CASES FOR SUMMER ACADEMY OF DERMATOPATHOLOGY-2025

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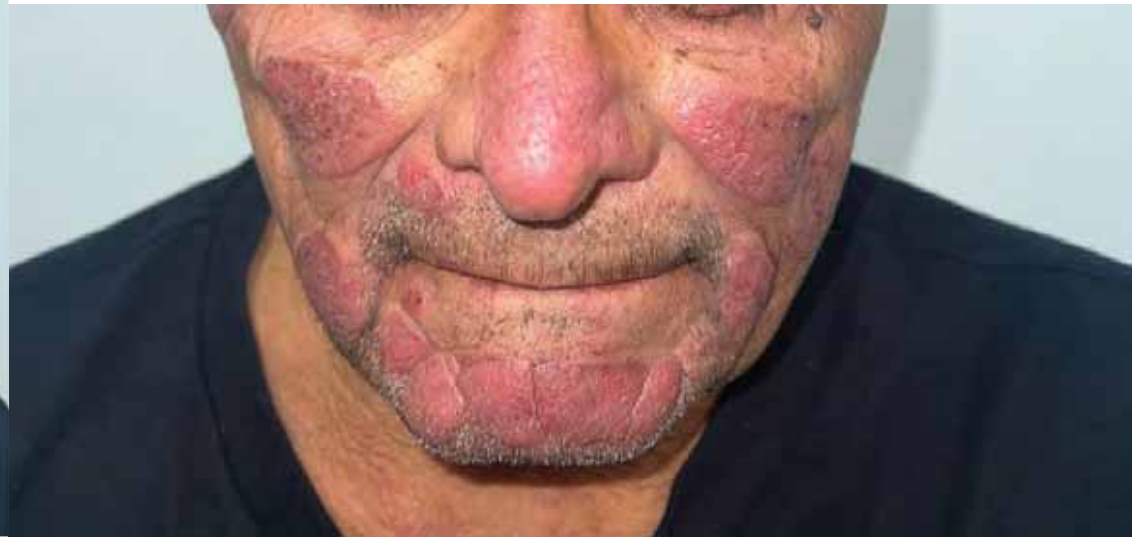
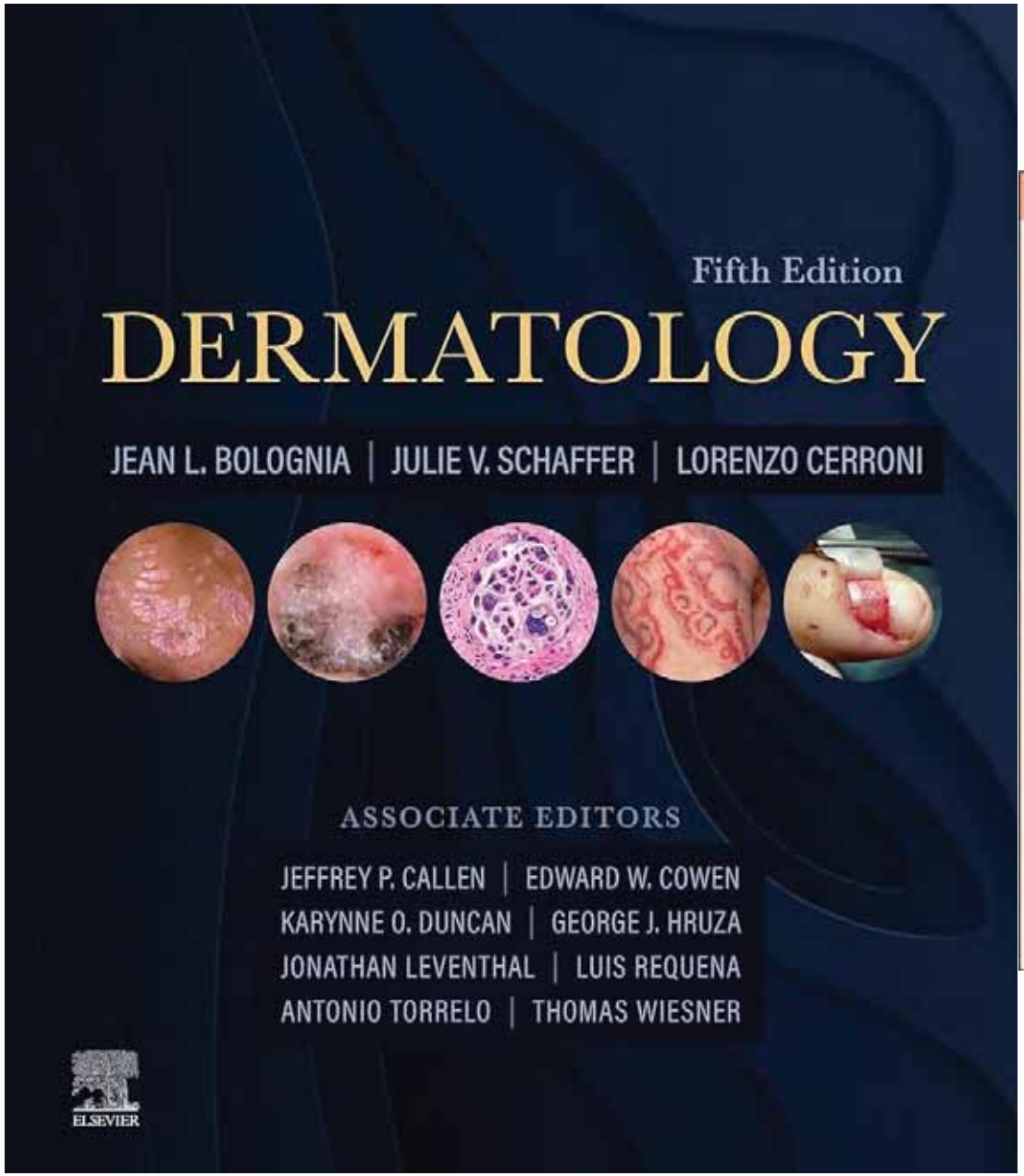
Fundación Jimenez Díaz, Universidad Autónoma,
Madrid, Spain

Case 1

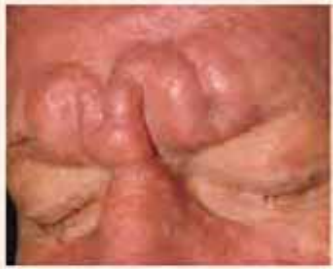
- A 71-year-old male, born in Paraguay, presented with erythematous plaques on the face that developed along the last two years. No systemic manifestations

Consultation from Dr. Laura Nájera, Madrid





LEONINE FACIES – ASSOCIATED DERMATOLOGIC DISEASES



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Viral-associated trichodysplasia
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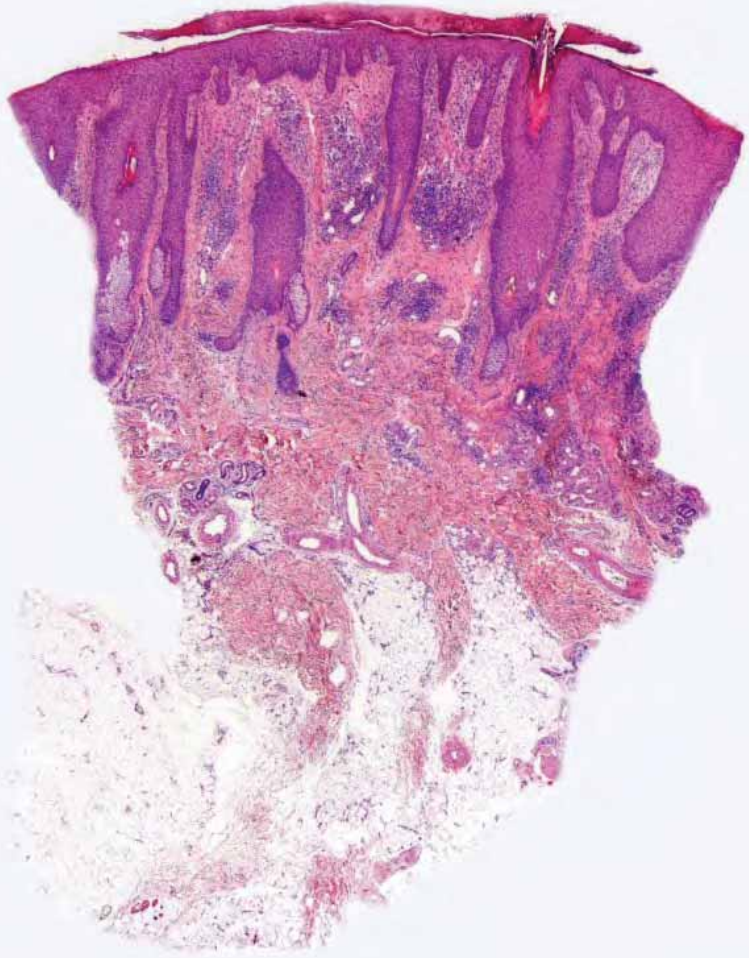

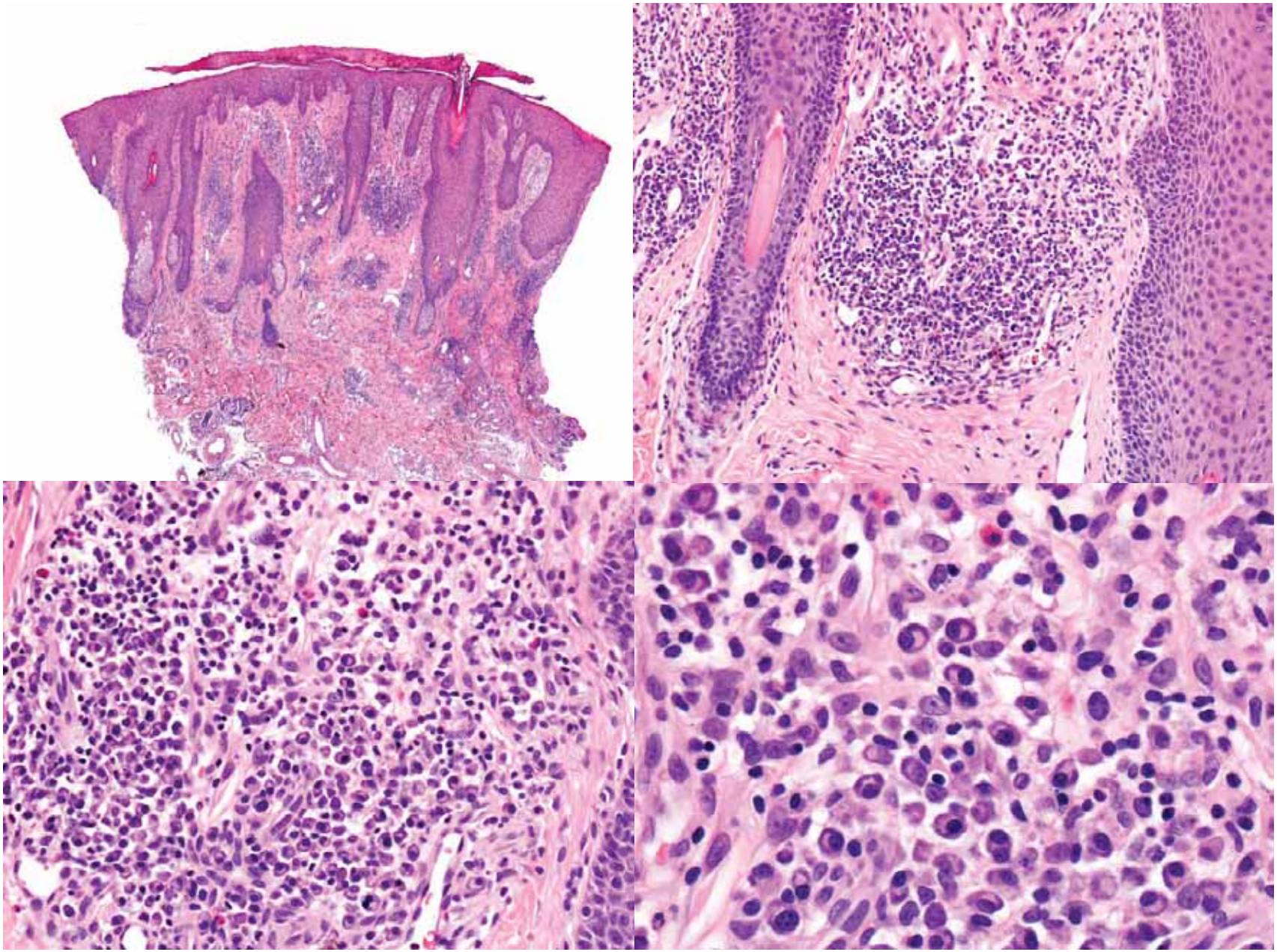

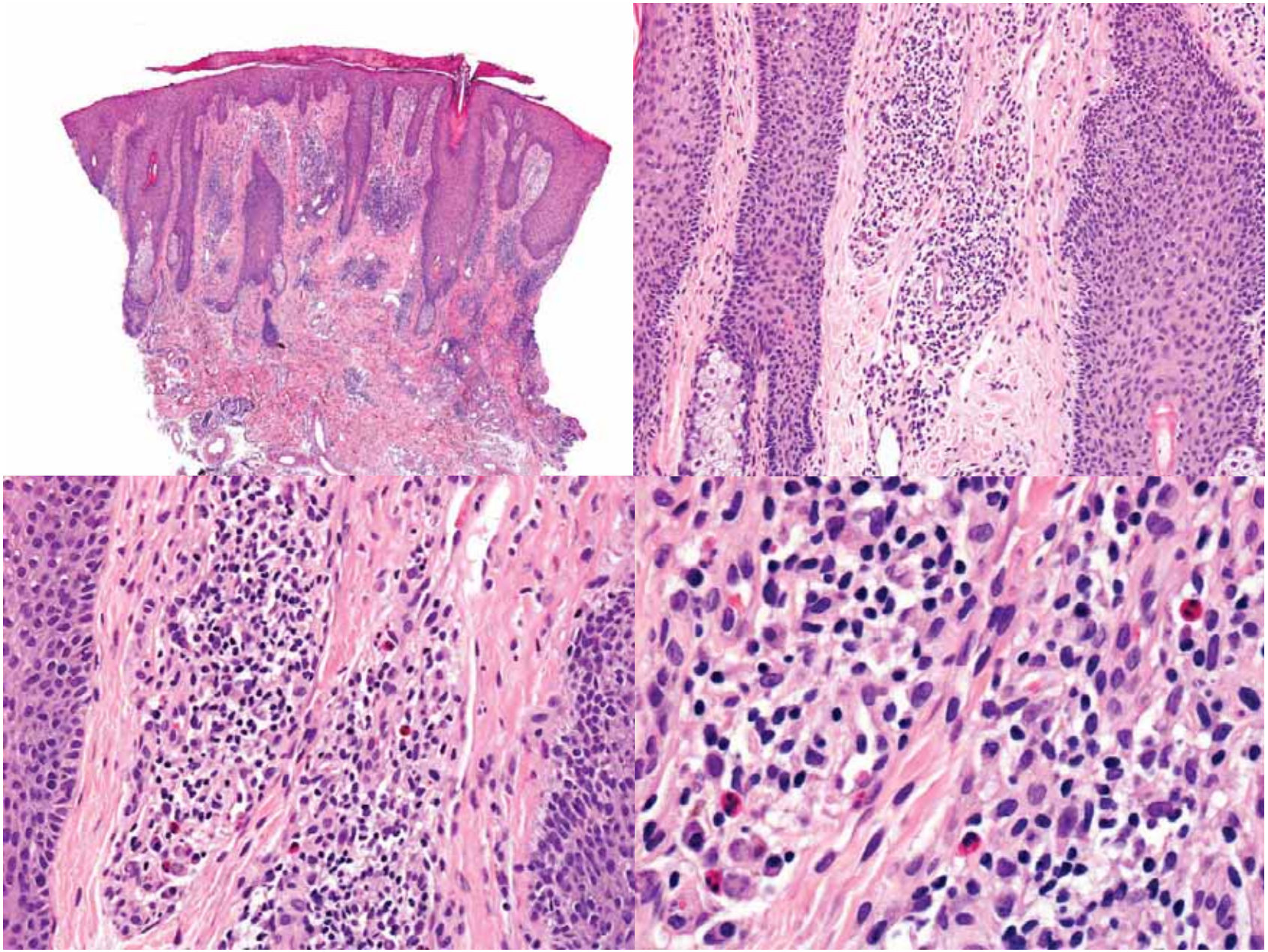

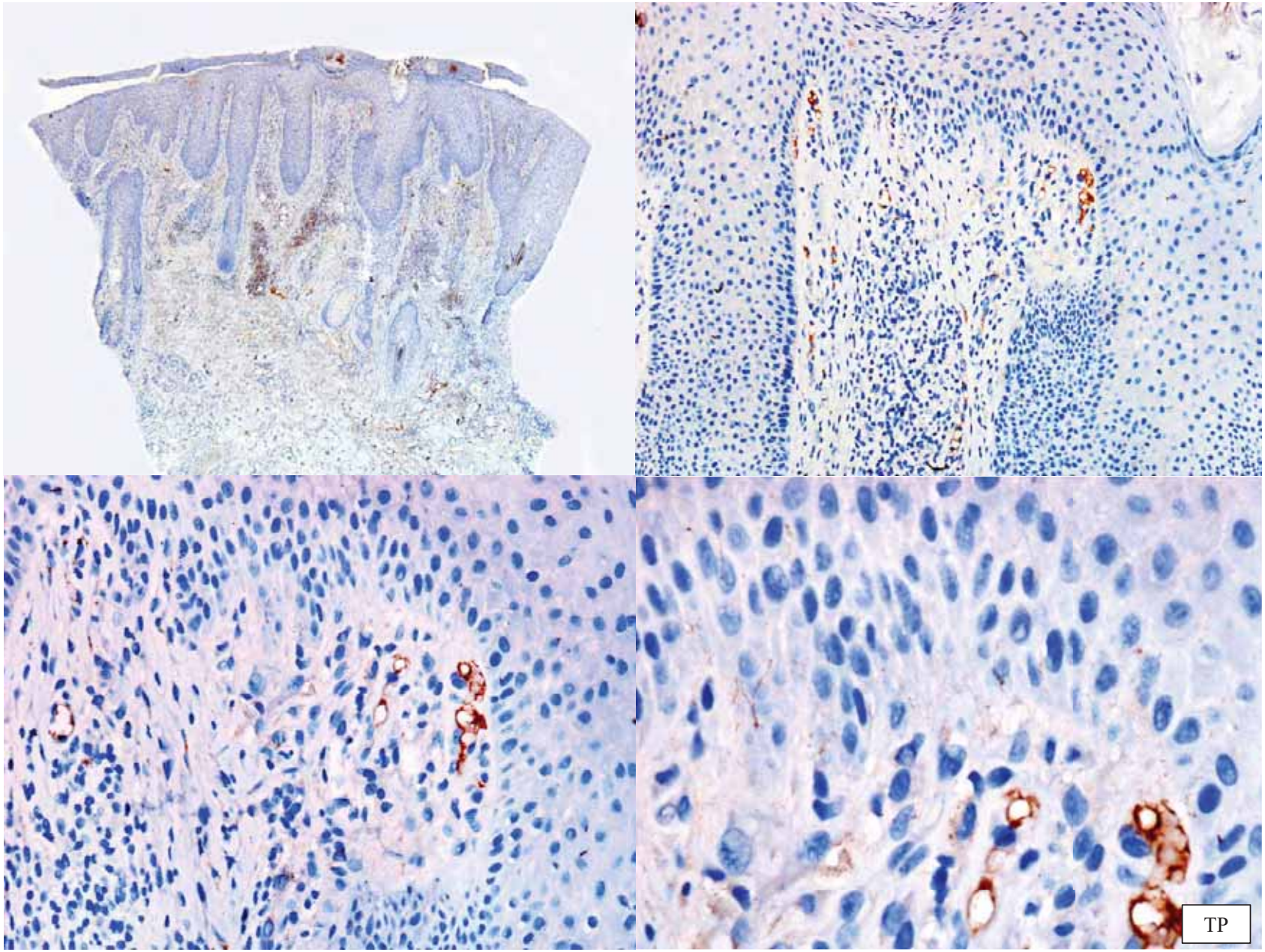
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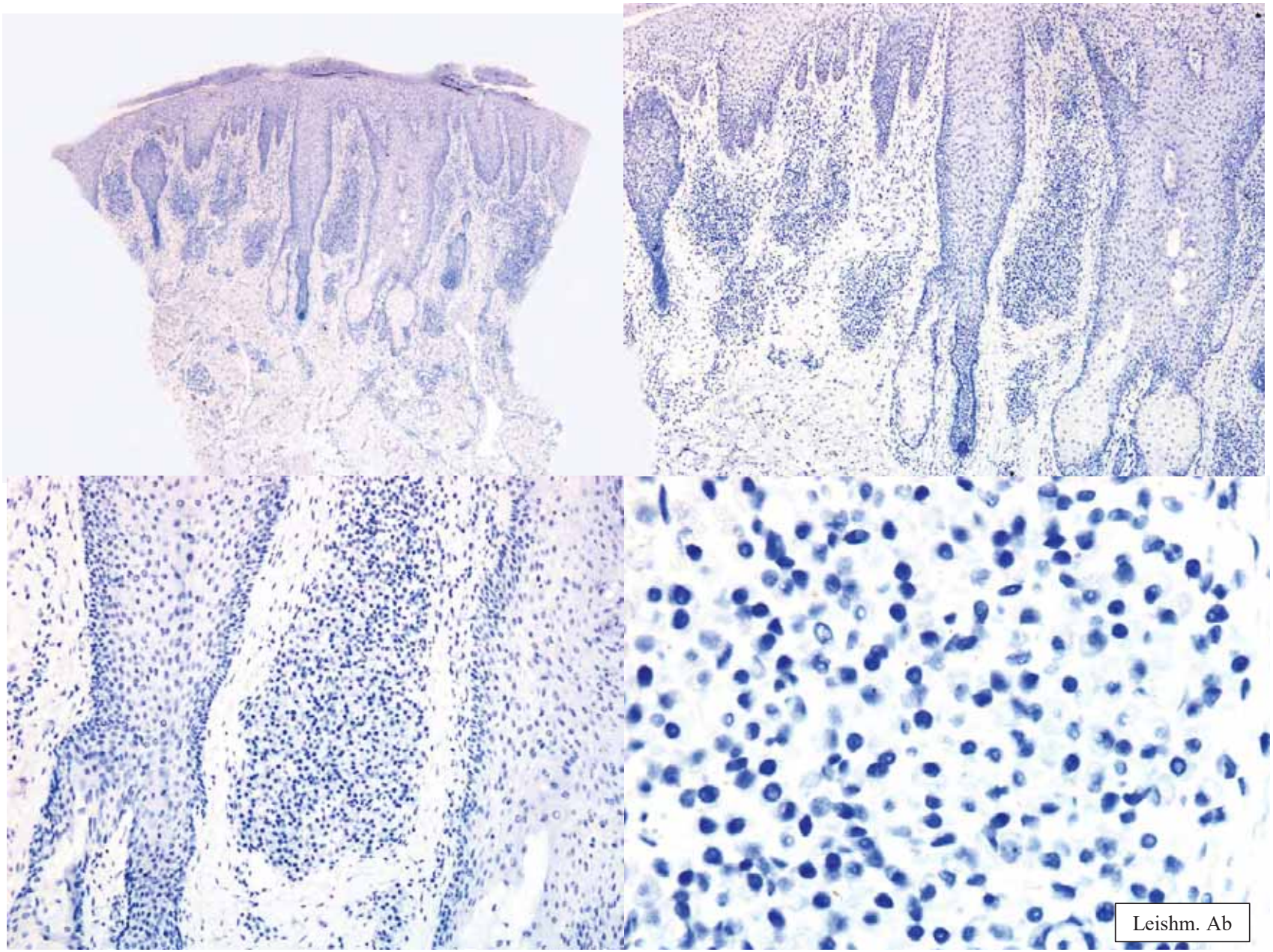
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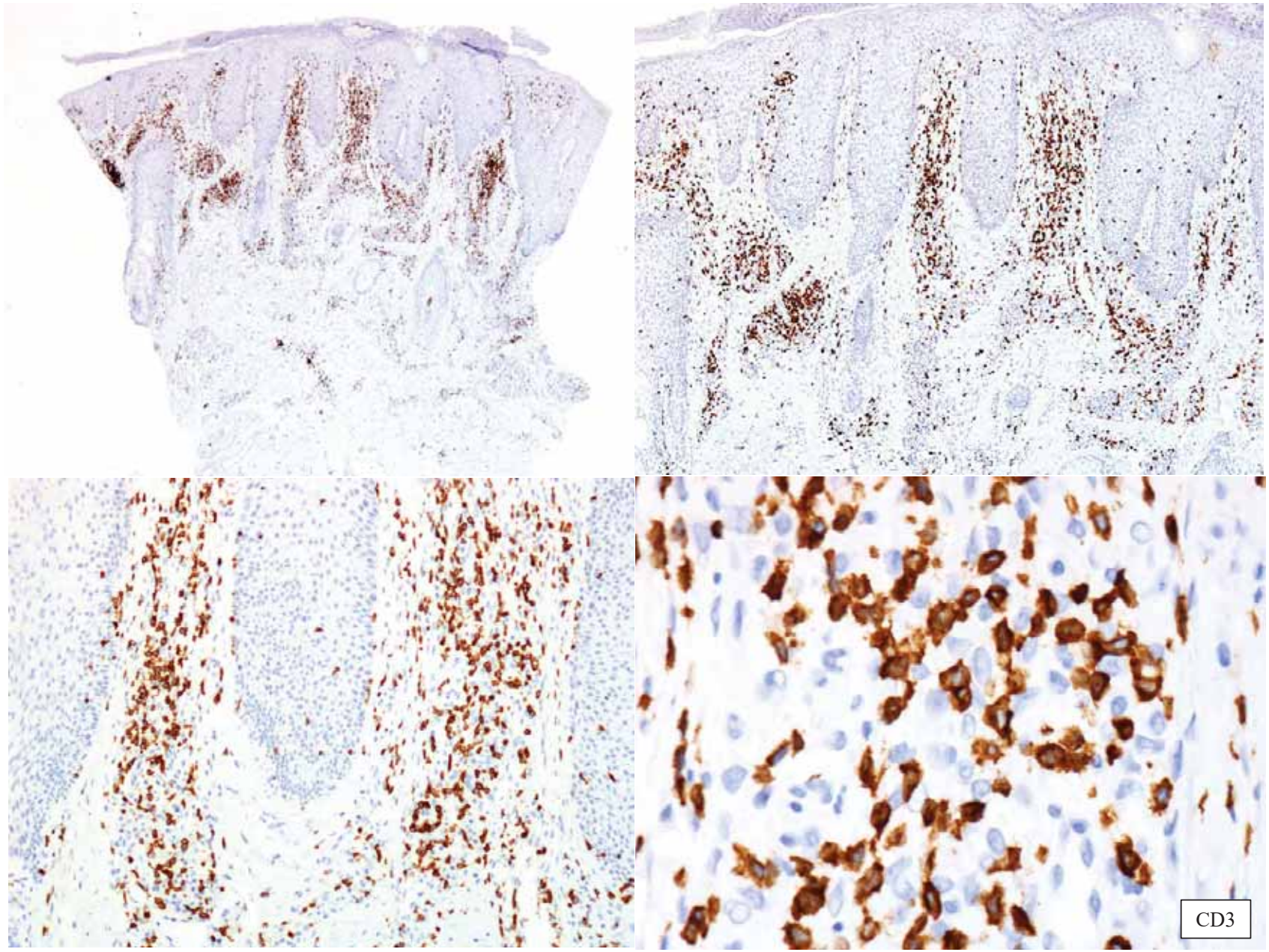
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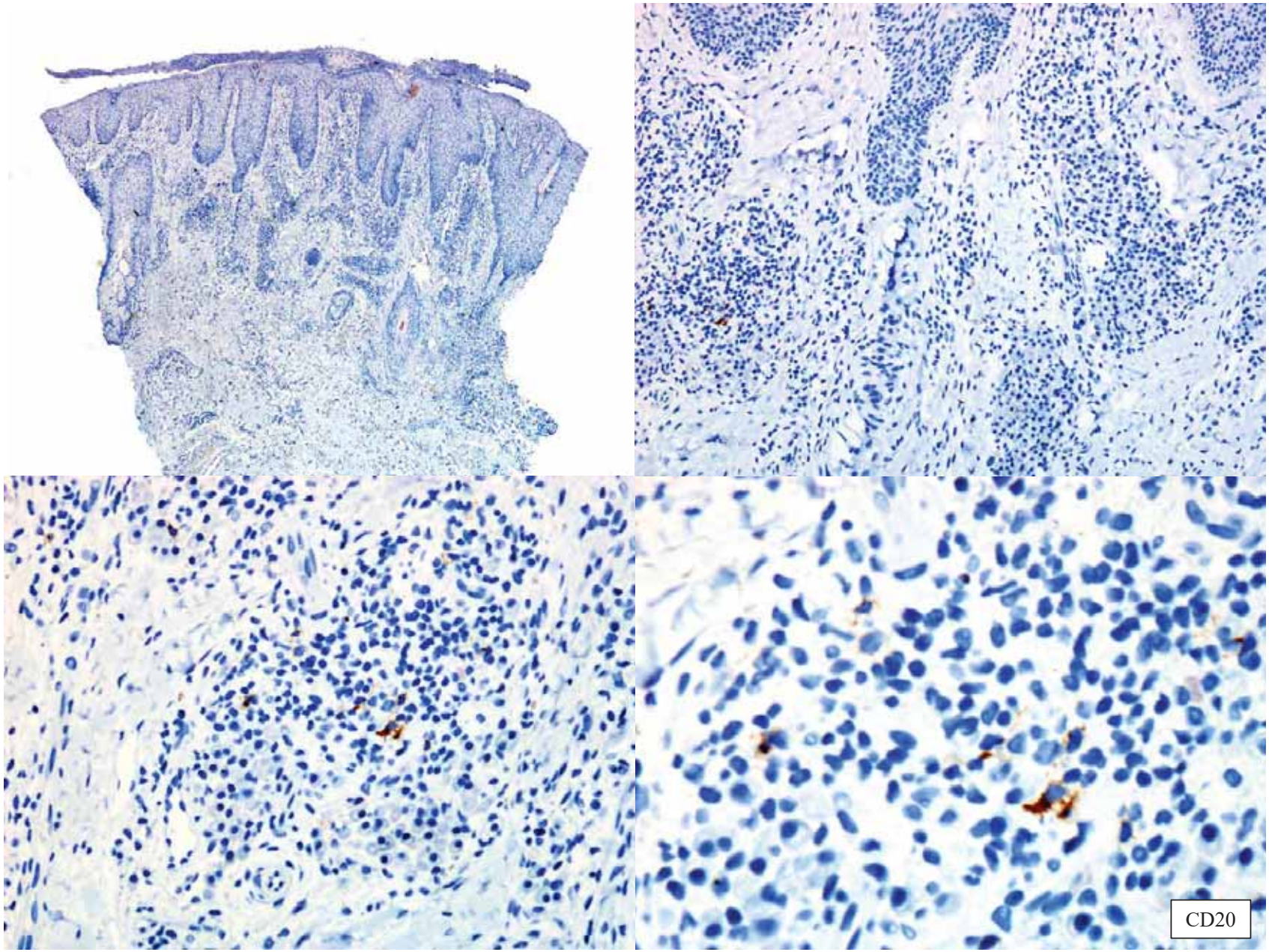
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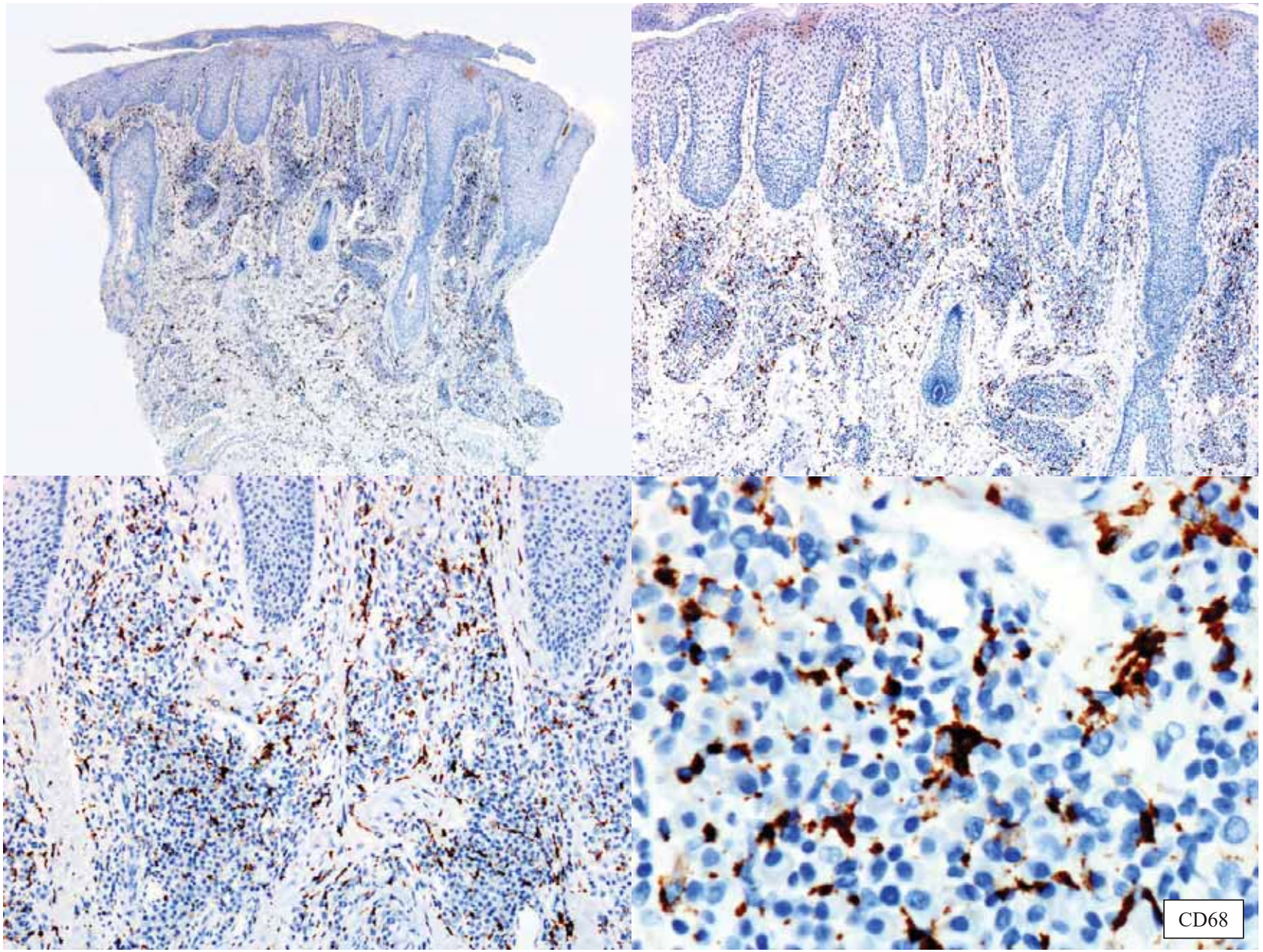
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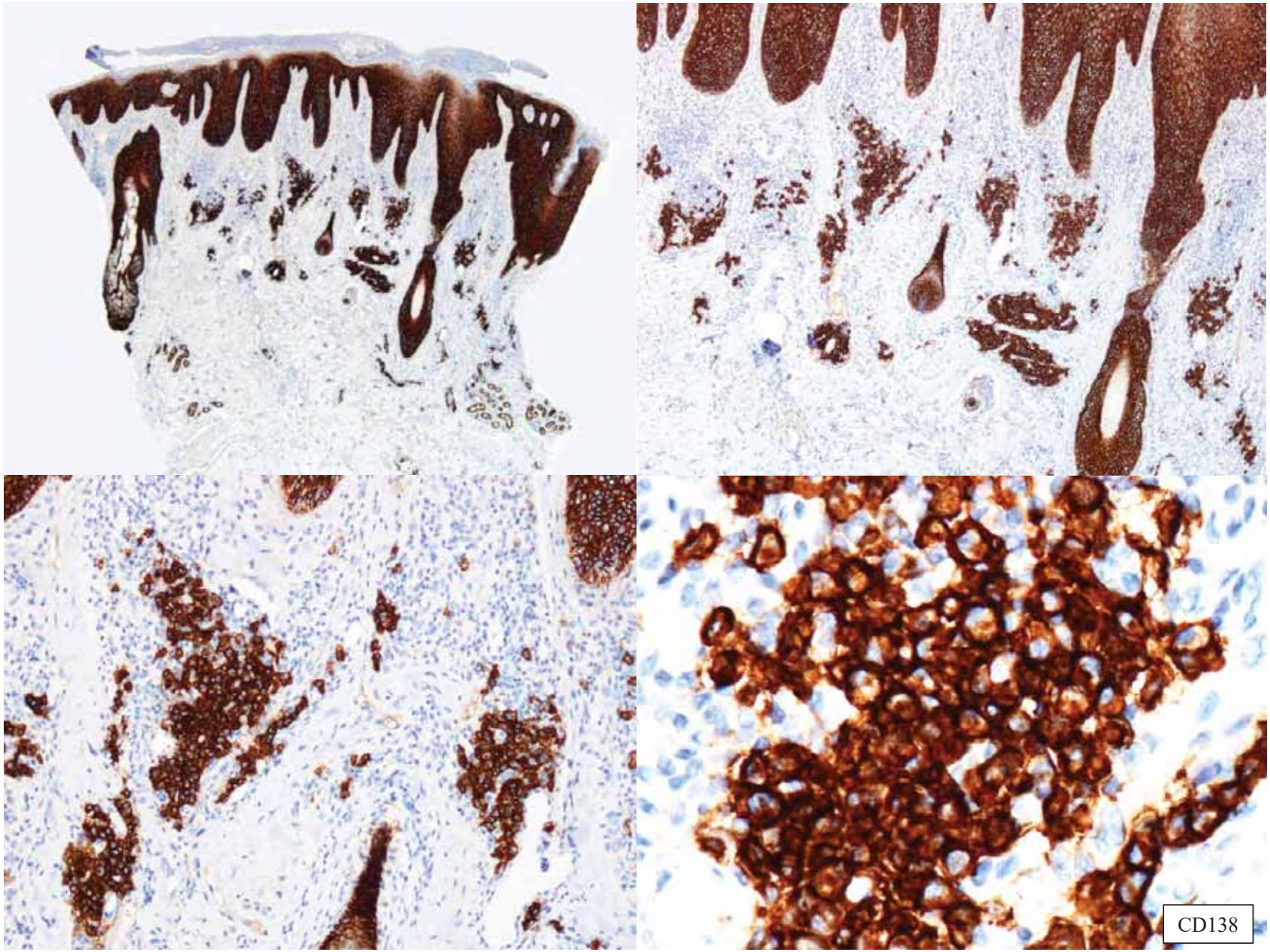
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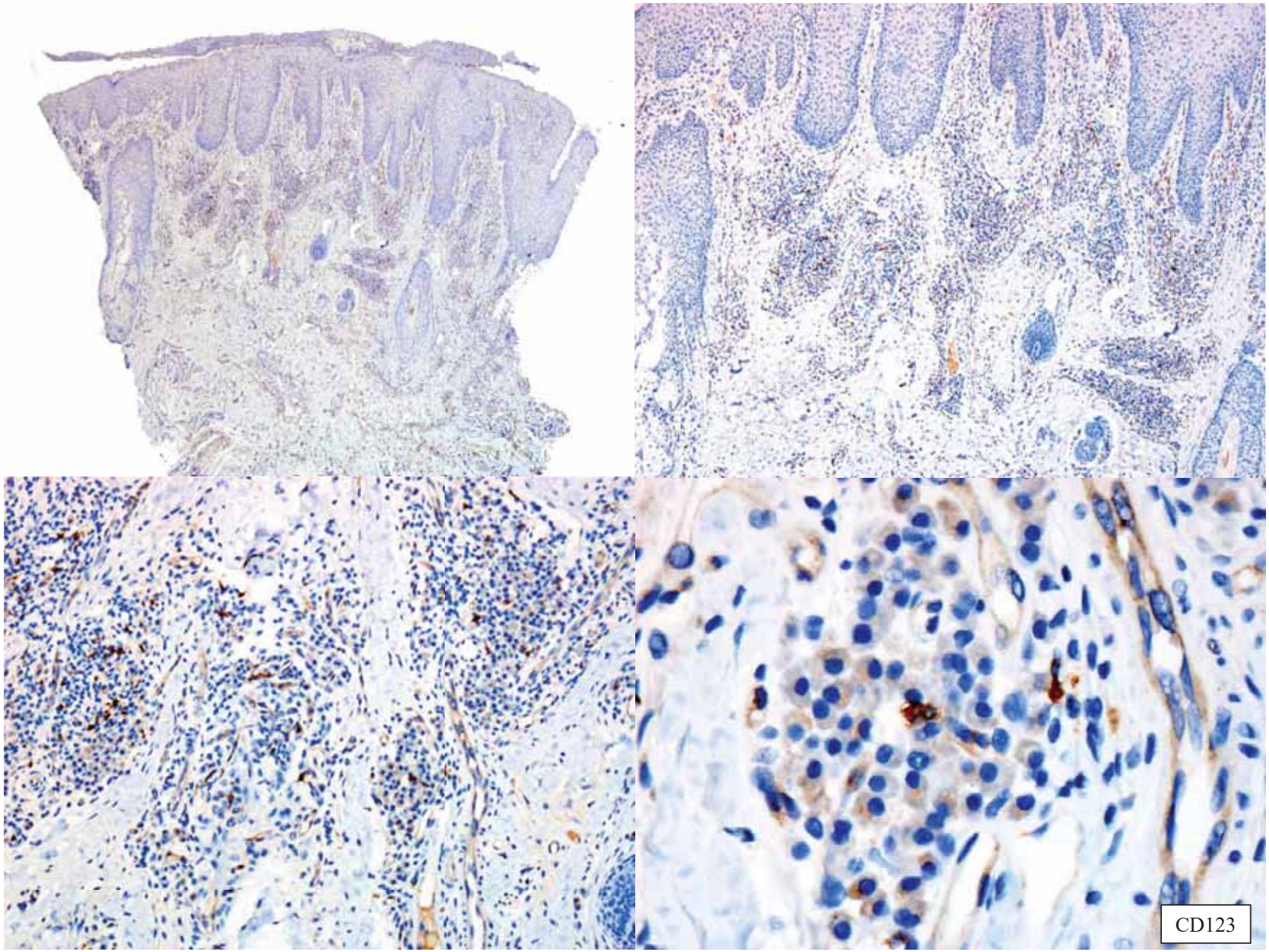
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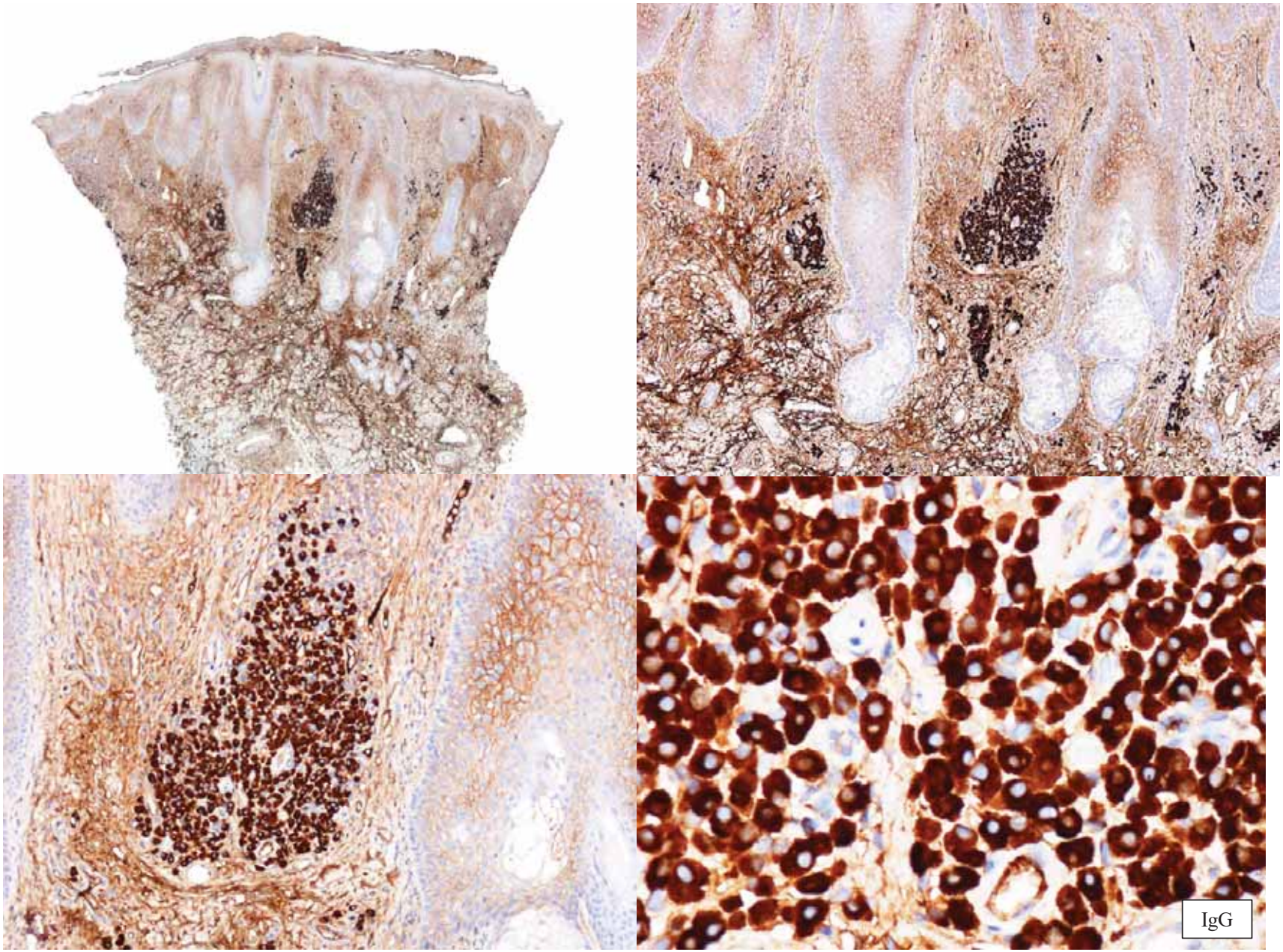
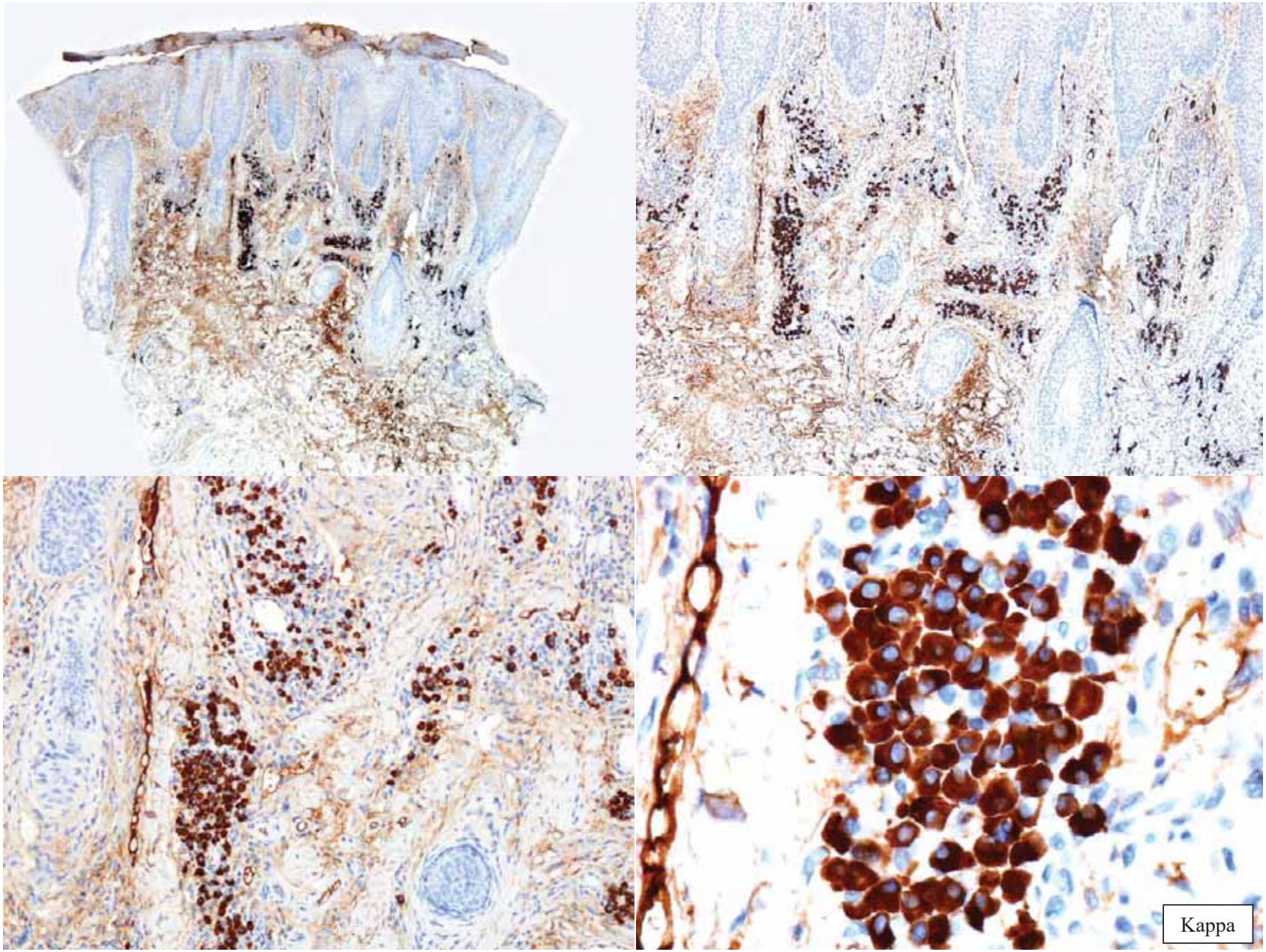
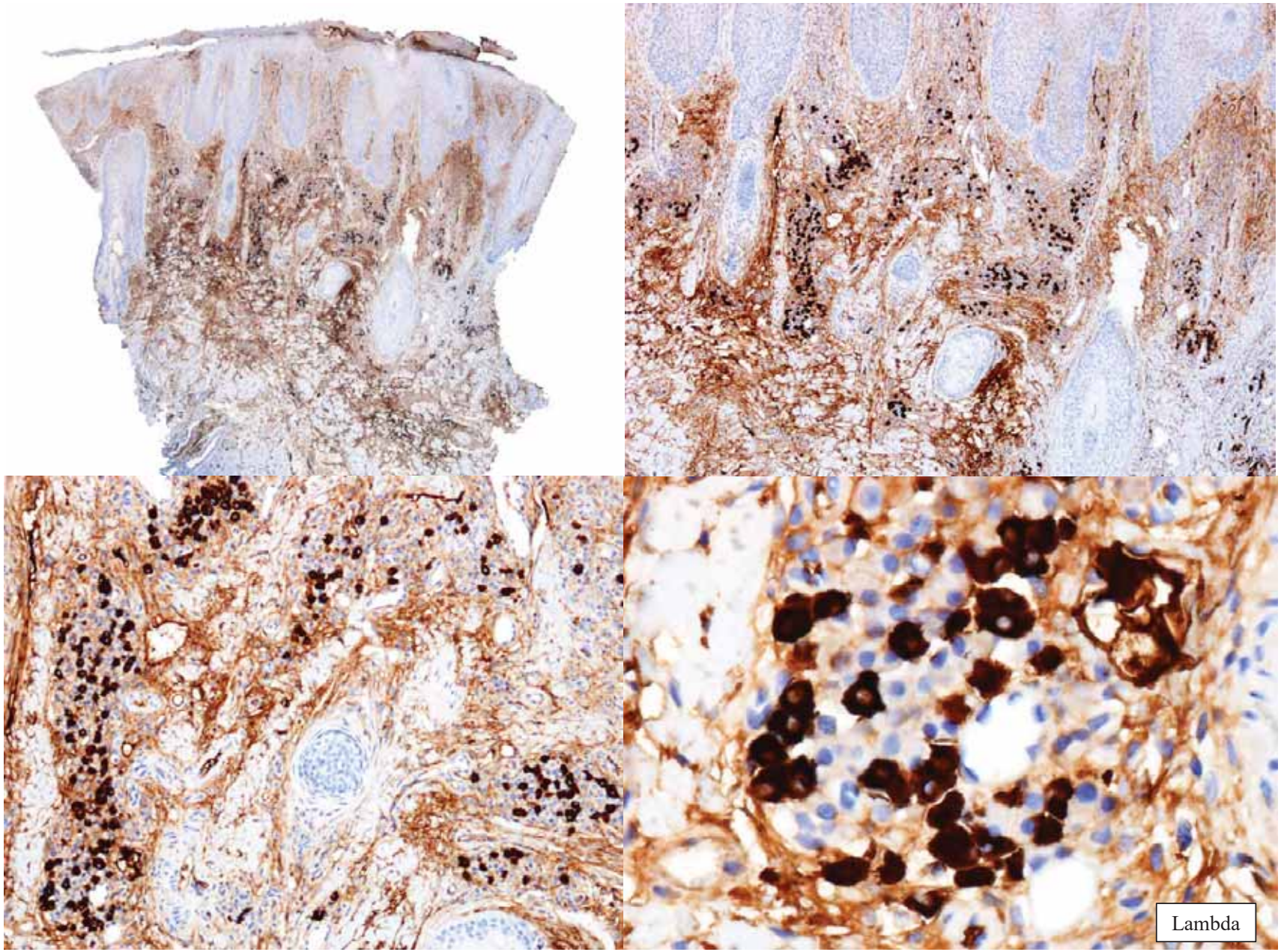
Case 1. Diagnosis

- Granuloma faciale


IgG


Kappa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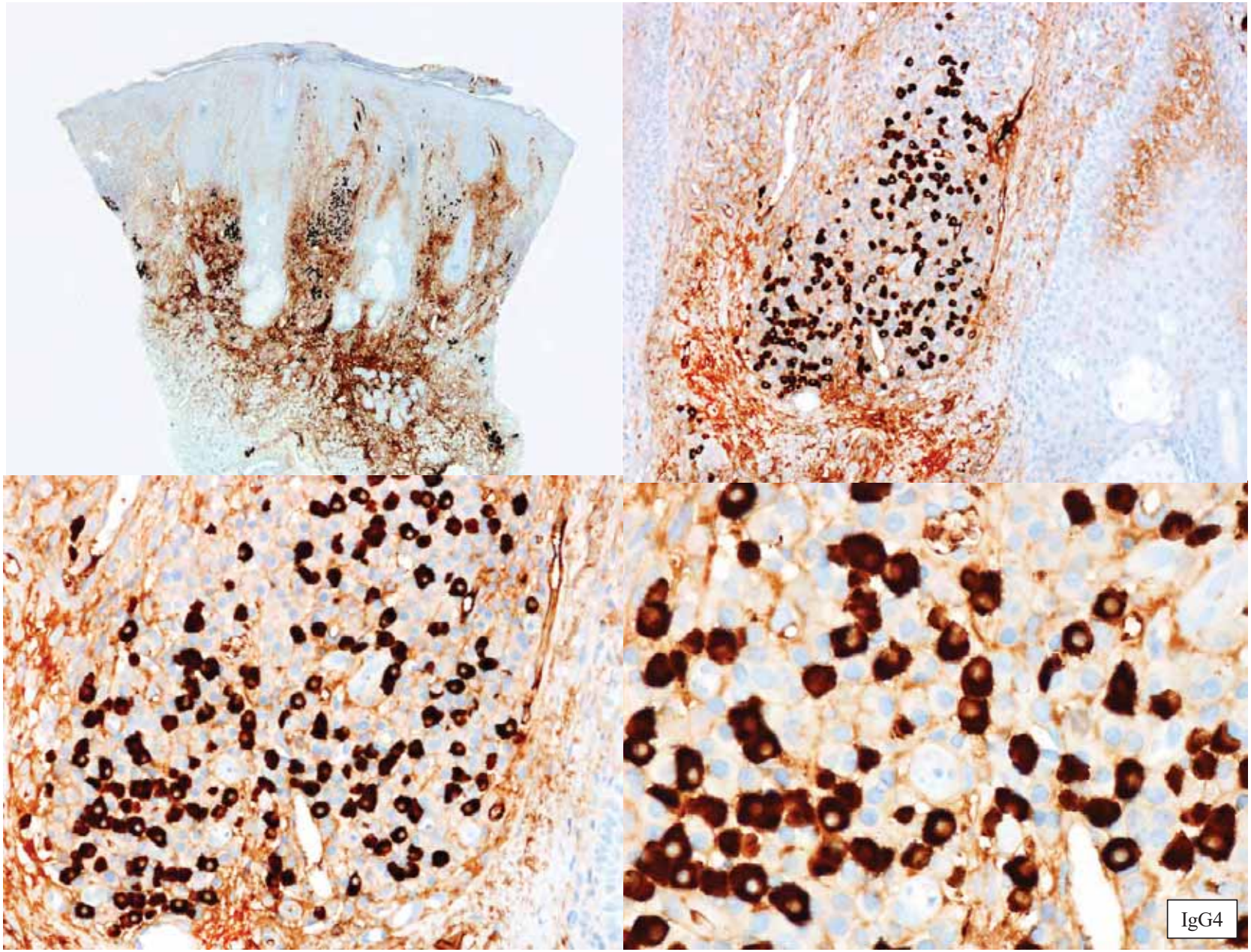
IgG4

Granuloma Faciale

A Cutaneous Lesion Sharing Features With IgG4-associated Sclerosing Diseases

Anna Maria Cesinaro, MD, Silvia Lonardi, BS,† and Fabio Facchetti, MD, PhD†*

Abstract: The pathogenesis of granuloma faciale (GF), framed in the group of cutaneous vasculopathic dermatitis, is poorly understood. The present study investigated whether GF might be part of the spectrum of IgG4-related sclerosing diseases (IgG4-RD). Erythema elevatum diutinum (EED), believed to belong to the same group of disorders as GF, was also studied for comparison. Thirty-one biopsies of GF obtained from 25 patients (18 men, 7 women) and 5 cases of EED (4 women and 1 man) were analyzed morphologically and for the expression of IgG and IgG4 by immunohistochemistry. The distribution of Th1, T regulatory and Th2 T-cell subsets, respectively, identified by anti-T-bet, anti-FoxP3, and anti-GATA-3 antibodies, was also evaluated. The dermal inflammatory infiltrate in GF contained eosinophils and plasma cells in variable proportions. Obliterative venulitis was found in 16 cases, and storiform fibrosis, a typical feature of IgG4-RD, was observed in 8 cases and was prominent in 3 of them. On immunohistochemical analysis 7 of 31 biopsies (22.6%) from 6 GF patients fulfilled the criteria for IgG4-RD (IgG4/IgG ratio >40%, and absolute number of IgG4 per high-power field >50). Interestingly, the 6 patients were male, and 4 showed recurrent and/or multiple lesions. In an additional 5 cases, only the IgG4/IgG ratio was abnormal. None of the 5 EED cases fulfilled the criteria for IgG4-RD. The T-cell subsets in GF were quite variable in number, GATA-3$^+$ lymphocytes were generally more abundant, but no relationship with the number of IgG4$^+$ plasma cells was found. The study indicates that a significant number of GF cases are associated with an abnormal content of IgG4$^+$ plasma cells; this association was particularly obvious in male patients and in cases presenting with multiple or recurrent lesions. As morphologic changes typically found in IgG4-RD, such as obliterative vascular inflammation and storiform sclerosis, are found in GF, we suggest that GF might represent a localized form of IgG4-RD.

Key Words: granuloma faciale, erythema elevatum diutinum, IgG4, IgG4-related sclerosing disease, immunohistochemistry

(*Am J Surg Pathol* 2013;37:66–73)

Granuloma faciale (GF) is a cutaneous reactive process framed in the group of chronic vasculitides; it is characterized by 1 or multiple erythematous purplish oval plaques and is typically located on the face, although involvement of extrafacial sites has been reported.[1] Early-stage GF is seldom biopsied and is characterized by a neutrophil-rich infiltrate with scant nuclear dust and fibrin in the vessel walls; full-blown GF lesions feature a dense inflammatory infiltrate comprising neutrophils, eosinophils, lymphocytes, and plasma cells, with formation of perivascular concentric fibrosis.[2] The pathogenesis of GF is poorly understood. Contradictory results have been obtained with direct immunofluorescence studies,[3–4] some of which revealed perivascular immunoglobulin and complement deposits, sustaining the vasculitic nature of GF. Other studies showed that the CD4$^+$ T cells are the dominant lymphocyte population in GF; these T lymphocytes have a restricted Vβ receptor repertoire, show an activated phenotype, and might release cytokines, including γ-interferon and interleukin 5, the latter being responsible for the recruitment of eosinophils.[5–6]

Several reports on the association of GF with eosinophilic angiocentric fibrosis (EAF) have been published.[7–9] EAF is a fibroinflammatory process involving the upper respiratory tract and the orbit that shares with GF the eosinophil-rich inflammatory infiltrate and concentric perivascular fibrosis. Interestingly, EAF has been recently proposed as a form of sclerosing diseases pathogenetically related to immunoglobulins G4.[10]

IgG4, representing the least common subclass of IgG (3% to 6% of the entire IgG fraction), is a T-helper cell 2 (Th2)-dependent IgG isotype, known to play a role in allergic reactions and bullous diseases of the skin.[11] IgG4 has been recently recognized as the main factor in causing a group of diseases consequently defined as IgG4-related diseases (IgG4-RD).[12–17] IgG4-RD affect mainly middle-aged to elderly men, who present mass in 1 or more anatomic sites, including the pancreas (where it is recognized as autoimmune pancreatitis type I), the hepatobiliary

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Correspondence: Anna Maria Cesinaro, MD, Dipartimento ad Attività Integrata di Laboratori, Anatomia Patologica e Medicina Legale, Struttura Complessa di Anatomia, Istologia e Citologia Patologica, Azienda Ospedaliero-Universitaria Policlinico di Modena, Via del Pozzo, 71,41124 Modena, Italy (e-mail: cesinaro.annamaria@policlinico.mo.it).

- 31 biopsies of GF obtained from 25 patients and 5 cases of EED
- The dermal inflammatory infiltrate in GF contained eosinophils and plasma cells in variable proportions
- 7 of 31 biopsies (22.6%) from 6 GF patients fulfilled the criteria for IgG4-RD (IgG4/IgG ratio >40%, and absolute number of IgG4 per high-power field >50).
- None of the 5 EED cases fulfilled the criteria for IgG4-RD.
- We suggest that GF might represent a localized form of IgG4-RD

Granuloma Faciale and Erythema Elevatum Diutinum in Relation to Immunoglobulin G4–Related Disease

An Appraisal of 32 Cases

Sima Kavand, MD,[1] Julia S. Lehman, MD,[2] and Lawrence E. Gibson, MD[2]

From the [1]Department of Medicine, Presence Saint Francis Hospital, University of Illinois, Evanston; and [2]Departments of Dermatology, Pathology and Laboratory Medicine, Mayo Clinic College of Medicine, Rochester, MN.

Key Words: Granuloma faciale; Erythema elevatum diutinum; IgG4-related disease; IgG4-related skin disease; IgG4; Cutaneous vasculitis

Am J Clin Pathol March 2016;145:401-406

DOI: 10.1093/AJCP/AQW004

ABSTRACT

Objectives: *To elucidate whether granuloma faciale (GF) and erythema elevatum diutinum (EED), two inflammatory skin dermatoses, meet the consensus histopathologic diagnostic criteria for immunoglobulin G4–related disease (IgG4-RD).*

Methods: *With institutional review board approval, we assessed the clinical, microscopic, and immunophenotypic features of skin specimens of patients with GF and EED. We compared these findings with previously published consensus diagnostic criteria for IgG4-RD.*

Results: *Thirty-two patients (GF, n = 25; EED, n = 7) met study inclusion criteria. Histopathologic findings of small-vessel vasculitis, dermal fibrosis, and plasma cell infiltrates were uniformly present, and eosinophilic inflammation was frequent. No specimen met diagnostic criteria for IgG4-RD.*

Conclusions: *Our results indicate that despite some histopathologic similarities between GF/EED and IgG4-RD, the cases did not meet the consensus immunohistochemical diagnostic criteria for IgG4-RD.*

Upon completion of this activity you will be able to:
- list the diagnostic criteria for IgG4-related skin disease.
- discuss the relationship between two skin disorders (granuloma faciale and erythema elevatum diutinum) and IgG4-related disease.
- describe the clinical differences between granuloma faciale and erythema elevatum diutinum.

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The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

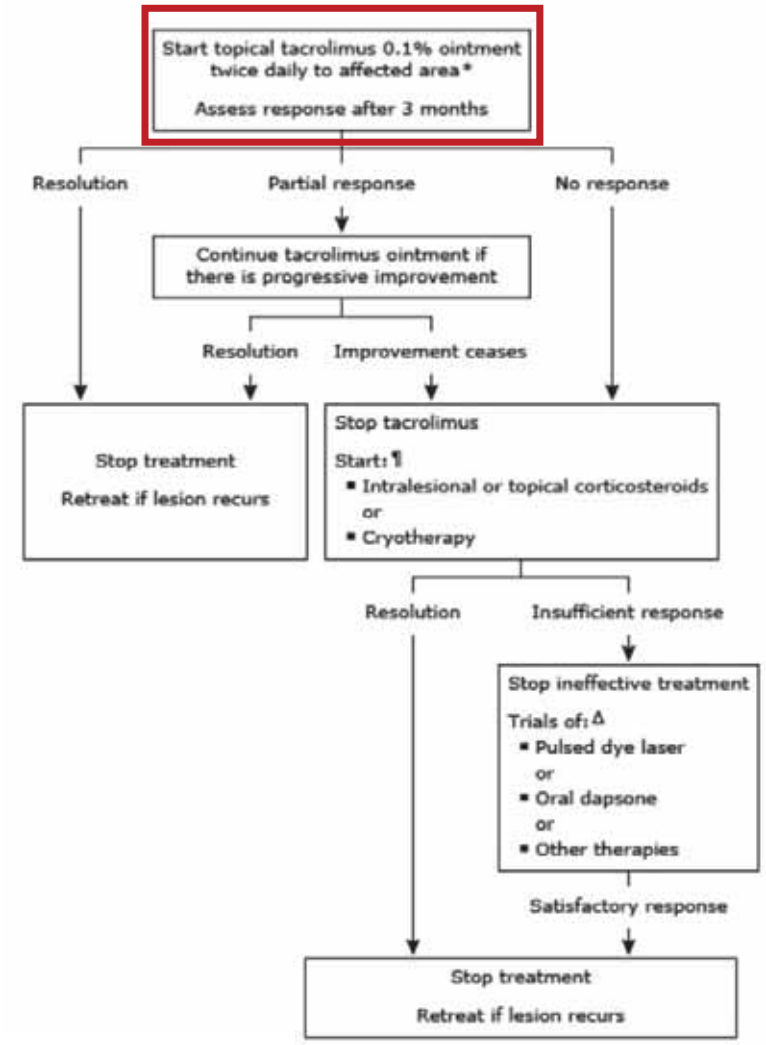
Exam is located at www.ascp.org/ajcpcme.

Immunoglobulin G4–related disease (IgG4-RD) is a fibroinflammatory condition that may affect one or more organs.[1] It most often manifests with mass-like lesions.[2-4] Dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, and obliterative venulitis are three major histopathologic criteria for disease diagnosis.[5] Eosinophil infiltration is a common finding seen in tissue affected by IgG4-RD, as is non–storiform fibrosis and occasional nonnecrotizing lymphoplasmacytic arteritis.[5,6]

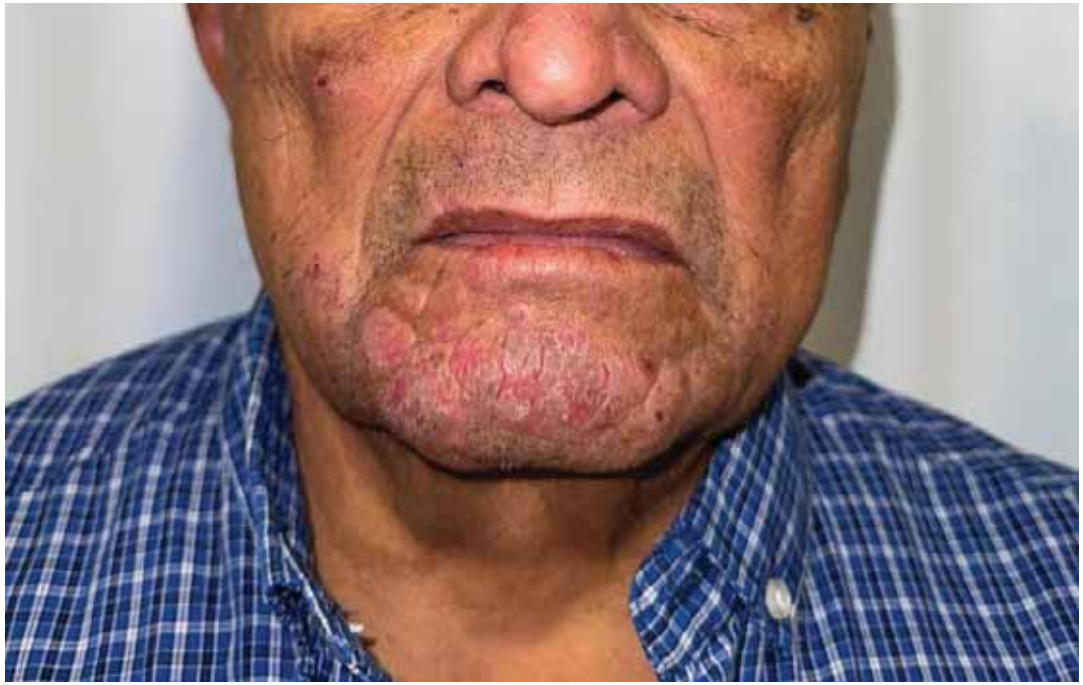
IgG4-RD embraces a wide variety of diseases, including autoimmune pancreatitis, Mikulicz disease, Riedel thyroiditis, interstitial nephritis, inflammatory aortic aneurysm, and others.[6] Despite the progress in disease recognition during recent years, little is known about the cutaneous manifestations of IgG4-RD.[7] Reported cases are limited and mostly described as erythematous nodules and plaques, prominently affecting the head and neck.[7-12]

- To elucidate whether granuloma faciale (GF) and erythema elevatum diutinum (EED) meet the consensus histopathologic diagnostic criteria for immunoglobulin G4–related disease (IgG4-RD)
- 32 patients (GF, 25; EED, 7)
- Histopathologic findings of small vessel vasculitis, dermal fibrosis, and plasma cell infiltrates were uniformly present, and eosinophilic inflammation was frequent
- No specimen met diagnostic criteria for IgG4-RD.
- Conclusions: Our results indicate that despite some histopathologic similarities between GF/EED and IgG4-RD, the cases did not meet the consensus immunohistochemical diagnostic criteria for IgG4-RD

Treatment of granuloma faciale in adults



Granuloma Facial. UpToDate. Dec 2024
Motaparthi K, Callen JP, Ofori AO.



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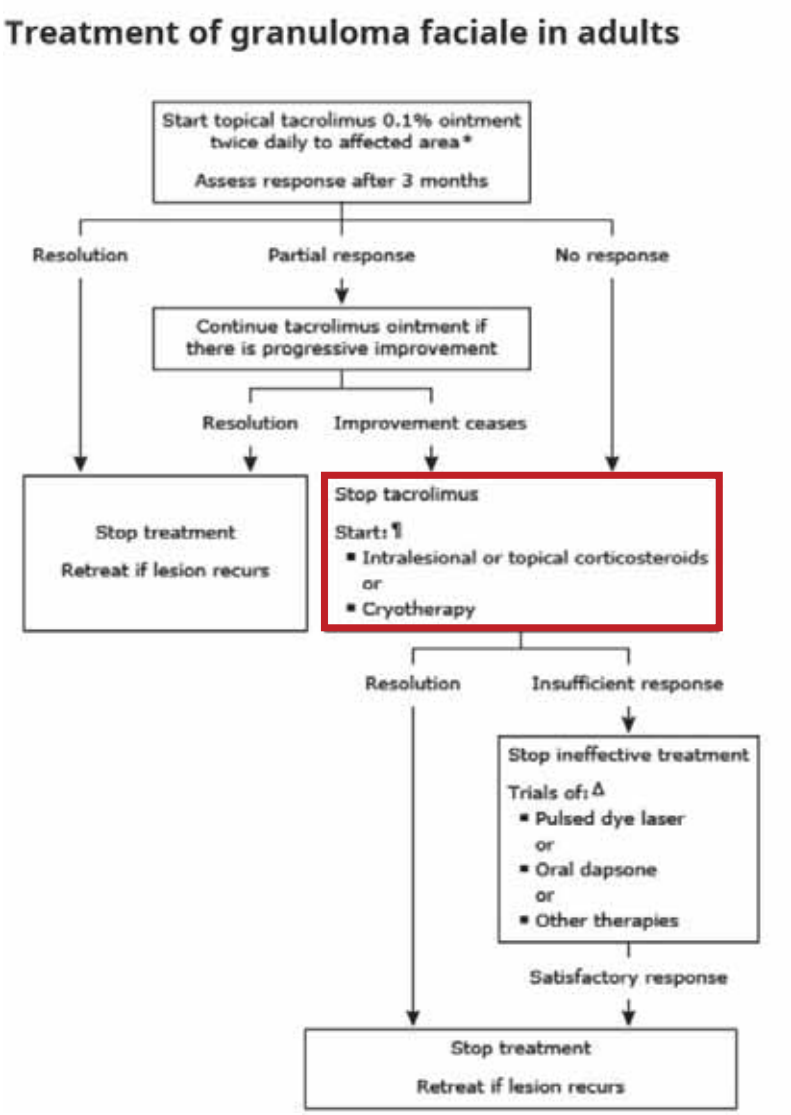

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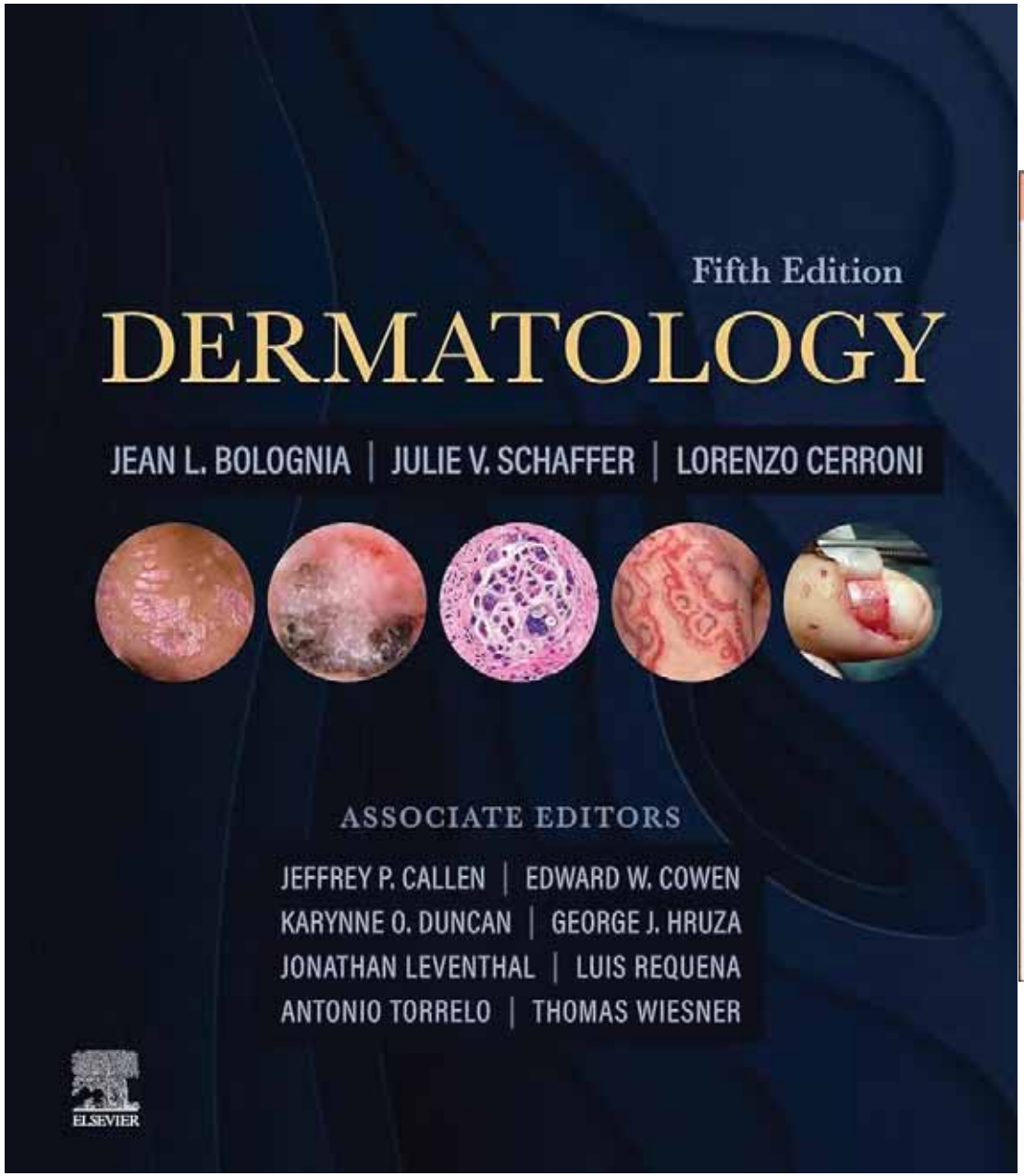
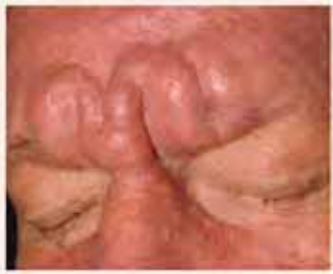


LEONINE FACIES – ASSOCIATED DERMATOLOGIC DISEASES



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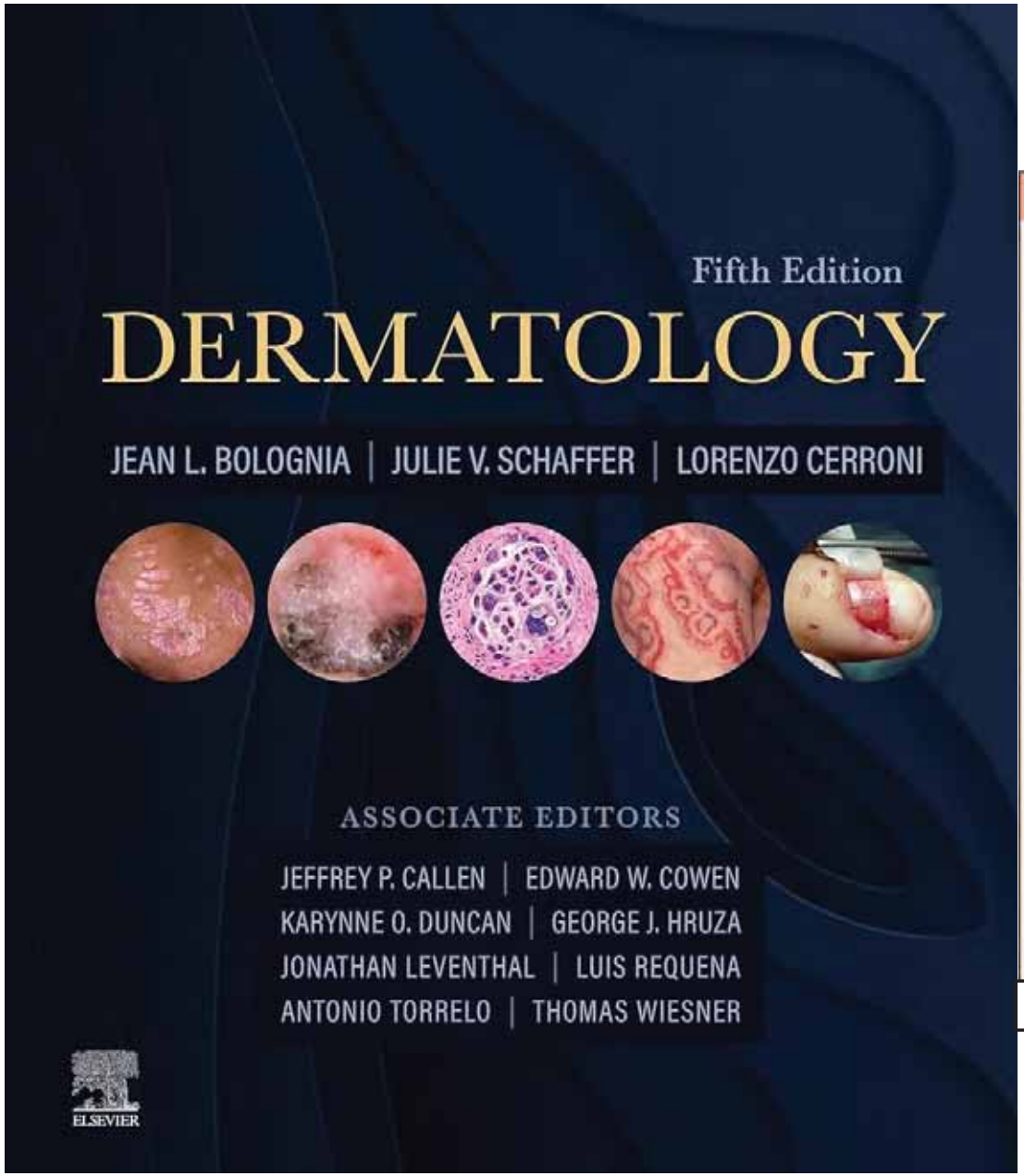

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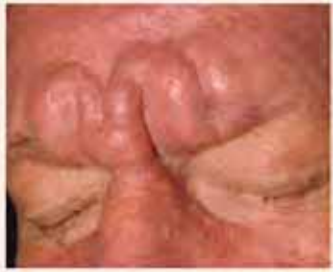

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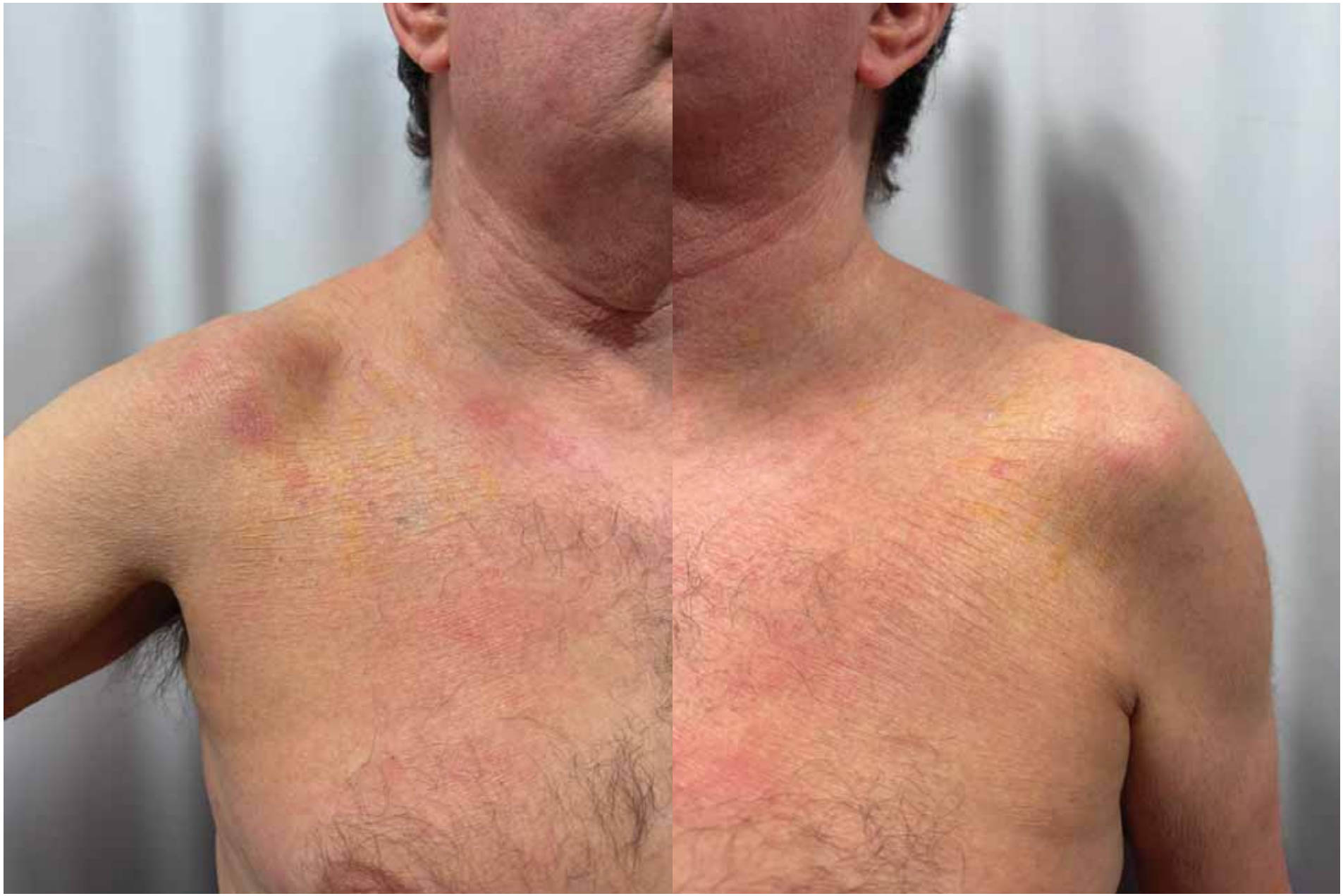
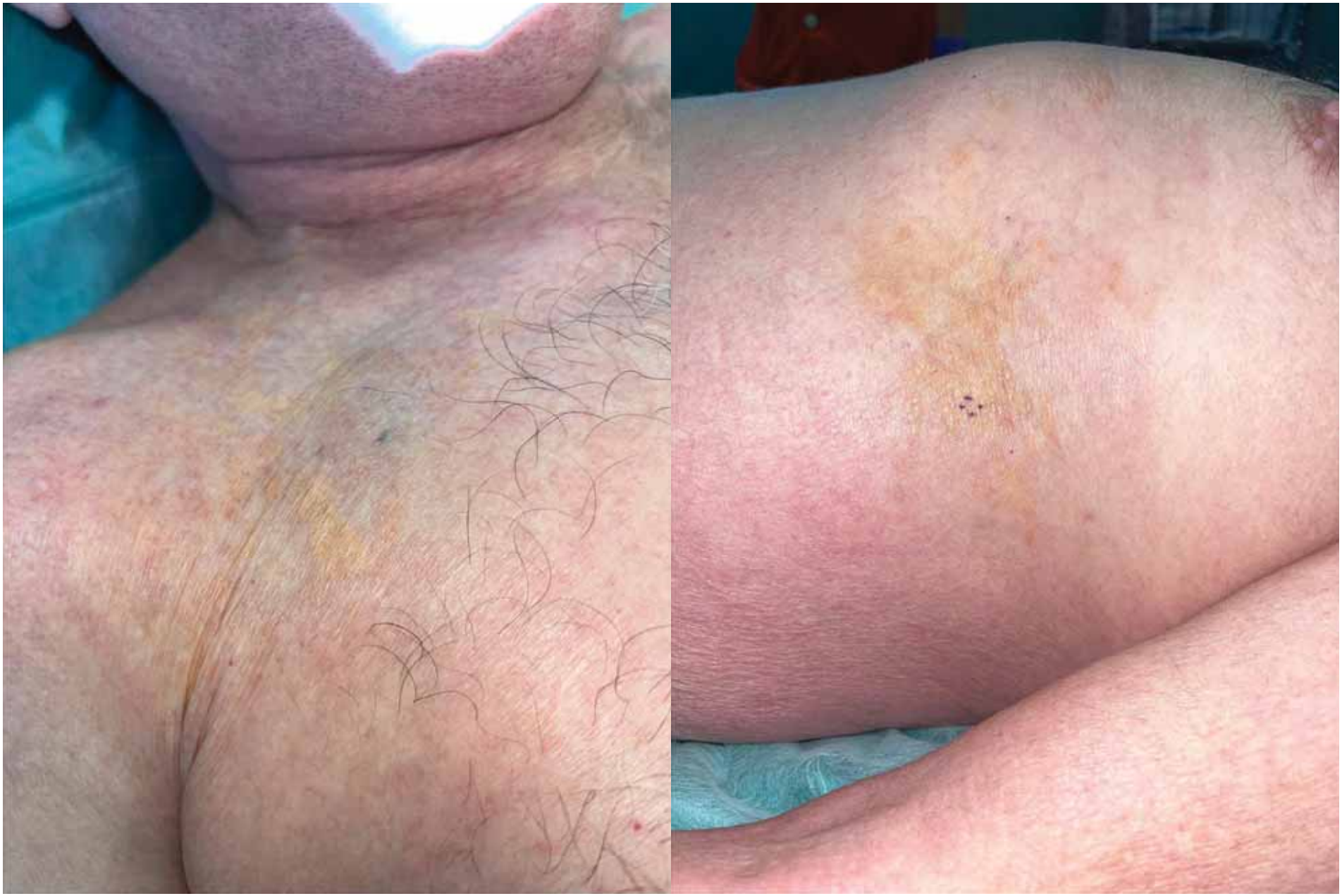
Granuloma faciale

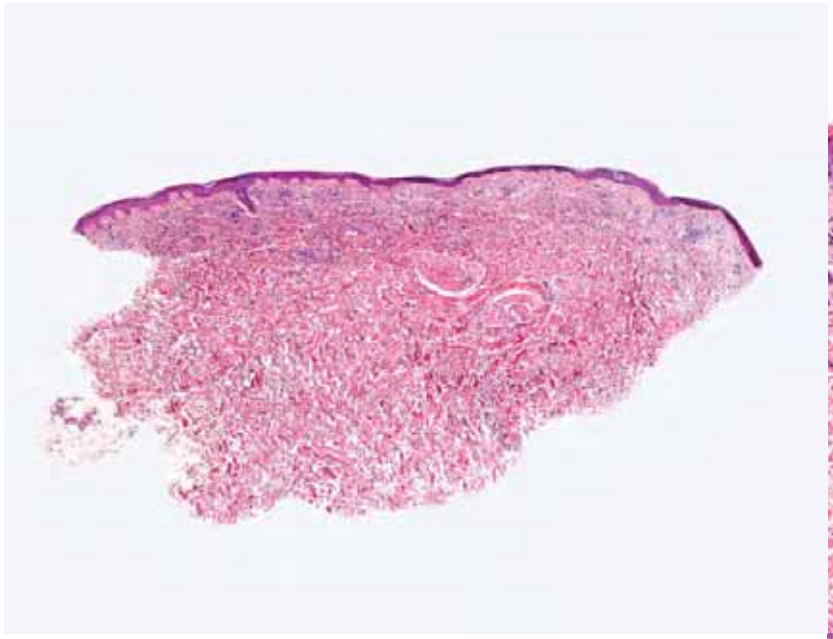
Case 2

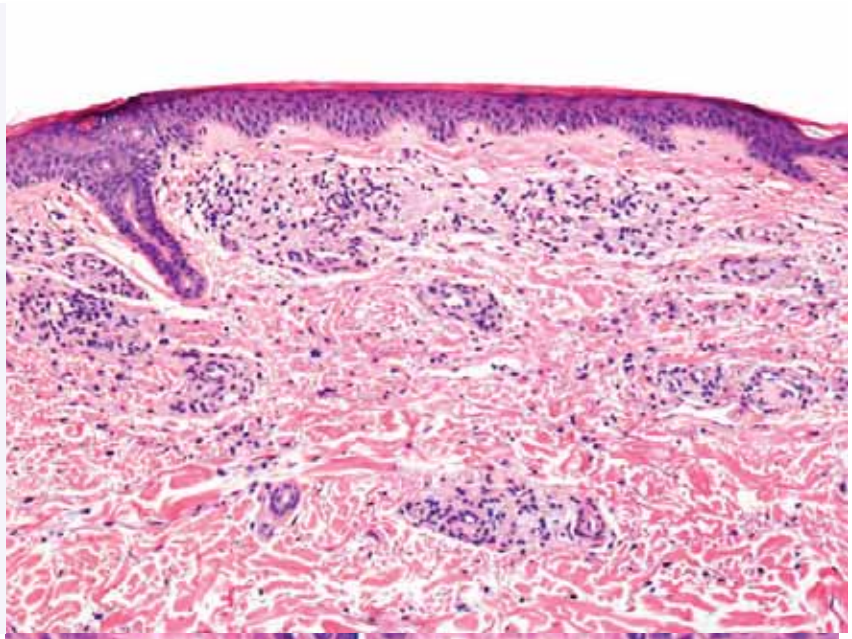
- A 62-year-old male, with history of cholestatic hepatopathy and hiperlipidemia, was receiving Dupilumab 300 mg/every 2 weeks for severe atopic dermatitis during the last two years. He developed widespread erythematous plaques with yellowish areas on the trunk and extremities

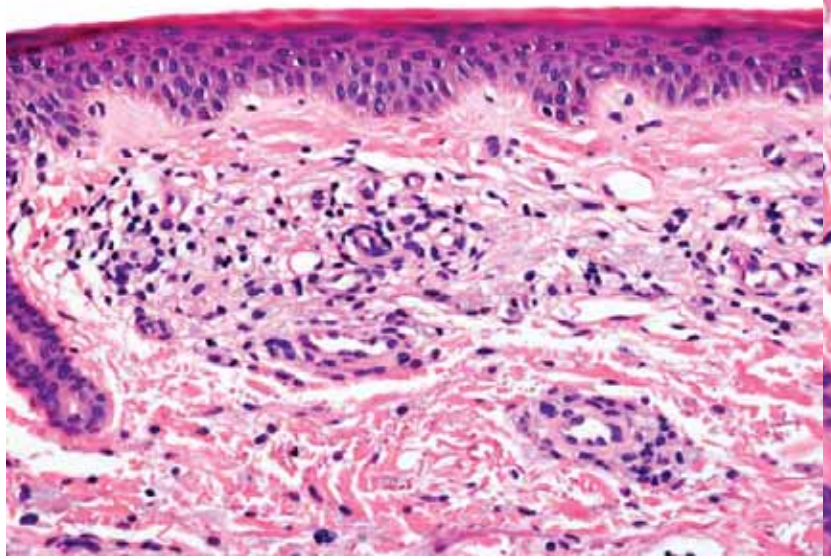
Consultation from Dr. Laura Nájera, Madrid

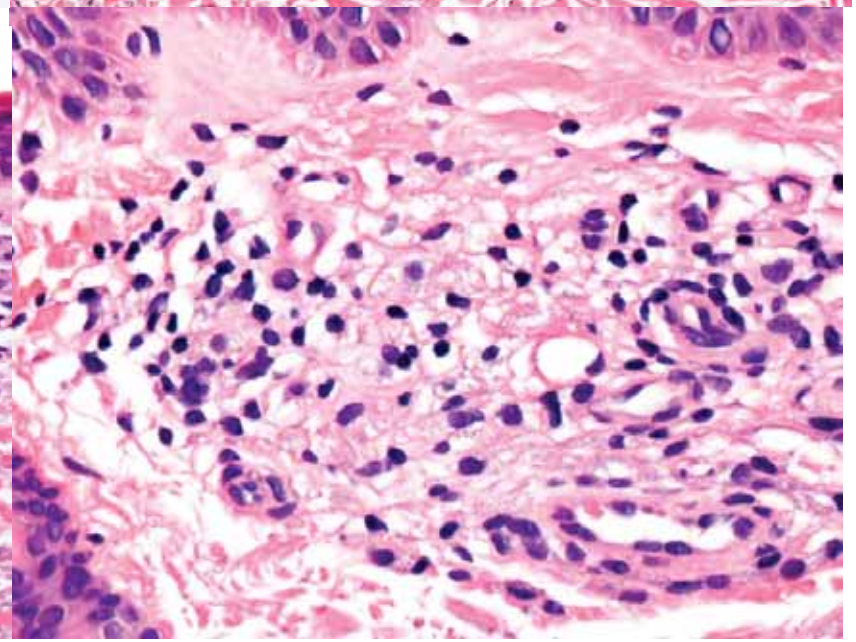


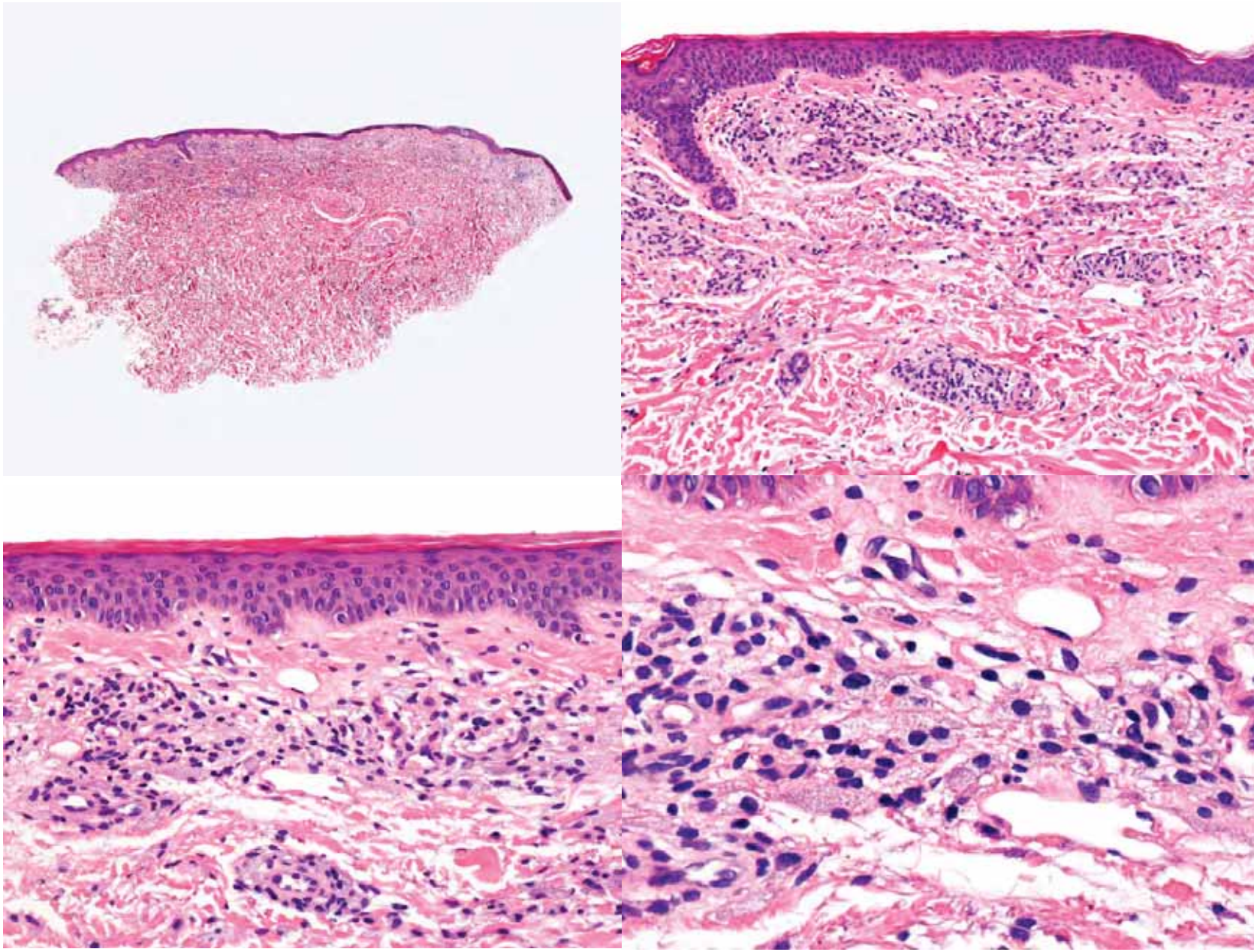


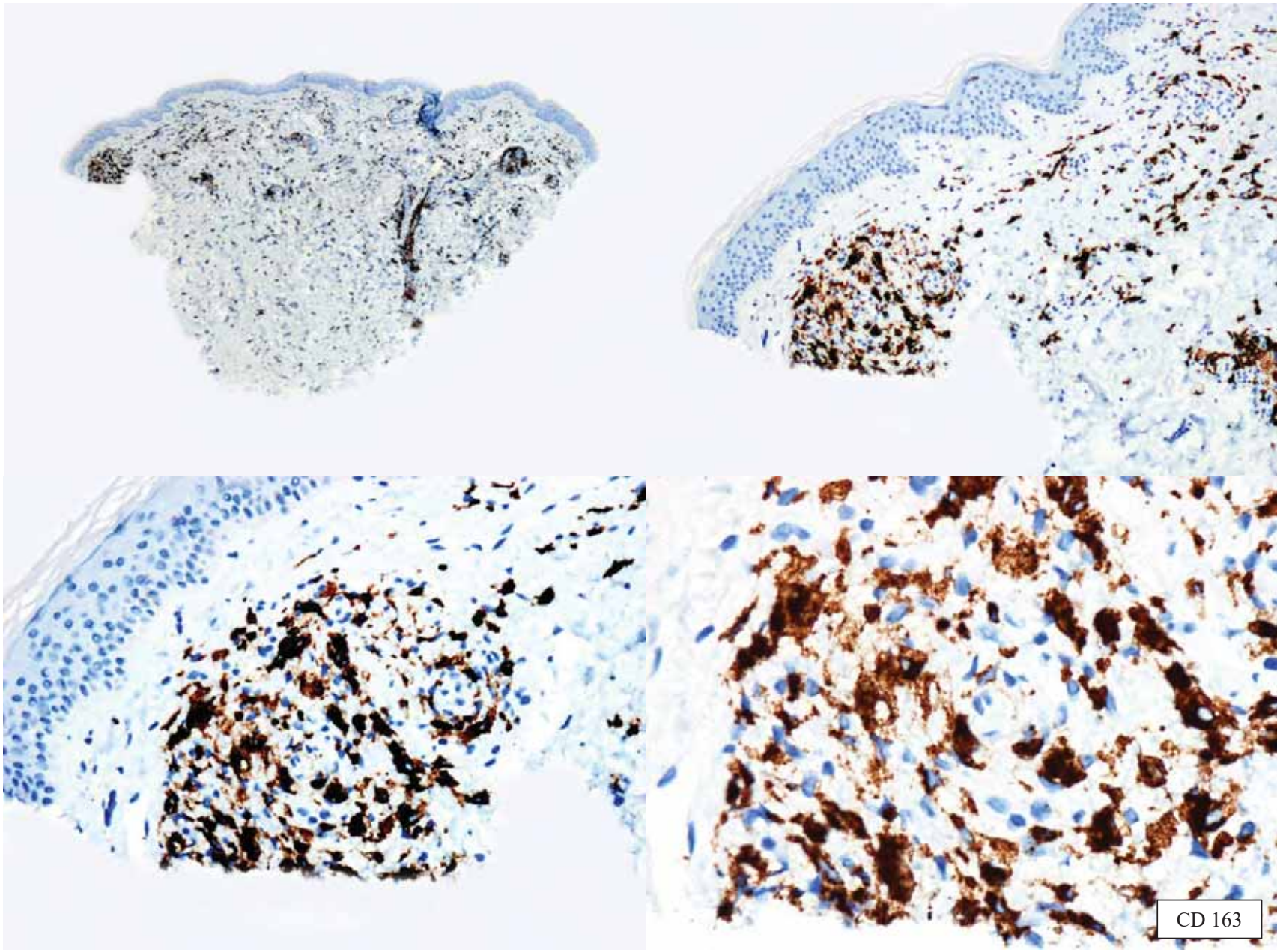








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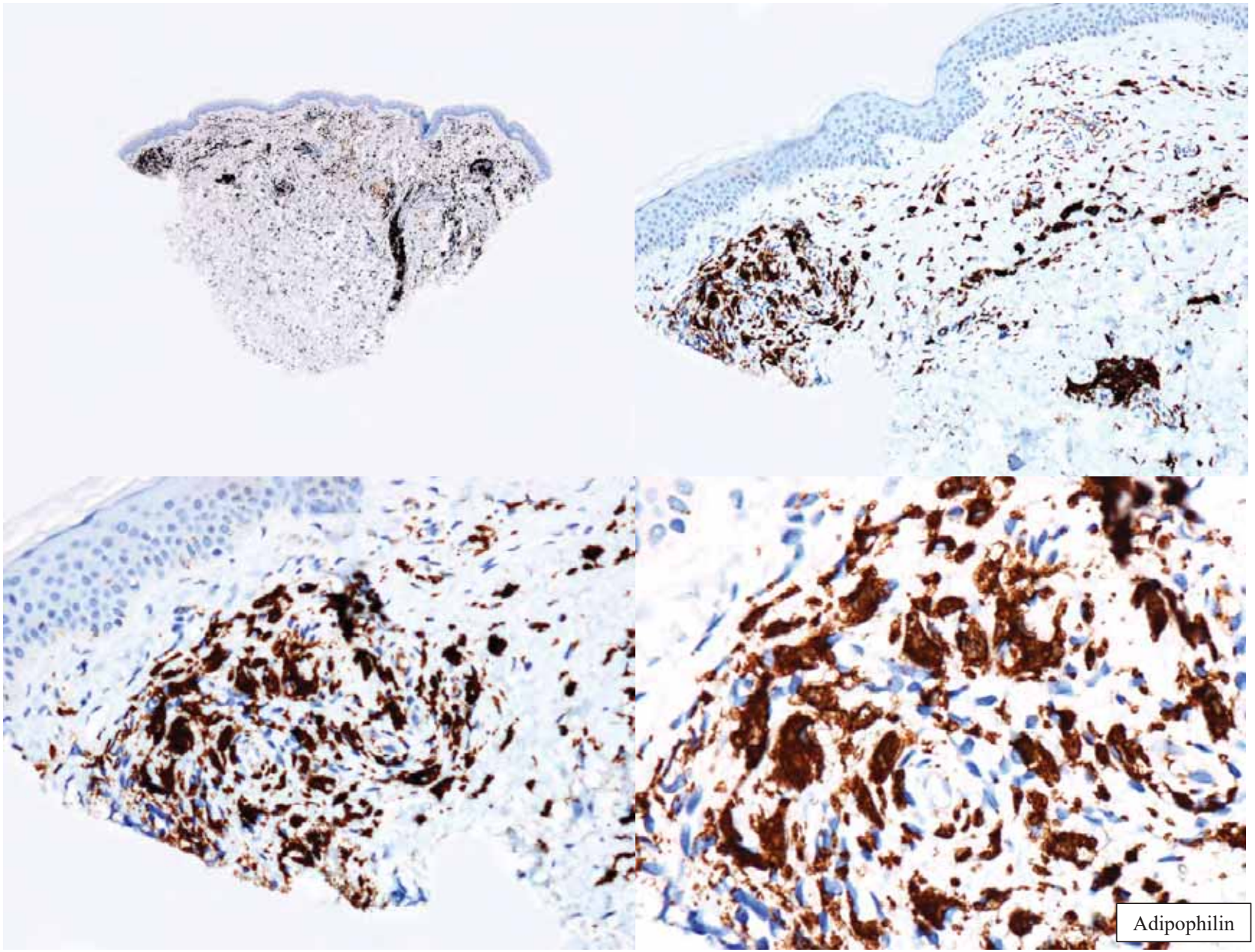
Adipophilin

Case 2. Diagnosis

- Foamy histiocytes in a cutaneous eruption due to Dupilumab in a patien with cholestatic hepatopathy and hyperlipidemia

Xanthomatous Cells in Cutaneous Graft-Versus-Host Disease Biopsies: A Clue for the Diagnosis of Hepatic Graft-Versus-Host Disease

Denise Gamé, MD, Lucia López, MD,† Concepción Román, MD, PhD,‡ and Ángel Santos-Briz, MD, PhD‡*

Abstract: Graft-versus-host disease (GVHD) is one of the most common and serious complications of hematopoietic stem-cell transplantation that mainly affects the skin, gastrointestinal tract, and liver. Hepatic GVHD is associated with high morbidity and mortality, and its diagnosis can be especially challenging because of nonspecific clinical signs and symptoms. It must be suspected in patients with elevated liver enzymes and cholestasis, especially in those with a history of preceding skin rash and diarrhea. We describe 3 patients with cutaneous and hepatic GVHD that presented with severe hypercholesterolemia and hypertriglyceridemia, and no xanthomatous macular lesions, in which cutaneous biopsies revealed the presence of xanthomatous dermal histiocytes. We propose that the presence of these xanthomatous cells in skin biopsies from patients with cutaneous GVHD could be a dermatopathological clue for the diagnosis of hepatic GVHD.

Key Words: graft-versus-host disease, xanthomatous cells, skin biopsies, liver, hypercholesterolemia

(*Am J Dermatopathol* 2018;40:754–757)

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a widely used treatment for a variety of malignant and nonmalignant hematological diseases. Graft-versus-host disease (GVHD) is one of the most common and serious complications of HCT, and is produced by an immune-mediated reaction of donor cells against host tissues. Although it is a multiorgan disease, the most common affected organs are the skin, gastrointestinal tract, and liver.[1–4] Hepatic GVHD is usually associated with high morbidity and mortality and its diagnosis can be especially challenging because of nonspecific clinical signs and symptoms.[5] In this article, we describe 3 cases of cutaneous and hepatic GVHD in which cutaneous biopsies revealed the presence of xanthomatous histiocytes. We propose that the presence of these lipid-rich macrophages in skin biopsies from patients with cutaneous GVHD could be a dermatopathological clue for the diagnosis of hepatic GVHD.

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The authors declare no conflicts of interest.

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CASE REPORTS

Patient 1

A 10-year-old white boy was diagnosed of severe idiopathic medullary aplasia and treated with methylprednisolone, thymoglobulin, cyclosporine, and granulocyte-colony stimulating factor for 3 months with no response. He underwent HCT from a related donor. Six weeks later, the patient developed an asymptomatic rash in his lateral neck, trunk, and upper extremities. Physical examination revealed erythematous small scaly macules and jaundice. No xanthomas were identified (Figs. 1A–C). Laboratory evaluation disclosed an increase in bilirubin [12.6 mg/dL (normal range: 0.1–1.2)], alkaline phosphatase [322 mg/dL (normal range: 40–129)], and alanine transaminase (ALT) [236 mg/dL (normal range: 1–41)] levels, with severe hyperlipidemia [cholesterol: 1416 mg/dL (normal range: 100–200), high-density lipoprotein (HDL) of 19.2 mg/dL (normal range: 35–120), low-density lipoprotein (LDL) of 65.9 mg/dL (normal range: 100–175), and triglycerides of 1080 mg/dL (normal range: 40–160)]. Skin and liver biopsies were consistent with cutaneous and hepatic GVHD. Treatment with methylprednisolone, cyclosporine, and topic corticosteroids was started, followed by photoapheresis with normalization of liver function and cholesterol levels after 8 weeks.

Patient 2

A 49-year-old man with a history of myelodysplastic syndrome with multilineage dysplasia refractory to azacitidine received a HCT from a human leukocyte antigen–matched nonrelated donor. Within the first 15-day posttransplantation, he presented with erythematous macular lesions on the face, neck, abdomen and back, and elevation of liver enzymes and diarrhea suggestive of acute GVHD (Fig. 2). On physical examination, no xanthomas were identified. Laboratory evaluation disclosed an increased in bilirubin (7.06 mg/dL), alkaline phosphatase (179 mg/dL), ALT (1033 mg/dL), aspartate transaminase (229 mg/dL), and gamma-glutamyl transpeptidase (GGT) (892 mg/dL) levels, with severe hyperlipidemia (cholesterol of 841 mg/dL, HDL of 14.5 mg/dL, LDL of 756 mg/dL, and triglycerides of 352 mg/dL). Skin and liver biopsies were consistent with cutaneous and liver GVHD. Treatment was started with mesenchymal stem cells transplantation, photoapheresis, and cyclophosphamide without response with exitus of the patient because of multiorgan failure.

Patient 3

A 40-year-old white man was diagnosed with B-cell acute lymphoblastic leukemia and treated with chemotherapy (vincristine,

- 3 patients with cutaneous and hepatic GVHD that presented with severe hypercholesterolemia and hypertriglyceridemia
- Xanthomatous macular lesions, in which cutaneous biopsies revealed the presence of xanthomatous dermal histiocytes.
- The presence of these xanthomatous cells in skin biopsies from patients with cutaneous GVHD could be a dermatopathological clue for the diagnosis of hepatic GVHD.

Foamy Macrophages in a Case of Mononucleosis With Amoxicillin-Induced Rash, Hyperlipidemia, and Hemophagocytic Lymphohistiocytosis

Guillermo Gonzalez-Lopez, MD, † Isabella Fried, MD,* Eva Schadelbauer, MD,* and Lorenzo Cerroni, MD**

Abstract: A 38-year-old man presented with fever, cough, and jaundice. Four days before, he had started taking amoxicillin/clavulanic acid. He subsequently developed a morbilliform rash, and, according to clinical features and blood analyses, a diagnosis of mononucleosis with Epstein–Barr virus–associated antibiotic-induced exanthema and secondary hemophagocytic lymphohistiocytosis was made. A skin biopsy revealed a superficial perivascular lymphohistiocytic infiltrate with interface dermatitis and many foamy macrophages in the papillary dermis and around the vessels of the superficial dermal plexus. A blood lipid test uncovered marked hypercholesterolemia and hypertriglyceridemia. After treatment with dexamethasone and immunoglobulin, the skin rash, liver function, and lipid profile progressively improved. Xanthomatous cells have been observed in skin biopsies of acute graft-versus-host disease with liver involvement, and these cells have been suggested to represent a clue to the presence of hepatic disease. In our case, underlying cholestatic hepatopathy with hyperlipidemia was present. We believe that the incidental finding of foamy cells in graft-versus-host disease cases and in our case are likely related to the presence of severe liver disease with cholestatic hepatopathy and secondary hyperlipidemia in different background conditions.

Key Words: mononucleosis, Epstein–Barr virus, foamy macrophages, dermatopathology

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INTRODUCTION

Infectious mononucleosis (IM) is a typical presentation of primary Epstein–Barr virus (EBV) infection. The development of morbilliform exanthema a few days after starting amoxicillin or ampicillin is well described in IM.[1] Since it is easily diagnosed both clinically and serologically, no biopsy is necessary in most cases, and only a few descriptions of the histological features have been published.[2,3] We report a case of IM with severe liver involvement and presence of foamy histiocytes in a biopsy specimen.

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The authors declare no conflicts of interest.

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CASE PRESENTATION

A 38-year-old man was admitted with a one-week history of fever, cough, submandibular lymphadenopathy, and diarrhea. Four days before admission, he had started taking amoxicillin/clavulanic acid and the day before had developed jaundice. Blood tests revealed elevated liver enzymes and hyperbilirubinemia. On the third day of admission, he was found to have positive levels of anti-VCA IgM against EBV, so the amoxicillin was stopped. One day later, he developed a morbilliform rash on his face and trunk (Fig. 1). A diagnosis of amoxicillin-induced rash in a patient with mononucleosis was made. Subsequently, his liver condition deteriorated, and 9 days after admission, his blood tests showed a bilirubin of 19.13 mg/dL (conjugated bilirubin: 16.06 mg/dL), alanine transaminase of 553 U/L, gamma-glutamyl transferase of 575 U/L, ferritin of 4305 ng/mL, and soluble interleukin-2 receptor of 9398.2 U/mL. Based on these results, a diagnosis of hemophagocytic lymphohistiocytosis (HLH) secondary to EBV infection was established, and at the same time, a skin biopsy was taken. The biopsy revealed a superficial perivascular lymphohistiocytic infiltrate with interface dermatitis, the latter characterized by vacuolization of the basal layer and isolated necrotic keratinocytes (Fig. 2). Remarkably, foamy macrophages were abundant in the papillary dermis and around the vessels of the superficial dermal plexus (Figs. 3, 4). Based on these findings, a blood lipid test was performed, which revealed a cholesterol level of 525 mg/dL (cLDL of 505 mg/dL) and triglycerides of 728 mg/dL. The patient was treated with dexamethasone and immunoglobulin, and the skin rash, liver function, and lipid profile progressively improved. Three weeks after discharge, he was completely asymptomatic and his lipid profile was back at near normal levels.

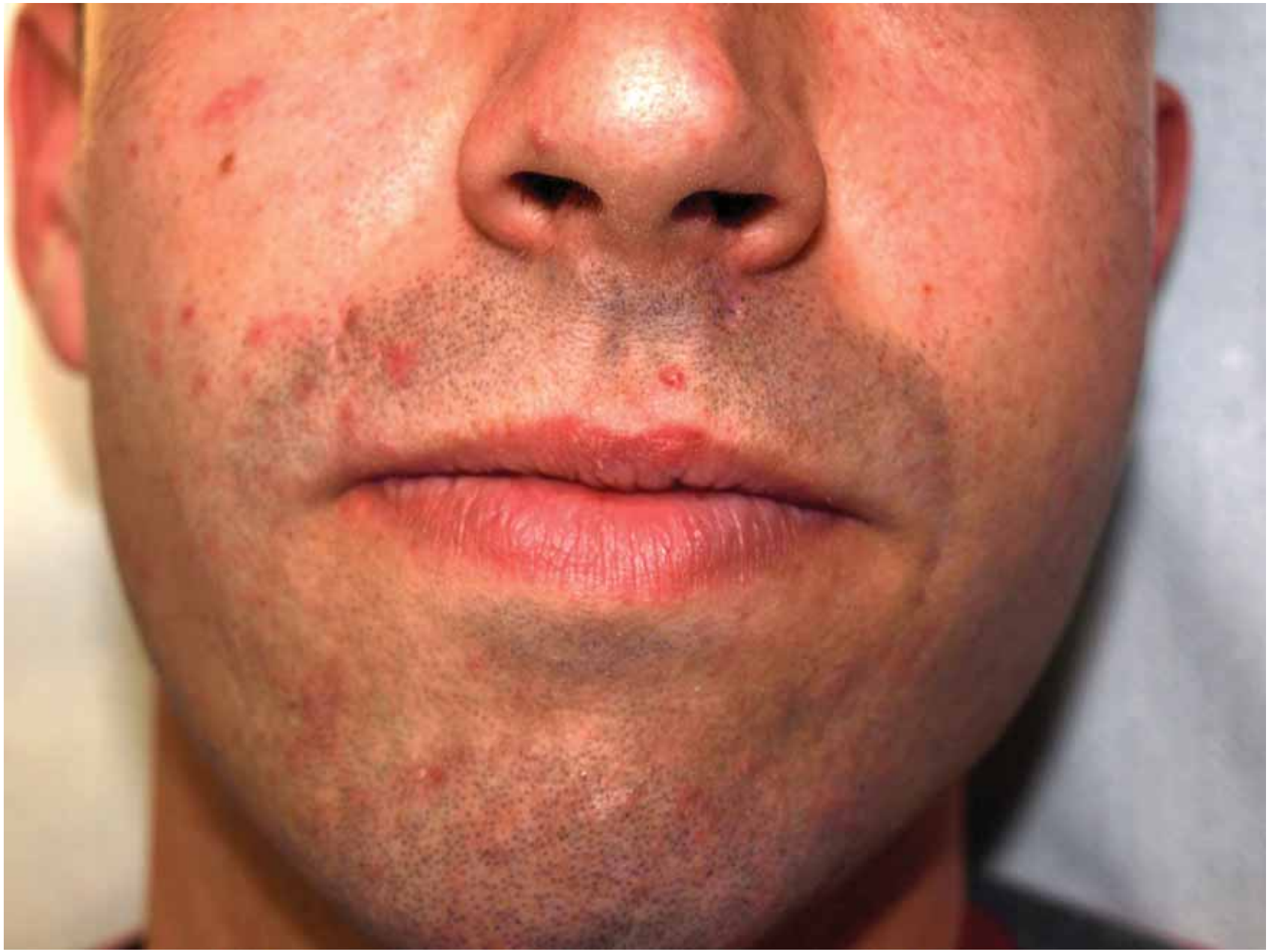
DISCUSSION

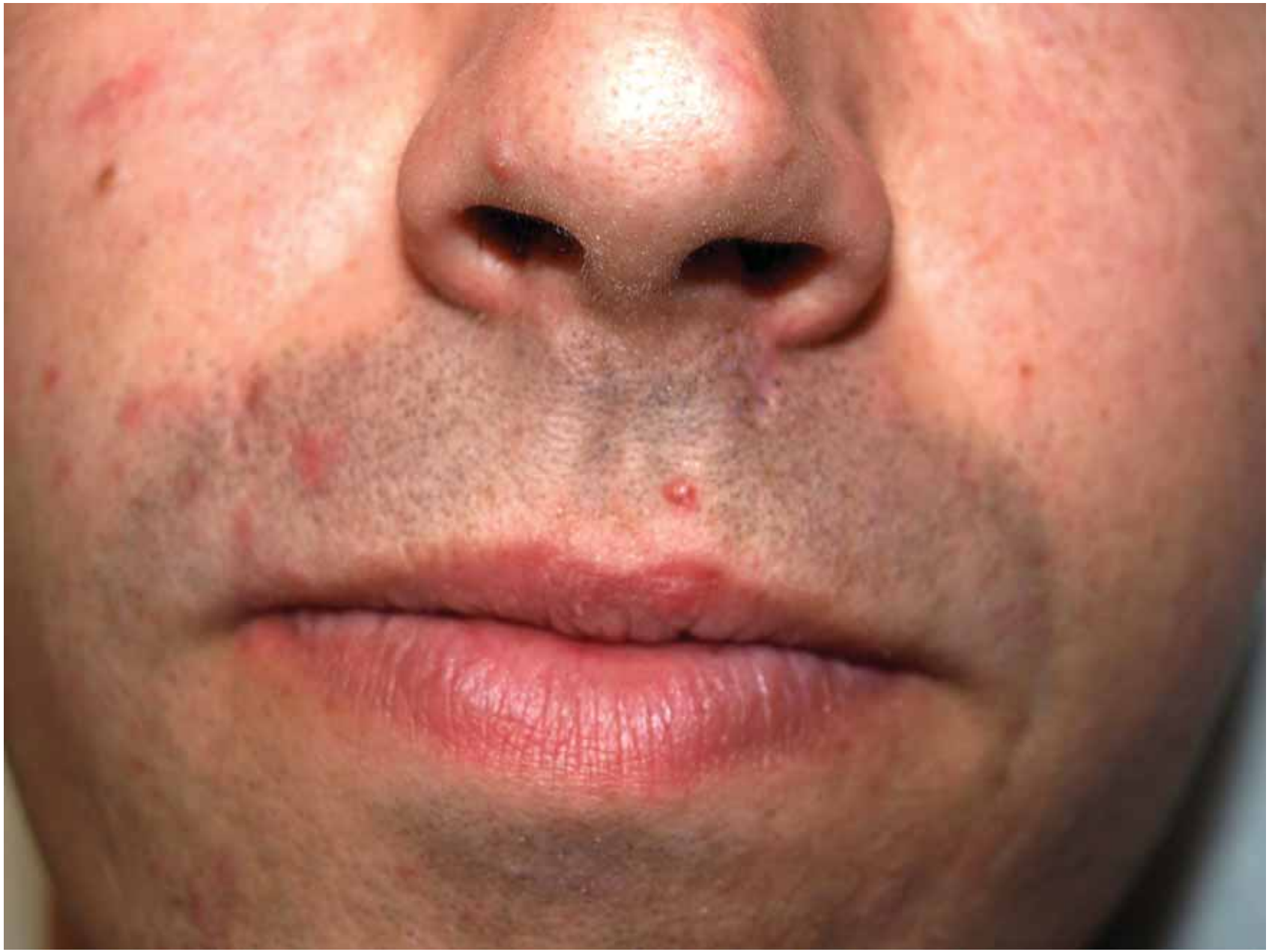
A morbilliform eruption occurs in 33%–56% of patients with IM who take antibiotics, most commonly amoxicillin or ampicillin, and preferentially involves the trunk, upper extremities, and face. It usually begins 2–10 days after the antibiotic is started.[4] There are few histopathological descriptions of the cutaneous rash of IM in the literature. A superficial perivascular lymphocytic infiltrate and interface dermatitis have been reported in patients with IM and antibiotic-induced rash, with one of the reported cases also displaying abundant nuclear dust.[4,5] To the best of our knowledge, the presence of foamy macrophages in this setting has not been described previously. The finding of xanthomatous cells, on the other hand, was observed in skin biopsies of 3 patients with acute graft-versus-host

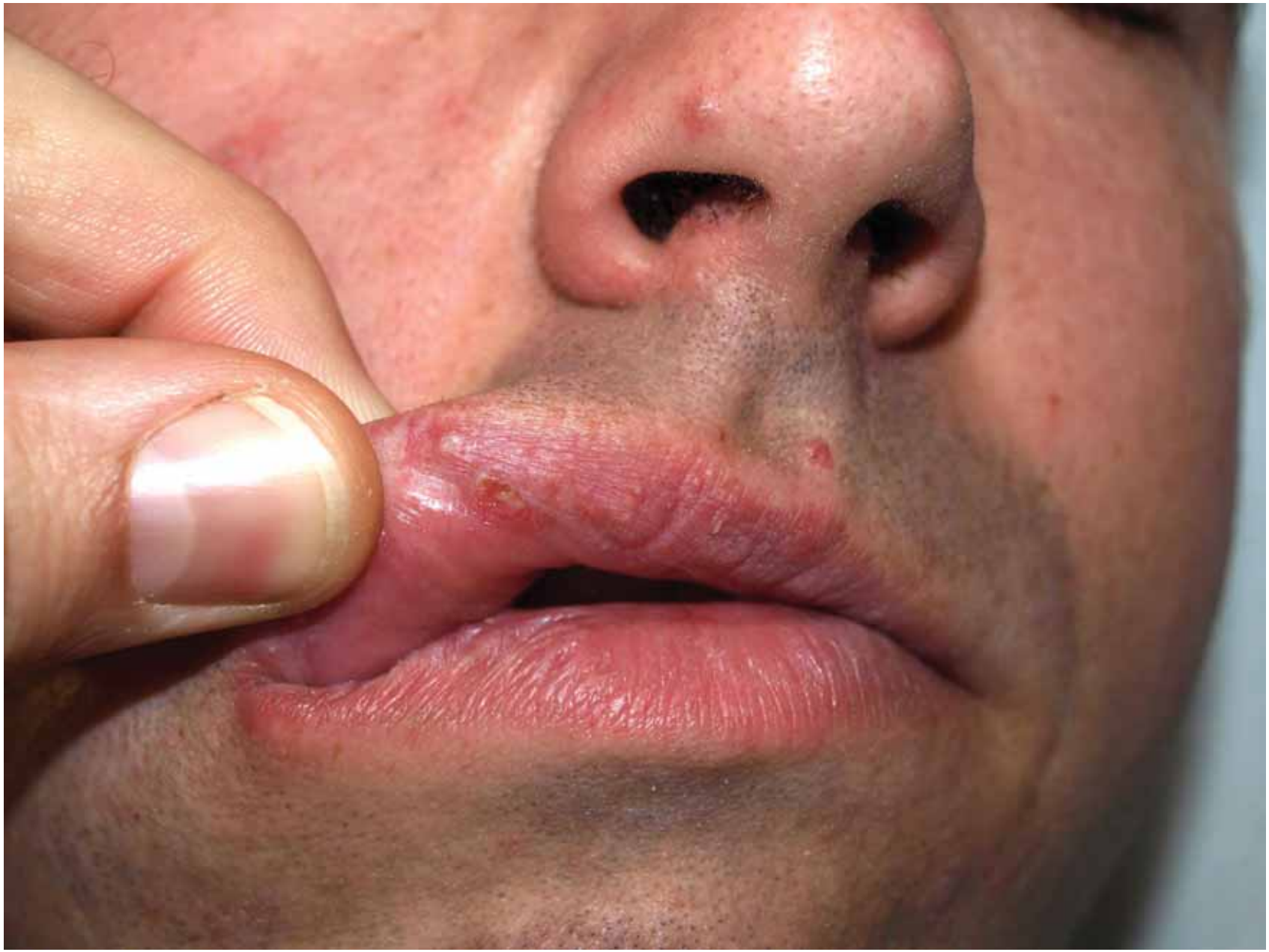
- A 38-year-old man with mononucleosis and amoxicillin-induced rash
- A blood lipid test uncovered marked hypercholesterolemia and hypertriglyceridemia.
- A skin biopsy revealed a superficial perivascular lymphohistiocytic infiltrate with interface dermatitis and many foamy macrophages in the papillary dermis and around the vessels of the superficial dermal plexus
- We believe that the incidental finding of foamy cells in graft-versus-host disease cases and in our case are likely related to the presence of severe liver disease with cholestatic hepatopathy and secondary hyperlipidemia in different background conditions

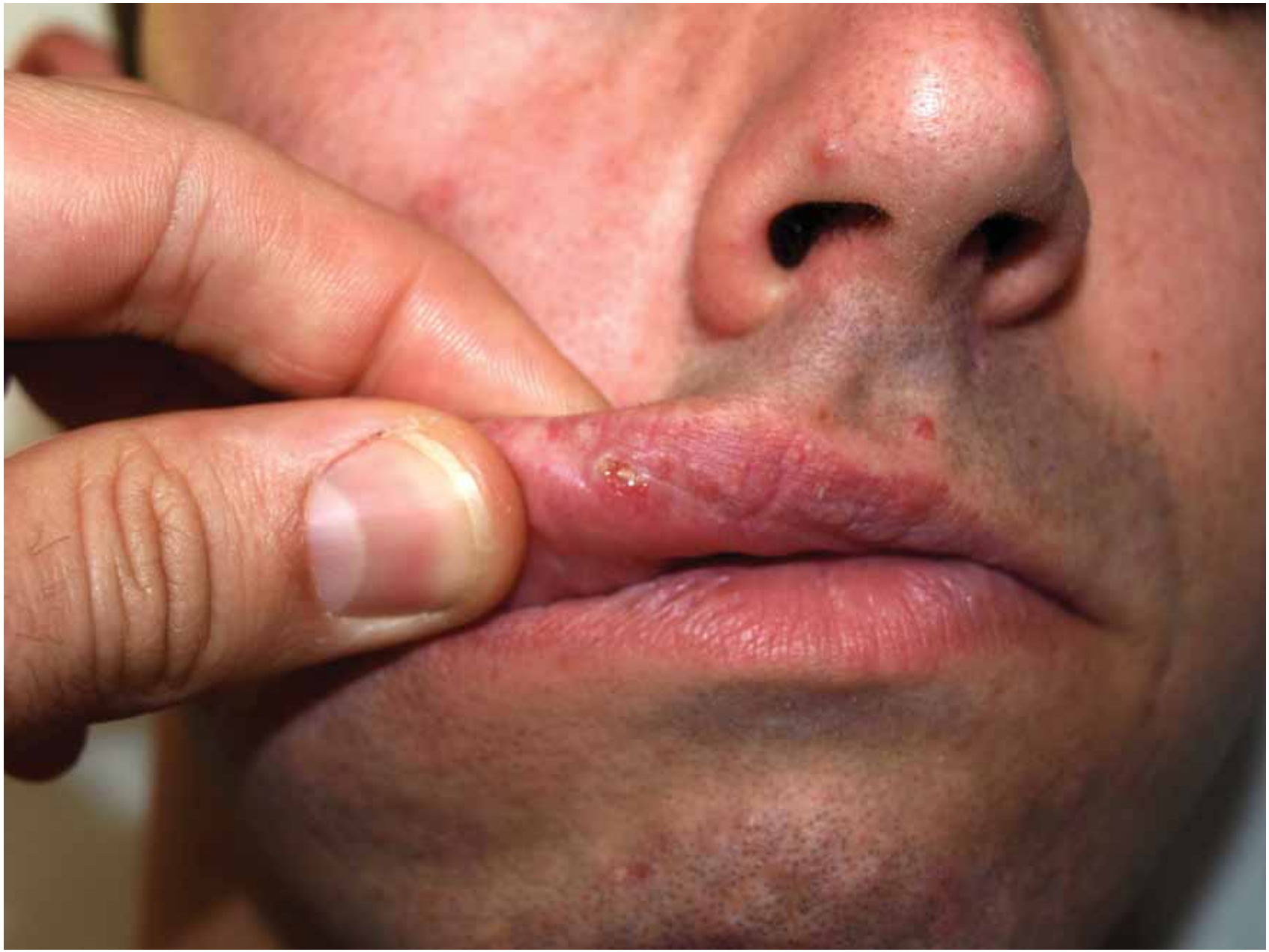
Case 3

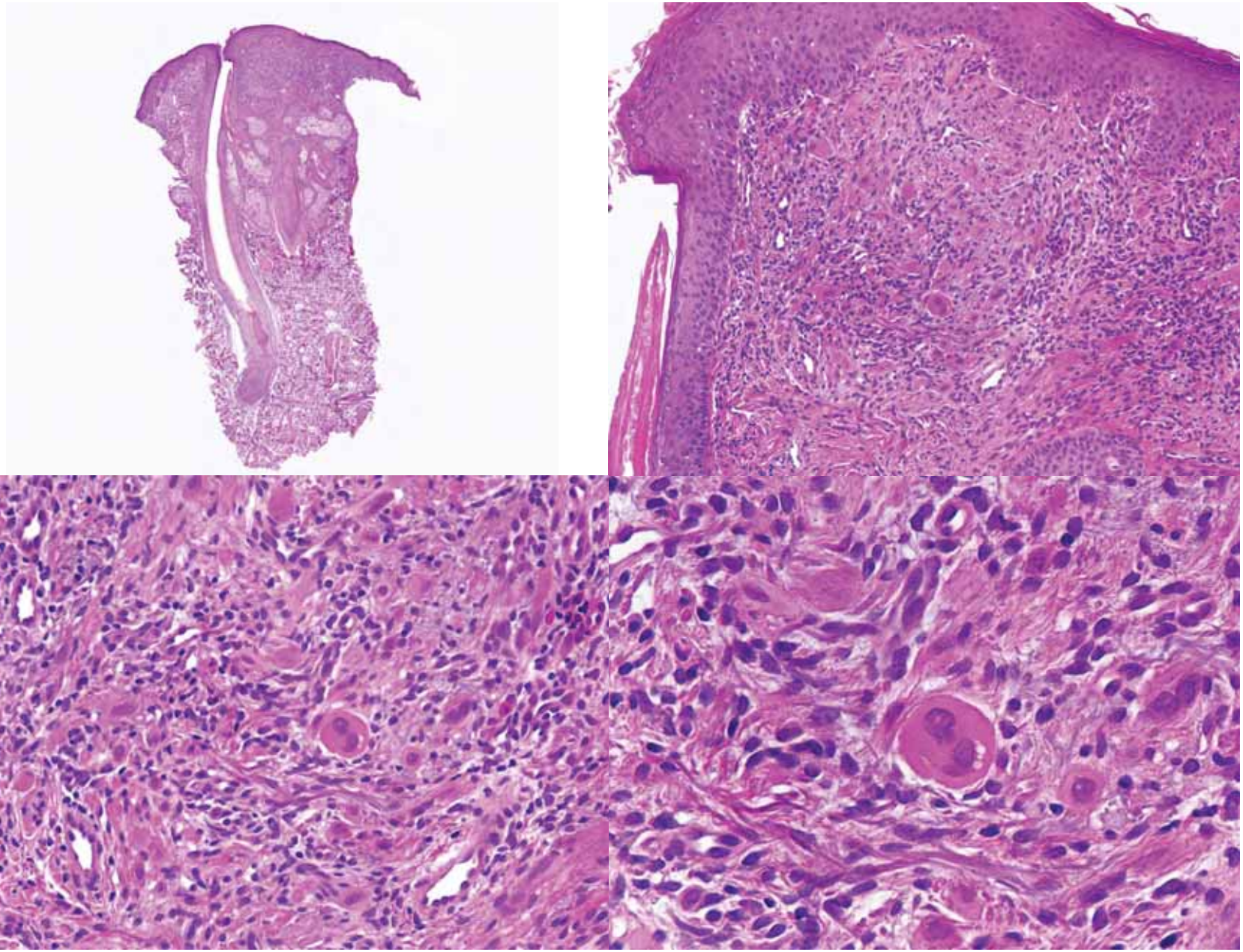
A 27-year-old male presented with asymptomatic papular lesions around the mouth that developed along the last two months

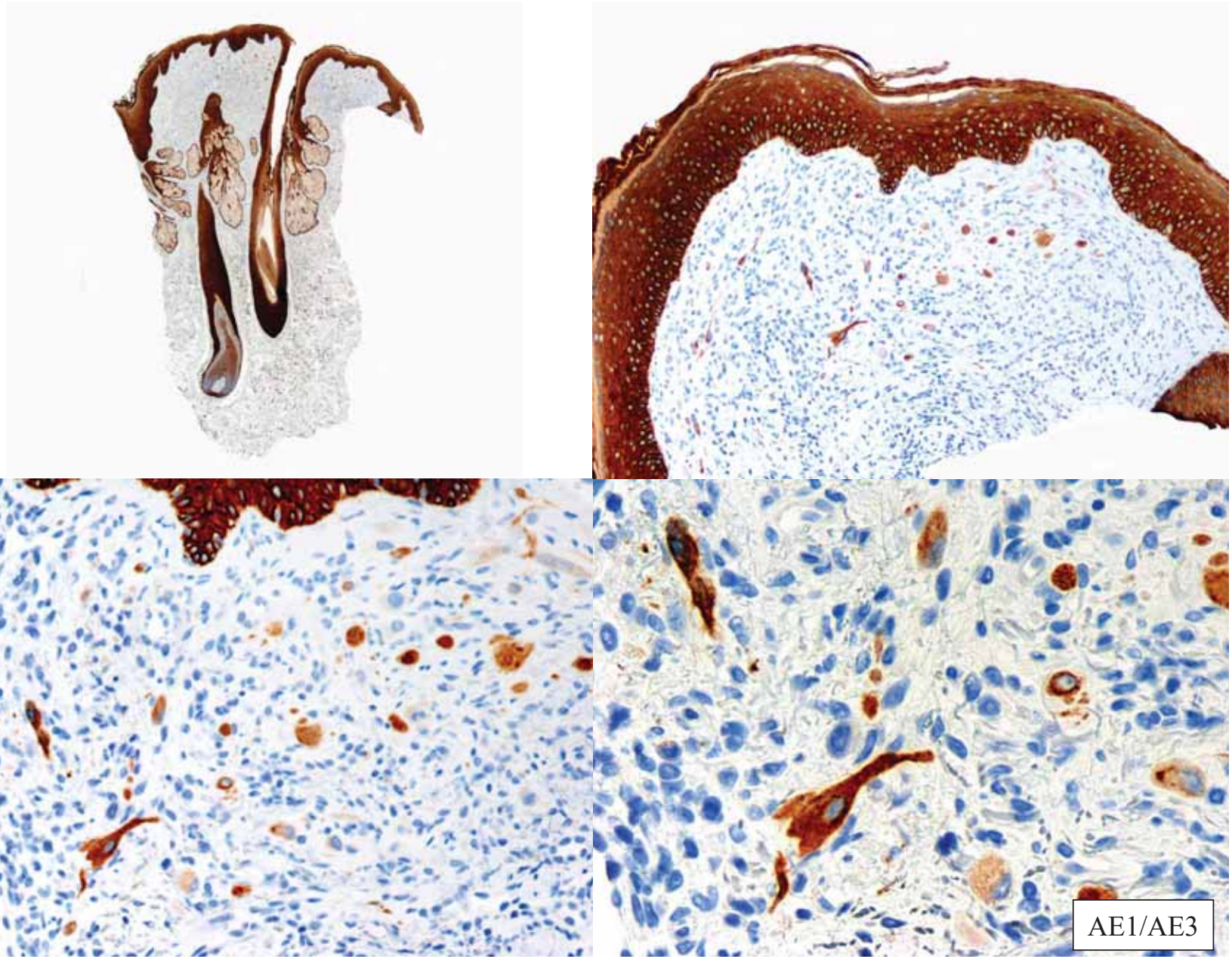








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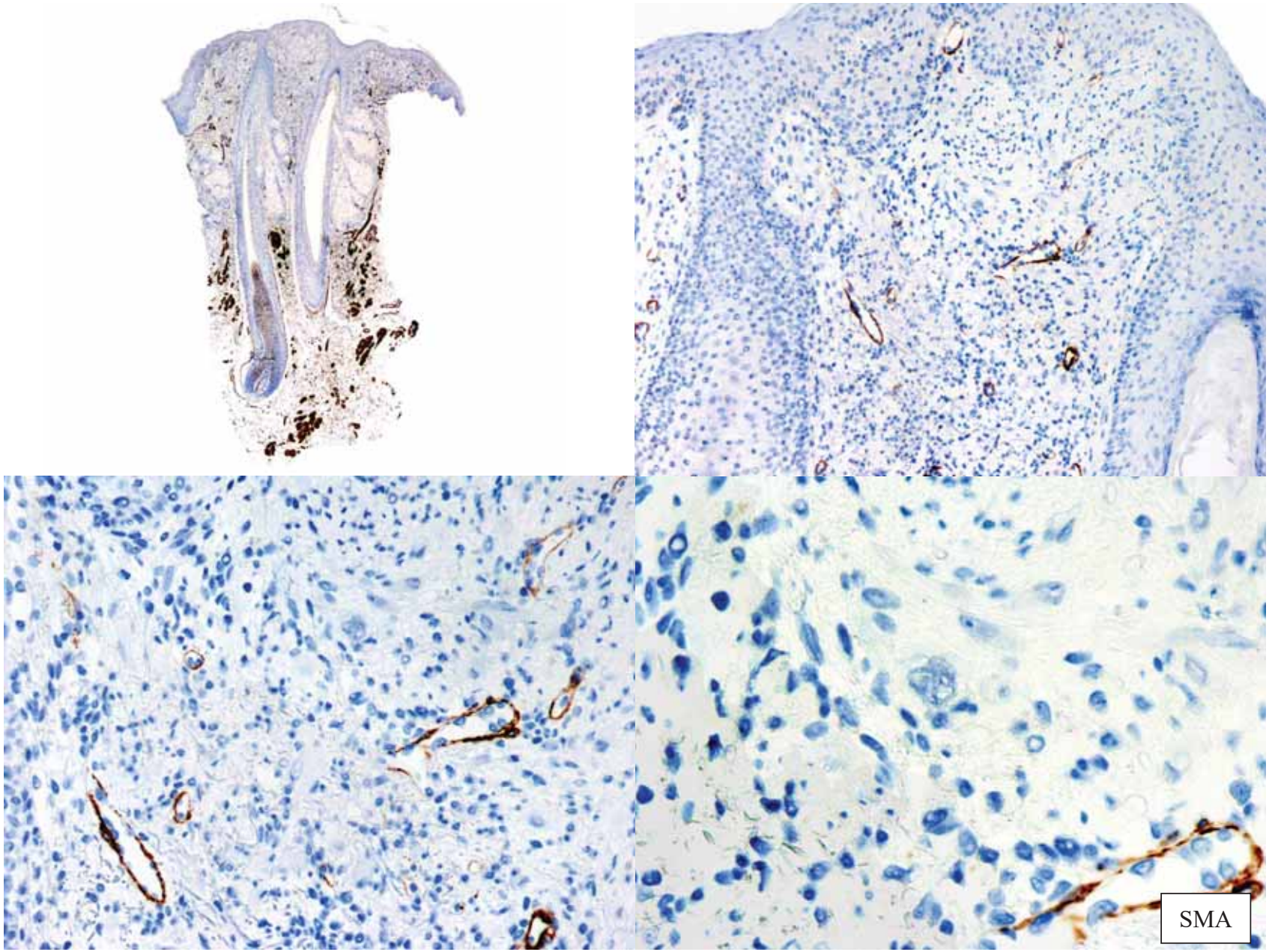
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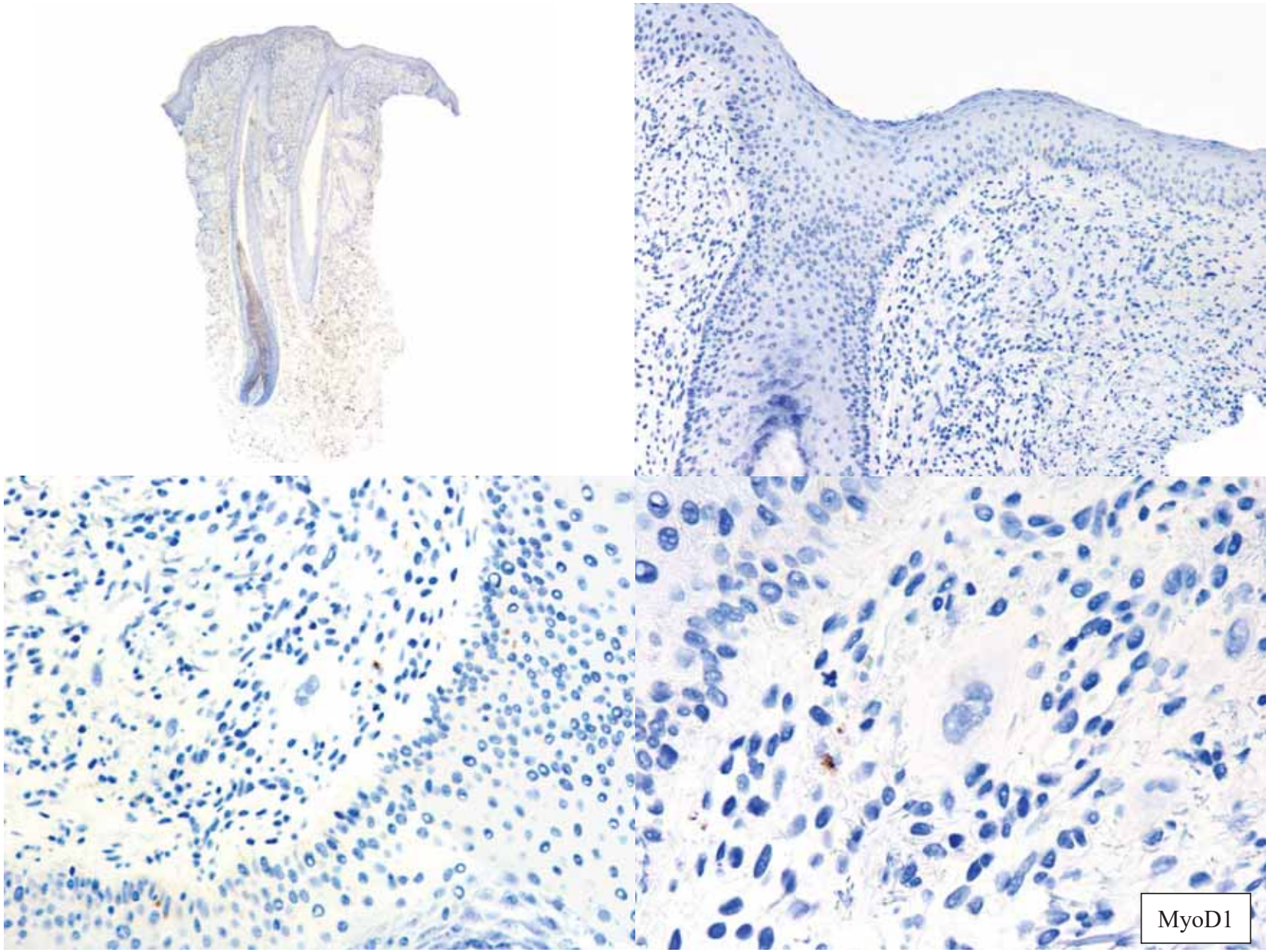
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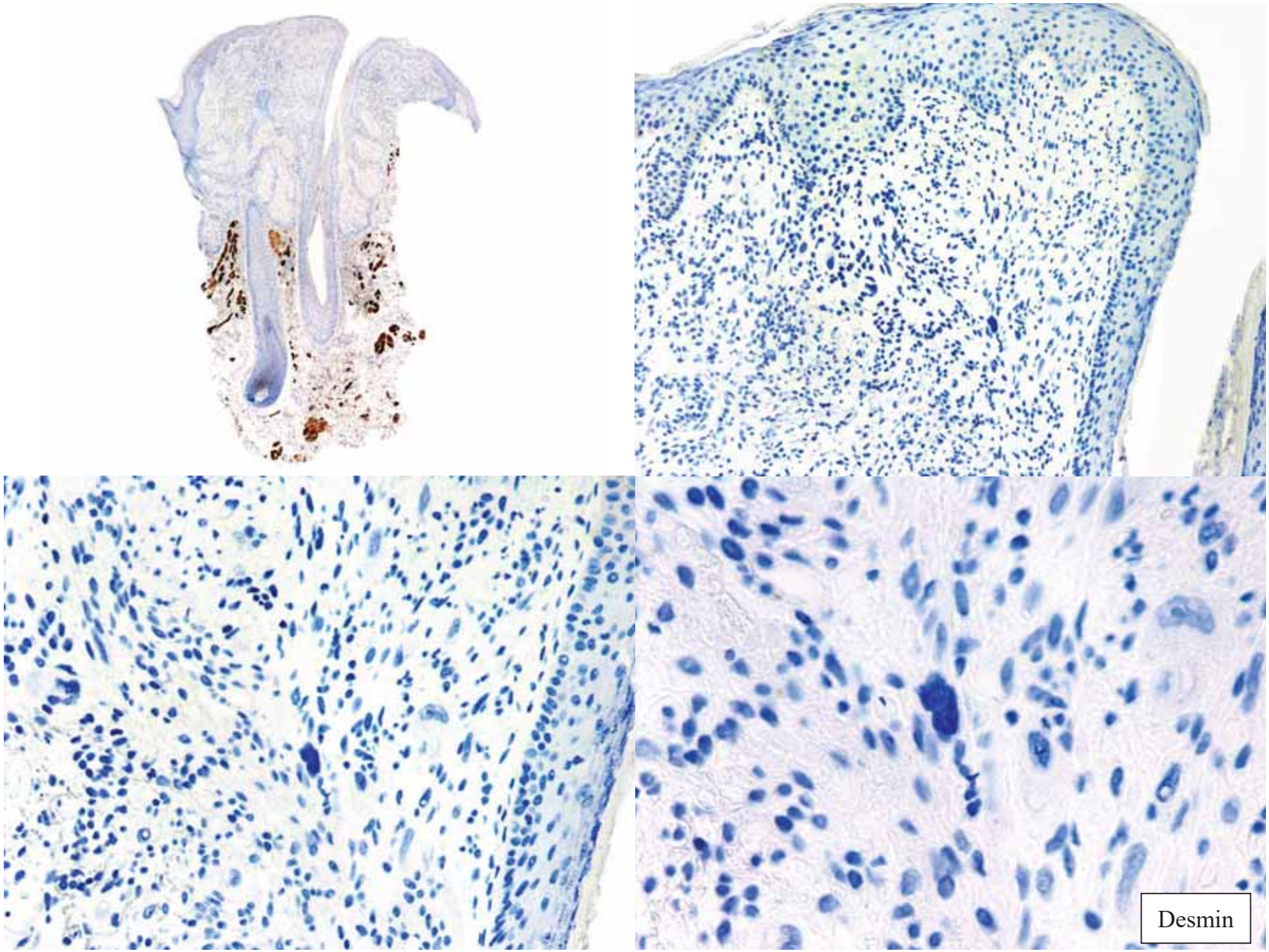
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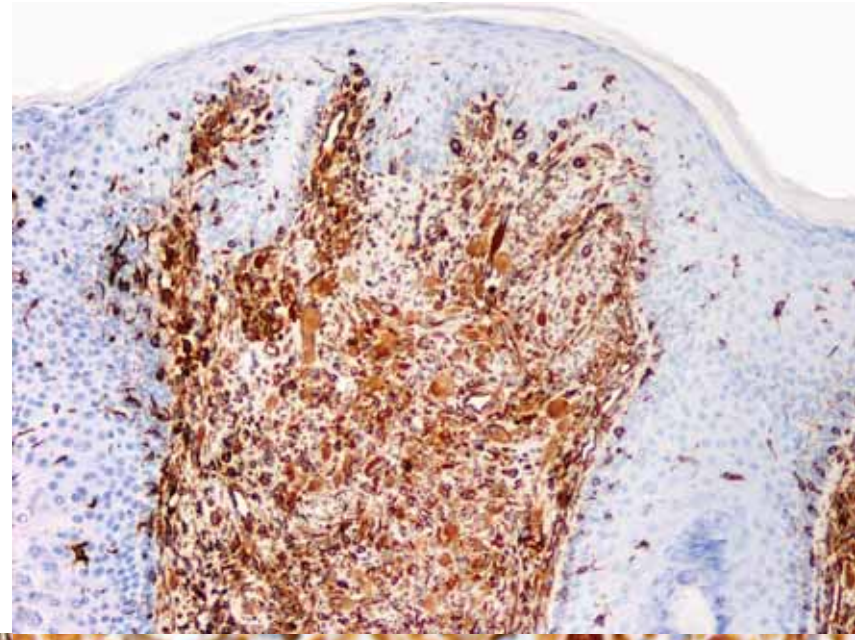
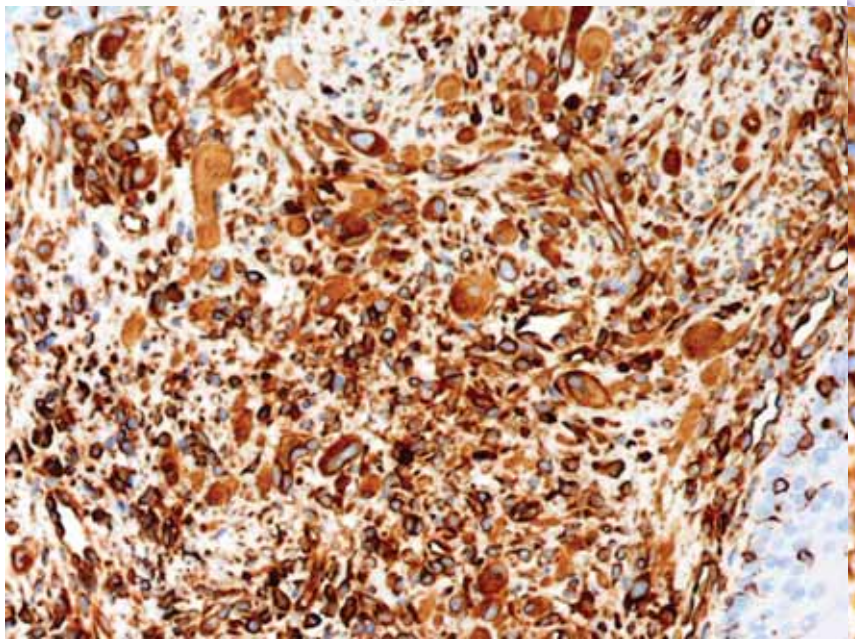
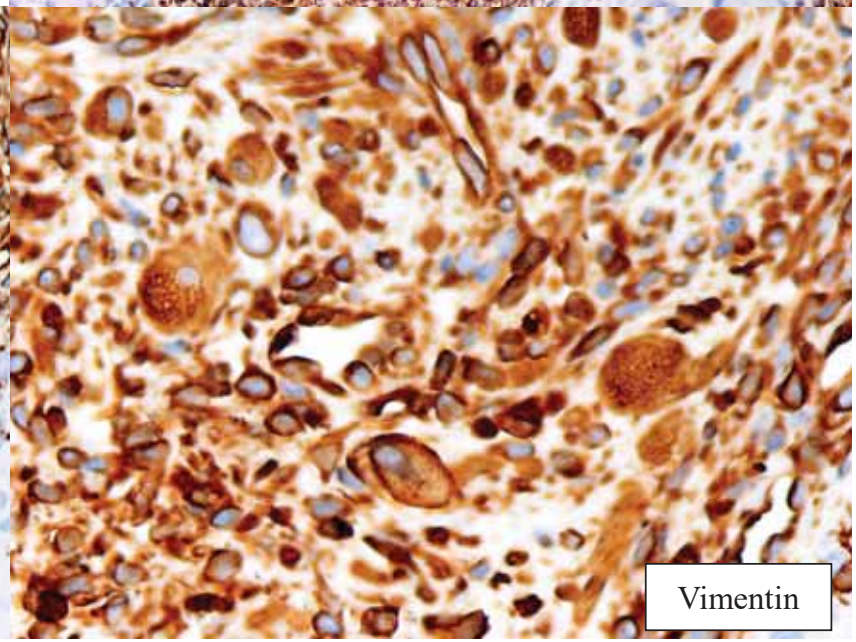
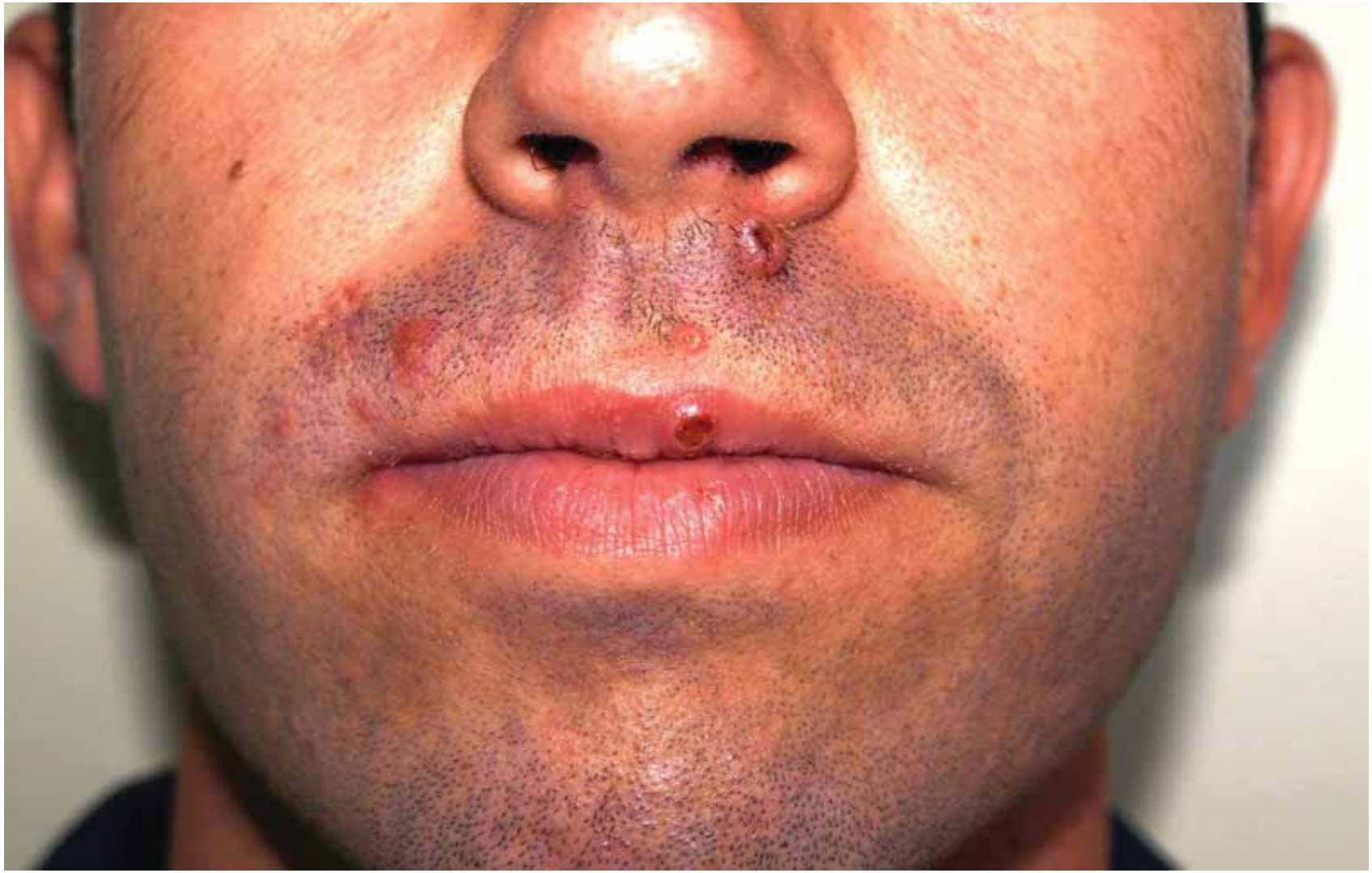
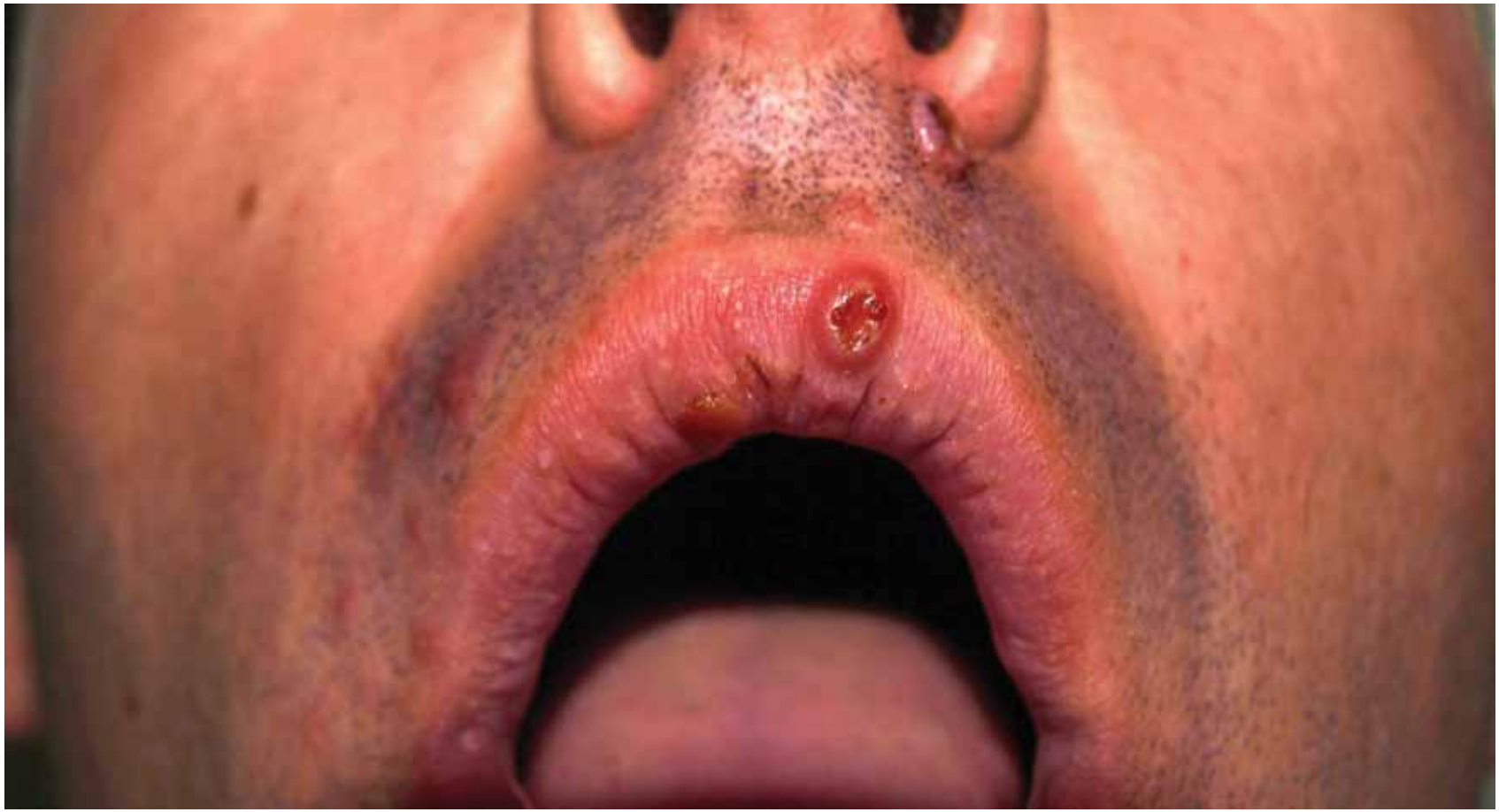


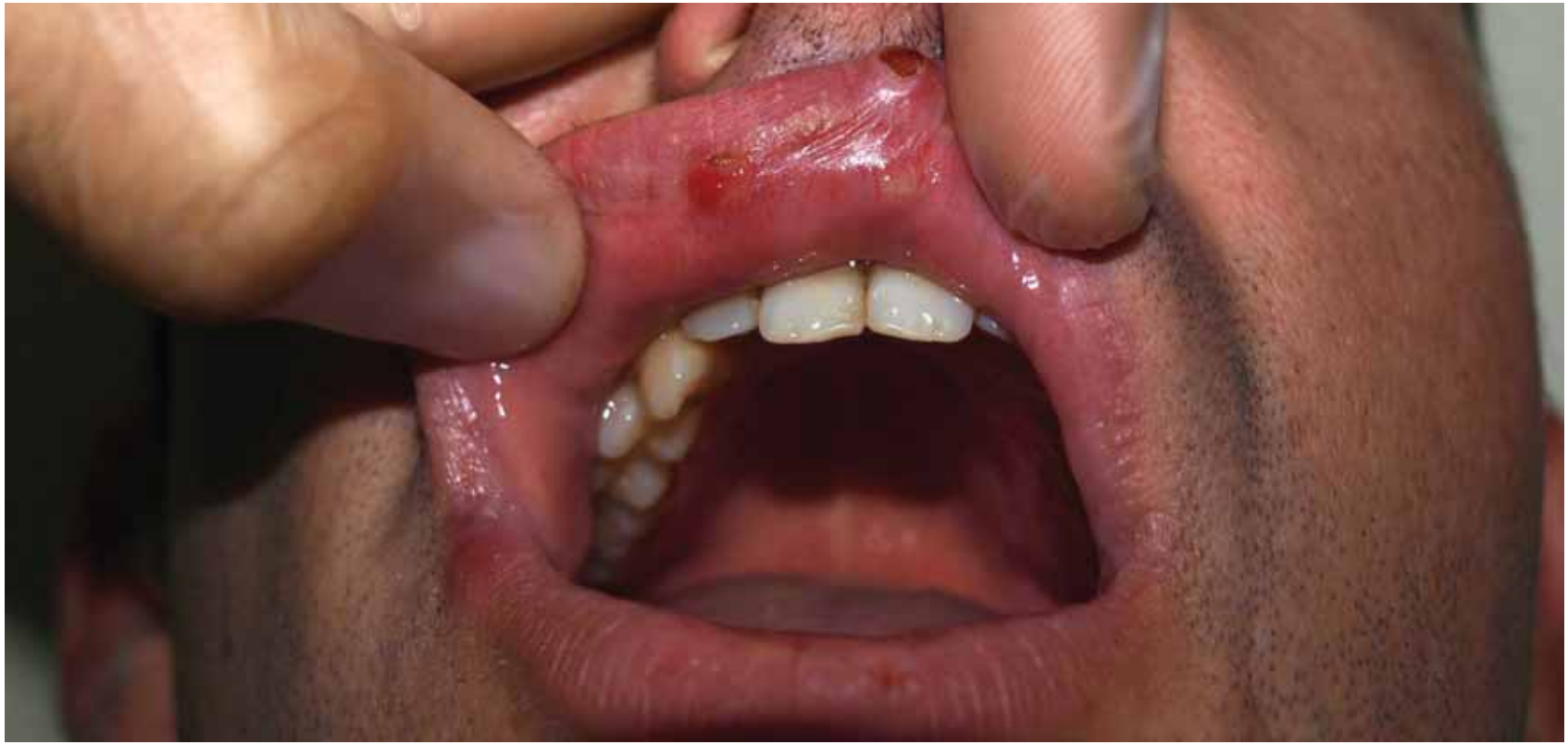


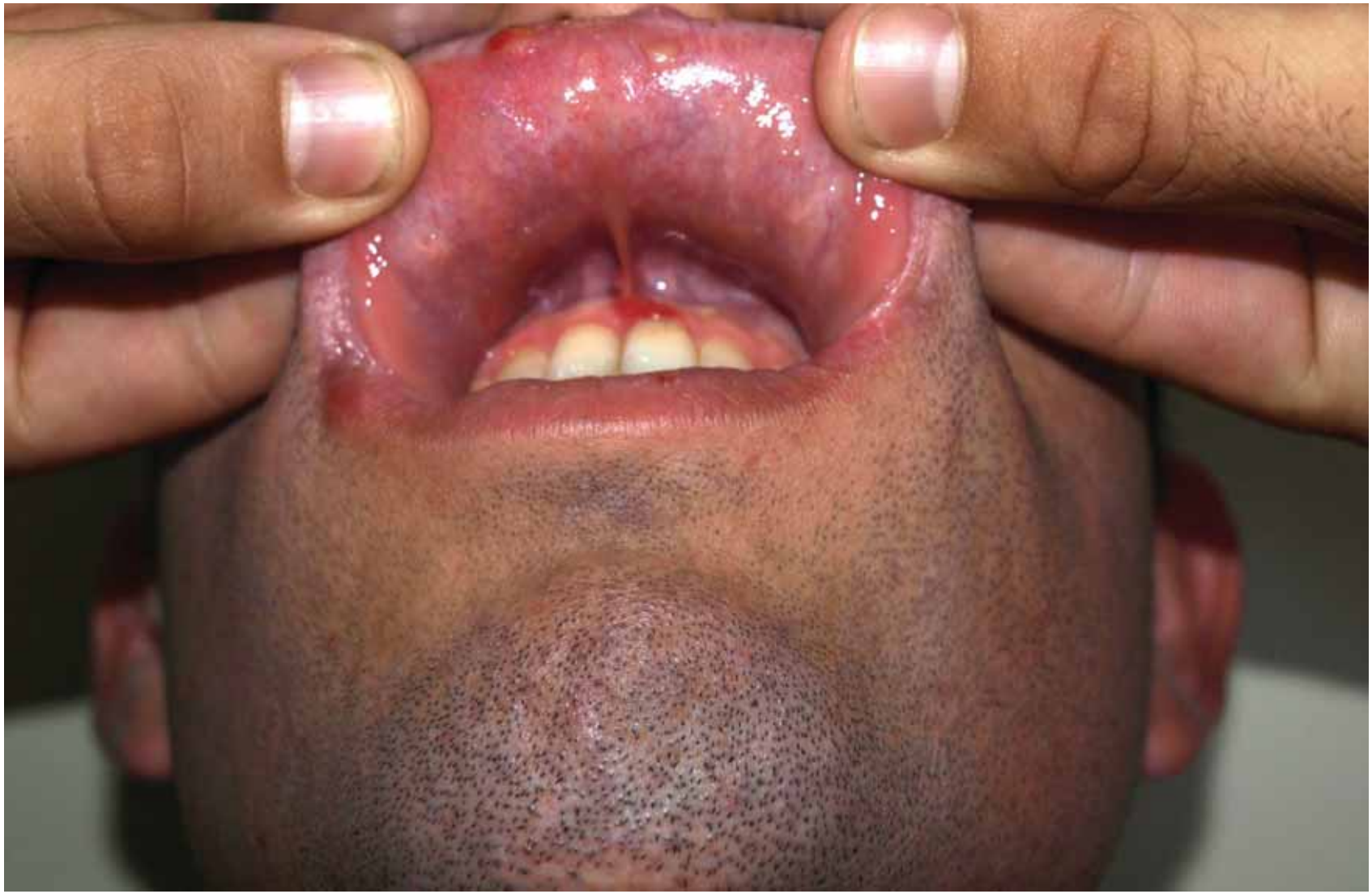

Vimentin

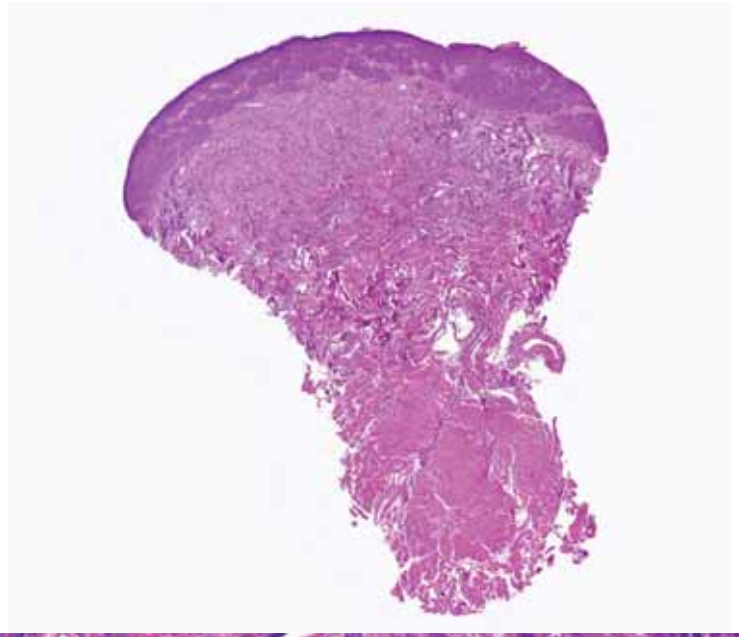
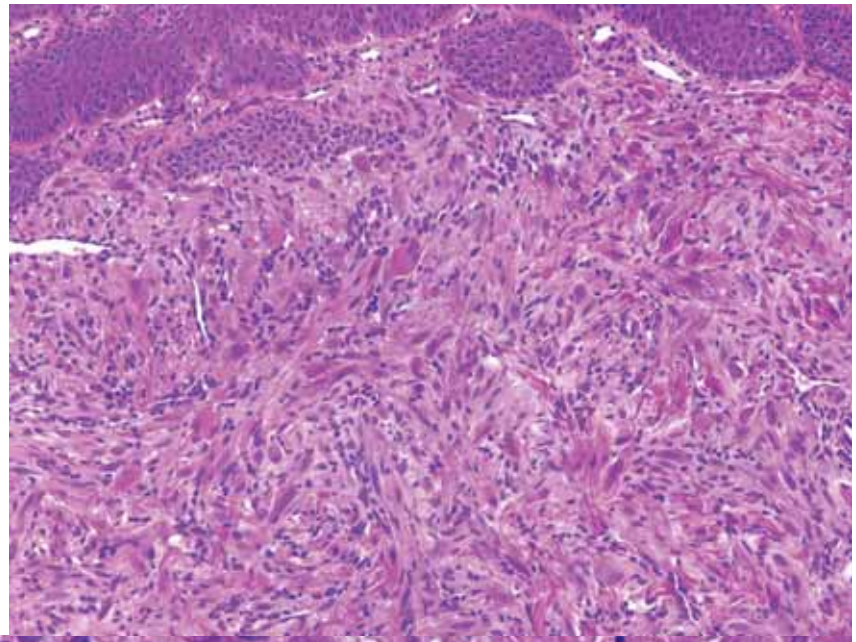
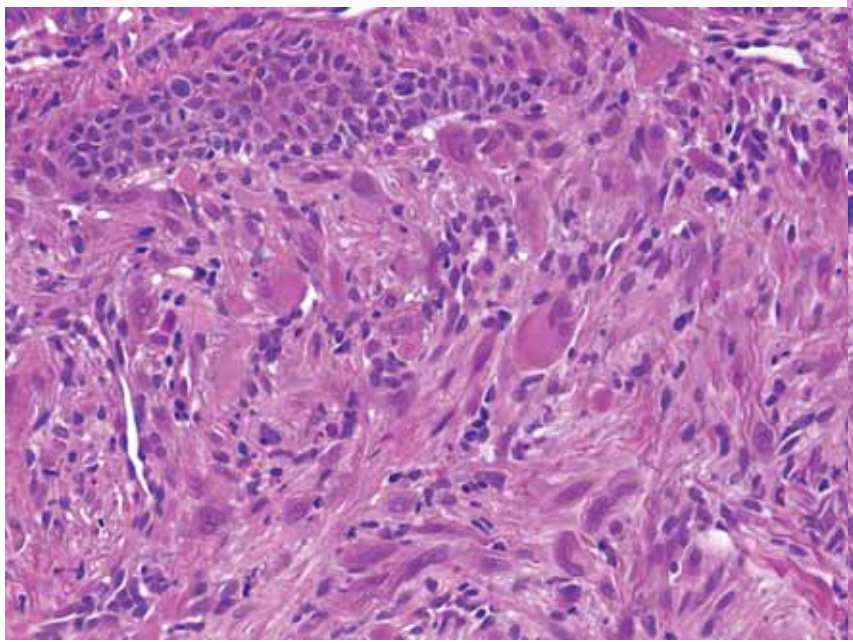
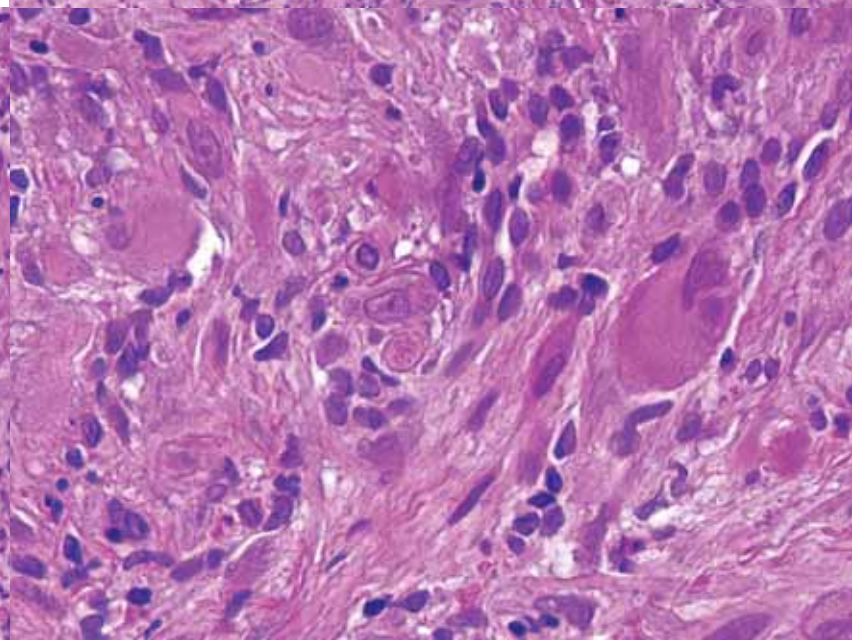
- Four months later…

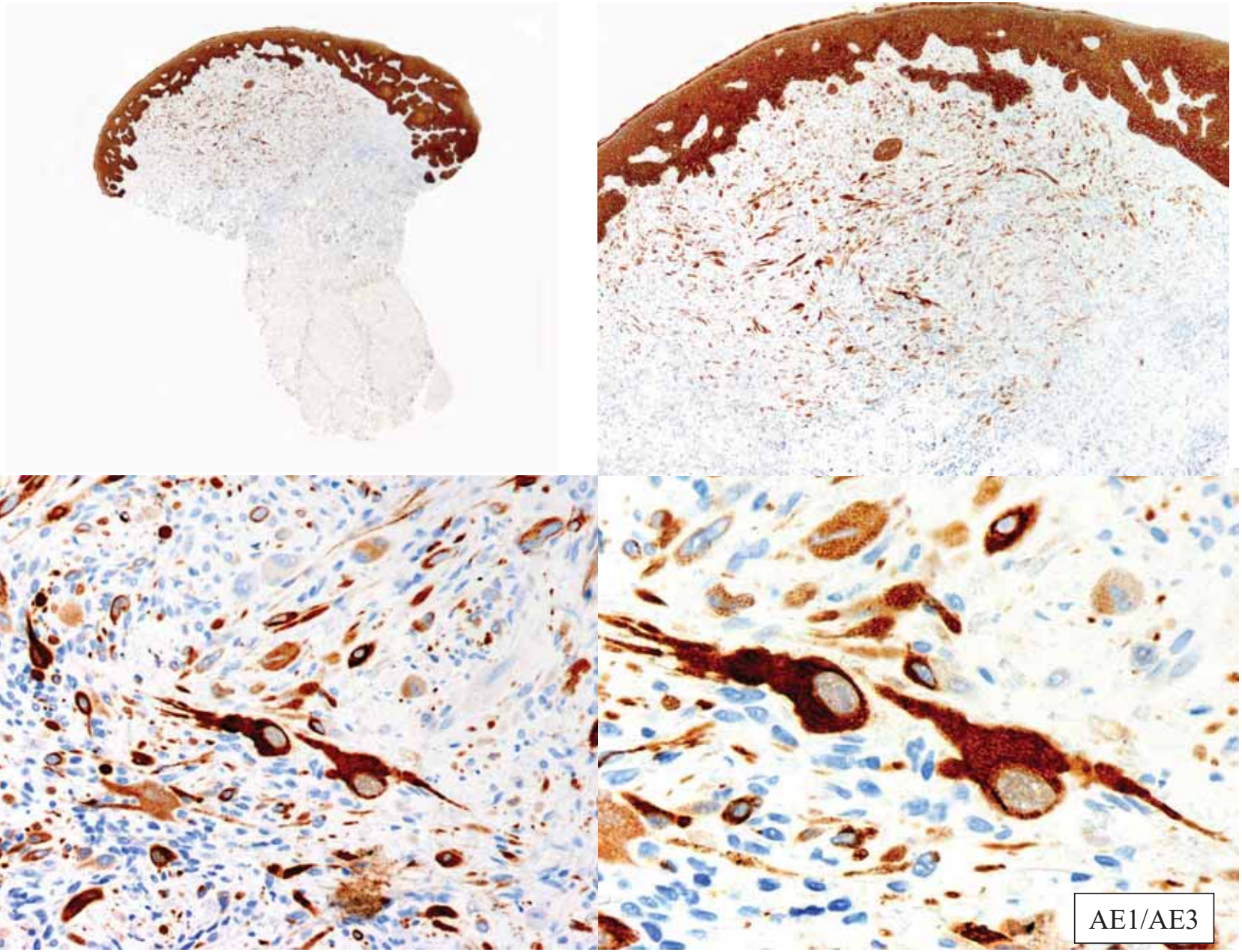






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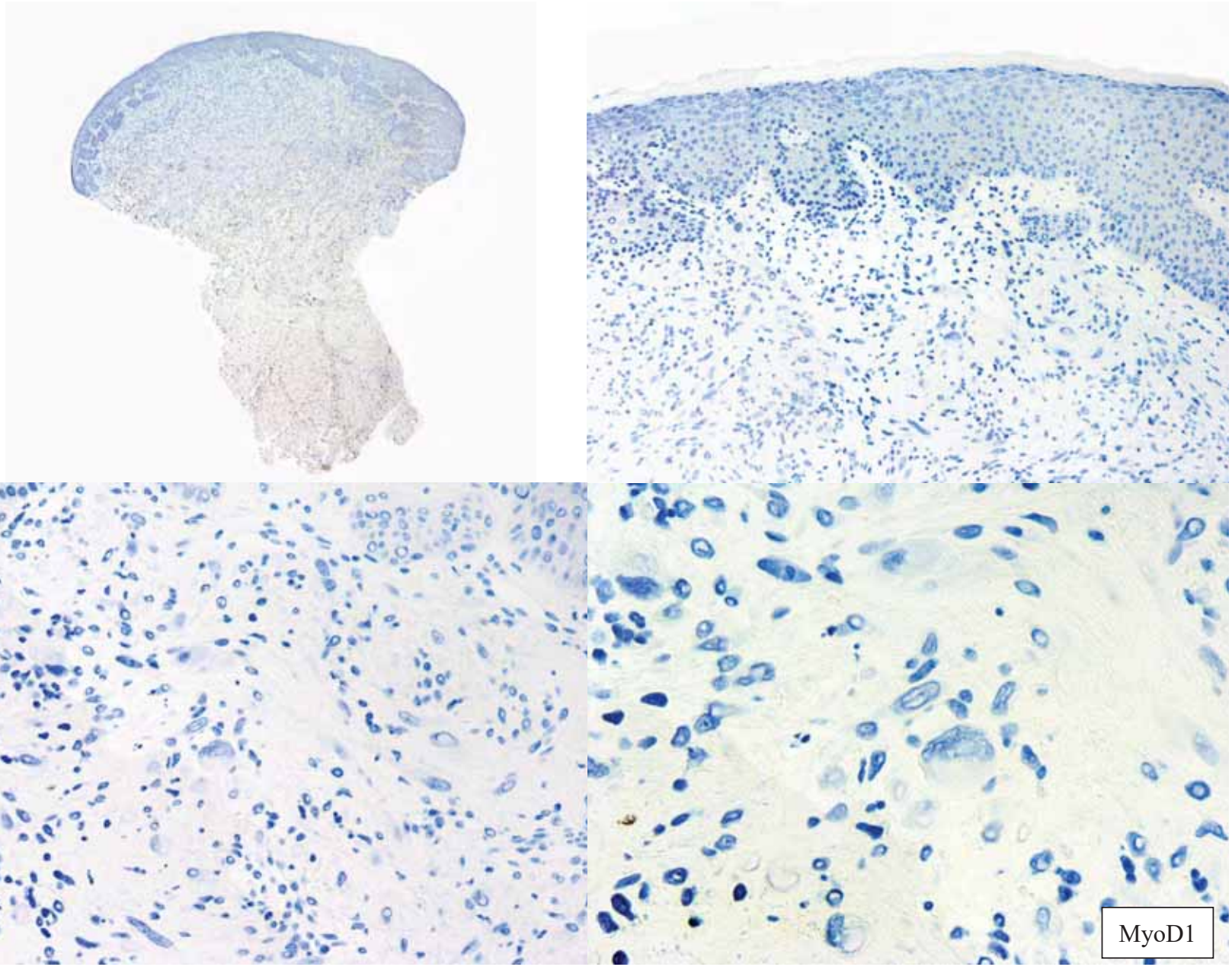
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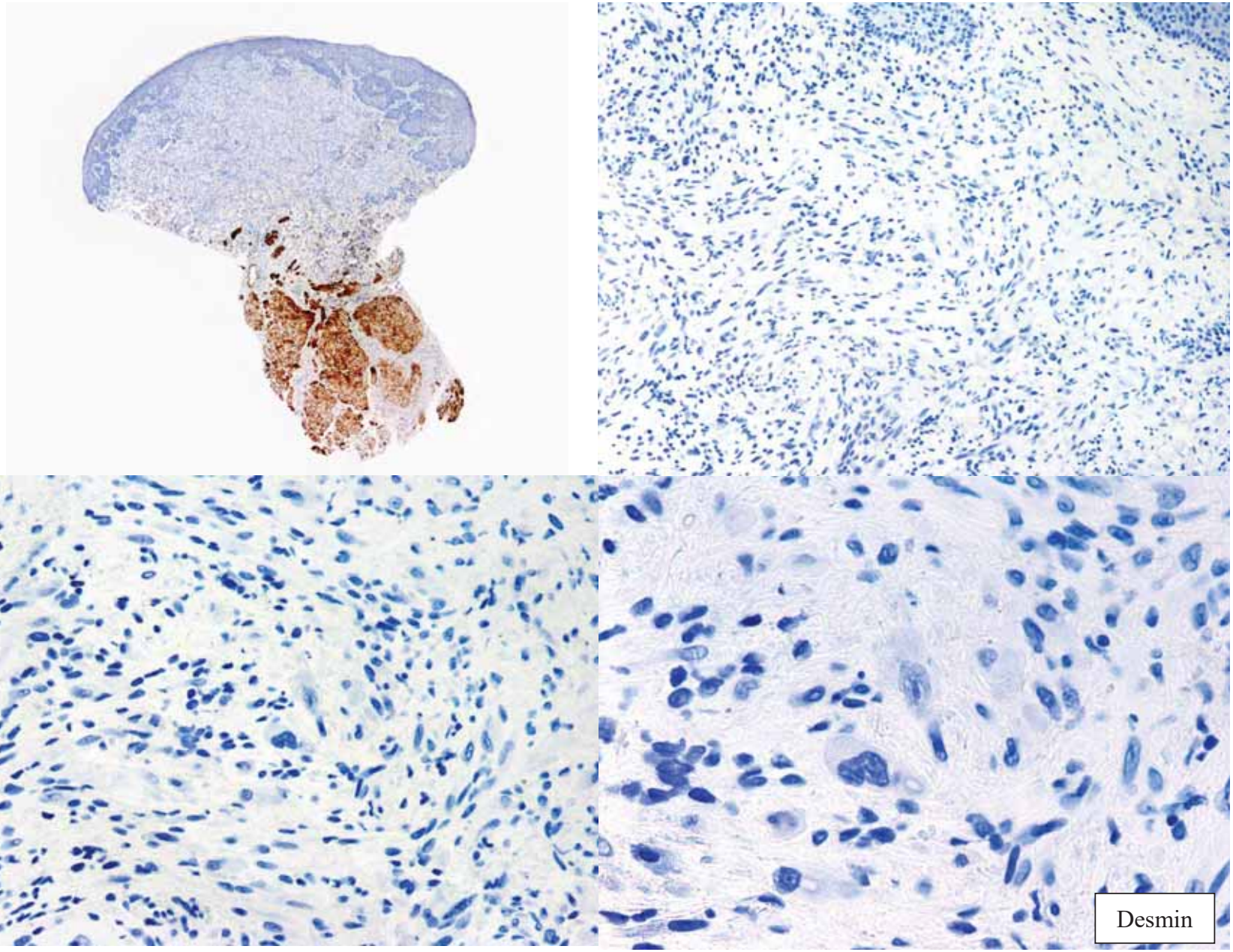
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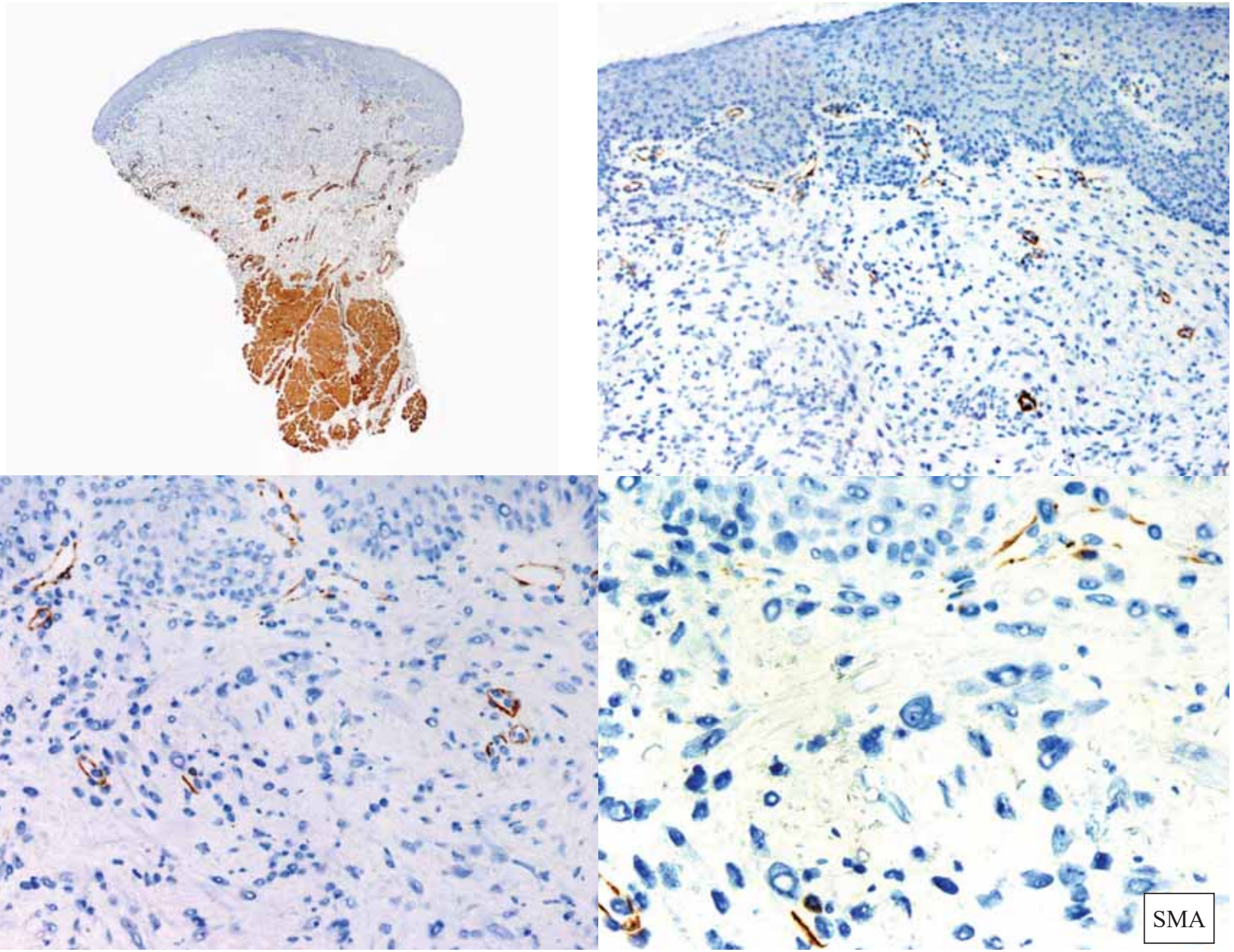
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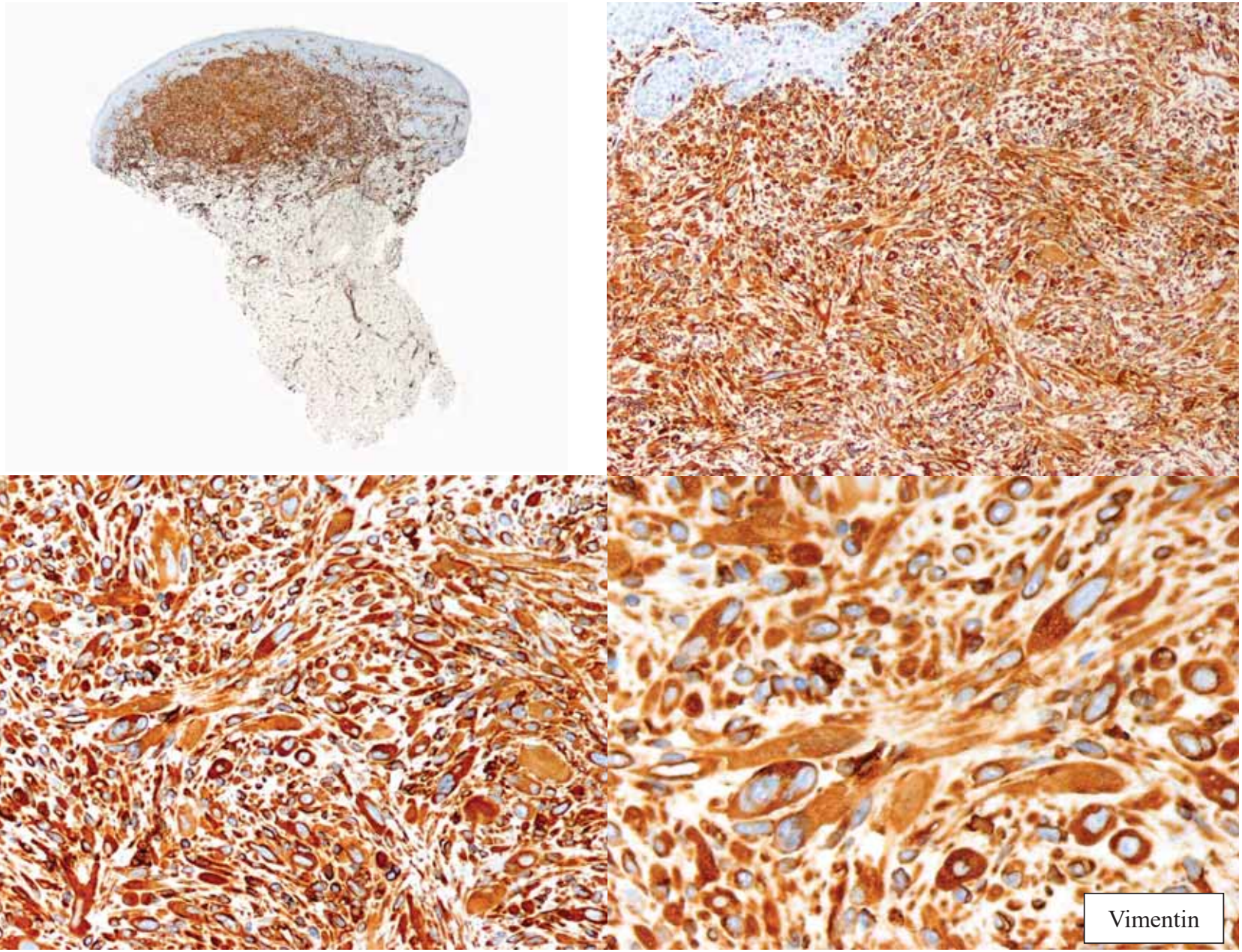
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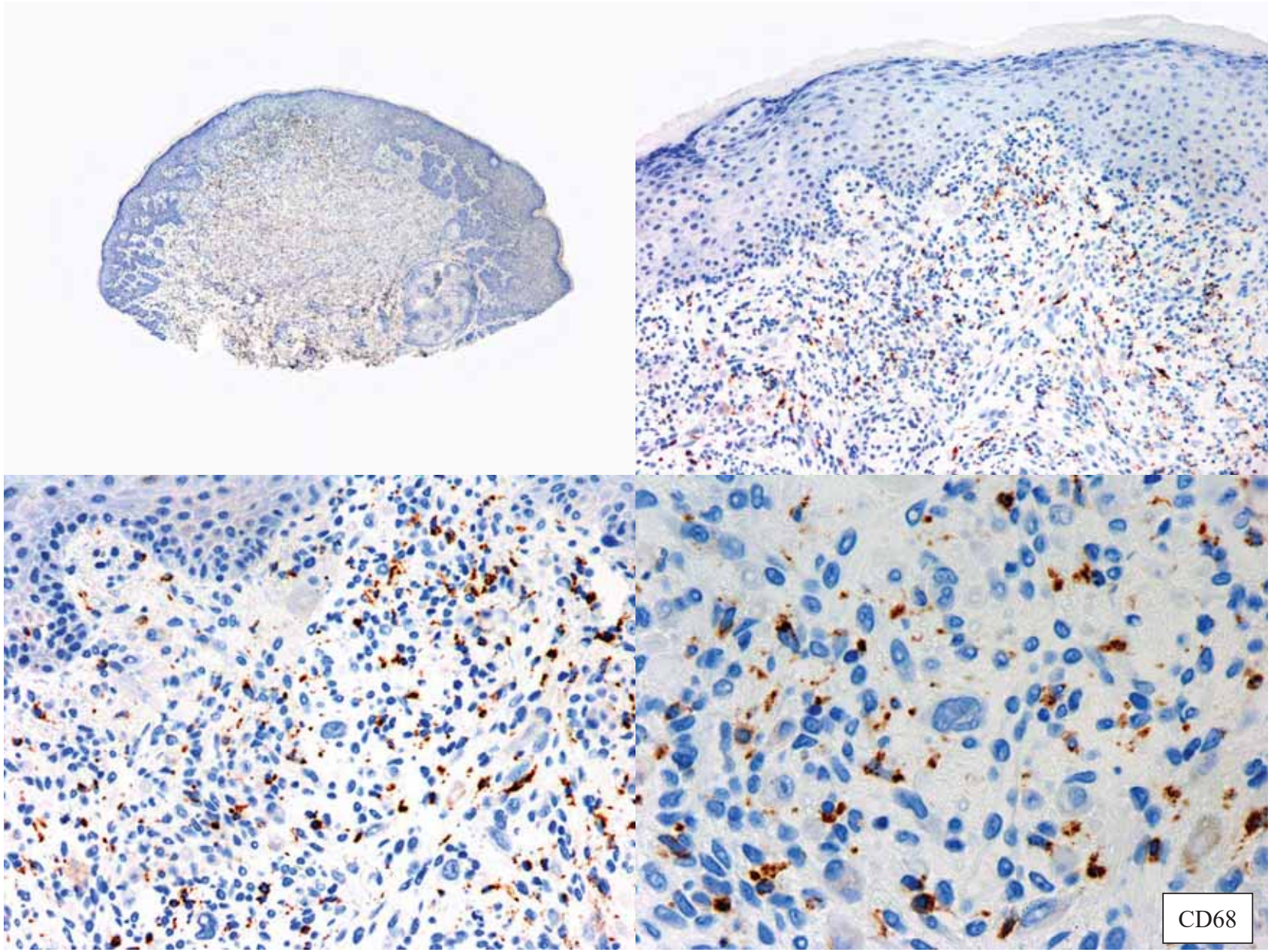
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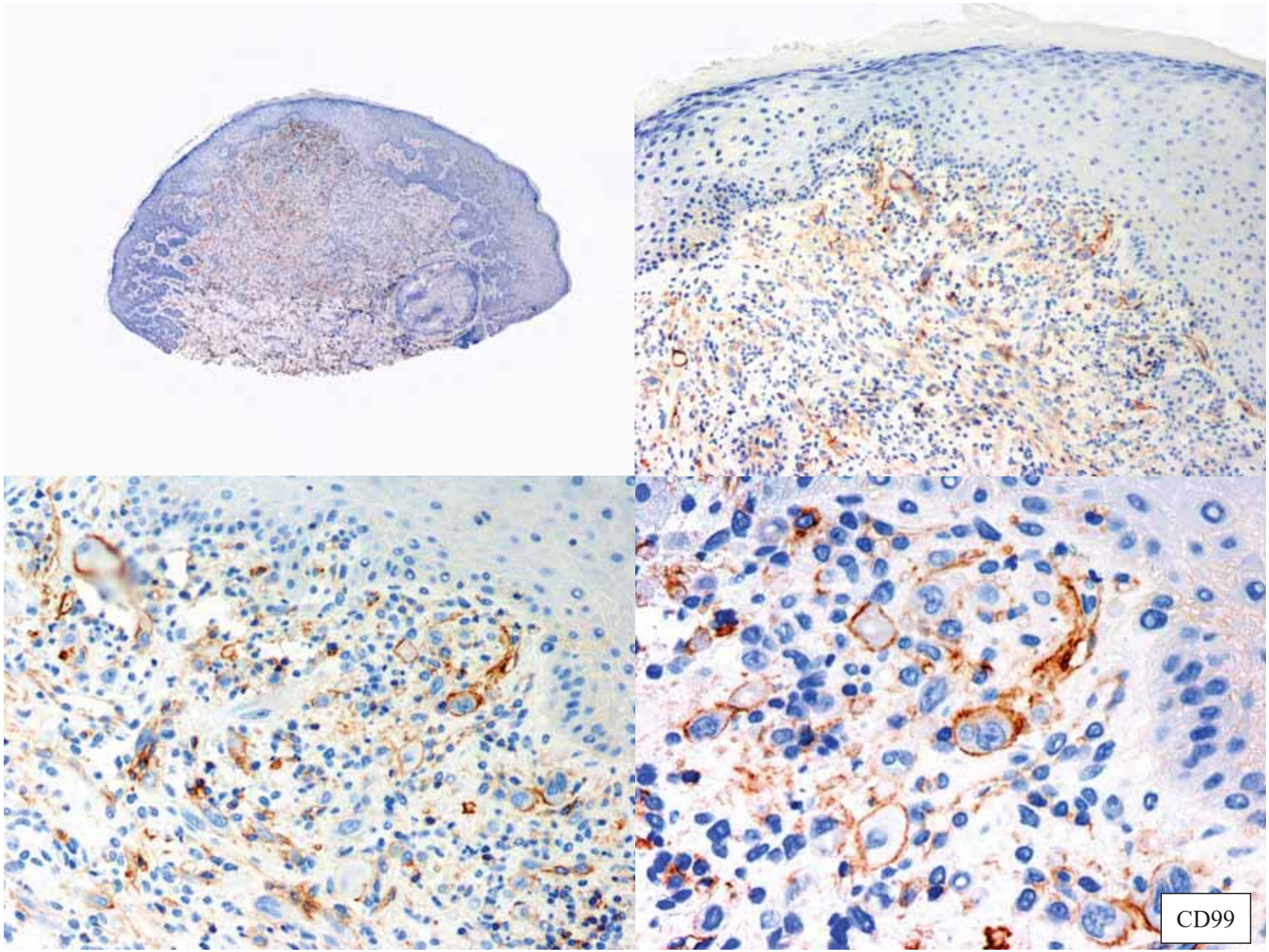
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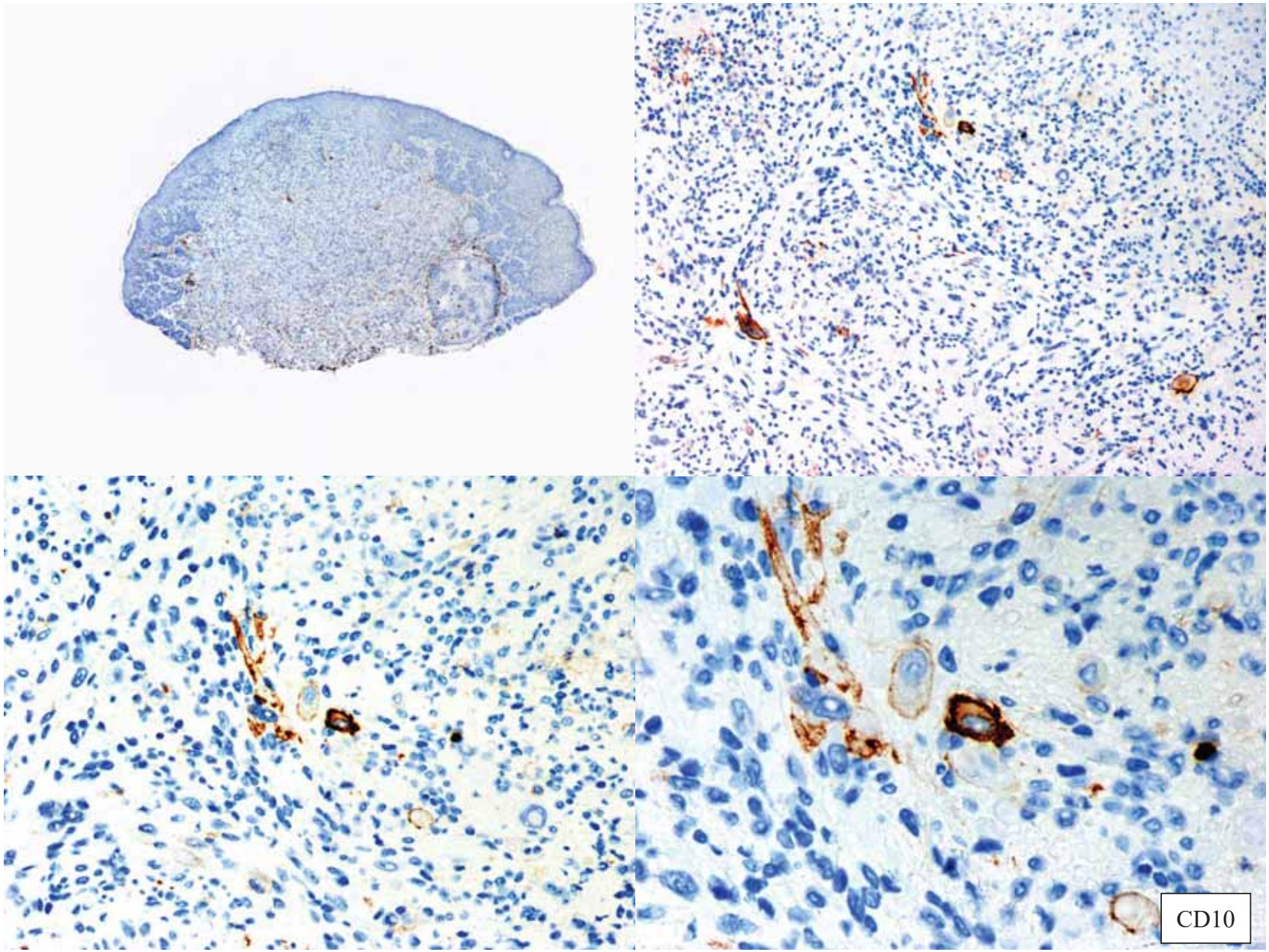
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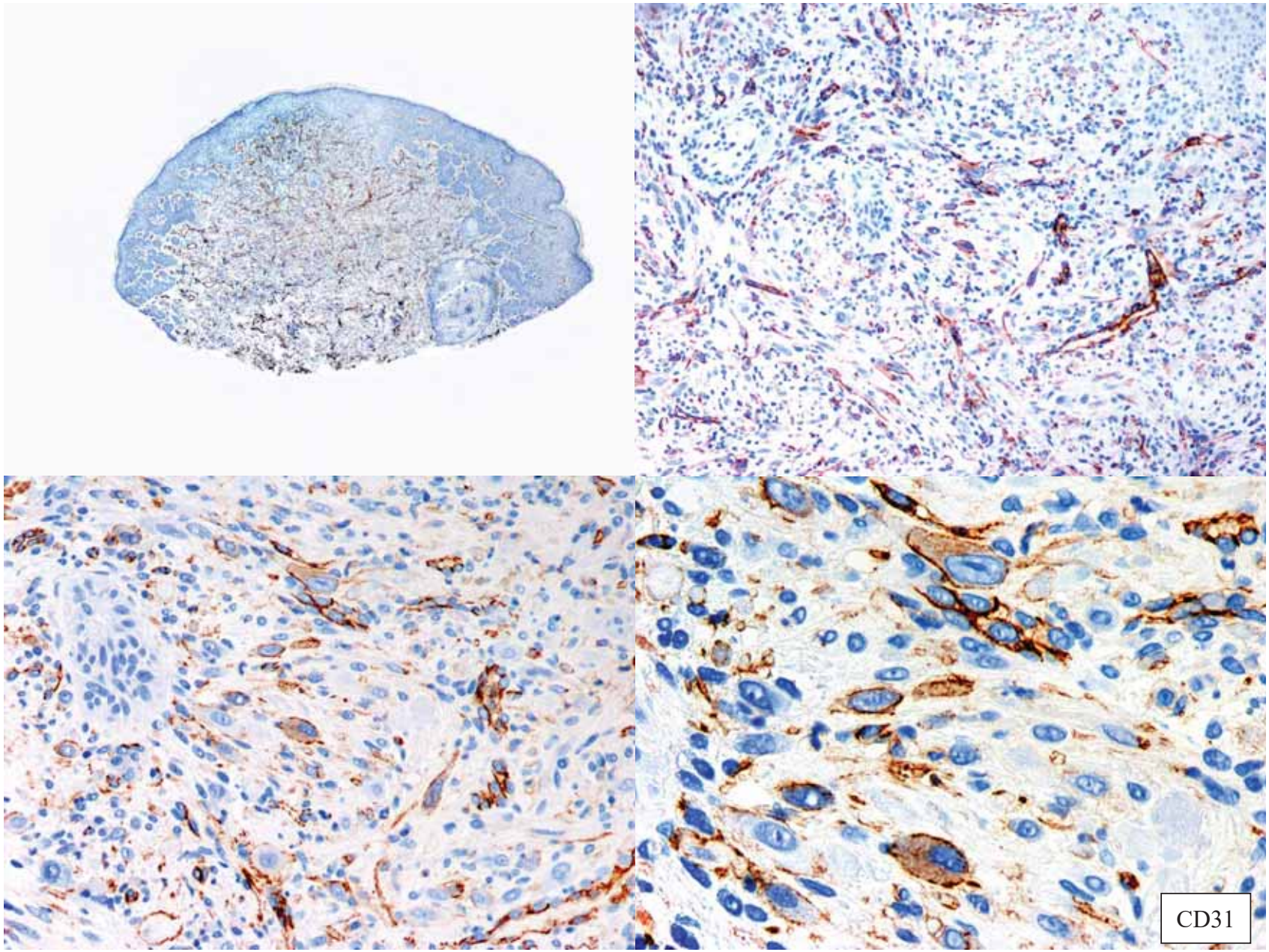
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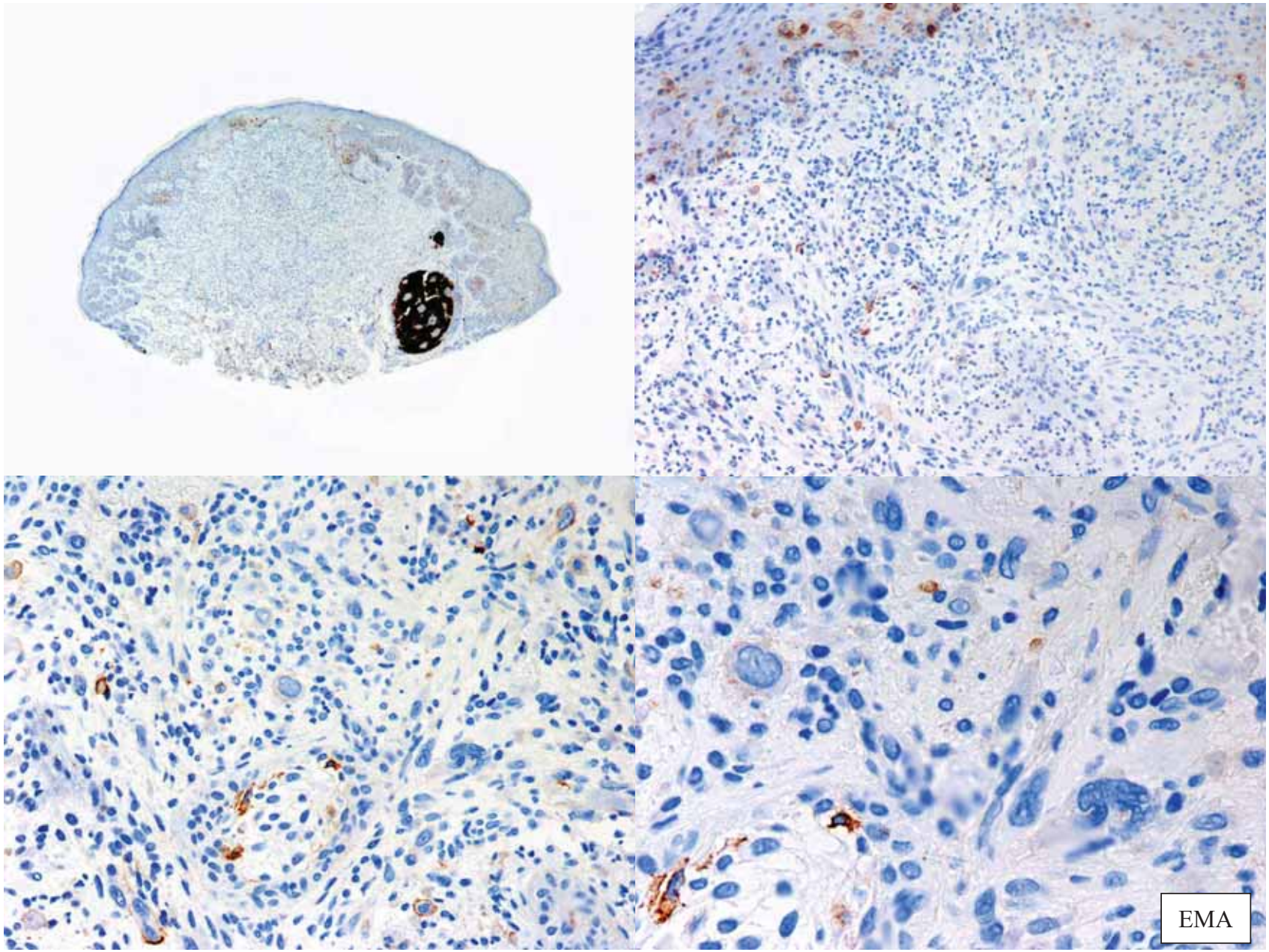
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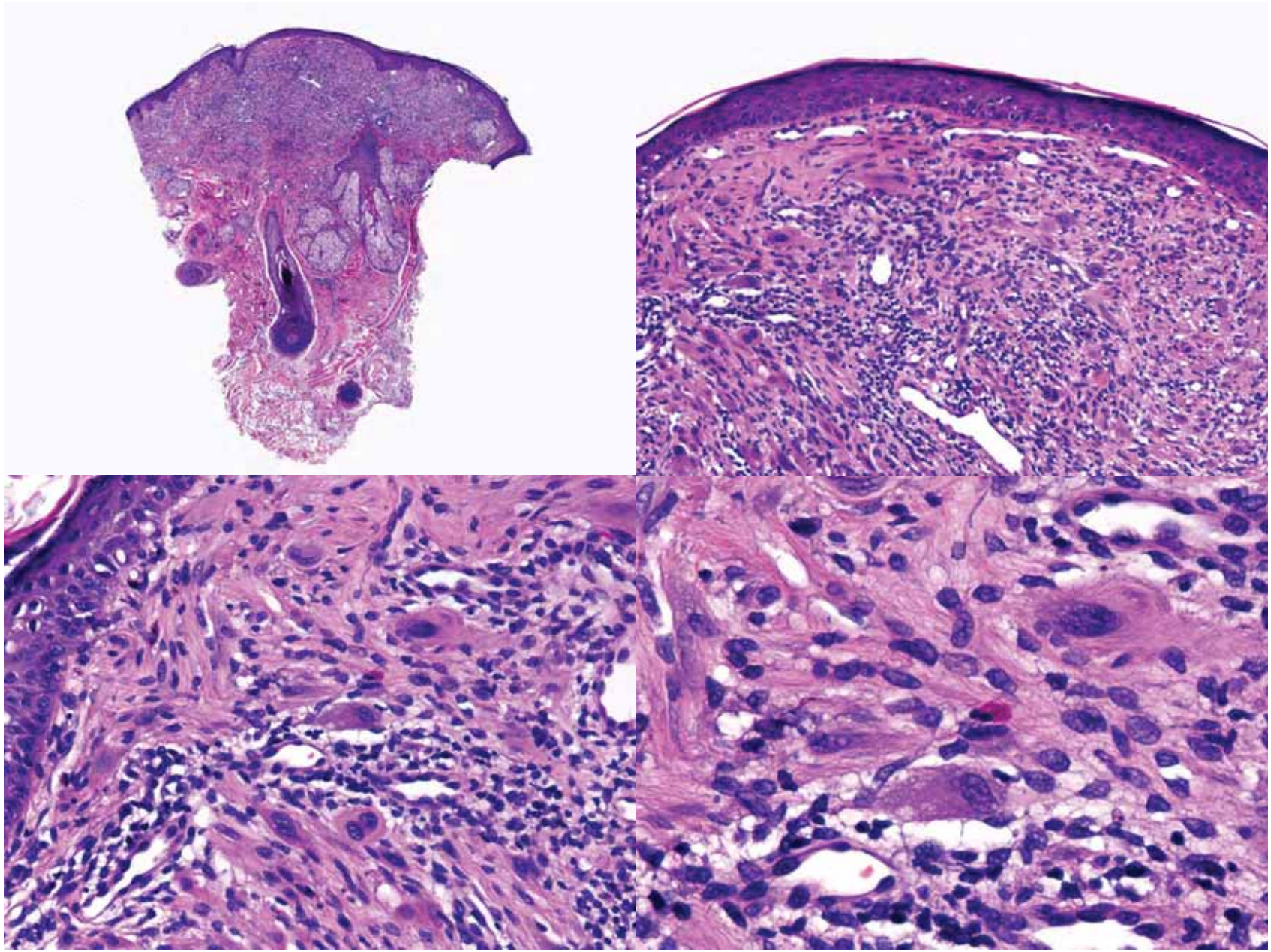
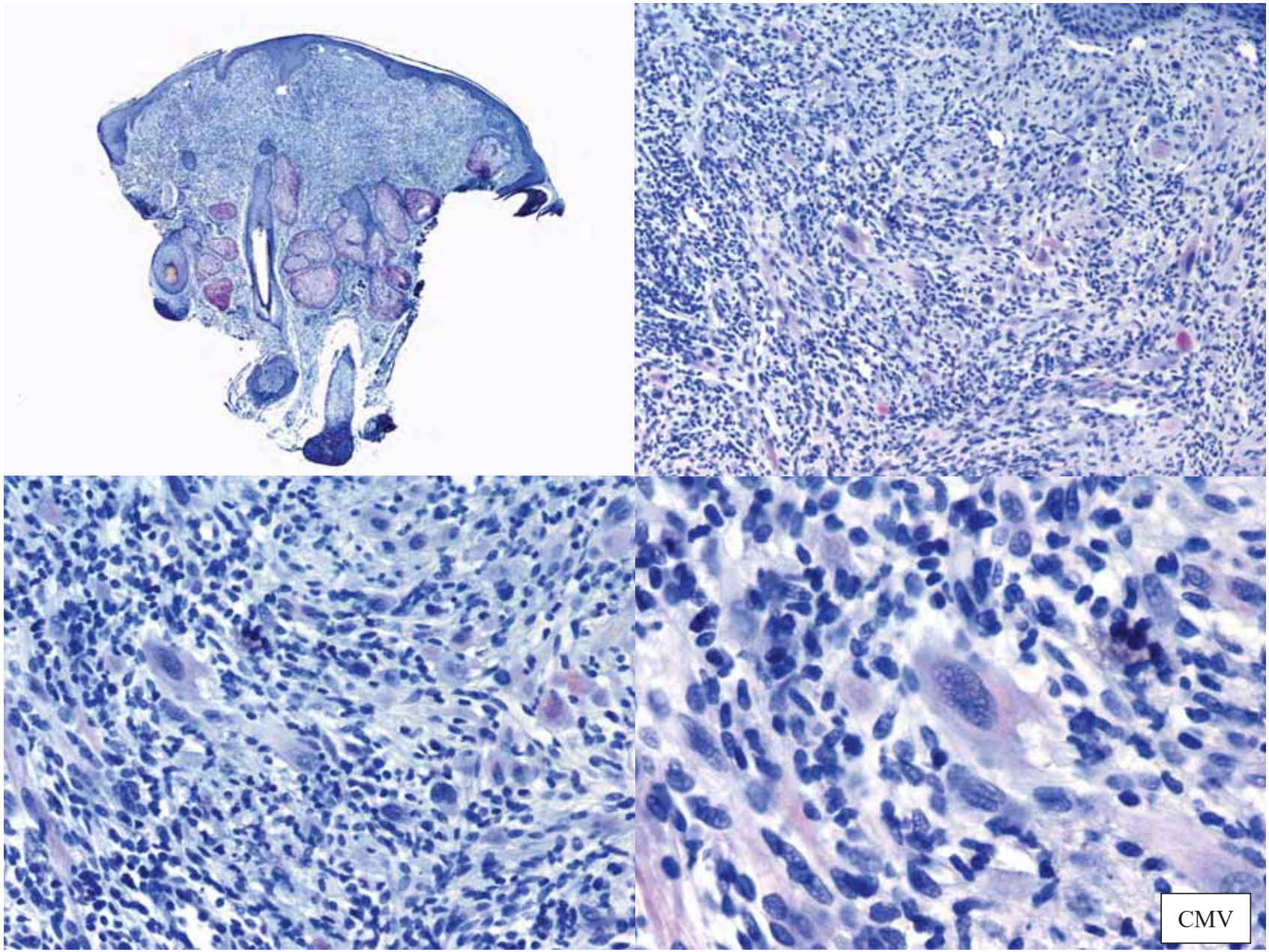
- Third biopsy...

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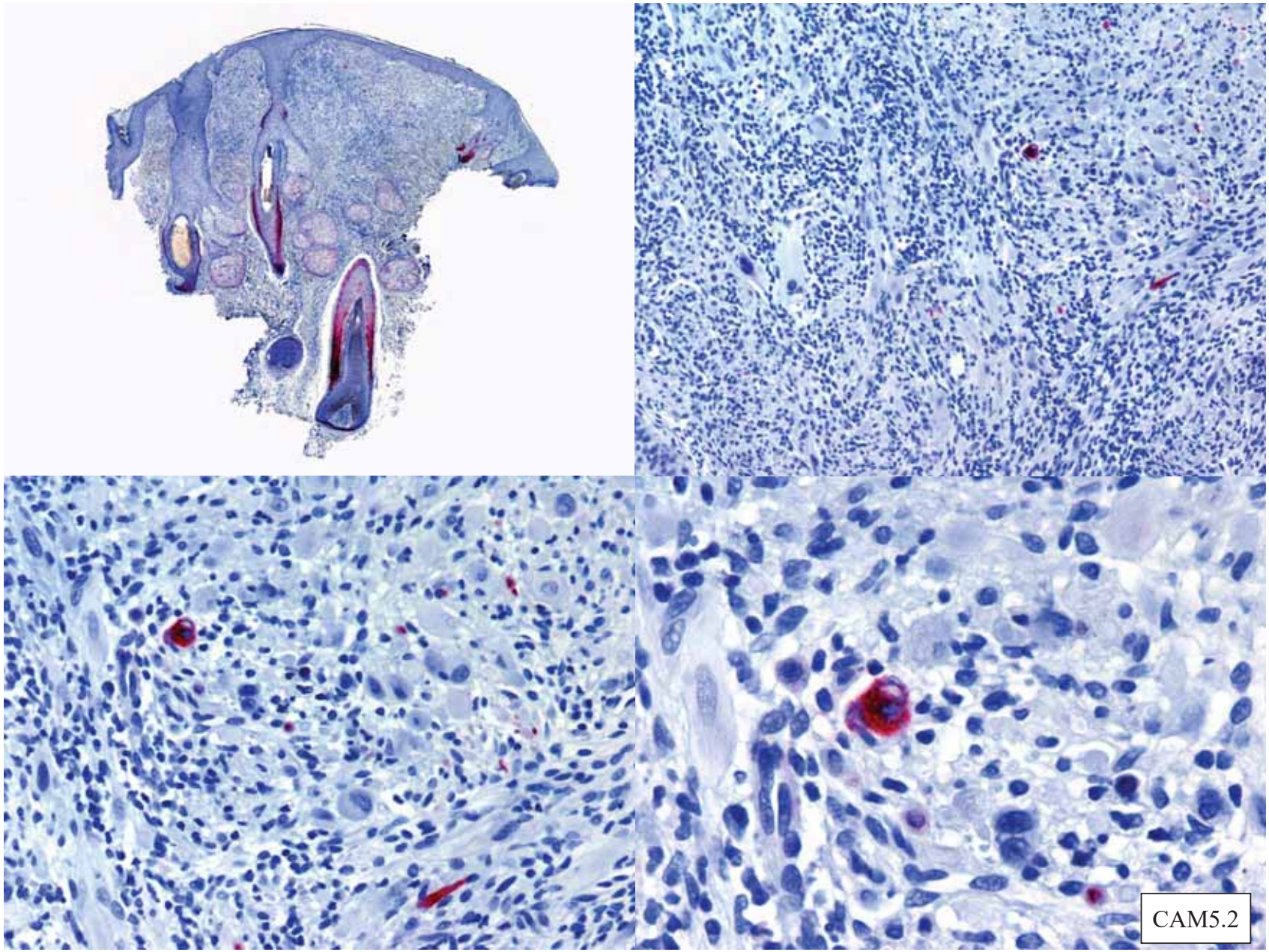
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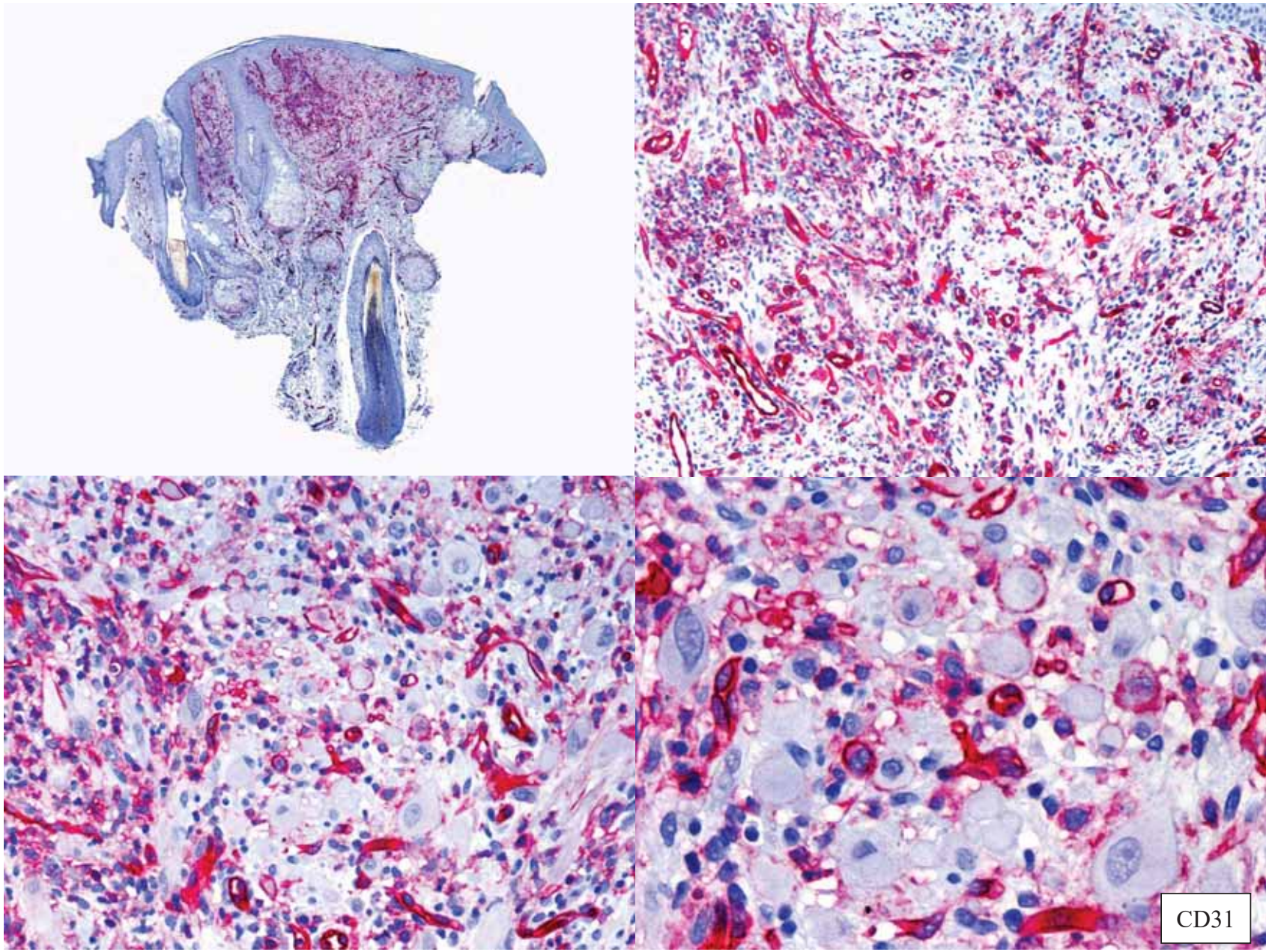
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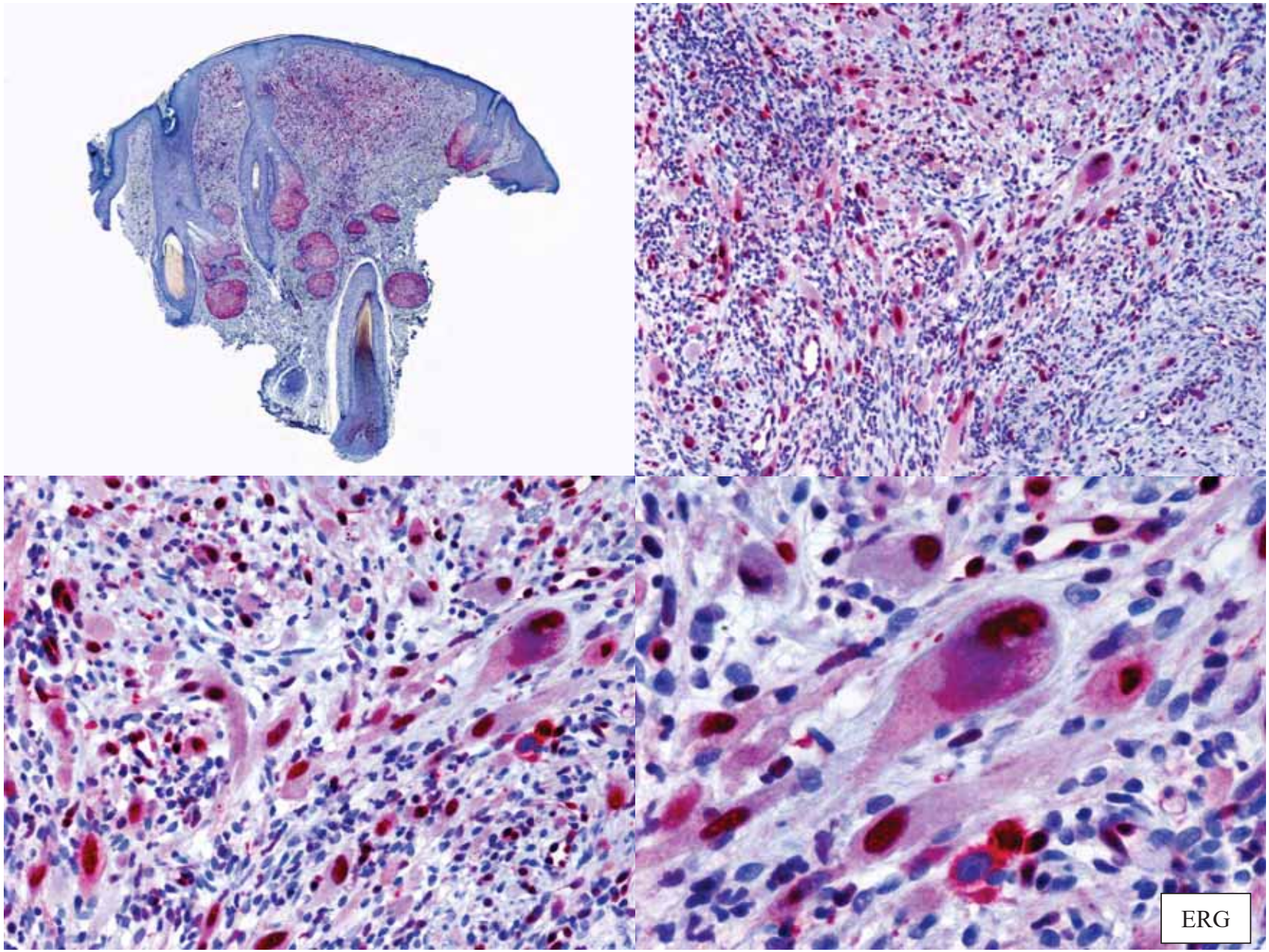
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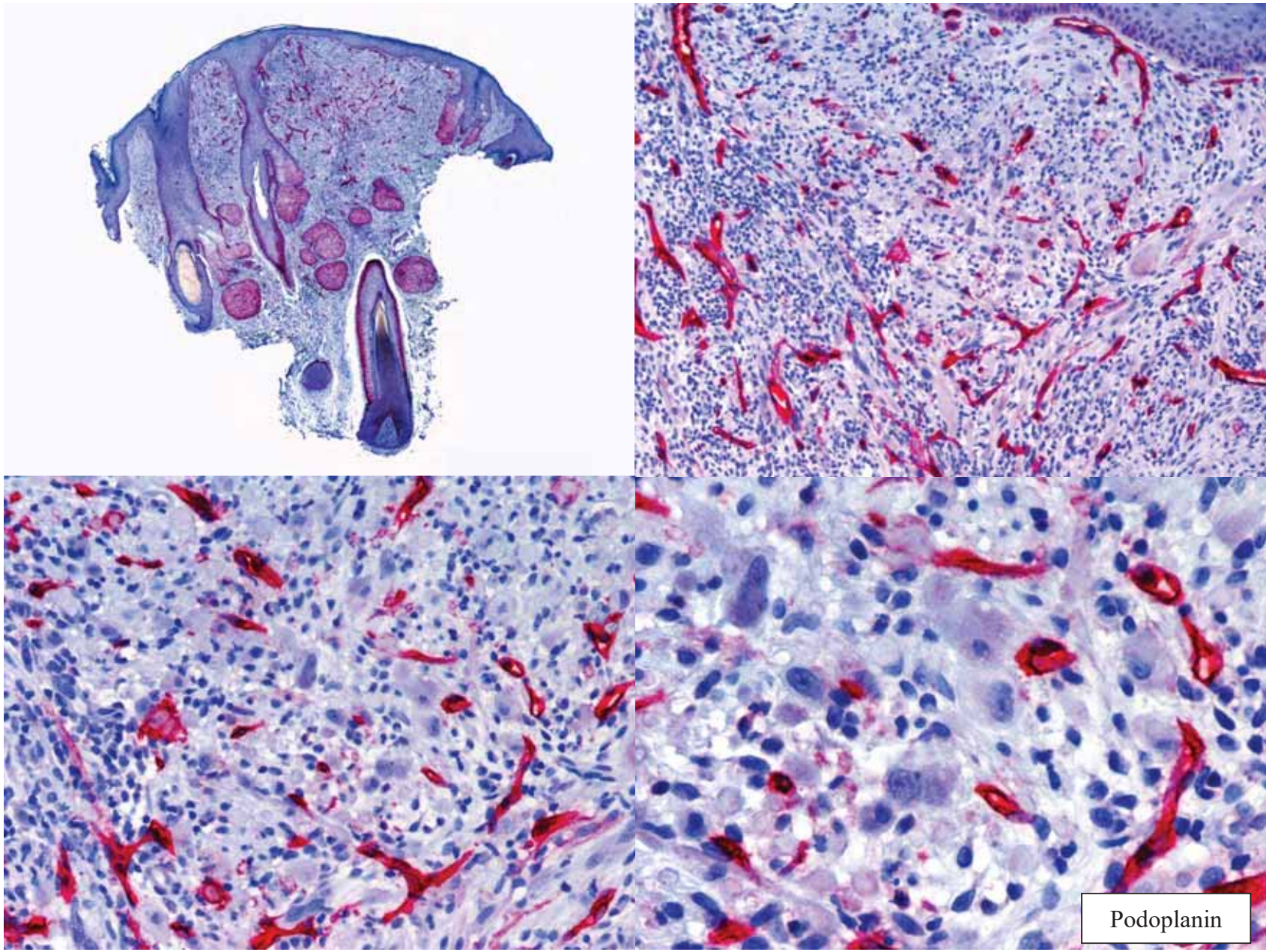
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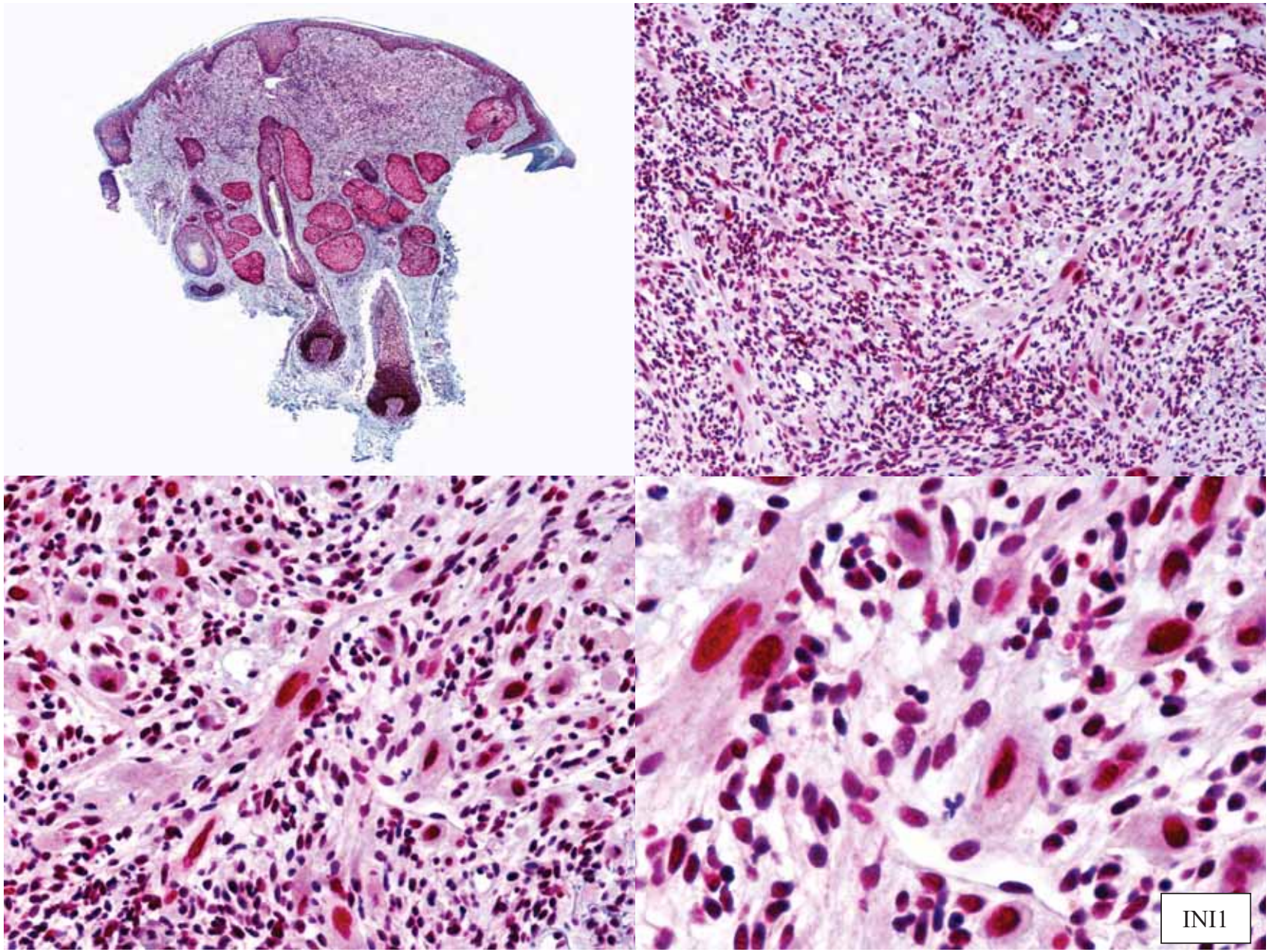
INI1

Case 3. Diagnossis

- Pseudomyogenic hemangioendothelioma

(epithelioid sarcoma-like hemangioendothelioma)

Pseudomyogenic Hemangioendothelioma: A Distinctive, Often Multicentric Tumor With Indolent Behavior

Jason L. Hornick, MD, PhD and Christopher D.M. Fletcher, MD, FRCPath

Abstract: A 1992 report described 5 keratin-positive spindle cell neoplasms with multifocal presentation in a single limb, which were proposed at that time to be a variant of epithelioid sarcoma. This tumor type is not widely recognized and is incompletely characterized. We examined 50 cases of this distinctive tumor to evaluate histologic, immunophenotypic, and clinical features. There was a 4.6:1 male predominance (mean age, 31 y; 82% ≤40 y). Half of the patients presented with painful nodules and the other half with painless nodules. Mean tumor size was 1.9 cm (range, 0.3 to 5.5 cm). Tumors arose in the lower limb (54%), the upper limb (24%), trunk (18%), or head and neck (4%). Thirty-three (66%) were multifocal lesions (ranging from 2 to 15 lesions), including 32 cases with involvement of multiple tissue planes. Of 205 total lesions, 64 (31%) involved the dermis, 42 (20%) involved the subcutis, 70 (34%) lesions involved muscle, and 29 (14%) lesions involved bone; all the lesions had infiltrative margins. The tumors were composed of loose fascicles and sheets of plump spindle cells with vesicular nuclei, variably prominent nucleoli, and abundant brightly eosinophilic cytoplasm, some with a strikingly rhabdomyoblast-like appearance. In all cases, a minority of cells were epithelioid. Twenty-seven tumors contained a prominent neutrophilic inflammatory infiltrate. Most tumors showed only mild nuclear atypia; 6 tumors contained foci of notably pleomorphic cells. The median mitotic rate was 1 per 10 HPF (range, 1 to 10). Seven tumors showed vascular invasion; 7 tumors had areas of necrosis. By immunohistochemistry, all tumors were diffusely positive for AE1/AE3 and FLI1; 22 of 47 tumors were variably positive for CD31. Focal positivity was seen for CAM5.2 (21 of 35), smooth muscle actin (14 of 42), epithelial membrane antigen (7 of 49 weak), and PAN-K (MNF116) (1 of 47). All were negative for CD34, desmin, and S100 protein and showed intact INI1 expression. Follow-up was available for 31 patients and ranged from 9 months to 17 years (mean, 4 y). Most lesions were treated by local excision. Eighteen (58%) patients had local recurrence or developed additional nodules in the same region, all but one, within 1 year of first presentation. Eight patients had postoperative radiation therapy and 6 patients had chemotherapy. Four patients had amputations for multifocal disease. One patient had a regional lymph node metastasis, and, thus far, only 1 patient has developed distant metastases (disseminated), 16 years after primary tumor excision. At the time of the last follow-up, 27 patients were alive with no evidence of the disease, 1 patient was alive with unknown disease status, 2 patients were alive with recurrent disease, and 1 patient died of the disease. In summary, we describe a distinctive type of rarely metastasizing ("intermediate") tumor affecting mainly young men and usually characterized by multifocality in different tissue planes of a limb. Although sharing some features with epithelioid sarcoma (skin/soft tissue of distal extremities, young adults, keratin positive), it differs by having predominantly myoid-appearing spindle cell morphology, expression of FLI1, common reactivity for CD31, lack of epithelial membrane antigen, CD34, and PAN-K expression, and intact INI1. The overall immunophenotypic findings favor endothelial differentiation. Despite the ominous presentation, follow-up thus far suggests an indolent clinical course with a small risk of distant metastasis. Although the precise nosologic status of this tumor type is uncertain, we propose the interim designation "pseudomyogenic hemangioendothelioma."

Key Words: hemangioendothelioma, epithelioid sarcoma, soft tissue tumor

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In 1992, Mirra et al[17] described 5 seemingly distinctive soft tissue tumors characterized by multifocal presentation in a single limb, often including osseous involvement, consisting of bland keratin-positive spindle cells with "fibrohistiocytic" or "myoid" cytomorphology. The investigators proposed that this tumor type was a variant of epithelioid sarcoma (the "fibroma-like" variant). No clinicopathologic series describing this tumor has been published until now. This tumor type is not widely recognized and its features are incompletely characterized. Furthermore, its relationship with epithelioid sarcoma remains uncertain.

In the mid-1990s, we began to recognize a group of tumors with distinctive histologic features and clinical presentation, which, over time, we realized were likely related to (or the same as) the tumors reported by Mirra et al.[17] We presented preliminary data with regard to such lesions, under the rubric "pseudomyogenic (fibroma-like) variant of epithelioid sarcoma"[10] at the United States and Canadian Academy of Pathology meeting in Denver, Colorado in March 2008. Since that time, after accruing

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Epithelioid Sarcoma-Like Hemangioendothelioma

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Sharon W. Weiss, M.D.

TABLE 1. *Summary of clinical information*

Case no.	Age (y), sex	Referring diagnosis	Location	Size (cm)	Treatment	Follow-up
1	54/M	Epith sarc	Thigh	2.2	WLE	NED 61 mo
2	23/M	Not provided	Knee	2	XRT	AWD 66 mo, developed multiple thigh masses
3	45/F	Epith sarc vs. low grade vascular tumor	Scalp	<2	WLE (2)	Rec 36 mo, NED after 2nd WLE 36 mo
4	18/F	Epith sarc vs. epithelioid angiosarcoma	Thigh (2 separate masses)	NA	WLE, Chemo, XRT	NED 39 mo
5	20/M	Epith sarc	Calf	3.5	WLE	NED 9 mo
6	17/F	Epith sarc	Chest wall	Small	Simple exc	Probable rec 6 mo
7	36/M	Epith sarc	Wrist and forearm	1–3	WLE, XRT	NED 3 mo

Epith sarc, epithelioid sarcoma; WLE, wide local excision; Chemo, chemotherapy; EXC, excision; XRT, radiation therapy; NED, no evidence of disease; AWD, alive with disease; Rec, recurrence.

Pseudomyogenic hemangioendothelioma

Clinical features

- More frequent in young adults
  - Male > Female (4:1)
  - Age: 20-50 years (median: 31 years)
- Most common locations: lower limbs. Other locations: face, trunk, upper extremities and abdominal wall
- Frequent multifocal presentation
- More than 50% of the patients show local recurrence after excision. One patient developed lymph node metastasis and other patient died with widespread metastatic disease

Pseudomyogenic hemangioendothelioma

Histopathologic features

- Poorly circumscribed lesion that involves the dermis and often extends to subcutaneous tissue
- Fascicular pattern with myxoid areas and neutrophilic infiltrate in the stroma
- Large cells with pleomorphic vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm (rhabdomyoblast-like cells)
- Sometimes. vascular invasion

POSITIVE	NEGATIVE	VARIABLE
AE1/AE3	CD34	CAM 5.2
CD31	F XIIIa	SMA
ERG	Podoplanin	EMA
FLI 1	Desmin	MNF-116
INI 1	Myogenin	
Vimentina	Myo D1	
	S100	
	CD10	
	CD99	

	Pseudomyogenic hemangioendothelioma	Epithelioid sarcoma	Epithelioid hemangioendothelioma	Epithelioid angiosarcoma
AE1/AE3	+	+	+ focal	+ focal
CD 31	+	-	+	+
FLI 1	+	+	+	+
ERG	+	-	+	+
INI 1	+	-	+	+
EMA	-	+	-	-
CD 34	-	+	+	+
Podoplanin	-	-	+	+

ELSEVIER

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Cancer Genetics

BRIEF COMMUNICATION

Translocation t(7;19)(q22;q13)—a recurrent chromosome aberration in pseudomyogenic hemangioendothelioma?

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Pseudomyogenic hemangioendothelioma is a recently described morphologic entity among soft tissue tumors. It is more common in young individuals, shows a male predominance, is often multifocal and involves different tissue planes, and shows a high propensity for local recurrence. To our knowledge, no genetic characteristics of this tumor type have been presented before. Here, we describe the finding of a balanced t(7;19)(q22;q13) as the sole anomaly in three lesions from a 14-year-old girl. By means of fluorescence in situ hybridization, the breakpoints could be delineated, but reverse transcriptase–polymerase chain reaction for putative fusion genes did not reveal any fusion transcript. Interphase fluorescence in situ hybridization on sections from nine other pseudomyogenic hemangioendotheliomas indicated the presence of an unbalanced der(7)t(7;19) in one of them. Thus, the translocation between chromosomes 7 and 19 seems to be a recurrent phenomenon and is likely to be of pathogenetic significance in at least a subset of pseudomyogenic hemangioendotheliomas.

Keywords Pseudomyogenic hemangioendothelioma; translocation; t(7;19)(q22;q13); SERPINE1

Soft tissue tumors are morphologically heterogeneous, including more than 100 distinct entities (1). In close to 20% of the subtypes, one or more gene fusions have been identified. With few exceptions, these gene fusions are due to chromosomal translocations that could be identified by G-banding analysis of cultured tumor cells. In spite of the fact that many, presently close to 50, gene fusions have already been identified in soft tissue tumors, cytogenetic data indicate that there are several more to be identified (2).

Recently, Hornick and Fletcher (3) described a new morphologic subtype, tentatively named pseudomyogenic hemangioendothelioma. After reviewing a series of 50 such tumors, they concluded that this tumor type is more common in young individuals (aged 20–50 years), that it shows a male predominance (M:F ratio of 4.6:1), that it is multifocal, often involving different tissue planes in two-thirds of the cases, and that it shows a high propensity for local recurrence (58% of the cases). The clinical and morphologic features, together with a characteristic immunophenotype, including expression of cytokeratin AE1/AE3, FLI1, and INI1 and lack of the cytokeratin-marker PAN-K, epithelial membrane antigen (EMA), and CD34, strongly suggested that these tumors form a distinct nosologic entity (3).

To our knowledge, no genetic data have been presented for pseudomyogenic hemangioendothelioma. In the present study, we report one case for which we performed chromosome banding analysis; a balanced t(7;19)(q22;q13) was found to be the sole anomaly. By means of fluorescence in situ hybridization (FISH), the breakpoints could be mapped, allowing for reverse transcriptase–polymerase chain reaction (RT-PCR) for putative fusion gene transcripts. In addition, interphase FISH was attempted on a series of 10 additional cases from which cut sections from paraffin-embedded tumor tissue were available.

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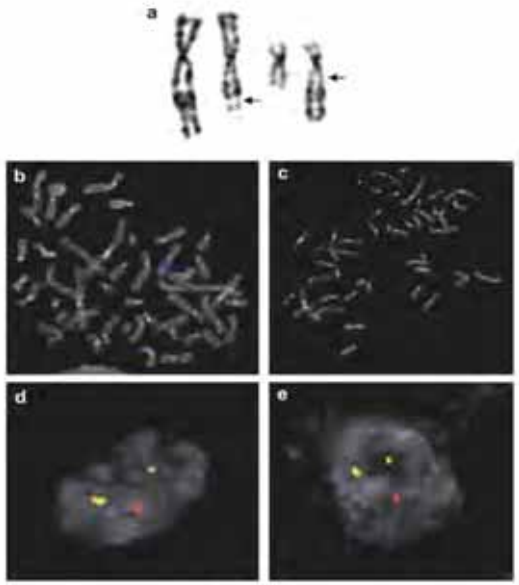

Figure 1 (a) Case 1. Partial karyotype showing the t(7;19)(q22;q13). Breakpoints are indicated by arrows. (b) Case 1. Metaphase FISH showing split signals with RP4–747G18 (blue), mapping to 7q22. (c) Case 1. Metaphase FISH showing split signals with CTB-171A8 (red), mapping to 19q13. (d) Case 2. Interphase FISH on sections from paraffin-embedded tissue showing co-hybridization of signals for 7q22 (red) and 19q13 (green). (e) Case 2. Interphase FISH on sections from paraffin-embedded tissue showing split signals for 7q22 (RP11-132A1, RP5-1106H4 and RP5-1059M17 in green; RP11-336D7 and RP11-395B7 in red). (A color figure can be found in the online version of this article.)

contains four known genes—*CEACAM19*, *CEACAM16*, *BCL3*, and *CBLC*. The analysis of transcriptional directions of the genes allowed us to consider as putative chimeric transcripts *SERPINE1/CBLC*, *SERPINE1/BCL3*, *SERPINE1/CEACAM16*, *AP1S1/CBLC*, *AP1S1/BCL3*, and *AP1S1/CEACAM16*; none of these were detected (data not shown).

Interphase FISH was attempted on cut sections from 10 cases of pseudomyogenic hemangioendothelioma (cases 2–11), and was technically successful in nine of them. By means of a pool of five probes flanking the breakpoint in chromosome 7 and six probes flanking the breakpoint in chromosome 19, at least 50 interphase nuclei from different areas were analyzed. Eight cases showed normal FISH signals, strongly suggesting that these cases were negative for the t(7;19). One tumor (from case 2) showed an abnormal FISH pattern in 25–30% of the nuclei, with one seemingly intact signal per chromosome and one fusion signal (Figure 1d). Additional FISH using only the BAC/PAC probes for chromosome 7, with different colors for the upstream and downstream probes, revealed a split signal (Figure 1e). Combined, these interphase FISH results would fit with an unbalanced der(7)t(7;19)(q22;q13).

Discussion

The finding of a balanced t(7;19) as the sole cytogenetic aberration represents what is to our knowledge the first genetic data of any type on pseudomyogenic hemangioendothelioma. The fact that the same translocation was seen in all three samples from the index case excludes the possibility that the translocation was an *in vitro* artifact. Furthermore, the consistent presence of cells with a normal female chromosome complement makes it highly unlikely that it is a constitutional aberration. Thus, it seems reasonable to conclude that the t(7;19) represents a somatic alteration. The pathogenetic significance, however, is more difficult to resolve. Because we did not have access to fresh material

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ORIGINAL PAPER

A novel *SERPINE1–FOSB* fusion gene results in transcriptional up-regulation of *FOSB* in pseudomyogenic haemangioendothelioma

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Abstract

Pseudomyogenic haemangioendothelioma (PHE) is an intermediate malignant vascular soft tissue tumour primarily affecting children and young adults. The molecular basis of this neoplasm is unknown. We here used chromosome banding analysis, fluorescence *in situ* hybridization (FISH), mRNA sequencing, RT–PCR and quantitative real-time PCR on a series of morphologically well-characterized PHEs to show that a balanced translocation, t(7;19)(q22;q13), detected as the sole cytogenetic aberration in two cases, results in fusion of the *SERPINE1* and *FOSB* genes. This translocation has not been observed in any other bone or soft tissue tumour. Interphase FISH on sections from eight additional PHEs identified the same *SERPINE1–FOSB* fusion in all cases. The role of *SERPINE1*, which is highly expressed in vascular cells, in this gene fusion is probably to provide a strong promoter for *FOSB*, which was found to be expressed at higher levels in PHEs than in other soft tissue tumours. *FOSB* encodes a transcription factor belonging to the FOS family of proteins, which, together with members of the JUN family of transcription factors, are major components of the activating protein 1 (AP-1) complex. Further studies are needed to understand the cellular impact of the aberrant expression of the *FOSB* gene, but as the t(7;19) resulting in the *SERPINE1–FOSB* fusion seems to be pathognomonic for PHE, FISH or RT–PCR could be useful for differential diagnostic purposes.

Keywords: pseudomyogenic haemangioendothelioma; gene fusion; SERPINE1; FOSB; RNA sequencing; sarcoma; paediatric

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No conflicts of interest were declared.

Introduction

Pseudomyogenic haemangioendothelioma (PHE), also sometimes known as epithelioid sarcoma-like haemangioendothelioma, is a rare soft tissue tumour, predominantly affecting children and young adults, with a male:female ratio of 4.6:1 [1–3]. The tumour is usually situated in the limbs or trunk, may involve skin, subcutis, muscle or (least often) bone, and is multicentric in more than 50% of cases. An unusual feature compared to other soft tissue tumours is that different tissue planes are often involved. The tumour is locally aggressive but distant metastases are rare [2].

The genetics of PHE remains poorly characterized, but a potentially recurrent translocation, t(7;19)(q22;q13), was recently reported by us [4]. Using fluorescence *in situ* hybridization (FISH), the breakpoints in chromosomes 7 and 19 in a case with cytogenetically detected t(7;19) were delineated; however, none of the genes implicated by the FISH results was found to be involved in a gene fusion. The results obtained from metaphase FISH analysis were also used for interphase FISH on nine additional cases from which only tissue sections were available. Among these, only one more case with a potentially unbalanced t(7;19) was found [4]. Since that publication, we have received one additional case of PHE for chromosome analysis. Again, a balanced t(7;19)(q22;q13) was found, prompting further in-depth analysis of the molecular consequences of this translocation. We here present the results obtained through mRNA sequencing, FISH, RT–PCR and quantitative real-time PCR.

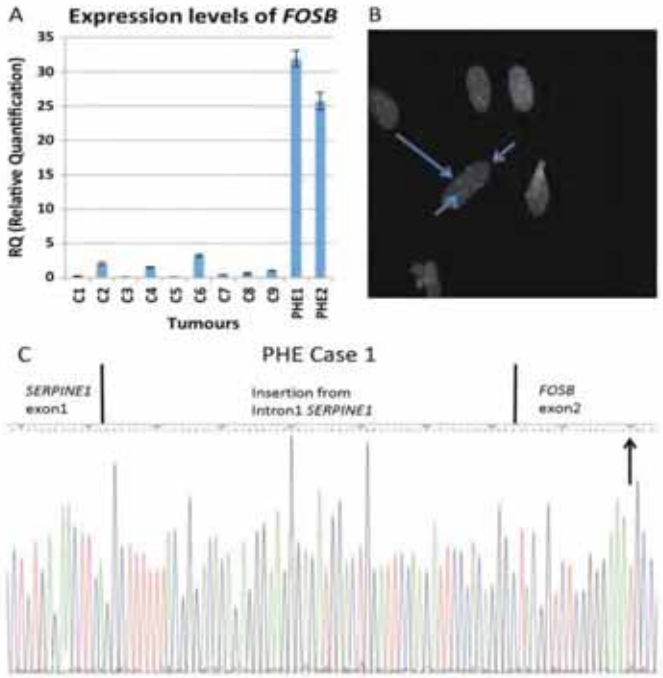

Figure 2. Genetic findings in pseudomyogenic haemangioendothelioma (PHE). (A) Quantitative qRT–PCR results for *FOSB* expression in two PHEs and nine control tumours, showing significantly higher expression levels in PHEs compared to controls. (B) Interphase FISH with BAC probes showing normal red (*SERPINE1*) and green (*FOSB*) signals (short blue arrows) and yellow fusion (*SERPINE1–FOSB*) signal (long blue arrow) in case 2. (C) Chromatogram showing the fusion junction in case 1; 61 nucleotides from intron 1 of *SERPINE1* were inserted at the fusion junction. The translation start codon in *FOSB* is indicated by a black arrow.

(Figure 2). In both tumours the breakpoints in *SERPINE1* were located in the non-coding exon 1. The breakpoint in *FOSB* was located in the beginning of exon 2 in case 1 and in the non-coding exon 1 in case 2. Both cases showed small insertions (61 bp in case 1, 59 bp in case 2) of material from intron 1 of *SERPINE1* at the fusion junction. In case 1, this introduced a new start codon, whereas the original start codon of *FOSB*, which was not present in the fusion in case 1, was retained in the fusion in case 2. The two metastases in case 2 showed the same fusion transcript as the primary tumour in the os calcaneus, verifying that they were metastases (data not shown).

Quantitative real-time PCR

The expression of *FOSB* was significantly higher in the two PHEs (cases 1 and 2) than in the tumours serving as controls (Figure 2; see also supplementary material, Figure S1).

Discussion

Pseudomyogenic haemangioendothelioma is a rare and recently described soft tissue tumour [1]. In the current WHO classification of soft tissue tumours, it is listed as an intermediate malignant, rarely metastasizing,

FOSB is a Useful Diagnostic Marker for Pseudomyogenic Hemangioendothelioma

Yin P. Hung, MD, PhD, Christopher D.M. Fletcher, MD, FRCPath, and Jason L. Hornick, MD, PhD

Abstract: Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma is a distinctive vascular neoplasm of intermediate biological potential with a predilection for young adults and frequent multifocal presentation. Pseudomyogenic hemangioendothelioma is characterized by loose fascicles of plump spindled and epithelioid cells with abundant eosinophilic cytoplasm and coexpression of keratins and endothelial markers. Recently, a *SERPINE1-FOSB* fusion has been identified as a consistent genetic alteration in pseudomyogenic hemangioendothelioma. *FOSB* gene fusions have also been reported in a subset of epithelioid hemangiomas. The purpose of this study was to assess the potential diagnostic utility of FOSB immunohistochemistry for pseudomyogenic hemangioendothelioma compared with other endothelial neoplasms and histologic mimics. We evaluated whole-tissue sections from 274 cases including 50 pseudomyogenic hemangioendotheliomas, 84 other vascular tumors (24 epithelioid hemangiomas [including 6 cases with angiolymphoid hyperplasia with eosinophilia histology], 20 epithelioid angiosarcomas, 20 epithelioid hemangioendotheliomas [17 CAMTA1 positive, 2 TFE3 positive], 10 spindle-cell angiosarcomas, and 10 epithelioid angiomatous nodules), and 140 other histologic mimics (20 each epithelioid sarcoma, proliferative fasciitis, nodular fasciitis, cellular benign fibrous histiocytoma, spindle-cell squamous cell carcinoma, spindle-cell rhabdomyosarcoma, and leiomyosarcoma). Immunohistochemistry for FOSB was performed following pressure cooker antigen retrieval using a rabbit monoclonal antibody. Diffuse nuclear immunoreactivity for FOSB (> 50% of cells) was observed in 48 of 50 (96%) pseudomyogenic hemangioendotheliomas and 13 of 24 (54%) epithelioid hemangiomas (including all angiolymphoid hyperplasia with eosinophilia type). Both FOSB-negative pseudomyogenic hemangioendothelioma cases were decalcified bone tumors. Only 7 other tumors showed diffuse FOSB expression: 2 proliferative fasciitis, 2 nodular fasciitis, 1 epithelioid angiosarcoma, 1 spindle-cell angiosarcoma, and 1 epithelioid hemangioendothelioma. Of note, the FOSB-positive epithelioid hemangioendothelioma was negative for CAMTA1 and TFE3. Focal weak FOSB staining was observed in a subset of histologic mimics and is therefore not diagnostically meaningful. In conclusion, FOSB is a highly sensitive and diagnostically useful marker for pseudomyogenic hemangioendothelioma. Immunohistochemistry for FOSB may be helpful to distinguish pseudomyogenic hemangioendothelioma from histologic mimics including epithelioid sarcoma and other vascular neoplasms. As expected, a subset of epithelioid hemangiomas expresses FOSB, including angiolymphoid hyperplasia with eosinophilia. Although occasional cases of nodular and proliferative fasciitis are positive for FOSB, distinction between these tumor types and pseudomyogenic hemangioendothelioma is usually straightforward based on morphology and other immunophenotypic findings.

Key Words: pseudomyogenic hemangioendothelioma, FOSB, immunohistochemistry, epithelioid hemangioma, angiolymphoid hyperplasia with eosinophilia

(*Am J Surg Pathol* 2017;41:596–606)

Pseudomyogenic hemangioendothelioma, also known as epithelioid sarcoma-like hemangioendothelioma, is a distinctive vascular neoplasm of intermediate biological potential, with a predilection for the extremities of young adults and frequent multicentric presentation.[1–3] Histologically, pseudomyogenic hemangioendothelioma displays loose fascicles or sheets of plump spindled and epithelioid cells with abundant eosinophilic cytoplasm, often with rhabdomyoblast-like cytomorphology. Pseudomyogenic hemangioendothelioma shows coexpression of endothelial markers (ERG, CD31) and keratins.[1,2] The diagnosis of pseudomyogenic hemangioendothelioma can be challenging, given its rarity and morphologic overlap with epithelioid sarcoma and other spindle-cell neoplasms. In contrast to the aggressive clinical course of epithelioid sarcoma, pseudomyogenic hemangioendothelioma is indolent with low metastatic potential.

The chromosomal translocation t(7;19)(q22;q13) leading to *SERPINE1-FOSB* gene fusion is a recurrent alteration in pseudomyogenic hemangioendothelioma.[4,5] *SERPINE1* encodes plasminogen activator inhibitor-1, which is highly expressed in endothelial cells.[6] FOSB, a member of the Fos transcription factor family and a component of the activator protein-1 (AP-1) protein complex, has been implicated in diverse biological

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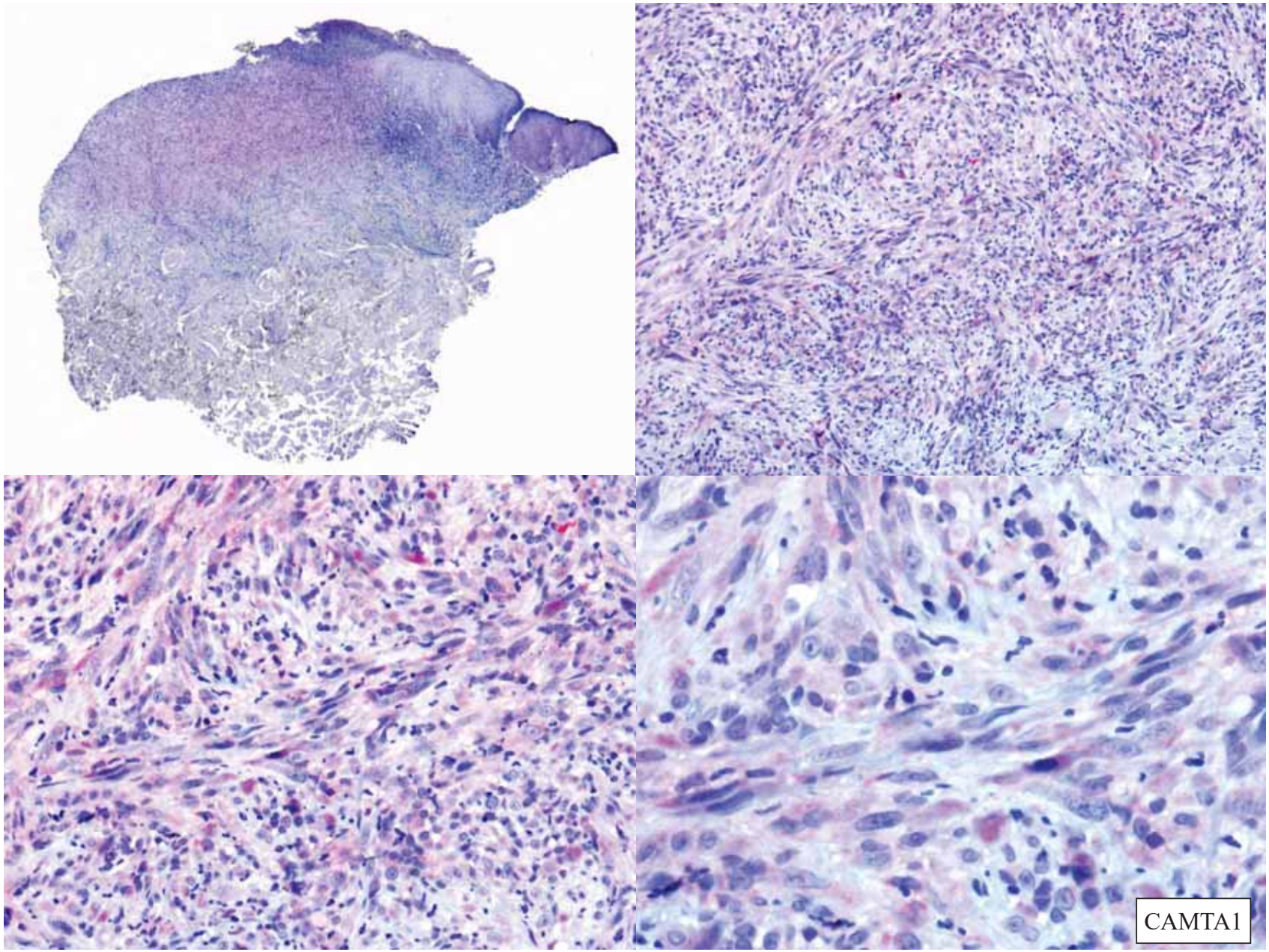
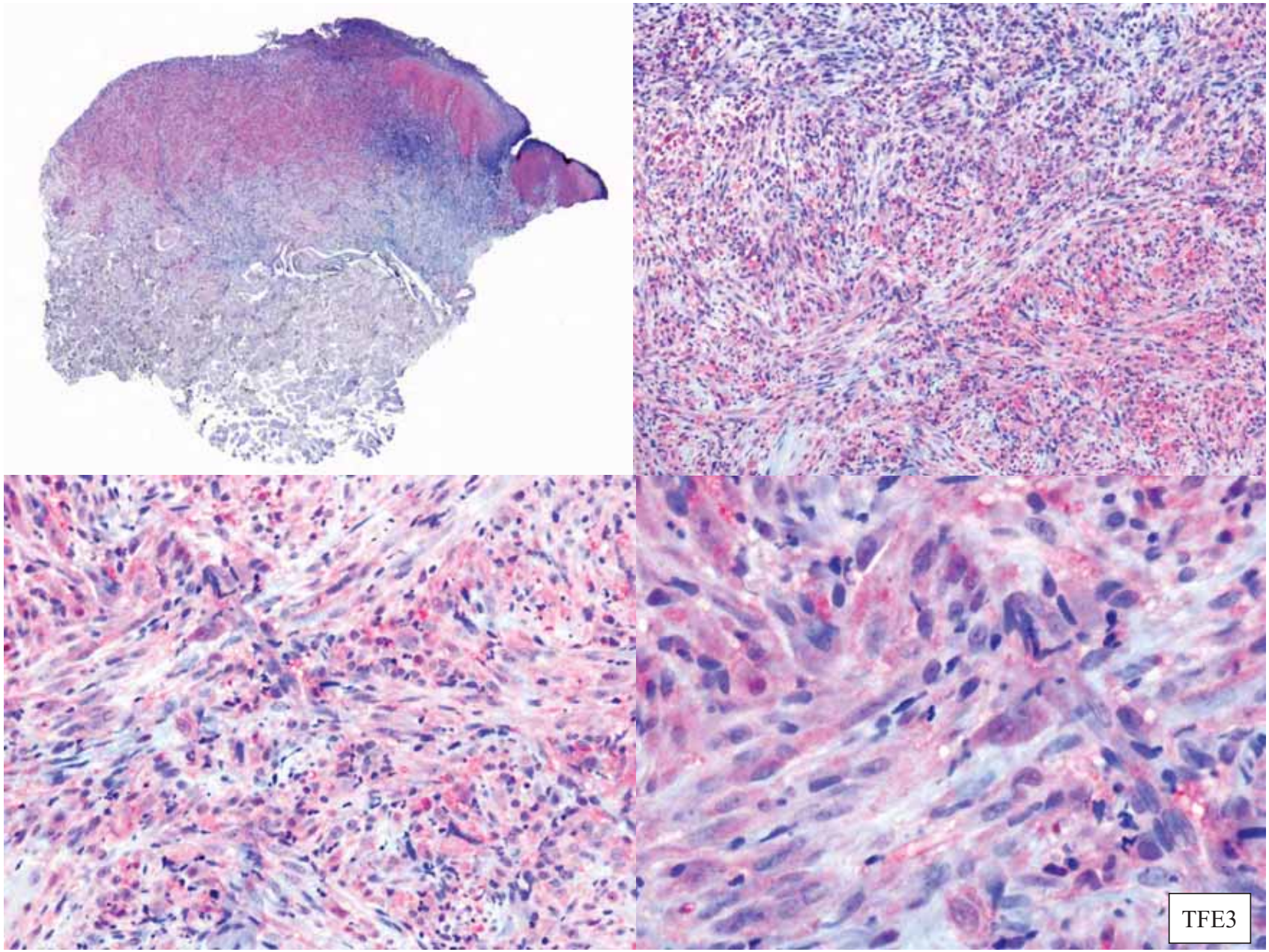
- 50 pseudomyogenic hemangioendotheliomas, 84 vascular tumors with epithelioid endothelial cells and 140 non-vascular tumors with epithelioid cells
- Strong nuclear positivity for FOSB in 48 of 50 (96%) cases of pseudomyogenic hemangioendothelioma and in 13 of 24 (54%) cases of epithelioid hemangioma (ALHE)
- Only 7 other tumors showed nuclear positivity for FOSB: 2 proliferative fasciitis, 2 nodular fasciitis, 1 epithelioid angiosarcoma, 1 spindle cell angiosarcoma and 1 epithelioid hemangioendothelioma
- FOSB is a very sensitive and specific marker for pseudomyogenic hemangioendothelioma


CAMTA1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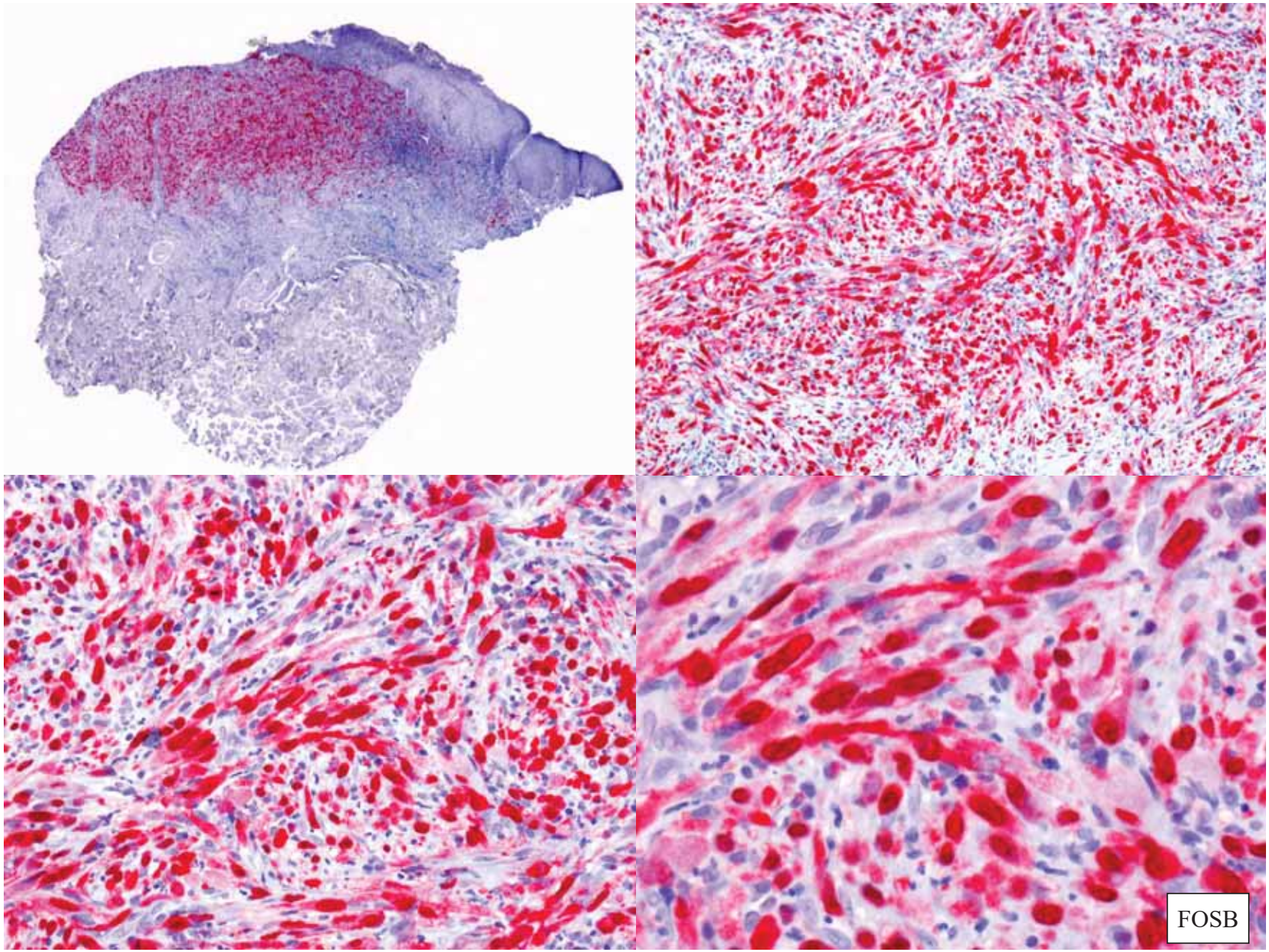
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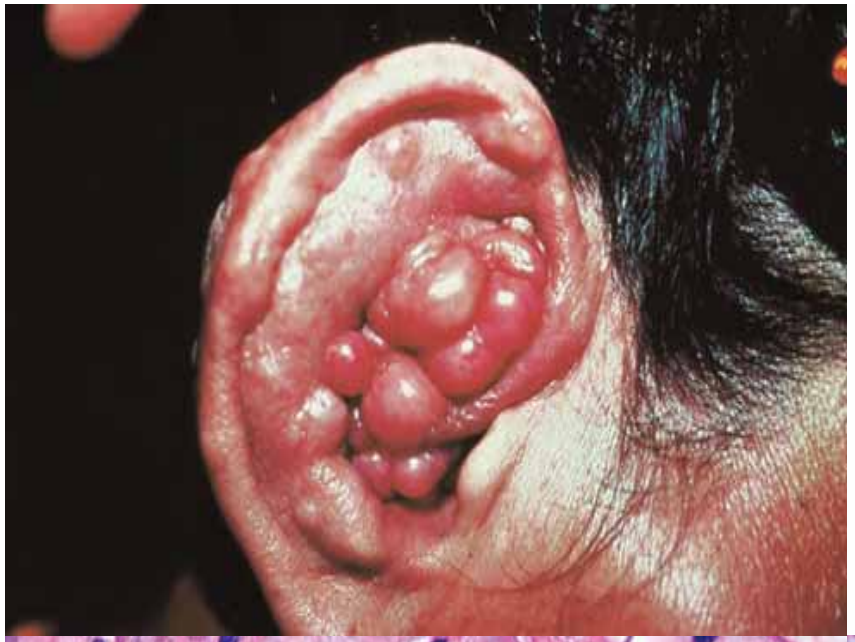
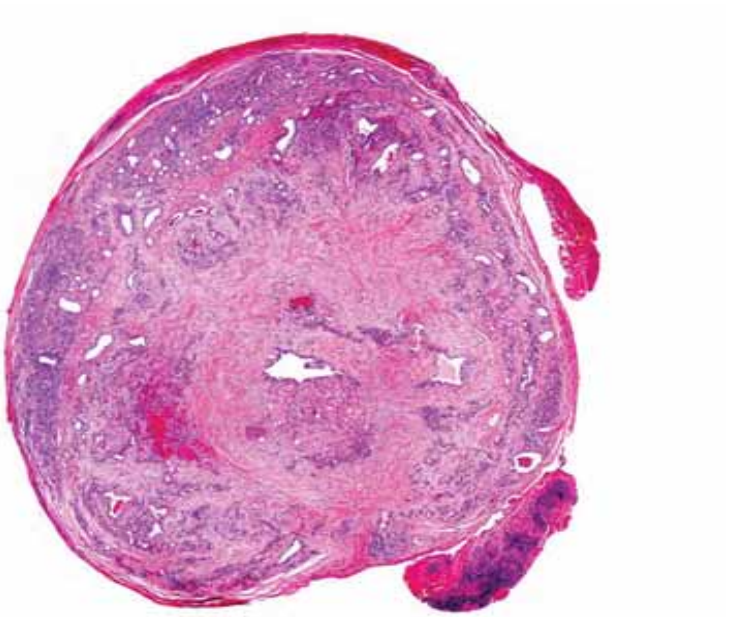
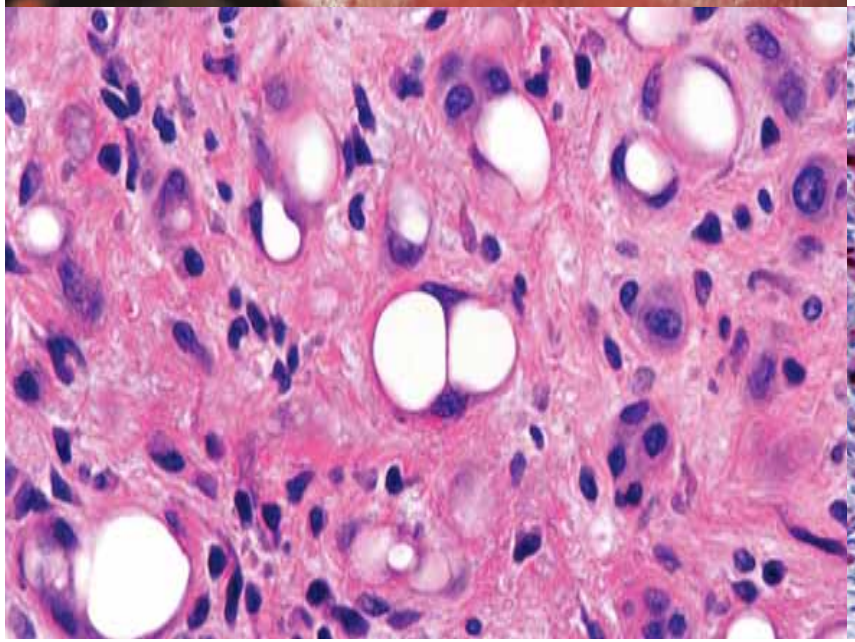
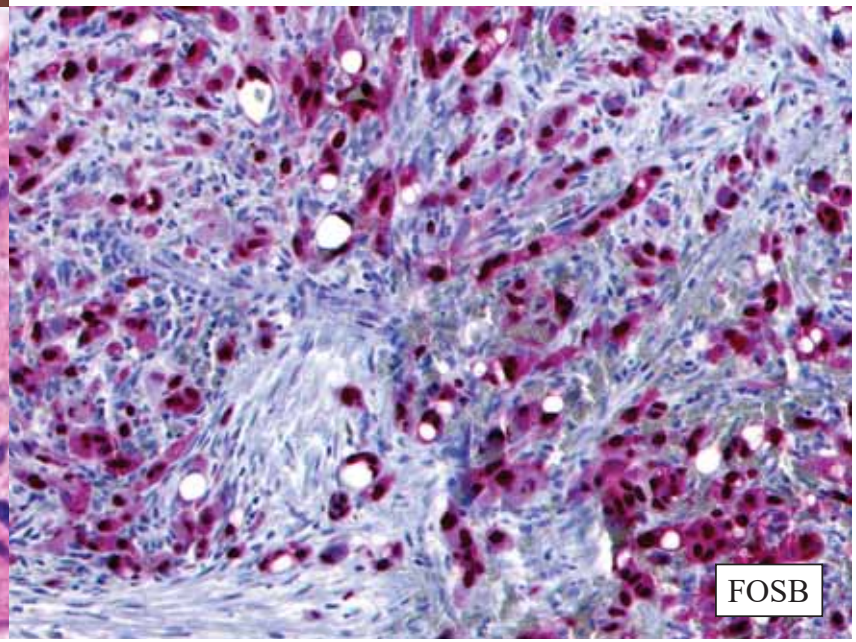


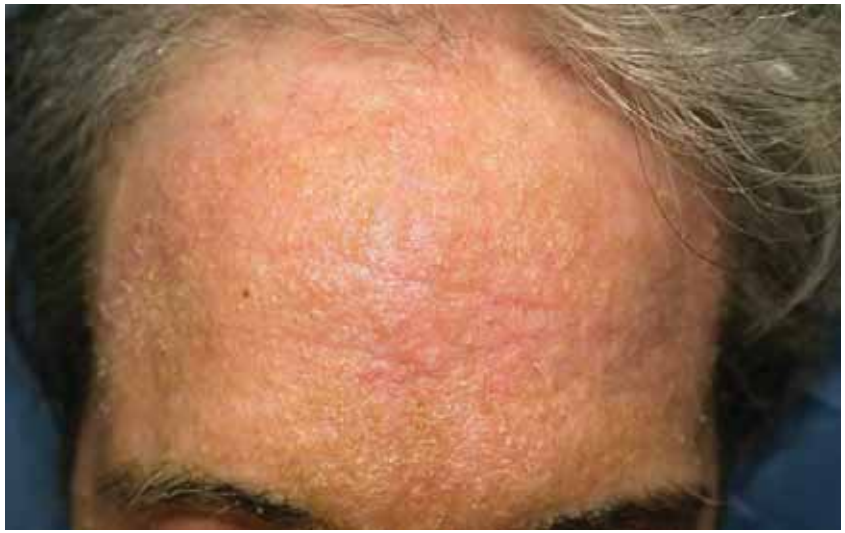


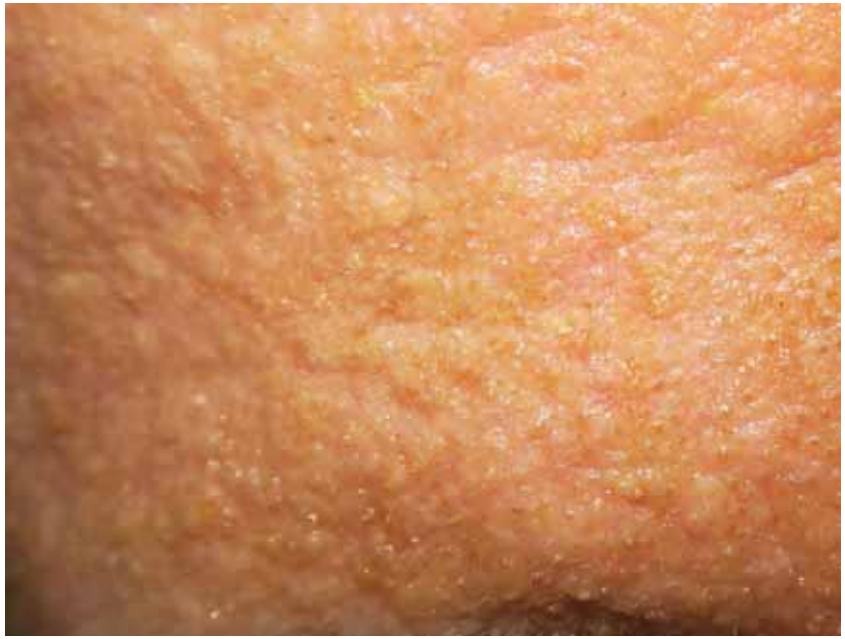


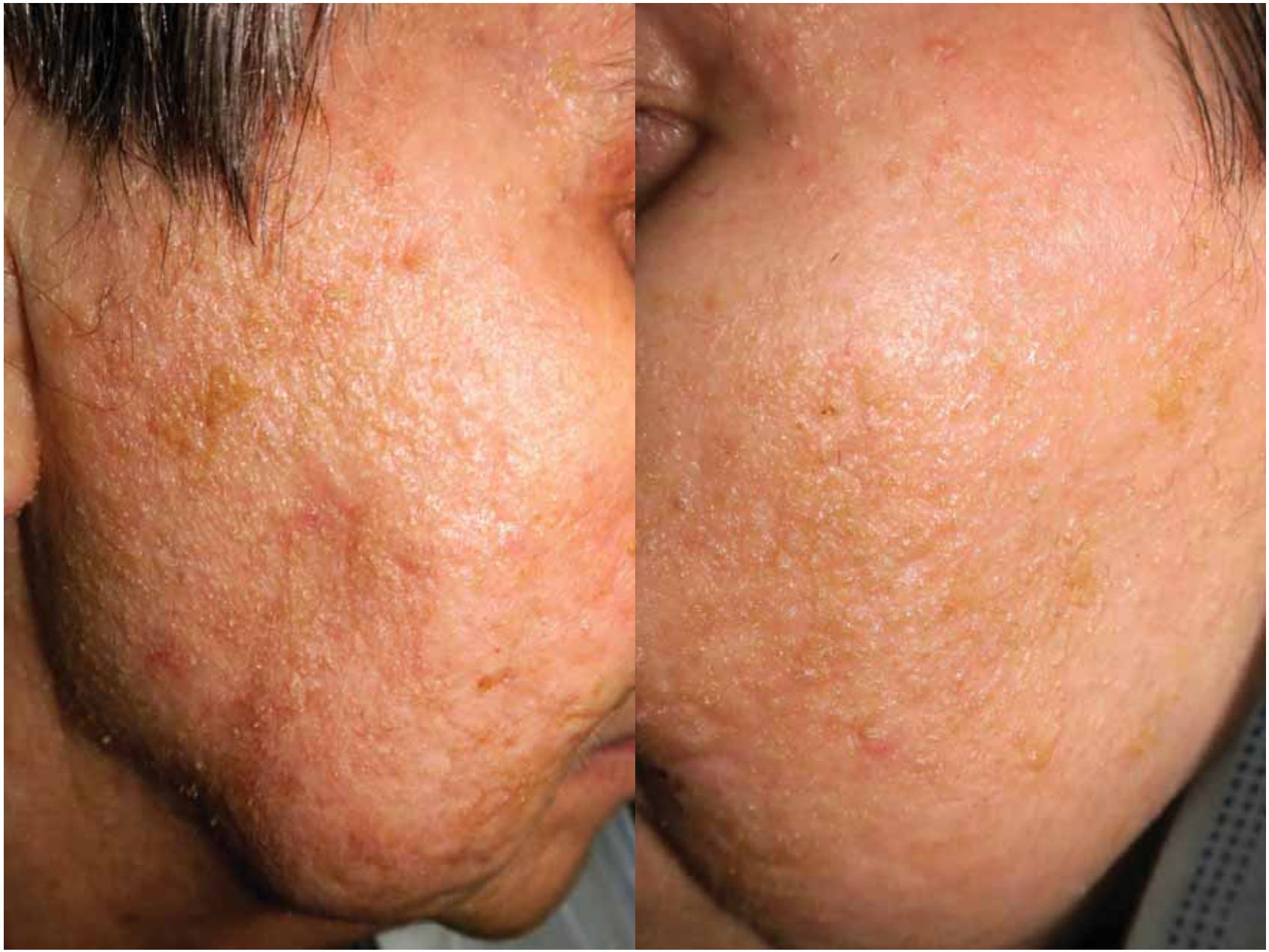

FOSB

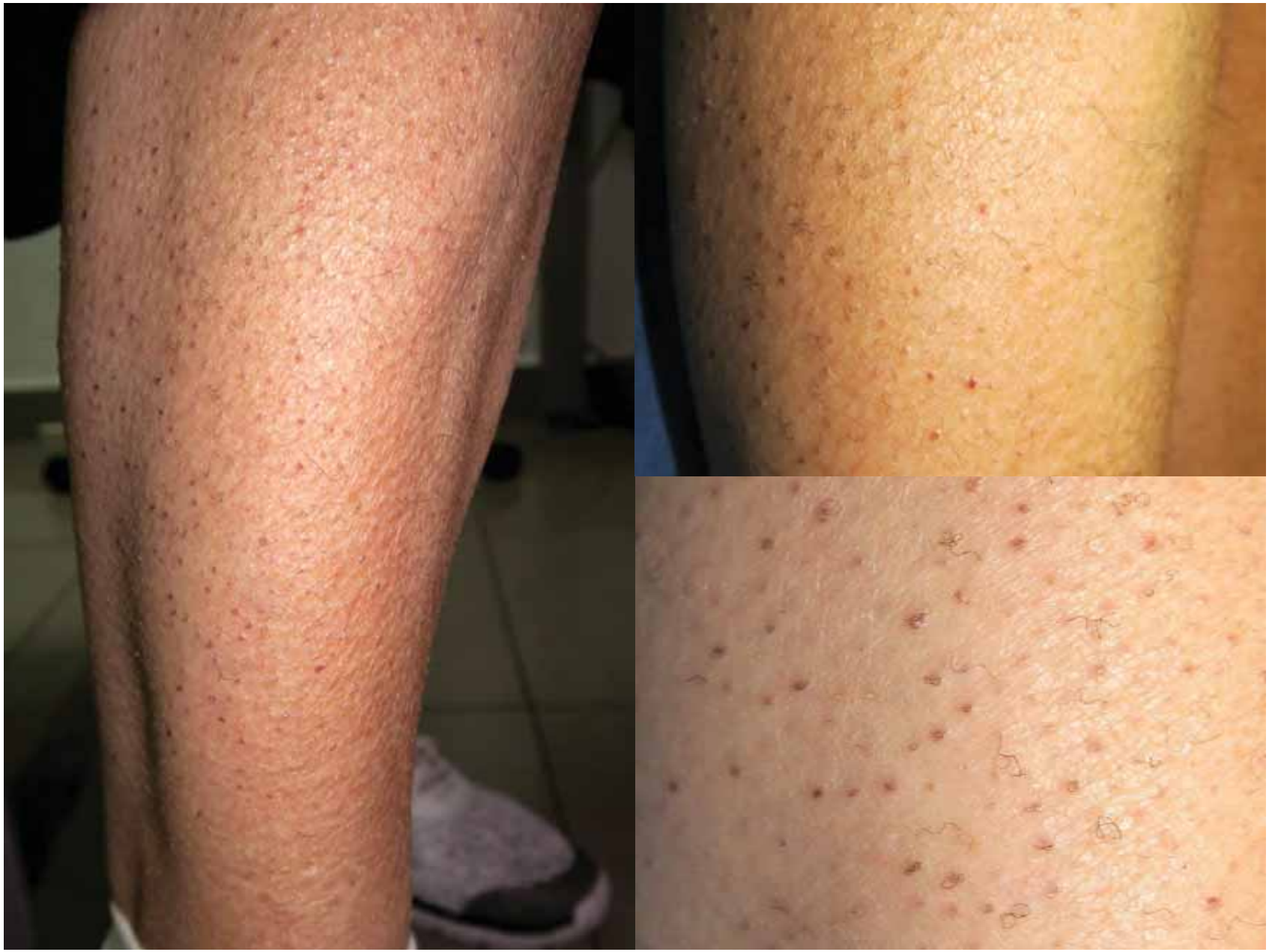
Case 4

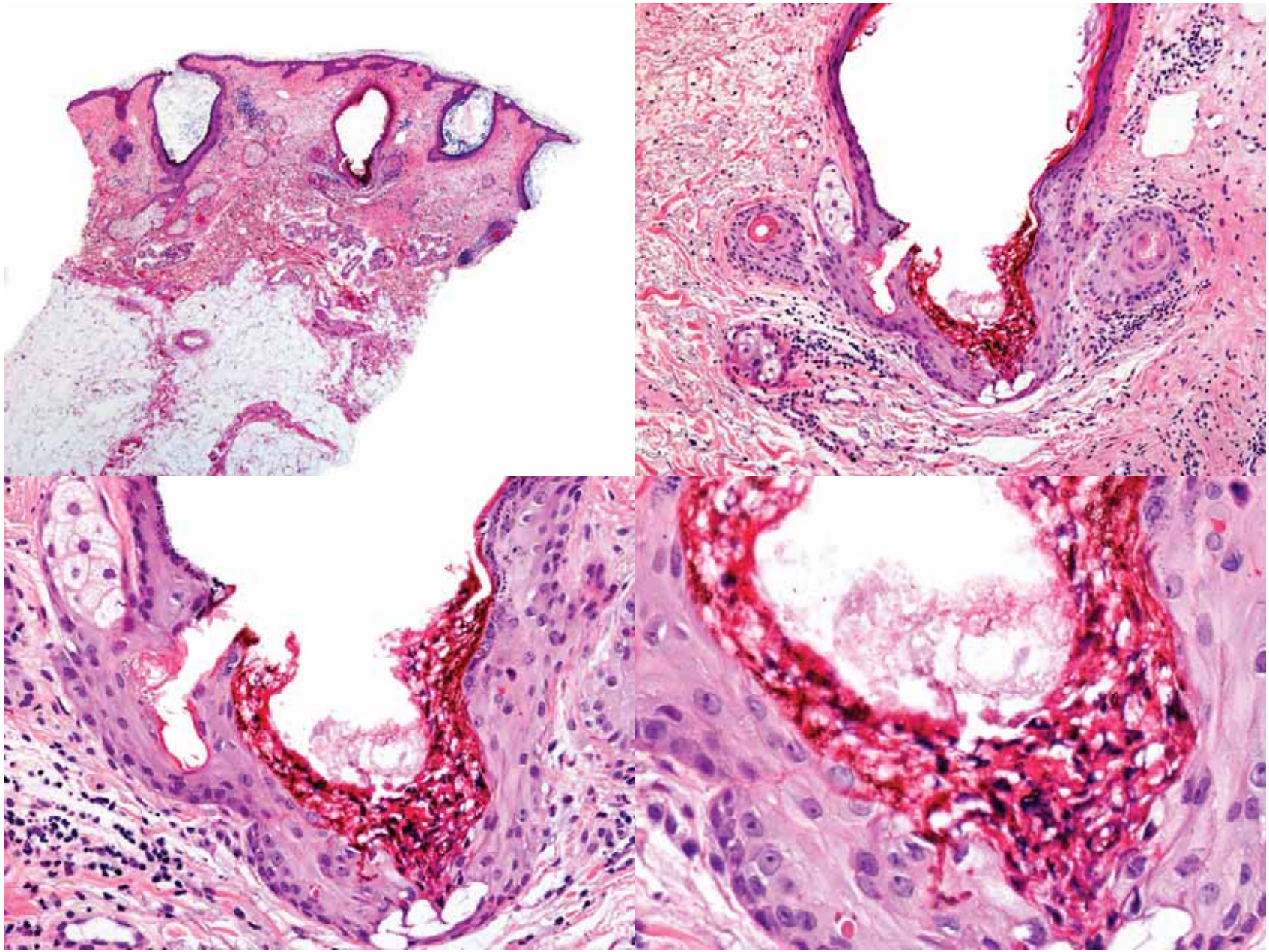
- A 62-year-old woman with history of depression presented with yellowish, scaly, waxy plaques on her forehead, nose and cheeks. Physical examination also revealed slight peeling and perifollicular erythema on her lower limbs

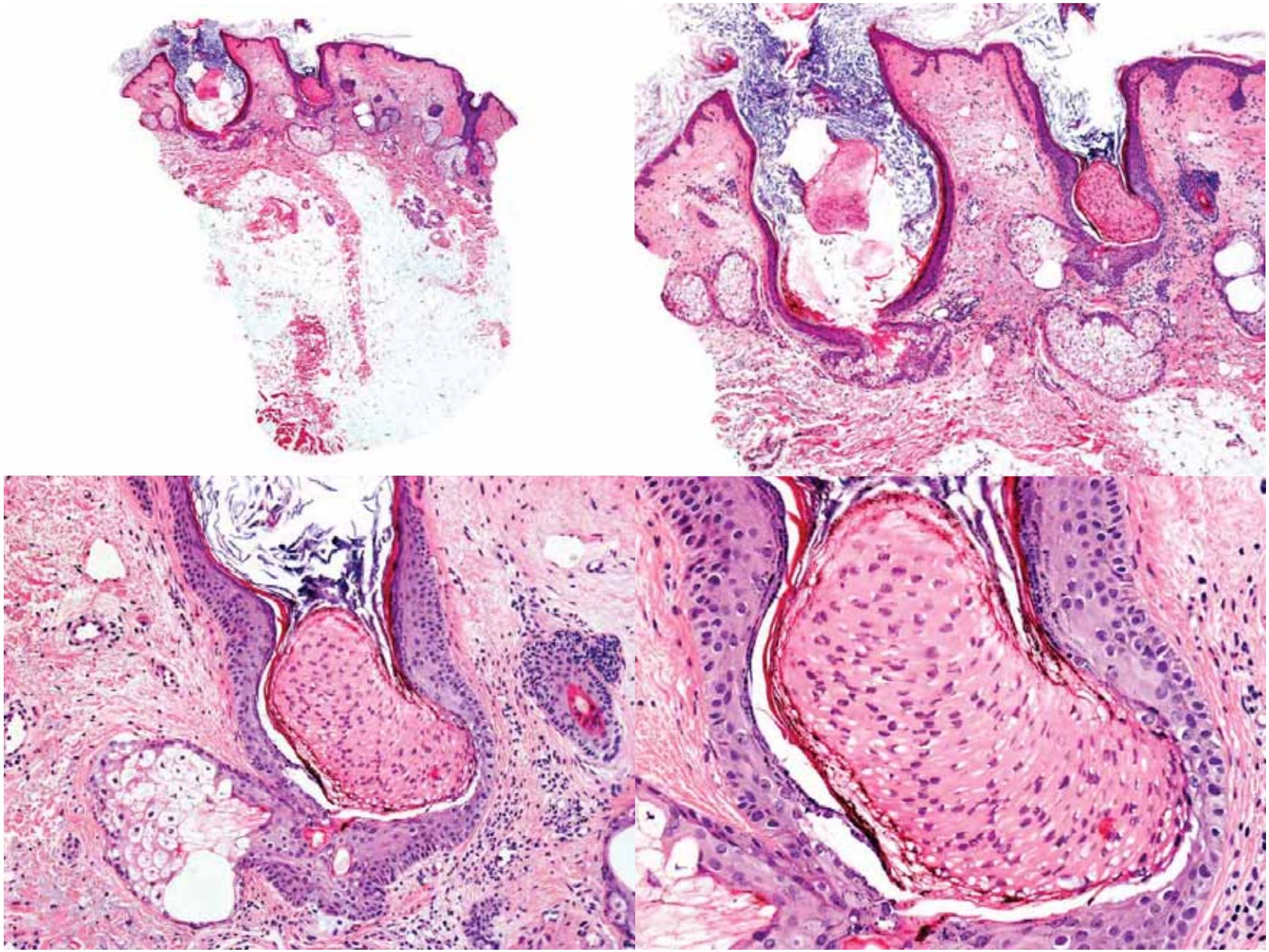


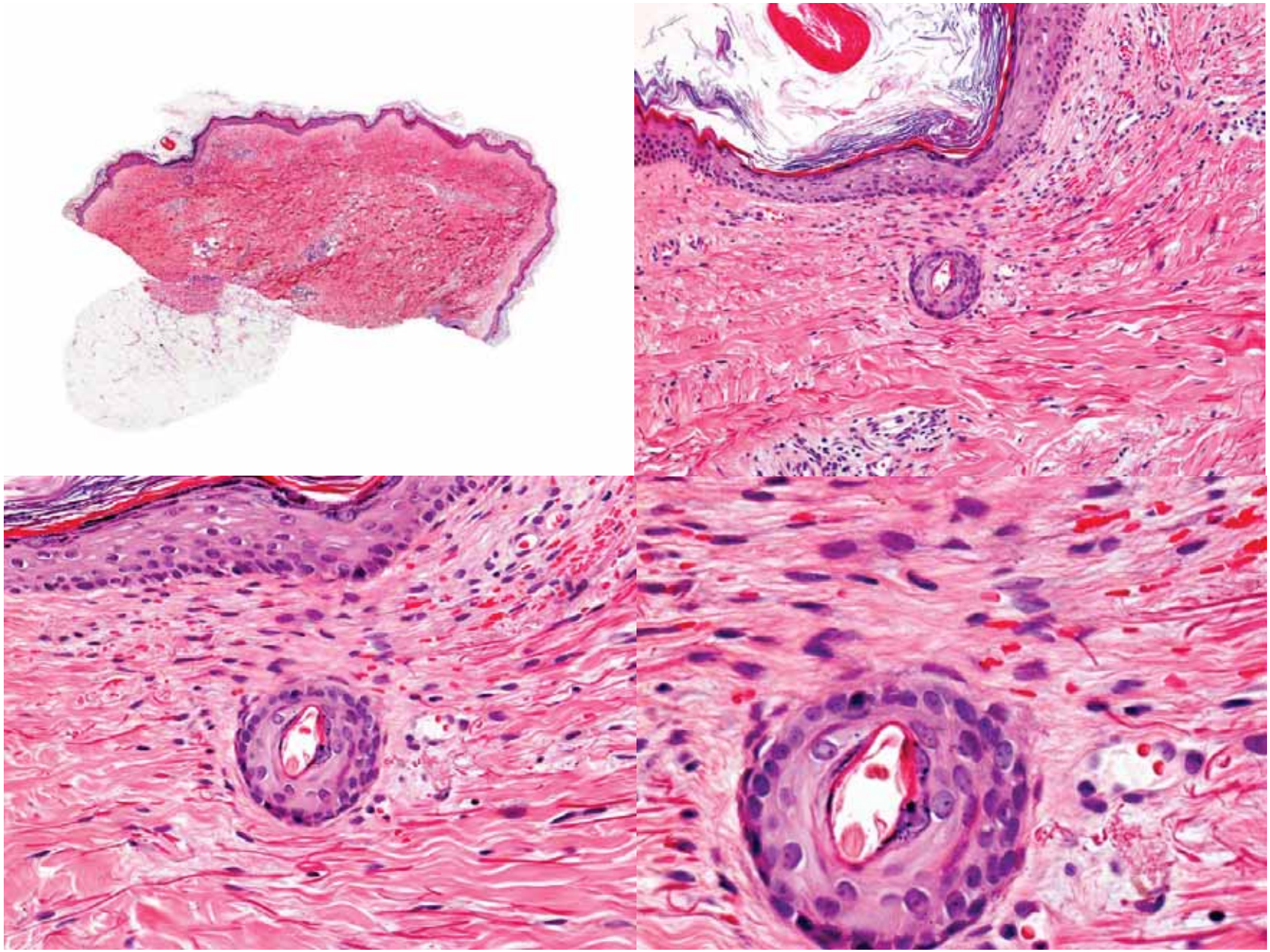


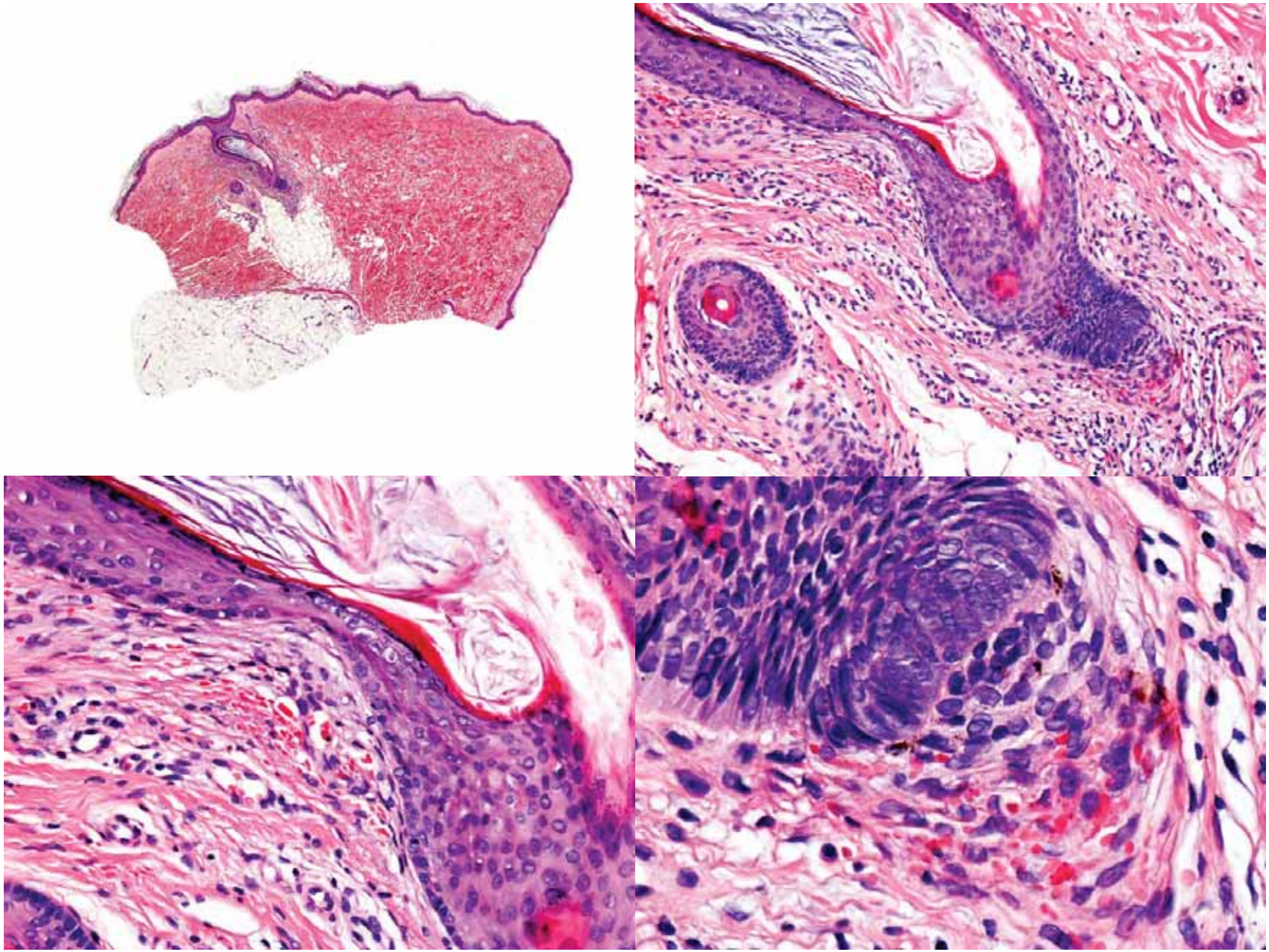












Case 4. Diagnosis

- Phrynoderma + Scurvy

Case 4. Laboratory findings

- Folic acid: 0.9 ng/mL (normal 2.7 -17.0 ng/mL)
- Vitamin C : 0.4 mg/dL (normal 0,8-0,9 mg/dL)
- Vitamin D: 10 ng/mL (normal 30-40 ng/mL)
- Zinc: 35 µg/dL (normal 70-150 µg/dL)
- Vitamin A: 30 mcg/dL (normal 20-60 mcg/dL)
- Vitamin E: 20 µmol α-tocopherol/L (normal 12 -46 µmol α-tocopherol/L)
- Vitamin B12: 200 pg/mL (normal 200 a 900 pg/mL)
- Proteins: 6,3 gr /dL (normal 6.0 a 8.3 g/dL)
- Albumin: 4,1 g/dL (normal 3.4-5.4 g/dL)

Phrynoderma

Clinical features

- Hyperkeratotic follicular papules and plaques with keratotic plugs
- Most common involved areas: the extensor surfaces of extremities and buttocks, although they can appear elsewhere or spread over the entire body
- Originally thought to be a cutaneous manifestation of vitamin A deficiency, but general malnutrition seems to be the strongest association, as it is not necessarily accompanied by low vitamin A levels
- Several studies have demonstrated association of phrynoderma with vitamin E, vitamin B complex and essential fatty acids deficiency, and improvement or resolution of the lesions following the correct replacement of the deficiency

Phrynoderma

Histopathologic features

- Prominent parakeratotic follicular plugging
- Lamellated hyperkeratosis next to hair follicles
- Atrophy of sebaceous glands
- Squamous metaplasia of eccrine and sebaceous ducts

Scurvy

Clinical features

- Nutritional disorder resulting from severe vitamin C deficiency, which results in capillary and tissue fragility and hemorrhage
- Cutaneous manifestations include dryness and roughness with hyperkeratotic follicular papules, corkscrew hairs, and perifollicular erythema, particularly on the legs and buttocks
- Gums may become friable, with swelling and bleeding
- Poor wound healing and blood vessel fragility manifested by petechiae and ecchymoses
- In more severe cases, bleeding can also occur into the gastrointestinal tract, muscles, joints and beneath the periosteum

Scurvy

Histopathologic features

- Thickened stratum corneum
- Twisted hair follicles with perifollicular fibrosis
- Extravasated red blood cells in the upper dermis and around hair follicles and other adnexal structures

Co-occurring features of scurvy and phrynoderma in the same patient

Cristina Moya-Martínez, MD,[a] Lara Haya-Martínez, MD,[a] Laura Fuertes-Vega, MD,[a] Carlos Santonja, MD,[b] and Luis Requena, MD[a]
Madrid, Spain

Key words: dermatopathology; nutritional deficiencies; phrynoderma; scurvy; social isolation; vitamin C.

INTRODUCTION

Cutaneous lesions can be the first manifestation of many systemic diseases, including nutritional deficiencies. Although it is rare in developed countries, scurvy can still occur in malnourished patients, and it is far from being eradicated. Low levels of vitamin C can interfere with multiple organic functions and potentially be life-threatening. Dermatologists must be aware of cutaneous signs of nutritional deficiencies in order to provide comprehensive management of their patients' nutritional status, sometimes together with social intervention. We report co-occurring clinical findings of scurvy and phrynoderma in a patient with a limited diet.

CASE REPORT

A 62-year-old woman with a personal history of depression presented with yellowish, scaly, waxy plaques on her forehead, nose, and cheeks (Fig 1, *A*). Physical examination revealed slight peeling and perifollicular erythema on her lower limbs (Fig 1, *B*). Two biopsy specimens were obtained from the facial and lower limb lesions for histopathologic study. The facial lesion showed dilated follicular infundibula filled with parakeratotic plugs (Fig 2, *A* to *D*). The biopsy specimen from the lower limb lesions showed hyperkeratosis, epidermal atrophy, mild lymphocytic perivascular and perifollicular inflammation, and marked red blood cell extravasation around hair follicles (Fig 3, *A* to *D*). The hair shafts of the involved follicles were twisted and fragmented. A histopathologic diagnosis of phrynoderma involving the face and scurvy involving the lower limbs was established. Laboratory evaluation disclosed low levels of folic acid, vitamin C, vitamin D, and zinc. Vitamins A, E, and B_{12}, proteins, and albumin were within normal limits. The patient was unemployed, living on her own, and on a low income. She reported not having eaten any fruits or vegetables in the previous months. The situation was brought to the attention of social services, and the patient was started on daily vitamins C, B_{12}, and D, folic acid, and zinc supplements. A profound restructuring of her diet was carried out, with significant improvement of her cutaneous lesions.

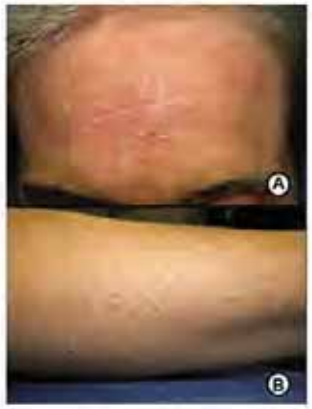


Fig 1. **A**, Yellowish, scaly, waxy plaques on the patient's forehead. **B**, Perifollicular erythema with corkscrew hairs and slight peeling on the lower limbs.

From the Dermatology Department[a] and Pathology Department,[b] Hospital Universitario Fundación Jiménez Díaz, Madrid.

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2352-5120

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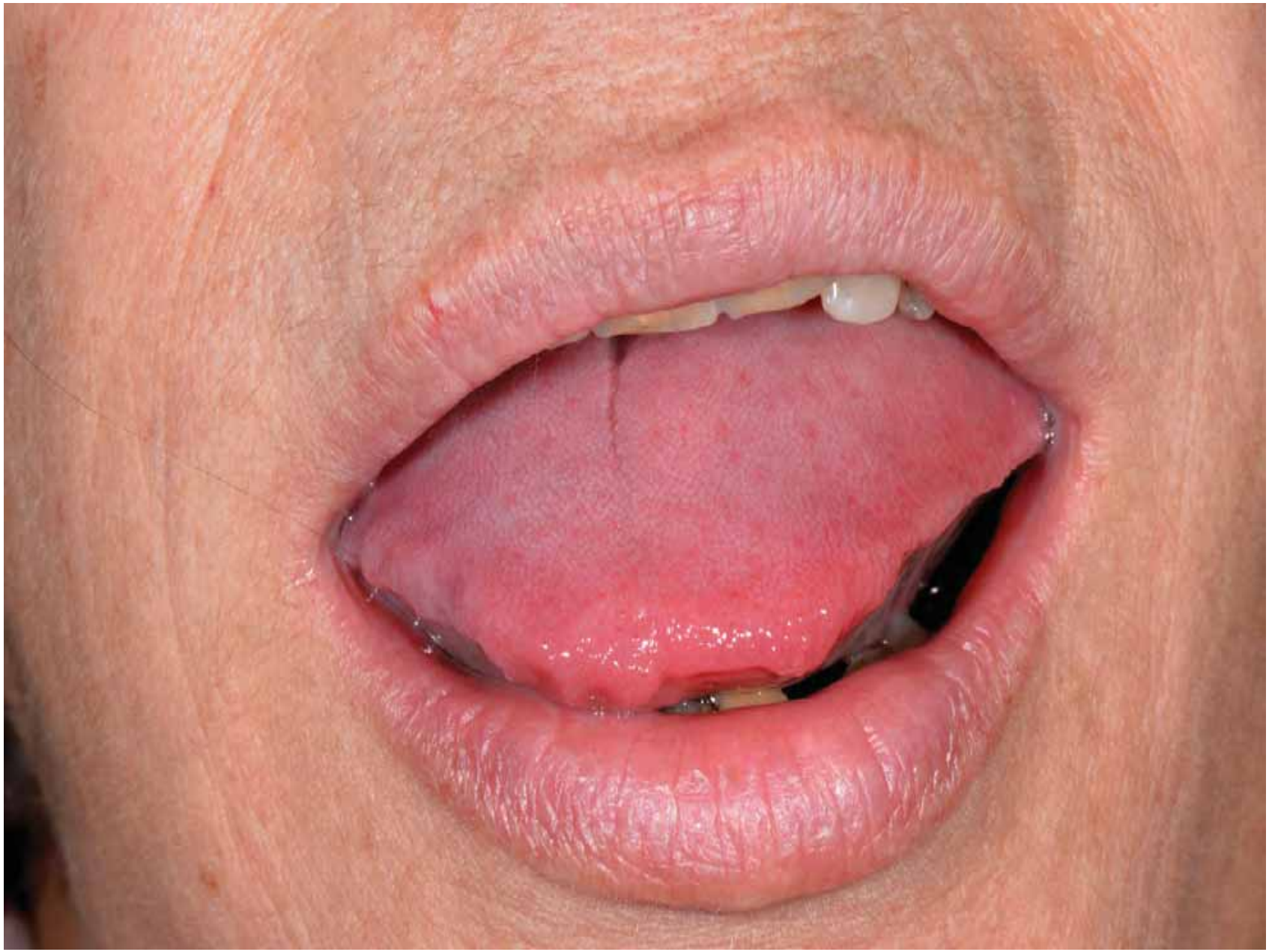
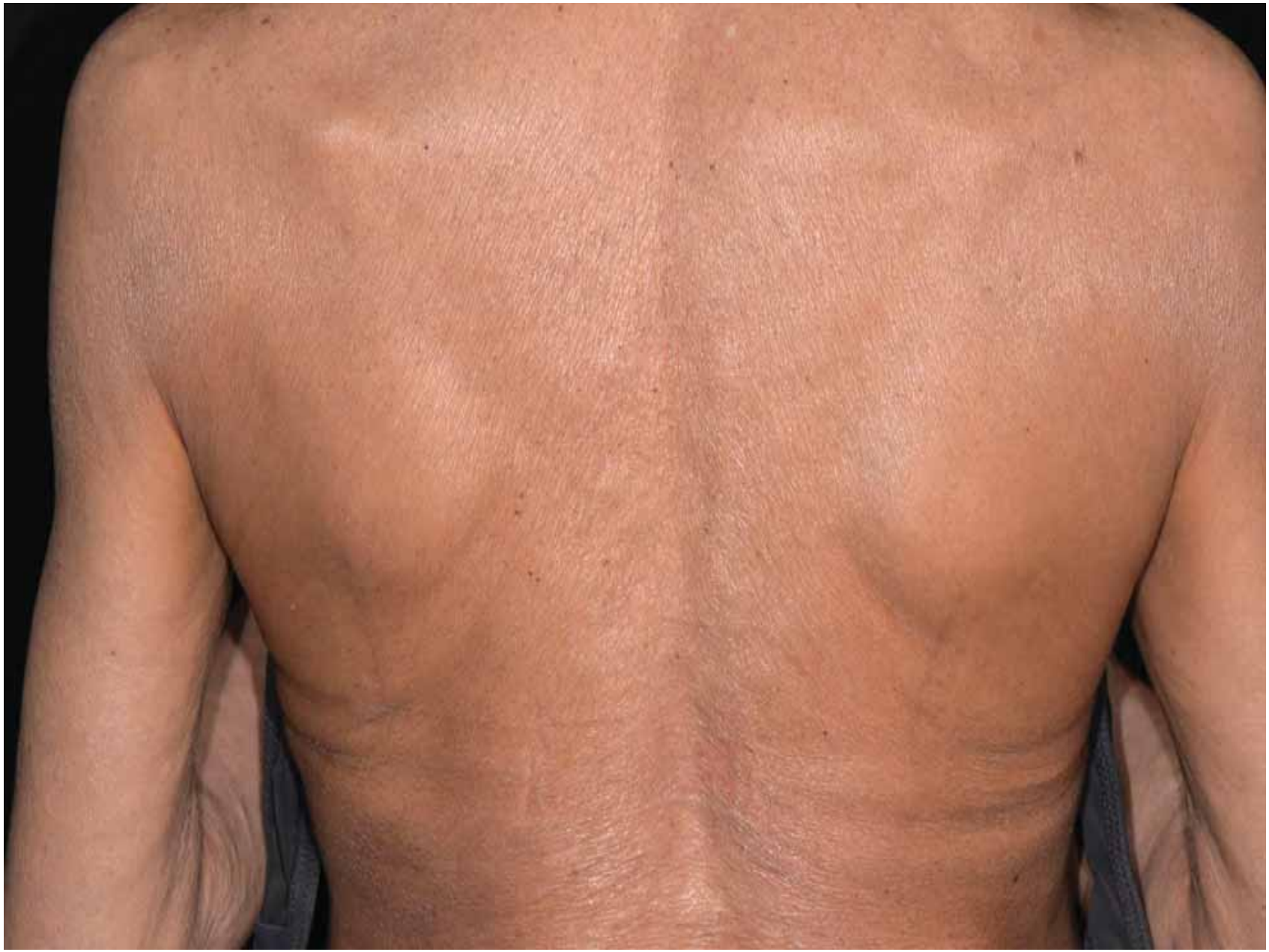
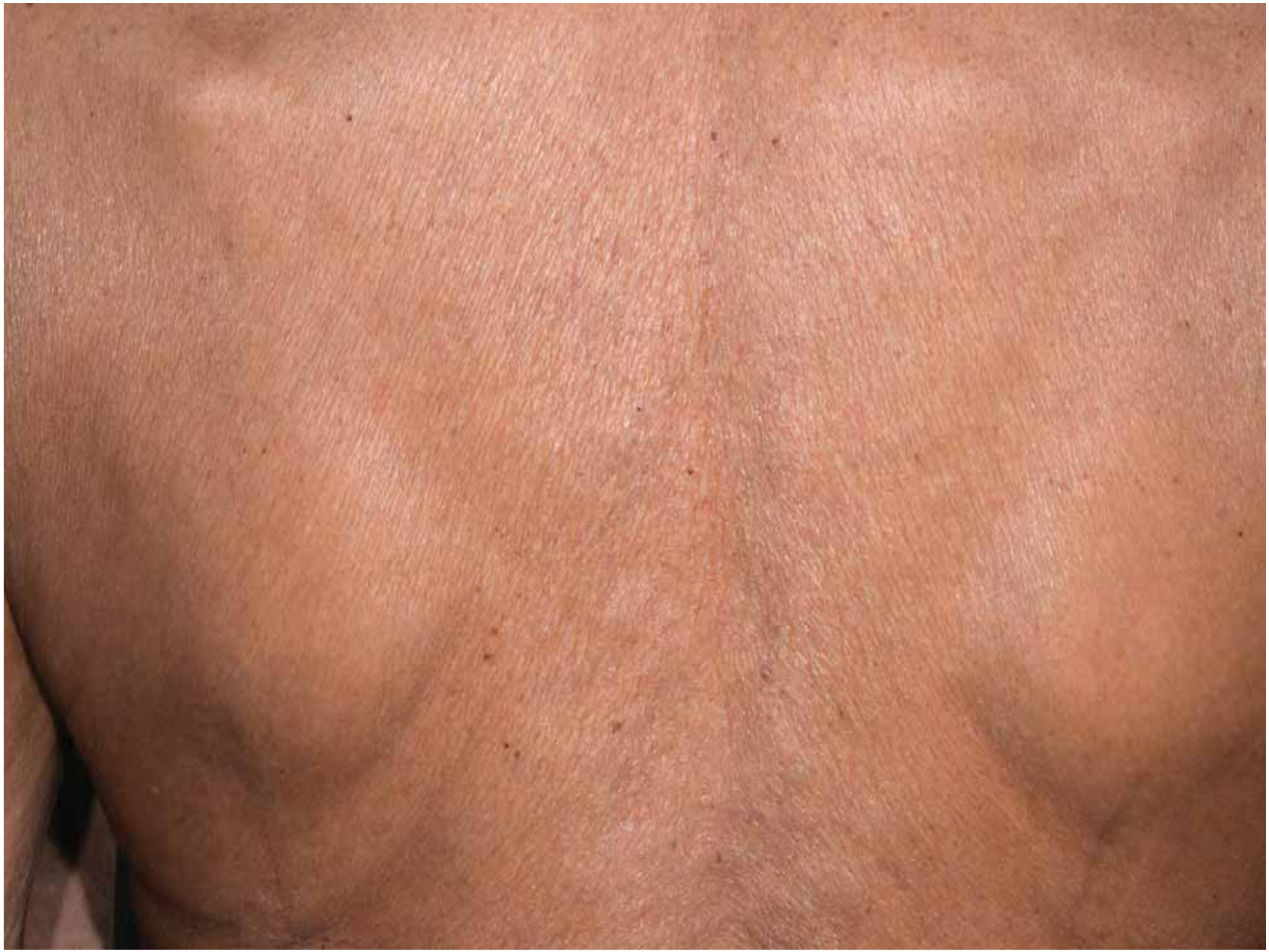
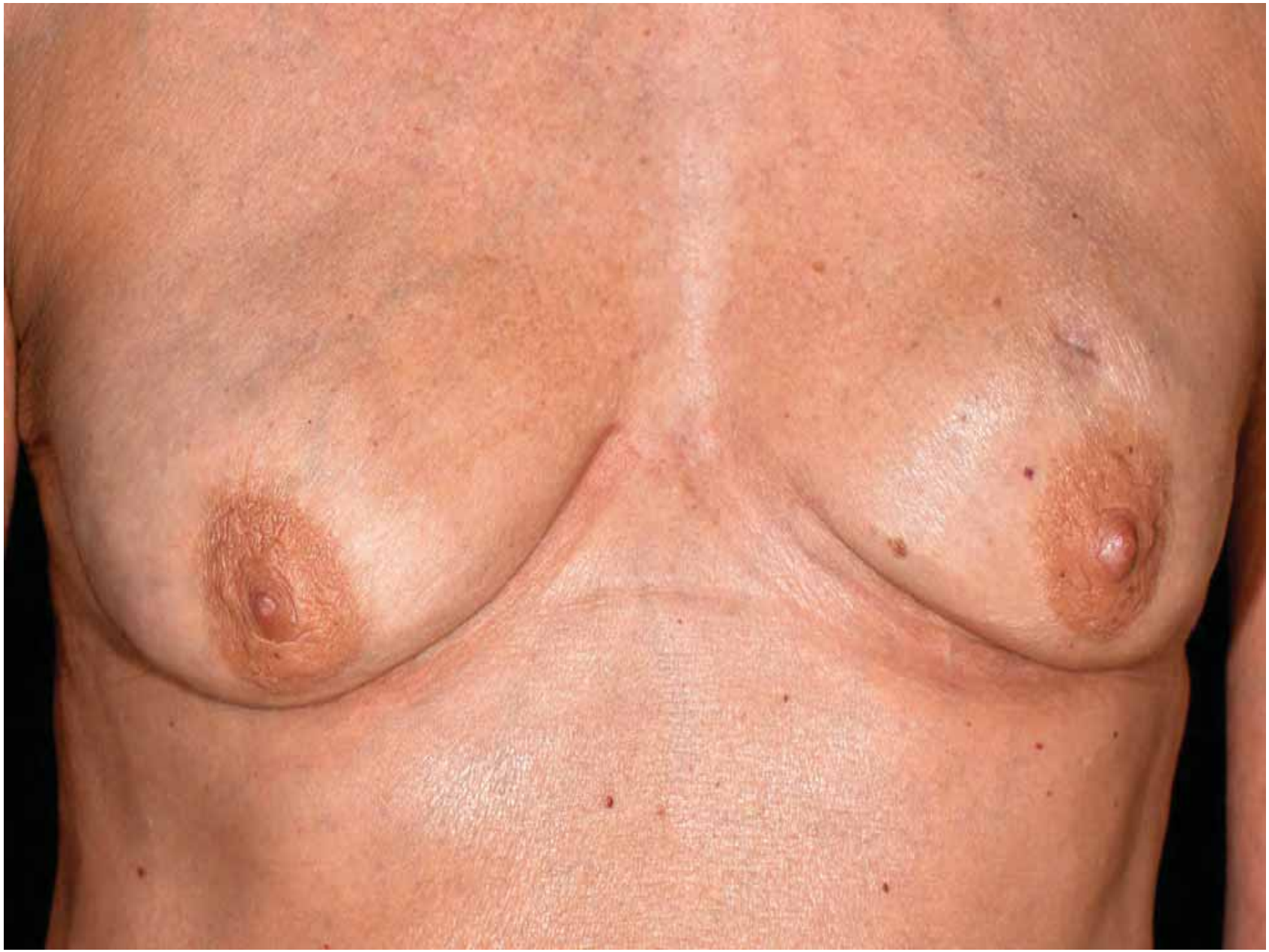
Case 5

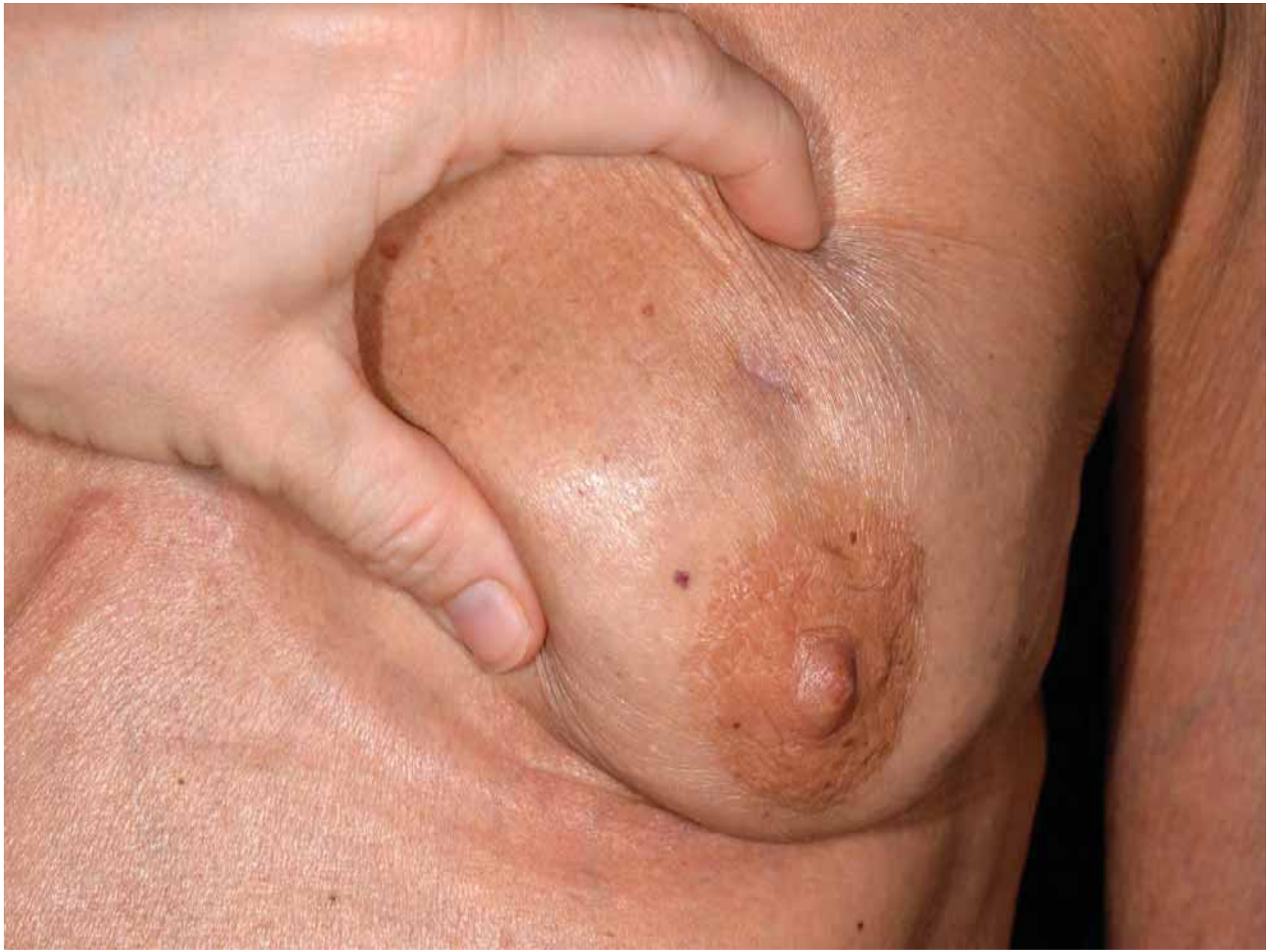
- A 63-year-old female with history of type Bence-Jones multiple myeloma treated with Bortezomib + Dexamethasone + Bone marrow autotransplant + Melphalan (2012); Bortezomib + Cyclophosphamide + Dexamethasone (2014); Lenalidomidae + Dexamethasone (2015).
- Myocardial and mesenteric involvement by AL amyloid.
- Bilateral carpal tunnel syndrome
- Dermatologic consultation: macroglossia and indurated skin on the anterior chest and back

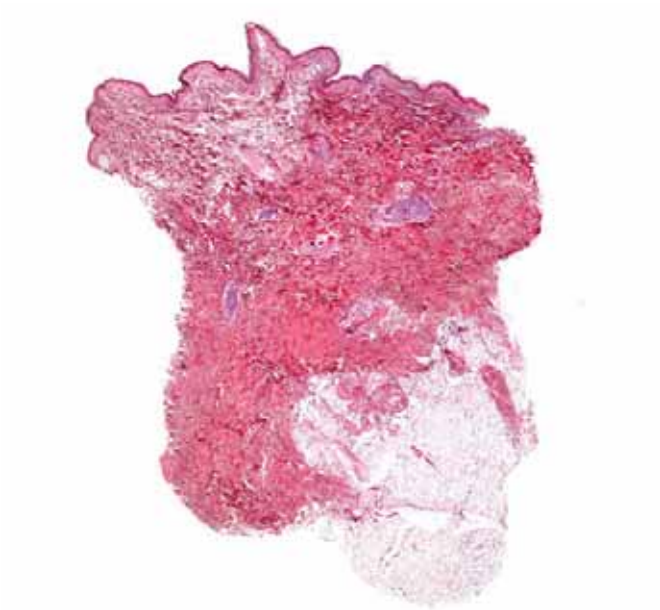


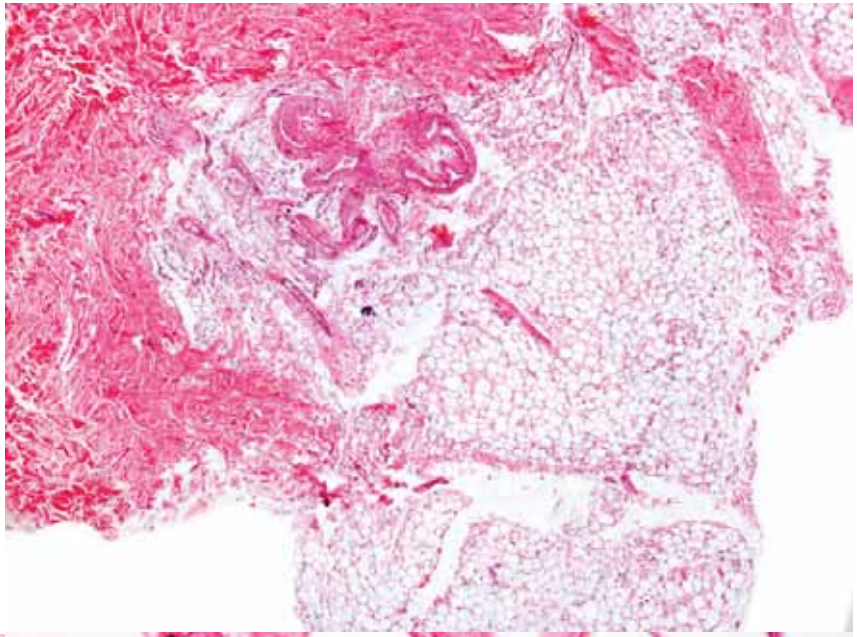


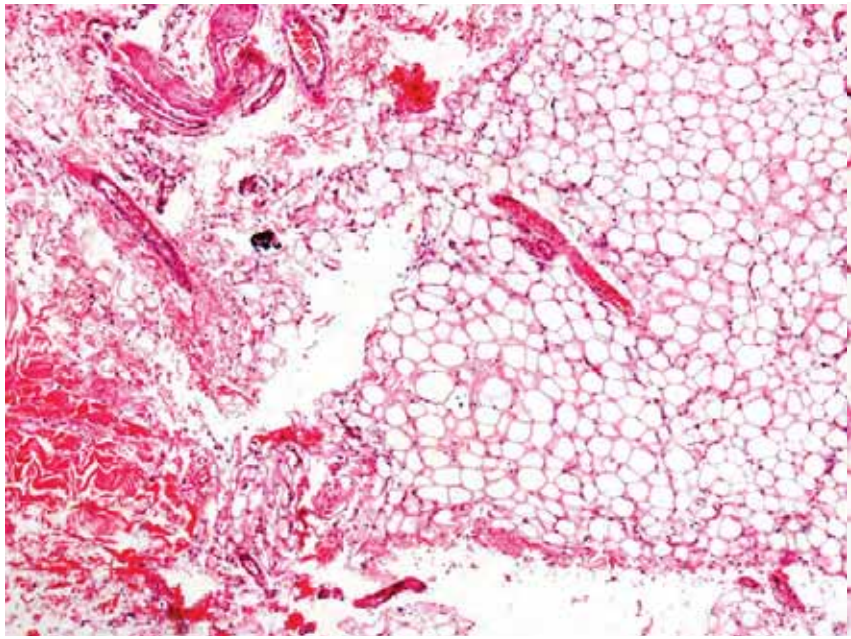


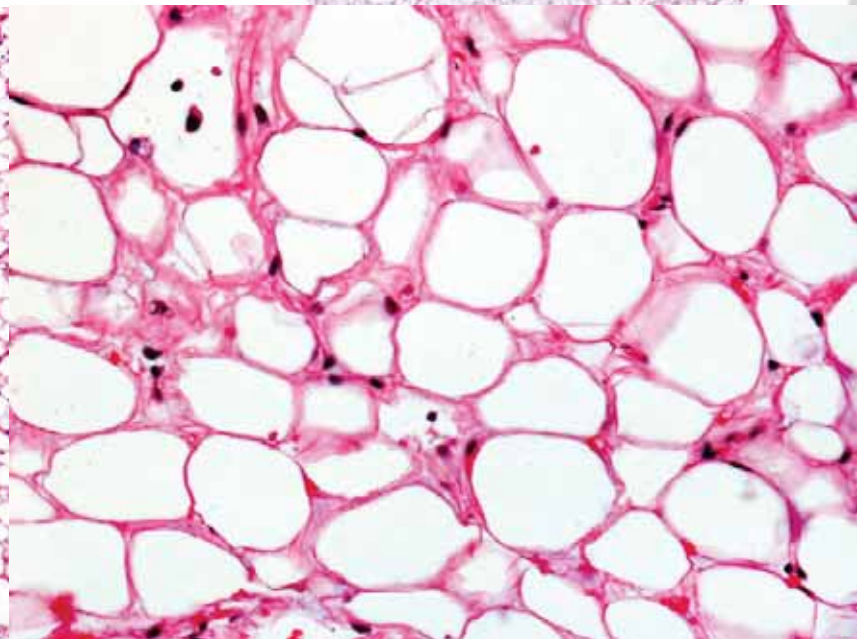


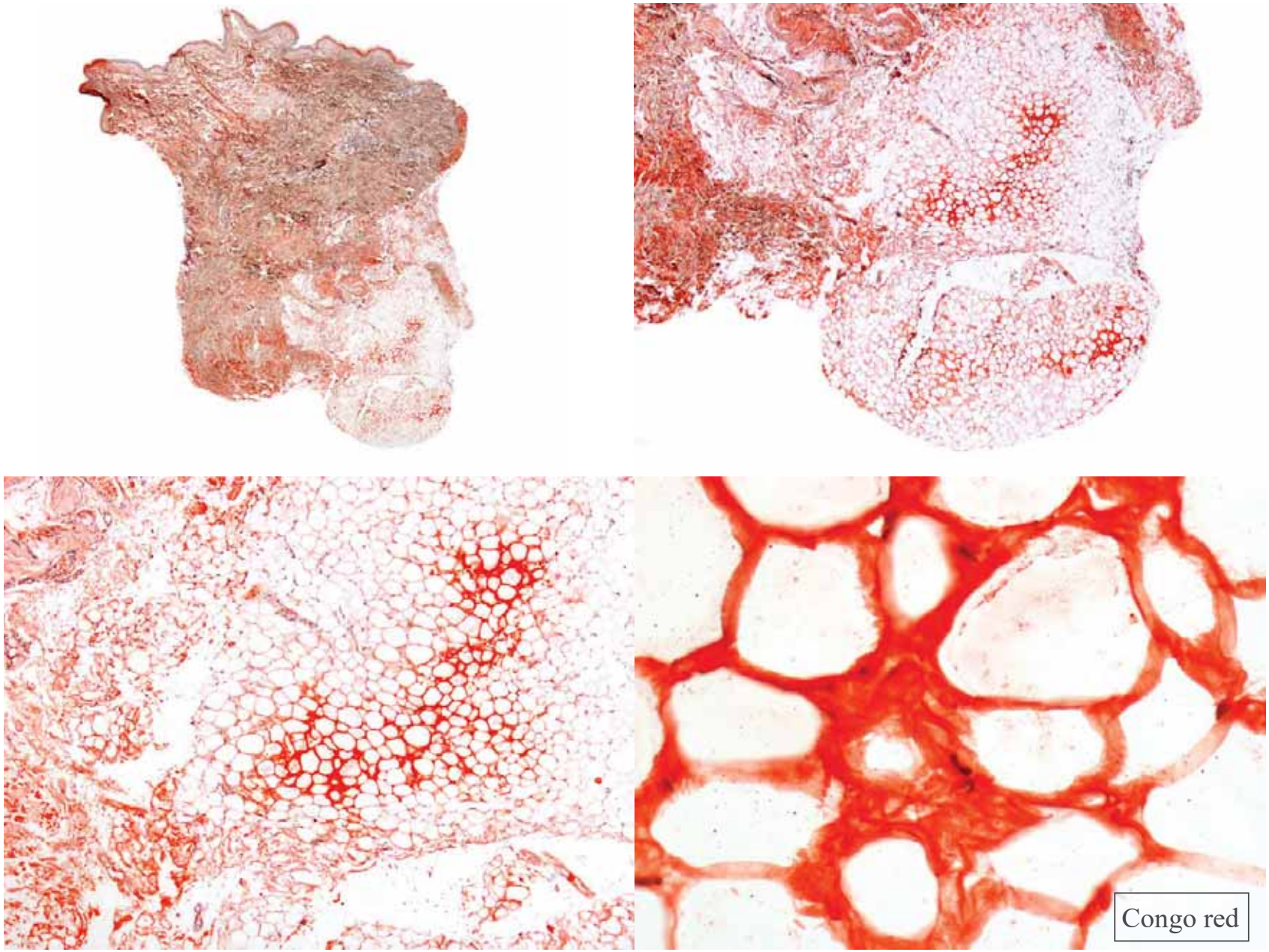


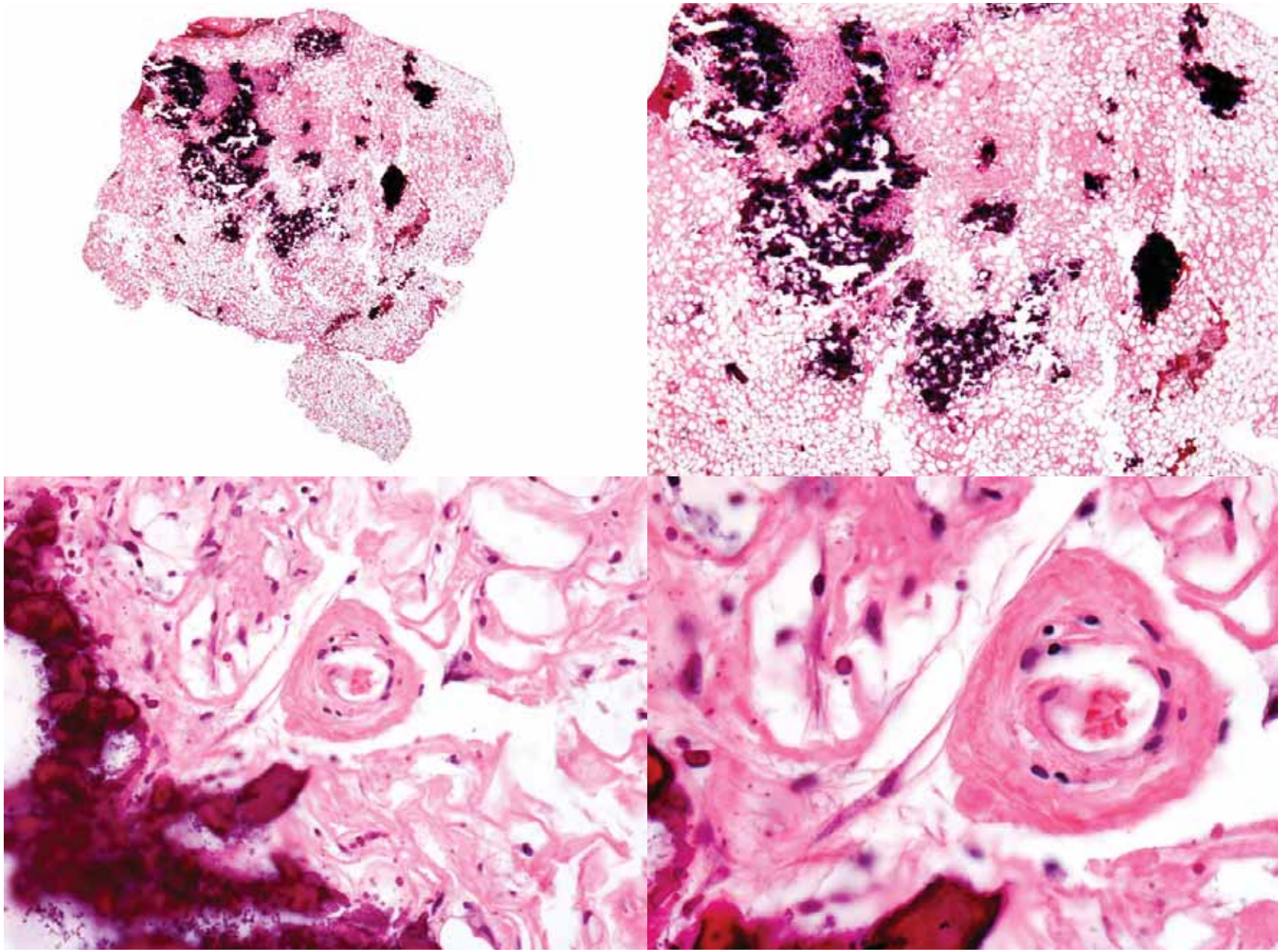


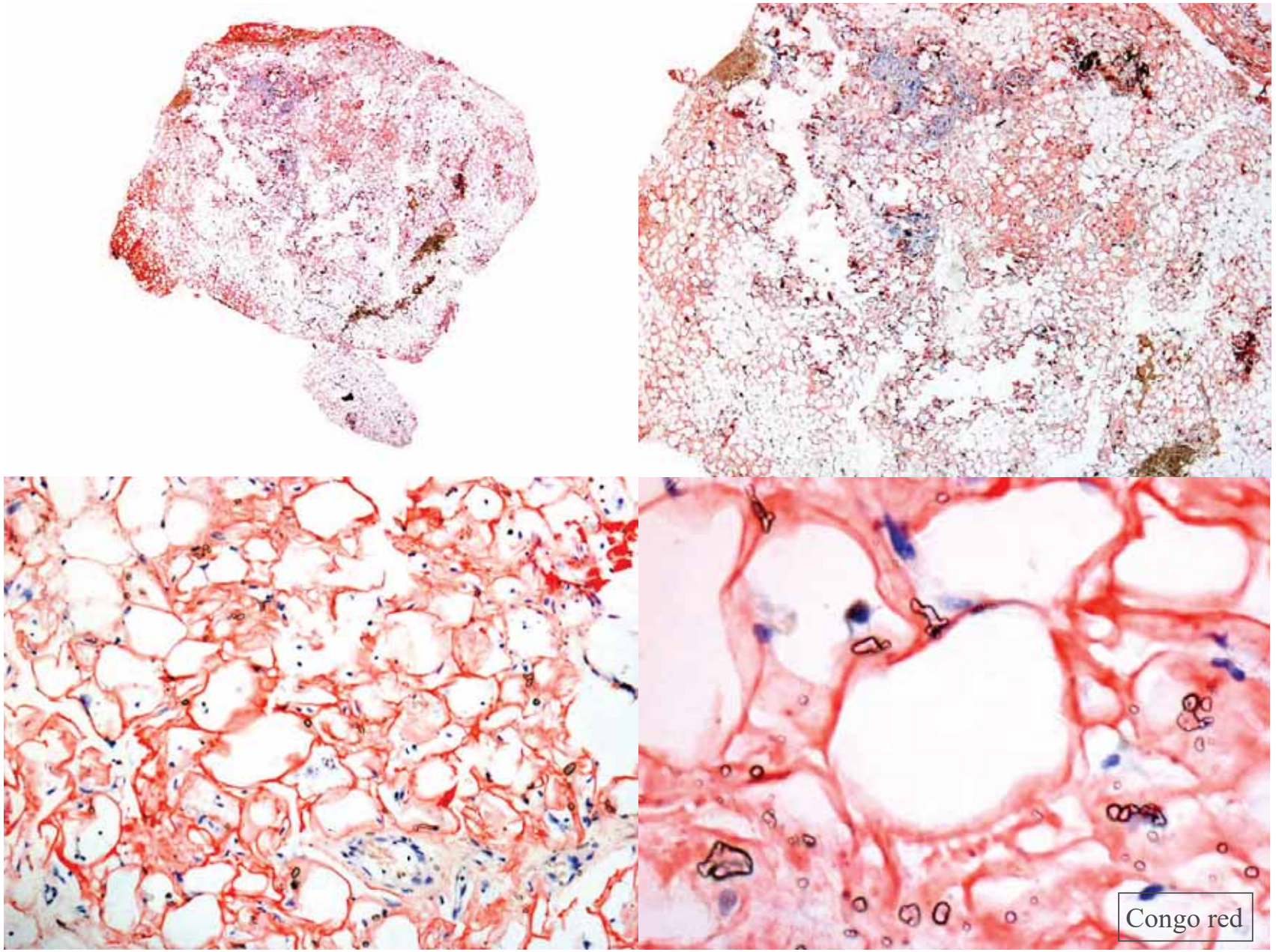







Congo red




Congo red

Case 5. Diagnosis

- Scleroderma amyloidosum

(Aus der Universitäts-Hautklinik Berlin. — Stellvertr. Direktor: Professor Dr. *Fr. Blumenthal.*)

Systematisierte Haut-Muskel-Amyloidose unter dem Bilde eines Sklerodermа amyloidosum.

Von

H. Gottron.

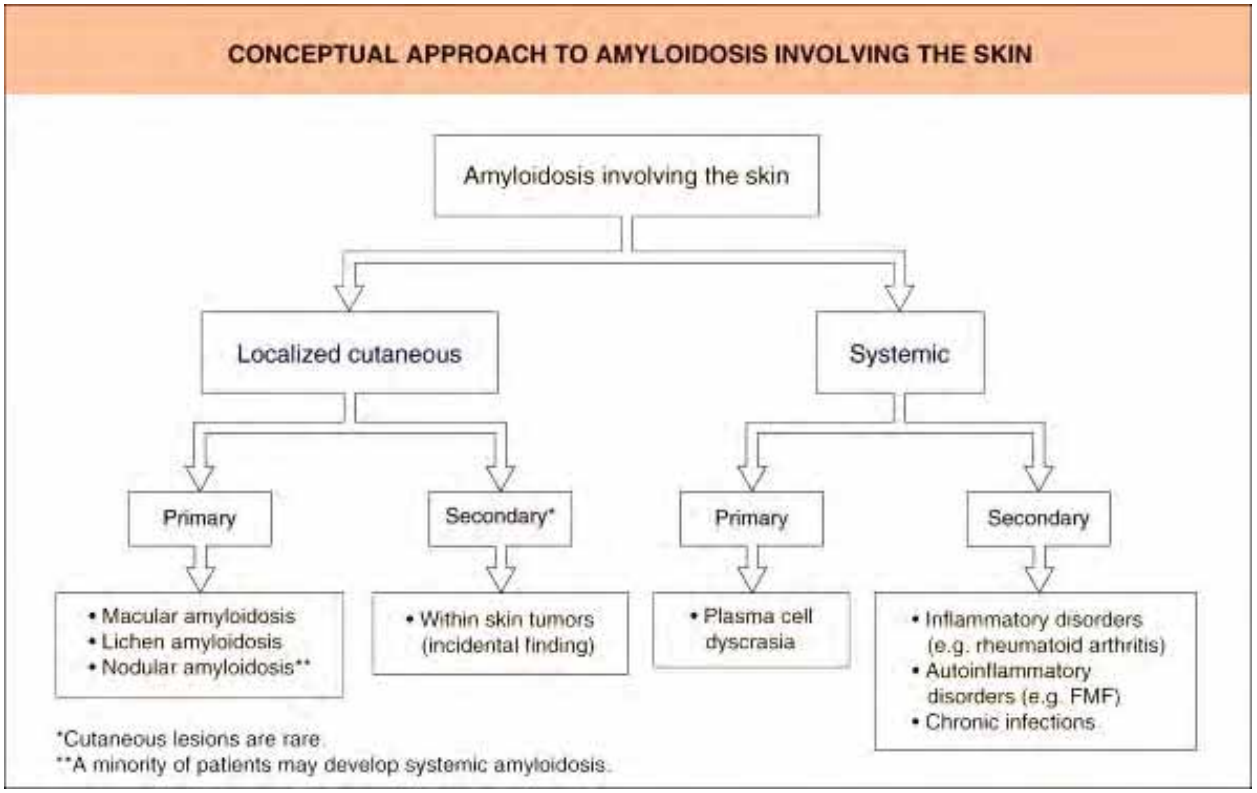
Mit 10 Textabbildungen.

(*Eingegangen am 30. Juni 1932.*)

Scleroderma amyloidosum

- Described by Gottron en 1932
- Primary systemic amyloidosis
- Clínically: sclerodermiform involvement of the skin, with +/- classic sign of systemic amyloidosis
- Histopathology: amyloid AL deposits on the dermis, subcutis and perivascular deposition
- Infrequent presentation of AL amyloidosis and even more uncommon associated with multiple myeloma

AMYLOIDOSIS



Amyloid
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Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee

Merrill D. Benson, Joel N. Buxbaum, David S. Eisenberg, Giampaolo Merlini, Maria J. M. Saraiva, Yoshiki Sekijima, Jean D. Sipe & Per Westermark

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To link to this article: https://doi.org/10.1080/13506129.2018.1549825

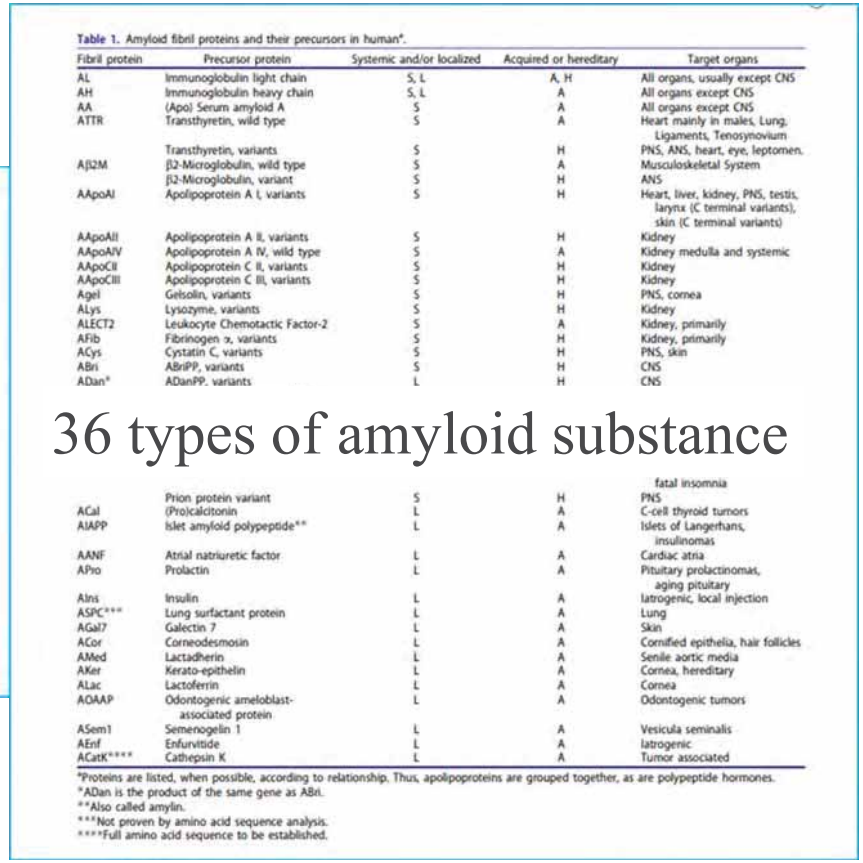

Table 1. Amyloid fibril proteins and their precursors in human*.

Fibril protein	Precursor protein	Systemic and/or localized	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) Serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, Lung, Ligaments, Tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomen.
Aβ2M	β2-Microglobulin, wild type	S	A	Musculoskeletal System
	β2-Microglobulin, variant	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
Agel	Gelsolin, variants	S	H	PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte Chemotactic Factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan*	ADanPP, variants	L	H	CNS
	Prion protein variant	S	H	fatal insomnia PNS
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide**	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC***	Lung surfactant protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic media
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfuvirtide	L	A	Iatrogenic
ACatK****	Cathepsin K	L	A	Tumor associated

*Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.
*ADan is the product of the same gene as ABri.
**Also called amylin.
***Not proven by amino acid sequence analysis.
****Full amino acid sequence to be established.

36 types of amyloid substance

AMYLOIDOSIS

CHEMICAL CLASSIFICATION OF AMYLOIDOSES		
Precursor protein	Amyloid protein	Clinical syndrome
Aβ precursor protein (AβPP)	Aβ	Alzheimer disease, aging
(Apo) serum AA *	AA	Secondary systemic amyloidosis (see Table 47.1), hereditary periodic fever syndromes (e.g. familial Mediterranean fever, Muckle–Wells syndrome, TRAPS; see Ch. 45)
Apolipoprotein AI	AApoAI	Hereditary apolipoprotein AI-associated amyloidosis; distribution of organ involvement, including skin, related to location of mutation
Apolipoprotein AII	AApoAII	Familial renal amyloidosis
β_2-microglobulin	Aβ_2M	Chronic hemodialysis
Calcitonin	ACal	Medullary carcinoma of the thyroid
Cystatin C	ACys	Hereditary cystatin C amyloid angiopathy †
Gelsolin	AGel	Familial amyloidosis, Finnish type
Immunoglobulin heavy chain (very rare) ‡	AH	Primary systemic amyloidosis
Keratin	AKer	Primary (localized) cutaneous amyloidosis
Immunoglobulin light chain	AL	Primary systemic amyloidosis (associated with plasma cell dyscrasia § » multiple myeloma), primary cutaneous nodular amyloidosis
Insulin	AIns	Firm nodule at sites of repeated insulin injections
Leukocyte chemotactic factor 2	ALect2	Progressive renal insufficiency and hepatic involvement; favors Mexican-Americans
Transthyretin	ATTR	ATTR amyloidosis: (1) familial amyloid polyneuropathy (*TTR* mutations); (2) familial amyloid cardiomyopathy (*TTR* mutations); and (3) wild-type ATTR amyloidosis/senile systemic amyloidosis/senile cardiac amyloidosis
Corneodesmosin	–	Hypotrichosis simplex of the scalp

AMYLOIDOSIS

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Corneodesmosin	–	Hypotrichosis simplex of the scalp

active serine proteinases. As EglinC has a very high affinity to HNE, which is abundantly present in venous leg ulcers, we suggest that HNE is one of the major proteinases responsible for growth factor inactivation in wound fluids from venous leg ulcers.

The biological activity of naturally occurring, endogenous TGF-β, which is released from cells as inactive precursor molecule, is primarily regulated by the extracellular micro-environment. Activation and inactivation of TGF-β is a highly regulated process which is known to involve proteolytic mechanisms and binding to extracellular molecules. We suggest that in chronic wounds the steady-state levels of active TGF-β may be significantly reduced due to enhanced proteolytic inactivation by HNE. Exogenous application of peptide growth factors at 'hyper'physiological concentrations may counteract endogenous growth factor inactivation by HNE. Furthermore, because of the strong patient-to-patient variation in HNE levels topically applied growth factors may have no predictable dose–response relationship in chronic ulcers. Further attempts to use peptide growth factors to ameliorate wound healing may well incorporate strategies that address the heterogeneous levels of proteolytic enzymes in chronic wounds.

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**Department of Dermatology,* D.COX
University Hospital, CH-4031 Basel,
Switzerland

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3 Roberts AB. Transforming growth factor-β: activity and efficacy in animal models of wound healing. *Wound Rep Reg* 1995; 3: 408–18.

Light chain multiple myeloma with peripheral leucocytosis presenting as scleroderma amyloidosum of the AA-type

SIR, Diffuse sclerosing skin changes have rarely been described in individual patients with primary systemic amyloidosis resembling scleroderma.[1–3] The term scleroderma amyloidosum was first used by Gottron in 1932 to describe this skin condition.[4] We report a patient with scleroderma amyloidosum and multiple myeloma associated with an unusual leucocytosis.

In December 1995, a 48-year-old Turkish woman underwent surgery for carpal tunnel syndrome of the right hand. Seven months later, she noticed increased induration of the skin, with swelling of the lips and painful induration of the tongue accompanied by hoarseness, difficulty in swallowing and dyspnoea. In addition, she suffered from recurrent diarrhoea, had had a weight loss of 5 kg and had experienced paraesthesiae of the right hand. On examination, she had a mask-like, tight, expressionless coarsened face with prominent

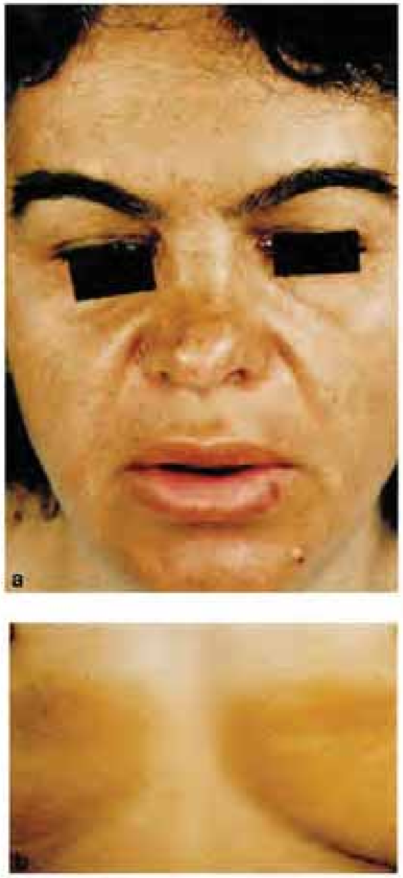


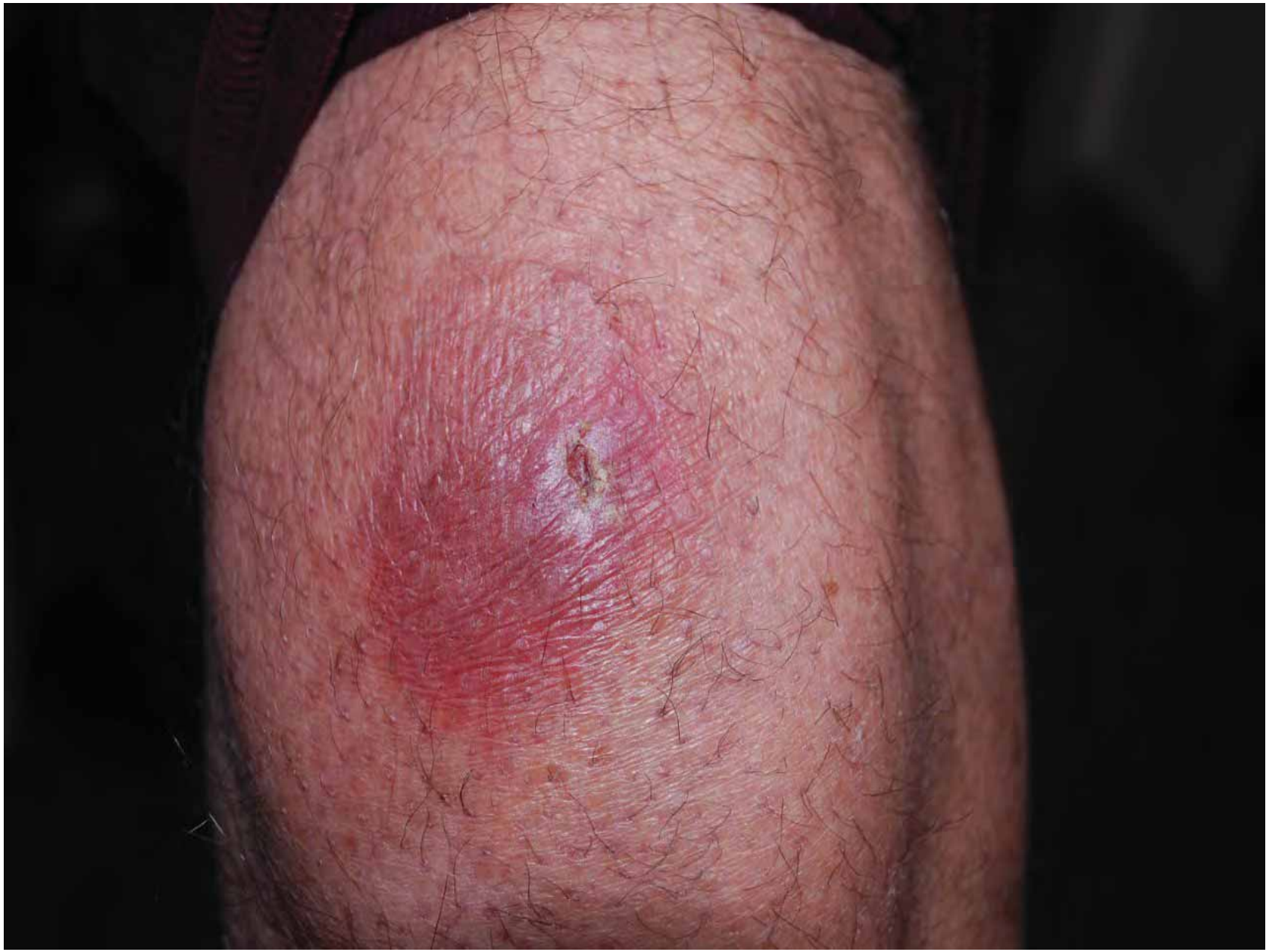
Figure 1. (a) The patient has a mask-like, expressionless face with a coarsened outline, resembling a leonine face, with lip swelling and smooth skin with loss of folds. (b) Waxy, plaque-like indurated skin is evident in the submammary and intermammary region, with brownish hyperpigmentation and small papules.

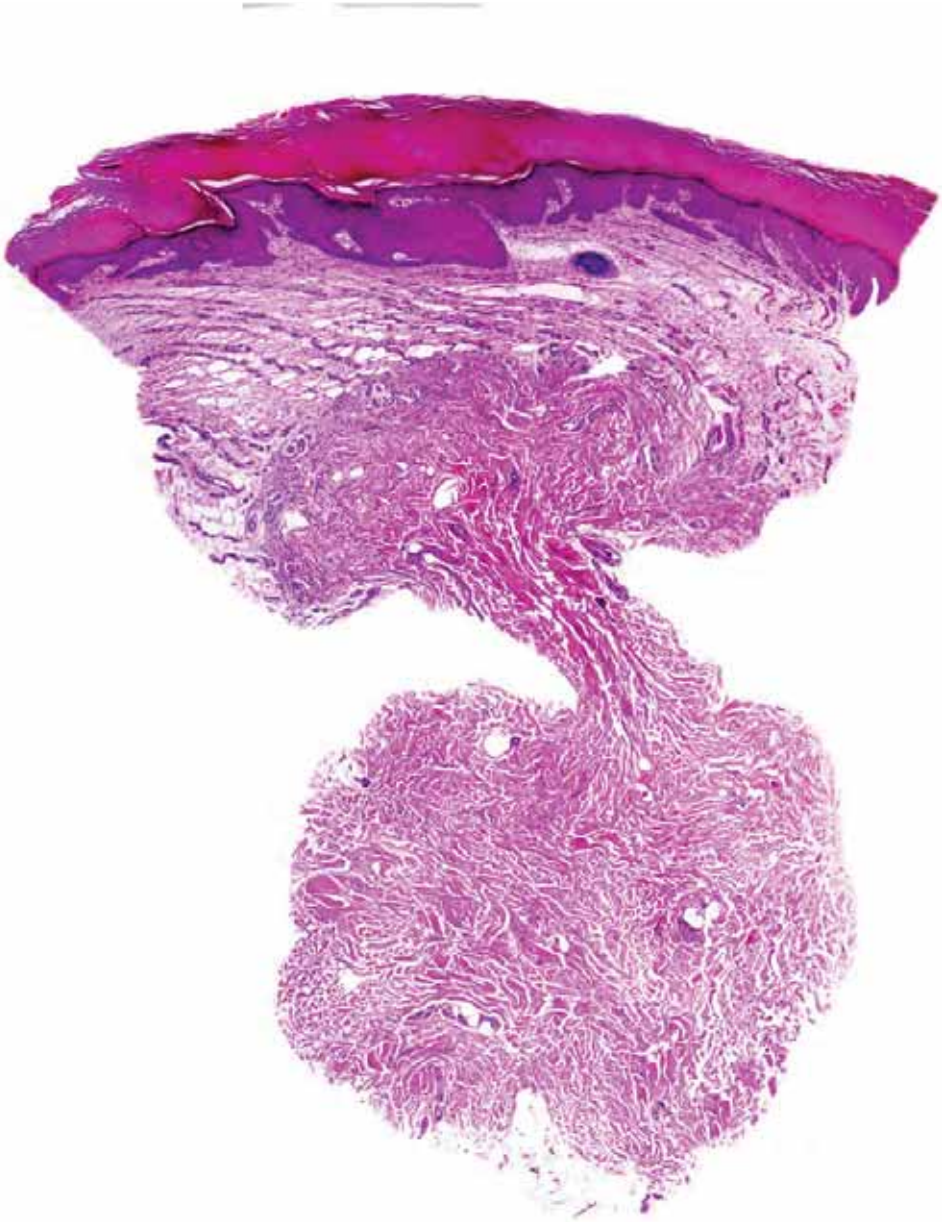
Br J Dermatol. 1999;140:1172-4.

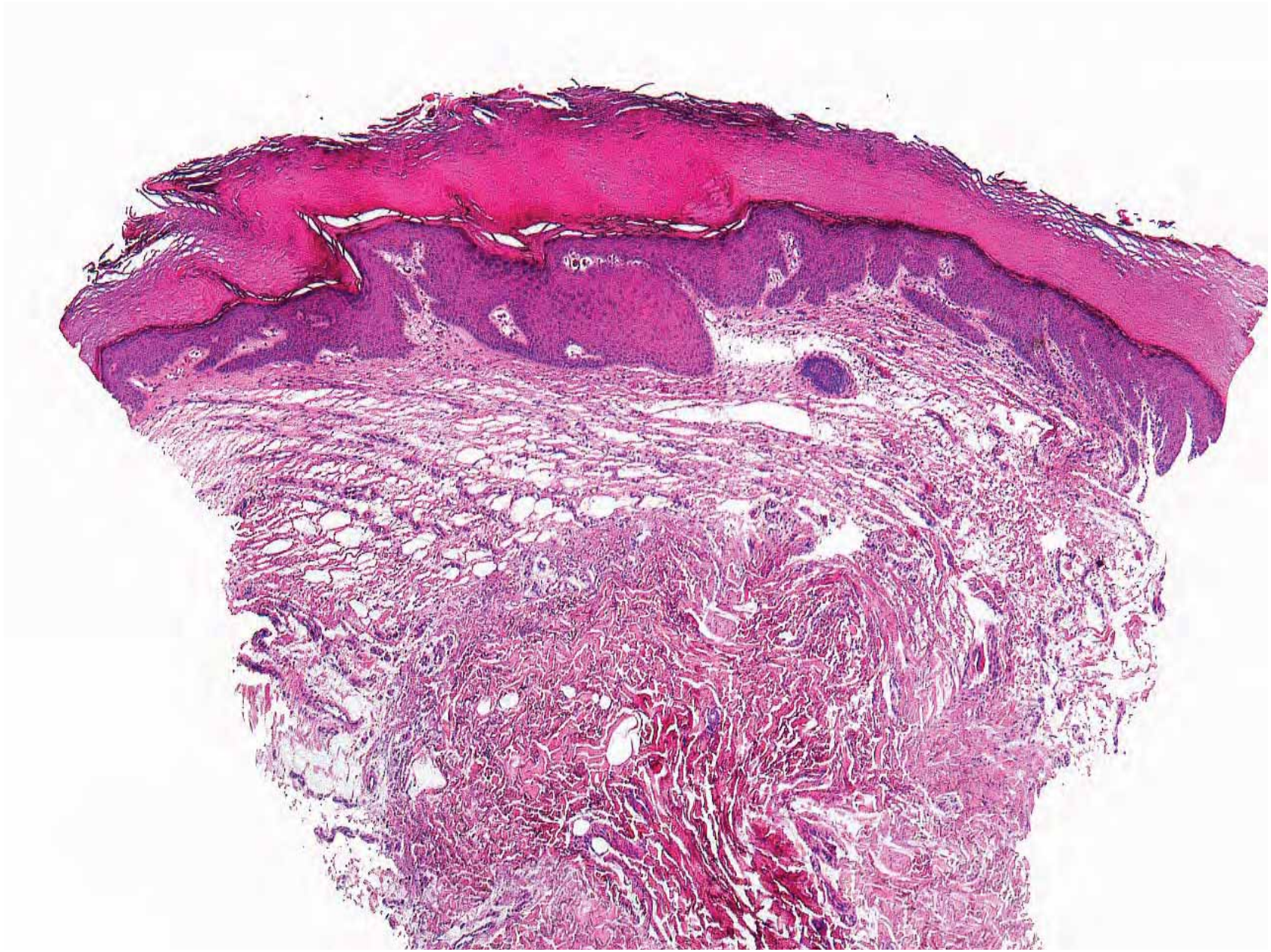
Histology of the submammary region revealed thick, homogenized, cell-poor collagen bundles surrounding atrophic sweat glands in the lower dermis, resembling fibrosclerosis as seen in scleroderma. However, Congo Red staining was positive with typical apple-green birefringence associated with collagen bundles, along elastic fibres, in dermal and subcutaneous vessels and in eccrine sweat glands. Because of amyloid deposits with fibrosclerotic changes of dermal connective tissue we made a diagnosis of scleroderma amyloidosum. A biopsy of the lower lip showed similar

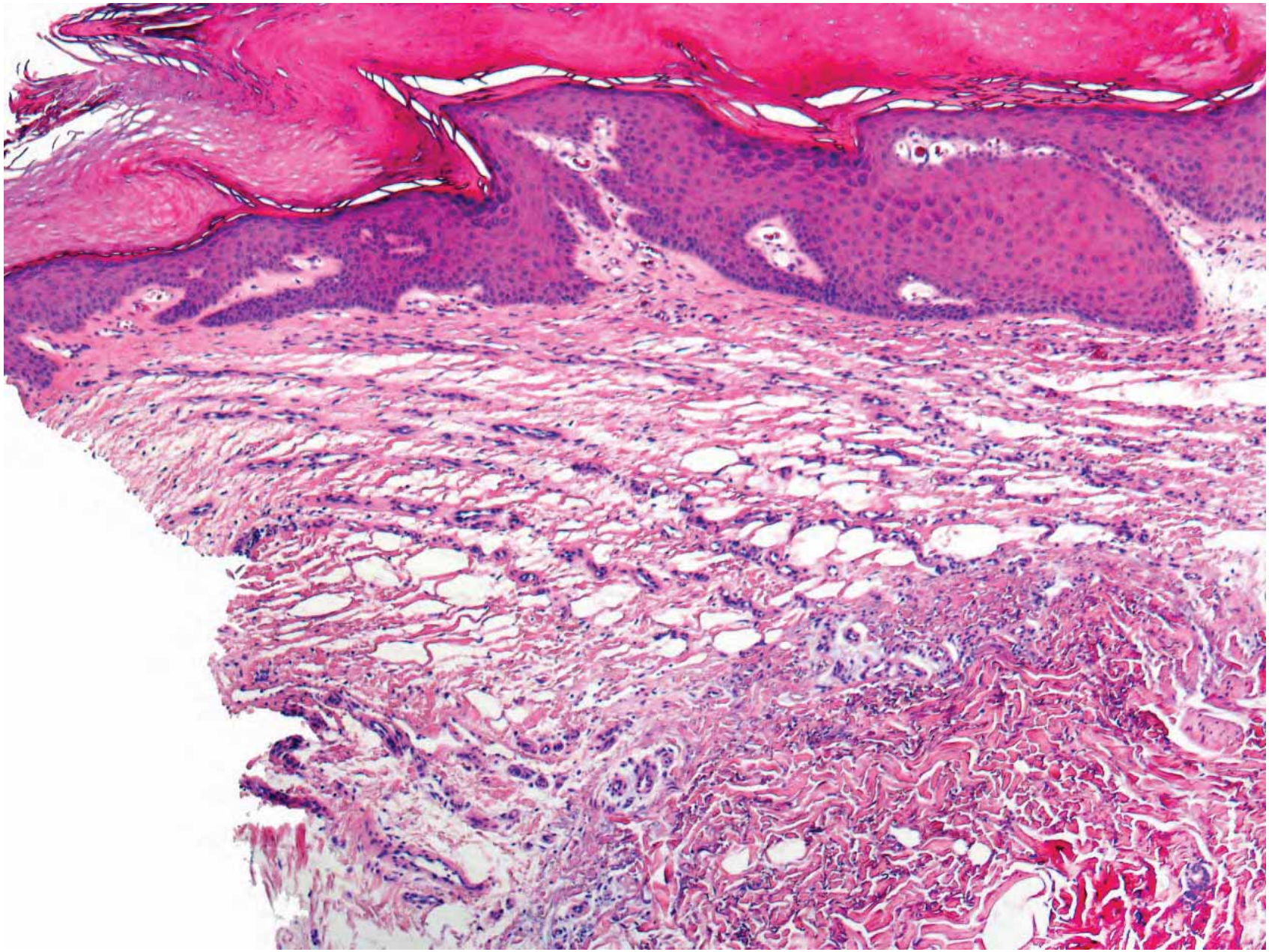
Case 6

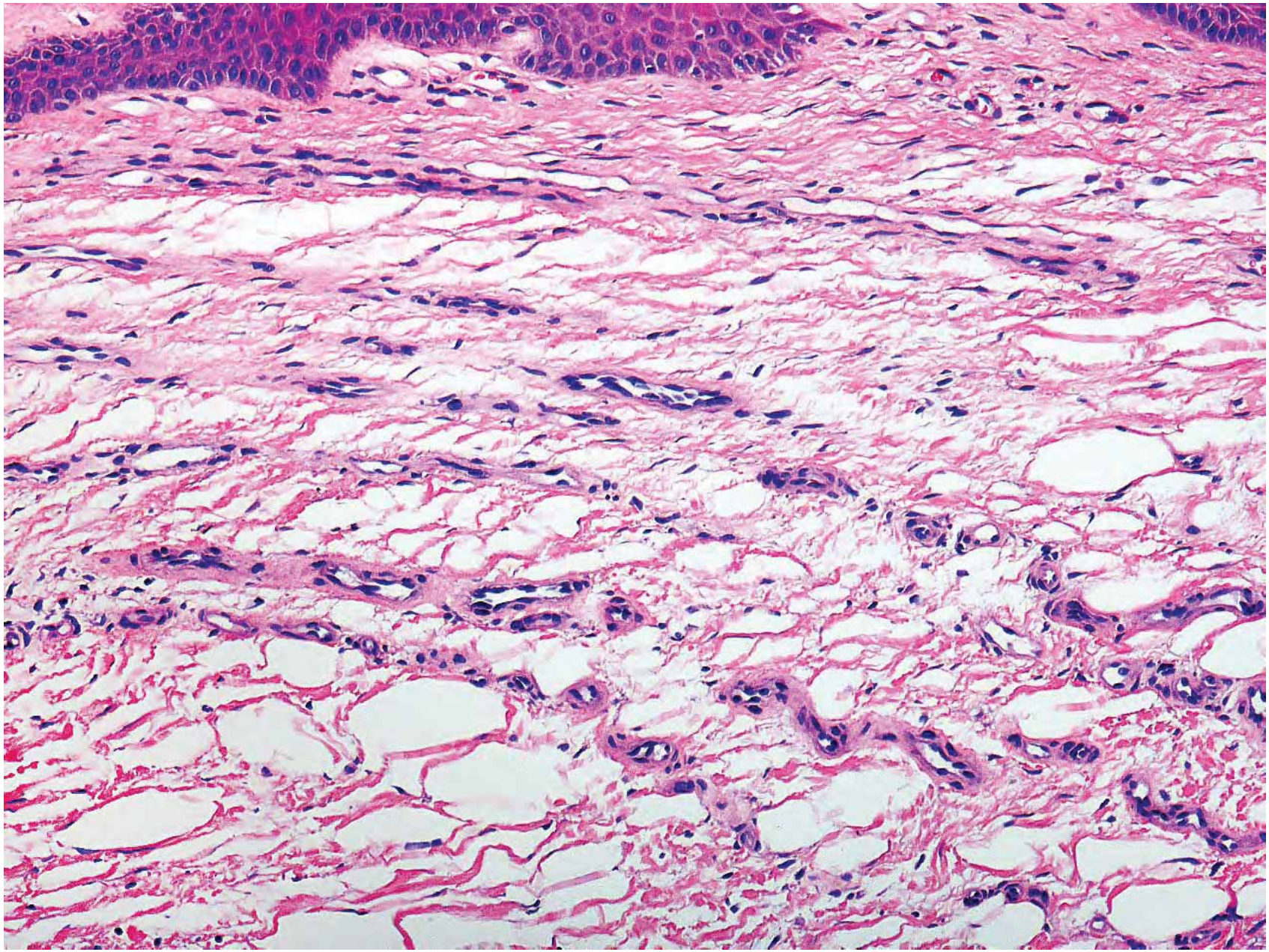
A 63-year-old male presented with an erythematous plaque on the lateral aspect of the right thigh.

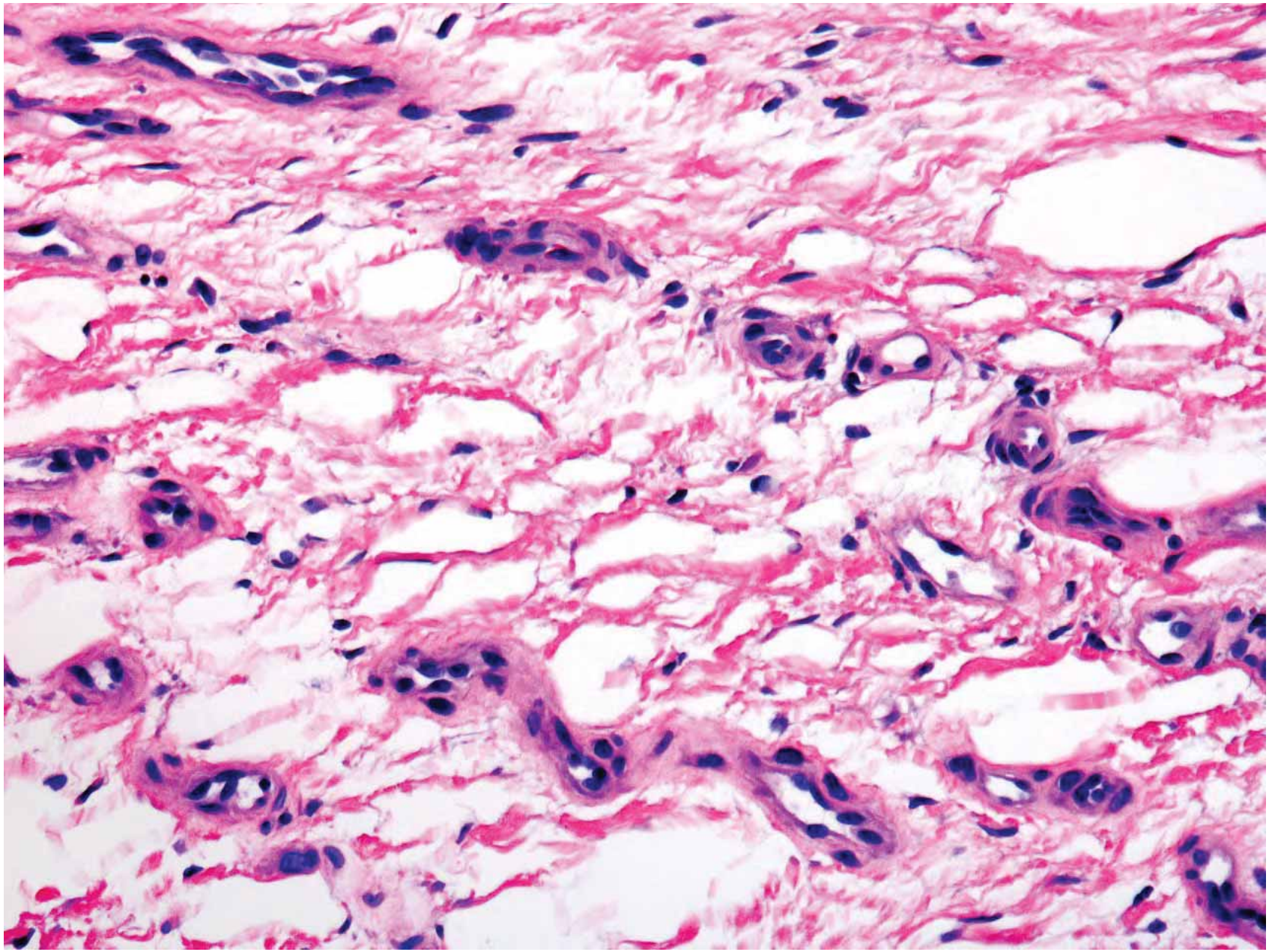


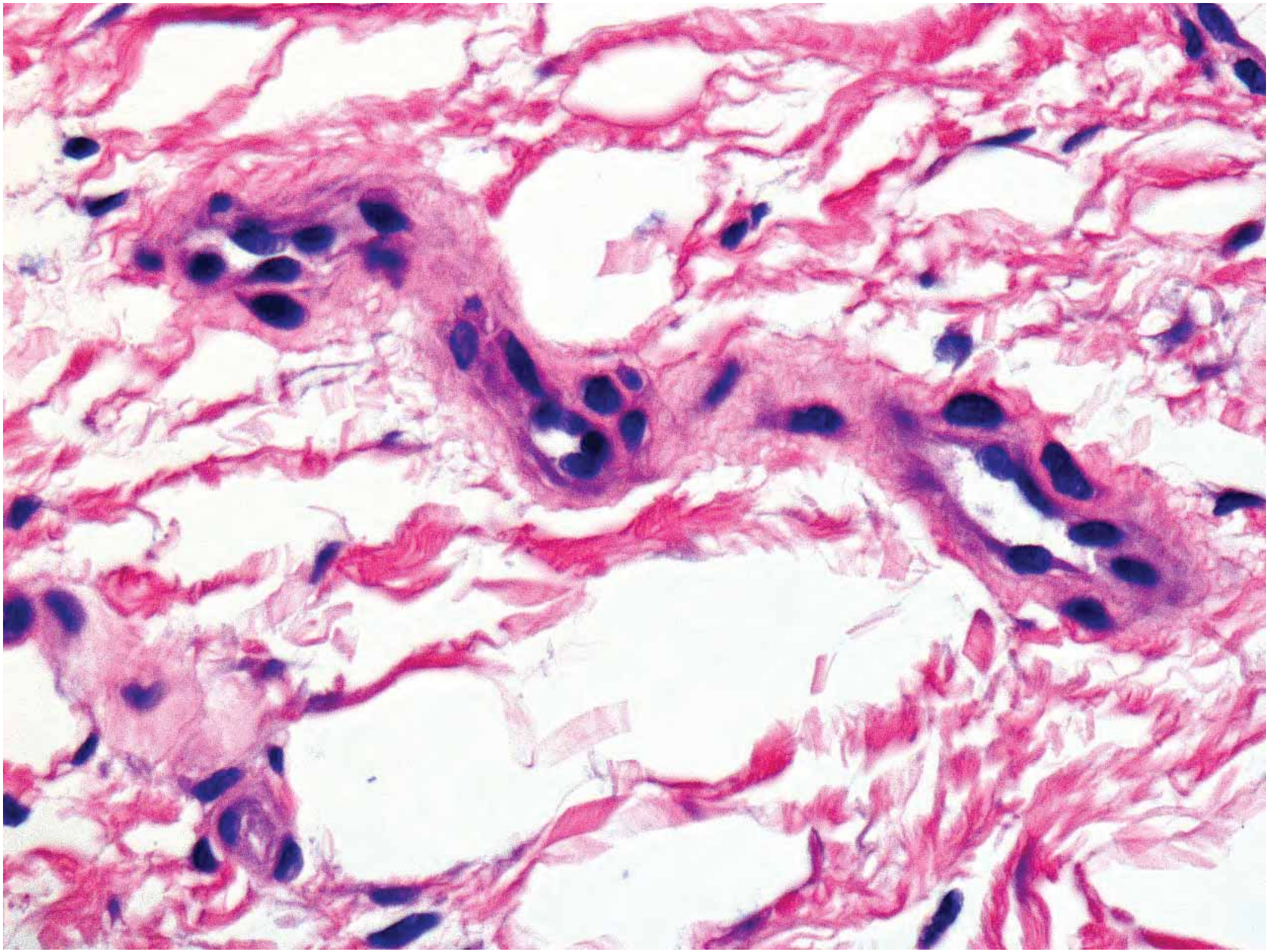


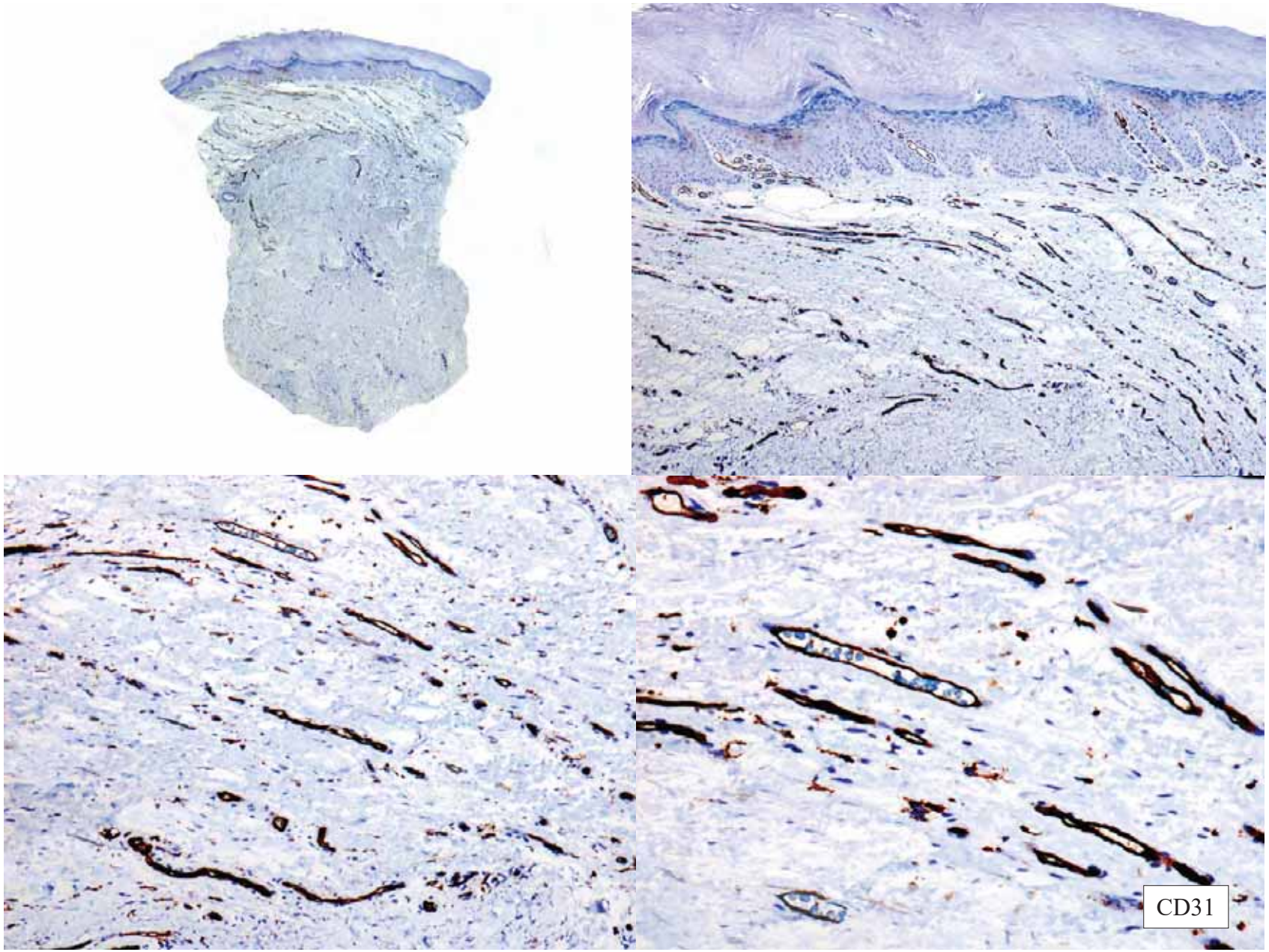








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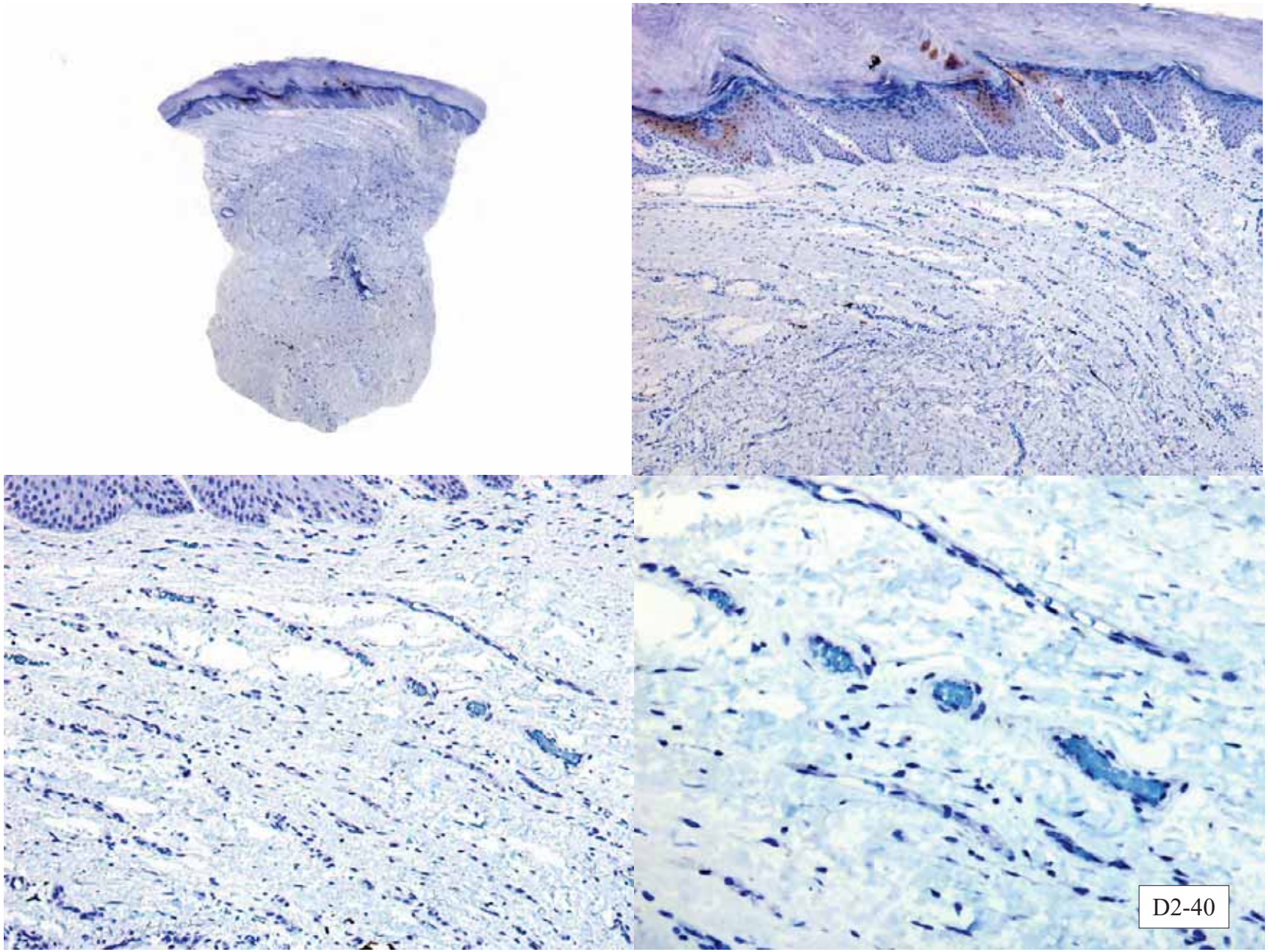
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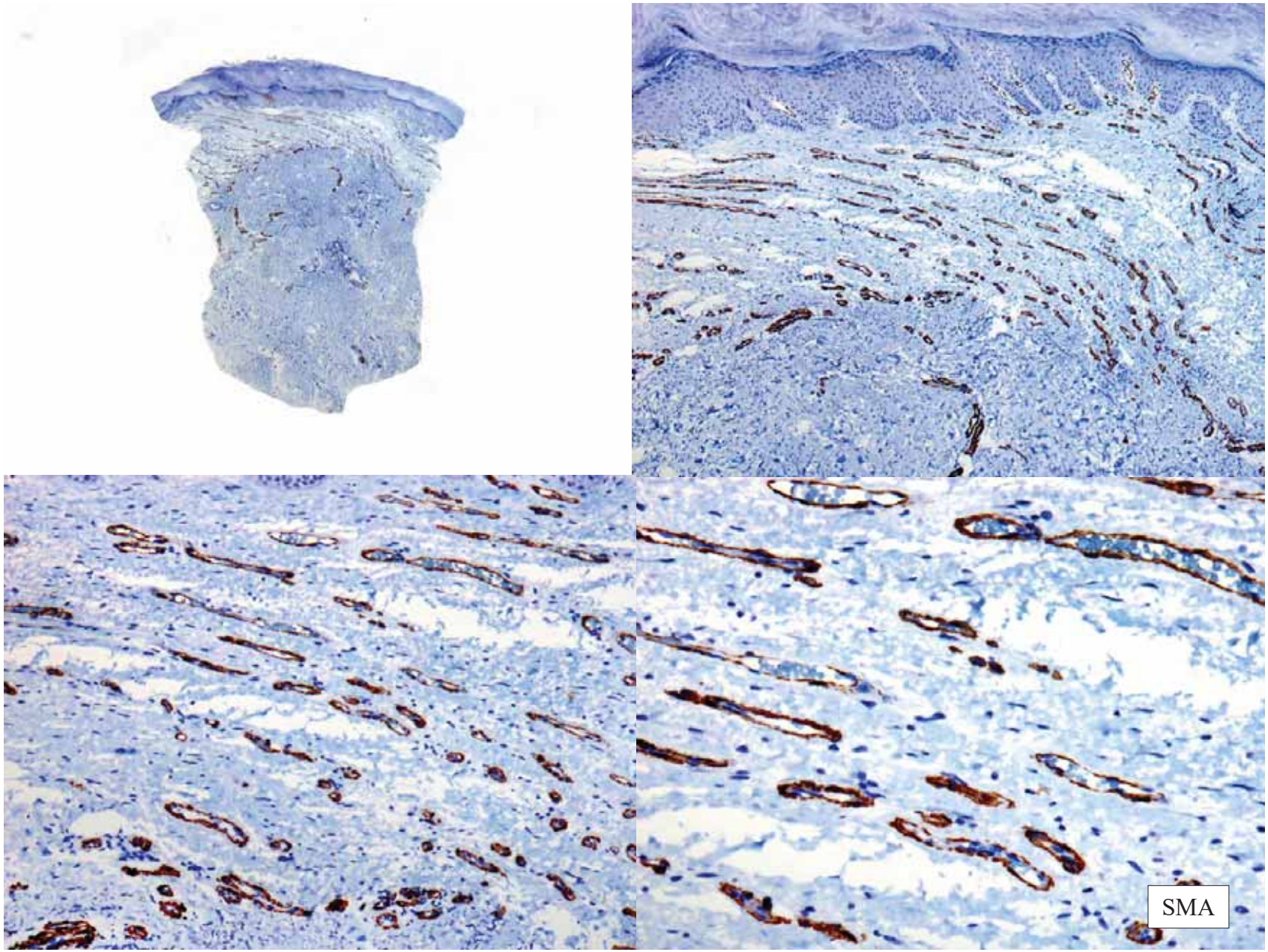
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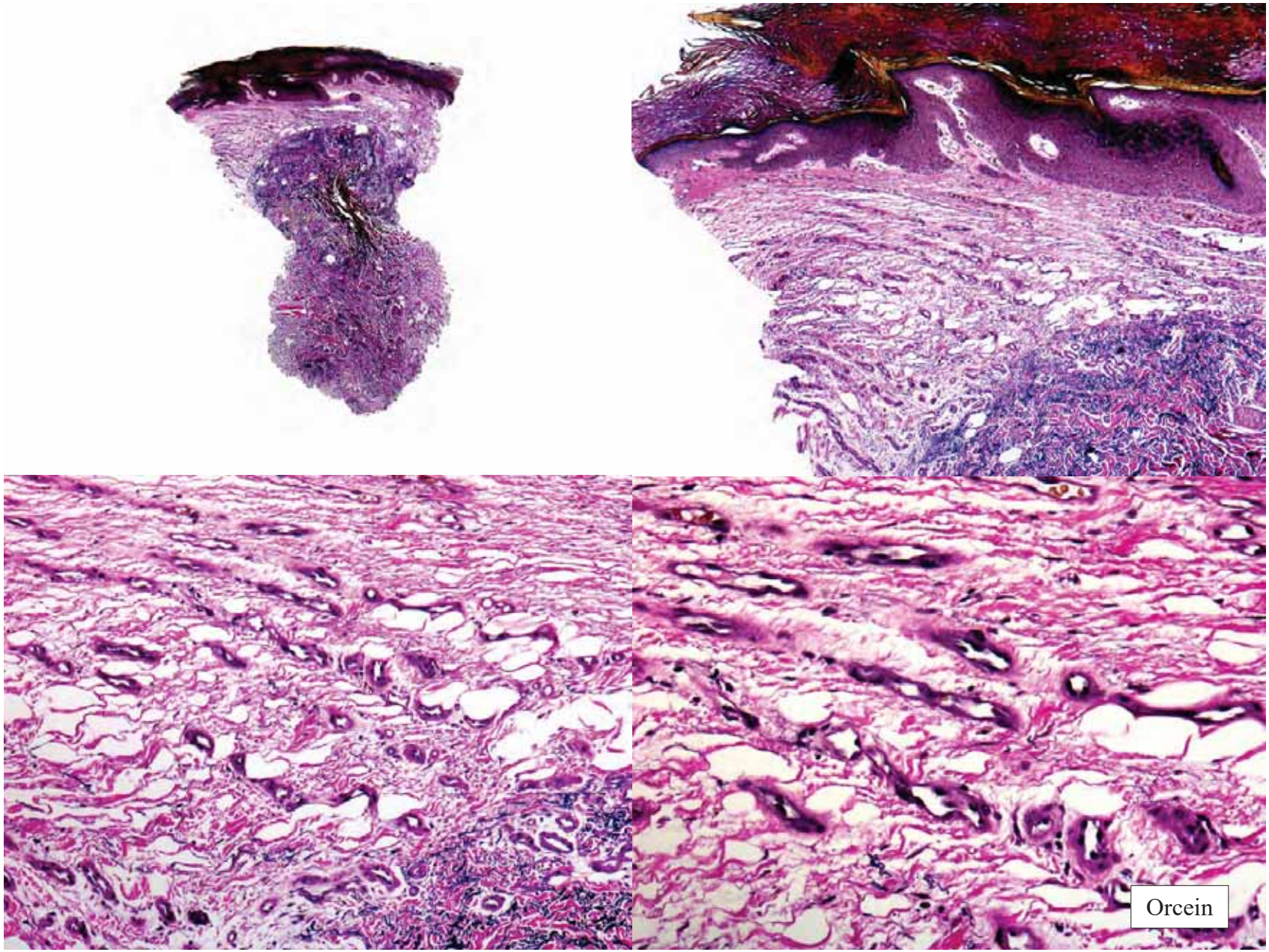
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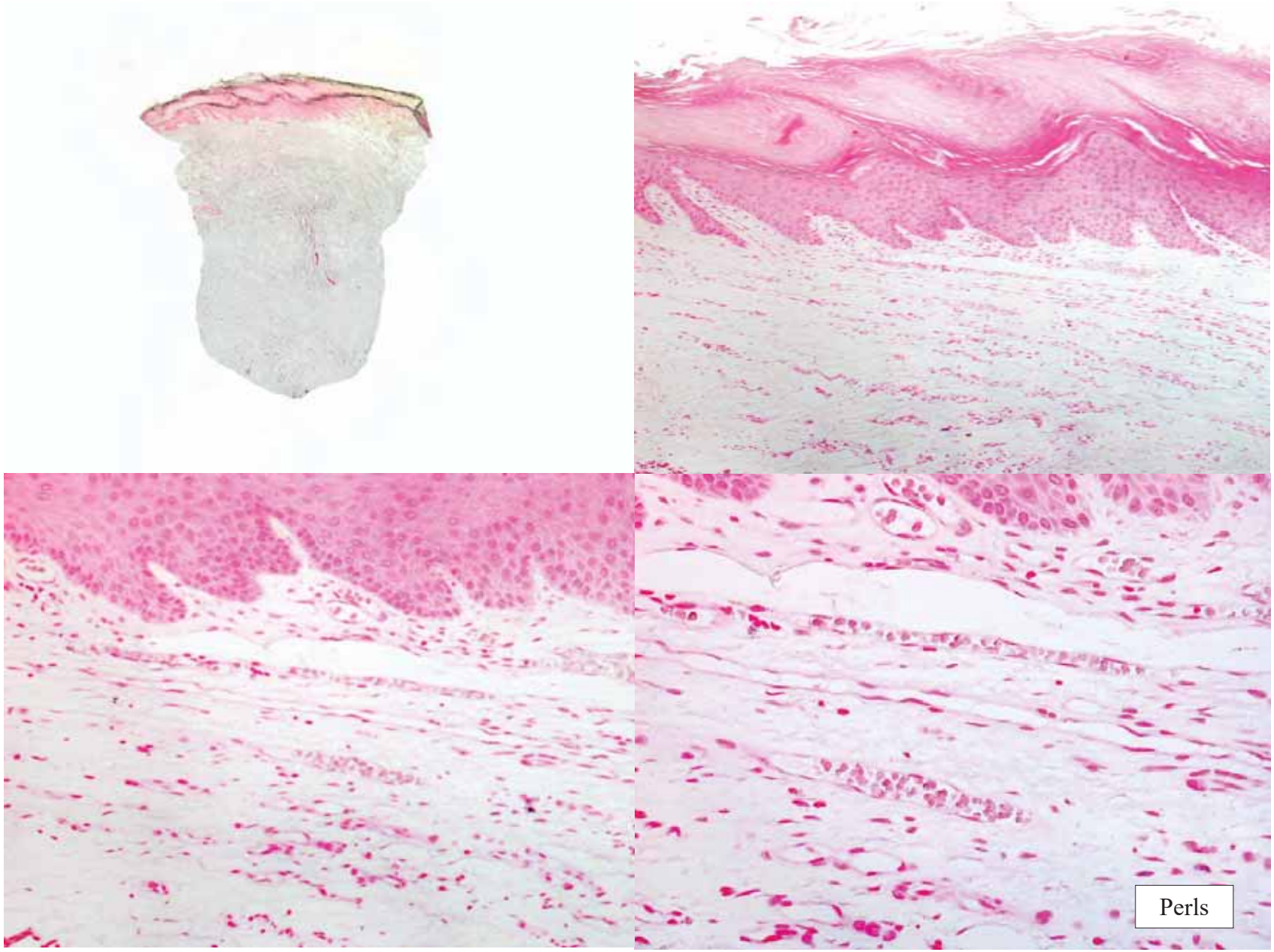
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Case 6. Diagnosis

- Poikilodermatous plaque-like hemangioma

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

Kristina Semkova, MD, MSc, MRCP, SCE (Dermatology), DipRCPath (Dermatopathology),[a] Richard Carr, FRCPath, DipRCPath (DMT),[b] Mark Grainger, MBBS, DipClinDermatol,[c] Ruth Green, MBChB,[d] Abdul Hafejee, MBChB, MRCP (UK),[e] Areti Makrygeorgou, MBBS,[f] Lucy Melly, BSc, MBChB, FRCPath,[g] Luisa Motta, FRCPath, Dip RCPath (Dermatopathology),[d] John Newsham, BSc (Hons), MBChB,[h] Caroline Owen, MBChB, MRCP,[g,i] Joanne Sillars, MBChB,[f] Saleem Taibjee, MBBCh, BMedSci, MRCPCH, DipRCPath (Dermatopathology),[b,j] and Eduardo Calonje, MD, DipRCPath (Dermatopathology)[a]
London, Warwick, Wimborne, Salford, Burnley, Manchester, Blackburn, Dorchester, and Poundbury, 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 histopathologic features in a case series of poikilodermatous plaque-like hemangioma.

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

Results: The lesions were usually solitary erythematous-to-violaceous poikilodermatous plaques on the lower extremities and pelvic girdle, with an indolent clinical course. Mean age of affected patients was 72 (range: 58-80) years, and there was a male predominance. Histology comprised a distinctive band-like proliferation of vascular channels suggestive of postcapillary venules within the superficial dermis with a background of fibrosis, edema, and loss of elastic fibers. Despite the clinical atrophic appearance, acanthosis was a frequent finding.

Limitations: Retrospective 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;81:1257-70.)

Key words: acquired hemangioma; mycosis fungoides; poikilodermatous plaque-like hemangioma; vascular proliferation.

From the Department of Dermatopathology, St. John's Institute of Dermatology, Guys and St Thomas' Foundation Trust, London[a]; Department of Histopathology, South Warwickshire National Health Services (NHS) Foundation Trust, Warwick Hospital, Warwick[b]; About Health Limited, Wimborne[c]; Department of Cellular Pathology, Salford Royal NHS Foundation Trust[d]; Dermatology Department, East Lancashire Hospitals NHS Trust, Burnley[e]; Dermatology West Ambulatory Care Hospital, Glasgow[f]; Department of Histopathology, Queen Elizabeth University Hospital, Glasgow[g]; The Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester[h]; Dermatology Department, Royal Blackburn Teaching Hospital, East Lancashire Hospitals NHS Trust[i]; Dermatology Department, Queen Elizabeth University Hospital, Glasgow[j]; Dorset County Hospital, Dorchester[k]; and Poundbury Cancer Institute.[l]

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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.03.060

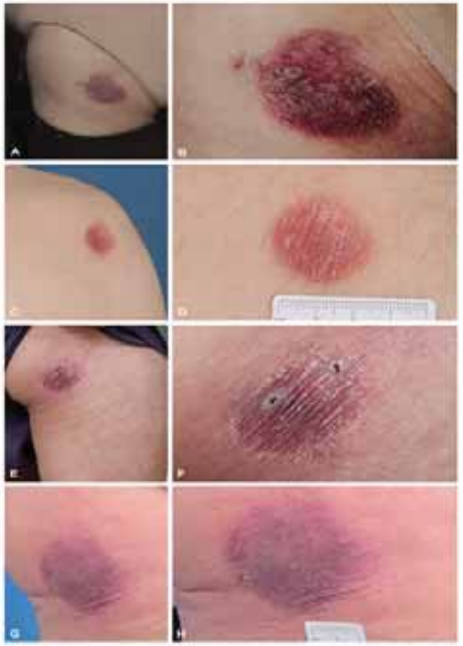
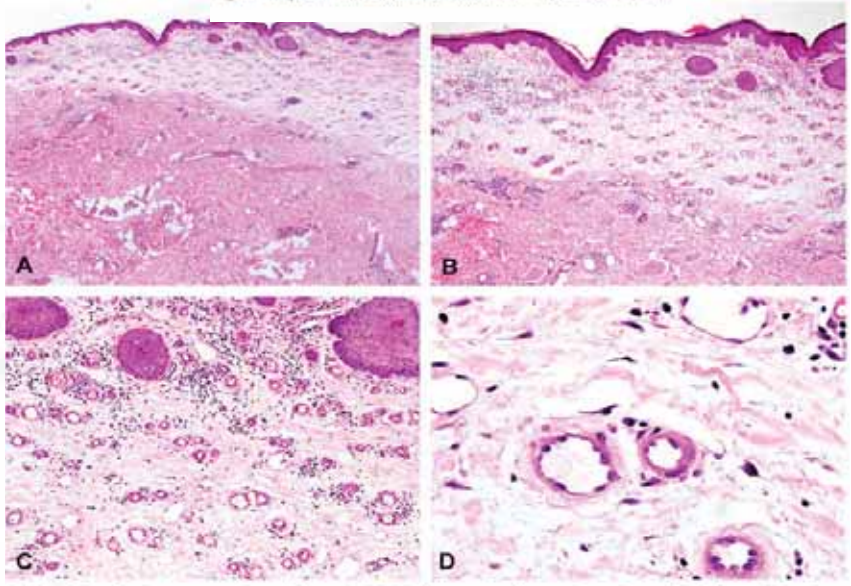


Fig 1. Clinical presentation. A and B, Case 3. C and D, Case 4. E and F, Case 9. G and H, Case 5.



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

Kristina Semkova, MD, MSc, MRCP, SCE (Dermatology), DipRCPath (Dermatopathology),[a]
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DipRCPath (Dermatopathology),[b,j] and Eduardo Calonje, MD, DipRCPath (Dermatopathology)[a]
London, Warwick, Wimborne, Salford, Burnley, Manchester, Blackburn, Dorchester, and Poundbury, England; and Glasgow, Scotland

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

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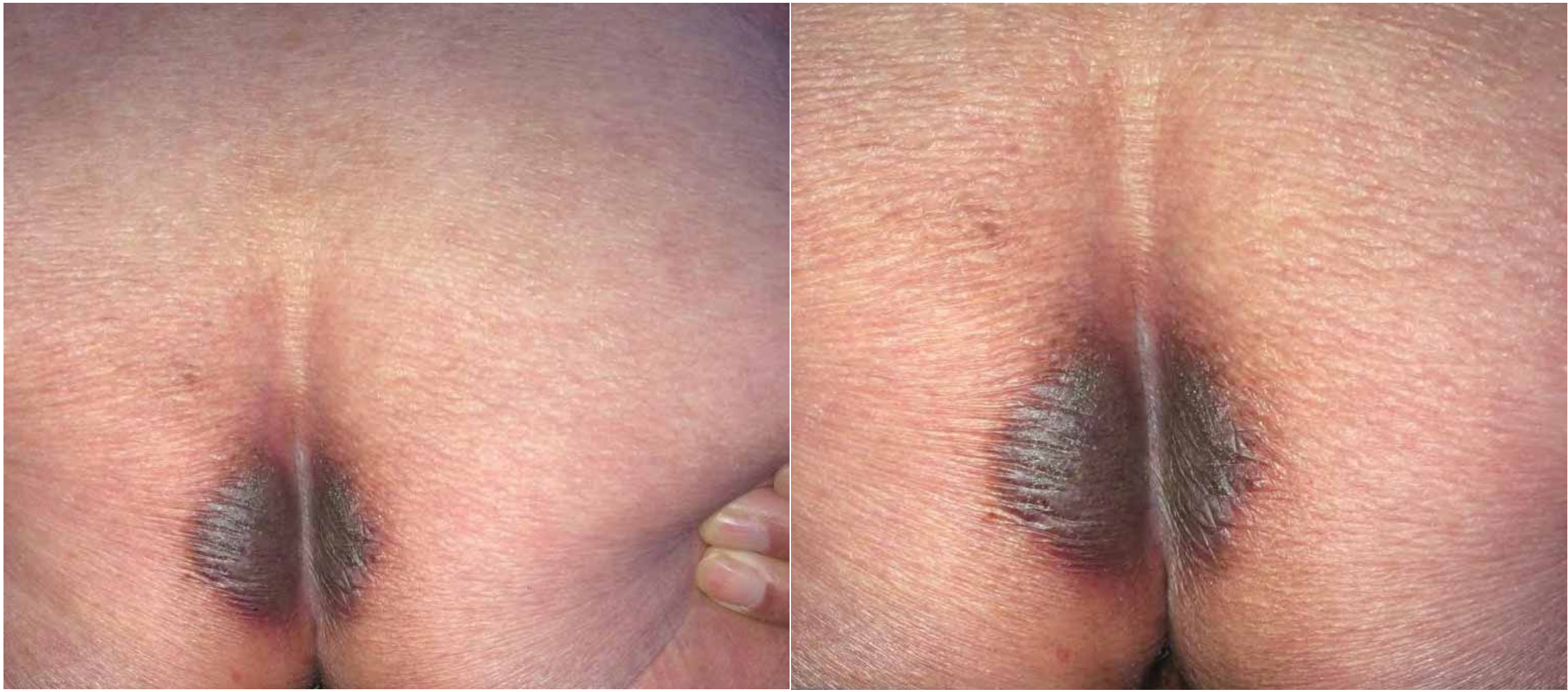
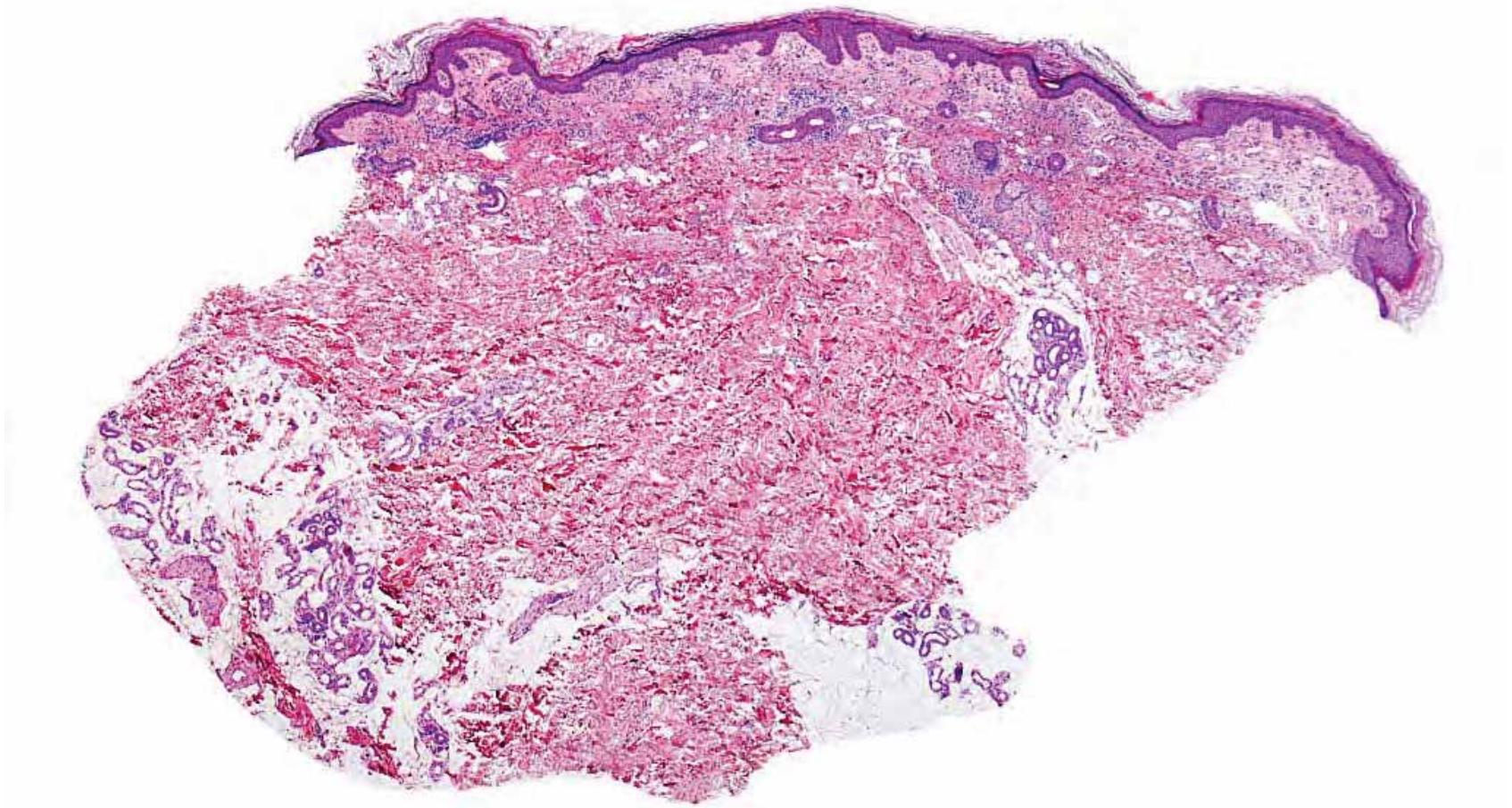
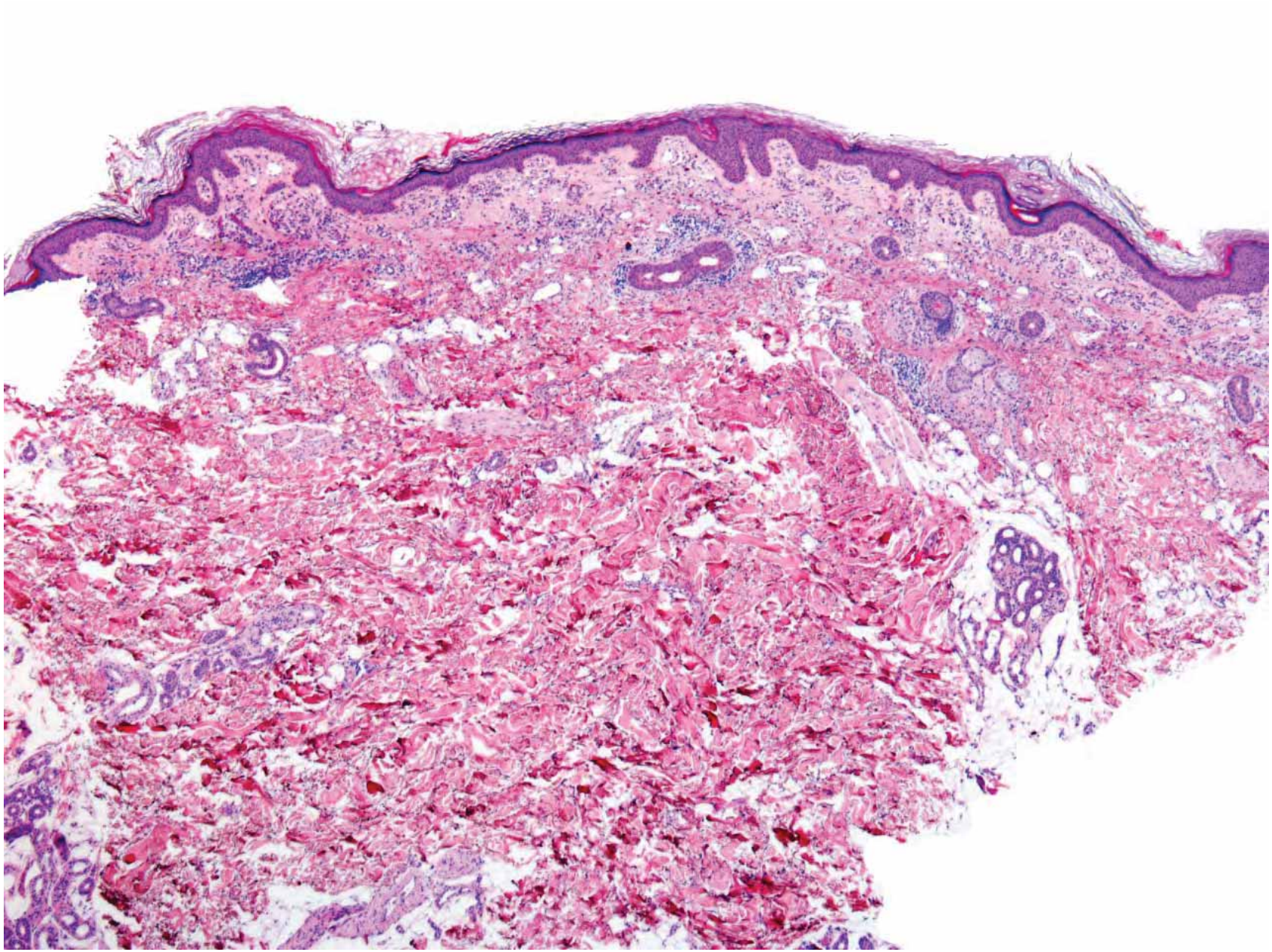
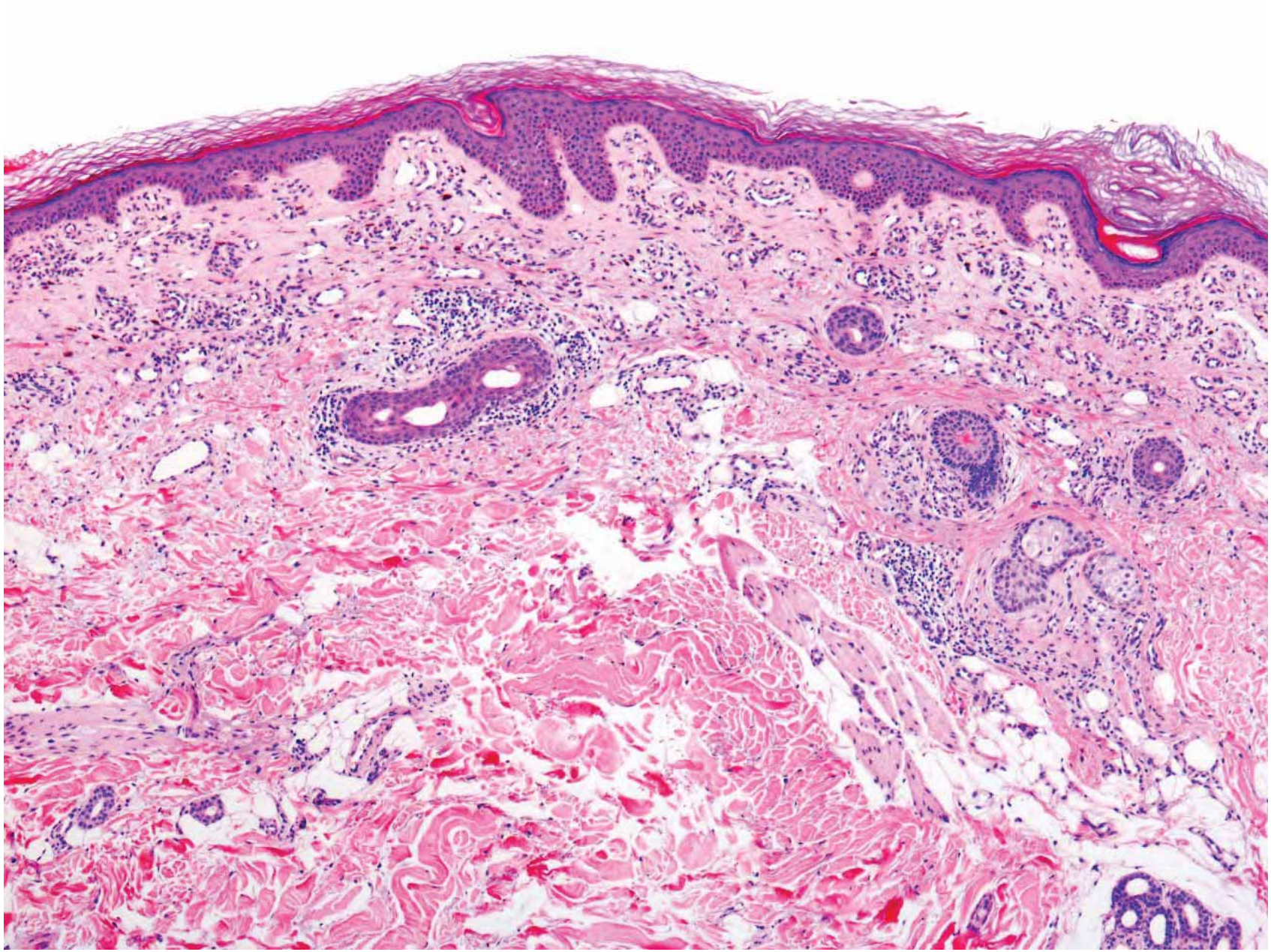
- Conclusion: Poikilodermatous plaque-like hemangioma is a distinctive and previously undescribed vascular proliferation defined by a constellation of consistent and reproducible clinical and histologic features.

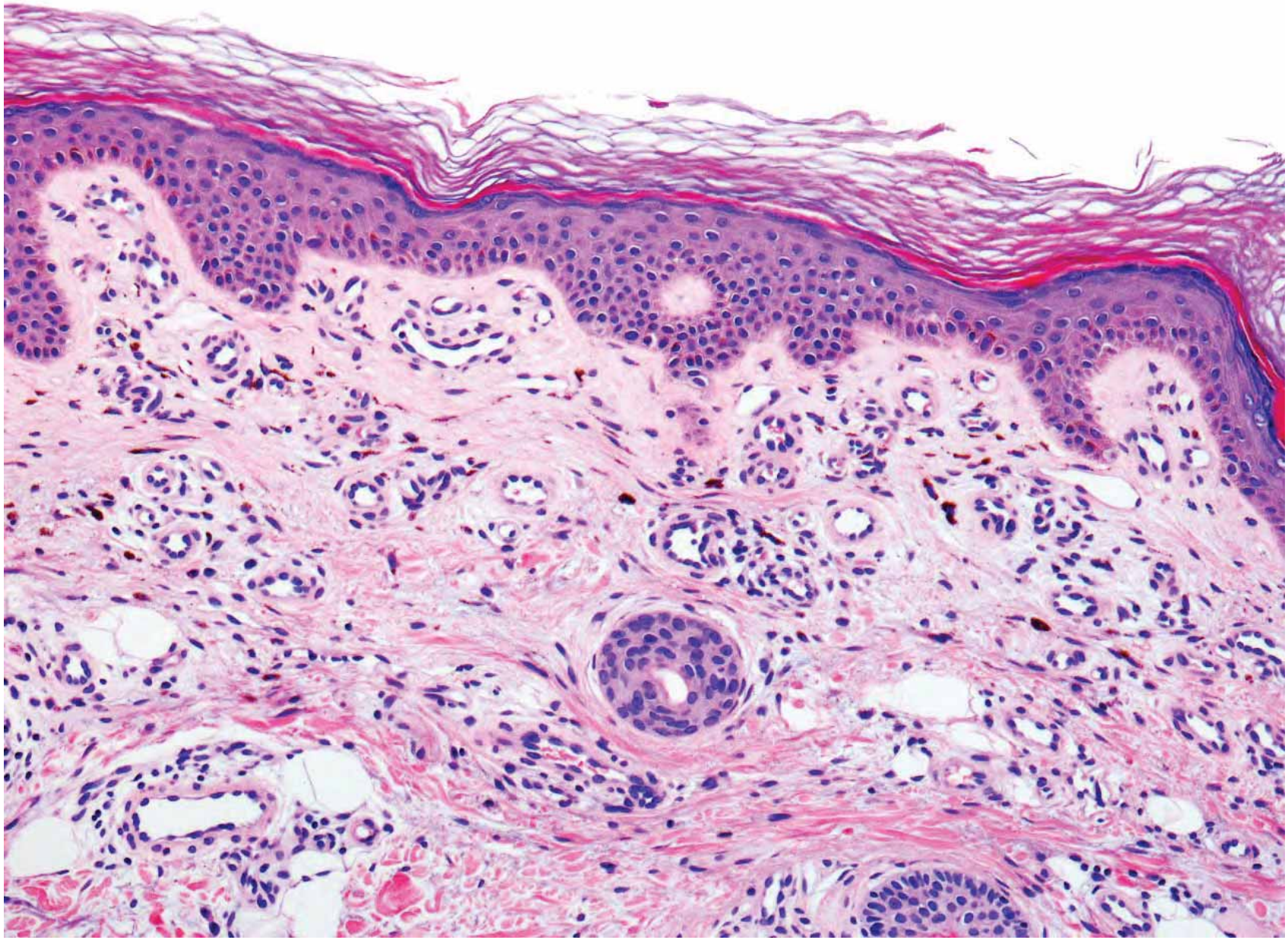
Case 7 (Vars 2020). A 79-year-old male presented with a pruriginous hyperpigmented plaque in the intergluteal fold.

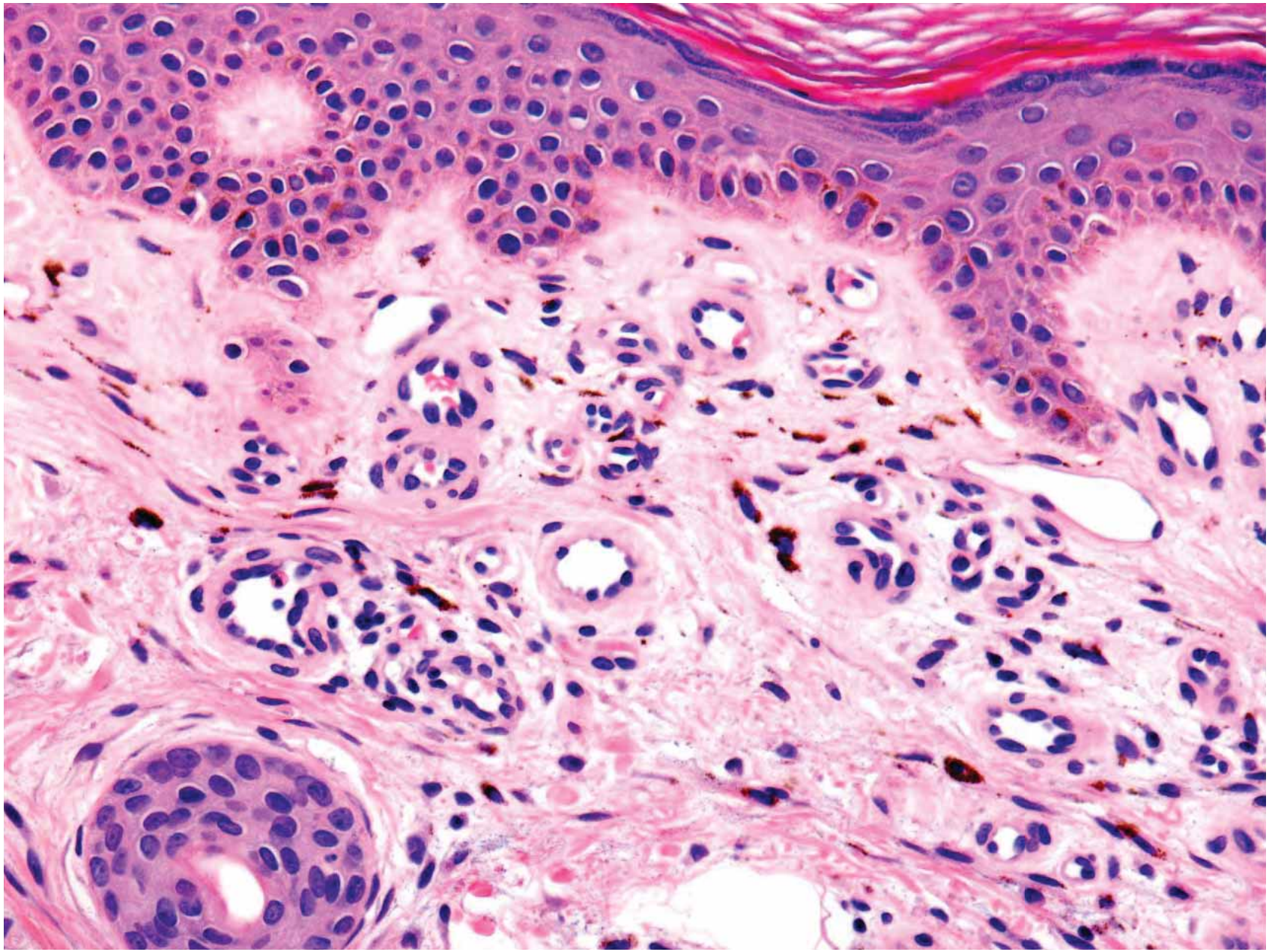


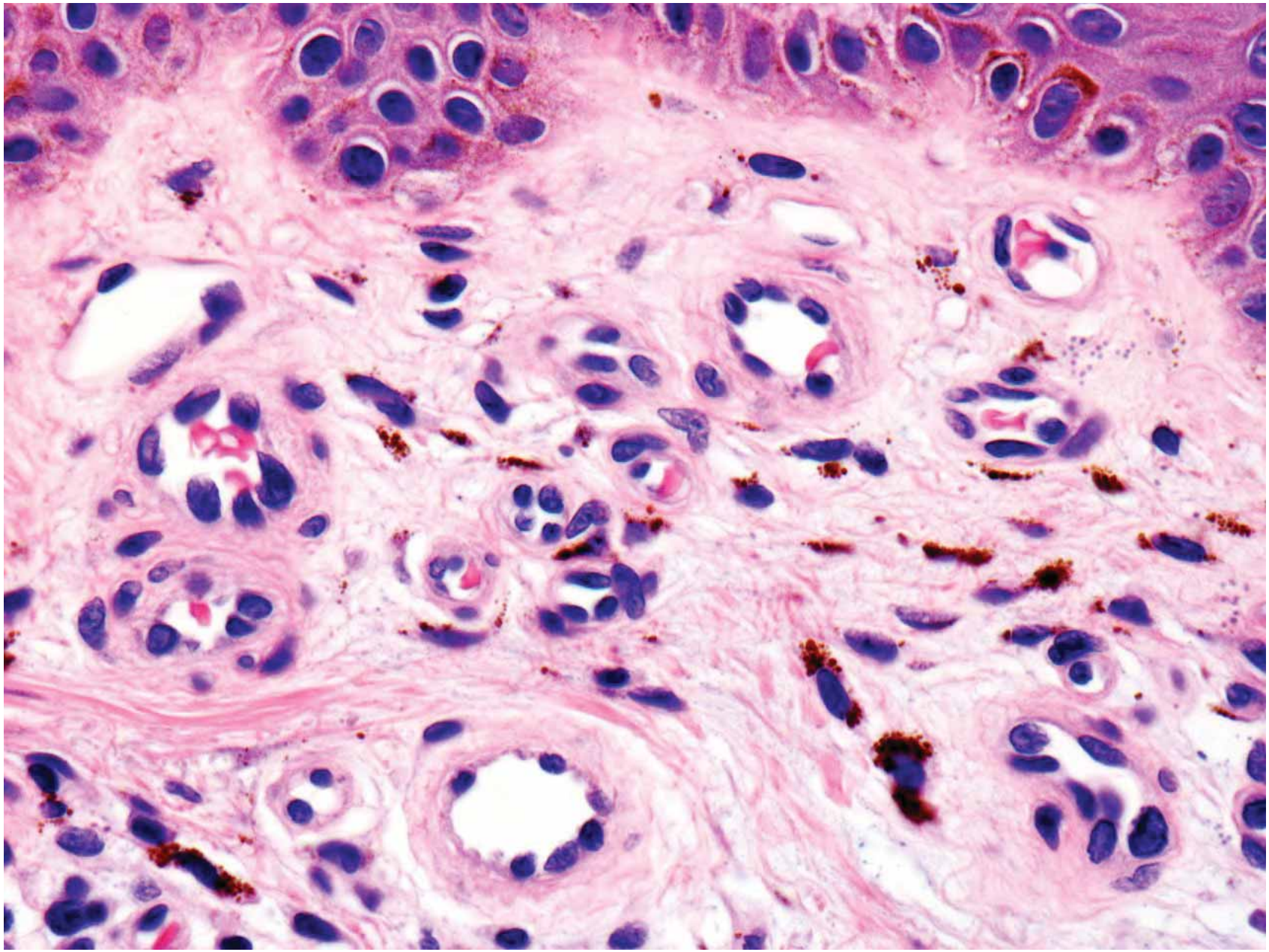


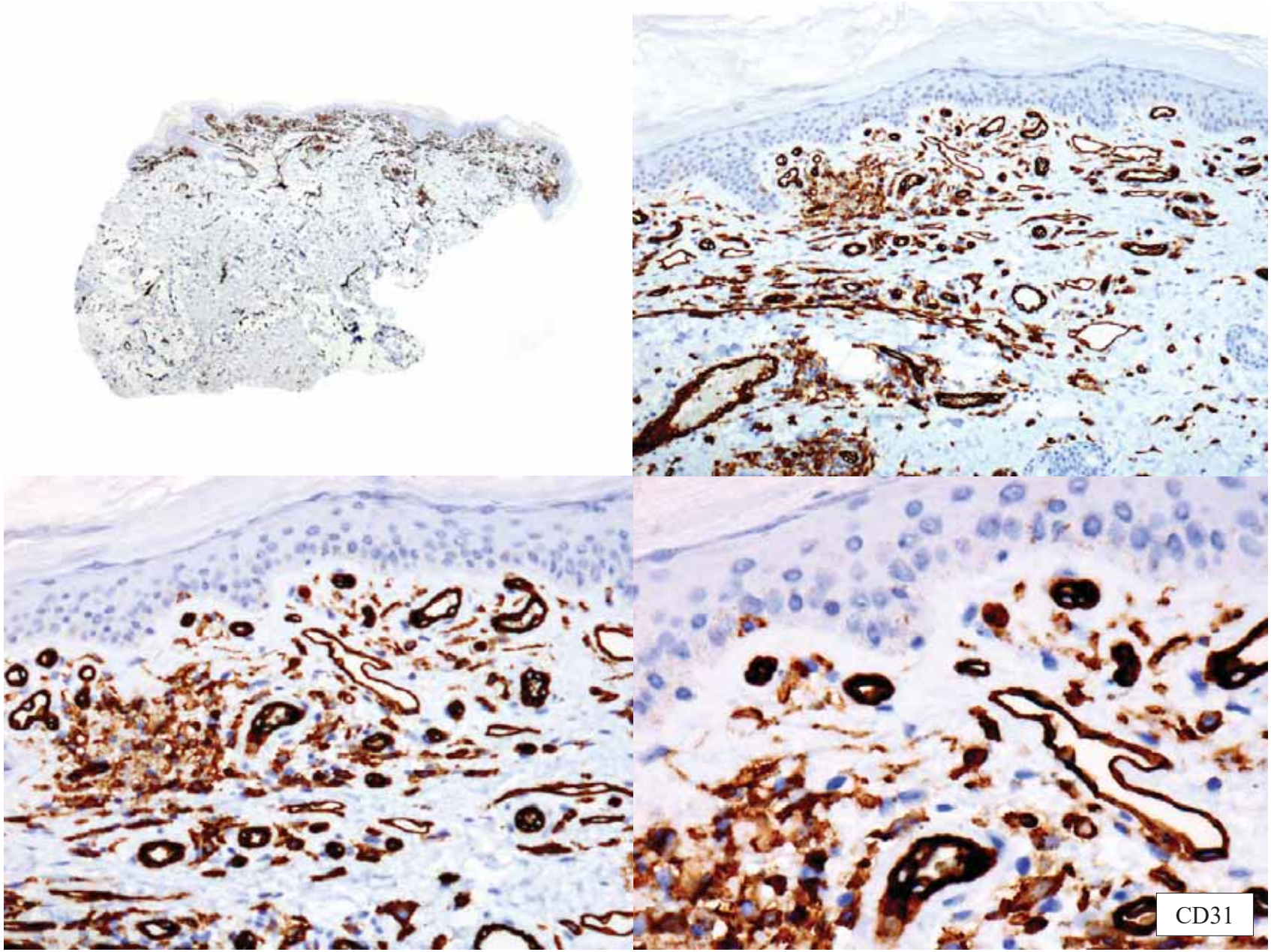








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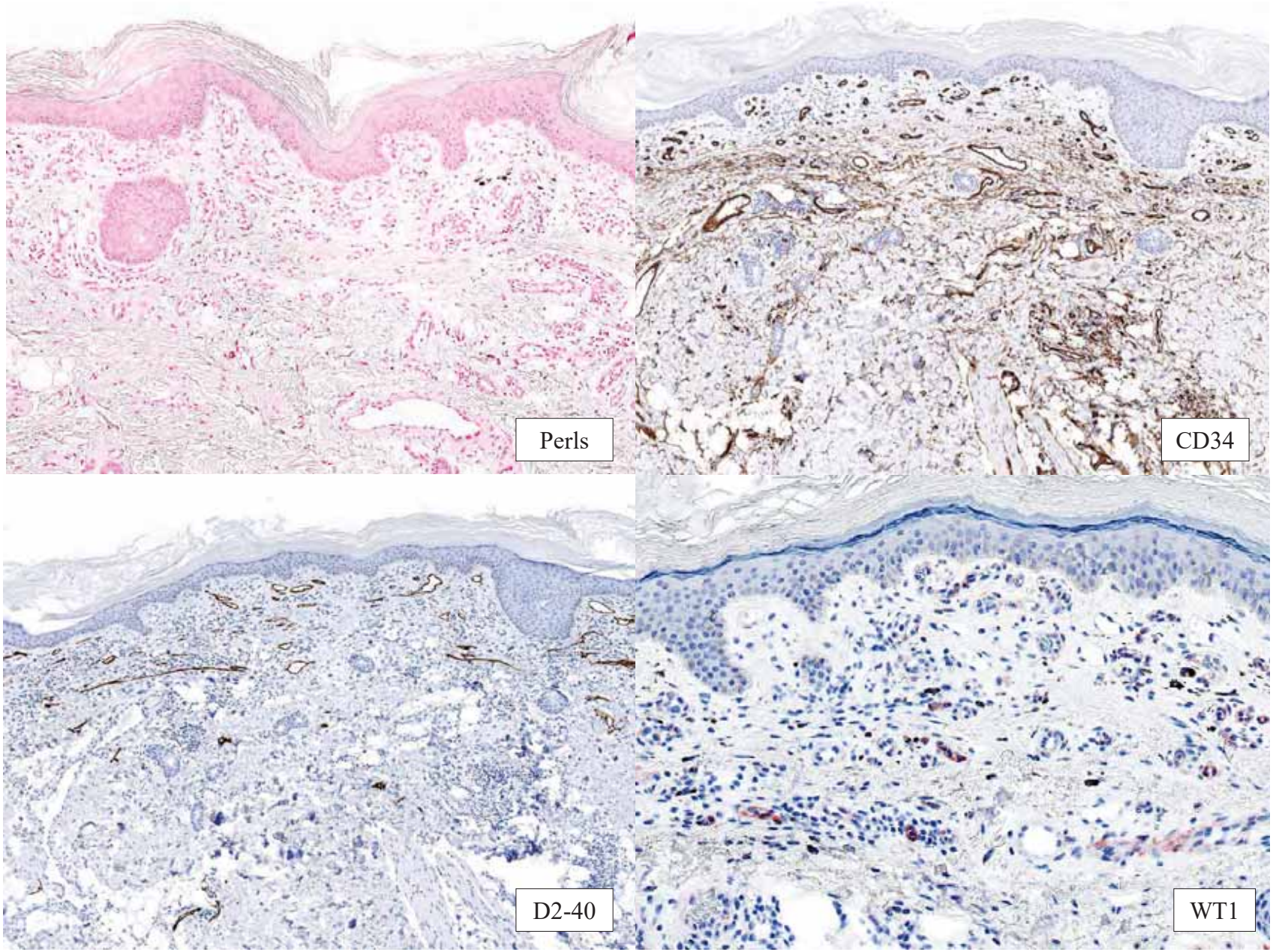
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Case 7 (Vars 2020). Diagnosis

- Senile gluteal dermatosis (prurigiform angiomatosis)

International Journal of Dermatology

Report

Senile gluteal dermatosis: a clinical study of 137 cases

Han-Nan Liu[1,2], MD, Wen-Jen Wang[1,2], MD, Chih-Chiang Chen[1,2], MD, Ding-Dar Lee[1,2], MD, and Yun-Ting Chang[1,2], MD, PhD

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Conflicts of interest: none declared.

Abstract

Background Senile gluteal dermatosis (SGD) is a common genital dermatosis but has gained little attention before. A large-scale clinical study of this disease is lacking.

Materials and methods We examined 162 consecutive outpatients with gluteal skin diseases of different causes. Fourteen skin biopsies were performed. Patient's age, gender, body mass index (BMI), way of sitting or lying, treatment response, and underlying systemic diseases were recorded.

Results About 137 (85%) patients could be defined as SGD. These patients, with a mean age of 79.4 ± 10.7 years and a mean BMI of 21.7 ± 10.8, presented with either partial (n = 43, 31%) or full-blown (n = 94, 69%) SGD lesions characterized by the sign of so-called "three corners of a triangle": brownish plaques on the gluteal cleft and each side of the buttocks. Male/female ratio was 130/7. Itching or pain of varying intensity was reported by 50 patients (36%) and 14 patients (10%), respectively. Eighty-six patients (63%) presented with horizontal hyperkeratotic ridges, a characteristic sign of SGD. Most patients spent most of the day sitting but reported no special way of sitting or lying. More than half of patients with SGD claimed no response to topical steroids and/or keratolytics. In comparison with patients with SGD, SGD-free patients were younger (61.3 ± 36 years, P = 0.0005) and heavier (BMI 26.2 ± 15.6, P < 0.0001) but showed no significant difference in the frequency of underlying systemic diseases.

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

Introduction

Senile gluteal dermatosis (SGD) was first reported in Japan in 1979 as hyperkeratotic lichenified skin lesions of the gluteal cleft and seemed to be a common genital dermatosis, but there 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 gluteal cleft, as we pointed out recently in a study involving 12 patients with SGD, scaly brownish plaques may also occur on each side of the buttocks and display a pattern of so-called three corners of a triangle." 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 gluteal area. We then opted to examine 162 consecutive outpatients who came to our OPD for their skin lesions on the gluteal area. SGD was defined as brownish scaly plaques on the gluteal cleft and each side of the buttocks forming complete or partial "three corners of a triangle". Patients with tinea, candidiasis, or cutaneous amyloidosis were excluded from the study. Patient's age, gender, body weight, the way they sit or lie on a chair or bed, and the response to the treatments were recorded. Fourteen skin biopsies were performed. Special attension was given to the types of chair or bed used by patients daily.

Underlying systemic diseases

Retrospective or concurrent patient chart review was performed to see if there was any significant association between SGD and underlying systemic illness. Relevant systemic diseases were arbitrarily defined as those that might have made patients more prone to long periods of sitting or lying, such as neurogenic disorders, malignant neoplasms, heart failure, chronic joint problems (spine or knee joints), and nutrition deficiencies. These diseases were included for analysis only if they had been present for at least five years before SGD was identified with multiple hospitalizations or with occasional hospitalization but frequent outpatient visits for the same problem.

- 137 patients with SGD, with a mean age of 79.4 years. Male/female ratio was 130/7.
- 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.
- SGD is a common dermatosis, mostly affecting the thinner elderly. Friction, pressures and long hours sitting seemed to be importan factors to trigger this dermatosis

ORIGINAL STUDY

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

Ana Ortins-Pina, MD, Luís Soares-de-Almeida, MD, PhD,*†‡ Ulrich Caroli, MD,§ Laura Held, MD,¶ Wolfgang Kempter, MD,¶ Arno Rütten, MD,¶ Thomas Mentzel, MD, PhD,¶ and Heinz Kutzner, MD, PhD†¶*

Background: Cutaneous benign angioproliferations can be diagnostically challenging and may mimic vascular tumors. Keratinocytes 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 normal 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 subepidermal lymphocytic infiltrate was present. Immunostaining with VEGF was positive in the upper 4/5 of the epidermis overlying the angioproliferation, in contrast with nonlesional 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 epidermal VEGF expression.

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

(*Am J Dermatopathol* 2020;42:29–34)

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 cells[2] 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 elastotic 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 contributing clinicians.

Study cases were selected upon the following criteria: clinical findings of asymptomatic flat prurigiform 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 nonlesional 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 nodule.

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

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The authors declare no conflicts of interest.

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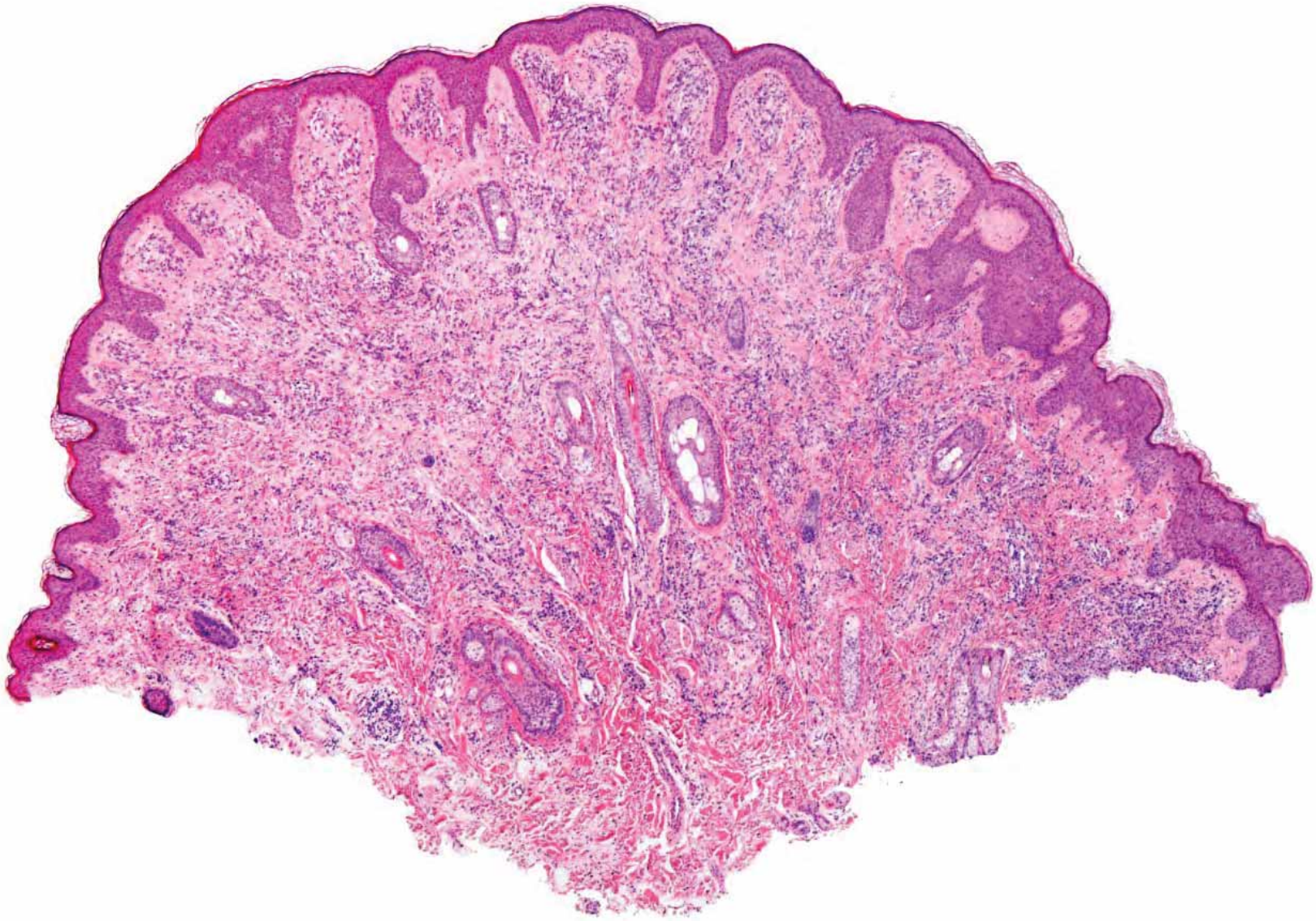
- 38 patients, median age 76 years, mostly men, presented with asymptomatic patches or plaques, most commonly located on the buttocks
- Microscopically, a prominent proliferation of dilated capillaries and postcapillary venules, underneath epidermal changes resembling lichen simplex chronicus
- Immunostaining with VEGF was positive in the upper 4/5 of the epidermis overlying the angioproliferation. Receptor VEGFR- 2 was expressed in the endothelia of neovessels.
- 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 epidermal VEGF expression.

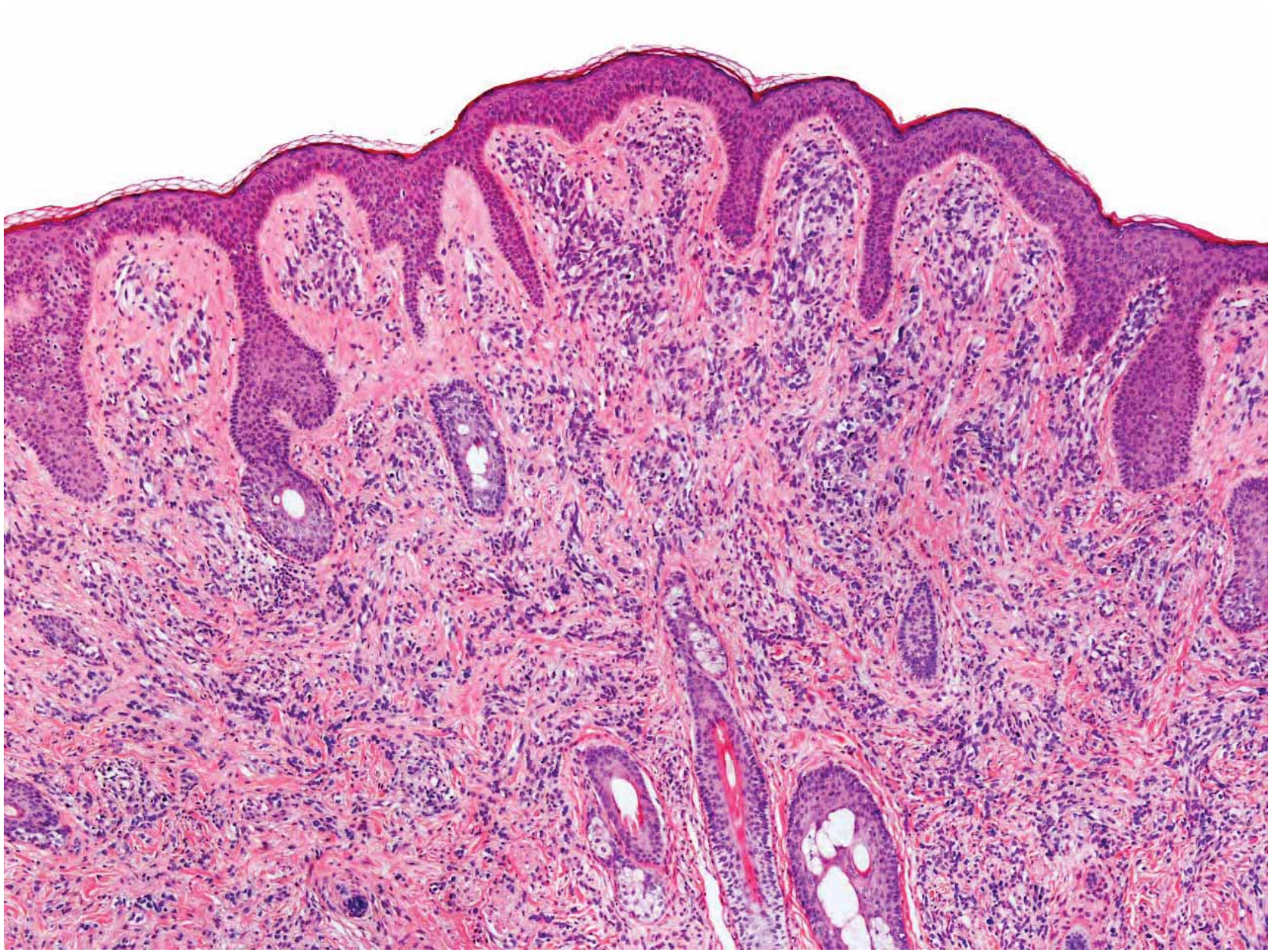
Personal opinion

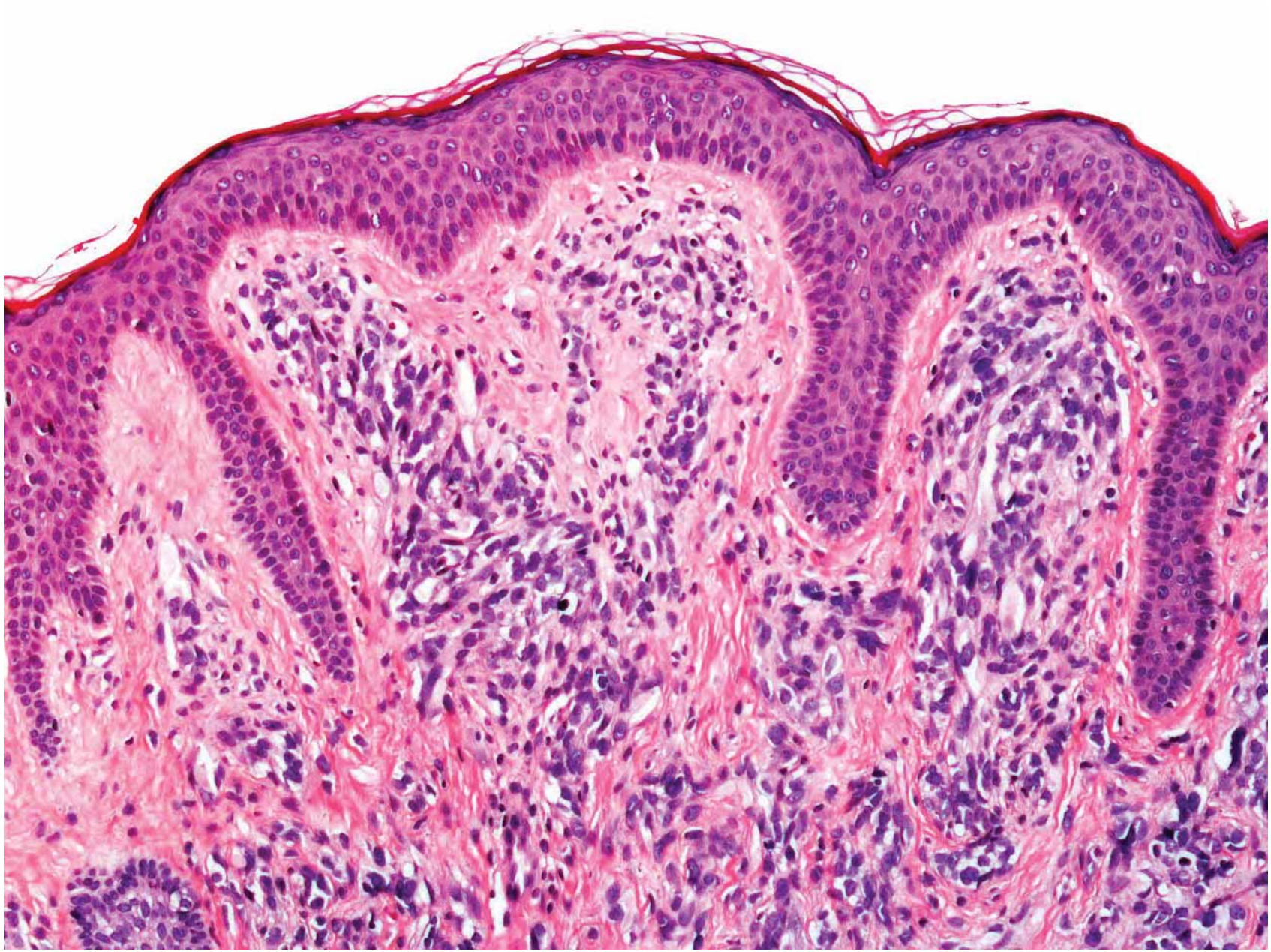
- Senile gluteal dermatosis, prurigiform angiomatosis and poikilodermatous plaque-like hemangioma are the same entity
- Probably this lesion is not a hemangioma, but a reactive process secondary to friction, pressure and long hours sitting in elderly patients

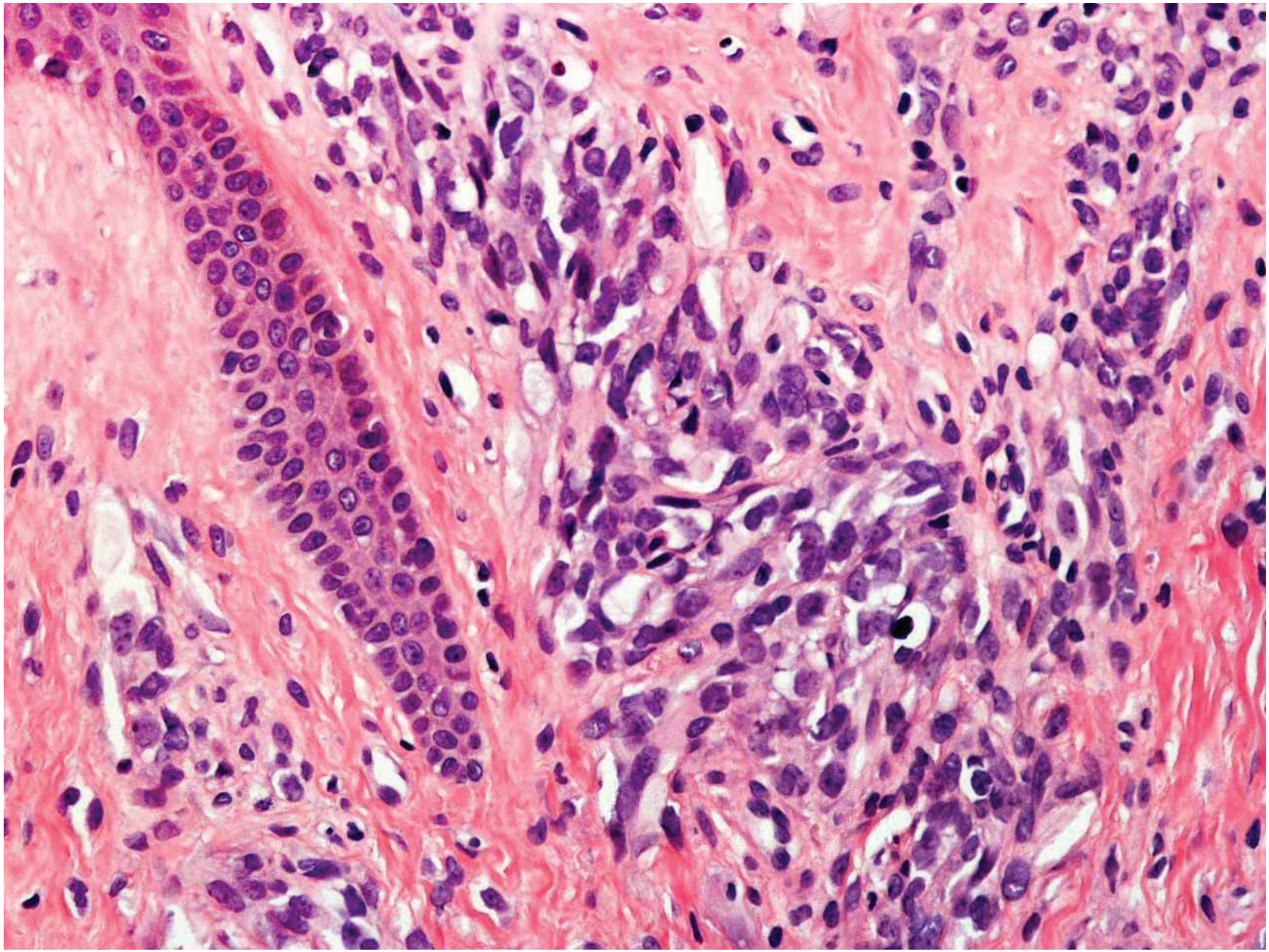
Case 7

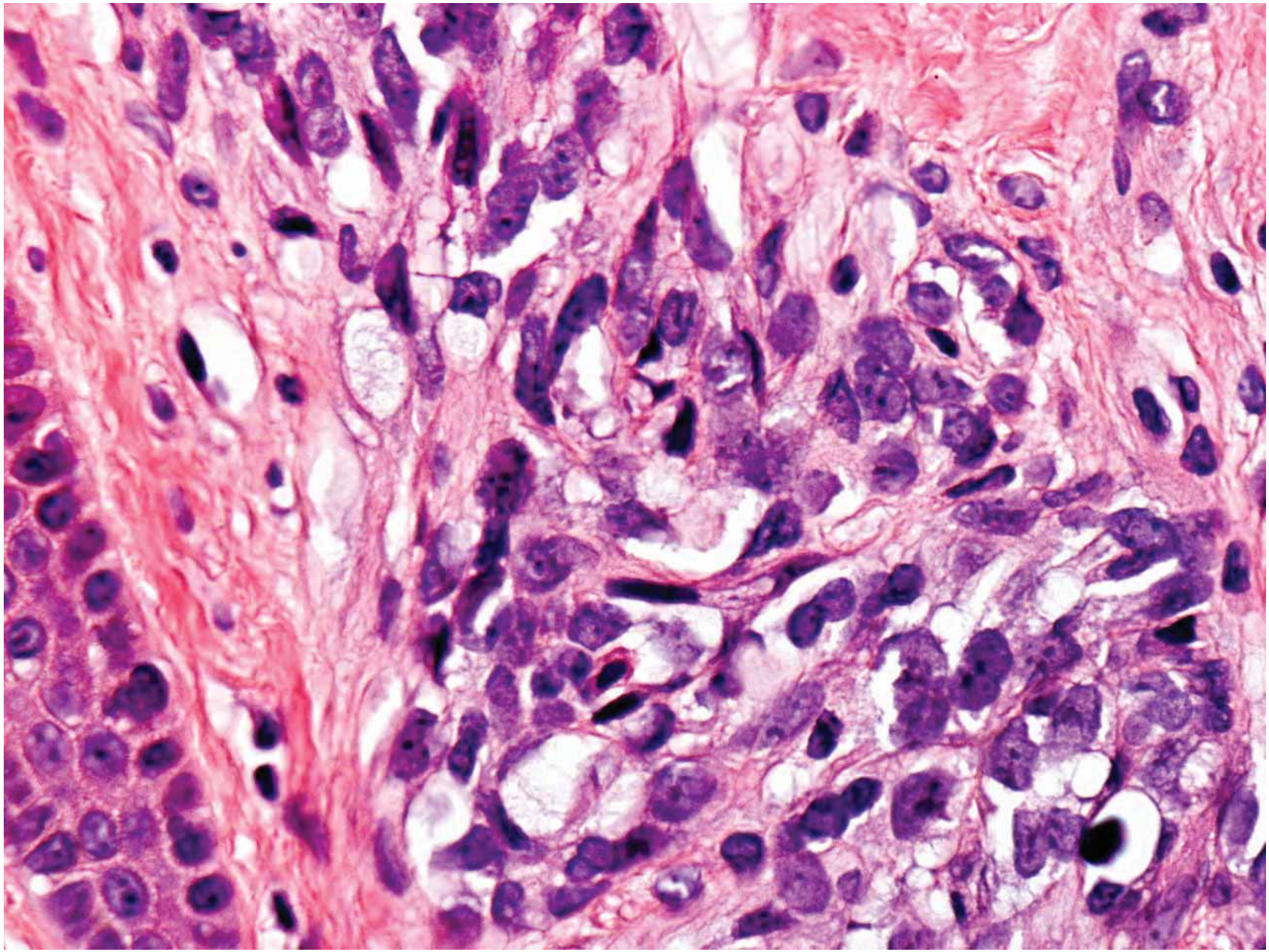
- A 3-year-old girl presented with a papular lesion on the right cheek that have been present for 6 months. Clinical diagnosis was wart *vs.* juvenile xanthogranuloma

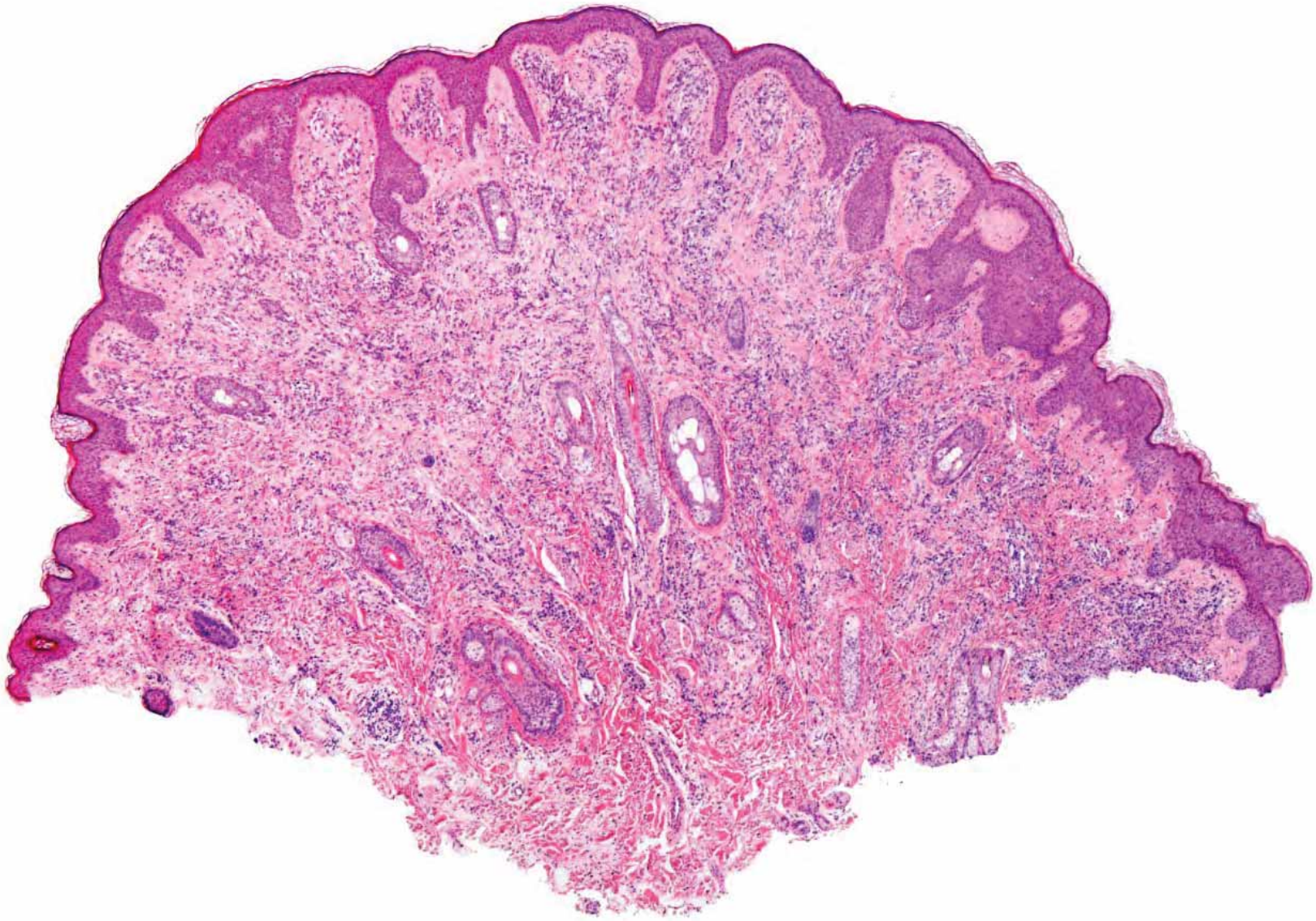


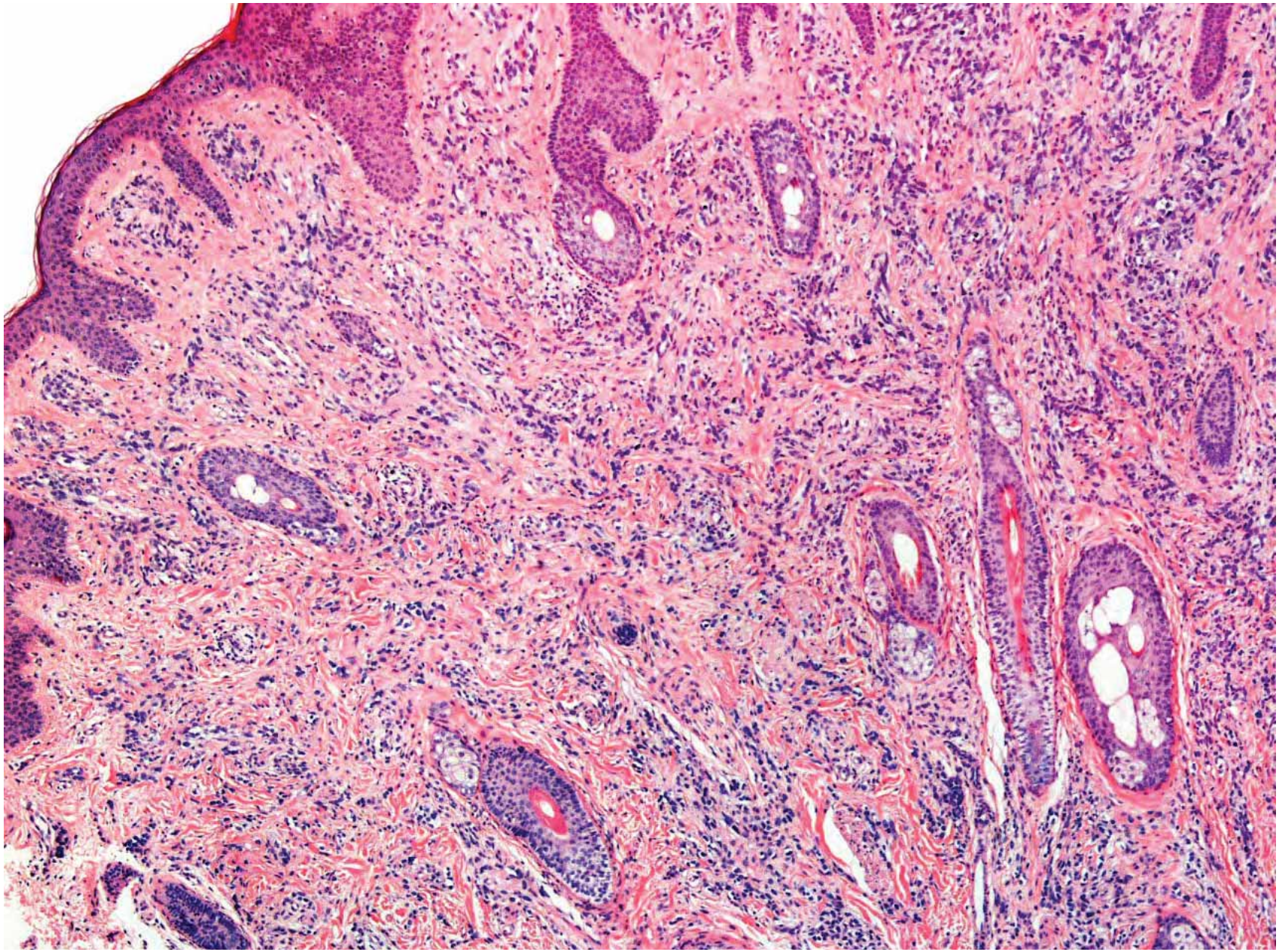


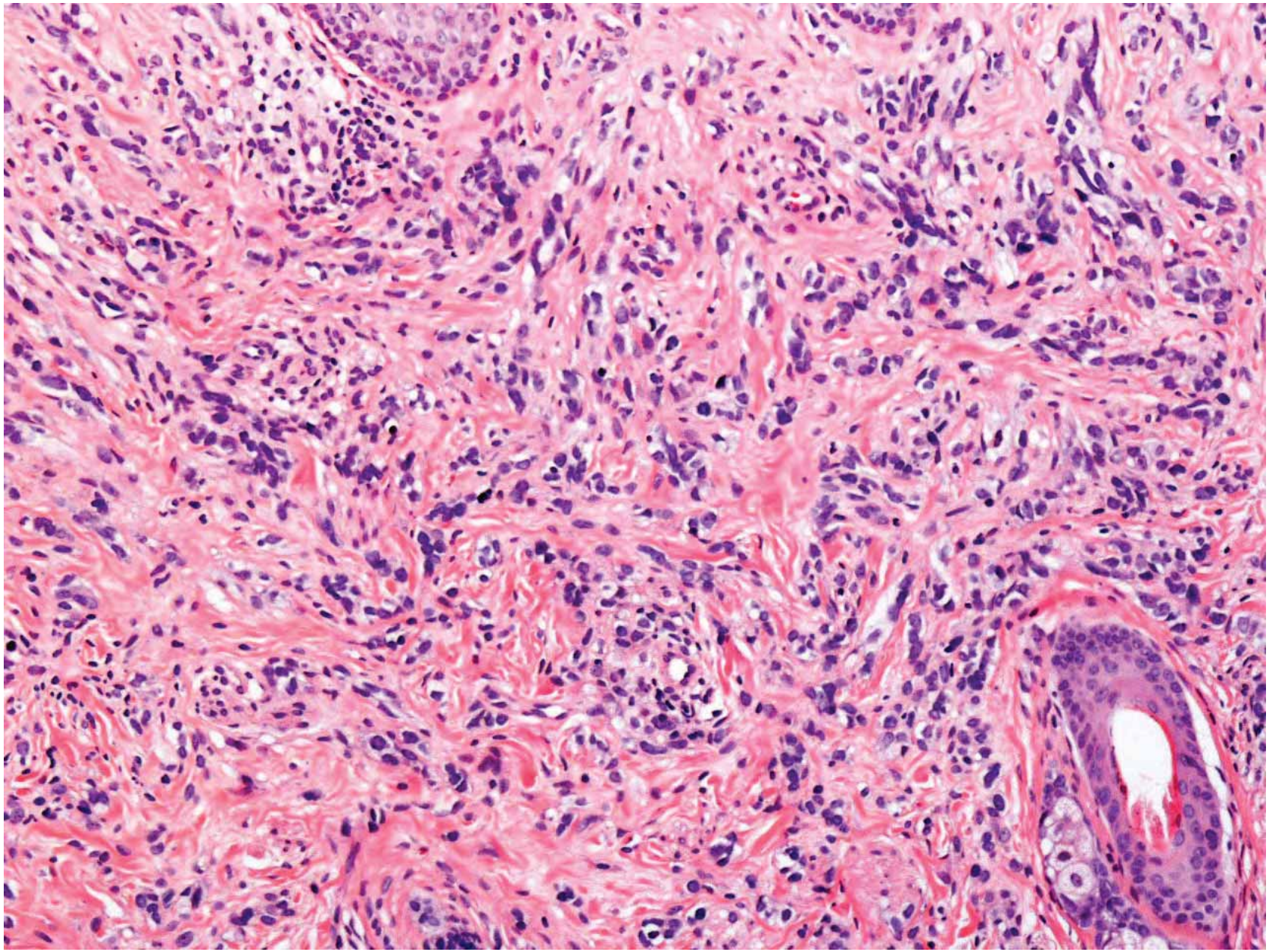


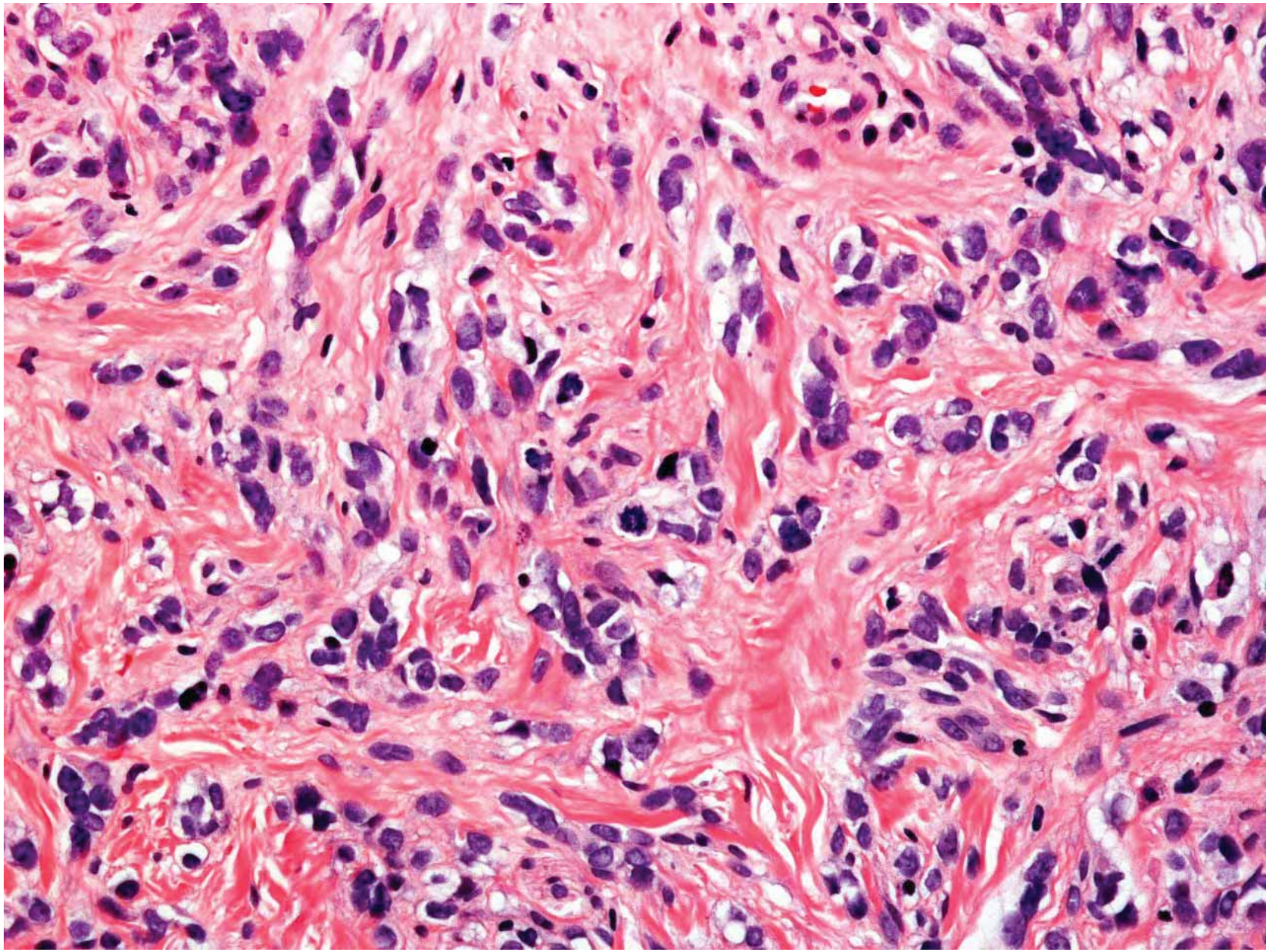


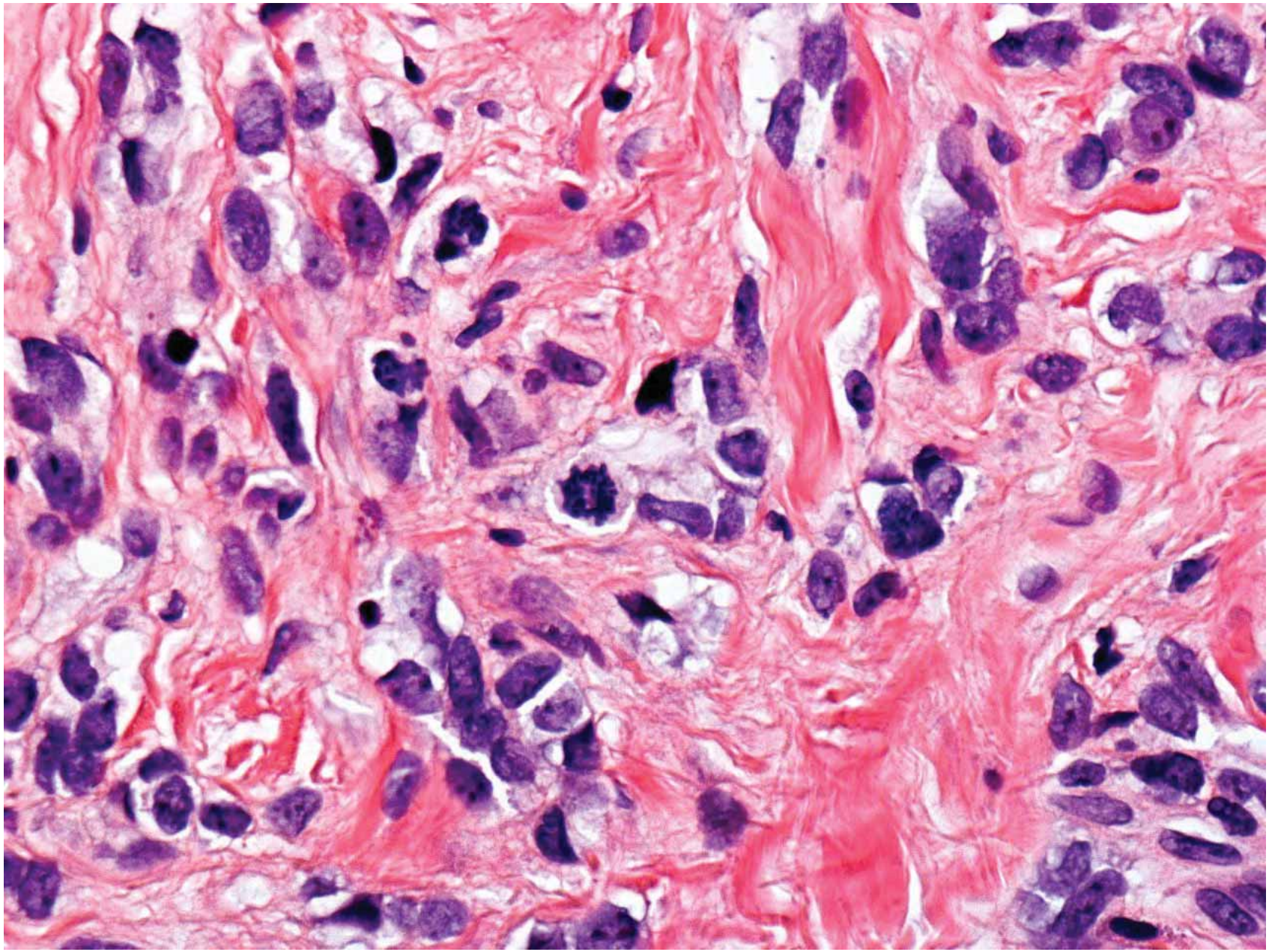


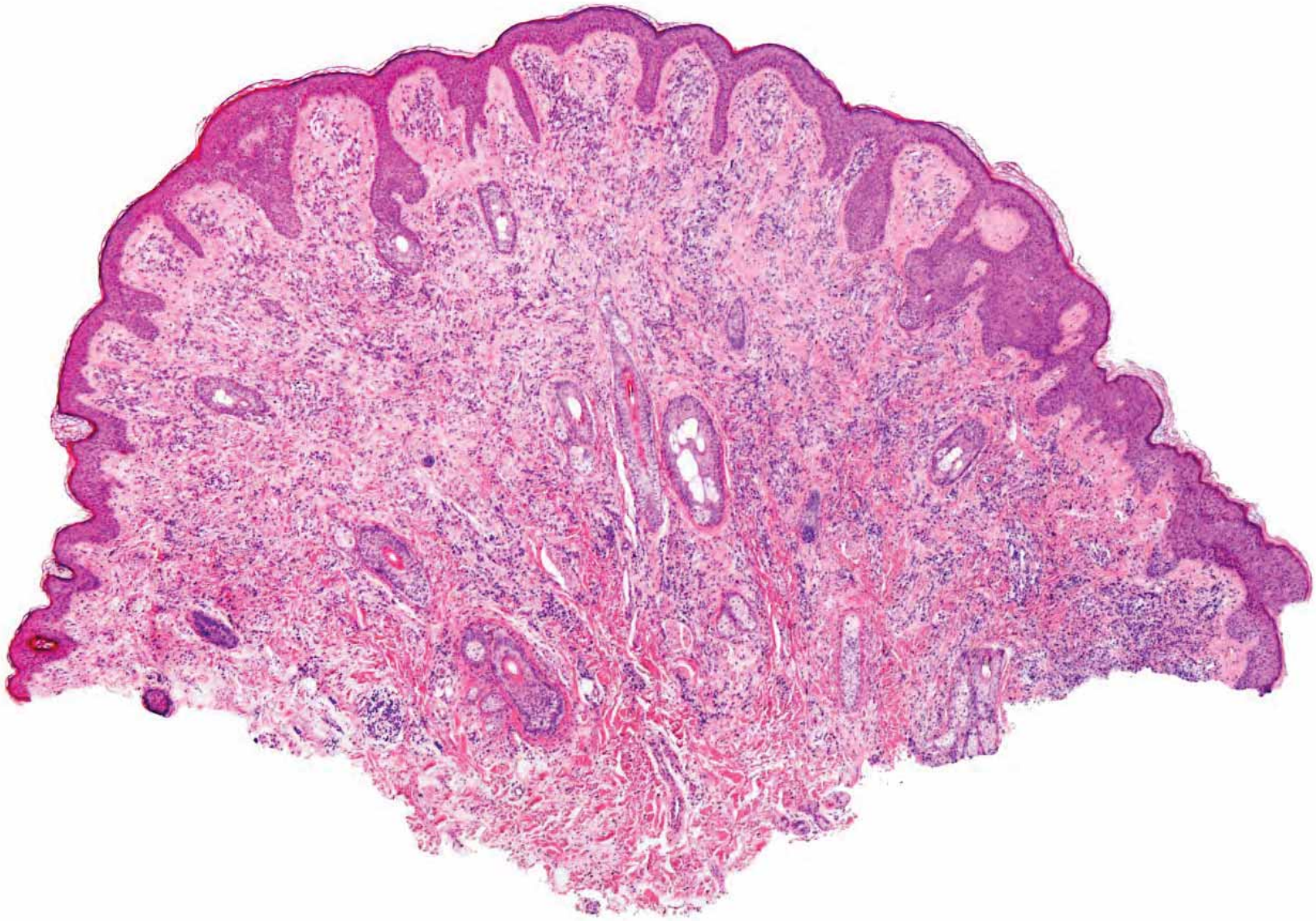


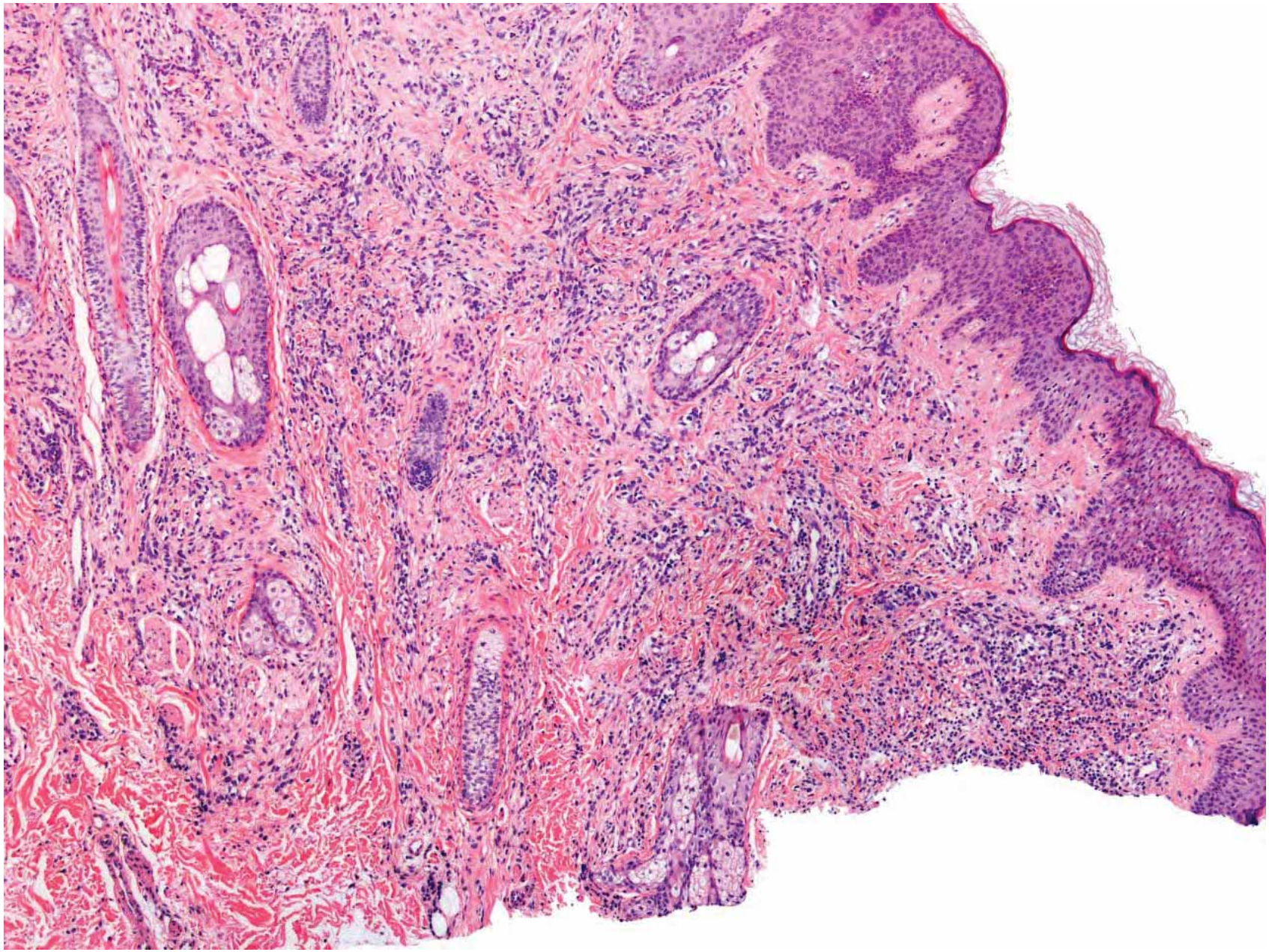


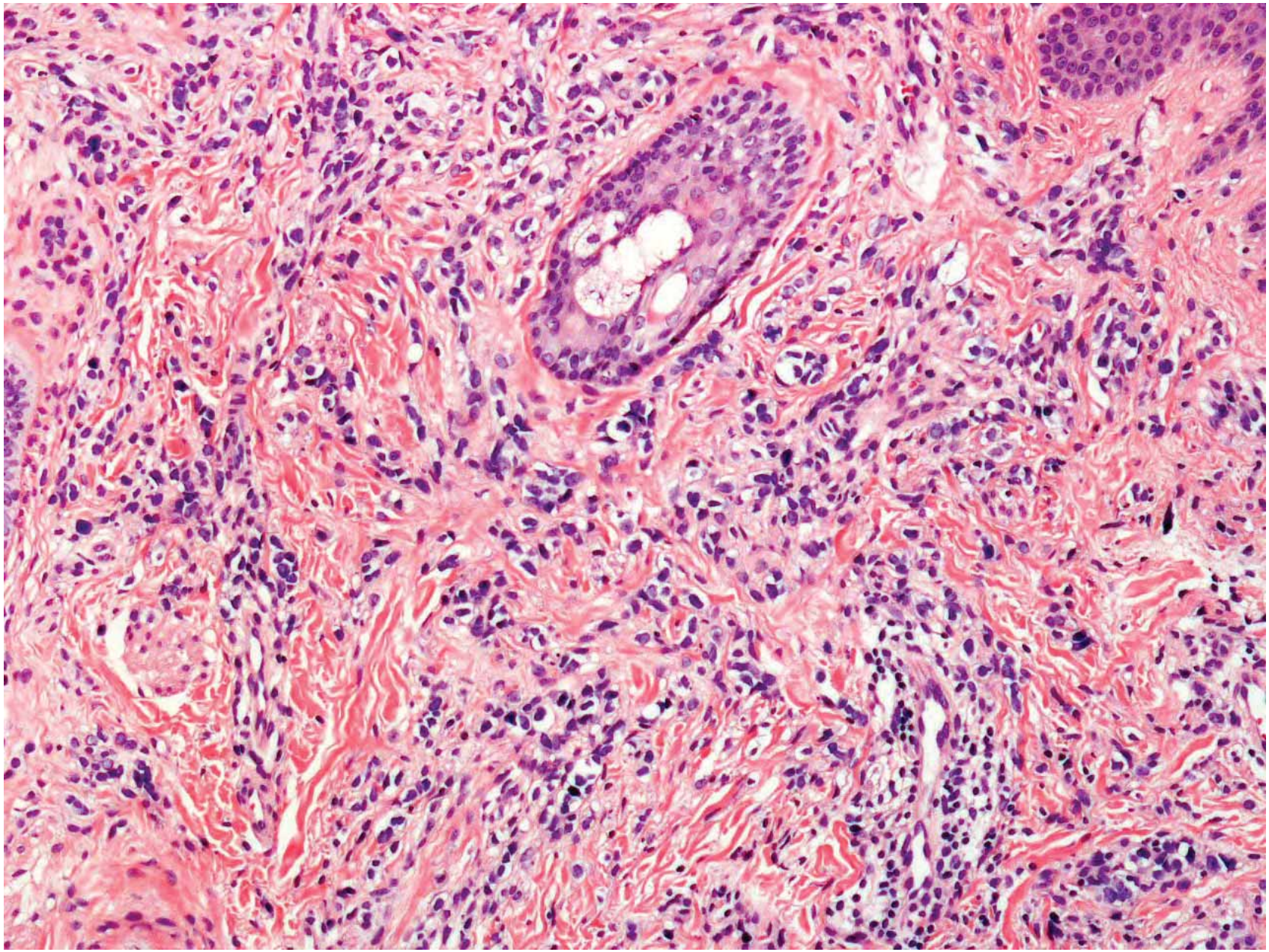


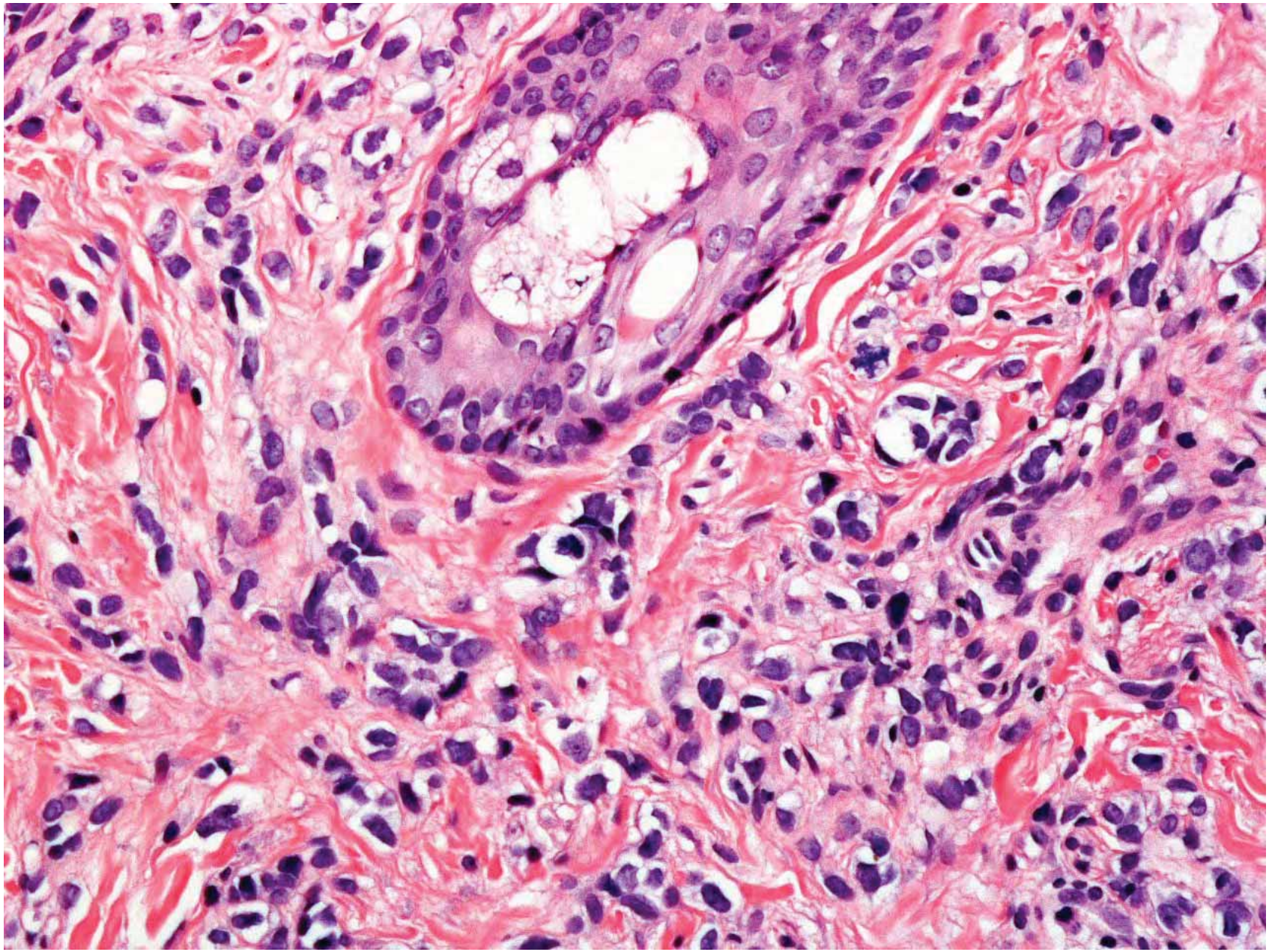


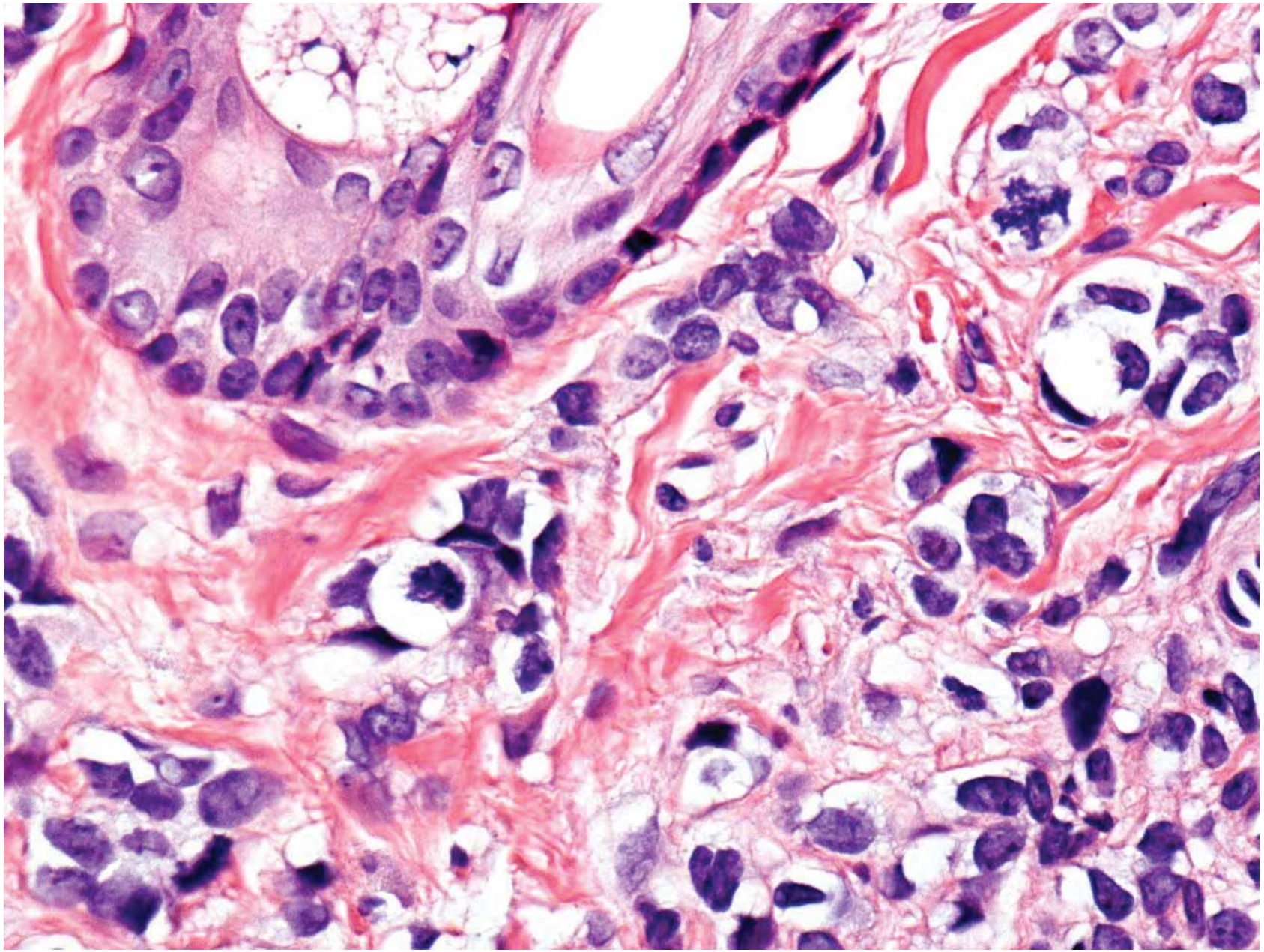






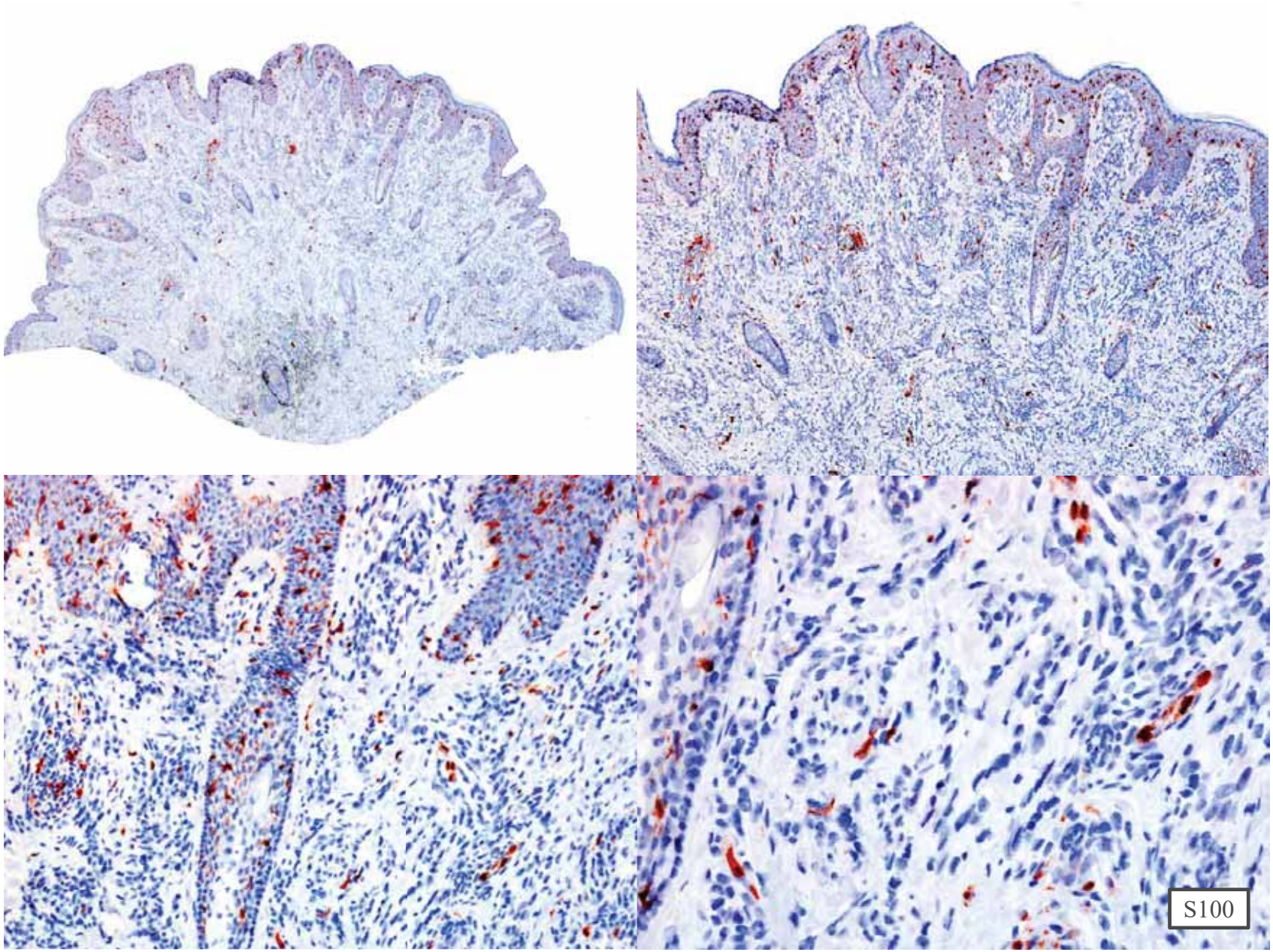






Case 7. Diagnosis

- Intradermal melanocytic nevus with some spitzoid features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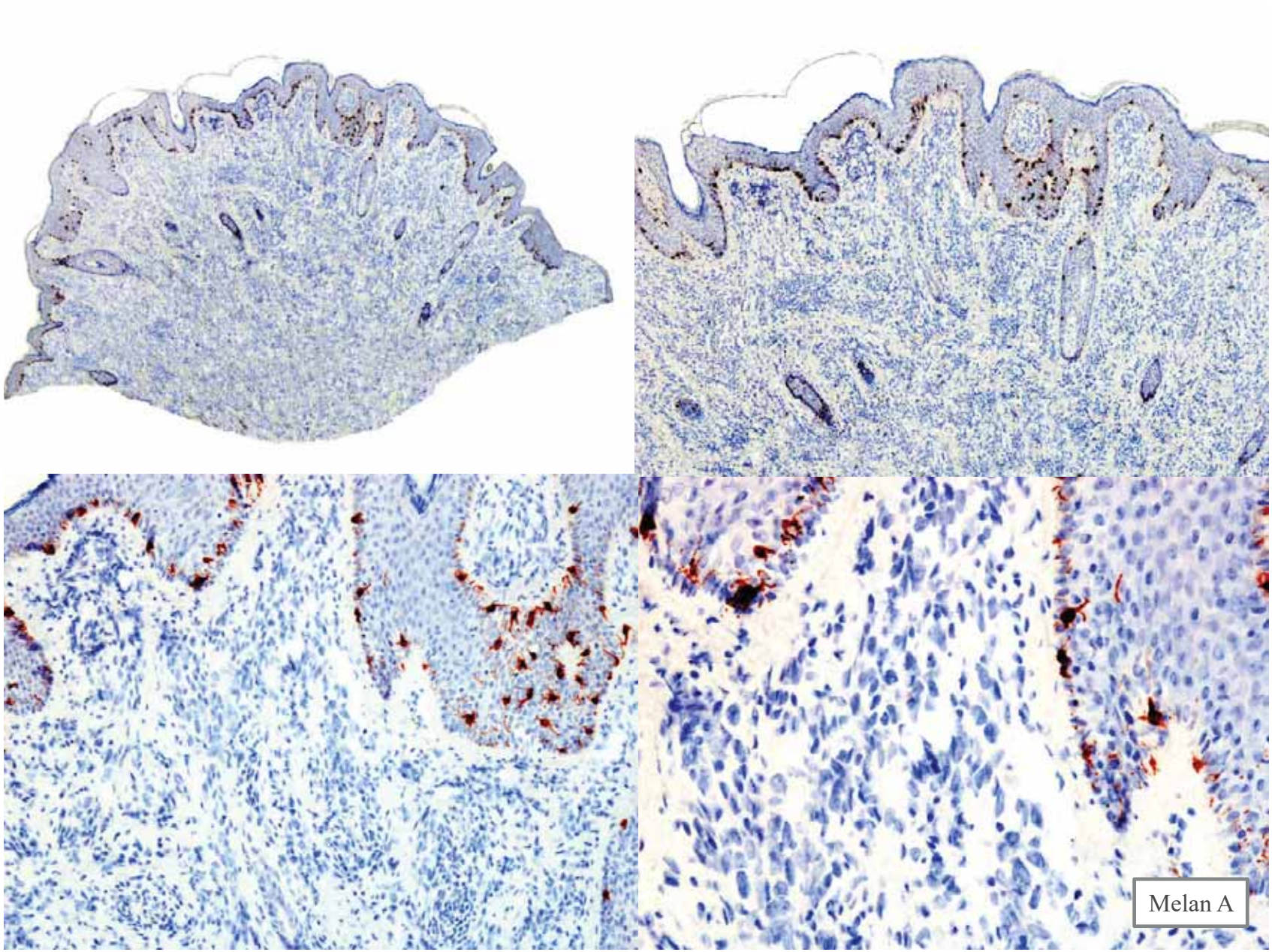
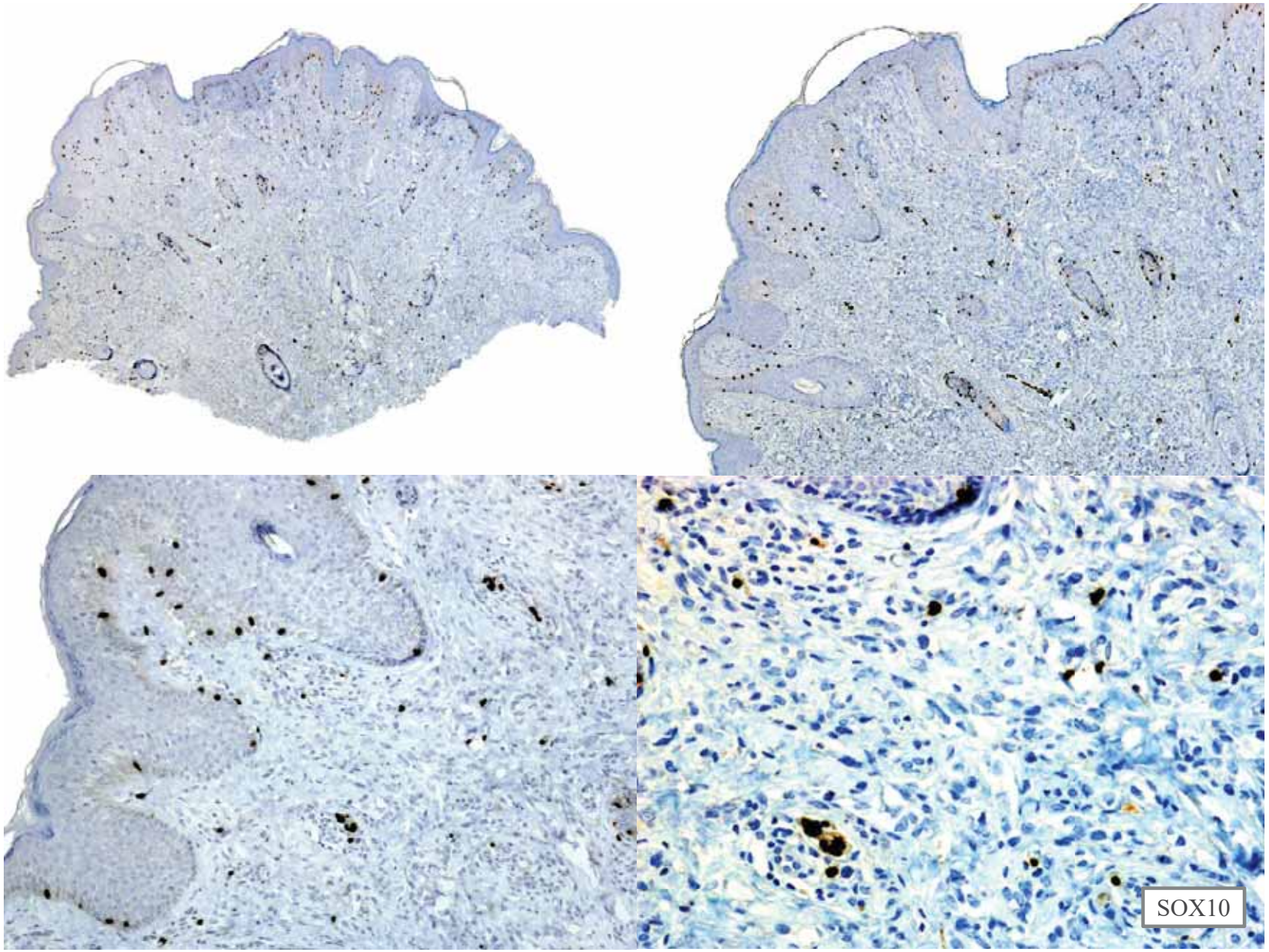
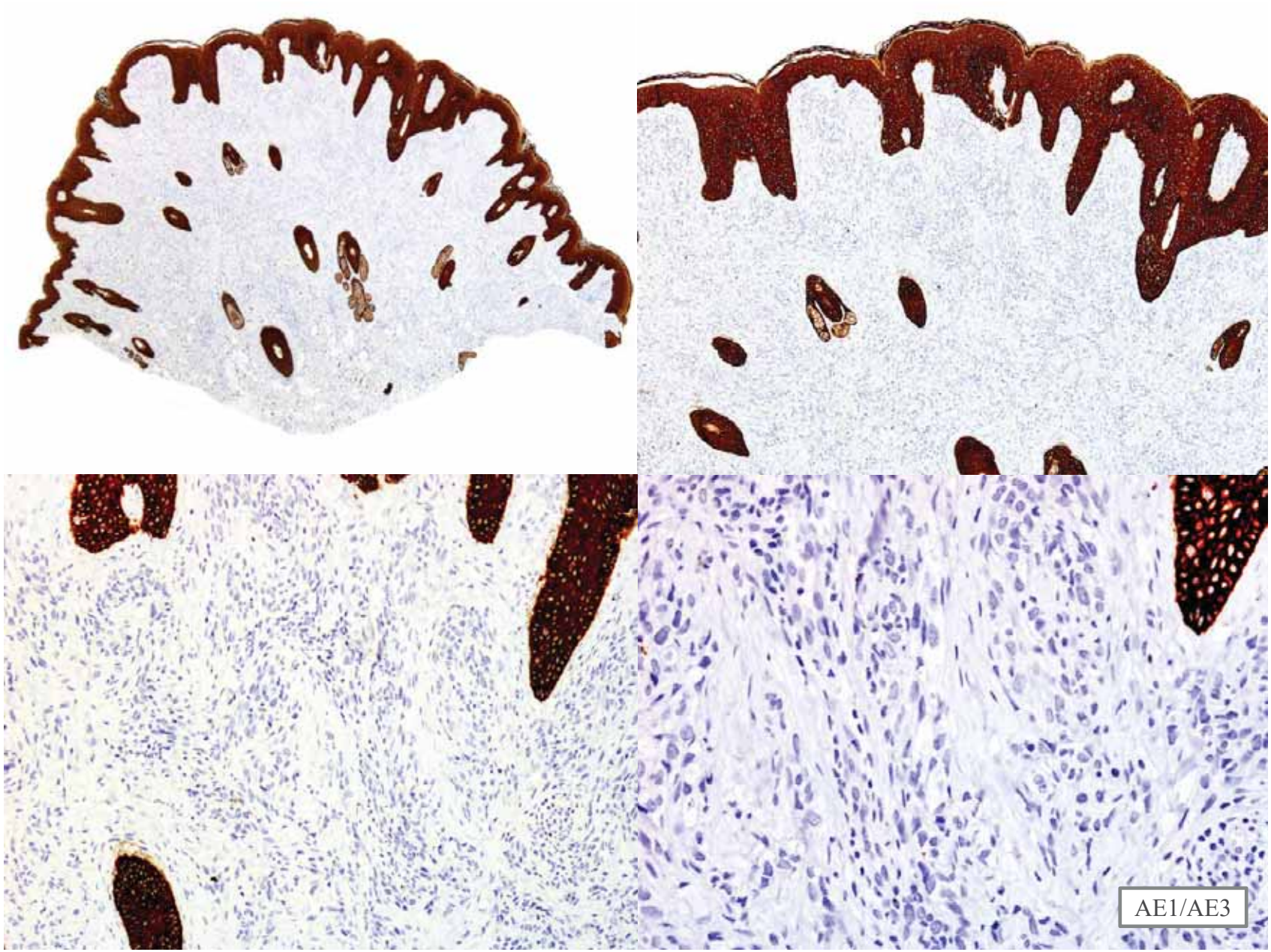

Melan A


SOX10

Case 7. Diagnosis

- ???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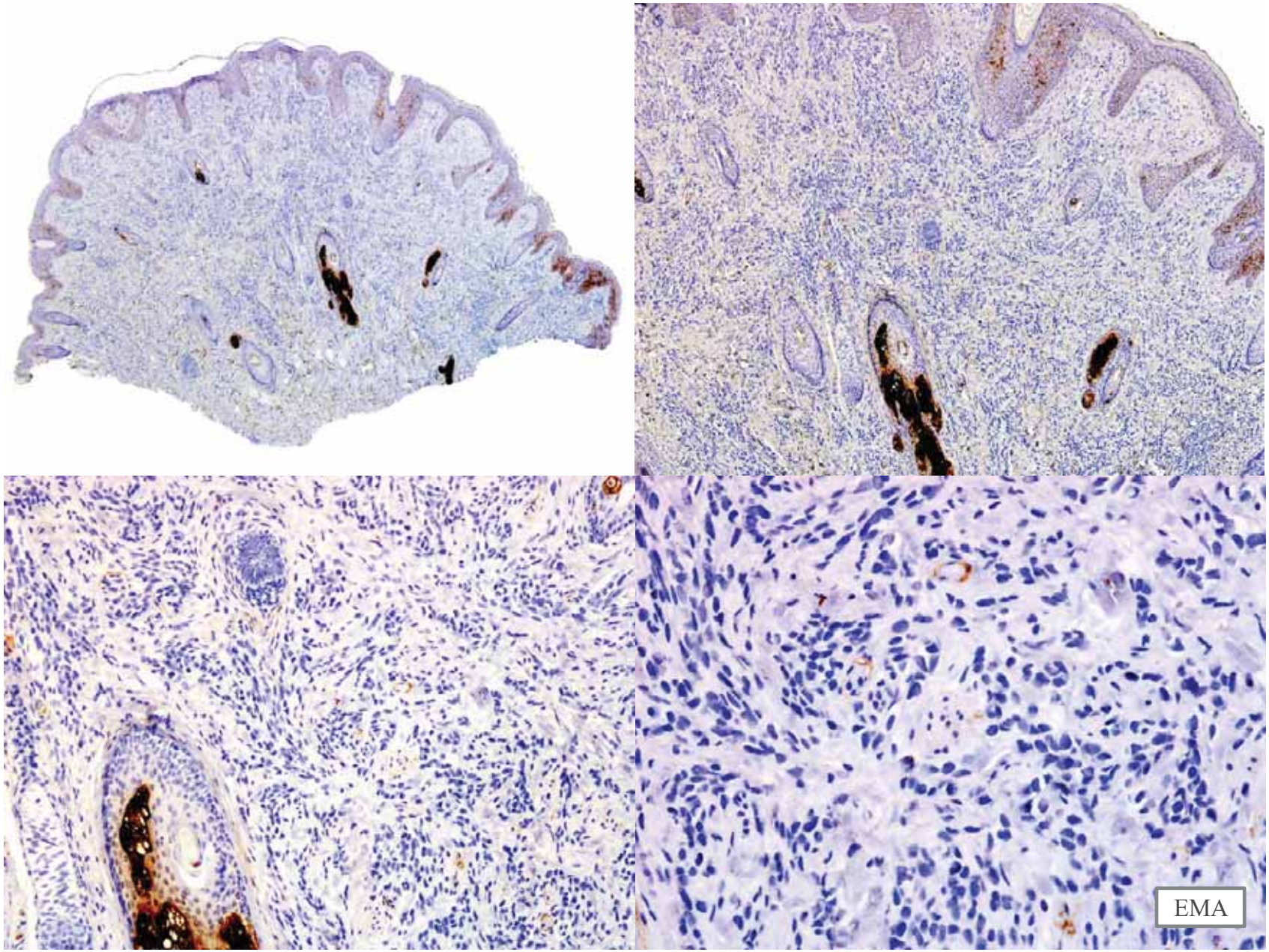
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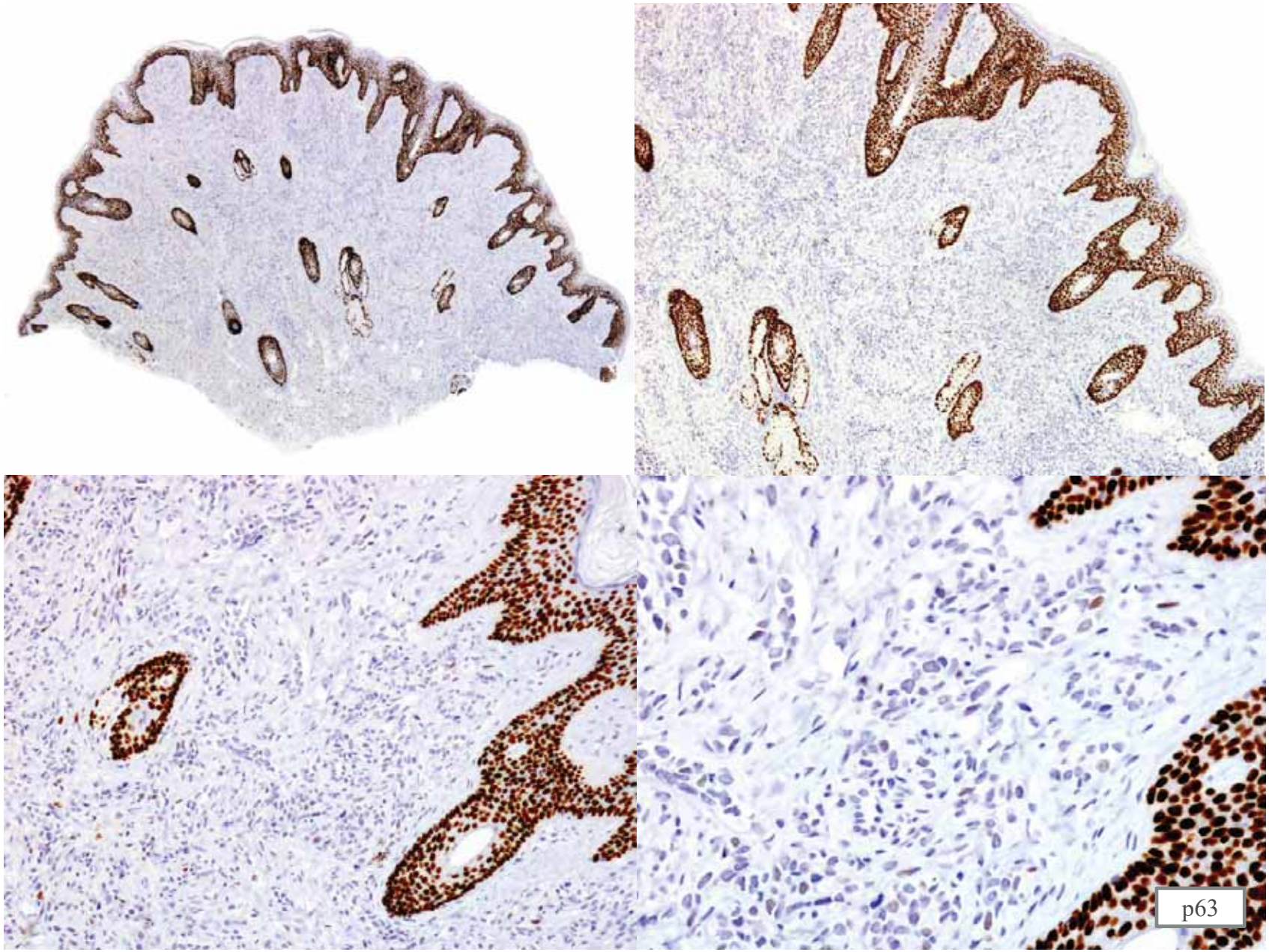
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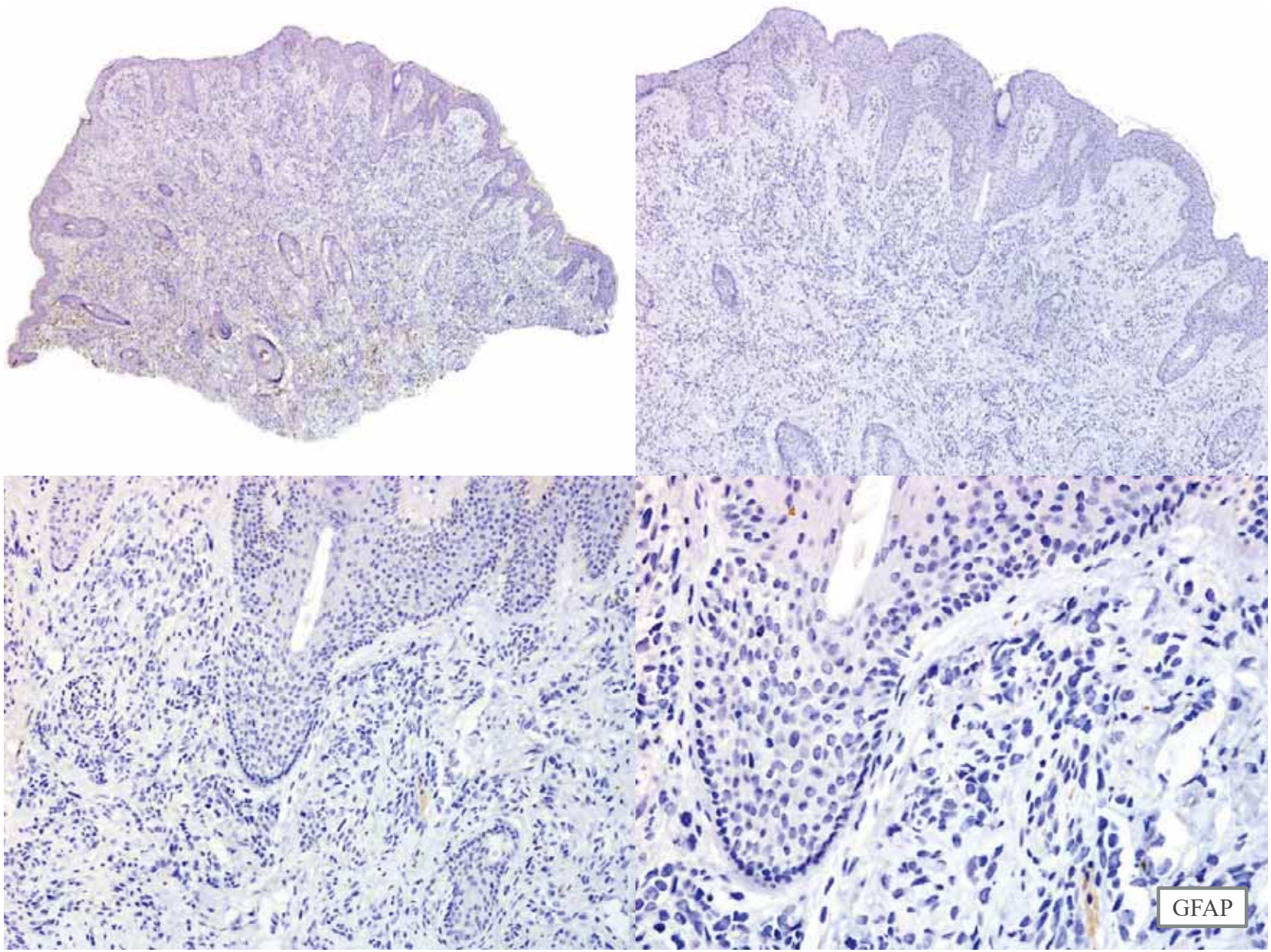
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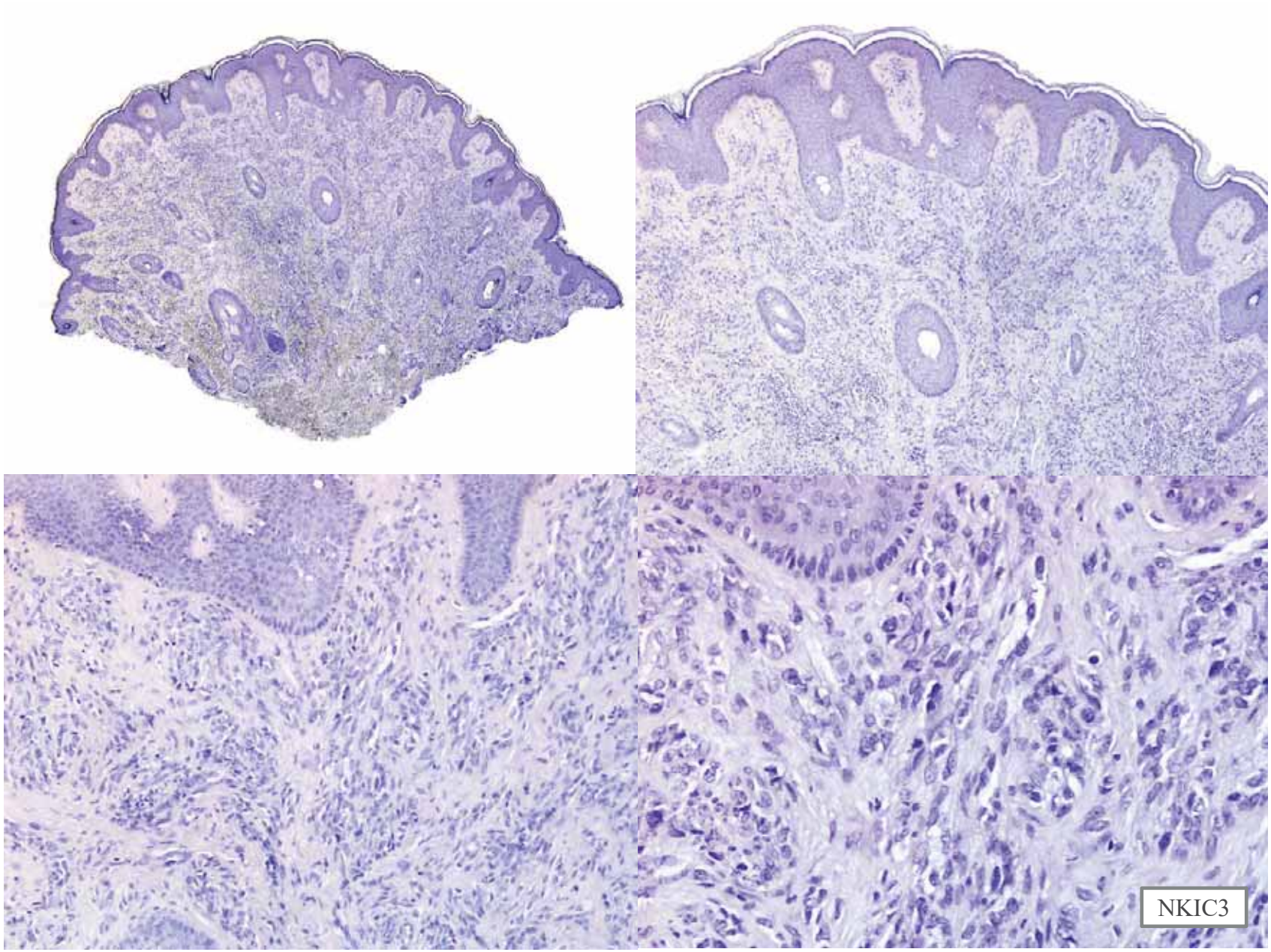
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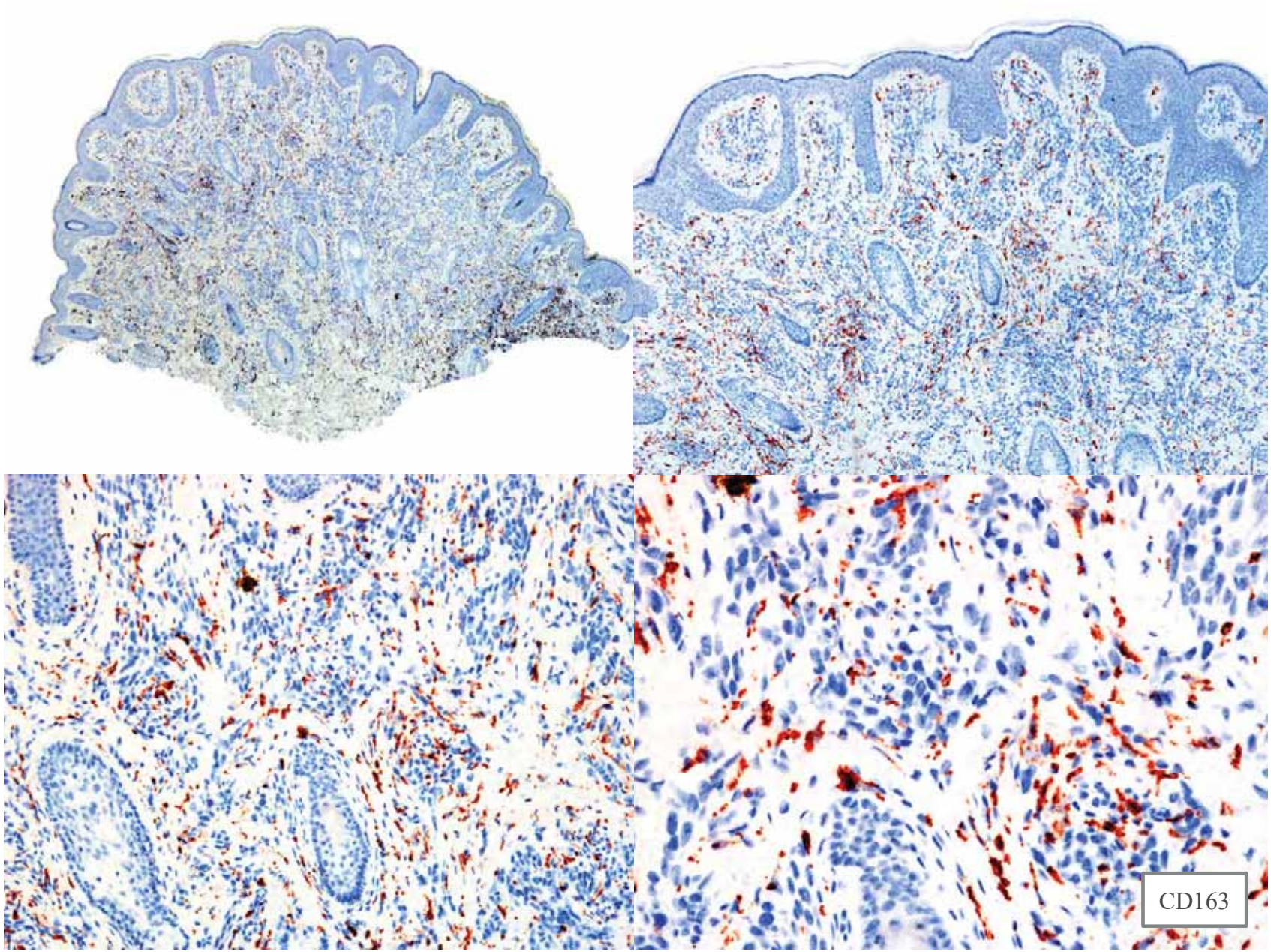
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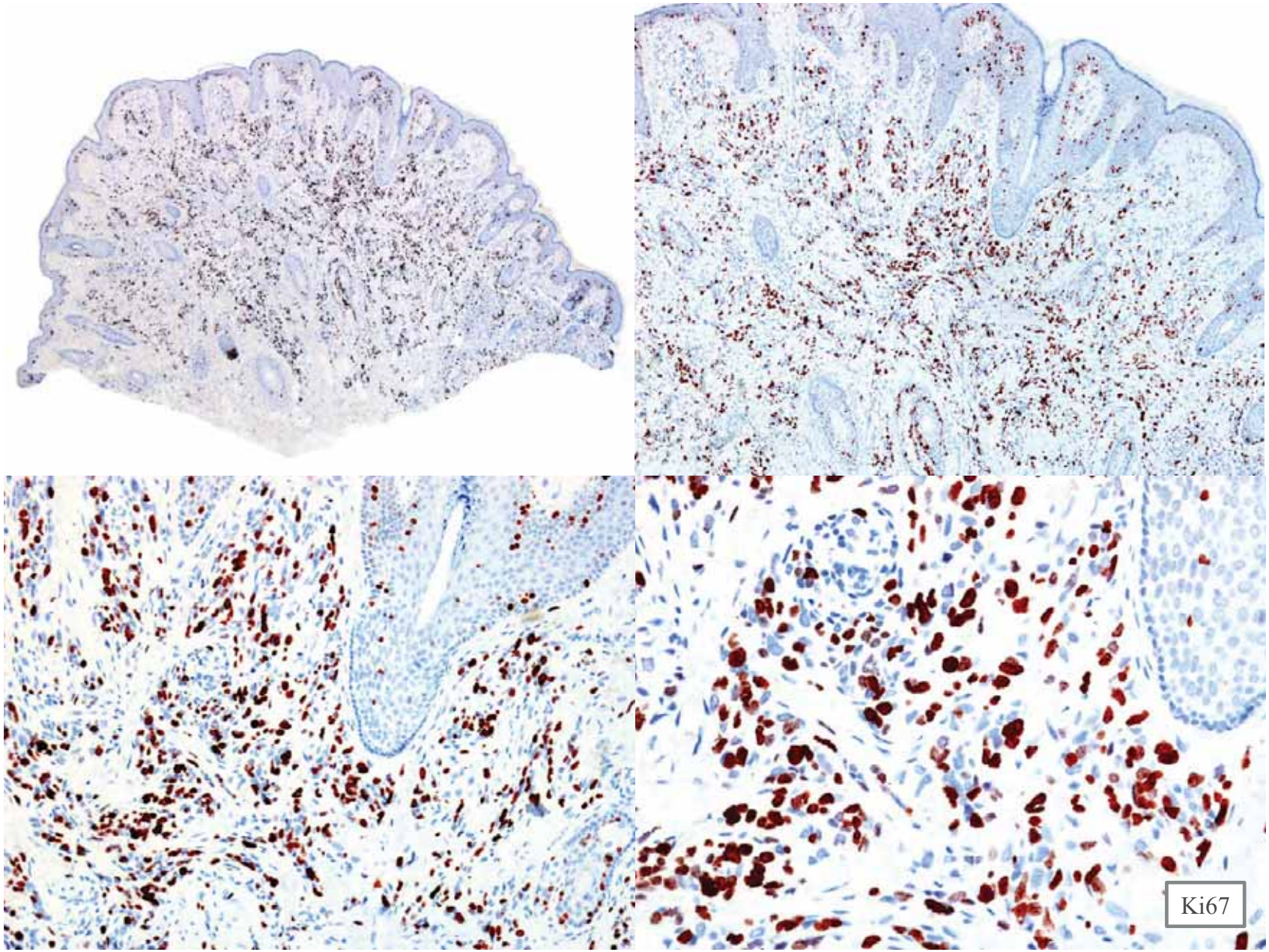
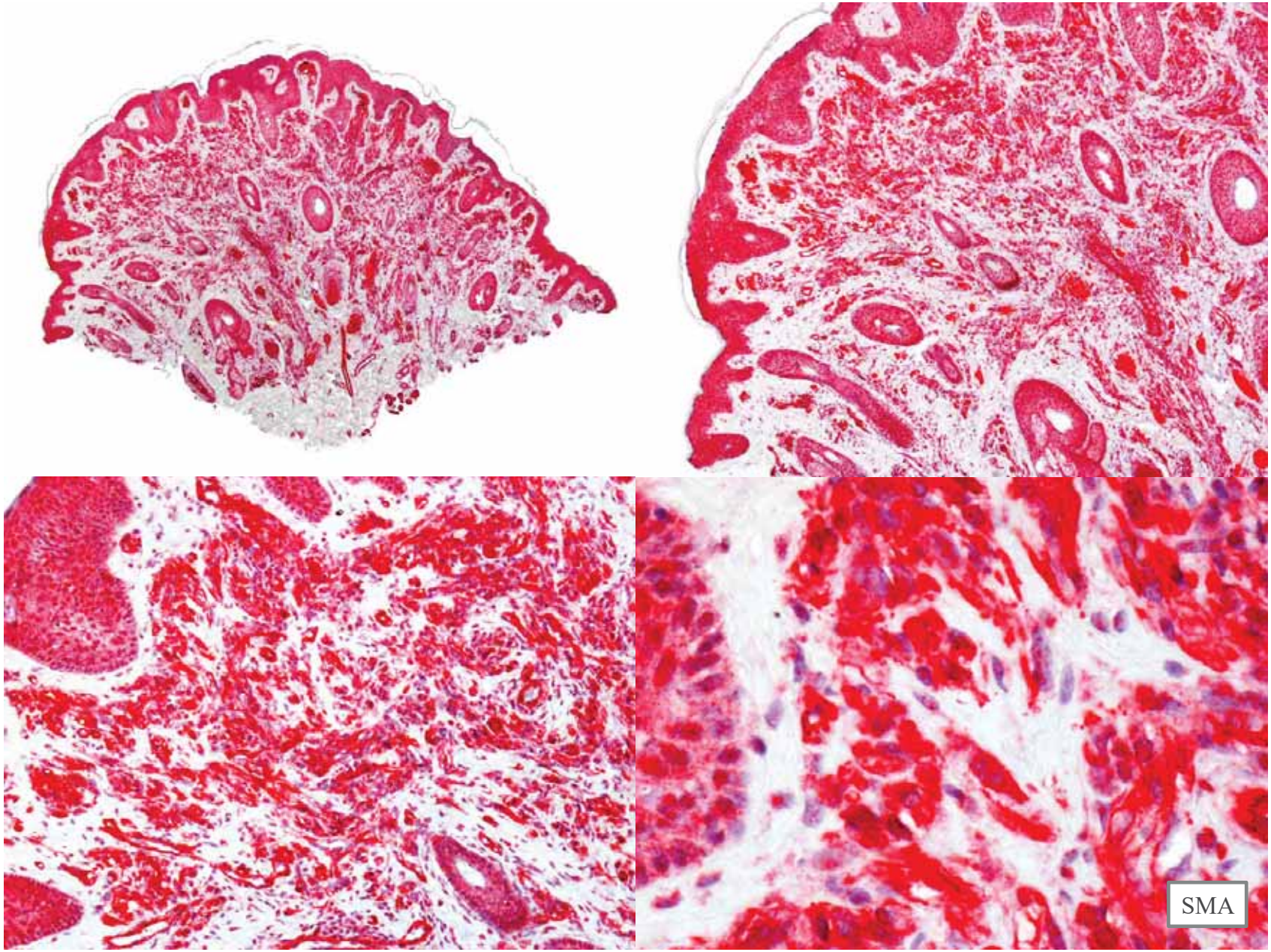

Ki67

Case 7. Diagnosis

- ???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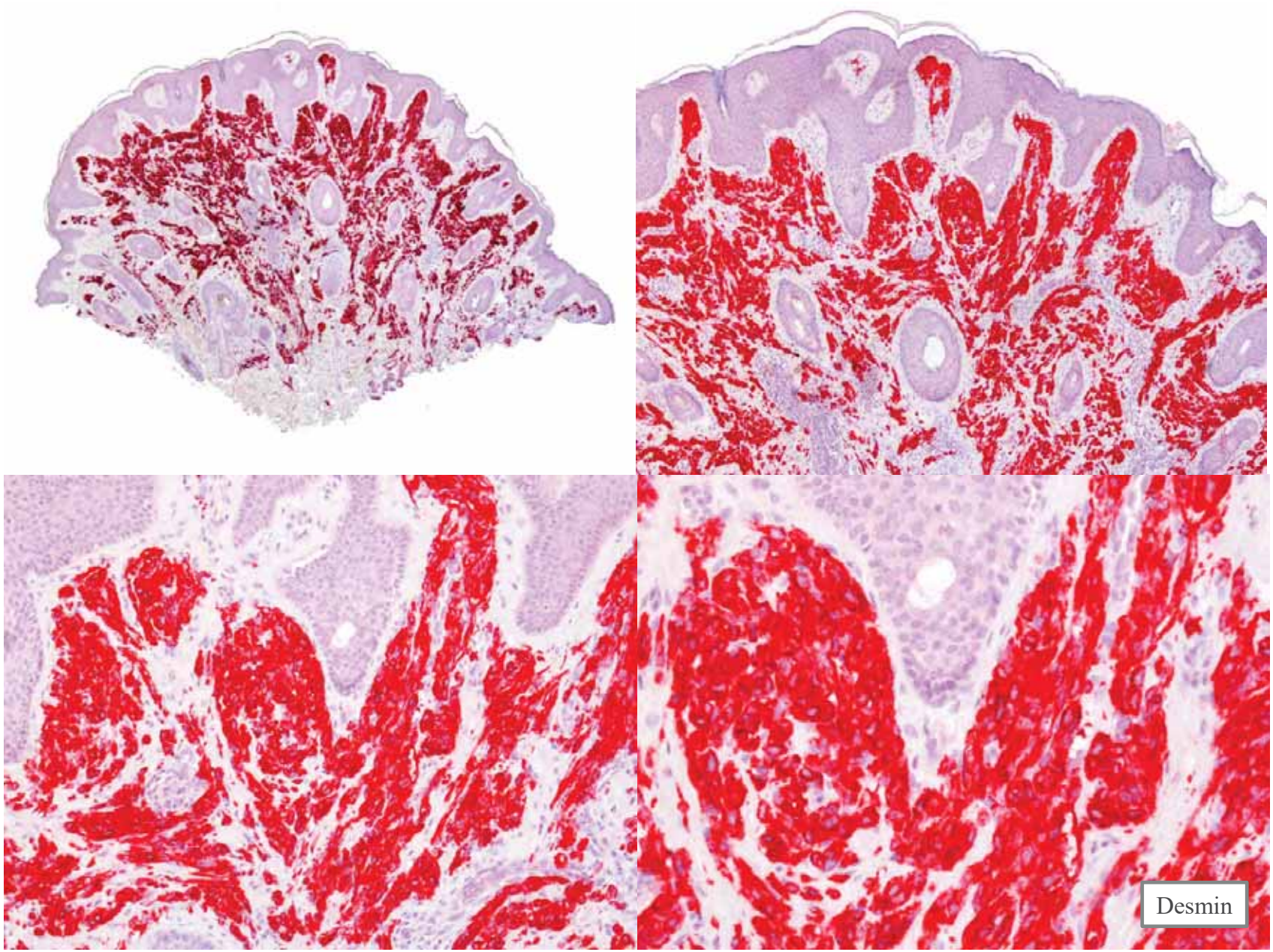
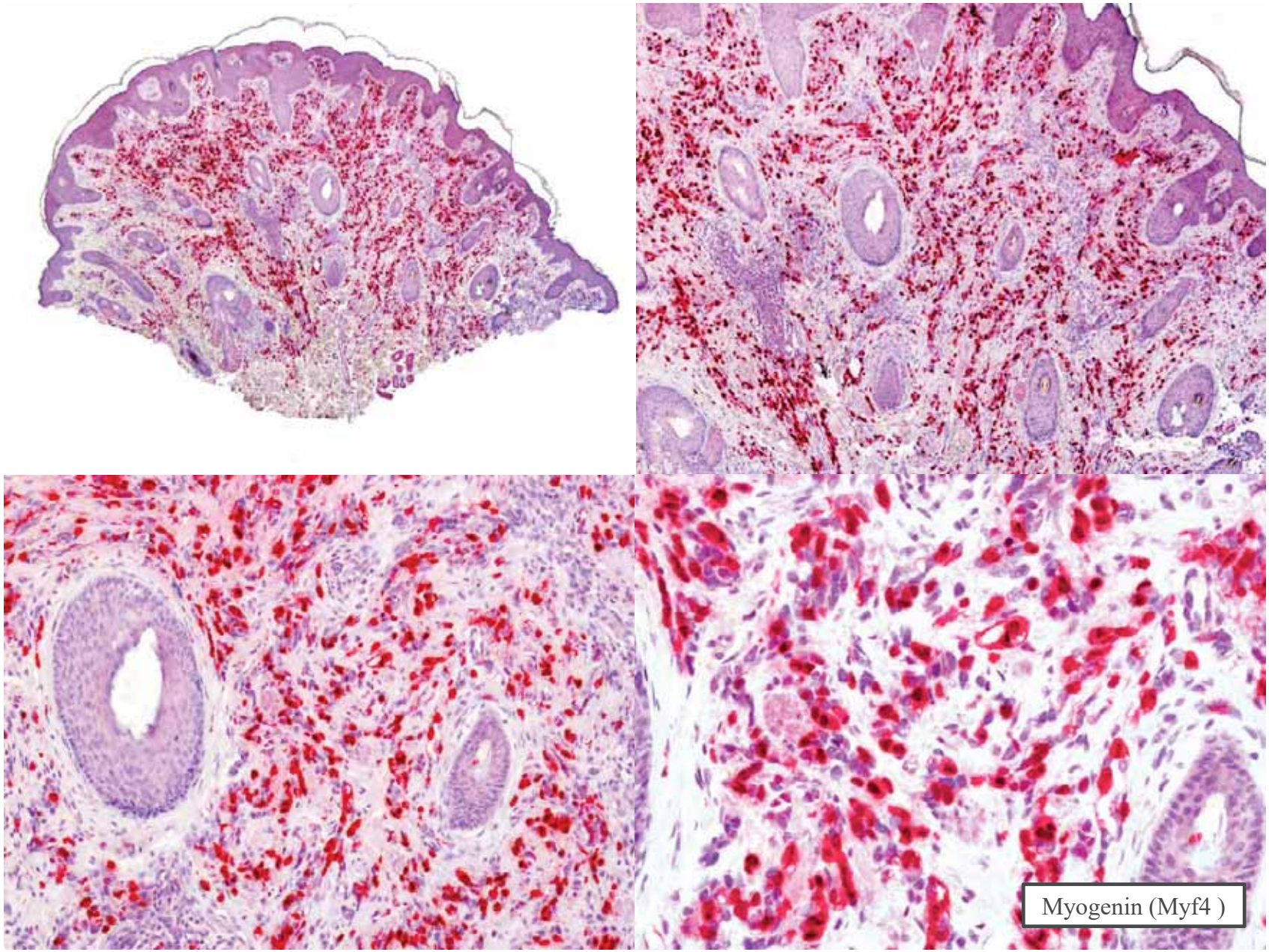
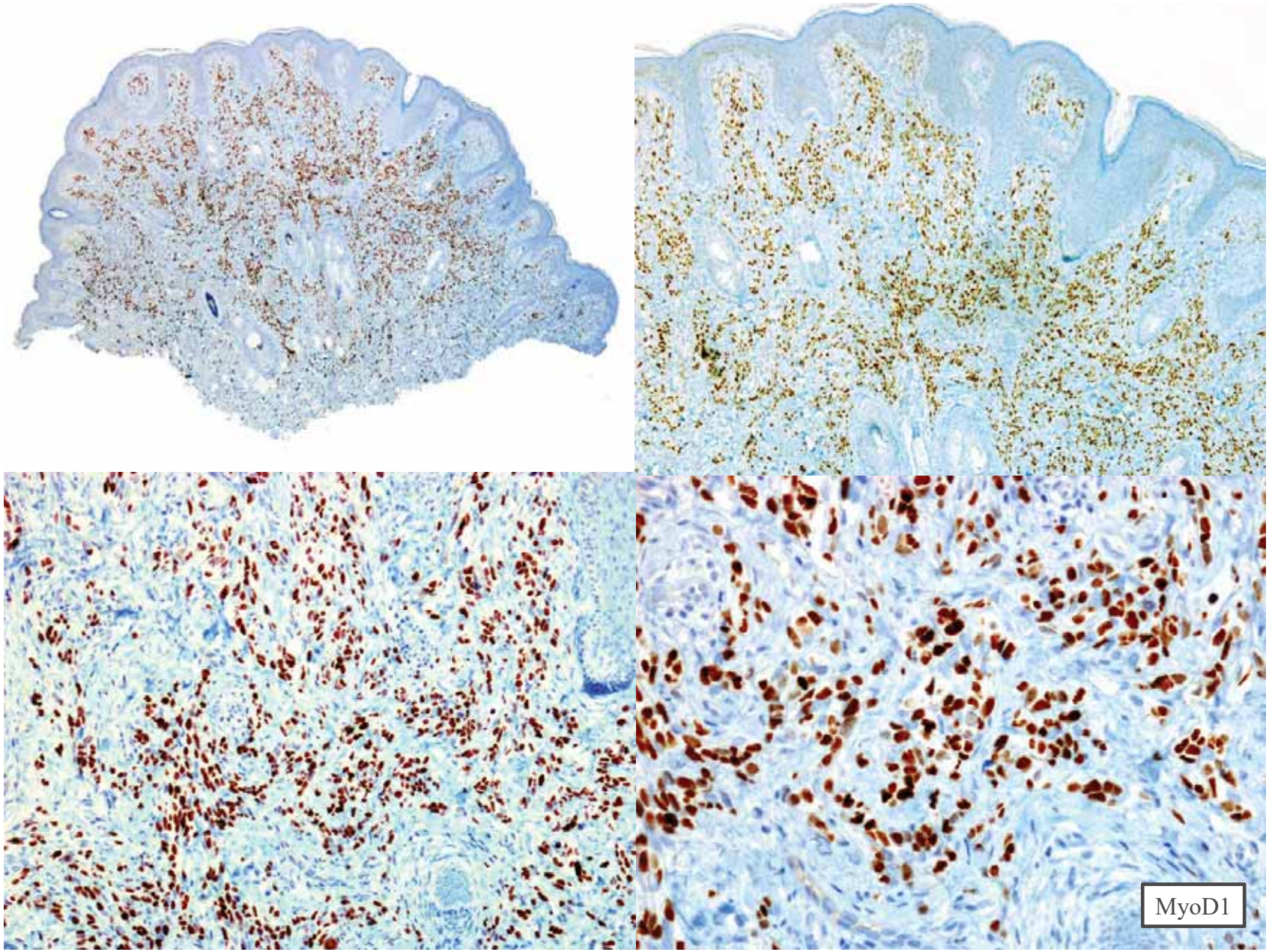

Desmin


Myogenin (Myf4)


MyoD1

Case 7. Diagnosis

- Primary cutaneous embryonal rhabdomyosarcoma

Dermatopathologie Friedrichshafen Bodensee

Dermatopathologische Gemeinschaftspraxis
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DR. MED. ARNO RUTTEN Dermatologe
PROF. DR. MED. THOMAS MENTZEL Pathologe
DR. MED. MARKUS HANTSCHKE Dermatologe
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Clinica de Nuestra Senora de la Concepción
Avda. de los Reyes Católicos 2
E-28040 Madrid

Friedrichshafen, den 15.10.2020
HK/BE

Ihre J-Nr.:	Unsere J-Nr.:	Patient:	
B 336510-20	K 002411-20	Unbekannt, Unbekannt	*01.01.1900

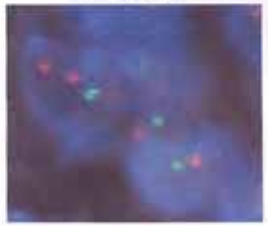
Result of the FISH analysis

FISH analysis for the detection of the translocation (1;13)(q35;q14)

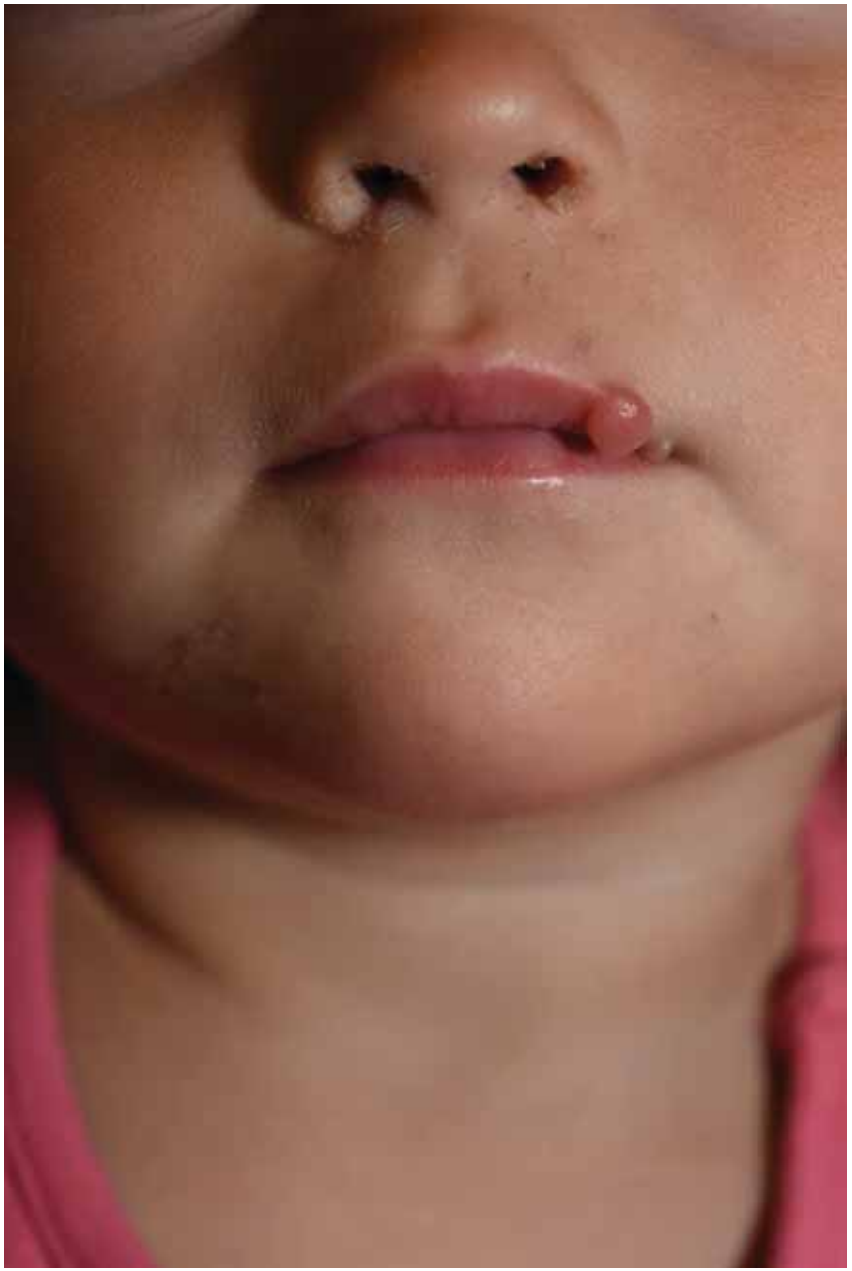
The translocation (1;13)(p36;q14) PAX7/FKHR (paired box gene 7, OMIM number 167410; forkhead box 01A, OMIM number 136533) could not be identified by FISH analysis.

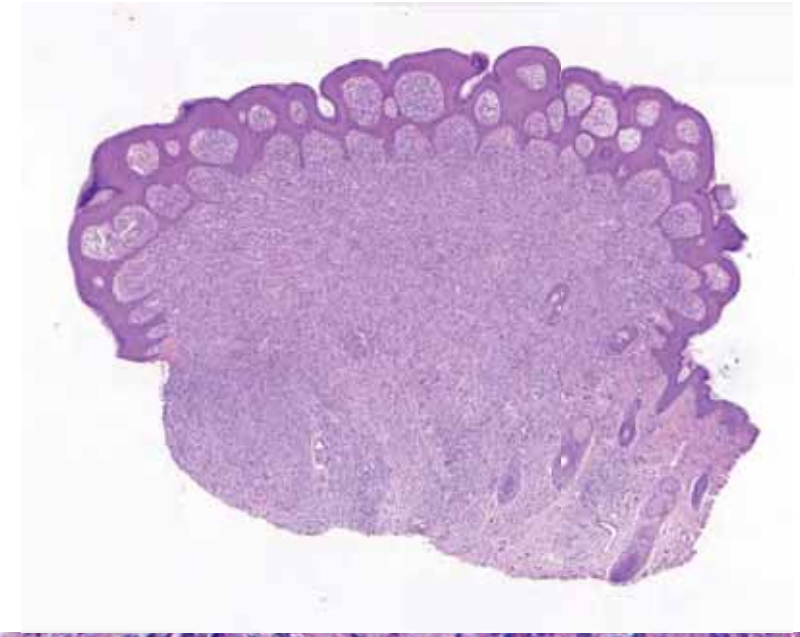
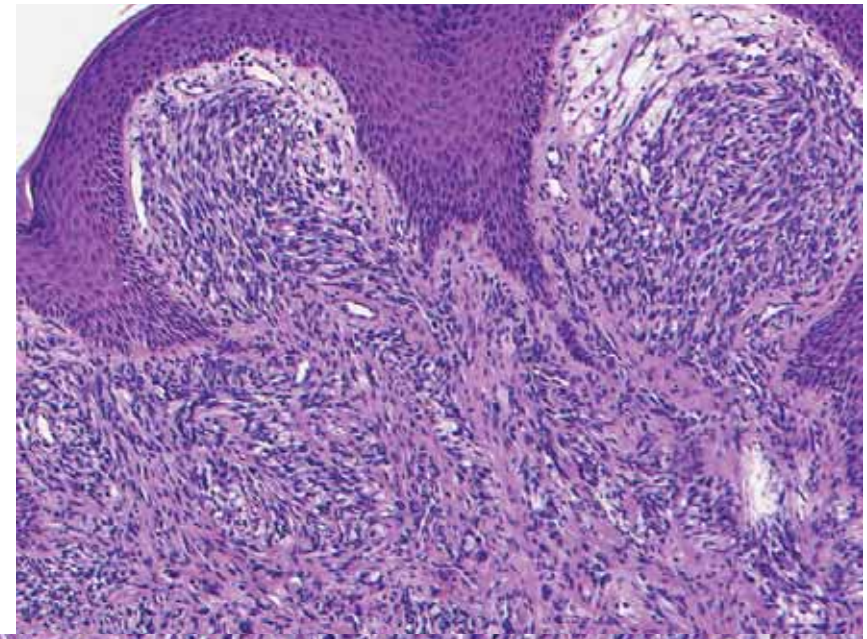
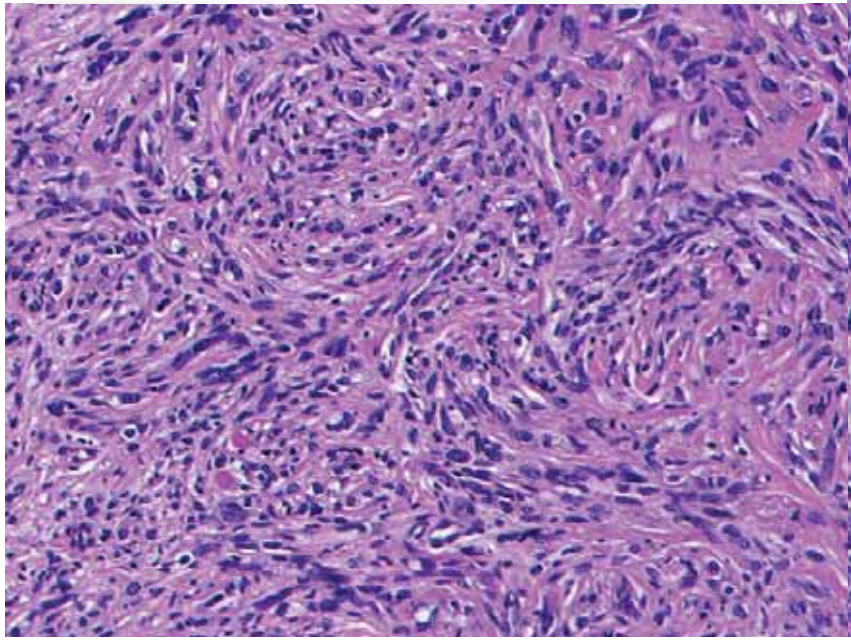
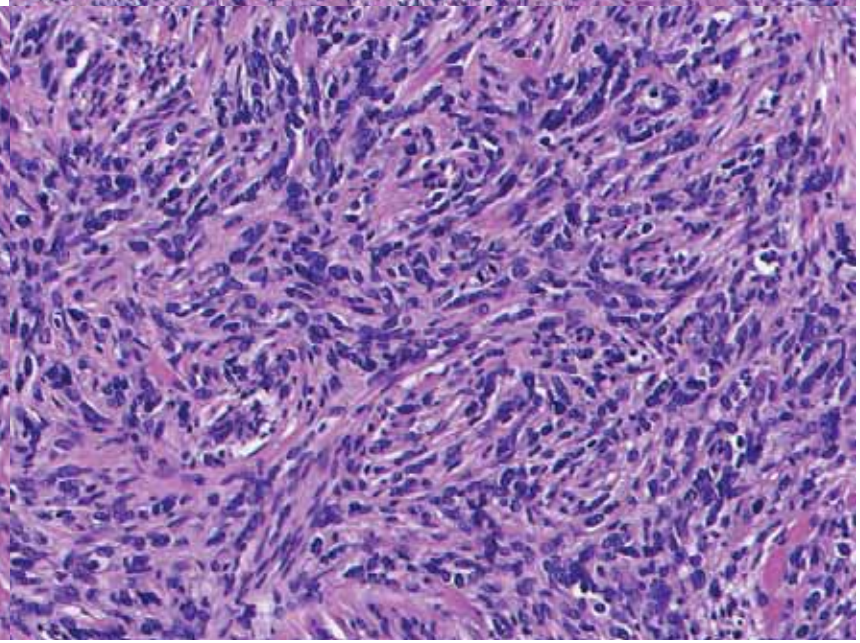
For the FISH analysis a rhodamine labeled (red signal) probe binding distally to the PAX7 breakpoint region and and a FITC labeled probe (green signal) binding proximally to the FKHR breakpoint region were hybridized to interphase nuclei. As no translocation is visible, both signals ly in different parts of the nucleus..

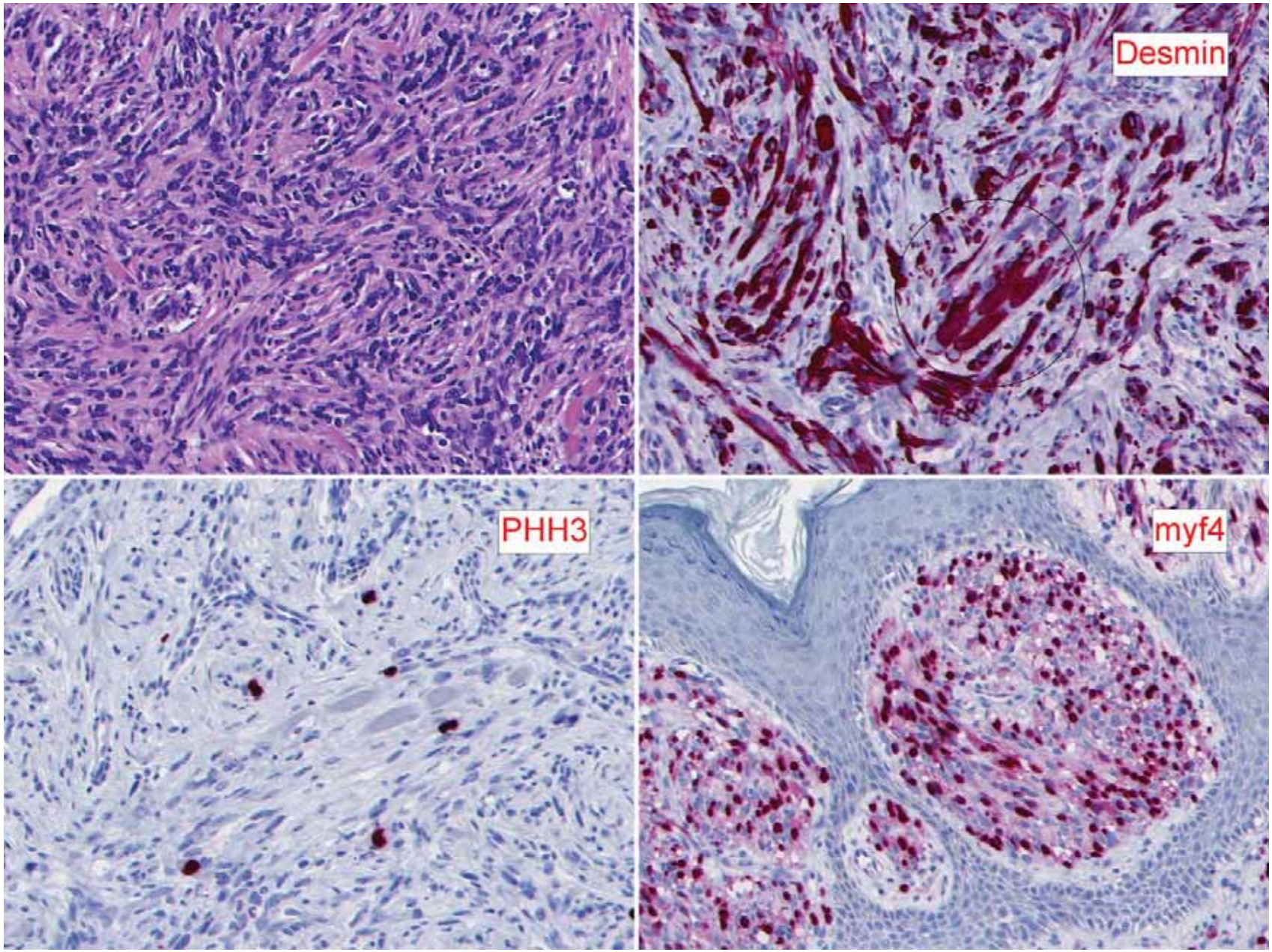
20/K 002411

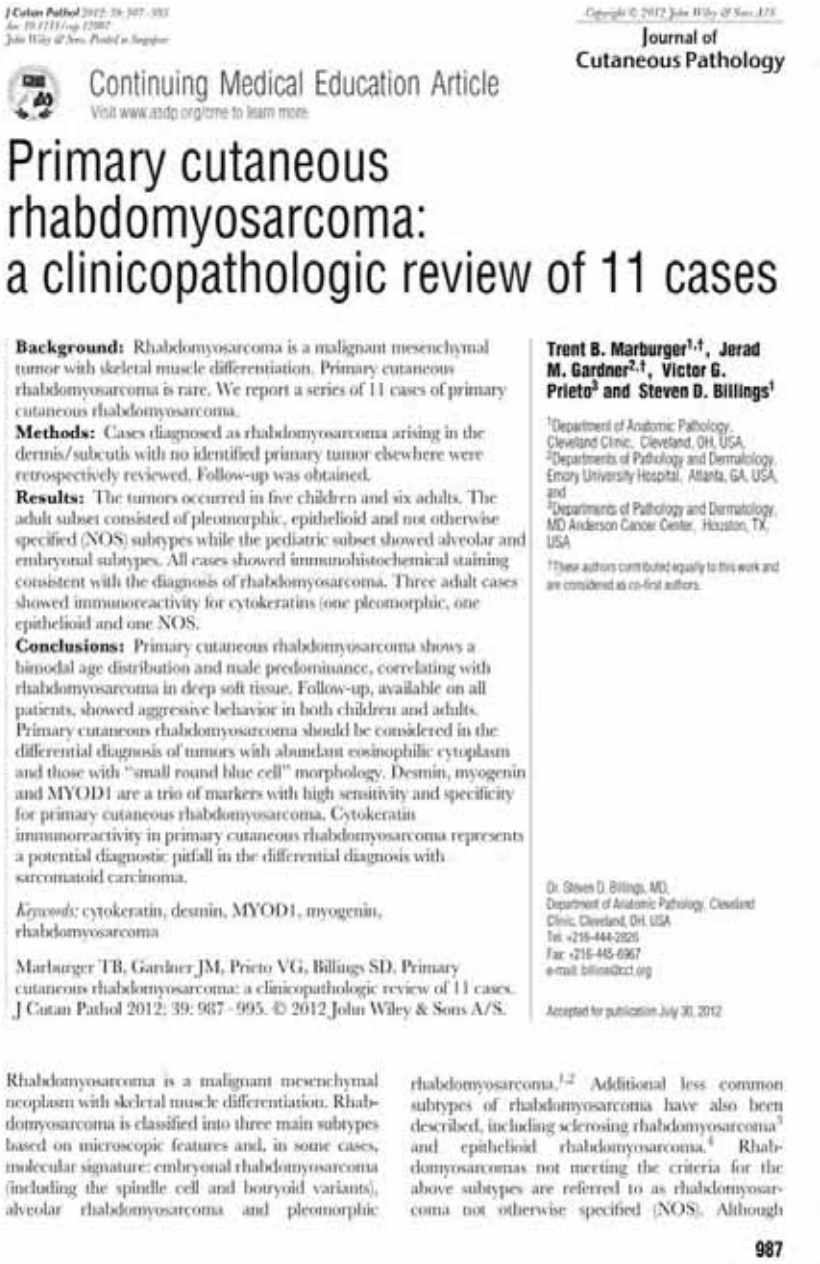


PD Dr. Kutzner / Dr. Palmedo 16.10.2020




Desmin
PHH3
myf4



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Primary cutaneous rhabdomyosarcoma: a clinicopathologic review of 11 cases

Background: Rhabdomyosarcoma is a malignant mesenchymal tumor with skeletal muscle differentiation. Primary cutaneous rhabdomyosarcoma is rare. We report a series of 11 cases of primary cutaneous rhabdomyosarcoma.
Methods: Cases diagnosed as rhabdomyosarcoma arising in the dermis/subcutis with no identified primary tumor elsewhere were retrospectively reviewed. Follow-up was obtained.
Results: The tumors occurred in five children and six adults. The adult subset consisted of pleomorphic, epithelioid and not otherwise specified (NOS) subtypes while the pediatric subset showed alveolar and embryonal subtypes. All cases showed immunohistochemical staining consistent with the diagnosis of rhabdomyosarcoma. Three adult cases showed immunoreactivity for cytokeratins (one pleomorphic, one epithelioid and one NOS.
Conclusions: Primary cutaneous rhabdomyosarcoma shows a bimodal age distribution and male predominance, correlating with rhabdomyosarcoma in deep soft tissue. Follow-up, available on all patients, showed aggressive behavior in both children and adults. Primary cutaneous rhabdomyosarcoma should be considered in the differential diagnosis of tumors with abundant eosinophilic cytoplasm and those with "small round blue cell" morphology. Desmin, myogenin and MYOD1 are a trio of markers with high sensitivity and specificity for primary cutaneous rhabdomyosarcoma. Cytokeratin immunoreactivity in primary cutaneous rhabdomyosarcoma represents a potential diagnostic pitfall in the differential diagnosis with sarcomatoid carcinoma.

Keywords: cytokeratin, desmin, MYOD1, myogenin, rhabdomyosarcoma

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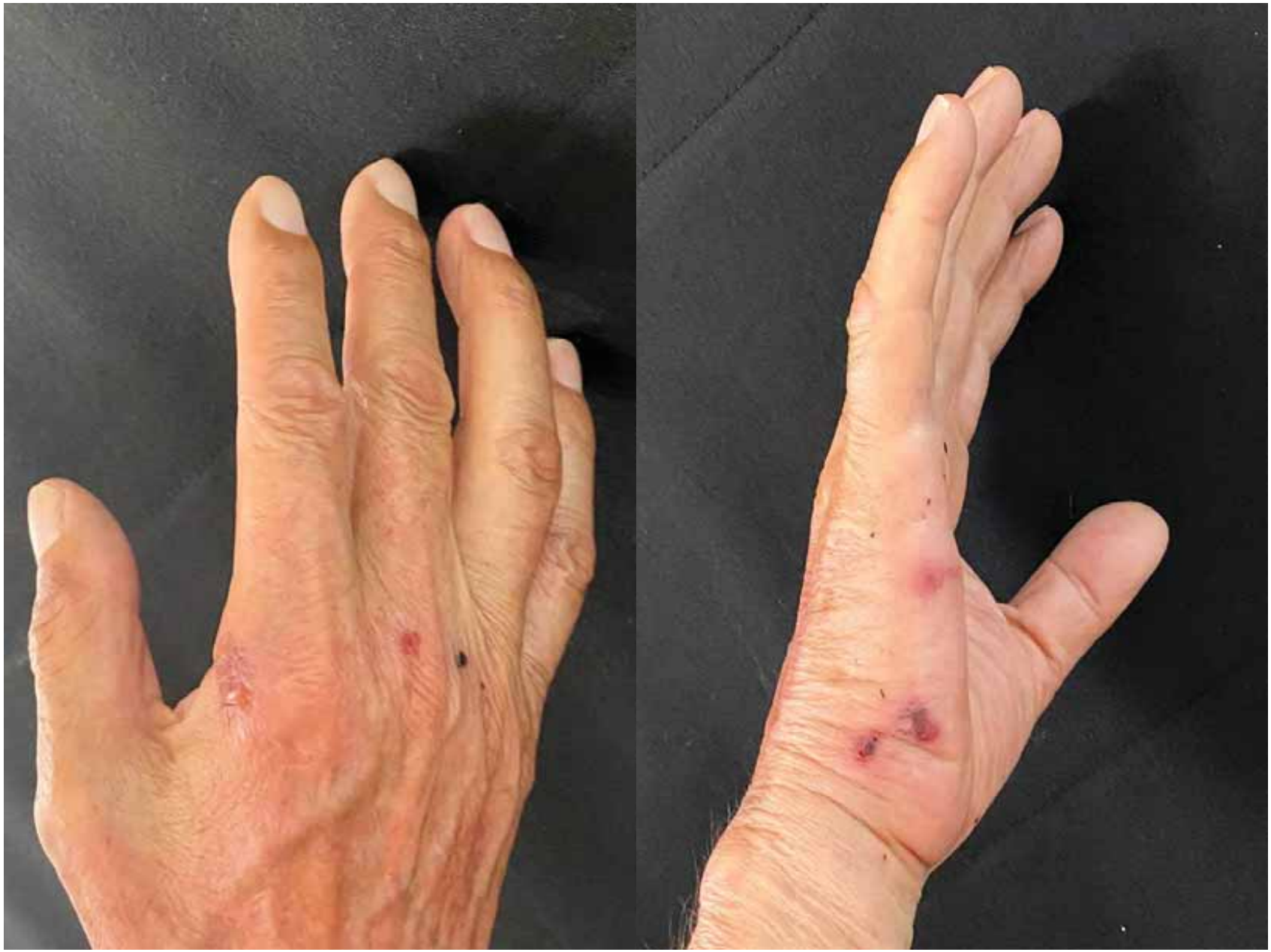
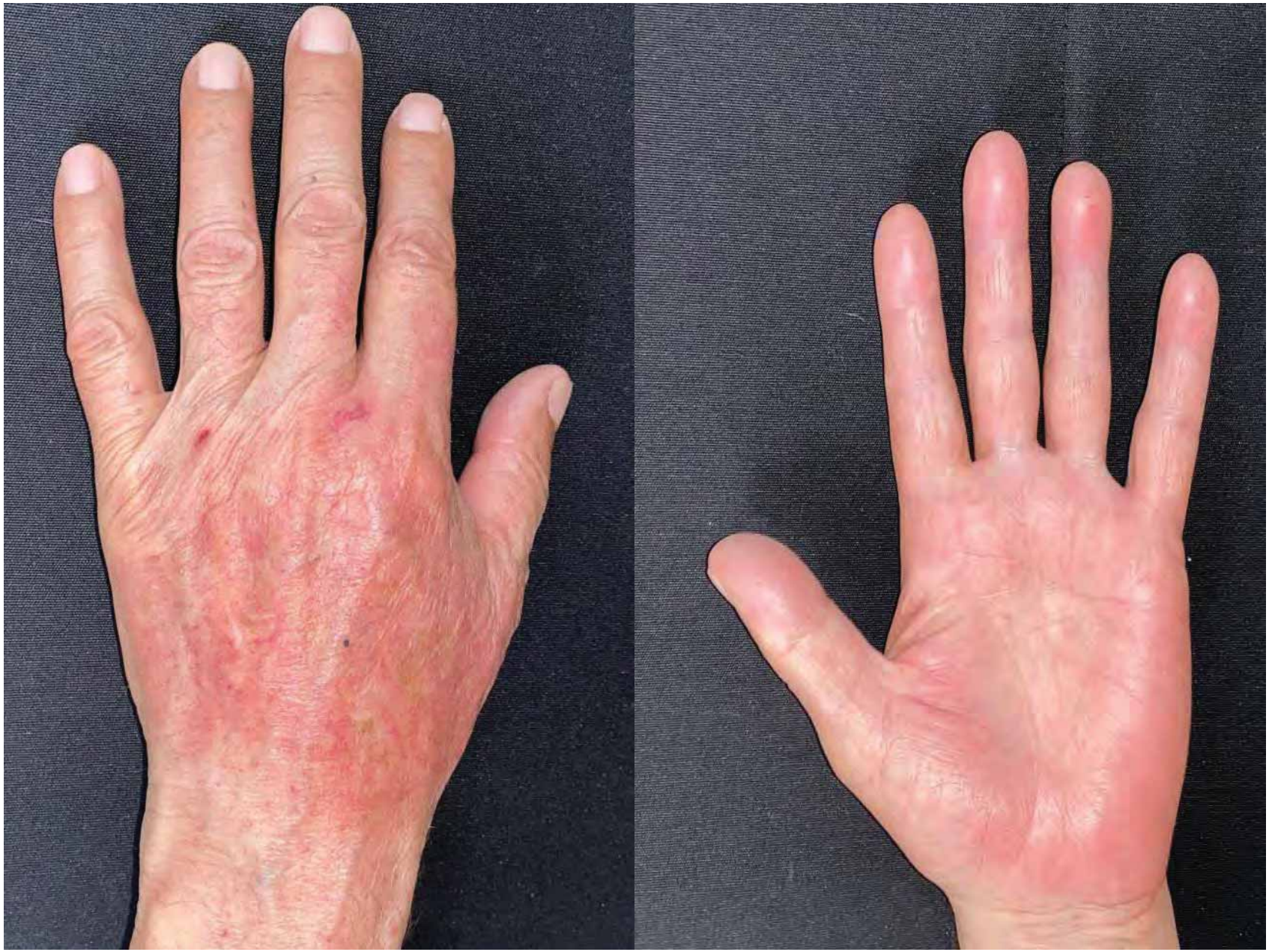
Rhabdomyosarcoma is a malignant mesenchymal neoplasm with skeletal muscle differentiation. Rhabdomyosarcoma is classified into three main subtypes based on microscopic features and, in some cases, molecular signature: embryonal rhabdomyosarcoma (including the spindle cell and botryoid variants), alveolar rhabdomyosarcoma and pleomorphic rhabdomyosarcoma.[1,2] Additional less common subtypes of rhabdomyosarcoma have also been described, including sclerosing rhabdomyosarcoma[3] and epithelioid rhabdomyosarcoma.[4] Rhabdomyosarcomas not meeting the criteria for the above subtypes are referred to as rhabdomyosarcoma not otherwise specified (NOS). Although

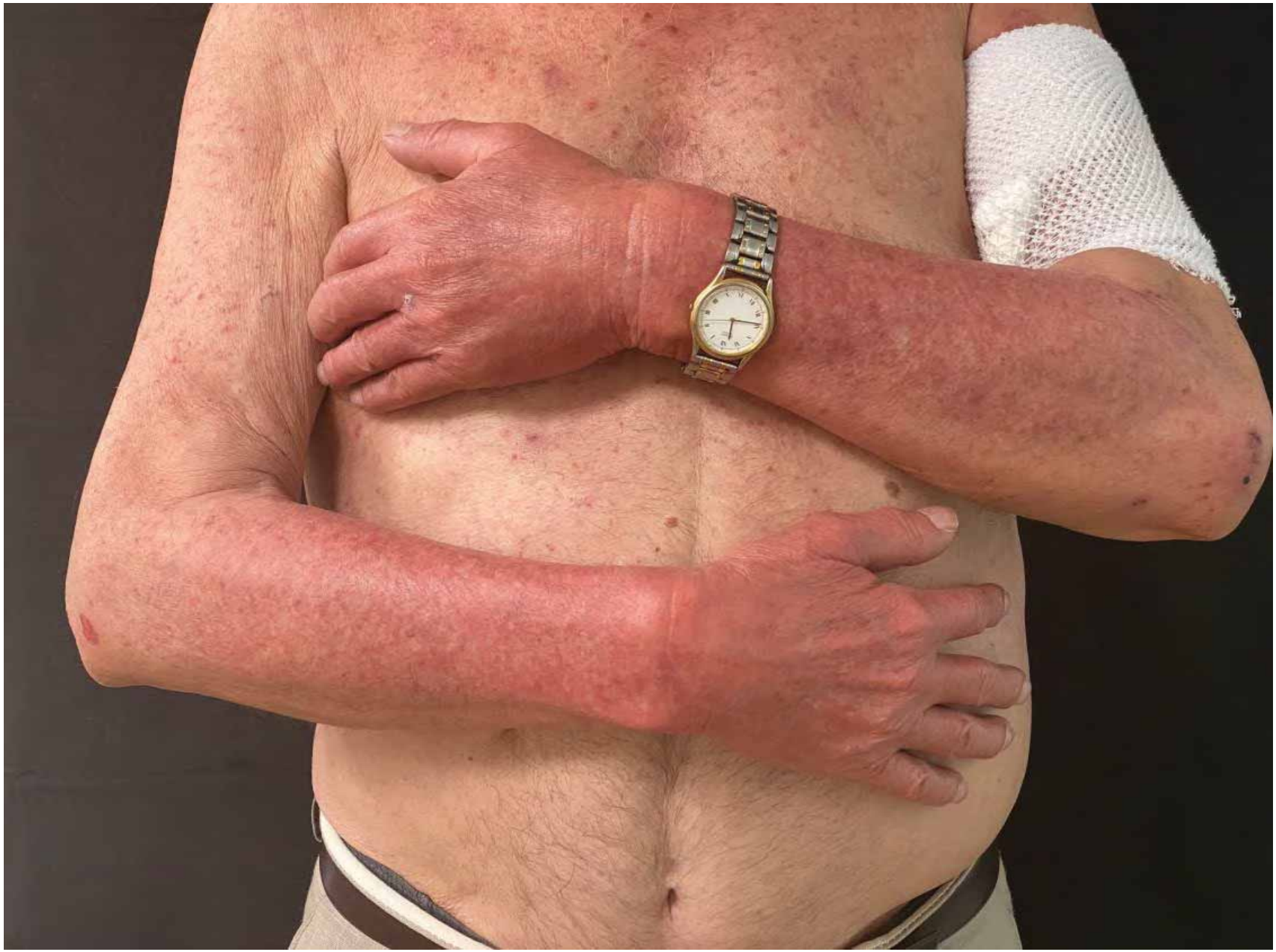
- Approximately, 60 cases of primary cutaneous rhabdomyosarcoma (PCR) have been described
- PCR shows a bimodal age distribution (children and elderly) and slight male predominance
- Three main subtypes of rhabdomyosarcoma: embryonal and alveolar (predominant in children) and pleomorphic (predominant in adults)
- Immunoreactivity for desmin, myogenin and MYOD1. In rare cases, cytokeratin immunoreactivity has been found in PCR.
- Follow-up of PCR showed aggressive behavior in both children and adults

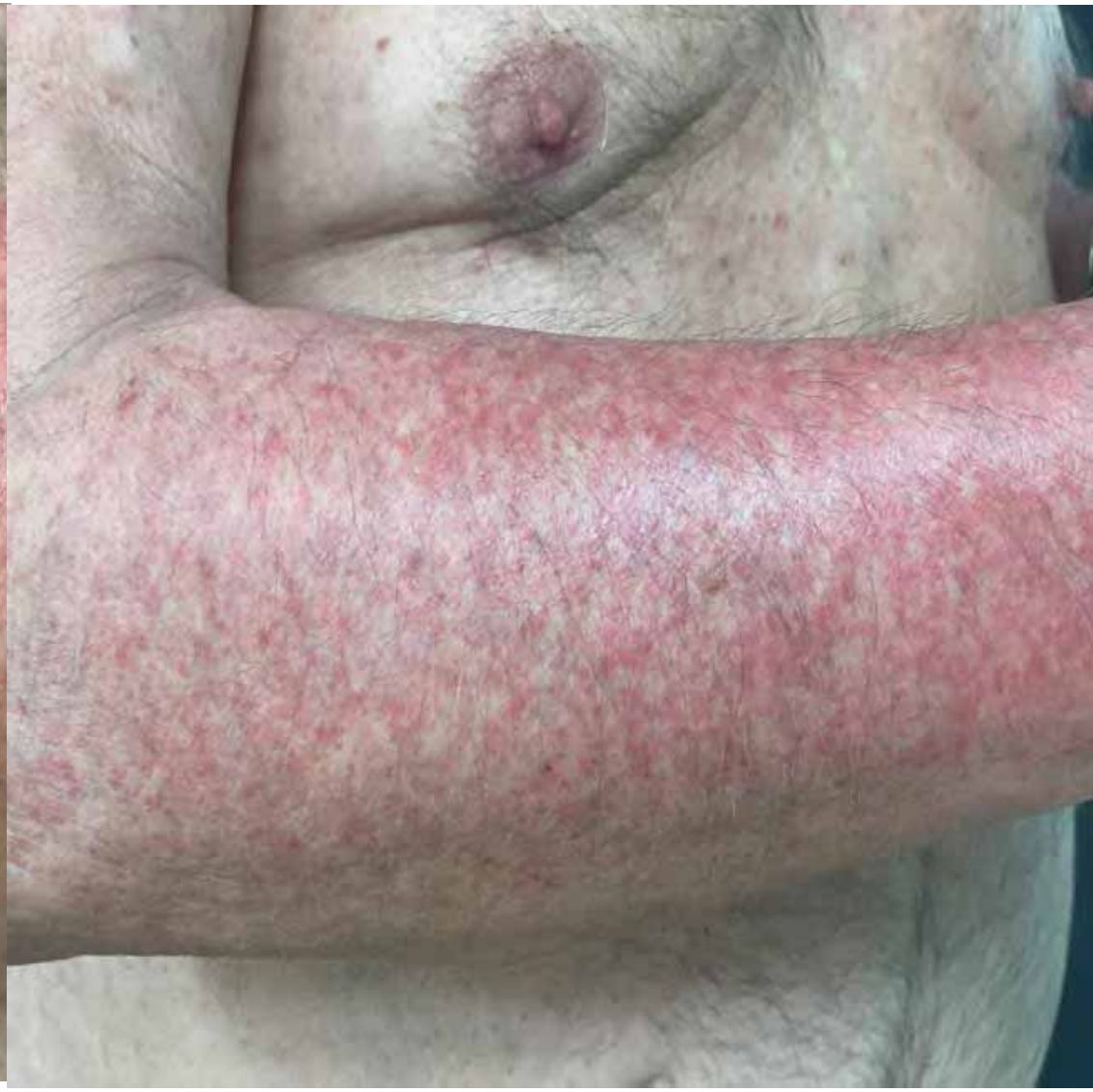
Case 8

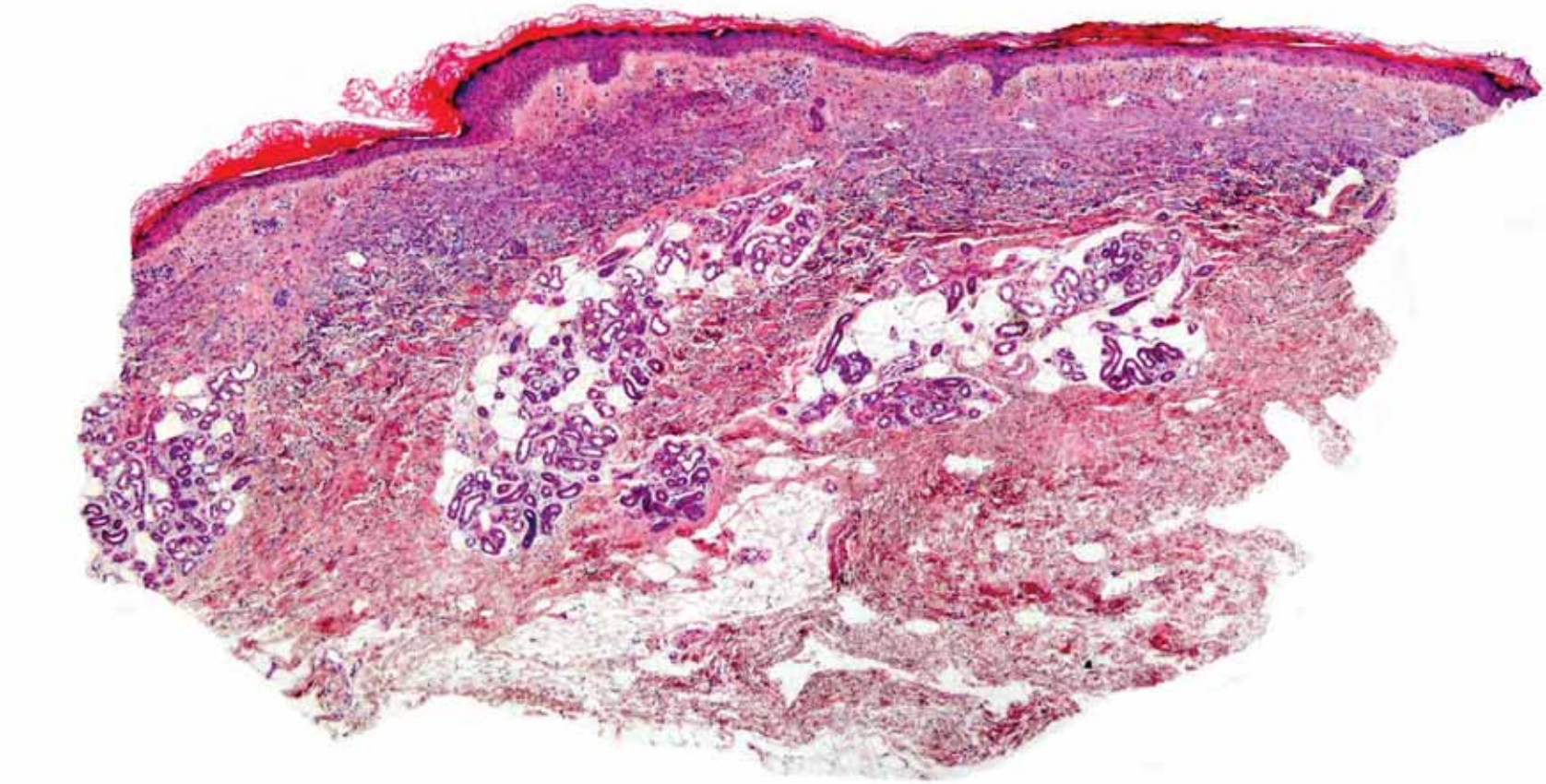
- An 86-year-old male with mantle cell lymphoma, which progressed in spite of two previous different chemotherapy regimens, started treatment with loncastuximab and ibrutinib. Three days later, cutaneous lesions appeared on the face, anterior chest, forearms and hands

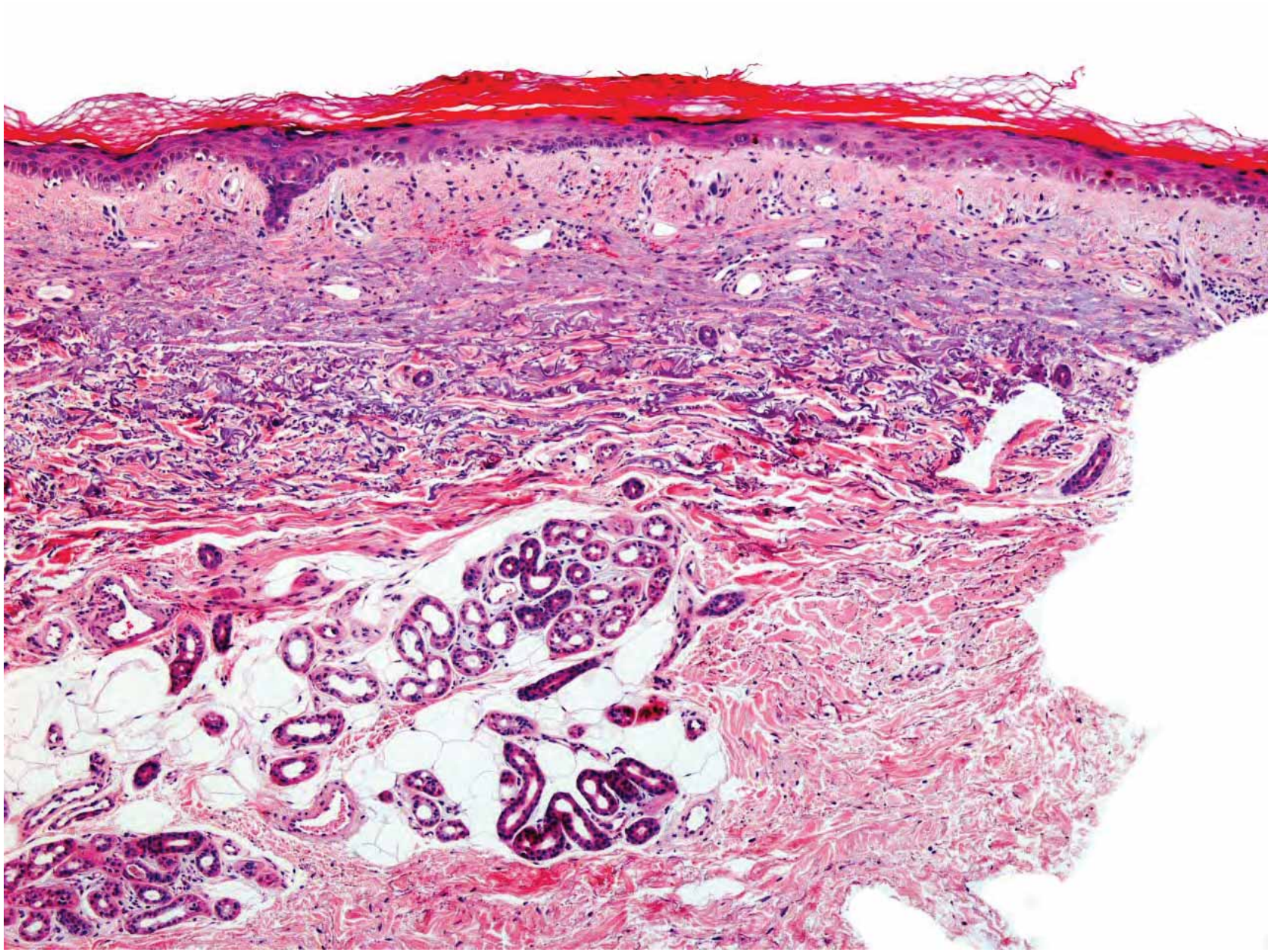


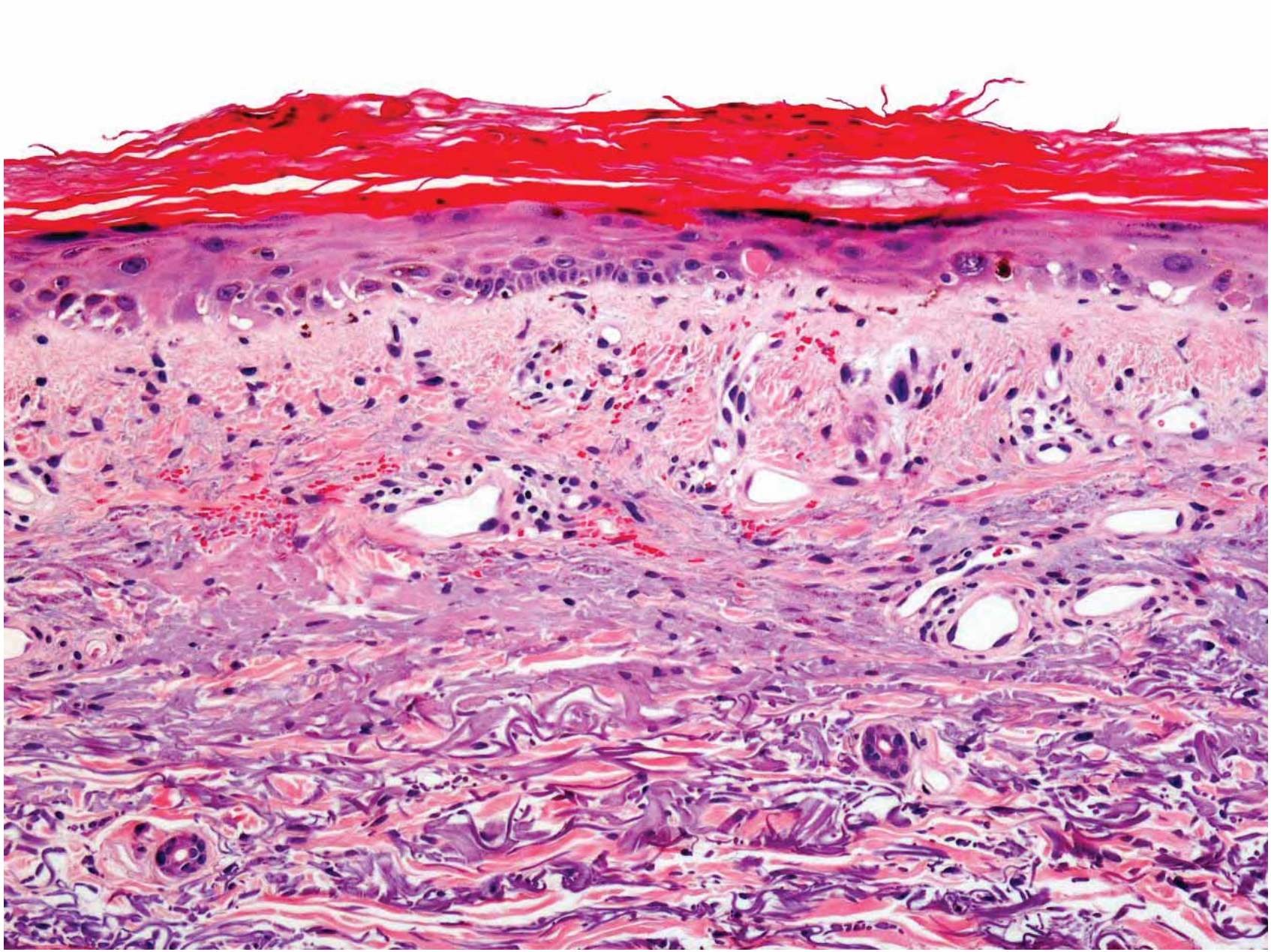


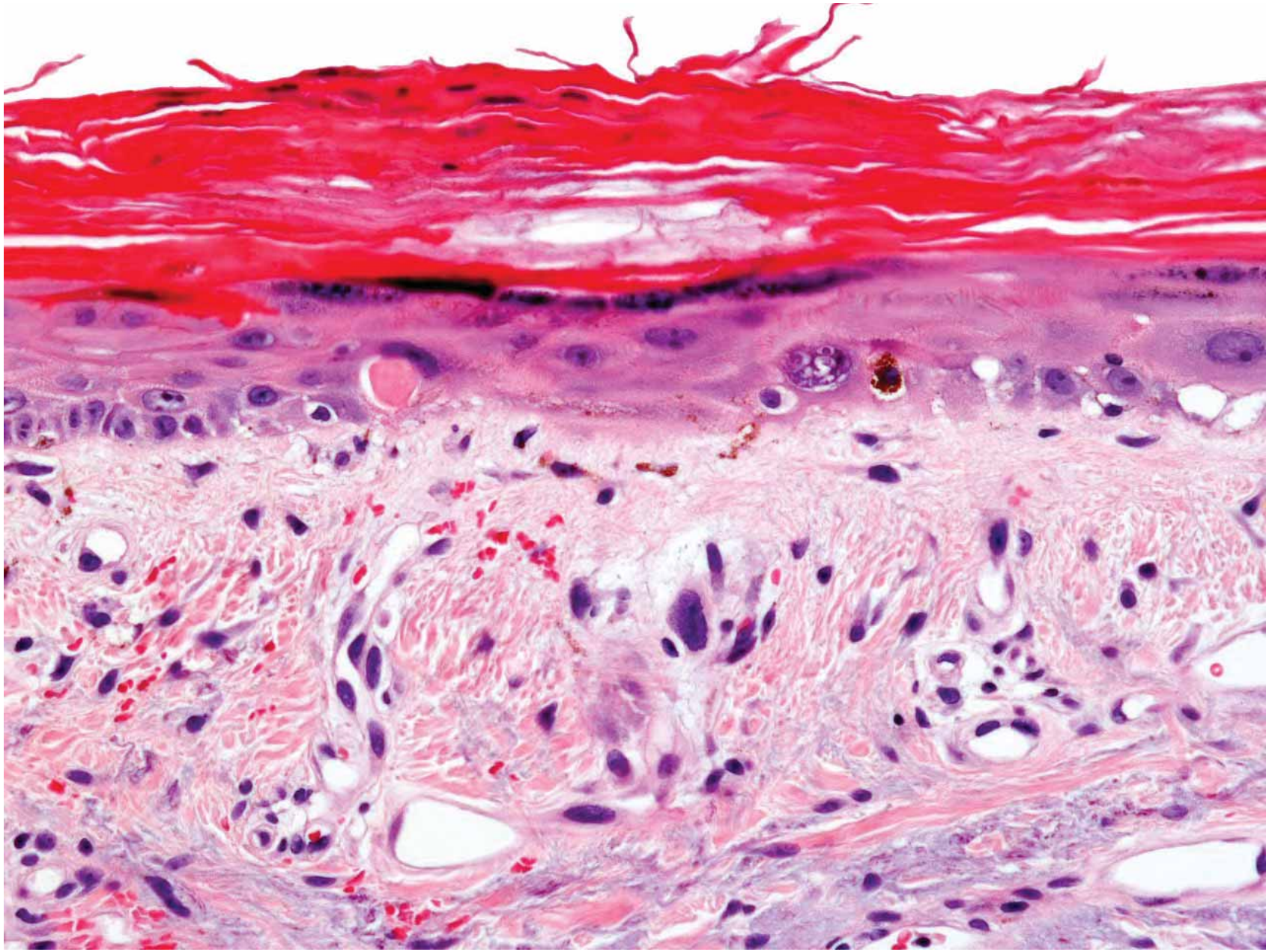


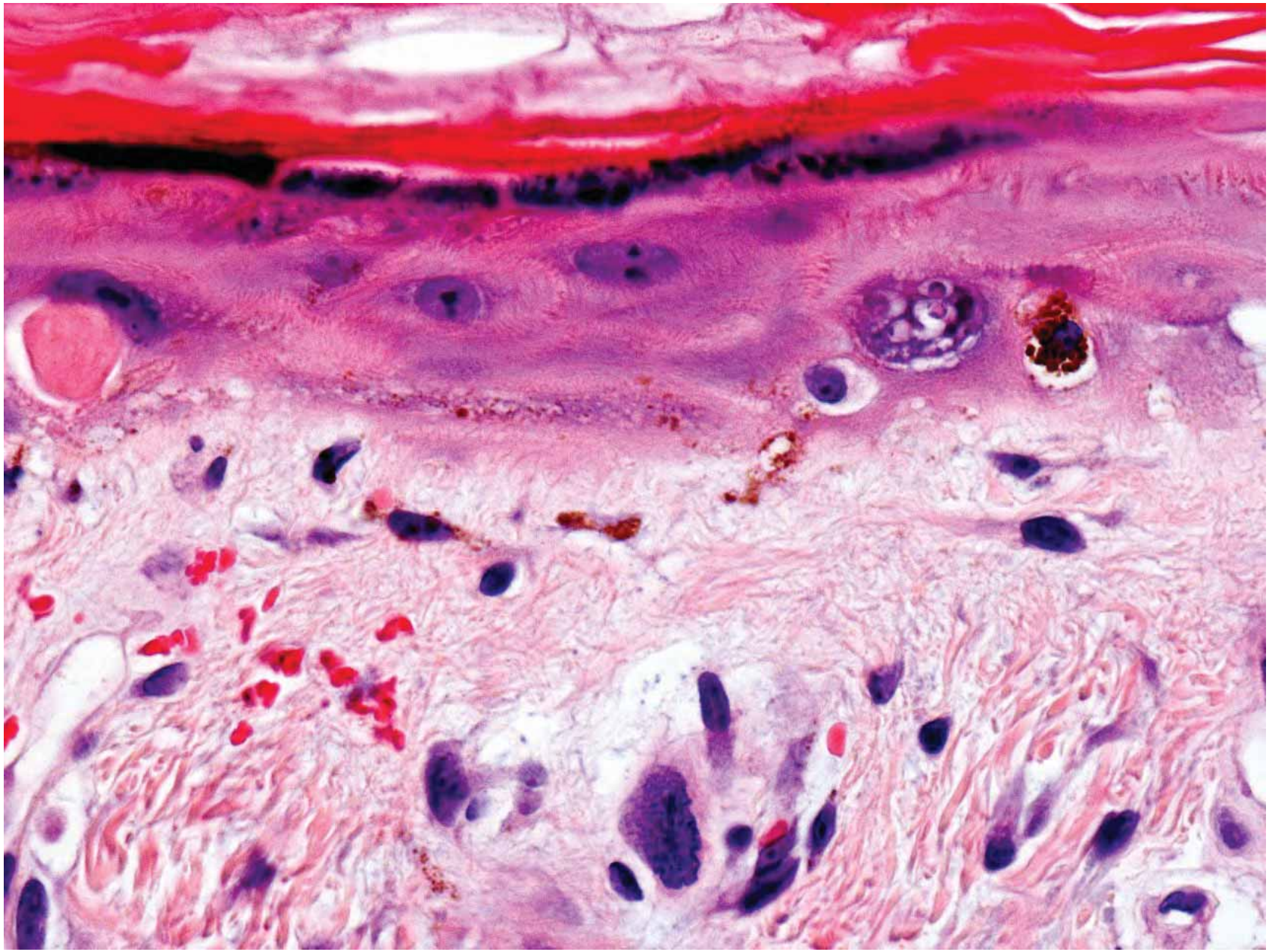



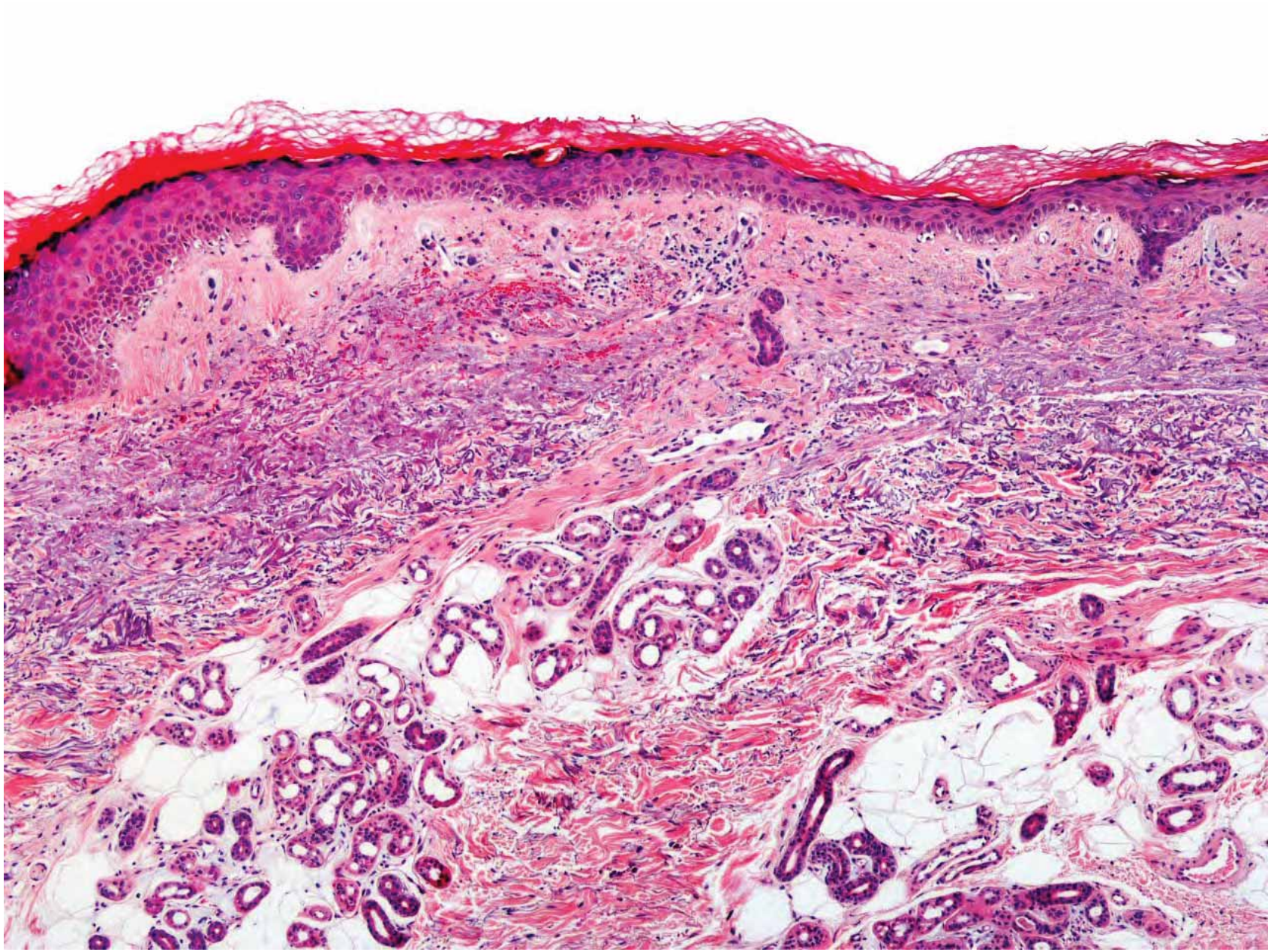


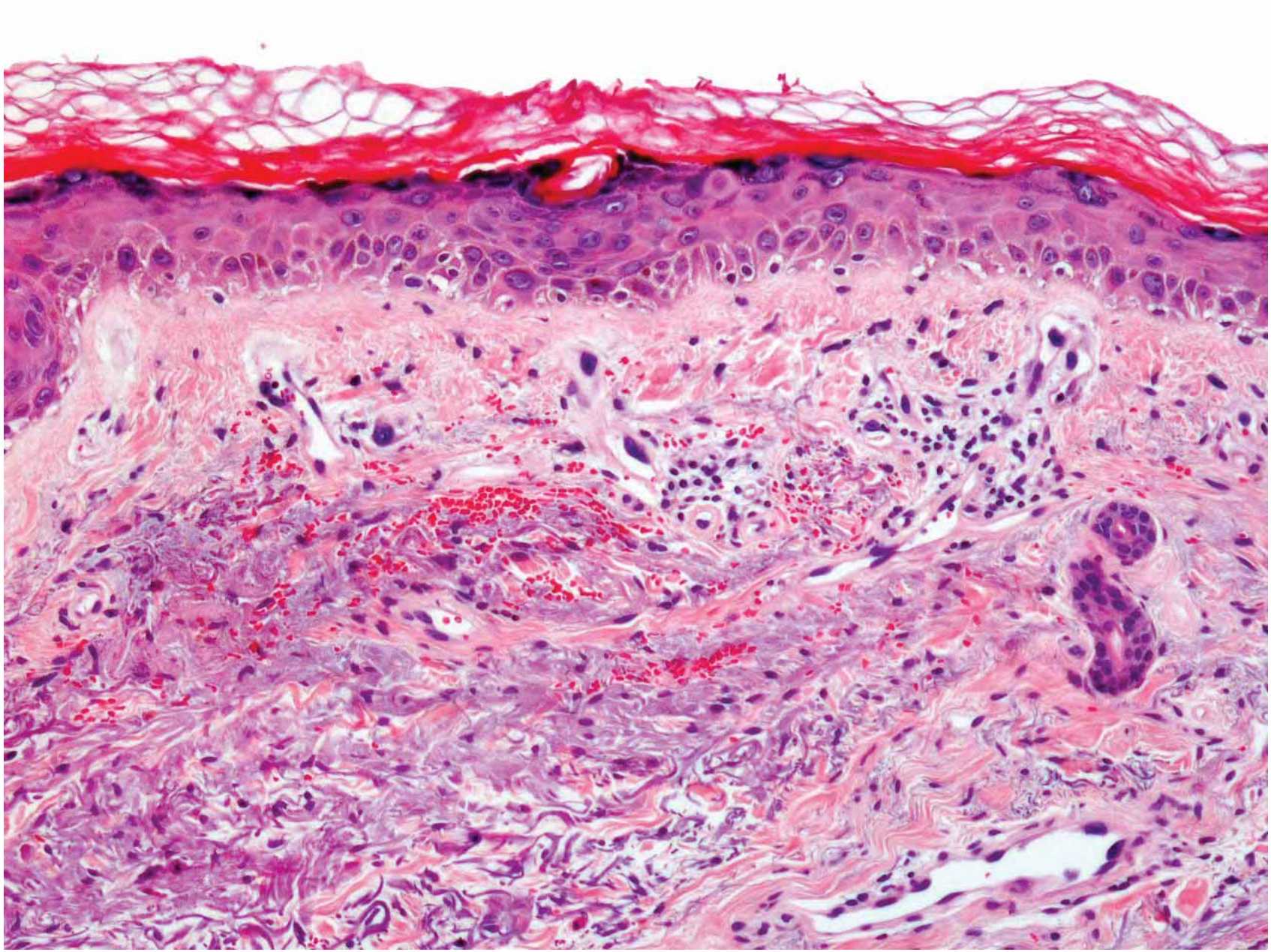


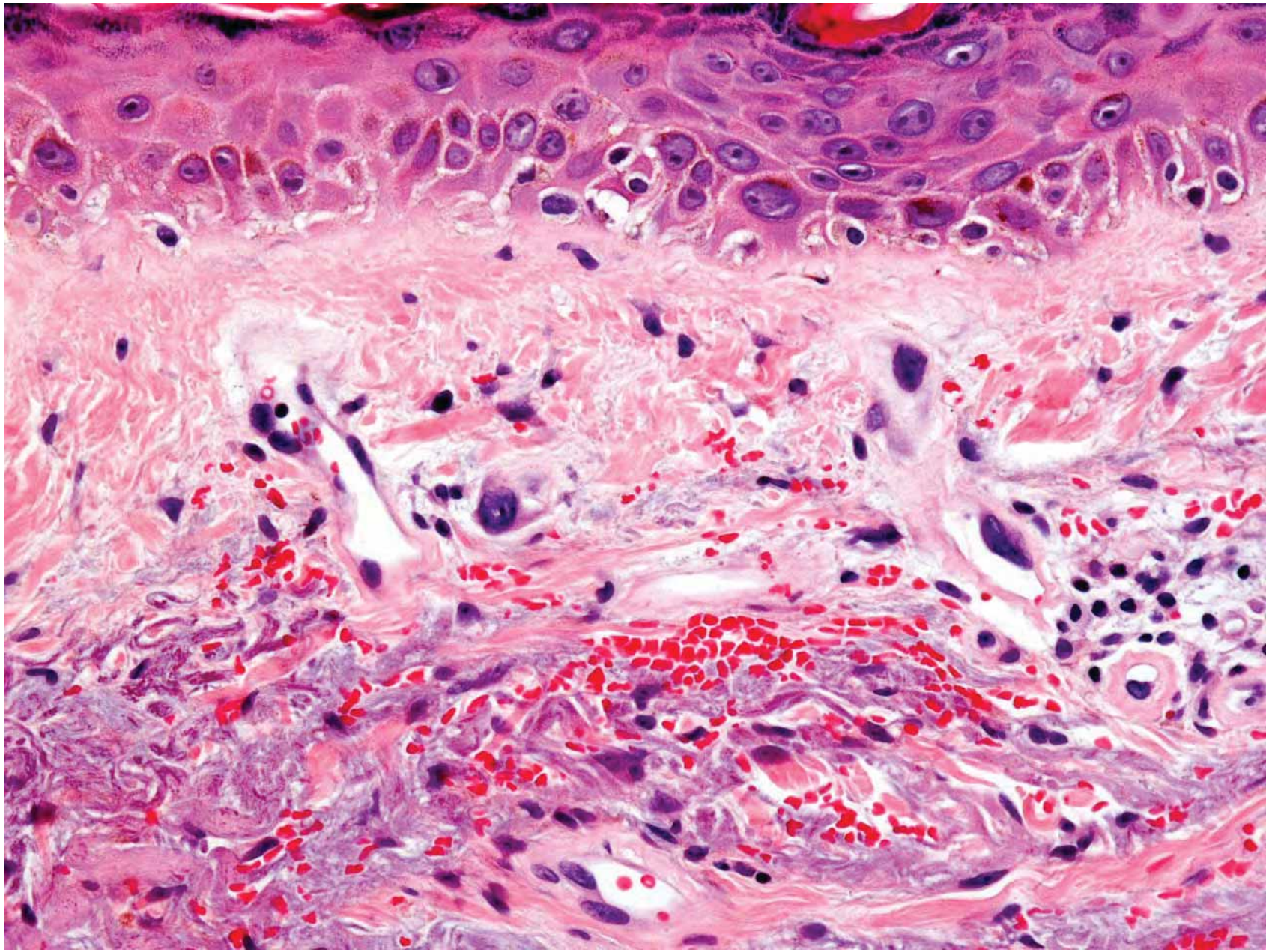


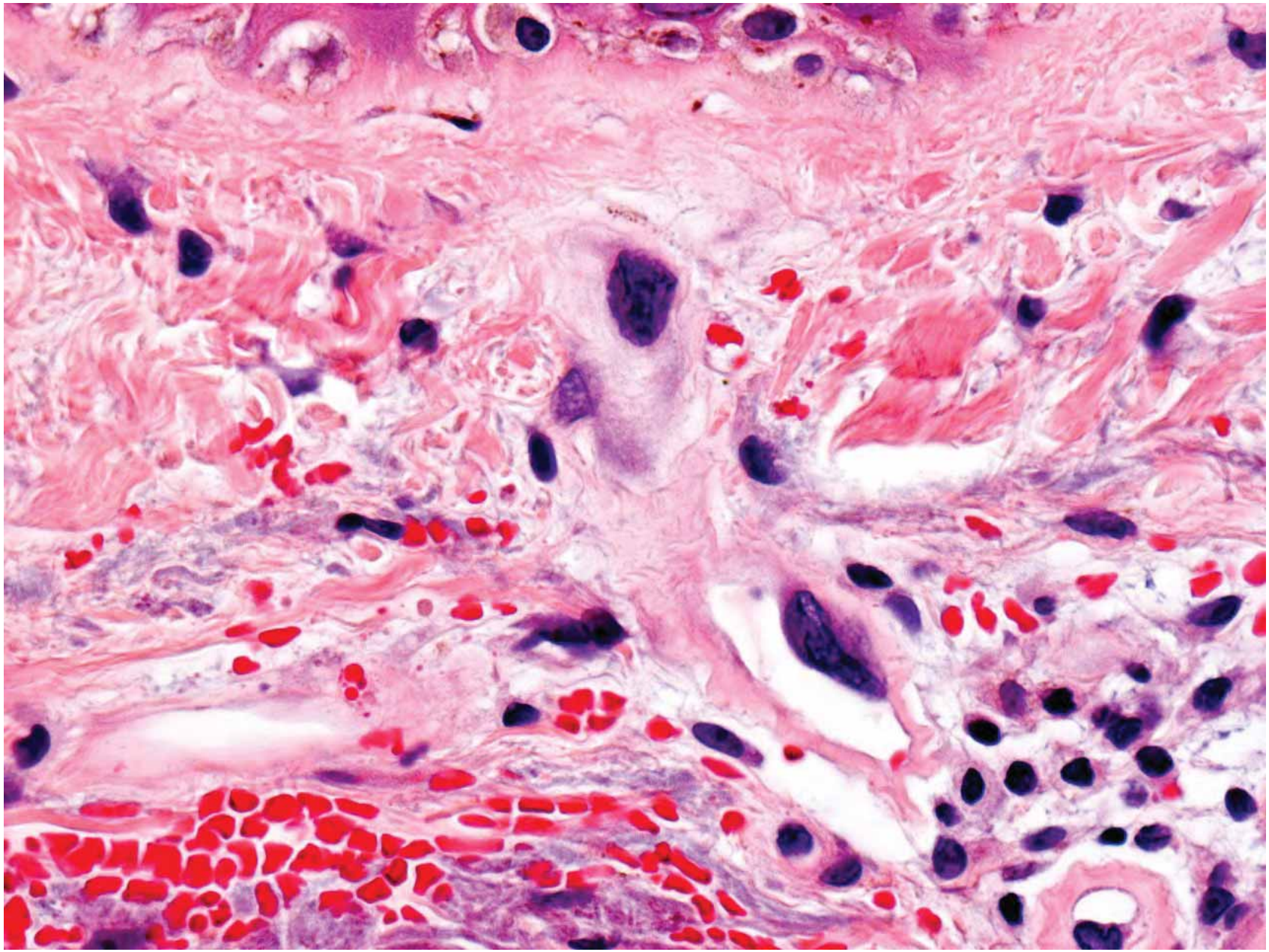


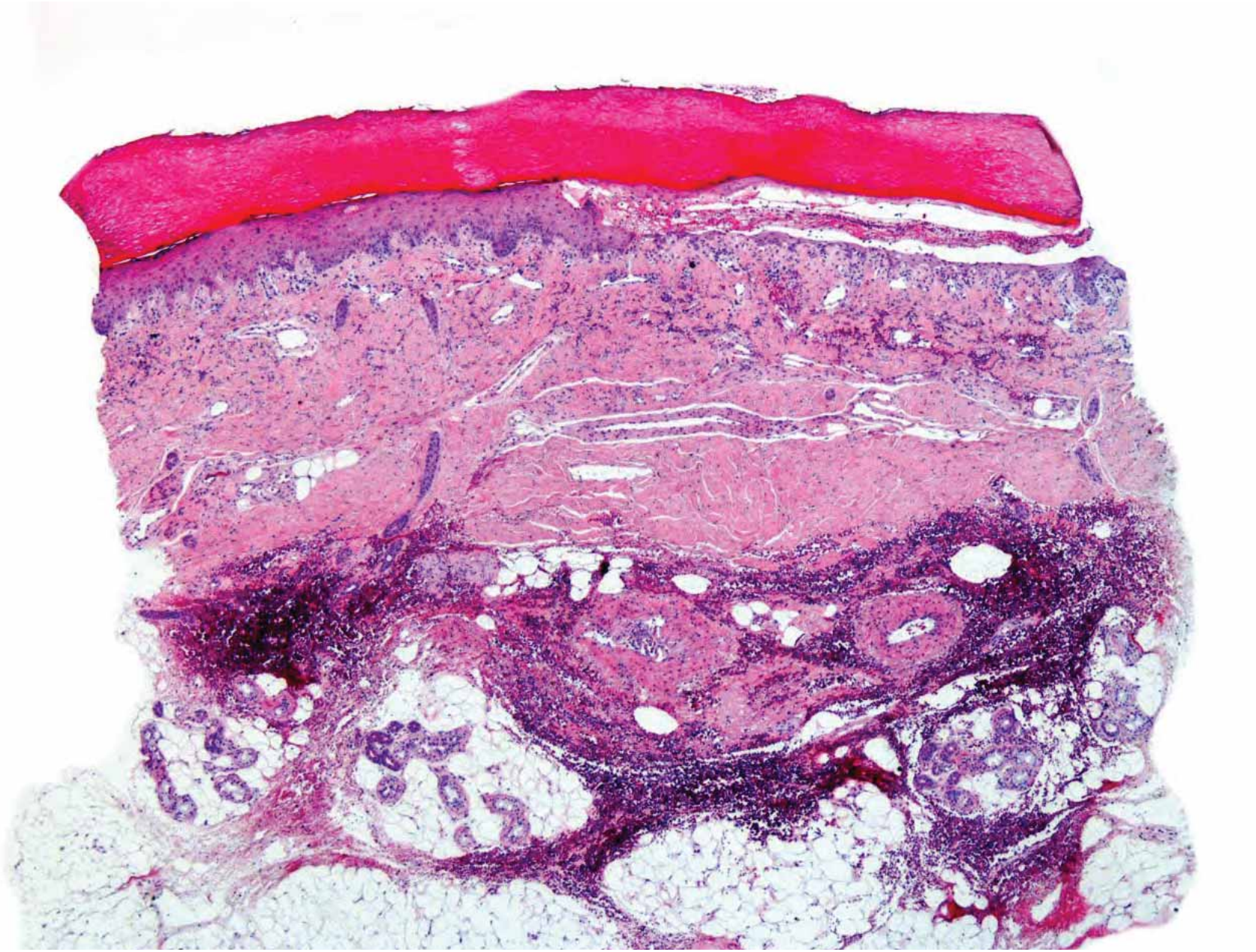


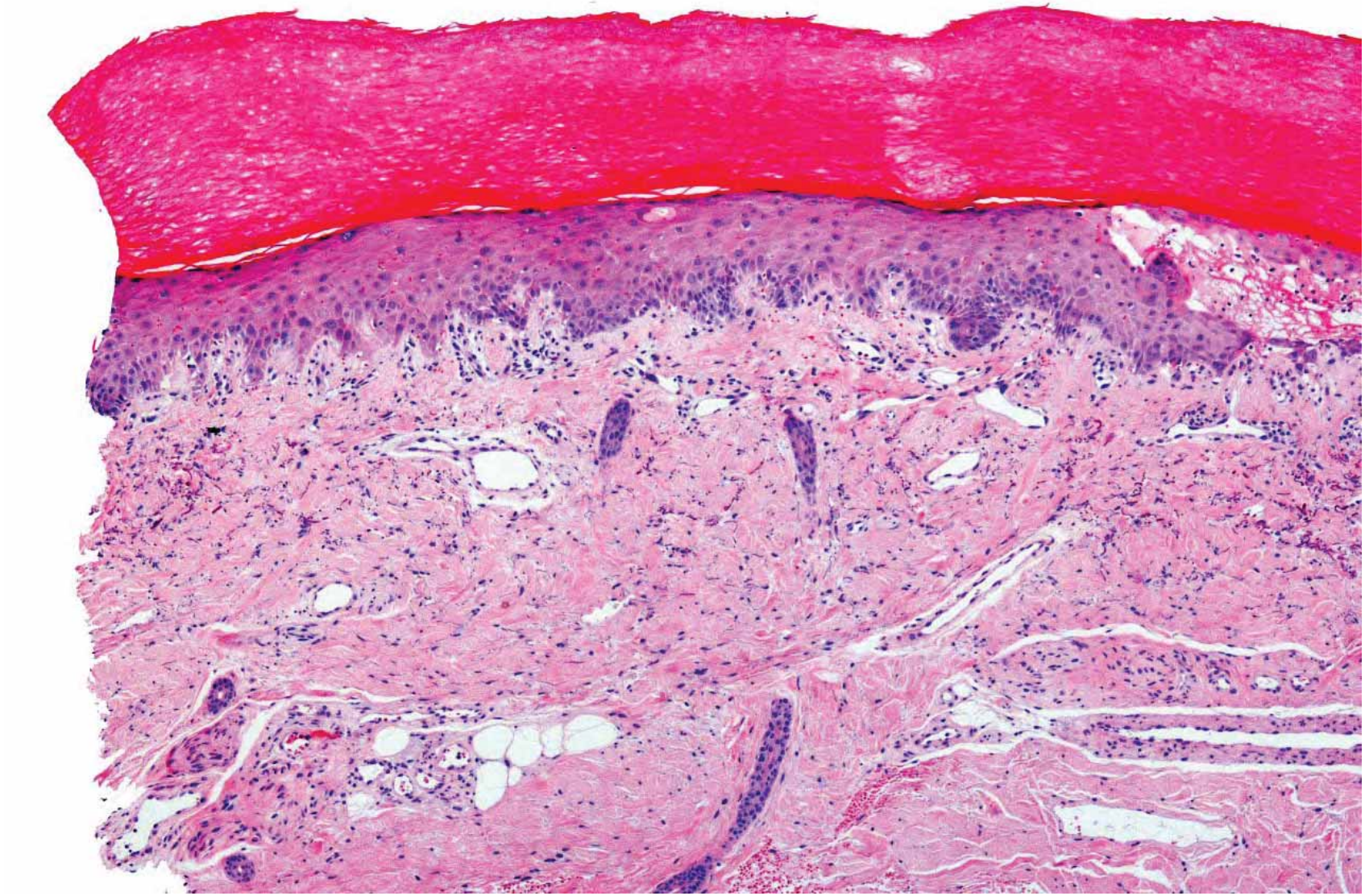


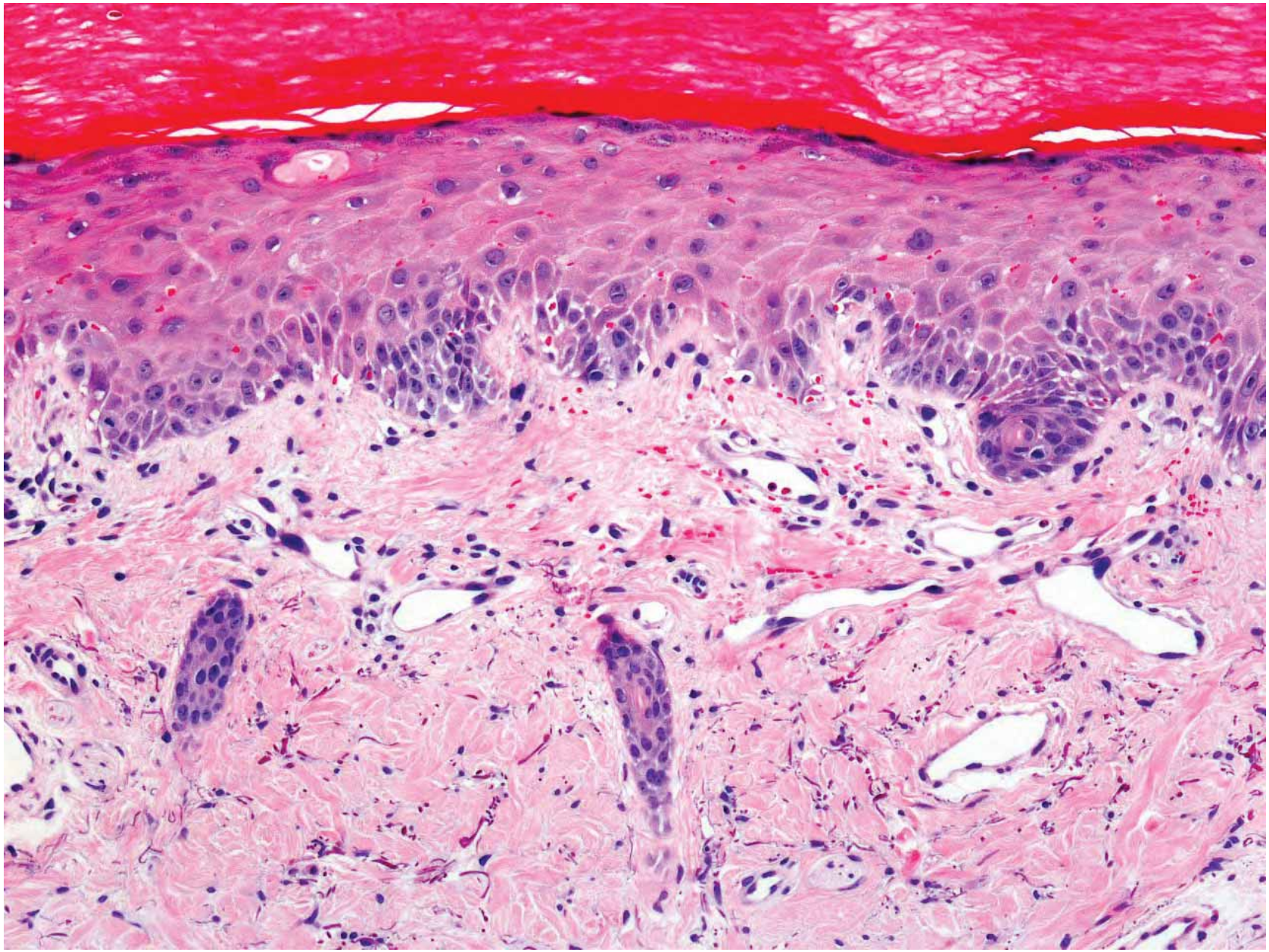


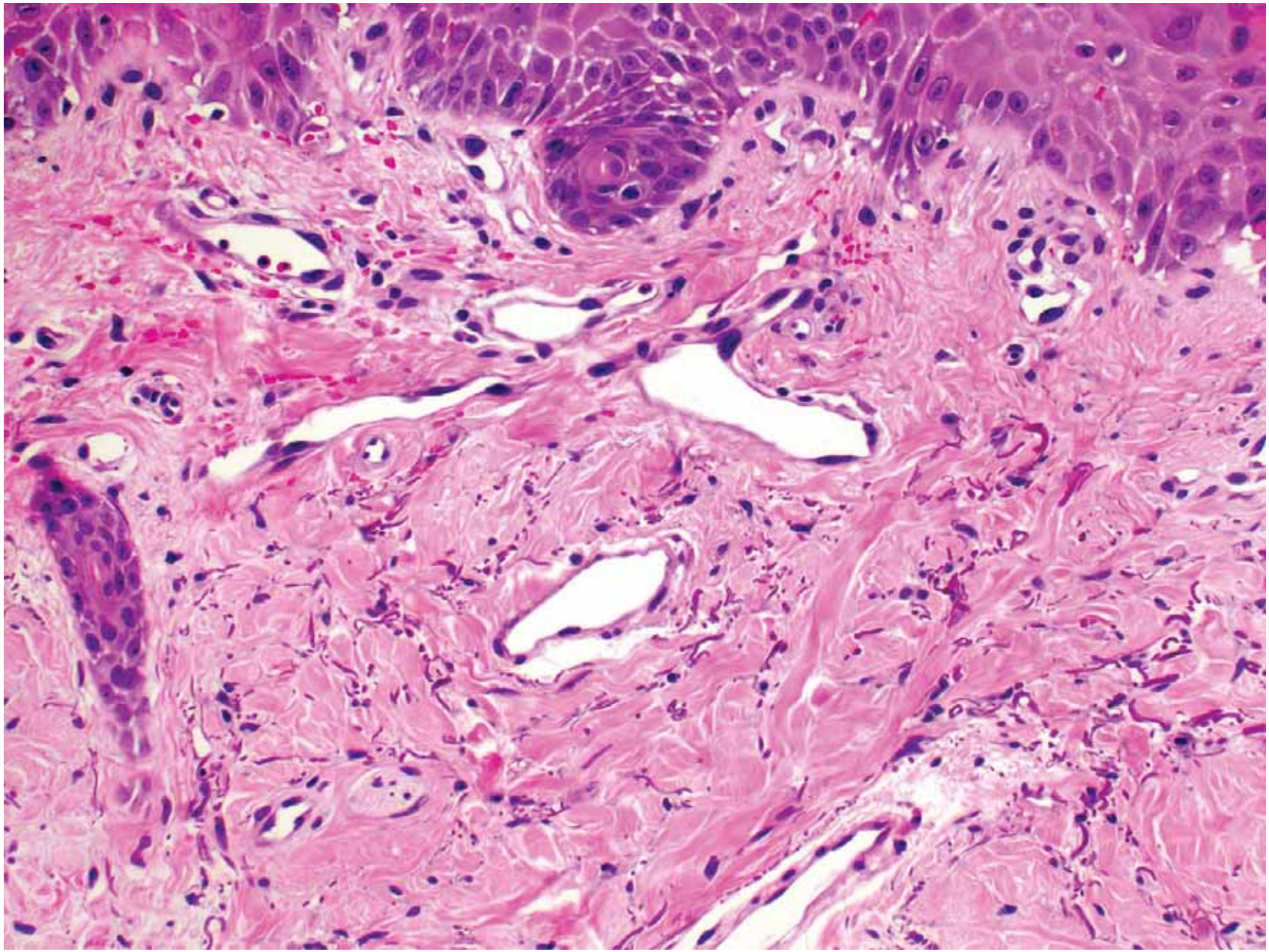


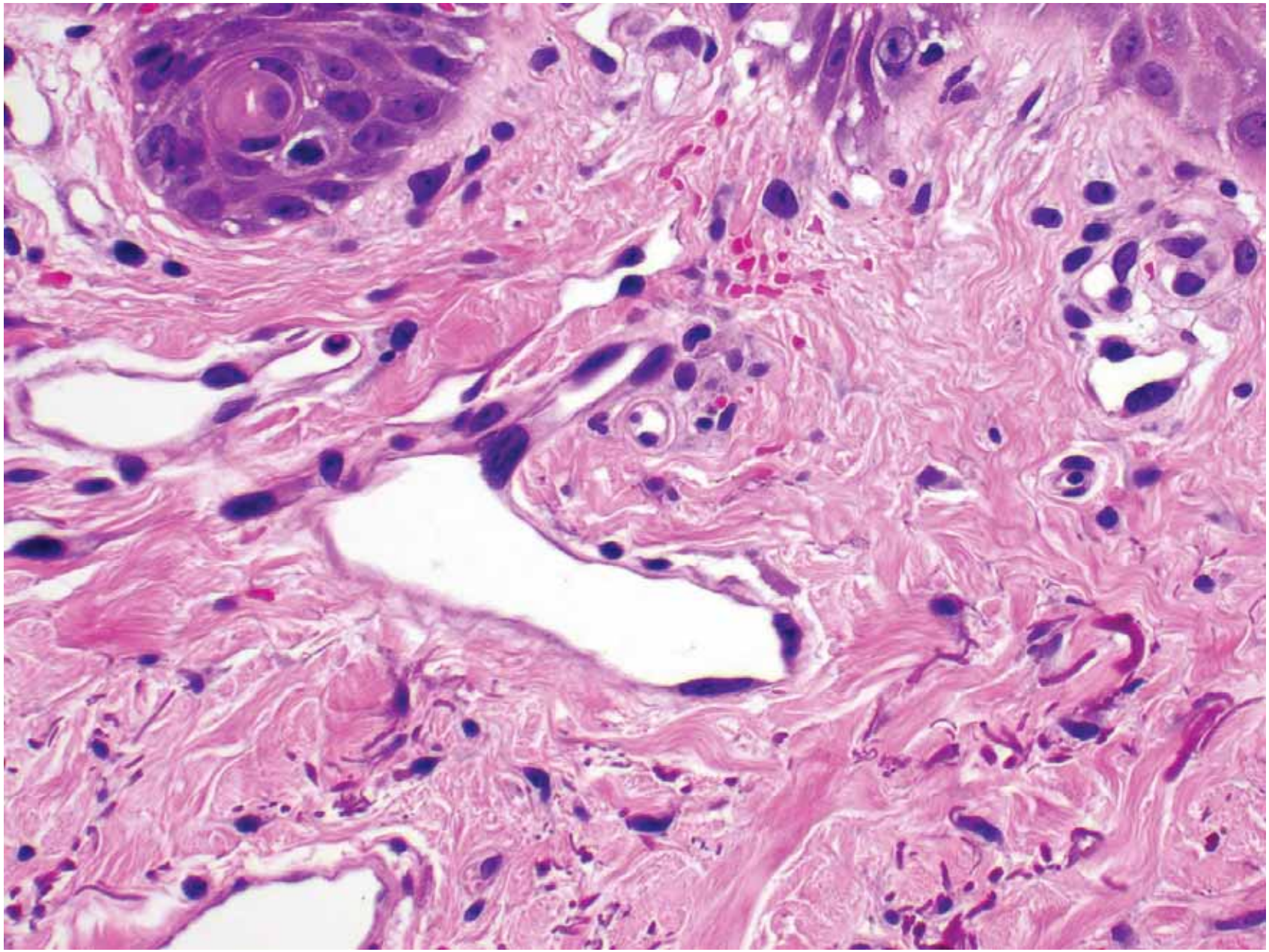


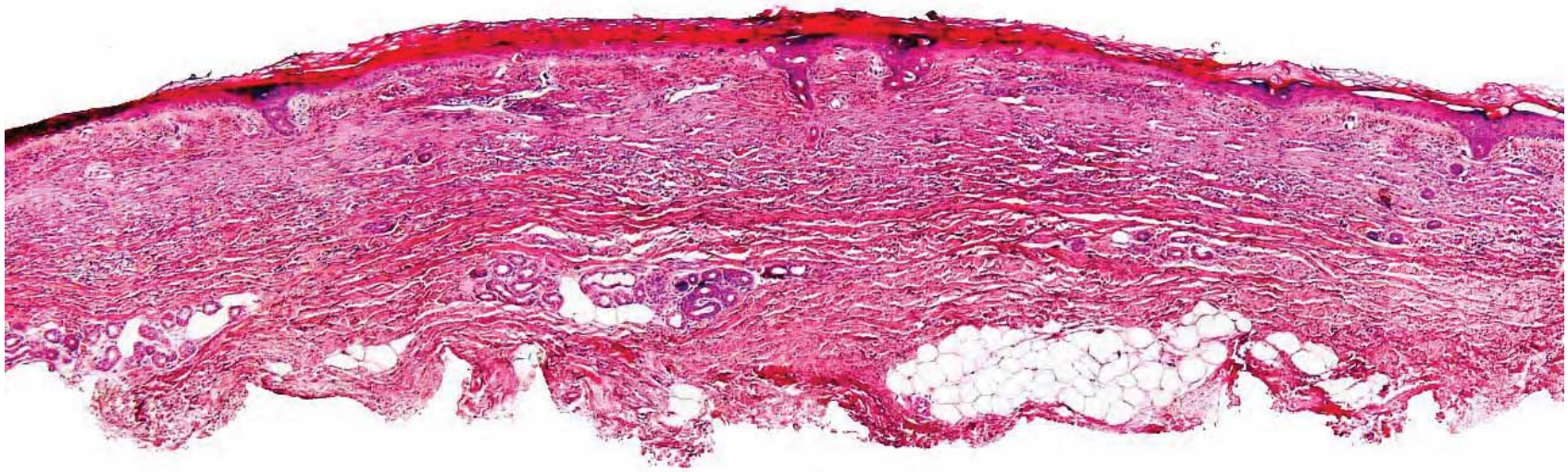


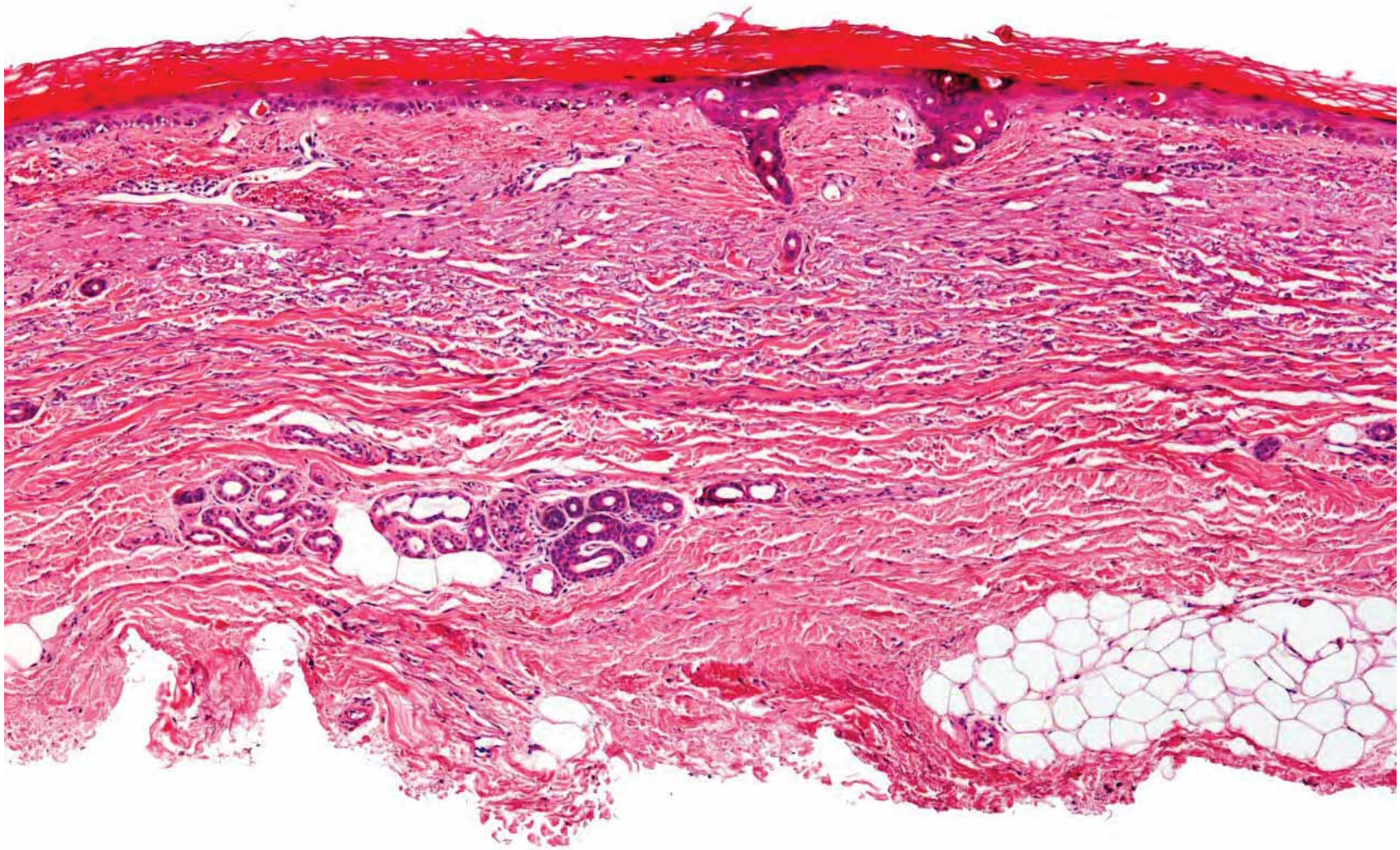


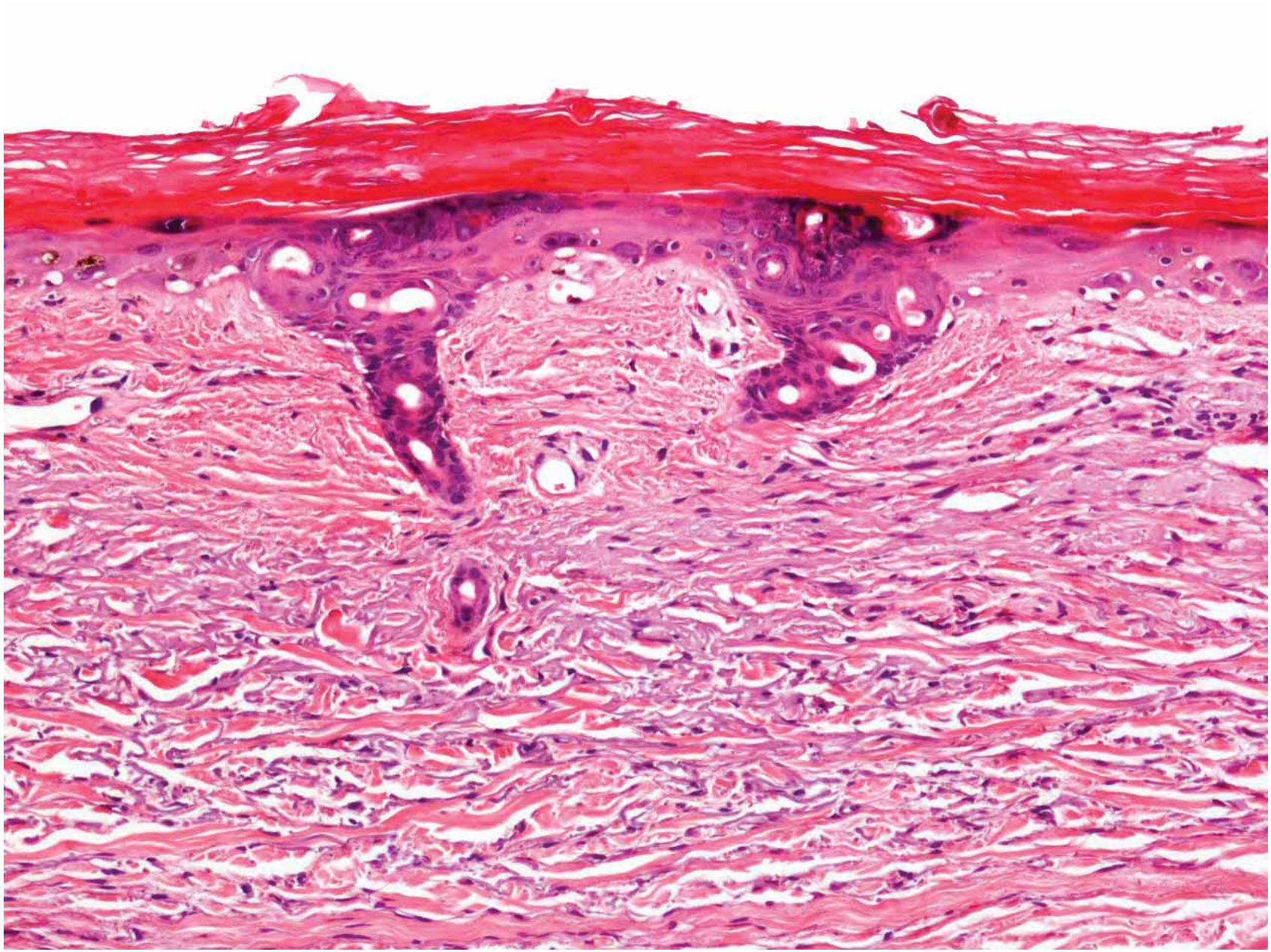


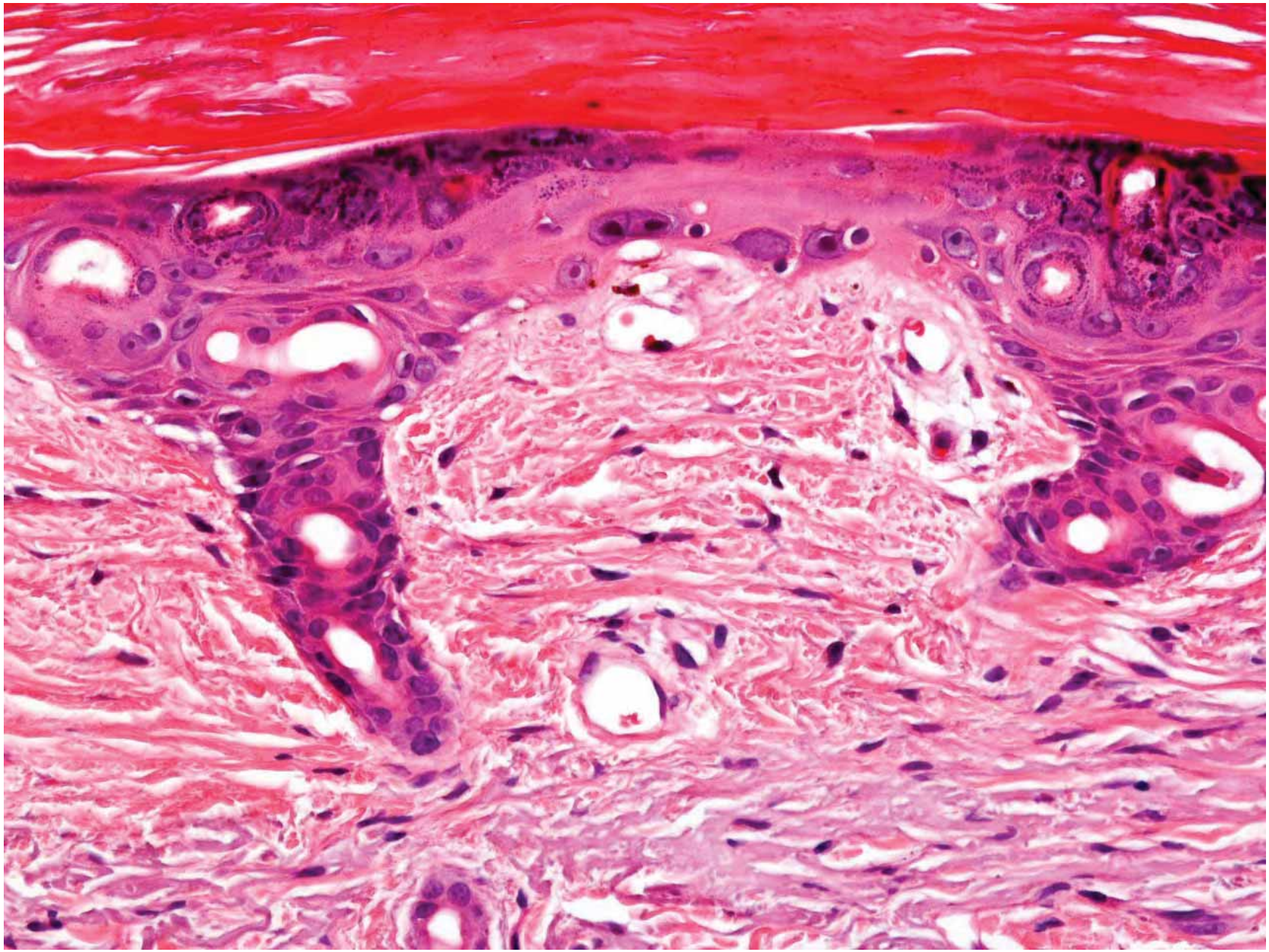


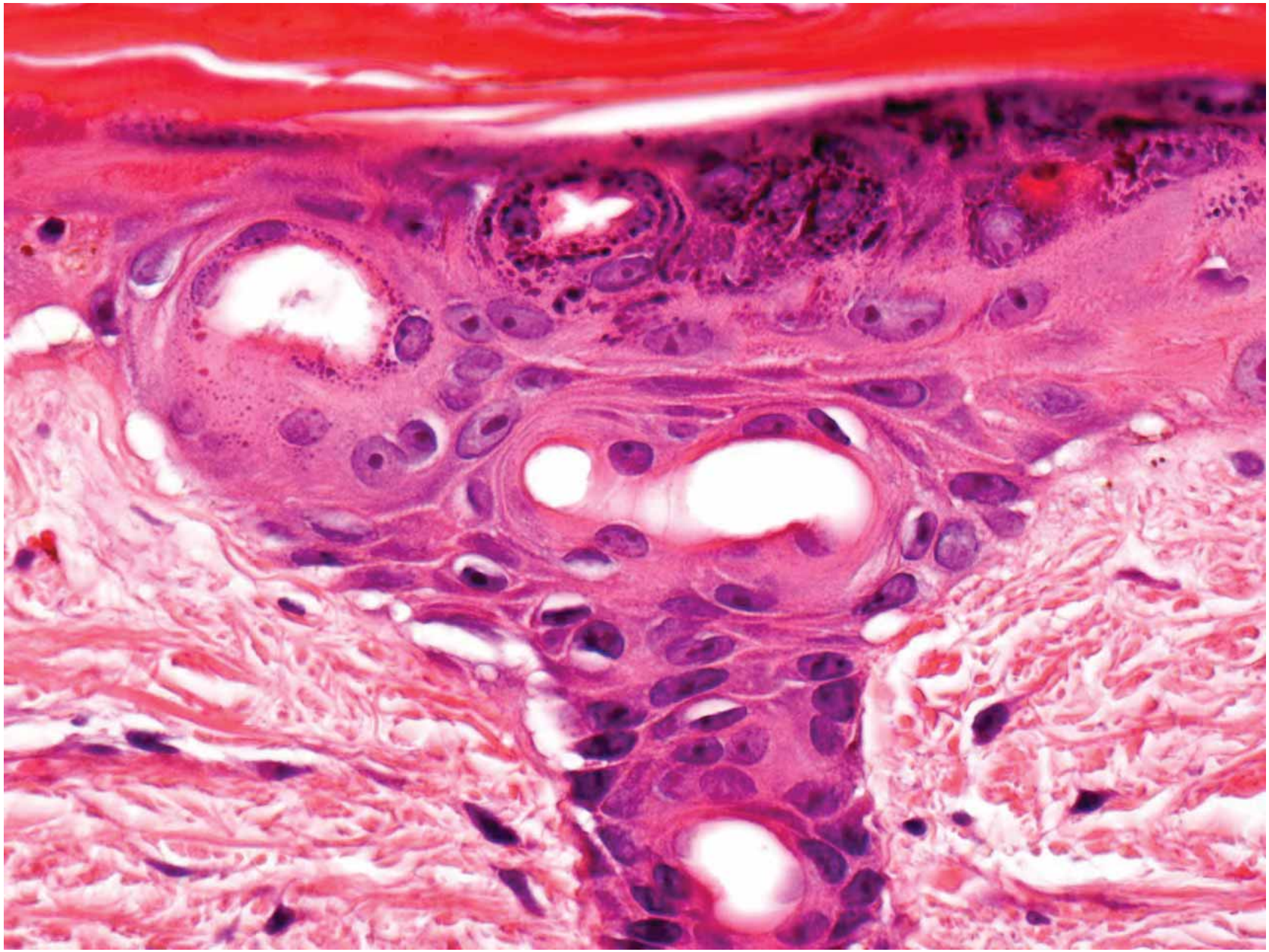


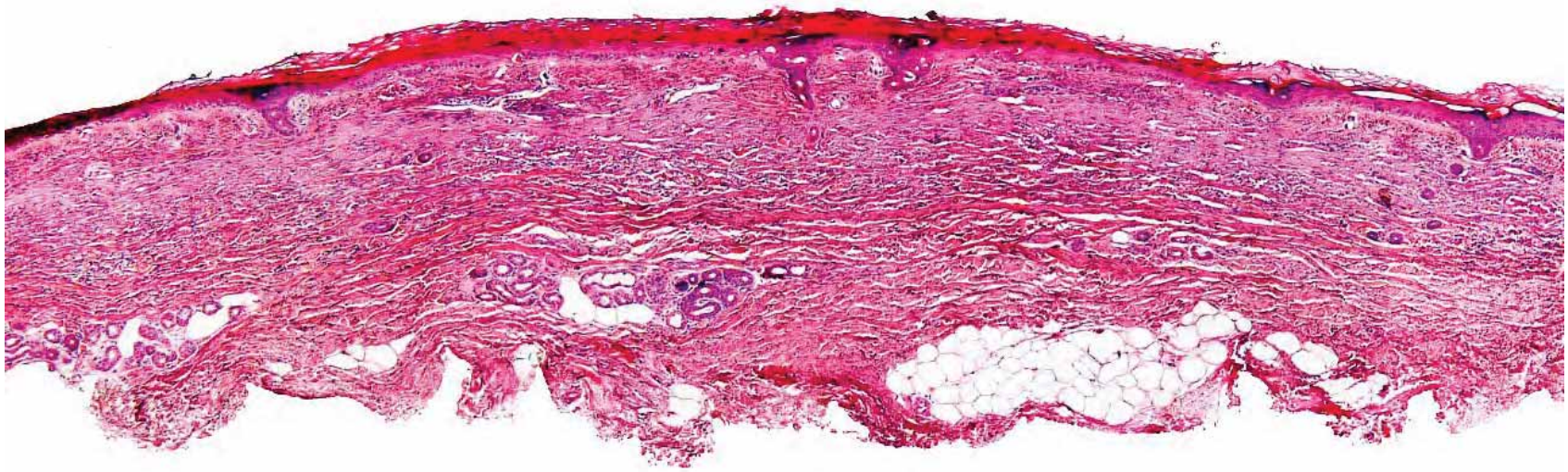


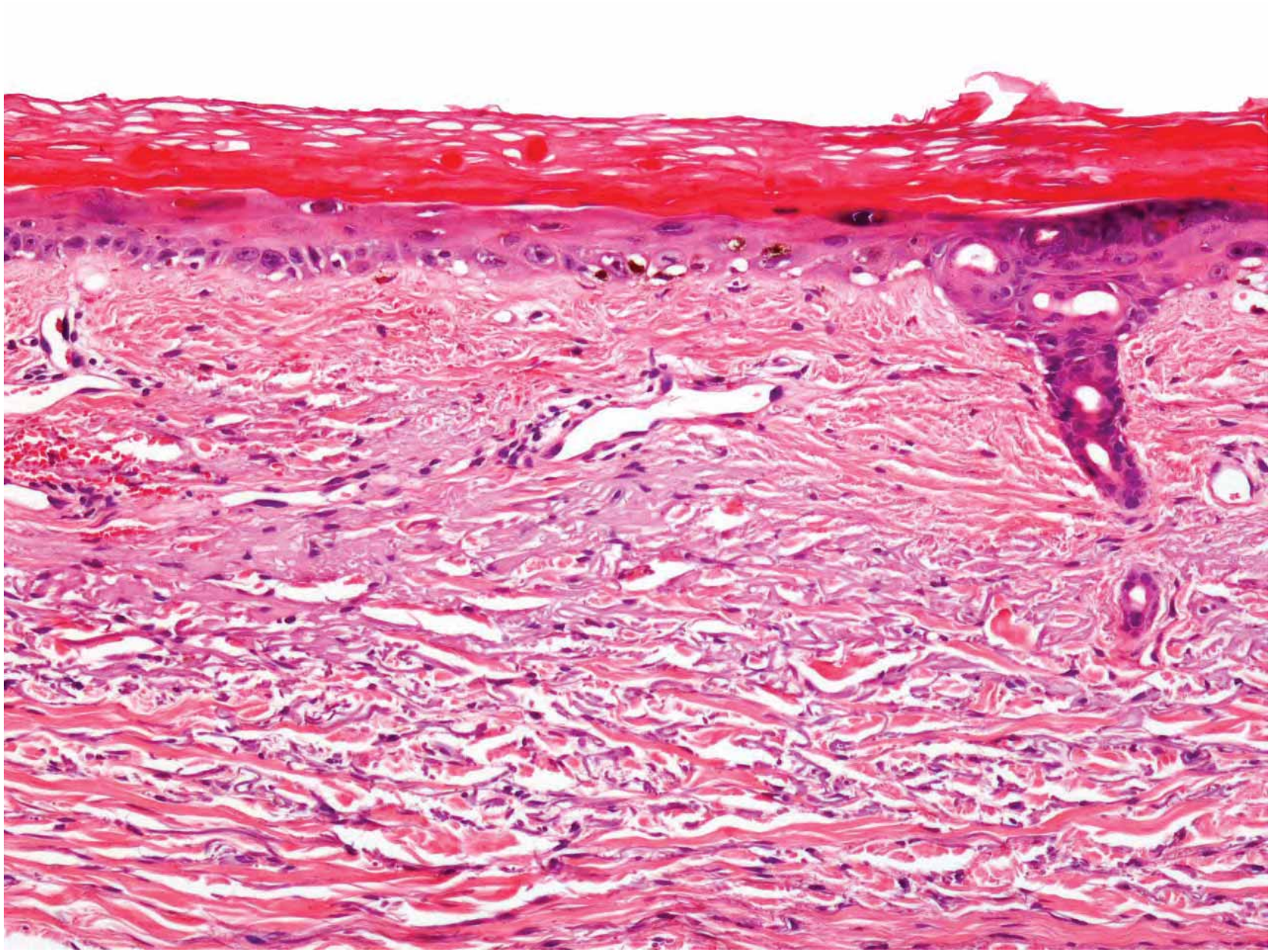


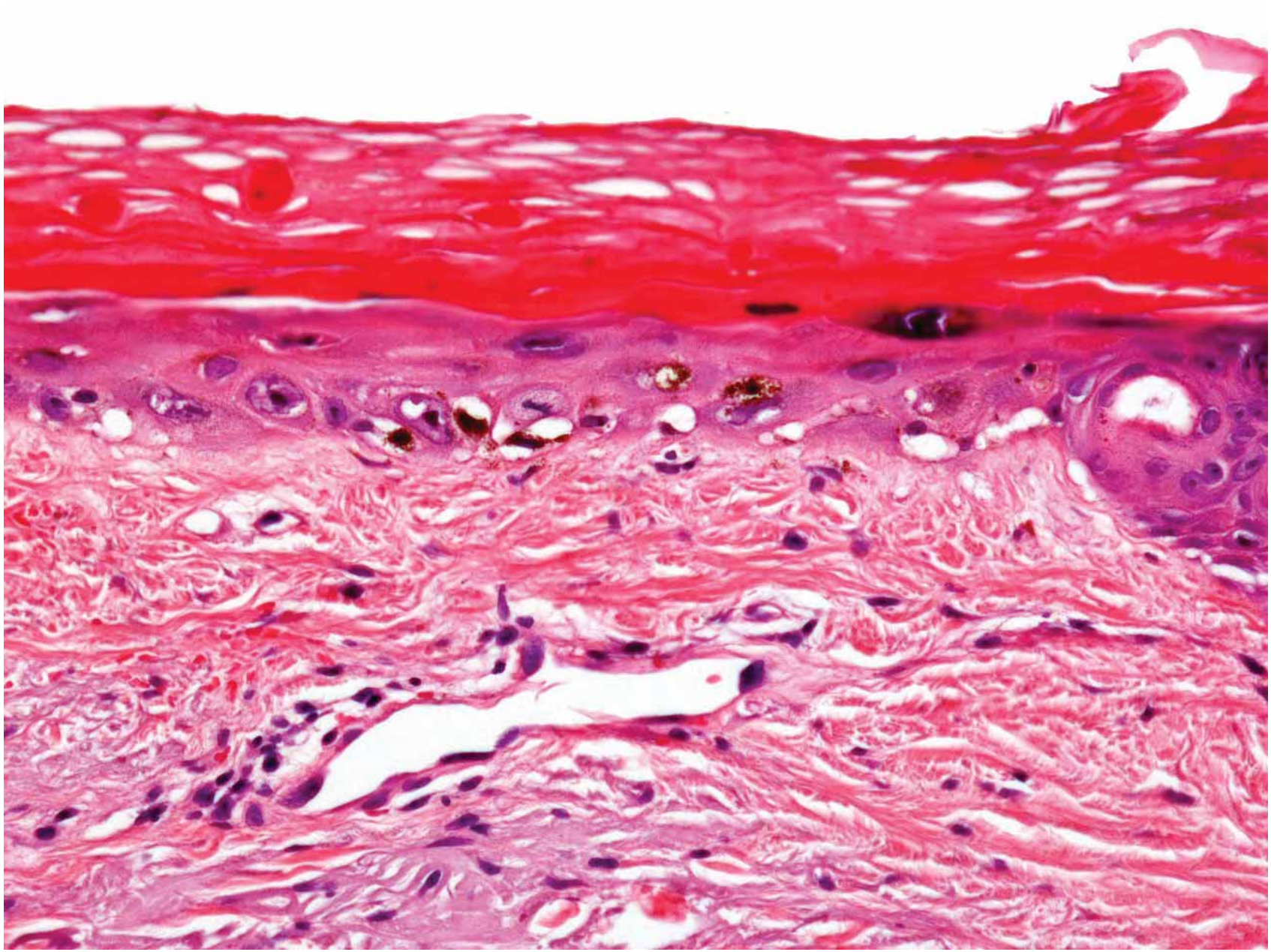


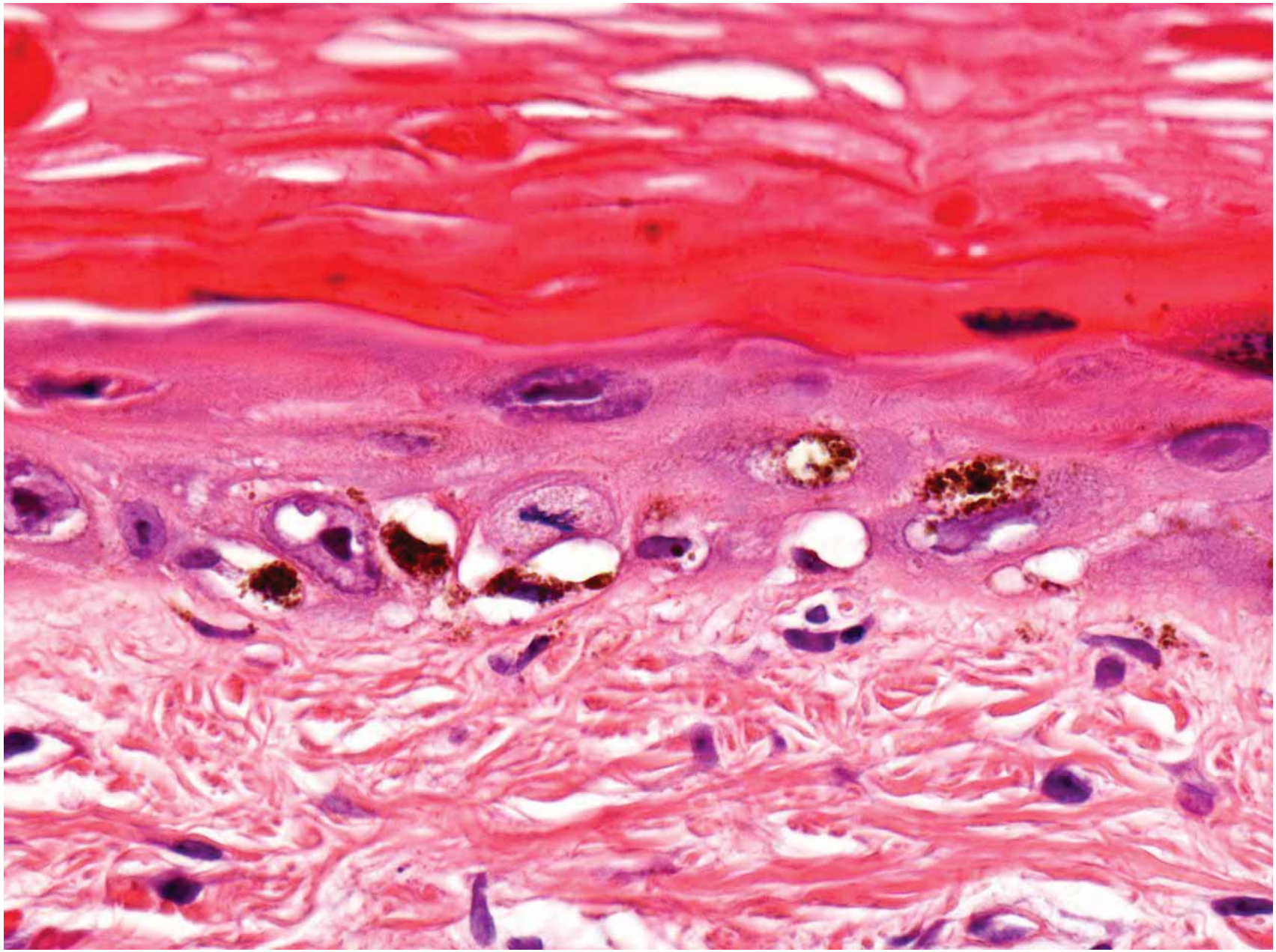


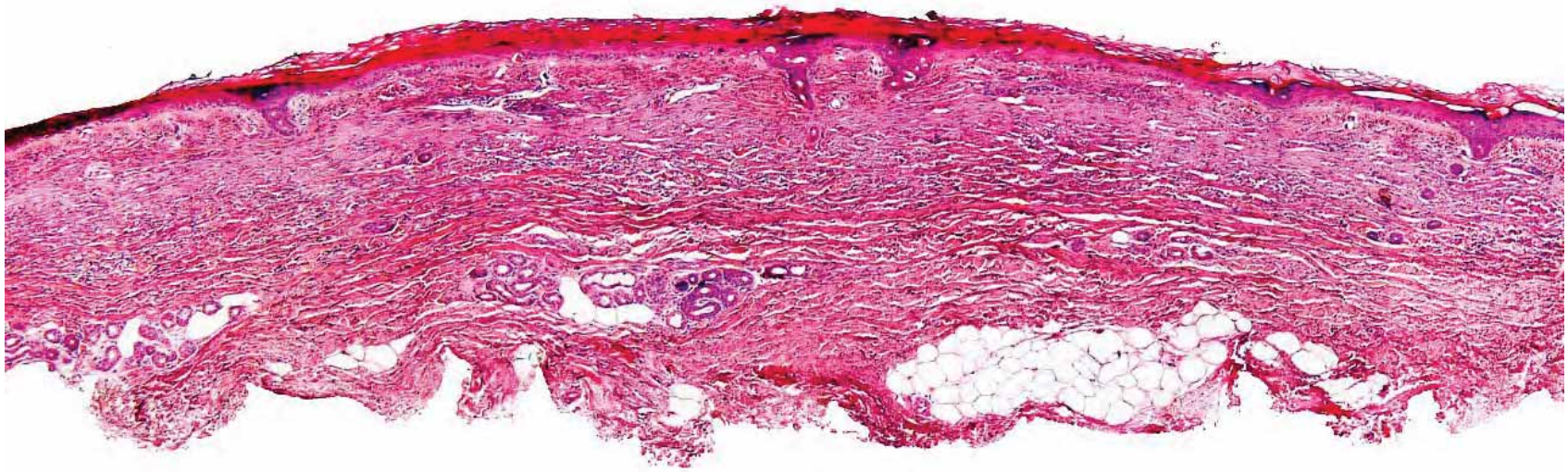


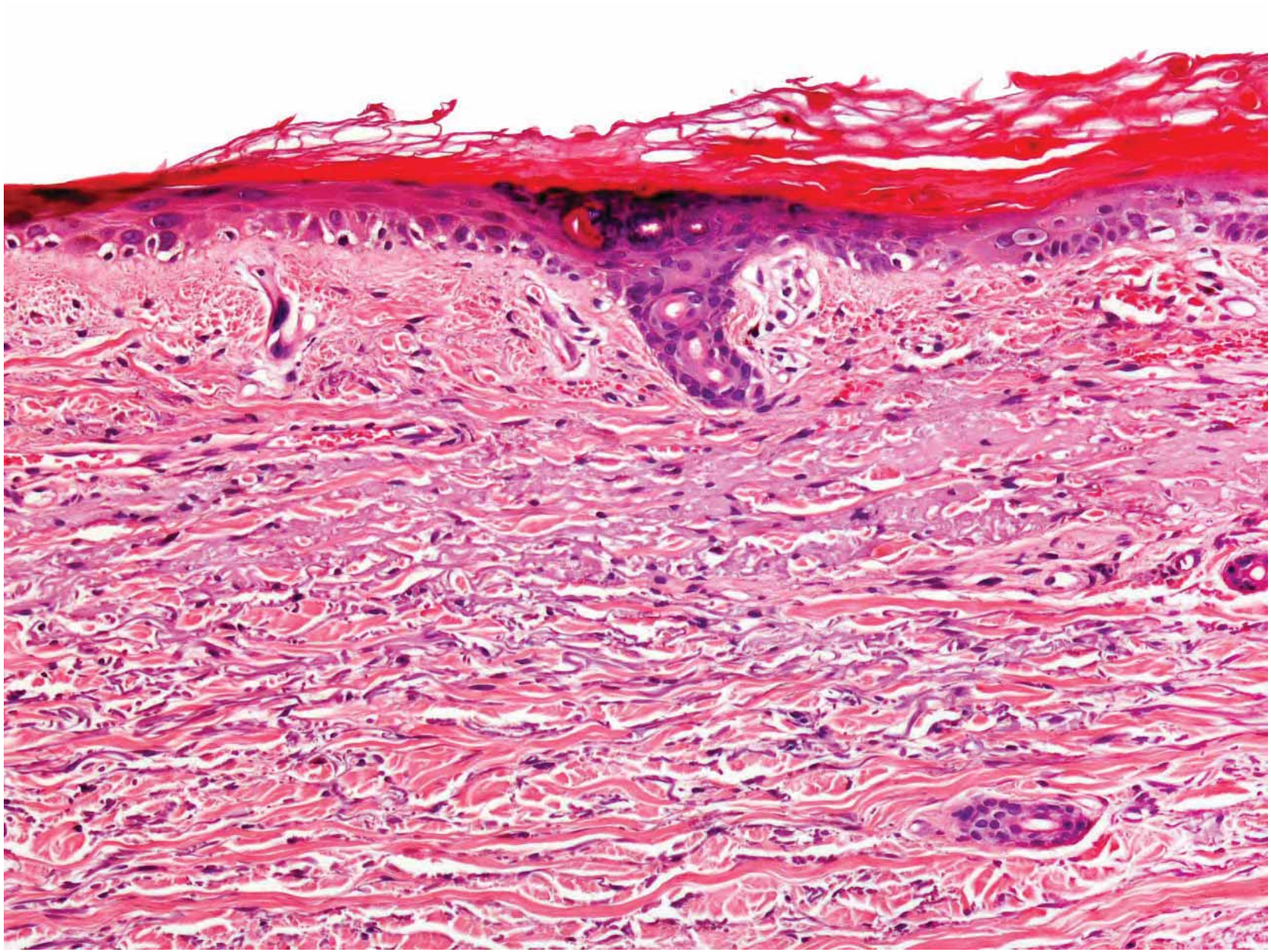


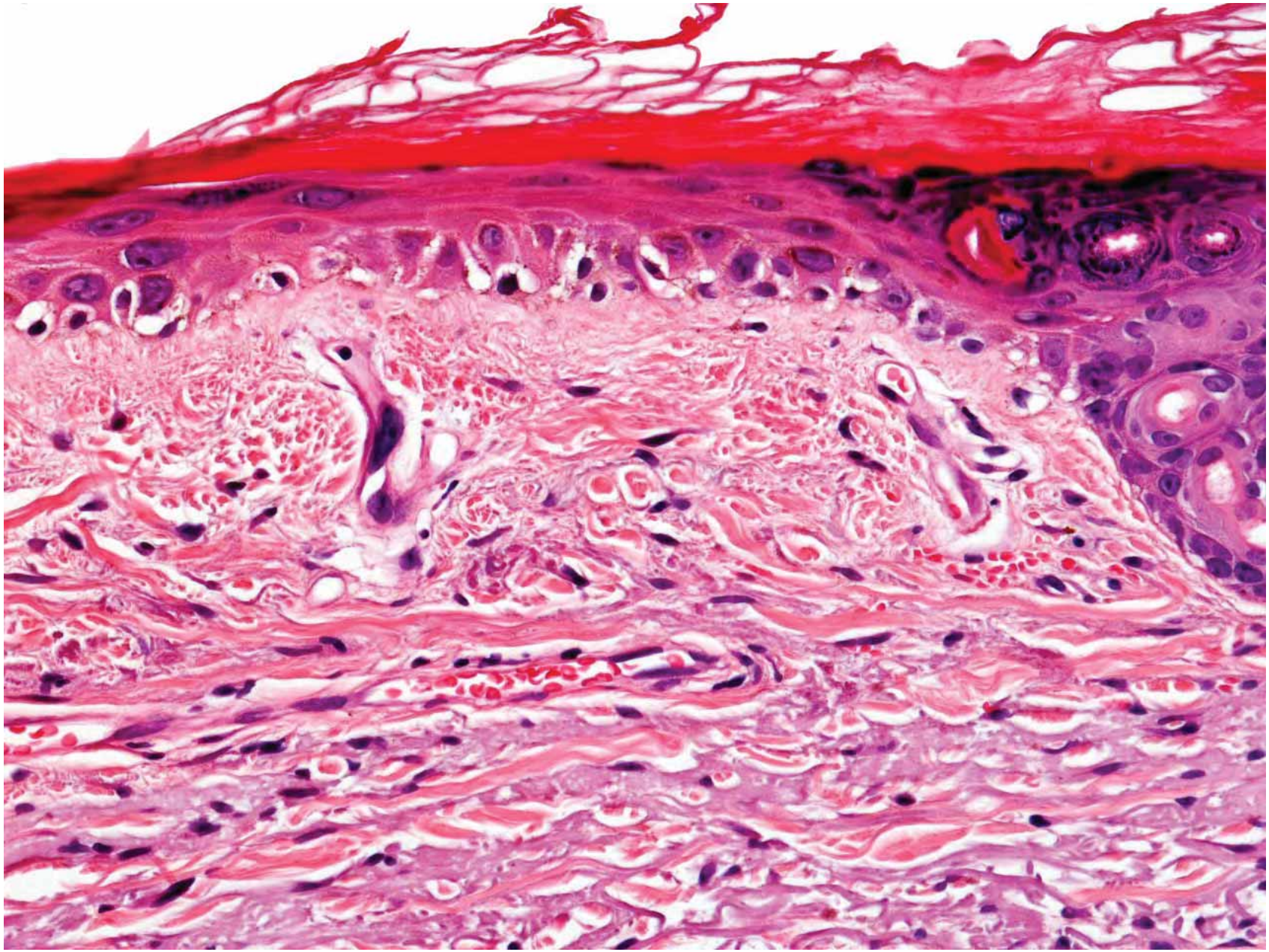


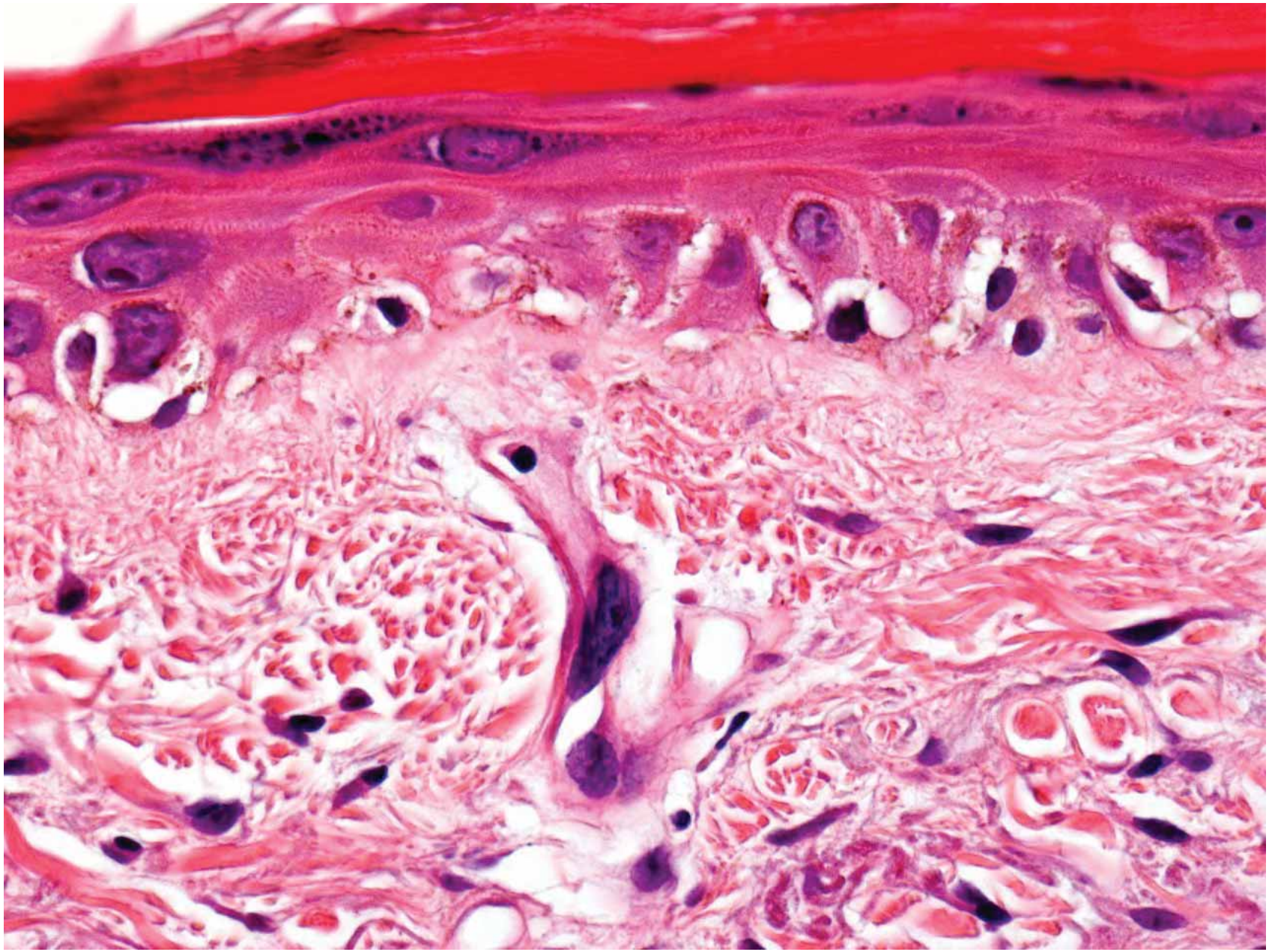


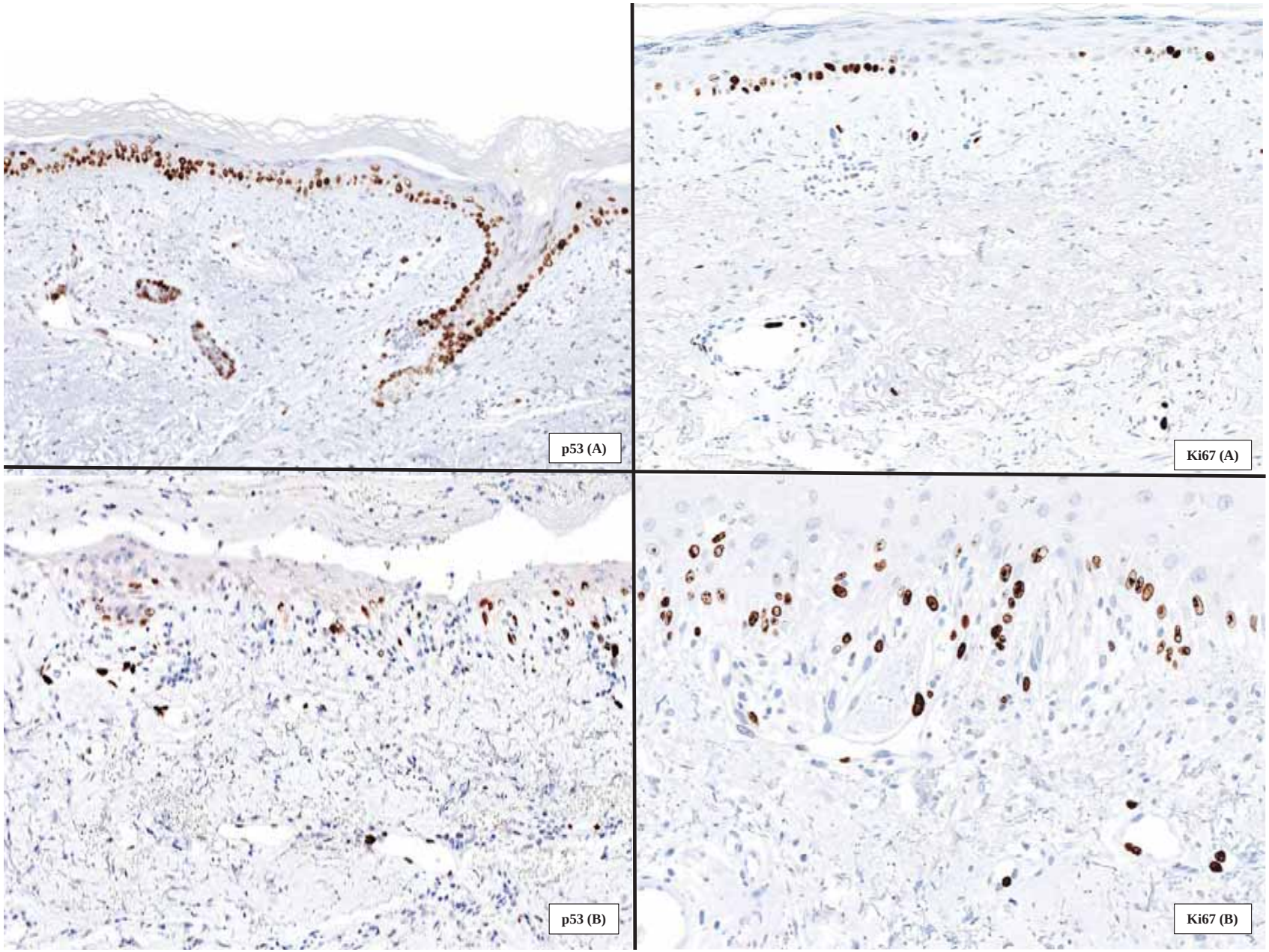











p53 (A)
Ki67 (A)
p53 (B)
Ki67 (B)

Case 8. Diagnosis

- Cutaneous eruption by Loncastuximab

- Loncastuximab is an anti-CD19 antibody for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.
- Severe cutaneous reactions occurred in some patients treated with Loncastuximab: Grade 3 cutaneous reactions occurred in 4% of the patients, and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

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CASE REPORT

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Cutaneous eruption with reactive endothelial atypia due to emerging targeted cancer therapies: Report of two cases with clinico-pathologic correlation

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Abstract

Targeted anticancer therapy is being used with greater frequency and dermatologic toxicities are among the most frequent adverse events of these drugs. However, histopathological features of these adverse events are not yet well characterized. We present two cases of clinically different cutaneous toxicities on two patients with hematologic neoplasia. They were treated with different drugs and in both cases medications shared inhibition of PI3K as mechanism of action. The skin biopsy specimen showed endothelial cell atypia with large nuclei and mitotic figures. To the best of our knowledge, no other cases with these striking histopathologic findings have been reported with PI3K inhibitors or other anticancer targeted therapy.

KEYWORDS
cutaneous drug eruption, endothelial atypia, PI3K inhibitors

1 | INTRODUCTION

Targeted therapy has led to personalized medicine in cancer treatment.[1] It is being used every day with greater frequency and therefore more frequent adverse events, including the cutaneous ones, are being reported. Dermatologic toxicities associated with targeted cancer therapy can be classified into four groups: (a) inflammatory, (b) immunobullous, (c) alteration of keratinocytes, and (d) alteration of melanocytes.[1,2] Histopathological features of these adverse events are not yet well characterized.

We present two cases of cutaneous eruptions presumed to be associated with different drugs of the PI3K inhibitors family, which showed atypical endothelial cells on the cutaneous biopsy specimen as the common histopathologic finding.

2 | CASE REPORTS

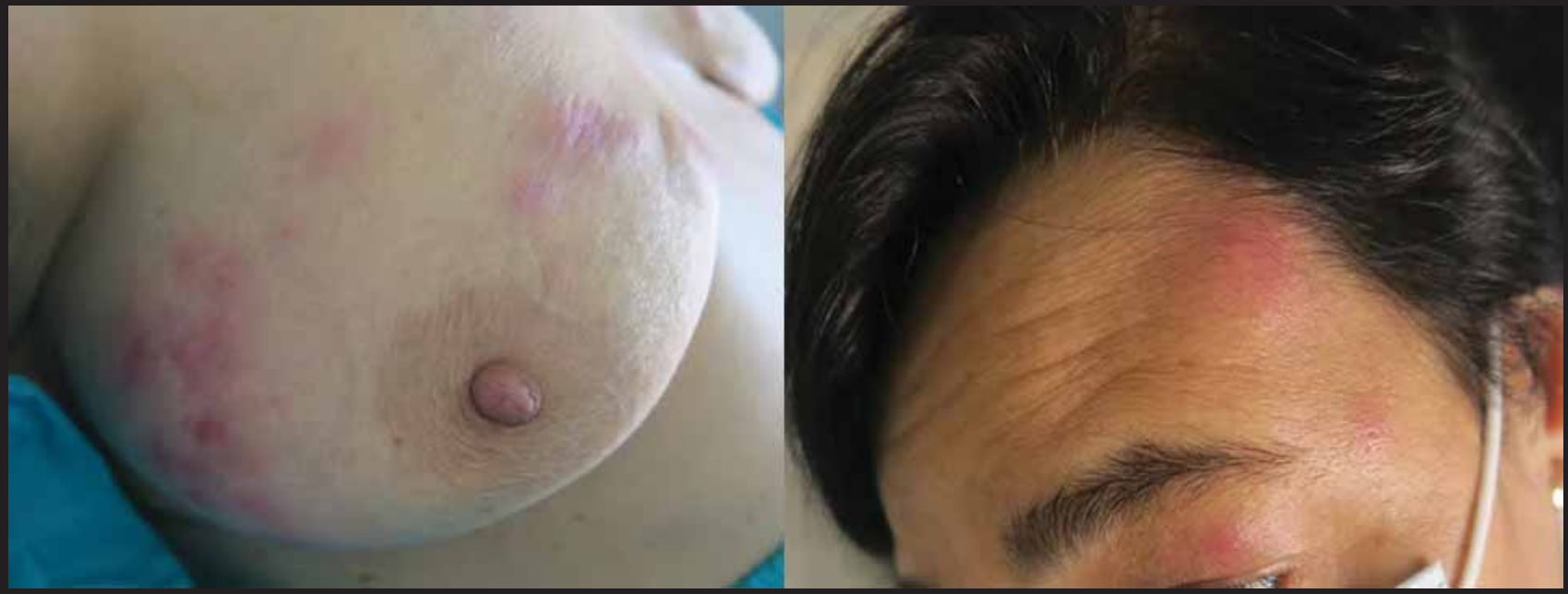
2.1 | Case 1

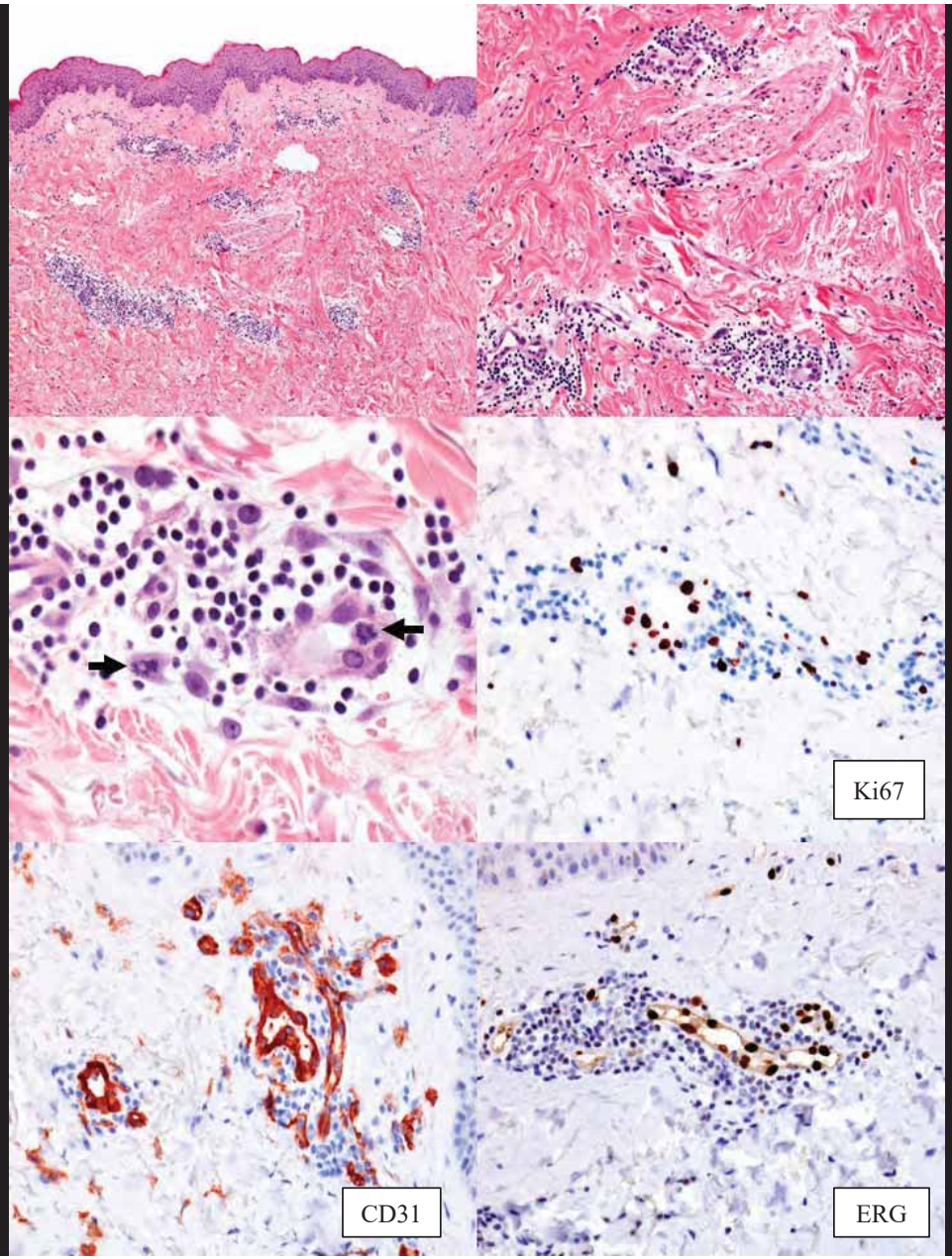
A 52-year-old woman presented to the emergency department with headache and dizziness. After laboratory investigations, she was diagnosed with acute myeloid leukemia (AML). No radiotherapy had been administered. She started treatment with chemotherapy (idarubicin and cytarabine) followed one month later of treatment with quizartinib. The day after starting quizartinib she developed pruritic erythemato-edematous nodules and plaques on the face, neck, and chest, clinically resembling Sweet syndrome (Figure 1). Histopathologic study showed scattered necrotic keratinocytes within the epidermis with mild superficial and deep perivascular lympho-histiocytic infiltrate within the dermis (Figure 2). No

Two cases with cutaneous eruptions showing endothelial atypia:

- Case 1: A 52-year-old woman with acute myeloid leukemia treated with quizartinib.
- Case 2: A 71-year-old woman had recurrent nodal follicular lymphoma treated with loncastuximab and durvalumab

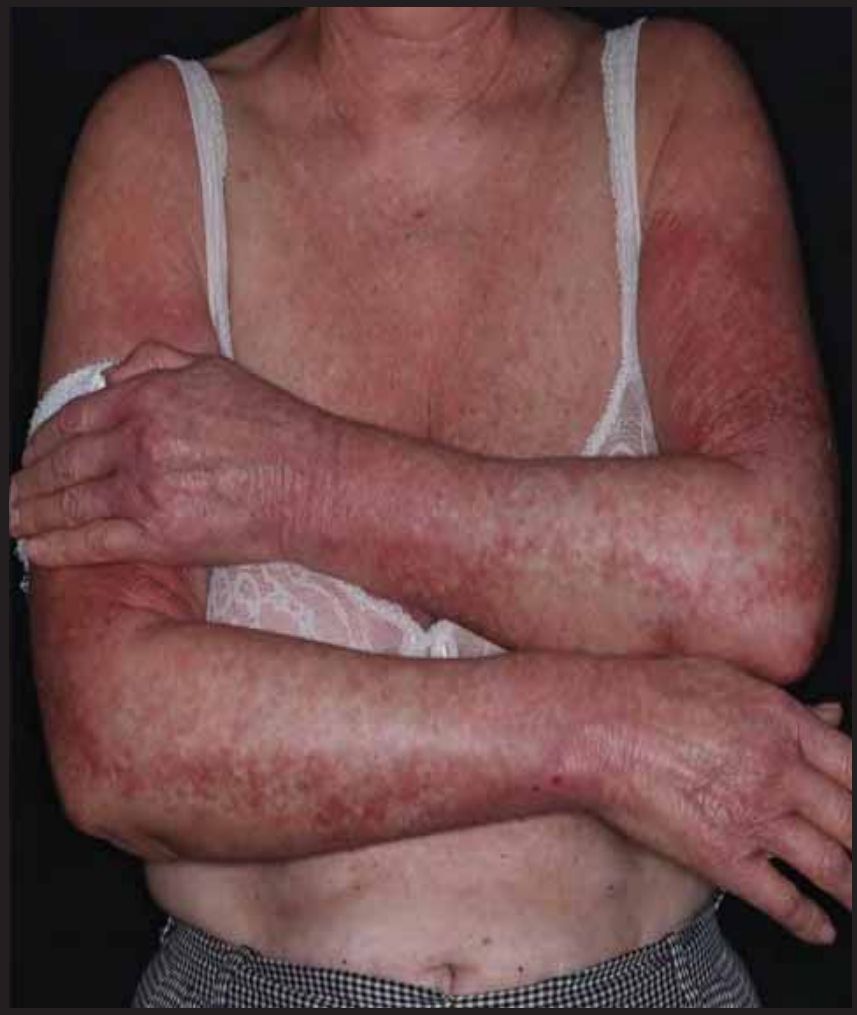
Case 1

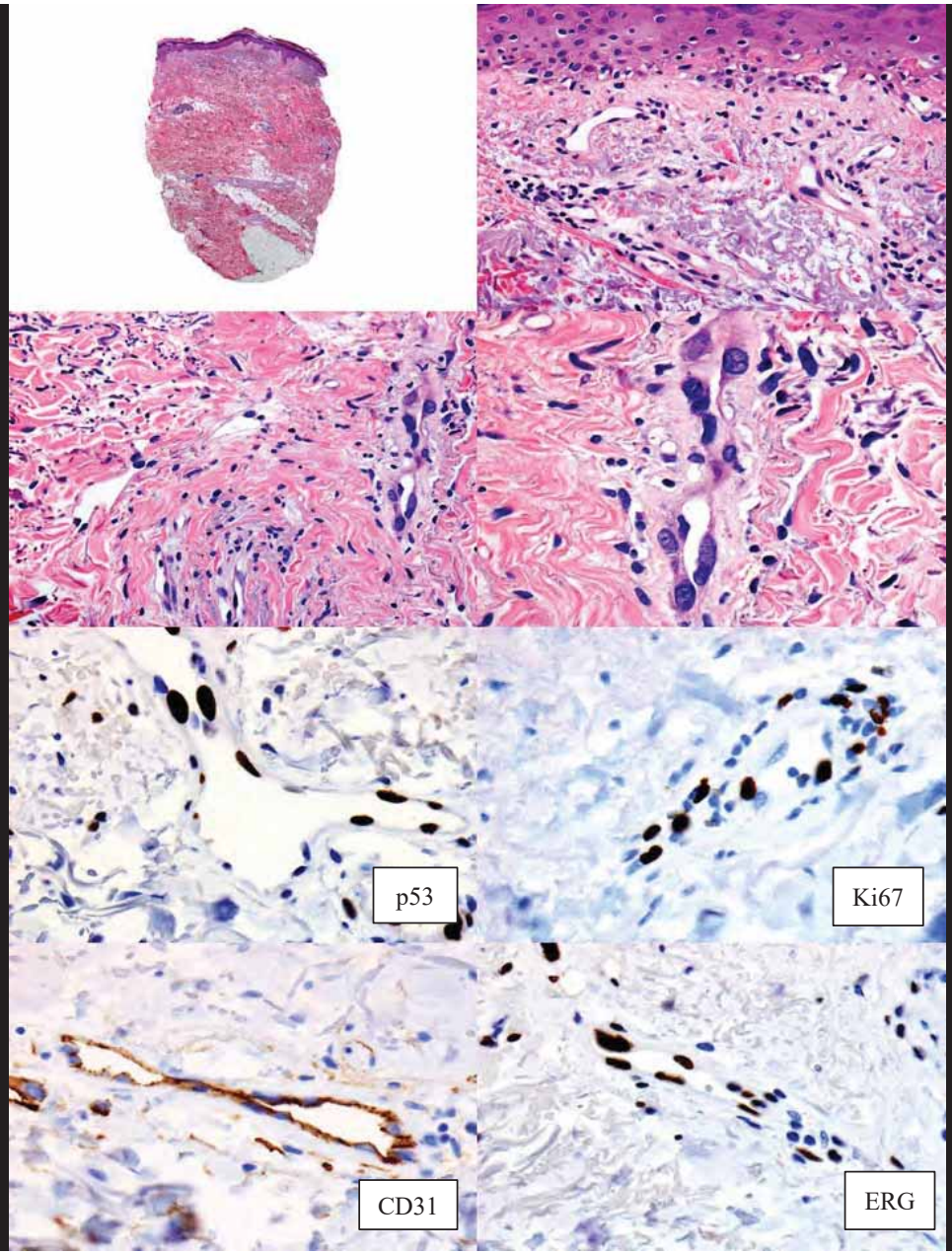




Case 1

Case 2





Case 2

PIK3CA mutations in vascular malformations

Sandra D. Castillo[a], *Eulalia Baselga*[b], *and Mariona Graupera*[a,c]

KEY POINTS

- Oncogenic *PIK3CA* mutations cause venous and lymphatic vascular malformations.
- *PIK3CA* mutations lead to a hyperproliferative phenotype of endothelial cells, probably as the main mechanisms for the pathogenesis of venous and lymphatic vascular malformations.
- *PIK3CA*-mutant vascular malformations present similar characteristics to developmental tumours.
- Repurposing PI3K inhibitors is an appropriate strategy for the treatment of *PIK3CA*-driven vascular malformations.

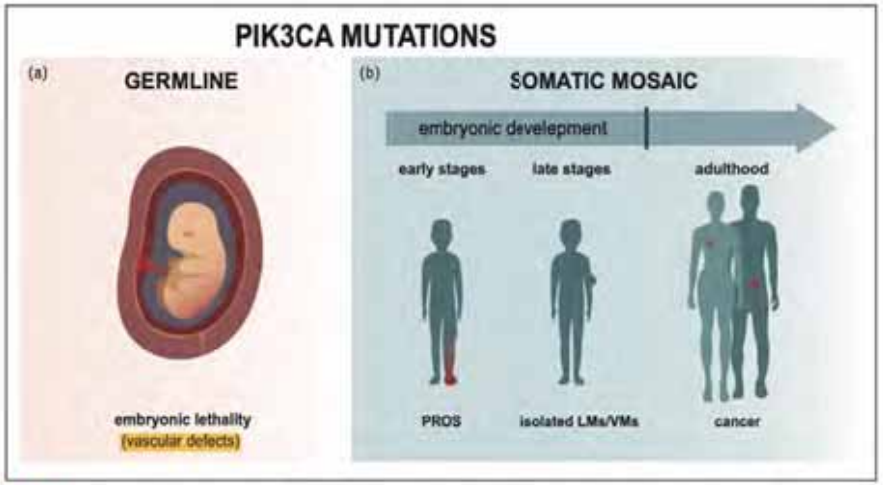


FIGURE 1. Effect of germline and somatic *PIK3CA* mutations during embryonic development and adulthood.