

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



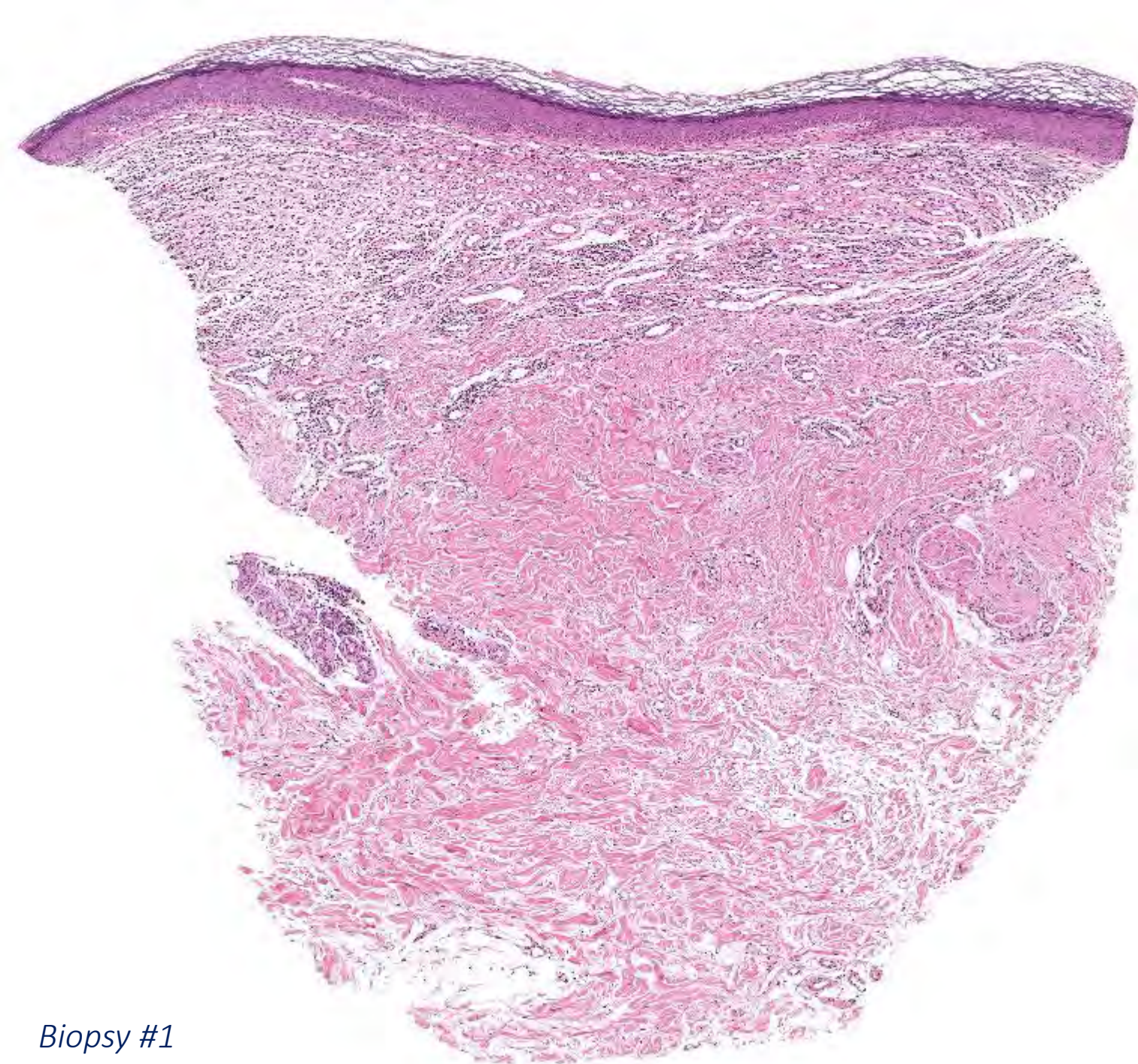
Clinicopathologic Conference

Lorenzo Cerroni

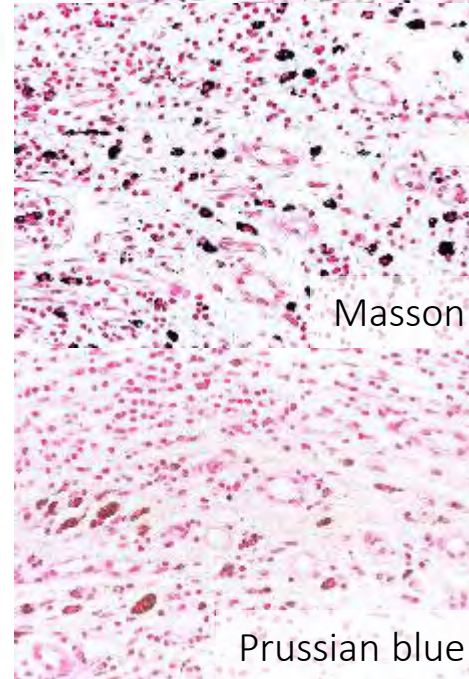
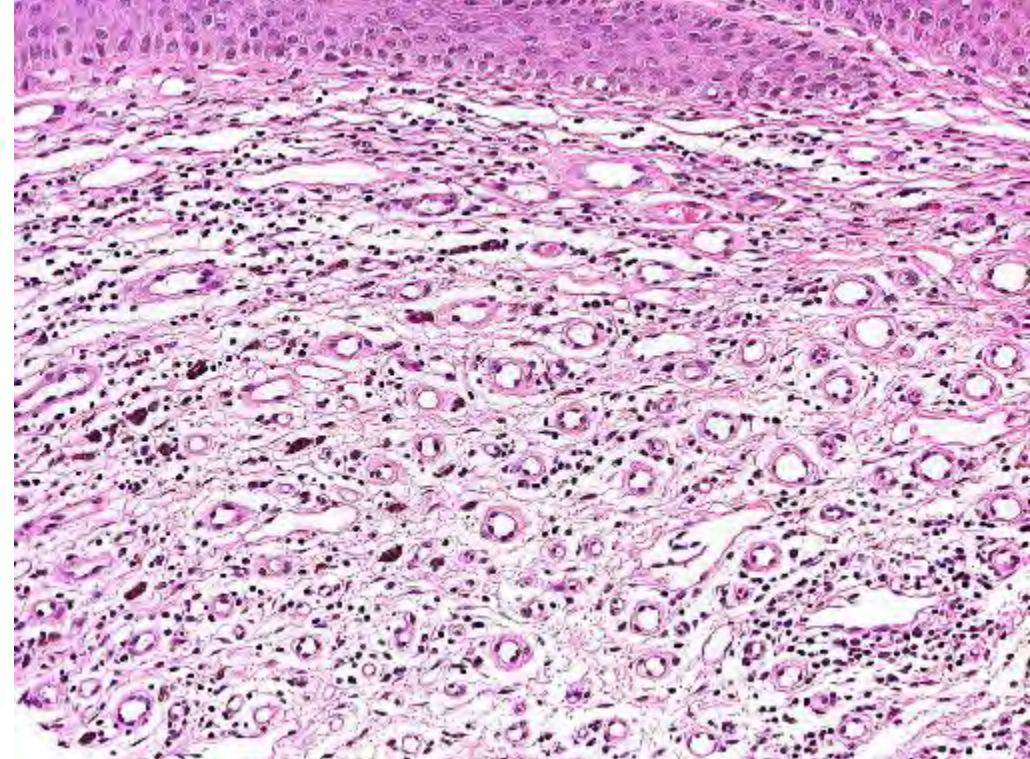


F, 81

History of pemphigus vulgaris (1st diagnosis 2,5 years before presentation; at present managed with mycophenolate-mofetil). According to the patient new lesion on the right flank for approximately 9 months. Two biopsies are taken.



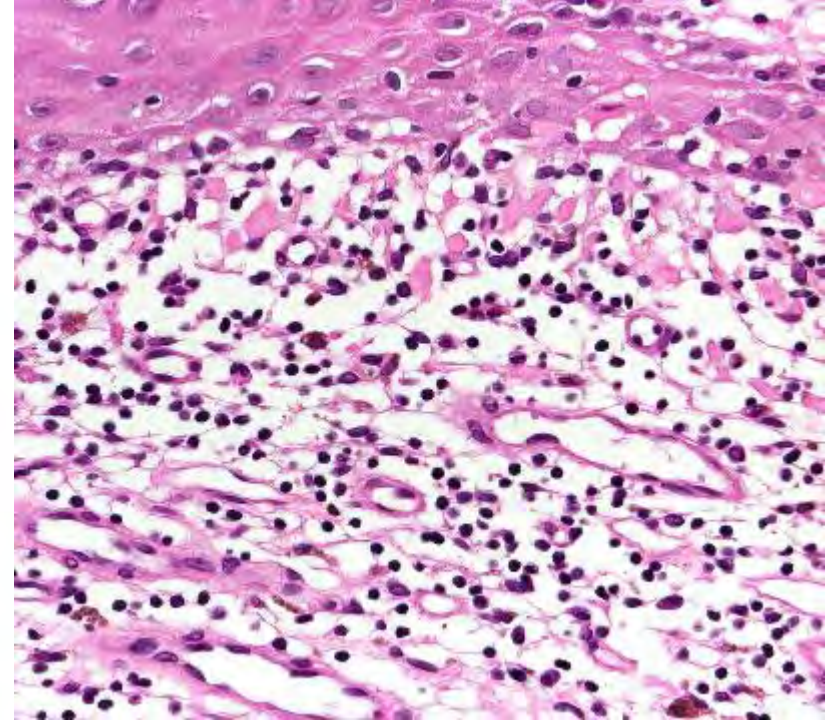
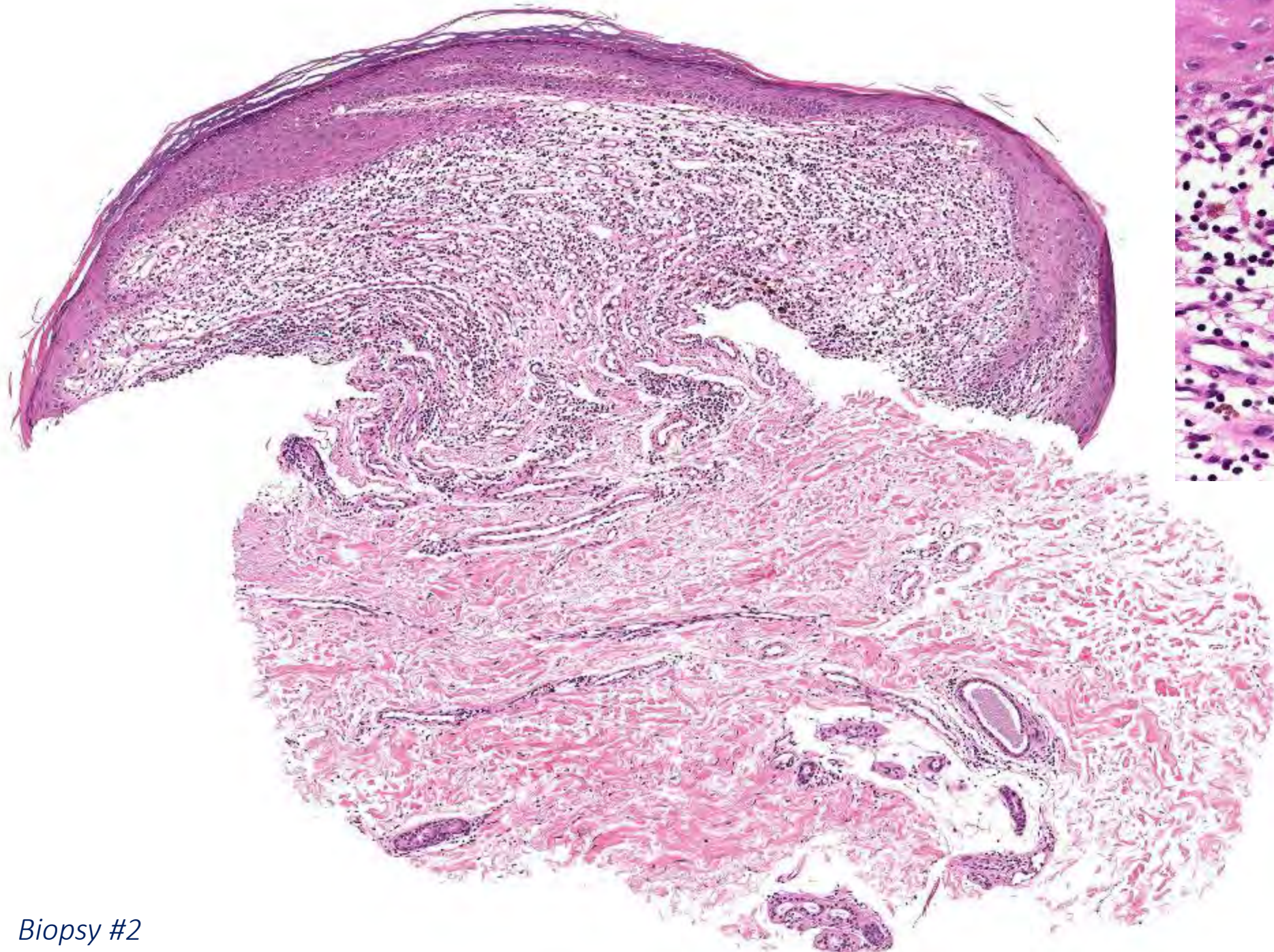
Biopsy #1



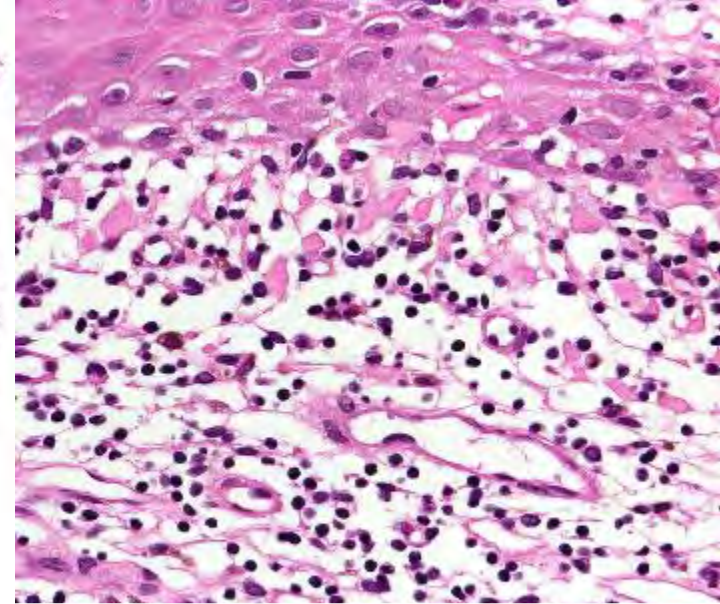
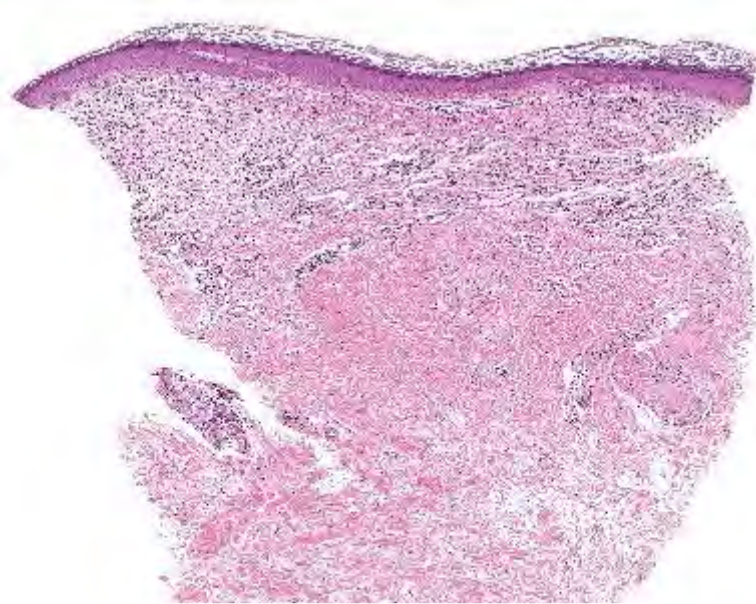
Masson



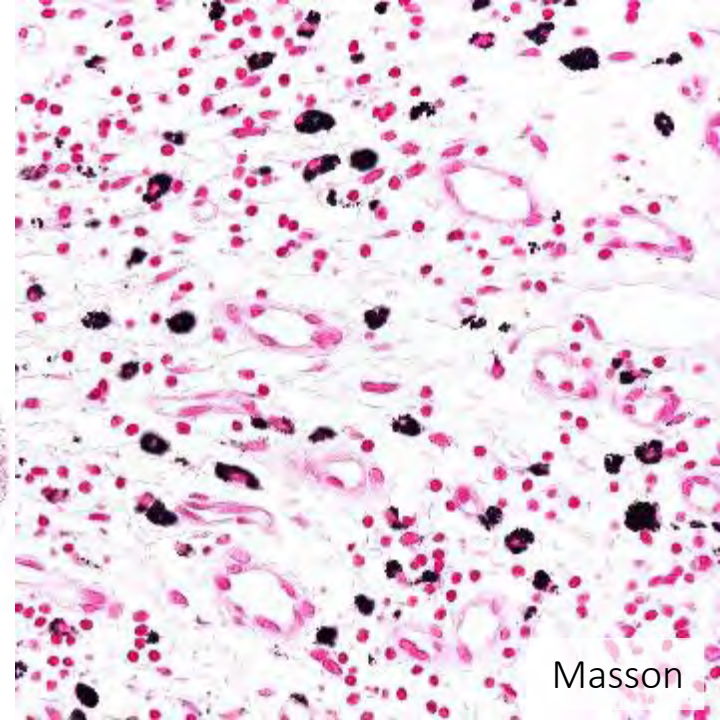
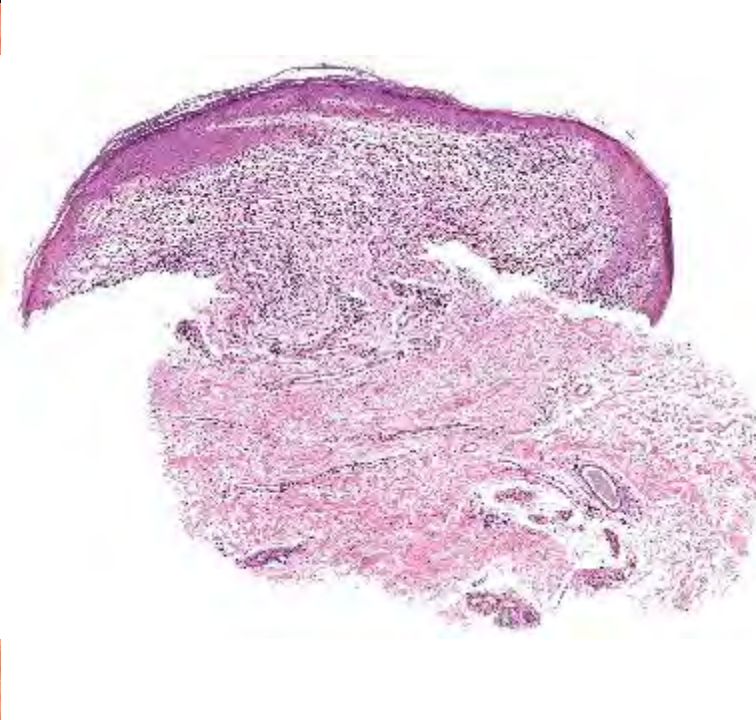
Prussian blue



Biopsy #2



Poikilodermatous plaque-like hemangioma



Poikilodermatous plaque-like hemangioma: Case series of a newly defined entity

Kristina Soukova, MD, MSc, MRCP, SCE (Dermatology), DipRCPath (Dermatopathology),¹ Richard Carr, FRCPATH, DipRCPath (DMT),² Mark Godinger, MBBS, DipClinDermatol,³ Ruth Green, MBChB,⁴ Abdul Haleem, MBChB, MRCP (UK),⁵ Anil Makyegeorgou, MBBS,⁶ Lucy Stelly, BSc, MBChB, FRCPATH,⁷ Luisa Morra, FRCPATH, DipRCPath (Dermatopathology),⁸ John Newsham, BSc (Hons), MBChB,⁹ Caroline Owen, MBChB, MRCP,¹⁰ Joanne Sillars, MBChB,¹¹ Saleem Tabbie, MBBS, BMedSci, MRCPCH, DipRCPath (Dermatopathology),¹² and Eduardo Calonje, MD, DipRCPath (Dermatopathology),¹³ London, Warwick, Wiltshire, Salford, Hammersmith, Blackburn, Darchester, and Bournemouth, England; and Glasgow, Scotland

Background: We present a distinctive type of acquired vascular proliferation for which we propose the name of poikilodermatous plaque-like hemangioma.

Objective: The aim of this study was to summarize the clinical and histologic features in a case series of poikilodermatous plaque-like hemangioma.

Methods: Sixteen cases were identified from the routine clinical and referral practices to the authors. Clinical characteristics, including demographic details and clinical morphology, were reviewed. The histopathologic features, including immunohistochemical staining results, were summarized.

Results: The lesions were usually solitary erythematous to violaceous poikilodermatous plaques on the lower extremities and plaques glabrous with subtle dilated osseous blood age of affected patients was 72 (range 54–90) years, and there was a male predominance. Histology comprised a diffuse band-like proliferation of vascular channels suggestive of postcapillary venules within the epidermal stroma with a background of fibrosis, edema, and loss of elastic fibers. Despite the clinical zosteriform appearance, metastasis was a frequent finding.

Limitations: Autopsy-based study.

Conclusion: Poikilodermatous plaque-like hemangioma is a distinctive and previously undescribed vascular proliferation defined by a constellation of consistent and reproducible clinical and histologic features. *J Am Acad Dermatol*. 2019;81:1257–1262.

Key words: acquired hemangioma, angiosarcoma, poikilodermatous plaque-like hemangioma, vascular proliferation.

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Conflicts of interest: None declared.
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DOI: 10.1016/j.jaad.2019.03.007



Fig 1. Clinical presentation. A and B, Case 3. C and D, Case 4. E and F, Case 5. G and H, Case 9.

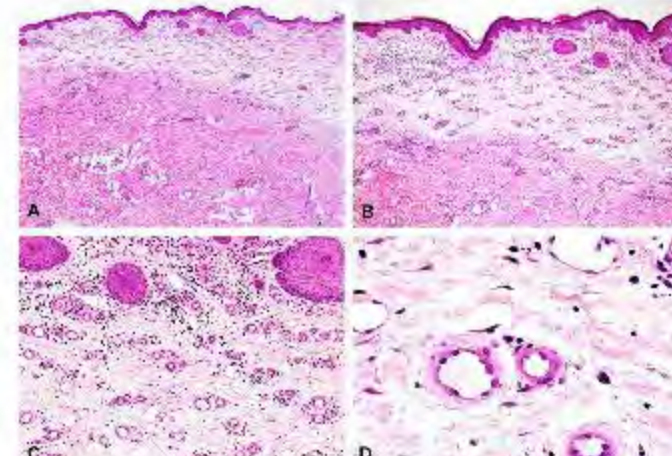


Fig 2. Histologic presentation of Case 3. (A-D, Hematoxylin-eosin stain; original magnification: A and B, $\times 20$; C and D, $\times 100$.)

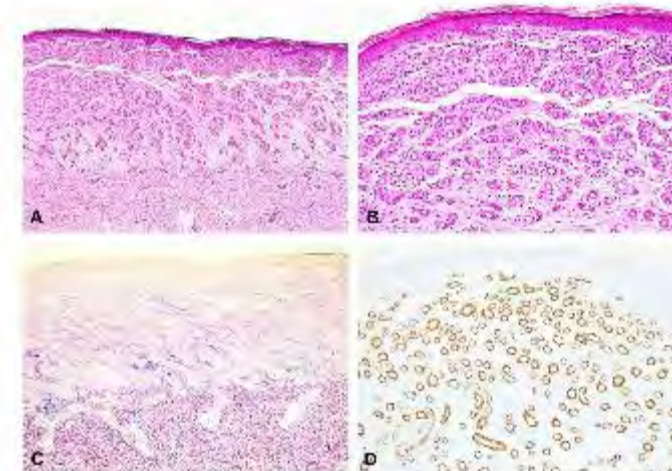
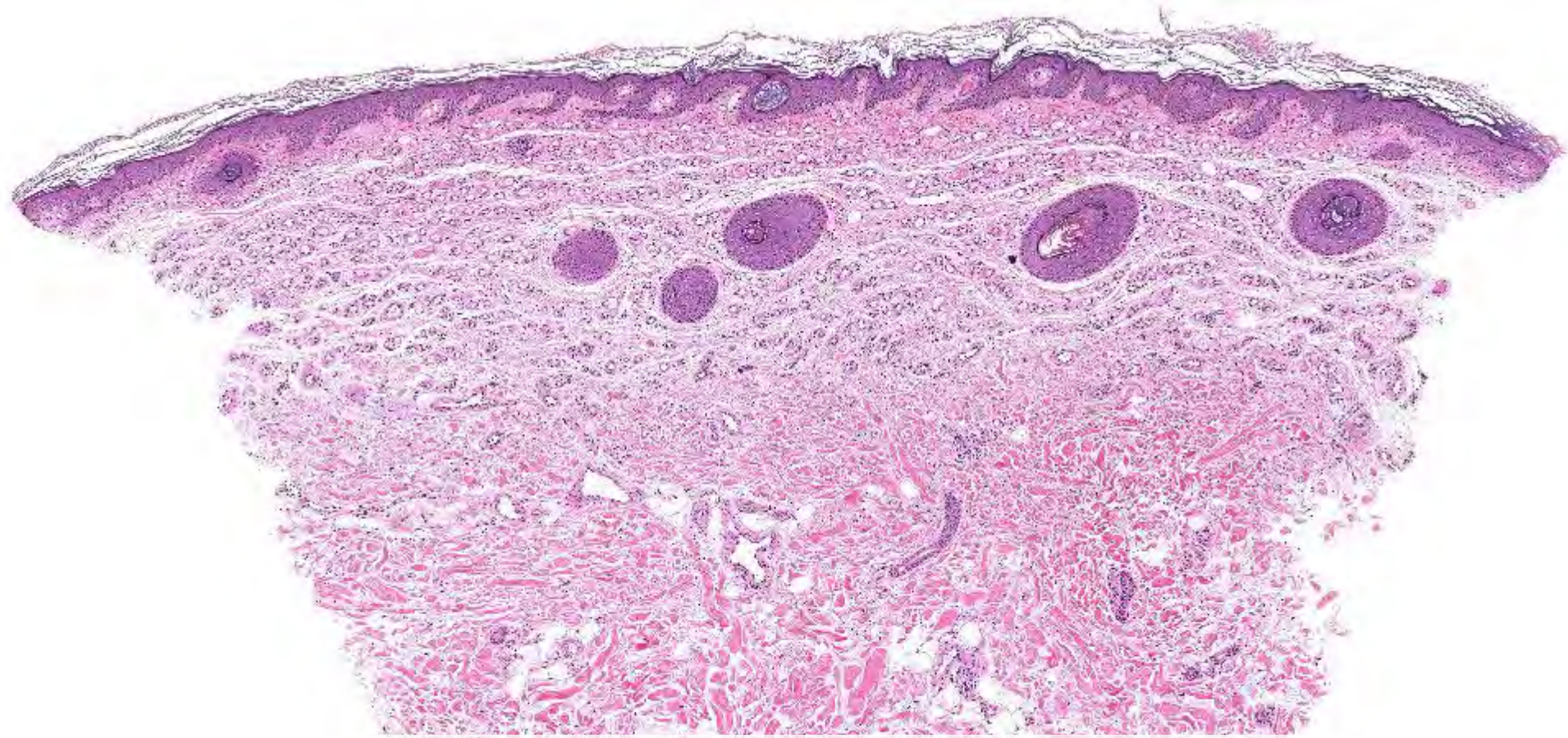
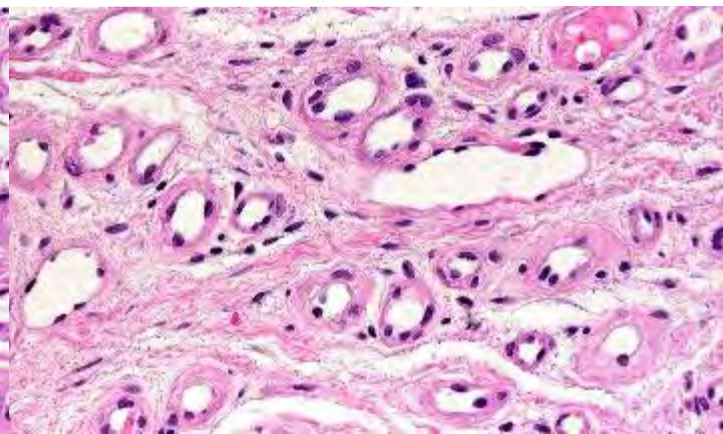
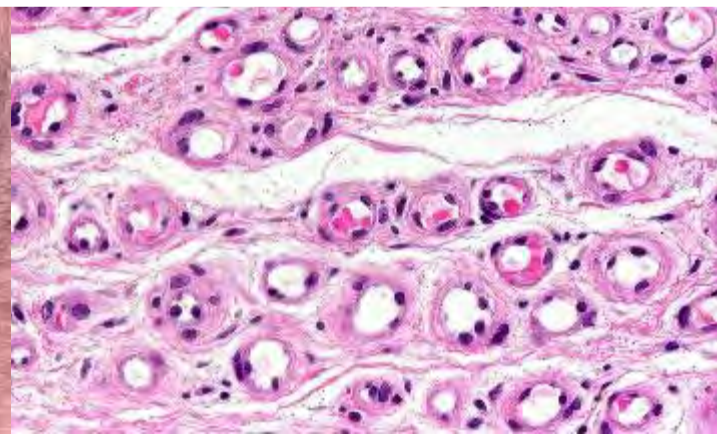
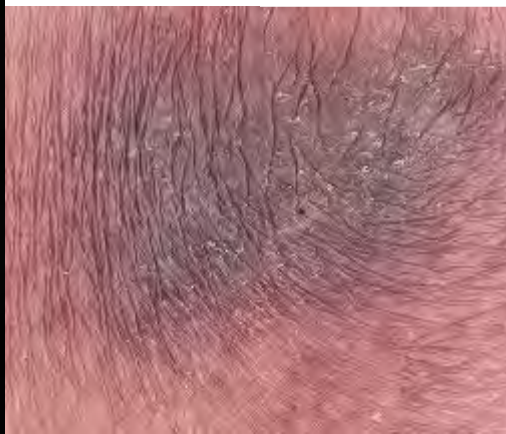


Fig 3. Histologic presentation of Case 8. (A and B, Hematoxylin-eosin stain; C, Elastic van Gieson stain; D, elastic van Gieson stain; E, CD31; F, D2-40; original magnification: A and C, $\times 20$; B and D-F, $\times 100$.)

16 cases; mean age 72 years
M:F = 7:1



Poikilodermatous plaque-like hemangioma

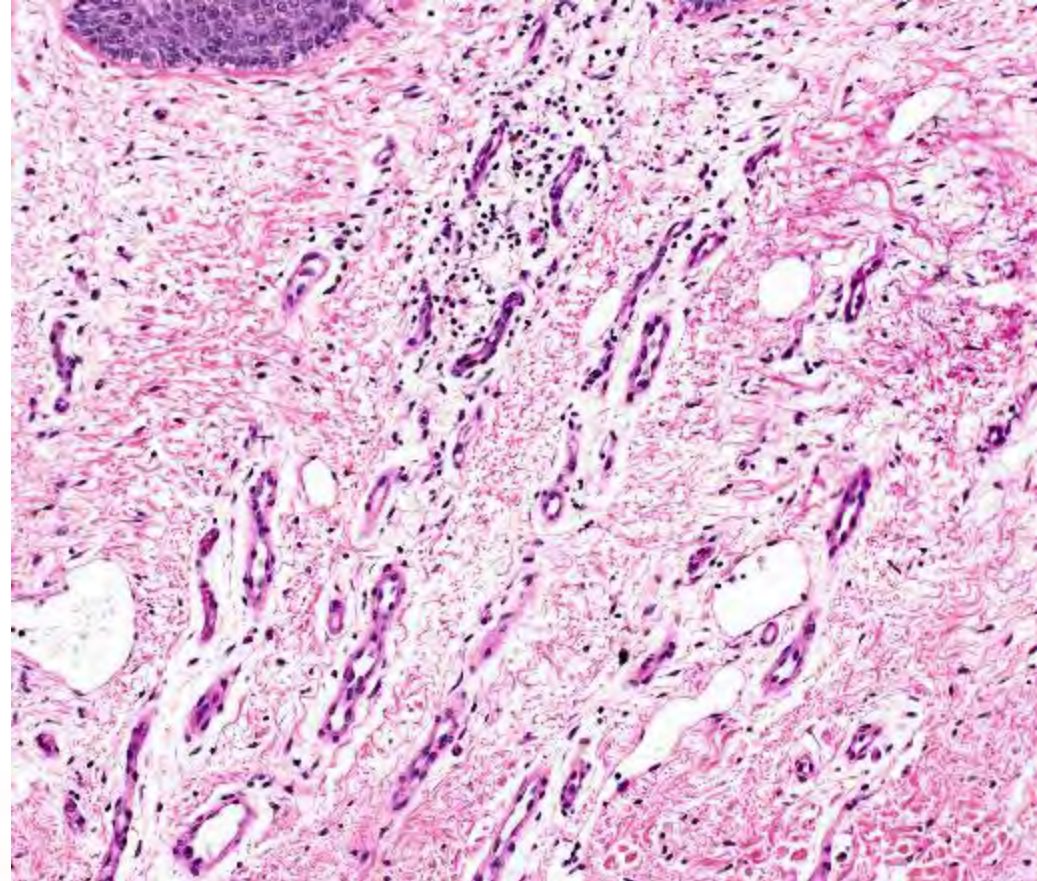
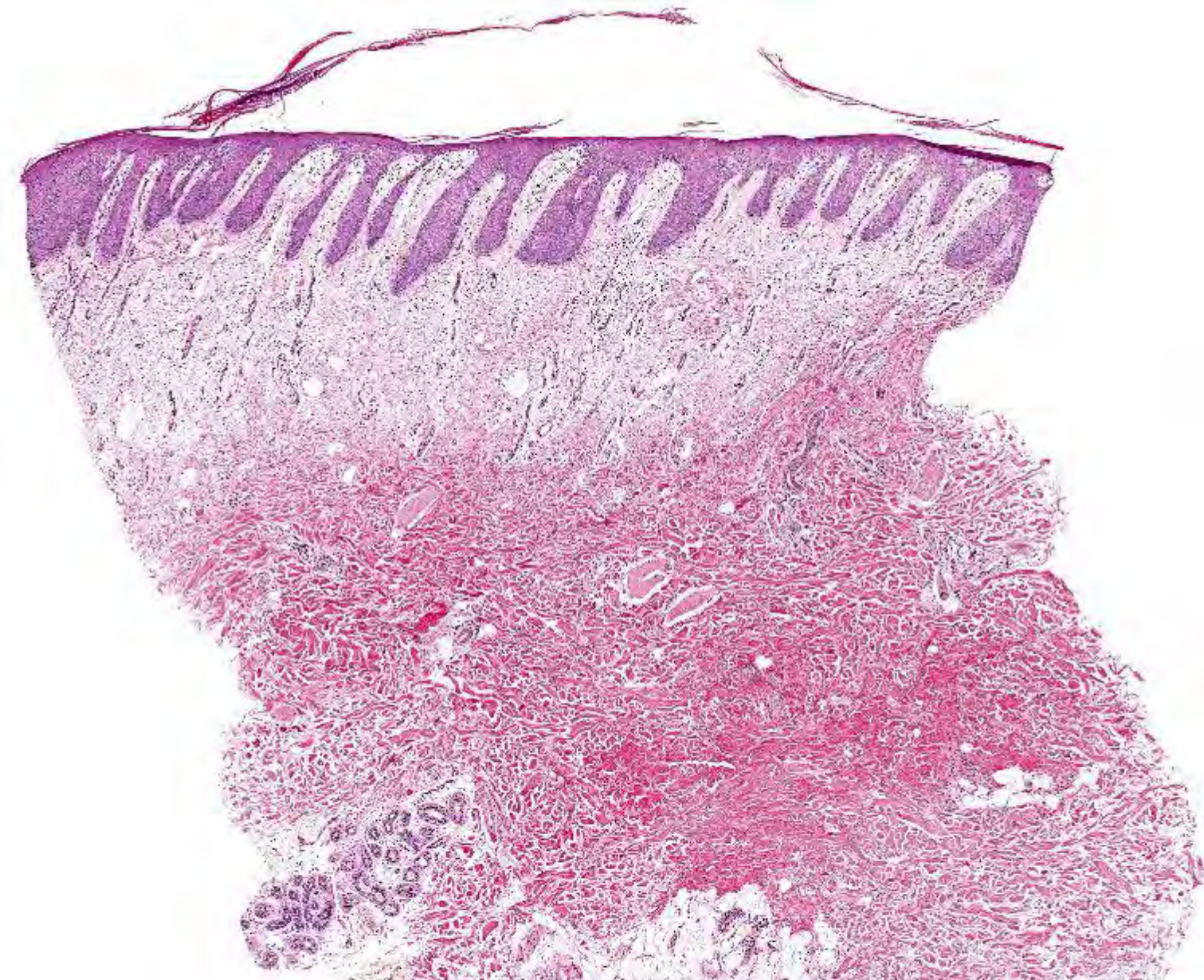




M, 76

History of psoriasis of the scalp (never verified histologically). Lesions on the buttocks present for some months.

A biopsy is taken.



Senile gluteal dermatosis

Report

Senile gluteal dermatosis: a clinical study of 137 cases

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Abstract

Background: Senile (Jugal) demostosis (JRD) is a common geriatric demostosis but has gained little attention before. A large-scale clinical study of this disease is lacking.

Materials and methods We examined 112 consecutive outpatients with glaucomatous skin diseases of different causes. Fourteen skin biopsies were performed. Patient's age, gender, body mass index (BMI), type of wiping or/lytic treatment, separate and underlying systemic diseases were recorded.

Results: Among 137 (55%) patients with AS defined as SVD. These patients, with a mean age of 79.4 ± 40.6 years and a mean BMI of 27.6 ± 10.0 , presented with either period $1 \text{ mm} < 3.2 \text{ mm}$ or $1 \text{ mm} \geq 3.2 \text{ mm}$ ($n = 31, 68\%$). SVD lesions characterized by the sign of specified three corners of a triangle, laterally placed on the distal distal and each side of the aortic. Mitral regurgitation was $133/7$, nothing in path of varying intensity was noticed by 50 patients (36%), and 14 patients (10%), respectively. Diastolic patients (52%) presented with mitral regurgitation, mitral regurgitation, a diastolic murmur of S3. Most patients spent most of the day sitting but reported no specific cause of sitting or lying. More than half of patients with SVD showed no response to total sinusitis (erythrocytosis) in association with patients with SVD. SVD-free patients were grouped ($P = 0.39$ years $P = 0.0005$) and heavier (BMI 28.2 ± 10.8 , $P < 0.0001$) but showed no skin signs. Difference in the frequency of underlying systemic diseases.

Conclusions: SGD is a common dermatosis, mostly affecting the thinner elderly. Friction, pressure and cold hours sitting seemed to be important factors to trigger this dermatosis.

Introduction

Single glomerular dysmaturation (SGD) was first reported in Japan in 1978 as hyperdysmature, sclerotized secretions of the glomerular cleft and assumed to be a common genetic dysmaturation, but since has been limited reporting in the West as well as minimal presence in major dermatology textbooks.¹⁻³

In addition to skin lesions on the glacial delt, as we pointed out recently in a study involving 12 patients with SCD, early brownish plaques may also occur on each side of the buttocks and display a pattern of so-called three corners of a triangle.⁴ However, a large-scale clinical study of this disease is still lacking.

Materials and methods

Patients

It was difficult to recruit willing patients for examination as it required them to expose their glans area. We then opted to examine 162 consecutive outpatients who came to our OPD for their skin lesions on the genital area. STD was defined as

overweight study patients on the gluteal (left and right) side of the buttocks forming complete or partial three corners of a triangle. Patients with three, partial corners, or cubitus or humerohumeral osteoarthritis were excluded from the study. Patient's age, gender, body weight, the way they sit or lie on a chair or bed, and the responses to the treatments were recorded. Between 300 therapies were performed. Special attention was given to the types of chair or bed used by patients daily.

Underlying systemic diseases

Heliopositive or concurrent patients that review was performed to see if there was any significant association between SCD and underlying systemic illness. Relevant systemic diseases were subdivided to free as those that might have made patients more prone to long periods of coma or syncope such as neurologic disorders, malignant neoplasms, heart failure, chronic joint problems (spine or knee joints) or nutrition deficiencies. These diseases were included for any year only if they had been present for at least five years before SCD was verified (all multiple hospitalizations or with occasional hospitalization but frequent outpatient visits for the same problem).



Figure 1 The skin manifestations of SGD. (a) The dominant clinical feature was brownish to darkish scaly plaques on the gluteal cleft and both sides of the buttocks, assuming a pattern of three corners of a triangle. (b) More inflamed type of SGD with multiple erosions. (c) Horizontal hyperkeratotic ridges were noted on the sacral skin lesion. (d) One patient showed a concomitant skin lesion on the hips corresponding with greater trochanter.

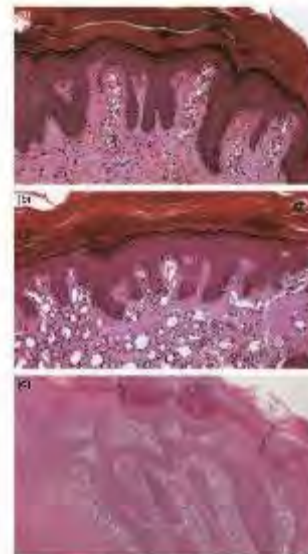


Figure 2 The histopathology of SGLT-3C. (a) Intraepithelial papillary hyperplasia, vascular dilatation in the papillary core, and squamous hyperplasia and keratinization are noted. (b, c) The mucosa was intact, and all clinical changes were found papillary dermal cores, and vessel dilatation protrusion extending down to the acanthotic dermis and dense lymphocytic infiltration (H&E, $\times 200$).

- 137 patients; M:F = 18,6:1; mean age 79.4 years
- Brownish plaques on the gluteal cleft and each side of the buttocks
- Most patients spent most of the day sitting but reported no special way of sitting or lying
- "Senile gluteal dermatosis is a common dermatosis, mostly affecting the thinner elderly. Friction, pressures and long hours sitting seemed to be important factors to trigger this dermatosis"

Prurigiform Angiomatosis: Reactive Angioproliferation in the Skin and Vascular Endothelial Growth Factors

Ann Ortins-Pina, MD,* Luis Soares-de-Almeida, MD, PhD,*†† Ulrich Caroli, MD,§ Lauren Hield, MD,§ Wolfgang Kemper, MD,§ Arno Rütten, MD,§ Thomas Mentzel, MD, PhD,§ and Heinz Kutzner, MD, PhD†§

Background: Cutaneous lichenoid angiomatosis can be diagnostically challenging and may mimic vascular tumors. Keratocytes express vascular endothelial growth factors (VEGFs). We studied the angiogenic factor expression pattern in cutaneous lesions with a distinctive pattern of remarkable dermal angiomatosis underlying prurigo-like epidermal changes.

Methods: Cases were selected retrospectively from 2012 to 2018, and their VEGF staining pattern was compared with control skin and other reactive skin conditions.

Results: Thirty-eight patients, median age 76 years, mostly men (74%), presented with asymptomatic patches or plaques, most commonly located on the buttocks ($n = 17$) and/or intergluteal fold ($n = 12$), often eliciting concern for neoplasia ($n = 19$). Microscopically, all cases featured a prominent proliferation of dilated capillaries and postcapillary venules, underneath epidermal changes resembling prurigo or lichen simplex chronicus. In one-third, a sub-epidermal lymphocytic infiltrate was present. Immunohistochemically, VEGF was positive in the upper 1/2 of the epidermis overlying the angioproliferation, in contrast with control skin, where VEGF positivity was limited to the stratum granulosum. Receptor VEGFR-2 was expressed in the endothelia of neovessels.

Conclusions: We propose the term prurigiform angiomatosis for the morphological picture of prurigo/lichen simplex chronicus-like epidermal hyperplasia with prominent dermal angioproliferation. Mechanical injury and inflammation are the likely triggers of this reactive angiogenesis pattern, driven by condensed VEGF expression.

Key Words: vascular endothelial growth factors; vascular endothelial growth factor receptors; neovascularization; prurigo; vascular skin diseases

(*Am J Dermatopathol* 2019;00:00-00)

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The authors declare no conflicts of interest.

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INTRODUCTION

Reactive angioproliferations on the skin can pose a diagnostic challenge, and in particular cases, they mimic vascular tumors.¹ One of the most important angiogenic factor is the vascular endothelial growth factor (VEGF-A, or VEGF), which regulates angiogenesis prominently through VEGF receptor 2 (VEGFR-2) signaling in vascular endothelial cells² and has been demonstrated to be upregulated and often an active player in reactive, inflammatory, and neoplastic skin diseases.³

Recently, Kacerovska et al described “acquired eosinophilic hemangioma-like changes” in lesions on the knee or elbow showing epithelial features of lichen simplex chronicus (LSC)/prurigo nodularis with a marked subepidermal vascular proliferation.⁴ The authors hypothesized the changes were reactive and probably associated with chronic pressure or repeated mechanical stimulation.

We report a series of cases with a similar pattern: prurigo/LSC-like epidermal hyperplasia and prominent benign dermal angioproliferation—for which we propose the descriptive term prurigiform angiomatosis. We discuss a pathogenesis model based on the expression pattern of VEGF and VEGFR-2.

MATERIAL AND METHODS

Formalin-fixed paraffin-embedded specimens were selected from the files of Dermatopathologie Friedrichshafen and Laboratory of Cutaneous Histopathology in Centro Hospitalar Lisboa Norte, from the last 7 years (dated between 2012 and 2018). All specimens had been fixed for more than 24 hours in 4% buffered formalin. Clinical information and follow-up were retrieved from the laboratory request forms and from consulting clinicians.

Study cases were selected upon the following criteria: clinical findings of asymptomatic flat prurigo-form lesions in conjunction with a distinct histopathological pattern of flat prurigo and prominent adjacent angiomatosis. Control samples were retrieved from the archives for immunohistochemistry studies. Normal skin at the non-lesional periphery of the study cases was used as a negative control. As positive controls, skin conditions with reactive epidermal acanthosis and angiogenesis were selected: regenerative scar, prurigo, granulation tissue, and Orf’s nodules.

Four-micron-thick sections were stained with hematoxylin and eosin. Immunostains were performed on



FIGURE 1. Prurigiform angiomatosis, clinical features. Commonly located on the intergluteal folds and/or buttocks, it typically presents as red-brown patches or plaques with a violaceous hue and a pale pink center; some have a yellow scale-crust and/or erosion (A–E).

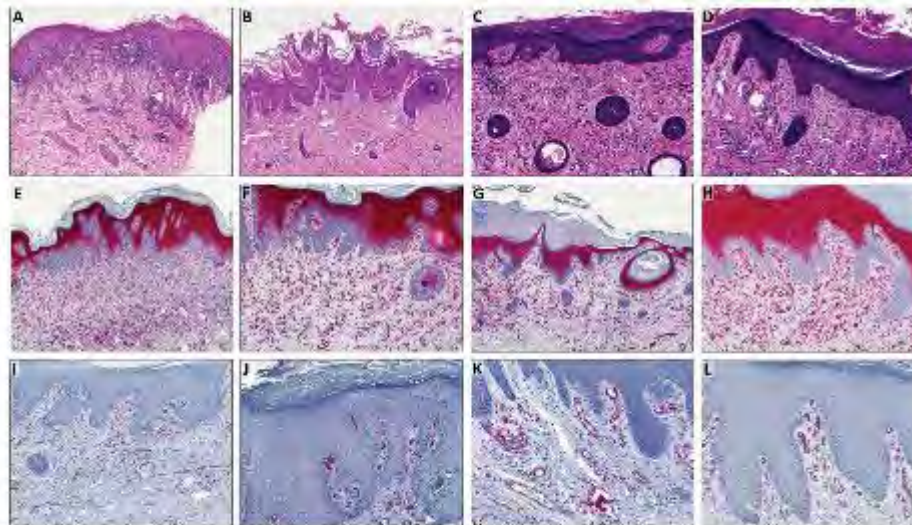


FIGURE 2. Prurigiform angiomatosis. Morphological features (A–D), hematoxylin-eosin; VEGF immunohistochemistry (E–H); VEGFR-2 immunohistochemistry (I–L) (original magnification, A and E $\times 40$, B, C, I, and J $\times 100$, D, G, H, and L $\times 400$).

- 38 patients; median age 76 years; M:F = 2,8:1
- Prominent proliferation of dilated capillaries and postcapillary venules, underneath epidermal changes resembling lichen simplex chronicus
- "We propose the term prurigiform angiomatosis for the morphological picture of prurigo/lichen simplex chronicus-like epidermal hyperplasia with prominent dermal angioproliferation"

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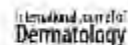
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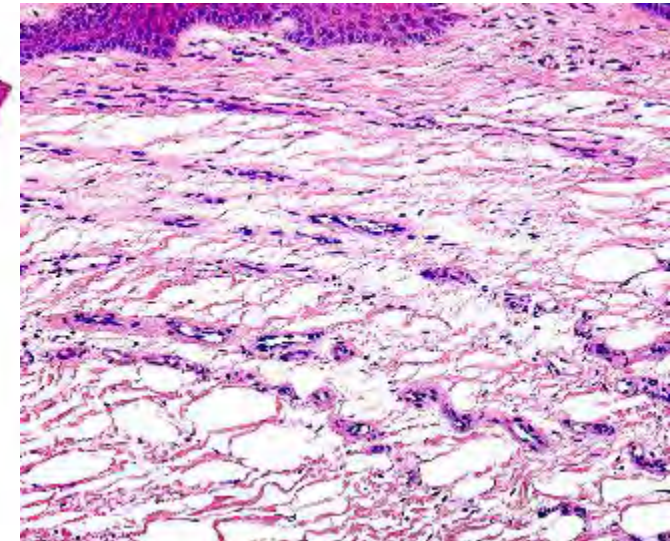
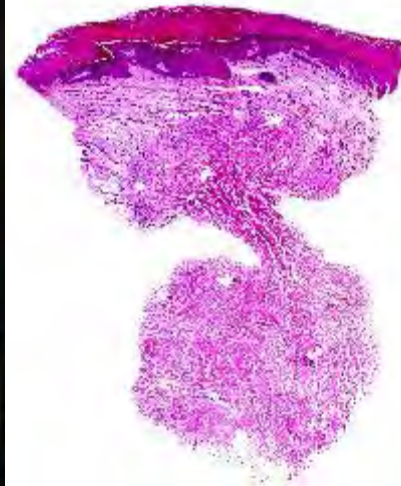


Graz, June 30 - July 4, 2025

**Course Director:
Lorenzo Cerroni, MD**

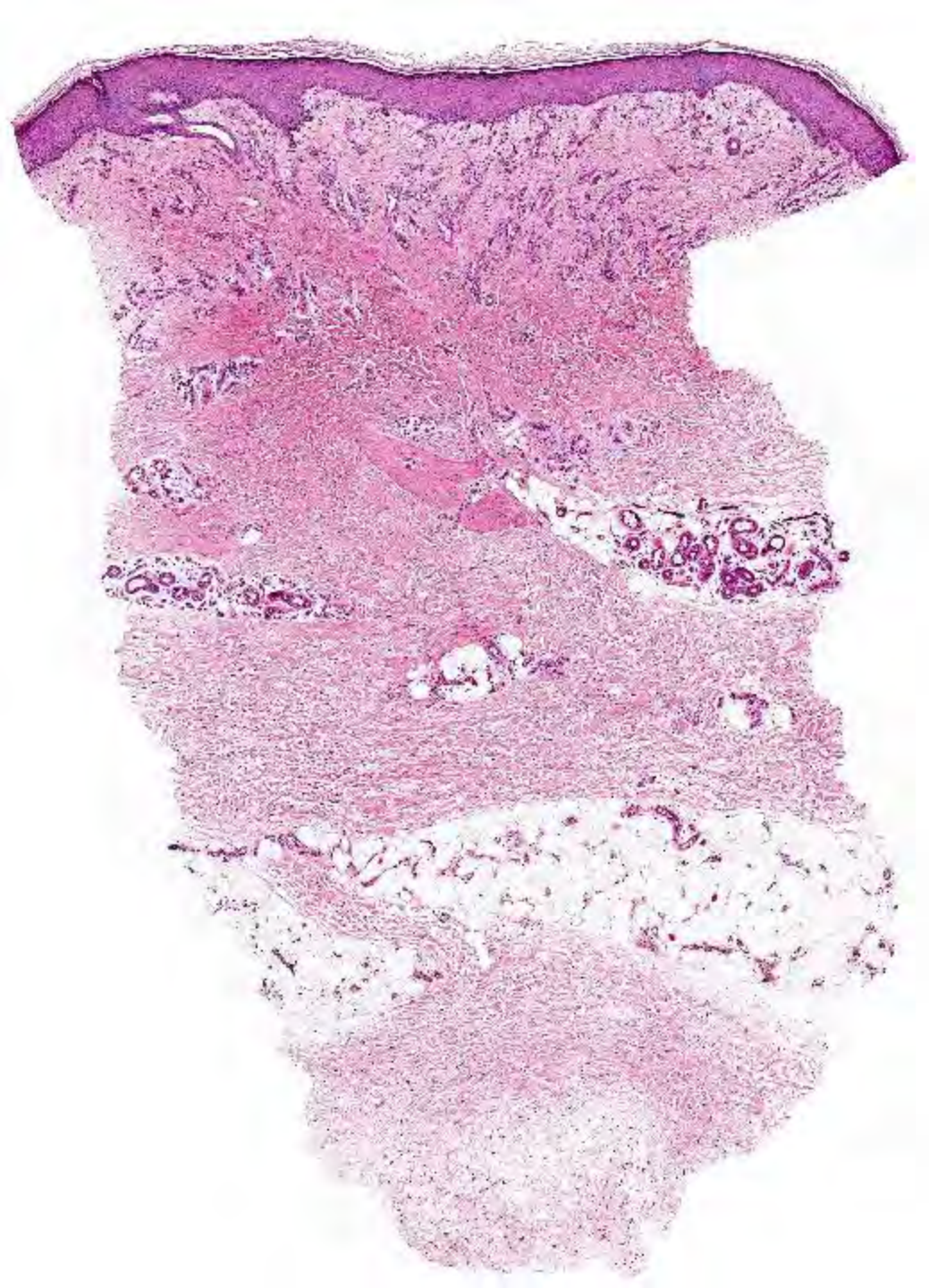
Dr. Luis Requena (El Catedrático) Interesting and teaching cases from Madrid

M, 63



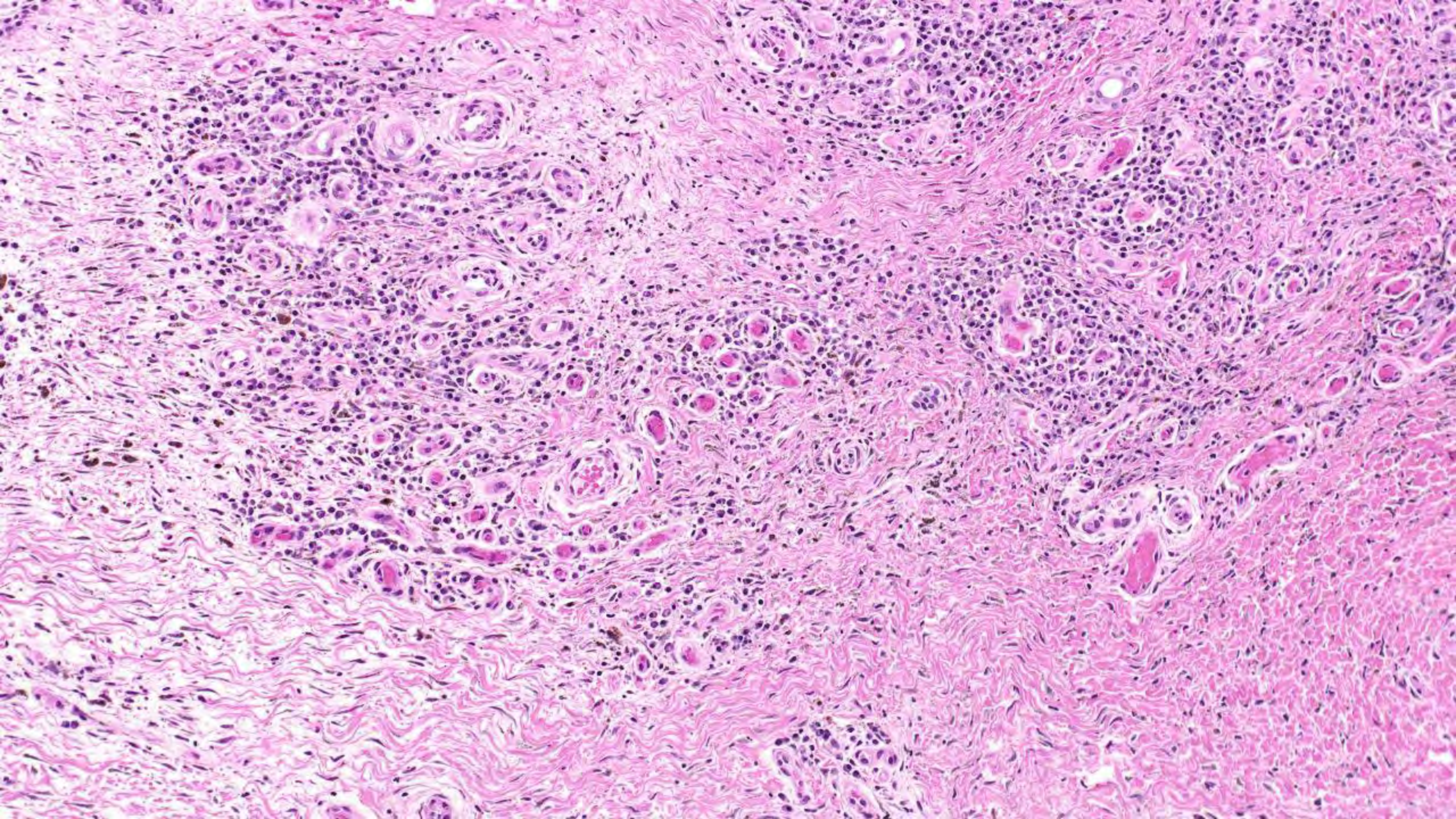
Personal opinion of El Catedrático:

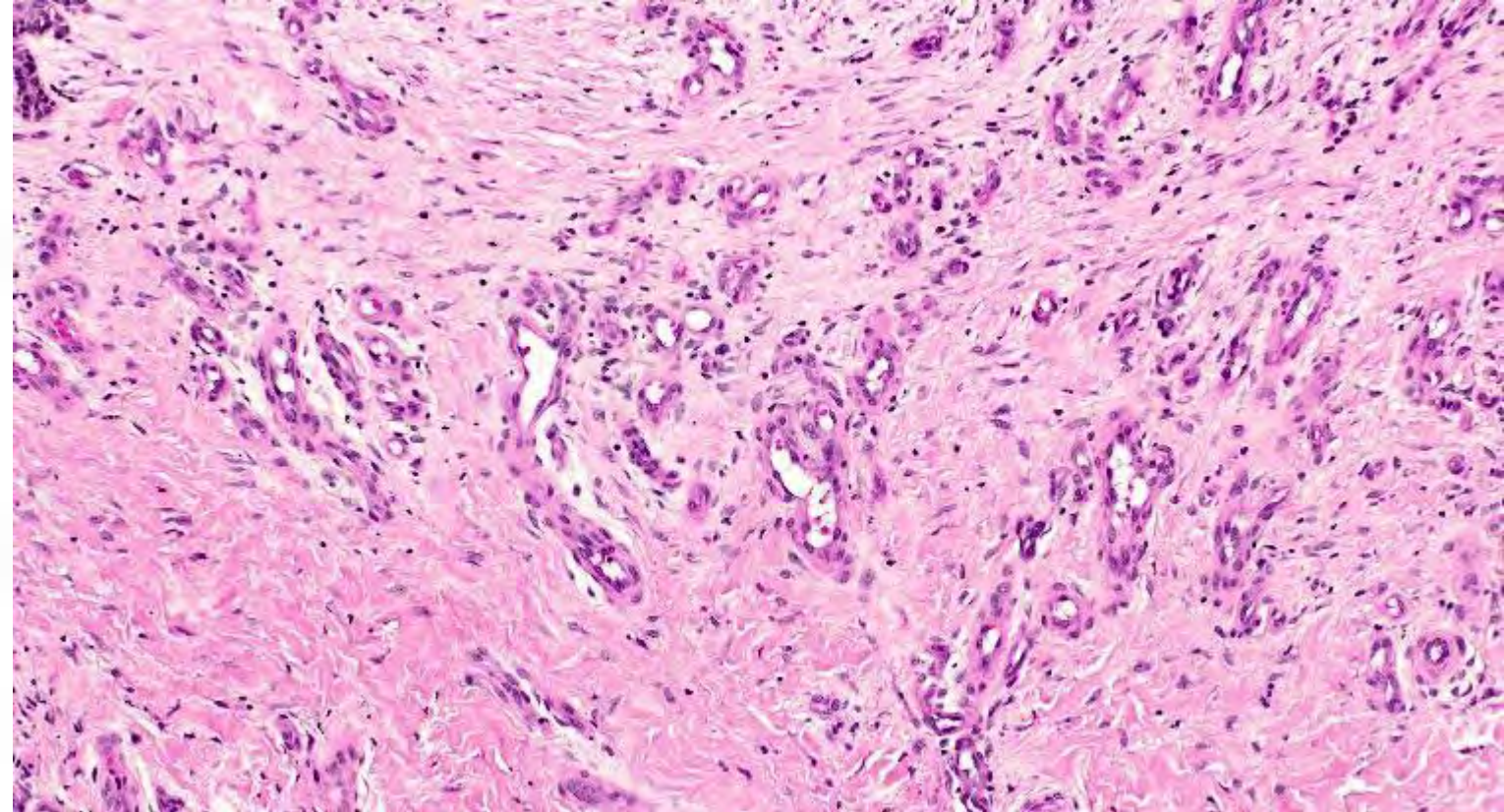
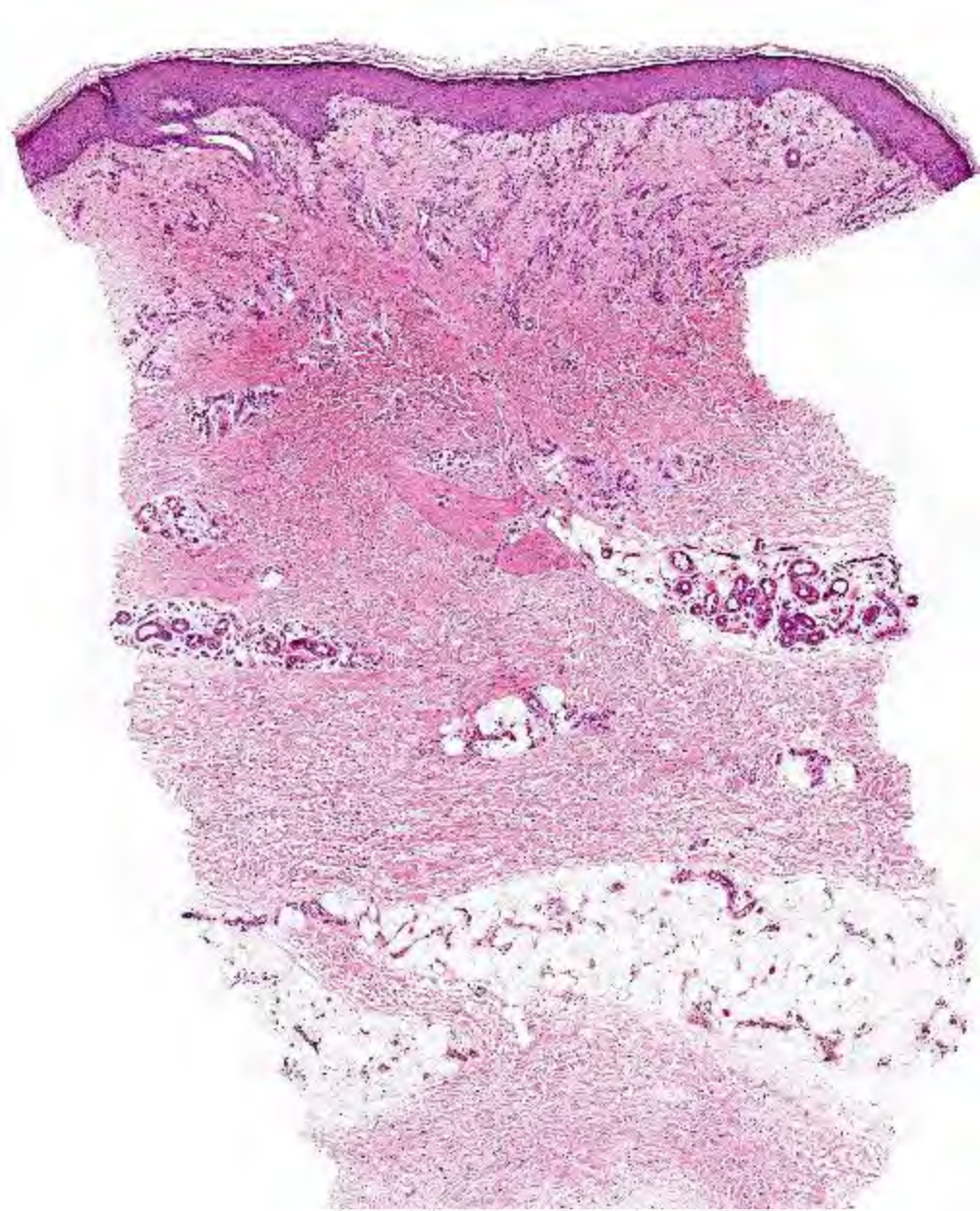
- Senile gluteal dermatosis, prurigiform angiomatosis and poikilodermatous plaque-like hemangioma are the same entity
- Probably this lesion is not a hemangioma, but a reactive process secondary to friction, pressure and long hours sitting in elderly patients



M, 71

According to the patient lesion on the left lower leg for 2 months. No improvement after 2 weeks of cefuroxime.



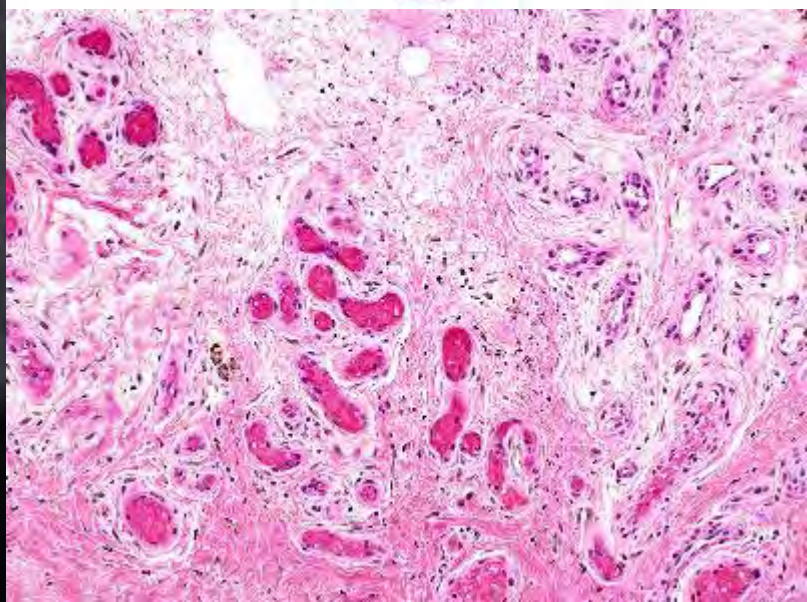
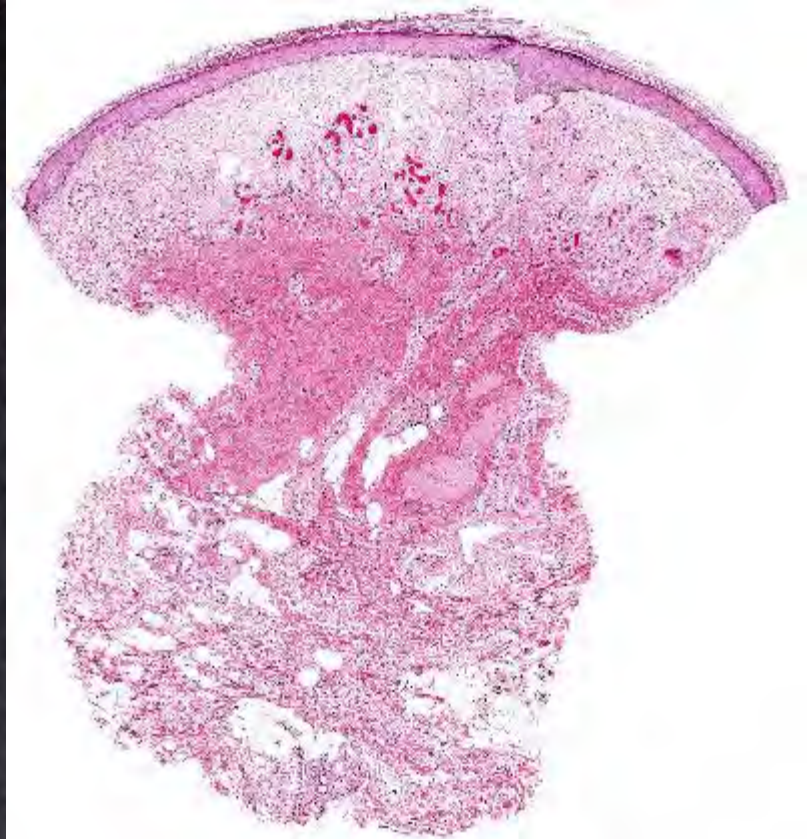


Stasis dermatitis

My personal opinion:

- Senile gluteal dermatosis, prurigiform angiomatosis and poikilodermatous plaque-like hemangioma belong to the spectrum of "stasis dermatitis"
- All these lesions show a variable proliferation of small capillaries, mostly within the superficial dermis; epidermal changes may or may not be present
- This proliferation of capillaries is not a hemangioma, but represents a reactive process secondary to different noxae, all of which result in alterations of the blood flow and reduced oxygen delivery to the skin (*chronic oxygen deprivation dermatitis – cODD*)

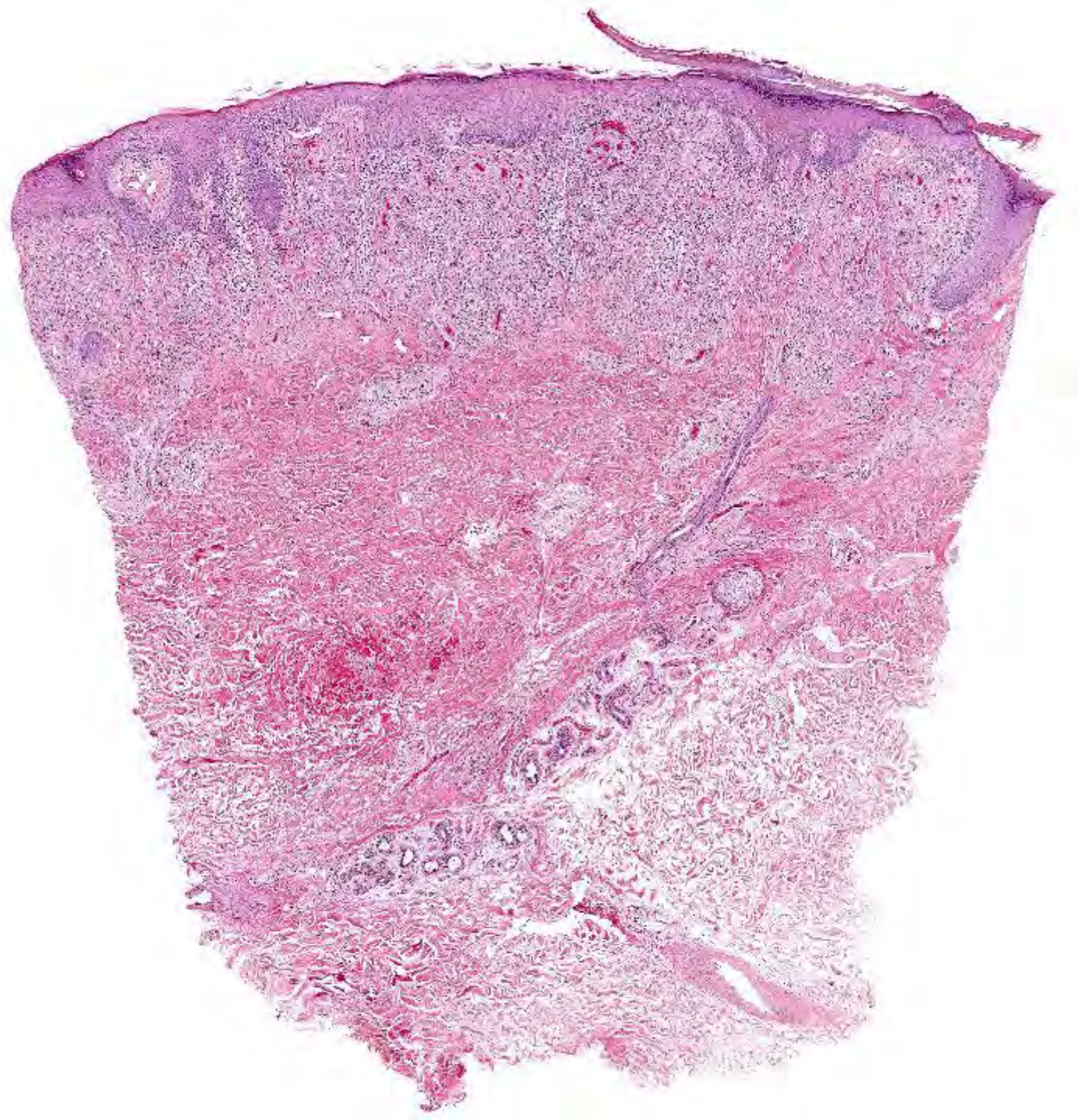
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M, 74



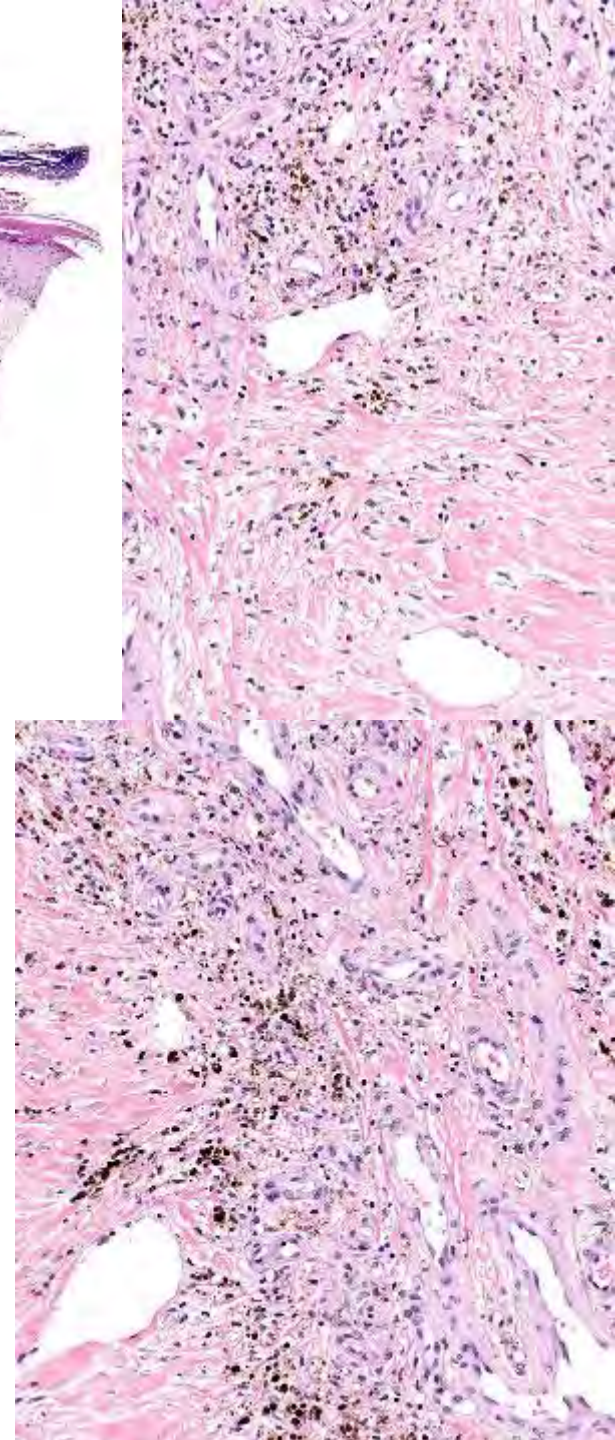
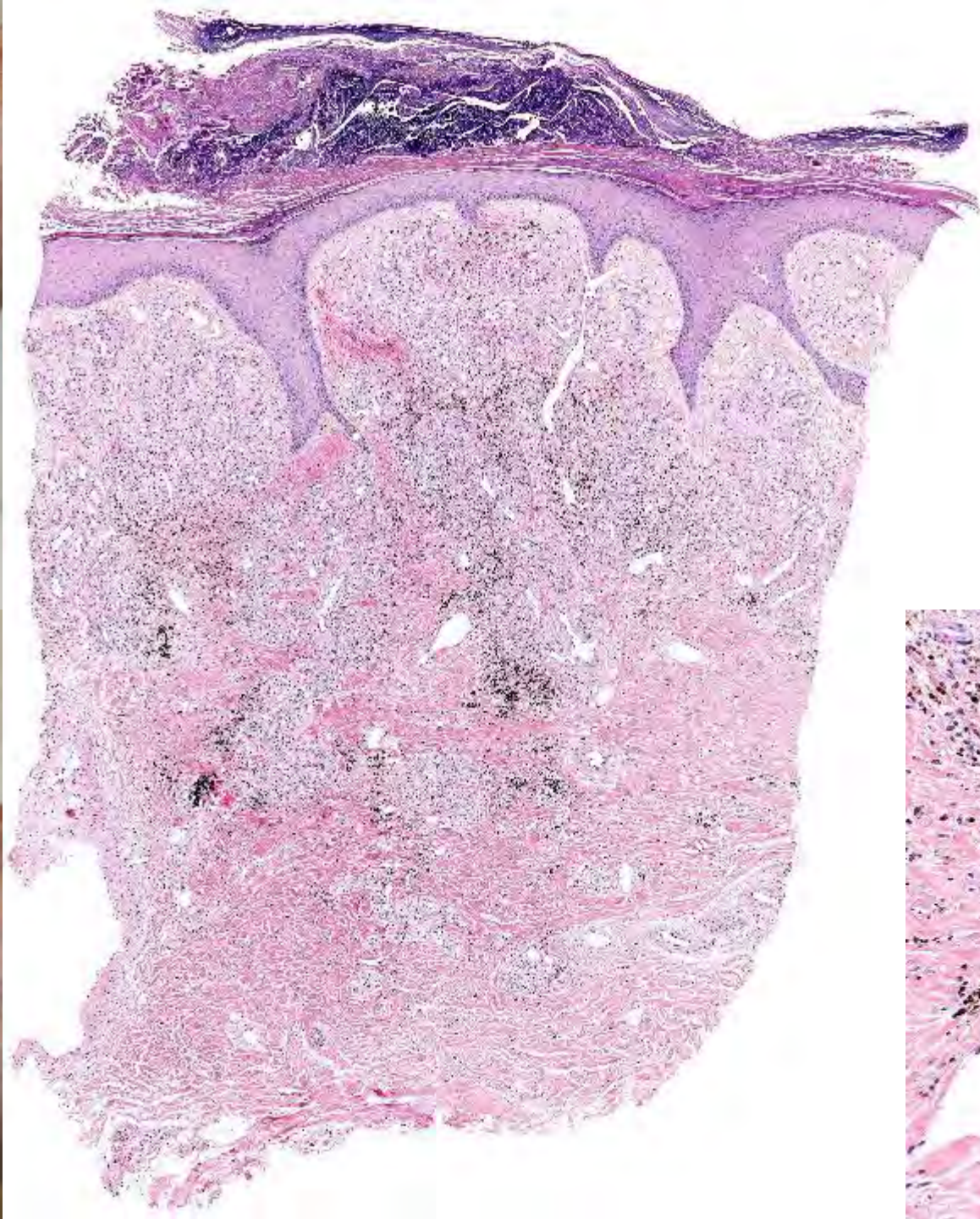
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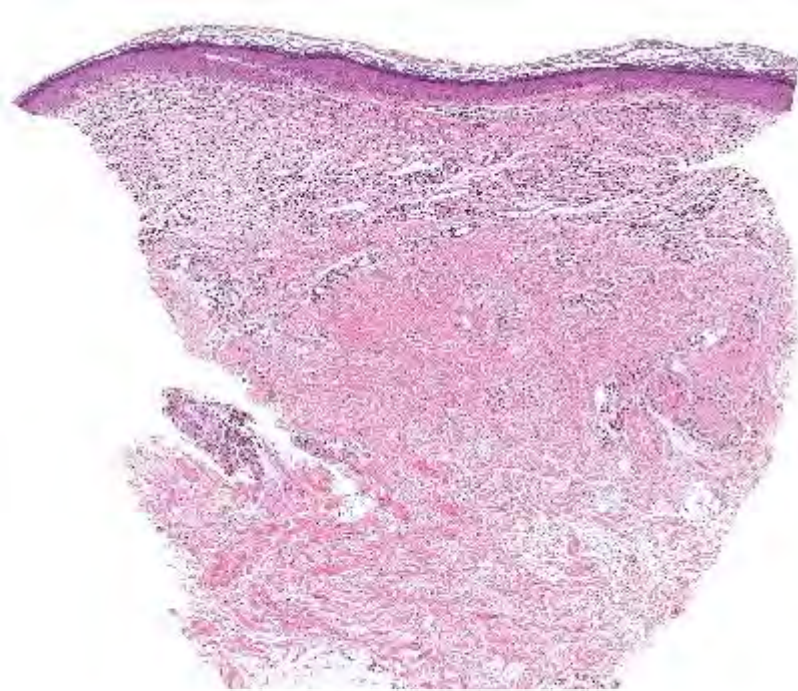
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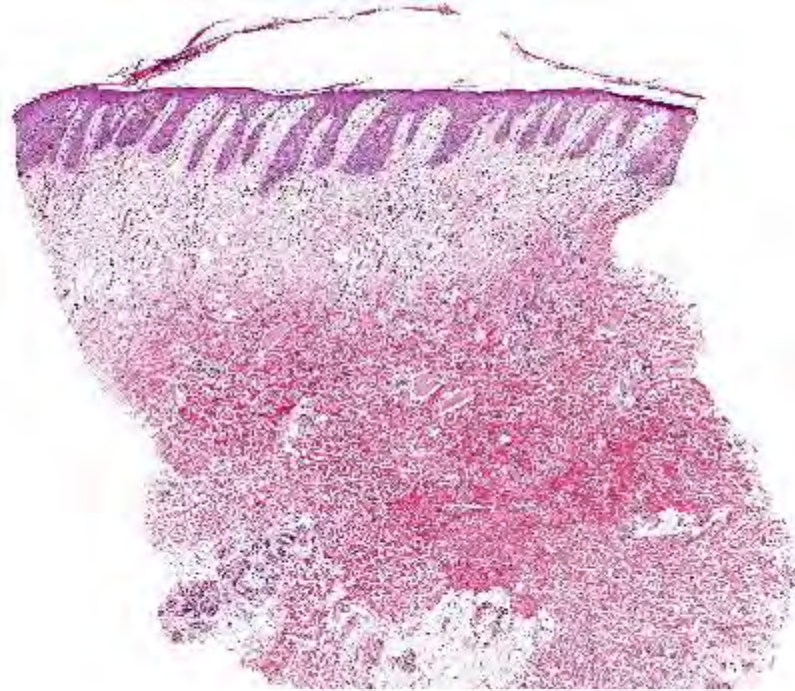
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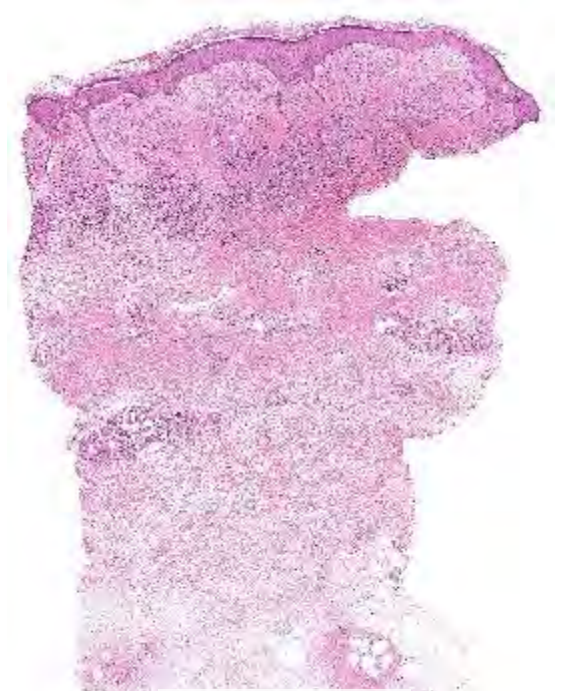
Chronic Oxygen Deprivation Dermatitis – cODD



Poikilodermatous plaque-like hemangioma



Senile gluteal dermatosis / Prurigiform angiomas



Stasis dermatitis



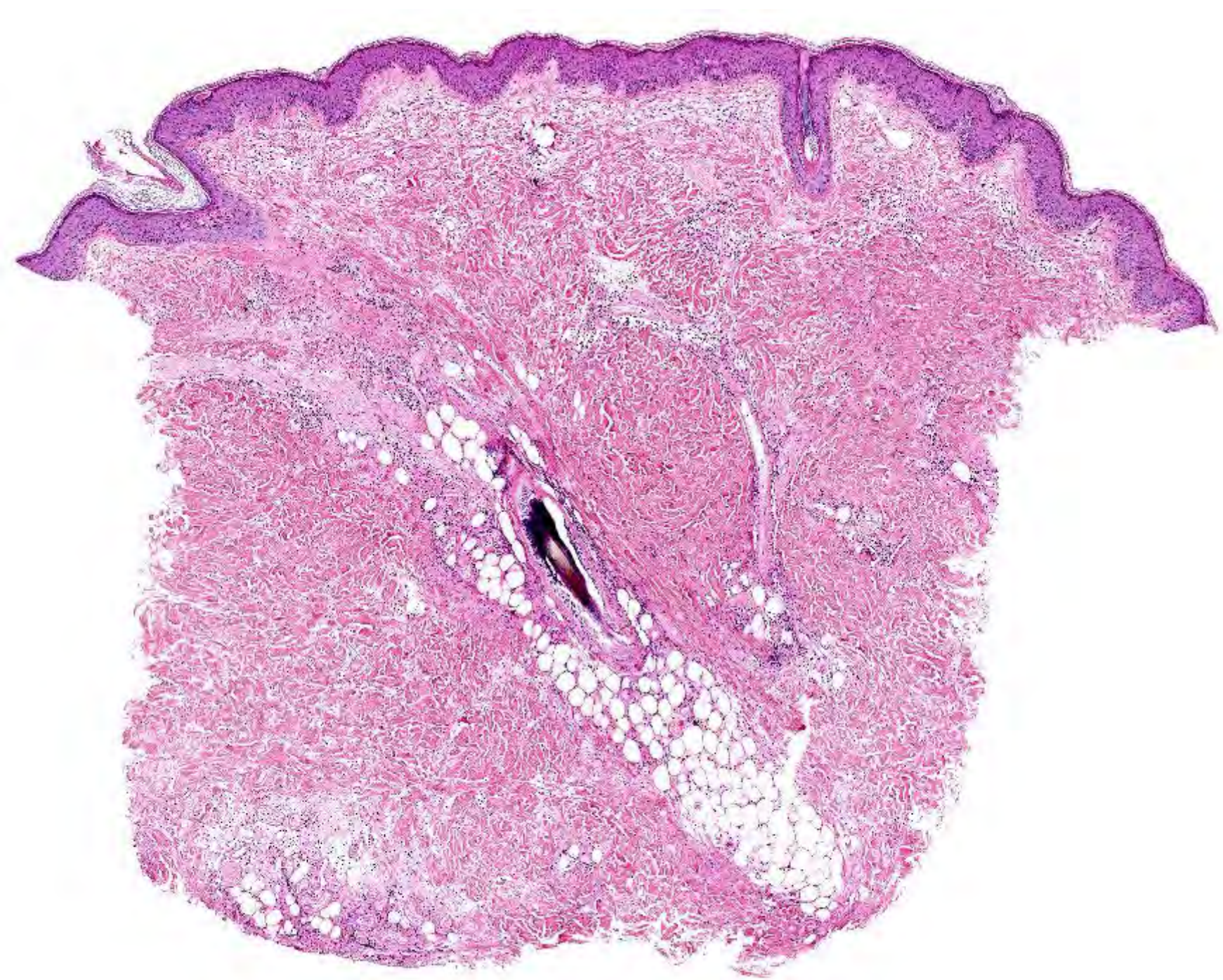
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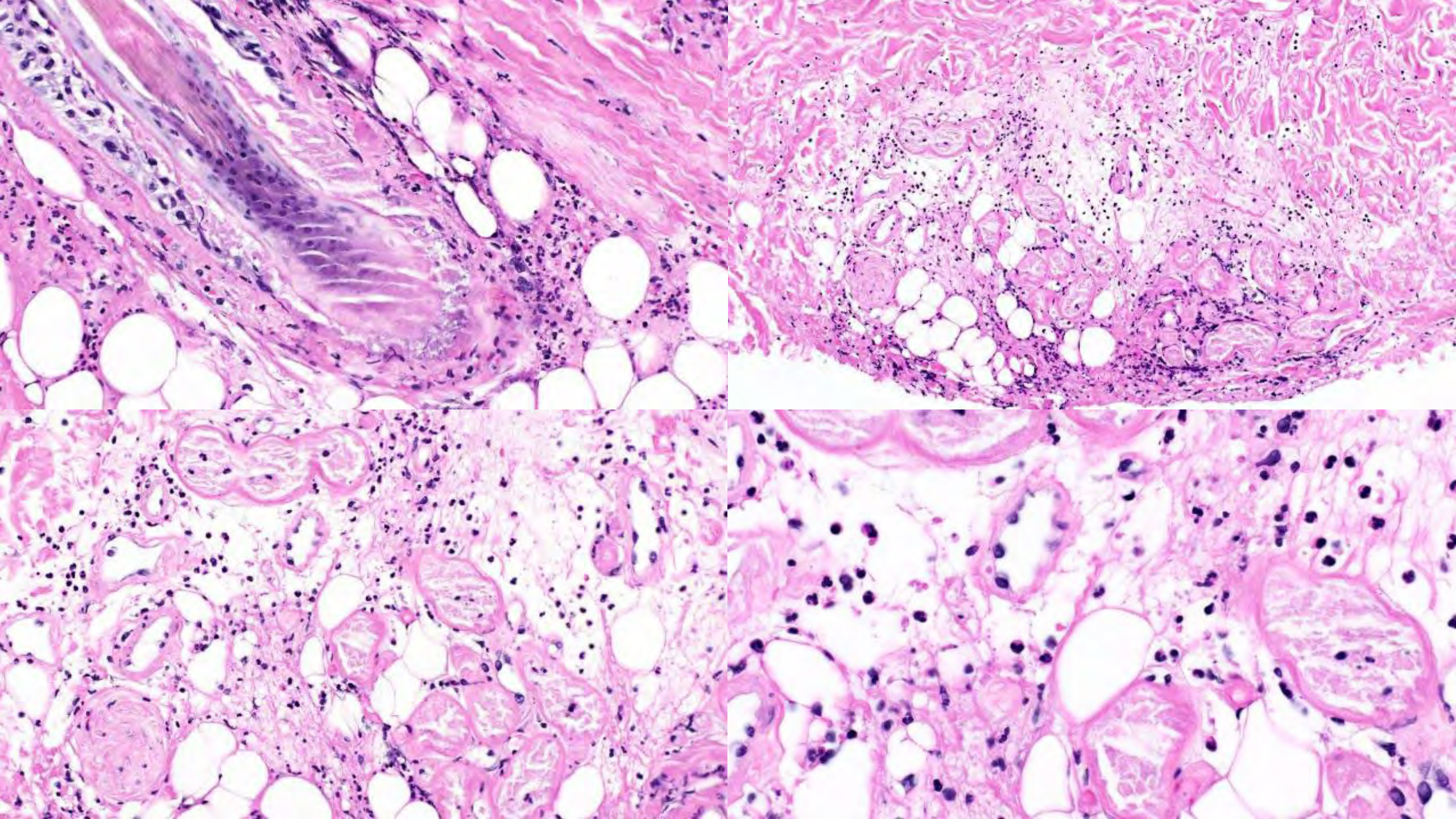
History of psychosis, hallucination, self-inflicted wounds, drug intake.

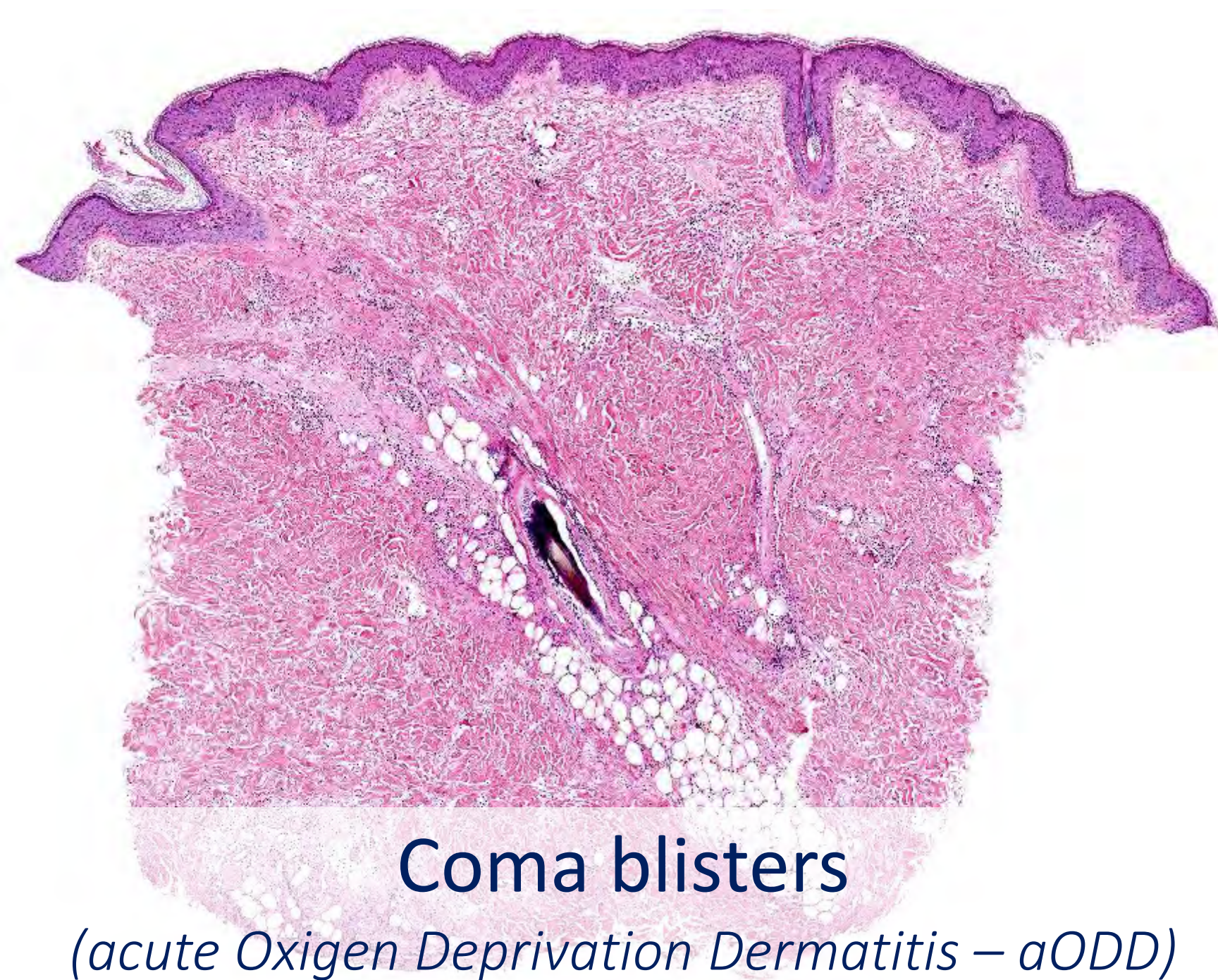
Found unconscious on the floor and taken to the hospital.

Two days later dermatological consultation for evaluation of partly bullous, fixed lesions on the skin.

A biopsy is taken.



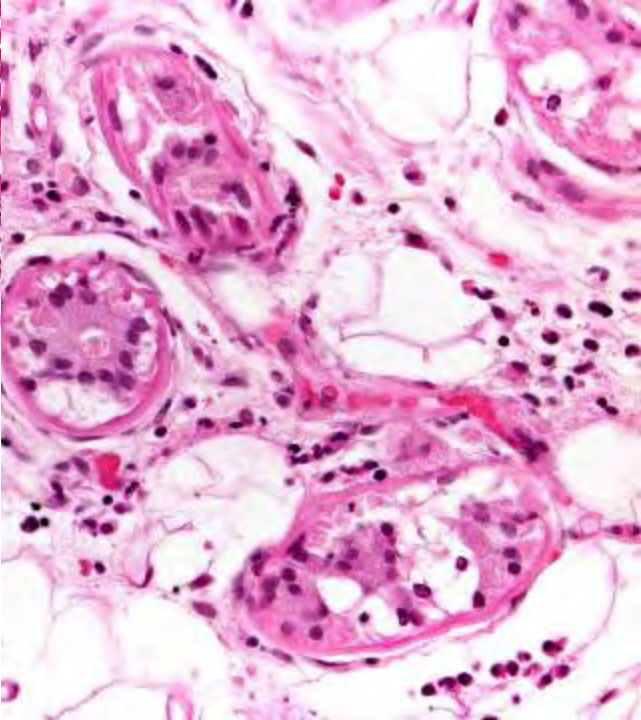
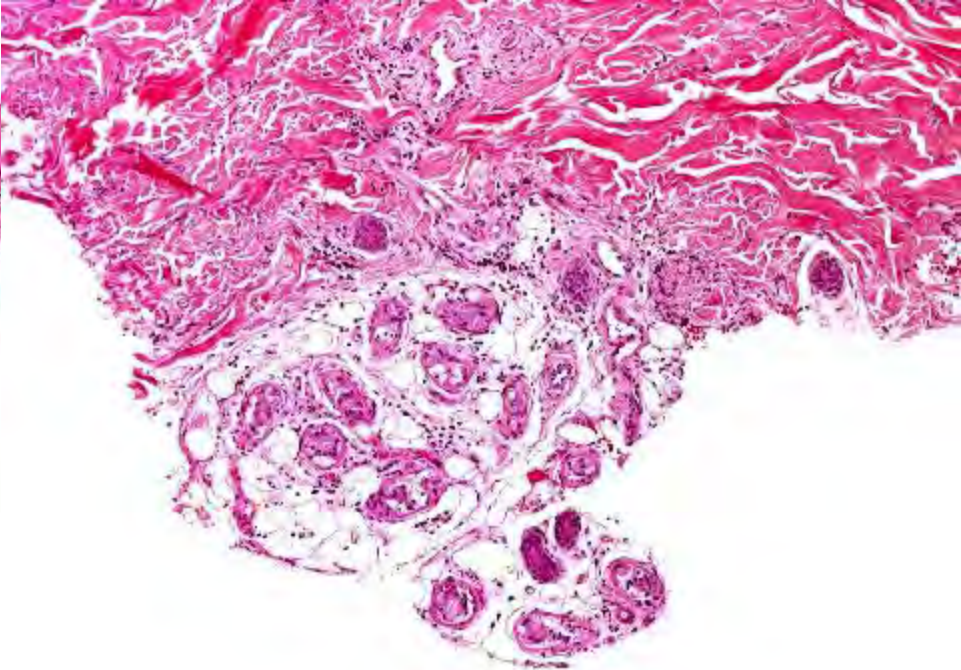




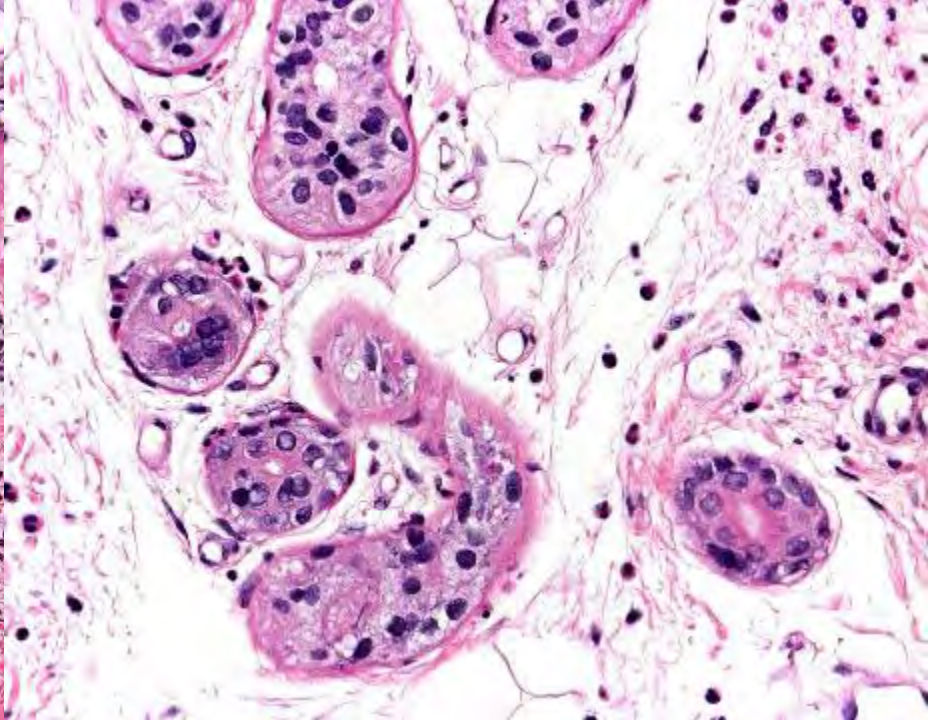
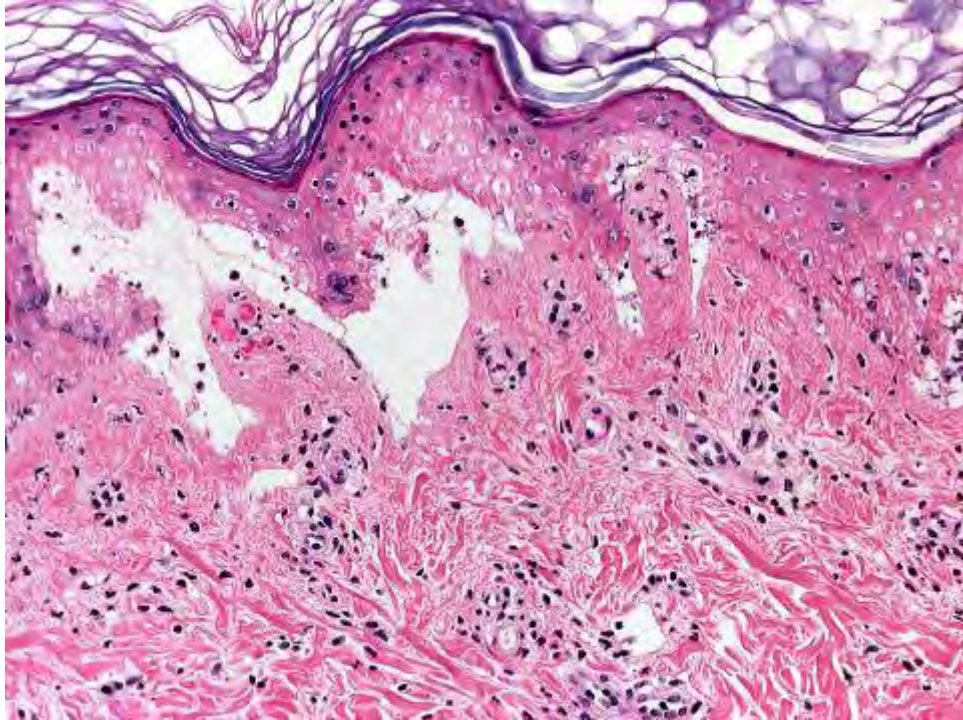
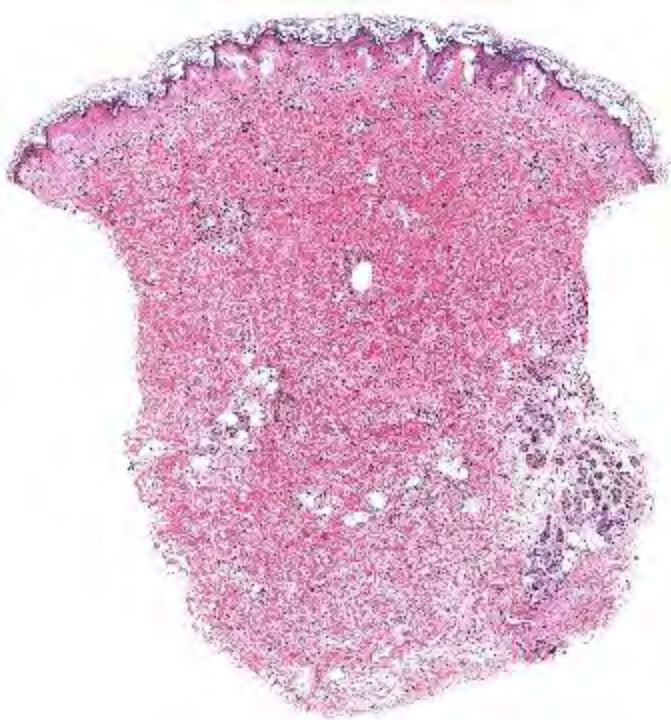
Coma blisters (coma bullae)

- Associated with several noxae (e.g., barbiturate, opioids or benzodiazepine overdose, CO intoxication, alcohol, viral encephalitis, hypoglycemia, cerebrovascular accidents)
- Have been observed also following surgical procedures requiring general anesthesia, and in non-comatose patients (particularly those with severe neurologic diseases or after prolonged immobilization)
- Most likely due to pressure-related ischemia; secretion of drugs through eccrine glands probably plays no role (necrosis of glands seen also in cases unrelated to drugs)
- All cases show similar histopathological features irrespective of the etiology / mechanism

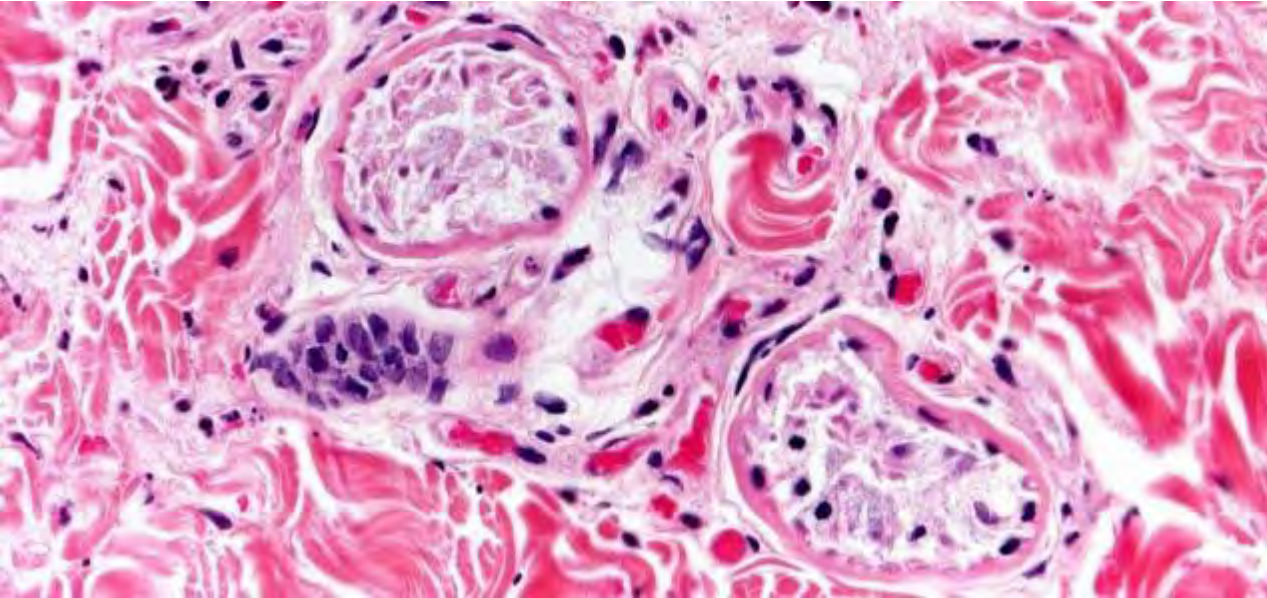
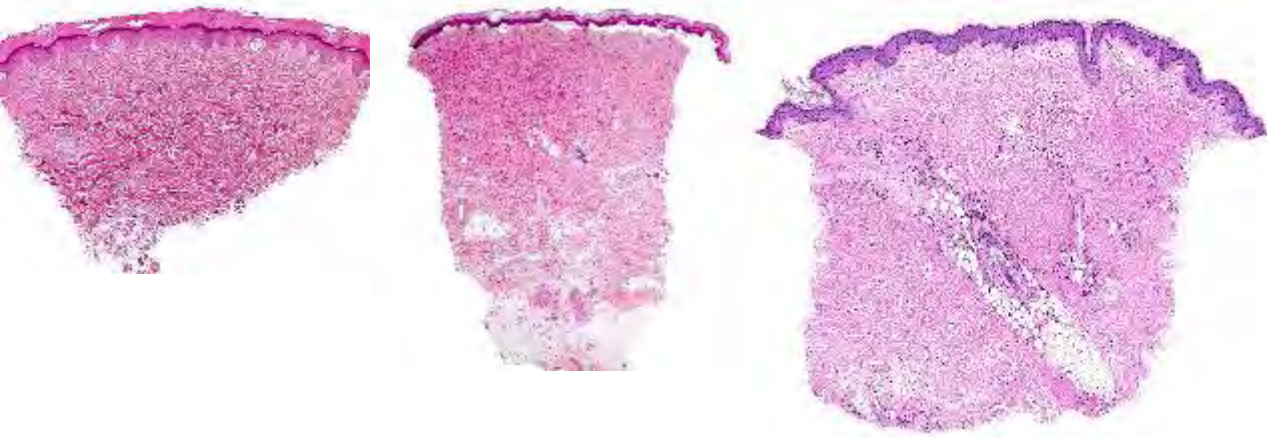
CO intoxication



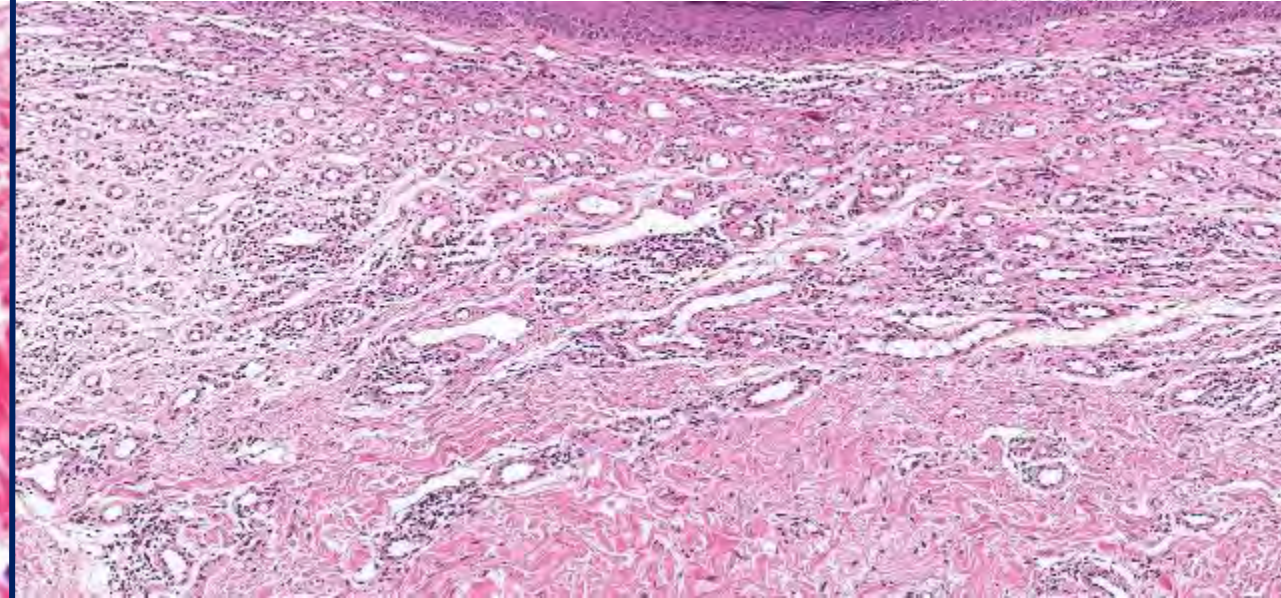
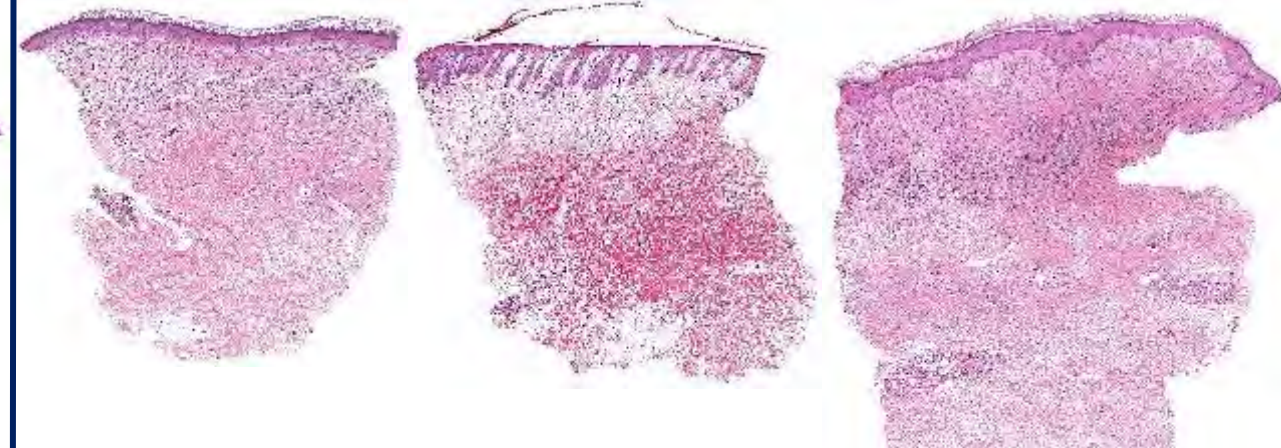
Barbiturate intoxication



Acute Oxygen Deprivation Dermatitis – aODD



Chronic Oxygen Deprivation Dermatitis – cODD



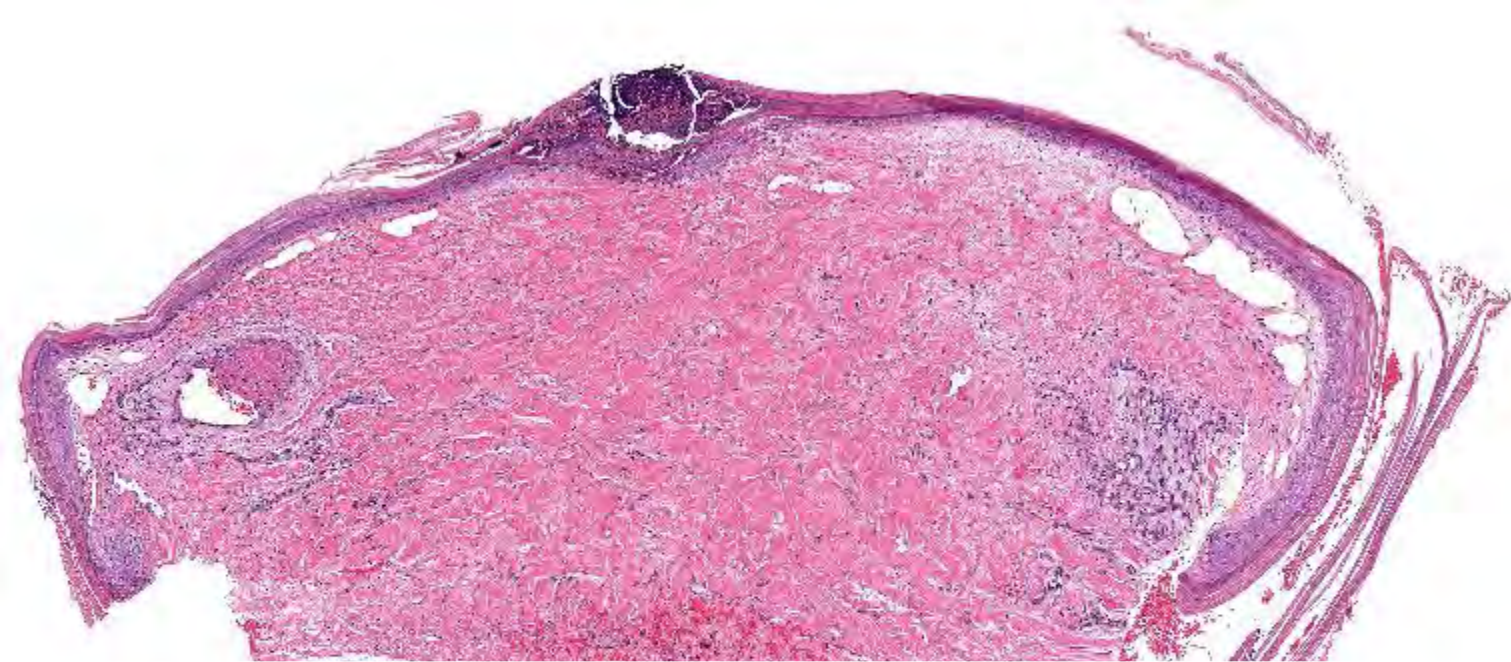


F, 73

Giant inguinal hernia.

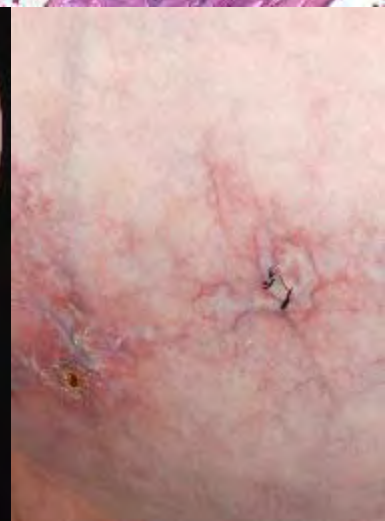
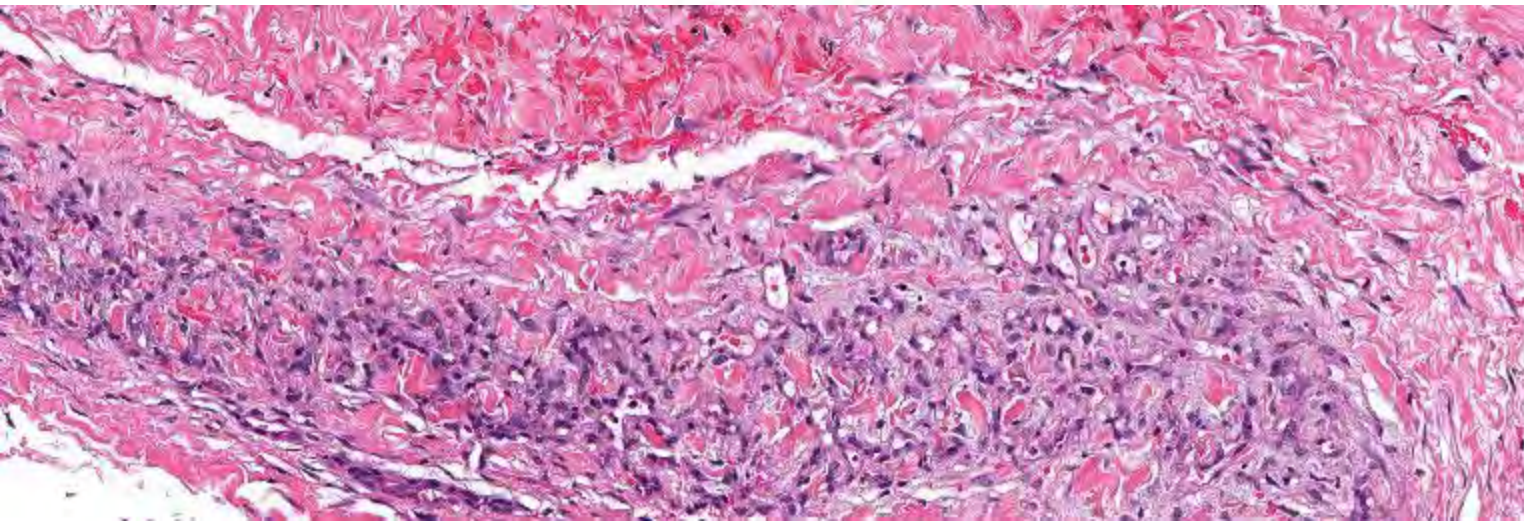
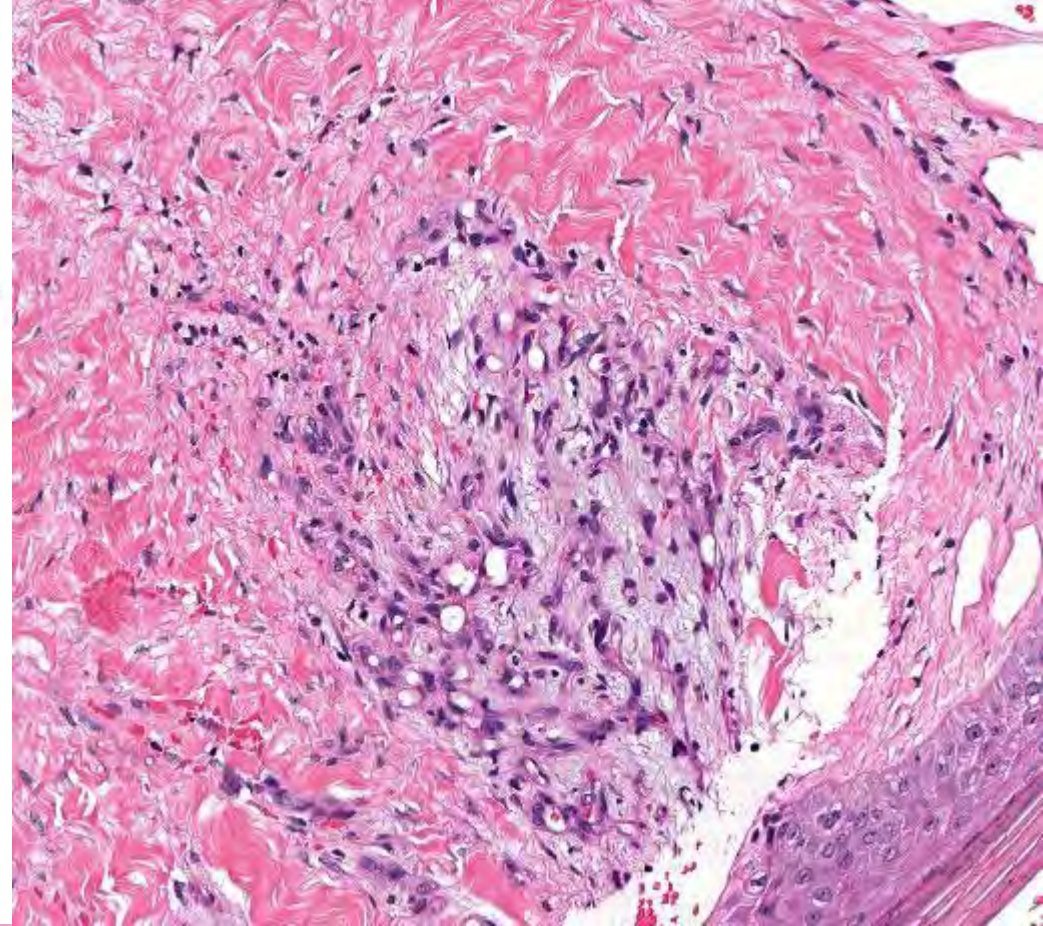
According to the patient partly ulcerative abdominal lesions for some months.

A biopsy is taken.



Diffuse dermal angiomas

(focal chronic Oxygen Deprivation Dermatitis)





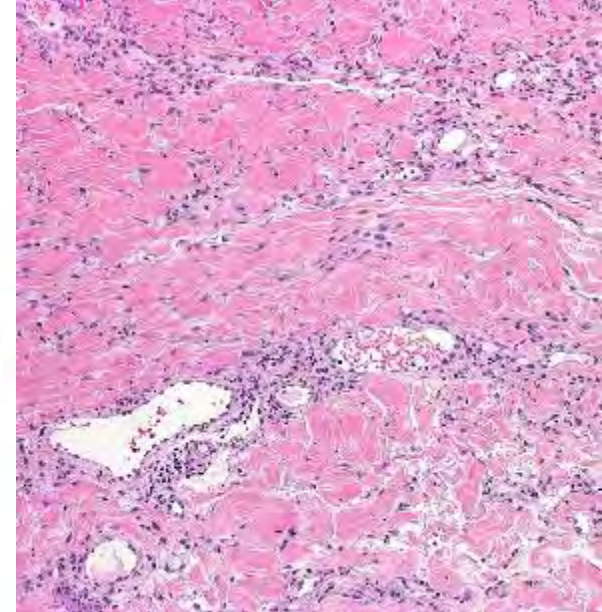
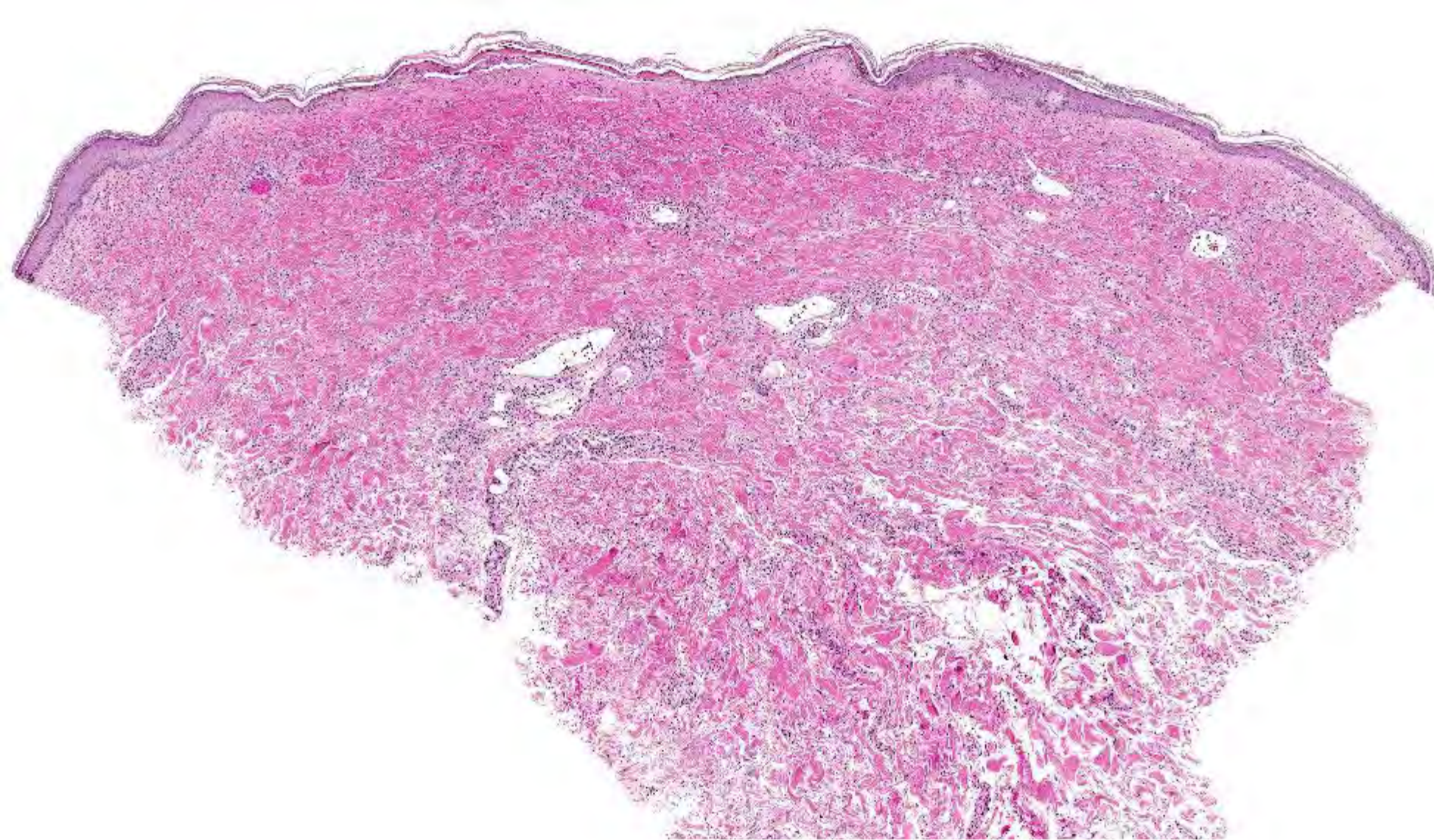
F, 70

History of dyslipidemia and essential hypertension, managed with furosemide, nebivolol, amlodipine, valsartan, ticagleror and cardioaspirin. Myocardial infarction 1 month before onset of skin lesions.

Painful, ulcerative lesions on the lower abdomen for 2 months.

A biopsy is taken.

(Consultation Dr. C. Cota, Roma)



Diffuse dermal angiomatosis
(focal chronic Oxygen Deprivation Dermatitis)

Diffuse dermal angiomatosis of the abdomen

Diffuse dermal angiomatosis (DDA) is a well-defined clinicopathological entity belonging to the cutaneous reactive angiomatoses, a group of benign vascular disorders characterized by intravascular and extravascular hyperplasia of endothelial cells with or without accompanying

EJD, vol. 25, n° 4, July-August 2015

lesions, except for slightly increased c-ANCA. Biopsy specimens obtained from a purpuric plaque and in the edge of the ulcer revealed a diffuse proliferation of vascular endothelial cells within the entire dermis with several to some capillary vessels and focal hemorrhage (figures 1B, C). Cholesterol crystals and vasculitis were not seen. The cells were positive for CD31 and Wt1 (figure 1D) and negative for HHV8 and p63/p40. A diagnosis of DDA was made. The patient was treated with potent topical steroids, resulting in a partial improvement within one month.

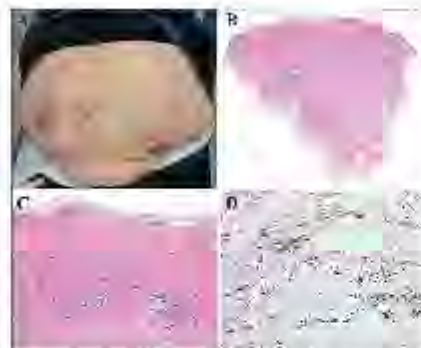


Figure 1. Diffuse dermal angiomatosis. A) Several, ill-defined, non-itchy, purpuric, partly necrotic patches and plaques on the abdomen. B) Histology reveals a diffuse vascular proliferation within the entire dermis. C) High-power view shows a proliferation of vascular endothelial cells in the dermis with telangiectatic vessels and focal hemorrhage. D) The cells are positive for Wt1.

secondary to autoimmune diseases [2]. A case related to myofasciitis after administration of intrathecal and peripheral intravenous immunoglobulin involves trunk and sites on the lower extremities, elbows, back of the hands and feet [3, 4].

Development of the situation has rarely been reported. In one patient, lesions of DDA appeared secondary to abdominal plastic, whereas another patient suffered from intra- and extracranial without evidence of exclusive vascular disease [5, 6]. Our patient had a history of obesity, dyslipidemia and hypertension, all of which represent risk factors for vasculocclusive disease. The ischemic etiology of DDA was further supported by the development of myocardial infarction and the development of ulcerations on the distal lower limbs. In addition, as hypothesized, the cases occurring on large pendulous breasts, recurrent traumatism over a fat-rich area could also contribute to neoangiogenesis, particularly in patients with a procoagulant state or vascular damage as our case.

In conclusion, DDA is a rare condition that should be readily diagnosed by clinicians. Recognition of risk factors and their management, with restoration of sufficient vascular supply to the affected sites is critical for the management of this condition. ■

Disclosure. Financial support: none. Conflict of interest: none.

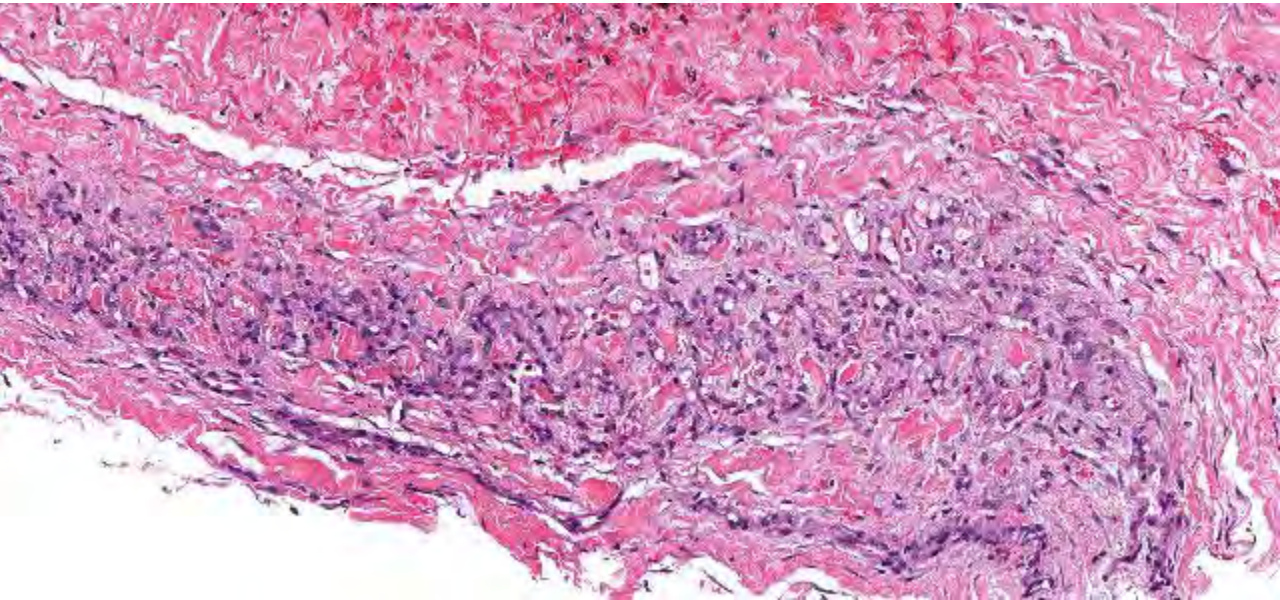
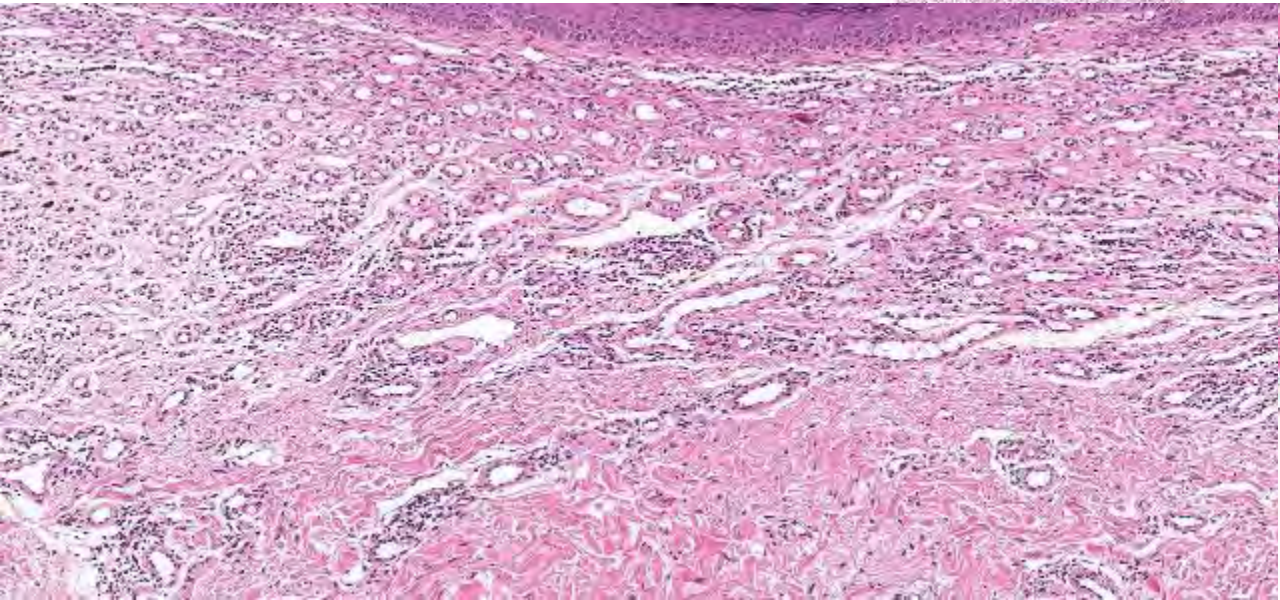
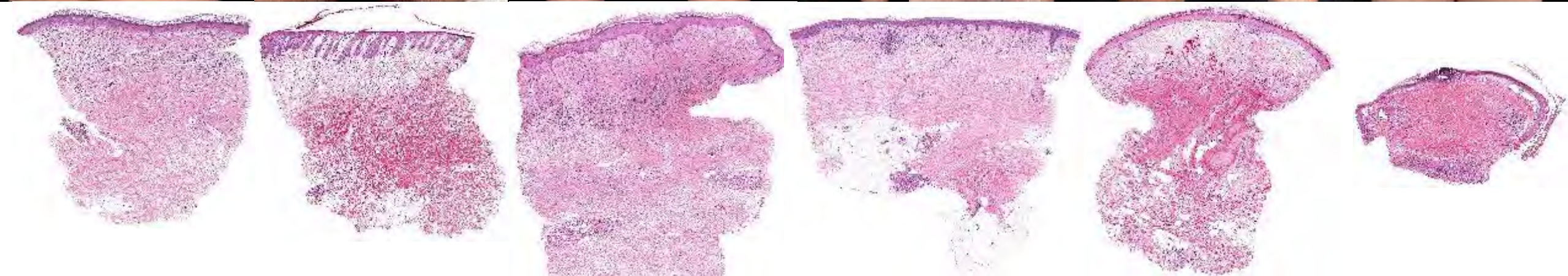
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Viviana LORA¹
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The ischemic etiology of DDA (*in this case*) was further supported by the development of myocardial infarction one month before the appearance of the cutaneous lesions. In addition, as hypothesized for cases occurring on large pendulous breasts, recurrent traumatism over a fat-rich area could also contribute to neoangiogenesis, particularly in patients with a procoagulant state or vascular damage.

Chronic Oxygen Deprivation Dermatitis – cODD

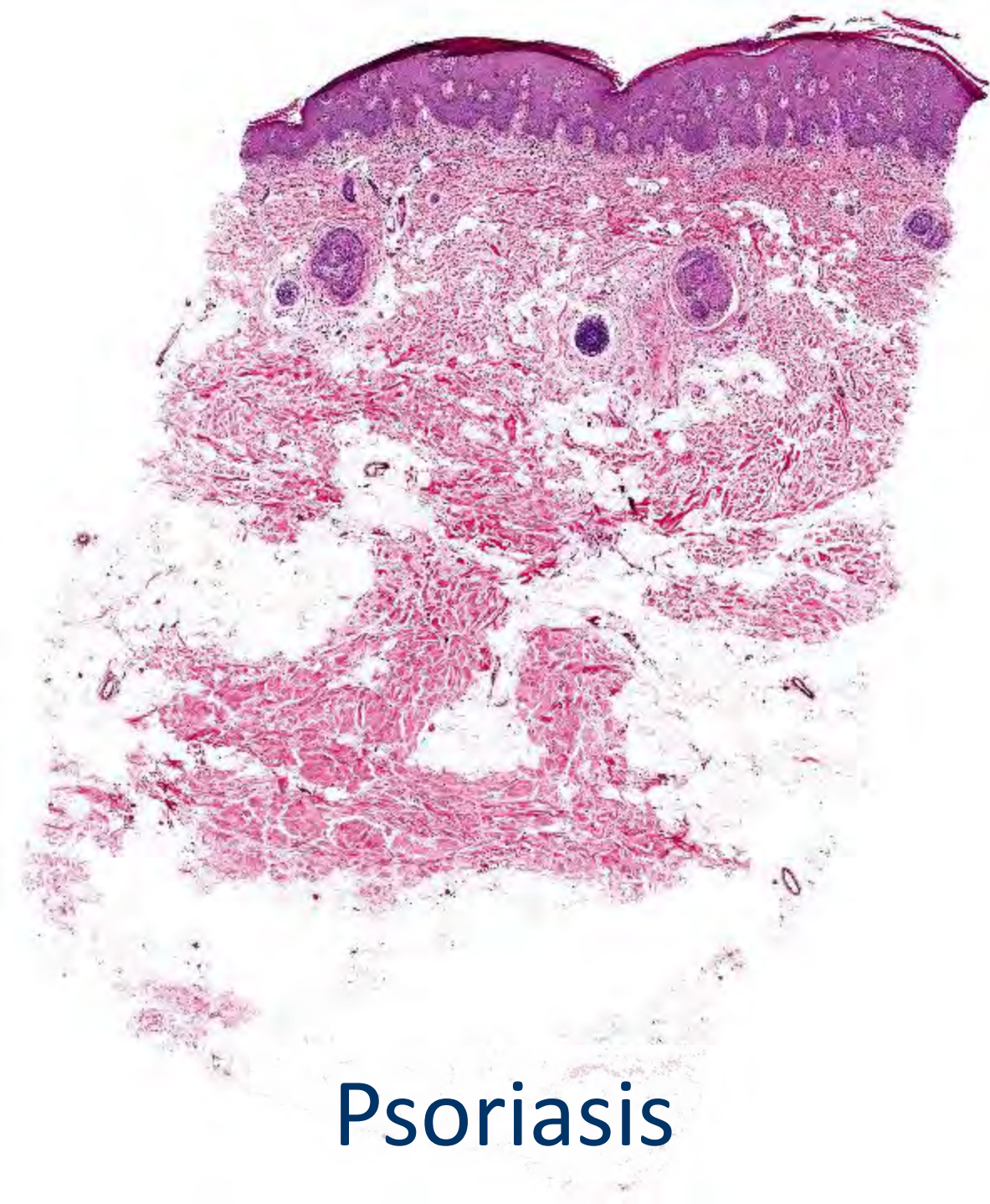




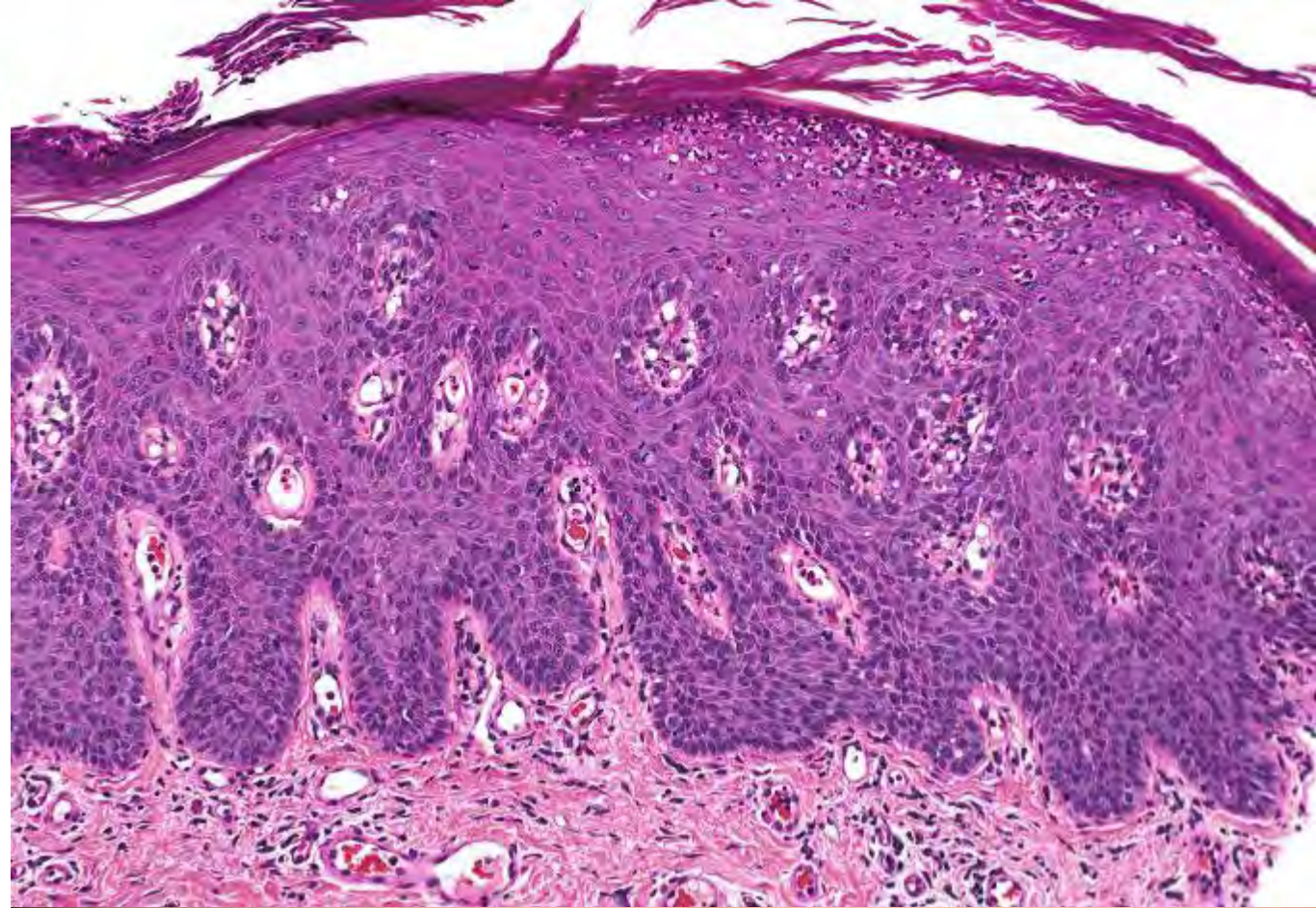
F, 66

According to the patient skin lesions on the buttocks for 10 years. No improvement (?) with different local treatments (the patient does not remember which).

A biopsy is taken.



Psoriasis



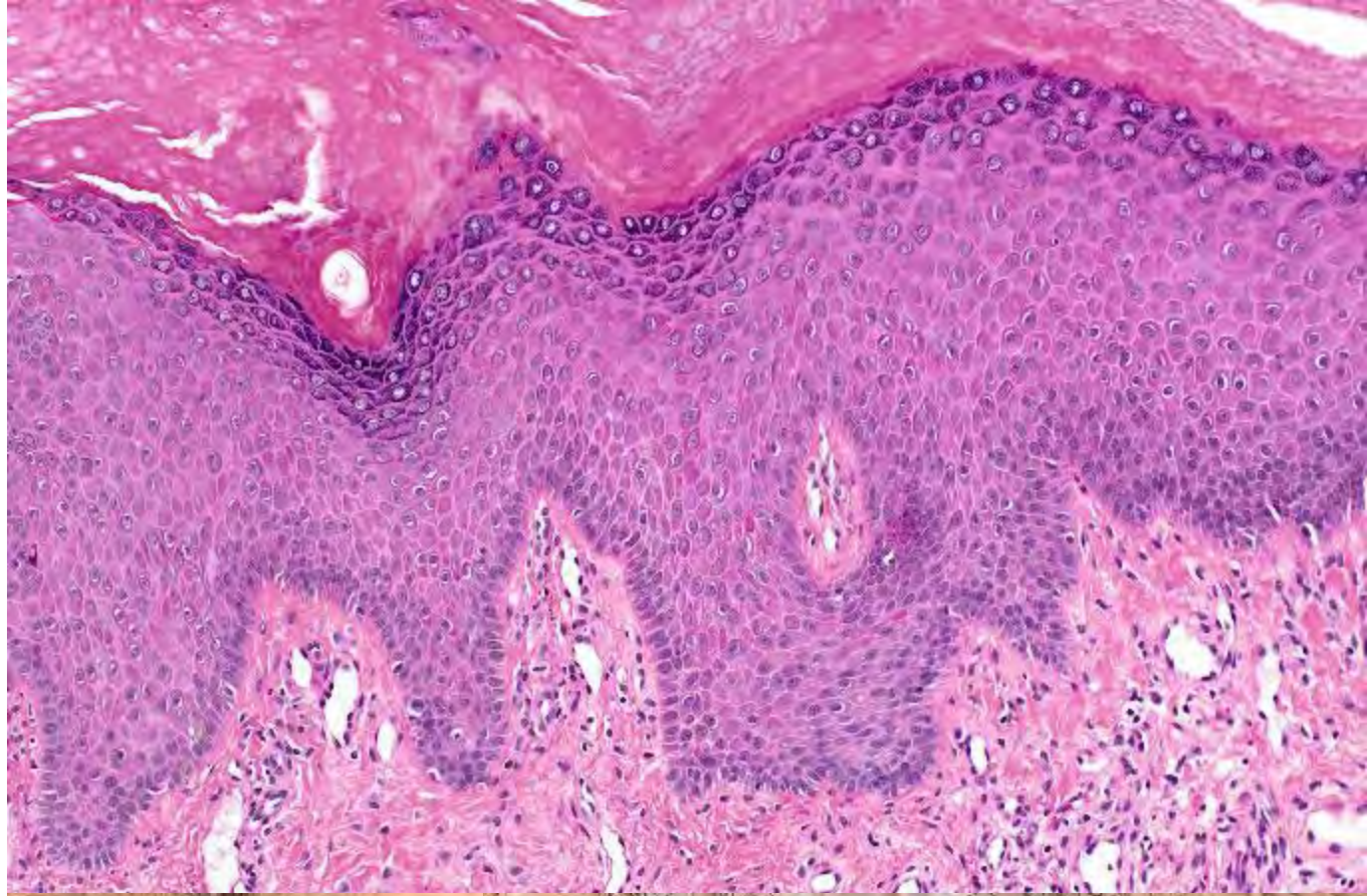


M, 23

According to the patient painful lesions in the perianal region for the last 2-3 months.

A biopsy is taken.





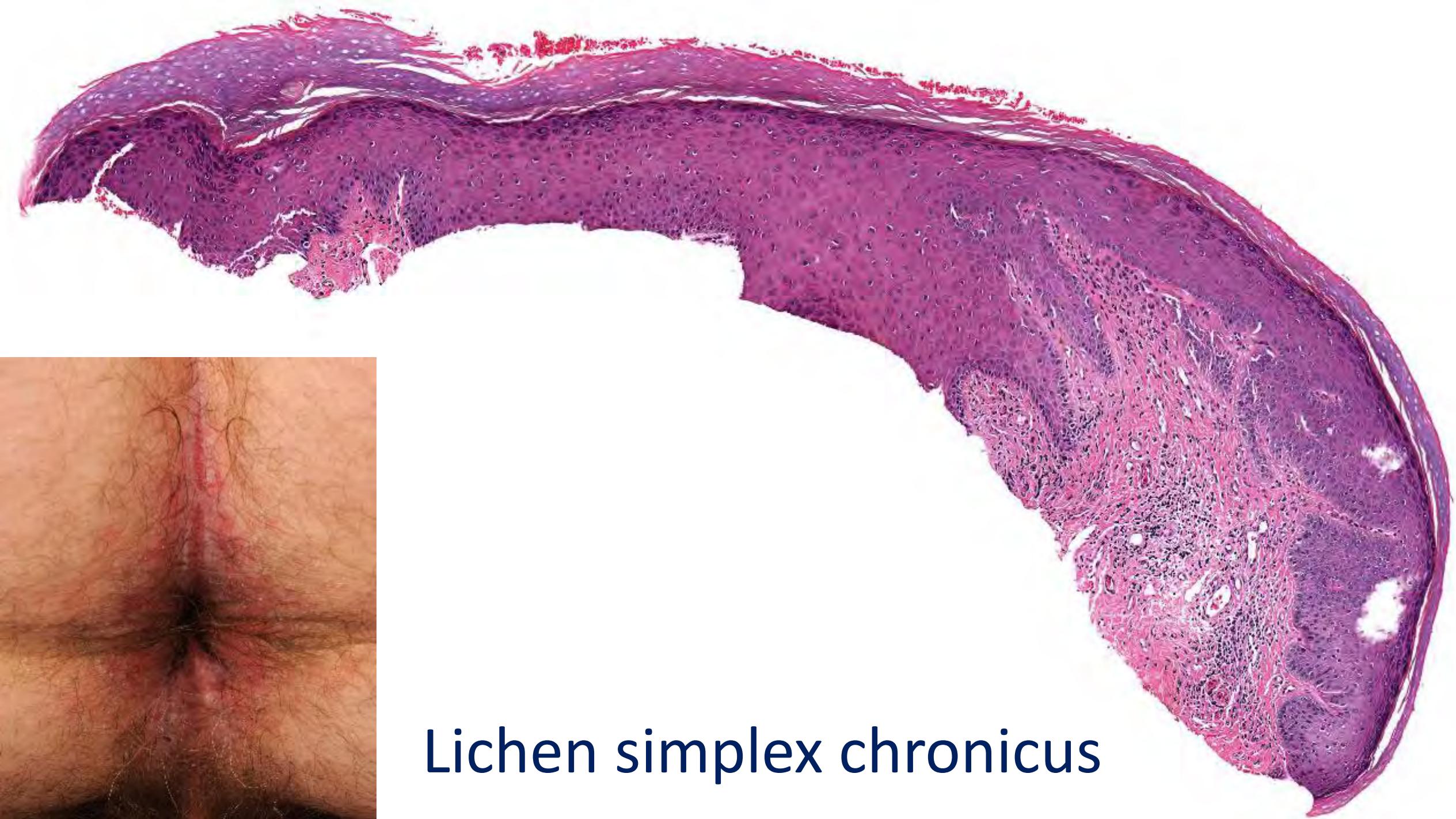
Lichen simplex
chronicus



M, 58

According to the patient itchy lesions in the rima ani for >1 year.

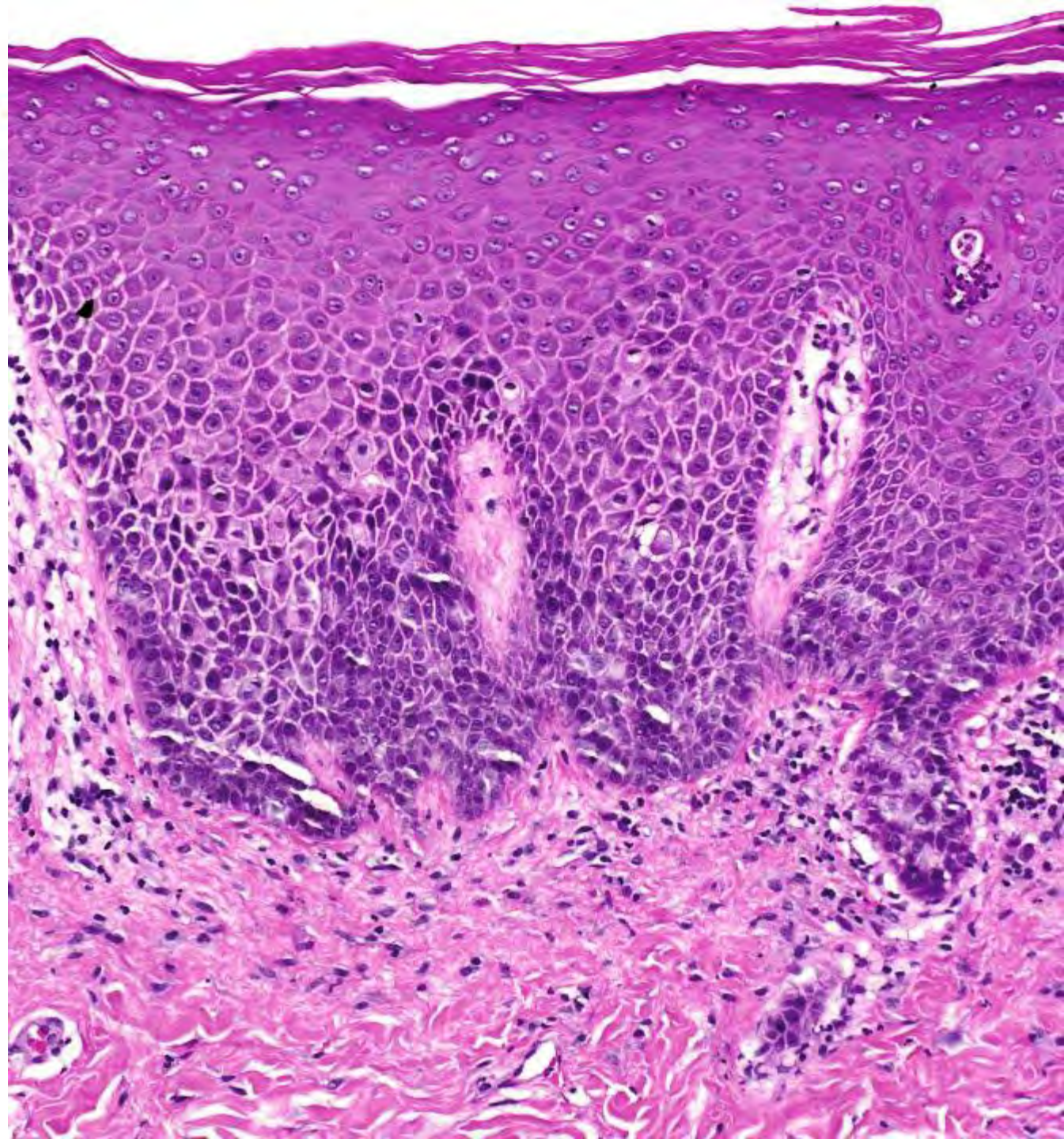
A biopsy is taken.

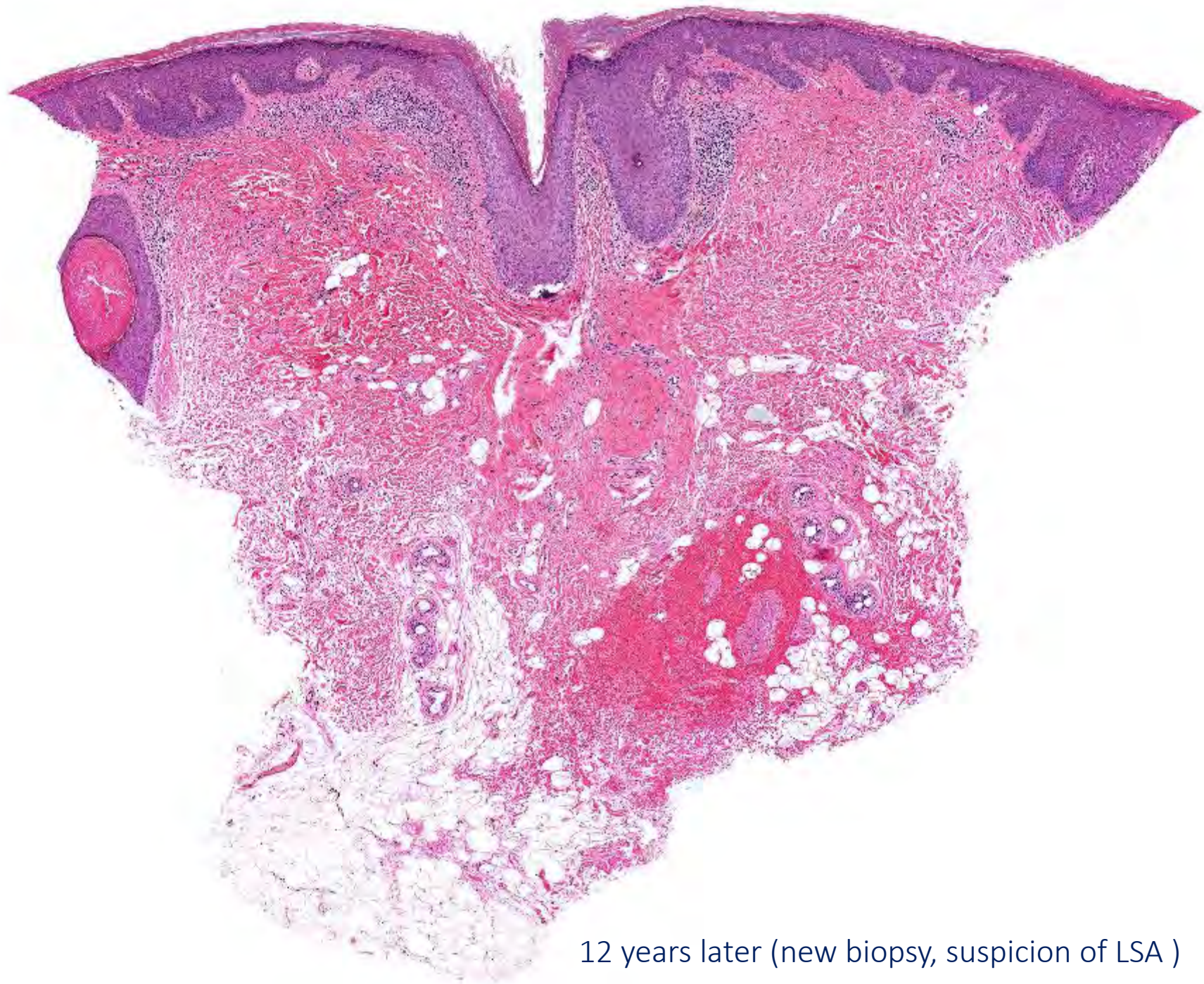


Lichen simplex chronicus



New biopsy 2 months later
(clinical suspicion of LSA)

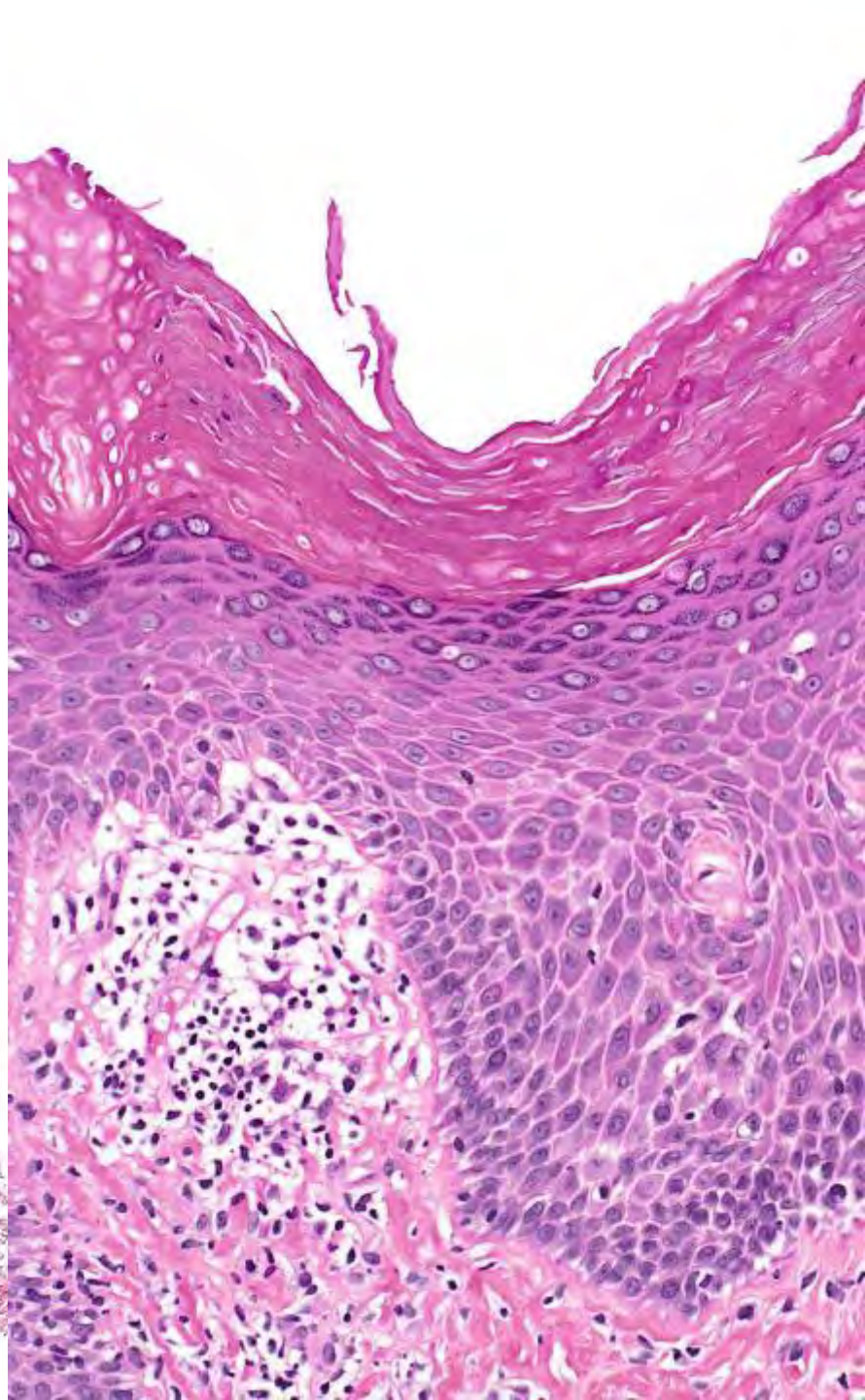




12 years later (new biopsy, suspicion of LSA)



5 more years later
(new biopsy, suspicion of LSA)



1st presentation



After 12 years



After 17 years



17 years of itchy rima ani

whitish areas (typical of LSC on
mucosae and intertriginous skin)
biopsied 4 times for suspicion of LSA

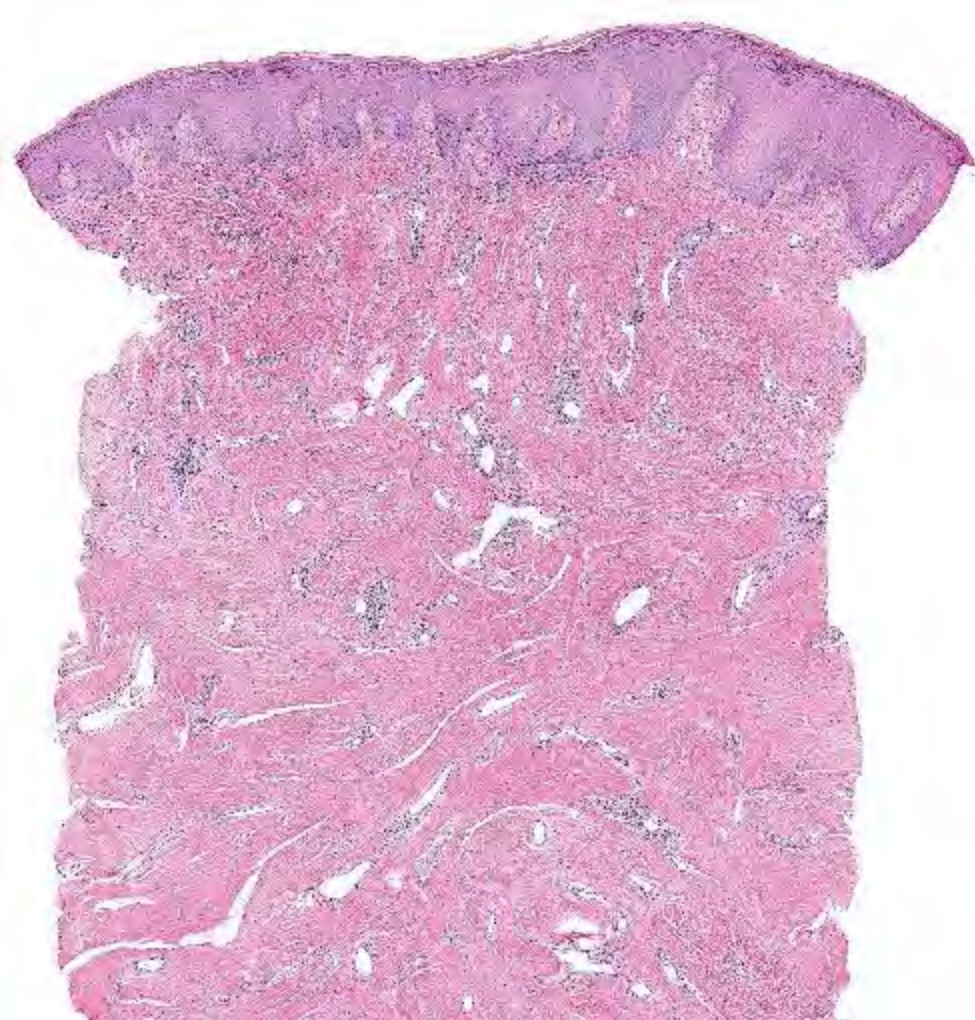


F, 63

History of abscess in the left perianal region 10 months before presentation.

According to the patient livid discoloration of the buttocks for at least 3 months.

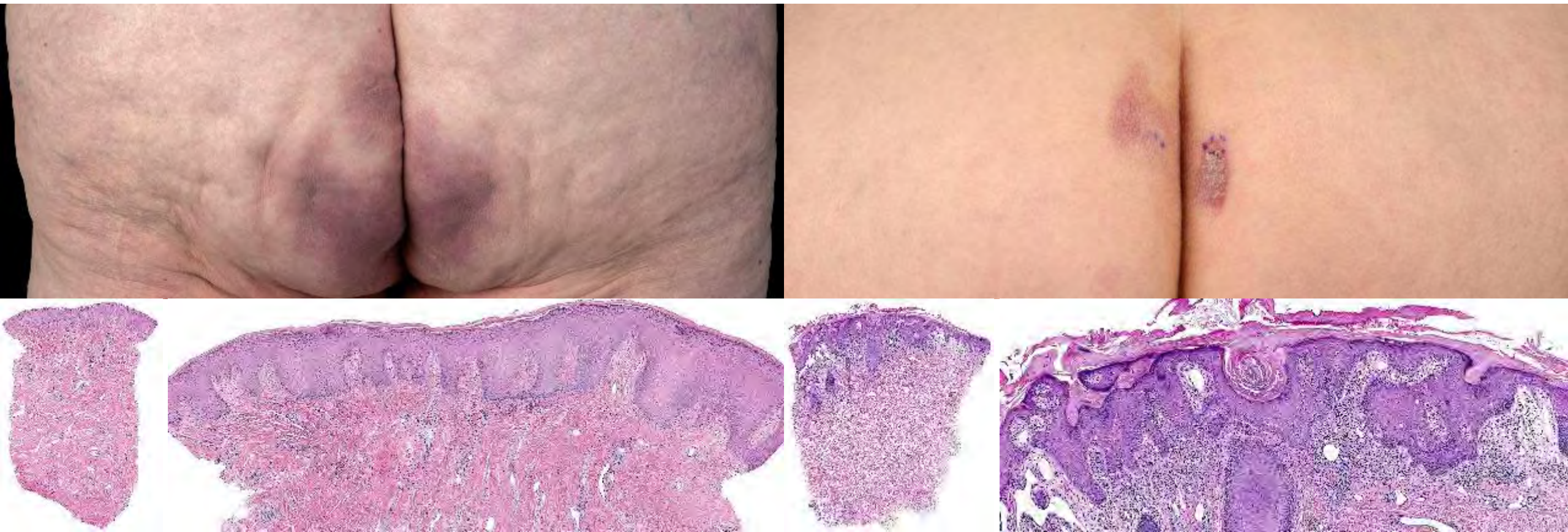
A biopsy is taken.



Chronic frictional dermatosis

(and early senile gluteal dermatosis)

There is a substantial difference between cODD and LSC, but cODD may show secondary changes of eczema and/or LSC



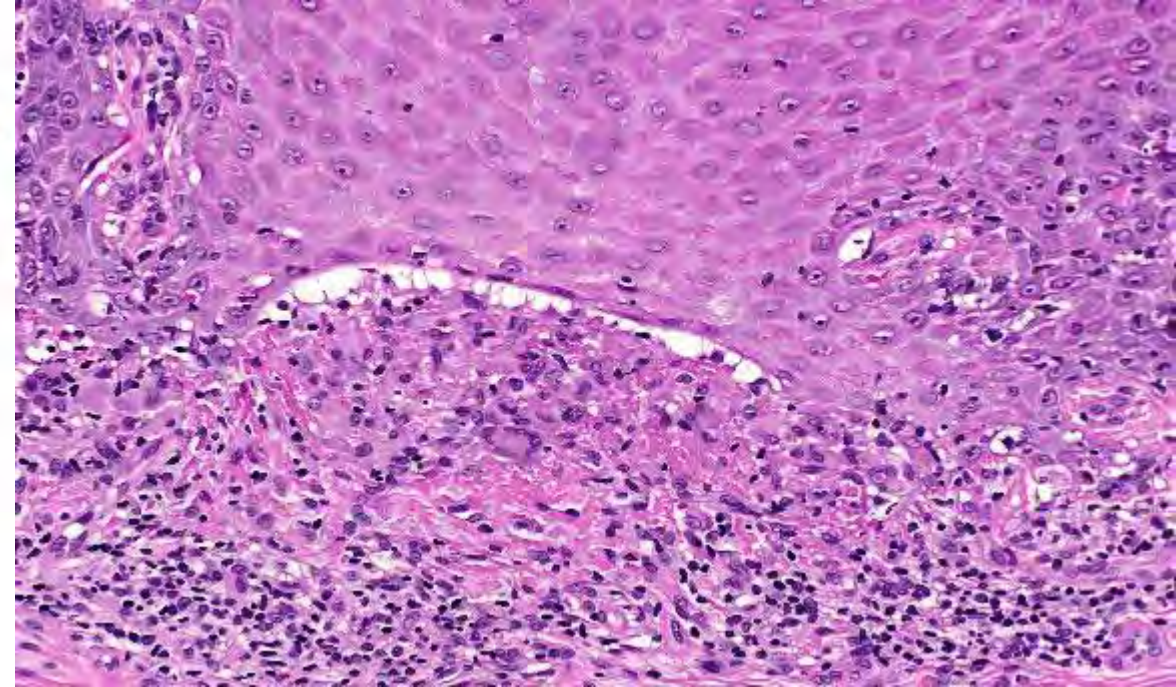
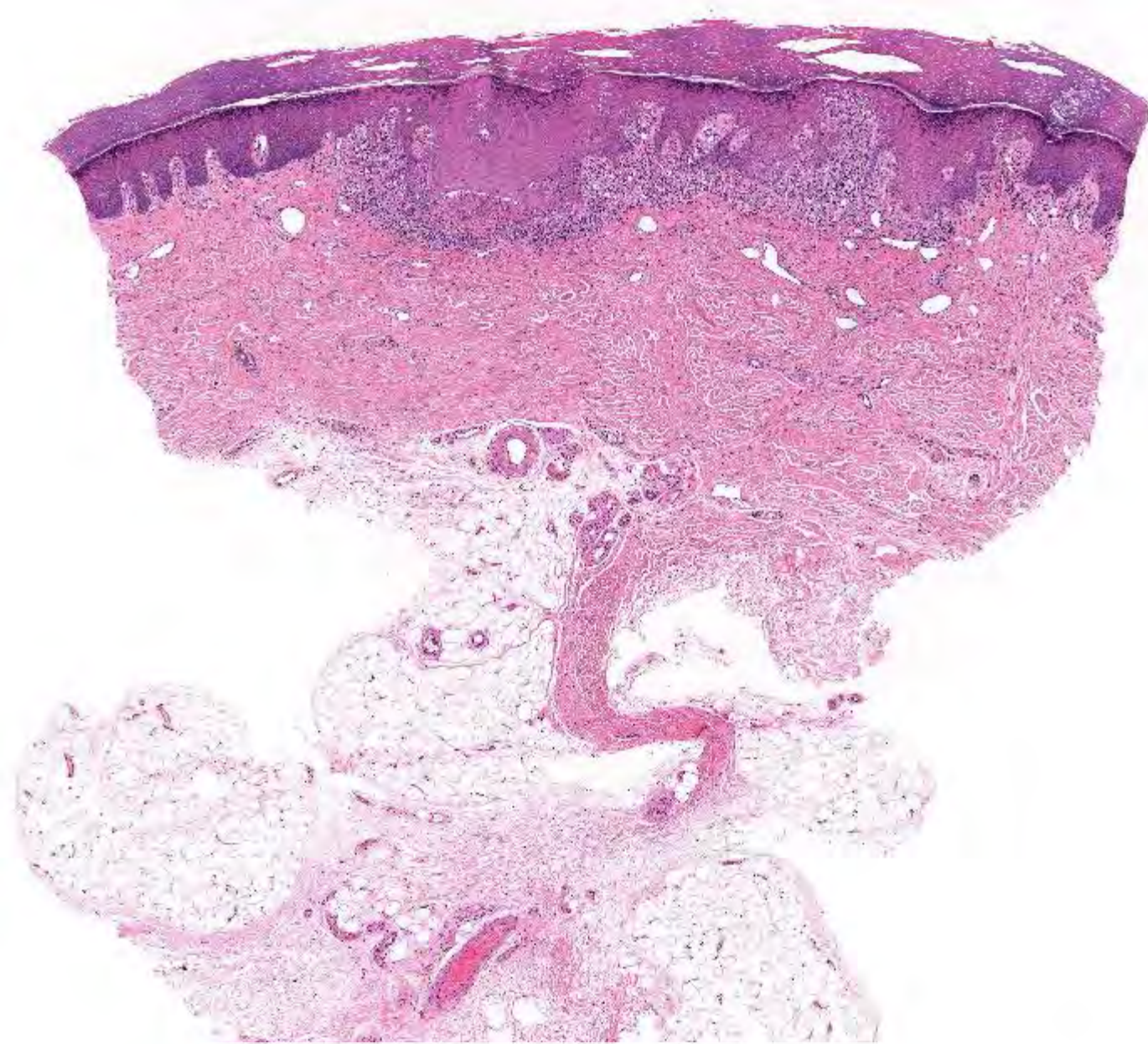


M, 75

History of lung carcinoma managed with pembrolizumab (6 cycles).

Onset of lesions on buttocks and extremities after the 3rd cycle (now present for 9 weeks).

A biopsy is taken (from the thumb).



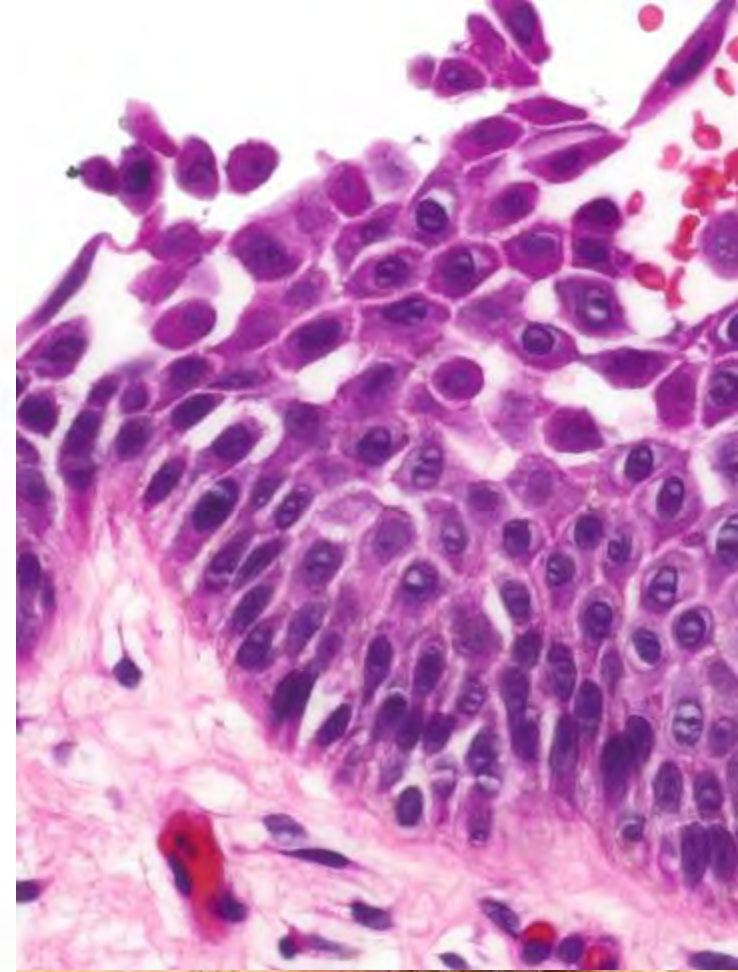
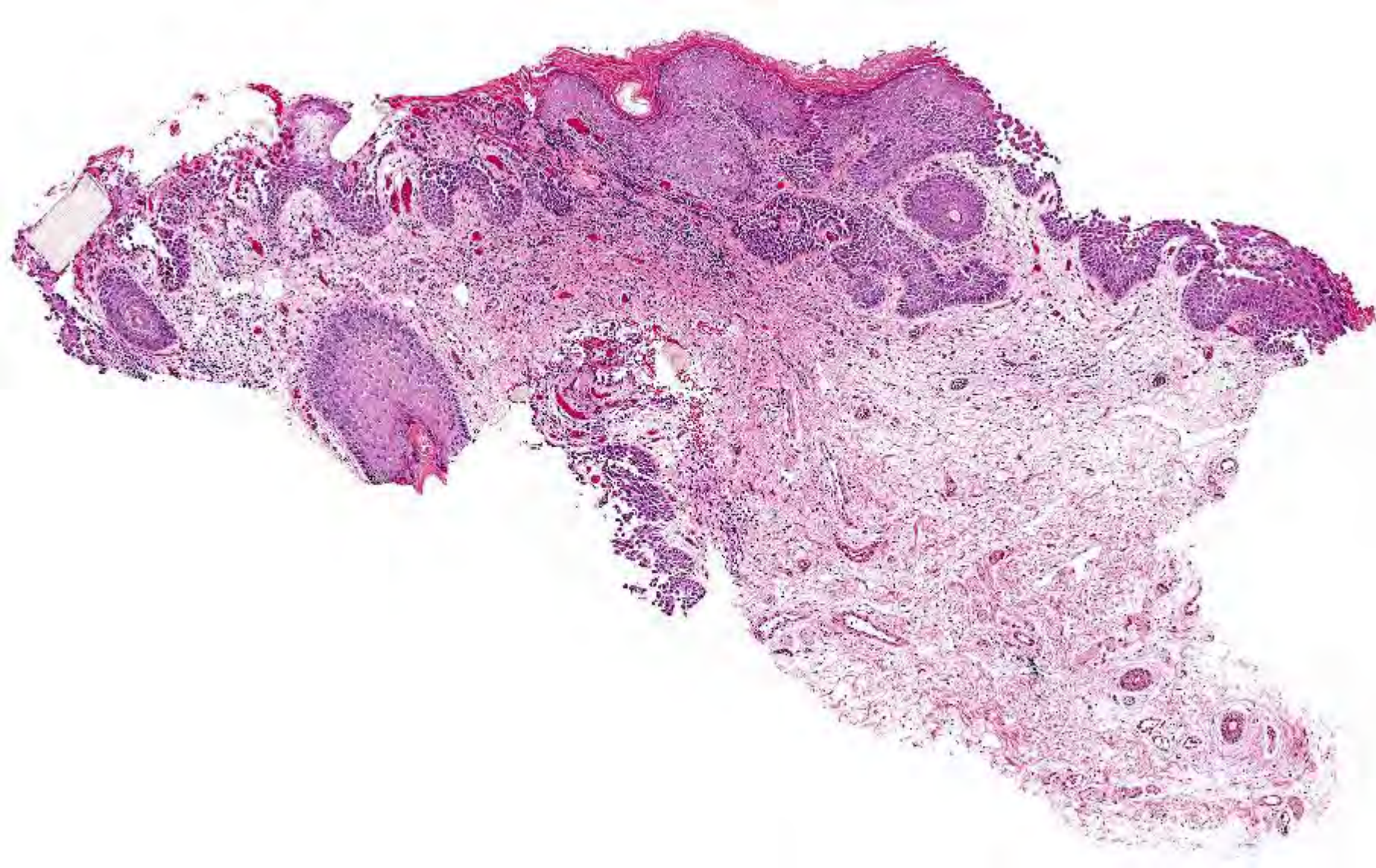
Lichen planus



M, 28

According to the patient partly erosive perianal lesions for 1,5 years; improvement in wintertime, worsening in summertime. A previous external biopsy was reported as "acantholytic dermatosis" (not available for review).

A new biopsy is taken.



Hailey-Hailey disease

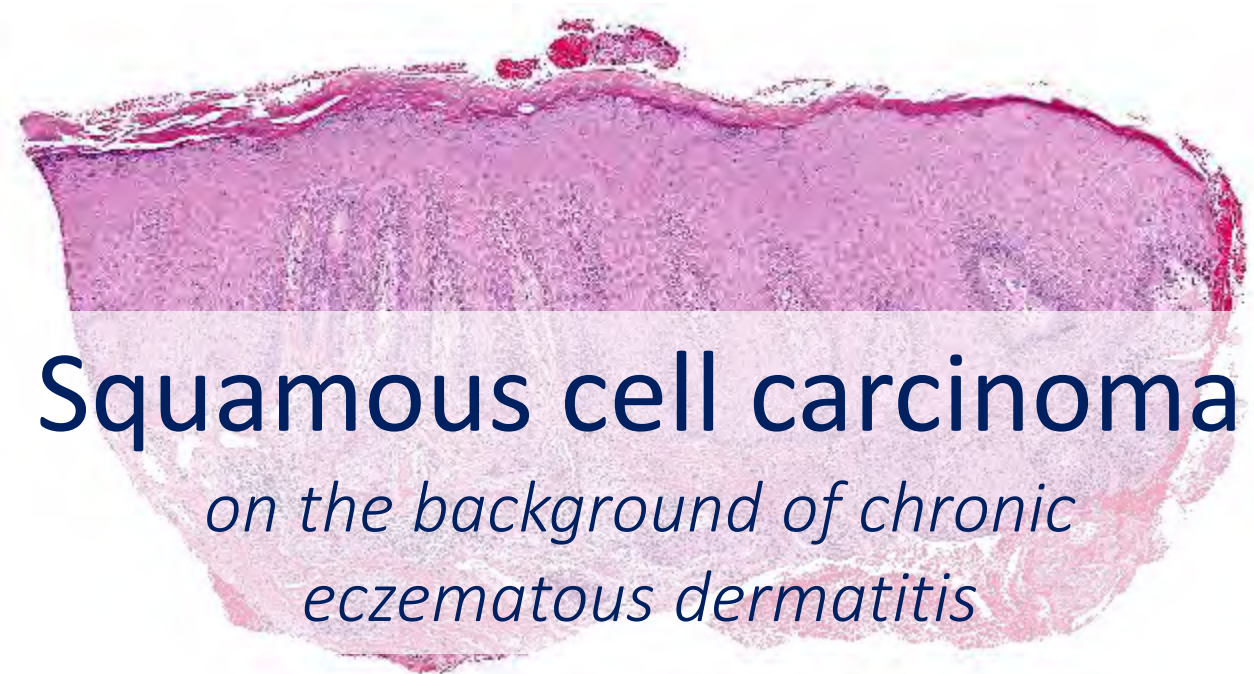
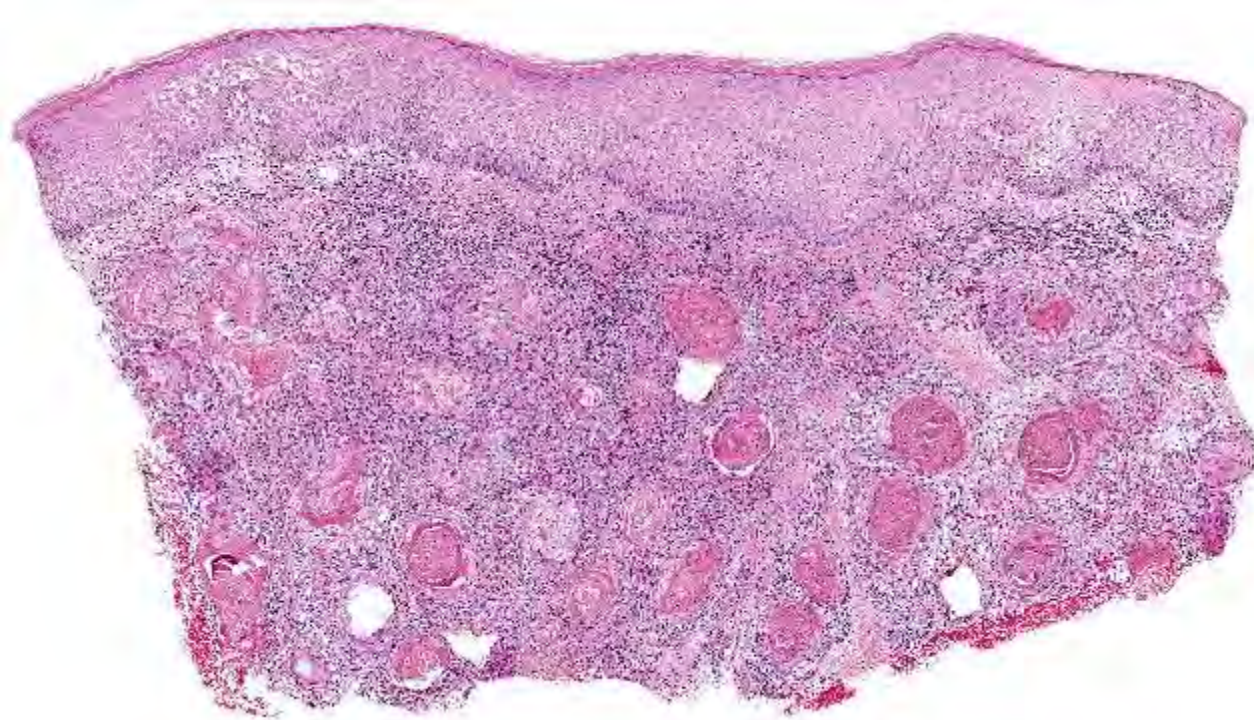


M, 51

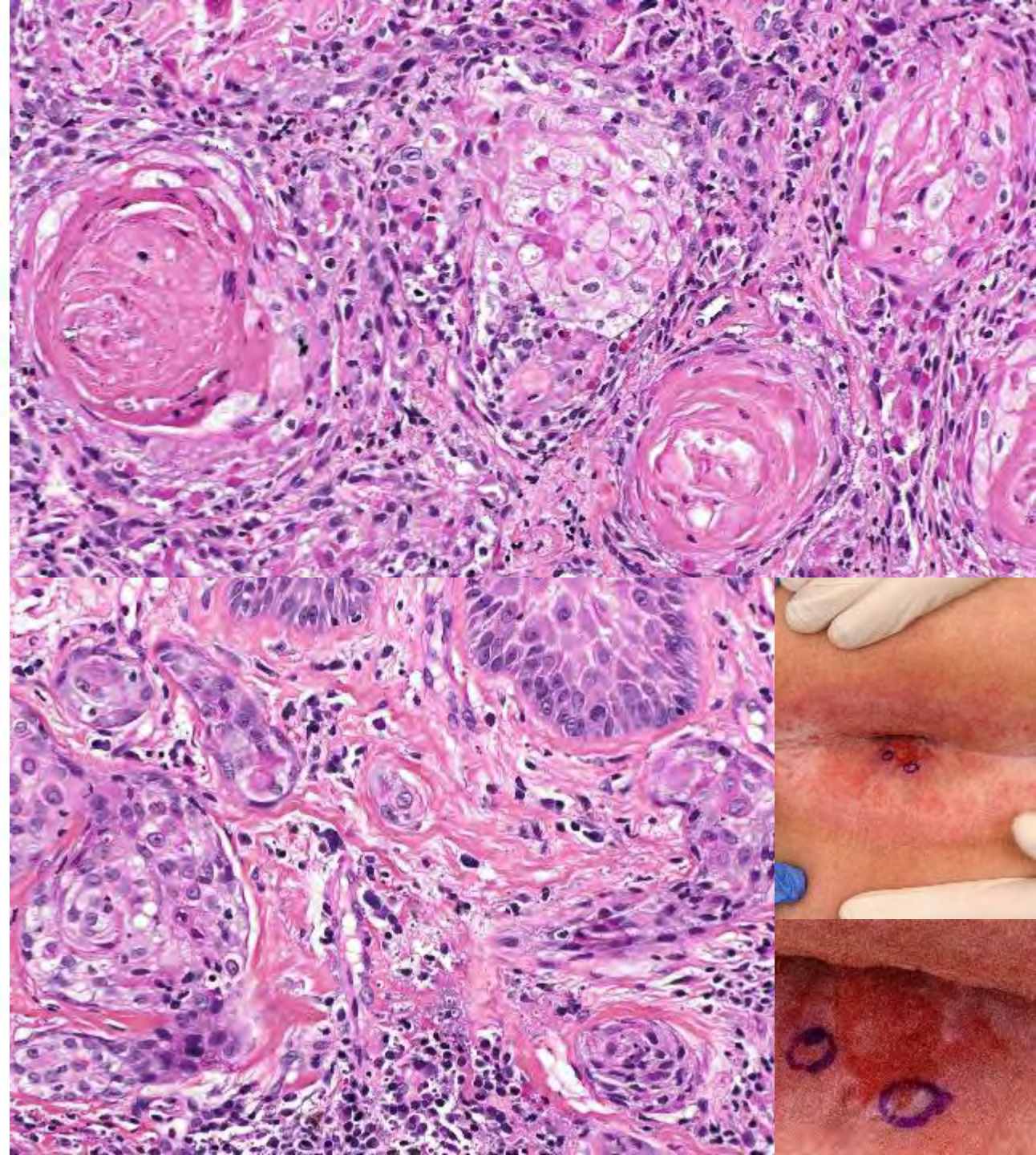
History of "anal carcinoma" (diagnosis made 5 years before presentation; CR after radiotherapy).

Perianal lesions since many years, getting worse for the last 6 weeks (the previous biopsy reported as "anal carcinoma" was performed for evaluation of "chronic eczema" of the perianal area).

A biopsy is taken.



Squamous cell carcinoma
*on the background of chronic
eczematous dermatitis*



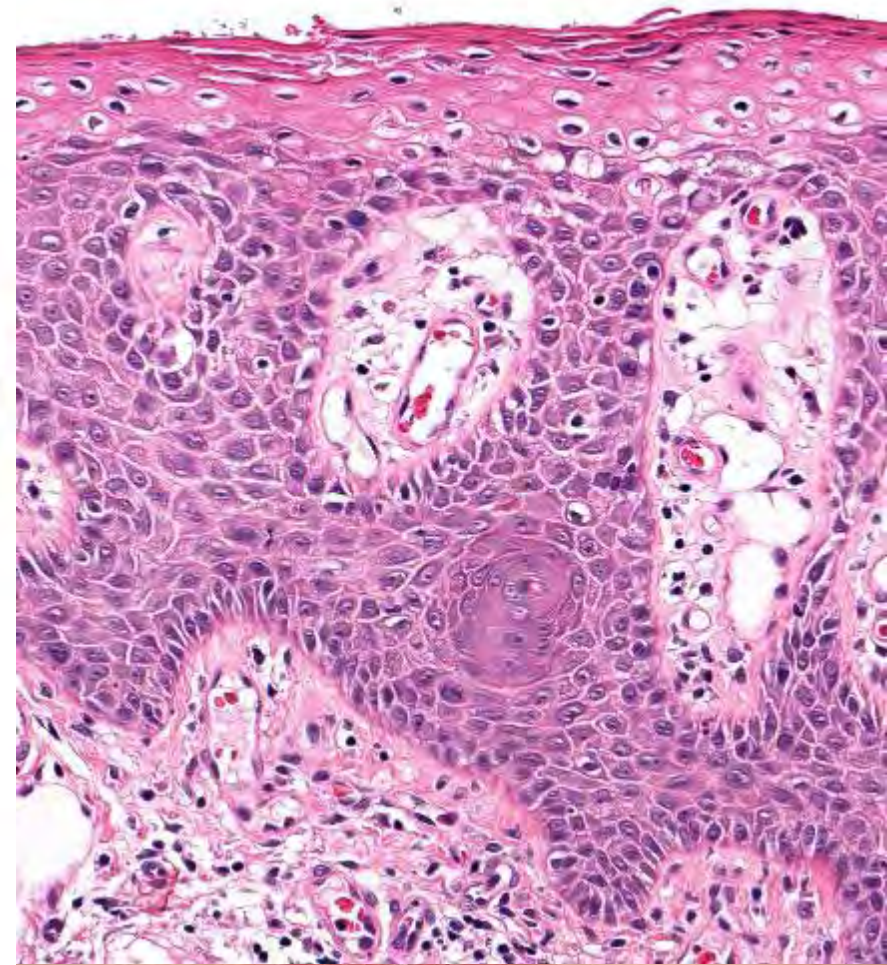
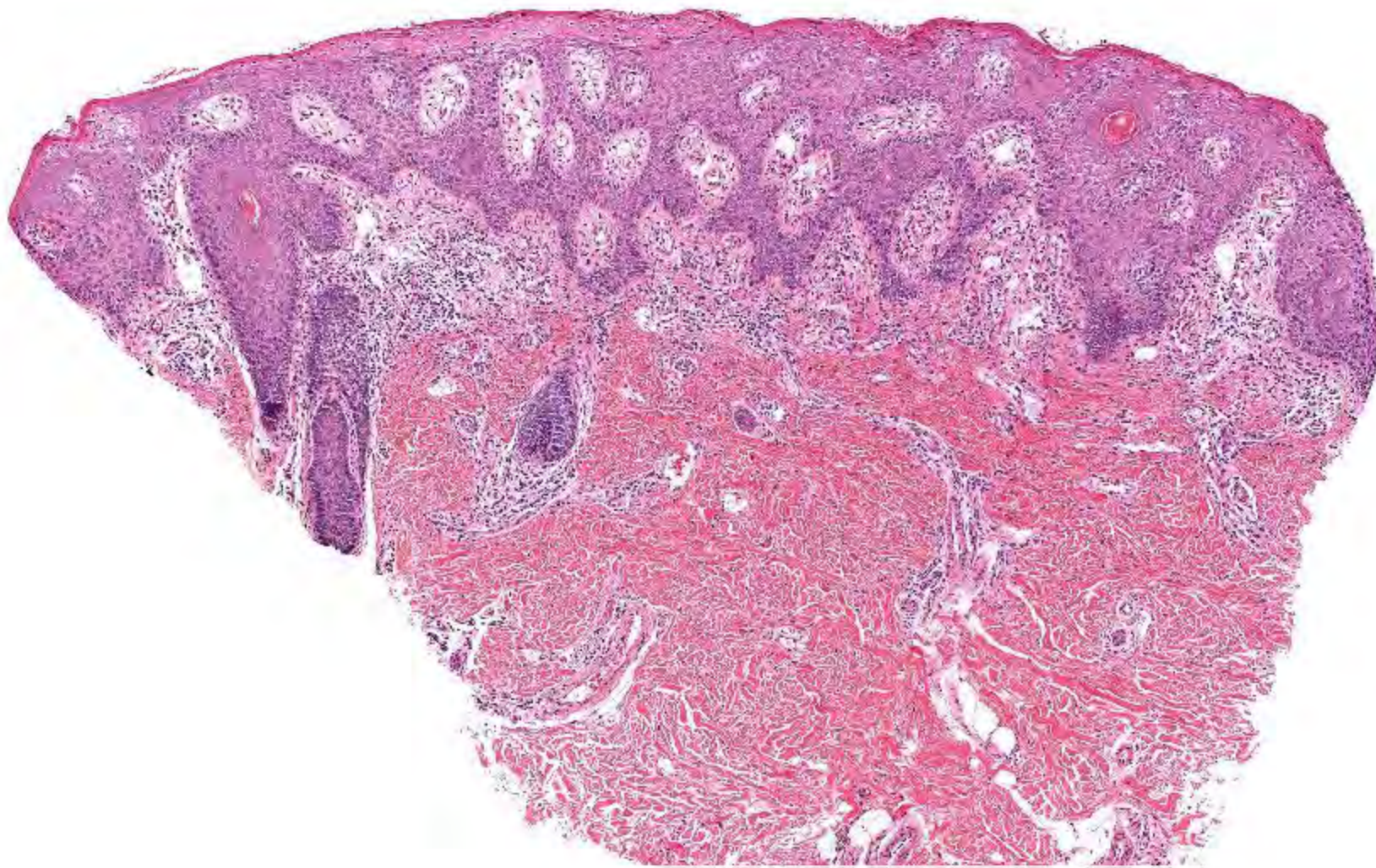


M, 6

Perianal eczematous dermatitis since the first months of life.

Recent diagnosis of Crohn disease.

A biopsy is taken.



Perianal eczema in Crohn disease (likely associated with zinc deficiency)

Zinc levels not measured; relapsing perianal lesions for >12 years



Clinical review

Cutaneous manifestations of Crohn's disease

Walter Burgdorf, M.D.
Oklahoma City, OK

Crohn's disease is a chronic inflammatory bowel disease which may have distinctive cutaneous manifestations. Included in this group are perianal, peristomal, and peristomal ulceration, as well as granulomatous cutaneous inflammation separate from gastrointestinal tract openings (metastatic Crohn's disease). In the oral cavity, both ulcerations and granulomatous nodules may occur. Malabsorption of nutrients may lead to several changes, including an acrodermatitis enteropathica-like syndrome secondary to zinc deficiency. Patients with Crohn's disease may also have pyoderma gangrenosum, erythema nodosum, cutaneous vasculitis, and other less specific changes. (*J Am Acad Dermatol* 32:689-695, 1981.)

Crohn's disease (CD) is an ulcerative granulomatous inflammatory disease originally named *regional ileitis* by Crohn et al¹ in 1932. In the intervening five decades, it has become apparent that CD is a multisystem disease with many skin and mucous membrane manifestations which may be related to the primary granulomatous process, to nutritional deficiencies, to therapy, or may be idiopathic in nature (Table I). In one study of 200 cases of CD, forty-four patients had cutaneous findings²; in all instances, the cutaneous changes followed the intestinal disease. But occasionally mucocutaneous lesions can lead to the diagnosis of CD prior to bowel involvement or help distinguish CD from other inflammatory bowel disease (Table II).

GRANULOMATOUS CUTANEOUS DISEASE

Since CD is characterized by the histologic demonstration of granulomas, we will consider the granulomatous cutaneous changes first. In either the bowel wall or the skin, sarcoidal granulomas without organisms are found. The differential diagnosis of such a finding is somewhat different

in the two sites: in the bowel, once tuberculosis has been ruled out, there are very few causes of sarcoidal granulomas other than CD. Sarcoidosis is never seen in the gut, but it, foreign body granulomas, and a variety of infections may mimic CD in the skin.

Perianal, peristomal, and peristomal inflammation are probably the most common cutaneous manifestations of CD. In the recent National Cooperative Crohn's Disease Study (NCCDS), 205 of 569 patients (36%) had perianal disease. Those with disease in the colon alone (47%) or colon and bowel (41%) were considerably more likely to have perianal involvement than those with small bowel disease alone (25%).³ Lockhart-Mummery and Morson⁴ found anal lesions in 81% of seventy-five patients with CD limited to the large intestine. Of this same group, 37% had perianal complaints as their presenting problem, while 52% initially complained of diarrhea.

These same authors define "anal lesion" as those "various conditions which can be found by inspection alone."⁴ Most common are perianal fissures and fistulas which usually can be distinguished from similar changes in non-CD patients because of their multiplicity, circumanal involvement, indolent undermined ulceration, and marked edema. The latter can be so severe as to

Table I. Cutaneous manifestations of Crohn's disease

Granulomatous cutaneous disease
Perianal, peristomal, peristomal ulceration
Metastatic Crohn's disease
Oral changes
Ulcerations
Aphthae-like ulcers
Linear ulcers
Mucosal cobblestoning
Nodules with granulomas
Nutritional changes
Acquired zinc deficiency
Striae
Idiopathic
Pyoderma gangrenosum
Erythema nodosum
Necrotizing vasculitis
Epidermolysis bullosa acquisita
Finger clubbing
Palmar erythema
Pustular response to trauma

Table II. Cutaneous manifestations which occasionally precede intestinal Crohn's disease

Perianal inflammation
Oral ulcerations and granulomatous nodules
Pyoderma gangrenosum

From the Department of Dermatology, University of Oklahoma Health Sciences Center.
Reprints available.

Zinc Deficiency: A Complication of Crohn's Disease

CRAIG McCLAIN, CAROL SOUTOR, and LESLIE ZIEVE

Department of Medicine and Dermatology, University of Minnesota, Minneapolis Veterans Administration Medical Center and Hennepin County Hospital, Minneapolis, Minnesota

Twenty-one of 52 patients with regional enteritis had low serum zinc concentrations on initial testing. Fifteen of 31 patients followed longitudinally had

low mean serum zinc concentrations. These patients also had dermatitis, hypoparathyroidism, and Crohn's disease complications related to zinc deficiency.

Zinc is an essential trace element and a variety of functions are known. It is involved in growth, reproduction, and differentiation, and is a cofactor for many enzymes.

Zinc deficiency in humans is associated with a variety of clinical abnormalities, including dermatitis, hypoparathyroidism, and Crohn's disease. It is a potential complication of Crohn's disease.

Crohn's disease and manifestations of zinc deficiency prompted us to evaluate the zinc status of patients with Crohn's disease.

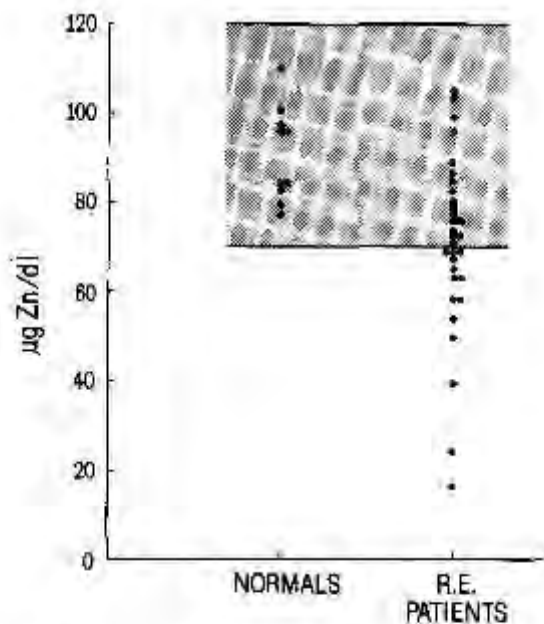


Figure 6. Mean serum zinc values (each dot represents approximately five individual determinations) for 31 patients with Crohn's disease followed longitudinally and normal controls.

Crohn's disease and manifestations of zinc deficiency prompted us to evaluate the zinc status of patients with Crohn's disease.

Zinc absorption in Crohn's disease

G. C. STURNIOLO,* M. M. MOLOKHIA,† R. SHIELDS,‡ AND L. A. TURNBERG§

From the Department of Medicine, Hope Hospital, University of Manchester School of Medicine, Salford

SUMMARY Zinc deficiency is a potential complication of Crohn's disease and we have searched for evidence of this and assessed the possibility that malabsorption of zinc might be a cause. Serum zinc concentrations in 33 patients suffering from Crohn's disease were significantly lower than in 58 normal control subjects ($9.18 \pm 2.3 \mu\text{mol}$ compared with $13.6 \pm 1.73 \mu\text{mol}$, $P < 0.0005$). Serum zinc correlated well with serum albumin concentrations and the low serum zinc may simply reflect the low serum albumin concentrations. Zinc deficiency was not apparent in five normal subjects after an oral dose of ^{65}Zn . Plasma appearance curves after an oral dose of ^{65}Zn in five normal subjects and in five Crohn's disease patients are shown. The range in five normal subjects is shown in the shaded area. The plasma appearance curves in Crohn's disease patients are significantly lower than in normal subjects.

Zinc is an essential trace element and a variety of functions are known. It is involved in growth, reproduction, and differentiation, and is a cofactor for many enzymes.

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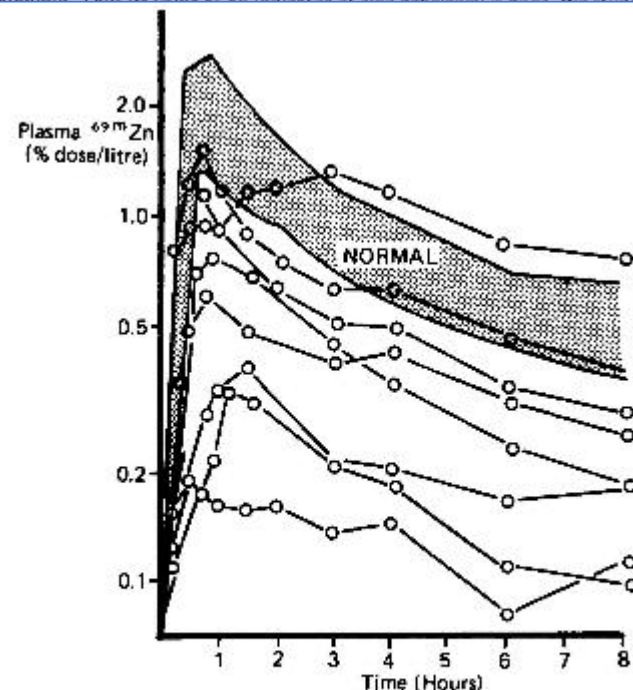


Fig. 1. Plasma appearance curves after an oral dose of ^{65}Zn . The range in five normal subjects is shown in the shaded area.

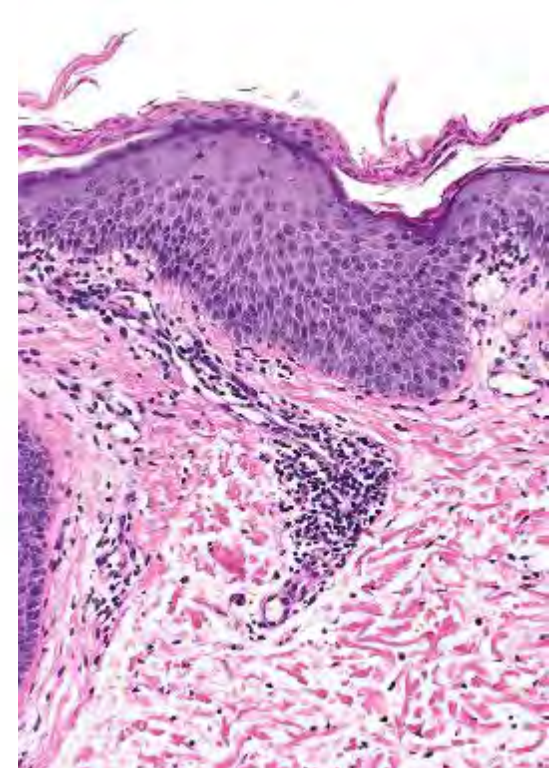
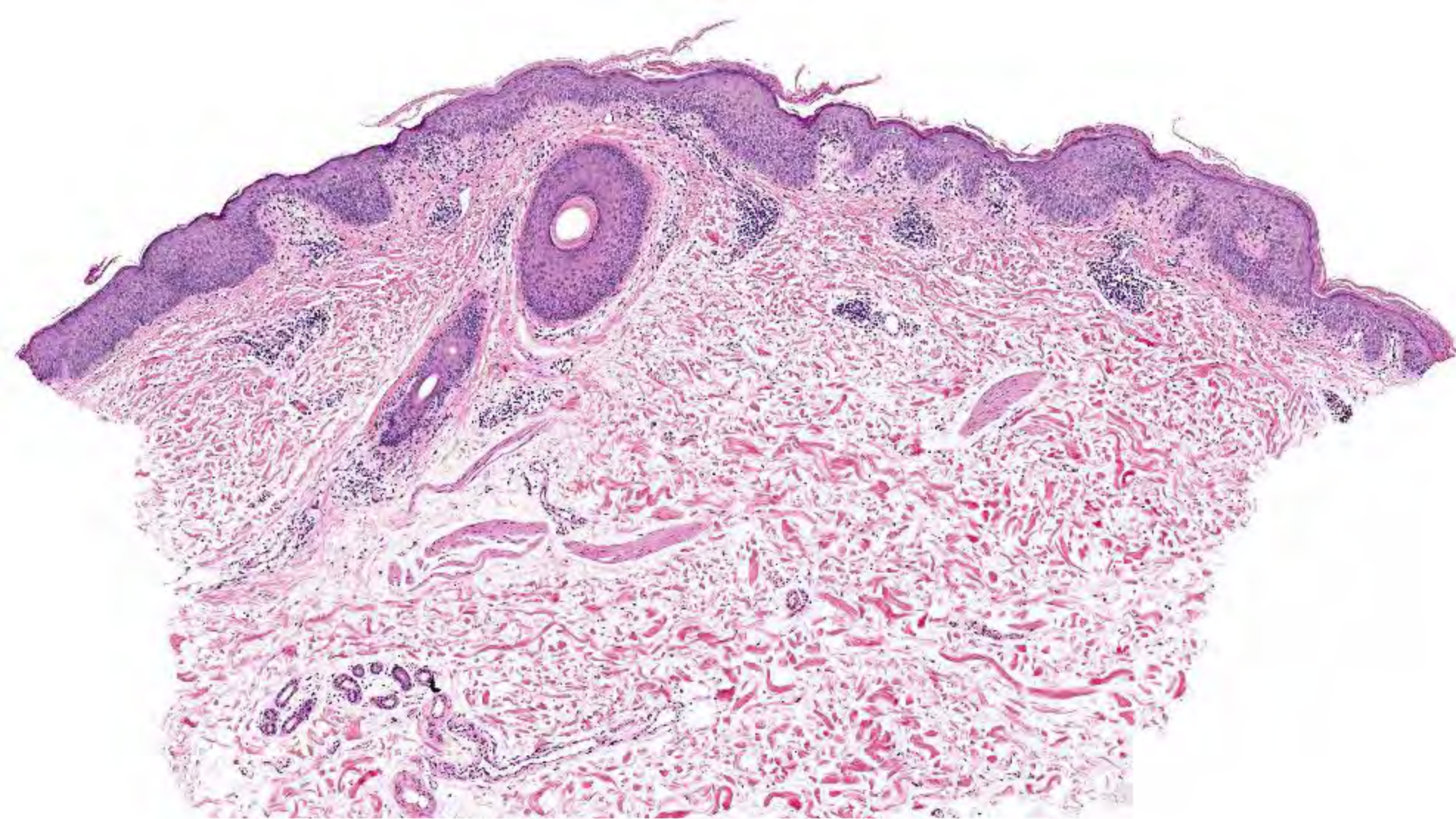


M, 37

According to the patient skin lesions on the genital area and buttocks for >4 weeks. No improvement with local steroids.

PCR positive for *Candida parapsilosis* (culture negative).

A biopsy is taken.



Acrodermatitis enteropathica

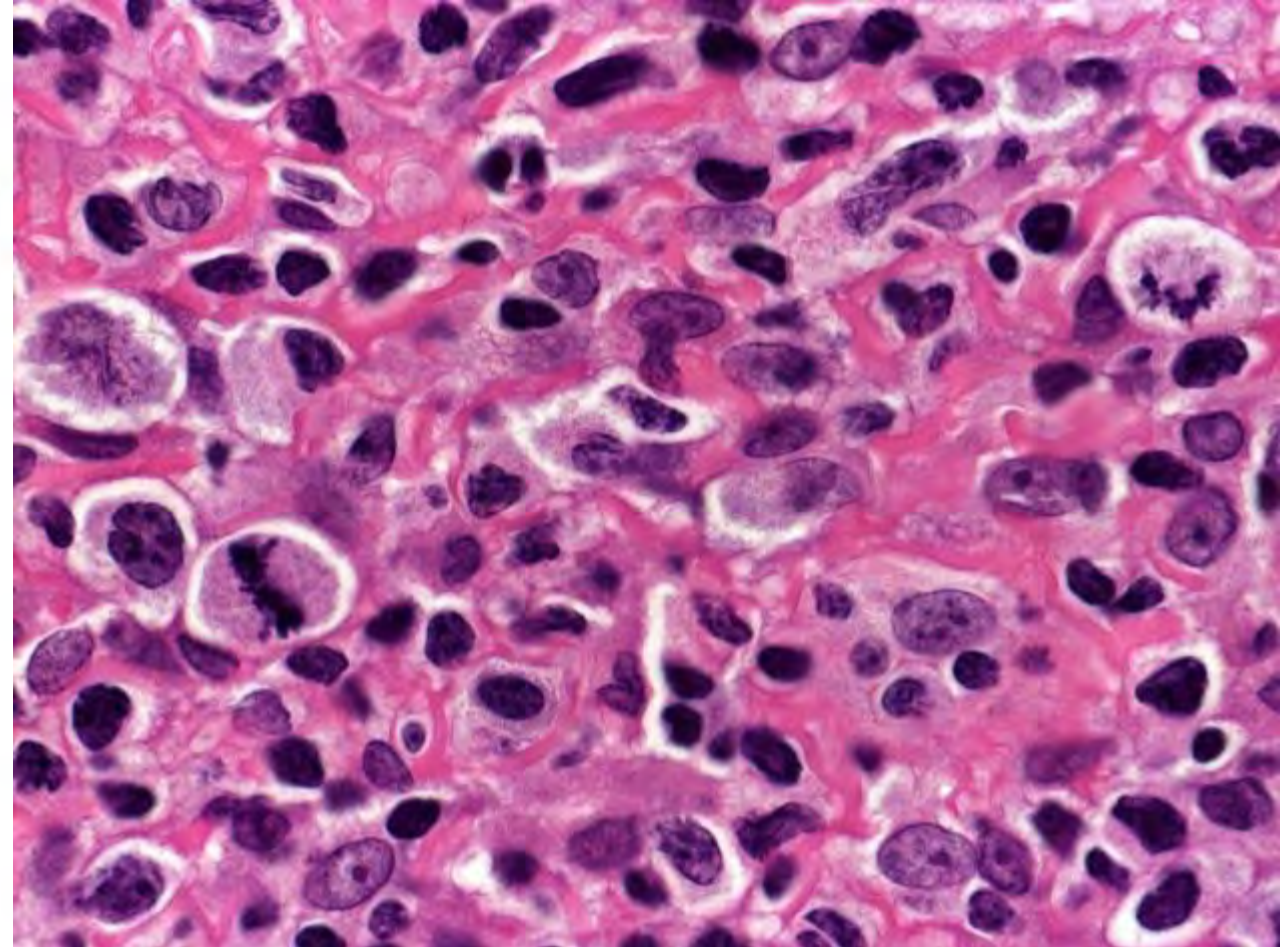
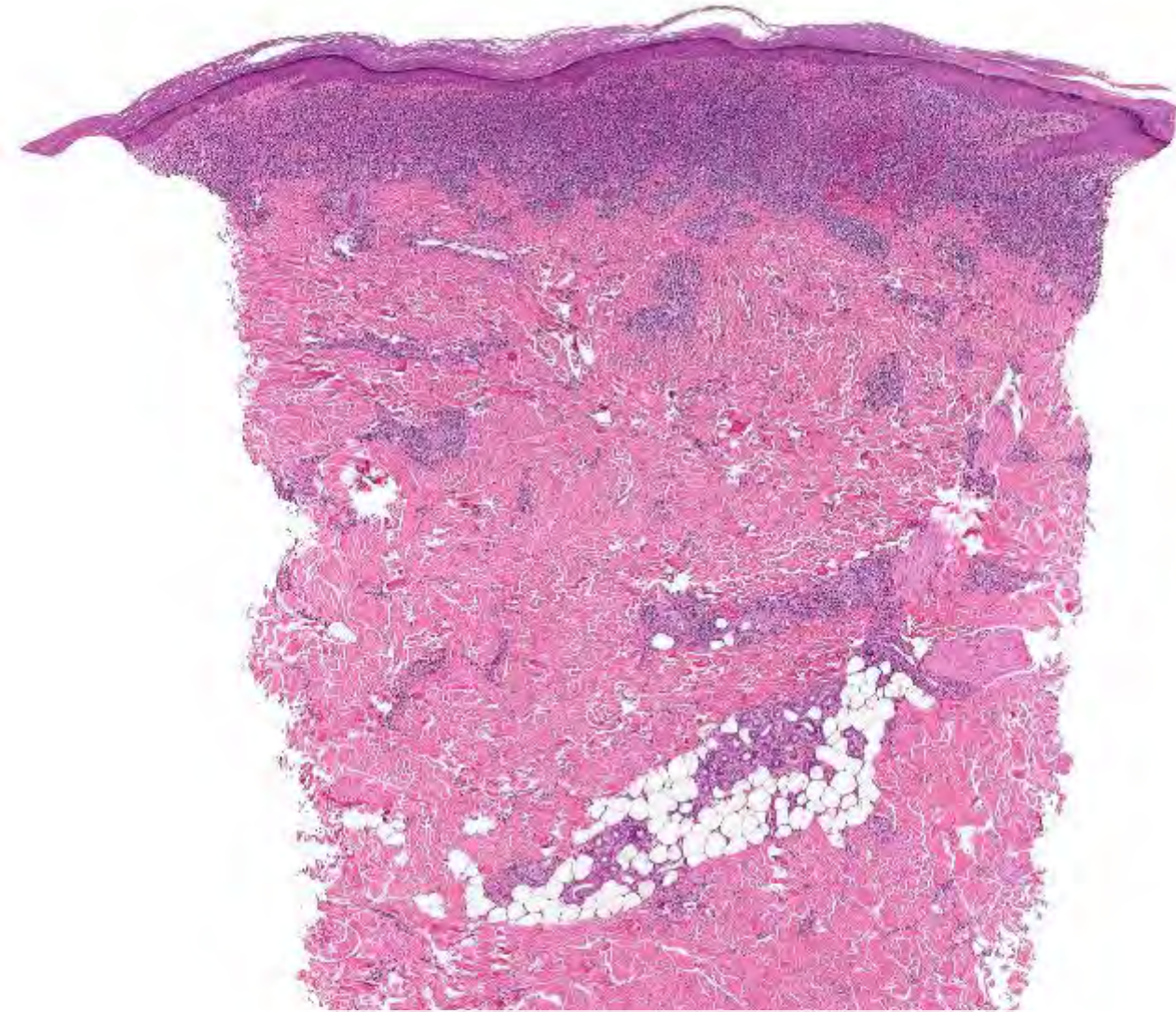
Zinc: 48 mcg/dL (80-120)



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)





F, 72

Sent by a private dermatologist for further management of "calcinosis cutis" on the left buttock.

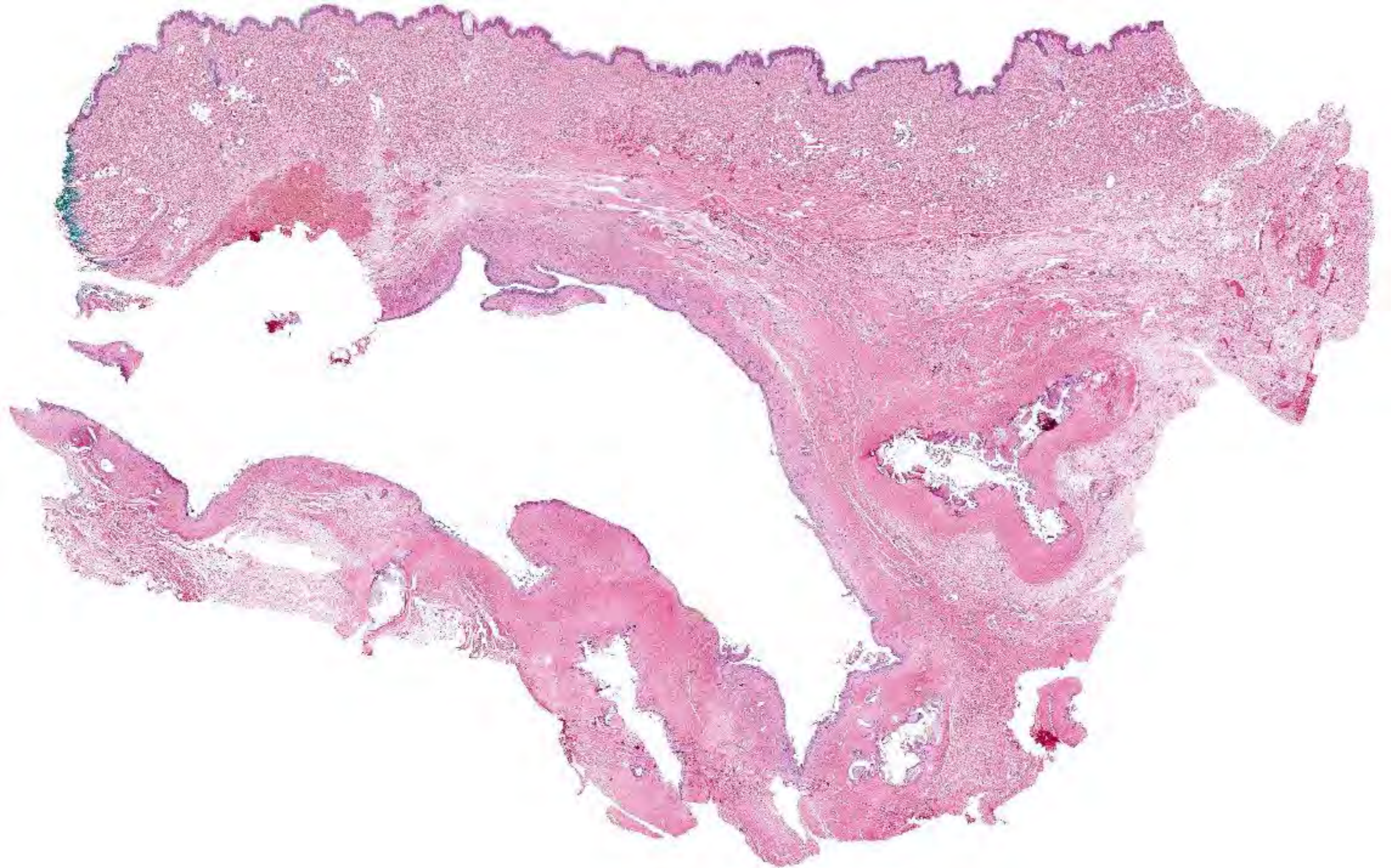
MR: calcified, not clearly cystic expansion without infiltration of the muscles.

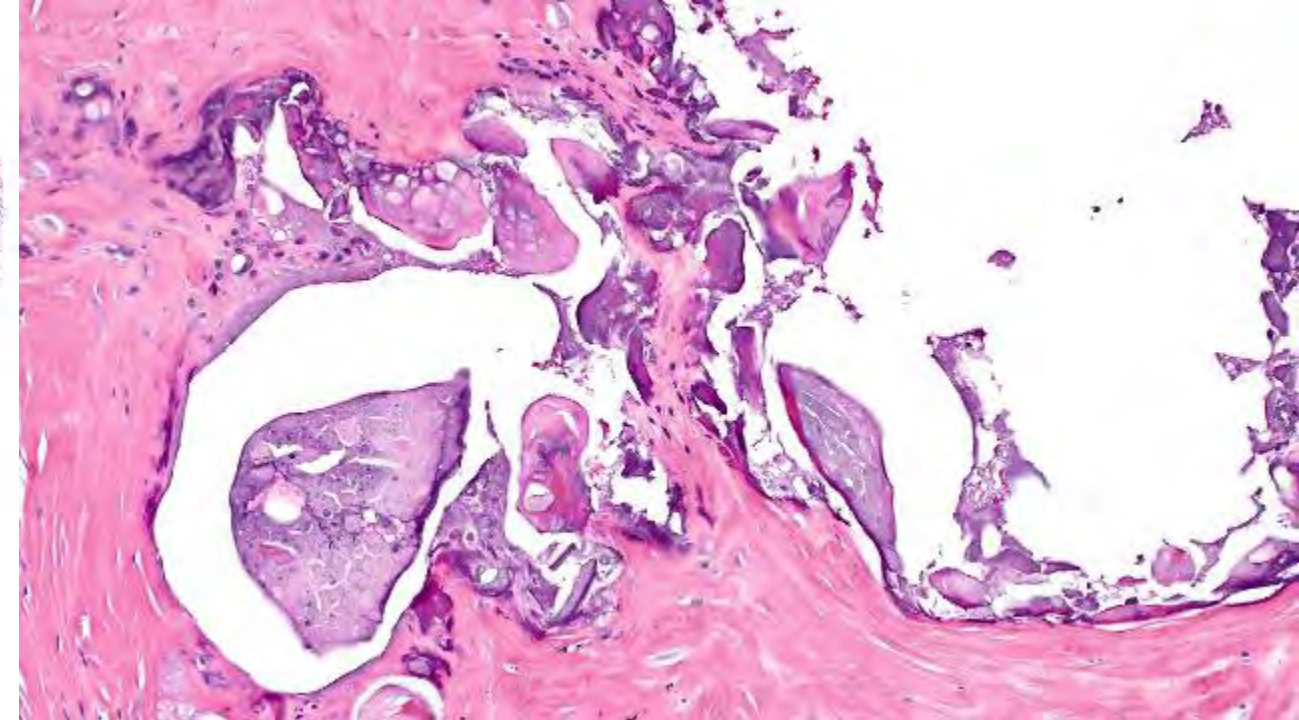
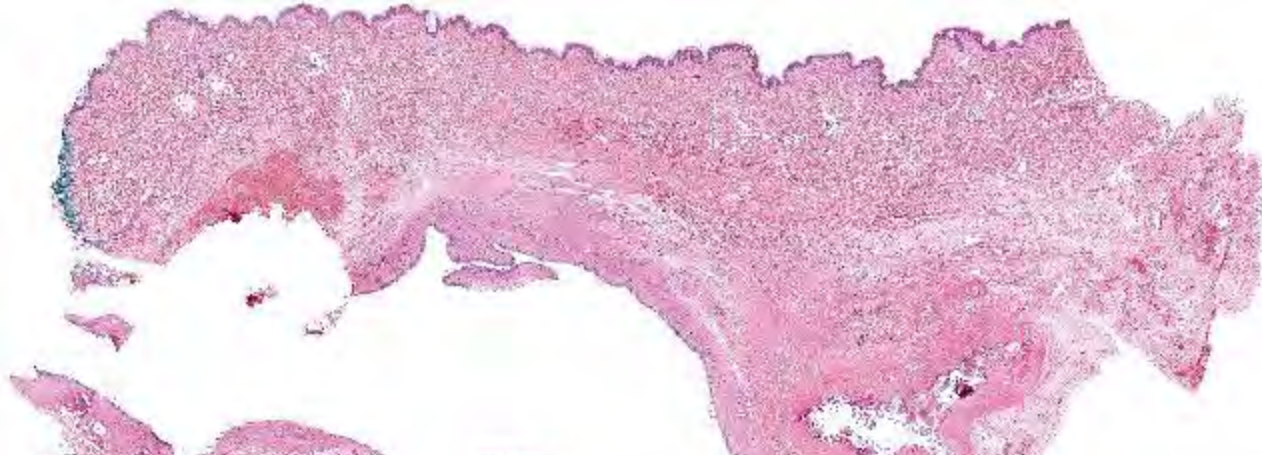
A biopsy is taken.



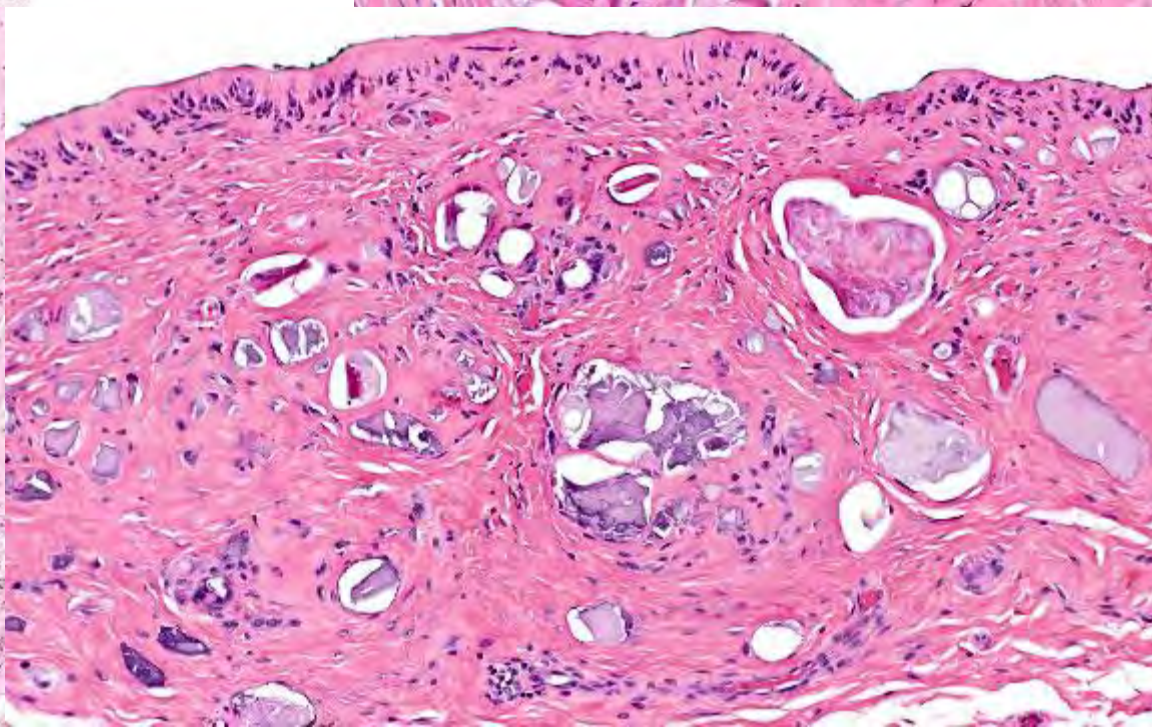
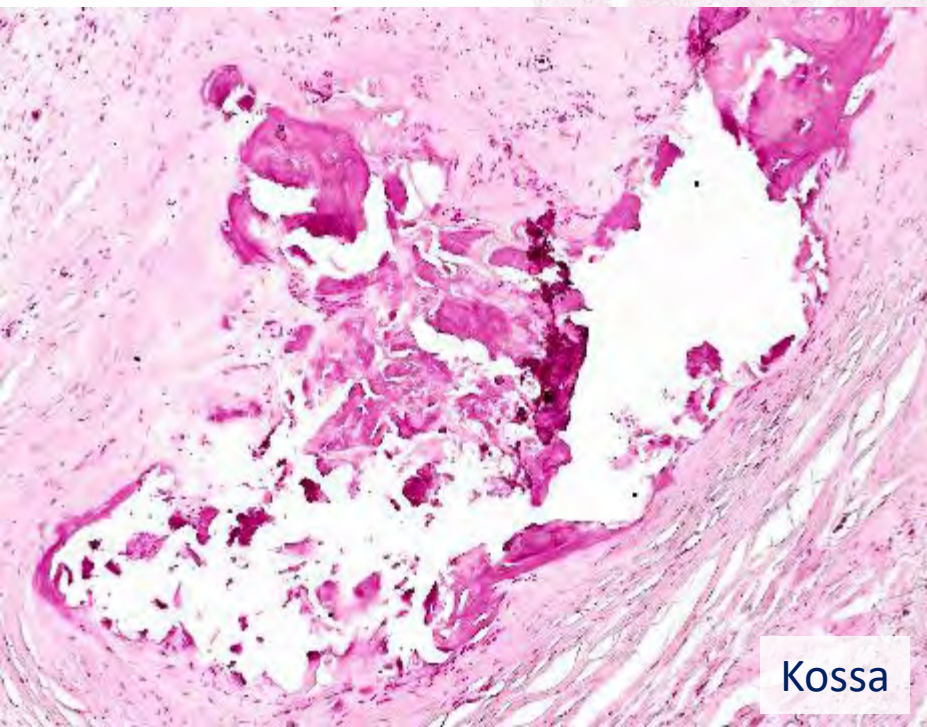
During surgery a whitish fluid comes out from the incision.

(Picture courtesy Doz. Dr. M. Horn)





Filler reaction
(consistent with copolyamide)

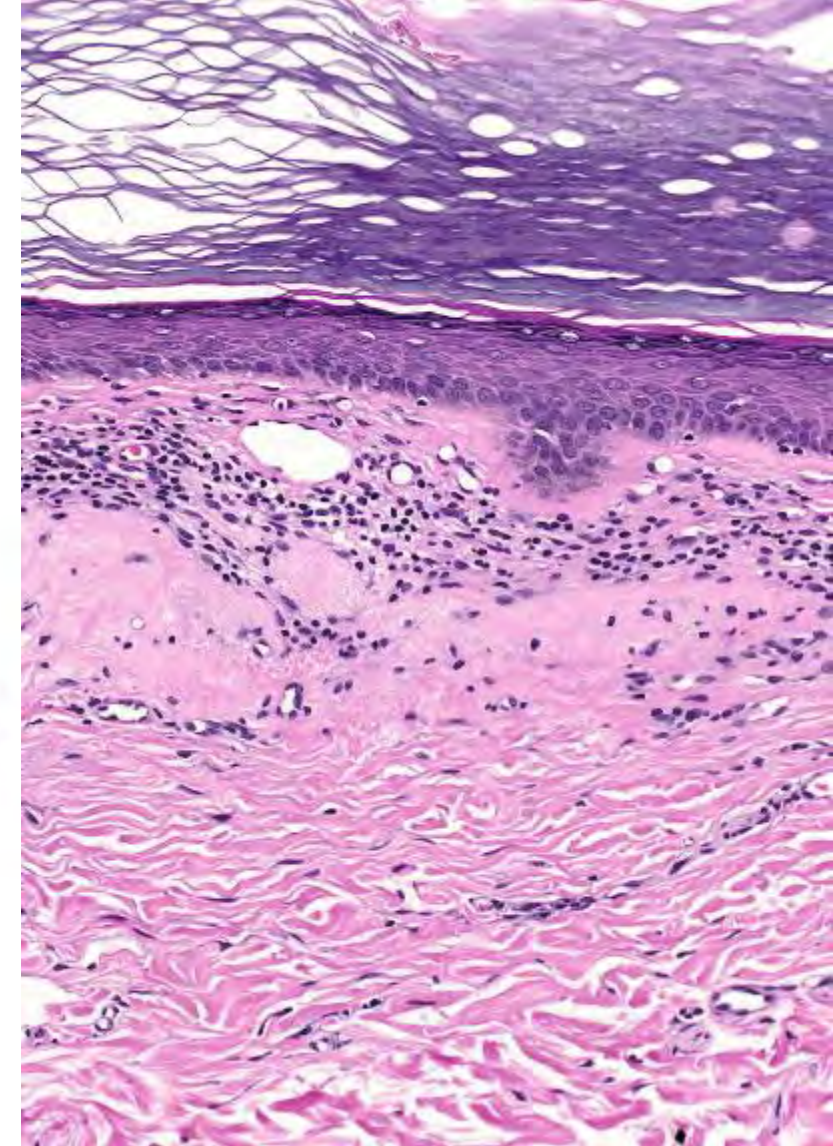


Kossa



F, 74

Asymptomatic perianal lesions for approximately 6 months, treated first with a "body cream" and then by a private dermatologist with a local steroid.

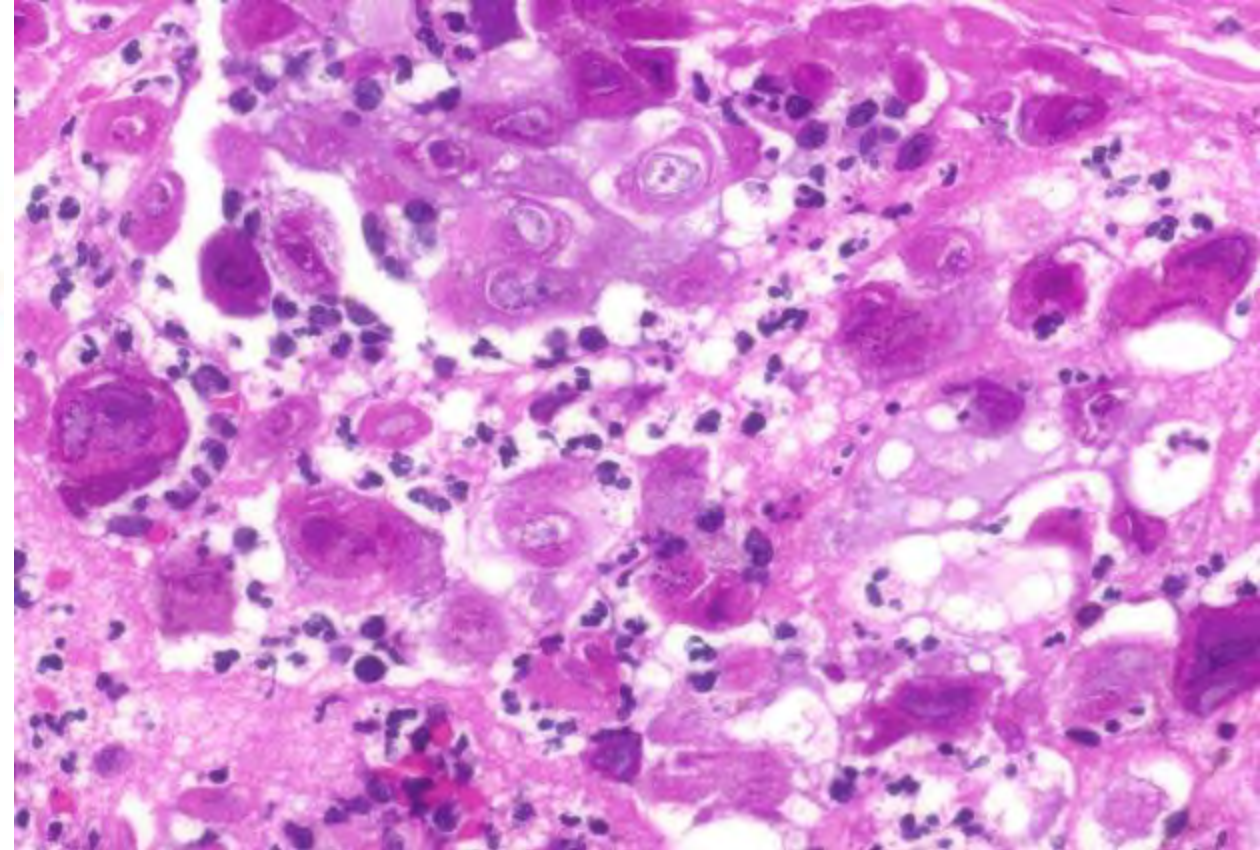
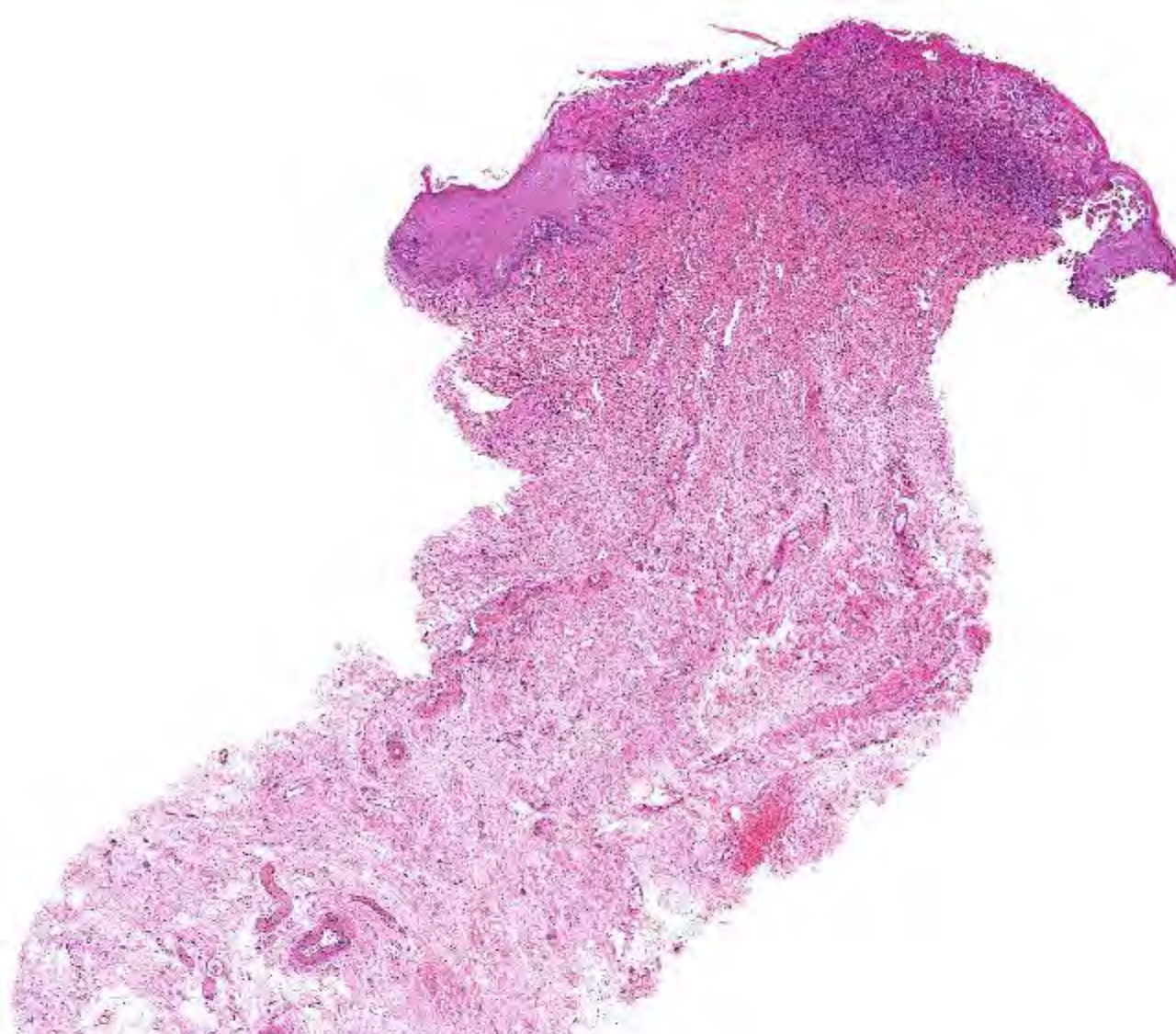


Lichen sclerosus
with lichen simplex chronicus-like horny layer



M, 63

History of stem cell transplantation 3 months before presentation (essential thrombocythemia with post-ETH myelofibrosis), and of cutaneous GVHD (grade 1, CR after local steroids). Immunosuppression with cyclosporin. Perianal lesion detected during hospitalization (duration unknown) and biopsied under a suspect clinical diagnosis of SCC.



Vegetating Herpes simplex
(*HSV2+ by PCR*)



Time of biopsy

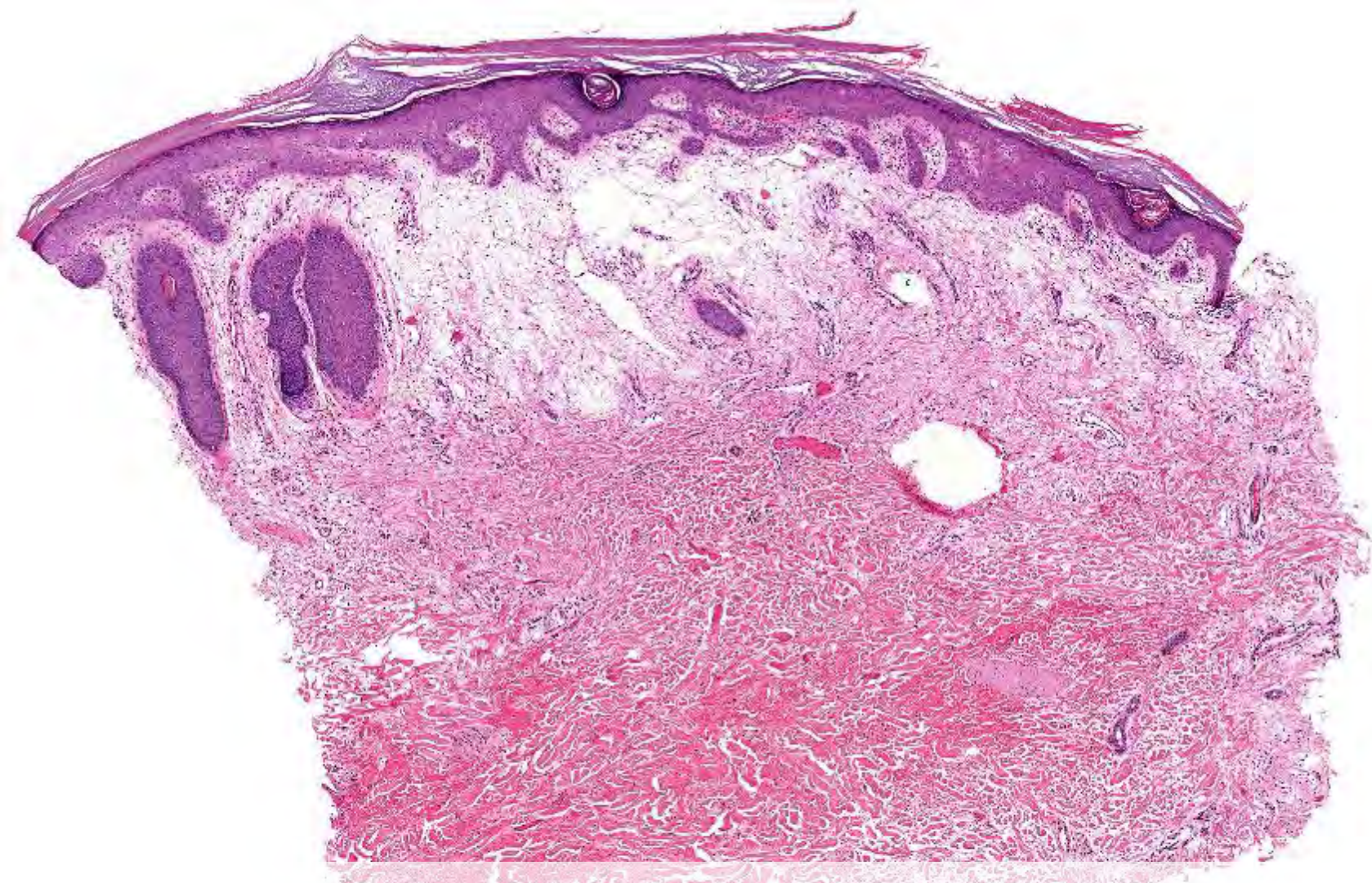
1 month later



M, 87

History of melanoma in situ (left upper arm) 4 years before presentation.
Perianal skin lesions of unknown duration, treated with intermittent local
steroids for the last several weeks (improvement / recurrences).

A biopsy is taken to rule out Bowen disease.



Edematous ("bullous")
lichen simplex chronicus

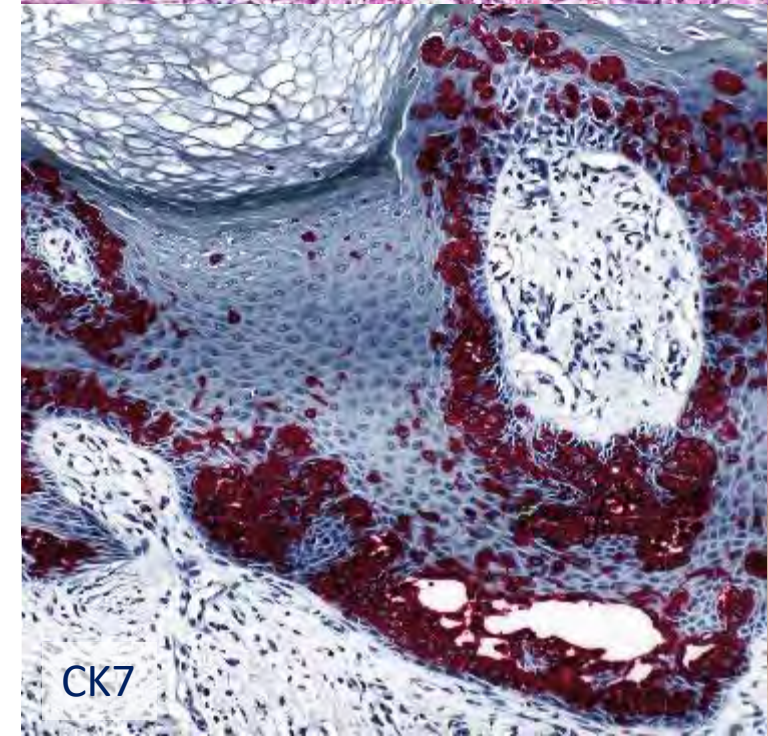
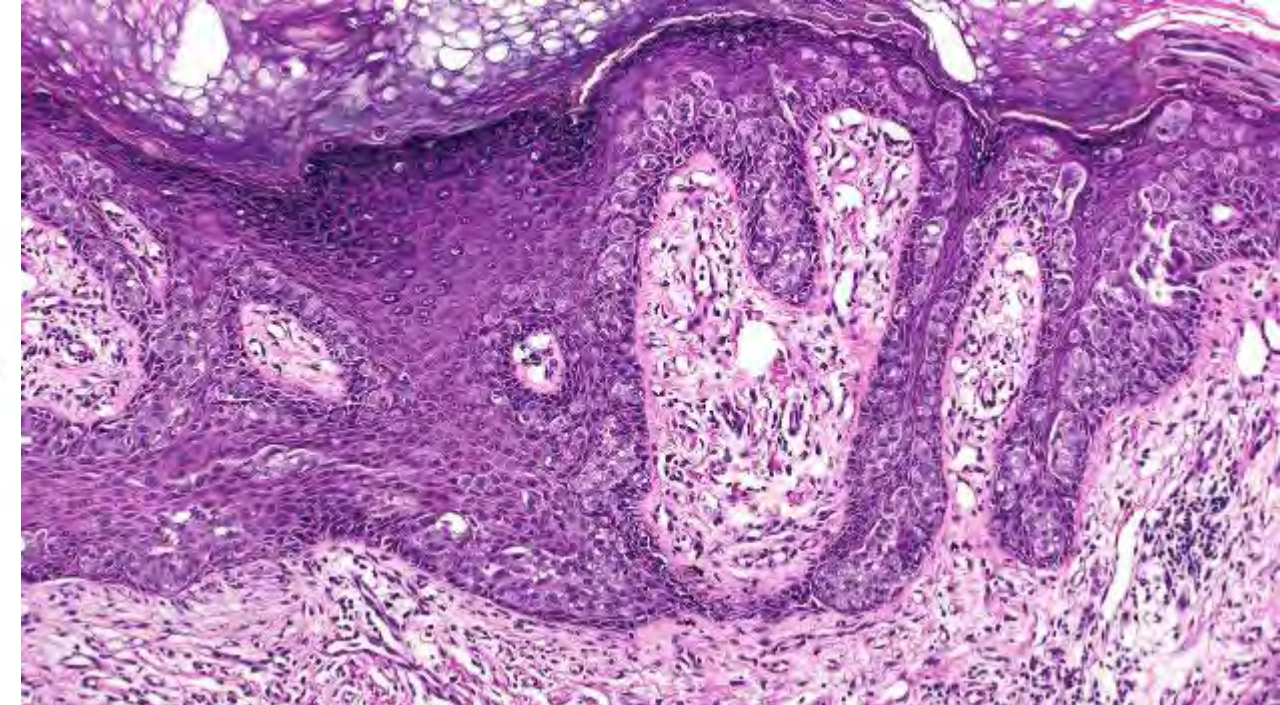
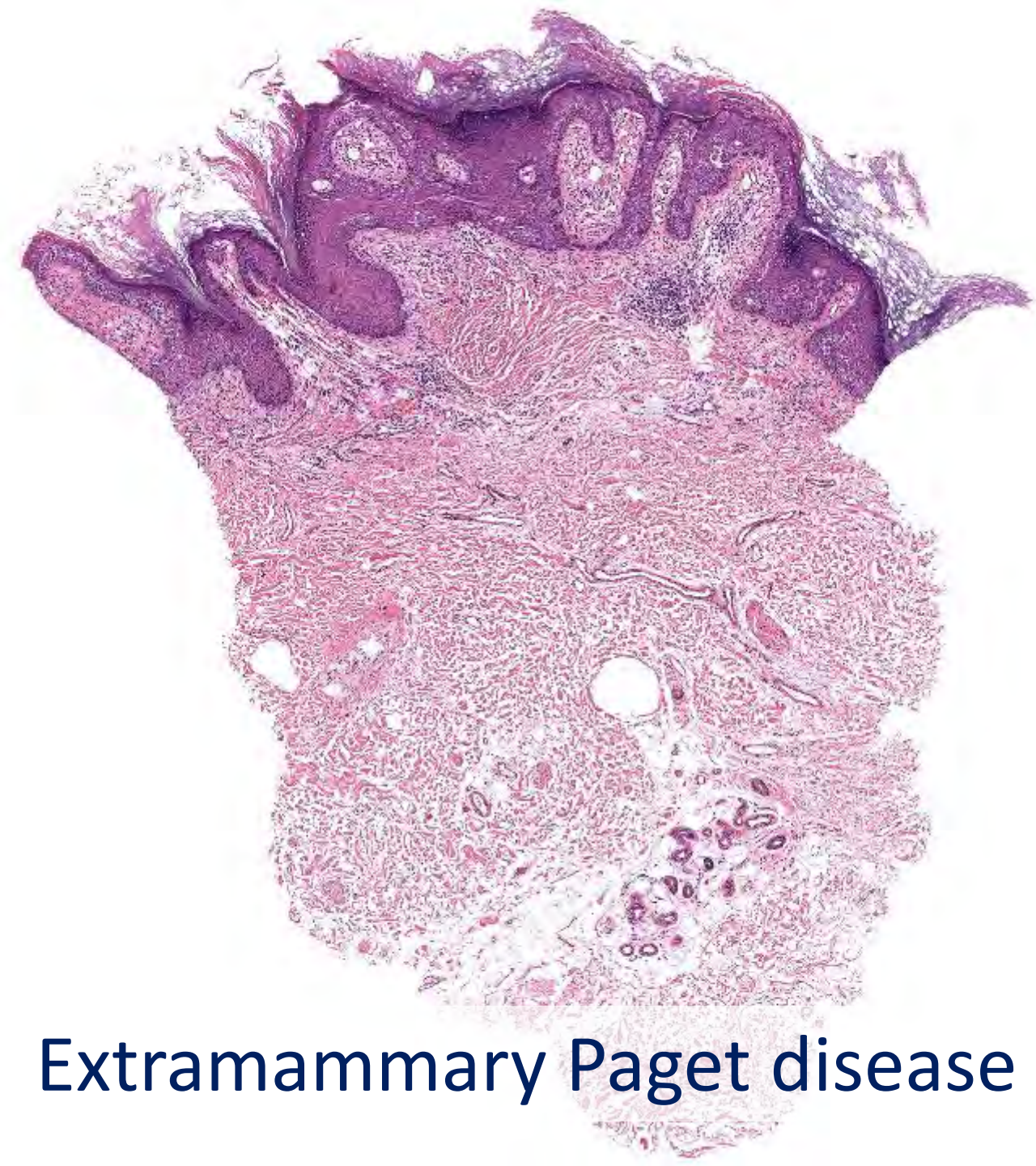




F, 81

According to the patient itchy lesions on the genital area present for some years. Treated by a private dermatologist with local steroids and antimycotic creams without improvement.

A biopsy is taken.



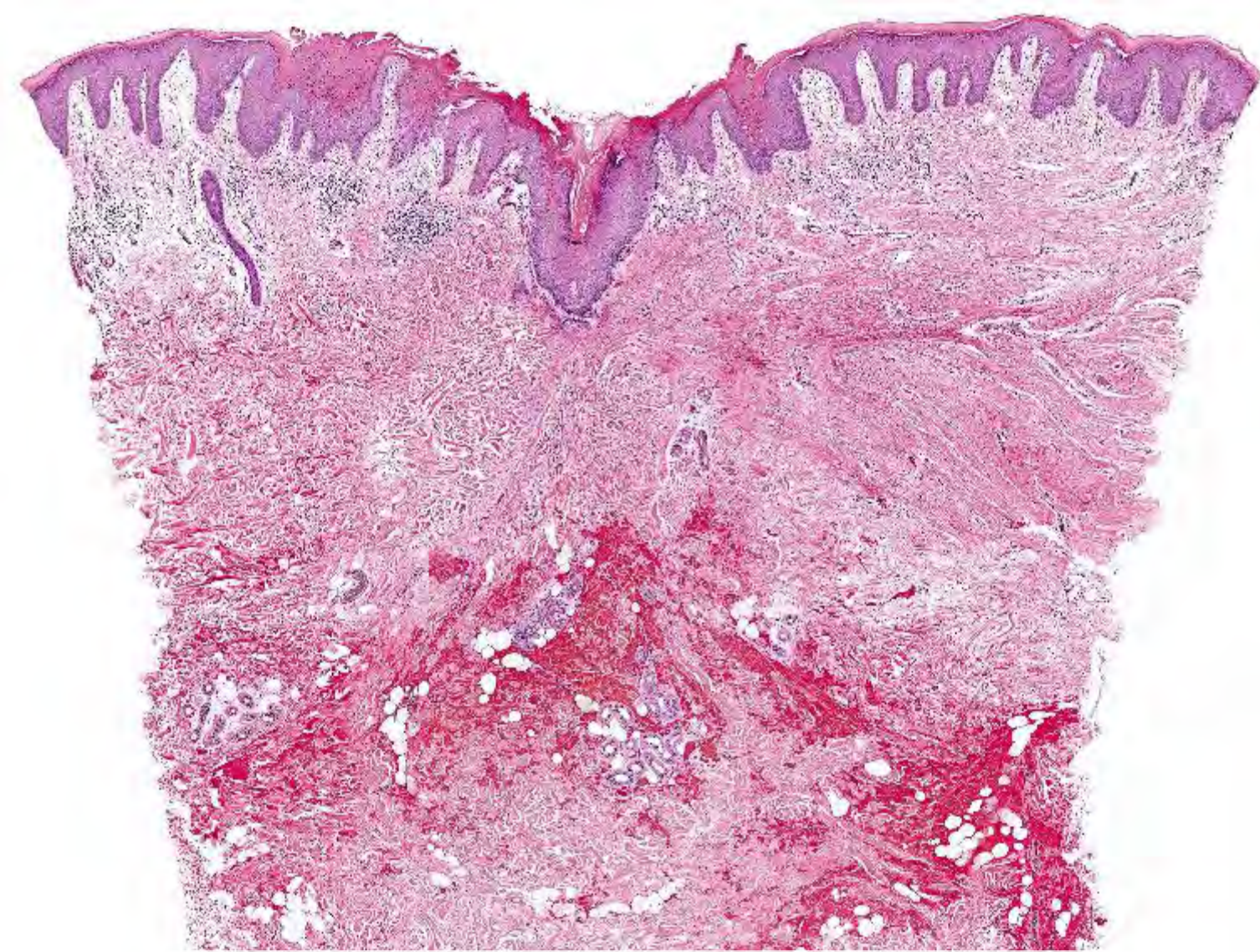
Extramammary Paget disease



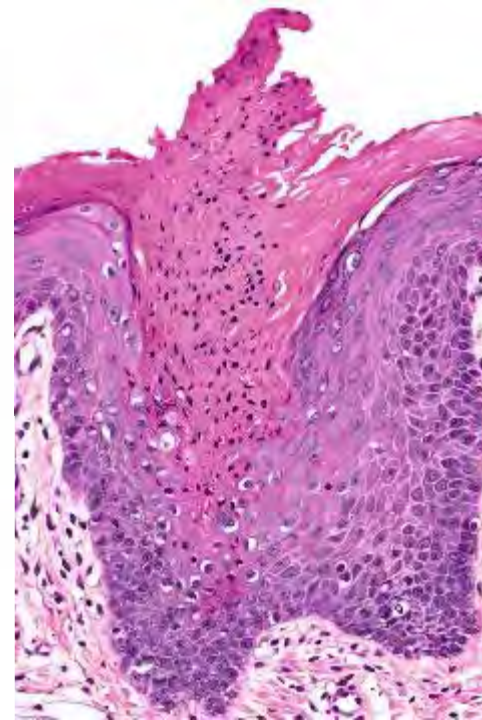
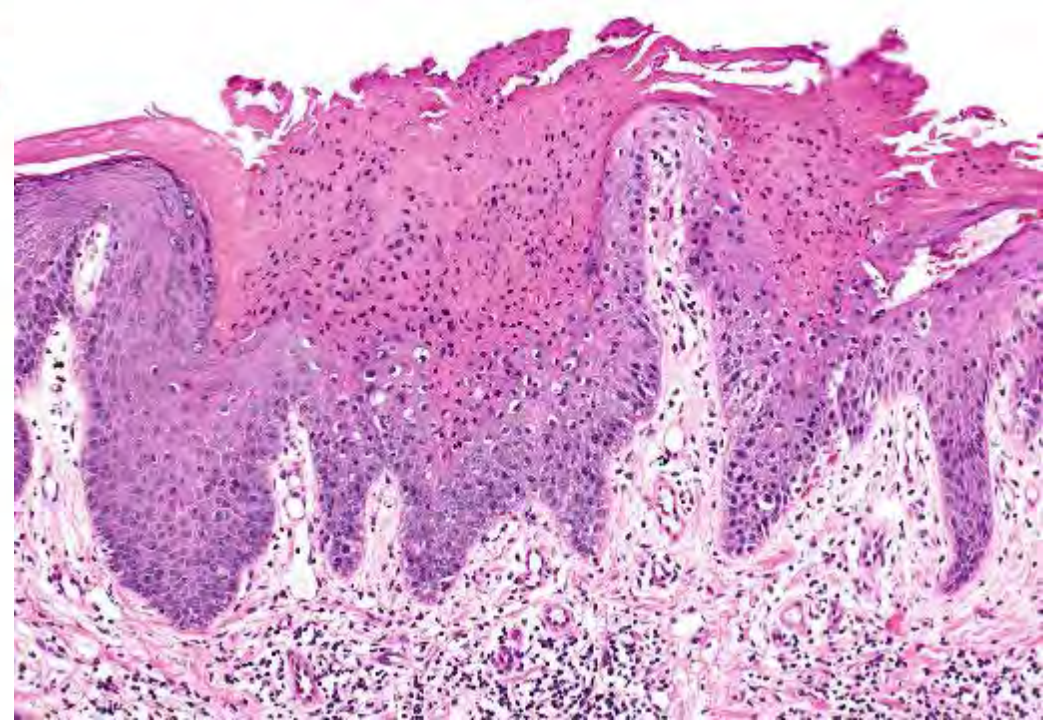
M, 61

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

A biopsy is taken.



Porokeratosis ptychotropica
& chronic eczema





1st presentation



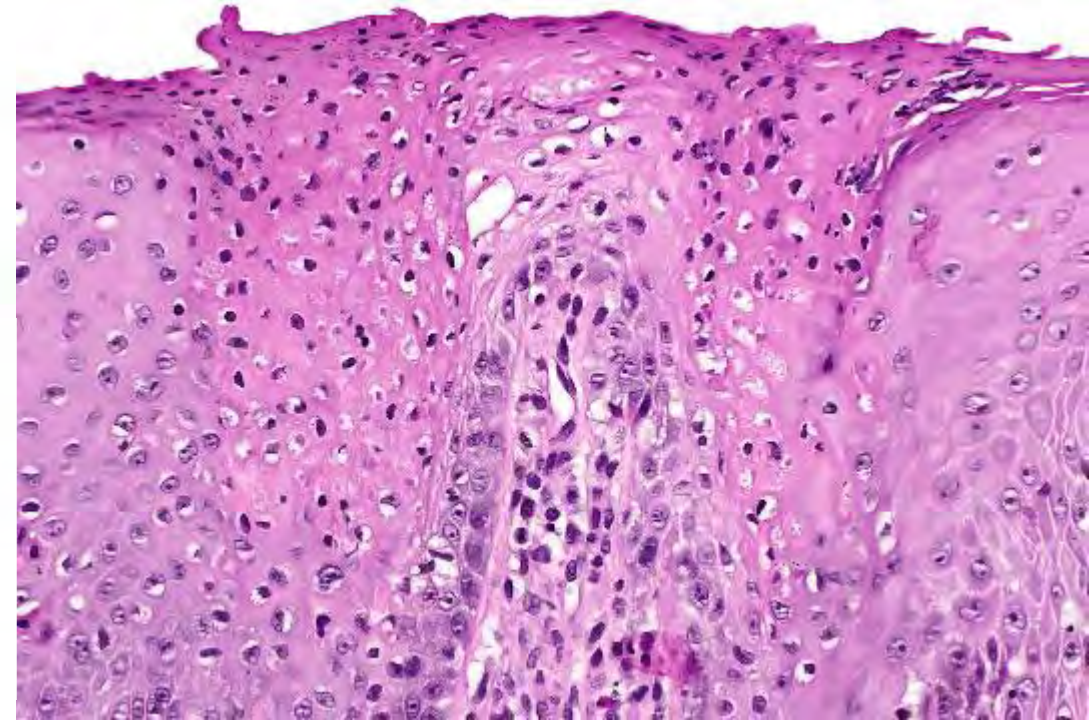
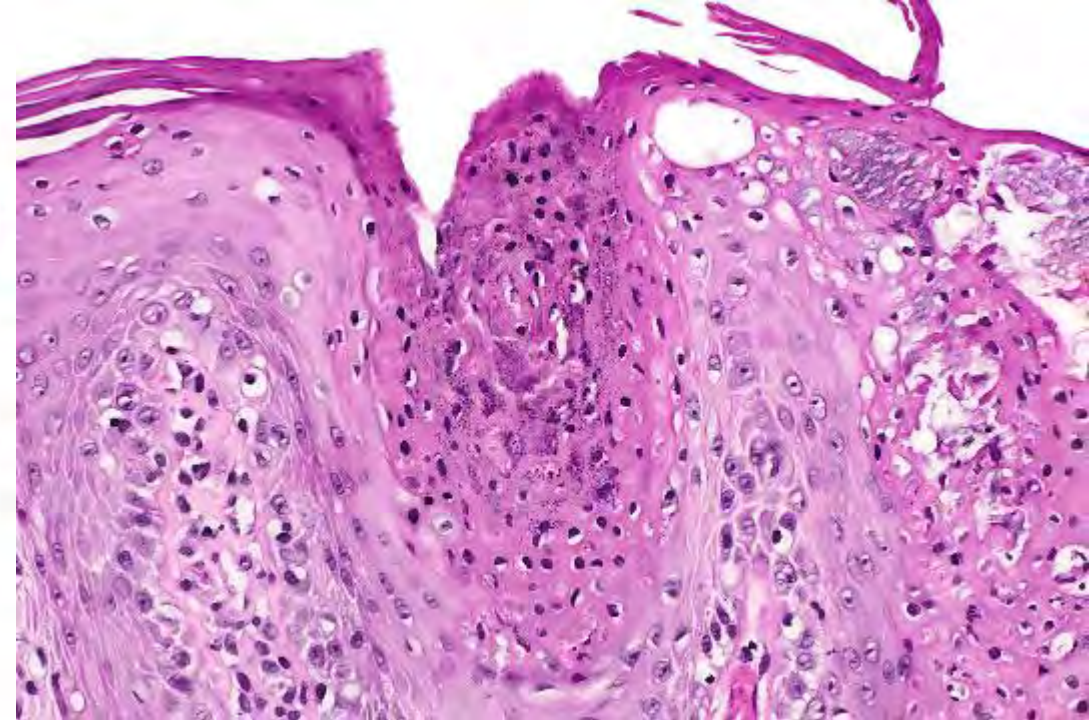
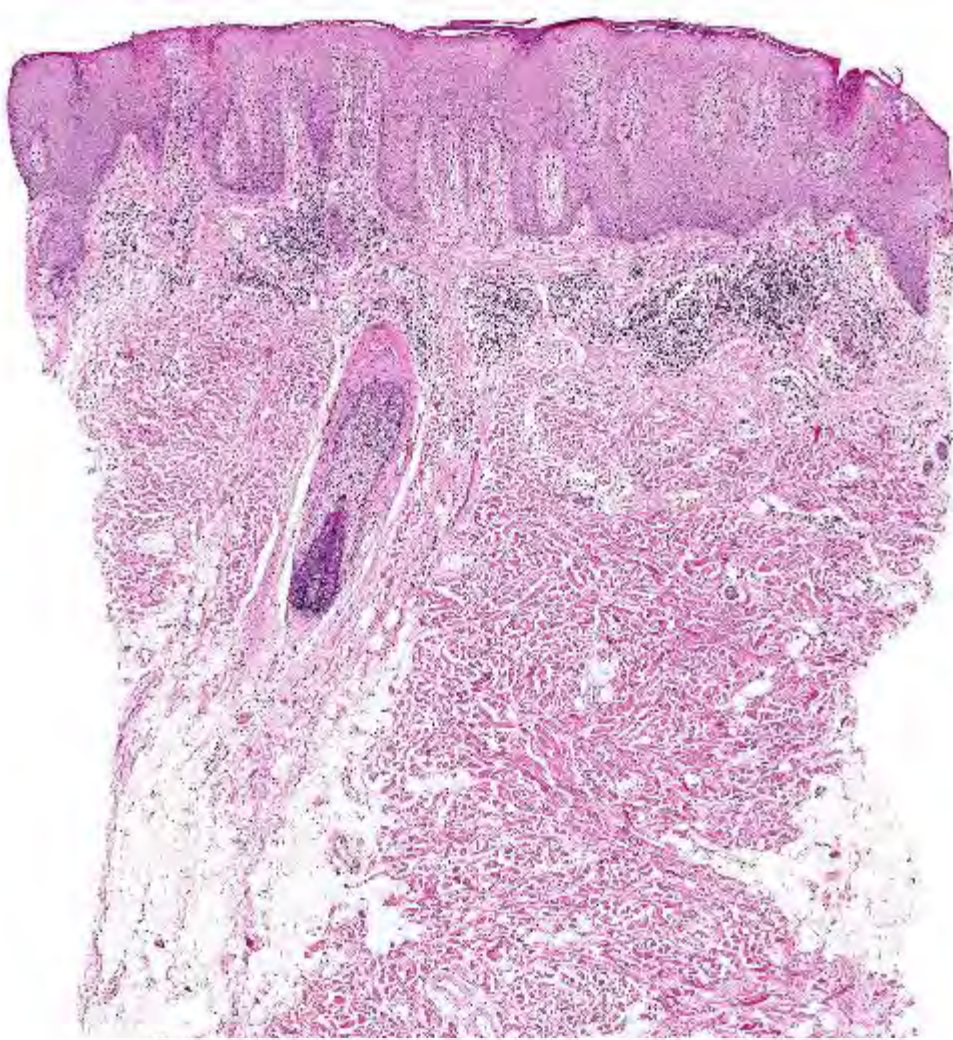
+10 months



+14 months



+18 months (new biopsy)



**Porokeratosis ptychotropica
& chronic eczema**

*(showing only the intraepidermal
portion of cornoid lamellae)*



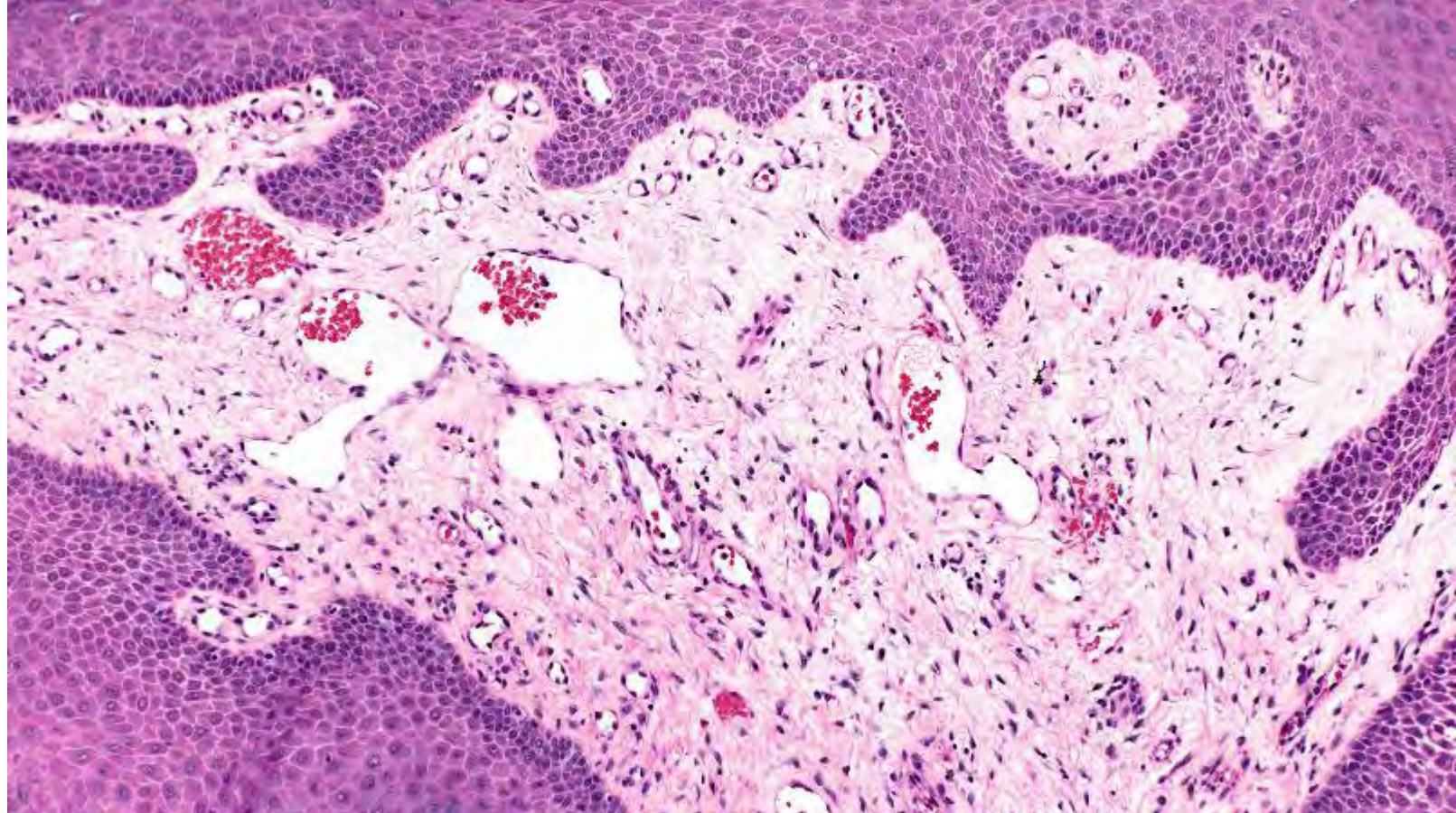
M, 64

Tetraparesis for 2 years; bed with anti-decubitus mattress. Sent by GP for evaluation of verrucous lesions on the buttocks.

A biopsy is taken.



Papillomatosis cutis
lymphostatica in
chronic lymphedema

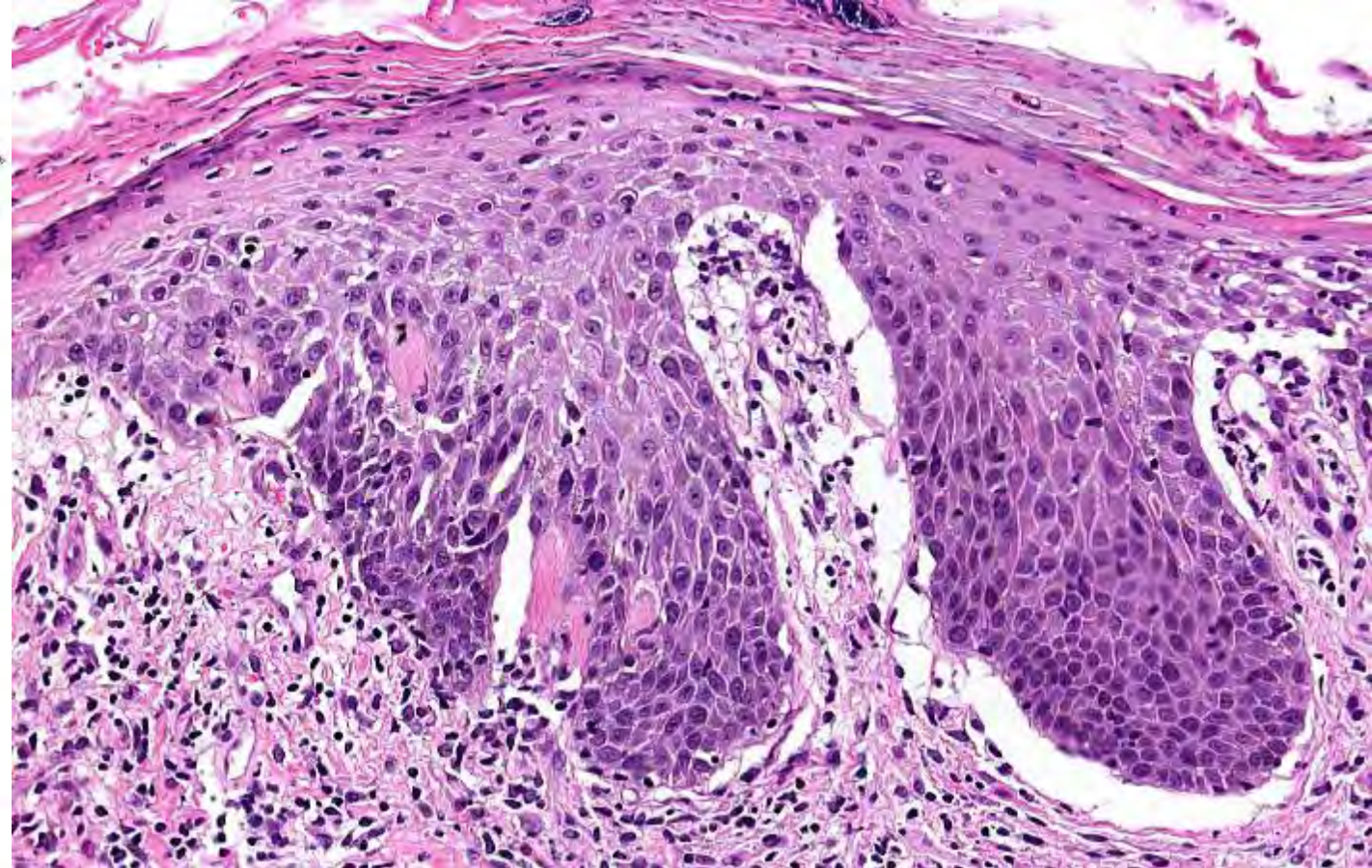
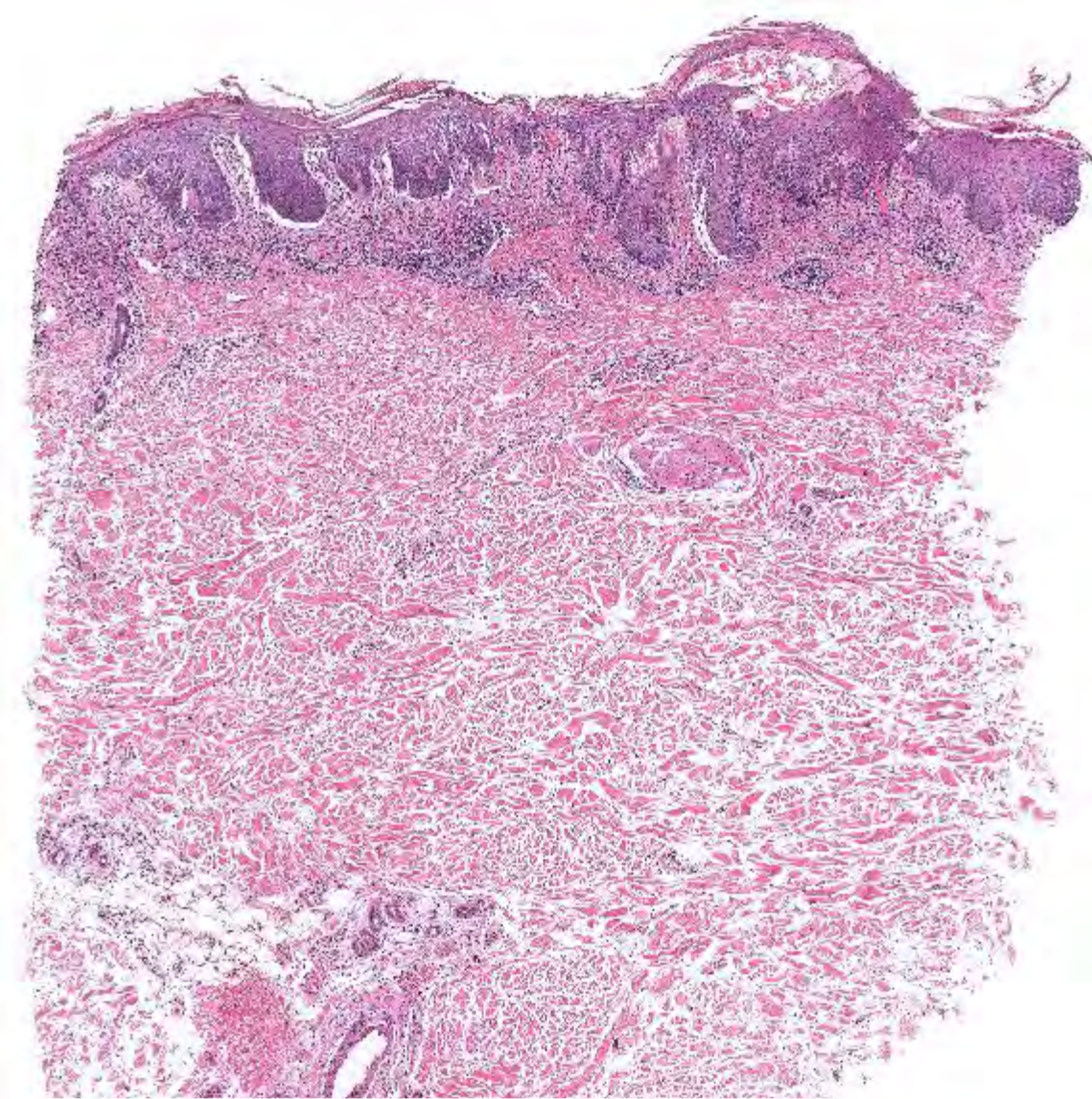




M, 75

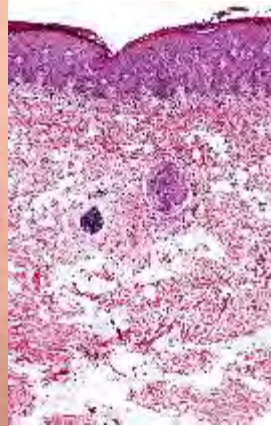
Lesions on the buttocks and groin for several weeks, subsequently spreading to the thighs and flanks.

A biopsy is taken.

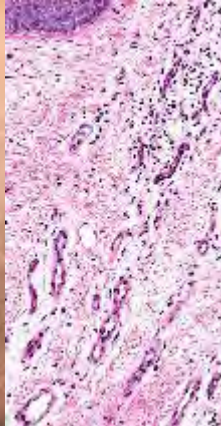


Glucagonoma syndrome
(pancreatic tumor)

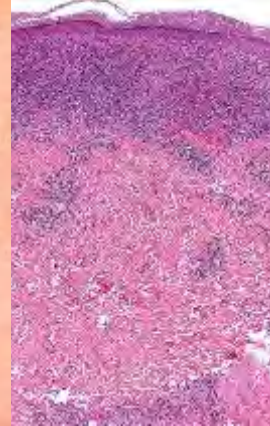




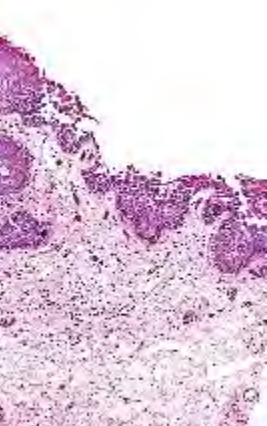
Psoriasis



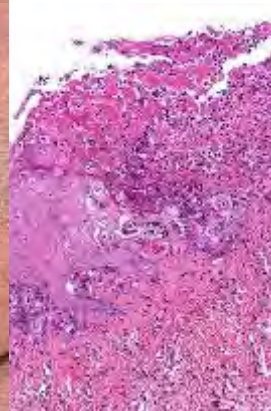
cODD



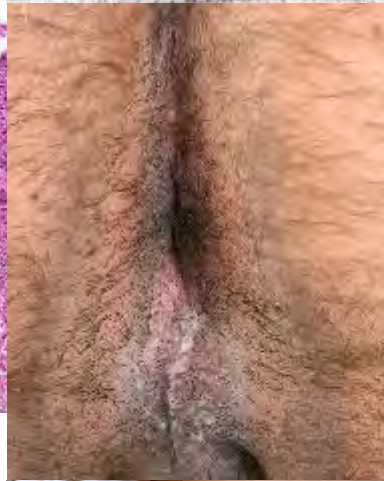
Mycosis fungoides



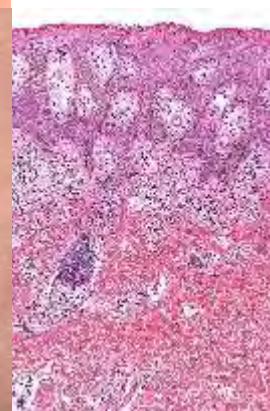
Hailey-Hailey



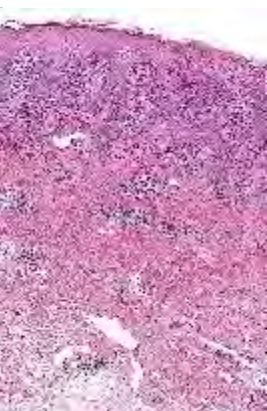
Herpes simplex



LSC



Crohn disease &
zinc deficiency



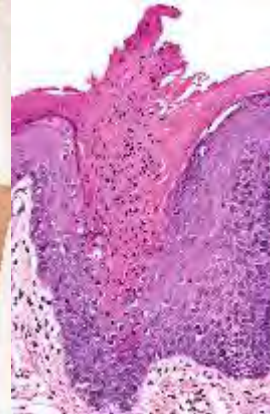
Syphilis



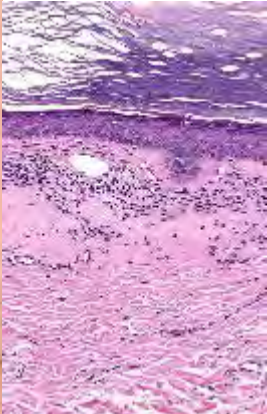
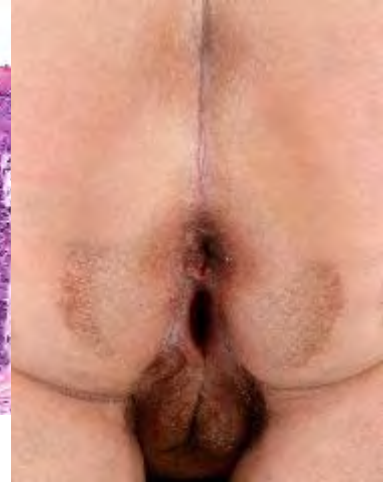
Lichen planus



Extramammary
Paget



Porokeratosis
ptychotropica

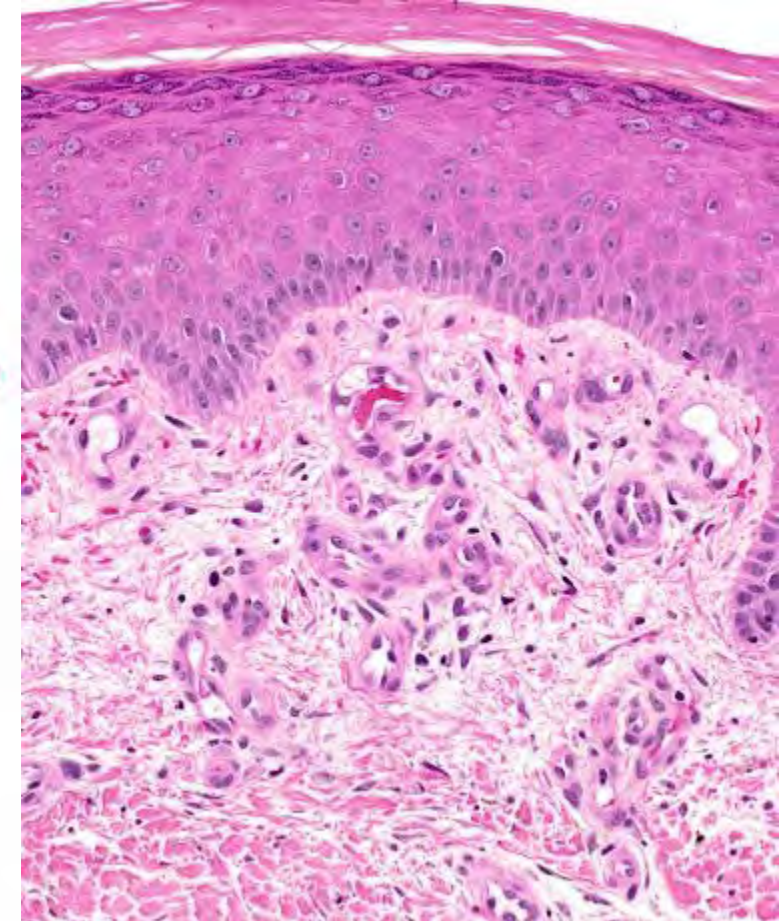
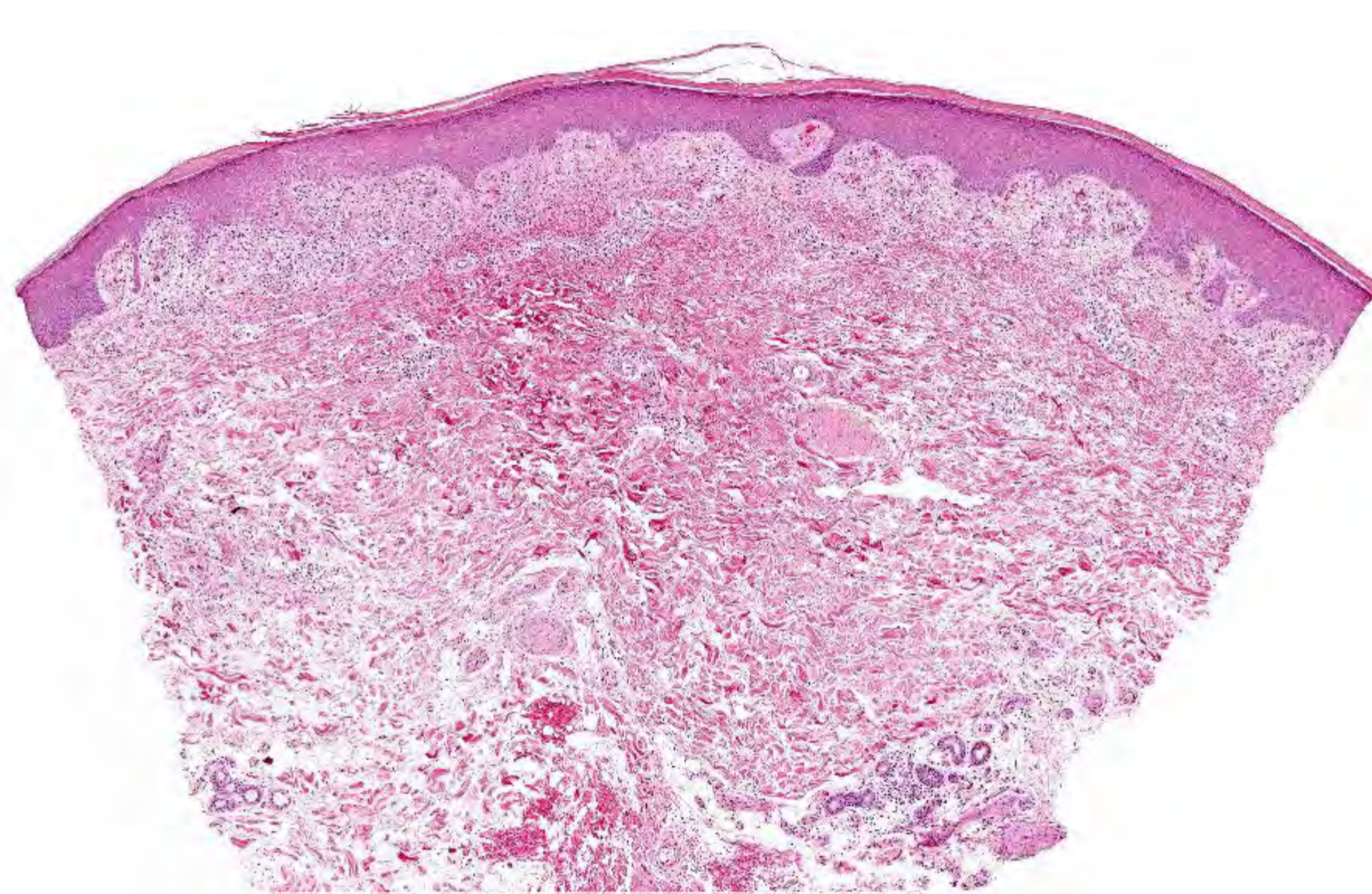


LSA



M, 83

History of Merkel cell carcinoma 6 months before presentation. Chronic lymphedema on both lower extremities. Hemorrhagic lesions on the right lower leg of unknown duration. A biopsy is taken.

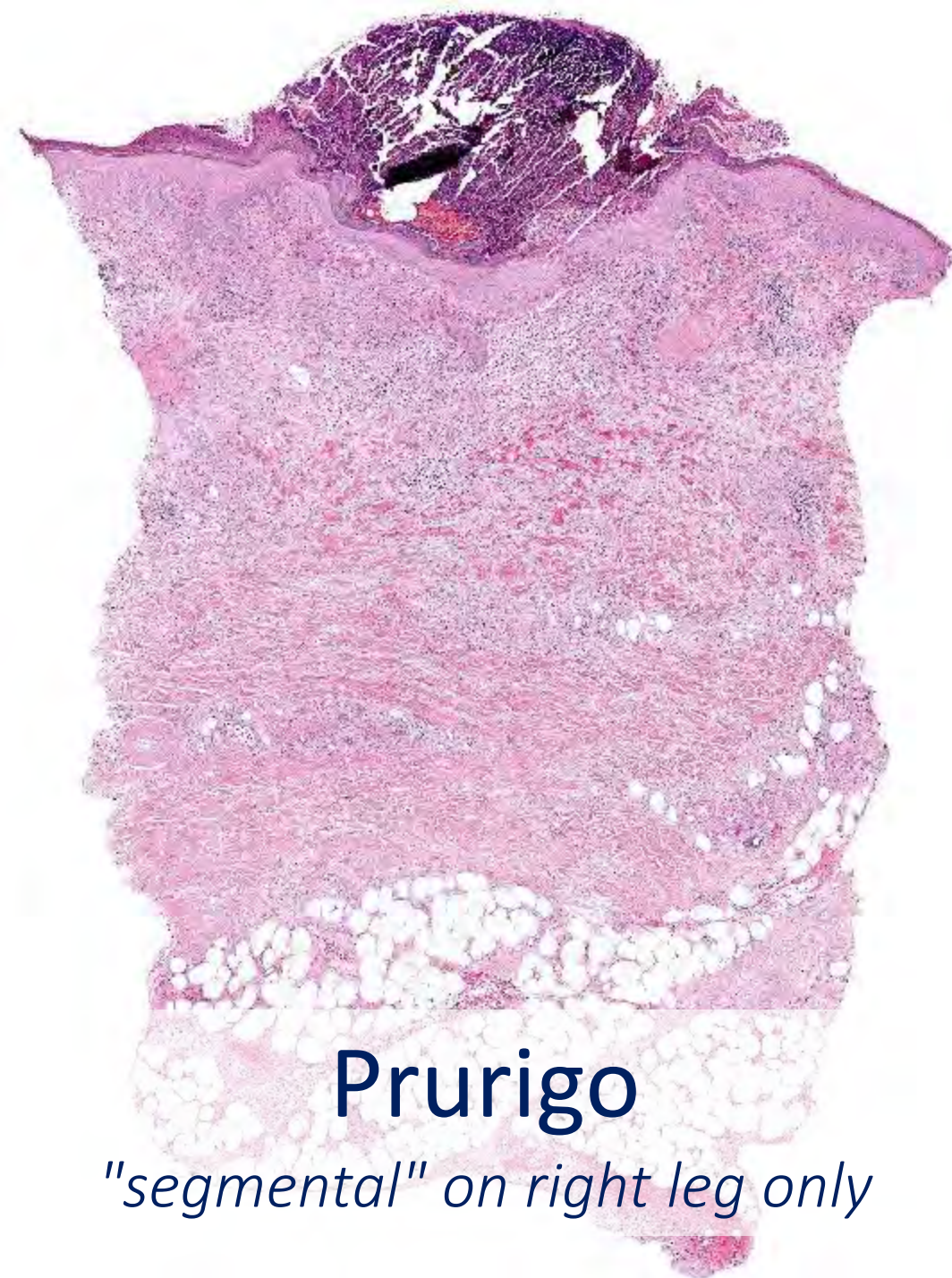


Unilateral, "nummular" stasis dermatitis
and chronic frictional changes



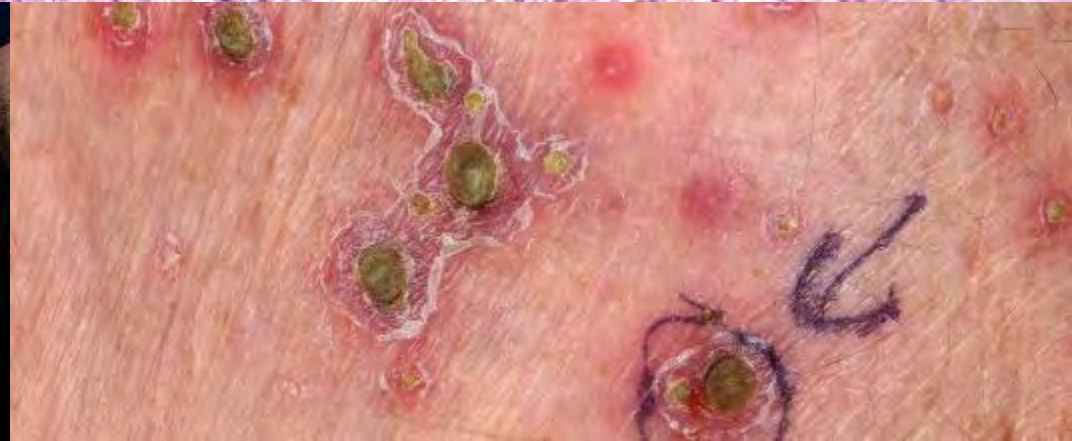
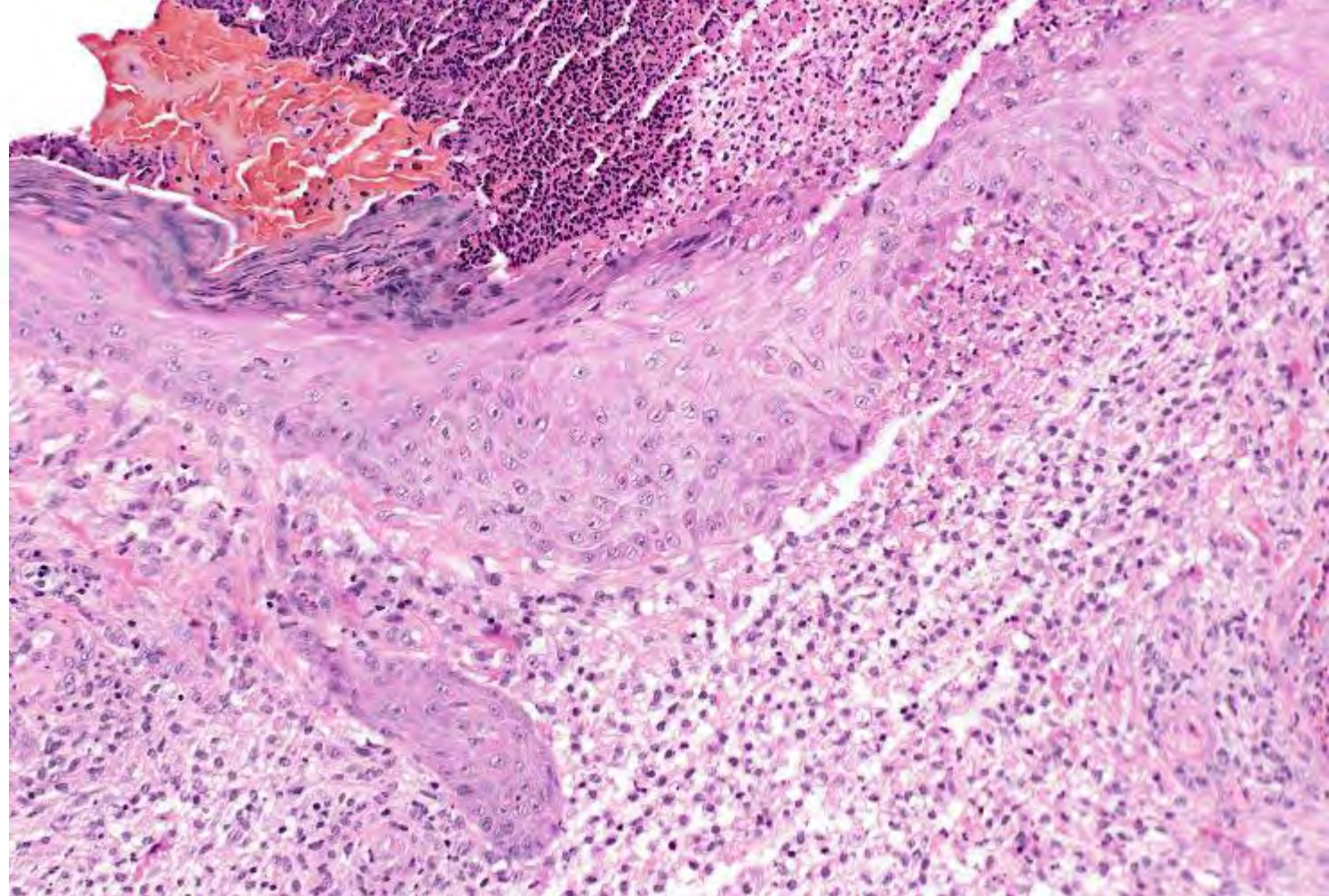
M, 84

Skin lesions on the right leg for approximately 3 weeks.
A biopsy is taken.



Prurigo

"segmental" on right leg only

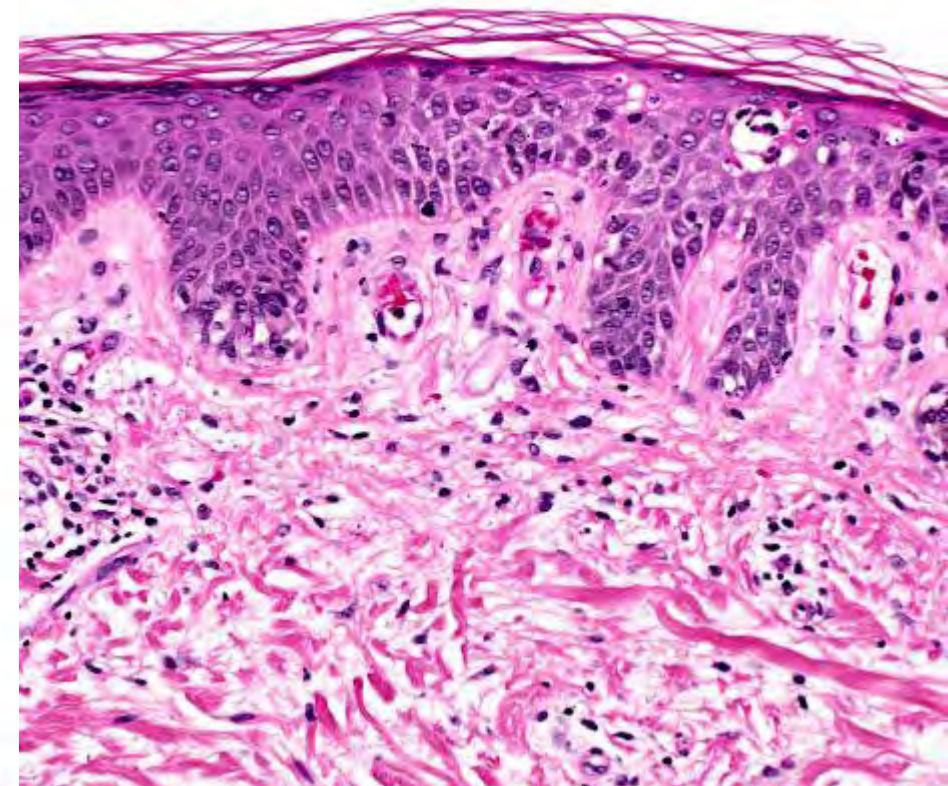
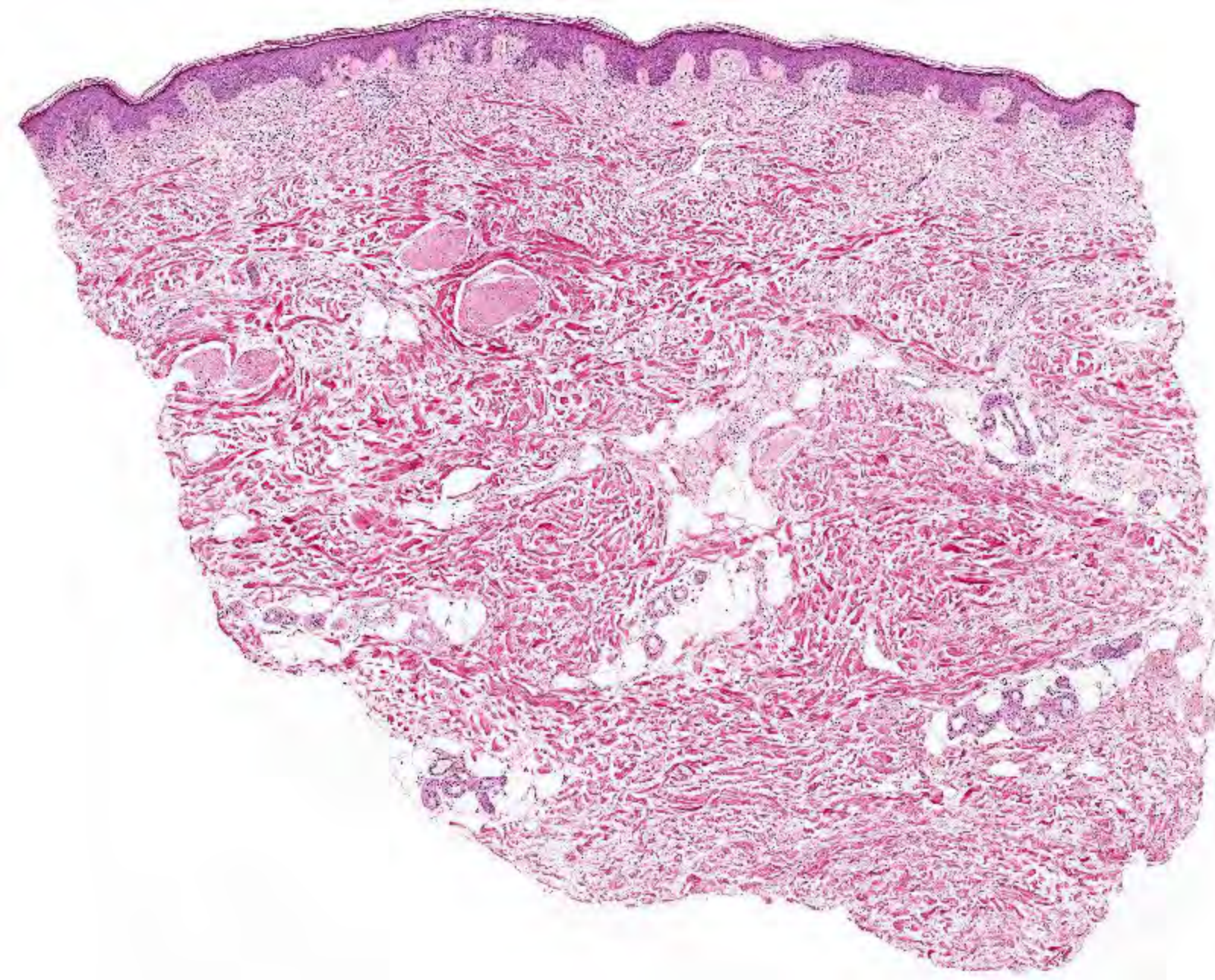




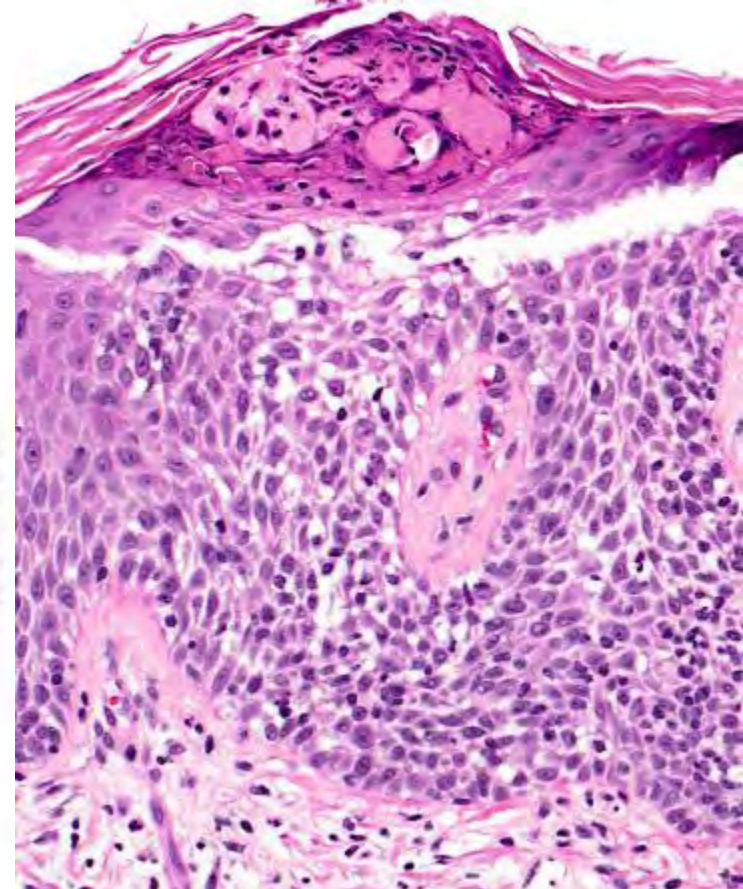
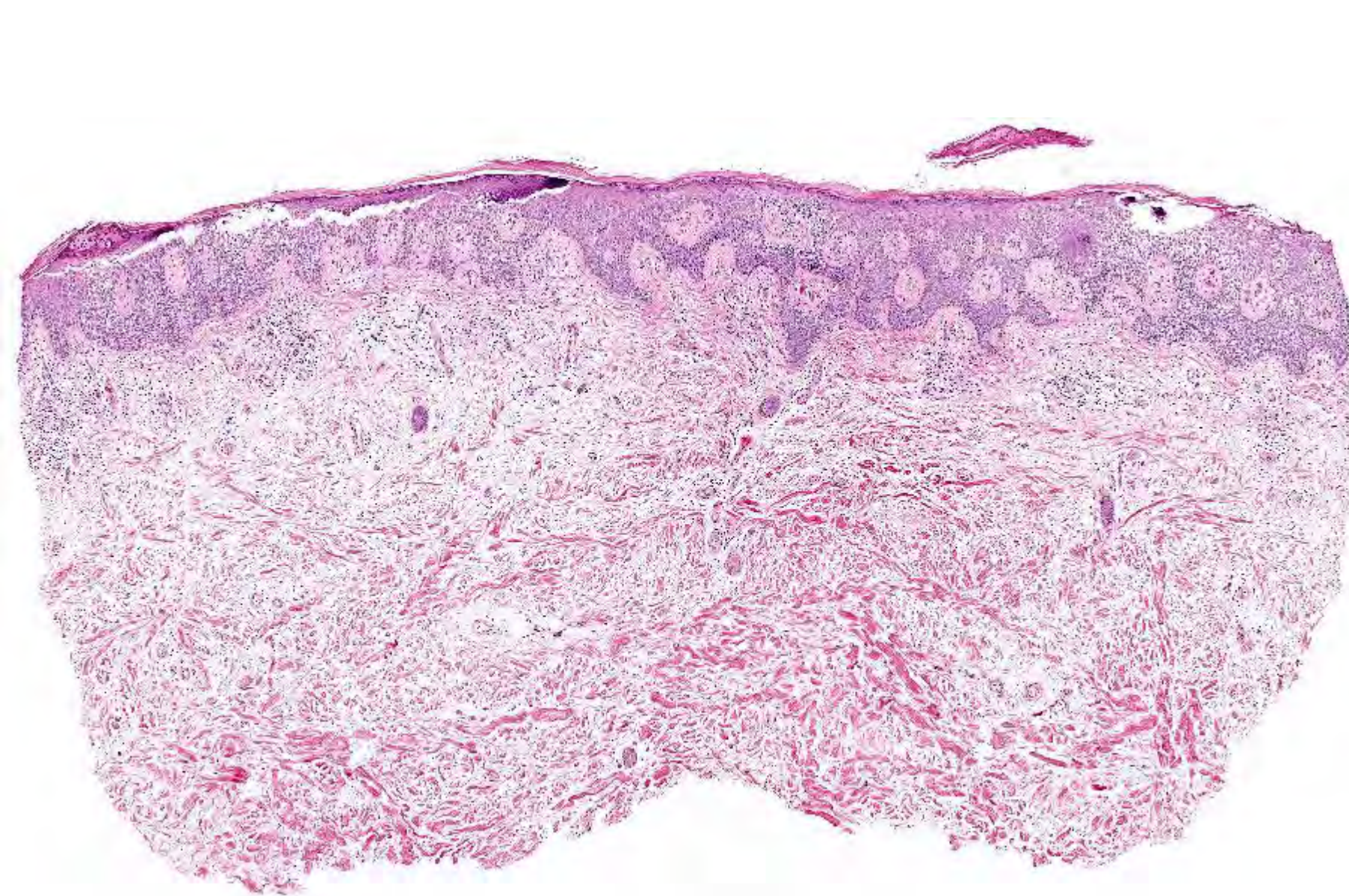
F, 70

According to the patient skin lesions on the left leg for 30-40 years. No improvement with various local treatments.

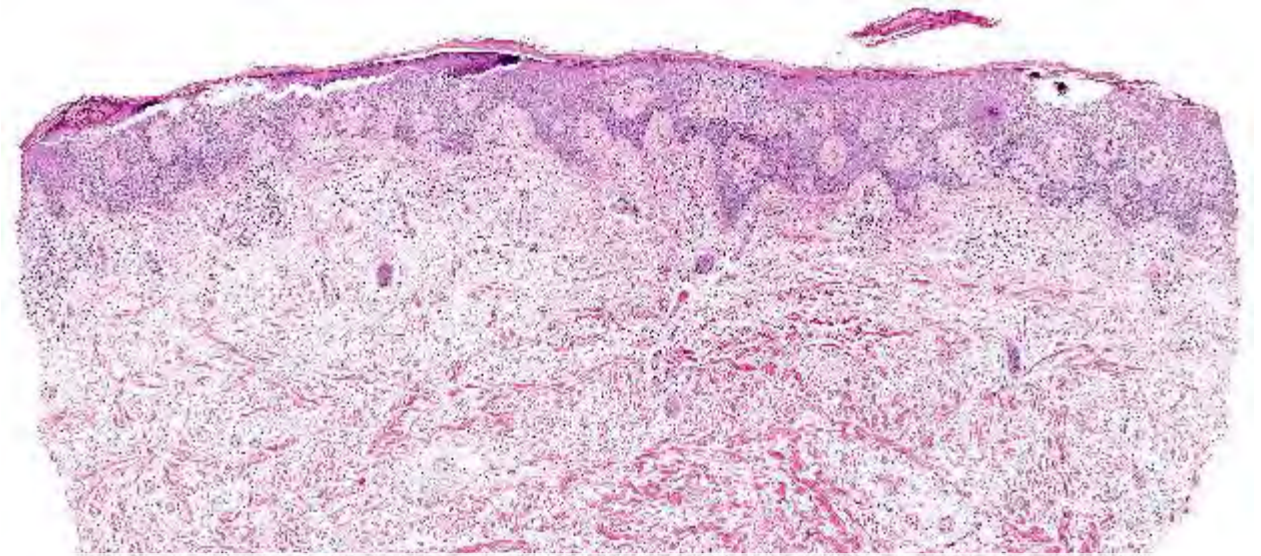
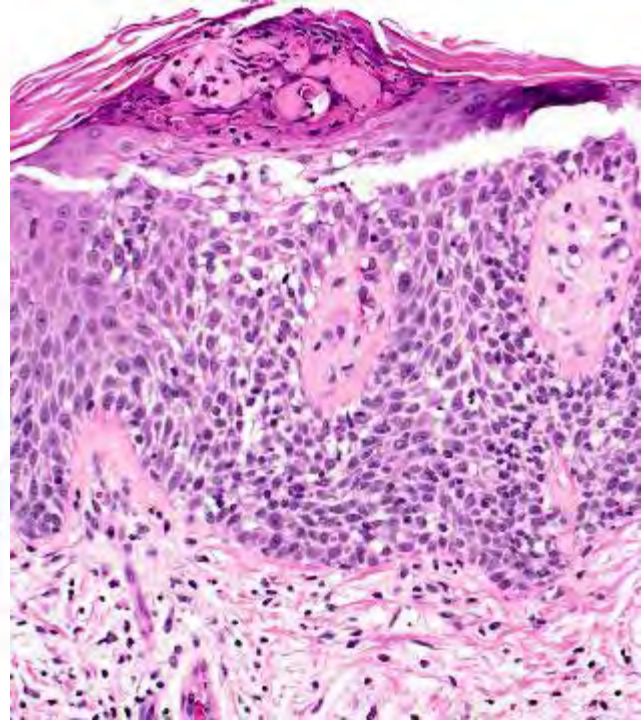
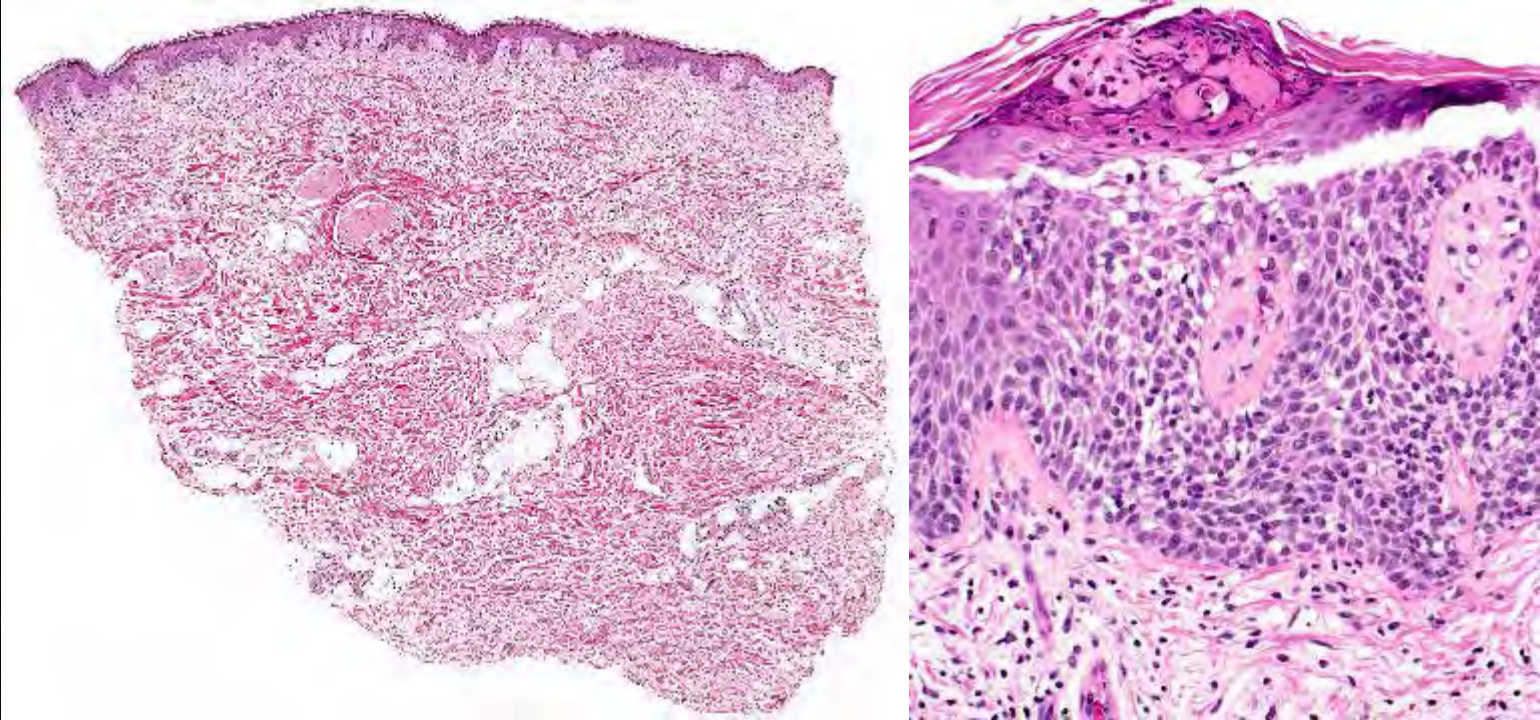
Two biopsies are taken.



Biopsy #1



Biopsy #2



Unilateral eczematous dermatitis

Unilateral leg dermatoses



Stasis dermatitis

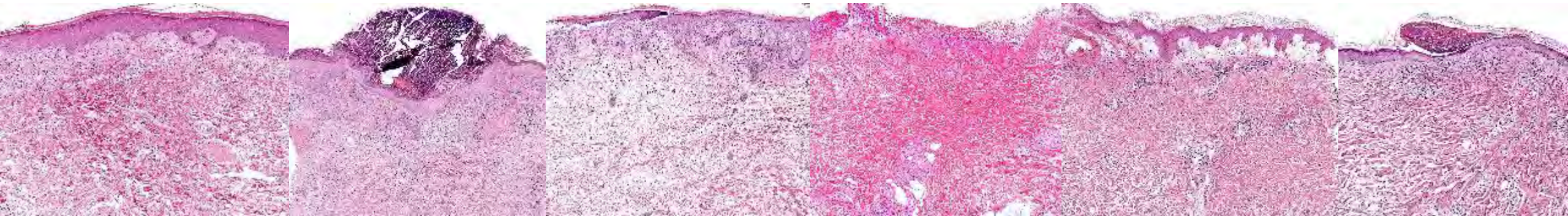
Excoriated prurigo

Eczema

Bullous impetigo

Erysipelas

Herpes zoster





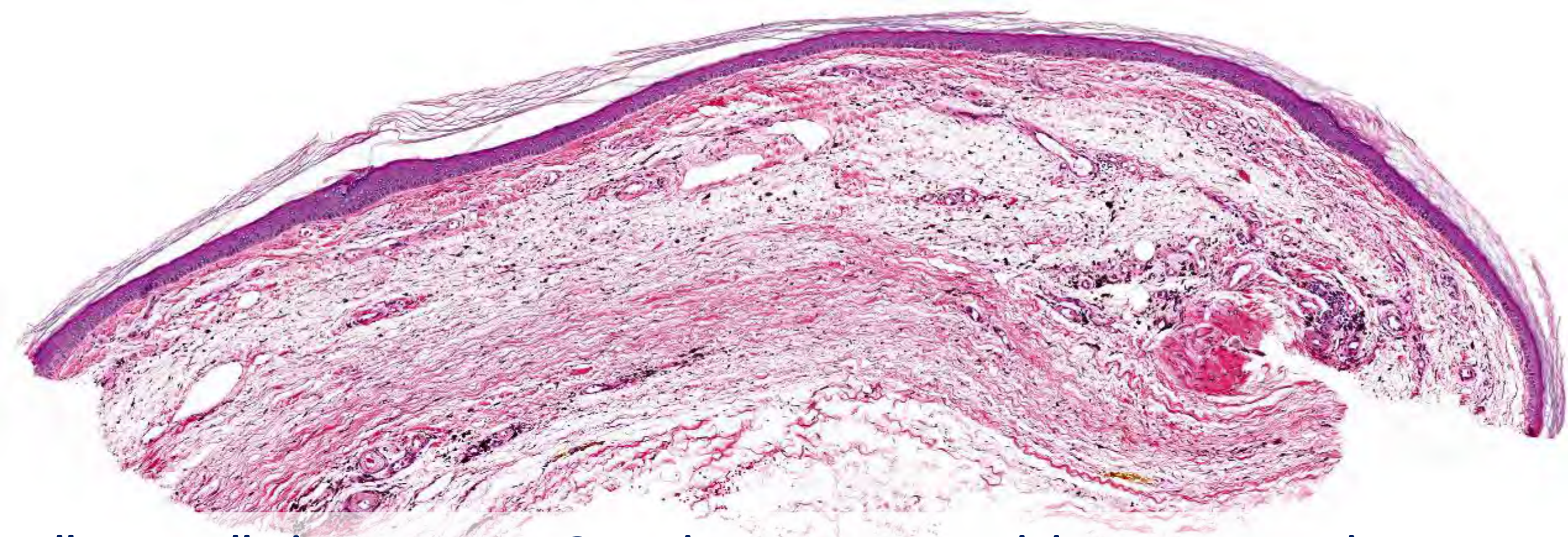
F, 65

Known SCLE.

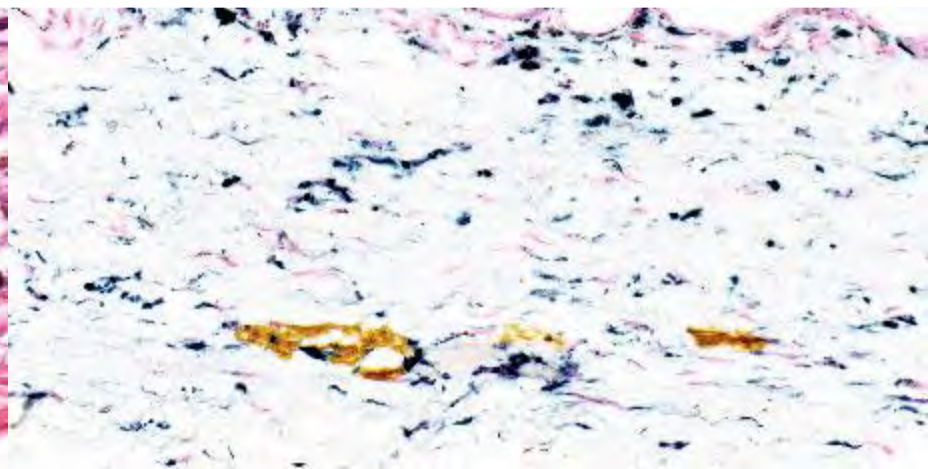
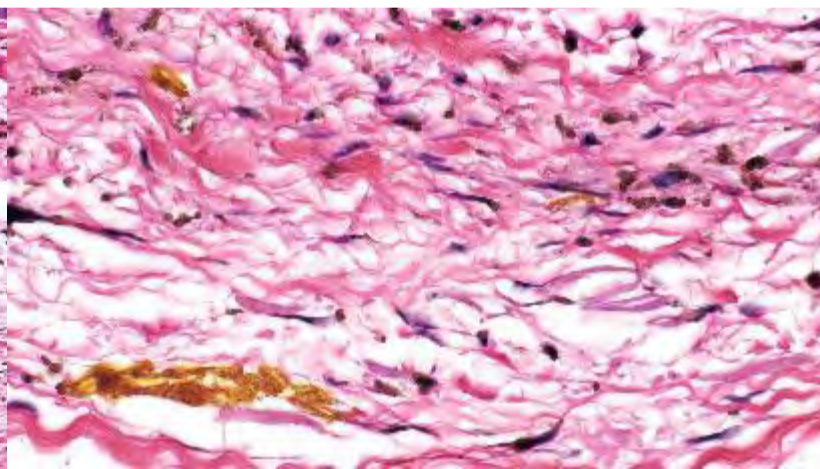
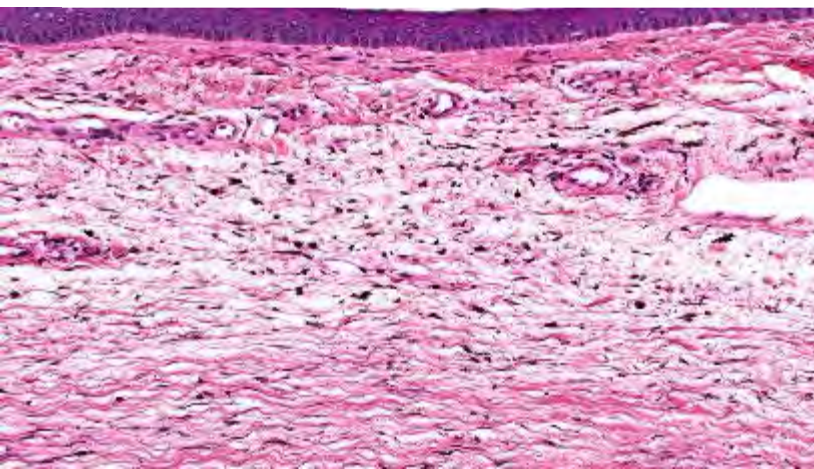
Previously managed with resochin, thalidomide, MTX, dapsone, mycophenolate mofetil, azathioprine, rituximab.

Treatment with hydroxychloroquine and mepacrine for the last 10 months.

A biopsy is taken.



"Stasis" dermatitis & ochronosis in chloroquine therapy



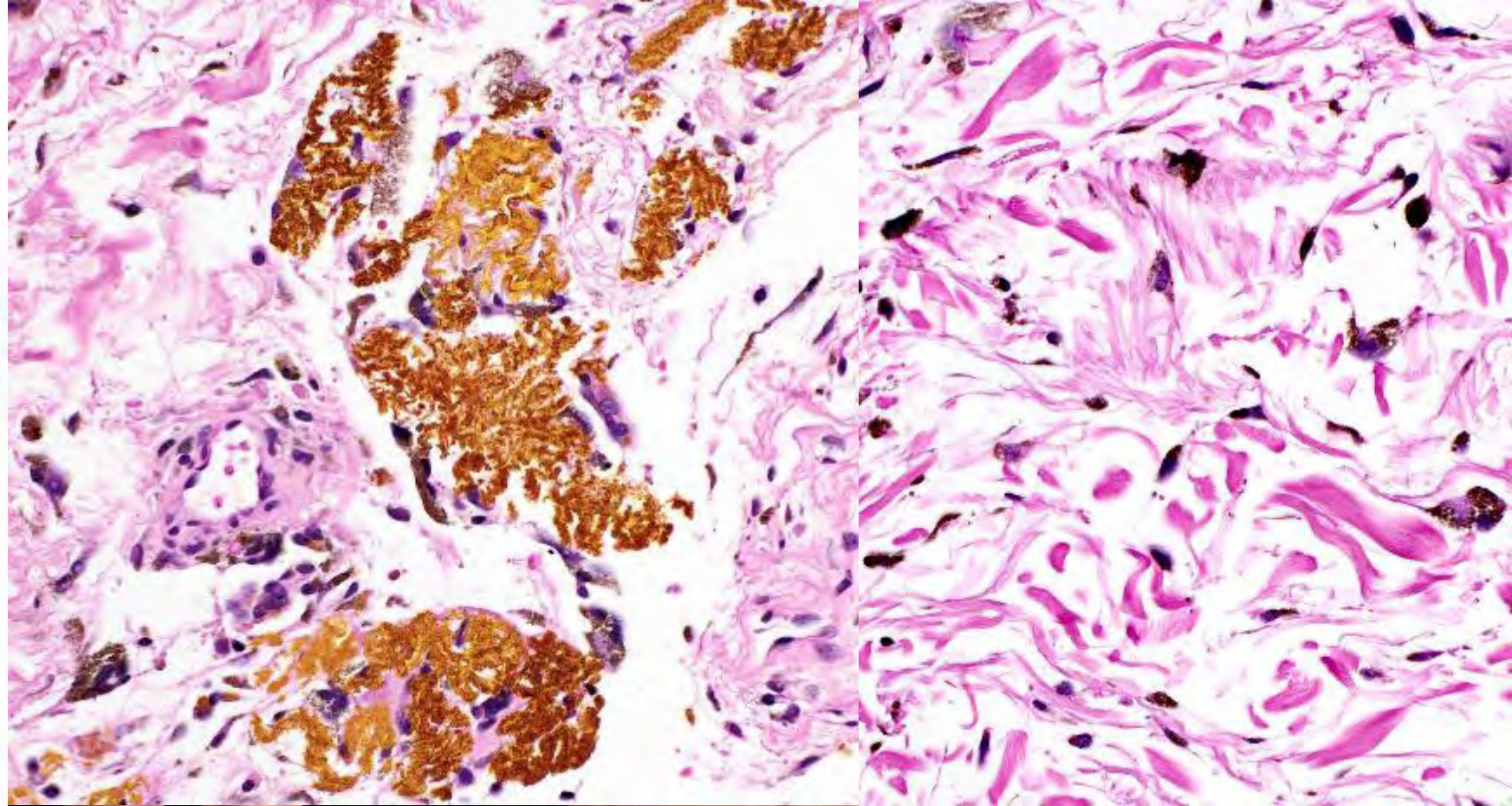
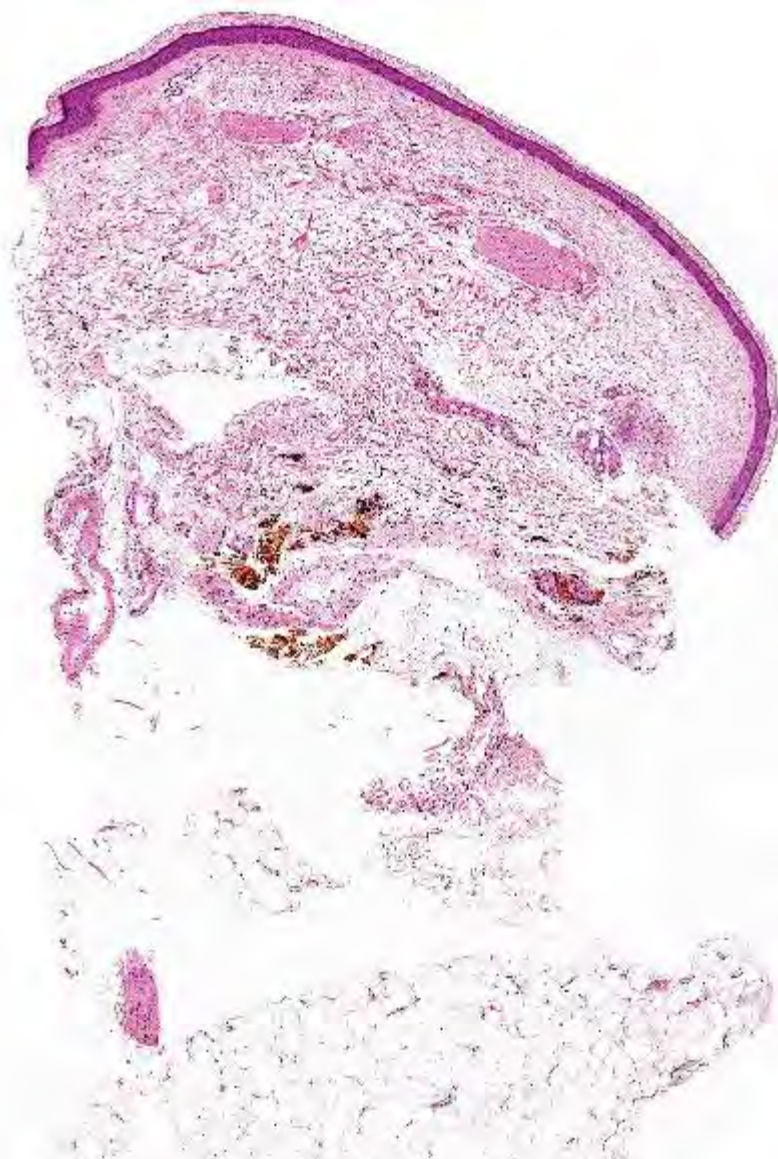


F, 50

History of SLE for the last 34 years, managed with several options over the years (at present systemic steroids, mepacrine, hydroxychloroquine, mycophenolate mofetil).

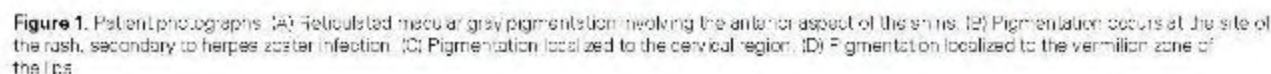
No active cutaneous lesions of SLE; blue-grey discoloration of both shins of unknown duration.

A biopsy is taken.



Ochronosis
hydroxychloroquine-induced





A case of exogenous ochronosis associated with hydroxychloroquine

Emre Tekgöz¹, Egehan Akınçoğlu², Muhammet Çınar¹, Sedat Yılmaz¹

Abstract

Exogenous ochronosis is characterized by hyperpigmented skin lesions that arise in association with long-term use of some drugs such as hydroxychloroquine. Although it generally develops in Asian individuals with typical localization of brown pigmentation, heavy doses and long-term use are associated with an increased degree of hyperpigmentation in patients with rheumatoid arthritis who were treated with hydroxychloroquine. In our case, a 66-year-old male patient with rheumatoid arthritis who had been taking 400 mg of hydroxychloroquine daily for 10 years developed pigmented skin lesions. In this case report, we present the patient undergoing treatment through which may be a therapeutic option. Pigmentations are distributed in the eyelids and in periorbital regions of the patient's face.

Keywords: Ochronosis, Exogenous, Hydroxychloroquine, Rheumatoid arthritis, Hydroxychloroquine

Introduction

Ochronosis is a form of melanosis that is caused by a chronic progressive metabolic disease or disorder due to long-term use of some drugs such as hydroxychloroquine. It is a benign disease, characterized by hyperpigmentation of the skin due to accumulation of melanin and 8-OH in the skin and forms the clinical picture of dermal fibrosis to the collagen tissue. It is a rare hyperpigmentation disorder, showing a long-term course and often due to local or systemic exposure to some drugs such as hydroxychloroquine. It is an acquired, distal, acral and facial, symmetrical and chronic form of melanosis. The clinical appearance is characterized by blue-black hyperpigmented macules, papules, nodules and plaques affecting the face and neck region. Although the hyperpigmentation is not completely characteristic, ochronosis may originate from the long-term use of 1540 mg of hydroxychloroquine associated with the long-term use of other antirheumatic drugs and hydroxychloroquine (1). Here we describe the clinical and histopathological findings of a patient with exogenous ochronosis (E-O) using hydroxychloroquine.

Case Presentation

A 66-year-old male, who was 80 years old, for almost 20 years with a diagnosis of RA, presented with bilateral periorbital, perioral and periauricular hyperpigmented, brown and black-colored patches on his forehead, cheeks and neck regions, which had occurred in the last year (Figure 1). One year before the admission, the patient had started using 400 mg hydroxychloroquine daily, along with low-dose prednisolone (5 mg/day). The patient had no known systemic diseases (diabetes mellitus) and he was not taking any other drugs simultaneously. On physical examination, we observed brown hyperpigmented macules and nodules on the neck and face, multiple brownish and blackish nodules on the hyperpigmented skin. From the nasal disc, occupying the periorbital region, on skin preparation both the white and the yellow and white were found in the nasal and ear, breast and buccal mucosa. A skin biopsy specimen from the hand presenting the lesion of hyperpigmentation was taken for histopathological examination. No abnormality was determined from the examination. The laboratory test results were as follows: hemoglobin: 11.0 g/dL, hematocrit: 35.0%, mean corpuscular volume: 90.9 fL, mean corpuscular hemoglobin concentration: 45 mg/dL, mean platelet factor: 30.1 fL/dL, and serum ferritin: 124.0 ng/mL. We were the first to use a skin biopsy specimen from the nose, a rare practice as that skin biopsy was not used in a skin biopsy specimen (2). Histology results were as follows: we were found to be normal (normal melanin) (Figure 2a). The results of the skin biopsy specimen were as follows: the patient was treated with 1540 mg of hydroxychloroquine daily for 10 years. A biopsy specimen was obtained from the region of hyperpigmentation on the cheek (Figure 2b). Histopathological examination of pigment granules within the collagen fibers and in the papillary dermis in the periorbital region of the face was observed (Figure 2c).



Figure 1. a-c. Hyperpigmentation of the face and neck



Figure 2. a-c. H&E x400 (a); iron stain x200 (b); Mart-1 x100 (c)

There were basophilia of the collagen fibers in the upper dermis. Small pigment granules were in macrophages or free in papillary dermis. Also these pigments were seen in the perivascular area of the dermis. The pigments were stained positively with Iron and Mart-1. Perivascular lymphocytic infiltrates were seen in upper dermis.



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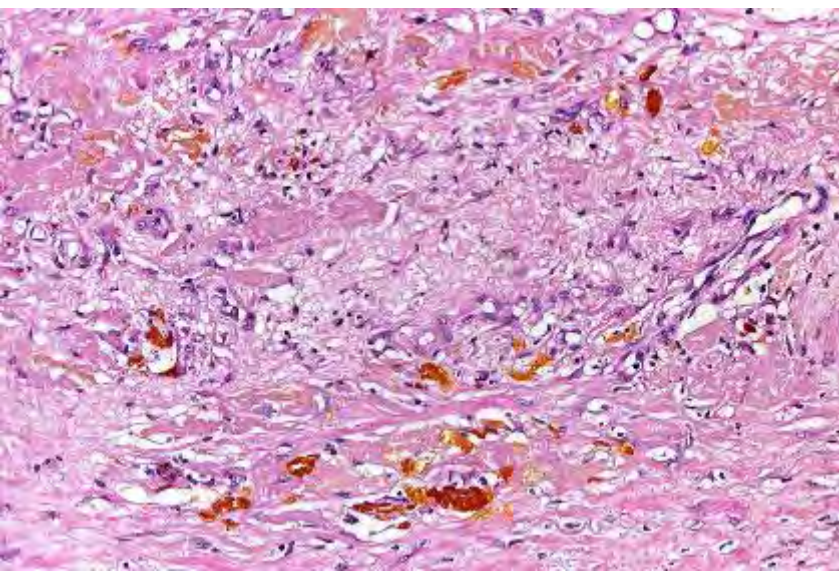
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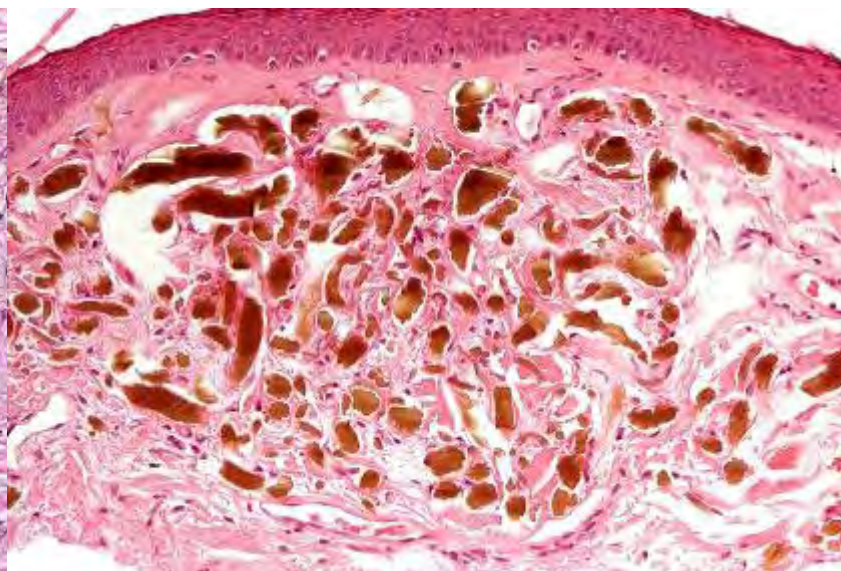
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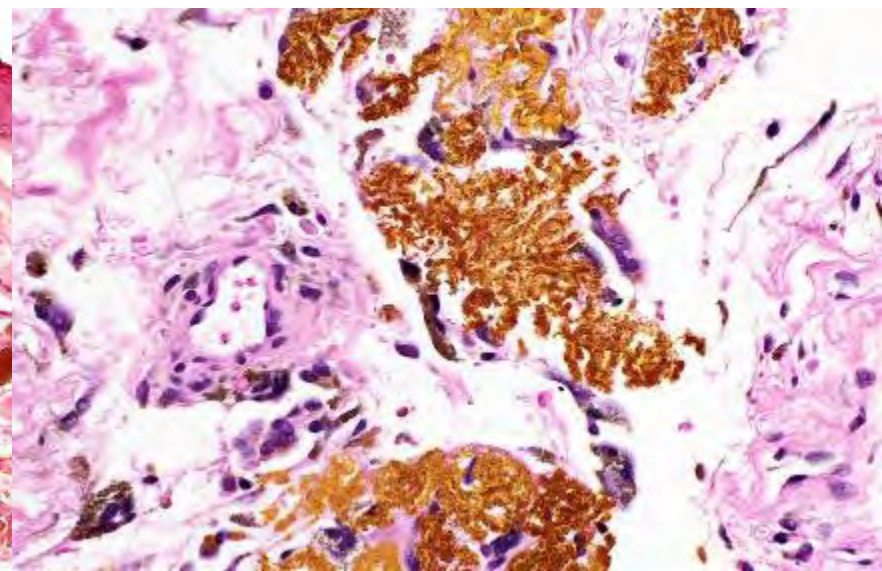
Alcaptonuria



Exogenous (hydroquinone)



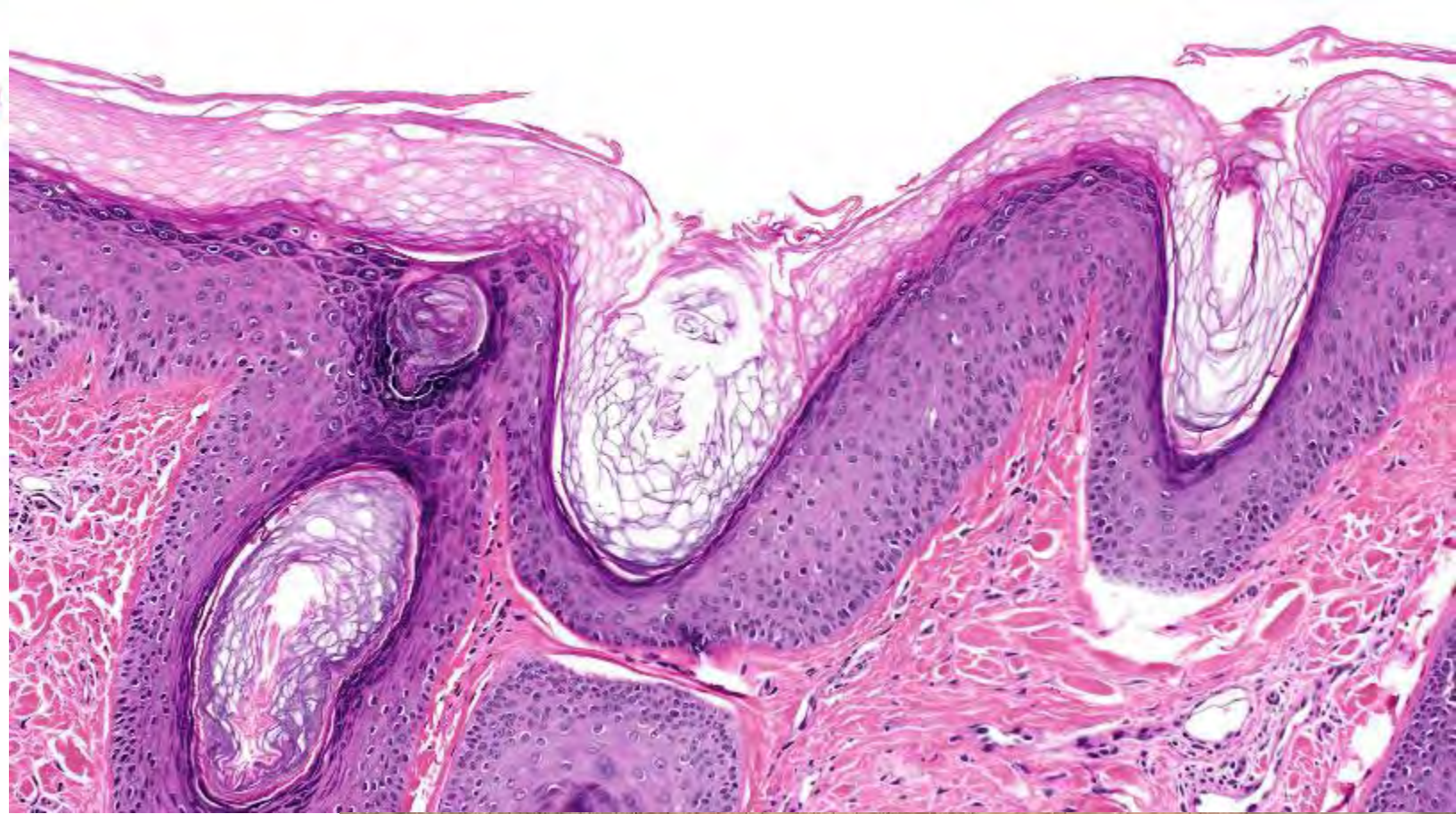
Hydroxychloroquine treatment





F, 67

According to the patient itchy lesions on the scalp for >1 year.
A biopsy is taken.



Chronic frictional
dermatosis



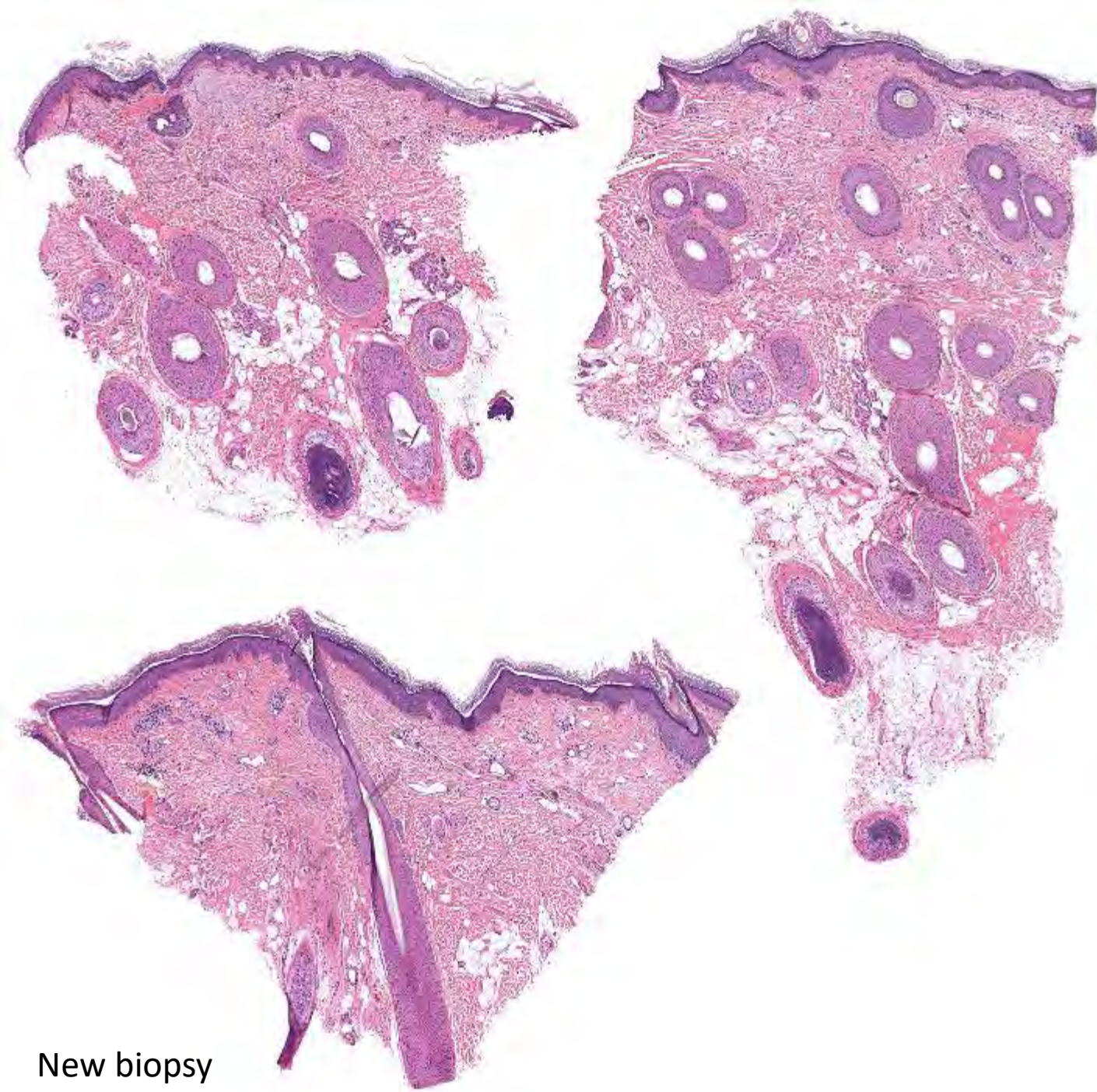


M, 69

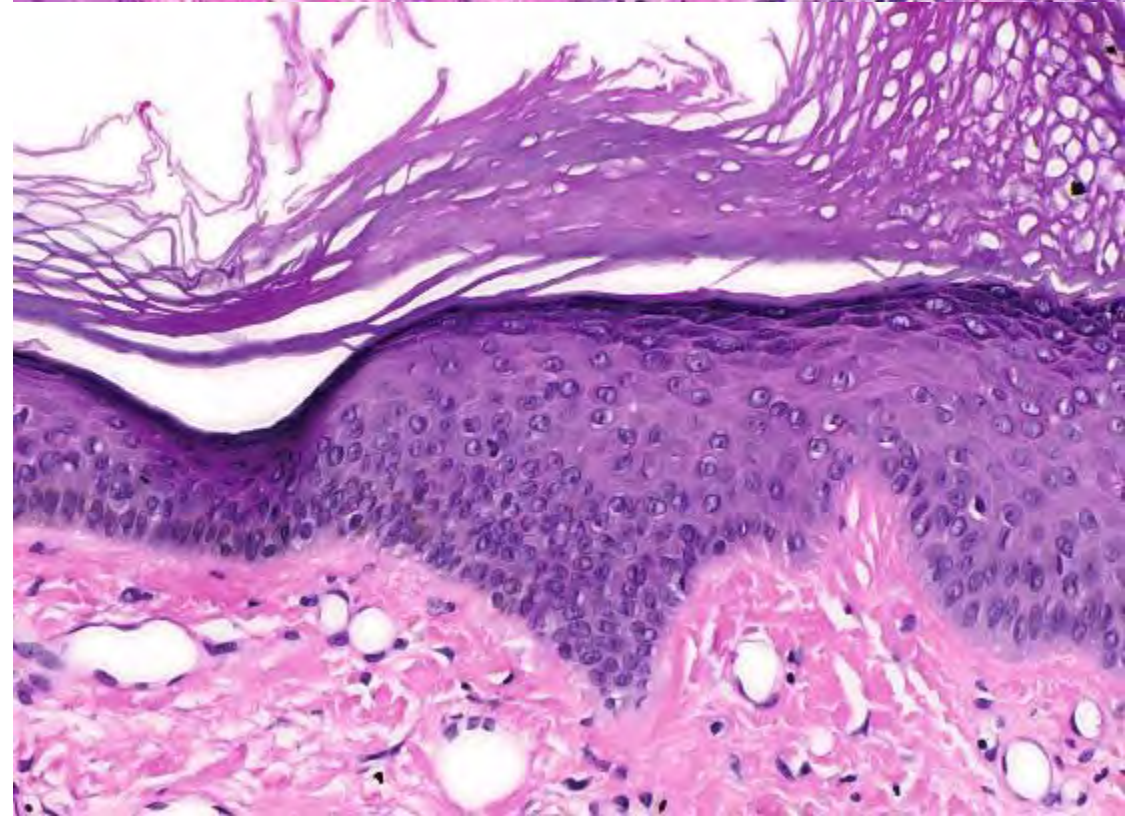
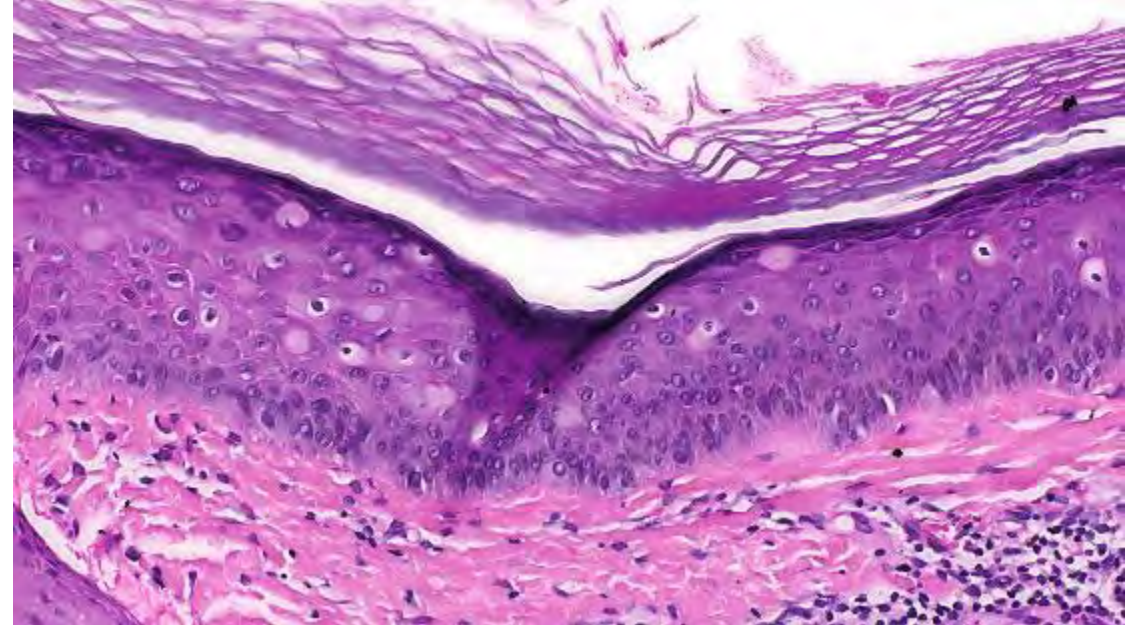
History of itchy scalp lesions for the last 11 years, with "black discoloration" of the hairs and itchy lesions on the entire body ("atopic dermatitis of the elderly").

A punch biopsy taken 9 years before was interpreted as "late stage of CDLE".

A new biopsy is taken.

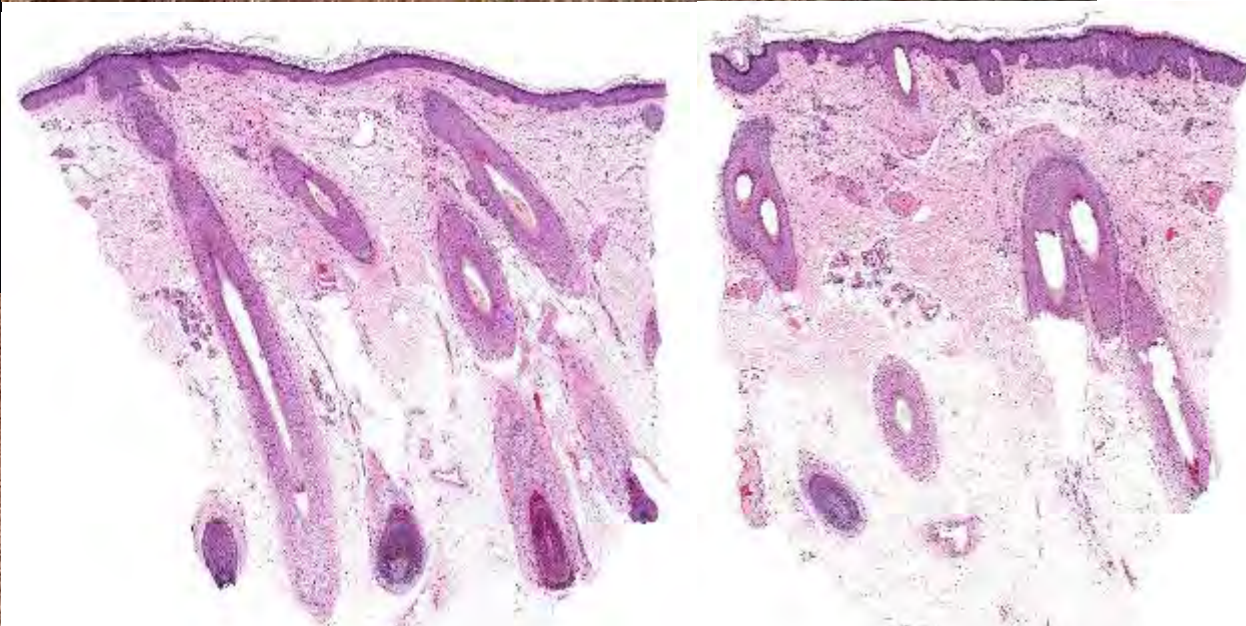


New biopsy

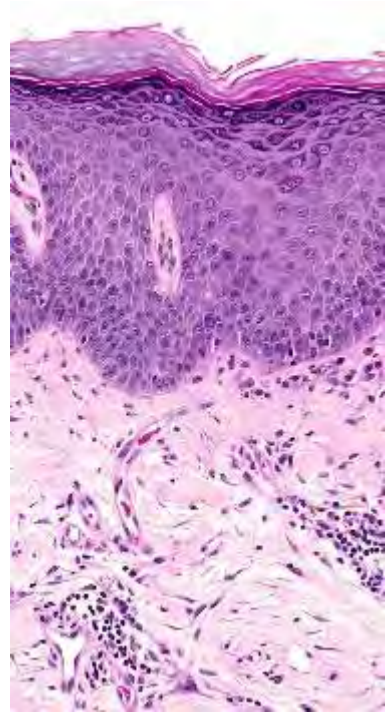




Clinical presentation 9 years before (one picture taken one day later than the others, after shaving the hairs).

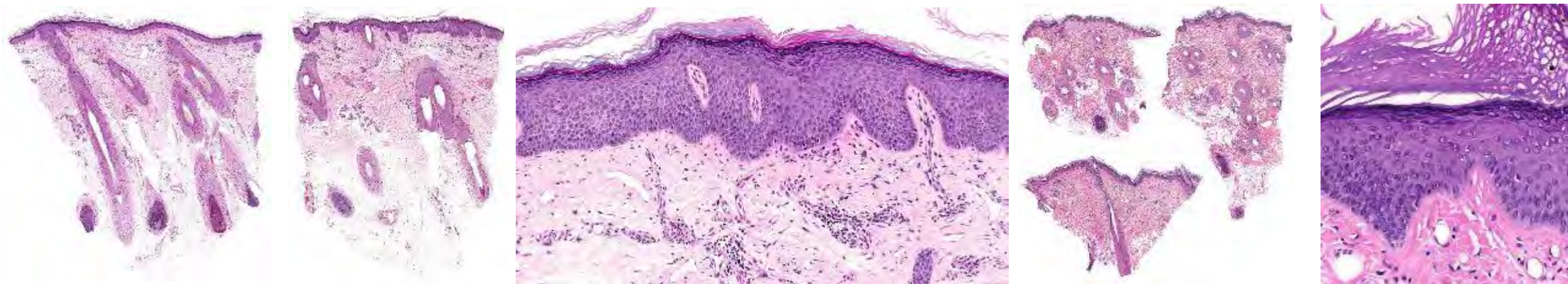


Original biopsy (reported as "late stage of CDLE")





Chronic frictional dermatosis (lichen simplex chronicus) *in a patient with "atopic dermatitis of the elderly"*

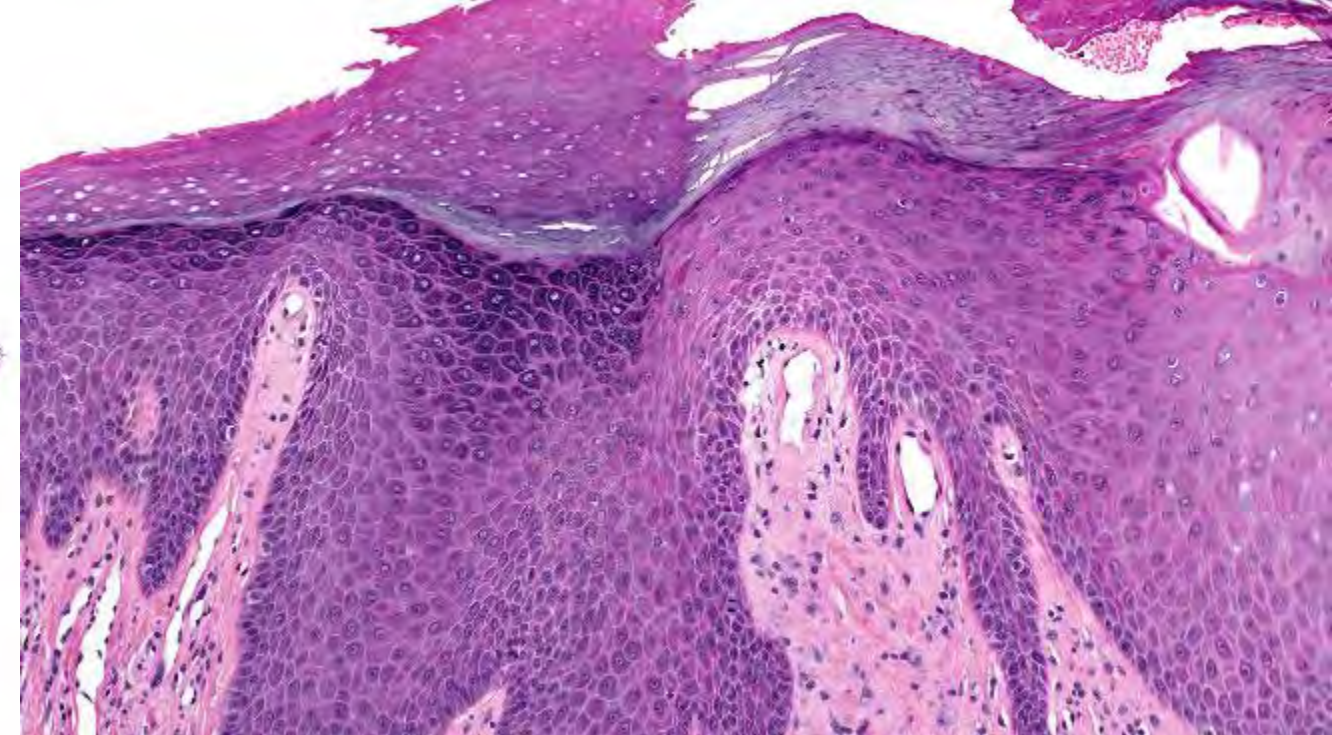
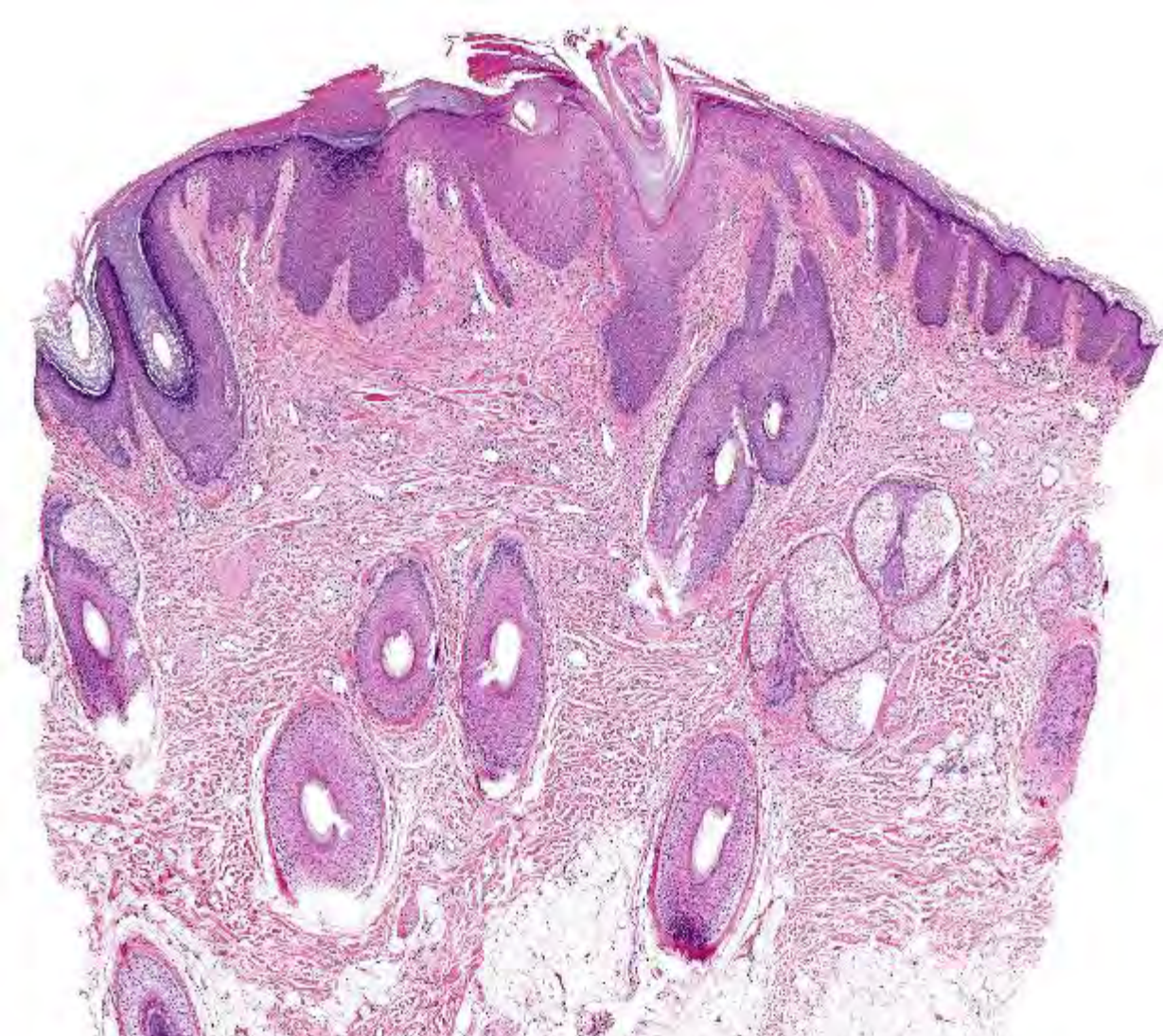




M, 56

According to the patient itchy skin lesions on the scalp for 9 months. Sent by a private dermatologist for a biopsy.

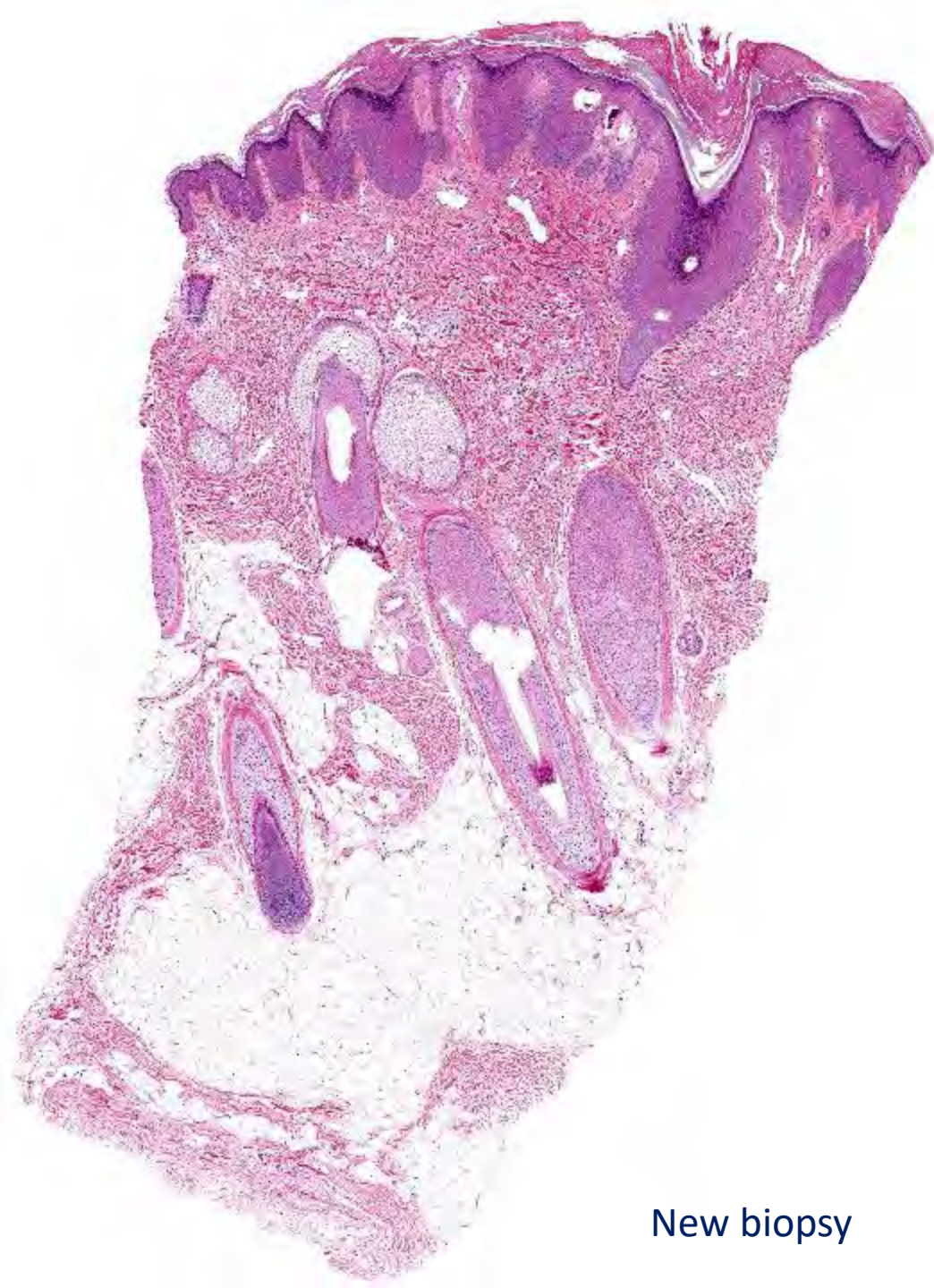
A biopsy is taken.



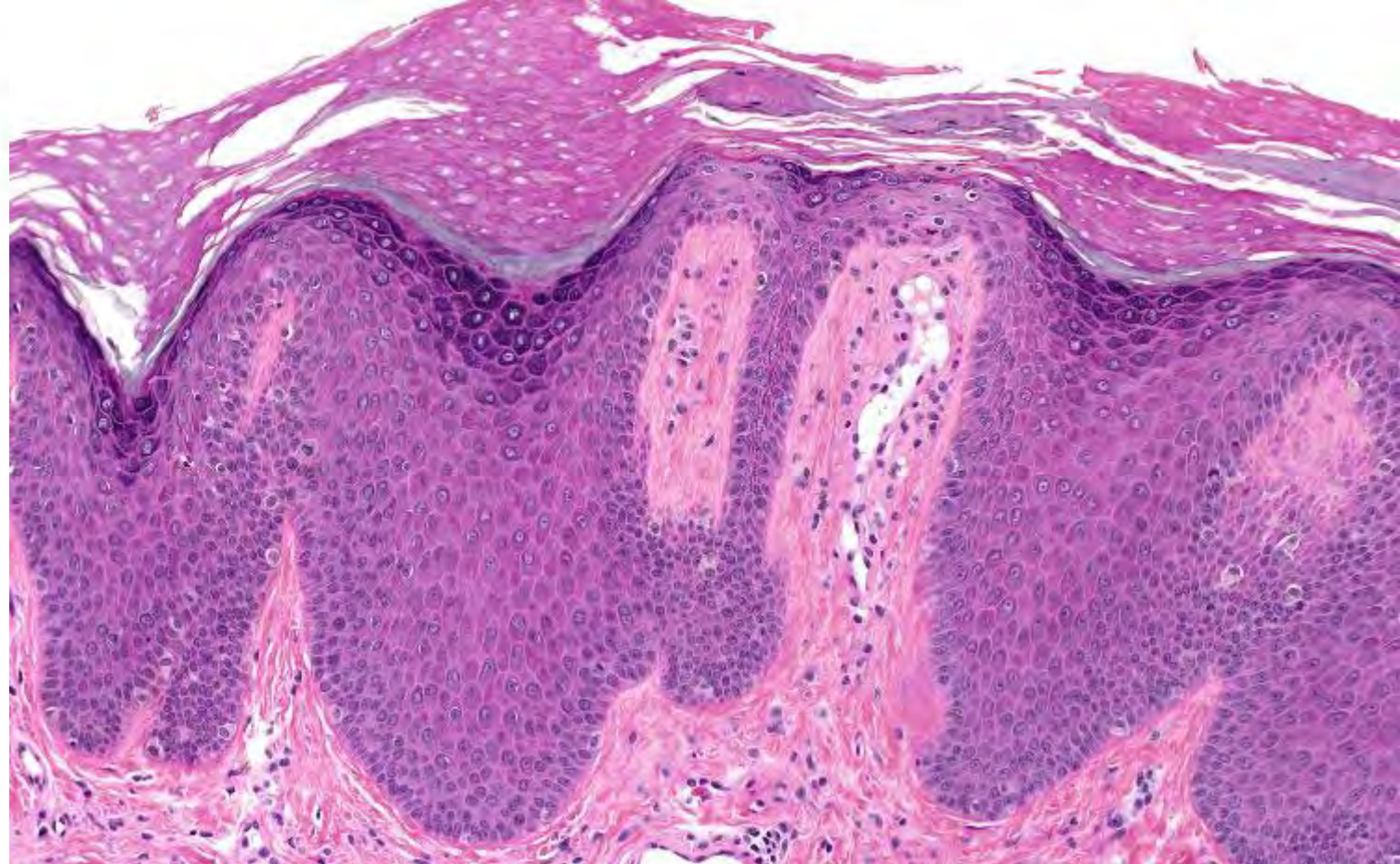
Prurigo /
Lichen simplex chronicus

Comes back 10 months later;
a new biopsy is taken





New biopsy



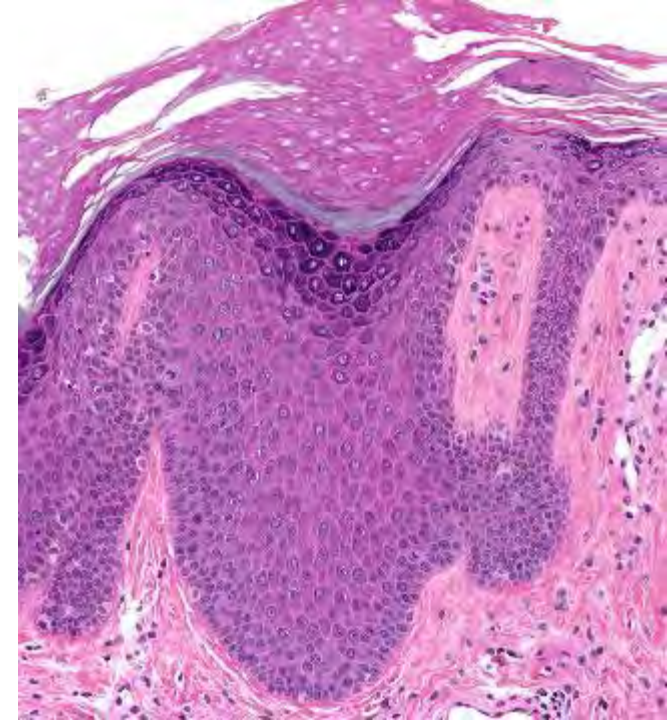
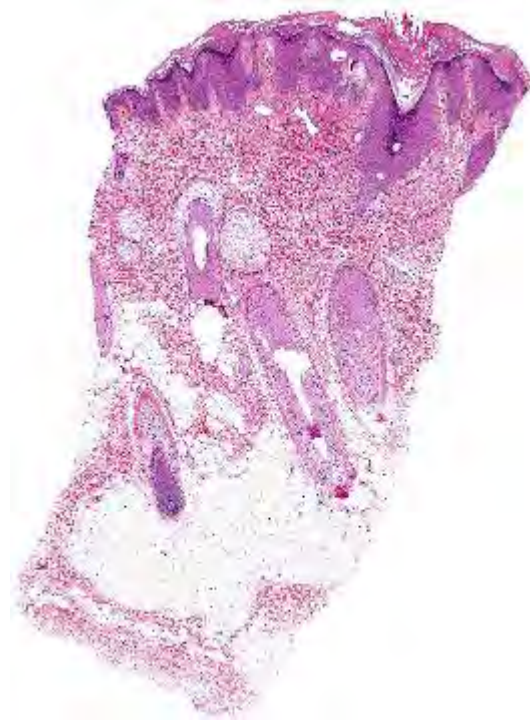
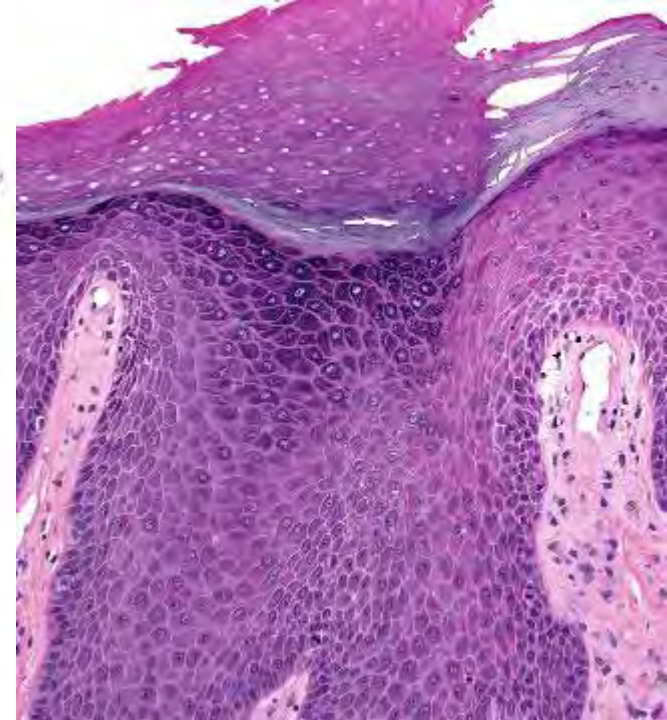
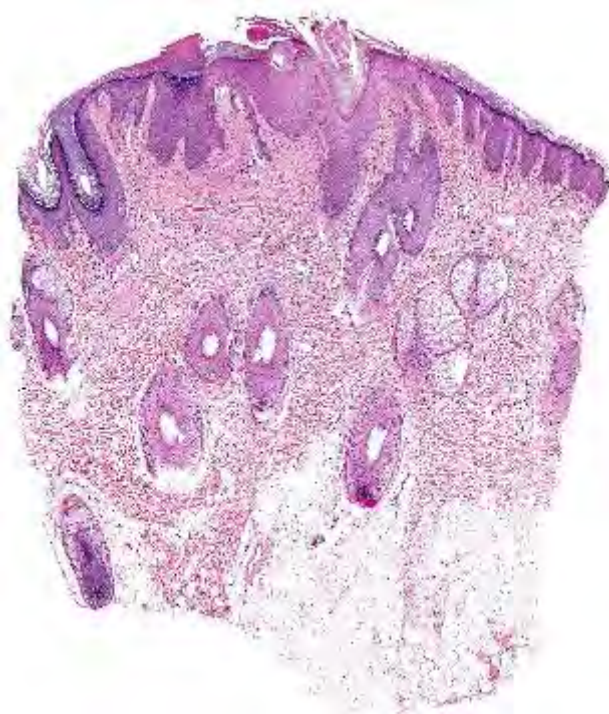
Comes back 12 more months later; no new biopsy (re-evaluation of old ones)



1st presentation

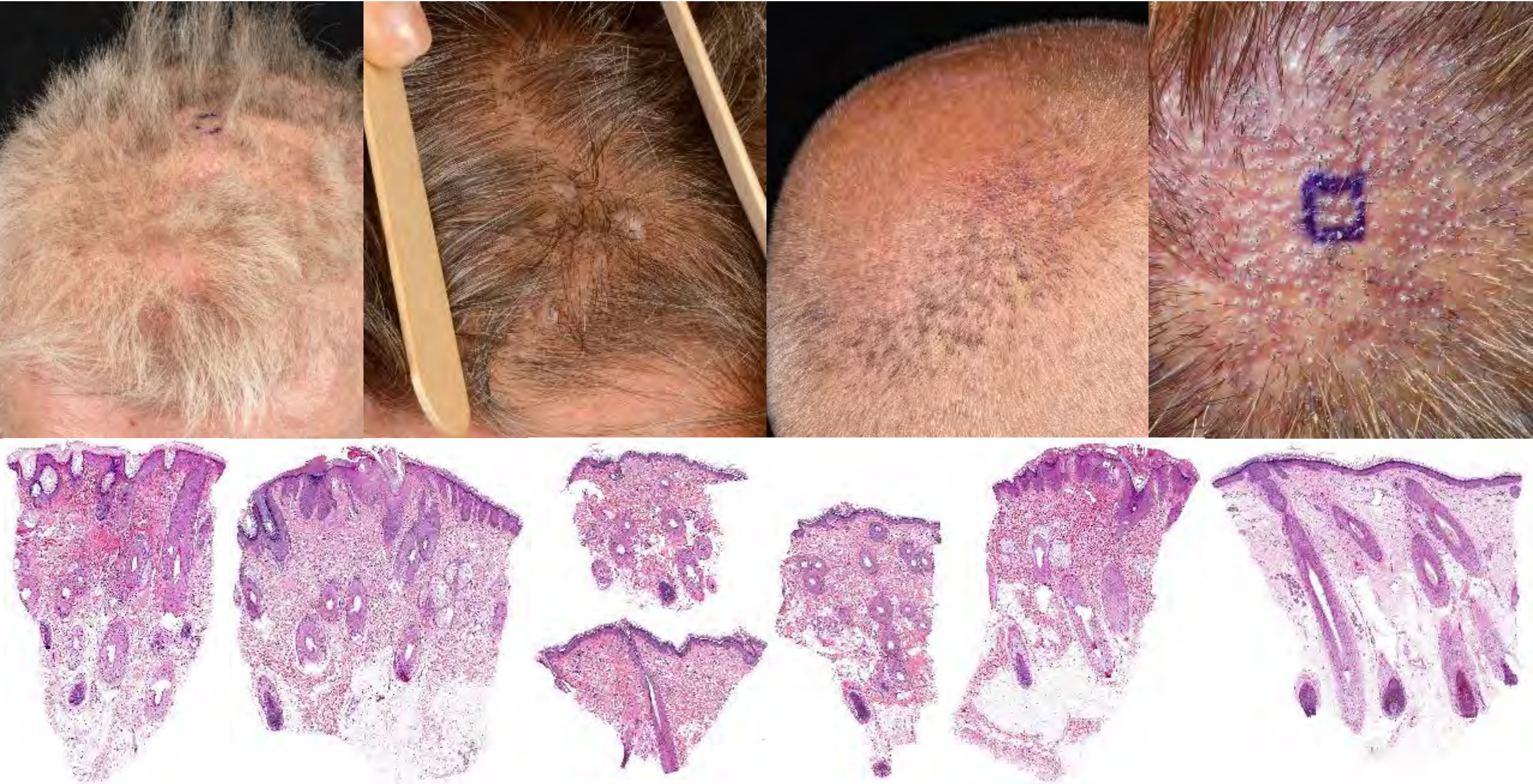


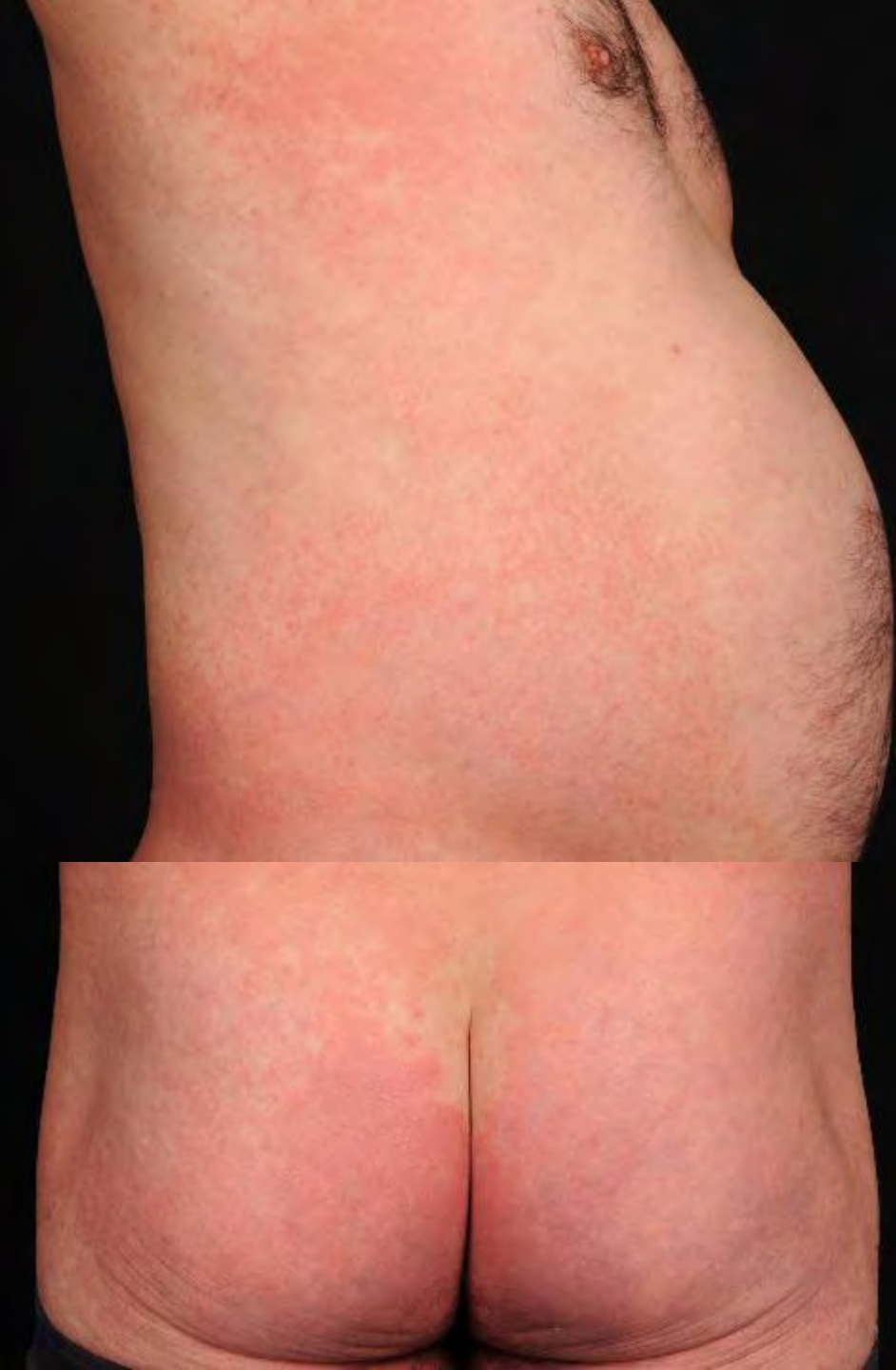
22 months later



Chronic prurigo of the scalp

Chronic frictional dermatosis (lichen simplex chronicus / prurigo) of the scalp



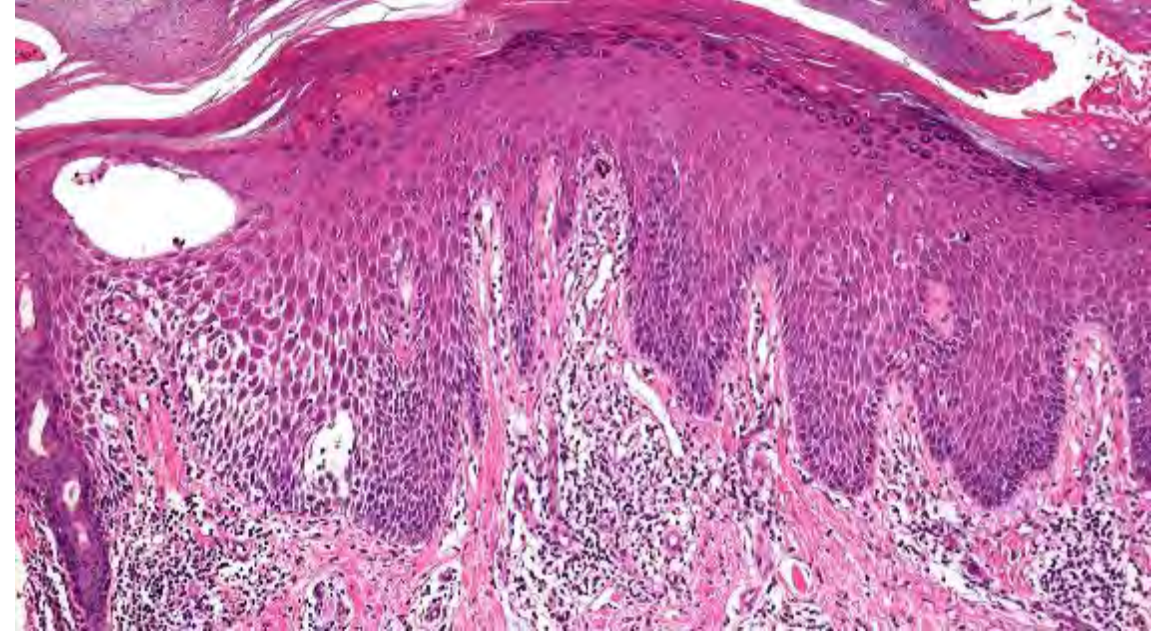
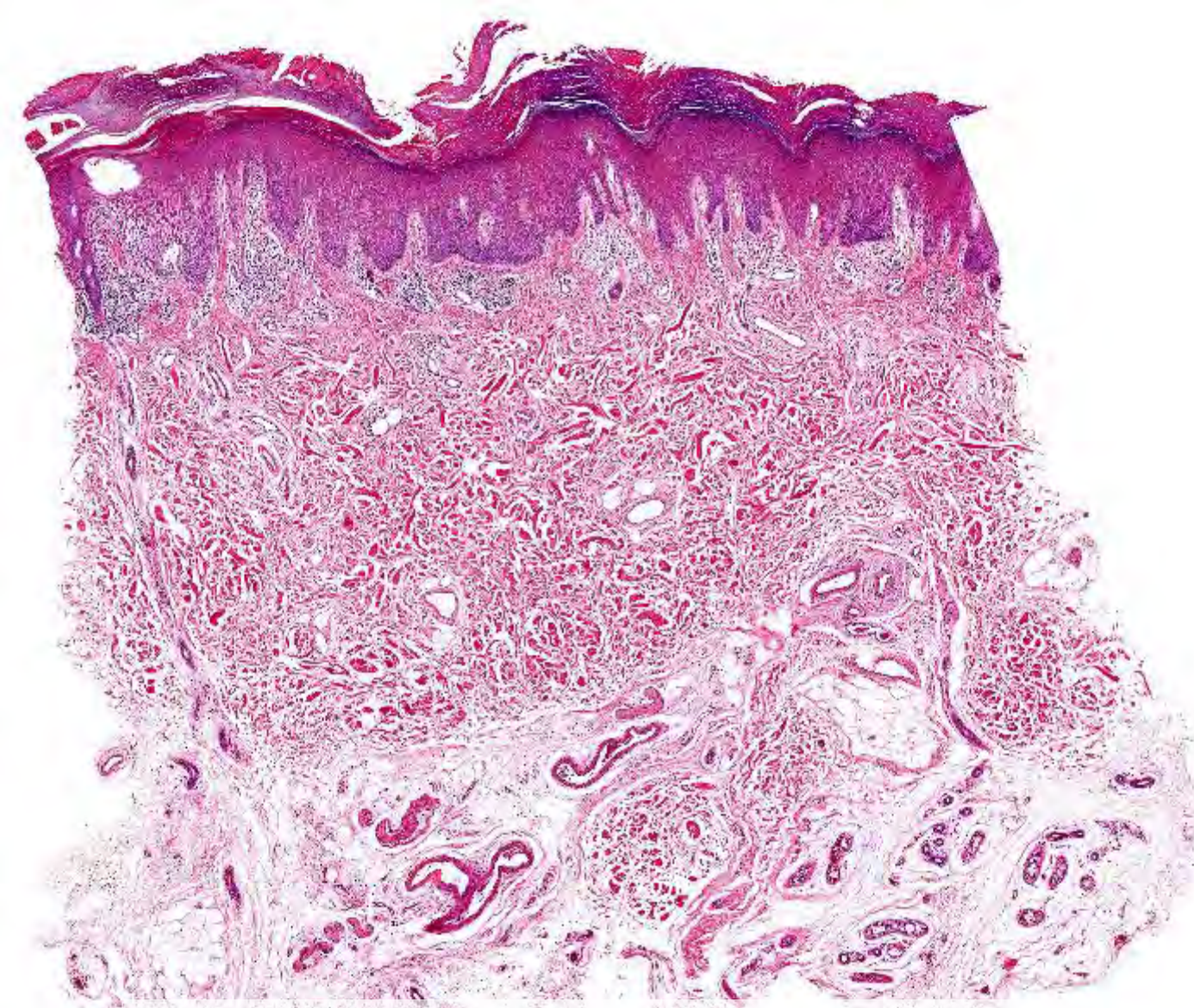


M, 49

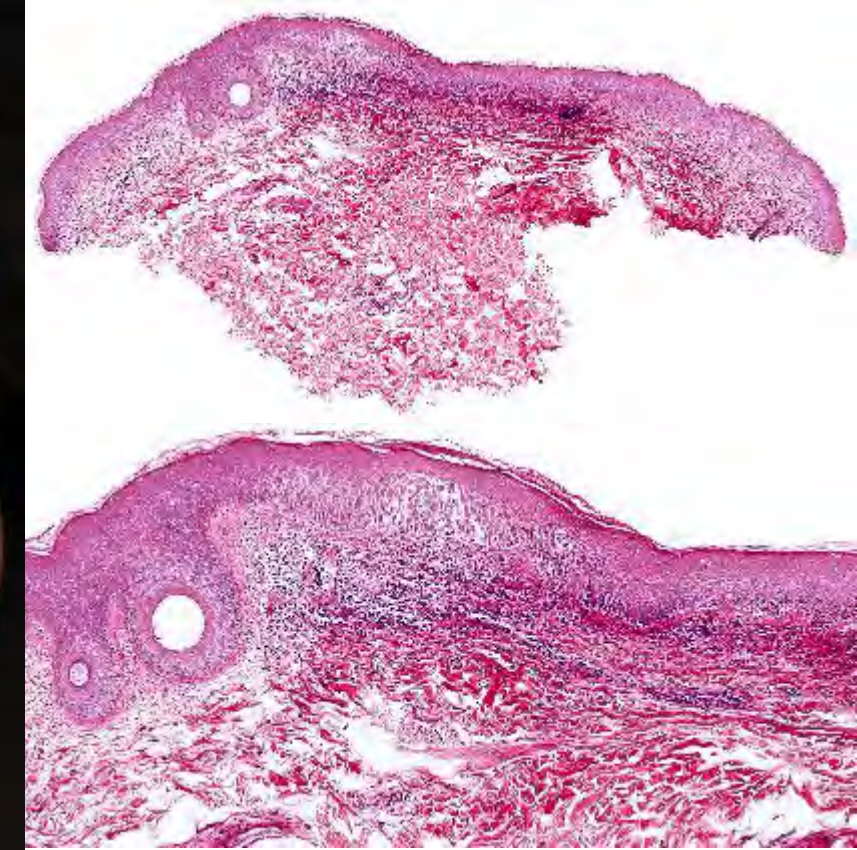
According to the patient generalized itchy skin changes and palmar hyperkeratoses for approximately 2 years.

Improvement with local steroids and during summertime. The patient reports an occupational exposure to metals (a patch-testing was negative).

A biopsy is taken from the left palm.



Eczematous dermatitis
(contact allergic ?)



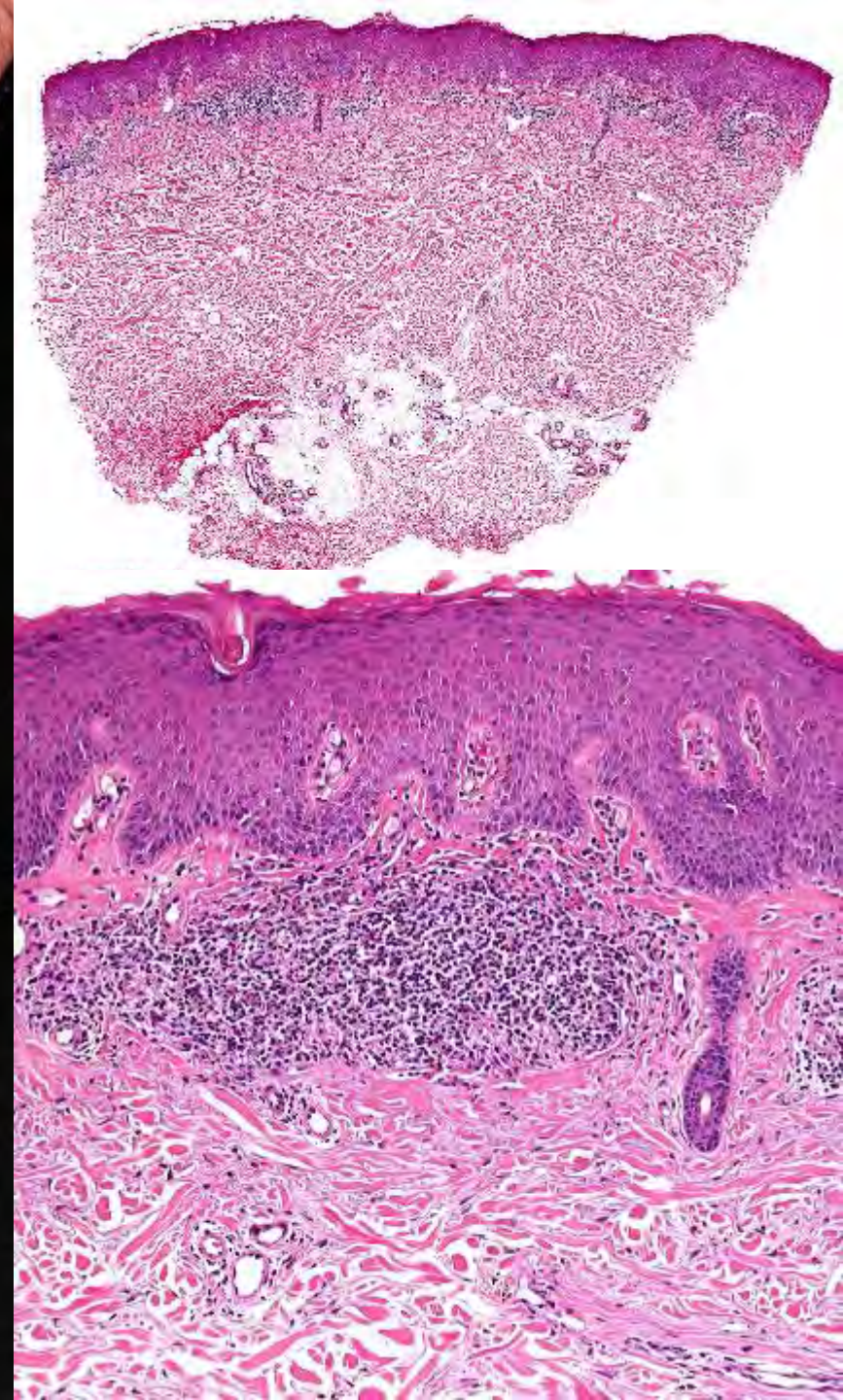
5 months later no improvement with local ointments, oral steroids, PUVA, Re-PUVA.

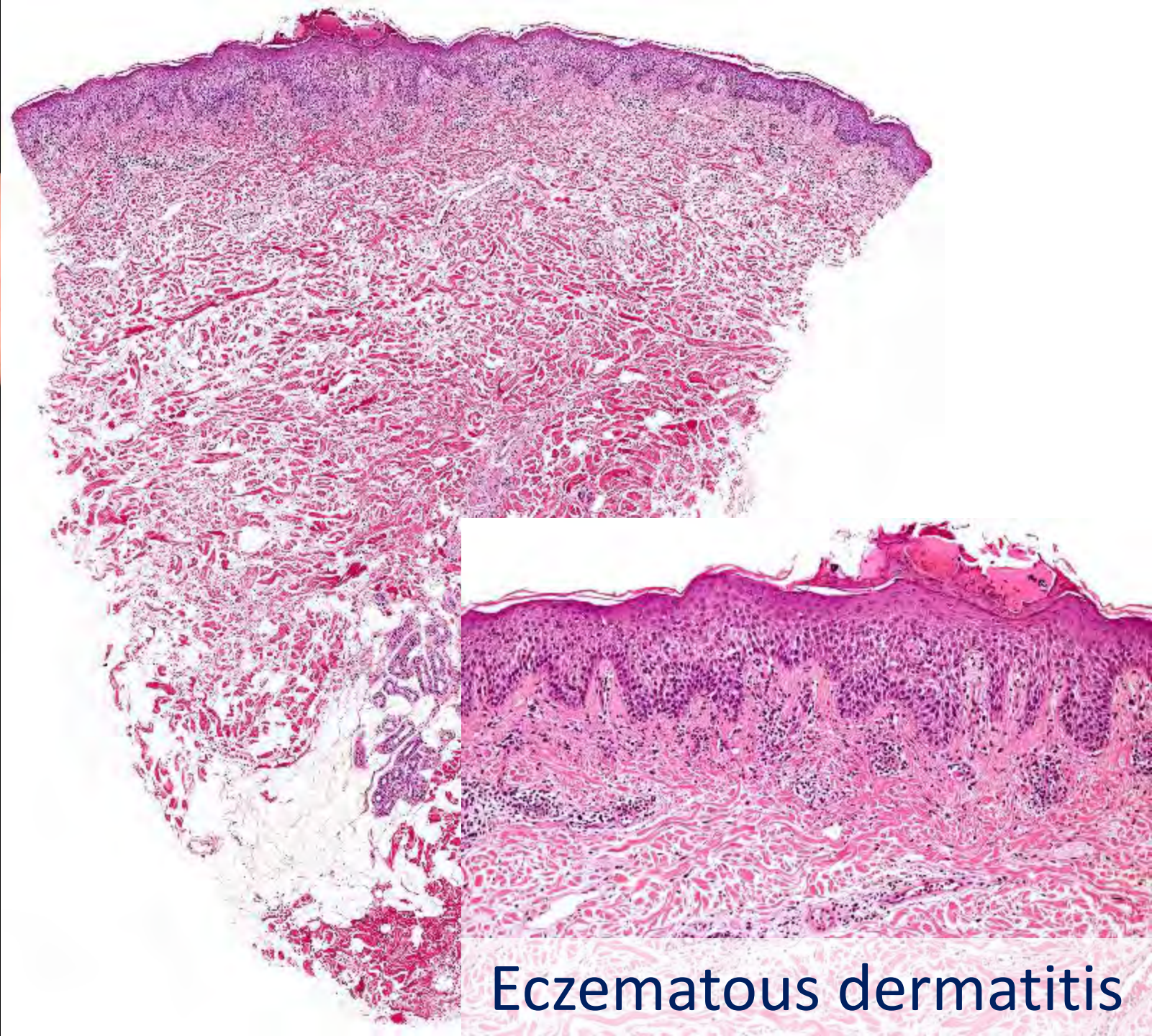
A new biopsy shows again the pattern of a spongiotic ("eczematous") dermatitis



4 more months later (9 months after first presentation) still generalized skin lesions. No improvement with alitretinoin.

Two new biopsies are taken (back of the right hand, right shoulder).





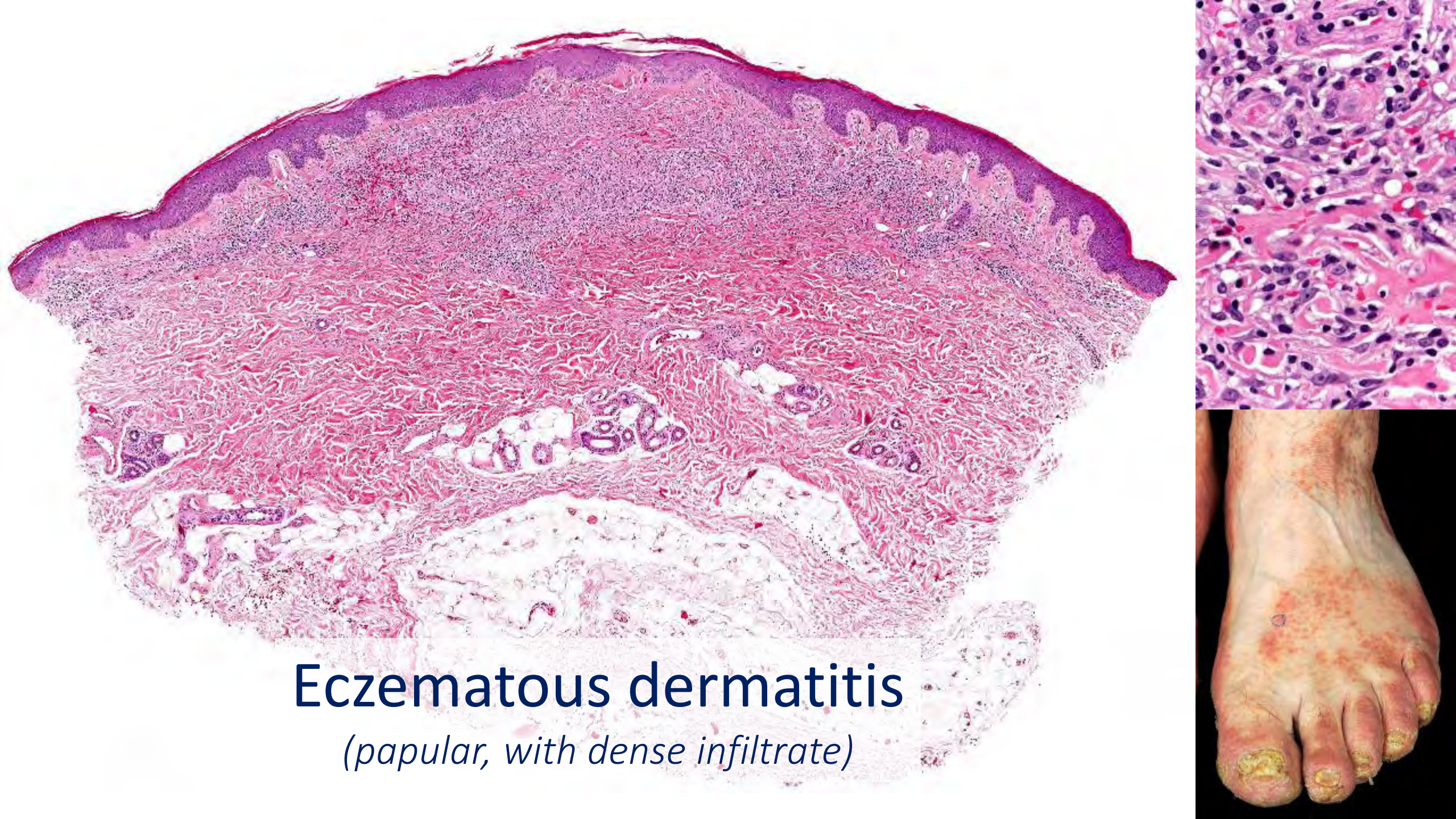
Eczematous dermatitis



2 more months later (11 months after first presentation) still generalized skin lesions.

No improvement with MTX.

New papular lesions on the back of the feet; a new biopsy is taken.



Eczematous dermatitis
(papular, with dense infiltrate)



5 more months later (16 months after first presentation) becomes erythrodermic.

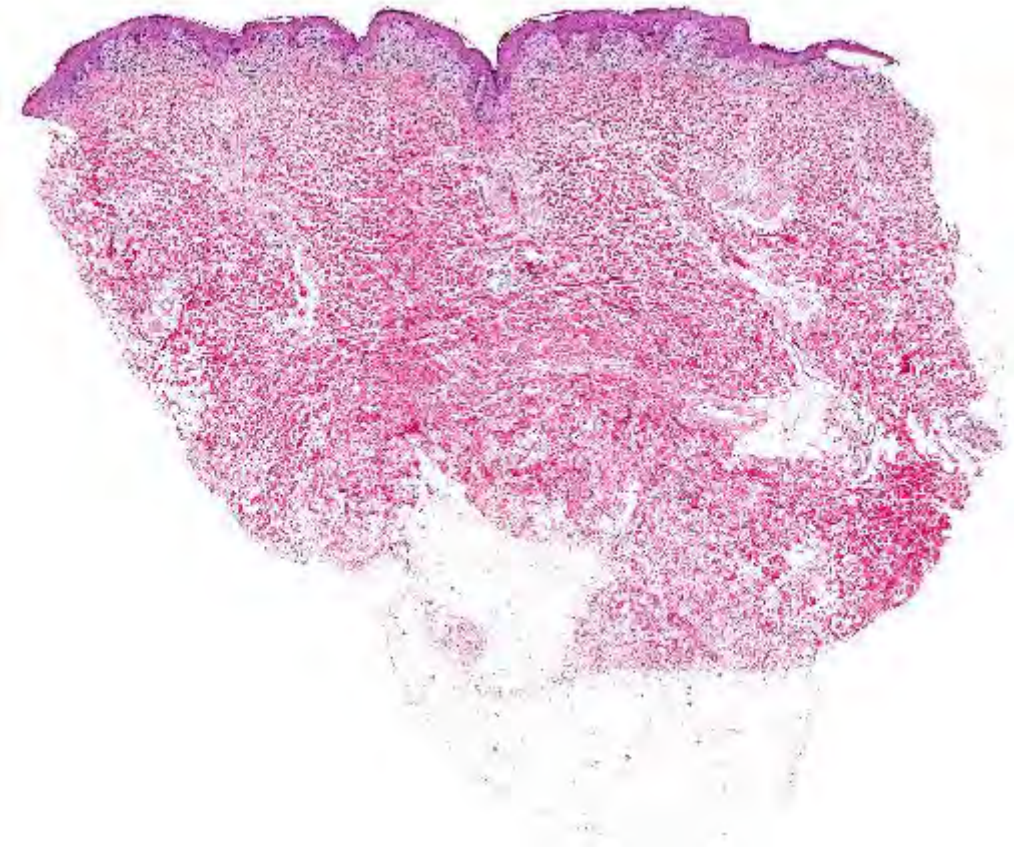


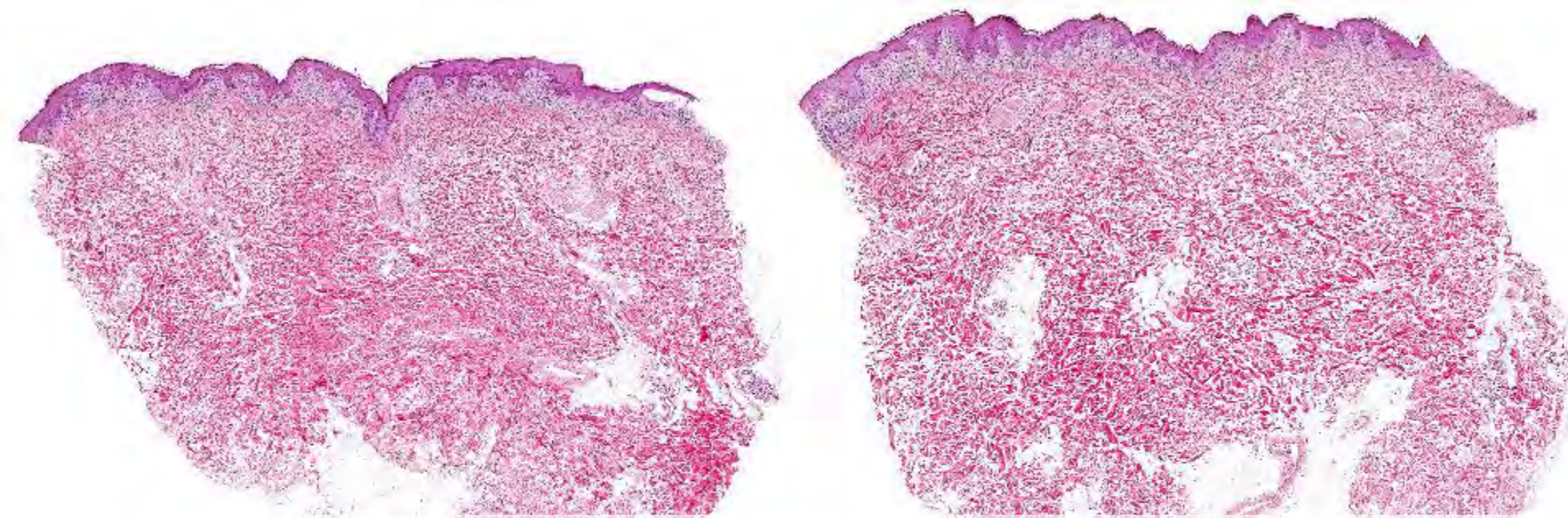


During the next 3 years managed as "atopic dermatitis vs. psoriasis vs. mycosis fungoides" with extracorporeal photopheresis, interferon alfa-2a, bath PUVA, oral steroids.

Recurrent poussées of erythroderma.

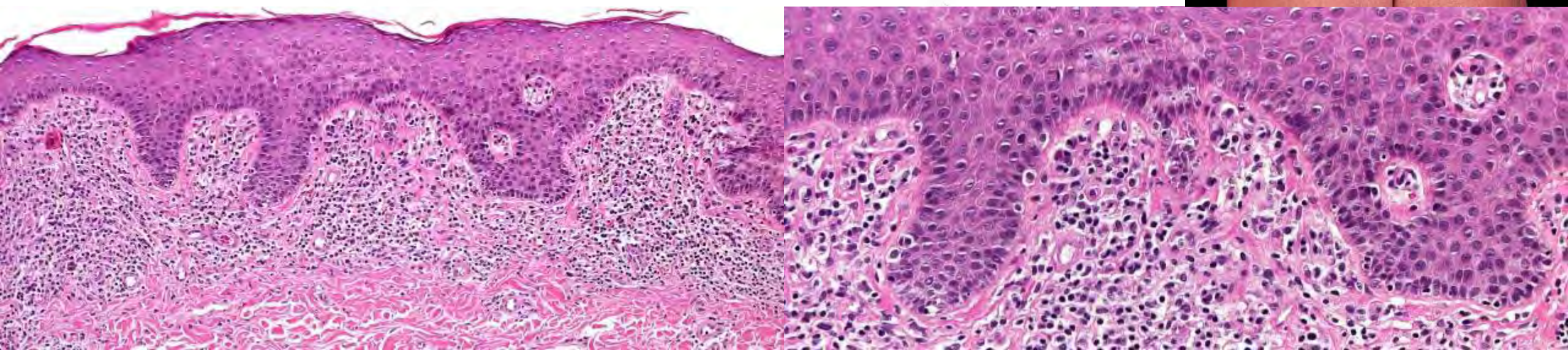
A new biopsy is taken (now >4 years after 1st presentation).





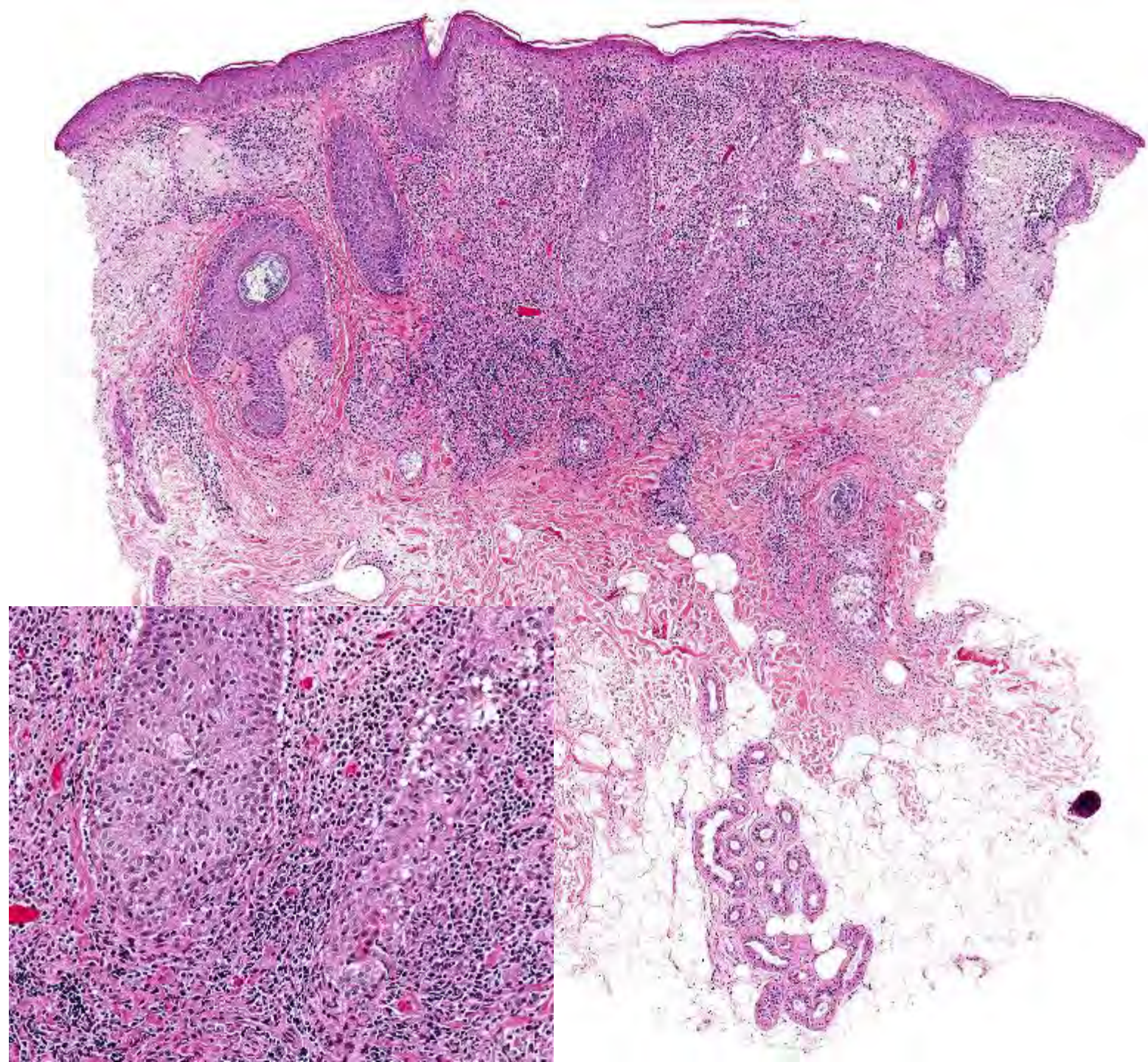
Most likely eczematous dermatitis

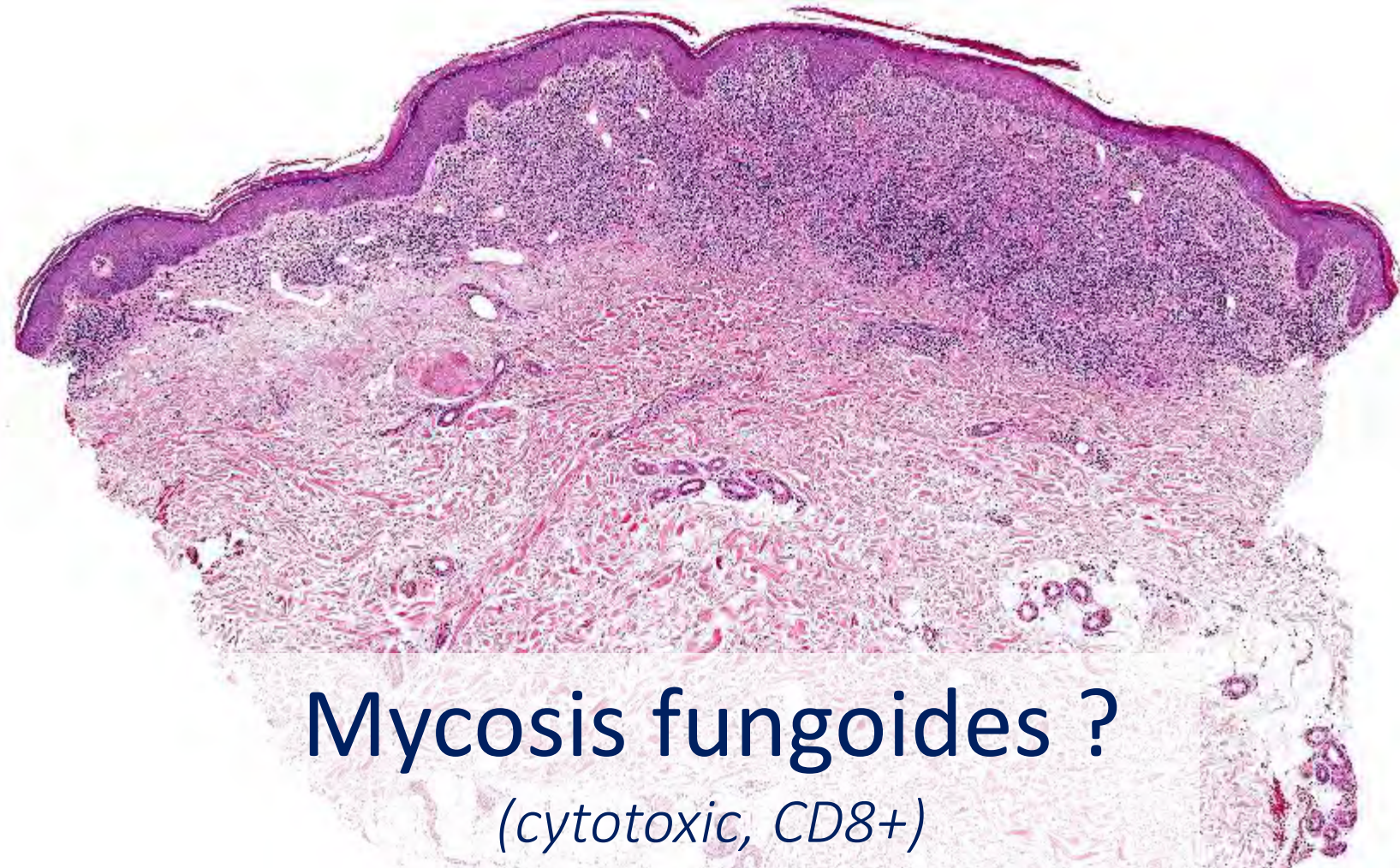
(the infiltrate becoming band-like, but no epidermotropism)



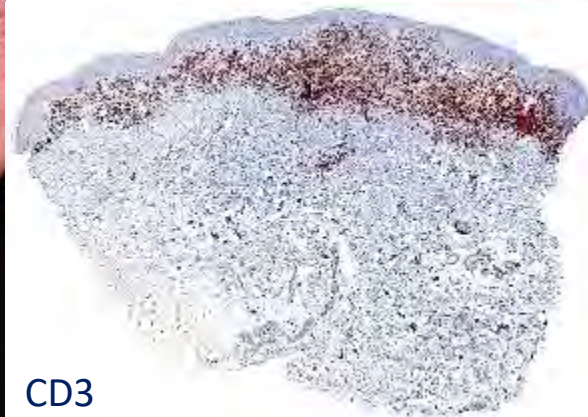
8 months later (now 5 years after 1st presentation) two new biopsies from lichenified lesions on the forehead and distal upper extremities.



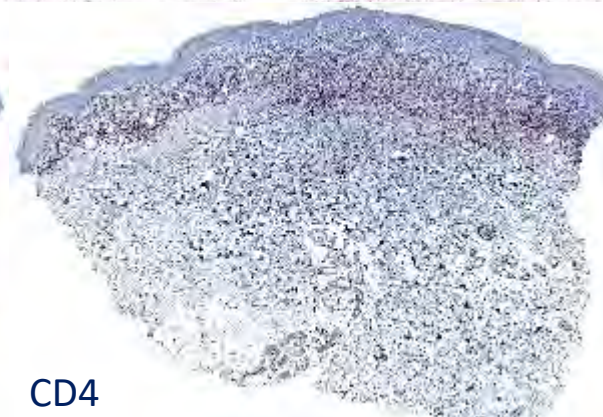




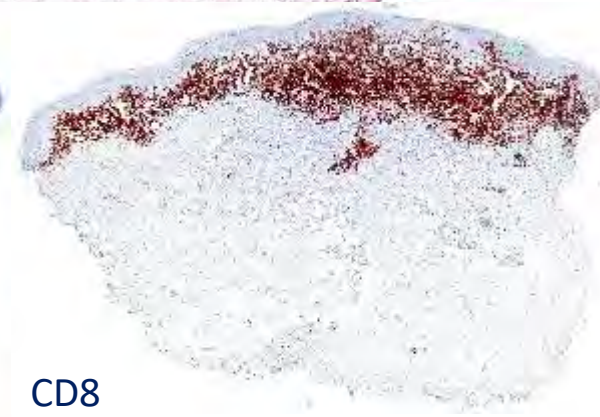
Mycosis fungoides ?
(cytotoxic, CD8+)



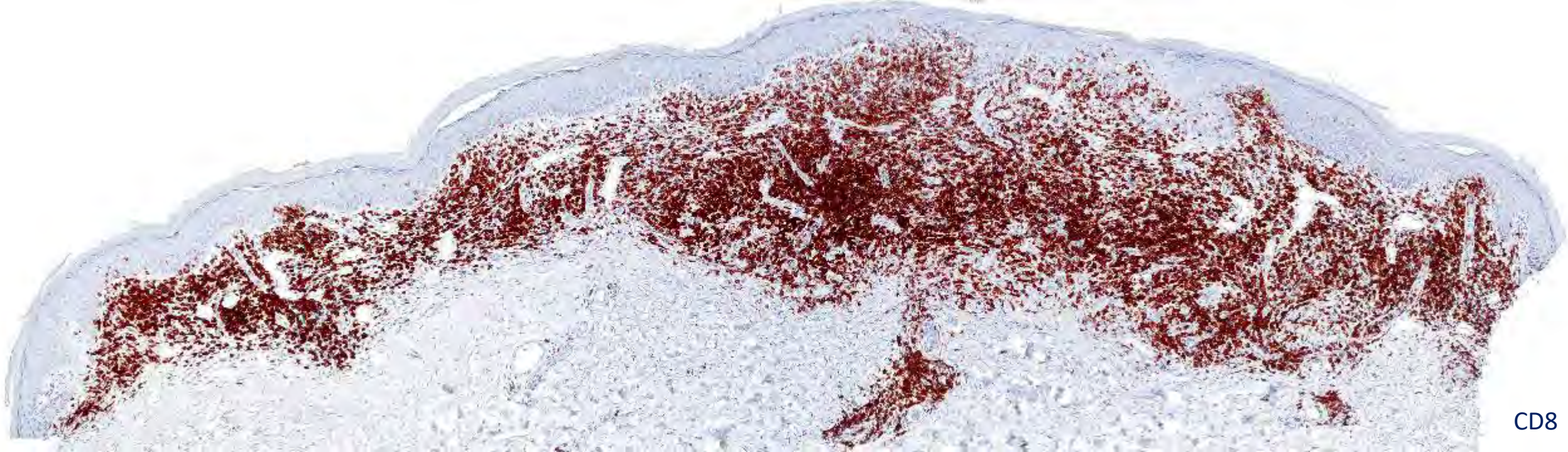
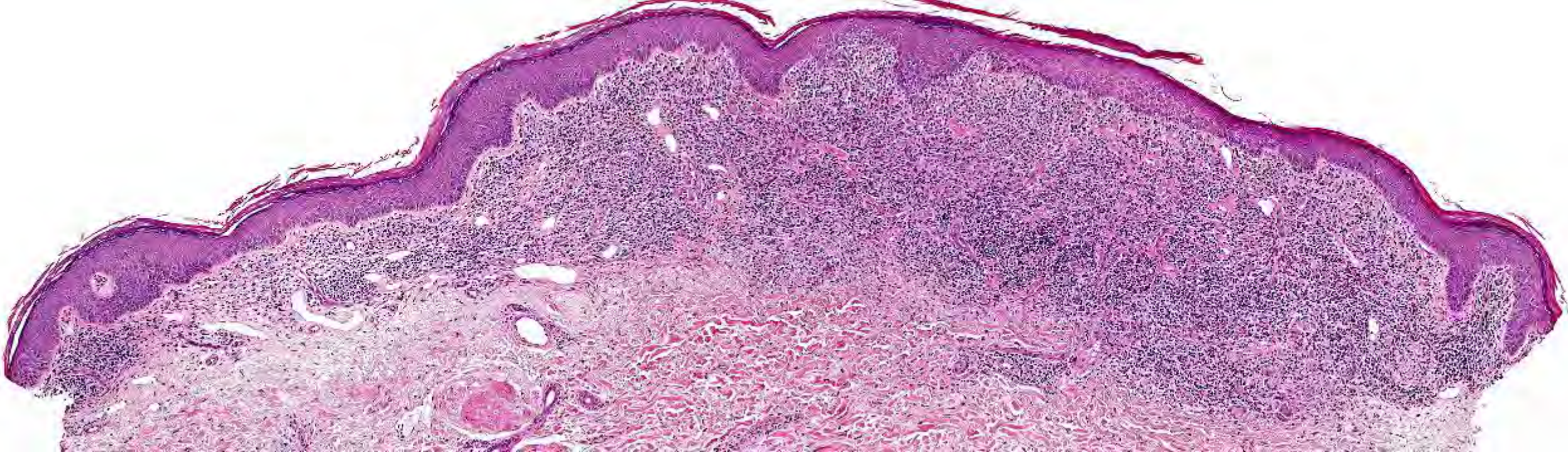
CD3



CD4



CD8



CD8

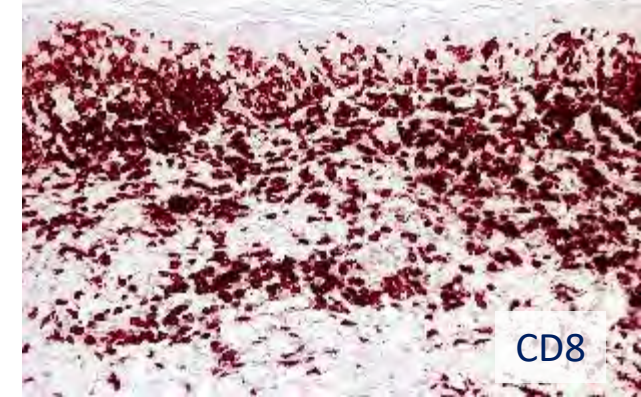
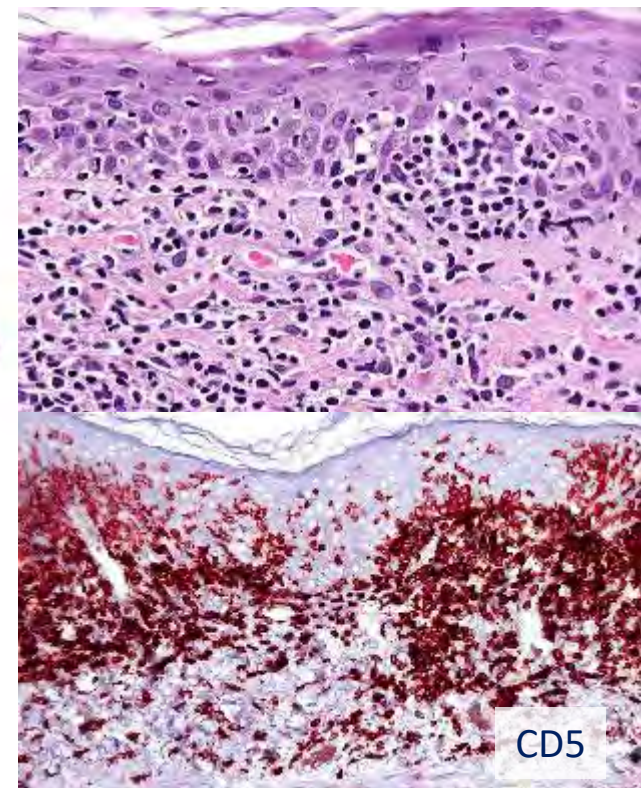
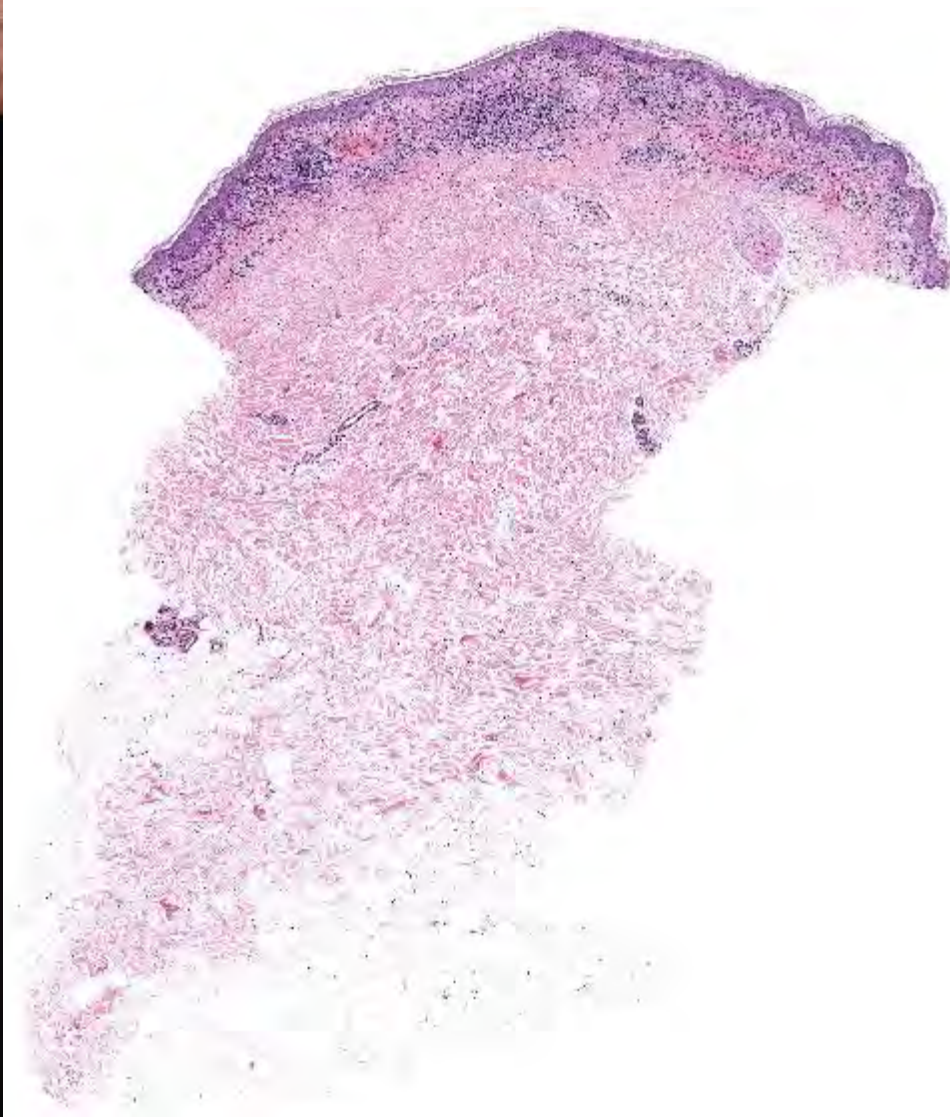
5 months later (now 5,5 years after 1st presentation) the erythroderma resolves and the lesions get in part a photodistribution. Still remarkable hyperkeratotic palmo-plantar lesions and also hyperkeratotic lesions at sites typical for psoriasis.

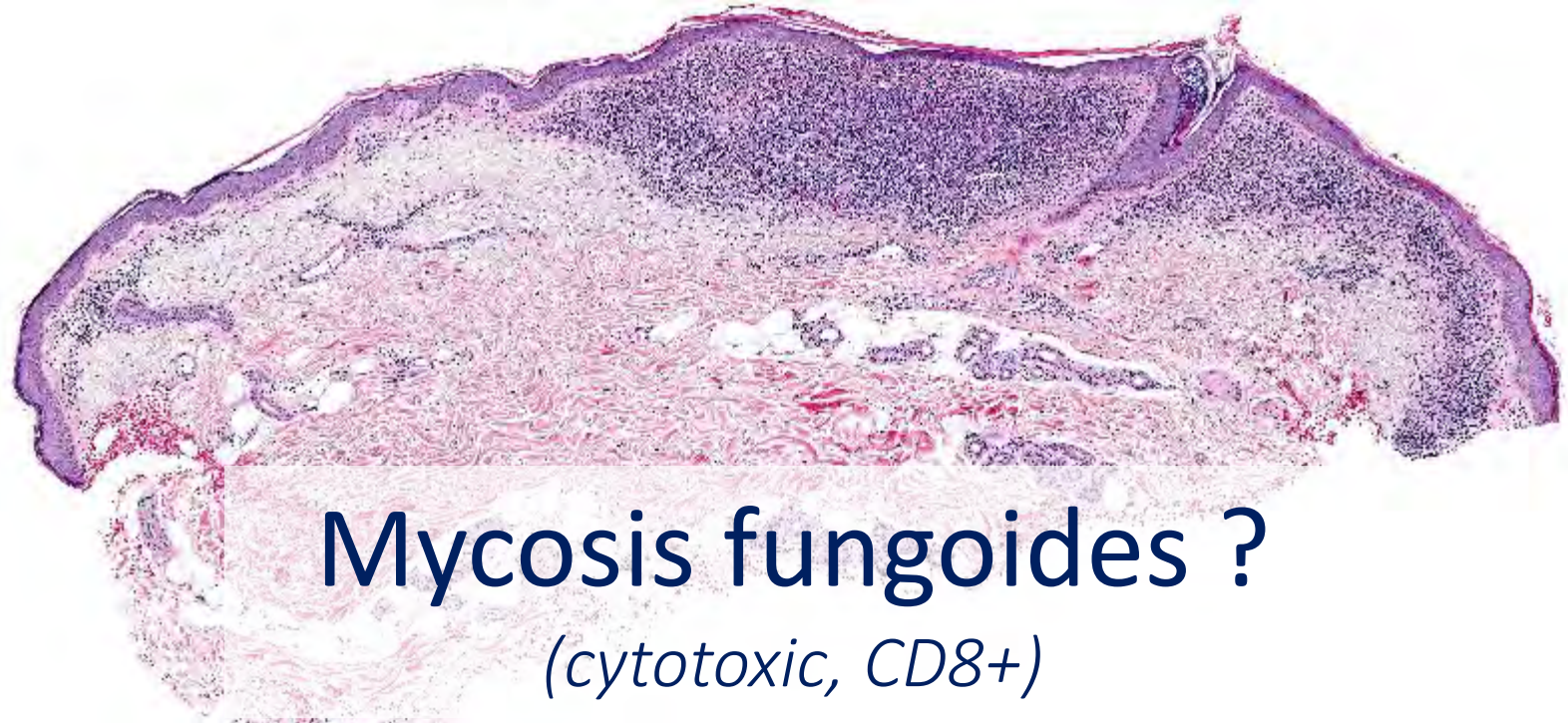




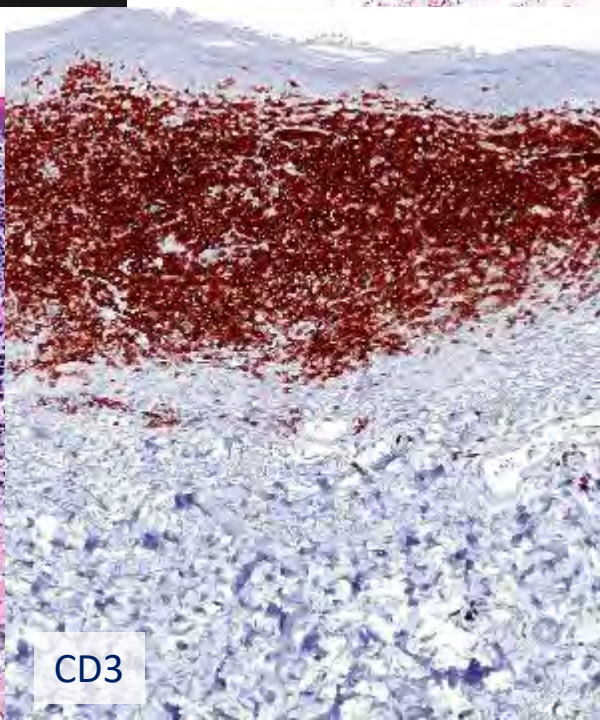
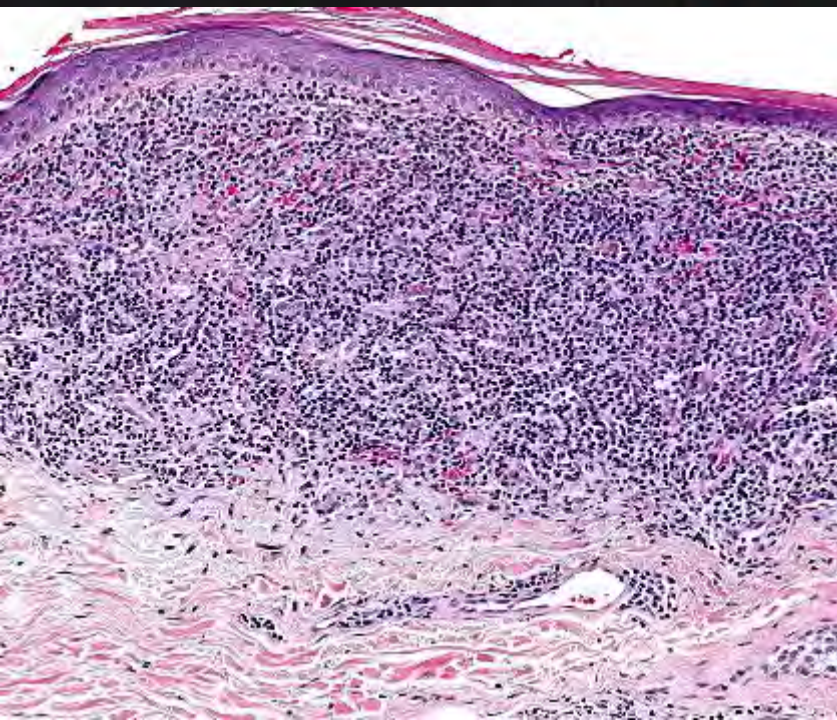
At this stage, a phototesting is performed, and it is positive for both UVA and UVB.

A biopsy is taken from the phototesting area, and a second one from the distal upper extremities.





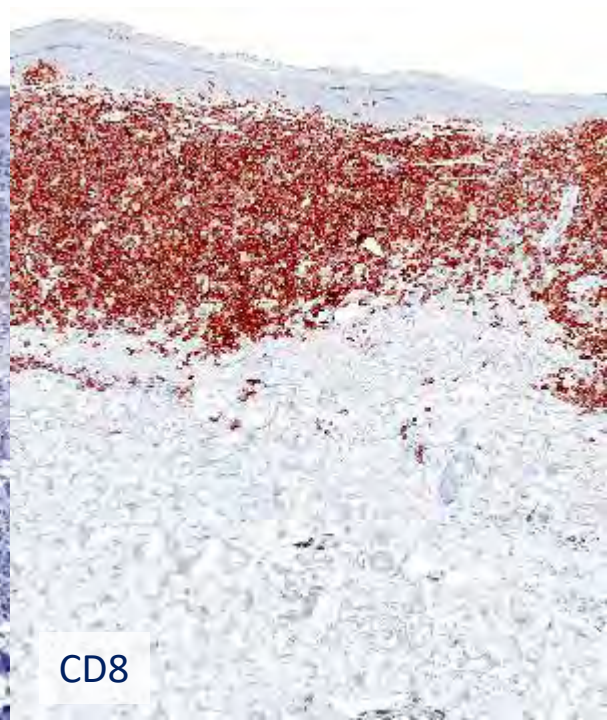
Mycosis fungoides ?
(cytotoxic, CD8+)



CD3



CD4

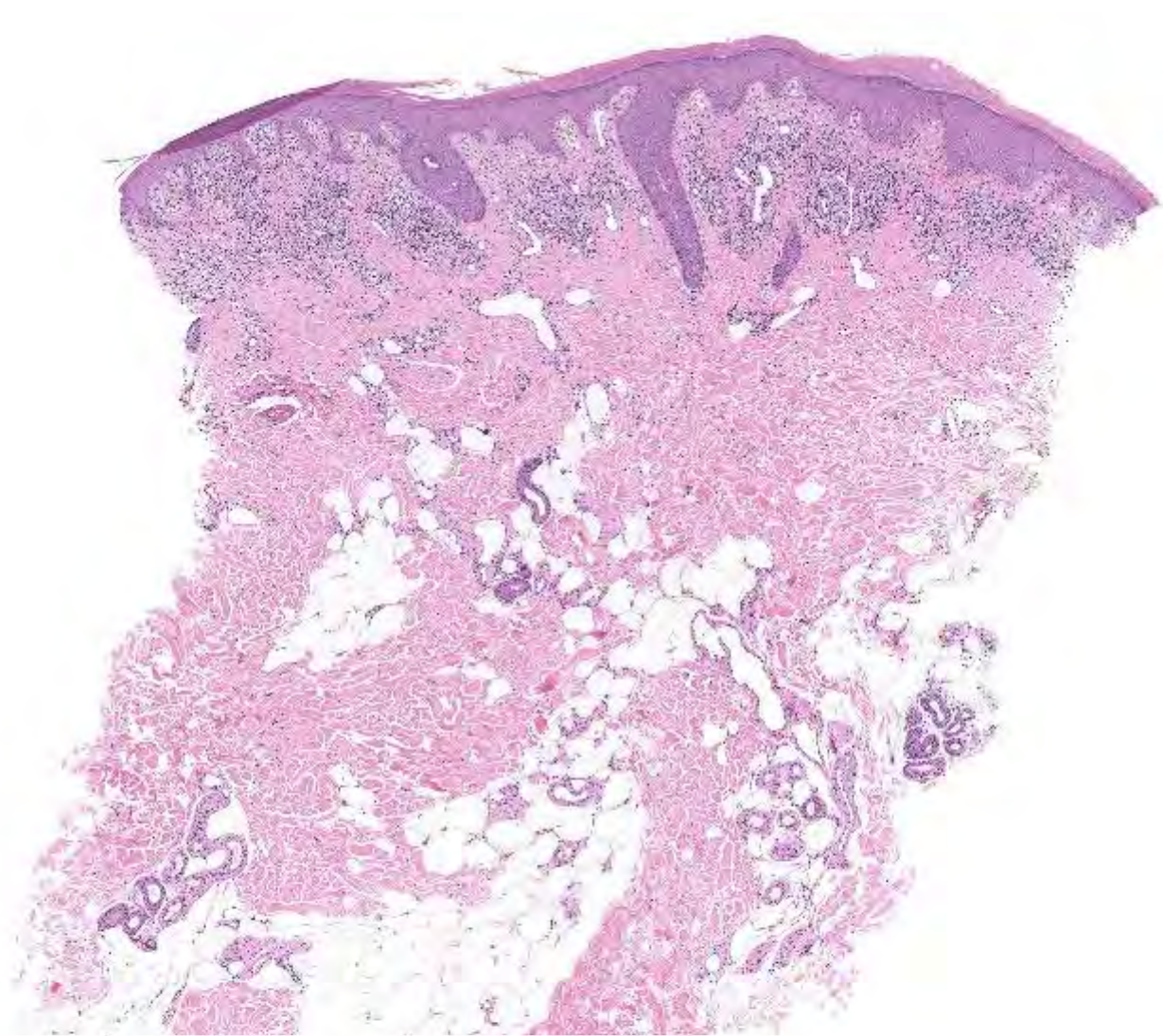


CD8

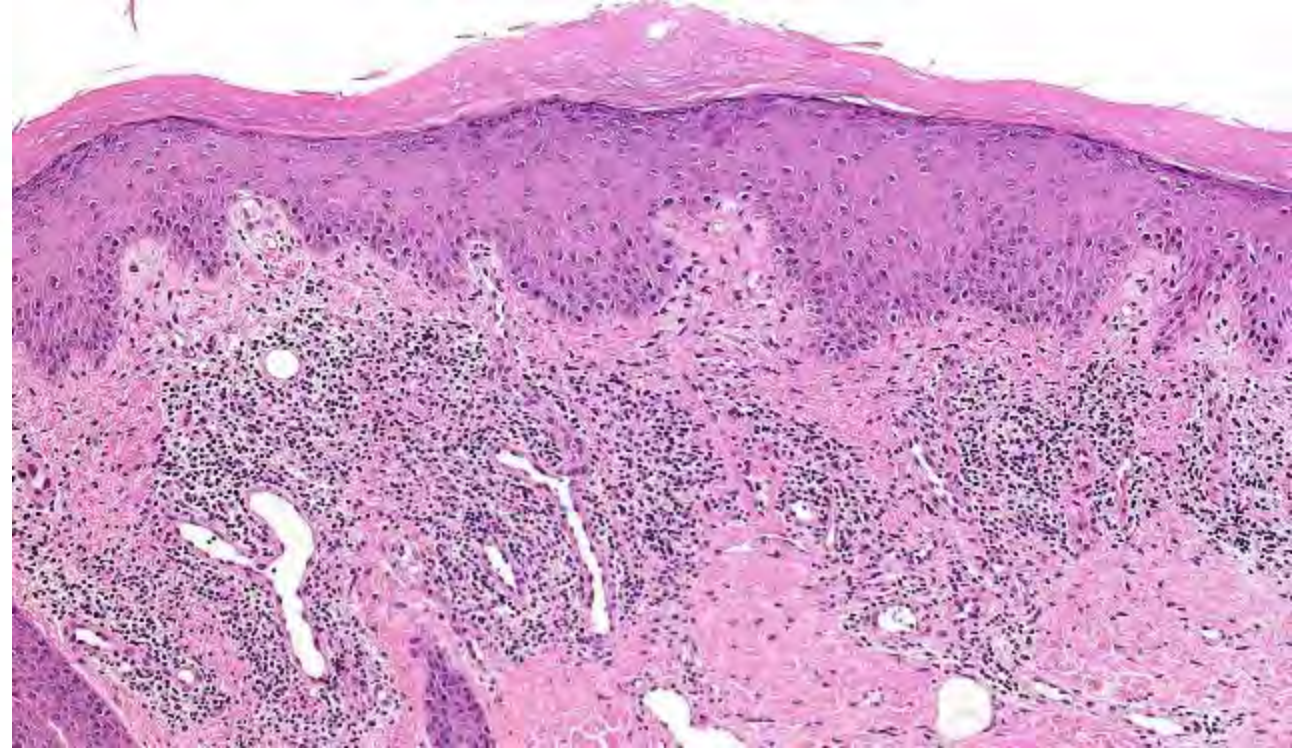


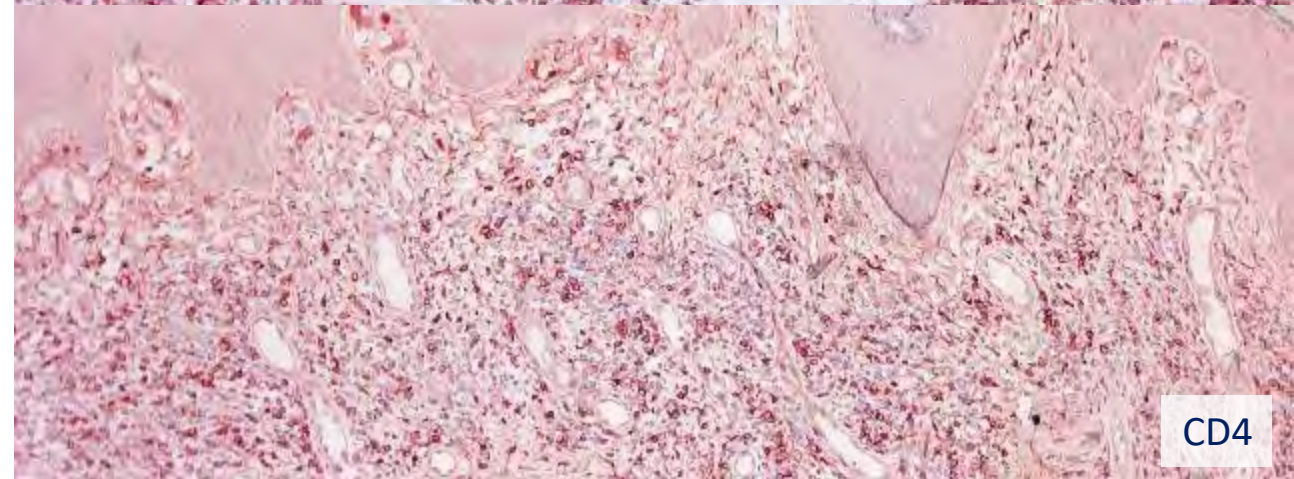
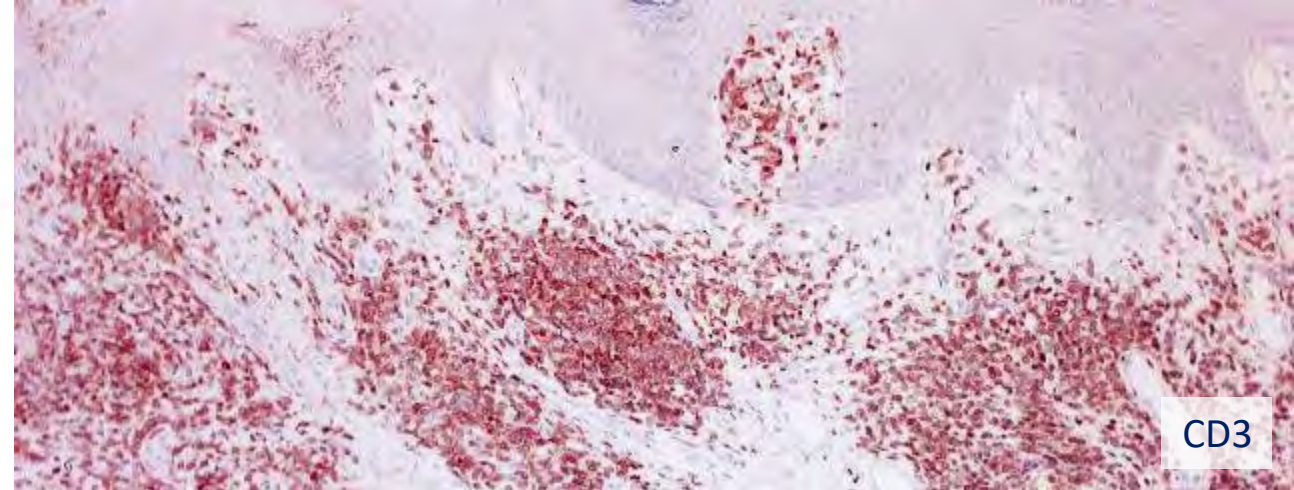
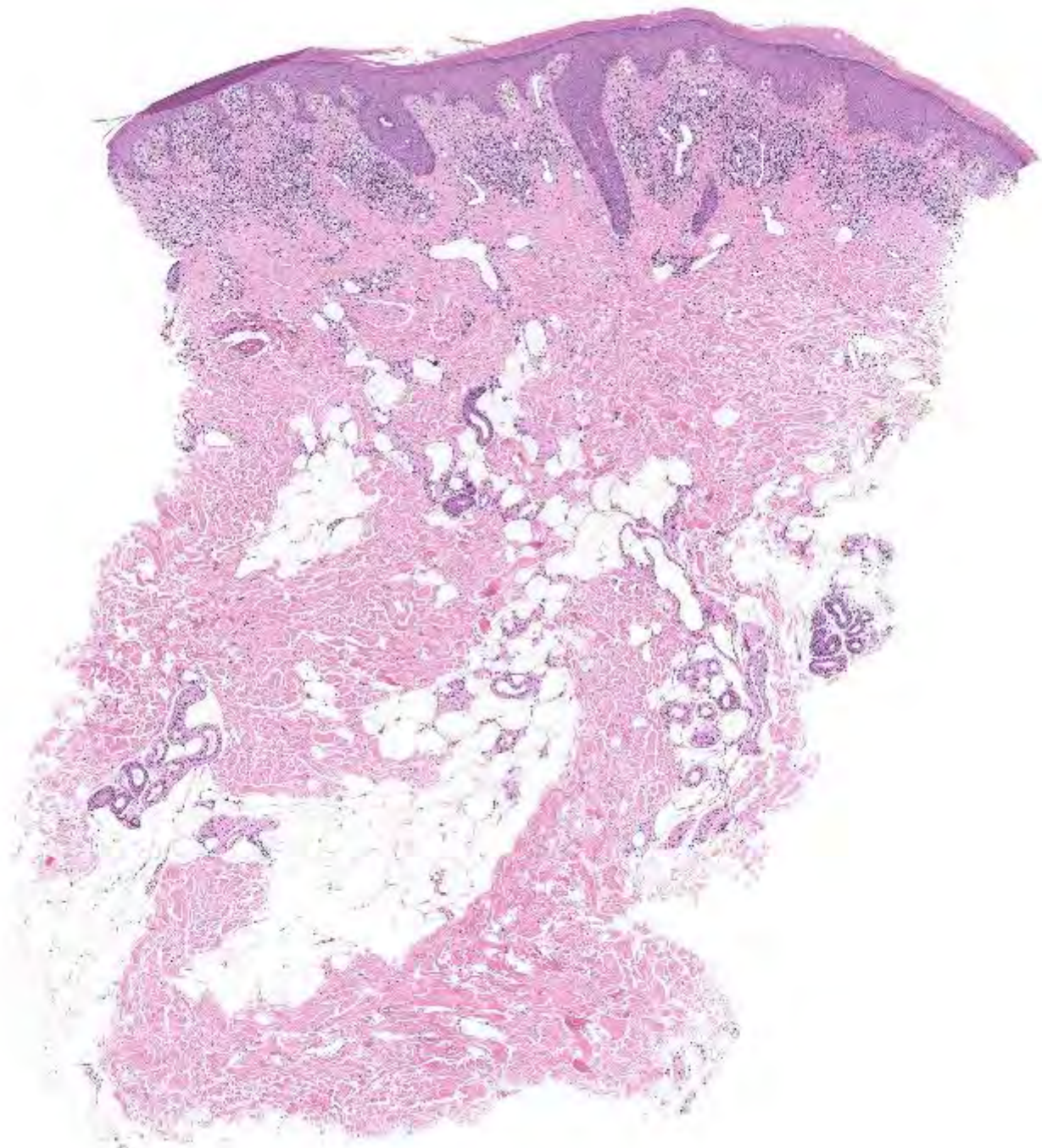
2,5 years later (now >8 years after 1st presentation) presents again with erosive lesions on the buttocks and groin. The lesions on the face almost completely resolved; still persistent palmo-plantar hyperkeratoses. A new biopsy is taken from the buttocks.





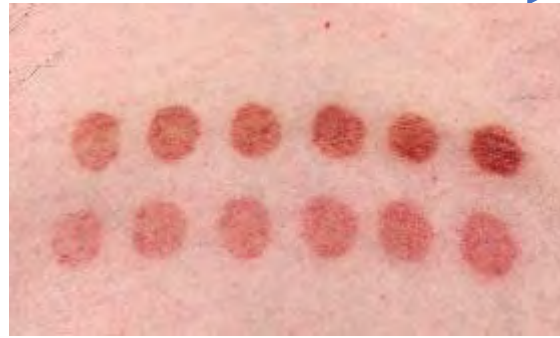
Chronic
eczematous dermatitis



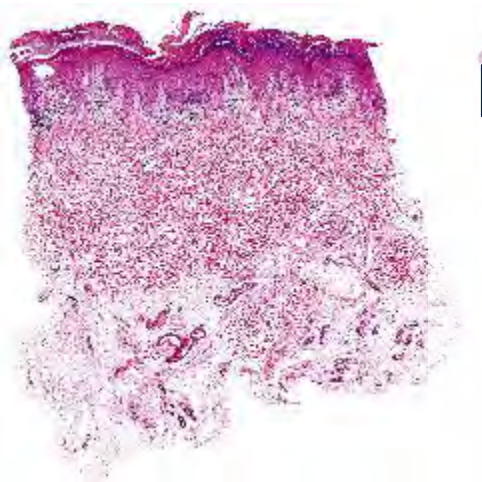




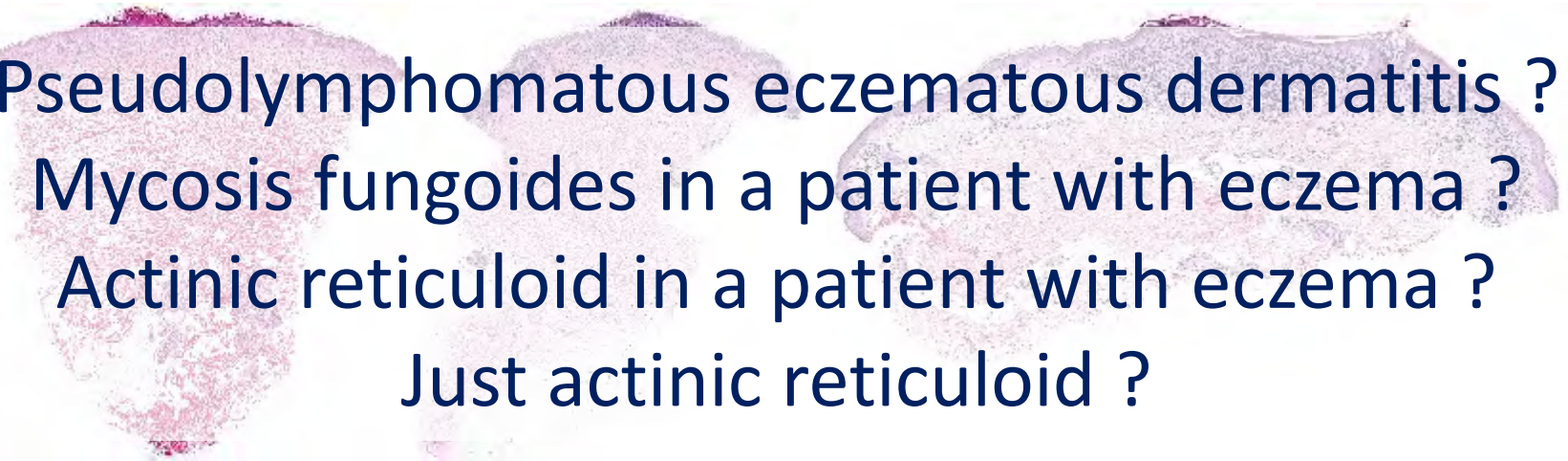
8,5 years



Over a period of >8 years several poussées of erythroderma on the background of a partly psoriasiform, partly eczematous, partly lichenified dermatitis with palmo-plantar hyperkeratoses. Positive phototesting. The biopsies at onset showed a pure spongiotic pattern, over time acquiring "MF-like" features (yet clear-cut epidermotropism in one biopsy only), getting back to an eczematous pattern in the last biopsy. All tested biopsies CD8+. Checked several times for presence of extracutaneous involvement (always negative).



Pseudolymphomatous eczematous dermatitis ?
Mycosis fungoides in a patient with eczema ?
Actinic reticuloid in a patient with eczema ?
Just actinic reticuloid ?





Over a period of >8 years several poussées of erythroderma on the background of a partly psoriasiform, partly eczematous, partly lichenified dermatitis with palmo-plantar hyperkeratoses. Positive phototesting. The biopsies at onset showed a pure spongiotic pattern, over time acquiring "MF-like" features (yet clear-cut epidermotropism in one biopsy only), getting back to an eczematous pattern in the last biopsy. All tested biopsies CD8+. Checked several times for presence of extracutaneous involvement (always negative).



Overlap actinic reticuloid / "atopic dermatitis"



M, 69

Eczematous ("atopic") dermatitis for the last few years.

In the last weeks lack of response to local treatment.

Two biopsies are taken.



1st presentation



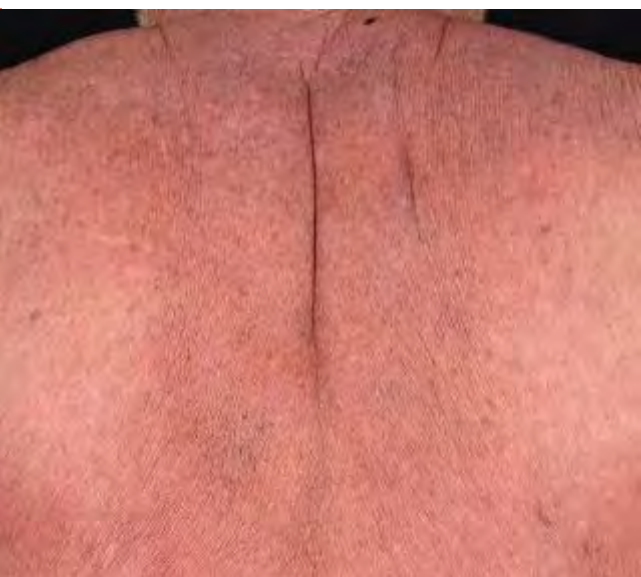
13 months later

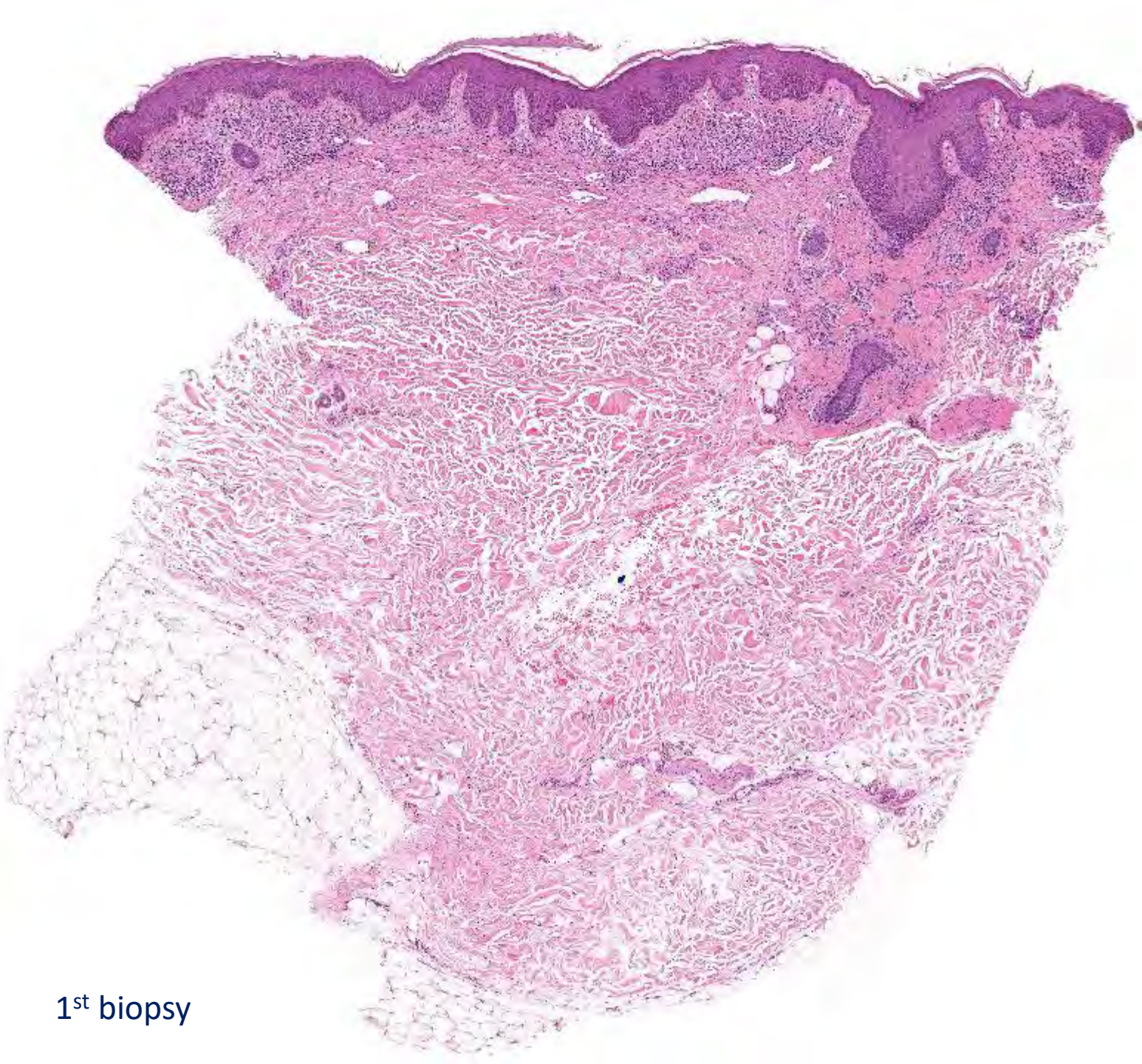


19 months later

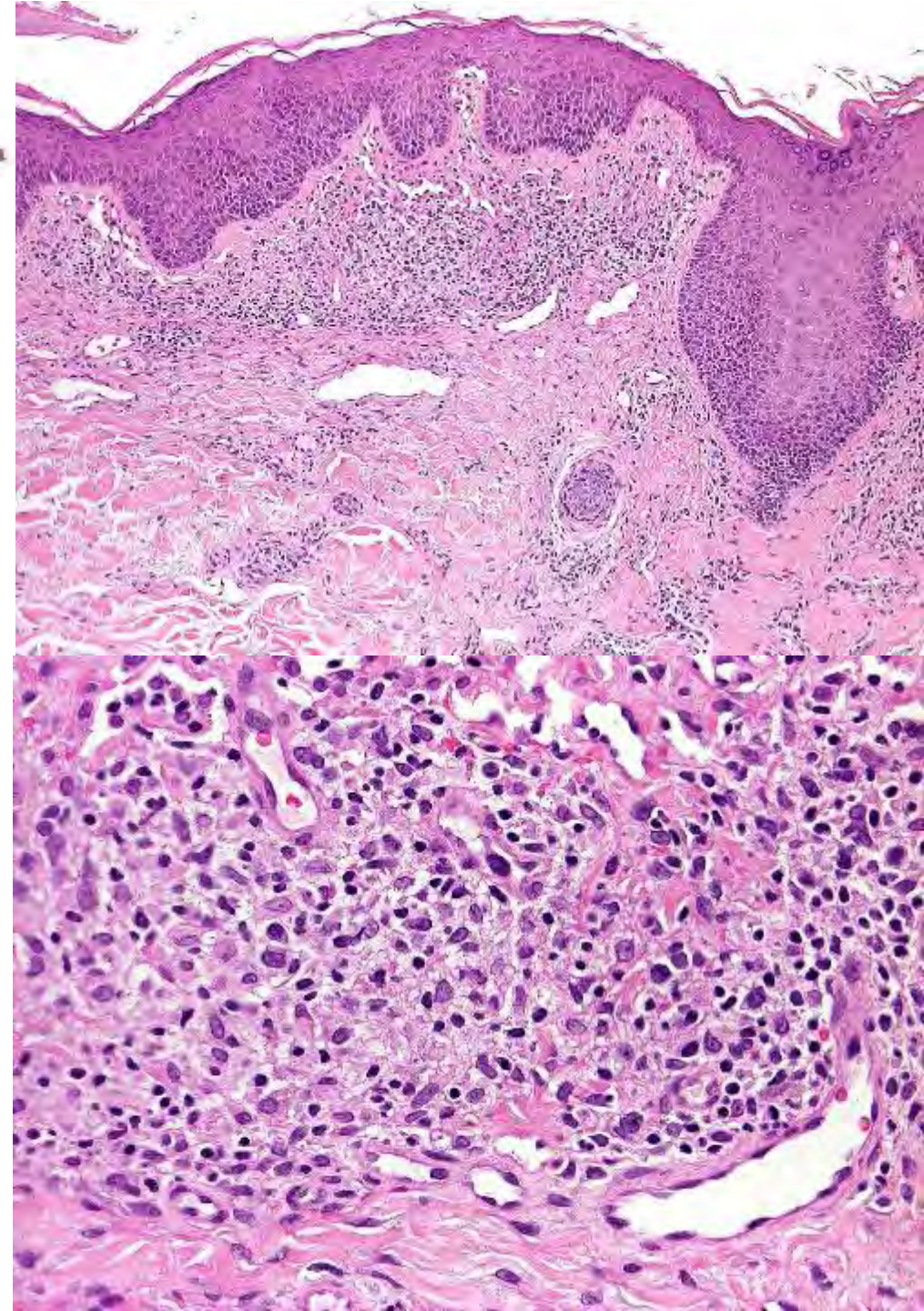


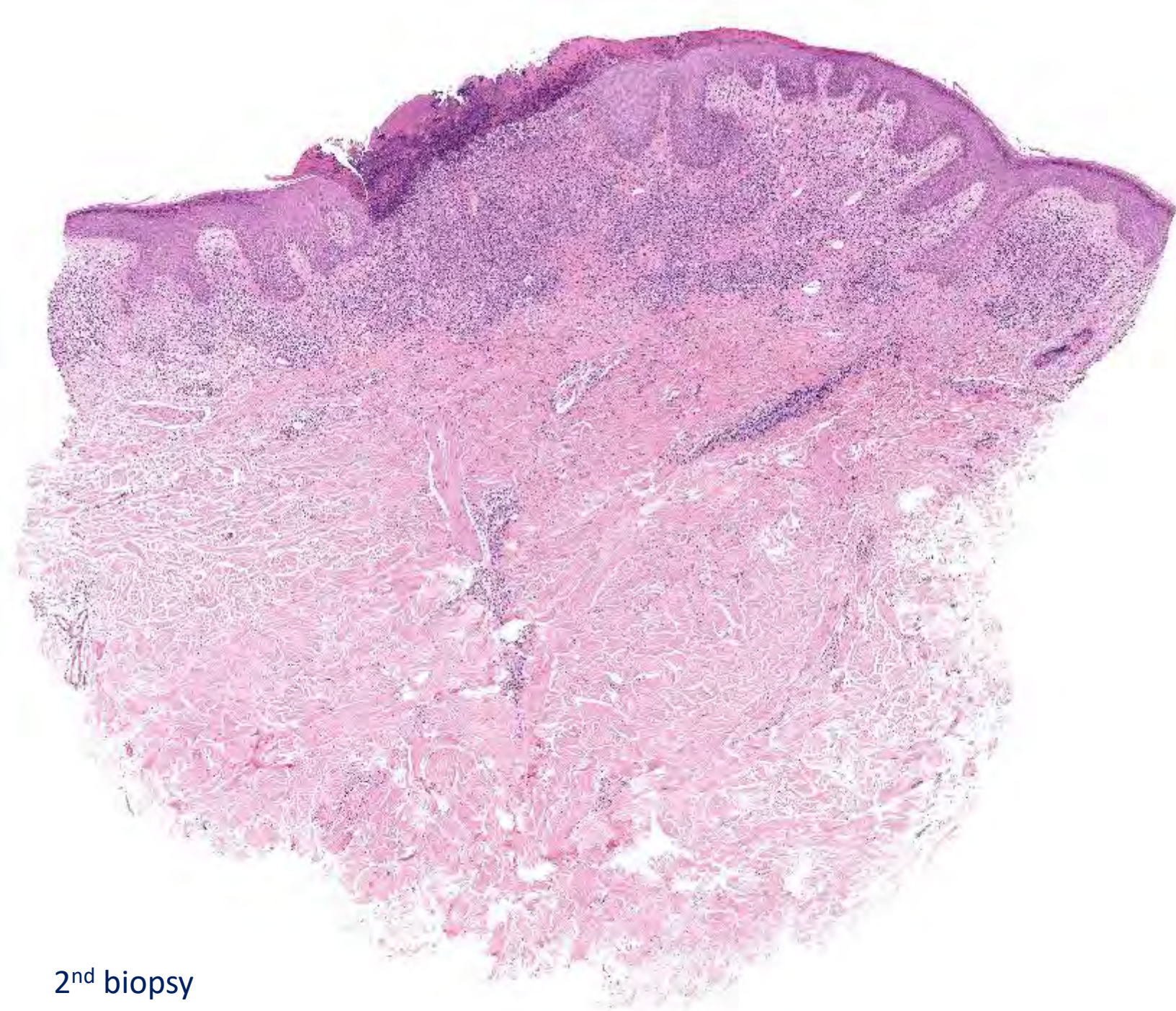
35 months later (biopsies)



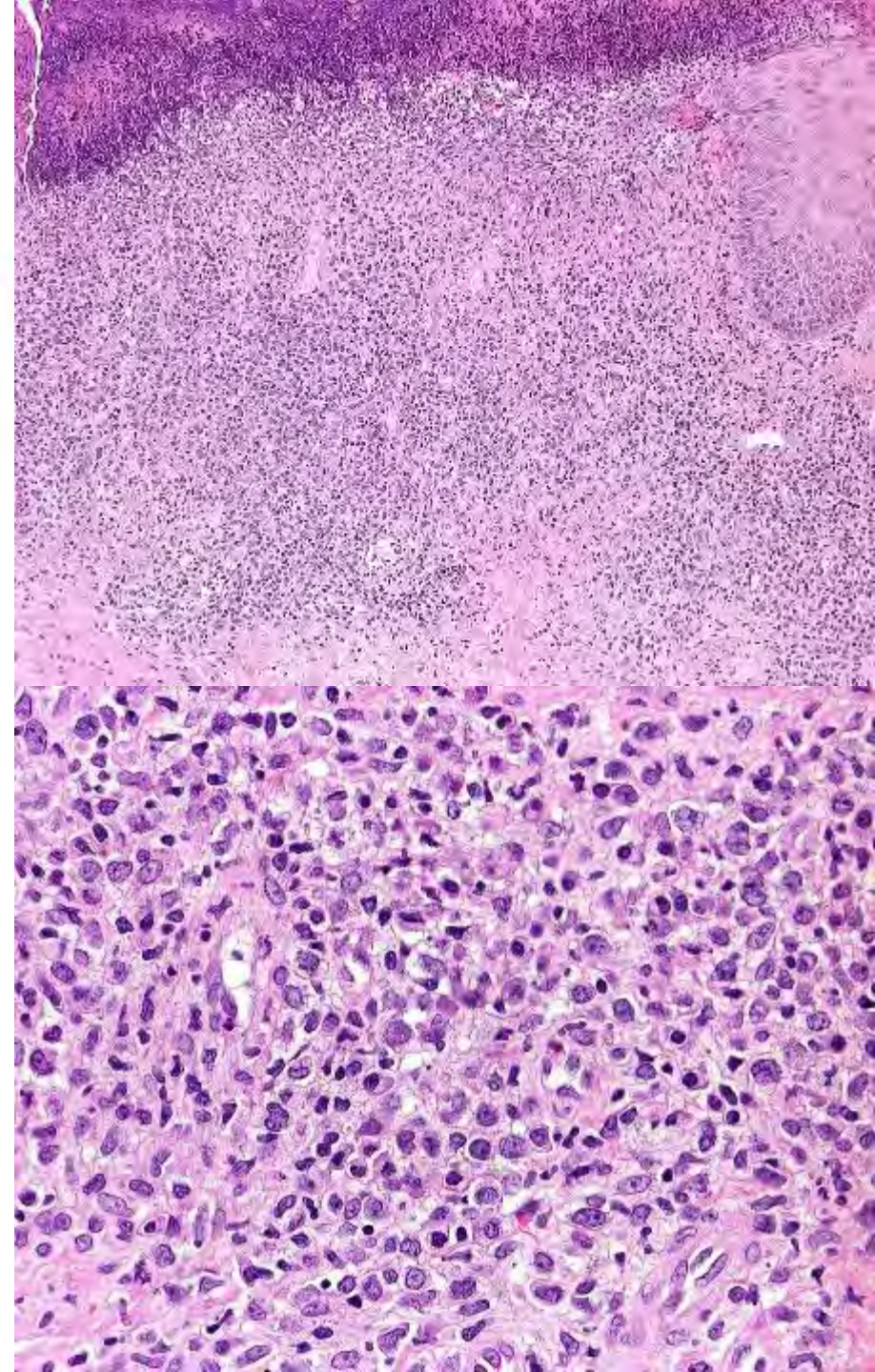


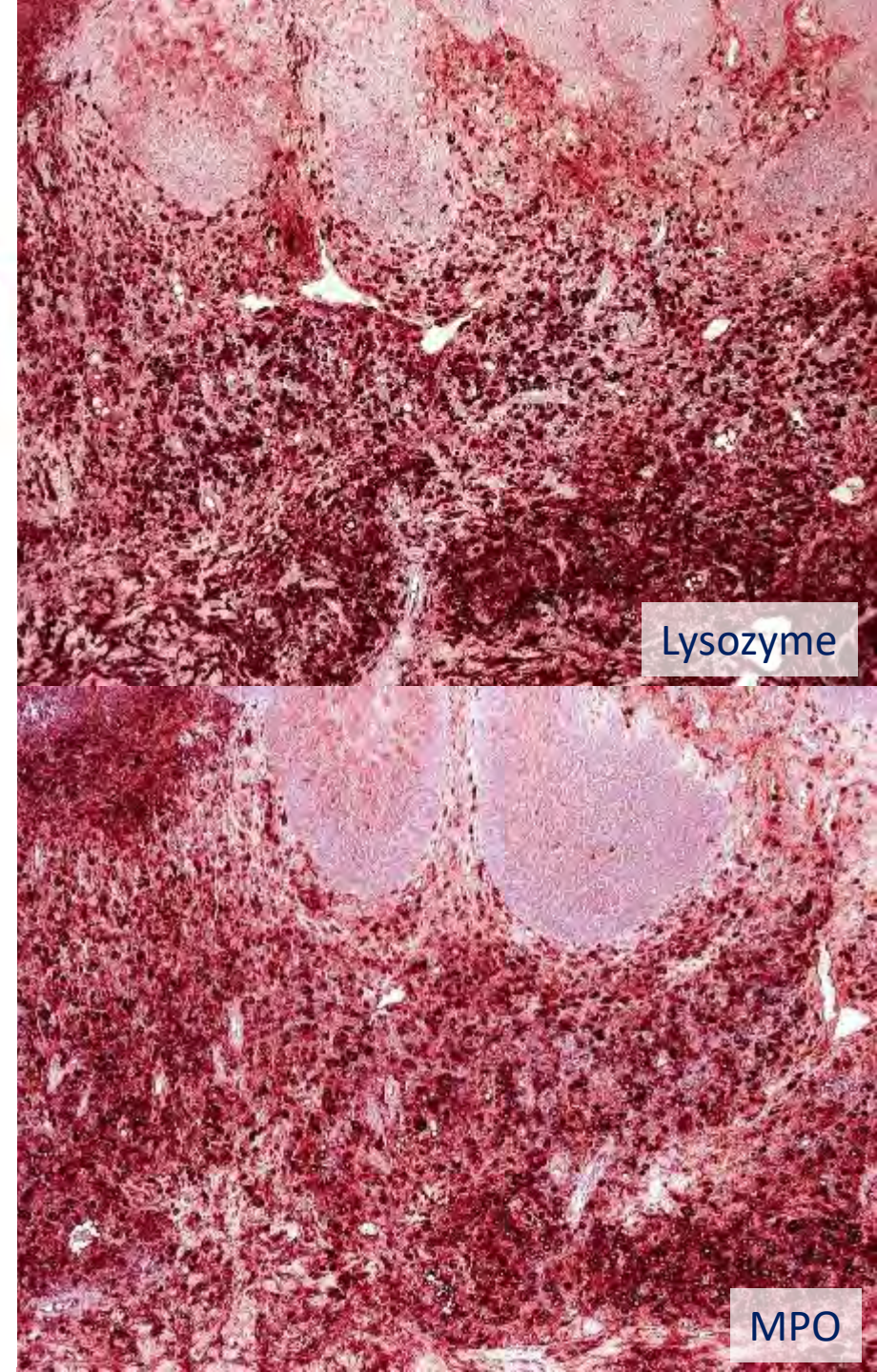
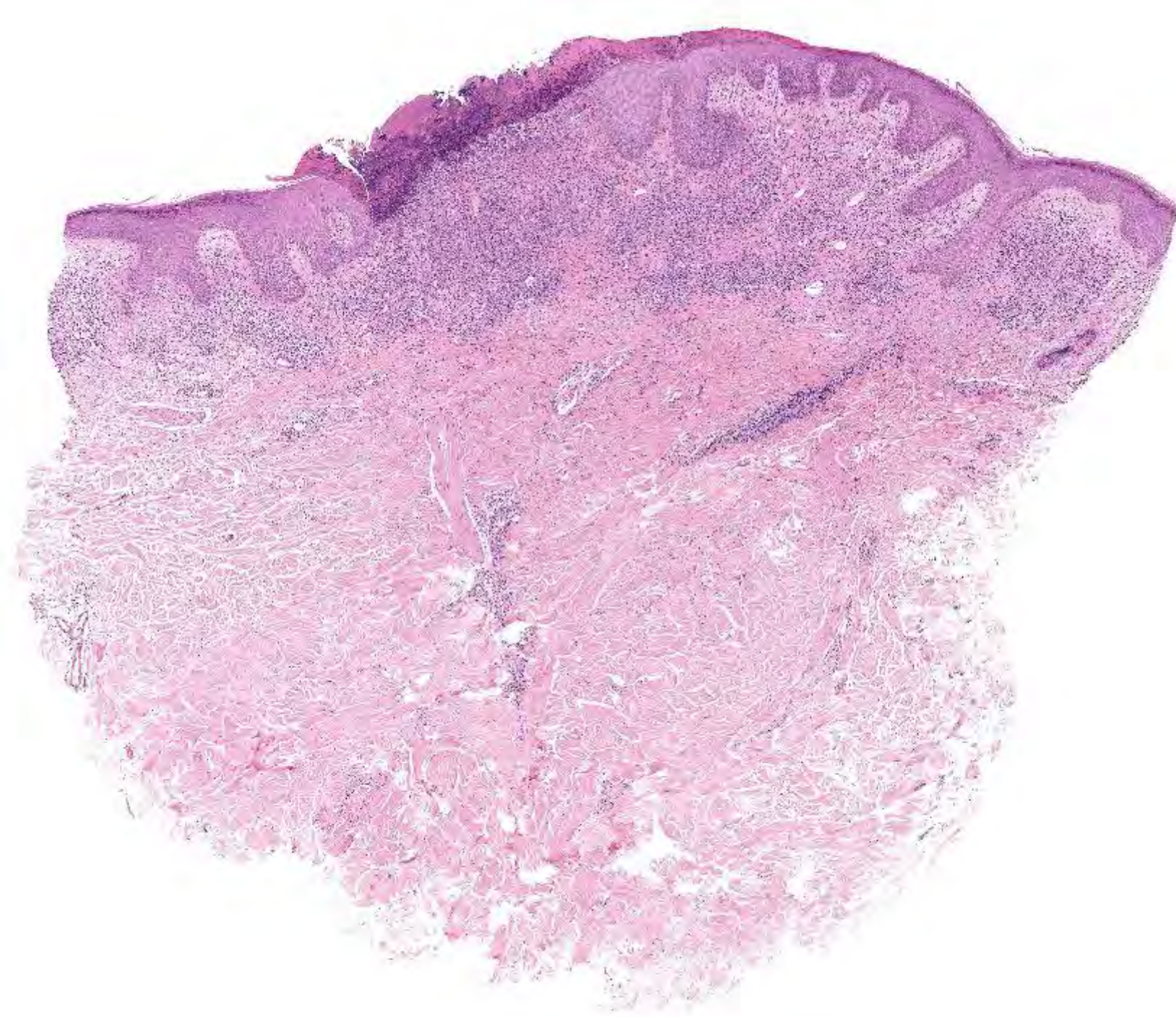
1st biopsy





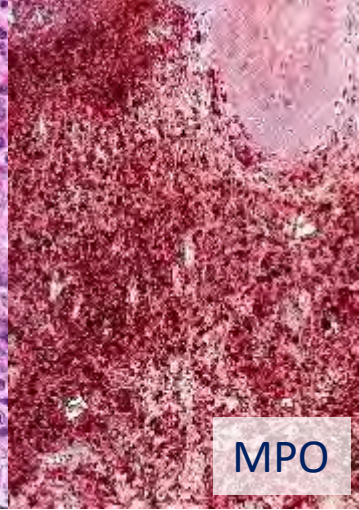
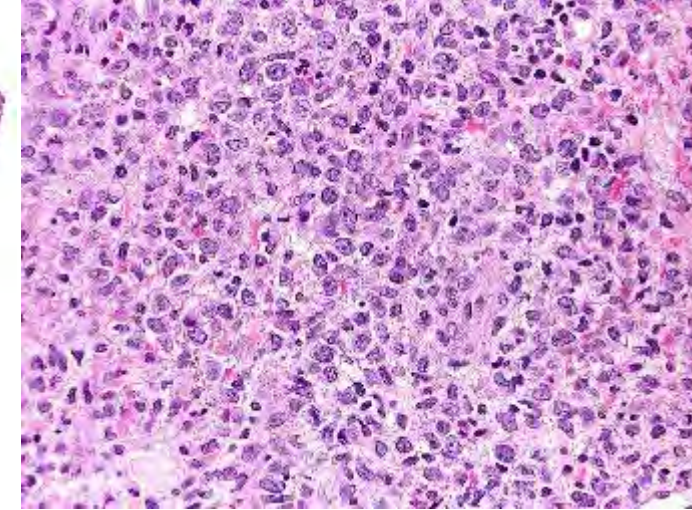
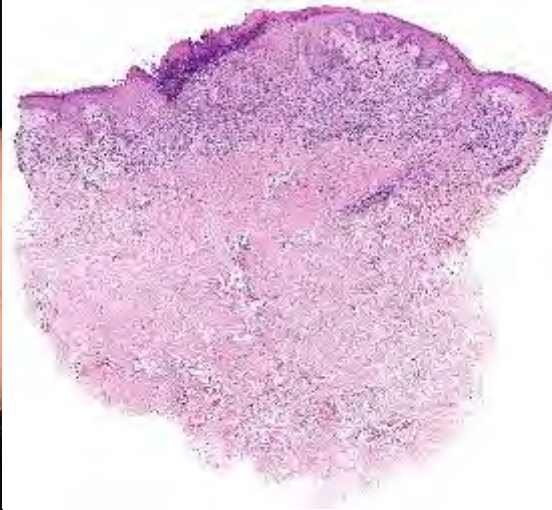
2nd biopsy



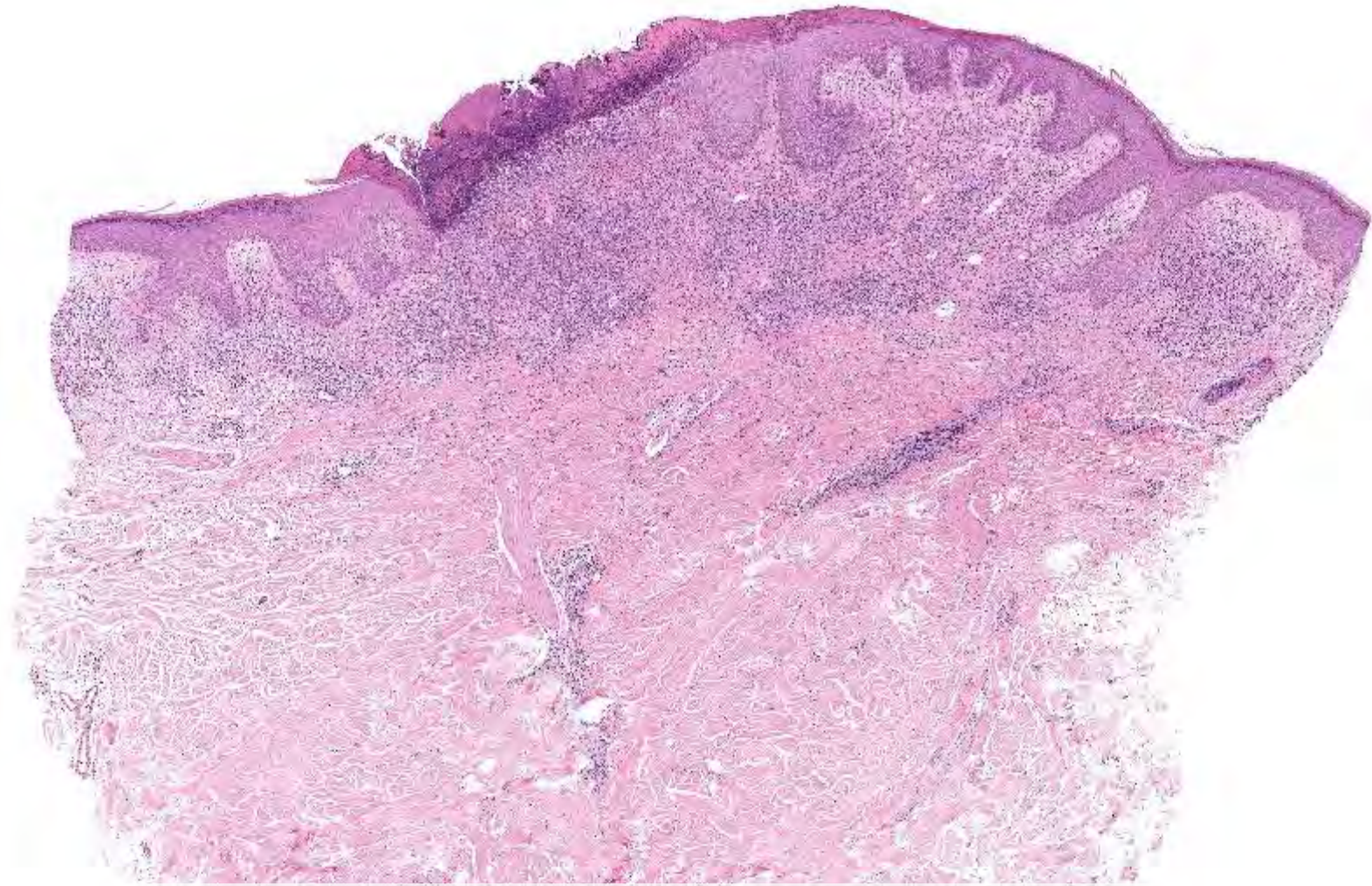


Lysozyme

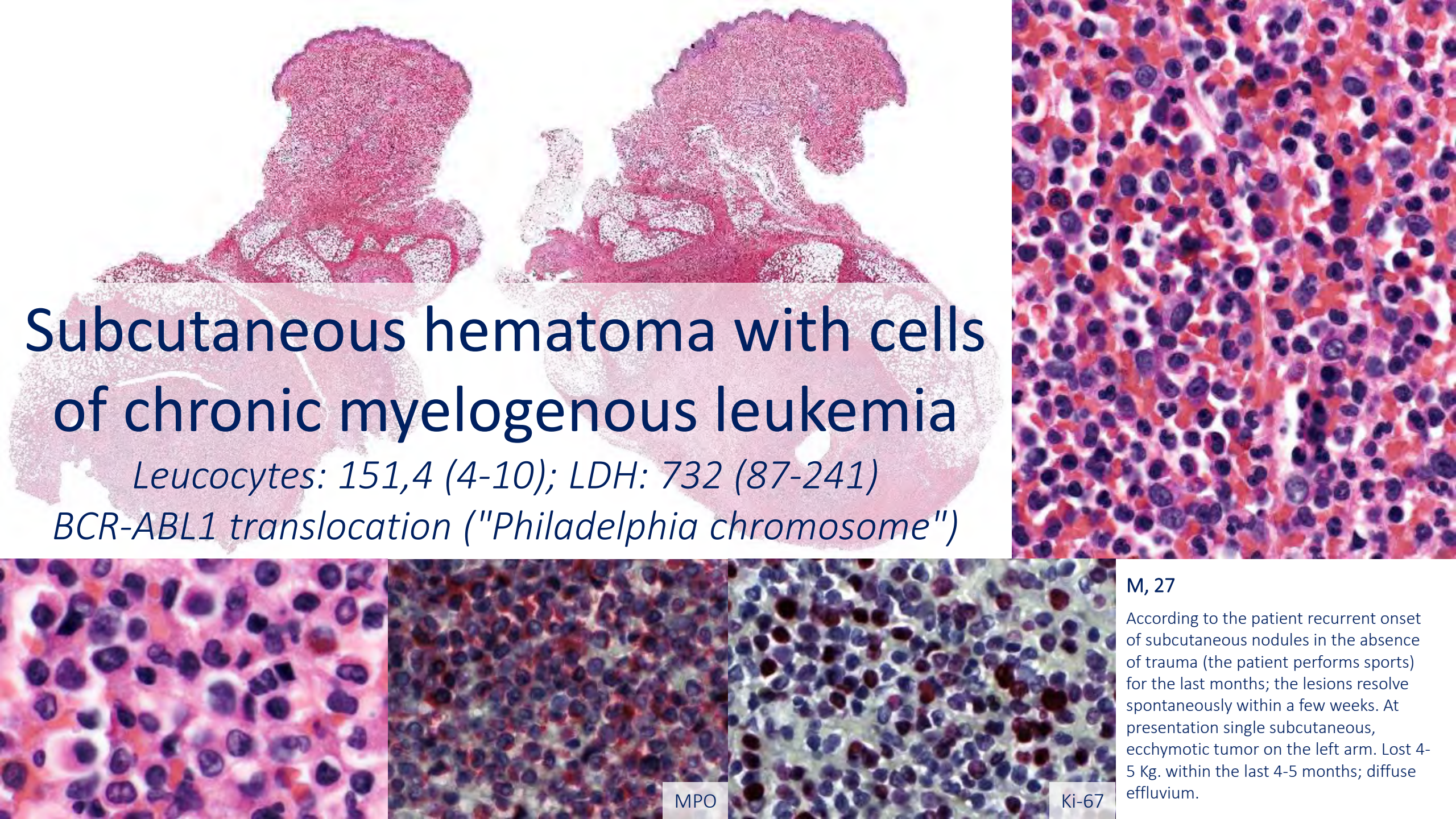
MPO



Eczematous ("atopic") dermatitis since a few years.
Alternation of improvement and worsening for the last 4 years.
Lack of response to conventional treatment; 2 skin biopsies show features of eczematous dermatitis but also an atypical mononuclear cell infiltrate.
Further investigations: pancytopenia; bone marrow biopsy shows myelodysplastic syndrome.
Four months later: worsening of the general conditions; bone marrow biopsy shows progression to AML.
Exitus 11 months later.



Specific infiltrate of myelogeneous leukemia at the site of eczematous ("atopic") dermatitis

The image is a composite of four histological sections. The top-left section shows a low-power view of a subcutaneous hematoma with clusters of myeloid cells. The top-right section is a high-power view showing a dense population of myeloid cells with dark, round nuclei. The bottom-left section is a high-power view of myeloid cells with prominent reddish-orange granules. The bottom-right section is a high-power view of myeloid cells with dark nuclei and granules, with a label 'MPO' overlaid. A label 'Ki-67' is overlaid on the bottom-right section. The text 'M, 27' is overlaid on the bottom-right section.

Subcutaneous hematoma with cells of chronic myelogenous leukemia

Leucocytes: 151,4 (4-10); LDH: 732 (87-241)

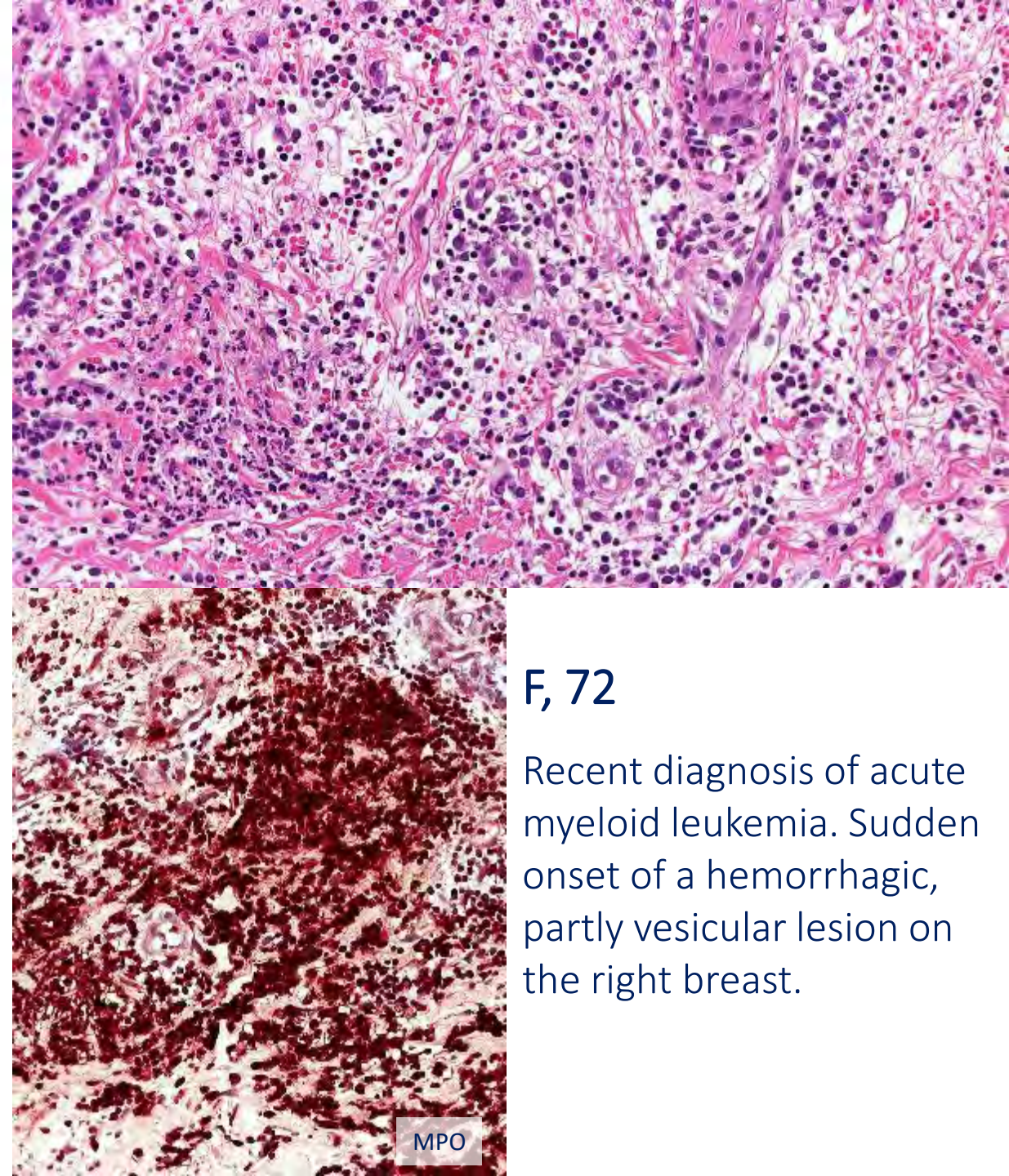
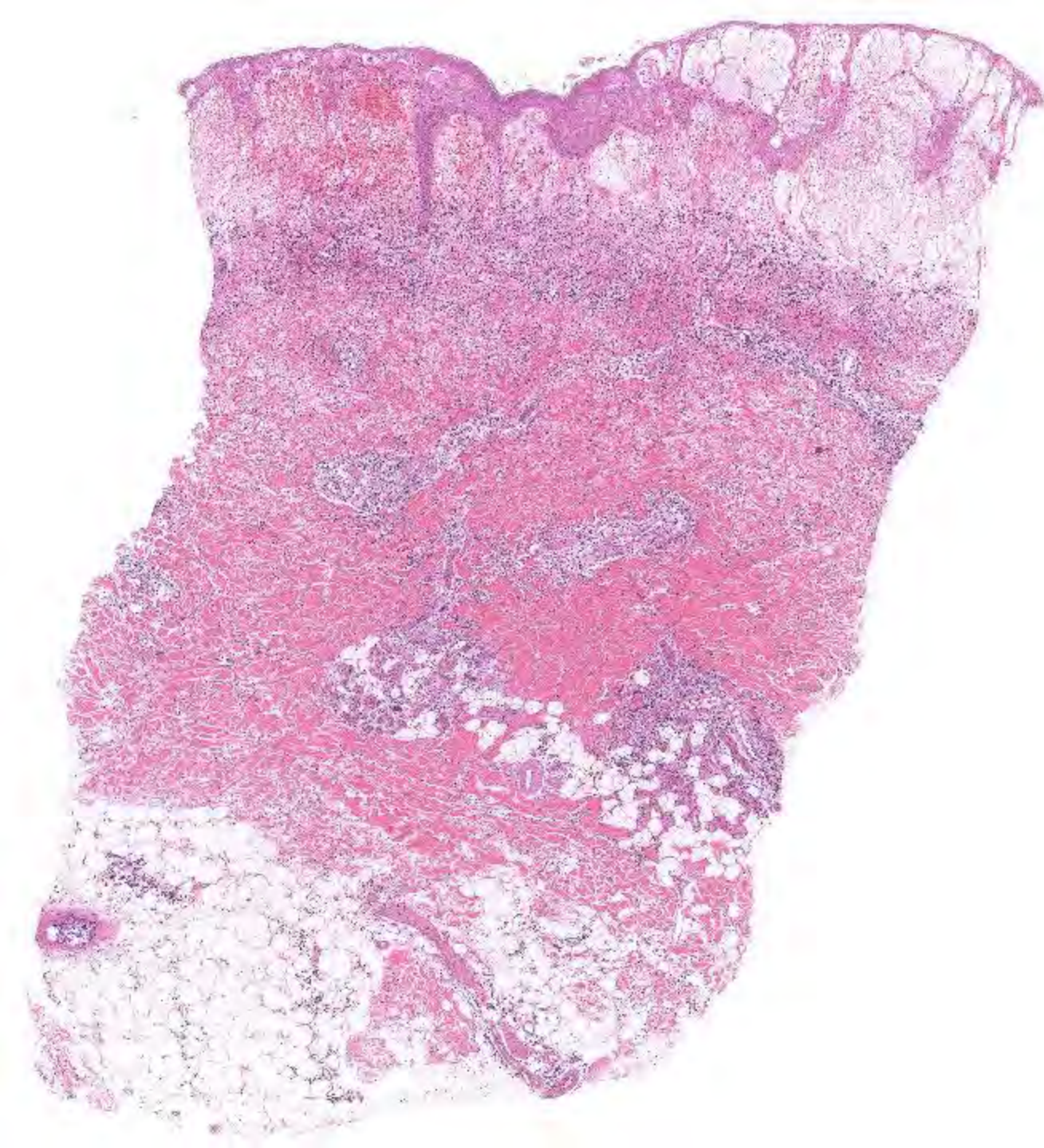
BCR-ABL1 translocation ("Philadelphia chromosome")

M, 27

According to the patient recurrent onset of subcutaneous nodules in the absence of trauma (the patient performs sports) for the last months; the lesions resolve spontaneously within a few weeks. At presentation single subcutaneous, ecchymotic tumor on the left arm. Lost 4-5 Kg. within the last 4-5 months; diffuse effluvium.

MPO

Ki-67



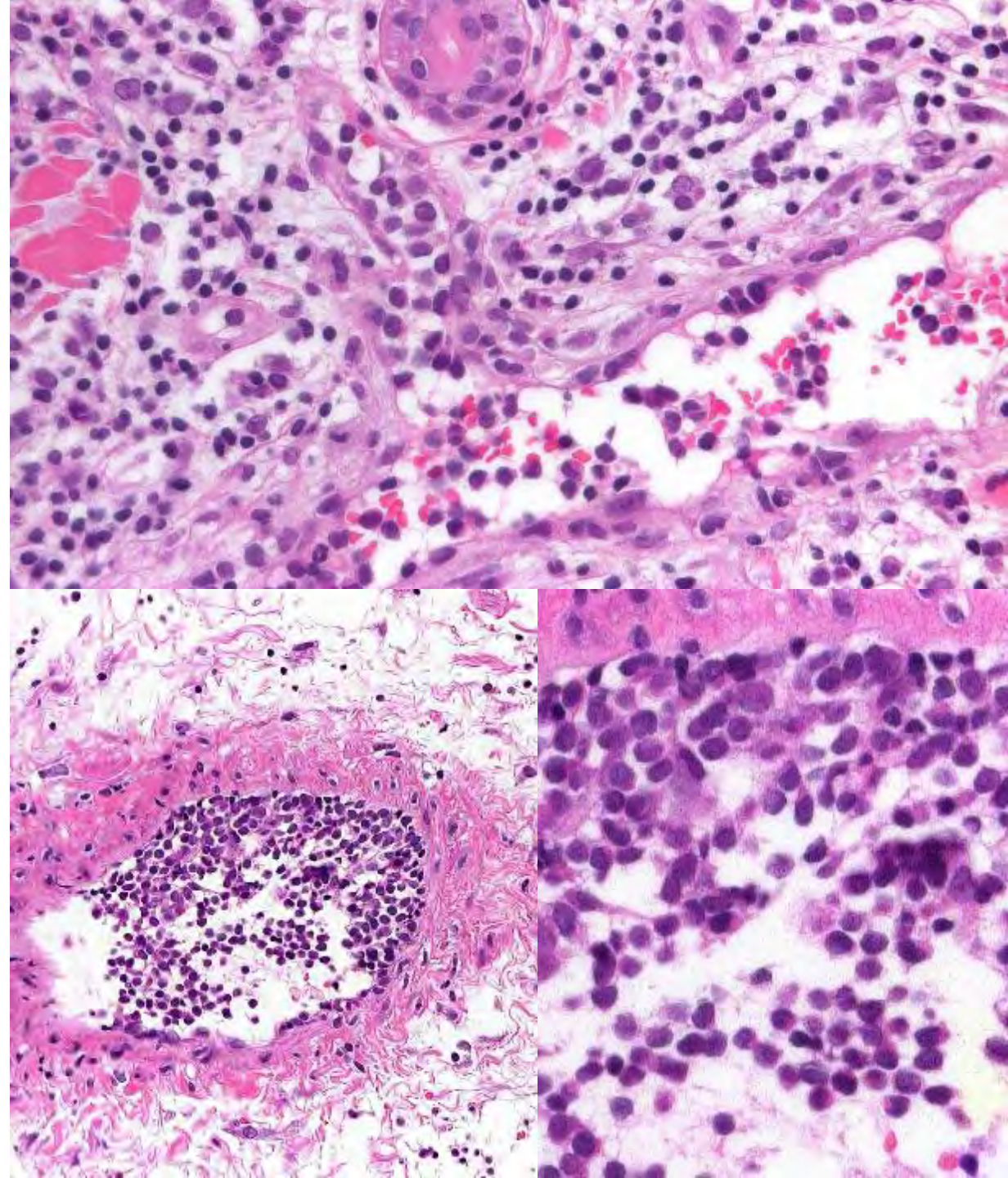
F, 72

Recent diagnosis of acute myeloid leukemia. Sudden onset of a hemorrhagic, partly vesicular lesion on the right breast.

MPO



Overlap AML / Sweet syndrome
with intravascular cells of AML





1st presentation



4 days later

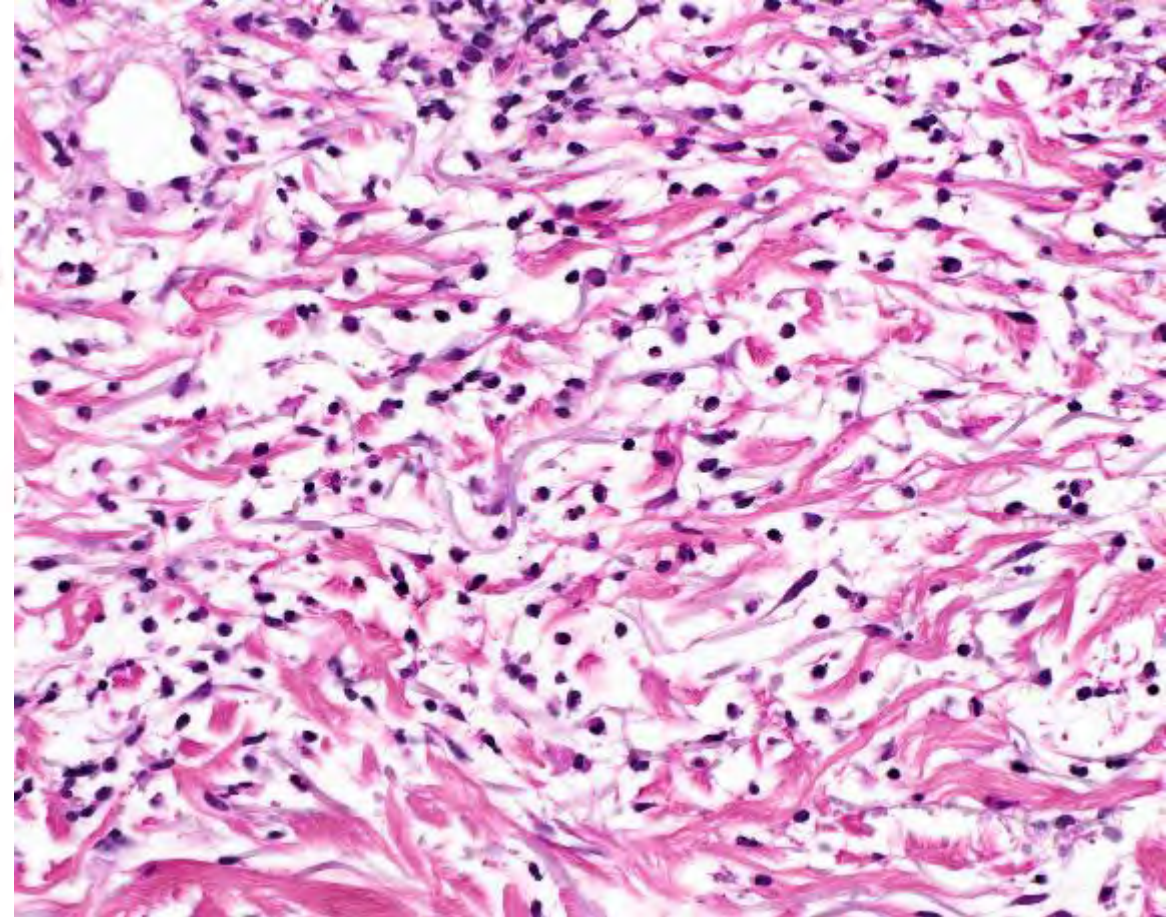
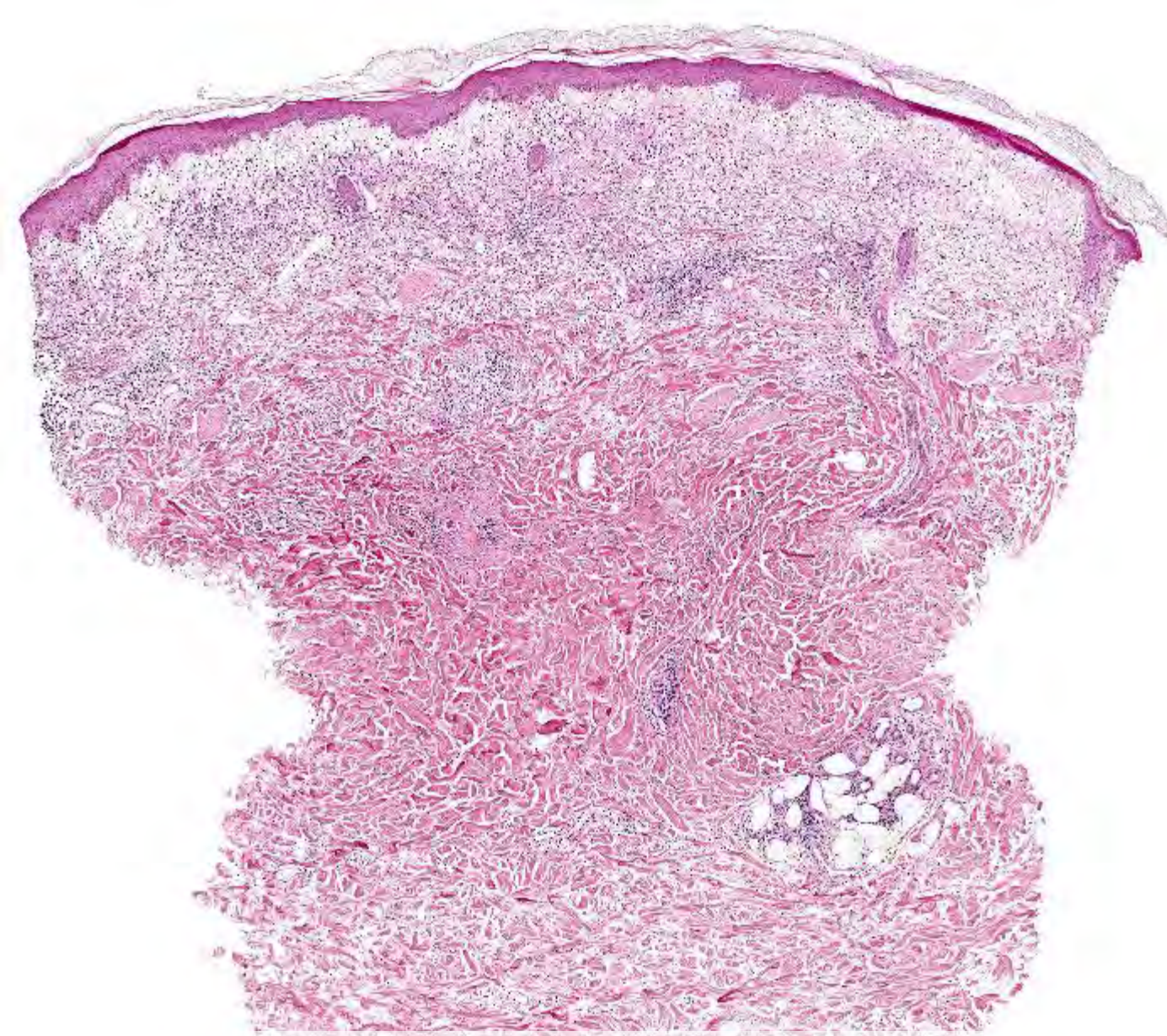


M, 67

According to the patient 6 months before presentation onset of lesions that "come and go".

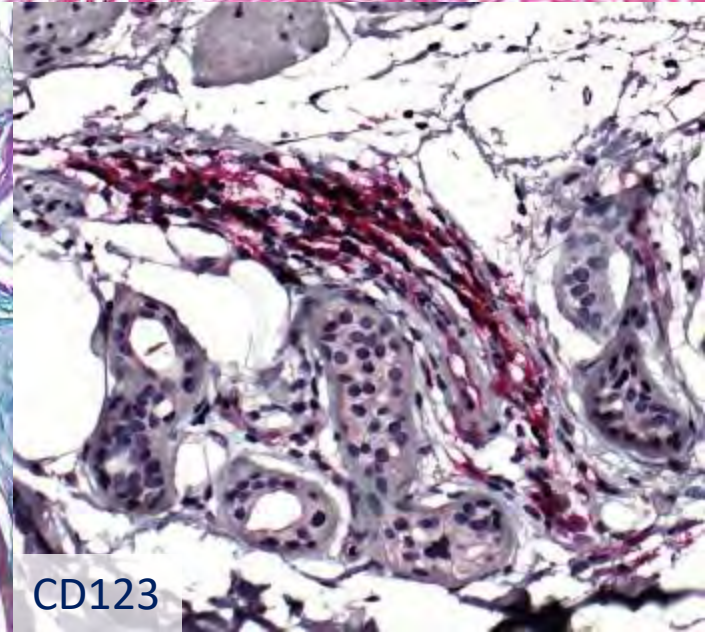
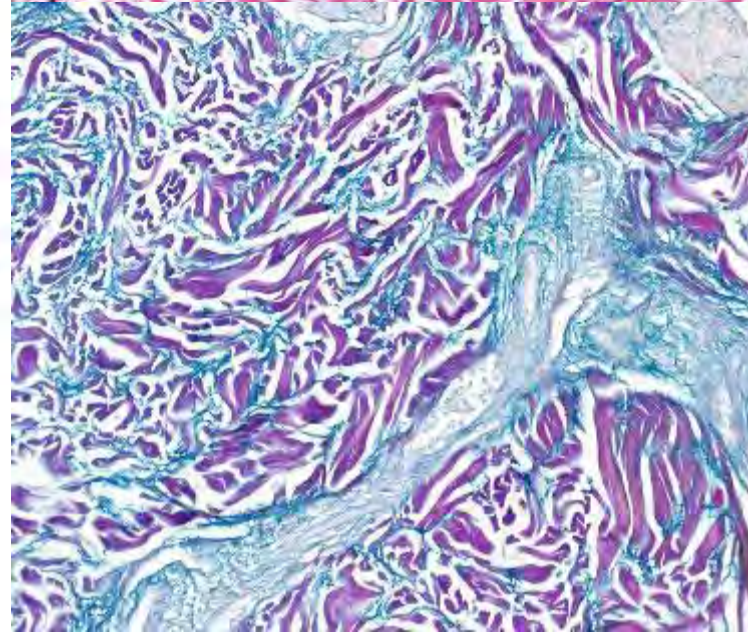
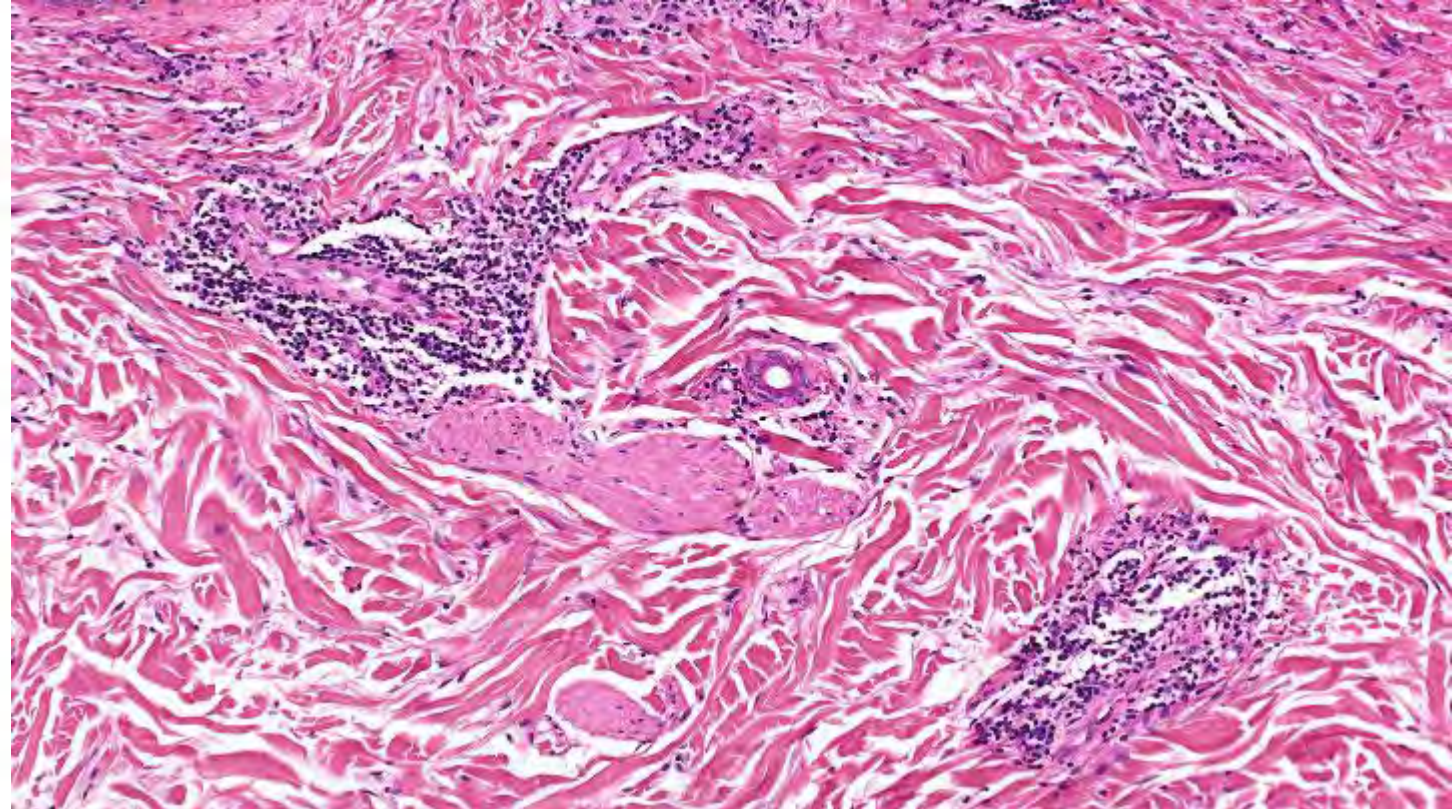
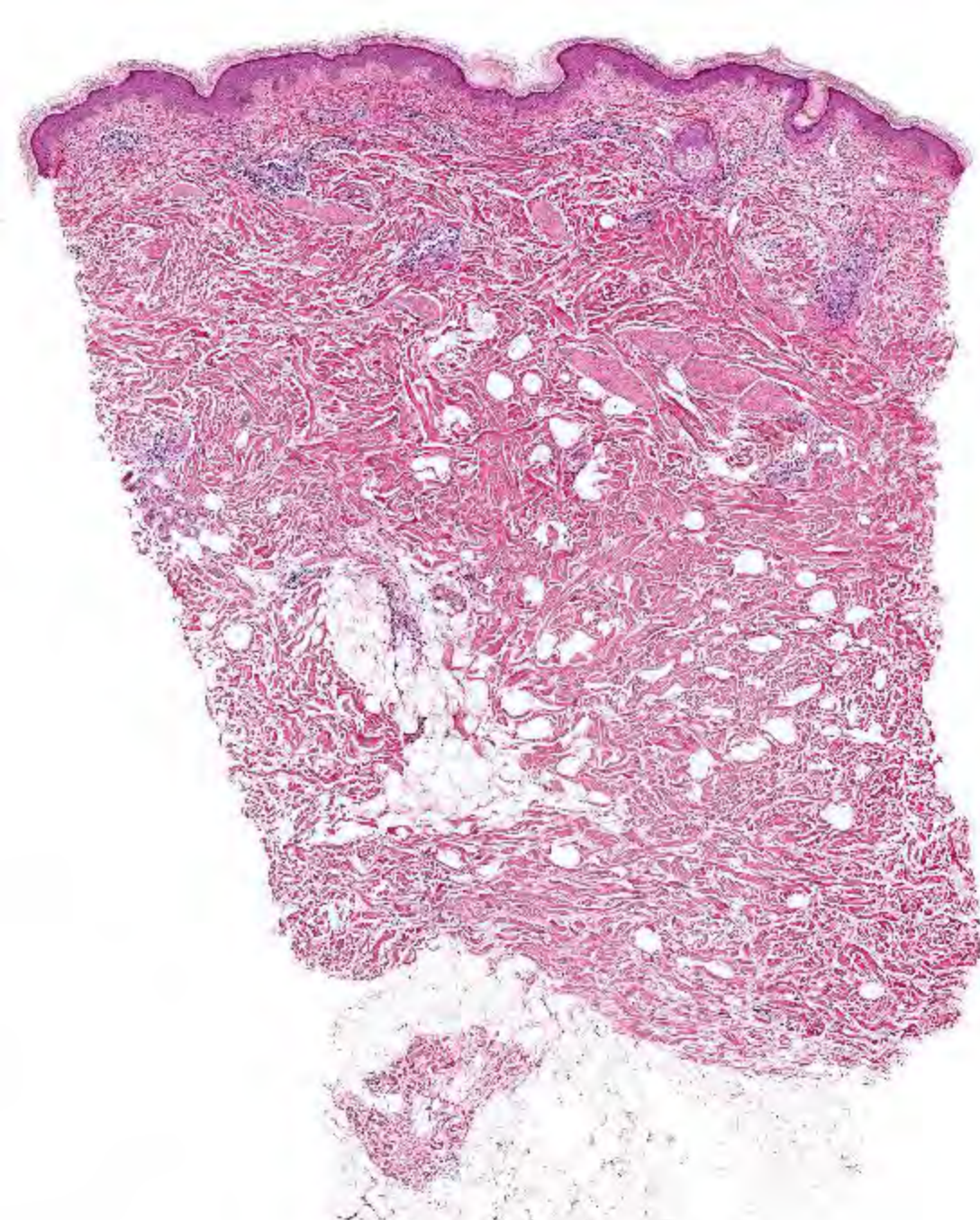
A biopsy taken by a private dermatologist short after onset of the first lesions was reported as "lymphocytic infiltration – suspicion of LE tumidus". Managed with hydroxychloroquine 200 mg/d for the last month.

A new biopsy is taken.



Sweet syndrome...

New biopsy



Biopsy taken 5 months earlier

CD123



1st presentation



16 days later



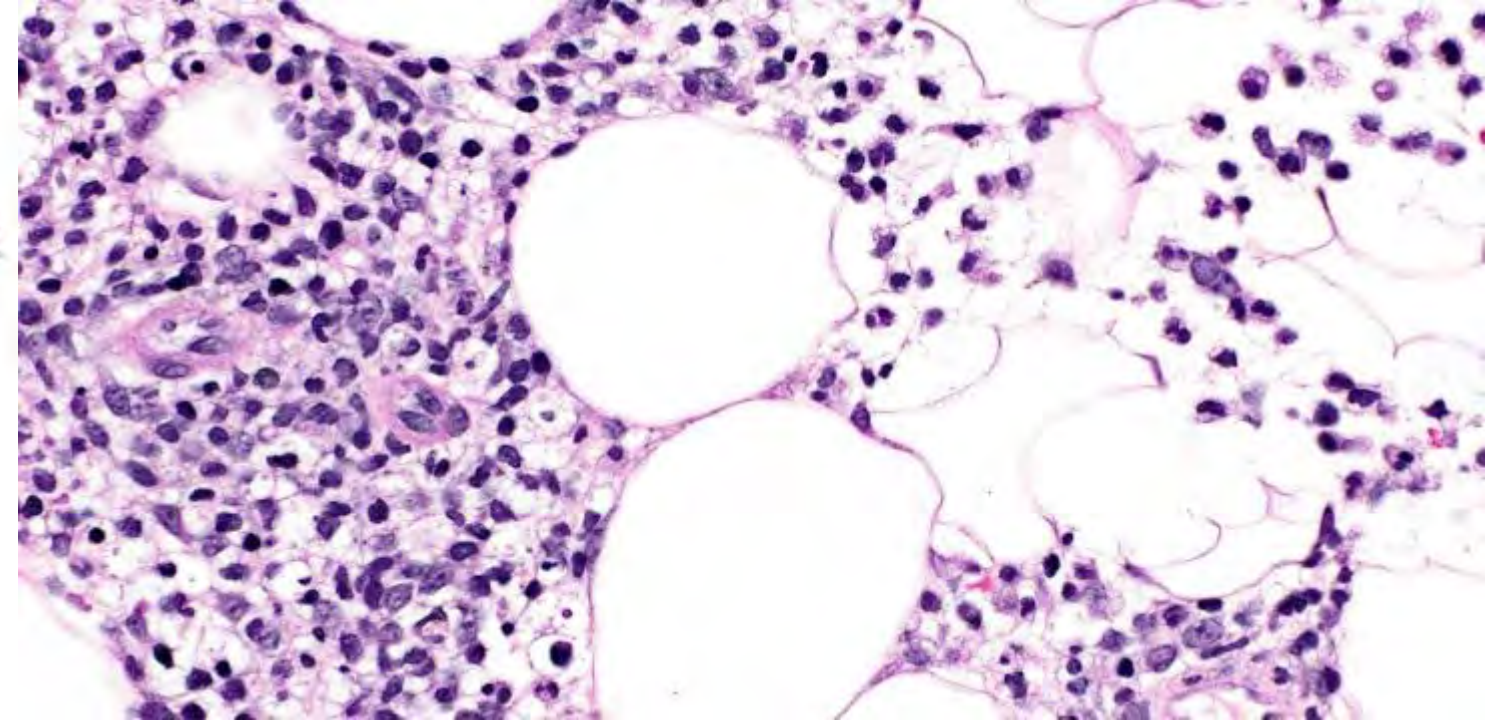
32 days later

*(after systemic steroids; local steroids still given;
hydroxychloroquine still given)*

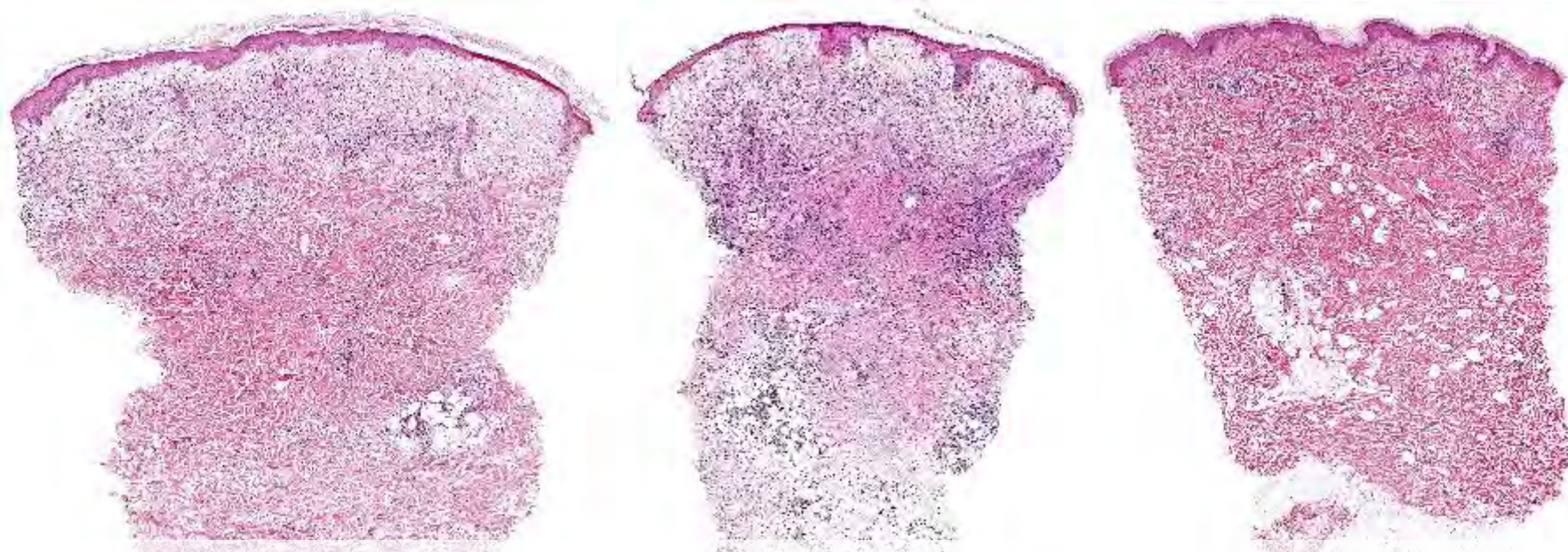
...Sweet syndrome in a patient with LE tumidus...



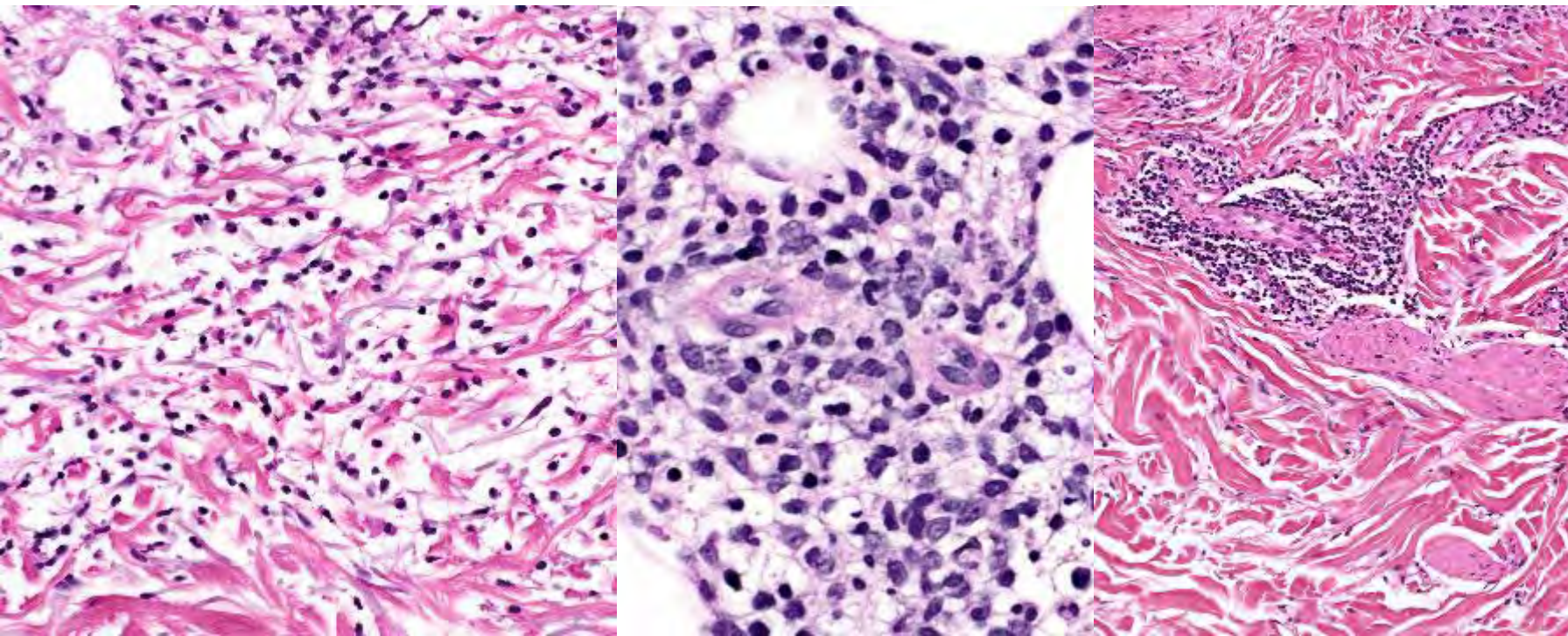
Five months later new episode of Sweet syndrome.
A new biopsy is taken.



...Histiocytoid
Sweet syndrome...



...Sweet syndrome, histiocytoid Sweet syndrome, & LE tumidus...





1st presentation



6 months later



18 months later

VEXAS syndrome

Mutation of the *UBA1* gene (p.M41L), variant allele frequency: 71.3%; intracytoplasmic vacuoles in bone marrow myelocytes.
Started on tocilizumab.

VEXAS syndrome

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

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

Considered as an autoinflammatory disorder.

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

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

Poor prognosis.

VEXAS syndrome

David B. Beck^{1,2,3}, Sophie Gerardin-Lavialle⁴, Yohei Kirino⁵, Bhavisha A. Patel⁶ & Samuele Ferrari^{1,7}

Abstract

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a disorder discovered in 2020 that bridges haematology, immunology and genetics. VEXAS syndrome arises from somatic mutations in *UBA1*, which encodes an E1 ubiquitin-activating enzyme, acquired in haematopoietic stem cells. These mutations disrupt ubiquitin-dependent protein homeostasis, triggering proteotoxic and inflammatory stress that drives systemic inflammation, cytopenias and clonal haematopoiesis. Clinically, VEXAS syndrome presents predominantly in older men with glucocorticoid-dependent inflammation, neutrophilic dermatoses, chondritis and myelodysplastic features. Diagnosis relies on characteristic clinical features and confirmation of *UBA1* mutations. Prognosis is dismal in many patients, and treatment remains largely empirical. Glucocorticoids and cytokine blockade are used to provide transient control over inflammation, and hypomethylating agents aim to eradicate the mutant clone and induce disease remission. Allogeneic stem cell transplantation offers a potential cure. VEXAS syndrome exemplifies a new paradigm linking somatic genetics, inflammation and clonal haematopoiesis, reshaping our understanding of adult-onset inflammatory disease.

Sectionne

- Introduction
- Epidemiology
- Mechanisms
- Diagnosis, signs and prevention
- Management
- Quality of life
- Outlook

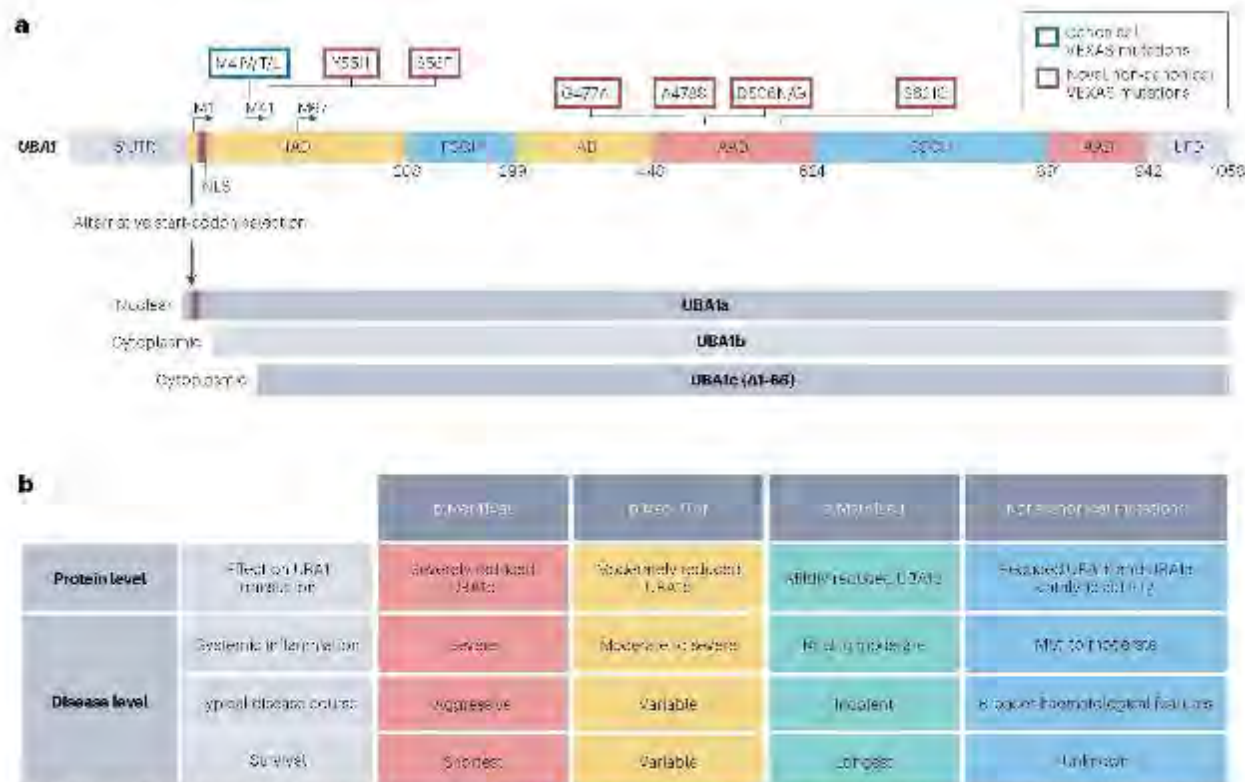


Fig. 1 | Genotype–phenotype correlations in VEXAS syndrome. **a**, Spectrum of canonical and most frequent non-canonical *UBA1* mutations and the effects of canonical mutations on *UBA1* protein isoform translation. **b**, Canonical *UBA1* Mer41 mutations associated with VEXAS (vacuoles, E enzyme, X linked, autoinflammatory, somatic) syndrome (p.Mer41Thr, p.Mer41Val and p.Mer41Leu) differentially affect *UBA1* translation, with p.Mer41Val causing the most severe reduction. These genotype-specific molecular effects correspond to differences in clinical penetrance and survival, with p.Mer41Val associated with the poorest outcomes and p.Mer41Leu with the most favourable outcomes.

Some non-canonical mutations (for example, S56I and G477A) reduce both UBA1 and UBA2 nuclear translocation and the manifestations are not clearly characterized; there is an indication for more prominent and broader haematological phenotype, including peripheral haemolysis of red blood cells, and malignant haematological disease beyond myelodysplasia. AAD, active adenylation domain; FCCH, first catalytic cysteine half domain; IAD, inactive adenylation domain; NLS, nuclear localization signal; SCCH, second catalytic cysteine half domain; UFD, ubiquitin fold domain; UTR untranslated region. Parta adapted from ref. 27, Springer Nature Limited.

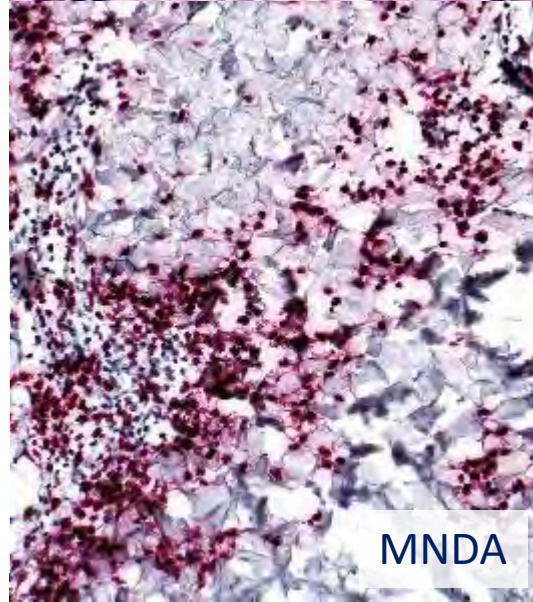
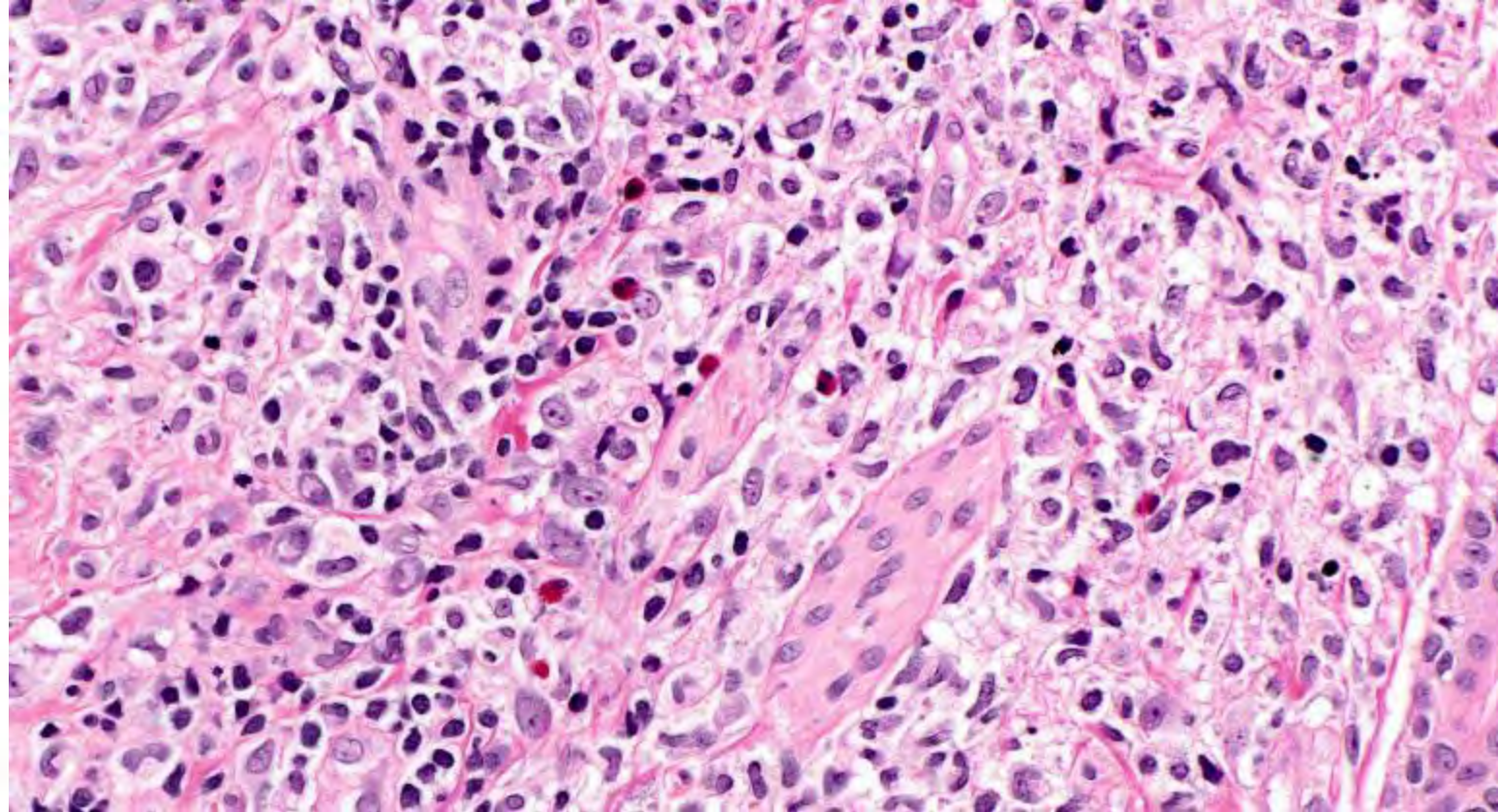
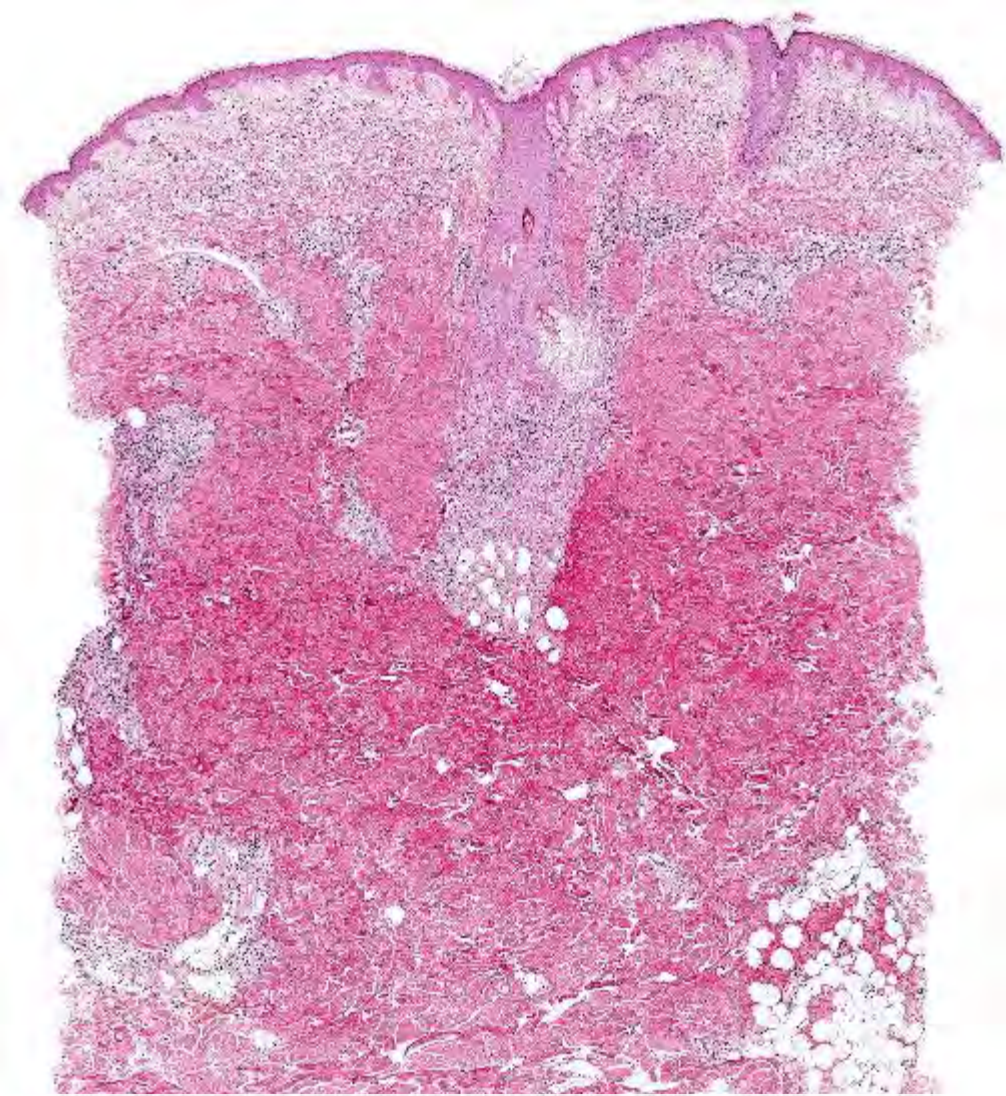
Center for Human Genetics and Genomics, NYU School of Medicine, New York, NY, USA; Department of Medicine, NYU Grossman School of Medicine, New York, NY, USA; Department of Pathology and Immunology, University of Medicine and Dentistry, Newark, NJ, USA; Department of Medicine, New York University School of Medicine, New York, NY, USA; National Defense Science and Engineering Graduate Department, Johns Hopkins University, Baltimore, MD, USA; Institute of Public Health, Johns Hopkins University, Baltimore, MD, USA; Infectious Disease Unit, Johns Hopkins University, Baltimore, MD, USA; Department of Stem Cell and Immunoregulation, Yoshida University, Yamato-cho 53-1, Sakai, Osaka, Japan; Immunology Branch, National Cancer Institute, Lung and Blood Institute, Bethesda, MD, USA; Institute of Health, Biomedical Media, Tokyo, Japan; Institute for Genome Medicine, Johns Hopkins University, Baltimore, MD, USA; Department of Medicine, University of Milan, Italy; Department of Pathology, University of Milan, Italy; Department of Pathology, University of Milan, Italy



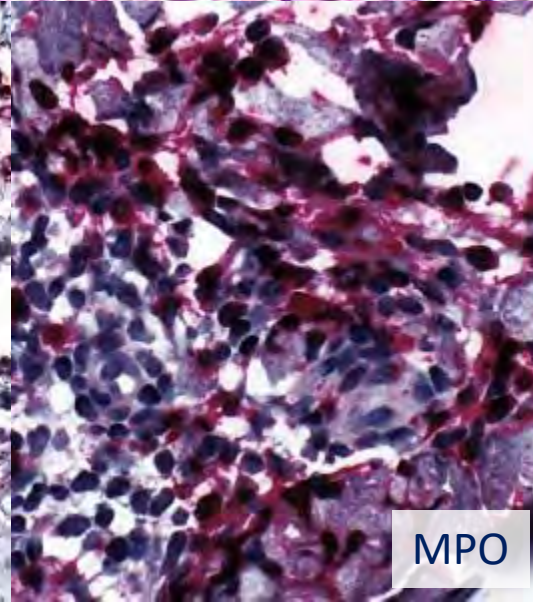
M, 57

Sent by a private dermatologist for evaluation of a recurrent urticaria for the last 3 years.

A biopsy is taken.



MND



MPO



"Histiocytoid" cell dermatitis
VEXAS syndrome
(*UBA1* gene mutation)



1st presentation

1 month later

Changing lesions, yet small and not clearly urticarial; the clinical differential diagnosis would include a Sweet syndrome; presence of histiocytoid cells within the infiltrate should raise the differential diagnosis of VEXAS syndrome in "urticarial" or "Sweet-like" dermatoses.

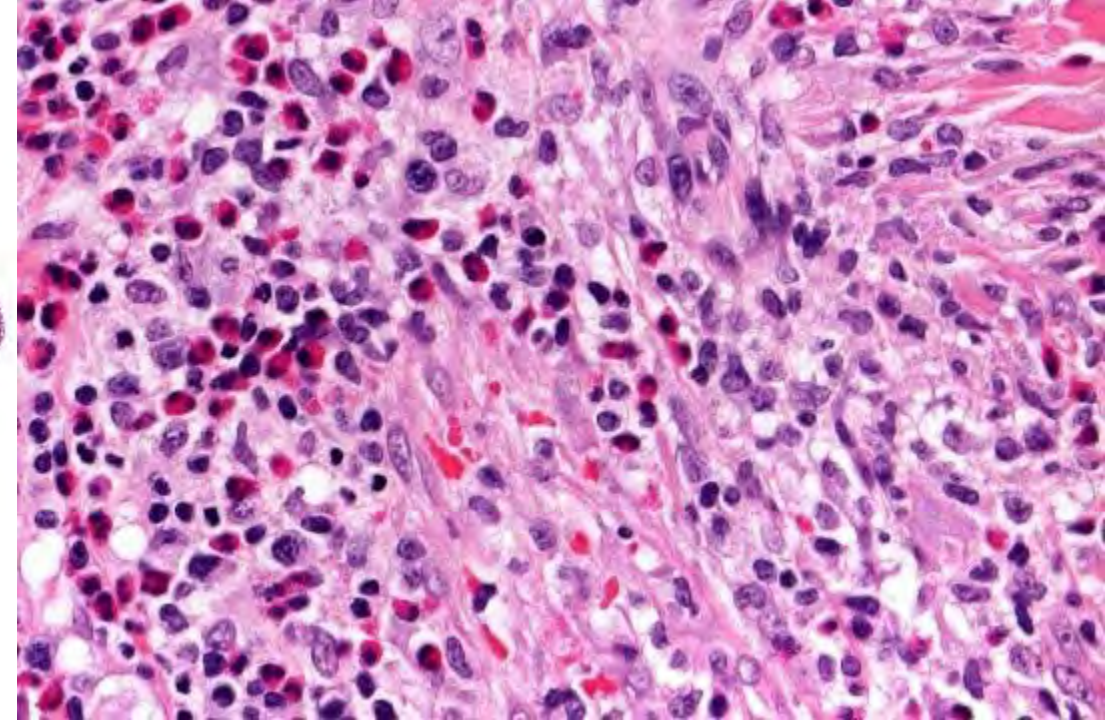
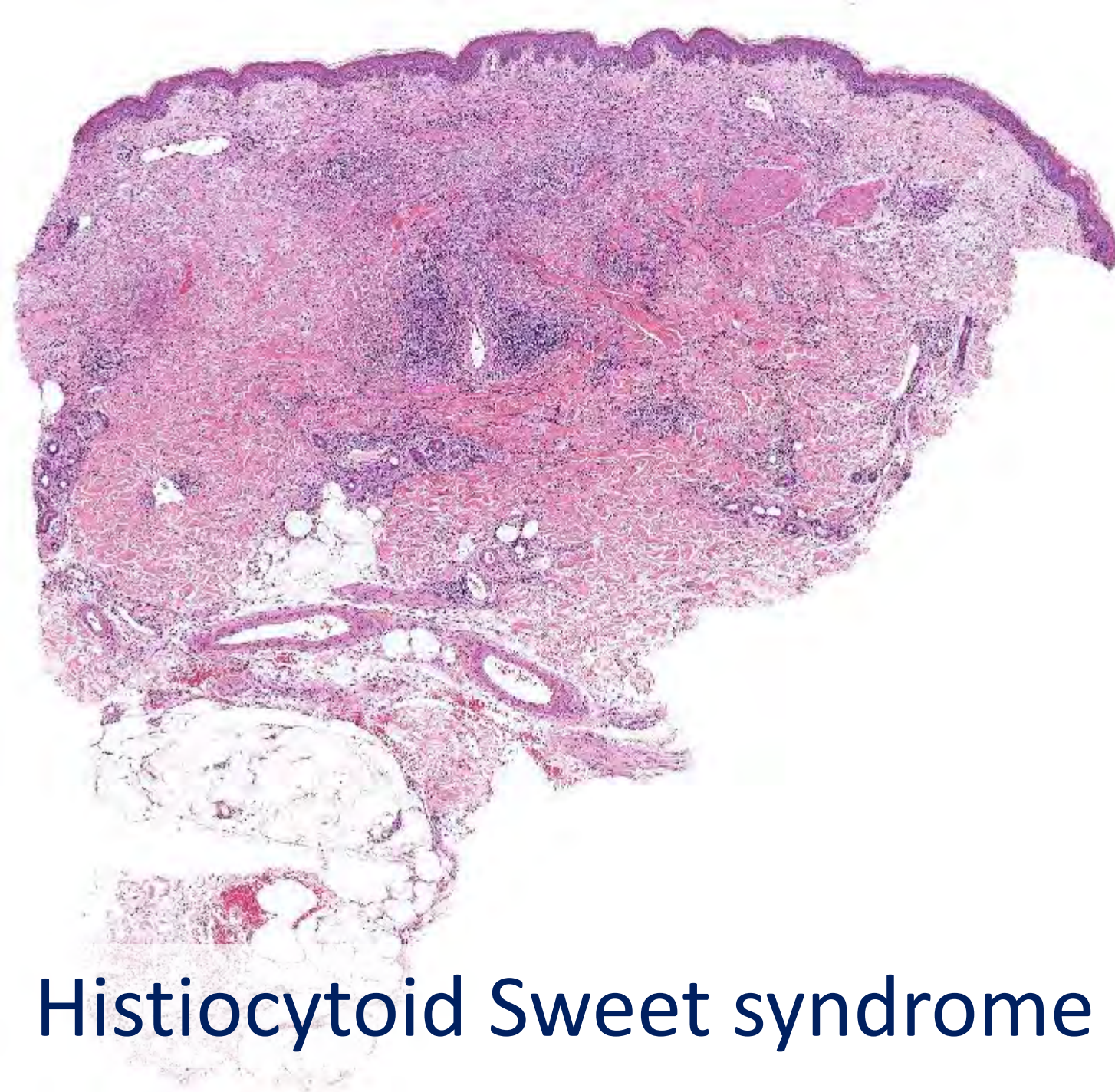


M, 58

According to the patient first onset of "recurring skin lesions" with fever for the last 3 years. In the last months systemic treatment with prednisone 25mg/d, tapered off and stopped a few weeks before presentation.

Since a few days onset of new lesions; fever.

A biopsy is taken.



Histiocytoid Sweet syndrome

Histiocytoid Sweet syndrome may indicate leukemia cutis: A novel application of fluorescence in situ hybridization

Rahul N. Chavan, MD, PhD,¹ Mark A. Cappel, MD,² Rhett P. Kettingling, MD,^{3,4} David A. Wada, MD,¹ Nicole M. Rochet, MD,² Ryan Knudson, BA, MBA,¹ and Lawrence E. Gibson, MD^{1,2,3}
Rochester, Minnesota; Jacksonville, Florida; and Salt Lake City, Utah

Background: In patients with malignancy-associated Sweet syndrome, a thorough evaluation for leukemia cutis should be considered.

Objective: We sought to describe the clinicopathologic characteristics of histiocytoid Sweet syndrome.

Methods: We retrospectively identified patients with histiocytoid Sweet syndrome at our institution from January 1992 through December 2010. We evaluated the underlying cutaneous infiltrate using immunohistochemistry and fluorescence in situ hybridization.

Results: We reevaluated all 22 patients with hematologic malignancy-associated Sweet syndrome. Six patients had a monocytoid infiltrate that was consistent with histiocytoid Sweet syndrome; subsequent evaluation of these patients demonstrated cytogenetic abnormalities on prior bone-marrow biopsy specimens. Fluorescence in situ hybridization analysis was feasible in cutaneous specimens from 5 of the 6 patients and demonstrated the same cytogenetic abnormalities that were identified on prior bone-marrow biopsy specimens in 4 patients. Therefore, these 4 patients may have had a form of leukemia cutis.

Limitations: This was a retrospective study.

Conclusion: For patients with histiocytoid Sweet syndrome, an underlying hematologic malignancy, and a monocytoid infiltrate on biopsy specimen, fluorescence in situ hybridization of the cutaneous infiltrate may be beneficial to identify cytogenetic abnormalities that may indicate leukemia cutis. (J Am Acad Dermatol 2014;70:1021-7.)

Key words: cytogenetic abnormalities; fluorescence in situ hybridization analysis; histiocytoid Sweet syndrome; leukemia cutis; malignancy-associated Sweet syndrome; Sweet syndrome.

In 1964, Sweet syndrome, also known as acute febrile neutrophilic dermatosis, was initially described by Robert Douglas Sweet.¹ Since then, Sweet syndrome has become part of a larger group of dermatologic diseases with an underlying neutrophilic infiltrate.² The diagnostic criteria of Sweet syndrome were delineated by Su and Lu,³ and one of the major criteria required for diagnosis is histopathologic evidence of a neutrophilic infiltrate, typically in the absence of leukocytoclastic vasculitis.³⁻⁵ Sweet syndrome can be associated with an

Abbreviations used

FISH: Fluorescence in situ hybridization
MLL: mixed lineage leukemia gene

underlying hematologic myeloid disorder, solid tumor malignancies, inflammatory bowel disease, and gastrointestinal upset and upper respiratory tract infections.⁶⁻⁹ A number of medications are also known to cause Sweet syndrome.¹⁰⁻¹²

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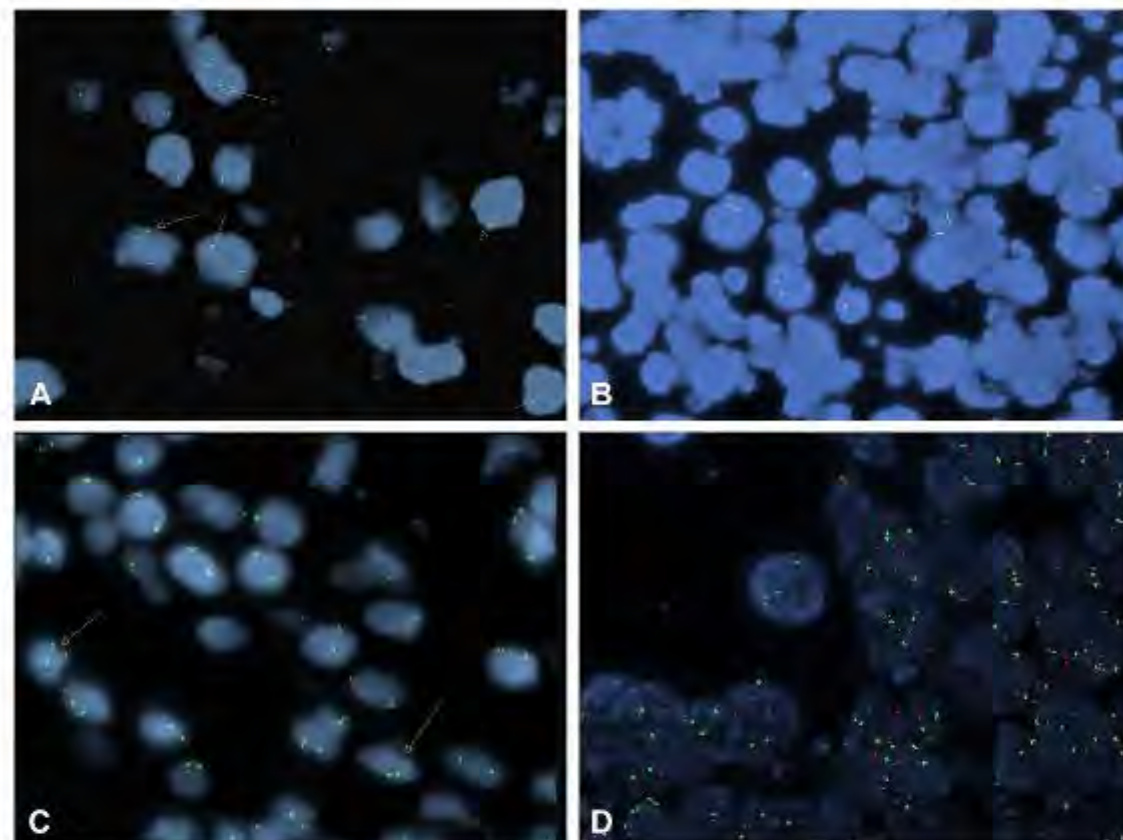


Fig 3. Evaluation of initial cutaneous biopsy specimens with fluorescence in situ hybridization to identify chromosomal abnormalities, which confirmed leukemia cutis in 4 patients. **A**, Arrows indicate fusion of DEK/CAN cells expressing the 6;9 translocation (DEK 6p23, red; CAN 9q34, green) in patient 1, consistent with leukemia cutis. **B**, Cells express the 9;22 translocation resulting in BCR/ABL fusion (ABL 9q34, red; BCR 22q11.2, green) in patient 2, indicative of leukemia cutis. **C**, Cells express the 7q deletion (7q32, red; centromere 7, green) in patient 8. Arrows indicate nuclei with deletion of D7S486, indicative of leukemia cutis in this patient. **D**, Approximately 10% of the cells in patient 12 demonstrated trisomy 8, consistent with leukemia cutis (centromere 8, green; cMYC 8q24.1, red).

Inflammatory Signatures in VEXAS Syndrome, Myelodysplasia Cutis, and Sweet Syndrome

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IMPORTANCE VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a hereditary disease caused by UBA1 somatic variants in hematopoietic progenitor cells, mostly involving adult men. It is associated with inflammatory-related symptoms, frequently involving the skin and other organically systems. Recently described myelodysplasia cutis (MDS-cutis) is a cutaneous manifestation of myelodysplasia in which clonal myelodysplastic cells infiltrate the skin. In both cases, skin lesions are driven by the infiltration of clonal activated myeloid cells and clinically and histologically mimic Sweet syndrome (SS), a neutrophilic skin disease.

OBJECTIVE To decipher the underlying mechanisms driving these 3 myeloid-related skin diseases (ie, VEXAS, MDS-cutis, and SS) compared with leukemia cutis (LC), a neoplastic process (ie, clonal skin condition), and healthy control (HC) skin samples.

DESIGN, SETTING, AND PARTICIPANTS This multicenter retrospective study on French patients had 10-year embedded skin samples of VEXAS syndrome, MDS-cutis, idiopathic SS, LC, and healthy controls using bulk RNA sequencing analyses was conducted in France. Patients included had a range of lesions of VEXAS syndrome, MDS-cutis, idiopathic SS, or LC. The data were analyzed from June 2022 to March 2024.

MAIN RESULTS AND MEASURES Differentially expressed genes between conditions were studied. These genes were used to characterize the environment in activated inflammatory pathways in each condition using Gene Set Enrichment Analysis and Ingenuity Pathway Analysis.

RESULTS Twenty patients with skin conditions (median [range] age, 67 [43–88] years; 11 [55%] men) were included. We had cutaneous lesions of VEXAS syndrome, 4 had MDS-cutis, 5 had idiopathic SS, and 5 had LC. They were compared with 5 healthy control skin samples. Bulk RNA sequencing analysis reveals that MDS-cutis and VEXAS syndrome lesions display closely related transcriptional profiles, highly enriched by cytokine responses, interferon signatures, and activation of the apoptosis pathway. A shared inflammatory environment between MDS-cutis, VEXAS syndrome, and idiopathic SS was observed, mostly relying on type I immune response (ie, type I and II interferons), along with the activation of tumor necrosis factor and interleukin (IL)-12 pathways. Conversely, LC is lower, activated transcriptional profile mainly enriched in cell cycle pathways.

CONCLUSIONS AND RELEVANCE The findings of this translational study highlight a common inflammatory pattern shared between VEXAS syndrome, MDS-cutis, and idiopathic SS skin samples. This suggests the potential for stratifying of interferon pathways in skin as affected with refractory nonbacterial myeloid-related skin diseases.

Supplemental content

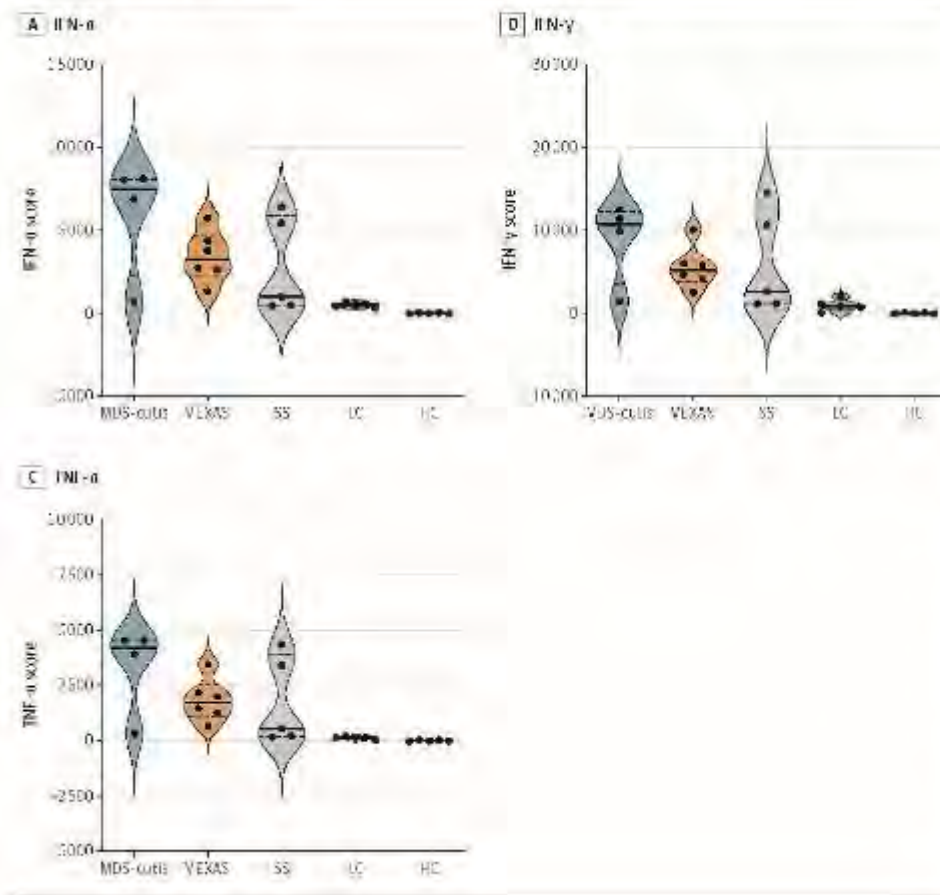
Author Affiliations: Author affiliations are found at the end of this article.

Occupational Information: The members of the IRIS-VEX Group appear in Supplement 3.

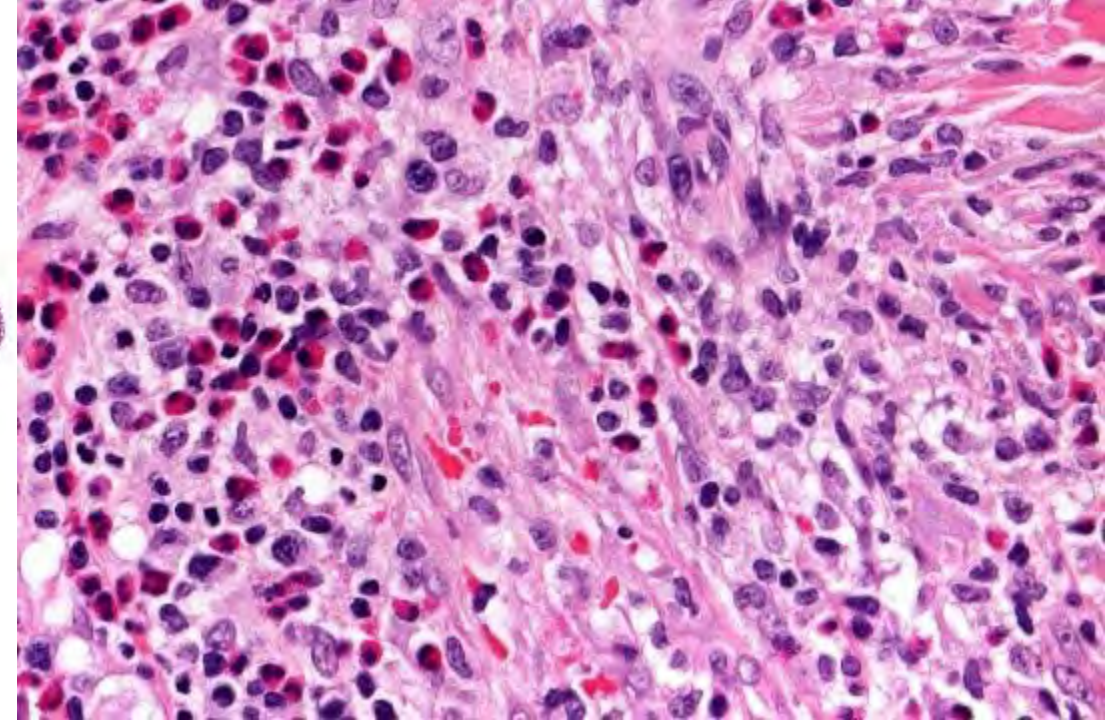
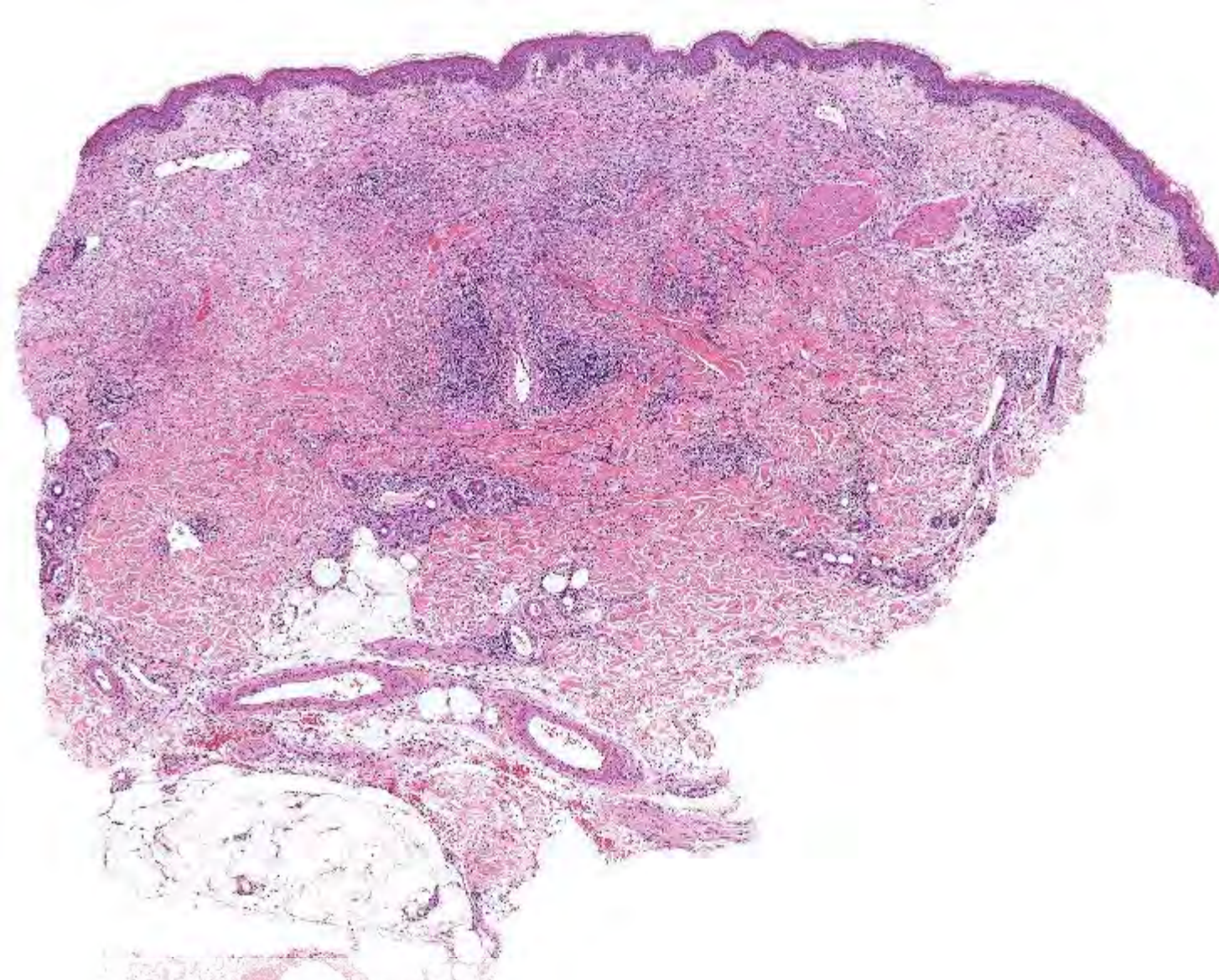
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Figure 2. Pathways Associated With Inflammation in VEXAS syndrome, Myelodysplasia Cutis (MDS-Cutis), and Sweet Syndrome (SS) Lesions



Z score of interferon (IFN)-α, IFN-γ, and tumor necrosis factor (TNF)-α responses were computed for VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, MDS-cutis, SS, and leukemia cutis (LC) compared with healthy control (HC) samples based on the Gene Set Enrichment Analysis (Hallmark dataset). Medians are represented by solid black lines and quartiles by dashed lines. Statistical tests performed included 1-way analysis of variance followed by Kruskal-Wallis posttest with HC set as reference.

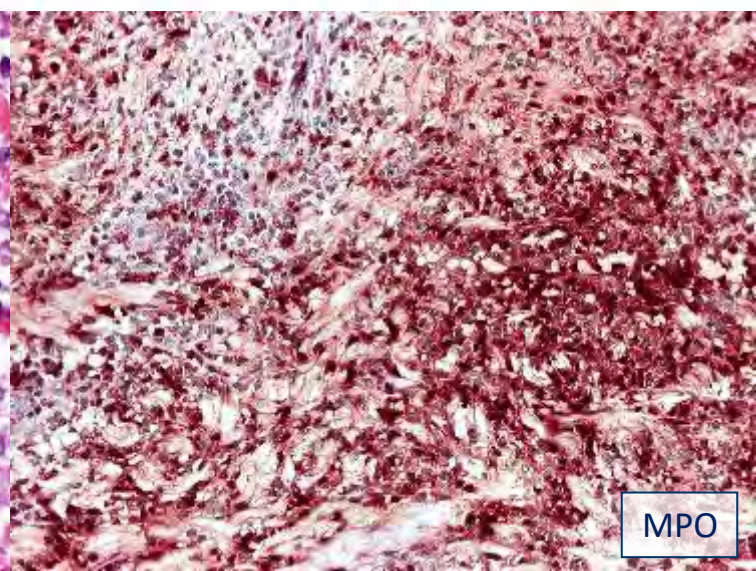
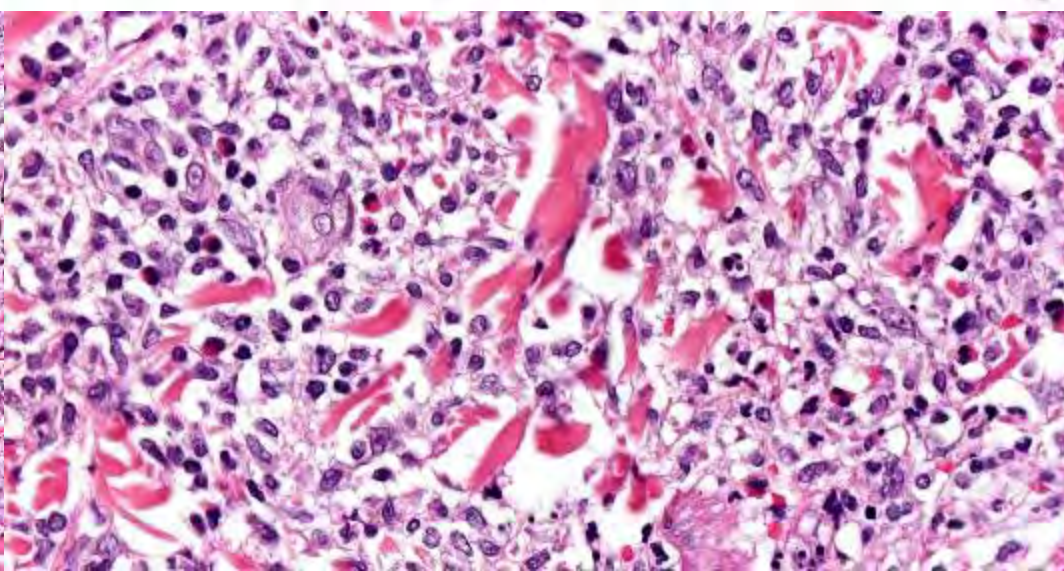
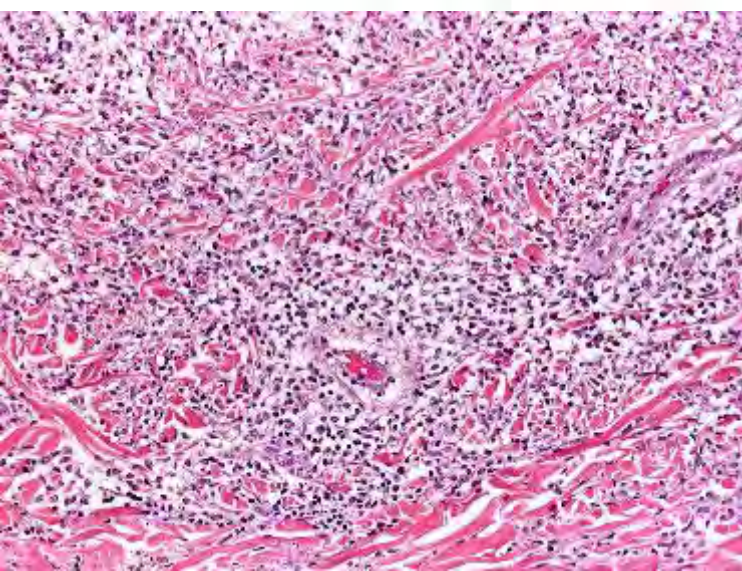
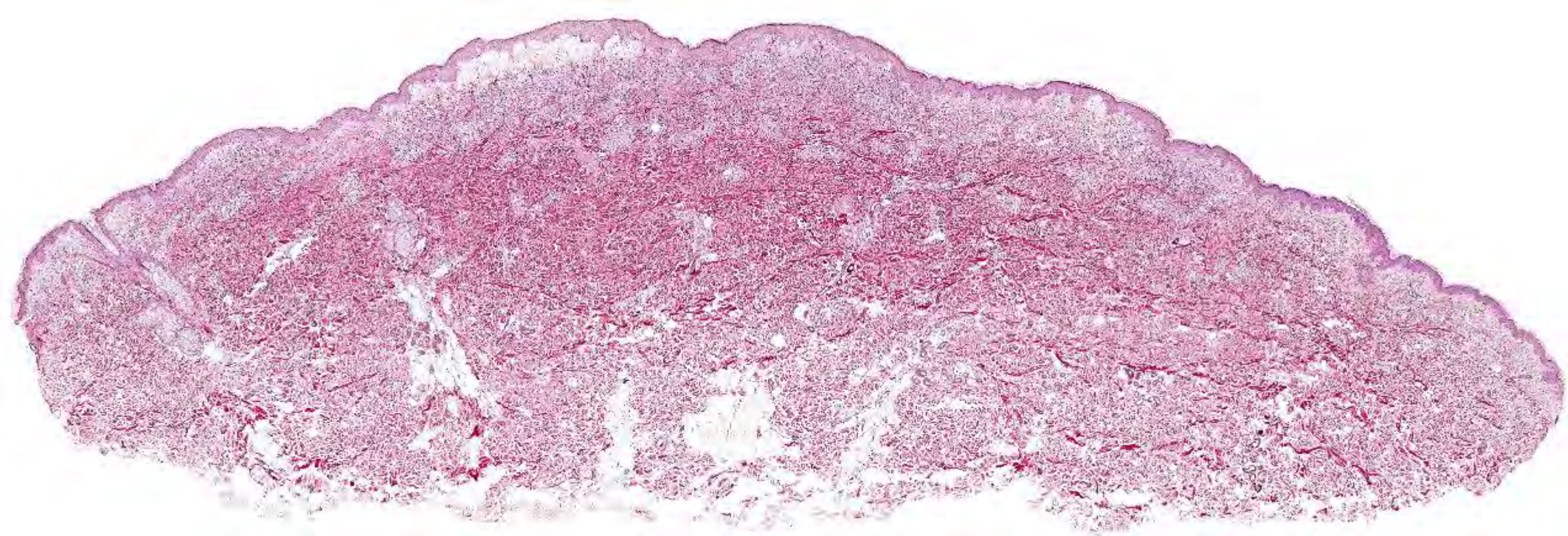


Histiocytoid Sweet syndrome

As a marker of a hematological disorder ?

1 year later (new biopsy)







1st presentation



1 year later

3-year history of recurrent skin lesions with fever. Managed with systemic steroids with good response but with recurrences after tapering the steroids. Hematological investigations (including bone marrow biopsy) negative. Several recurrences, always with fever, in the 6 years following first observation. No development of a hematological disease. Died of a cerebrovascular accident 6,5 years after first presentation (without any sign of a hematological disorder).

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Histiocytoid Sweet's Syndrome: A localized cutaneous proliferation of macrophages frequently associated with chronic myeloproliferative disease

Background: Histiocytoid Sweet's syndrome was originally described as cutaneous lesions of Sweet's syndrome where the infiltrate is mostly composed of histiocytoid mononuclear cells. The putative cell has been interpreted as an immature neutrophil based on the intense expression of myeloperoxidase. **Methods:** To better understand the nature of the infiltrate and potential mechanisms leading to this distinct form of cutaneous inflammatory cell influx, thirteen cases of histiocytoid Sweet's syndrome, encountered in the routine and consult practice of one of the authors, were studied. The clinical features and microscopic findings are summarized. **Results:** The study comprised eight men and five women aged from 23 to 80. There was a significant association with underlying myeloproliferative disease. In particular, five patients had underlying myelodysplastic syndrome. One patient had unspecified chronic myeloproliferative disorder and another had AML. Two cases were triggered by drug therapy (Cox-2 inhibitors). One patient had familial Mediterranean fever. The eruption was asymptomatic and an aggressive clinical course was not observed in most cases. Skin biopsies were composed of striking angiocentric and interstitial mononuclear cell infiltrates, often accentuated in the deeper dermis and subcutaneous fat. There was marked leukocytoclasia. Neutrophils were sparse or absent. These cells were strongly positive for CD163 and either expressed CD16 or myeloperoxidase. Variable positivity for myeloid dendritic cell markers including CD11c, BDCA-3, TCL1 oncogene, MxA and CD123 was observed. **Conclusion:** The histiocytoid cells of histiocytoid Sweet's syndrome define a novel subset of activated monocyte. This variant of Sweet's syndrome has a significant association with underlying myeloproliferative disease.

Key words: histiocytoid Sweet's syndrome, Sweet's syndrome, clonal cutaneous monocytosis

Article received on 29/2/05

13 cases

5 patients had MDS

1 patient had AML

1 patient had unspecific chronic myeloproliferative disorder

described histiocytosis, Sweet's syndrome, in patients with underlying myeloproliferative disorders [2, 5, 6, 9, 15, 26, 28].

Herein, we describe 13 cases of triglyceridemia-Sweet's syndrome. We propose an infectious trigger for this disorder, & further understanding of this elevated triglyceride and profound leukocytosis leading to this distinct form of an eruption.

Materials and methods

Thirteen cases of histiocytoid Sweet's syndrome were retrieved from the constitutive files of one of the authors during the time frame of 2008 to 2014. Nine of these cases were presented in an abstract form at the United States

Historically, the term has been used to describe a disease resembling histiocytoid Sweet's syndrome [2-28]. Given the possibility of the influence for MPO, it was originally hypothesized that the monocyteoid cells implicated in histiocytoid Sweet's syndrome represented immature neutrophils in a state of maturation arrest. Although the original series reported underlying myelophagoid leukaemia in only 7 (21%) cases, there have been a number of subsequent miners which

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Research

JAMA Dermatology | Original Investigation

Clinicopathologic, Immunohistochemical,
and Molecular Features of Histiocytoid Sweet Syndrome

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Keywords: *Self-esteem, self-esteem threat, self-esteem threat sensitivity, self-esteem threat sensitivity scale, self-esteem threat sensitivity scale-2*

IMPORTANCE Histocytoid Sweet syndrome is a rare histopathologic variant of Sweet syndrome. The nature of the histocytoid infiltrate has generated considerable controversy in the literature.

OBJECTIVE: The main goal of this study was to conduct a comprehensive overview of the hematologic and clinical phenotype of the infant with a hemolytic disorder and Sweet syndrome. We also analyze whether this variant of Sweet syndrome is more frequently associated with hematologic malignancies than classic Sweet syndrome.

DESIGN This is a retrospective case series study of the clinicopathologic, immunohistochemical, and molecular features of 55 patients with a dermally originating diagnosis of histiocytoid Sweet syndrome who was conducted in the dermatology departments of University hospitals and a research laboratory of dermatopathology.

MAIN RESULTS AND MEASUREMENTS: The clinical, histopathological, immunohistochemical, and follow-up features of 22 patients with histiocytoid Sweet syndrome were analyzed. In some cases, cyrogenetic studies of the dermal infiltrate were also performed. We compare our findings with those of other authors.

RESULTS There was no difference in the age of the 35 study patients (23 females; median age, 48 years; age range, 5–95 years; and 12 male; median age, 42 years; age range, 4–95 years) who were mainly composed of myeloperoxidase-positive human neutrophilic granulocytes with histioid morphology. No cytogenetic anomalies were found in the infiltrate except in 1 case in which neoplastic cells of chronic myelogenous leukaemia were intermingled with the cells of histioid Sweet's syndrome. Anti-leukoblastic agents were also used in our most cases with a mixed immunoprofile, but they appeared to be a minor component of the infiltrate. Histioid Sweet's syndrome was not more frequently related with haematologic malignancies than classical neutrophilic Sweet's syndrome.

CONCLUSIONS AND RELEVANCE The dermal infiltrate of cutaneous lesions of histiocytosis X (Sweet syndrome) is composed mostly of immature cells of myeloid lineage. The infiltrate should not be interpreted as leukemic cutis.

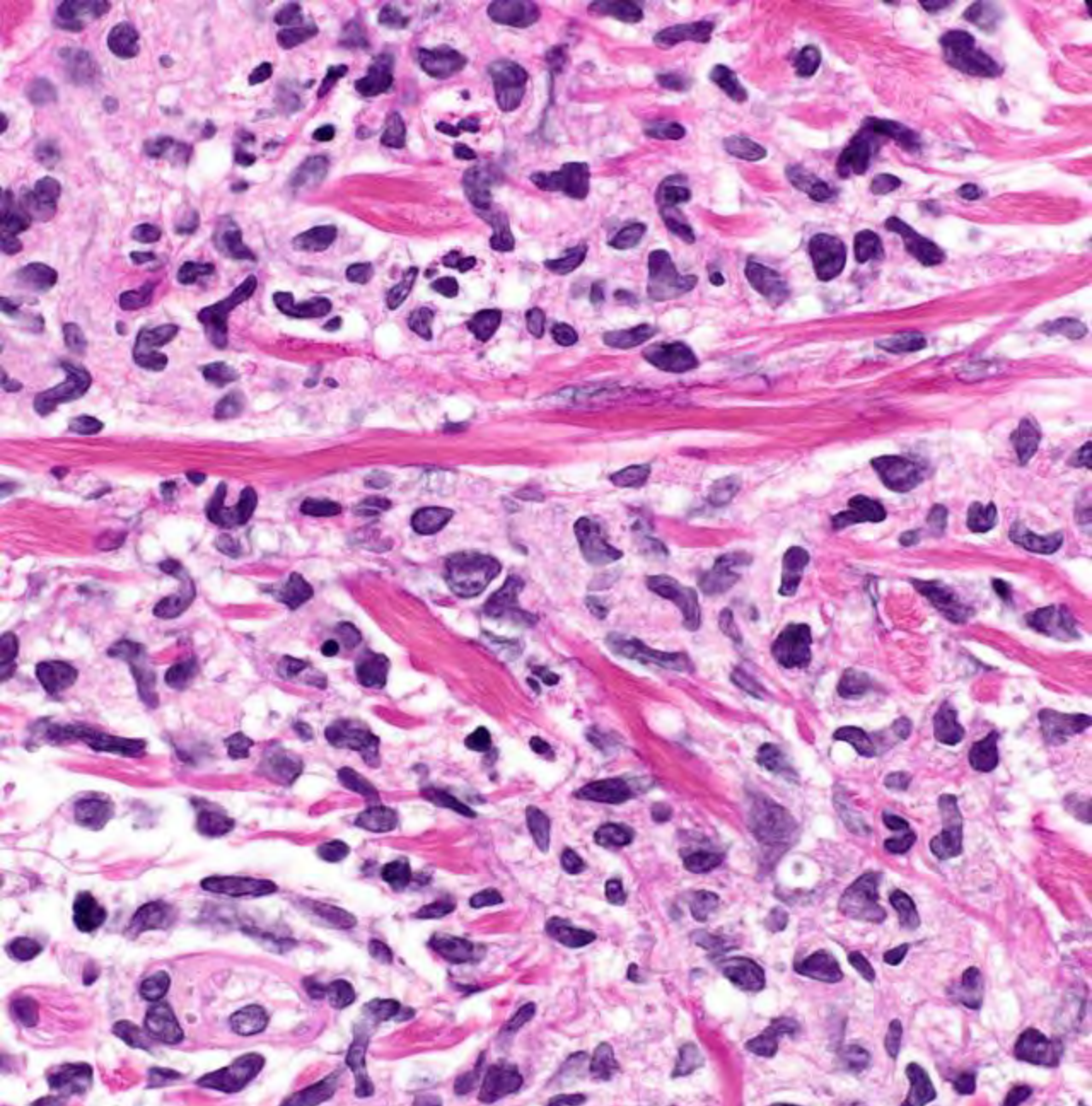
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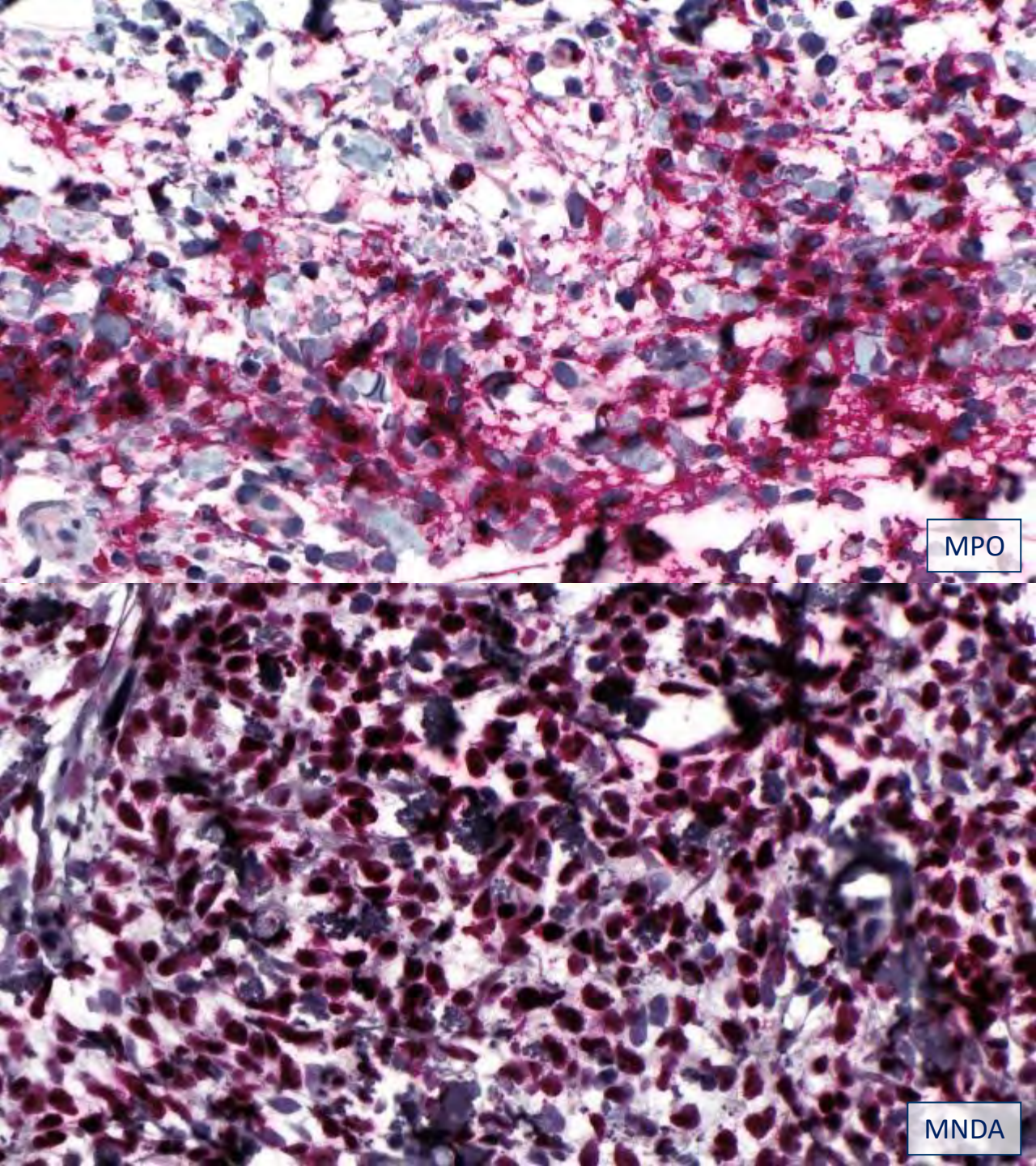
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 alch@iastate.edu

33 cases

1 patient had CML



Histiocytoid cells (immature myeloid cells) may be the marker of a hematological disorder, but their presence is not synonymous with it



MPO

MNDA