recurrence. The purpose of our study was to identify such risk factors for recurrence of leg erysipelas and to characterize the epidemiological and clinical profile of the affected patients.

2. Materials and methods

2.1. Patients and study design

The study was a retrospective analysis of all patients (18 years and older) hospitalized and diagnosed with leg erysipelas at the dermatology department of UHC Ibn Rochd, Casablanca, between January 2015 and April 2020. Erysipelas was defined as an acute skin infection with an expanding painful erythematous and edematous plaque having relatively well-demarcated borders. All anatomic sites were initially considered but due to the high percentage of lower-limb erysipelas in both groups, we only considered erysipelas of the leg in our study. Patients with bullous and hemorrhagic erysipelas were included in the study, but those

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Table 1
Distribution of the number of erysipelas episodes in the recurrent group.

Number of recurrences	2	3	4	5	6	8	10	11
Number of patients	48	59	23	2	2	1	2	1
%	34.78%	42.75%	16.66%	1.44%	1.44%	0.72%	1.44%	0.72%

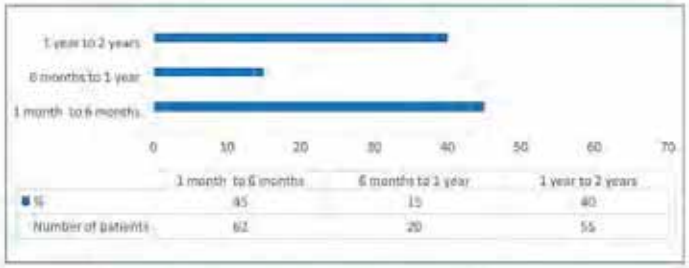


Fig. 1. Time between the first and second episodes in the recurrent erysipelas group.

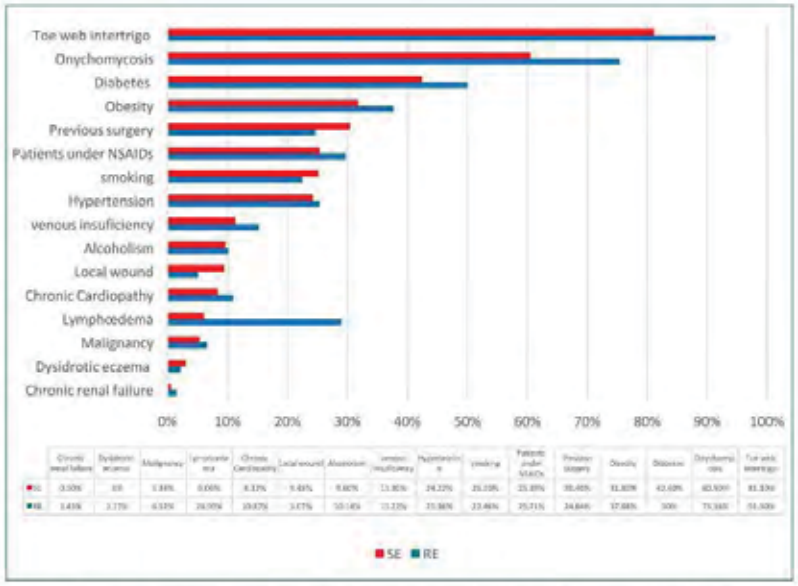
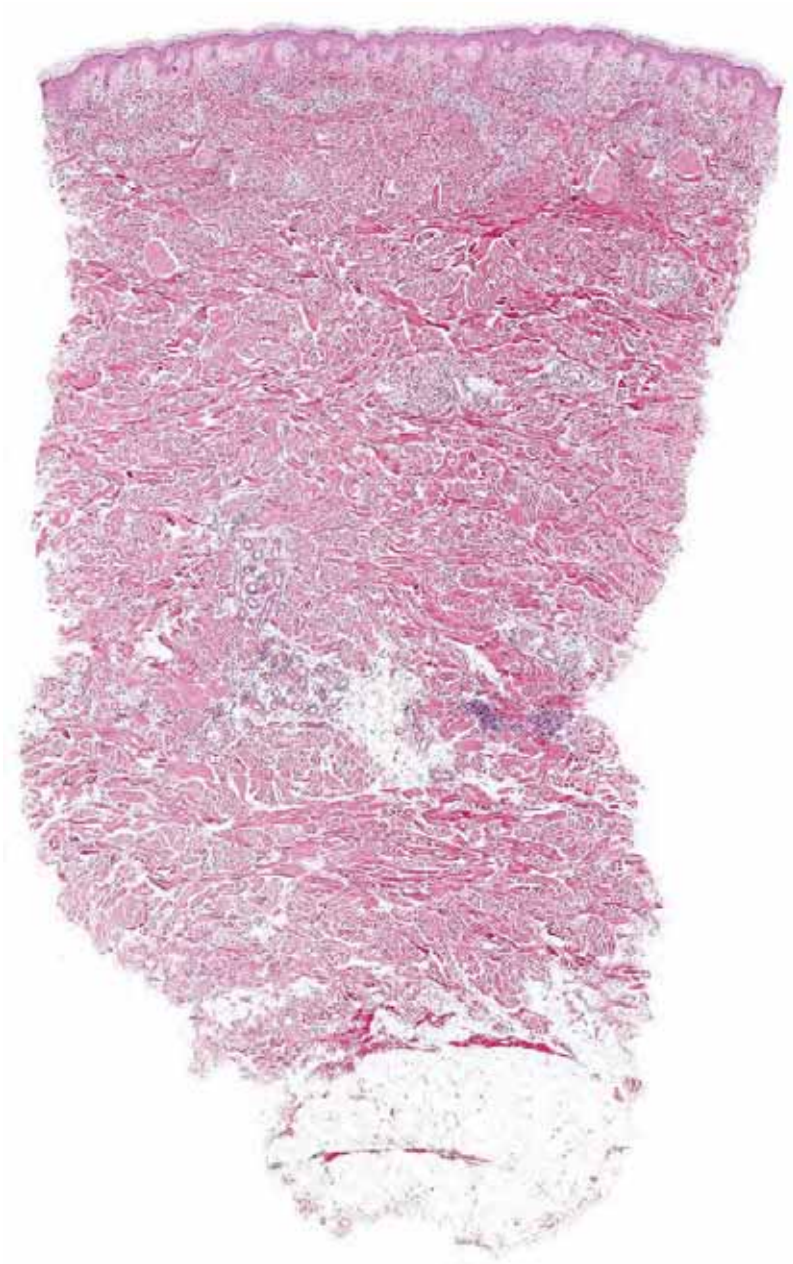


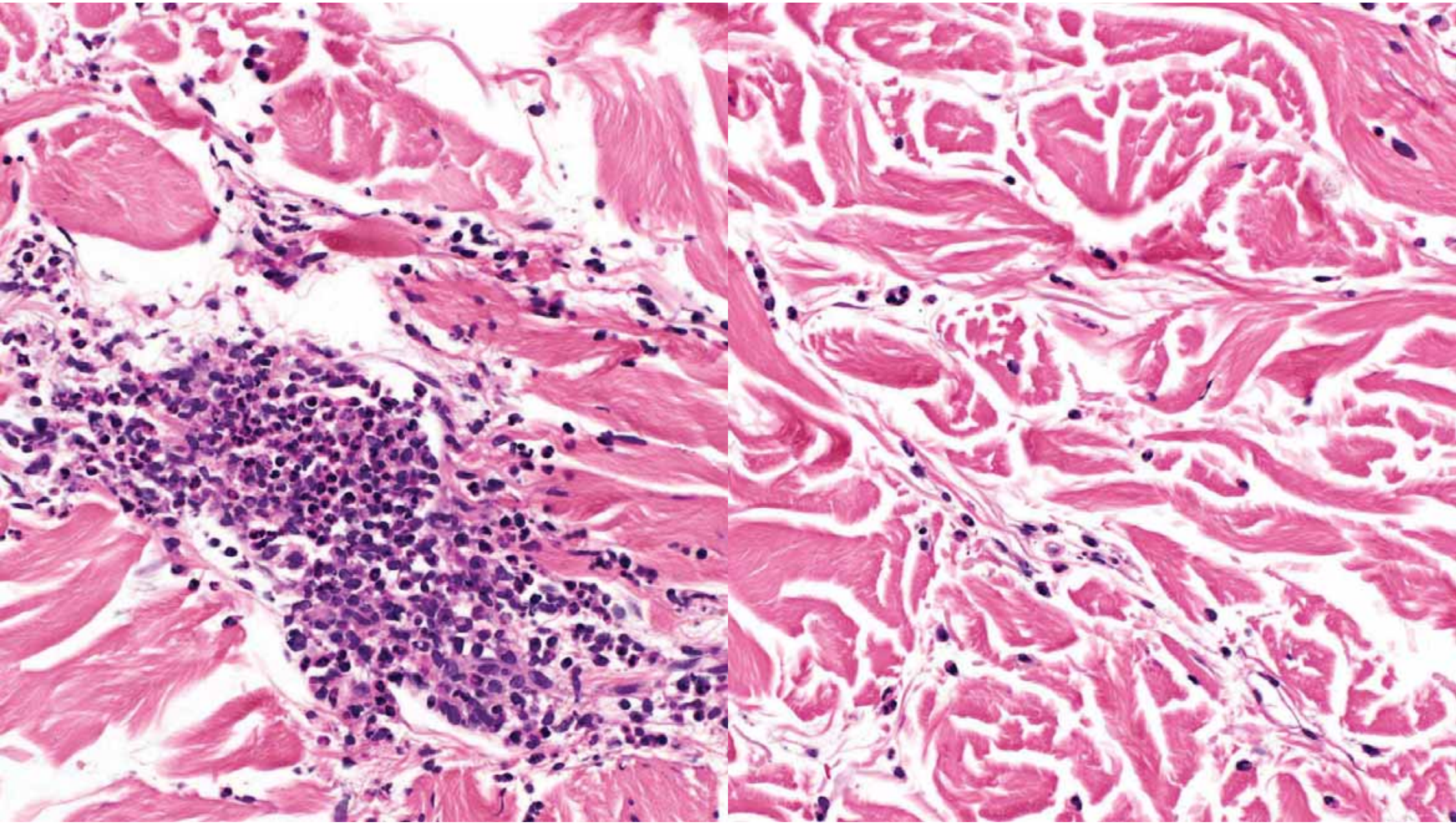
Fig. 2. Comparison between predisposing conditions for erysipelas in the single-episode and recurrent erysipelas groups.

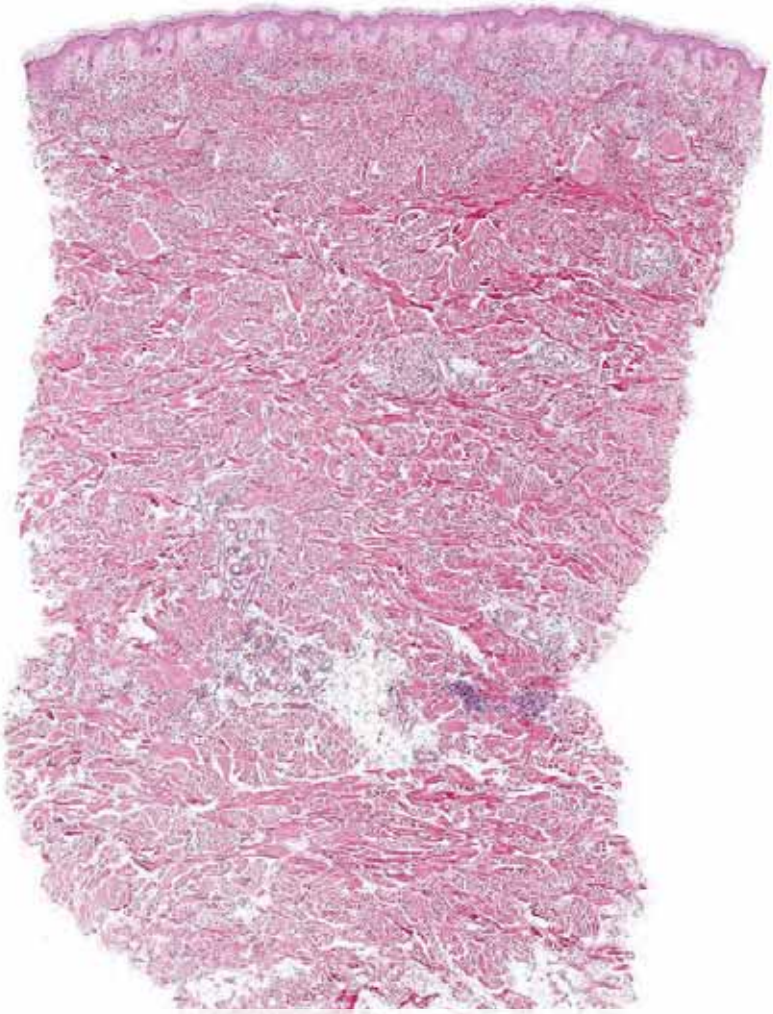


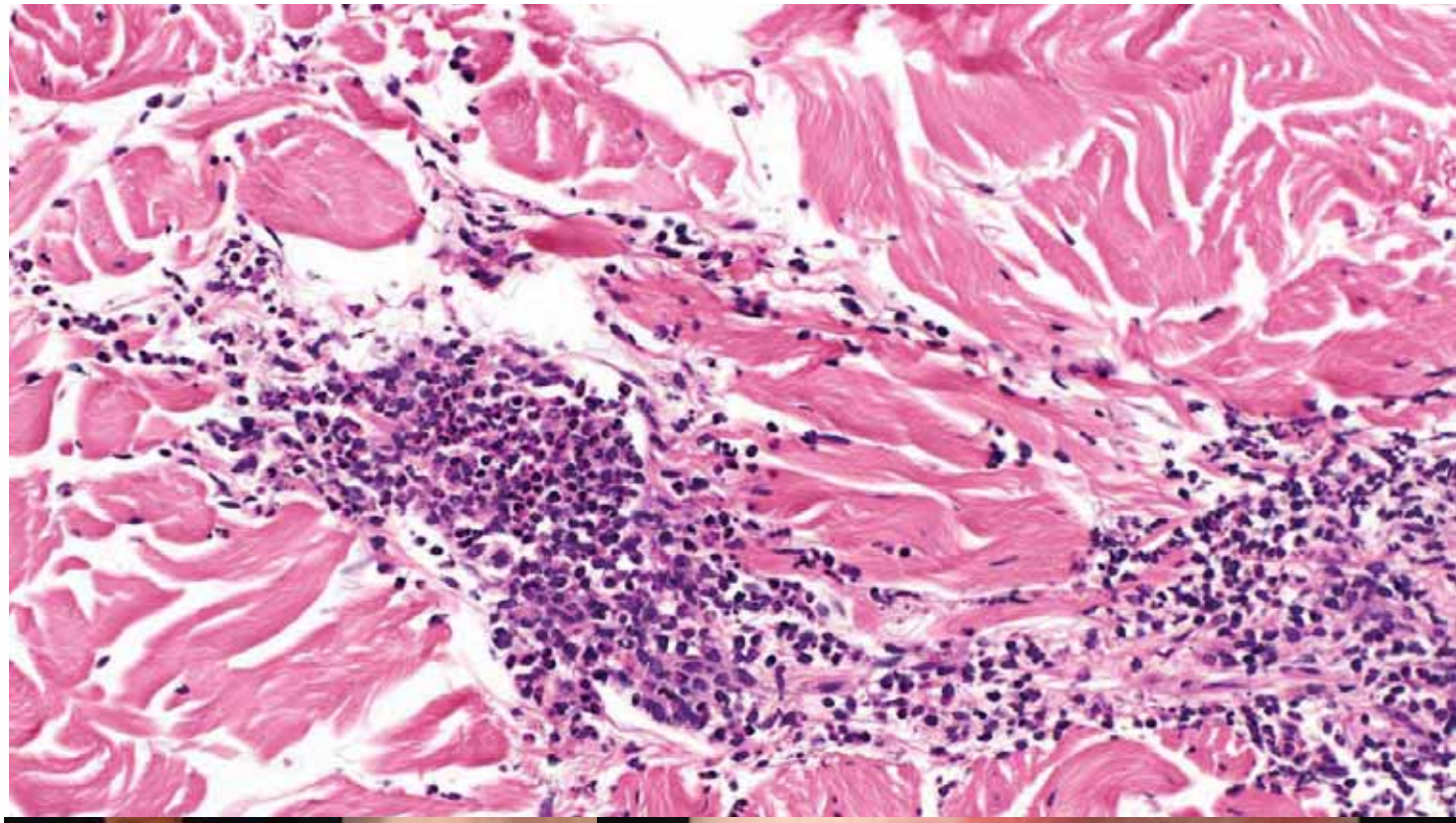
Case 25

M, 65. According to the patient slightly itchy and burning skin lesions on the back for 1 week.

Five days previously painful hemorrhoids and shiver (managed with NSAID and oral antibiotics).







Erysipelas

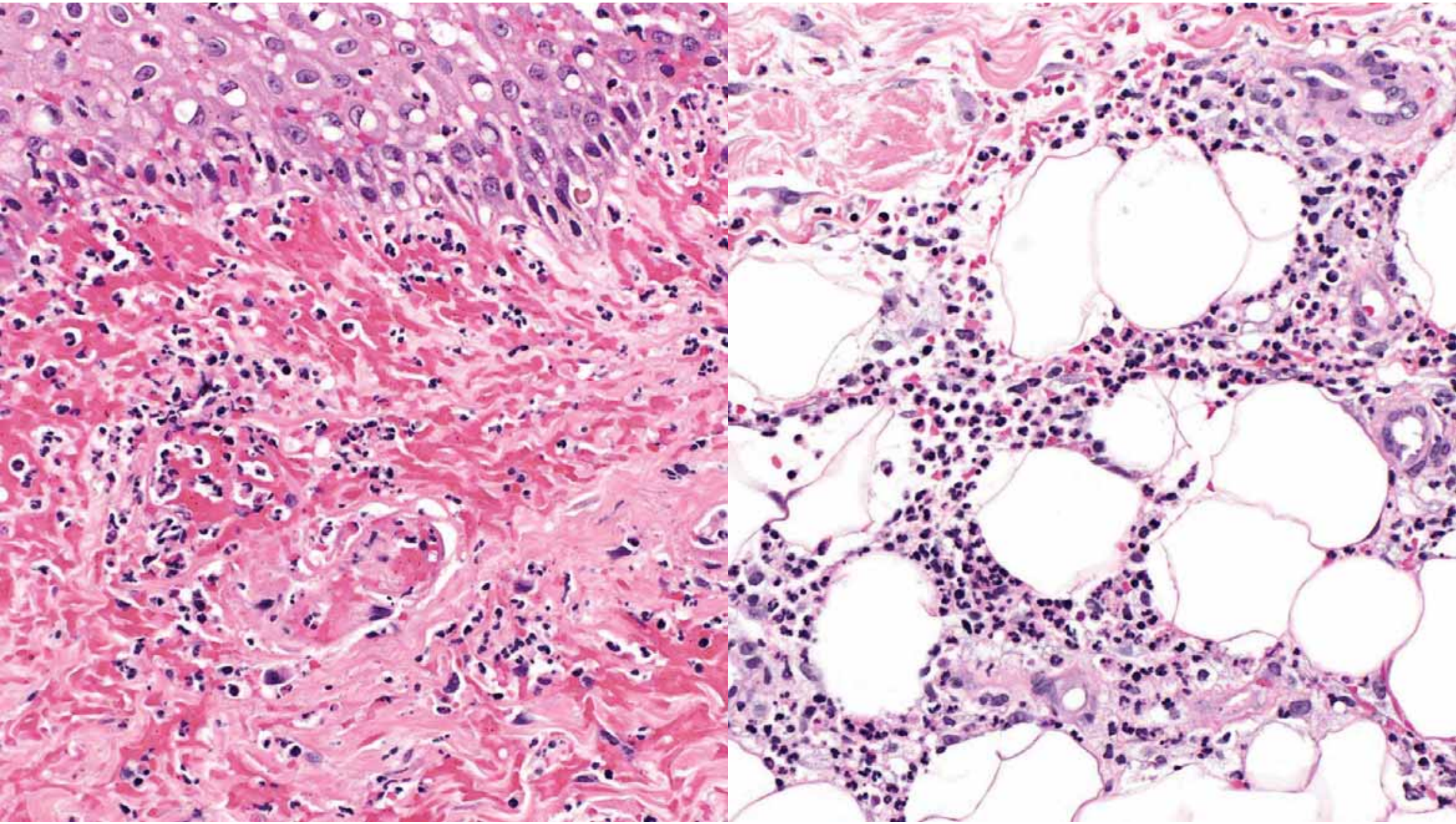
(Leukocytes: 10.300; CRP: 27,6)

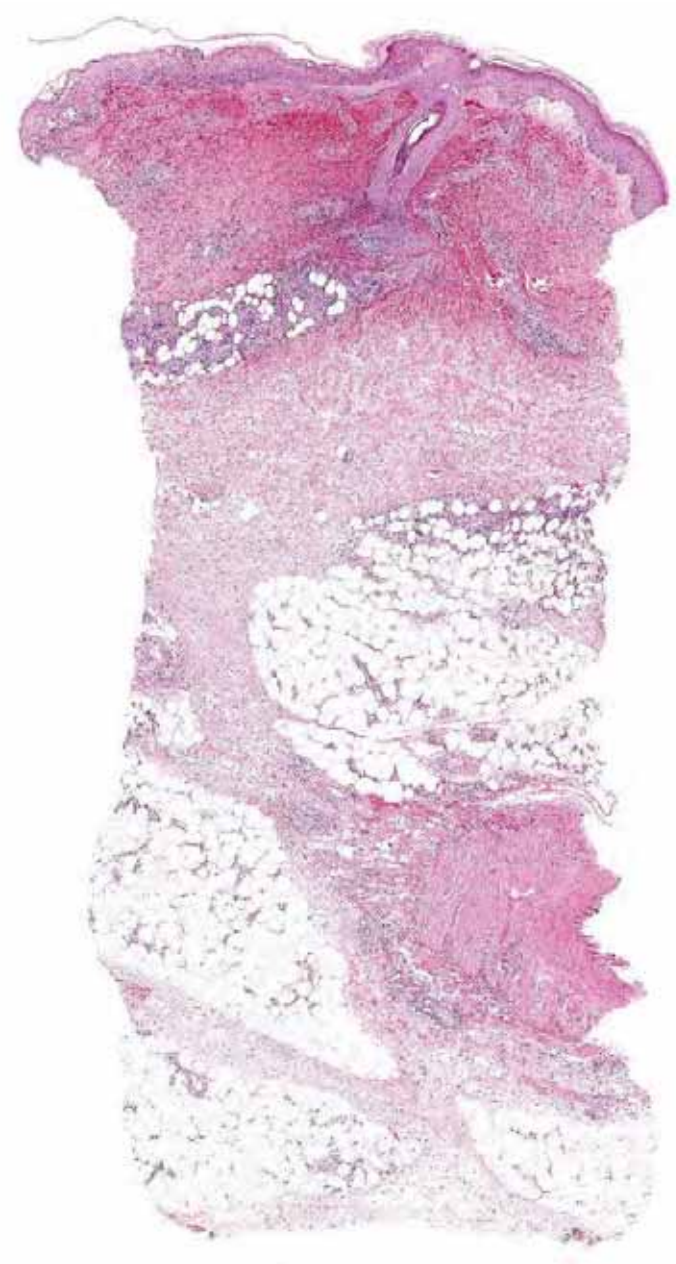
Erysipelas on the trunk

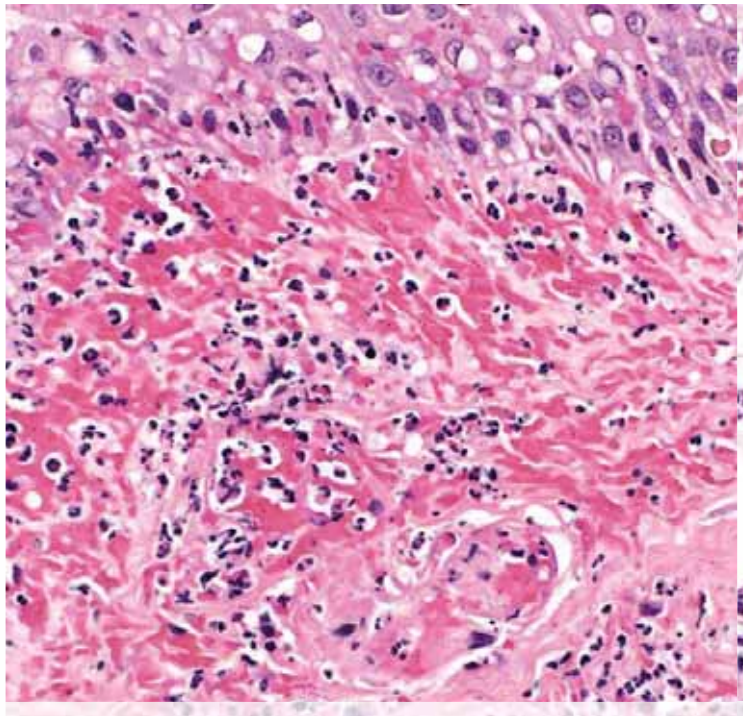
Case 26

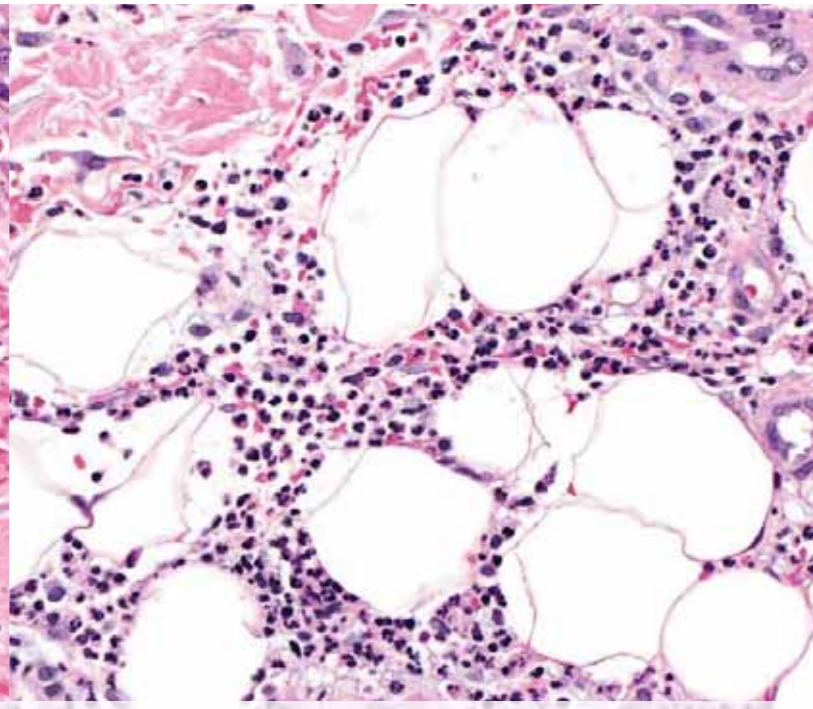
M, 50. According to the patient skin lesions on both lower extremities for 3 weeks. Visited the GP 2 days before presentation (prescribed doxycycline 200mg/d). Leukocytes: 19.46; CRP: 38.9.

Admitted as in-patient.

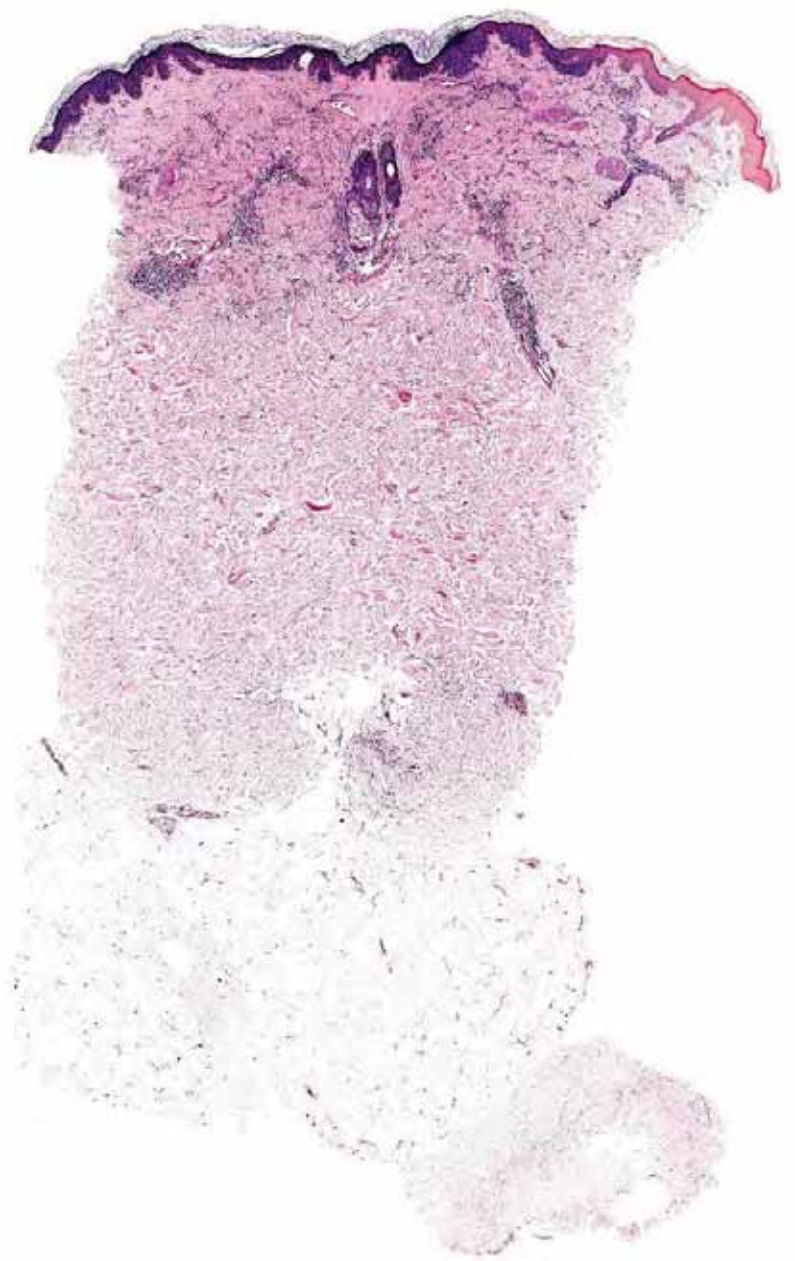






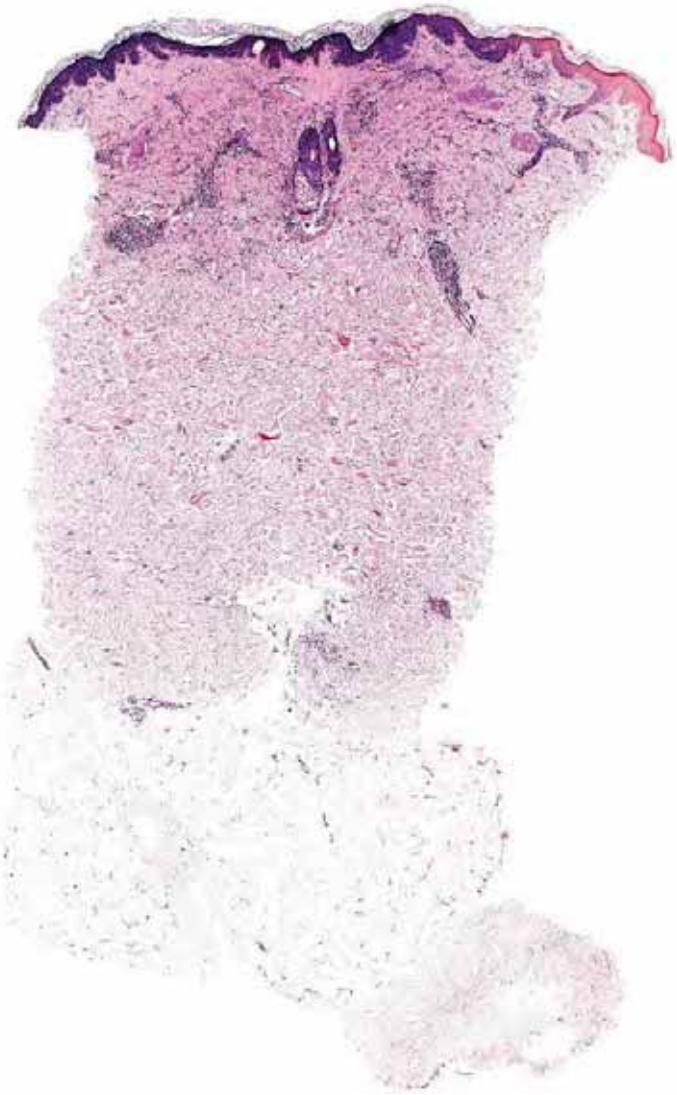


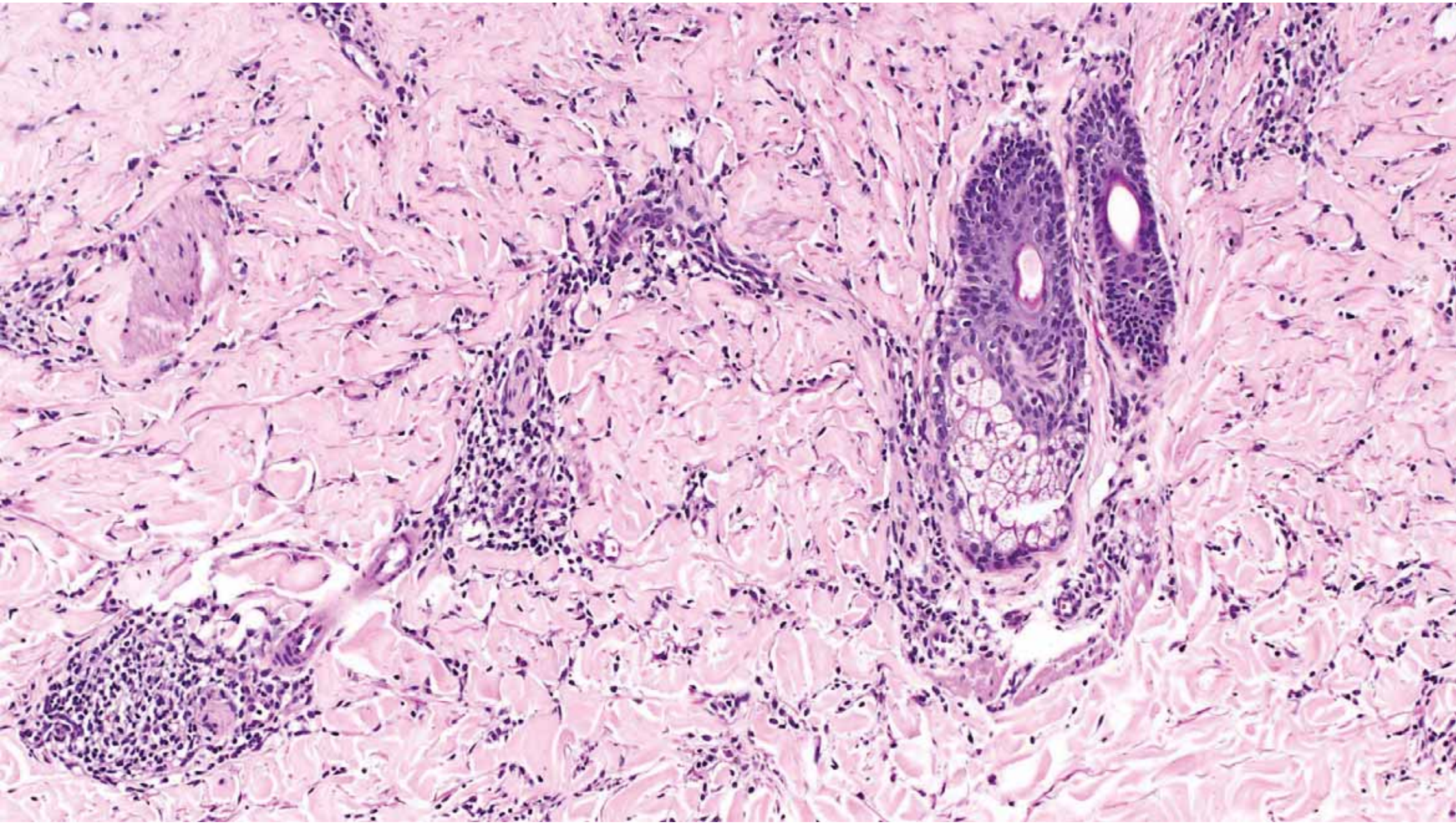
Erysipelas & leukocytoclastic vasculitis

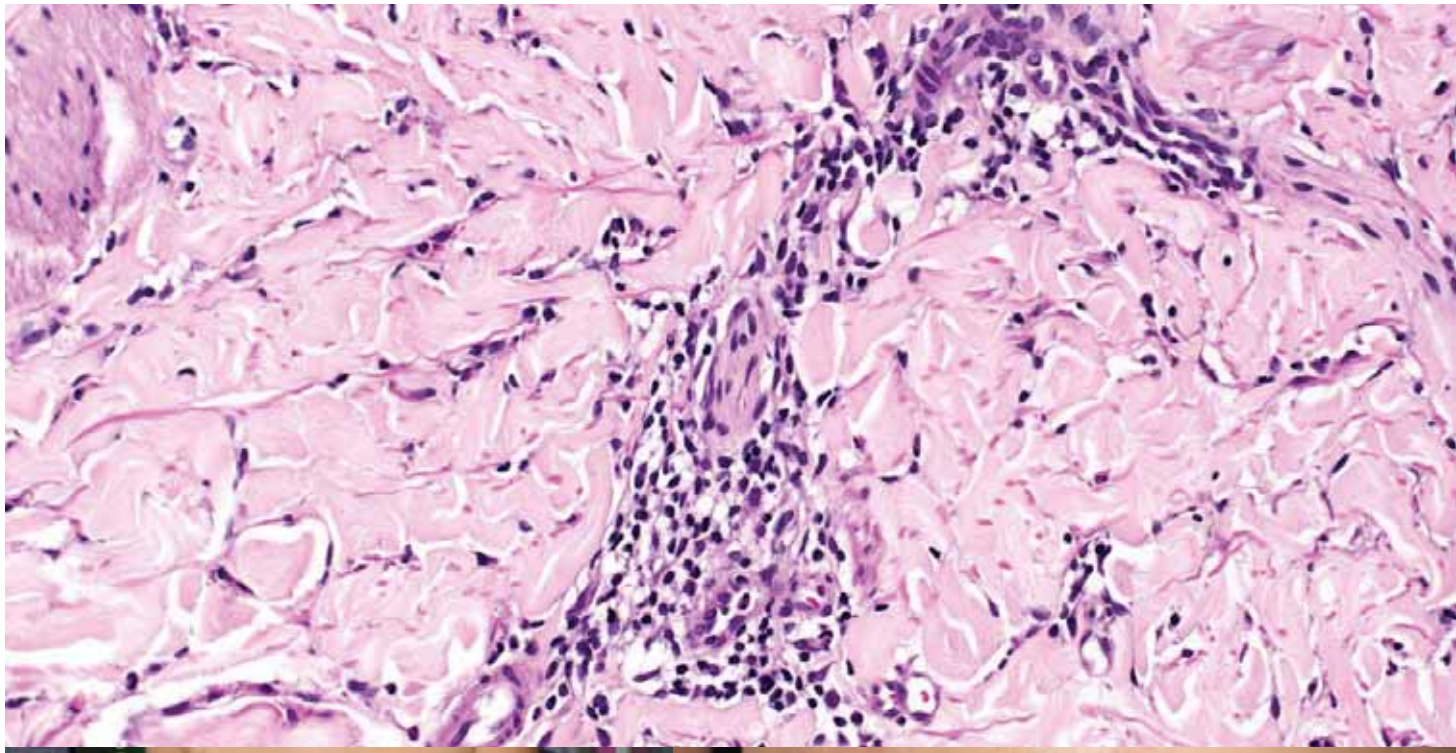


Case 27

F, 6. According to the parents progressively enlarging skin lesions for approximately 8 months.







Morphea (segmental)

1st presentation (age 6)

Age 7

Age 9

Age 16

Age 20

Managed over the years with systemic steroids, mycophenolate mofetil, UVA-1, ceftriaxone i.v., cyclosporin A, methotrexate.

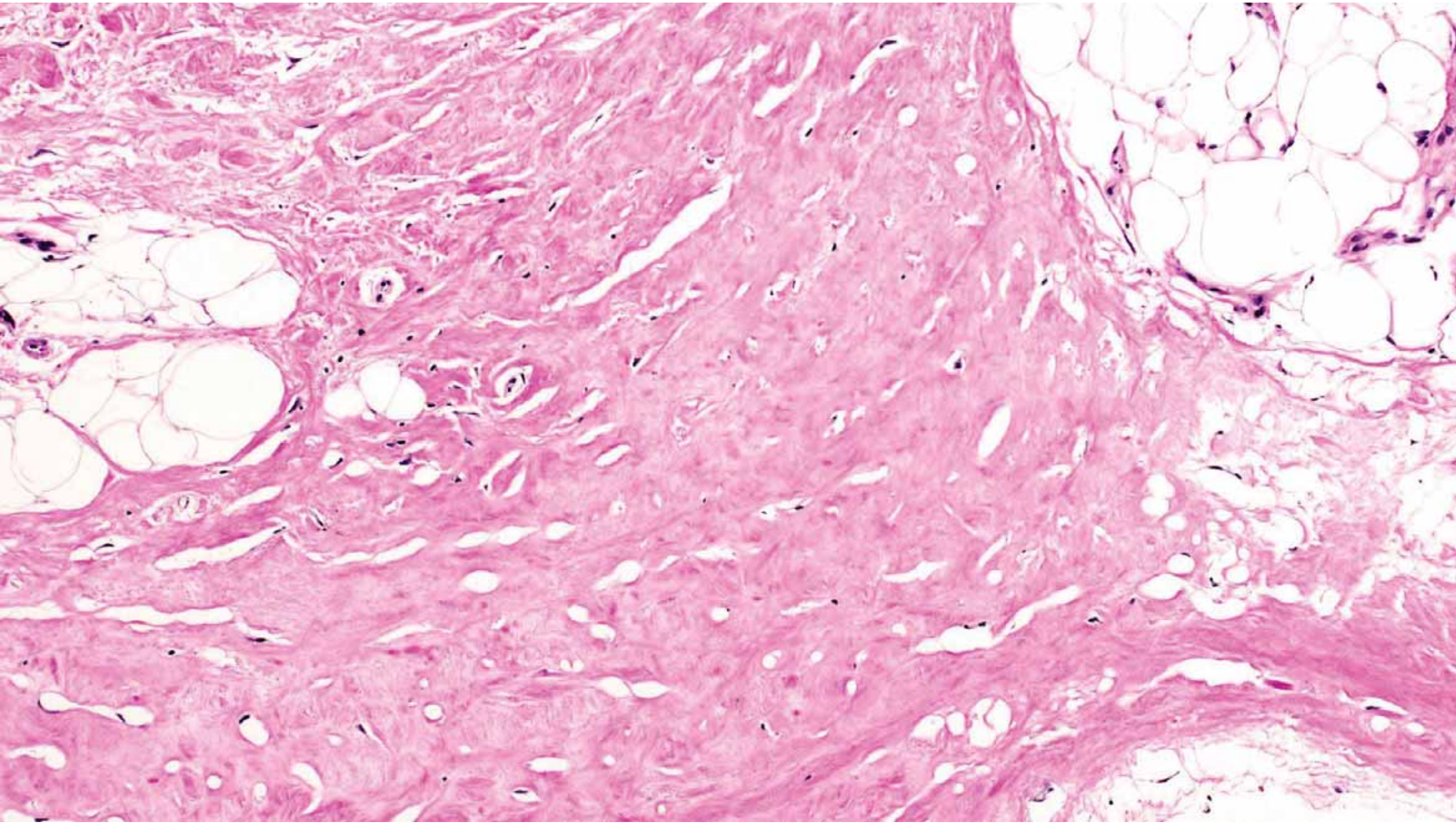
Case 28

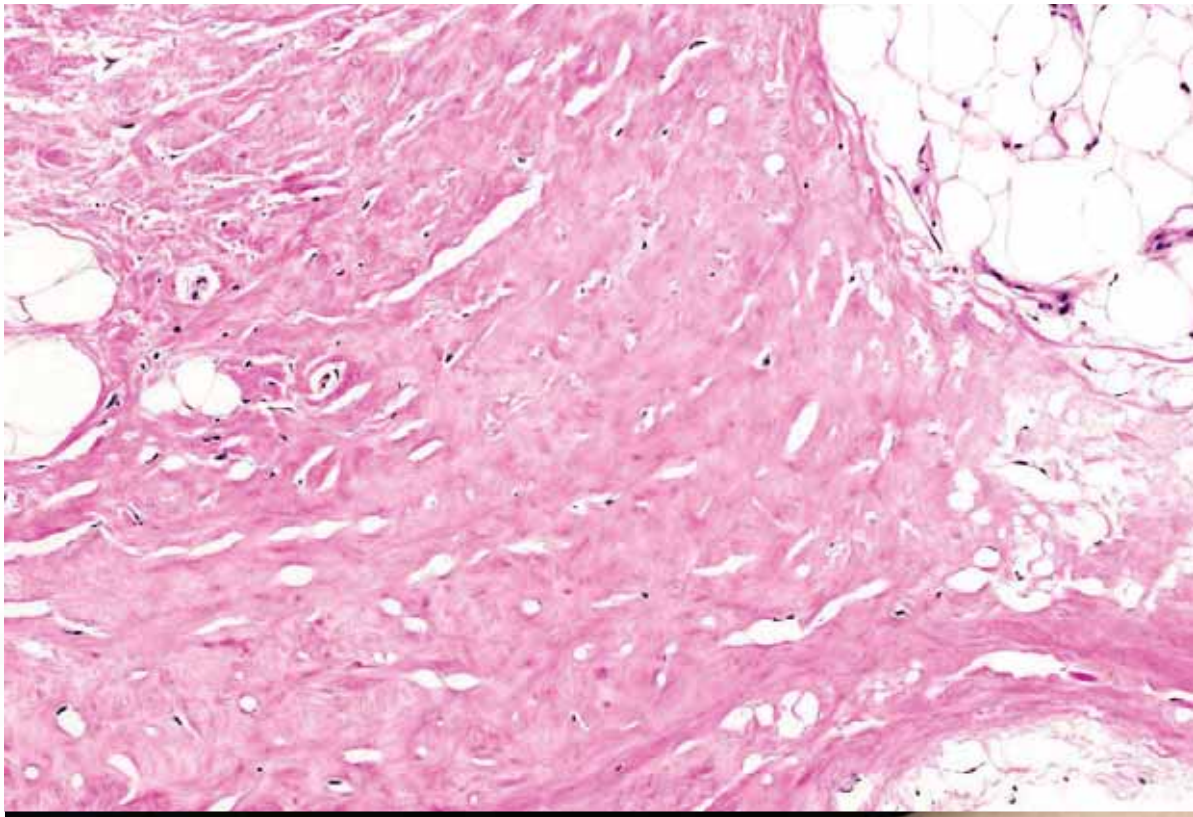
M, 77

History of melanoma of the left upper arm 4 years before presentation (managed with surgical excision and local radiotherapy).

Erythematous, partly erosive lesions on the irradiated area.

A biopsy is taken under the suspect clinical diagnosis of angiosarcoma.





Chronic radiation dermatitis

(post-radiation morphea?)

Previous melanoma

Chronic radiation dermatitis

Latency: >90 days after irradiation (up to several years)
Poikilodermatic, sclerotic lesions

Post-radiation angiosarcoma

Latency: 2 - >50 yrs. (median: ~7 yrs.)
Hemorrhagic, non-indurated lesions

Postirradiation Morphea: A Case Report With a Review of the Literature and Summary of the Clinicopathologic Differential Diagnosis

Pamela A. Morganroth, MS, BS, Danielle DeHoratius, MD,† Heather Curry, MD,‡ and Rosalie Elenitsas, MD*†*

Abstract: Postirradiation morphea is a rare complication of radiation therapy which often presents as an erythematous indurated plaque and may be mistaken for recurrent or metastatic carcinoma. Histologic examination is essential for distinguishing postirradiation morphea from malignant processes and from other types of radiation dermatitis and infectious cellulitis. We report a case of postirradiation morphea and review the postirradiation morphea literature. In addition, we summarize the clinical and histopathologic characteristics of the various forms of postirradiation skin disease, including postirradiation morphea: acute, subacute, and chronic radiation dermatitis; and radiation recall dermatitis.

Key Words: postirradiation morphea, radiation dermatitis, radiation-induced morphea, breast sclerodermia, morphea, breast cancer

(*Am J Dermatopathol* 2010;0:000–000)

INTRODUCTION

When a patient with a history of breast cancer presents with new onset erythema and induration of the breast, the clinical differential diagnosis includes cancer recurrence, metastasis, and a new primary carcinoma. However, if the patient received radiation therapy as part of her cancer treatment, postirradiation morphea, a rare but well-documented complication of radiation therapy, should also be considered. Morphea, also known as localized scleroderma, classically begins with an erythematous skin lesion which becomes progressively indurated and may be clinically indistinguishable from cutaneous manifestations of malignancy. Histologically, however, morphea is characterized by a distinct sequential pattern of inflammation followed by dermal and subcutaneous collagen sclerosis. The histology can be distinguished not only from malignancy but also from other entities in the differential diagnosis, including acute and chronic radiation dermatitis, radiation recall dermatitis, and cellulitis.

Most reports of postirradiation morphea involve breast cancer patients, but the phenomenon has also been documented in patients who received radiation for lymphoma[1] and endocervical,[2] gastric,[3] and endometrial[4] carcinomas and in one patient who underwent fluoroscopically guided repair of an abdominal aortic aneurysm.[5] Unlike acute and chronic radiation dermatitis, postirradiation morphea does not appear to be dependent on the radiation dose, does not have a consistent temporal relationship to the radiation, and may involve locations beyond the area of irradiation. Because postirradiation morphea is not predictable based on the patient's radiation history and has a nonspecific clinical presentation, histologic examination is crucial for establishing the diagnosis and excluding the more worrisome malignant possibilities.

We report a case of postirradiation morphea, review the postirradiation morphea literature, and summarize the clinical and histopathologic characteristics of the various dermatologic complications of radiation therapy. The purpose of this report and literature review is to describe the distinguishing characteristics of postirradiation morphea and to bring this rare radiation complication to the attention of dermatologists and dermatopathologists alike so that it will not be missed in the clinical or histopathologic differential diagnosis.

CASE REPORT

In January 2003, a 45-year-old woman had a left lumpectomy for a 3.5-cm raised infiltrating ductal and infiltrating lobular carcinoma in the upper outer quadrant of the left breast. Axillary lymph node resection showed metastases in 20 of 23 nodes, and a staging work-up revealed no systemic metastatic disease. The tumor was estrogen and progesterone receptor positive and HER2 negative with a normal DNA index. The carcinoma was staged as T2N2M0, and the patient received adjuvant chemotherapy (doxorubicin and cyclophosphamide then paclitaxel) followed by radiation therapy. Over a period of 52 days, standard tangential beam irradiation was delivered to the left breast using 6 MeV (70% of dose) and 23 MeV (30% of dose) photons at a dose of 46.8 Gy in 26 fractions. The tumor bed in the left breast was boosted an additional 20 Gy in 10 fractions (using 16 MeV electrons prescribed to the 90% isodose line). Irradiation was delivered using a right anterior oblique field to the left supraclavicular fossa at a dose of 45 Gy in 25 fractions (using 6 MeV photons prescribed to a depth of 3 cm). The left axilla was also

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TABLE 2. Clinical and Histopathologic Characteristics of Postirradiation Skin Disease

	Histopathology	Clinical	Time Course
Postirradiation morphea	Early inflammatory stage: interstitial and perivascular lymphoplasmacytic infiltrate, slight collagen thickening	Early: erythematous or violaceous patches or mildly edematous plaques	Weeks to decades after conclusion of radiation course
	Intermediate stage: inflammatory infiltrate in subcutaneous fat and around eccrine coils, thickened collagen bundles	Late: lesions become indurated	
	Late sclerotic stage: thick, swollen, hypocellular collagen bundles in reticular dermis, sparse inflammation, replacement of subcutaneous fat by sclerotic collagen	Lesions may have a "peau d'orange" appearance and can be painful	
Acute radiation dermatitis	Epidermis: scattered apoptotic keratinocytes, edema	Erythema, edema, alopecia, and hyperpigmentation	Generally occurs weeks after radiation treatment
	Dermis: dermal and endothelial cell edema, vasodilation, erythrocyte extravasation, fibrin thrombi	Vesiculation, ulceration, and erosion may occur with overdose	
Chronic radiation dermatitis	Epidermis: atrophy, hyperkeratosis, features of interface dermatitis	Poikilodema (atrophy, telangiectasias, hypopigmentation and/or hyperpigmentation)	Generally occurs months to years after radiation treatment
	Dermis: collagen sclerosis, scattered large atypical radiation fibroblasts, fibrous thickening of deep vessels, superficial telangiectasias	May occur with or without history of acute radiation dermatitis	May be evident earlier if representative of progression from acute radiation dermatitis
	Absence of skin appendages		
Subacute radiation dermatitis	Epidermis: interface dermatitis with satellite cell necrosis, epidermal inflammatory infiltrate	Overlapping features of acute and chronic dermatitis	Generally occurs weeks to months after radiation treatment
	Dermis: papillary dermal and perivascular inflammatory infiltrate, no collagen sclerosis or atypical fibroblasts		
	Mimics acute cutaneous graft-versus-host disease		
Radiation recall dermatitis	Nonspecific and not well documented	Pruritic maculopapular erythematous rash, blistering, desquamation	Days to years after radiation therapy
	Overlaps with acute radiation dermatitis	Occurs at the site of previous radiation after taking a medication (classically chemotherapeutic agents)	
	Fibrosis and radiation fibroblasts may also be present		

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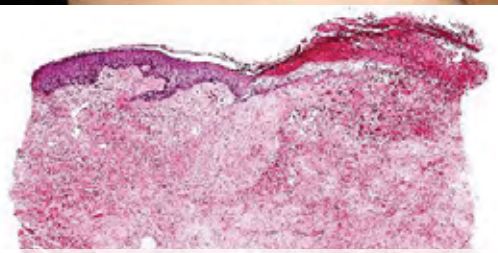
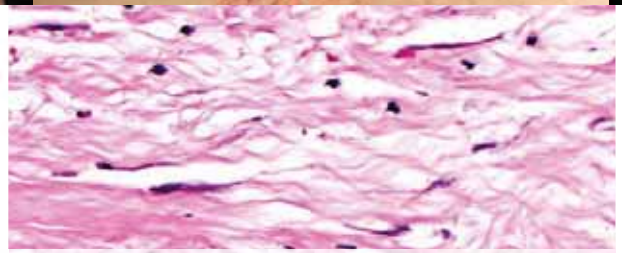
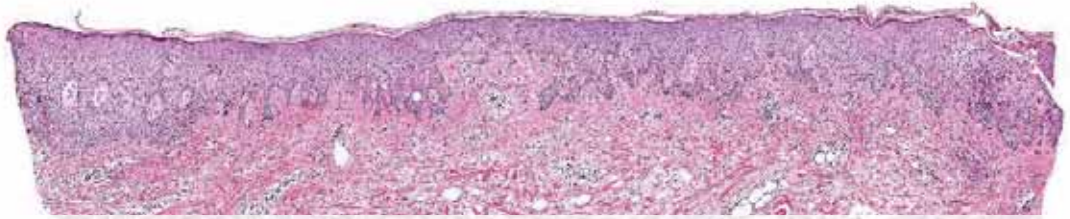
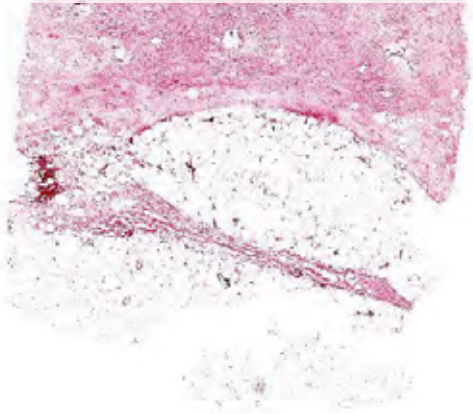
Online ahead of print.

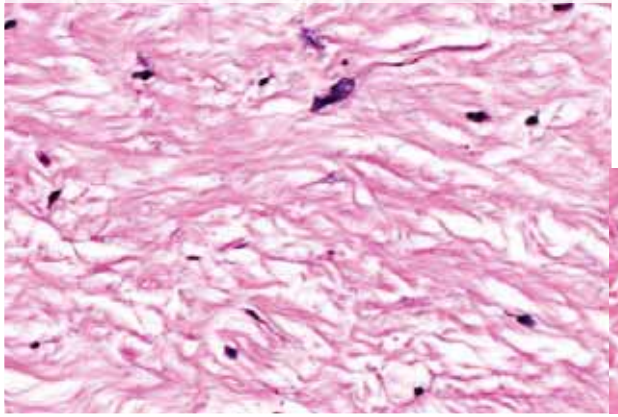


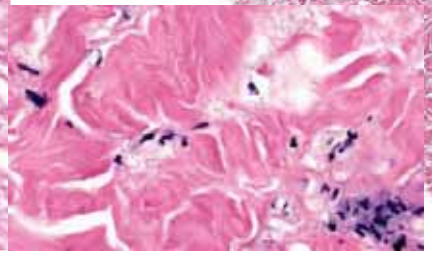


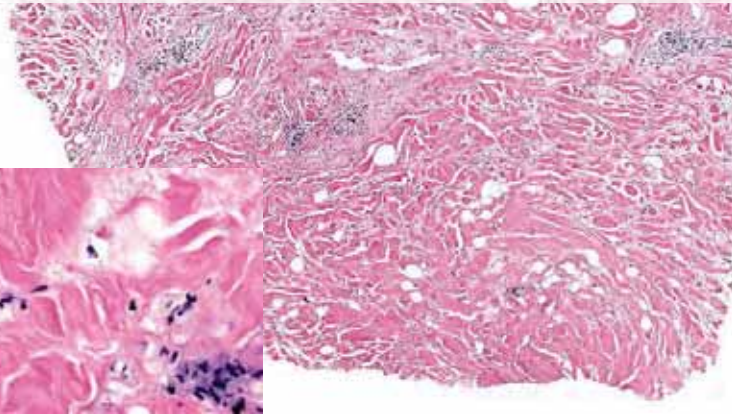


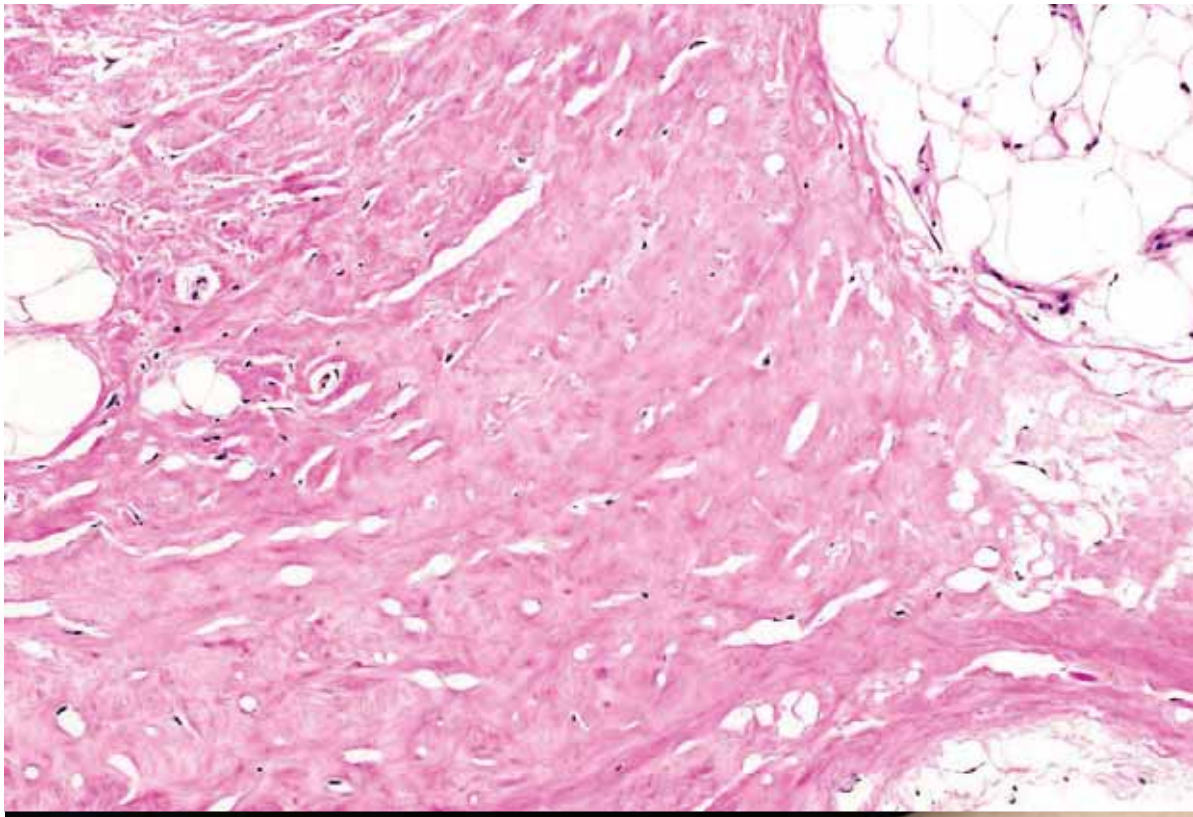
Can late stages of chronic radiation dermatitis be distinguished histopathologically from late stages of post-radiation morphea?









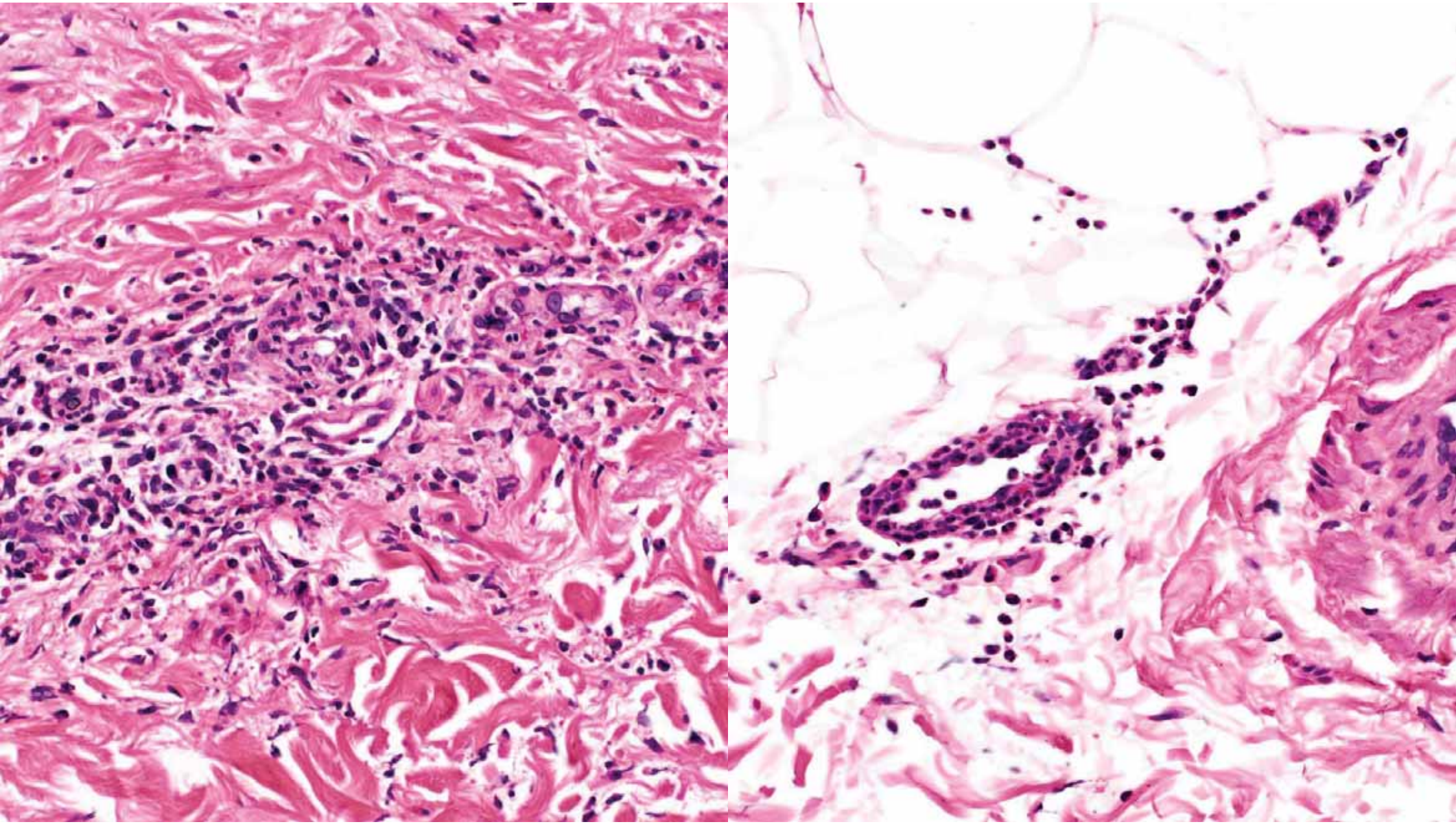


Chronic radiation dermatitis

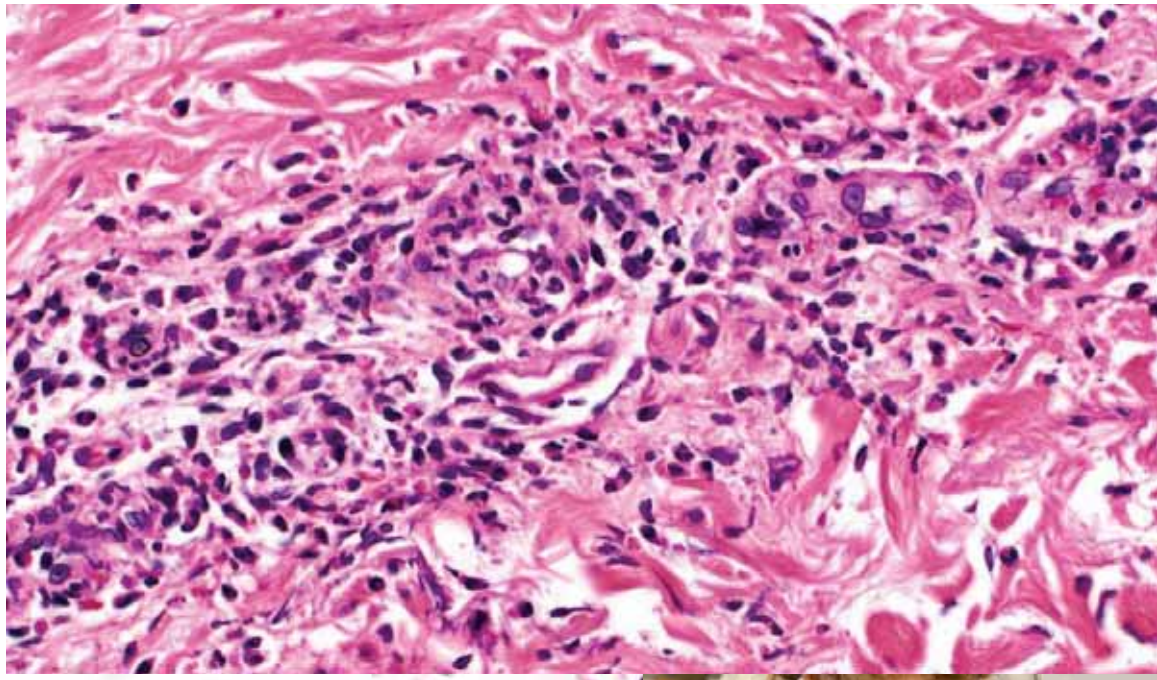
Case 29

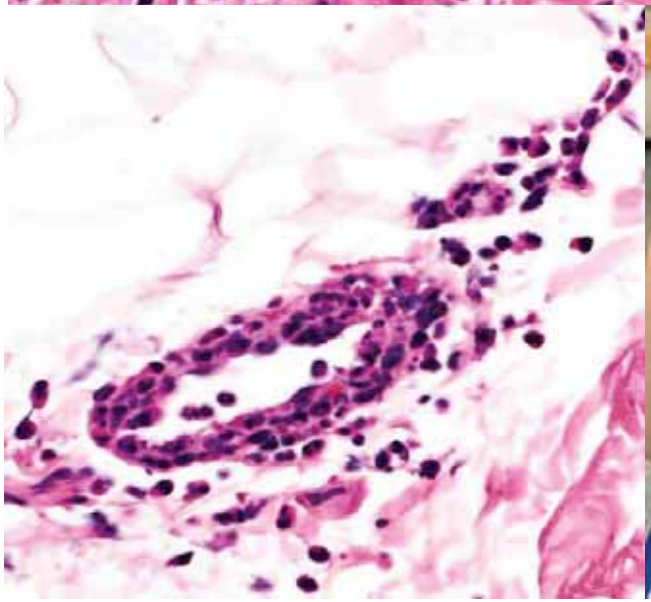
F, 23. According to the patient itchy skin lesions for 5 days.

A biopsy is taken under the clinical diagnosis of multilocular erythema migrans.



Urticaria





1st presentation
2 days later

Actas Dermosifiliogr. 2012;103(6):511-519

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ORIGINAL ARTICLE

Neutrophilic Urticaria or Urticaria With Predominantly Neutrophilic Inflammatory Infiltrate: Study of Its Clinical and Histopathologic Characteristics and Its Possible Association With Rheumatic Disease☆

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KEYWORDS
Urticaria;
Neutrophilic urticaria;
Urticaria-vasculitis;
Immune disease

ABSTRACT

Introduction: Neutrophilic urticaria, described by Winkelmann in 1985, has yet to be completely defined and its clinical significance is poorly understood. Nevertheless, recent publications suggest that it could be a marker for rheumatic disease. The primary objective of this study was to compare the prevalence of rheumatic disease in 2 groups of patients with urticaria: those with conventional urticaria (non-neutrophilic inflammatory infiltrate) and those with neutrophilic urticaria.

Material and methods: We retrospectively reviewed all biopsy samples taken from urticarial lesions in our hospital between January 1, 1999 and June 28, 2009. Urticaria was classified according to predefined morphologic and histopathologic patterns. We compared the clinical and histologic characteristics of neutrophilic urticaria with those of conventional urticarias in the 84 patients included.

Results: Of the 84 patients, 57.1% had neutrophilic urticaria. We did not find significant differences between the percentages of patients with rheumatic disease between the neutrophilic and nonneutrophilic urticaria groups. In patients with acute urticaria, we found a significantly higher proportion of samples with histopathologic signs of neutrophilic urticaria as opposed to conventional histopathology. Patients with neutrophilic urticaria also had higher white blood cell counts.

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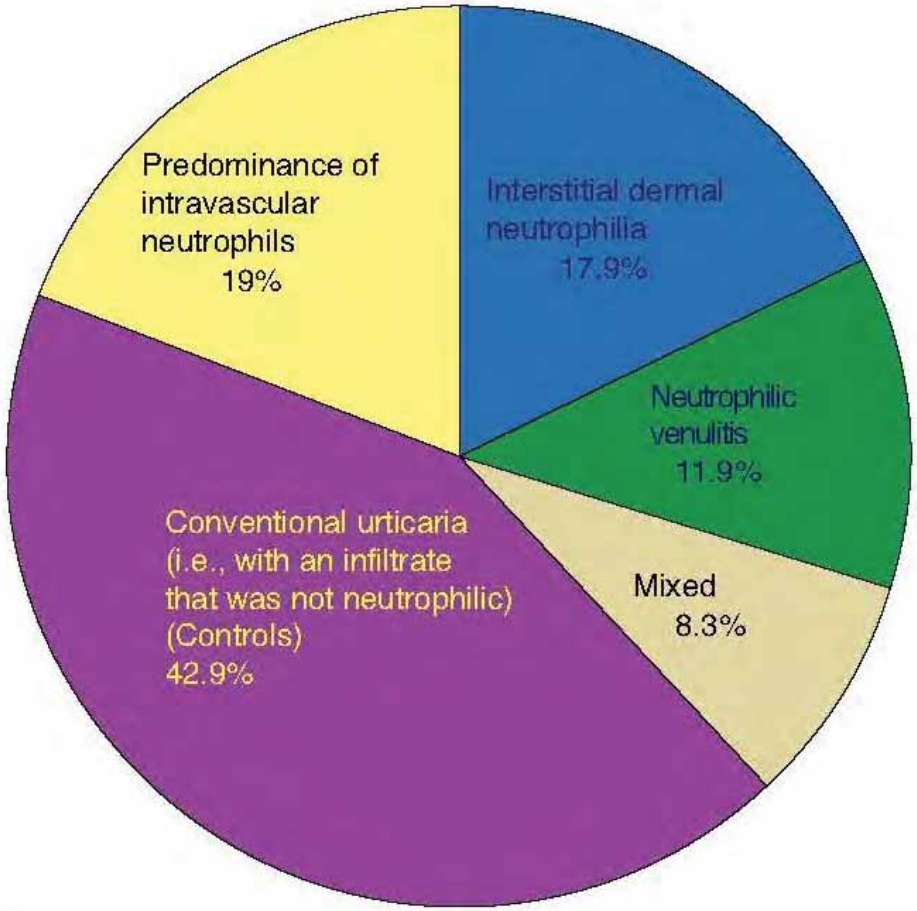
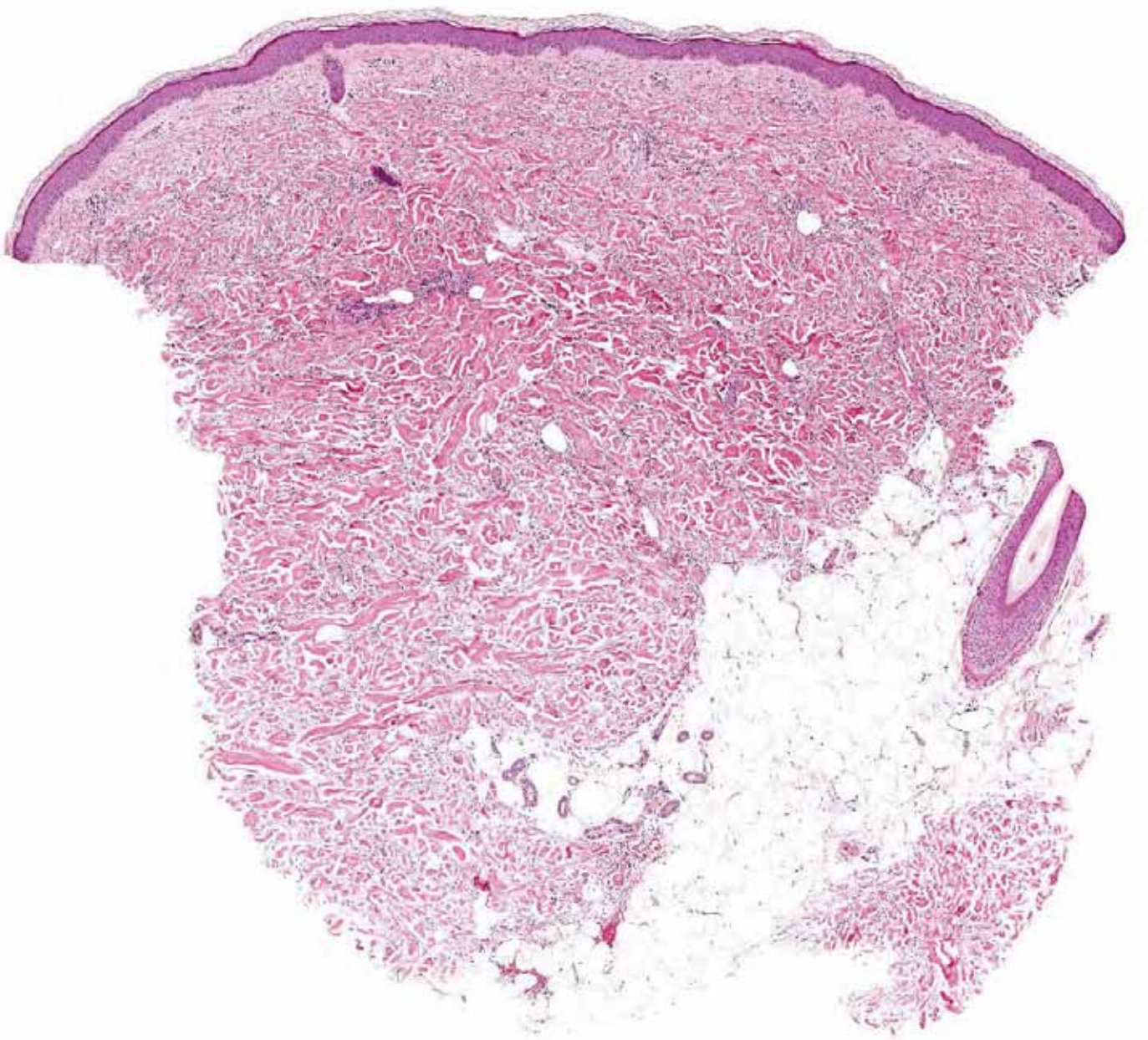
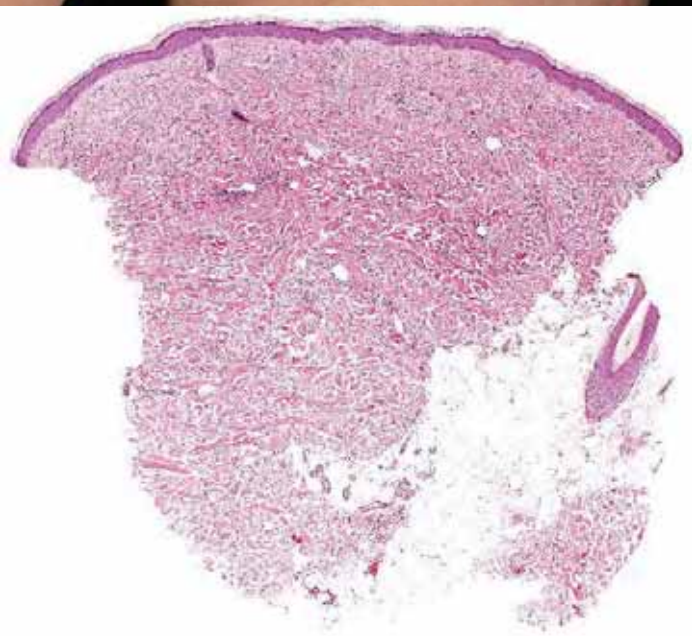


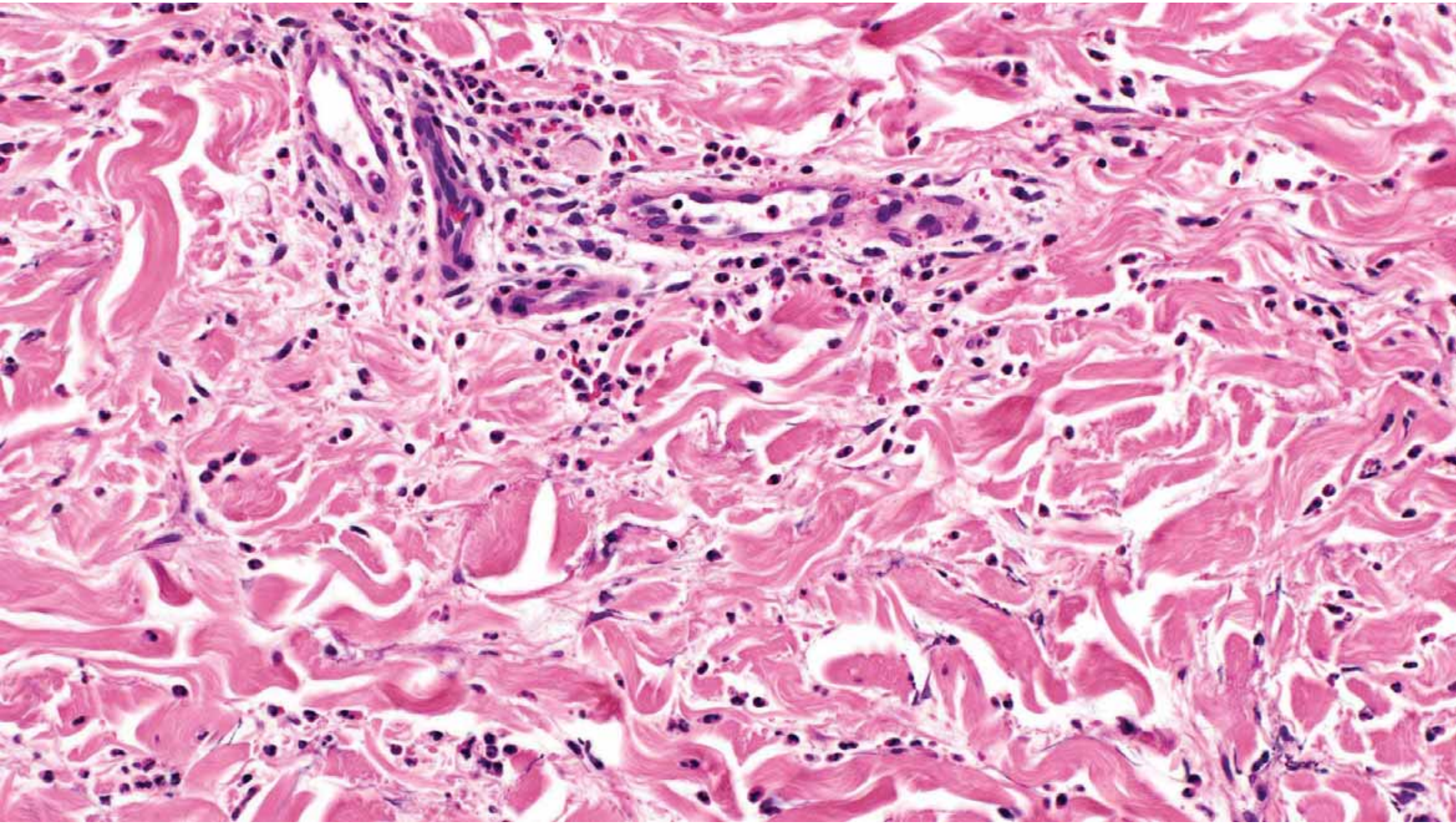
Figure 6 Distribution of the 84 cases by histopathologic subtypes.

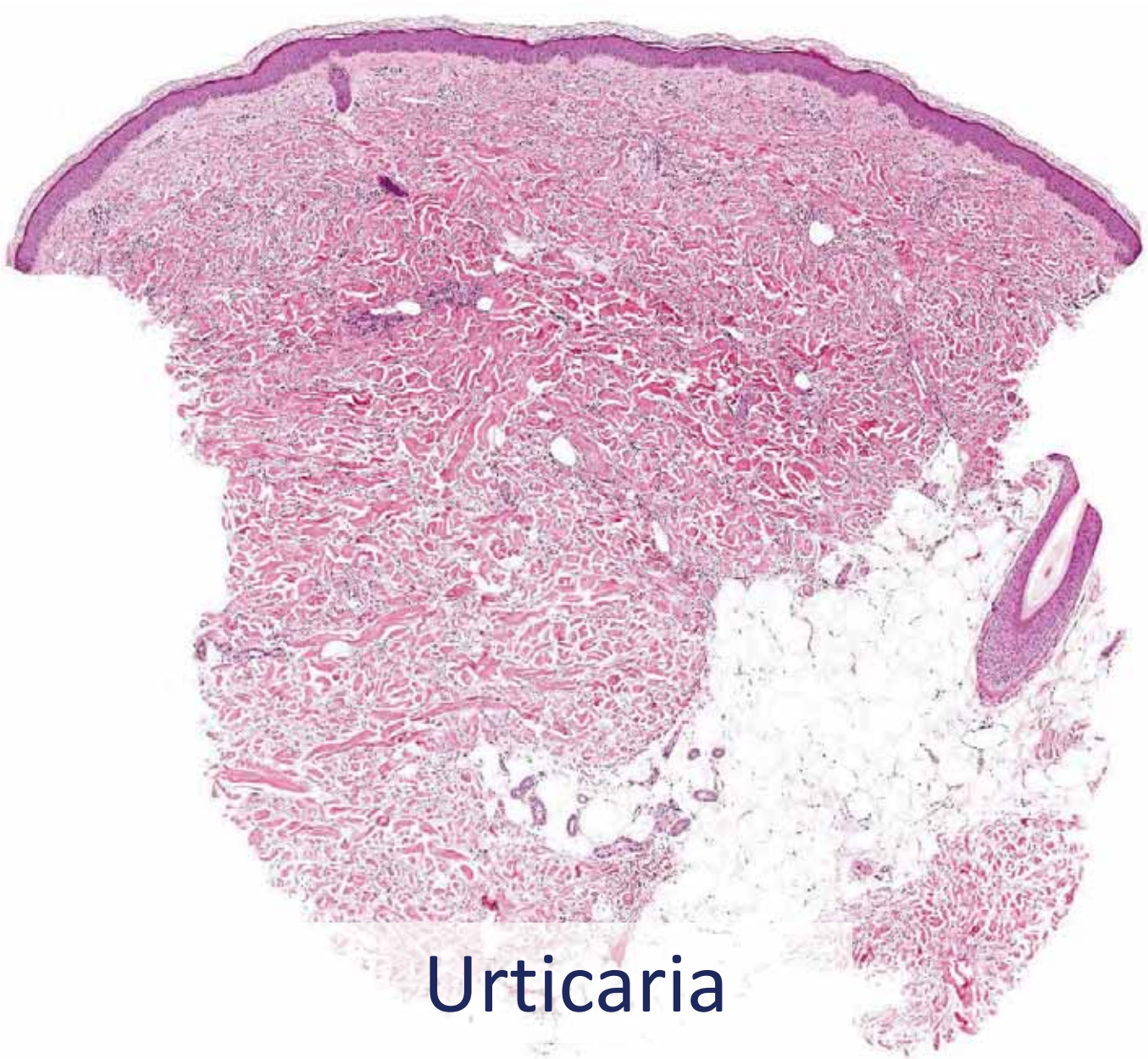


Case 30

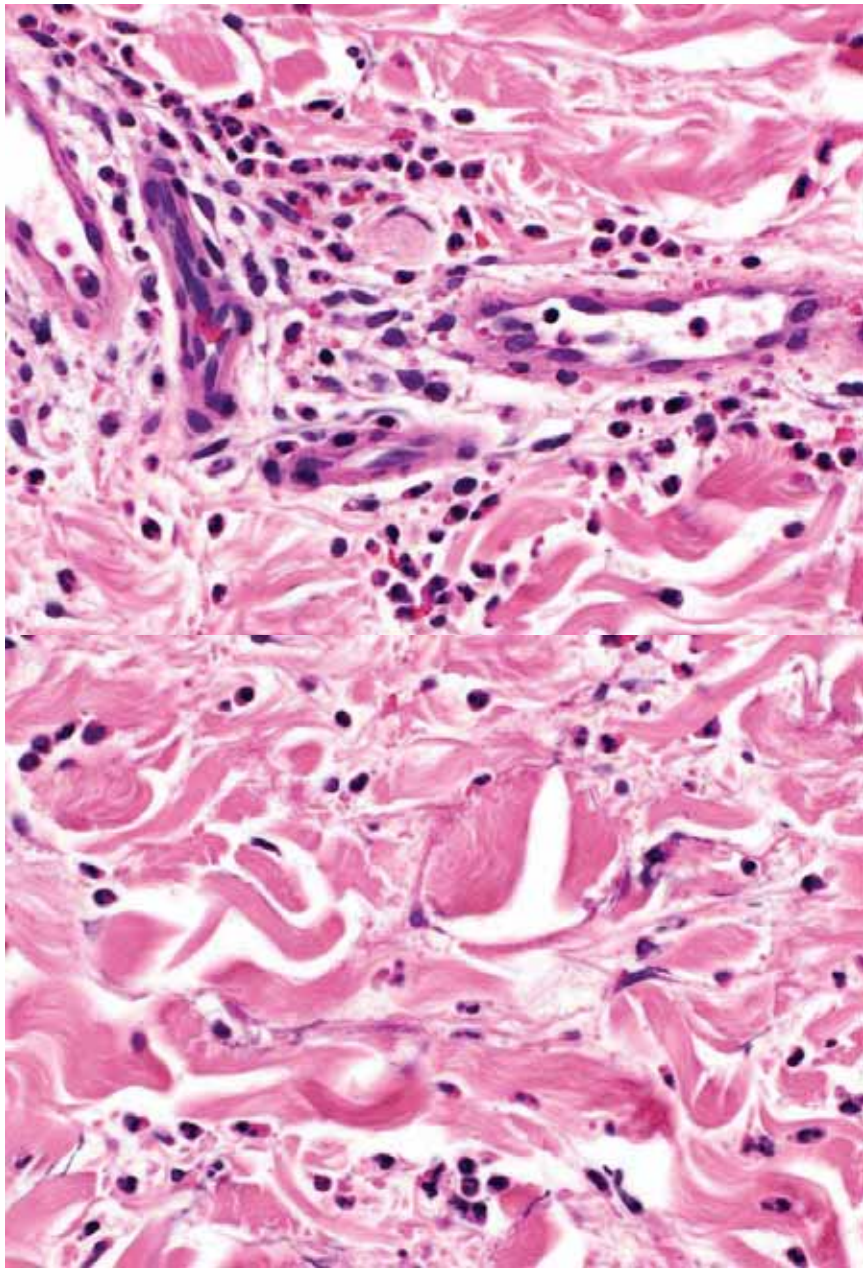
F, 29. Overnight onset of itchy skin lesions. A few days before gastrointestinal pain; no diarrhea, no fever. Several drugs taken during the last days because of the gastrointestinal symptoms (butylscopolamine, dexibuprofen, metamizole, paracetamol, sucralfat, pantoprazole).







Urticaria

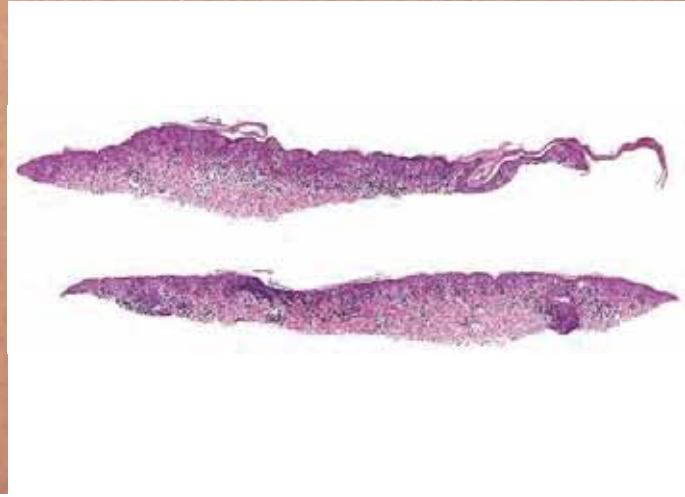


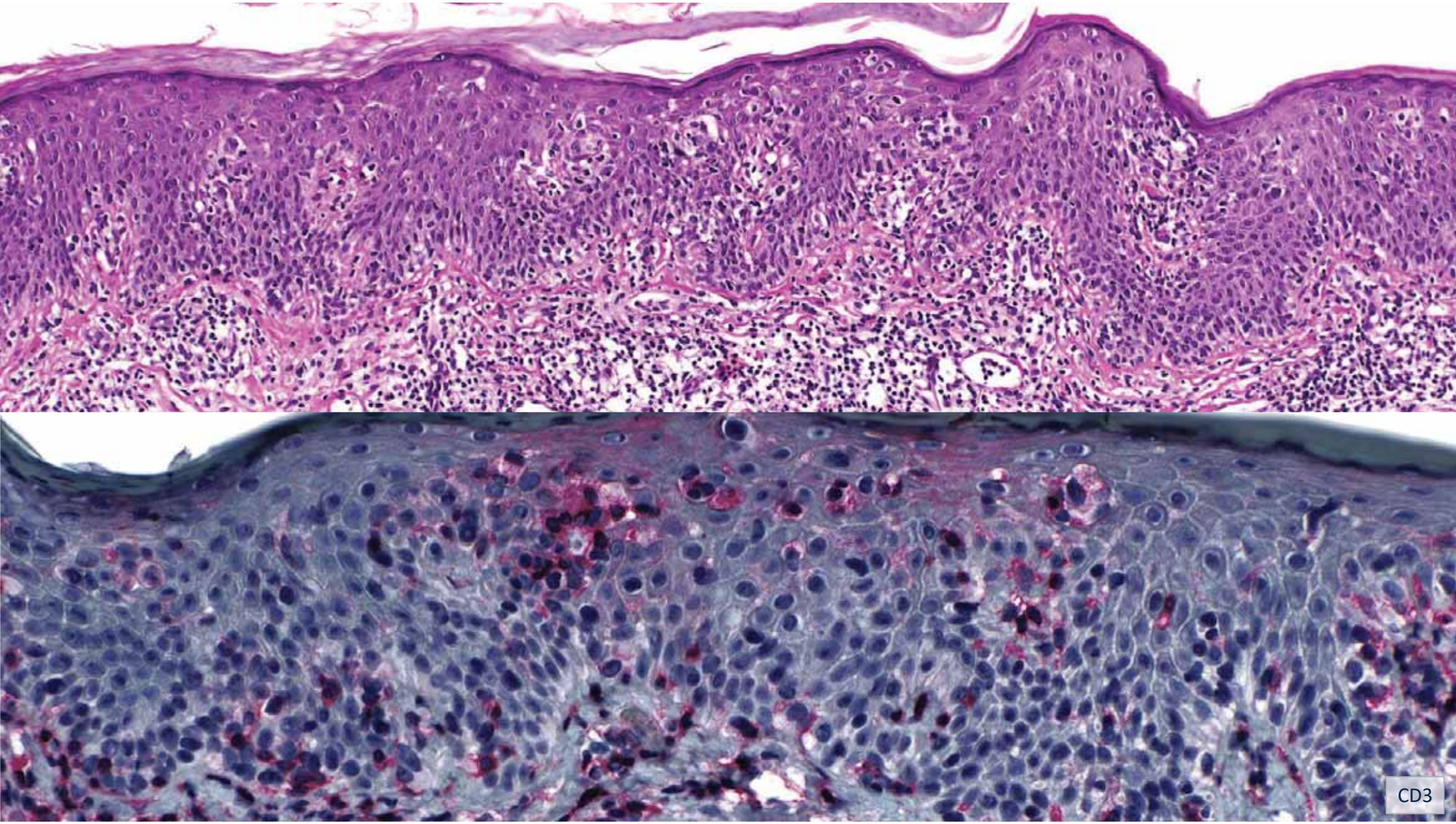
Urticaria

- A cutaneous reaction pattern and not a specific disease
- Acute (usually never biopsied), chronic (persisting >6 weeks) (may be biopsied)
- Related to different triggers (e.g., infections, drugs); in many cases "idiopathic"
- "Urticarial" dermatoses may be observed in many contexts including among others autoinflammatory syndromes, rheumatological disorders, autoimmune diseases
- Histopathological features often referred to as "invisible dermatosis"; slight edema, sparse perivascular infiltrates of lymphocytes admixed with some eosinophils; in my experience variable numbers of neutrophils not uncommon
- "Neutrophilic urticaria" usually refers to cases with moderately dense infiltrates with prominent neutrophils but without signs of vasculitis
- "Urticaria vasculitis" usually refers to cases with urticarial lesions clinically, which histopathologically show signs of vasculitis

Case 31

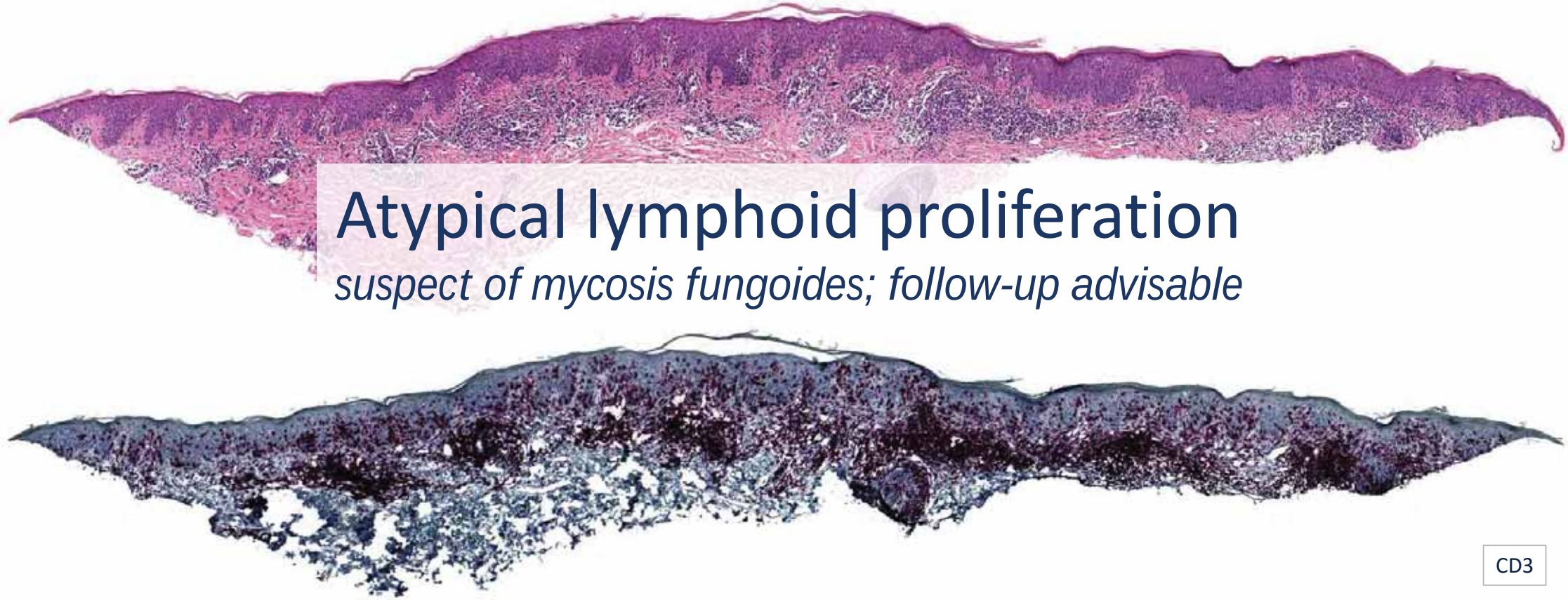
F, 54. According to the patient solitary, asymptomatic lesion on the left buttock for approximately 1 year. A recent biopsy was interpreted as "psoriasiform-lichenoid dermatitis, suspicious for mycosis fungoides". The biopsy is re-evaluated.



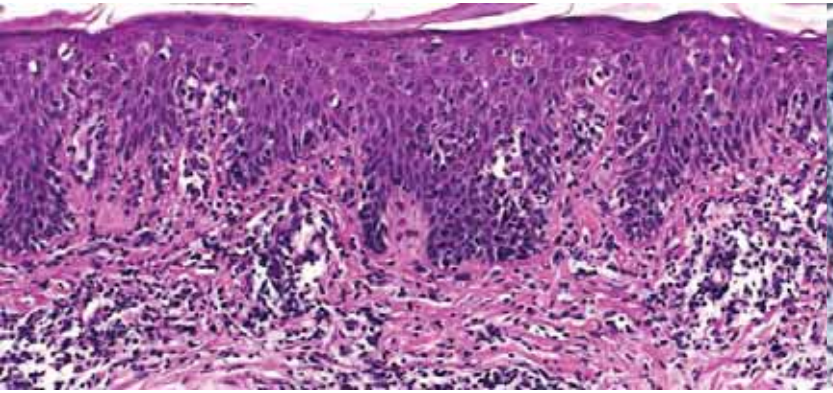

CD3

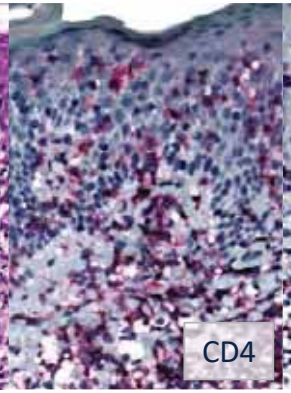
Atypical lymphoid proliferation

suspect of mycosis fungoides; follow-up advisable

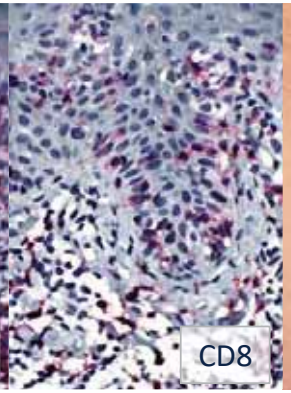


CD3

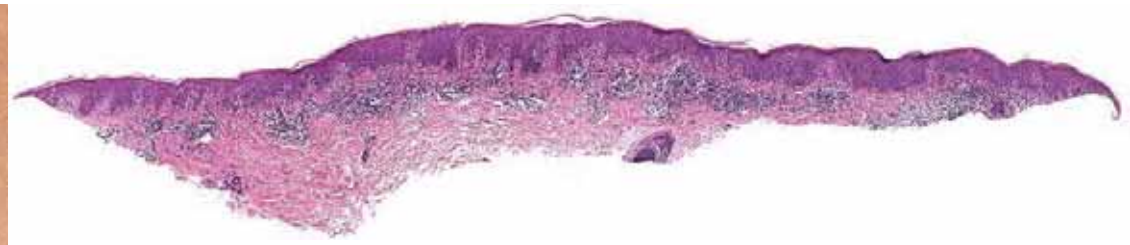


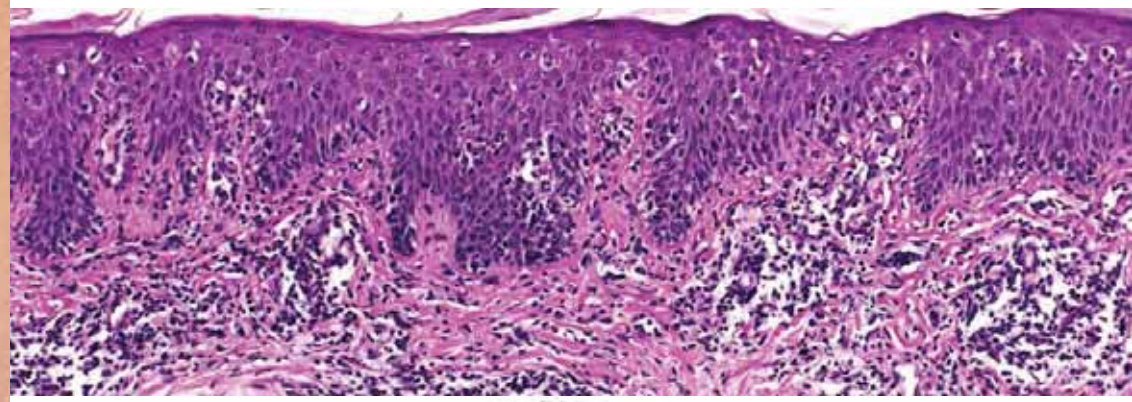


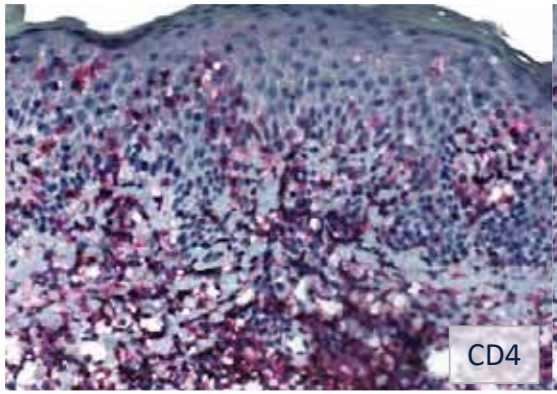
CD4

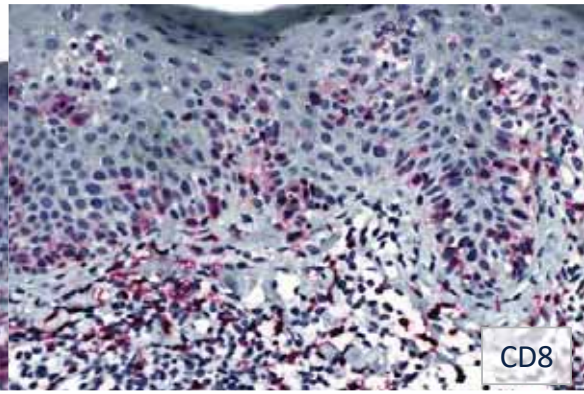


CD8







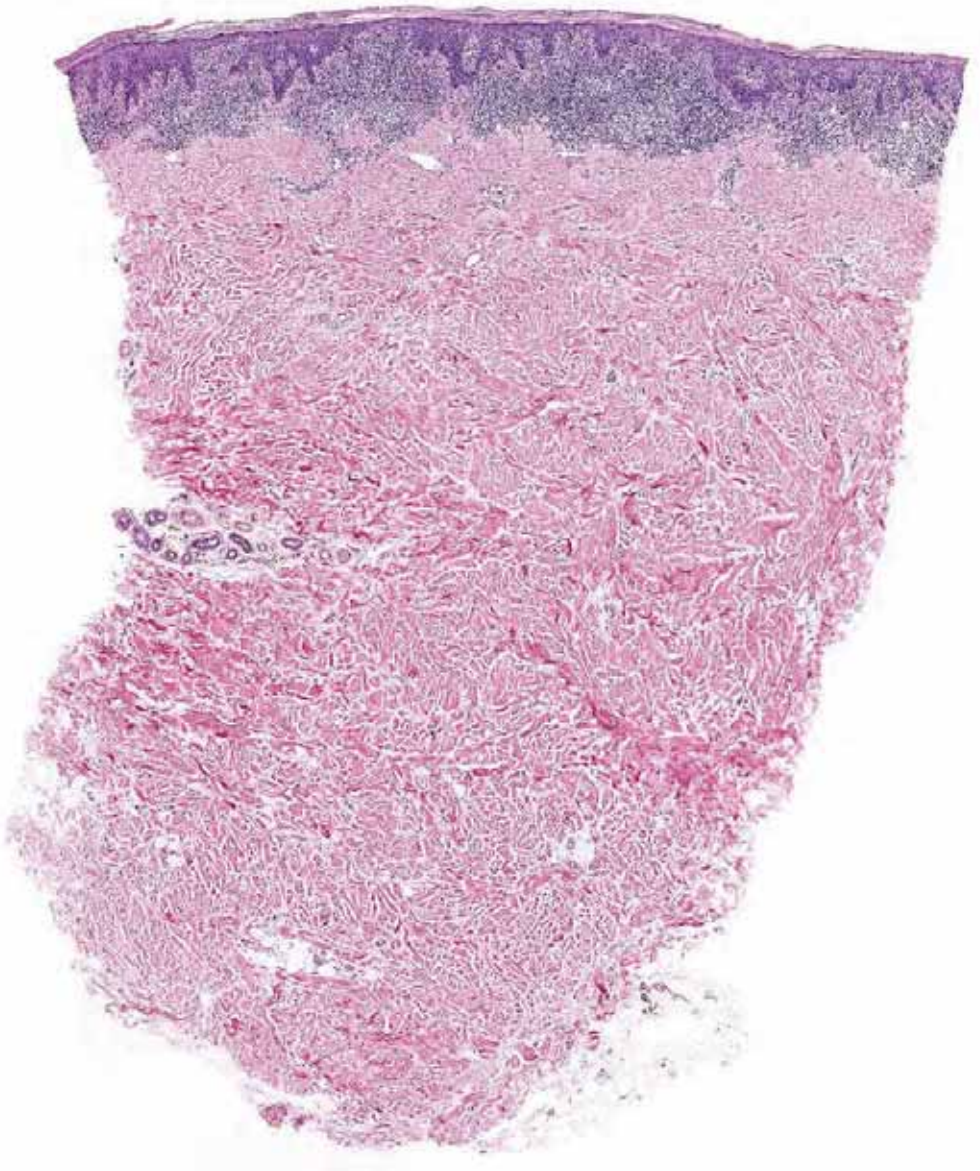


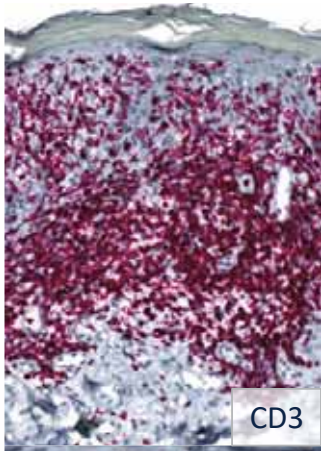
Features supporting a diagnosis of psoriasis
Scaly erythematous plaque; epidermal hyperplasia.
Features militating against a diagnosis of psoriasis
Solitary lesion; band-like lymphoid infiltrate with prominent epidermotropism.

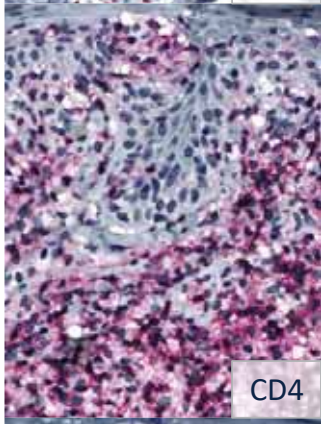
Features supporting a diagnosis of mycosis fungoides
Prominent epidermotropism; dense band-like lymphoid infiltrate.
Features militating against a diagnosis of mycosis fungoides
Solitary lesion; mixture of CD4+ and CD8+ intraepidermal lymphocytes.

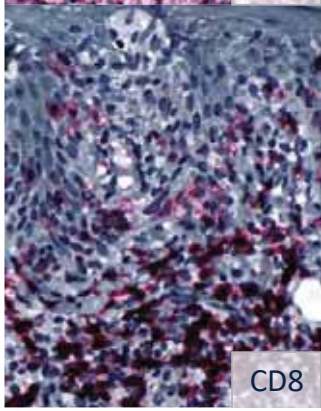
Features militating against a diagnosis of eczematous dermatitis
Solitary, sharply circumscribed lesion; absence of spongiosis.

15 months later *(local steroids only);* new biopsy

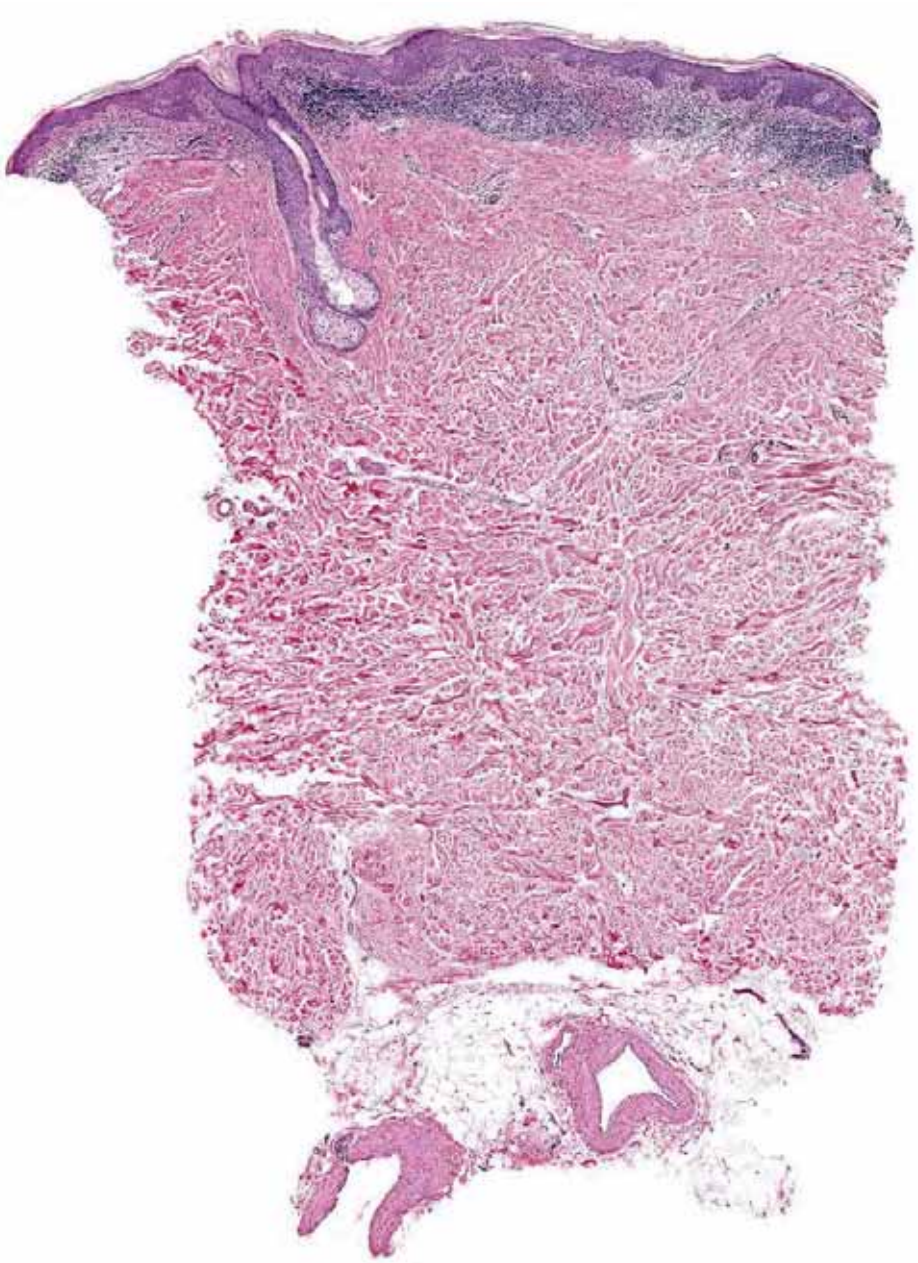


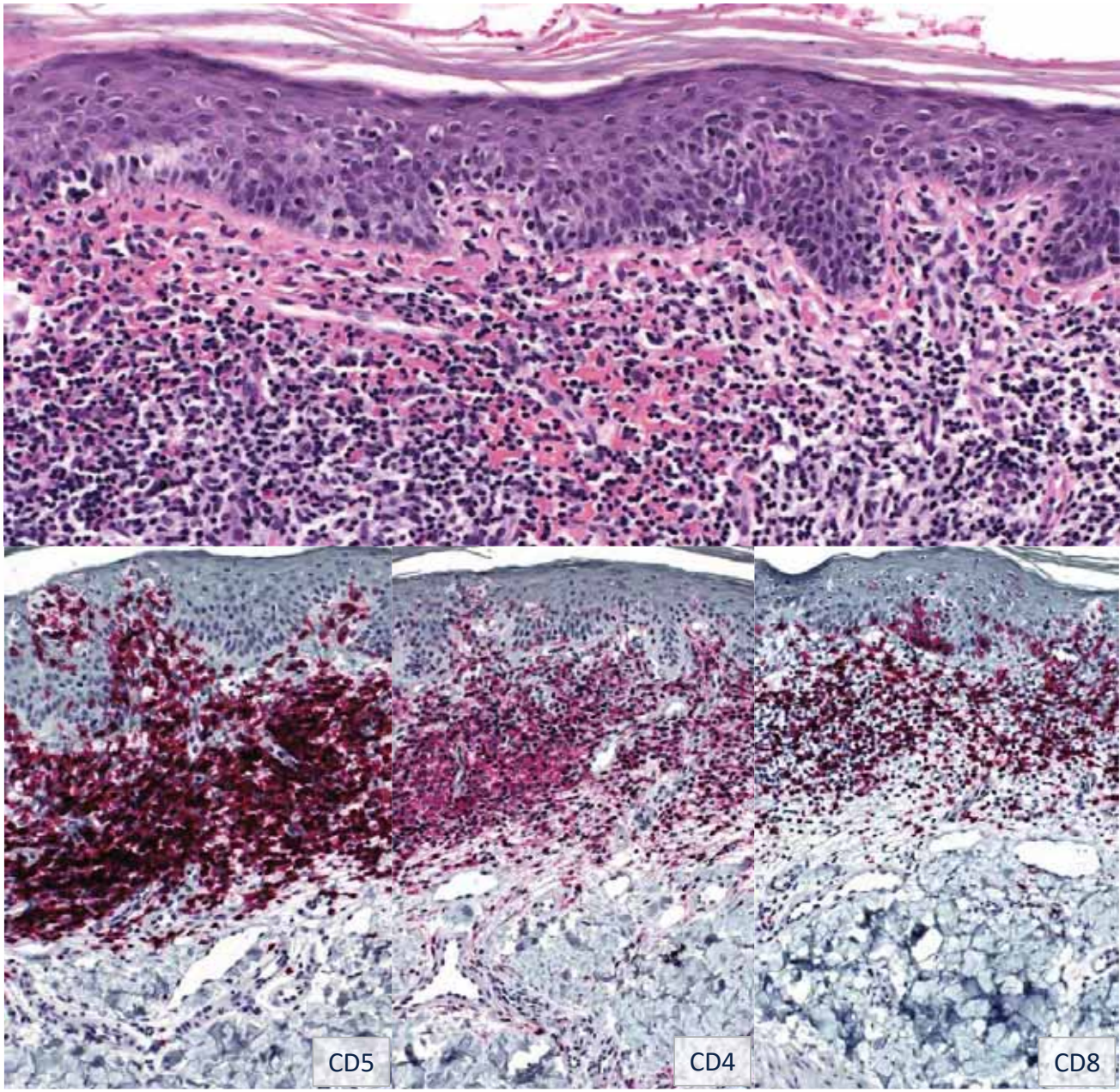




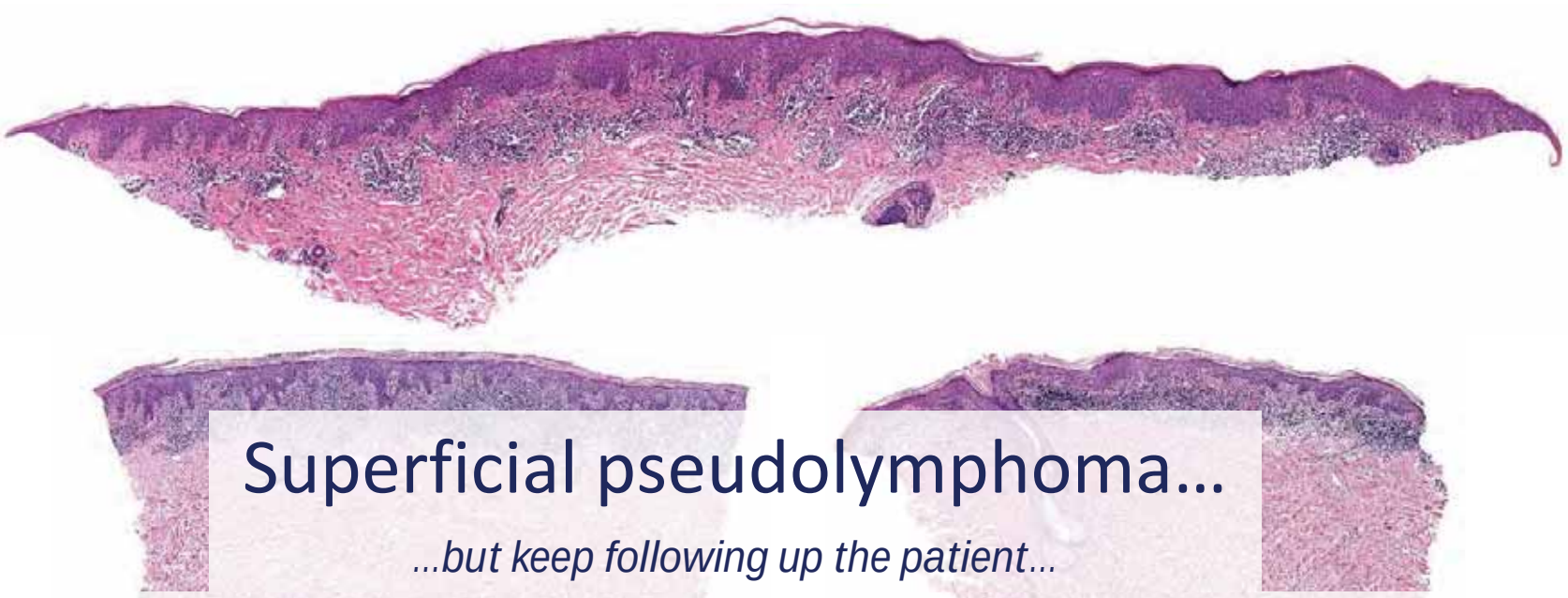


Further 15 months later; new biopsy




CD5
CD4
CD8

1st presentation
2,5 years later



Superficial pseudolymphoma…

…but keep following up the patient…

Features supporting a diagnosis of psoriasis
Scaly erythematous plaque; epidermal hyperplasia.

Features militating against a diagnosis of psoriasis
Solitary lesion at presentation; no response to local steroids; no new lesions after 2,5 years; band-like lymphoid infiltrate with prominent epidermotropism in 3 biopsies.

Features supporting a diagnosis of mycosis fungoides
No response to local steroids; slow growth; persistent lesion over a period of 2,5 years; dense band-like lymphoid infiltrate with prominent epidermotropism in 3 biopsies.

Features militating against a diagnosis of mycosis fungoides
Solitary lesion; mixture of CD4+ and CD8+ intraepidermal lymphocytes.

Features militating against a diagnosis of eczematous dermatitis
Solitary, sharply circumscribed lesion not responding to local steroids and growing slowly over a period of 2,5 years; absence of spongiosis.

The American Journal of Dermatopathology 21(6):518-524, 1999

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Solitary Skin Lesions With Histopathologic Features of Early Mycosis Fungoides

Lorenzo Cerroni, M.D., Regina Fink-Puches, M.D., Laila El-Shabrawi-Caelen, M.D., H. Peter Soyer, M.D., Philip E. LeBoit, M.D., and Helmut Kerl, M.D.

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma that usually begins with cutaneous patches that evolve into plaques and tumors. A few recent reports describe a solitary variant of MF distinct from localized pagetoid reticulosis, a disease in which solitary verrucous lesions occur on acral skin. Solitary skin lesions with some of the histopathologic features of MF rarely occur during treatment with several drugs, especially antidepressants or antihistamines. We analyzed the clinicopathologic features of 20 patients with solitary skin lesions showing histopathologic features of patch- or early plaque-stage MF. Eight men and 12 women (mean age 50.6, range 23–82, median 49) had solitary, small erythematous patches or plaques located on the trunk (16 cases, 6 of them on the breast), upper extremities (3 cases), and inguinal region (1 case). Ten patients were treated with one or more drugs; only two of them received antidepressants or antihistamines. Histopathologic examination revealed in all cases a band-like infiltrate in the upper dermis, frequently with epidermotropism of solitary lymphocytes. Atypical lymphocytes were present in a minority of cases. Immunohistology showed a predominance of CD3+ T lymphocytes, in most cases admixed with clusters of CD20+ B-cells. Only a small proportion of the infiltrate was CD8+. Molecular analysis of the rearrangement of the T-cell receptor genes was performed in 16 cases using the polymerase chain reaction (PCR) technique and revealed a monoclonal band in 8 of them. After surgical excision, 2/14 patients had a recurrence near the surgical scar. In 18 patients with complete follow-up data, no evidence of "classic" MF could be observed after a mean follow-up of 31.9 months. Solitary skin lesions with the histopathologic features of MF can be considered as a distinct clinicopathologic entity, probably representing a solitary variant of mycosis fungoides.

Key Words: Solitary mycosis fungoides—Cutaneous T-cell lymphoma—Cutaneous T-cell pseudolymphoma—Pseudolymphomatous drug eruptions.

In the medical literature, there are only a few reports regarding patients who have solitary cutaneous patches or plaques showing the histopathologic features of mycosis fungoides. There seems to be no agreement about the classification of these lesions, for they have been variously classified as "solitary mycosis fungoides" or "cutaneous T-cell pseudolymphoma" (1–7). The histopathologic features are different from those of localized pagetoid reticulosis (Woringer-Kolopp disease), and are often indistinguishable from "classic" early mycosis fungoides (8,9). In a few of the reported cases, an association with drugs has been documented (1,2).

In this study we analyzed the clinical, histopathologic, immunohistochemical, and molecular genetic features of lesions from 20 patients who had solitary skin patches or plaques showing histopathologic features of mycosis fungoides.

PATIENTS AND METHODS

Data on 20 patients presenting clinically with solitary skin patches or plaques showing histopathologic features of mycosis fungoides were collected retrospectively from the files of the Department of Dermatology, University of Graz, Austria, and of the Dermatopathology Section, Departments of Dermatology and Pathology, University of California, San Francisco, CA, USA. Patients with solitary skin tumors were not included in this study.

Histology and Immunohistochemistry

Twenty-nine biopsies were available for histologic study. In every case one Hematoxylin and eosin (H&E) section was prepared. Immunohistology was performed on formalin-fixed, paraffin-embedded tissue sections using a three-step immunoperoxidase method as described previously (10). Antigen unmasking was obtained by microwave heating of sections before application of the

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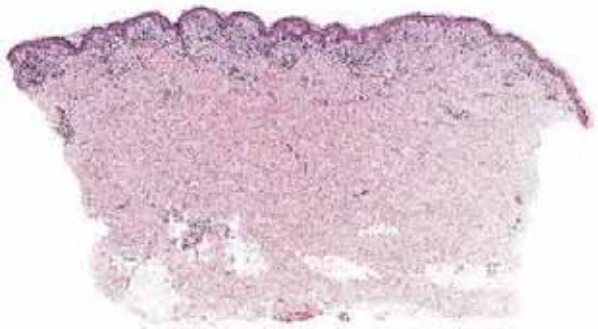
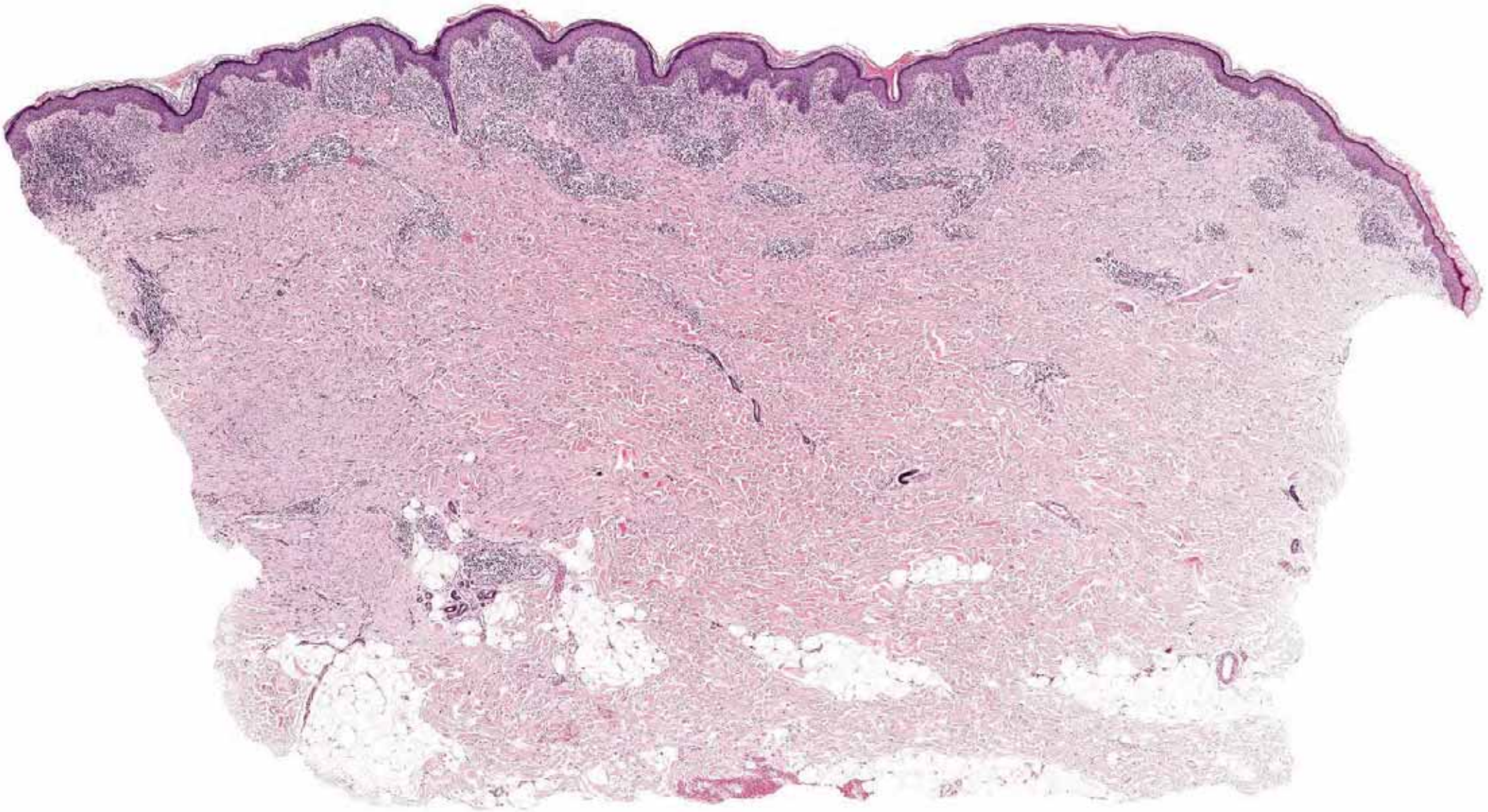
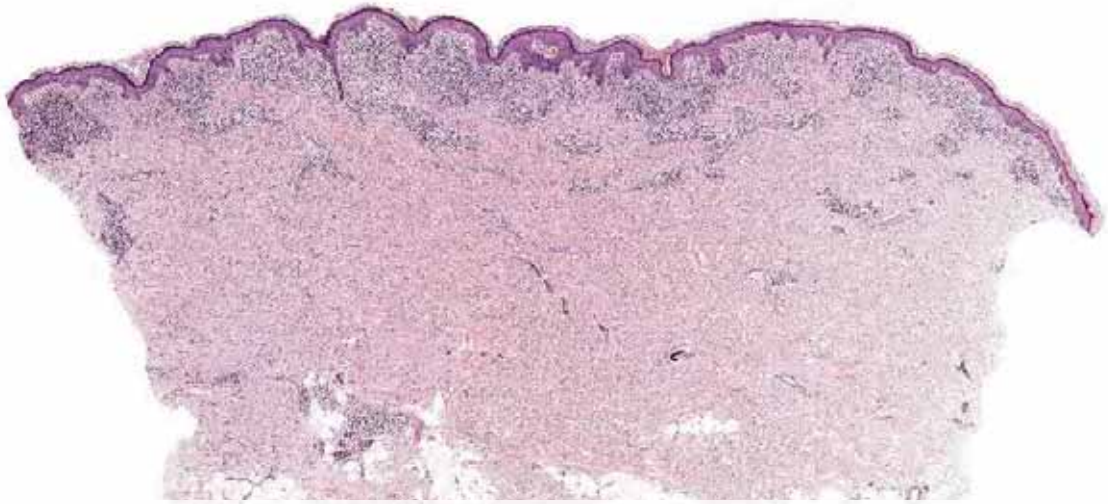
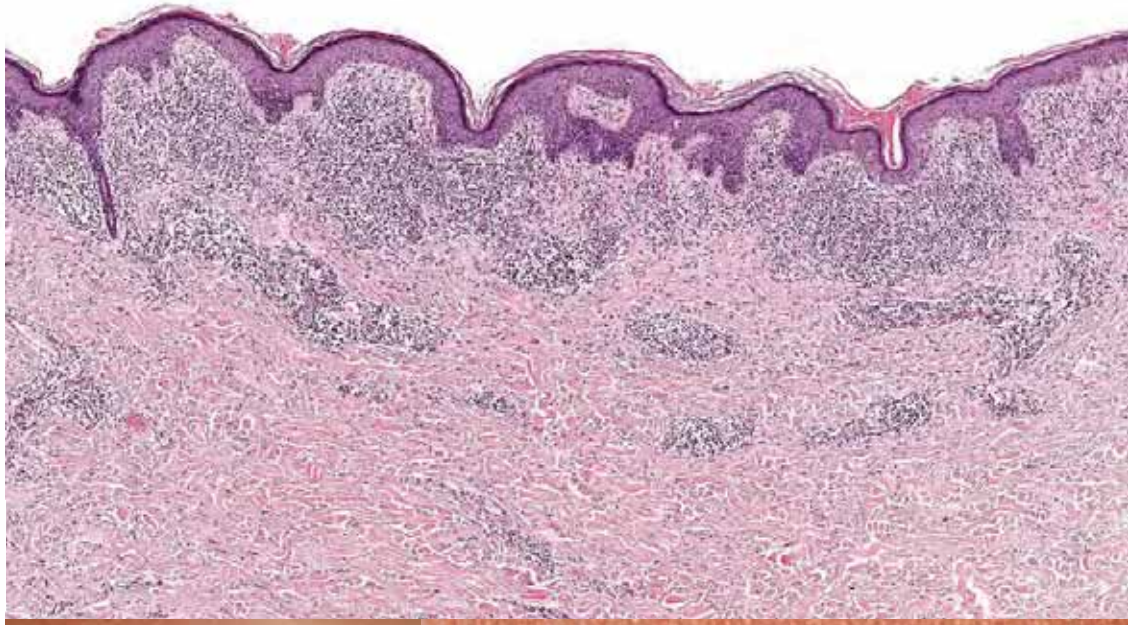


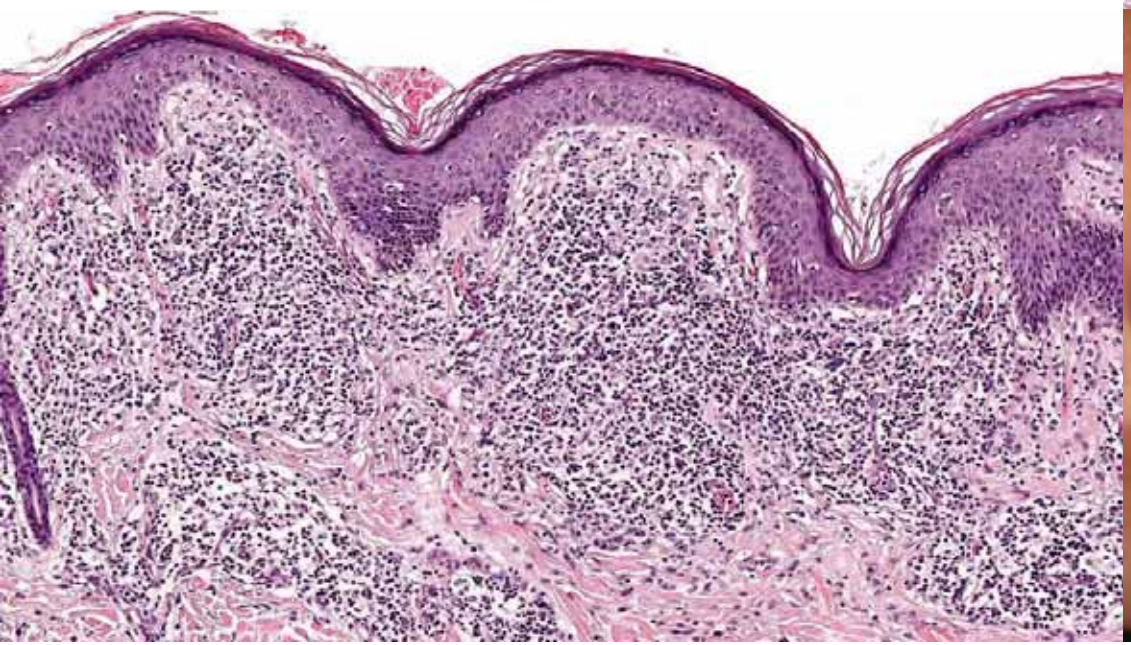
FIG. 1. A: Solitary lesion on the breast. B: Detail showing a small plaque without scaling.







Superficial pseudolymphoma



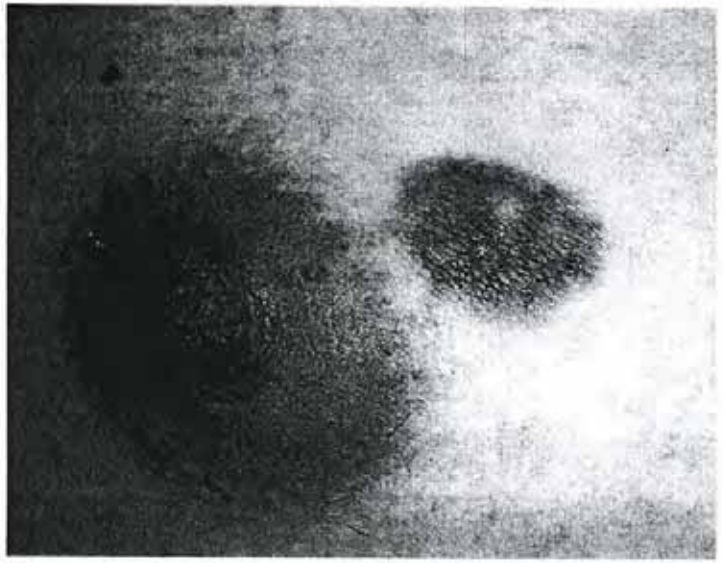
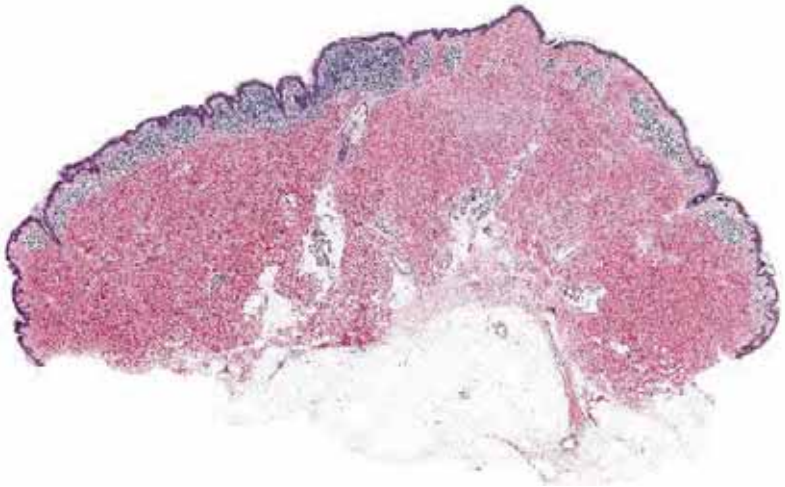
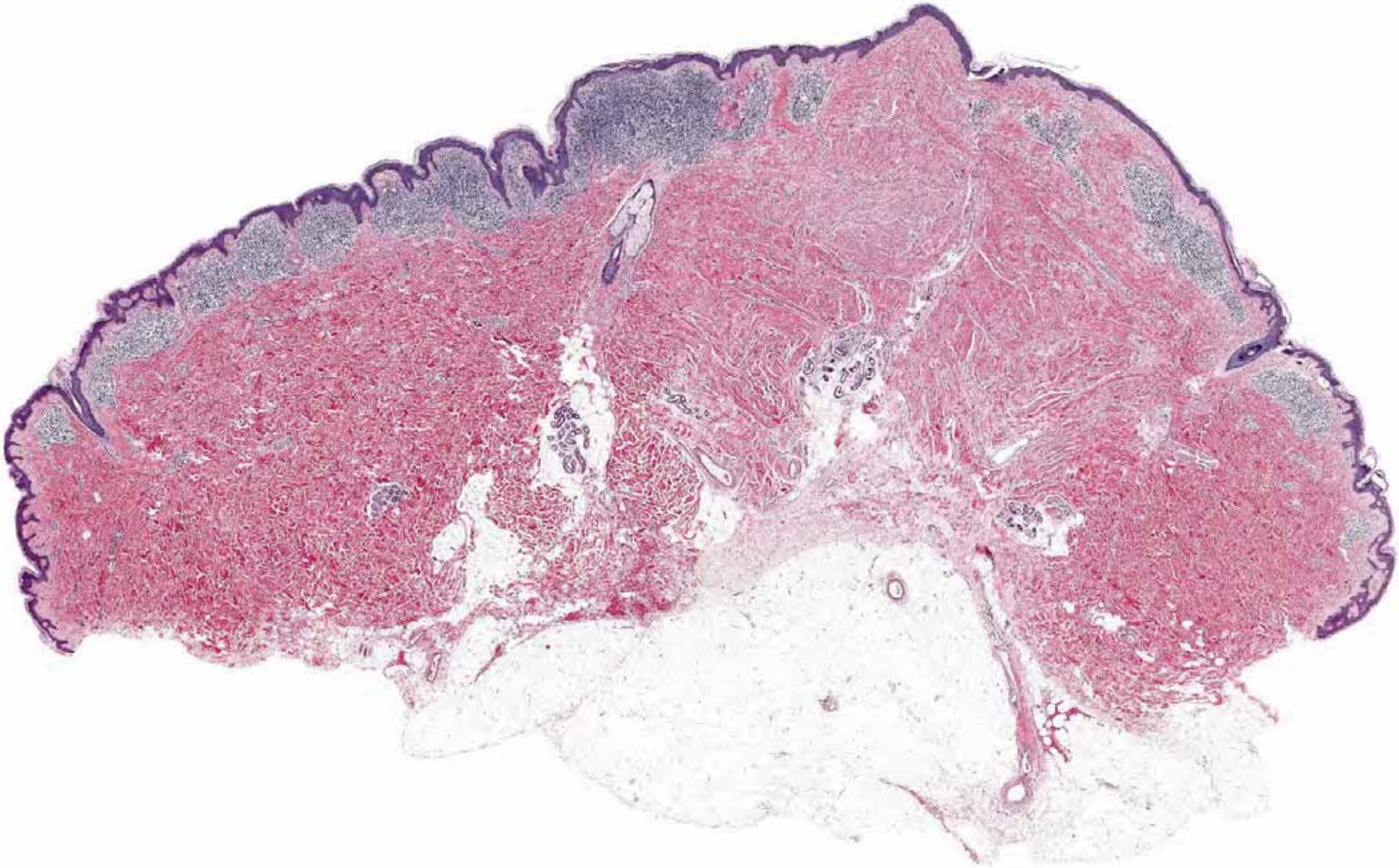
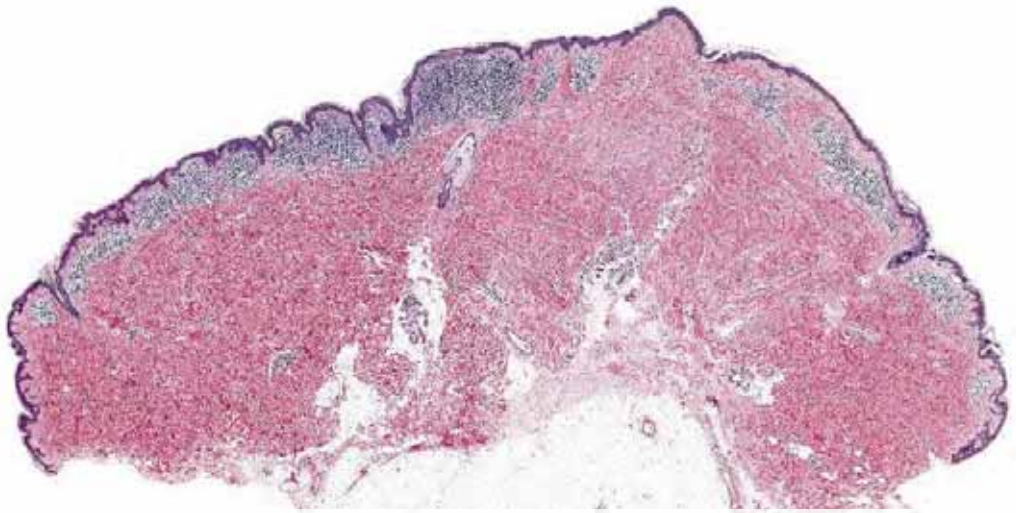


FIG. 2. Small erythematous plaque near the nipple. The whitish area corresponds to the site of a previous punch biopsy.







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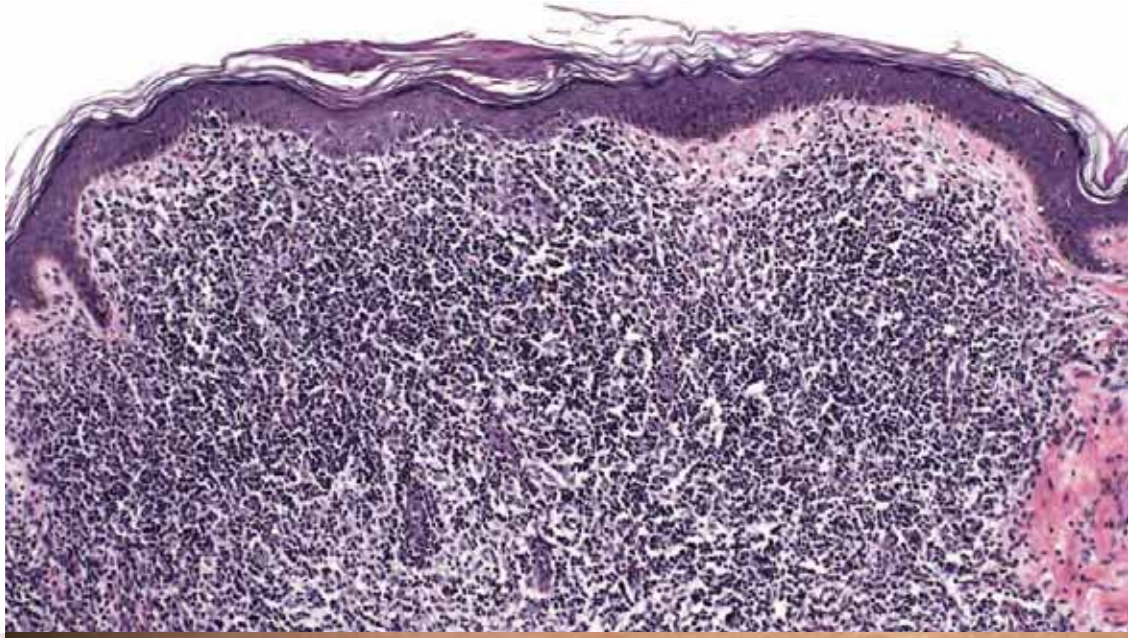

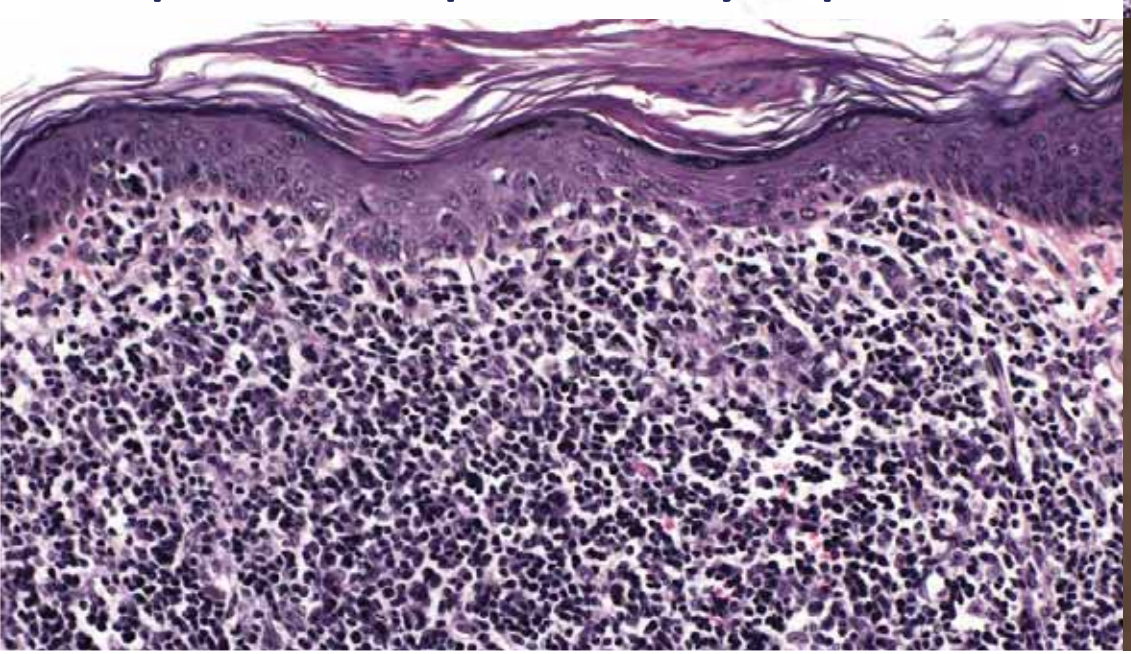

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Solitary Skin Lesions With Histopathologic Features of Early Mycosis Fungoides

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Mycosis fungoides (MF) is a cutaneous T-cell ly
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Key Words: Solitary mycosis fungoides—Cut
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TABLE 1. *Clinical data, drug history, and results of PCR analysis of TCR genes*

Patient no	Sex	Age	Location	Drugs	PCR analysis of TCR genes	Treatment	Follow-up (months)	
1	F	59	back	no	P	TE	A&W (45)	A&W (83)
2	F	53	breast	[illegible]	M	TE	A&W (50)	A&W (176)
3	F	45	breast	Developed new lesions	P	TE	A&W (26)	A&W (194)
4	F	23	breast	no	M	TE	A&W (76)	A&W (258)
5	F	44	inguinal	unknown	nd	TE	LFU	LFU
6	M	63	breast	no	P	TE	A&W (7)	A&W (27)
7	M	71	flank	no	nd	TE	A&W (38)	A&W (196)
8	M	47	arm	unknown	P	TE	LFU	D- (30)
9	M	47	back	no	M	TE	A&W (75)	A&W (239)
10	M	75	flank	Isosorbide 5-mononitrat	M	TE	A&W (48)	A&W (48)
11	M	36	back	Clofibrate; Atenololi, Allopurinol	M	local steroids	A&D (15)	A&W (35)
12	F	51	breast	Developed new lesions & LyP	P	local steroids	A&D (8)	A&W (167)
13	F	58	back	Enalapril; Coumecin; Hydrochlorothiazide Sucralfate; Ranitidine; Famotidine	P	local steroids	A&D (11)	A&W (176)
14	F	58	breast	Levothyroxine	M	local steroids	A&D (57)	A&W (118)
15	F	29	abdomen	Levothyroxine	P	TE	A&W (23)	A&W (184)
16	F	70	arm	Levothyroxine; Isradipine; Allopurinol; Bisoprolol; Terbutaline; Chlordiazepoxide; Amitriptyline; Ketotifene	P	TE	A&W (22)	A&W (207)
17	F	34	back	no	M	TE	recurrence (36)	
18	F	43	back	Fluoxetine	M	local steroids	A&D (18)	
19	M	24	back	no	P	local steroids	A&D (8)	
20	M	82	arm	[illegible] Naproxen; Acetyl Salicylic acid; Acetaminophen	P	TE	recurrence (12)	

PCR, polymerase chain reaction; TCR, T-cell receptor; nd, not done; TE, total excision; recurrence, recurrence within surgical scar; PB, punch biopsy; M, monoclonal band; P, polyclonal smear; A&W, alive and well; A&D, alive with persistent disease; LFU, lost to follow-up.

San Francisco

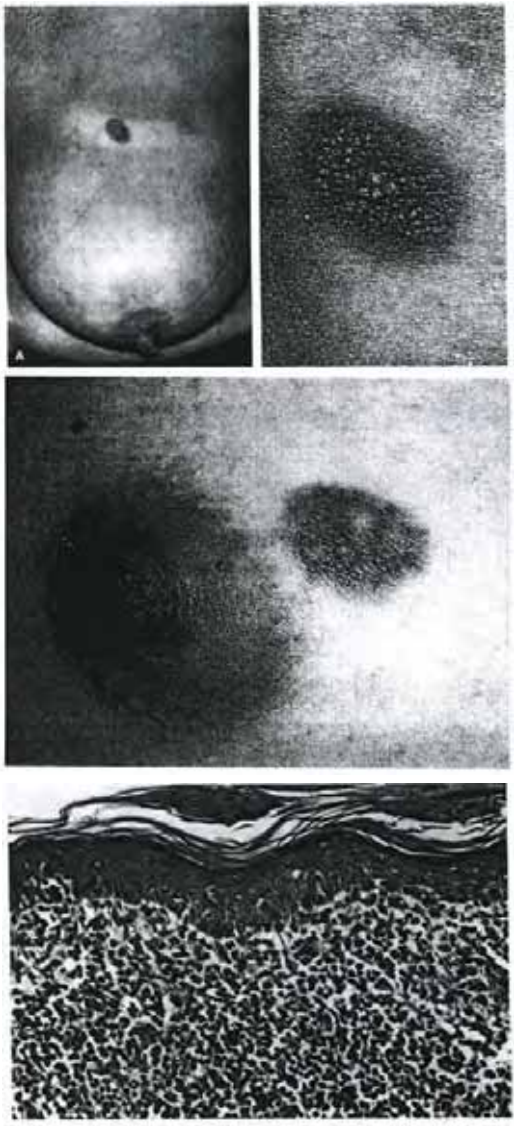

FIG. 5. Small lymphocytes predominate; note small intraepidermal collection of lymphocytes.

Solitary nonepidermotropic T cell pseudolymphoma of the skin

Sebastian C. J. van der Putte, M.D.,* Johan Toonstra, M.D.,**
Paul C. Felten,** and Willem A. van Vloten, M.D.** *Utrecht, The Netherlands*

A possibly new type of T cell pseudolymphoma is described in three cases. It presented as a small, solitary lesion on the trunk of 3 to 5 months' duration. It was slightly elevated, round, and erythematous, with a diameter of 1 to 2 cm. It showed a tendency to regress spontaneously. In sharp contrast to its benign clinical appearance and biologic behavior, a distinct malignant histopathologic picture was observed, however. It was characterized by a nonepidermotropic bandlike subepidermal infiltrate dominated by large T lymphocytes with cerebriform nuclei identical in morphologic and immunologic characteristics to the abnormal cellular component of cutaneous T-cell lymphomas. (J AM ACAD DERMATOL **14**:444-453, 1986.)

The differentiation between malignant lymphomas and pseudolymphomas of the skin is often a source of serious diagnostic perturbation. Pseudolymphomas have been defined as disorders in which a histologic picture strongly suggesting malignant lymphoma stands in sharp contrast to benign biologic behavior.[1] Recently, cutaneous pseudolymphomas have been subclassified into simulators of B and T cell lymphomas.[1] Classification of the T cell pseudolymphoma is based on the resemblance of the infiltration pattern and/or the cytomorphologic characteristics of the infiltrative cells to cutaneous T cell lymphomas, i.e., mycosis fungoides, Sézary's syndrome, and pagetoid reticulosis. The criteria included reactions to sunlight,[2,3] drugs,[4-6] arthropods,[7-9] viruses,[10] and contact allergens.[9,11-14] Pagetoid reticulosis[1,15,16] and lymphomatoid papulosis[1,17-20] have still escaped exact categorization as either low-grade malignant lymphomas or pseudolymphomas.

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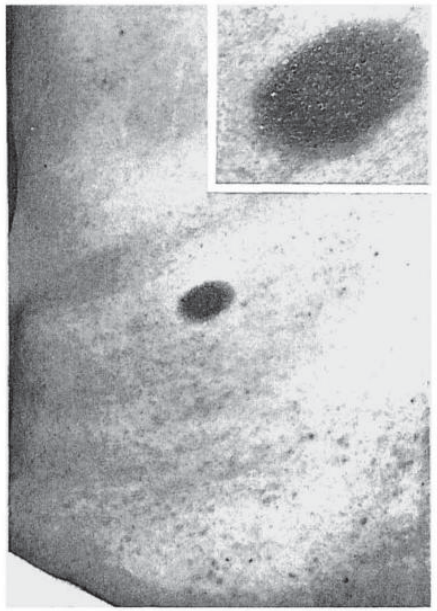

Fig. 1. Case 1. Solitary 2 × 1.5-cm erythematous plaque on the back, existing for 7 months. It showed a tendency toward spontaneous regression shortly before excision. *Inset:* Detail.

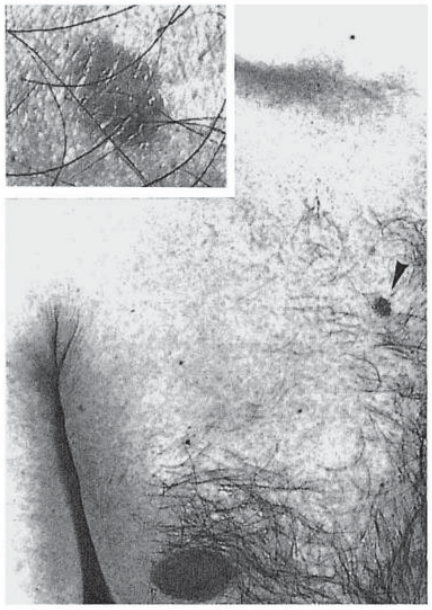

Fig. 2. Case 3. Solitary 1-cm erythematous plaque on the chest *(arrow)*, existing for 3 months. One year later, it had almost completely disappeared spontaneously. *Inset:* Detail.

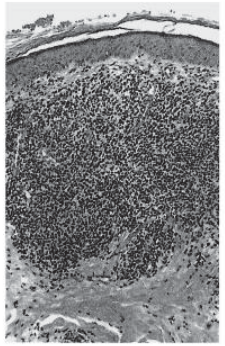

Fig. 3. Case 3. Plaque lesion showing the characteristically subepidermal bandlike infiltrate. (×80.)

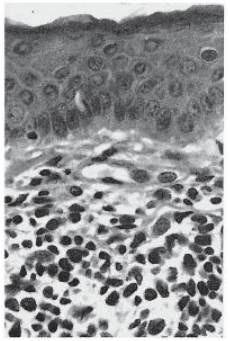

Fig. 4. Case 3. Only rarely, a few lymphocytes invade the epidermis. Mononuclear cells with abnormally large hyperchromatic and irregular nuclei form a conspicuous part of the dermal infiltrate. (×400.)

Unilesional Mycosis Fungoides or Lymphomatoid Keratosis?

I read with interest in a recent issue of the ARCHIVES the "Off-Center Fold" case report by Evans et al[1] of an asymptomatic scaly plaque measuring 1.1×1.5 cm, which showed histological features of mycosis fungoides (MF) and was interpreted as an example of unilesional MF.

Mycosis fungoides has received a great deal of public exposure in Australia with the death of Paul Eddington, the British actor, and more recently the public struggle of a patient with advanced MF who elected to undergo voluntary euthanasia under the recent controversial legislation passed in the Australian Northern Territory. The public perception of MF is that of a terminal disease.

I recall being sent for review the histopathologic material of 3 patients who underwent excision biopsies of solitary lesions measuring 1 to 2 cm in diameter that were associated with a short history of change and pruritus. While the histopathologic material on the slides showed features of MF, there was also a lichenoid element present. Subsequent clinical review of the patients showed no evidence of MF and 2 of the patients underwent a hematologic review, including scans for lymph node involvement, the results of which were negative.

From the clinical and histological standpoint I have interpreted these cases as examples of a possible variant of lichenoid keratosis showing lymphomatoid features. In the absence of compelling evidence of MF in this group of patients, I would be inclined to avoid this diagnosis. While the concept of unilesional MF is certainly acceptable, I suspect that we may need to be more rigorous in defining this type of presentation. I would be cautious of accepting the case presented by Evans et al[1] as an example of unilesional MF, despite the histological features.

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Darlinghurst NSW 2010, Australia

1. Evans L, Mackey SL, Vidmar DA. An asymptomatic scaly plaque. *Arch Dermatol*. 1997;133:231-236.

SECTION EDITOR: ANTOINETTE F. HOOD, MD

An Asymptomatic Scaly Plaque

LT Larry Evans, MC, USN; LCDR Steven L. Mackey, MC, USN; CAPT Dennis A. Vidmar, MC, USN; National Naval Medical Center, Bethesda, Md

REPORT OF A CASE

A 44-year-old man presented to our clinic for evaluation of a single asymptomatic lesion on his right flank that had been present for 4 months. He reported that the lesion had quickly arisen but had remained unchanged for the past 3 months. Physical examination revealed a 1.1×1.5-cm, erythematous, slightly scaly plaque with central clearing and atrophy (**Figure 1**). He had no other cutaneous lesions. He had been evaluated 2 months previously, and a biopsy had been performed on a portion of the lesion to rule out basal cell carcinoma.

An excisional biopsy was performed (**Figure 2** and **Figure 3**).

What is your diagnosis?

Figure 1.

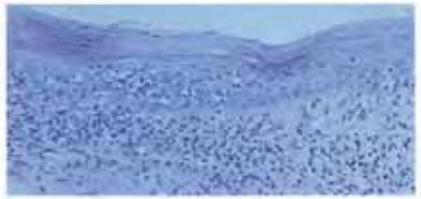

Figure 2.

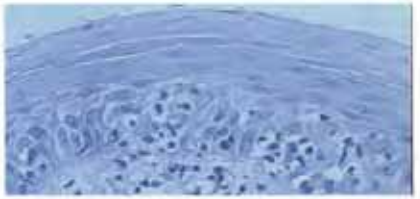

Figure 3.

An Asymptomatic Scaly Plaque

DIAGNOSIS: Unilesional mycosis fungoides (MF).

HISTOPATHOLOGIC FINDINGS

The biopsy specimen revealed compact orthokeratosis with a slightly atrophic epidermis. There was a dermal infiltrate of atypical, hyperchromatic lymphocytes that had convoluted nuclei with significant epidermotropism and formation of Pautrier microabscesses.

DISCUSSION

Mycosis fungoides is a cutaneous T-cell lymphoma. Clinically, the lesions range from patches to plaques to nodules. Histologically, MF is characterized by an infiltrate of large hyperchromatic, atypical-appearing T helper cells with epidermotropism and the formation of Pautrier microabscesses. Unilesional MF has been reported, but it is a very rare condition.[1-4] Unlike typical MF, unilesional MF presents as a single lesion that responds to local treatment, such as excision or radiotherapy, and does not progress to systemic disease. Histologically and clinically, our patient's lesion was consistent with MF. It was excised completely. On follow-up at 18 months, the patient had not developed any new lesions and has had an apparent cure.

In 1940, Woringer and Kolopp[5] described a patient with a single lesion that histologically revealed a pagetoid invasion of atypical-appearing mononuclear cells with an overlying hyperplastic epidermis with an atypical dermal inflammatory infiltrate. Since that report, Woringer-Kolopp disease, also known as pagetoid reticulosis, has been described as a benign localized variant of MF with prominent epidermotropism. Recent reports, however, have demonstrated that unilesional MF exists as a distinct entity that differs from Woringer-Kolopp disease both clinically and histologically.[3,4] Clinically, Woringer-Kolopp disease is usually characterized by a single verrucous plaque located on the extremities with polycyclic borders and central clearing. It is characterized histologically by an infiltrate of numerous mononuclear cells with large hyperchromatic and irregularly shaped nuclei that are surrounded by a halo-like clear space with significant epidermotropism as a distinguishing feature. Unilesional MF, in contrast, is an eczematoid, parapsoriasiform, or poikilodermatic patch or plaque that is more consistent with clinical MF.[2] Histologically, these lesions are identical to MF. Woringer-Kolopp disease and solitary MF have been studied with immunohistochemistry, electron microscopy, enzyme histochemistry, and monocyte chemotaxis. These studies have demonstrated that Woringer-Kolopp disease arises from a proliferation of an abnormal clone within the epidermis, while solitary MF results from the invasion of the epidermis by atypical mononuclear cells. The abnormal cells of Woringer-Kolopp disease are confined to the epidermis, with numerous mitotic figures at the dermoepidermal junction, while MF is characterized by abnormally large cells above and below the dermoepidermal junction, with few mitotic figures.[1-4]

Clinically and histologically, there are many disorders that may resemble MF, including actinic reticuloid, lymphomatoid contact dermatitis, lymphomatoid papulosis, lymphomatoid granulomatosis, and arthropod bite reaction. However, there are clinical differences that enable the distinction to be made. Furthermore, "mycosis cells" are not pathognomonic of MF. Atypical lymphoid cells with folded hyperchromic nuclei have been described in conditions such as discoid lupus erythematosus, lichen planus, psoriasis, solar keratosis, basal cell carcinoma, and parapsoriasis.[1]

In summary, unilesional MF represents a distinct entity that resembles conventional MF both histologically and clinically in the morphological appearance of its lesions. Unilesional MF is thought to be a benign condition that does not progress to systemic disease. However, patients with unilesional MF fungoides must continue to receive follow-up after treatment to ensure that progression does not occur.

The opinions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

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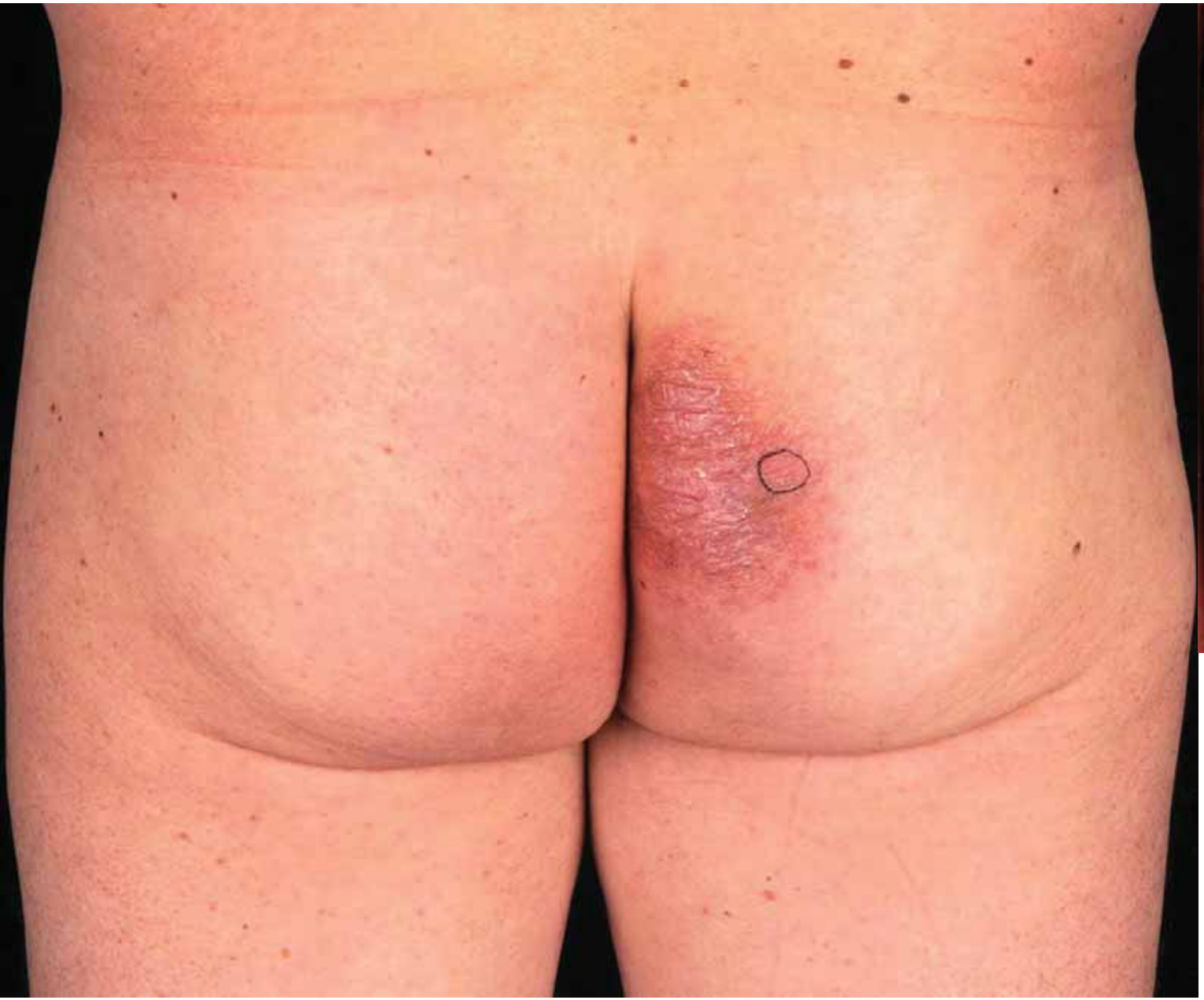
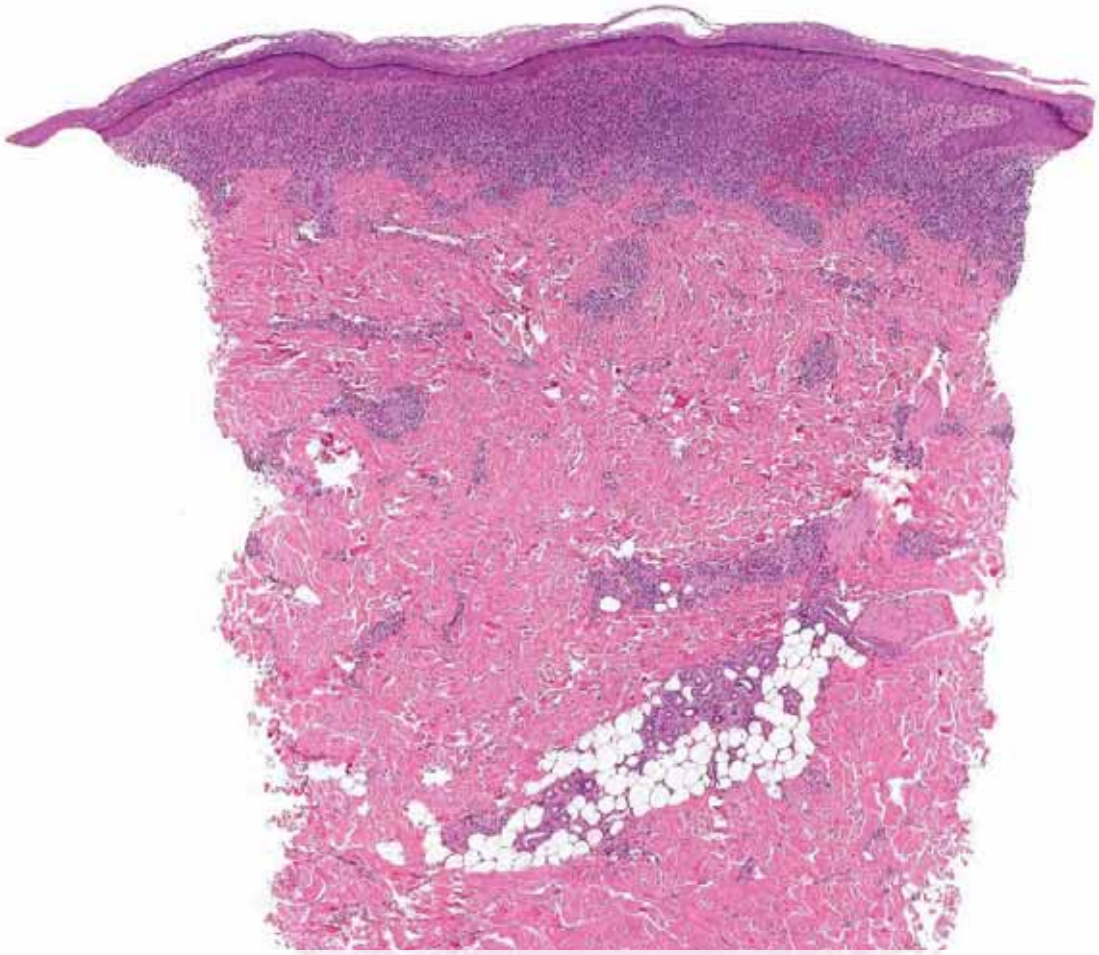
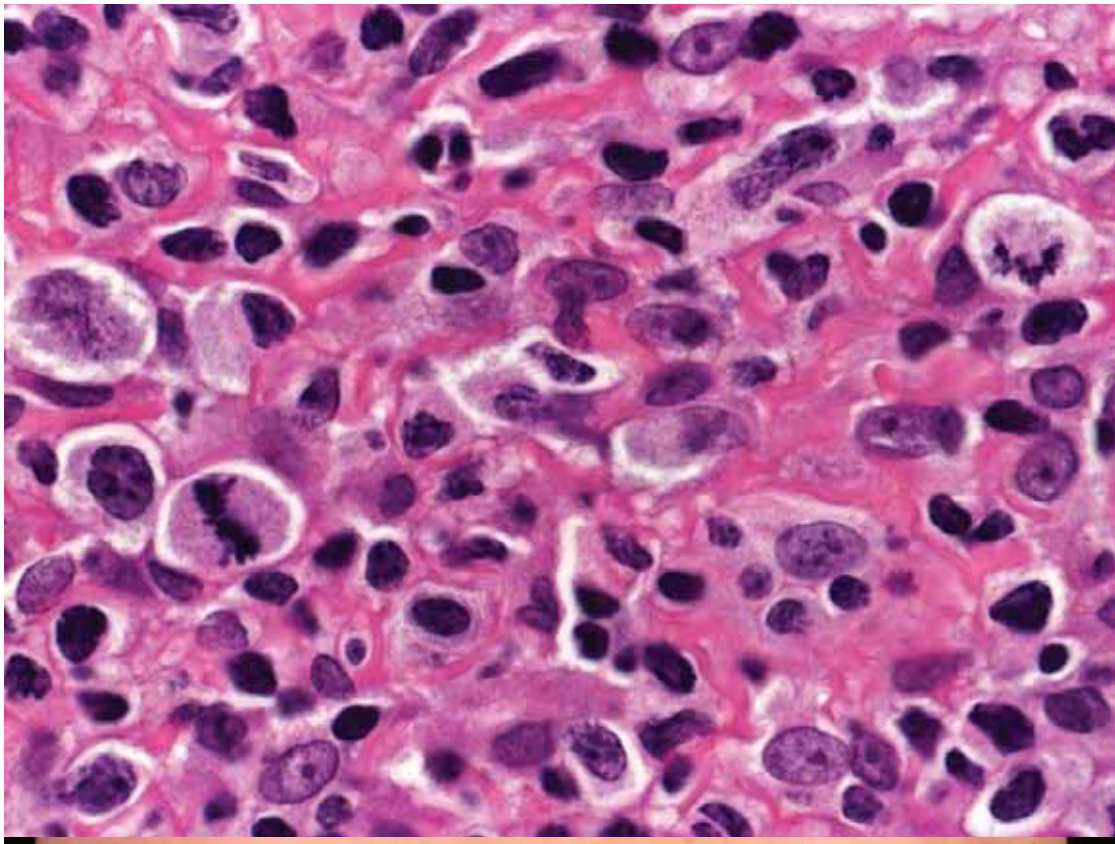


M, 46

According to the patient solitary, slowly growing lesion on the right buttock for >10 years.

A biopsy is taken.



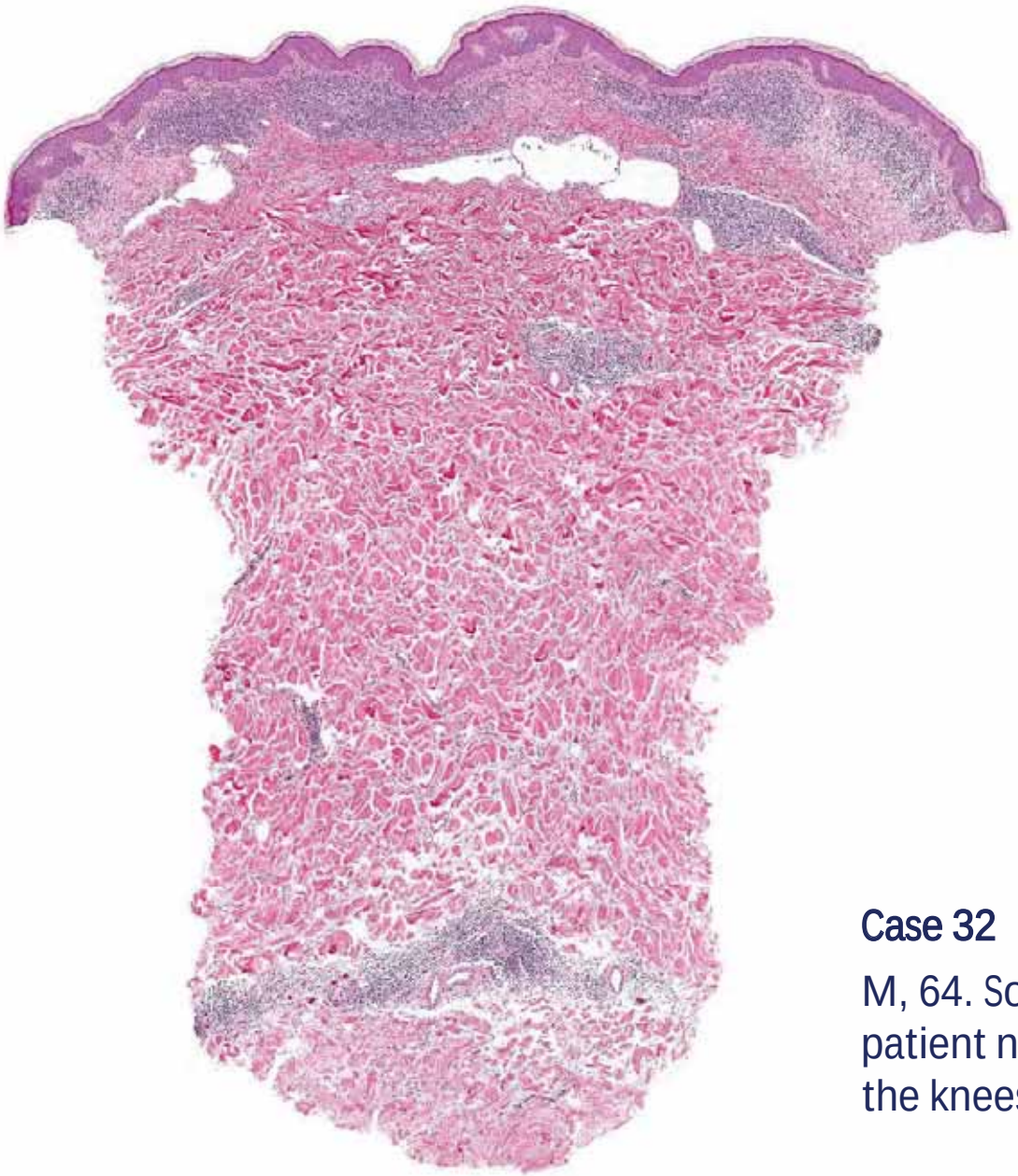


Mycosis fungoides

(solitary with large cell transformation)

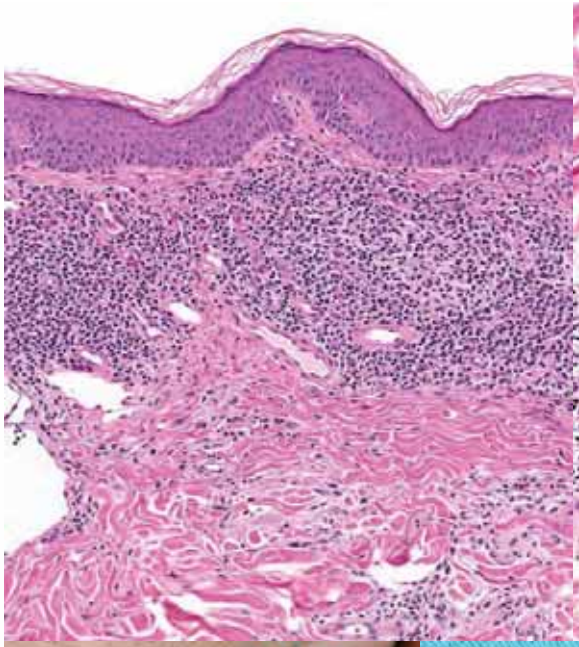
Solitary mycosis fungoides

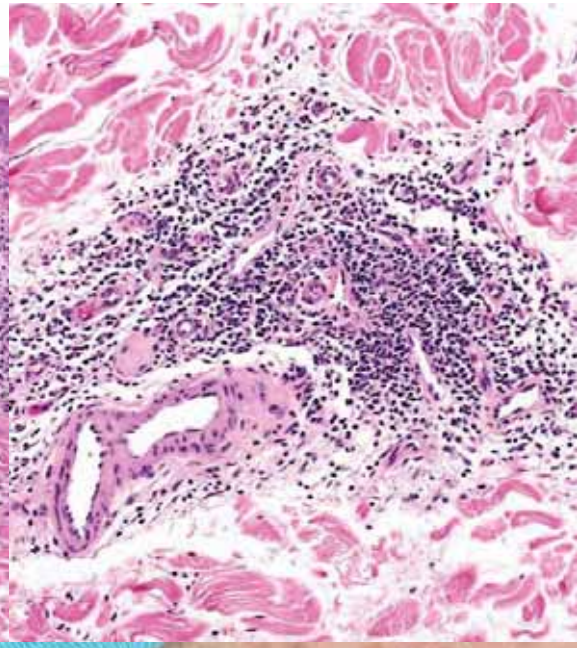
- Most cases of pagetoid reticulosis (truly solitary or restricted to a small area)
- Very rare cases of "conventional" mycosis fungoides
- *Not in genital skin (MF-like lichen sclerosus, MF-like balanitis or vulvitis)*
- *Not on the nipple (MF-like nevoid hyperkeratosis)*
- *Not on palms or soles (MF-like psoriasis)*
- *Not hypopigmented (MF-like vitiligo)*
- Solitary mycosis fungoides is a diagnosis of exclusion – and it may still be wrong...

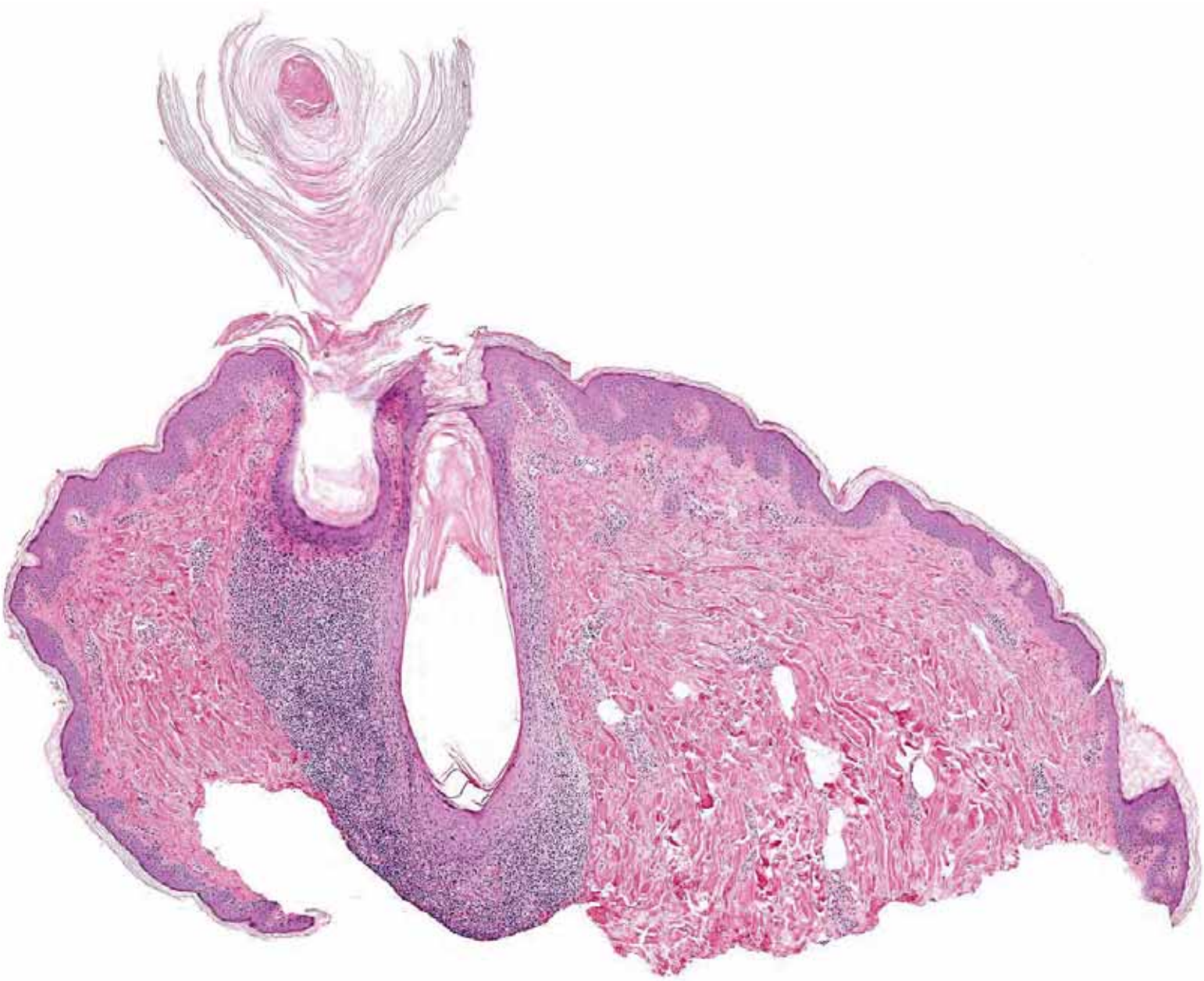


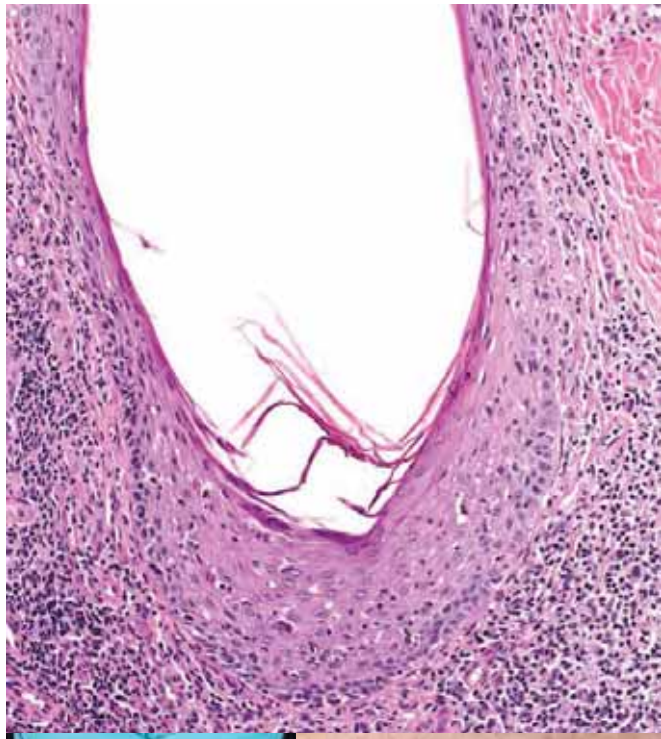
Case 32

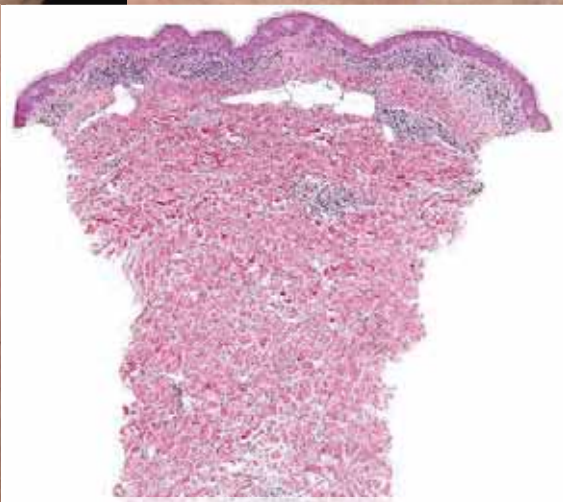
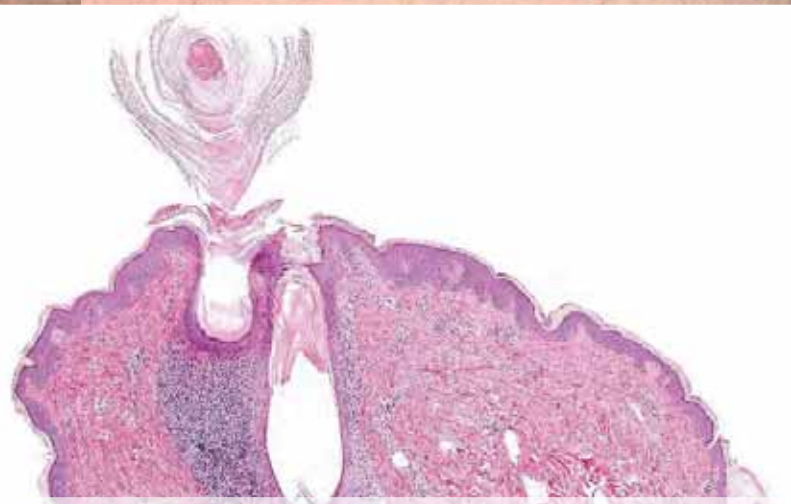
M, 64. Sometimes itchy lesion on the left thigh, for 2 years; the patient noticed also keratotic lesions on the left wrist and back of the knees, and an alopecic area on the abdomen.



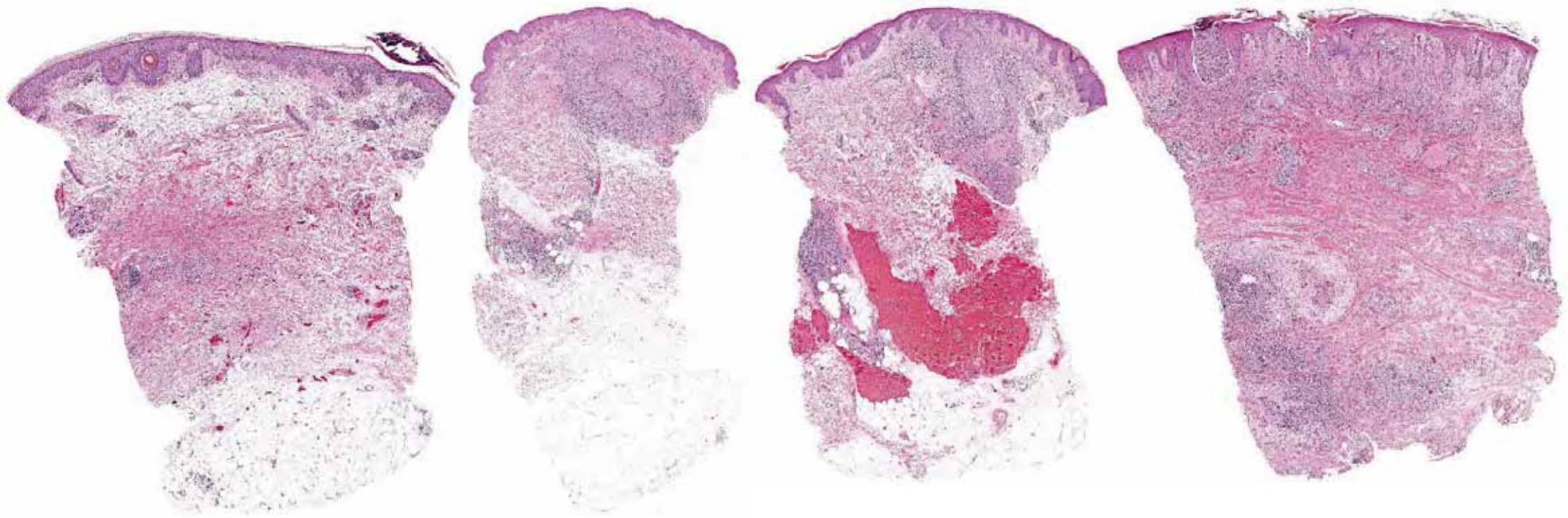






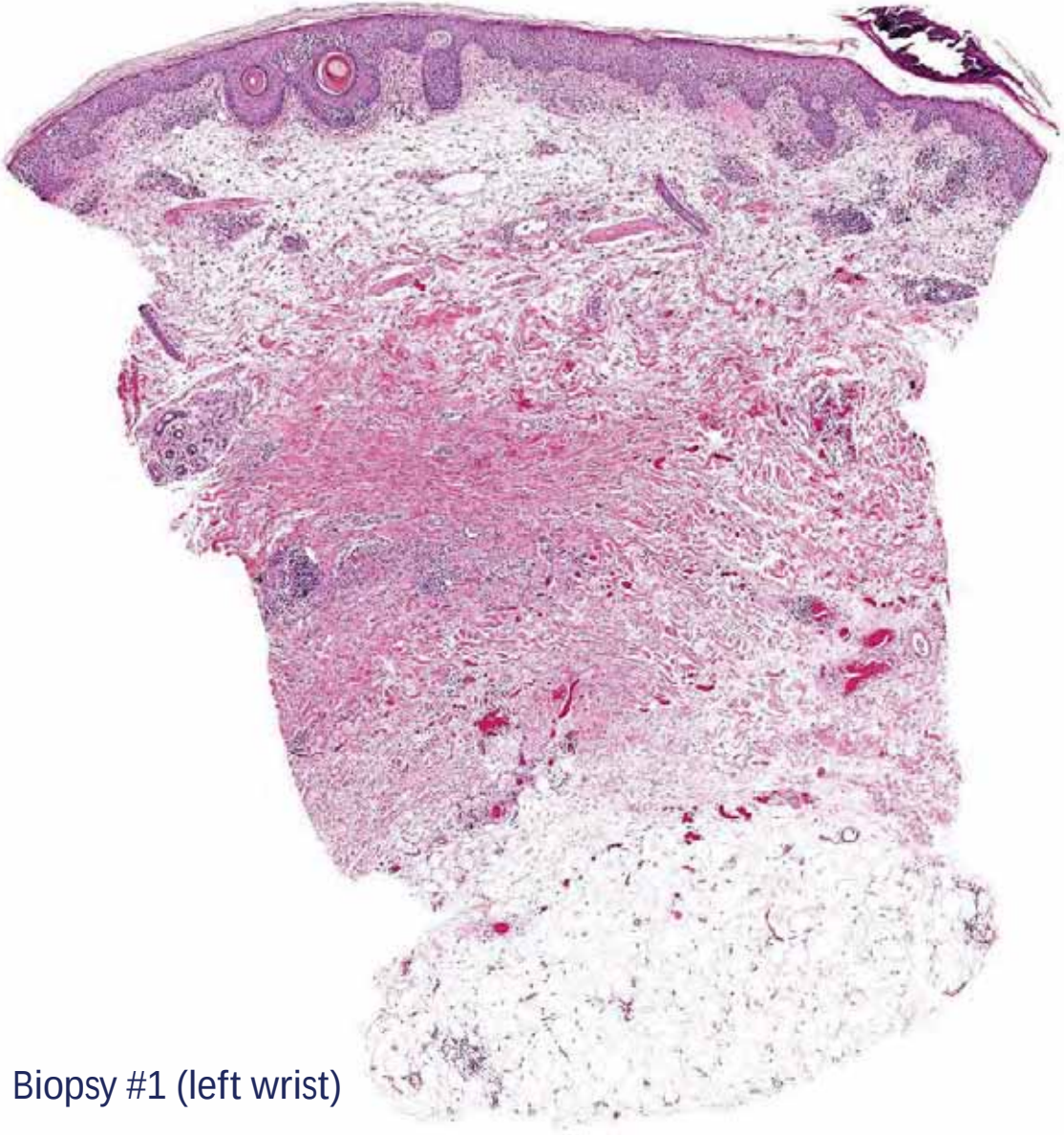



Adnexotropic mycosis fungoides

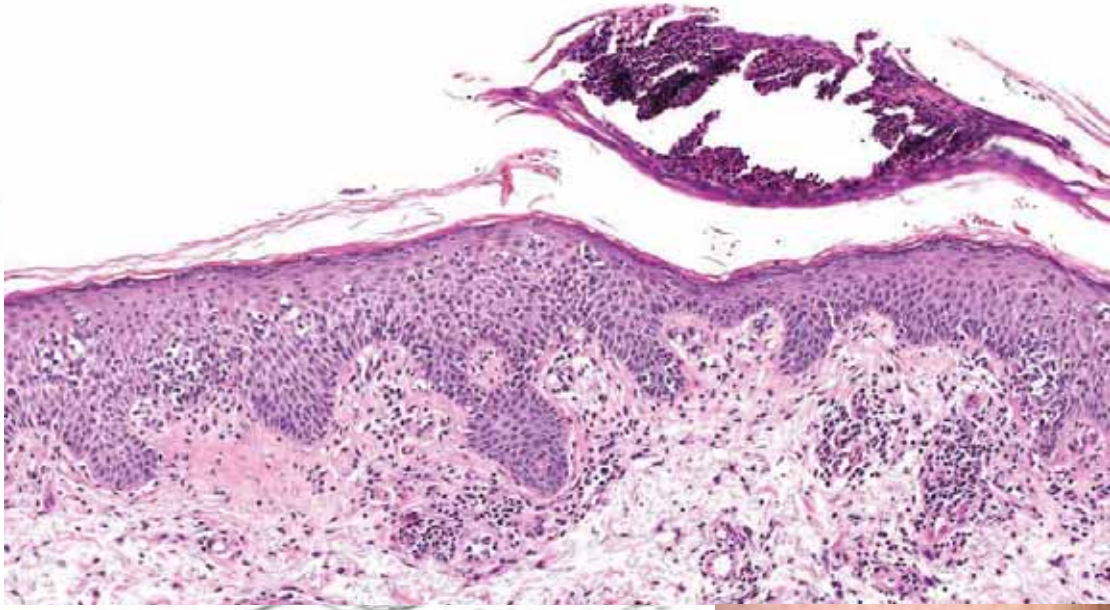


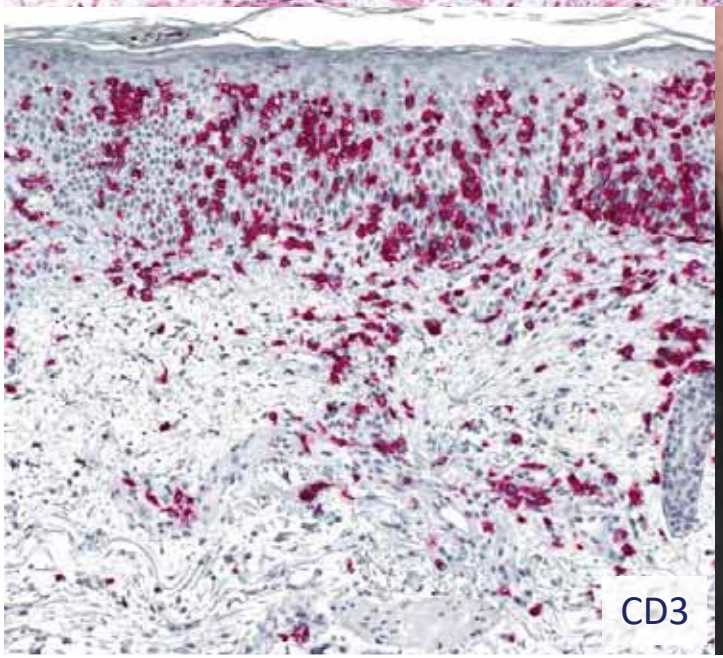
Case 33

M, 56. Sent by a private dermatologist for "exacerbation of a chronic folliculitis" present for 12 years and diagnosed at onset of the disease as keratosis pilaris. According to the patient erosions on the left wrist for the last 8 days.



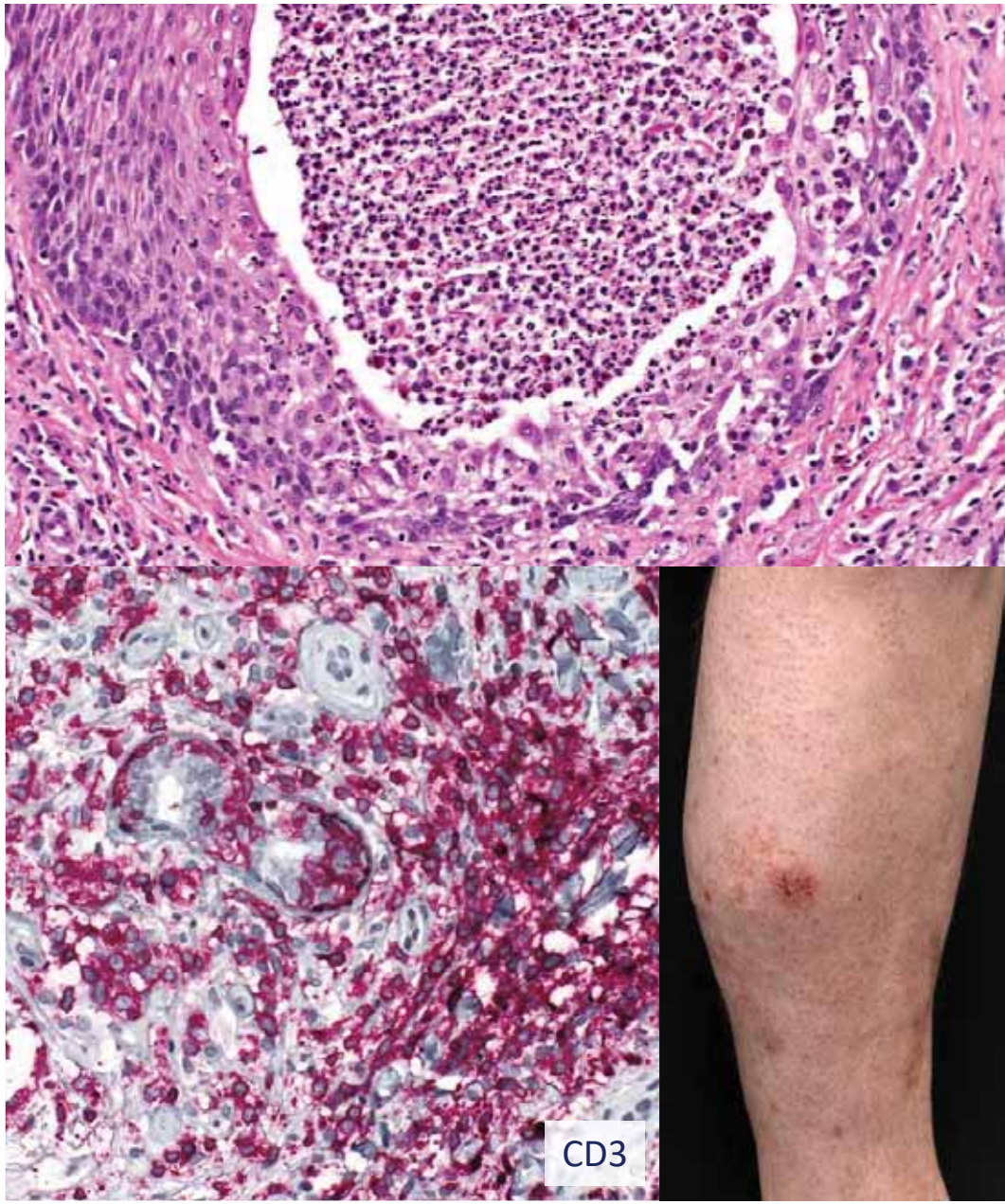
Biopsy #1 (left wrist)

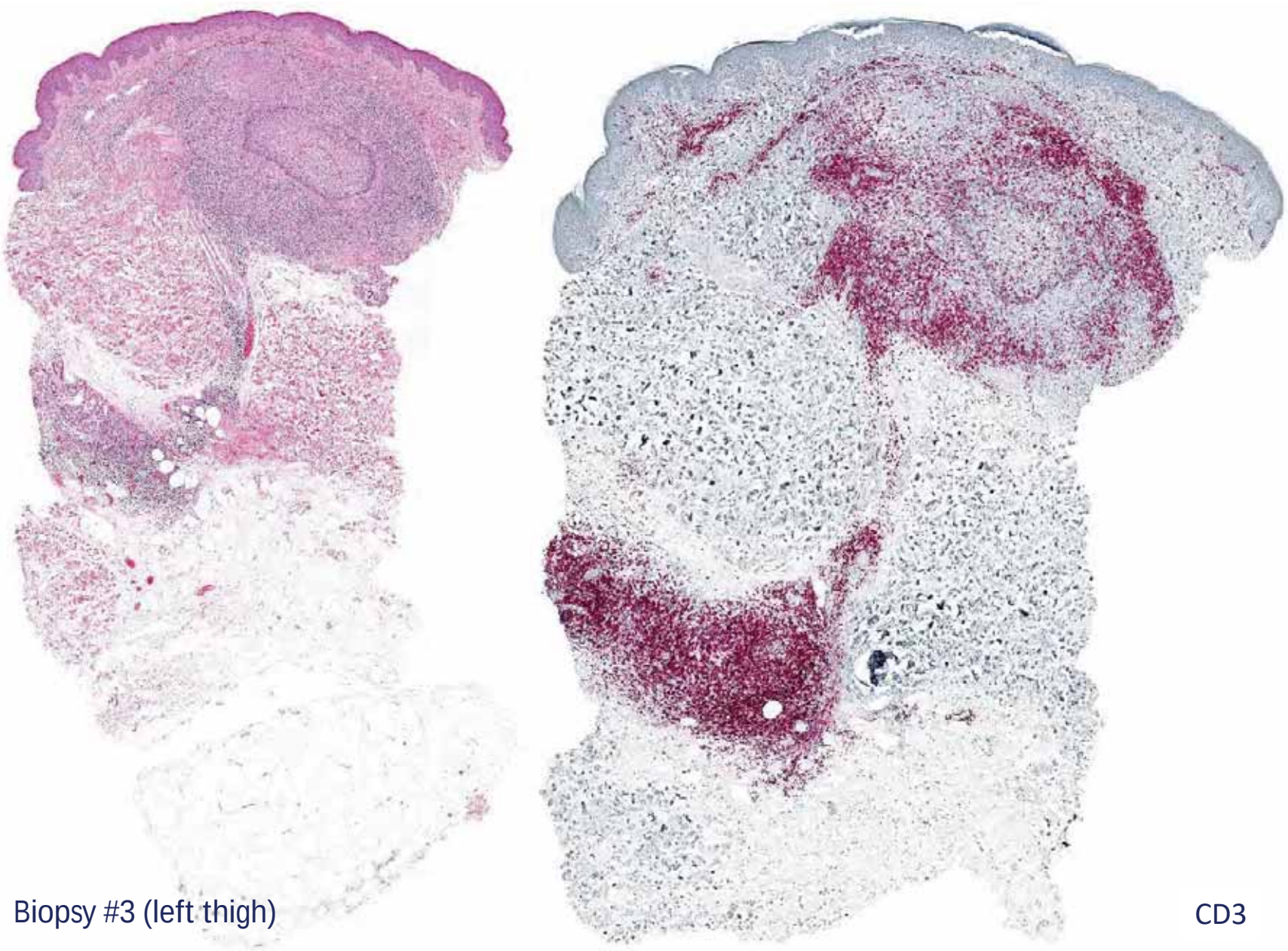




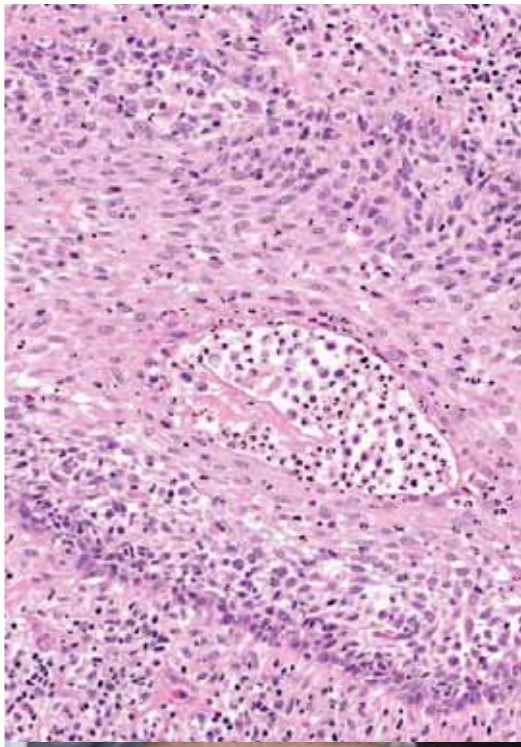
CD3

Biopsy #2 (left leg)

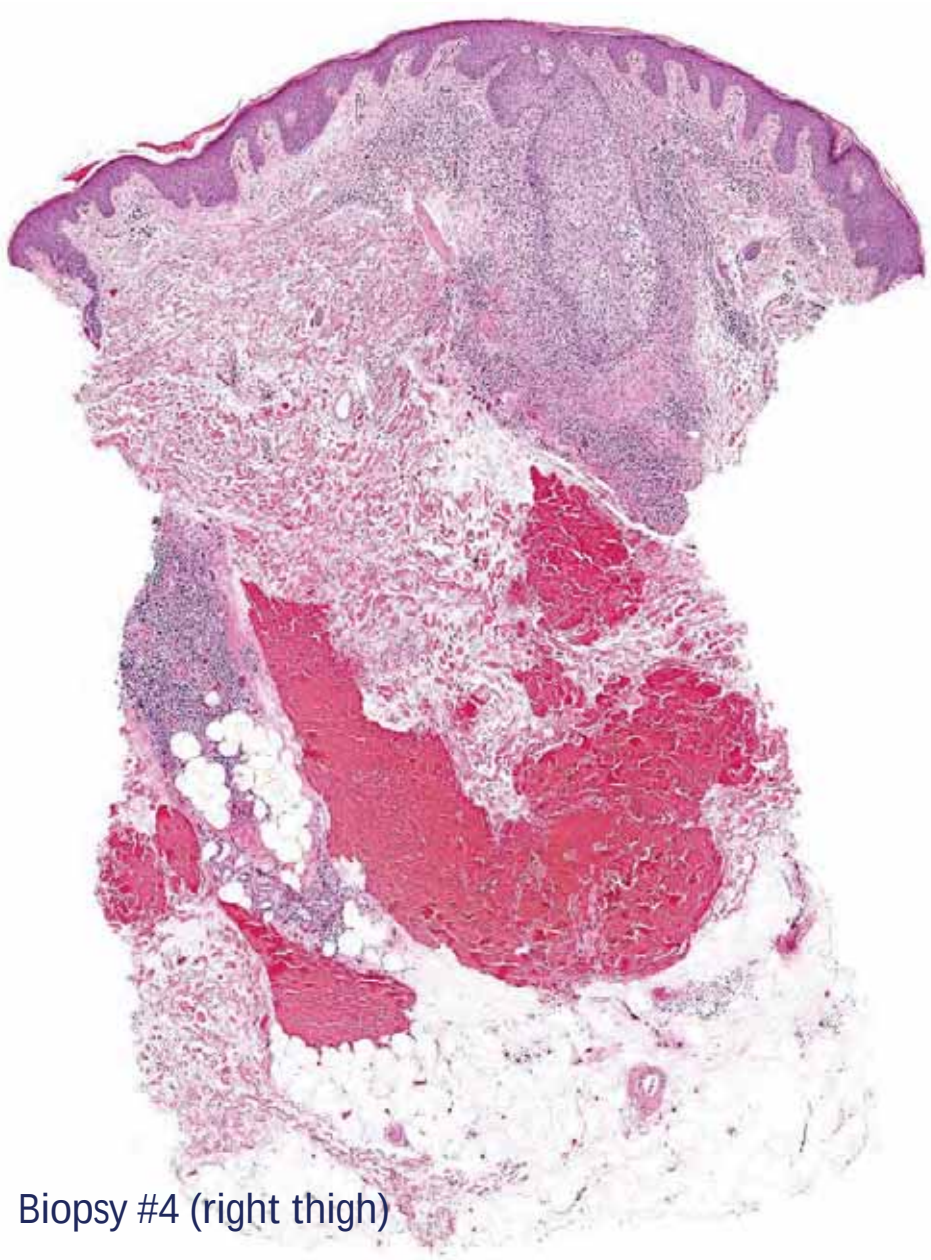




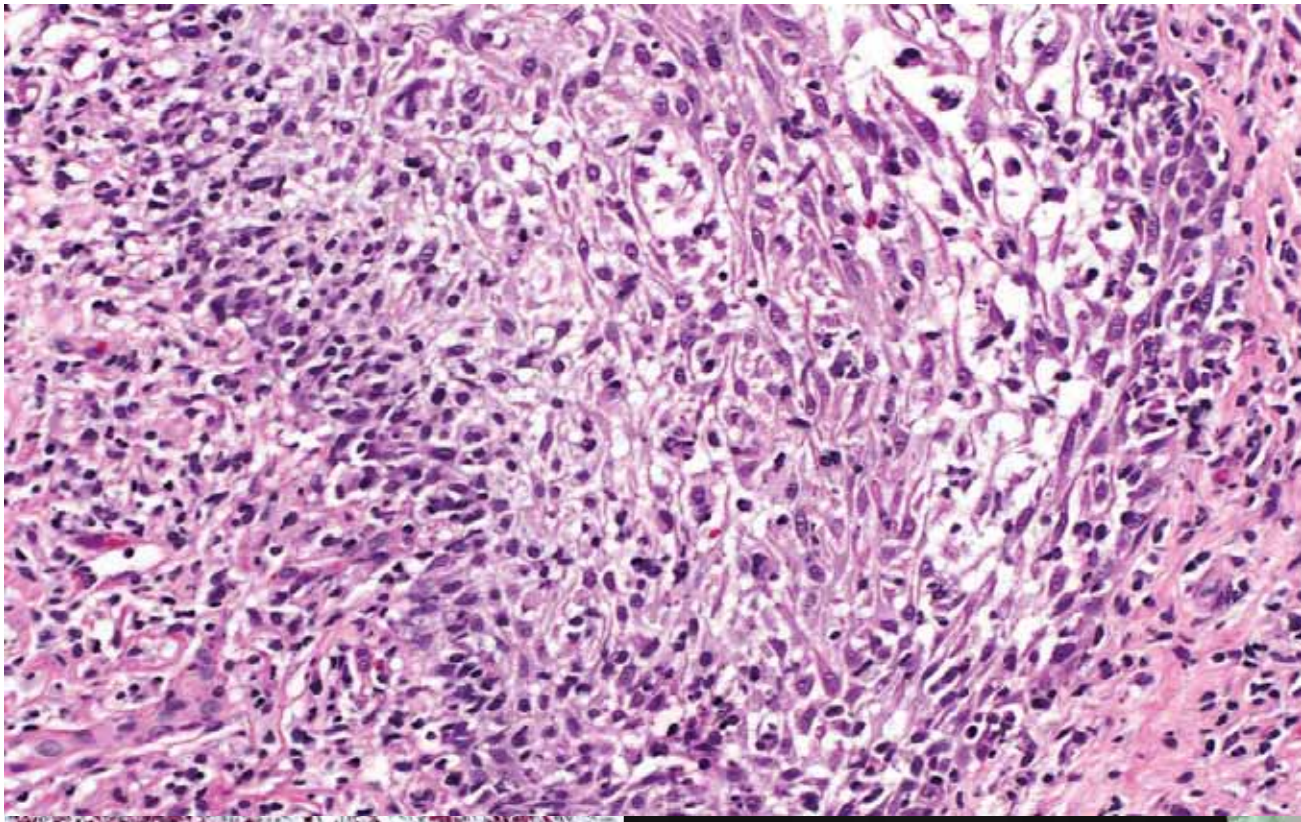
Biopsy #3 (left thigh)

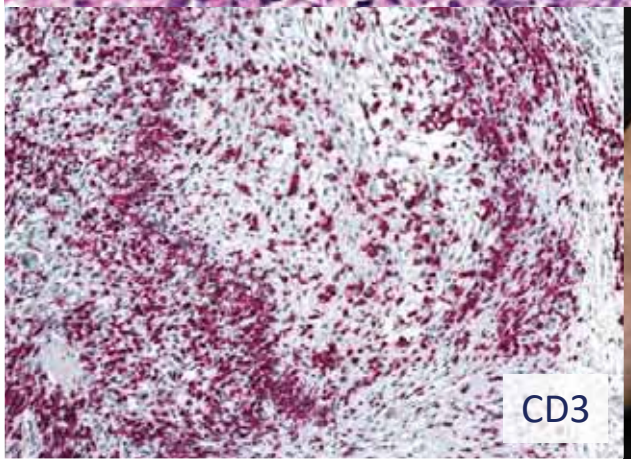


CD3



Biopsy #4 (right thigh)





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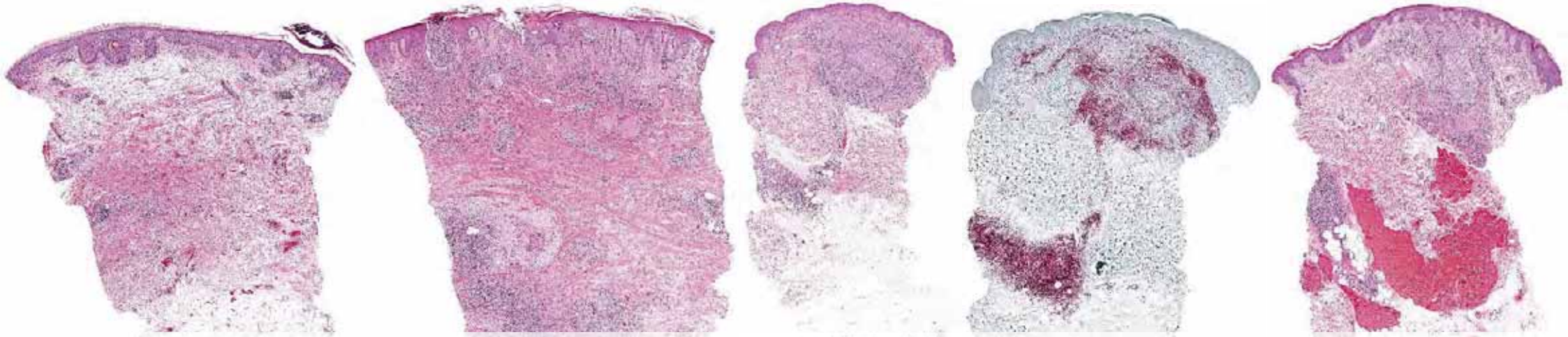
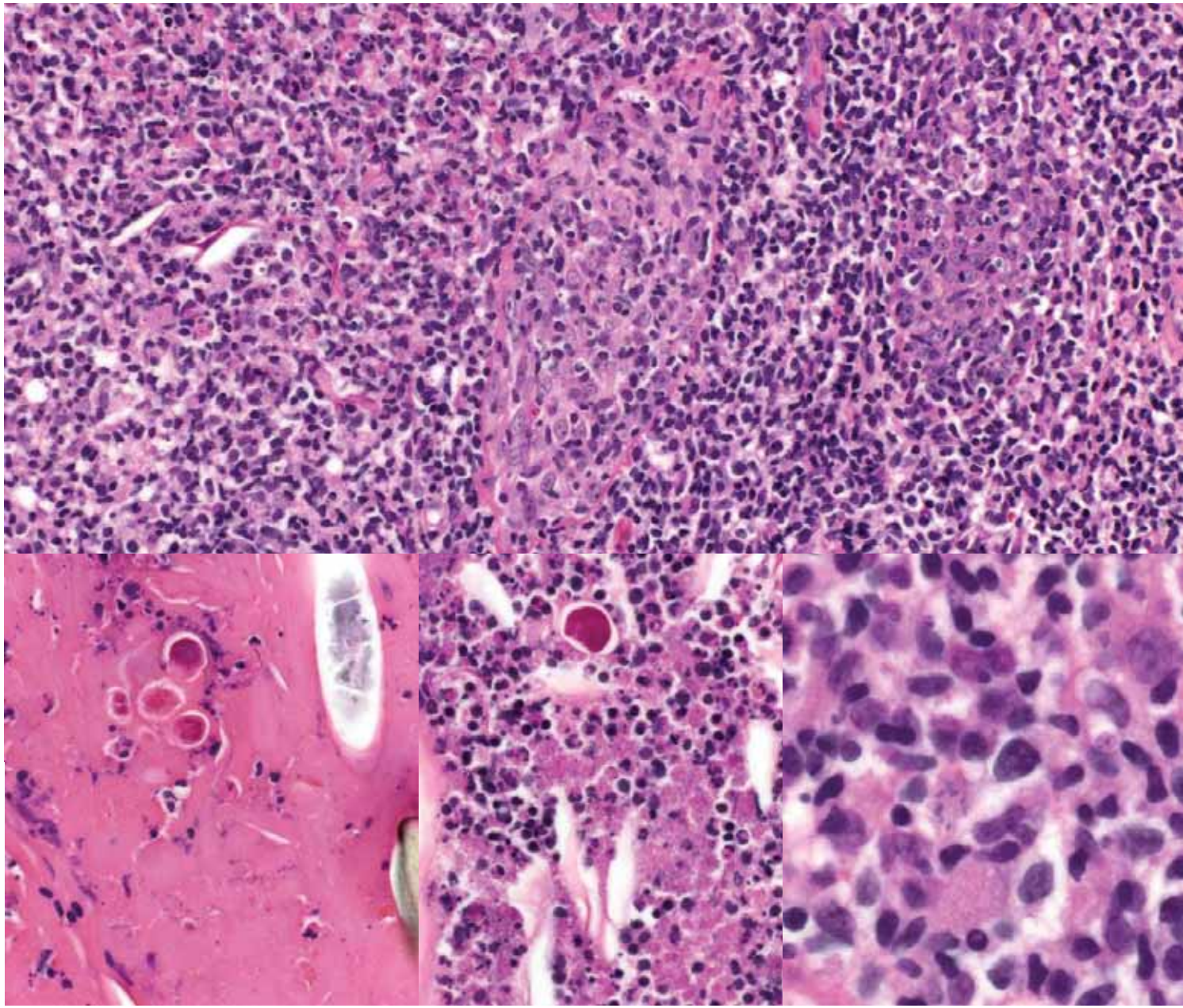


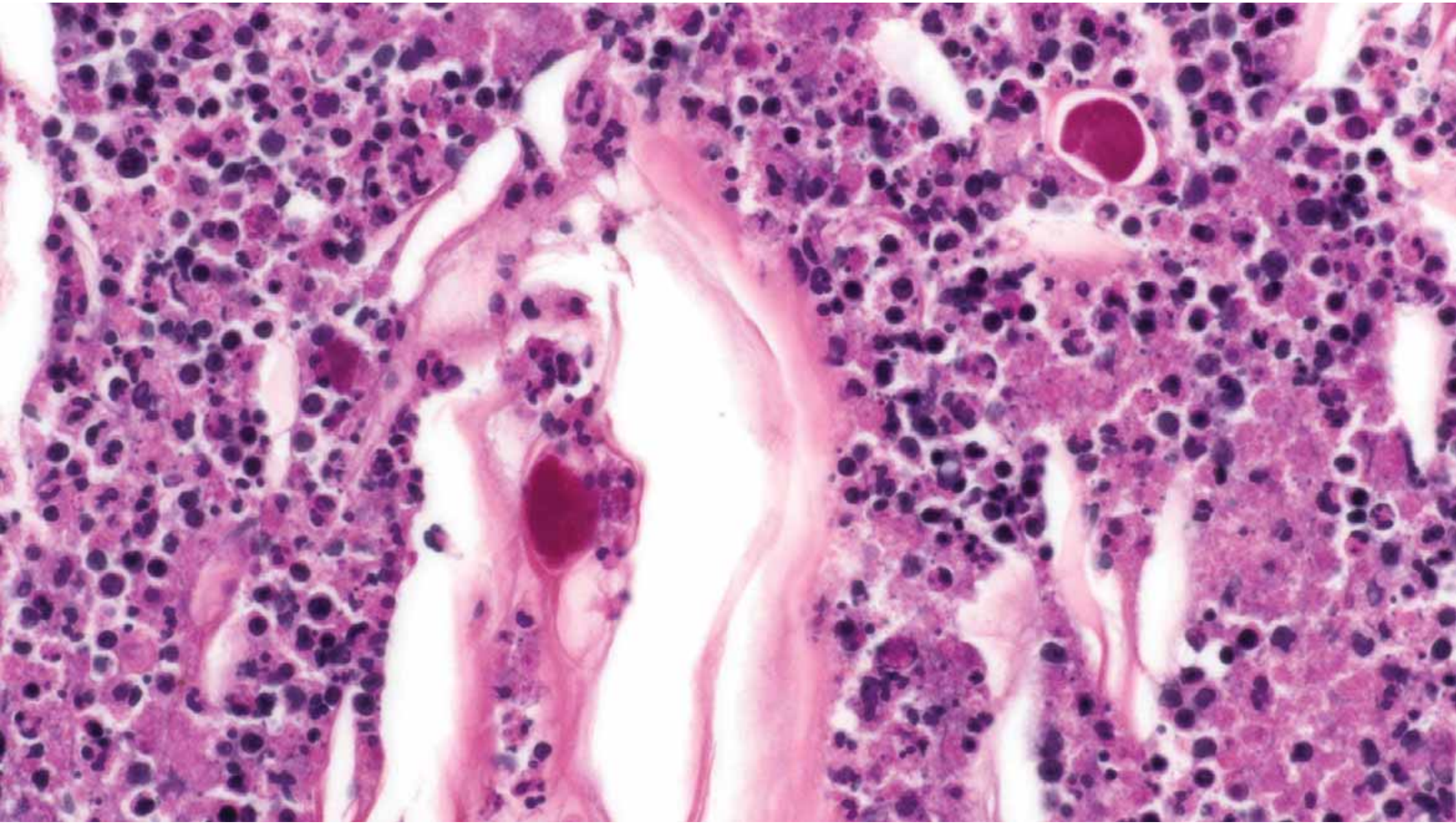
Adnexotropic (pilotropic & syringotropic) mycosis fungoides

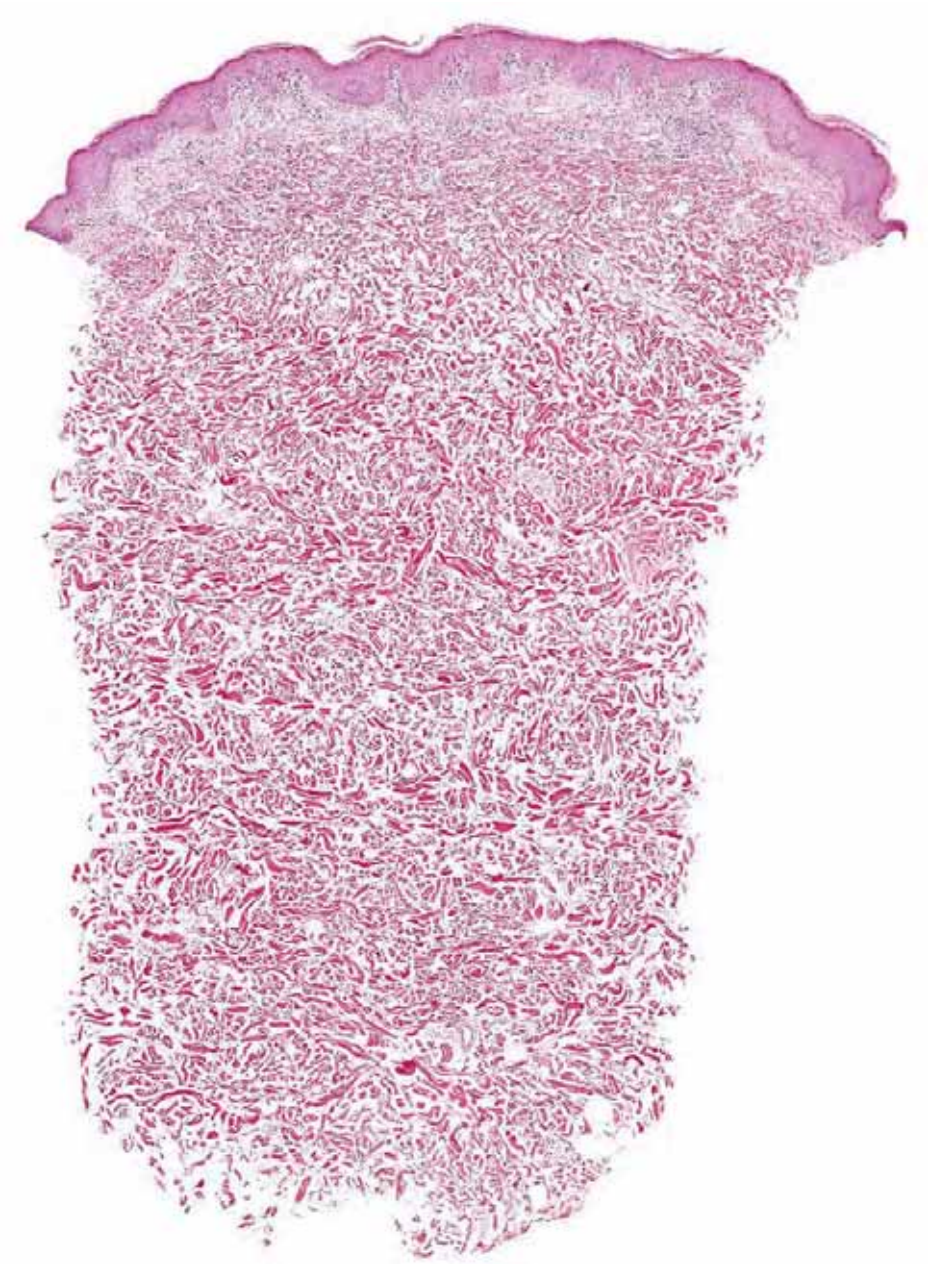
Case 34

F, 37. According to the patient painful, reddish papules on the right elbow for a few weeks.

Pseudolymphomatous molluscum contagiosum





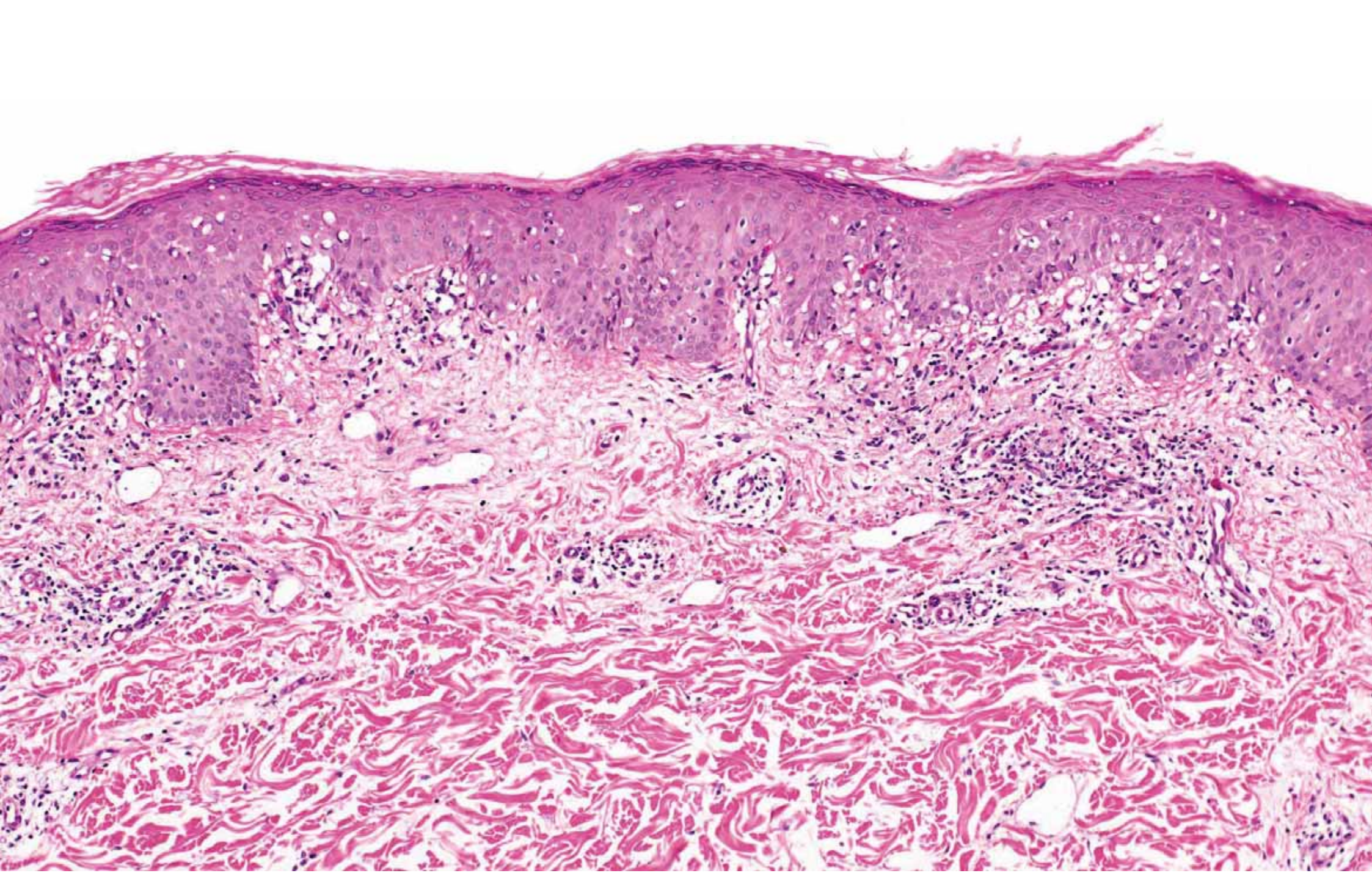


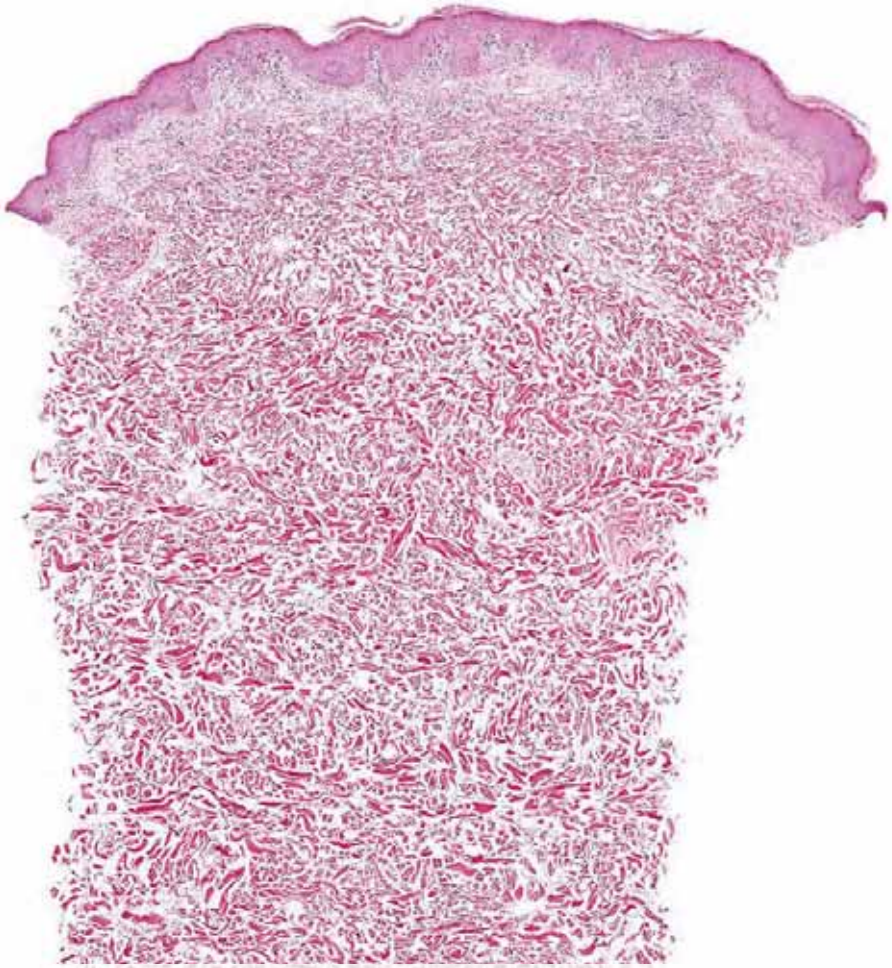
Case 35

M, 48. According to the patient skin lesions for >1 year. A previous biopsy was diagnosed as mycosis fungoides.
Managed for 2 months with UVB 311nm.

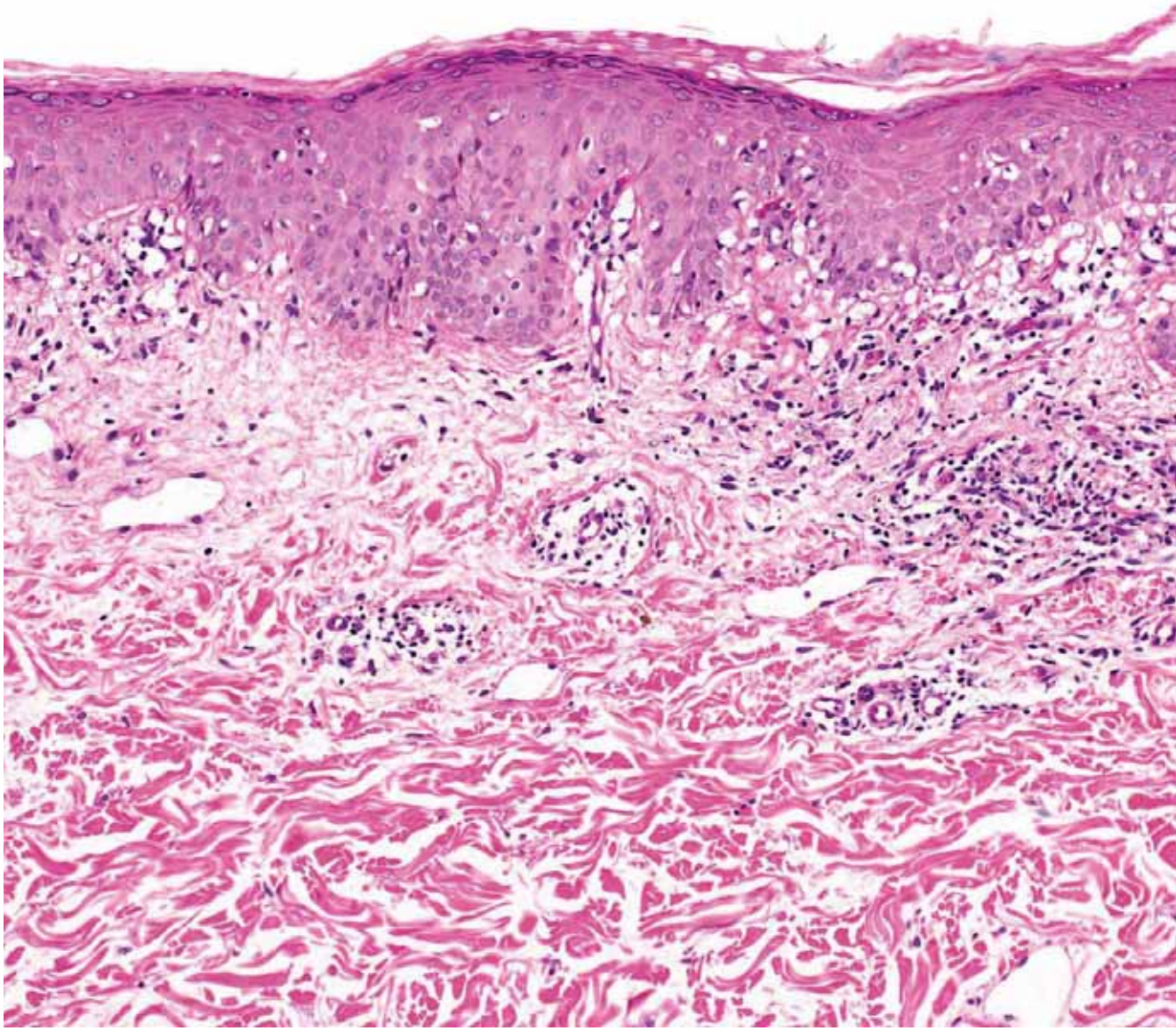
CASUAL LOC CASUAL LOC

CASUAL LOOK

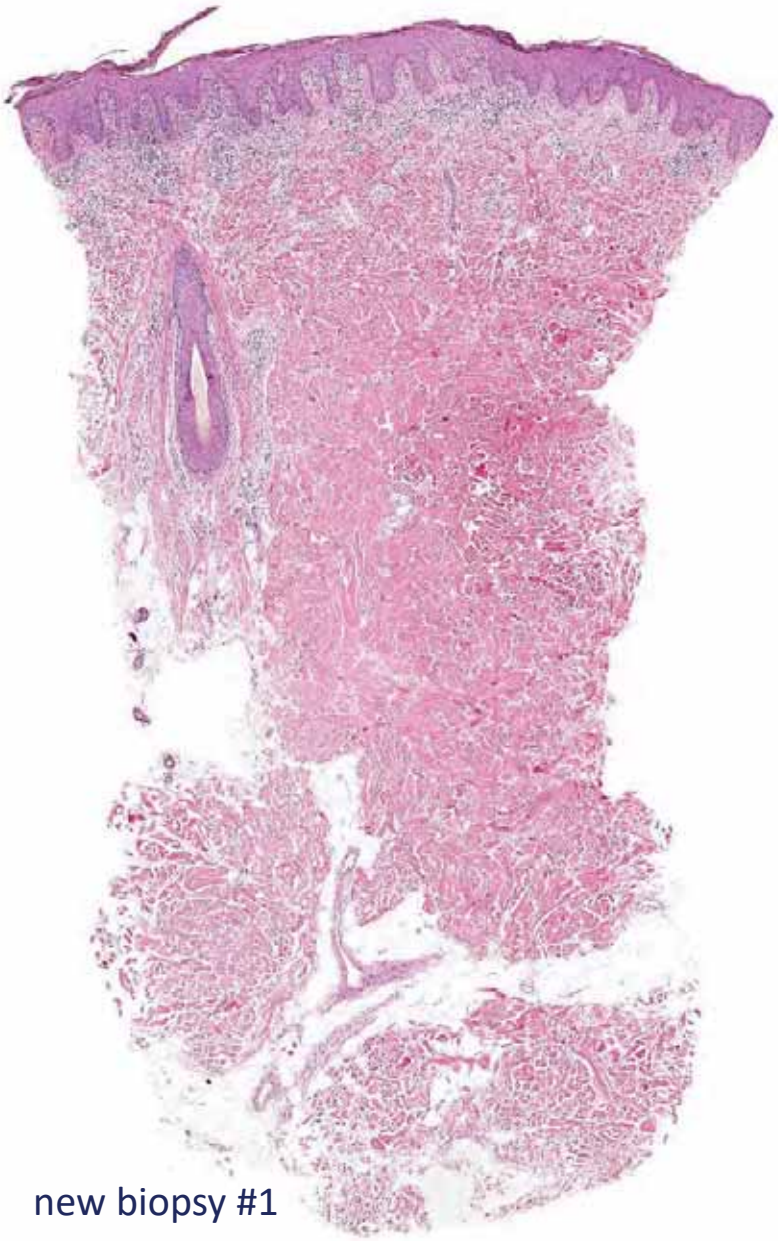




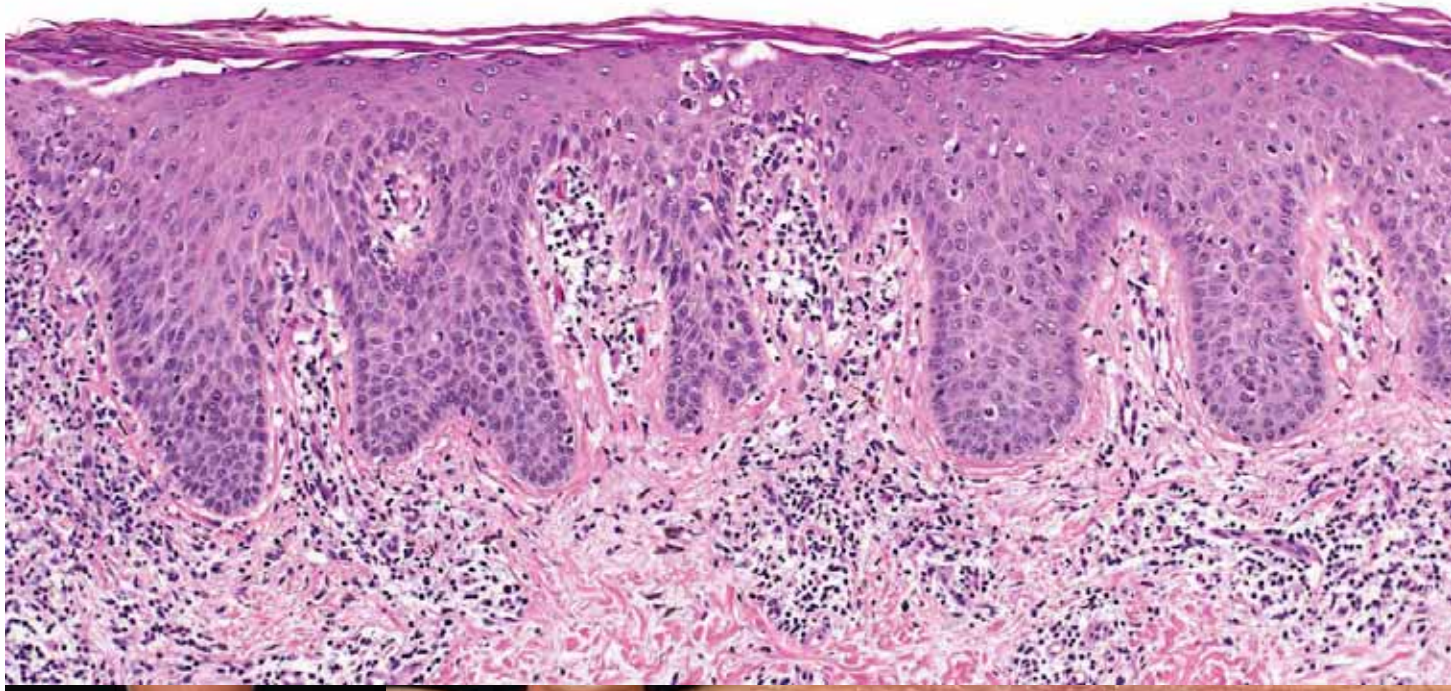
Early
mycosis fungoides

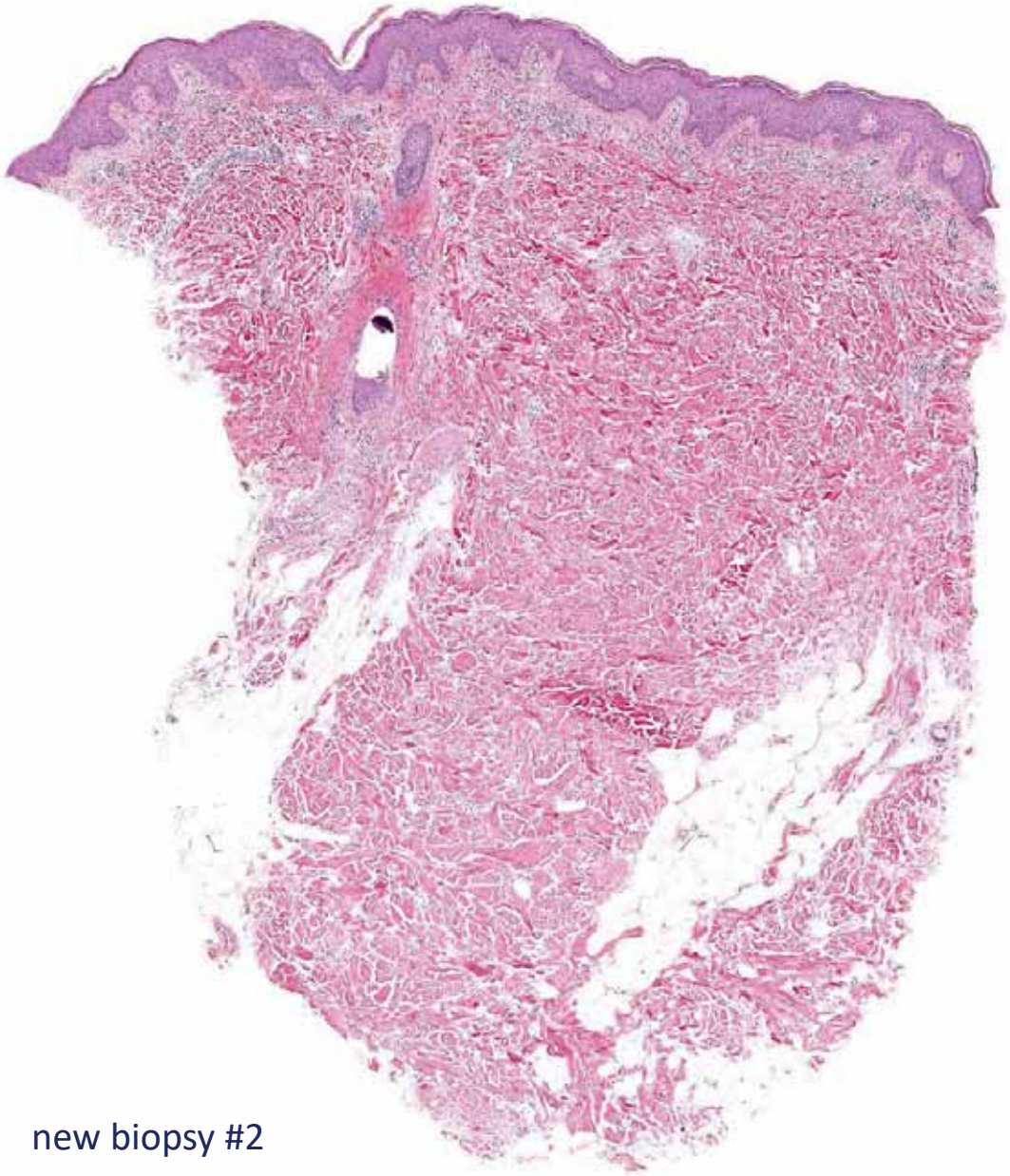


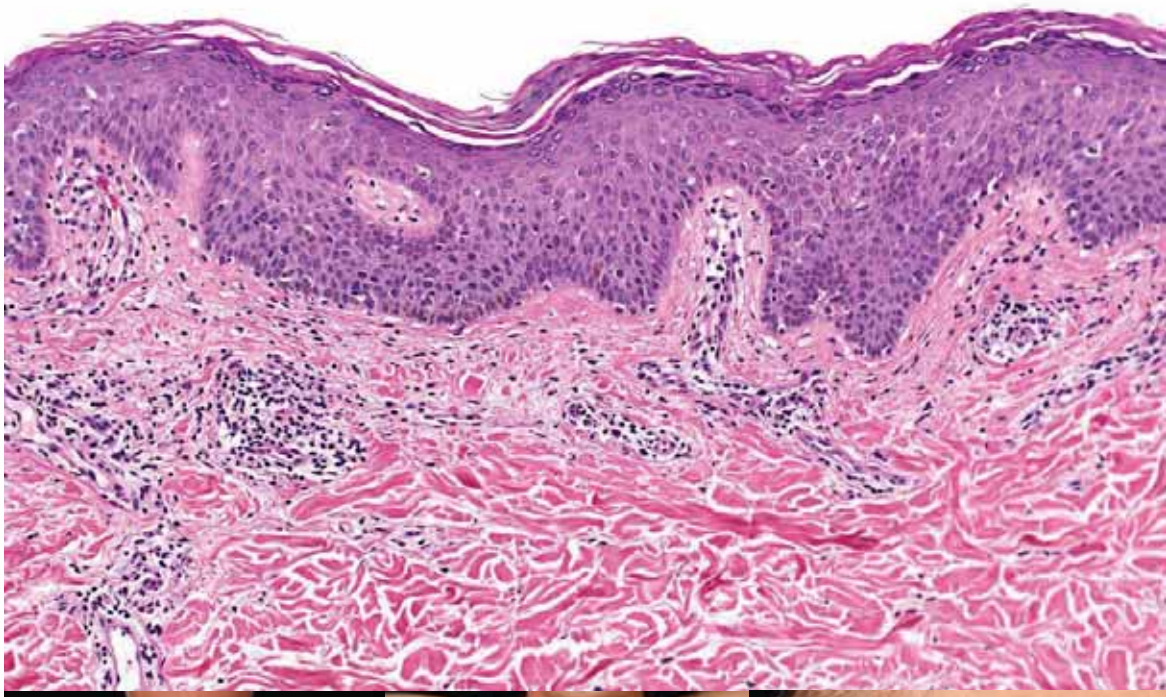
1st biopsy taken one year earlier (no clinical pictures)



new biopsy #1

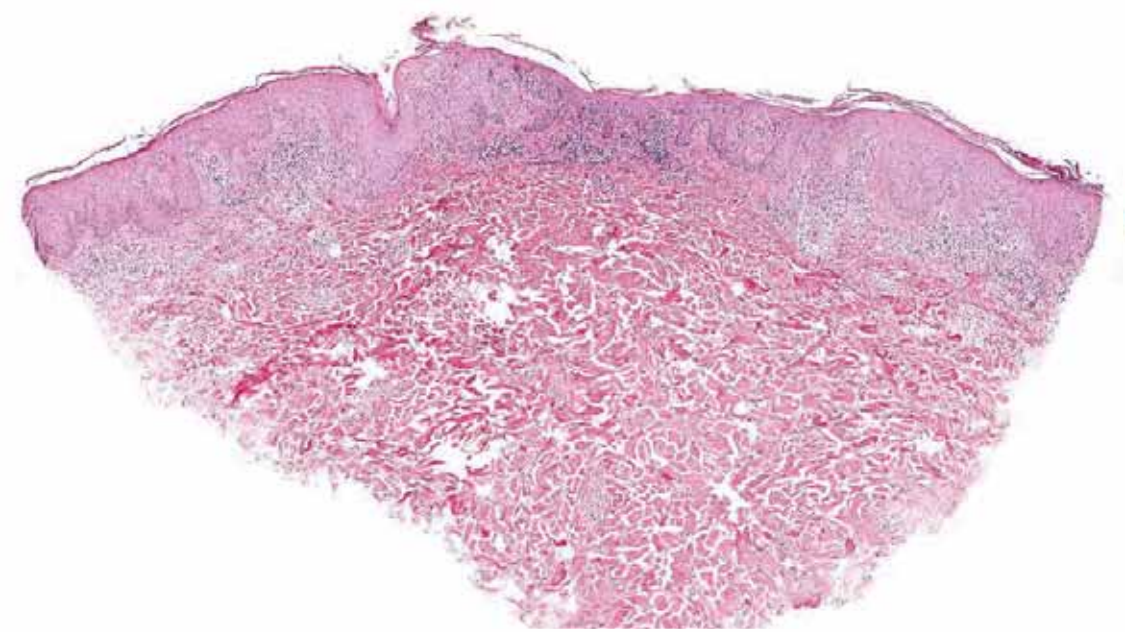


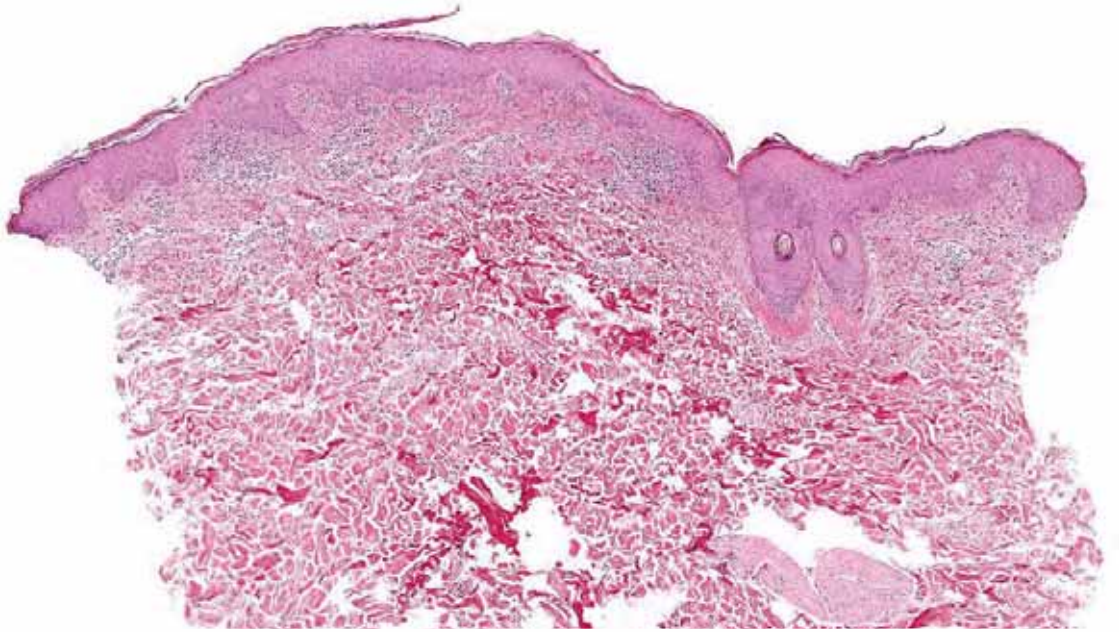


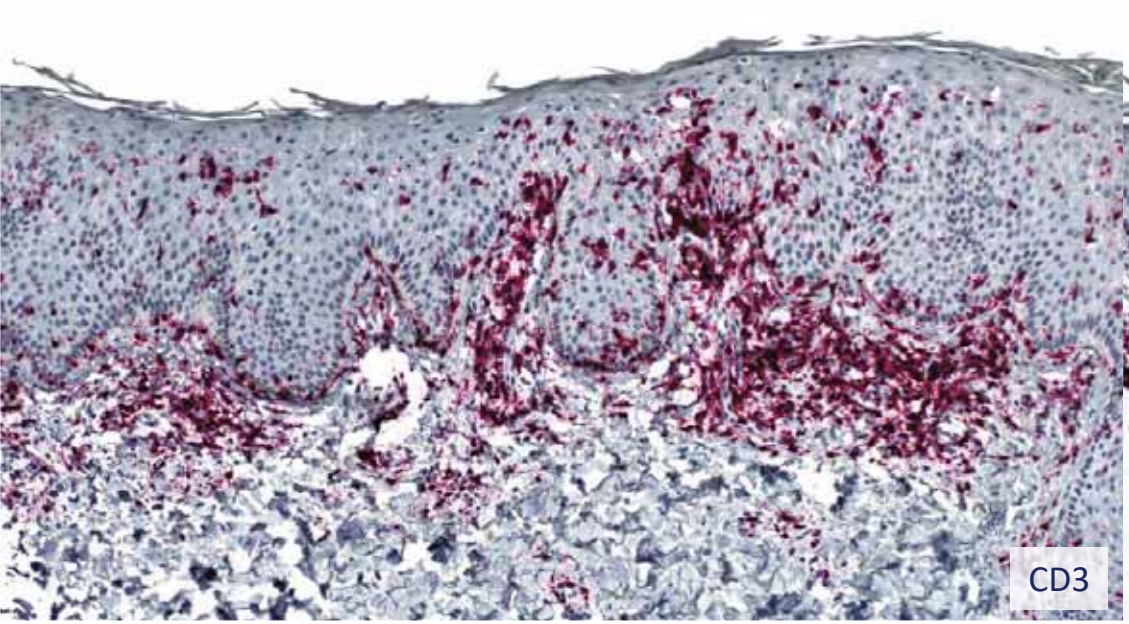


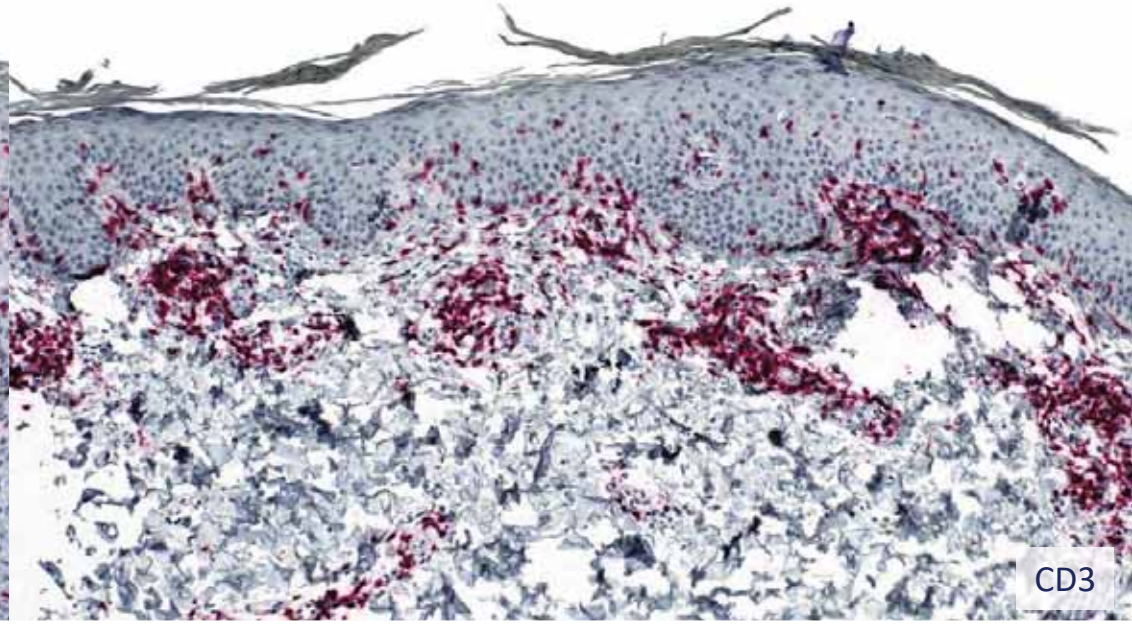
new biopsy #2

2 years later (2 new biopsies taken)

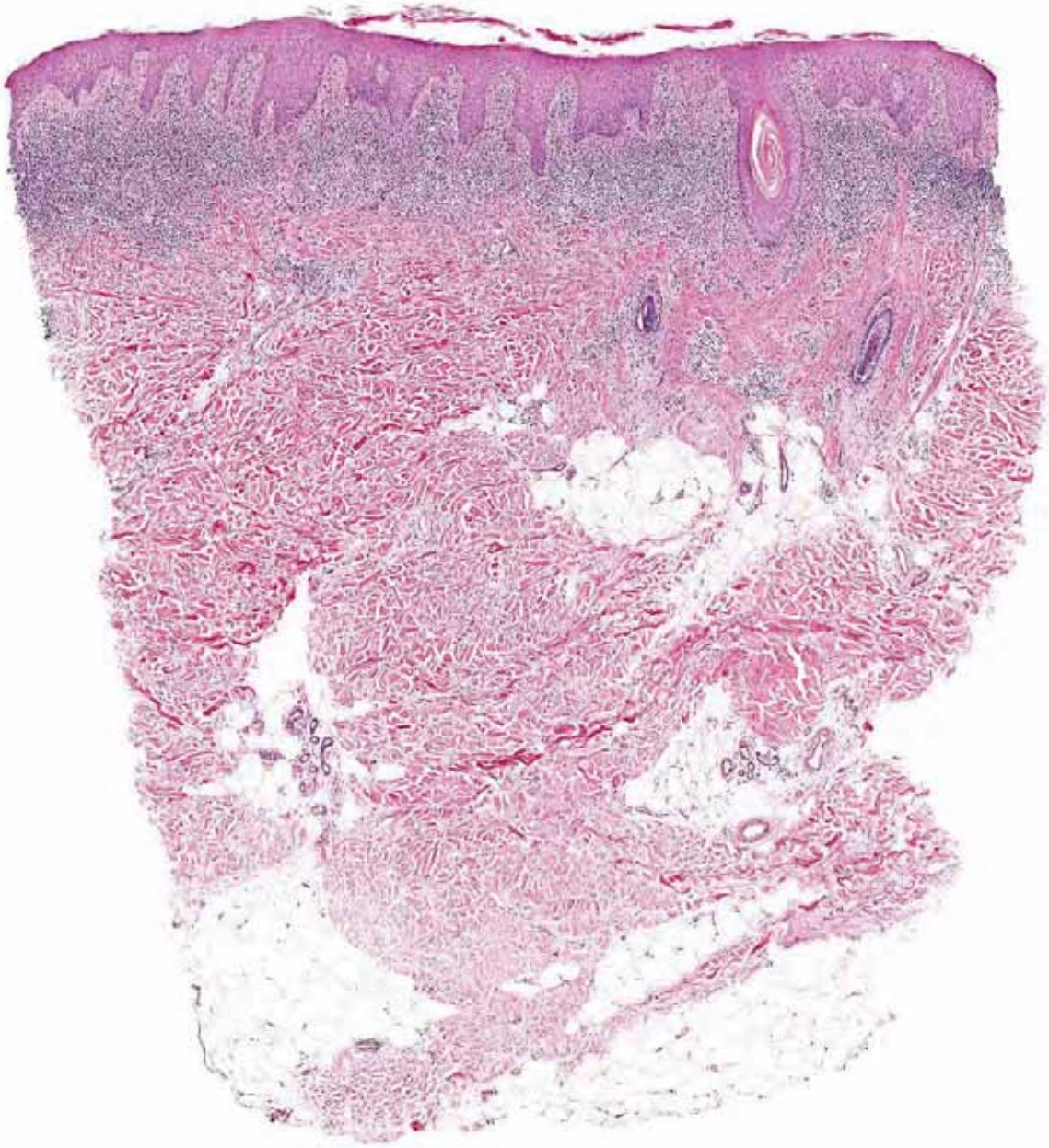


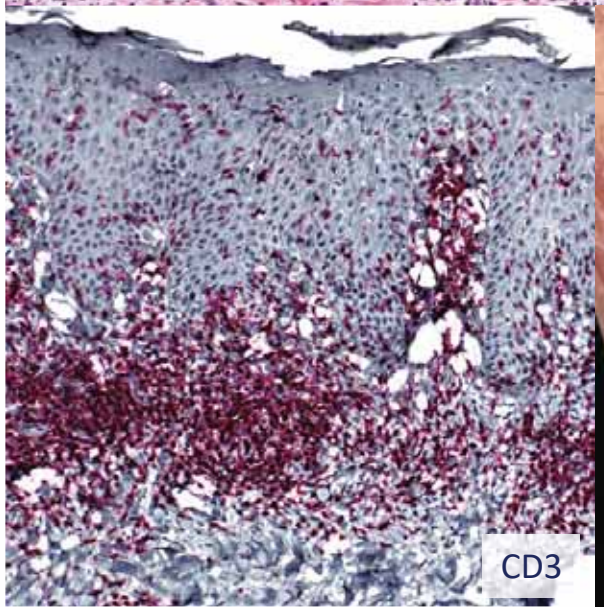


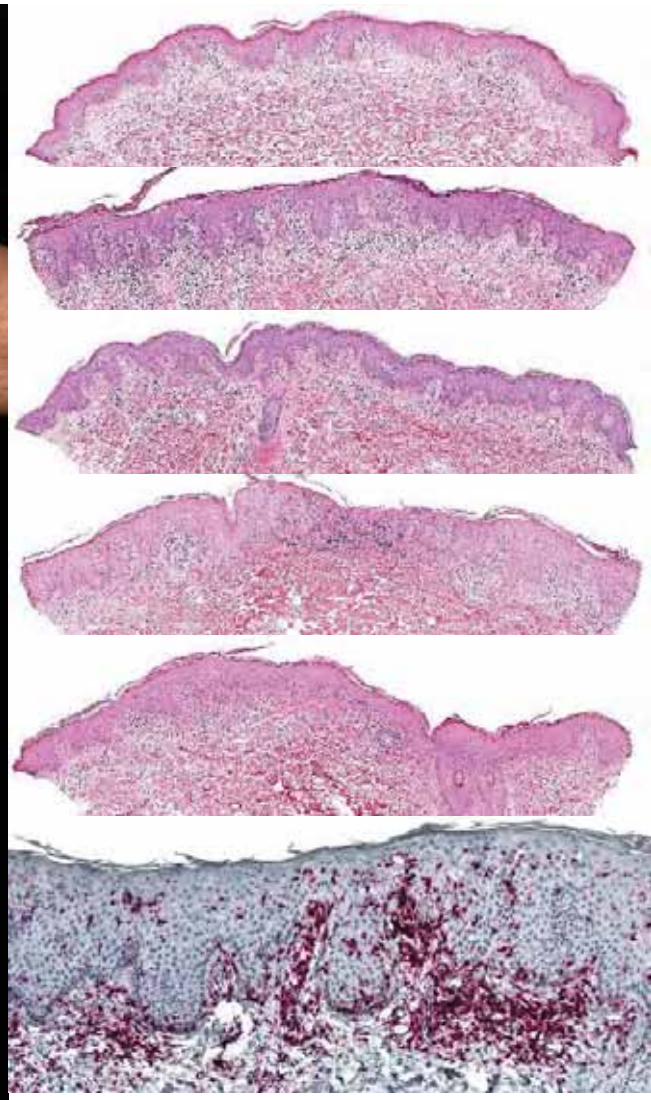

CD3


CD3

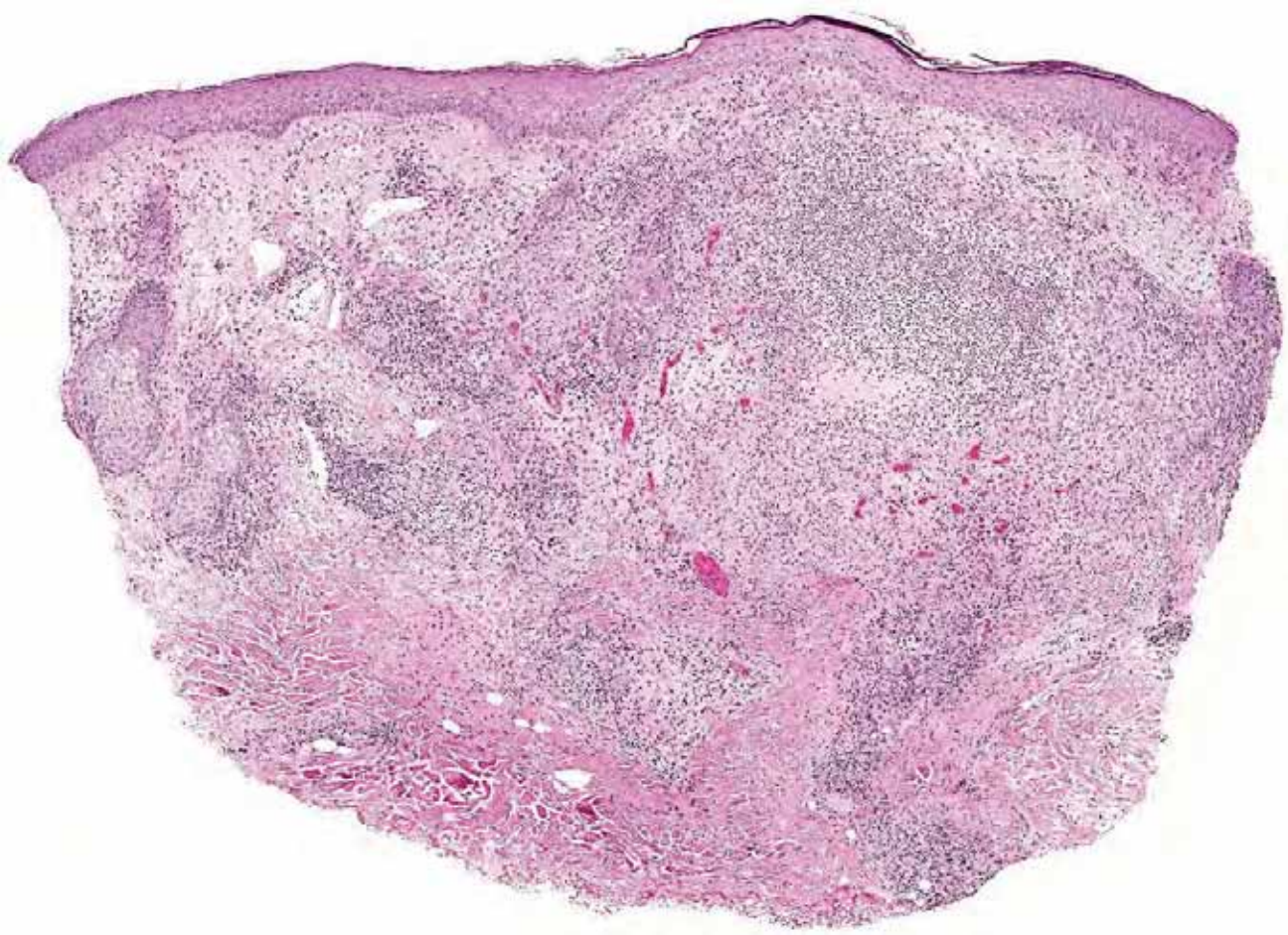
1 more year later (1 new biopsy taken)

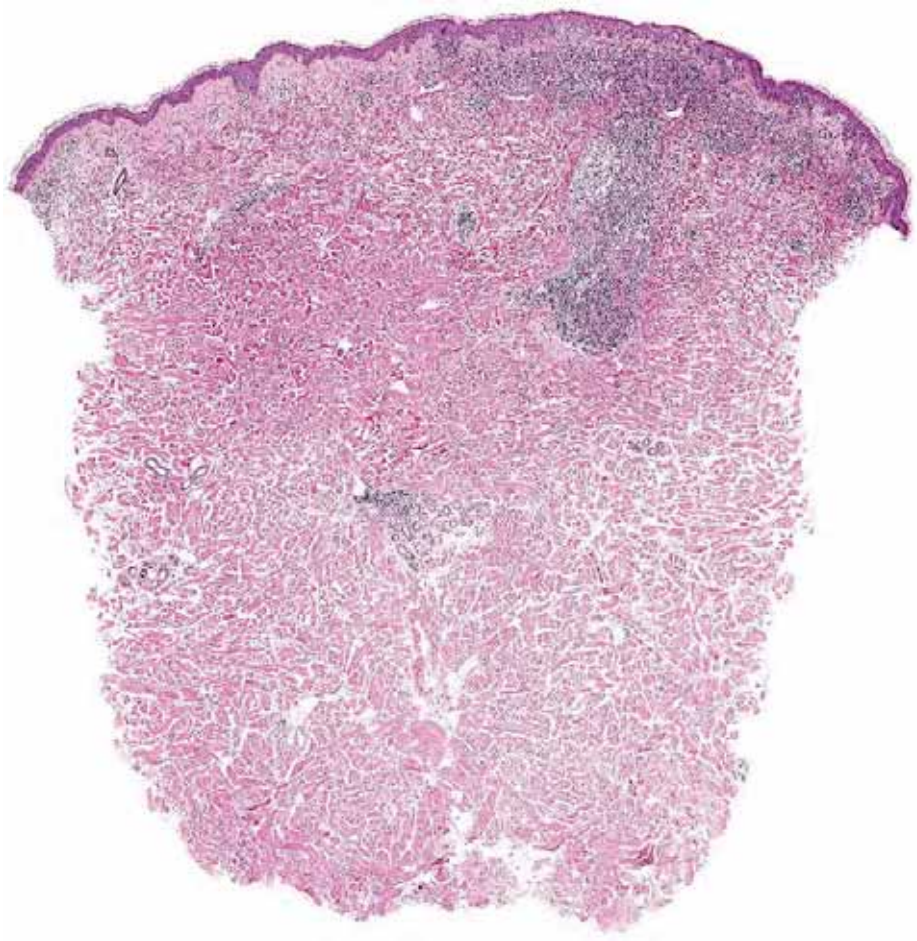



CD3



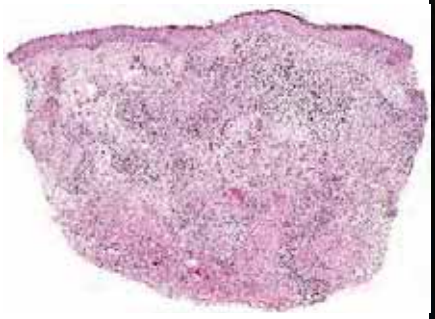
A total of 5 biopsies showing neither a band-like infiltrate nor Darier's nests, the only diagnostic criterion being represented by the presence of disproportionate epidermotropism.

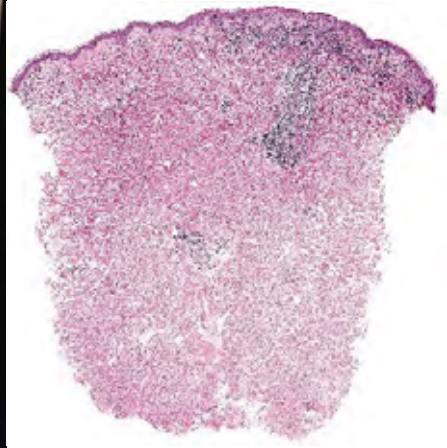


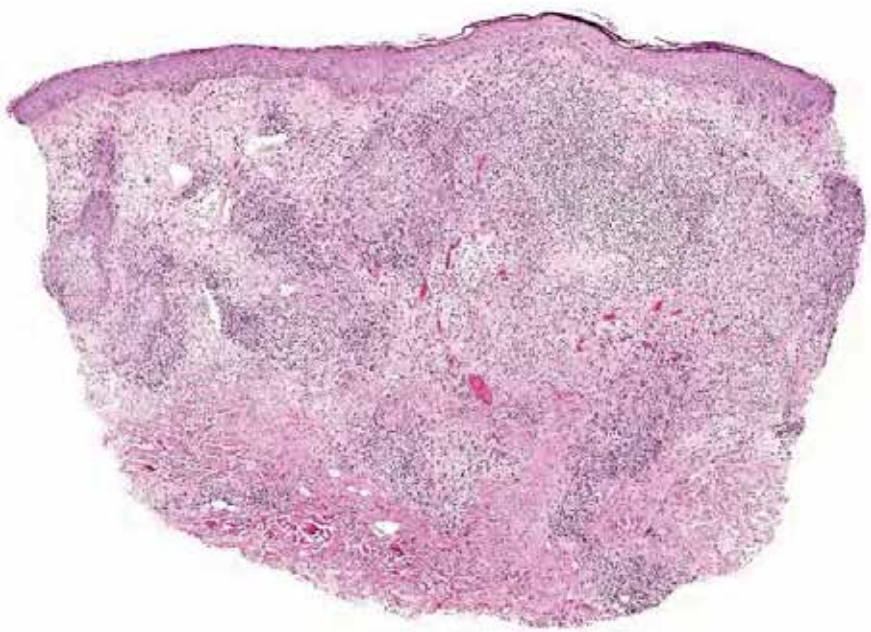


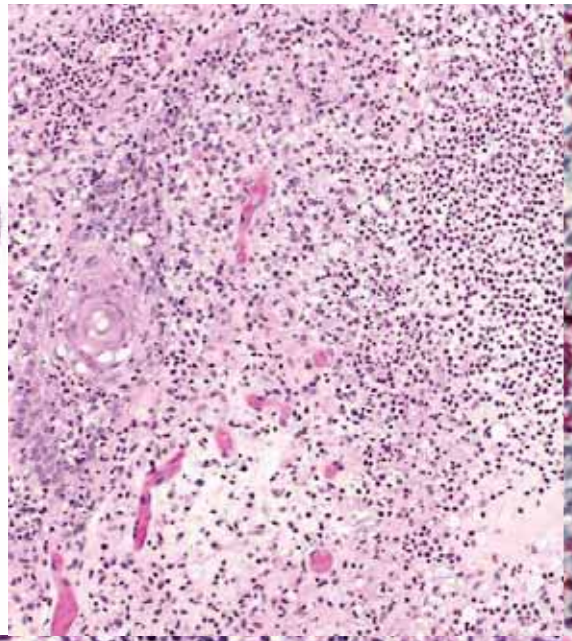
Case 36

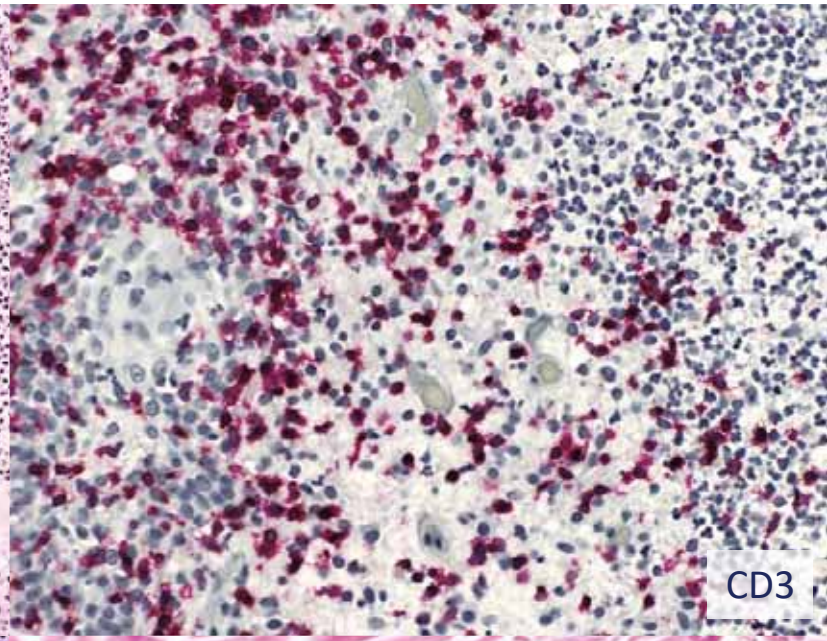
M, 61. 6-year history of adnexotropic mycosis fungoides. Onset of new pustular lesions.

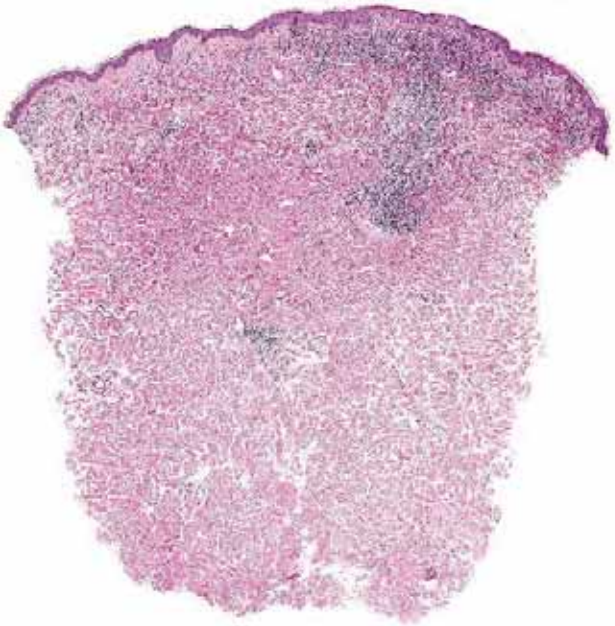


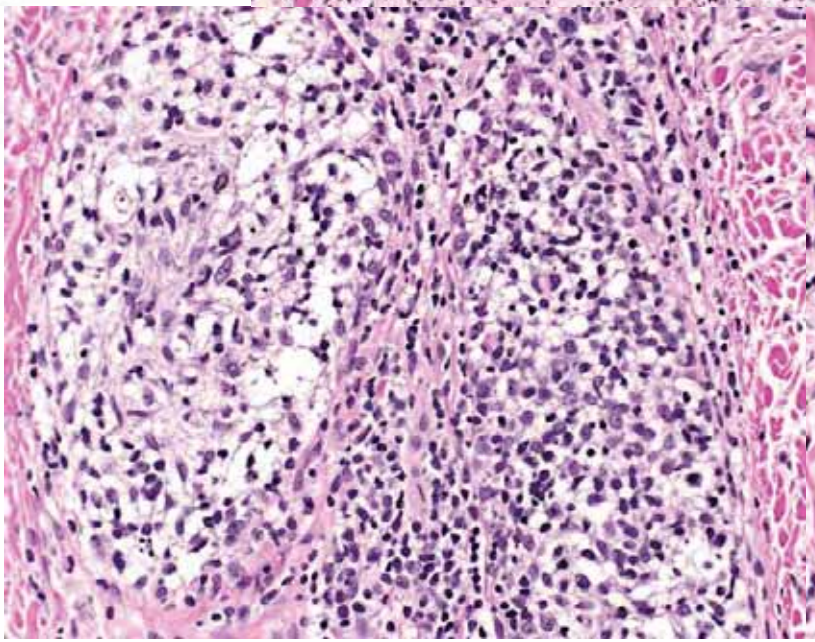


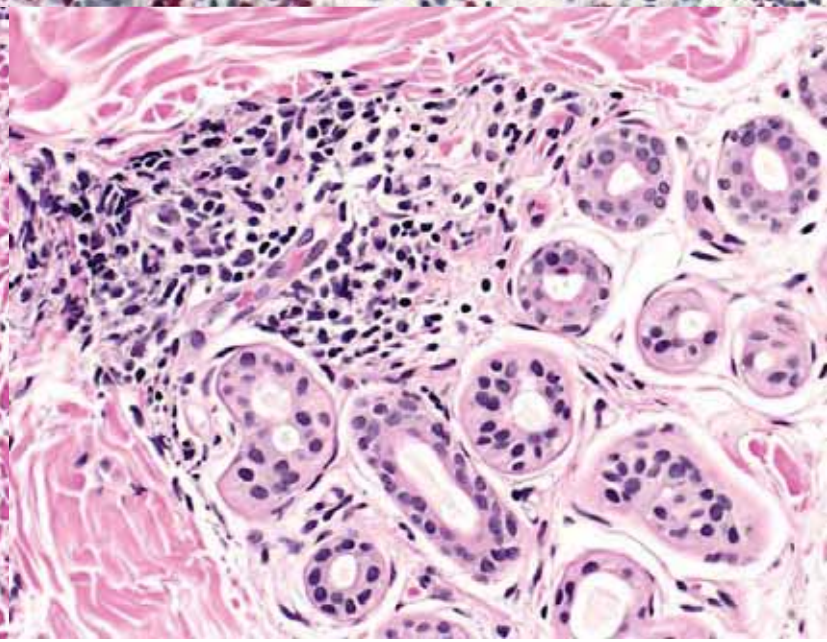




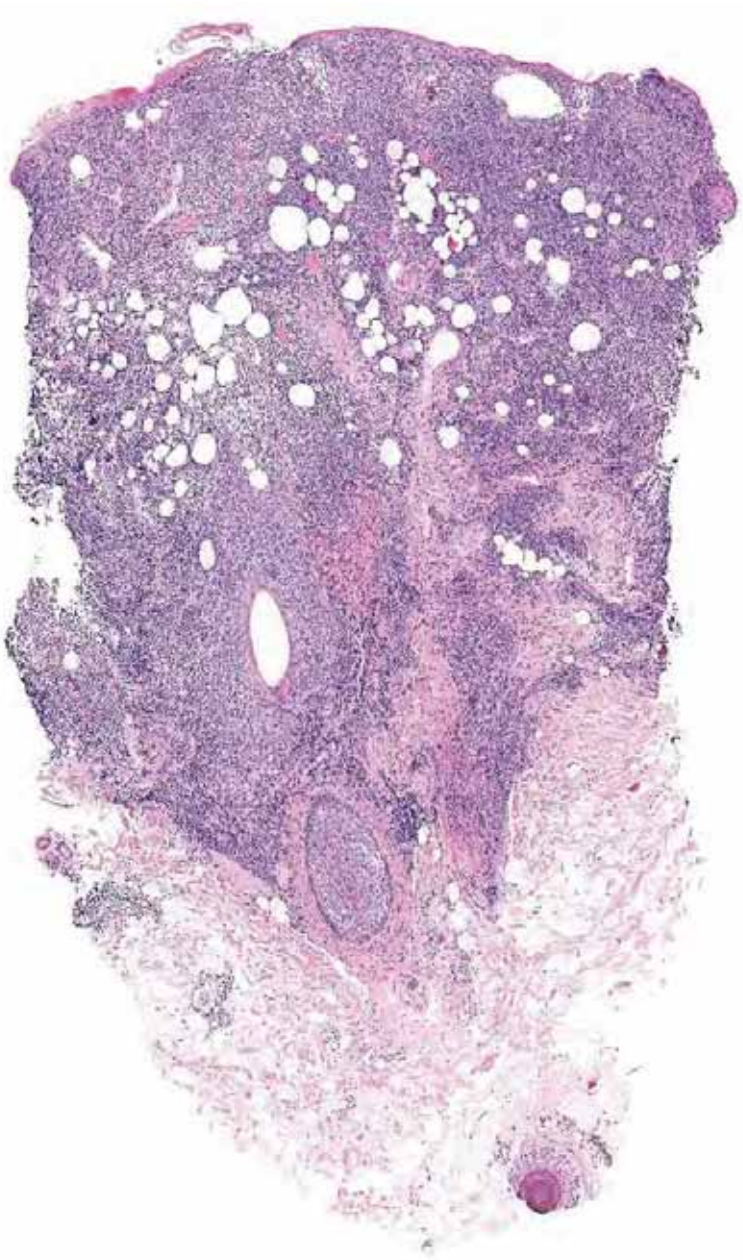

CD3

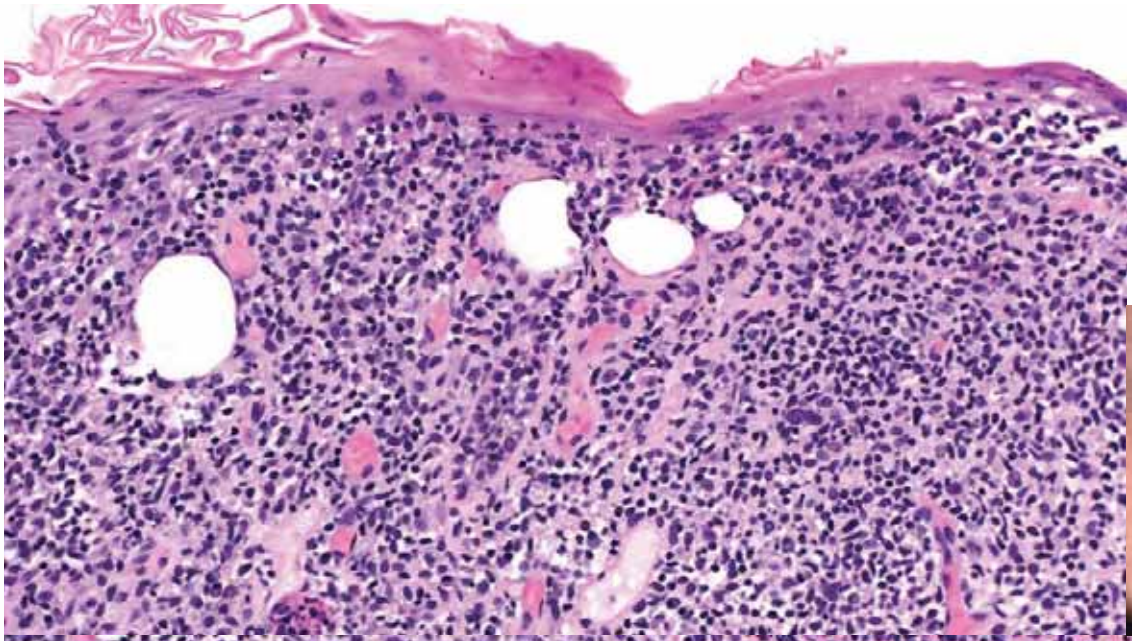


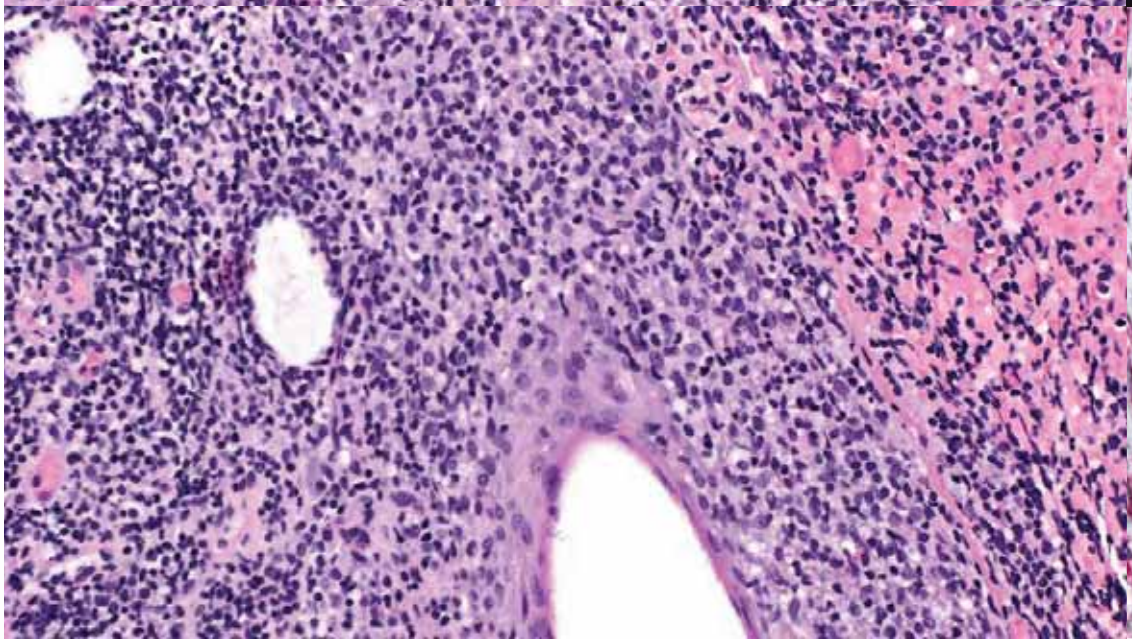


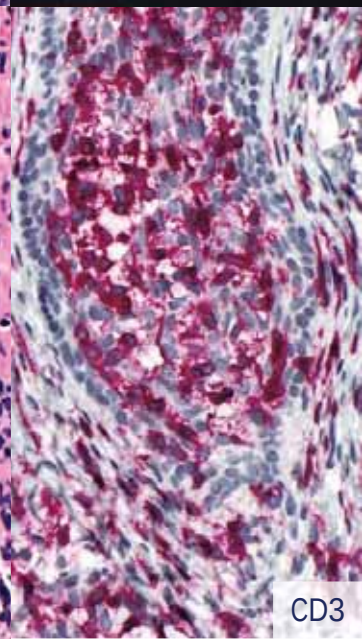


6 years previously









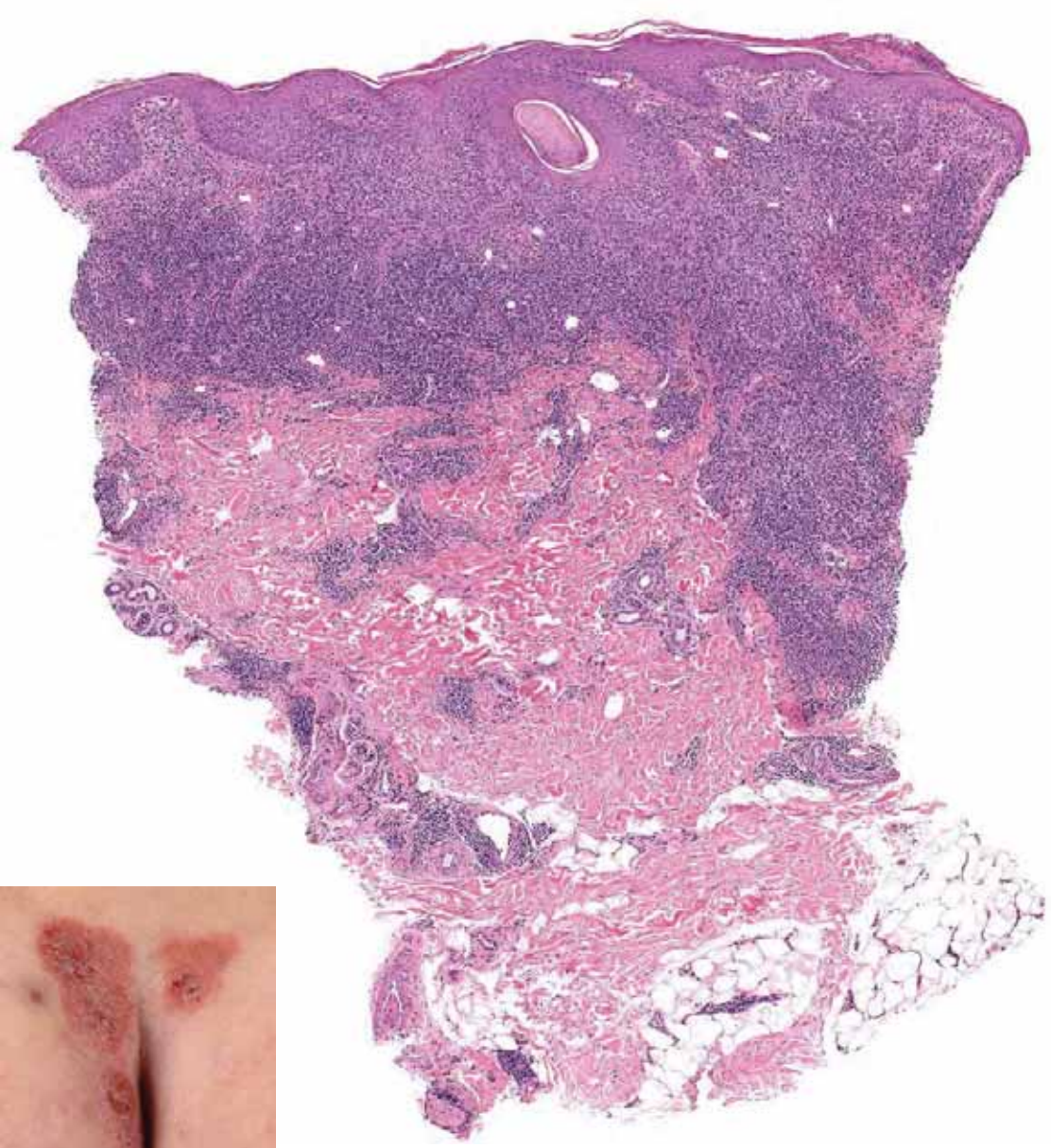
CD3

2 months later
8 months later

17 months later (gel PUVA)

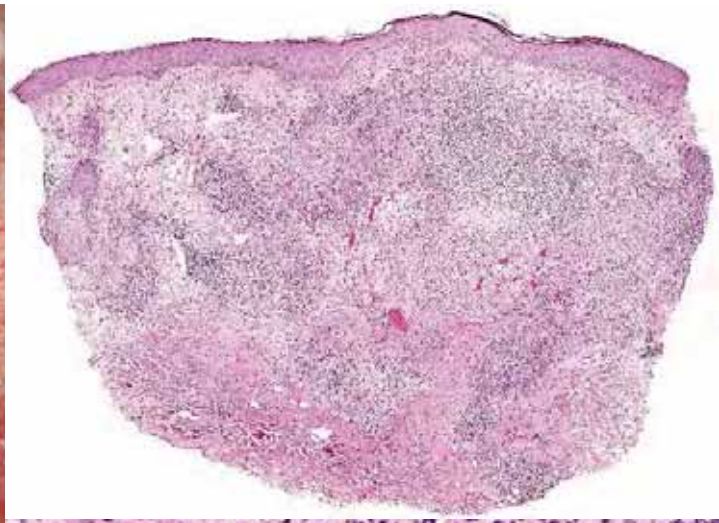
20 months later

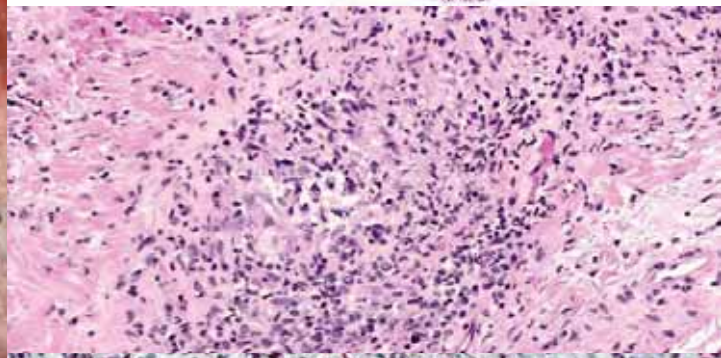
42 months later

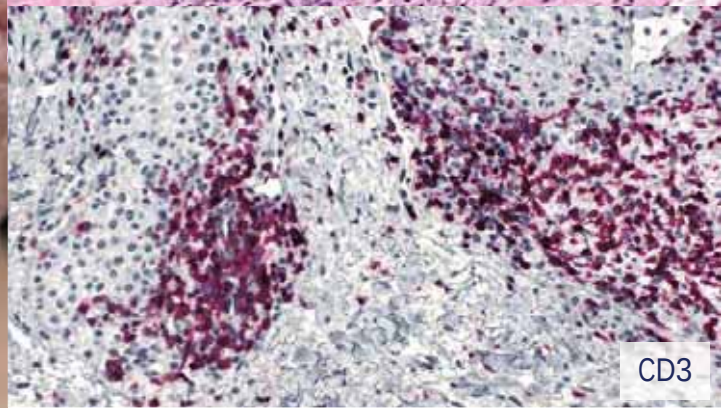


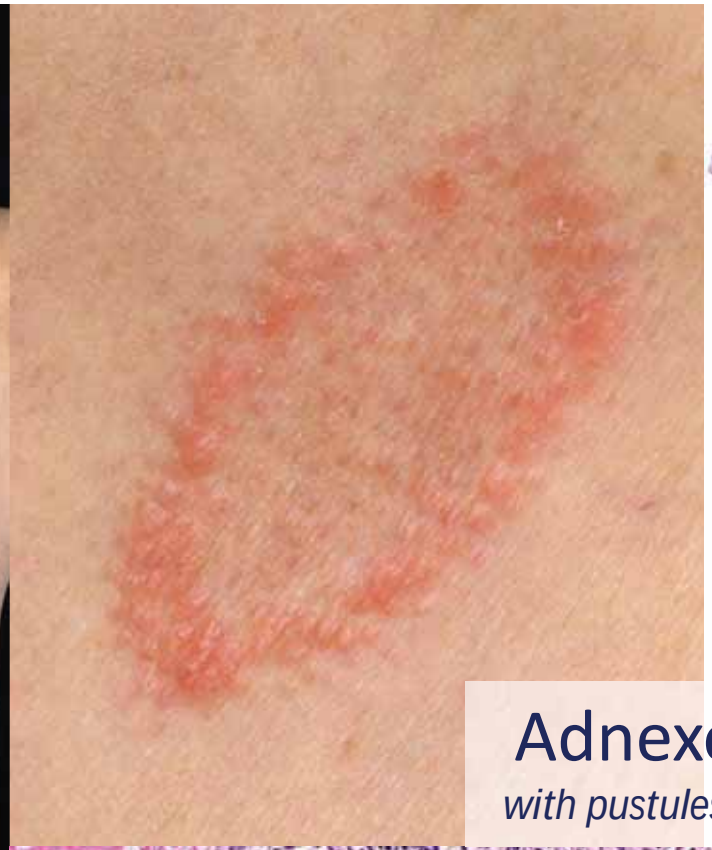
62 months later

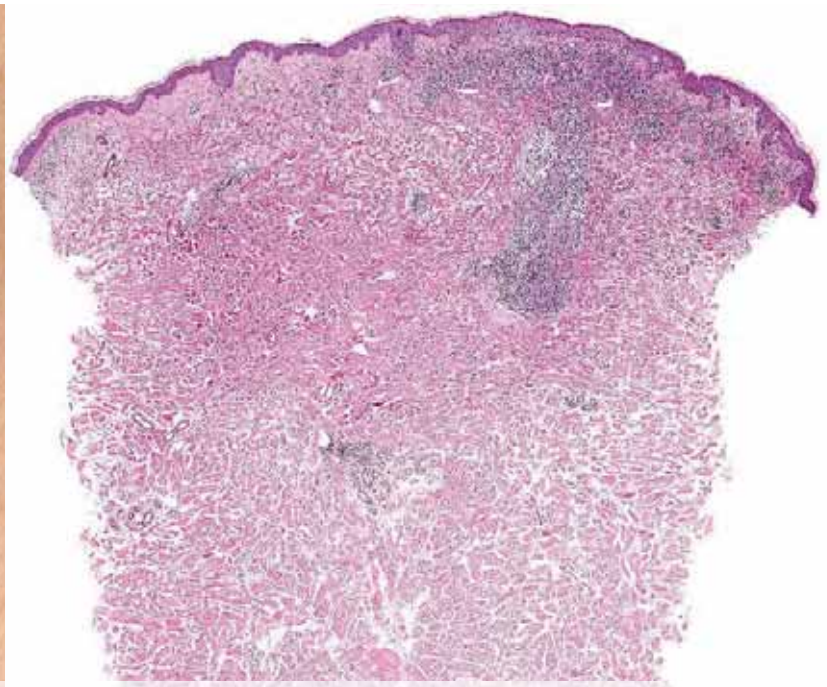
72 months later





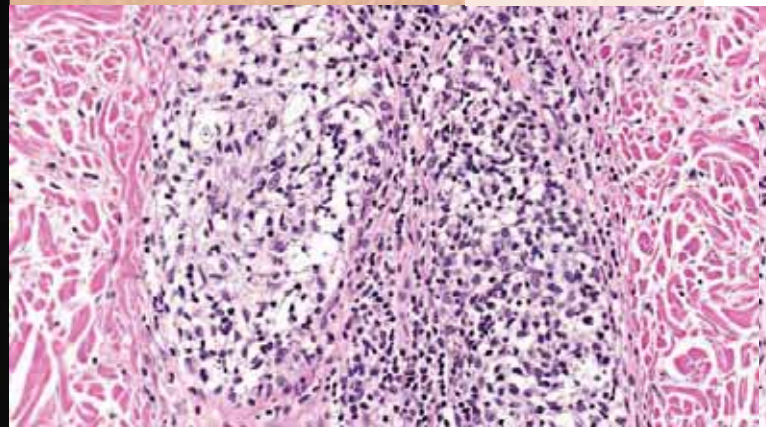


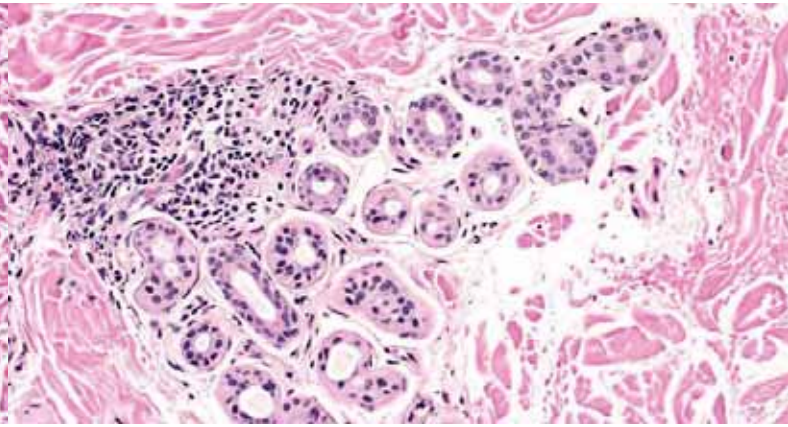


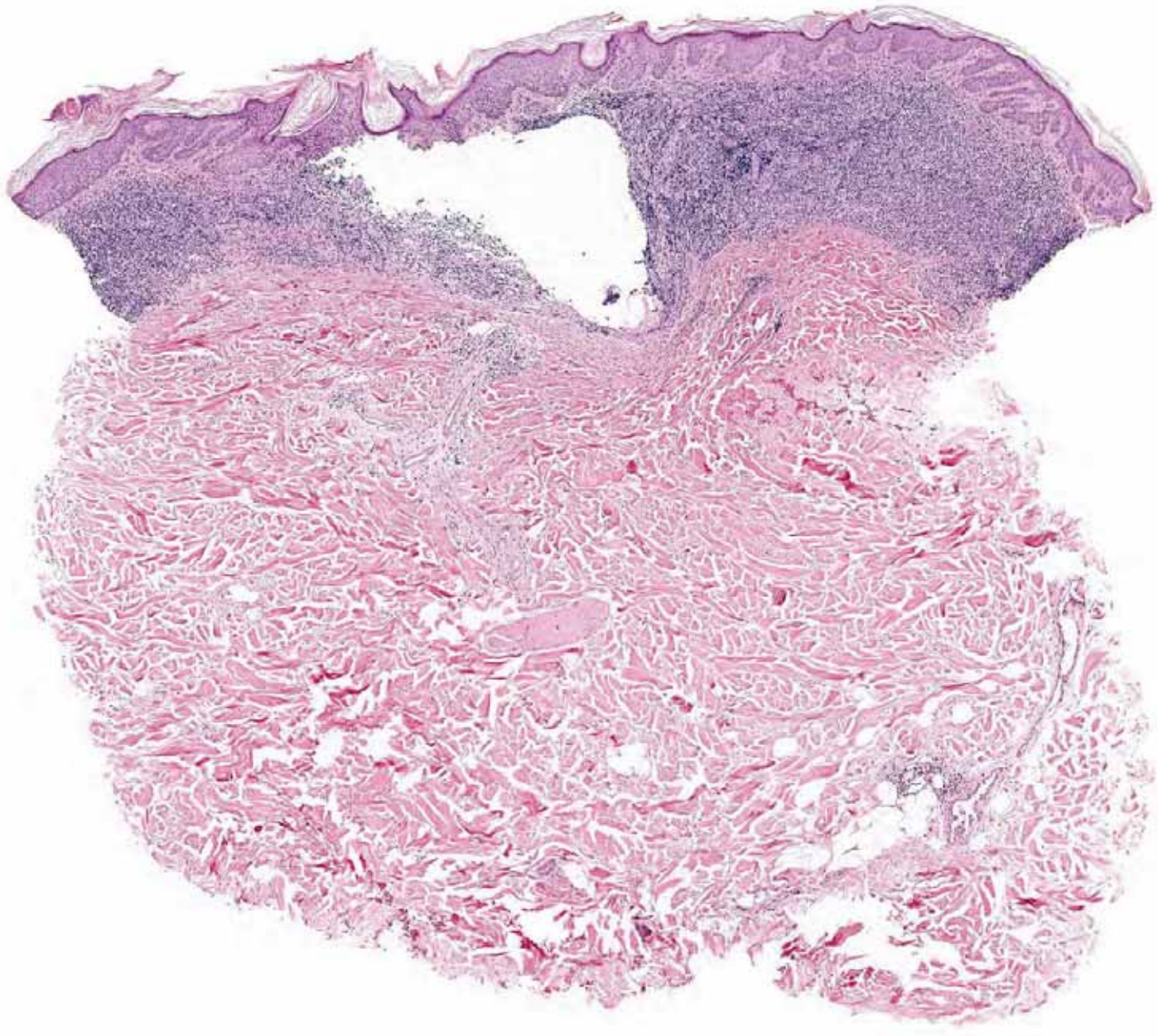


Adnexotropic mycosis fungoides

with pustules ("pustular MF"), starting with a solitary lesion

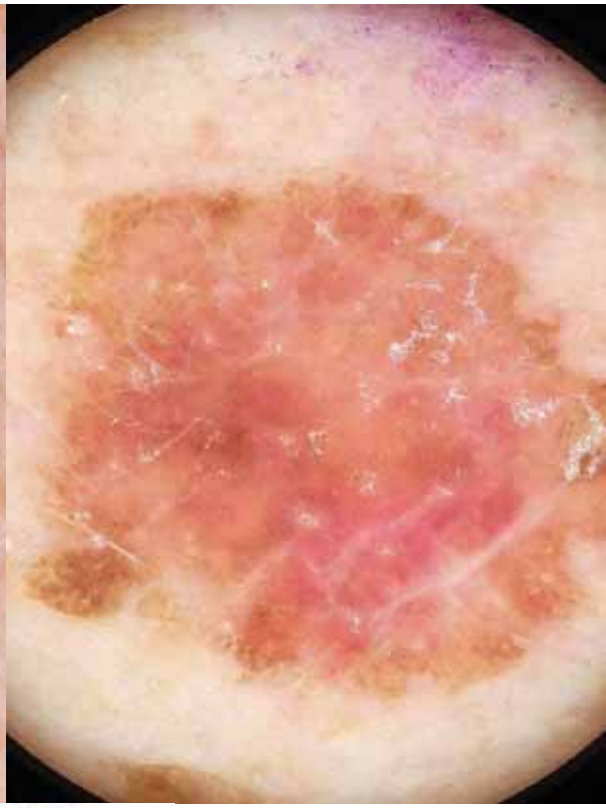


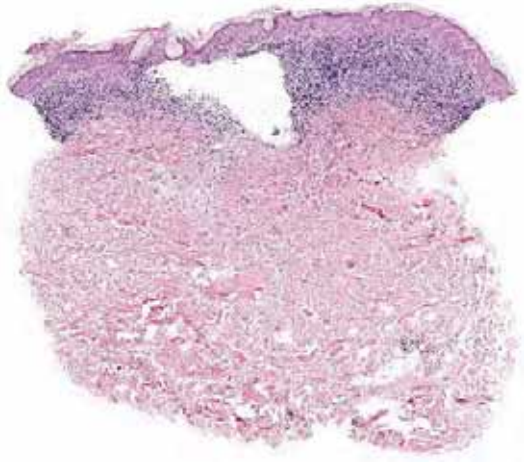


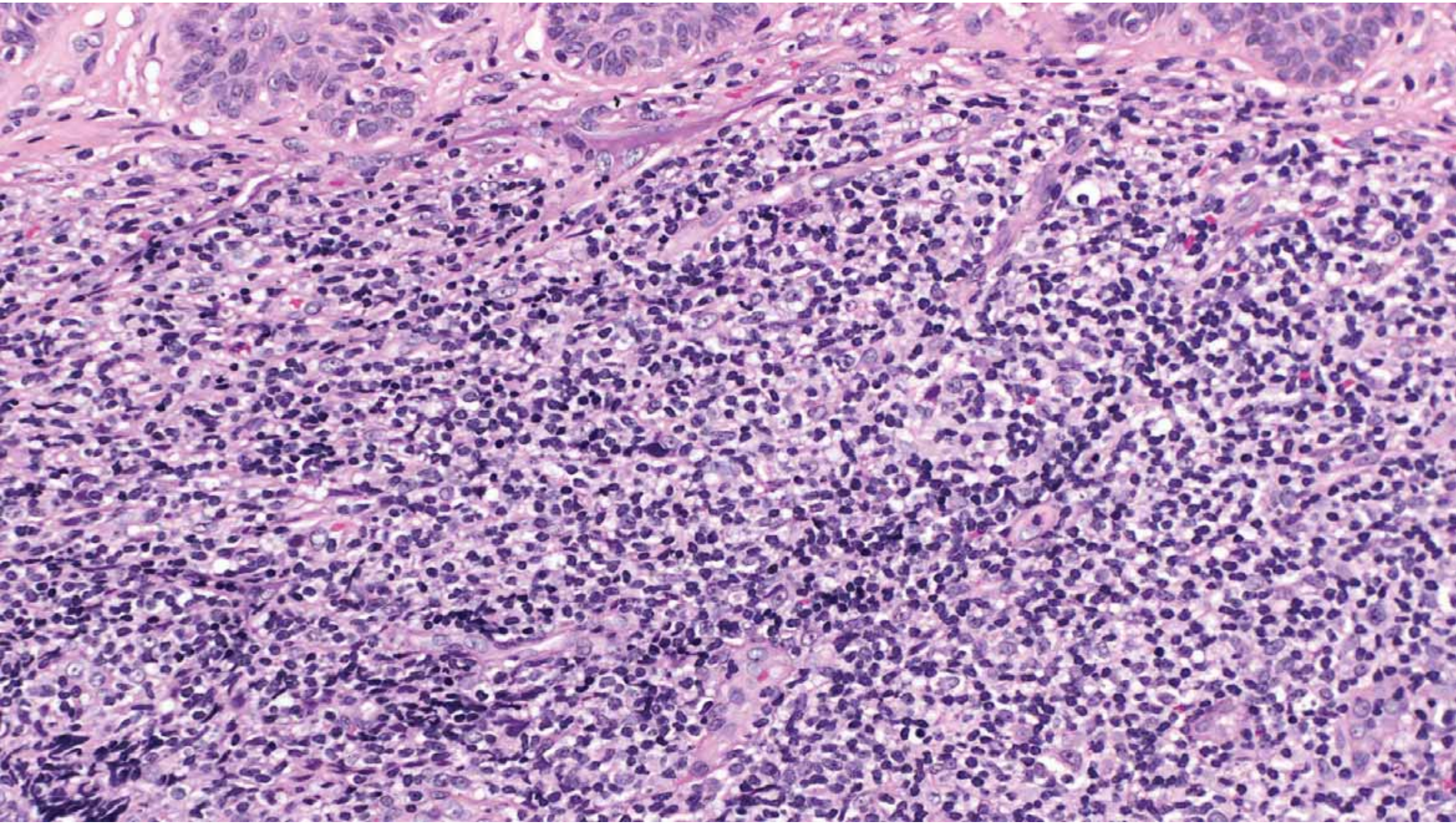


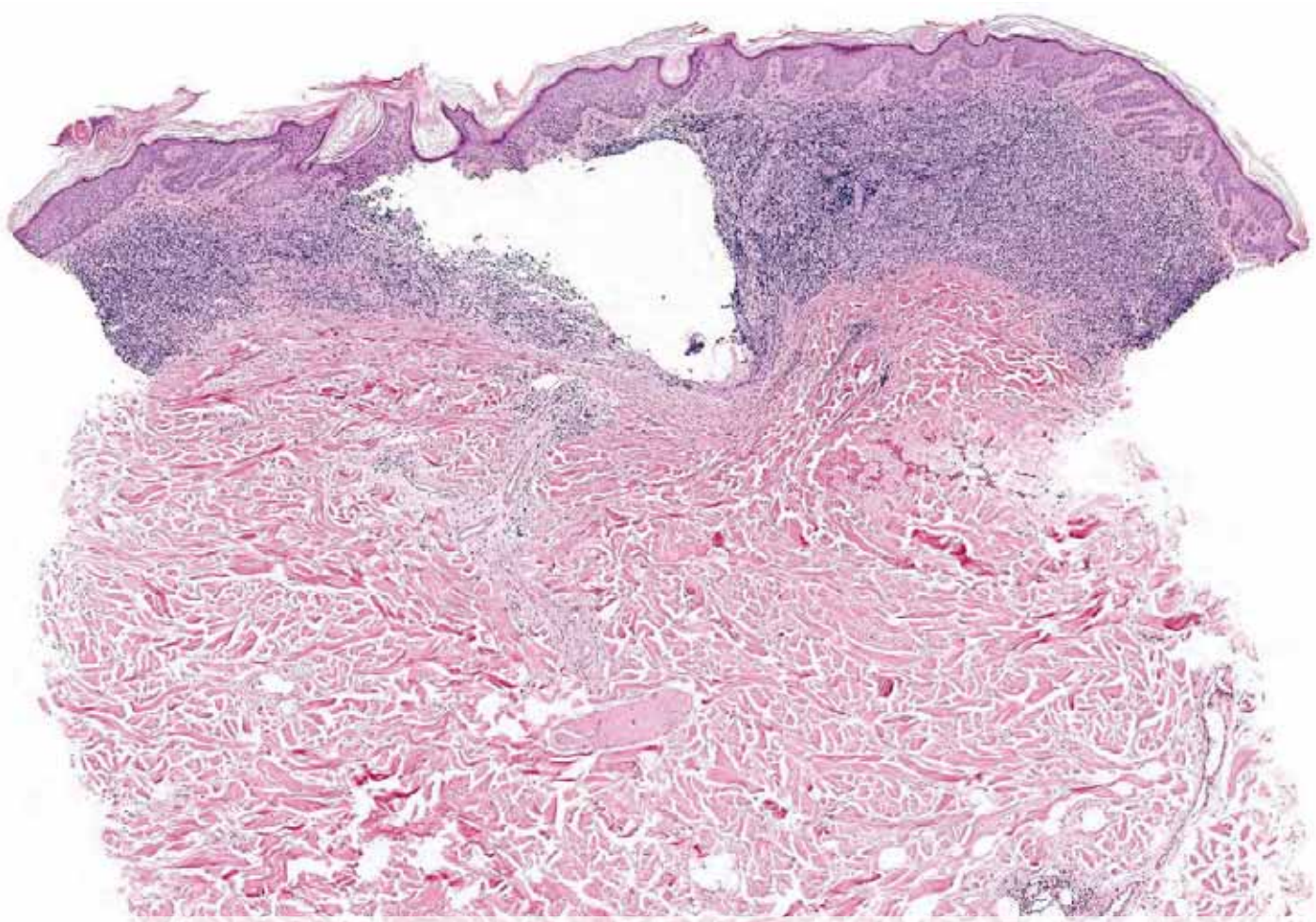
Case 37

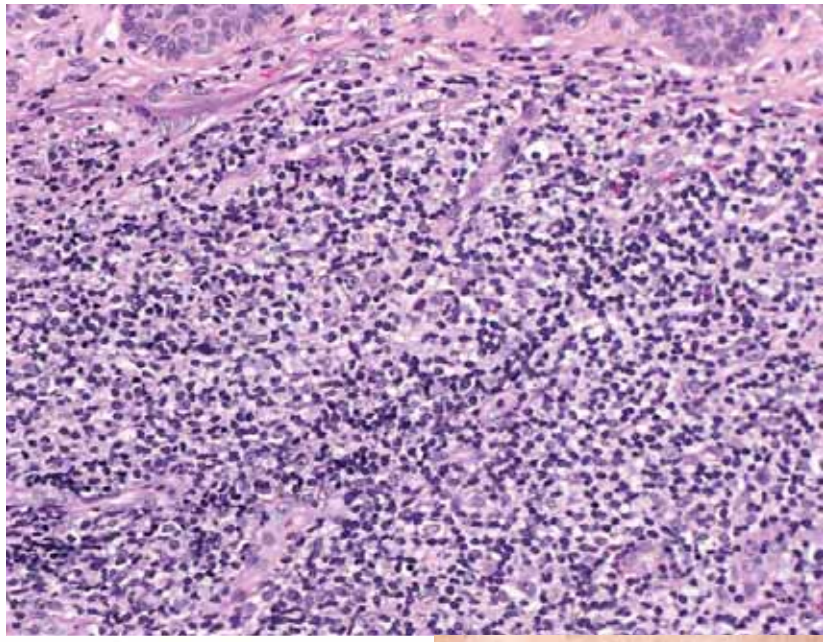
M, 79. History of non-melanoma skin cancers. According to the patient "new" lesion on the right back (not mentioned in the chart 16 months previously).

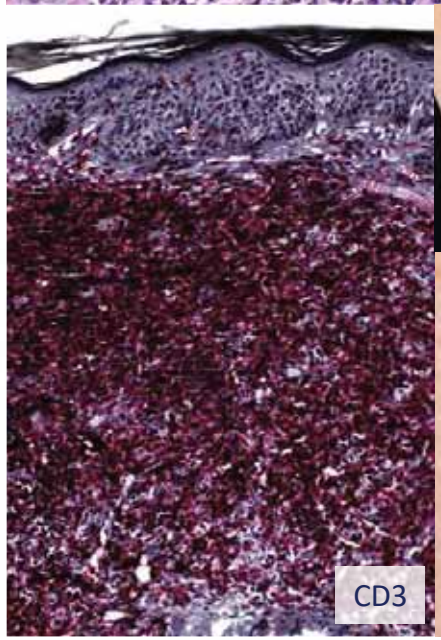


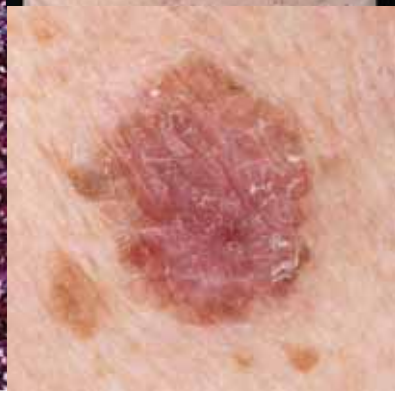




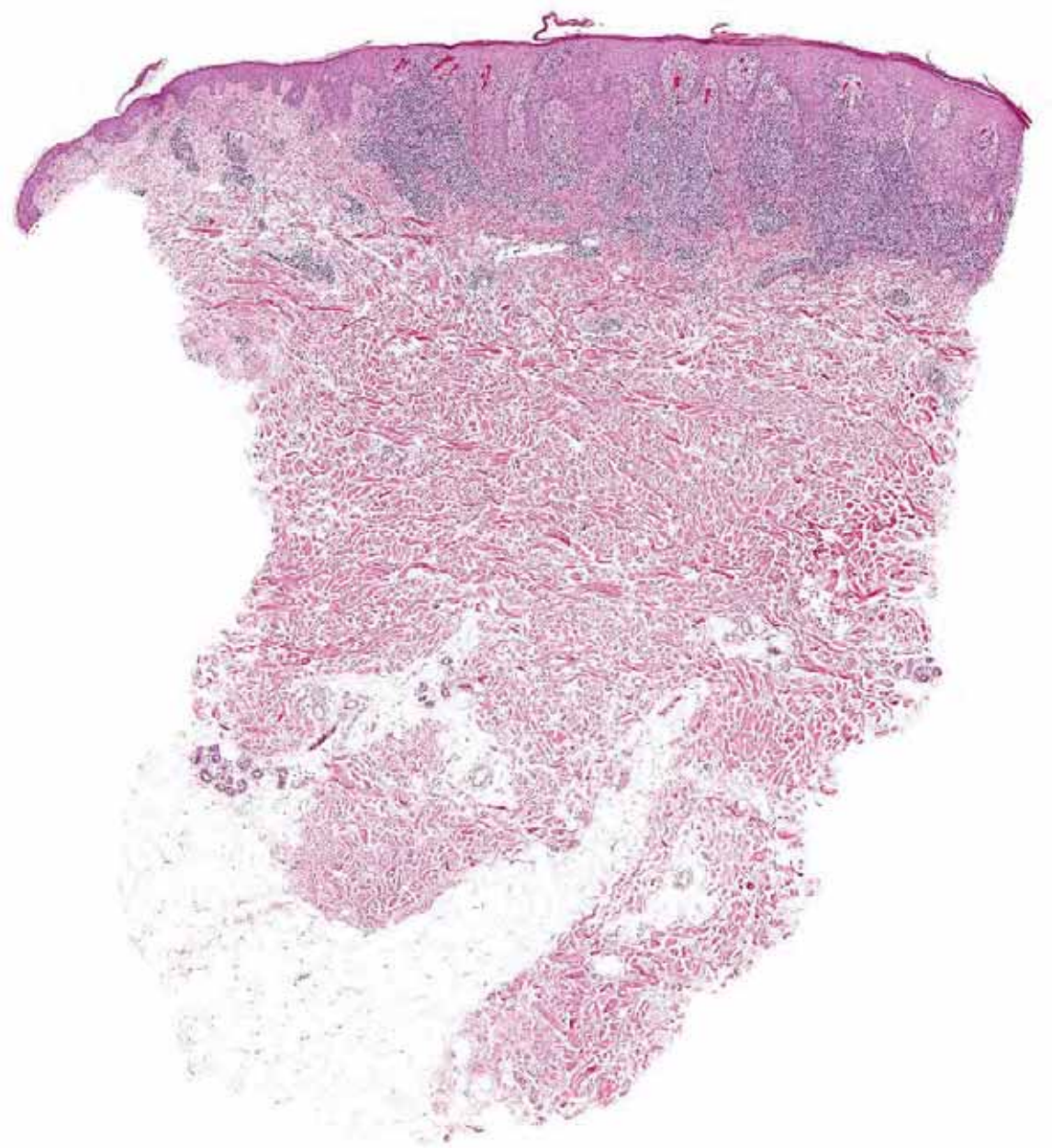






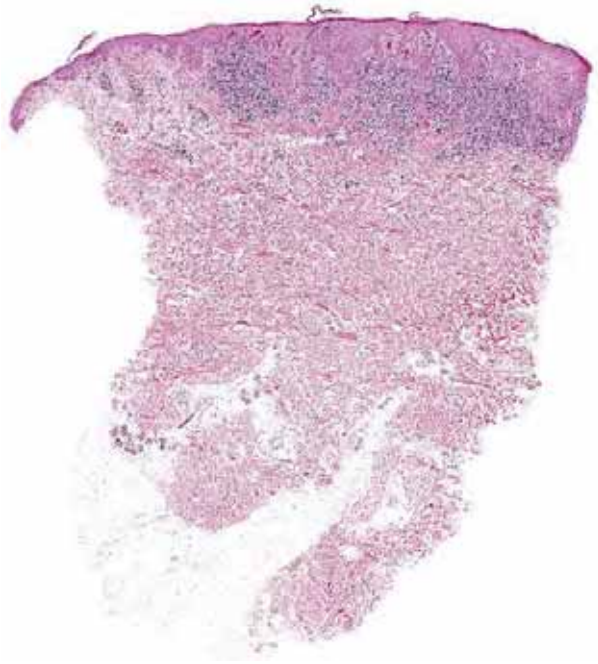


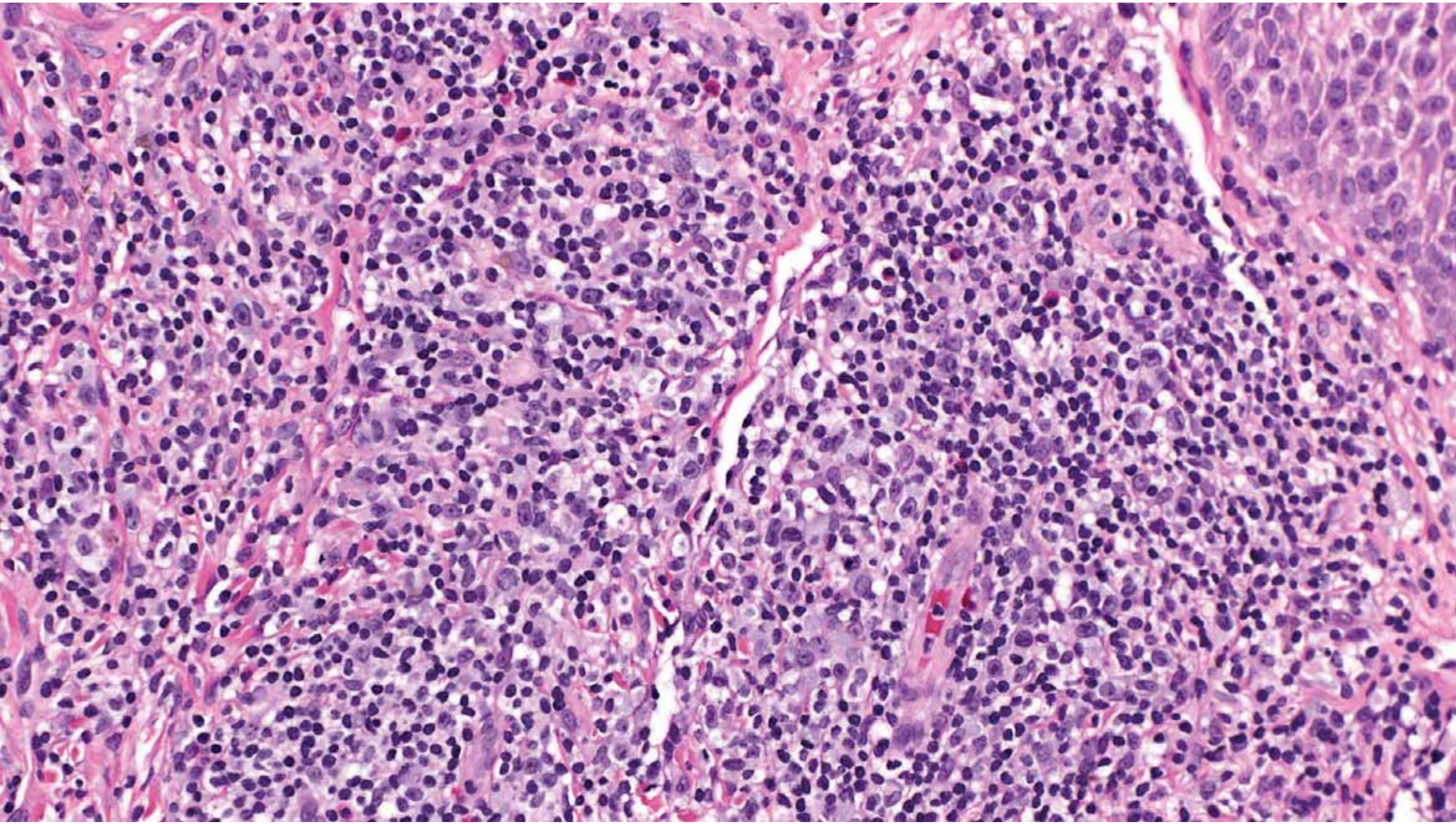
Seborrheic keratosis with pseudolymphomatous infiltrate

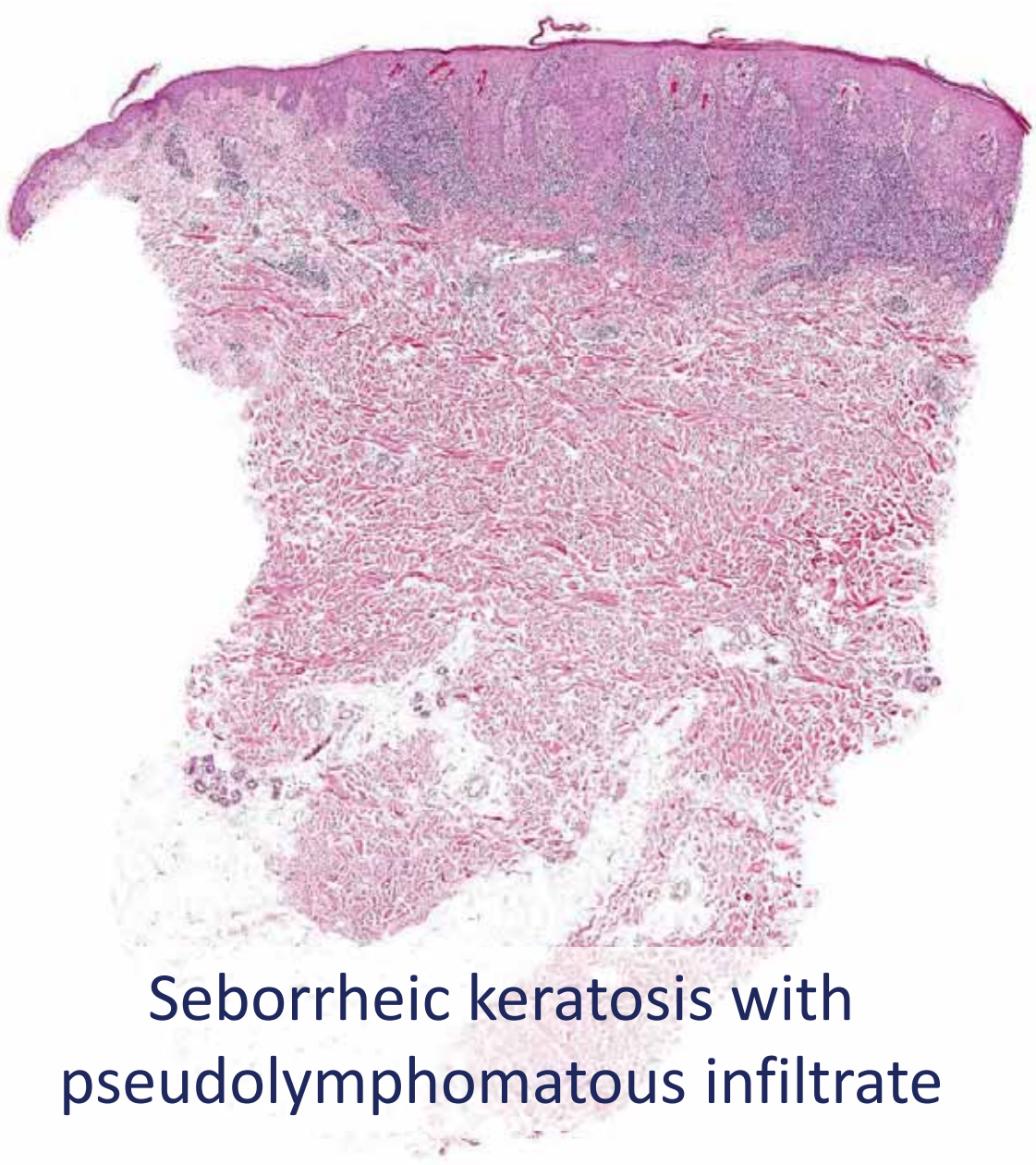


Case 38

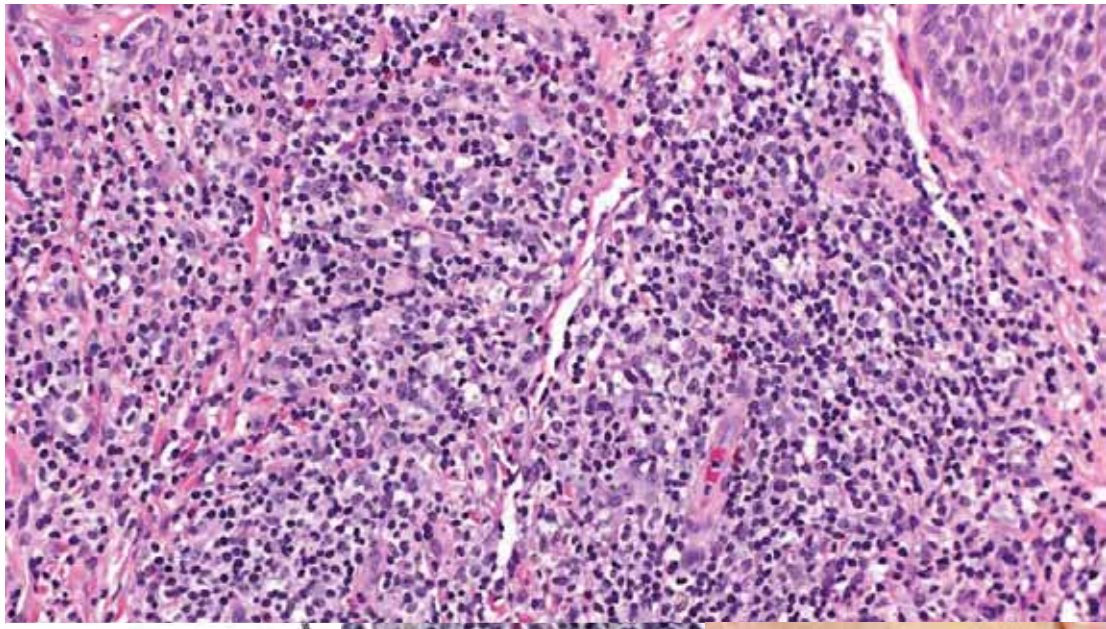
F, 62. According to the patient itchy lesions in the sub- and inframammary region for a few days. In the same area "warty" lesions present already for a "long time".

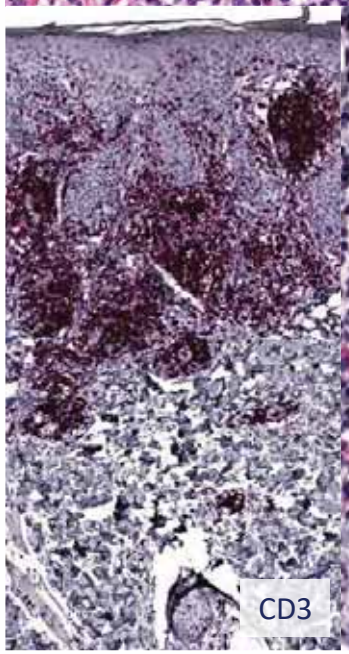


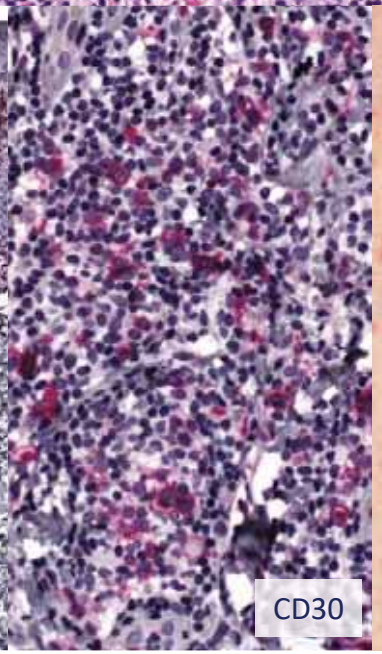


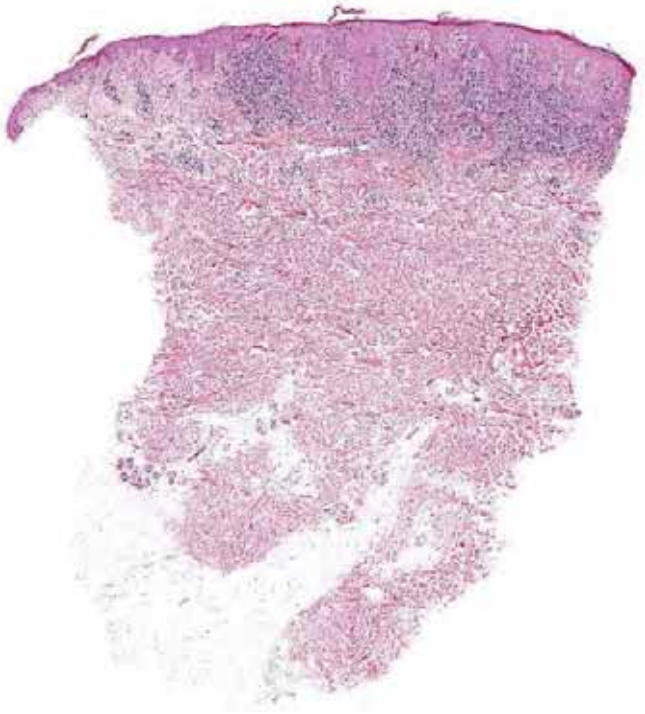


Seborrheic keratosis with pseudolymphomatous infiltrate



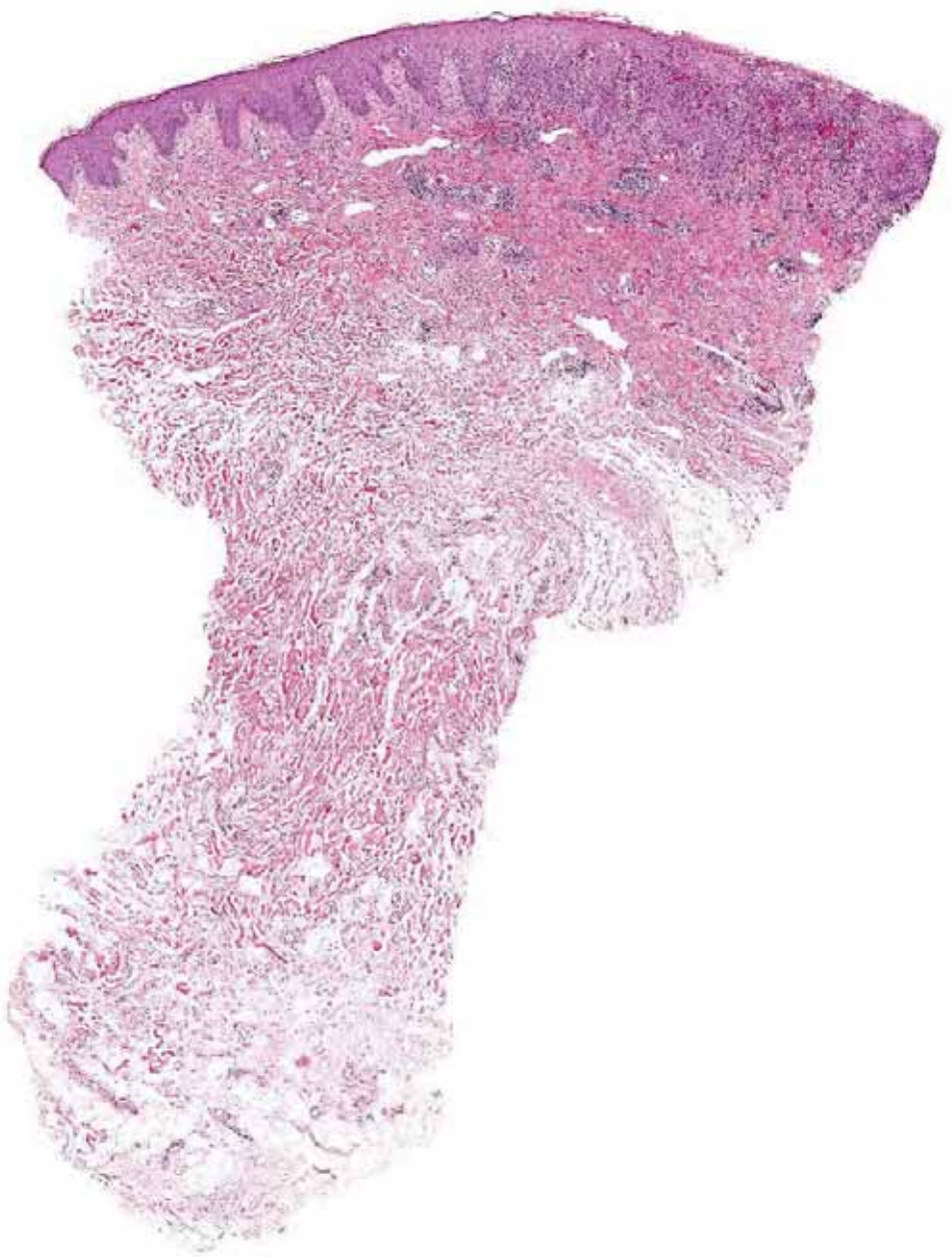






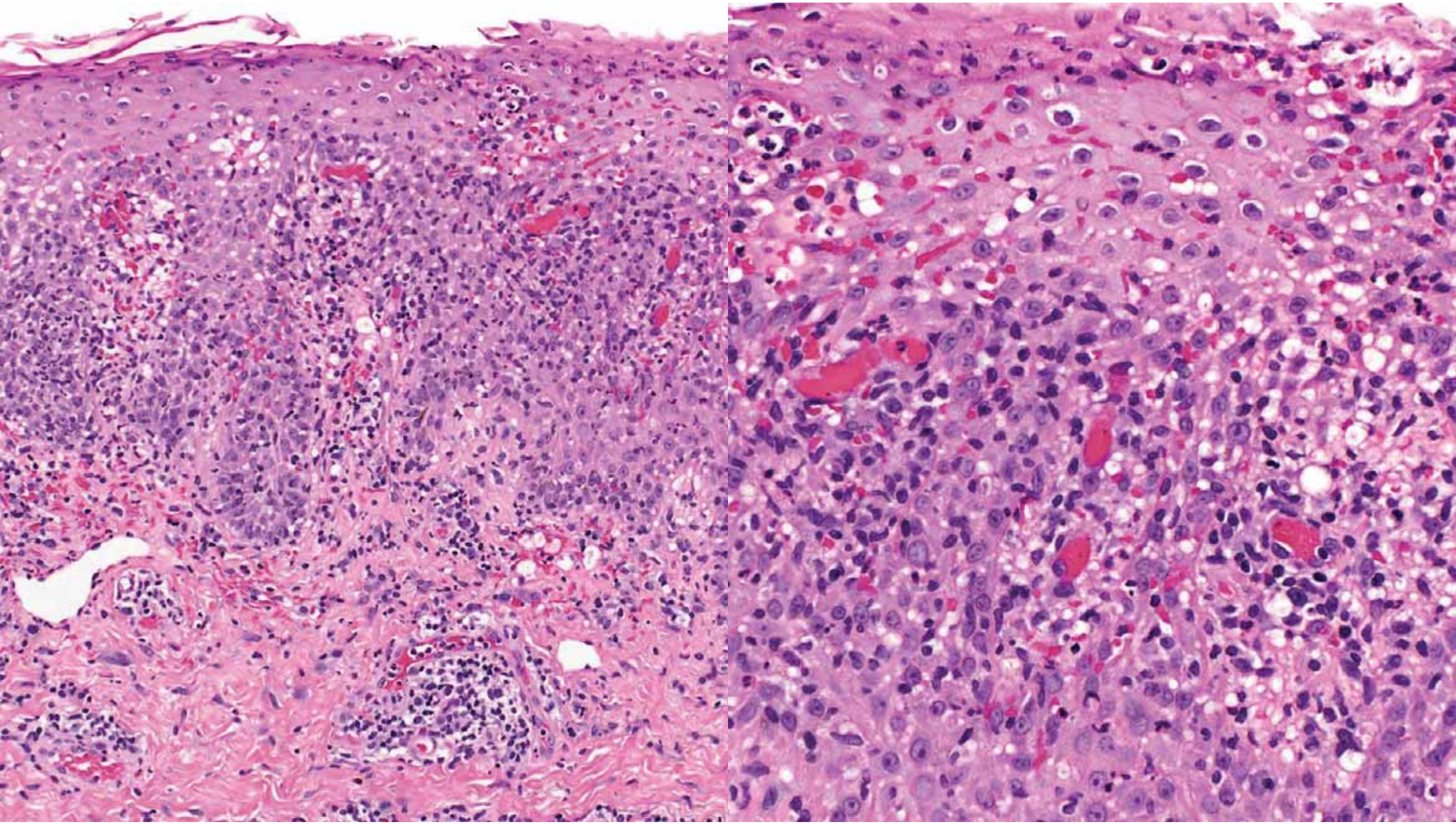
Clinically, inflammation restricted to the seborrheic keratoses

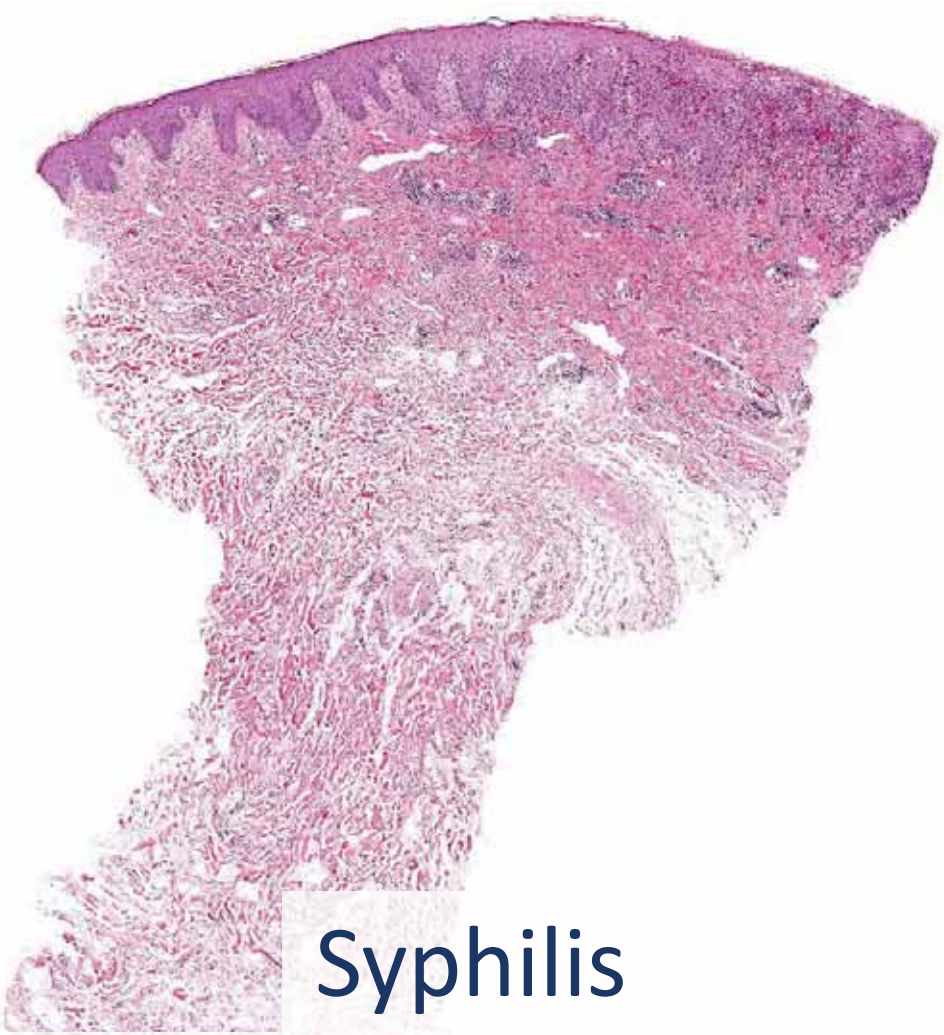
Histopathologically, inflammatory infiltrate restricted to the area of hyperplastic epidermis



Case 39

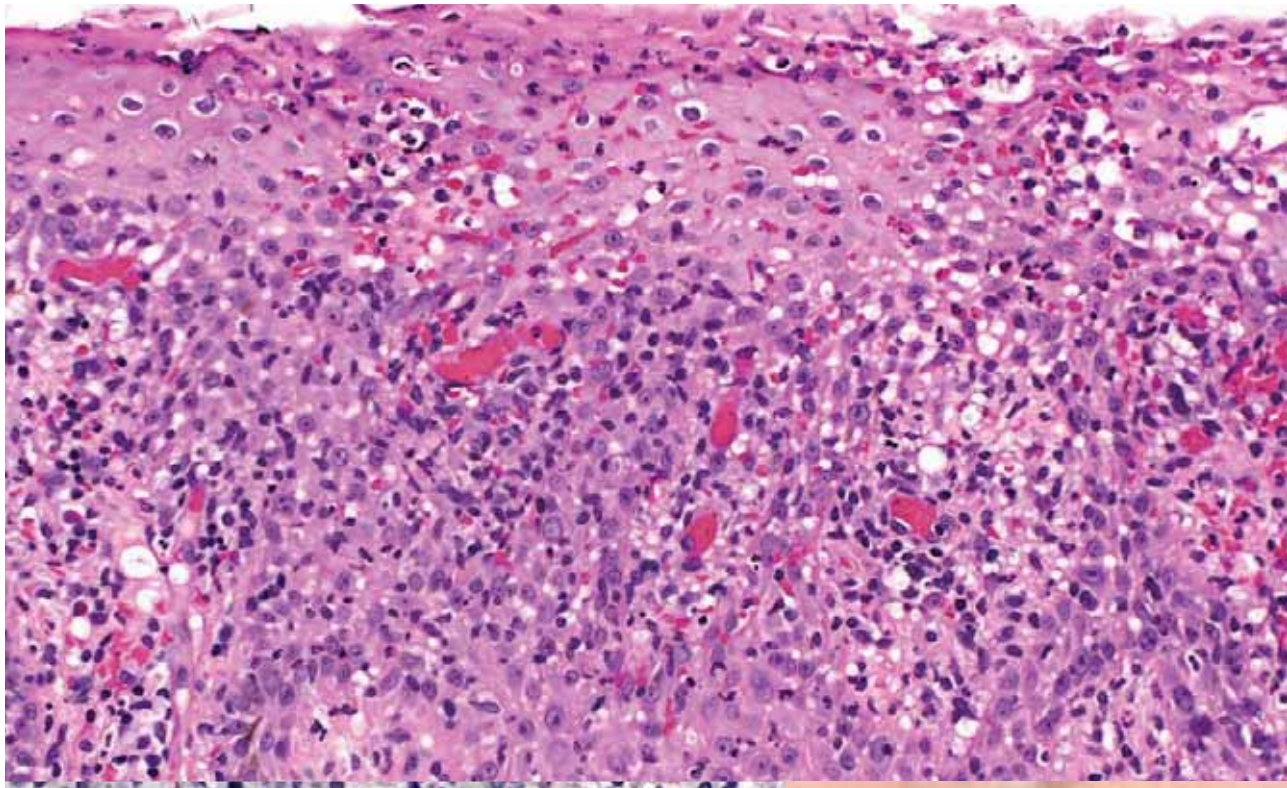
M, 50. According to the patient slightly itchy perianal lesions for 2 months. No improvement with local steroids.

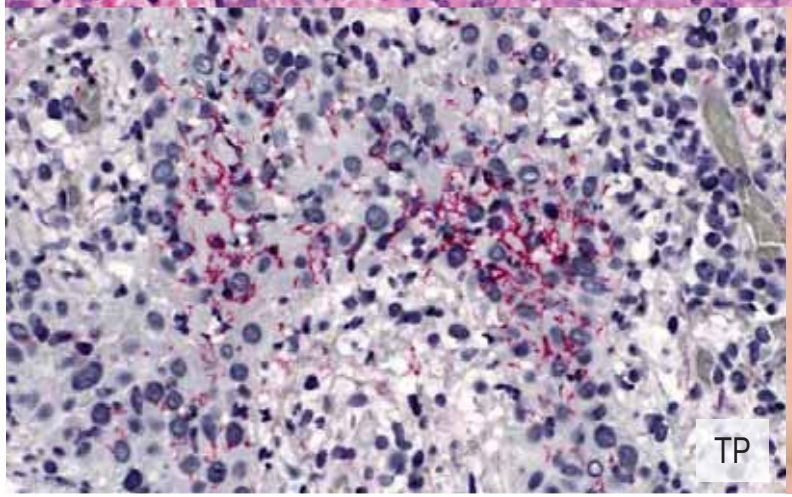




Syphilis

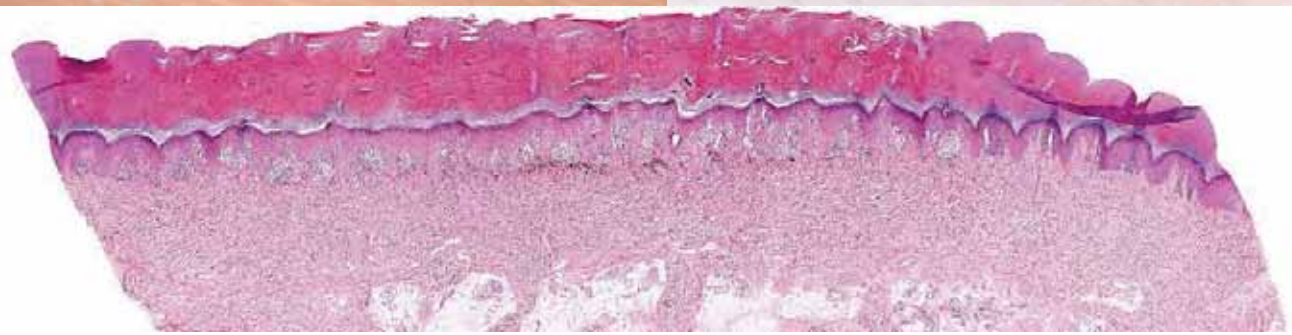
1st infection serologically in 2021, managed only 2 years later with one injection of benzathine benzylpenicillin (insufficient therapy). VDLR increase in the last 5 months (sign of a second, recent infection).

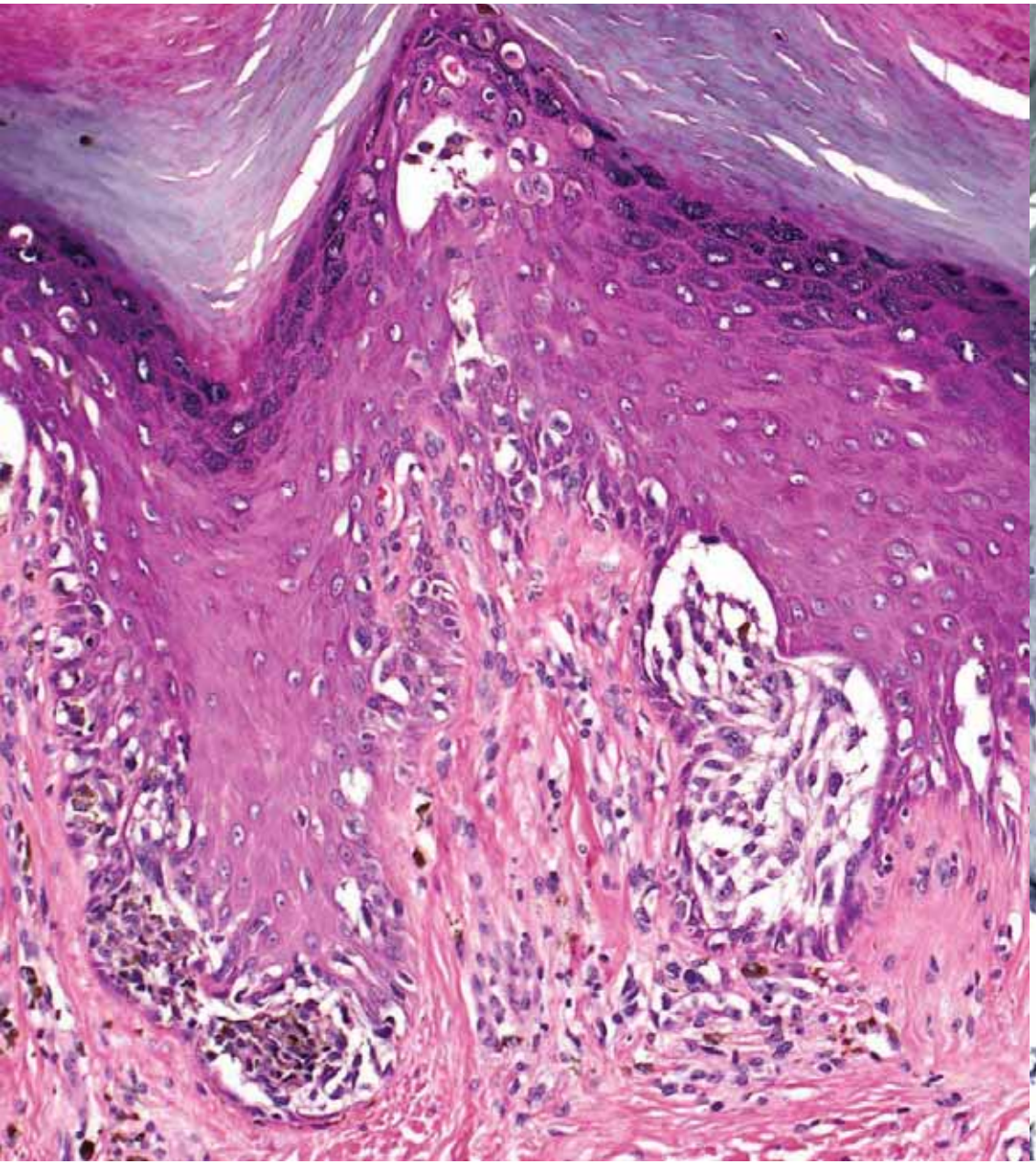


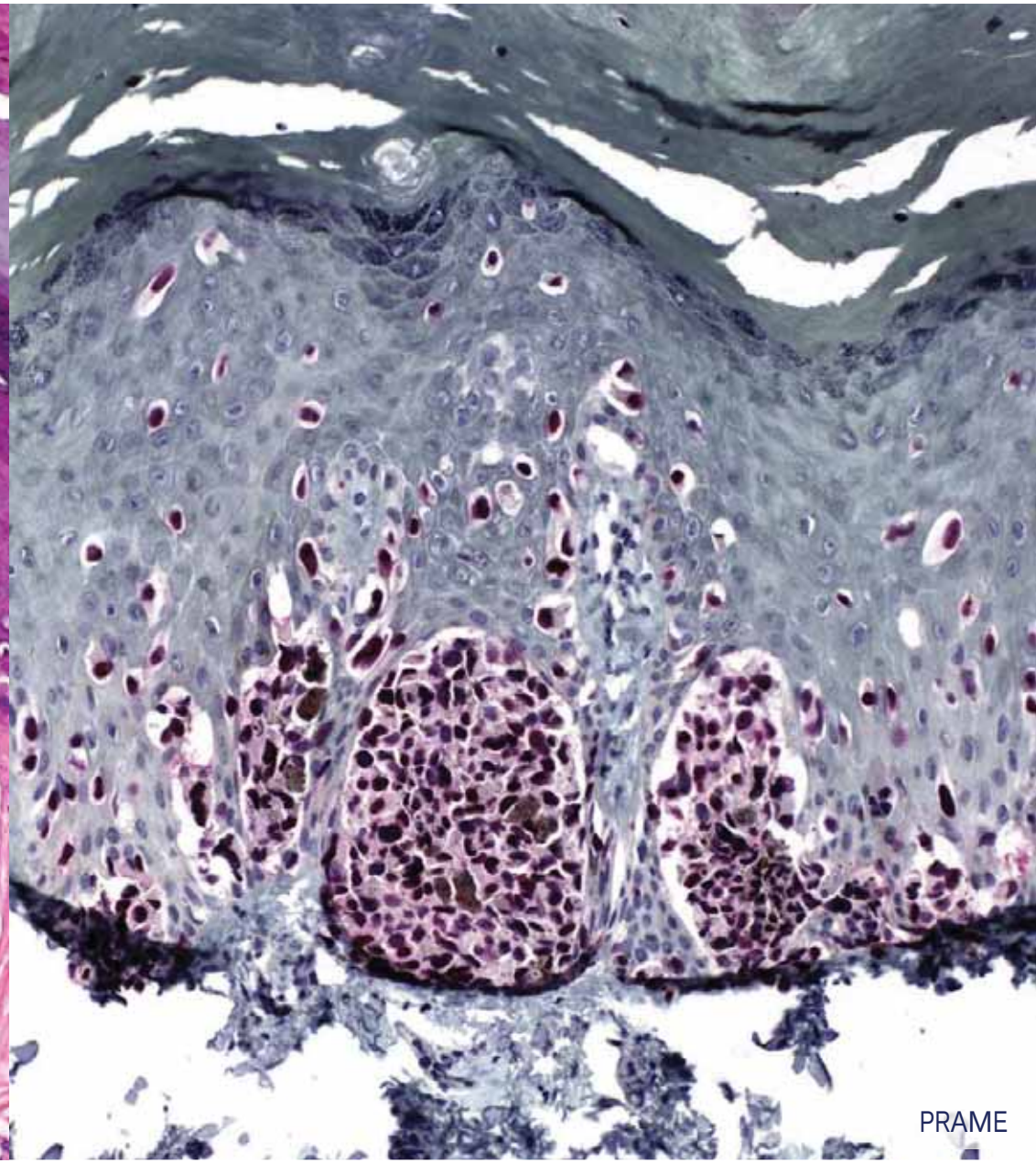


Case 40

M, 69. The patient noticed a pigmentation on the right sole 1 month before presentation.

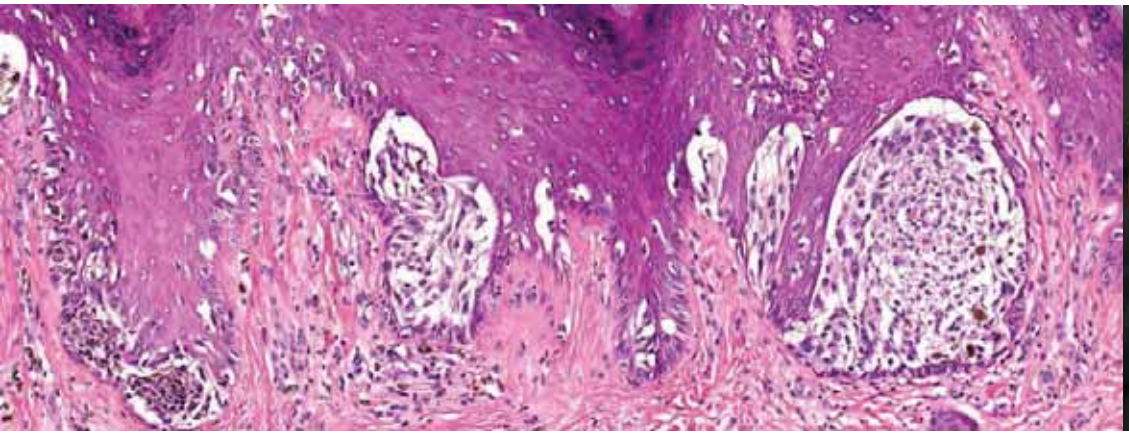






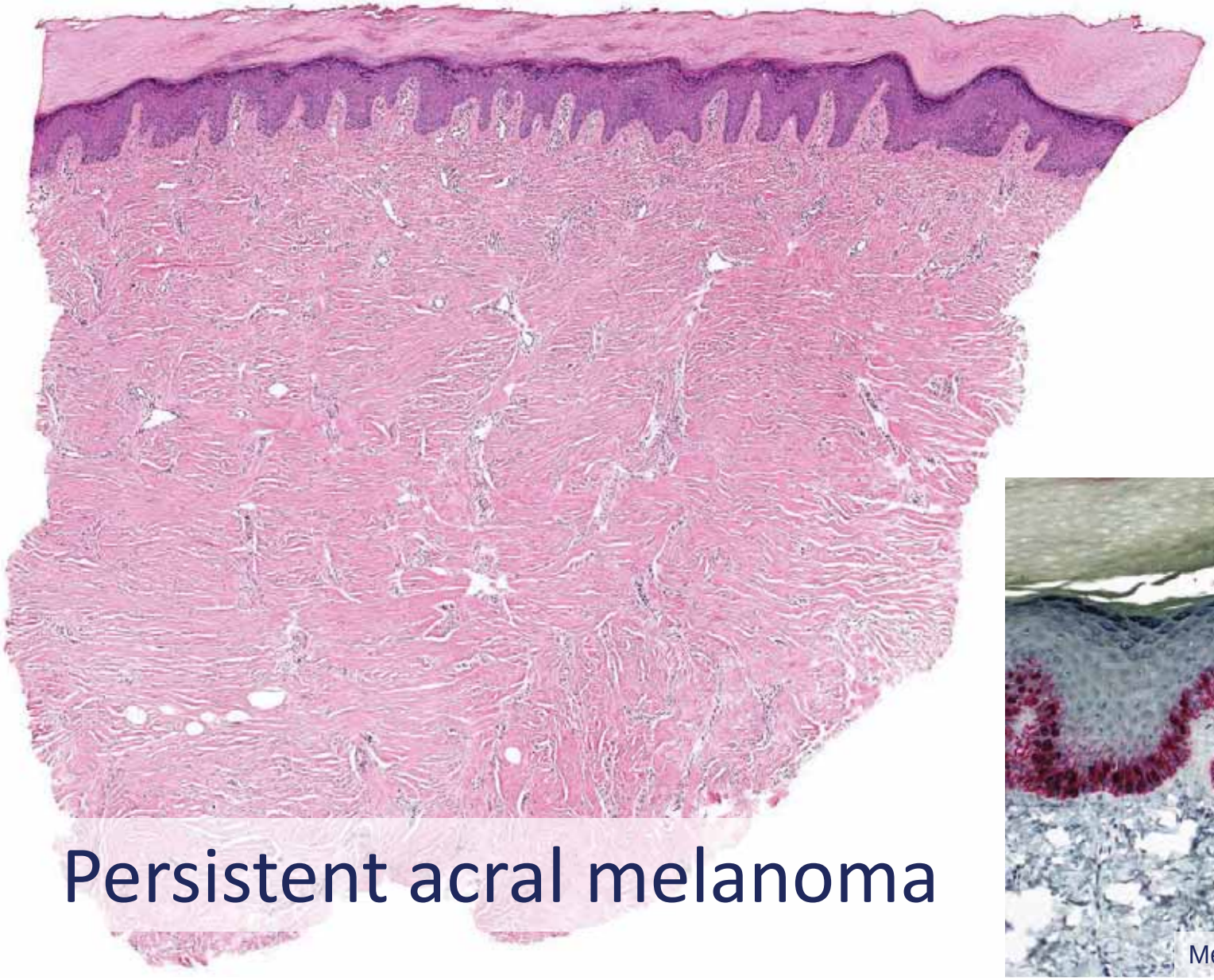
PRAME

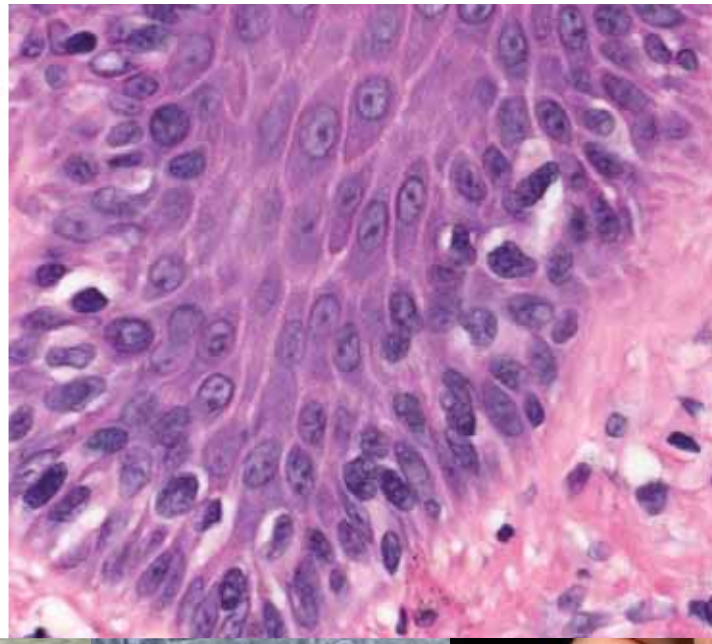
Acral melanoma

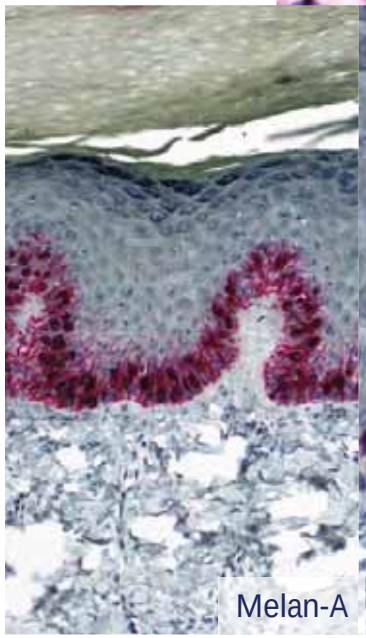


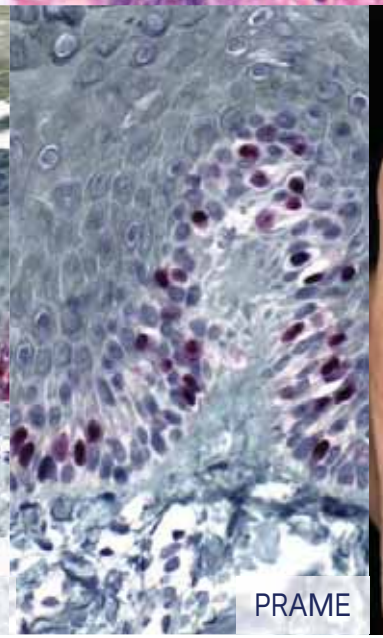
At time of surgery
4 months later

17 months after surgery









Persistent acral melanoma

[CANCER RESEARCH 60, 1968–1973, April 1, 2000]

Gene Amplifications Characterize Acral Melanoma and Permit the Detection of Occult Tumor Cells in the Surrounding Skin[1]

Boris C. Bastian,[2] Mohammed Kashani-Sabet, Henning Hamm, Tony Godfrey, Dan H. Moore II, Eva-B. Bröcker, Philip E. LeBoit, and Dan Pinkel

Cancer Center [B. C. B., M. K.-S., T. G., D. H. M., P. E. L., D. P.], Departments of Pathology [B. C. B., M. K.-S., P. E. L.] and Dermatology [B. C. B., M. K.-S., P. E. L.], University of California-San Francisco, San Francisco, California 94143, and Department of Dermatology, University of Würzburg, D-97080 Würzburg, Germany [H. H., E. B.]

ABSTRACT

Acral melanoma (AM) is commonly distinguished from superficial spreading melanoma (SSM), the most common type of melanoma, by its clinical presentation as well as its ethnic distribution. However, justification for such a distinction is controversial because of histological overlap and lack of prognostic significance. We analyzed chromosomal aberrations of 15 AMs and 15 SSMs that were comparable for tumor thickness and patient age, using comparative genomic hybridization. All AMs had at least one (mean, 2.0) gene amplification, significantly more than the SSMs, in which only 2 of 15 (13%) had one amplification each ($P < 0.0001$). At least 15 different genomic regions were amplified in AM. These involved small portions of chromosomal arms, sometimes including known oncogenes implicated in melanoma. The most frequently amplified regions in AMs occurred at 11q13 (47%), 22q11 13 (40%), and 5p15 (20%). Comparison of the amplification levels of invasive and noninvasive portions of the tumors using fluorescence *in situ* hybridization suggested that amplifications occurred before the formation of the invasive portion. The finding of amplifications of 11q13 in three of five additional cases of AM *in situ* further supports the notion that amplifications arise early in the progression of AM. Very significantly, we found isolated melanocytes with amplifications in the epidermis up to 3 mm beyond the histologically recognizable extent of the melanomas in 5 of 15 invasive AMs. In conclusion, our data show that AM is a distinct type of melanoma characterized by focused gene amplifications occurring early in tumorigenesis, and that malignant cells are present beyond the histologically detectable boundary, thereby revealing one mechanism of local recurrence.

INTRODUCTION

The clinical and histological presentations of cutaneous melanoma are associated with anatomical location, sun exposure, age, and ethnicity. These patterns led to a classification of cutaneous melanoma into superficial spreading, nodular, lentigo maligna, and acral types (1). However, justification for such a classification is controversial because of histological overlap (2, 3) and lack of prognostic significance (4–6).

AM[3] exhibits several distinct clinical and epidemiological features. It develops on palmar, plantar, and subungual skin (7), sites that have little exposure to sunlight and are protected from UV radiation by a thick stratum corneum. Therefore, it is unlikely that UV radiation plays an important role in the pathogenesis of AM. The overall incidence is similar across all racial groups (8), with AM being the most common type of melanoma in dark-skinned peoples (9, 10).

Most melanomas begin within the epidermis (*in situ* melanoma) and progress through a period of lateral expansion to an invasive lesion that has metastatic capacity (11). Melanoma has a potential to recur locally if not excised with a safety margin of clinically and histologically uninvolved skin (12).

In a previous study of 32 randomly selected primary cutaneous melanomas by CGH, we noted that gene amplifications [>3-fold increase in copy number (13)] were infrequent in melanomas in general but found multiple amplifications in a single AM that we analyzed (14). Here we show that AM universally demonstrates a unique type of genomic instability that is characterized by amplifications of small genomic regions. Some of these regions contain genes of known significance in melanoma progression. This is consistent with the general view that amplified regions in tumors frequently contain oncogenes or drug-resistance genes, the increased dosage of which confers a selective advantage to the cells (13). We show that these amplifications are detectable in the *in situ* stage of AM and are found in isolated intraepidermal melanocytes in histologically normal-appearing skin surrounding the melanomas.

MATERIALS AND METHODS

Study Populations

Fifteen cases that had been archived under the diagnosis of invasive AM were retrieved from the archival material of the Department of Dermatology, University of Würzburg, the Dermatopathology Section, and the Melanoma Center of the University of California, San Francisco. Two AMs were from the toe, 10 from the sole, and 3 were from the foot without further specification. By histology, 12 AMs were of the acral lentiginous type, two were unclassifiable because the radial portions of the tumors were not represented in the specimen, and one had overlapping features with SSM. As controls, 15 cases comparable for patient age (±5 years) and tumor thickness (<1.5 mm, 1.5–4.0 mm, and >4.0 mm) that had been archived as SSMs were retrieved. Histological reassessment showed typical features of SSM in all 15 controls. For the analysis of AM *in situ*, five cases were retrieved from the database of the Melanoma Center at the University of California, San Francisco.

CGH

DNA Extraction. Tumor-bearing tissue was microdissected from 30-μm sections (2–20 per tumor) using H&E-stained sections as guidance. DNA extraction and labeling was performed as published by Isola *et al.* (15). The amount of DNA obtained ranged from 2 to 12 μg/specimen.

DNA Labeling. All measurements were performed in duplicates: once with 1 μg of tumor DNA labeled with fluorescein-12-dUTP (DuPont, Inc., Boston, MA) and 200 ng of Texas red-5-dUTP-labeled reference DNA ("standard" labeling); and a second time with the labeling reversed, as described earlier (14).

Controls and Threshold Definitions. Normal DNA and DNA from tumor cell lines with known aberrations were used as negative and positive controls for CGH, respectively. We regarded a region as aberrant when: (*a*) either the standard labeling or the reverse labeling resulted in a tumor:reference fluorescent ratios <0.80 or >1.2; or (*b*) both the standard and the reverse labeling resulted in tumor:reference fluorescent ratios of <0.85 or >1.15 (14).

FISH

Dual-color FISH was carried out on tissue sections of the tumors that showed amplification by CGH. Probes mapping to amplified

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[2] To whom requests for reprints should be addressed, at University of California San Francisco Cancer Center, Box 0808, San Francisco, CA 94143-0808. Phone: (415) 476-1269; Fax: (415) 476-8218; E-mail: bastian@cc.ucsf.edu.

[3] The abbreviations used are: AM, acral melanoma; SSM, superficial spreading melanoma; FISH, fluorescence *in situ* hybridization; CGH, comparative genomic hybridization; FGF, fibroblast growth factor.

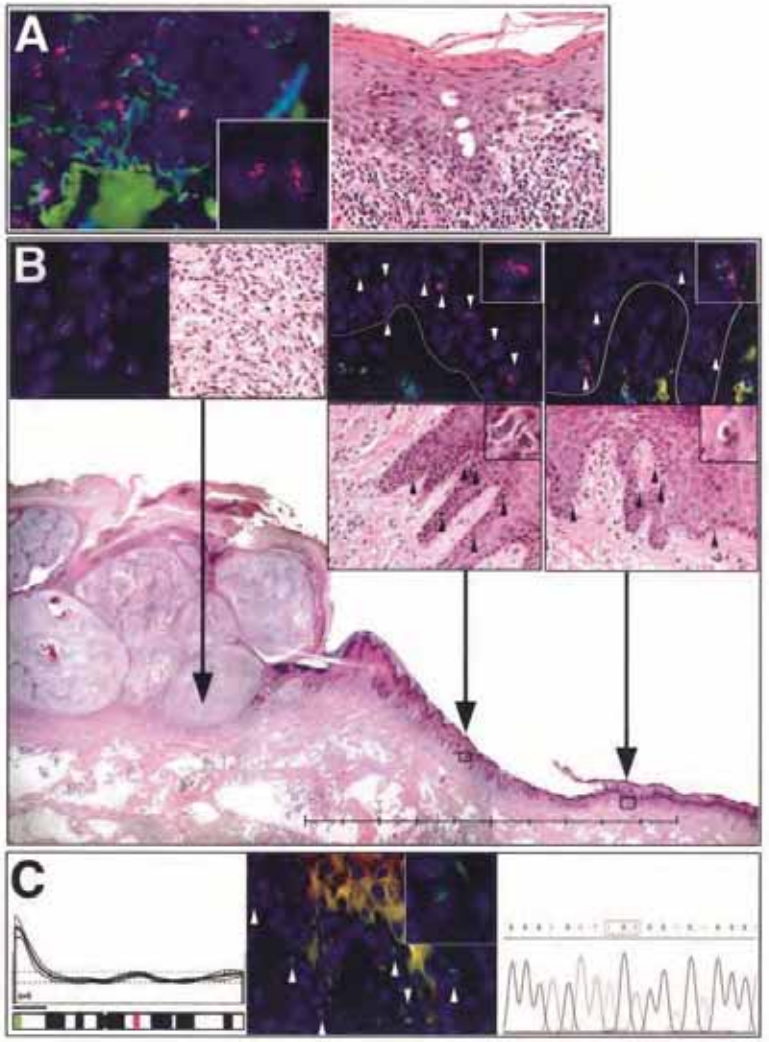

Fig. 2. *Analyses of three separate areas of AM. A*, FISH and H&E of an *in situ* AM (case AM2). *Left*, a *red*-labeled clone (RMC11P005) mapping to 11q13.2 and a *green*-labeled reference probe for 11p15.5 (RMC11P022) show amplification of 11q13.2 in basal melanocytes with an average copy number >10 (*inset*). FISH images represent one focal plane so that not all signals of a nucleus are visible. *Right*, histology shows melanocytic cells confined to the basal epidermis and a dense lymphocytic infiltrate in the papillary dermis. *B*, FISH and H&E of case AM04. The *low magnification image* shows the invasive portion on the *left*, with *in situ* portion and the adjacent skin on the *right*. *Bar*, 1 mm. The *panels above* show higher magnification views (×16) of areas indicated by *arrows*. FISH was performed with the same probe combination as described in Fig. 2*A*. The *left top* is a high magnification of the invasive portion with spindled tumor cells showing over 15 *red* signals and two to three green signals per nucleus by FISH. The *middle top* shows the *in situ* portion with scattered basal melanocytes with large hyperchromatic nuclei of atypical shape (*black arrowheads* and *inset* in H&E panel). FISH shows multiple cells in the basal epidermis with amplifications of the *red* signal (*white arrowheads* and *inset*). The *white line* indicates the dermo-epidermal boundary. The *right panel* shows an area of marginal skin most distant from the invasive portion where FISH could detect cells with amplifications (field cells) indicated by *white arrowheads*. Histologically, basal melanocytes show no clear signs of atypia (*black arrowheads* and *inset*). *C*, CGH, FISH, and sequence analysis of case AM09. The *left panel* shows the *fluorescence ratio profile* of chromosome 11 as determined by CGH, indicating a focused amplification of chromosome 11p15. The *green* and *red bars* on the chromosome ideogram indicate the location of the probes used for FISH, depicted in the *middle panel*. The green-labeled probe for chromosome 11p15 contained the *HRAS* gene. FISH analysis of an area 5 mm distant from the invasive part of the tumor shows isolated basal melanocytes (field cells) with amplifications of *HRAS* (*arrows* and *inset*). The *right panel* shows the sequence profile of a portion of exon 1 of *HRAS* for this case with a T→G mutation of codon 12 (*bottom*).

Bastian B, et al. *Cancer Res* 2000;60:1968-1973

ORIGINAL ARTICLE

Distribution and Significance of Occult Intraepidermal Tumor Cells Surrounding Primary Melanoma

Jeffrey P. North[1,2], Trishim Kageshita[3], Daniel Pinkel[4,5], Philip E. LeBoit[5,6] and Boris C. Bastian[4,6]

Primary melanoma can recur at the excision site if not excised with a safety margin of surrounding uninvolved skin. To characterize the nature of residual melanoma in the skin surrounding primary tumors targeted by safety margins, we used array comparative genomic hybridization and fluorescent *in situ* hybridization to detect and spatially map aberrations in the skin adjacent to acral melanomas. Melanocytic cells with genetic amplifications in histopathologically normal skin (field cells) were detected exclusively in the epidermis in 84% of 19 cases, with a mean extension of 6.1 mm (*in situ* melanomas) and 4.5 mm (invasive melanomas) beyond the histopathological margin. Genetic profiling of these field cells indicated that they represent an early phase of disease preceding melanoma *in situ*. The extent of field cells did not correlate with tumor depth or diameter, indicating that tumor depth is not suited to predict the extent of field cells. These results demonstrate that, on acral sites, melanoma field cells extend significantly into seemingly normal skin. These field cells provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision.

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INTRODUCTION

The primary treatment of melanoma is surgical excision. However, when not excised with sufficient safety margins of apparently uninvolved skin, melanoma can regrow at the primary excision site despite the absence of histologically recognizable melanoma at surgical margins. Even when employing standard safety margins, disease still recurs in a small proportion of cases. Local recurrences are proposed to be of two types, each with different prognostic implications (Troidman and McNoer, 1963; Olsen, 1970). In the first, melanoma recurs after an apparently complete excision because a histologically unrecognizable form of melanoma extending beyond the surgical margin remains. In this case, the recurrent melanoma typically has an intraepidermal component and develops through the same evolutionary stages as the original tumor, progressing from *in situ* to invasive growth. Alternatively, melanoma can recur locally from discontinuous, that is, metastatic, spread of the invasive component of the primary melanoma. This distinction is clinically important. Removal of persistent melanoma of the first type before it had evolved to a state capable of metastasis would be curative for the patient. By contrast, widening the margins to capture local metastatic deposits is less likely to provide lasting benefit, because local evidence of metastasis is often a marker of the widespread dissemination of potentially lethal cells.

Recently, we reported the finding of genetically abnormal melanocytes in histologically normal epidermis adjacent to melanomas on the non-hair-bearing skin of the palms and soles, that is, acral melanomas (AM) (Bastian *et al.*, 2000a). These cells could be recognized using fluorescent *in situ* hybridization (FISH) because their genomes contained the characteristic high level of DNA amplifications we had found in the genomes of invasive AMs. They were termed "field cells" (Bastian *et al.*, 2000a). Even after identification of field cells by their genetic abnormalities, we could not develop histopathologic criteria to recognize them because they were not sufficiently increased in number, abnormally distributed, or markedly atypical compared to normal melanocytes. FISH analysis of one melanoma that had recurred at the primary site repeatedly after multiple excisions with histologically negative surgical margins showed field cells at the excision margin. This suggested that field cells may be a form of occult melanoma that, if left behind, leads to local recurrence

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Abbreviations: AM, acral melanoma; CGH, comparative genomic hybridization; FISH, fluorescent *in situ* hybridization; H&E, hematoxylin and eosin

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Table 1. Case characteristics

Case no.	Age	Sex	Site	Tumor depth	Histologic width	FC width beyond H&E	FC at margin	Patient follow-up after excision
AM 134	85	F	Sole	*In situ*	32.5 mm	1.5 mm	–	No recurrence 60 months
AM 159	66	F	Sole	*In situ*	16.0 mm	—	–	No recurrence 57 months
AM 136	75	F	Sole	*In situ*	24.0 mm	3.0 mm	–	No recurrence 52 months
AM 179	—[1]	—[1]	—[1]	*In situ*	25.5 mm	6.0, 6.5[2]	+	No recurrence 38 months
AM 117	40	M	Sole	*In situ*	40.0 mm	3.0 mm	+	No recurrence 94 months
AM 118	73	M	Sole	0.4 mm	28.0 mm	10.5, 12.5[2]	+	Regional+systemic metastasis 54 months, died 57 months
AM 180	—[1]	—[1]	—[1]	1.6 mm	14.0 mm	4.0 mm	–	Recurrence 32 months, dead 39 months
AM 108	63	M	Sole	1.8 mm	17.0 mm	—	–	No recurrence 68 months
AM 169	66	M	Sole	2.3 mm	39.5 mm	4.5 mm	+	Dead 47 months (stroke), no recurrence
AM 165	74	F	Sole	2.5 mm	30.5 mm	2.5 mm	–	No recurrence 60 months
AM 125	83	M	Sole	2.7 mm	9.5 mm	6.5 mm	–	Inguinal skin metastasis 9 months, still alive 58 months
AM 133	84	F	Sole	2.8 mm	14.5 mm	2.5 mm	–	No recurrence 60 months
AM 130	69	F	Sole	2.9 mm	12.0 mm	3.0 mm	–	No recurrence 56 months
AB 1	84	F	Palm	3.0 mm	10.0 mm	9.0, 5.0[2]	–	No recurrence 23 months
AM 50	—[1]	M	Sole	3.2 mm	24.0 mm	4 mm	–	No recurrence 12 months
AM 110	63	M	Sole	3.5 mm	18.0 mm	2 mm	–	No recurrence 88 months
AM 126	77	M	Toe nail	4.1 mm	22.5 mm	4.5 mm	–	Inguinal LN metastasis 25 months, died 32 months
AM 132	57	M	Toe nail	4.8 mm	15.5 mm	—	–	No recurrence 65 months
AM 114	77	M	Sole	9.5 mm	42.5 mm	6.5 mm	+	Incomplete operation/stage 4, died 12 months

FC, field cell; LN, lymph node.
[1]Data not available.
[2]Field cells extended past the histologic margin to both sides of the melanoma; distances in mm.

"These field cells provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision."

Persistence of acral melanoma:

Around the scar: From field cells (up to >6 mm. from main tumor)
Within the scar: From neoplastic melanocytes growing along the eccrine ducts ?