CLUES FOR DIAGNOSIS IN DERMATOPATHOLOGY

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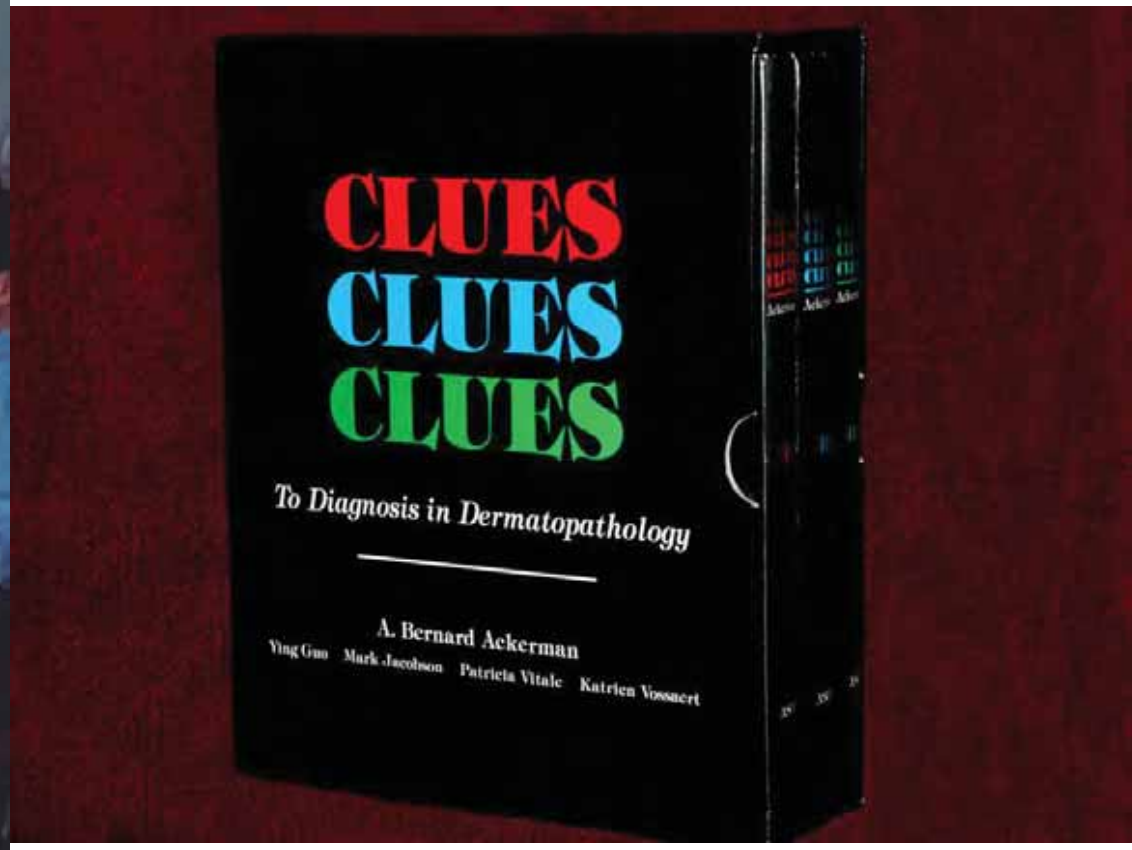
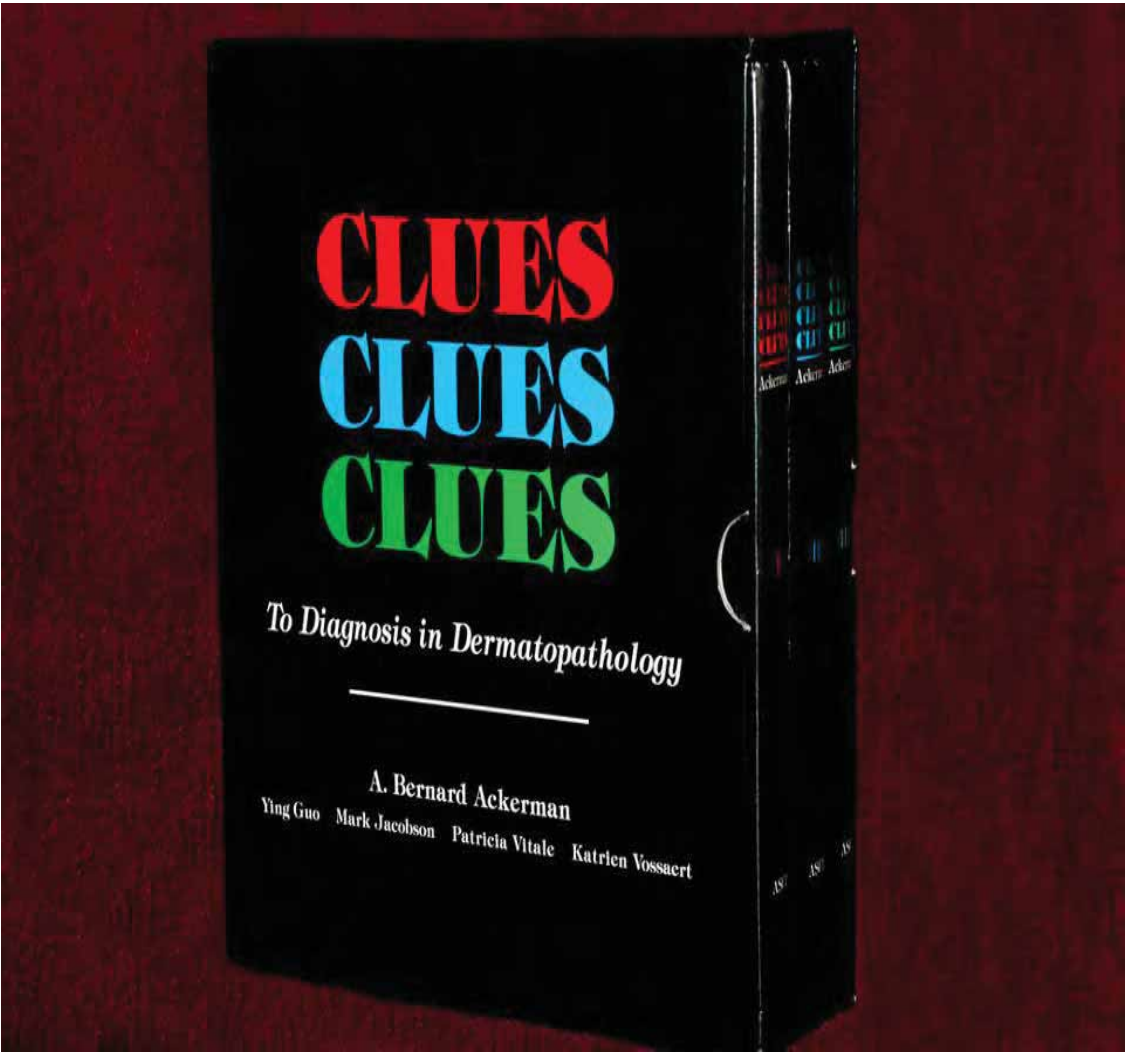
Clue. Definition in the Oxford Medical Dictionary

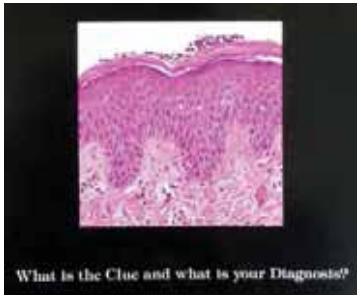
- A clue is a fact, circumstance, or principle which, being taken hold of and followed up, leads through a maze, perplexity, difficulty or intrincate investigation


CLUES
CLUES
CLUES
To Diagnosis in Dermatopathology
A. Bernard Ackerman
Ying Guo
Mark Jacobson
Patricia Vitale
Katrien Vossaert

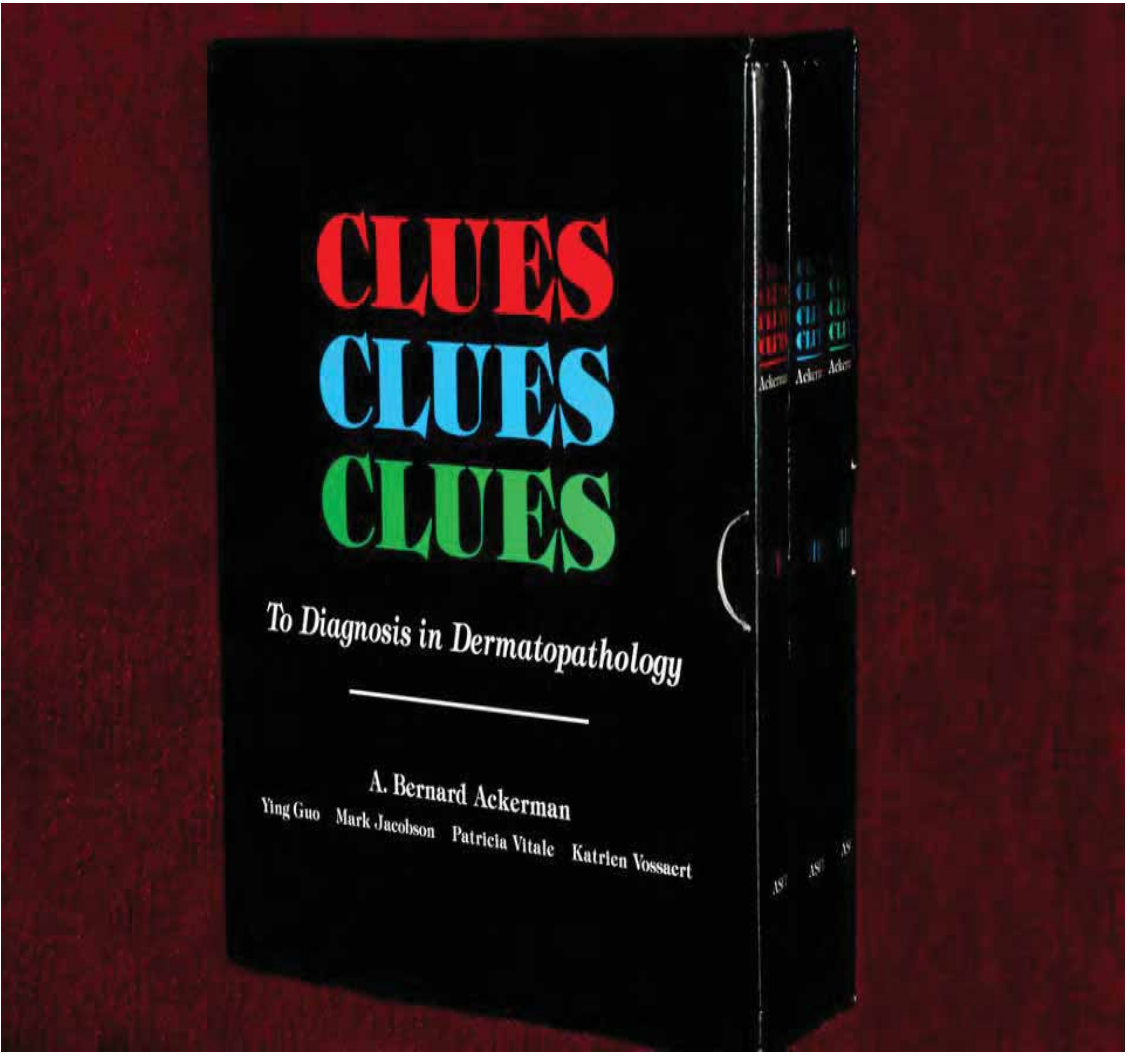
Clues in Dermatopathology (A.B. Ackerman)

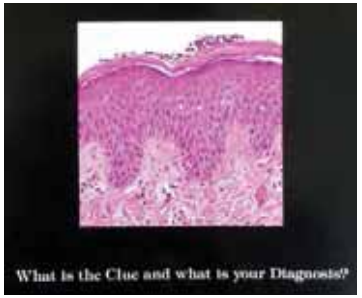
- Histopathologic findings that are helpful for specific diagnosis, although they are not absolutely specific of any entity





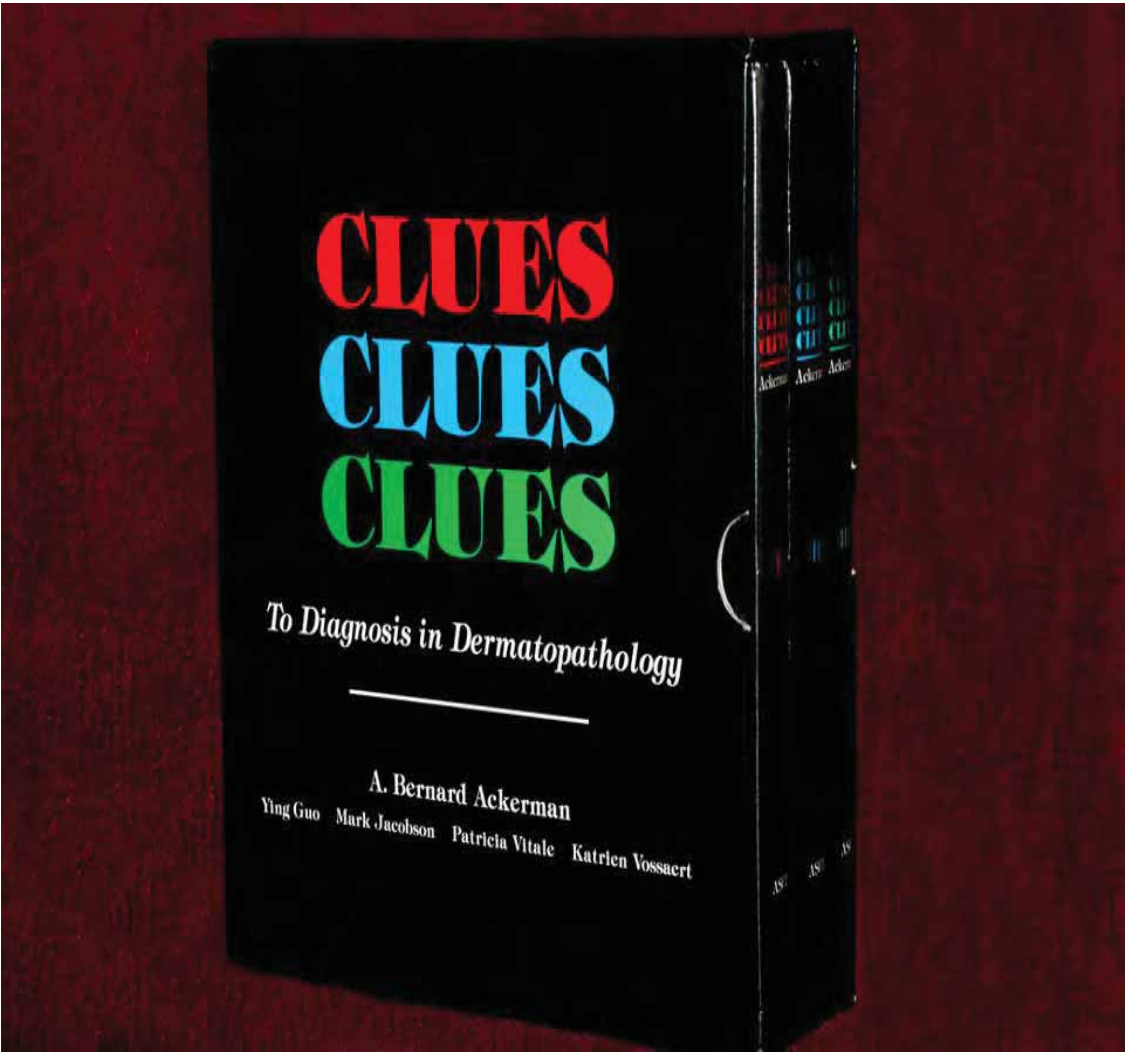
One, or more, collections of neutrophils atop a stratum corneum are a clue to suppurative folliculitis

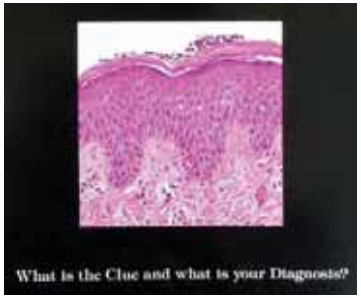




One, or more, collections of neutrophils atop a stratum corneum are a clue to suppurative folliculitis

Innumerable packets of melanin arrayed parallel to corneocytes in a thickened laminated stratum corneum across the entire front of a melanocytic proliferation are a clue to a benign melanocytic neoplasm





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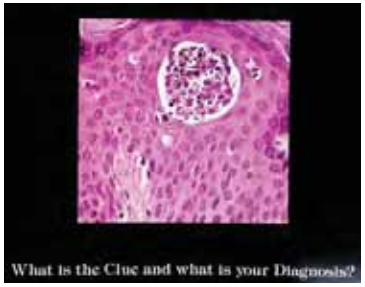
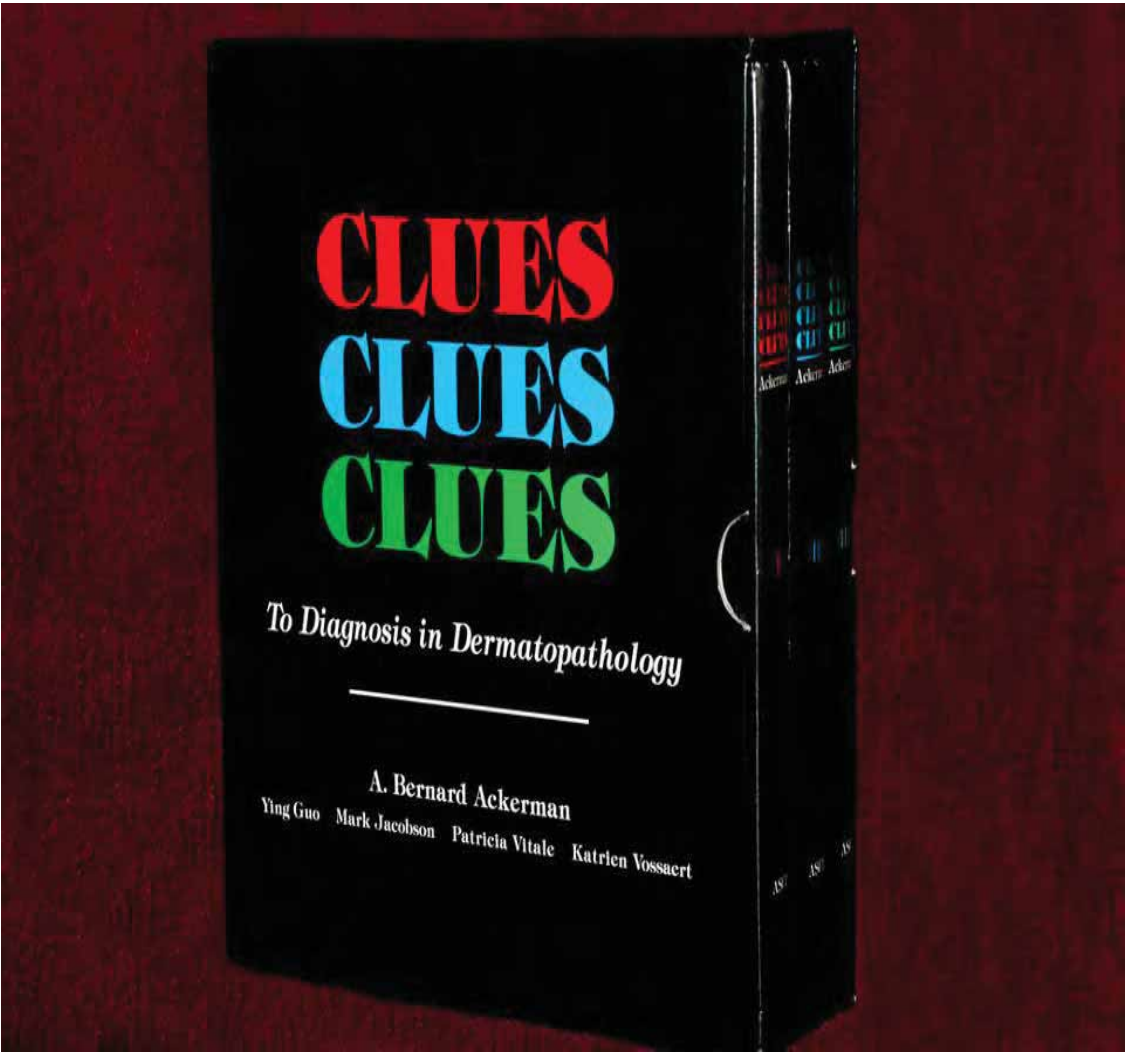
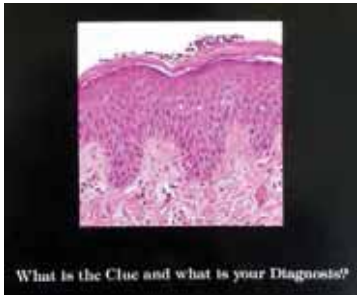


In an apparent lesion of mycosis fungoides replete with Pautrier's "microabscesses", abundant lymphocytic nuclear "dust" within intraepidermal collections of atypical lymphocytes is a clue to adult-T-cell leukemia/lymphoma caused by HTLV-1.





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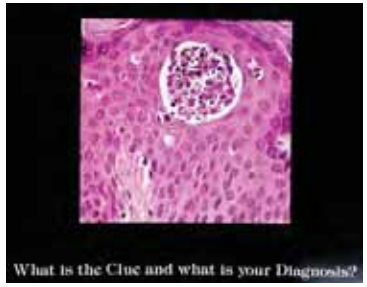

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Clumps of melanin within pleated hair shafts are a clue to trichotillomania.

A. B. Ackerman. “Do you understand now what is a clue?”

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L. Requena “Yes, I got it”

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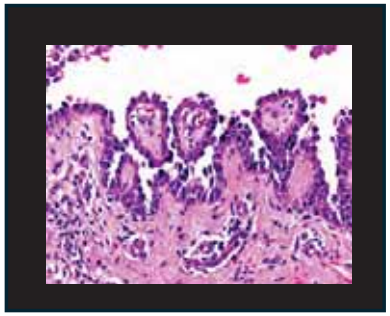
L. Requena “Yes, I got it”

A. B. Ackerman. “ OK. Give some examples of clues”

Examples of clues in Dermatopathology proposed by L. Requena to A.B. Ackerman



- An epidermal basal layer showing “a row of tombstones keratinocytes” is a clue to pemphigus vulgaris

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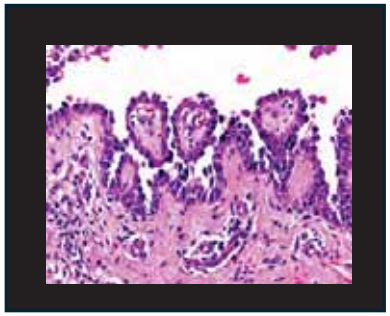

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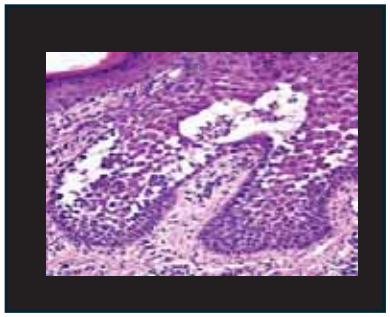

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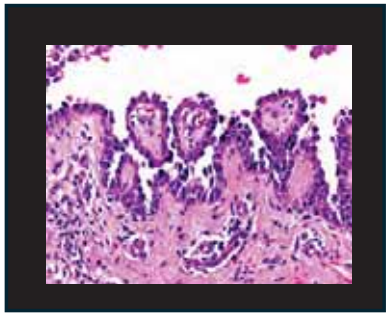

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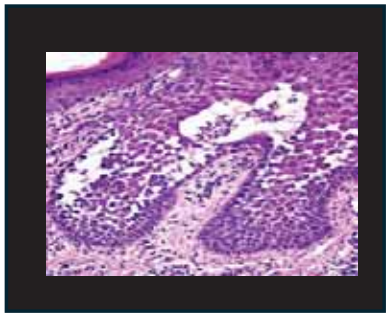

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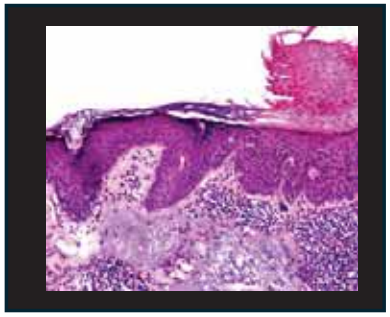


- A sharp slanting curvilinear transition border between normal and atypical epidermis in a “flute pick” configuration is a clue to solar keratosis

A.B. Ackerman response:

“No!!!! These are histopathologic cliches!”

Clues in Dermatopathology. Definition

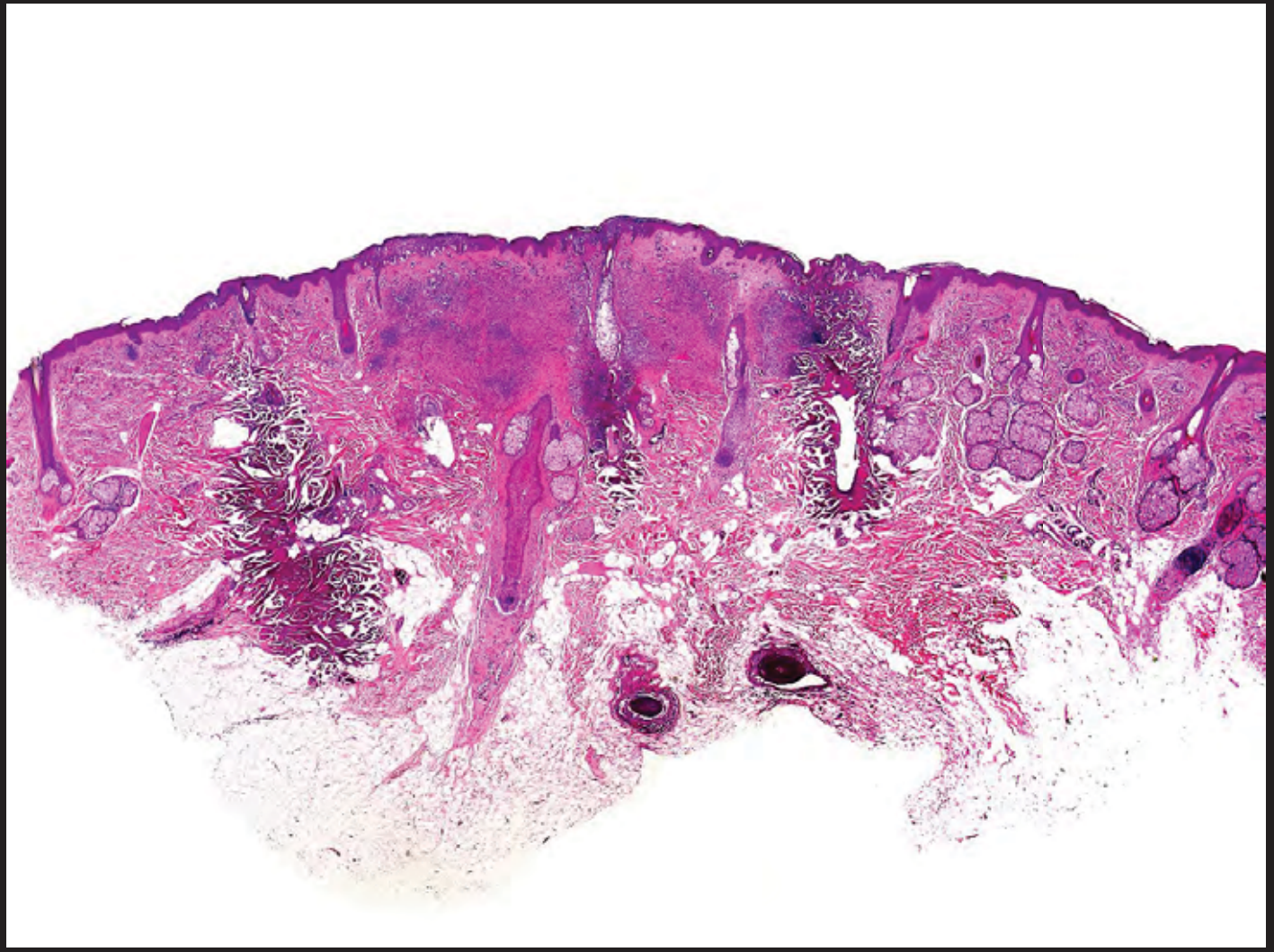
- When the histopathologic finding had been described by A.B. Ackerman: it was a ***clue***

Clues in Dermatopathology. Definition

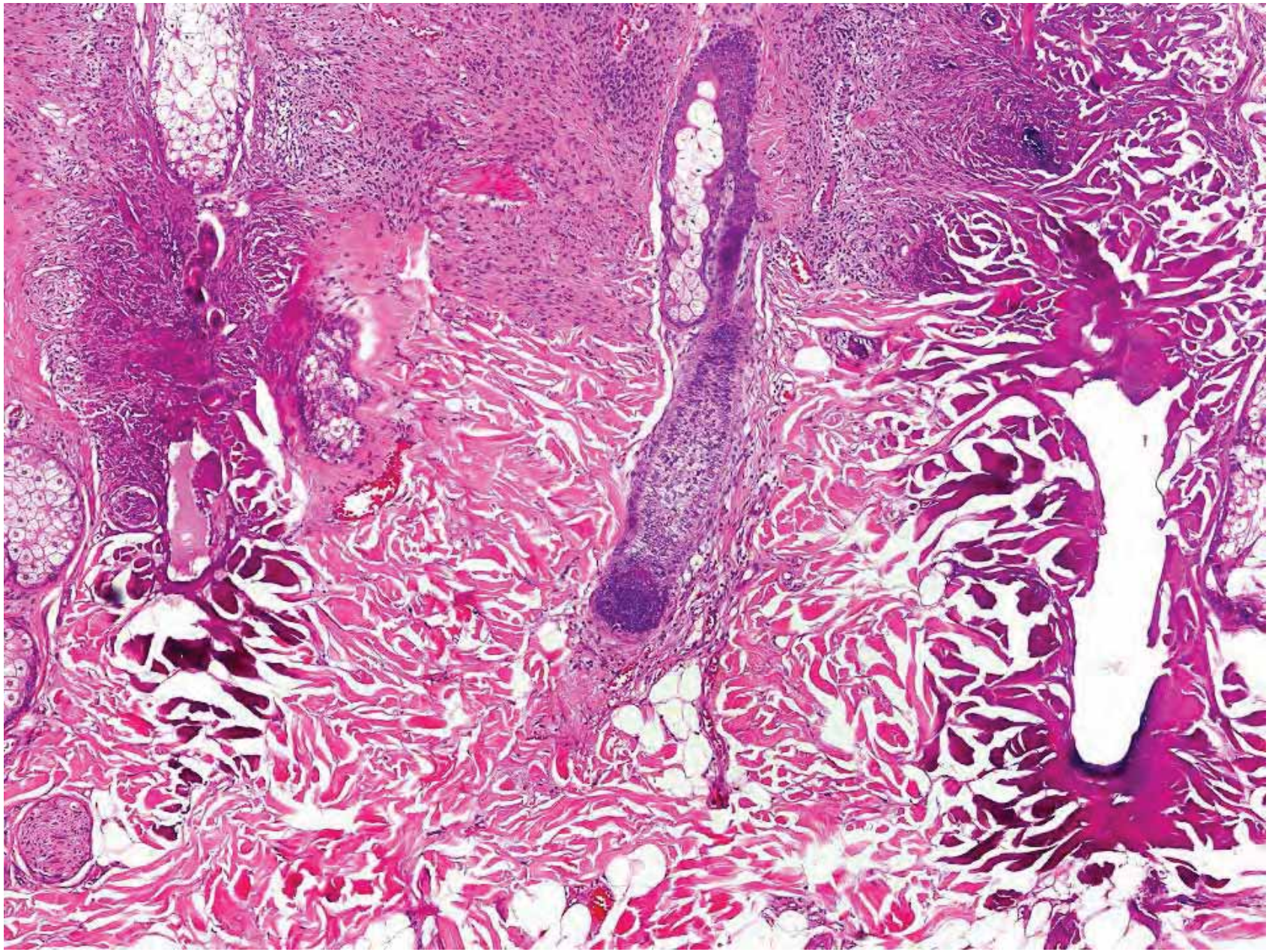
- When the histopathologic finding had been described by A.B. Ackerman: it was a ***clue***
- When the histopathologic finding had been described by anybody else: it was a ***cliche***

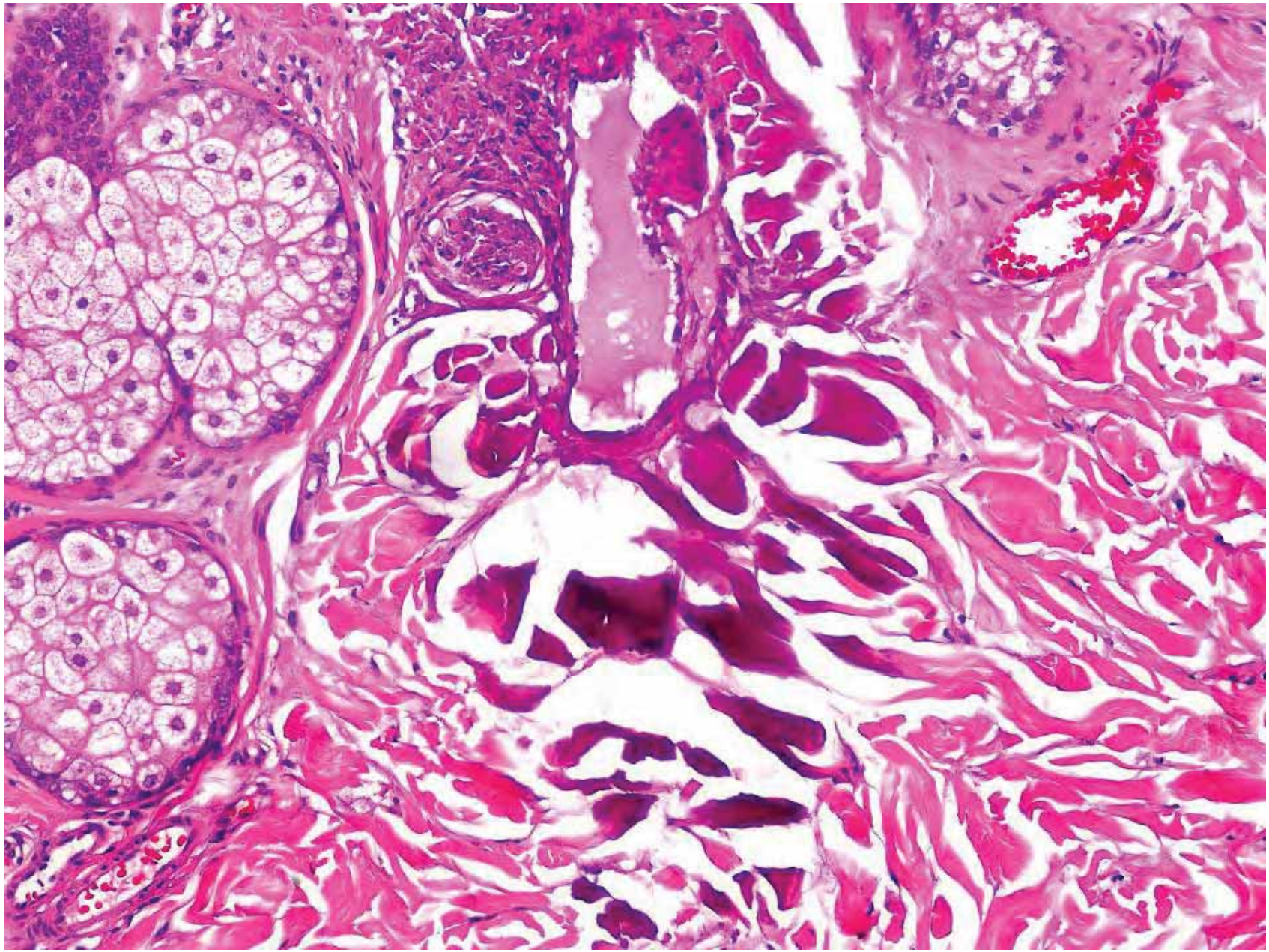
CLICHES PROPOSED BY DR. REQUENA

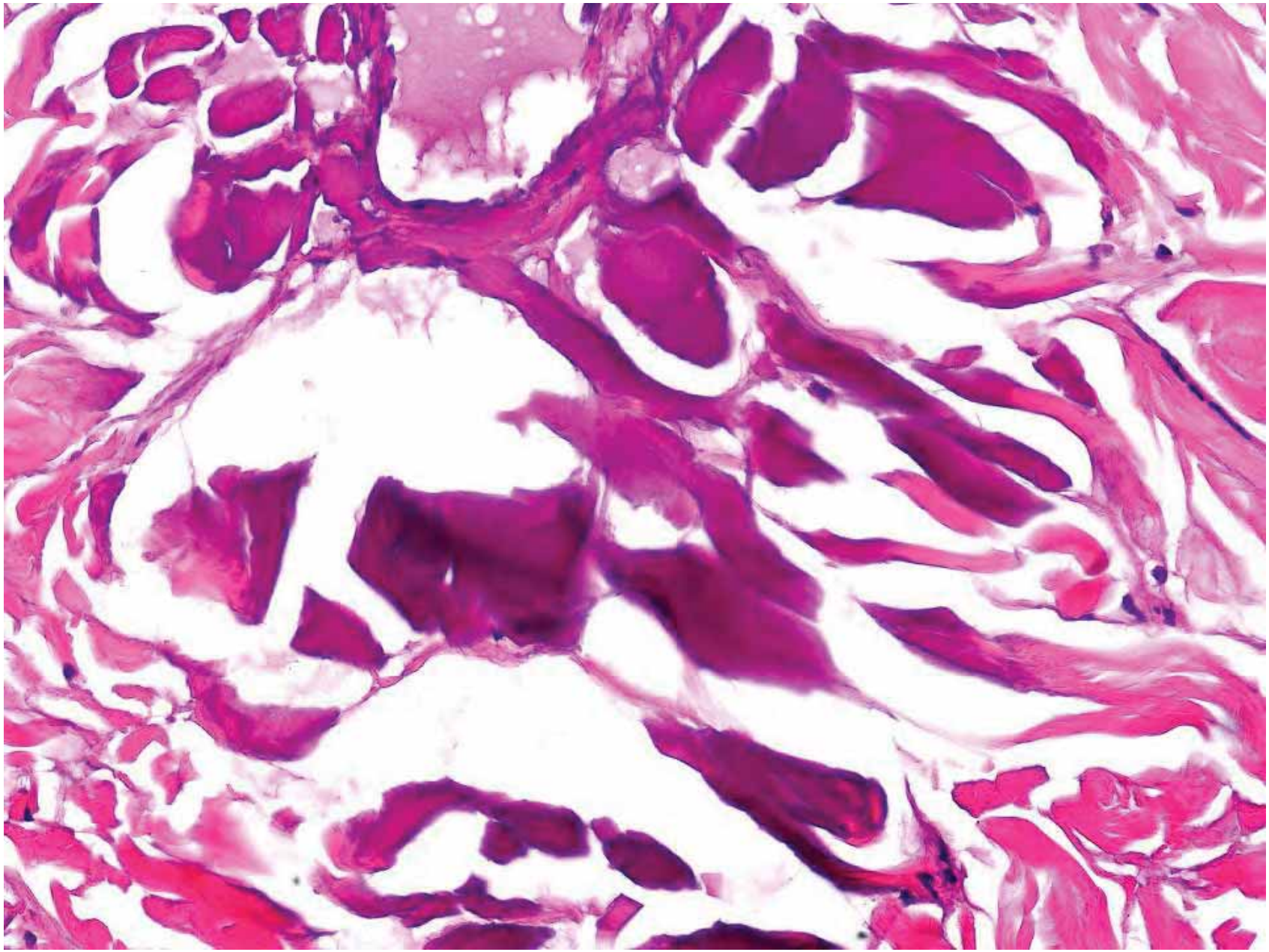
1

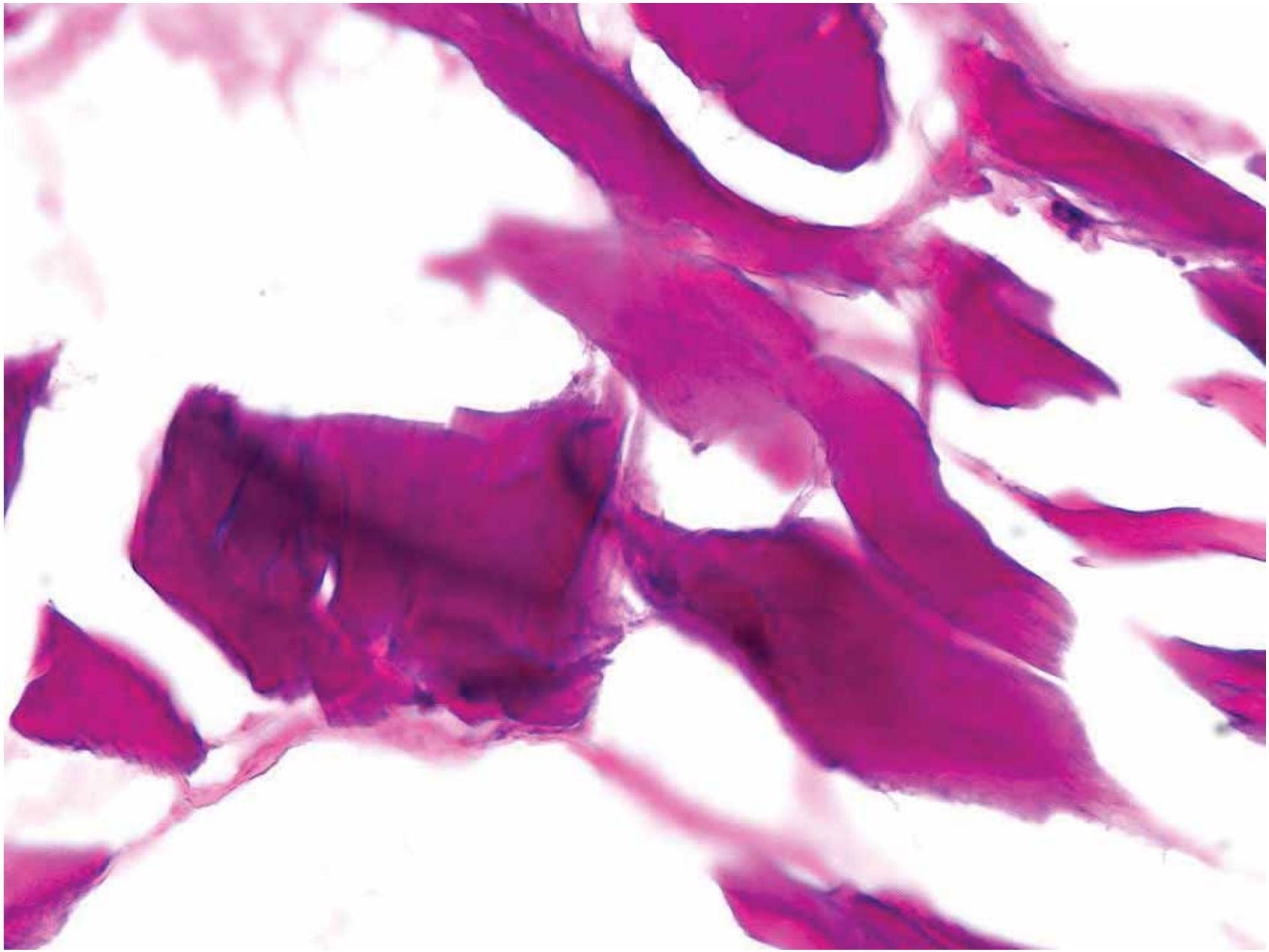


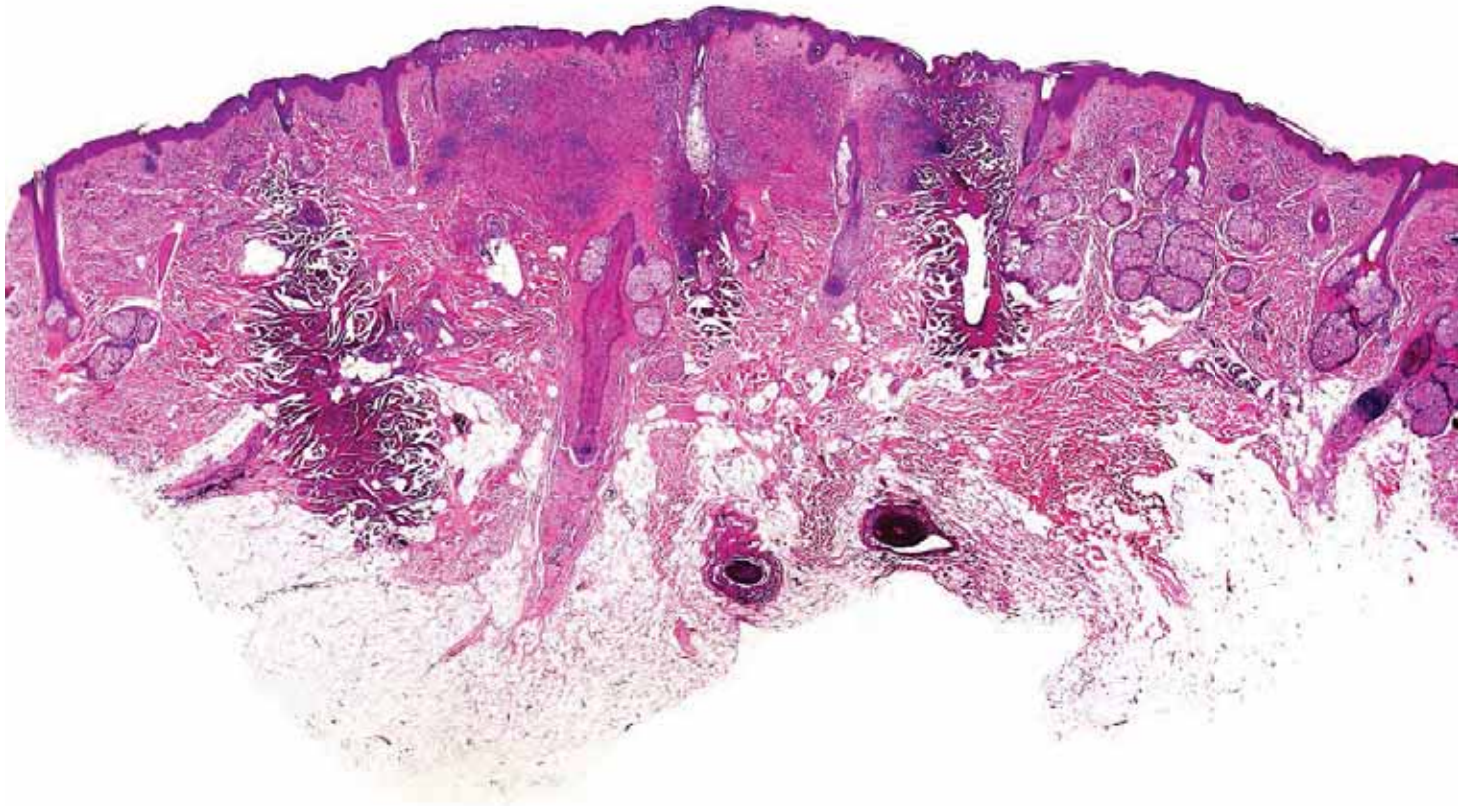
What is the *cliche* and what is the diagnosis?



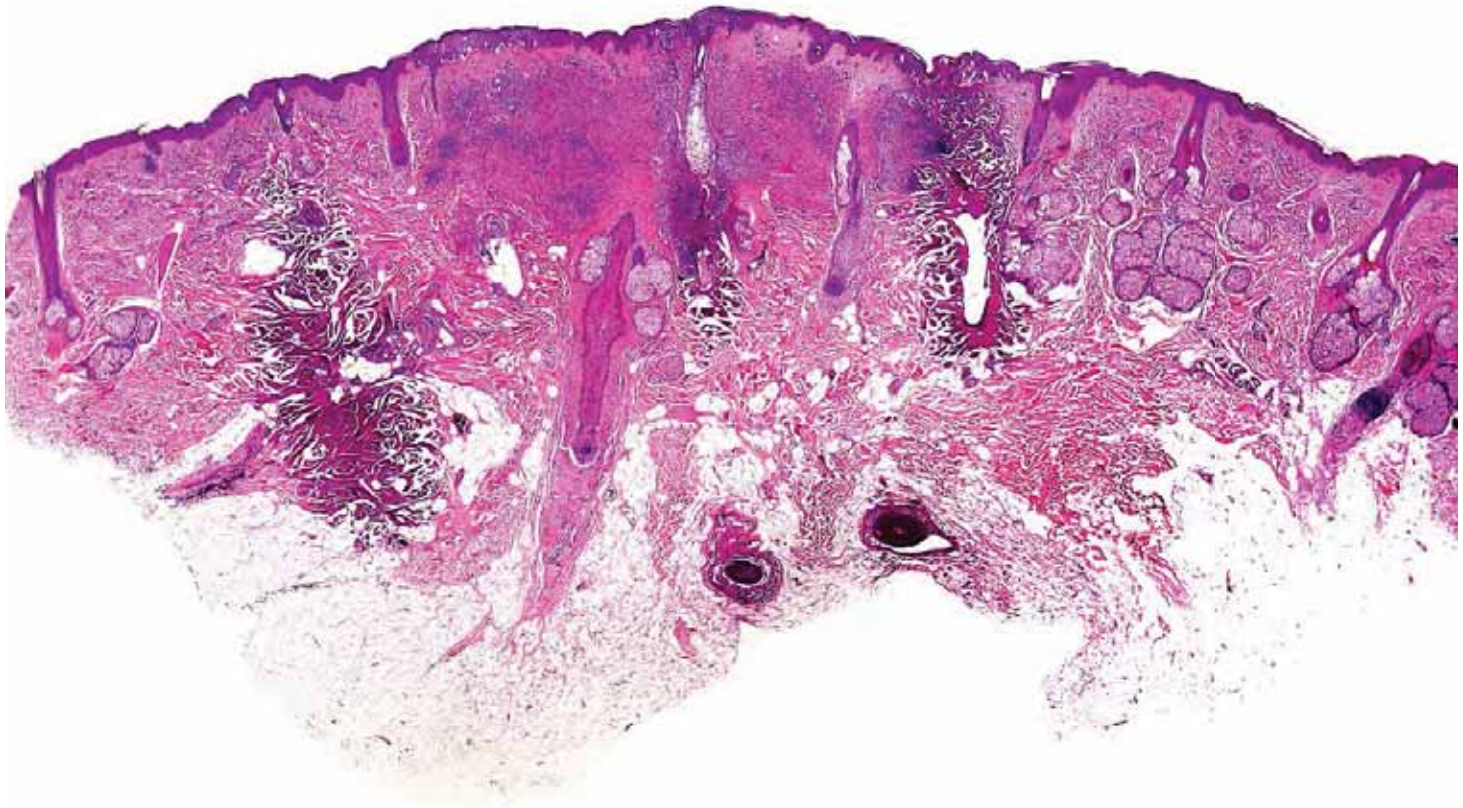




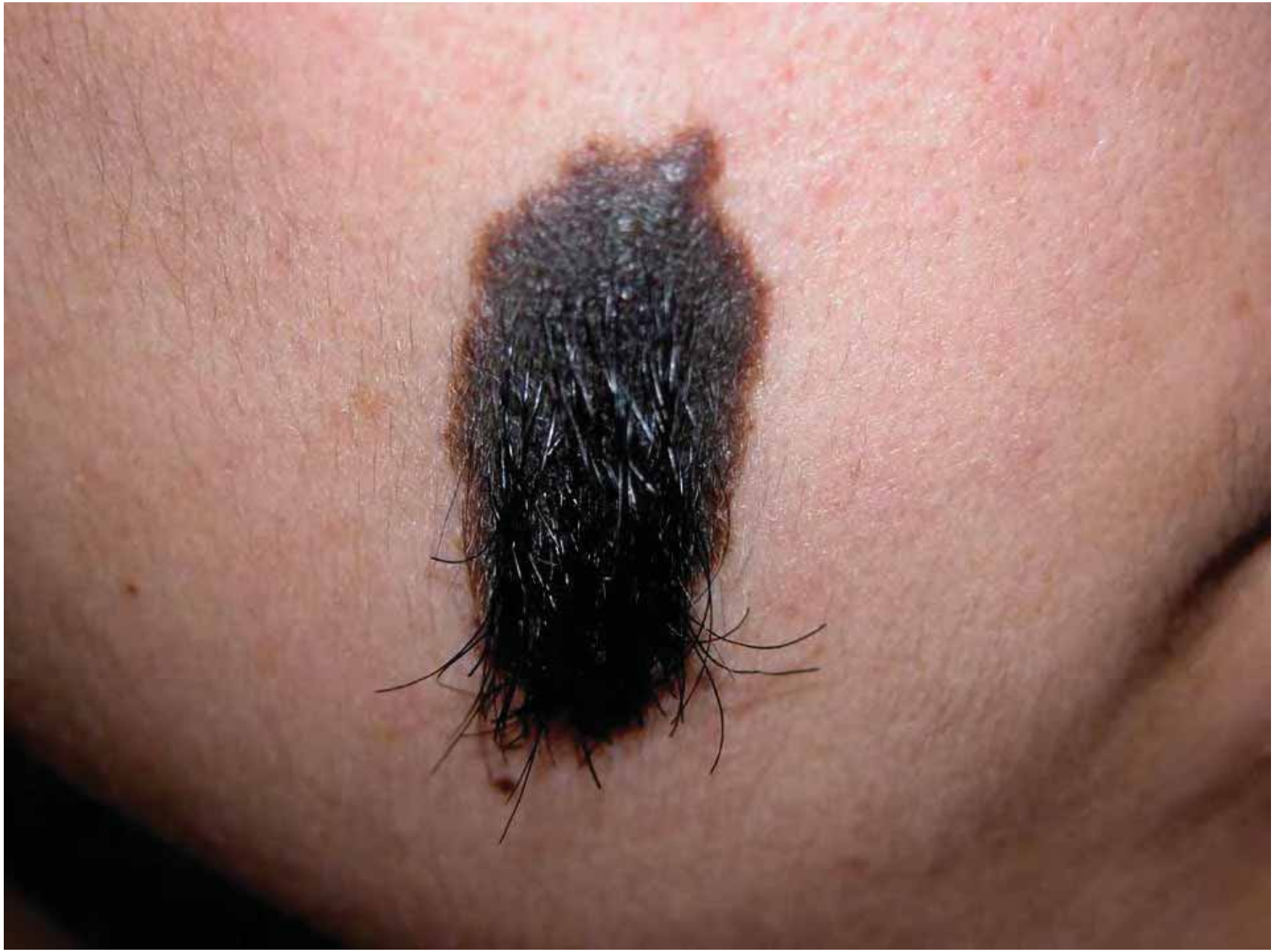




Vertical columns of basophilic degeneration replacing hair follicles are *cliches* to…



Vertical columns of basophilic degeneration replacing hair follicles are *cliches* to electro-epilation in a congenital melanocytic nevus ...

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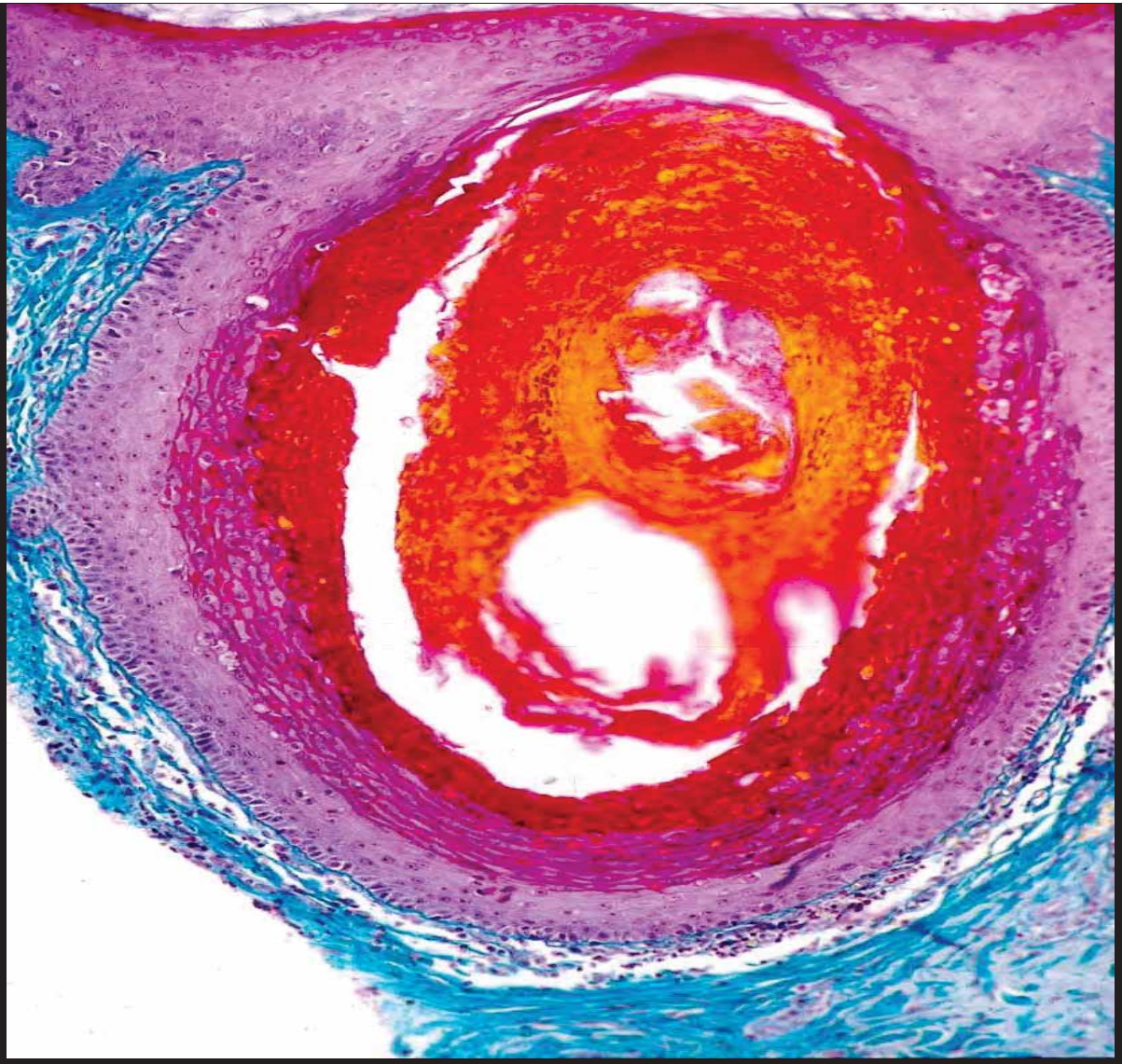

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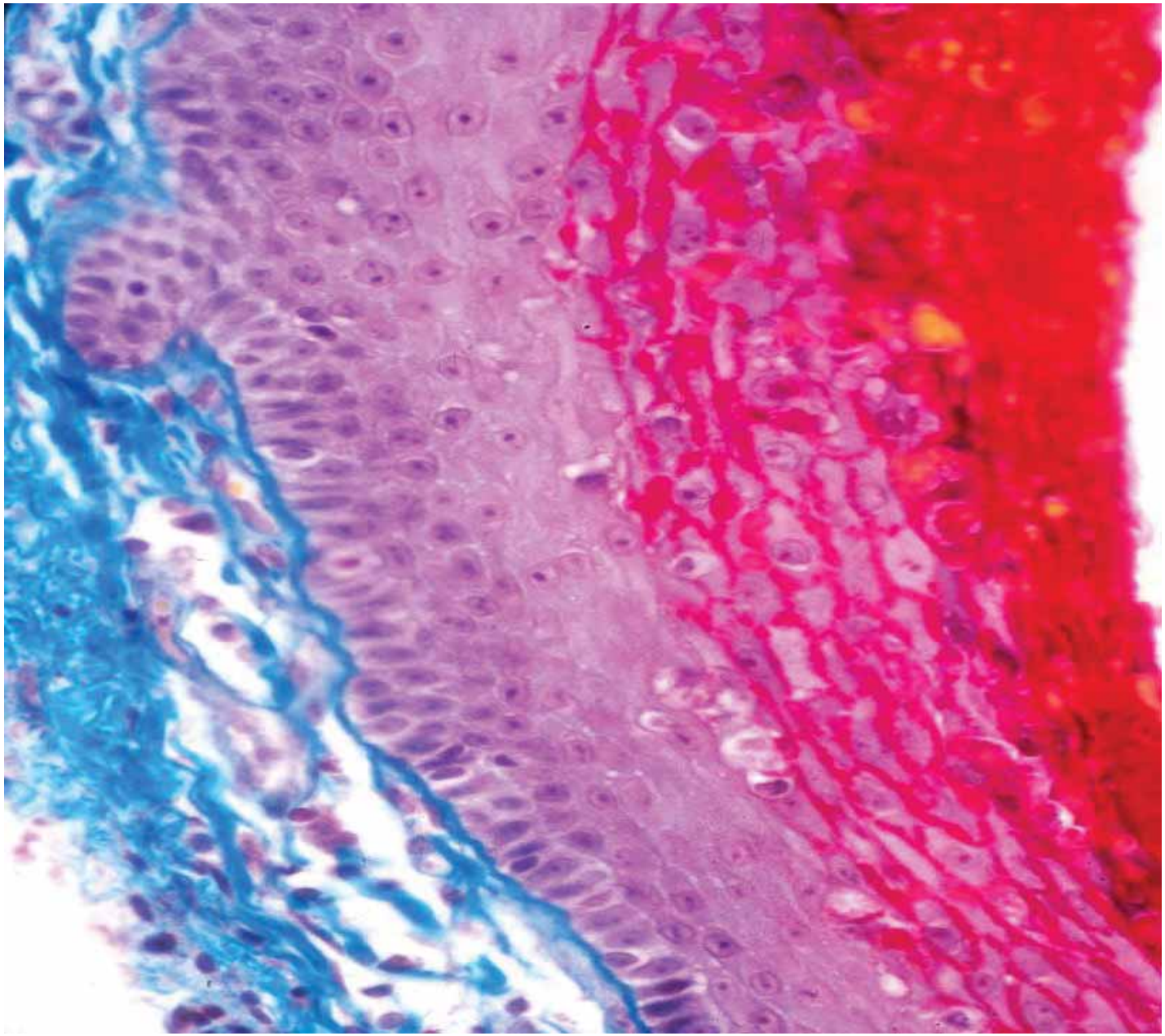
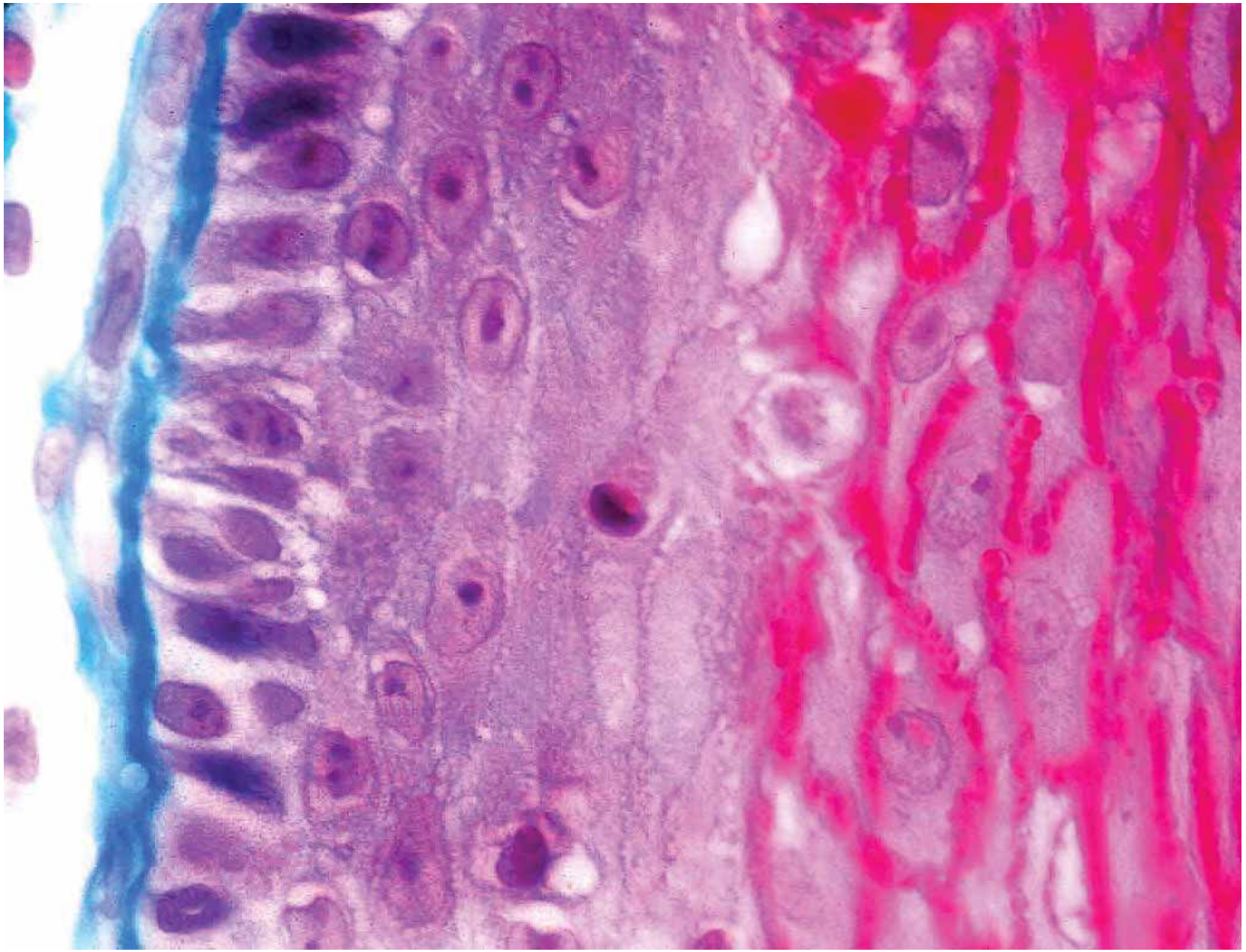
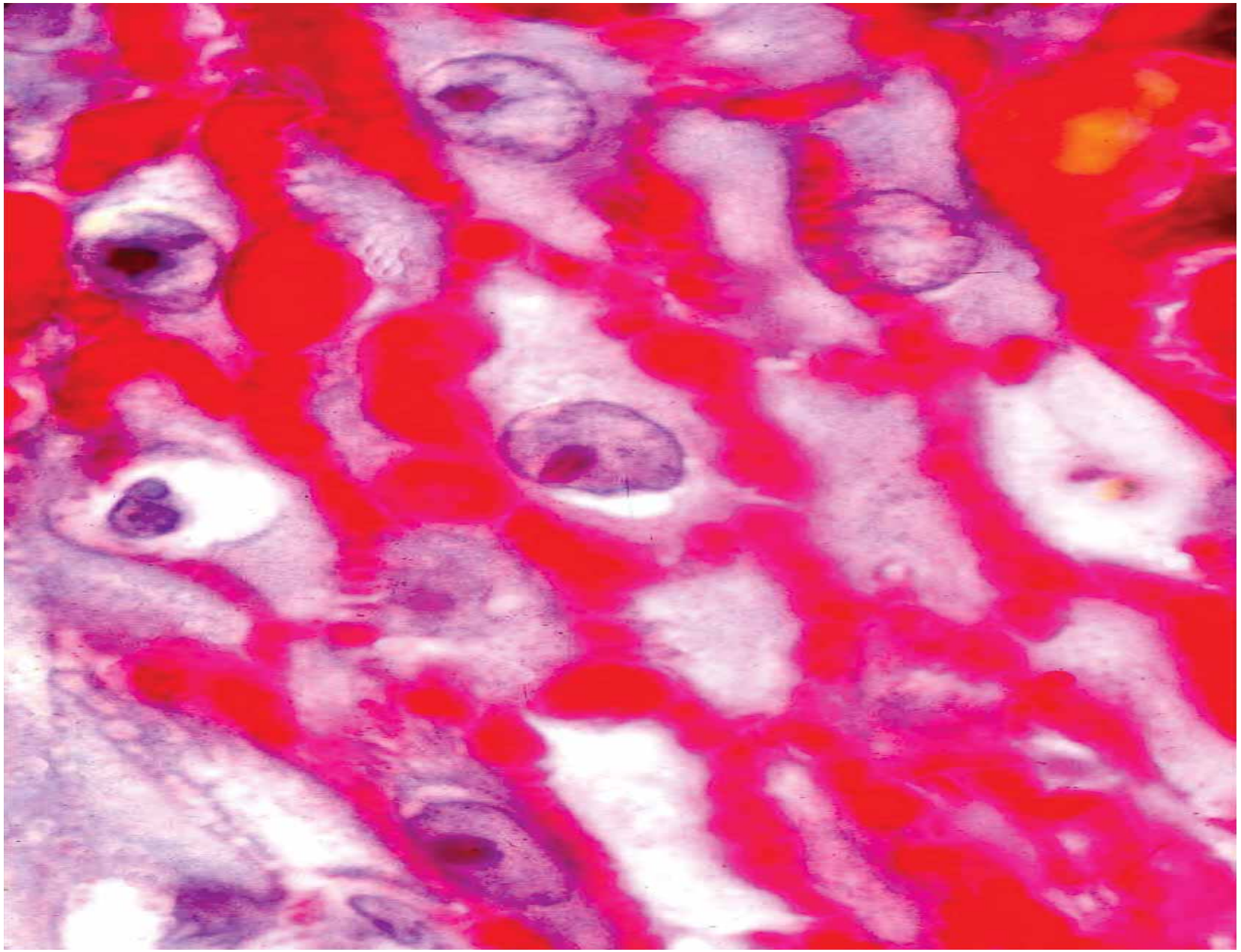
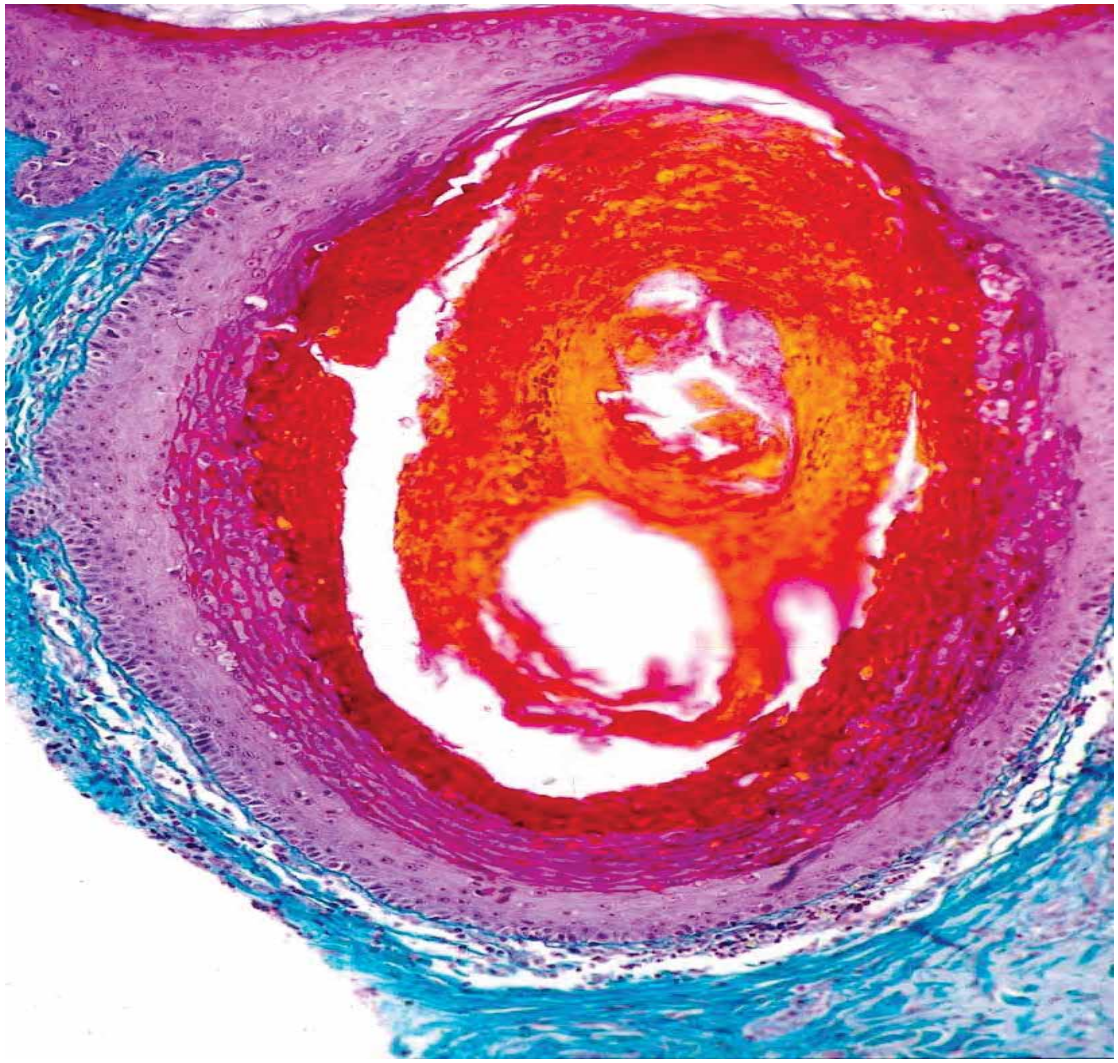
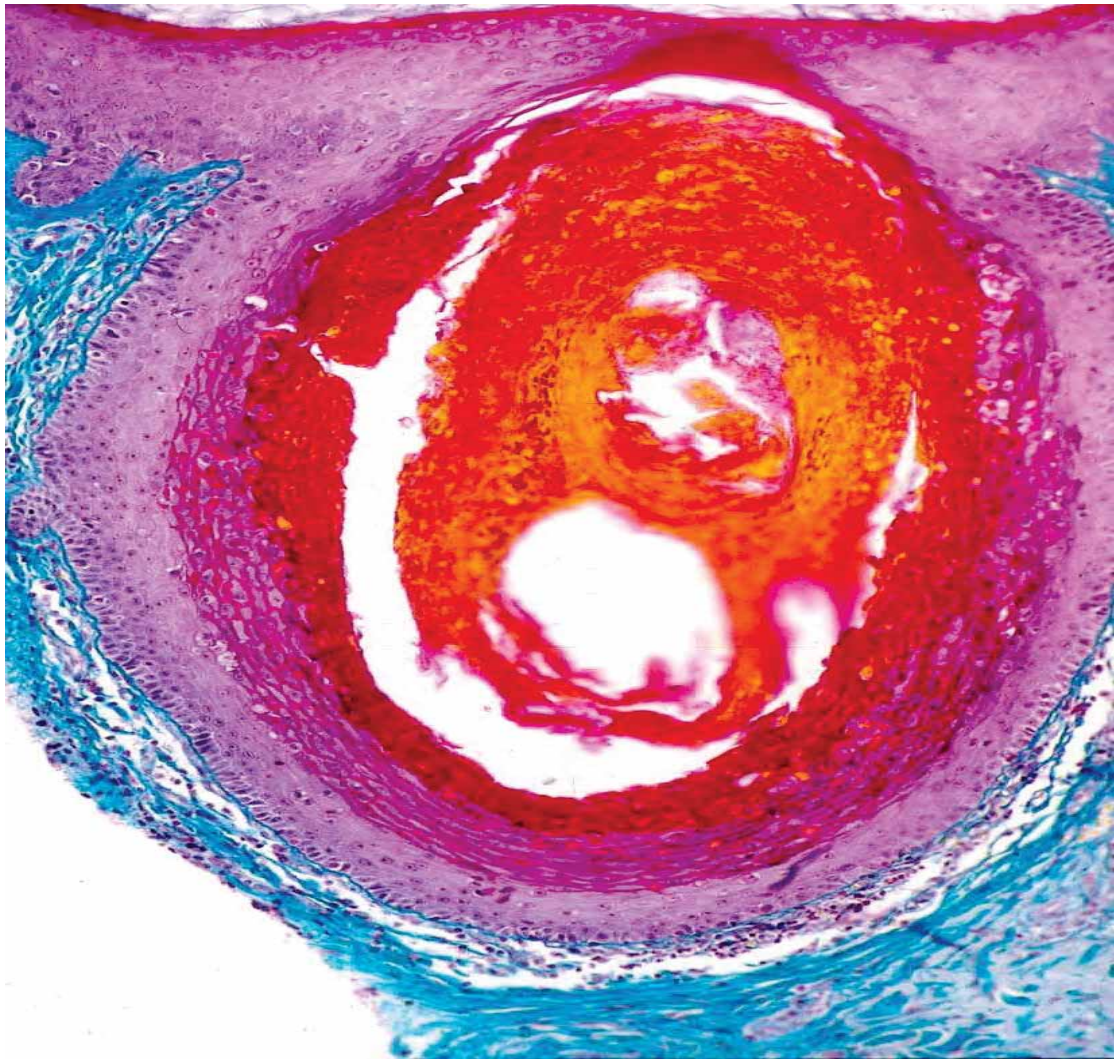




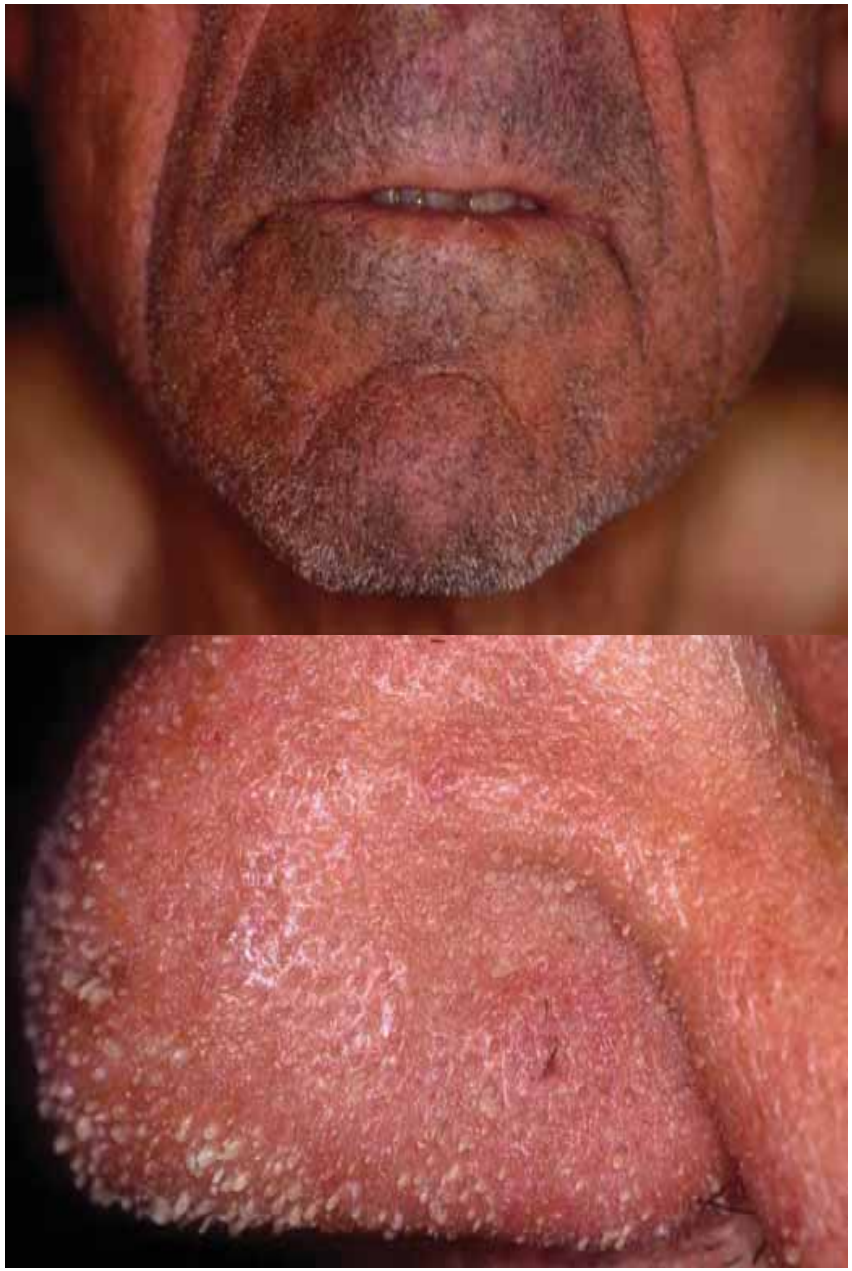


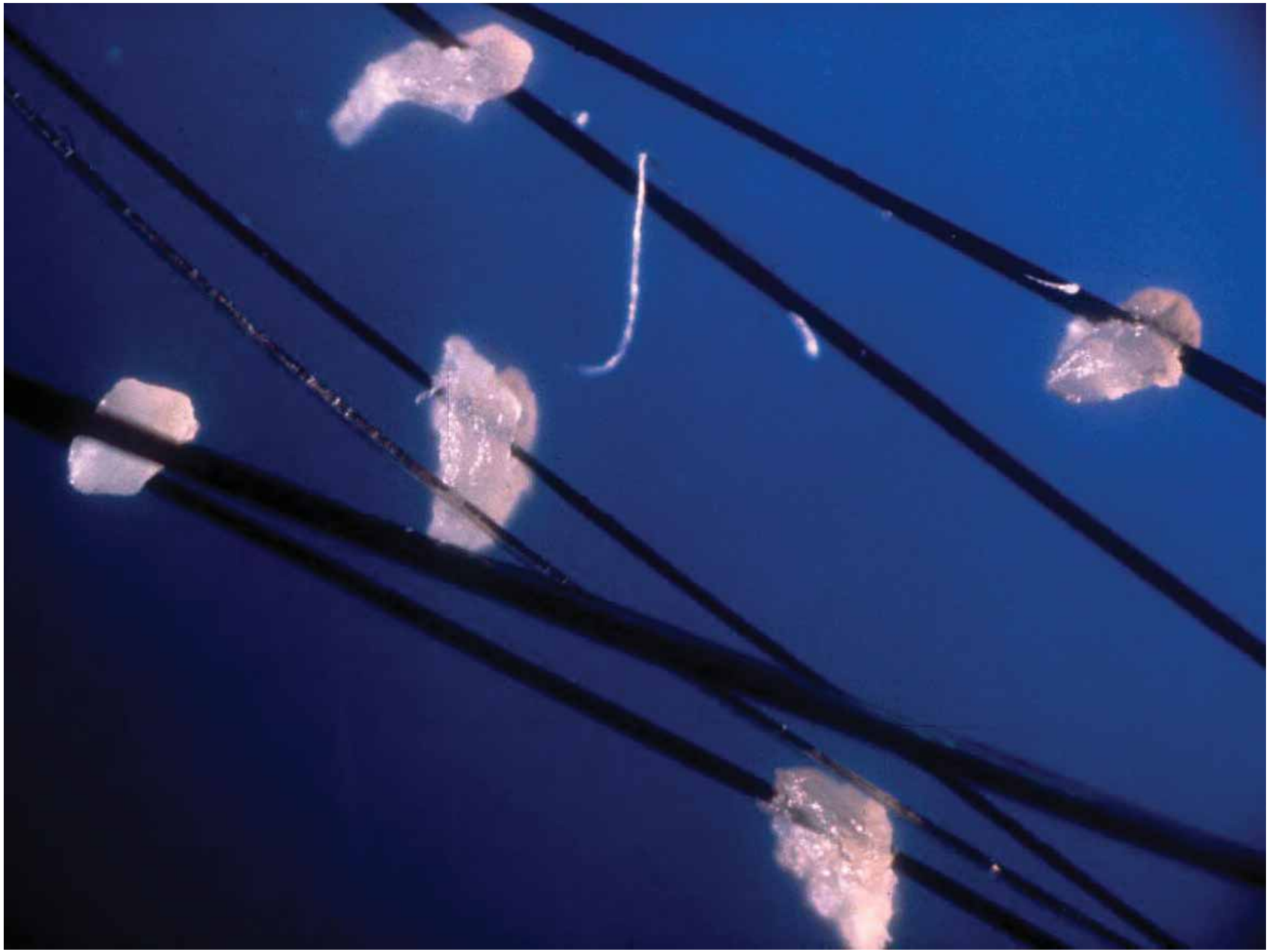


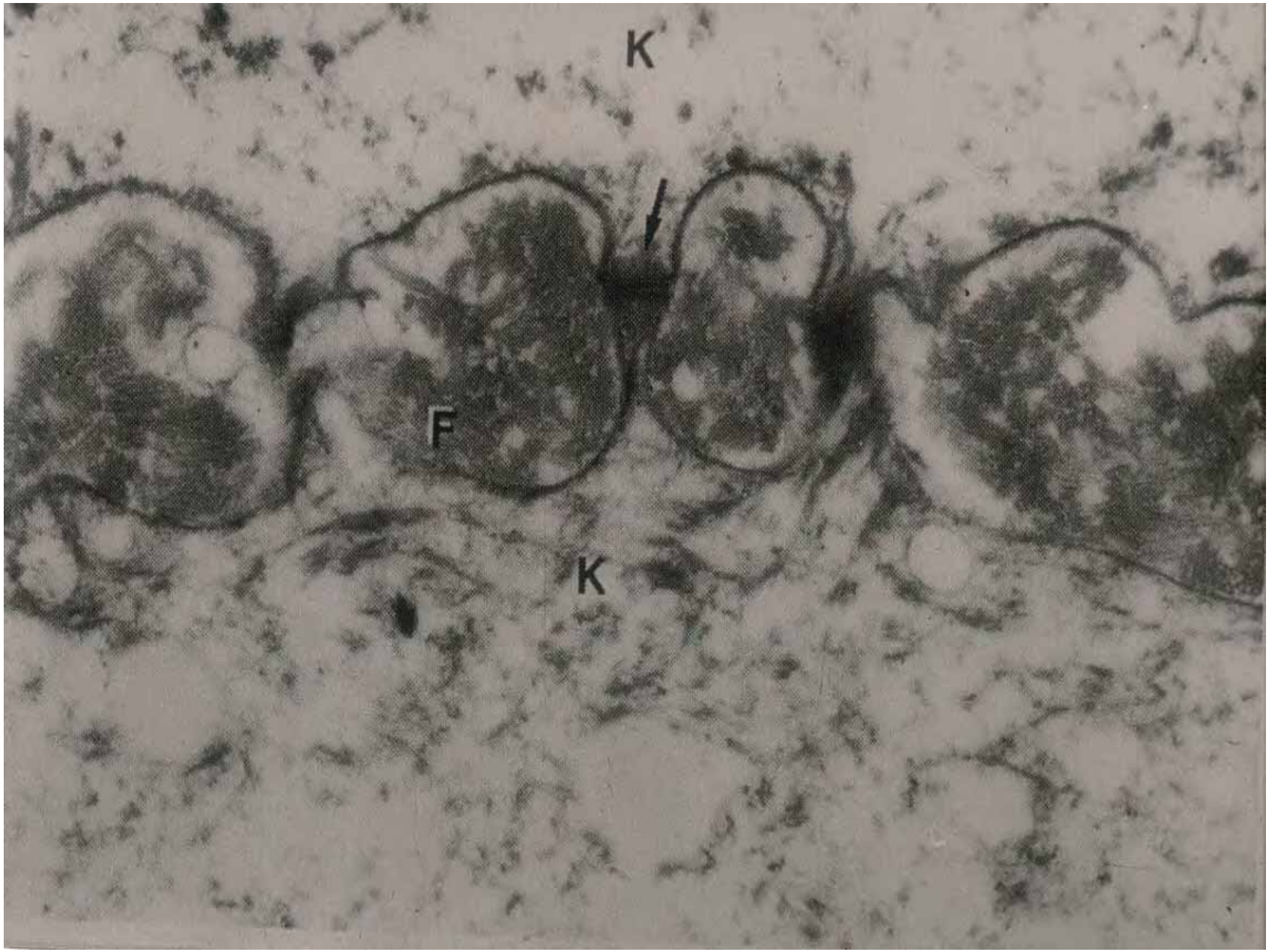
Intercellular eosinophilic deposits in the inner half of the infundibular epithelium is a *cliche* to …



Intercellular eosinophilic deposits in the inner half of the infundibular epithelium is a *cliche* to follicular spicules of the nose due to cryoglobulinemia



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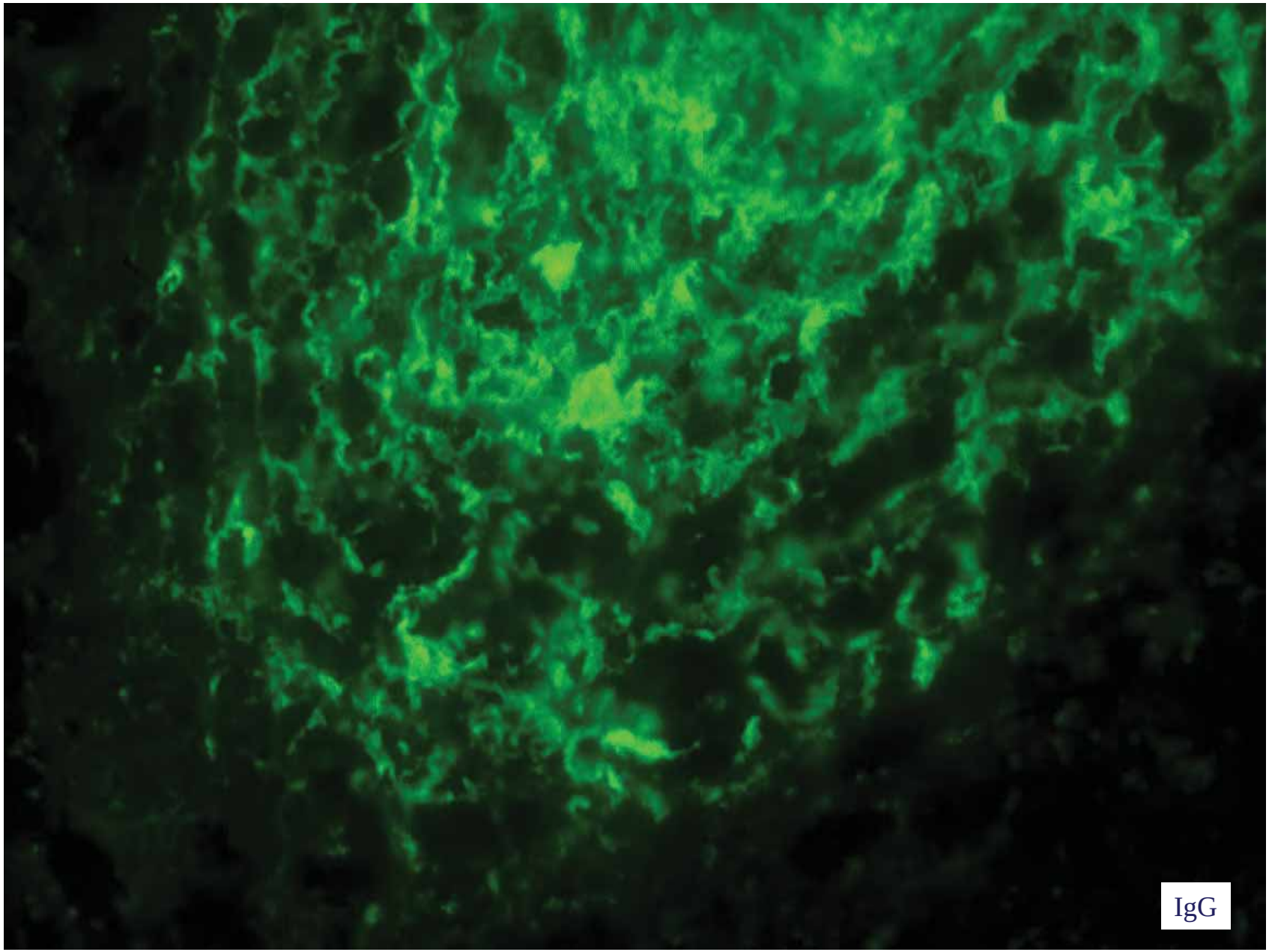
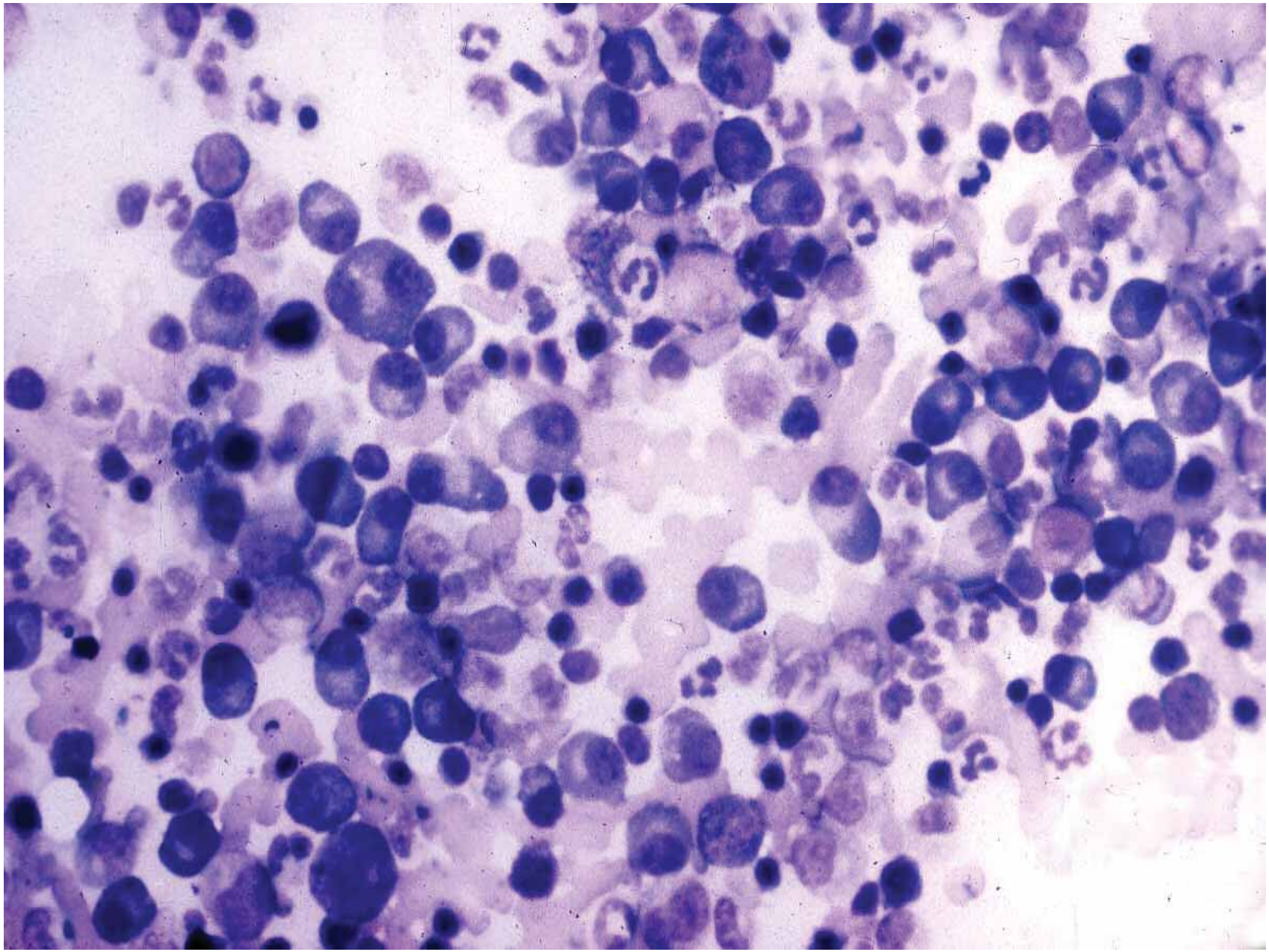
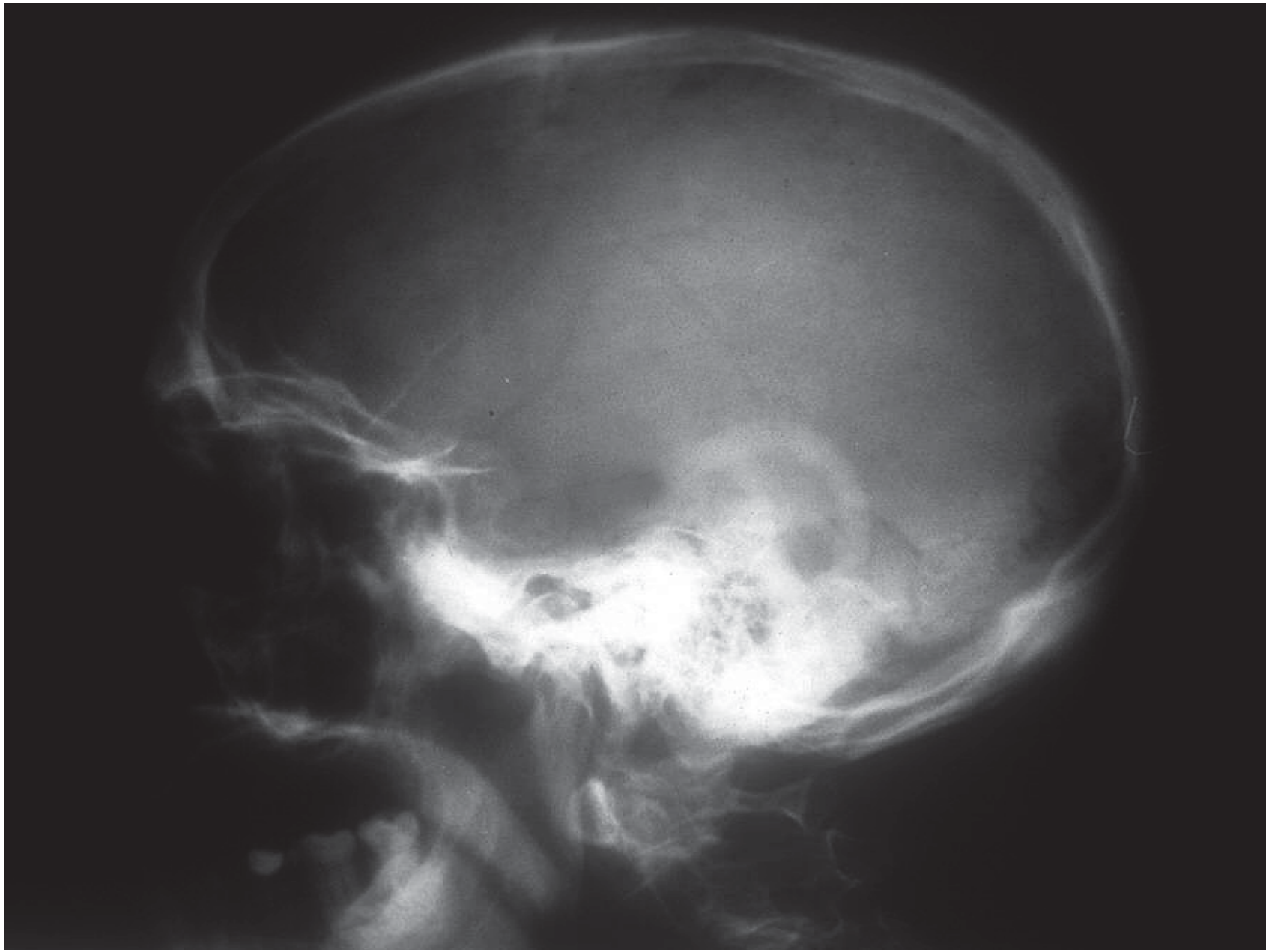
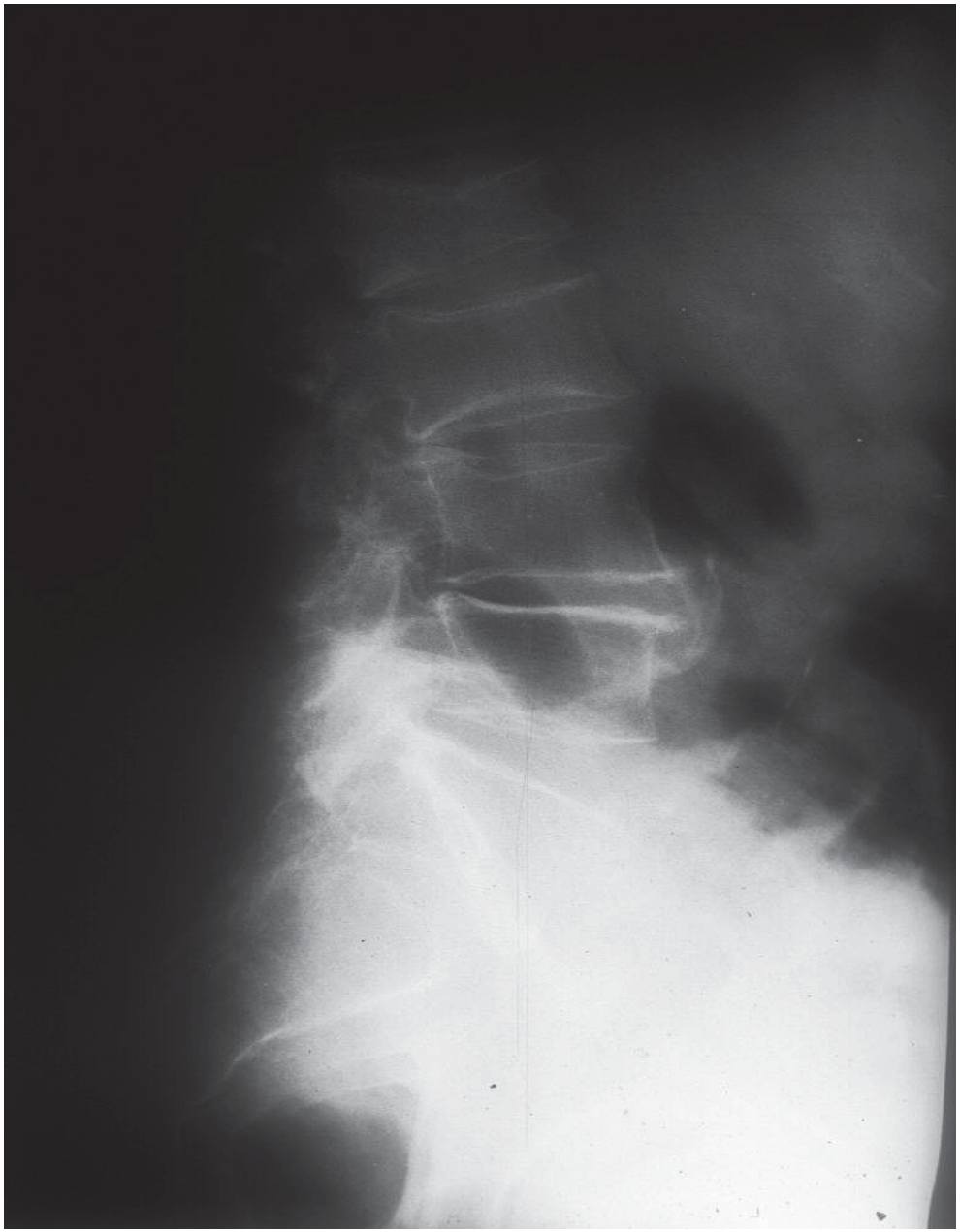
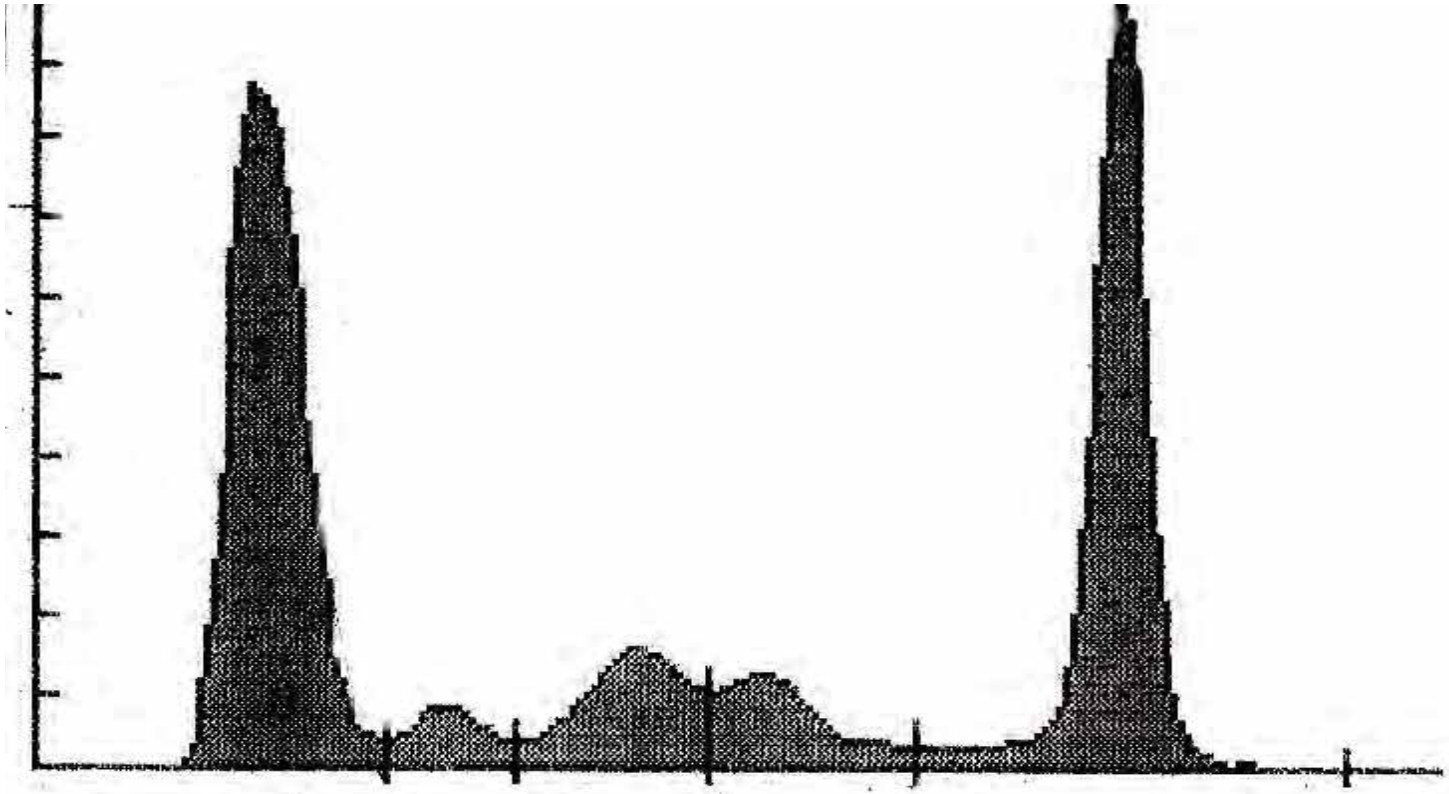

IgG

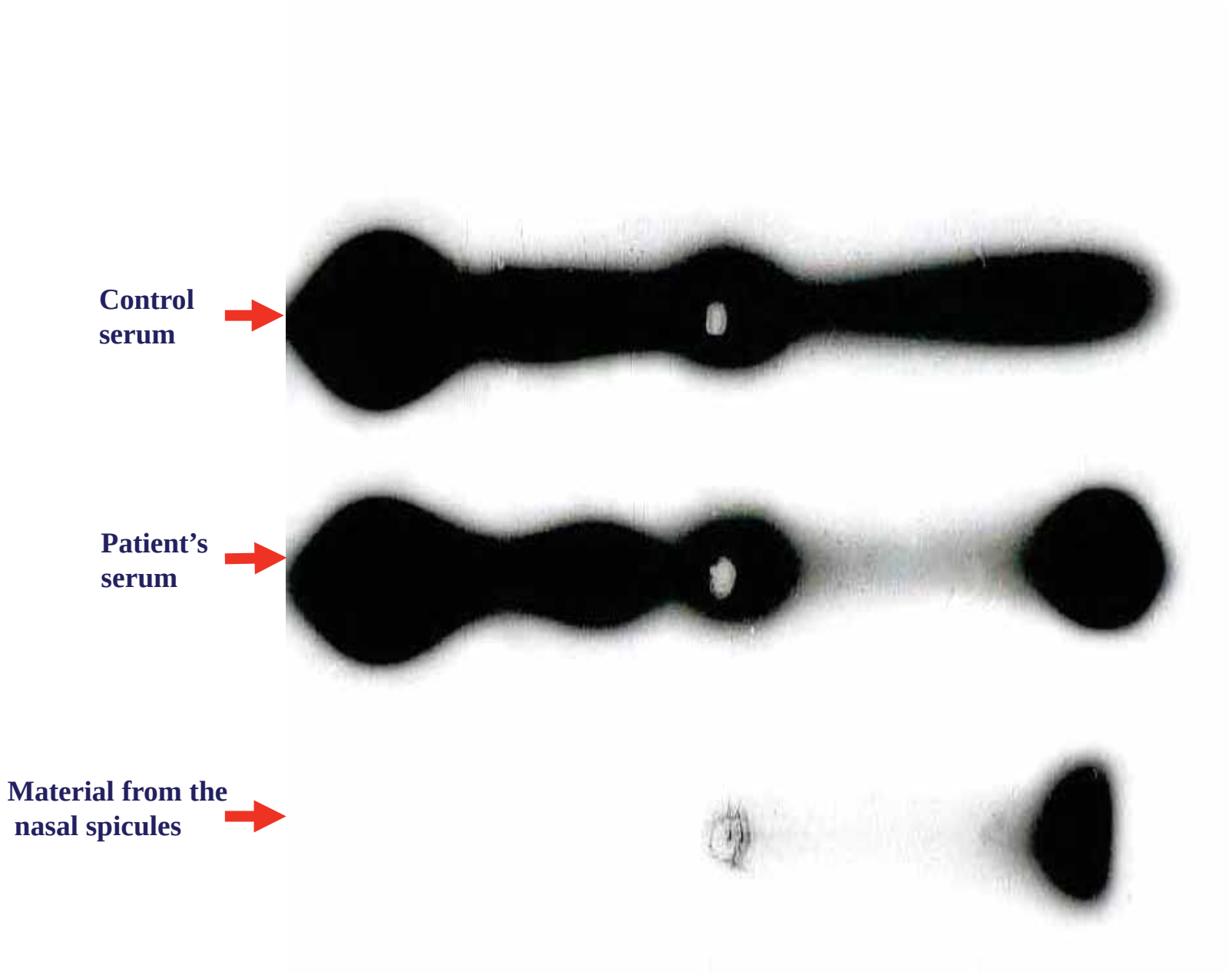


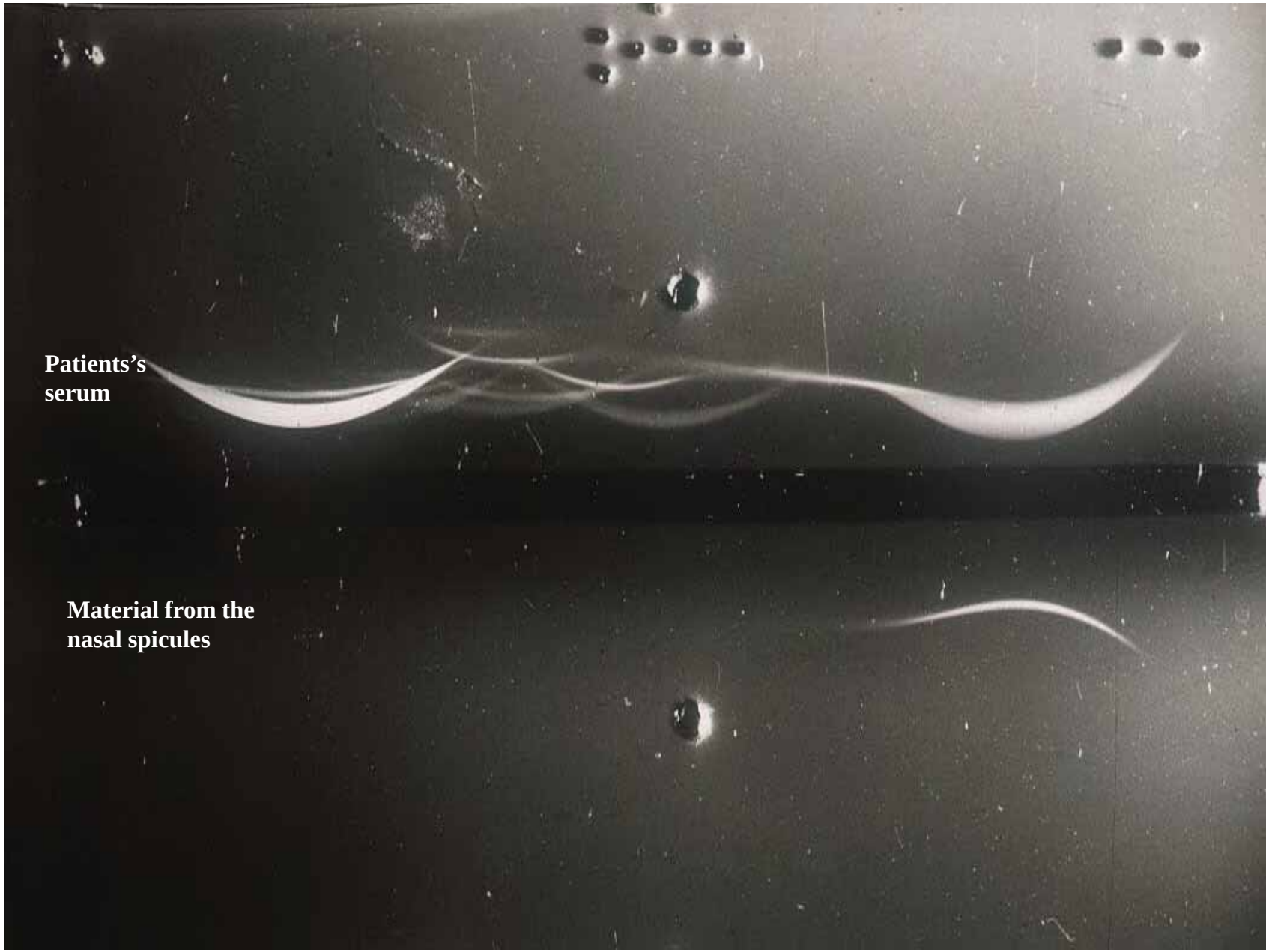






FRACTION	%	G/DL	REFERENCE RANGE		
ALBUMINA	41.4	4.1	3.6	-TO-	5.3
ALFA 1	4.1	0.4	0.2	-TO-	0.4
ALFA 2	10.9	1.1+	0.4	-TO-	0.9
BETA	8.3	0.8	0.6	-TO-	1.2
GAMMA	35.3	3.5+	0.7	-TO-	1.7
TOTAL		9.9+	6.5	-TO-	8.2
A/G	0.71				


Control serum
Patient's serum
Material from the nasal spicules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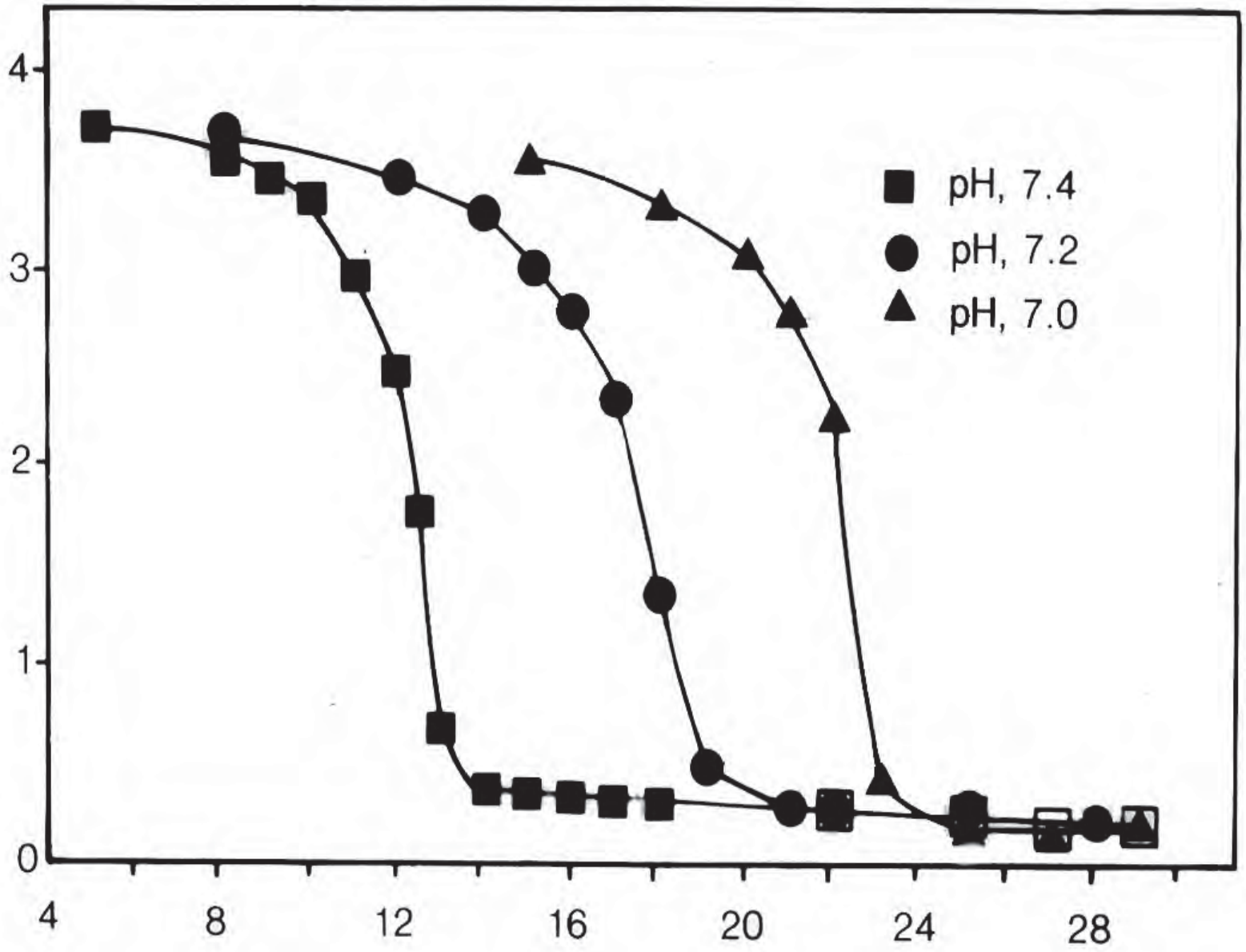
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Follicular spicules of the nose: A peculiar cutaneous manifestation of multiple myeloma with cryoglobulinemia

Luis Requena, MD,[a] José Luis Sarasa, MD,[b] Fernando Ortiz Masllorens, MD,[c] Lucia Martín, MD,[a] Enric Piqué, MD,[a] Mercedes Olivares, MD,[a] María Carmen Fariña, MD,[a] Elena Prieto, MD,[d] Eloy Pacho, MD,[e] and Juan Gómez Octavio, MD[e] *Madrid, Spain*

We describe a patient with multiple myeloma and cryoglobulinemia who had spicules with a horny appearance in the follicular openings of the face, particularly on the nose. Histopathologic study demonstrated that these spicules consisted of eosinophilic homogeneous deposits in the intercellular spaces between keratinocytes in the upper layers of the follicular infundibulum. Direct immunofluorescence, ultrastructural, and biochemical investigations revealed that these eosinophilic deposits were cryoprecipitates composed of IgG-κ with electrophoretic characteristics identical to those of the paraprotein present in the serum of the patient. Hence we believe that these lesions are best referred to as pseudohyperkeratotic spicules of the nose, and that they are a characteristic cutaneous manifestation of patients with multiple myeloma and cryoglobulinemia. (J AM ACAD DERMATOL 1995;32:834-9.)

Cutaneous manifestations in patients with multiple myeloma have been classified as specific and nonspecific.[1] The specific skin lesions include extramedullary plasmocytomas and secondary cutaneous involvement by direct extension from underlying bone tumors. The nonspecific manifestations include cutaneous findings that occur as a result of abnormal levels of proteins, cytopenia, or myelomatous involvement of internal organs. Since Bluefarb's publication,[1] several reports have described additional cutaneous findings in patients with multiple myeloma. These findings include pyoderma gangrenosum,[2-4] leukocytoclastic vasculitis,[5] necrobiotic xanthogranuloma,[6] scleromyxedema,[7] Sweet's syndrome,[8, 9] subcorneal pustular dermatosis,[10, 11] POEMS syndrome,[12-14] scleredema,[15] angioedema with C1 inhibitor deficiency,[16] and plane xanthoma.[17] All these cutaneous manifestations have recently been reviewed.[18] A characteristic, although uncommon, cutaneous manifestation in patients with multiple myeloma and cryoglobulinemia consists of spicules with horny appearance that develop in follicular openings of the face, particularly on the nose.

We describe a 79-year-old man with IgG-κ multiple myeloma and cryoglobulinemia who had follicular spicules, composed mostly of IgG-κ, on his face.

CASE REPORT

A 79-year-old man had multiple filiform spicules on his face. The patient had a 30-year history of chronic obstructive airway disease. His medications included fenoterol, budesonide, and theophylline. Examination revealed multiple, minute follicular spicules, mostly on the nose (Fig. 1), forehead, cheeks, chin, and, to a lesser extent, on the shoulders, arms, and upper portions of the back. These spicules could be removed easily without bleeding. Scattered on the scalp, many hair shafts showed tiny white adherent particles of the same material, mimicking nits of hair casts. A mottled, red to blue, reticulated vascular pattern suggestive of livedo reticularis was evident on the anterior aspect of the knees, and purpuric lesions, some with a necrotic surface and covered by hemorrhagic crusts, were present on both ankles.

Roentgenographic examination showed small osteolytic defects in the skull and in two vertebrae that were

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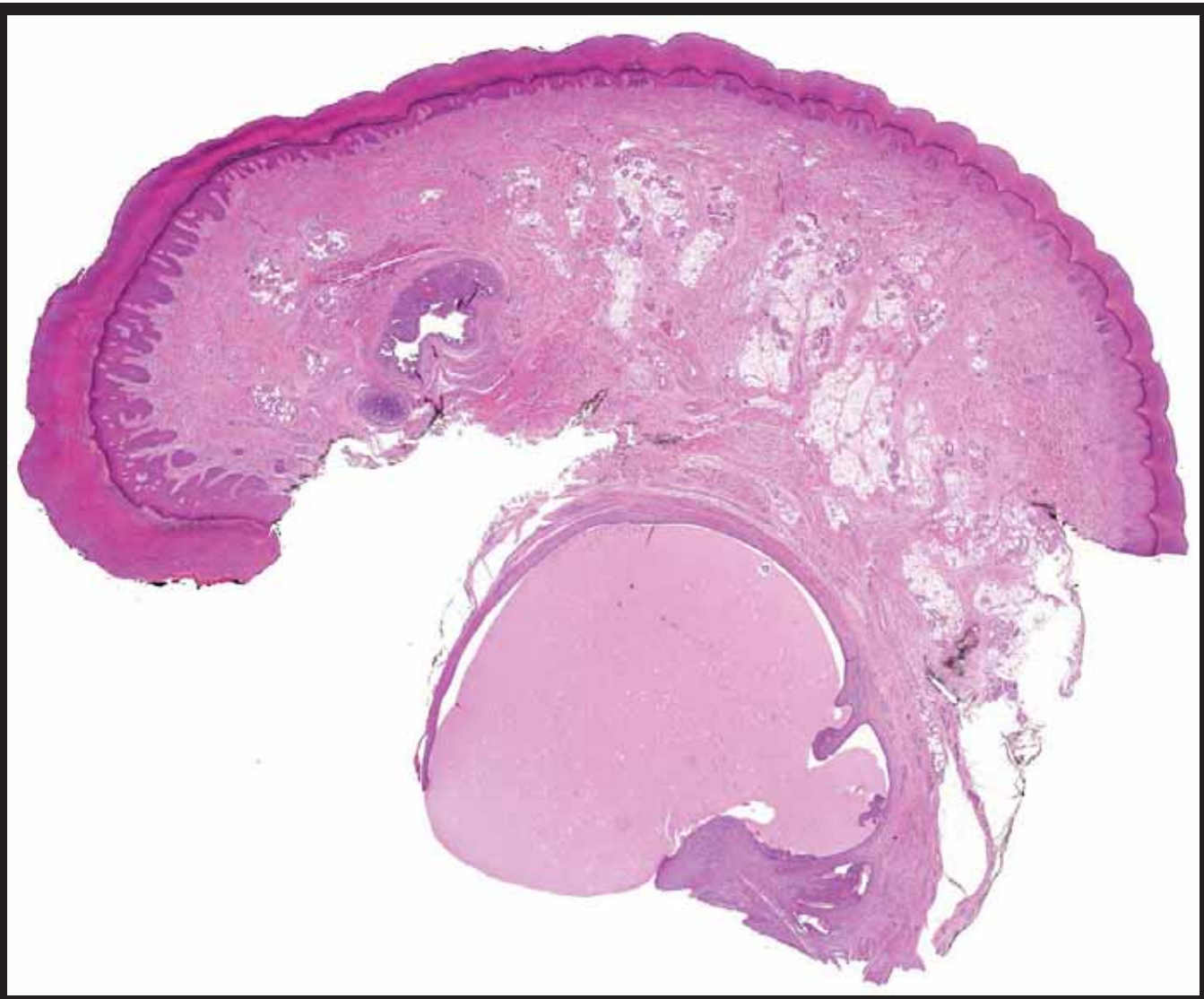

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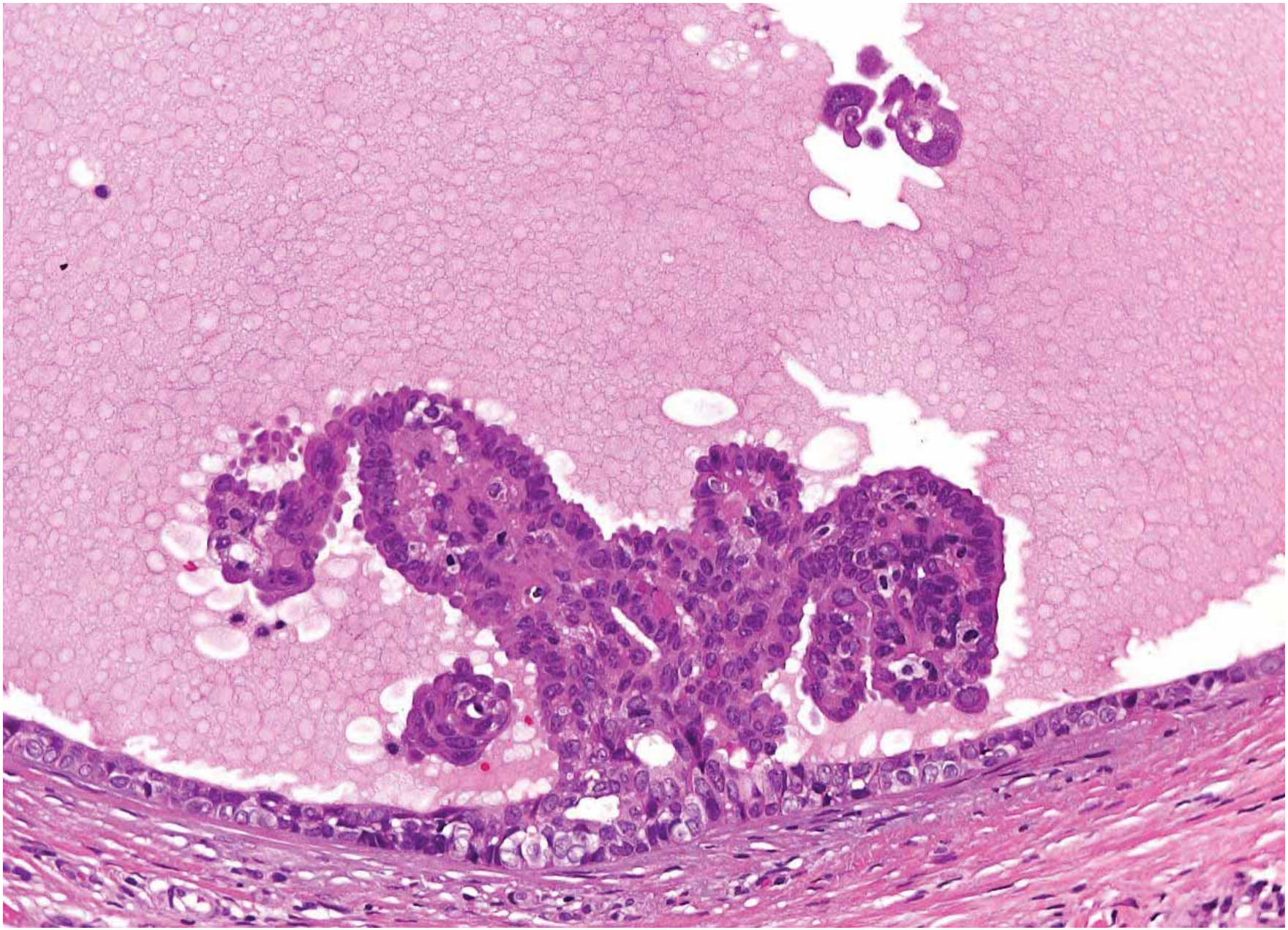
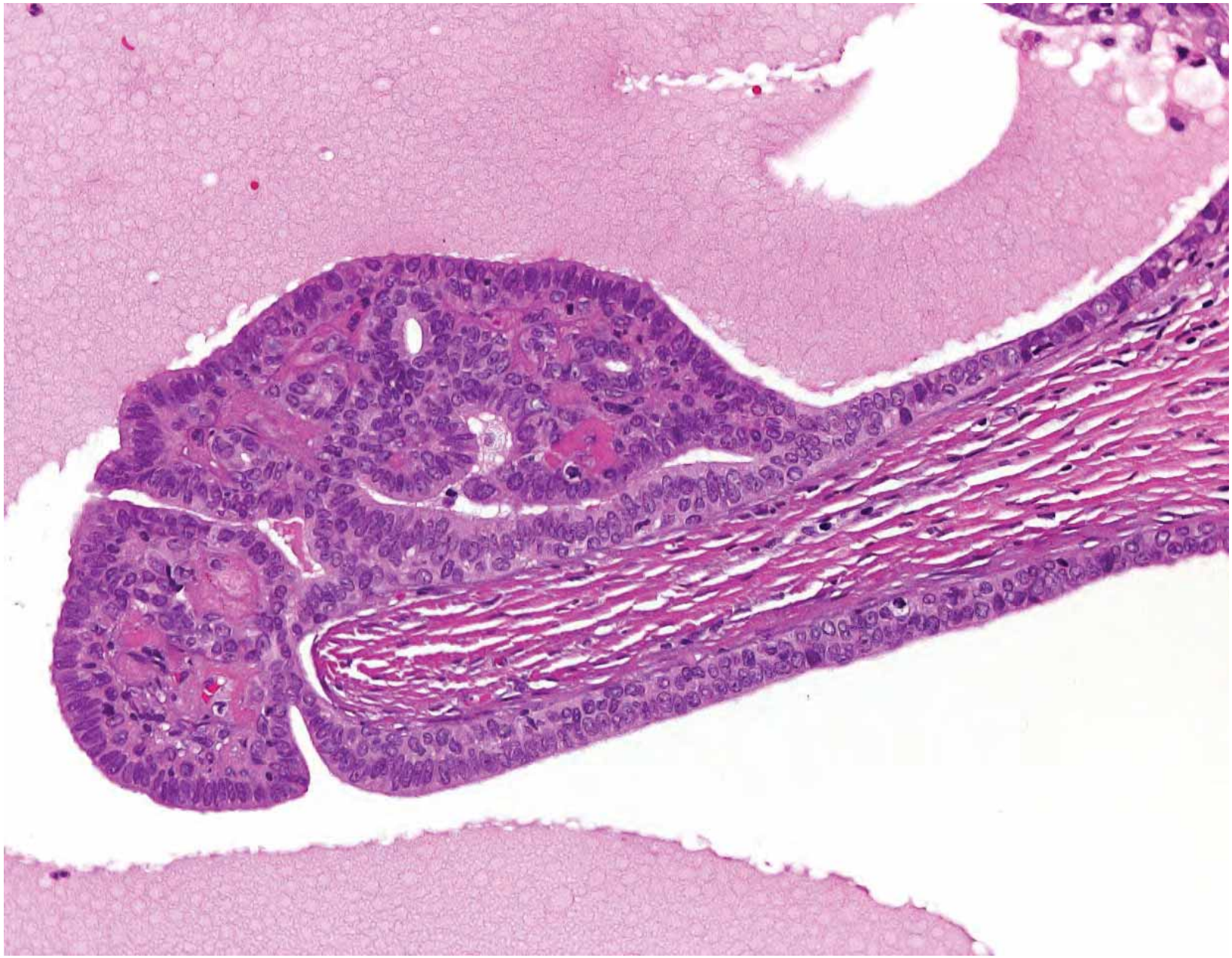
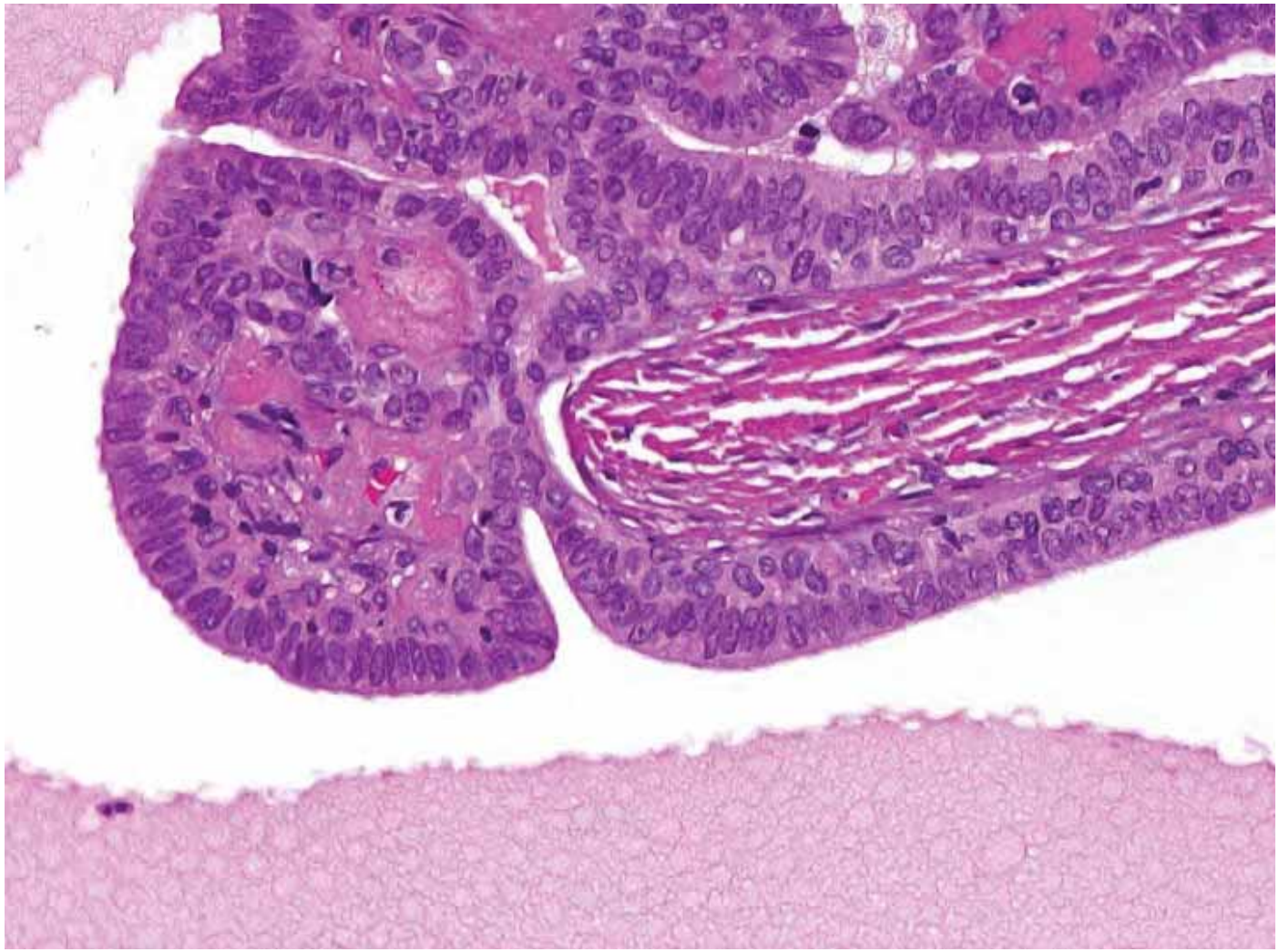
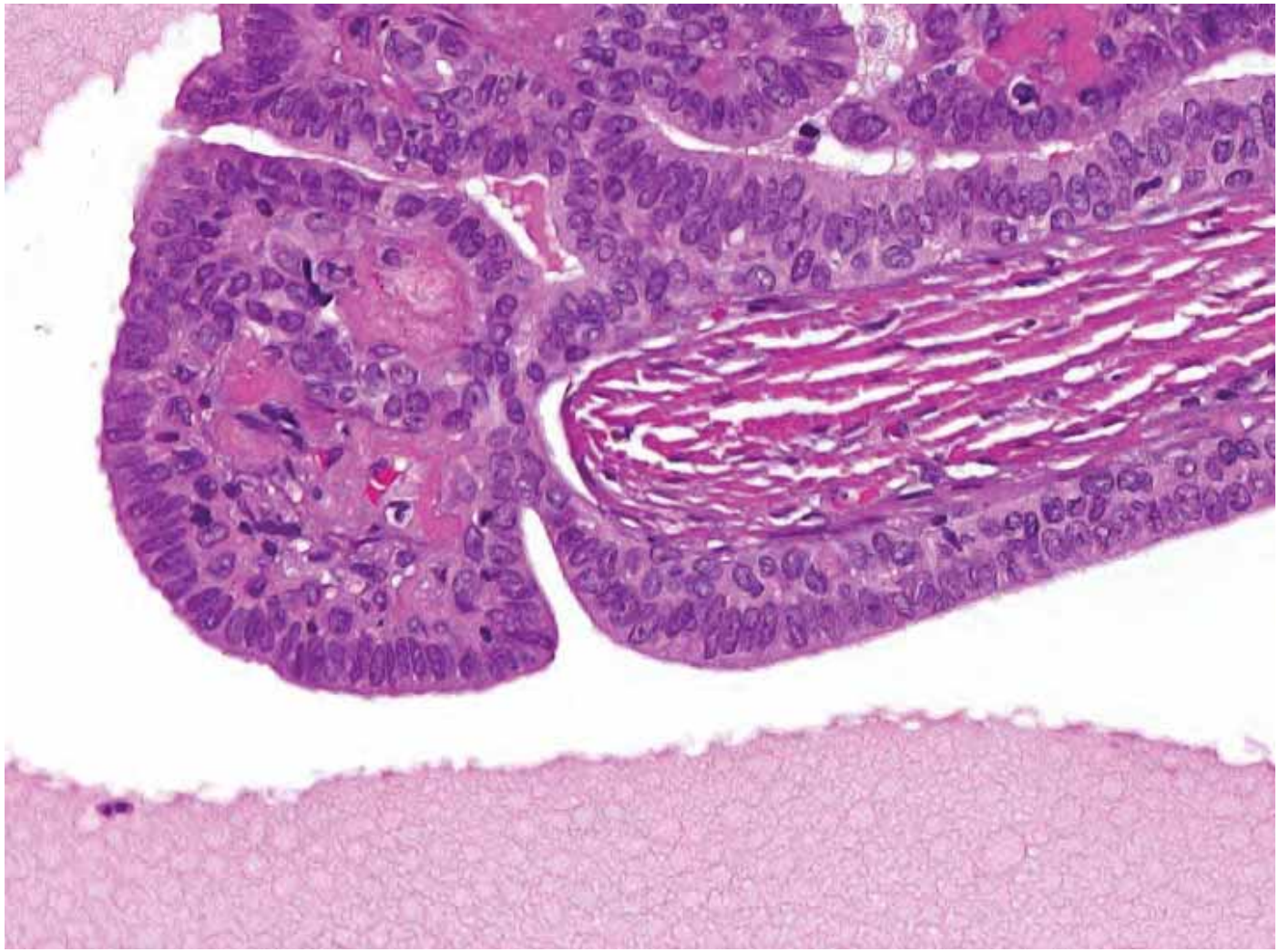
What is the *cliche* and what is the diagnosis?





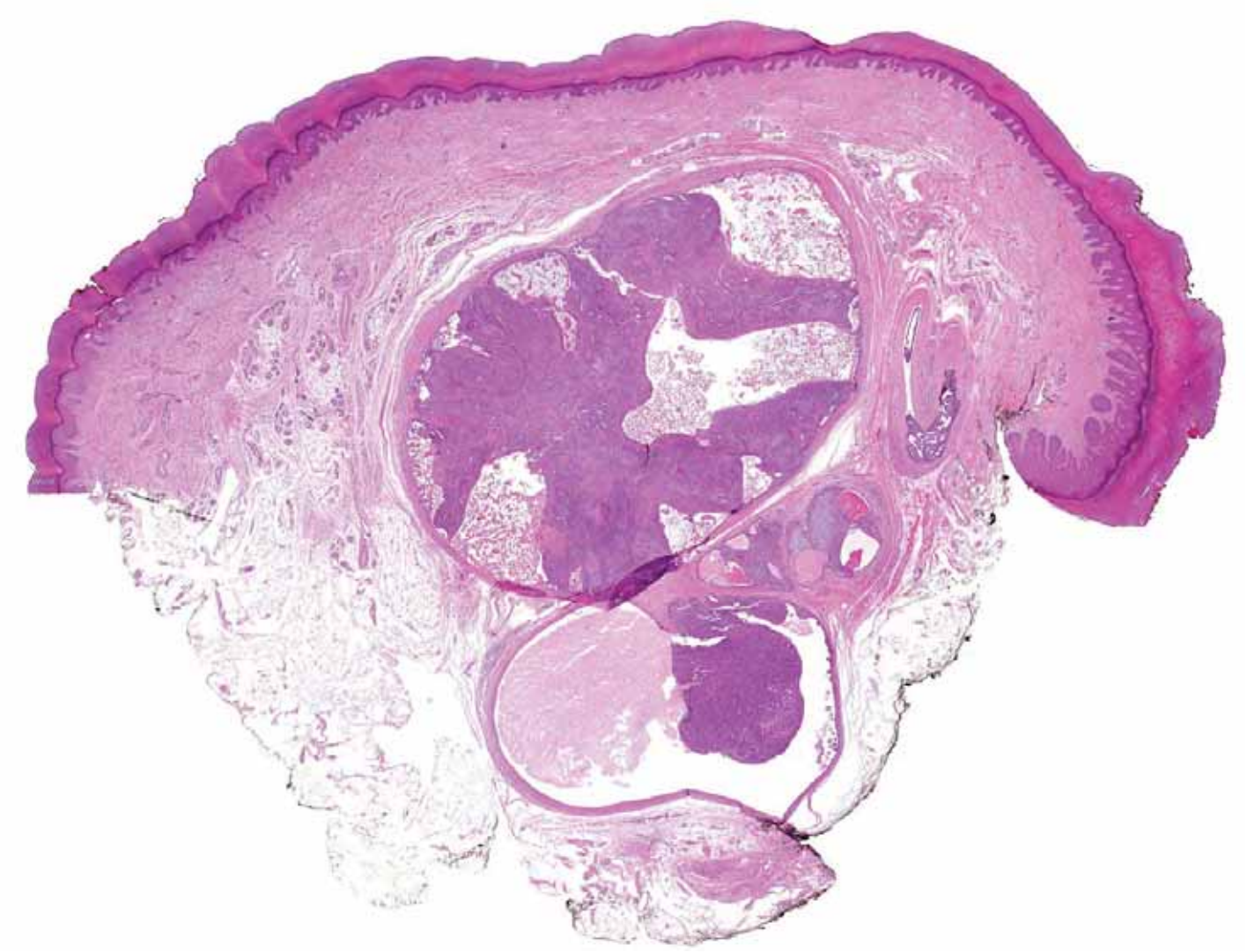


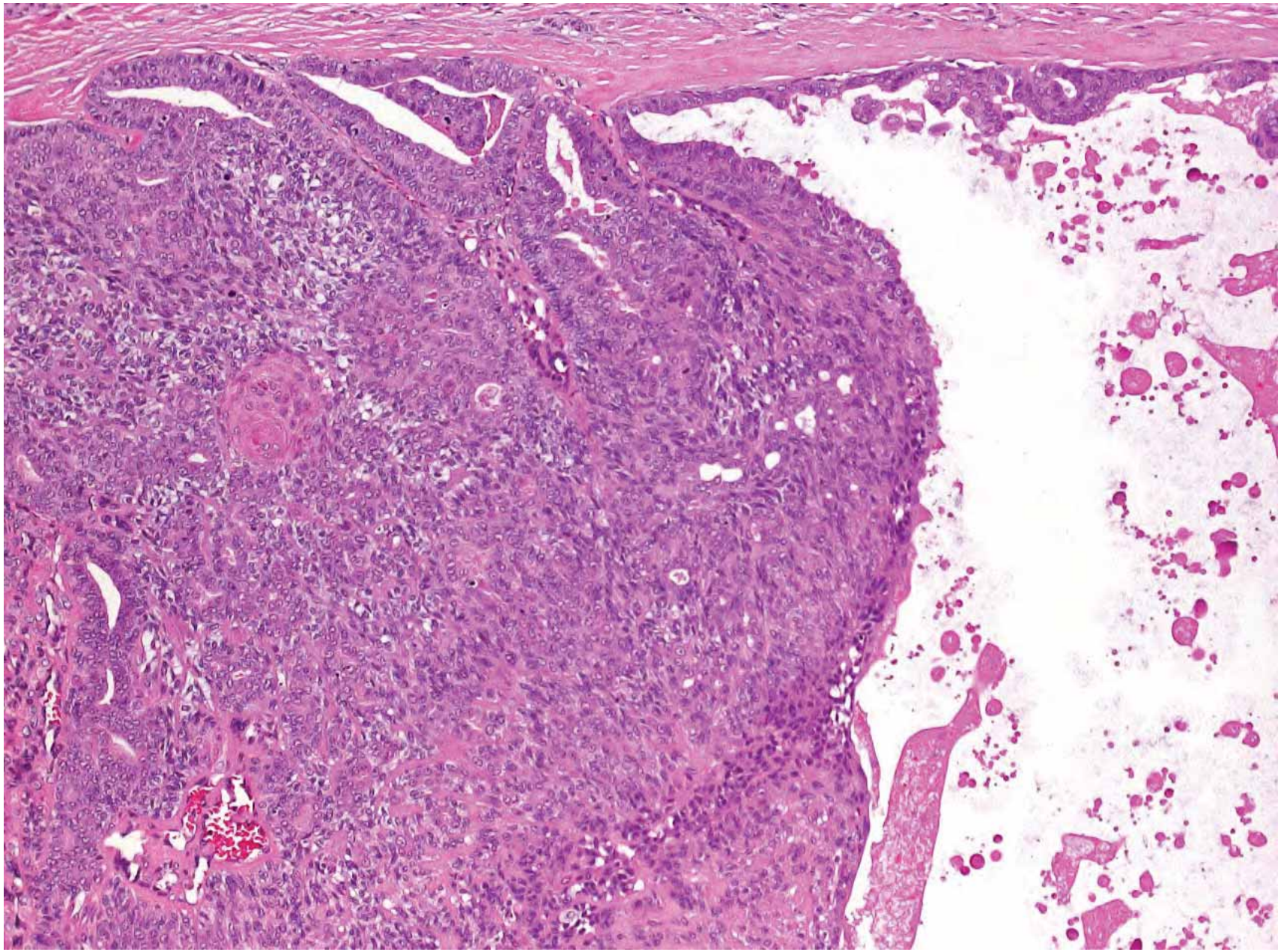
An apocrine hidrocystoma-like kesion on the fingertips or toes is a *cliche* to…

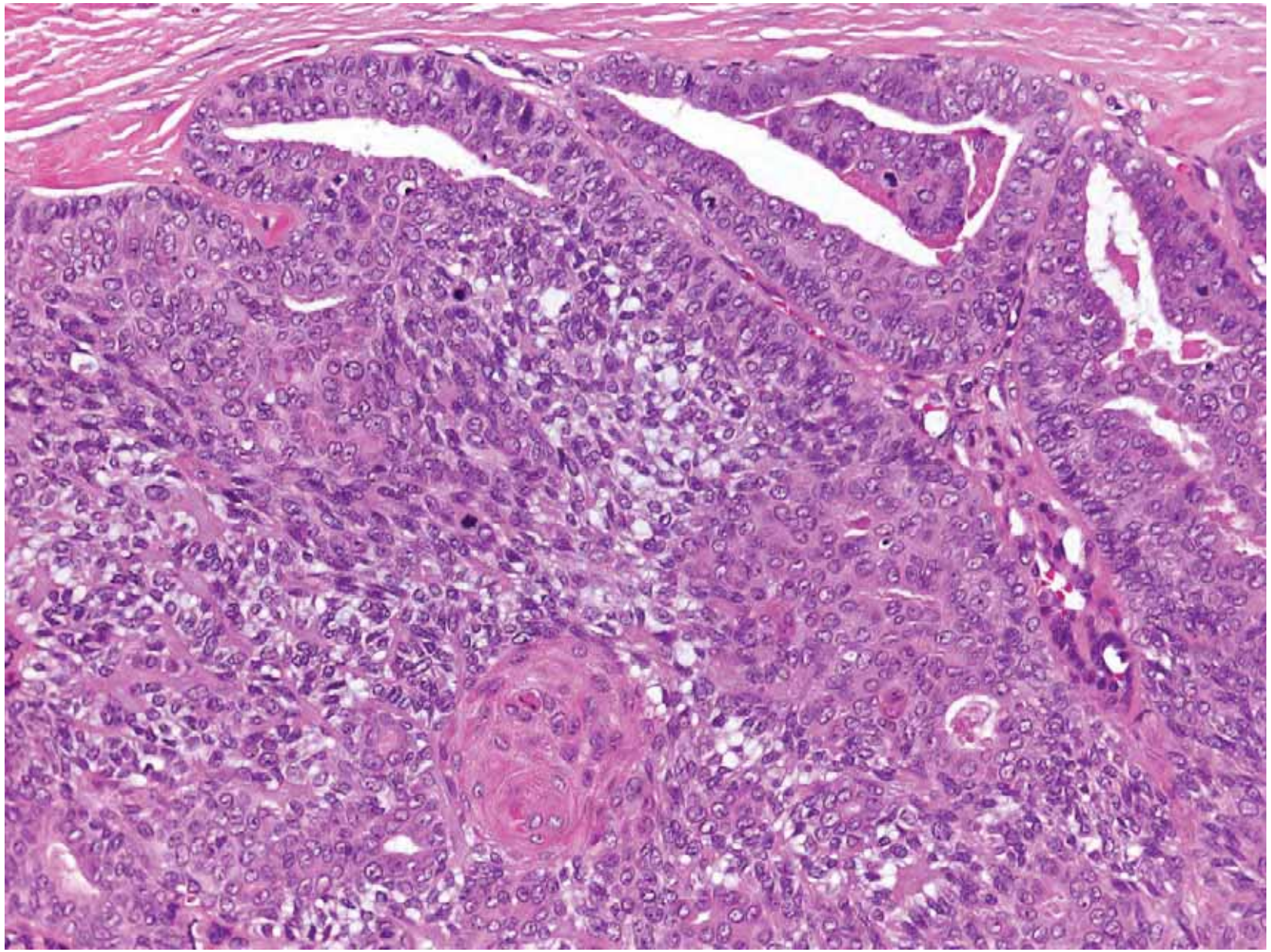


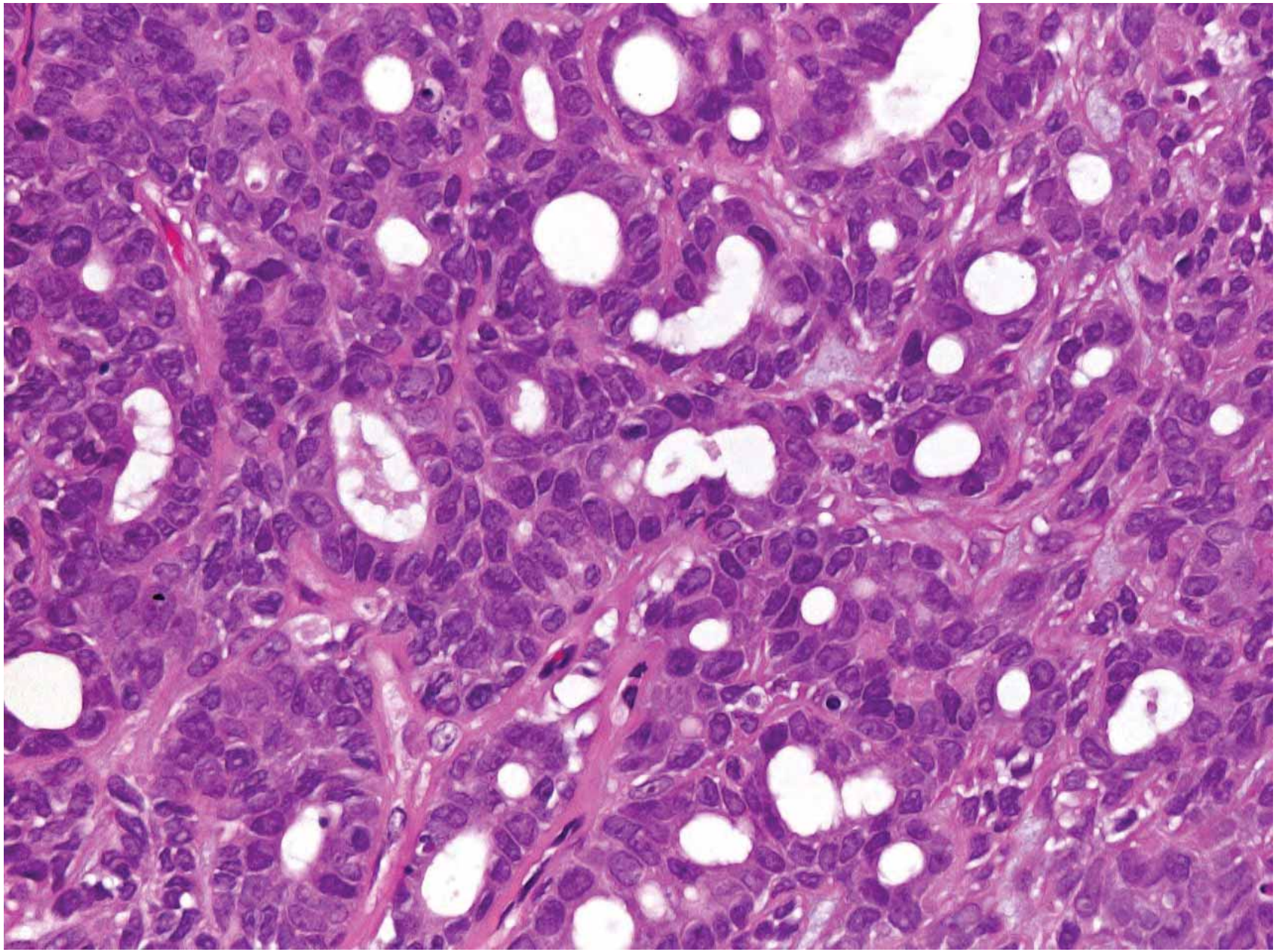
An apocrine hidrocystoma-like kesion on the fingertips or toes is a *cliche* to digital papillary adenocarcinoma

Deepers sections of the same biopsy…









"Apocrine Hidrocystoma and Cystadenoma"–like Tumor of the Digits or Toes

A Potential Diagnostic Pitfall of Digital Papillary Adenocarcinoma

Ana-María Molina-Ruiz, MD, Mar Llamas-Velasco, MD,† Arno Rütten, MD,‡ Lorenzo Cerroni, MD,§ and Luis Requena, MD**

Abstract: Digital papillary carcinoma (DPC) is a rare, underreported, and often misdiagnosed malignant tumor of the sweat glands. It is often located on the digits and toes and most commonly occurs in male individuals in their fifties to seventies. Because of lack of pain, slow growth, and an inconspicuous appearance, clinical diagnosis is often missed or delayed. In contrast, apocrine hidrocystoma (AH) is a cystic adenoma that arises from the apocrine secretory coil, and it is extremely rare for AHs to develop on the digits. We report 7 cases of DPC, including clinical course, histopathologic and immunohisto chemical findings, and therapeutic approach in which the initial histopathologic diagnosis in all cases was AH or cystadenoma. However, complete excision of the neoplasms led to a final diagnosis of DPC. After an adequate treatment, no recurrence or metastasis was found in any of the cases described. All the cases studied showed similar histopathologic and immunohisto chemical findings. The initial incisional biopsy showed large unilocular or multilocular cystic spaces situated within the dermis, lined by a double layer of epithelial cells with tiny papillary structures. No cellular atypia, necrosis, or pleomorphism was observed. However, complete excision revealed neoplastic lesions involving the dermis and/or subcutis, with an infiltrative pattern and papillary projections into luminal spaces. Immunoperoxidase studies showed positivity for CK7, S-100 protein, CEA, p63, smooth muscle actin, and calponin. DPC is a rare but life-threatening malignancy, therefore it is important to be able to identify such a lesion both clinically and histopathologically, treat it, and monitor the patient for the tumor's potential recurrence and metastasis. Pathologists and dermatopathologists should be aware that a histopathologic diagnosis of AH or cystadenoma on the fingers and toes should be established with caution, because probably those lesions represent the superficial and cystic component of an underlying DPC, and a wider excision should be performed.

Key Words: aggressive digital papillary adenocarcinoma, digital papillary carcinoma, apocrine, hidrocystoma, apocrine cystadenoma tumors of sweat glands, tumor of digits and toes

(*Am J Surg Pathol* 2016;40:410–418)

Digital papillary carcinoma (DPC) is a rare malignant sweat gland tumor with metastatic potential that was first recognized by Helwig[1] in 1984. A series of 57 cases from the material of the Armed Forces Institute of Pathology (AFIP) of the United States were initially classified as either aggressive digital papillary adenoma (ADPA) or aggressive digital papillary adenocarcinoma (ADPAca).[2] Of the 57 patients in that series, 40 were found to have ADPA and 17 had ADPAca. The latter were differentiated from the former by findings such as poor glandular differentiation, cellular atypia, necrosis, pleomorphism, and invasion of bone, soft tissue, and vasculature. In 1998, in a monography dedicated to neoplasms with apocrine differentiation, some of us reported that the neoplasms labeled as adenoma and adenocarcinoma by Kao and coworkers represented a single pathologic process and that all were adenocarcinomas.[3] Later Duke et al[4] retrospectively analyzed the same material from the AFIP and found that, of the 30 cases initially diagnosed as ADPA, 9 recurred and 3 progressed to metastatic lesions. In the light of these findings, they also concluded that all lesions suspected to be adenomas should be treated as if they were ADPAca. Other investigators also found that lesions initially diagnosed as adenomas have metastatic potential and agree that the term ADPA should be abandoned.[5] In fact, in the 2006 World Health Organization (WHO) classification of skin tumors, ADPA and ADPAca were grouped together in a single entity under the term DPC.[6] No large-scale studies have been conducted because this is quite a rare neoplasm, which often is misdiagnosed clinically, a fact that may delay the standard treatment of excision or amputation. Once diagnosed and treated, careful follow-up is necessary to monitor for metastasis.

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- 7 cases of DPC in which the initial histopathologic diagnosis in all cases was apocrine hidrocystoma or cystadenoma
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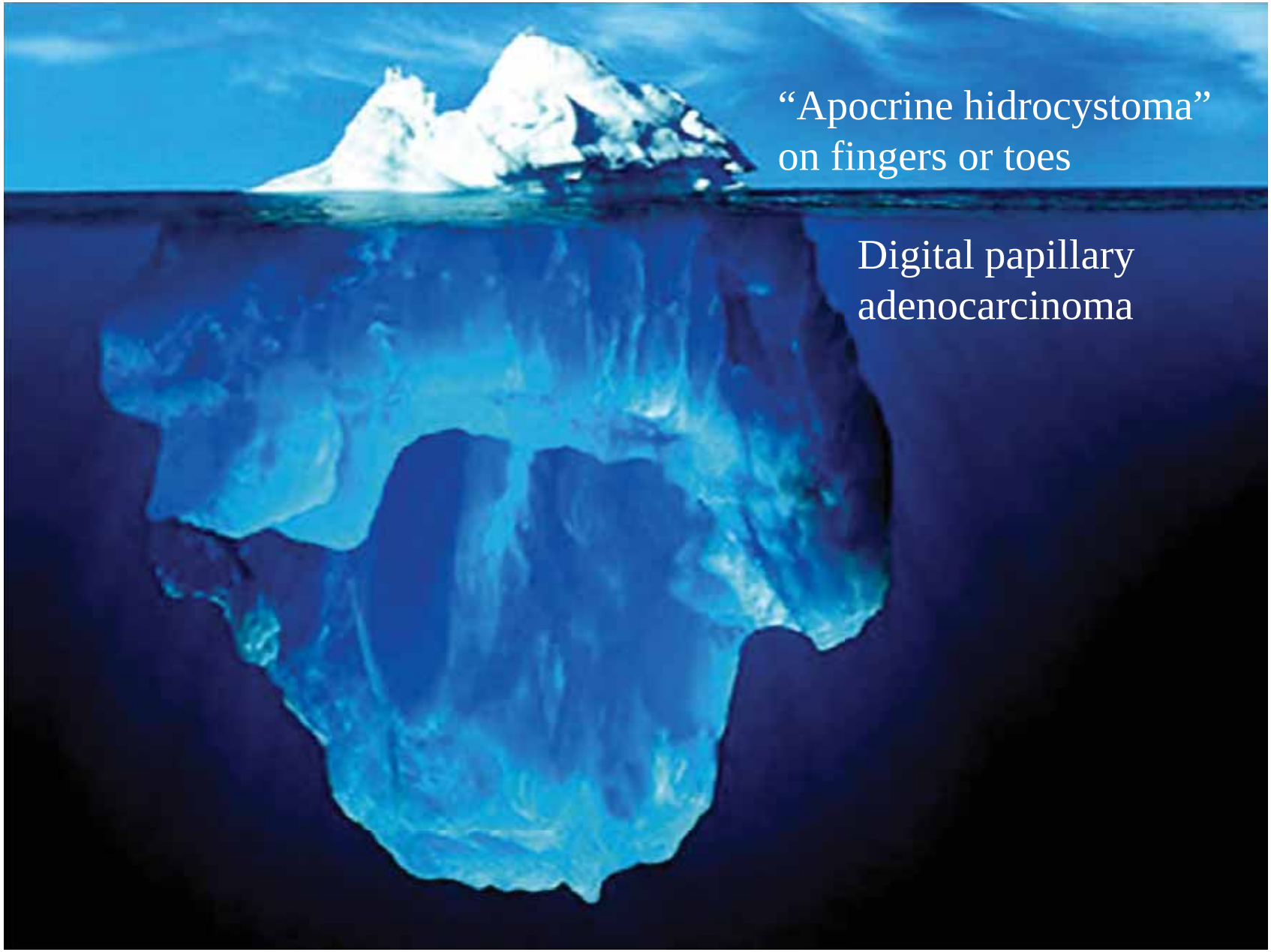
“Apocrine hidrocystoma”
on fingers or toes
Digital papillary
adenocarcinoma

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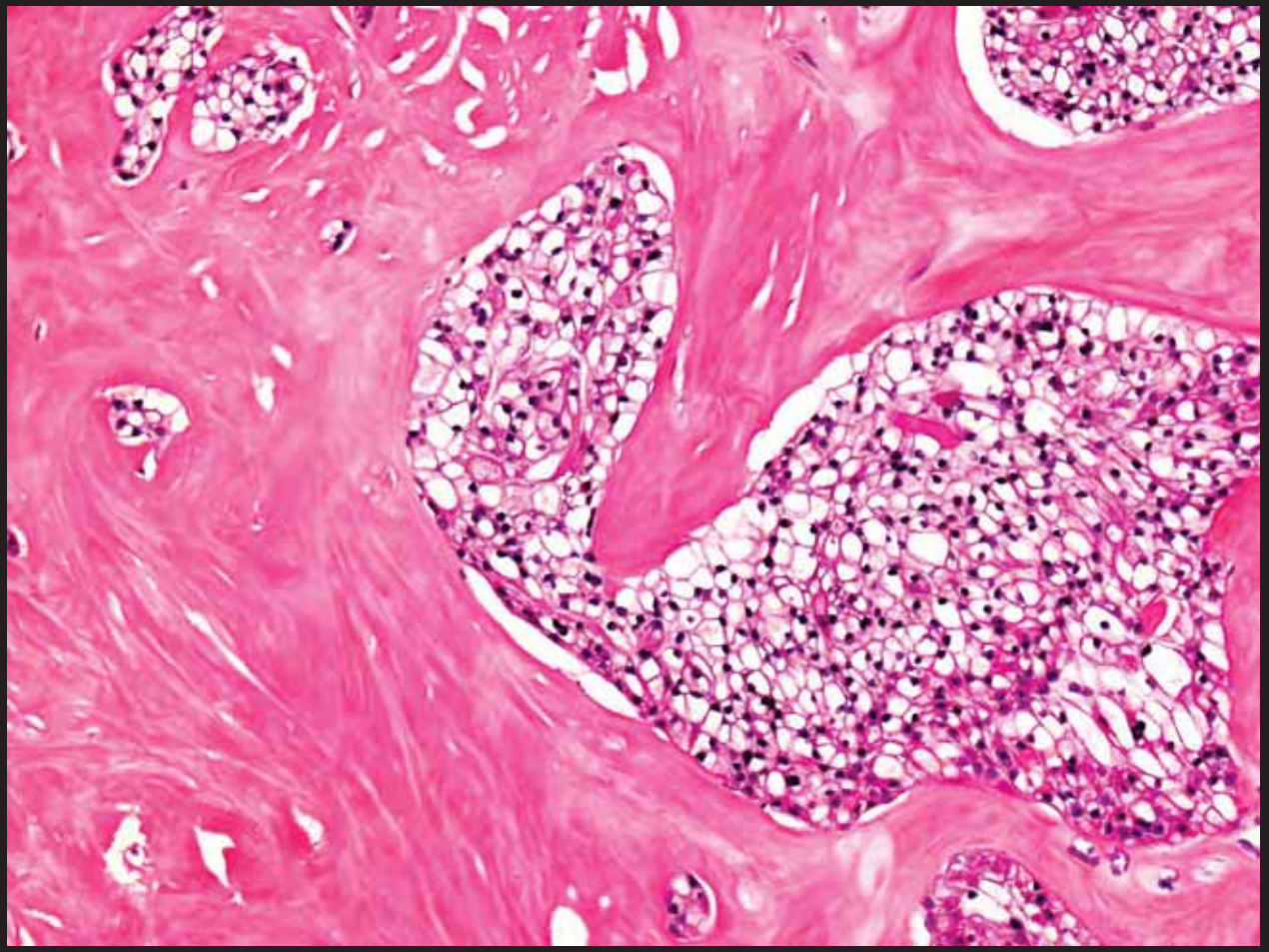
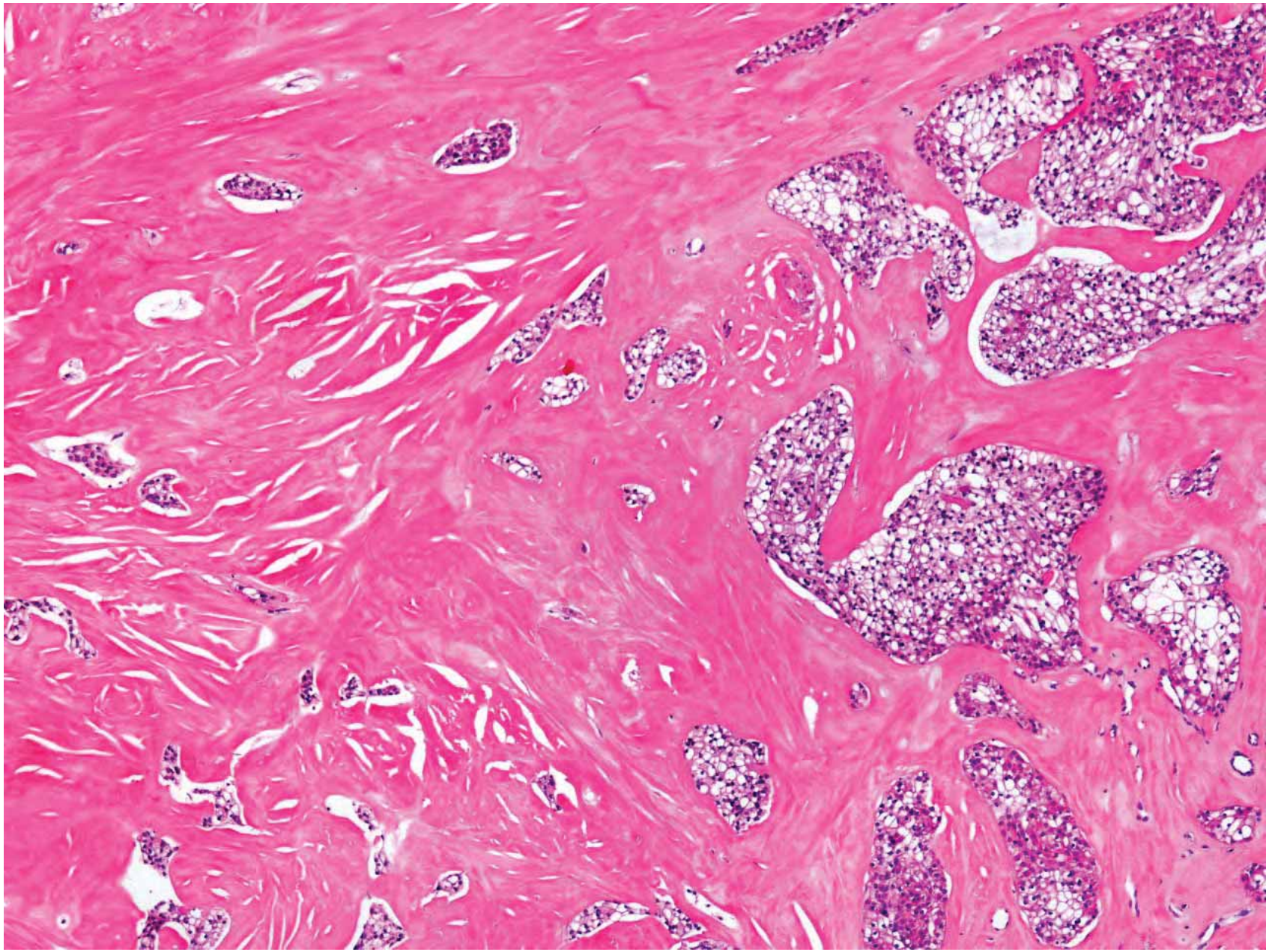
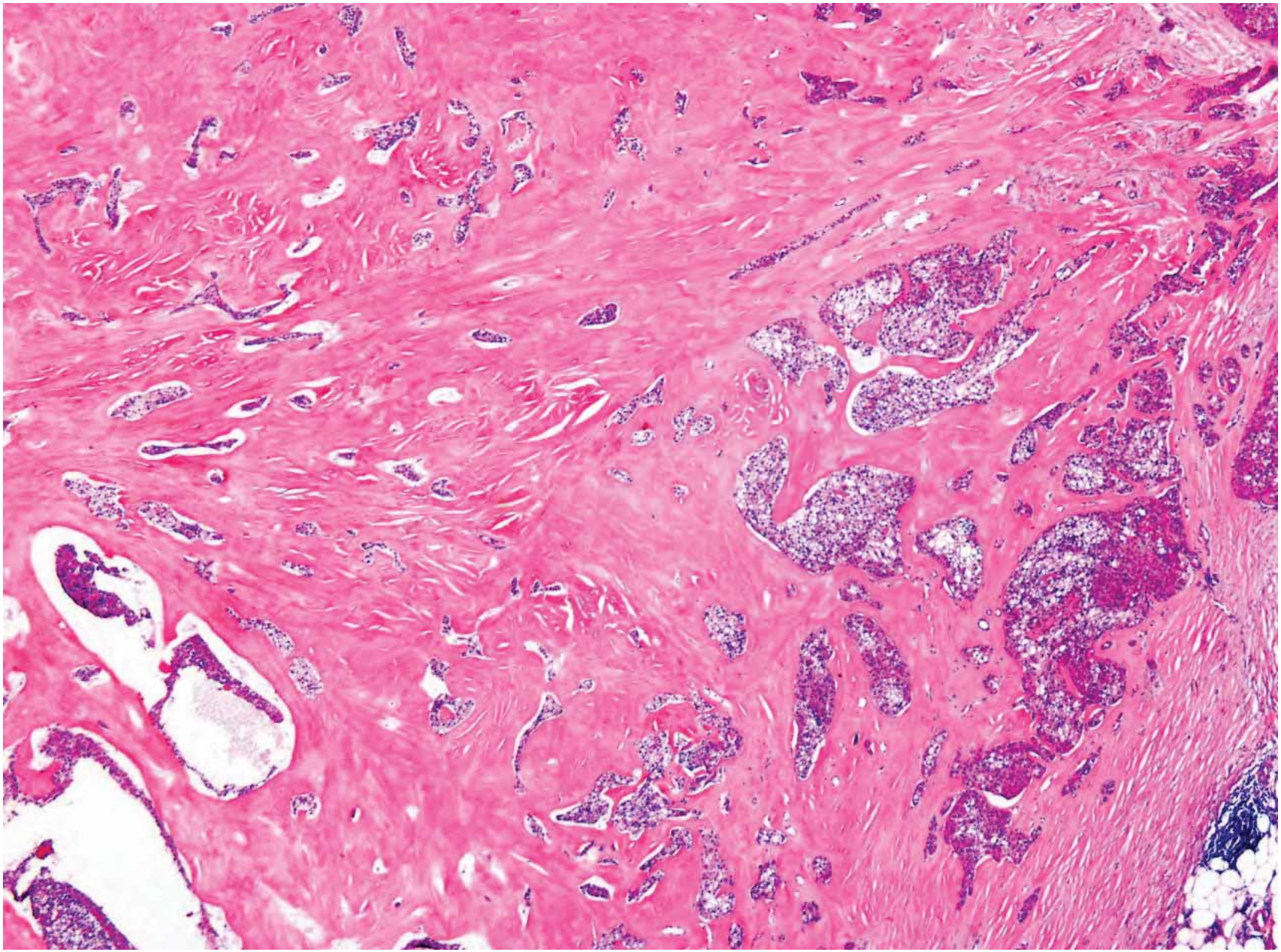
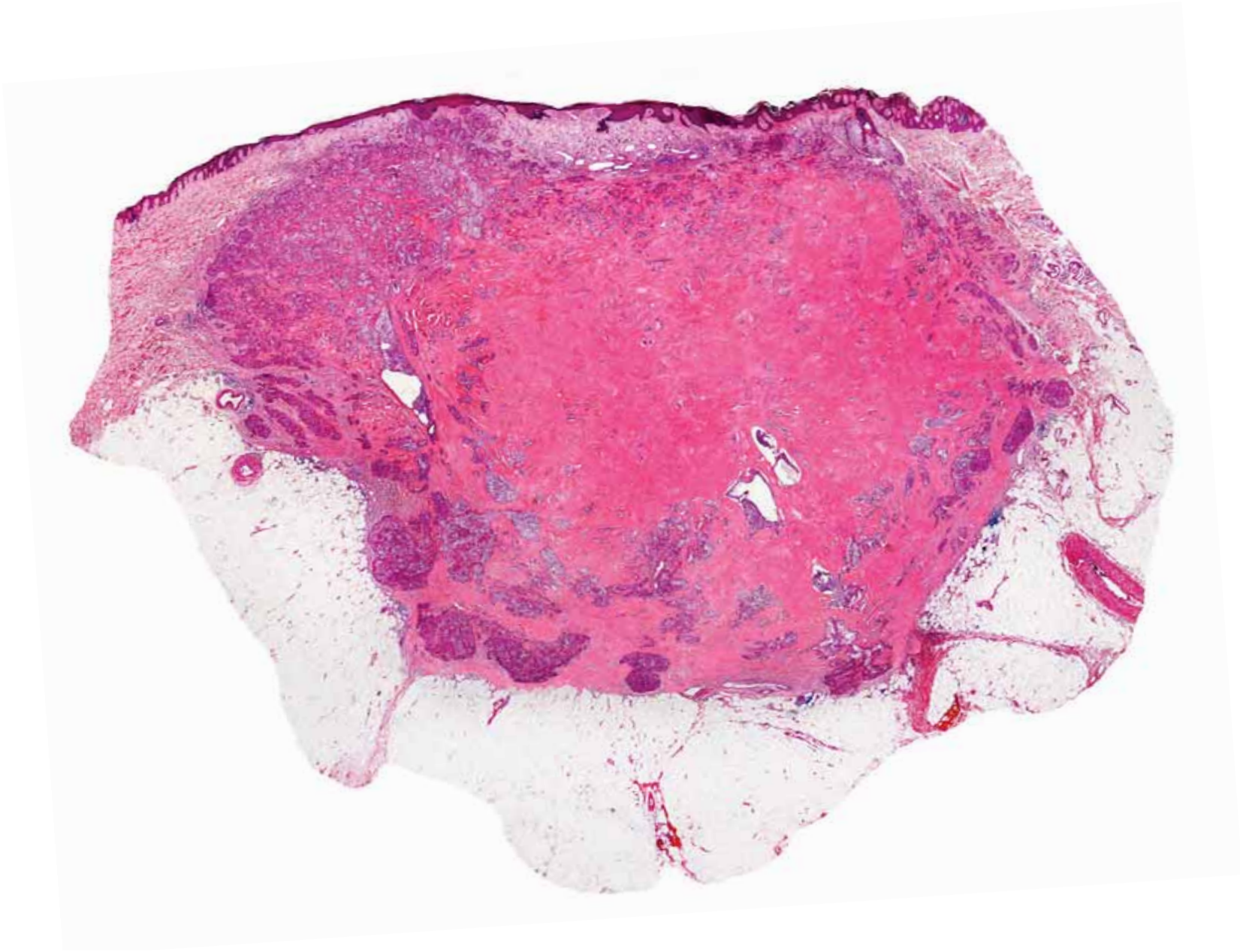
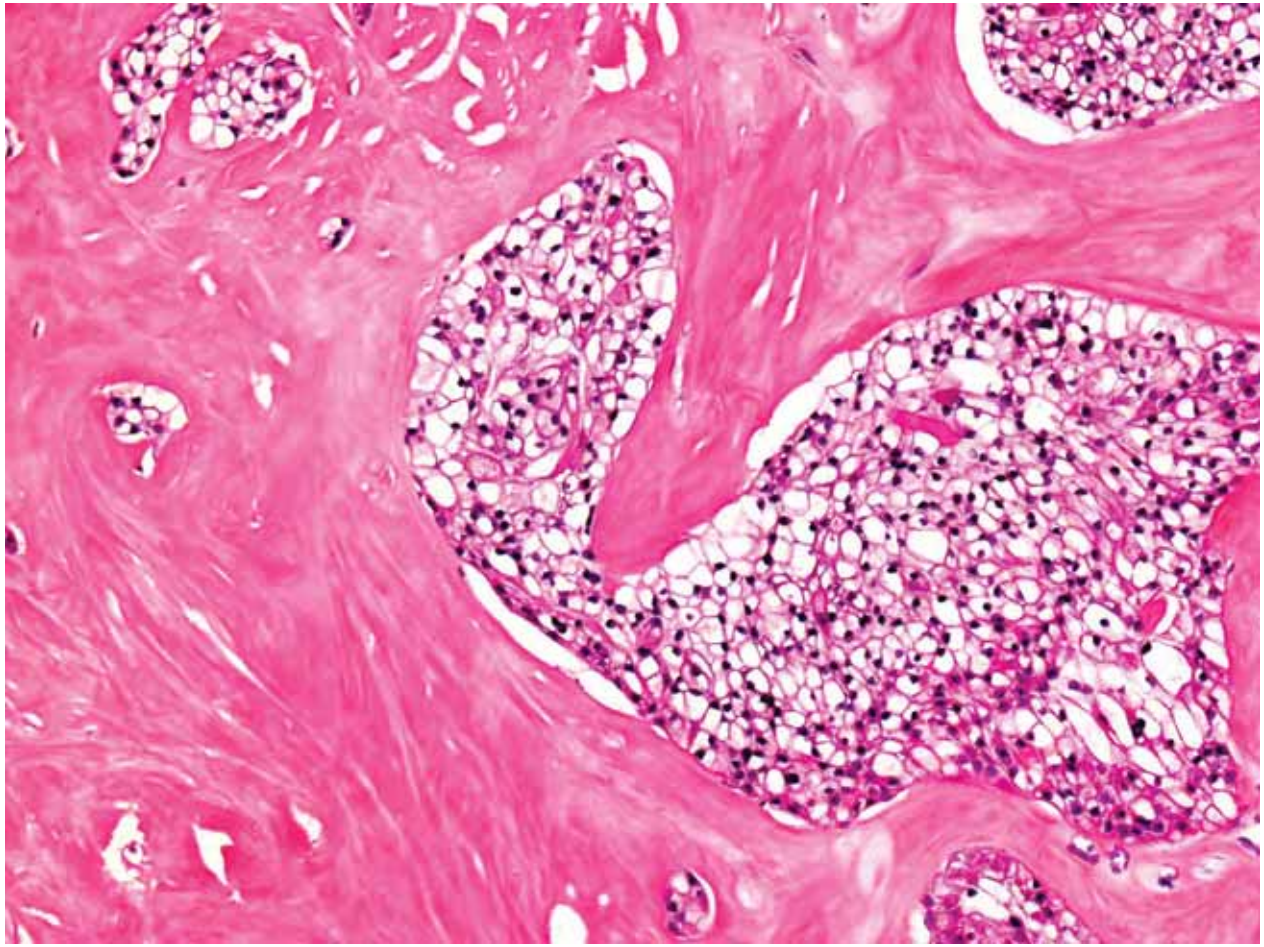


What is the *cliche* and what is the diagnosis?

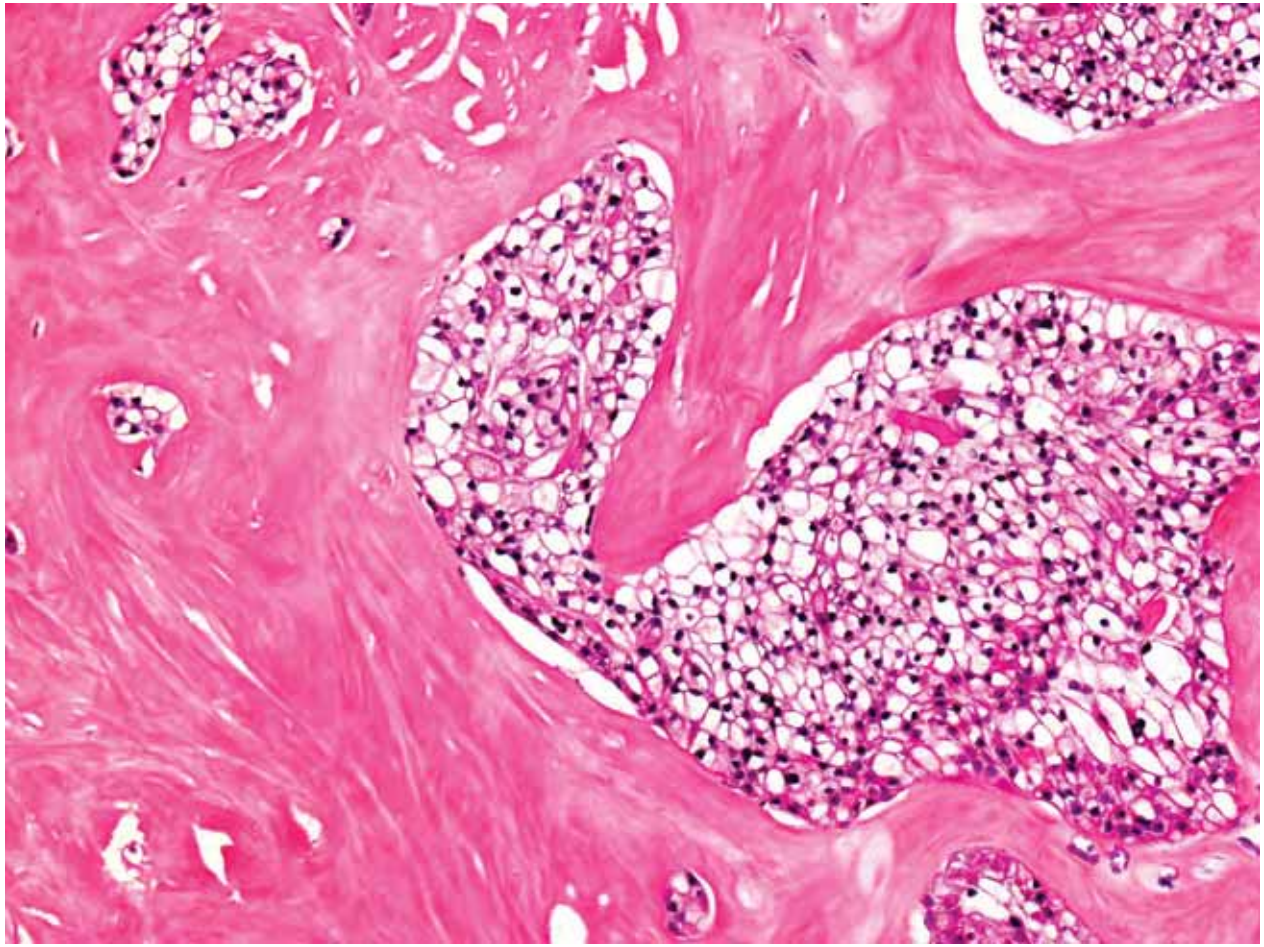






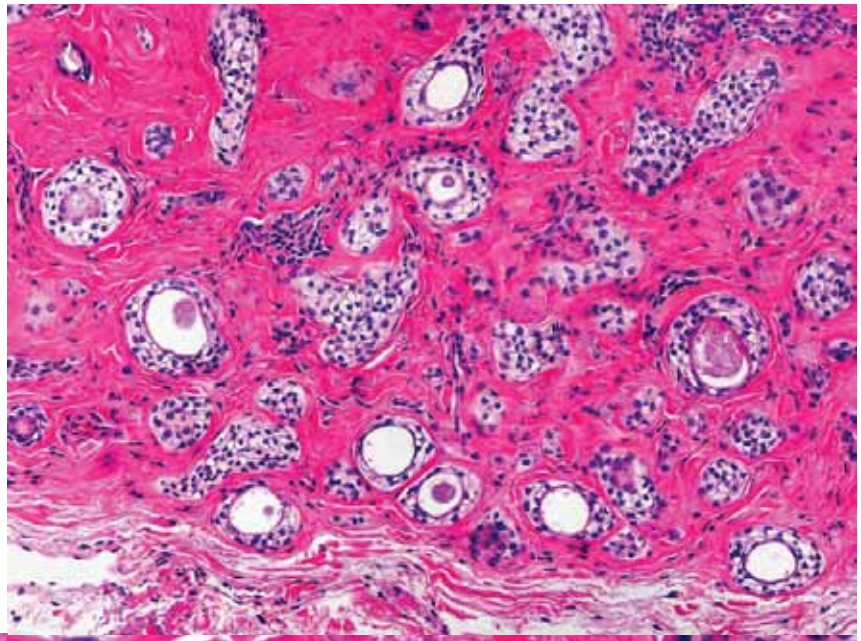


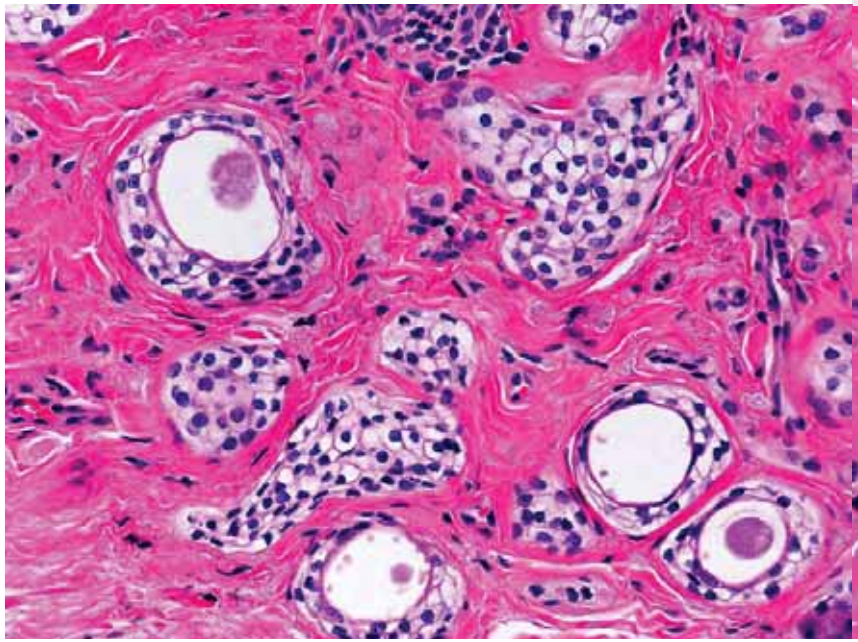
Solid aggregates of epithelial clear cells embedded in a sclerotic stroma is a *cliche* to…

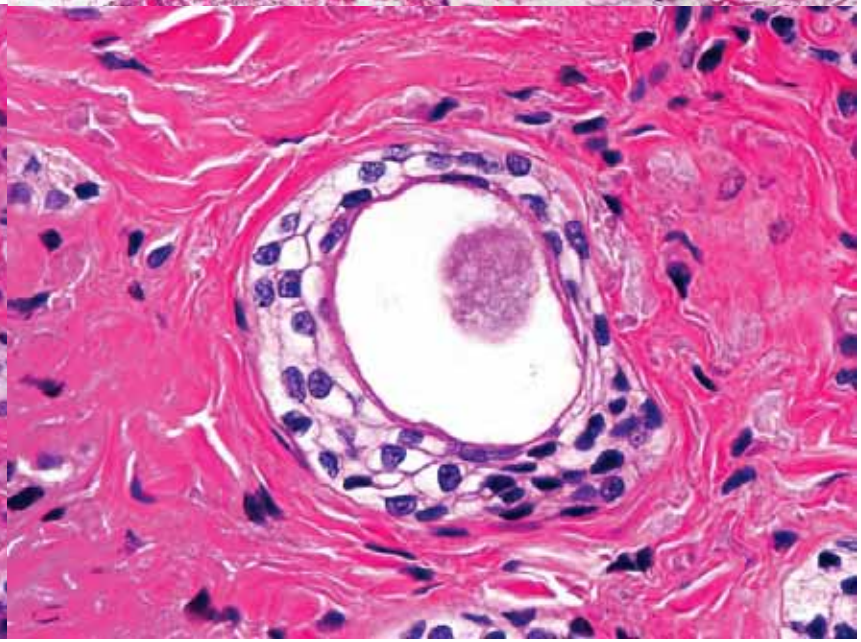


Solid aggregates of epithelial clear cells embedded in a sclerotic stroma is a *cliche* to clear-cell apocrine hidradenoma or…

Clear cell syringoma, or…







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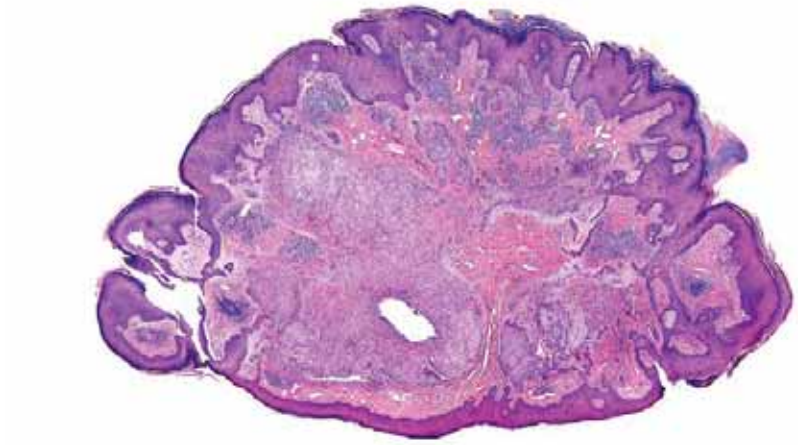

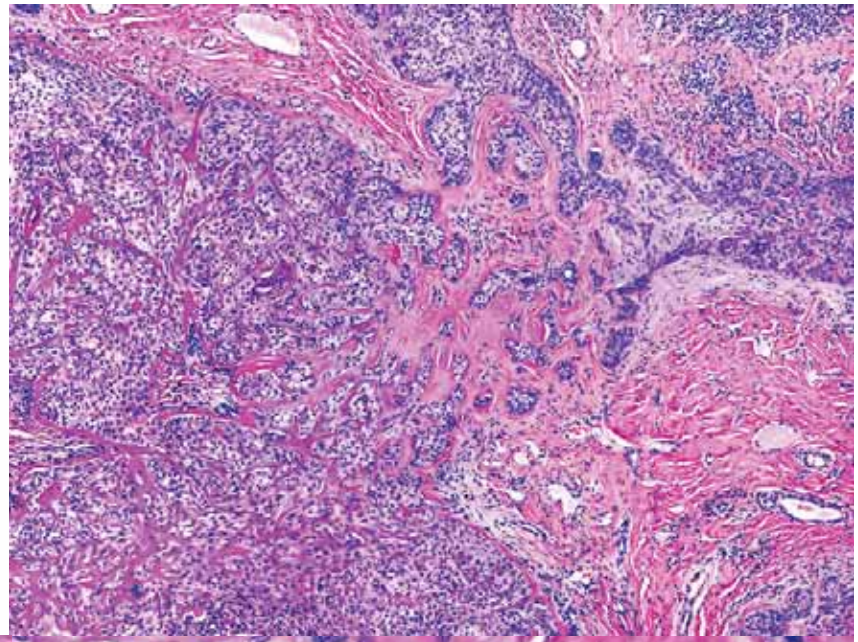

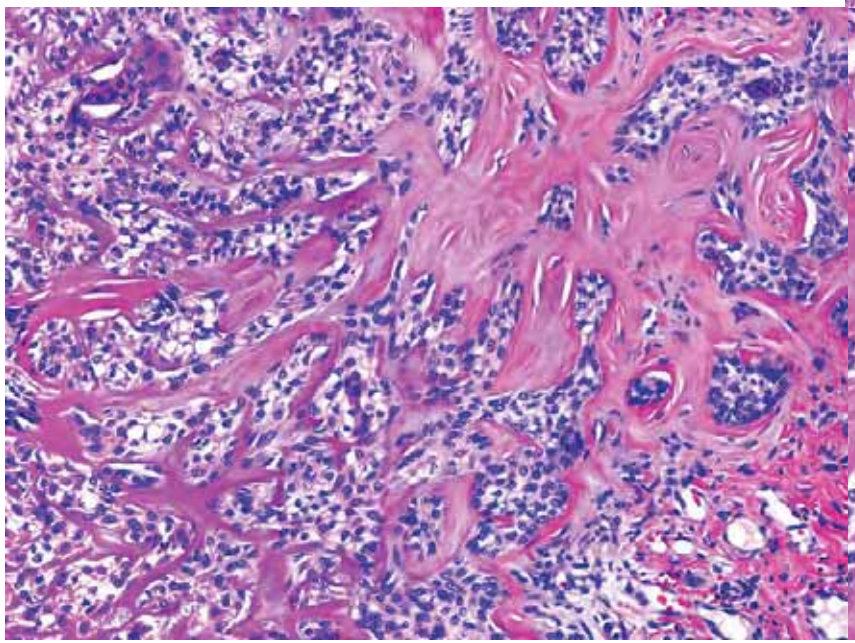

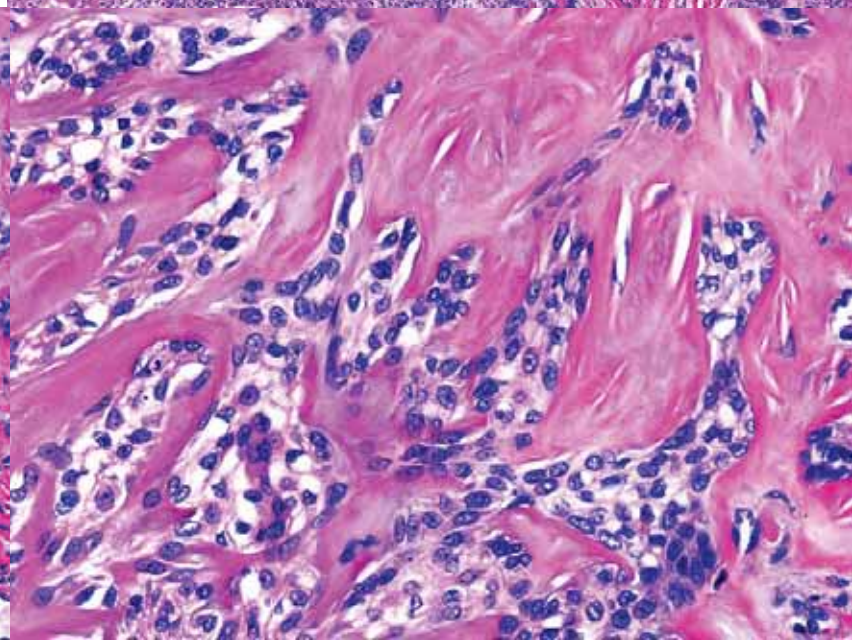

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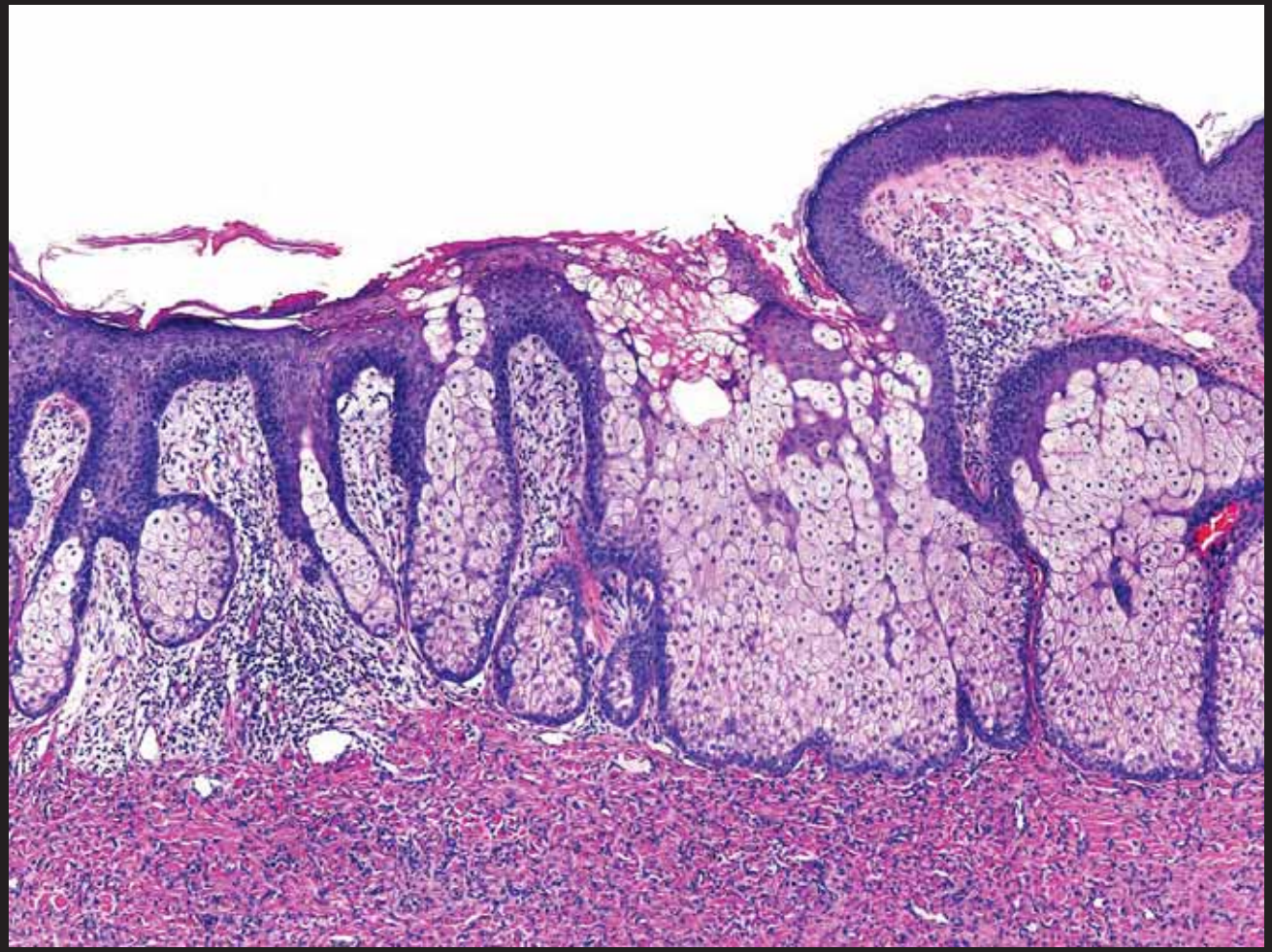

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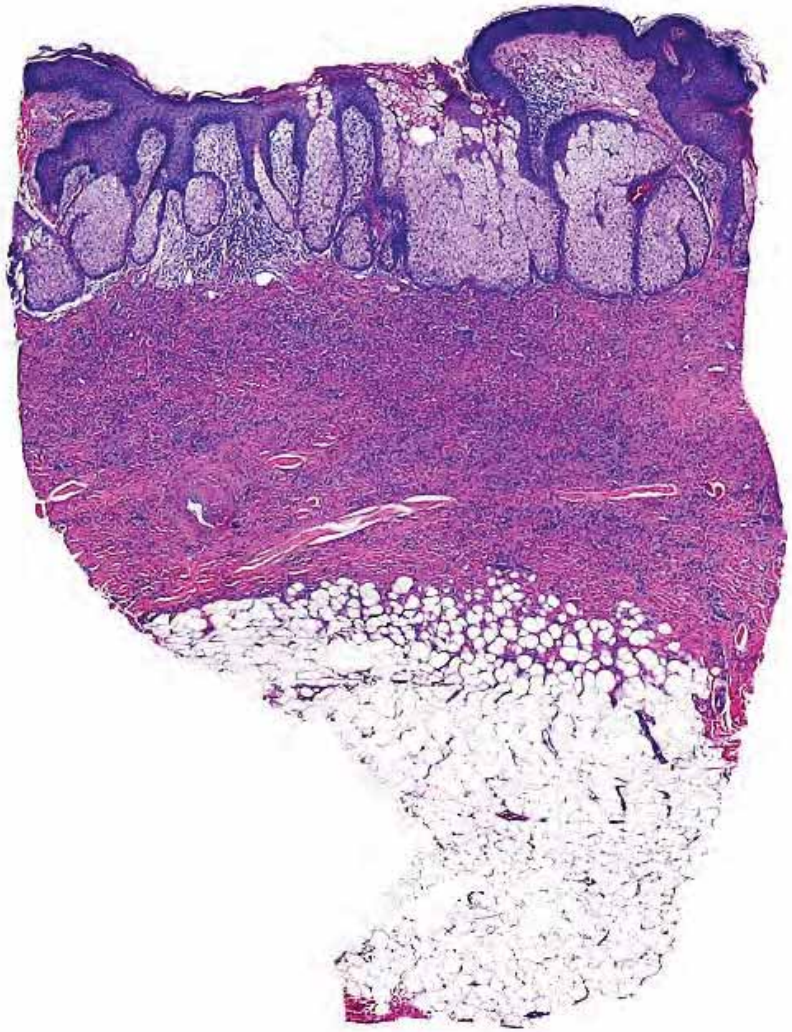
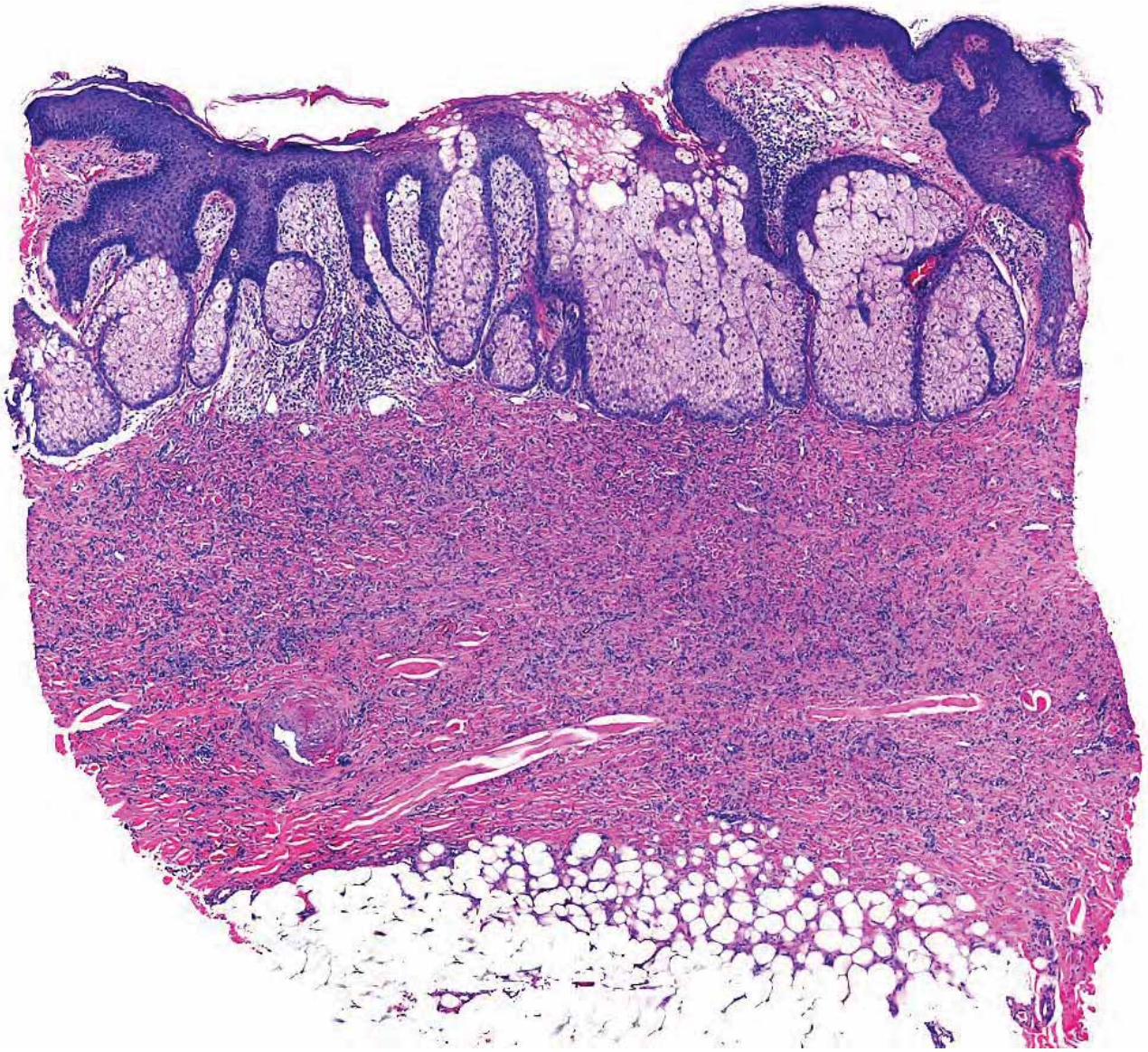
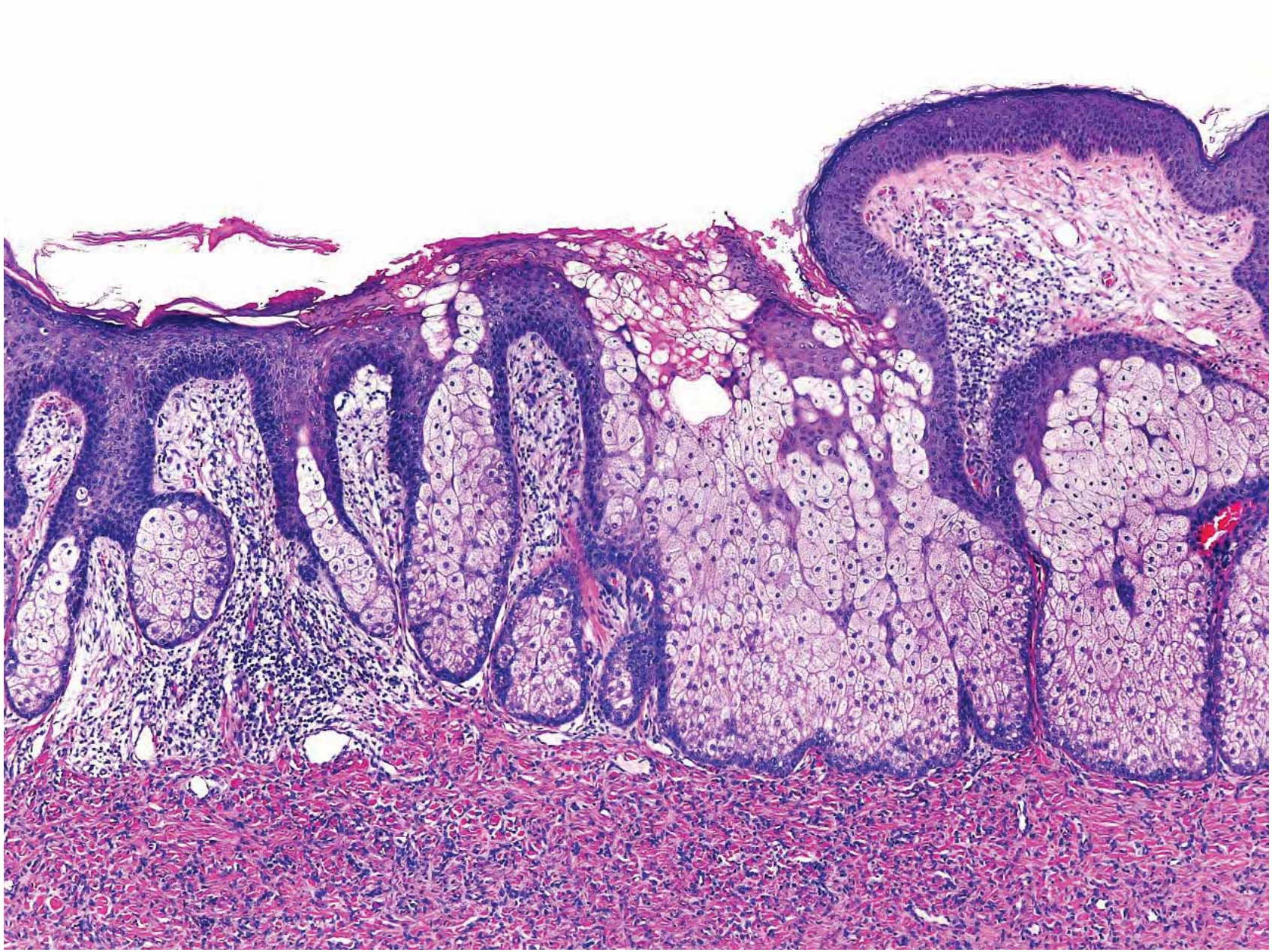
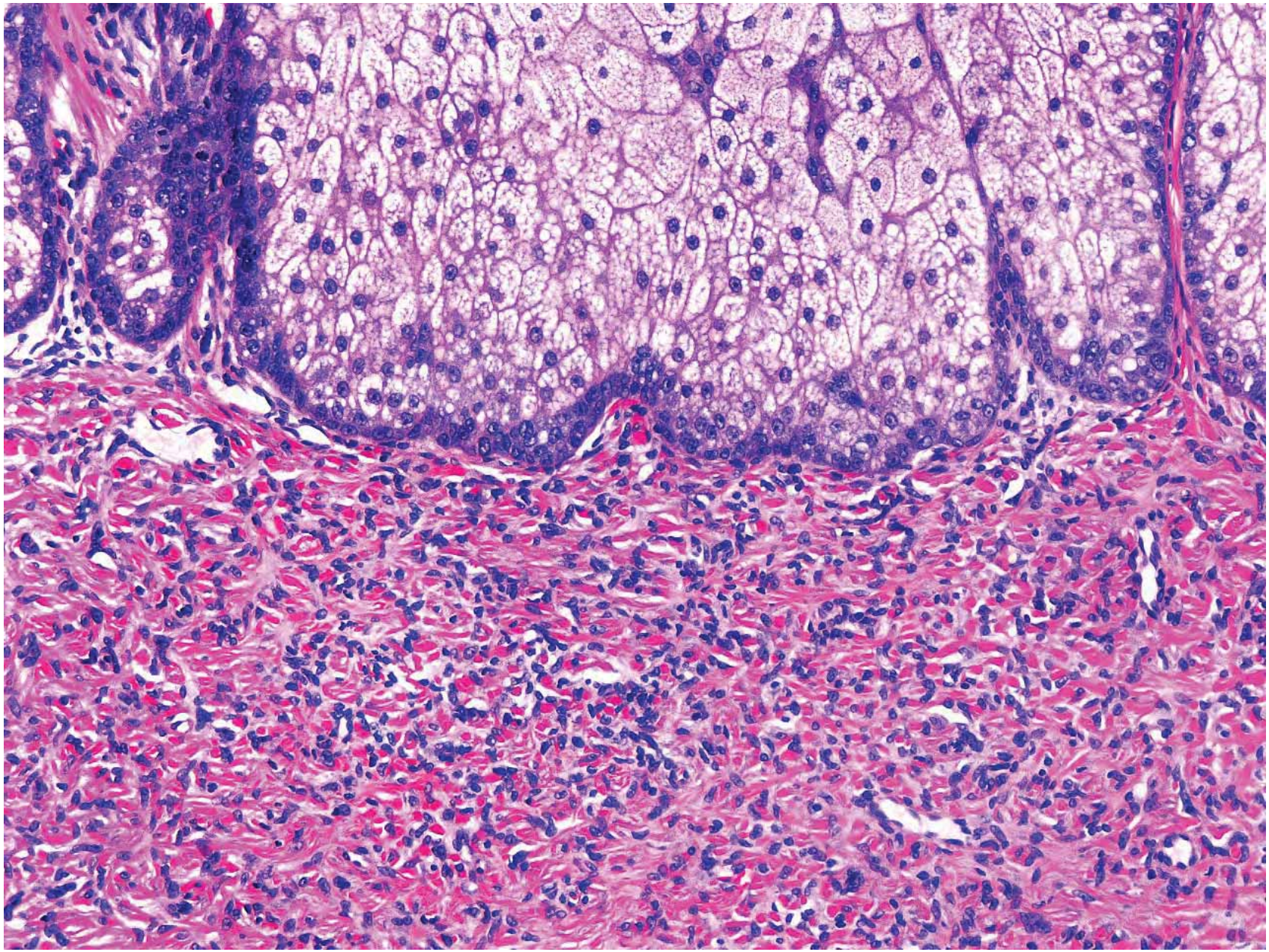
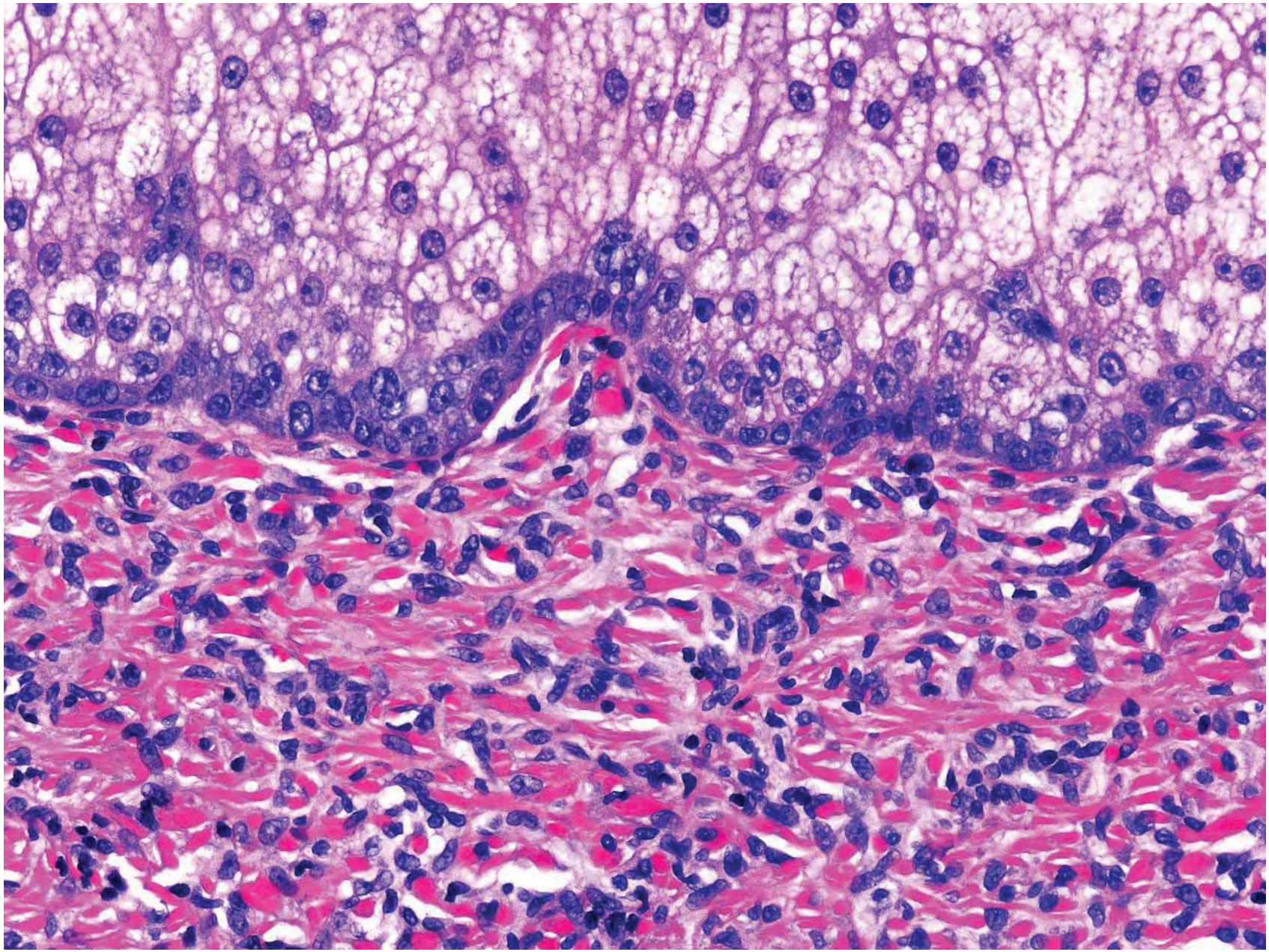
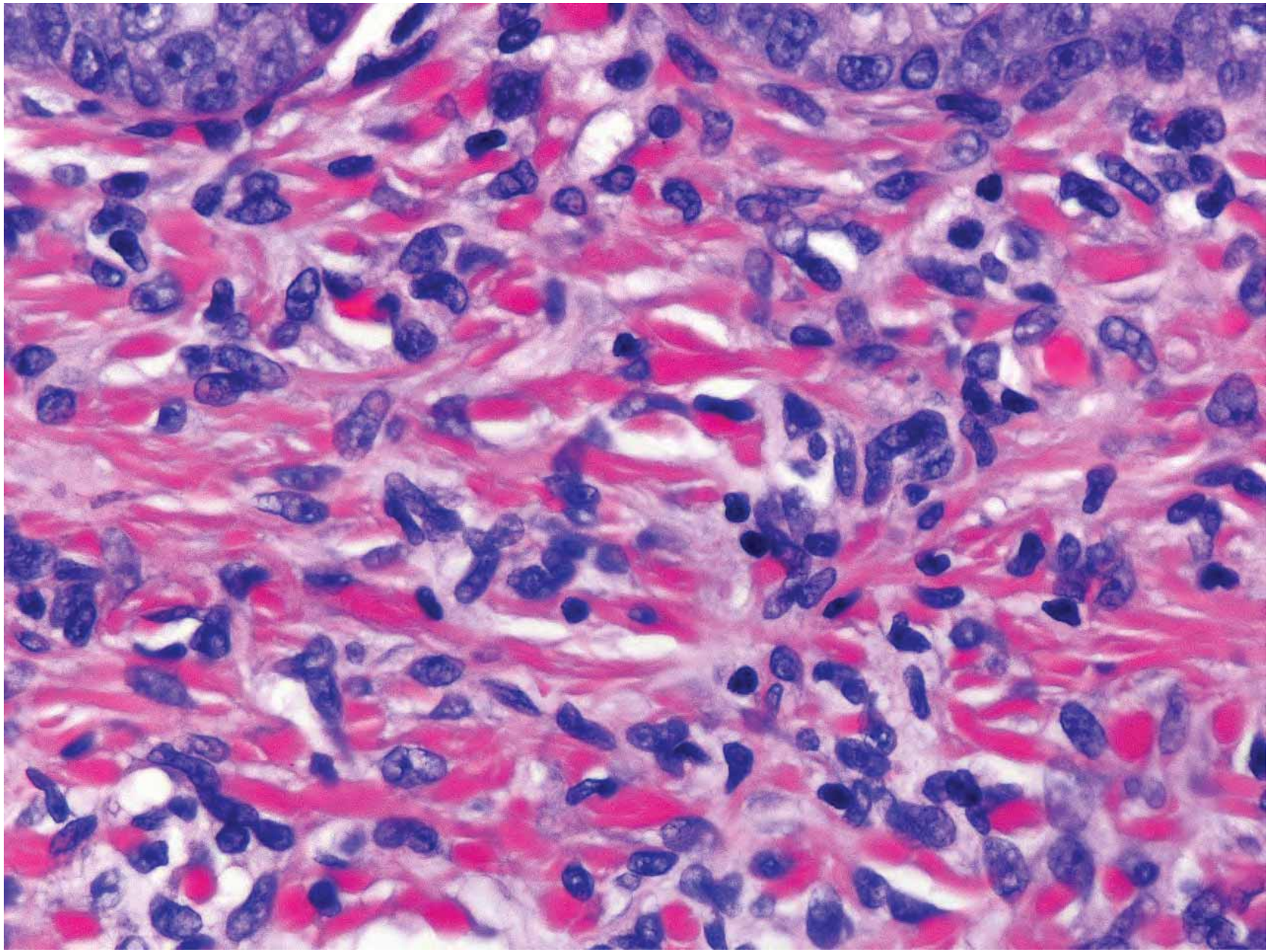


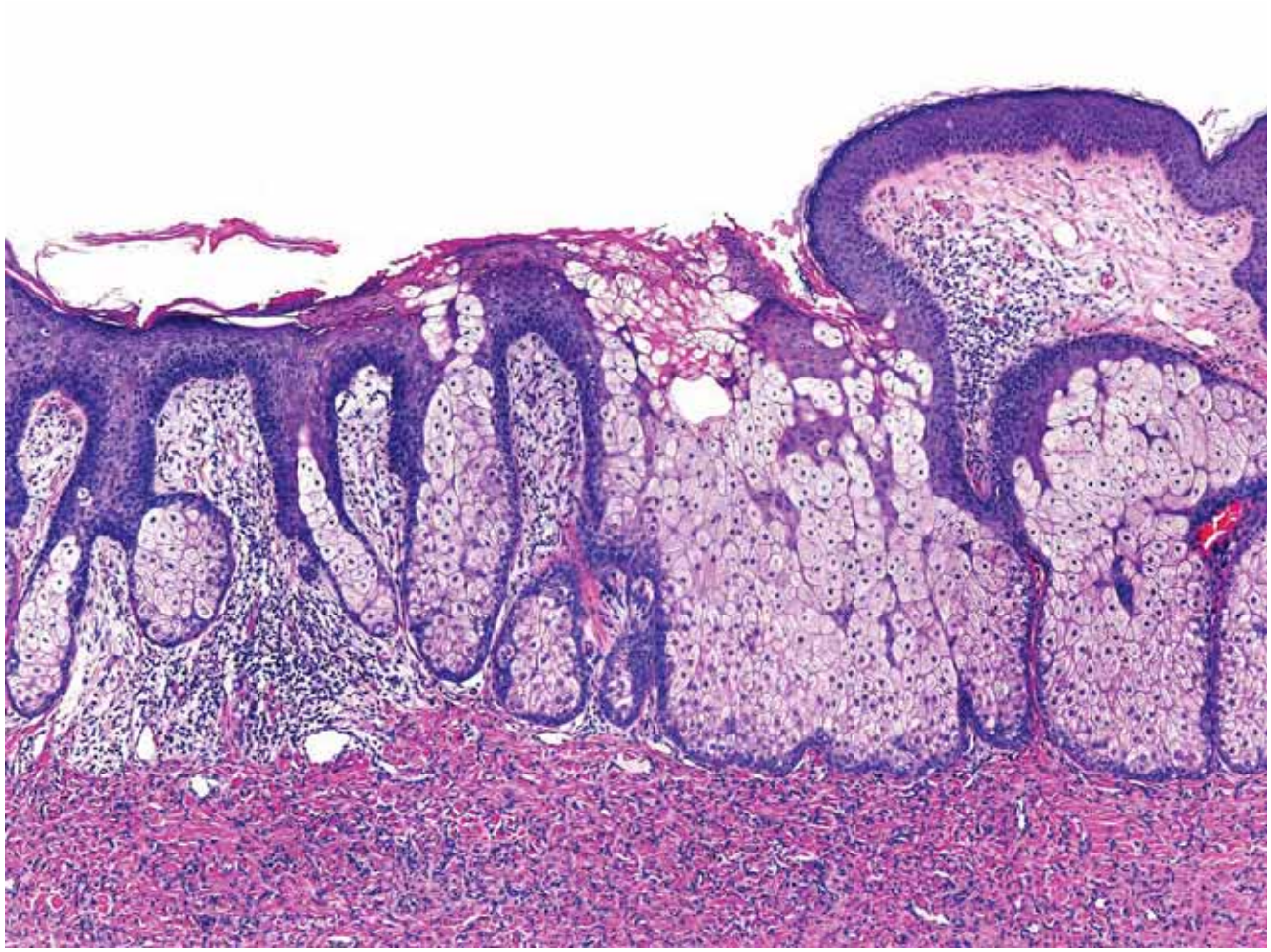




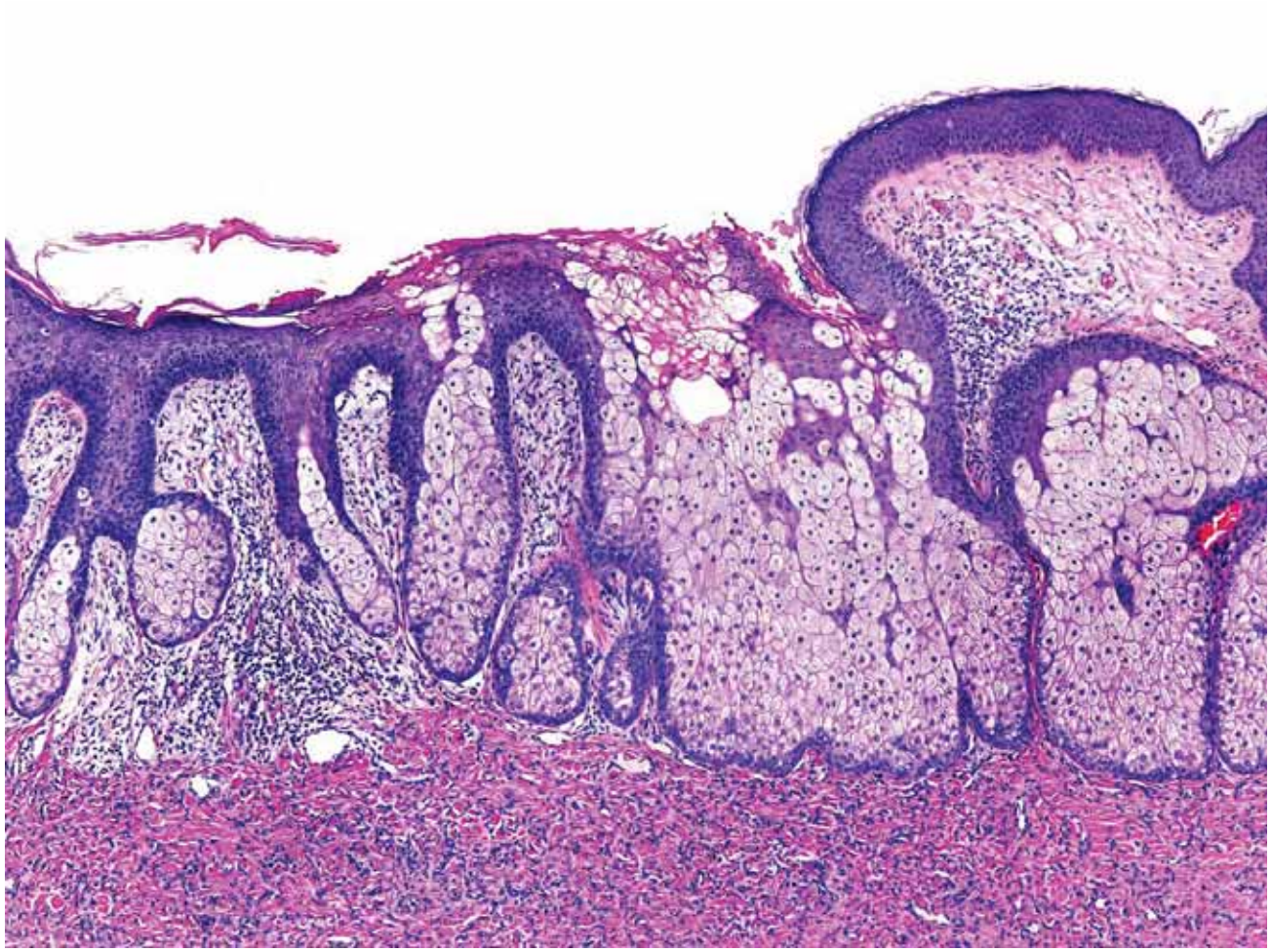








Hyperplastic sebaceous glands above a fibroblastic proliferation is a *cliche* to …



Hyperplastic sebaceous glands above a fibroblastic proliferation is a *cliche* to dermatofibroma with sebaceous induction

Plate-like sebaceous hyperplasia overlying dermatofibroma

Epidermal hyperplasia, sometimes with primitive hair follicle-like differentiation, is a characteristic finding overlying dermatofibroma. We here report plate-like sebaceous hyperplasia overlying a dermatofibroma. Such changes are interpreted as a result of inductive epithelial effect by the dermatofibroma on the overlying epidermis.

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Luis Requena, Elia Roó, Evaristo Sánchez Yus

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Accepted July 8, 1991

Characteristically, the epidermis overlying a dermatofibroma is hyperplastic and consists of regular elongation of the rete ridges, usually associated with hyperpigmentation of the basal cell layer. In some cases, this epidermal hyperplasia is reminiscent of an adenoid seborrheic keratosis (1). Occasionally, a distinctive type of basaloid hyperplasia with differentiation into primitive hair follicle-like tissue occurs overlying a dermatofibroma (2). Some authors (3) have considered these features to be a result of regressed hair follicles pushed up against the overlying epidermis by the dermal cellular proliferation, whereas others interpret the epidermal changes as a reaction to influences from the underlying fibrohistiocytic proliferation (1, 4). At times, this basaloid proliferation may be so extensive that it resembles superficial basal cell carcinoma (5), and in rare instances, invasive nodular basal cell carcinoma develops overlying a dermatofibroma (6, 7). Finally, coincidental findings in the epidermis overlying dermatofibromas include focal acantholytic dyskeratosis (8, 9), epidermolytic hyperkeratosis (1), pale cell acanthoma-like changes (1), and squamous cell carcinoma in situ (10).

We present here the first case, to our knowledge, of a dermatofibroma with overlying plate-like sebaceous hyperplasia as the result of an inductive epithelial effect of the dermatofibroma on the overlying epidermis.

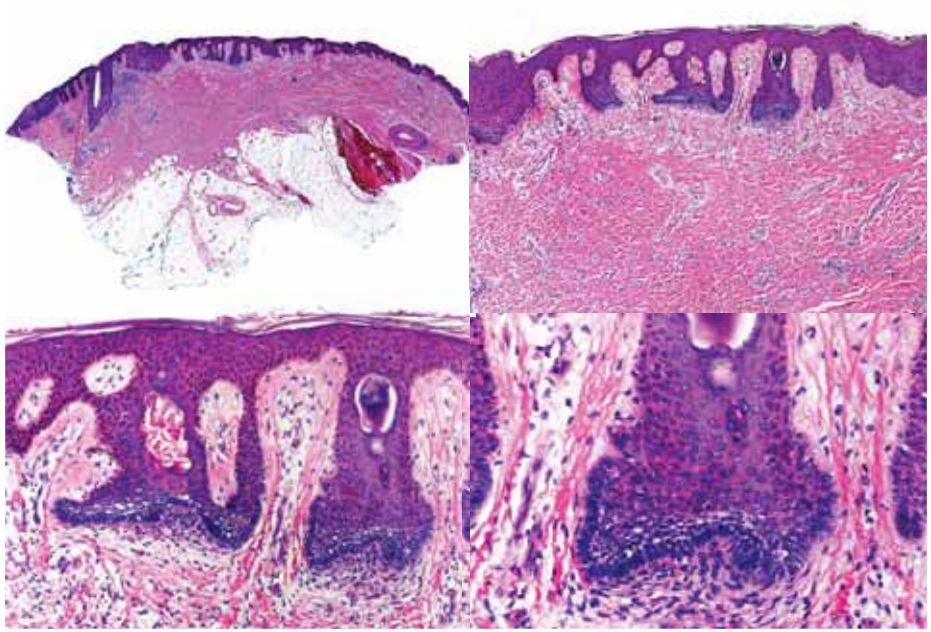
Case report

A 42-year-old woman noted a slowly growing, firm, nodular lesion on her right arm. It had been present for 10 years and was asymptomatic. Examination revealed a 2 × 1 cm oval, firm nodule on the lateral aspect of her right arm. The nodule was covered by a slightly hyperpigmented surface. There was no lymphadenopathy and the remainder of the physical findings were within normal limits. The lesion was surgically excised.

Histopathologic examination revealed a highly cellular infiltrate of spindle cells filling the full-thickness of the dermis (Fig. 1). At both lateral margins, the spindle cells tended to wrap around thickened collagen bundles. The overlying epidermis was hyperplastic and hyperpigmented. In this epidermis, the most striking finding consisted of the presence of a large number of mature sebaceous lobules in a plate-like arrangement (Fig. 2), with their ducts opening directly to the surface. These ducts did not contain hair shafts, and there was no evidence of connection to hair follicles. This plate-like sebaceous hyperplasia was circumscribed and limited to the area overlying the dermatofibroma.

Discussion

Epidermal basaloid hyperplasia with follicular differentiation is not exclusive to dermatofibroma. It has also been noted in other situations such as over intradermal melanocytic nevus or granular cell tumor, and rarely in such chronic inflammatory dermatoses as prurigo nodularis or psoriasis (11). Epidermal hyperplasia over inflamed areas in the upper dermis may be due, in some instances, to release of prostaglandins of the E series by the inflammatory cell infiltrate (12). Another plausible explanation for the hyperplastic epidermis overlying dermatofibromas would be the presence of young collagen with abundant ground substance in the papillary dermis that could behave as embryonic mesenchyme, resulting in the formation of primary epithelial germs and immature hair follicles (13). Kollar (14) in-



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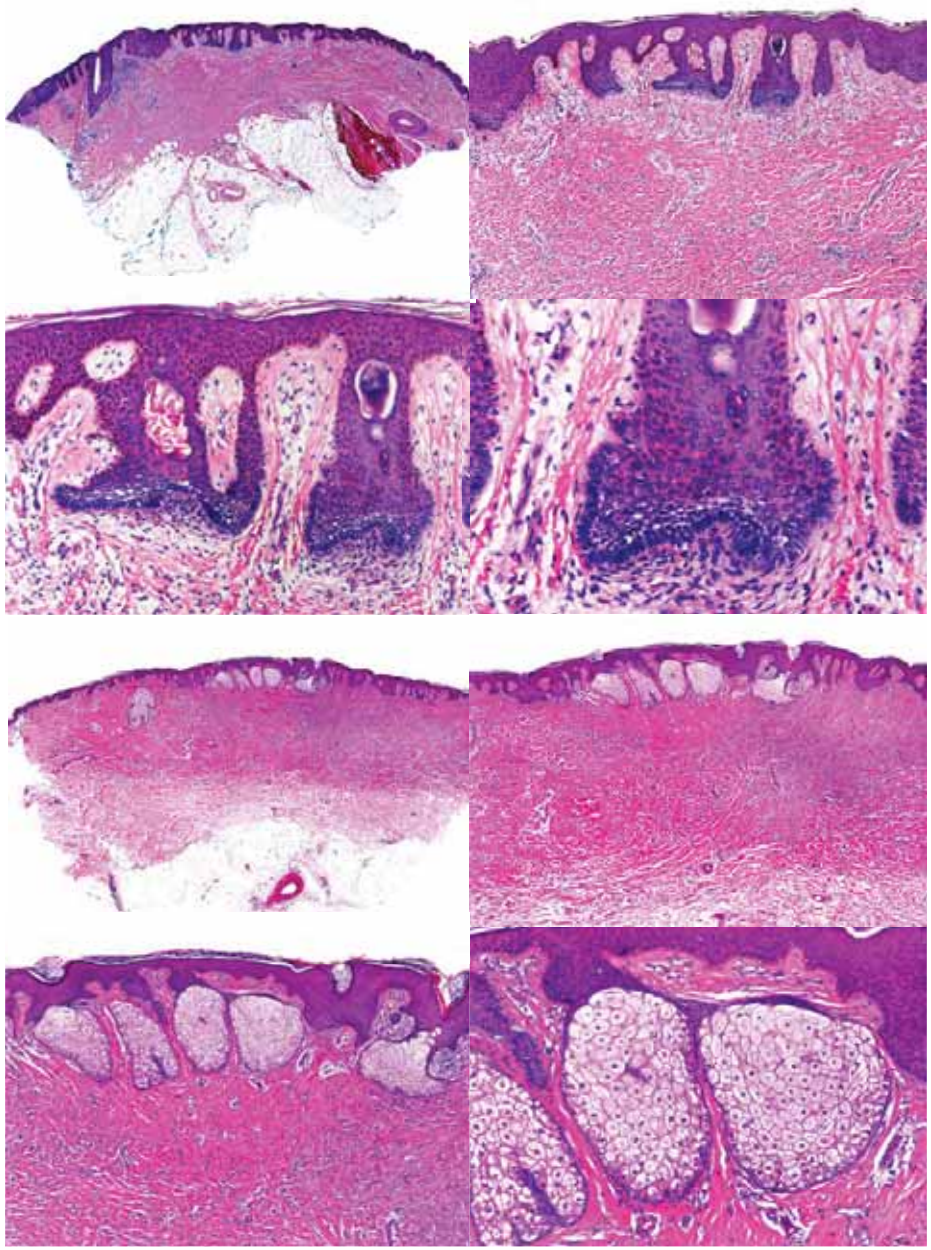

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We present here the first case, to our knowledge, of a dermatofibroma with overlying plate-like sebaceous hyperplasia as the result of an inductive epithelial effect of the dermatofibroma on the overlying epidermis.

Case report

A 42-year-old woman noted a slowly growing, firm, nodular lesion on her right arm. It had been present for 10 years and was asymptomatic. Examination revealed a 2 × 1 cm oval, firm nodule on the lateral aspect of her right arm. The nodule was covered by a slightly hyperpigmented surface. There was no lymphadenopathy and the remainder of the physical findings were within normal limits. The lesion was surgically excised.

Histopathologic examination revealed a highly cellular infiltrate of spindle cells filling the full-thickness of the dermis (Fig. 1). At both lateral margins, the spindle cells tended to wrap around thickened collagen bundles. The overlying epidermis was hyperplastic and hyperpigmented. In this epidermis, the most striking finding consisted of the presence of a large number of mature sebaceous lobules in a plate-like arrangement (Fig. 2), with their ducts opening directly to the surface. These ducts did not contain hair shafts, and there was no evidence of connection to hair follicles. This plate-like sebaceous hyperplasia was circumscribed and limited to the area overlying the dermatofibroma.

Discussion

Epidermal basaloid hyperplasia with follicular differentiation is not exclusive to dermatofibroma. It has also been noted in other situations such as over intradermal melanocytic nevus or granular cell tumor, and rarely in such chronic inflammatory dermatoses as prurigo nodularis or psoriasis (11). Epidermal hyperplasia over inflamed areas in the upper dermis may be due, in some instances, to release of prostaglandins of the E series by the inflammatory cell infiltrate (12). Another plausible explanation for the hyperplastic epidermis overlying dermatofibromas would be the presence of young collagen with abundant ground substance in the papillary dermis that could behave as embryonic mesenchyme, resulting in the formation of primary epithelial germs and immature hair follicles (13). Kollar (14) in-

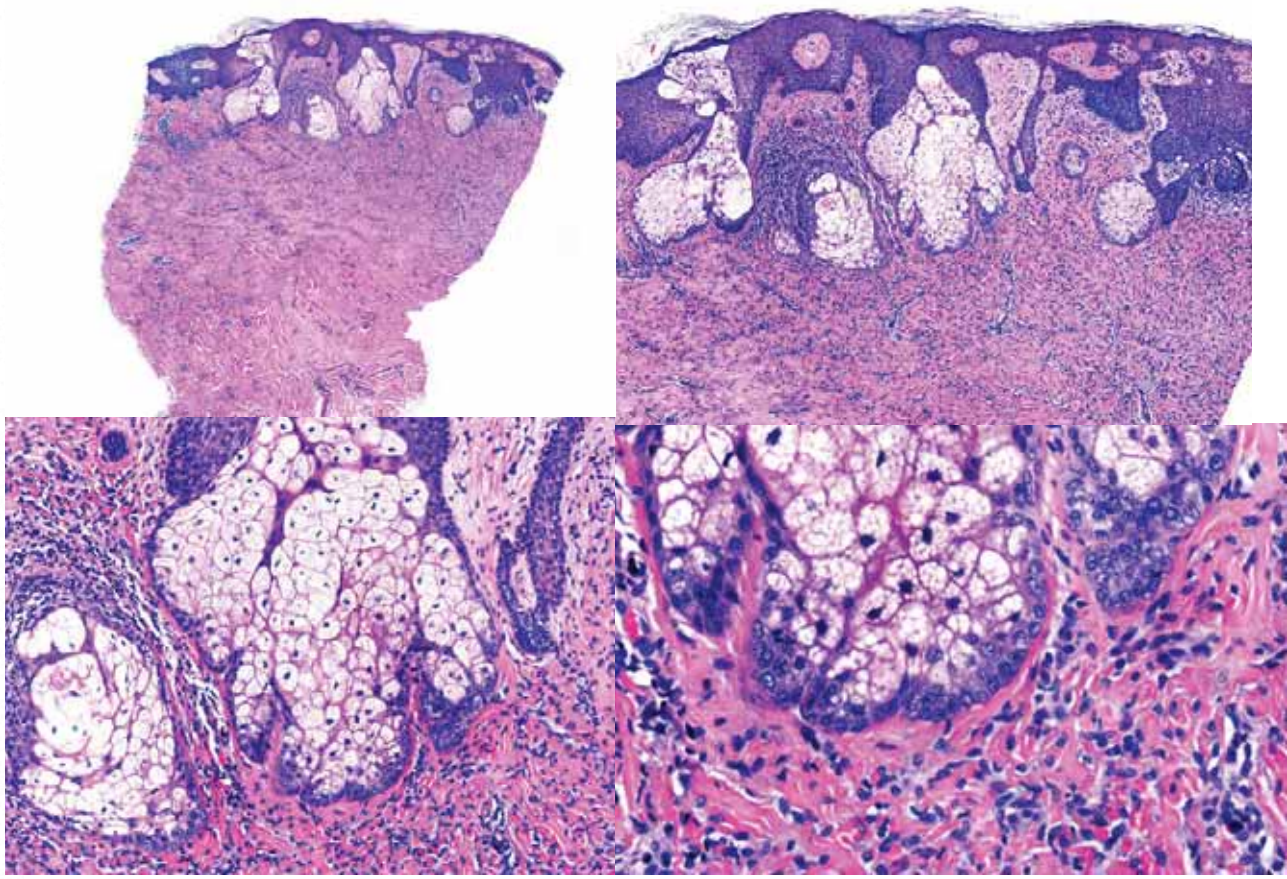

Plate-like sebaceous hyperplasia overlying dermatofibroma

Epidermal hyperplasia, sometimes with primitive hair follicle-like differentiation, is a characteristic finding overlying dermatofibroma. We here report plate-like sebaceous hyperplasia overlying a dermatofibroma. Such changes are interpreted as a result of inductive epithelial effect by the dermatofibroma on the overlying epidermis.

Requena L, Roó E, Yus ES. Plate-like sebaceous hyperplasia overlying dermatofibroma. J Cutan Pathol 1992: 19: 253–255.

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Accepted July 8, 1991

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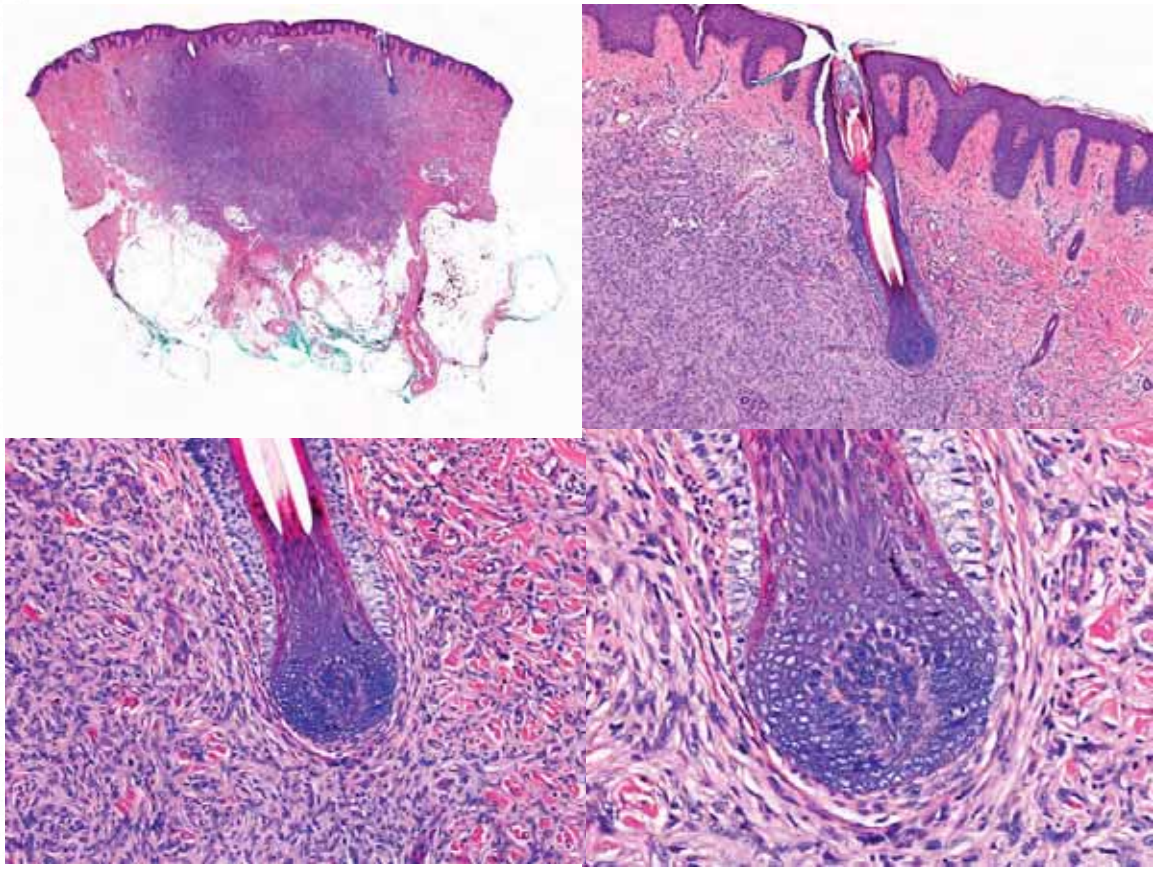

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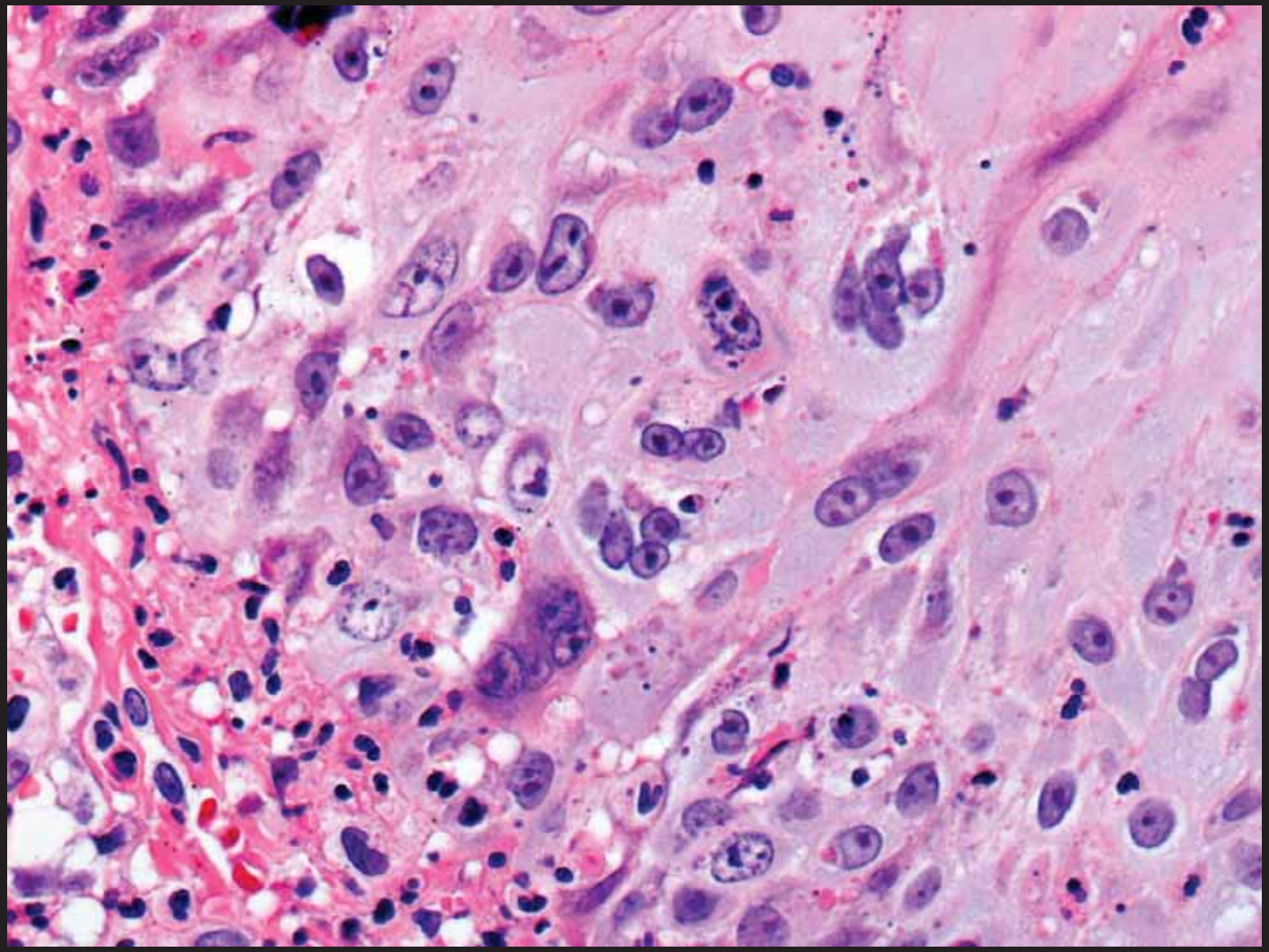
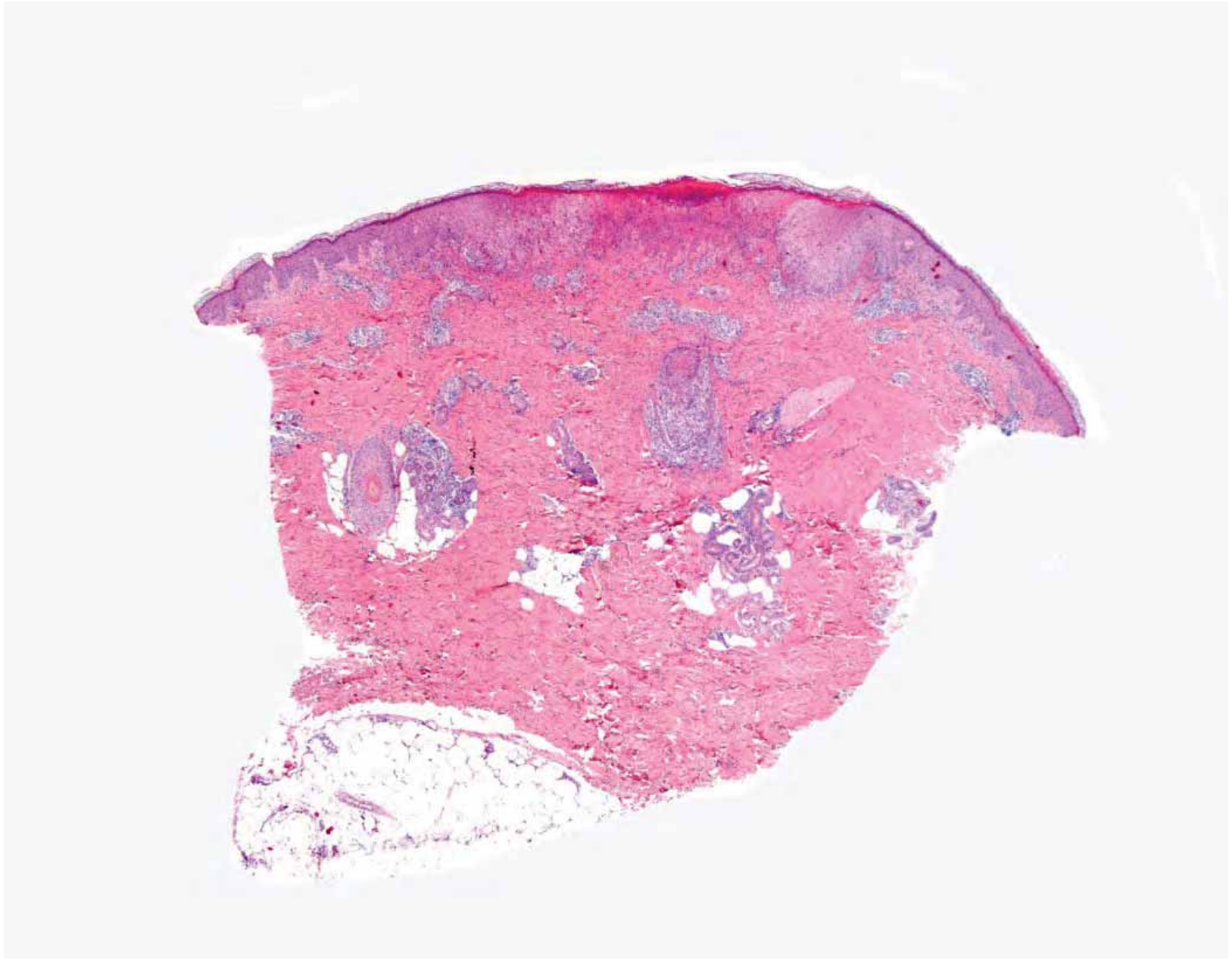
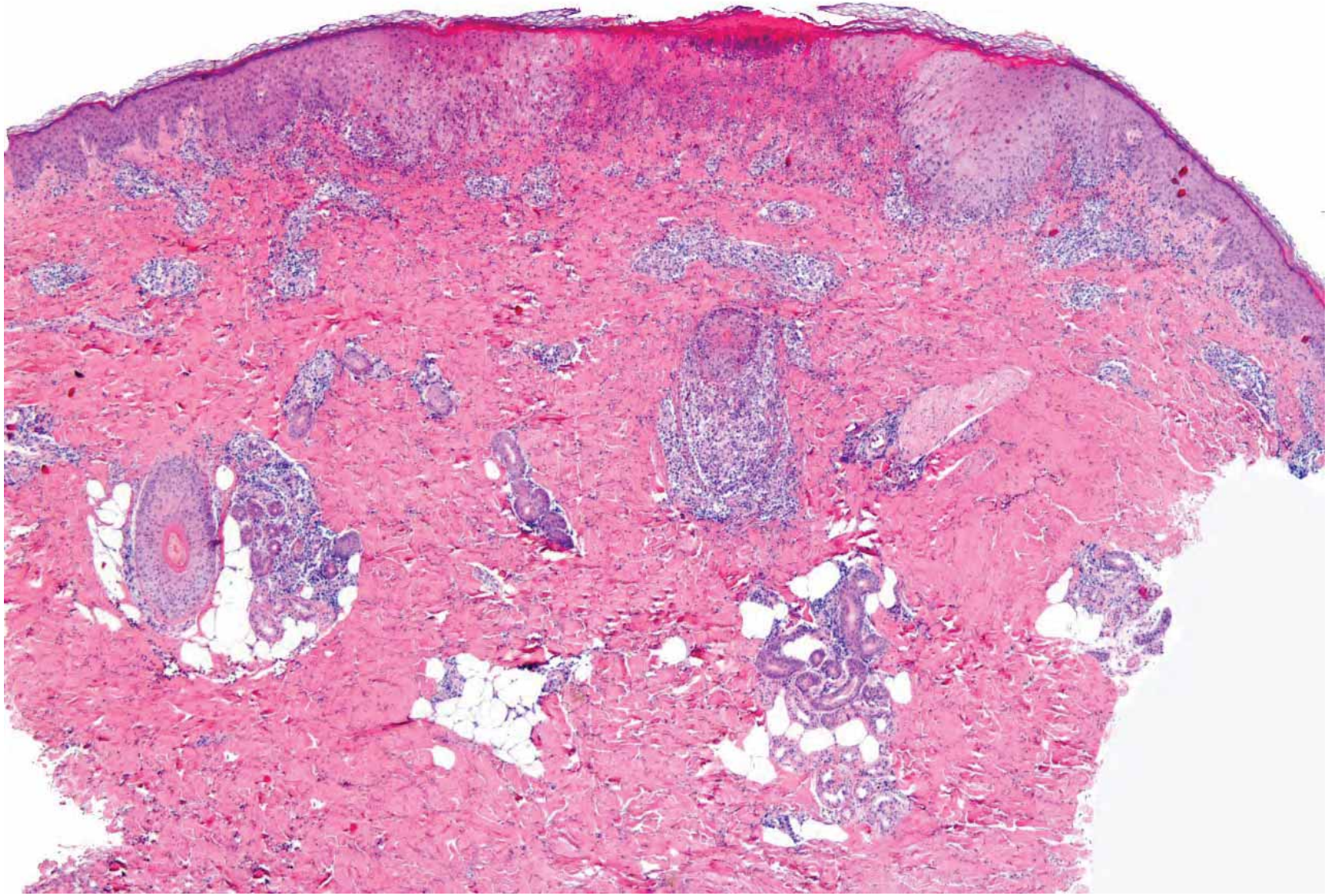
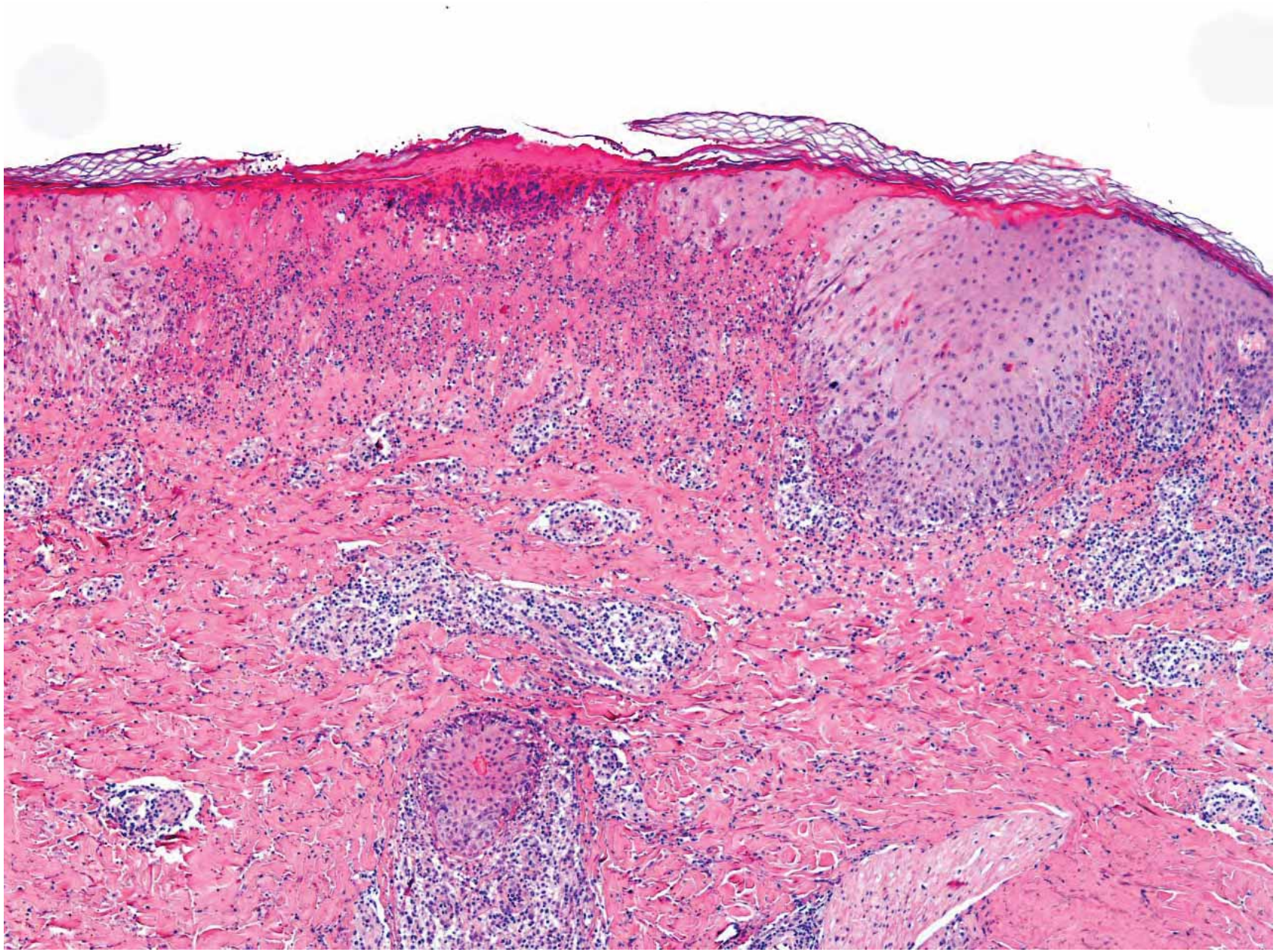
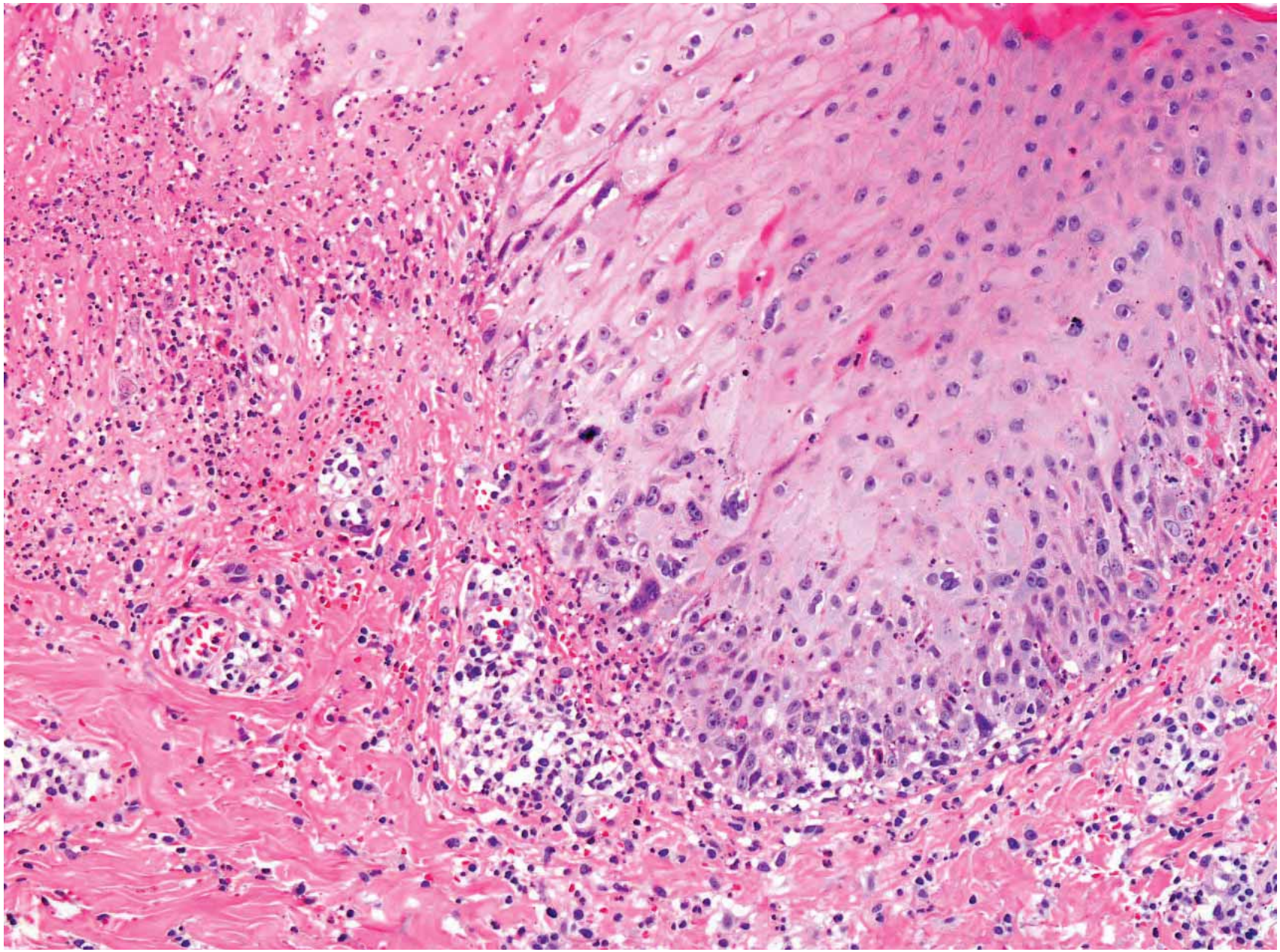


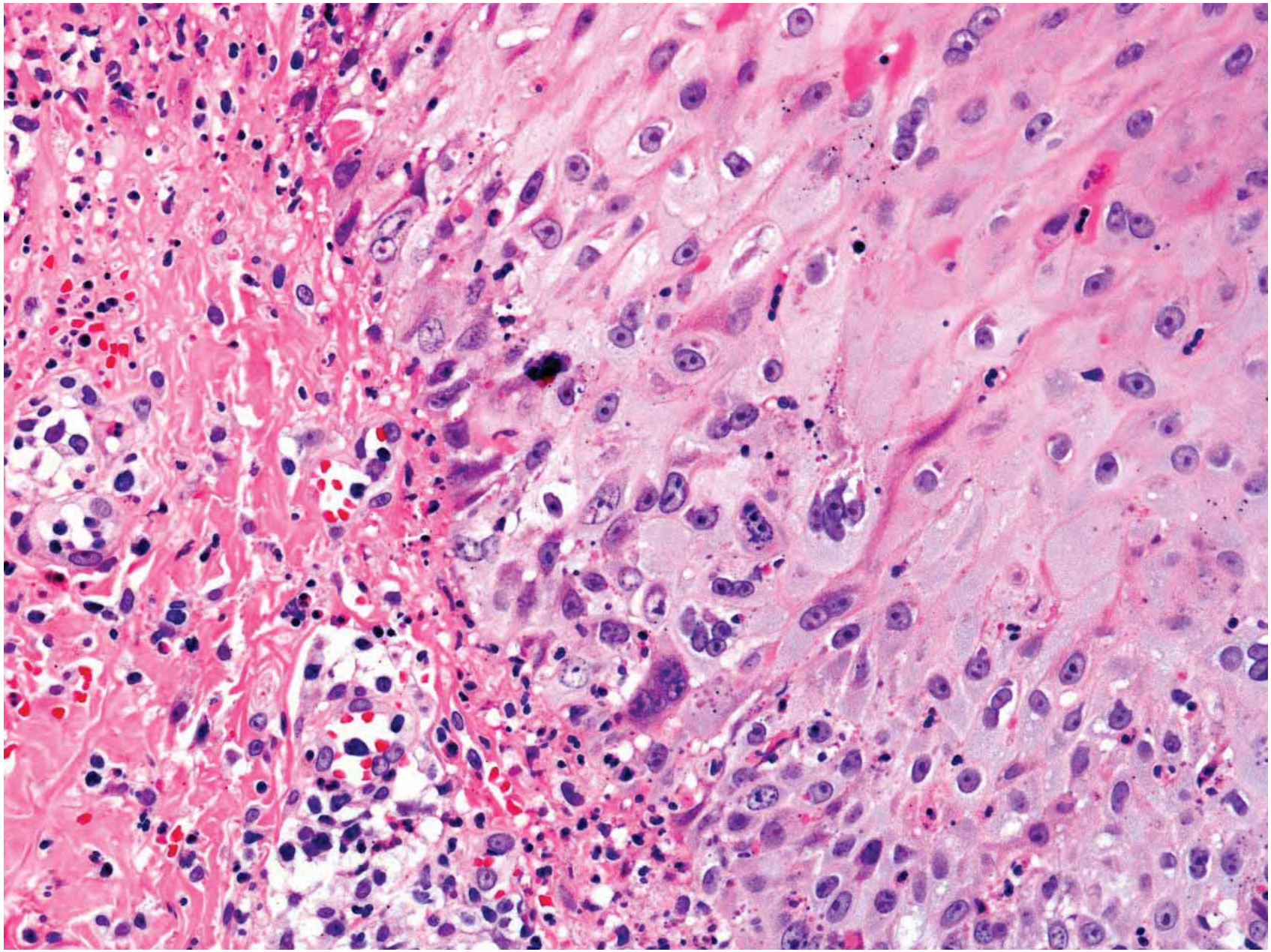
What is the *cliche* and what is the diagnosis?

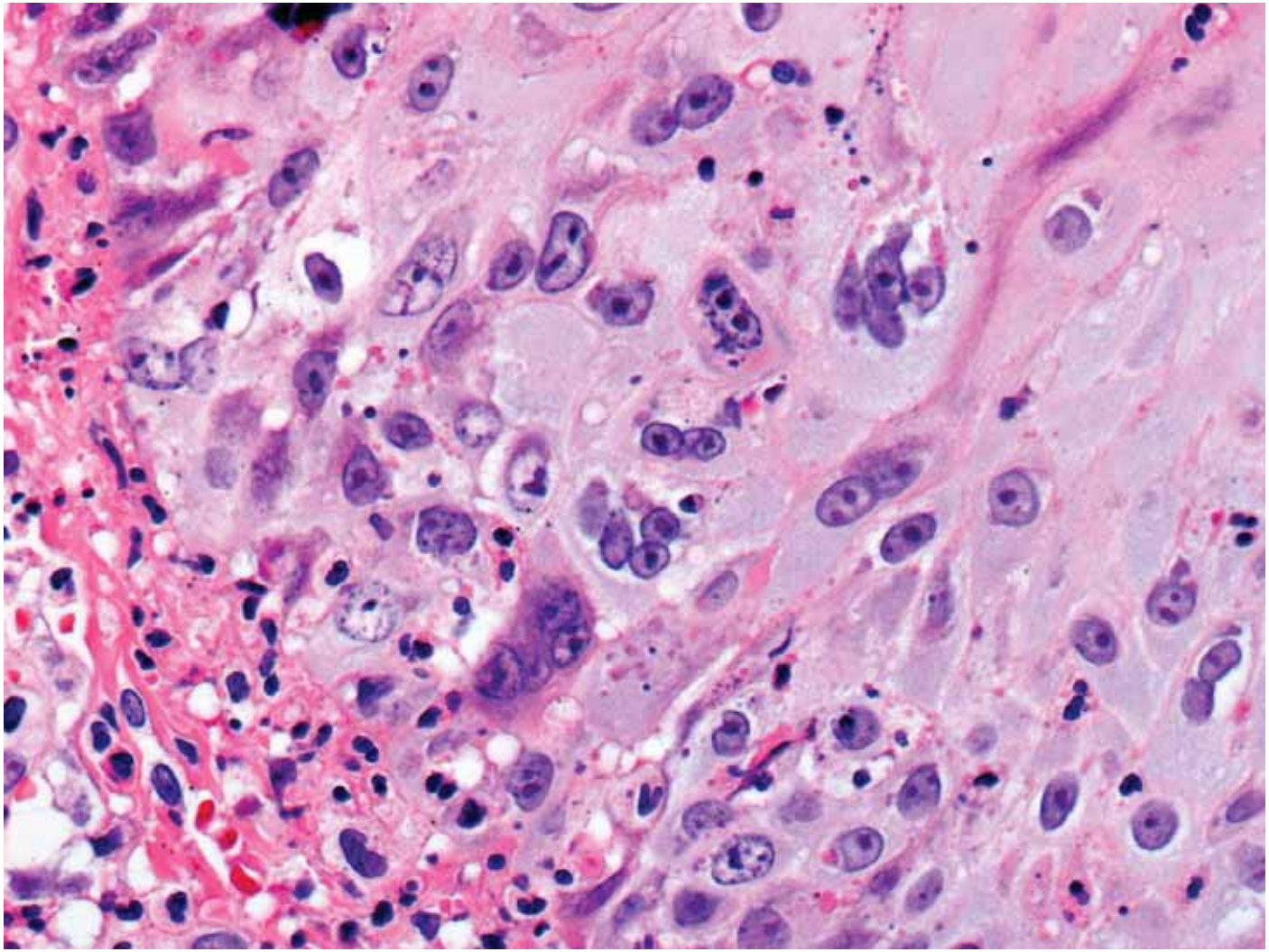




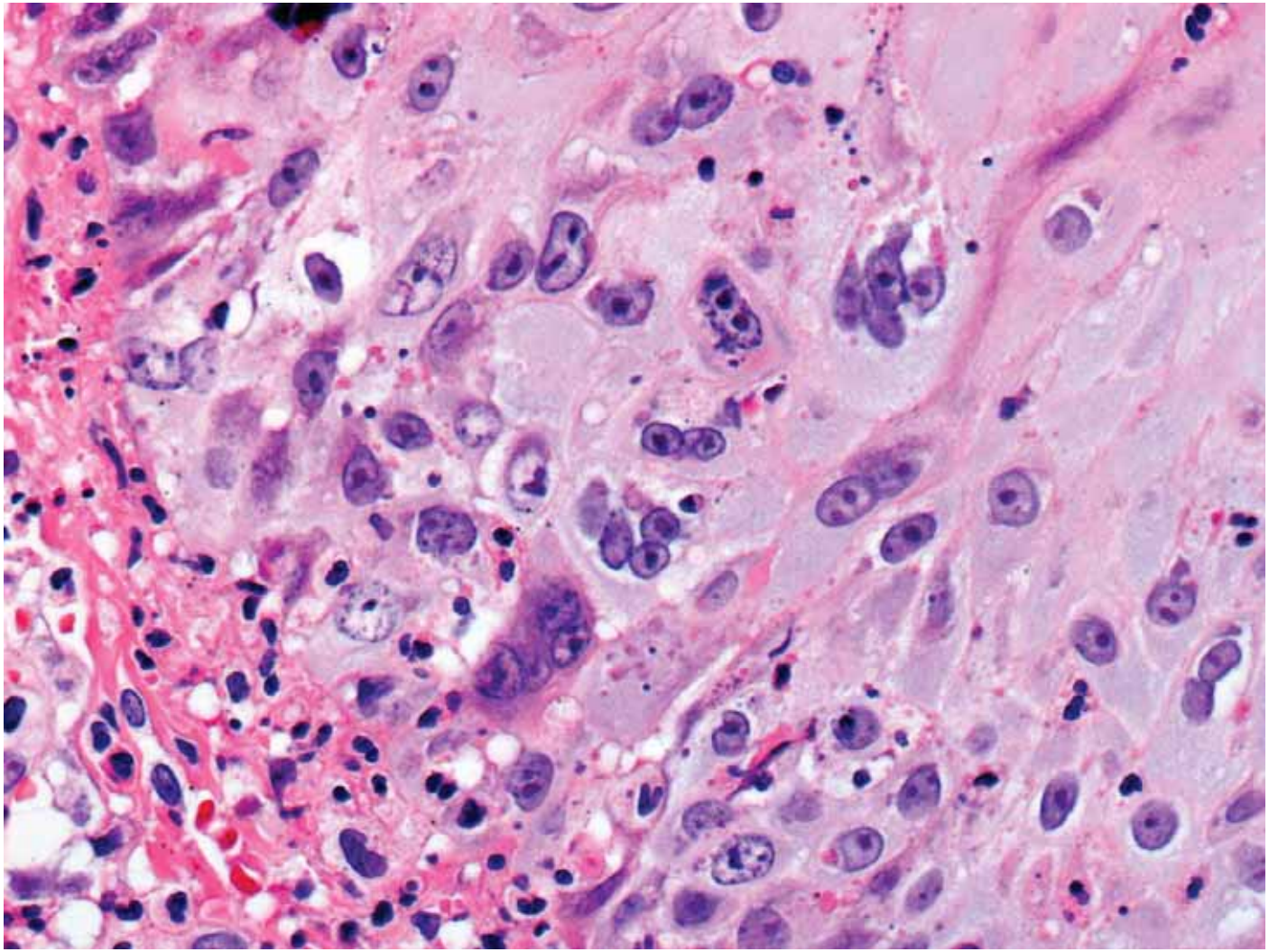




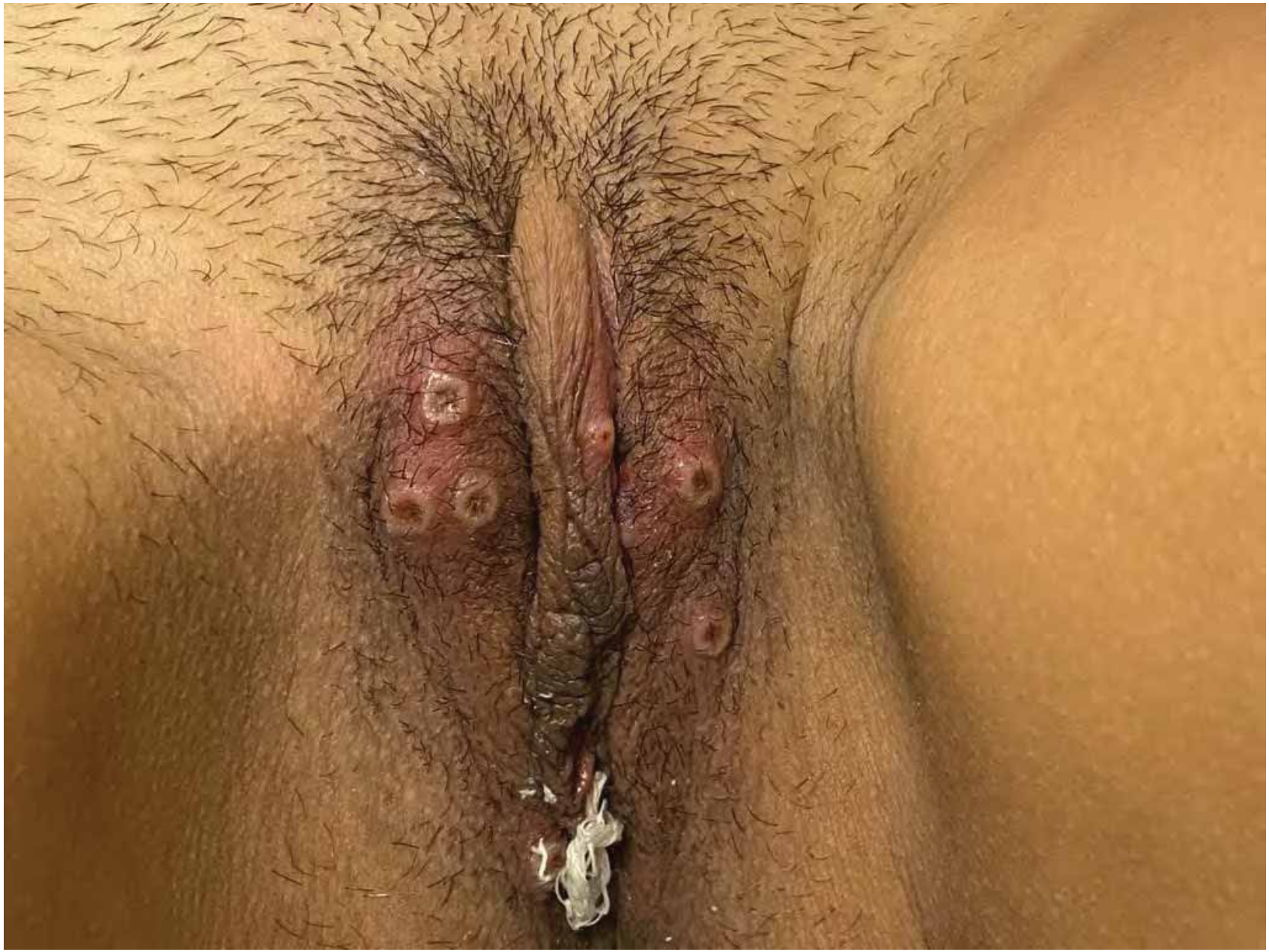




Intraepidermal atypical multinucleated keratinocytes are a *cliche* to…



Intraepidermal atypical multinucleated keratinocytes are a *cliche* to monkeypox



Clinical, histopathologic, immunohistochemical, and electron microscopic findings in cutaneous monkeypox: A multicenter retrospective case series in Spain

Francisco José Rodríguez-Cuadrado, MD,[a] Laura Nájera, MD,[b] Dolores Suárez, MD,[b] Gala Silvestre, MD,[b] Diego García-Fresnadillo, Pathology Technician,[b] Gaston Roustan, MD,[a] Laura Sánchez-Vázquez, MD,[c] Margarita Jo, MD,[c] Carlos Santonja, MD,[c] María Concepción Garrido-Ruiz, MD,[d] Ana María Vicente-Montaña, MD,[e] José Luis Rodríguez-Peralto, MD,[d] and Luis Requena, MD[f]

Background: The worldwide outbreak of monkeypox has evidenced the usefulness of the dermatologic manifestations for its diagnosis.

Objective: To describe the histopathologic and immunohistochemical findings of monkeypox cutaneous lesions.

Methods: This is a retrospective histopathologic and immunohistochemical study of 20 patients with positive *Monkeypox virus* DNA polymerase chain reaction and immunohistochemical positivity for *Vaccinia virus* in cutaneous lesions. Four cases were also examined by electron microscopy.

Results: The most characteristic histopathologic findings consisted of full-thickness epidermal necrosis with hyperplasia and keratinocytic ballooning at the edges. In some cases, the outer root sheath of the hair follicle and the sebaceous gland epithelium were affected. Intraepithelial cytoplasmic inclusion bodies and scattered multinucleated keratinocytes were occasionally found. Immunohistochemically, strong positivity with anti-*Vaccinia virus* antibody was seen in the cytoplasm of ballooned keratinocytes. Electron microscopy study demonstrated numerous viral particles of monkeypox in affected keratinocytes.

Limitations: Small sample size. Electron microscopic study was only performed in 4 cases.

Conclusion: Epidermal necrosis and keratinocytic ballooning are the most constant histopathologic findings. Immunohistochemical positivity for *Vaccinia virus* was mostly detected in the cytoplasm of the ballooned keratinocytes. These findings support the usefulness of histopathologic and immunohistochemical studies of cutaneous lesions for diagnosis of monkeypox. (J Am Acad Dermatol 2023;88:856-63.)

Key words: dermatopathology; electron microscopy; histopathology; immunohistochemistry; monkeypox; virology.

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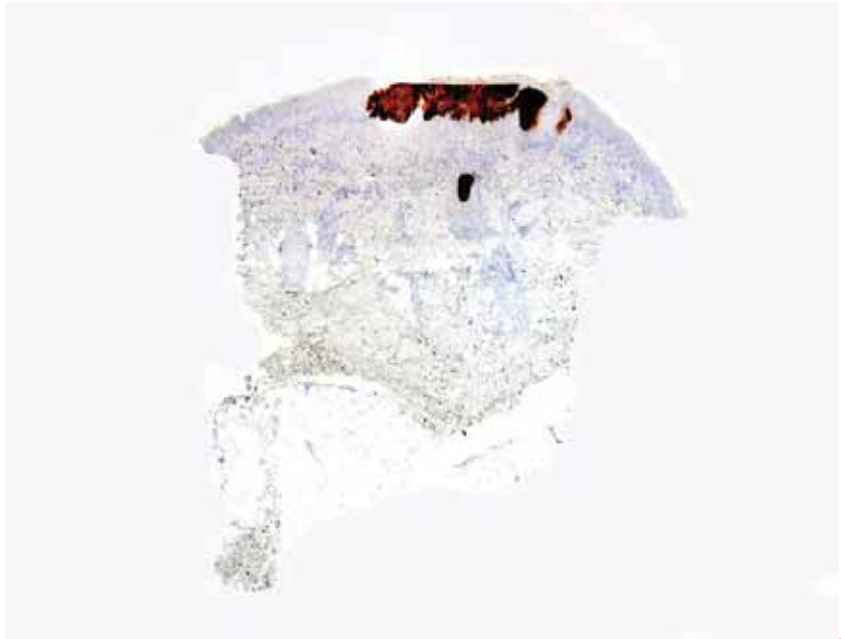
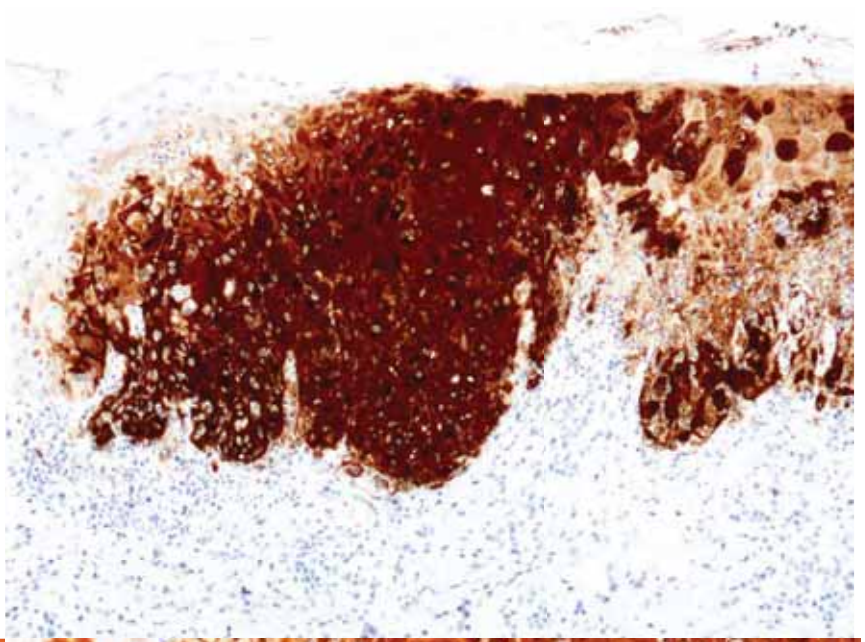
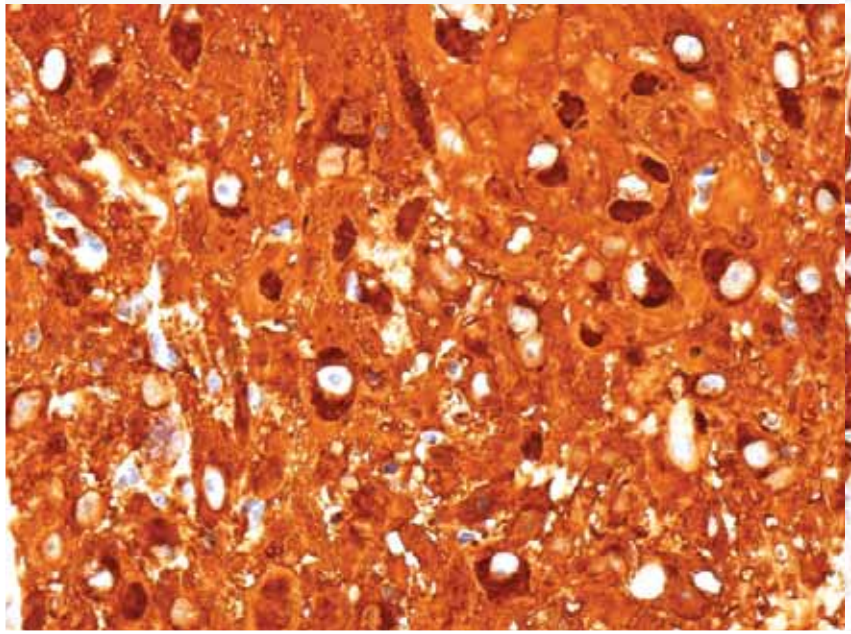
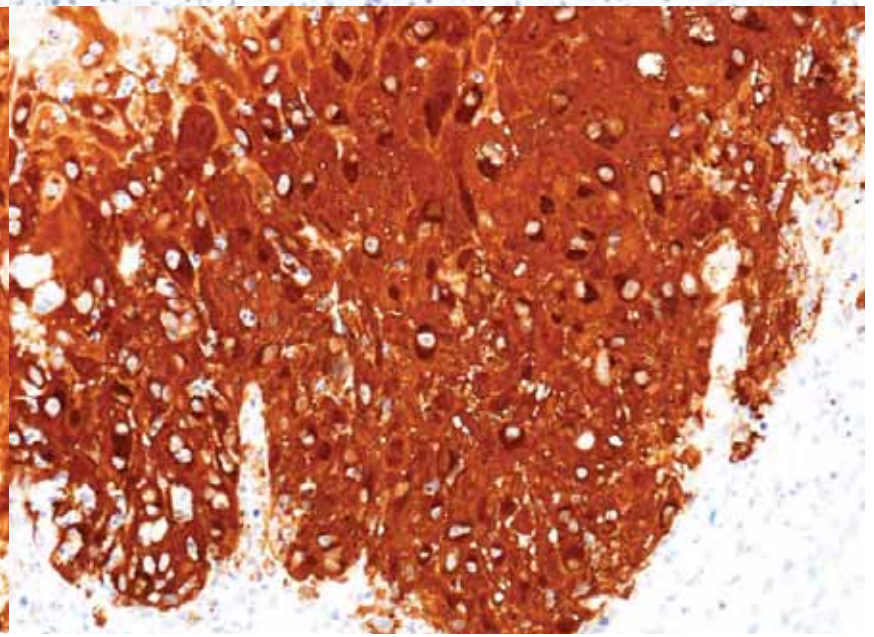


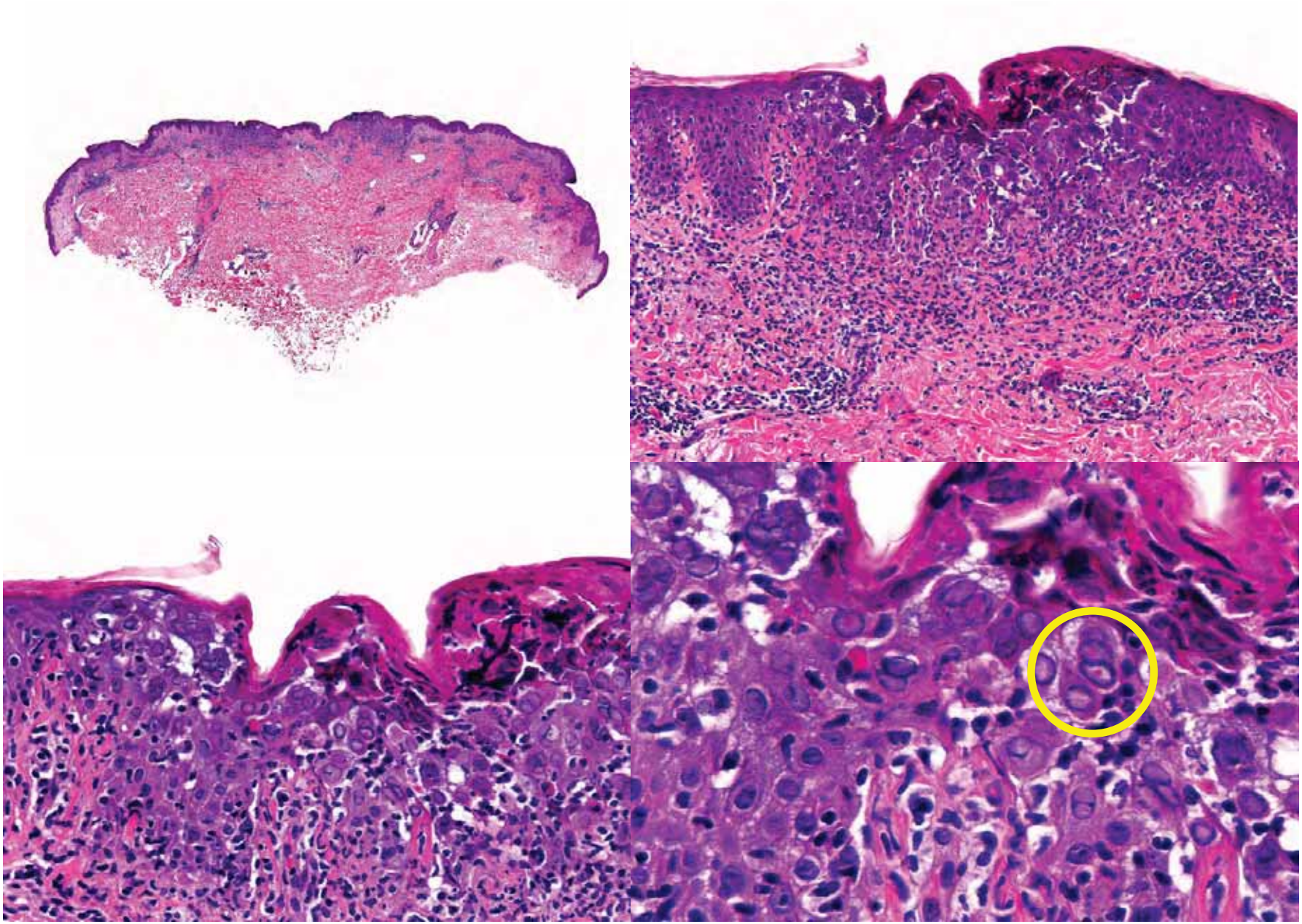


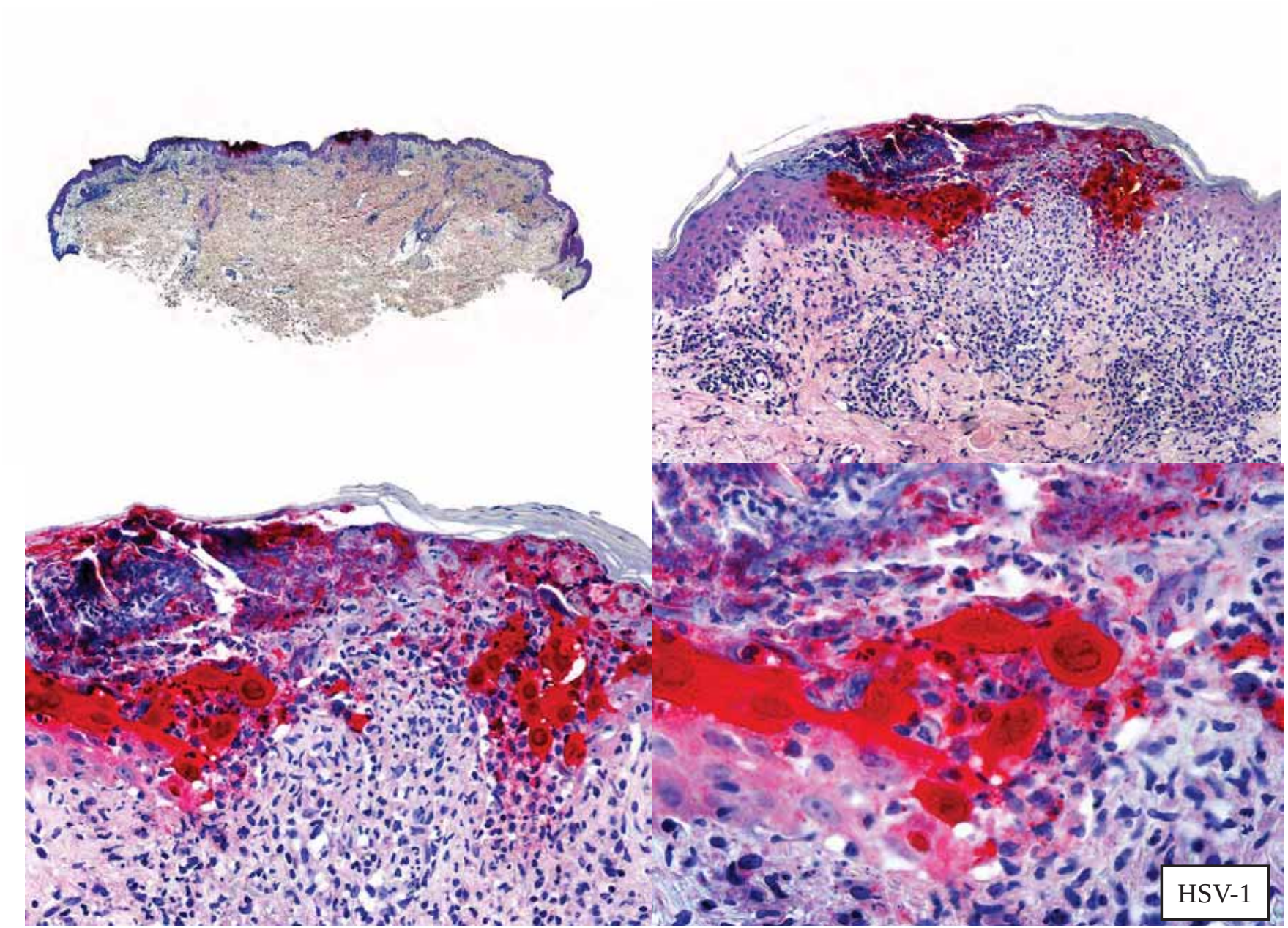




Anti-vaccinia virus Ab

But…

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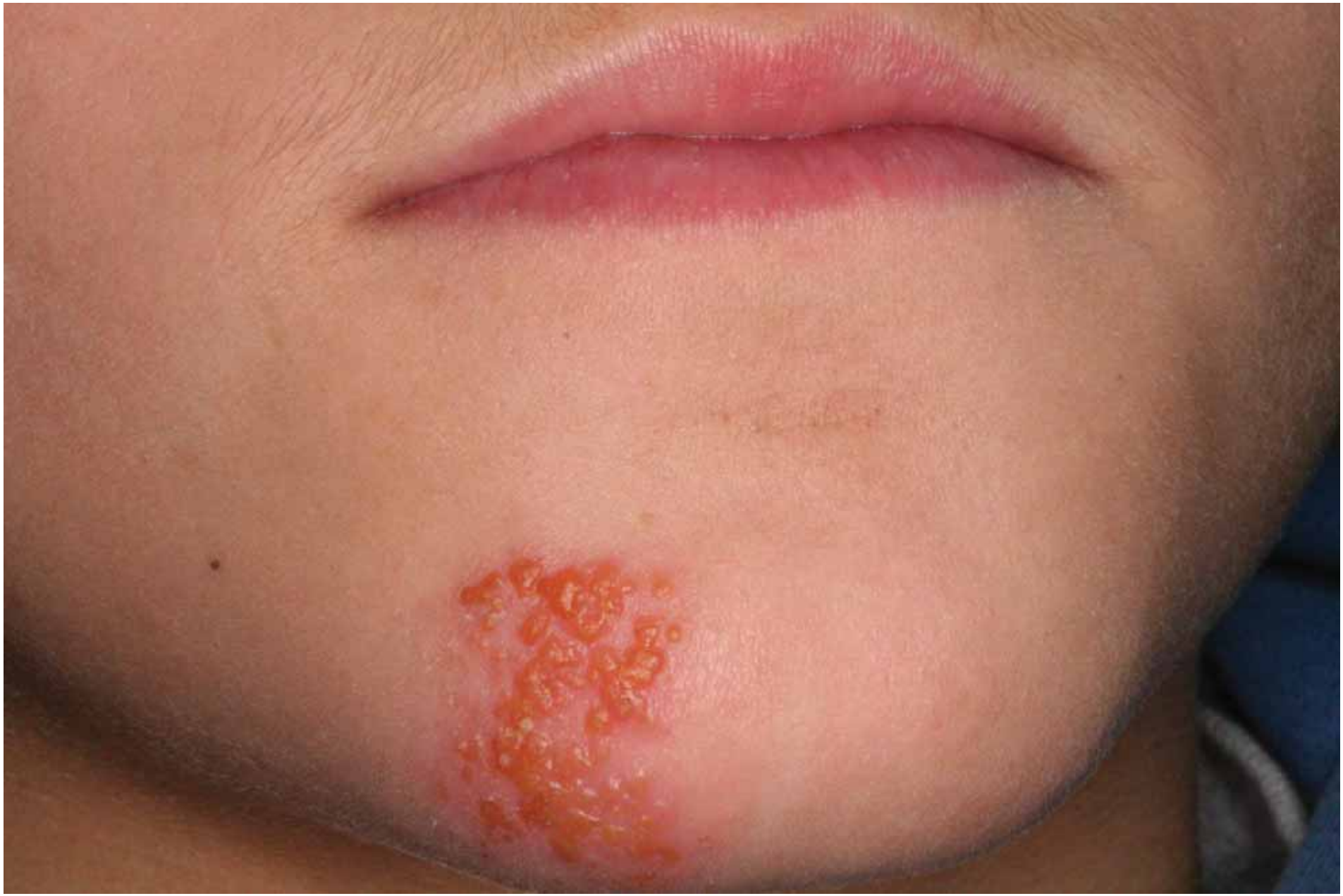

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ORIGINAL ARTICLE

Detection of multinucleated giant cells in differentiated keratinocytes with herpes simplex virus and varicella zoster virus infections by modified Tzanck smear method

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ABSTRACT

Herpes simplex virus (HSV) and varicella zoster virus (VZV) infections induce the formation of intraepidermal vesicles containing acantholytic cells and multinucleated giant cells in the skin. The Tzanck smear is most commonly used to diagnose cutaneous herpetic infections, but it leads to many false-positive and -negative results. This study aimed at establishing a method detecting much larger multinucleated giant cells using the Tzanck smear because these cells characterize the viral cytopathic effect in skin infections. Morphological changes were analyzed among several layers of keratinocytes with HSV- or VZV-related cutaneous lesions, clinically and *in vitro*. We compared the sensitivity of the Tzanck smear to detect large acantholytic cells using both the removed roof tissue part (our approach) and the floor of the lesion (conventional approach) of a fresh vesicle. Large acantholytic cells were detected 2.0-times more frequently in the removed roof tissue part of the vesicle than in the floor of the lesion. Round cells were much larger in the removed roof tissue part of the vesicle corresponding to the granular or prickle layer of the epidermis than in its floor of the lesion corresponding to the basal or prickle layer with the Tzanck smear. Differentiated cultured keratinocytes formed multinucleated giant cells by cell-to-cell fusion with resolution of cell membrane with VZV infection. Differentiated keratinocytes promote multinucleated giant cell formation by cell-to-cell fusion with HSV-1 or VZV infection. To increase the sensitivity, the Tzanck smear should be prepared from the removed roof tissue part of a fresh vesicle to detect multinucleated giant cells in herpetic infections.

Key words: acantholytic cell, herpes simplex virus, multinucleated giant cell, Tzanck smear, varicella zoster virus.

INTRODUCTION

The *Alphaherpesvirinae* subfamily includes herpes simplex viruses (HSV) and varicella zoster virus (VZV), which are neurotropic and epidermotropic. Keratinocytes (KC) infected with HSV and VZV can develop herpes simplex, genital herpes and eczema herpeticum among others, and varicella (chicken pox) and herpes zoster (shingles), respectively, that commonly cause the cutaneous lesions: vesicles, bullae, pustules, erosion and crusts.

Histologically, HSV or VZV infections are characterized by intraepidermal vesicles associated with intercellular edema, acantholytic cells (AC) and multinucleated giant cells (MGC) with intense mixed inflammatory cells in the underlying dermis (Fig. 1). These infections are diagnosed by specific (e.g. the direct fluorescent antibody test, immunochromatography, polymerase chain reaction and loop-mediated isothermal amplification) and non-specific methods (the Tzanck smear and skin biopsies).

The Tzanck smear is a method used to detect cytological findings, and is most commonly used to diagnose various kinds of skin diseases including herpetic infections, pemphigus, Darier's disease, Hailey-Hailey disease and bullous impetigo because it is simple, rapid, non-invasive and cost-effective.[1,2] The material gently scraped from the bottom of the lesion is smeared onto a microscopic slide, allowed to air dry and stained with May-Grünwald-Giemsa stain.[3–5] The positivity of the Tzanck smear detecting AC and/or MGC for herpetic infections is between 42% and 90%.[1,6] Furthermore, false-positive and -negative rates have been reported to be 3–13% and 28%, respectively.[7,8] The accuracy of the Tzanck smear for diagnosing herpetic infections depends not only on the type and duration of the cutaneous lesion, but the skill and experience of the interpreter.[9,10] A part of these problems can be

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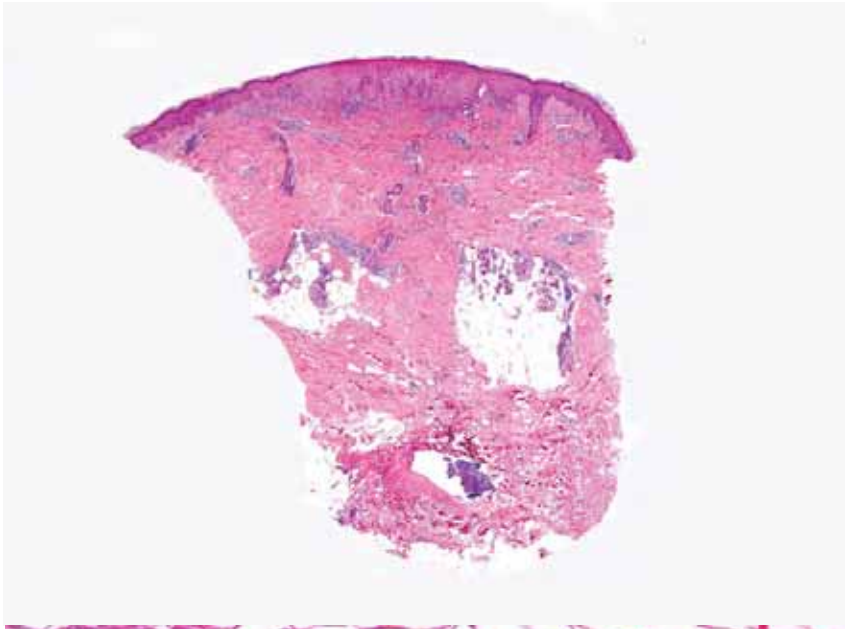

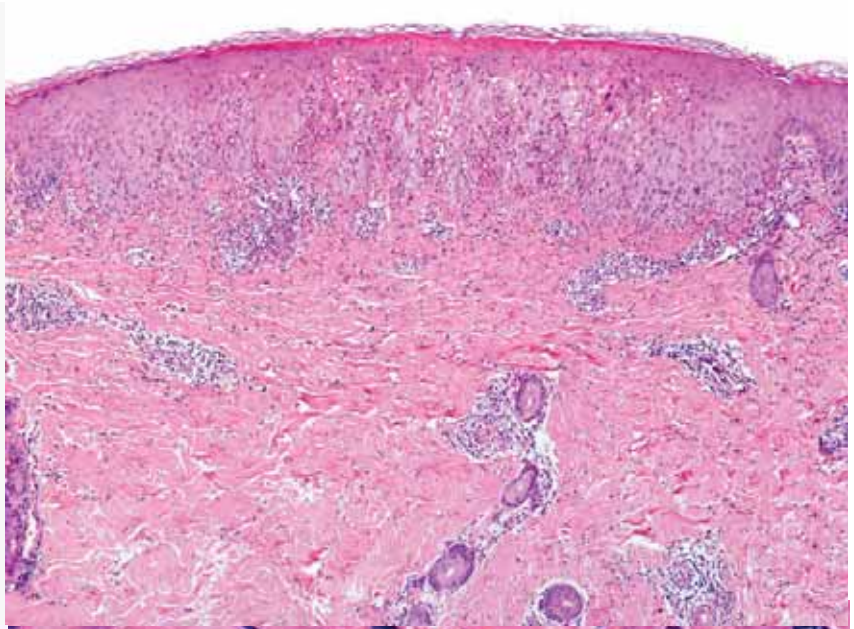

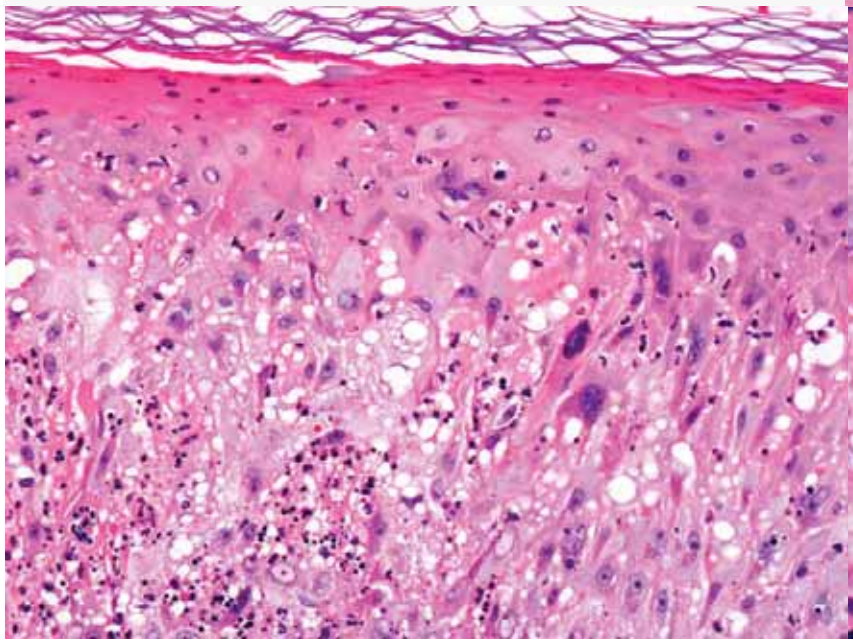

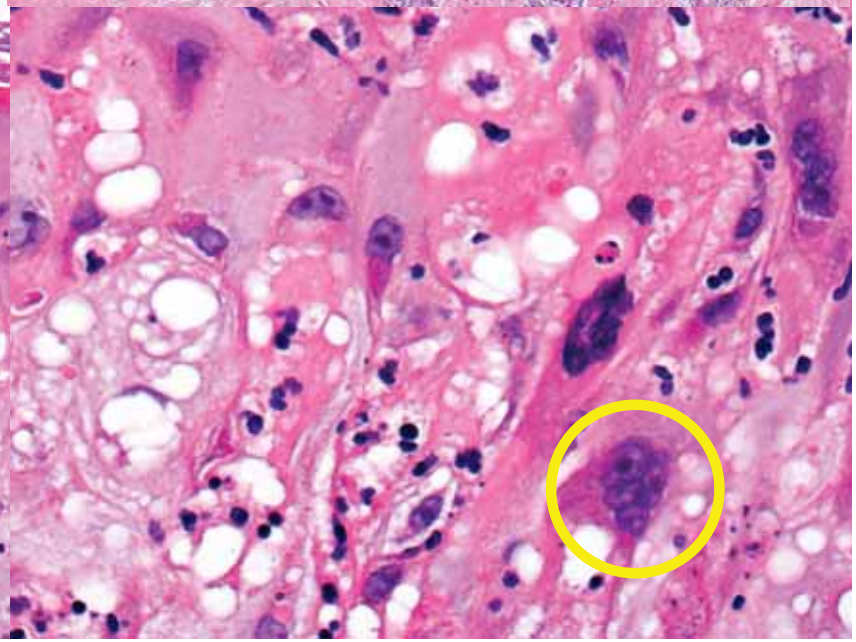

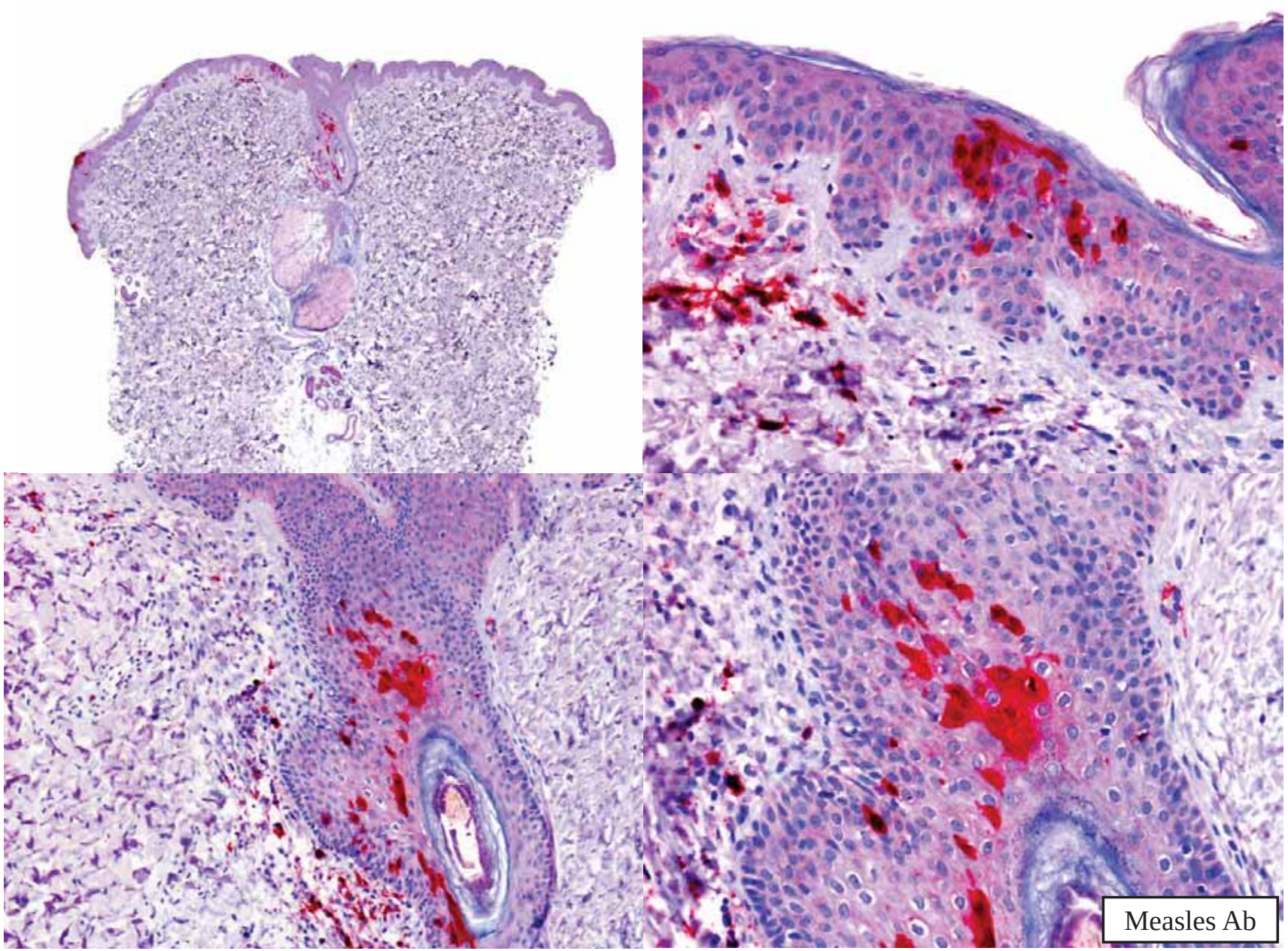
Measles Ab

Follicle and Sebaceous Gland Multinucleated Cells in Measles

Jorge Magdaleno-Tapial, MD, Cristian Valenzuela-Oñate, MD, Macarena Giacaman-von der Weth, MD, Blanca Ferrer-Guillén, MD, Marta García-Legaz Martínez, MD, Álvaro Martínez-Domenech, MD, Pablo Hernández-Bel, PhD, and Víctor Alegre-de Miquel, PhD

Abstract: We report the case of a 32-year-old man with measles in which skin biopsy helped to establish a definitive diagnosis. Follicular involvement is a common histopathologic feature of measles. Multinucleated epidermal and follicular cells are distinctive findings.

Key Words: measles, multinucleated giant keratinocytes, follicle, sebaceous gland

(*Am J Dermatopathol* 2019;41:289–292)

Measles is a highly contagious viral disease caused by a virus belonging to the *Paramyxoviridae* family, genus *Morbillivirus*.[1] Maculopapular rash appears 3 or 4 days after the onset of fever, malaise, and headache in conjunction with cough, coryza, and conjunctivitis. Measles virus is transmitted by airborne respiratory droplets entering the respiratory tract or by direct contact with respiratory secretions. The disease is largely self-limiting in immunocompetent and immunized individuals.[2] The incidence of measles has increased in the last 2 years and is currently considered a re-emerging disease. Patients who survive the virus can develop respiratory and neurological complications.[3] The exanthem following measles infection is clinically distinctive but can be confused it with other infectious or allergic exanthems. Histopathologic study of skin biopsies can help to stablish a correct diagnosis.

A 32-year-old healthy man consulted to the Dermatology Department with a 4-day history of fever. Skin rash and dry cough developed the day before admission. On examination, the patient was febrile (38.9°C). Scarcely confluent, craniocaudally distributed, macular exanthema was present. Palms and soles were spared. Serous conjunctivitis and discrete photophobia were present. Palpable cervical and submandibular adenopathy were noted. Examination of the oral cavity revealed whitish macules on an erythematous base on both mucous membranes, such as "grains of salt on a red background." Blood tests revealed lymphopenia (200 cells/mL) and elevated glutamic pyruvic transaminase (185 IU/L). All other parameters were normal. Chest radiograph was normal. The patient was admitted for symptomatic treatment and air isolation. Serological tests and a punch biopsy were performed. Measles-specific IgM antibodies confirmed the diagnosis.

Histopathologic study of skin biopsy showed mild superficial perivascular dermatitis with vacuolar interface dermatitis and focal vesicular dermatitis in follicular and interfollicular epidermis. Focal keratinocytic dysmaturation and apoptosis were observed. Hyperkeratosis with parakeratosis was also noted (Fig. 1). Major changes were observed in follicular and sebaceous epithelia. Multiple dyskeratotic keratinocytes were present in follicles and sebaceous glands. Multinucleated keratinocytes showed a glassy cytoplasm and 3–6 irregularly shaped nuclei with indistinct nucleoli (Fig. 2). The dermis showed a mild superficial, perivascular, and periadnexal lymphocytic and eosinophilic infiltrate. Electron microscopy of follicular syncytial epithelial giant cells (SEGCs) showed isolated capsid particles within the cytoplasm and secretory vesicles, measuring approximately 40–60 nm in diameter (Fig. 3).

Measles, a member of the *Paramyxoviridae* family, is an enveloped virus with a single-strand, negative-sense RNA genome. The hemagglutinin protein communicates with extracellular receptors and initiates cell-to-cell binding, whereas the fusion protein is responsible for cell membrane fusion and formation of the multinucleated giant cells, which are characteristics of measles.[2]

Migratory movements and the decrease in vaccination rates have led to numerous outbreaks of measles both in Europe and the United States In classic measles, cutaneous changes present as an enanthem (Koplik spots) followed by an exanthem in a cephalocaudal distribution.[1] Primary viremia causes viral dissemination through lymphoid tissues and Warthin–Finkeldey giant cells. Secondary viremia involves other organs through infected lymphocytes and monocytes with subsequent formation of SEGCs.[4] Although it is usually a self-limited infection, possible complications include otitis media, pneumonia, laryngotracheobronchitis, diarrhea, and

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J. Magdaleno-Tapial wrote most of the original draft of the paper. C. Valenzuela-Oñate, M. Giacaman-von der Weth, and B. Ferrer-Guillén have participated in writing the paper. M. García-Legaz Martínez and P. Hernández-Bel have followed the patient. V. Alegre-de Miquel and Á. Martínez-Domenech have performed the histological study of the samples. V. Alegre-de Miquel has followed the patient and has reviewed the pertinent raw data on which conclusions of this study are based. All authors have read and approved the final version of the manuscript submitted.

The authors declare no conflicts of interest.

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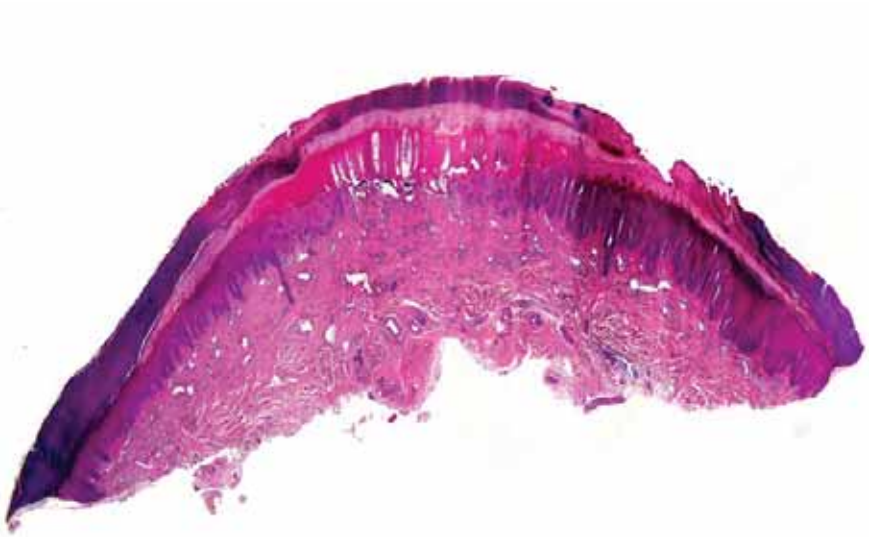
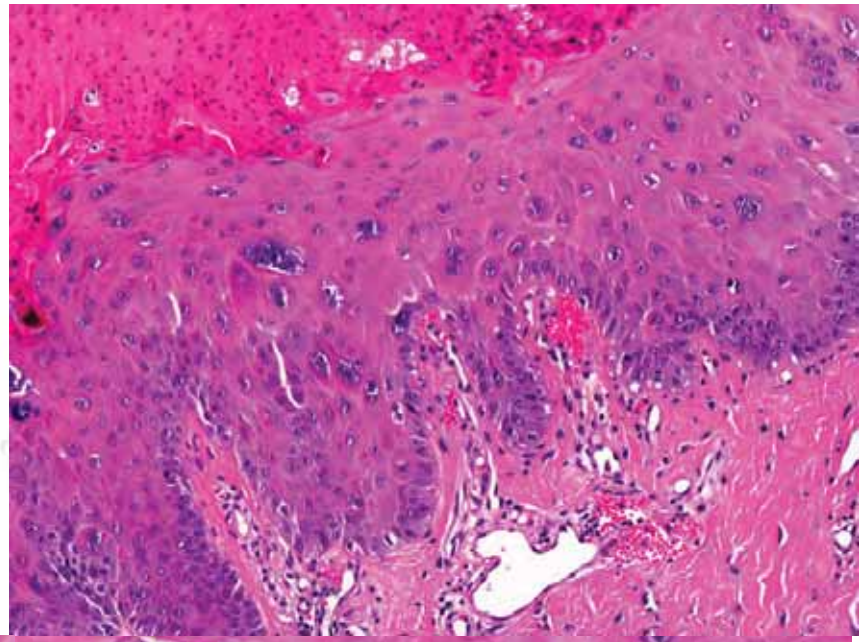
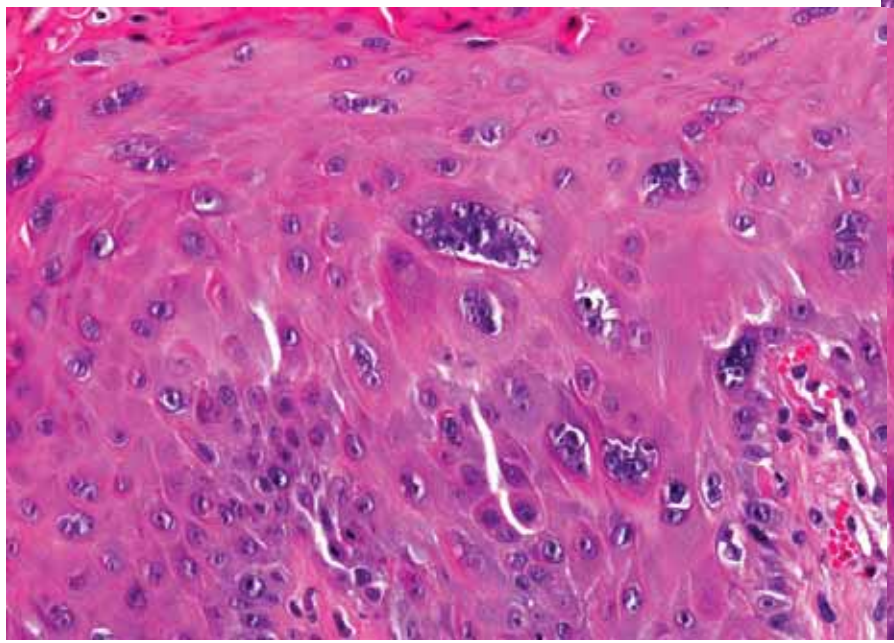
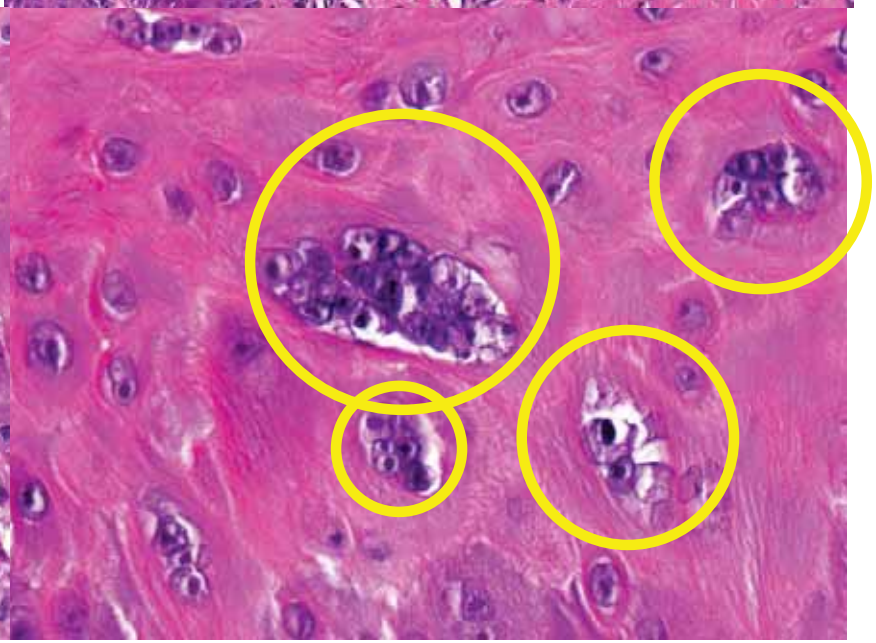








The American Journal of Dermatopathology
Volume 6 Number 2
April 1984

Thomas R. Wade, M.D.

A. Bernard Ackerman, M.D.

The effects of resin of podophyllin on condyloma acuminatum

ABSTRACT The effects of resin of podophyllin on lesions of condyloma acuminatum have posed problems to pathologists who sought to differentiate them histologically from squamous cell carcinoma *in situ*. The most striking histologic changes in lesions of condyloma acuminatum following application of resin of podophyllin occur within the first 48 hours. They are pallor of the epidermis secondary to both intracellular and intercellular edema, numerous necrotic keratinocytes in the lower half of the epidermis, and a marked increase in the number of mitotic figures there. Within the edematous papillary dermis, there is a scattered infiltrate of lymphocytes, histiocytes, and neutrophils. The absence of nuclear atypia, multinucleated keratinocytes, and dyskeratotic cells, and the presence of the orderly sequence of maturation of keratinocytes within the epidermis permit histologic differentiation of podophyllin-treated condyloma acuminatum from true squamous-cell carcinoma *in situ*. The acute histologic changes induced by podophyllin begin to wane by 72 hours after the resin has been applied. At this time, necrotic keratinocytes are found mostly within the upper portion of the epidermis and few mitotic figures are seen. By 1 week after application of podophyllin there are virtually no histologic abnormalities within the epidermis.

Am J Dermatopathol 6:109–122, 1984.

From the Departments of Dermatology and Pathology of Emory University School of Medicine, Atlanta, Georgia (TRW), and New York University School of Medicine, New York, New York (ABA).

"Podophyllin treatment changes the histologic picture of condyloma acuminatum so that it may easily be confused with carcinoma."[1]

H. Z. Lund, 1957

"It is readily evident that these histologic changes [in condylomata acuminata treated by podophyllin] resemble abnormalities seen in squamous cell epitheliomas . . . It is our contention that the differentiation between malignant tissue changes and those induced by applications of podophyllin is difficult. Under practical conditions it may be impossible."[2]

G. F. Machacek and D. R. Weakley, 1960

"This drug [podophyllin] . . . can produce changes in cell morphology strongly suggesting squamous cell carcinoma."[3]

W. Caro, 1975

"The histologic effects of podophyllin . . . may mimic some of the atypical changes seen with carcinoma *in situ* . . . A correct interpretation of condyloma biopsies is therefore extremely difficult if the lesion has been recently exposed to podophyllin. These effects diminish with time but may last six weeks or more."[4]

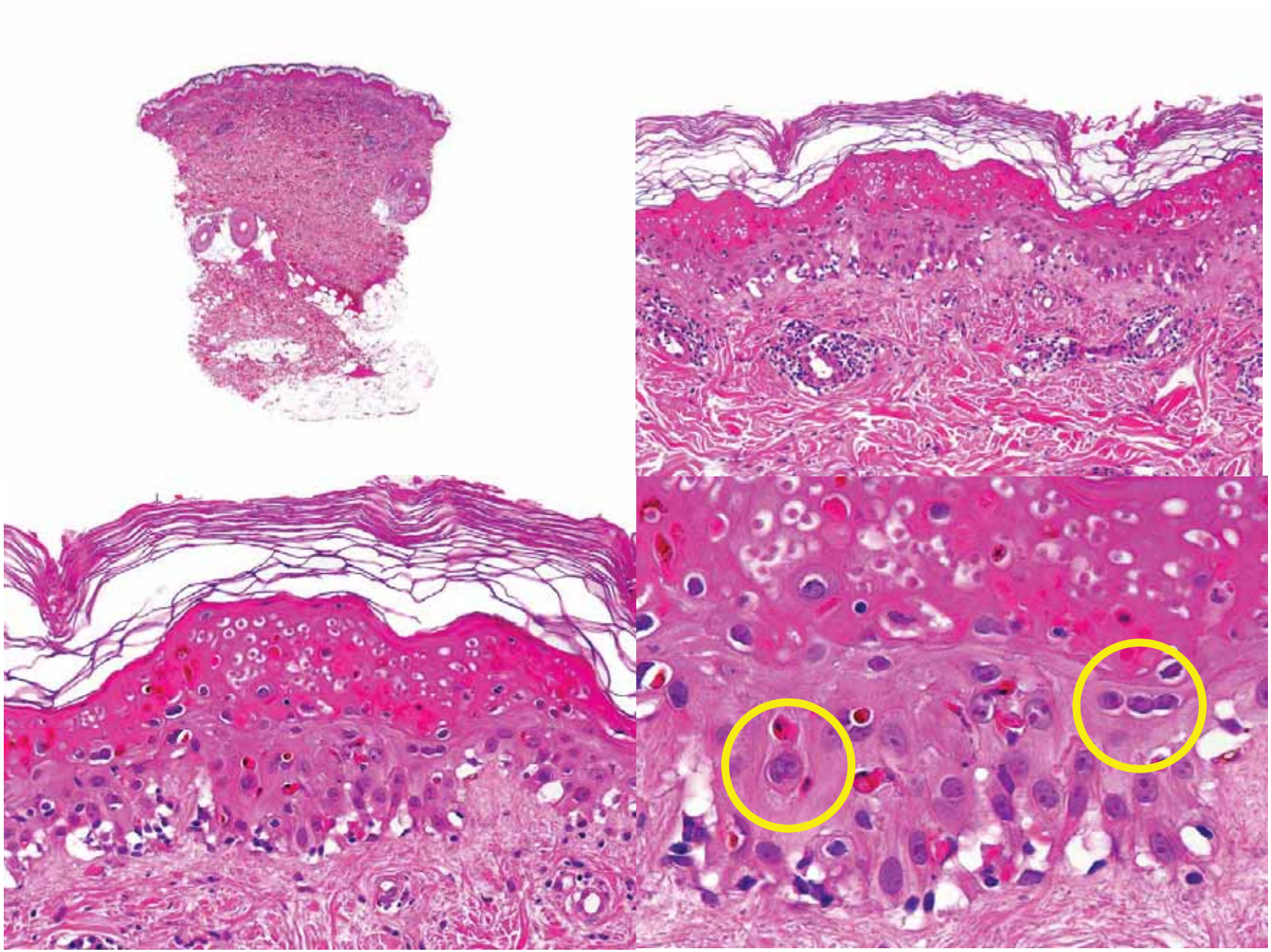
E. G. Friedrich, 1976

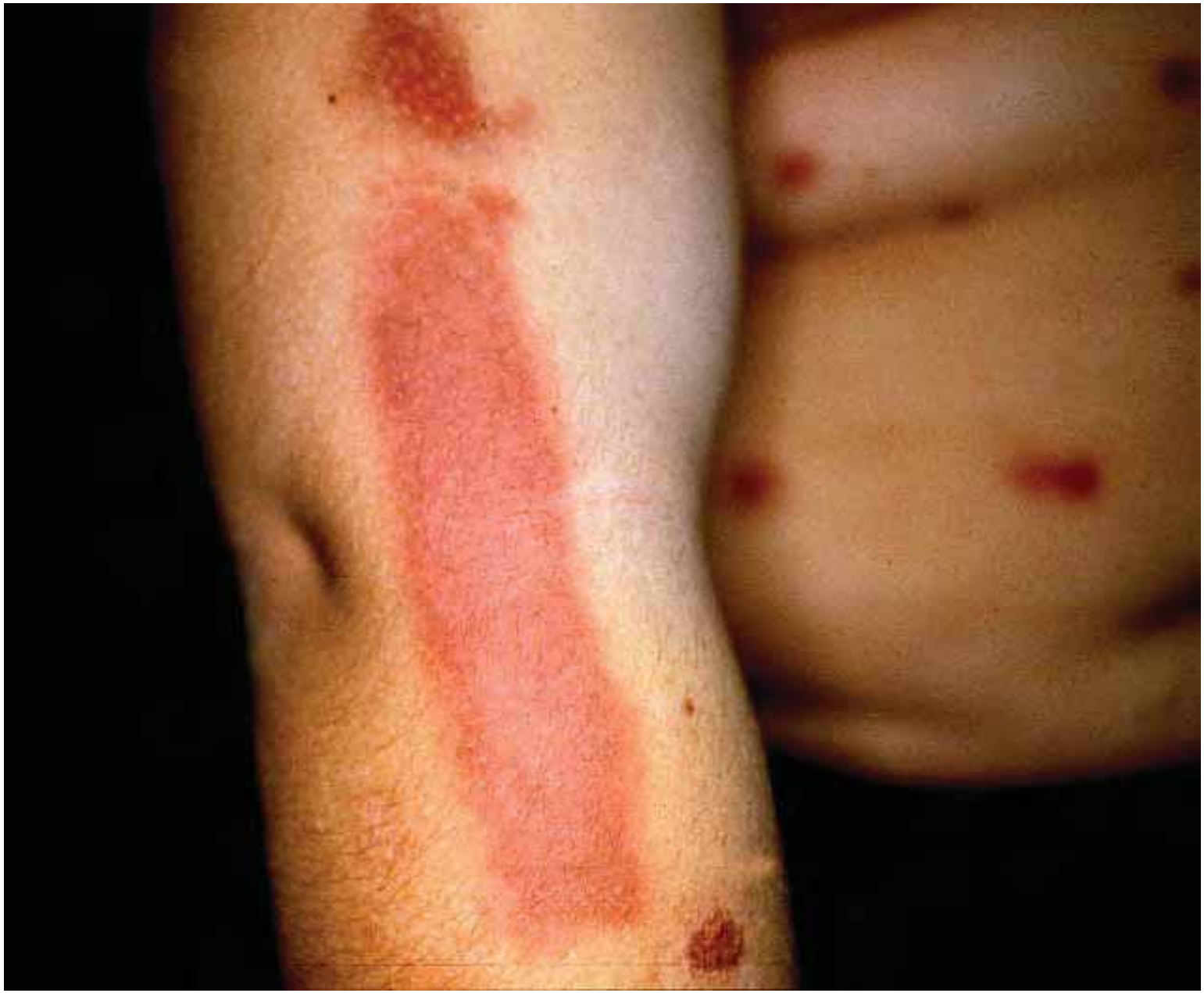
"The application of this chemical resin [podophyllin] when applied to epithelium induces the formation of 'podophyllin cells' which can be easily confused with the atypical malignant cells seen in squamous cell carcinomas on microscopic examination."[5]

A. Friedman-Kien, 1976

"The marked epithelial atypia secondary to podophyllin therapy . . . must be differentiated from the features of carcinoma in situ, which they closely resemble."[6]

E. G. Friedrich and E. J. Wilkinson, 1977





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doi: 10.1111/cup.12744
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Journal of
Cutaneous Pathology

Epidermal multinucleated keratinocytes: a histopathologic clue to dermatitis artefacta

Dermatitis artefacta is a psycho-cutaneous disorder characterized by self-inflicted cutaneous injuries, often in association with an underlying psychiatric disorder or as a response to external stressors. Cutaneous lesions suggestive of dermatitis artefacta are dependent on the means of injury and thus may be morphologically variable, but typically have geometric shapes, spare hard-to-reach anatomic areas, and are present in variable stages of evolution at any specific time. Although a dermatologist may be suspicious of dermatitis artefacta in a given patient, making a definitive diagnosis is extremely challenging. Patients often clinically evade questioning and deny creating skin lesions, and histopathologic evaluation of lesional biopsies usually reveals non-specific epidermal and dermal changes and inflammation. Thus, identification of clues that lend support to a diagnosis of dermatitis artefacta would be welcomed by both clinicians and pathologists. Here we present a case of dermatitis artefacta with a unique, yet previously reported, histopathological finding of multinucleated keratinocytes within the epidermis. Although probably uncommon and dependent on the etiology of cutaneous injury, we believe this finding is important for dermatopathologists to be aware of as a potential diagnostic clue when evaluating biopsies in patients suspected to have dermatitis artefacta.

Keywords: dermatitis artefacta, keratinocytes, multinucleated giant cells

Gutierrez D, Schowalter MK, Piliang MP, Fernandez AP. Epidermal multinucleated keratinocytes: a histopathologic clue to dermatitis artefacta. J Cutan Pathol 2016; 43: 880–883. © 2016 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

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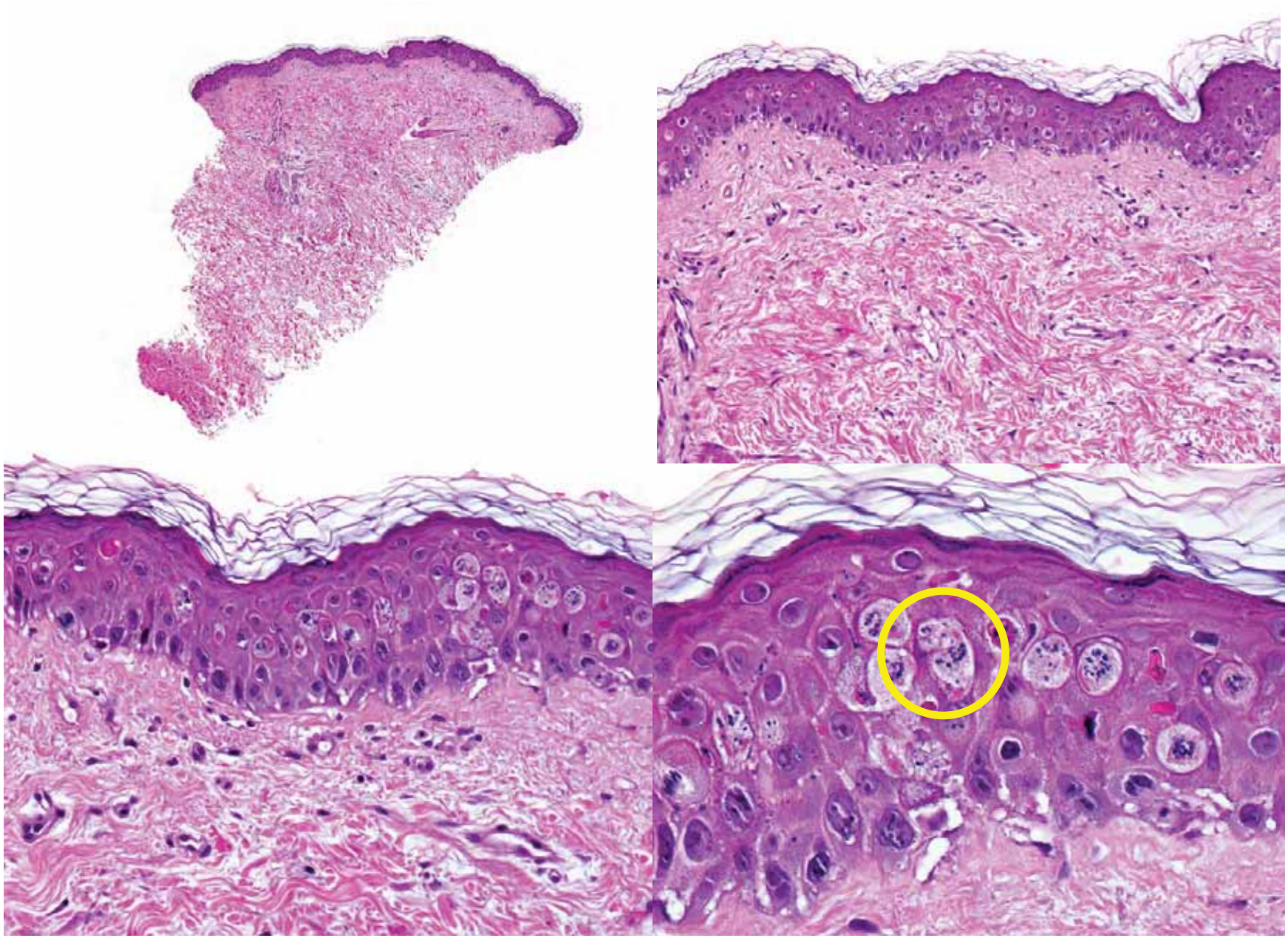
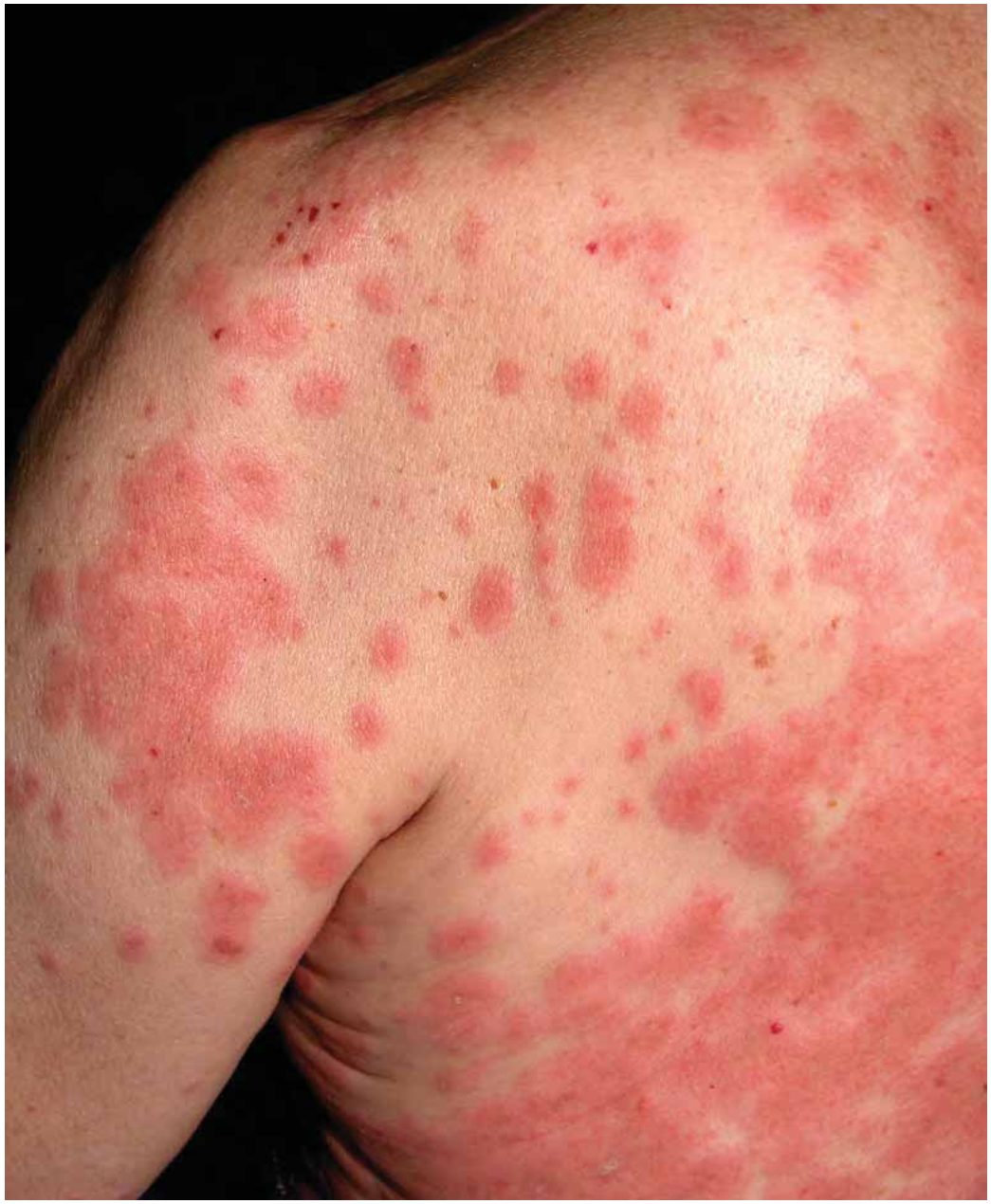
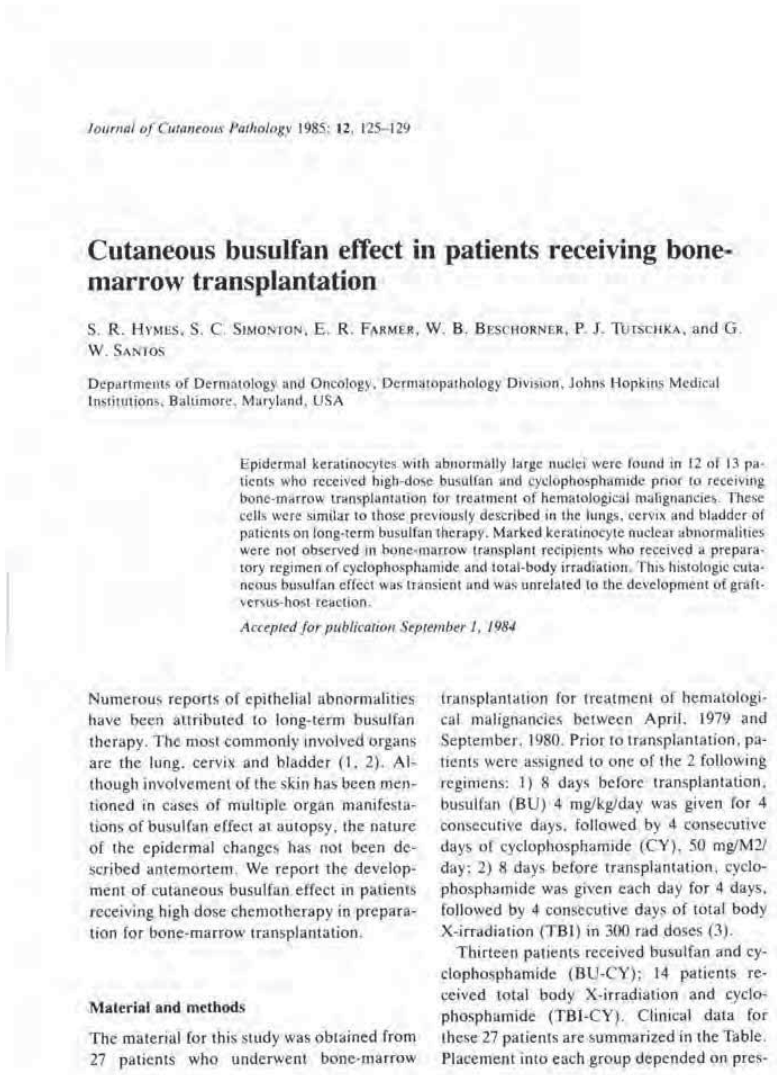
Dermatitis artefacta, or factitial dermatitis, is characterized by self-inflicted cutaneous injuries. This disorder is predominantly seen in women with underlying psychiatric diagnoses and is exacerbated frequently during periods of increased stress. The clinical morphology of skin injuries in dermatitis artefacta is highly variable and includes erythematous, ecchymotic, vesicular and/or ulcerative lesions depending on the method of injury. Regardless of morphology, dermatitis artefacta typically displays geometric or other unusual patterns, which are sharply demarcated from surrounding normal skin and spare anatomic areas that are difficult







Journal of Cutaneous Pathology 1985: **12**, 125–129

Cutaneous busulfan effect in patients receiving bone-marrow transplantation

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Epidermal keratinocytes with abnormally large nuclei were found in 12 of 13 patients who received high-dose busulfan and cyclophosphamide prior to receiving bone-marrow transplantation for treatment of hematological malignancies. These cells were similar to those previously described in the lungs, cervix and bladder of patients on long-term busulfan therapy. Marked keratinocyte nuclear abnormalities were not observed in bone-marrow transplant recipients who received a preparatory regimen of cyclophosphamide and total-body irradiation. This histologic cutaneous busulfan effect was transient and was unrelated to the development of graft-versus-host reaction.

Accepted for publication September 1, 1984

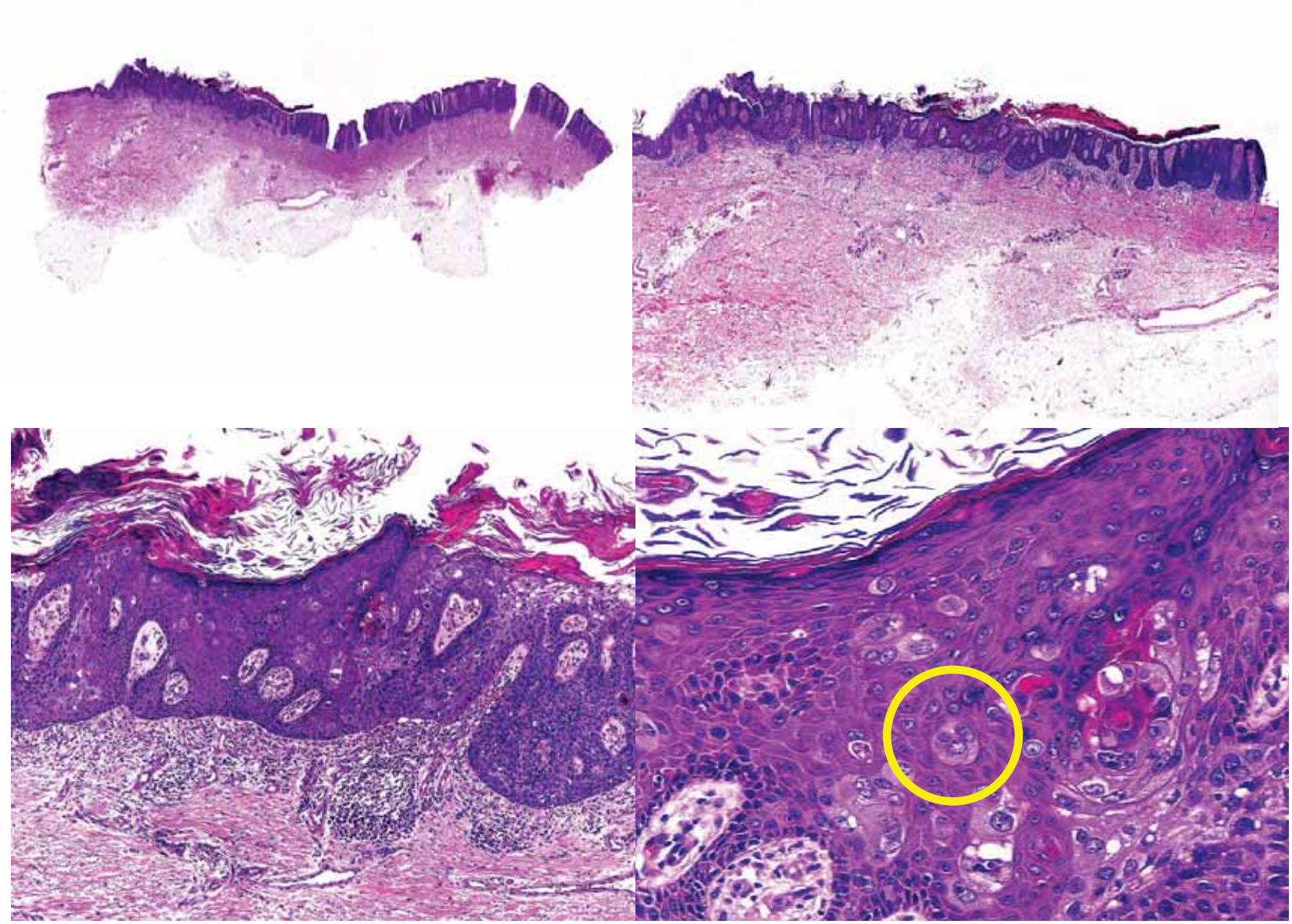
Numerous reports of epithelial abnormalities have been attributed to long-term busulfan therapy. The most commonly involved organs are the lung, cervix and bladder (1, 2). Although involvement of the skin has been mentioned in cases of multiple organ manifestations of busulfan effect at autopsy, the nature of the epidermal changes has not been described antemortem. We report the development of cutaneous busulfan effect in patients receiving high dose chemotherapy in preparation for bone-marrow transplantation.

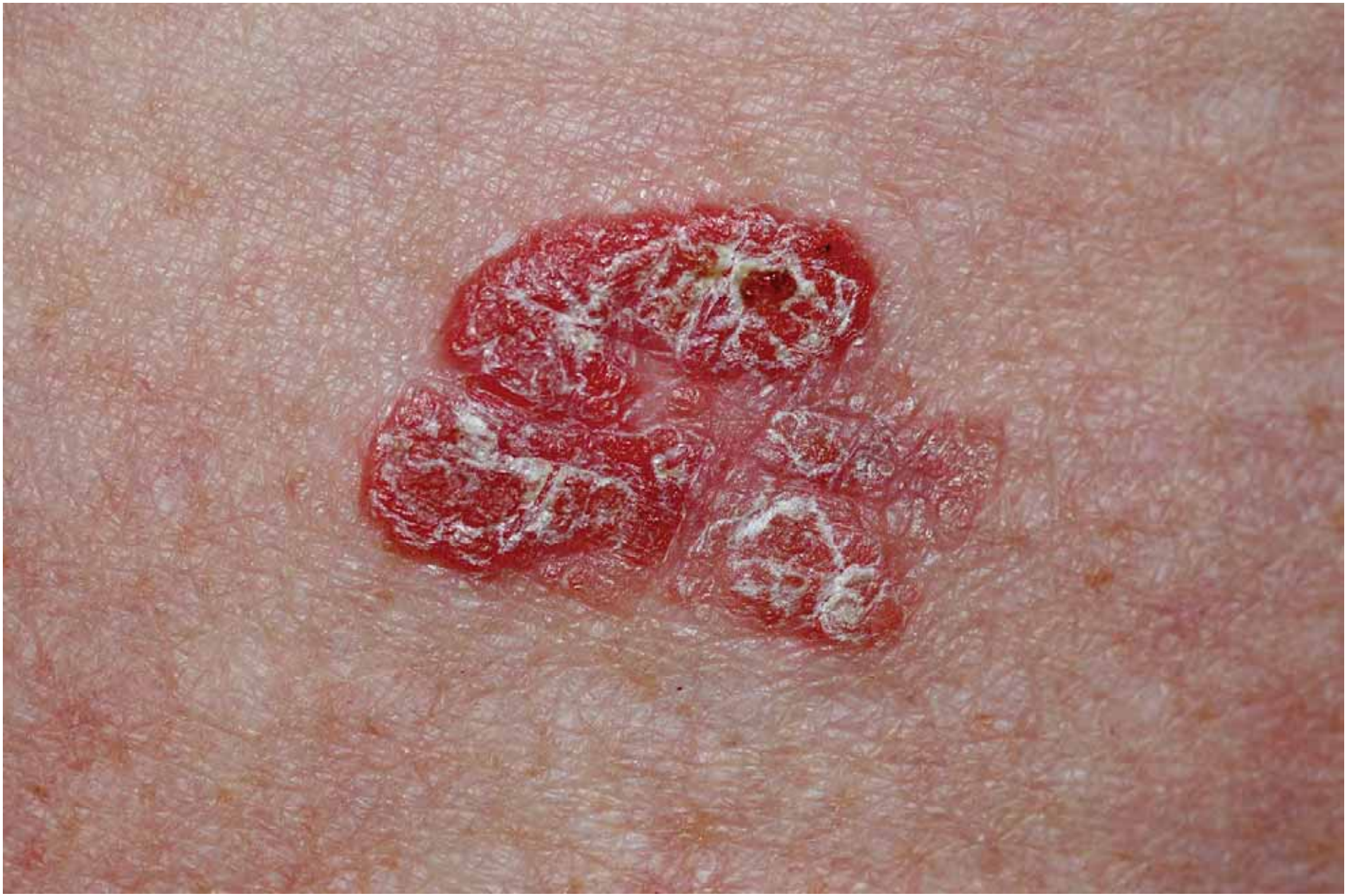
Material and methods

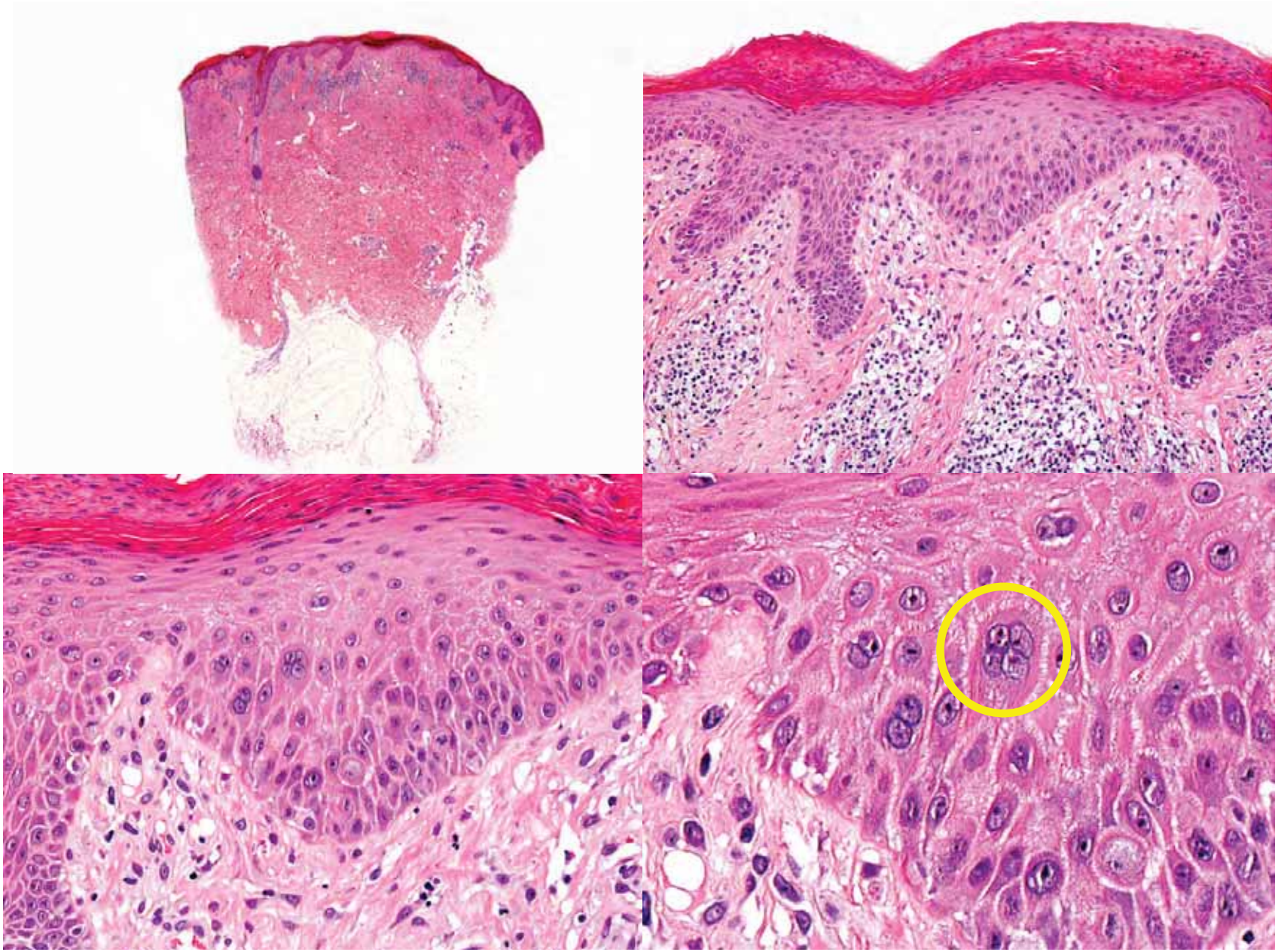
The material for this study was obtained from 27 patients who underwent bone-marrow transplantation for treatment of hematological malignancies between April, 1979 and September, 1980. Prior to transplantation, patients were assigned to one of the 2 following regimens: 1) 8 days before transplantation, busulfan (BU) 4 mg/kg/day was given for 4 consecutive days, followed by 4 consecutive days of cyclophosphamide (CY), 50 mg/M2/day; 2) 8 days before transplantation, cyclophosphamide was given each day for 4 days, followed by 4 consecutive days of total body X-irradiation (TBI) in 300 rad doses (3).

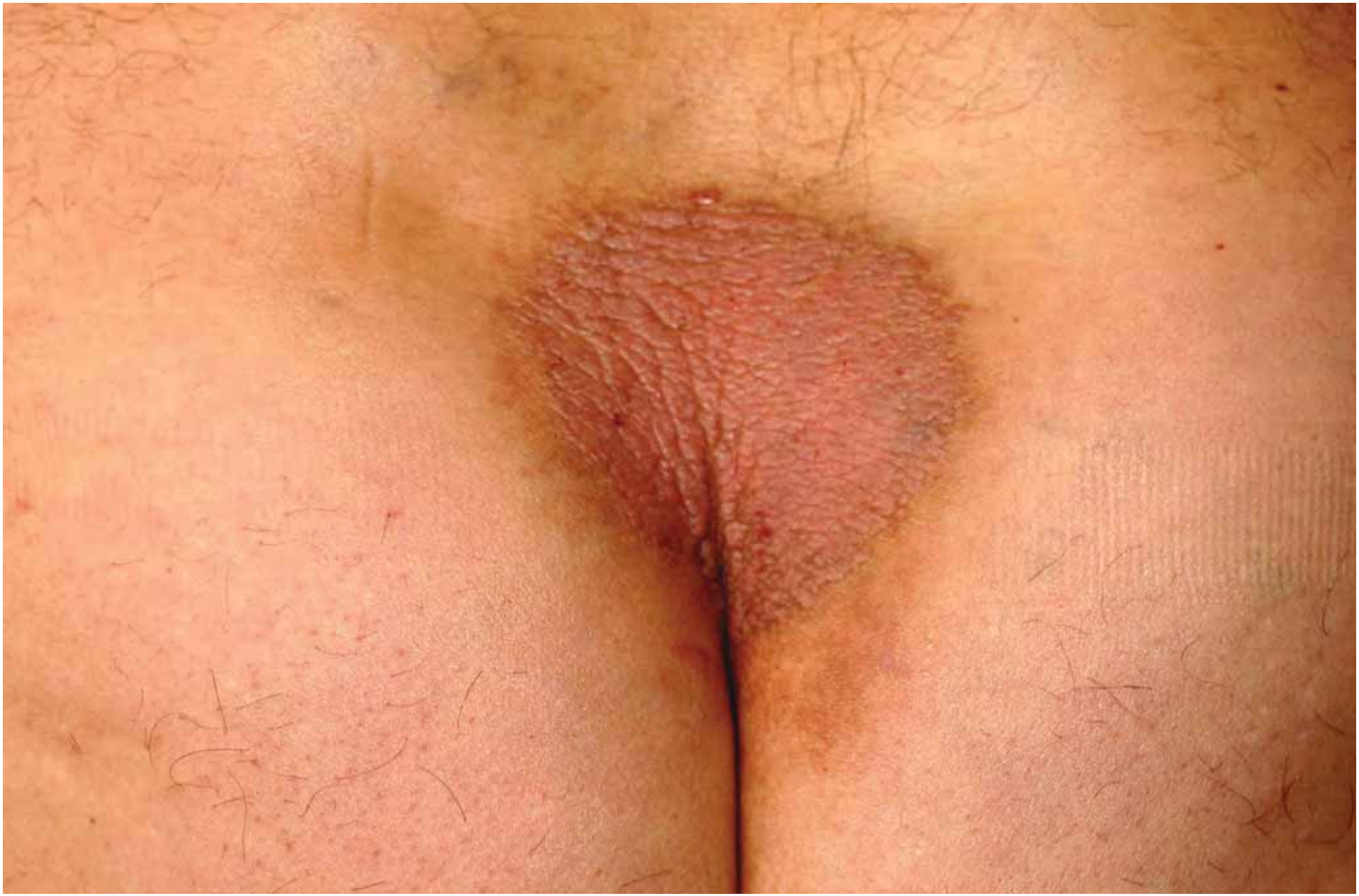
Thirteen patients received busulfan and cyclophosphamide (BU-CY); 14 patients received total body X-irradiation and cyclophosphamide (TBI-CY). Clinical data for these 27 patients are summarized in the Table. Placement into each group depended on pres-

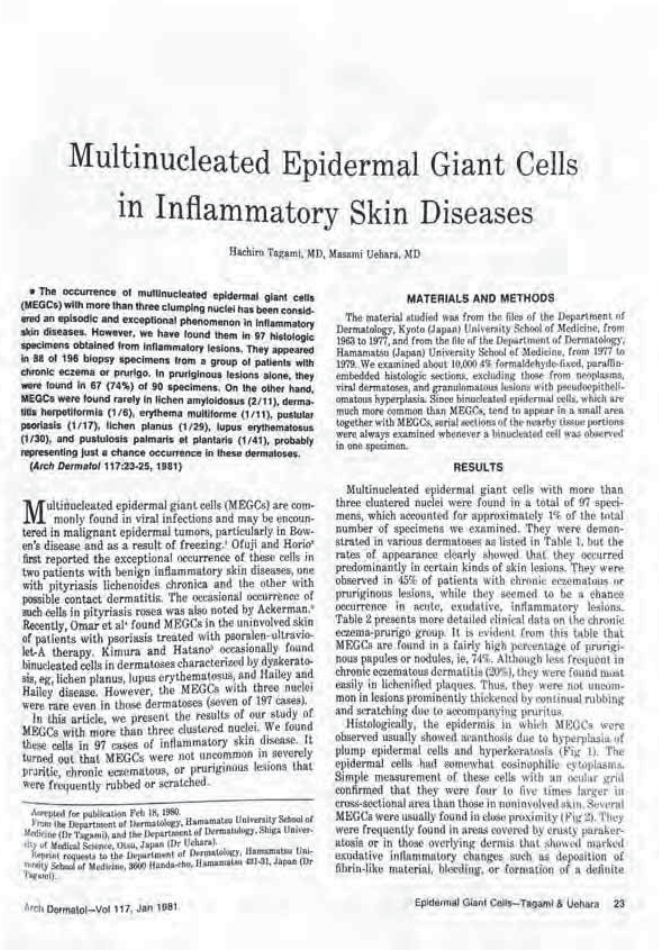
- Necrotic and multinucleated keratinocytes with large and pleomorphic nuclei
- Similar atypical epithelial cells have been described in lung, cervix and bladder of patients receiving busulfan (“Busulfán cells”).











Multinucleated Epidermal Giant Cells in Inflammatory Skin Diseases

Hachiro Tagami, MD, Masami Uehara, MD

The occurrence of multinucleated epidermal giant cells (MEGCs) with more than three clumping nuclei has been considered an episodic and exceptional phenomenon in inflammatory skin diseases. However, we have found them in 97 histologic specimens obtained from inflammatory lesions. They appeared in 88 of 196 biopsy specimens from a group of patients with chronic eczema or prurigo. In pruriginous lesions alone, they were found in 67 (74%) of 90 specimens. On the other hand, MEGCs were found rarely in lichen amyloidosus (2/11), dermatitis herpetiformis (1/6), erythema multiforme (1/11), pustular psoriasis (1/17), lichen planus (1/29), lupus erythematosus (1/30), and pustulosis palmaris et plantaris (1/41), probably representing just a chance occurrence in these dermatoses.
(*Arch Dermatol* 117:23-25, 1981)

Multinucleated epidermal giant cells (MEGCs) are commonly found in viral infections and may be encountered in malignant epidermal tumors, particularly in Bowen's disease and as a result of freezing.[1] Ofuji and Horio[2] first reported the exceptional occurrence of these cells in two patients with benign inflammatory skin diseases, one with pityriasis lichenoides chronica and the other with pityriasis lichenoides et varioliformis acuta. Because of possible contact dermatitis. The occasional occurrence of such cells in pityriasis rosea was also noted by Ackerman.[3] Recently, Omar et al[4] found MEGCs in the uninvolved skin of patients with psoriasis treated with psoralen-ultraviolet-A therapy. Kimura and Hatano[5] occasionally found binucleated cells in dermatoses characterized by dyskeratosis, eg, lichen planus, lupus erythematosus, and Hailey and Hailey disease. However, the MEGCs with three nuclei were rare even in those dermatoses (seven of 197 cases).

In this article, we present the results of our study of MEGCs with more than three clustered nuclei. We found these cells in 97 cases of inflammatory skin disease. It turned out that MEGCs were not uncommon in severely pruritic, chronic eczematous, or pruriginous lesions that were frequently rubbed or scratched.

Accepted for publication Feb 18, 1980.
From the Department of Dermatology, Hamamatsu University School of Medicine (Dr Tagami), and the Department of Dermatology, Shiga University of Medical Science, Otsu, Japan (Dr Uehara).
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MATERIALS AND METHODS

The material studied was from the files of the Department of Dermatology, Kyoto (Japan) University School of Medicine, from 1963 to 1977, and from the file of the Department of Dermatology, Hamamatsu (Japan) University School of Medicine, from 1977 to 1979. We examined about 10,000 4% formaldehyde-fixed, paraffin-embedded histologic sections, excluding those from neoplasms, viral dermatoses, and granulomatous lesions with pseudoepitheliomatous hyperplasia. Since binucleated epidermal cells, which are much more common than MEGCs, tend to appear in a small area together with MEGCs, serial sections of the nearby tissue portions were always examined whenever a binucleated cell was observed in one specimen.

RESULTS

Multinucleated epidermal giant cells with more than three clustered nuclei were found in a total of 97 specimens, which accounted for approximately 1% of the total number of specimens we examined. They were demonstrated in various dermatoses as listed in Table 1, but the rates of appearance clearly showed that they occurred predominantly in certain kinds of skin lesions. They were observed in 45% of patients with chronic eczematous or pruriginous lesions, while they seemed to be a chance occurrence in acute, exudative, inflammatory lesions. Table 2 presents more detailed clinical data on the chronic eczema-prurigo group. It is evident from this table that MEGCs are found in a fairly high percentage of pruriginous papules or nodules, ie, 74%. Although less frequent in chronic eczematous dermatitis (20%), they were found most easily in lichenified plaques. Thus, they were not uncommon in lesions prominently thickened by continual rubbing and scratching due to accompanying pruritus.

Histologically, the epidermis in which MEGCs were observed usually showed acanthosis due to hyperplasia of plump epidermal cells and hyperkeratosis (Fig 1). The epidermal cells had somewhat eosinophilic cytoplasms. Simple measurement of these cells with an ocular grid confirmed that they were four to five times larger in cross-sectional area than those in noninvolved skin. Several MEGCs were usually found in close proximity (Fig 2). They were frequently found in areas covered by crusty parakeratosis or in those overlying dermis that showed marked exudative inflammatory changes such as deposition of fibrin-like material, bleeding, or formation of a definite

Grape Cells (Multinucleated Keratinocytes) in Noninfectious Dermatoses: Case Series and Review of the Literature

Sarah A. Sweeney, MD, Daryl J. Sulit, MD,† Erin G. Adams, MD,† Katerina R. Shvartsman, MD,† and Ronald P. Rapini, MD**

Abstract: Multinucleated keratinocytes (also known as multinucleated epidermal giant cells) are a frequently overlooked histological finding in noninfectious inflammatory dermatoses. They are [illegible] found in conditions characterized by chronic rubbing and [illegible], such as lichen simplex chronicus or prurigo nodularis, and may be a helpful clue in making the clinical diagnosis. This finding may not be differentiated from other conditions characterized by [illegible] keratinocytes on histopathology, specifically herpes [illegible], varicella zoster, or measles viral infections. The authors report a case series of 2 patients with unique clinical presentations [illegible] but similar histopathologic findings on biopsy. The histopathologic findings in both cases demonstrated multinucleated keratinocytes, which were related to manipulation of the epidermis.

Key Words: multinucleated keratinocytes, grape cells, lichen simplex chronicus, prurigo nodularis, factitial disorder, multinucleated cells of the vulva

(*Am J Dermatopathol* 2015;37:e141–e146)

CASES

Case 1 is a healthy 16-year-old white female with an 8-month history of tender, annular, erythematous, papules and plaques on the [illegible] and extremities. The first lesions appeared on the legs and hips, [illegible] by the trunk. She denied preceding trauma or medication usages. Some of the areas became [illegible]. Serum studies for [illegible] including diseases were unremarkable. Complete blood [illegible], complete metabolic panel, antineutrophil cytoplasmic antibodies, and antinuclear antibodies were within normal limits; [illegible] and oral corticosteroids and oral antibiotics were not helpful. [illegible] review of systems revealed no other complaints. Social history was significant for ongoing divorce and custody battle in her parents.

On physical examination, there were geometric tan patches on [illegible] abdomen and upper extremities with a noninflammatory border [illegible] central clearing. On the left medial lower leg, there was a linear [illegible] of annular tan patches with central clearing. There was an [illegible] plaque on the right lateral dorsal foot (Fig. 1). Two

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The authors declare no conflicts of interest.

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biopsies on the right lateral foot were performed—1 for direct immunofluorescence and 1 for hematoxylin and eosin stain. Direct immunofluorescence examination was negative. Hematoxylin and eosin–stained slides showed superficial epidermal necrosis, multinucleated keratinocytes at all levels of the epidermis, and a sparse superficial perivascular inflammatory infiltrate. The number of nuclei varied from 5 to 15 per cell. No viral changes were seen (Figs. 2 and 3). Immunohistochemistry stains for herpes simplex virus (HSV) 1, HSV 2, and varicella zoster virus were negative.

The patient's examination, pathologic findings, and history of [illegible] stressful life events led to the diagnosis of factitial disorder. When confronted, the patient denied any purposeful manipulation of her skin. She was lost to follow-up.

Case 2 is a 40-year-old gravida 3 para 1 white woman presented for evaluation of a white-appearing vulvar mucosal plaque noticed during routine gynecologic annual examination. She did not know how long the lesion was present, but she reported occasional mild pruritus in the area. It was not painful. She had a medical history of Hashimoto hypothyroidism. She did not have any history of a genital herpes infection.

On physical examination, there was an ill-defined lichenified white plaque localized to the inner aspect of the right labia minora (Fig. 4). There were no similar appearing lesions on the remainder of her [illegible] examination.

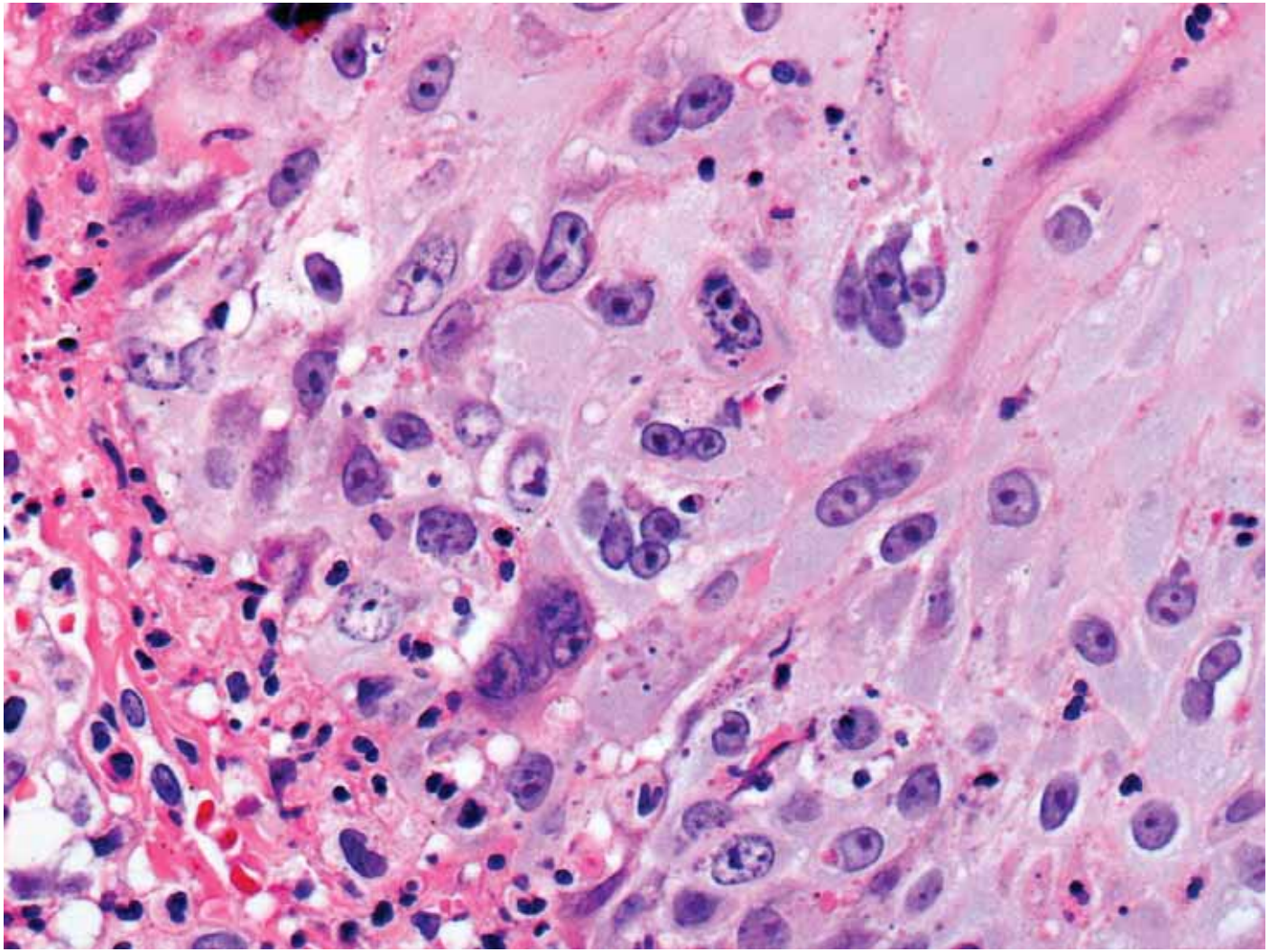
A shave biopsy was performed to rule out leukoplakia and lichen sclerosus. The biopsy showed prominent hyperkeratosis, hypergranulosis, and acanthosis in the epidermis. Focally, there were several multinucleated epidermal giant cells present in the lower third of the epidermis. The number of nuclei varied from 3 to 11 per cell. In the dermis, there was superficial dermal fibrosis with sparse inflammation. Sclerosis and hyalinization of dermal collagen was not identified (Figs. 5 and 6). Morphologic features of leukoplakia, vulvar intraepithelial neoplasia, condyloma acuminatum, lichen planus, and lichen sclerosus were not seen. HSV 1, HSV 2, and varicella zoster virus immunohistochemistry stains were negative. Periodic acid–Schiff stain did not demonstrate fungal elements.

The patient's history, examination, and histopathologic findings led to the diagnosis of lichen simplex chronicus with multinucleated atypia of the vulva. She tried topical clobetasol 0.05% ointment daily for over 8 weeks with minimal results. The vulvar white plaque persisted.

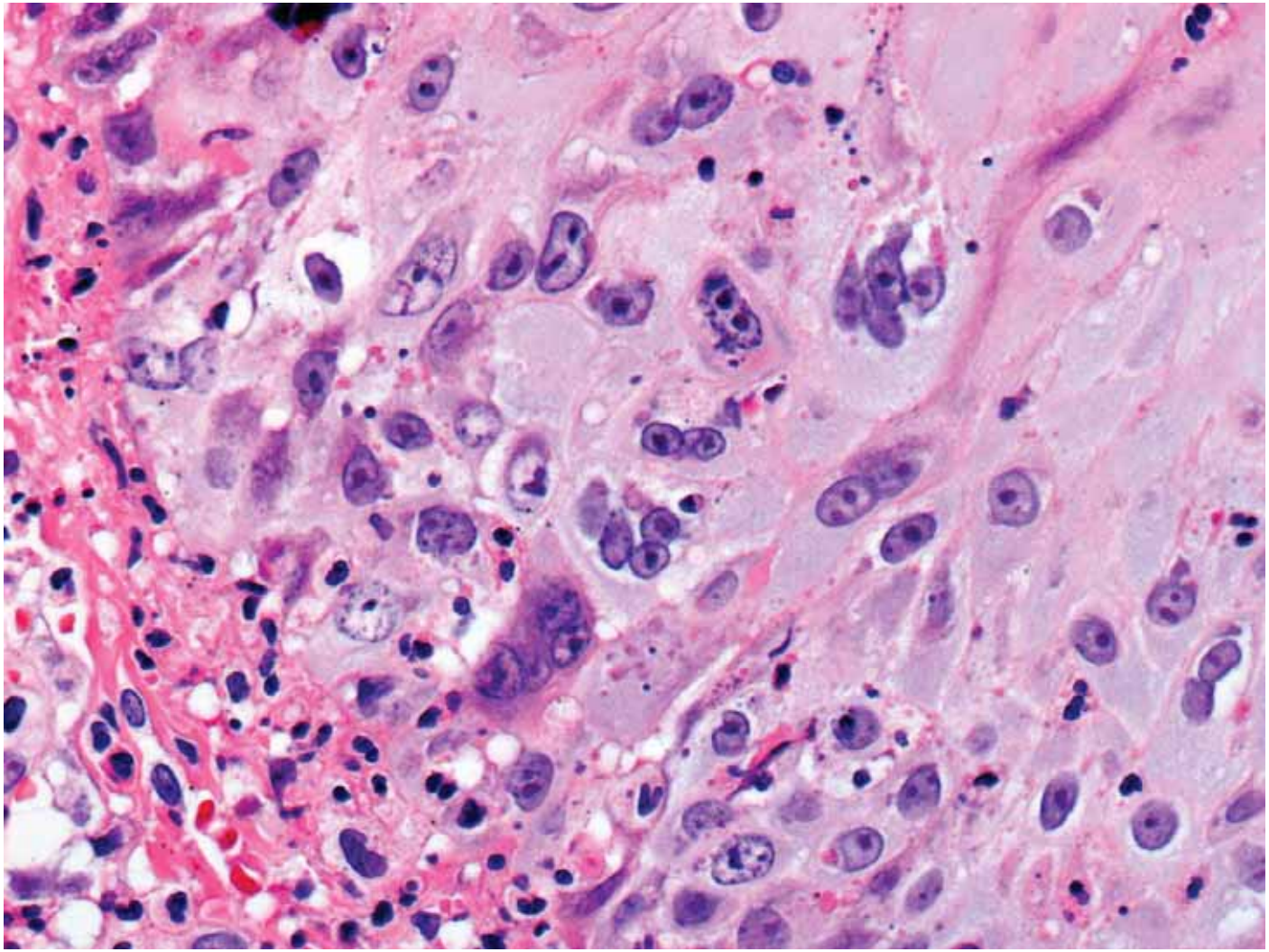
DISCUSSION

Multinucleated keratinocytes are a characteristic pathologic finding in cutaneous viral infections with herpes simplex and varicella zoster[1] and measles.[2] They are also rarely reported in dyskeratotic dermatoses, such as lichen planus.[3] Multinucleated keratinocytes with at least 3 clumped nuclei

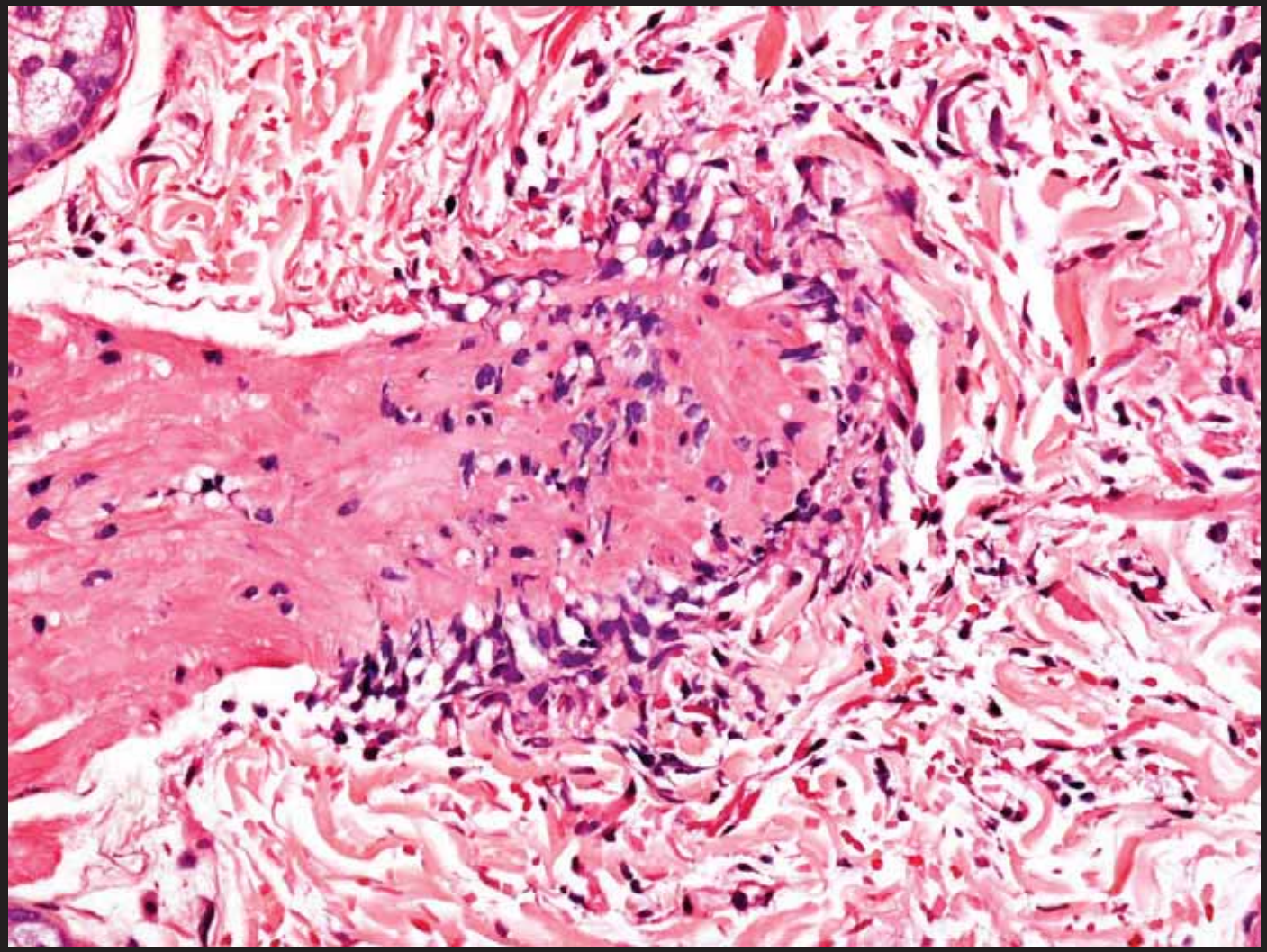
- Herpes simplex
- Varicella zoster
- Measles
- Monkeypox
- Condyloma acuminatum treated with podophyllin
- Drug eruption: Busulfan, phenytoin
- Pityriasis rosea
- Lichen simplex chronicus and prurigo nodularis
- Lichen planus
- Lichen amyloidosis
- Lupus erythematosus
- Dermatitis herpetiformis
- Pemphigus vulgaris
- Erythema multiforme
- Pustular psoriasis
- Factitial dermatosis
- Contact dermatitis
- Pityriasis lichenoides chronica
- Bowen disease



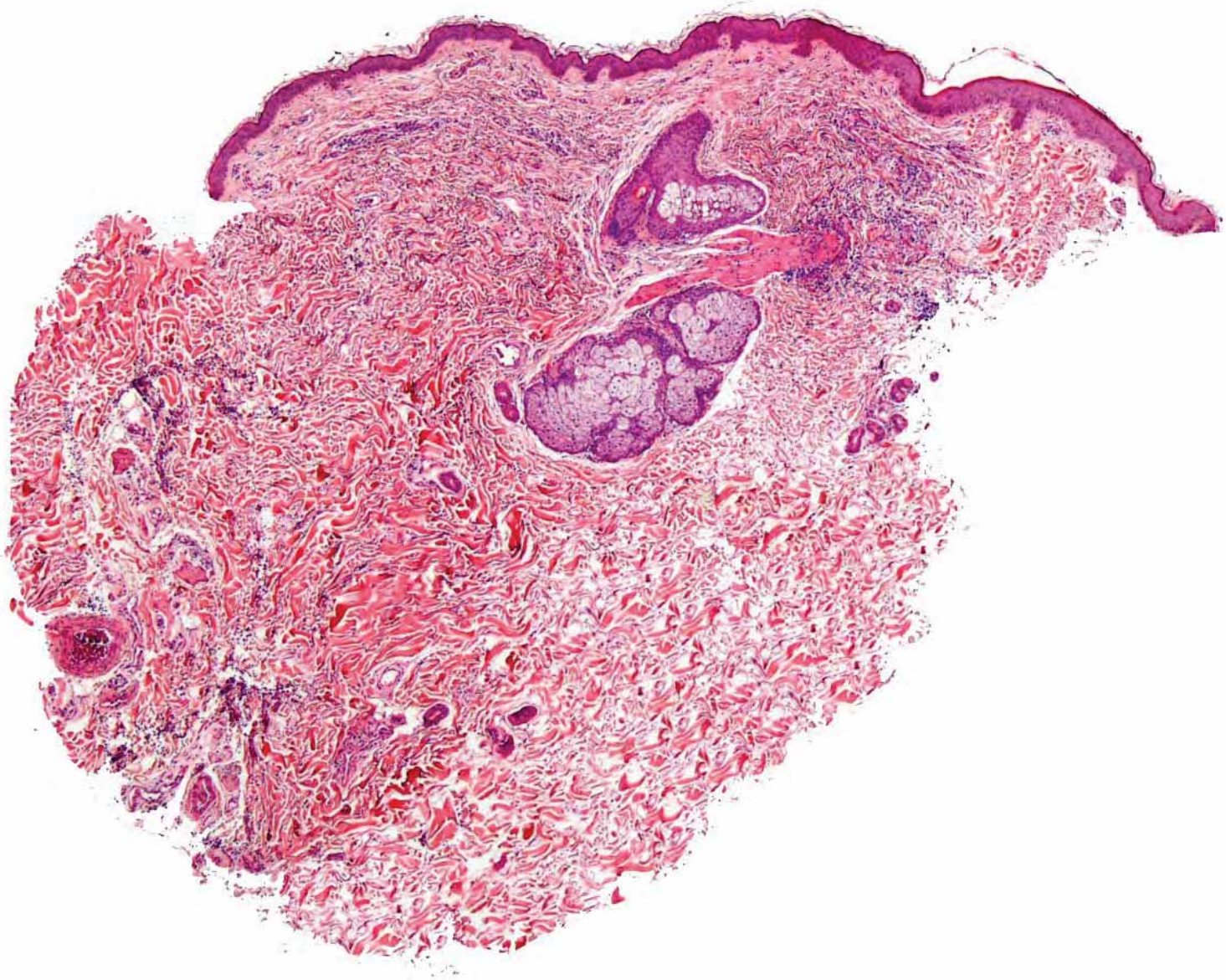
Intraepidermal atypical multinucleated giant cells are a *cliche* to …

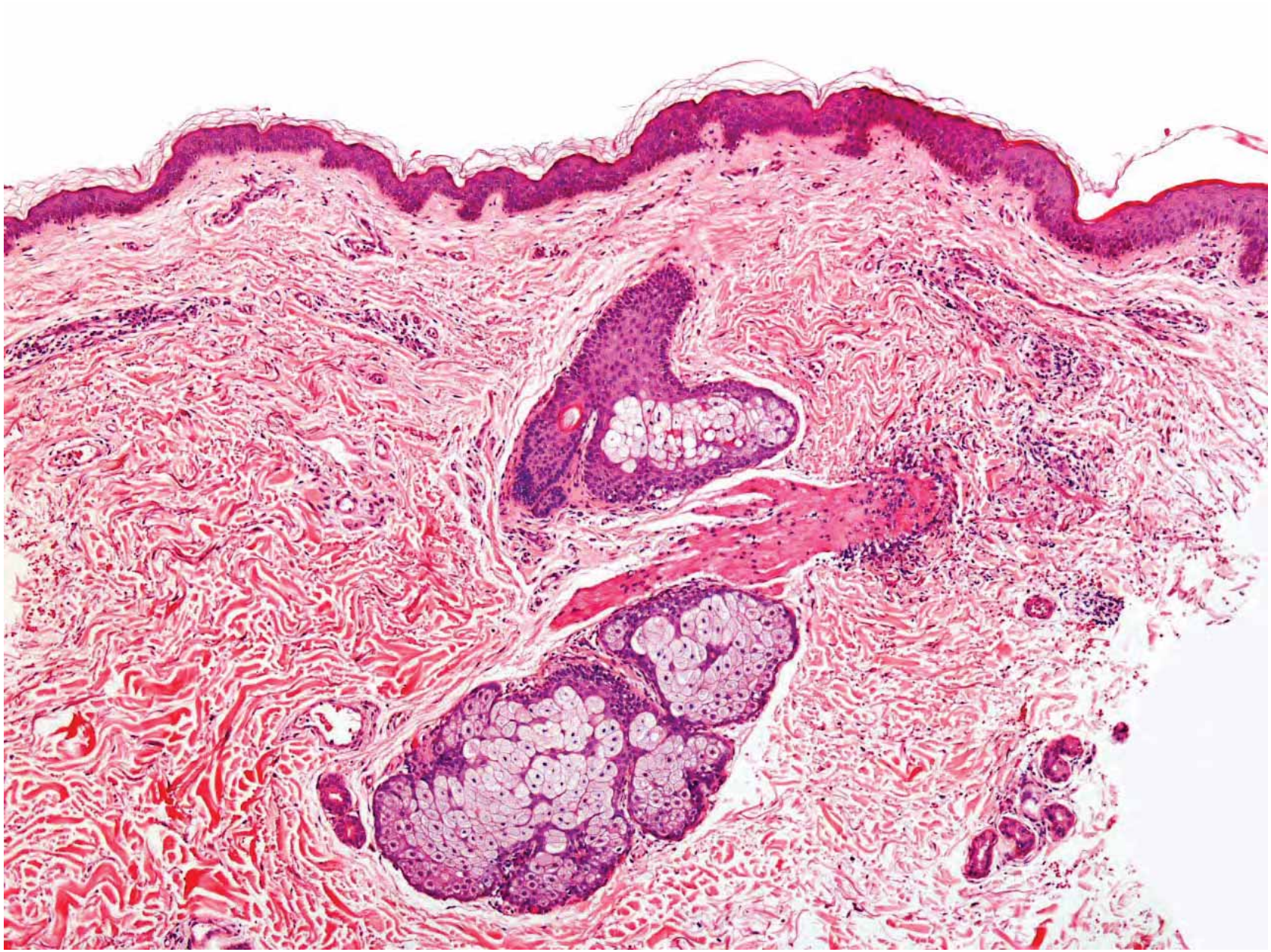


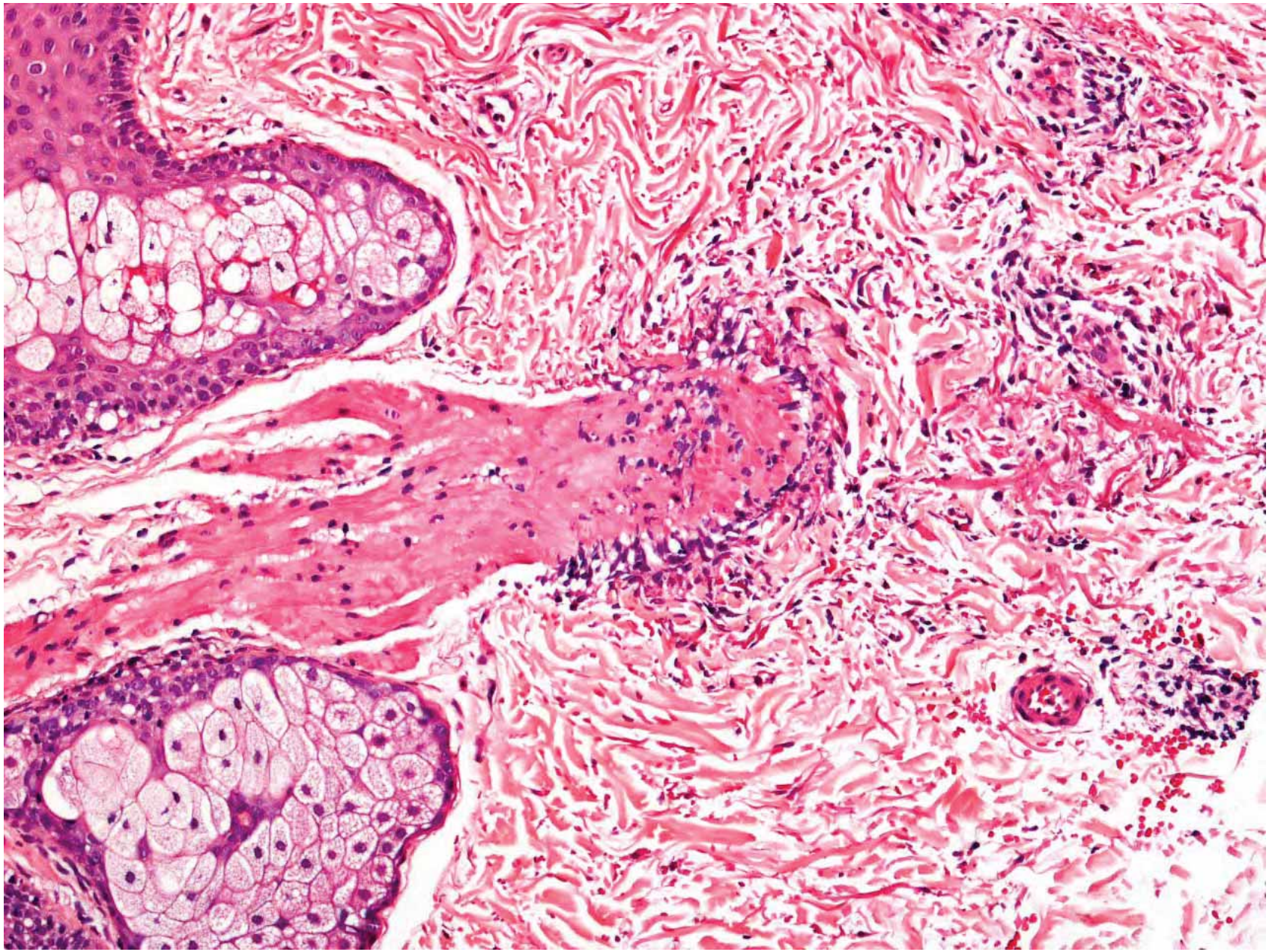
Intraepidermal atypical multinucleated giant cells are a *cliche* to nothing, because they are completely non-specific

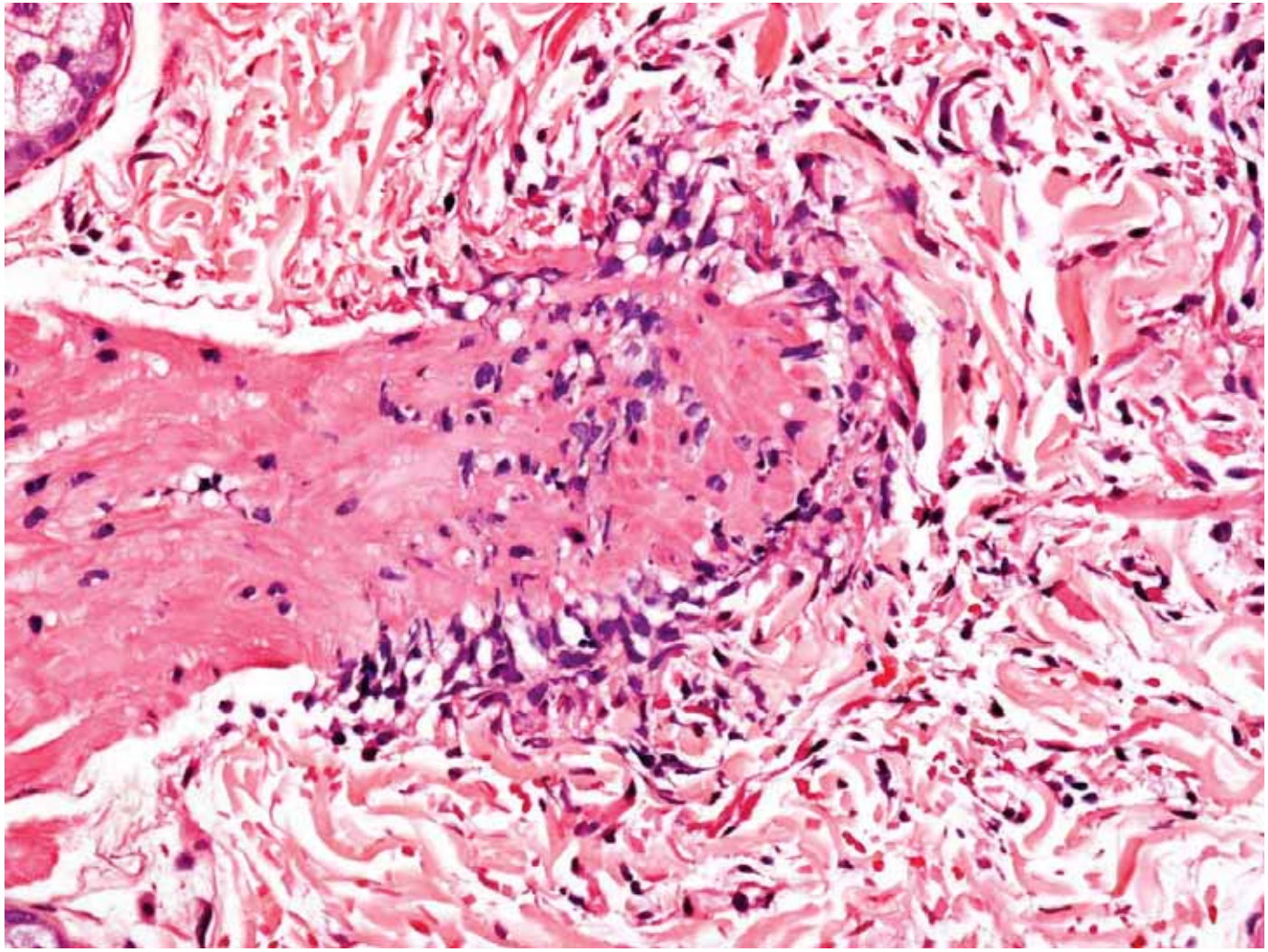


What is the *cliche* and what is the diagnosis?

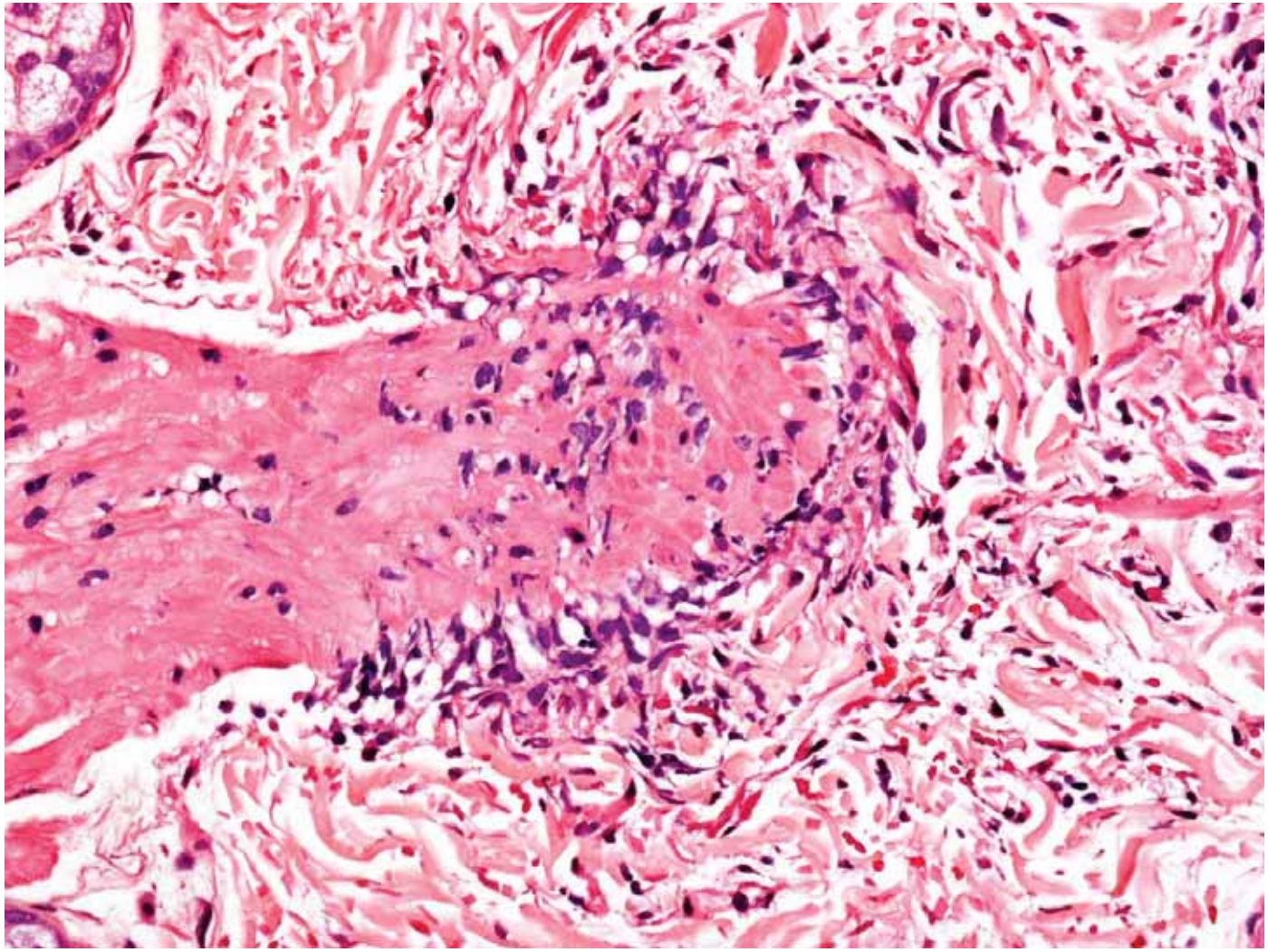




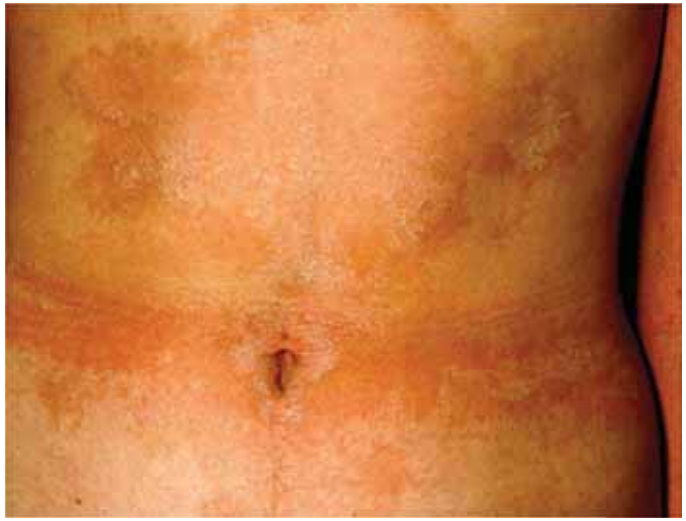


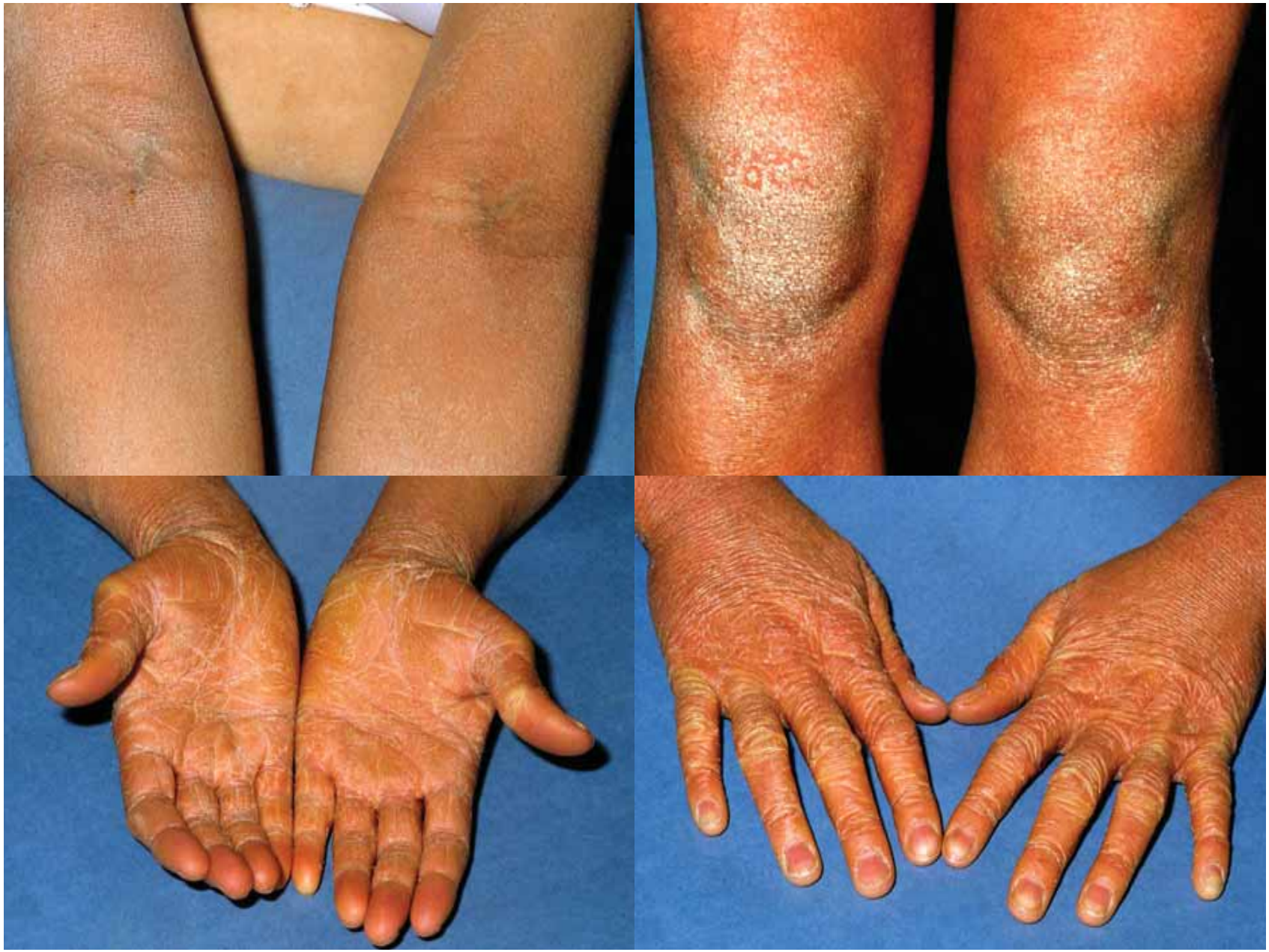


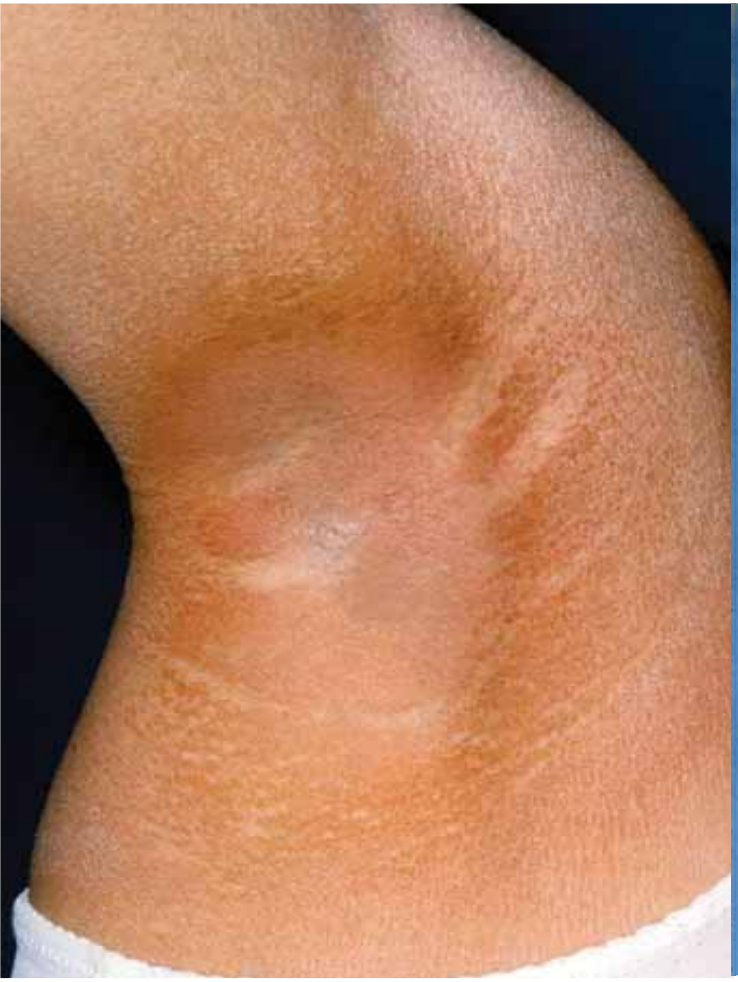
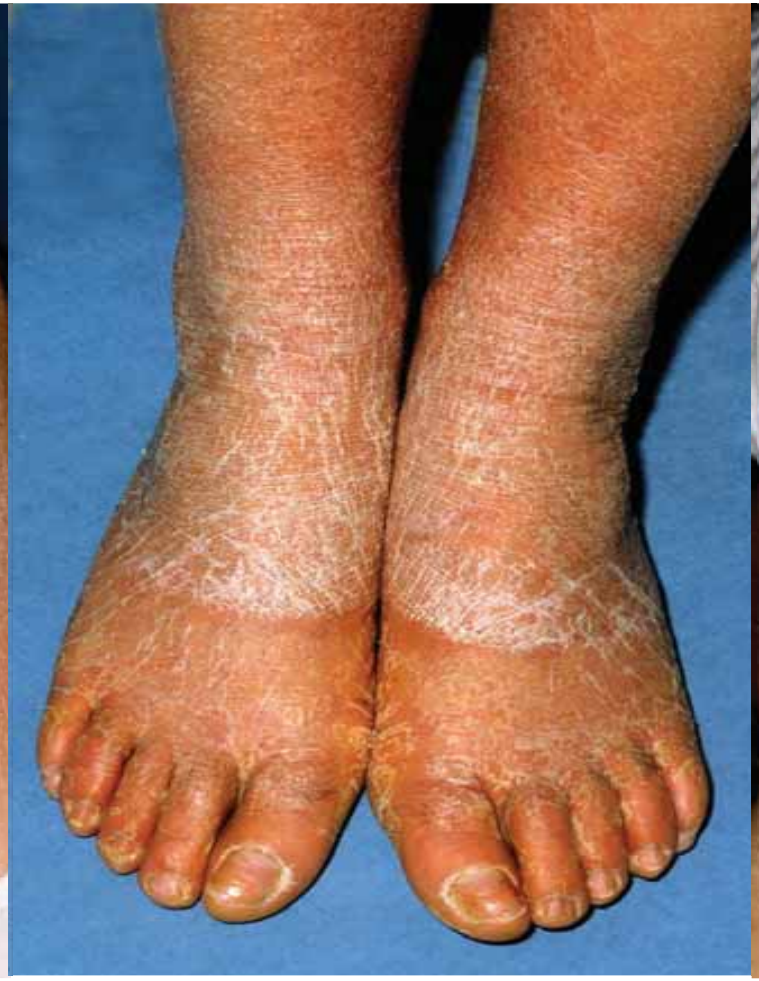
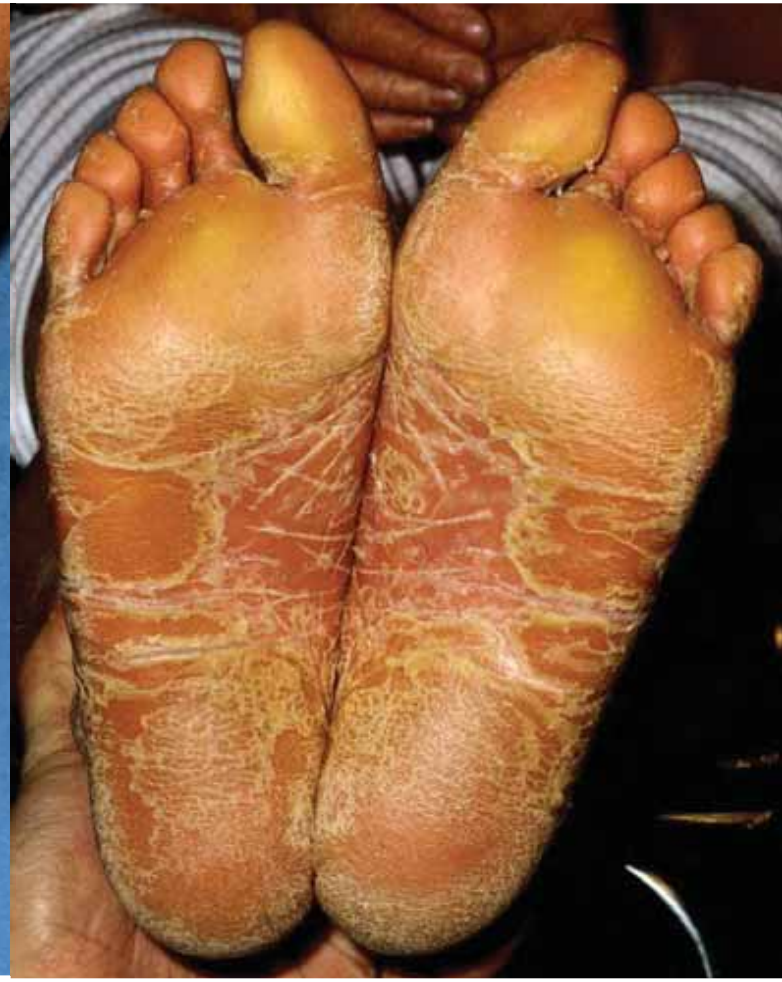
Arrector pili myositis is a *cliche* to…



Arrector pili myositis is a *cliche* to dermatomyositis associated with pityriasis rubra pilaris (Wong dermatomyositis)





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Medical and Health Department, Hong Kong

DERMATOMYOSITIS: A CLINICAL INVESTIGATION OF TWENTY-THREE CASES IN HONG KONG

K. O. WONG

SUMMARY.—Twenty-three cases of dermatomyositis are reported of which 12 (52%) were associated with internal malignancy. In the patients over 40 years of age, malignant diseases were encountered in 69%, while only one of 7 cases under 40 had associated malignancy. Nasopharyngeal carcinoma accounted for 75% of the malignant disease.

A distinctive skin eruption, consisting of hyperkeratotic, follicular, erythematous papules, is described. On the face, trunk and limbs, the papules tended to become confluent. Along the tendons and over the bony prominences on the backs of the hands and feet, the eruption was usually arranged in a linear fashion. There was alopecia of the scalp. On the palms and soles were hyperkeratotic papules or plaques. The occurrence of this form of eruption in dermatomyositis may be influenced by racial factors.

British Journal of Dermatology 1997; **136**: 768–771.

Dermatomyositis with a pityriasis rubra pilaris-like eruption: a little-known distinctive cutaneous manifestation of dermatomyositis

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Summary A pityriasis rubra pilaris-like eruption has been described in patients with dermatomyositis. These patients showed generalized follicular hyperkeratosis and diffuse thickening of the palms and soles. Histopathological findings consisted of keratotic plugging of the follicular infundibulum and features of erector pili myositis. We report on an 18-year-old woman with dermatomyositis. The diagnosis was established by characteristic enzymatic alterations, electromyographic pattern of myositis and the findings in a muscle biopsy, although the patient had no evidence of muscular weakness during a follow-up of 14 years. She developed an erythematous and squamous eruption associated with diffuse palmoplantar keratoderma. Histopathological features consisted of a papillomatous epidermis with spicules of compact eosinophilic hyperkeratosis over the tips of papillae that were not related to hair follicles. Pityriasis rubra pilaris-like eruption seems to be a characteristic although uncommon cutaneous manifestation in dermatomyositis.

Cutaneous manifestations of dermatomyositis include erythema over joints (Gottron sign), erythematous papules on the metacarpophalangeal and interphalangeal joints (Gottron papules), erythema and scaling of photoexposed areas, periorbital oedema and violaceous erythema of the upper eyelids (heliotrope rash),[1,2] nail changes including periungual telangiectasis and cuticle hypertrophy with punctate infarcts,[3] poikiloderma, calcinosis cutis, vasculitis,[4,5] localized lipoatrophy,[6] panniculitis[7–12] and bullous lesions.[13–17]

Hyperkeratotic skin eruption is a rare manifestation of dermatomyositis and only a few cases have been reported in the literature.[18–23] In all these cases, follicular accentuation of the lesions has been emphasized, and terms such as pityriasis rubra pilaris-like eruption,[20] dermatomyositis with spinulosis,[21] or dermatomyositis with follicular hyperkeratosis,[23] have been used to describe this eruption.

We report on an 18-year-old woman with dermatomyositis who developed a hyperkeratotic skin eruption clinically resembling pityriasis rubra pilaris, but the histology showed that the hyperkeratosis was not related to hair follicles. We review the literature on this peculiar cutaneous manifestation in patients with dermatomyositis.

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Case report

An 18-year-old woman had a 7-year history of a scaling cutaneous eruption and palmoplantar keratoderma. Examination revealed hyperkeratotic plaques with whitish scaling involving the trunk and upper and lower extremities. The lesions were more prominent on the knees (Fig. 1), axillae and anterior aspect of the abdomen, where islands of unaffected skin were intermingled with erythematous plaques. Hyperkeratotic lesions were also present on the dorsum of the hands and feet and palms (Fig. 2) and the soles showed yellowish diffuse palmoplantar keratoderma. The scalp and the nails were normal. Heliotrope coloration of the eyelids, Gottron's papules and muscular weakness were not present.

Abnormal laboratory values include serum creatine kinase level 5580 U/l (normal 10–110), serum aldolase activity 30 U/l (normal 0·5–3), lactate aminotransferase 134 IU/l (normal 0–40), lactate dehydrogenase 498 IU/l (normal 90–180), erythrocyte sedimentation rate 60 mm in the first hour (normal up to 20), serum IgG

International Journal of Dermatology

Case report

Wong's dermatomyositis: a new case and review of the literature

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Introduction

The association of dermatomyositis and pityriasis rubra pilaris is uncommon, but it is now well-characterized with several cases described in the literature.[1–12] Usually, these patients exhibit classical cutaneous lesions of dermatomyositis and stereotypical lesions of pityriasis rubra pilaris. The histopathological findings depend on the type of biopsied lesion, because lesions of dermatomyositis show interface dermatitis of vacuolar type, and pityriasis rubra pilaris lesions show psoriasiform epidermal hyperplasia with parakeratosis alternating both in horizontal and vertical arrangements. Herein we report a patient with dermatomyositis and pityriasis rubra pilaris who showed a combination of the histopathological findings in the same biopsy.

Case report

A 49-year-old woman, with a complex dermatological history, had been previously diagnosed in different institutions with subacute cutaneous lupus erythematosus, erythema multiforme, and pityriasis rubra pilaris. Previous treatments included topical sunscreens and short periods of oral corticosteroids at variable doses of prednisone between 20 and 40 mg/d. No topical corticosteroids have been applied on her face. She presented in our department for evaluation of asymptomatic cutaneous lesions on her face and extremities associated with muscular weakness and myalgia of the upper and lower limbs.

On physical examination, she presented different types of cutaneous lesions (Fig. 1). On the upper eyelids, the skin showed a poikilodermatous appearance, with violaceous erythema alternating with areas of hypo- and hyperpigmentation and slight atrophy. The palms and soles showed an erythematous keratoderma, with scattered areas of unaffected skin. On the dorsum of the hands and feet, anterior thighs, and antecubital folds, there were erythematous scaling plaques, which resulted from confluent follicular papules.

Histopathological study of the eyelid lesions showed vacuolar interface dermatitis with superficial perivascular sparse lymphocytic infiltrate and interstitial accumulation of mucin between collagen bundles of the reticular dermis (Fig. 2). The epidermis was scattered with dyskeratoses, and the stratum corneum showed focal areas of parakeratosis. No thickening of the basal membrane was seen. Lesions of palmar skin showed psoriasiform dermatitis, with hyperkeratosis composed of alternating areas of orthokeratosis and parakeratosis, which were arranged in both horizontal and vertical directions. Many dyskeratotic keratinocytes were also seen scattered within the epidermis.

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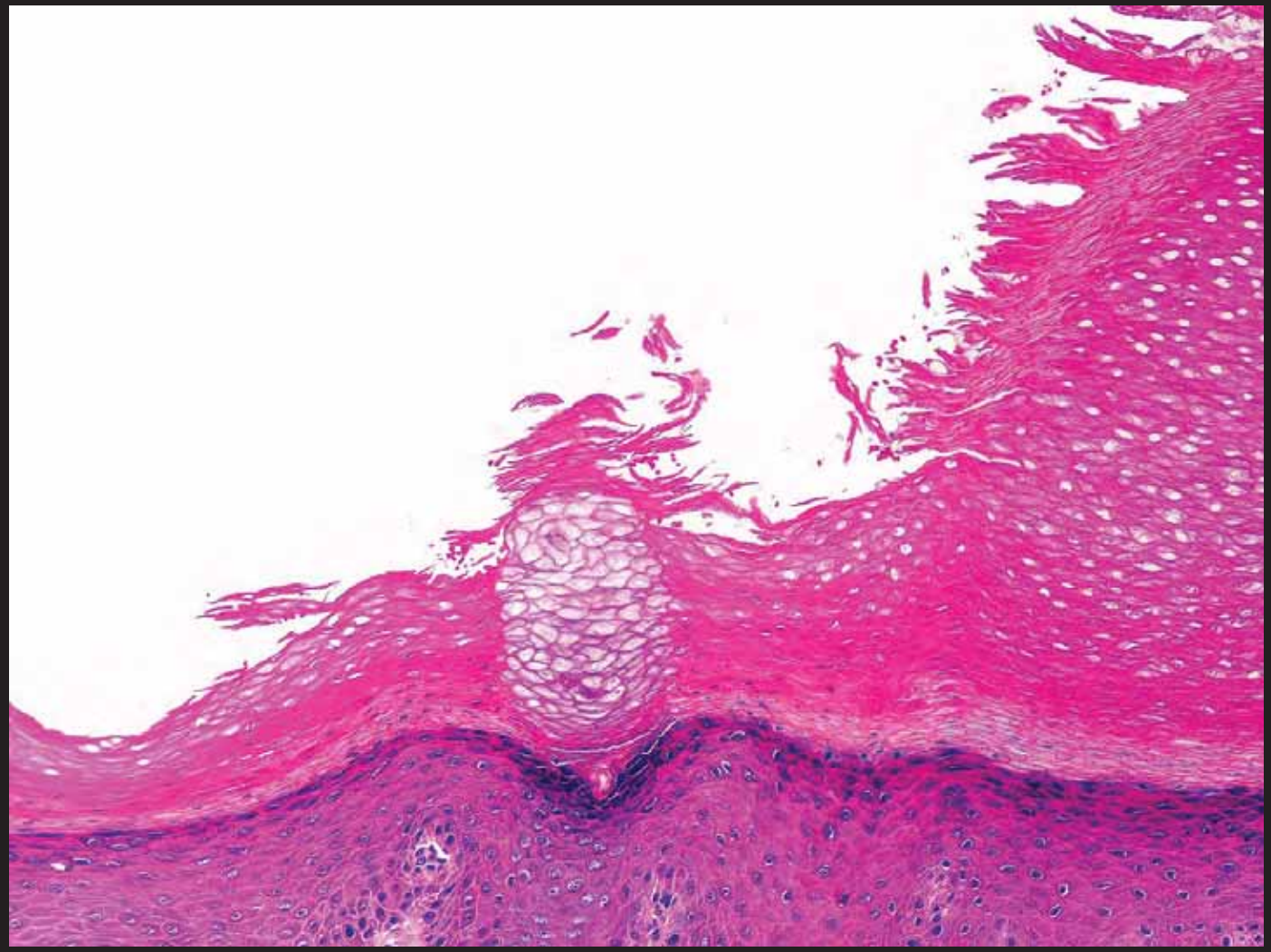
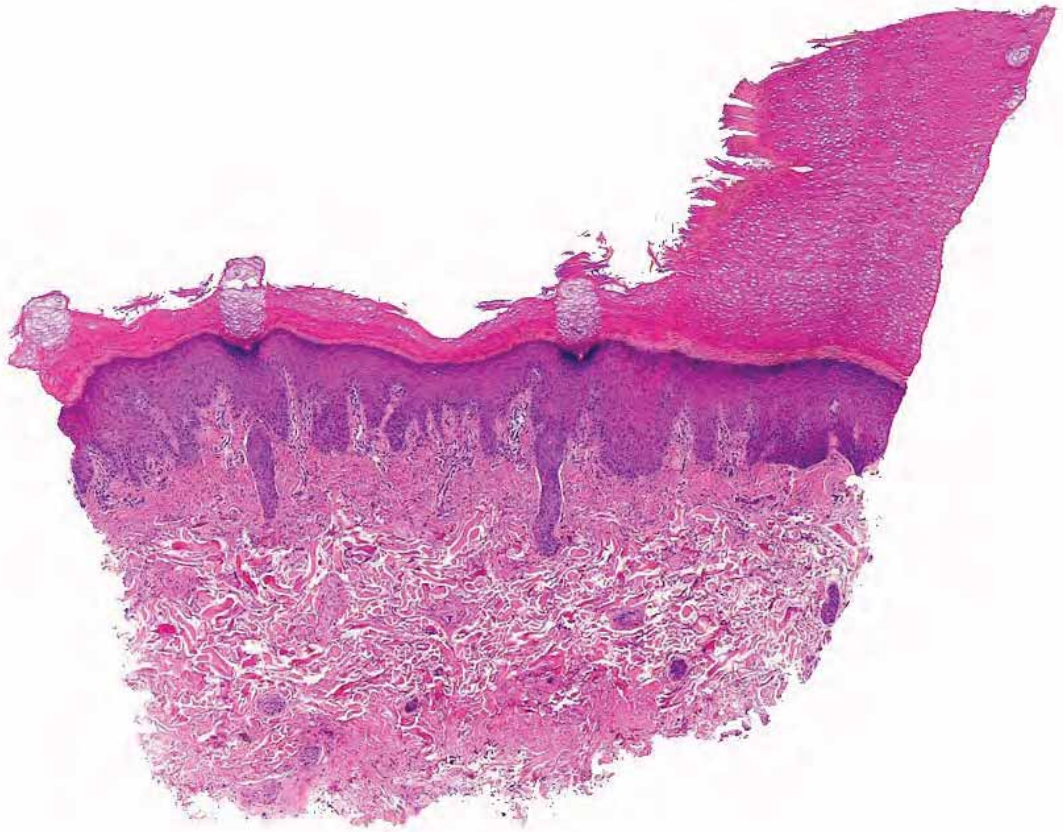
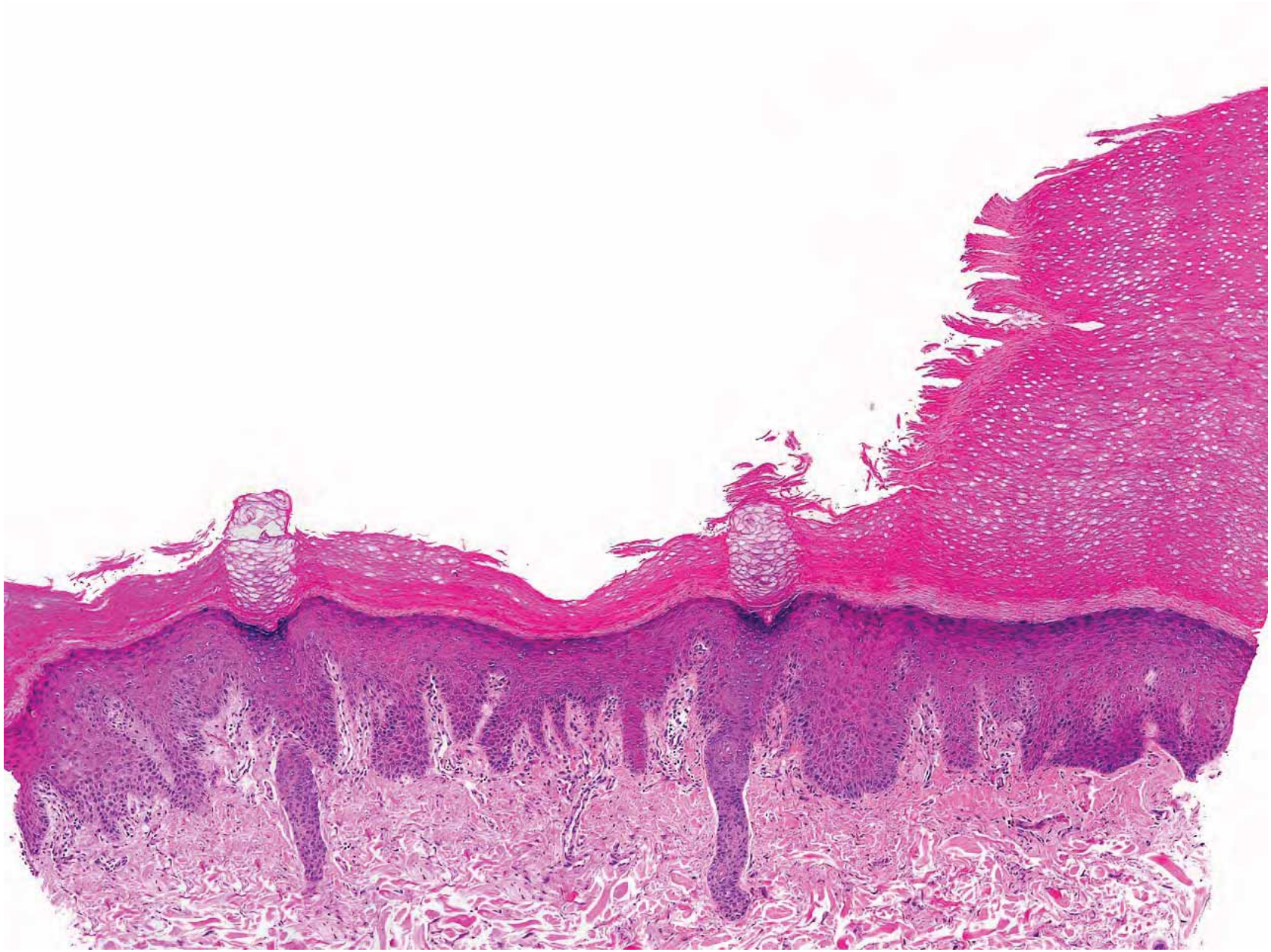
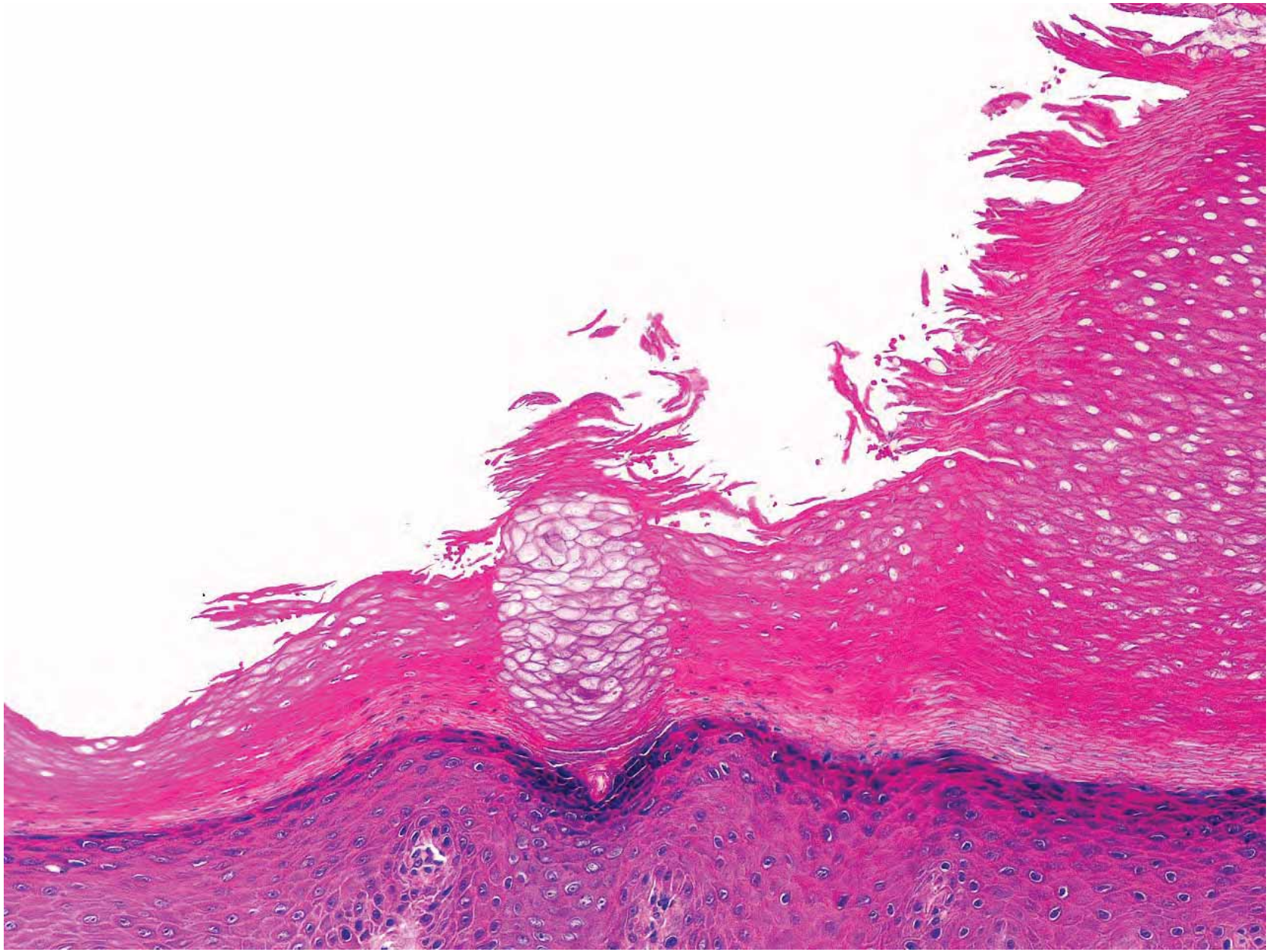
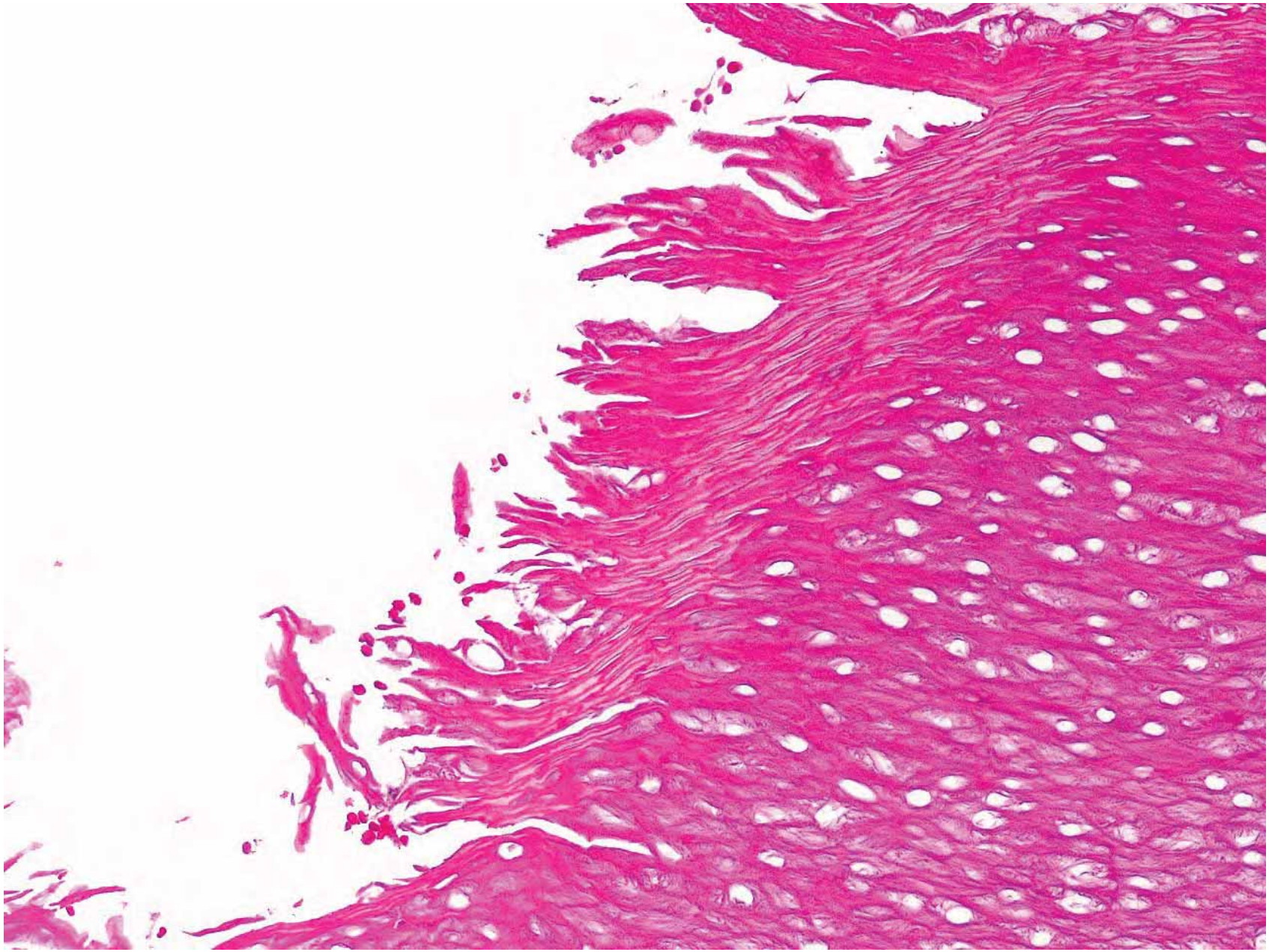


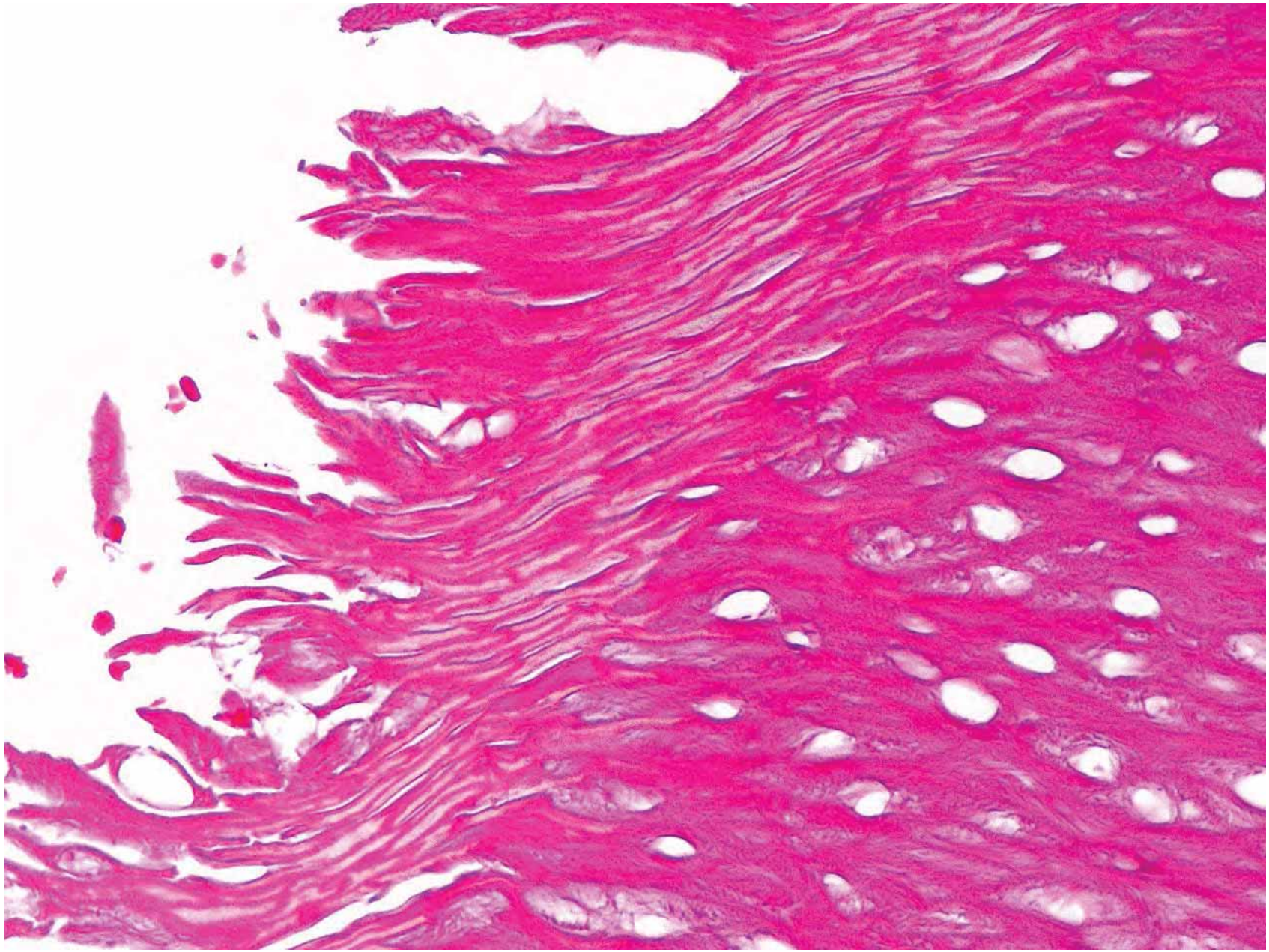
What is the *cliche* and what is the diagnosis?

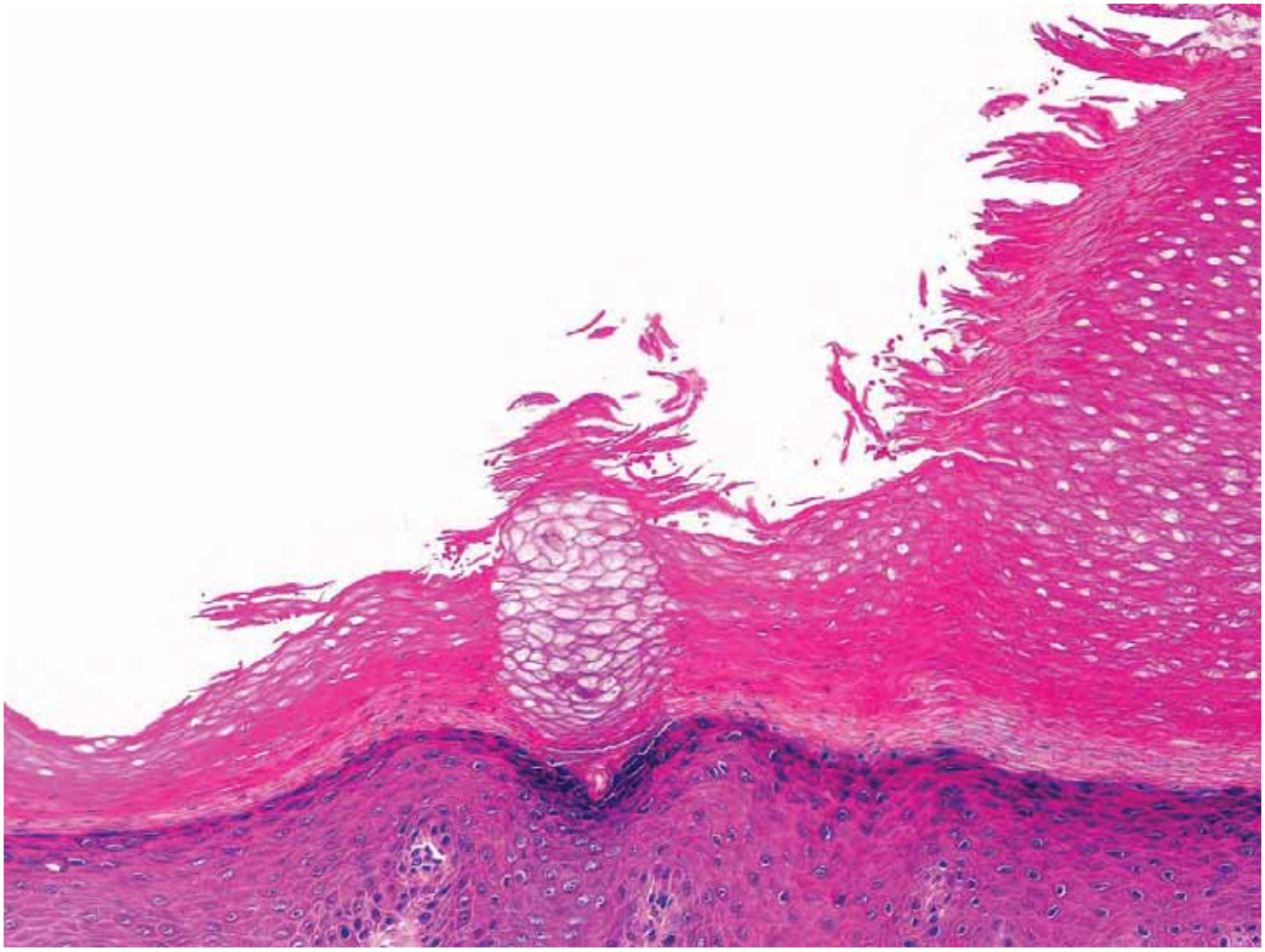




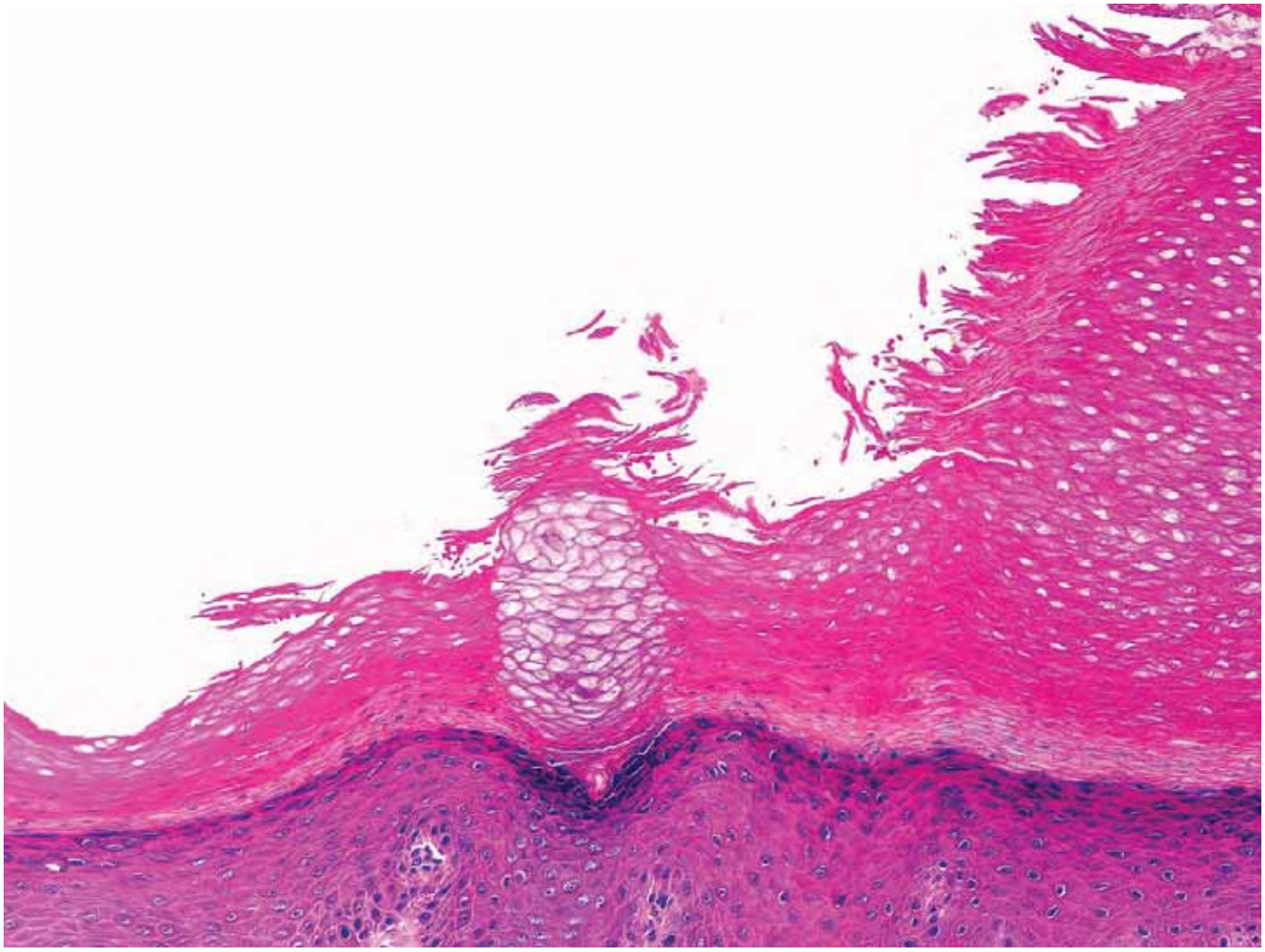








A depression in the horny layer with frayed border is a *cliche* to…



A depression in the horny layer with frayed border is a *cliche* to circumscribed palmar or plantar hypokeratosis

The “frayed flag” sign

Circumscribed palmar or plantar hypokeratosis: A distinctive epidermal malformation of the palms or soles

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Valencia and Madrid, Spain; Friedrichshafen, Germany; and Santiago, Chile

Background: Epidermal malformations of the skin include a group of heterogeneous developmental defects that result from errors in morphogenesis of the epidermis during intrauterine life.

Objective: The purpose of this study was to report the clinical and histopathologic features of a distinctive epidermal malformation involving the skin of the palms or soles.

Methods: Ten patients were included in this study. All of them showed the same clinical features that consisted of a solitary circumscribed and circular area of erythematous depressed skin on the palm or on the sole. Diagnosis was confirmed by histopathologic study.

Results: All patients were middle aged or elderly. Nine patients were women and one was a man. The lesions showed predilection for the skin of the thenar and hypothenar regions of the palm or the medial side of the sole. Histopathologic study demonstrated a depression of the epidermis, with a sharp stair between normal and involved skin. The epidermis covering the depression showed markedly thinner horny layer and a slightly diminished granular cell layer when compared with adjacent noninvolved skin. Keratinocytes of the squamous cell layer, granular cells, and corneocytes showed, otherwise, a normal appearance. Serial sections failed to demonstrate cornoid lamellation.

Conclusion: On the basis of the clinical and histopathologic findings in these 10 patients, we have named this malformation circumscribed palmar or plantar hypokeratosis. This lesion seems to be a distinctive entity that has not been previously described. (J Am Acad Dermatol 2002;47:21-7.)

Epidermal malformations of the skin include a group of heterogeneous developmental defects that result from errors in morphogenesis of the epidermis during intrauterine life. Malformations of epidermis and cutaneous adnexa have been classified into the following categories:[1] (1) keratinocyte malformations, (2) hair follicle malformations, (3) sebaceous malformations, (4) apocrine malformations, (5) eccrine malformations, and (6) Becker's nevus. Table I summarizes the entities included in each one of these categories.

We describe 10 patients with a distinctive epidermal malformation involving the skin of the palms or the soles. Clinically, the lesions consisted of acquired, solitary, circumscribed, circular areas of erythematous depressed skin. The lesions appeared in 9 middle-aged or elderly women and in a 45-year-old man. They had predilection for the skin of the thenar and hypothenar regions of the palm or the medial side of the sole. Histopathologic study demonstrated a depression of the epidermis, with a sharp stair between normal and involved skin. The epidermis covering the depression showed markedly thinner horny layer and slightly diminished granular cell layer when compared with adjacent noninvolved skin. Serial sections failed to demonstrate cornoid lamellation; thus a diagnosis of palmar porokeratosis was ruled out. On the basis of the

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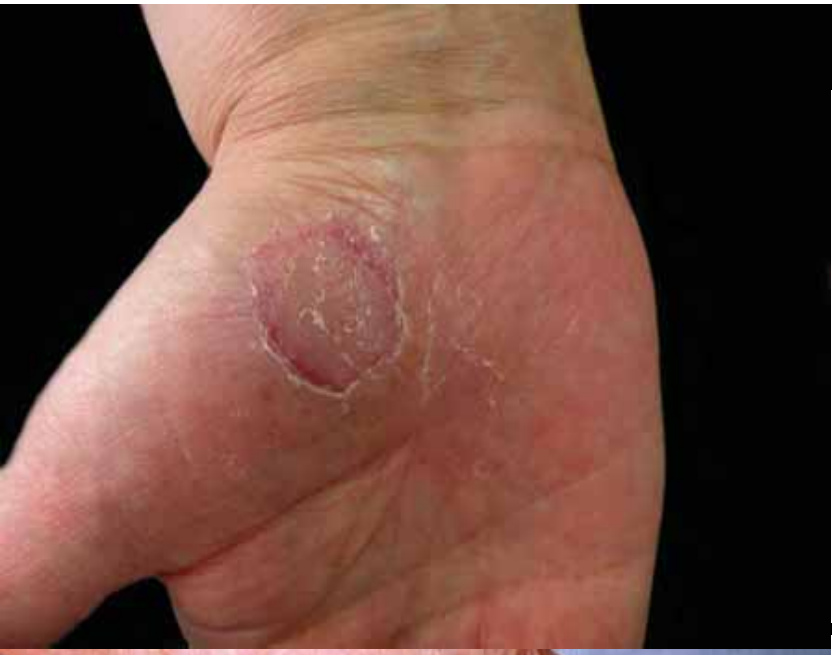
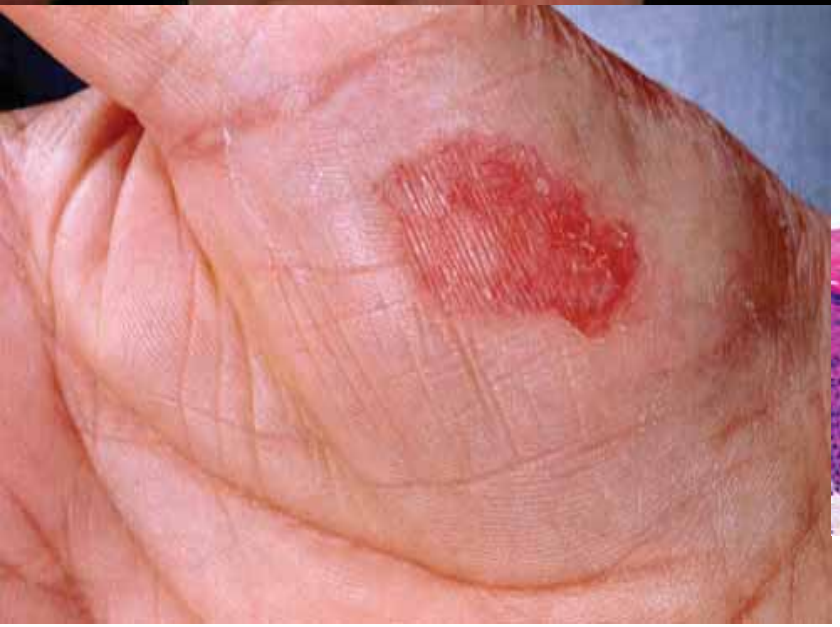
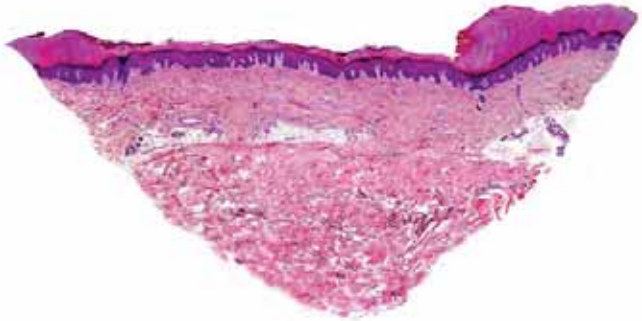
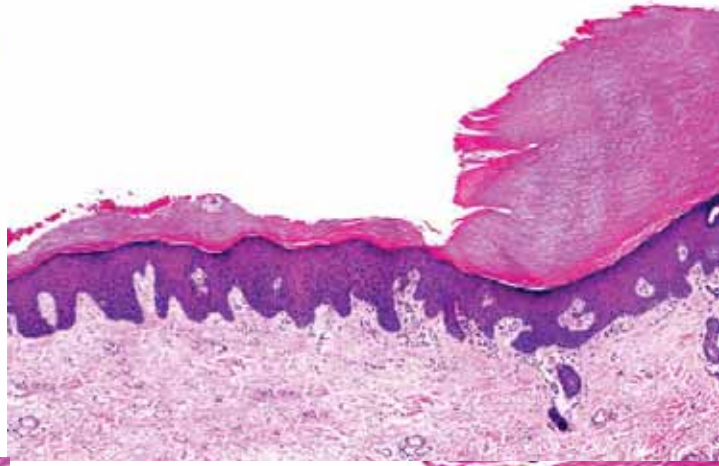
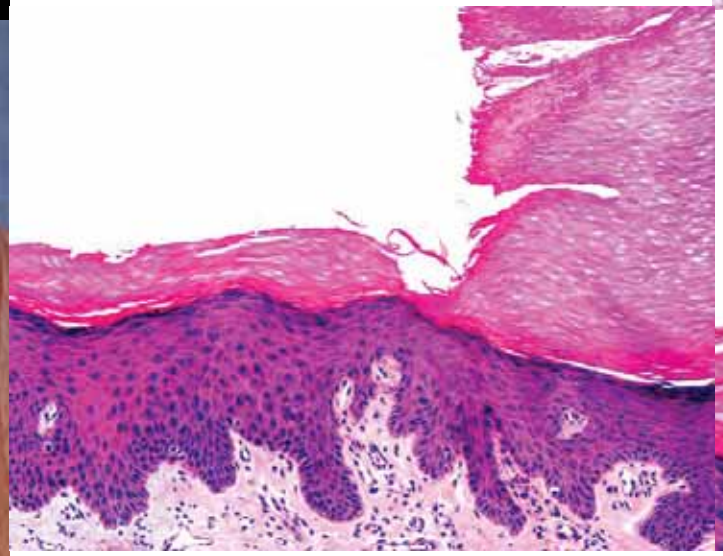
- Ten patients with of a solitary circumscribed and circular area of erythematous depressed skin on the palm or on the sole
- Histopathologic study demonstrated that the epidermis covering the depression showed markedly thinner horny layer and a slightly diminished granular cell layer when compared with adjacent noninvolved skin
- Keratinocytes of the squamous cell layer, granular cells, and corneocytes showed, otherwise, a normal appearance
- Serial sections failed to demonstrate cornoid lamellation.

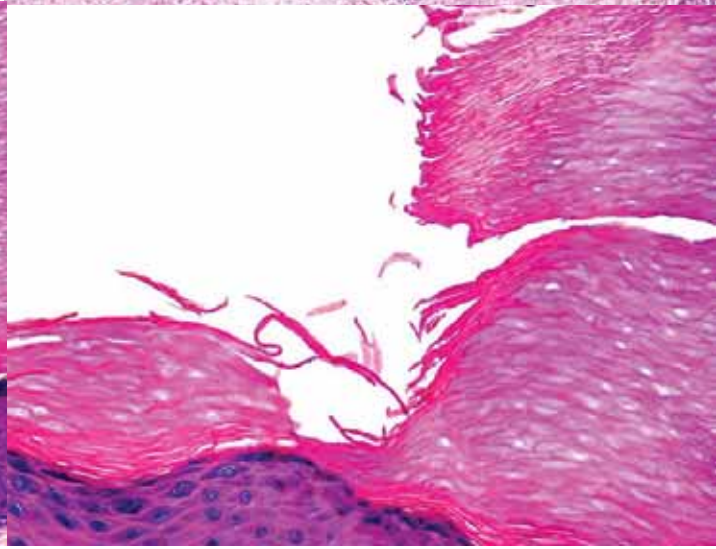


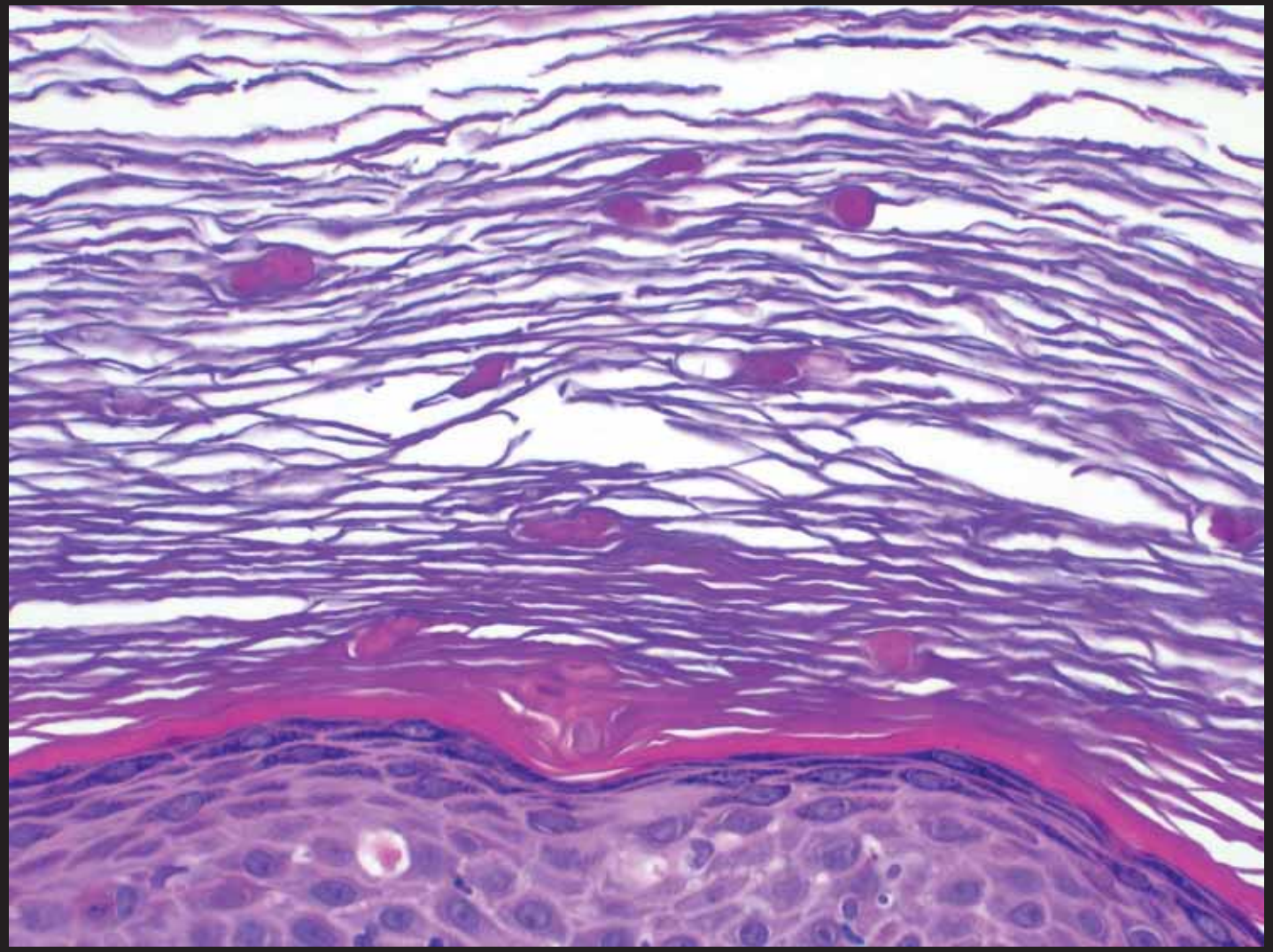












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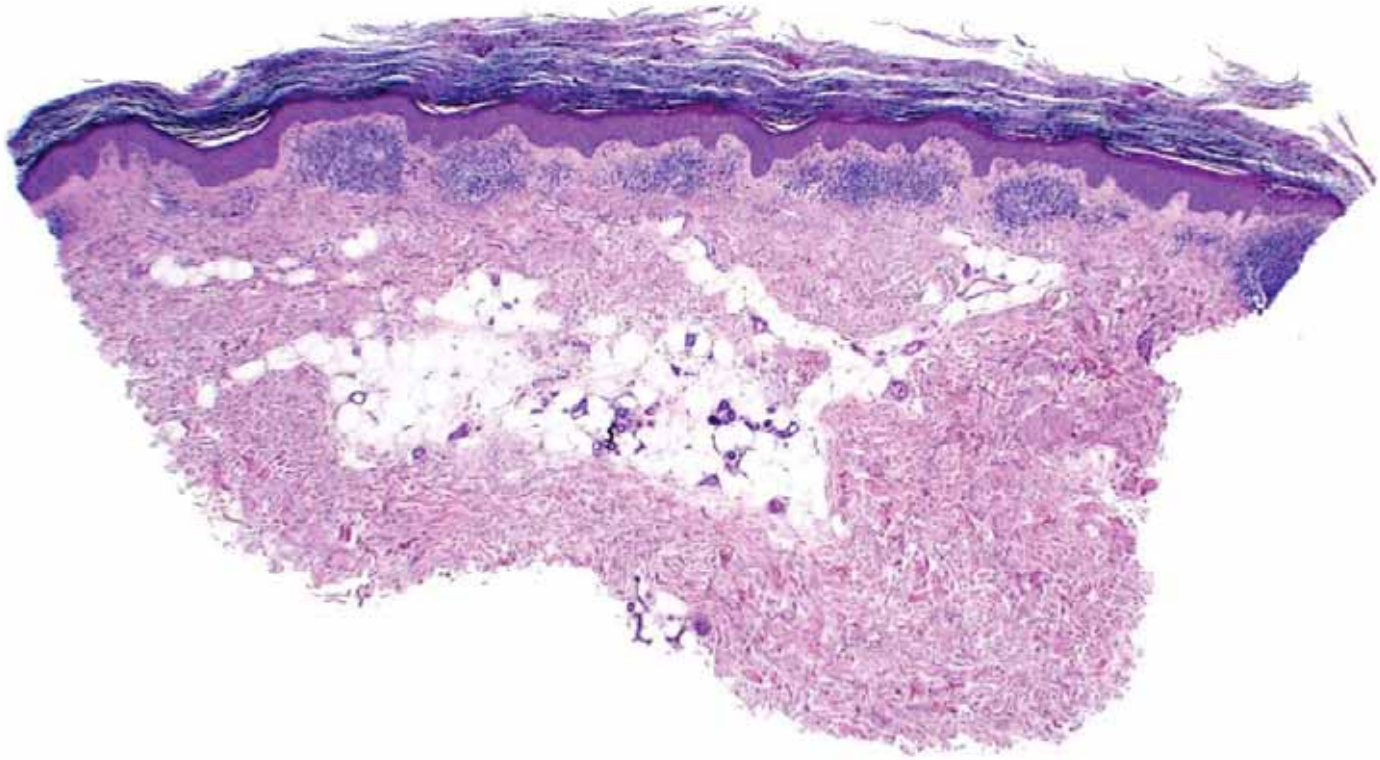
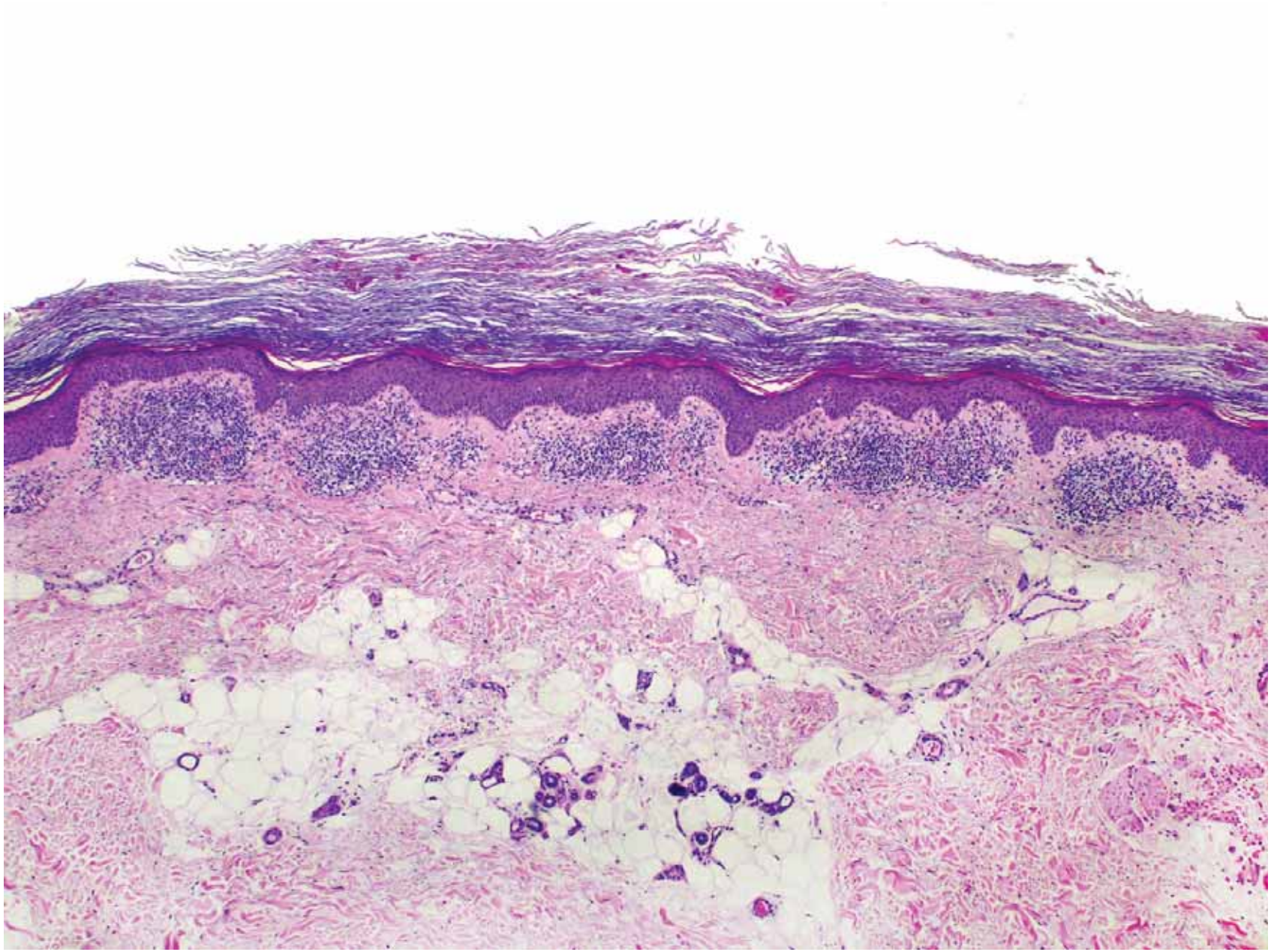
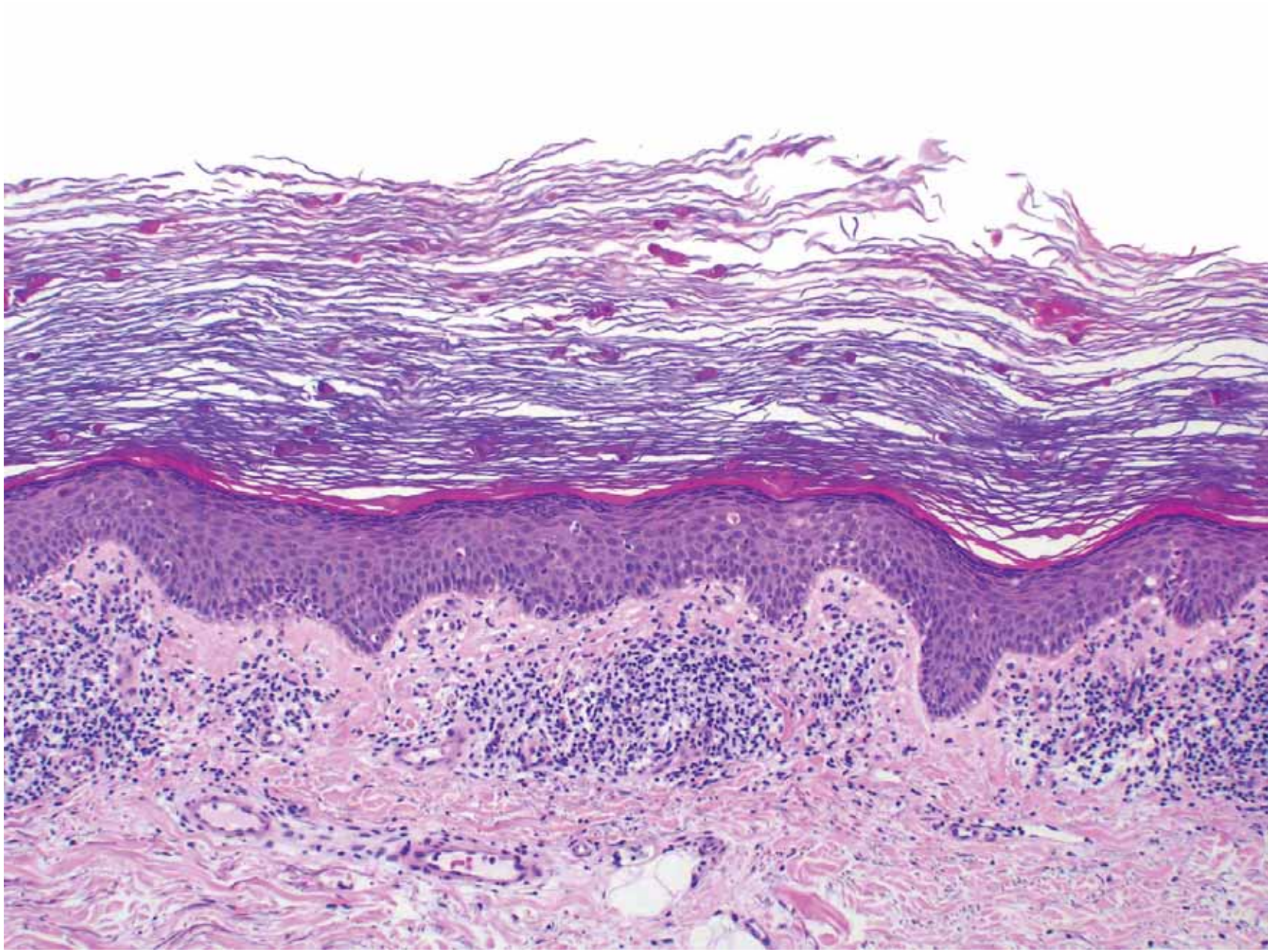
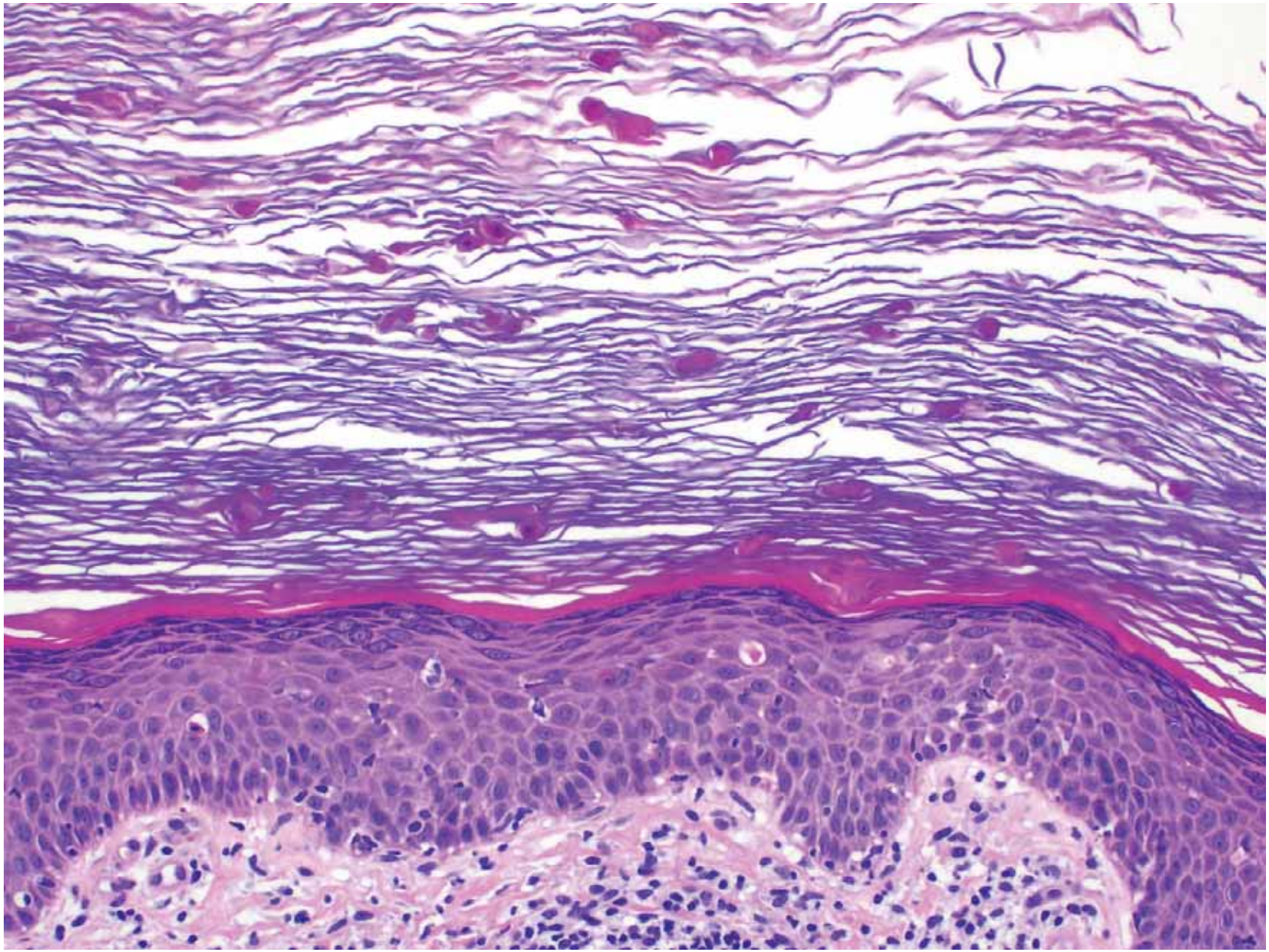
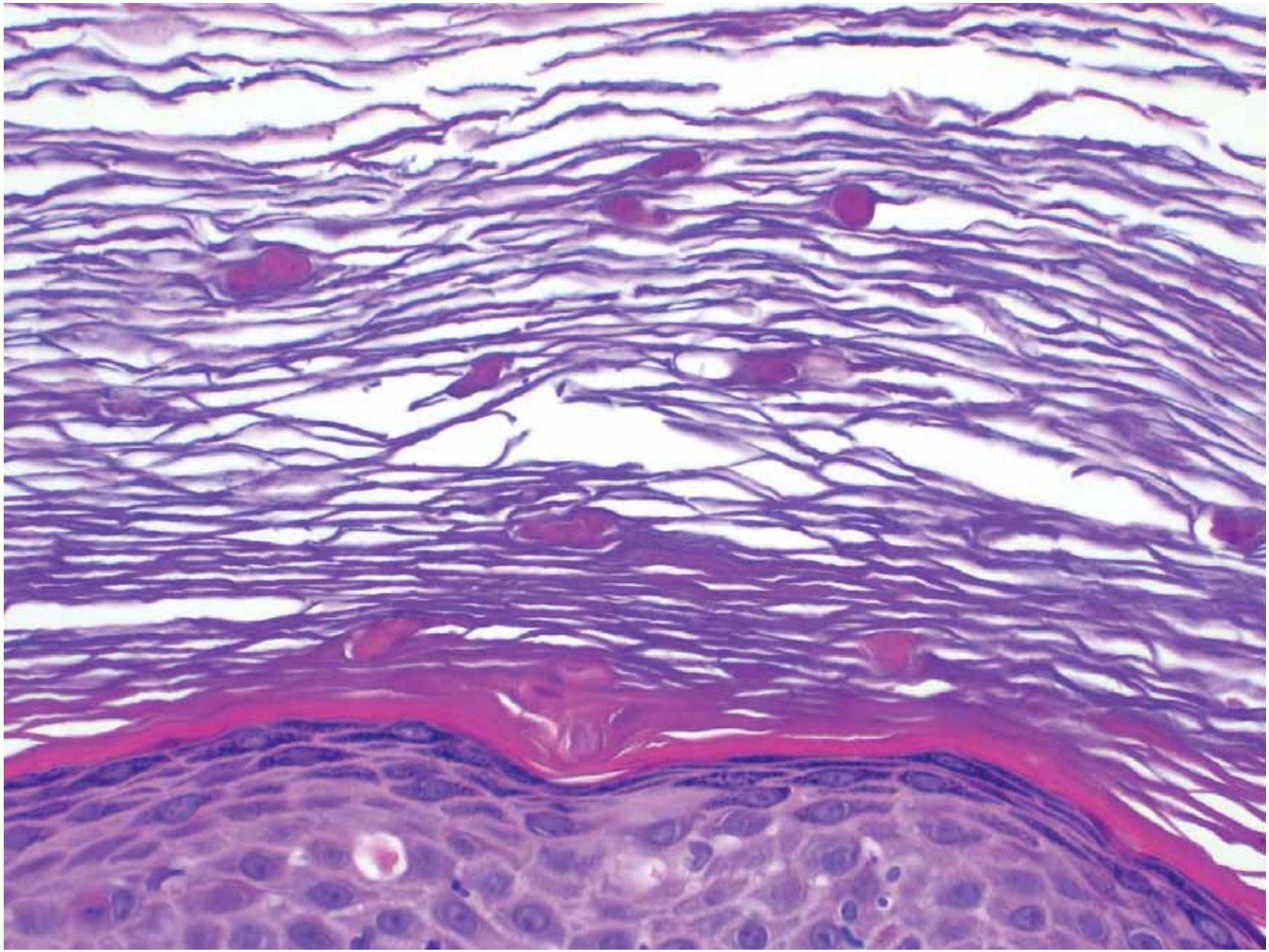
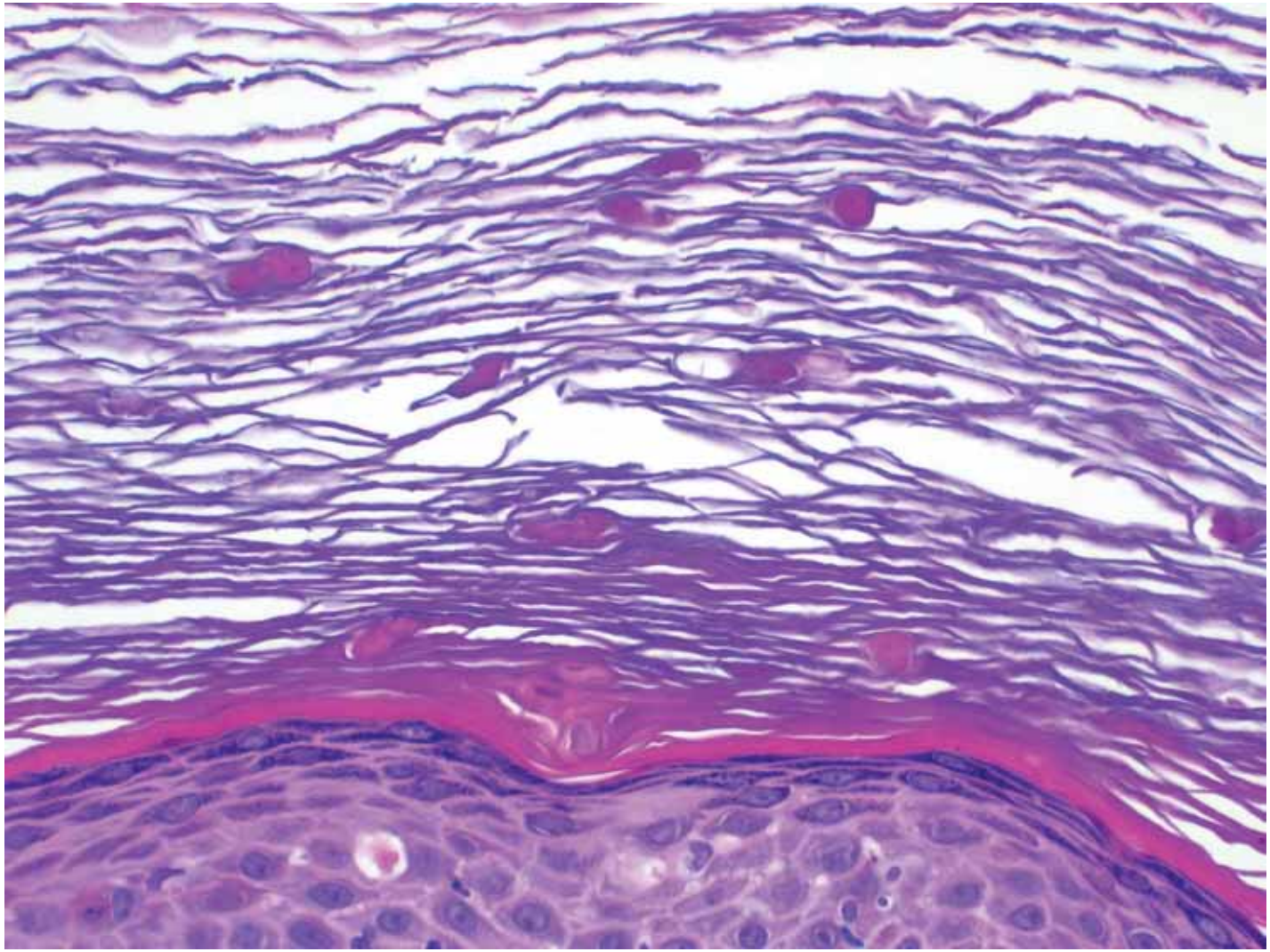




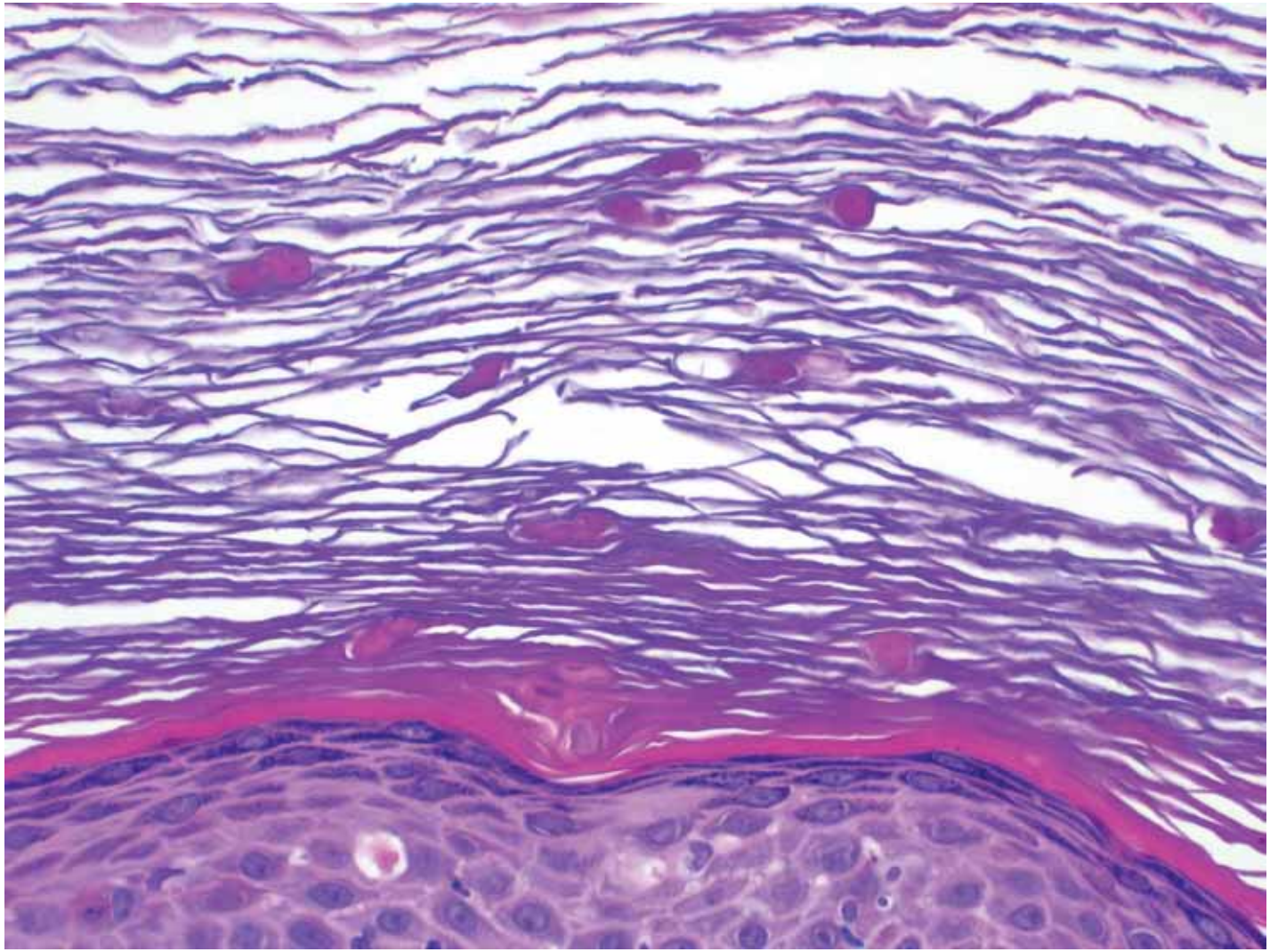








Numerous dyskeratotic cells scattered in the horny layer are a *cliche* to …



Numerous dyskeratotic cells scattered in the horny layer are a *cliche* to autoimmune collagen vascular disease

Histopathology of persistent papules and plaques in adult-onset Still's disease

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Tainan, Taiwan

Background: Persistent plaques and linear pigmentation have been reported as specific skin lesions in some patients with adult-onset Still's disease (AOSD).

Objective: We sought to characterize the histologic findings of AOSD-associated persistent rash in 11 cases and correlate the histologic findings with the clinical features.

Methods: From 1988 to 2004, 17 cases fulfilling Yamaguchi's criteria for AOSD in our hospital were reviewed and 11 (65%) manifested persistent papules and plaques. The pathology of 13 biopsy specimens of persistent eruption from 9 patients was reviewed.

Results: The 11 patients consisted of 3 men and 8 women with age of onset ranging from 19 to 67 years (average 34.7 years). Evanescent Still's rash was recorded in 9 patients. The persistent rash manifested as pruritic, red, violaceous, or brownish scaly or crusted lichenoid papules and plaques usually widely distributed over the trunk, neck, face, and extensor sides of the extremities. Lesions arranged in a bizarre linear pattern resulting from scratching were noted in some patients. Three patients died of severe disease, systemic complications, or both. The histology of persistent papules and plaques was characterized by: (1) multiple individual necrotic keratinocytes, singly or in aggregates, mainly located in the upper epidermis, including the normal or parakeratotic horny layer; and (2) infiltration of lymphocytes and neutrophils in the papillary and middermis. Other less common findings included basal vacuolar alteration, nuclear dust, and subcorneal or intracorneal pustules.

Conclusions: A clinically and pathologically distinct form of persistent lichenoid eruption was commonly observed in our patients with AOSD. The combination of multiple individual necrotic keratinocytes in the upper epidermis and a dermal infiltrate of neutrophils allow for histologic differentiation of this persistent eruption from most other lichenoid and interface dermatitides and may facilitate an earlier diagnosis of AOSD. (J Am Acad Dermatol 2005;52:1003-8.)

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder characterized clinically by high spiking fever, polyarthralgia/arthritis, a salmon-pink evanescent rash, lymphadenopathy, liver dysfunction, and splenomegaly.[1,2] Marked hyperferritinemia is characteristic of AOSD and is regarded as a marker of disease activities.[3] Elevated levels of IL-6 and IL-18 also have been shown to correlate with disease activity.[4-7] The typical Still's rash has been observed in up to 87% of patients with AOSD[8] and is regarded as a major diagnostic criterion with high sensitivity and specificity.[2] The histology of the typical evanescent rash is characterized by a relatively sparse perivascular mixed inflammatory infiltrate containing some neutrophils.[2]

Nonevanescent skin lesions has been reported in sporadic cases with active AOSD.[9-11] Two patients manifested pruritic persistent plaques characterized by brownish coalescent papules with adherent scales clinically, and necrotic keratinocytes in the epidermis with a neutrophilic infiltrate in the dermis histologically.[10,11] This type of persistent rash may represent a specific manifestation of this syndrome,

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Reprint requests: Julia Yu-Yun Lee, MD, Department of Dermatology, College of Medicine, National Cheng-Kung University Hospital, 138 Sheng-Li Rd, Tainan 704, Taiwan. E-mail: yylee@mail.ncku.edu.tw.
0190-9622/$30.00

doi:10.1016/j.jaad.2005.02.032

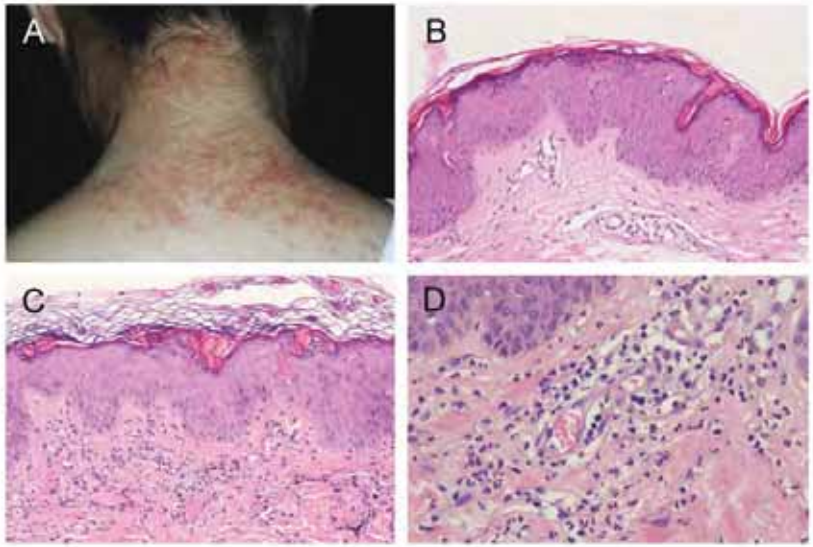

Fig 1. A 31-year-old Taiwanese woman presenting with spiking fever, arthralgia, evanescent rash, and widespread persistent pruritic lesions. Numerous erythematous papular lesions are present on nape of neck (**A**). Biopsy specimen of neck lesion reveals many necrotic keratinocytes, singly and in aggregates, distributed from spinous to horny layer. Neutrophil-rich infiltrate is present in papillary dermis (**C, D**). Biopsy specimen of maculopapular lesion on wrist reveals milder changes with necrotic keratinocytes in upper half of epidermis and sparse perivascular infiltrate. Note basal layer is spared (**B**). (**B** to **D**, Hematoxylin-eosin stain; original magnifications: **B** and **C**, ×100; **D**, ×200).

Observational Study

Medicine

OPEN

Dyskeratotic cells in persistent pruritic skin lesions as a prognostic factor in adult-onset Still disease

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Abstract

Adult-onset Still disease (AOSD), a systemic inflammatory disorder, is characterized by high fever, evanescent rash, arthritis, and hyperferritinaemia. AOSD is also reported to be associated with other skin lesions, including persistent pruritic papules and plaques. This study aimed to assess the significance of dyskeratotic skin lesions in Japanese AOSD patients.

We retrospectively assessed the histology of persistent pruritic skin lesions and evanescent rashes and the relationship between dyskeratotic cells, serum markers, and outcomes in 20 Japanese AOSD patients, comparing AOSD histology with that of dermatomyositis (DM), drug eruptions, and graft-versus-host disease (GVHD).

As the results, Persistent pruritic lesions were characterized by scattered single keratinocytes with an apoptotic appearance confined to the upper layer of the epidermis and horny layer without inflammatory infiltrate. In contrast to AOSD, the histology of DM, drug eruption, and GVHD demonstrated dyskeratotic cells in all layers of the epidermis with inflammatory infiltrate. AOSD with evanescent rash showed no dyskeratotic cells. The dyskeratotic cells in pruritic AOSD lesions stained positive for ssDNA and terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling, indicating apoptosis. Serum IL-18 was significantly higher in AOSD patients with dyskeratotic cells than those without, and generally required higher doses of glucocorticoids, immunosuppressants, and biologic agents. Two of ten AOSD patients with dyskeratotic cells died from hemophagocytic lymphohistiocytosis.

In conclusion, Persistent pruritic AOSD skin lesions are characterized by dyskeratotic cells with apoptotic features, involving the upper layers of the epidermis. There may be a link to elevated IL-18. This dyskeratosis may be a negative prognostic indicator.

Abbreviations: AOSD = adult-onset Still disease, G-CSF = granulocyte-colony stimulating factor, IFN = interferon, IL = interleukin, MAP = mitogen-activated protein, mRNA = messenger ribonucleic acid, NF-κB = nuclear factor-kappa B, ssDNA = single-stranded deoxyribonucleic acid, STAT = signal transducer and activator of transcription, TNF = tumor necrosis factor, TUNEL = terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling.

Keywords: adult-onset Still disease, apoptosis, dyskeratosis, IL-18

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NMA, KHO, and YT contributed equally to this manuscript.

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The authors declare no conflict of interest.

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Key Messages

- Unlike the more common evanescent rash, persistent pruritic lesions can be seen in AOSD.
- The pruritic lesions have dyskeratotic cells, which are apoptotic and confined to the upper epidermis.
- Pruritic lesions, often accompanied by elevated IL-18, may be a negative prognostic indicator.

1. Introduction

Adult-onset Still disease (AOSD) is an acute systemic inflammatory disorder that is characterized by high spiking fevers, an evanescent salmon-colored rash, arthralgia/arthritis, and hyperferritinaemia. Diagnosis is difficult, and sometimes delayed. AOSD is a diagnosis of exclusion, after infection, malignancy, and other connective tissue diseases have been ruled out. The typical evanescent salmon-colored rash is said to occur in about 75% of

Abstract

Adult-onset Still disease (AOSD), a systemic inflammatory disorder, is characterized by high fever, evanescent rash, arthritis, and hyperferritinaemia. AOSD is also reported to be associated with other skin lesions, including persistent pruritic papules and plaques. This study aimed to assess the significance of dyskeratotic skin lesions in Japanese AOSD patients.

We retrospectively assessed the histology of persistent pruritic skin lesions and evanescent rashes and the relationship between dyskeratotic cells, serum markers, and outcomes in 20 Japanese AOSD patients, comparing AOSD histology with that of dermatomyositis (DM), drug eruptions, and graft-versus-host disease (GVHD).

As the results, Persistent pruritic lesions were characterized by scattered single keratinocytes with an apoptotic appearance confined to the upper layer of the epidermis and horny layer without inflammatory infiltrate. In contrast to AOSD, the histology of DM, drug eruption, and GVHD demonstrated dyskeratotic cells in all layers of the epidermis with inflammatory infiltrate. AOSD with evanescent rash showed no dyskeratotic cells. The dyskeratotic cells in pruritic AOSD lesions stained positive for ssDNA and terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling, indicating apoptosis. Serum IL-18 was significantly higher in AOSD patients with dyskeratotic cells than those without, and generally required higher doses of glucocorticoids, immunosuppressants, and biologic agents. Two of ten AOSD patients with dyskeratotic cells died from hemophagocytic lymphohistiocytosis.

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Journal of Cutaneous Pathology

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ORIGINAL ARTICLE

Histopathologic Features of Acral Skin Biopsies in Dermatomyositis Patients and Comparison to Histopathologic Features in Non-Acral Biopsies

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Keywords: acral | dermatomyositis | Gottron | histology | histopathology | mucin | skin

ABSTRACT

Background: Acral lesions may represent the best/only skin lesions to biopsy in patients suspected to have dermatomyositis (DM). However, histopathologic features of acral DM skin lesions are poorly characterized.

Methods: We reviewed 50 acral biopsies from 46 DM patients and assessed numerous histopathologic features. The majority of biopsies (42/50; 84%) were sampled from either Gottron papules or signs. We compared histopathologic features in acral biopsies to those in 197 non-acral DM skin biopsies. We also compared histopathologic features in acral biopsies based on the presence of various clinical features.

Results: Interface dermatitis, dyskeratotic keratinocytes, and superficial perivascular inflammation were common in DM acral biopsies. However, the absence of >1 hallmark histopathologic feature (interface dermatitis, dyskeratosis, dermal mucin) was relatively common (56%). The presence of all three hallmark histopathologic features was significantly more likely in non-acral compared with acral DM biopsies (68% vs. 44%; $p = 0.0021$). The hallmark histopathologic feature most commonly lacking in acral compared with non-acral biopsies was increased dermal mucin. Histopathologic features in acral biopsies did not significantly differ based on acral location, DM subtype, therapeutic regimen, or myositis-associated/myositis-specific antibody status.

Conclusions: Pathologists should recognize that acral biopsies in DM patients may lack hallmark histopathologic features commonly seen in biopsies from non-acral locations.

1 | Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) that predominantly affects the skin and muscles. Although DM can often be diagnosed clinically, confirmation of an accurate diagnosis is typically pursued to rule out the mimicker diseases and in patients with mild manifestations that make diagnosis challenging. Accurately diagnosing DM is important for numerous reasons, including for providing an opportunity to promptly detect and treat potential underlying malignancies or interstitial lung disease.

As the skin is involved in all patients and is easily accessible, one of the most common procedures in a DM diagnostic work-up is a lesional skin biopsy. Additionally, the 2017 European League Against Rheumatology/American College of Rheumatology

ABSTRACT

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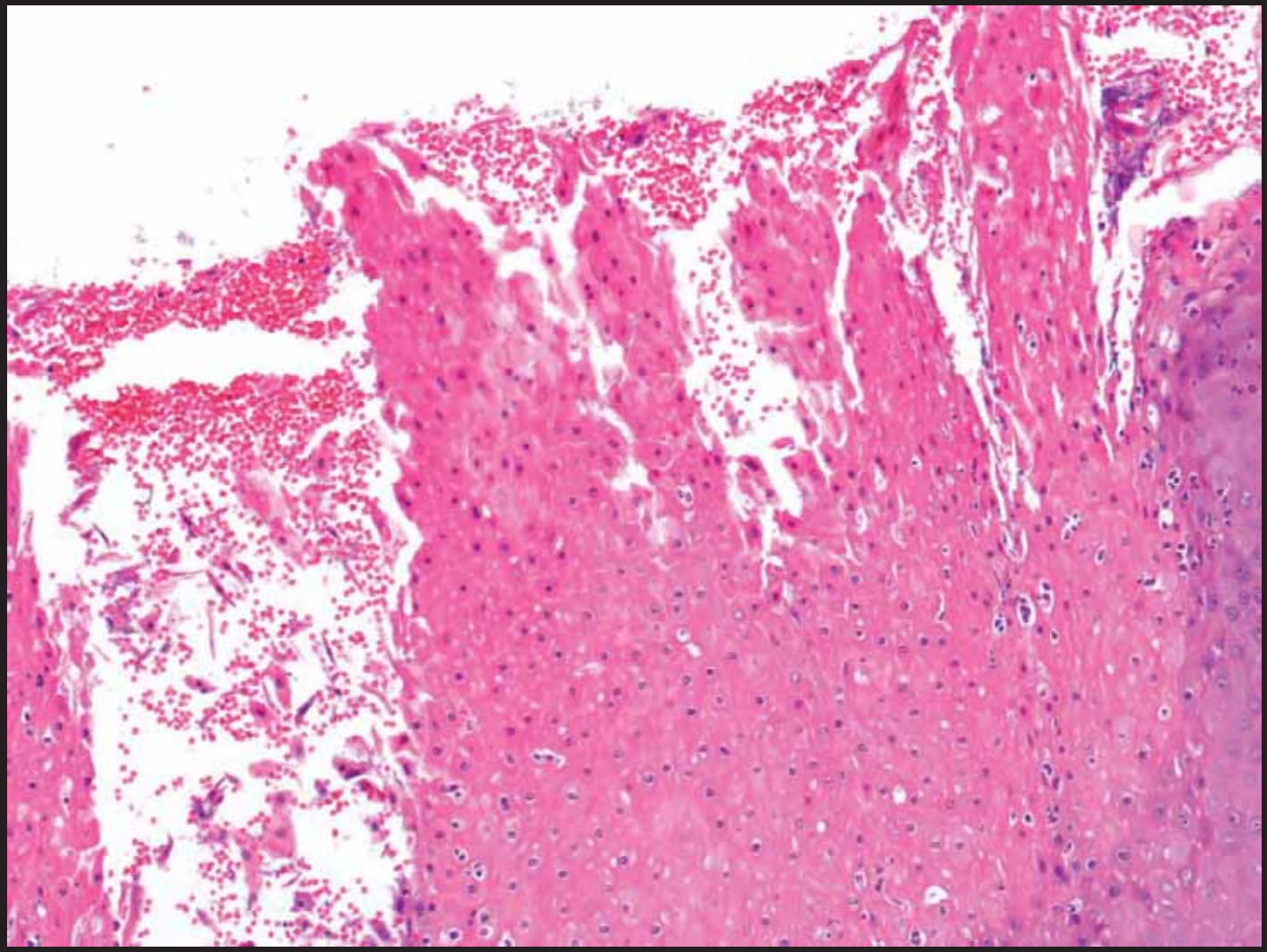
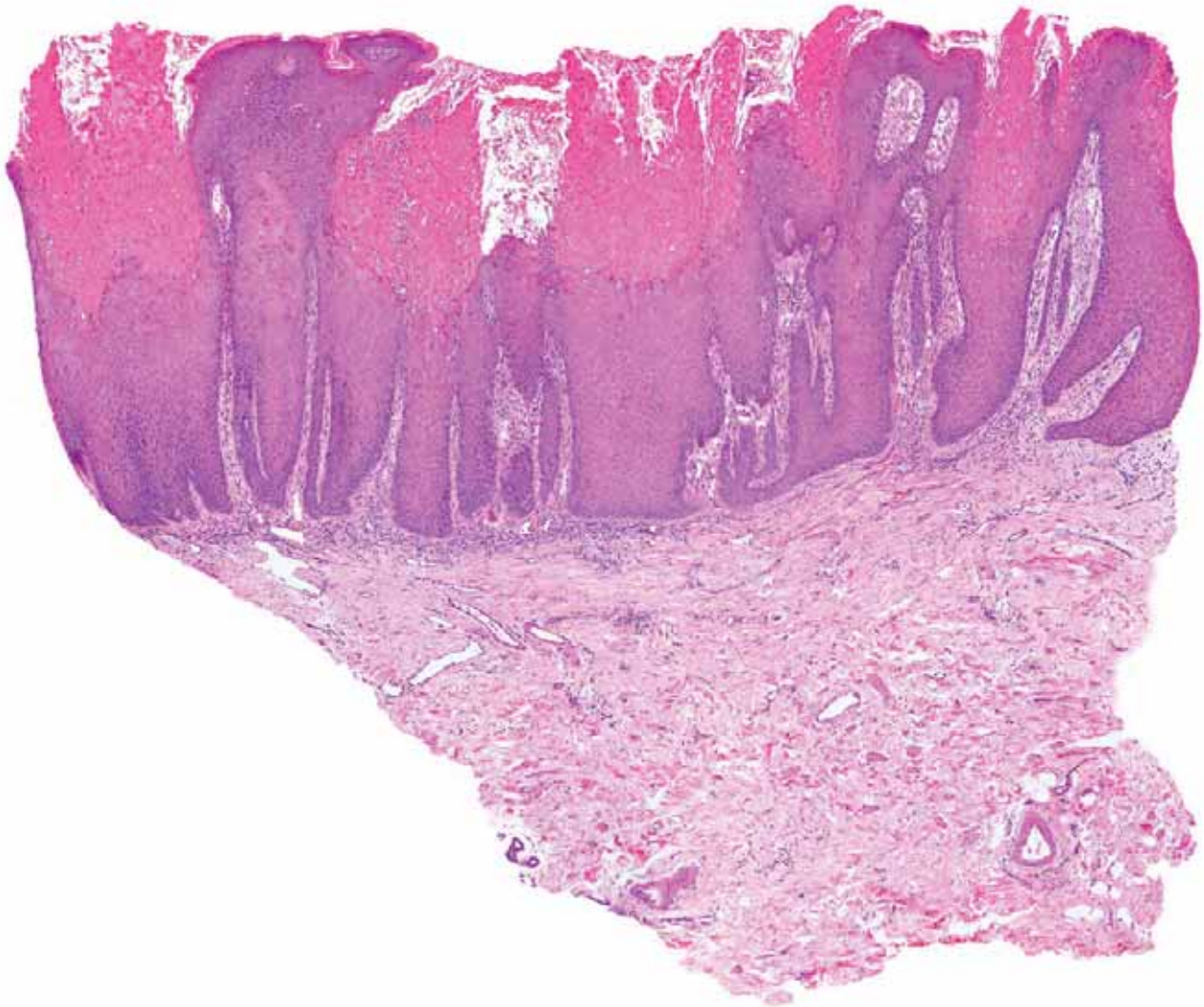
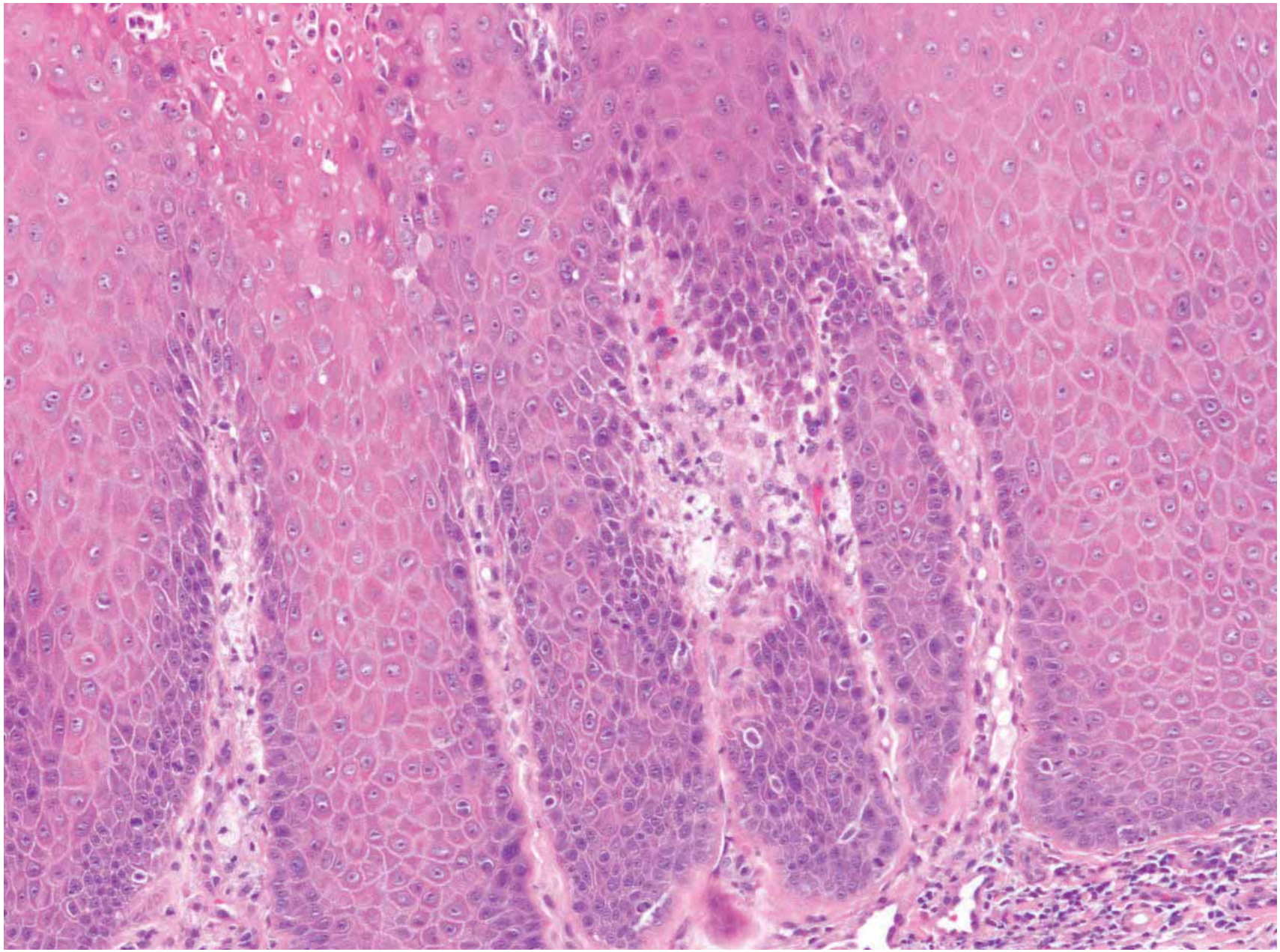
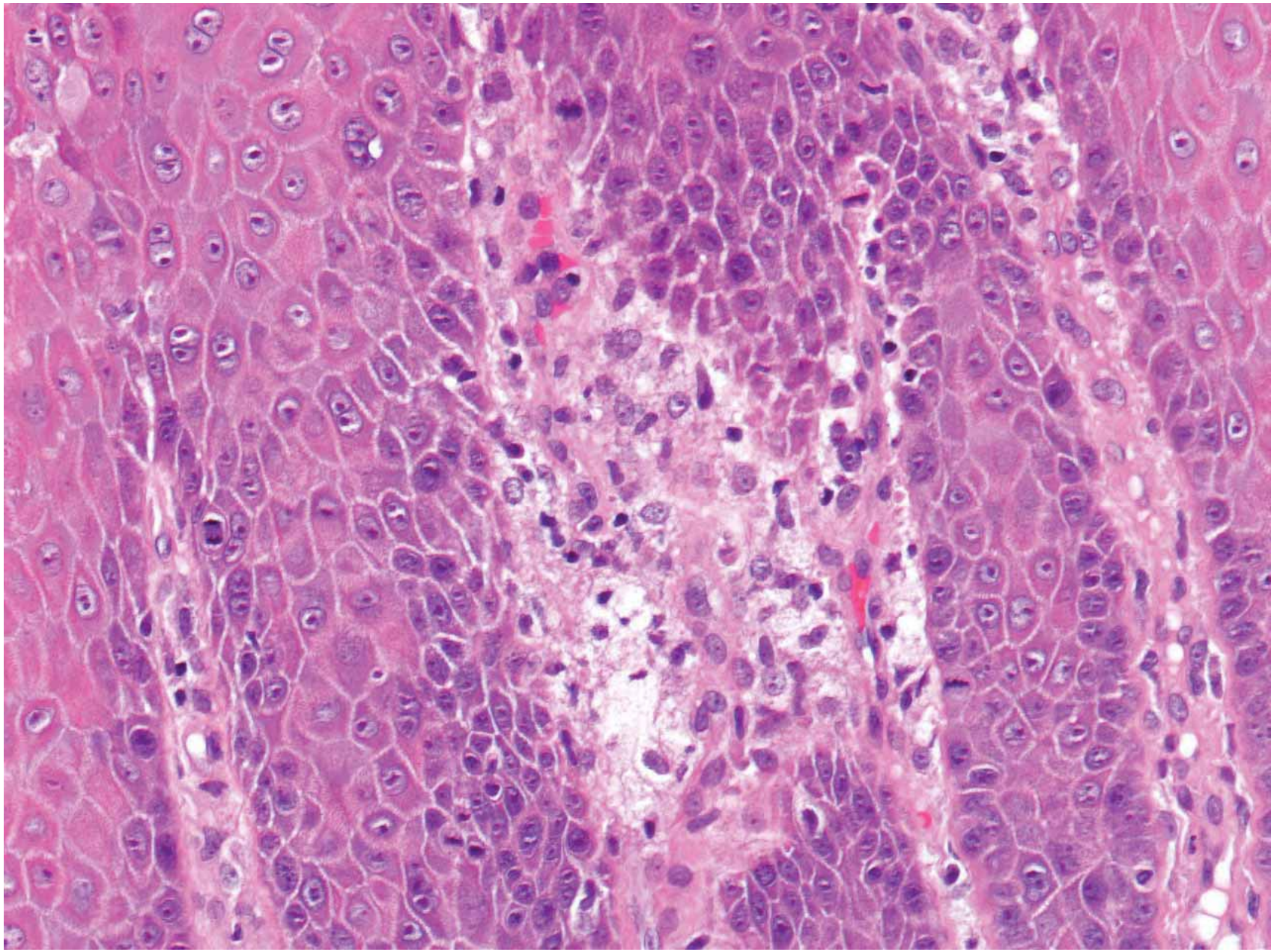
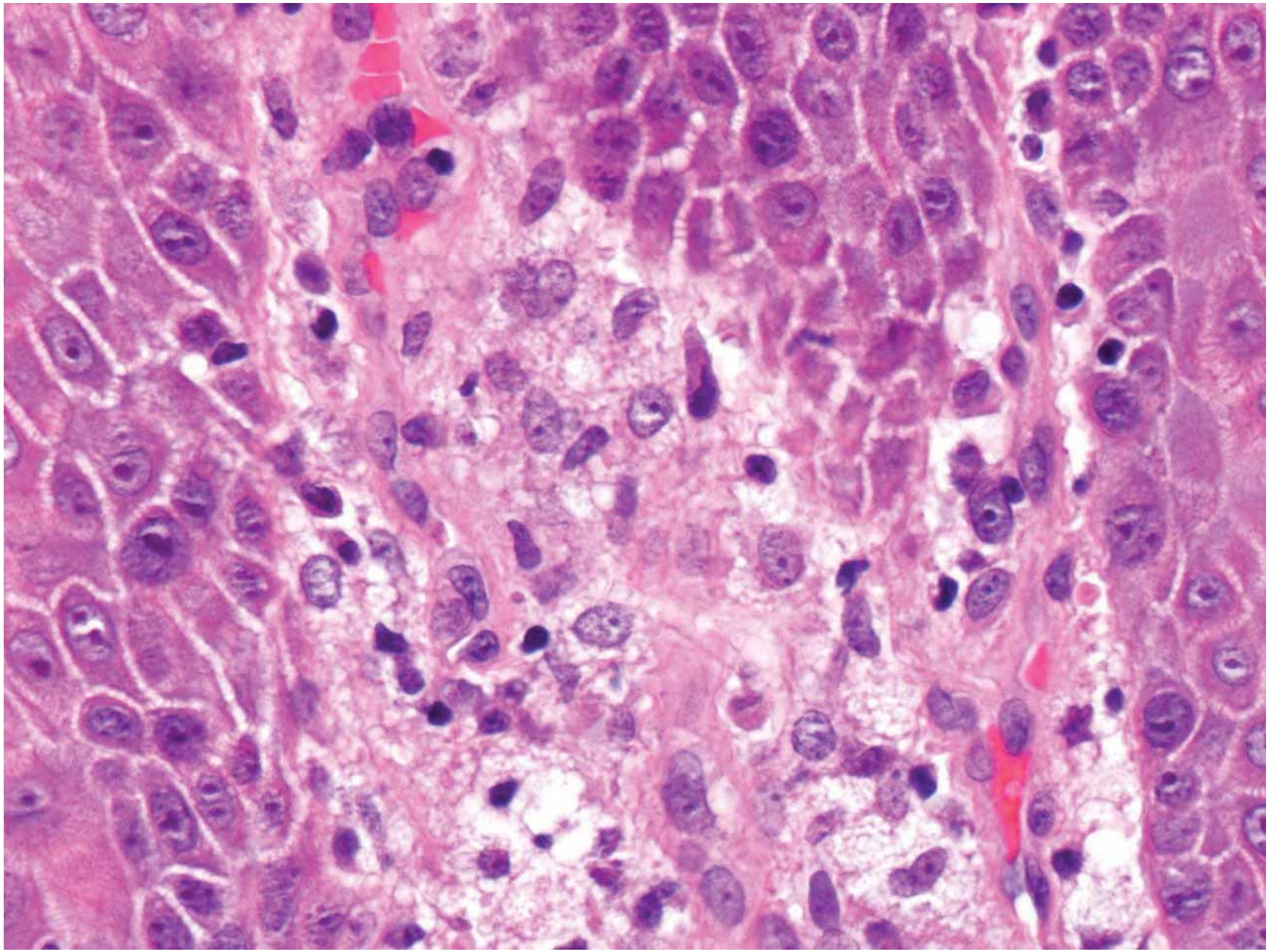


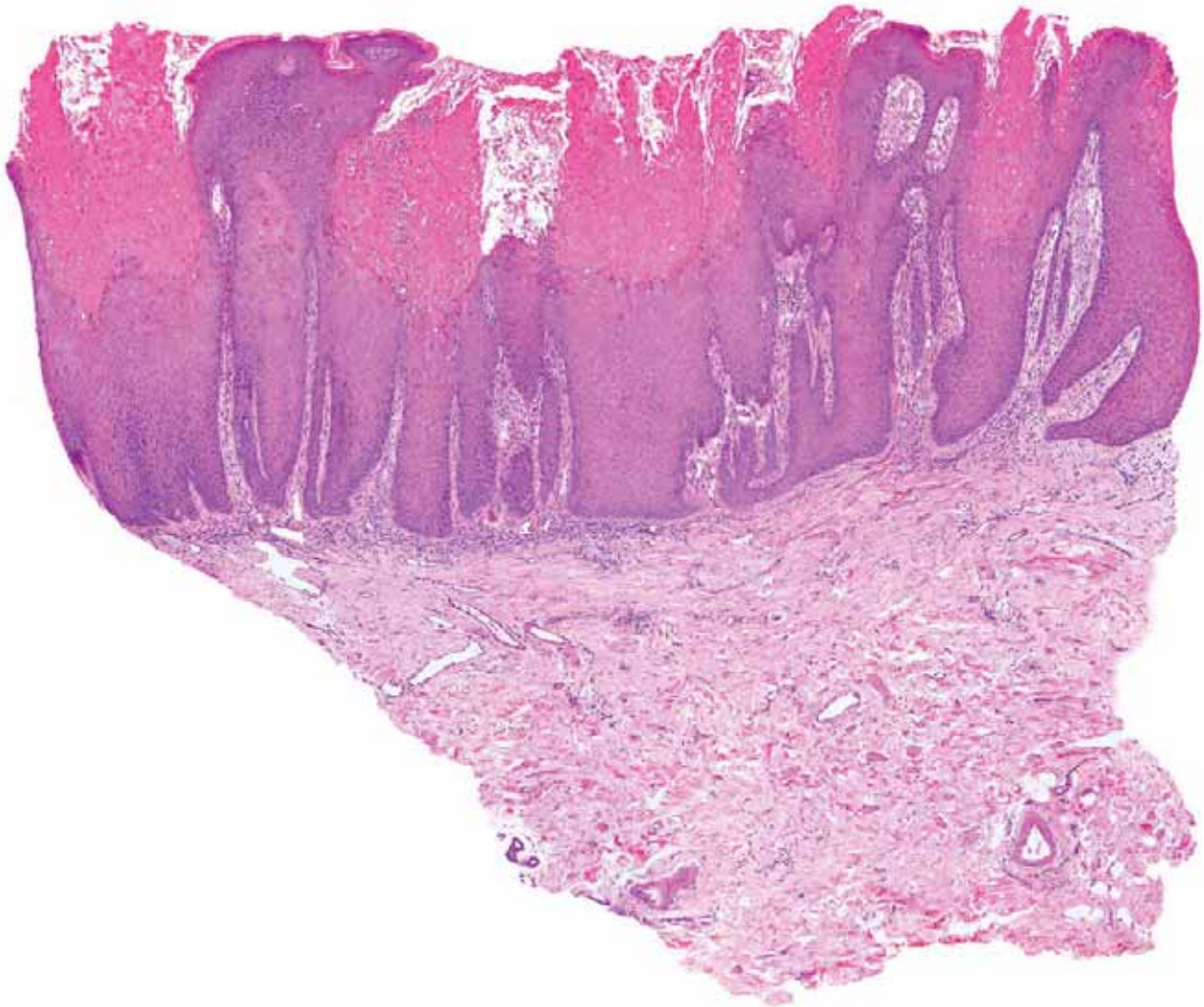
What is the *cliche* and what is the diagnosis?

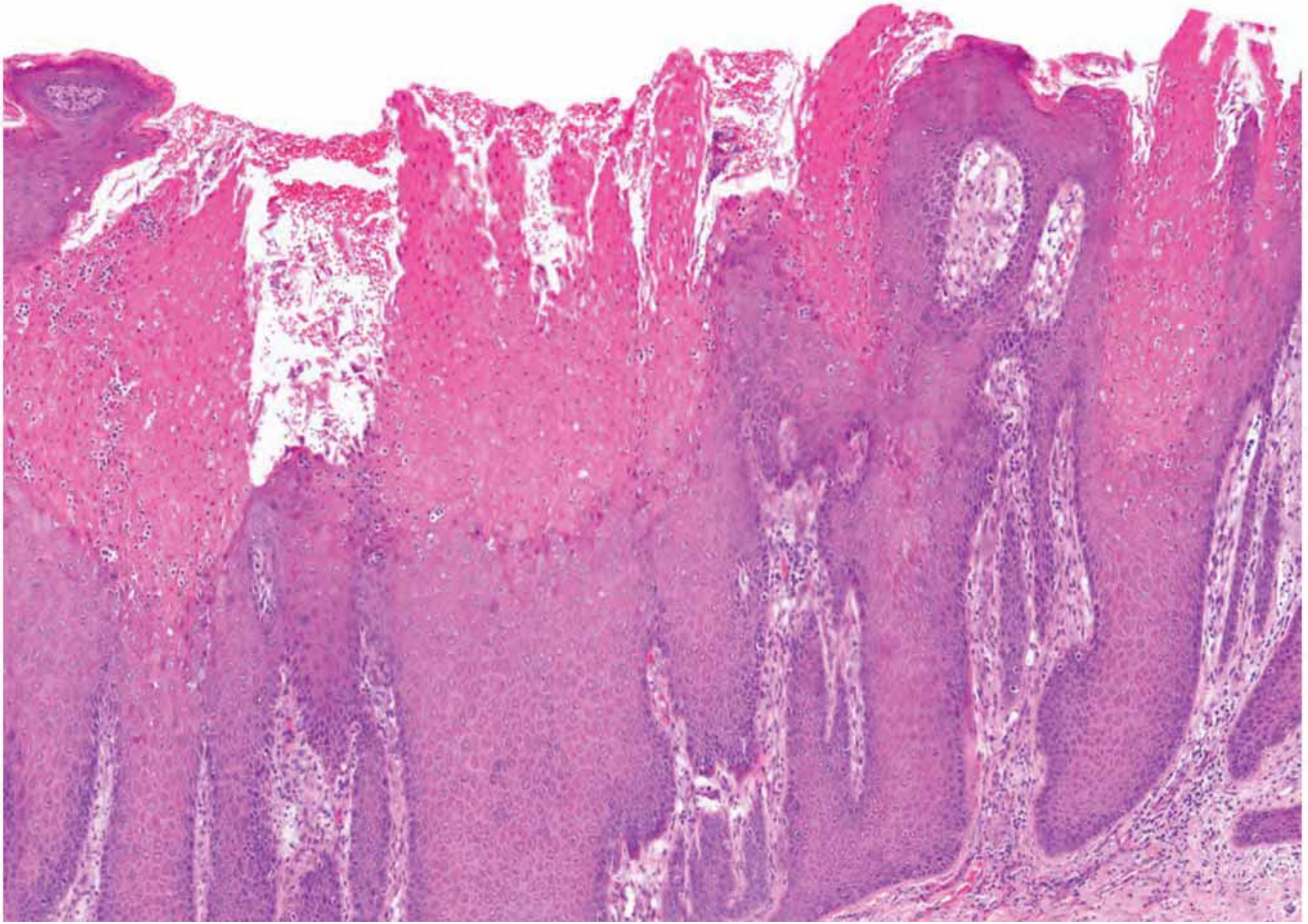


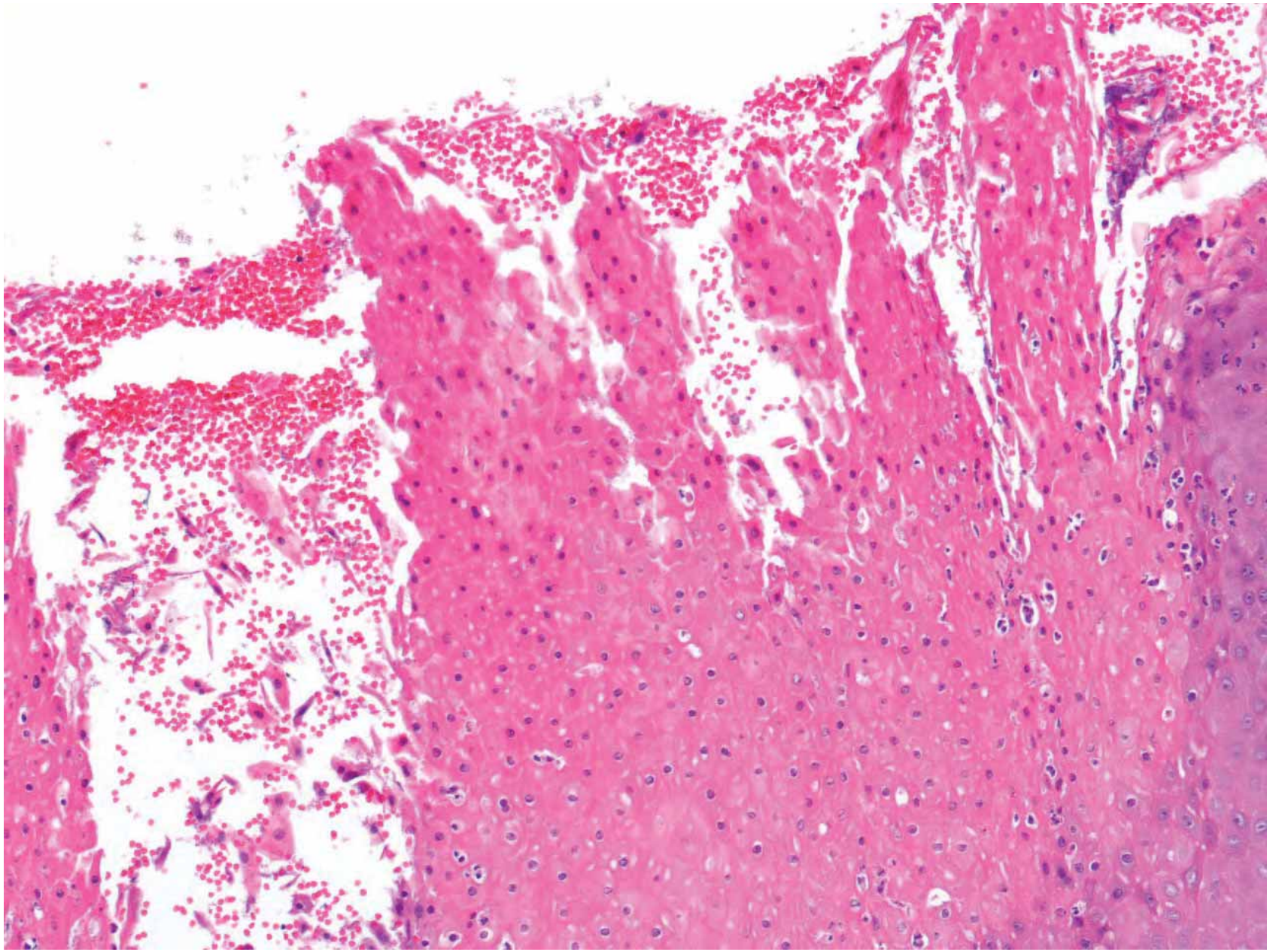


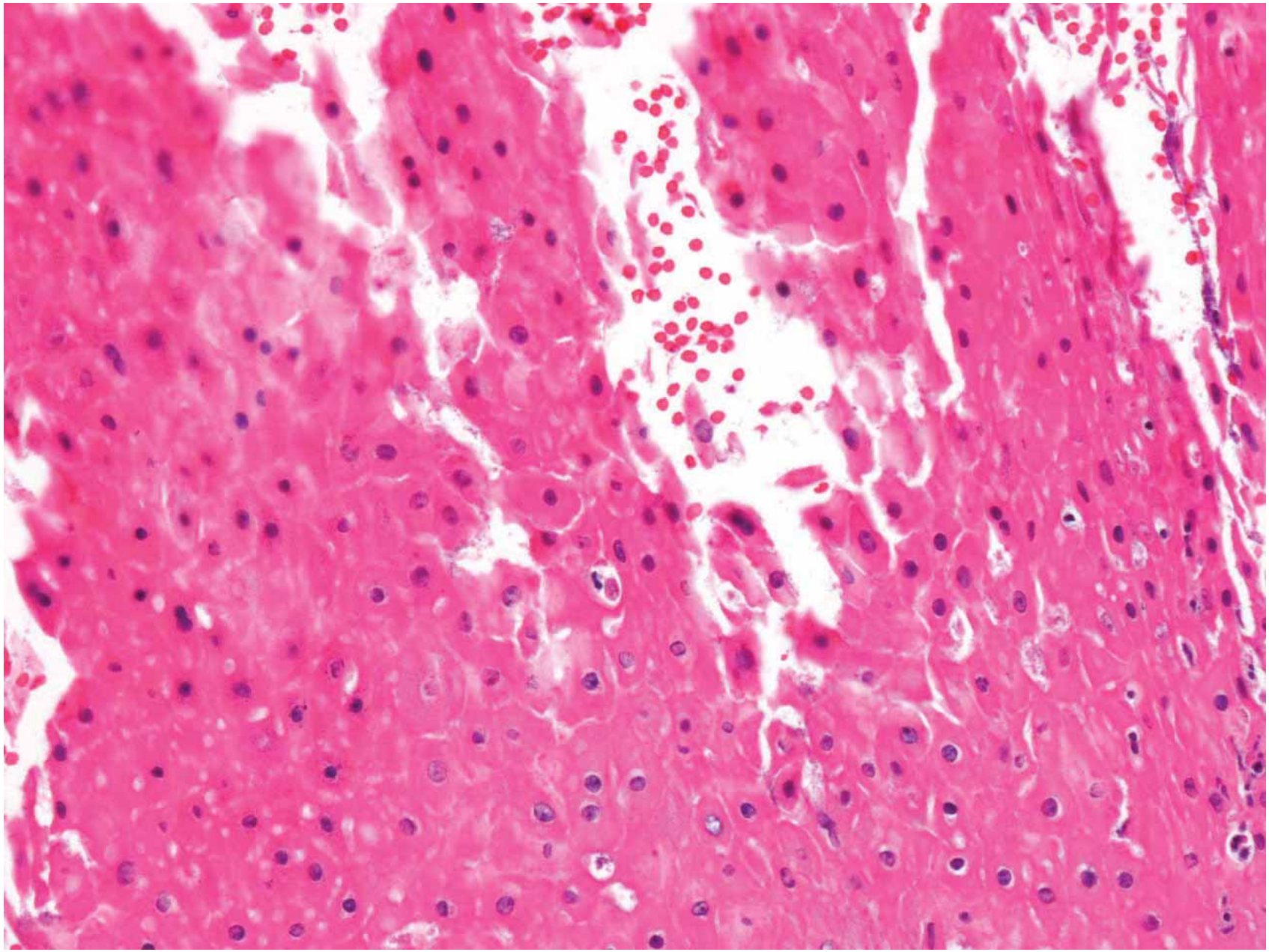


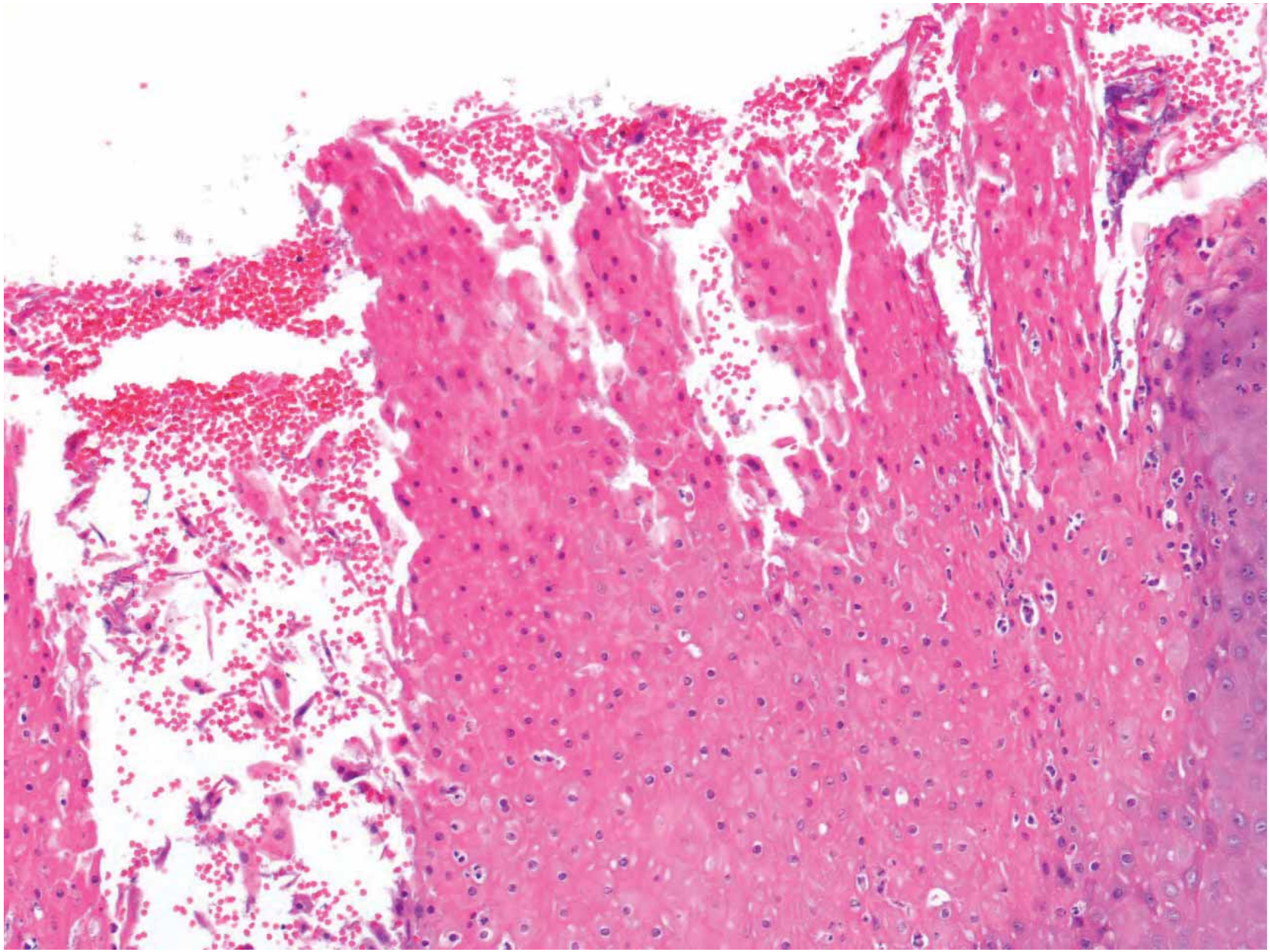


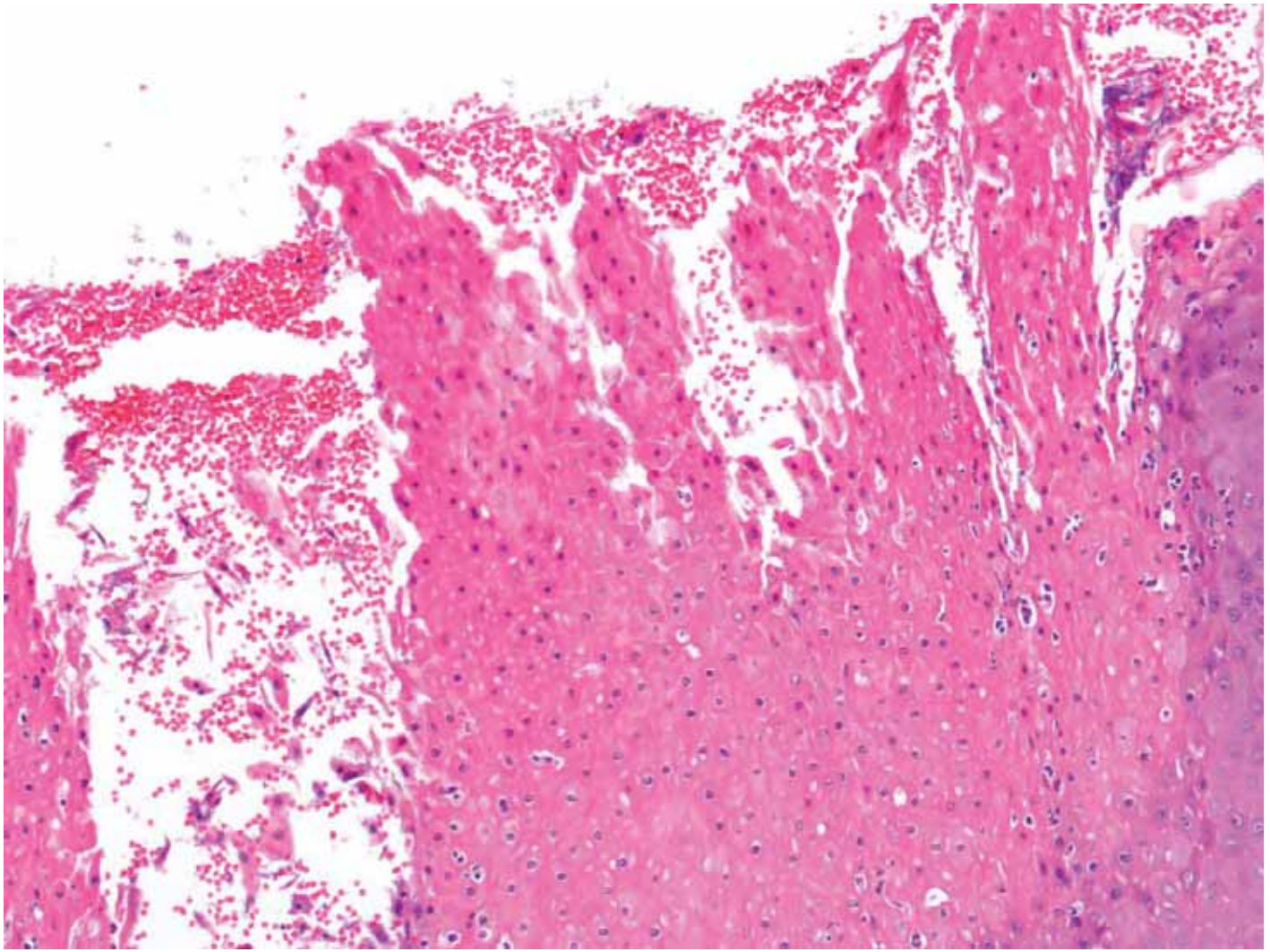




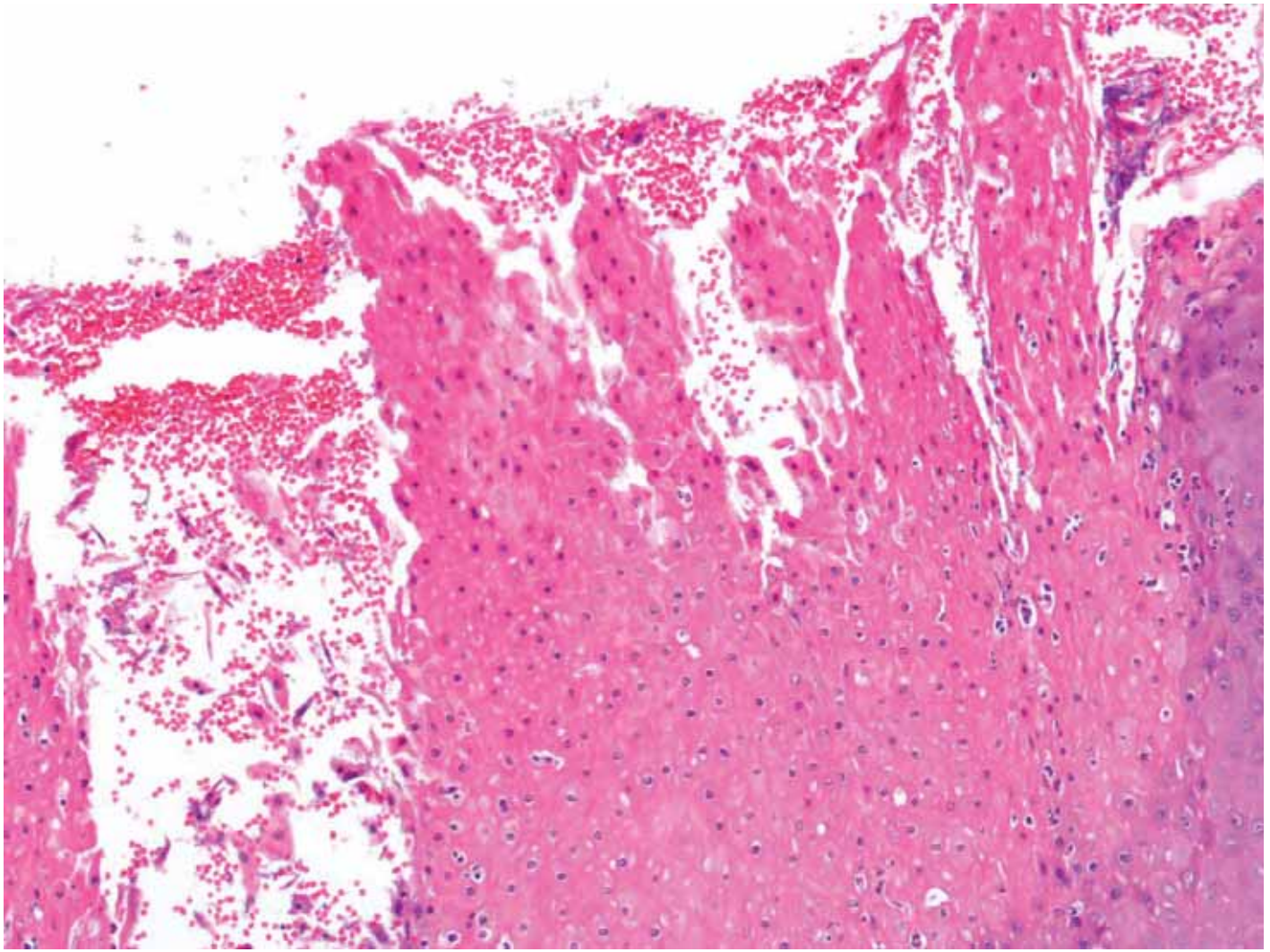




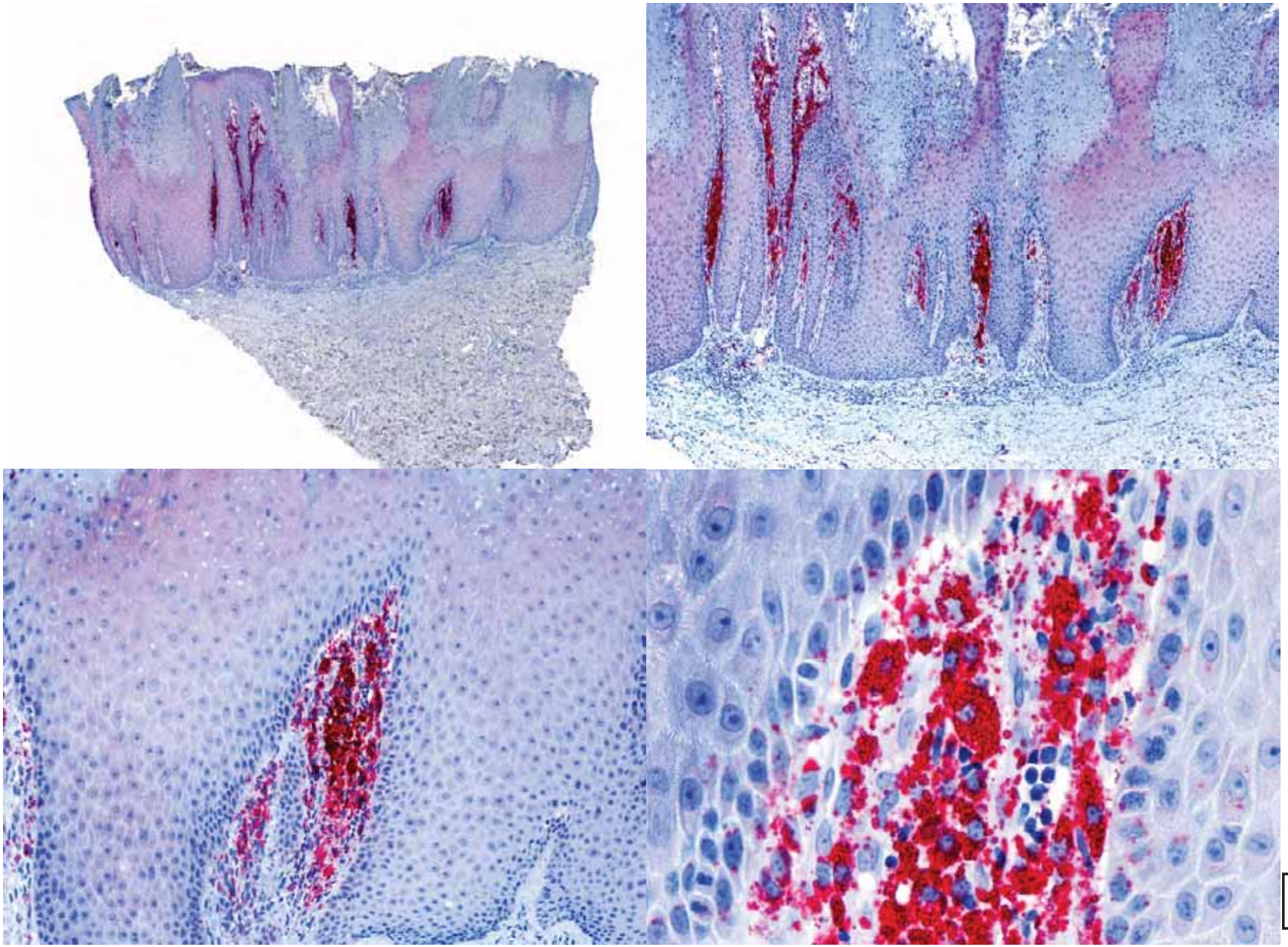




Acantholytic corneocytes atop a parakeratotic horny layer in a hyperplastic epidermis is a *cliche* to…



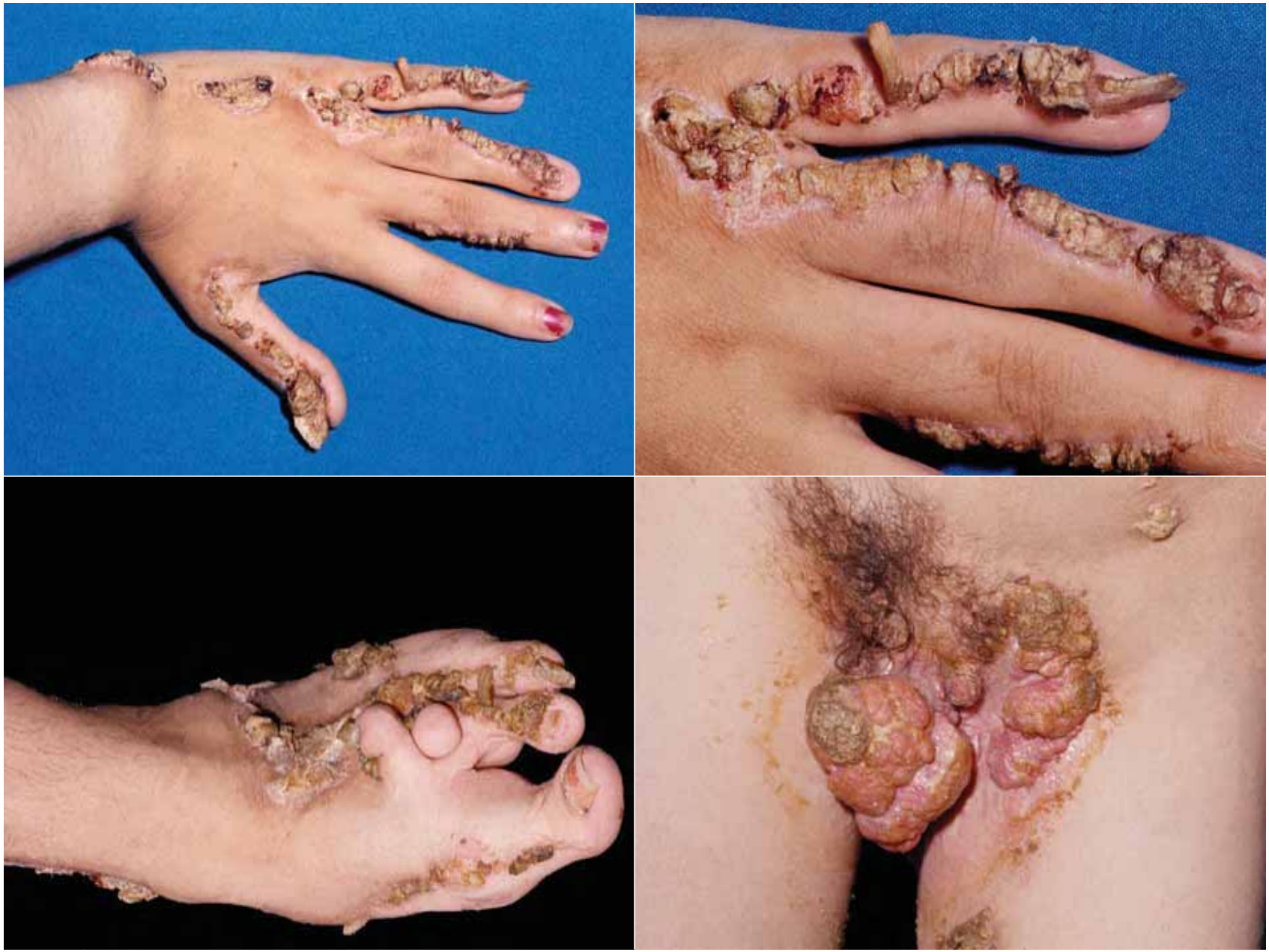
Acantholytic corneocytes atop a parakeratotic horny layer in a hyperplastic epidermis is a *cliche* to CHILD syndrome or verruciform xanthoma

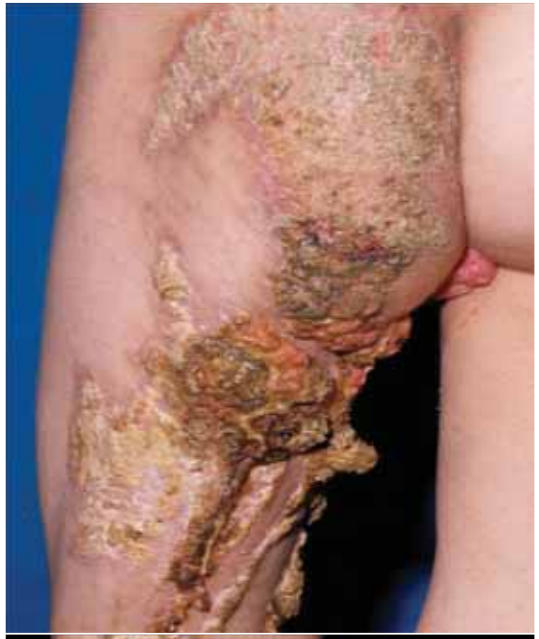


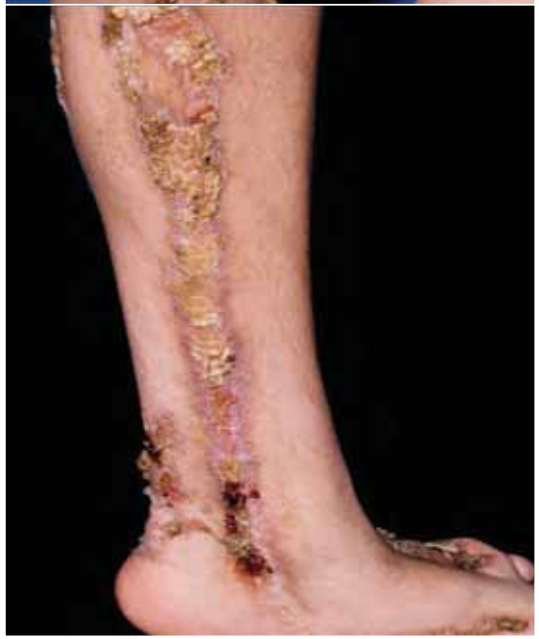
Adipophilin

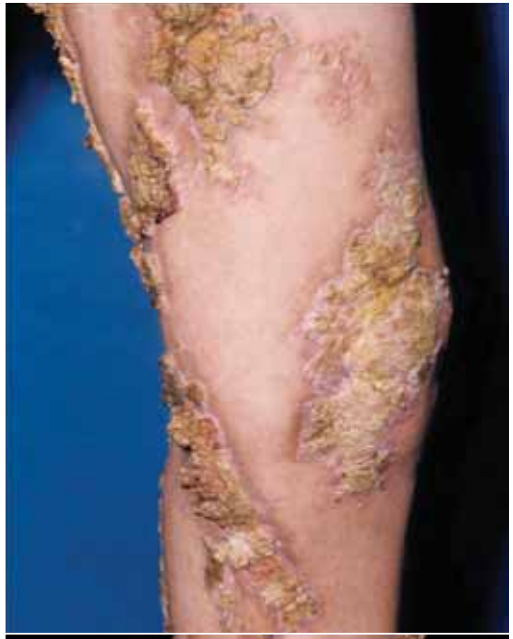
CHILD SYNDROME

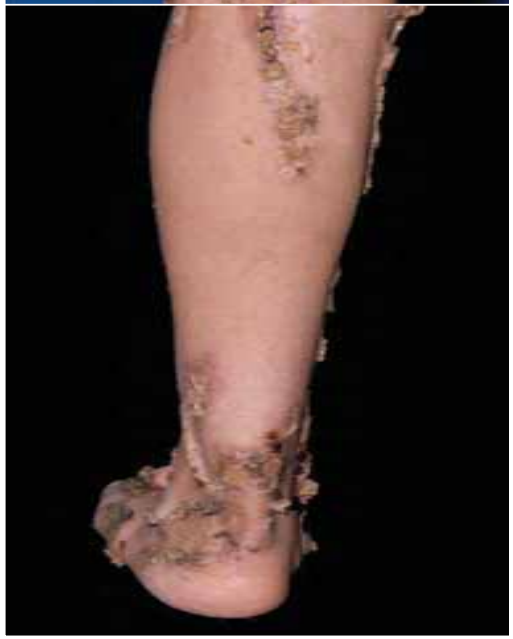
- CHILD syndrome is an X-linked, dominant disorder with a male-lethal trait.
- CHILD syndrome results from mosaicism inactivating the NAD(P)-dependent steroid dehydrogenase-like (NSDHL) protein gene, leading to decreased or absent 3-β-hydroxysteroid dehydrogenase function
- 3-β-hydroxysteroid dehydrogenase is involved in cholesterol biosynthesis
- "CHILD" for ***c***ongenital ***h***emidysplasia, ***i***chthyosiform erythroderma, and ***l***imb ***d***efects,
- Histopathology: identical to verruciform xanthoma. Both lesions show acantholytic corneocytes

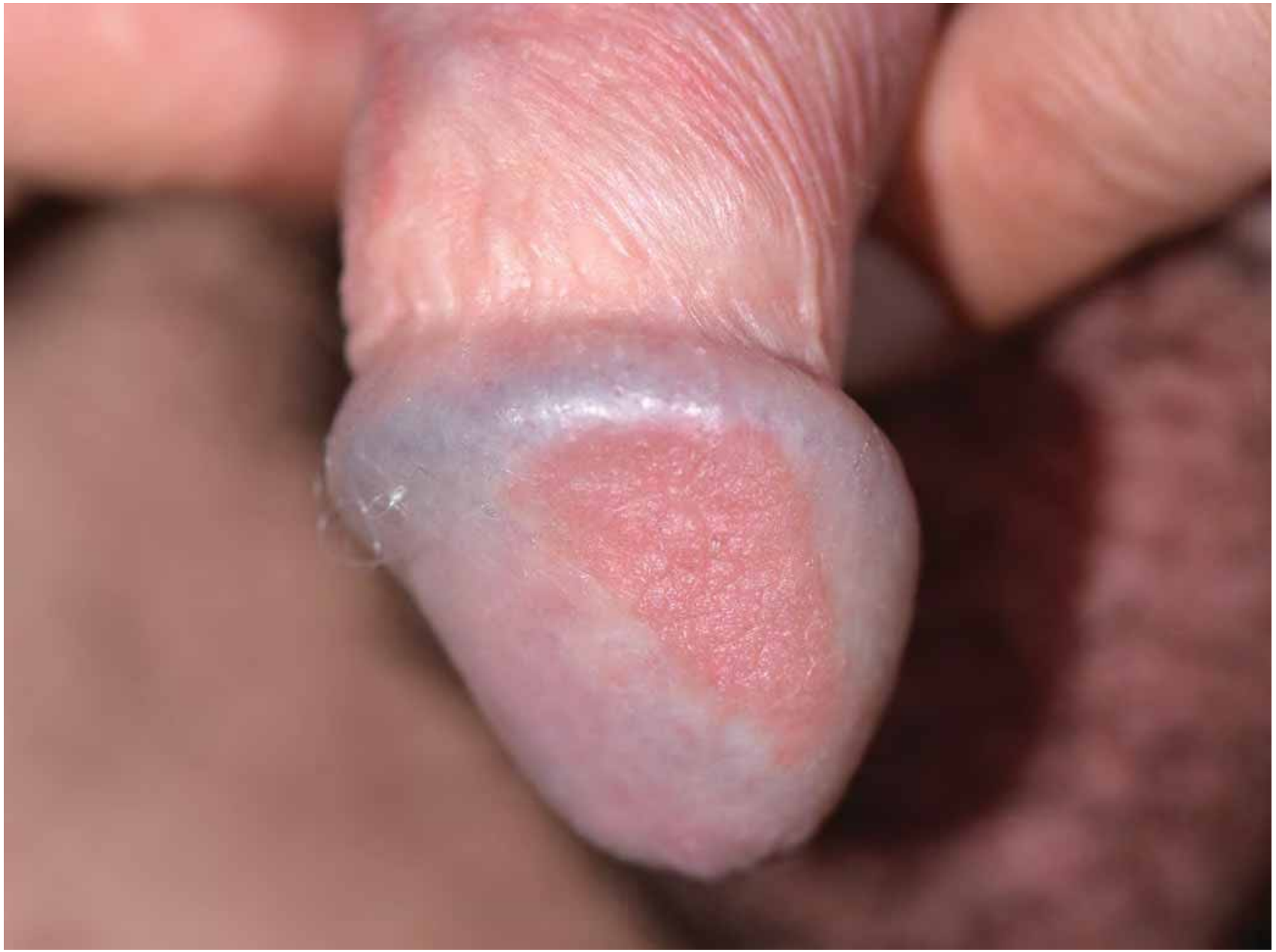


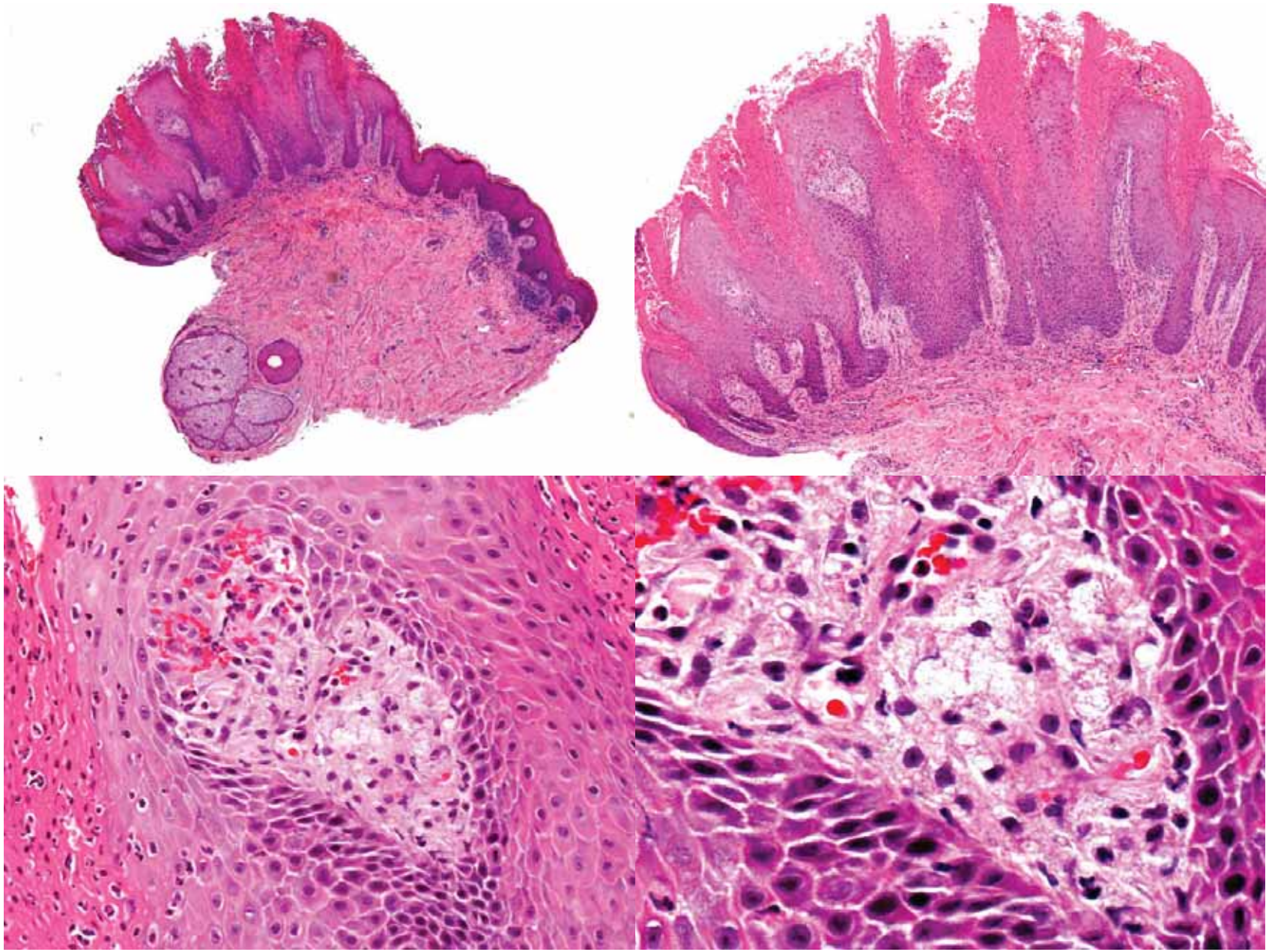


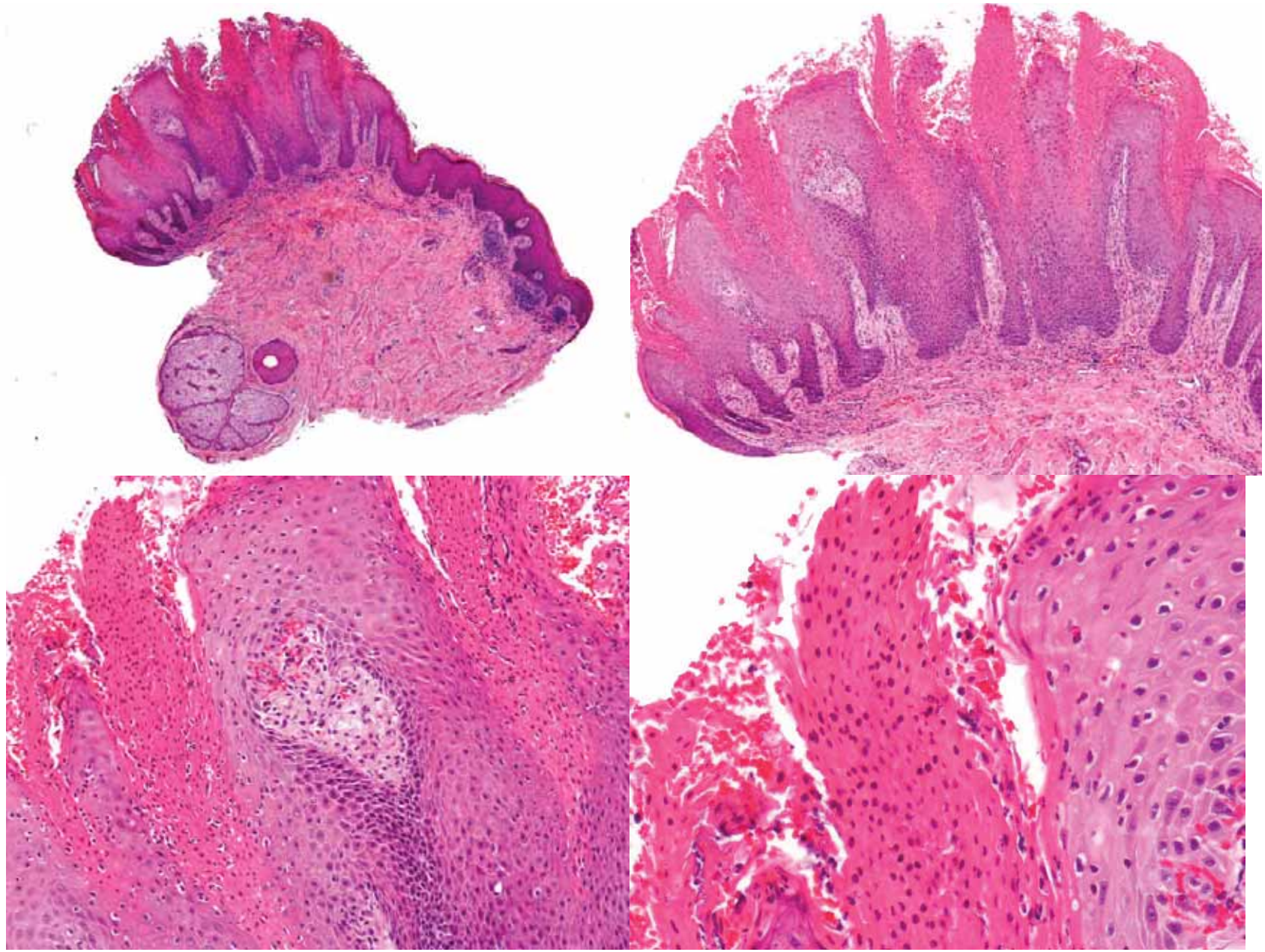












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Acrosyringeal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology

Clinicopathologic review of 29 cases

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Erythema multiforme (EM) is caused by various insults, frequently an infectious agent or a drug. It is current practice that histologic identification of the precipitating factor is not possible. We have observed a pattern of acrosyringeal concentration of keratinocyte necrosis in certain cases of EM and retrospectively studied 29 consecutive cases of EM to establish clinicopathologic correlation for this finding.

Acrosyringeal concentration was observed in 10 of 29 specimens, all 10 clinically drug related (Group 1). Nineteen specimens lacked this pattern (Group 2) of which 3 cases were clinically drug related (sensitivity= 0.8, specificity= 1.0). Eosinophils were present in the dermal infiltrate of 6 specimens from Group 1 and 2 specimens from Group 2 (p=0.025).

Acrosyringeal concentration of keratinocyte necrosis in EM occurs in drug-related cases and is more likely to be accompanied by a dermal inflammatory infiltrate containing eosinophils. Drug concentration in sweat may explain this pattern with subsequent toxic and immunologic mechanisms leading to the fully evolved lesion.

Zohdi-Mofid M, Horn TD. Acrosyringeal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology.
J Cutan Pathol 1997: 24: 235–240. © Munksgaard 1997.

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Accepted September 5, 1996

Erythema multiforme (EM) is a relatively common cutaneous disease that is acute, self-limited and characterized by specific findings in response to many stimuli. The typical clinical lesion consists of concentric erythema with central edema forming a target or bulls-eye appearance (1, 2). Lesions may be widely distributed, but frequently occur on palms and soles. Histopathologically, changes involve both the epidermis and dermis, generally classified as interface dermatitis (1–3). Characteristic features fall within a spectrum of changes coinciding with stages of clinical presentation and site of sampling within the individual lesion with some combination of dermal lymphocytic inflammation, vacuolar change of the basal epidermis, flattening of basal keratinocytes, exocytosis of lymphocytes into the epidermis, and scattered necrotic keratinocytes at several epidermal levels (1–5).

Controversy exists over whether EM, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are in fact different diseases or points on a continuous spectrum. To clarify this, members of an international panel recently proposed a consensus classification based on the pattern of epidermal detachment and the nature of the skin lesions. They suggested that the spectrum of EM be restricted to patients with detachment below 10% of body surface area with skin lesions described as typical target lesions or raised edematous atypical lesions, with or without mucosal involvement (6). Assier et al. furthermore suggested that there exists a correlation between clinical as-

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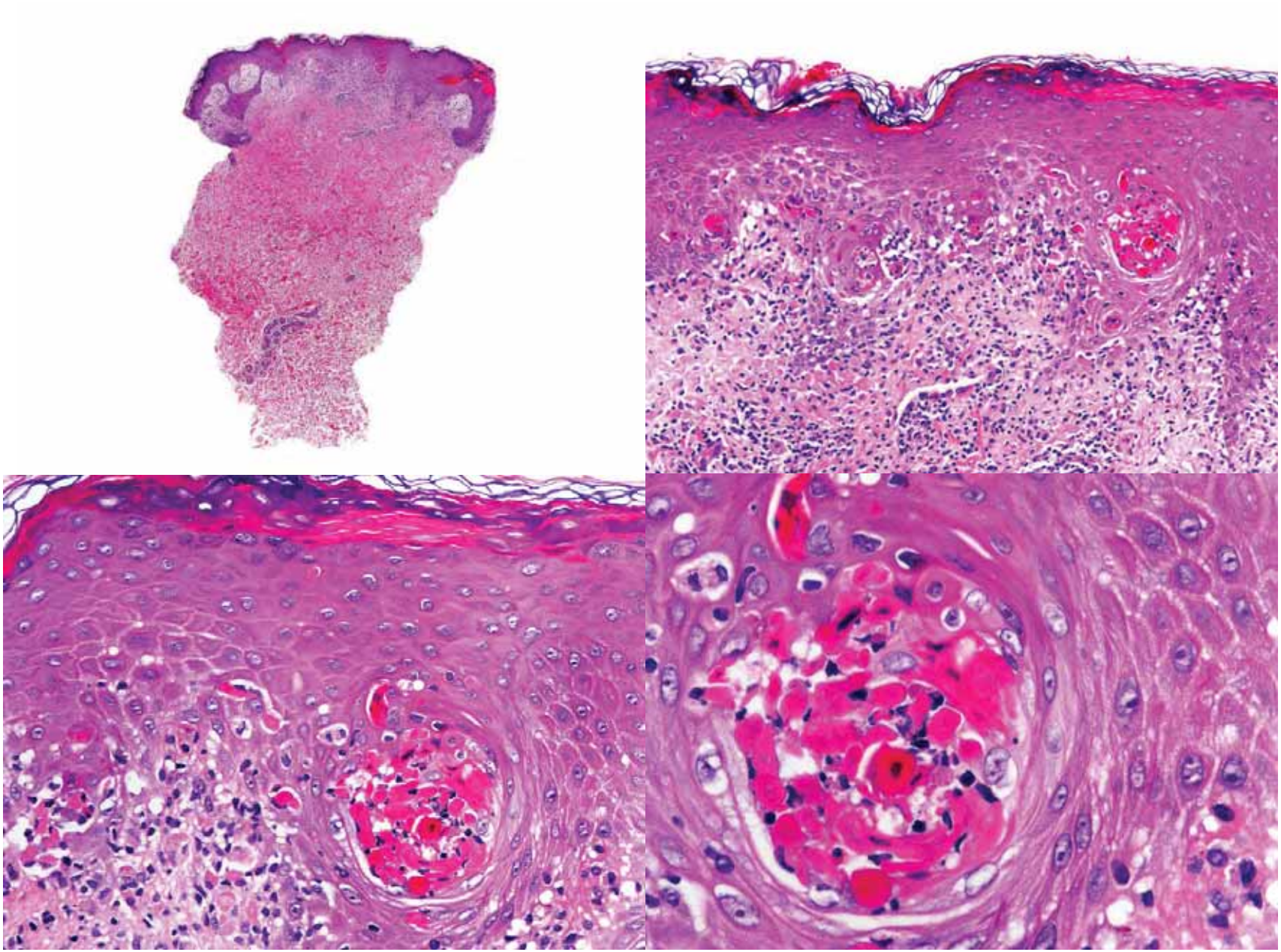

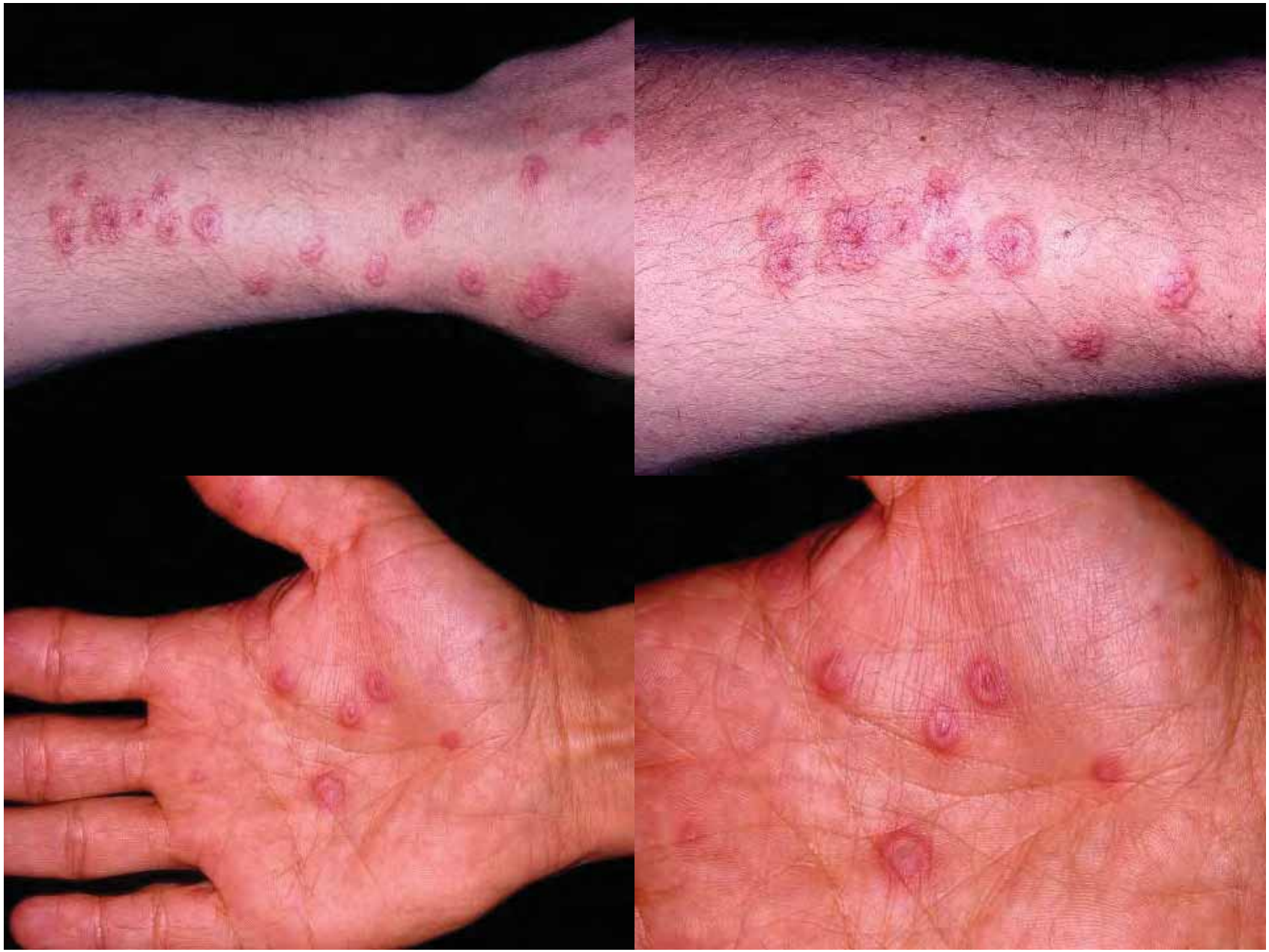

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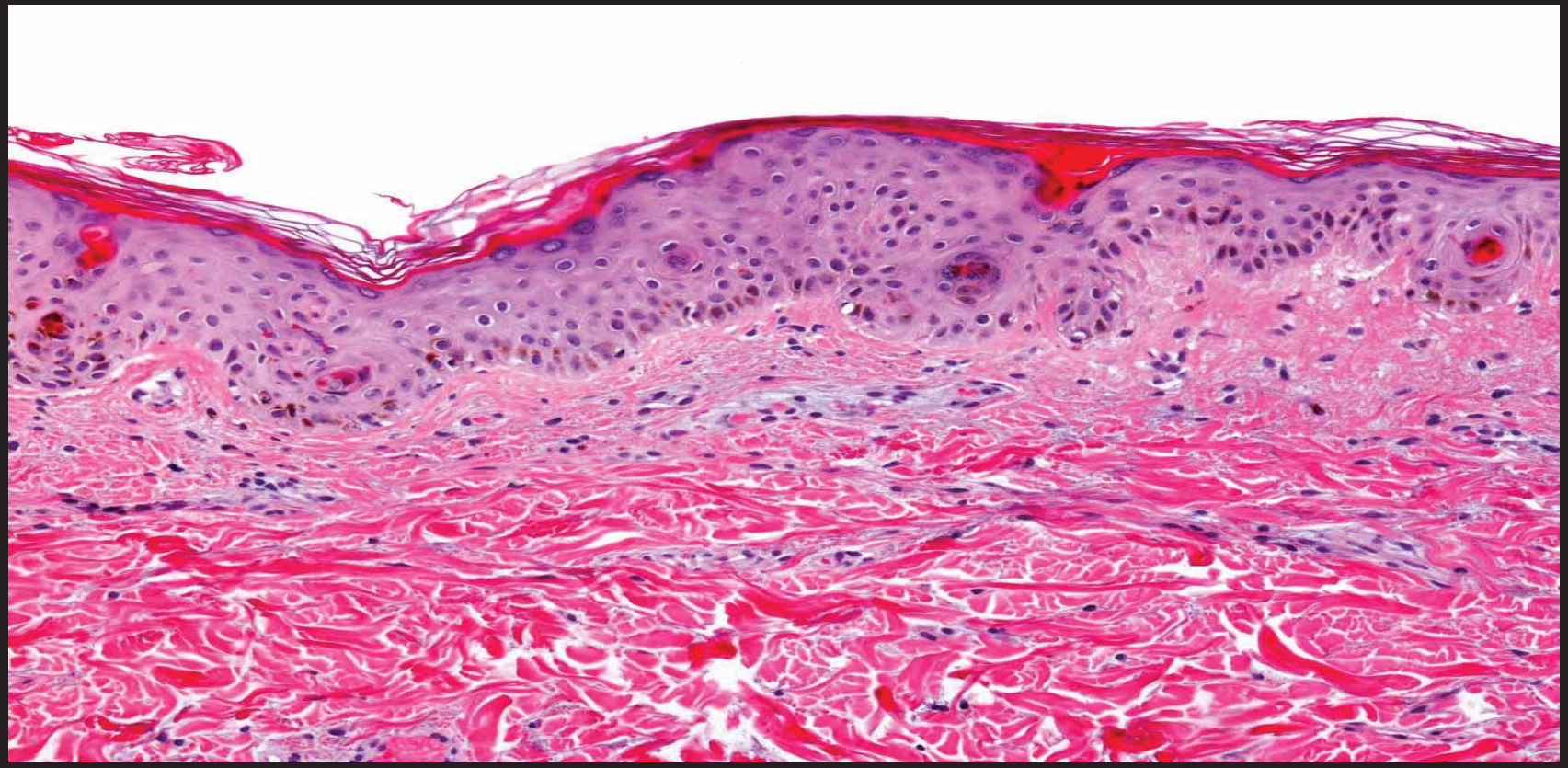
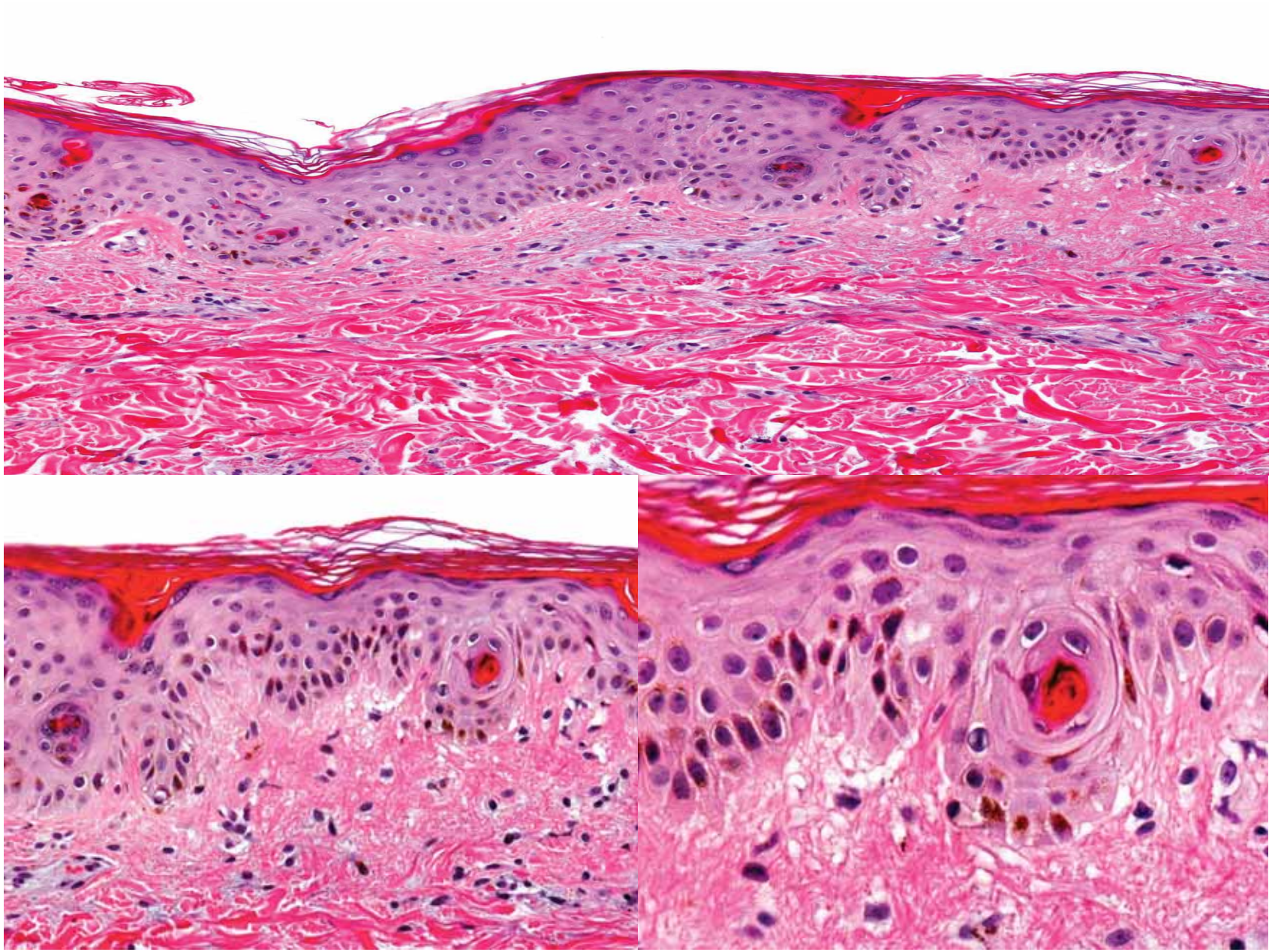
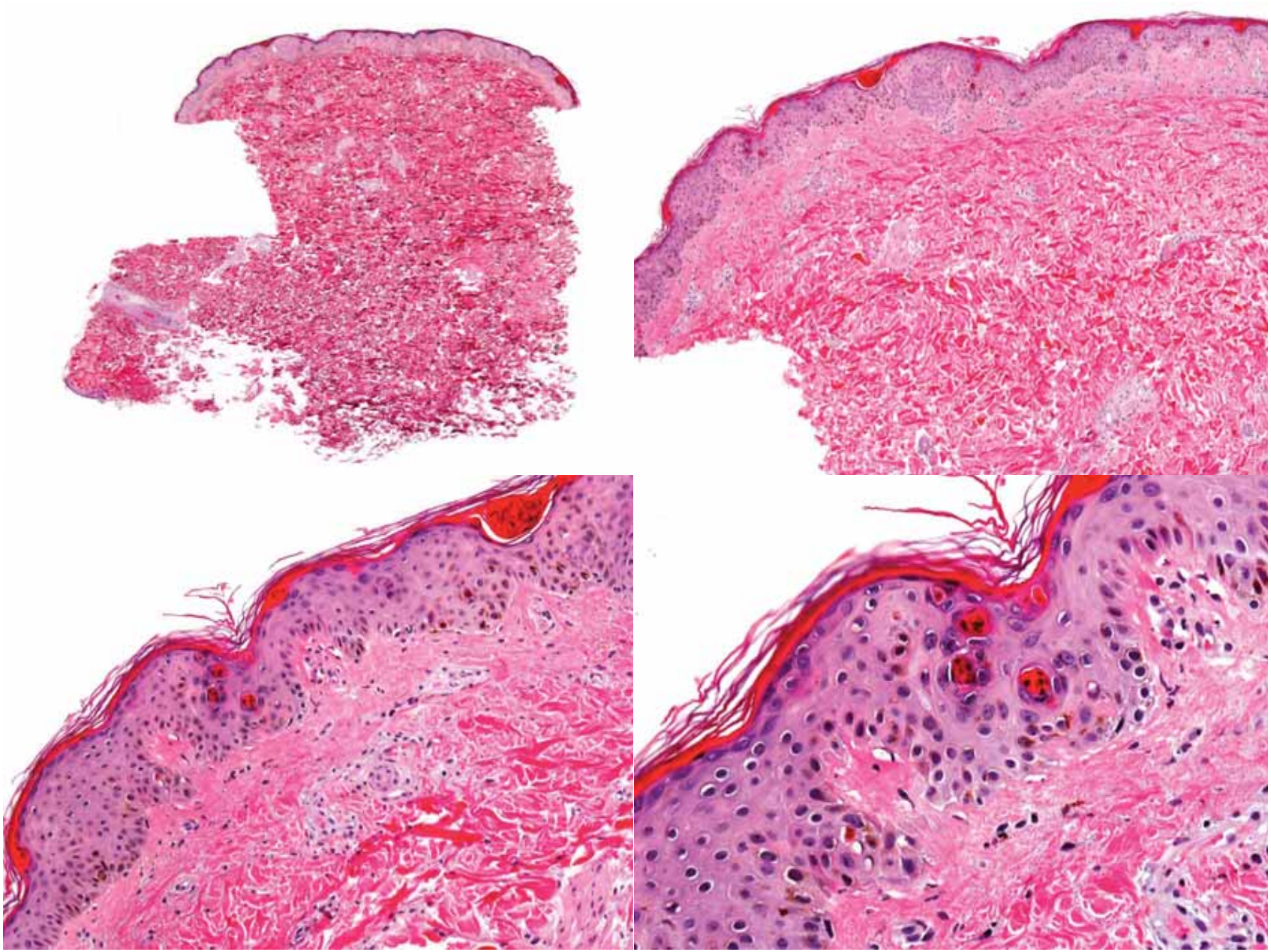
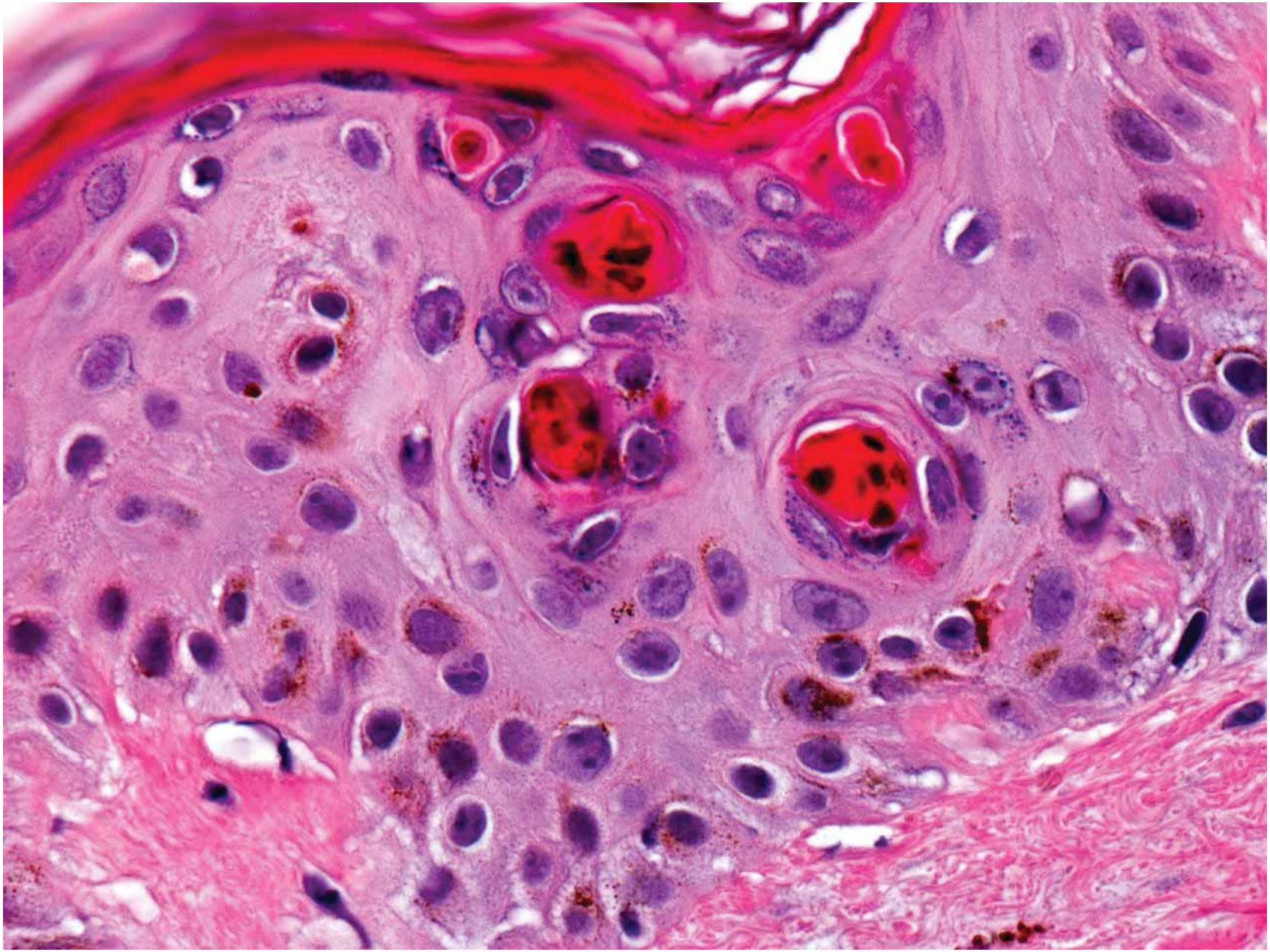


What is the *cliche* and what is the diagnosis?

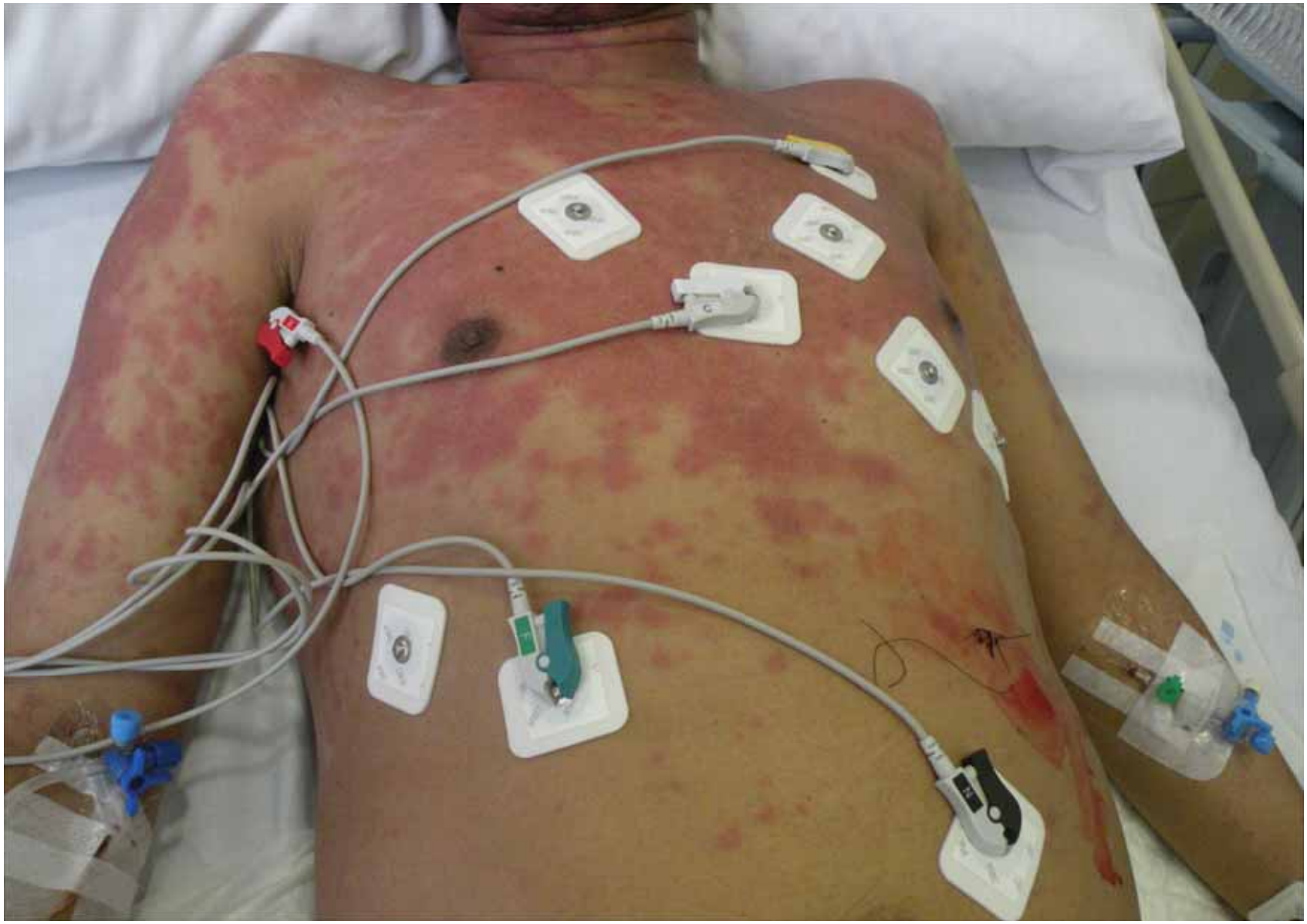


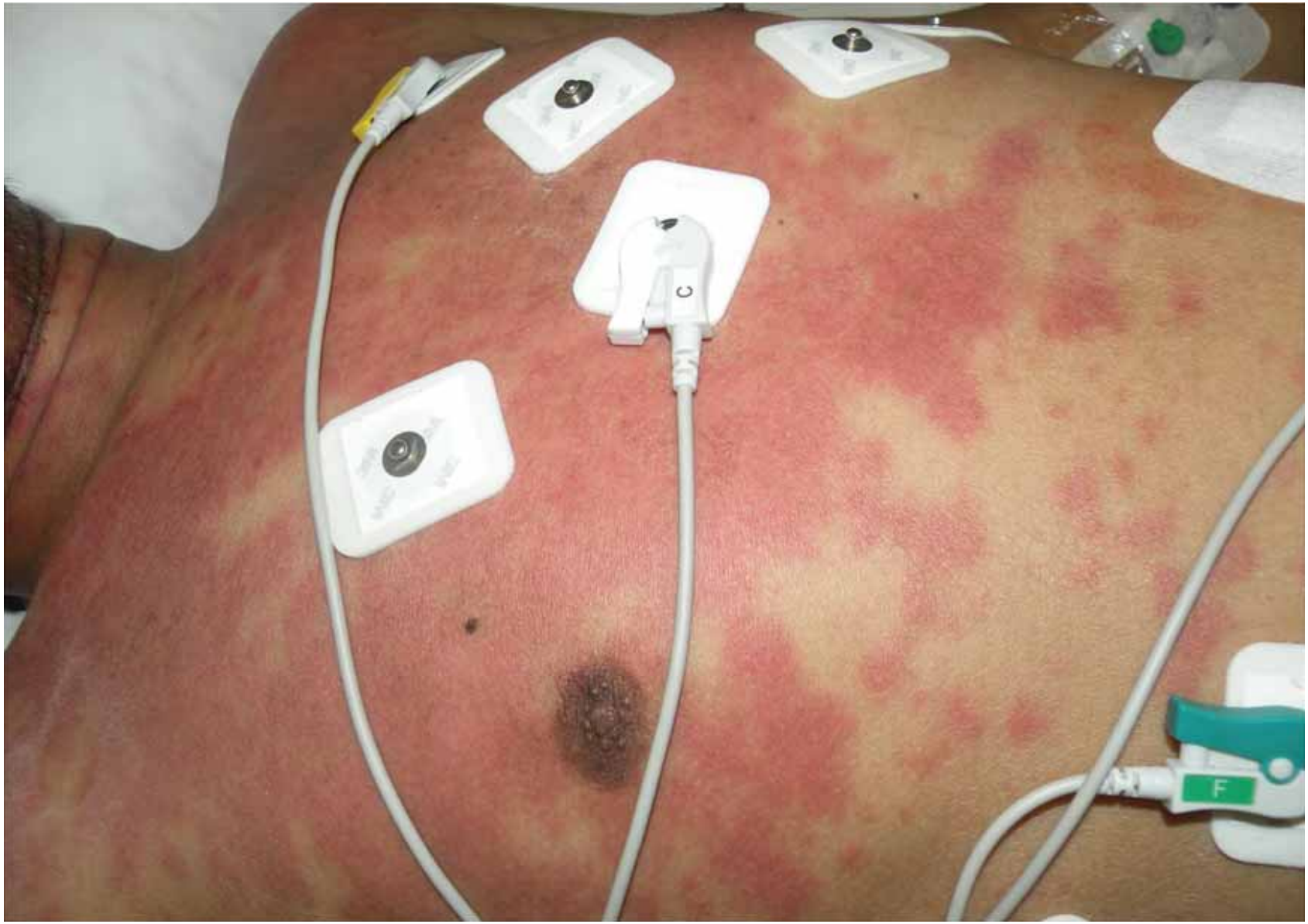




Cliche 12. Clinical history

- A 37-year-old male was diagnosed with systemic lupus erythematosus in 2011 and since then he was taken hydroxychloroquine.
- In April 2013, he presented with fever, cardiogenic shock, pancytopenia, proteinuria of 1.5 gr/24 h, pneumonitis, pleuritis and a cutaneous eruption involving the face, hands and anterior chest.

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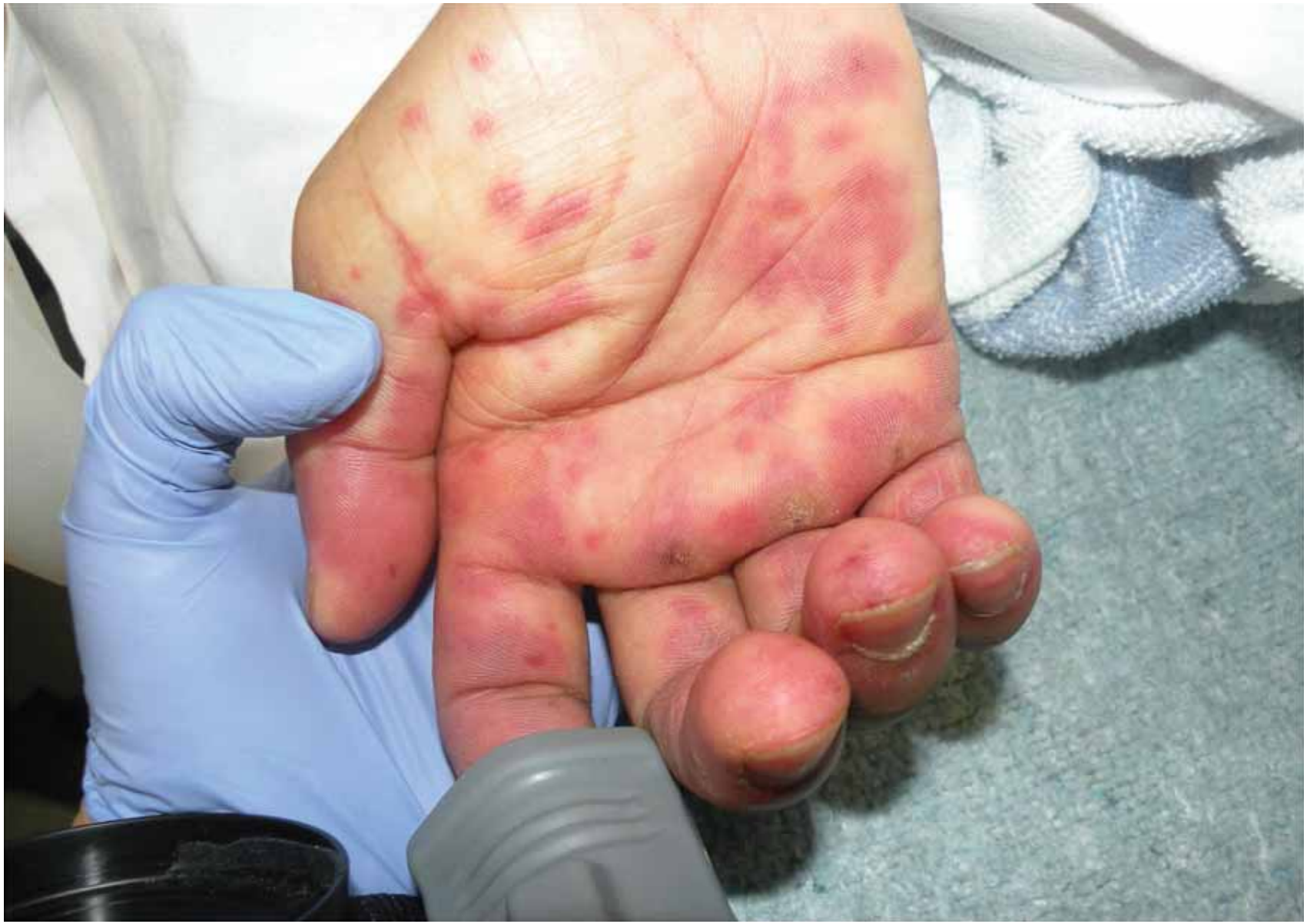
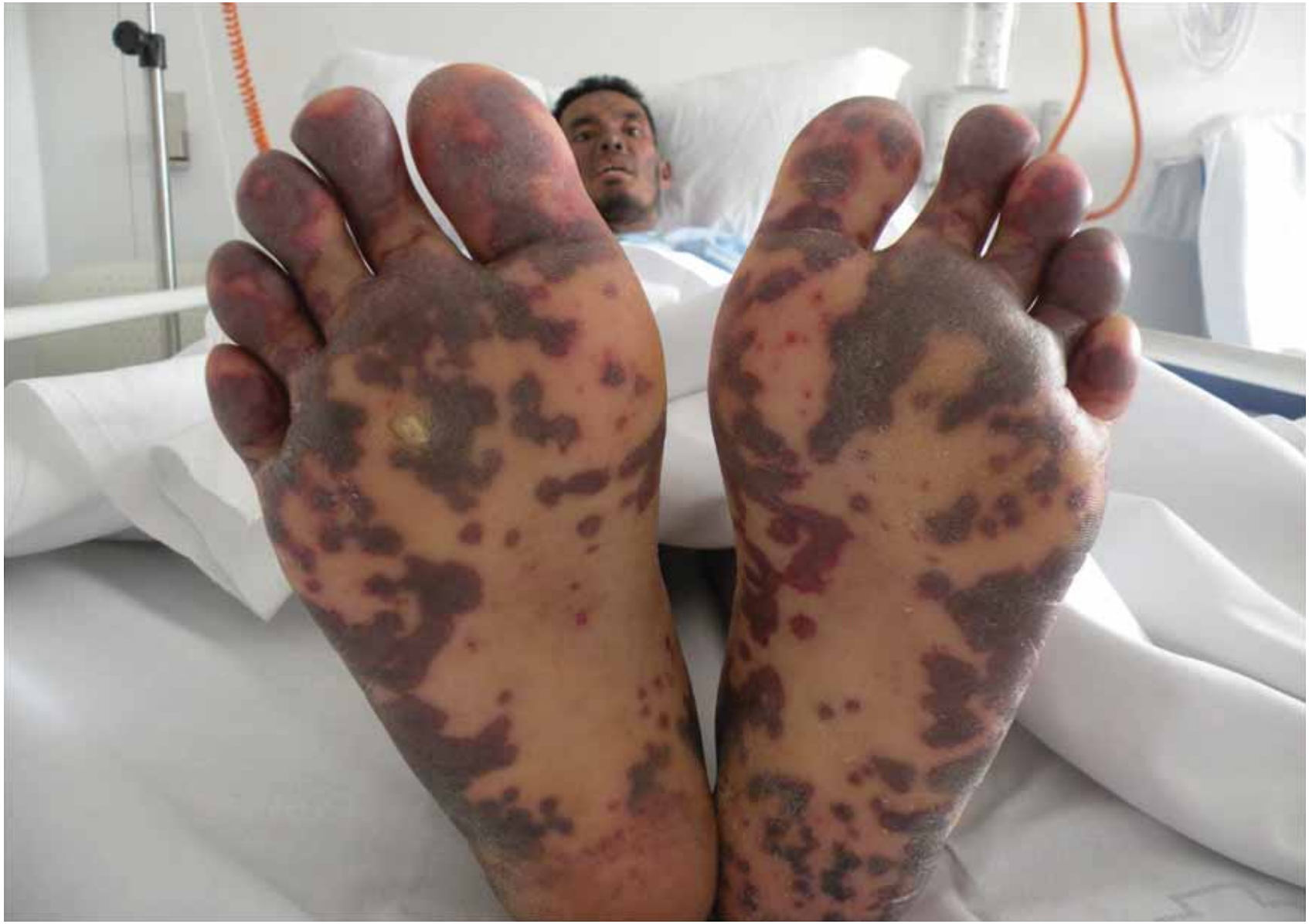
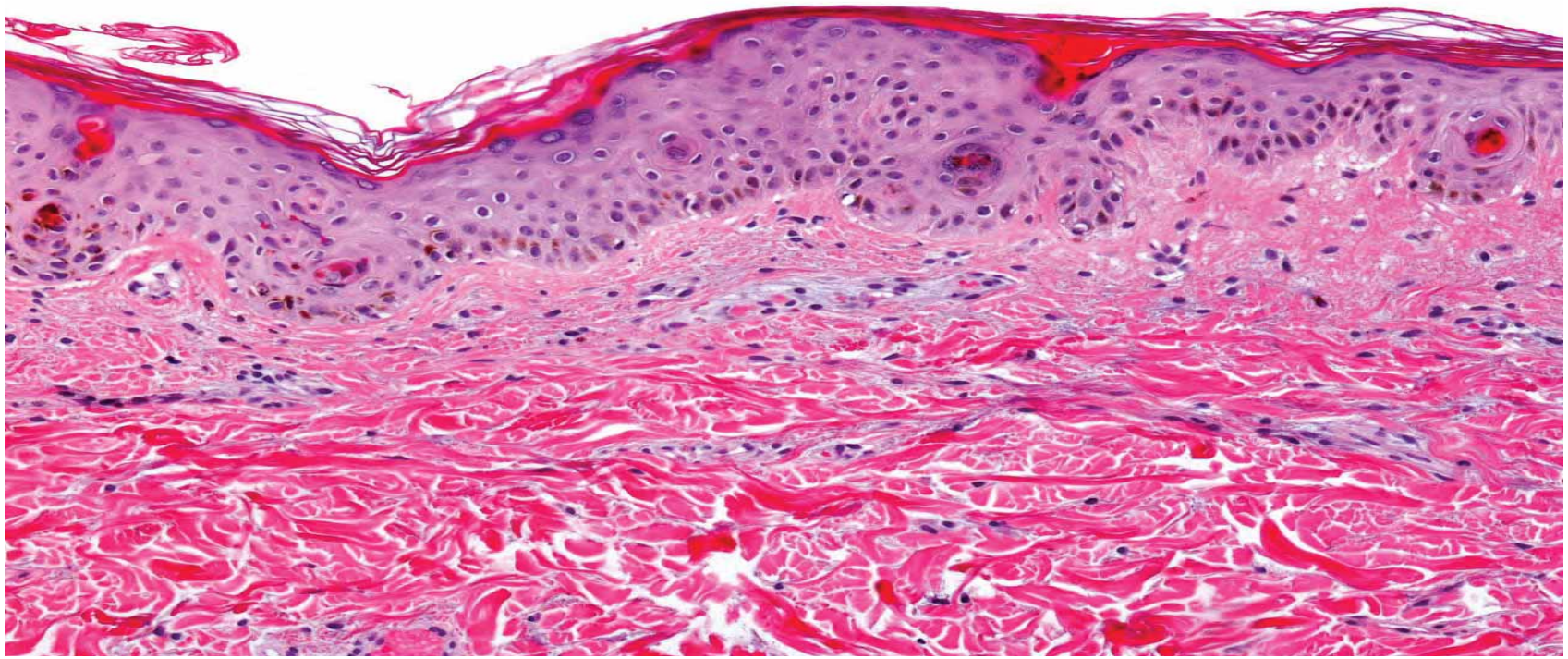
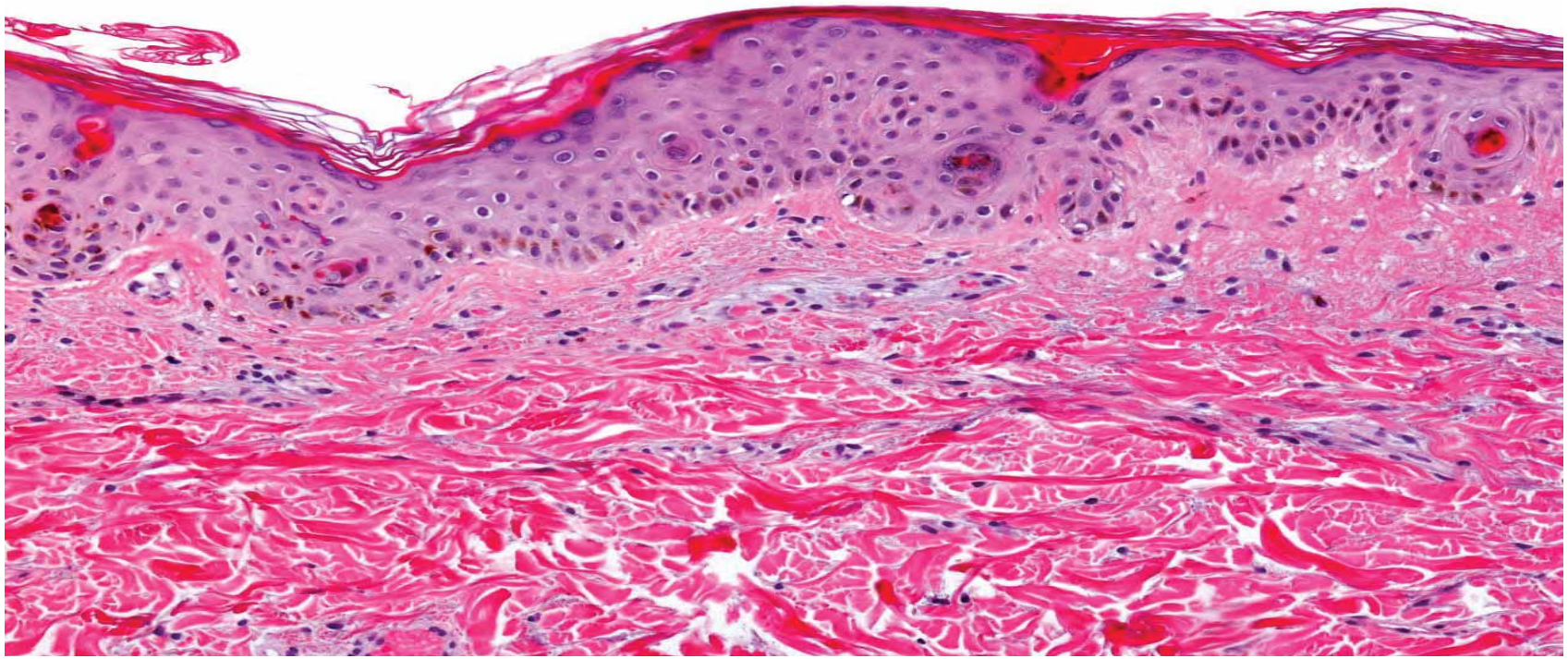






Acrosyringeal concentration of necrotic keratinocytes is a *cliche* to …



Acrosyringeal concentration of necrotic keratinocytes is a *cliche* to systemic lupus erythematosus

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Lupus erythematosus with exclusive involvement of the acrosyringia

Cutaneous lesions of lupus erythematosus (LE) show a broad spectrum of clinicopathologic features. Histopathologically, besides typical patterns such as interface dermatitis, perivascular lymphocytic infiltrate and dermal mucin deposits, an involvement of the eccrine structures, especially the acrosyringium, may be observed. We describe the case of a 21-year-old woman with a 4-year history of systemic LE, who presented with a 'butterfly' rash over the cheeks as well as erythematous macules on the arms and décolleté. Biopsy from one lesion on the arm revealed interface changes, necrotic keratinocytes and exocytosis of lymphocytes restricted only to the regions of the acrosyringia. The epidermis between affected acrosyringia was normal with no hints of interface dermatitis. The eccrine glands and coils were not affected. In the dermis there were only sparse inflammatory infiltrates. Differential diagnoses such as erythema multiforme, drug eruption and lichen planus could be ruled out because of histopathologic features and clinical presentation. This is an example of a peculiar histopathological variant of cutaneous LE, characterized by exclusive involvement of the acrosyringia. The histopathologic features represent a pitfall in the diagnosis and can be correctly interpreted only upon correlation with clinical data.

Fried I, Wiesner T, Cerroni L. Lupus erythematosus with exclusive involvement of the acrosyringia.
J Cutan Pathol 2010; 37: 91–93. © 2009 John Wiley & Sons A/S.

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Cutaneous Lupus Erythematosus With Histopathologic Changes Restricted to the Acrosyringia

Claudia Bernárdez, MD, Lara Vallés, MD,* Carlos Santonja, MD,† and Luis Requena, MD**

Abstract: Cutaneous lupus erythematosus may present as an isolated condition or as part of a systemic disease, being acute cutaneous lupus erythematosus, the skin manifestation, more closely related to systemic involvement. The histopathologic findings may show a wide variety of features, which show overlap among different clinical presentations. The exclusive involvement of the eccrine units, including eccrine coils, dermal ducts, and acrosyringia is extremely uncommon. We present the second case of systemic lupus erythematosus (SLE) with histopathologic involvement mostly located in the acrosyringia. The patient was a 37-year-old male with multiorgan failure who, in the context of flare-up of SLE, presented cutaneous lesions consisting of erythematous and edematous macules and plaques on the face, arms, and anterior chest. Histopathologic examination demonstrated necrotic keratinocytes confined to the acrosyringia as the main finding. It was associated with sparse inflammatory infiltrate in the superficial dermis, mostly composed of lymphocytes. The epidermis between the acrosyringia was spared. Our case was clinically almost identical to the one previously described, being a patient with a severe SLE and widespread cutaneous involvement and receiving treatment in the intensive care unit. The main differential diagnosis, both clinically and histopathologically was drug-related erythema multiforme. Clinicopathologic correlation is necessary to establish a correct diagnosis. SLE with histopathologic involvement mostly of the acrosyringia is a rare histopathologic variant of the disorder.

Key Words: systemic lupus erythematosus, acrosyringia, acute cutaneous lupus erythematosus

(*Am J Dermatopathol* 2014;36:994–996)

INTRODUCTION

Lupus erythematosus (LE) is a frequent autoimmune disorder that may present a wide spectrum of clinicopathologic manifestations. Cutaneous LE may present as an isolated condition or as part of a systemic disease, being acute cutaneous lupus erythematosus, the most common cutaneous manifestation related to systemic involvement. It usually presents itself as symmetric butterfly-like erythema and edema on the cheeks but may be also a more widespread morbilliform eruption.[1] Histopathologic study of skin lesions remains as the main tool for an accurate diagnosis of cutaneous LE. LE shows a broad spectrum of histopathologic findings, which may be always present or appear related to a specific stage of the lesions. Acute cutaneous lupus erythematosus lesions may exhibit nonspecific findings, such as scattered necrotic keratinocytes at the basal epidermal layer, edema of the upper dermis, and superficial perivascular lymphohistiocytic infiltrate.[2] Involvement of the eccrine units, including eccrine coils, dermal ducts, or acrosyringia has been rarely described.[3]

We present the case of a patient with systemic lupus erythematosus (SLE) and cutaneous lesions with the histopathologic peculiarity of the preferable involvement of the acrosyringia. In the literature, we have only found 1 previously reported similar case.

CASE REPORT

A 37-year-old Philippine male was diagnosed of SLE in 2011. At presentation, he had facial erythema, asthenia, arthralgia, and laboratory findings consistent with SLE (leukopenia due to lymphopenia, positive antinuclear antibodies [repeated positive antinuclear antibodies higher than 1/160]), associated with positive anti-dsDNA antibodies and a skin biopsy showing vacuolar degeneration of the basal layer of the epidermis and reduplication of the basement membrane. He initiated treatment with hydroxychloroquine, 200 mg twice a day.

On April 2013, he consulted to the Emergency Department because of malaise associated with fever and the appearance of cutaneous lesions initially on his face, which later extended to the

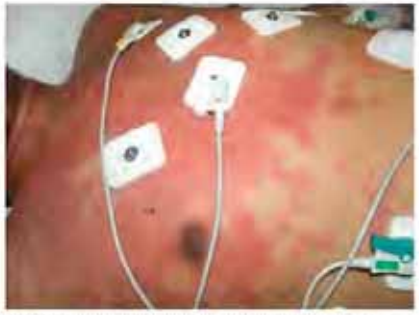

FIGURE 1. Erythematous rash involving the anterior chest.

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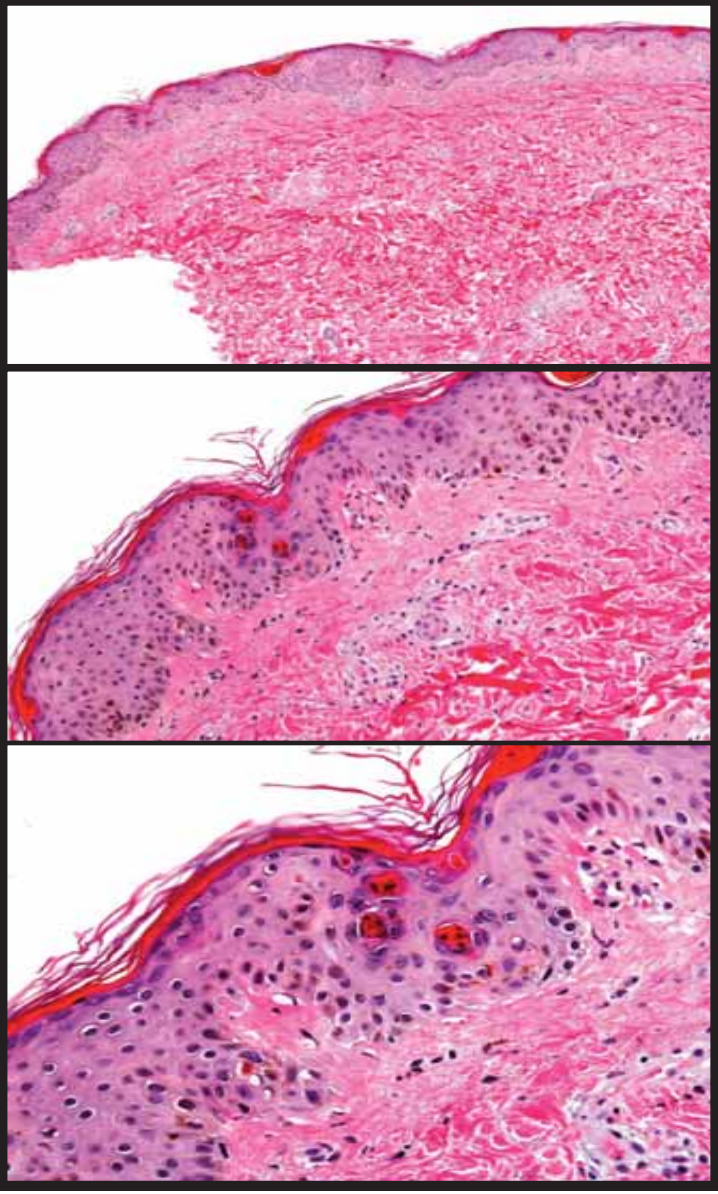
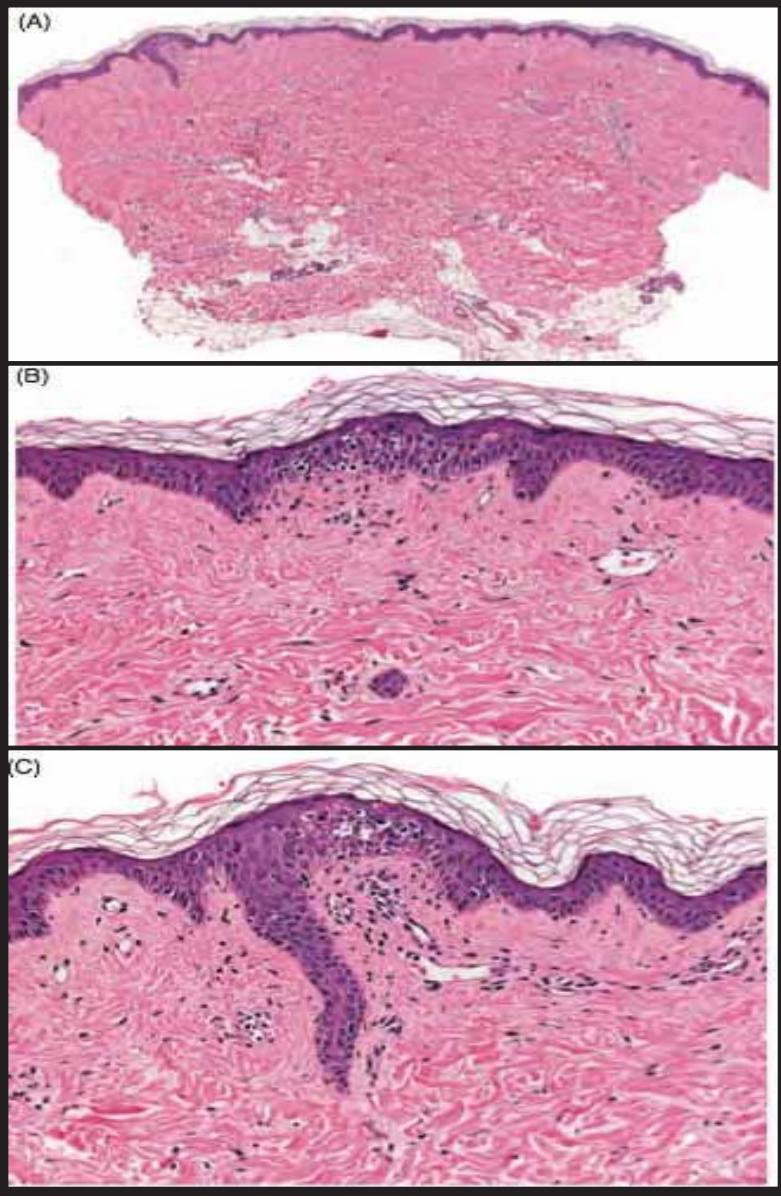
Our case

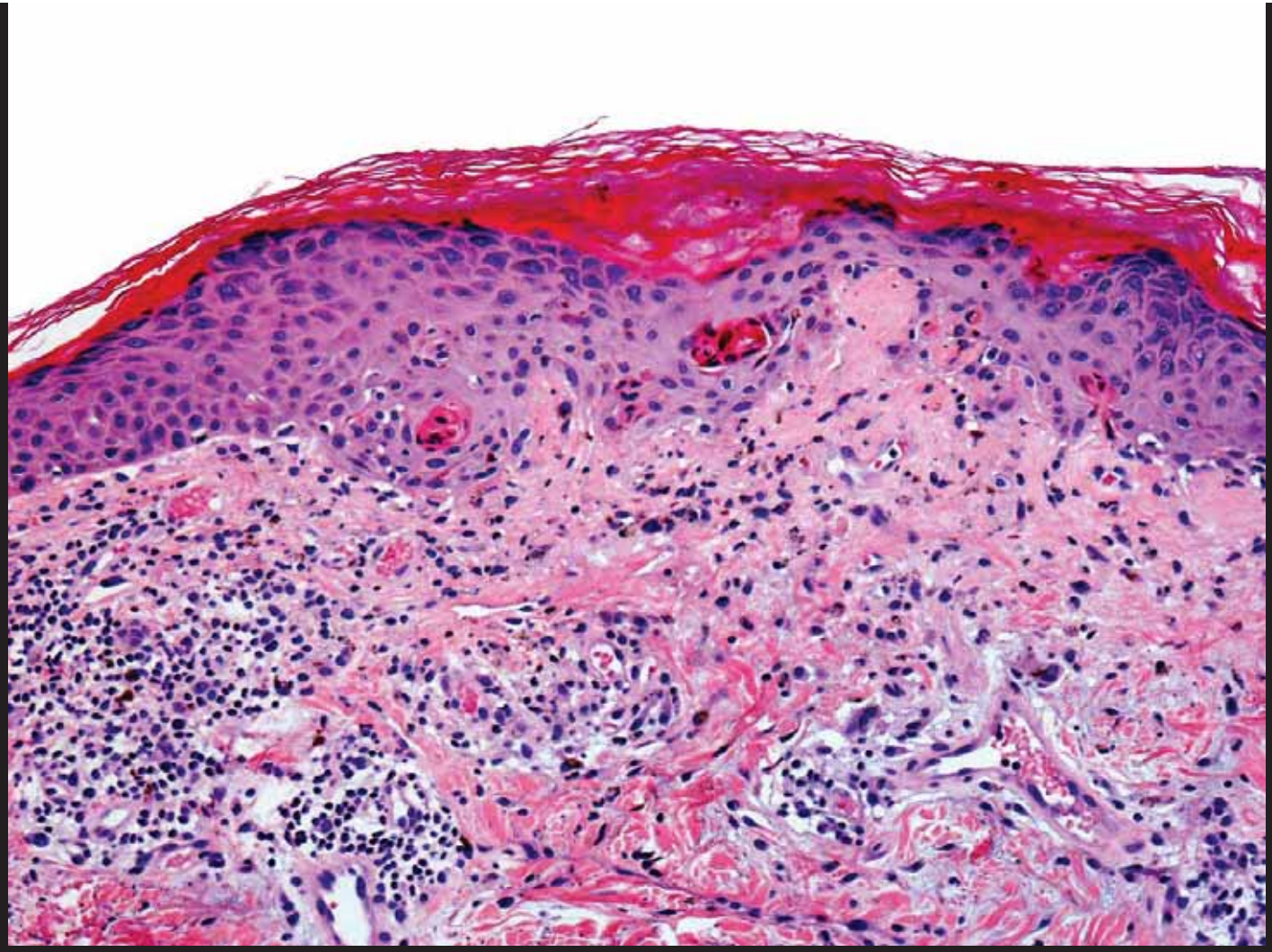


Cerroni's case

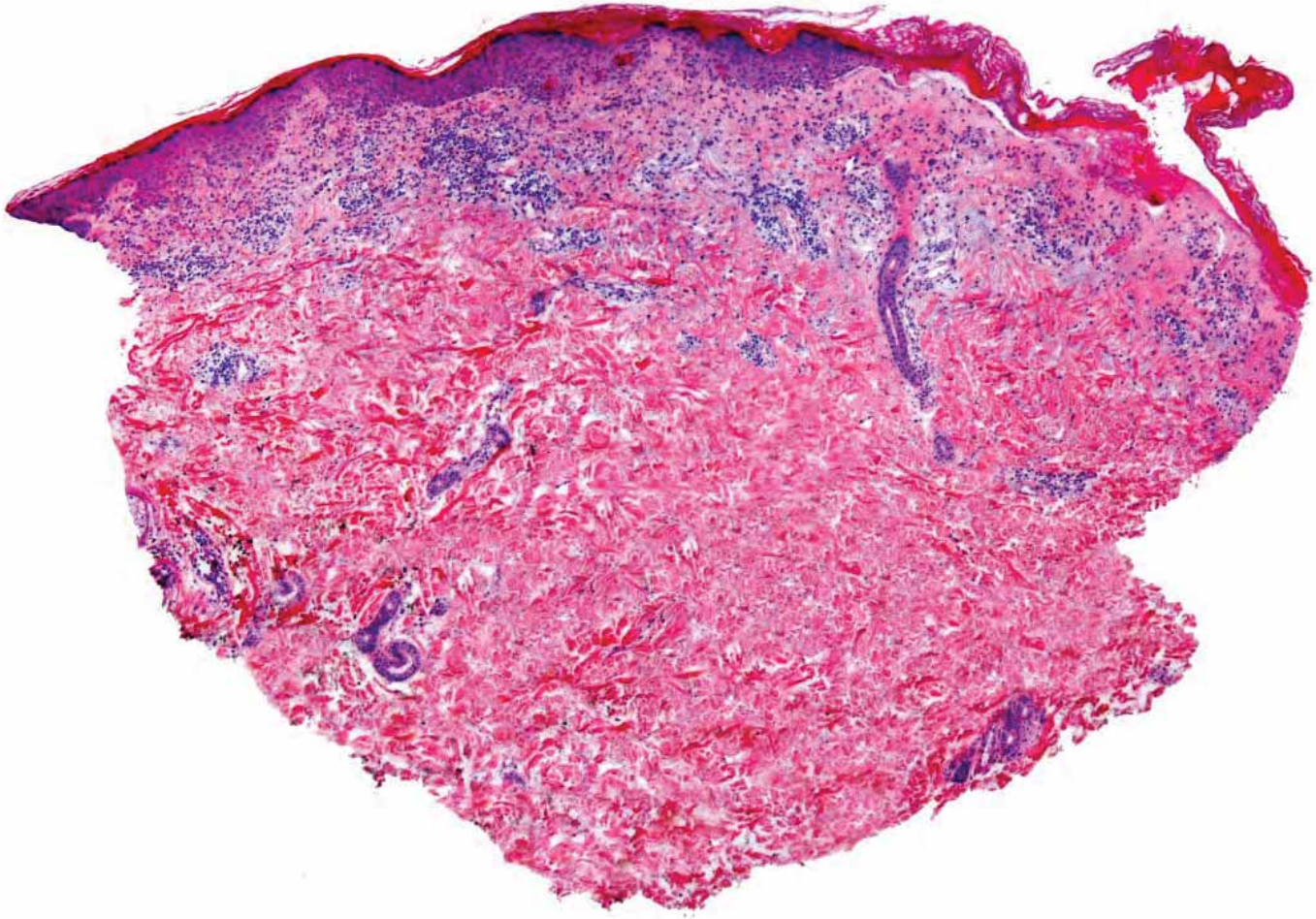


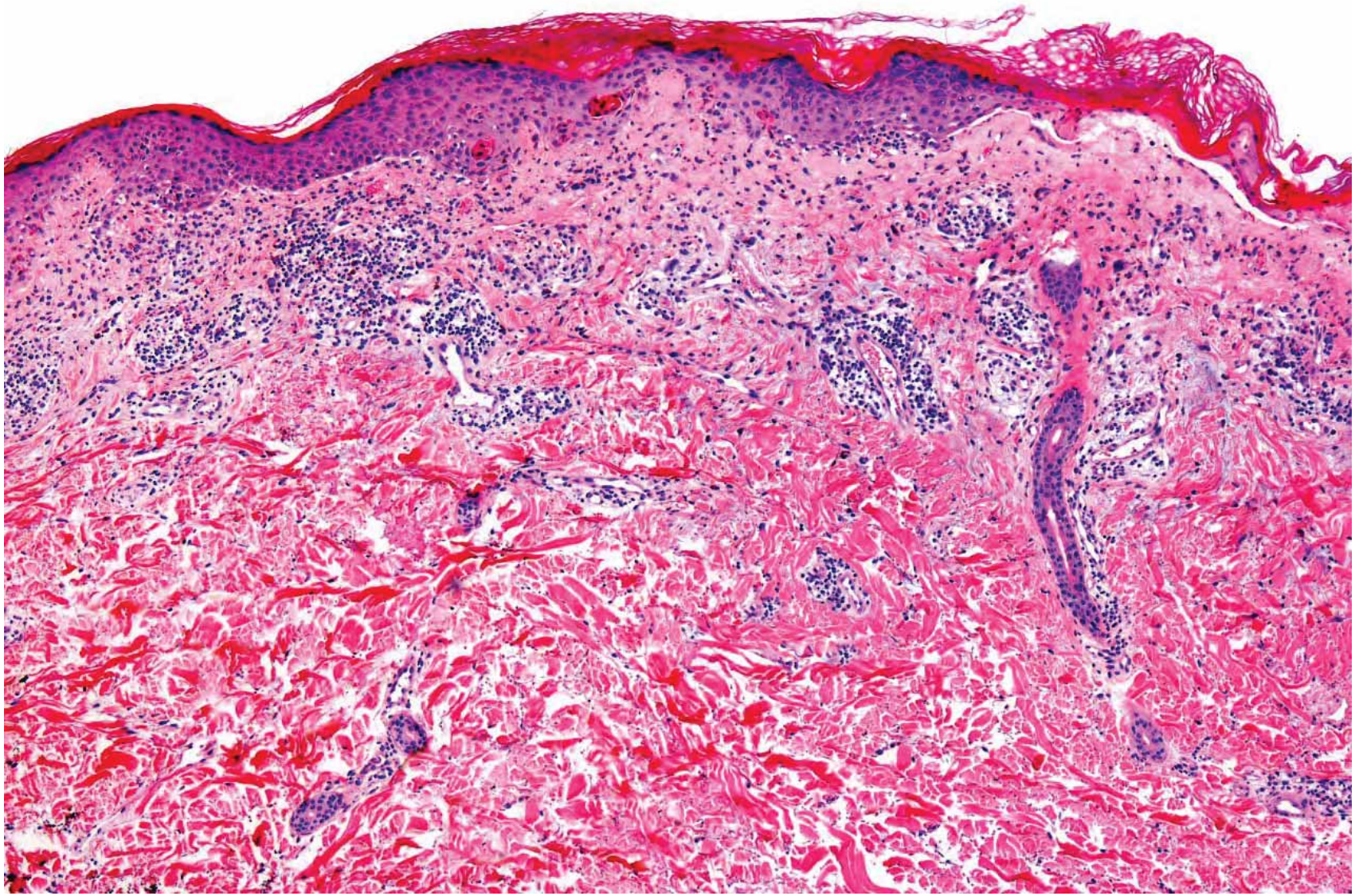
	Our case	Cerroni's case
Sex /Age	Male / 37 years	Female / 21 years
Years of evolution of SLE	2	4
Cutaneous lesions	Facial rash, erythematous plaques on the neck, chest and limbs	Facial rash, erythematous macules on the arms and upper chest
Antibodies	Anti ds-DNA Abs anti-RNP Abs	Anti ds-DNA Abs Anti-RNP and Anti-Sm Abs Antiphospholipid Abs
Involvement	CNS, cutaneous, muscular, skeletal, renal, pulmonar and hematologic	CNS, cutaneous, muscular, skeletal, renal, pulmonar and hematologic
Histopathologic findings	Exclusive involvement of the acrosyringia	Exclusive involvement of the acrosyringia
Follow-up	Recover	Death

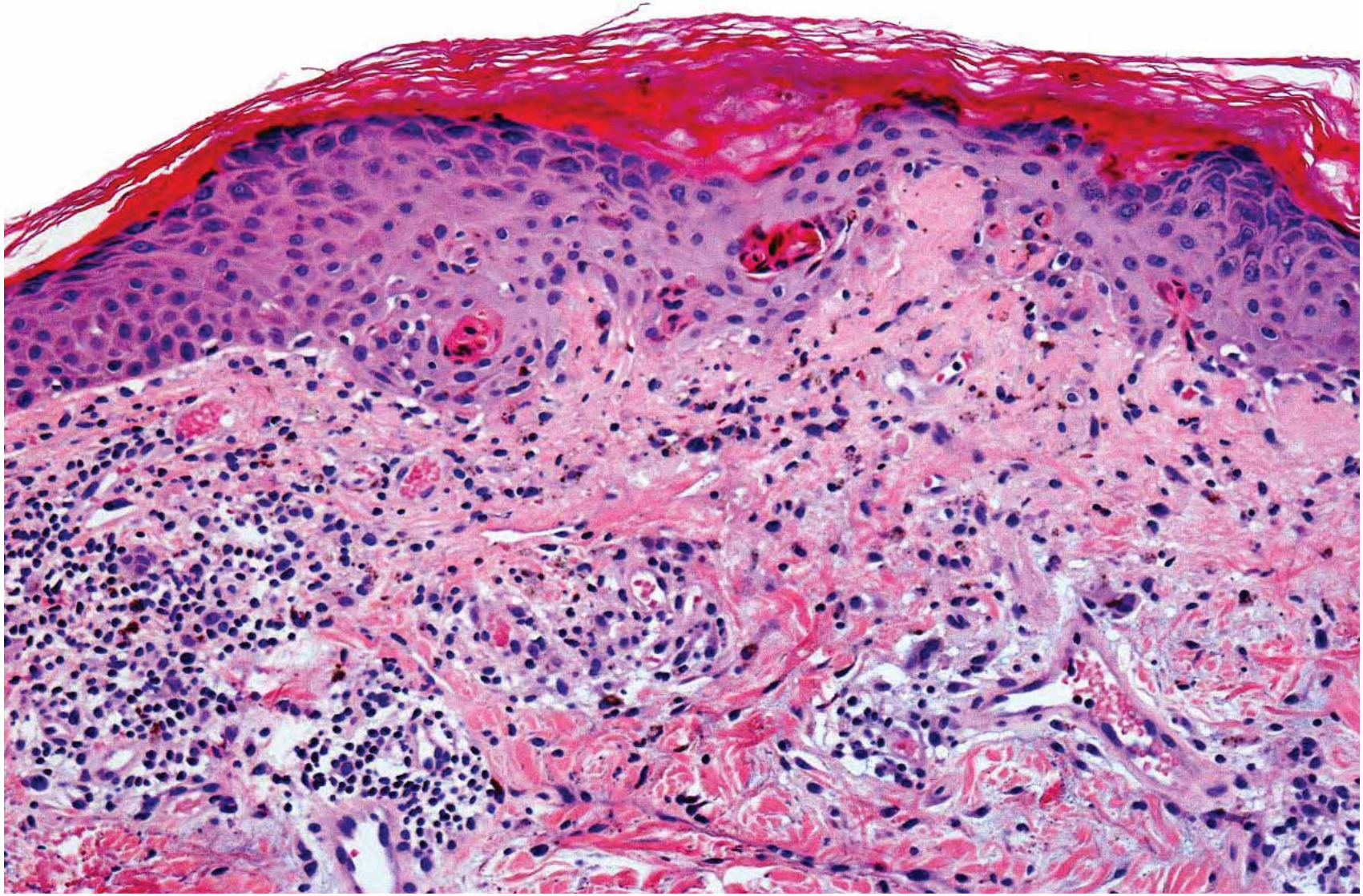
But….

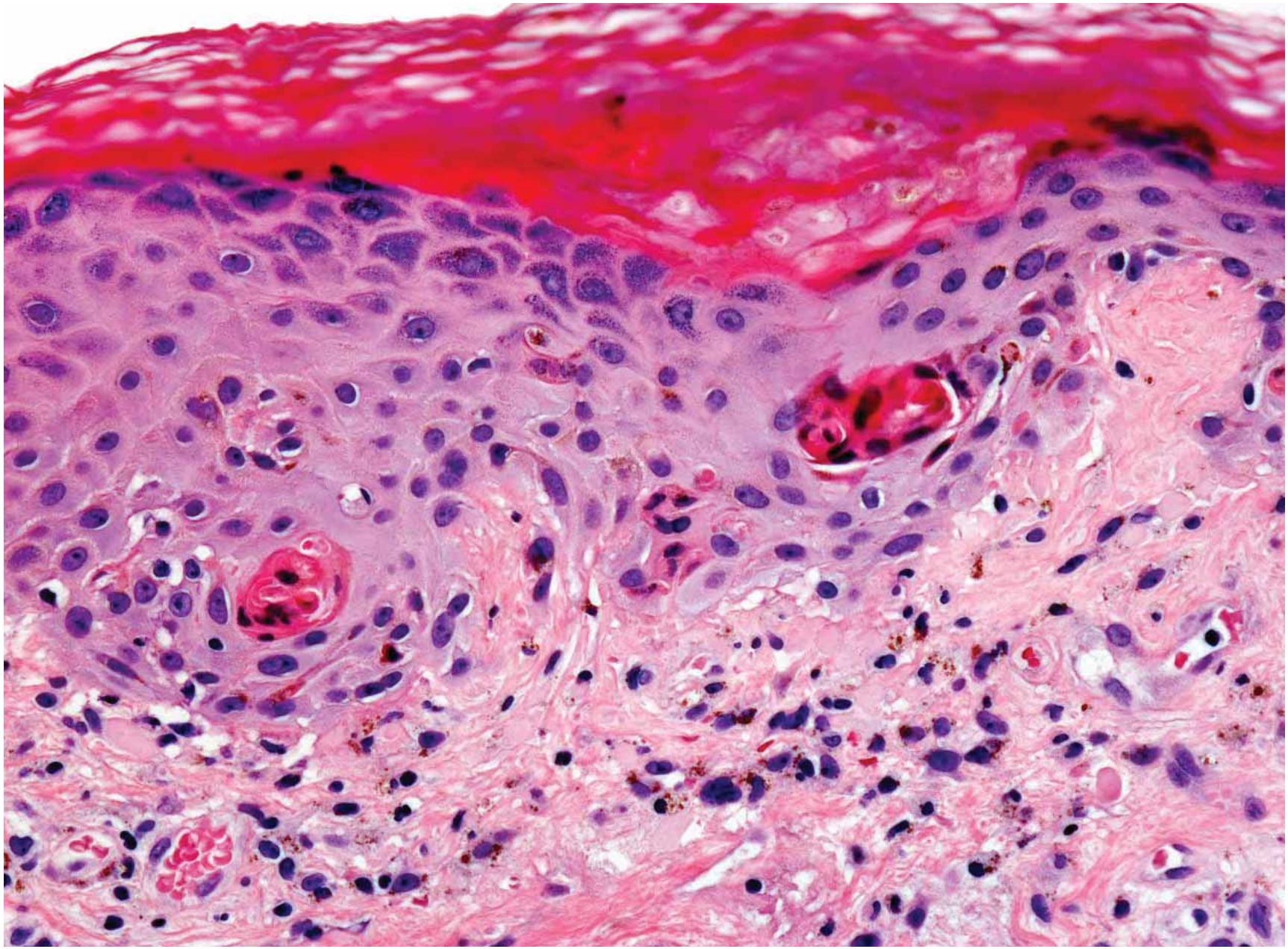


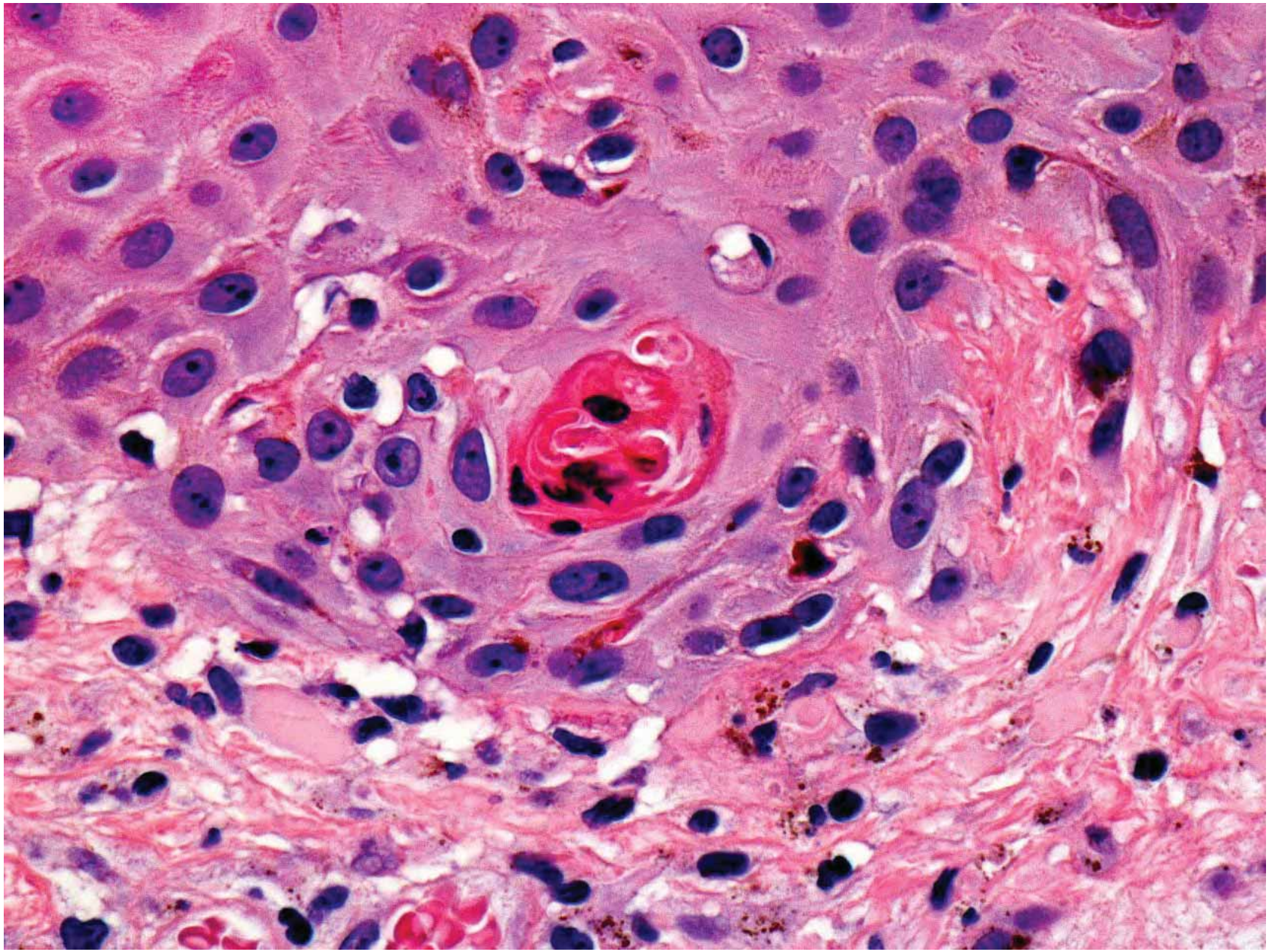
What is the *cliche* and what is the diagnosis?

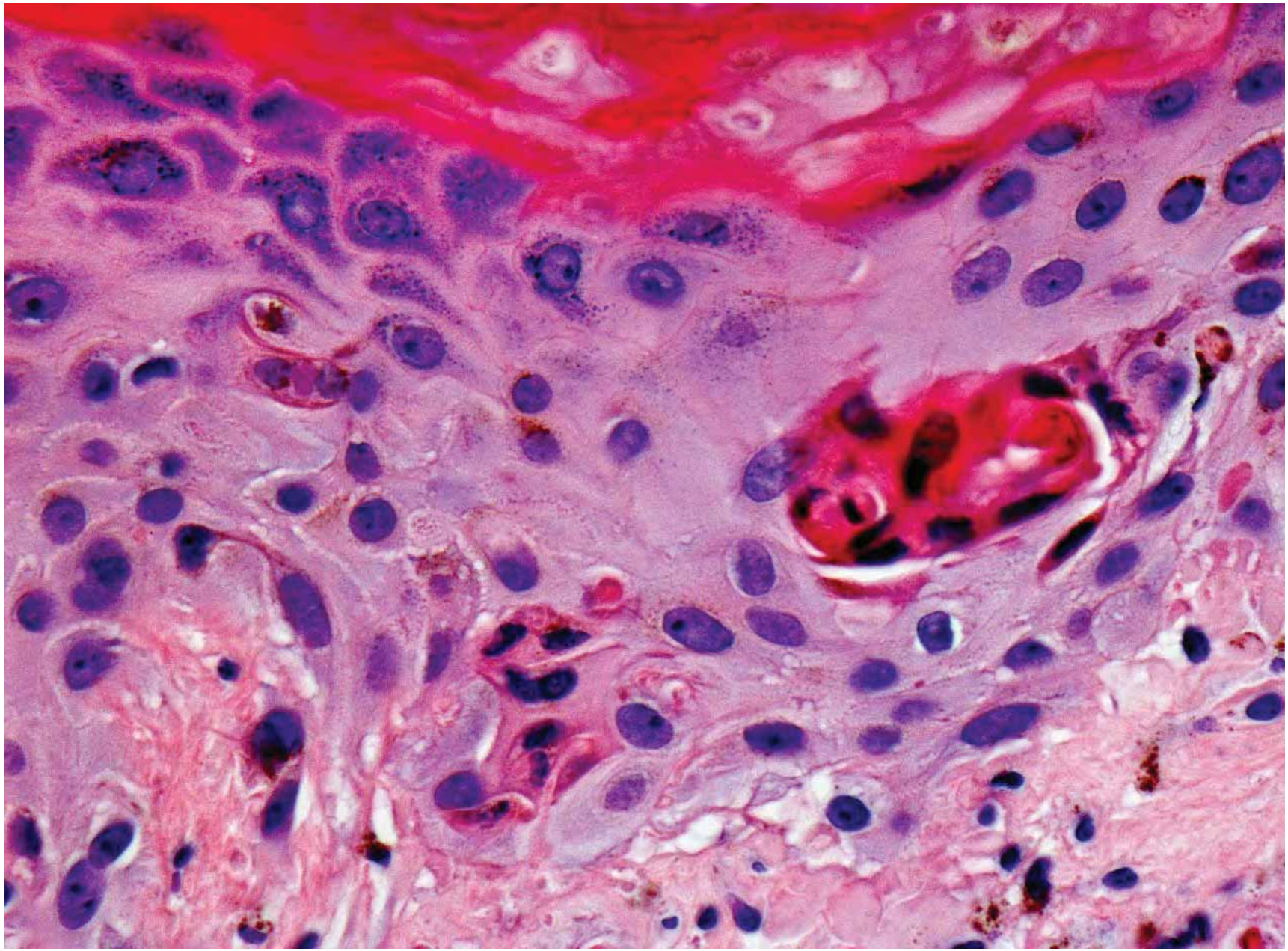


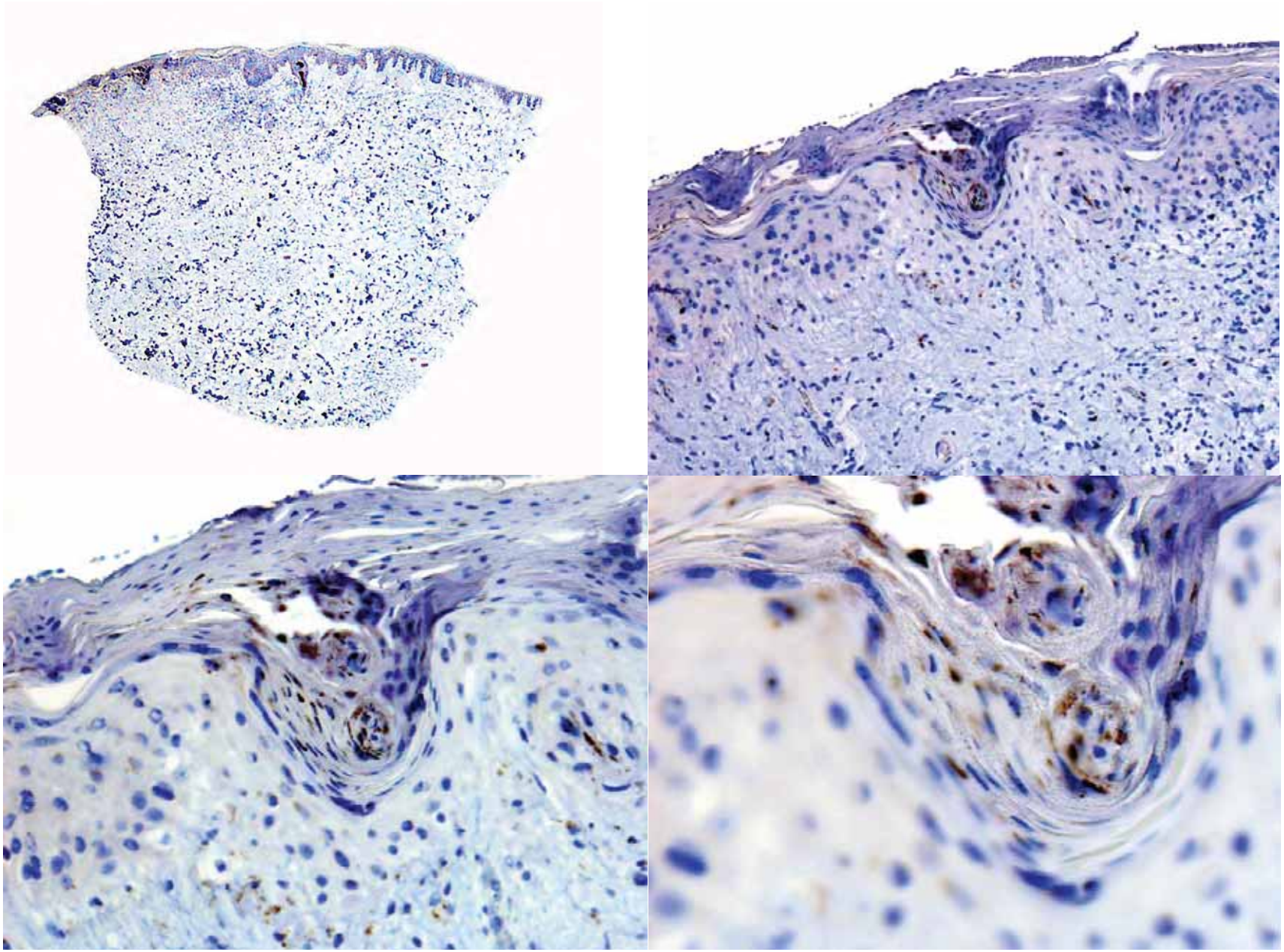












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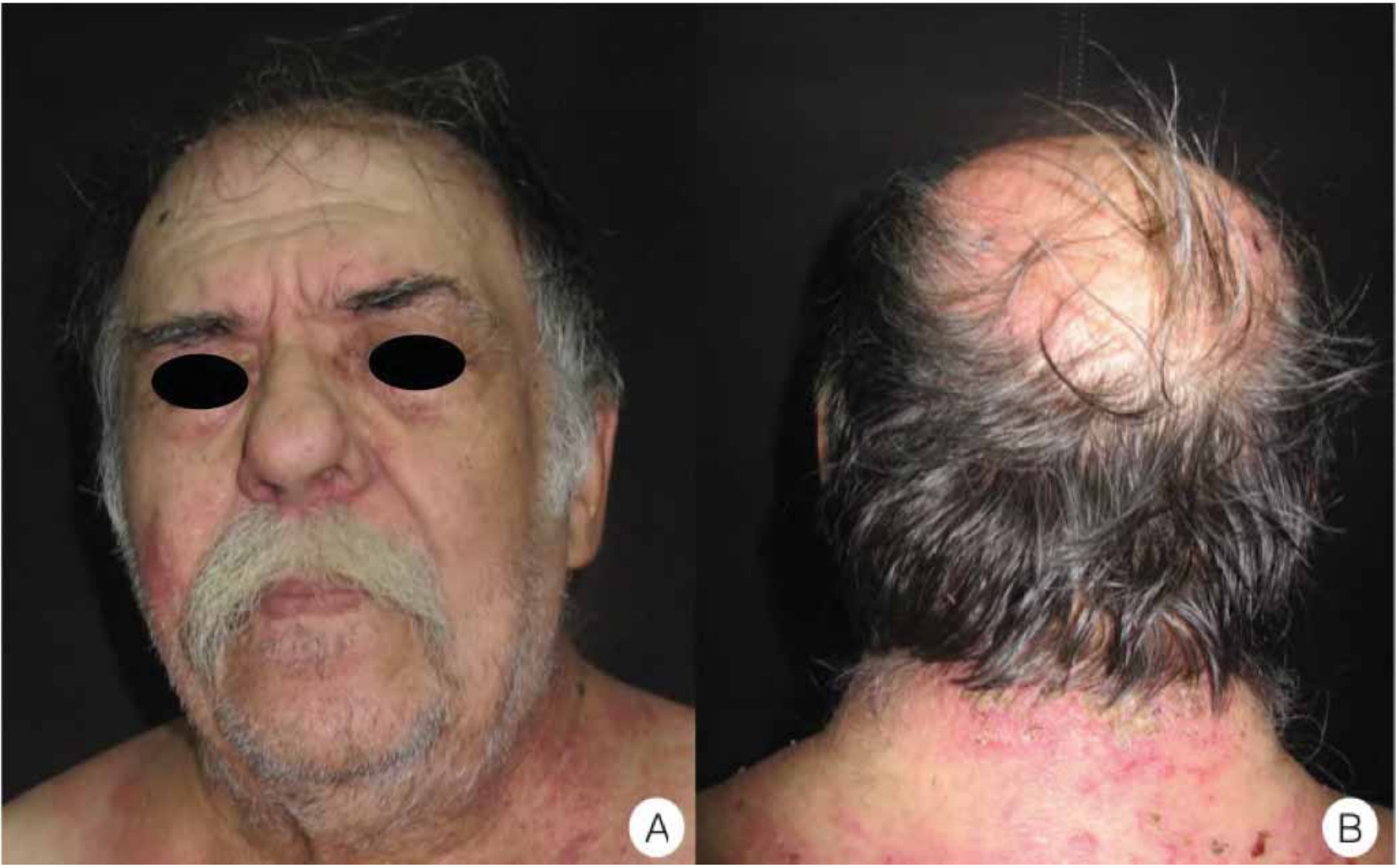
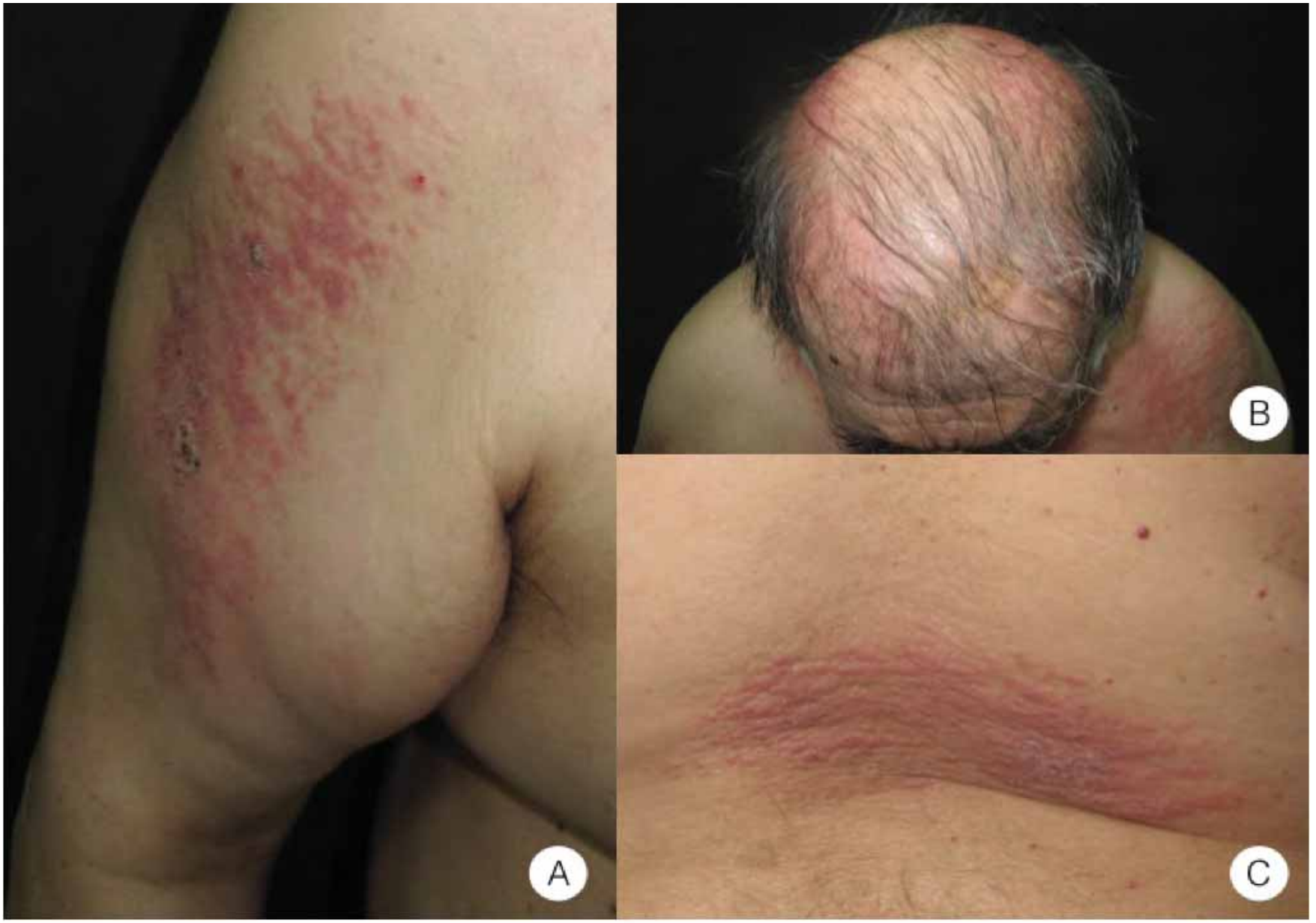


- A 67-year-old male with lung cancer developed muscular weakness and pruritic skin lesions
- Skin biopsy showed interface dermatitis with vacuolar degeneration of the basal layer, dermal mucin deposits, and necrotic keratinocytes in the acrosyringia
- Autoimmunity tests showed positivity for antinuclear antibodies and anti-NXP2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Anti-NXP2–Positive Paraneoplastic Dermatomyositis With Histopathologic Changes Confined to the Acrosyringia

Jose Luis Ramirez-Bellver, MD, Elena Macias, MD,* Claudia Bernárdez, MD,* Joaquin López-Robles, MD,* Maria del Carmen Vegas-Sánchez, MD,† Jose Luis Díaz-Recuero, MD,* Hernán Quiceno, MD,‡ and Luis Requena, MD**

Background: Paraneoplastic syndromes consist of a group of disorders that are not related to the extension of the primary tumor or its metastases and that might be the first manifestation of a hidden neoplasm. It is a well-known association between dermatomyositis (DM) and cancer, especially gynecological tumors in women and lung cancer in men.

Methods: We describe the case of a 67-year-old male who developed muscular weakness and pruritic skin lesions. Skin biopsies were performed and histologic findings were consistent with DM.

Results: Skin biopsy showed interface dermatitis with vacuolar degeneration of the basal layer, dermal mucin deposits, and necrotic keratinocytes in the acrosyringia, a finding that has been previously reported in lupus erythematosus but not in DM. Autoimmunity tests showed positivity for antinuclear antibodies and anti-NXP2, a recently described antibody associated with juvenile DM and, more rarely, with paraneoplastic DM.

Conclusion: We present the first case in the literature with histopathologic changes of DM affecting the acrosyringia. Besides, our patient autoimmunity results support the utility of the new myositis-specific autoantibodies and its relation with a clinical phenotype.

Key Words: dermatomyositis, paraneoplastic dermatomyositis, acrosyringium involvement

(*Am J Dermatopathol* 2017;39:e3–e7)

INTRODUCTION

Dermatomyositis (DM) is a rare condition characterized by skin lesions and proximal muscular weakness, although several cases of amyopatic DM have been reported.[1] It may affect young people (juvenile DM) or patients over the sixth decade of life (adult DM).[2] In this latter case, it is mandatory to rule out the association with a malignant internal neoplasm, as long as up to 25%–30% of cases show such association,[3] especially mammary and ovarian cancer in women and lung cancer in men.[2] Paraneoplastic DM can precede, appear concomitant, or develop after the diagnosis of the internal malignancy.[4] Histopathologic features of DM include interface dermatitis with vacuolar degeneration of the basal layer, necrotic keratinocytes, dermal mucin, epidermal necrosis, and superficial perivascular lymphocytic infiltrate.[5] Involvement of the acrosyringia has not been reported previously in this entity, although there are 2 reports of this histopathologic peculiarity in cutaneous lesions of patients with systemic lupus erythematosus.[6,7] Laboratory tests show increased levels of serum muscular enzymes, and recently, several autoantibodies have been associated with distinct clinical subsets of DM.[8,9]

We present a case of paraneoplastic DM with the histopathologic peculiarity of the preferable affection of the acrosyringia. Moreover, the autoantibody anti-NXP2 resulted positive, supporting the association between this antibody and paraneoplastic DM.

CASE REPORT

A 67-year-old man presented with a 2-week history of a pruritic eruption affecting the trunk, scalp, and upper extremities. His medical history included hypertension and chronic obstructive pulmonary disease, for which he was under medical treatment with enalapril and inducaterol with ipratropium. He was a former smoker, with a pack/year index of >100.

On physical examination, multiple erythematoviolaceous lesions distributed on both the anterior and posterior aspects of his neck, lateral aspects of his arms, scalp, and lower back region were seen (Figs. 1, 2). Epidermal necrosis was seen in the lesions of the arm and posterior neck. No lesions on his hands or elbows were observed. When asked, he reported mild symmetrical proximal muscle weakness.

Laboratory examination revealed elevated serum levels of creatine kinase (395 IU/L), myoglobin (187 ng/mL), and aldolase (10.52 IU/L). Erythrocyte sedimentation rate was also elevated (60 mm/h). Complete blood count, liver and thyroid function tests, serum levels of calcium, albumin, and phosphate, and levels of alkaline phosphatase, parathyroid hormone, and electrolytes were within the normal limits.

Immunological investigations were performed: indirect immunofluorescence (Hep-2 slides; INOVA Diagnostics, San Diego, CA),

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The authors declare no conflicts of interest.

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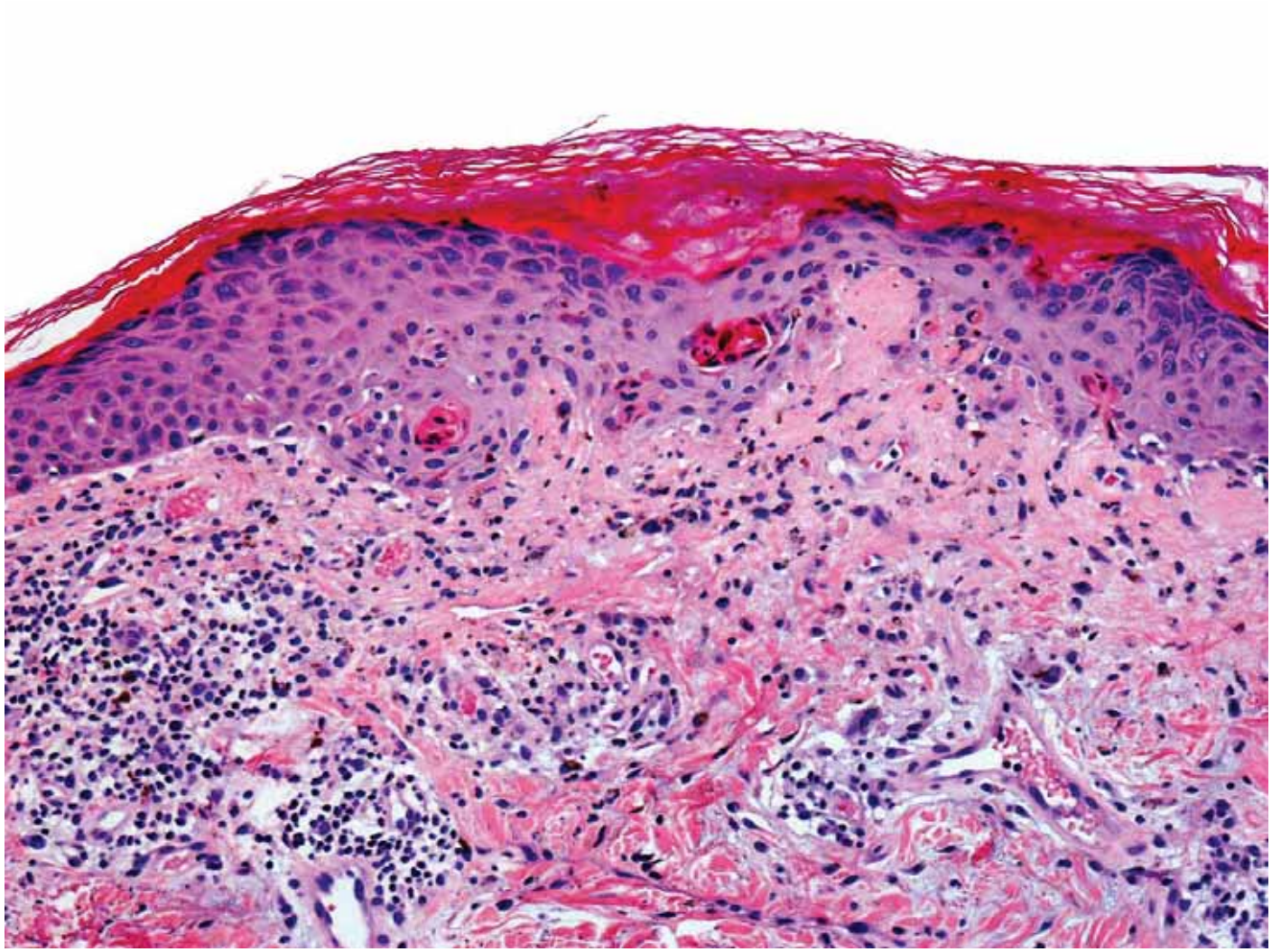
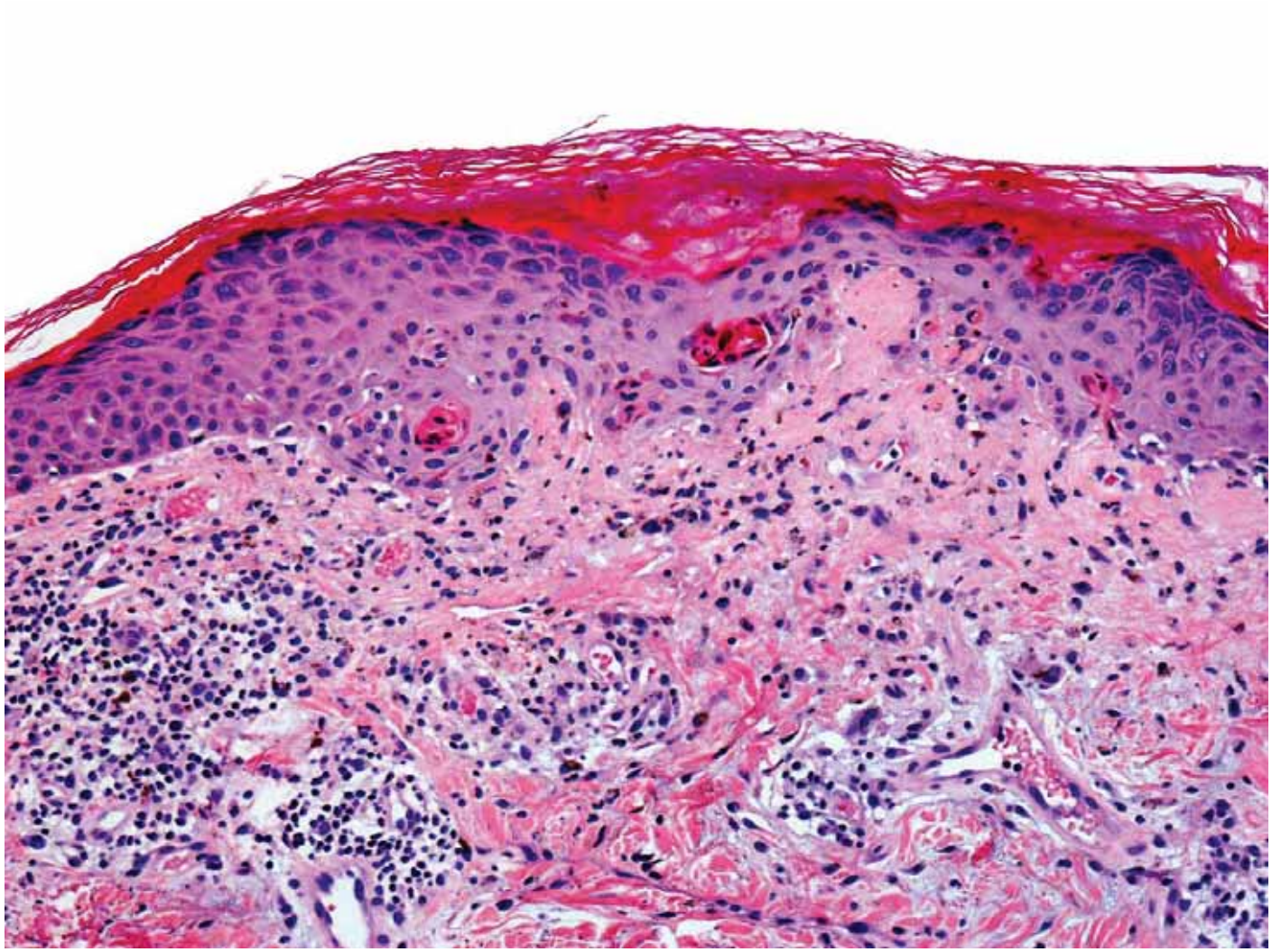
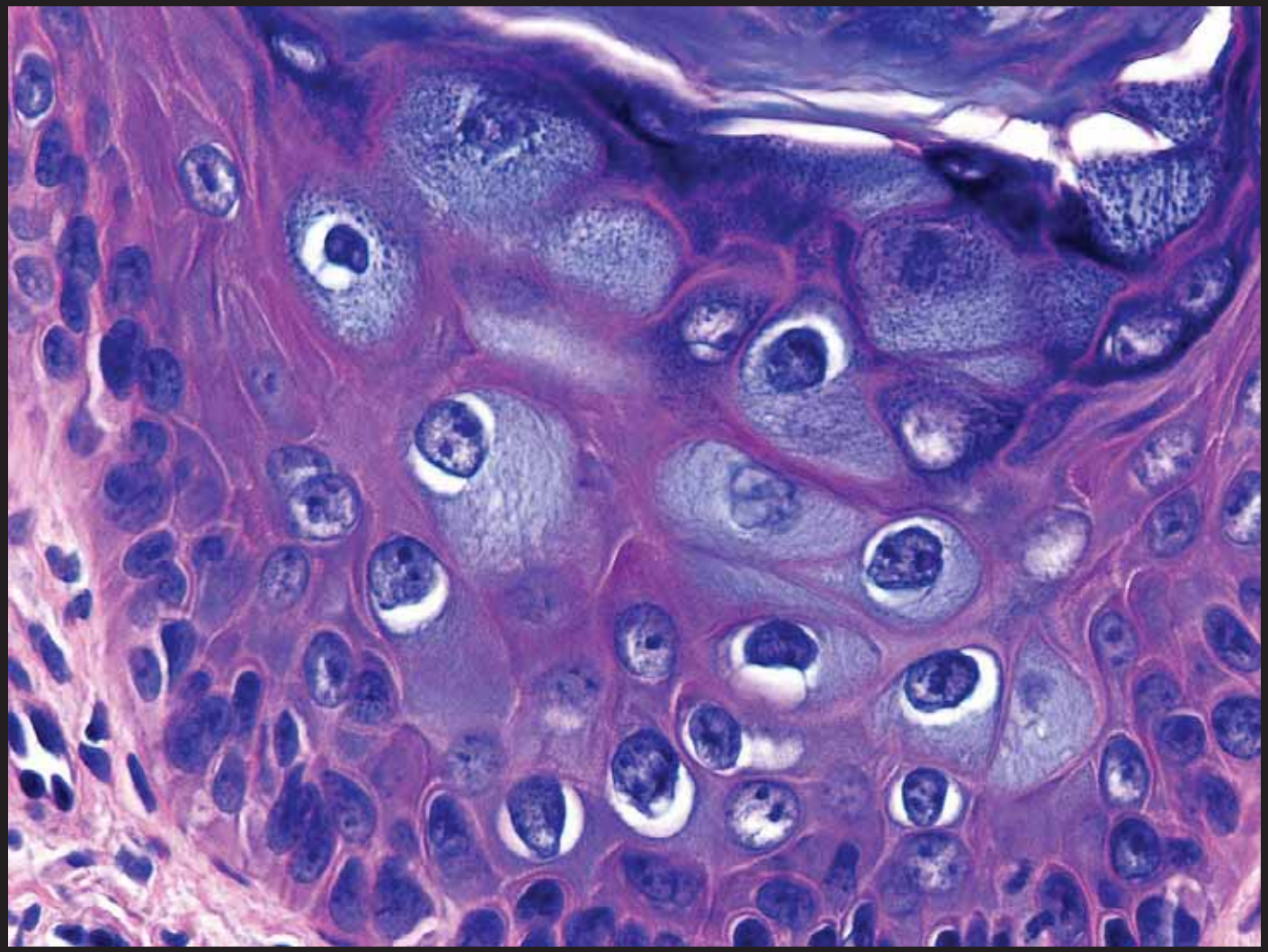


Acrosyringeal concentration of necrotic keratinocytes is a *cliche* to…



Acrosyringeal concentration of necrotic keratinocytes is a *cliche* to EM, systemic lupus erythematosus or dermatomyositis

	Acute LE and dermatomyositis	Drug-induced EM
Clinical features	Erythemato-edematous macules and plaques	Target-like lesions, frequent mucosal involvement
Present disease	Related with acute outbreak of systemic LE or dermatomyositis	Related with the administration of new medications
Histopathology	- Necrotic keratinocytes in and around acrosyringia - No eosinophils - Focal parakeratosis	- Necrotic keratinocytes in and around acrosyringia - Sometimes, some eosinophils - No focal parakeratosis
Treatment	Corticosteroids/immunomo-dulators	Withdrawal medication



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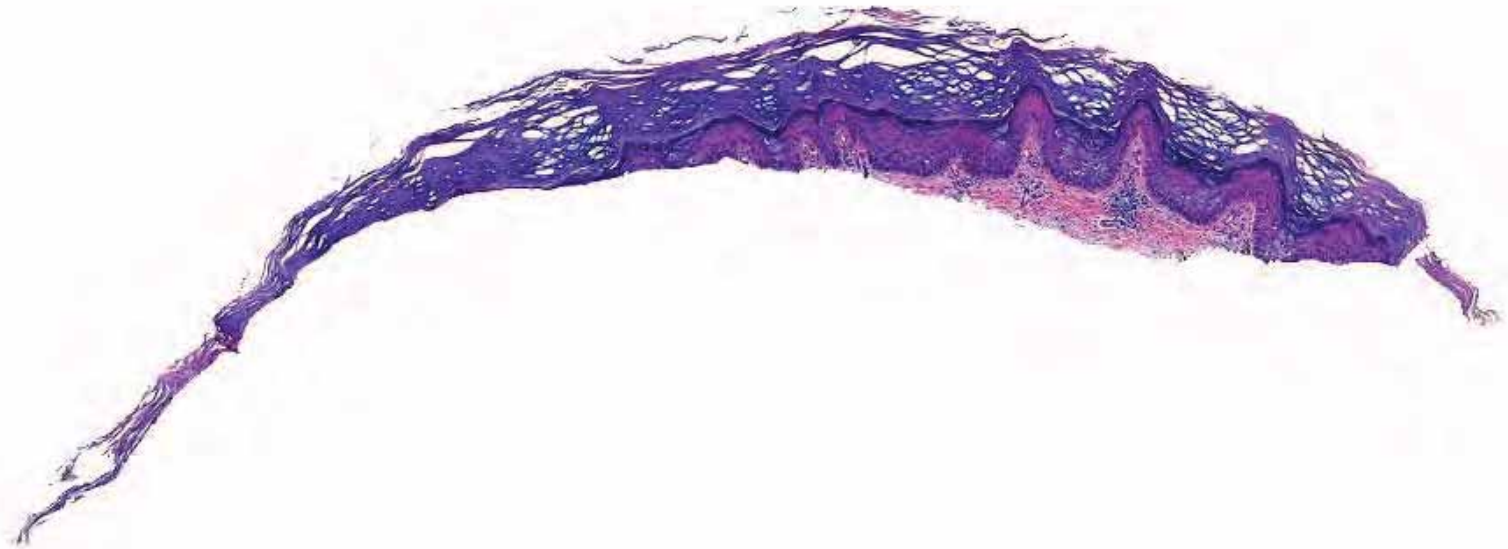
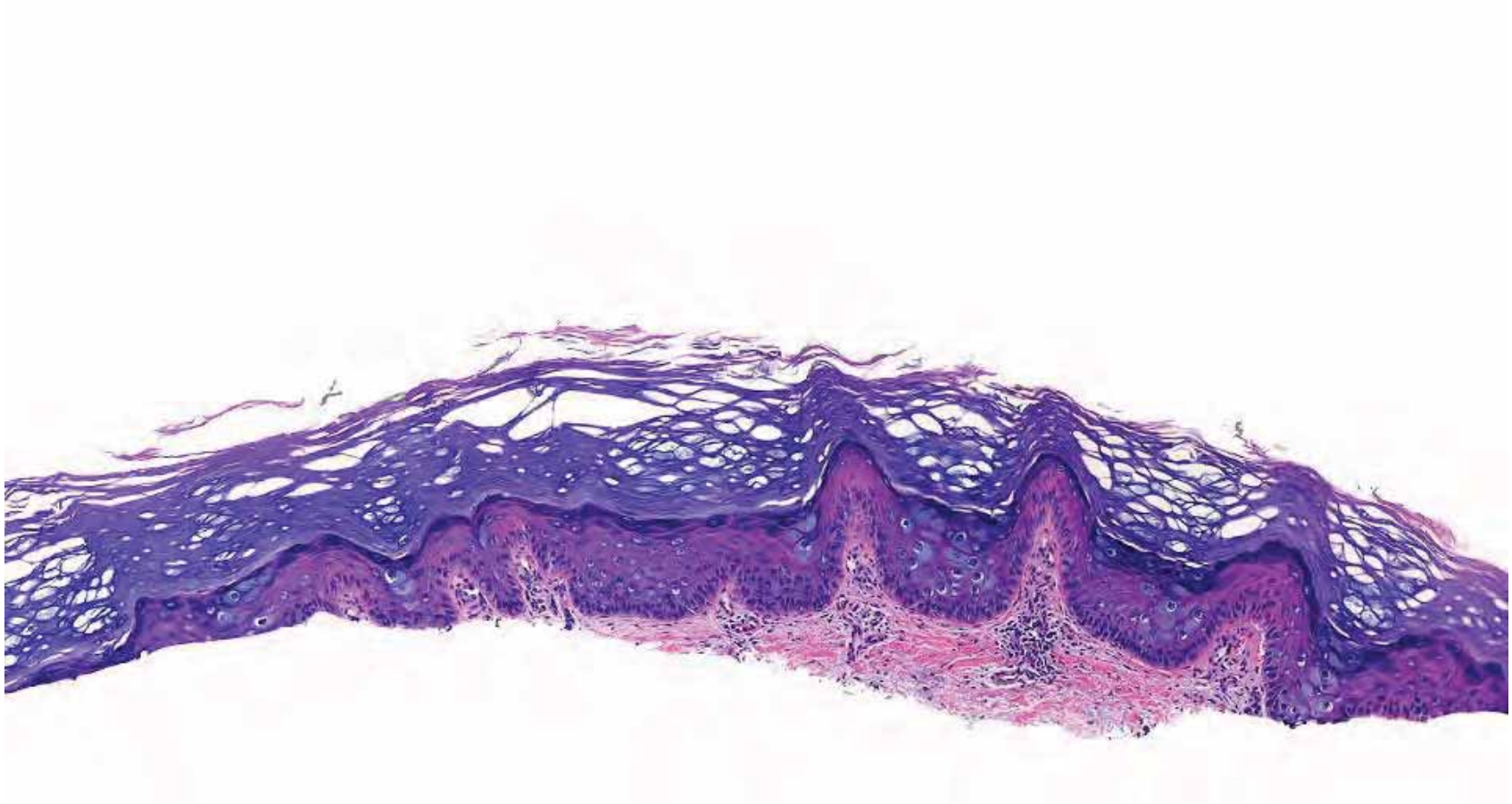
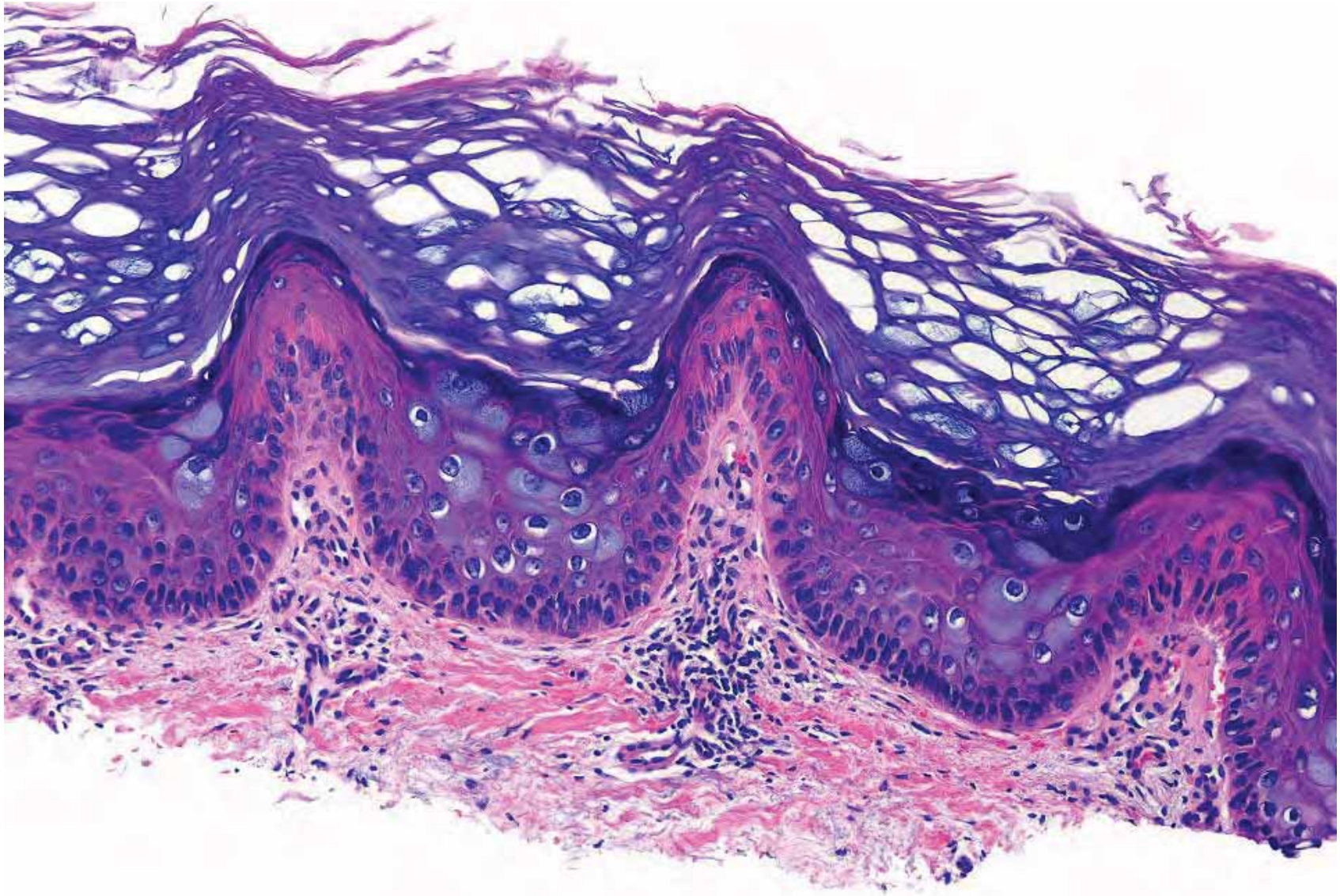
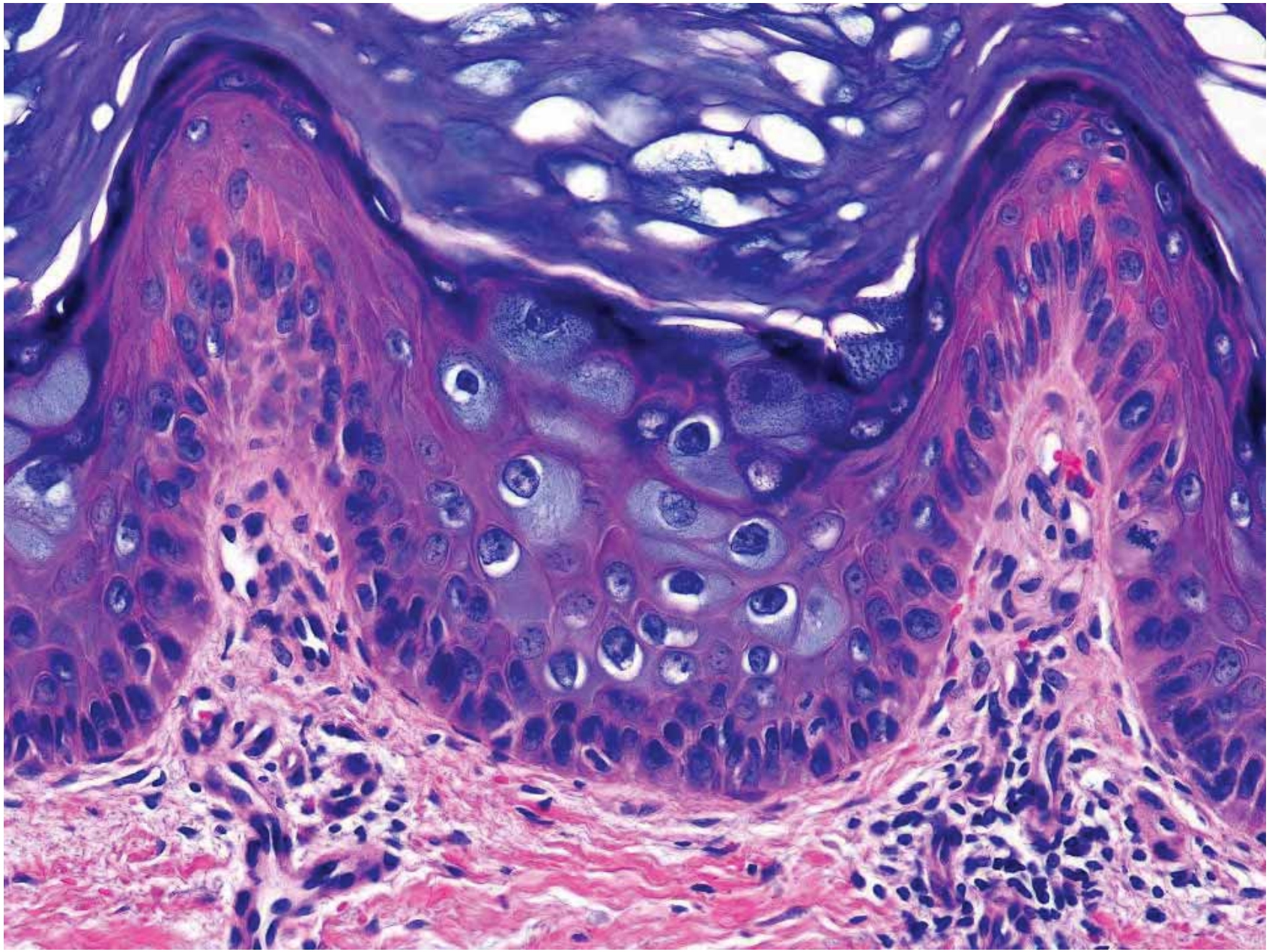
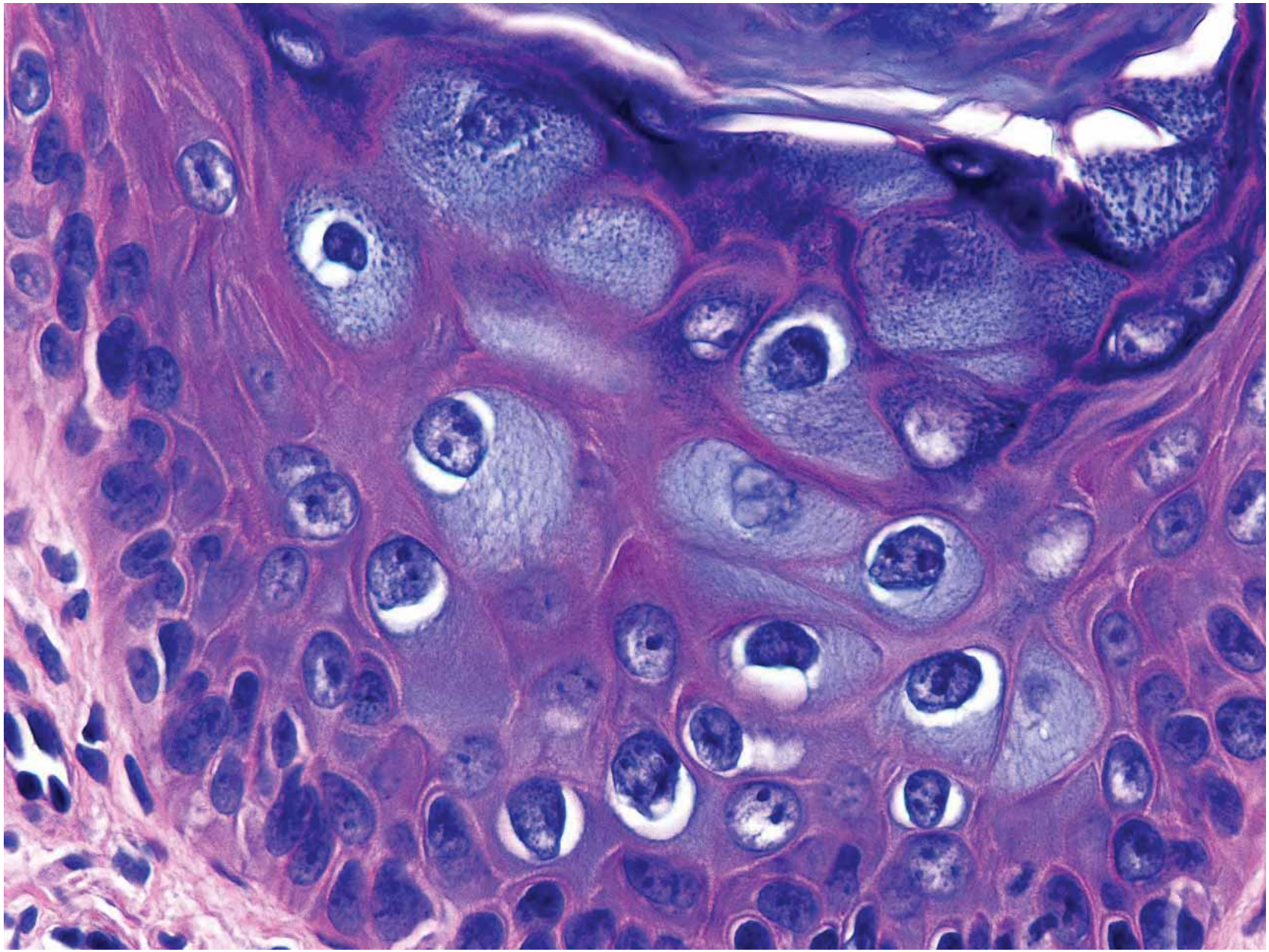
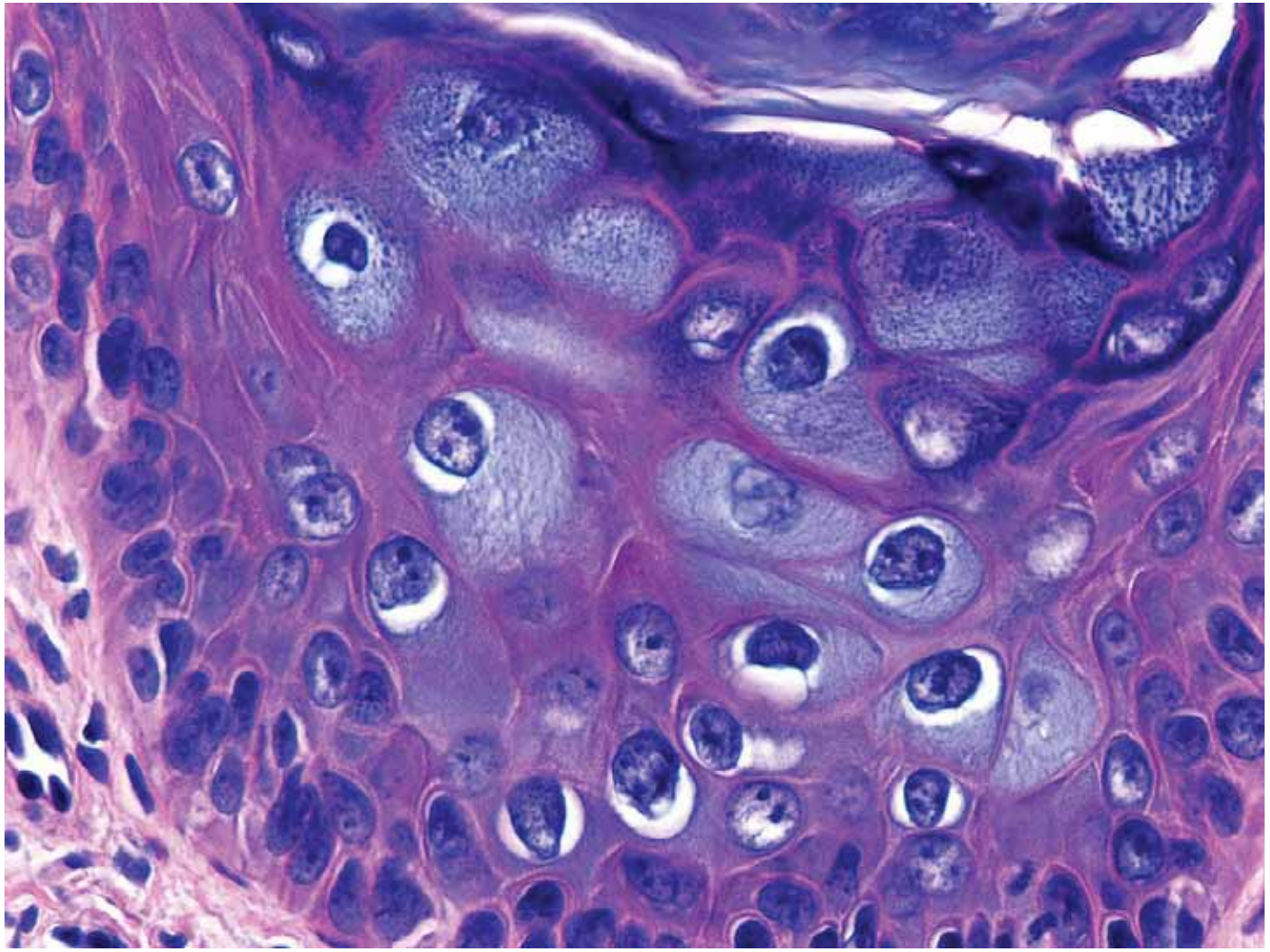




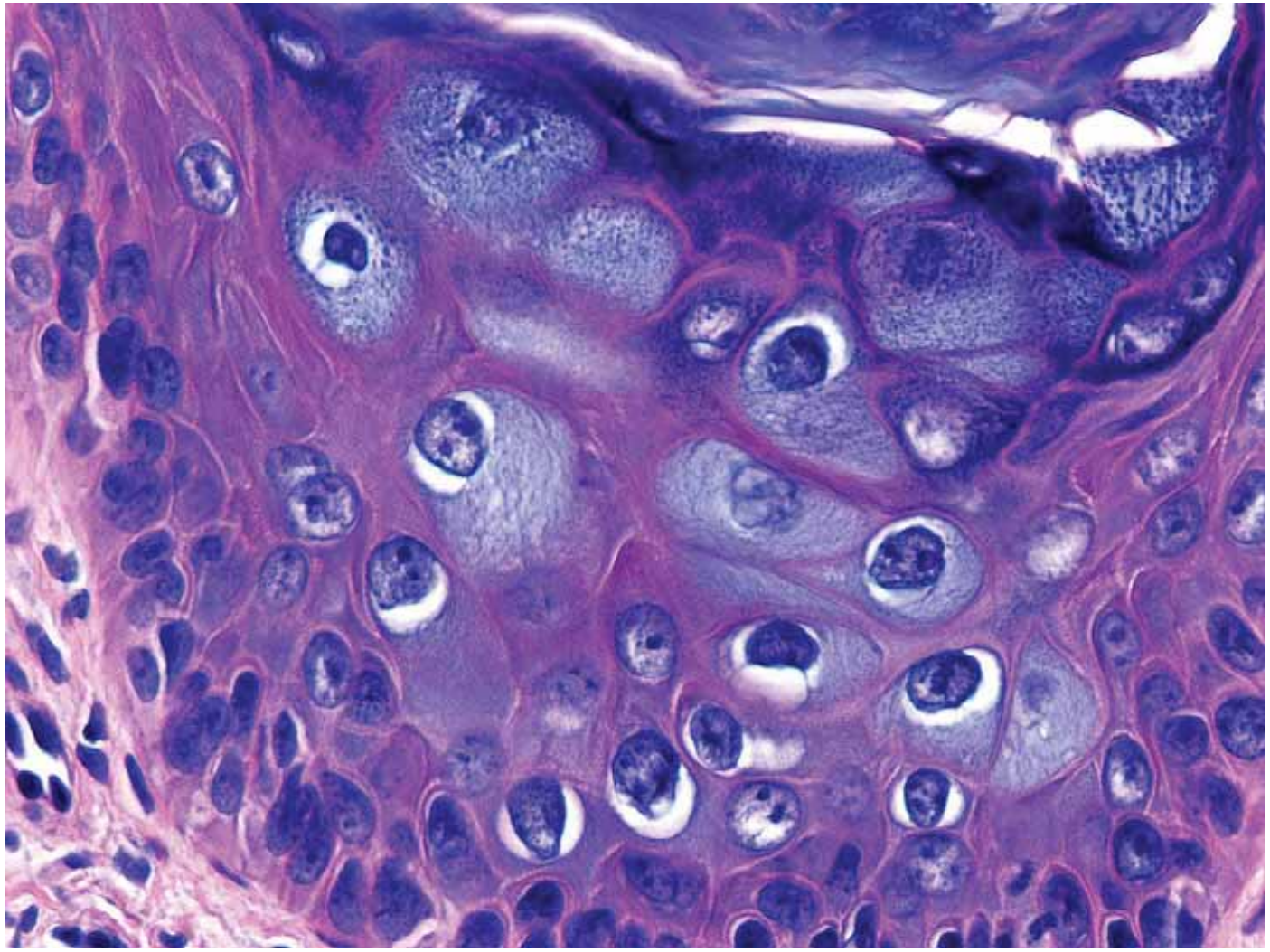




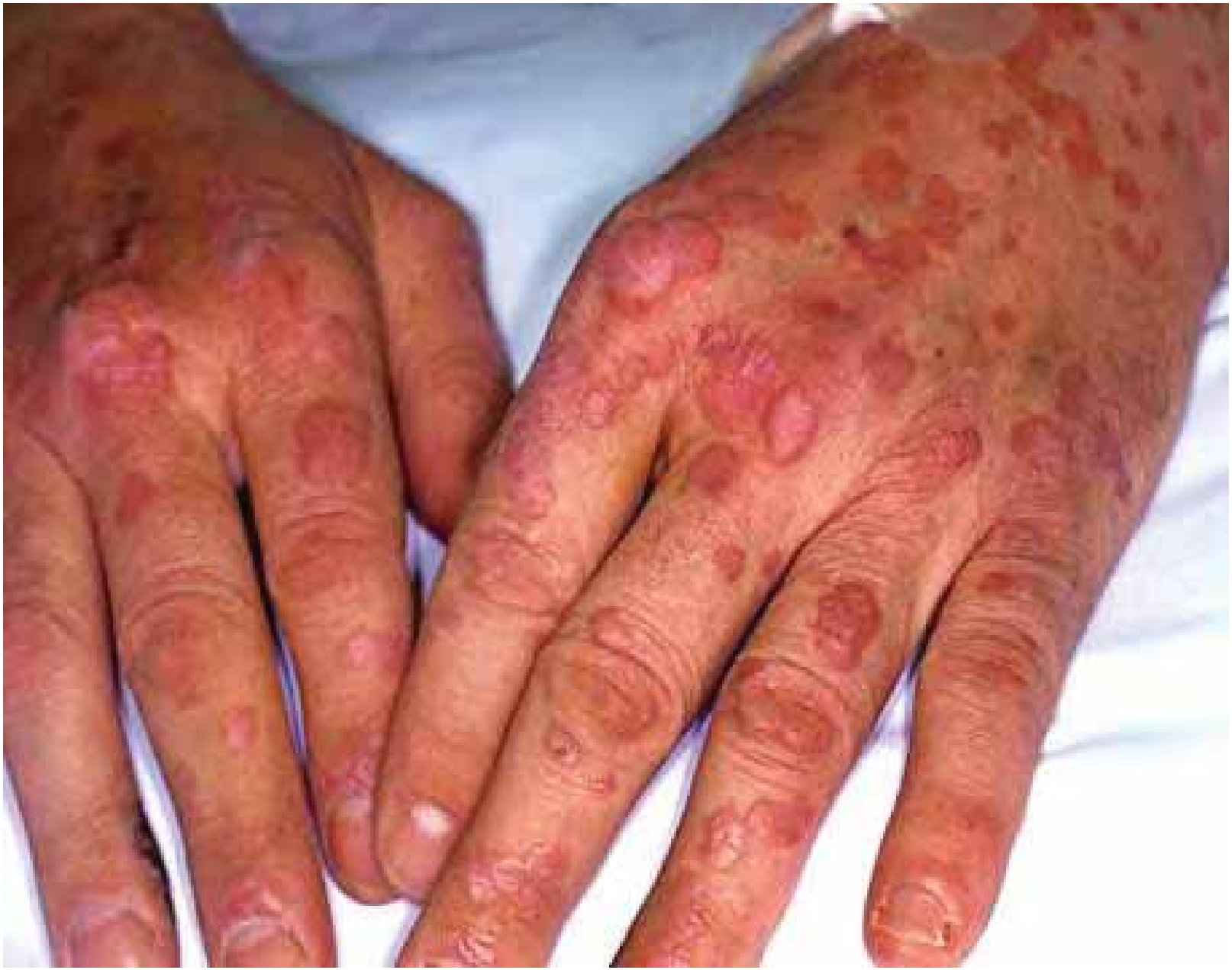




Large bluish keratinocytes at the the upper layers of the epidermis are a *cliche* to…



Large bluish keratinocytes at the the upper layers of the epidermis are a *cliche* to wart in AIDS patients



Swollen keratinocytes: a histologic marker of unusual human papillomavirus-type infection and immunosuppression

Cutaneous papillomavirus infection is common in patients who are immunosuppressed. We describe swollen keratinocytes in the granular layer in lesions from four patients who had human immunodeficiency virus infection. These cells were similar to those described in skin lesions of epidermodysplasia verruciformis. Amplification of DNA from the lesions revealed an amplimer for human papillomavirus using a consensus primer for a highly conserved region of the L1 open reading frame; however, specific binding was not noted when radiolabelled probes for human papillomavirus types 6, 11, 16, 18, and 33 were used. We conclude that the presence of these distinctive swollen cells strongly suggests immunosuppression and quite possibly infection by a less common papillomavirus type.

Penneys NS, Friend A, Zhu W-Y, Leonardi C. Swollen keratinocytes: a histologic marker of unusual human papillomavirus-type infection and immunosuppression. J Cutan Pathol 1992: 19: 217–220.

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Accepted July 26, 1991

Infection by human papillomavirus (HPV) produces a variety of histologic changes, many of which are strongly suggestive of the presence of this group of viruses. Little has been written describing histologic changes associated with HPV types that are not commonly found in the skin in routine infections. Prior to the introduction of the AIDS pandemic, our experience with rare HPV-type infection was limited to lesions in patients who had epidermodysplasia verruciformis (EDV) or who were iatrogenically immunosuppressed. A much larger pool of immunosuppressed persons now exists because of the presence of human immunodeficiency virus (HIV) infection.

A distinctive swollen keratinocyte has been described in the stratum malphighii and granular zone of the epidermis in patients who have EDV (1, 2) and recently in certain skin lesions in patients who have HIV (3, 4). We have collected 4 cases in which these cells were noted. All patients were found to be infected by HIV. Analysis of tissues from these cases by polymerase chain reaction (PCR) revealed a positive HPV signal using a consensus primer. Following amplification, incubation with specific probes for HPV types 6, 11, 16, 18, and 33 revealed no reaction product. In the absence of EDV, we feel that the presence of these distinctive cells in the epidermis should alert the dermatopathologist to the possibility of immunosuppression (usually secondary to HIV) and of infection by a less common type of HPV.

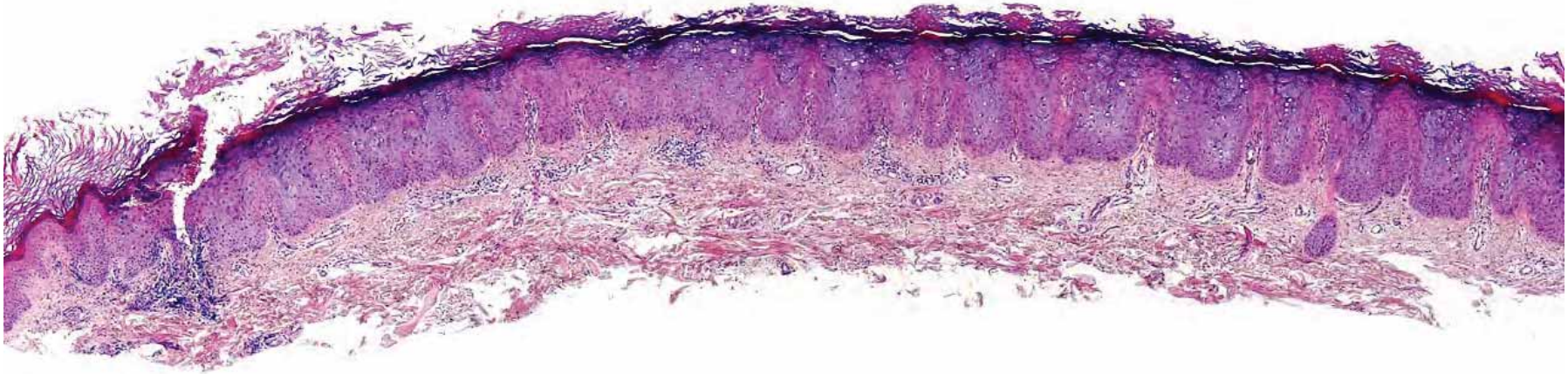
Material and methods

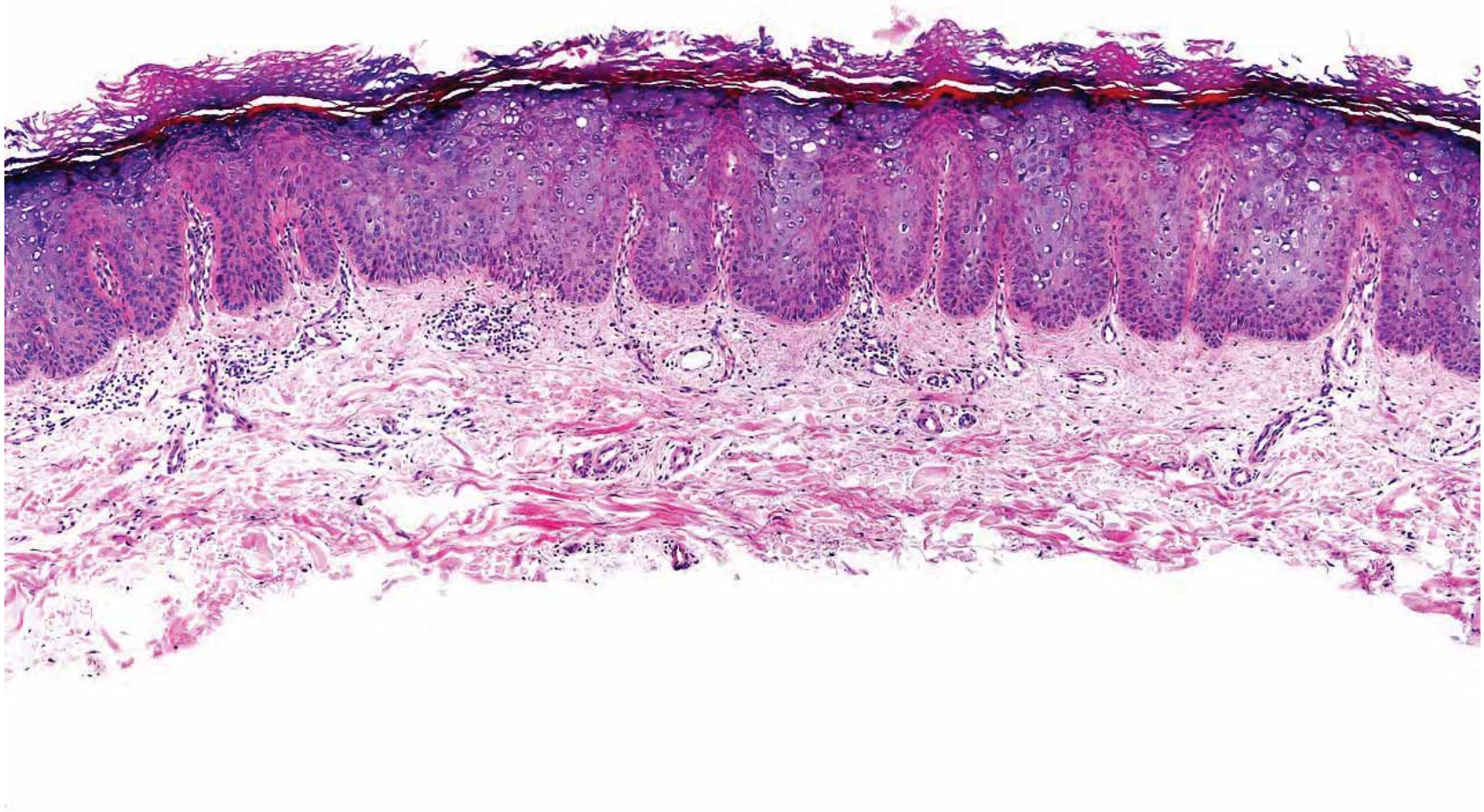
Cases – Histologic slides and paraffin blocks from 4 cases in which swollen keratinocytes in the epidermis had been noted were retrieved from the dermatopathology files of the Division of Dermatopathology at the University of Miami School of Medicine. All tissues had been formalin-fixed and routinely processed. The cases were reviewed, and two to four 6 µm sections were obtained from each block and placed in a microfuge tube for further analysis.

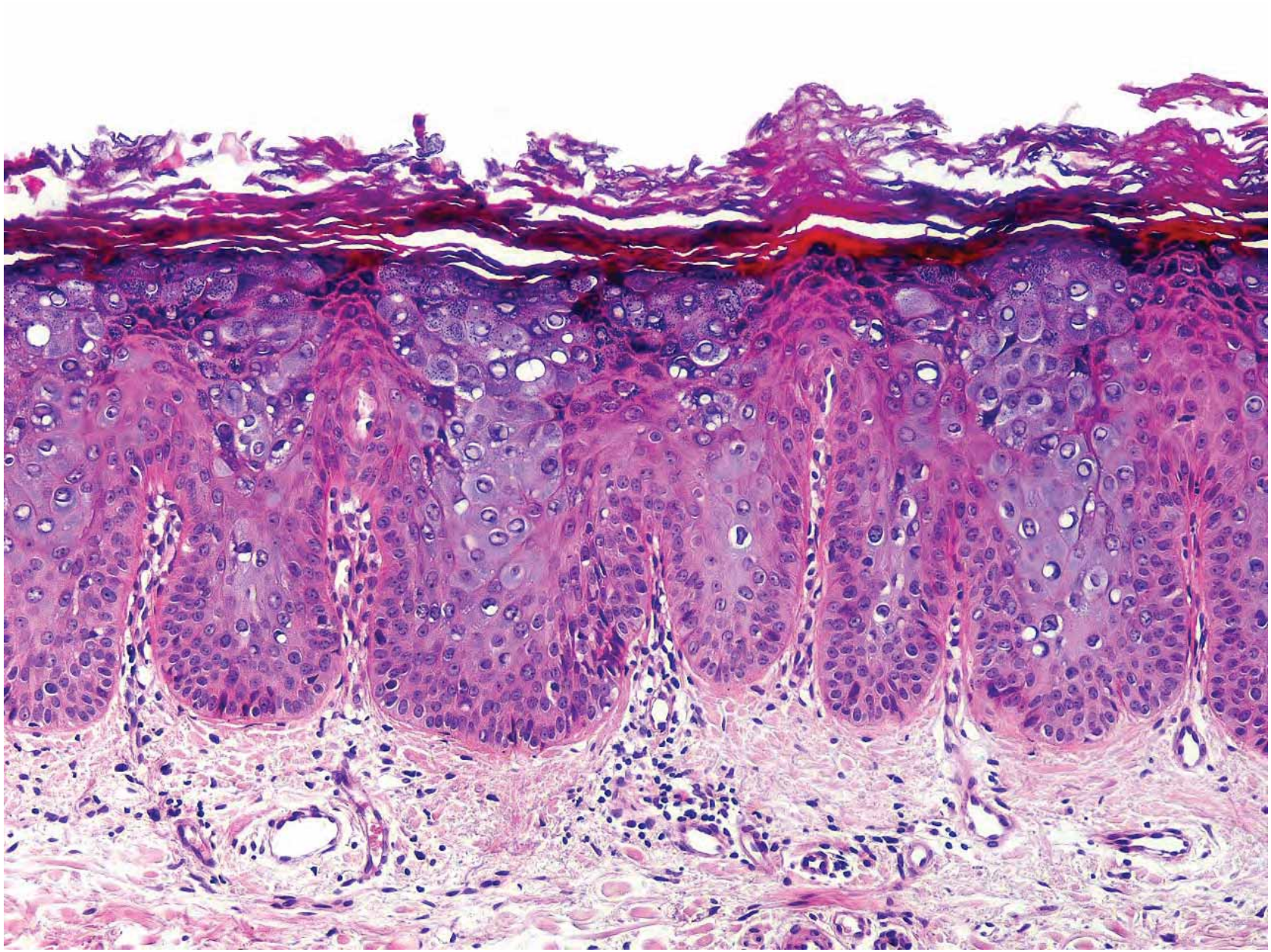
Sample preparation – Genomic DNA was extracted from paraffin with 1.5 ml of xylene at 55°C for 15 min. The tissue was pelleted at low speed (12,000 × g, 3 min), resuspended in 1 ml of absolute ethanol at room temperature, and repelleted at low speed. Af-

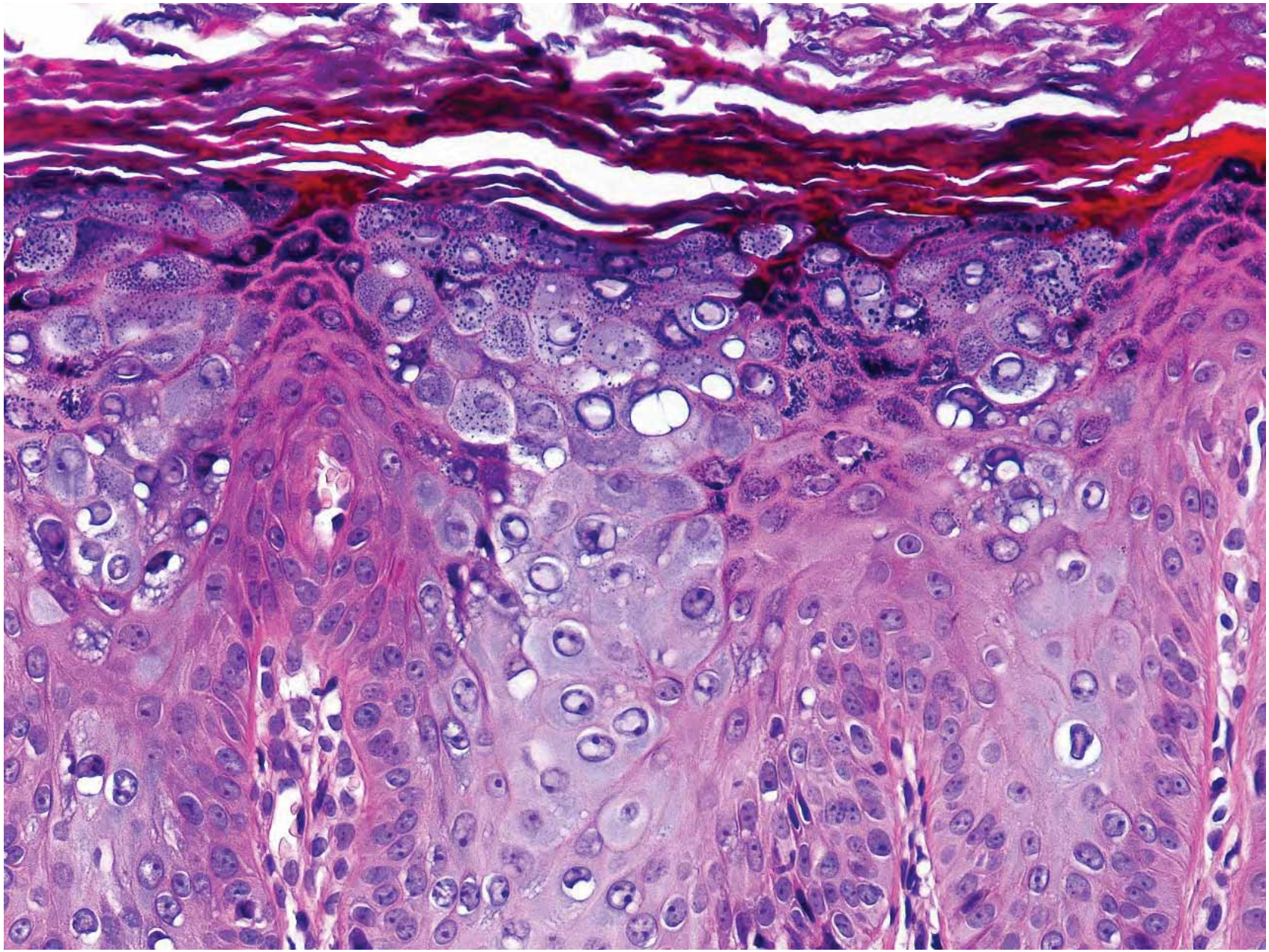
- Swollen keratinoeytes in the granular layer in lesions from four patients who had human immunodeficiency virus infection
- These cells were similar to those described in skin lesions of epidermodysplasia verruciformis.
- Amplification of DNA from the lesions revealed an amplimcr for human papillomavirus using a consensus primer for a highly conserved region of the Ll open reading frame
- The presence of these distinctive swollen cells strongly suggests immunosuppression and quite possibly infection by a less common papillomavirus type.

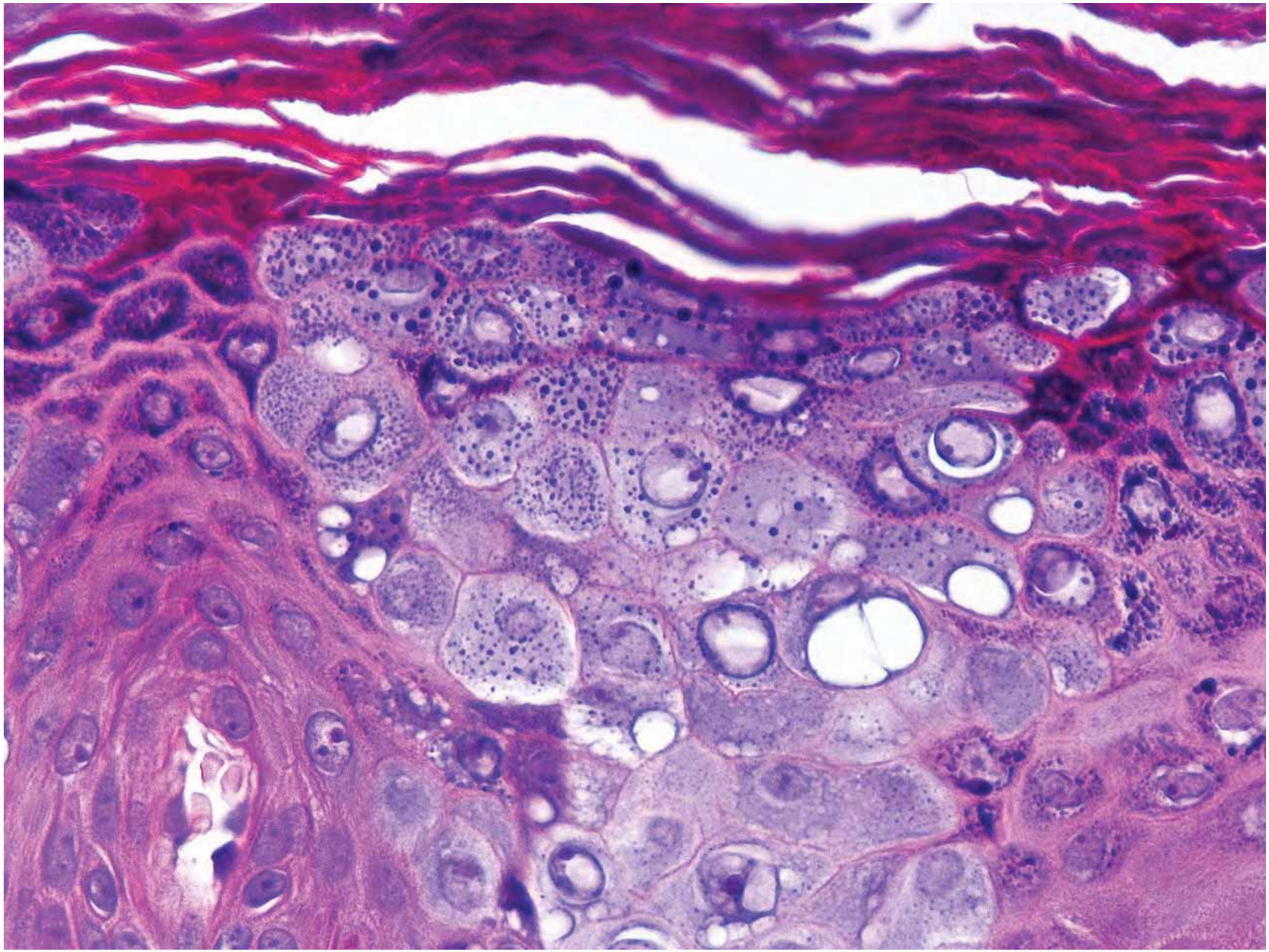
But….

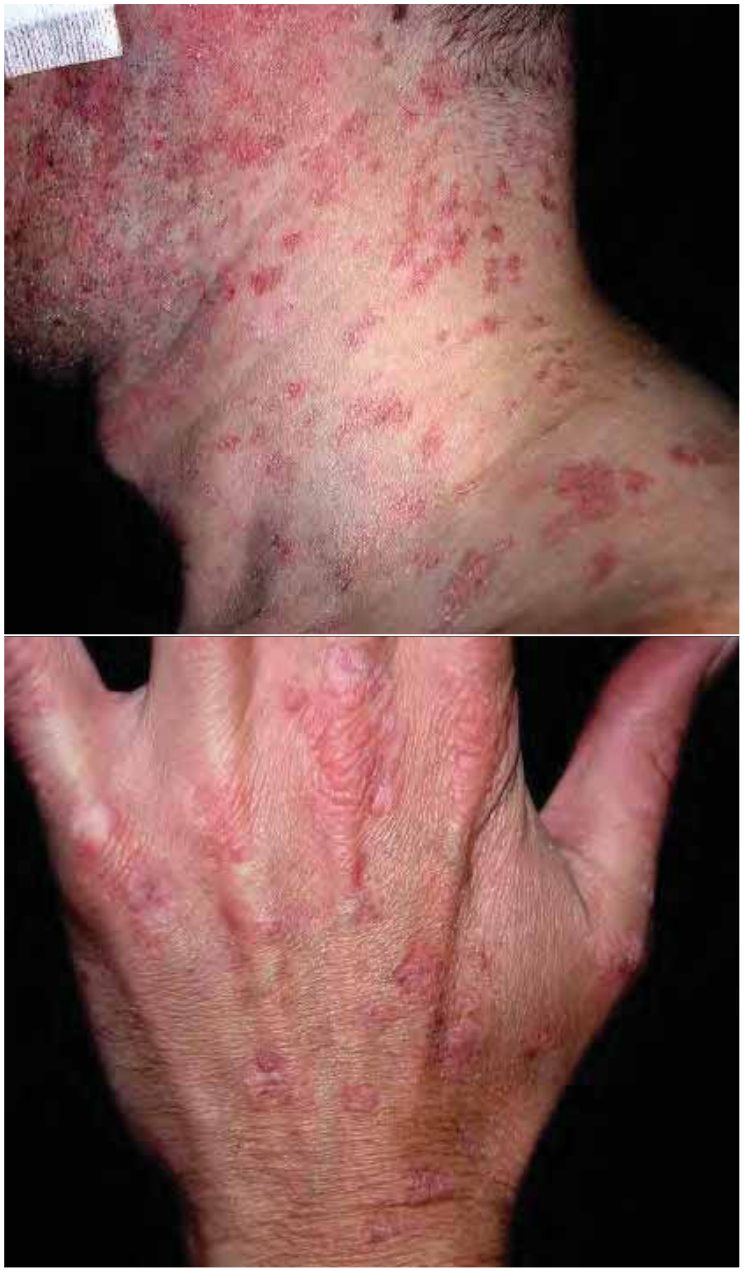


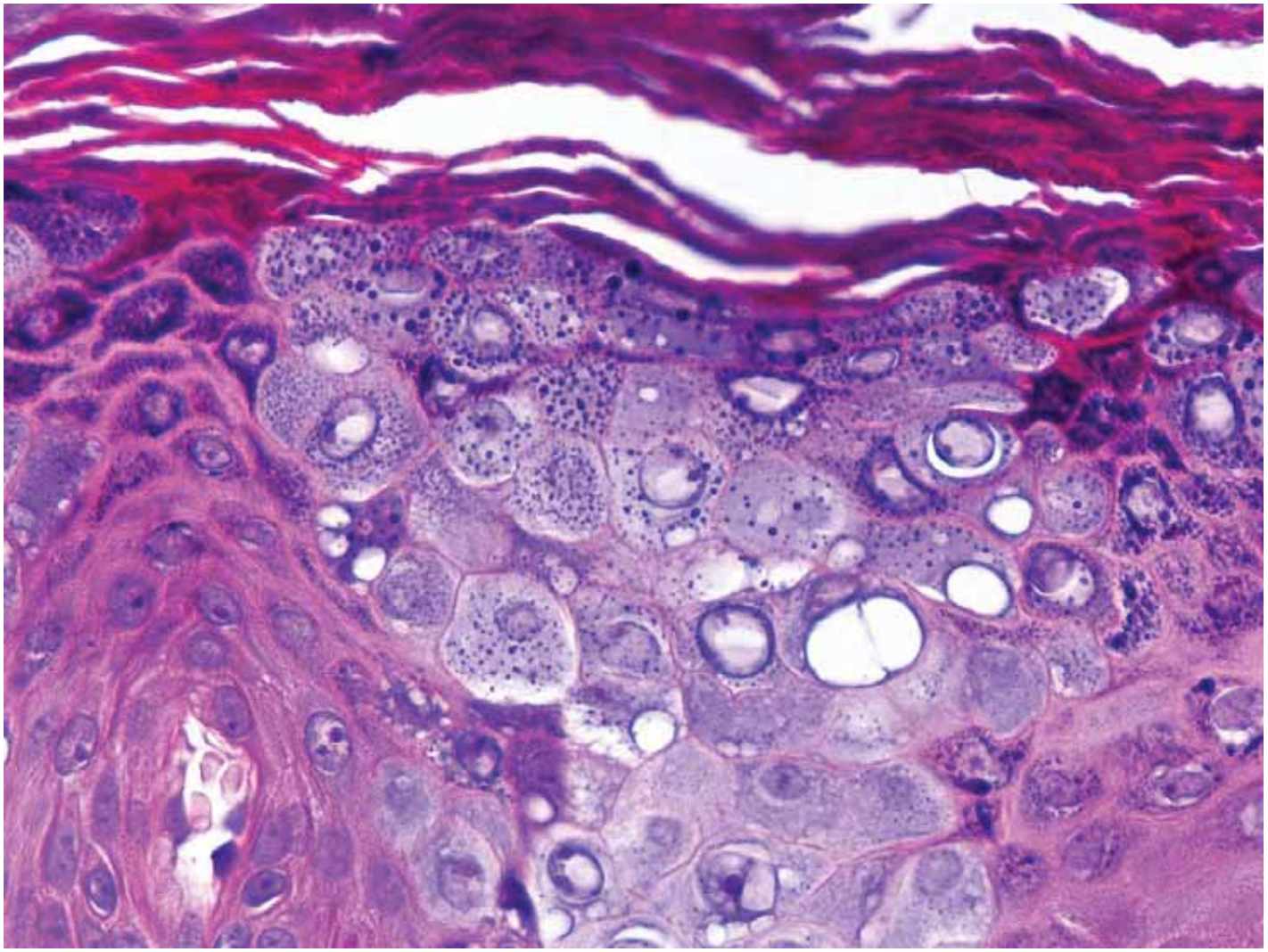






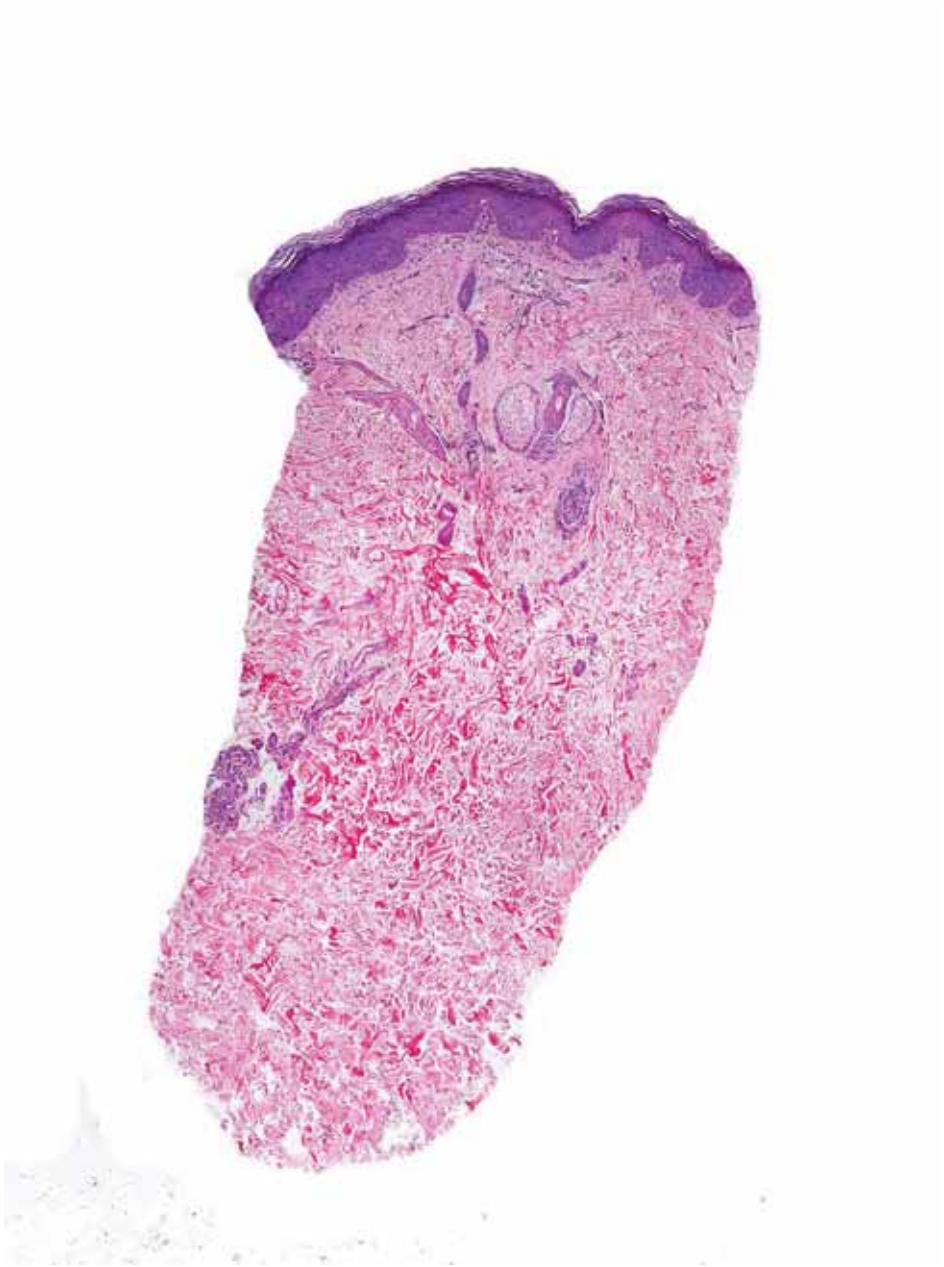


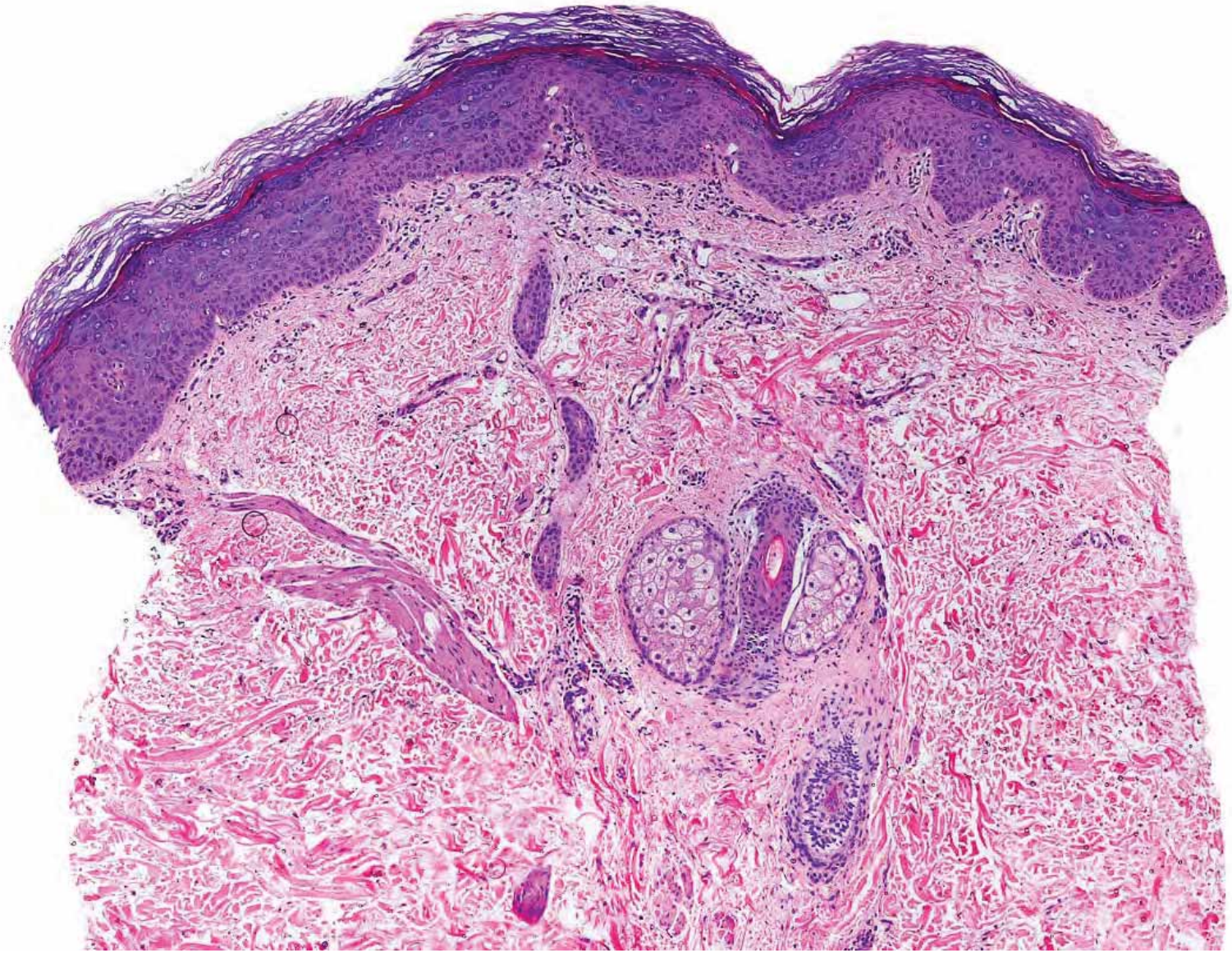


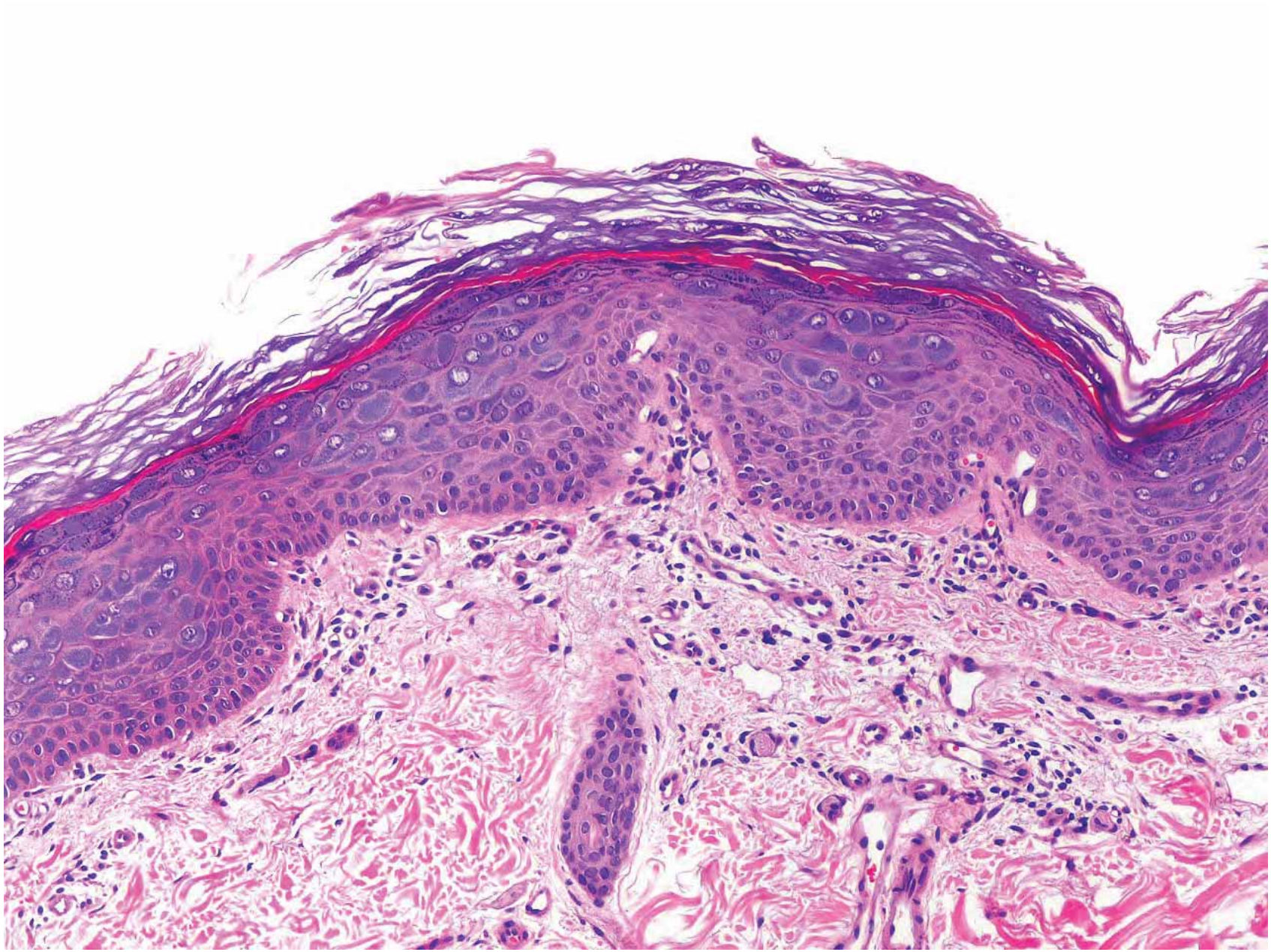


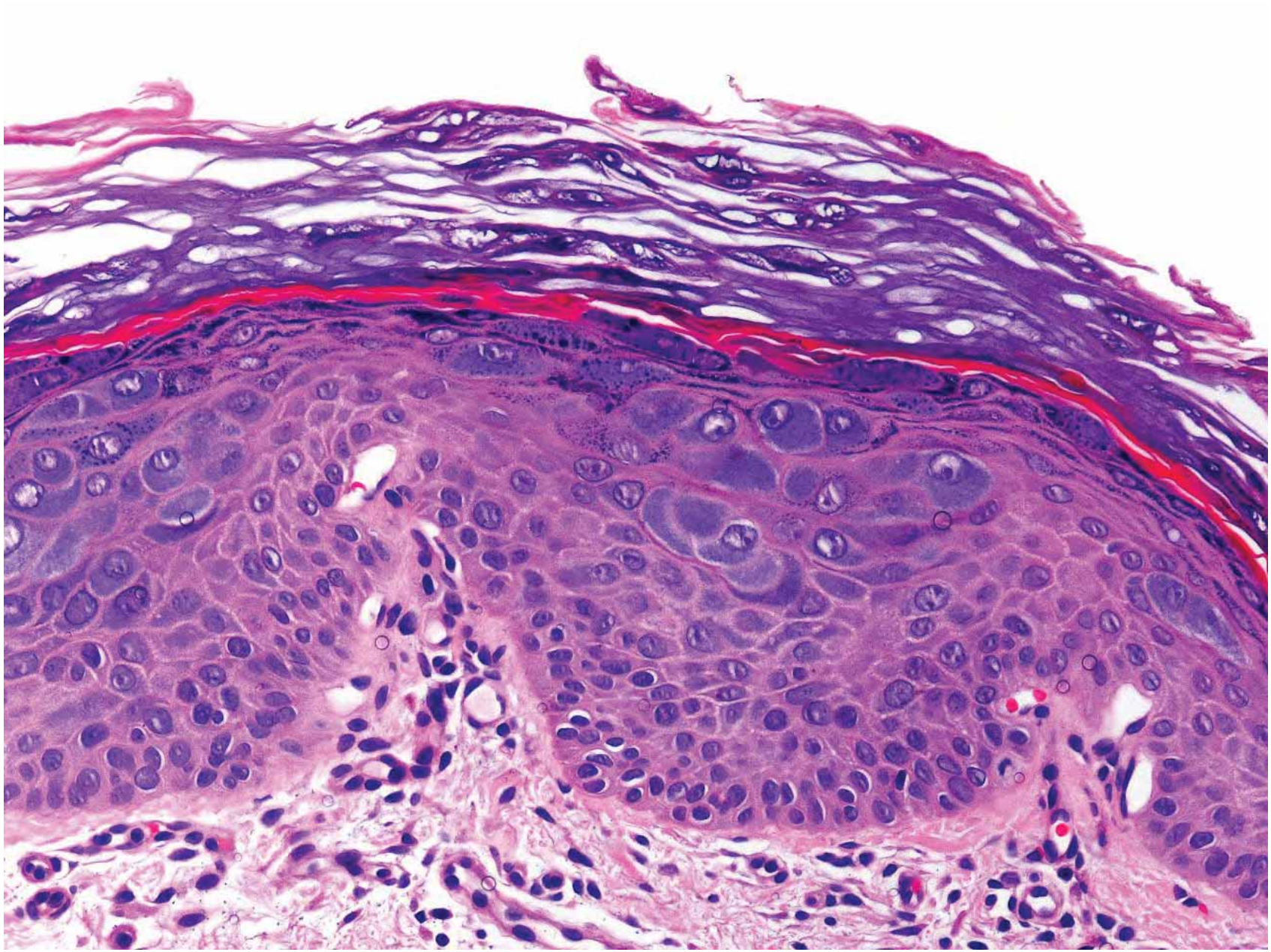
Large bluish keratinocytes at the the upper layers of the epidermis are a *cliche* to wart in AIDS patients and wart in epidermodysplasia verruciformis

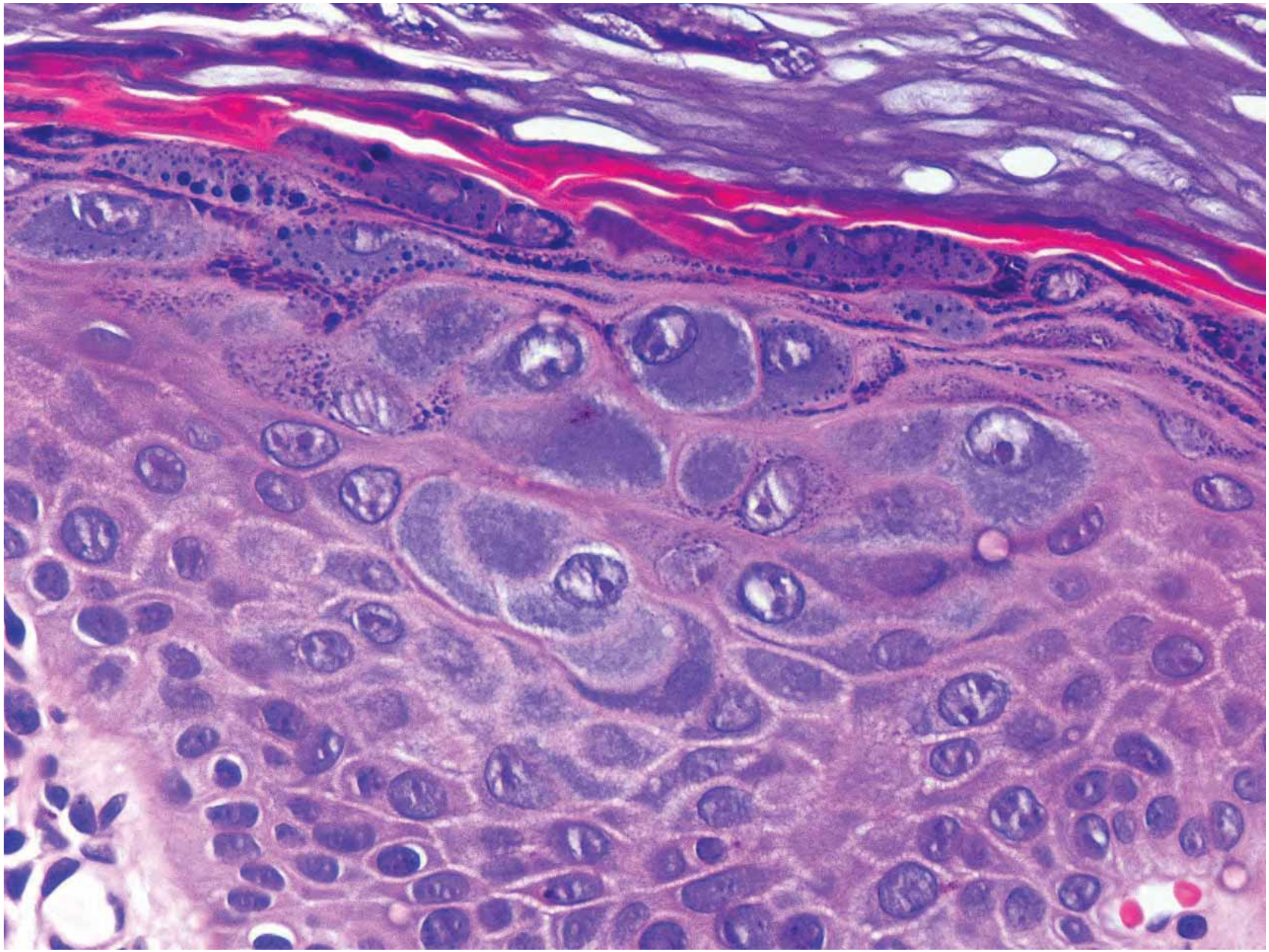
But….

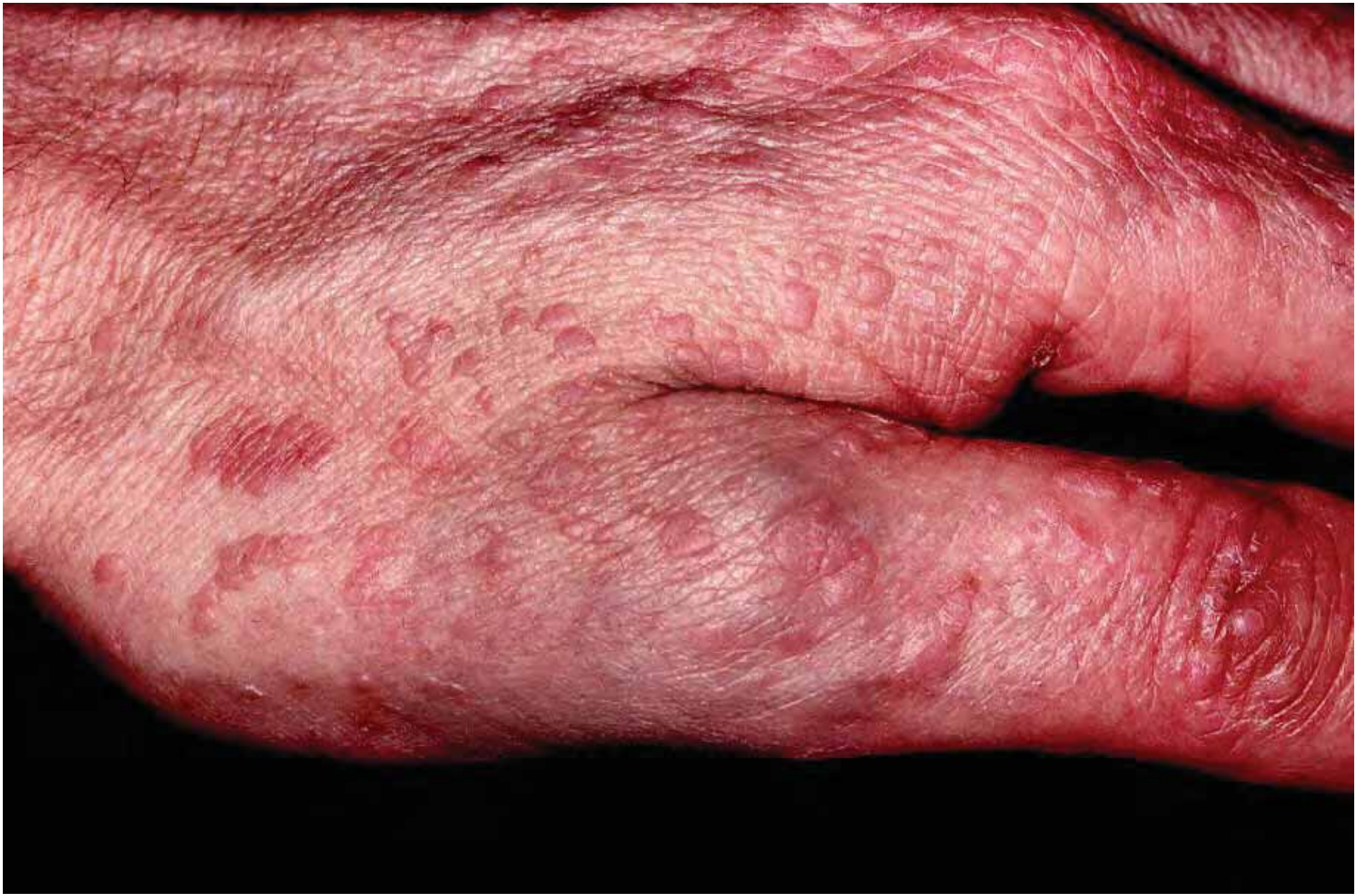


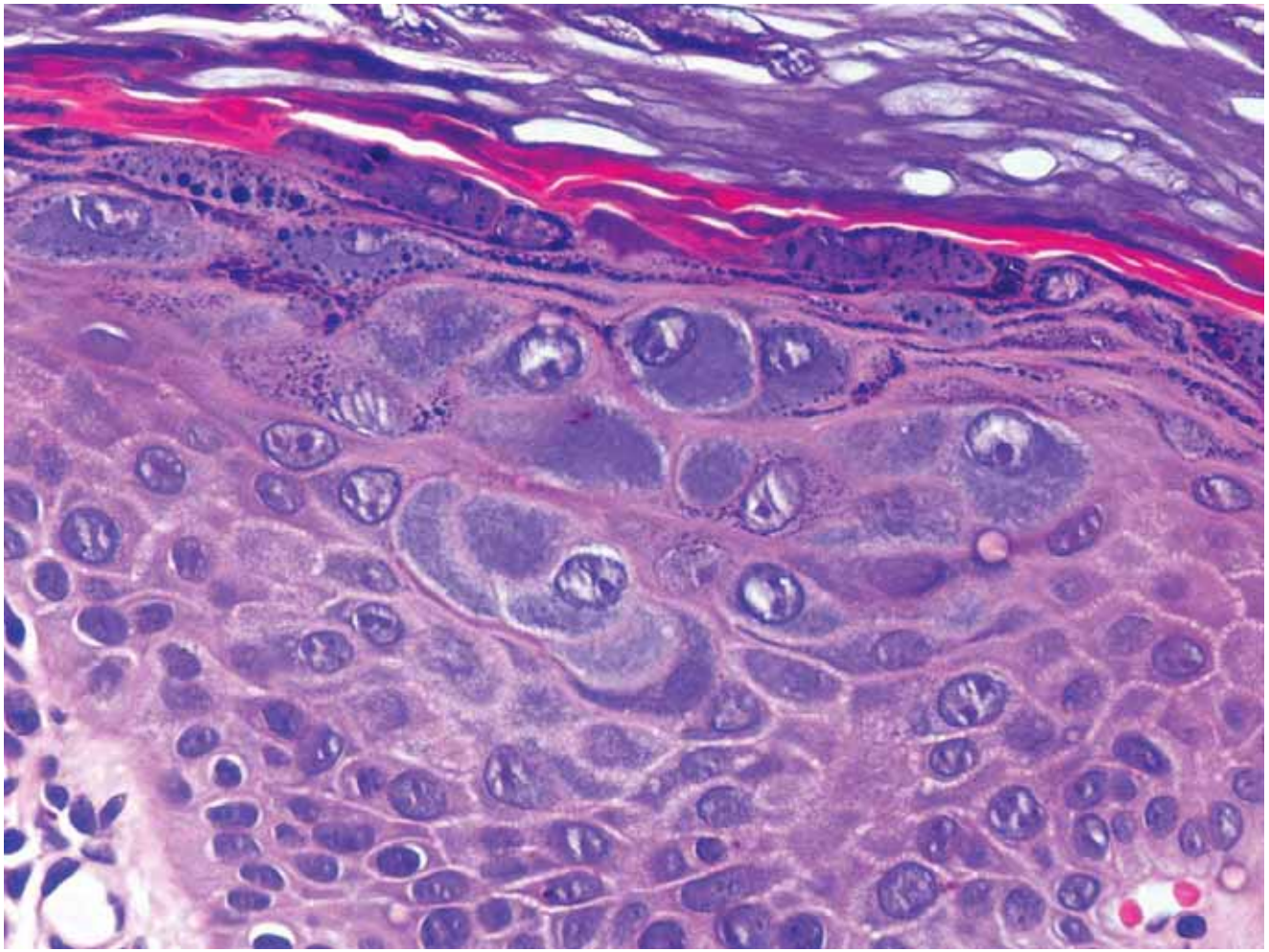




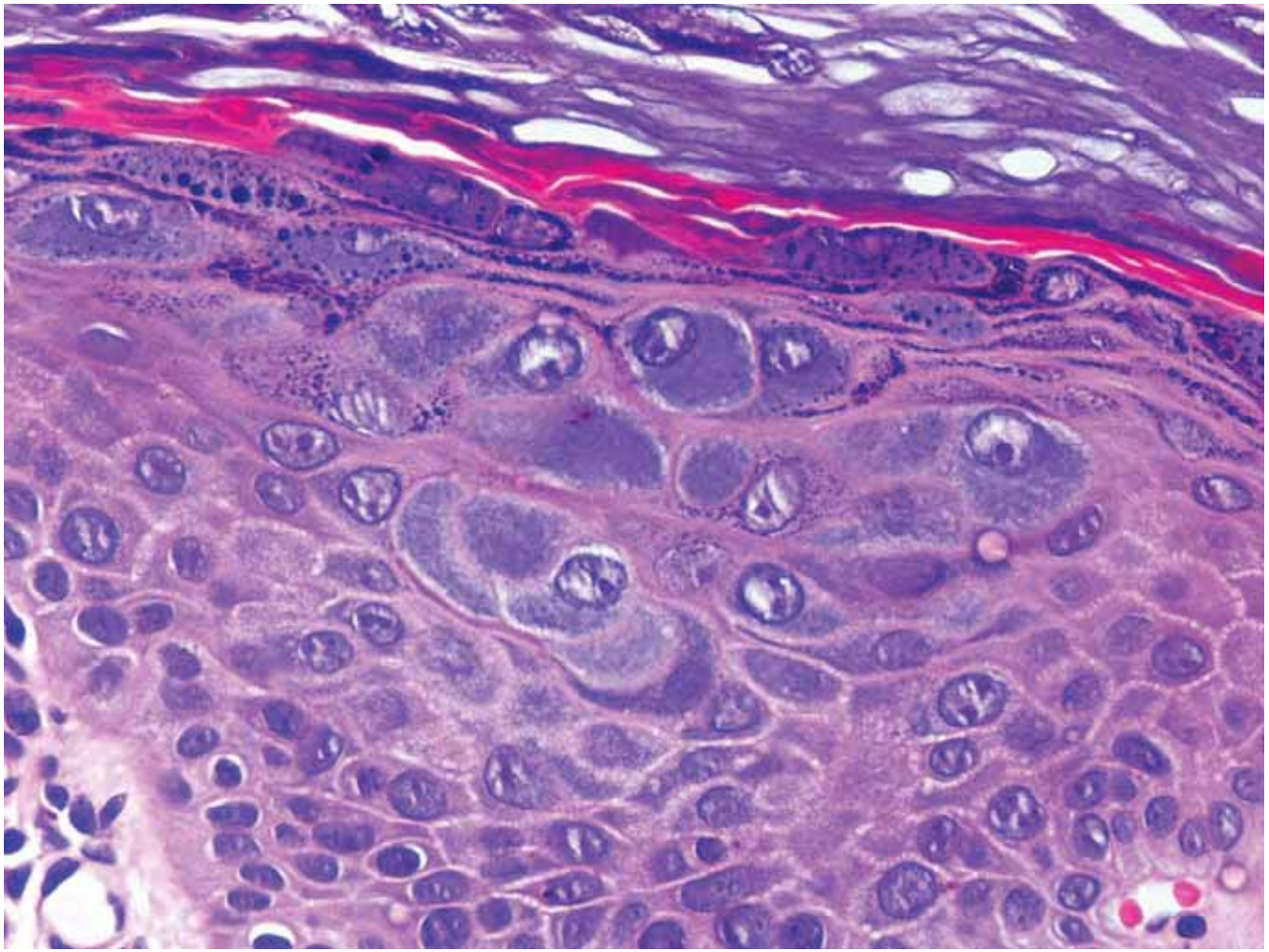








Large bluish keratinocytes at the the upper layers of the epidermis are a *cliche* to wart in AIDS patients, wart in epidermodysplasia verruciformis and wart in immunocompetent patients



Large bluish keratinocytes at the the upper layers of the epidermis are a *cliche* to warts, and nothing else