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

Clinicopathological spectrum of atopic dermatitis and related conditions

Lorenzo Cerroni

Atopic dermatitis

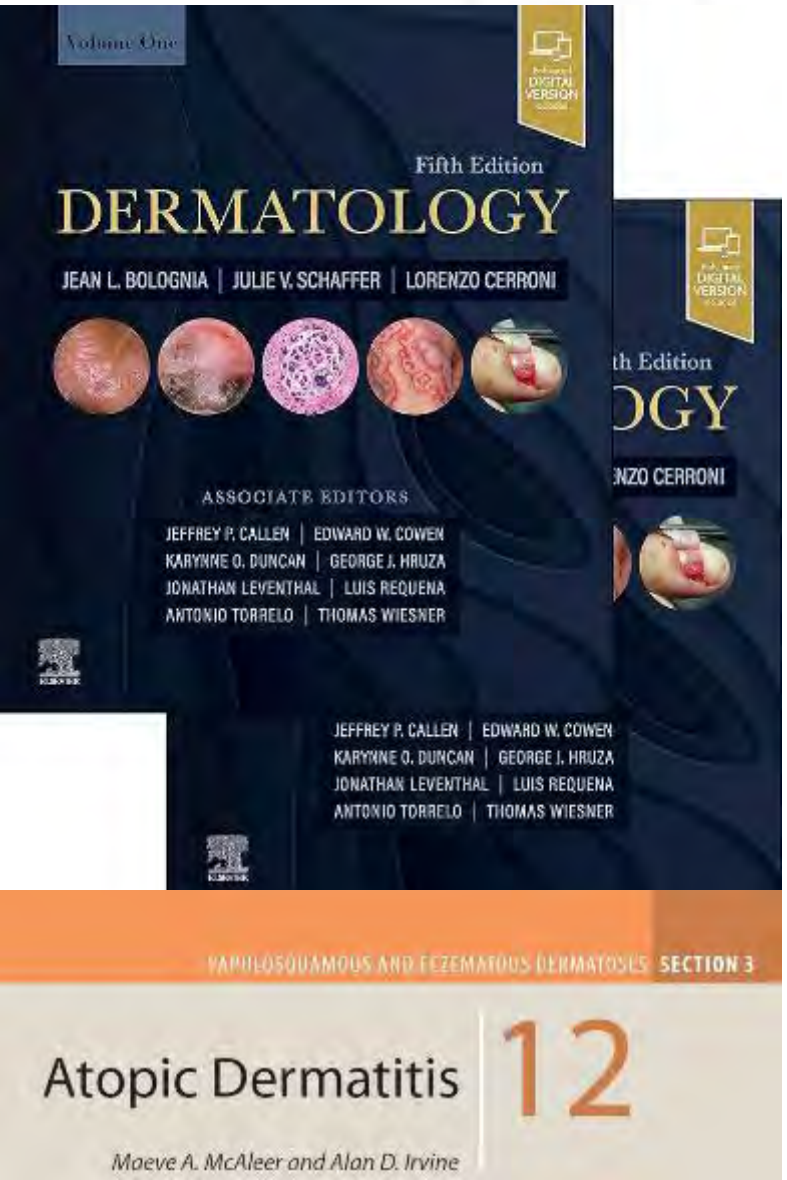
- "Atopy" refers to the tendency to develop IgE-mediated allergic reactions such as allergic rhinitis, asthma and atopic dermatitis
- Several patients (20-30%) with the clinical phenotype of atopic dermatitis have no evidence of IgE sensitization (non-IgE-associated atopic dermatitis)
- Infantile (<2); ~60% of patients go into remission by the age of 12
- Childhood (2-12)
- Adolescent / Adult (>12)
- Senile (>60)
- Many (regional) variants
- Association with other diseases (esp. infections, ichthyosis vulgaris)

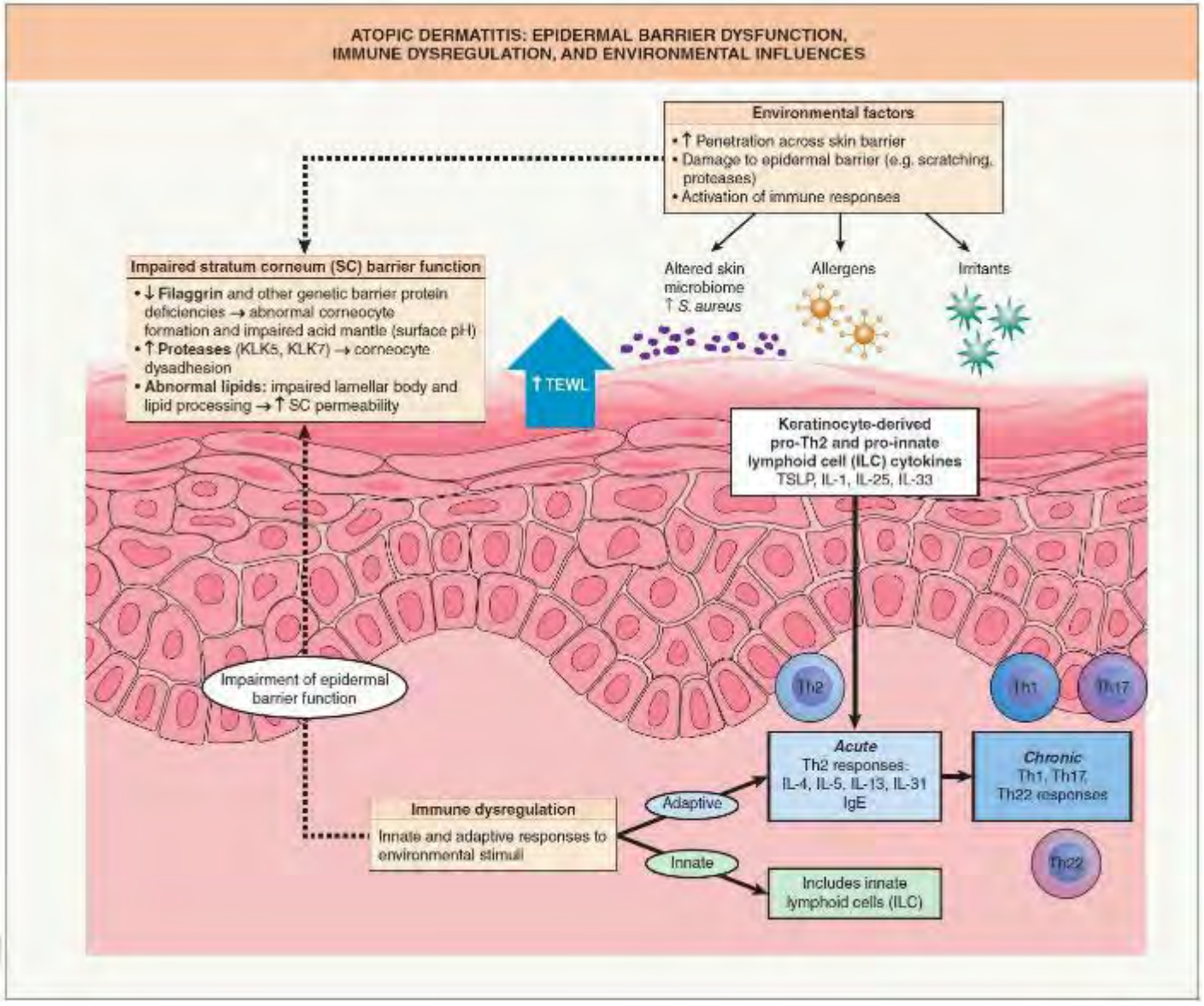
On the Classification of the Phenomena of Hypersensitiveness

Arthur F. Coca and Robert A. Cooke

J Immunol May 1, 1923, 8 (3) 163-182;

1st mention of "atopy"





Atopic Dermatitis 12

Maeve A. McAleer and Alan D. Irvine

Essential features
(must be present and are sufficient for diagnosis)

- Pruritus
- Typical eczematous morphology and age-specific distribution patterns
- Chronic or relapsing course

DIAGNOSTIC FEATURES AND TRIGGERS OF ATOPIC DERMATITIS (AD)

Essential features: must be present and are sufficient for diagnosis

- Pruritus
  - Rubbing or scratching can initiate or exacerbate flares ("the itch that rashes")
  - Often worse in the evening and triggered by exogenous factors (e.g. sweating, rough clothing)
- Typical eczematous morphology and age-specific distribution patterns (see Fig. 12.3)
  - Face, neck, and extensor extremities in infants and young children
  - Flexural lesions at any age
  - Sparing of groin and axillae
- Chronic or relapsing course

Important features: seen in most cases, supportive of diagnosis

- Onset during infancy or early childhood
- Personal and/or family history of atopy (IgE reactivity)
- Xerosis
  - Dry skin with fine scale in areas *without* clinically apparent inflammation; often leads to pruritus

Associated features: suggestive of the diagnosis, but less specific (see Figs. 12.3 & 12.15)

- Other filaggrin deficiency-associated conditions: keratosis pilaris, hyperlinear palms, ichthyosis vulgaris
- Follicular prominence, lichenification, prurigo lesions
- Ocular findings: recurrent conjunctivitis, anterior subcapsular cataract; periorbital changes: pleats, darkening
- Other regional findings, e.g. perioral or periauricular dermatitis, pityriasis alba
- Atypical vascular responses, e.g. midfacial pallor, white dermographism*, delayed blanch

Triggers

- *Climate:* extremes of temperature (winter or summer), low humidity
- *Irritants:* wool/rough fabrics, perspiration, detergents, solvents
- *Infections:* cutaneous (e.g. *Staphylococcus aureus*, molluscum contagiosum, herpes simplex) or systemic (e.g. URI)
- *Environmental allergies:* e.g. to dust mites, pollen, contact allergens
- *Food allergies:*
  - Trigger in small minority of AD patients, e.g. 10%–30% of those with moderate to severe, refractory AD
  - Common allergens: egg > milk, peanuts/tree nuts, (shell)fish, soy, wheat
  - Detection of allergen-specific IgE (via blood and skin prick tests) does *not* necessarily mean that allergy is triggering the patient's AD

*Stroking the skin leads to a white streak that reflects excessive vasoconstriction.

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MINI REVIEW

Deciphering atopic dermatitis heterogeneity: a short review on the translational revolution from endotypes to immunotypes

Alvaro Prados-Carmona[1,2,3] | Husein Husein-ElAhmed[2,4] | Francisco J. Navarro-Triviño[2,5,6] | Ricardo Ruiz-Villaverde[1,2]

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Correspondence
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Summary
Atopic dermatitis is the most prevalent chronic inflammatory skin disease, classically defined by its eczematous lesions and relapsing course. However, growing evidence over the past decade has revealed that this disease is in fact far more heterogeneous than previously thought – both in its clinical manifestations and in the underlying molecular and immunological mechanisms. This short review explores the evolving conceptual framework used to analyze atopic dermatitis, encompassing clinical presentations (phenotypes), immune polarization profiles (immunotypes), and the background disease-related and context-related factors that shape them. The aim of this review is to highlight how such heterogeneity influences disease severity, progression, and therapeutic response, particularly in the context of increasingly personalized treatment strategies. By synthesizing accumulated scientific and clinical insights, this short review provides clinicians with a practical guide to navigating the complex spectrum of AD and its underlying therapeutic targets. Recognizing and interpreting this multidimensional variability is essential for understanding disease course and optimizing treatment selection.

KEYWORDS
[illegible]

INTRODUCTION AND RELEVANCE

The more we discover about the underlying factors driving disease development and progression in atopic dermatitis (AD), the more our understanding of its broad spectrum of clinical manifestations continues to grow. This knowledge has also paved the way for a new era of therapeutic strategies in patients with AD.[1] However, the existence of such heterogeneity in clinical presentations under the umbrella of a single disease can pose a significant challenge for definitive diagnosis, precise classification of disease subtype, and appropriate treatment selection.

CLINICAL EVALUATION

Despite advances in the molecular and immunological understanding of the disease, there is no single definitive diagnostic test for AD. Diagnosis still relies on established clinical criteria and a detailed patient history. However, current diagnostic criteria may not fully capture the diverse presentations of AD across different populations and disease stages.[2]

It is well established that the distribution of lesions varies with age. In infants, AD commonly affects the face, trunk, and extensor surfaces, typically sparing the diaper area. In older children and adults, flexural involvement (such as antecubital and popliteal fossae) becomes more prominent, and adults can also frequently exhibit hand dermatitis.[3] Additionally, AD lesions can present in three

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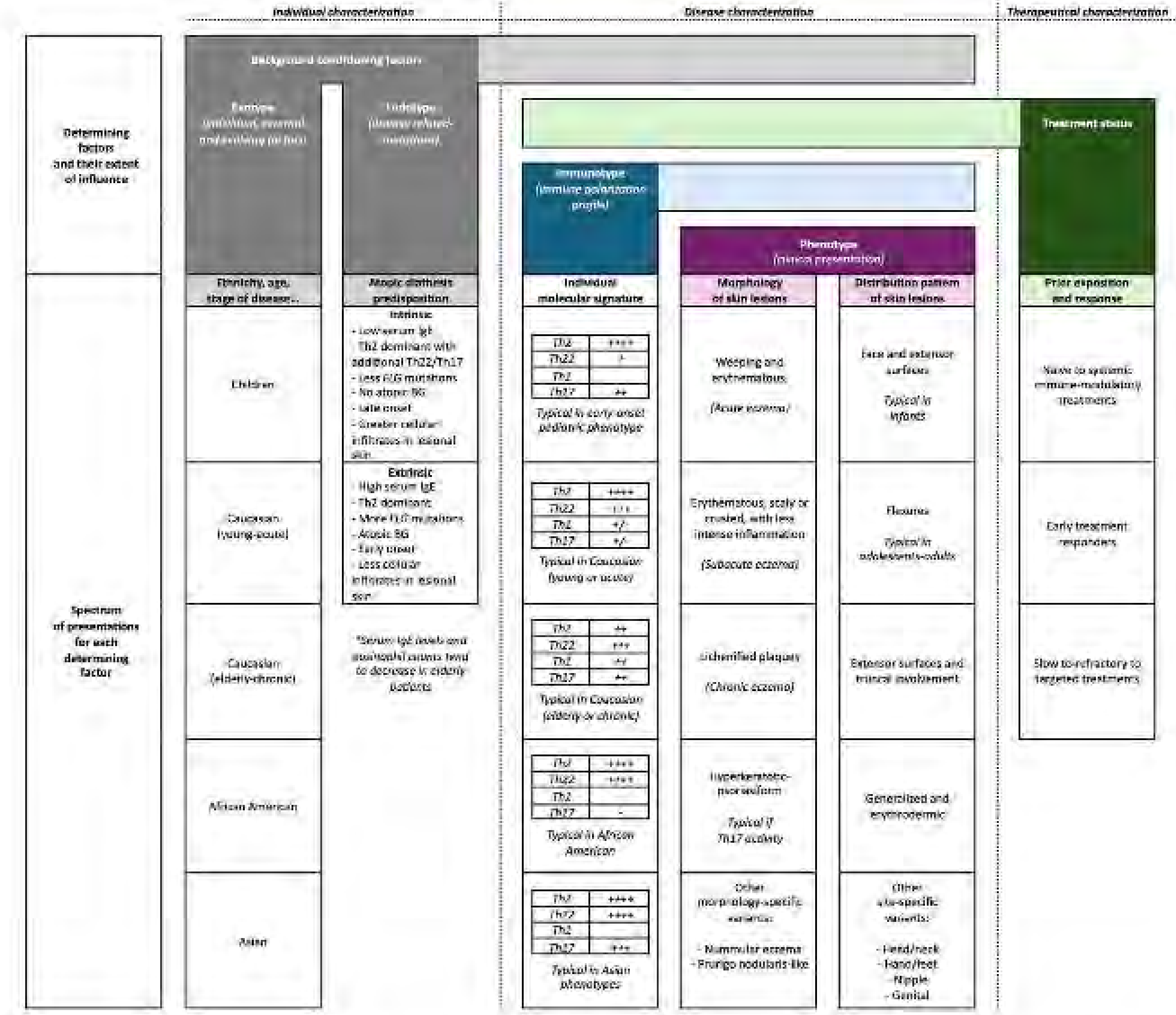

FIGURE 1 Conceptual framework of the heterogeneity of AD. There are various possibilities for each of the variables that define the individual clinical picture. This figure summarizes the diverse clinical presentations (phenotypes), immune profiles (immunotypes), background factors, and treatment status of the patient. Both phenotype and immunotype are influenced by background determinants and treatment status. Other factors including disease severity and comorbidities will influence the final patient profile.

Clinical consequences of age-related skin barrier dysfunction: Part II. Approach to barrier dysfunction in the geriatric population

Maggie Sanders, BS,[a] Rachel Waldrab, BS,[b,c] Nelly Kokikian, BS,[b,c] Catherine M. Ni, MD,[b] and Amy R. Vandiver, MD, PhD[b,c]

Publication History
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Aging is associated with significant changes in skin structure and function, which lead to distinct clinical needs in geriatric dermatology patients. By understanding the relationship between altered skin function with aging and the clinical implications for geriatric dermatology patients, dermatologists can quickly a preventative approach and manage age-related skin pathology. The second article of this 2-part continuing medical education series reviews the most common conditions affecting geriatric dermatology patients and specific treatment considerations (J Am Acad Dermatol 2025;93:917-28.)

Key words: aging; barrier dysfunction; [illegible]

From the Kirk Kerkorian School of Medicine at University of Nevada, Las Vegas, Nevada[a]; Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California[b]; and Division of Dermatology, Department of Medicine, Samuel Oschin School of Medicine, University of California, Los Angeles, California[c]

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Correspondence: Amy R. Vandiver, MD, PhD, Greater Los Angeles Veterans Affairs Healthcare System and Division of Dermatology, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, 11301 Wilshire Boulevard, Building 500, Room 3301, Los Angeles, CA 90073. Email: avandiver@mednet.ucla.edu.

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blood–brain barrier (reviewed in[15]), and thus hypothesized that declining barrier function with age may increase the risk of dementia through increased systemic inflammation.[15] This theory is supported by population data demonstrating an association between decreased skin barrier function and decline in some cognitive measures with age,[15] as well as an association between atopic diseases in older adults and increased risk of both vascular dementia and Alzheimer disease.[8]

Age-associated changes in skin barrier function thus have broad consequences impacting not only cutaneous health, but also have broader effects on function and health for aging patients and their caregivers. It is vital that physicians consider and prioritize treating skin barrier dysfunction and associated conditions in their older patients.

CLINICAL MANIFESTATIONS OF AGE-RELATED BARRIER DYSFUNCTION

Key points

- Common manifestations of disrupted barrier function include xerosis cutis, atopic dermatitis (AD), contact dermatitis, stasis dermatitis, hypersensitivity dermatitis, drug reactions, seborrheic dermatitis, and cutaneous infections.
- The age-related skin barrier changes can lead to conditions that significantly affect the quality of life and overall well-being of geriatric patients.

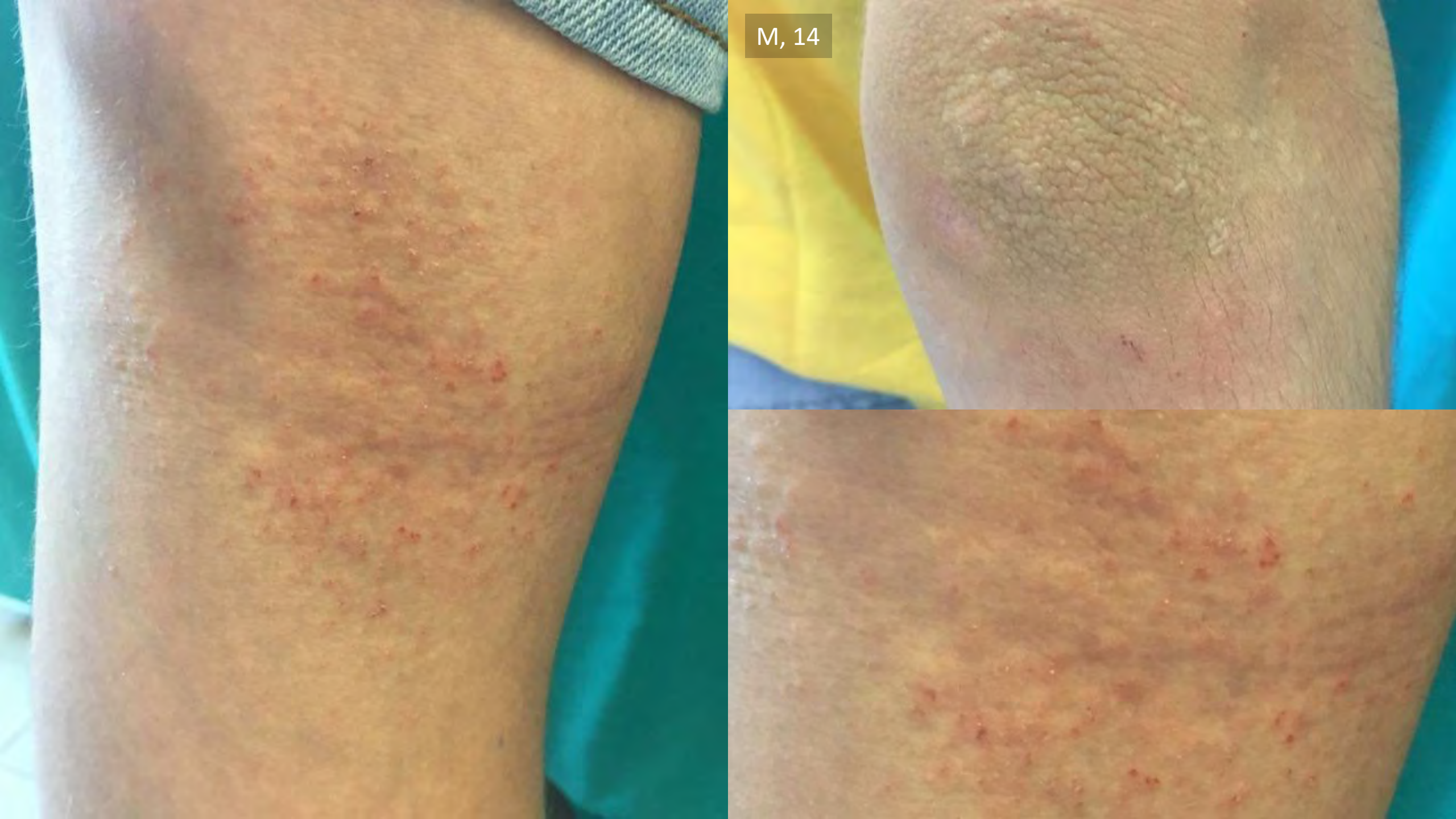
The clinical impact of skin aging is seen daily in dermatology clinics through many of the conditions identified more commonly in older patients. Below, we highlight the most diagnosed dermatoses in geriatric patients. Although increased benign and malignant neoplasia is also noted in the studies discussed above, these are addressed extensively elsewhere.[16,17]

Xerosis cutis. Xerosis cutis is a dermatologic condition that is especially common in elderly adults. It is estimated that between 58% and 58% of elderly adults experience xerosis.[18,19] Xerosis is directly linked to the altered stratum corneum structure and lipid content of the aged epidermis, which alter the absorptive and retentive properties.[20,21] In addition, some medications and preexisting conditions, including radiation, end-stage renal disease, thyroid disease, HIV, and malignancies, increase the risk of xerosis in the elderly.[22] The most common presentation of xerosis in elderly adults is pruritic, cracked, scaling skin of the lower portion of the legs (Fig 1), but may also include the hands or trunk. The pruritus resulting from xerosis may cause secondary lesions due to scratching or rubbing of the skin, resulting in an increased risk of cutaneous infections.

AD. AD is a chronic dermatologic disease in which patients experience dry skin, pruritus, and eczematous dermatitis due to skin barrier defects. Although the onset of AD is most common in the first 5 to 6 months of a child's life, increased frequency is also reported in the geriatric population, with disease seen in 11.6% of adults aged >75 years in 1 cohort.[23] AD in geriatric patients is often more active and severe than in other age groups.[24] In comparison with child populations, elderly patients with AD showed less frequent lesions of the face and flexor surfaces.[25] Intriguingly, elderly patients with AD show significantly lower levels of serum immunoglobulin E and eosinophils than children and young adults with AD,[26] suggesting possible differences in the pathogenesis or systemic impacts of AD.

Contact dermatitis. Due to immunosenescence and weakening of the epidermal barrier, elderly patients are at a significantly increased risk of developing both irritant and allergic contact dermatitis.[27] Additionally, older patients are at an increased risk of exposures predisposing them to the onset of contact dermatitis. Frequent exposure to topical treatments in patients with stasis dermatitis or skin wounds increases the risk of experiencing allergic contact dermatitis. Similarly, irritant contact dermatitis is particularly common in the groin and buttock region in older adults, with incontinence-associated dermatitis documented in 3.4% of older adults experiencing incontinence[28] and up to 23% of adults admitted to long-term care facilities.[29] In older adults, rash due to contact dermatitis is most frequently found on the lower extremities, whereas in children, it more often presents on the face and hands.[30] In addition, studies focused on patch testing indicate elderly patients have shown a delayed onset of skin reaction to an exposure, less intense reactions, and slower recovery periods after a reaction occurs.[31]

Stasis dermatitis. In the United States, stasis dermatitis is estimated to affect 6% of patients aged >50 years.[32] It manifests as erythema, pruritus, and thick scale of the lower portion of the legs (Fig 2). There is an increased risk of developing stasis dermatitis in elderly patients when venous insufficiency is present due to the existing barrier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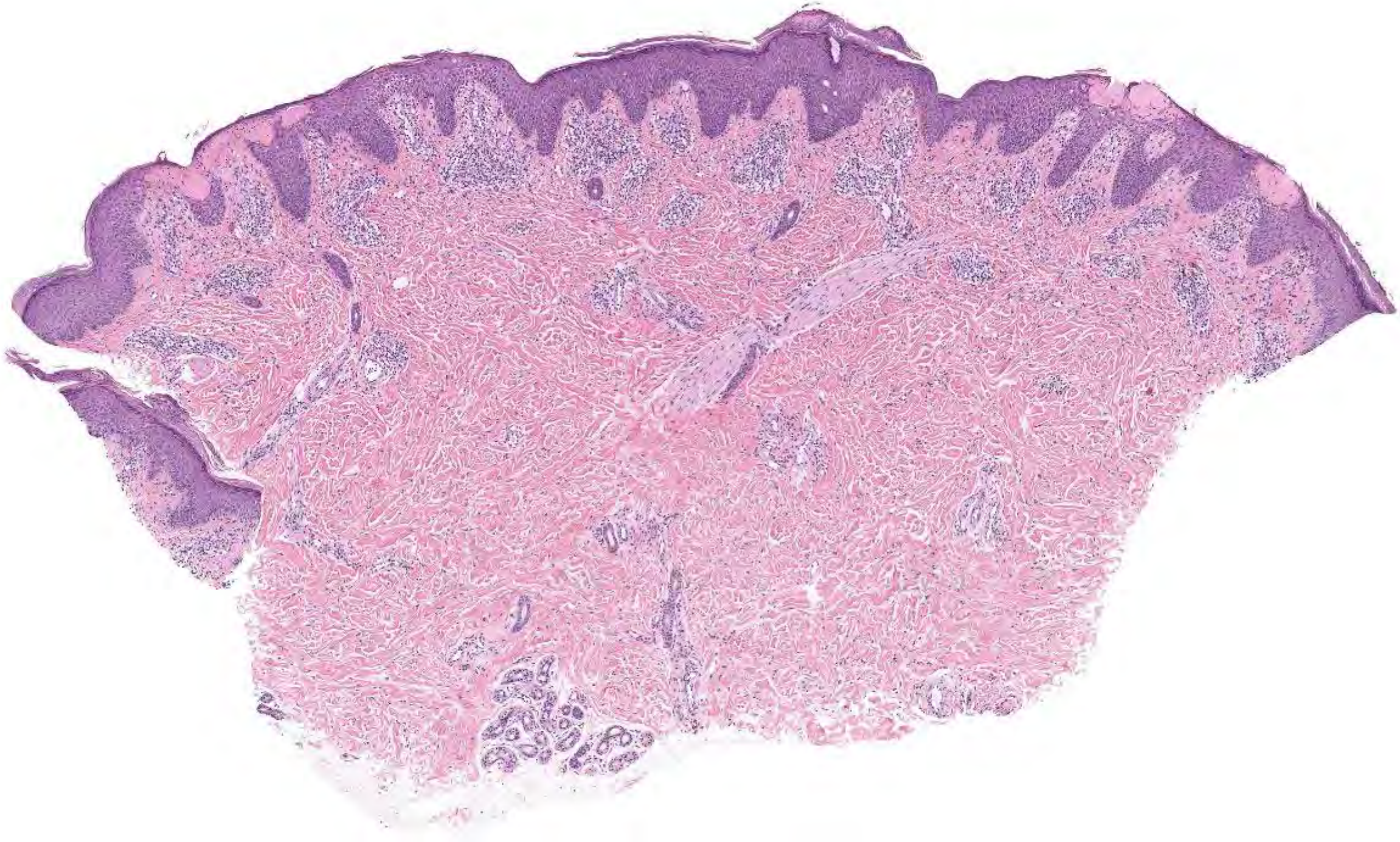

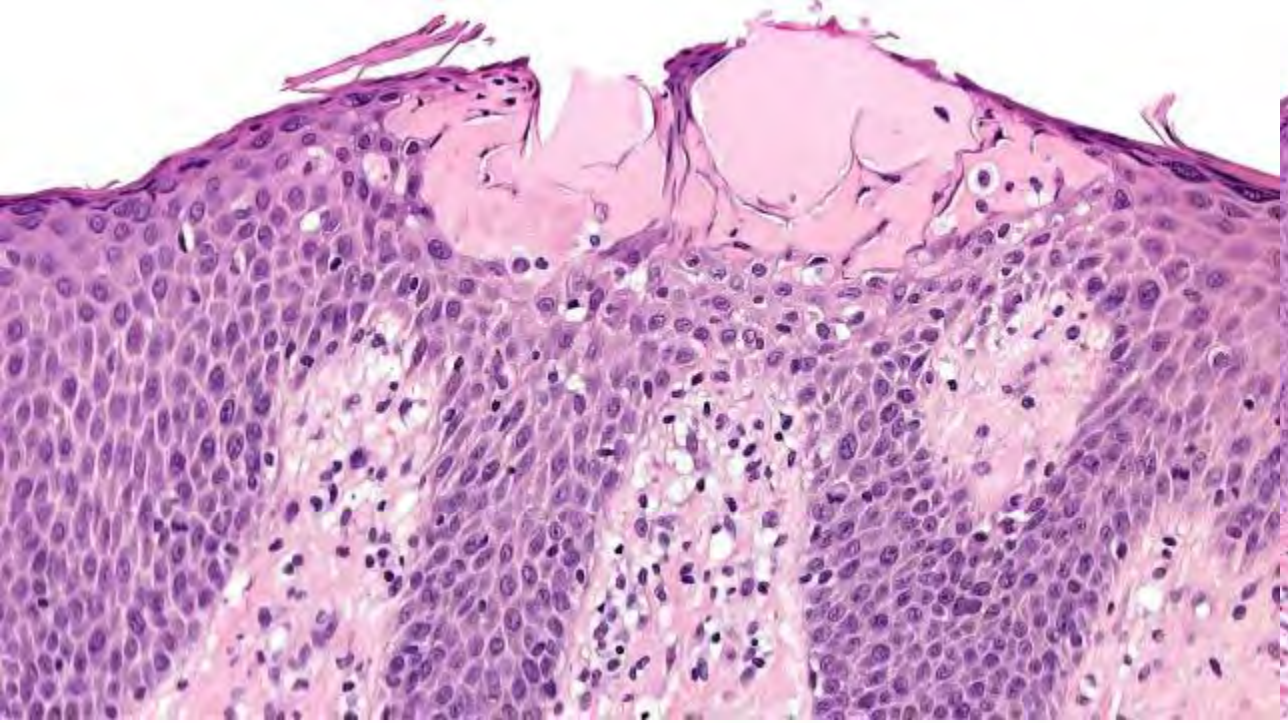
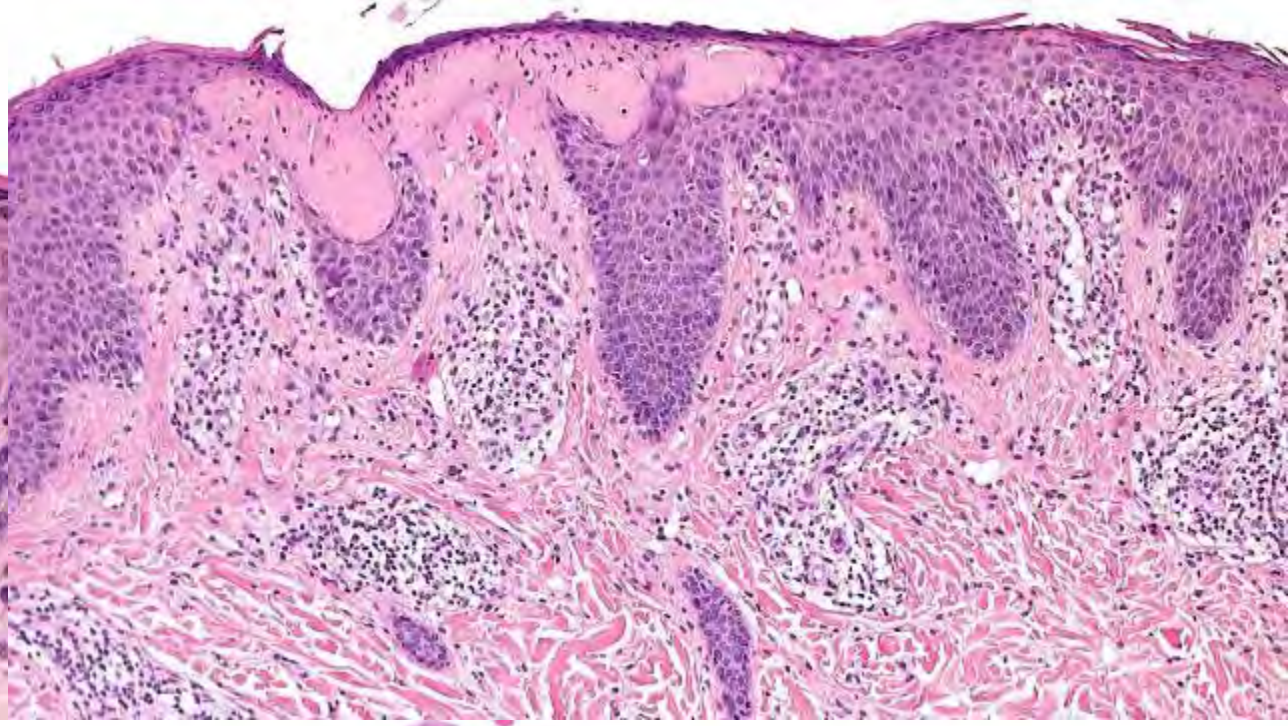
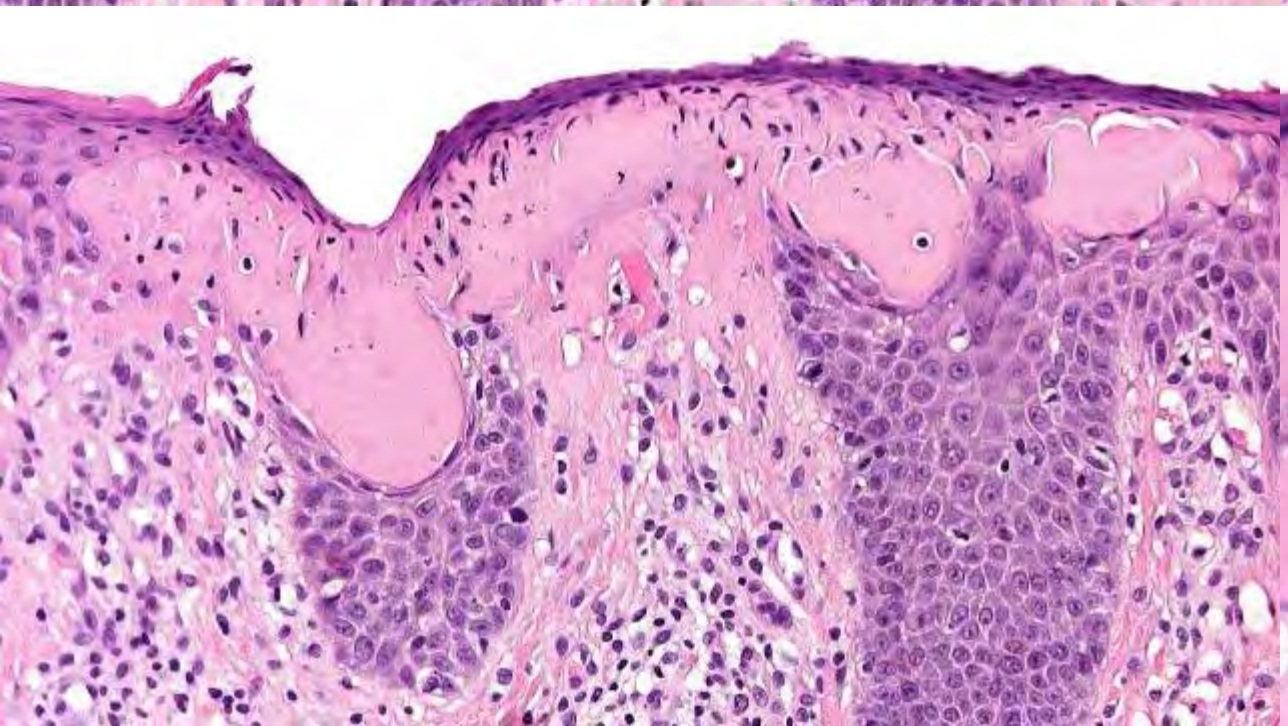
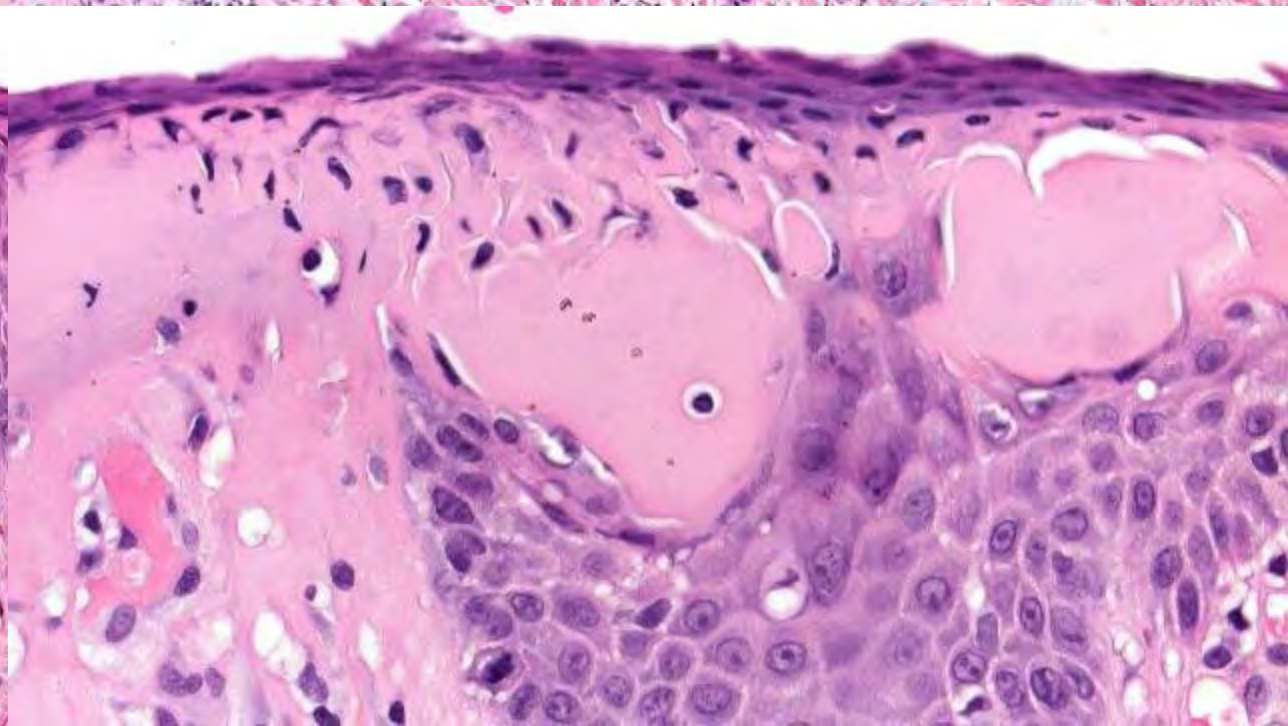

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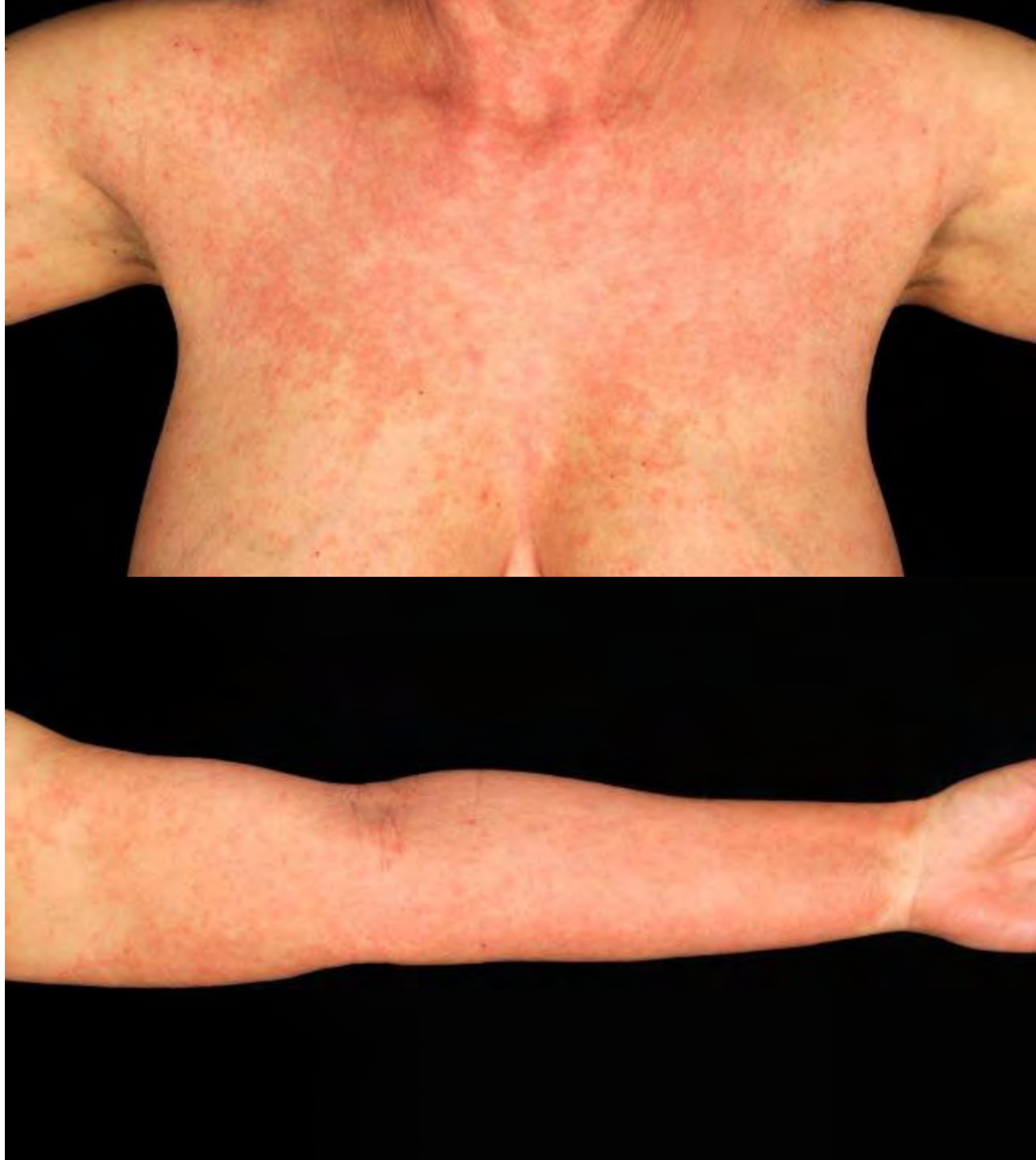

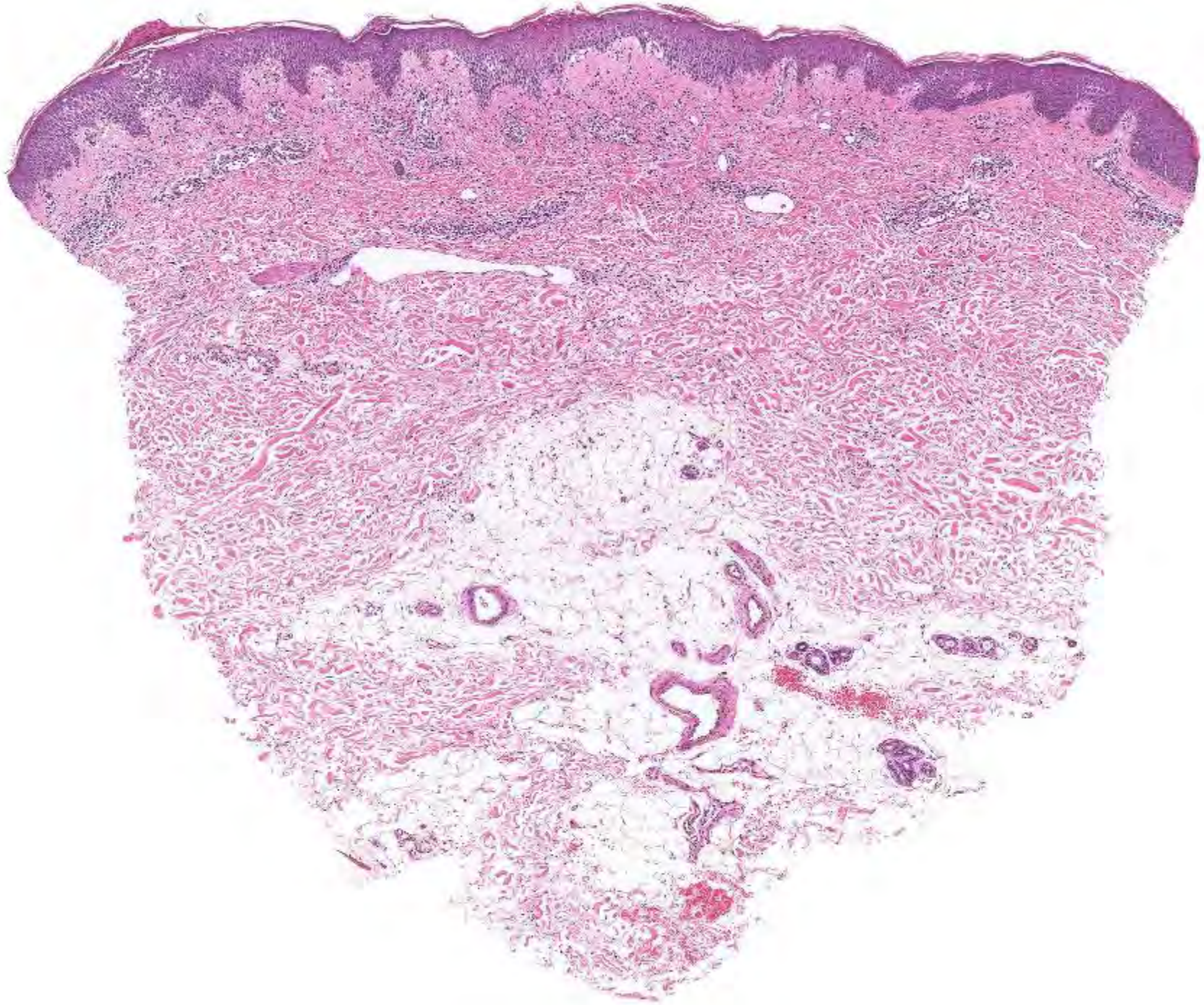

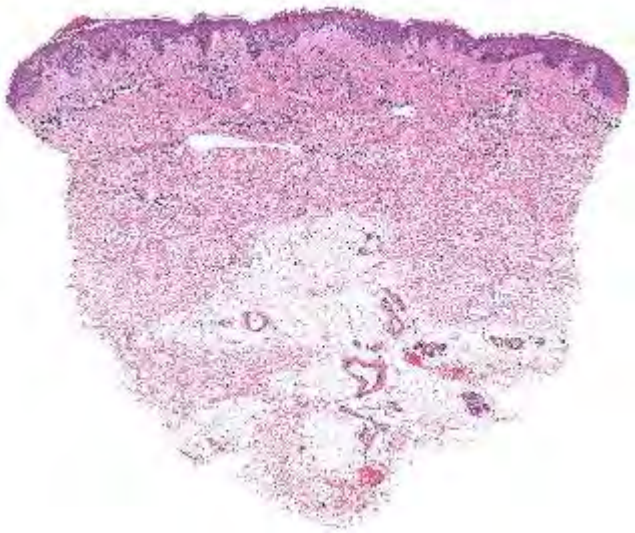

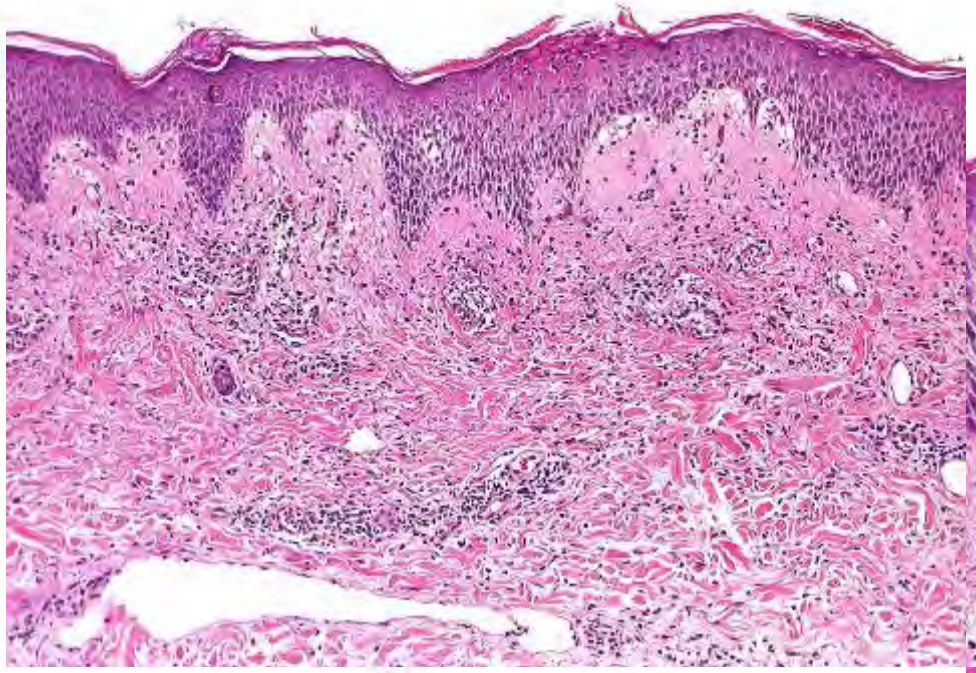

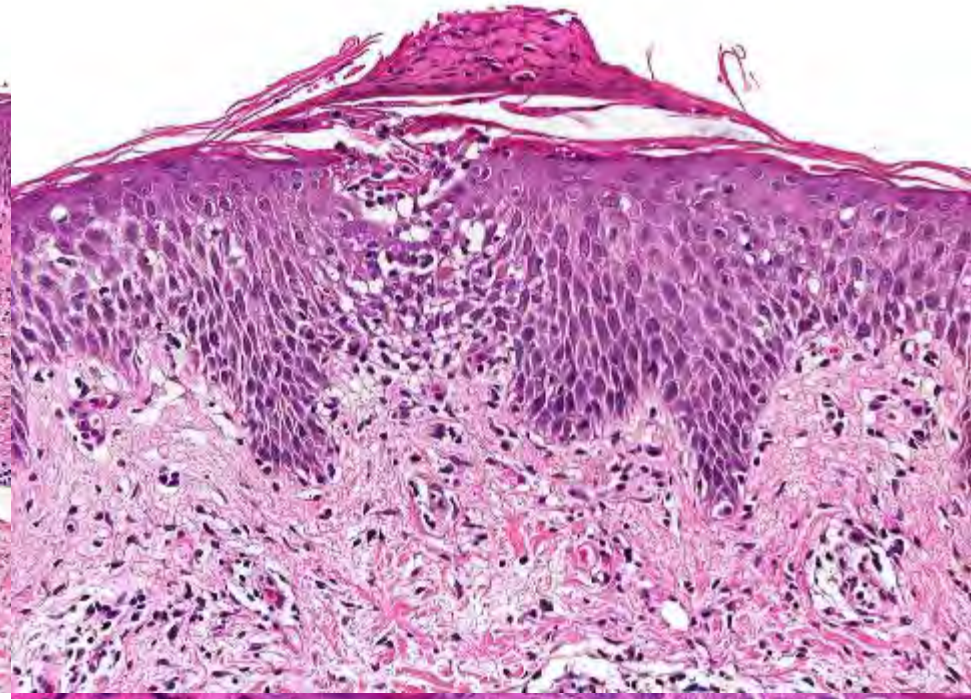

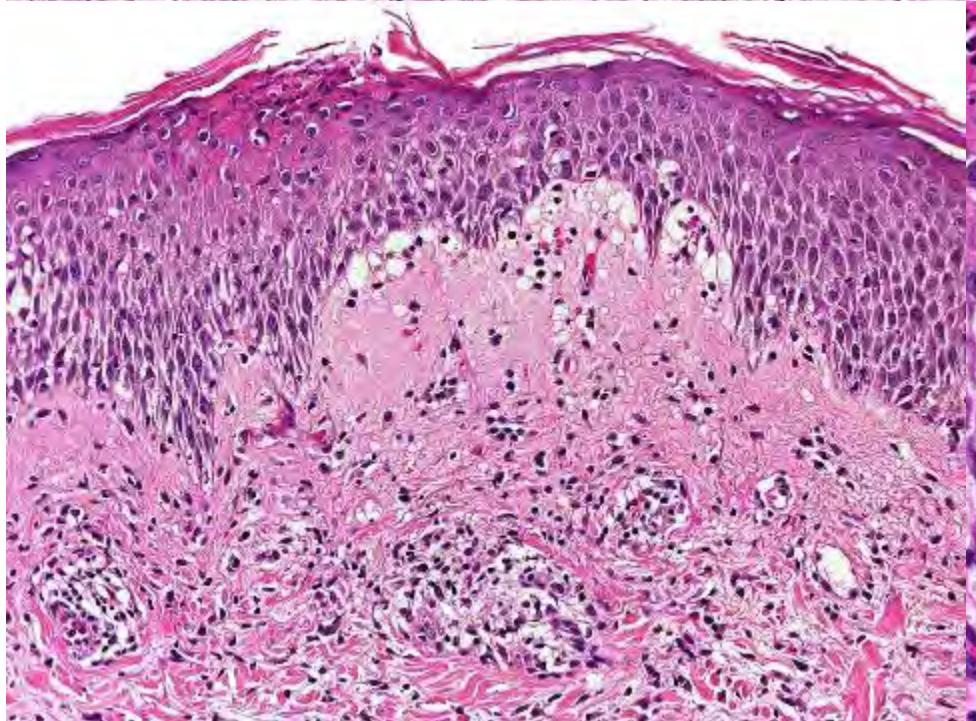

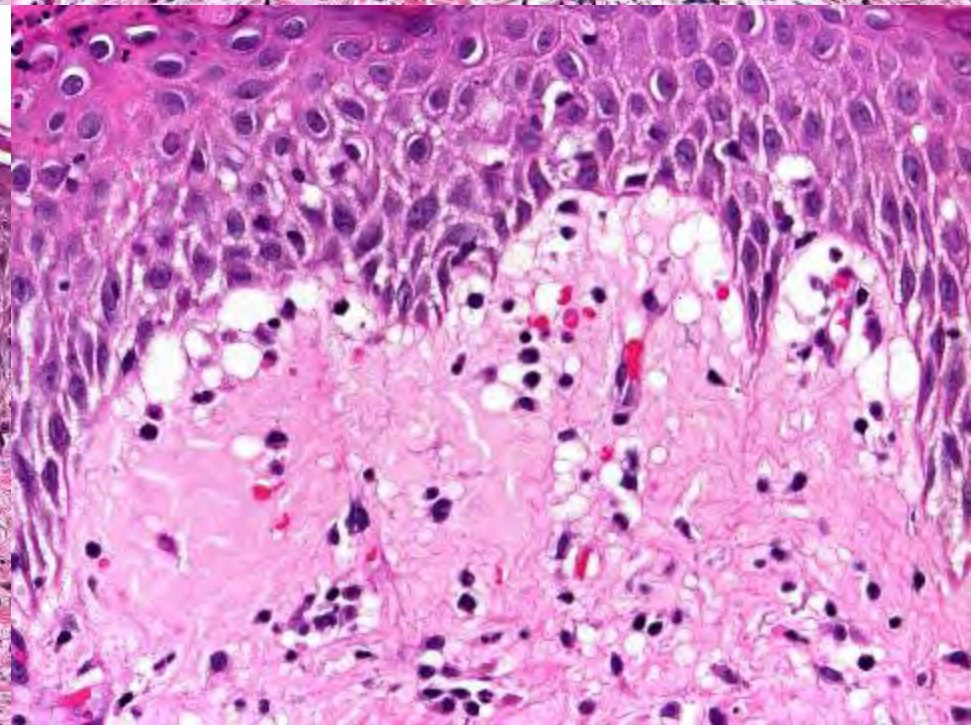

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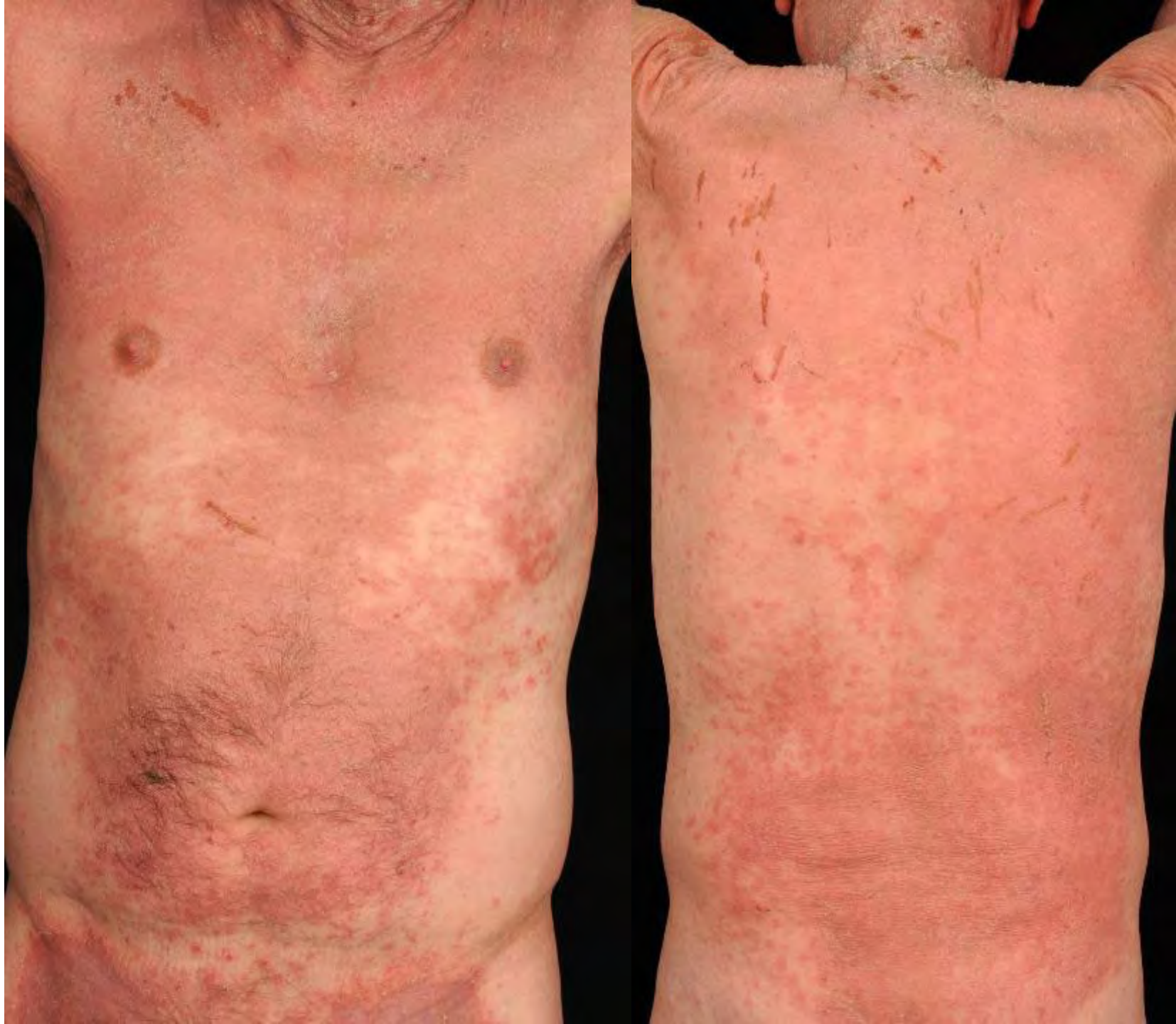

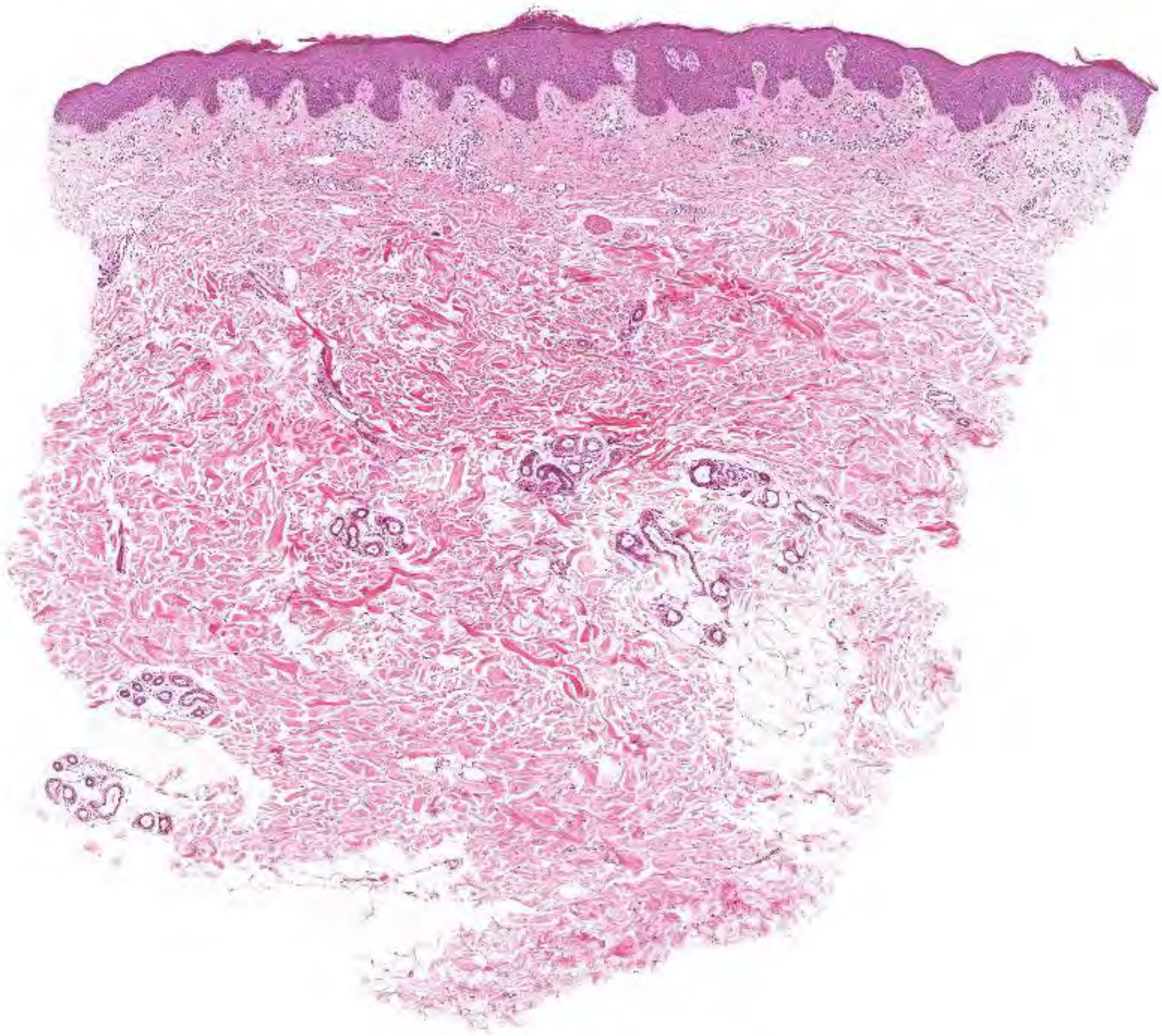

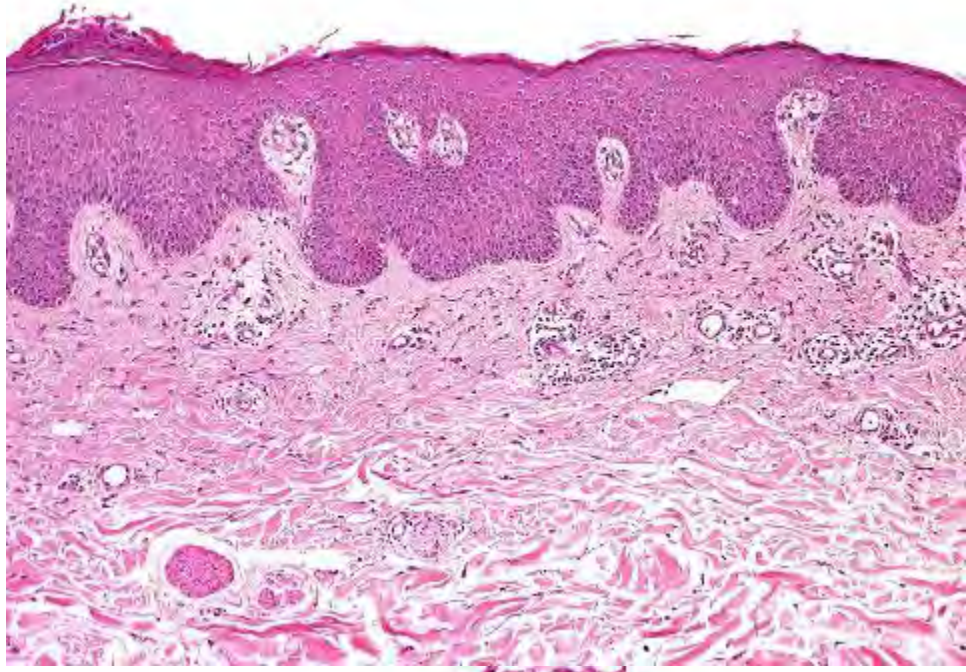

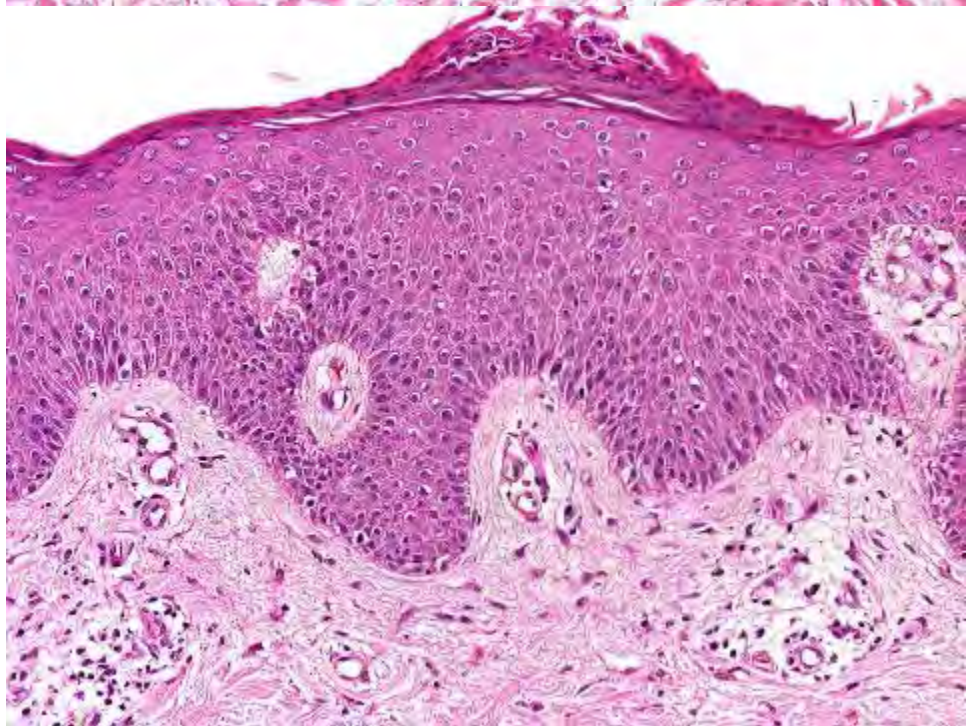

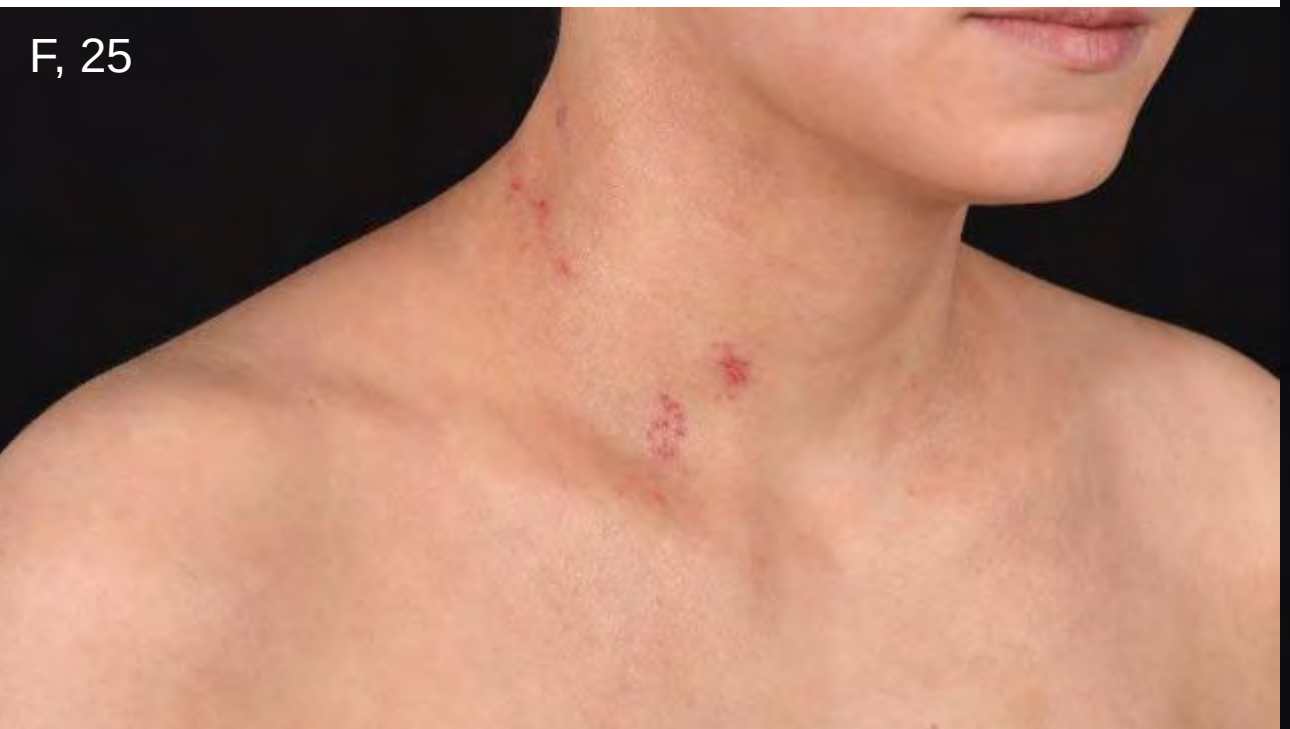
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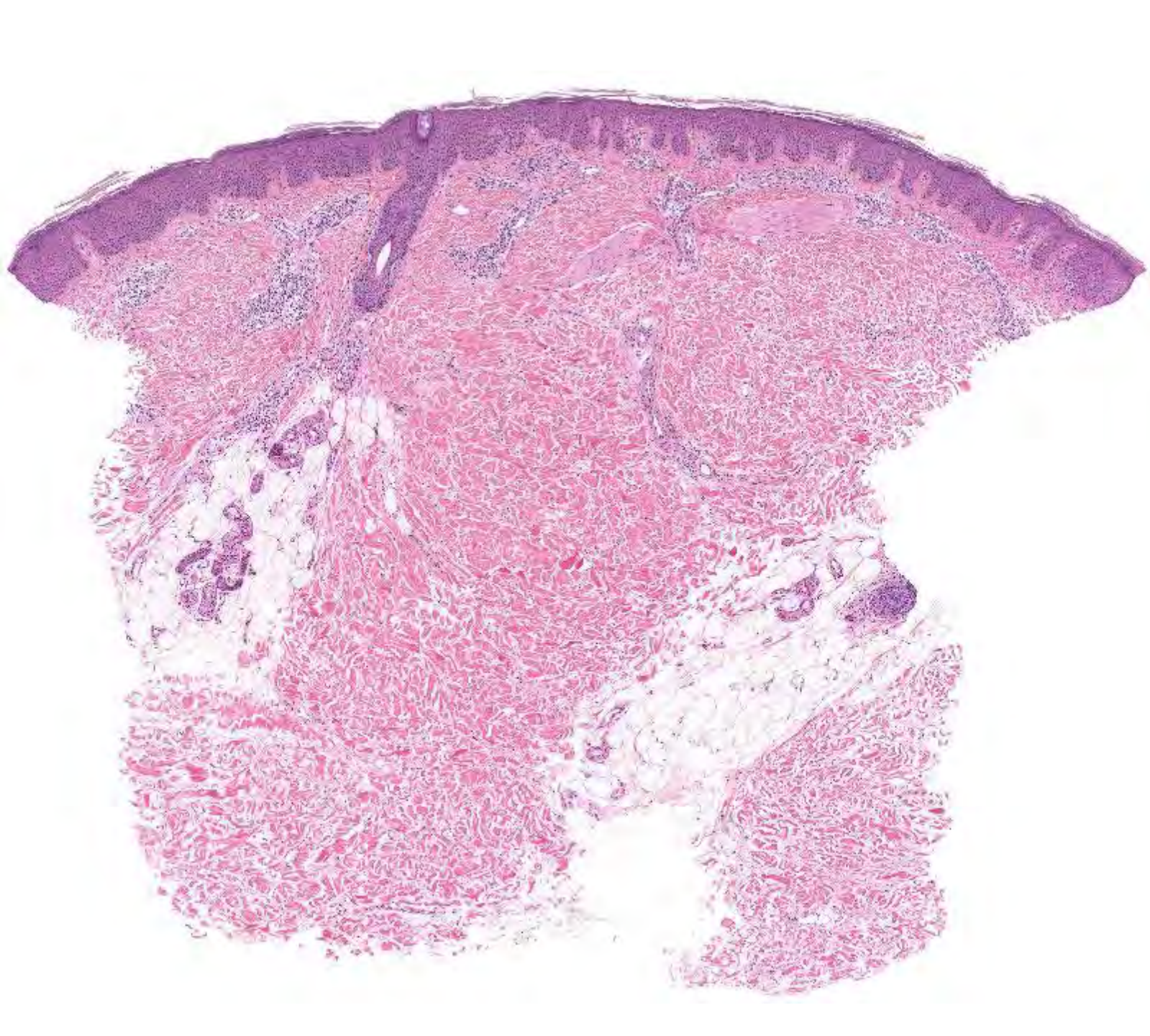

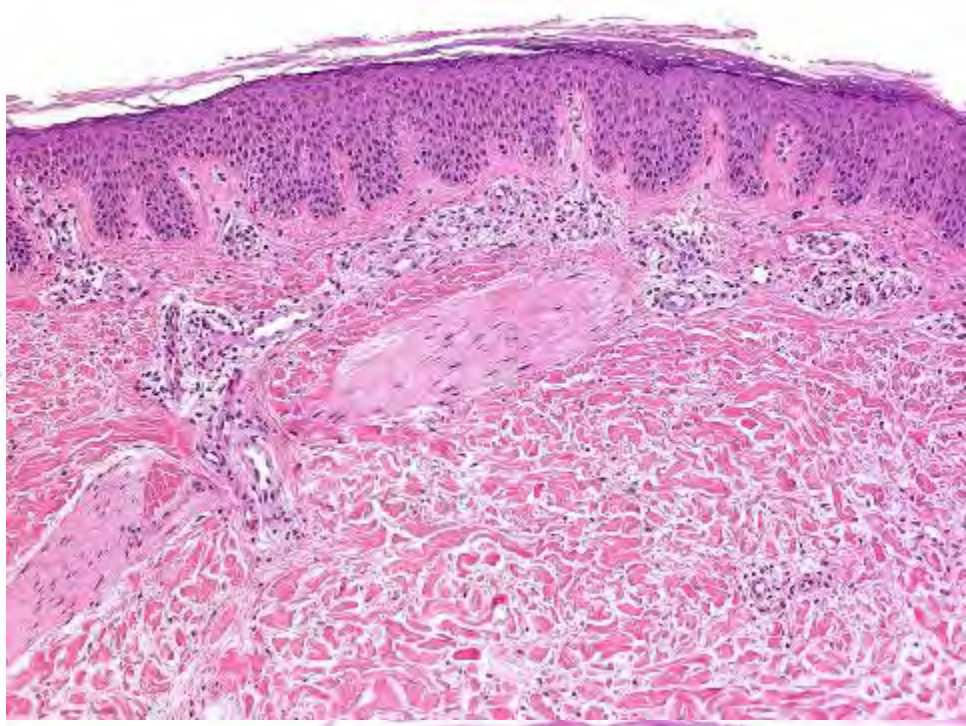

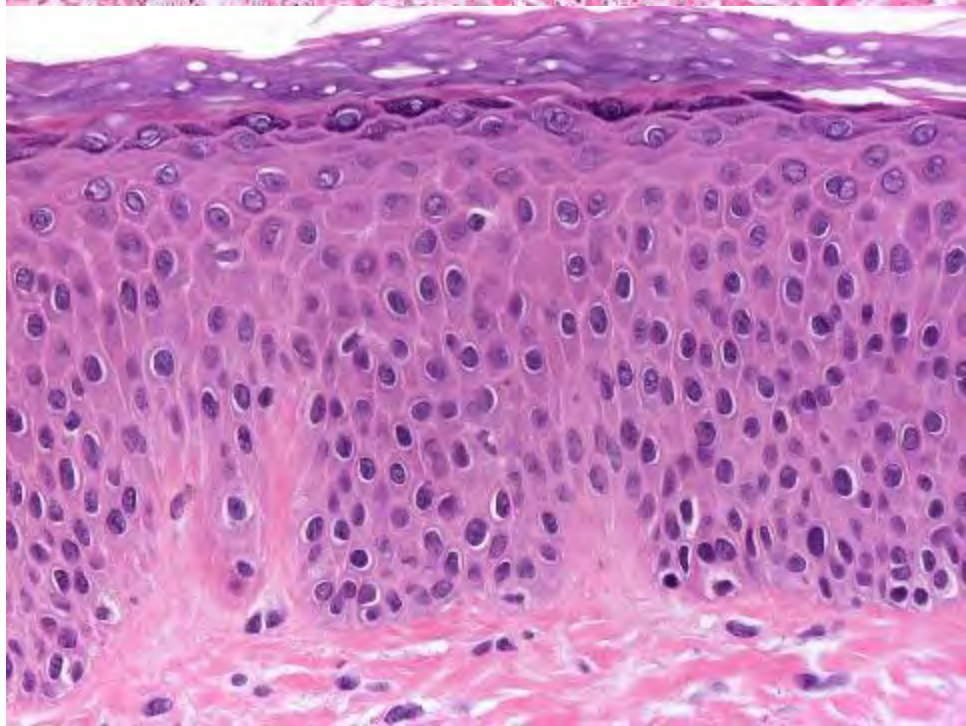

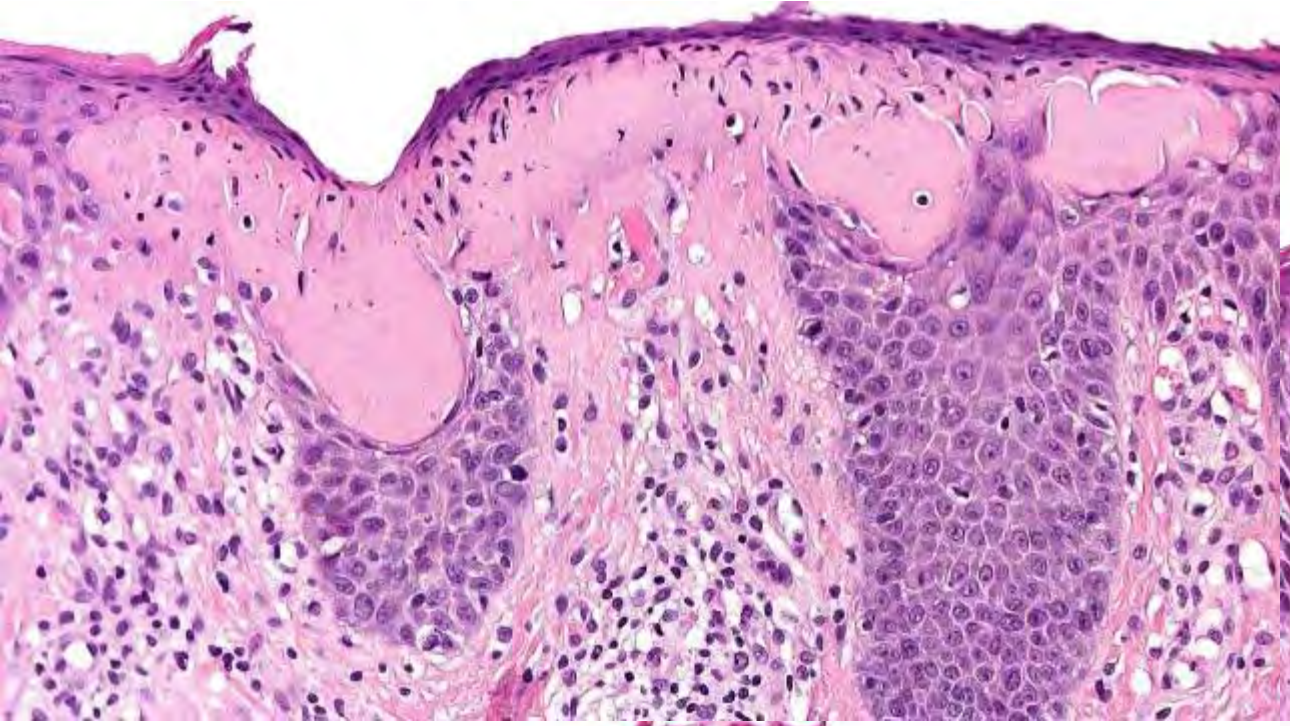
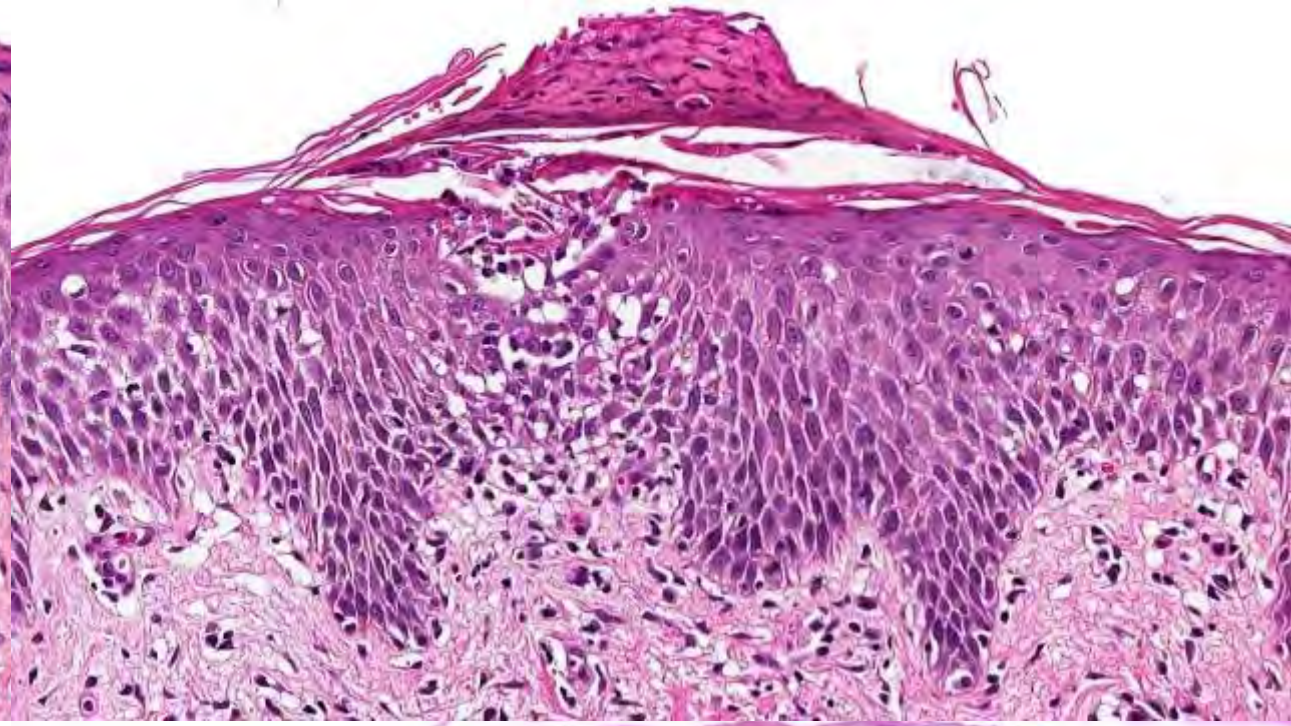
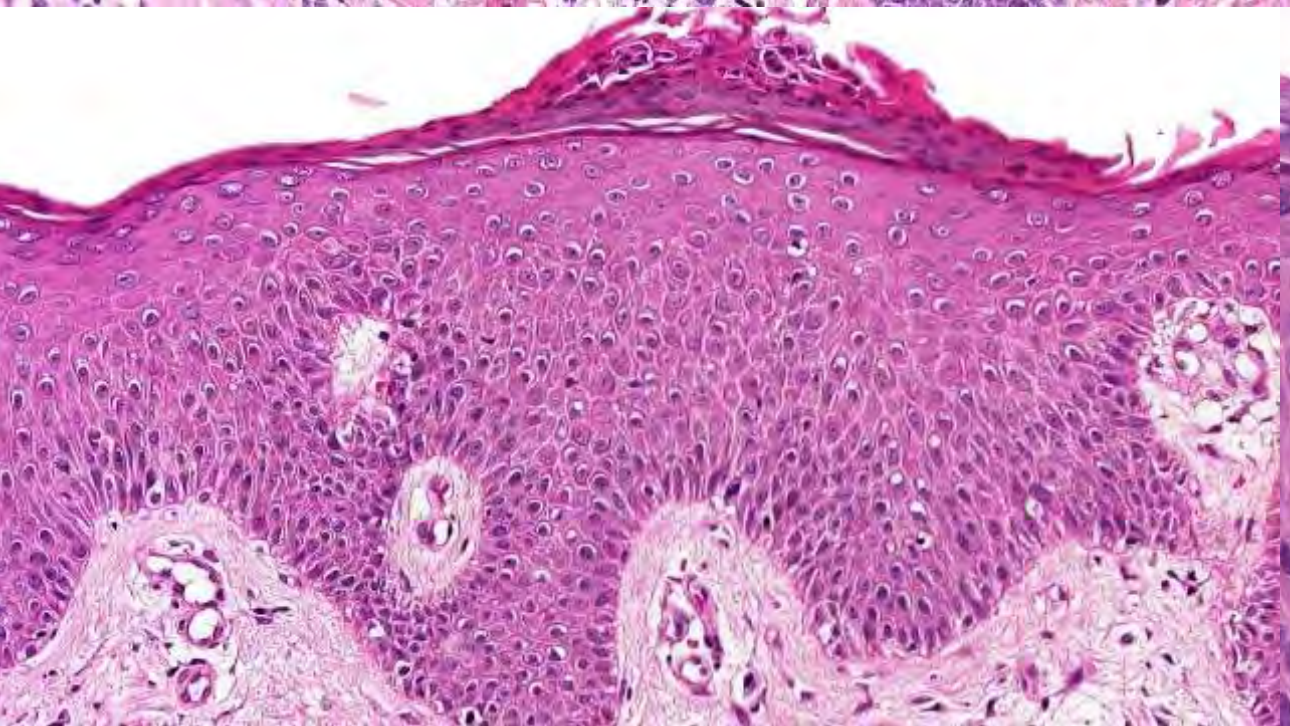
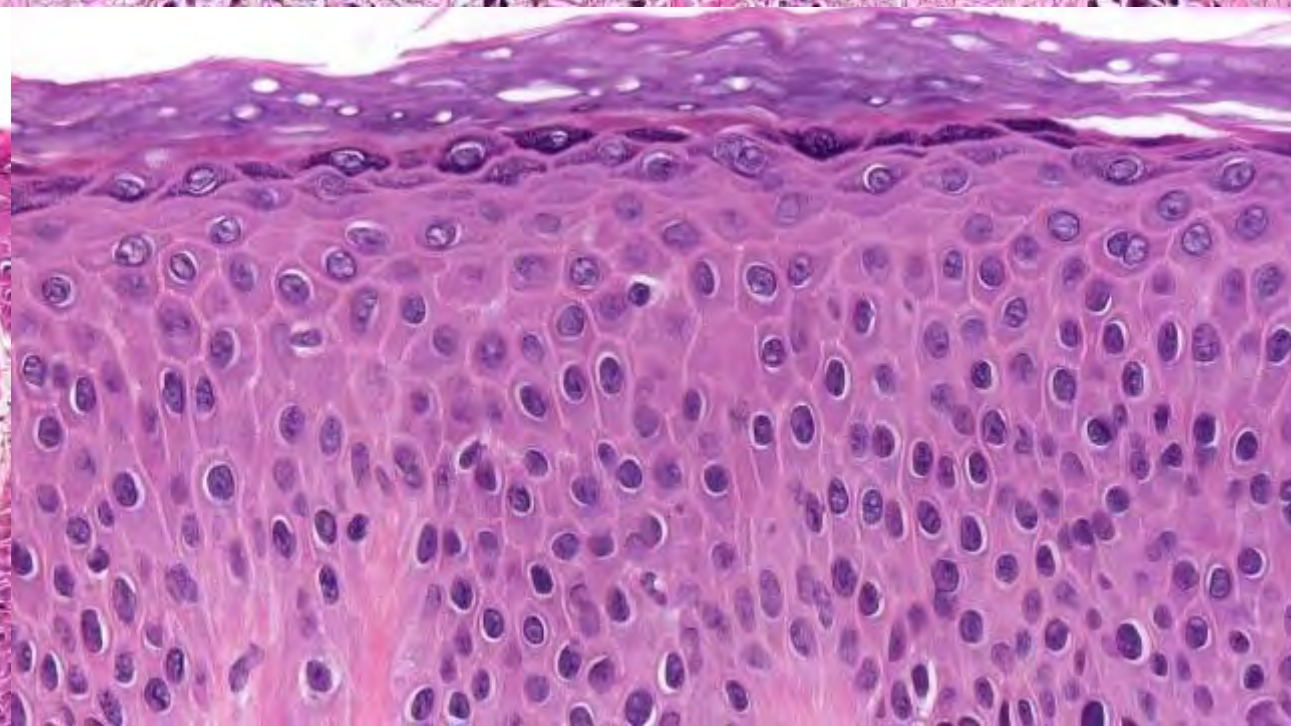

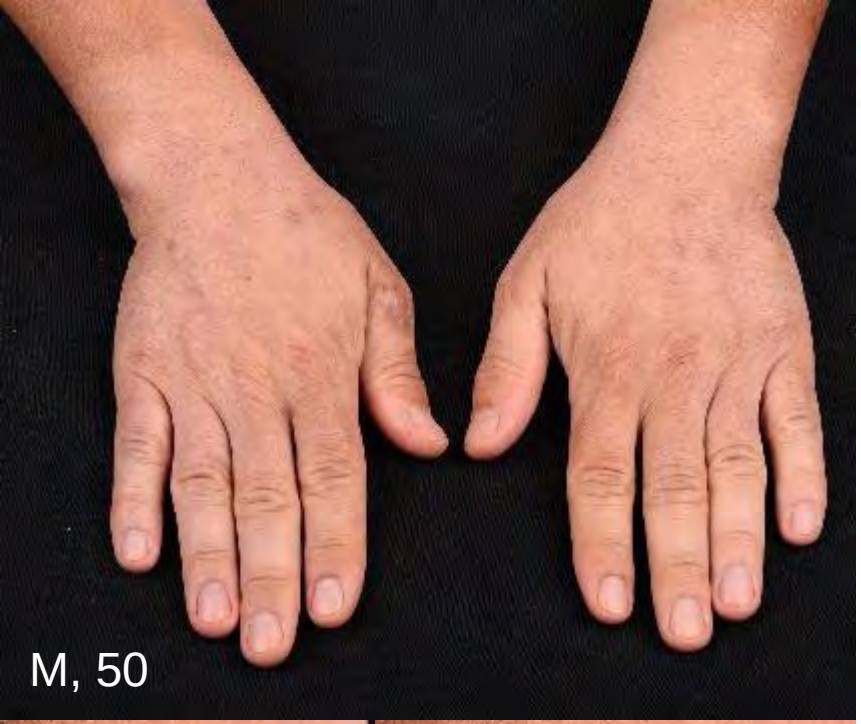
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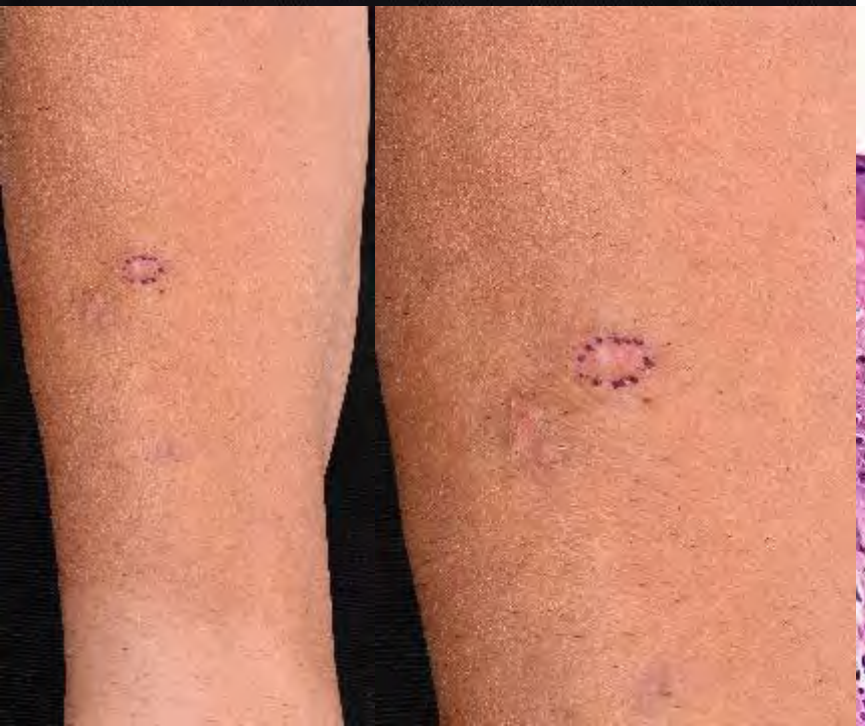

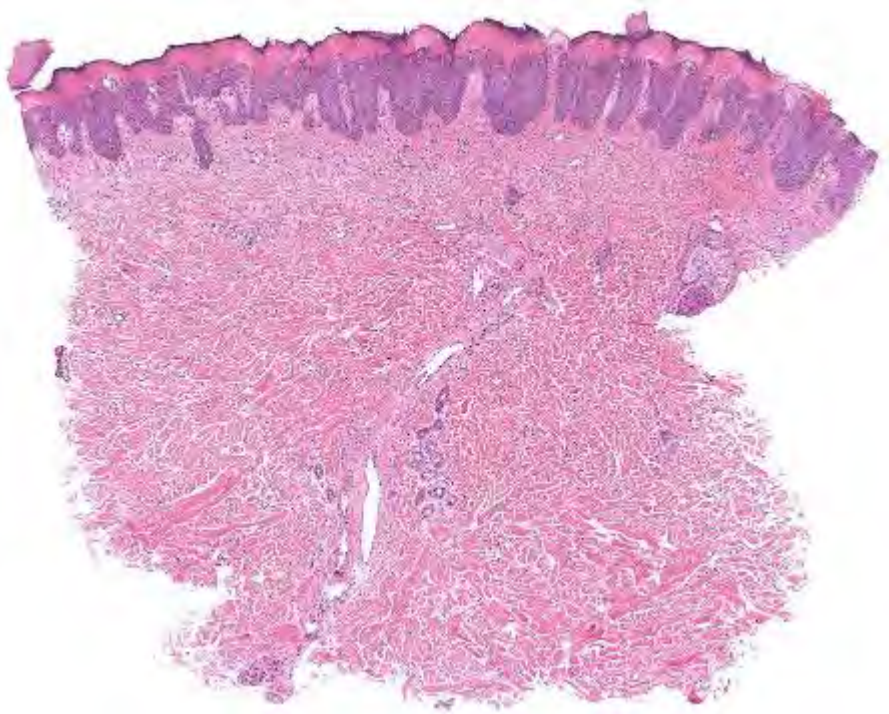

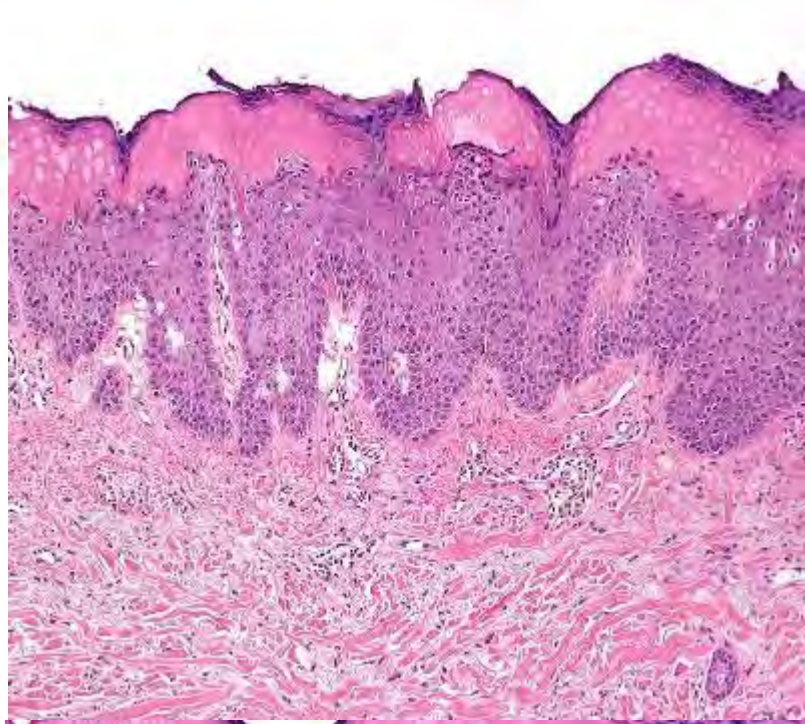

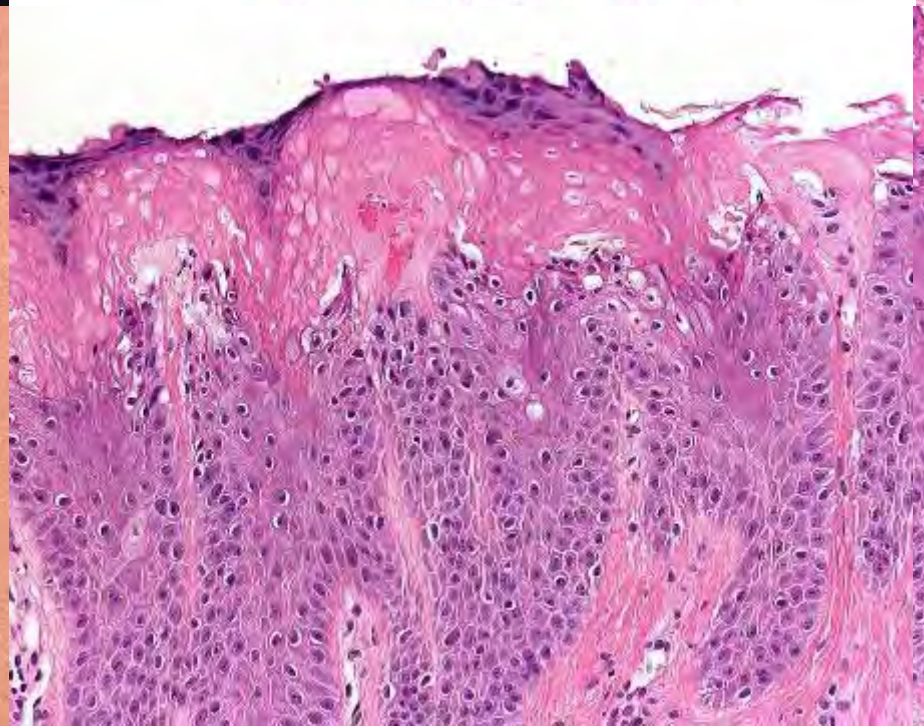

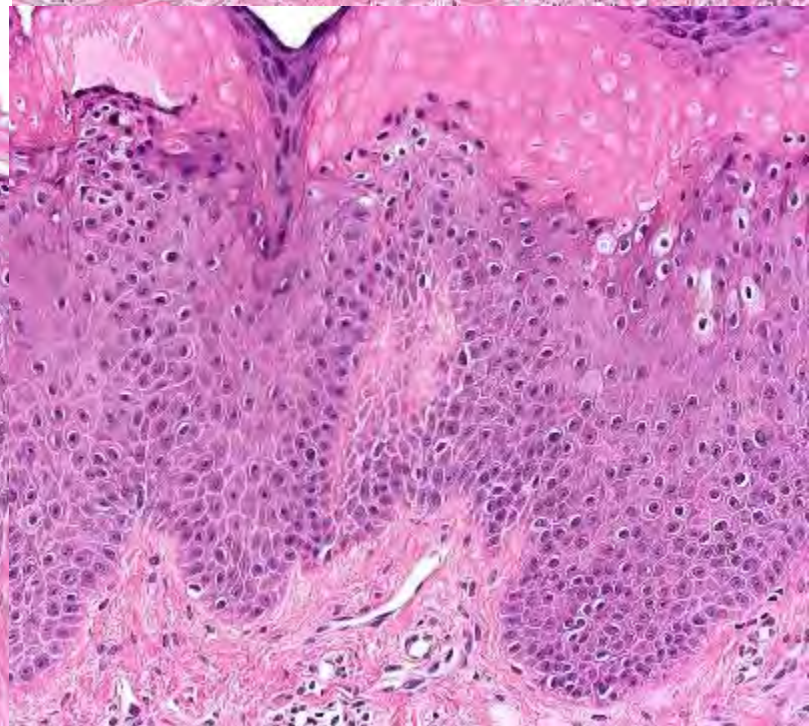

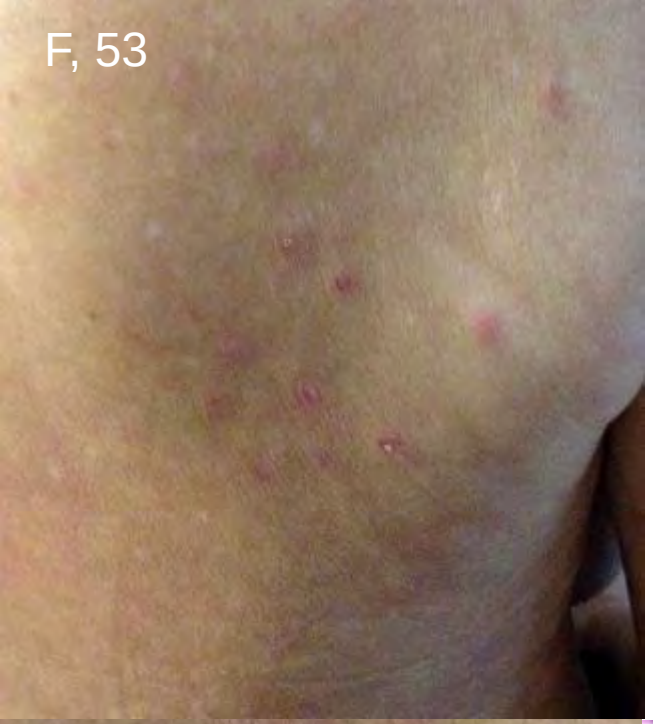
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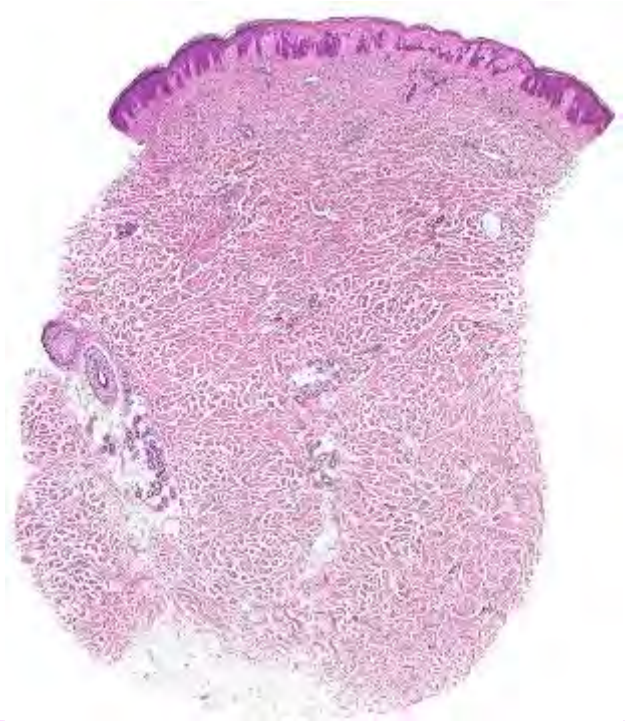
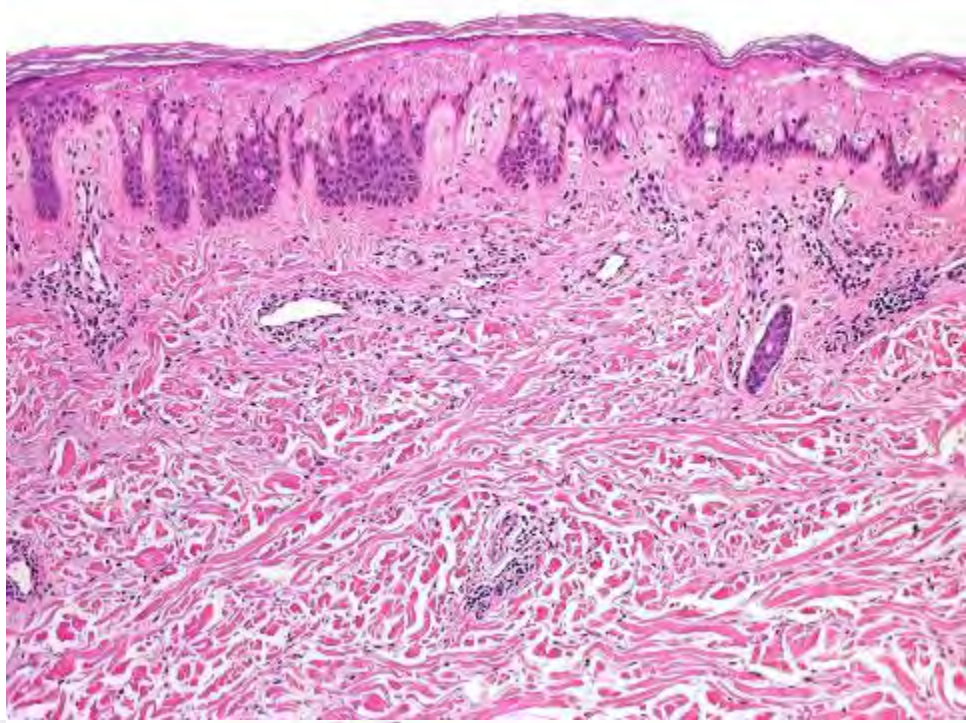
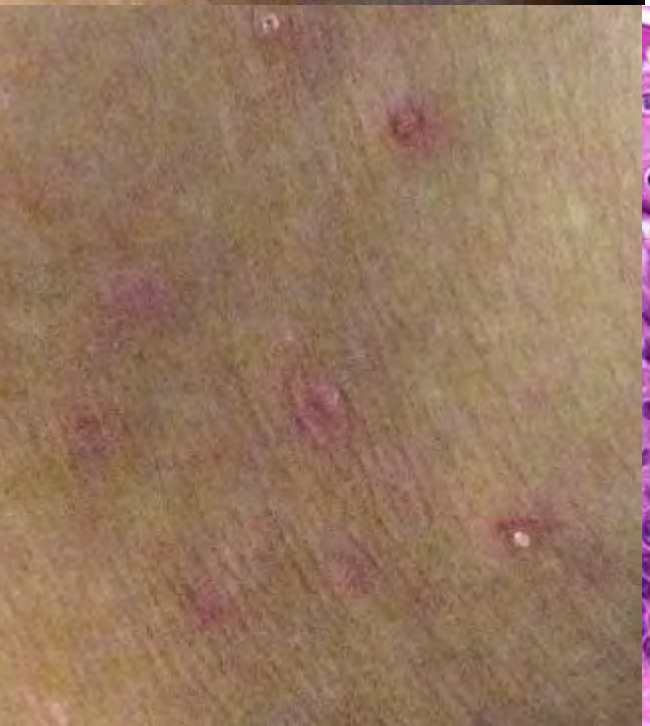
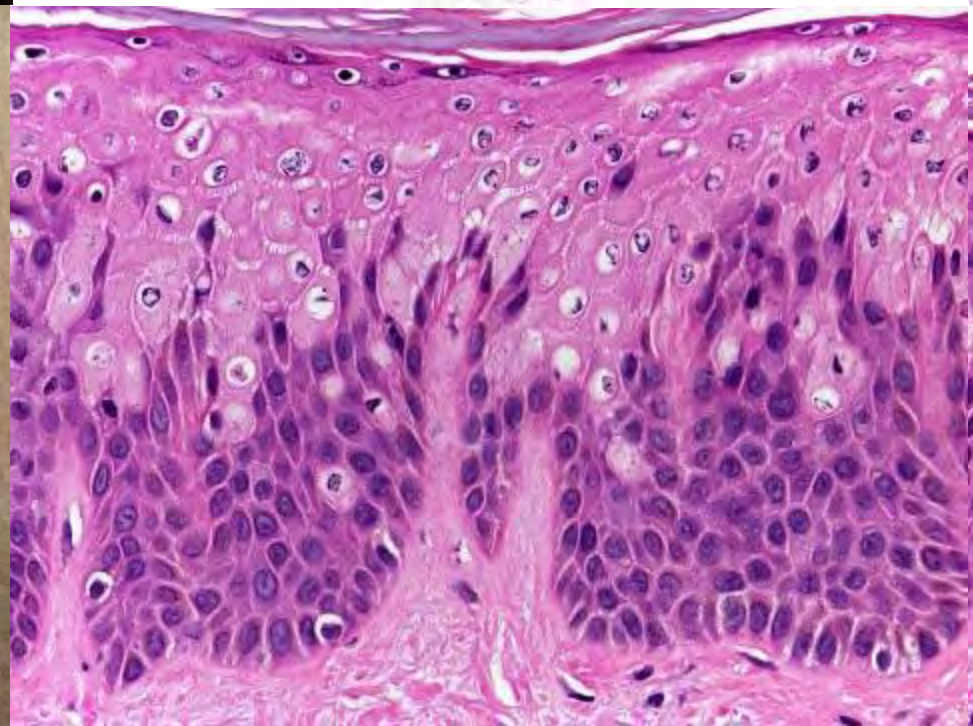
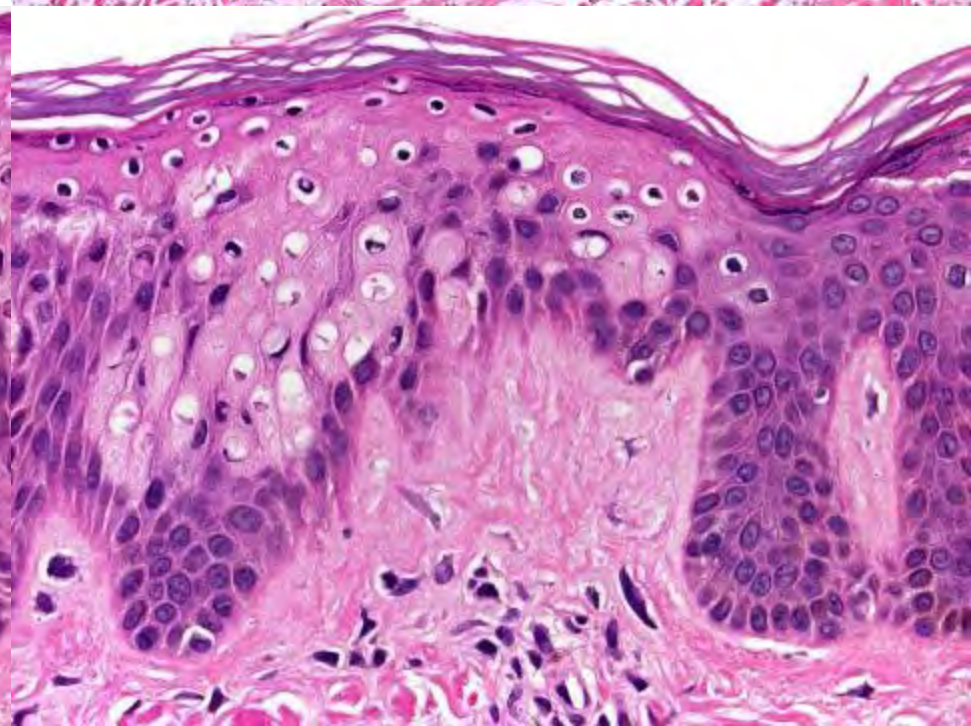








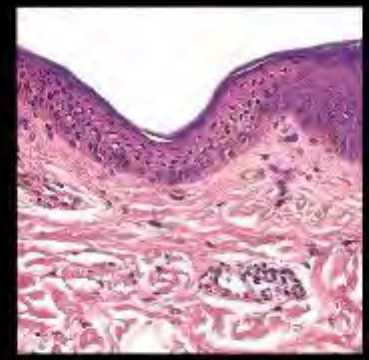


CLUES CLUES CLUES CLUES

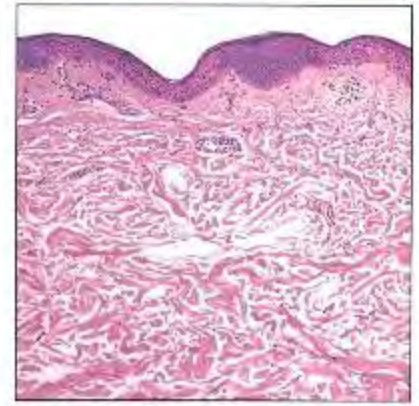
To Diagnosis in Dermatopathology

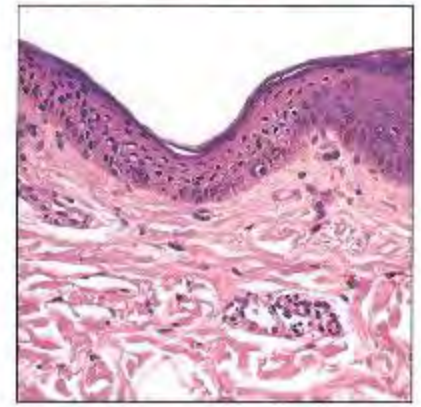
A. Bernard Ackerman
Mark Jacobson Patricia Vitale

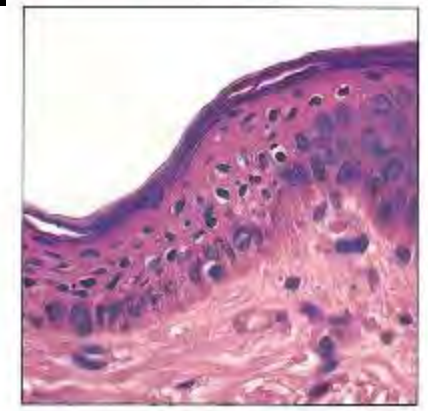
CLUE
22



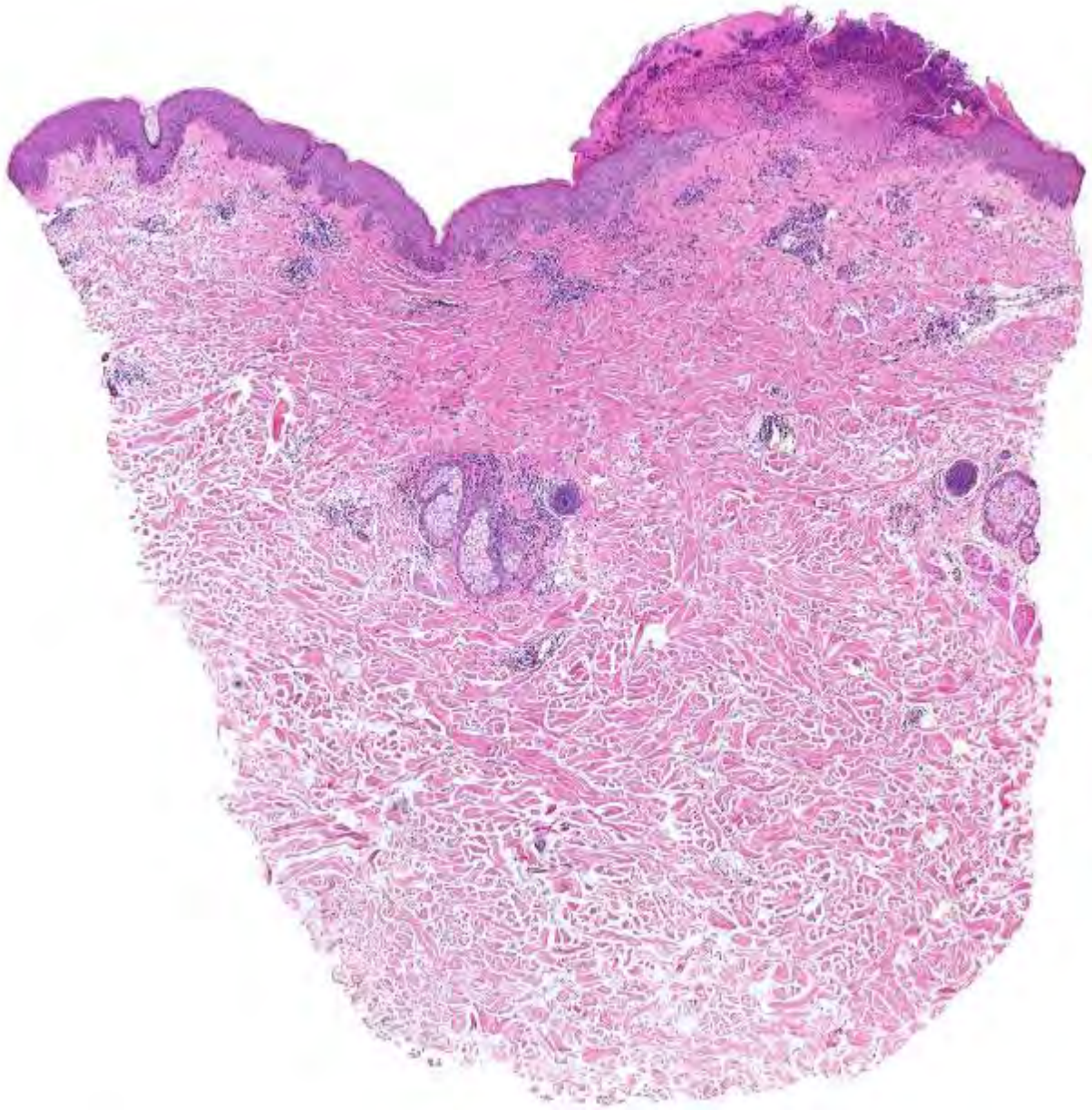
What is the Clue and what is your Diagnosis?

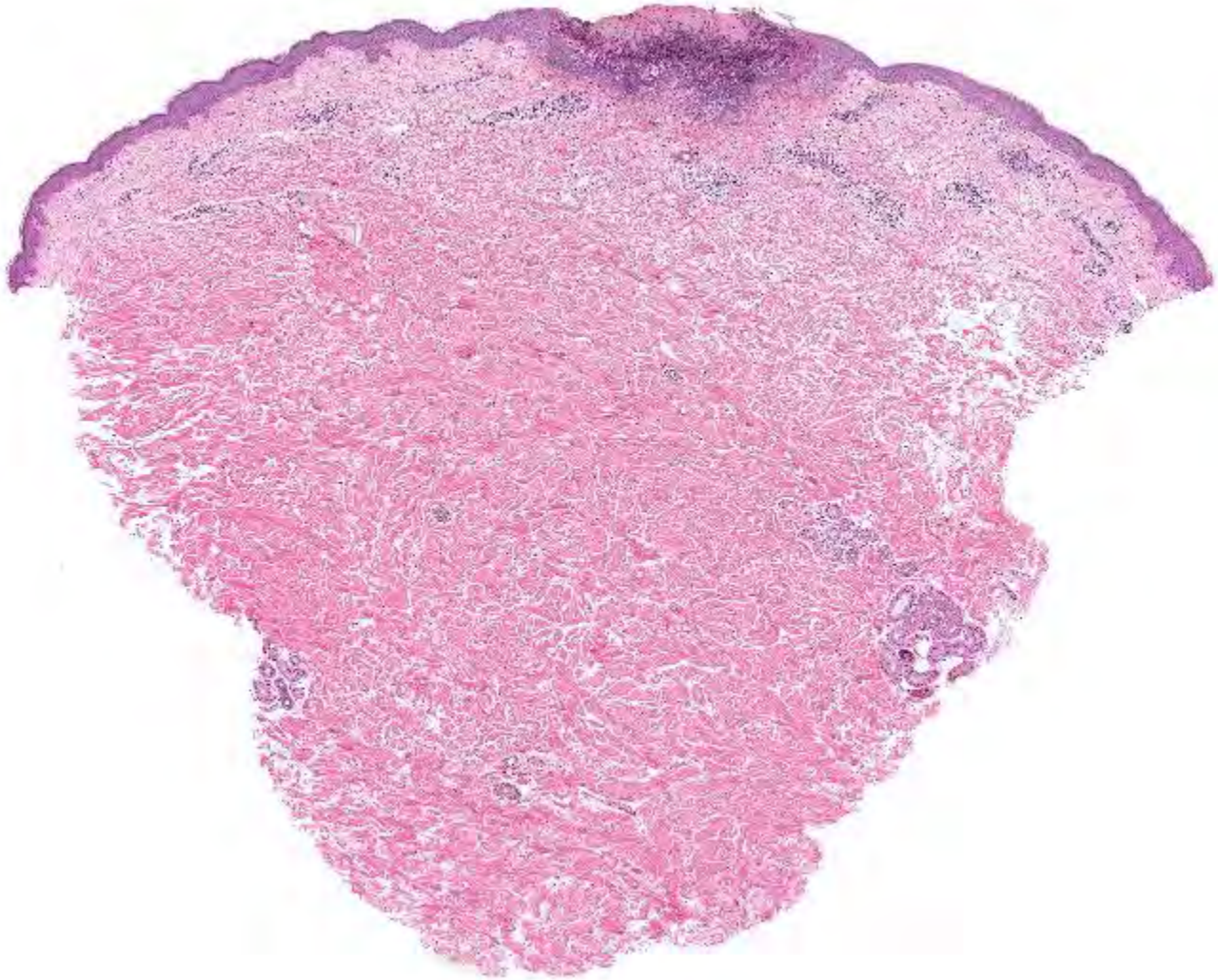




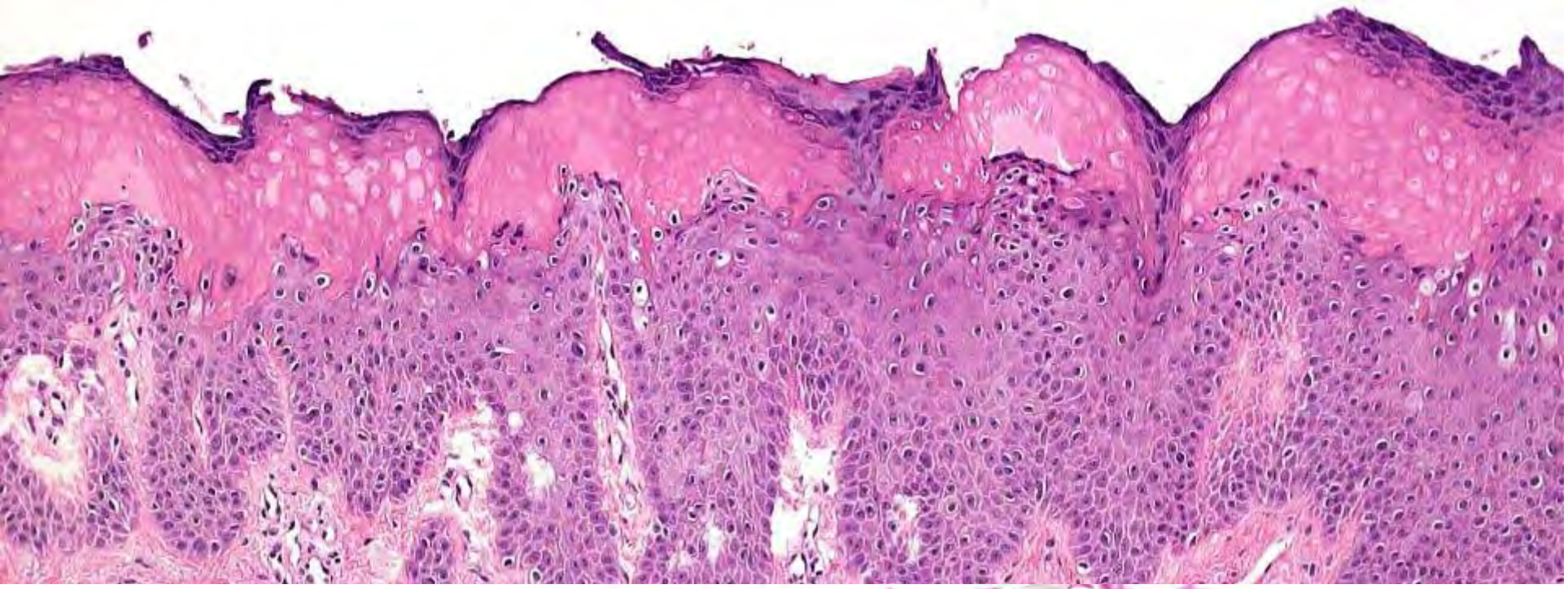


Focal necrosis of the upper part of the epidermis is a clue to excoriation

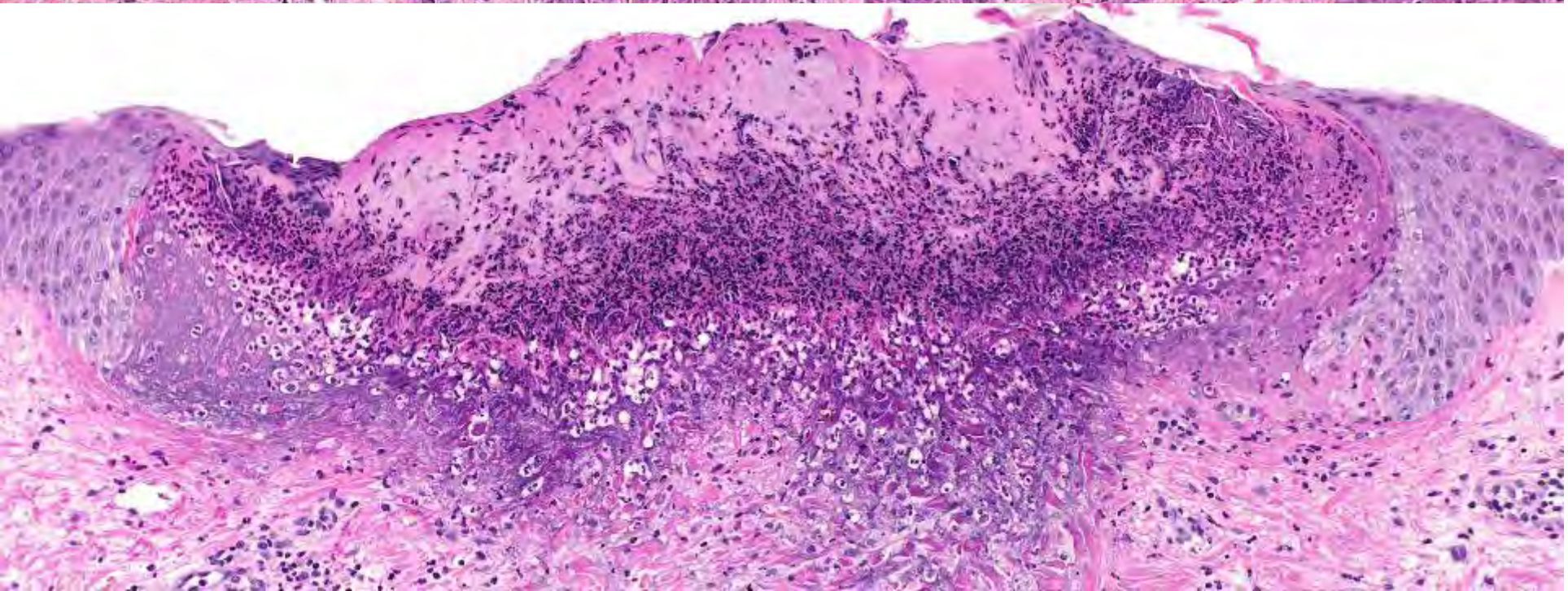




Necrosis of upper keratinocytes usually not found at the edge of "conventional" excoriated prurigo



rubbing

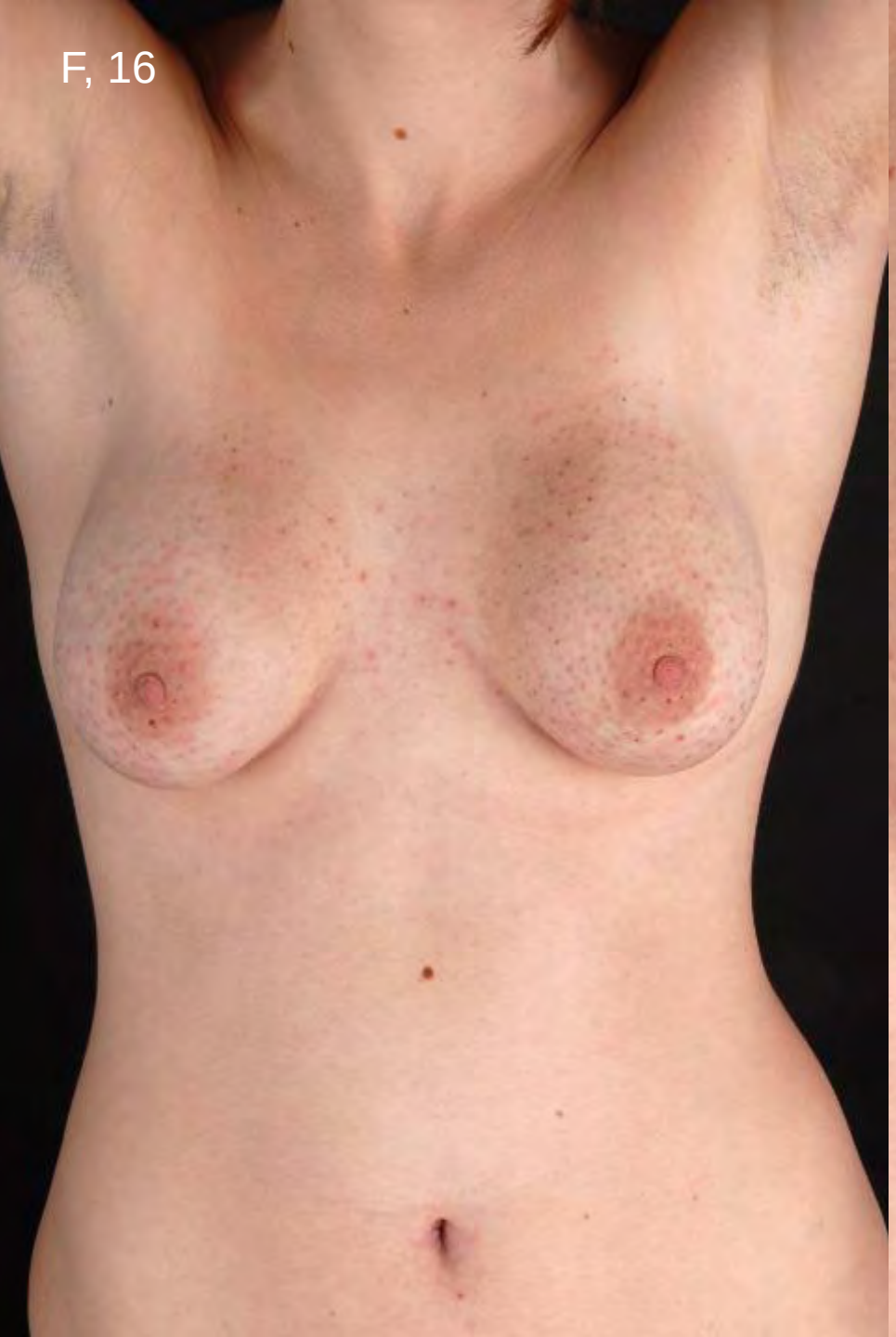


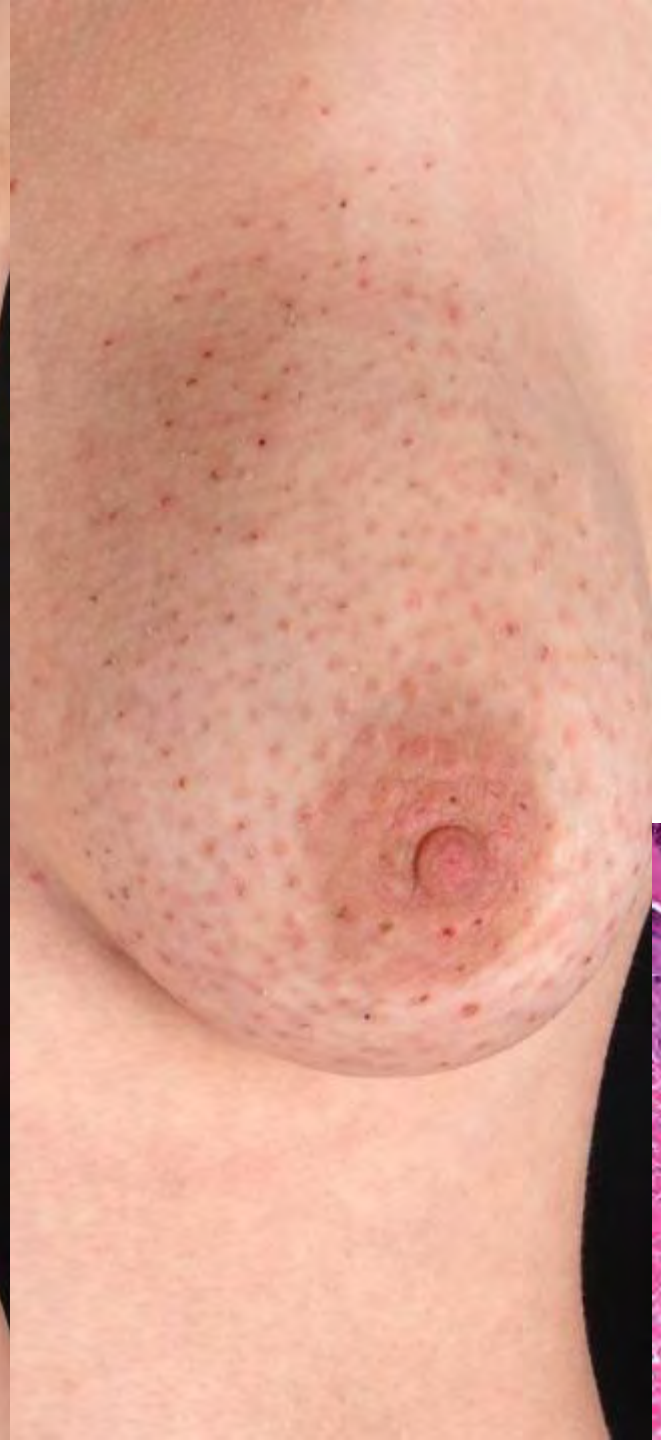
scratching

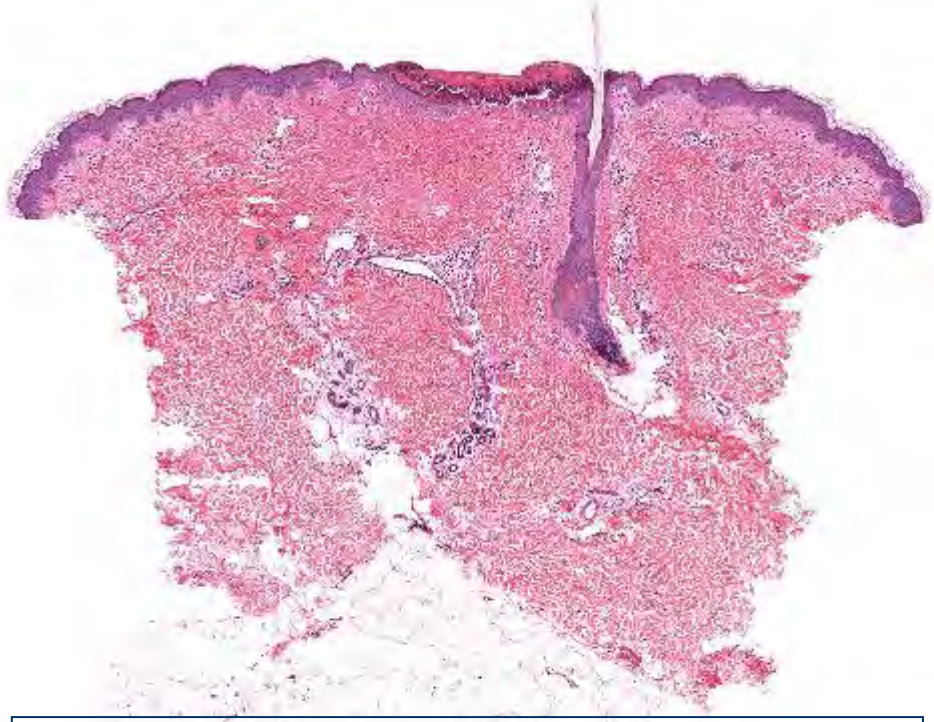
Necrosis of upper keratinocytes

- Necrosis of upper keratinocytes is observed as a consequence of vigorous rubbing
- Observed in persistent pruritic condition (i.e., never observed at the site of acute pruriginous conditions such as arthropod bite reactions)
- Not specific for a "disease" but usually found in chronic, relapsing pruriginous conditions (including atopic dermatitis and related conditions)
- Usually not found at the edge of acute prurigo

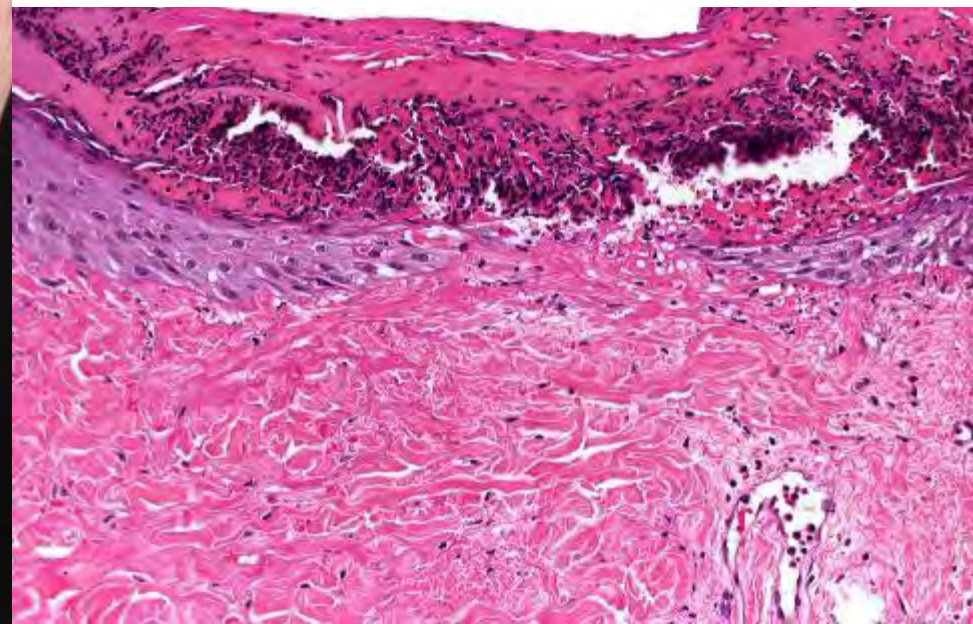
F, 16

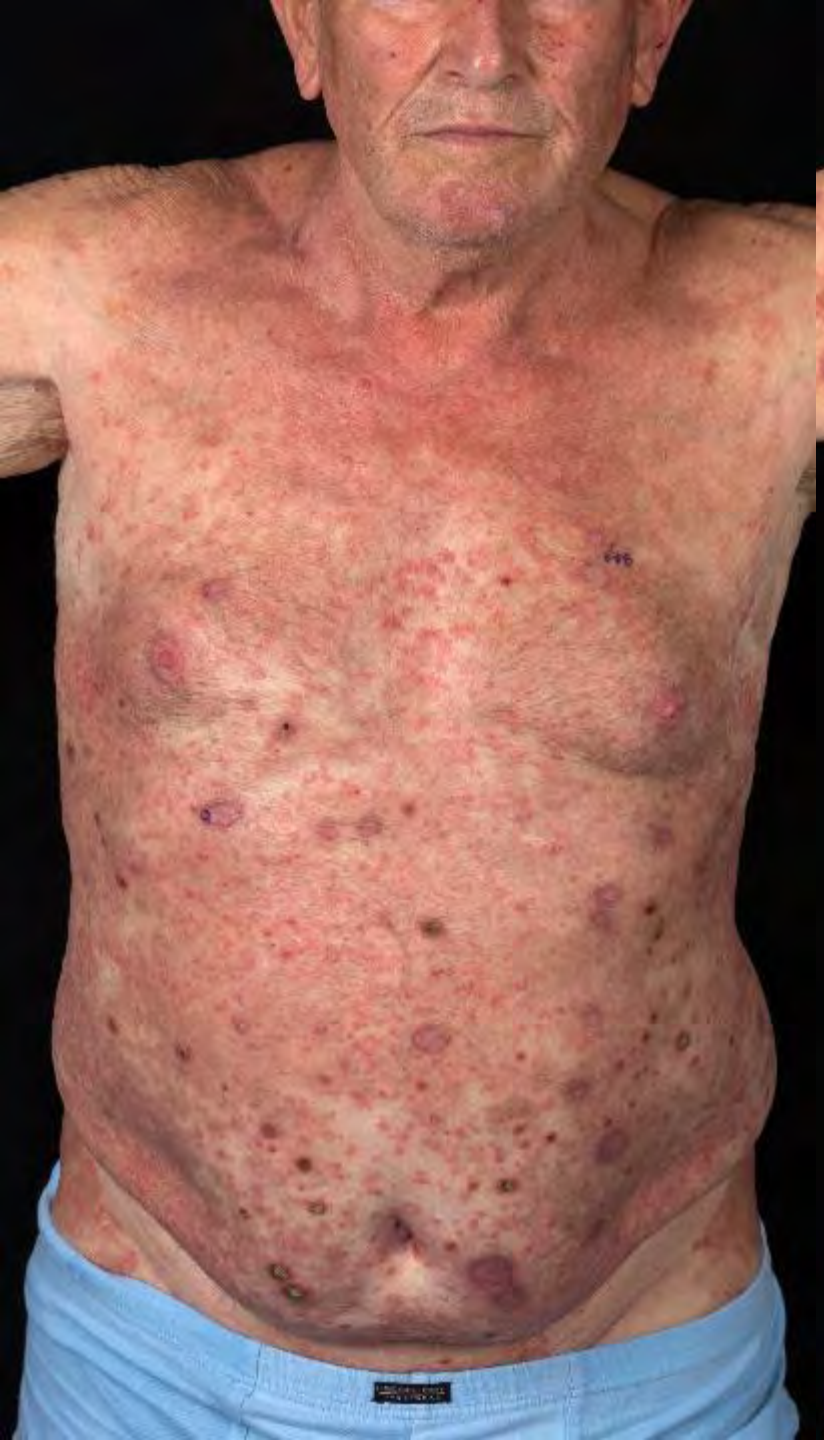


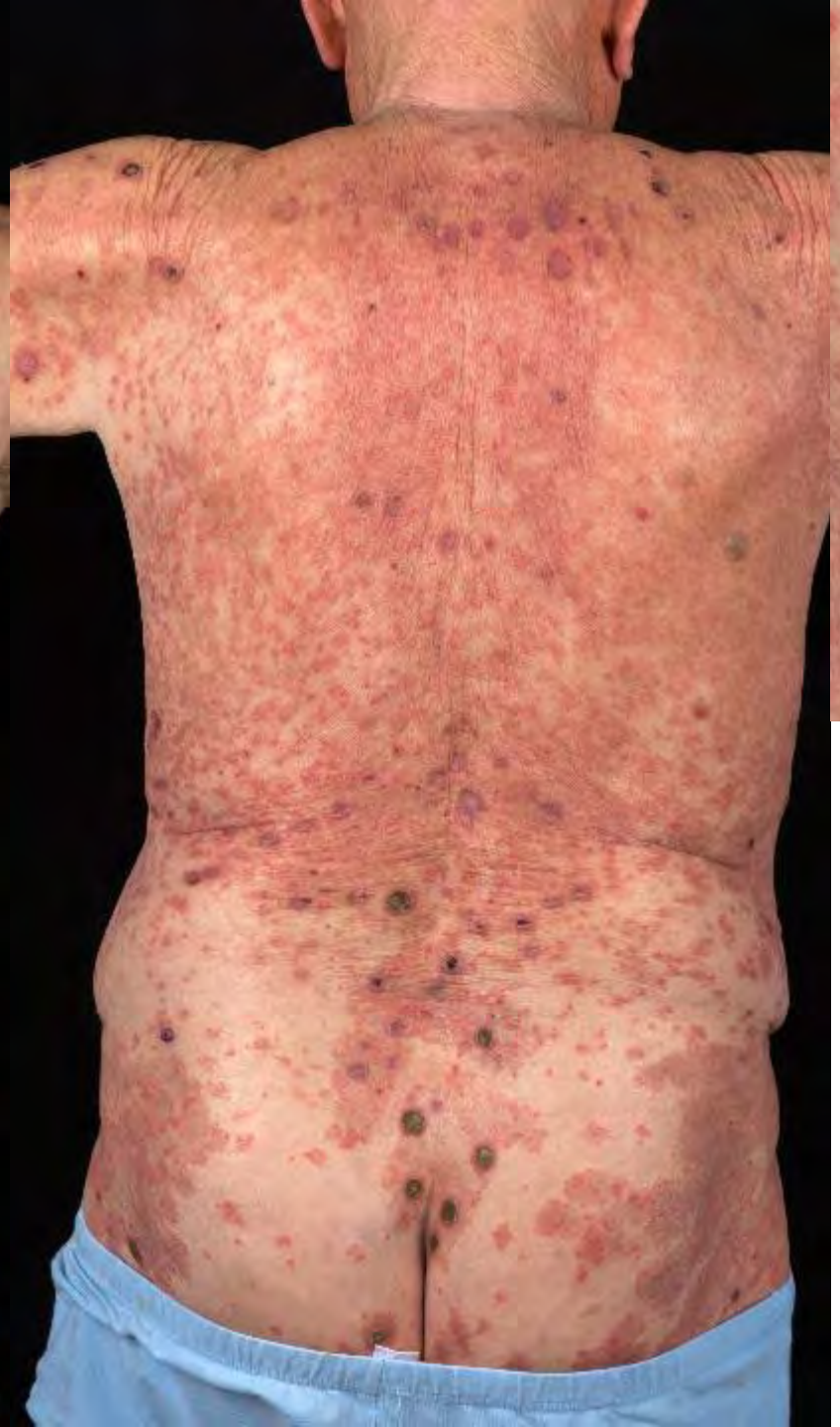


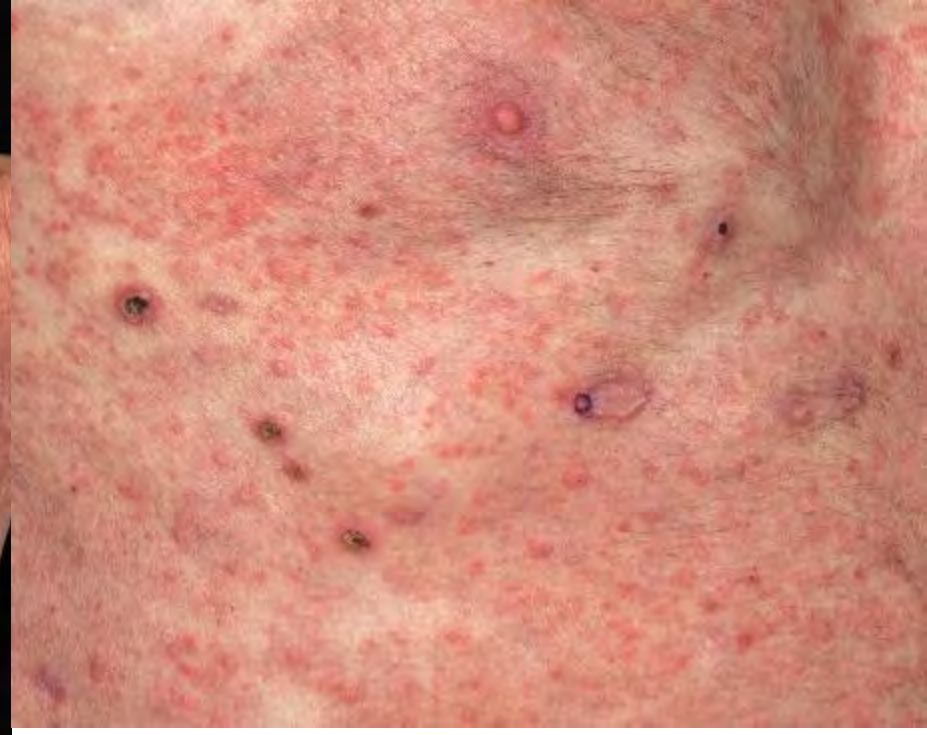


Prurigo type of atopic dermatitis



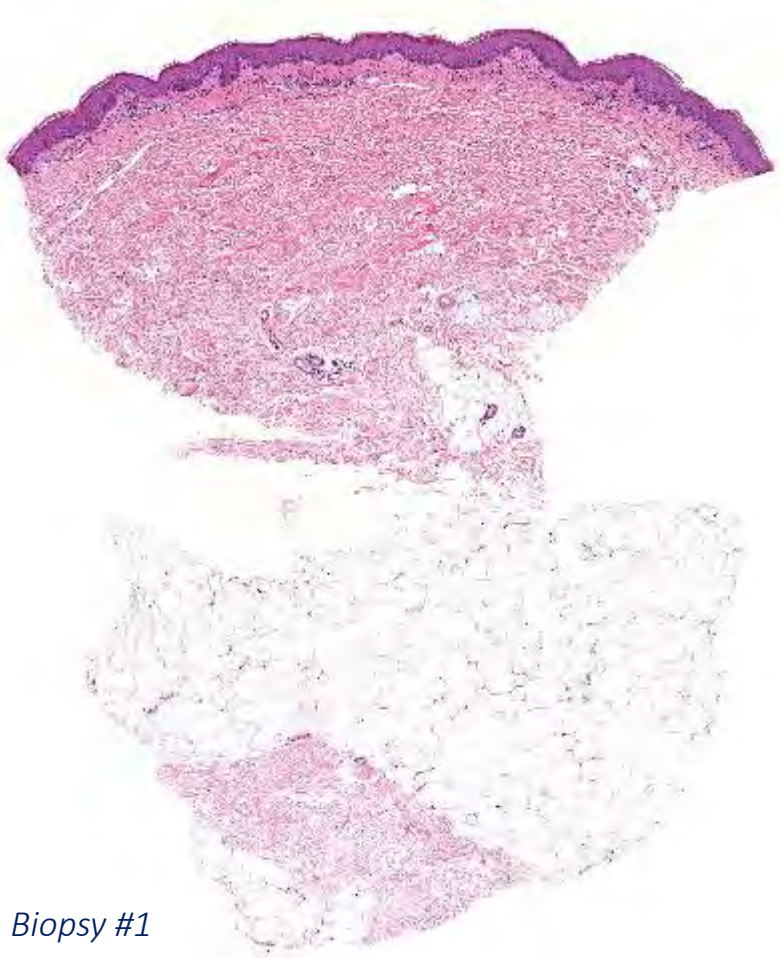




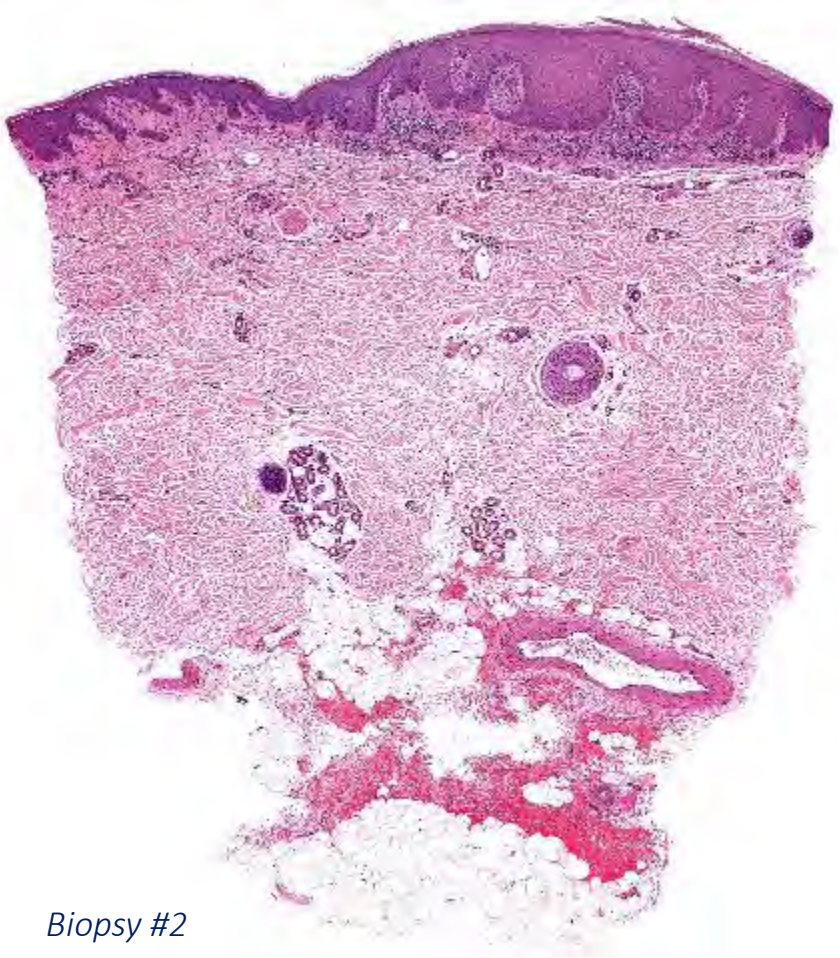


M, 83

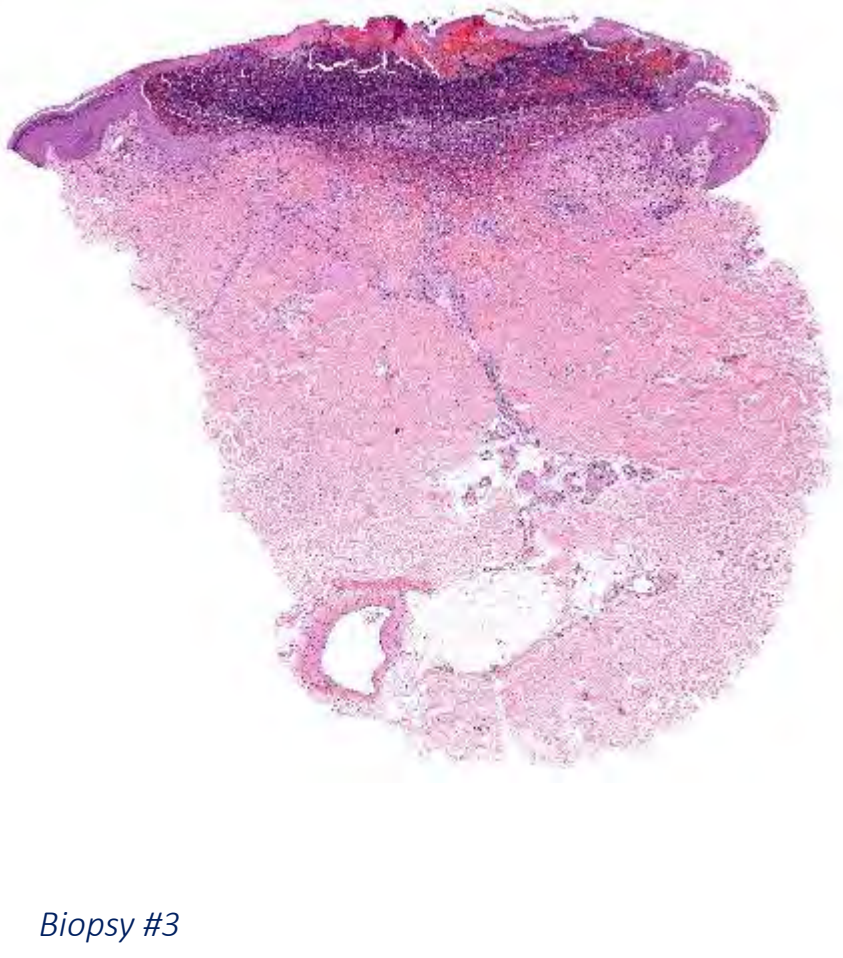
History of diabetes mellitus II.
Recent diagnosis of B-CLL (same time of actual presentation; no treatment).
According to the patient very itchy skin lesions for >2 years. Previous clinical diagnoses of bullous pemphigoid and drug eruption could not be confirmed.
A few months before presentation onset of crusted, well demarcated lesions.
Three biopsies are taken from different areas of the body.



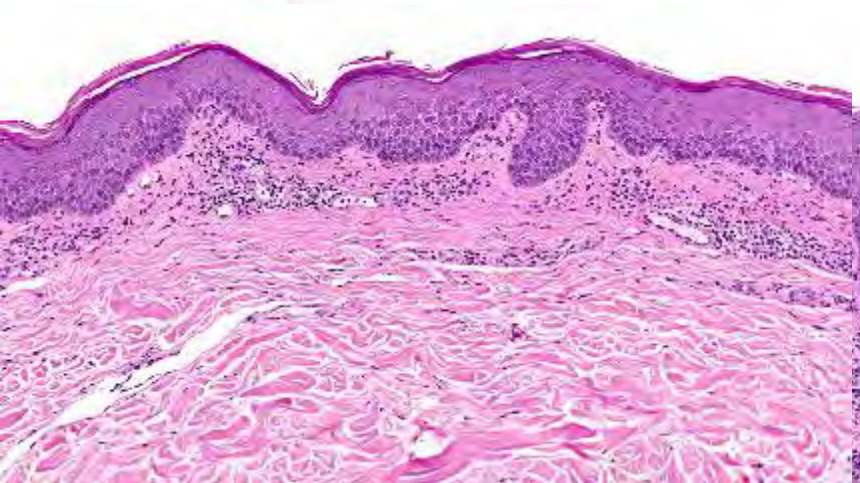
Biopsy #1

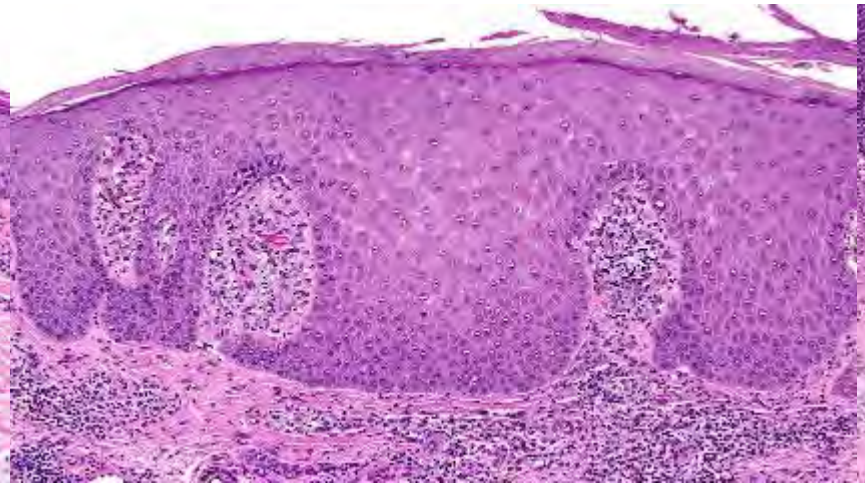


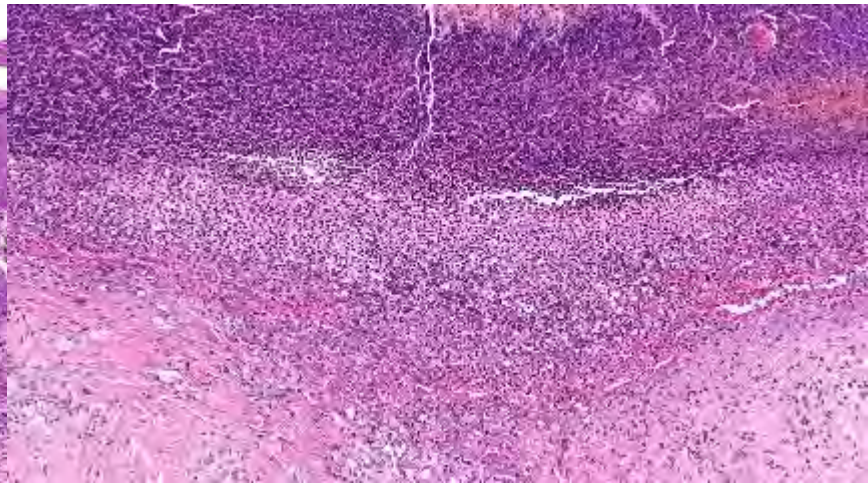
Biopsy #2

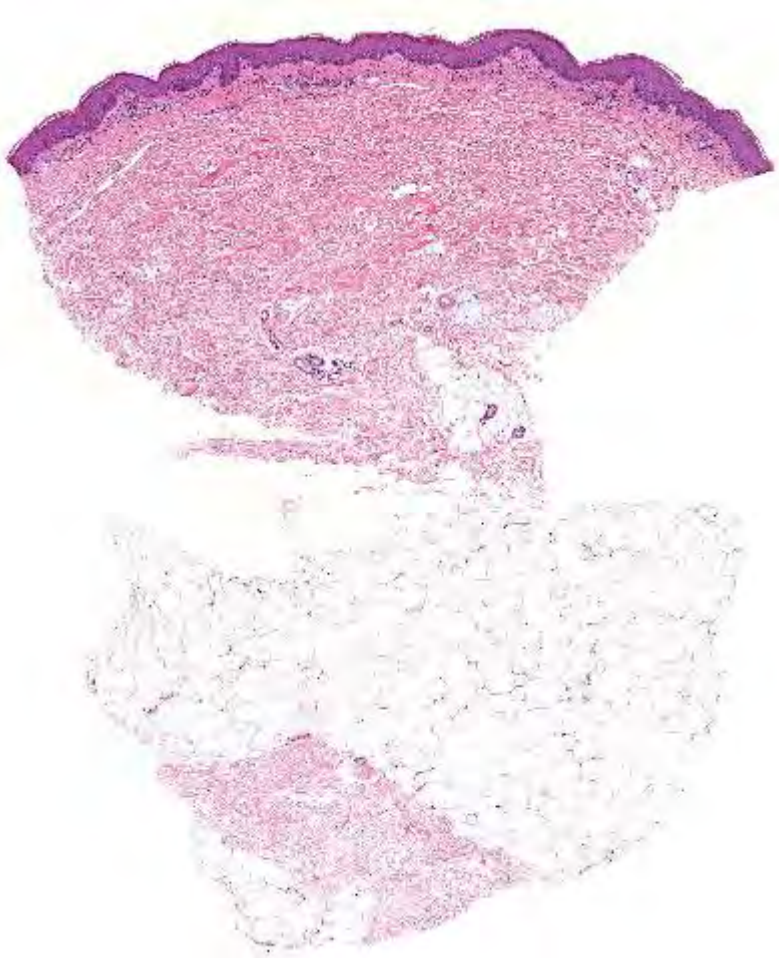


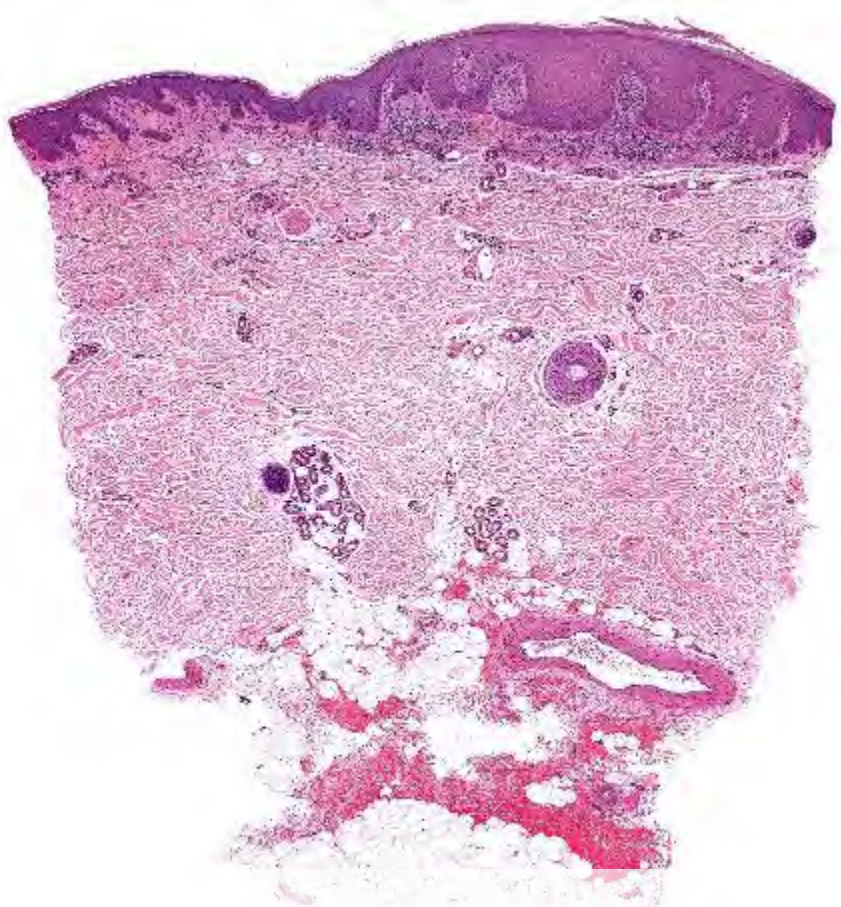
Biopsy #3

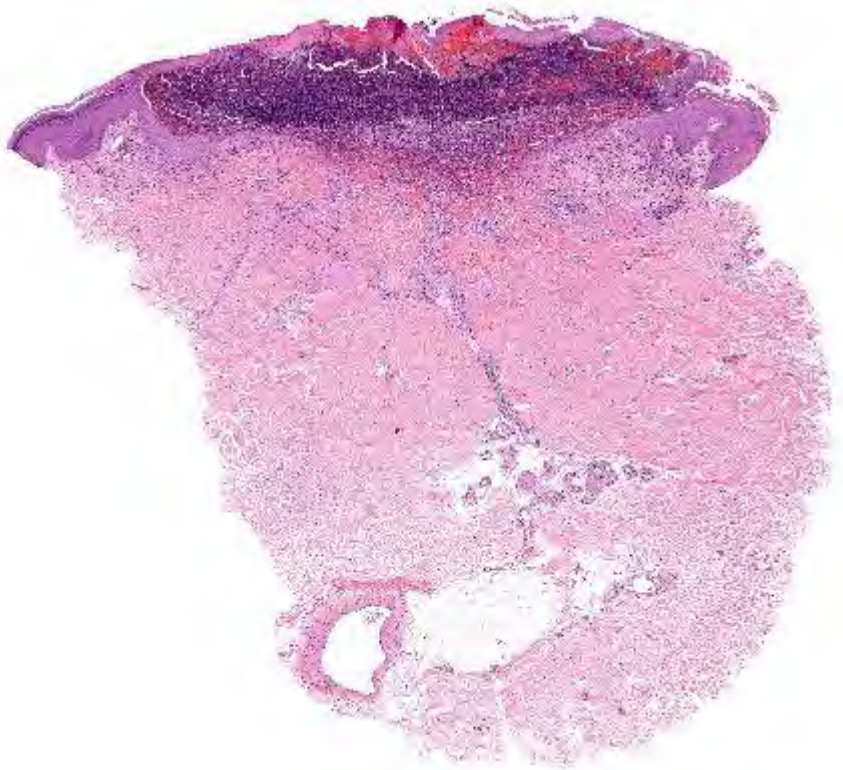


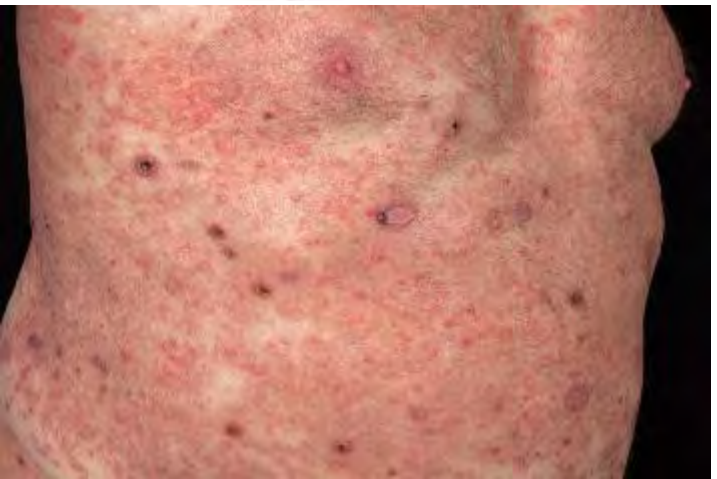








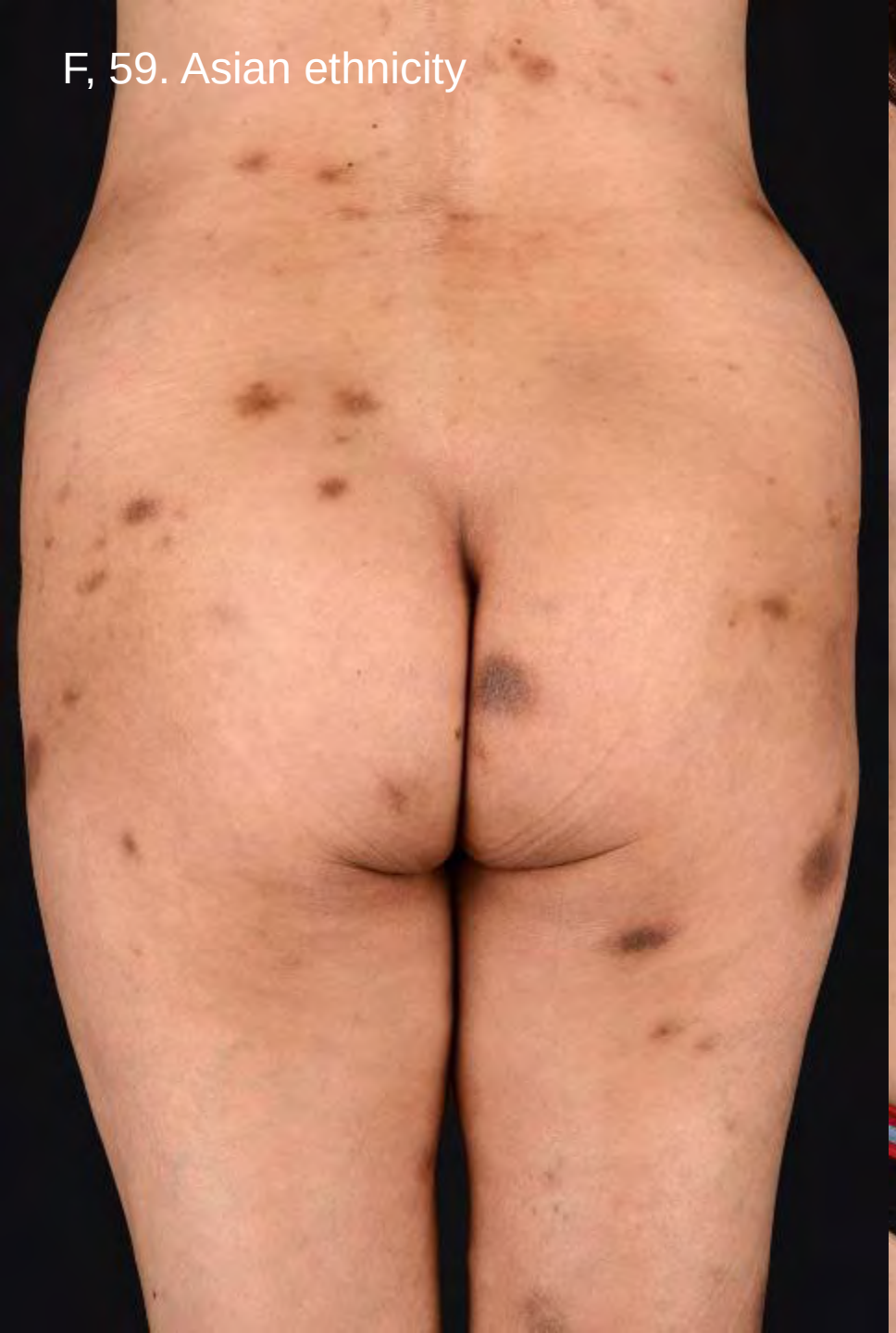


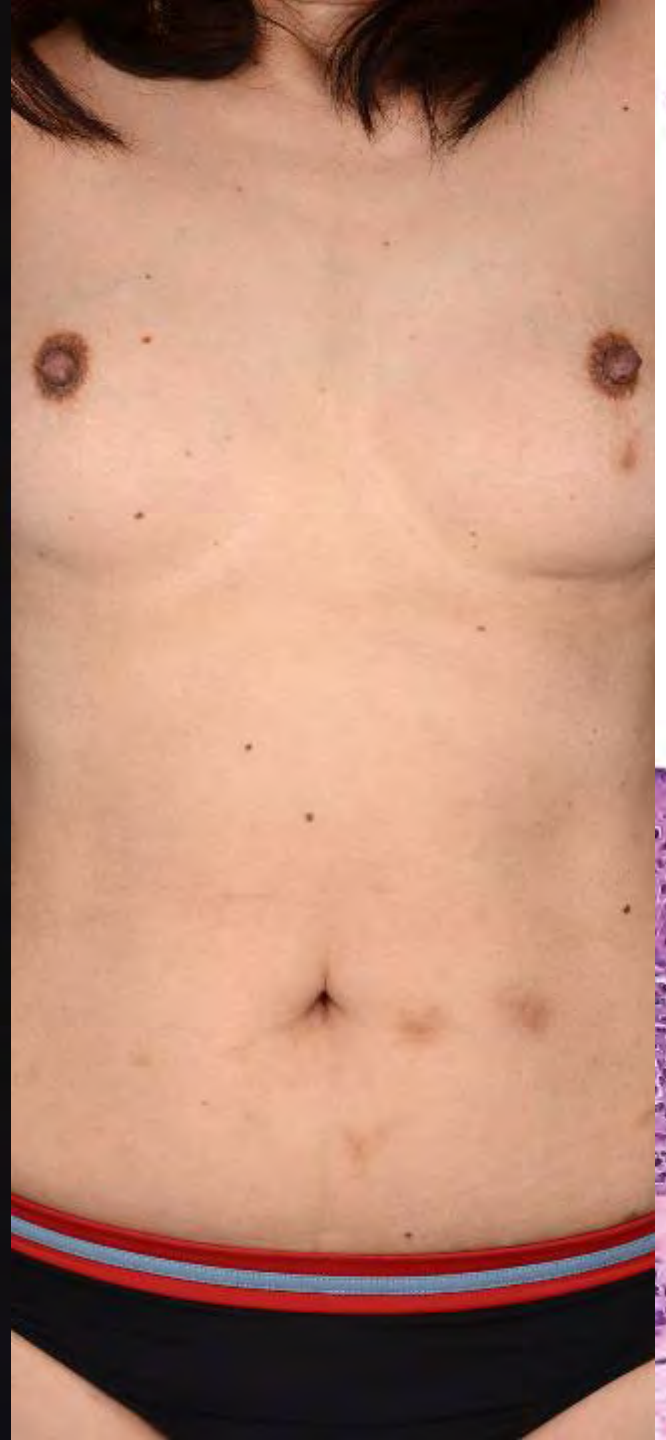


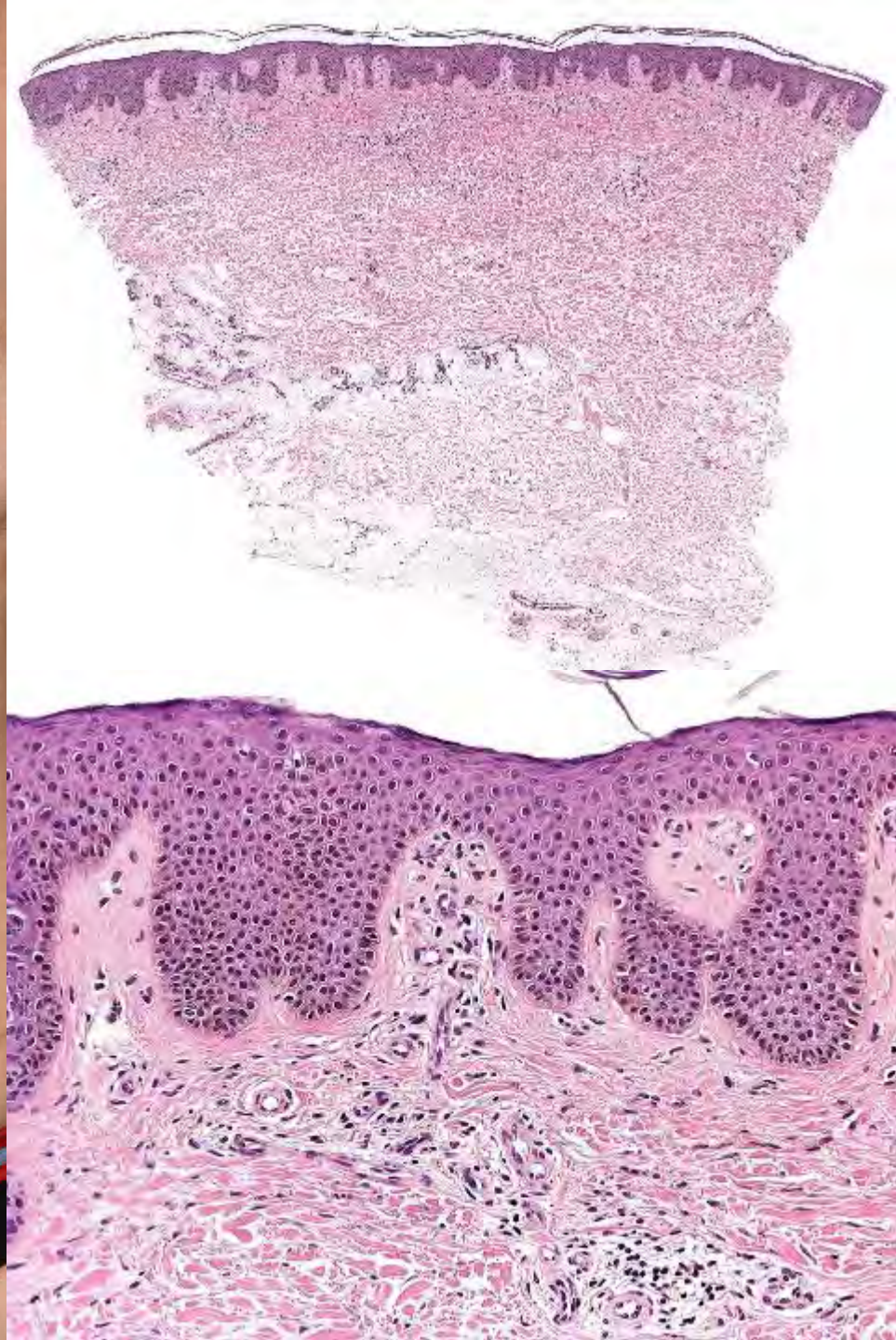
Different clinicopathological faces of "eczema in the elderly":

spongiotic dermatitis, lichen simplex chronicus, excoriated prurigo / perforating collagenosis

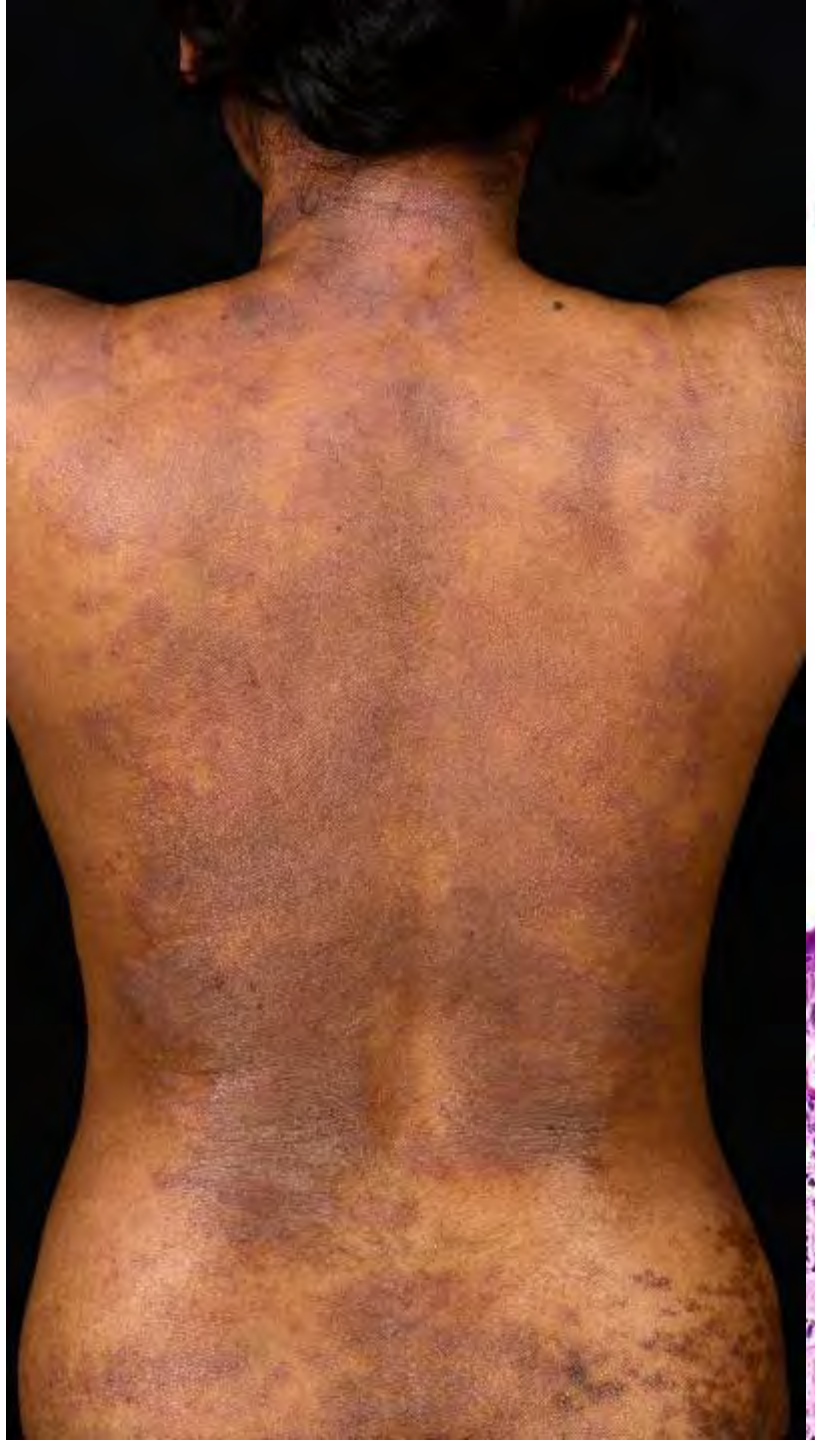
F, 59. Asian ethnicity

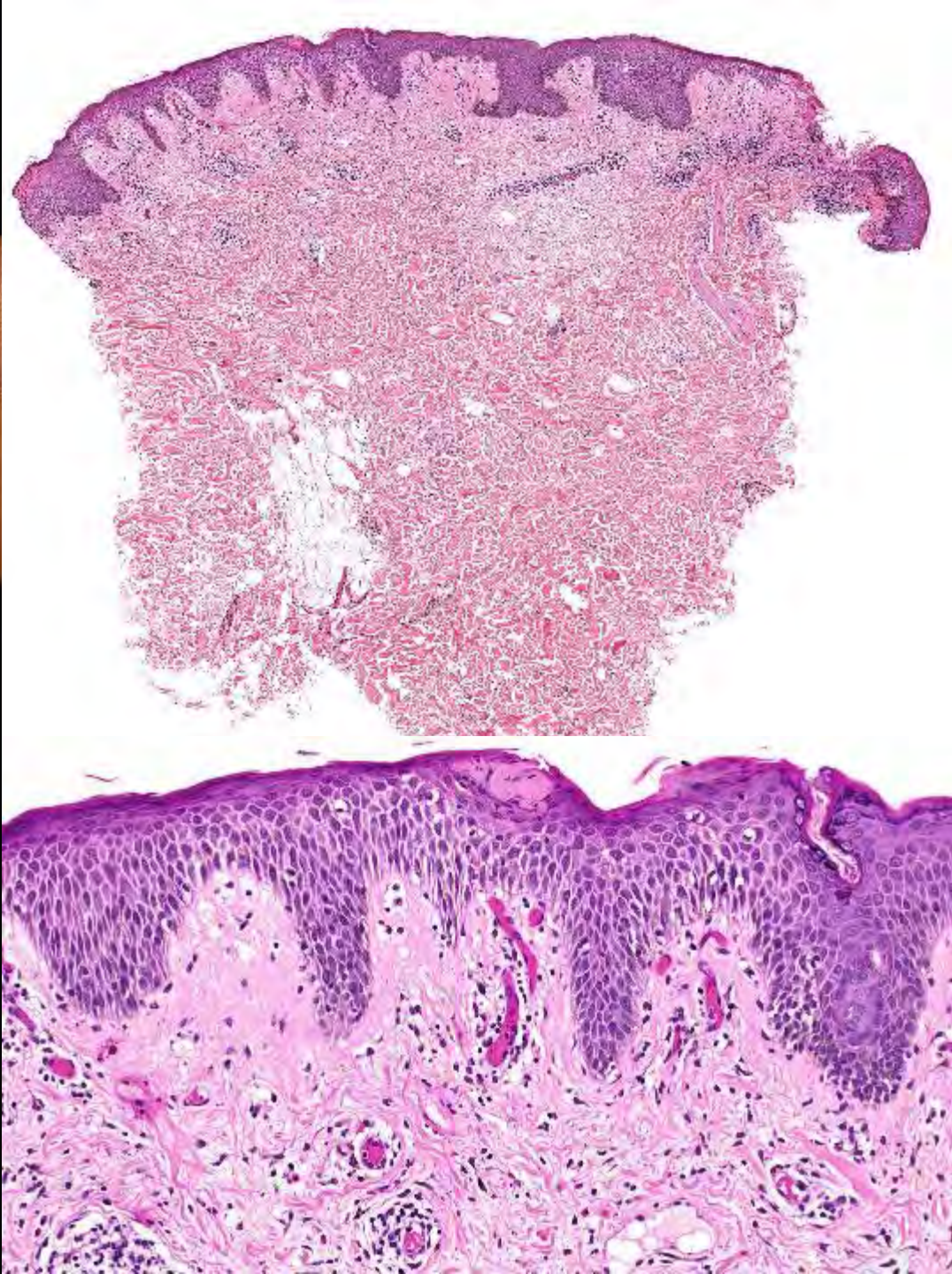


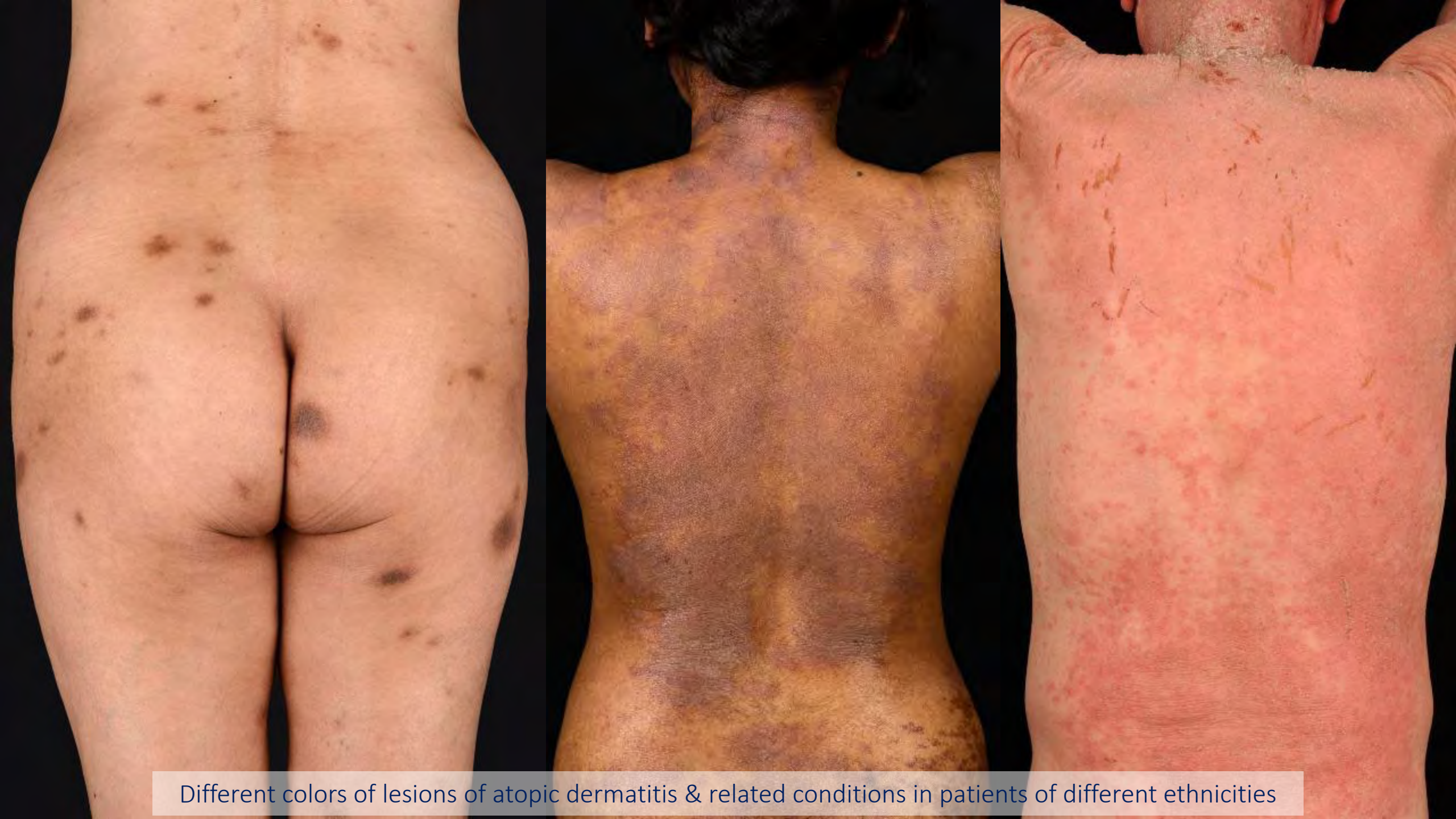




F, 25

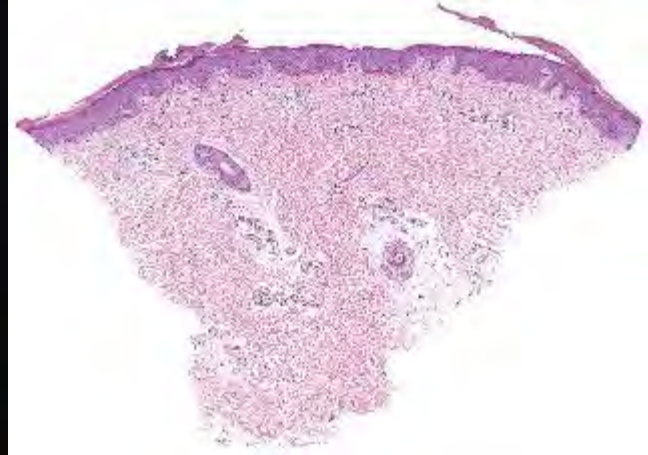


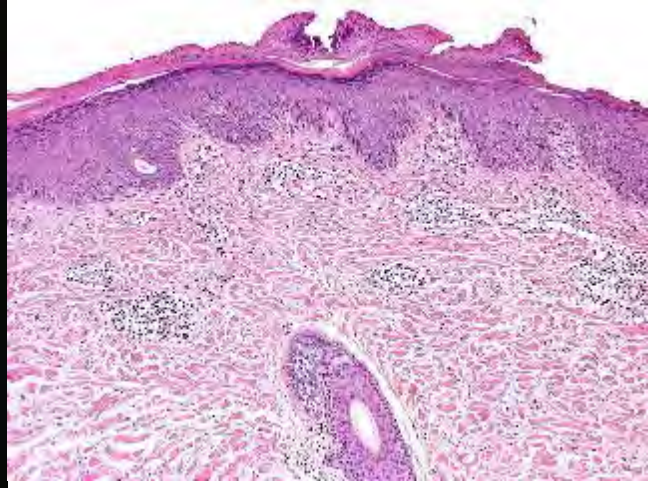


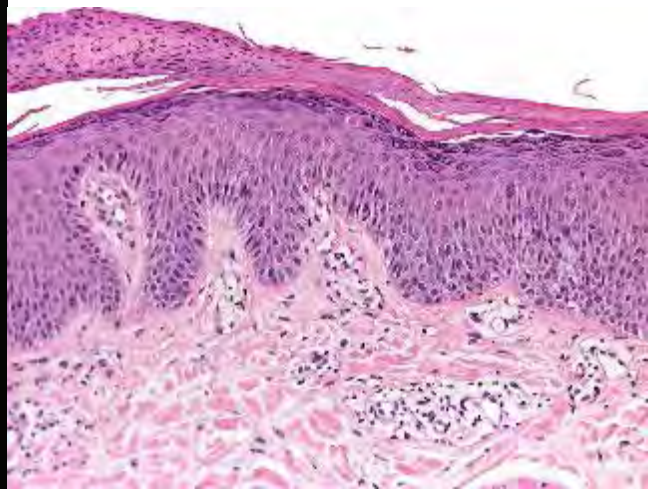


Different colors of lesions of atopic dermatitis & related conditions in patients of different ethnicities

F, 22







Photoaggravated atopic dermatitis

ORIGINAL ARTICLE

Photosensitive atopic dermatitis – a neglected subset: Clinical, laboratory, histological and photobiological workup

E. Ellenbogen,[1]* U. Wassermann,[2] S.C. Hofmann,[2] P. Lehmann[2]

[1]Department of Dermatology, [illegible] Medical Center, [illegible], Israel
[2]Department of Dermatology and Allergology, [illegible], Germany
*Correspondence: E. Ellenbogen. E-mail: [illegible]

Abstract

Background Photosensitive atopic dermatitis (PhAD) is a poorly recorded entity characterized clinically by a pruritic localized rash in patients who fulfil the criteria for atopic dermatitis (AD).

Objectives The aim of this retrospective study was to define significant clinical, laboratory and immunologic parameters as well as protocols and procedures for diagnosing PhAD.

Methods We conducted a single-centre retrospective analysis of 17 patients with long-standing AD who in the disease course suddenly developed photosensitivity. All patients with suspected PhAD treated in our department between 2009 and 2014 were included in the study. Diagnostic methods were immunologic parameters, prick and patch testing, histology and photoprovocation procedures.

Results Onset of photosensitivity was observed during spring, summer and during exposure to artificial UVR (UV therapy) radiation as part of the patients' treatment regimen. Symptoms appeared 3.5 months on average after AD diagnosis was established. Although the MED (Minimal erythematous dose) was normal compared to a control group, all patients tested with photoprovocation methods exhibited a positive result. Two types of reactions were observed: papular and eczematous reactions, both types having similar histology. The wavelength spectrum most commonly involved was UVA. The disease seems to affect women more often than men. Predilection sites included face, neck, exposed trunk areas and arms. Patients with PhAD had persistent eczematous lesions in non-sun-exposed skin. IgE levels were elevated in 11/17 patients (65%), with a median value of 269 kU/L.

Conclusion PhAD is an underreported subset of atopic dermatitis which is rarely discussed. This study suggests that severe features including atopic diathesis, eczematous lesions in UVR-exposed body regions and positive photoprovocation reaction are suggestive of PhAD as the likely diagnosis. Typically, the atopic eczema starts without a sign of photosensitivity, however, in a subgroup of AD patients after a few months to years, a switch occurs leading to PhAD.

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Conflicts of interest

None declared.

Funding sources

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The sun's radiation reaching the earth has complex effects on human skin, beneficial as well as detrimental.

The beneficial application of UV radiation as phototherapy is well established in various inflammatory dermatoses. This method was well studied in patients suffering from atopic dermatitis (AD); its positive effects can be attributed to several factors. In addition to immunosuppressive actions, UV radiation (UVR) may also increase the thickness of the stratum corneum, and reduce the colonization of *Staphylococcus aureus* in the skin, thus preventing the well known superantigen linked exacerbations of A.D.[1]

The spectrum of skin disorders related to sunlight ranges from acute sunburn, familiar to every individual, through various forms of photosensitivity (photodermatoses) to the chronic sun damaged, aged skin and cutaneous malignancies.

Photodermatoses (PD) are a group of skin disorders that are precipitated by exposure to sunlight; these disorders can be broadly classified into four major groups according to their

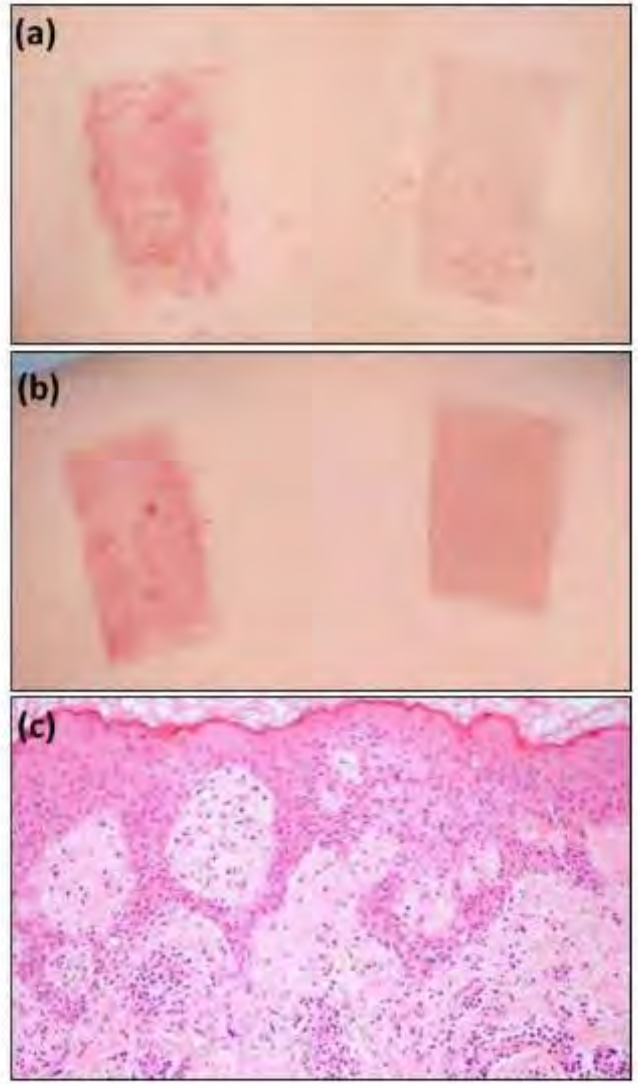

Figure 3 Results 3 days after photoprovocation with UVB (left) and UVA-1 (right). (a) Papular variant (PLE type) of PhAD, (b) eczematous variant (PhAD type), (c) typical histopathological picture of a positive eczematous photoprovocation reaction (H&E, ×10 magnification).


Fifth Edition
DERMATOLOGY
JEAN L. BOLOGNIA | JULIE V. SCHAFFER | LORENZO CERRONI
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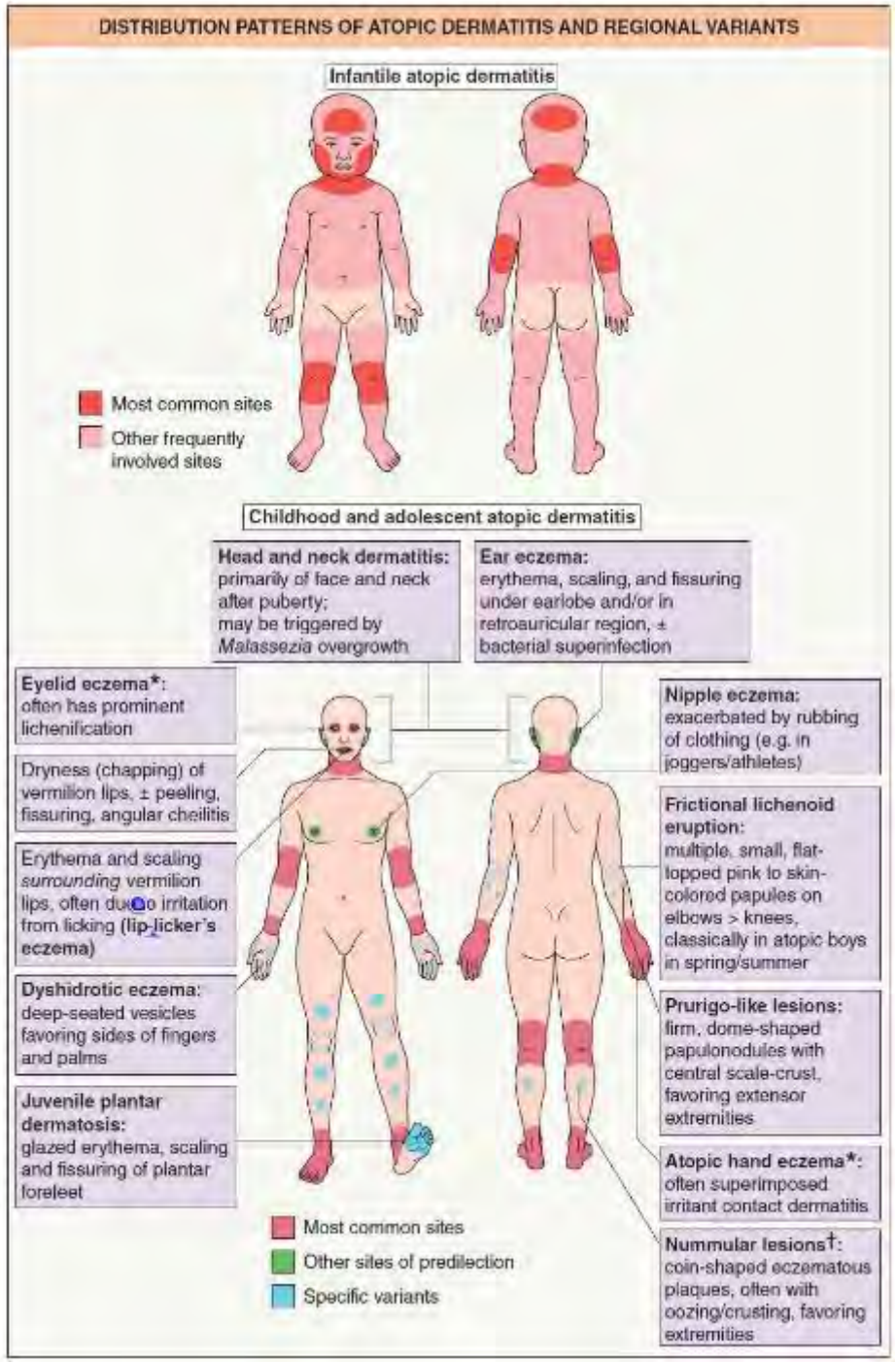
SECTION 2
Atopic Dermatitis
12
Maeve A. McAleer and Alan D. Irvine


DISTRIBUTION PATTERNS OF ATOPIC DERMATITIS AND REGIONAL VARIANTS
Infantile atopic dermatitis
Most common sites
Other frequently involved sites
Childhood and adolescent atopic dermatitis
Head and neck dermatitis: primarily of face and neck after puberty; may be triggered by Malassezia overgrowth
Ear eczema: erythema, scaling, and fissuring under earlobe and/or in retroauricular region, ± bacterial superinfection
Eyelid eczema*: often has prominent lichenification
Dryness (chapping) of vermilion lips, ± peeling, fissuring, angular cheilitis
Erythema and scaling surrounding vermilion lips, often due to irritation from licking (lip-licker's eczema)
Dyshidrotic eczema: deep-seated vesicles favoring sides of fingers and palms
Juvenile plantar dermatosis: glazed erythema, scaling and fissuring of plantar forefeet
Nipple eczema: exacerbated by rubbing of clothing (e.g. in joggers/athletes)
Frictional lichenoid eruption: multiple, small, flat-topped pink to skin-colored papules on elbows > knees, classically in atopic boys in spring/summer
Prurigo-like lesions: firm, dome-shaped papulonodules with central scale-crust, favoring extensor extremities
Atopic hand eczema*: often superimposed irritant contact dermatitis
Nummular lesions†: coin-shaped eczematous plaques, often with oozing/crusting, favoring extremities
Most common sites
Other sites of predilection
Specific variants

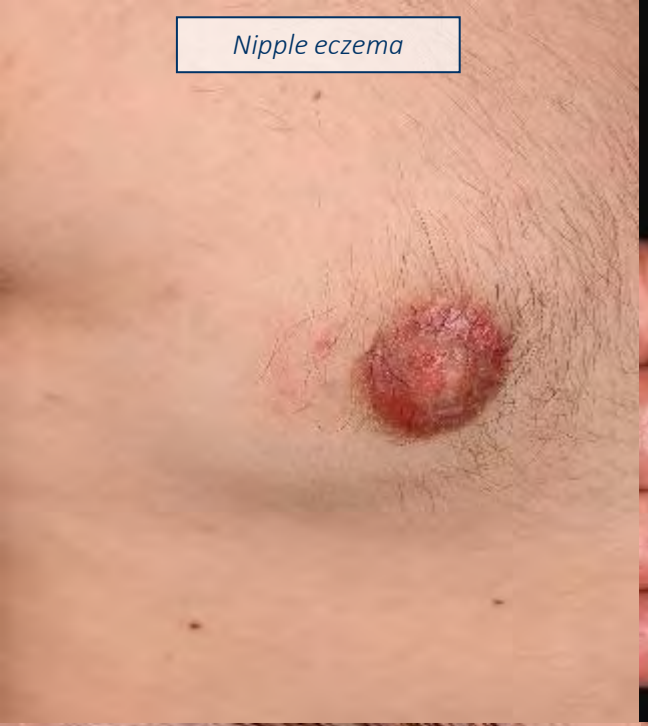
Atopic dermatitis – Clinicopathological spectrum

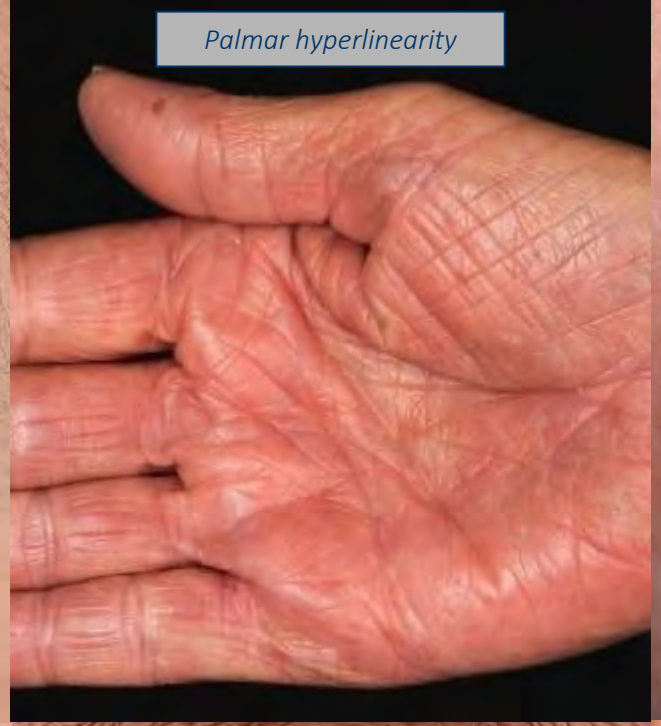
- Cheilitis sicca
- Lip eczema (licker's eczema)
- Ear eczema
- Eyelid eczema
- Nipple eczema
- Head and neck dermatitis
- Juvenile plantar dermatosis
- Atopic hand eczema
- Dyshidrotic eczema
- Prurigo form of atopic dermatitis
- Nummular (discoid) lesions
- Frictional lichenoid eruption
- Pityriasis alba
- Sandpaper dermatitis
- Follicular hyperkeratosis
- Erythrodermic atopic dermatitis
- "Pseudotumoral" atopic dermatitis

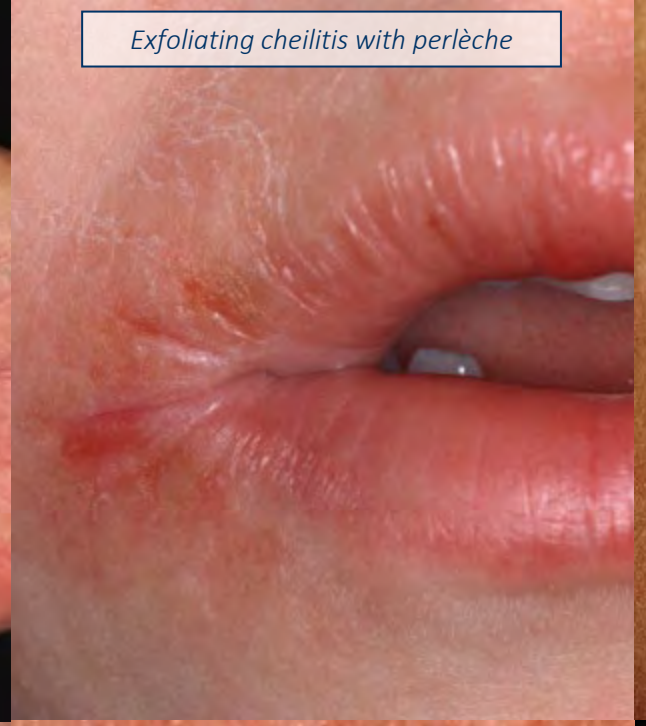
- Lichenoid
- Granulomatous
- Insect bite-like
- Pseudolymphomatous
- Post-inflammatory hyperpigmentation
- Interface dermatitis
- Angiomatous
- Linear – superimposed

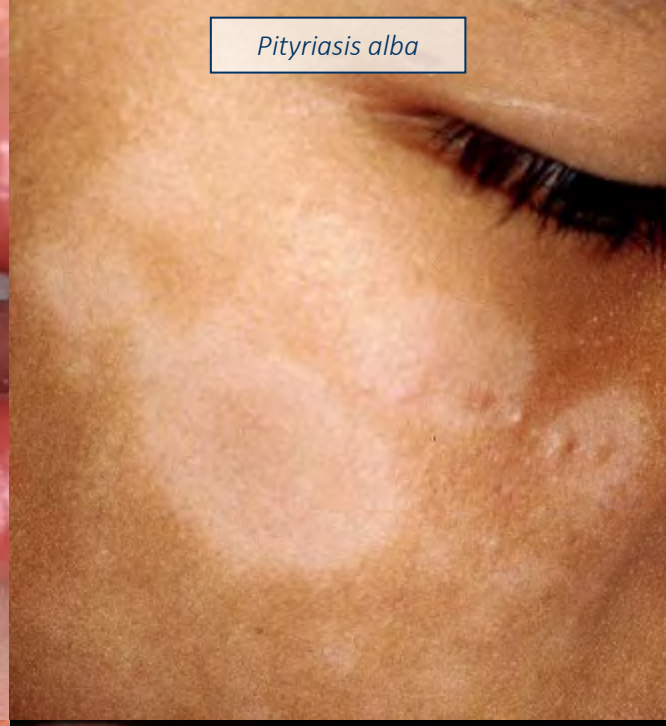
- Association with other diseases
  Ichthyosis vulgaris
  Immune deficiencies
  "Psoriatic neurodermatitis" (?)
  Herpes viruses
  Staphylococcal infections
  Other diseases

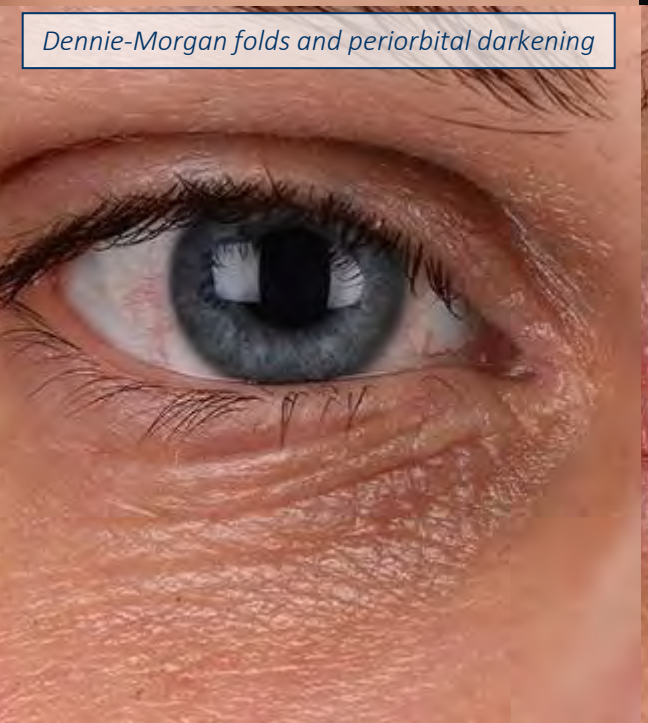
- Other rare presentations


Nipple eczema

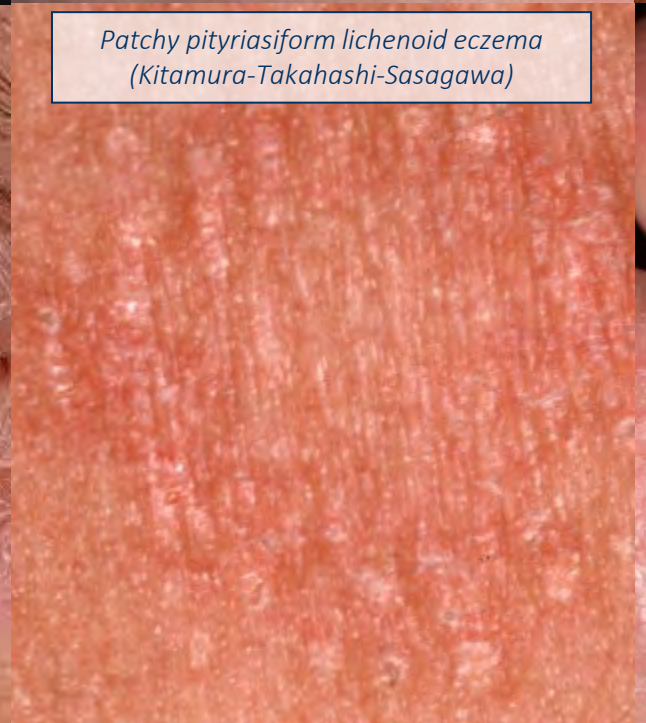

Palmar hyperlinearity

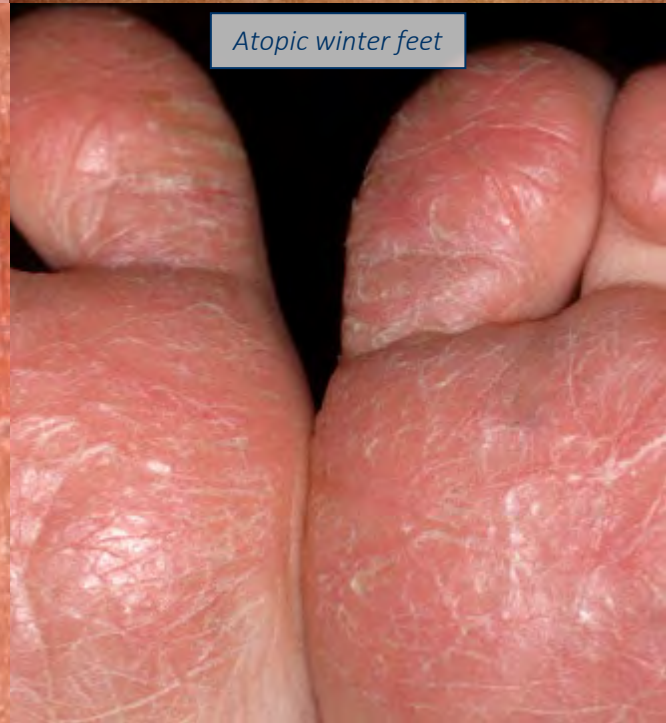

Exfoliating cheilitis with perlèche

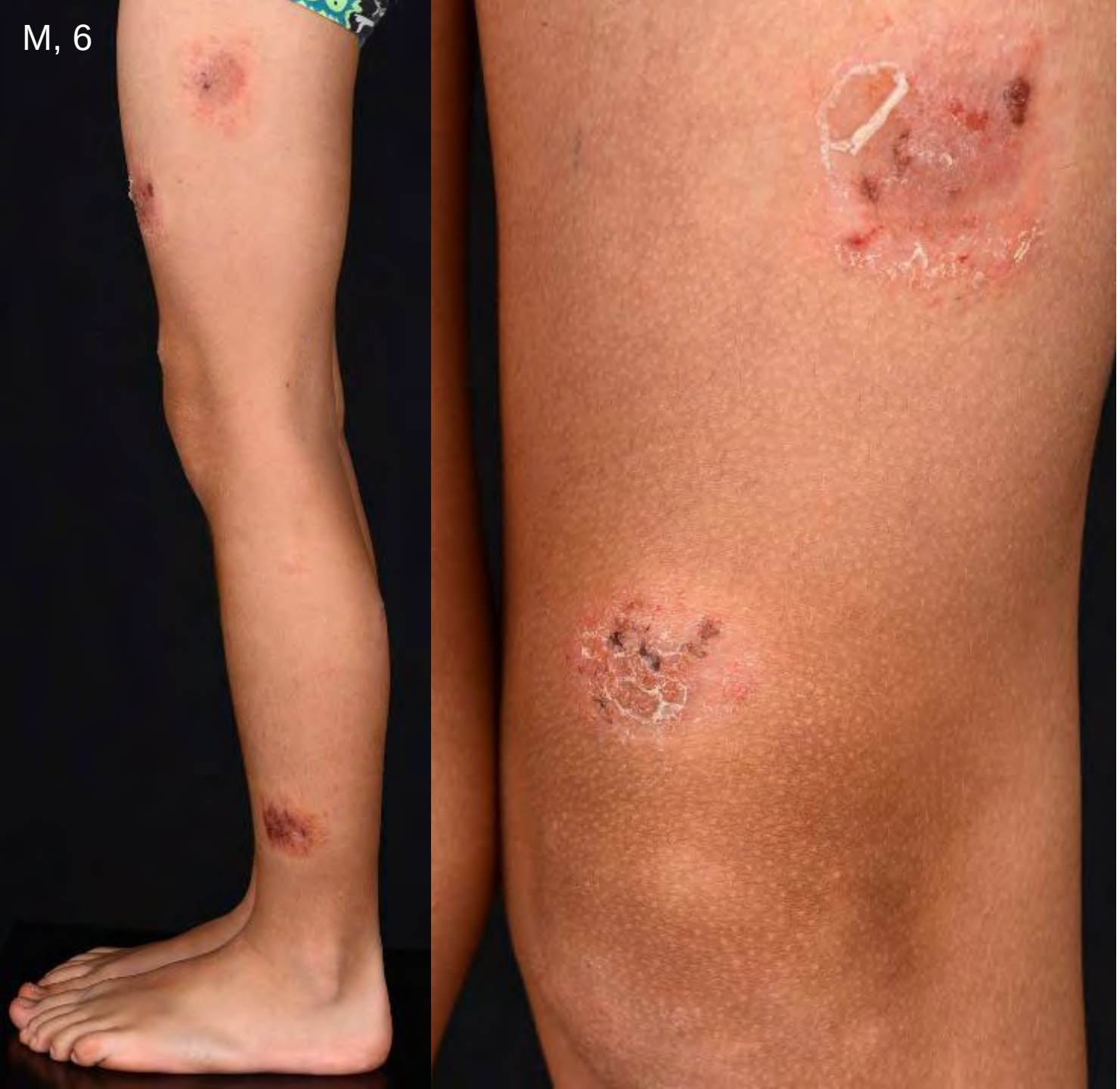

Pityriasis alba

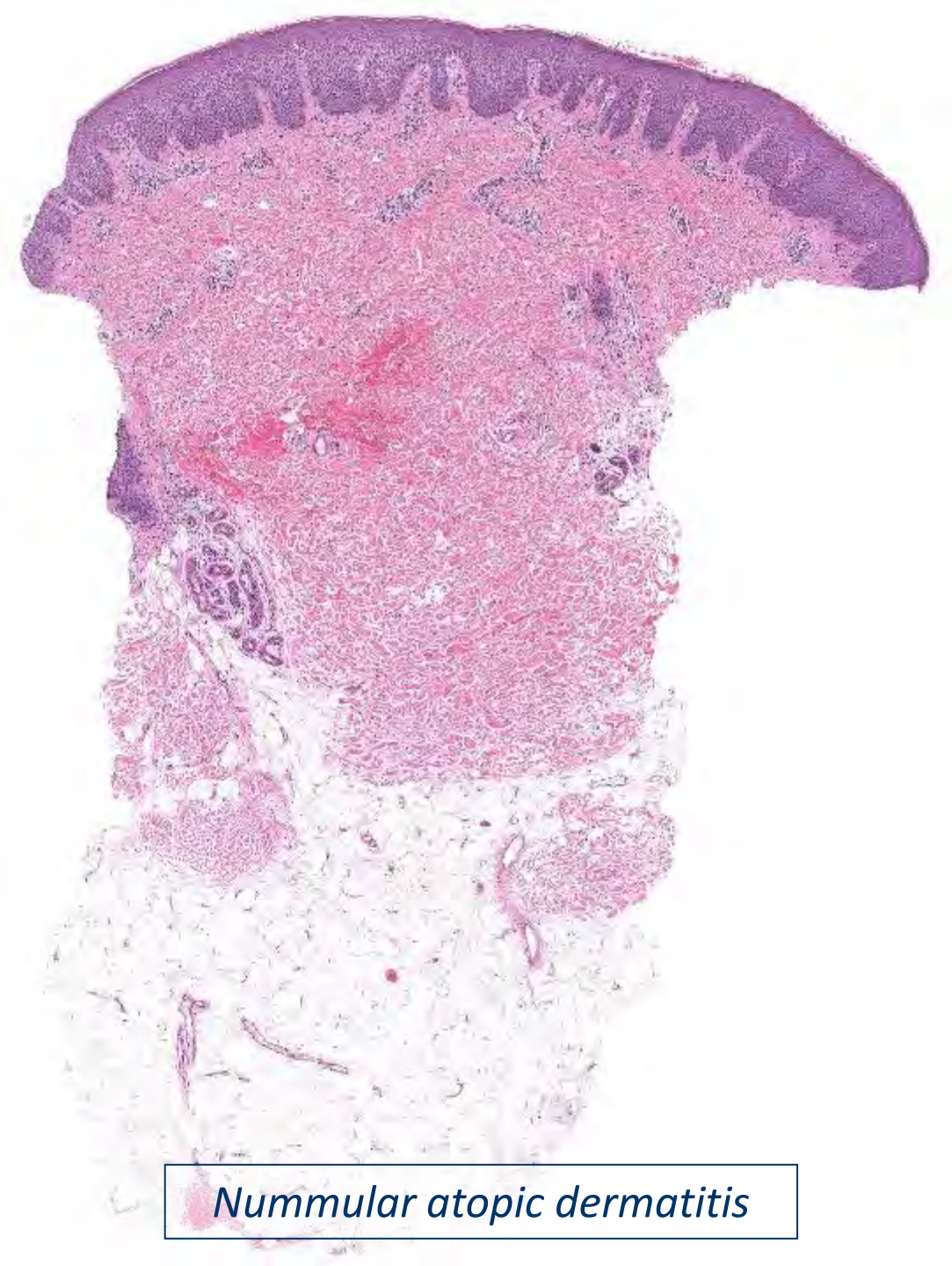

Dennie-Morgan folds and periorbital darkening


Eyelid eczema with lichenification

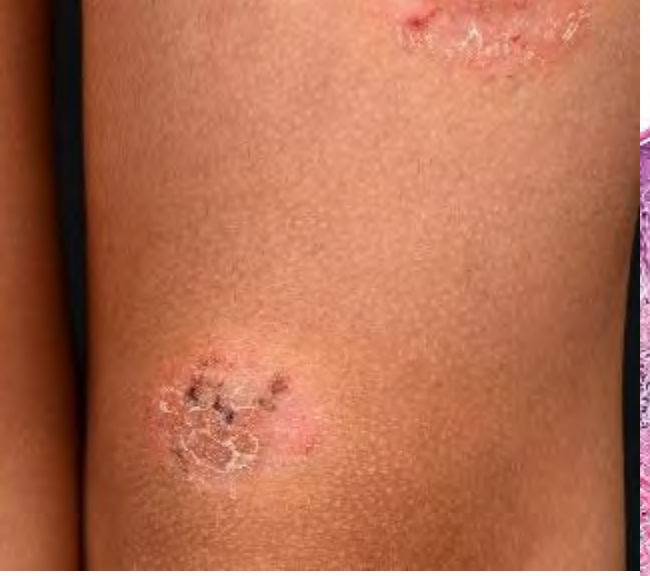

Patchy pityriasiform lichenoid eczema
(Kitamura-Takahashi-Sasagawa)

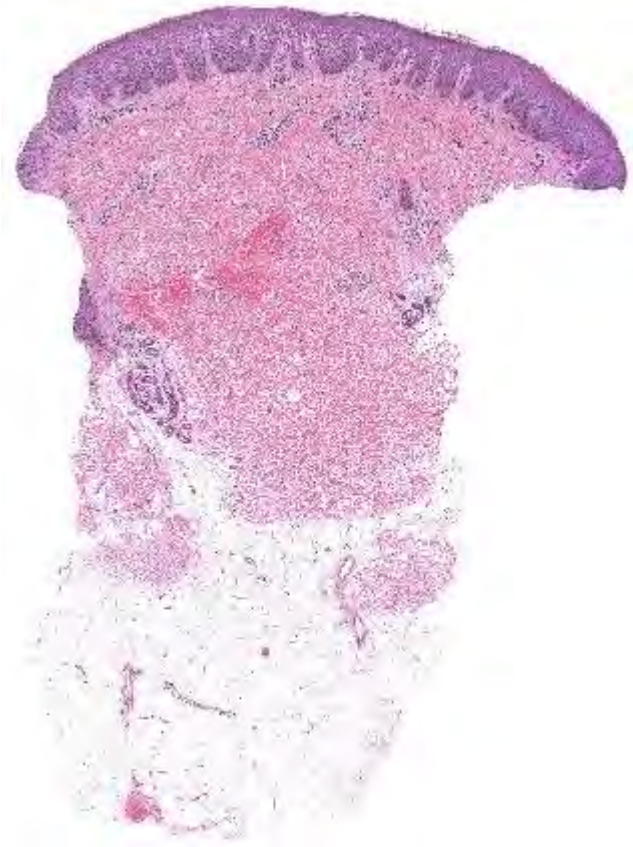

Atopic winter feet

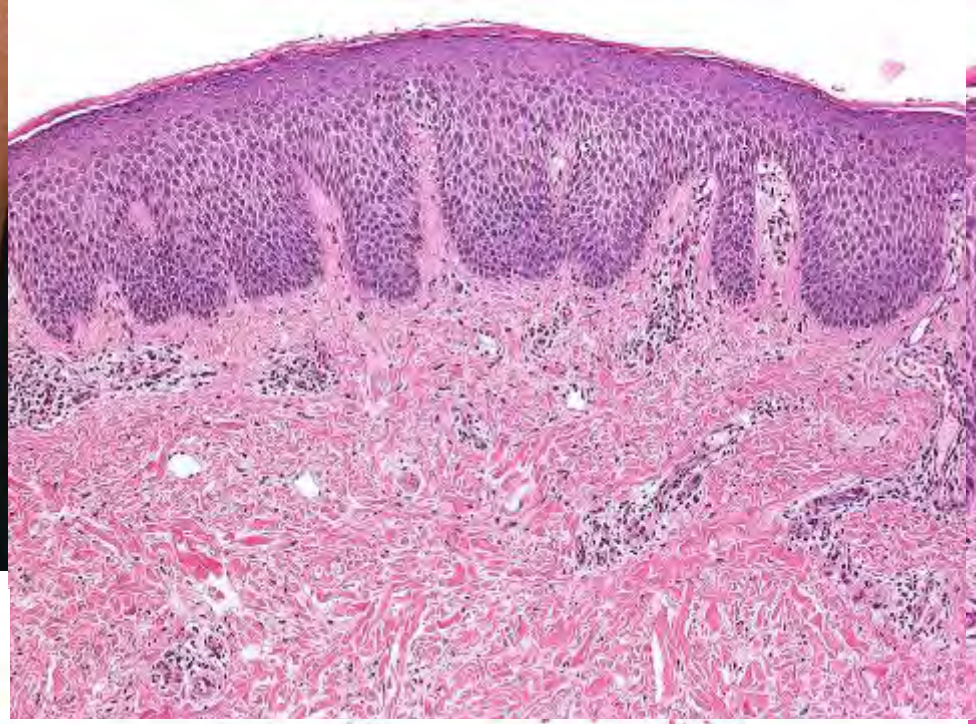


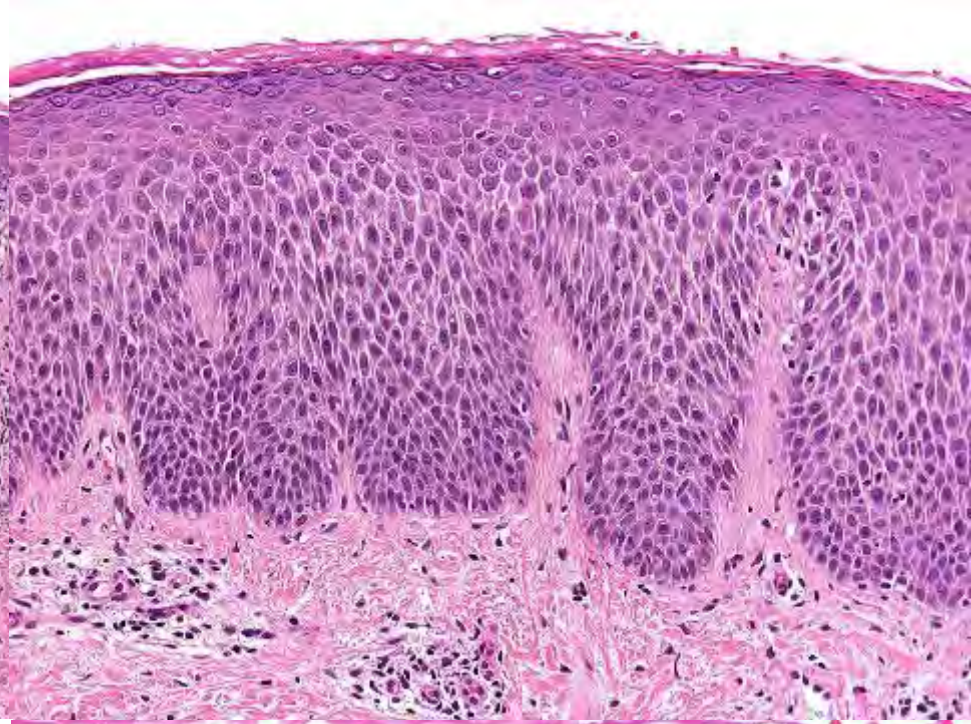


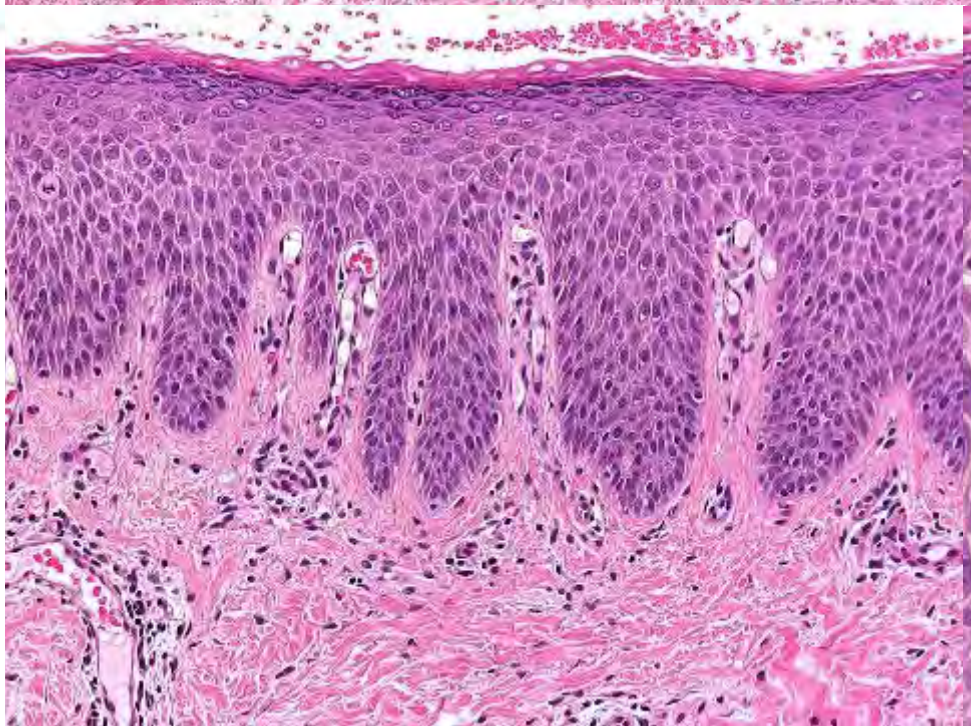
Nummular atopic dermatitis

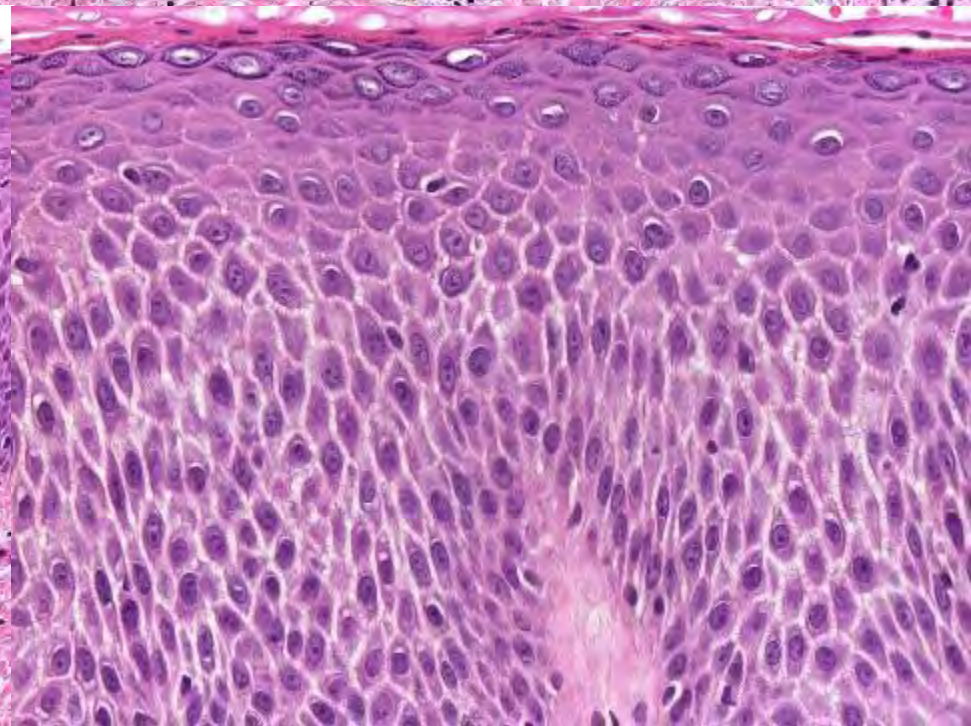




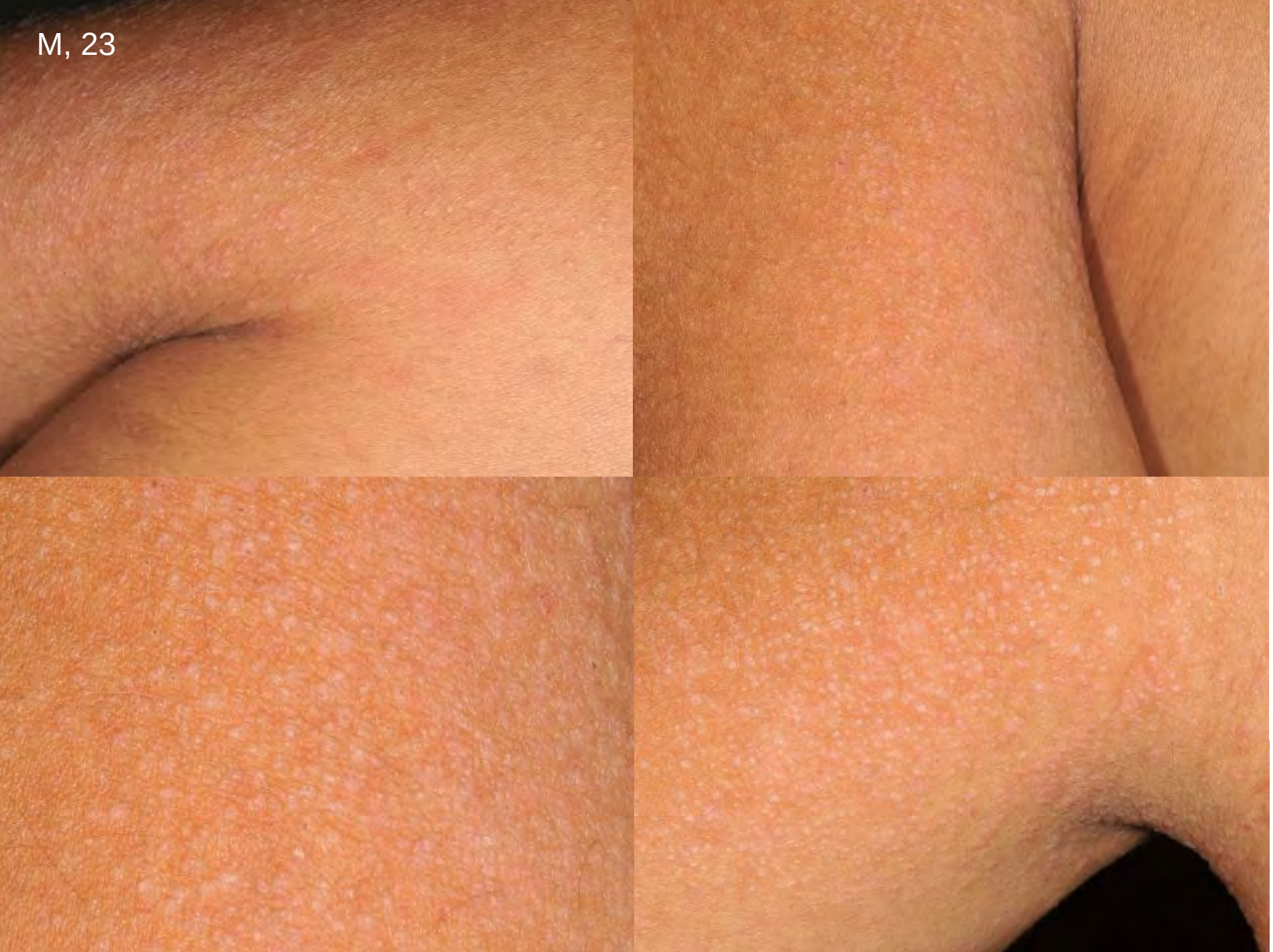


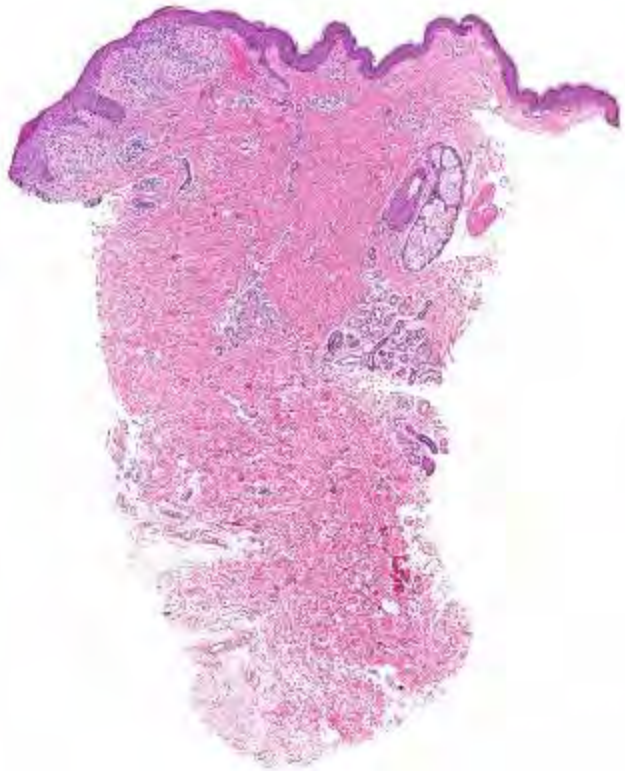




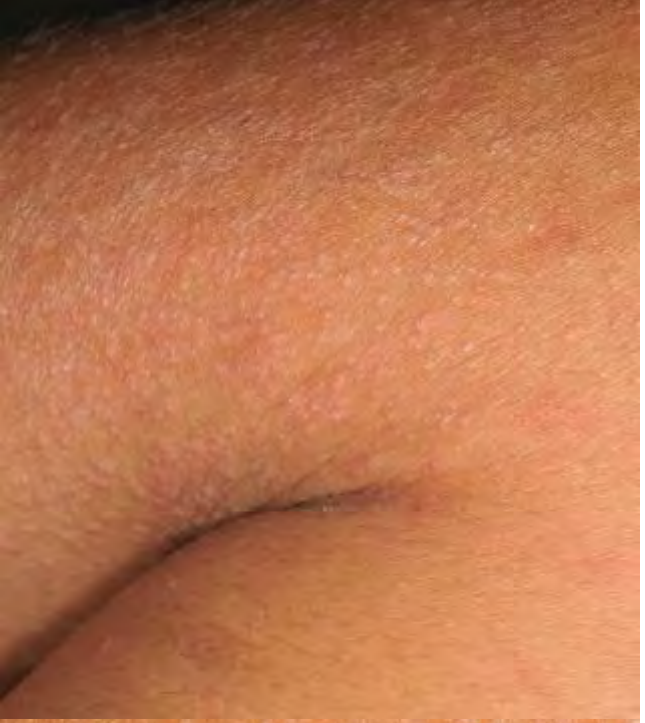


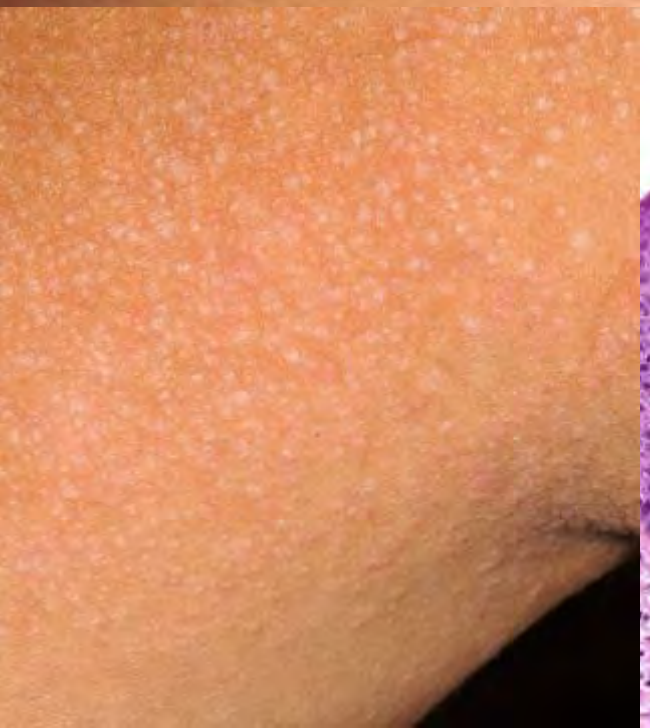
M, 23

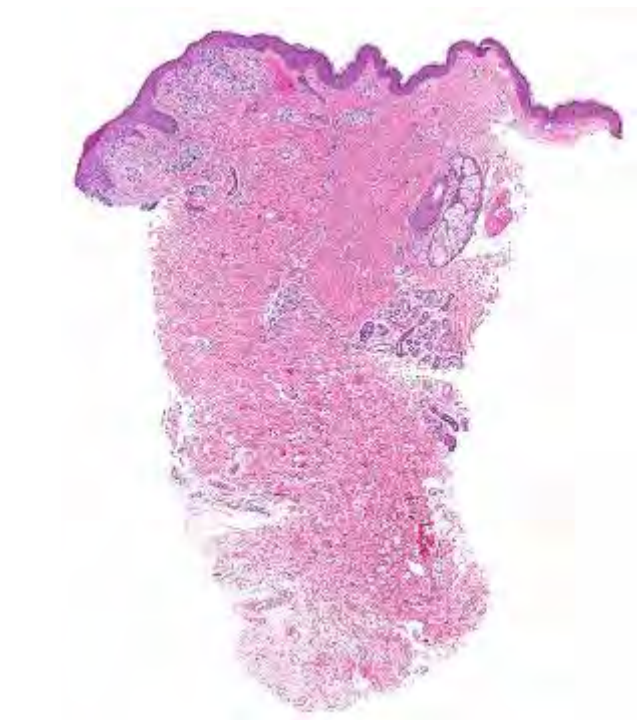


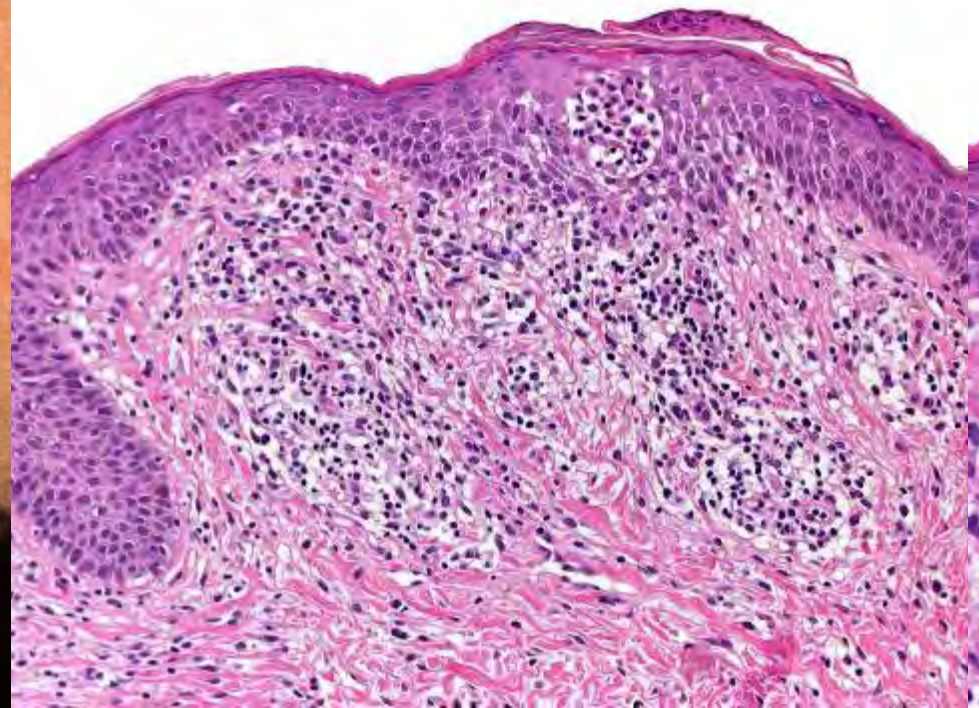


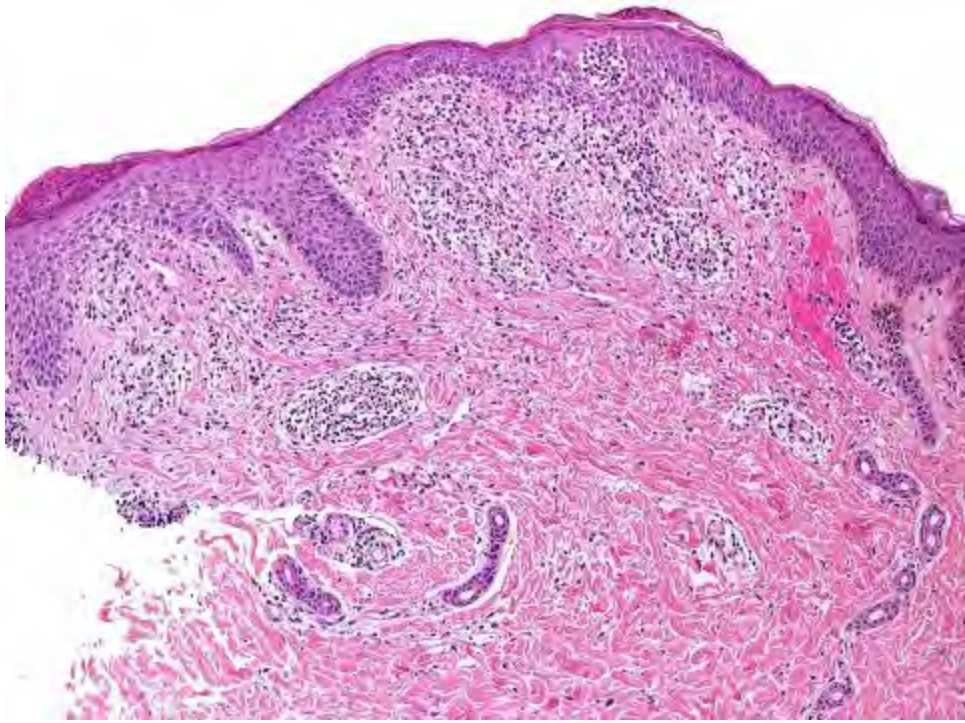
"Sandpaper dermatitis"

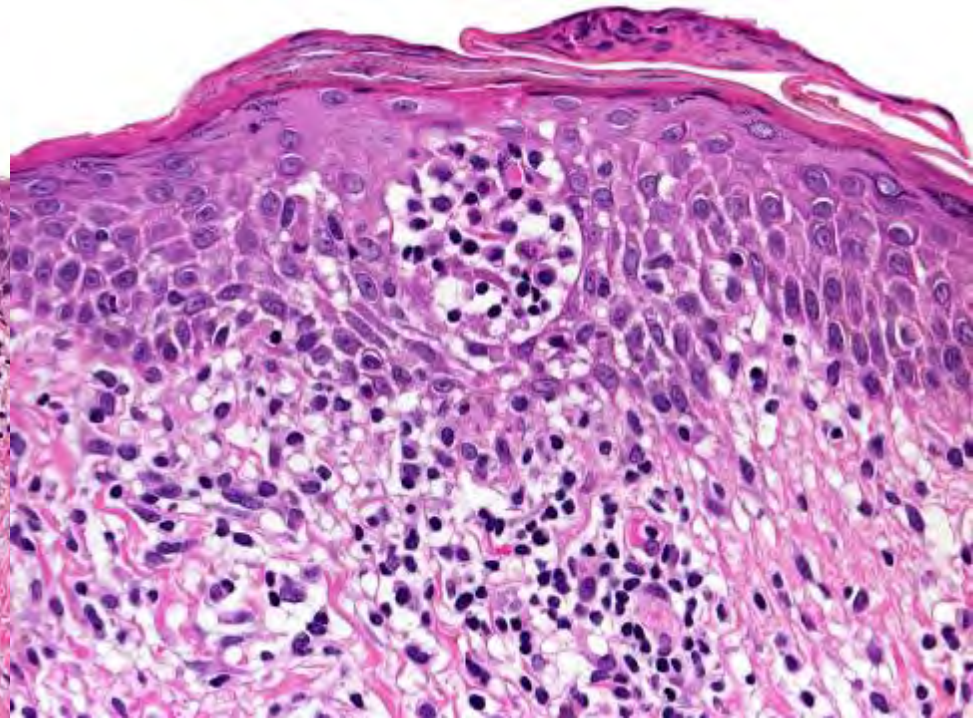












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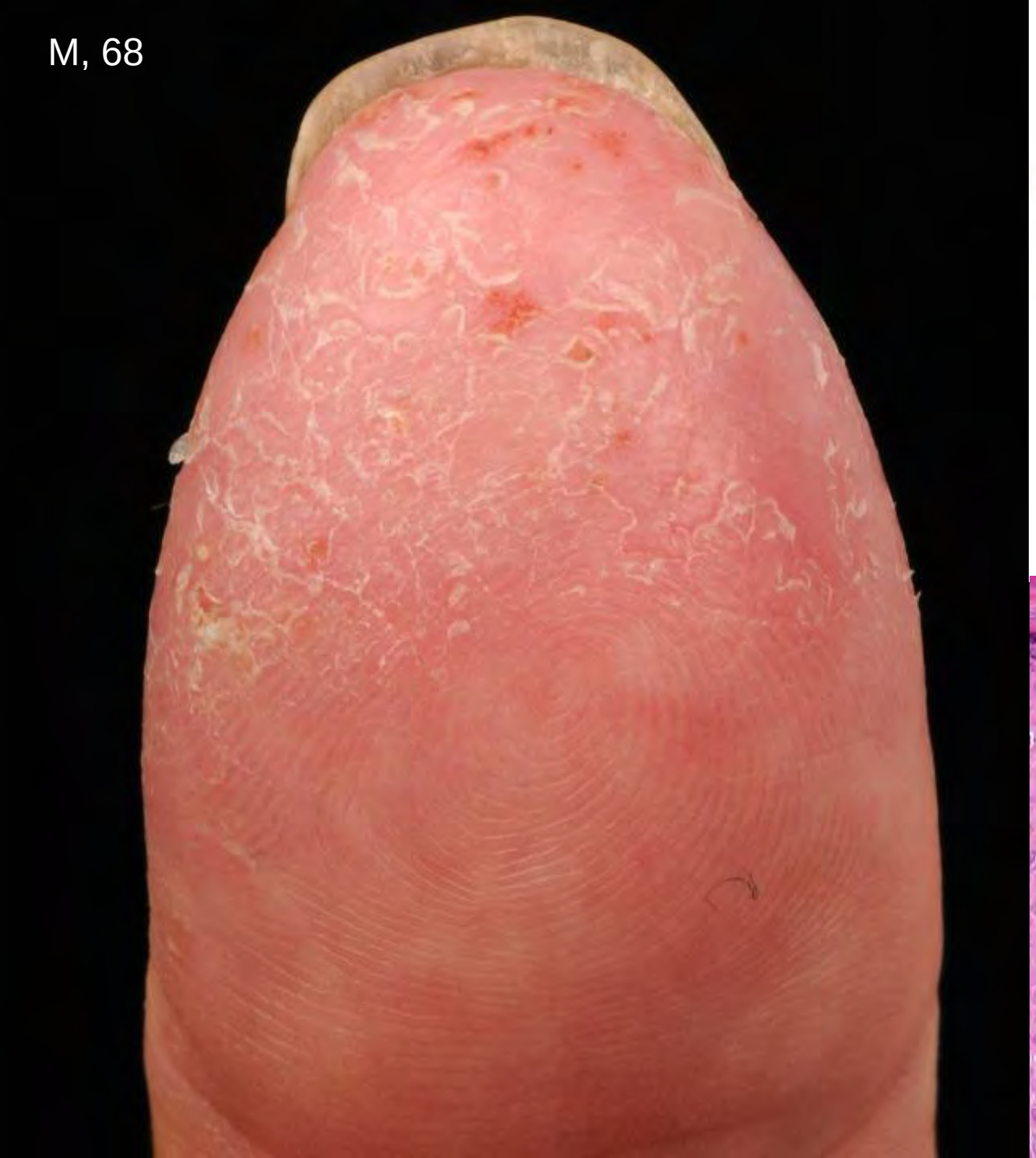
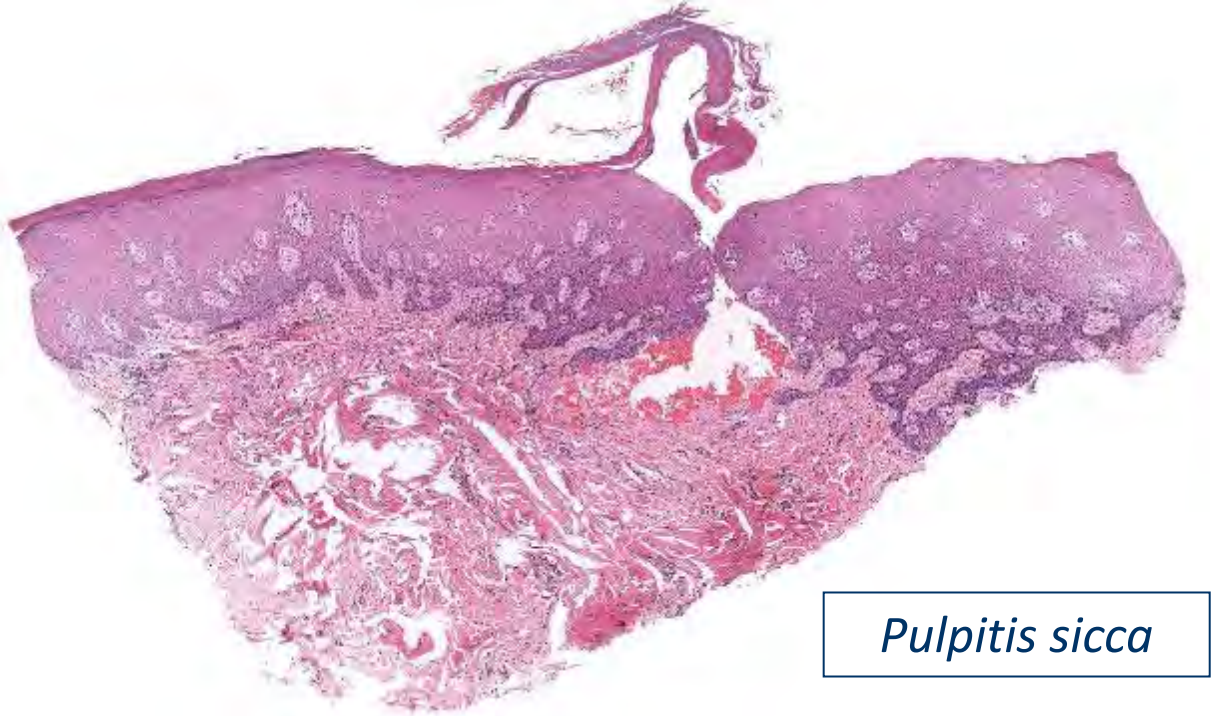
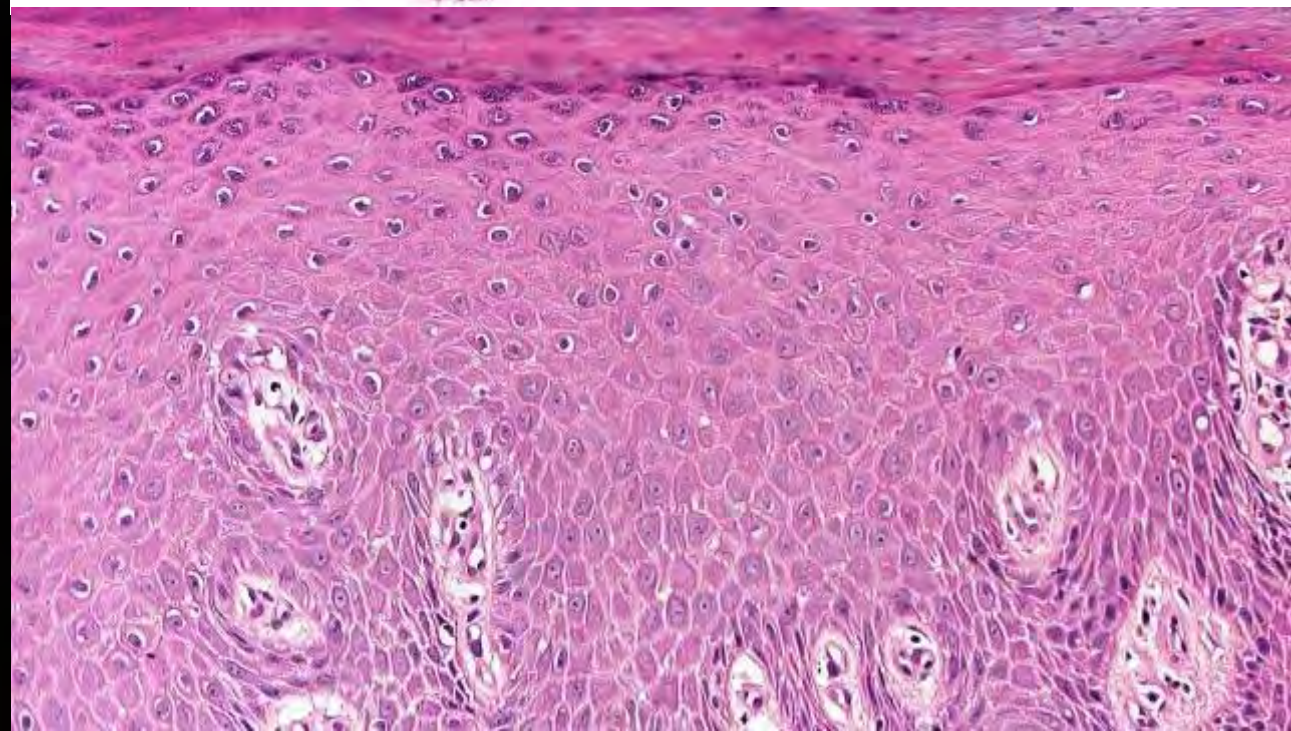
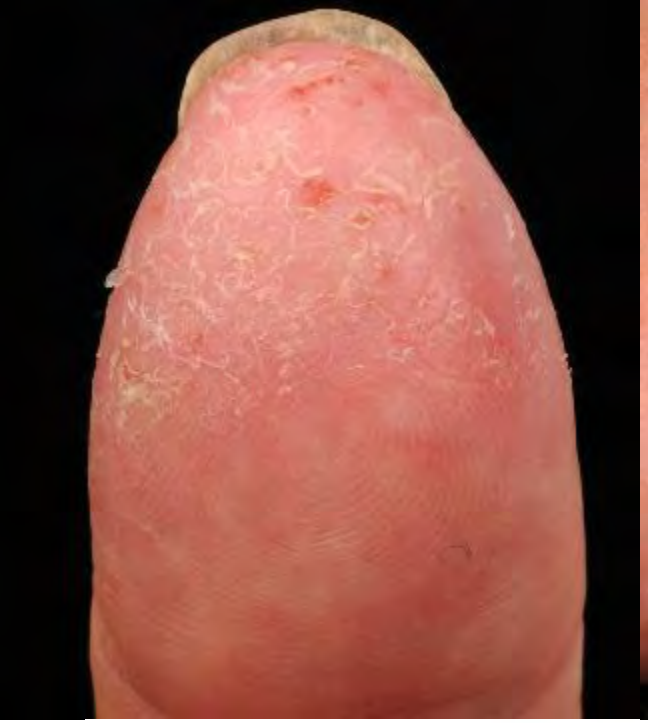
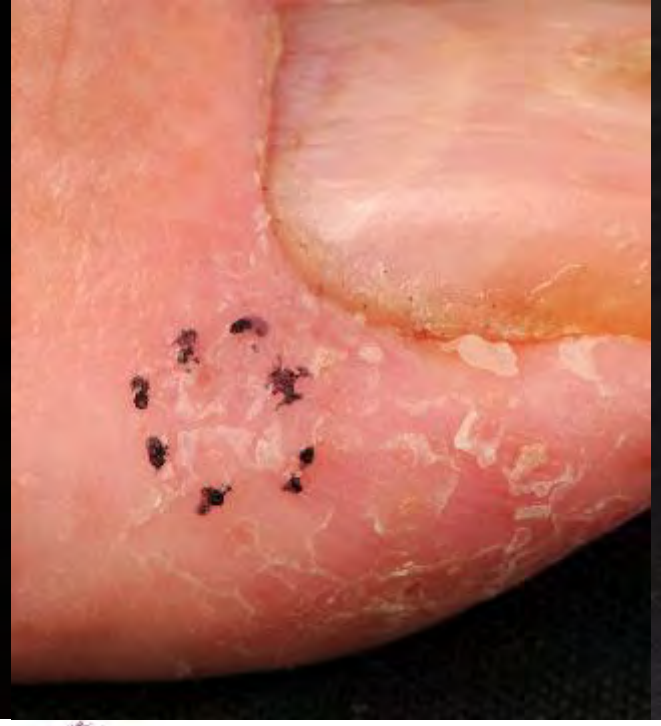


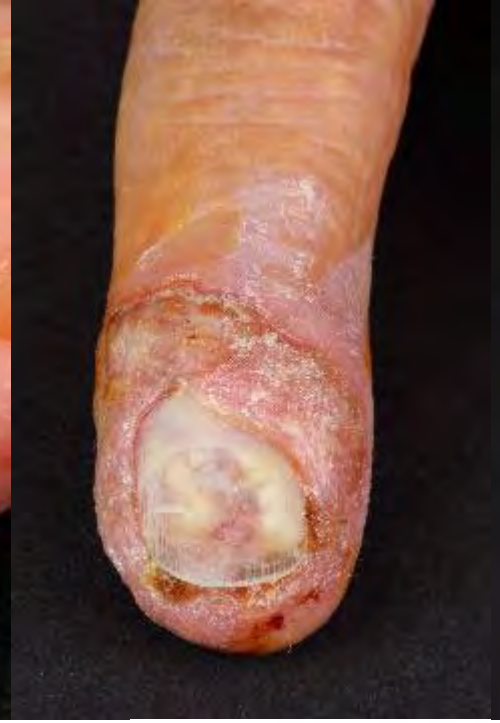


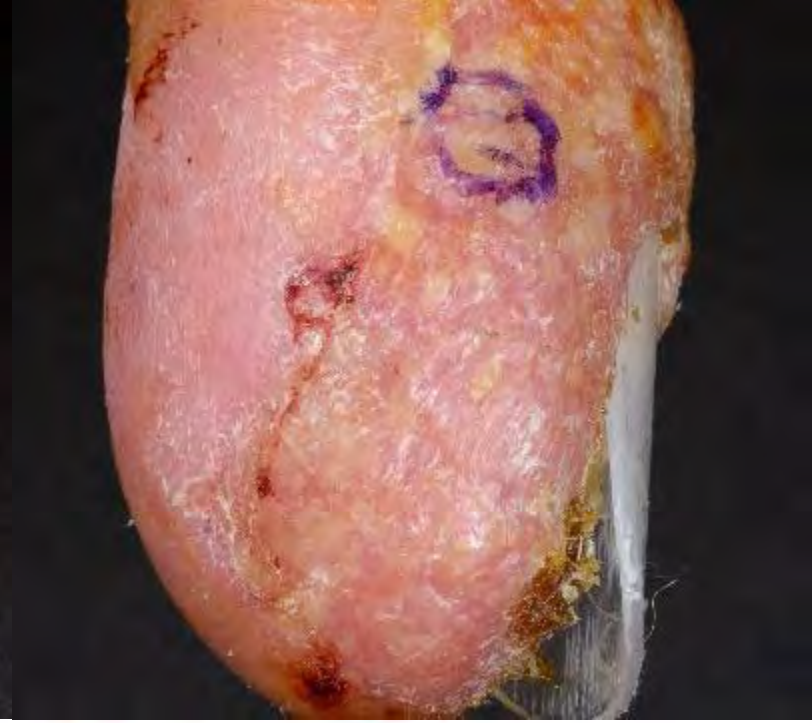
Pulpitis sicca

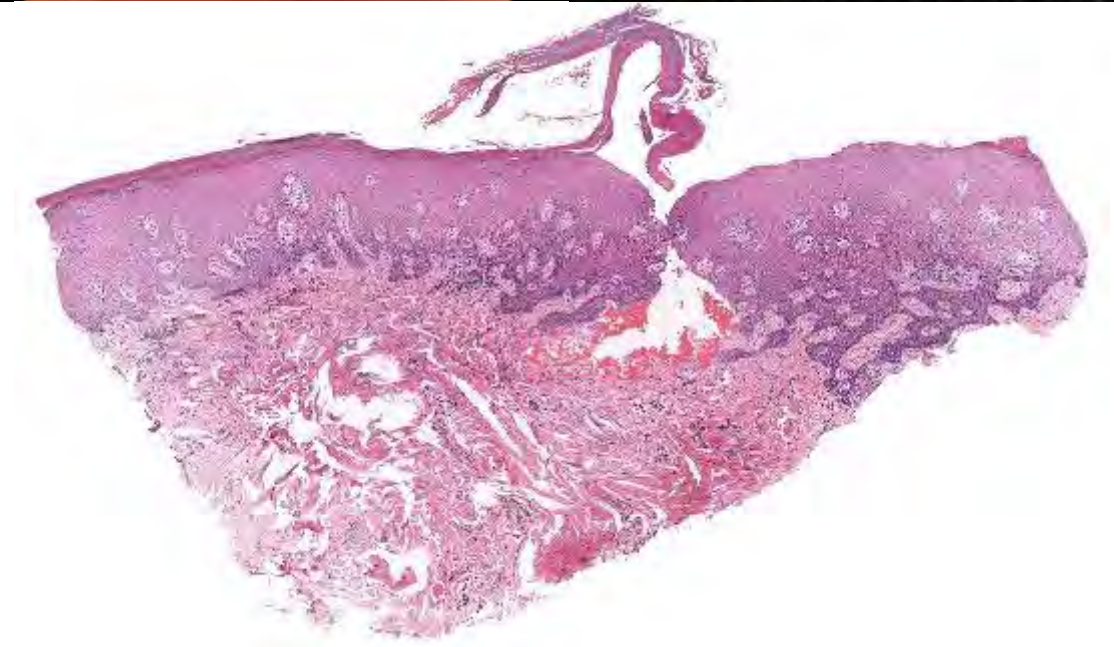




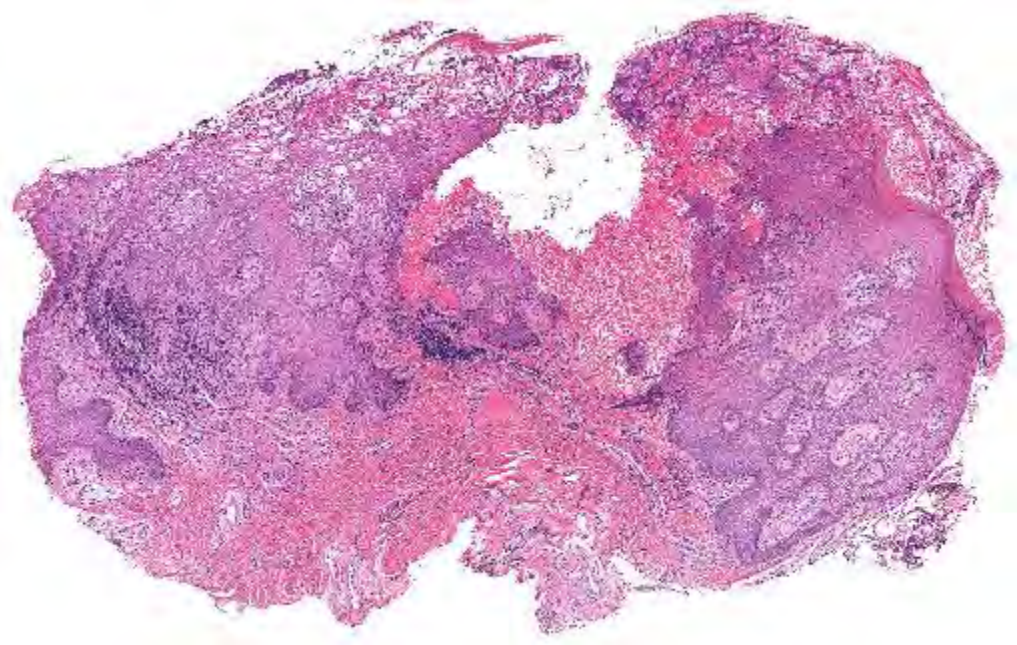






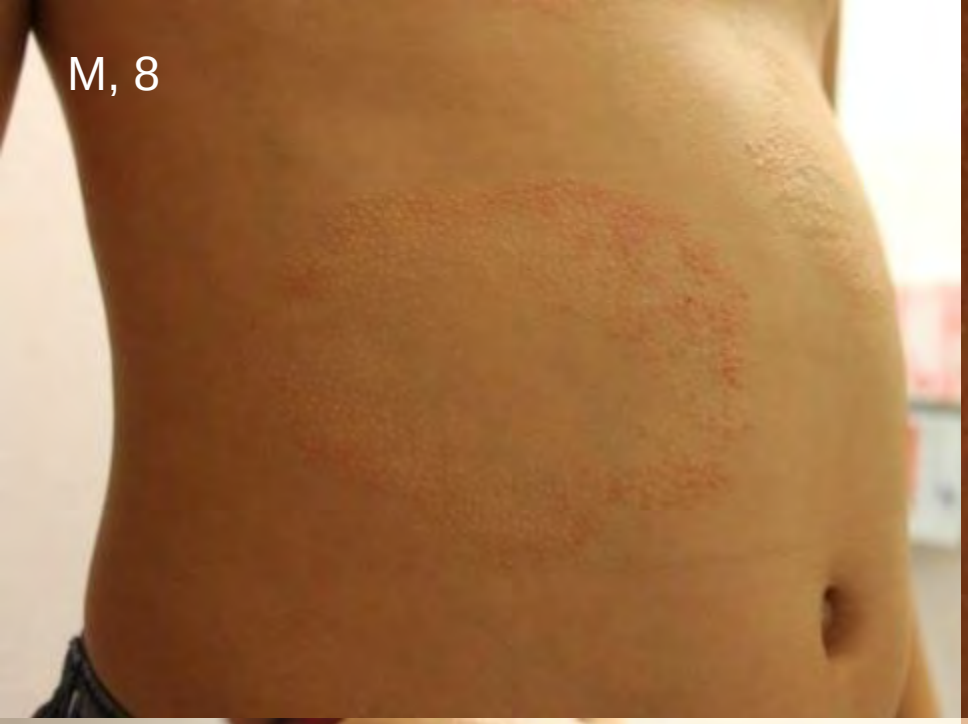


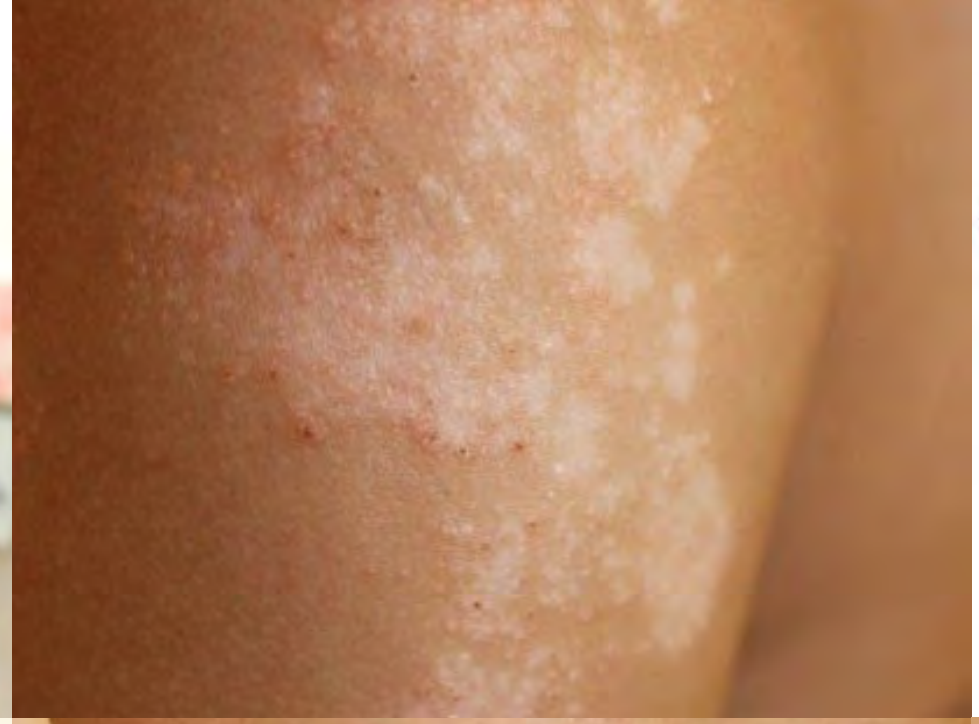
Atopic dermatitis (pulpitis sicca) – *Psoriasiform spongiotic pattern*

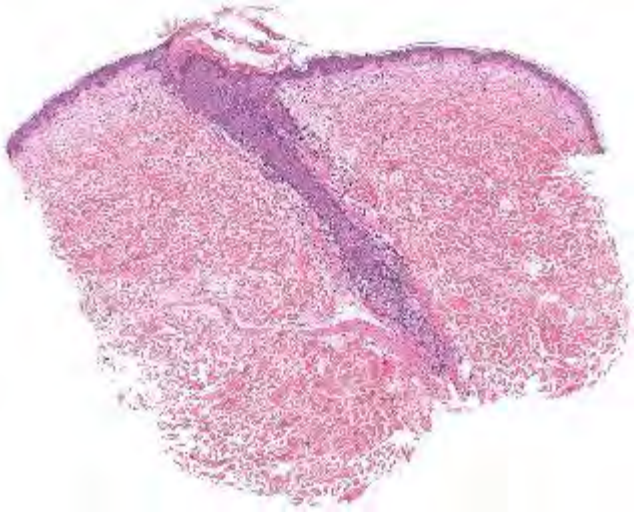


Psoriasis (acrodermatitis continua Hallopeau) – *Pustular pattern*

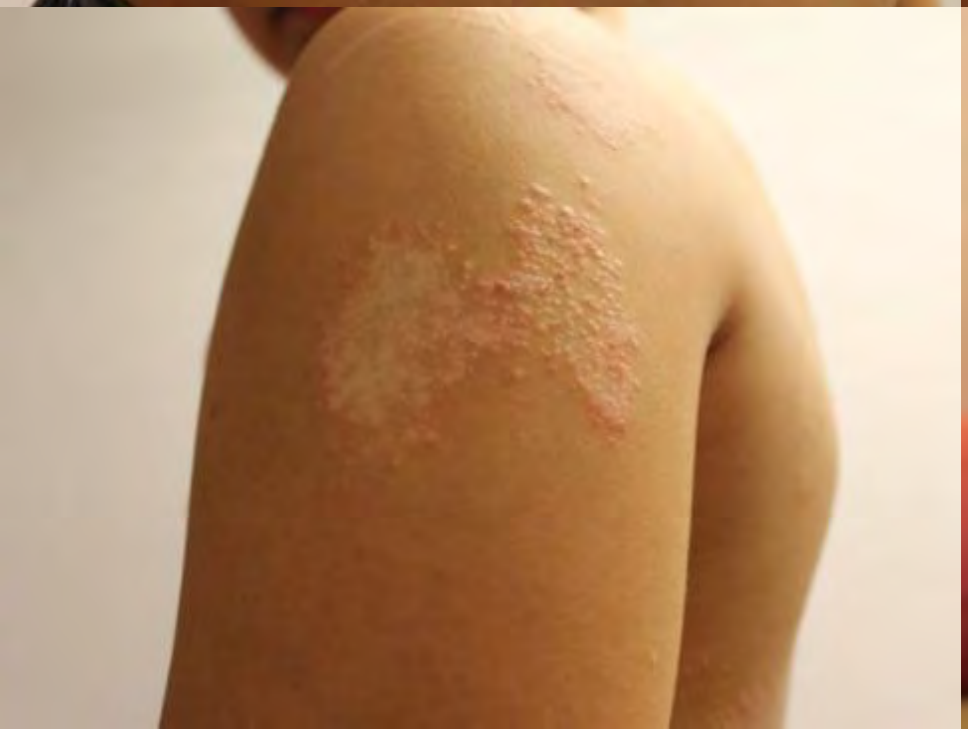
M, 8

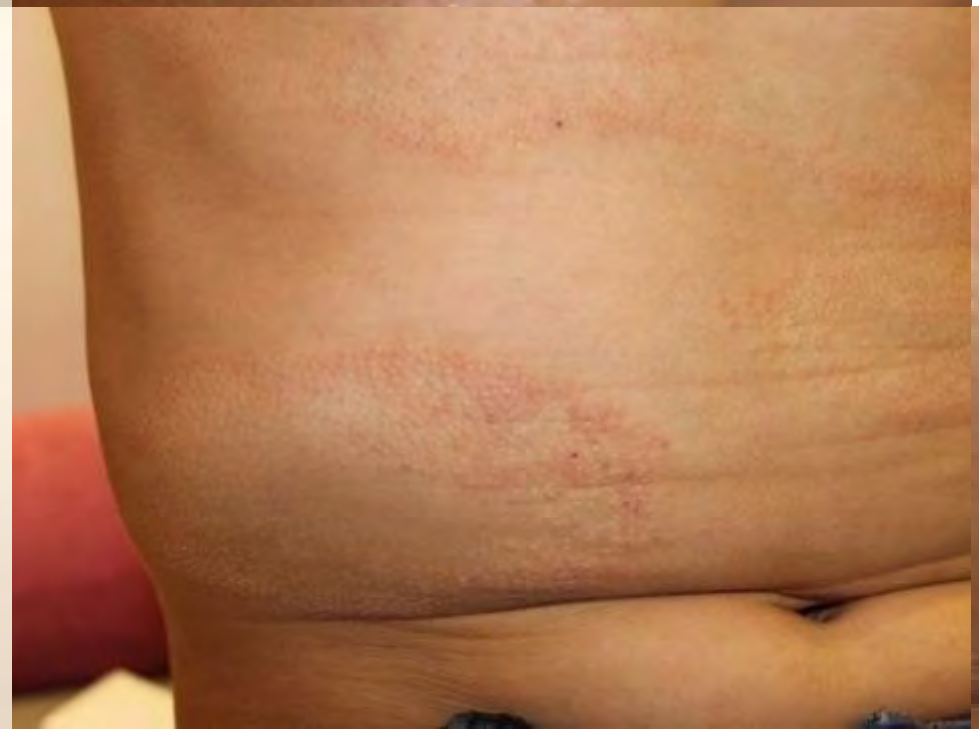


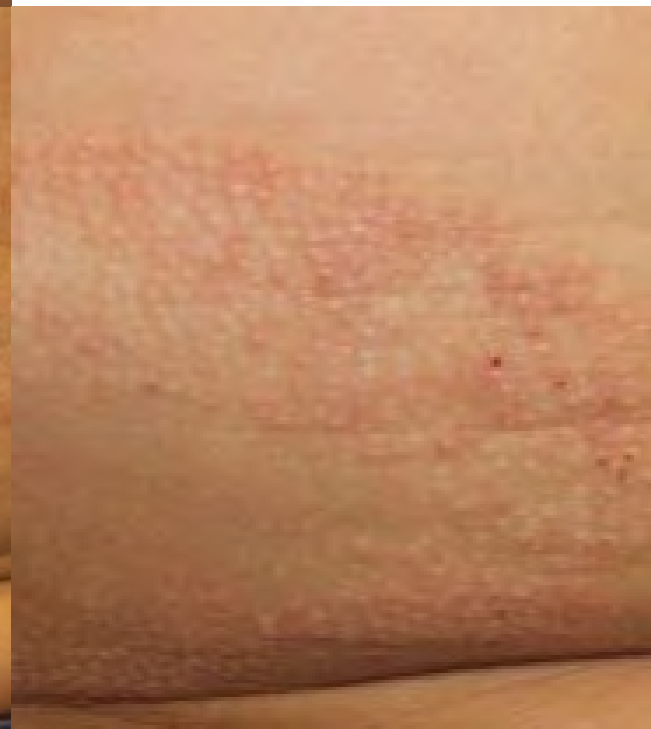


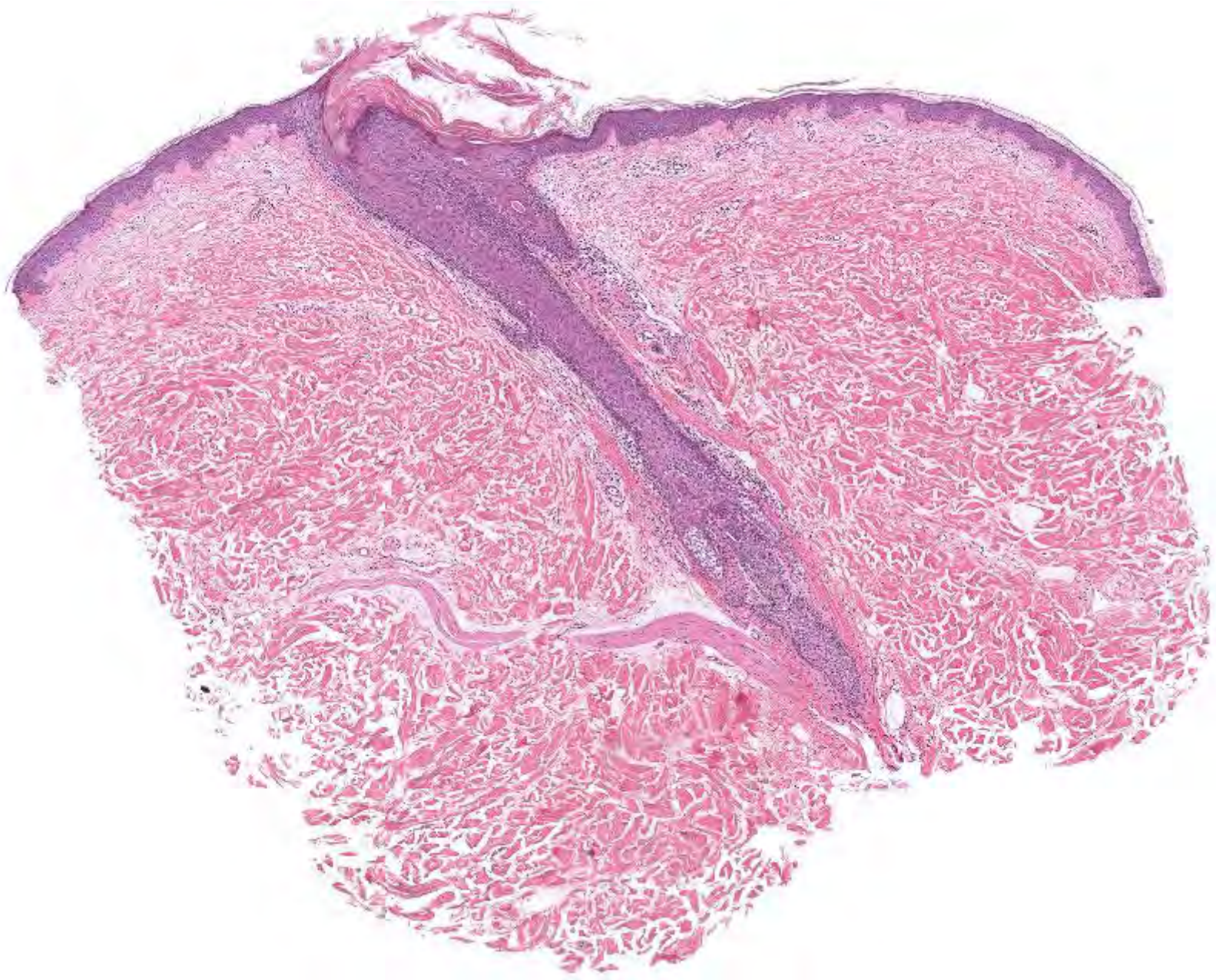


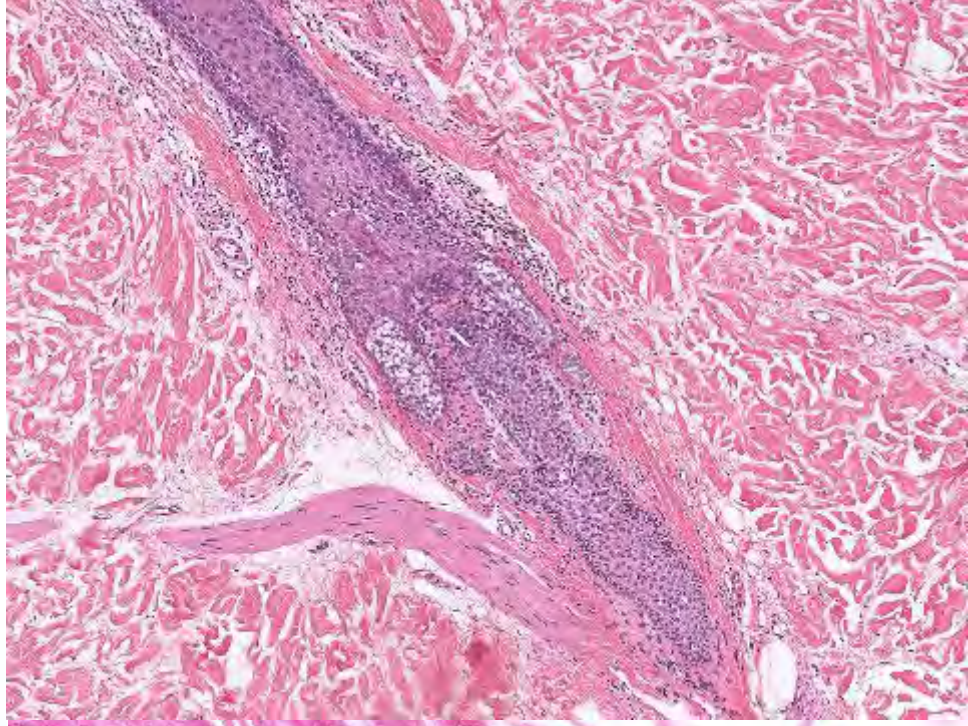
Follicular hyperkeratoses

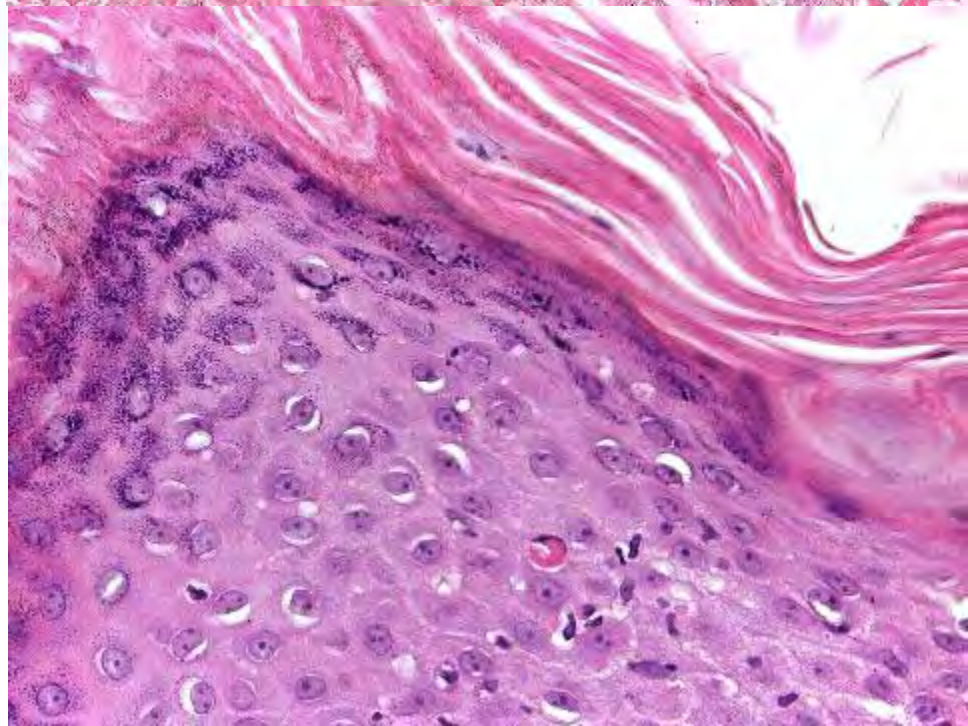












8 Minimal Variants of Atopic Eczema

E. Wuthrich

In: Handbook of atopic eczema, 2006

8.4 Patchy Pityriasiform Lichenoid Eczema: The Follicular Form of Atopic Eczema

Patchy pityriasiform lichenoid eczema is a dry, only slightly itching, follicular form of atopic eczema occurring in childhood. Its first description is attributable to Japanese authors as far back as 1950 [48]. In a 1966 paper published in German, Kitamura [49] mentioned that together with Takahashi and Sasagawa he had described a plaque shaped, lichenoid, scaly eczema as an independent dry type of childhood eczema. This type, evidently common in Japan, was allocated by Sasagawa in 1967 to the group of atopic eczema [50]. In 1981, we described this at that time scarcely known manifestation of atopic eczema in childhood [51]. Thus, clinically there are partly confluent areas with densely juxtaposed, mildly bran-like, scaly, nonhyperkeratotic, skin-colored papules (Figs. 8.19–8.21). They are found, with a generally dry integument, especially on the trunk but also on the nape of the neck and the knees. Histologically, these itchy "goose flesh spots" exhibit a spongiosis of the follicular epithelium and an intra- and perifollicular lymphohistiocytic infiltration, which indicated the eczematous nature of this condition [48–51] (Fig. 8.22). Pruritus is usually present, though not always severe. Mildly scaly depigmented areas, rather like pityriasis alba [52, 53], and isolated, frequently asymmetric, typical lichenified foci on the backs of the hands or elbows are occasionally present. In our series, a discrete perennial or seasonal allergic rhinitis was frequently associated. Progression of the disease is observed particularly in winter, whereas summer visits to the seaside usually lead to improvement or healing of the rash. Ofuji and Uehara [54] also found similar itchy follicular papules in 96% of their patients with atopic eczema, particularly on the lateral parts of the trunk. They suggested that these lesions probably constitute the primary efflorescence of atopic eczema.

Fig. 8.19. Follicular form of atopic eczema (patchy pityriasiform lichenoid eczema, Kitamura-Takahashi-Sasagawa): plaque-shaped "goose flesh spots" on infrascapular region of back (1-year-old boy, dark skinned)

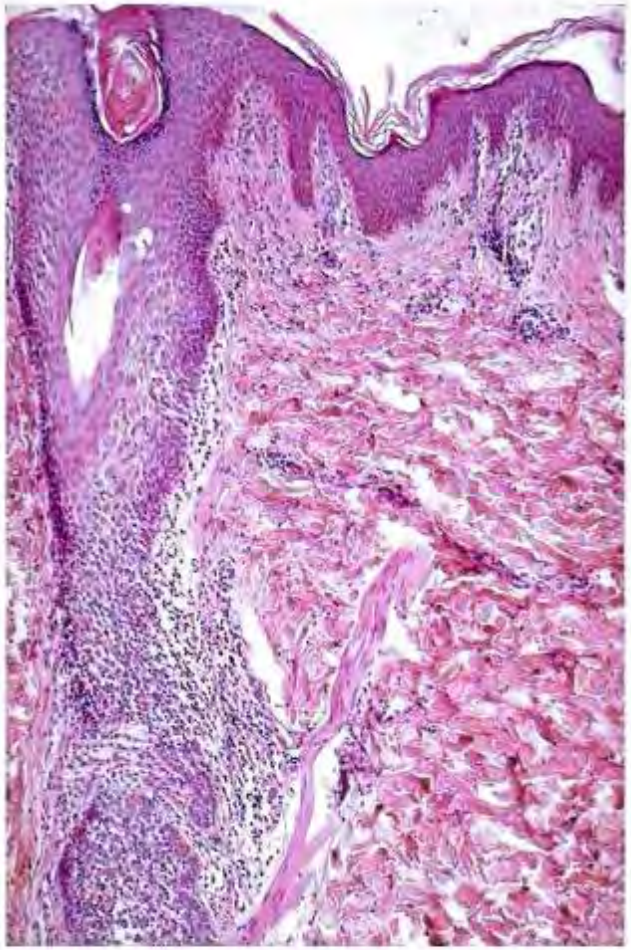


Fig. 8.21. Histologic findings showed the follicular form of atopic eczema in a 10-year-old girl: follicular papule with spongiosis of the epidermis and lymphohistiocytic intra- and perifollicular infiltration

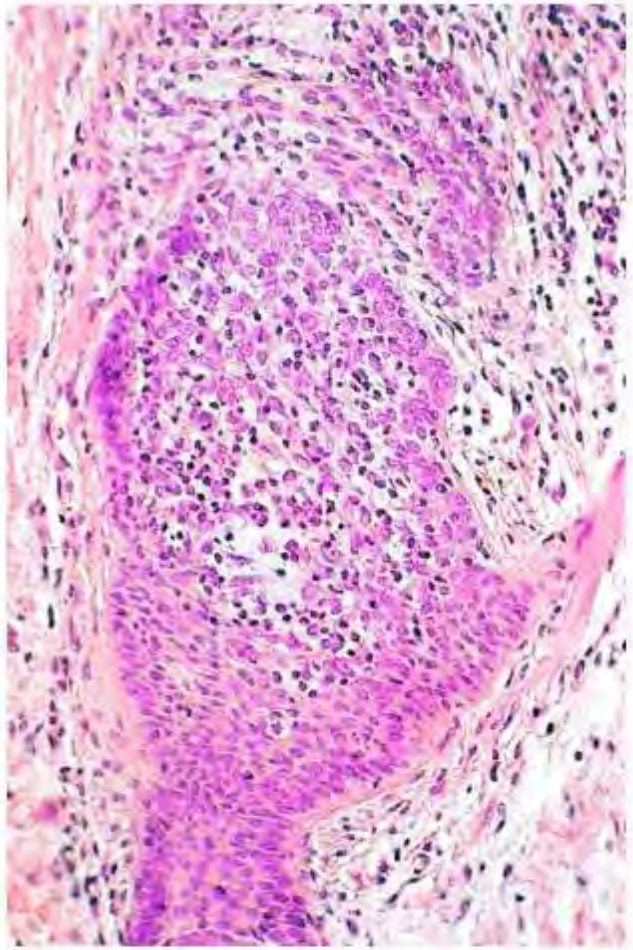
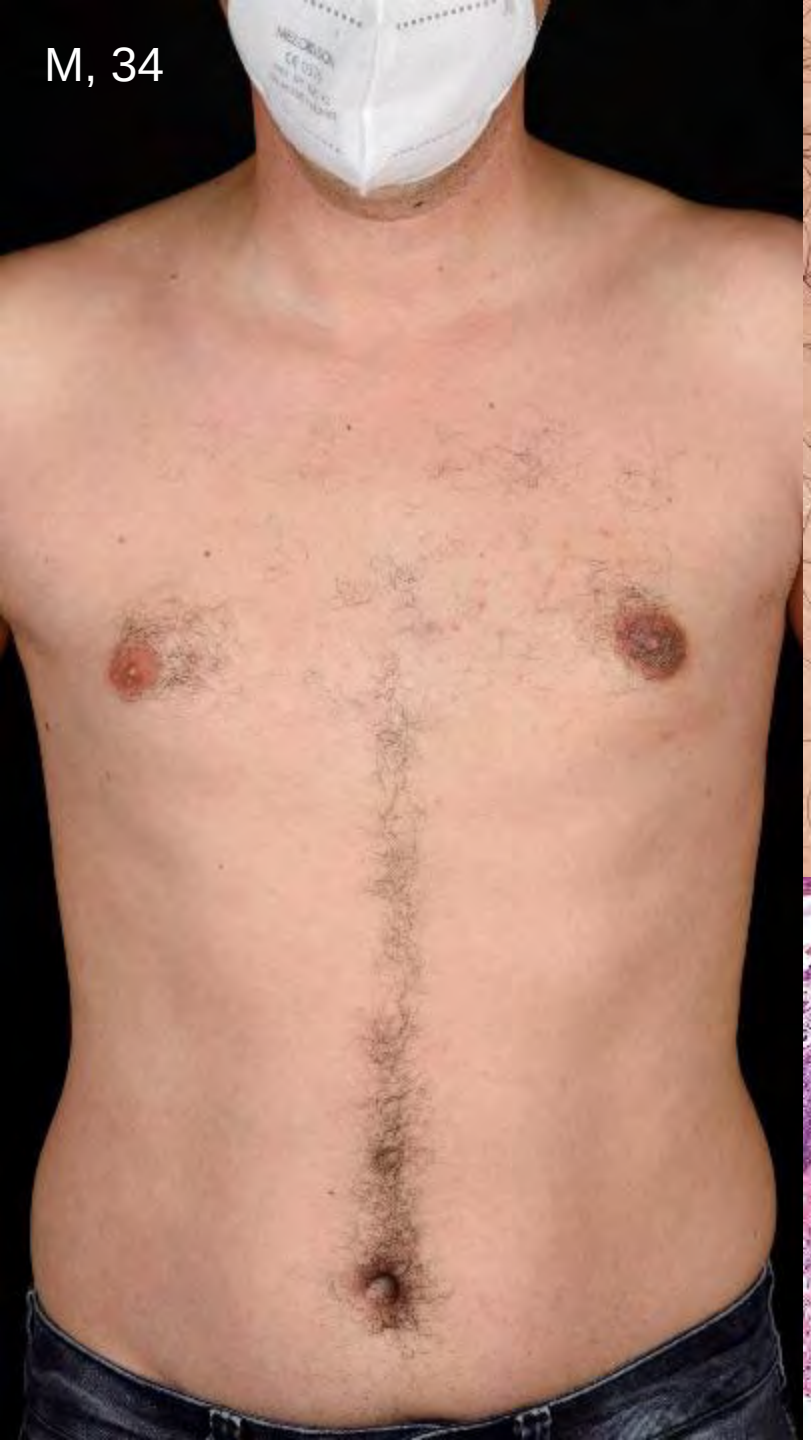
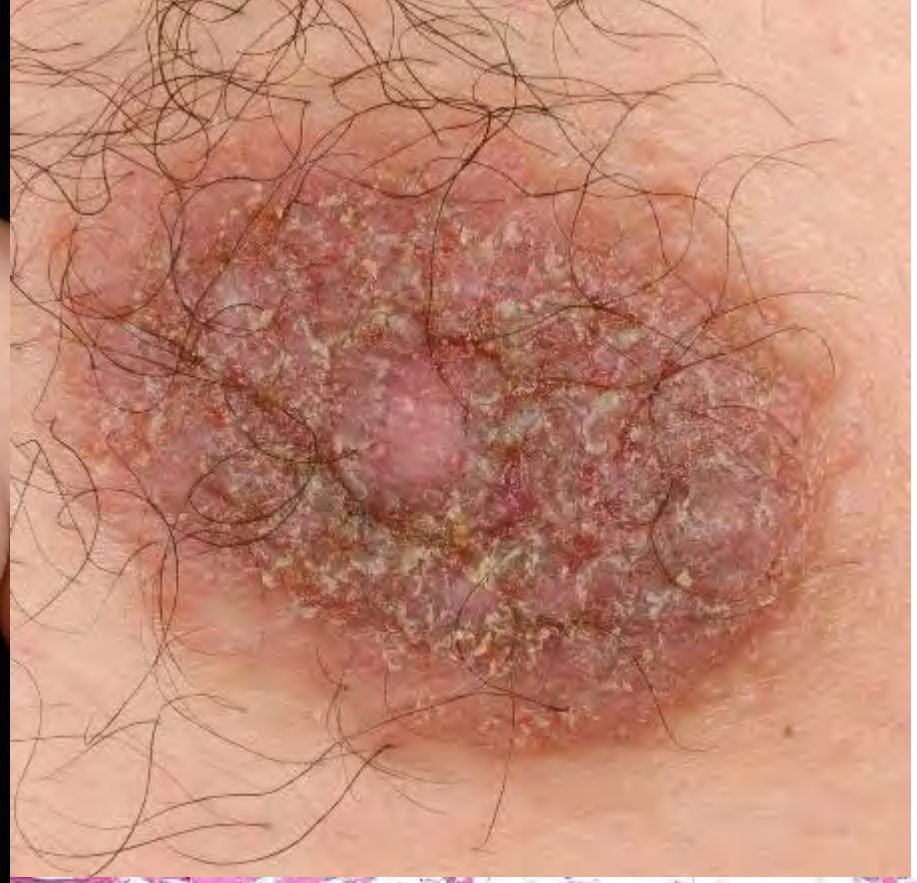
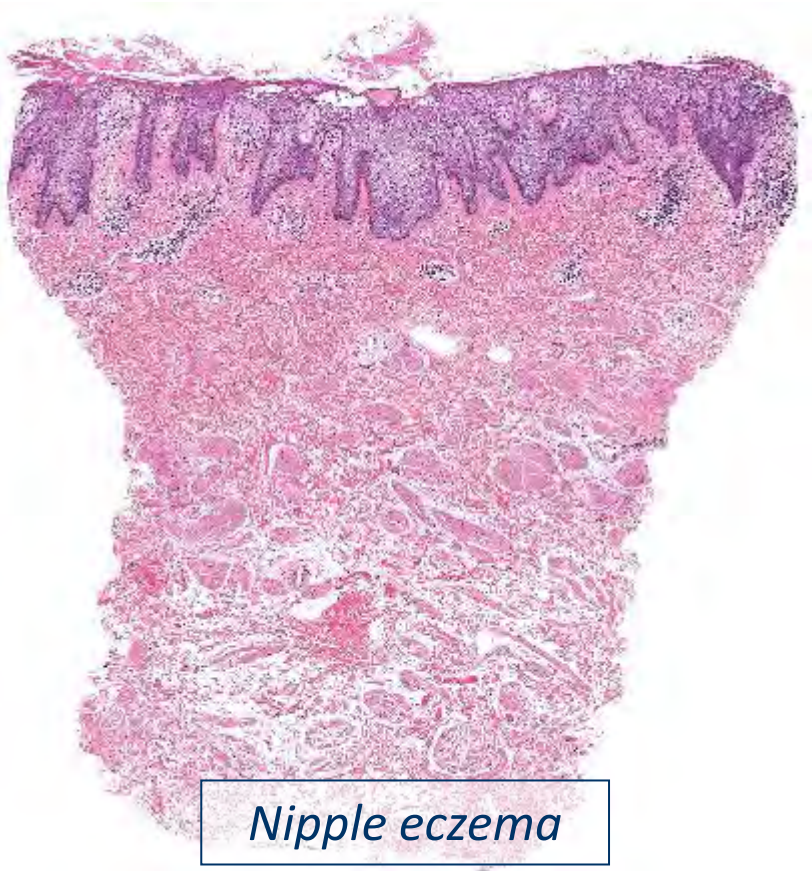


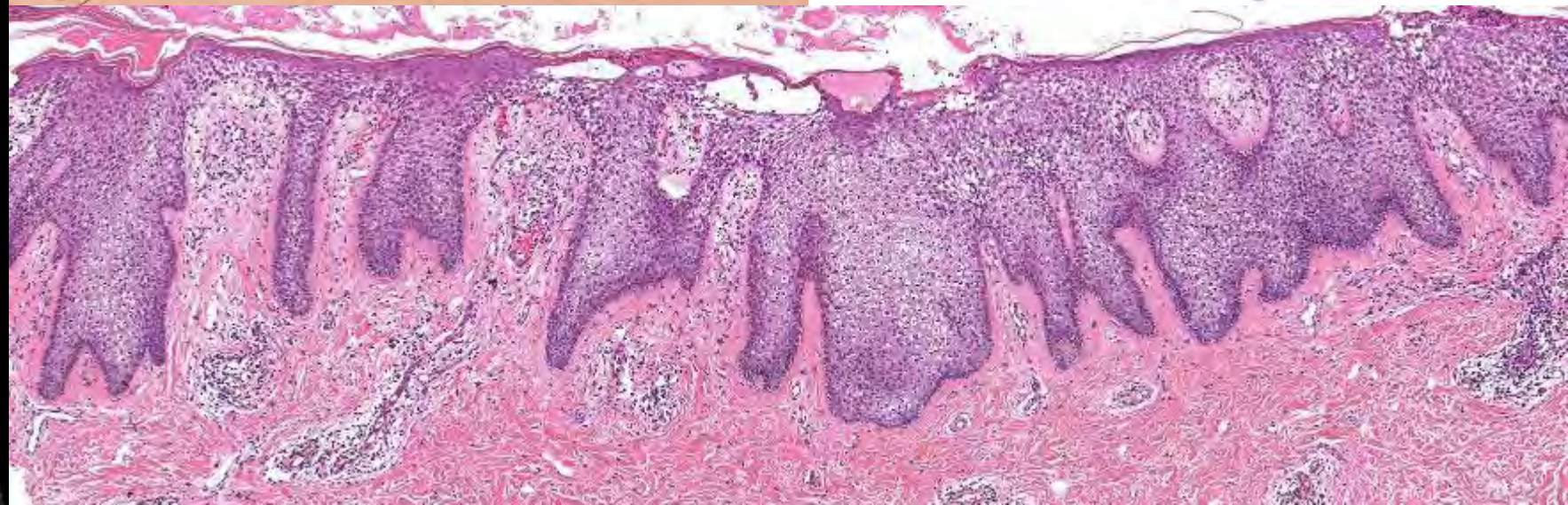
Fig. 8.22. Histologic findings: spongiosis of follicular epithelium with lymphohistiocytic infiltration (same patient as in Fig. 8.21)

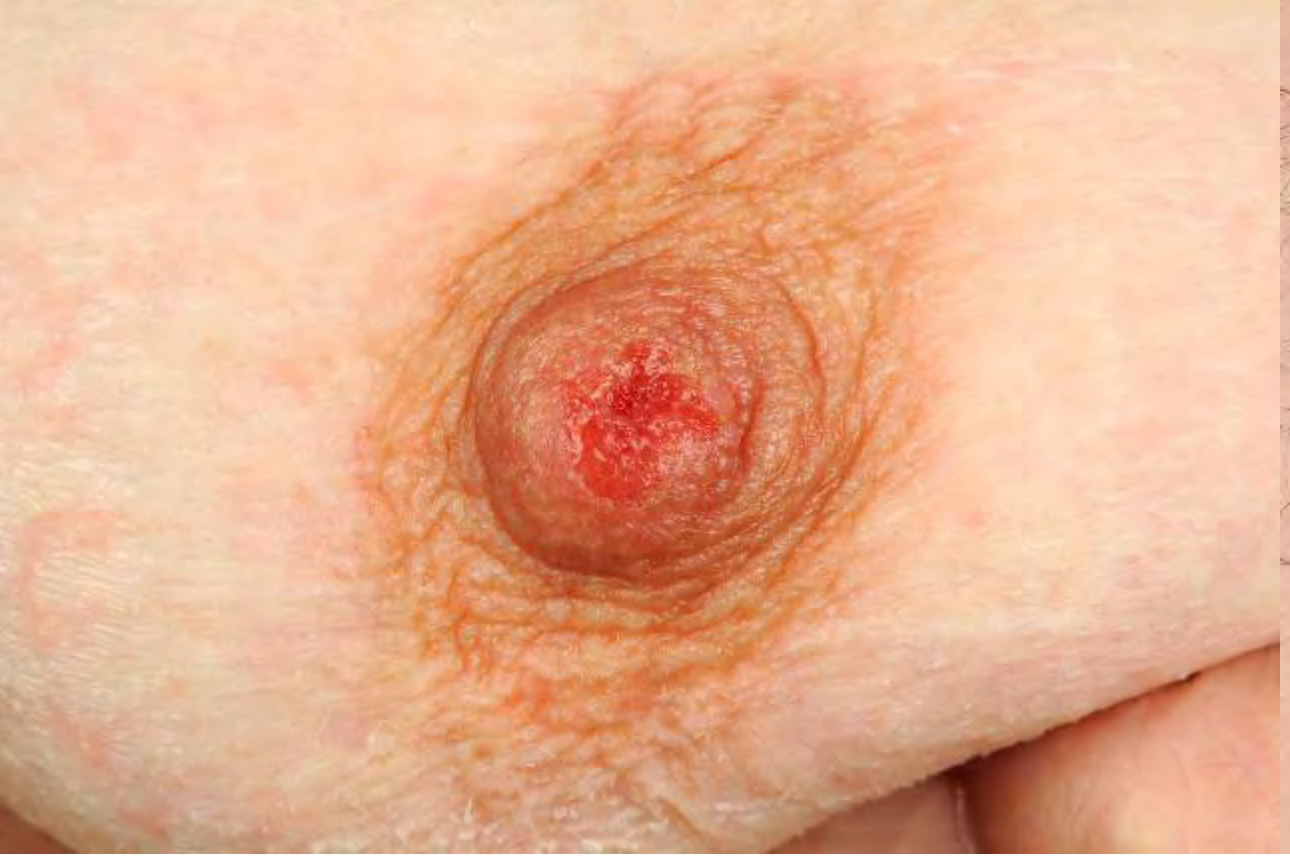


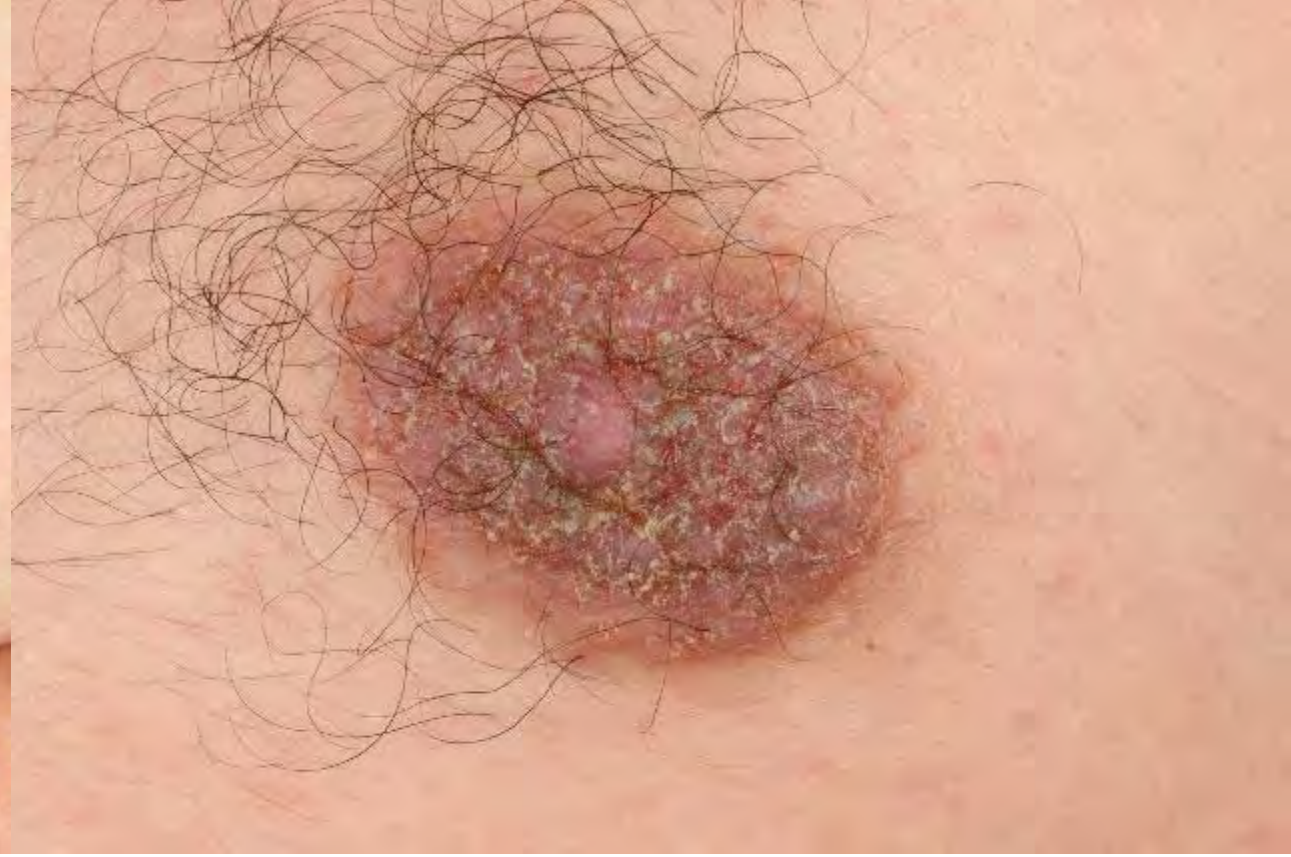




Nipple eczema





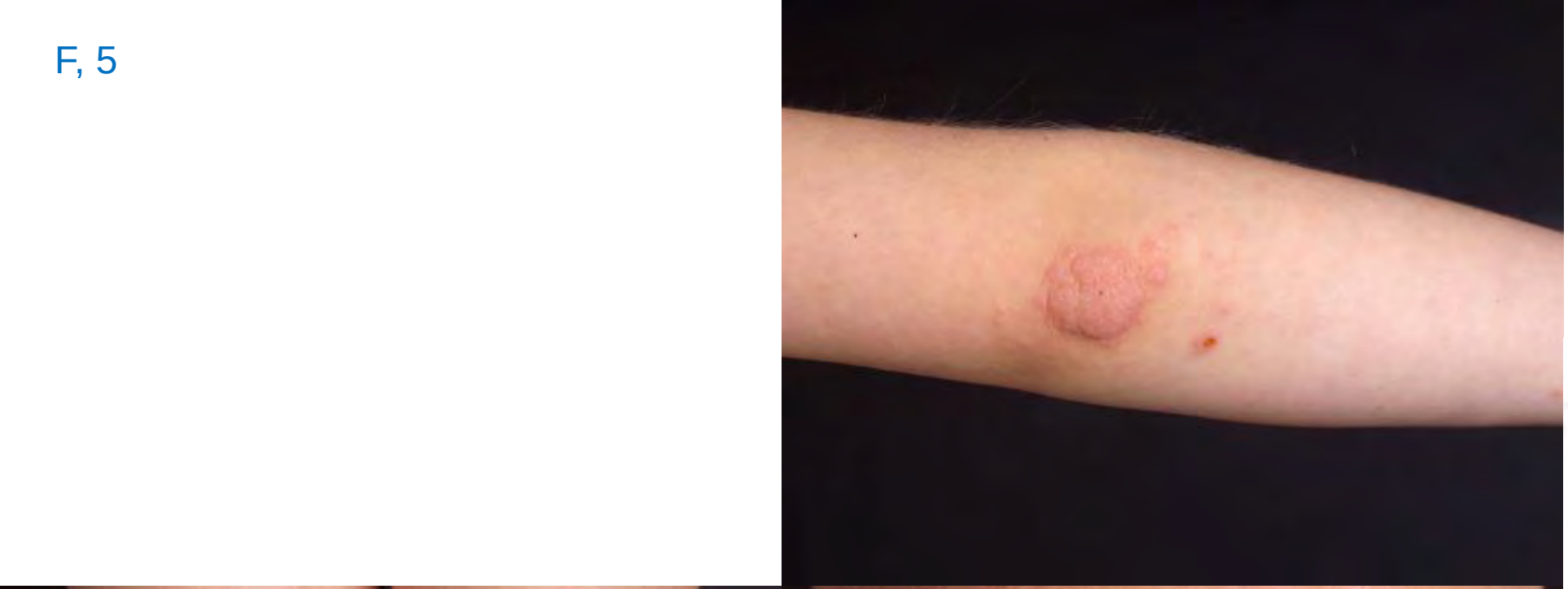


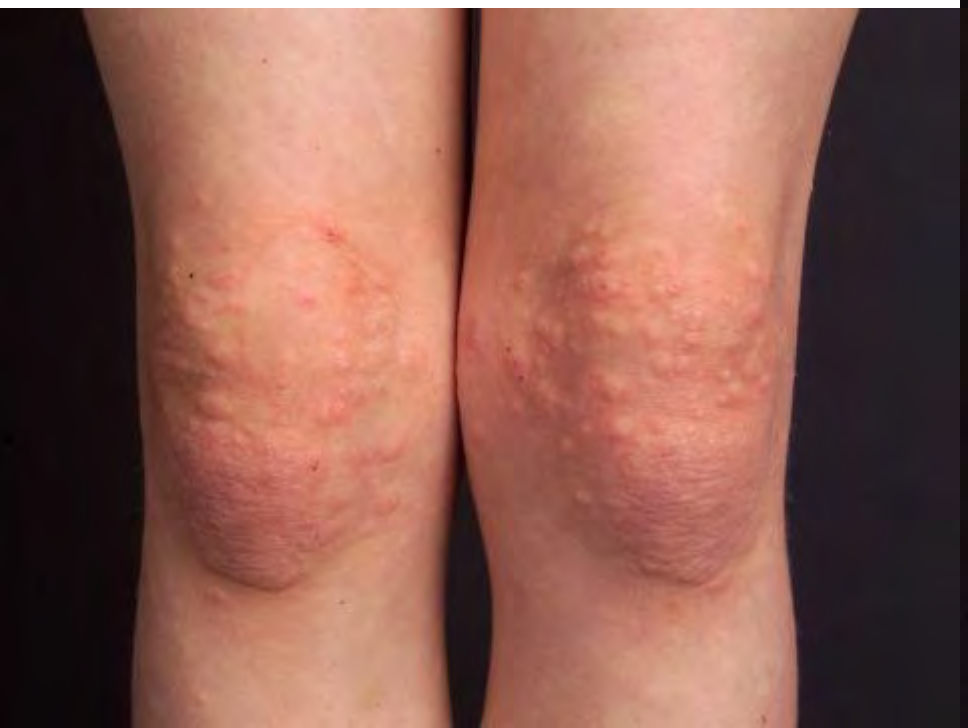
Mammary Paget disease

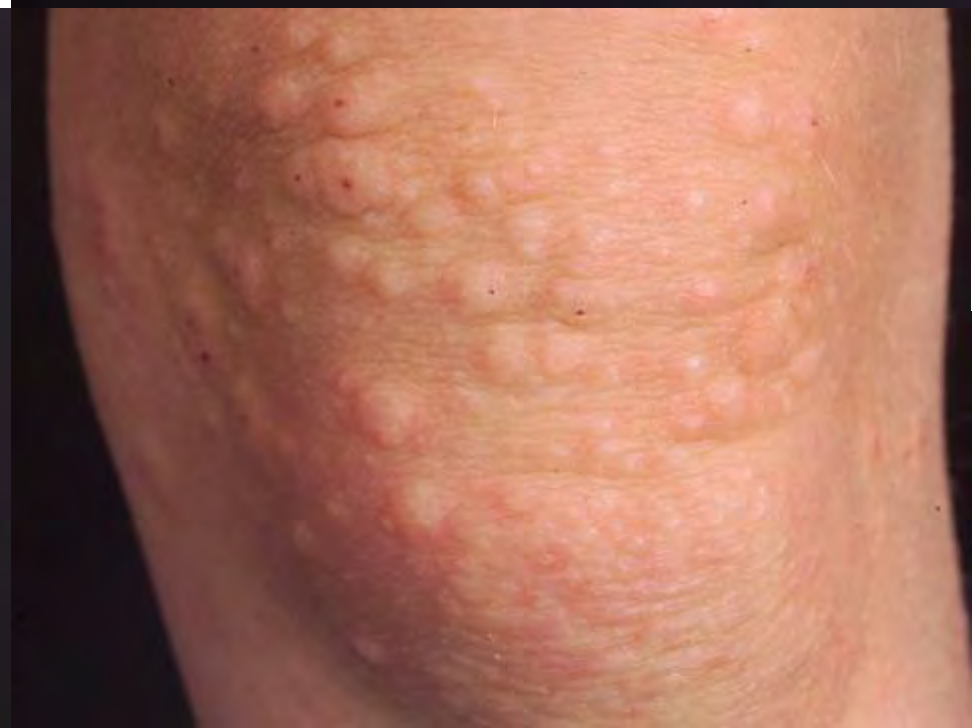
Eczema of the (nipple) areola

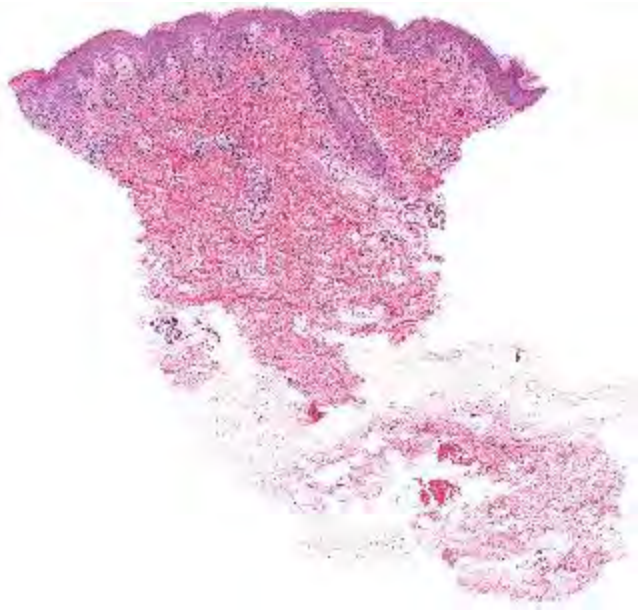
- Clinically different (at onset in Paget nipple > areola, in eczema areola > nipple)
- Age and gender matter (mammary Paget disease mostly in elderly women)
- History matters (Paget disease does not spread rapidly to the entire areola; eczema is itchy)
- Management of patients with eczematous clinical presentation: 10-14 days local treatment with steroids *before* biopsy

F, 5

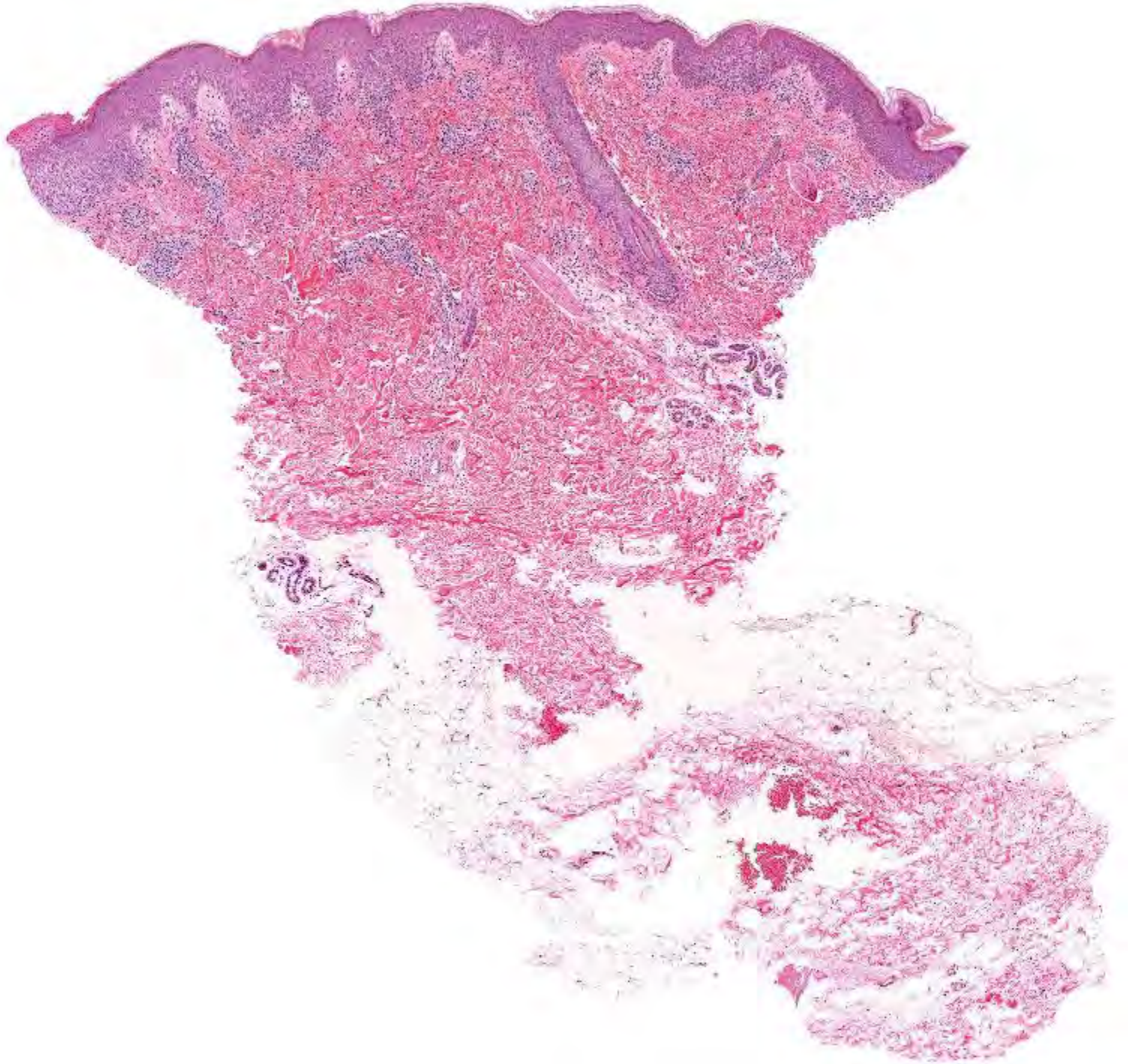


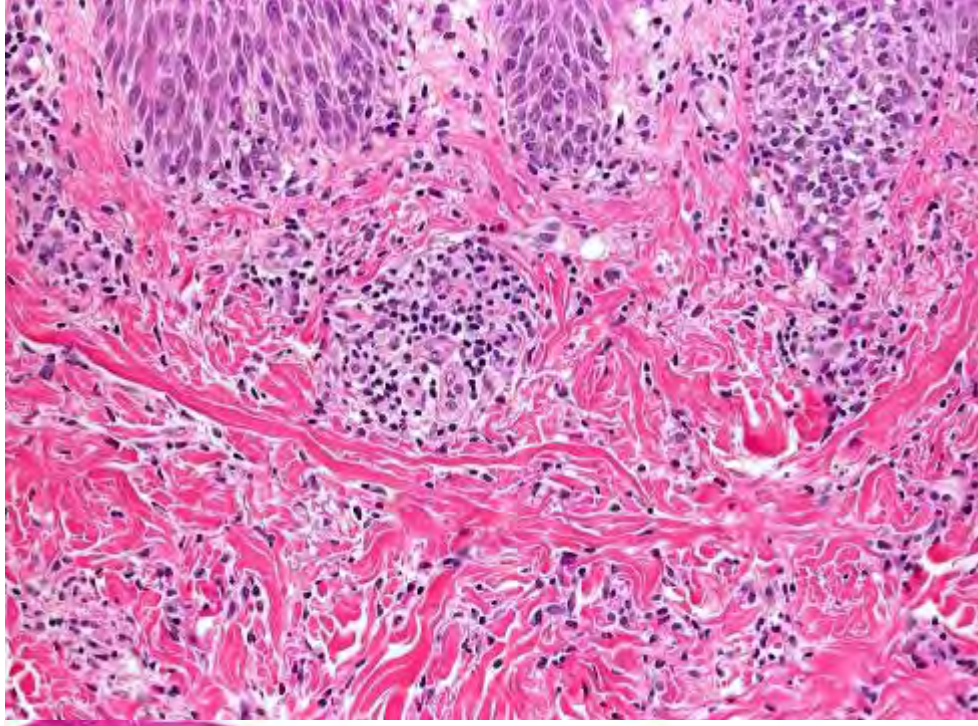


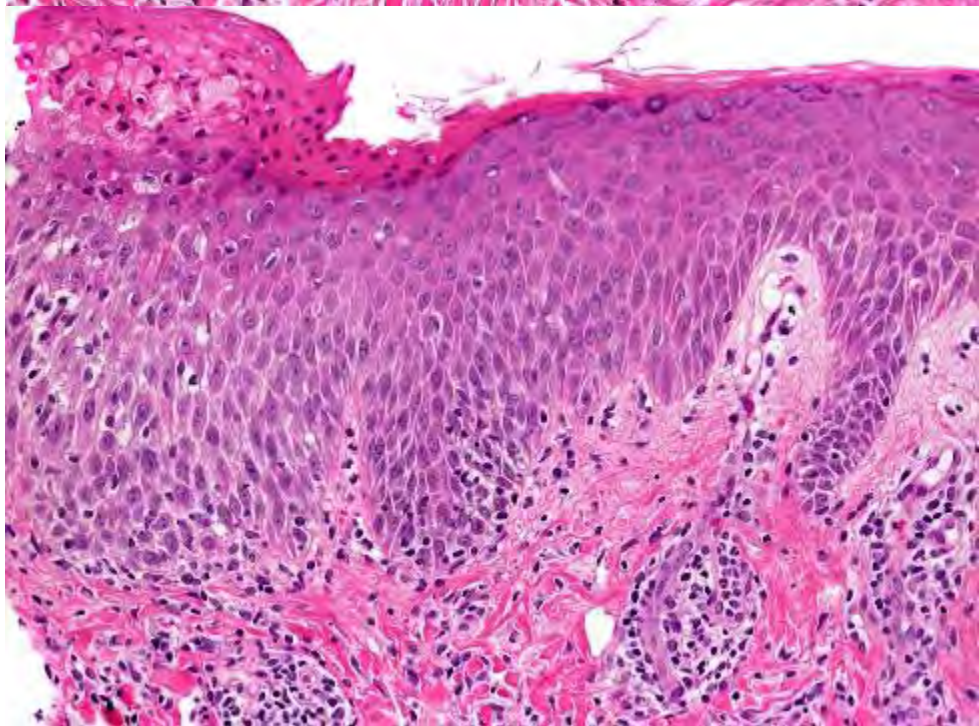




Frictional lichenoid eruption







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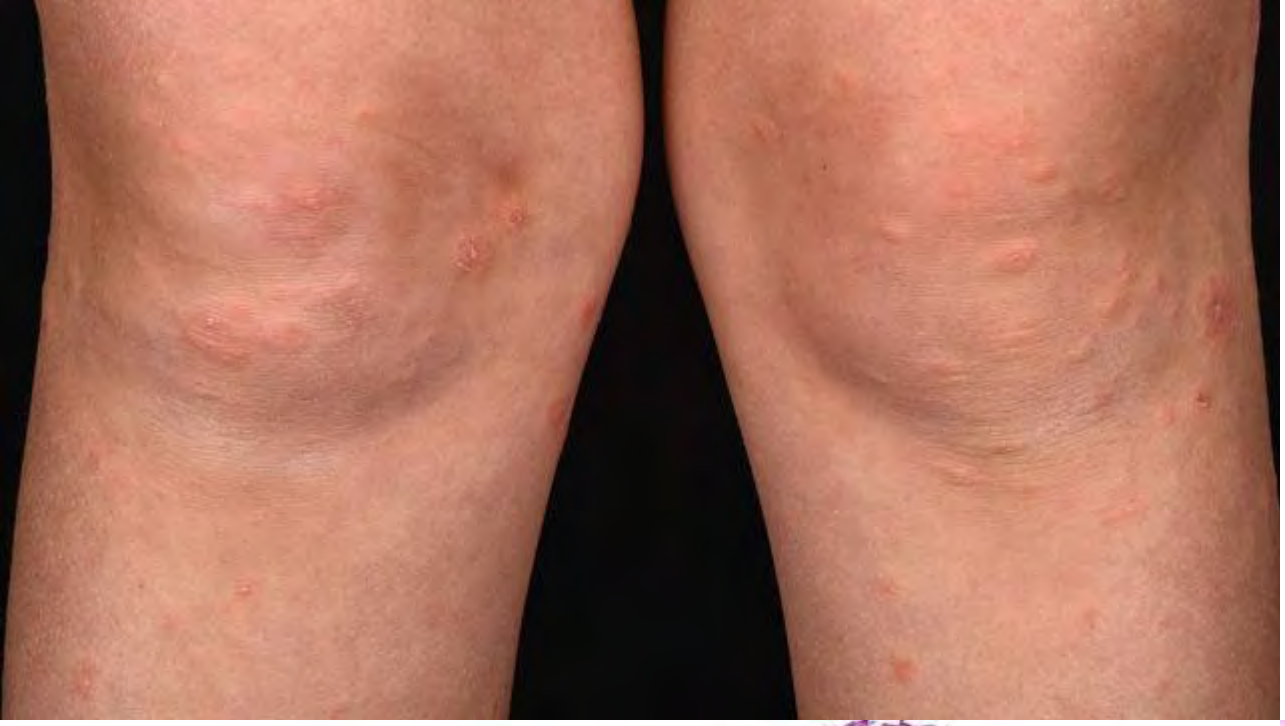

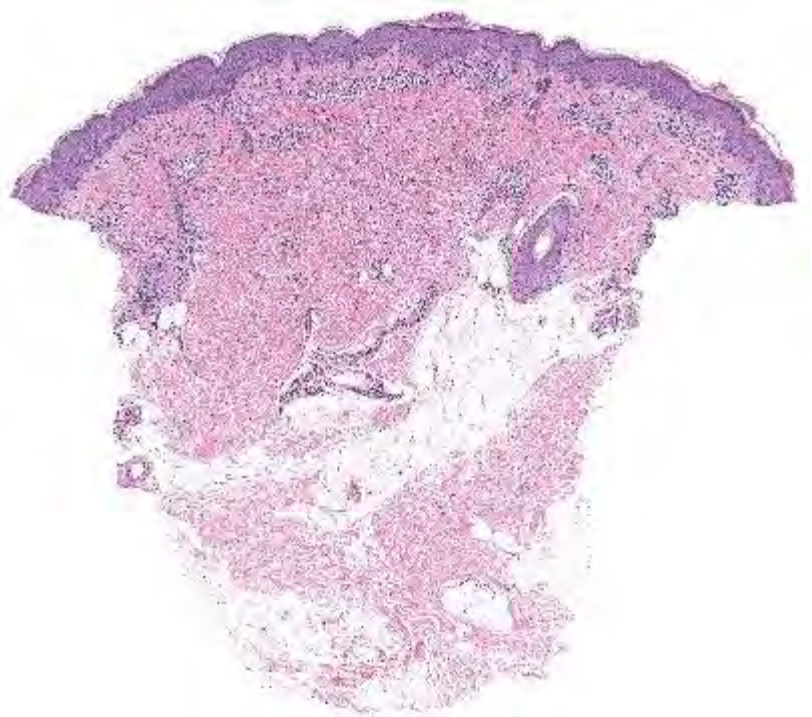

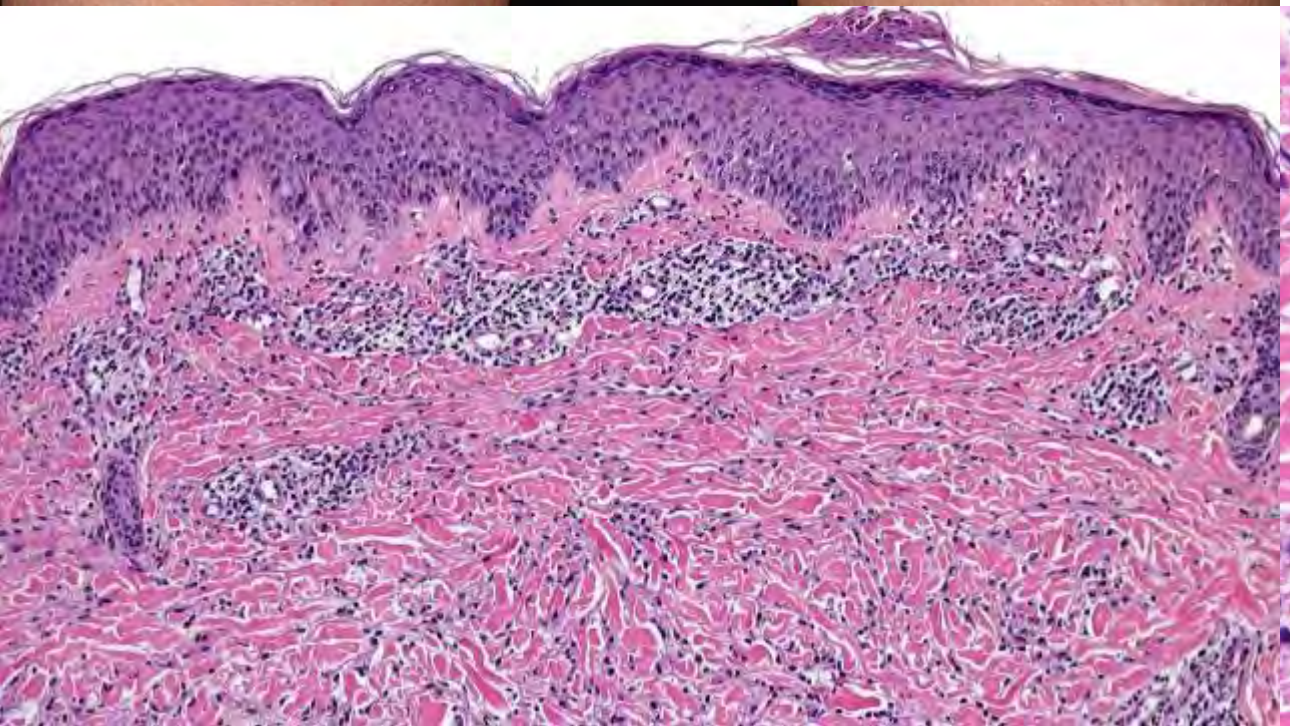

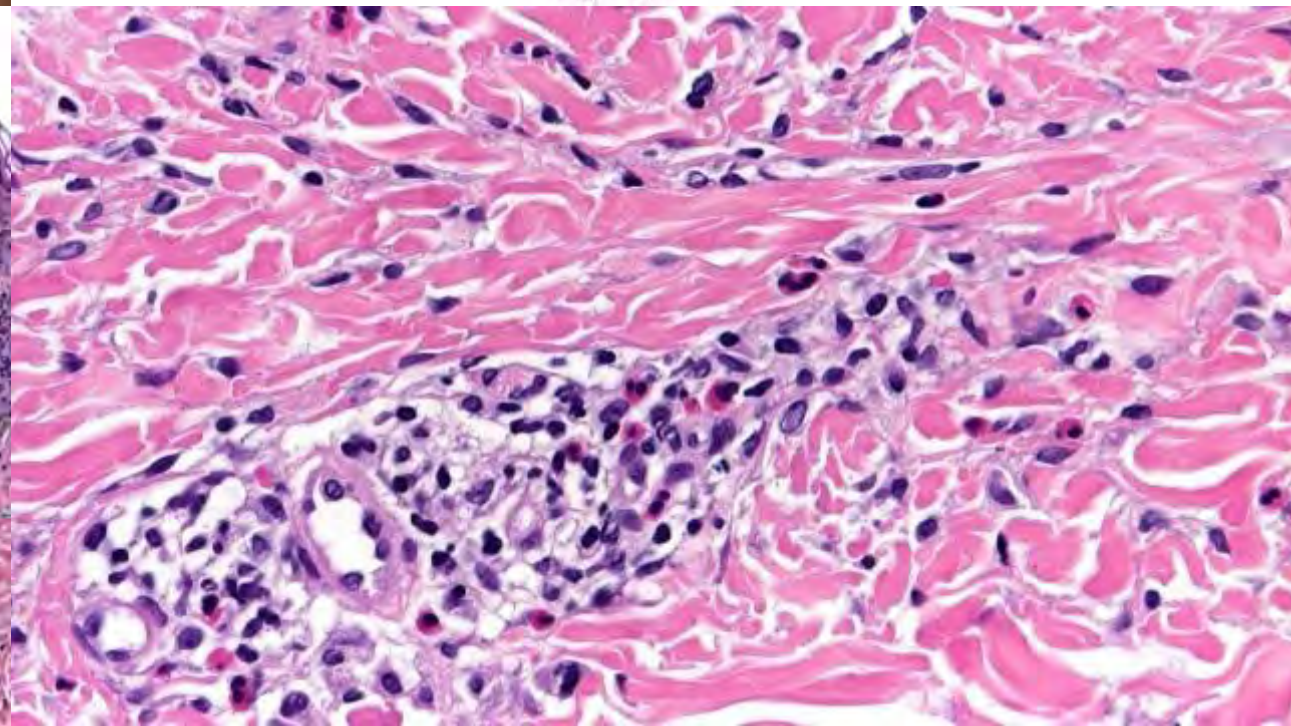

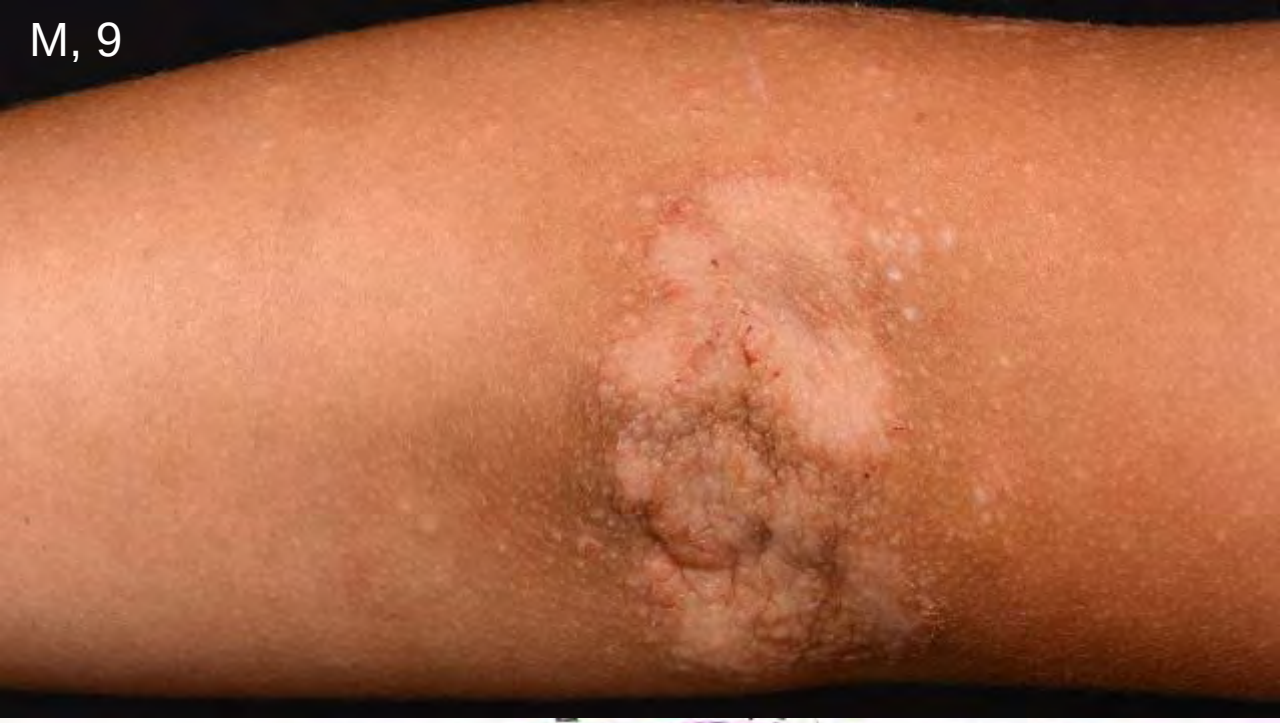
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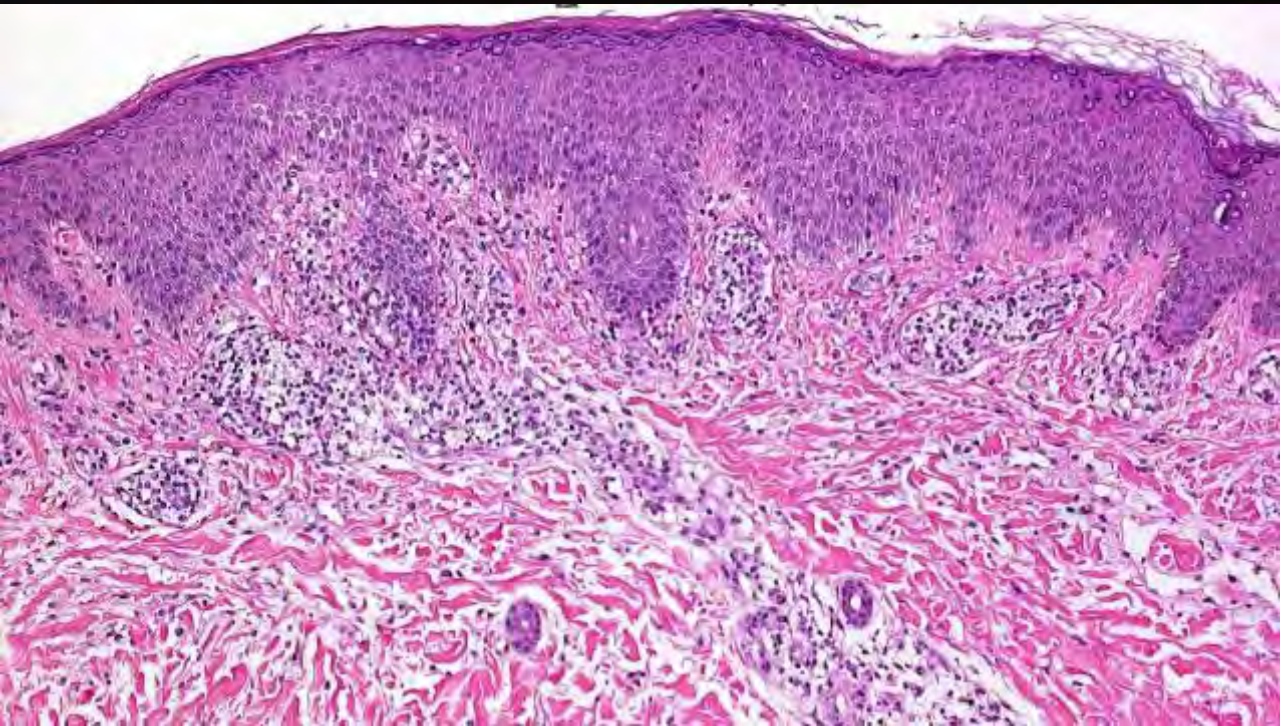
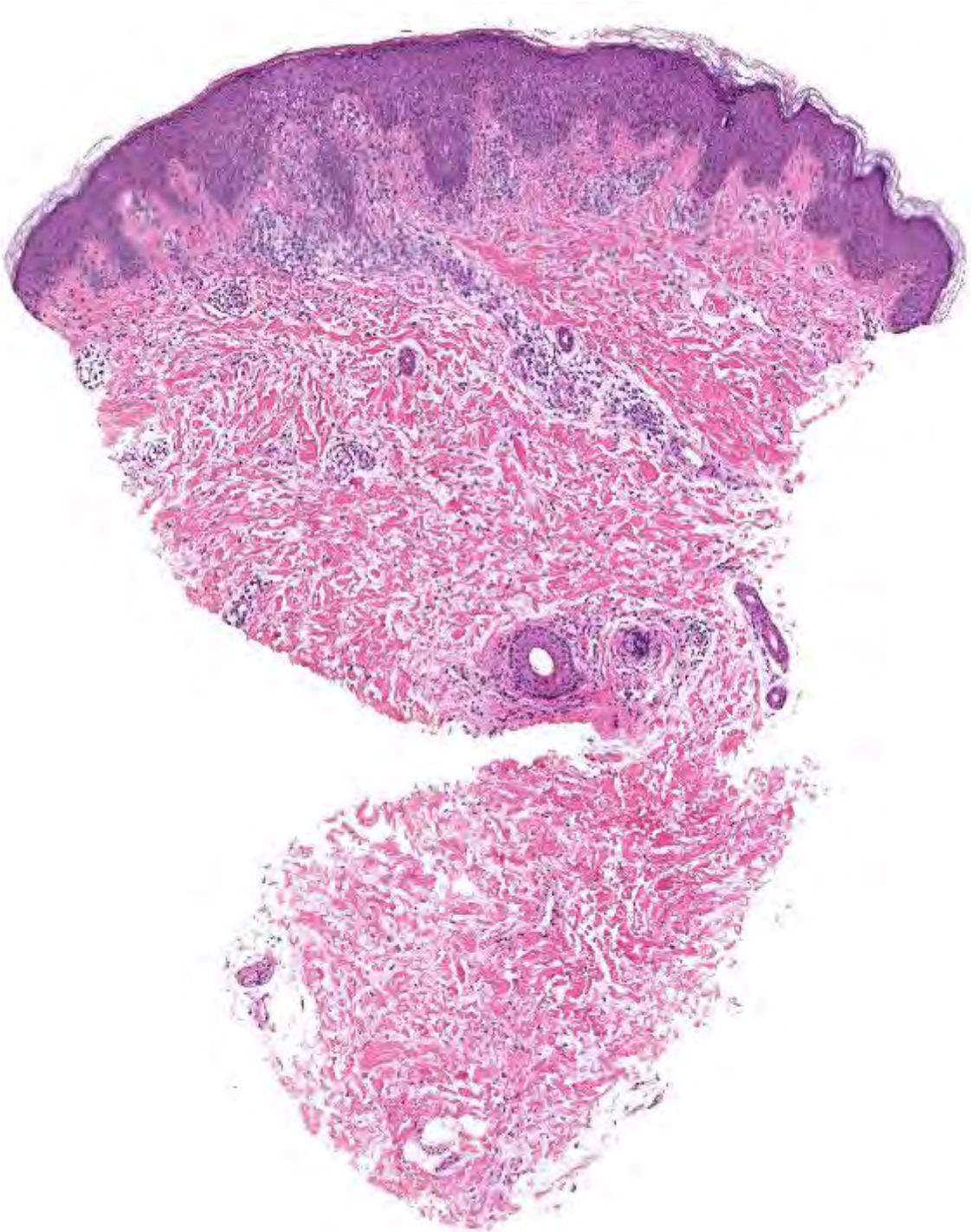
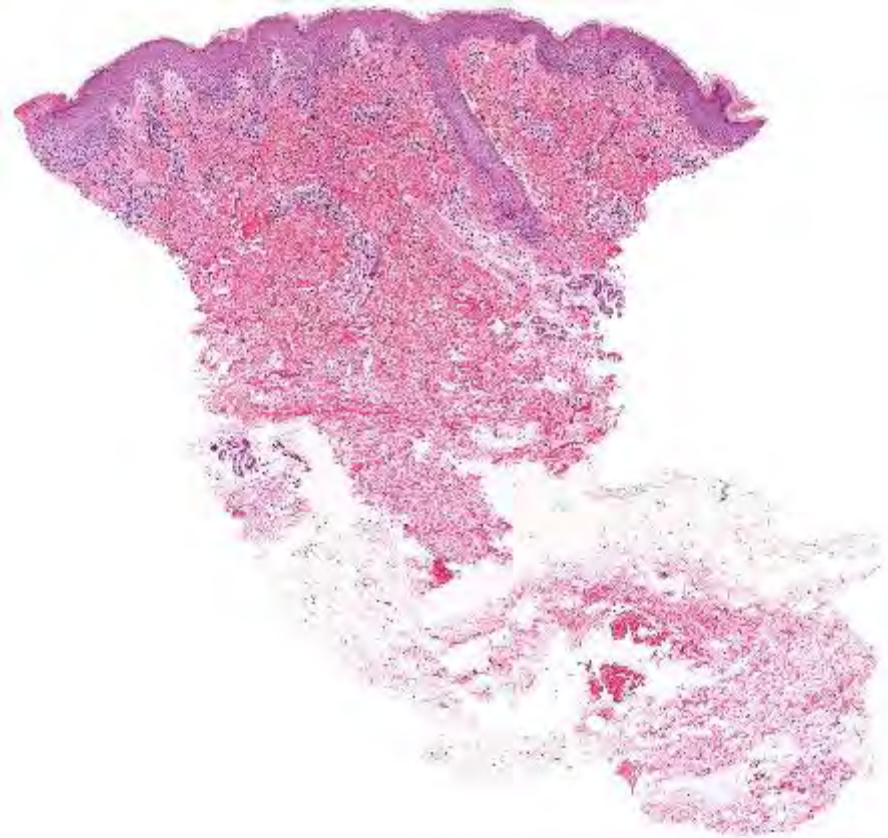
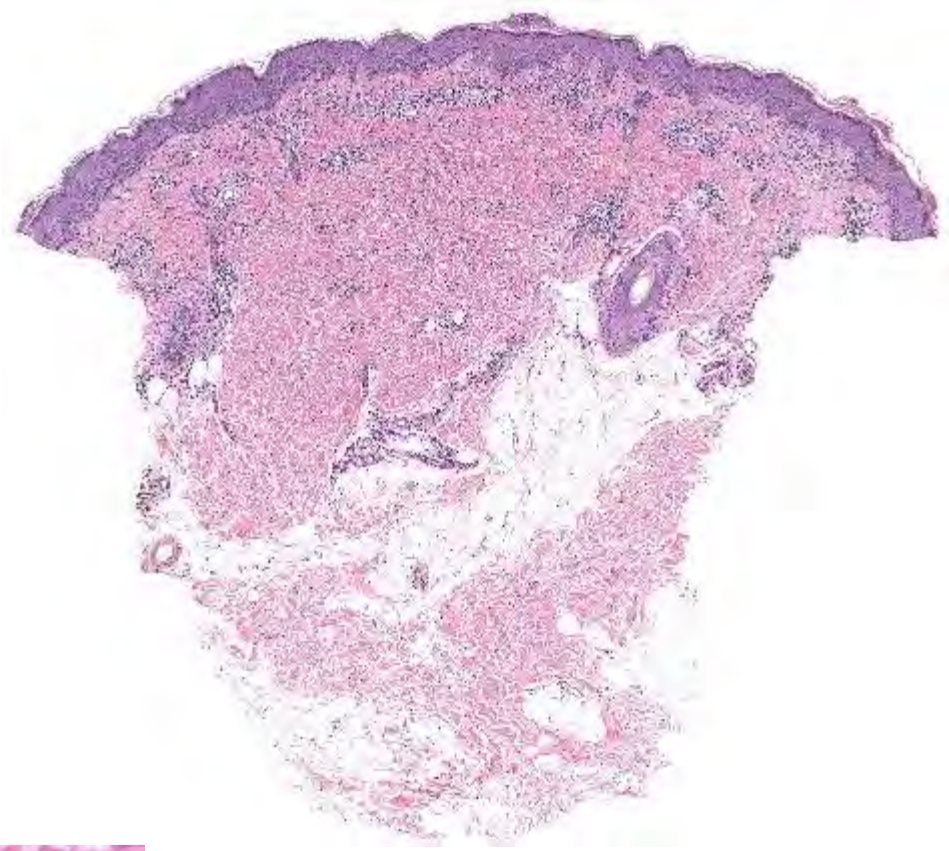
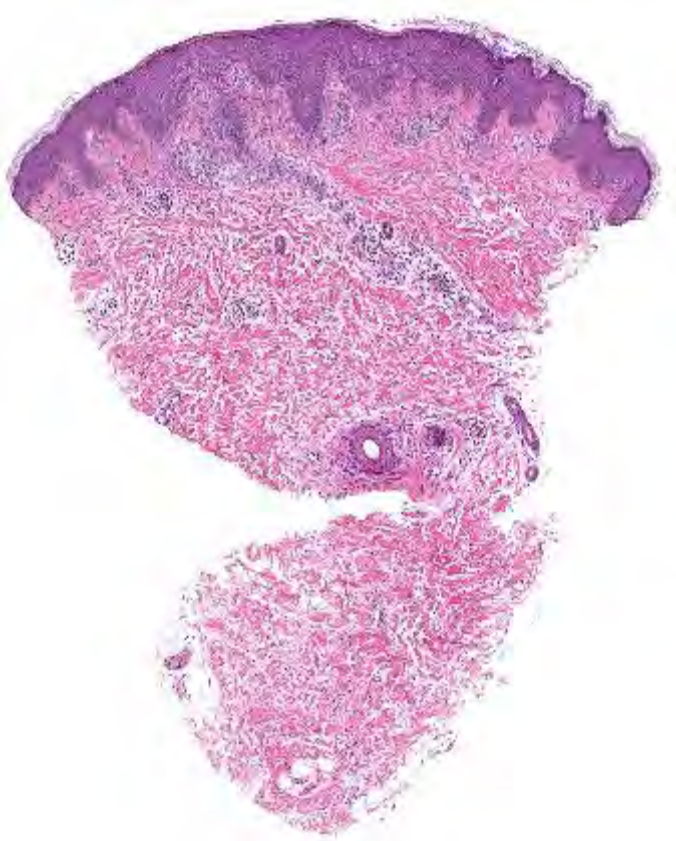
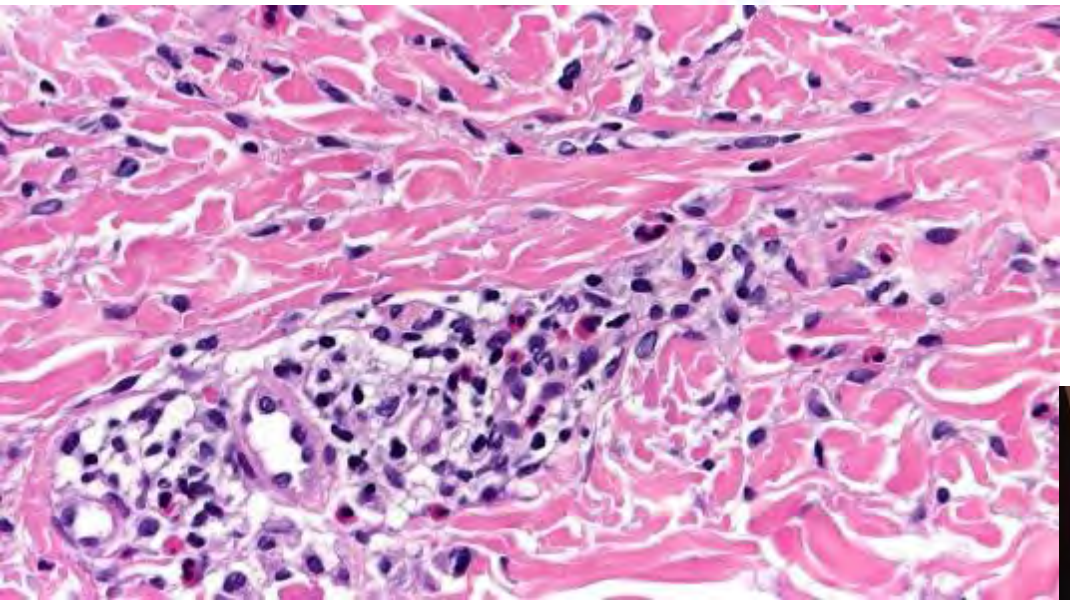




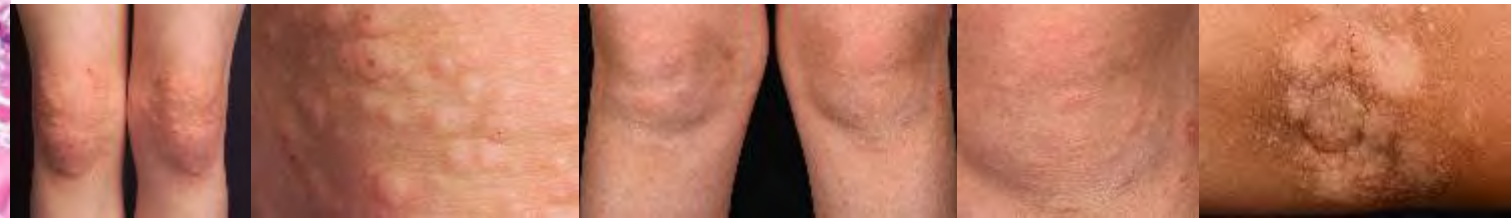


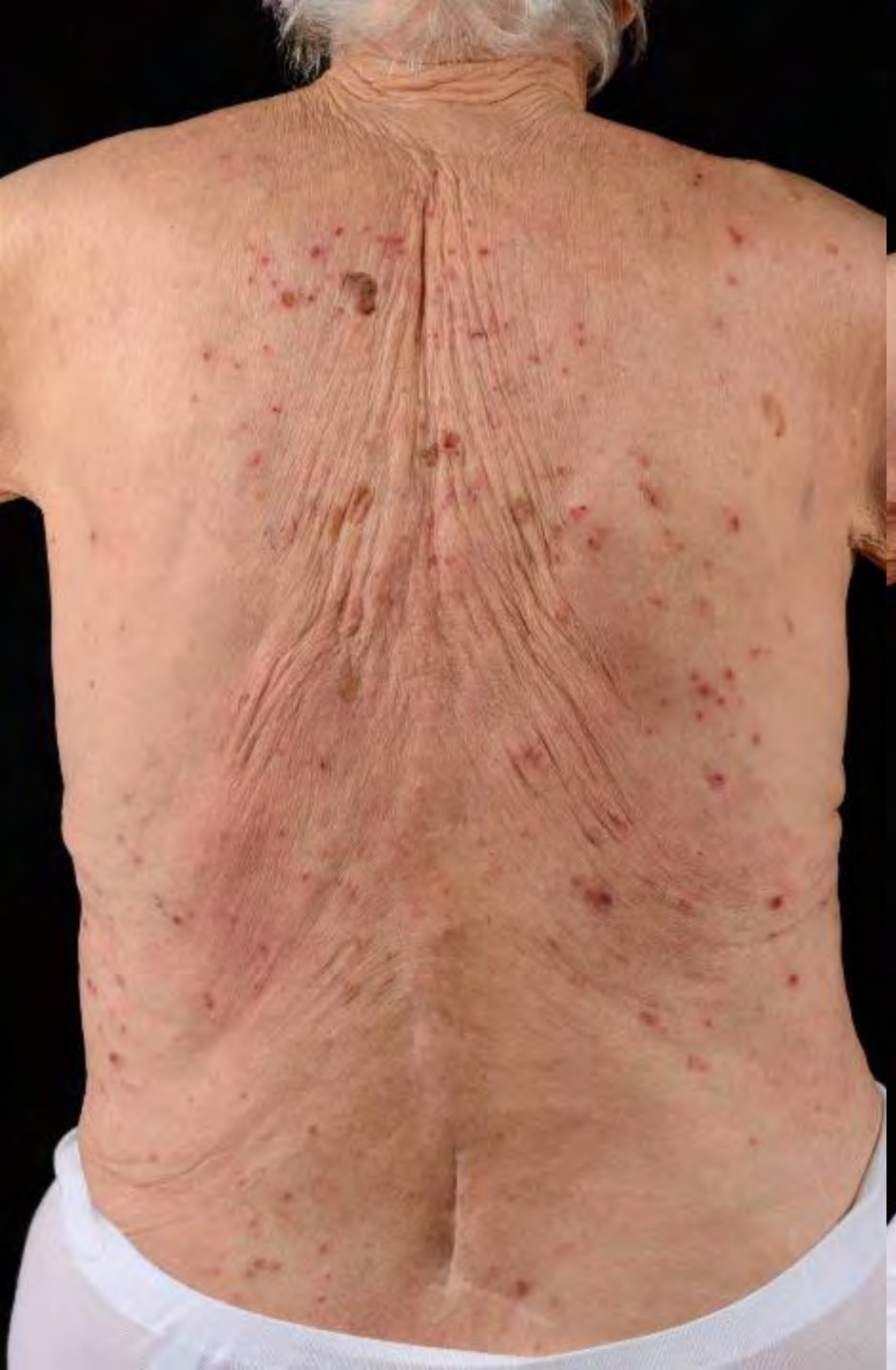


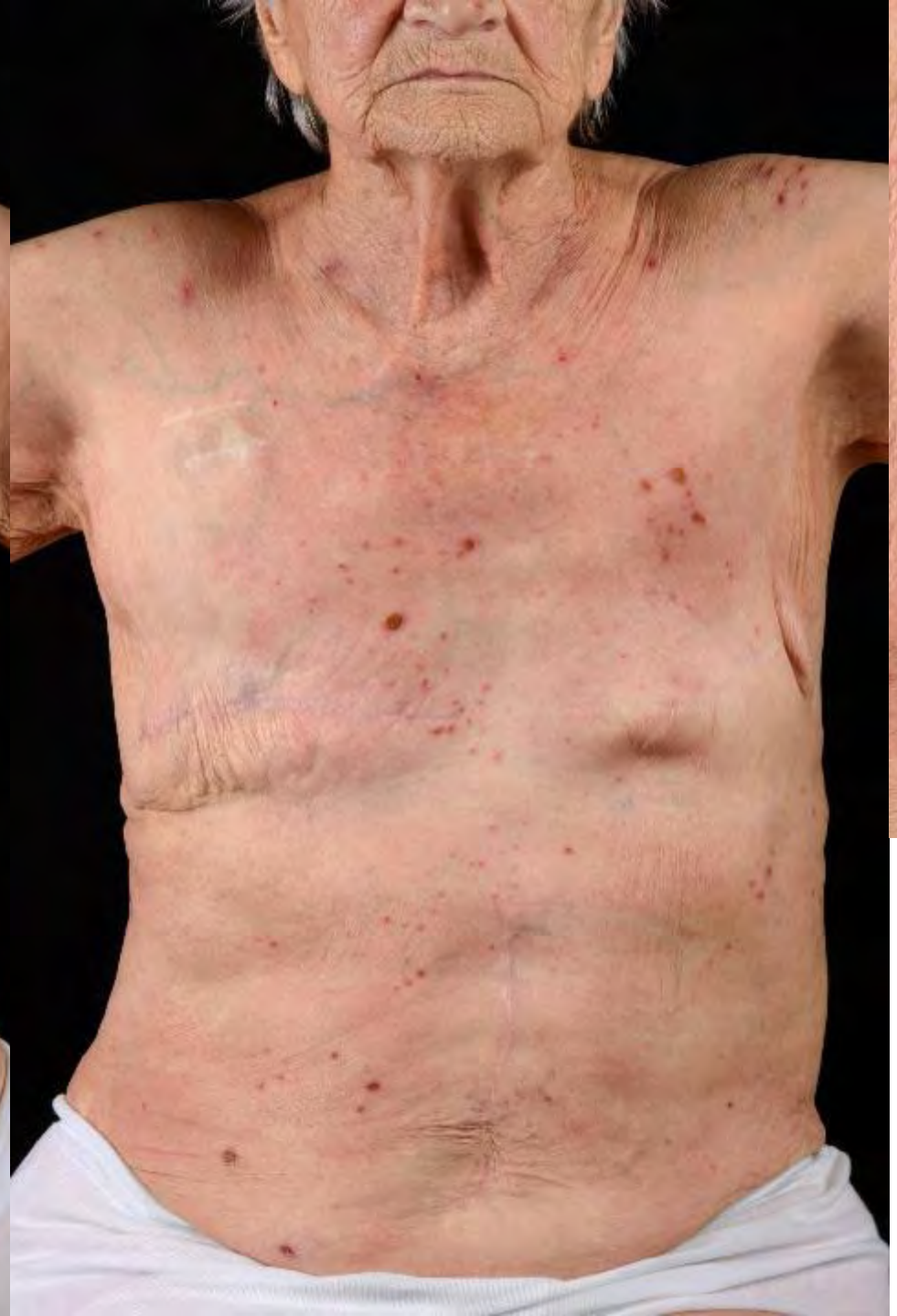


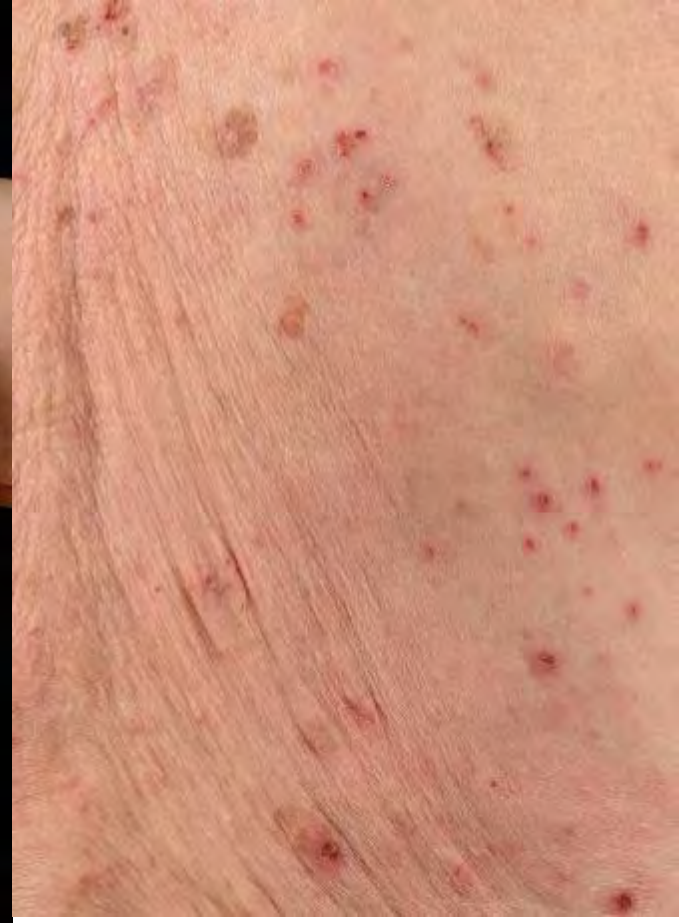


Frictional lichenoid eruption in atopic dermatitis is histopathologically indistinguishable from a local hypersensitivity reaction (and may be a clinical mimicker of it as well)





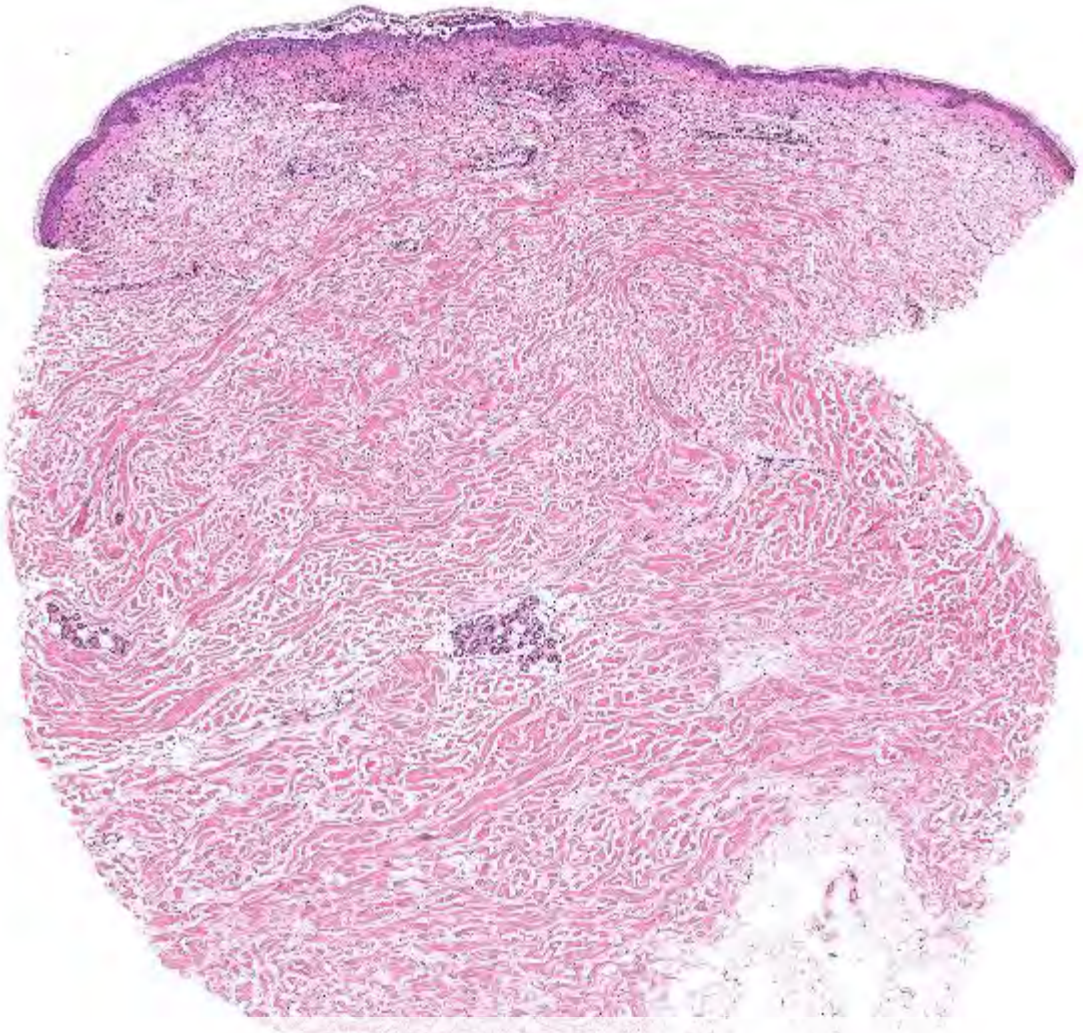


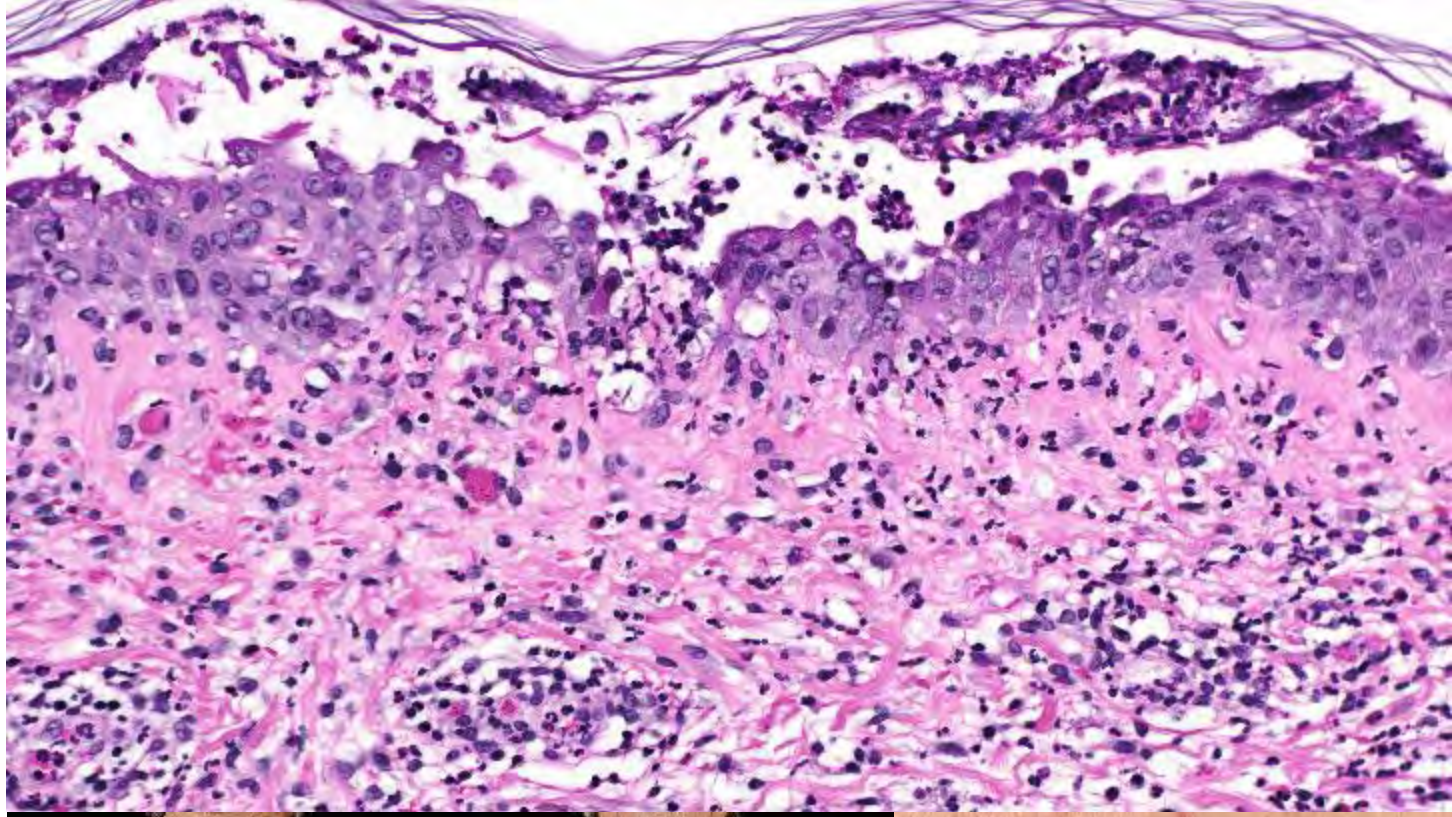


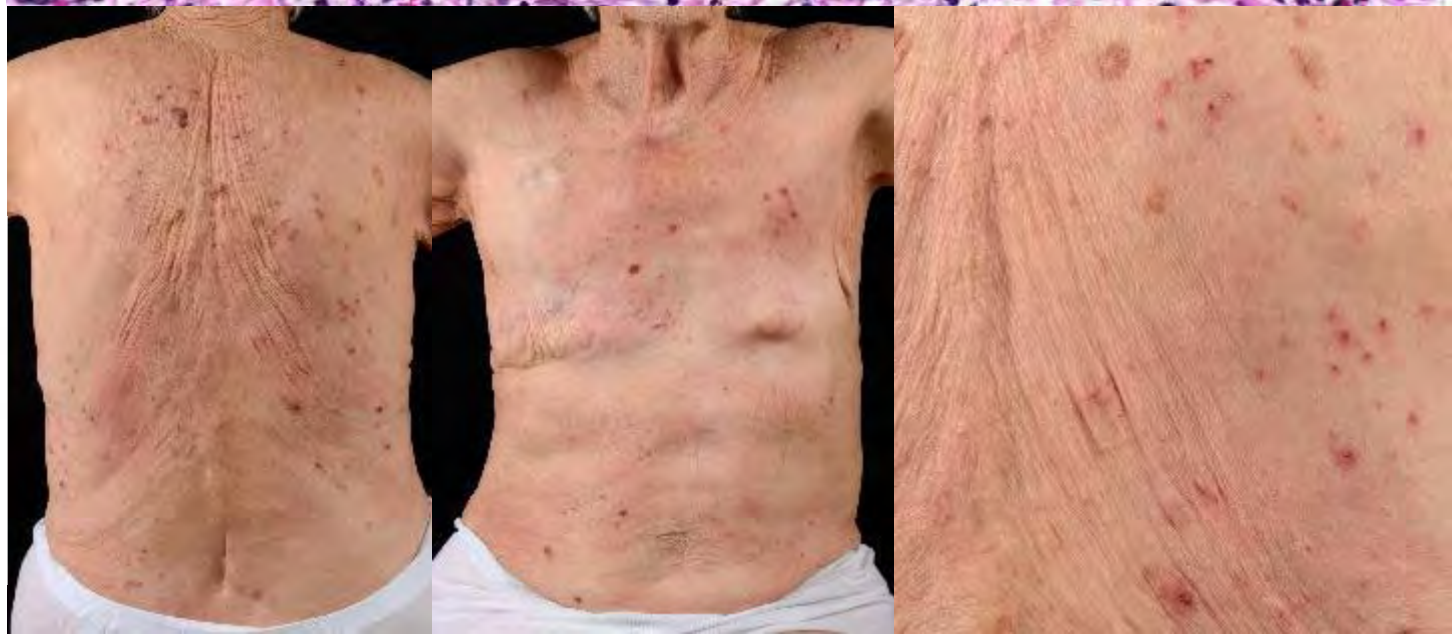
F, 86

According to the patient generalized itchy lesions for 1 month. History of breast carcinoma (left and right breast 7 and 2 years previously, respectively).

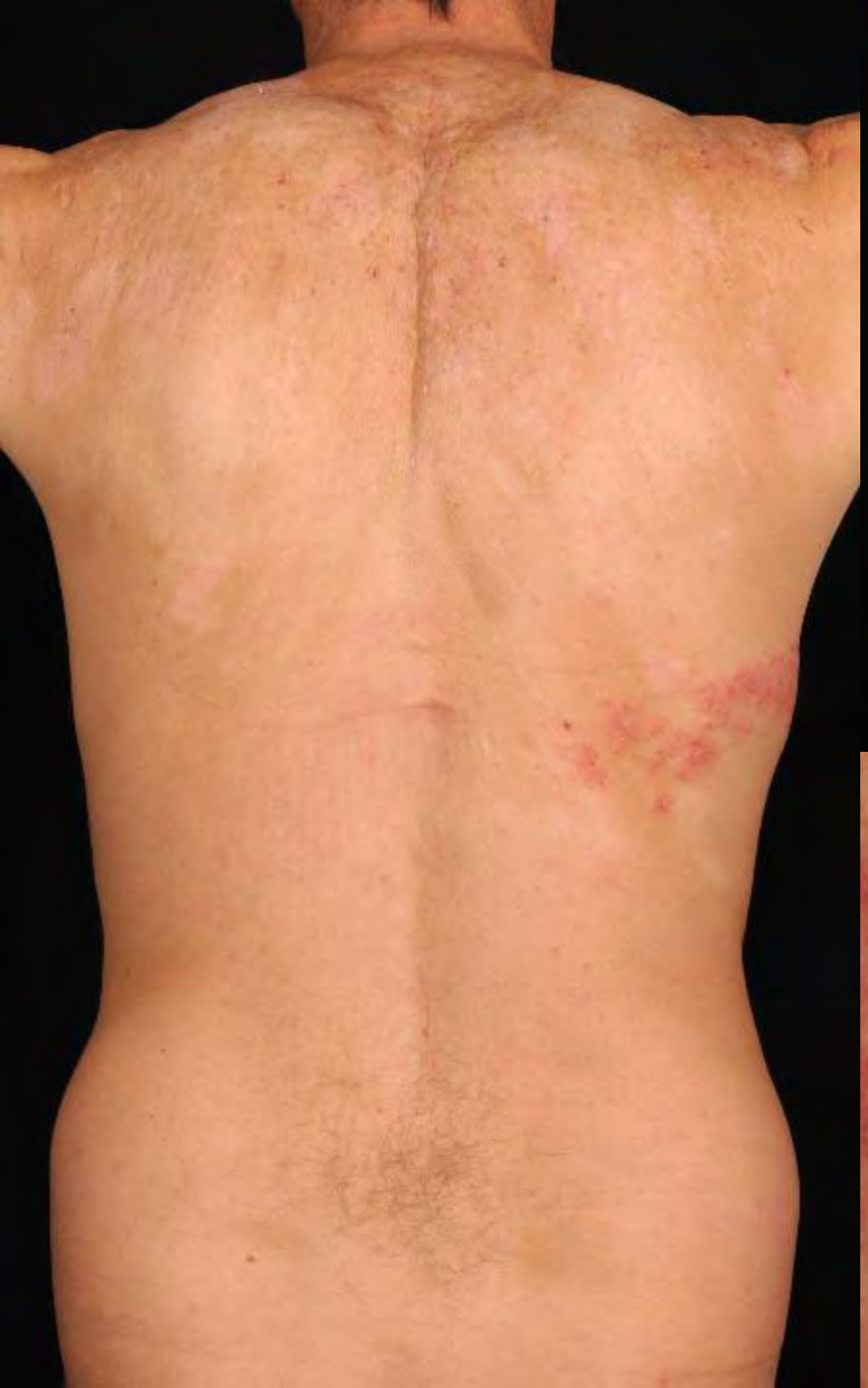
A biopsy is taken.

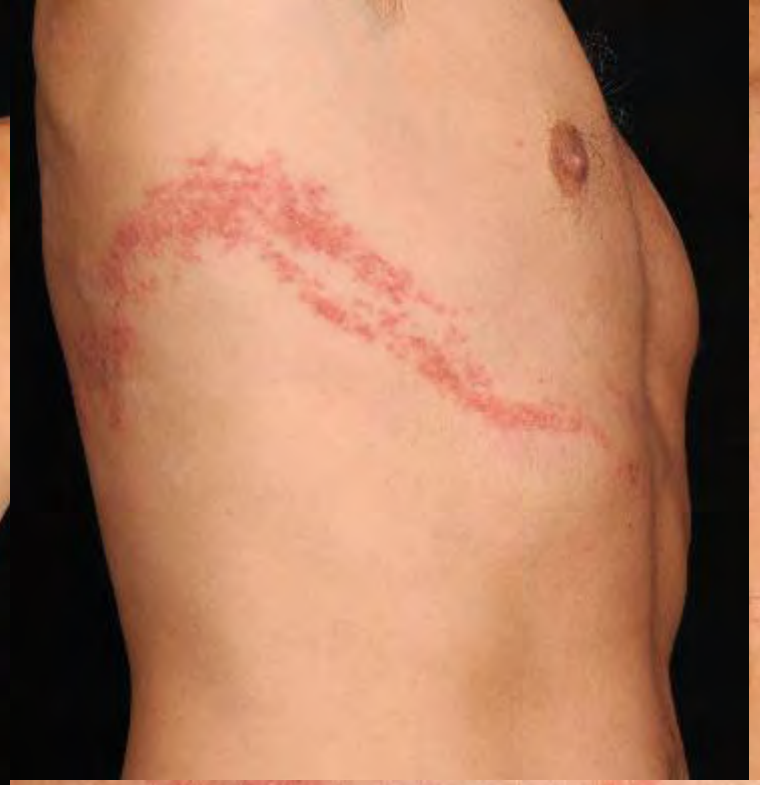


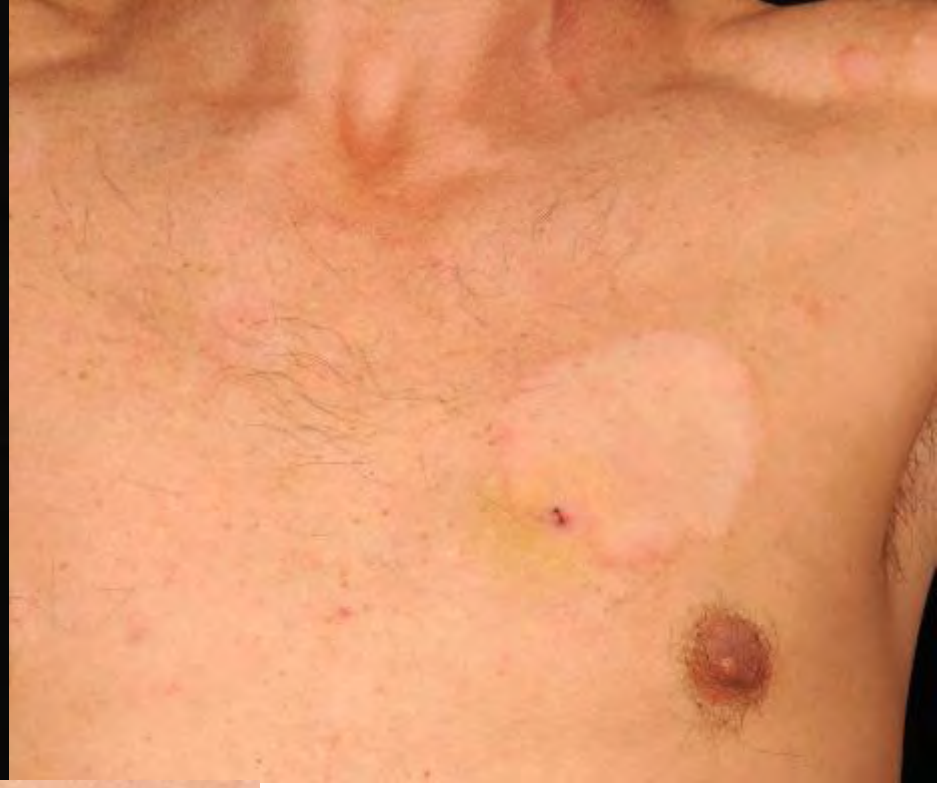


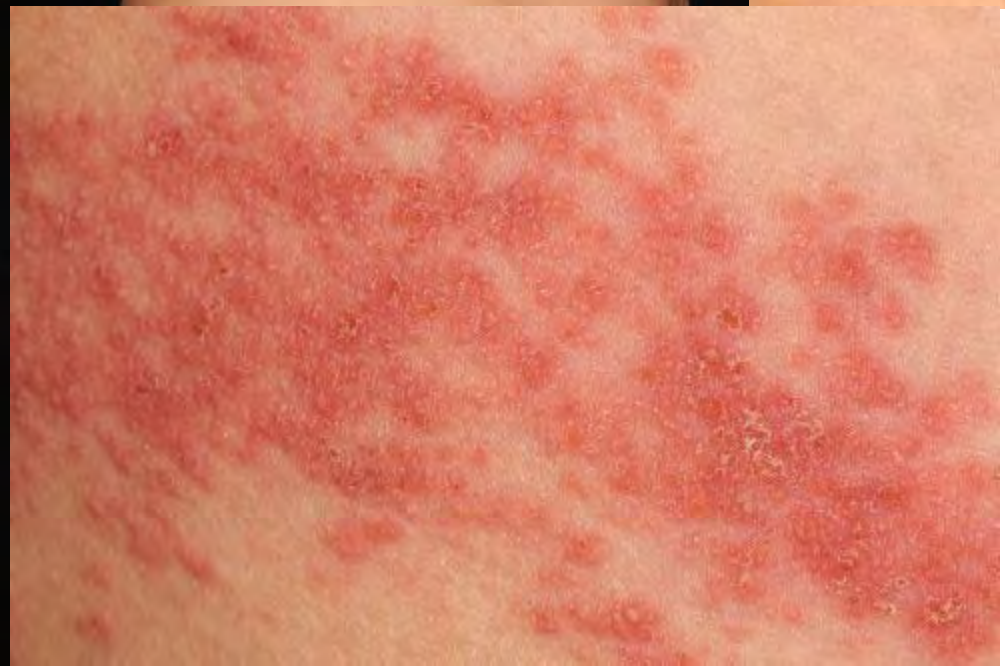


Impetiginized eczematous (atopic) dermatitis of the elderly







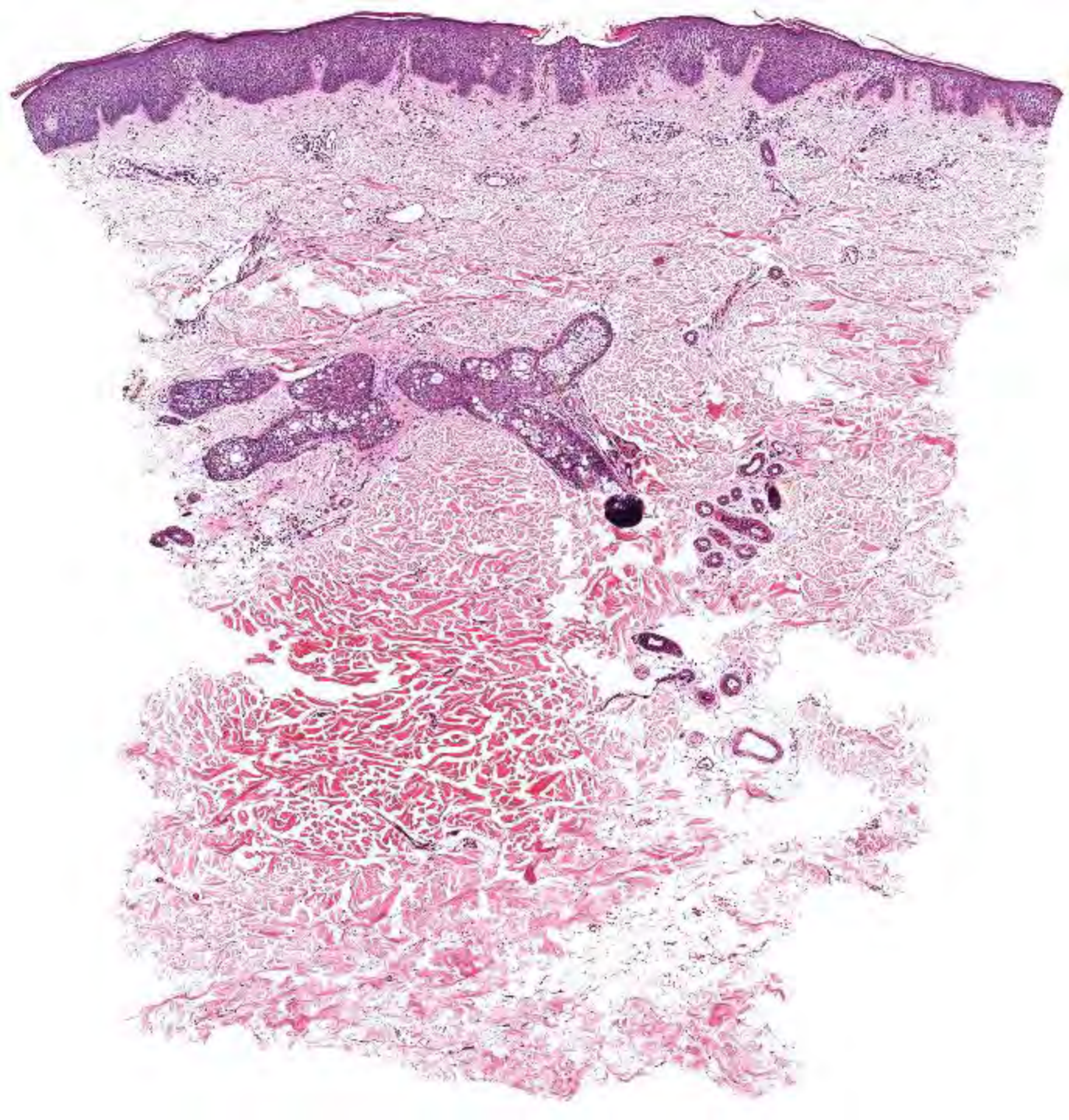


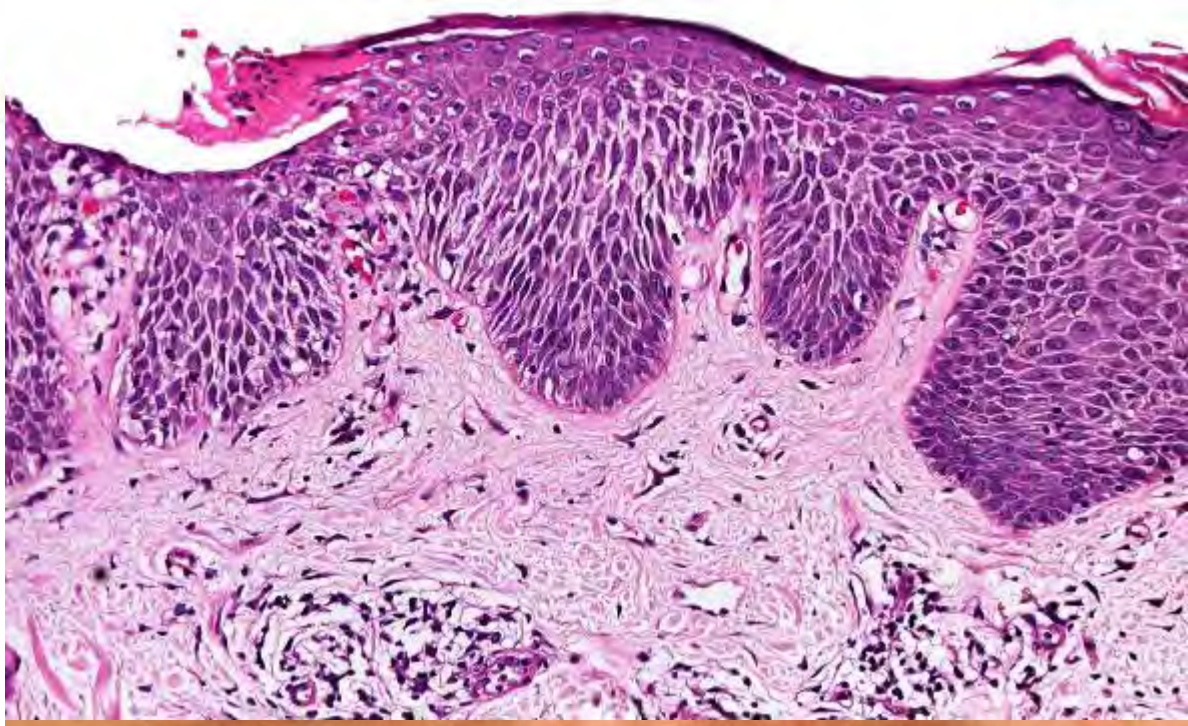
M, 42

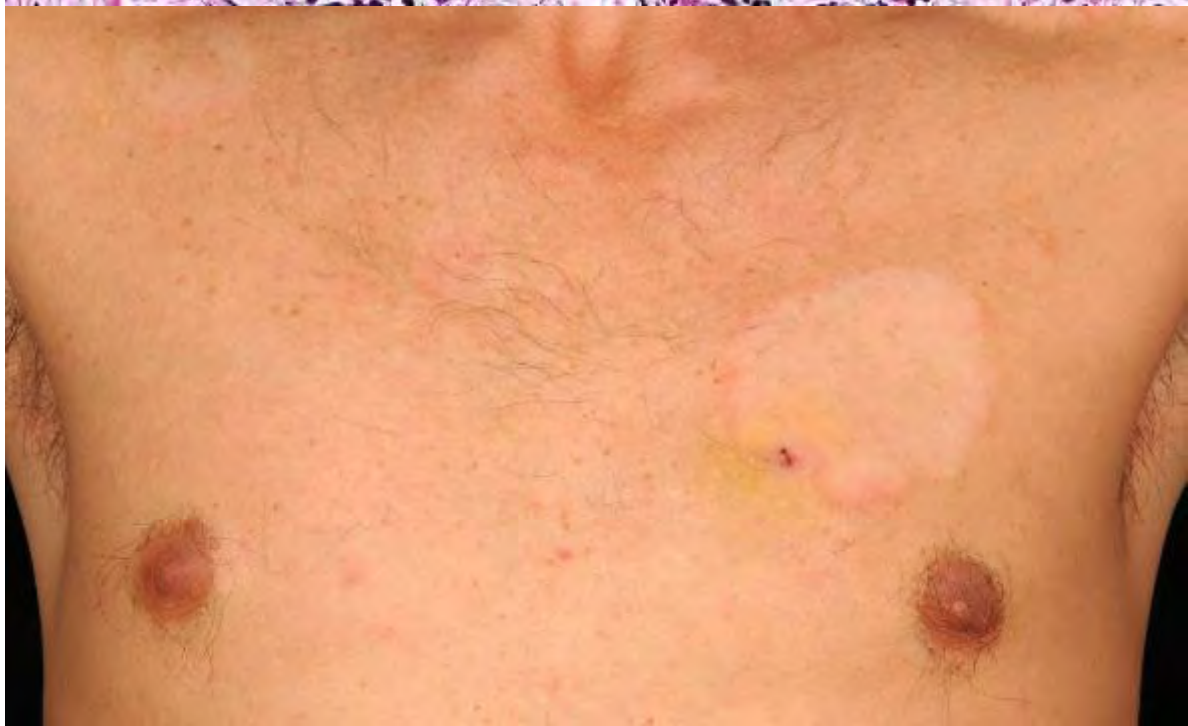
Atopic diathesis.

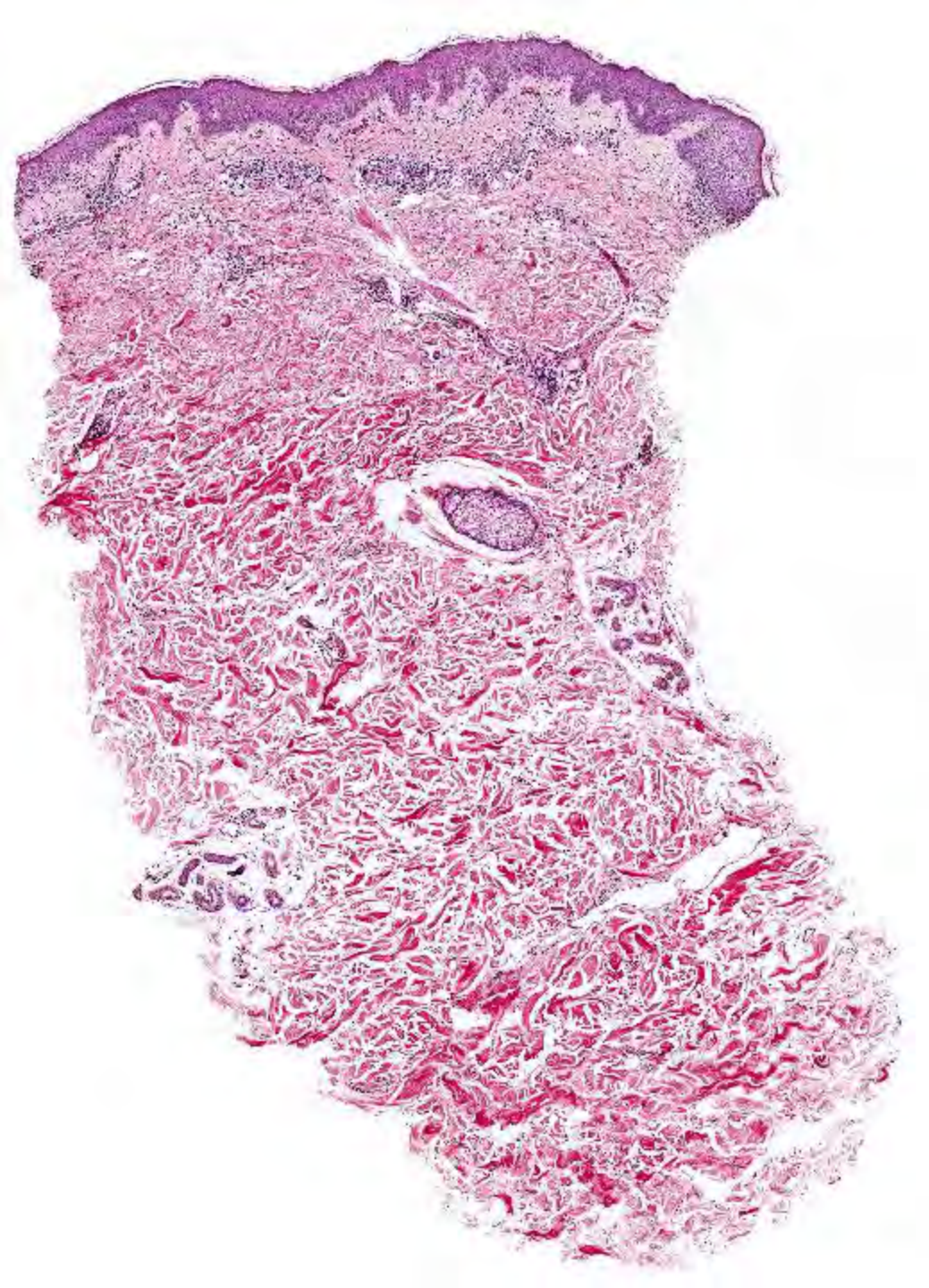
According to the patient linear rash for 2 days, starting on the right hand (duration of other lesions unknown).

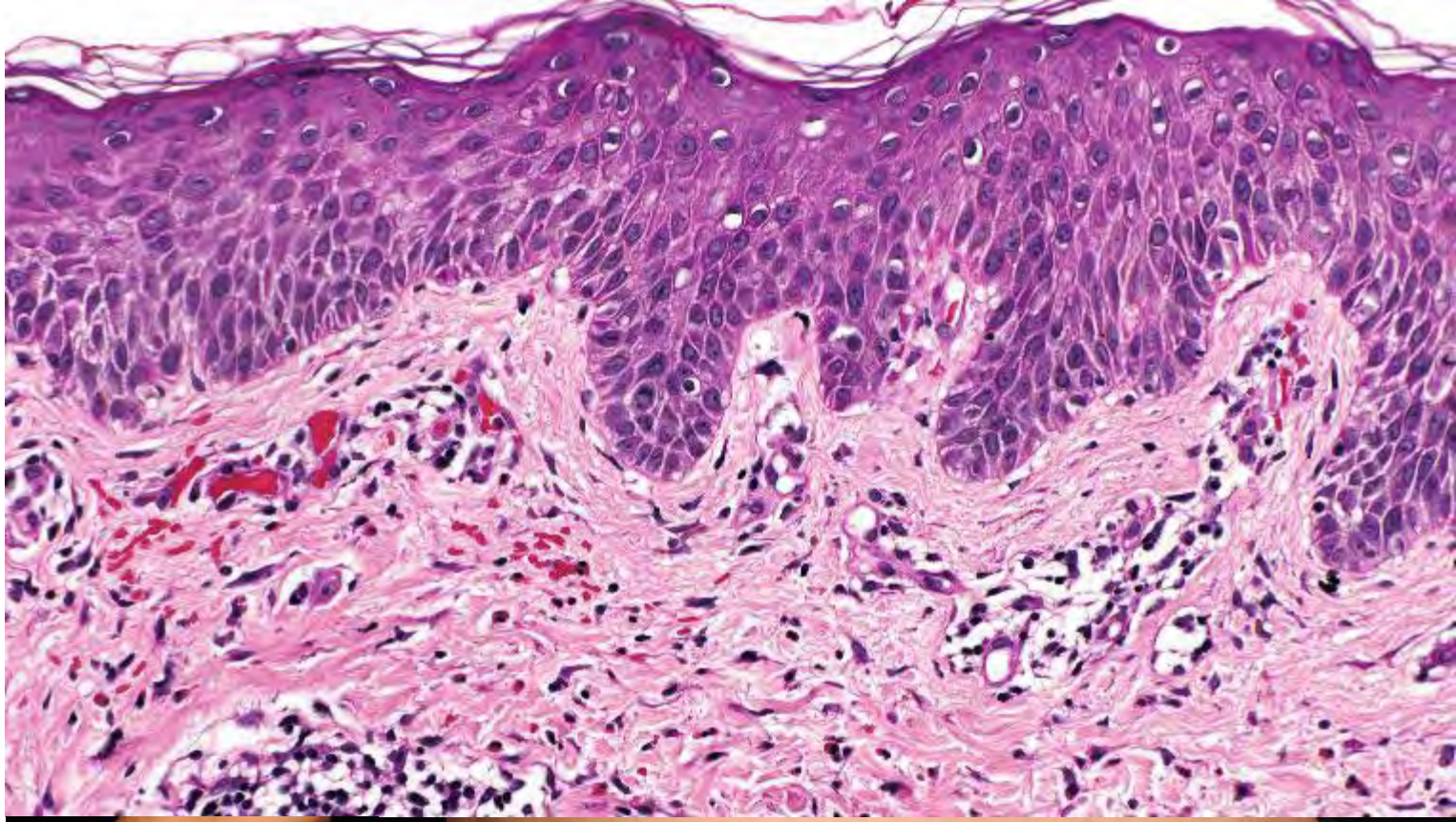
Two biopsies are taken (left breast, right flank).

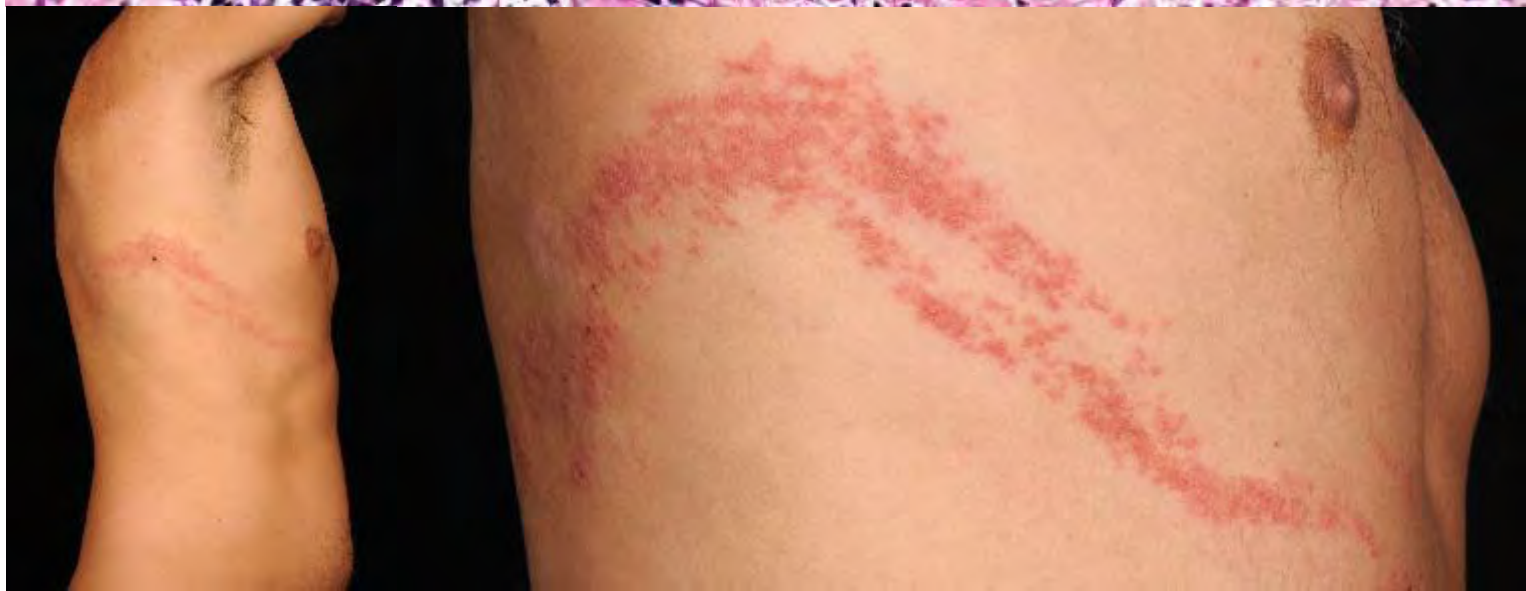


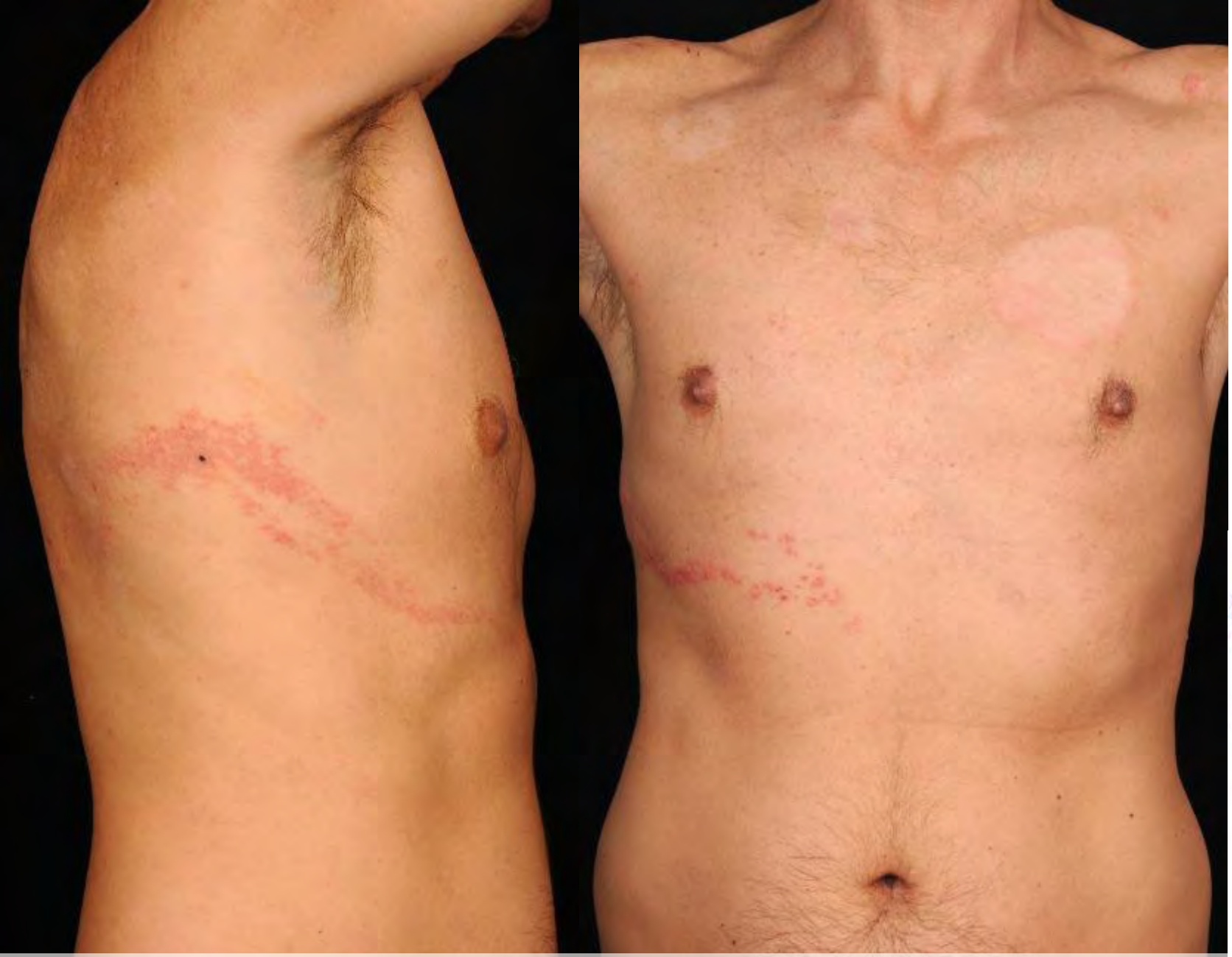


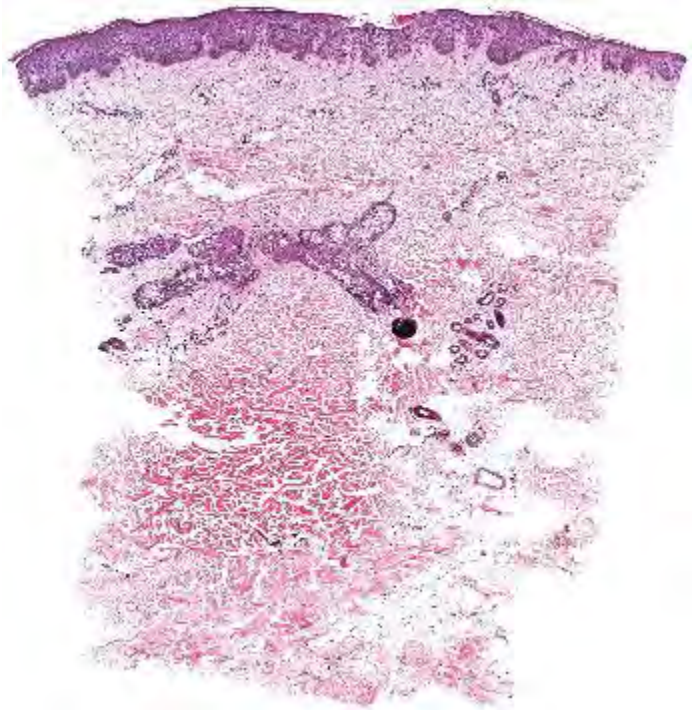


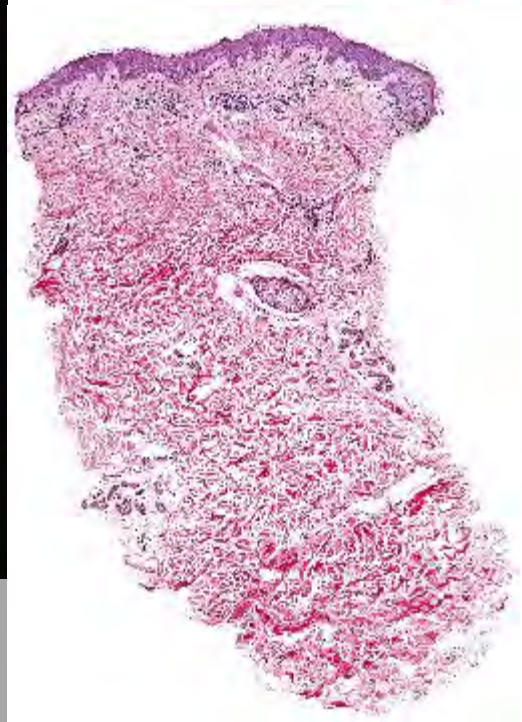


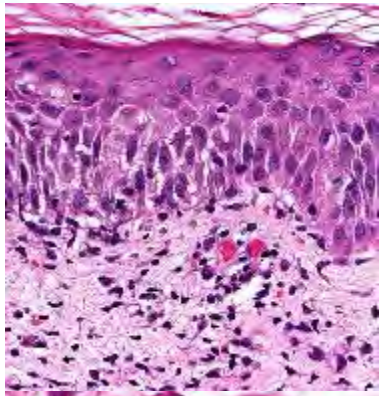


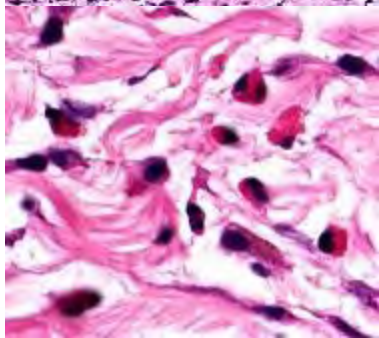










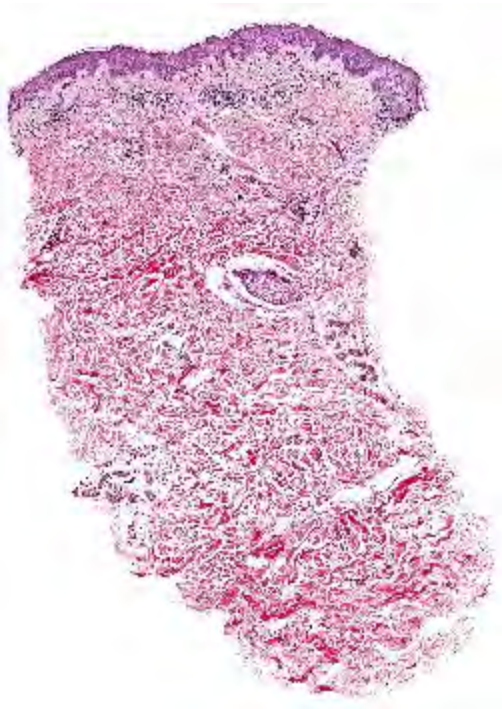


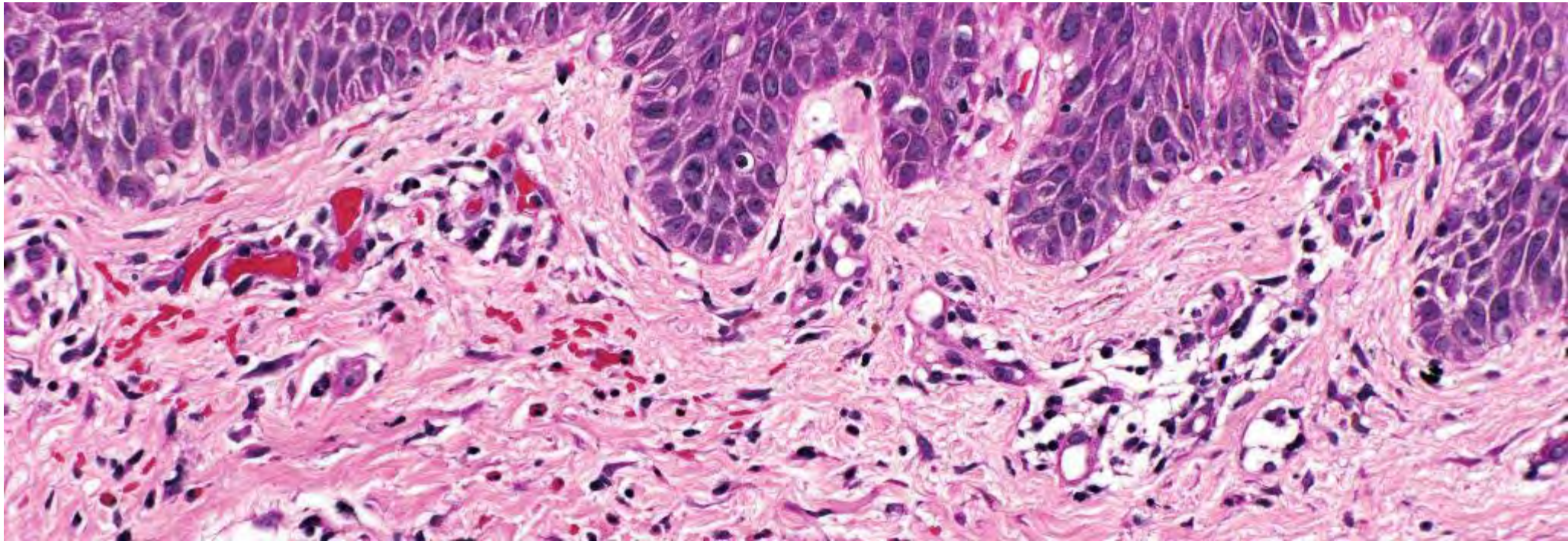
Superimposed linear atopic dermatitis

First presentation (2-day-old lesions)

+ 32 days (local steroids)

+ 120 days





SPECIAL ARTICLE

Superimposed segmental manifestation of polygenic skin disorders

Rudolf Happle, MD
Marburg, Germany

In common acquired skin disorders with a polygenic background such as psoriasis, a linear or otherwise segmental arrangement may sometimes be noted. The segmental involvement tends to be rather severe and may be associated with milder, nonsegmental lesions of the same disorder. Such cases may be best explained by an early postzygotic event in the form of loss of heterozygosity involving one of the genes that predispose to the disorder. The following pertinent examples are reviewed in this article: psoriasis vulgaris, pustular psoriasis, atopic dermatitis, lichen planus, systemic lupus erythematosus, pemphigus vulgaris, vitiligo, graft-versus-host disease, granuloma annulare, erythema multiforme, and drug eruption to ibuprofen. Such cases should not be categorized as a "type 1 segmental manifestation" because this term exclusively applies to monogenic traits. Whereas in polygenic disorders the more descriptive term "superimposed segmental manifestation" seems appropriate. The concept of early loss of heterozygosity offers a plausible explanation as to why the segmental involvement tends to appear at a rather young age and often precedes the development of milder, nonsegmental lesions of the same disorder. The segmental lesions are not infrequently difficult to treat, and family members may show the disorder in a nonsegmental form. On the other hand, the theory of isolated vertical postzygotic second-hit mutation may help consolidate the origin of polygenic skin disorders at the molecular level. (J Am Acad Dermatol 2007;57:650-9.)

Many inherited skin disorders are monogenic traits having a polygenic background. The distribution of lesions tends to be symmetric and more or less diffuse. Remarkably, however, by way of exception, they may occur in a linear, unilateral, or otherwise segmental arrangement, which is sometimes found to be superimposed on less severe, disseminated, symmetric lesions of the same disorder. Such pronounced segmental involvement has tentatively been explained by the assumption that, at an early developmental stage, loss of heterozygosity (LOH) involving one of the predisposing genes occurred in a somatic cell and gave rise to a patch of homozygous or hemizygous tissue.[1,2] LOH may result from various mutational mechanisms such as mitotic recombination, gene conversion, point mutation, deletion, or mitotic nondisjunction.[2]

Analogously, in monogenic skin disorders with autosomal dominant mode of inheritance a type 2 segmental involvement may originate from postzygotic LOH implying loss of the corresponding wild-type allele in a heterozygous carrier.[3] Such phenomenon (mosaic manifestation) can be distinguished from a type 1 segmental involvement that refers to homozygosity for a postzygotic new mutation occurring in an otherwise healthy embryo.

In polygenic disorders, however, these designations are not applicable because in such diseases it appears to be impossible to discriminate between a type 1 and type 2 segmental manifestation. Hence, in these traits the less specific terms "isolated" versus "superimposed" segmental manifestation are preferable.[4]

The idea that LOH may explain a segmental arrangement of a polygenic skin disorder was first presented in 1929, with linear psoriasis as a paradigm.[5] In the meantime, the number of disorders exemplifying this concept has considerably increased.[6] Such cases have been published under various designations such as mosaic psoriasis,[7] atopic dermatitis with unusually severe flares along a line of Blaschko,[8] zosteriform lichen planus,[9] systematized linear granuloma annulare,[10] and oral lichen planus.[11] pustular psoriasis with a swirling linear pattern,[12] or mosaic vitiligo.[13]

To make dermatologists familiar with this new concept, an overview of pertinent case reports is presented in the following paragraphs.

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Correspondence to: Rudolf Happle, MD, Department of Dermatology, University of Marburg, Deutschhausstrasse 9, 35033 Marburg, Germany. E-mail: happle@mailer.uni-marburg.de.
0190-9622/$32.00

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The segmental involvement tends to be rather severe and may be associated with milder, nonsegmental lesions of the same disorder. Such cases may be best explained by an early postzygotic event in the form of loss of heterozygosity involving one of the genes that predispose to the disorder.

Superimposed linear psoriasis
Superimposed segmental manifestation of pustular psoriasis
Superimposed linear atopic dermatitis
Superimposed linear lichen planus
Superimposed linear manifestation of systemic LE
Superimposed linear pemphigus vulgaris
Superimposed segmental vitiligo
Superimposed linear graft-versus-host disease
Superimposed segmental granuloma annulare
Superimposed linear erythema multiforme
Superimposed linear drug eruption

DOI: 10.1111/pde.13611

BRIEF REPORT

Superimposed linear atopic dermatitis

Angela Hernández Martín MD[1]
Rudolf Happle MD[2]
Antonio Torrelo MD[1]
[1]Department of Dermatology, Hospital Infantil del Niño Jesus, Madrid, Spain,
[2]Department of Dermatology, Medical Center, University of Freiburg, Freiburg, Germany

Abstract

Superimposed linear atopic dermatitis is rarely manifested in polygenic disease as a counterpart to type 2 segmental mosaicism of monogenic skin diseases. Linear arrangement following Blaschko lines represents more severe disease on a generalized background of atopic dermatitis, perhaps reflecting clonal loss of heterozygosity. Only three cases of superimposed linear atopic dermatitis have been reported, we describe three additional cases.

1 | INTRODUCTION

In a patient with polygenic skin disease, the presence of more severe cutaneous involvement of the same disease showing a mosaic arrangement is called a superimposed segmental manifestation of the skin disease.[1] Examples of this include linear dermatomyositis on a background of disseminated dermatomyositis,[2] segmental vitiligo in patients with generalized vitiligo,[3] linear psoriasis in patients with underlying plaque-type psoriasis,[4] and linear lichen planopilaris in patients with classical lichen planopilaris.[5] Superimposed linear atopic dermatitis has been rarely described.[6,7] We present three patients with persistent linear atopic eczema superimposed on a background of chronic, generalized atopic eczema.

2 | CASE REPORTS

Three patients, a 4-year-old girl, a 2-year-old girl, and a 15-year-old boy (Table 1, Figures 1 and 2), presented with linear eczematous skin disease in the relapsing course of atopic dermatitis. One patient (Case 3) also had asthma. Examination revealed erythematous, extensively pruritic papules, vesicles, and excoriations following a unilateral linear arrangement. They were located on the right leg (Cases 1 and 2) and the trunk and limbs on the left side (Case 3). All patients also had widespread disseminated involvement with milder lesions (Figures 1B and 2B,C). Initiation of systemic and topical therapy was proposed.

3 | DISCUSSION

In monogenic disorders, there are two types of segmental mosaicism. One is a postzygotic mutation in type 1 segmental manifestation of an autosomal-dominant disease. In type 2 segmental mosaicism, the individual presents solely with a segmental manifestation of an autosomal-dominant disease. In type 2 segmental mosaicism, the individual has different bilaterally arranged skin diseases and a more severely involved area of the same disease in a segmental arrangement.[1,8] Type 2 segmental mosaicism implies a postzygotic germline mutation and loss of heterozygosity (LOH) during early embryonic

TABLE 1 Summary of reported cases of superimposed linear atopic dermatitis (AD)

Reference	Age, years	Sex	Location of segmental lesion	Arrangement	Concomitant relapsing AD	Age at onset of linear AD, years	Age at onset of generalized AD	Evolution	Atopic disease background
Taieb et al[6]	9	Female	Left arm from axilla to wrist	Linear, unilateral	+	7	6 mo	Improved after 6 wk	Eczema, house dust mite, cat sensitization, allergic rhinitis
Fathi et al[7]	36	Male	Left lower abdomen, leg, foot	Linear, unilateral		36	Childhood	Chronic, relapsing	Allergic rhinoconjunctivitis
Kawachi et al[6]	65	Male	Left leg	Linear, unilateral	+	62	4 mo	Chronic, recurrent	Chronic pruritus
Case 1	4	Female	Right leg	Linear, unilateral	+	4	6 mo	Unknown	Eczema
Case 2	2	Female	Right leg	Linear, unilateral	+	2	2 y	Improved after 4 wk	Eczema
Case 3	15	Male	Trunk, left arm, leg	Linear, unilateral	+	15	2 mo	Chronic, recurrent, flare-ups for 2 yr	Asthma

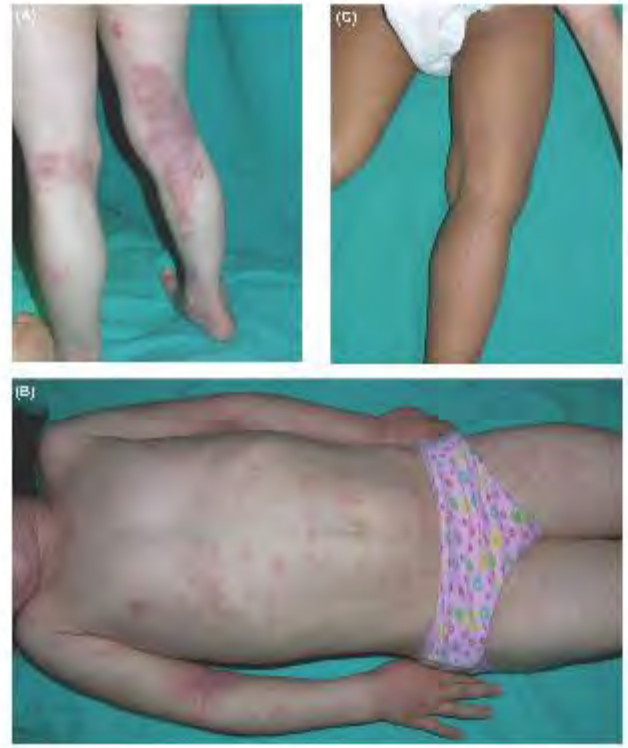


FIGURE 1 Case 1: A, Linear arrangement of lesions in the inner part of her right leg. B, Generalized papules and plaques. Case 2: C, Wild atopic dermatitis and a line of eczema on the back of her right leg

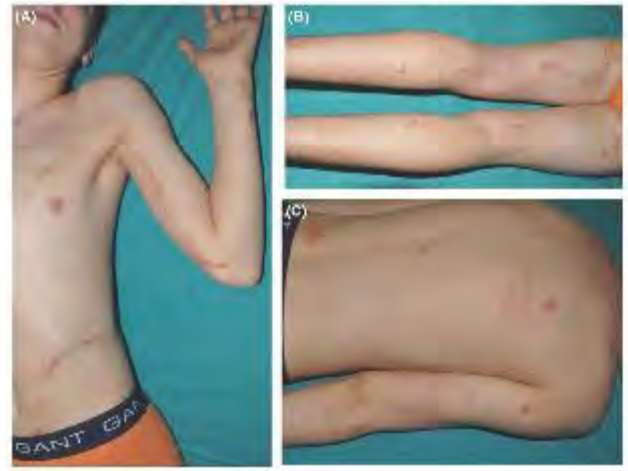
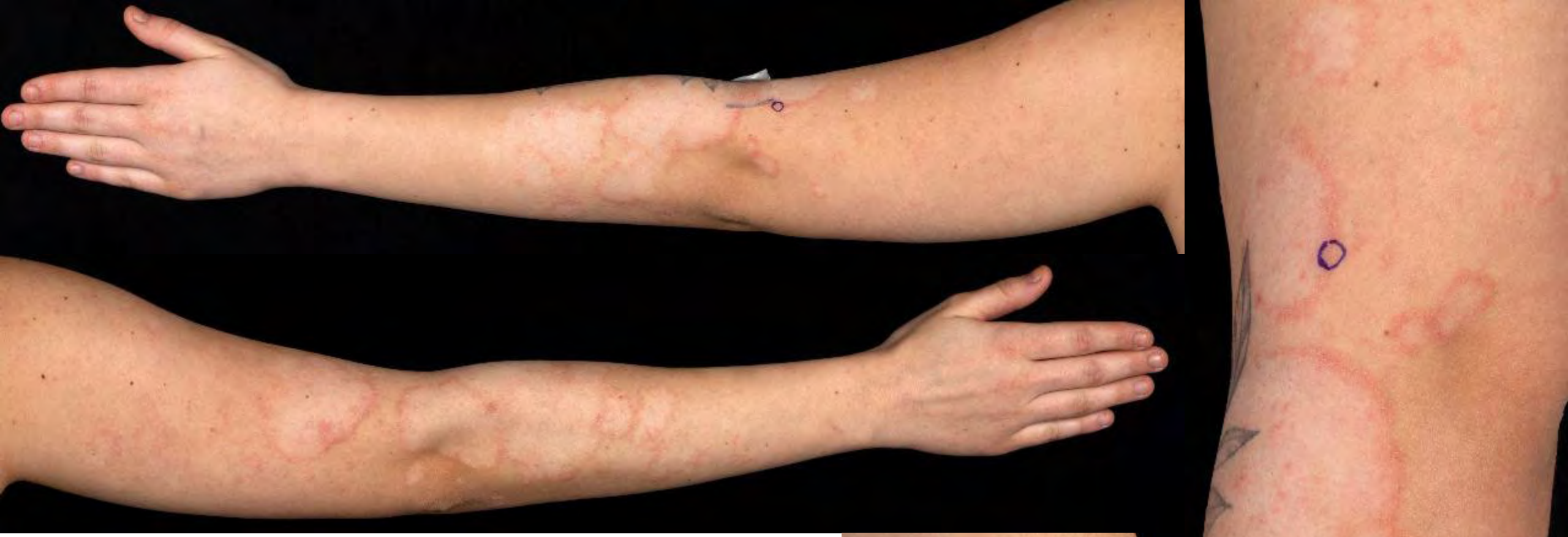


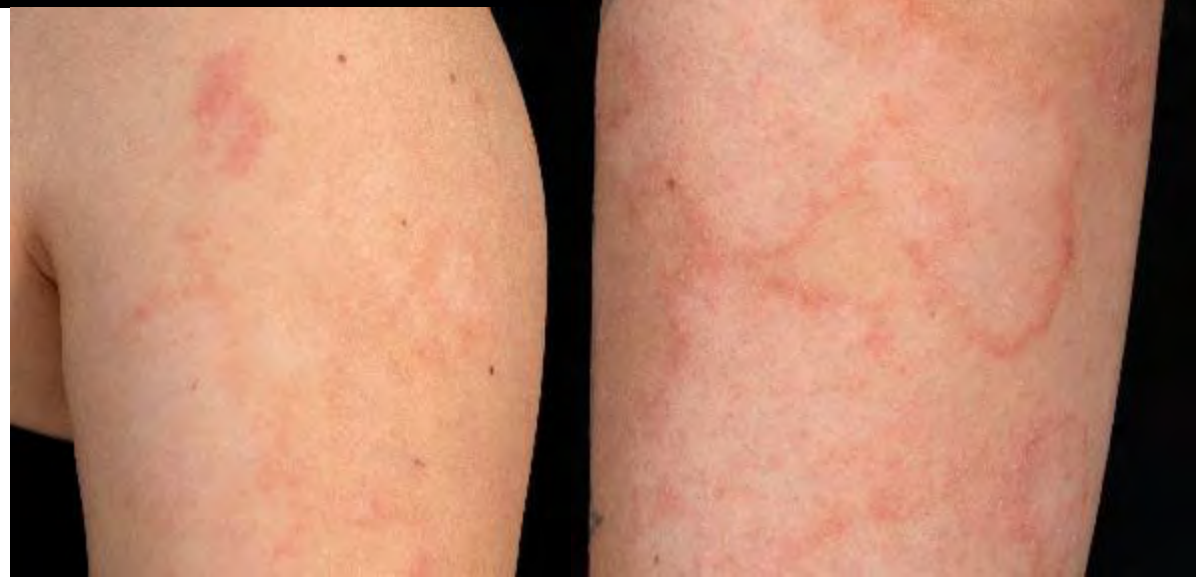
FIGURE 2 Case 3: A, Eczematous lesions following a Blaschko linear eczema affecting the left side of the body trunk and arm. B, C, Diffuse eczema papules and plaques on the back and both legs

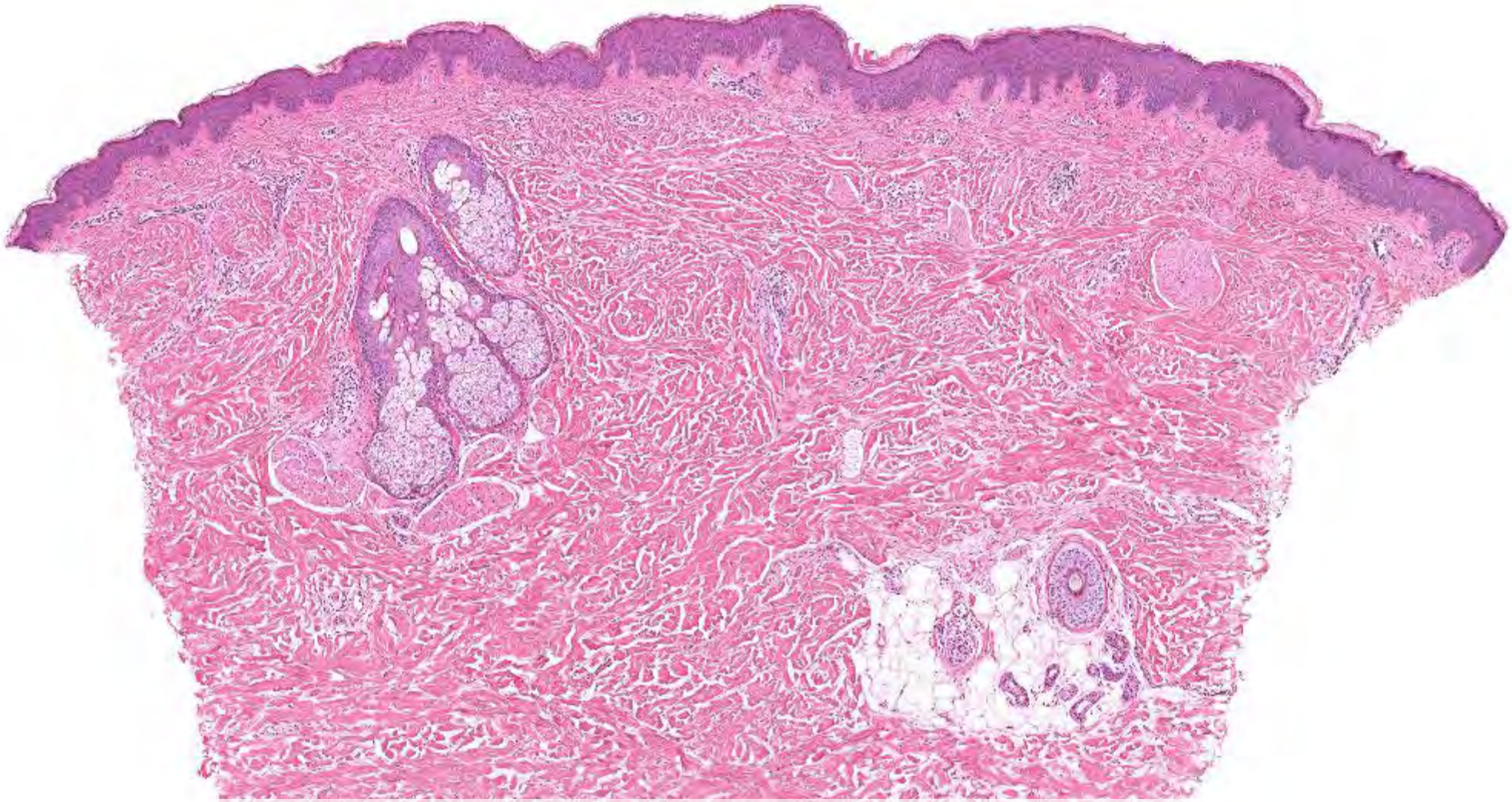


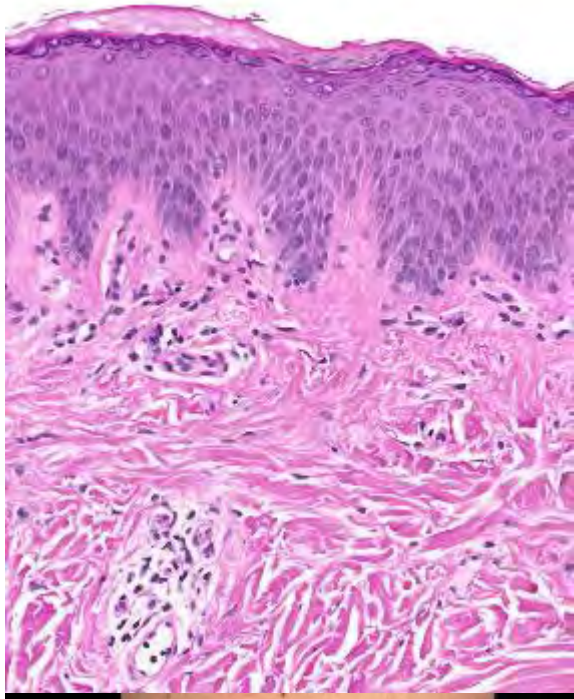
F, 19

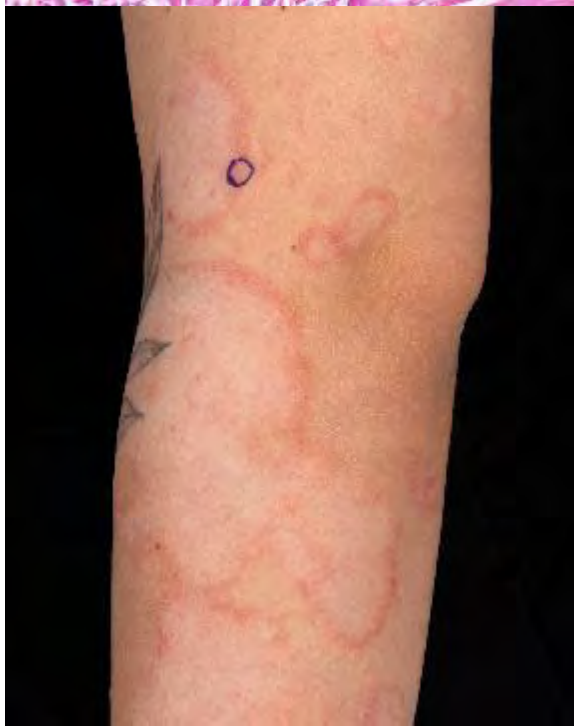
According to the patient itchy skin lesions present for approximately 6 months. No other cutaneous or extracutaneous symptoms.

A biopsy is taken.





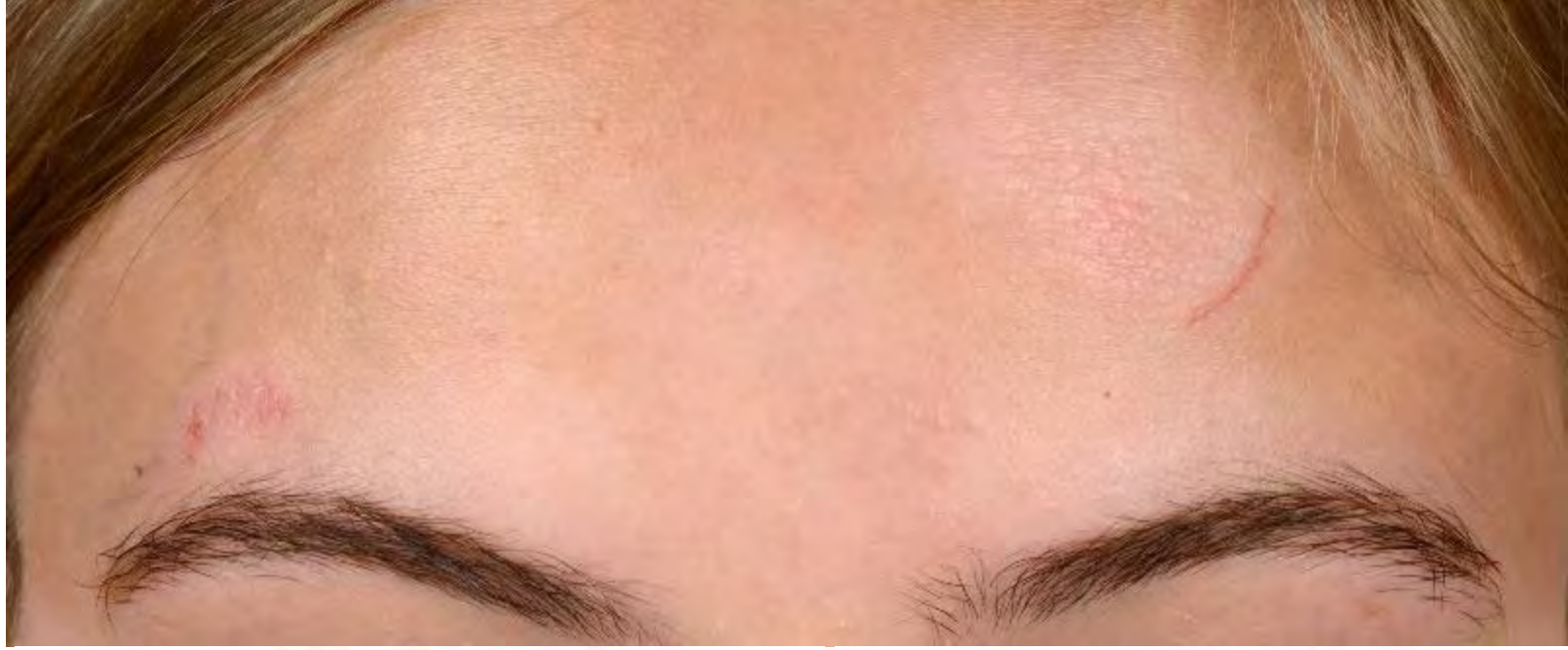


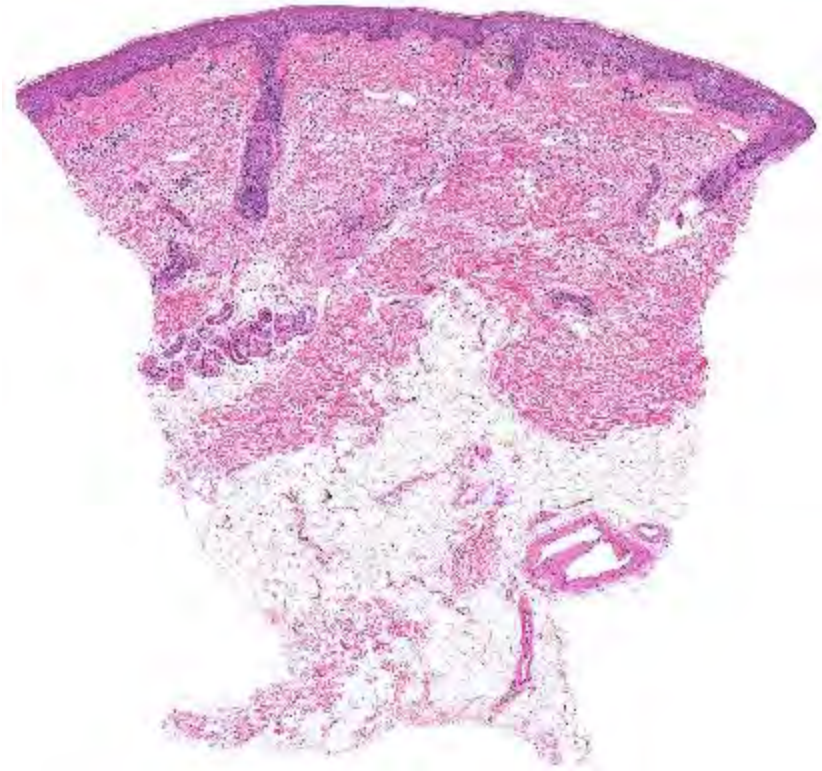


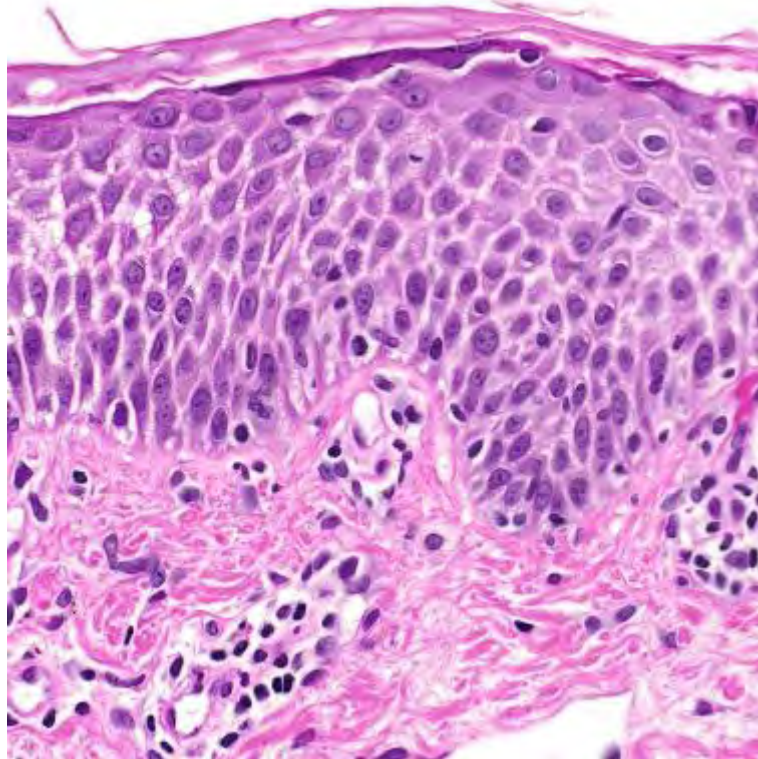
Eczematous ("atopic") dermatitis with post-inflammatory hypopigmentation

F, 16

ANA: 1:640. DFS70 Abs: 107.0/+ U/mL (-10.0)







Pityriasis alba

ORIGINAL ARTICLE

DDG

Anti-DFS70 antibodies are associated with atopic dermatitis and can cause misdiagnosis of connective tissue disease

Bettina Santler[1] | Louisa Wimmer[1] | Bernhard Schlueter[2] | Jan Ehrchen[1]

Summary

Background and Objectives: Antinuclear antibodies (ANA) detected by HEp2 cell immunofluorescence staining are characteristic finding in patients with connective tissue disease (CTD). However, even detection of highly elevated ANA is not conclusive for CTD and can result in misdiagnosis. Anti-DFS70 antibodies are ANA, which may also be highly elevated in people without CTD. Thus, we wanted to evaluate whether they could cause misdiagnosis of CTD. Since anti-DFS70 antibodies have been associated with atopic dermatitis (AD) in Japan, we wanted to investigate this association and its potential diagnostic relevance in Germany.

Patients and Methods: We retrospectively analyzed data of 40 patients referred for first consultation on CTD and prospectively analyzed the prevalence of anti-DFS70 antibodies in 110 AD patients and 89 controls.

Results: We could not confirm CTD in 75% of our referred patients, 26% of whom had already received systemic treatments. DFS70-typical fluorescence staining was detected in 36% and definitive anti-DFS70 antibodies in 12.5% of these patients. DFS70-typical fluorescence staining was detected in 22% of AD patients and anti-DFS70 antibodies in 10% (versus 5.6% and 0% in control patients, $P < 0.001$).

Conclusions: Anti-DFS70 antibodies are significantly associated with AD and could be responsible for misdiagnosis of CTD.

INTRODUCTION

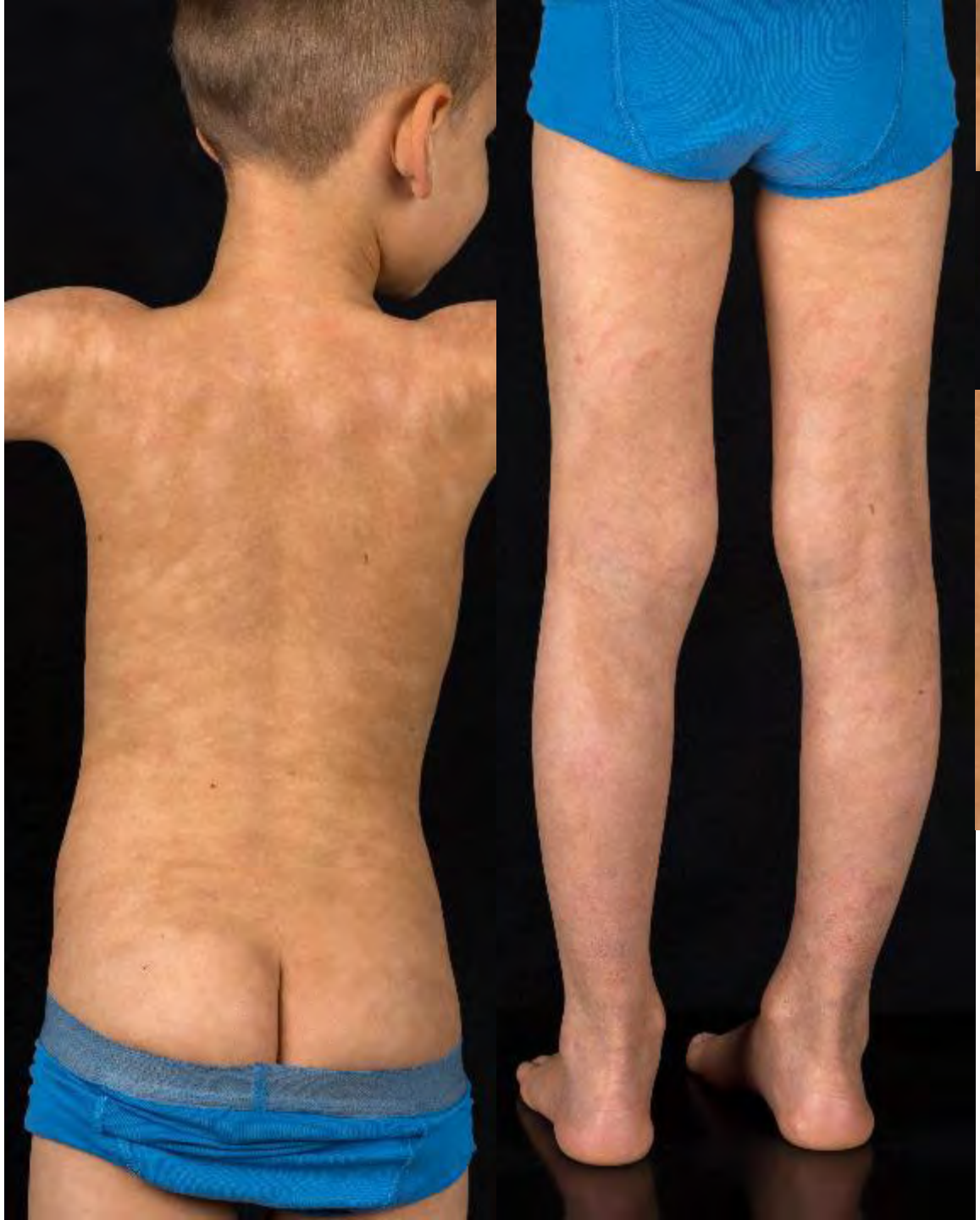
Antinuclear antibodies (ANA) are autoantibodies targeting various components of the human nucleus, for example double-stranded deoxyribonucleic acid (anti-dsDNA antibodies), centromeric proteins (anti-centromere antibodies) and proteins such as Ro52 and Ro60 (anti-Ro antibodies/anti-SS-A antibodies) among many others. Autoantibodies against cytoplasmic proteins (for example anti-Jo-1 antibodies) or other types of cellular structures are generally also called ANA although they do not target nuclear proteins. The indirect immunofluorescence (IF) assay on HEp-2 cells is considered to be the gold standard of detection methods of ANA. Further tests such as ELISA (enzyme-linked immunosorbent assay) or line blot then allow the detection of specific autoantibodies (for example, anti-dsDNA antibodies, anti-centromere antibodies). The IF also provides an immunofluorescence pattern that allows a rough estimation of the autoantibodies present before more specific tests such as ELISA are used. An international expert group (International Consensus on Antinuclear Antibody [ANA] Patterns/ICAP) has defined 29 IIF ANA patterns (AC-1 to AC-29); their descriptions are available on the ICAP's website (www.anapatterns.org).

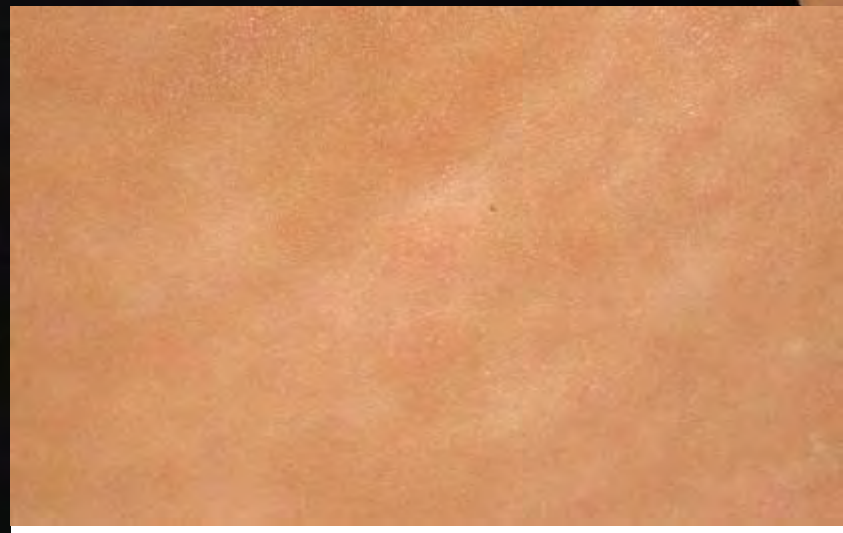
Antinuclear antibodies are an integral piece in the diagnostic process of autoimmune connective tissue diseases (CTD) such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), dermatomyositis or mixed connective tissue disease (which is a type of CTD with its own diagnostic criteria). While the detection of ANA alone has a very low specificity for diagnosis of CTD, the detection of ANA and specific autoantibodies, such as anti-dsDNA antibodies, facilitates

TABLE 5 DFS pattern and anti-DFS70 antibodies in our study and control group.

	Study group (n = 110)	Control group (n = 89)	
Anti-DFS70 antibodies	10% (11)	0% (0)	$P < 0.001$
DFS pattern	22.7% (25)	5.6% (5)	$P < 0.001$
DFS pattern without anti-DFS70 antibodies	12.7% (14)	5.6% (5)	$P = 0.088$

DFS70-typical fluorescence staining was detected in 22% of AD patients and anti-DFS70 antibodies in 10% (versus 5.6% and 0% in control patients, $P < 0.001$). (…)
Anti-DFS70 antibodies are significantly associated with AD and could be responsible for misdiagnosis of CTD.

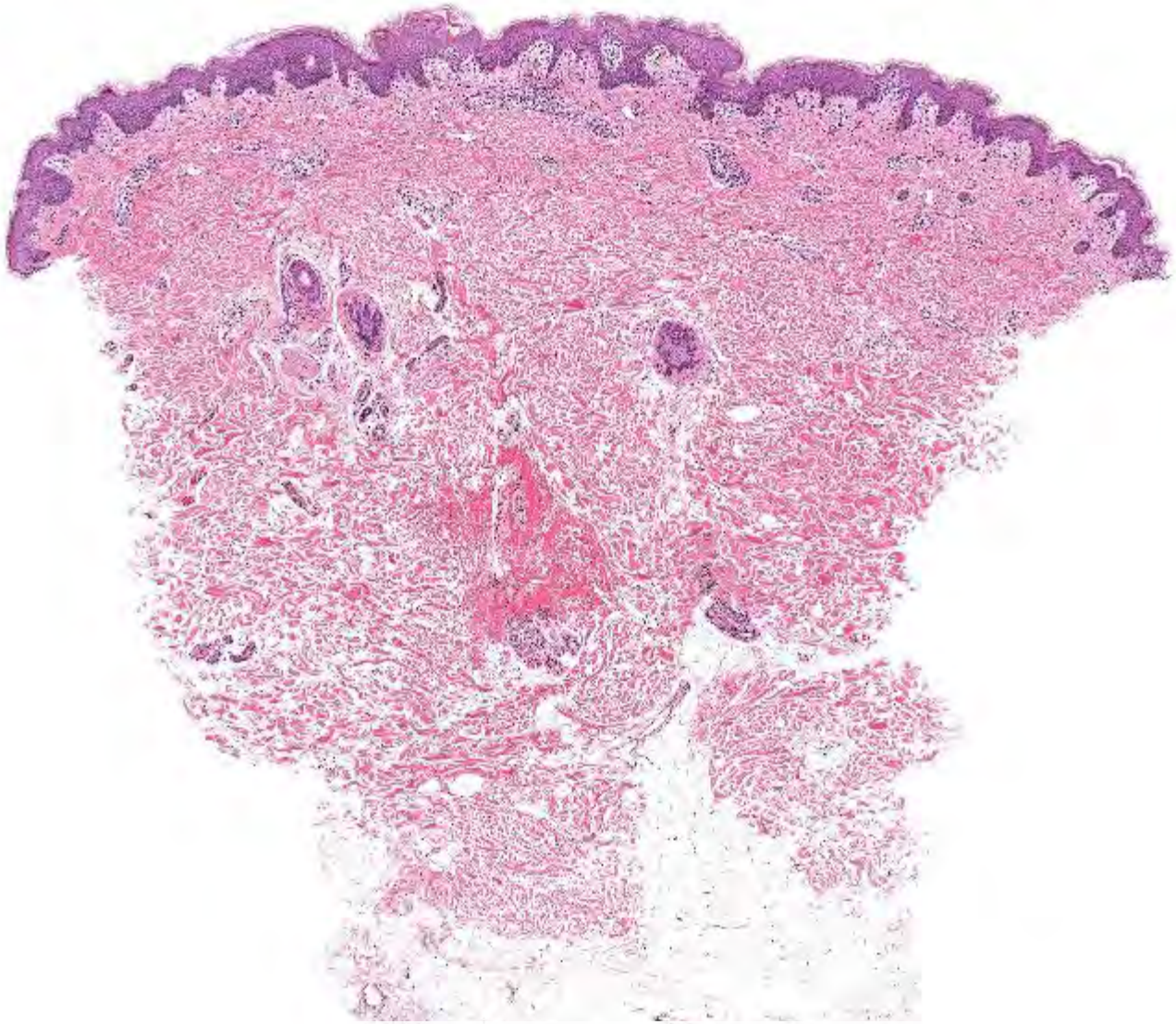


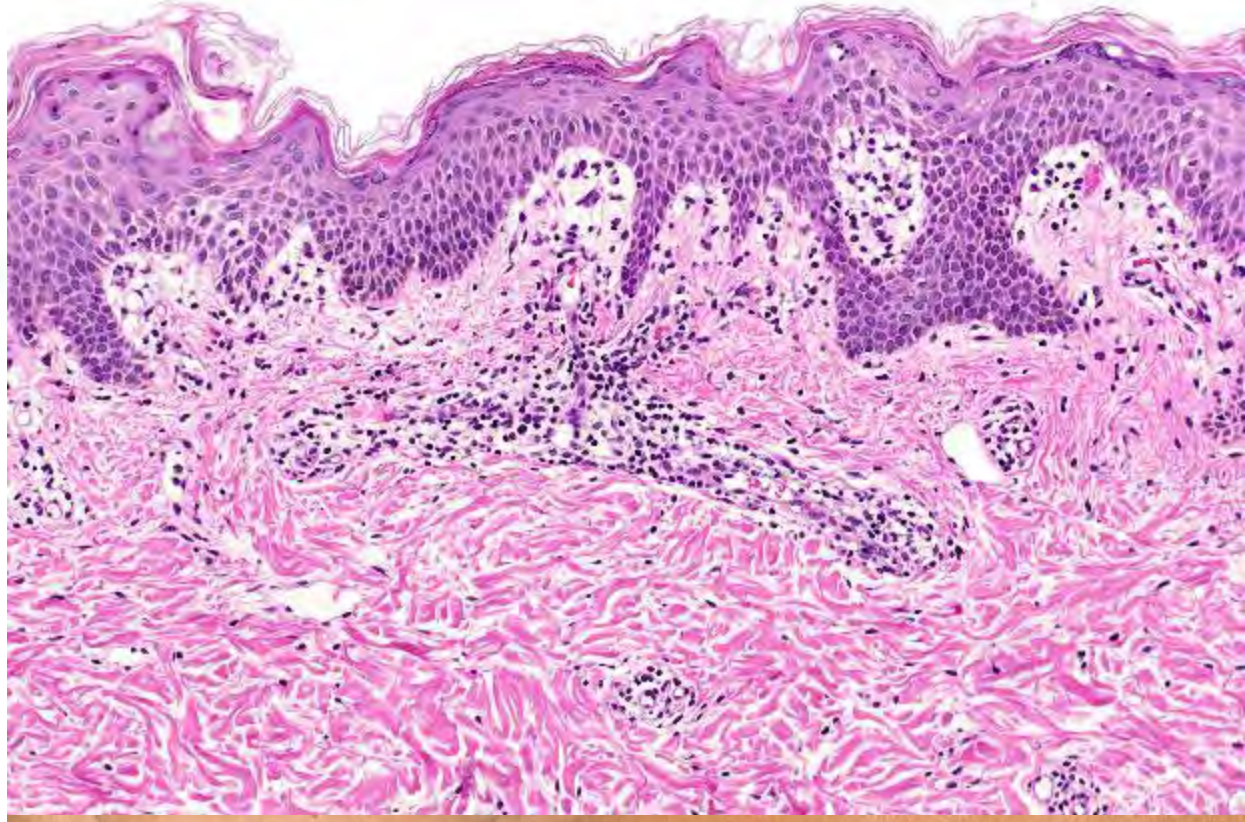


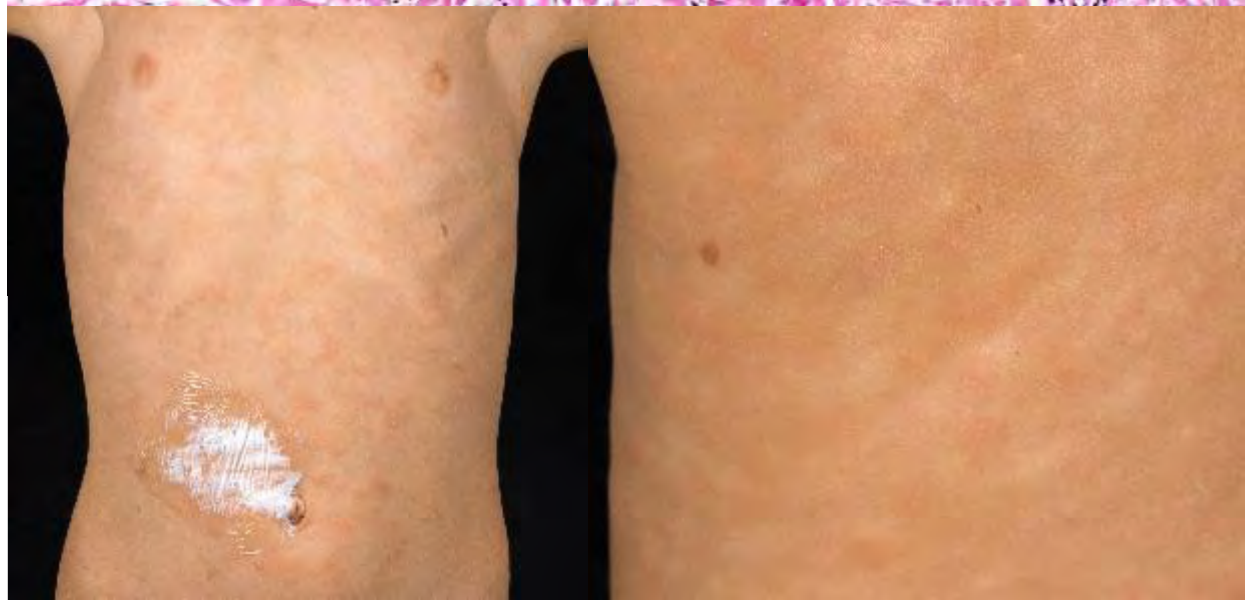
M, 6

Itchy skin lesions for >6 months.

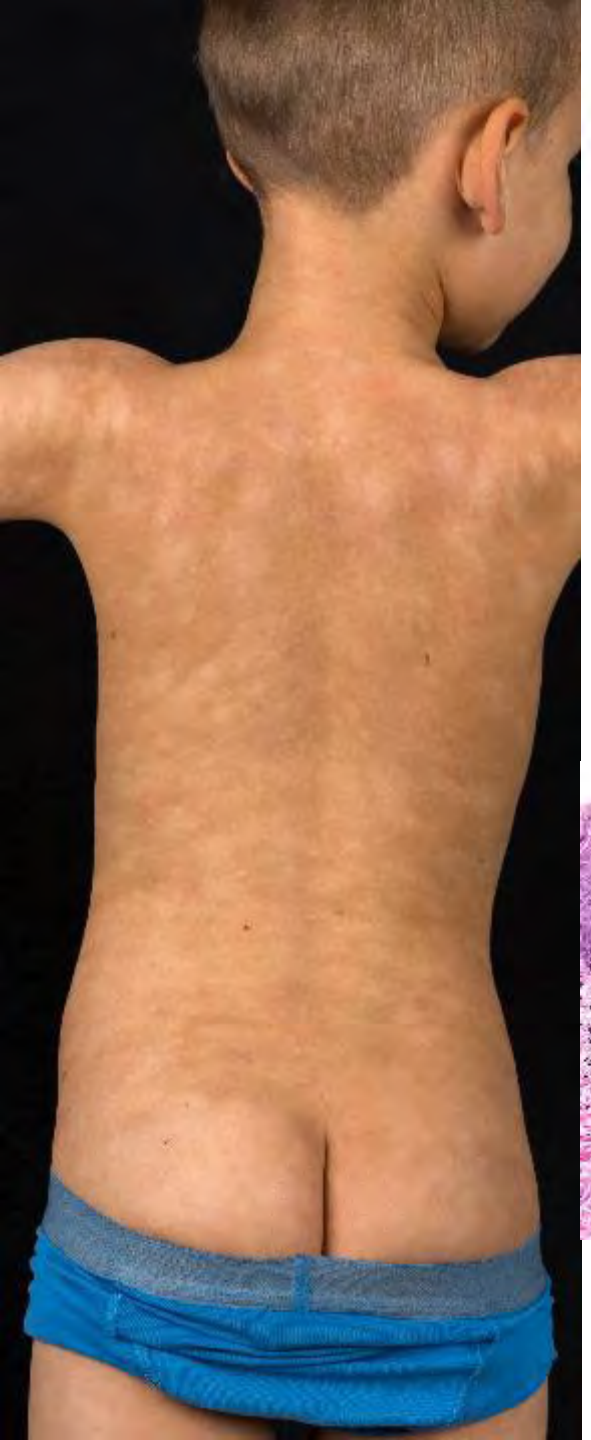
A biopsy is taken.

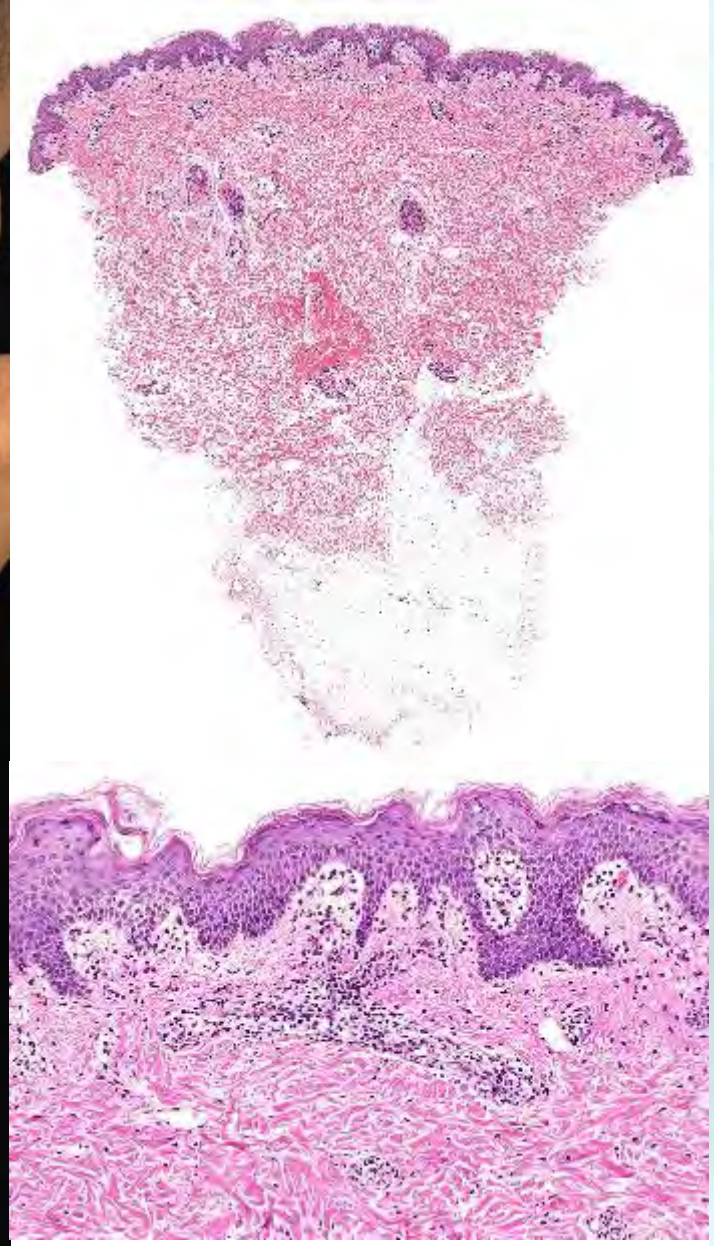




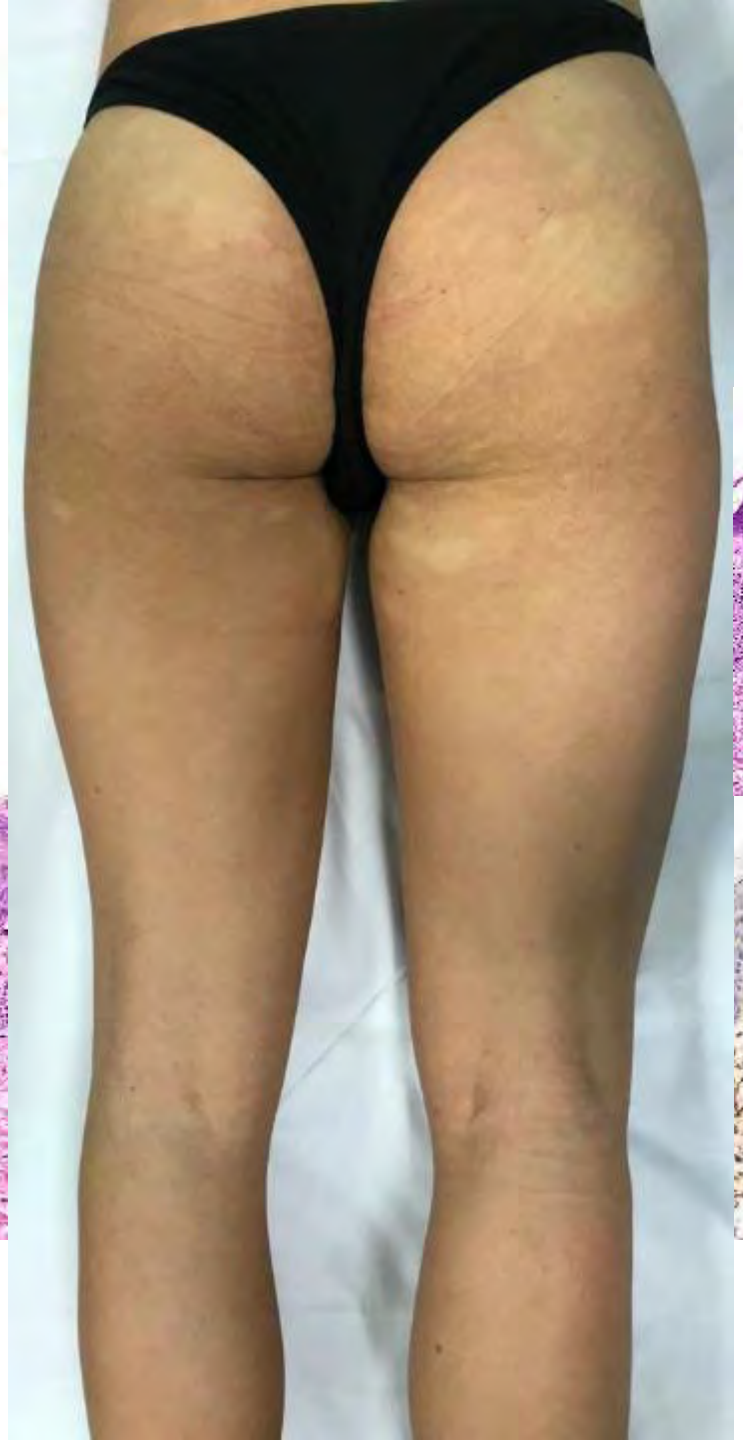


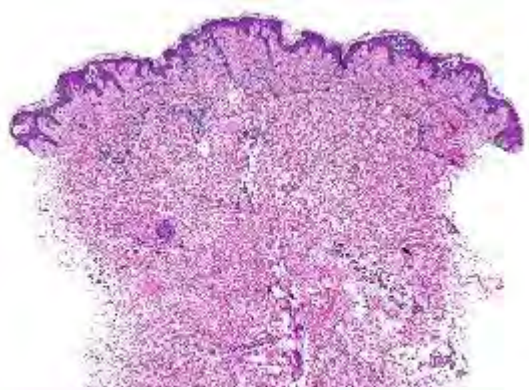
Pityriasis alba
in atopic dermatitis

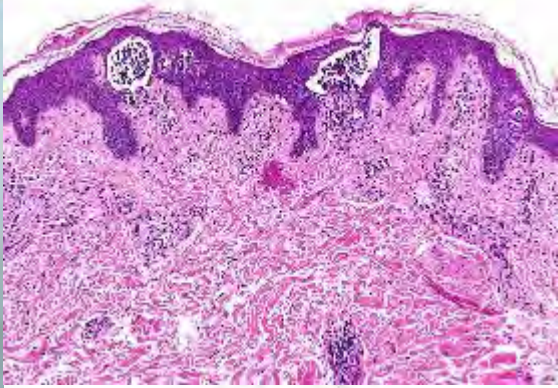


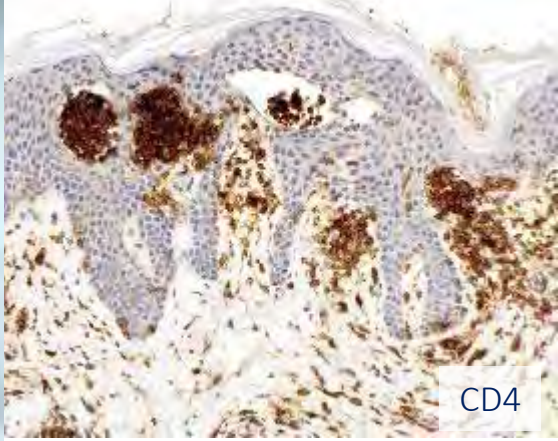


Atopic dermatitis

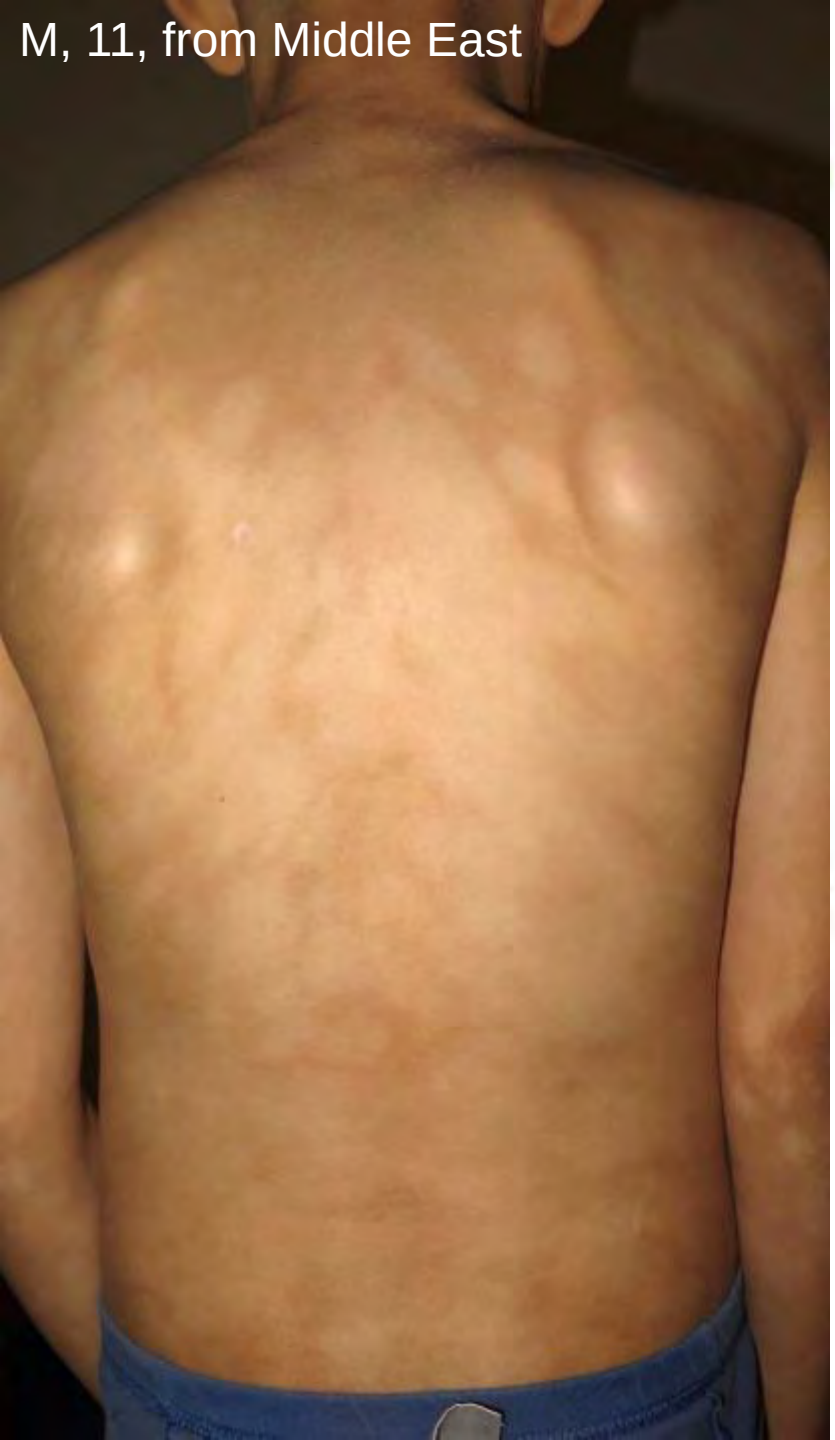


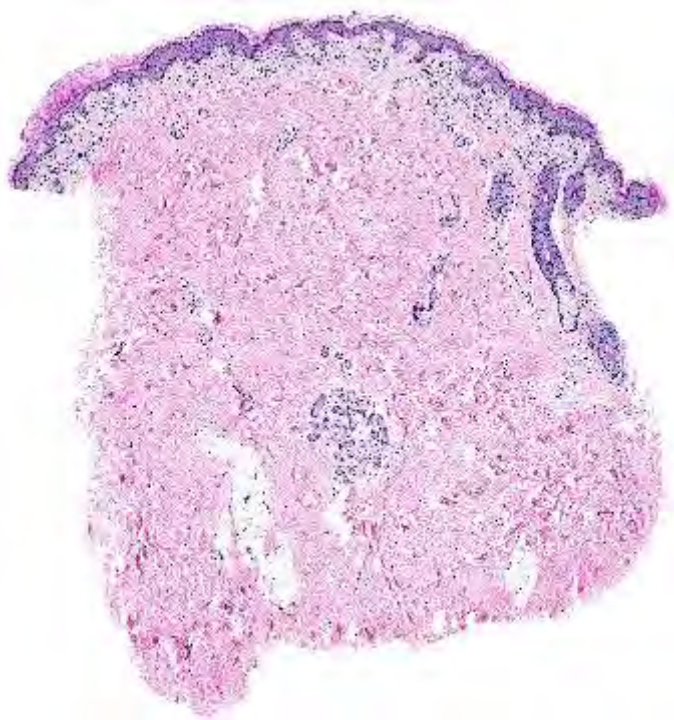


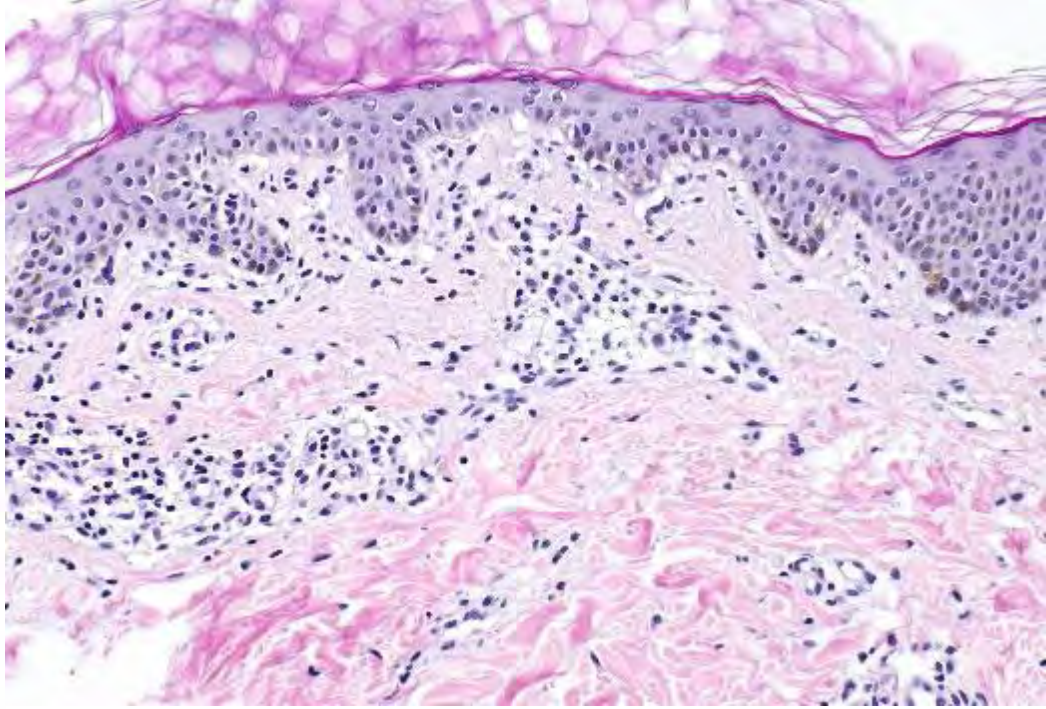




Mycosis fungoides

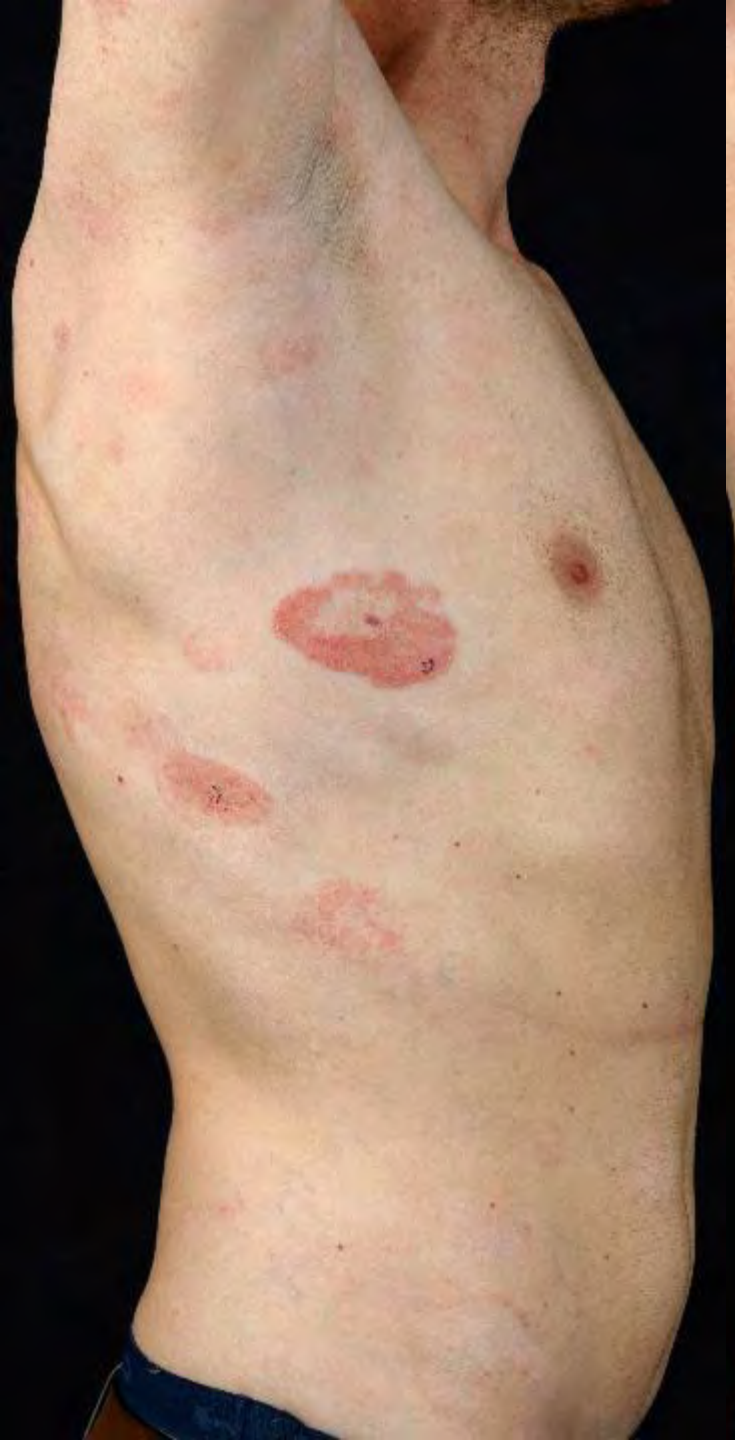


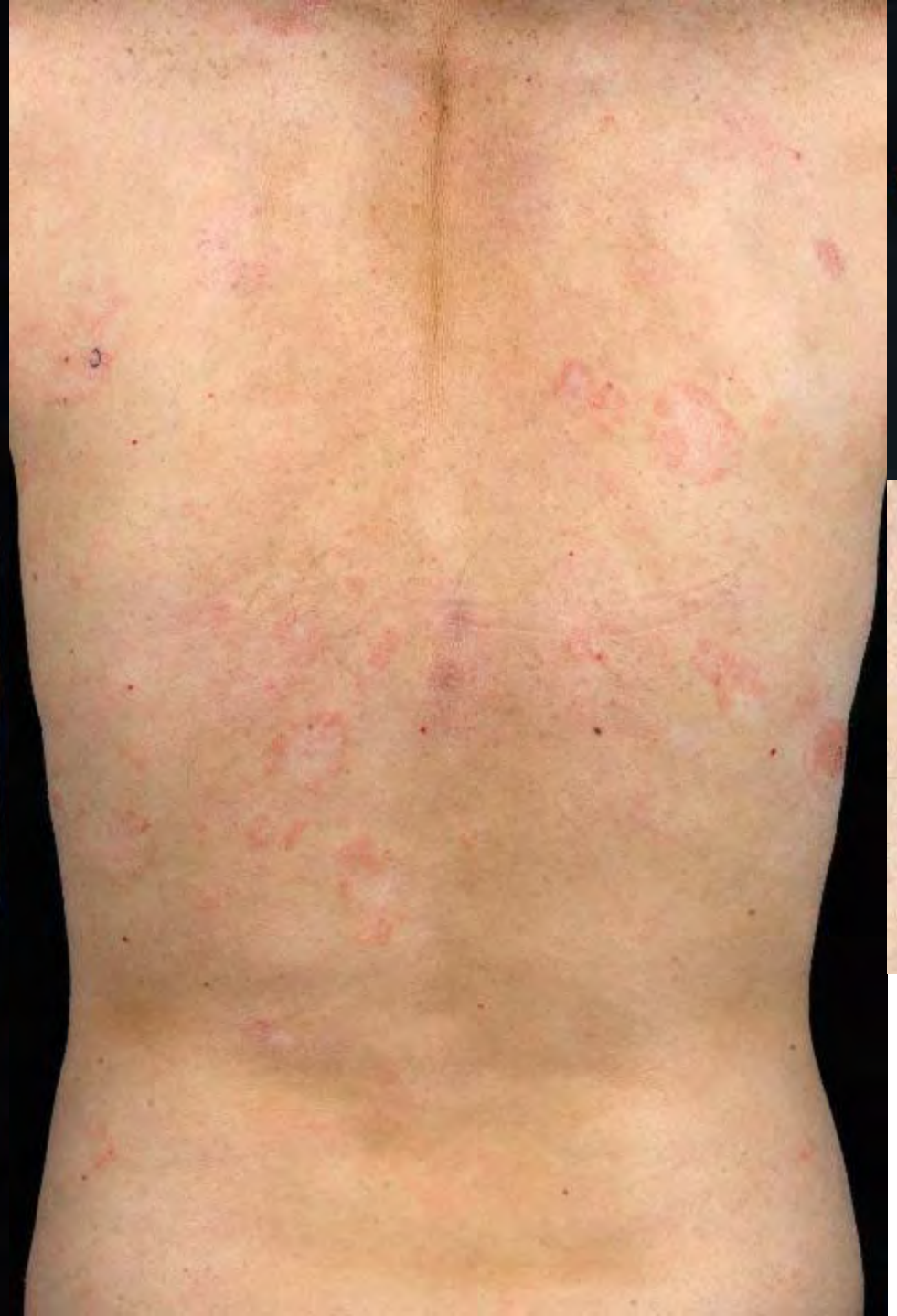


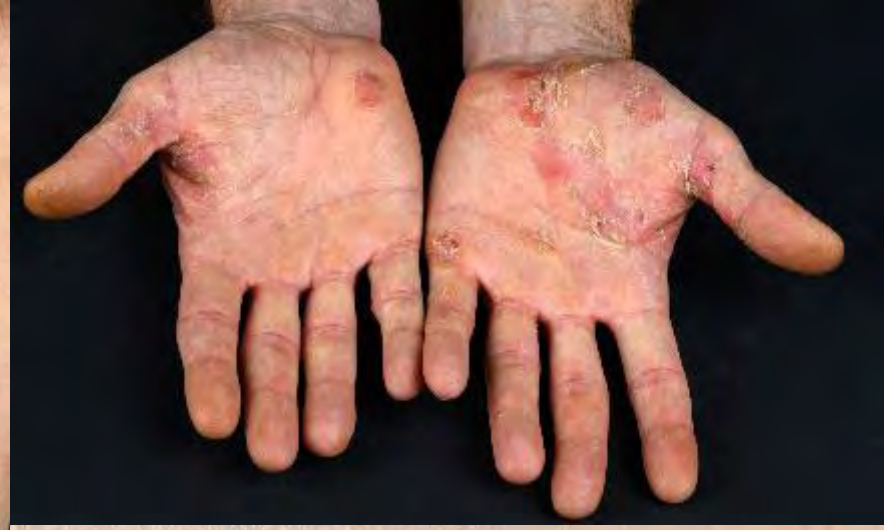


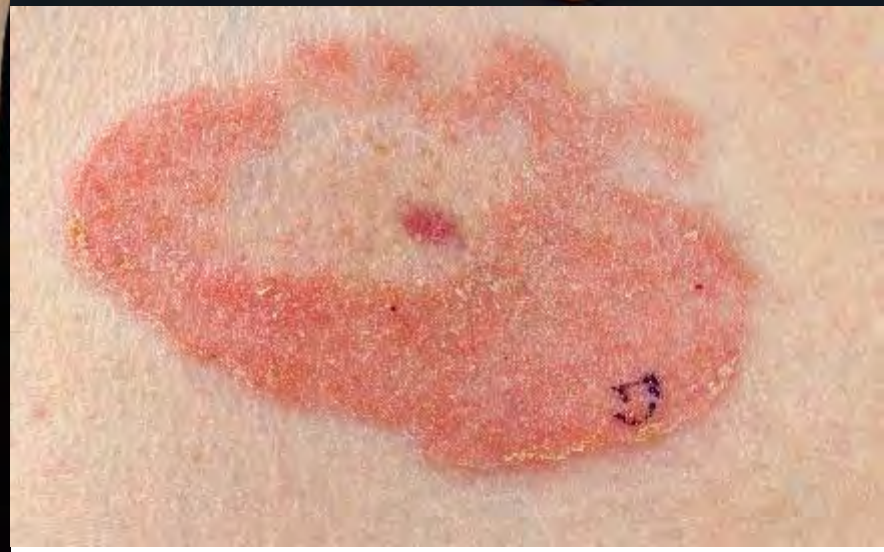
A word of caution concerning hypopigmented mycosis fungoides in children

- Clinical presentation often indistinguishable from that of atopic dermatitis
- Diagnosis based mostly on histology (band-like infiltrate with some epidermotropic lymphocytes)
- Mostly CD8+ phenotype (like many cases of AD)
- Long-term survival (decades) without more aggressive manifestations of the disease
- *Are all cases really examples of MF?*
  (Probably not – my opinion)





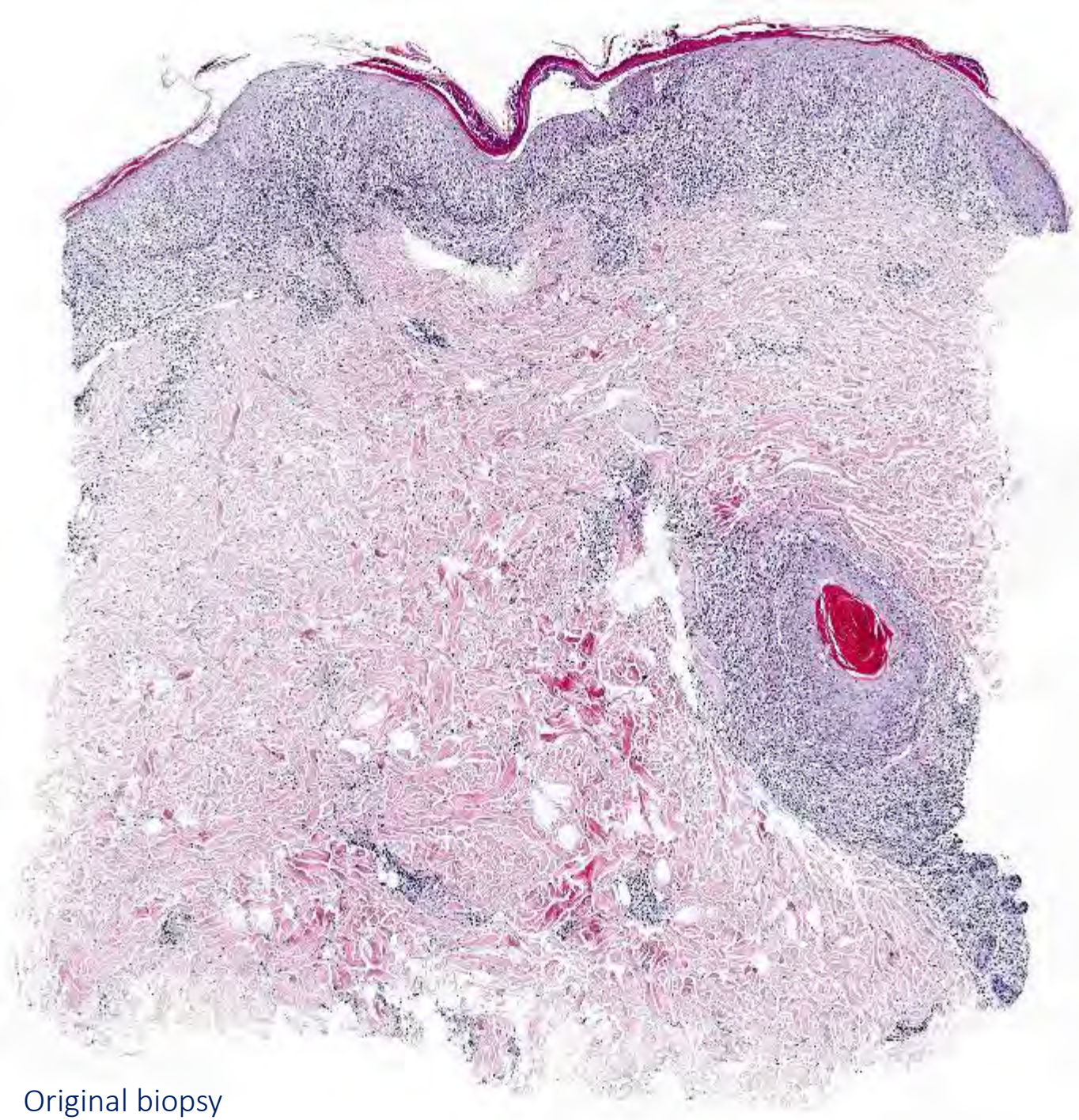


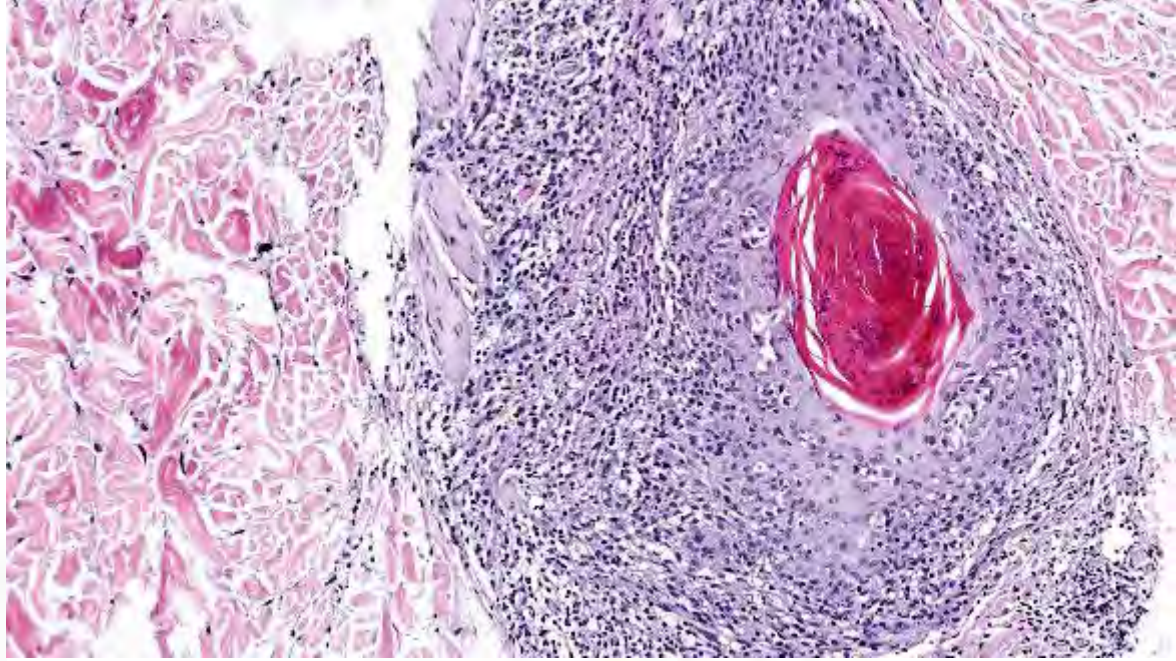


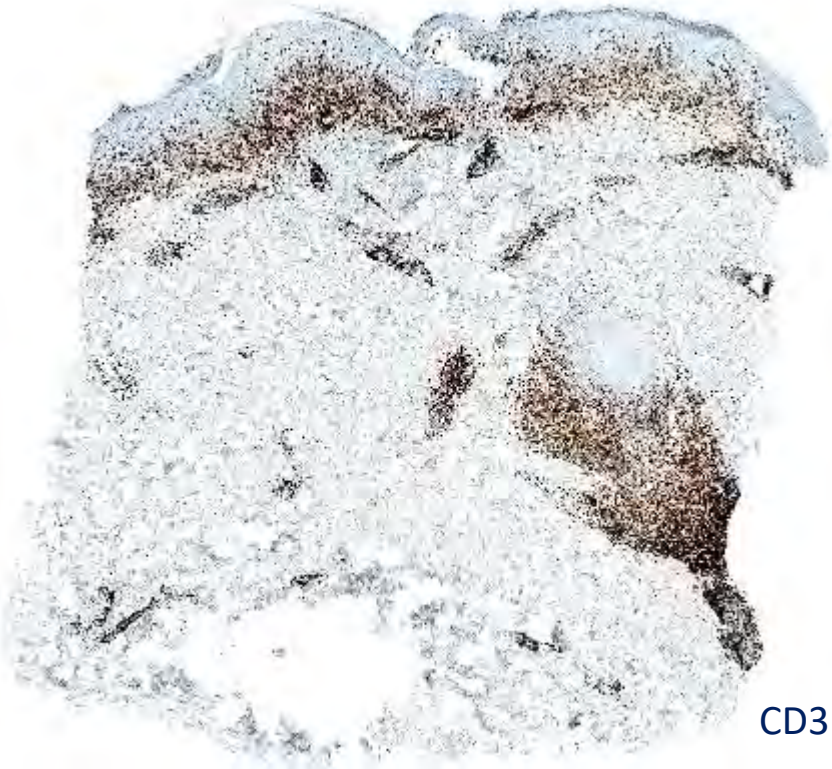
M, 37

According to the patient itchy skin lesions for 10 years, managed previously with dupilumab with improvement. A previous external biopsy was reported as suspicious for adnexotropic MF.

Three biopsies are taken.

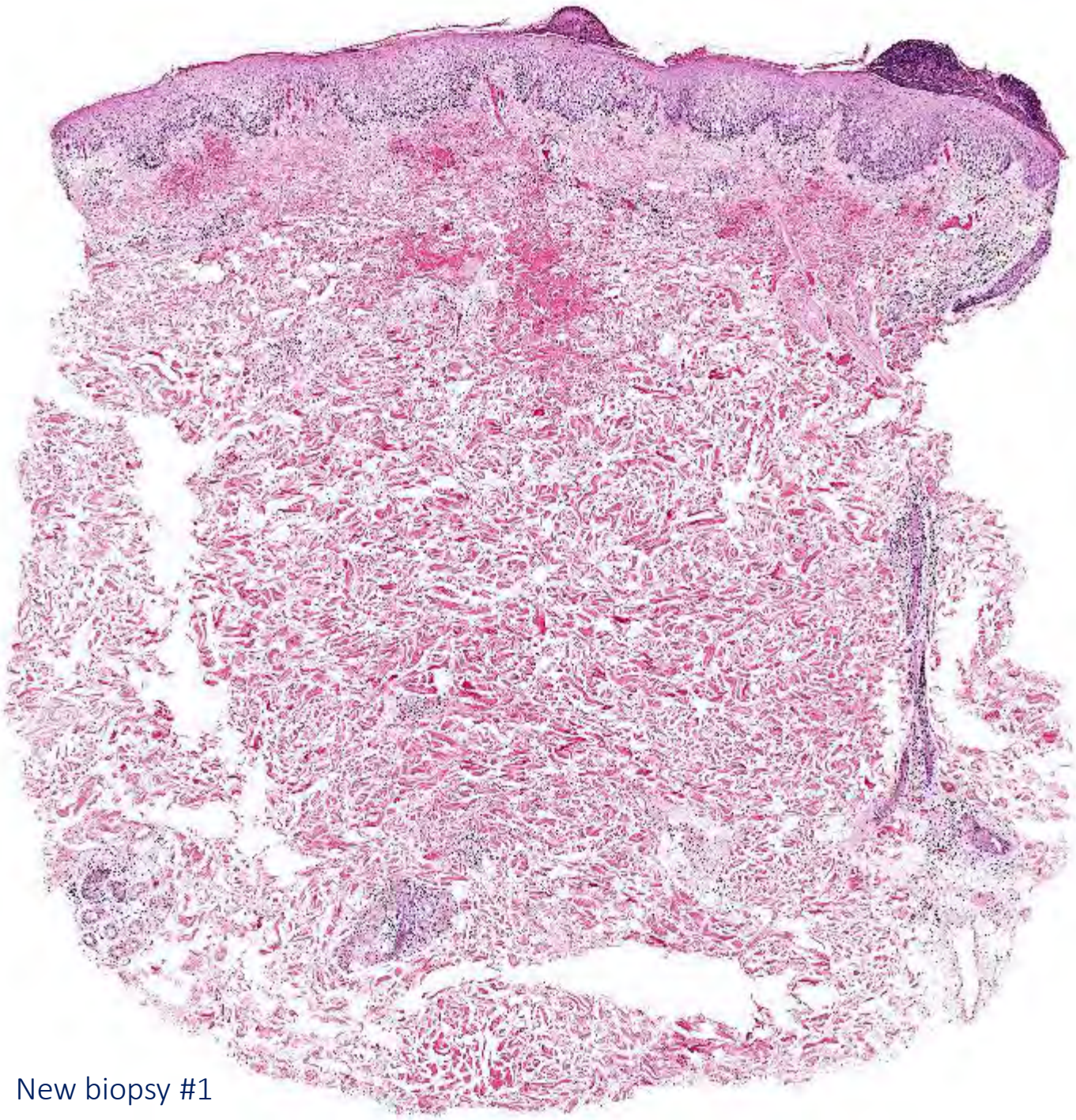




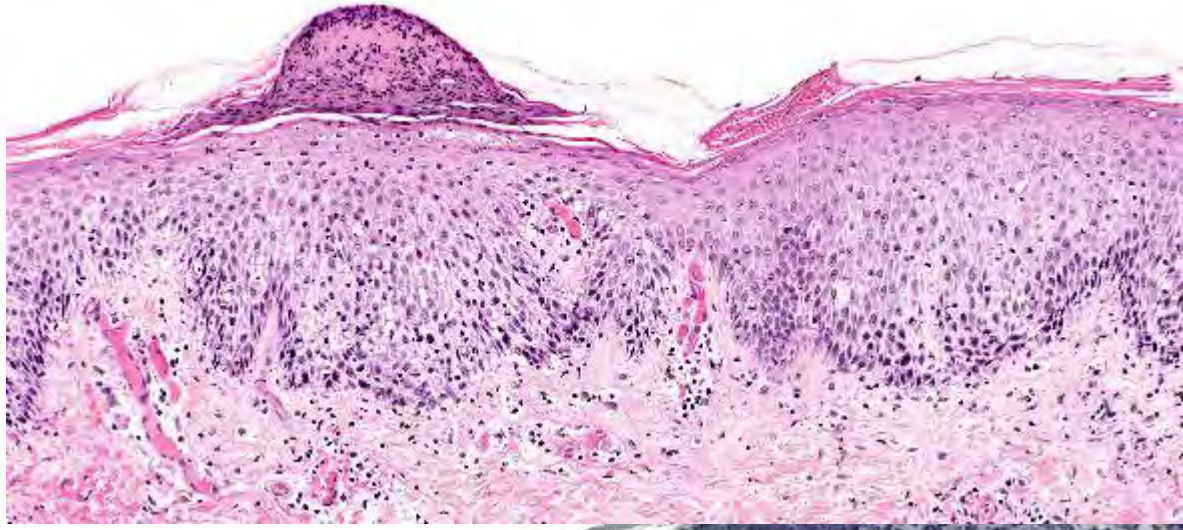


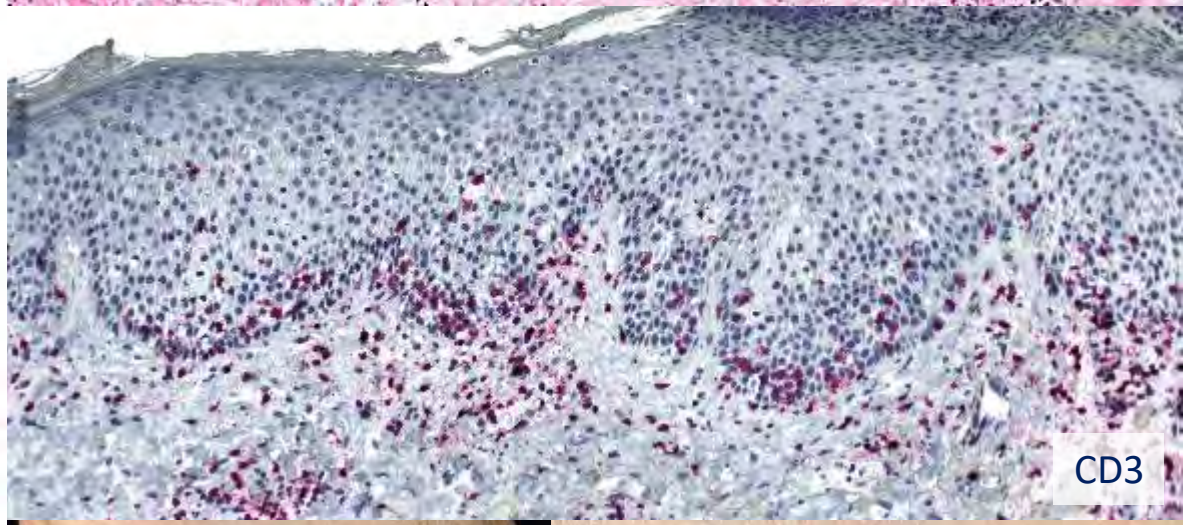
Original biopsy

CD3

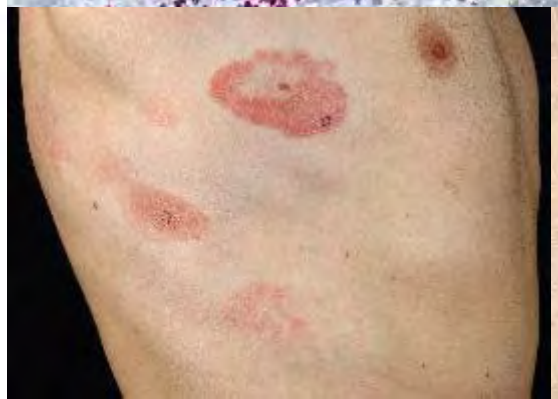


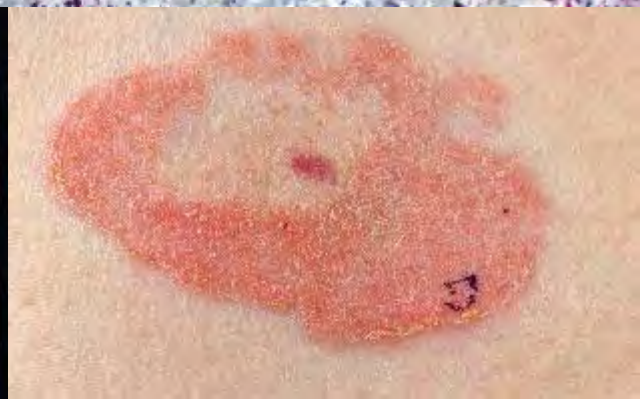
New biopsy #1

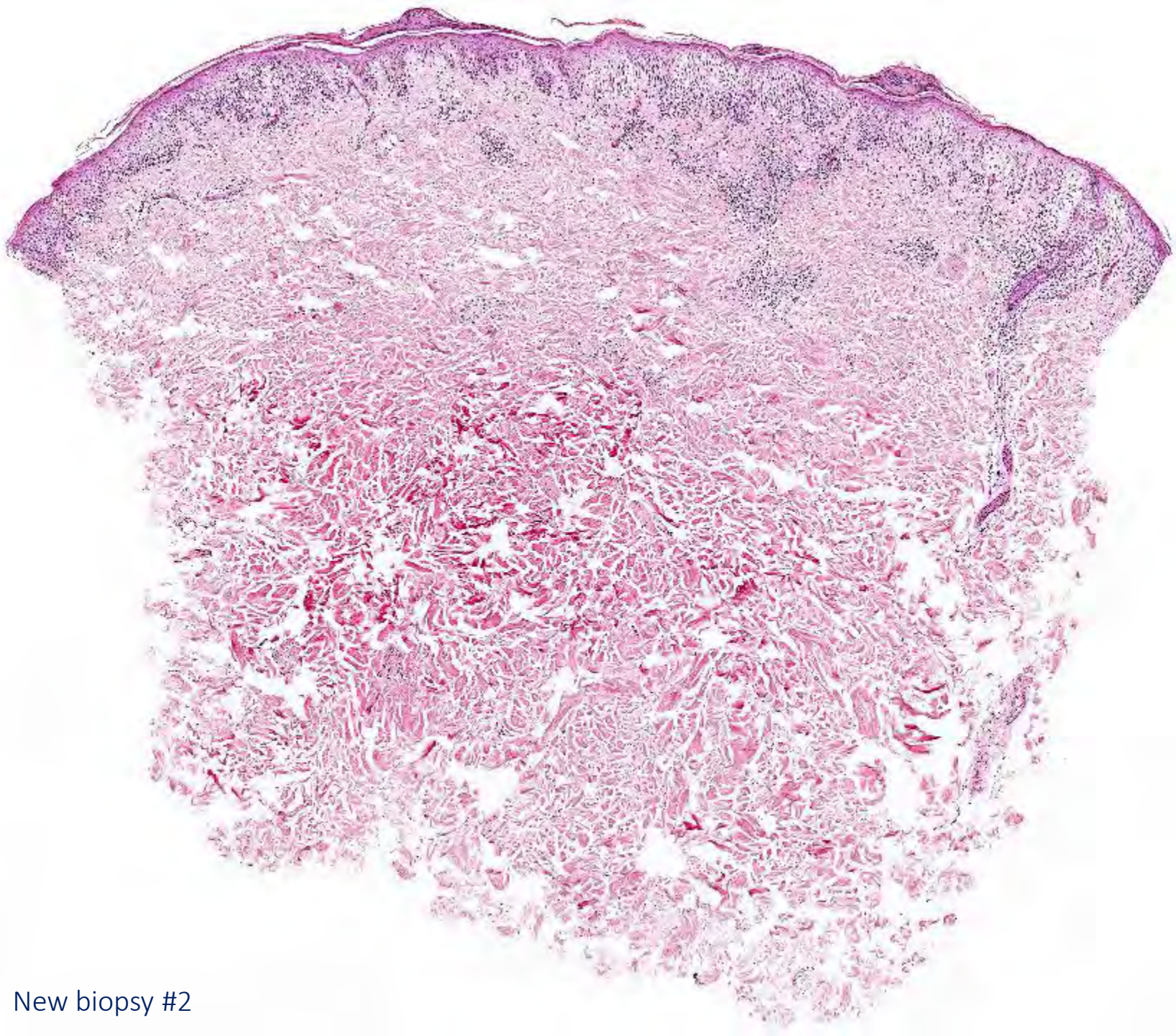


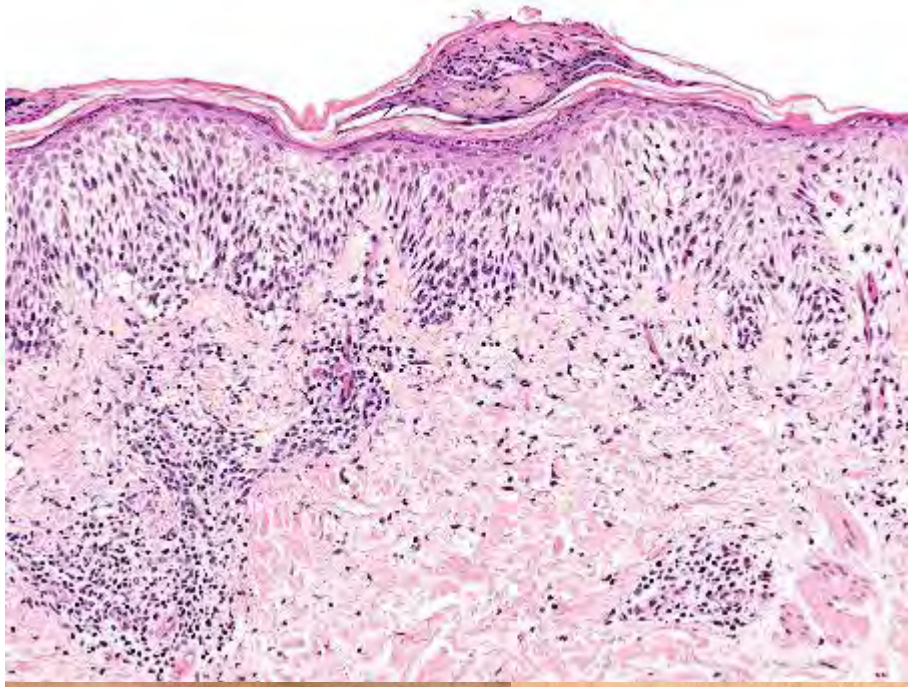


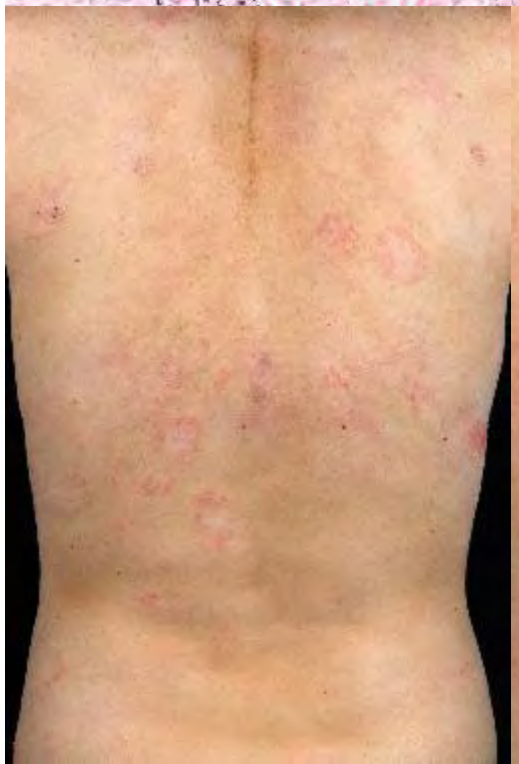
CD3

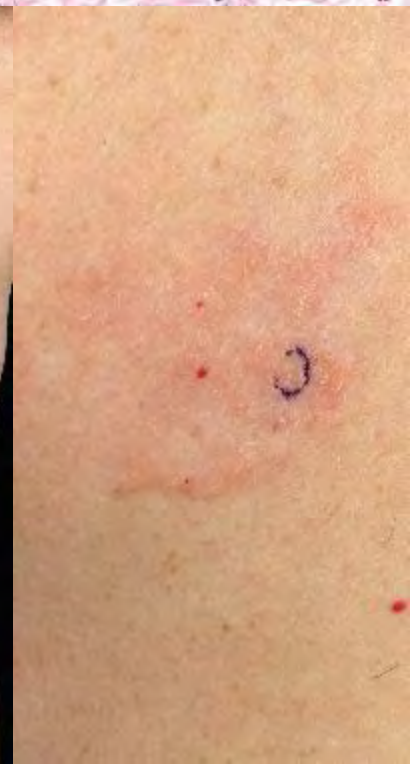












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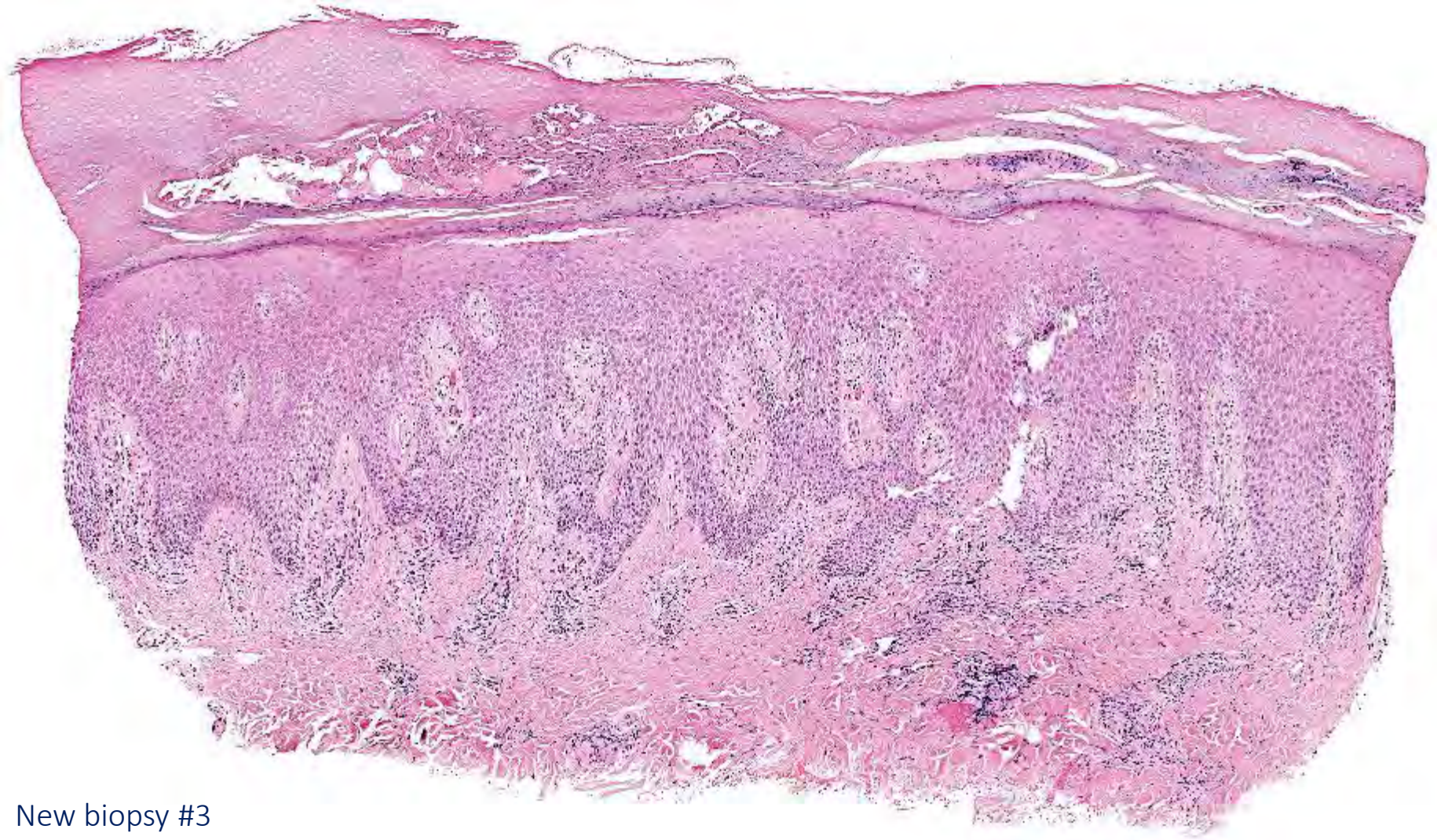
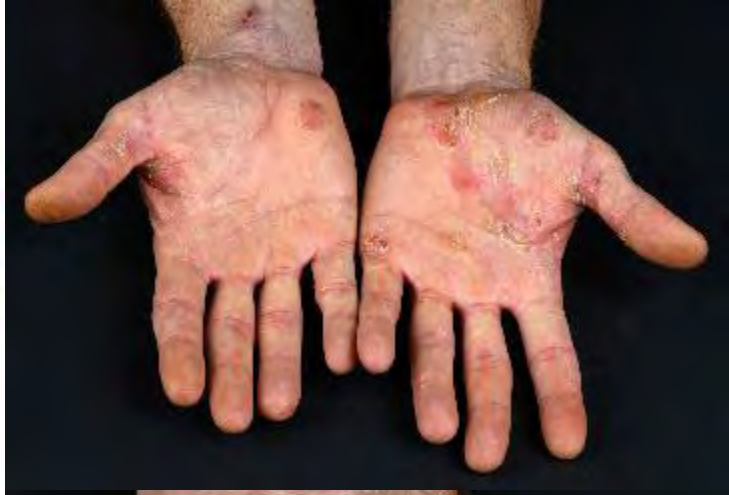
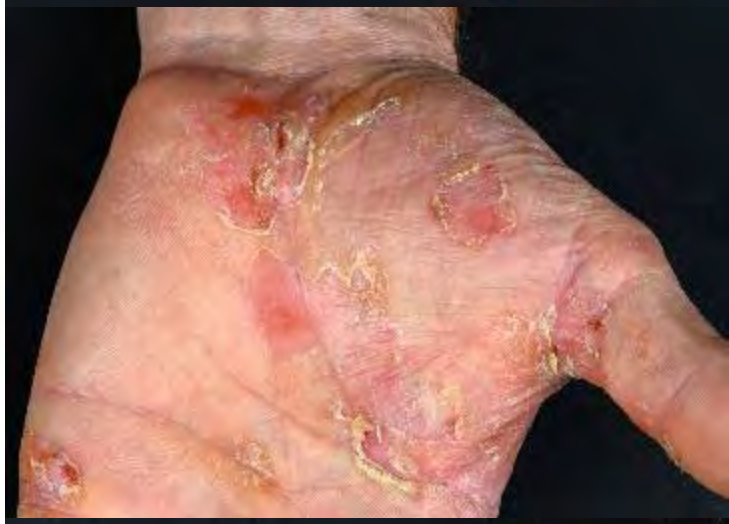
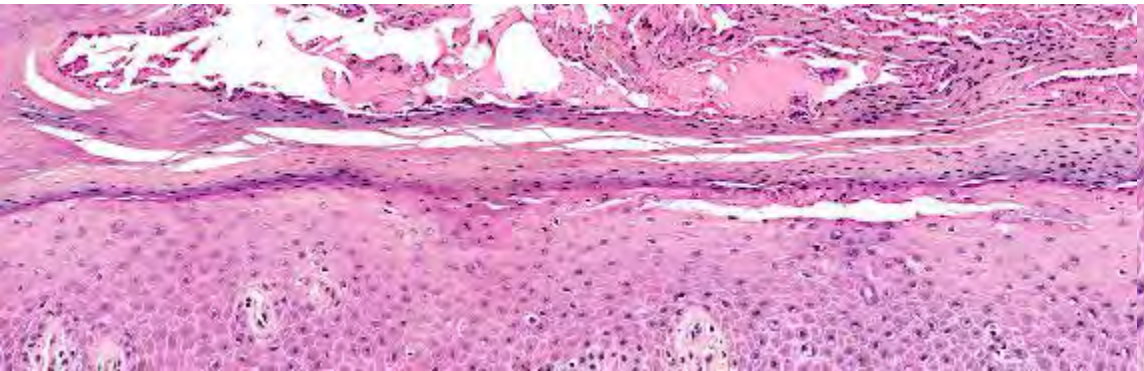
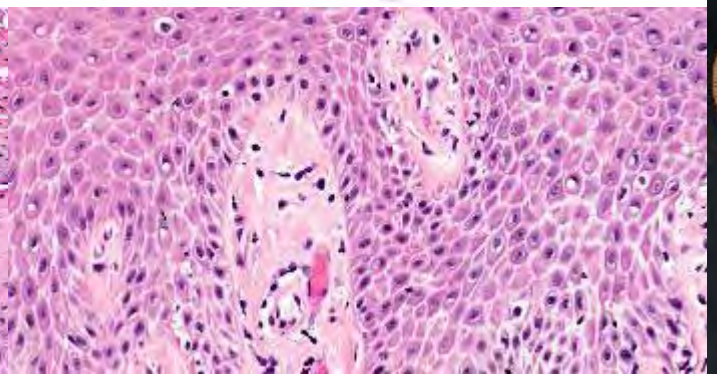


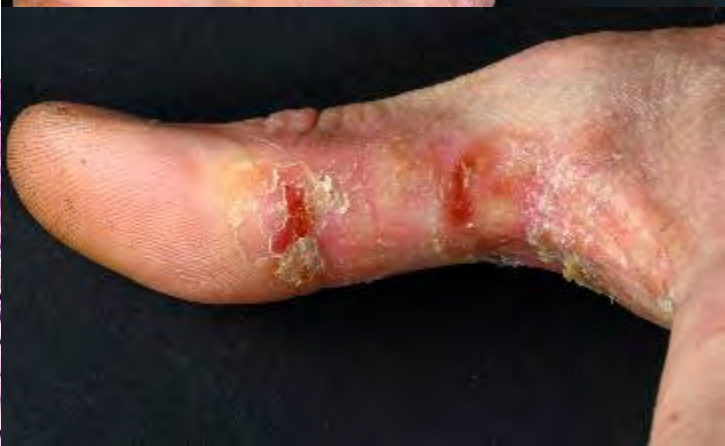




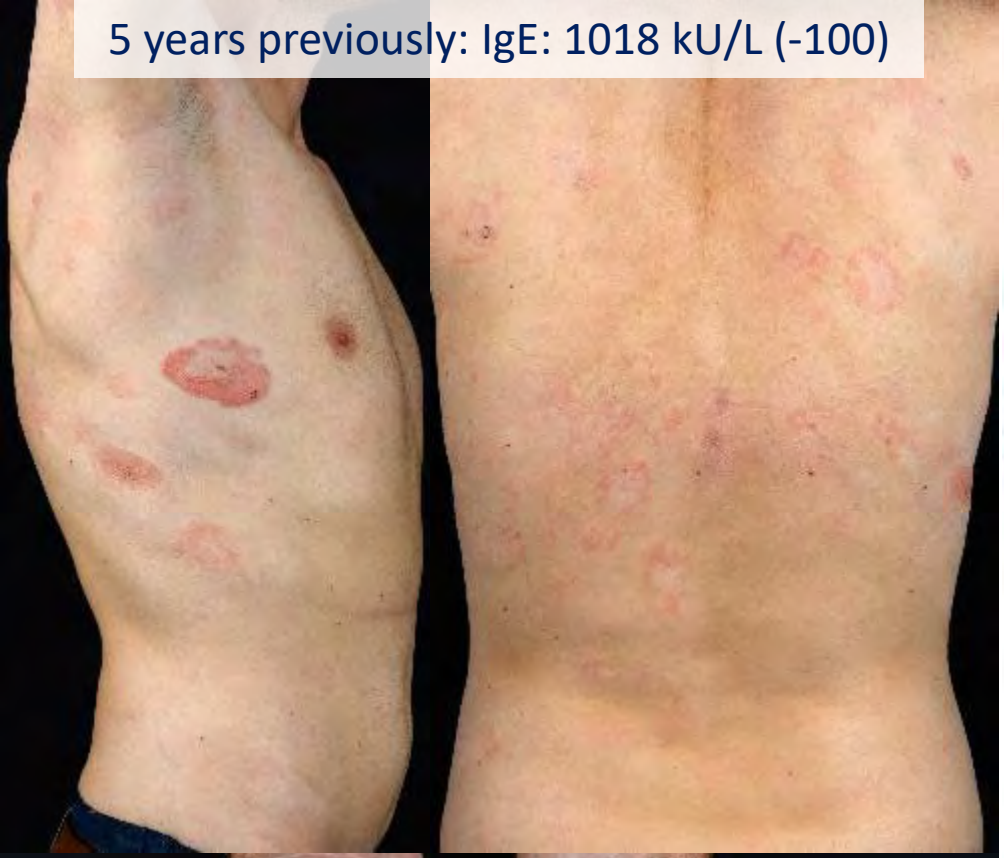
New biopsy #3

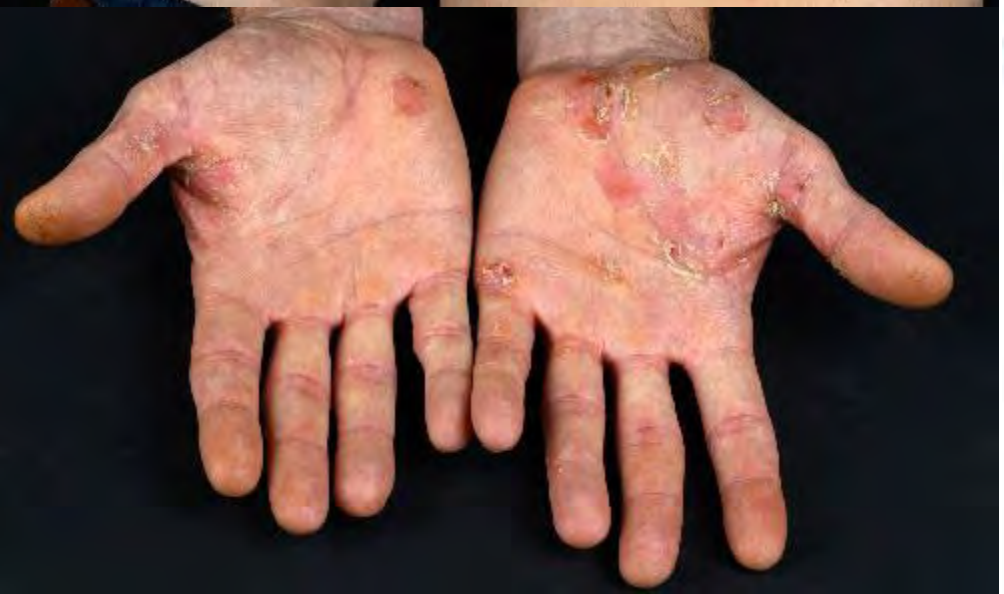


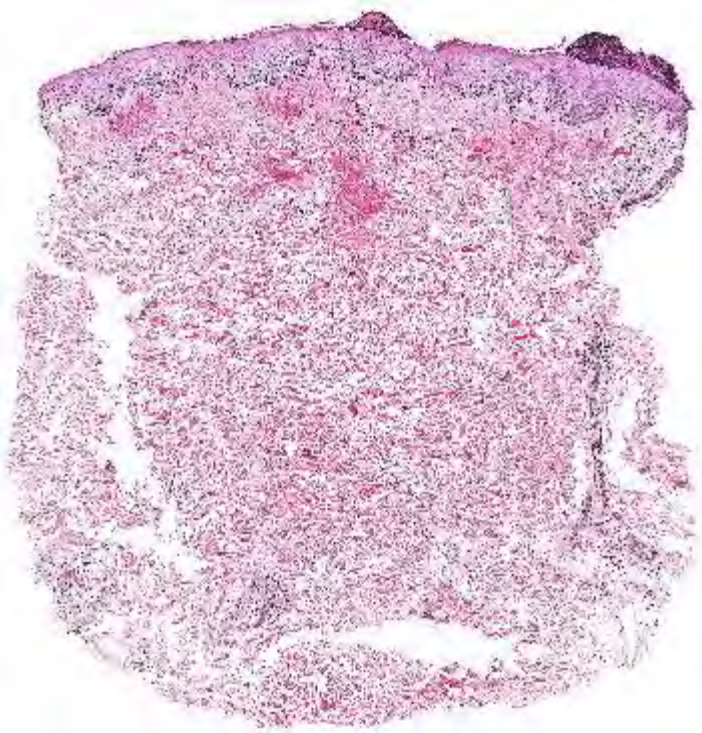


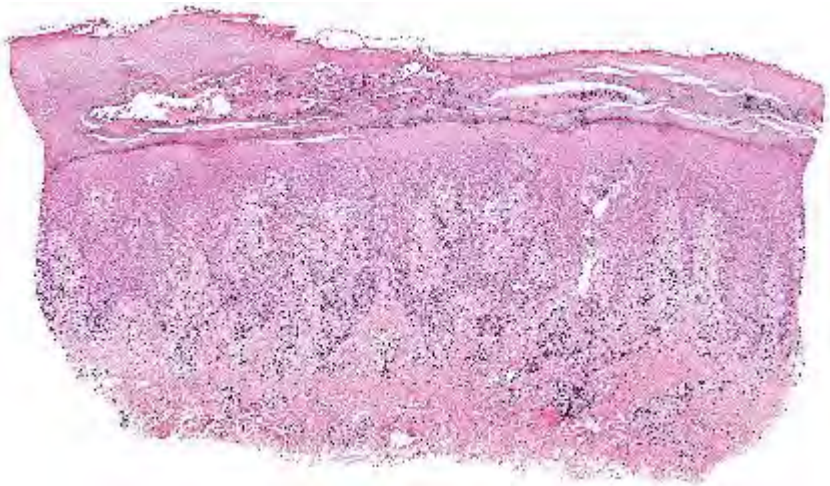


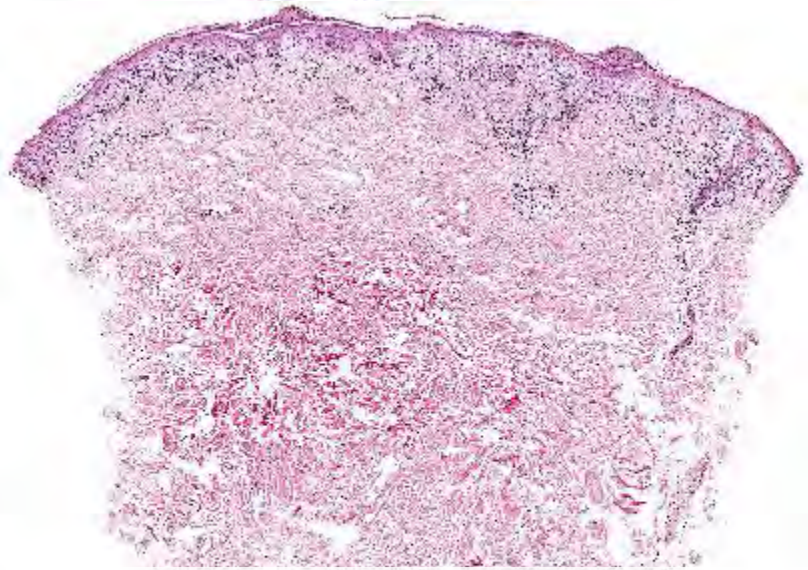
5 years previously: IgE: 1018 kU/L (-100)

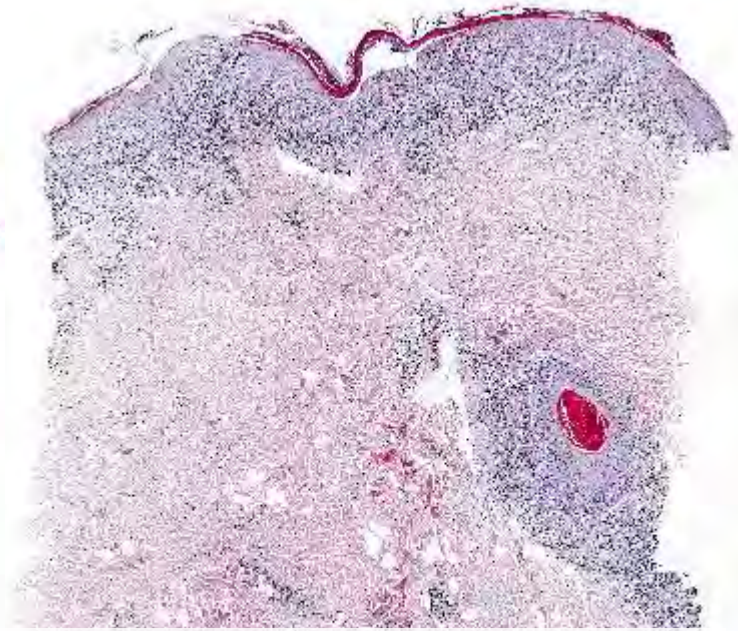




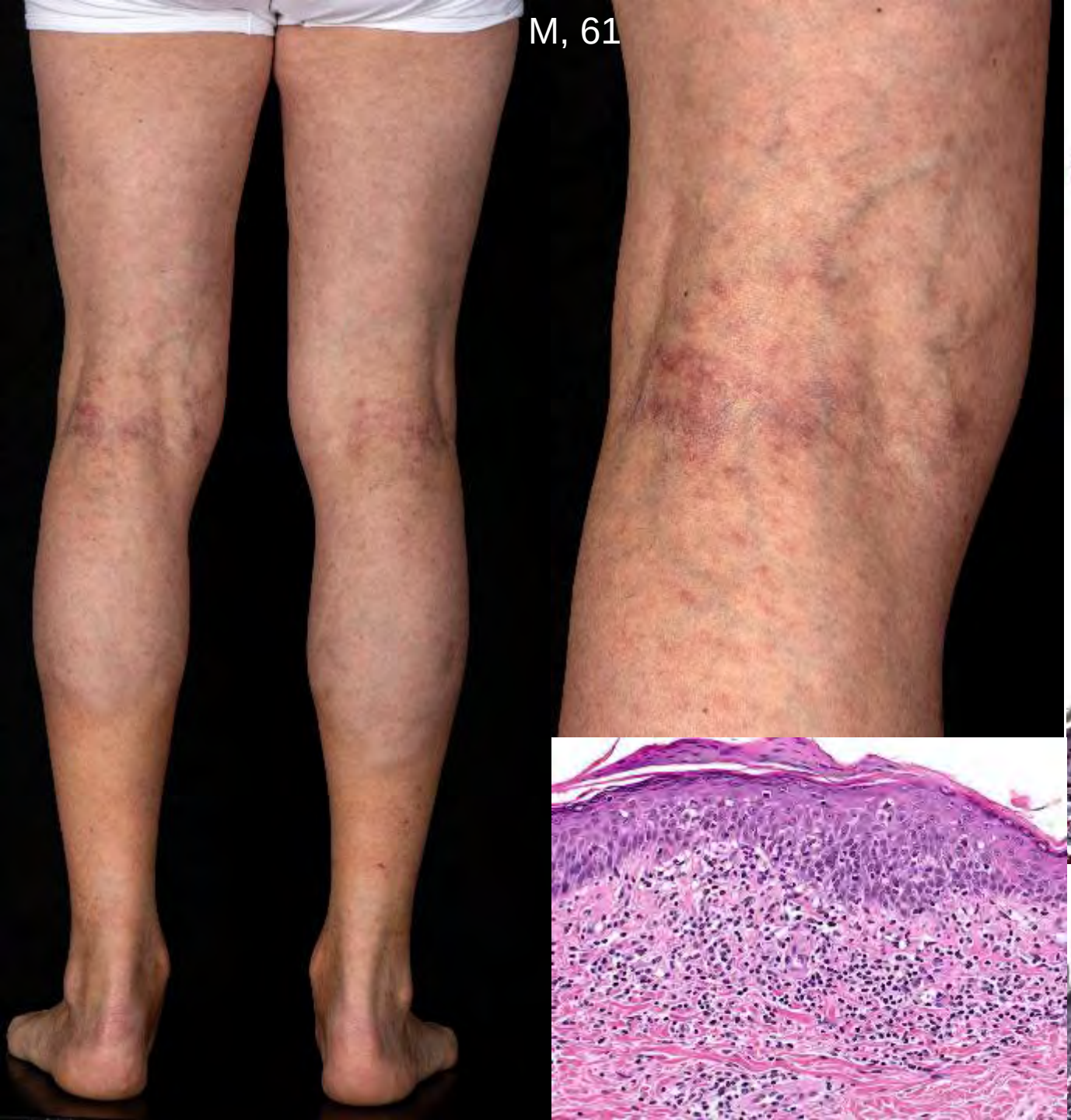


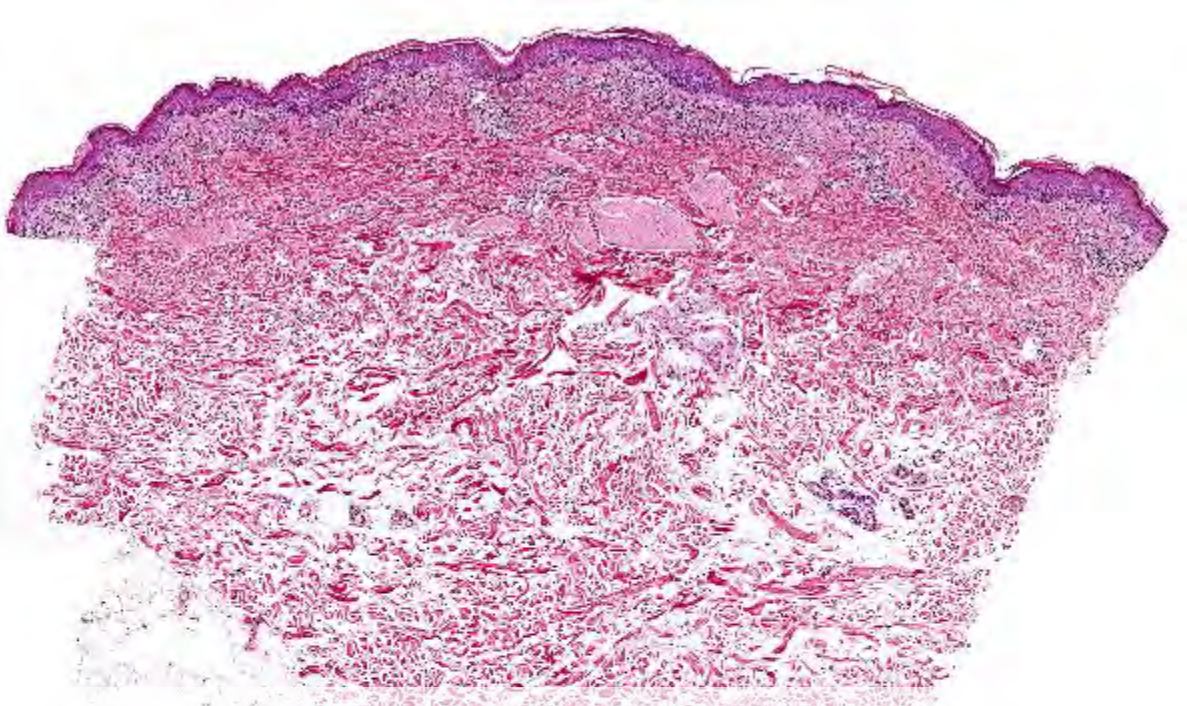




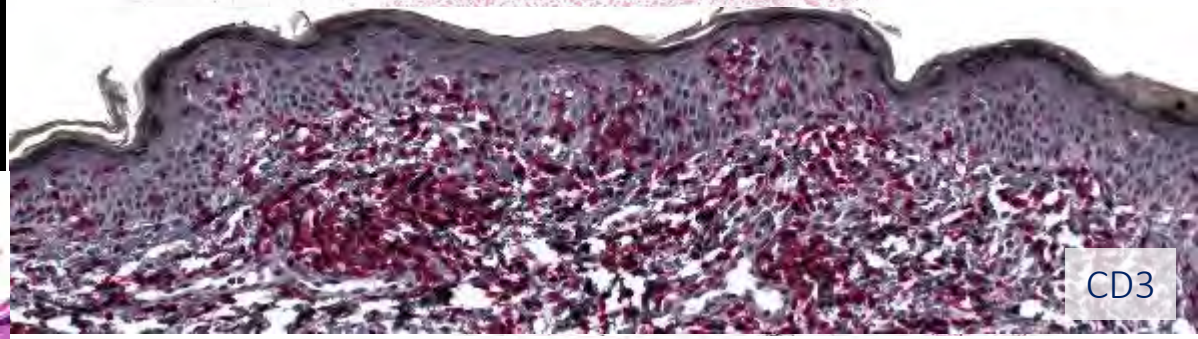


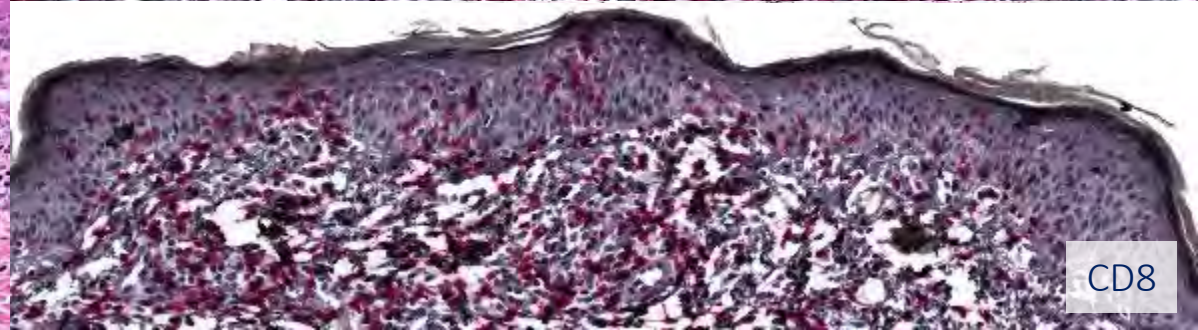
"Lymphomatoid" atopic dermatitis





Lymphomatoid eczematous dermatitis





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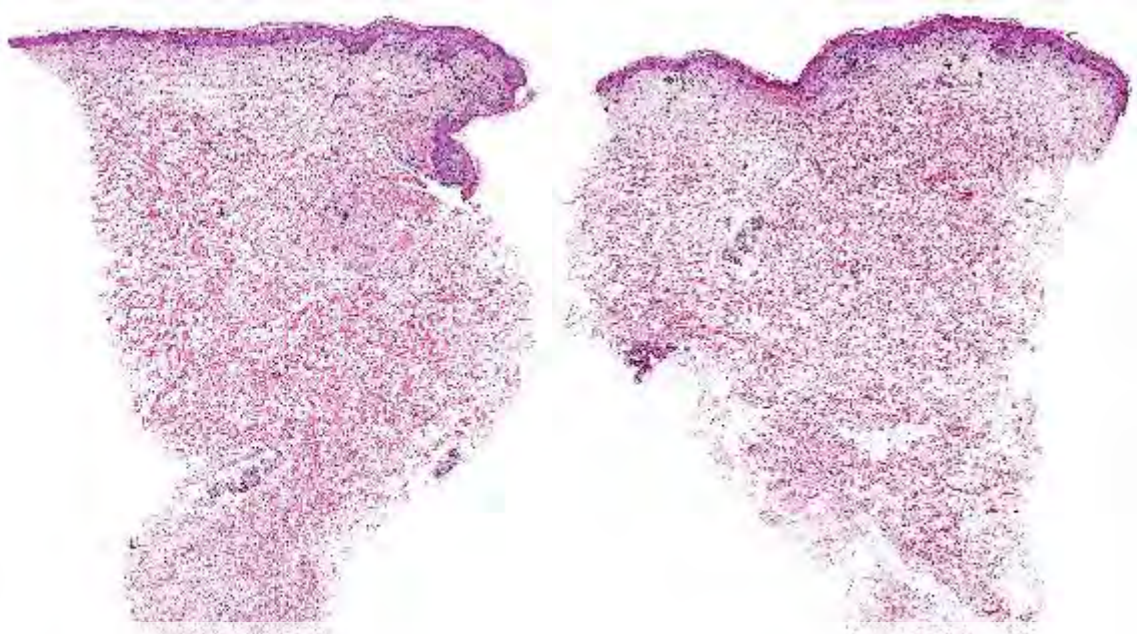
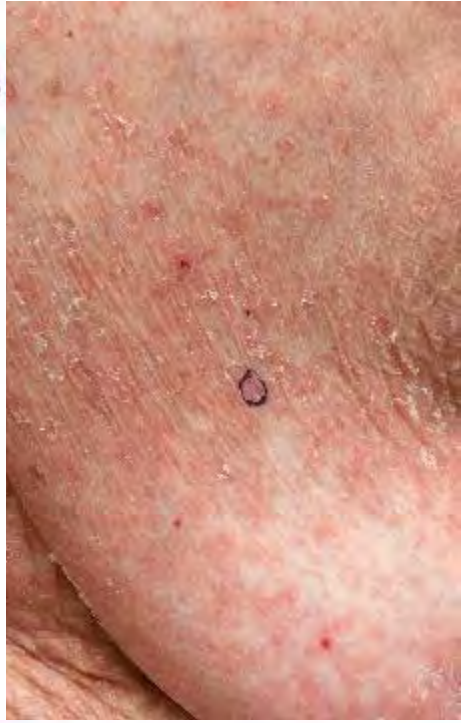
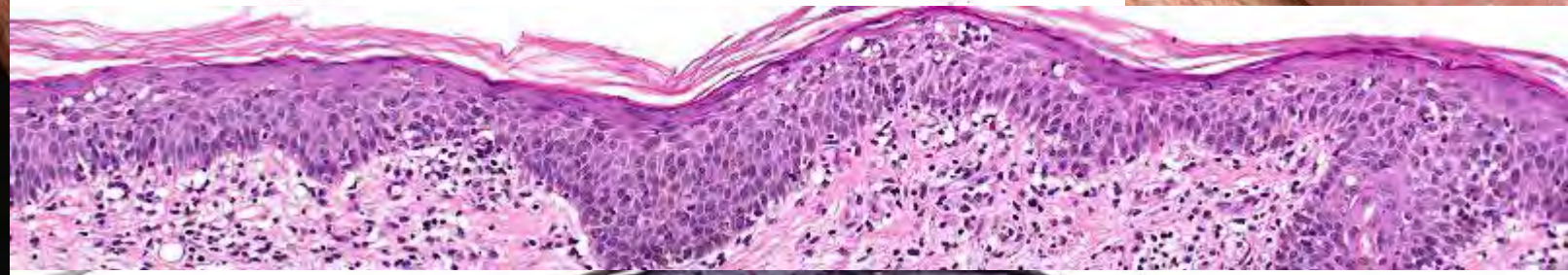
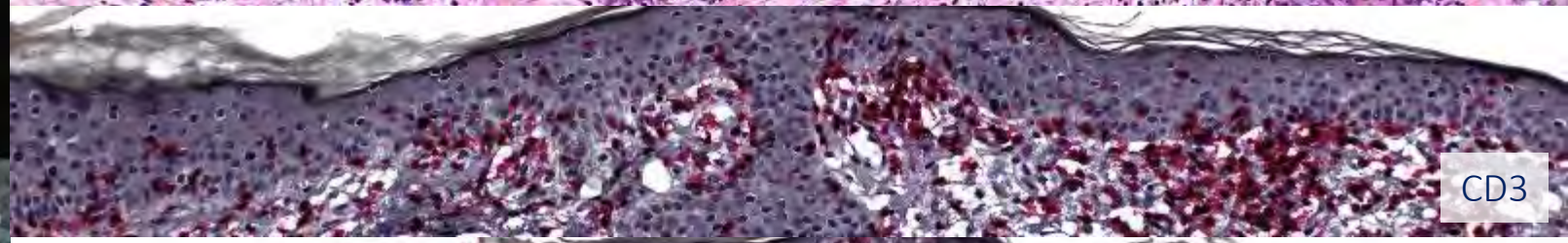




Lymphomatoid eczematous dermatitis





Contact Dermatitis 1976: 2: 139–143

Lymphomatoid contact dermatitis

A syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides

J. Gómez Orbaneja, L. Iglesias Diez, J. L. Sánchez Lozano and L. Conde Salazar

Hospital Clinico de San Carlos, Facultad de Medicina, Madrid 3, Spain

Four cases have been studied which were clinically suggestive of mycosis fungoides because of their infiltrated plaque-like lesions, but in which the suspicion of a topical hypersensitivity arose when a positive patch test was obtained with the striker part of a box of matches.

Key words: contact dermatitis – mycosis fungoides.

Received for publication October 30, 1975

We have had occasion to observe several cases which could be interpreted clinically, from the morphological character and persistence of the lesions, as a form of xanthoerythrodermia perstans or parapsoriasis-en-plaques; with their complaint of intense pruritus they were reminiscent of mycosis fungoides. Several cases were histologically diagnosed as such. We consider it important to report these cases because they are caused by a hypersensitivity reaction.

Case histories

Case 1. A 54-year-old male had noticed a dry, pruritic erythematous plaque about the size of the palm of his hand on his right thigh about four months earlier. The plaque grew progressively in area and in depth. Some time later, a similar lesion appeared on his left thigh. The first lesion appeared in August 1973. During the ensuing months, there arose multiple erythematous, oedematous, ill-defined lesions all over the face, retroauricular areas and the sides of the neck. Their course was one of remissions and exacerbations. Topical treatment with corticosteroids did not produce any improvement. Later, he developed another lesion on the left pectoral area. Examination showed on both thighs two plaque-like lesions, about 10 cm wide, which were erythematous, scaly, intensely infiltrated and with well-defined borders. Violaceous erythematous, scaly infiltrated plaques were also found on the face, behind the ears and on the neck. There was another plaque, the size of the palm of a hand, on the left pectoral region; it had the same features as the others. Multiple biopsies were obtained which showed a dense infiltrate, band-like with histiocytes, lymphocytes and some eosinophils. There was lymphocytic exocytosis, sometimes forming nests and in some areas, limited spongiosis. The histologic picture and its clinical counterpart were like that of infiltrated mycosis fungoides.

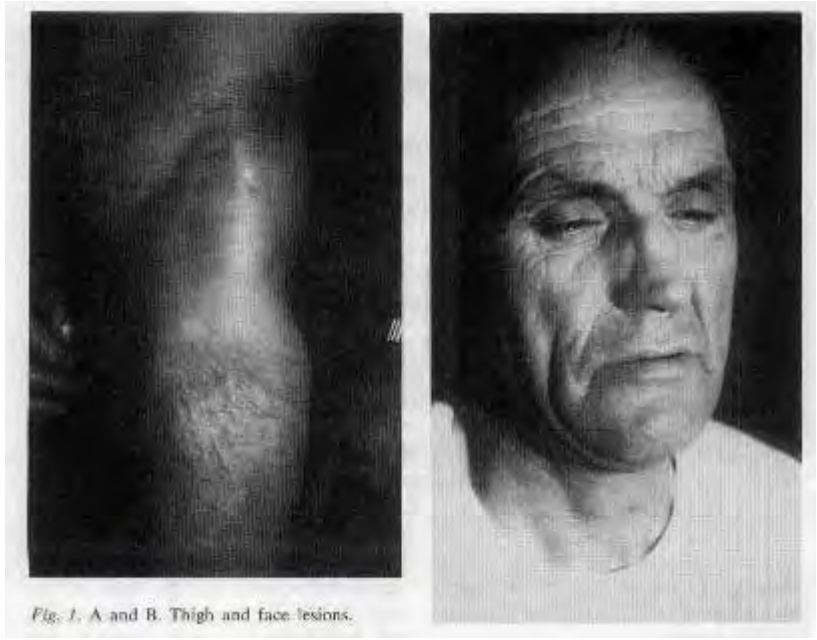


Fig. 1. A and B. Thigh and face lesions.

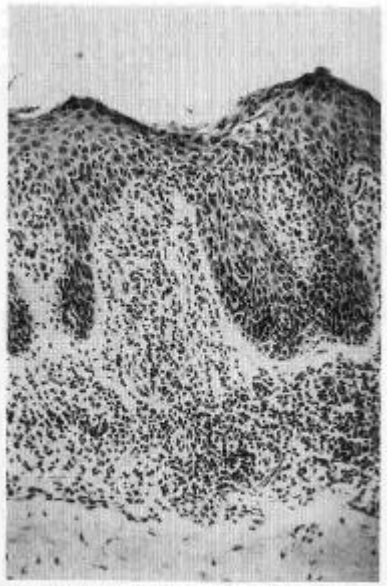


Fig. 2. Acantholytic epidermis. In the dermis there is a dense infiltrate in the form of a superficial band.

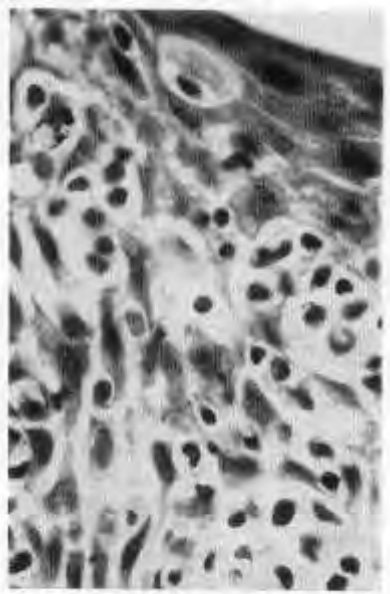


Fig. 3. Lymphocytic exocytosis sometimes forming nests, and limited spongiosis.

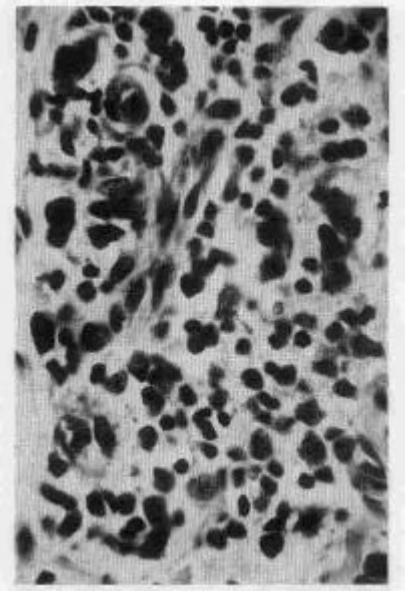
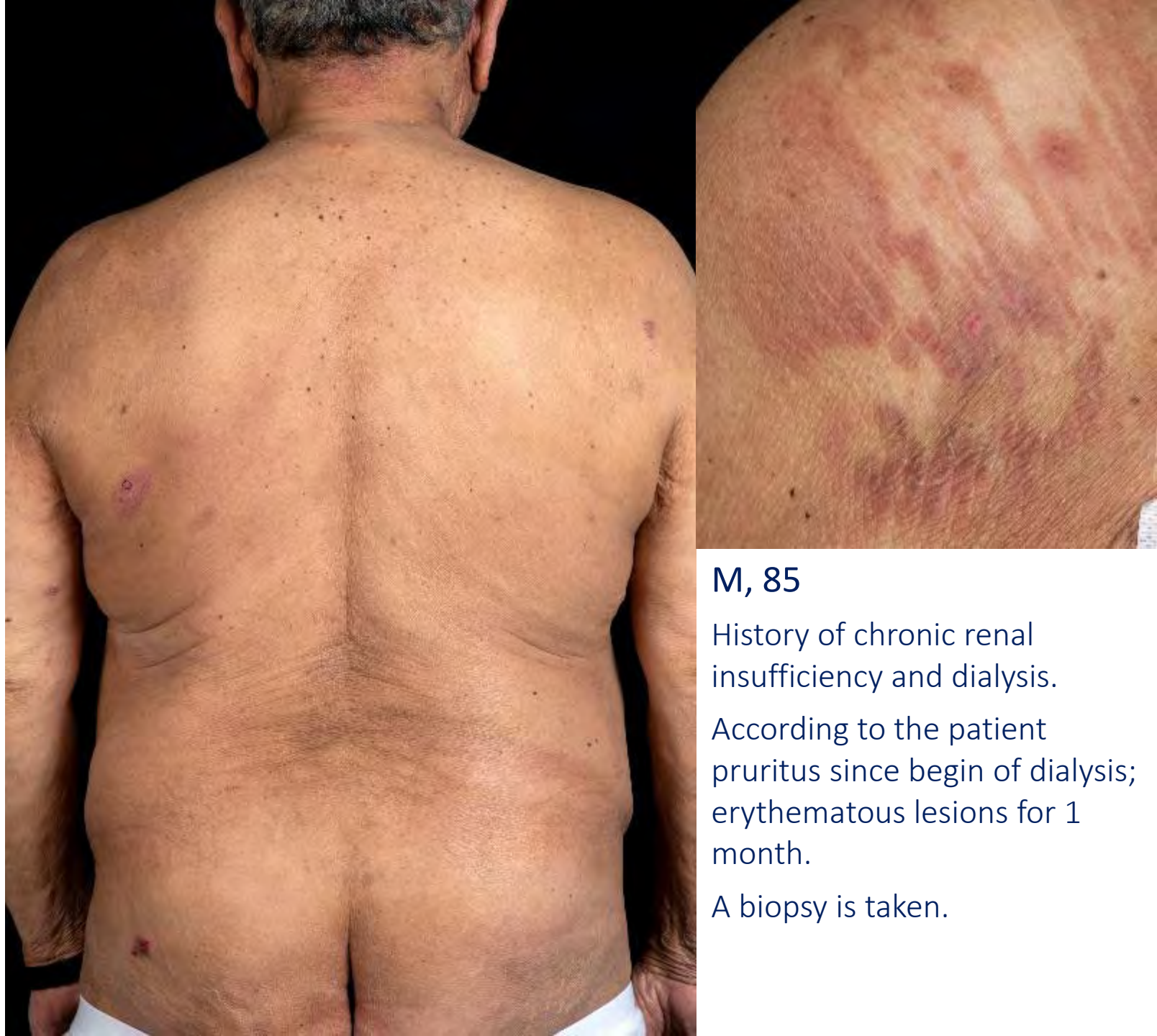


Fig. 4. Dense infiltrate of histiocytes and lymphocytes, some of which are hyperchromatic.

In my experience not restricted to contact dermatitis; may be observed in any "eczematous" dermatitis, including atopic dermatitis, xerosis cutis, and lichen simplex chronicus among others.

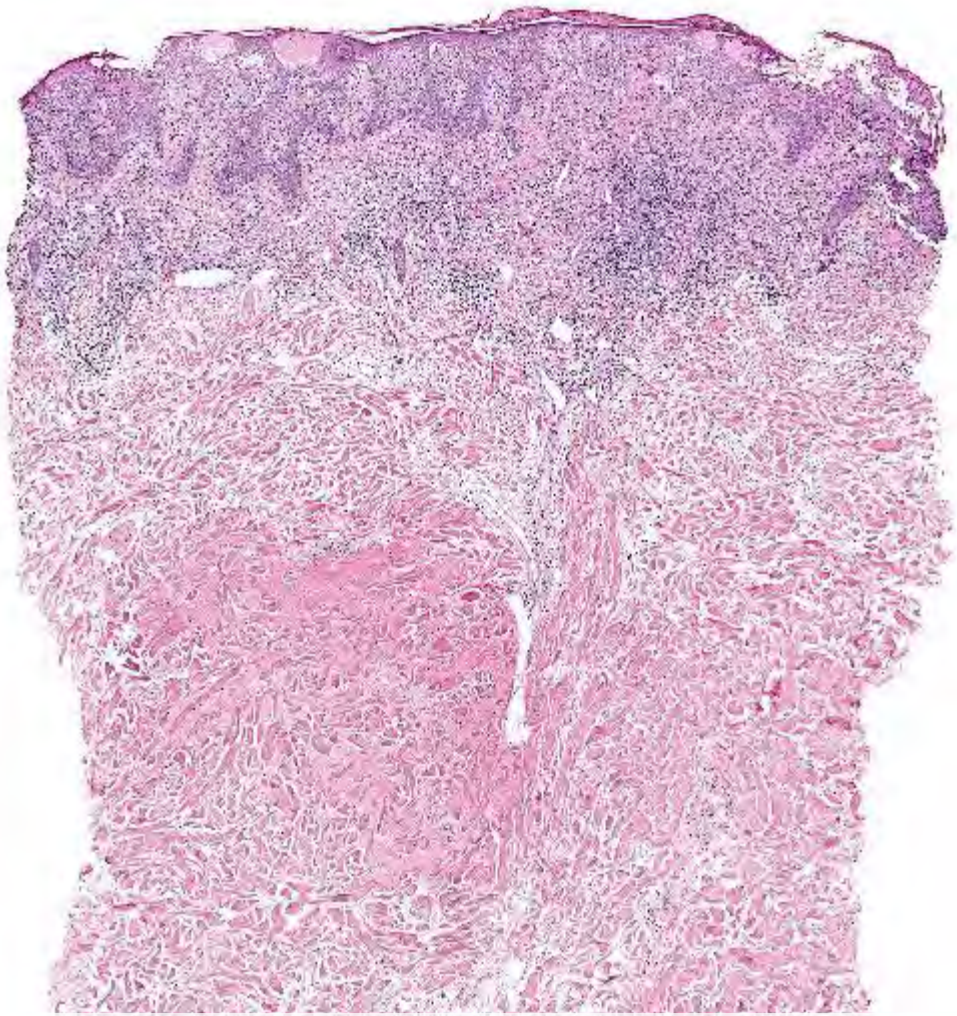


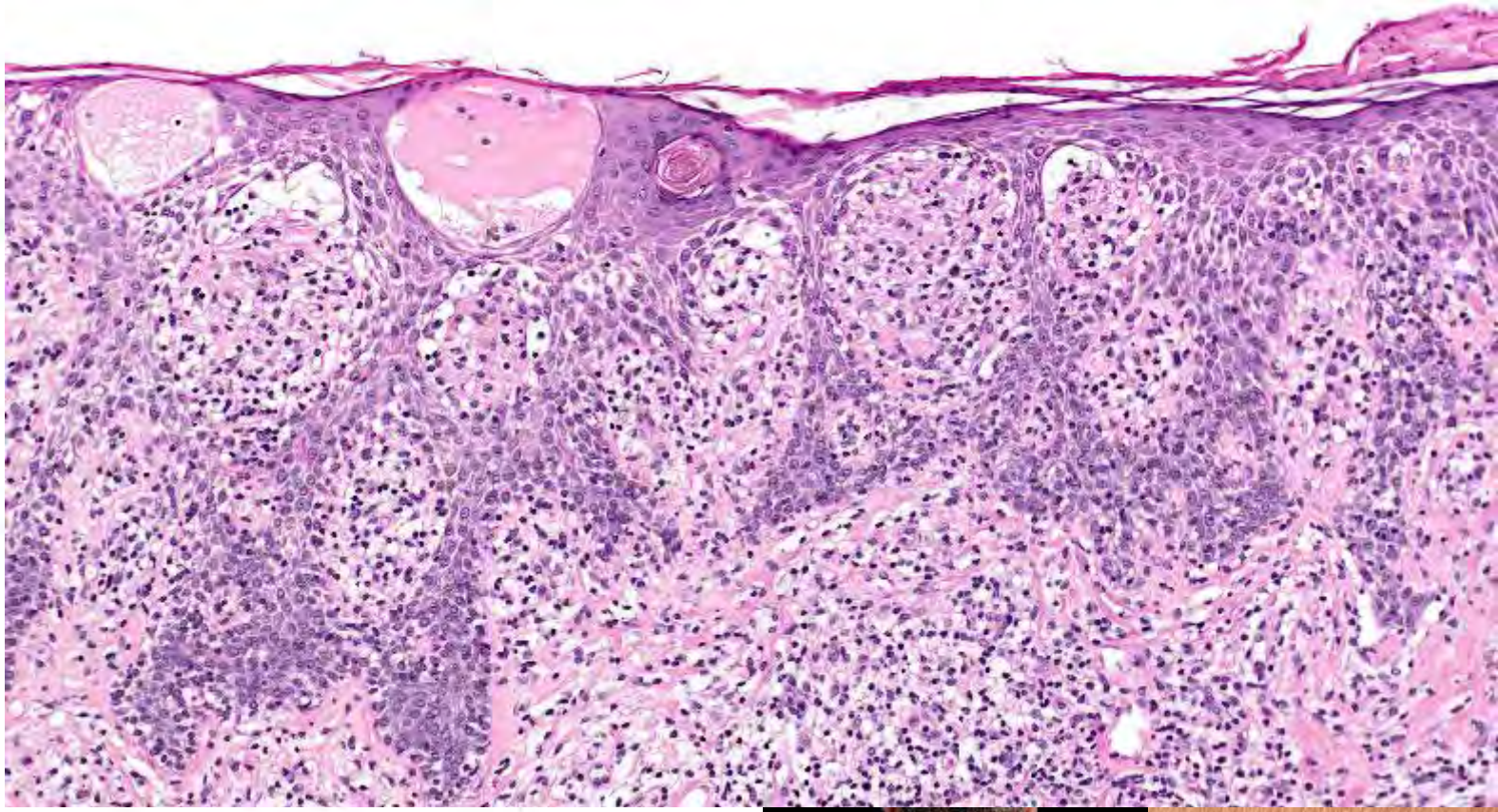
M, 85

History of chronic renal insufficiency and dialysis.

According to the patient pruritus since begin of dialysis; erythematous lesions for 1 month.

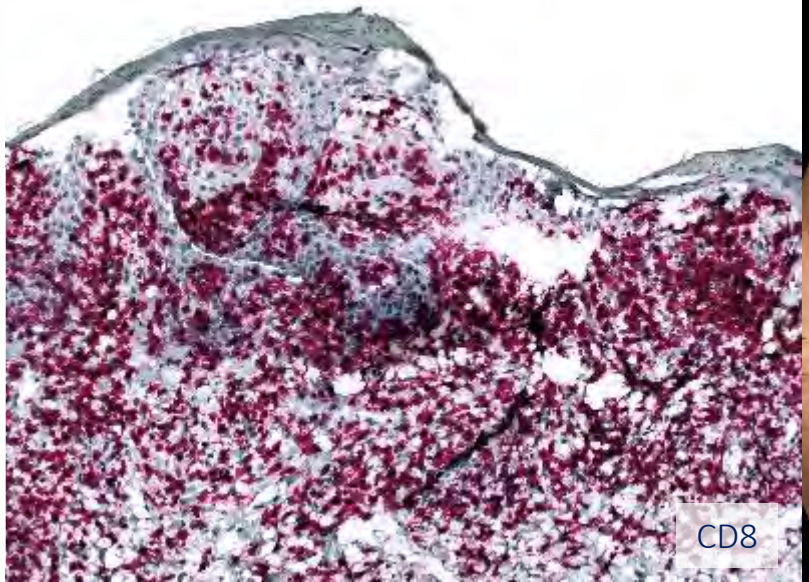
A biopsy is taken.

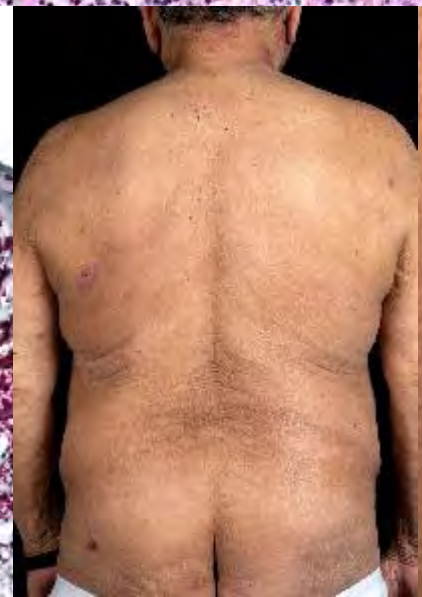


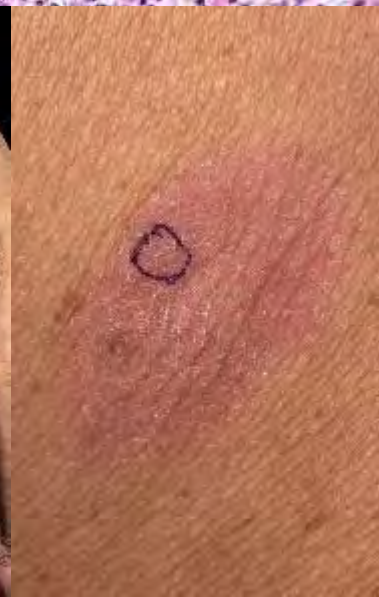


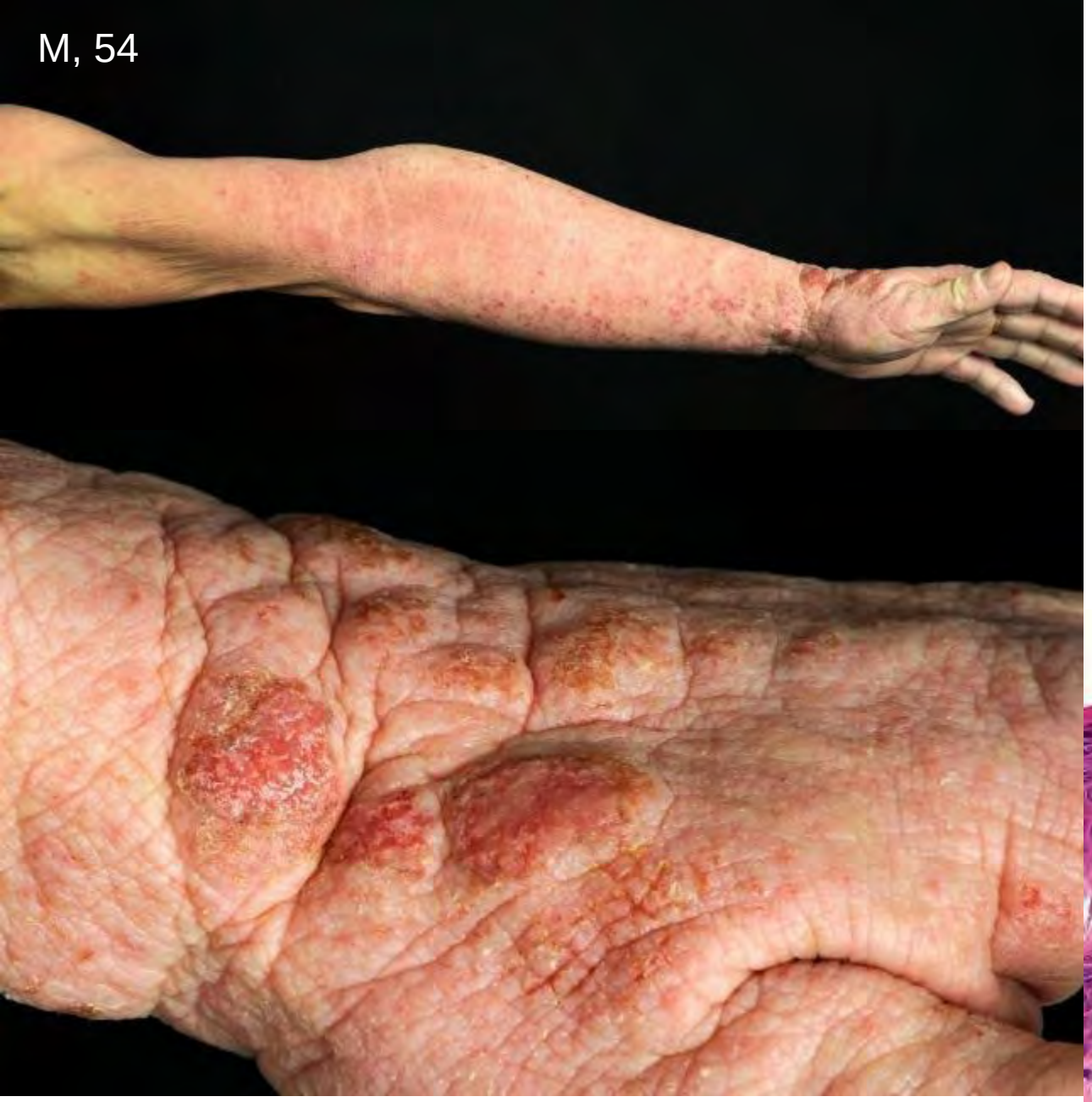
Eczematous dermatitis in dialysis

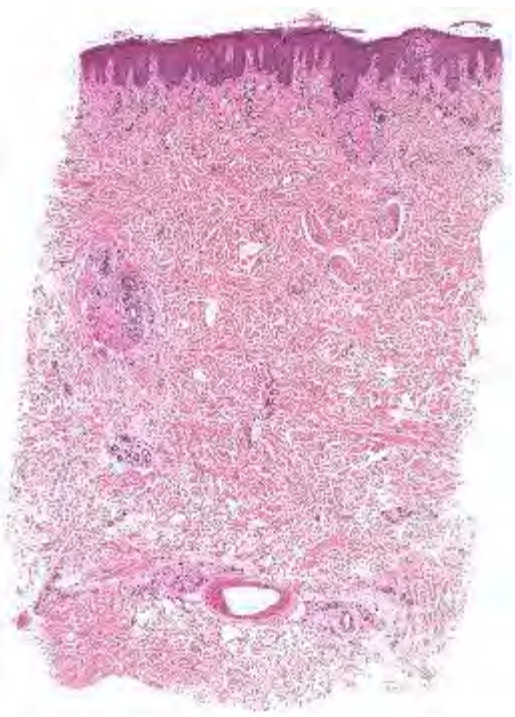
(pseudolymphomatous)

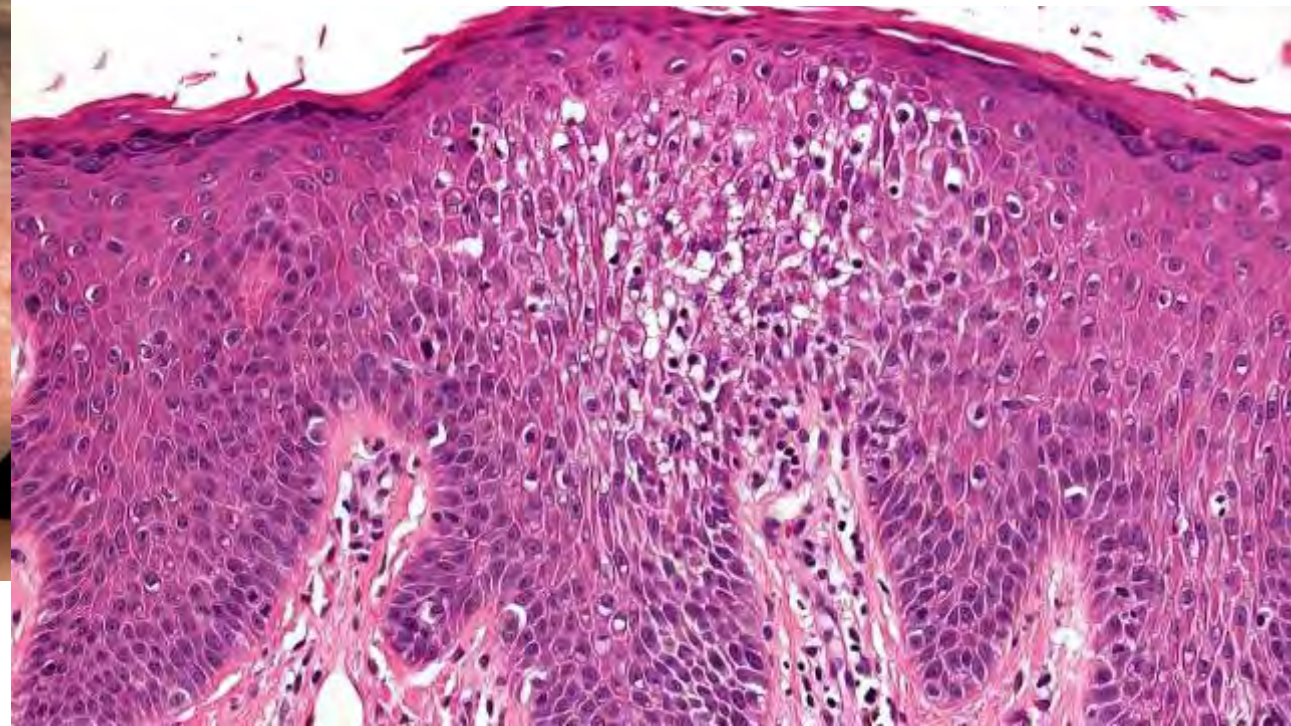




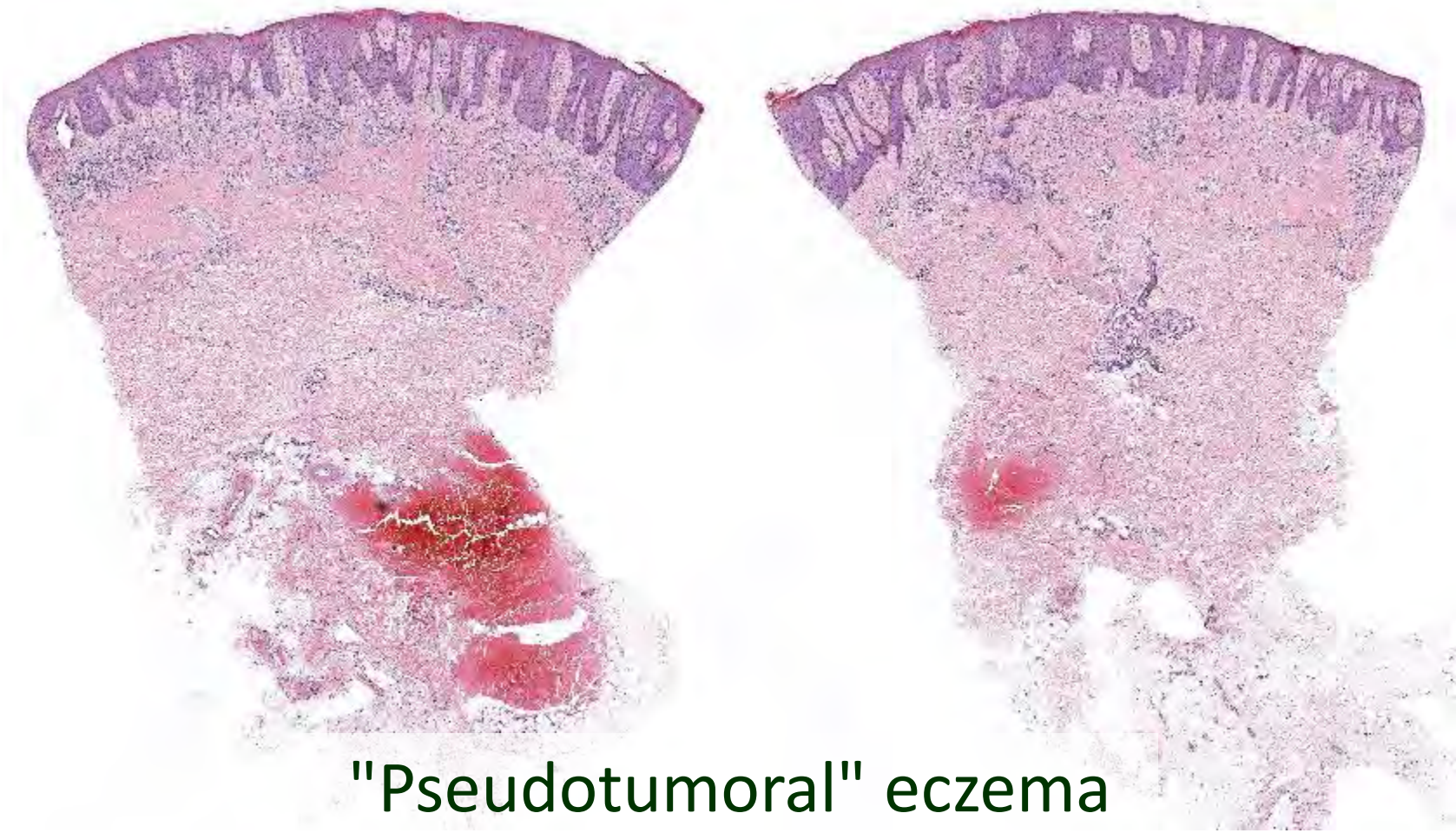








"Pseudotumors" in atopic dermatitis

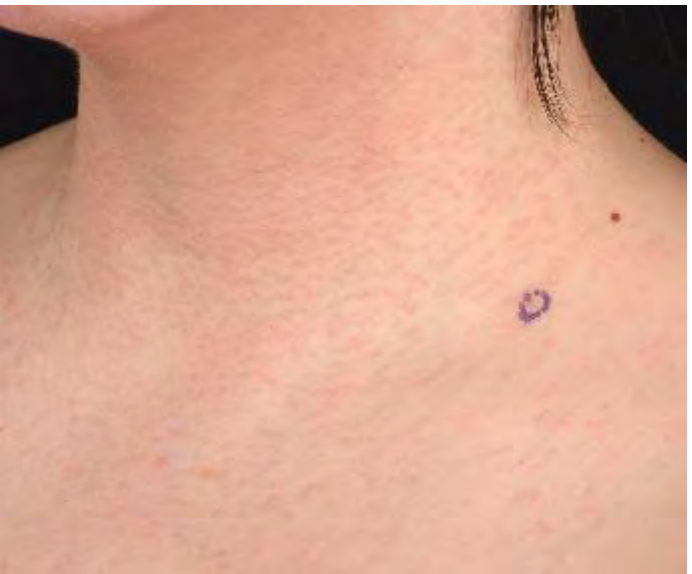


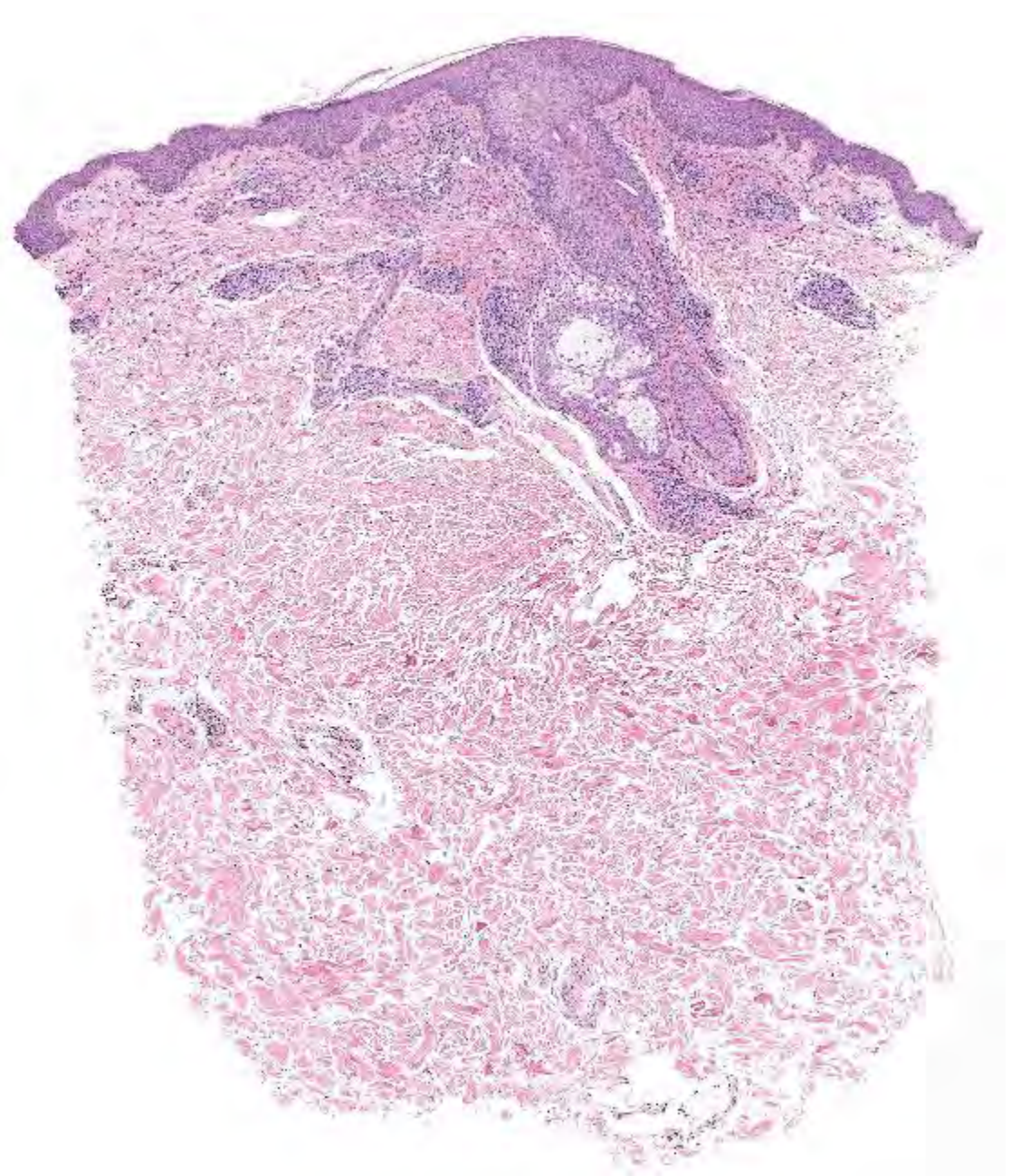
"Pseudotumoral" eczema

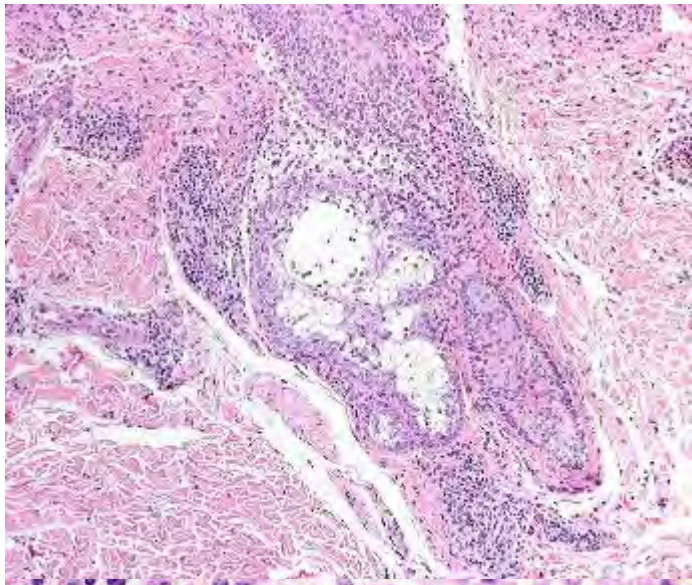
Lesions in chronic eczematous dermatitis may show prominent epithelial hyperplasia and present clinically as "tumors" (e.g., facies leonina in actinic reticuloid).
"Pseudotumors" are due to prominent lichenification, pseudoepitheliomatous epidermal hyperplasia, and/or fibrosis due to repeated excoriation.
The inflammatory infiltrate may be dense and cause problems in the differential diagnosis with cutaneous T-cell lymphomas.

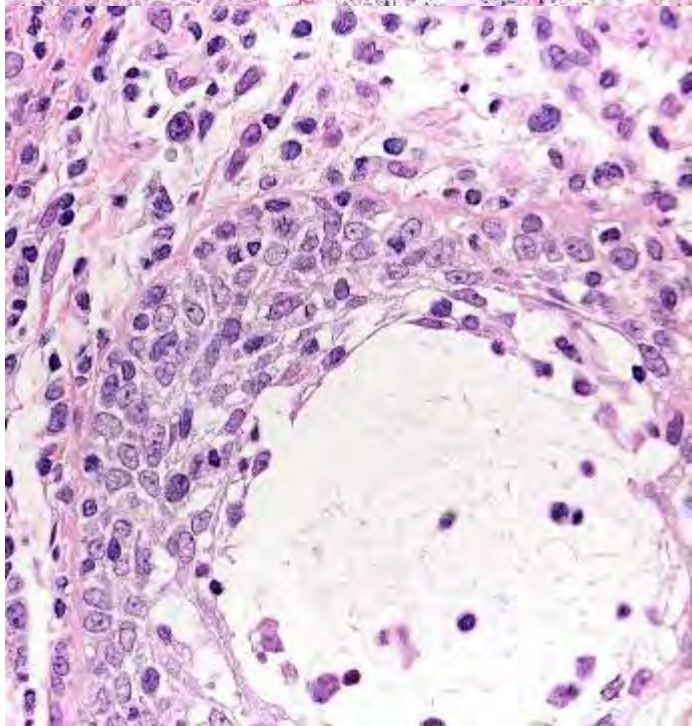
Eczematous (atopic) dermatitis with follicular mucinosis

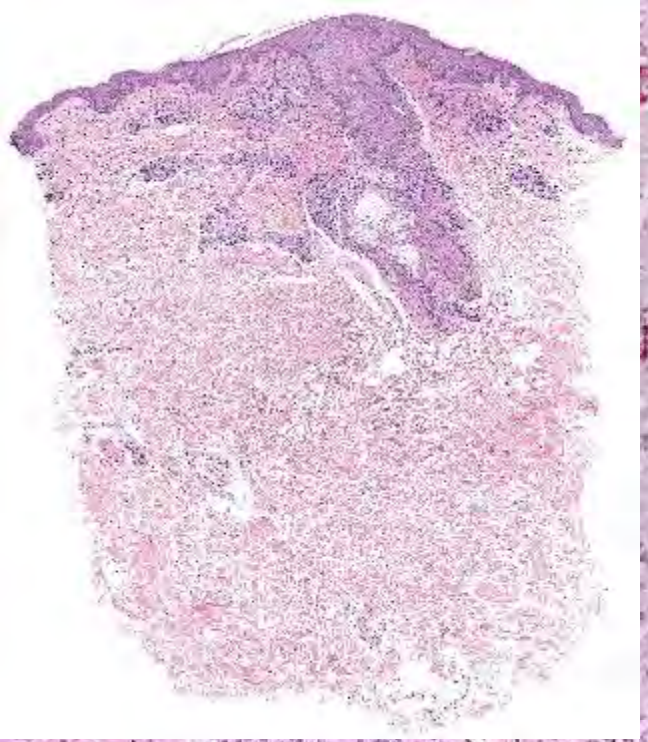
F, 25

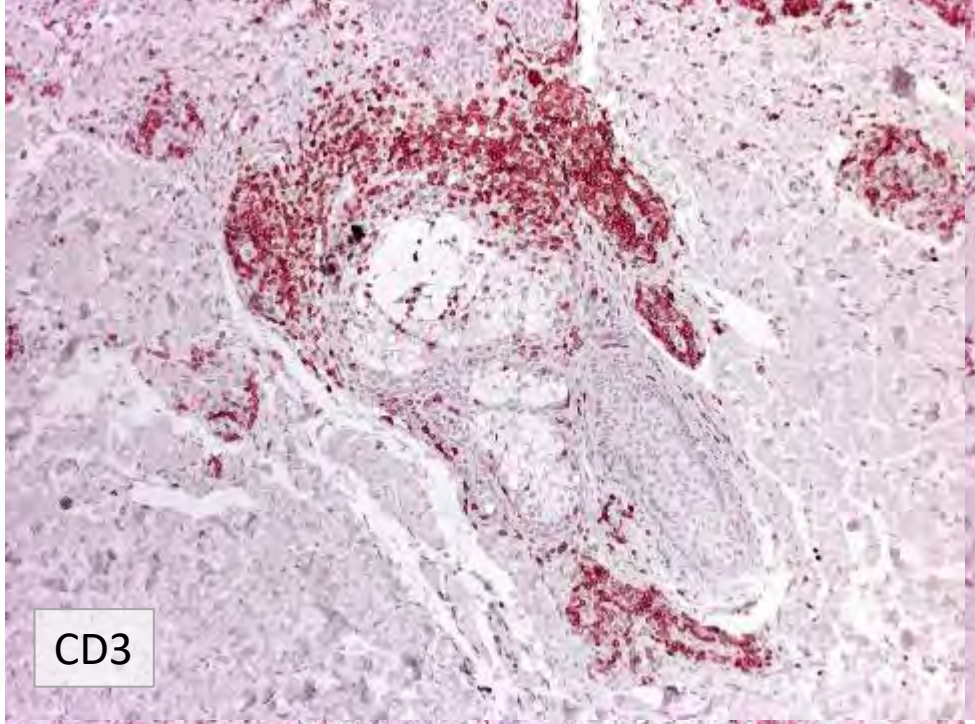








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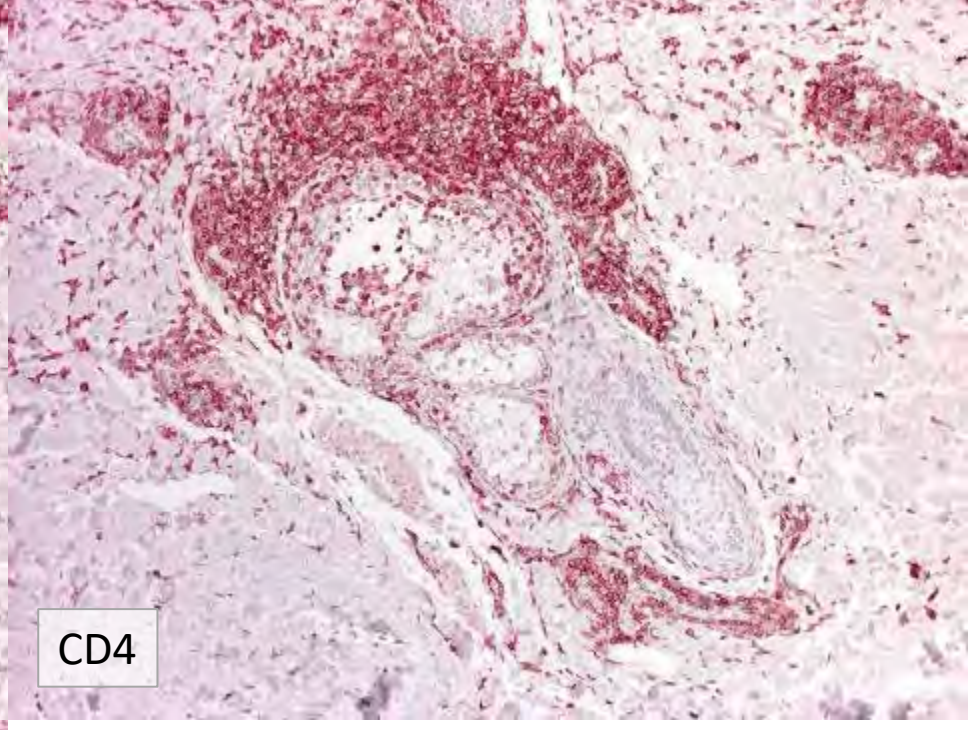
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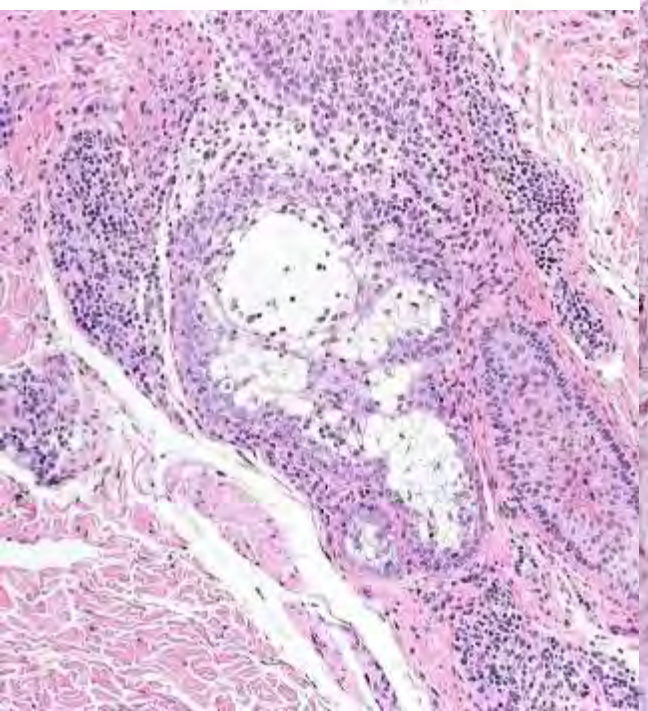
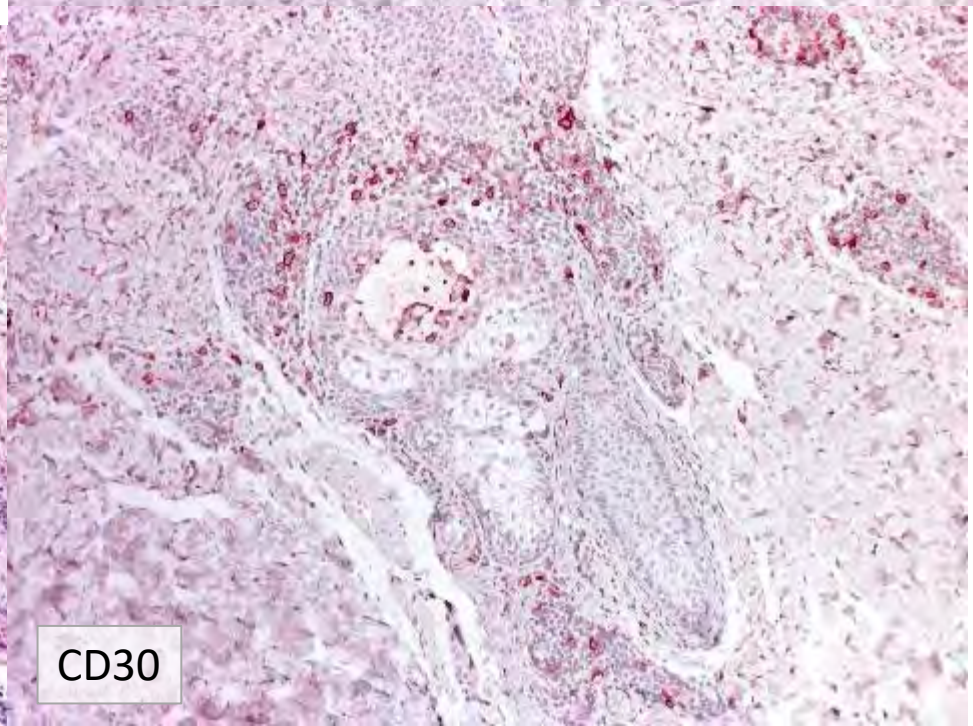



CD30

Follicular Mucinosis Associated With Nonlymphoid Skin Conditions

José M. Mir-Bonafé, MD, Javier Cañueto, MD,* Emilia Fernández-López, MD,* and Ángel Santos-Briz, MD†*

Background: Follicular mucinosis coexisting with lymphoproliferative disorders has been thoroughly debated. However, it has been rarely reported in association with inflammatory disorders.

Methods: Thirteen cases have been retrieved, and those with cutaneous lymphoma or alopecia mucinosa were excluded.

Results: Follicular mucinosis was found in the setting of squamous cell carcinoma, seborrheic keratosis, simple prurigo, acne vulgaris, dextromethorphan-induced phototoxicity, polymorphous light eruption (2 cases), insect bite (2 cases), tick bite, discoid lupus erythematosus, drug-related vasculitis, and demodecidosis. Unexpectedly, our observations revealed a preponderating accumulation of mucin related to photo-exposed areas, sun-associated dermatoses, and histopathologic solar elastosis. The amount of mucin filling the follicles apparently correlated with the intensity of perifollicular inflammatory infiltrate, which was present in all cases. The concurrence of dermal interstitial mucin was found in 7 cases (54%).

Conclusions: The concurrence of interstitial dermal mucinosis or the potential role of both ultraviolet radiation and the perifollicular inflammatory infiltrates in its pathogenesis deserves further investigations. Precise recognition and understanding of this distinctive, reactive histological pattern may prevent our patients from unnecessary diagnostic and therapeutic strategies.

Key Words: follicular mucinosis, mucin, hair follicle, alopecia mucinosa, ultraviolet radiation, bone marrow transplantation

Am J Dermatopathol 2014;36:705–709)

INTRODUCTION

Follicular mucinosis (FM) refers to a reactive histopathological finding characterized by the deposition of mucin within the hair follicle and/or the sebaceous gland epithelium.[1] It was first observed in the setting of alopecia mucinosa (AM) in 1957 by Pinkus[2] in patients, which combined this microscopic finding with clinical alopecia. Since then, many authors have used both terms "AM" and "FM" indistinctively, with the resultant terminological confusion. However, in addition to AM, FM has also been described related to mycosis fungoides, folliculotropic mycosis fungoides, hematologic malignancies, and inflammatory skin conditions. Consequently, FM is currently regarded as a tissue-reaction pattern and not a condition per se or a pathognomonic finding for any disease.

The aim of this study was to add further associations and to highlight that FM may be a reactive histological pattern to a wide range of disorders with a benign outcome. Because terminology from the literature has been confusing, the appropriate understanding and recognition of this incidental finding may prevent patients from unnecessary and sometimes aggressive diagnostic and therapeutic procedures.

PATIENTS AND METHODS

All cases with histopathological findings of FM were retrospectively retrieved from January 2009 to January 2012 from the files of the Department of Dermatology, University Hospital of Salamanca, Spain. The inclusion criteria was the histopathological evidence of FM, and the exclusion criteria were the presence of alopecia or the final diagnosis of AM or primary cutaneous lymphoproliferative disorder. Clinical data included age, sex, site, and relevant medical history. All specimens were stained with Hematoxylin and Eosin, colloidal iron, and periodic acid-Schiff (PAS). Histopathologically, the following parameters were semiquantitatively graded from 1+ to 3+: (1) amount of mucin filling the follicles, (2) amount of mucin within interstitial tissue, (3) intensity of perifollicular inflammatory infiltrate, and (4) presence of solar elastosis. Finally, type of predominant inflammatory cells and other relevant histopathological findings were described. Respective treatments were noted, and all patients have been followed up to date.

RESULTS

Clinical Features

Thirteen patients (8 women and 5 men) were analyzed. FM was not previously suspected in any case. The median age of patients was 51 years (ranging from 22 to 80 years). Clinical associations included tick bite lesion (Fig. 1A), insect bite (2 patients), squamous cell carcinoma (Fig. 1B), seborrheic keratosis, dextromethorphan-induced phototoxicity (Fig. 1C), cutaneous chronic lupus erythematosus (Fig. 1D), prurigo simple, acne vulgaris, polymorphous light eruption (in 2 patients), vasculitis (Figs. 1E, F), and demodecidosis (Fig. 1G).

From the Departments of †Dermatology, and ‡Pathology, University Hospital of Salamanca, Salamanca, Spain.

The authors declare no conflicts of interest.

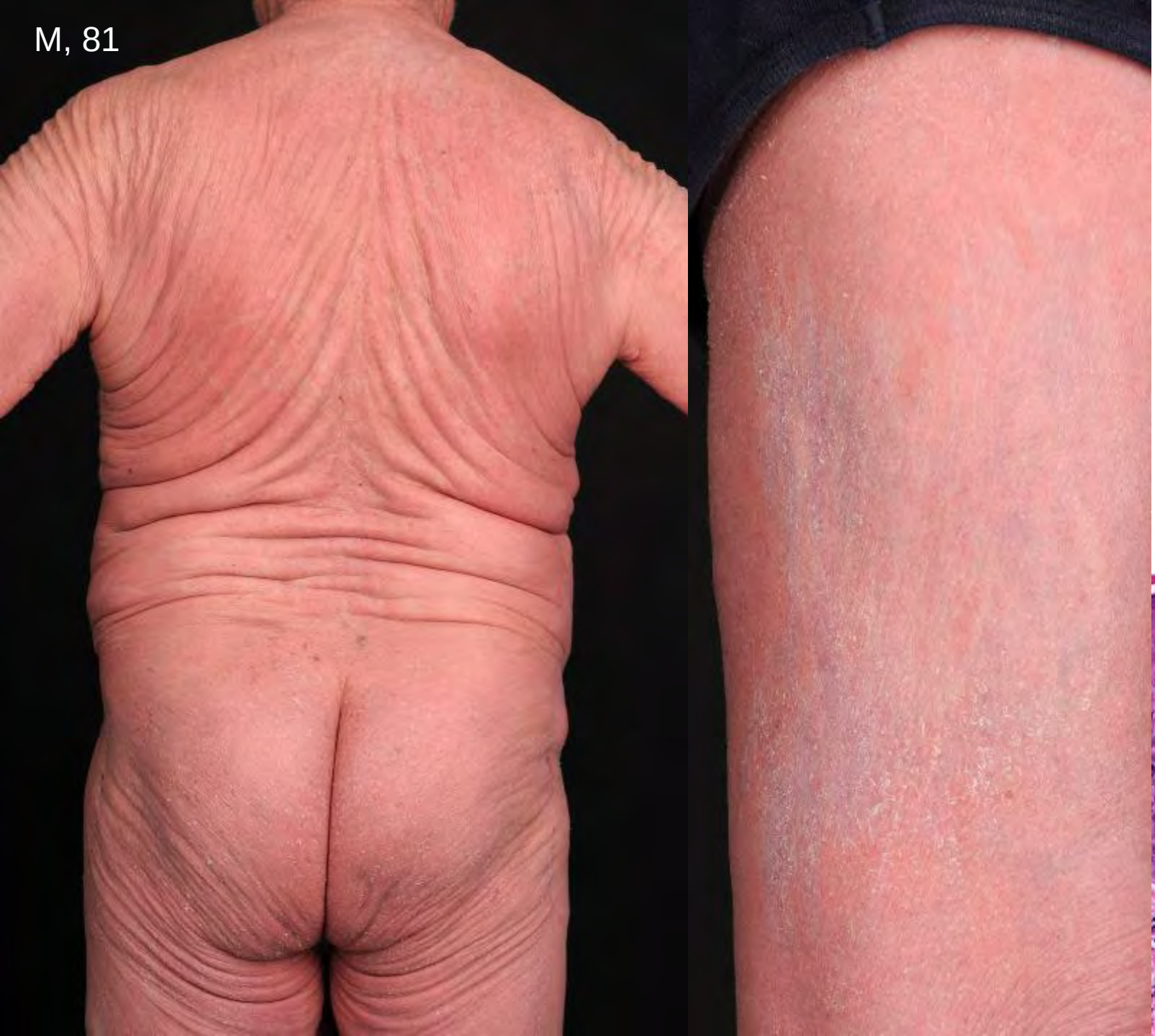
Reprints: José M. Mir-Bonafé, MD, Department of Dermatology, University Hospital of Salamanca, Paseo de San Vicente 58-182, 37007 Salamanca, Spain (e-mail: mirbonafe@gmail.com).

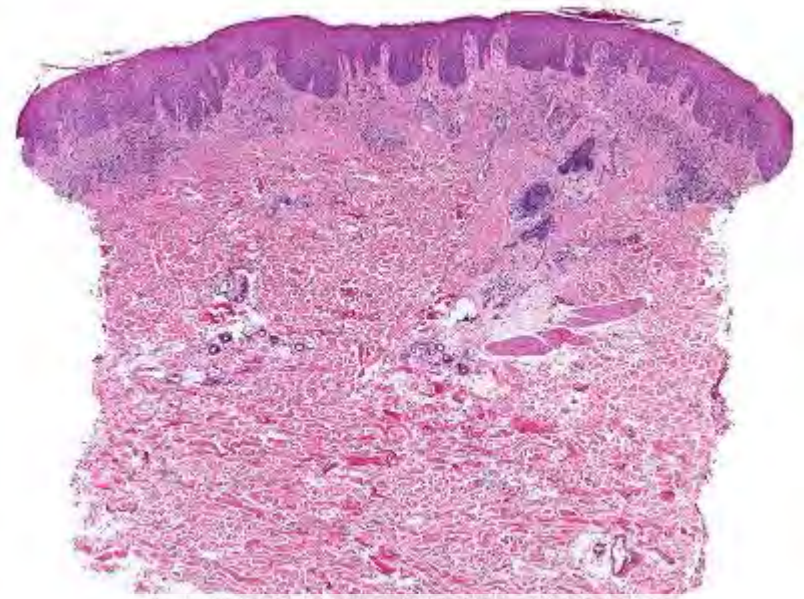
TABLE 1. Follicular Mucinosis Asociated With Nonlymphoid Disorders: Histopathological Findings of 13 Cases

Patient Number	Associated Dermatosis	Sex-Age, yr	Follicular Mucinosis (1+ to 3+)	Dermal Interstitial Mucinosis (1+ to 3+)	Perifollicular Inflammatory Infiltrate (1+ to 3+)	Dermal Elastosis (1+ to 3+)
1	Dextromethorphan	M-65	++	+	++	+++
2	SCC	M-80	+	No	++	+++
3	SK	F-39	+	No	+	+
4	DEL	M-43	+++	+++	++	+
5	Insect bite	M-73	++	No	+++	No
6	Insect bite	M-57	+	+	++	No
7	Tick	F-51	++	+	+++	No
8	Prurigo	F-43	+	+	++	+
9	Acne vulgaris	F-22	+	No	+	No
10	PLE	F-78	++	No	+++	+++
11	PLE	F-35	++	No	++	+
12	Post-BMT Vasculitis	F-66	(a) ++	+	++	+
			(b) No	No	++	No
13	Post-BMT demodecidosis	F-35	+++	++	++	No

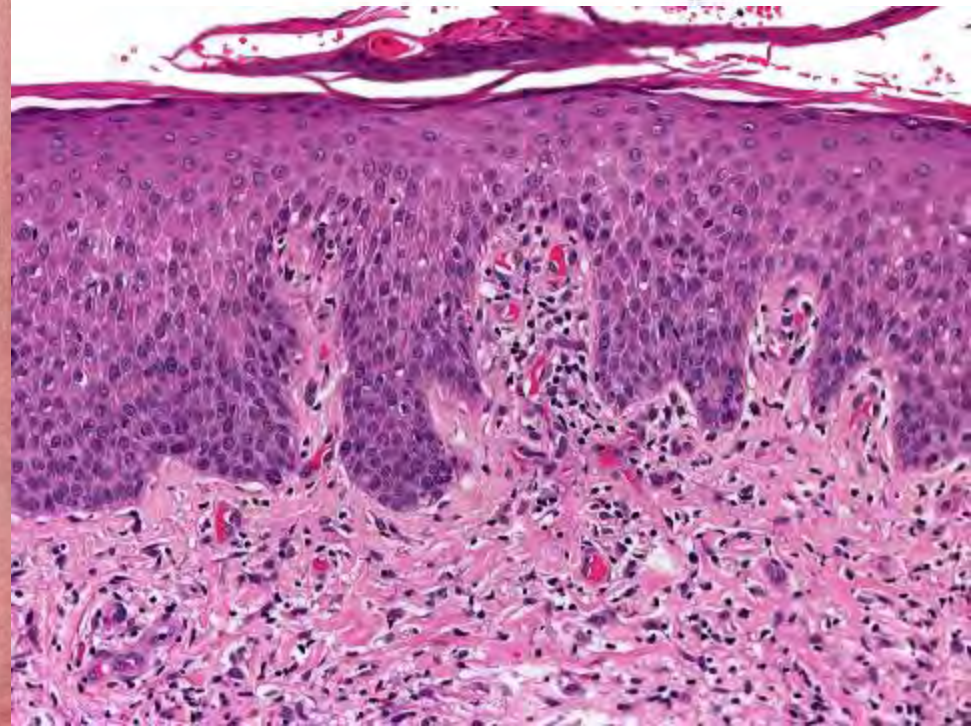
12 (a) indicates biopsy from the right retroauricular area; 12 (b) indicates biopsy from the pubis.
+, mild; ++, moderate; +++, intense; DEL, discoid lupus erythematosus; PLE, polymorphous light eruption; SCC, squamous cell carcinoma; SK, seborrheic keratosis.

M, 81

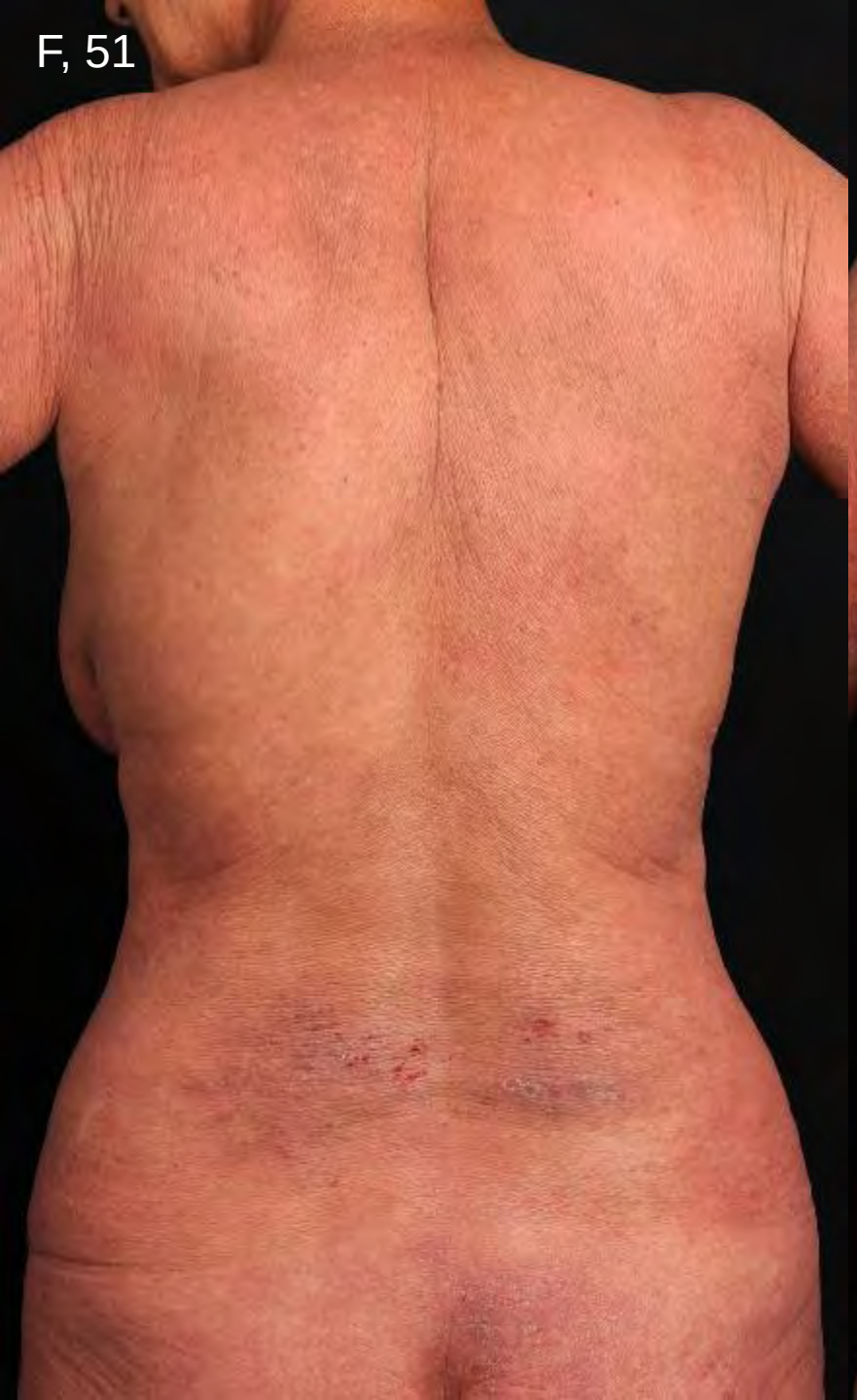


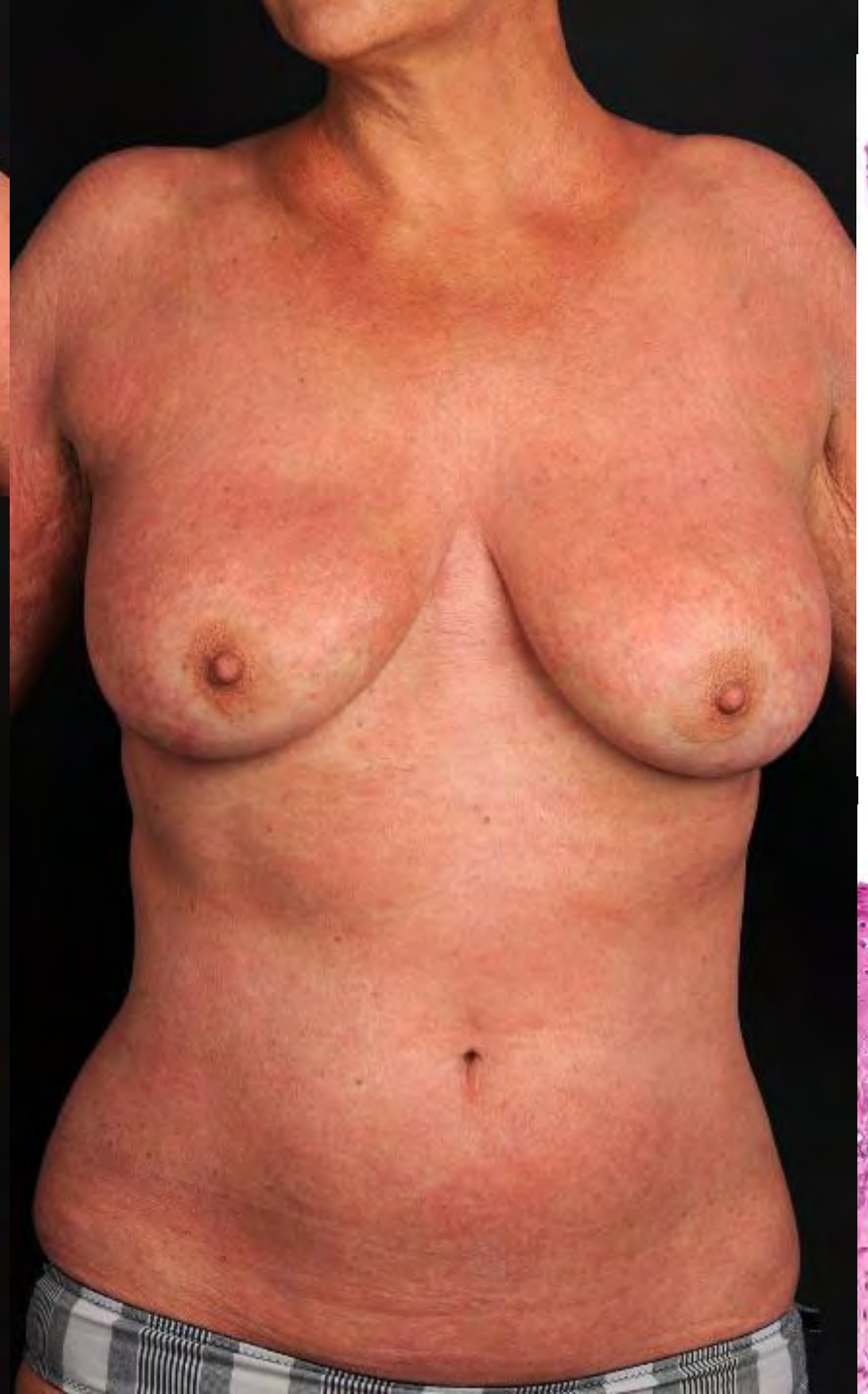


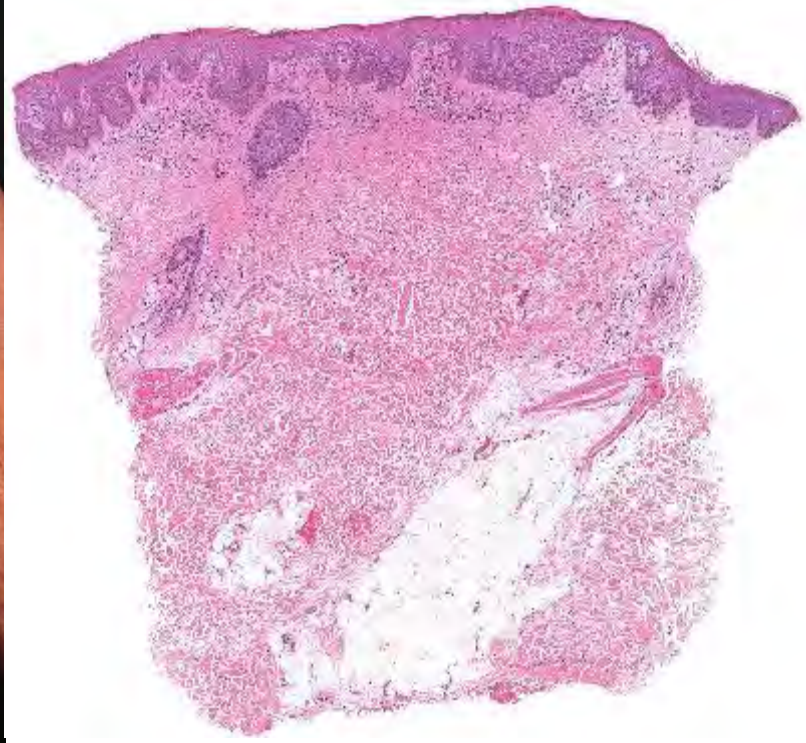
Erythrodermic atopic dermatitis

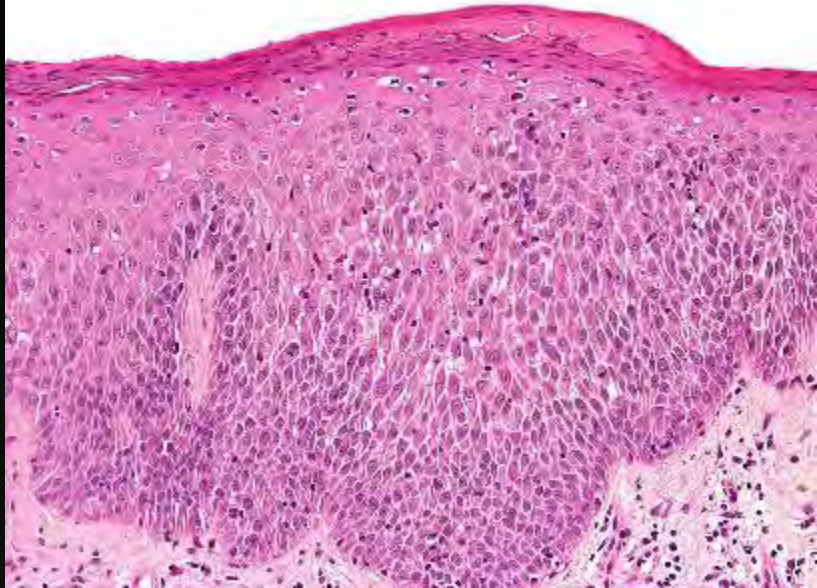


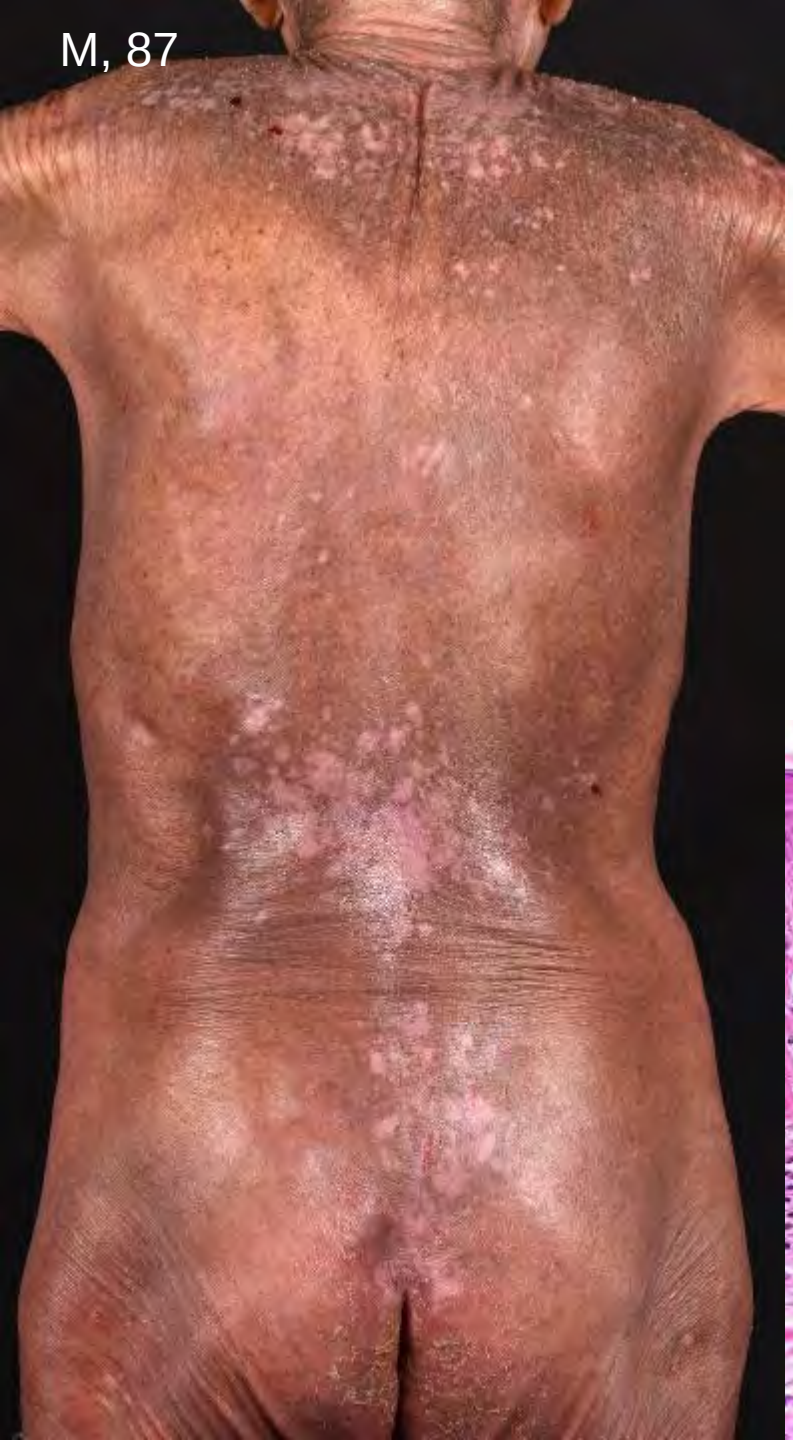
F, 51

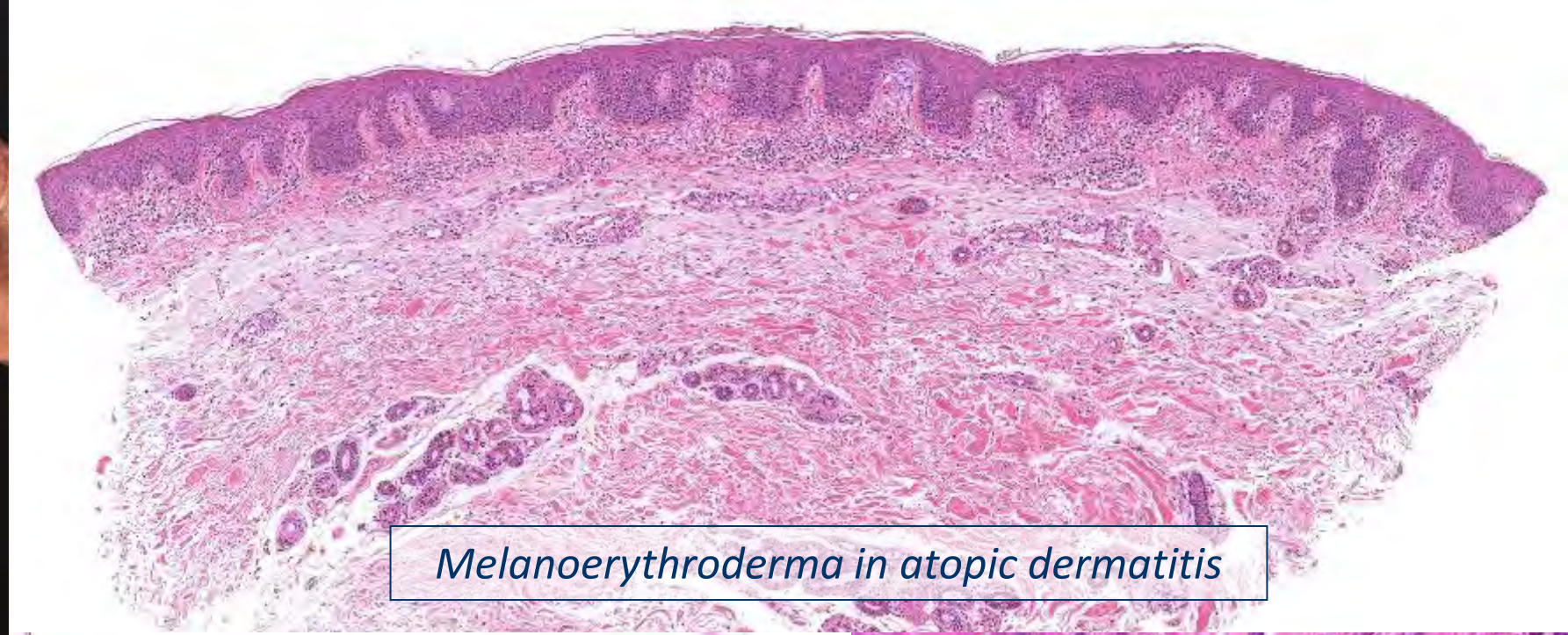




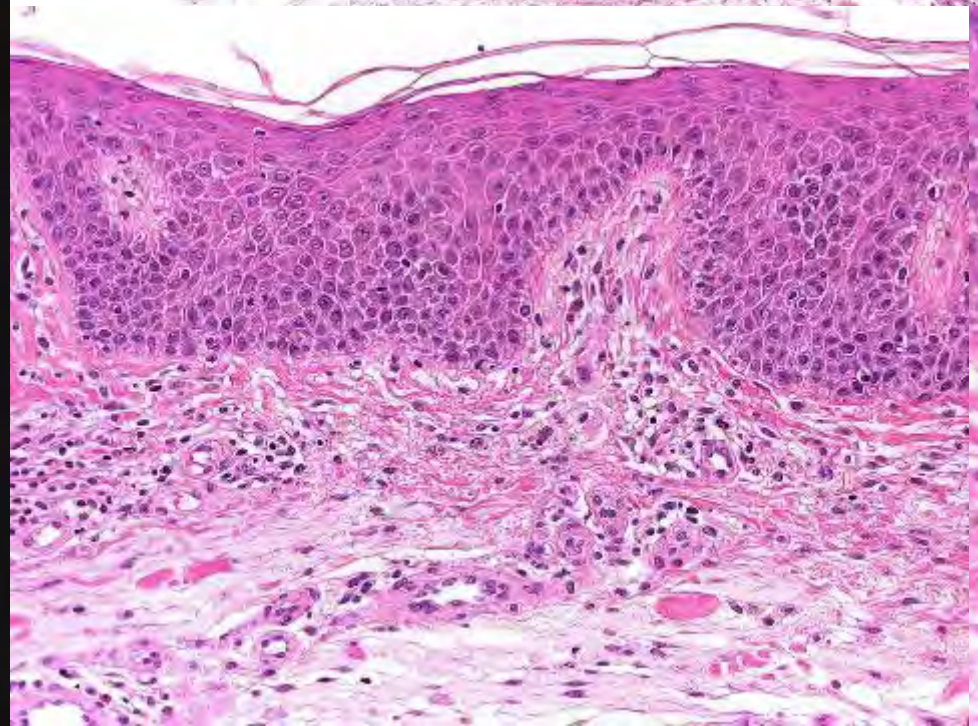


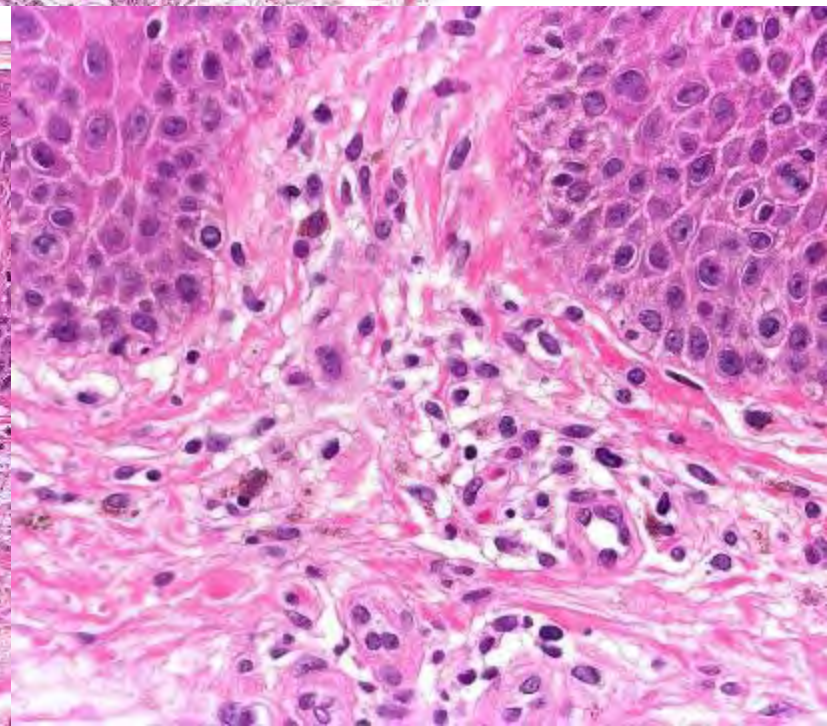






Melanoerythroderma in atopic dermatitis

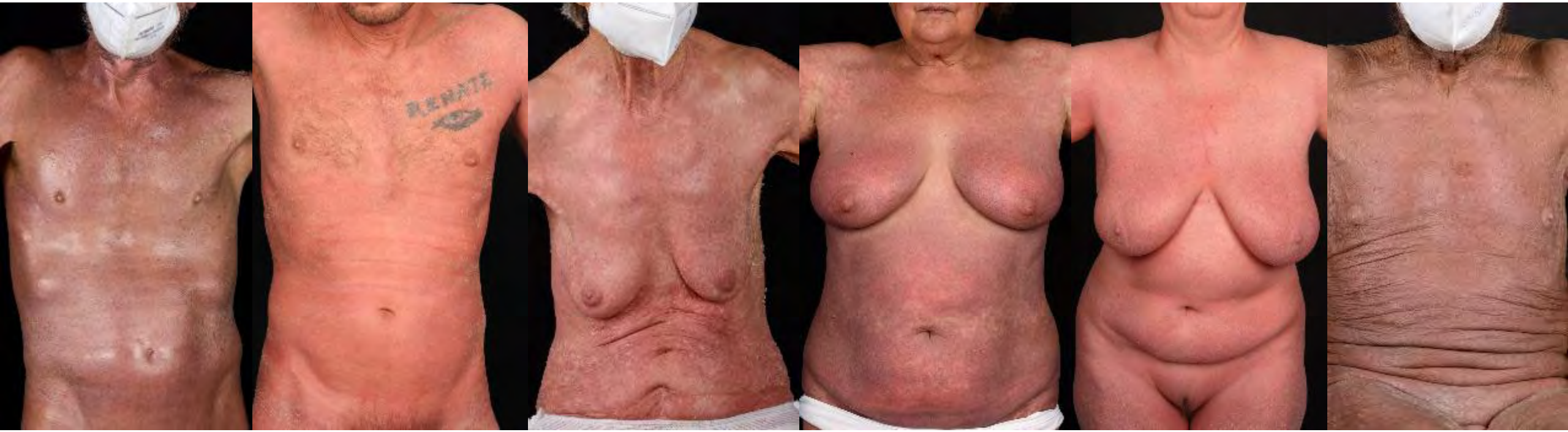




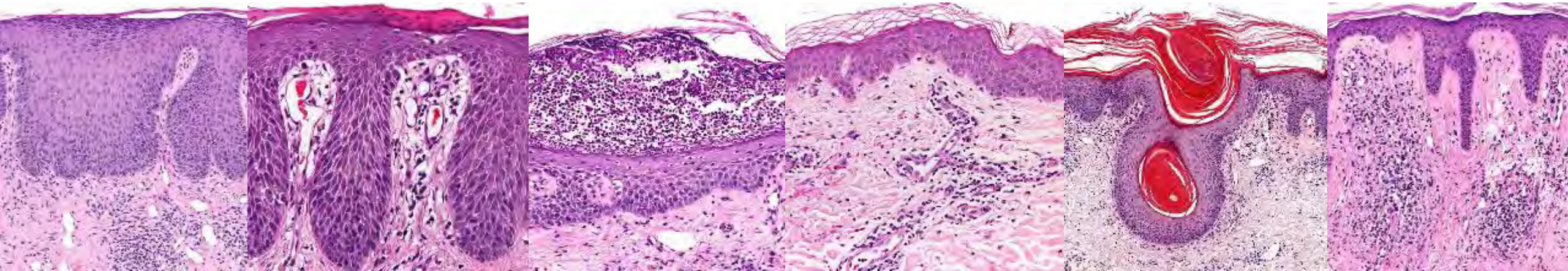
Erythroderma in atopic dermatitis

- Usually in patients with history of moderate to severe atopic dermatitis; Any age
- Intense pruritus
- Excoriations and prurigo-like lesions frequently found; Lichenification oft prominent
- Histopathological features similar to those of "conventional" atopic dermatitis: acanthosis, spongiosis, compact orthokeratosis and parakeratosis, variable lymphocytic infiltrate, oft eosinophils; intraepidermal lymphocytes

Red man syndrome – A dermato(patho)logist's nightmare…



Atopic dermatitis | "Conventional" psoriasis | Pustular psoriasis / AGEP overlap | Drug eruption | Pityriasis rubra pilaris | Sézary syndrome



Journal of Cutaneous Pathology

Histopathology in erythroderma: review of a series of cases by multiple observers

Noreen M.G. Walsh[1], Robert Prokopetz[2], Victor A. Tron[3], Douglas M. Sawyer[4], A. Kevin Watters[5], Scott Murray[2] and Catherine Zip[1]

[1]Department of Pathology and [2]Division of Dermatology, Department of Medicine, Victoria General Hospital and Dalhousie University, Halifax, Nova Scotia, [3]Dynacare Laboratories, Ottawa, Ontario, [4]Department of Pathology, Vancouver Hospital and University of British Columbia, Vancouver, British Columbia, [5]Department of Pathology, Red Deer Regional Hospital Centre, Red Deer, Alberta and [6]Department of Pathology, The Montreal General Hospital and McGill University, Montreal, Quebec, Canada

This study examines the utility of objective histopathological criteria in the evaluation of adult patients with erythroderma. A series of 56 skin biopsies, from 40 erythrodermic patients, was reviewed separately by 3 Canadian dermatopathologists who were unaware of clinical details of the cases. The final diagnosis (gold standard), in each instance, had already been determined by others, based on clinicopathologic data and response to therapy. Direct comparison revealed that the mean accuracy of the histopathological diagnoses was 53% (range: 48–66%), a favorable result in view of the difficulty of the task at hand. Additional points of information which tended to emerge from the study are as follows: (i) identification, by microscopy alone, of spongiotic dermatitis, cutaneous T-cell lymphoma and psoriasis, as underlying causes of erythroderma was more successful than that of drug eruptions and pityriasis rubra pilaris; (ii) the epidermotropism which characterizes cutaneous T-cell lymphoma may be mistaken for inflammatory interface changes seen in drug eruptions and vice versa, thus constituting a pitfall in diagnosis; (iii) finally, it appears that submission of multiple simultaneous biopsies, rather than a single specimen, from patients with erythroderma would be likely to enhance the accuracy of histopathological diagnosis.

Walsh NMG, Prokopetz R, Tron VA, Sawyer DM, Watters AK, Murray S, Zip C. Histopathology in erythroderma: review of a series of cases by multiple observers. J Cutan Pathol 1994: 21: 410–423. © Munksgaard 1994.

Dr Noreen M.G. Walsh, Division of Anatomical Pathology, Victoria General Hospital, 1278 Tower Rd, Halifax, Nova Scotia, Canada, B3H 2Y9

Accepted June 9, 1994

"Direct comparison revealed that the mean accuracy of the histopathological diagnosis was 53% (range: 48-66%), a favorable result in view of the difficulty of the task at hand."

1994

Histopathologic Diagnosis of Lymphomatous Versus Inflammatory Erythroderma: A Morphologic and Phenotypic Study on 47 Skin Biopsies

Caroline Ram-Wolff, PhD, Nadine Martin-Garcia,*† Armand Bensussan, PhD,‡ Martine Bagot, PhD,‡§ and Nicolas Ortonne, PhD*†*

Abstract: Erythroderma may be secondary to a cutaneous T-cell lymphoma (CTCL) and various other erythrodermic inflammatory dermatoses (EID), and their histopathologic distinction is often difficult. The aim of this study was to determine if morphological parameters, namely: the presence of b-catenin, and JunB (previously shown to be expressed by CTCL cells), the epidermal CD8:CD3 ratio, and CD30 expression may help in the histopathologic diagnosis of erythroderma, especially in differentiating CTCL and EID. We retrospectively reviewed a series of 47 skin biopsies from patients with erythroderma (18 CTCL and 29 EID). The diagnosis of each case was established using clinical, biological and histopathologic data. After a blind assessment of the hematoxylin-eosin-safran stained slides, a correct diagnosis of the underlying cause of erythroderma was made only in 31% of cases. A correct differential diagnosis between lymphoma and EID was done with certainty in 57% of cases. Various morphologic and phenotypic parameters were then recorded and we compared their frequency in the CTCL versus the EID group. With the exception of atypical lymphocytes, the moderate to high density of dermal infiltrates and Pautrier microabscesses, only found in CTCL, no morphologic parameter was found to be specific of CTCL, although single lymphocytes epidermotropism, telangiectasias, and slight lymphocytic dermal infiltrate were significantly more frequent in EID. A low (<10%) CD8:CD3 ratio in the epidermal lymphocytic infiltrate and dermal CD30+ lymphocytes were significantly more frequent in CTCL. JunB expression by lymphocytes was specific of CTCL, but was inconstant in our series (17%). We found β-catenin expression in a minority of cases from both the CTCL and EID groups. Among EID, dermal suprapapillary thinning was specific of psoriasis. Neutrophils exocytosis and edema of papillary dermis are significantly more frequent in psoriasis, and [illegible] phological and phenotypical parameters are helpful in making a differential diagnosis between erythrodermic CTCL and EID using

Key Words: erythroderma, Sézary syndrome, histopathology, CD30, β-catenin, JunB

(*Am J Dermatopathol* 2010;32:755–763)

INTRODUCTION

Erythroderma may result from several causes, including cutaneous T-cell lymphomas (CTCL), especially Sézary syndrome (SS), and several erythrodermic inflammatory diseases (EID), mostly psoriasis, drug eruptions or atopic dermatitis.[1] It is difficult to establish the underlying cause in practice, since clinical and histological aspects are not specific. Especially, it is necessary to differentiate EID from SS, which is an aggressive lymphoma and requires an early and appropriate management.[2] Erythroderma can present with a large variety of histologic patterns. However, there have been only few series detailing the histologic features of erythroderma. The identification of a monoclonal T-cell population has been proved to be of high value for the diagnosis of CTCL,[3–7] but is not fully specific, unless a similar T-cell clone is found in the blood and skin.[8] New markers of SS have been described in the past 10 years using flow cytometry studies on circulating CD4+ T cells (loss of CD26, CD7, and CD49d),[9–12] and molecular studies in sorted circulating T cells or skin samples (Twist, EphA4, and T-plastin).[13,14] Notably, CD158k/KIR3DL2 was shown to be highly specific for malignant CD4+ T cells, allowing diagnosis of SS in the blood using flow cytometry and in the skin using reverse transcription polymerase chain reaction.[15–17] Among new [illegible] shown to be suitable for immunohistochemistry on paraffin embedded skin biopsies. Beta-catenin is a ubiquitously cytoplasmic protein [illegible] pathway, which plays an important role in embryonic [illegible] study has shown that β-catenin is expressed in high grade CTCL.[22] Indeed, immunohistochemical analysis demonstrated β-catenin expression in a majority of SS samples (70%) and in a proportion of mycosis fungoides. JunB is a member of the Jun family of proteins that are components of the activator protein 1 (AP-1) transcription factor complex. AP-1 members are involved in cell proliferation and apoptosis, thus contributing to oncogenesis.[23] Recent studies have shown

(AP-HP), Créteil Cedex, France; ‡INSERM U955, Hôpital Henri Mondor, Créteil, France; §INSERM U976, Hôpital Saint-Louis, Paris, France; and ¶Université Paris 7, Paris, France.

Reprints: Nicolas Ortonne, PhD, Université Paris XII, Faculté de Médecine, Hôpital Henri Mondor, AP-HP, Département de Pathologie, AP-HP, 94010 Créteil Cedex, France (e-mail: nicolas.ortonne@hmn.aphp.fr).

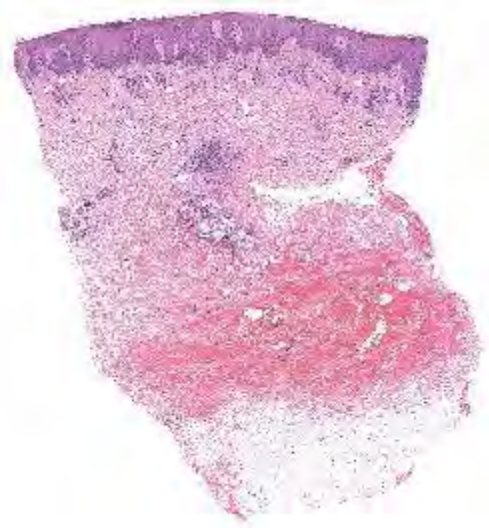
"After a blind assessment of the hematoxylin-eosin-safran stained slides, a correct diagnosis of the underlying cause of erythroderma was made only in 31% of cases."

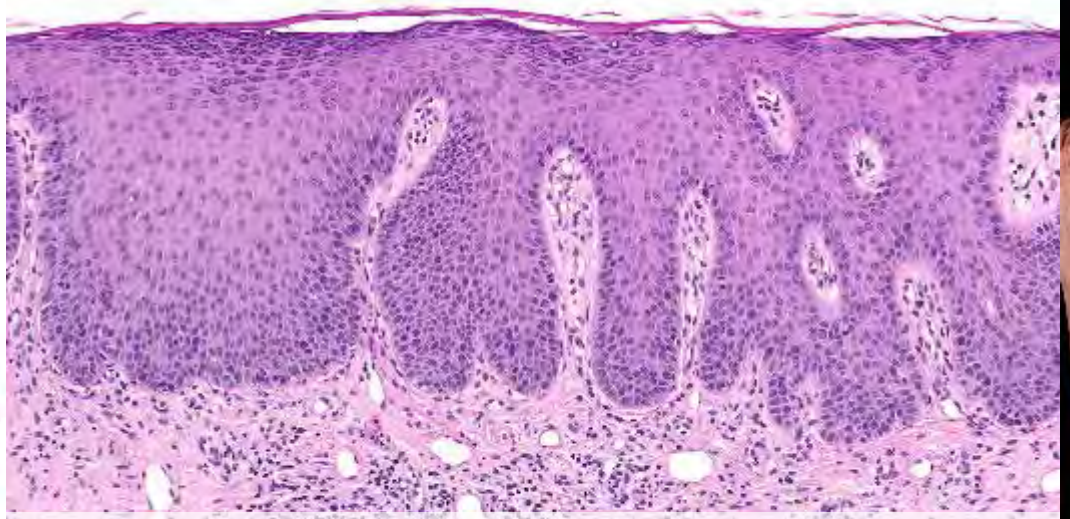
2010

1st presentation

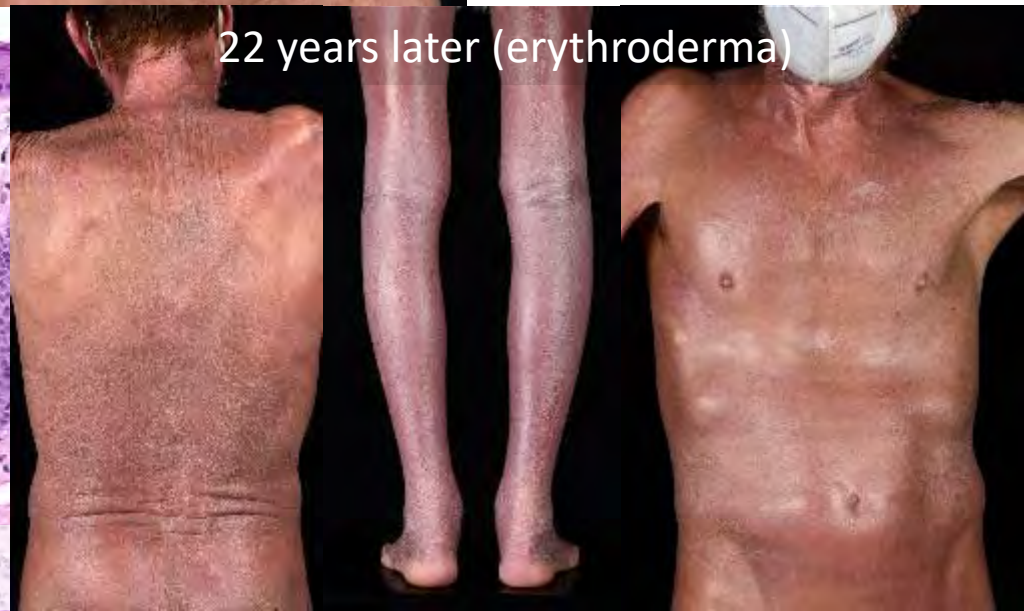
6 years later

19 years later (eczema herpeticum)





22 years later (erythroderma)



Atopic dermatitis evolving to erythroderma

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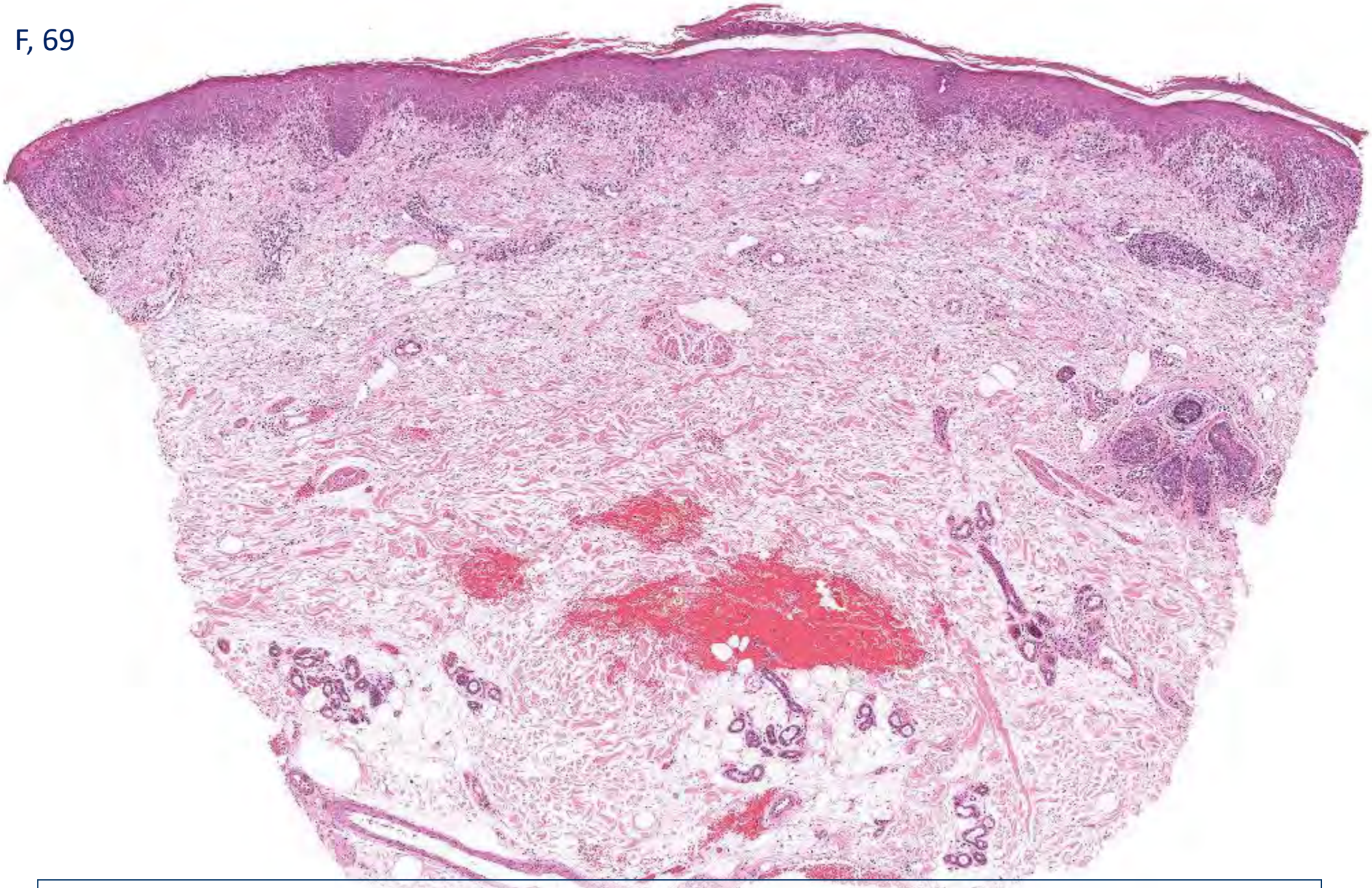
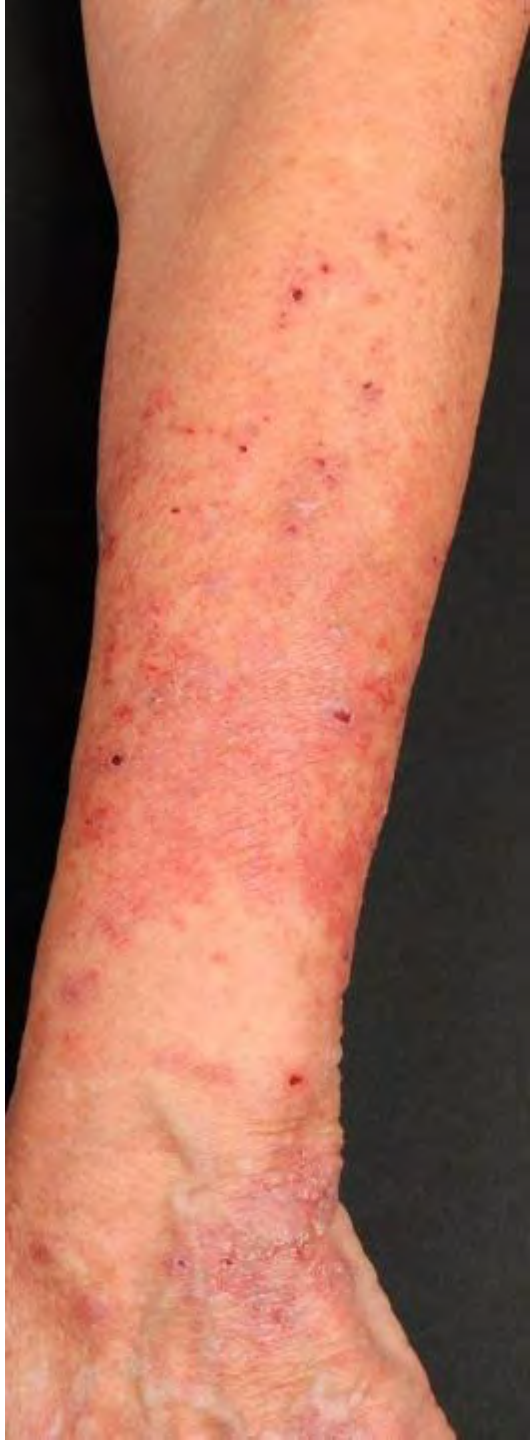
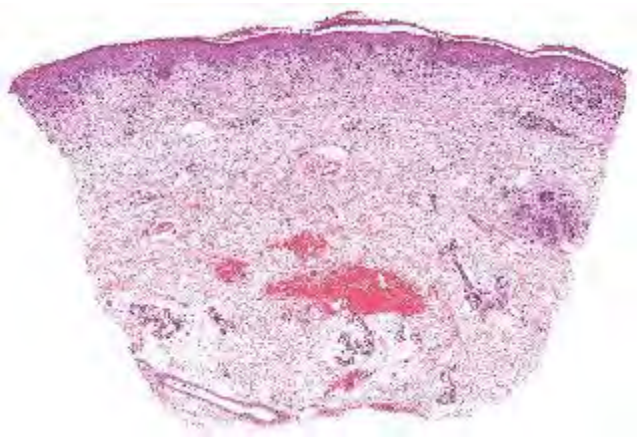




Some unusual histopathological findings in atopic dermatitis



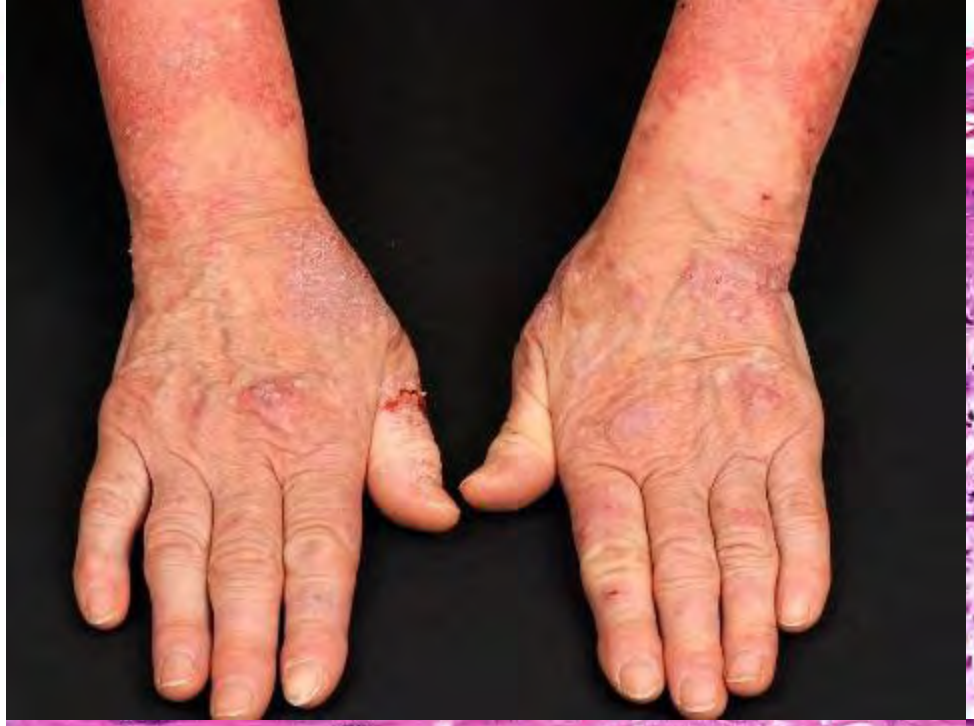
ANA & subsets: negative.

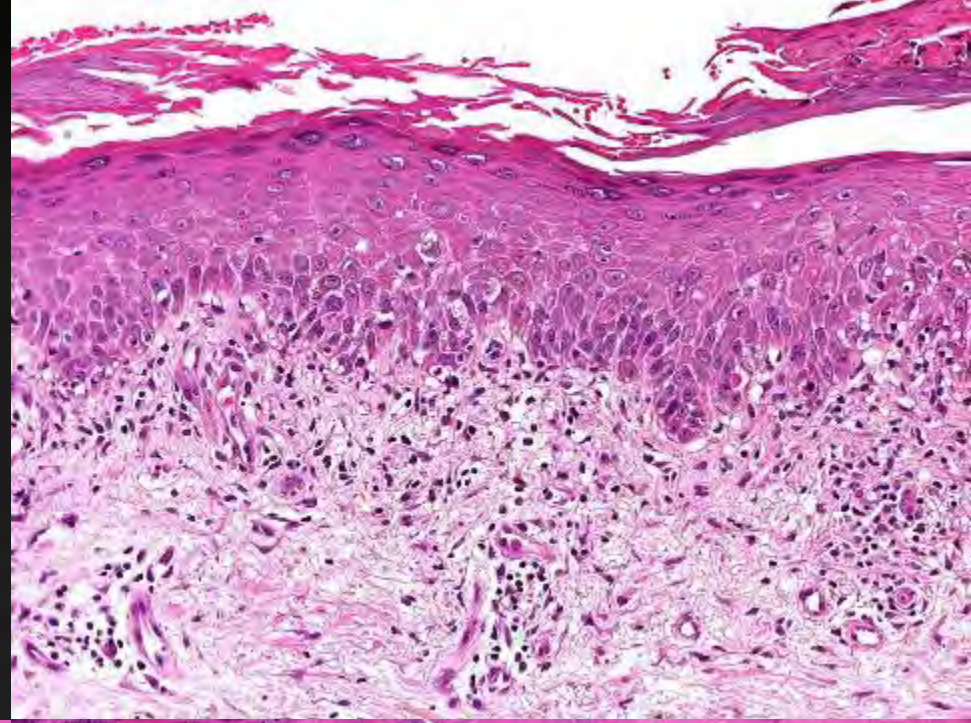
Complete resolution after 4 weeks of local steroids.

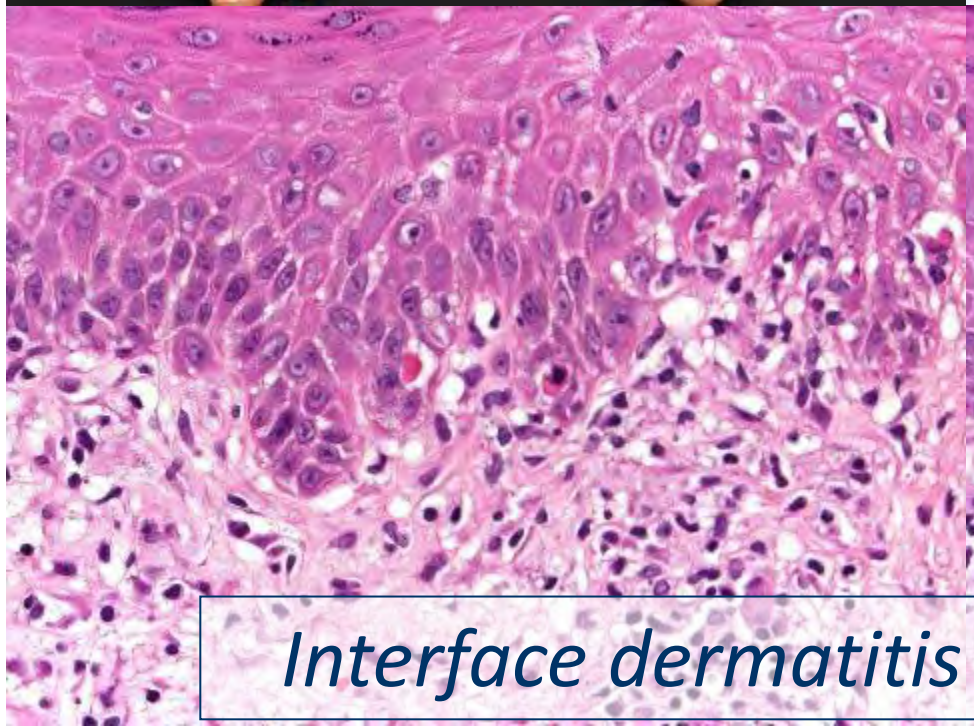
Recurrent itchy, eczematous lesions for >6 years with eyelid eczema.

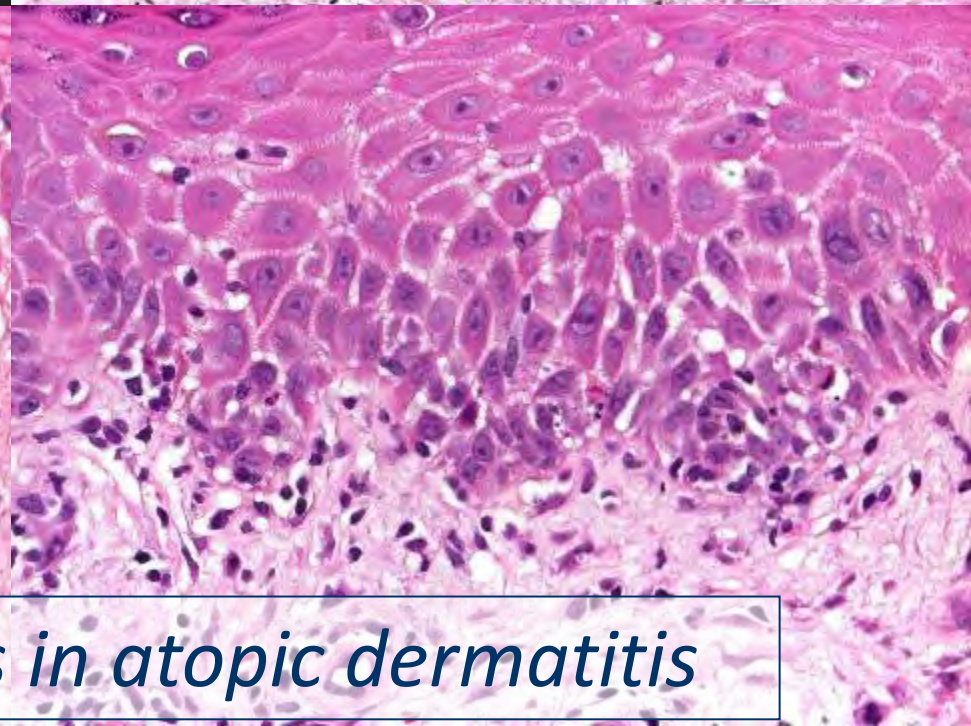
During 12 years follow-up recurrent crops of eczematous lesions particularly on the face and the lower and upper extremities.

No clinical signs of cutaneous LE.









Interface dermatitis in atopic dermatitis

Allergy, Asthma & Clinical Immunology

REVIEW | Open Access

Atopic dermatitis and risk of autoimmune diseases: a systematic review and meta-analysis

Abstract

Background: [illegible]

Methods: [illegible]

Results: [illegible]

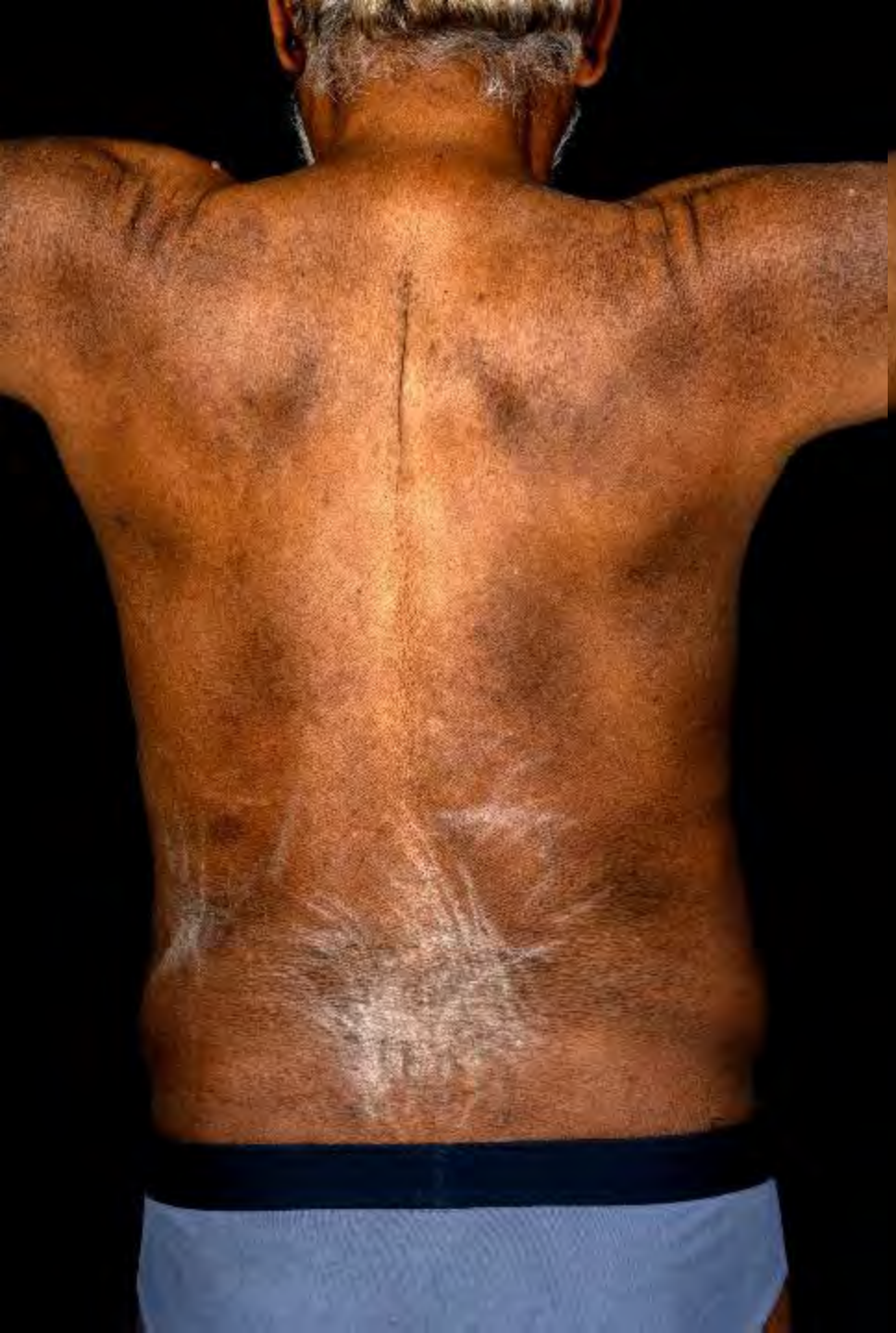
Conclusion: [illegible]

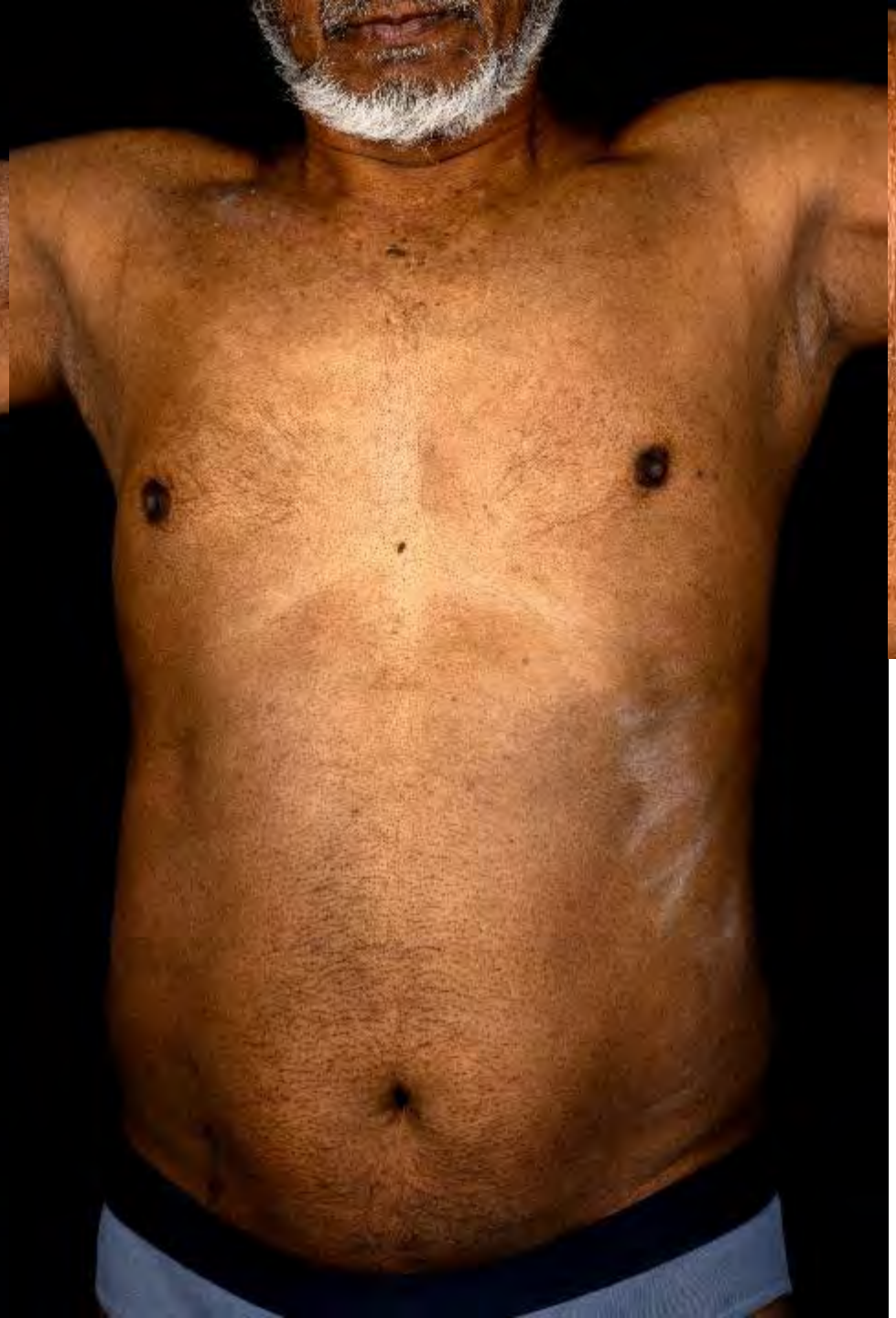
Introduction

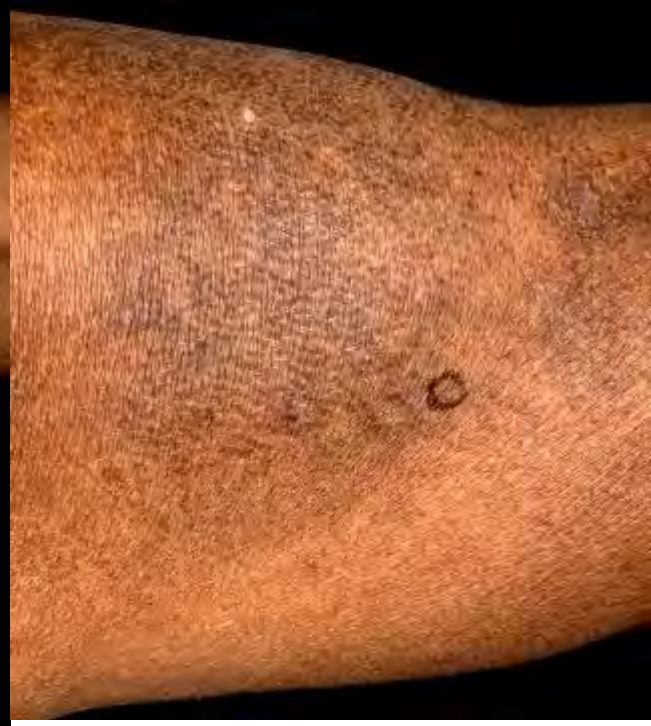
Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions. Nowadays, AD has become a major public health issues because of its high prevalence, considerable patient-burden as well as increased healthcare utilization. Meanwhile, AD brought huge economic burden to patients. To date, AD has affected at least 230 million people worldwide and being the leading cause of the non-fatal disease burden within skin conditions [1–4]. Potential mechanisms included epidermal barrier dysfunction, immune dysregulation and alteration of microbiome, which were modulated by genetic and environmental factors [5]. It has been reported that AD may be associated with allergic comorbidities including asthma, allergic rhinitis, food allergy and non-allergic comorbidities including psychological disorders, cardiovascular disorders,

Table 3 Results of pooling odds ratio and risk ratio of included studies

Type of autoimmune disease	Cross-sectional/case–control studies			Cohort studies		
	Studies(n)	Case/control(n)	OR (95% CI)	Studies(n)	Case/control(n)	RR (95% CI)
Alopecia areata	4	87,139,761/88,638,587	9.72 (4.38–21.59)	3	1,443,111/2,410,018	2.98 (1.36–6.53)
Systemic lupus erythematosus	4	88,496,787/88,412,647	1.74 (1.34–2.19)	2	1,585,927/2,940,046	2.20 (1.44–3.38)
Vitiligo	6	88,529,196/89,676,032	3.61 (2.31–5.63)	2	1,402,804/2,248,790	1.64 (1.27–2.13)
Celiac disease	4	88,571,653/88,361,659	1.98 (1.51–2.60)	1	1,393,570/2,170,618	1.41 (1.32–1.50)
Crohn's disease	5	87,101,613/87,416,984	1.66 (1.50–1.84)	3	3,000,852/2,776,586	1.38 (1.17–1.63)
Ulcerative colitis	5	87,101,613/87,416,984	1.95 (1.57–2.44)	2	1,607,282/8,972,054	1.49 (1.05–2.11)
Rheumatoid arthritis	5	88,527,141/89,675,474	1.18 (1.01–1.37)	3	1,462,324/2,946,824	1.38 (1.16–1.63)







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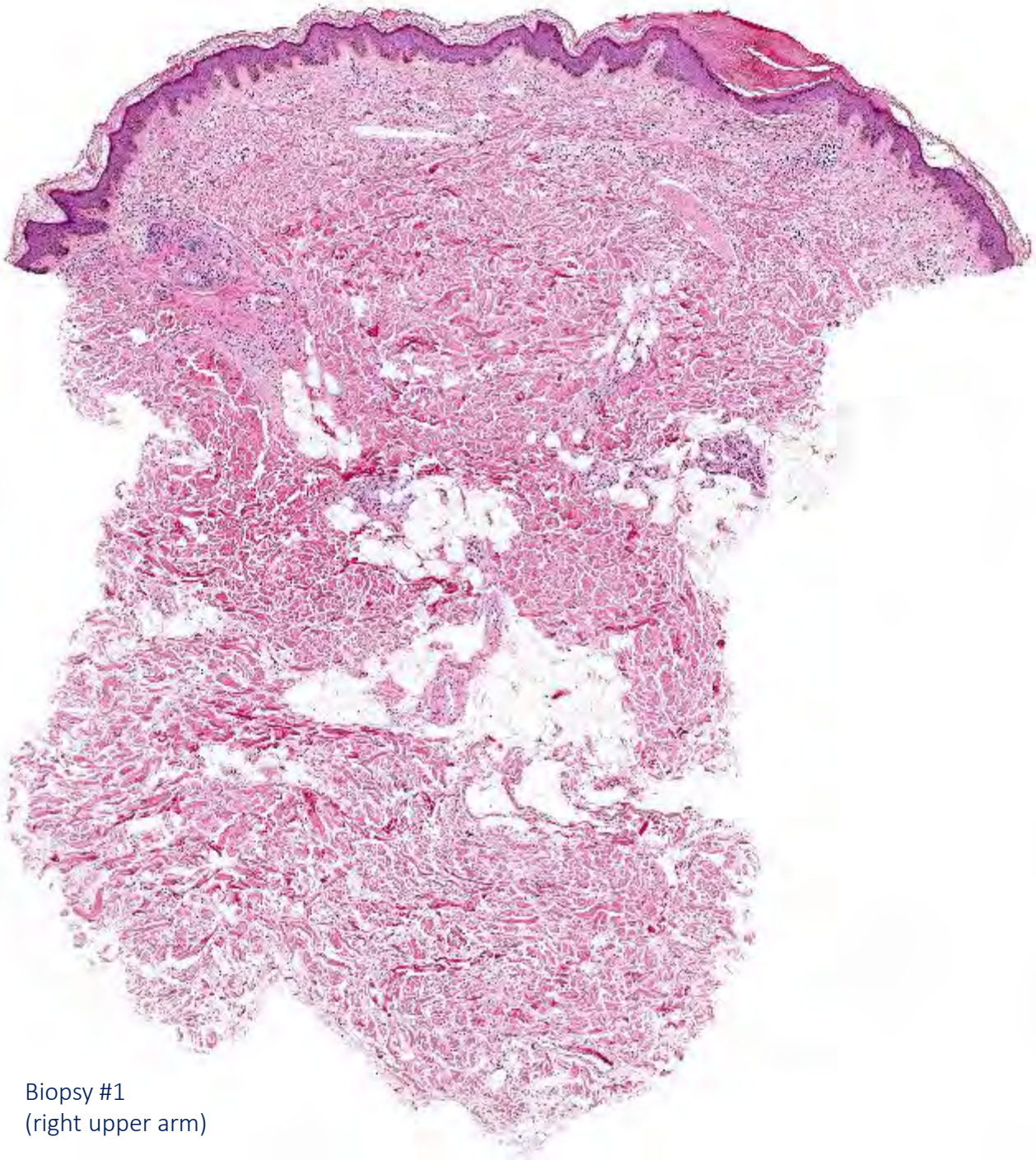
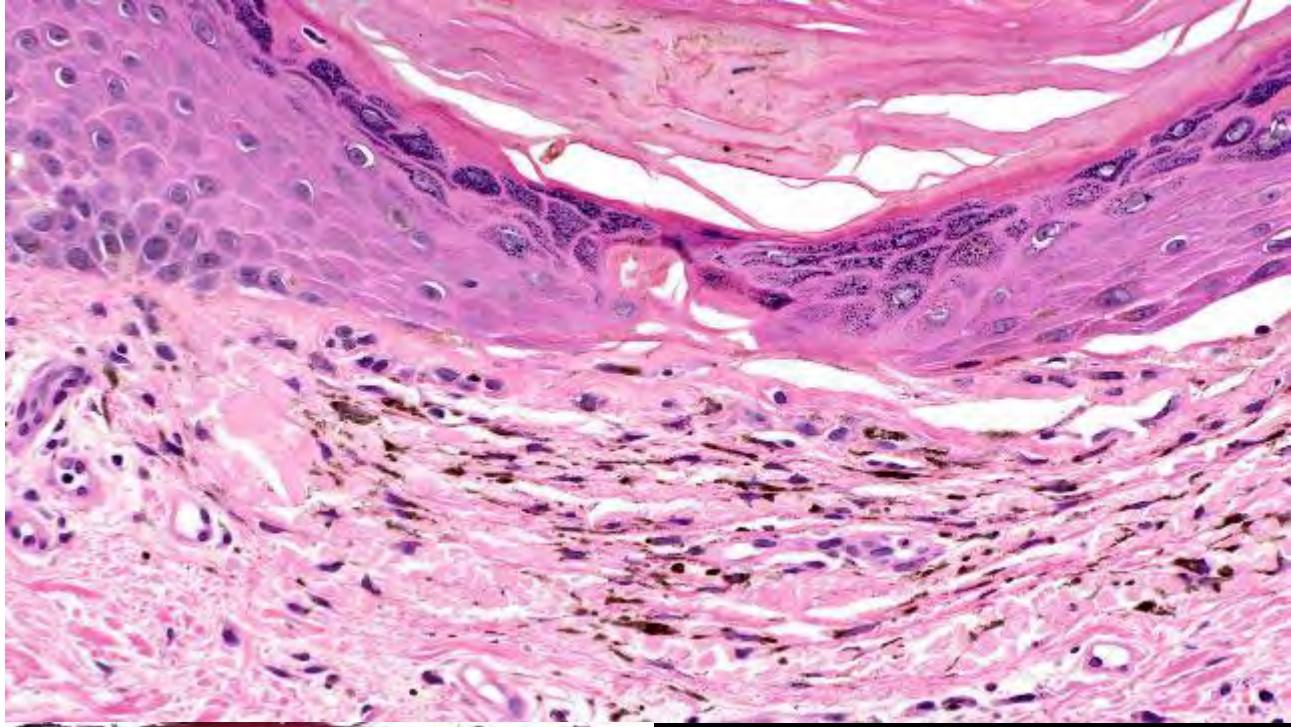
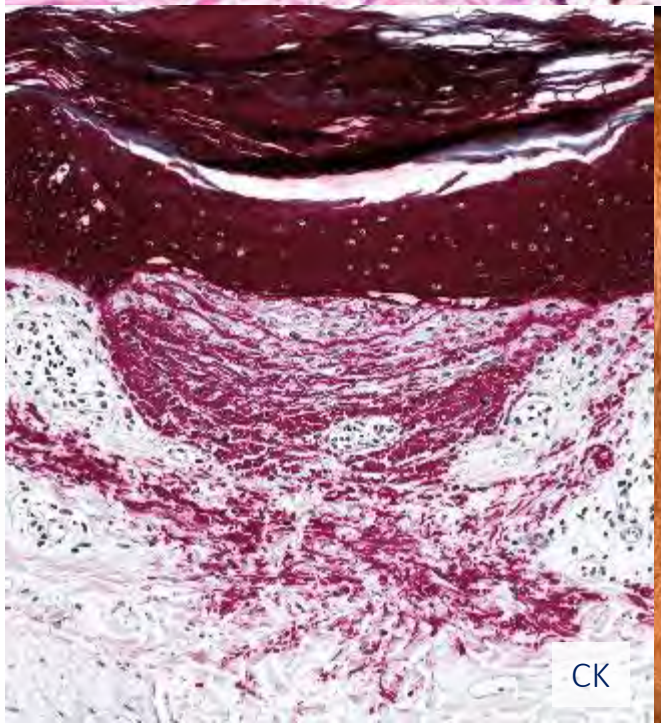
According to the patient generalized pruritus for at least 5 years. Slight elevation of serum tryptase (24,7).

Two biopsies are taken.



Biopsy #1
(right upper arm)





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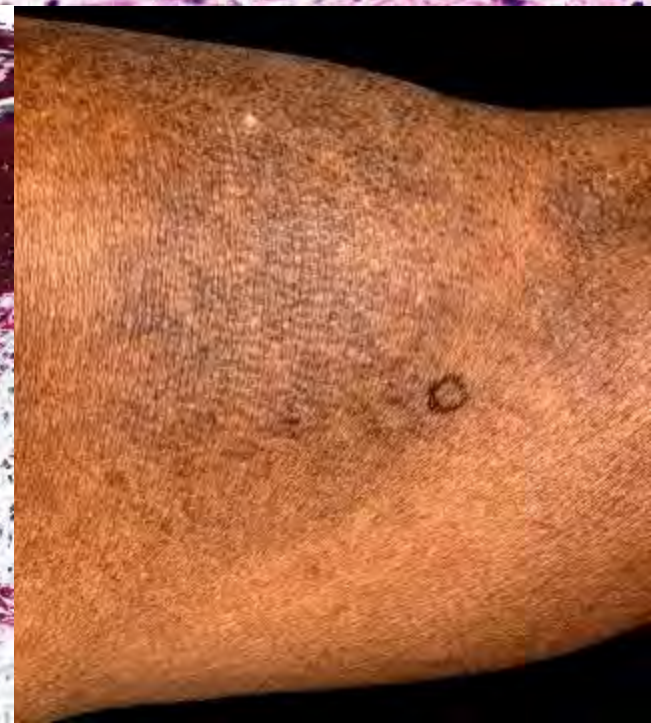
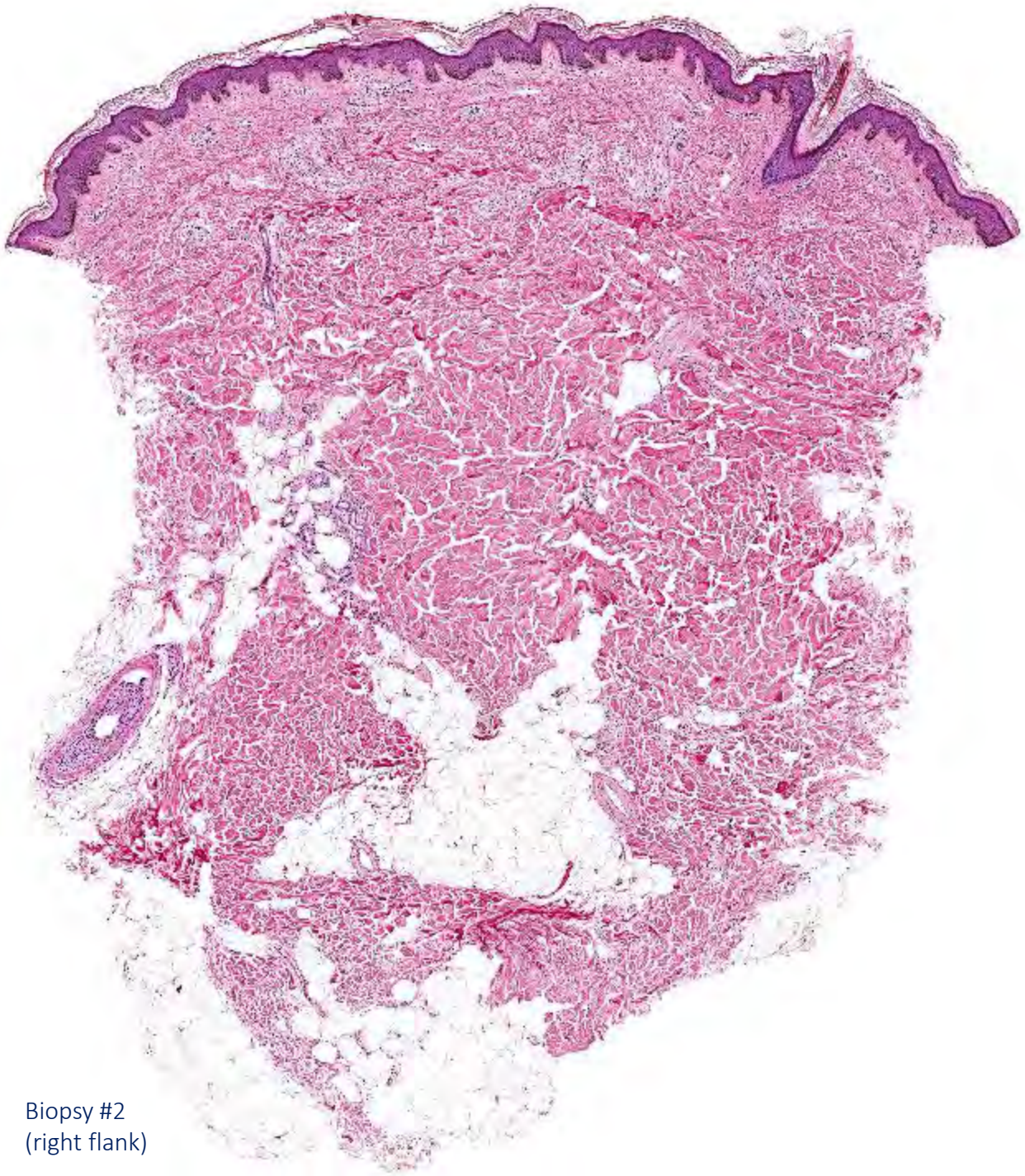
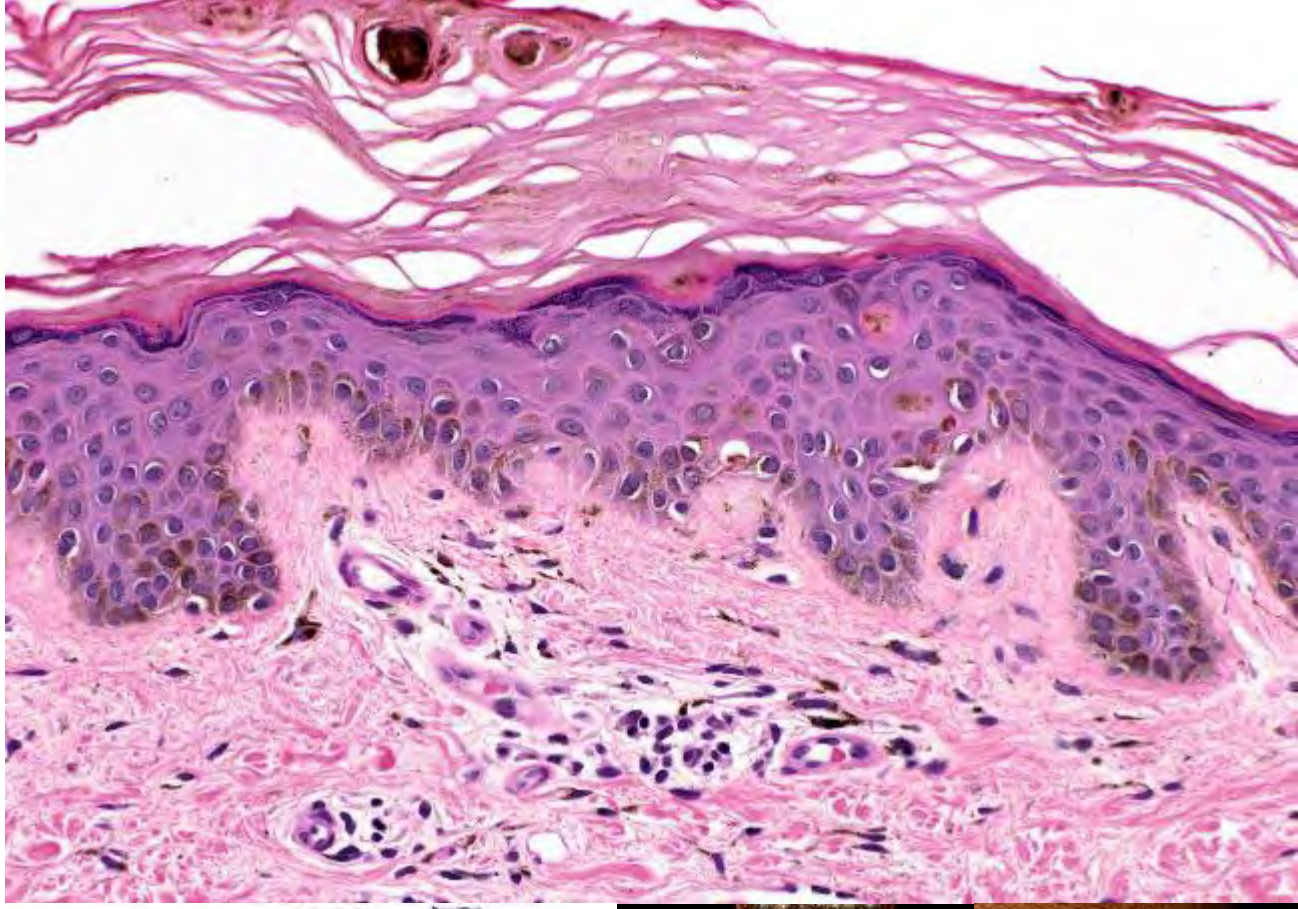
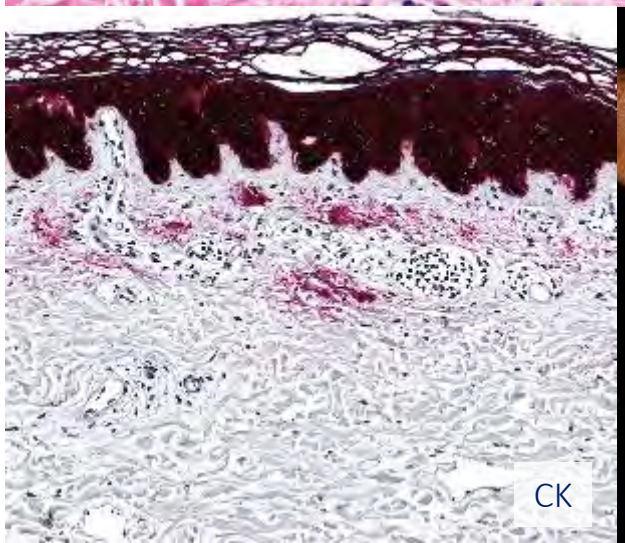




Biopsy #2
(right flank)





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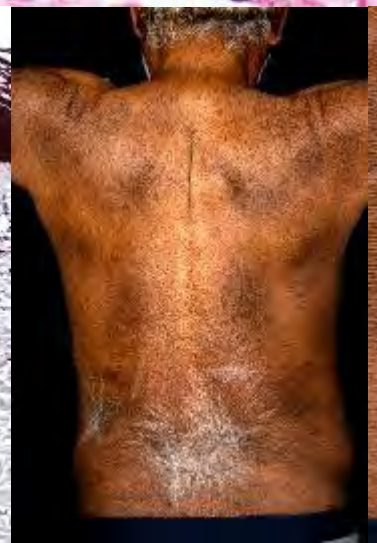
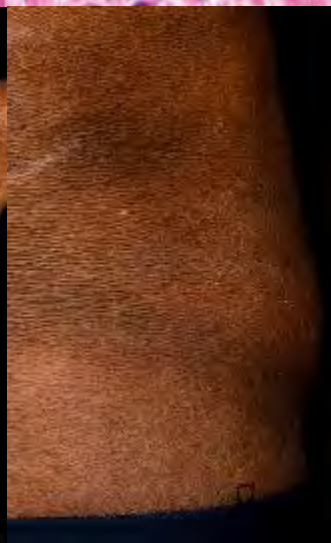
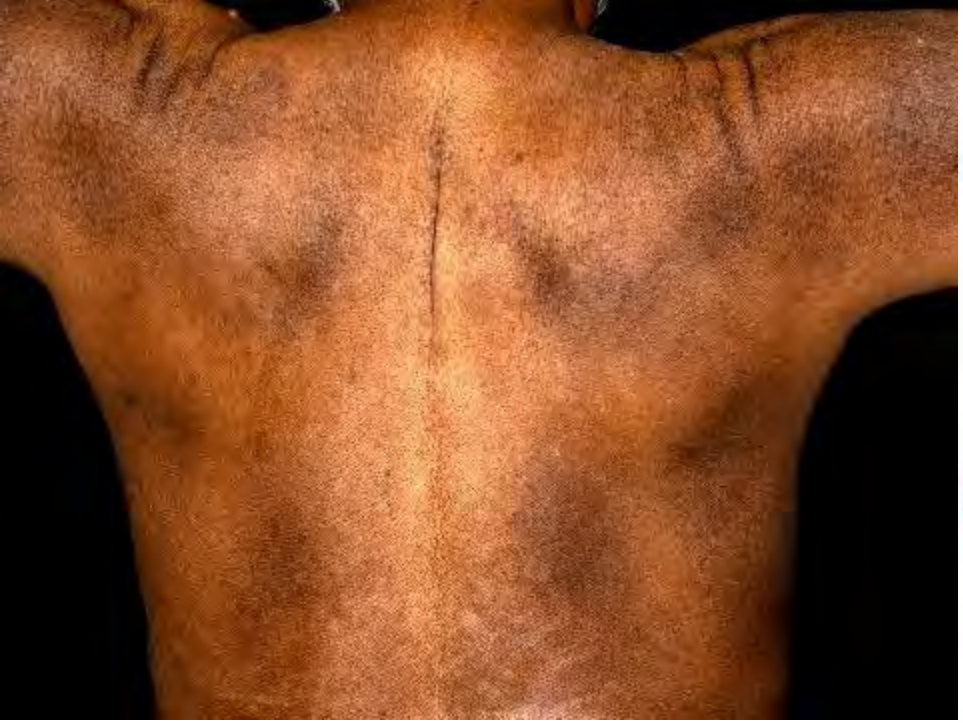
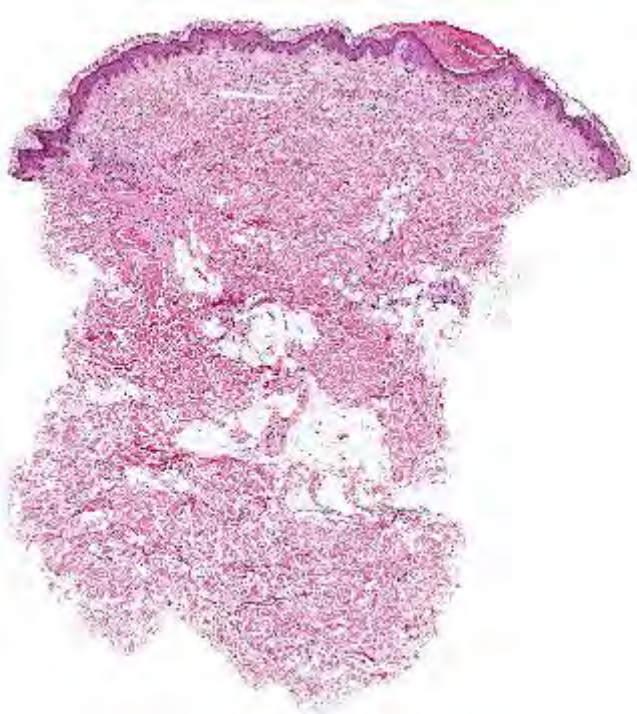
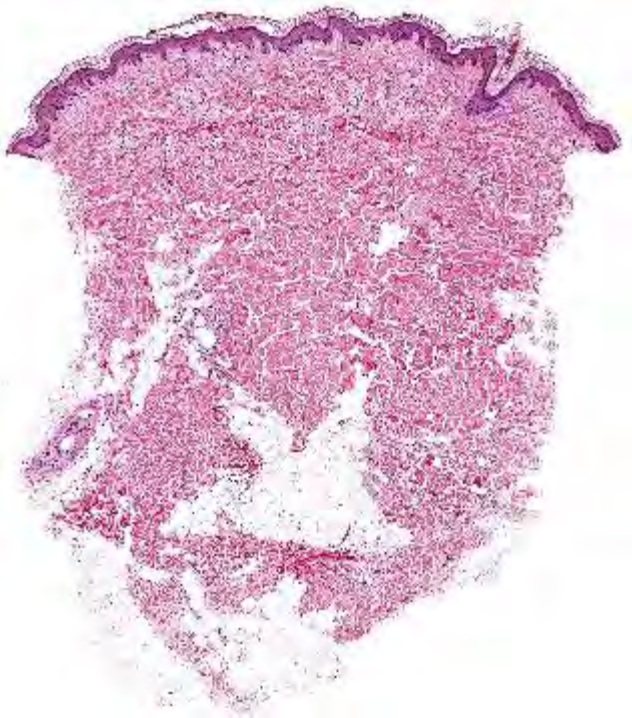
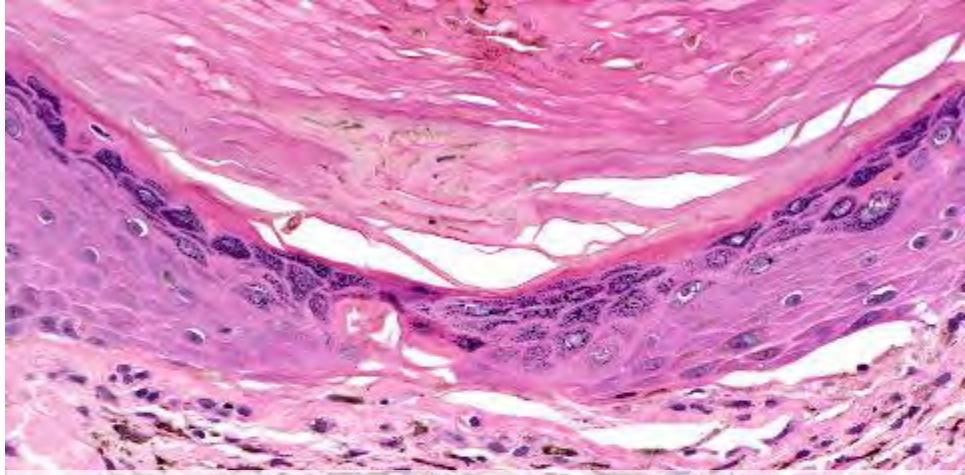






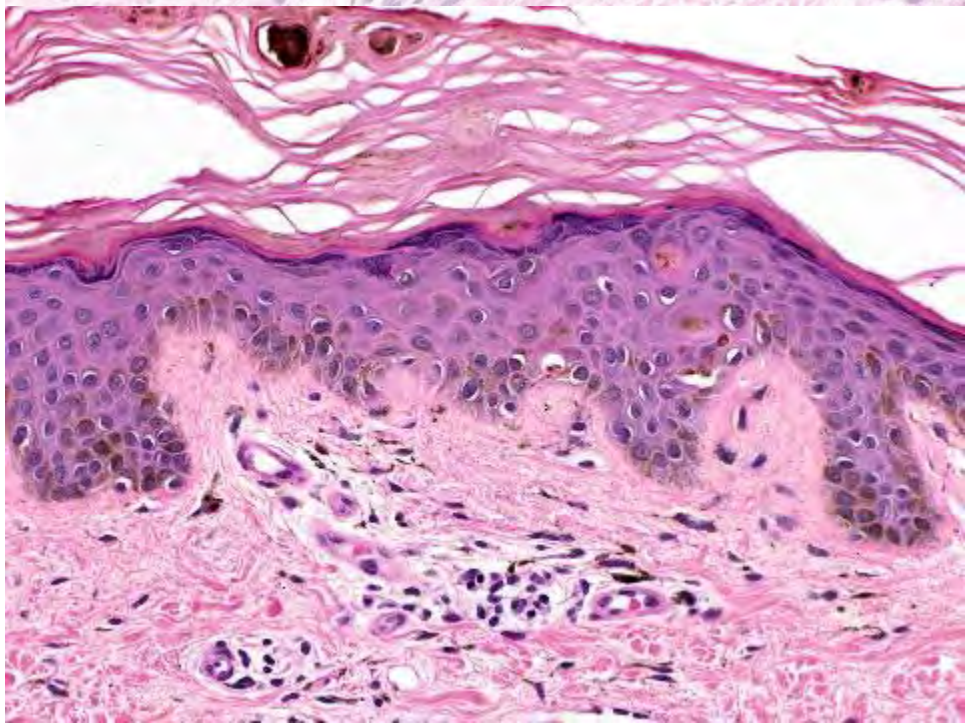






"Atopic" dermatitis

with biphasic amyloidosis



Deposition of amyloid K may be observed after chronic rubbing (lichen amyloidosus, macular amyloidosis).

Production of amyloid K occurs only in some cases of frictional dermatosis (more commonly in people from Asia, Middle-East and South America), and presence of amyloid K in a biopsy specimen depends also on the site of biopsy (i.e., a given biopsy may be negative).

In this patient, *histopathologically* combination of aspects of both lichen amyloidosus and macular amyloidosis (biphasic amyloidosis); *clinically* picture of atopic dermatitis.

Biphasic amyloidosis: link between macular and lichenoid forms*

MARTIN H. BROWNSTEIN, KEN HASHIMOTO† AND GERALD GREENWALD

Departments of Pathology and Dermatology, New York Medical College–Metropolitan Hospital Center, New York, N.Y. and (Memphis Veterans Administration Hospital and the Division of Dermatology, Department of Medicine, Memphis, Tennessee

Accepted for publication 3 August 1972

SUMMARY

A woman manifested lichen amyloidosus of the right lower limb and macular amyloidosis of her left leg with congenitally impaired cutaneous sensation. Another patient had bilateral lichenoid amyloidosis of her legs. Unilateral triamcinolone injections produced the picture of macular amyloidosis in the treated leg. Light and electron microscopic studies of biopsies from both patients showed similar amyloid deposits in the papillae; the significant difference was epidermal hyperplasia in the lichenoid lesions. We suggest the term biphasic for the existence of both macular and lichenoid amyloidosis in the same patient.

The dramatic clinical picture of intensely pruritic keratotic papules in lichenoid amyloidosis contrasts sharply with the subtle pigmentary changes found in the macular variety. Nevertheless, it has recently been suggested (Brownstein & Hashimoto, 1972) that these conditions may represent the same basic disease process, and that the essential differences are due mainly to secondary hyperplastic changes of the epidermis.

Our purpose here is to present evidence of an intimate relationship between these disorders by describing two patients with biphasic amyloidosis—lichen amyloidosus of one lower limb and macular amyloidosis of the other.

CASE REPORTS

Case 1

A Puerto Rican woman aged 47 complained of a pruritic eruption that had been present on the right lower limb for several years. She was born with orthopaedic deformities and neurological defects of the left leg, and had never been able to walk normally.

On examination there were several plaques between the right ankle and mid-tibial area, consisting

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Requests for reprints: Dr Brownstein, Post Office Box 571, Great Neck, New York, 11022, U.S.A.

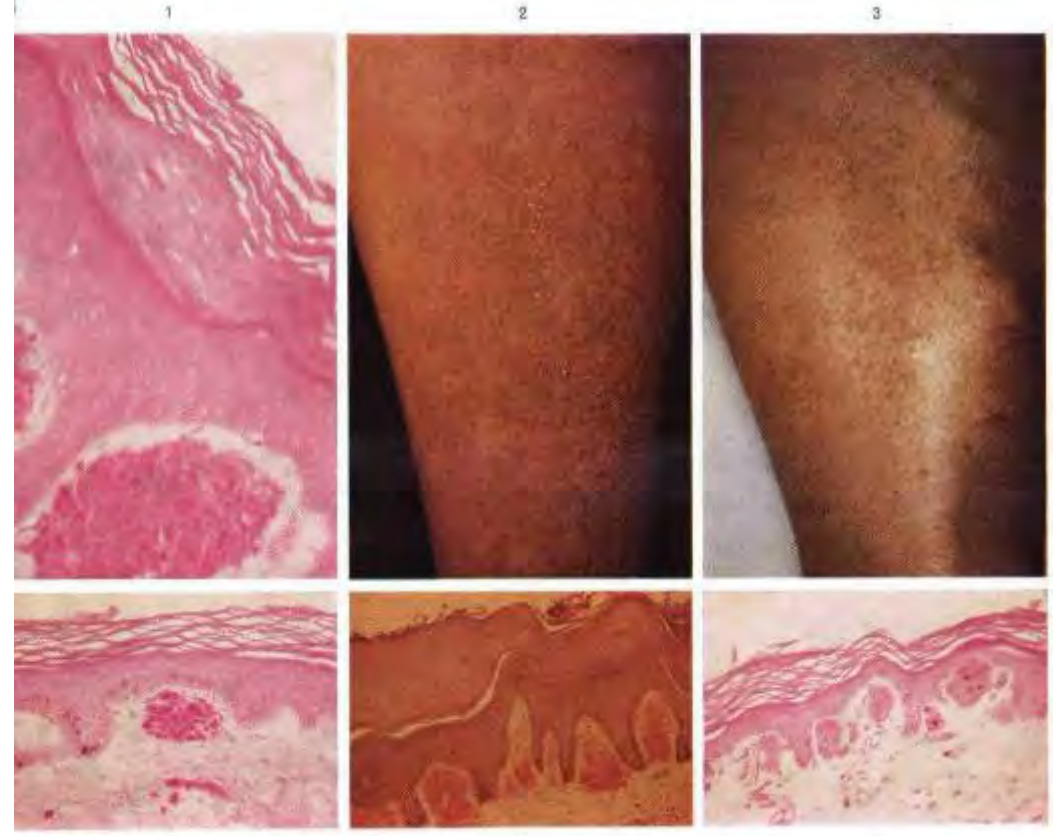


PLATE 1. Case 1. Lichen amyloidosus of right pretibial area; epidermal hyperplasia and metachromatic material in papillary corium. Crystal violet (×750).
PLATE 2. Case 2. Lichen amyloidosus of left shin before therapy.
PLATE 3. Case 2. Macular amyloidosis of left shin after therapy.
PLATE 4. Case 1. Macular amyloidosis of left pretibial area; normal epidermis and amyloid deposits in papillary dermis. Crystal violet (×500).
PLATE 5. Case 2. Lichen amyloidosus of left shin before therapy. Epidermal hyperplasia and amyloid deposits in dermal papillae. Crystal violet (×500).
PLATE 6. Case 2. Macular amyloidosis of left shin after therapy. Normal epidermis and amyloid deposition in papillary bodies. Crystal violet (×500).

Dermatologica 158: 433–437 (1979)

Diffuse Biphasic Cutaneous Amyloidosis

T.R. Bedi and B.N. Dutta

Departments of Dermatology and Pathology, Post-Graduate Institute of Medical Education and Research, Chandigarh

Key Words. Amyloidosis · Skin

Abstract. 2 patients with primary localized cutaneous amyloidosis were seen to have widespread macular and lichenoid types of lesions. Diffuse areas of pigmentation appeared to transform gradually over years into lichen amyloidosus as a result of chronic irritation of the skin from scratching. There was no evidence of systemic amyloidosis.

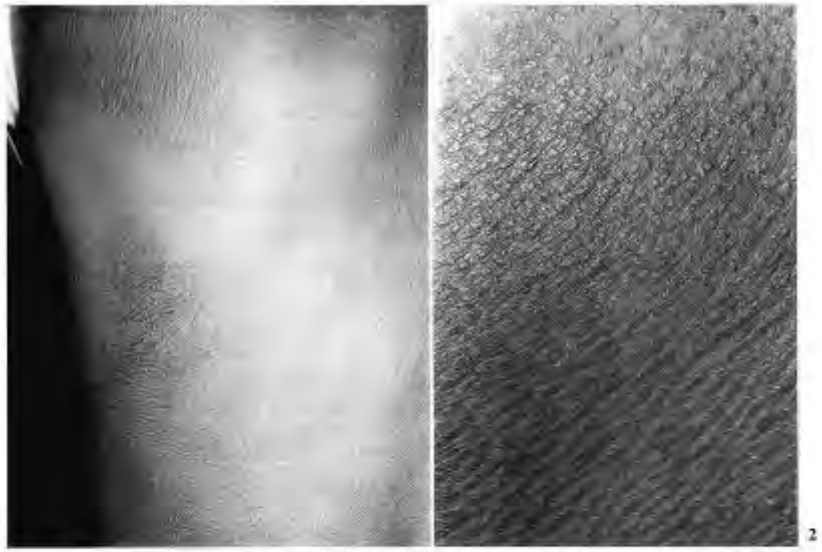


Fig. 1. Case 1. Characteristic 'rippling' pattern in PLCA on the background of diffuse pigmentation on the back.

Fig. 2. Case 1. Closely aggregated flat 'lichen' papules of LA.

British Journal of Dermatology (1992) 127, 641–644

Diffuse primary cutaneous amyloidosis

J.F.BOURKE, J.BERTI-JONES AND D.A.BURNS

Department of Dermatology, Leicester Royal Infirmary, Leicester LE1 5WW, U.K.

Accepted for publication 22 June 1992

Summary A case of extensive primary cutaneous amyloidosis exhibiting both macular and lichenoid lesions is reported. Lesions were arranged in a distinctive linear pattern covering much of the trunk and limbs, in places following Blaschko's lines. The coexistence of macular and lichenoid lesions suggests that this is an unusual variant of biphasic cutaneous amyloidosis.

Primary cutaneous amyloidosis is defined as cutaneous amyloidosis in the absence of other systemic or dermatological disease.

It may be classified into three principal categories: macular, lichenoid (lichen amyloidosus) and nodular.[1] The nodular form is rare. It is characterized by the development of single or multiple nodules, most com-

limbs. There were areas of telangiectasia, purpura, scaling and hyperkeratosis. Lichenoid lesions were prominent on the legs. The pattern varied from reticulate over the thighs (Fig. 1) to whorled on the back (Fig. 2) with a well-demarcated linear arrangement over areas

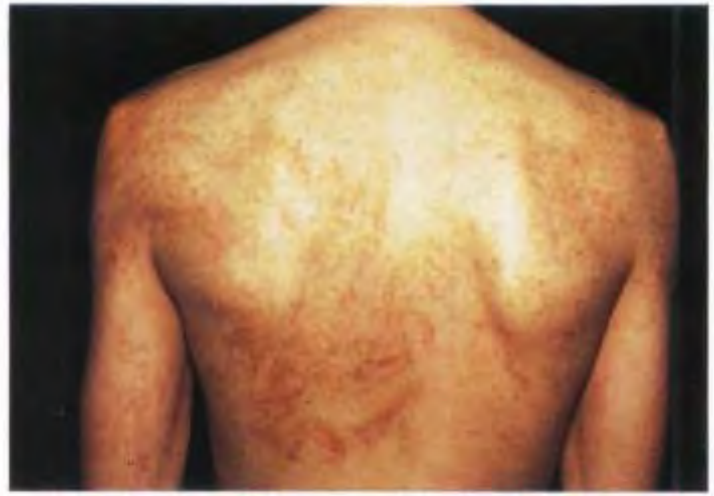
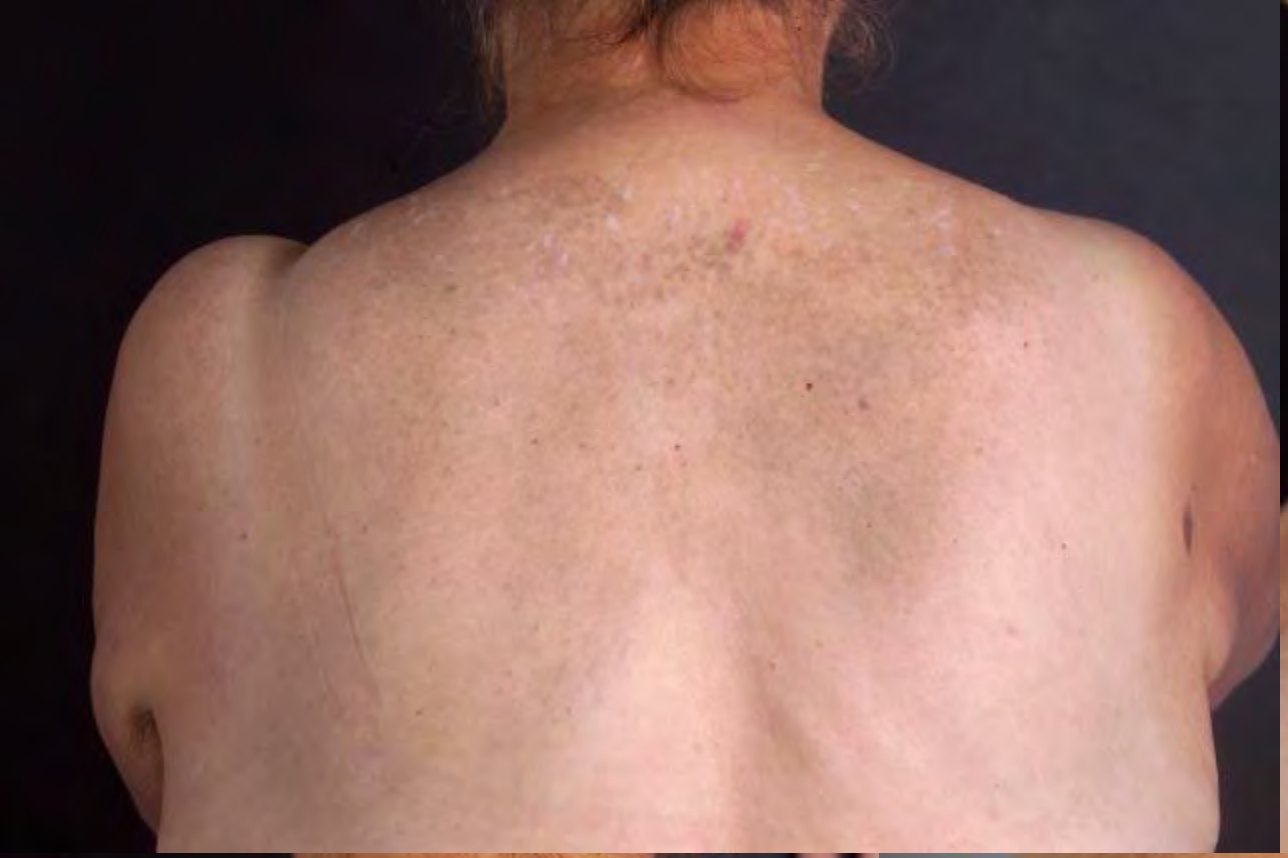
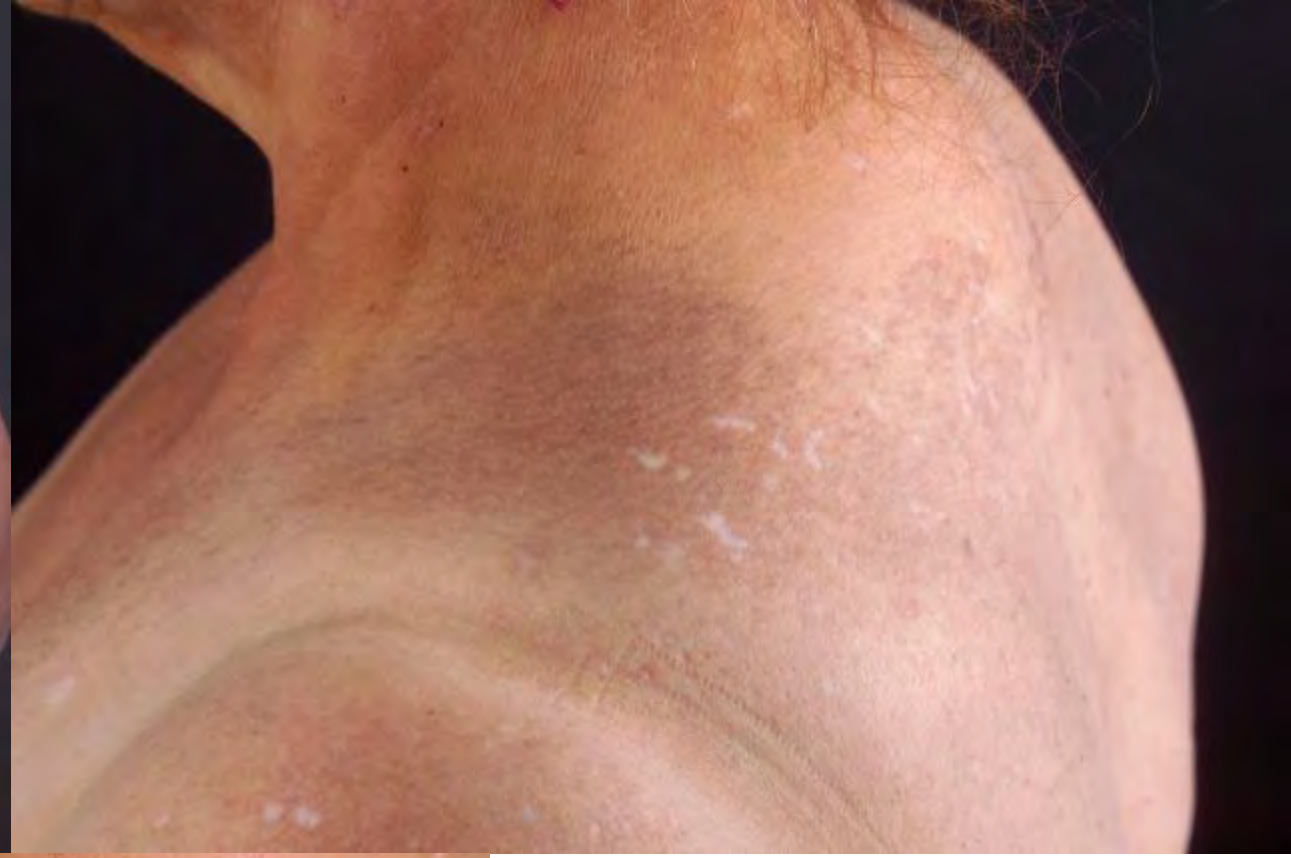


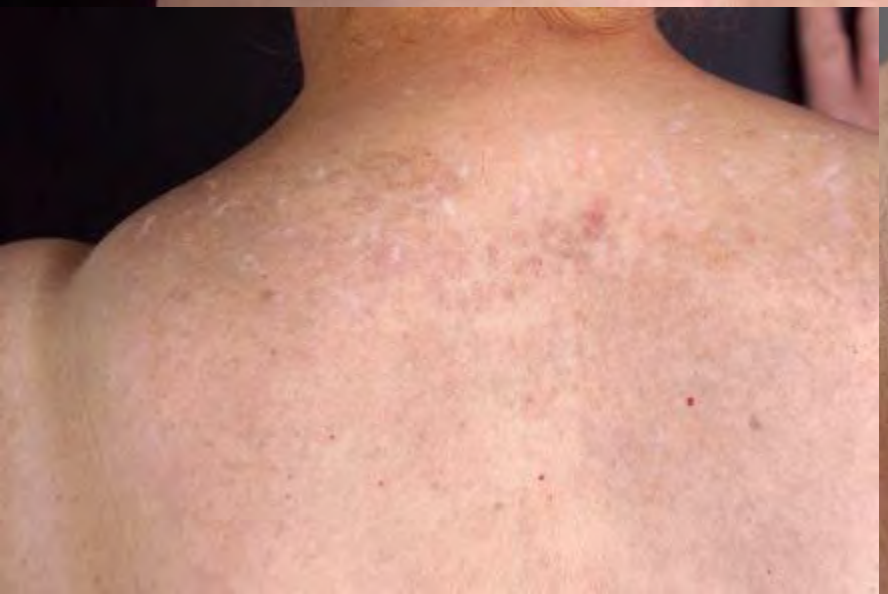
Figure 2. Macular lesions in a whorled and arcuate distribution on the back.

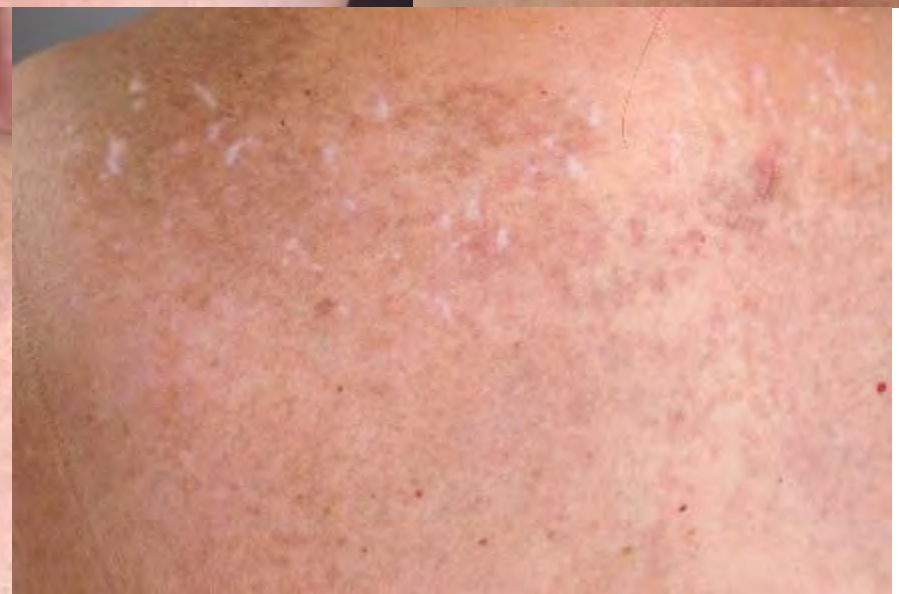
Figure 1. Lichenoid lesions in a reticulate pattern on the right thigh.

Correspondence to J.F.Bourke.









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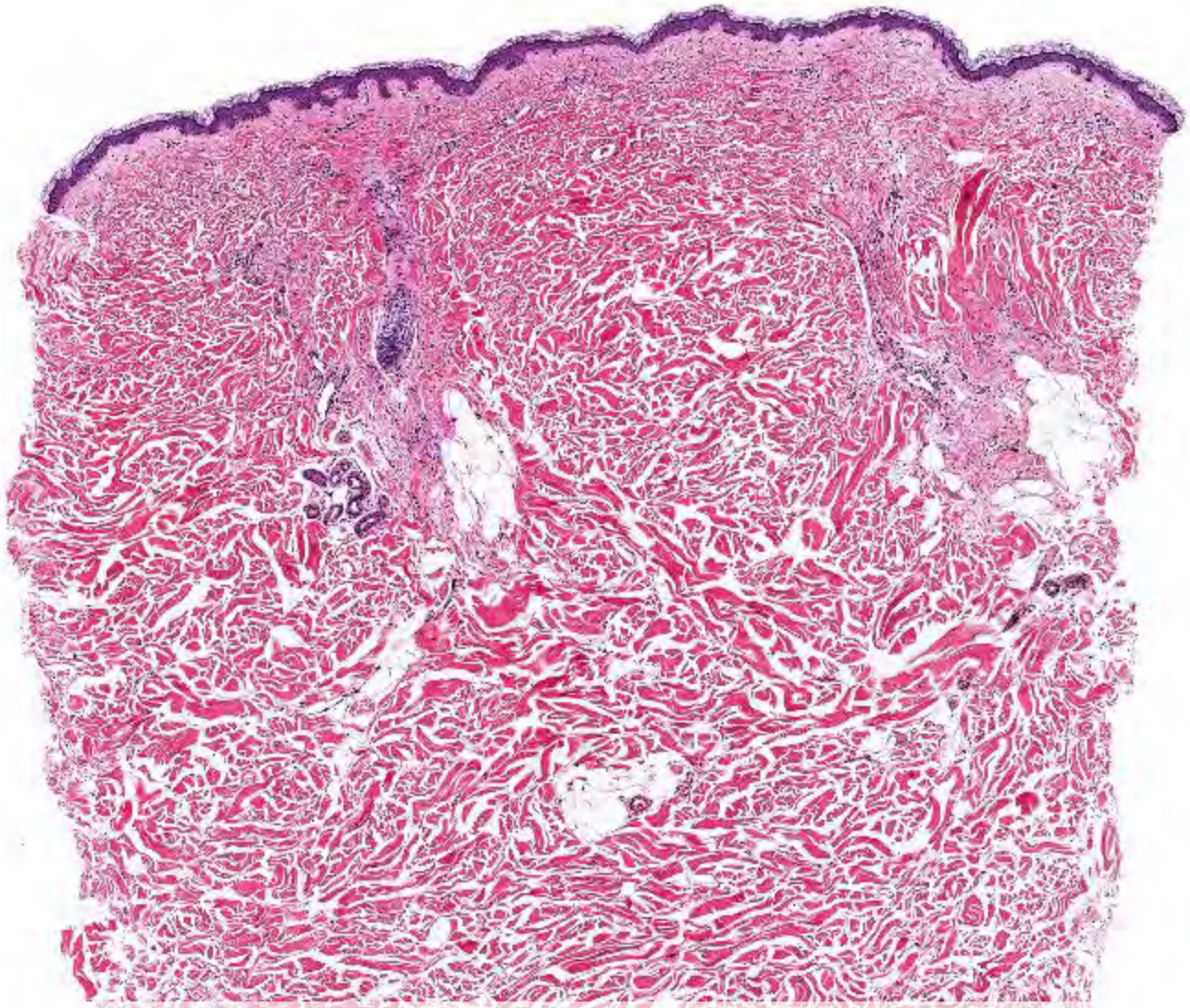
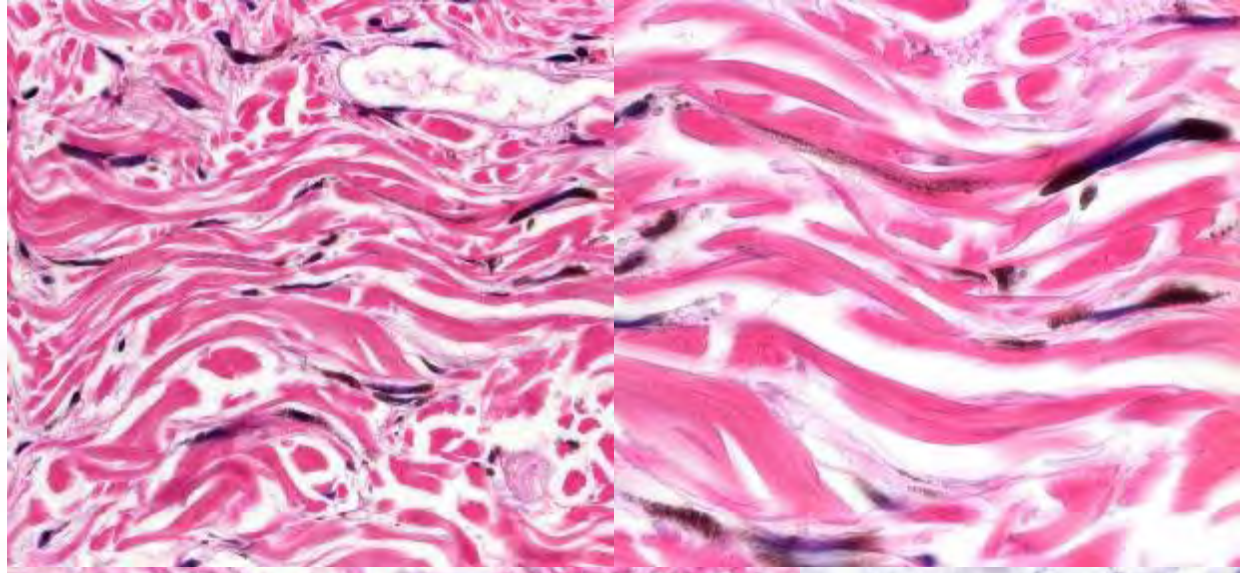
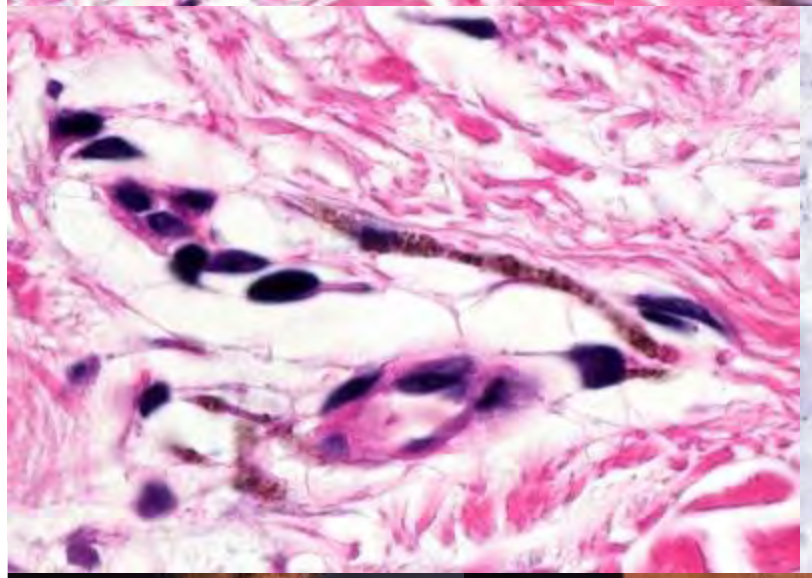
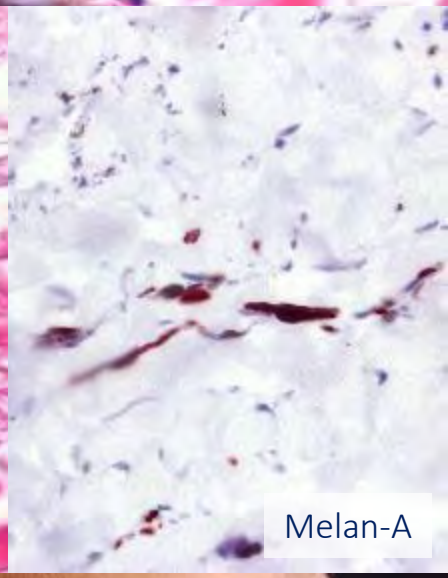
Slowly growing, itchy, hyperpigmented lesions on the shoulders for 10 years.

A biopsy is taken.



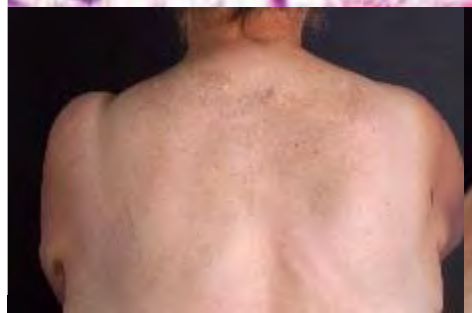


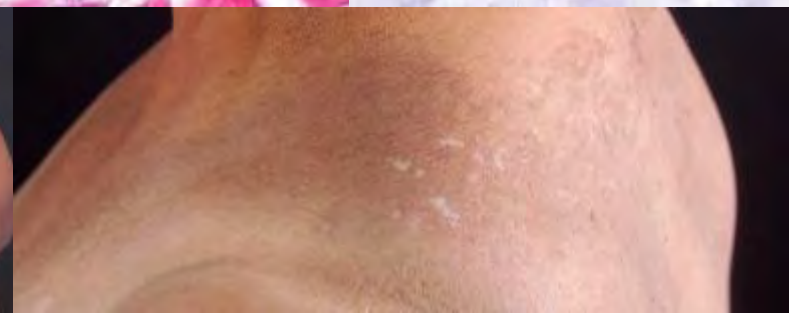




Acquired dermal melanocytosis

associated with chronic pruritus / atopic dermatitis of the elderly





Acquired, bilateral nevus of Ota–like macules

Yoshiaki Hori, M.D., Makoto Kawashima, M.D., Kuniaki Oohara, M.D., and Atsushi Kukita, M.D. *Nakakoma-Gun, Yamanashi-Ken, and Tokyo, Japan*

Blue-brown macules of the face occurring on both sides of the forehead, temple, eyelids, malar area, alae of the nose, and root of the nose are often observed in middle-aged Japanese women. These lesions histologically are a form of dermal melanocytosis as shown by electron microscopic examination. They differ clinically from nevus of Ota. The differential diagnosis includes nevus of Ota, Riehl's melanosis (female facial melanosis), and melasma. The differences between them are discussed. (J Am Acad Dermatol **10**:961-964, 1984.)

The nevus of Ota is usually unilaterally located in the areas innervated by the first and second branches of the trigeminal nerve. It is a macular lesion with a mixture of small brown patches and blue macules, and it is usually congenital, but may appear later in life (in the second decade). The size and intensity of pigmentation may increase with advancing age. Pigmented macules are also often present in ocular, oral, or nasal mucosal membranes.[1]

Recently, we have observed acquired blue-brown macules of the face occurring bilaterally on the forehead, temples, eyelids, cheeks, and/or nose. These macules are similar clinically to nevus of Ota, female facial melanosis (Riehl's melanosis), or melasma. They usually appear in the fourth or fifth decade of life in Japanese women (only rarely in Japanese men) and are not observable in ocular and mucosal membranes.

From the Department of Dermatology, Yamanashi Medical College, Nakakoma-Gun, Yamanashi-Ken, and the Department of Dermatology, University of Tokyo Faculty of Medicine, Bunkyo-Ku, Tokyo.

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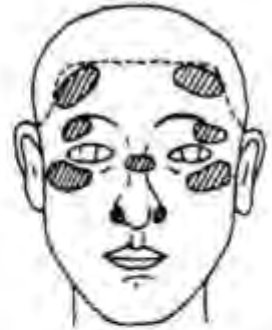
Reprint requests to: Dr. Yoshiaki Hori, Department of Dermatology, Yamanashi Medical College, 1110, Shimokato, Tamaho-Mura, Nakakoma-Gun, Yamanashi-Ken, Japan 409-38.



1. lateral sites of the forehead
2. upper eyelids
3. malar area
4. root of the nose
5. alae of the nose

Fig. 1. Distribution of pigmented macules in acquired, bilateral nevus of Ota–like macules.

Table I. Classification of circumscribed dermal melanocytoses[3]

1.	Mongolian spots
2.	Blue nevus (macular type)
3.	Nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris)
4.	Acquired, bilateral nevus of Ota–like macules
5.	Nevus of Ito (nevus fuscoceruleus acromiodeltoideus)
6.	Blue macule associated with progressive systemic scleroderma[4]

 DOI 10.1111/j.1365-2133.2005.06381.x

Acquired symmetrical dermal melanocytosis (naevus of Hori) developing after aggravated atopic dermatitis

T. Murakami, Y. Sumi* and M. Mizoguchi*

Dermatology Division, Yaotsu City Seto Hospital, & *Mizuho University School of Medicine, Yaotsu, Japan.
*Department of Dermatology, St Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, 216-8511, Japan.

Correspondence
Yasuaki Sumi MD.
E-mail: sumi@marianna-u.ac.jp

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Key words:
acquired symmetrical dermal melanocytosis, atopic dermatitis, naevus of Hori

Conflicts of interest:
None declared

Summary

Background Acquired symmetrical dermal melanocytosis (ASDM) is a pigmentary disorder characterized by blue-brown macules most frequently seen on the face of young and middle-aged Asian women. ASDM developing after cutaneous skin diseases has not been previously reported.

Objectives To characterize the clinical and histopathological features of ASDM associated with atopic dermatitis (AD) and to elucidate the differences between AD-associated ASDM and idiopathic ASDM.

Methods Sixteen patients with ASDM associated with AD were examined clinically and histopathologically and were compared with 69 patients with idiopathic ASDM.

Results The AD patients associated with ASDM consisted of four men and 12 women with a mean age of 32·8 ± 12·1 years. Most patients remembered that the pigmented macules appeared in cases where refractory eczema had existed for a long time. The marked predominance in females and the appearance in the early reparative period were common features of AD-associated ASDM and idiopathic ASDM. AD-associated ASDM was most commonly observed on the forehead (68·8%) and on the backs of the hands (30·0%), whereas 89·9% of idiopathic ASDM was seen on the cheeks. There was no significant difference in the number of dermal melanocytes between AD-associated ASDM and idiopathic ASDM. Electron microscopic studies demonstrated many mature melanocytes and smaller numbers of immature melanocytes in the dermis. Some melanocytes were seen adjacent to mast cells.

Conclusion AD-associated ASDM does not appear to be rare in Japan. ASDM may be triggered in AD patients by sunlight exposure, some alterations in skin permeance and/or persistent cutaneous inflammation. Histamine and stem cell factor produced by mast cells may play crucial roles in the pathogenesis of AD-associated ASDM.

Acquired symmetrical dermal melanocytosis (ASDM) (naevus of Hori) was first identified and described by Hori *et al.* in 1984 as acquired, bilateral naevus of Ota-like macules.[1] That study reviewed 23 patients with blue and blue-brown macules on the face, often observed in middle-aged Japanese women. Since then, several series of patients with ASDM, including our own, have been reported from Taiwan[2] and Japan,[3,4] revealing that the pigmented macules are not limited to the face but are also found on other parts of the body, most frequently on the upper extremities.[3,4] The dermal melanocytosis in the pigmented macules exists in the upper and mid-dermis, in contrast to the pathological findings of naevus of Ota where the pigmentation cells are distributed diffusely throughout the upper and lower dermis.[1,2,4] The onset of pigmented macules in ASDM is usually between the second and the fourth decade of life.[1–4]

Similar conditions have been described under several different terms, such as nevus fusco-caeruleus zygomaticus,[5] acquired dermal melanocytosis of the face and extremities,[6] acquired dermal melanocytosis,[4,7] and acquired bilateral nevus of Ota-like macules (Hori's naevus).[3,8] It may not be appropriate to include the name 'naevus of Ota' in the terminology for this condition, as the pigmented macules of ASDM are distinct from naevus of Ota both clinically and histopathologically.[1,3,4] Although acquired dermal melanocytoses with asymmetrical distribution has been reported in

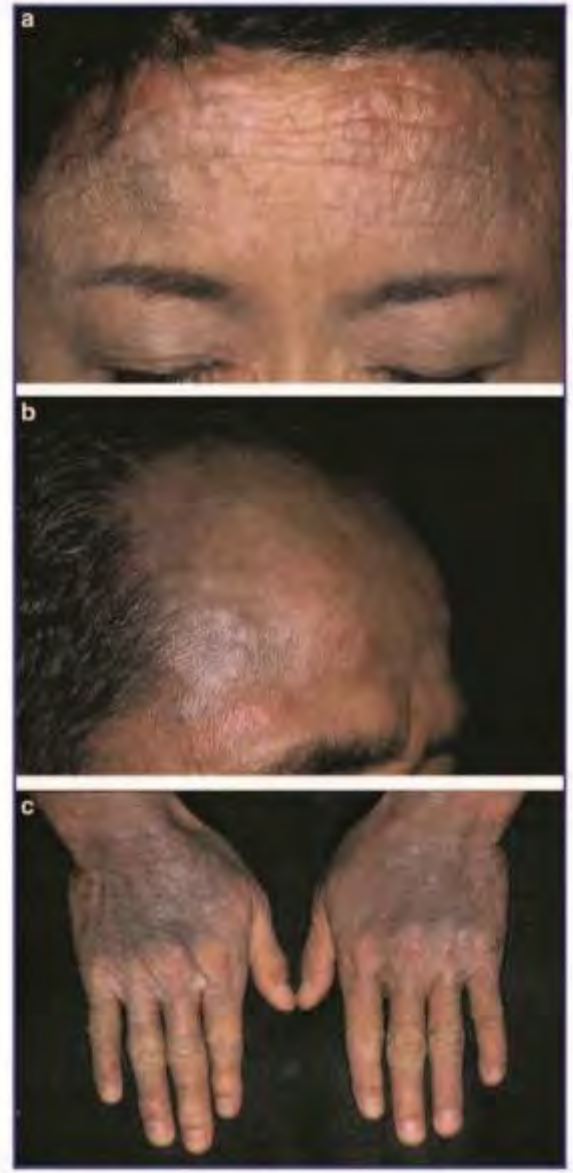


Fig 1. Clinical findings of atopic dermatitis-associated acquired symmetrical dermal melanocytosis. Poorly demarcated blue–grey macules on both sides of the forehead (a,b) and on the backs of the hands (c) with concomitant atopic eczema.

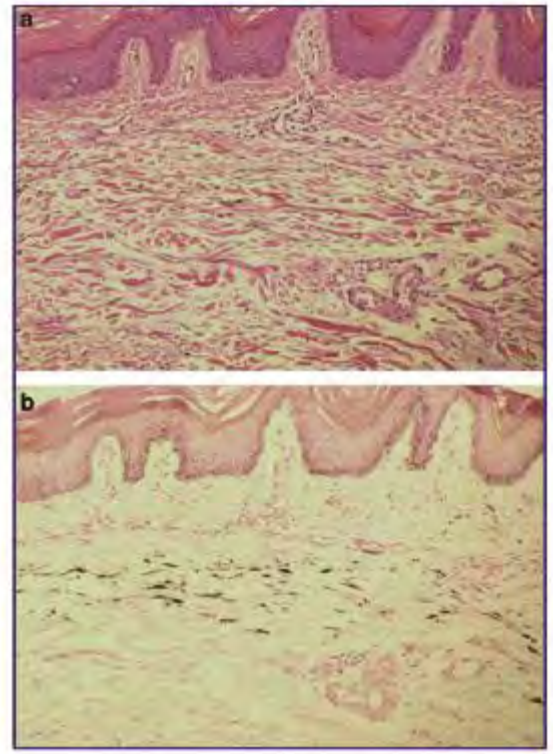
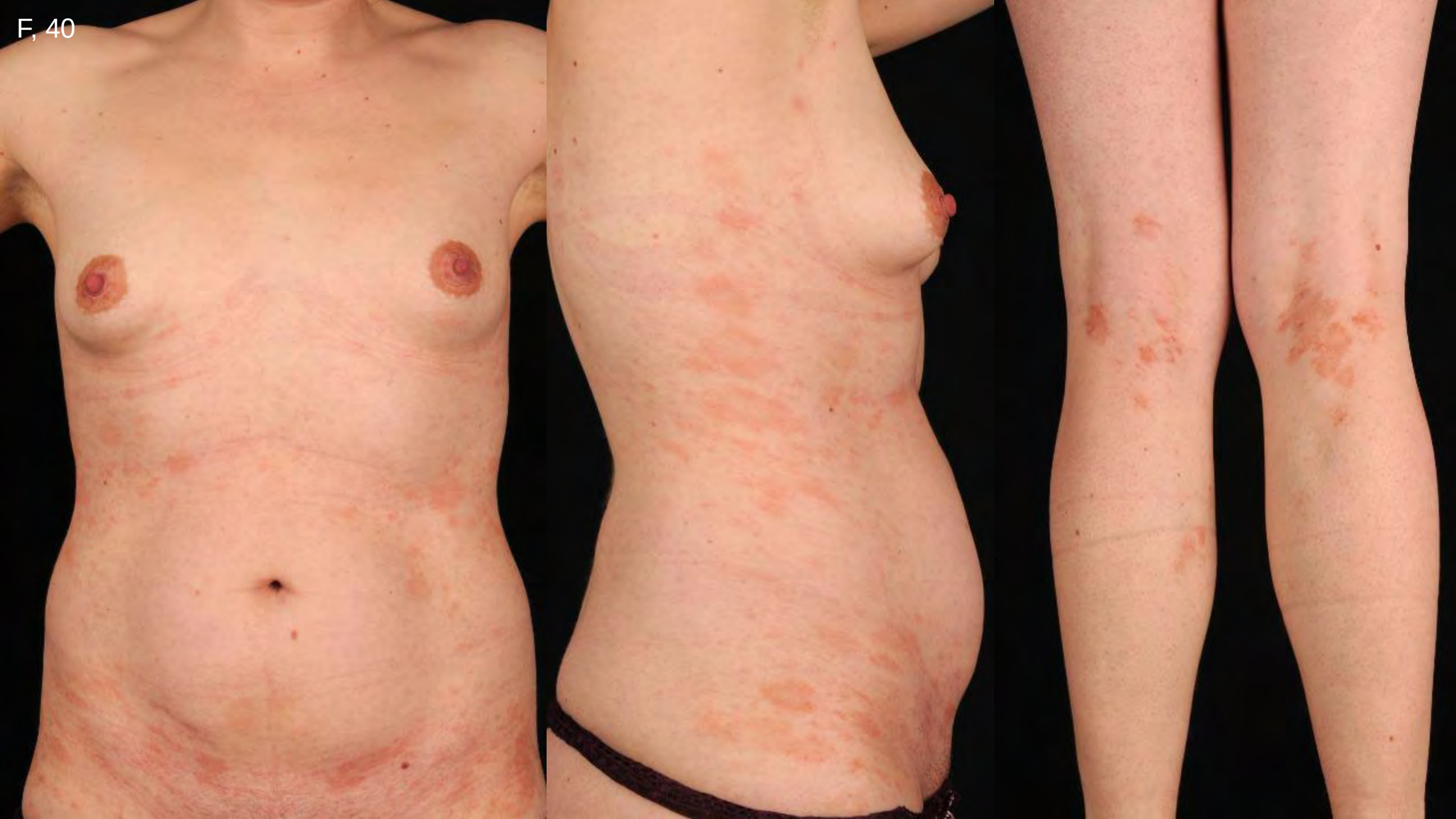


Fig 2. Histopathological findings of atopic dermatitis-associated acquired symmetrical dermal melanocytosis. (a) Haematoxylin–eosin staining; (b) Masson–Fontana staining.

Table 1 Distribution of lesions in patients with acquired symmetrical dermal melanocytosis (ASDM)

	AD-associated ASDM	Idiopathic ASDM
Forehead	11 (68·8%)*	21 (30·4%)
Eyelids	1 (6·3%)	7 (10·1%)
Cheeks	6 (37·5%)	62 (89·9%)**
Nasal radix	2 (12·5%)	13 (18·8%)
Nasal alae	3 (18·8%)	21 (30·4%)
Lips	1 (6·3%)	1 (1·4%)
Arms and hands	8† (50·0%)**	4 (5·8%)
Legs and feet	0 (0%)	2 (2·9%)
Total cases	16	69

†Backs of the hands in all cases. *$P < 0.05$, **$P < 0.01$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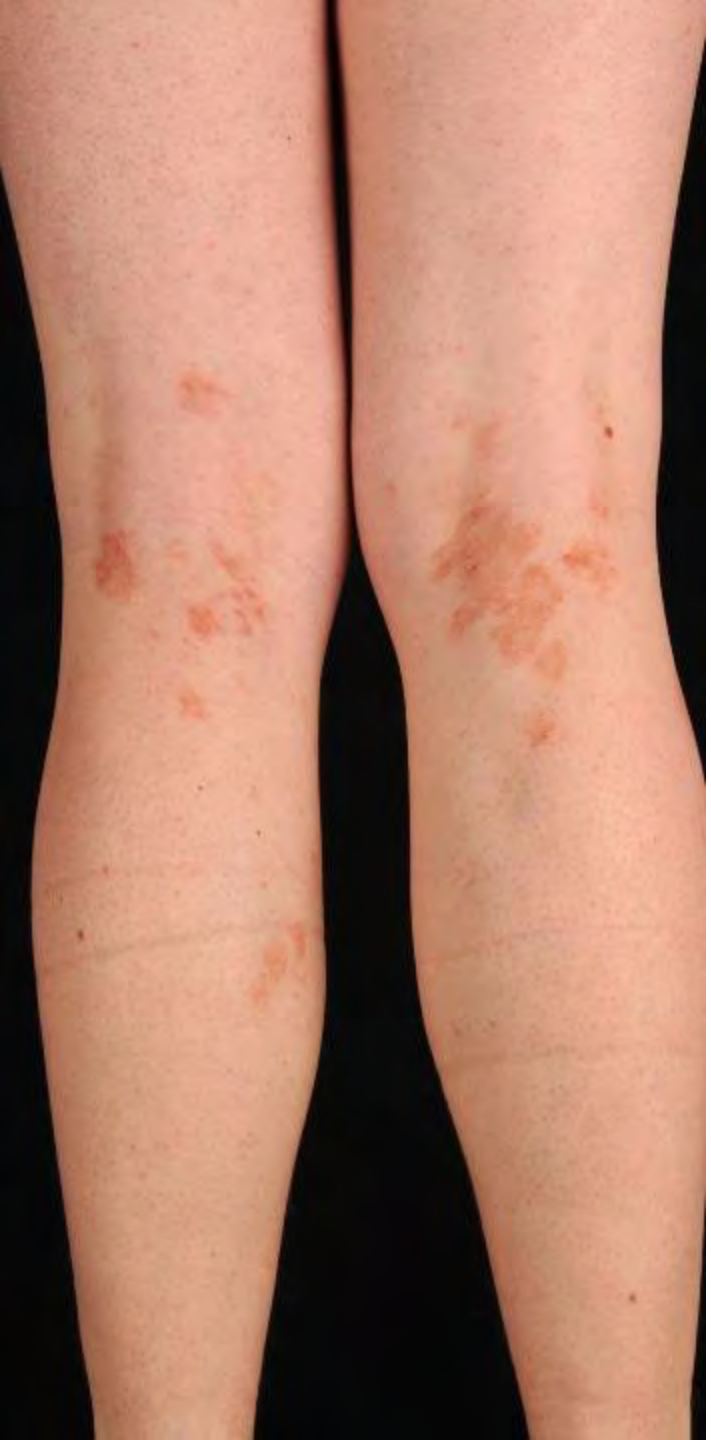
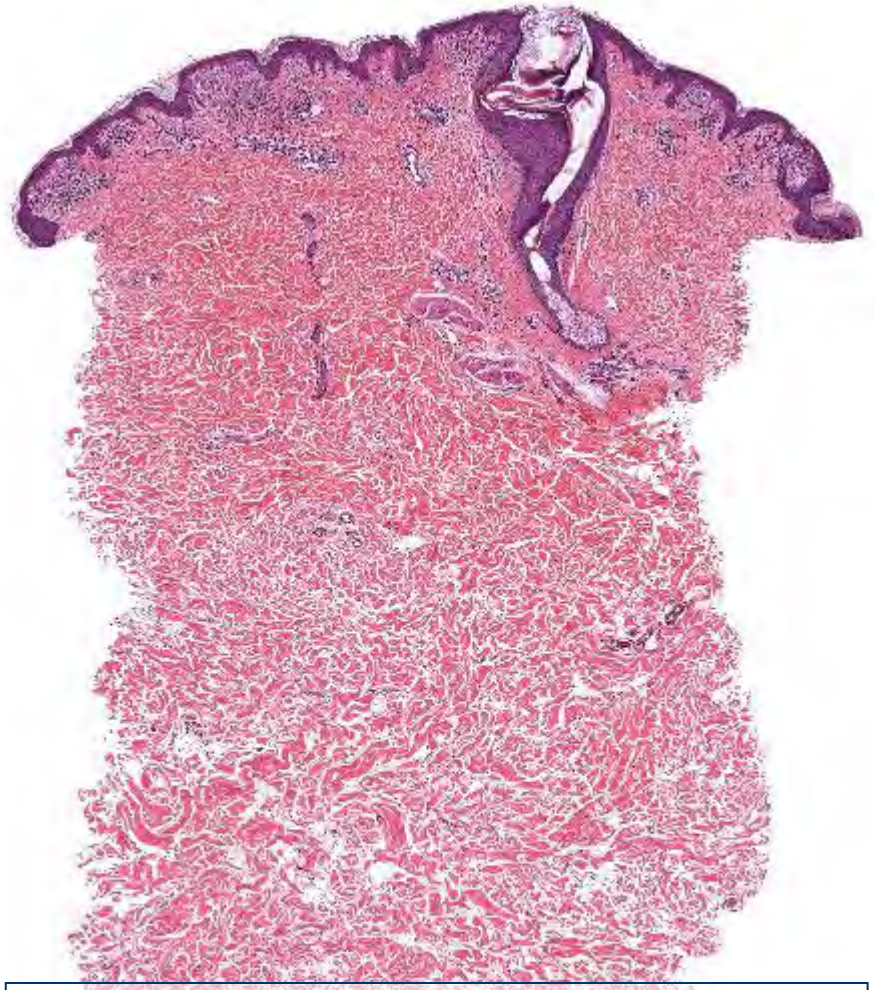
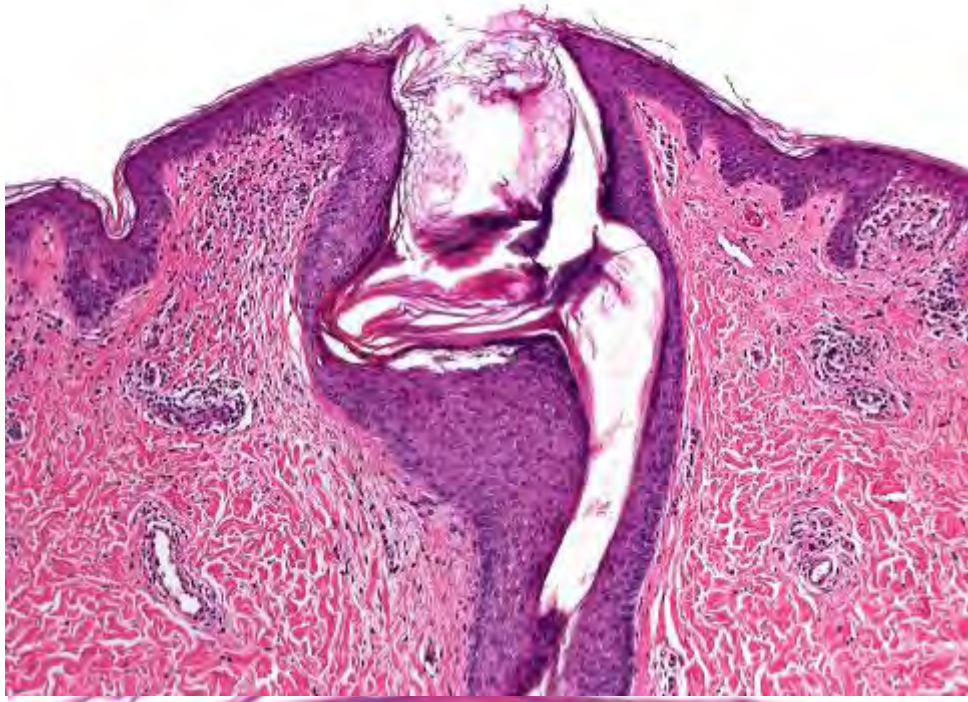
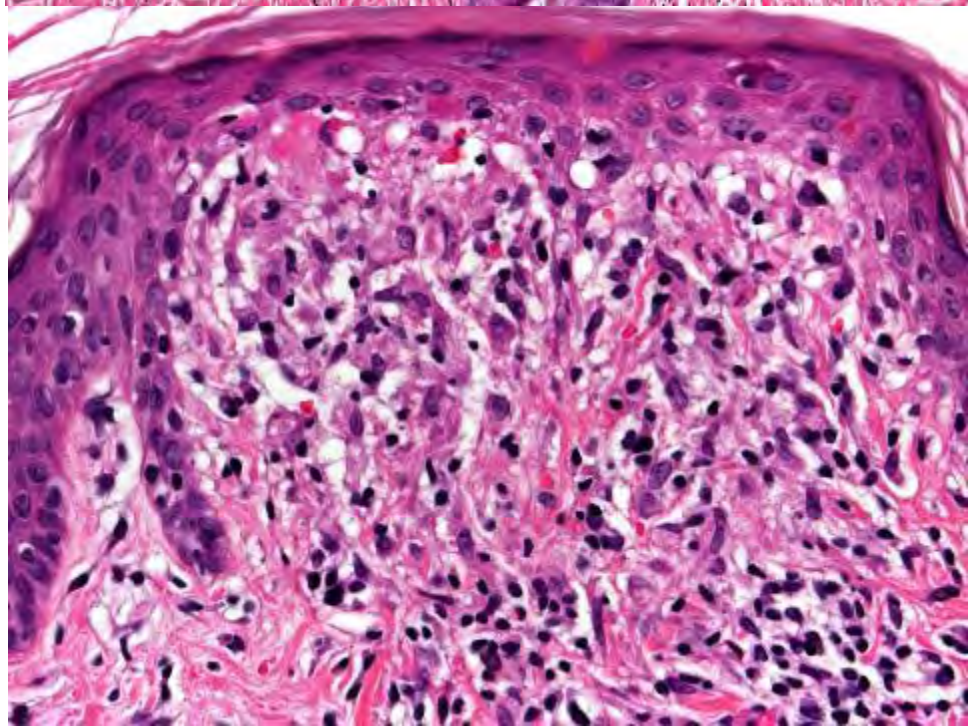
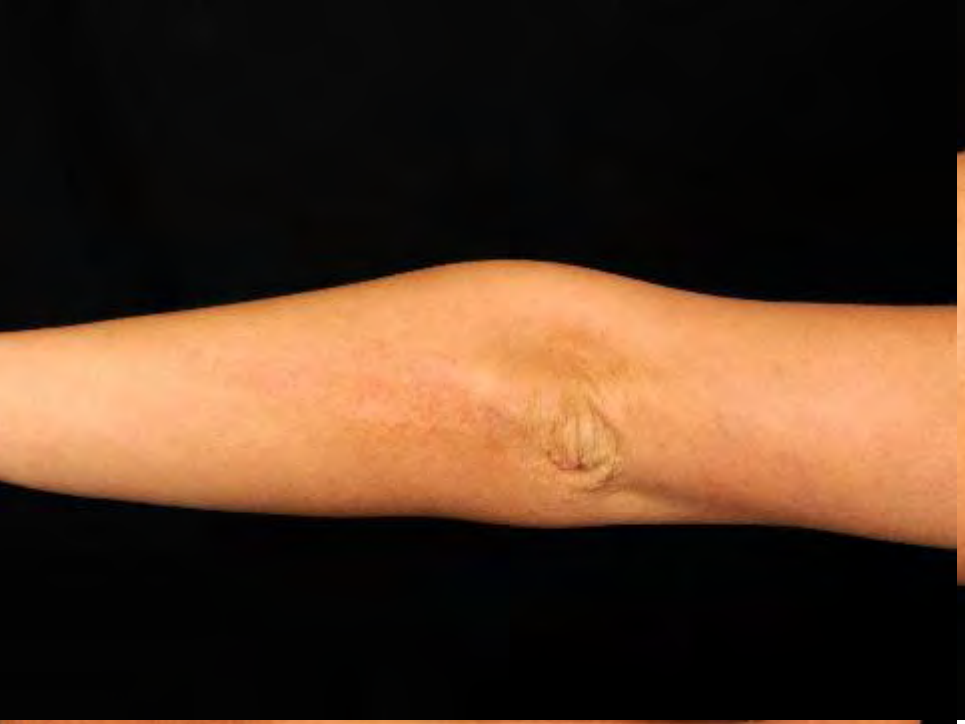
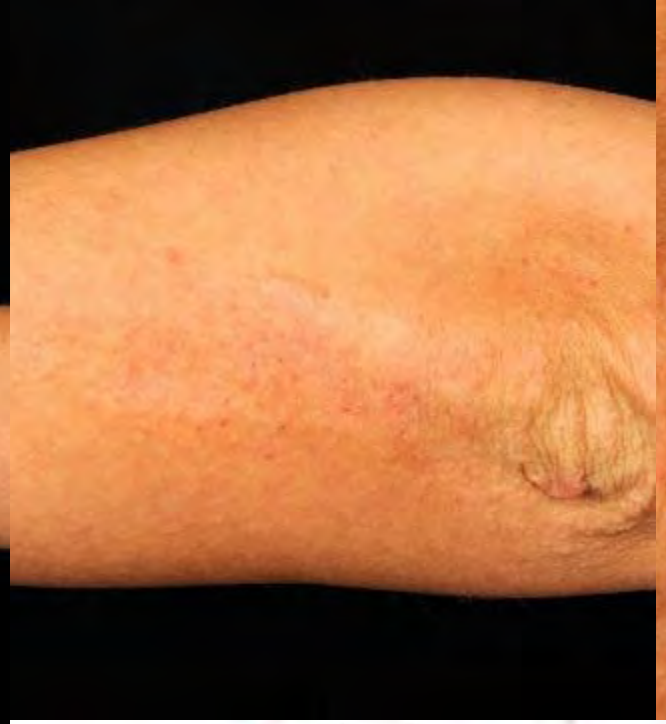
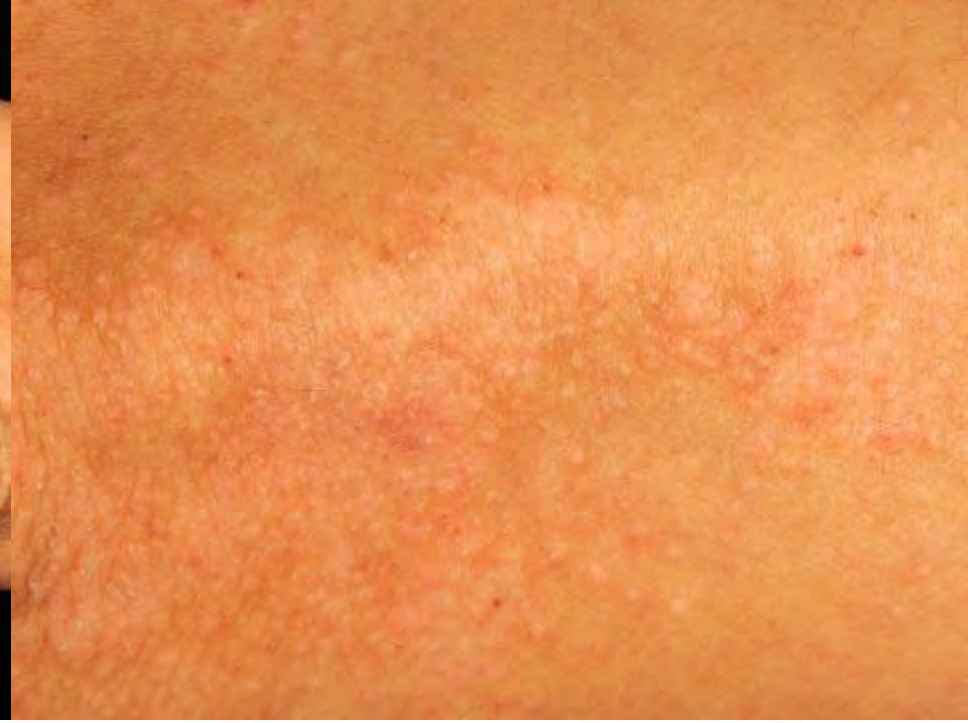
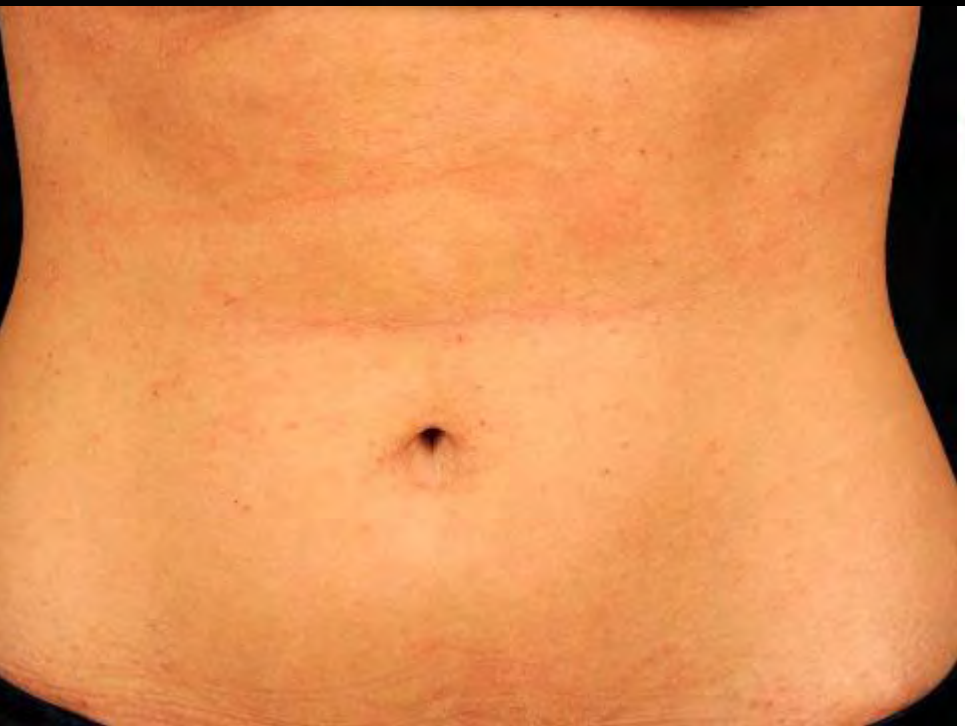
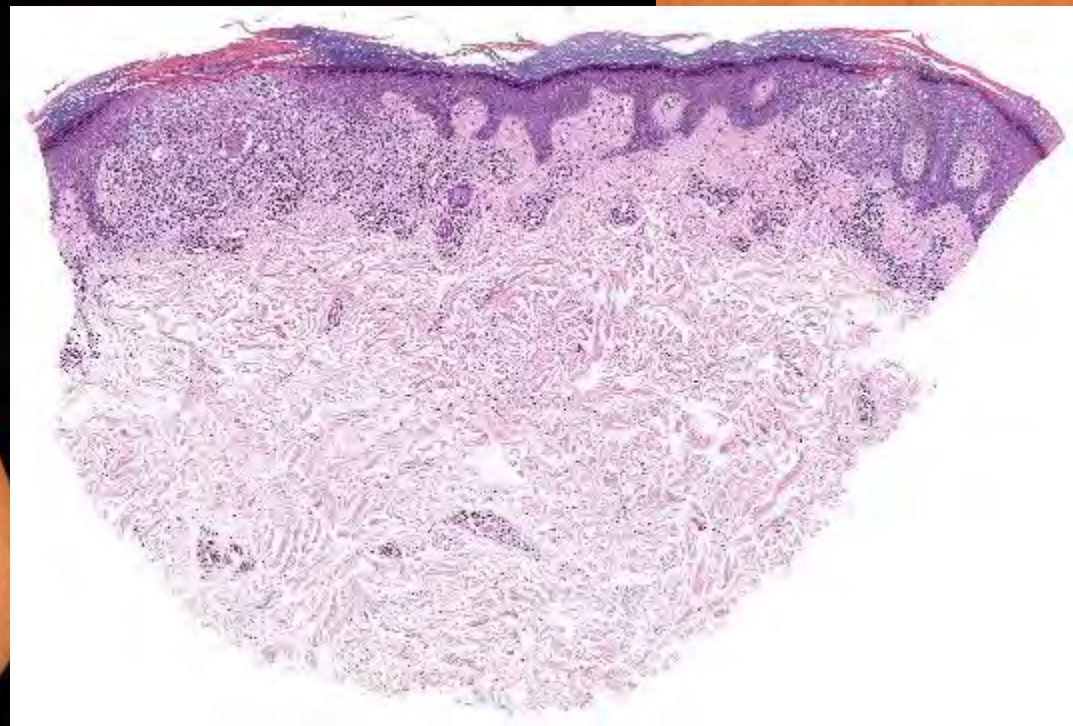
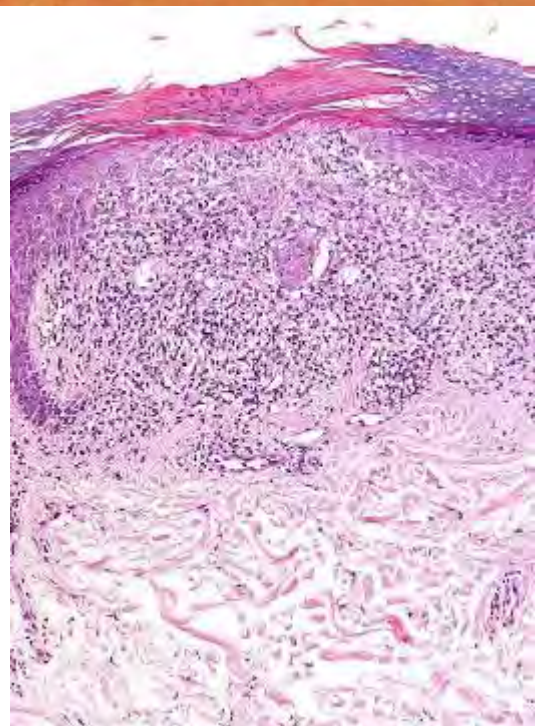








Atopic dermatitis with follicular hyperkeratosis and lichen nitidus-like granulomatous infiltrate

Abnormal Morphology of Blood Vessels in Erythematous Skin From Atopic Dermatitis Patients

Moe Tsutsumi, PhD,† Maki Fukuda, BS,† Junichi Kumamoto, BS,*† Makiko Goto, PhD,*† Sumiko Denda, PhD,*† Kenshi Yamasaki, MD, PhD,§ Setsuya Aiba, MD, PhD,§ Masaharu Nagayama, PhD *‡ and Mitsuhiko Denda, PhD*†*

Abstract: Previous studies suggest that altered peripheral blood circulation might be associated with erythema or inflammation in atopic dermatitis (AD) patients. However, the overall structure of blood vessels and capillaries in AD skin is poorly understood because most studies have involved light microscopic observation of thin skin sections. In the present study, we compared the 3-dimensional structures of peripheral blood vessels of healthy subjects and AD patients in detail by means of 2-photon microscopy. In skin from healthy subjects, superficial vascular plexus and capillaries originating from flexuous blood vessels were observed. However, skin from AD patients contained thickened, flexuous blood vessels, which might be associated with increased blood flow, in both erythematous and nonlesional areas. However, patients with lichenification did not display these morphological changes. Diffuse dilation of vessels was not observed in either erythematous or lichenification lesions. These results might be helpful for developing new clinical strategies to treat erythema in AD patients.

Key Words: two-photon microscopy, peripheral blood vessel, vascular plexus

(*Am J Dermatopathol* 2016;38:360–364)

INTRODUCTION

In the dermis of normal subjects, the vascular system is organized into a deep and superficial horizontal plexus from which capillaries originate.[1] In acute inflammation, blood vascular endothelial cells are activated by multiple inflammatory mediators [such as vascular endothelial growth factor (VEGF)], leading to typical signs of inflammation as a result of both increased blood flow because of vessel dilation and edema formation because of increased vessel permeability. For example, the number and size of blood vessels are increased in inflamed skin of K14-VEGF-A transgenic mice compared with uninflamed skin.[2] Accordingly, previous reports suggest that altered peripheral blood circulation might be associated with erythema in atopic dermatitis (AD) patients. For example, the amount of VEGF in lesional scales in AD was 25 times higher than that in normal stratum corneum.[3] Steinhoff et al[4] suggested that the vascular system, including endothelial cells and smooth muscle cells, is intimately involved in the clinical symptoms of AD, including erythema, edema, leukocyte recruitment, and white dermographism, and they proposed that endothelial cells play a crucial role in the pathophysiology of AD.

These reports led us to hypothesize that the 3-dimensional structure of blood vessels and capillaries is altered in the erythematous skin of AD patients. To examine this question, light-microscopic observation of thin sections, as usually used, is inadequate because it cannot differentiate between increased vessel branching and increased total length of vessels. Therefore, we used 2-photon microscopy, which is a fluorescence imaging technique that allows imaging of tissue to a considerable depth to compare the 3-dimensional morphologies of blood vessels in the upper layer of dermis of healthy subjects and AD patients.

METHODS

Sample Collection

Skin samples were obtained from 10 Japanese healthy subjects and 9 AD patients with lichenification (20–37 years; mean age of 24 years; 12 men and 6 women). The study protocol was fully discussed with each patient and informed consent was obtained. The study was conducted in accordance with the guidelines of the National Institutes of Health and Declaration of Helsinki protocols and was approved by the ethics committees of Shiseido Research Center and Tohoku University Hospital. Tape stripping was performed 10–30 times under local anesthesia with lidocaine, and then a 3 mm punch biopsy was obtained from the back skin. In the case of AD patients, samples were taken from regions of erythema or lichenification and noninvolvent regions. The specimens were immediately immersed in 4% paraformaldehyde overnight at 4°C.

Immunohistochemical Study

After the 4% paraformaldehyde treatment, samples were kept in 30% sucrose until they sank to the bottom. Then, one half of each sample was embedded in optimal cutting temperature compound (Tissue-Tek; Sakura Finetek, Torrance, CA) and

From the †Japan Science and Technology Agency, CREST, Kawaguchi, Japan; ‡Shiseido Research Center, Yokohama, Japan; §Research Institute for Electronic Science, Hokkaido University, Sapporo, Japan; and ¶Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan.

The authors declare no conflicts of interest.

Reprints: Mitsuhiko Denda, PhD, Shiseido Research Center, 2-2-1, Hayabuchi, Tsuzuki-ku, Yokohama 224-8558, Japan (e-mail: mitsuhiko.denda@shiseido.co.jp).

Skin from AD patients contained thickened, flexuous blood vessels, which might be associated with increased blood flow, in both erythematous and nonlesional areas.

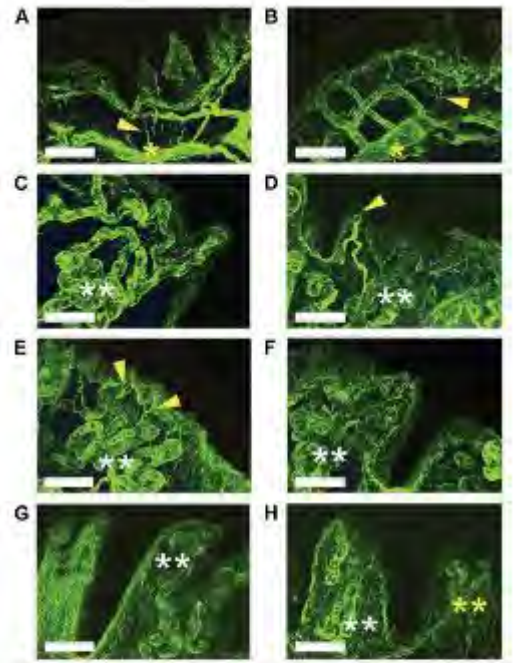
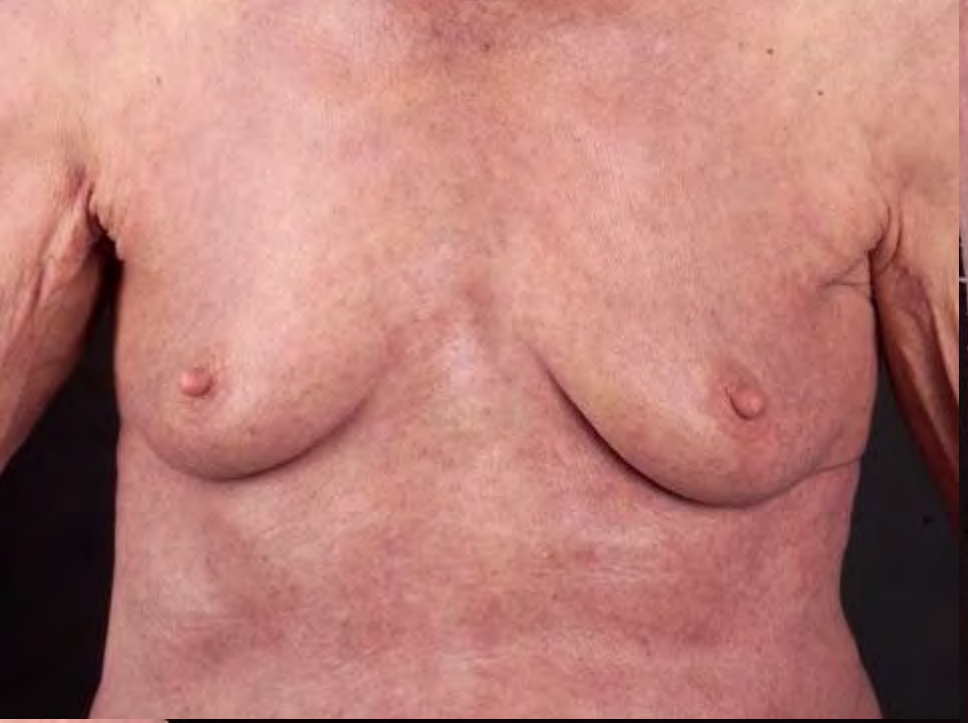
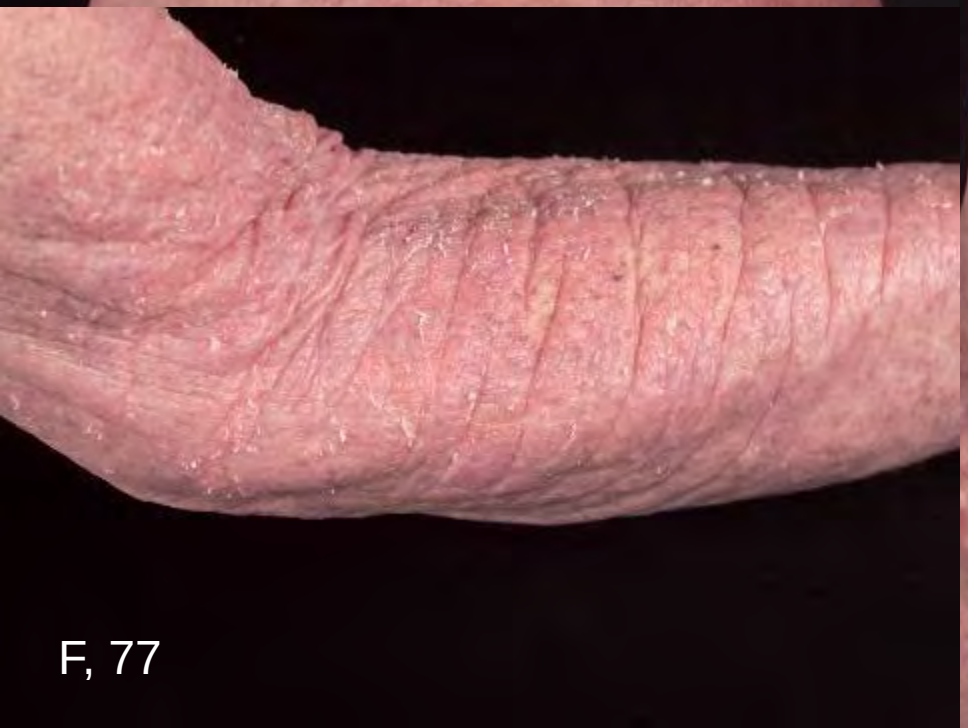
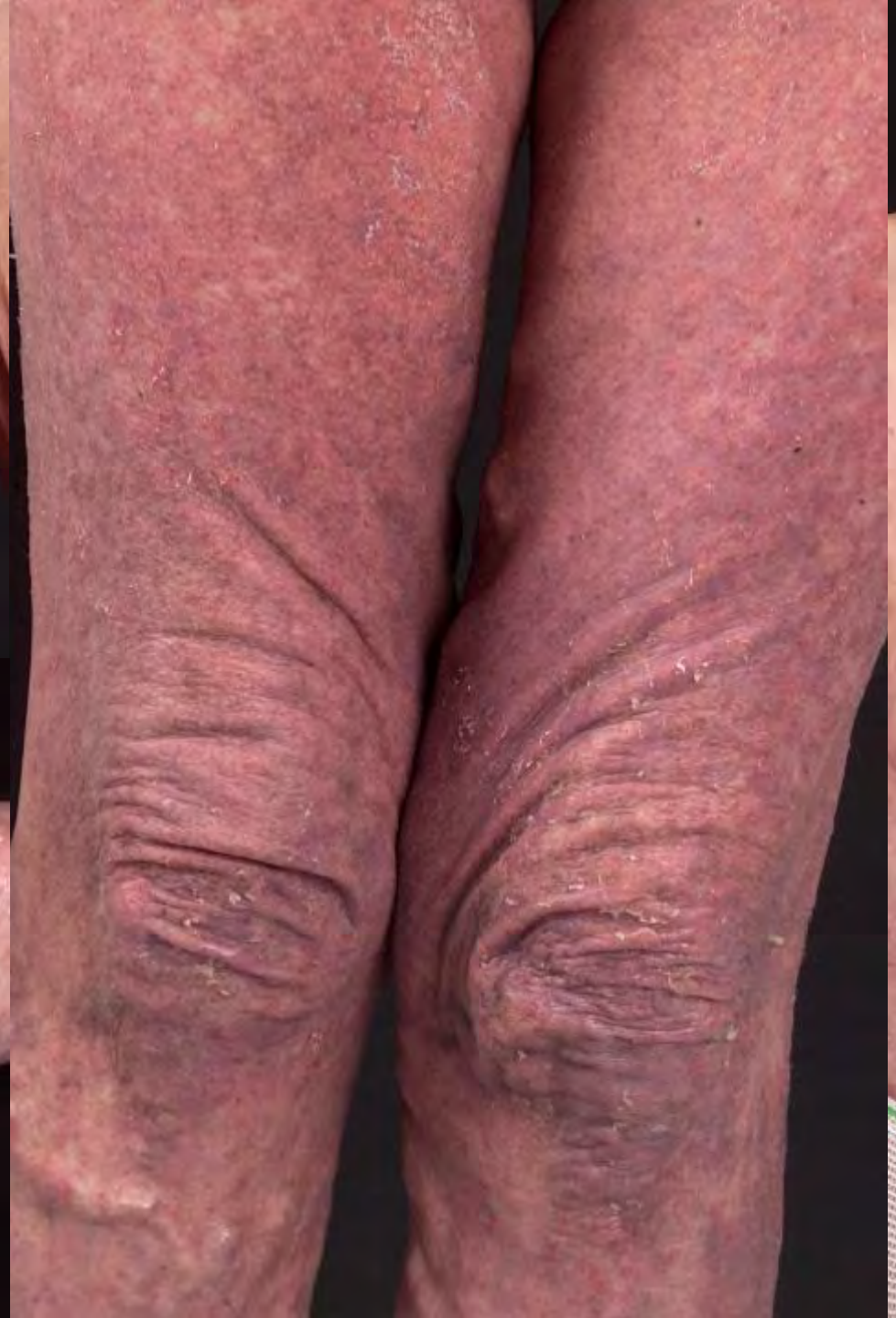
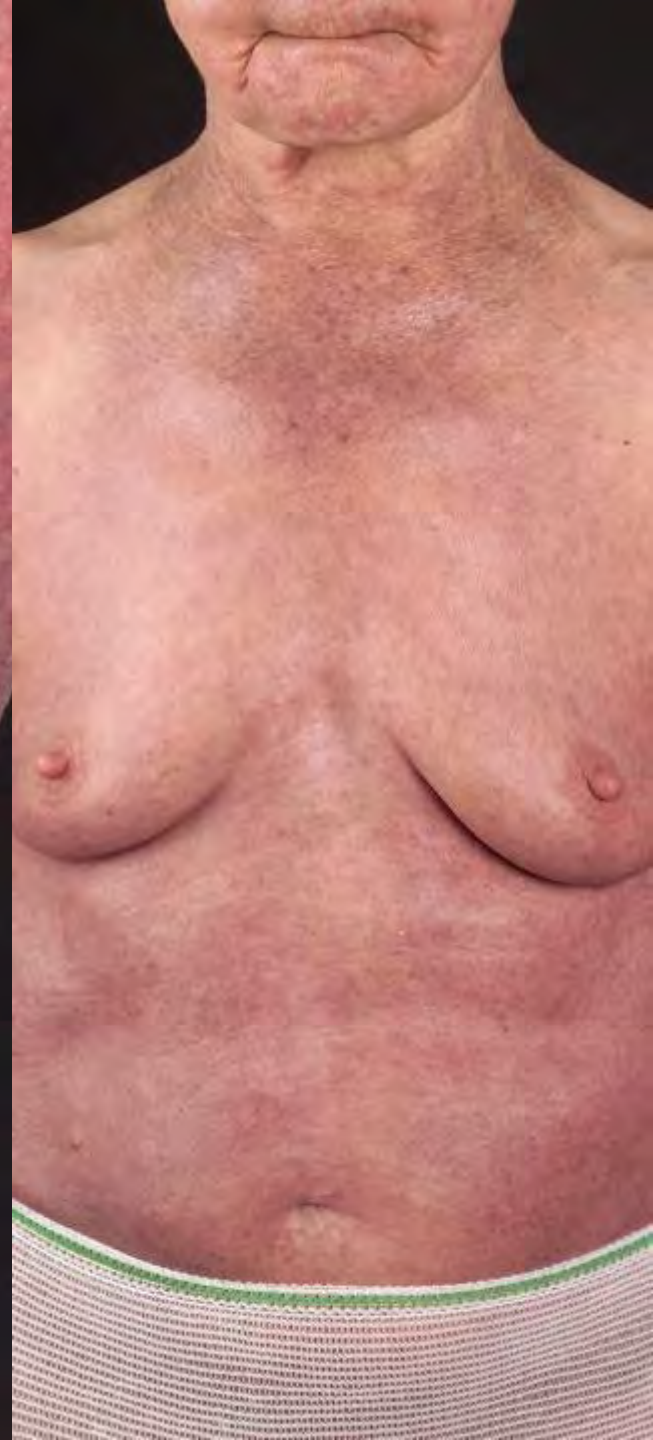


FIGURE 1. Representative images of peripheral blood vessels and capillaries in skin. A and B, Healthy subjects. Superficial vascular plexus (yellow asterisks) and capillary loops (yellow arrowheads) originating from the vascular plexus were observed. C and D, Erythematous lesional skin of AD patients. Flexuous complex structures were observed (double white asterisks). E and F, Nonlesional skin of AD patients. Flexuous complex structures were seen, similar to those in erythematous lesional skin (double white asterisks). A few capillary loops originating from flexuous blood vessels were observed in (D, E) (yellow arrowheads). G and H, Lesional skin with lichenification of AD patients. A few flexuous structures were observed (double white asterisks). Bars = 50 μm.









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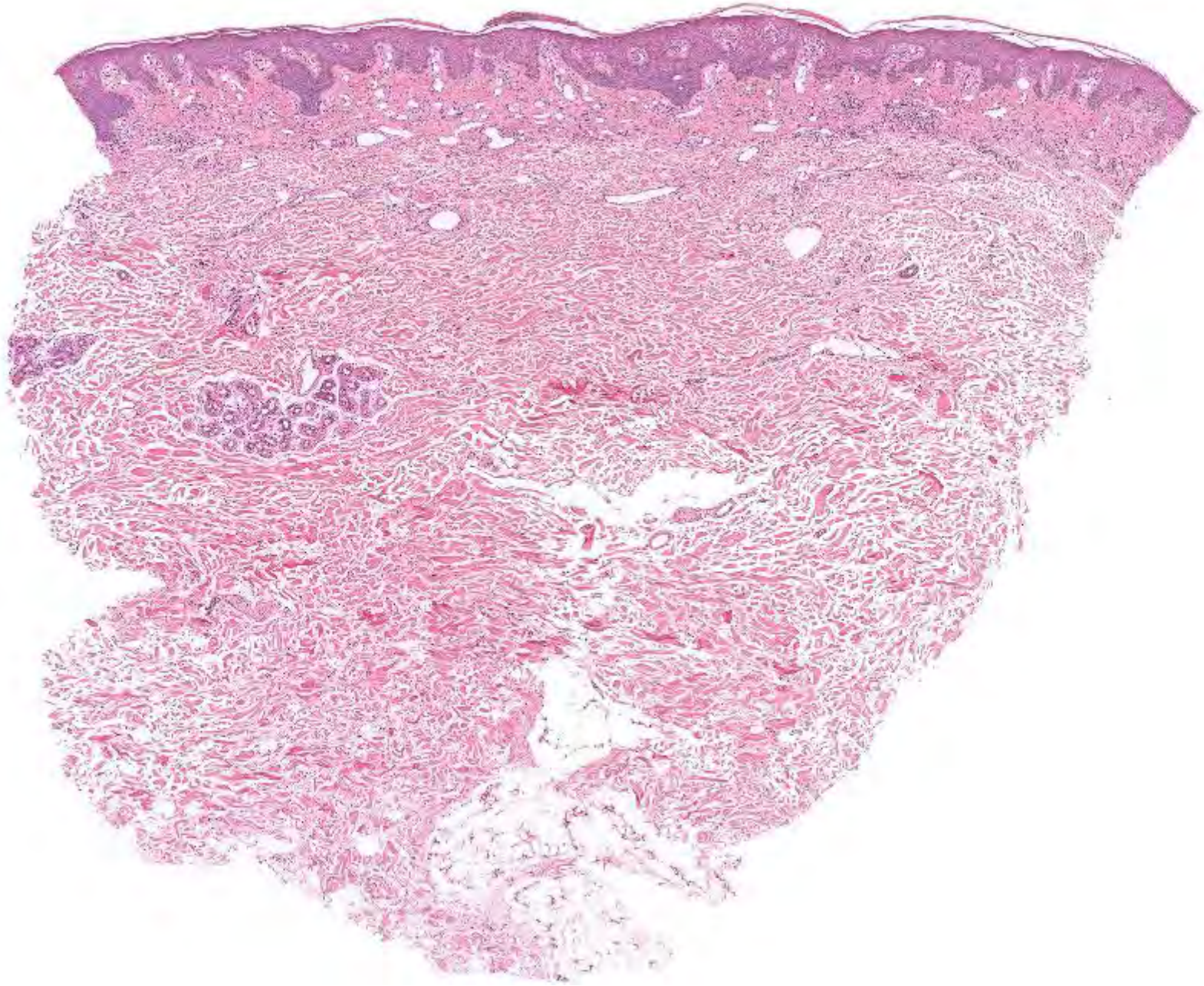

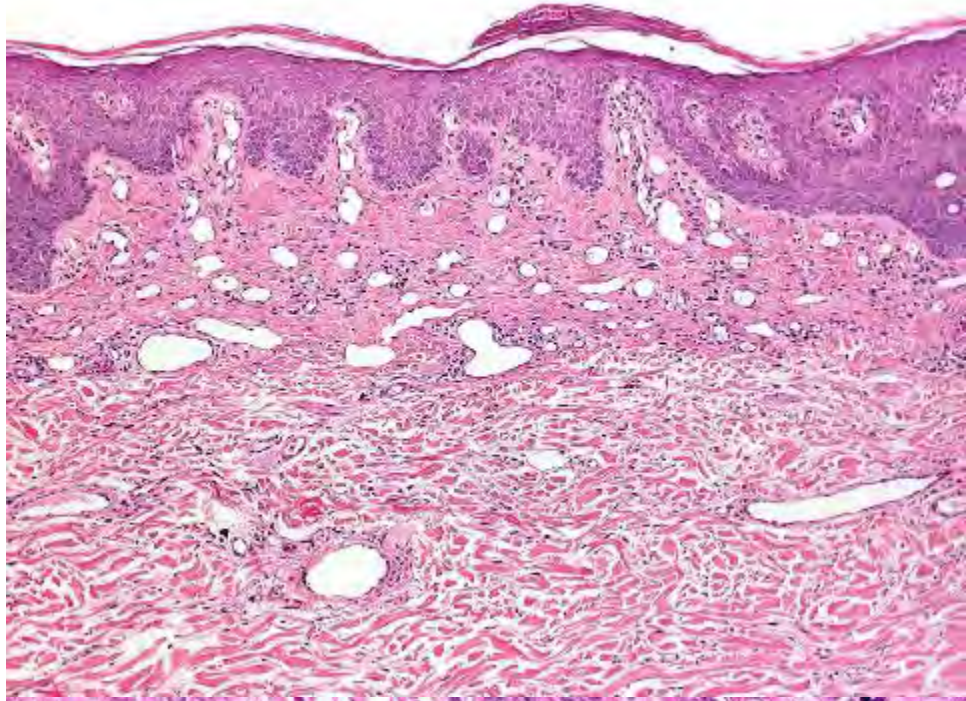

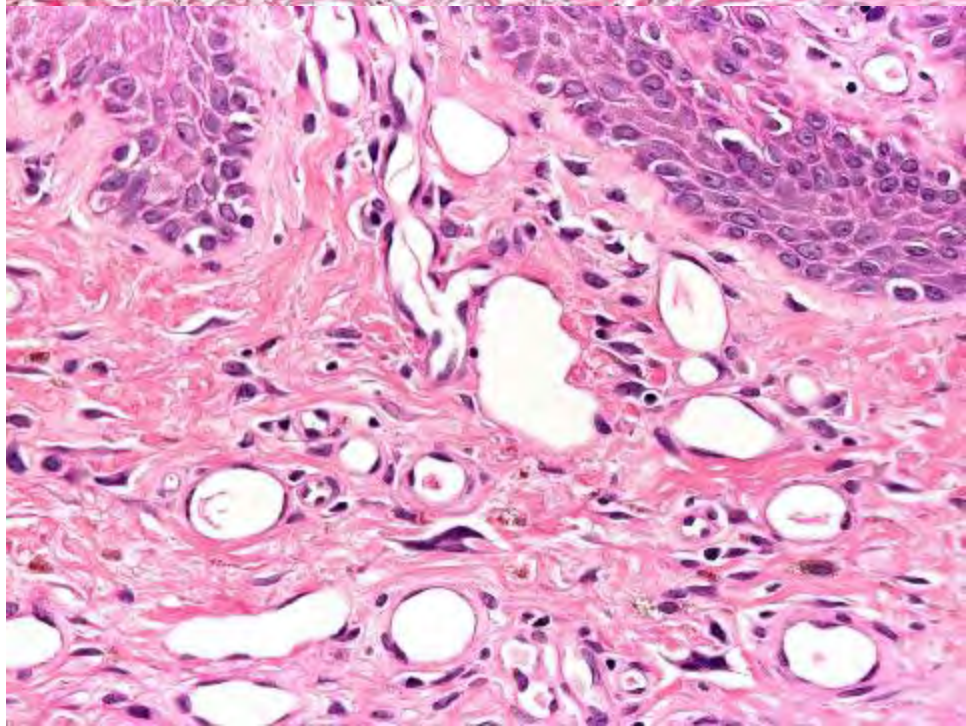

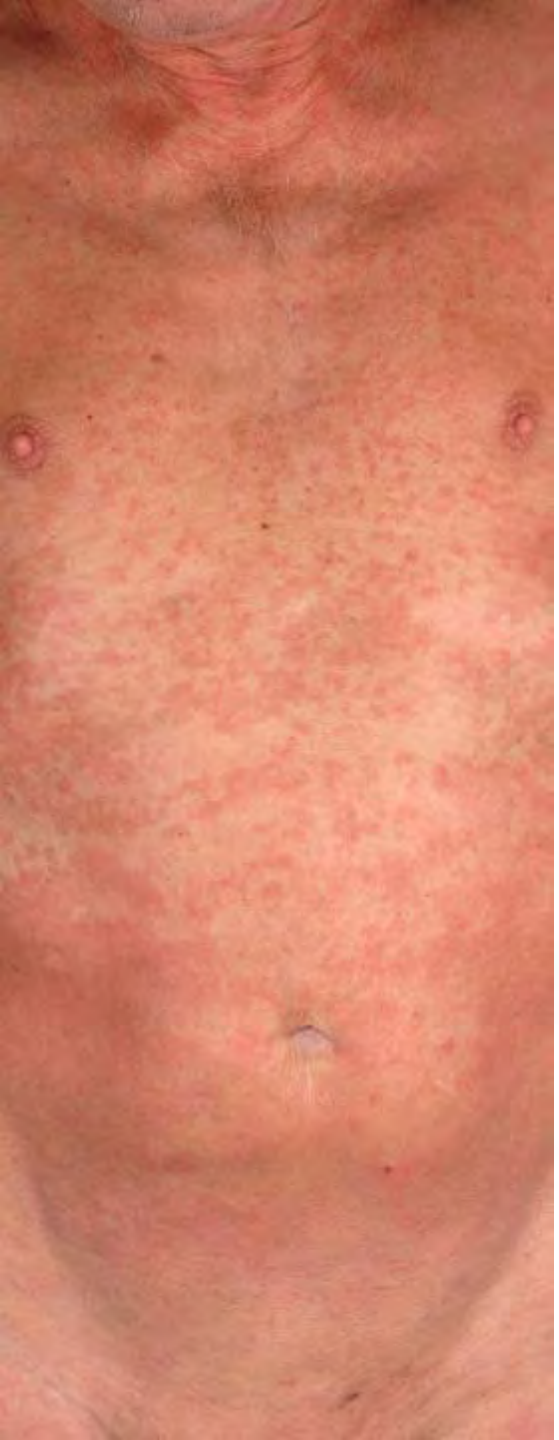

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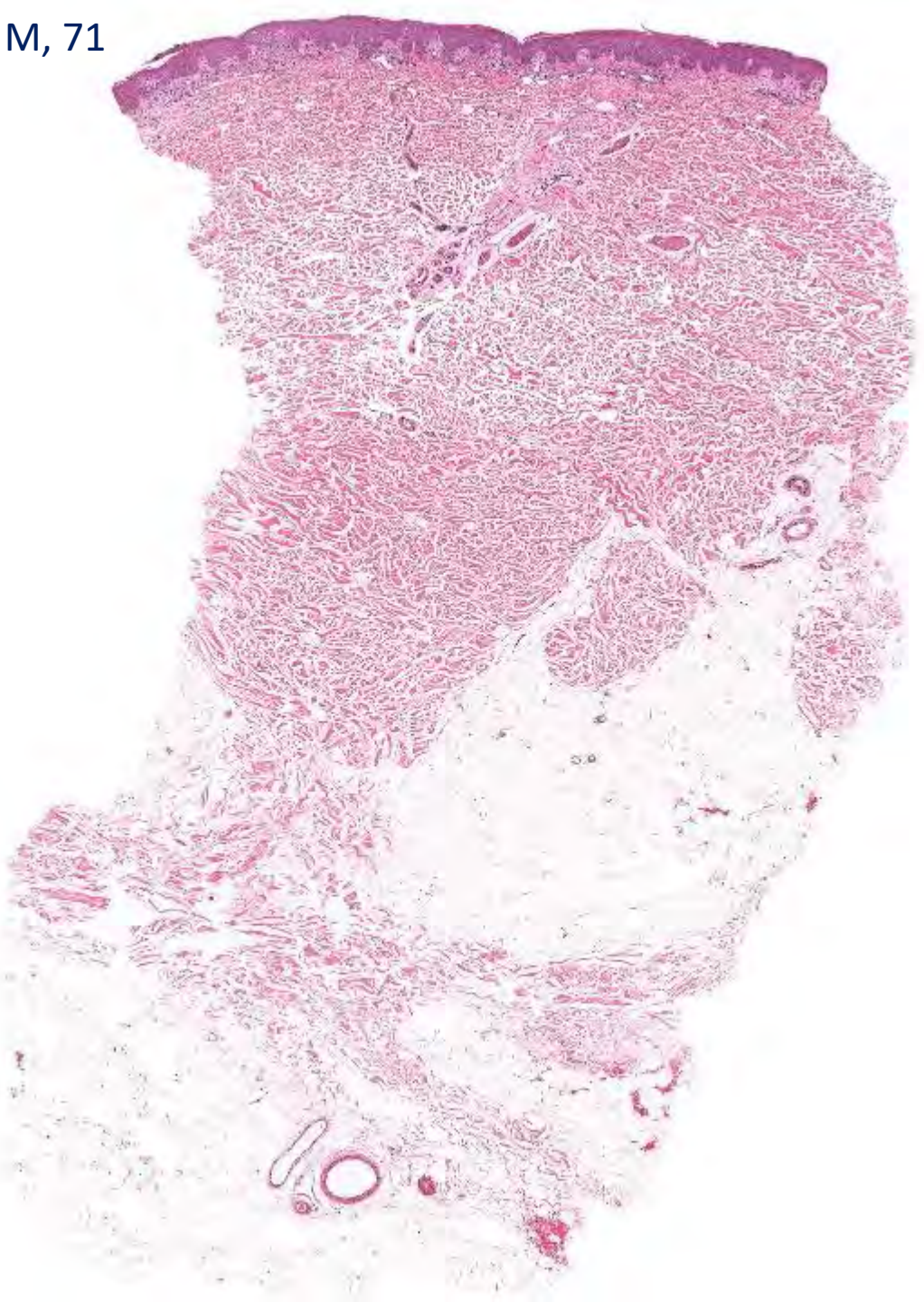

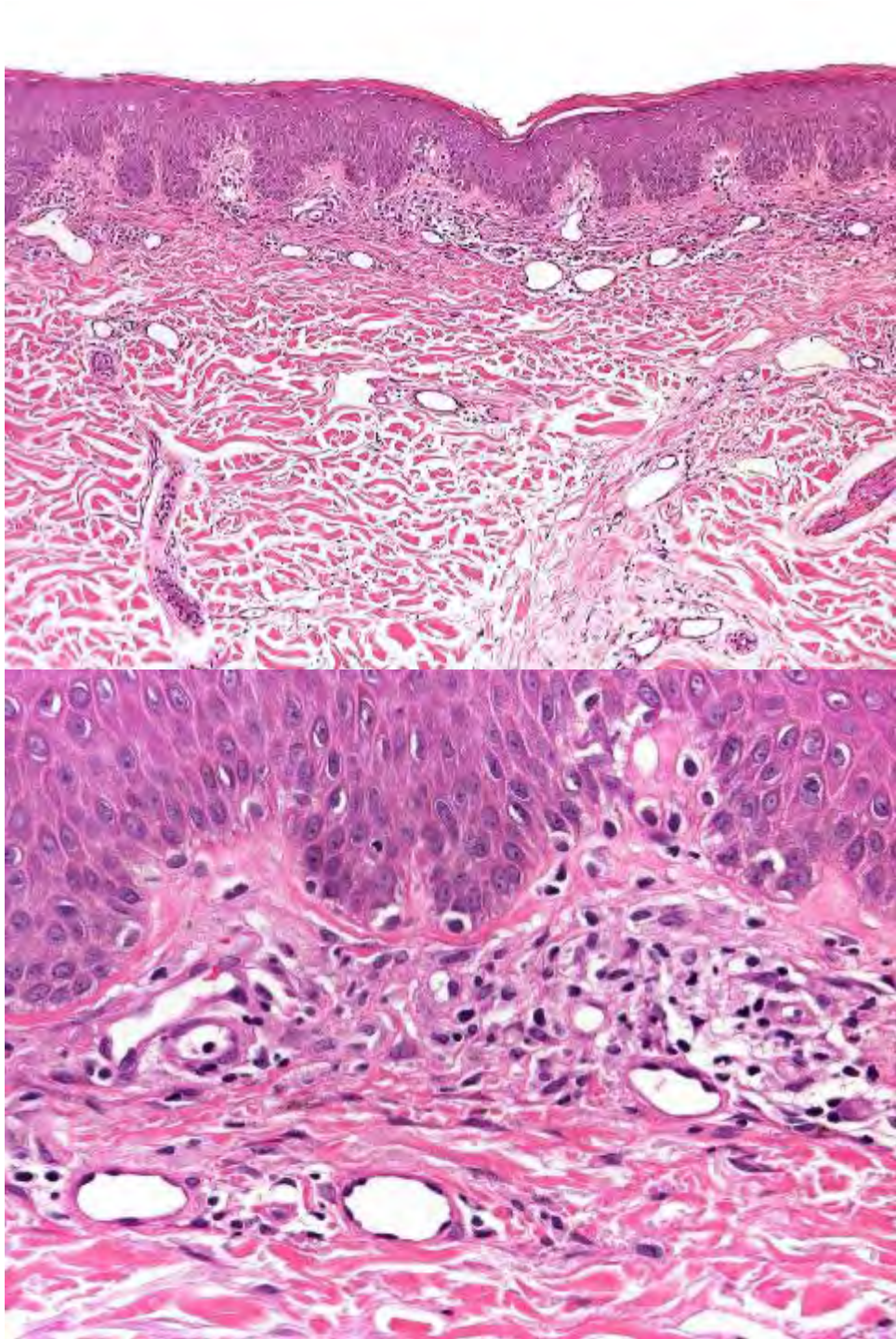

Angiogenesis and lymphangiogenesis in inflammatory skin disorders

Gilda Varricchi, MD, PhD, Francescopaolo Granata, MD, PhD, Stefania Loffredo, PhD, Arturo Genovese, MD, and Gianni Marone, MD
Naples, Italy

Angiogenesis, the growth of new blood vessels from pre-existing vessels, occurs physiologically in wound healing, during inflammatory diseases, and in tumor growth. Lymphangiogenesis can be activated in inflammation and tumor metastasis. The family of vascular endothelial growth factors (VEGFs) and angiopoietins are essential for angiogenesis and lymphangiogenesis. The angiogenic process is tightly regulated by VEGFs, angiopoietins, and endogenous inhibitors. VEGFs and angiopoietins exert their effects by activating specific receptors present on blood and lymphatic endothelial cells. There is now compelling evidence that cells of innate and adaptive immunity (macrophages, mast cells, neutrophils, eosinophils, lymphocytes) are a major source of angiogenic and lymphangiogenic factors. Chronic inflammatory skin diseases such as psoriasis and atopic dermatitis are characterized by altered angiogenesis, lymphangiogenesis, or both. Also such acute inflammatory skin disorders as urticaria, ultraviolet B–induced damage, and angioedema are associated with changes in angiogenic factors. In systemic sclerosis there is a switch from proangiogenic to antiangiogenic factors that play a role in the defective vascular process of this disorder. As yet, there are no clinical trials showing that canonical VEGF/VEGF receptor-targeted strategies can modulate inflammatory skin diseases. Novel strategies targeting other angiogenic/lymphangiogenic pathways should also be investigated. (J Am Acad Dermatol 2015;73:144-53.)

Key words: angioedema; angiogenesis; atopic dermatitis; interleukin-17; lymphangiogenesis; macrophages; mast cells; psoriasis; urticaria; vascular endothelial growth factor.

Angiogenesis, the growth of new blood vessels from pre-existing ones, is an essential process during embryonic and postnatal development.[1] In adults, angiogenesis occurs physiologically in the menstrual cycle and wound healing, and during inflammatory diseases and tumor growth.[2] Lymphangiogenesis occurs in embryonic development and can be reactivated in adulthood during inflammation, wound healing, and tumor metastasis.[3-5]

In 1971 Judah Folkman[6] suggested that tumor growth is angiogenesis-dependent and that inhibition of angiogenesis could be of therapeutic value. In 1983 Harold Dvorak and collaborators isolated "vascular permeability factor," a potent permeability factor several logs more potent than histamine.[7] In 1989, Napoleone Ferrara and collaborators sequenced a mitogen for endothelial cells that they called "vascular endothelial growth factor" (VEGF).[8] Cloning of VEGF showed it to be the same vascular permeability factor.[7] The VEGF family comprises VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor.[1] VEGF-A and VEGF-B are key regulators of blood vessels, whereas

Abbreviations used:

Ang:	angiopoietin
IL:	interleukin
NRP:	neuropilin
TSP:	thrombospondin
UV:	ultraviolet
VEGF:	vascular endothelial growth factor
VEGFR:	vascular endothelial growth factor receptor

From the Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research (CISI), University of Naples.
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Reprint requests: Gianni Marone, MD, Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy. E-mail: marone@unina.it.
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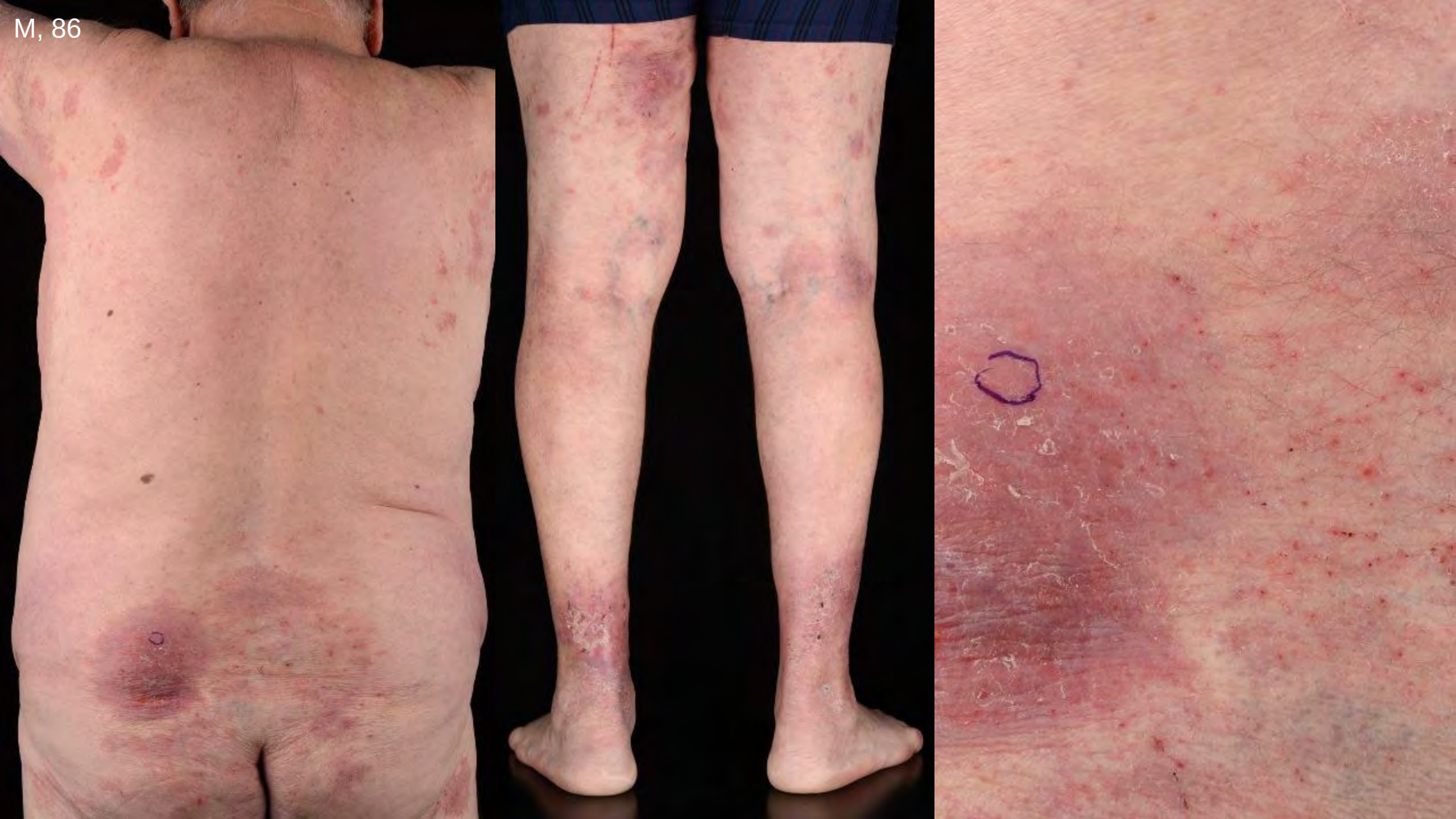
CAPSULE SUMMARY

- Chronic inflammatory skin disorders such as psoriasis, atopic dermatitis, and systemic sclerosis are characterized by altered angiogenesis, lymphangiogenesis, or both.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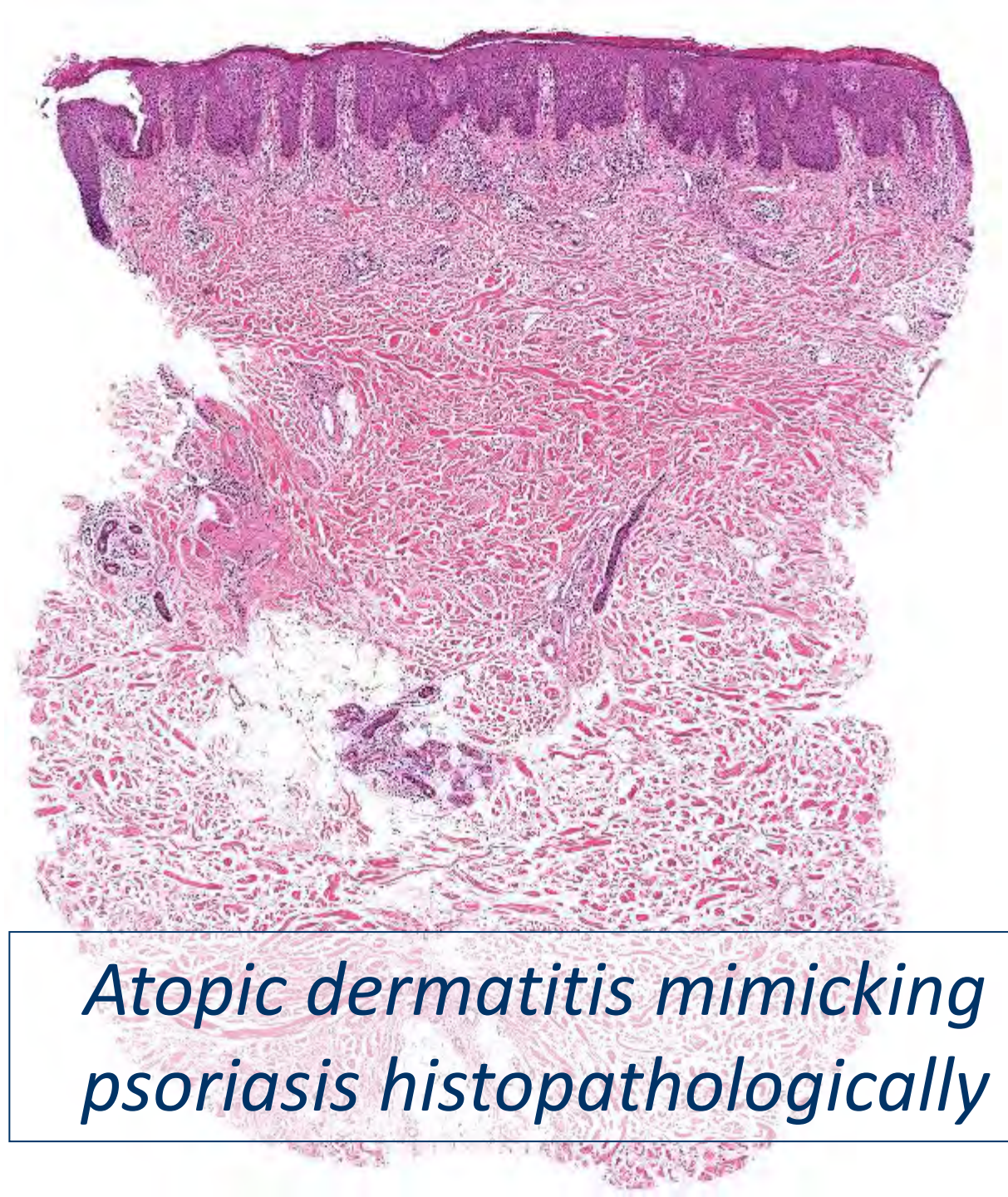
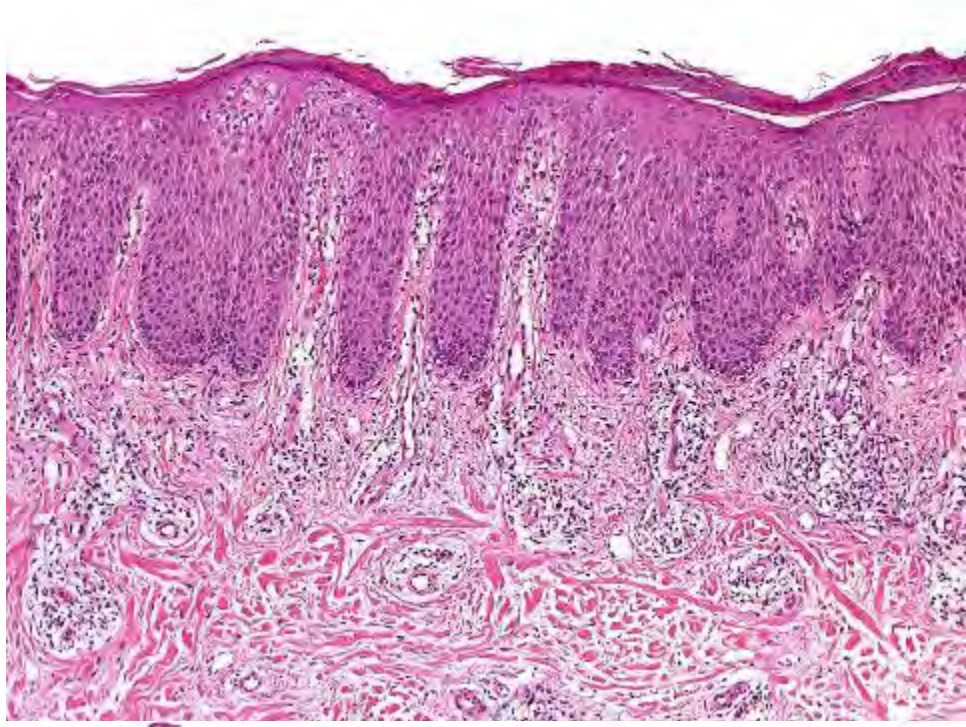
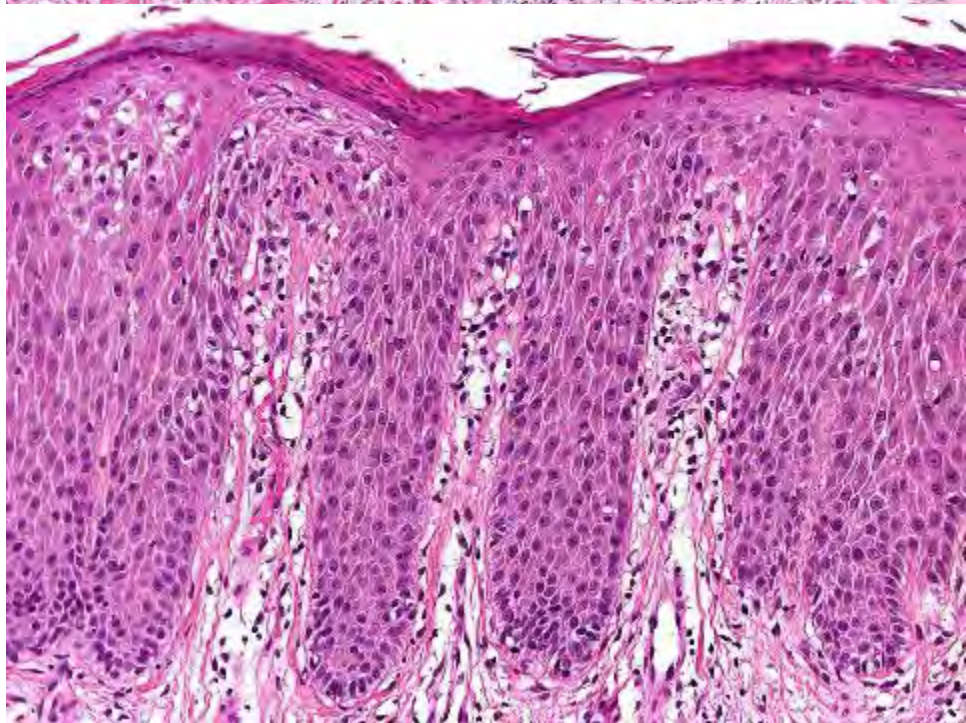
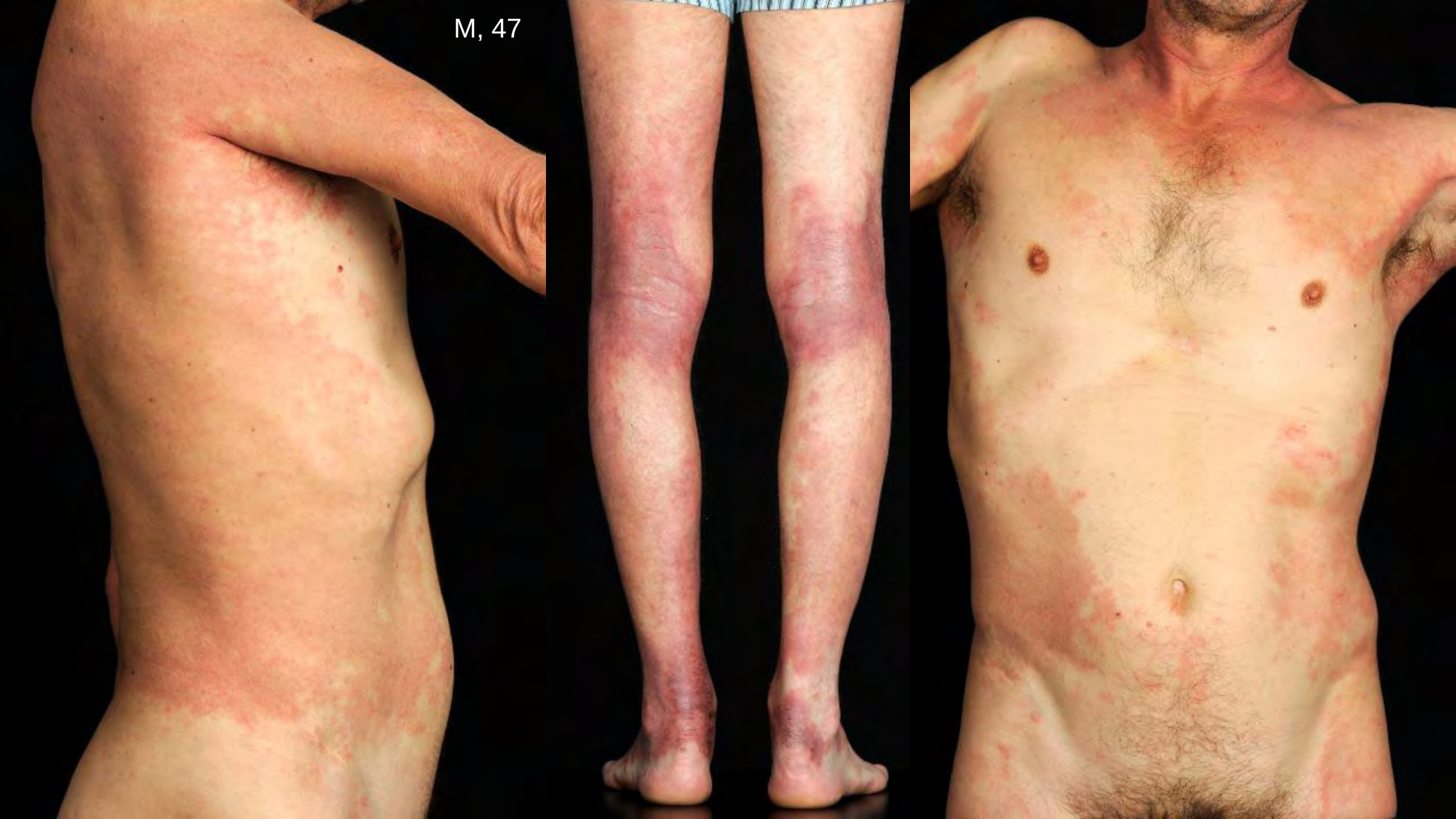






Atopic dermatitis mimicking psoriasis histopathologically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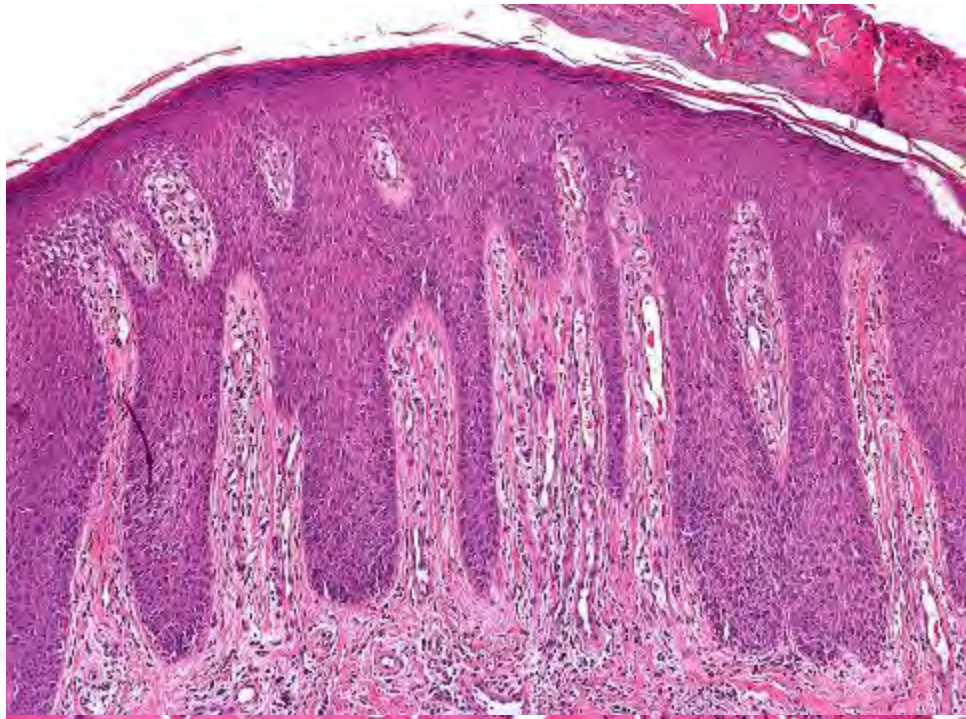
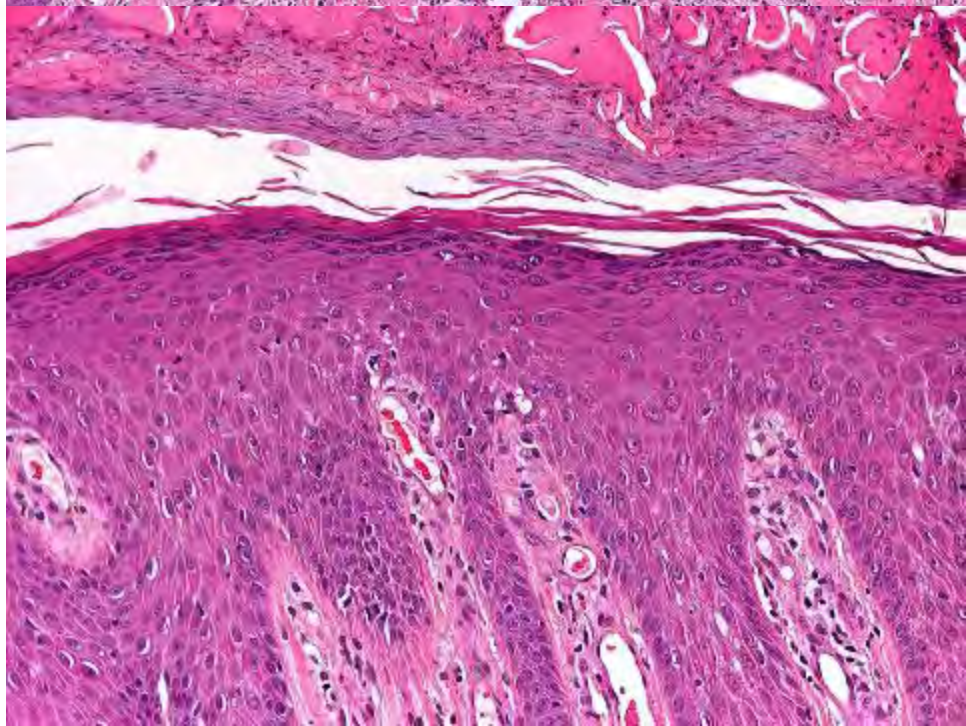
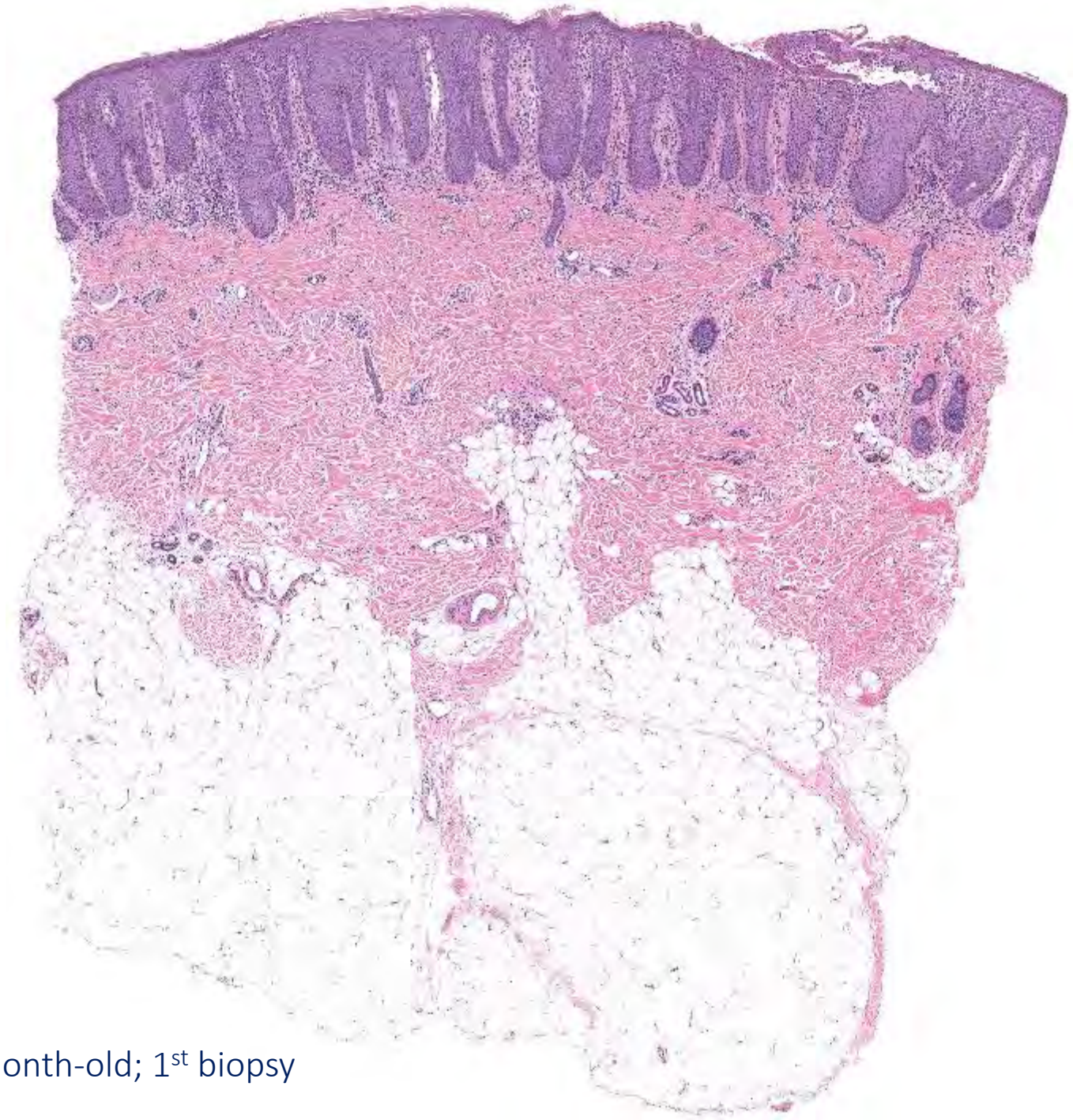
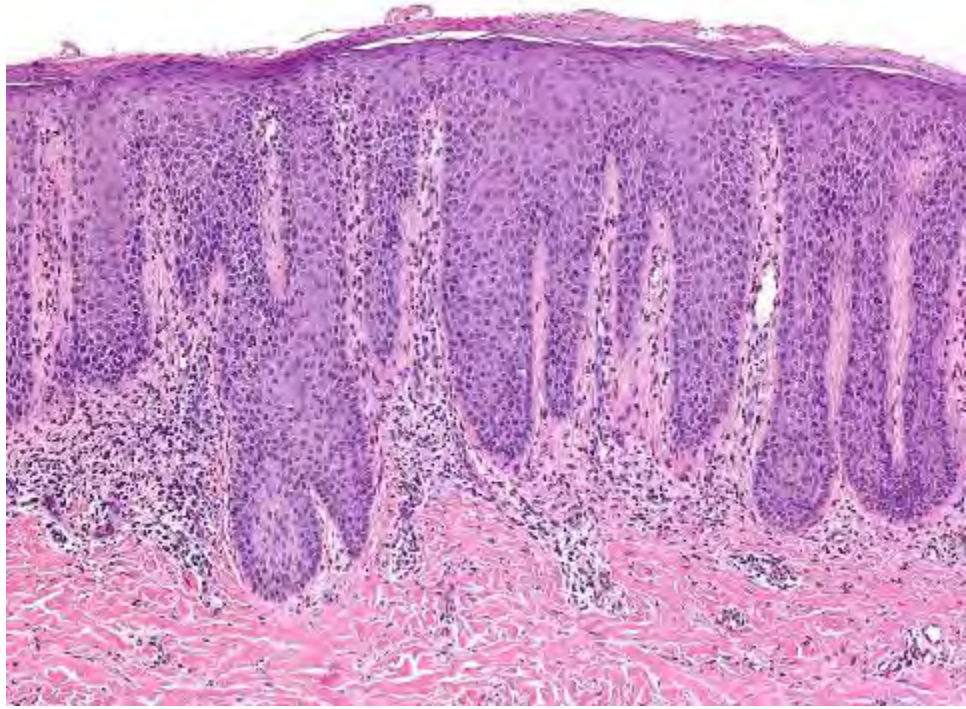
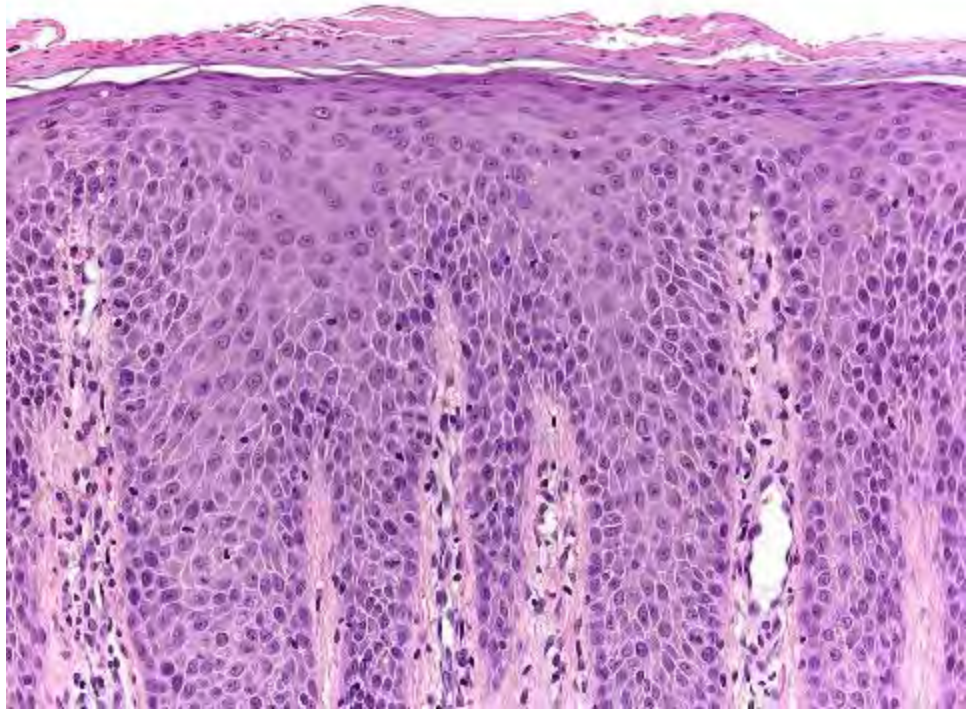




Atopic dermatitis mimicking psoriasis histopathologically

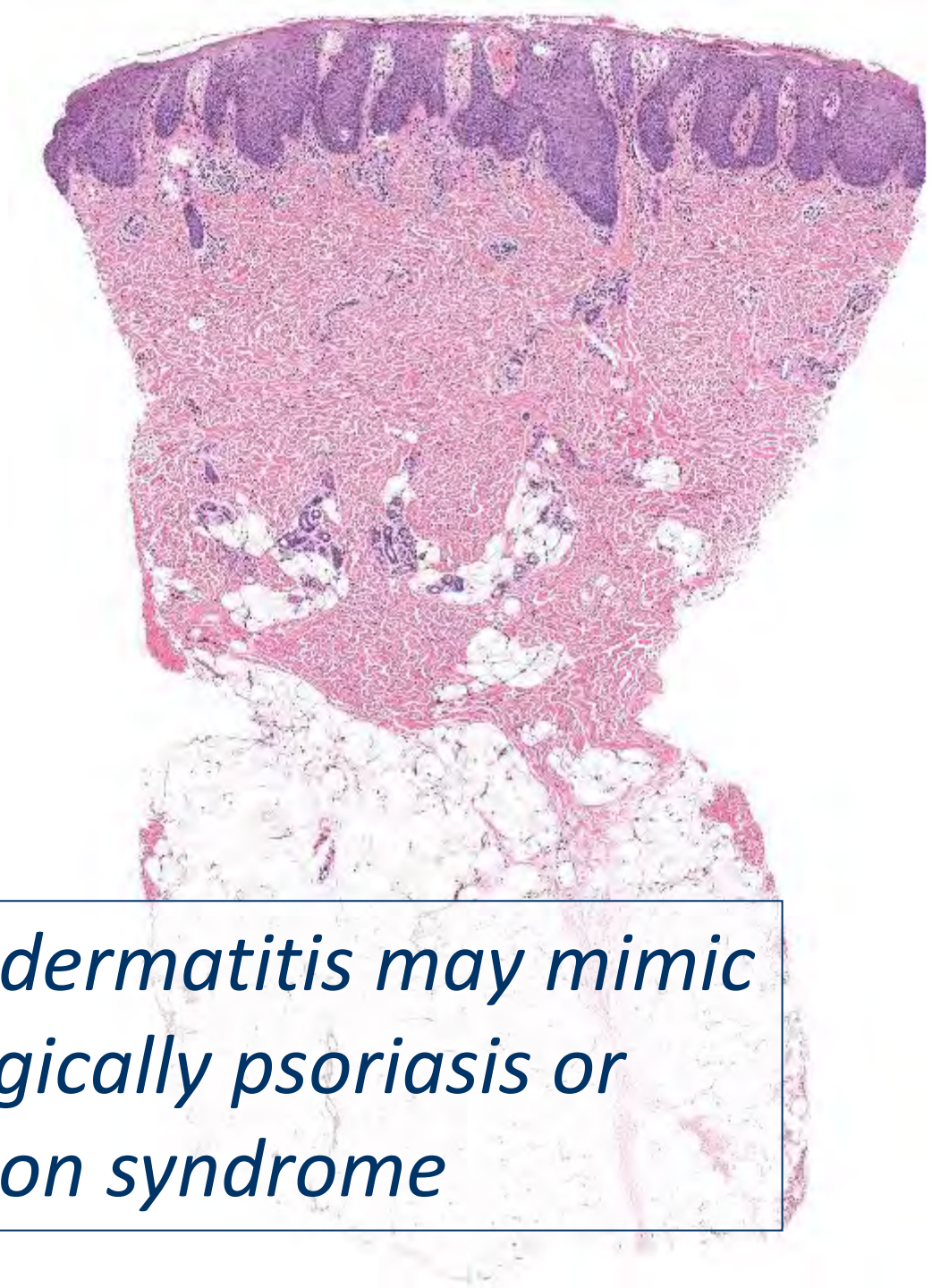






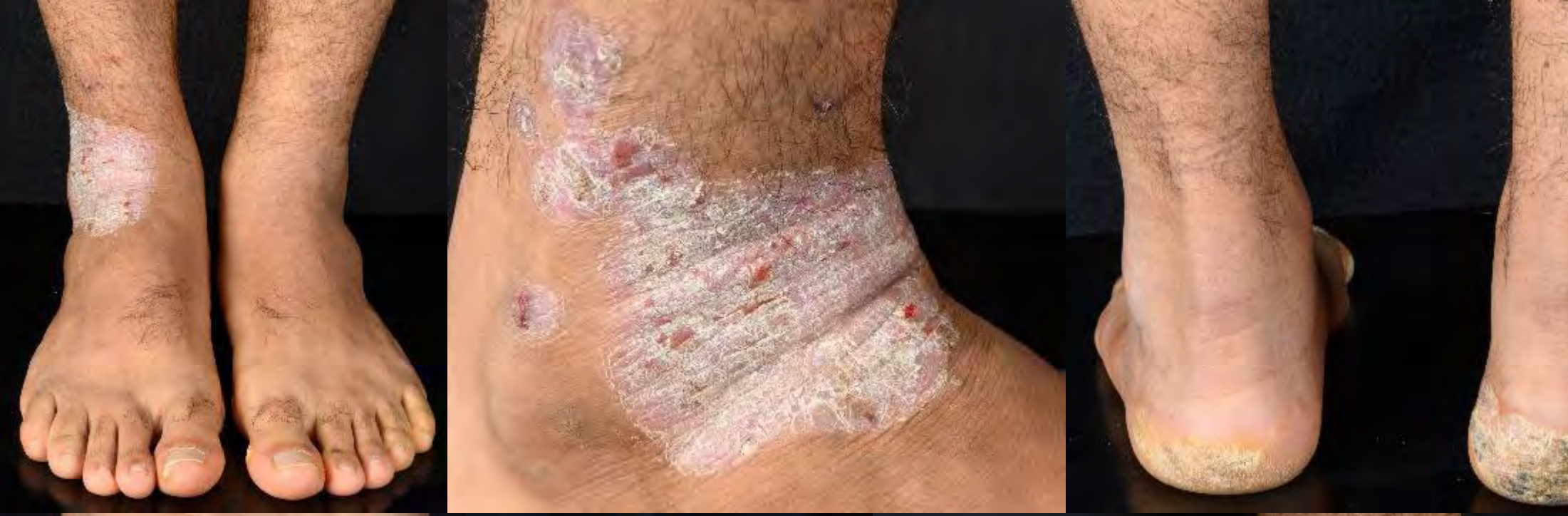
M, 8 month-old; 1st biopsy

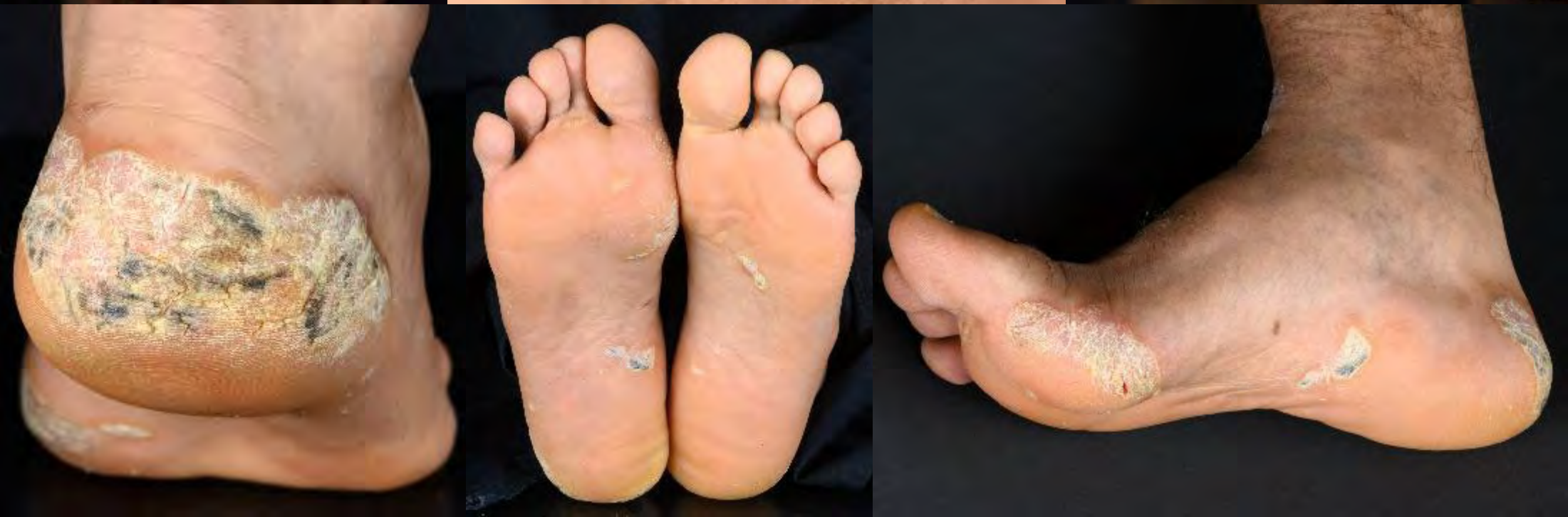
- Onset on the face at age of 2 months; subsequently erythroderma
- Markedly elevated IgE (2478 kU/L; normal 0-3.80)
- Intolerance to several substances (incl. cow milk, eggs)
- Brother had atopic dermatitis (improved during puberty)
- Improvement with local pimecrolimus



2nd biopsy

Neonatal atopic dermatitis may mimic histopathologically psoriasis or Netherton syndrome





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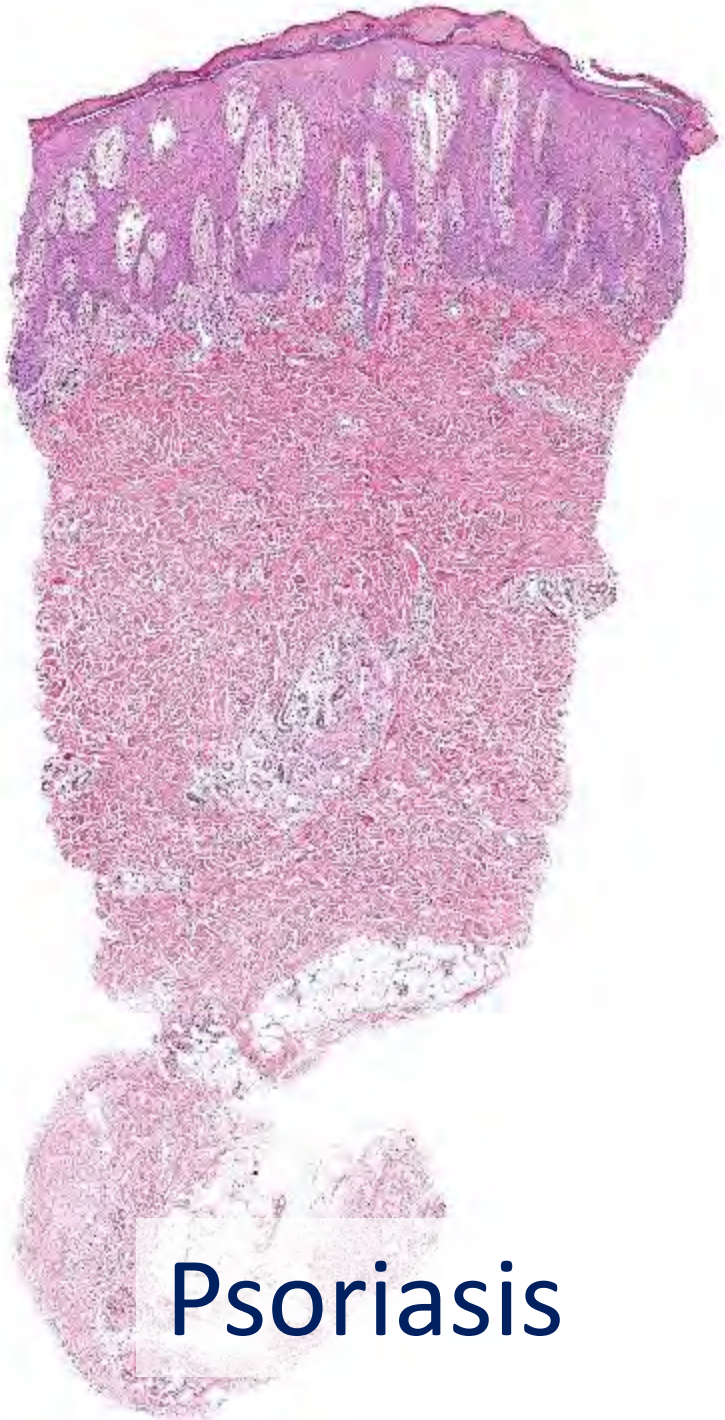
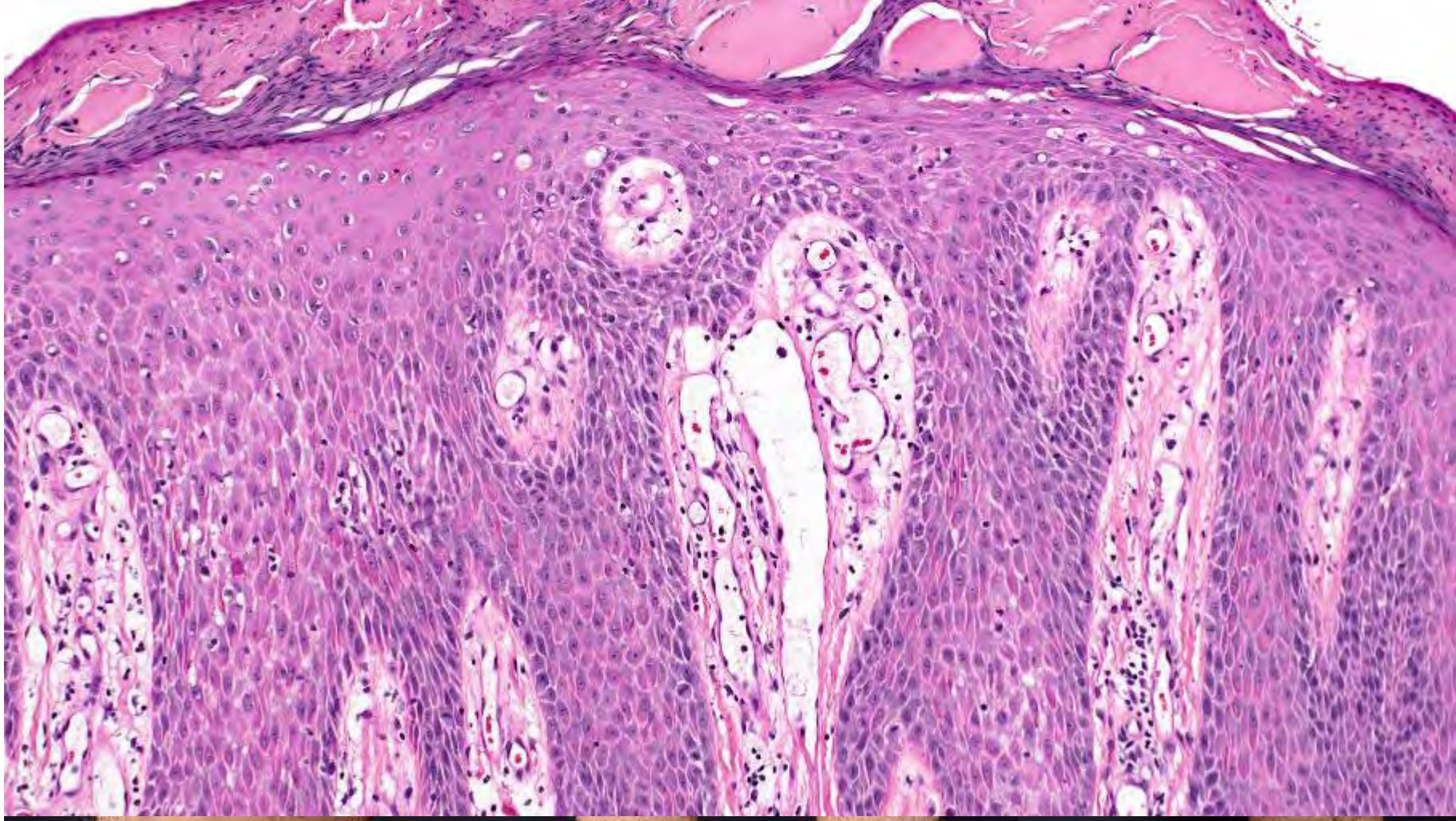
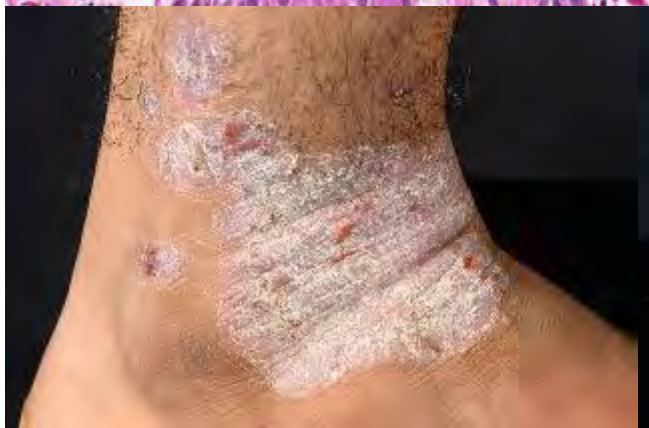
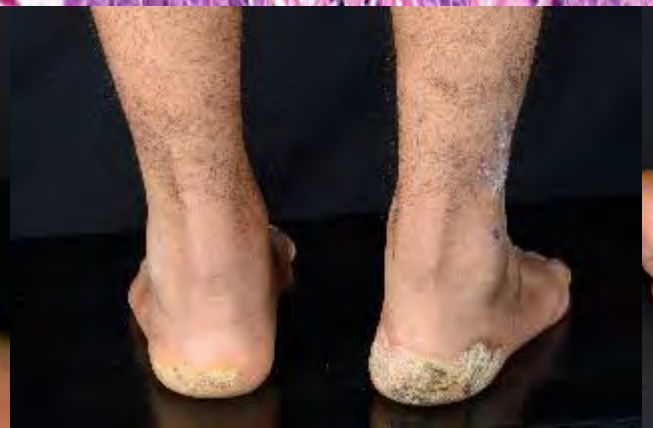
According to the patient lesions on the lower legs and feet for >1 year, diagnosed clinically as lichen simplex chronicus.

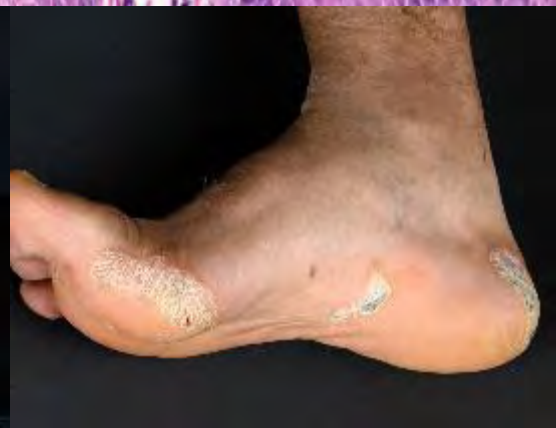
A biopsy is taken.



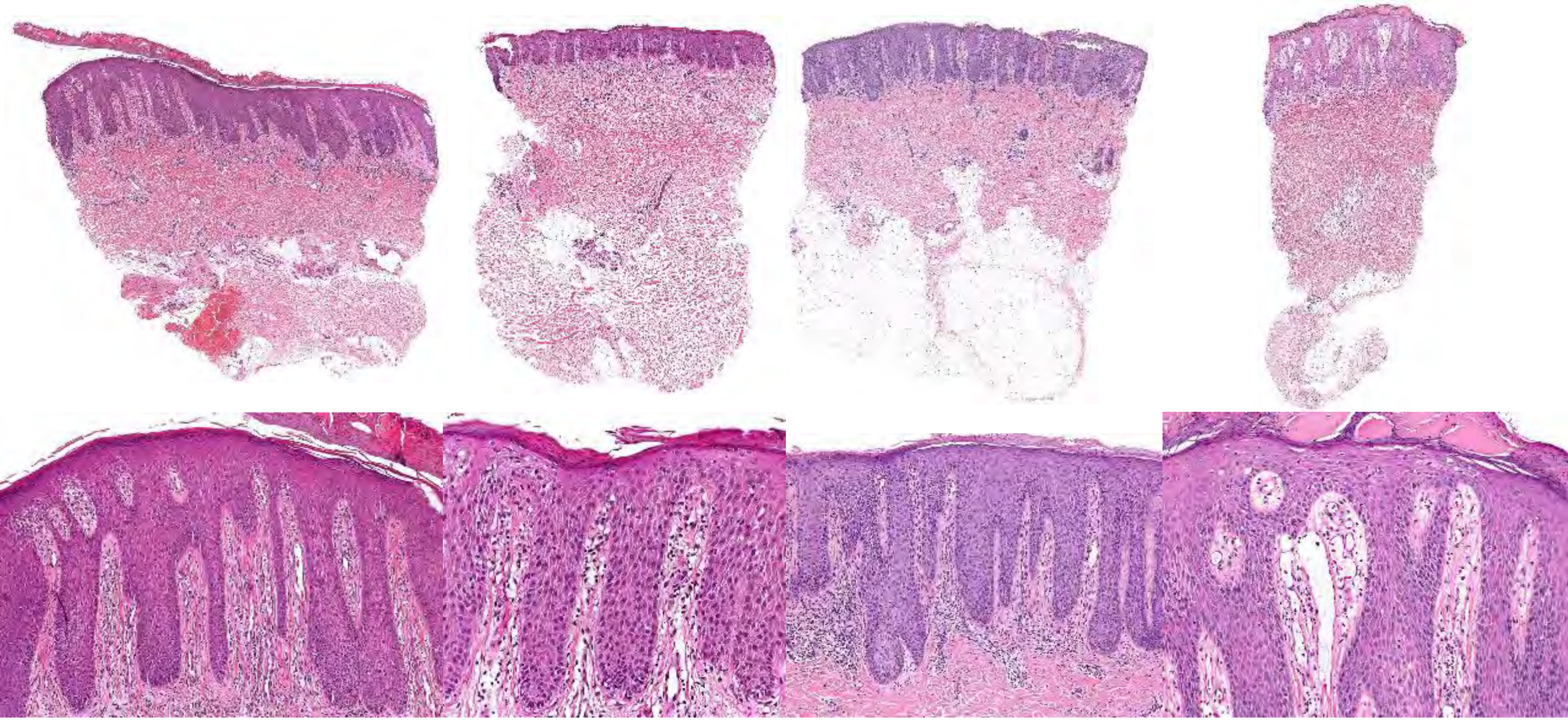






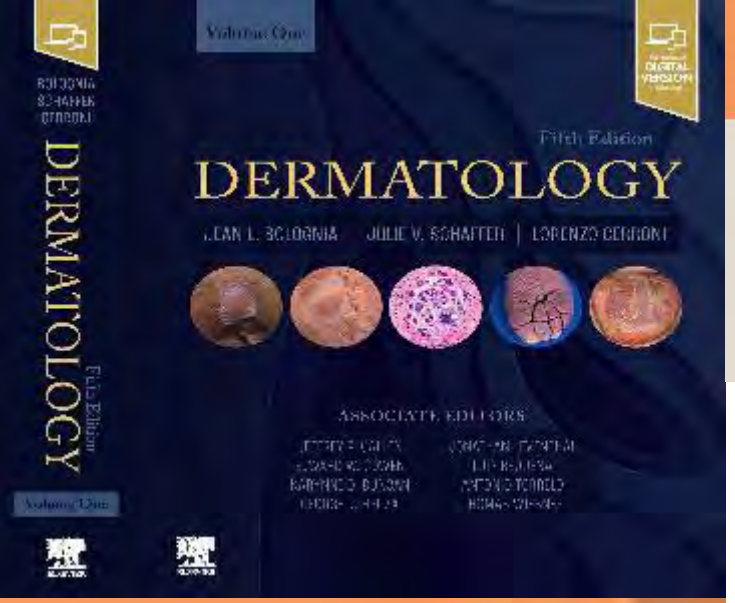


Psoriasis



Atopic dermatitis may mimic psoriasis histopathologically

Psoriasis may be eczematized



Psoriasis 8

Peter C.M. van de Kerkhof and Lars Iversen

The relationship between psoriasis and lichen simplex chronicus

"A bi-directional relationship exists between lichen simplex chronicus (LSC) and psoriasis. If a psoriatic lesion is pruritic, superimposed LSC may develop and the surface becomes shiny with increased skin markings. Because the LSC itself is pruritic, the resultant rubbing may worsen the psoriasis (Koebner phenomenon). The patient then enters a vicious cycle. Therapeutic regimens must address both disorders."

JEADV ISSN 1468-3083

ORIGINAL ARTICLE

Clinical and histopathological findings of 'psoriatic neurodermatitis' and of typical lichen simplex chronicus

S Gunasti,*† SS Marakli,† I Tuncer,‡ N Ozpoyraz,§ VI. Aksungur†

†Cukurova University, Dermatology, Adana, Turkey, ‡Cukurova University, Pathology, Adana, Turkey, §Cukurova University, Psychiatry, Adana, Turkey

Keywords
epidermal hyperplasia, excoriation, itching, lichen simplex chronicus, psoriasis

*Corresponding author, Department of Dermatology, Cukurova University, Adana, Turkey. tel. +90 322 338 64 26; fax +90 322 338 66 56; E-mail: sugunasti@yahoo.com; cuderm@cu.edu.tr

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Abstract

Background We have seen several patients with itchy lichenified plaques located bilaterally on the elbows and/or knees and have named this condition 'psoriatic neurodermatitis' (PN).

Objective The purpose of this study was to compare clinical and histopathological characteristics of these patients to those of patients with typical lichen simplex chronicus (LSC).

Methods Nineteen patients with PN and 34 patients with typical LSC were included. Besides clinical dermatological evaluation, the prick test was carried out on 49 patients; the Phadiatop test on 40 patients; the patch test with European standard series on 47 patients; histopathological evaluation on 39 patients; and clinical psychiatric examination on 38 patients.

Results Almost exclusively, PN was seen in females and was located on the extremities. It caused more plaques than typical LSC did. In PN, the plaques were smaller, sharper, more keratotic and less excoriated, and had fewer lichenoid papules around them. Itching was usually more severe in the evening, while resting and in a hot environment in typical LSC, but not in PN. In plaques of PN, microabscesses in the horny layer, hypogranulosis, regular acanthosis and thinning of the suprapapillary plates were more frequent, and hyperpigmentation in the basal layer was less. In patients with PN, depressive disorder was found more frequently; and generalized anxiety disorder or psychosomatic characteristics, less. There were no significant differences in the results of prick, Phadiatop and patch tests between patients with PN and those with typical LSC.

Conclusion In our opinion, it is most likely that the so-called PN is itchy psoriasis superimposed by LSC.

Introduction

Both plaque psoriasis and lichen simplex chronicus (LSC) [illegible] discuss from one another. In particular, the distribution [illegible] individual lesions are quite different. Plaque psoriasis usually presents as many plaques located [illegible] even, symmetrical fashion. On the other hand, LSC usually shows only one or a few plaques in one or a few anatomical regions. The surface of a psoriatic plaque is typically covered by abundant silvery scales. These scales are not tightly adhered so that they can be easily removed [illegible] On the other hand, a plaque of LSC usually less [illegible] surface. These lines form a criss-cross pattern so that flat-topped quadrilateral facets are produced. This change is called lichenification.

We have seen several patients with itchy plaques resembling those of psoriasis in distribution with a bilateral

In our opinion, it is most likely that the so-called "psoriatic neurodermatitis" is itchy psoriasis with superimposed LSC.

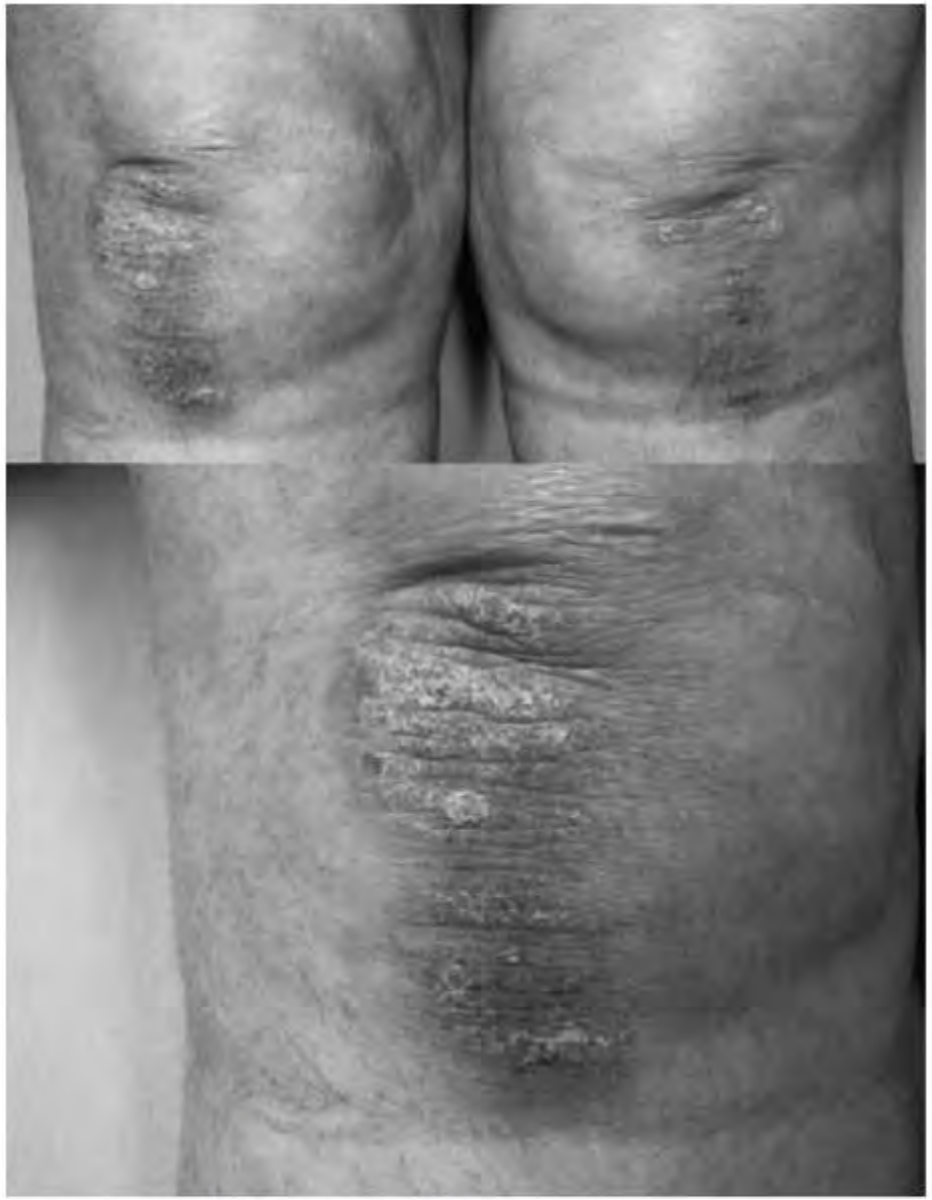

fig. 1 Lichenified plaques on both knees in a patient with psoriatic neurodermatitis (upper) and the close-up appearance of one of these plaques (lower).

Psoriasis With Eczematous Features: A Retrospective Clinicopathologic Study

Ariella R. Noorily, BA, Maressa C. Criscito, MD,† Jeffrey M. Cohen, MD,‡ and Nooshin K. Brinster, MD†*

Background: Dermatopathologists sometimes encounter patients with features of psoriasis vulgaris and additional changes of eczematous dermatoses. These cases are challenging to diagnose, and the clinical implications are unclear. In the age of targeted therapy, it is important to improve our understanding of these findings so that patients are managed appropriately.

Objective: To characterize the clinical characteristics, histopathological features, diagnostic workup, successful treatment, and outcomes of patients with overlapping histopathologic features of psoriasis vulgaris and eczema.

Methods: We conducted a retrospective chart review of 20 patients who had received the histopathologic diagnosis of psoriasis vulgaris with eczematous changes noted on skin biopsy. A database that included information about clinical characteristics, clinicopathologic histopathological findings, diagnostic workup, treatment modalities, and outcomes was created and analyzed.

Results: Twenty patients were included in this study, with an average age of 57.3 years. After clinicopathologic correlation, most patients were diagnosed with psoriasis (85%), and the remainder were determined to have an eczematous dermatitis. Thirty-five percent of patients were diagnosed with allergic contact dermatitis, either in combination with psoriasis (6 patients) or alone (1 patient). Topical glucocorticoids were the most common effective therapy used, and systemic therapies were required in nearly half of patients for successful treatment.

Conclusion: This study offers insights into the clinically and histopathologically challenging diagnosis of psoriasis vulgaris with eczematous changes and offers the diagnostic term "eczematized psoriasis" to describe these patients. The presence of allergic contact dermatitis should be considered in these patients.

Key Words: general dermatology, medical dermatology, psoriasis, eczema, allergic contact dermatitis, eosinophils

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From the †New York University Grossman School of Medicine, New York, NY; ‡The Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine, New York, NY; and §The Department of Dermatology, Yale School of Medicine, New Haven, CT.

The authors declare no conflicts of interest.

Correspondence: Nooshin K. Brinster, MD, Dermatopathology Unit, New York University Grossman School of Medicine, 240 East 38th Street, 14th Floor, New York, NY 10016 (e-mail: nooshin.kenner@nyulangone.org).

INTRODUCTION

Although the classic histopathologic features of psoriasis vulgaris are well established, the diagnosis can be challenging in routine practice. This may be for a variety of reasons as follows: previous treatment, which can modify pathologic changes; the natural evolution of lesions, such that early or rapidly developing lesions do not have all the findings seen in long-standing disease; or location, such as acral, intertriginous, and head and neck sites, where there may be more pronounced spongiosis and therefore considerable overlap with eczematous dermatoses.[1]

The advent of targeted therapies, such as inhibitors of tumor necrosis factor alpha (TNF-α) and interleukins (IL)-17 and IL-23, has made it even more important to definitively diagnose psoriasis and distinguish it from eczematous dermatoses for which these treatments are not indicated and for which other medications, such as dupilumab, an IL-4 receptor inhibitor, may be more appropriate.[2] In the course of routine dermatopathology practice, we have encountered patients with many features of psoriasis vulgaris and additional changes resembling eczematous dermatoses, namely spongiosis, serum crust, and dermal eosinophils. These cases are challenging to diagnose, and the clinical implications are unclear. The purpose of this study is to characterize the clinical and histopathological findings of these patients to better enhance diagnosis and facilitate appropriate management and treatment.

MATERIALS AND METHODS

We conducted a retrospective chart review and analysis of skin biopsies of patients diagnosed with "psoriasis vulgaris" who also had the terms "eczematous" or "eczematized" in the diagnostic line or pathology note at the dermatopathology section of the New York University (NYU) between October 2016 and April 2019. The study was approved by the NYU Institutional Review Board. Tissue sections were cut at 5 μm, and hematoxylin and eosin–stained specimens were reviewed by a board-certified dermatopathologist. Detailed descriptive pathologic characterizations were made, including quantification of dermal eosinophils. All tissue sections on the slides were examined, and eosinophils were counted at high power (×200). The highest number counted was recorded per one tissue section per case. Intravascular eosinophils were excluded. This methodology for counting eosinophils was based on previously published protocols.[1,2]

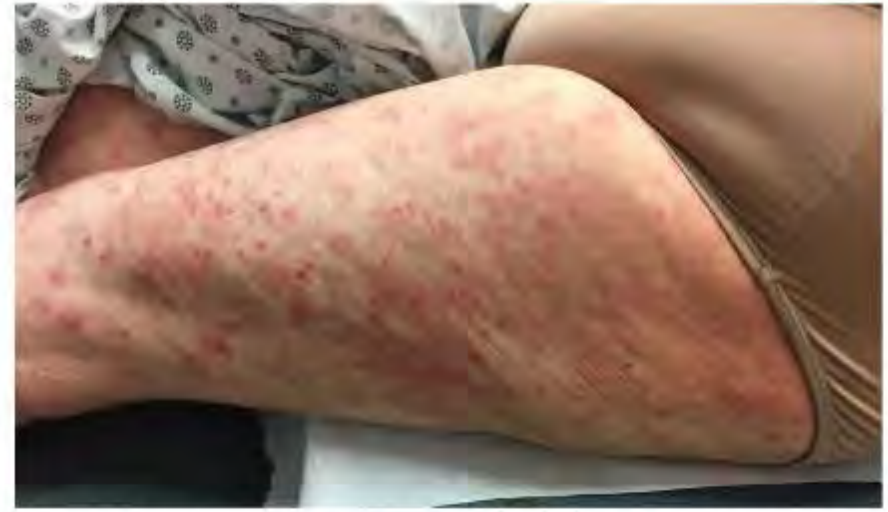

FIGURE 1. Discrete erythematous, scaly papules coalescing into plaques on the lower extremities. This patient was determined to have psoriasis with superimposed ACD to fragrance.

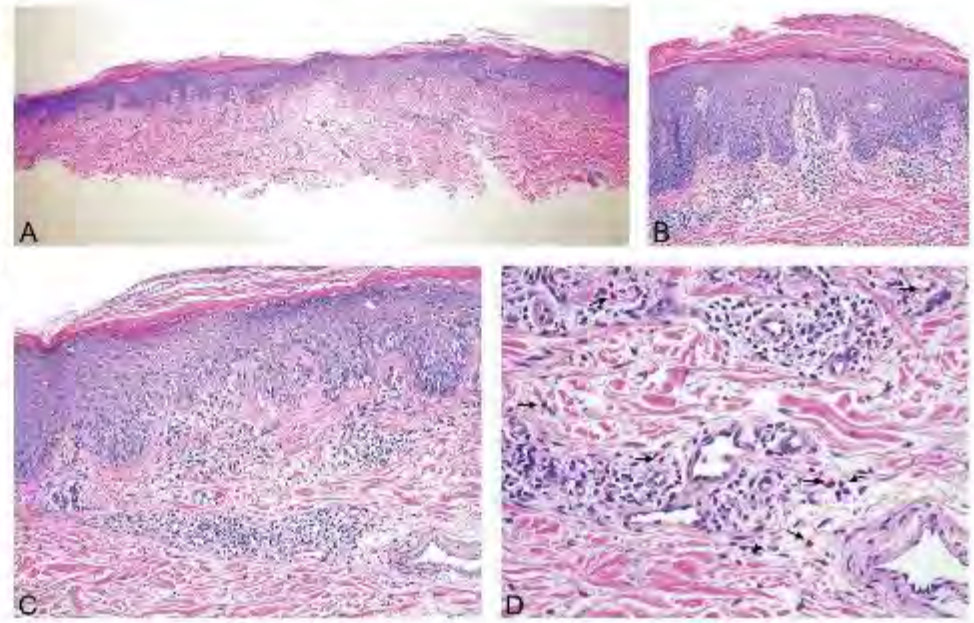

FIGURE 3. A, Shave biopsy showing psoriasiform and eczematous changes from patient in Figure 1 (hematoxylin and eosin stain, ×40). B, Higher power illustrating psoriasiform hyperplasia, suprapapillary plate thinning, and confluent parakeratosis overlying an absent granular cell layer. There are also intracorneal neutrophils and dilated papillary dermal vessels (hematoxylin and eosin stain, ×200). C, Adjacent area with epidermal spongiosis, less regular psoriasiform hyperplasia, and parakeratosis with a subjacent diminished granular layer (hematoxylin and eosin stain, ×200). D, Higher power of dermal infiltrate with perivascular and interstitial lymphocytes and eosinophils. There are 8 eosinophils in this field identified with the black arrows (hematoxylin and eosin stain, ×400).

Gene Expression–Based Molecular Test as Diagnostic Aid for the Differential Diagnosis of Psoriasis and Eczema in Formalin-Fixed and Paraffin-Embedded Tissue, Microbiopsies, and Tape Strips

Felix Fischer[1,2], Anaïs Doll[1,2], Deniz Uereyener[1], Sophie Roenneberg[1], Christina Hillig[1], Lucca Weber[1], Verena Hackert[1], Martin Meine[1], Ali Farnoud[1], Peter Seiringer[3], Jenny Thomas[3], Philipp Anand[3], Larissa Cramer[3], Franziska Schlenker[3], Roland Zengerle[4,5], Pontus Jonsson[6], Manja Jargosch[7,8], Fabian J. Theis[7,9], Carsten B. Schmidt-Weber[7], Tilo Biedermann[7], Michael Flowell[10], Kristian Reich[11], Kilian Eyerich[12], Michael Menden[13], Natalie Garzorz-Stark[1], Felix Lauffer[1,14] and Stefanie Eyerich[1]

Highly effective targeted therapies are available to treat noncommunicable chronic inflammatory skin diseases. In contrast, the exact diagnosis of noncommunicable chronic inflammatory skin diseases is complicated by its complex pathogenesis and clinical and histological overlap. Particularly, the differential diagnosis of psoriasis and eczema can be challenging in some cases, and molecular diagnostic tools need to be developed to support a gold standard diagnosis. The aim of this work was to develop a real-time PCR-based molecular classifier to distinguish psoriasis from eczema in formalin-fixed and paraffin-embedded skin samples and to evaluate the use of minimally invasive microbiopsies and tape strips for molecular diagnosis. In this study, we present a formalin-fixed and paraffin-embedded–based molecular classifier that determines the probability for psoriasis with a sensitivity/specificity of 92%/100%, respectively, and an area under the curve of 0.97, delivering comparable results to our previous published RNAprotect-based molecular classifier. The psoriasis probability, as well as levels of *MOS2* expression, positively correlated with the disease hallmarks of psoriasis and negatively with eczema hallmarks. Furthermore, minimally invasive tape strips and microbiopsies were effectively used to differentiate psoriasis from eczema. In summary, the molecular classifier offers broad usage in pathology laboratories as well as outpatient settings and can support the differential diagnosis of noncommunicable chronic inflammatory skin diseases on a molecular level using formalin-fixed and paraffin-embedded tissue, microbiopsies, and tape strips.

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[1]Medical Oncology, Dermatology, Hematology, Center Munich, Muehlberg, Germany; [2]Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany; [3]Biomedical GmbH, Freiburg, Germany; [4]Laboratory for MEMS Applications, Department of Microsystems Engineering—IMTEK, University of Freiburg, Freiburg, Germany; [5]HSG-IMIT–Institut für Mikro- und Informationstechnik, Villingen-Schwenningen, Germany; [6]Karolinska Institutet, Department of Medicine, Solna, Unit of Hematology and Transfusion Medicine, Stockholm, Sweden; [7]Center of Allergy and Environment, Technical University of Munich and Helmholtz Center Munich, Munich, Germany; [8]Department of Mathematics, Technical University of Munich, Garching, Germany; [9]CytoTech, San Diego, California, USA; [10]Translational Research in Inflammatory Skin Diseases, Initiative, Medical Center Hamburg-Eppendorf, Hamburg, Germany; [11]Center for Dermatology and Venereology, Universitätsklinikum Freiburg, Freiburg, Germany

[12]These authors contributed equally to this work.

Correspondence: Stefanie Eyerich, Center of Allergy and Environment, Technische Universität and Helmholtz Center Munich, Biedersteiner Str. 29, Munich 80802, Germany. E-mail: stefanie.eyerich@tum.de

Abbreviations: AD, atopic dermatitis; FFPE, formalin-fixed and paraffin-embedded; MC, molecular clustering; NGS, next-generation sequencing

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INTRODUCTION

Psoriasis and eczema are among the most prevalent and relevant skin diseases worldwide, with an incidence rate for both diseases together of at least 2% (Boyland et al., 2020; Deckers et al., 2018; Vender et al., 2018). Although more than a dozen immune-modulating therapies, particularly mAbs targeting specific cytokines or their receptors, have been made available over the last decade, allowing a highly effective treatment of affected patients (Paek et al., 2021), the ultimate breakthrough would include the development of accurate diagnostic tools. Diagnosis of both diseases largely depends on a subjective visual examination and histopathological examination. Because of phenotypical overlaps of both diseases, up to 50% of cases with a palmoplantar localization are misdiagnosed (Kolesnik et al., 2020). To close this important diagnostic gap, a gene expression–based classifier using *MOS2* and *CCL27* as marker genes has been proposed, and its clinical validity has been examined and proven in various patient cohorts (Bieber et al., 2020; Brunner et al., 2018; Cuenca-Barrales et al., 2019; Quaranta et al., 2019; Stölzel et al., 2019; Renert-Yuval et al., 2021). But the

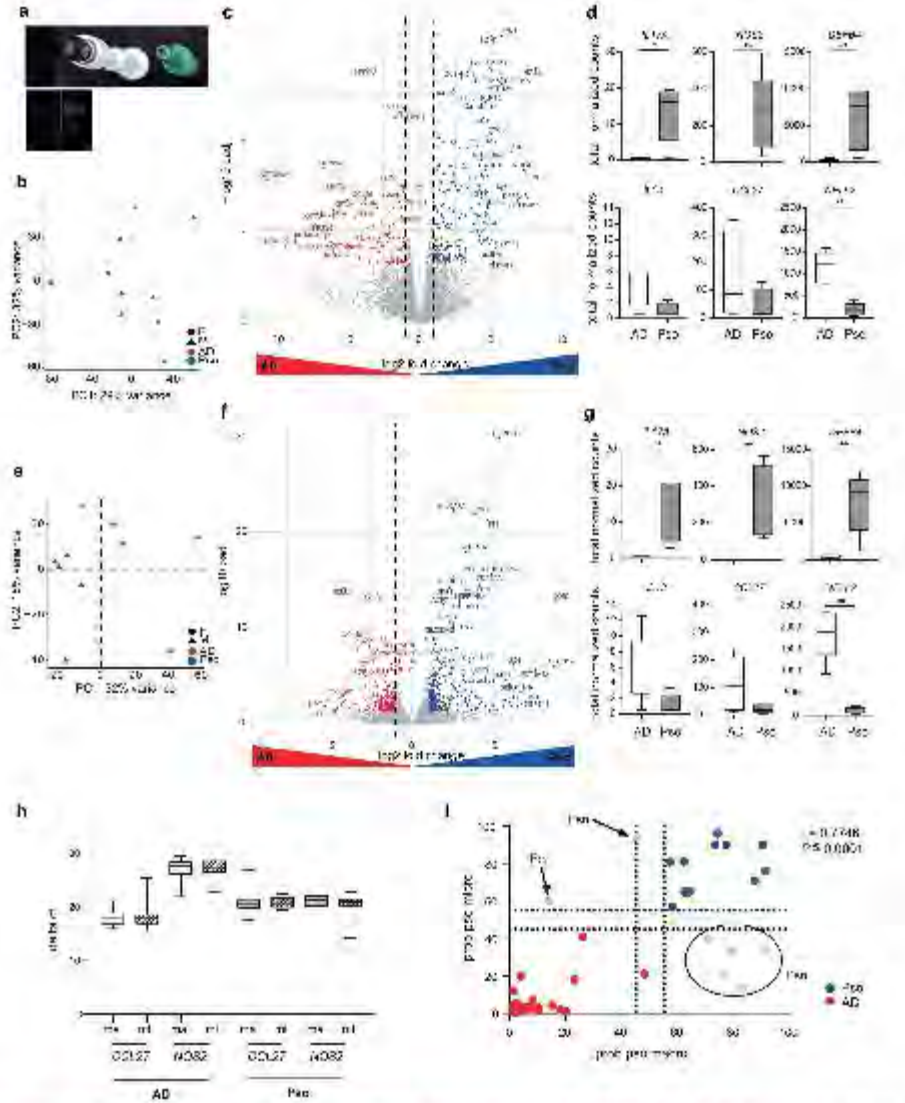
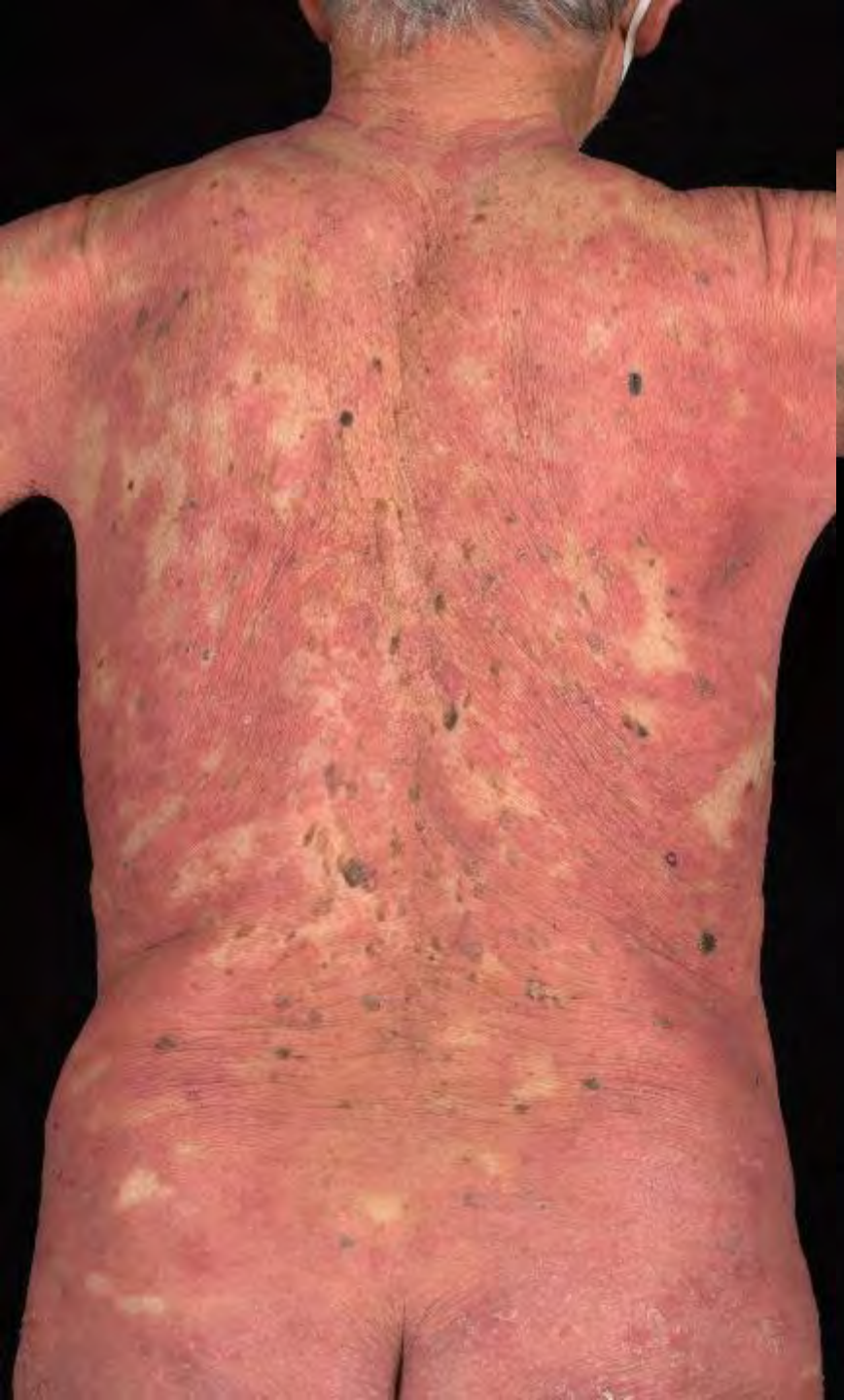
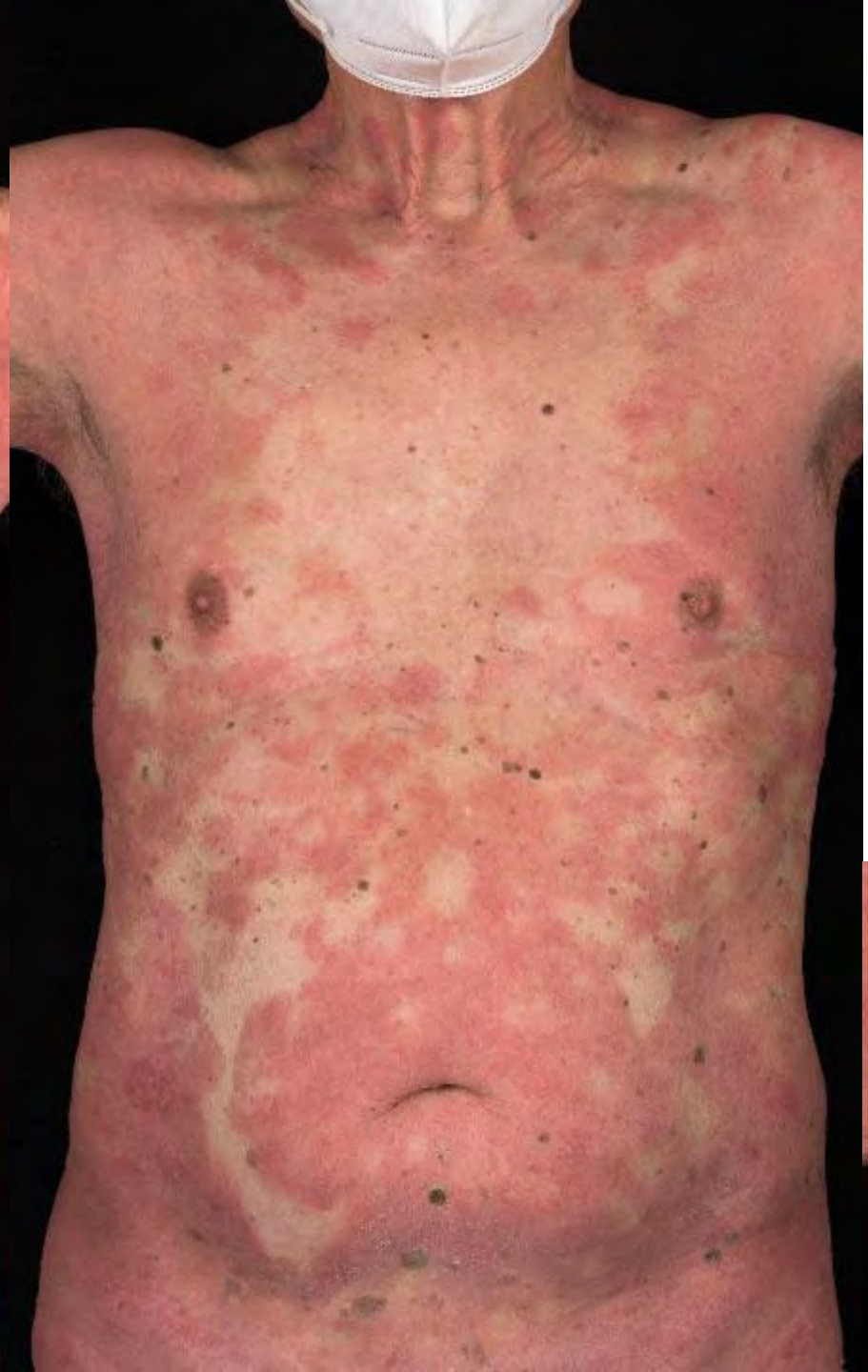


Figure 2. Macro- and microbiopsies show comparable gene expression profiles enabling the use of microbiopsies for molecular diagnosis. (**a**) Comparison of invasive (6 mm punch) macro biopsies and minimally invasive (4 mm) microbiopsies. (**b**) PCA analysis of the microbiopsy cohort (Pso, n = 7; AD, n = 3). (**c**) Volcano plot of significantly regulated genes (Padj < 0.05, log2foldchange > 1.5) in microbiopsies examined by RNA sequencing. (**d**) The marker genes for AD (*MOS2* and *CCL27*) and Pso (*IL36G* and *KRT16*) pathogenesis in microbiopsies. Significance was determined by Wald test (Padj < 0.05). (**e**) PCA of the combined microbiopsy and macro biopsy cohort (Pso, n = 7; AD, n = 3). (**f**) Volcano plot of significantly regulated genes (Padj < 0.05, log2foldchange > 1.5) in macrobiopsies determined by RNA sequencing. (**g**) Marker genes for AD (*MOS2* and *CCL27*) and Pso (*IL36G* and *KRT16*) pathogenesis in macrobiopsies. Significance was determined by the Mann-Whitney *U* test (*P* < 0.05, ** *P* < 0.01). (**h**) The delta Ct values for *MOS2* and *CCL27* normalized to the housekeeper for macro- and microbiopsy samples in AD





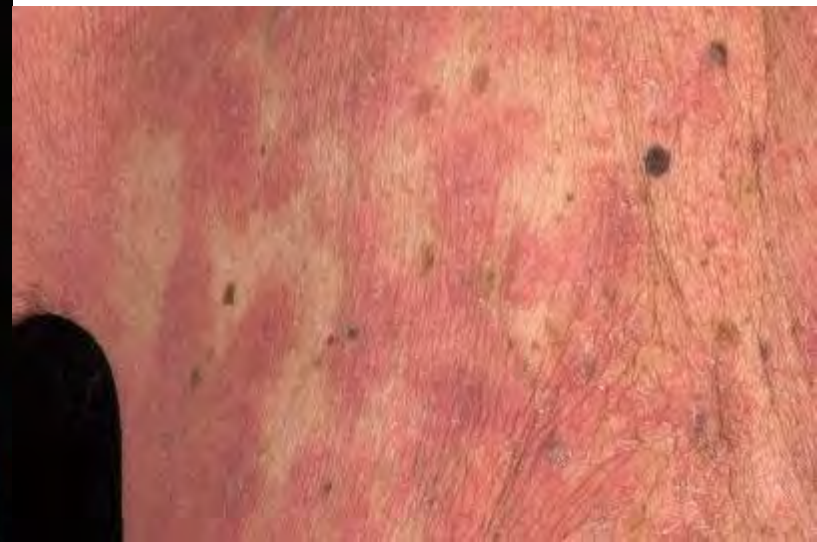
M, 83

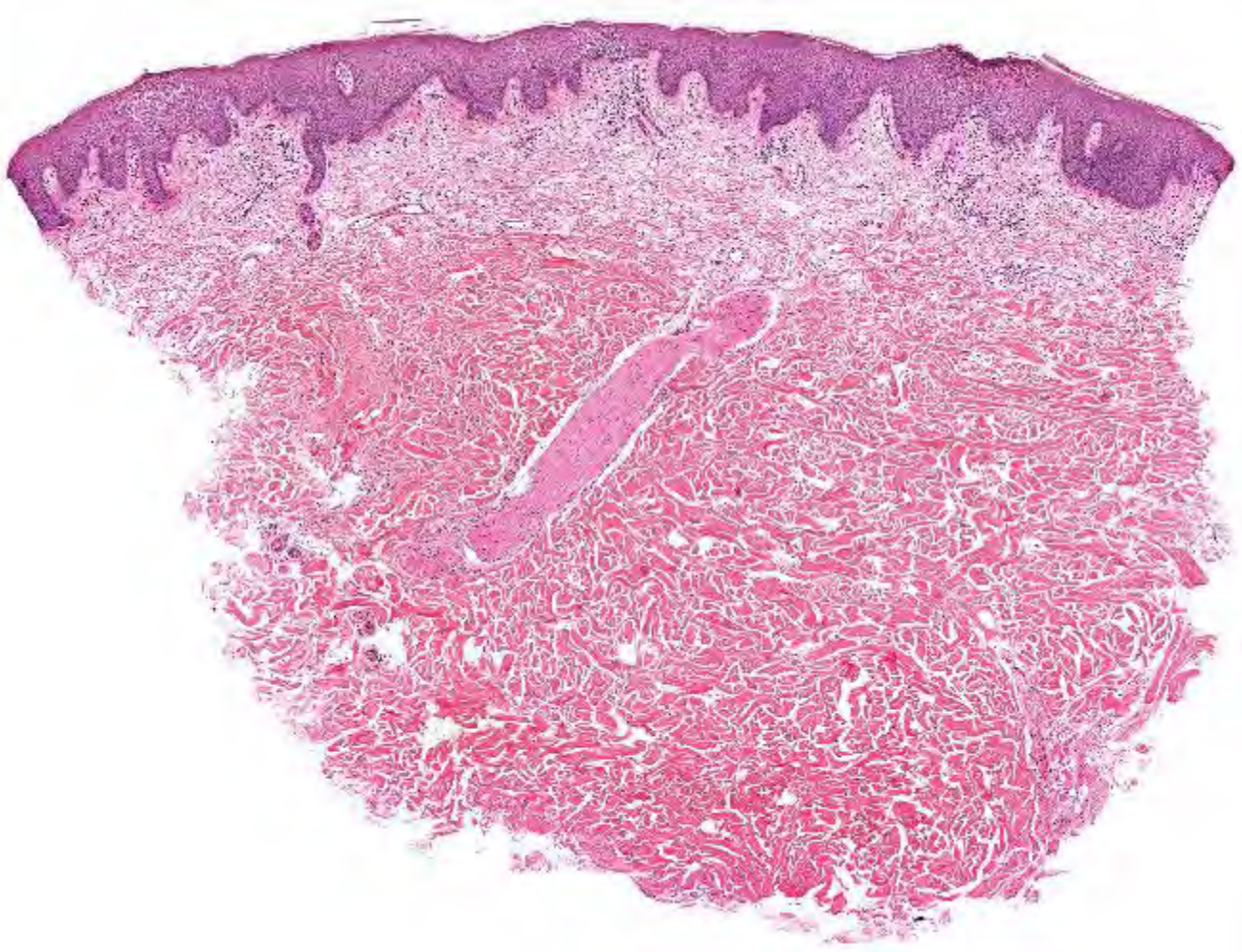
History of melanoma 7 years before presentation (no treatment at present).

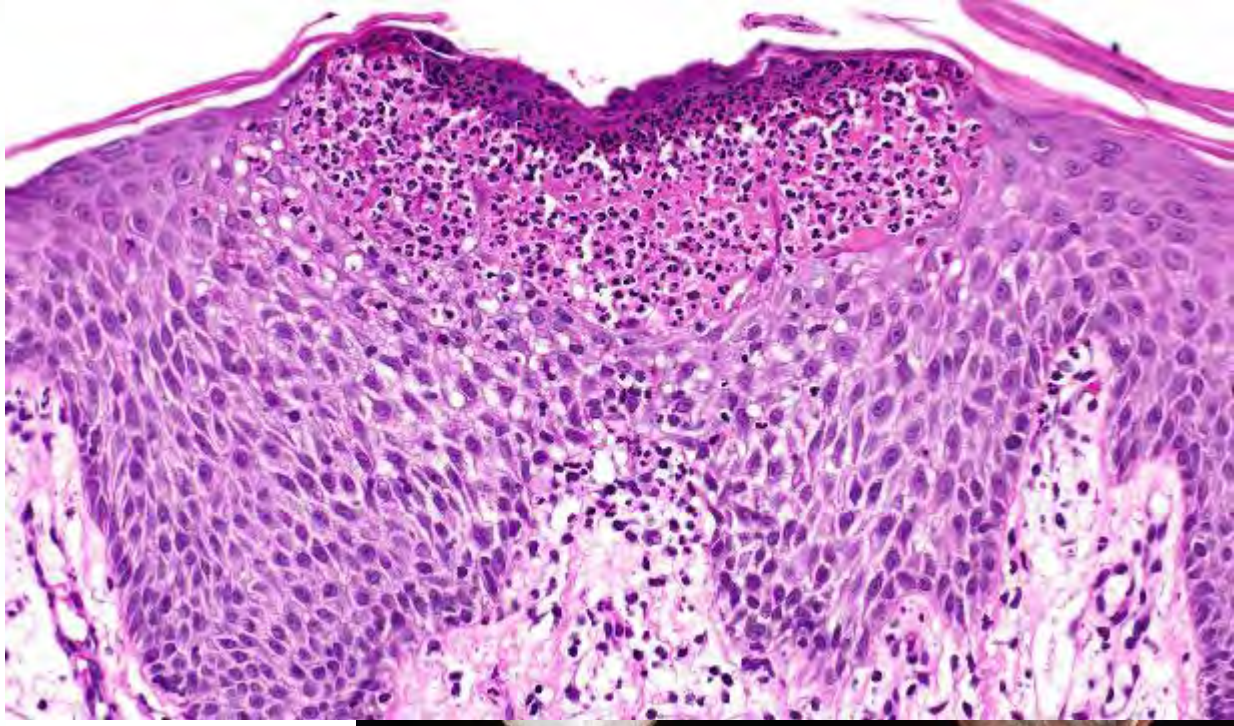
According to the patient skin lesions starting on the extremities and buttocks approximately 2 years before presentation.

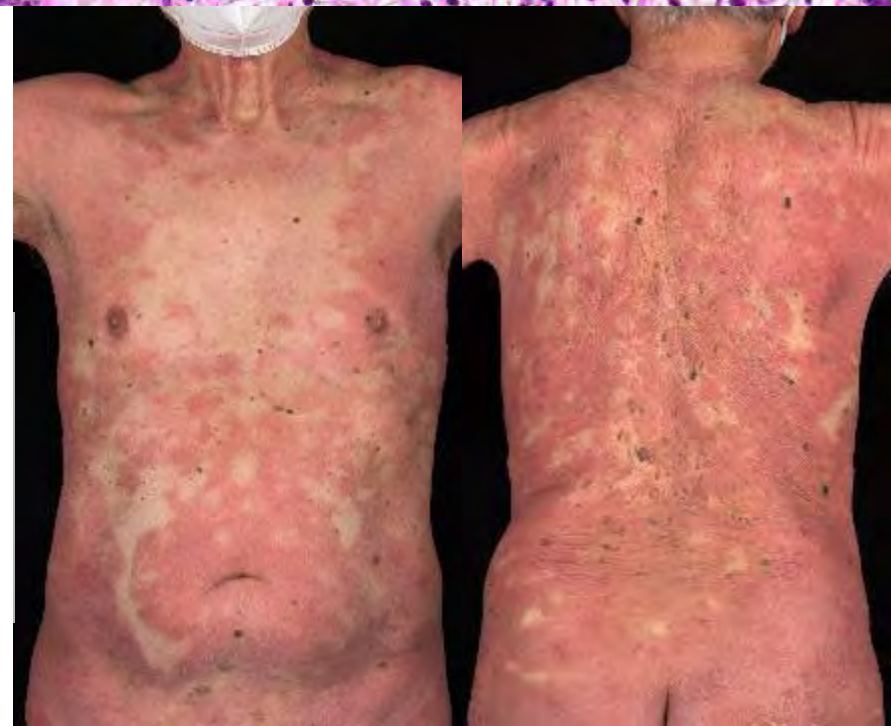
One year before presentation improvement under systemic steroid (prescribed by the GP), then rapid worsening.

A biopsy is taken under the clinical suspect diagnosis of pityriasis rubra pilaris.



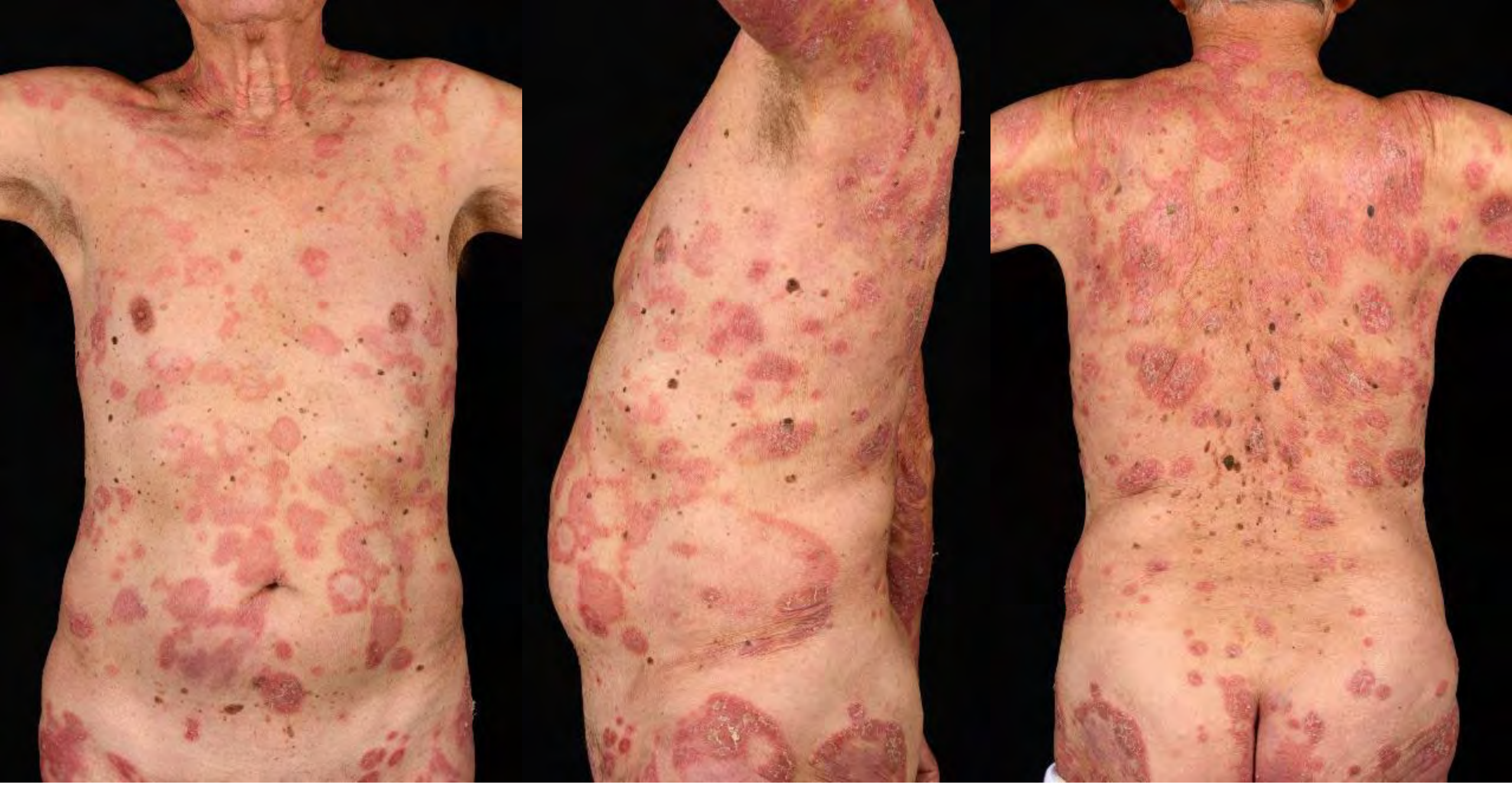




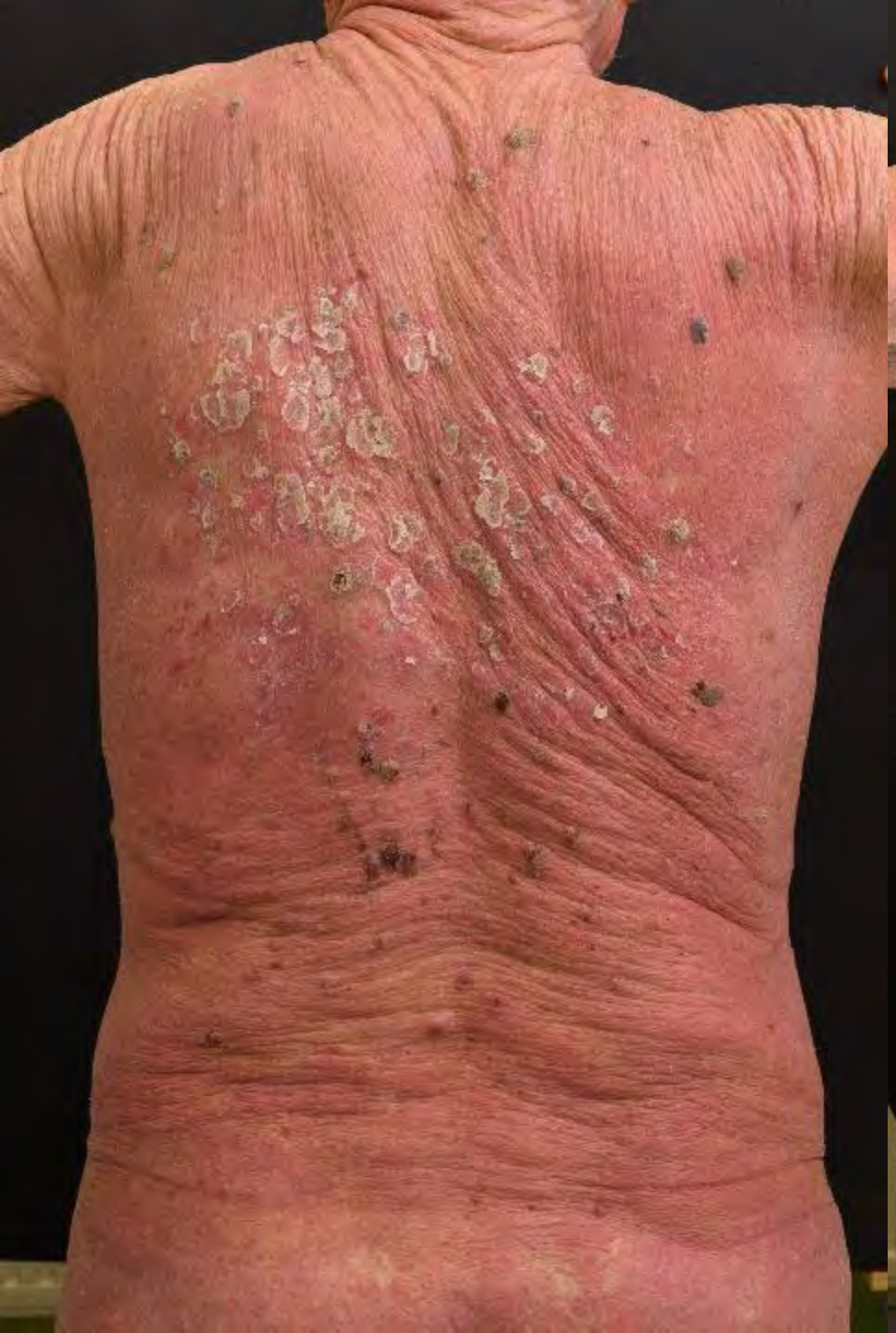


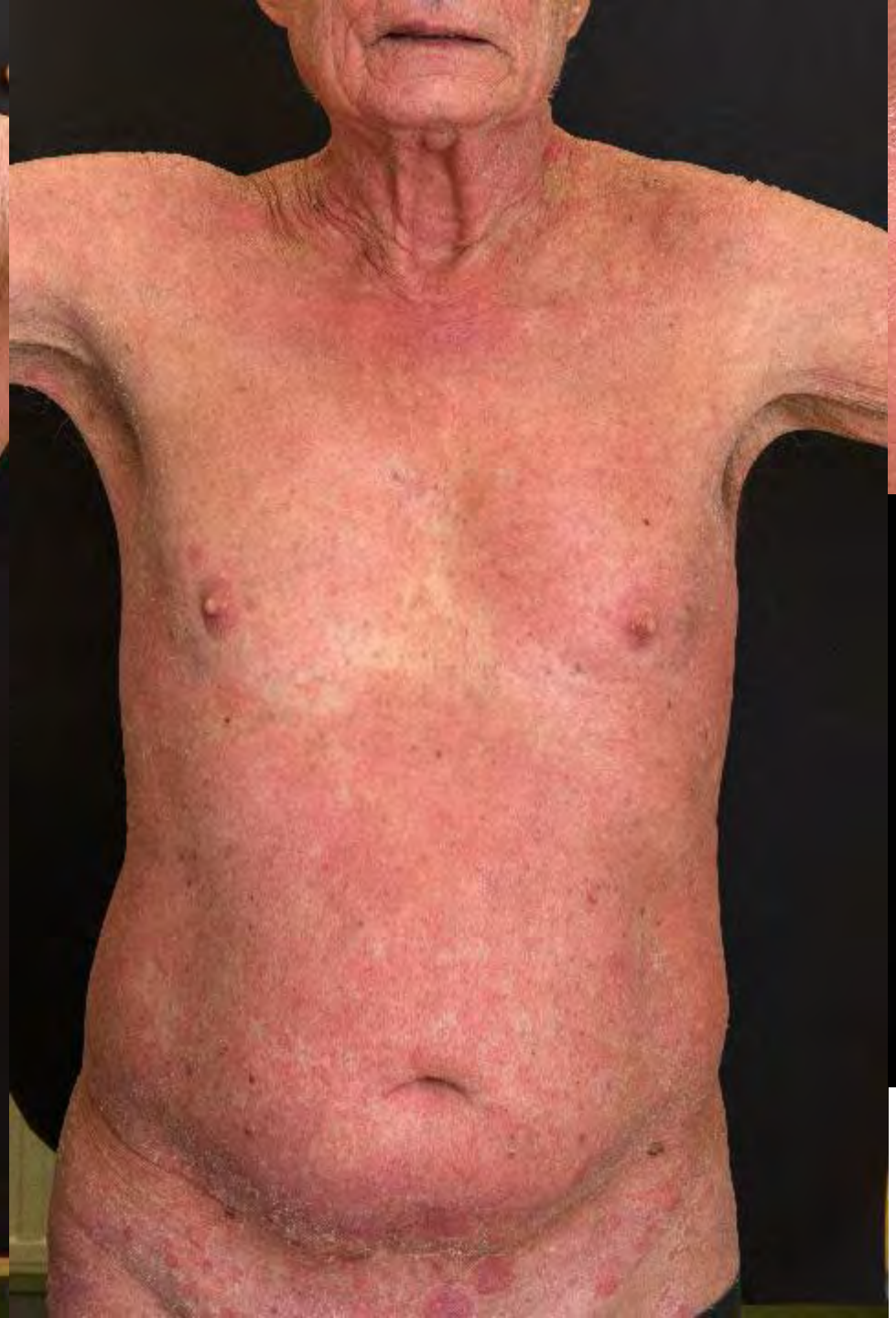
Suberythrodermatic psoriasis

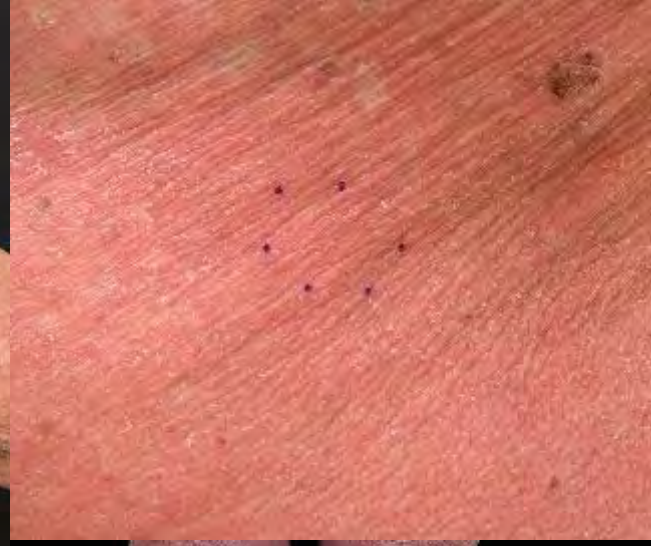
with "nappes claires"

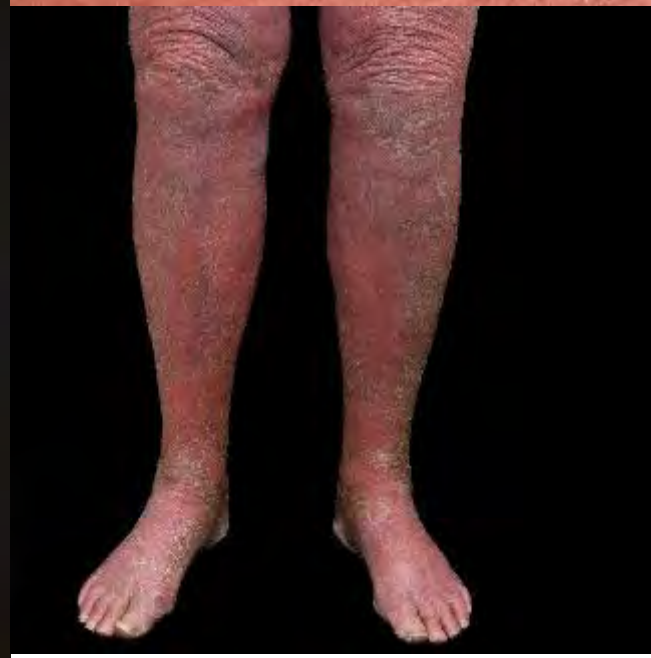


2 years later

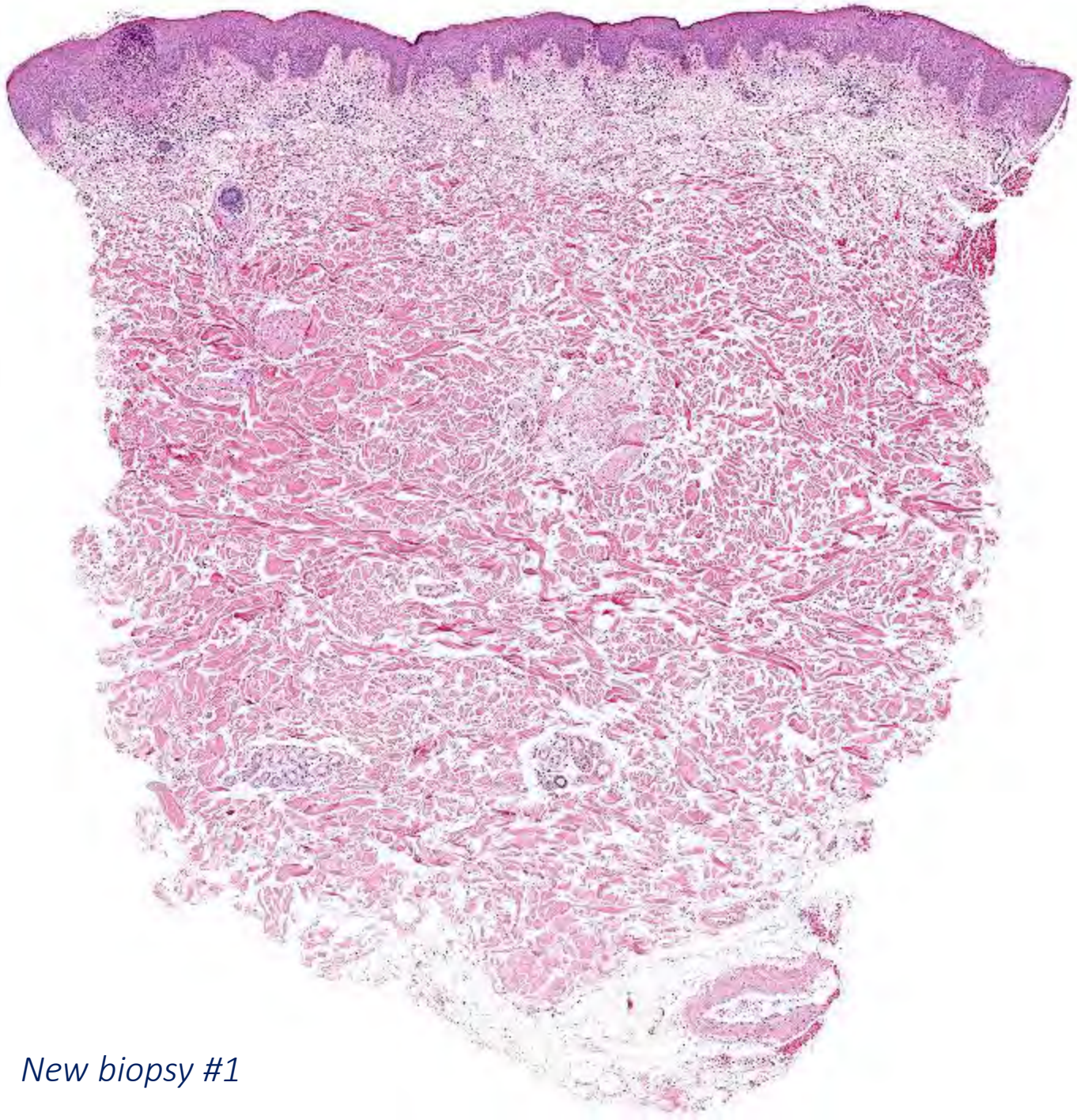


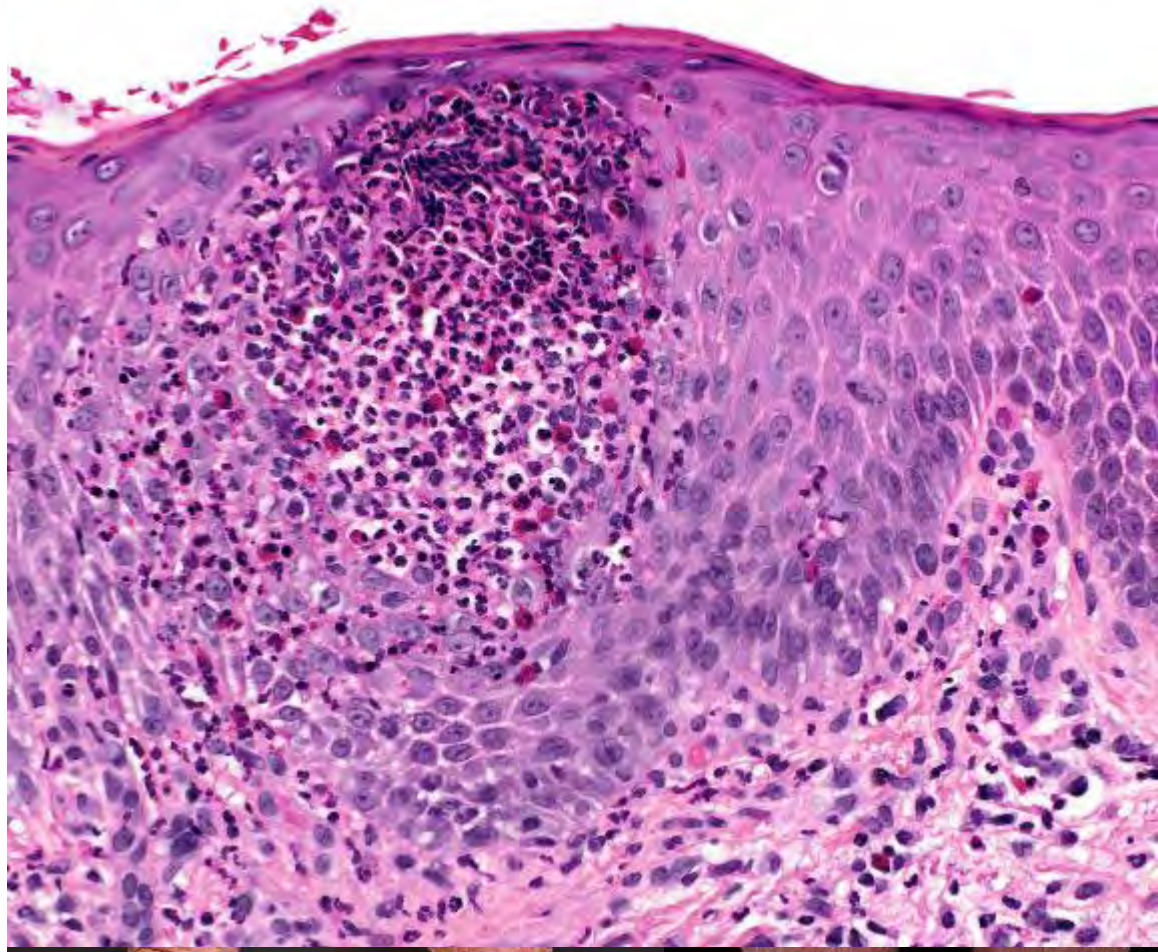


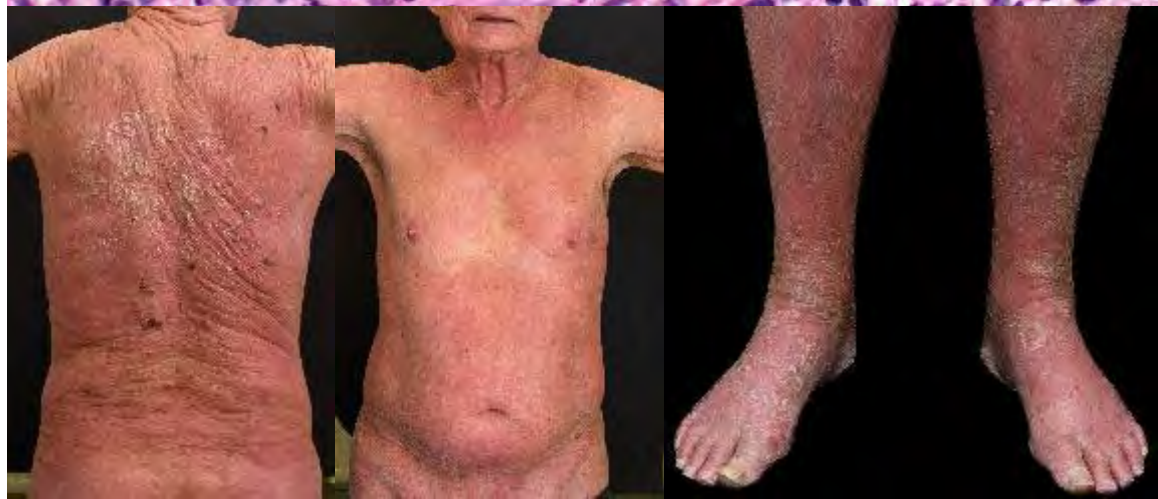




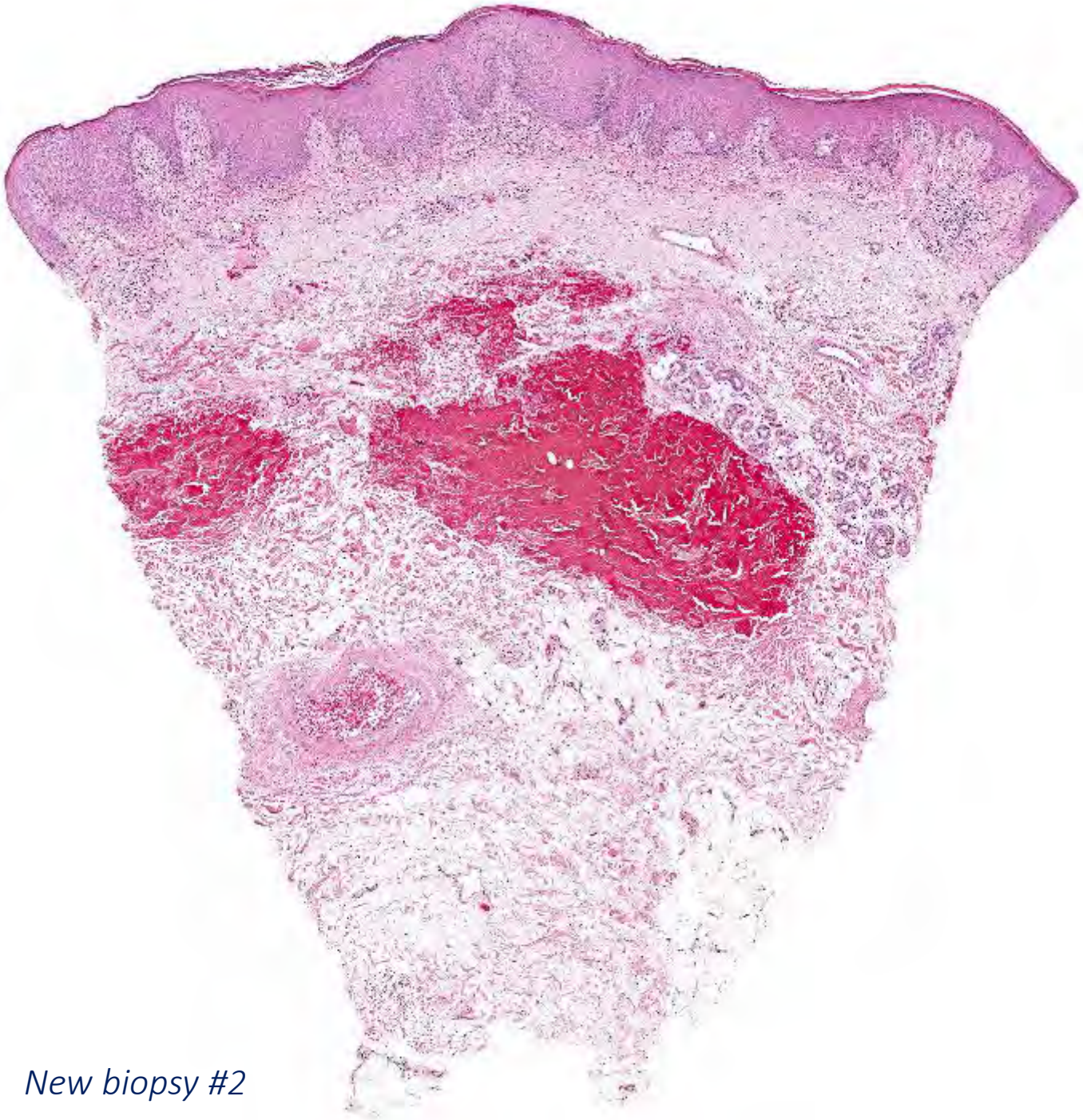
Managed over time with ixekizumab, risankizumab, PUVA.
3 years after 1st presentation becomes erythrodermic with an "eczematous" aspect. Two new biopsies are taken.



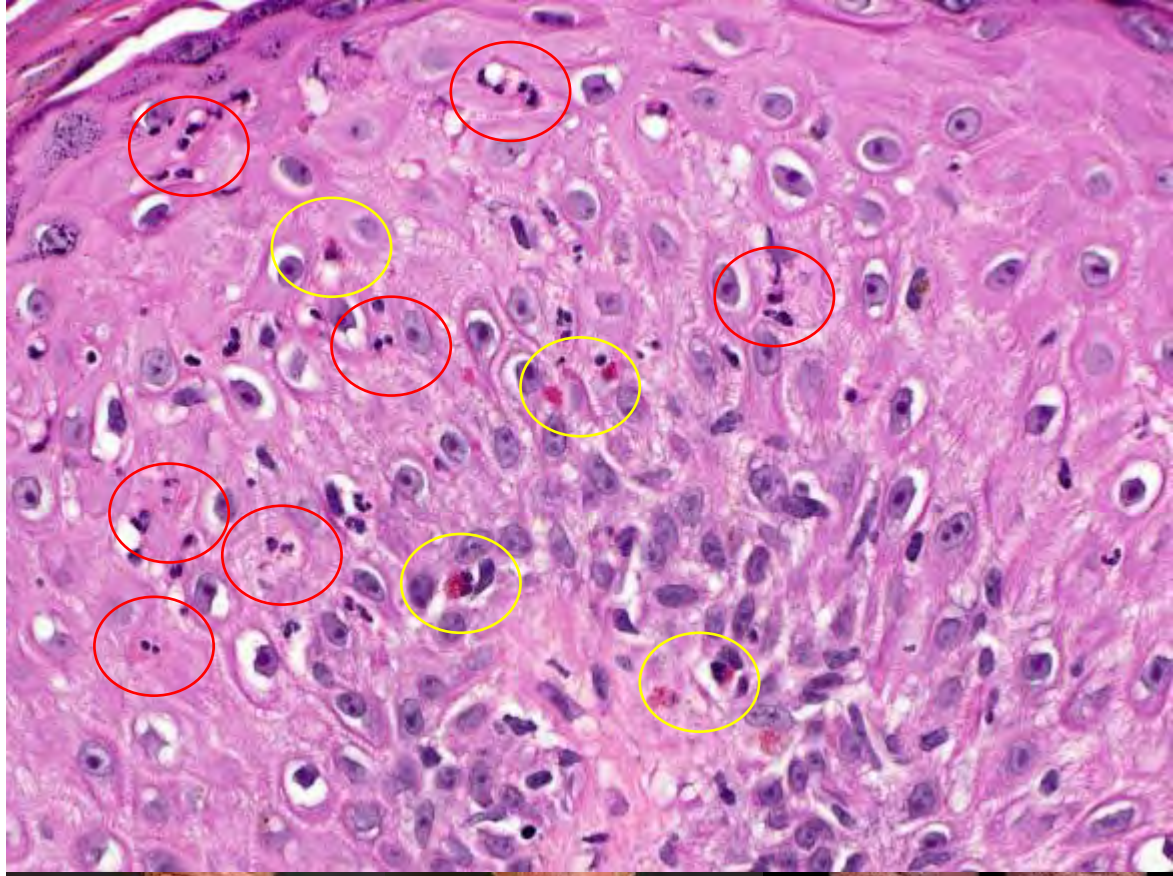


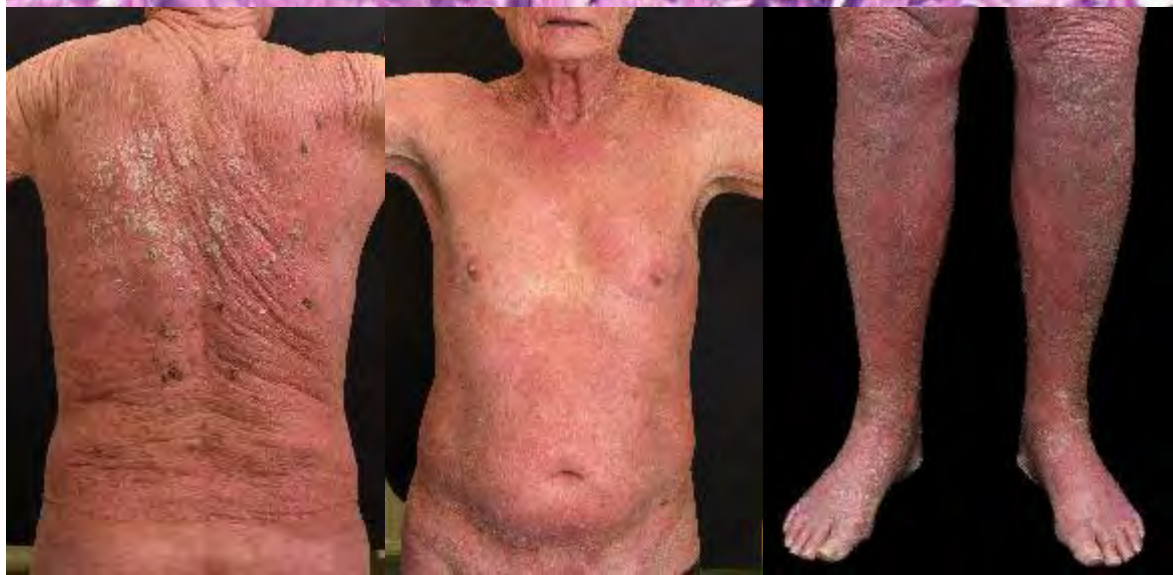


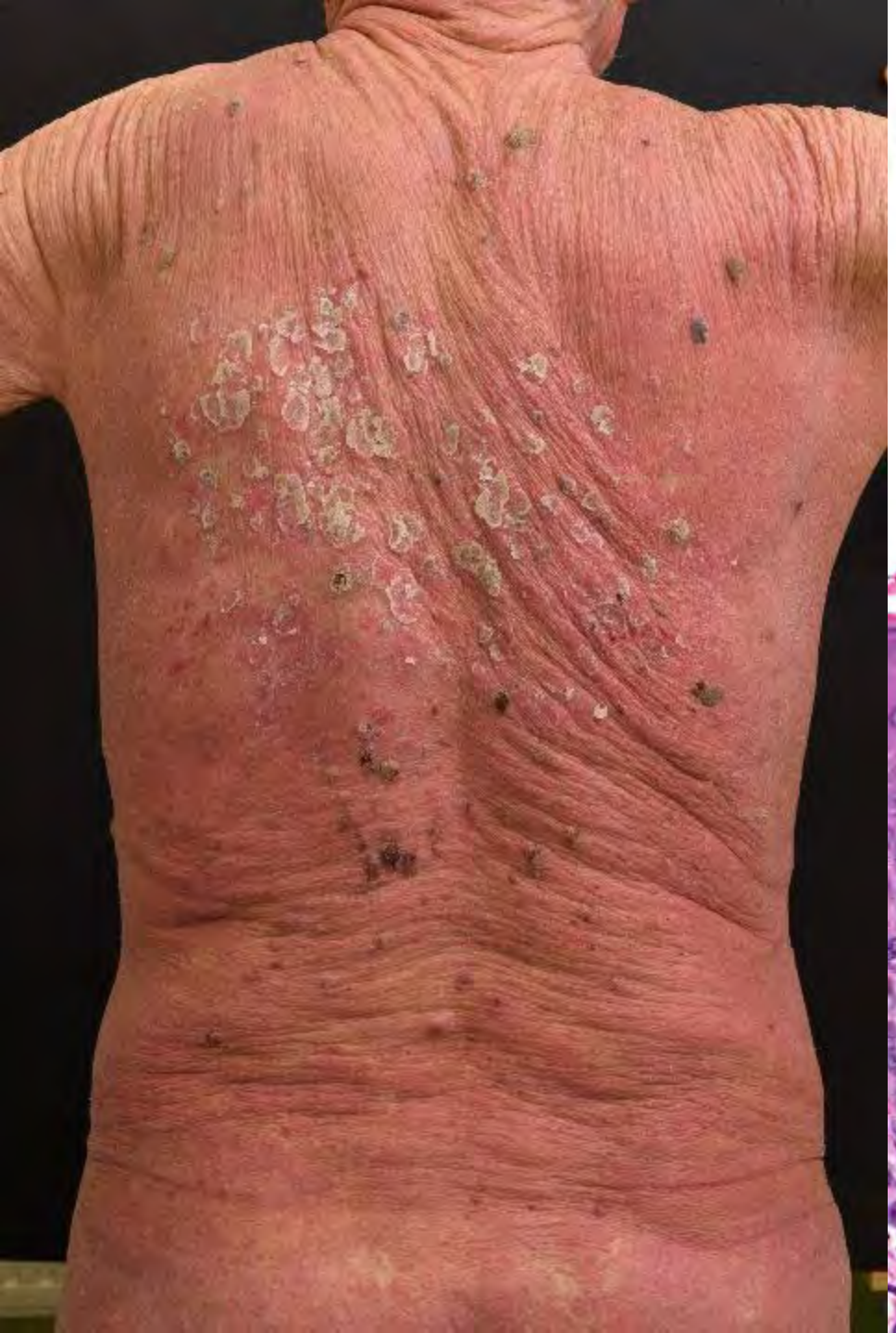
New biopsy #1

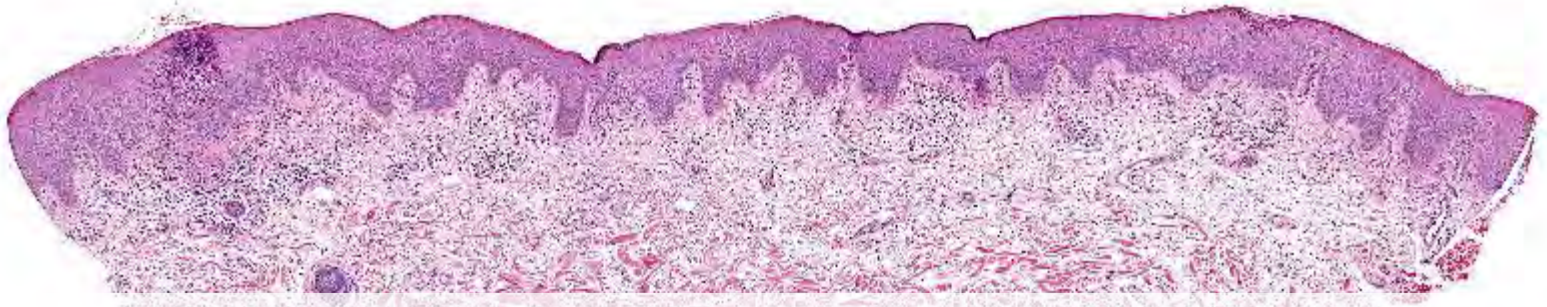


New biopsy #2



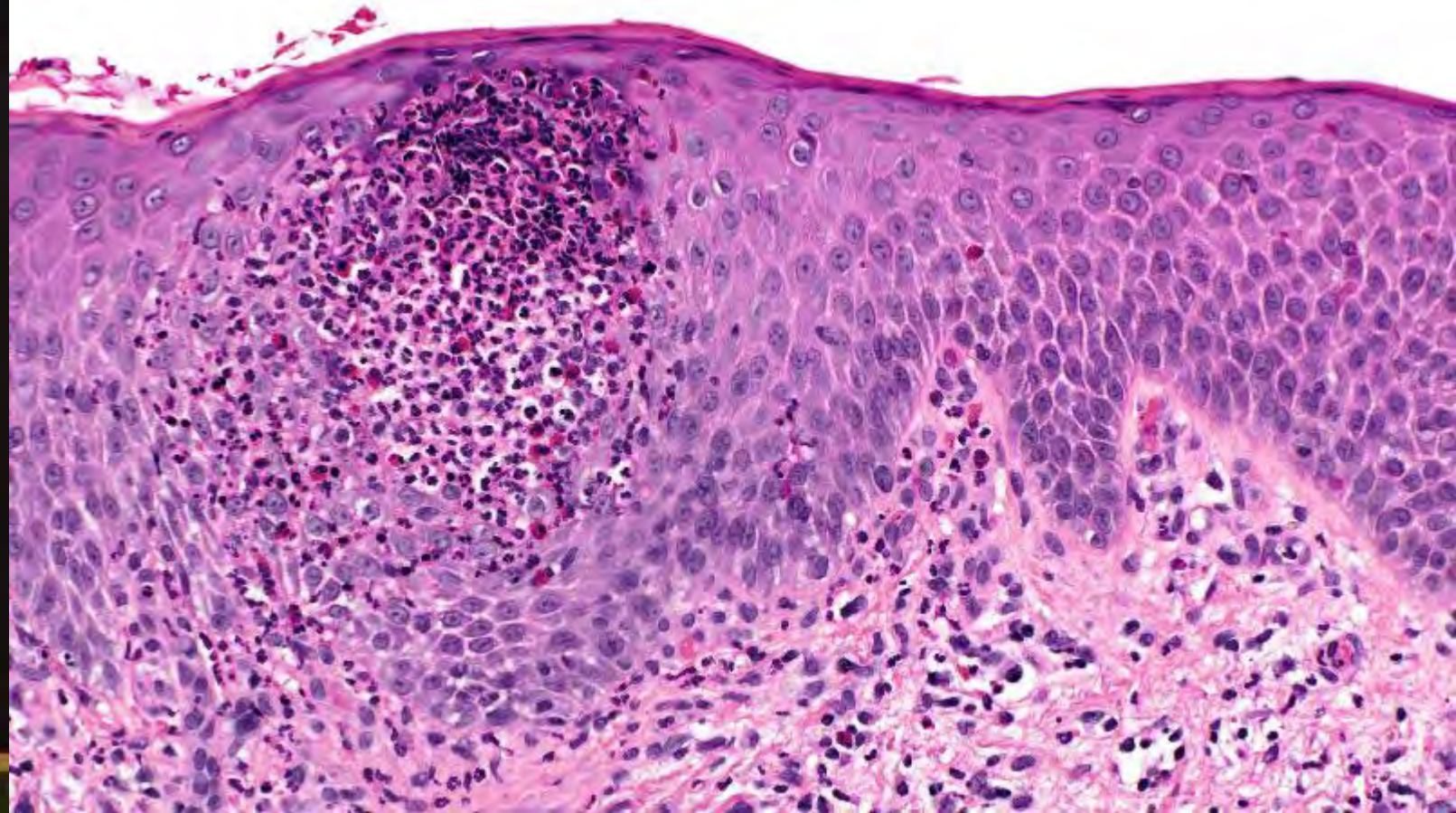


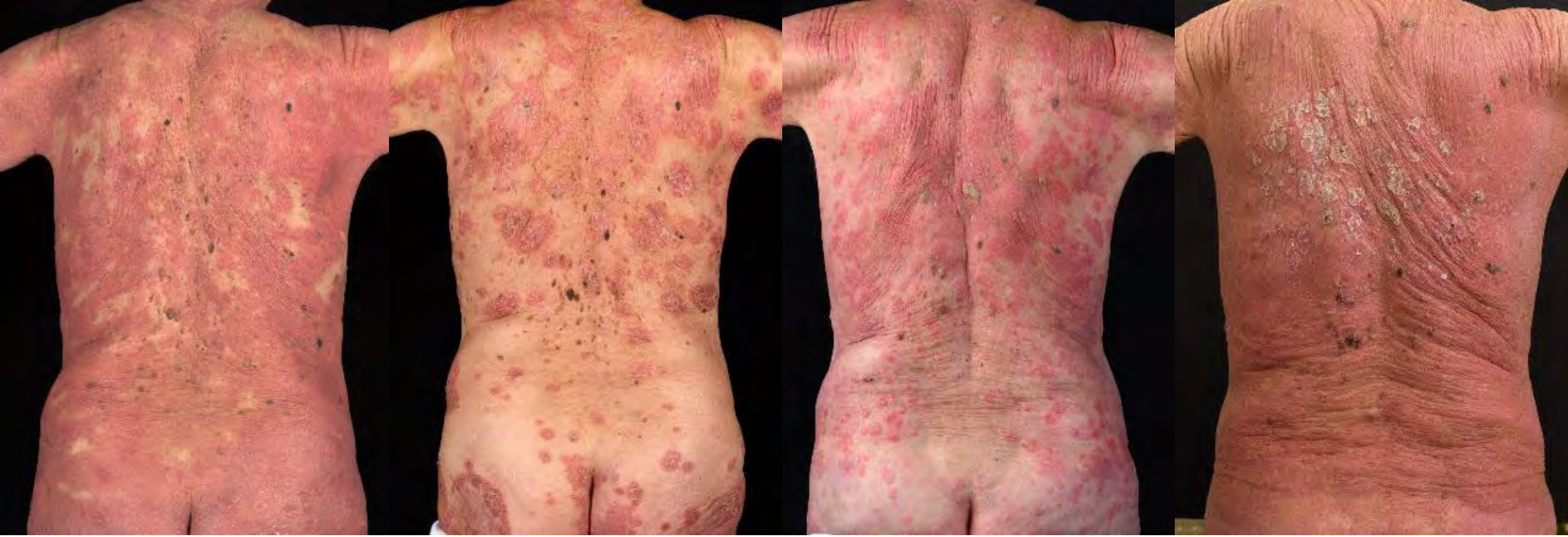




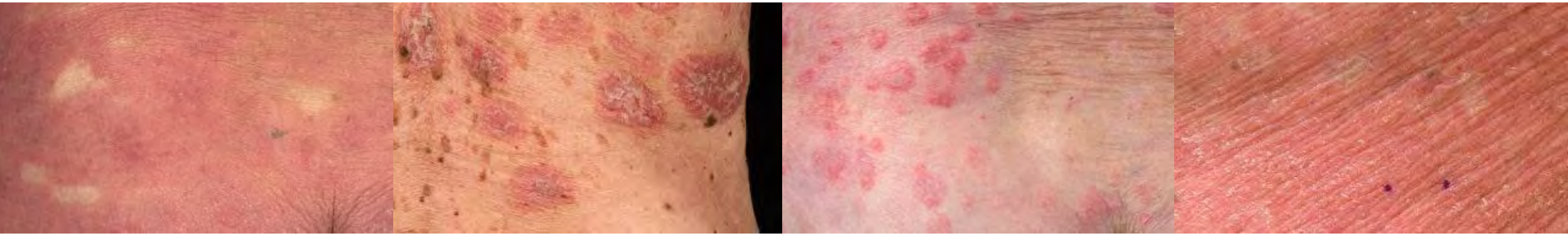
Psoriasis & atopic dermatitis of the elderly

IIF: negative; scabies: negative; IgE: >5000 kU/L





1st presentation | 2 years later | 3 years later | 3 years + 2 months later



Psoriasis and atopic dermatitis may coexist in one and the same biopsy specimen

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OPEN ACCESS

Beyond the dichotomy: understanding the overlap between atopic dermatitis and psoriasis

Mengmeng Li, Jiangyi Wang, Qingfeng Liu, Youqing Liu, Wenyan Mi, Wei Li and Jingyi Li

In summary, these histopathological differences - such as spongiosis and a preserved granular layer in AD versus parakeratosis and neutrophil presence in PSO - underscore the diagnostic distinctions between the two conditions, offering critical insights into their underlying pathologies.

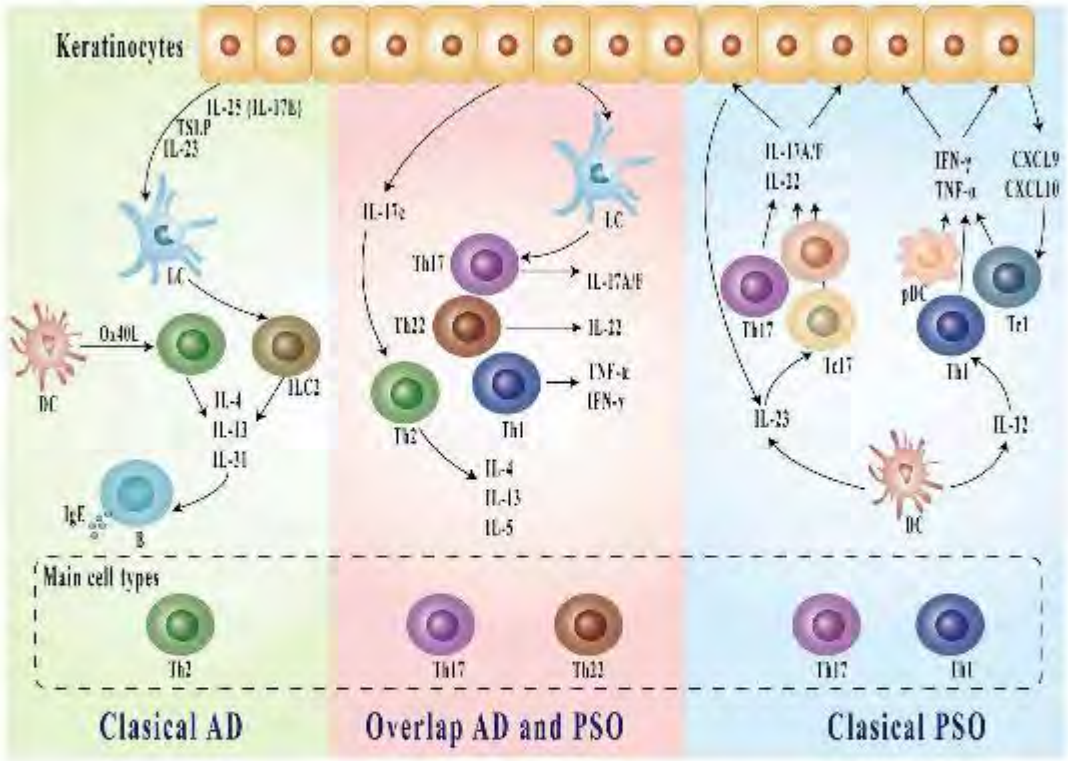

FIGURE 1
Immunologic pathways in classical AD, overlapping AD and PSO, and classical PSO. Classical AD is characterized by Th2-dominant inflammation, where IL-4, IL-13, and IL-31 from Th2 cells stimulate B cells to produce IgE. In the overlapping AD and PSO, both Th17 and Th22 cells are involved, producing IL-17A/F, IL-22, TNF-α, and IFN-γ. Classical PSO features predominant Th17 and Th1 responses, with production of inflammatory cytokines including IL-17A/F, IL-22, TNF-α, and IFN-γ, as well as chemokines CXCL9 and CXCL10. Keratinocytes interact with these pathways by releasing various cytokines and mediators including TSLP, IL-25, and IL-23. AD, atopic dermatitis; PSO, psoriasis; DC, dendritic cells; LC, Langerhans cells; pDC, plasmacytoid dendritic cells; Th, T helper cells; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; CXCL, C-X-C motif chemokine ligand.

AD and PSO are two distinct diseases in terms of mechanisms, but they can coexist in clinical settings (…). Their coexistence within the same clinical profiles presents a complex challenge, highlighting the nuanced interplay of immune responses in dermatological conditions. We propose naming the condition characterized by their overlap as psoriasis dermatitis (PD).

Dermatological Research
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Contrasting disease patterns in psoriasis and atopic dermatitis*

P. Christophers and T. Henseler
Department of Dermatology, University of Kiel, D-2300 Kiel, Federal Republic of Germany

Summary. In this report we investigate the simultaneous occurrence of psoriasis and atopic dermatitis (AD) as well as the association with infectious skin diseases. Among 29,159 patients hospitalized between 1953 and 1983, 8.5% (2,467 patients) were treated for psoriasis, while 1.6% (470 patients) were hospitalized for AD treatment. On the basis of incidence rates for both diseases, 36 patients (0.14%) with both psoriasis and AD were expected to be seen. However, the two conditions were simultaneously present in 2 patients only.

Approximately 30% of the AD patients were suffering from either bacterial or viral infection, while this complication occurred in 6.7% of psoriatics. In addition, among 48 patients hospitalized for eczema herpeticum 39 were atopics and none was psoriatic. The data demonstrate that the occurrence of psoriasis and AD in one and the same patient is quite rare and this may be related to conflicting immune defense patterns. Thus, increased sensitization against foreign procein together with high susceptibility to cutaneous infection present in AD is in contrast to high phagocyte responsiveness in psoriasis, where concurrent infections are rare.

Key words: Psoriasis — Atopic dermatitis — Infection

Psoriasis and atopic dermatitis (AD) are among the most common diseases of the skin. Within the caucasian population the incidence of psoriasis is estimated to be near 2% [2, 6], while the incidence rates of AD are reported to be nearly 5% in younger age groups [10, 19].

Since both psoriasis and AD occur with such marked frequency, it would appear reasonable to assume that there is a proportion of patients in whom both skin disorders may be seen simultaneously. Because the coexistence of both conditions could reveal important pathophysiologic aspects, we investigated in detail the question of simultaneous occurrence of psoriasis and atopic dermatitis. The results indicate that psoriasis and AD occur rarely within the same patient. In addition, the conditions represent mutually exclusive disease patterns associated with a distinct set of diseases.

Materials and methods

[illegible] were analyzed of 29,159 hospitalized patients of the Department of Dermatology, University of Kiel, containing clinical disease data, e.g., diagnosis, associated disorders, age at onset, laboratory findings as well as treatment results. From these data pertinent to psoriasis and atopic dermatitis were released. The period of [illegible] was from 1953 to 1983. Diseases occurring simultaneously, and [illegible] of hospitalizations were counted. [illegible] the observed frequencies of both disease in one period we [illegible] elementary statistical theorem: in independent events the product of observed frequencies, each of them with one special attribute, is the frequency of subjects showing both attributes simultaneously. Data shown here are only from patients for whom their skin condition was so severe, that inpatient hospital treatment was necessary.

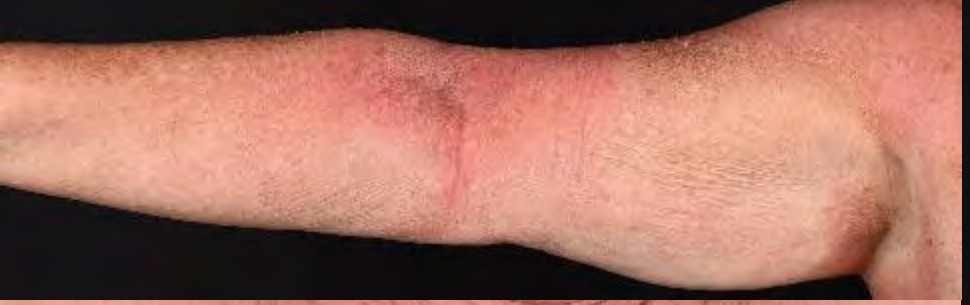
[illegible] analysis was used to calculate differences in [illegible] psoriatics and AD patients. The minimal significant level accepted is $p = 0.05$.

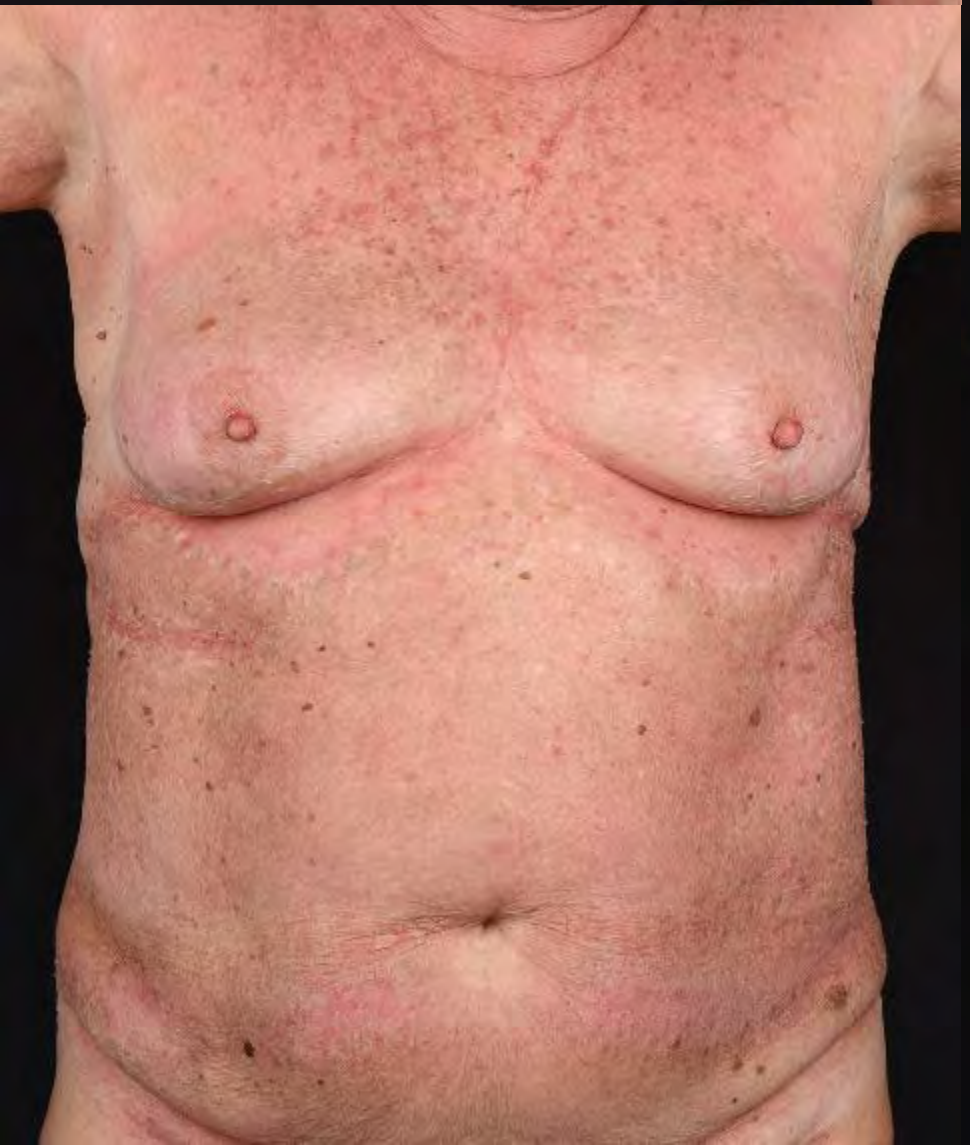
Results

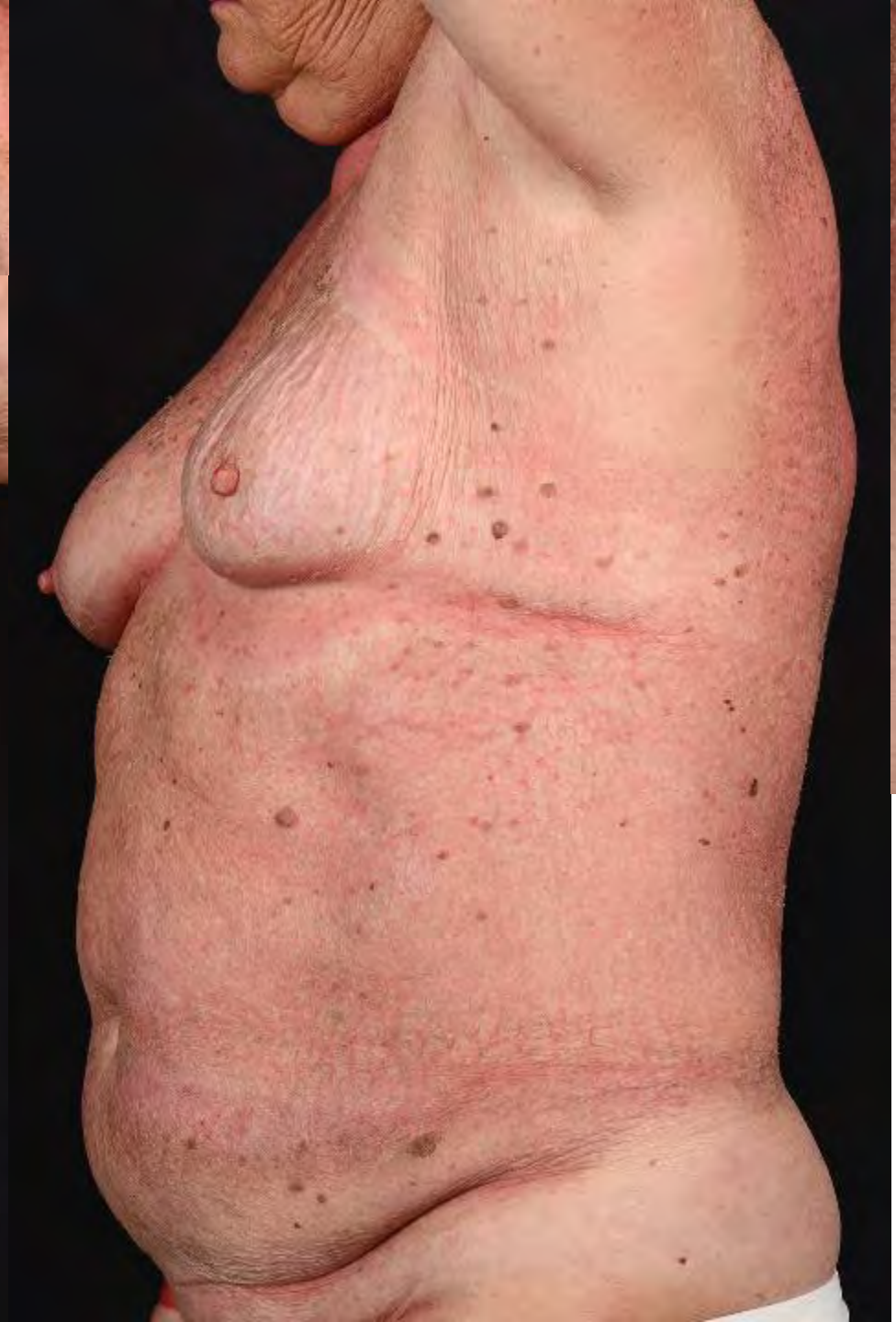
Among a total of 29,159 hospitalized patients, 2,467 patients (8.5%) suffered from psoriasis (first diagnosis) and 470 patients (1.6%) were hospitalized for AD treatment. The ratio of sex is nearly the same in psoriatics (57.1% males) AD patients (52.8% males). The average age at the time of admission was 38 years in psoriasis and 17 years in AD. Two patients presented with both diseases at the same time (Table 1).

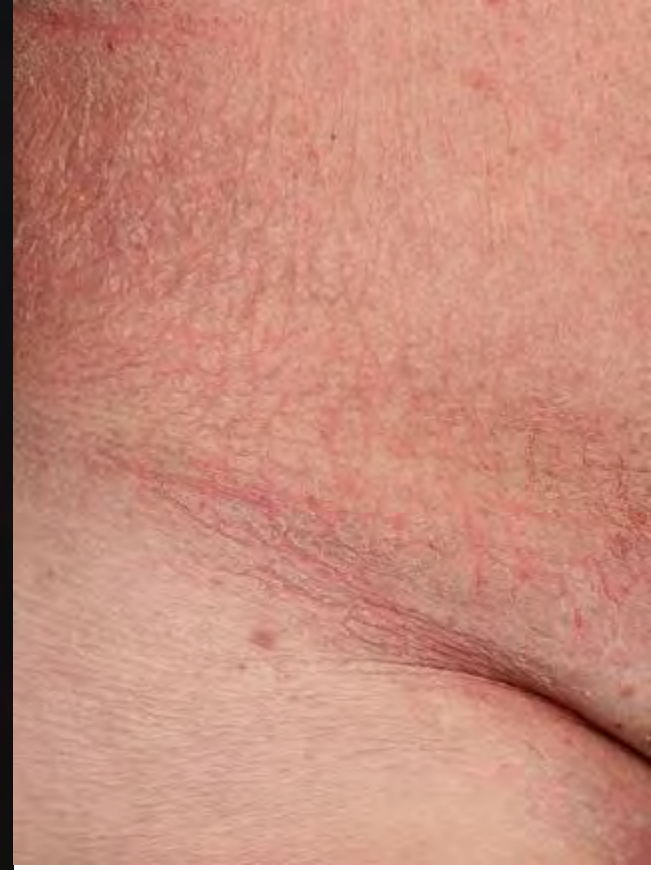
* Supported by Deutsche Forschungsgemeinschaft [illegible]
[illegible] requests to: Peter Christophers, M.D. (address as above)

Among 29,159 patients, 8.5% (2,467 patients) were treated for psoriasis, while 1.6% (470 patients) were hospitalized for AD treatment. On the basis of incidence rates for both diseases, 36 patients (0.14%) with both psoriasis and AD were expected to be seen. However, the two conditions were simultaneously present in 2 patients only.









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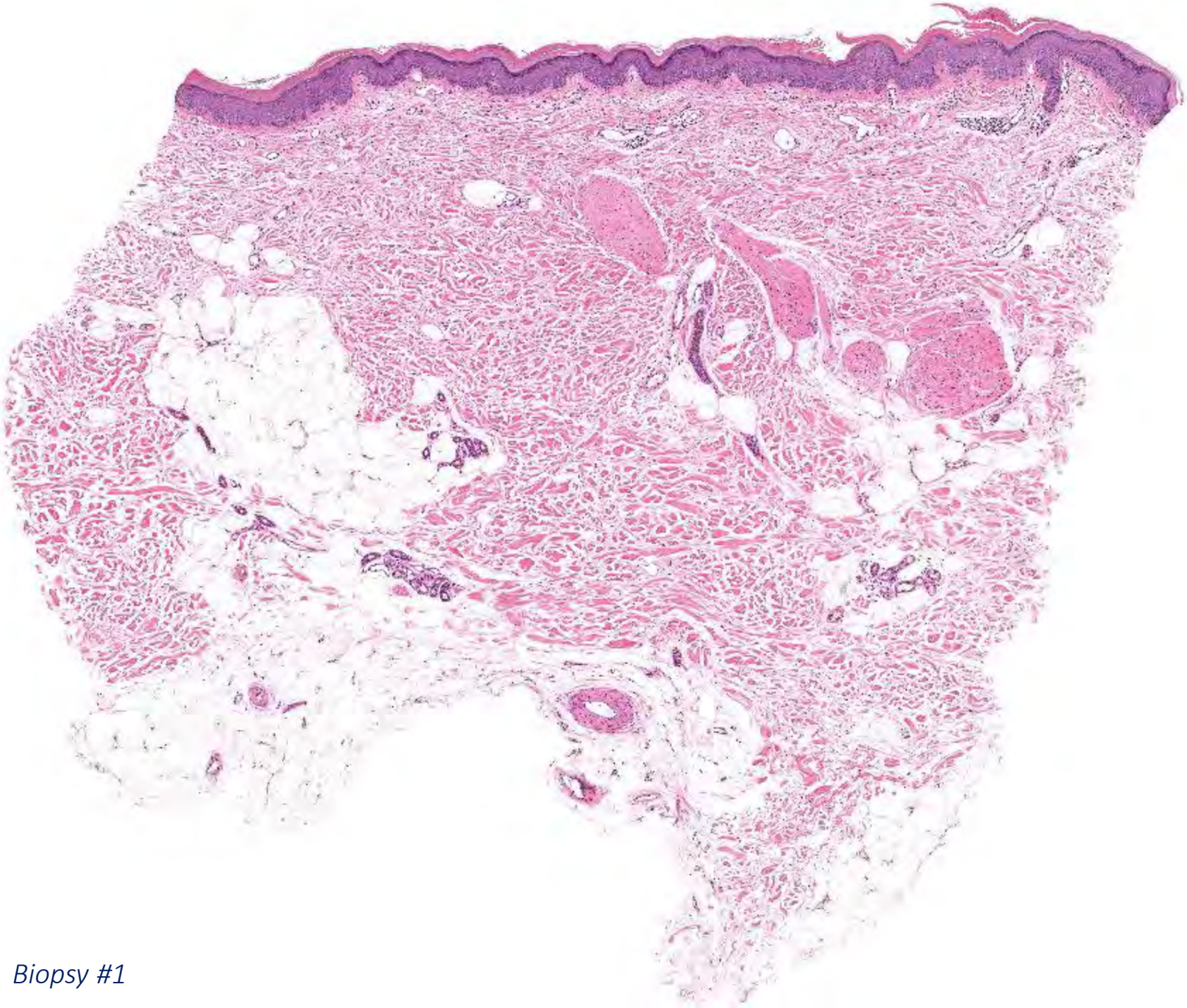
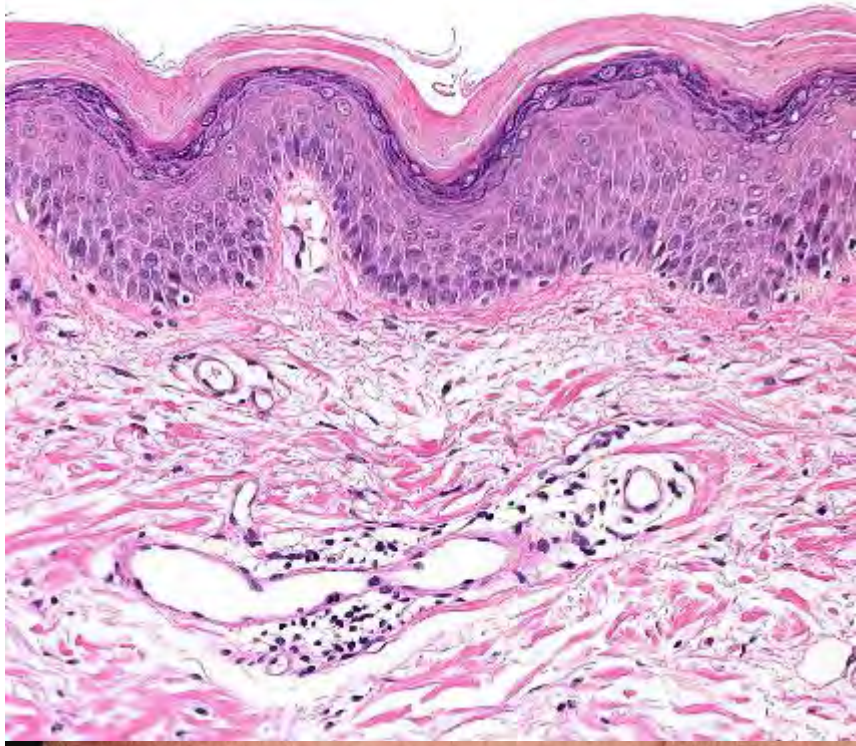
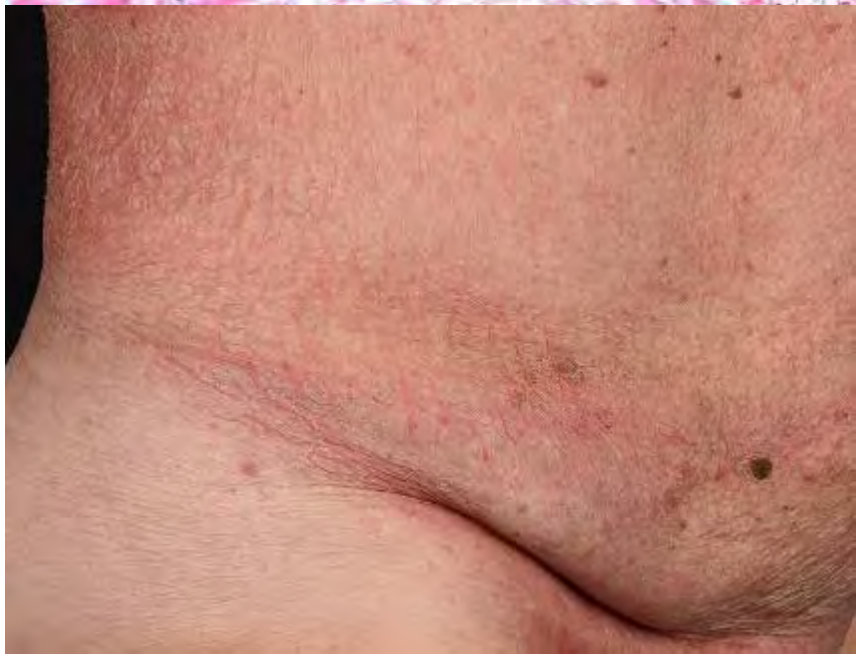
According to the patient skin changes for one week (4 years previously in the out-patient chart no mention of eczematous / ichthyosiform lesions).

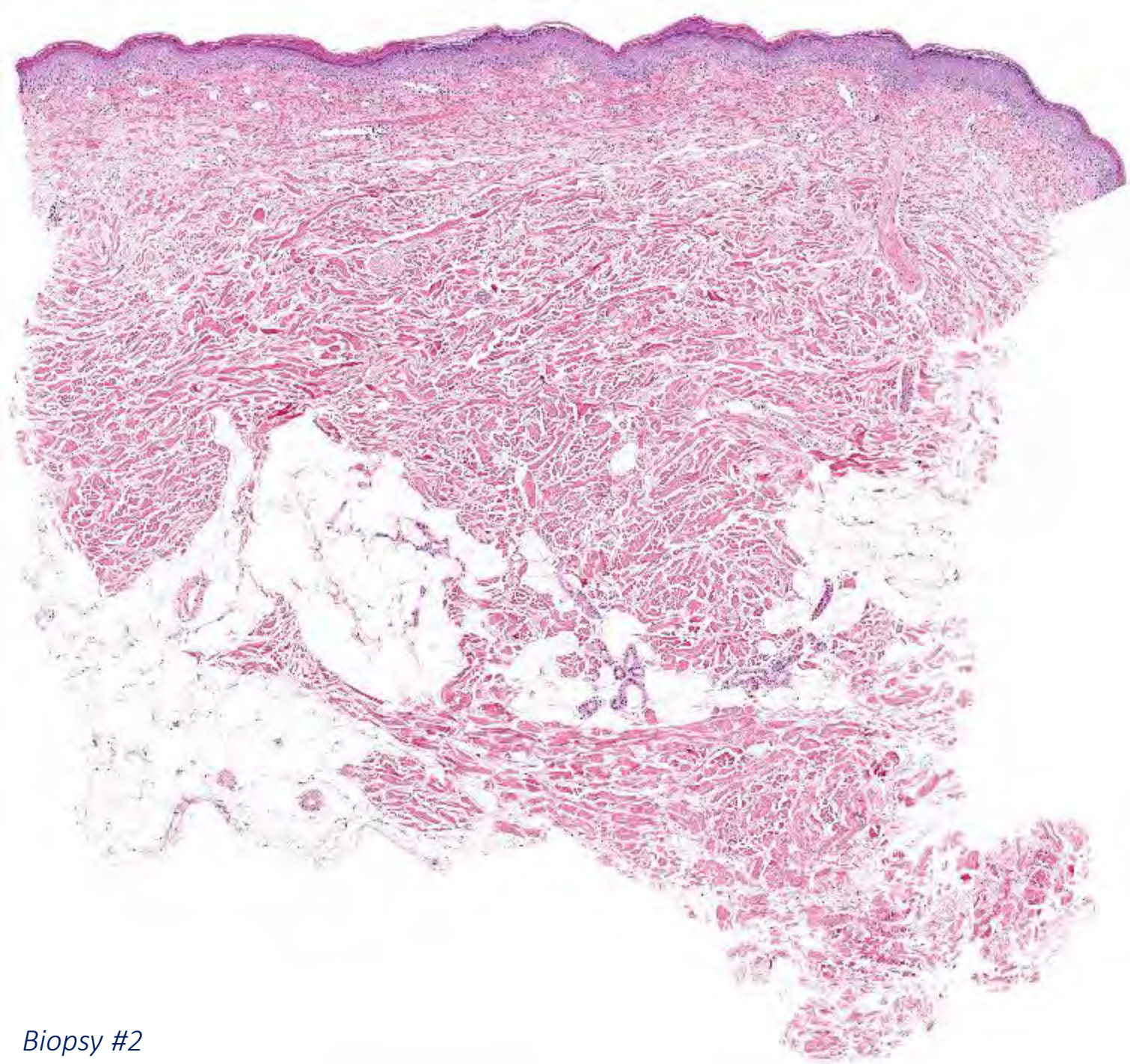
Two biopsies are taken.

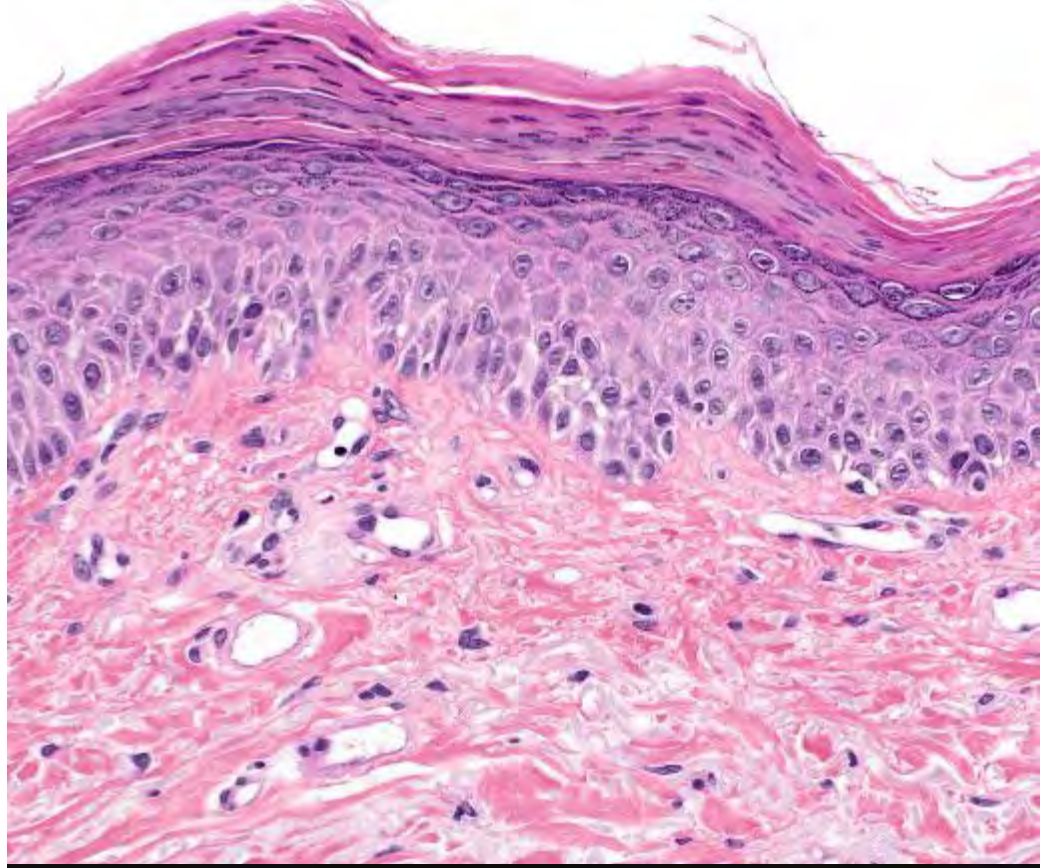


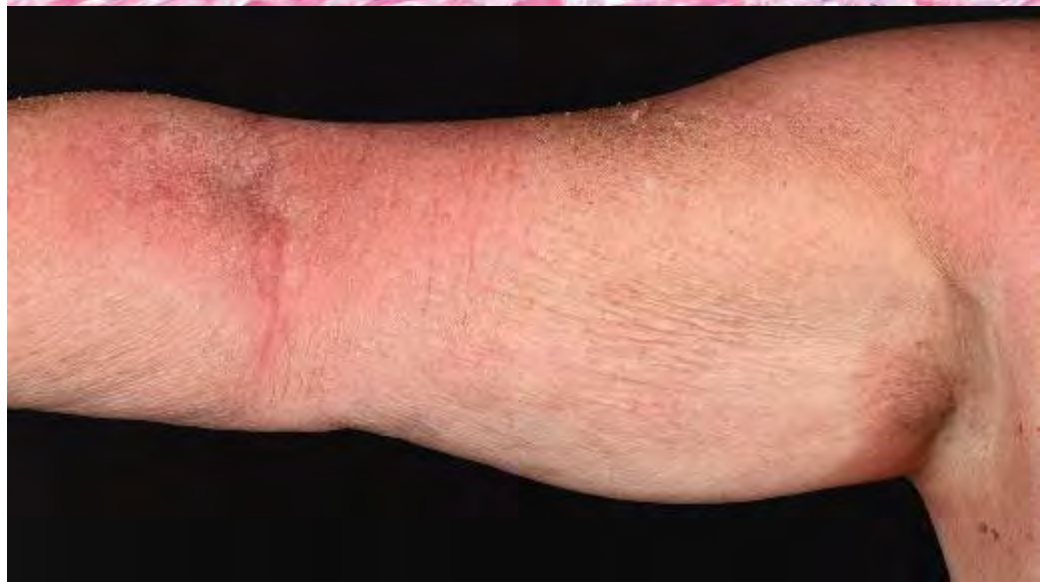




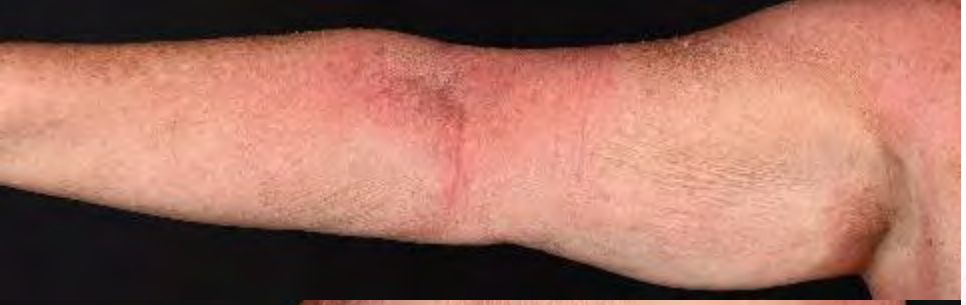
Biopsy #1

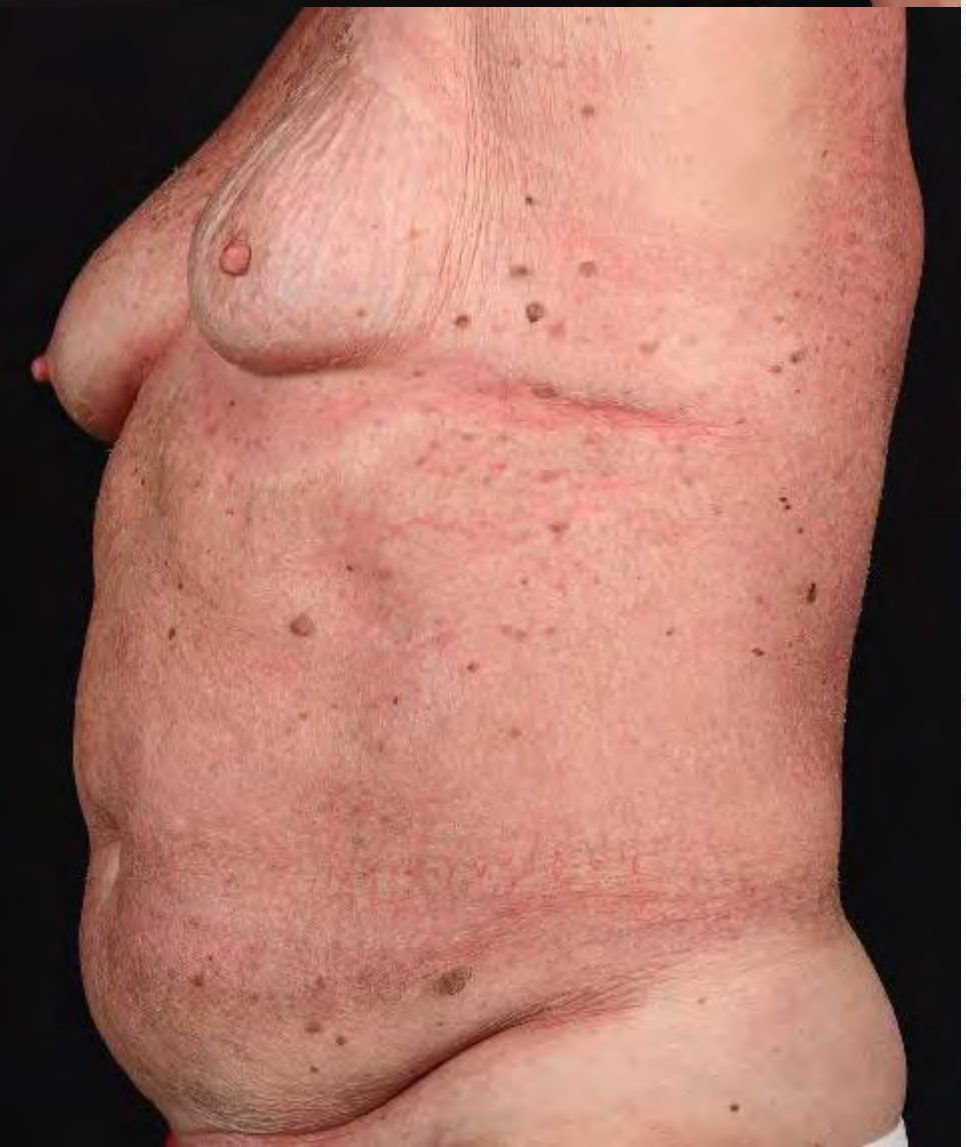


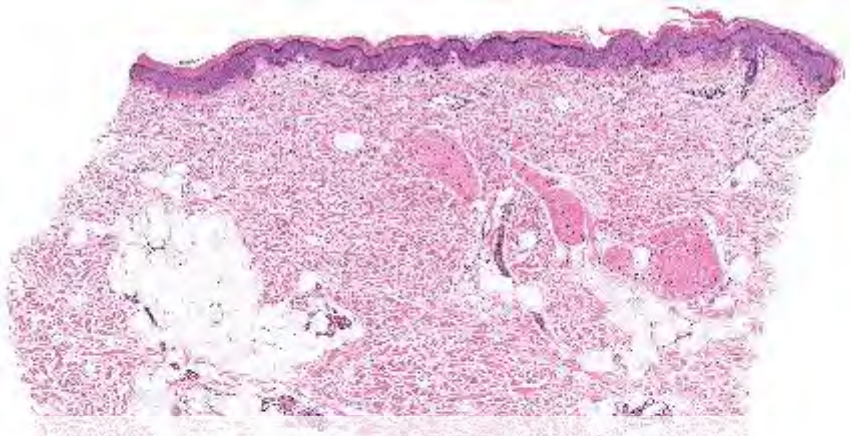




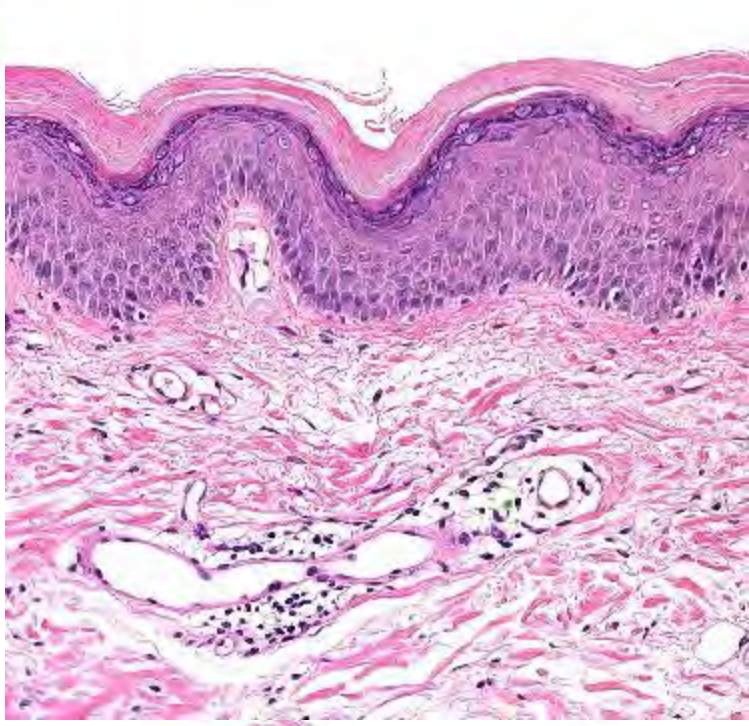
Biopsy #2

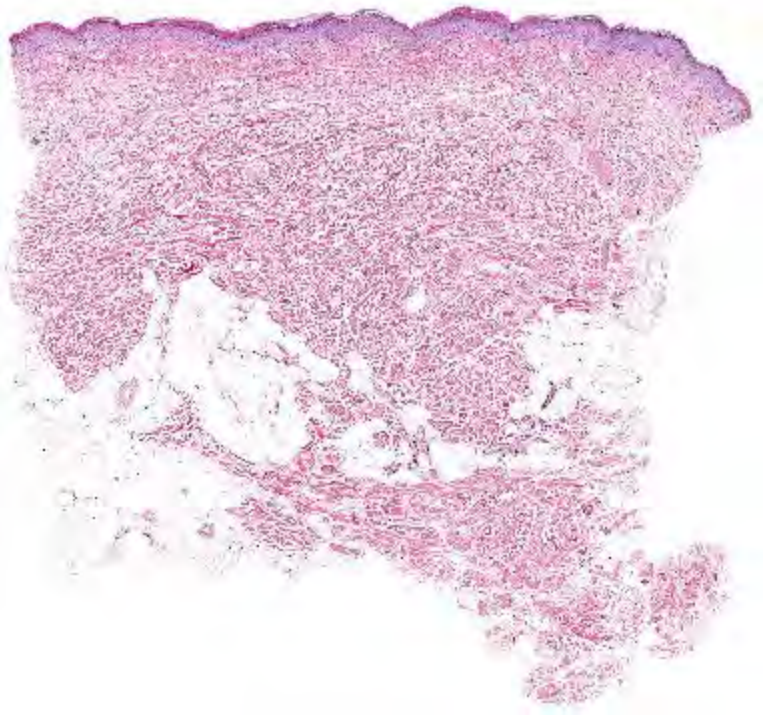


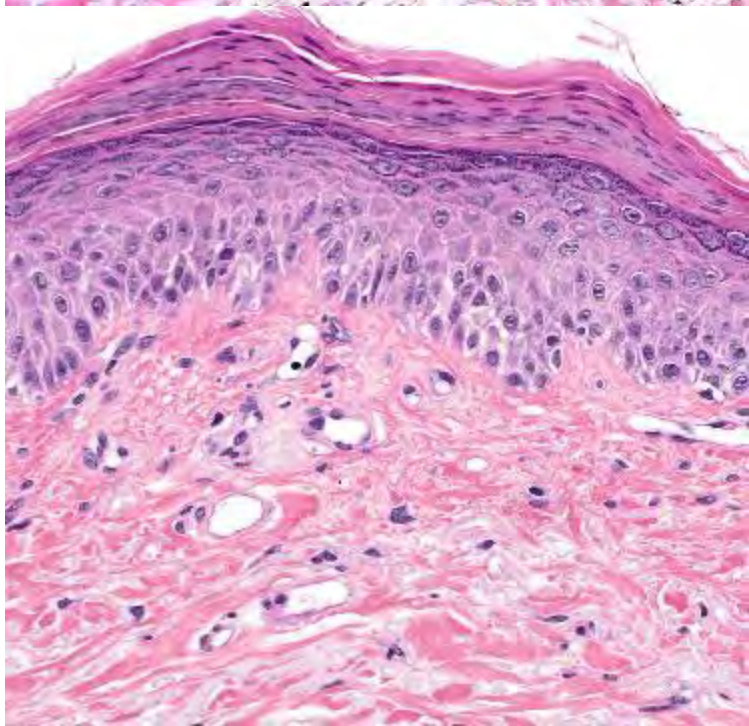




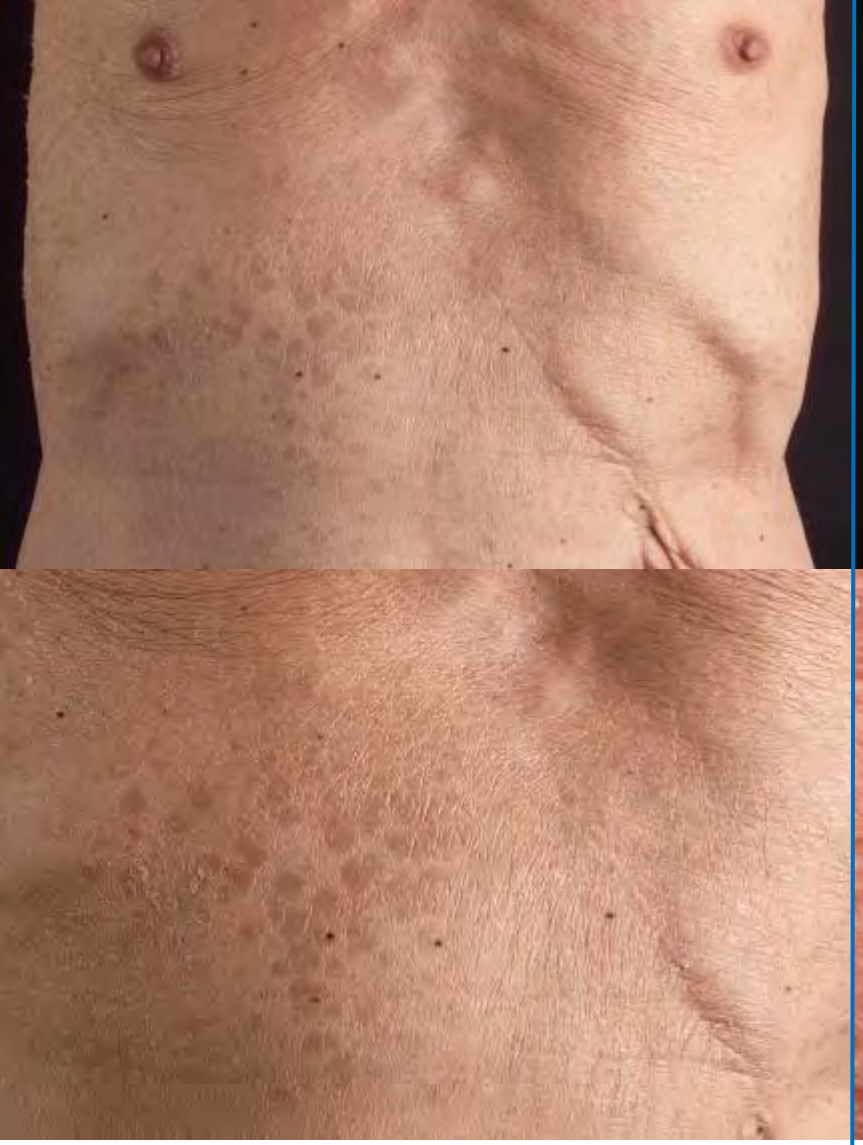
Ichthyosiform atopic dermatitis







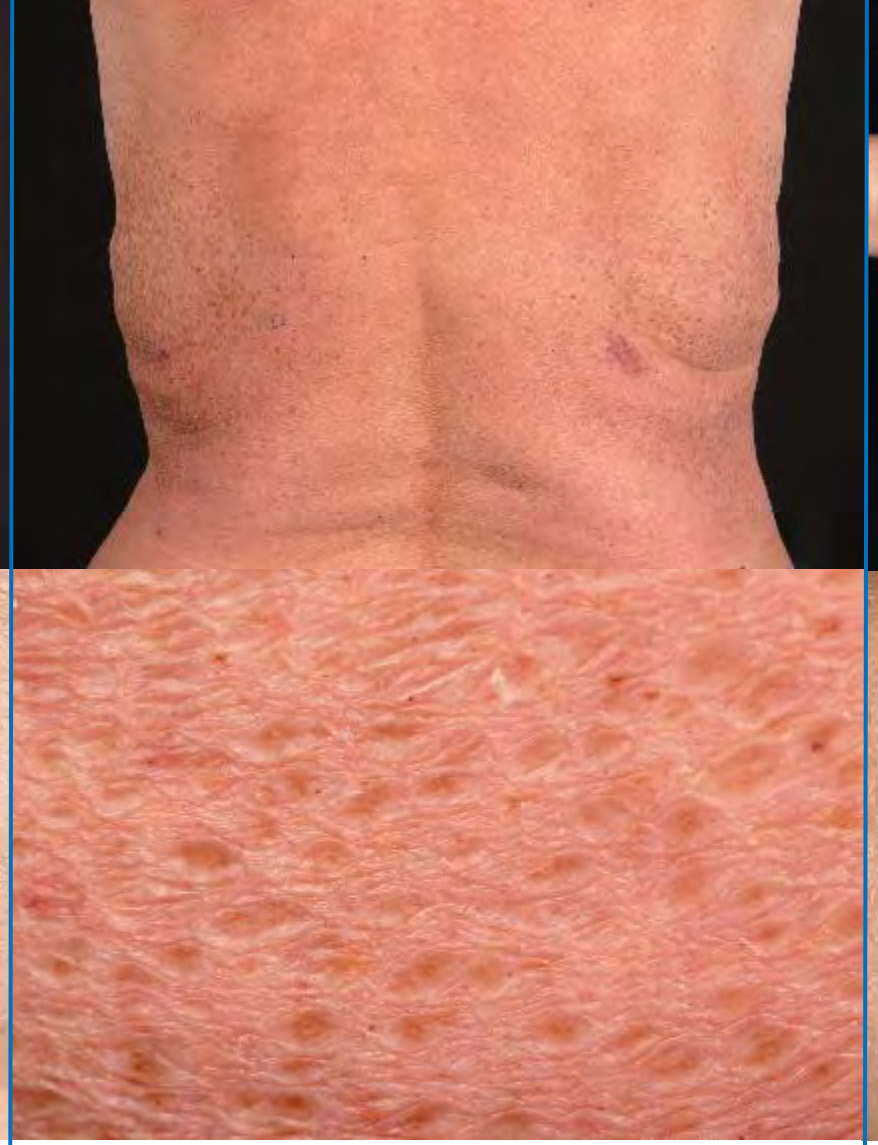
ASSOCIATED FEATURES OF ATOPIC DERMATITIS ("ATOPIC STIGMATA")	
Xerosis	• Important feature that is present in most patients with AD • Often most prominent on the lower legs; may be generalized • Dry skin with fine scale in areas without clinically apparent inflammation • Typically worse during the winter • Impaired epidermal barrier function from decreased water content in the stratum corneum leads to easier entry of irritants, which can promote pruritus and initiate an inflammatory response
Ichthyosis vulgaris	• Autosomal semidominant disorder with incomplete penetrance caused by mutations in the filaggrin gene (*FLG*; see text and Ch. 57) • ~15% of patients with AD have moderate-to-severe ichthyosis vulgaris; conversely, >50% of patients with ichthyosis vulgaris have AD • Excessive fine, whitish to brown scaling that favors the lower legs (especially the shins) and spares the flexures
Keratosis pilaris	• Common condition that affects >40% of patients with AD and ~75% of those with ichthyosis vulgaris • Onset typically in childhood; may improve after puberty (especially facial involvement) • Affects the lateral aspect of the upper arms, thighs, and lateral cheeks (especially in children) > trunk and extensor aspects of the distal extremities • Keratotic follicular papules, often with a rim of erythema (see Fig. 12.17A) or a background of patchy erythema (especially on the cheeks) • The *keratosis pilaris rubra (KPR)* variant features numerous tiny, "grain-like" follicular papules superimposed on prominent confluent erythema (see Fig. 12.17B); often widespread on face & ears > trunk & proximal extremities, and tends to persist after puberty; presence of erythema rather than hyperpigmentation differentiates KPR from erythromelanosis follicularis faciei et colli, and a lack of atrophy in KPR differentiates it from keratosis pilaris atrophicans (see Ch. 38) • Keratolytic agents and topical retinoids are sometimes used to decrease the hyperkeratotic component, but the benefit is limited and these agents can be irritating, especially in AD patients; treatment with vascular lasers (e.g. pulsed dye laser) can sometimes improve associated erythema
Palmar and plantar hyperlinearity	• Increased prominence of the palmar and, less often, plantar creases • Associated with ichthyosis vulgaris and *FLG* mutations
Dennie–Morgan lines	• Symmetric, prominent horizontal fold(s) (single or double) just beneath the margin of the lower lid, originating at or near the inner canthus and extending one-half to two-thirds the width of the lid
Periorbital darkening ("allergic shiners")	• Skin around the eyes appears gray to violet–brown, while the rest of the facial skin is rather pale • Periorbital edema and lichenification may also be seen
Anterior neck folds	• Horizontal folds across the middle of the anterior neck
Hertoghe sign	• Absence or thinning of the lateral eyebrows
White dermographism	• Stroking the skin leads to a white streak that reflects excessive vasoconstriction • Most apparent on the forehead • Midfacial pallor and a delayed blanch response represent additional manifestations of aberrant vascular reactivity in patients with atopic dermatitis
Follicular prominence	• "Goose bump-like" appearance of the skin, most often on the trunk (see Fig. 12.7) • More commonly observed in children with darkly pigmented skin



M, 52

Chronic renal insufficiency managed with dyalysis. Skin changes for 1 year.

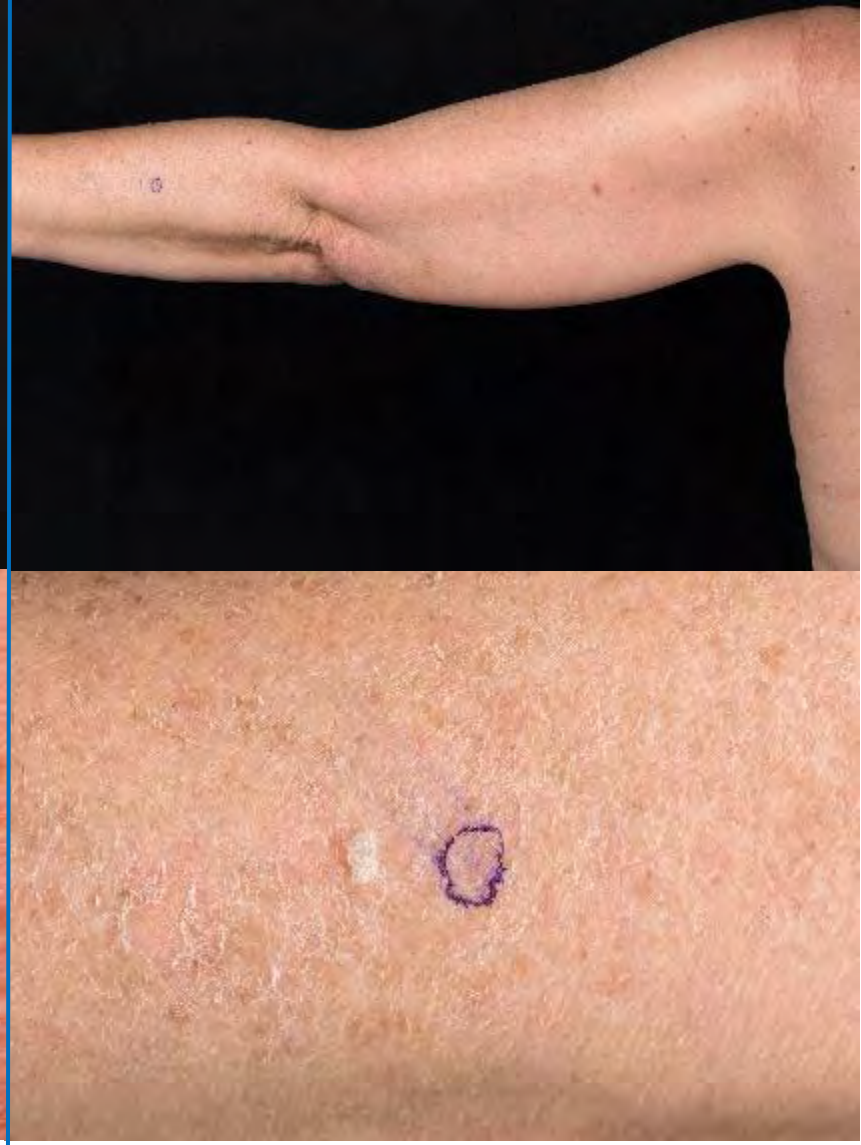
A biopsy is taken.



F, 70

Itchy skin lesions for a long time.

A biopsy is taken.

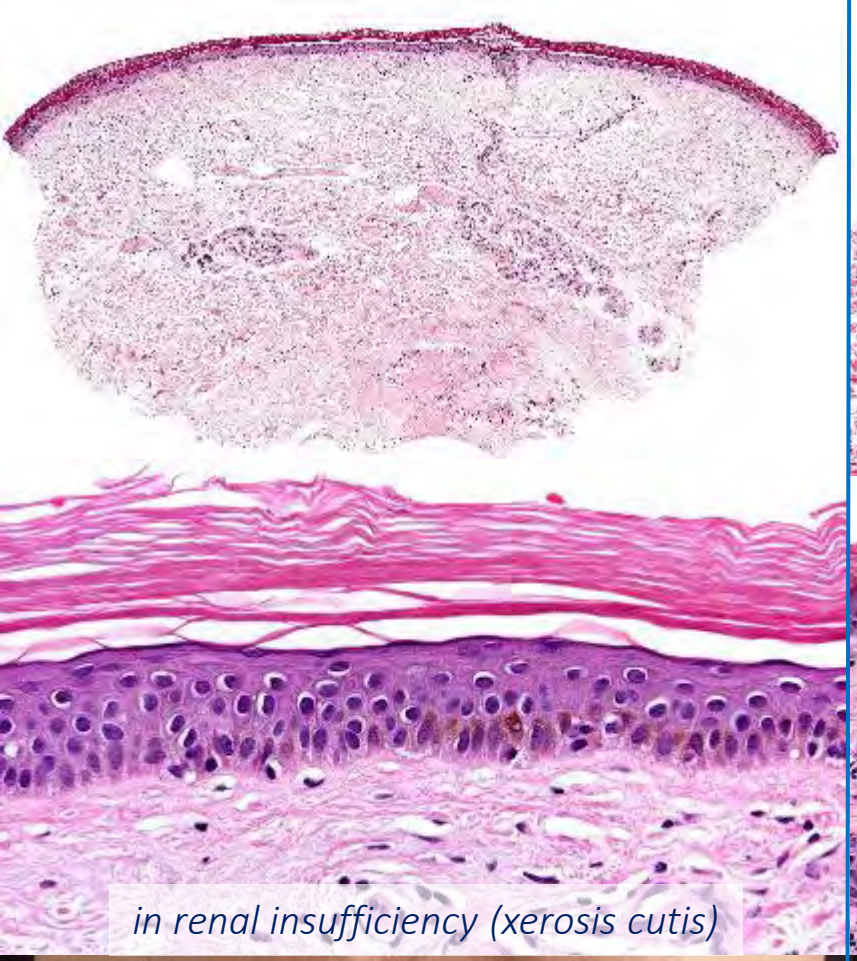


F, 56

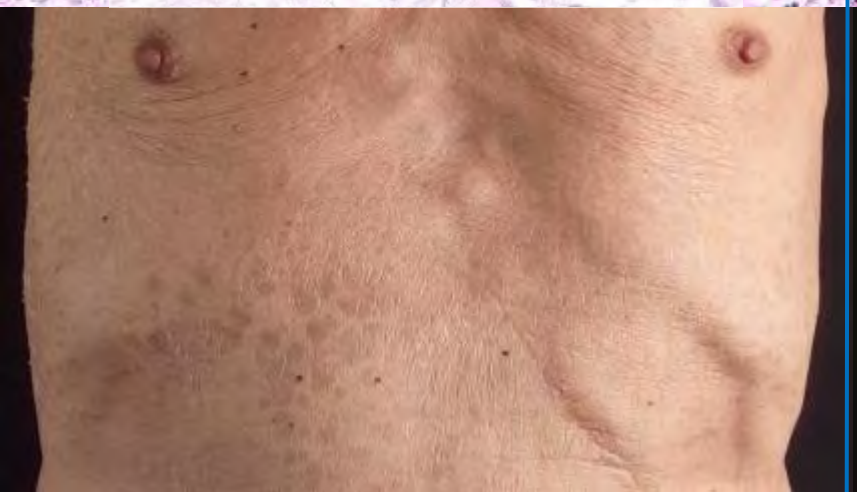
History of psoriatic arthritis, in the last 4 years managed with upadacitinib. Scaly lesions on the upper extremities for several months.

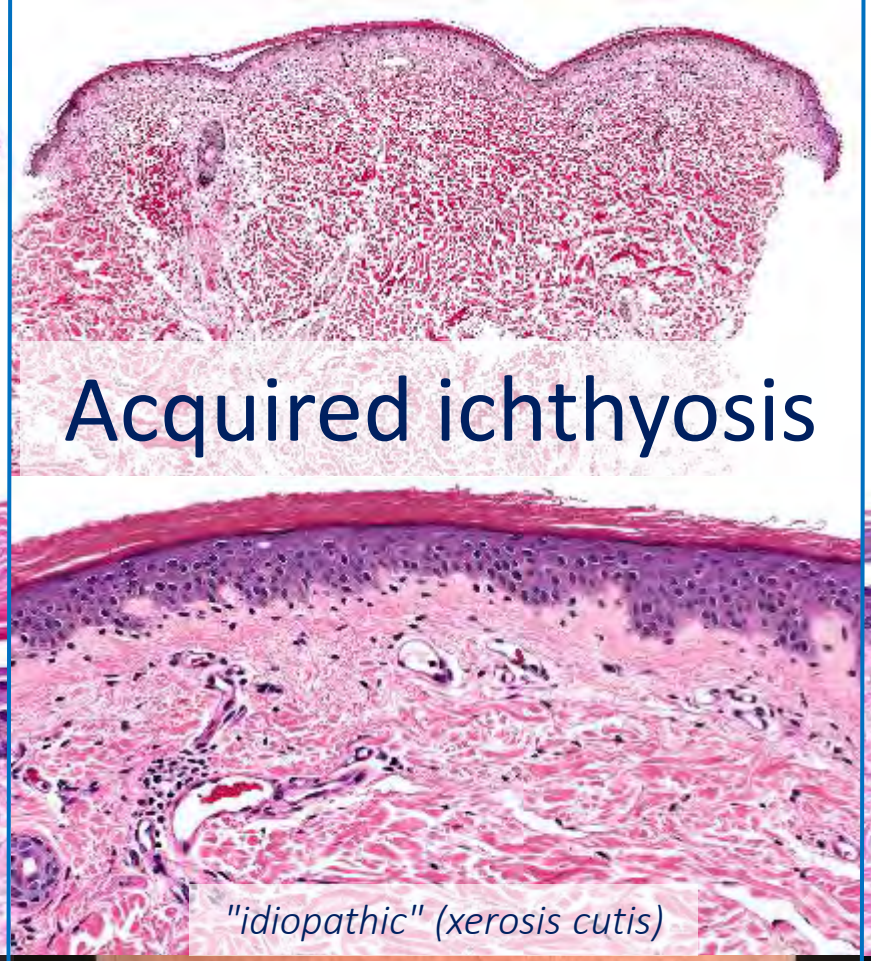
A biopsy is taken.

Acquired ichthyosis

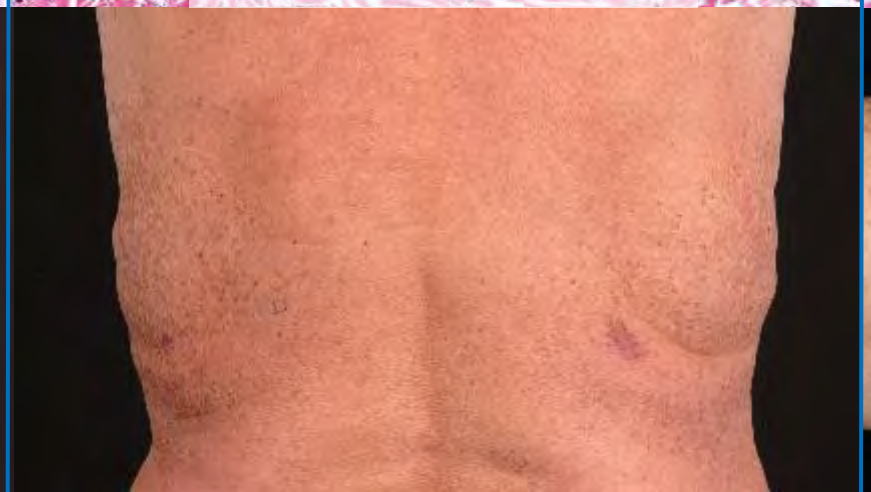


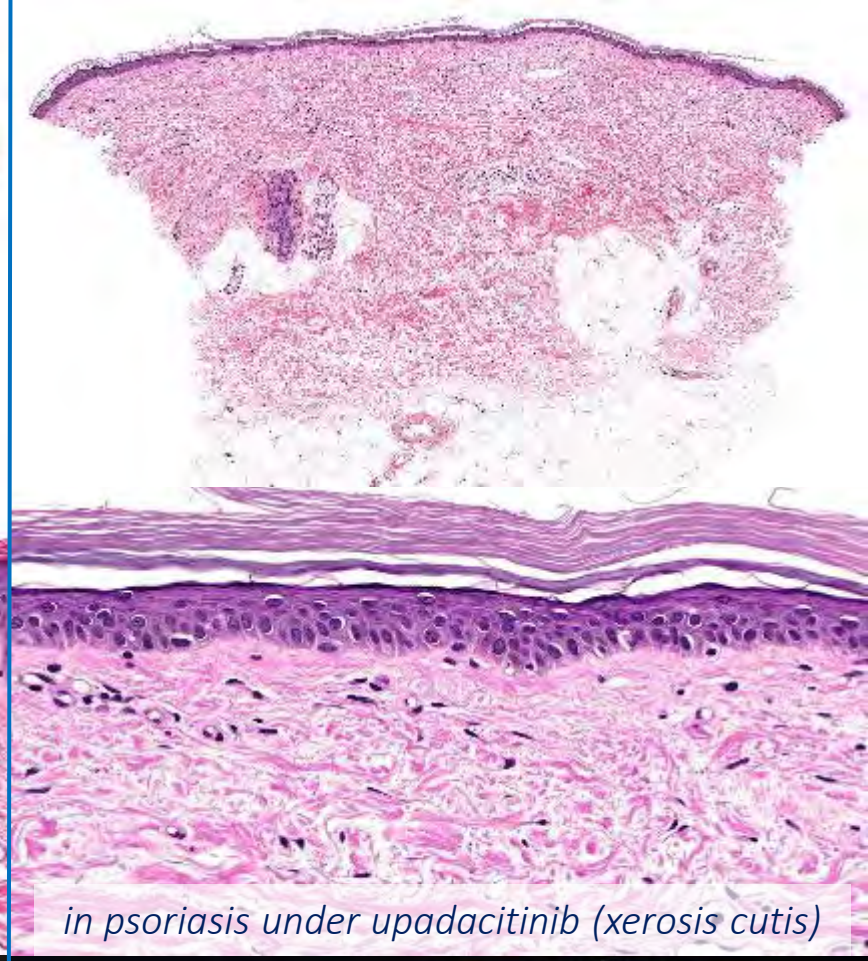
in renal insufficiency (xerosis cutis)



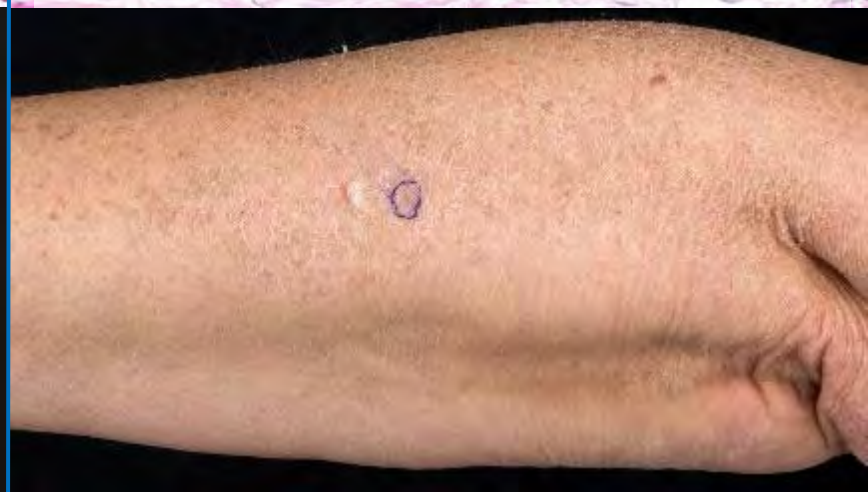


"idiopathic" (xerosis cutis)





in psoriasis under upadacitinib (xerosis cutis)



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https://doi.org/10.1007/s00403-023-02658-5

REVIEW

Acquired ichthyosis: a clinical review

Roger Haber[1] · Joelle Feghali[2,3] · Umer Nadir[1] · Michael D. Yi[1] · Brian A. Cahn[1]

Received: 6 June 2023 / Revised: 11 June 2023 / Accepted: 28 June 2023 / Published online: 3 July 2023

Abstract
Acquired ichthyosis (A
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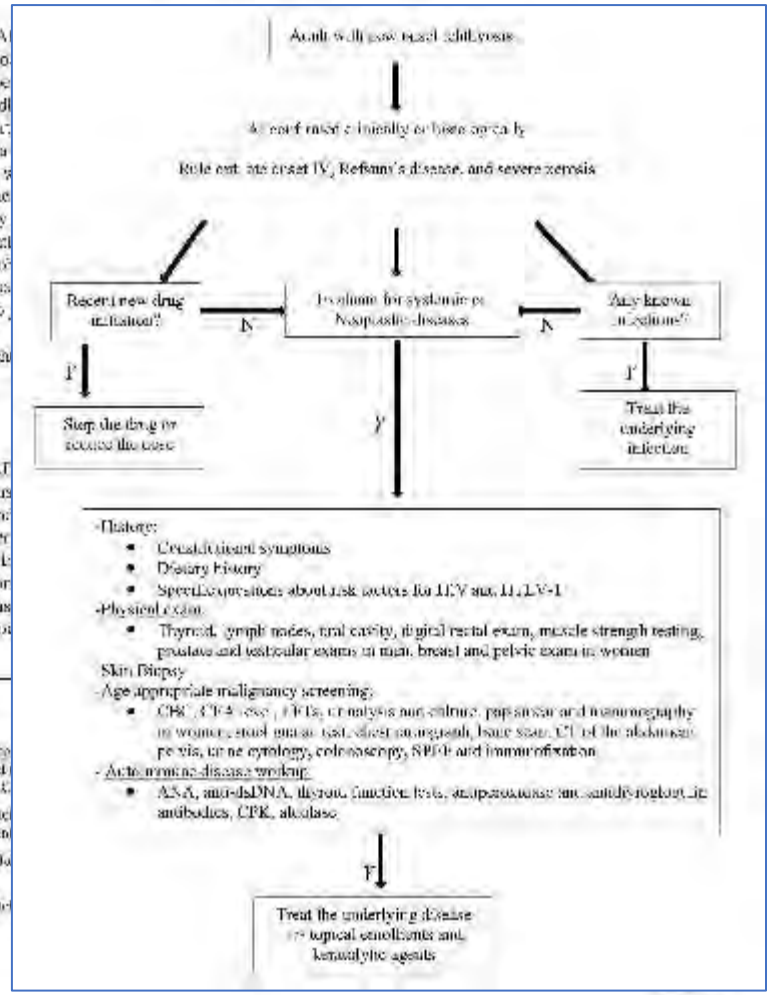

Brian A. Cahn
bcahn@dc.edu

Department of Dermatology, Boston Medical Center, 850 South Wood Street, Medicine Lower Level 2, Chicago, IL 60612, USA

Department of Dermatology, University Medical Center, Beirut, Lebanon

Faculty of Medicine, Beirut, Lebanon

Introduction

Acquired ichthyosis (AI) is a cutaneous disorder characterized by keratinization of the skin and the presence or absence of granular layer. It can be a disorder of cornification and, broad, have been as hereditary, drugs, endo

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REVIEW ARTICLE

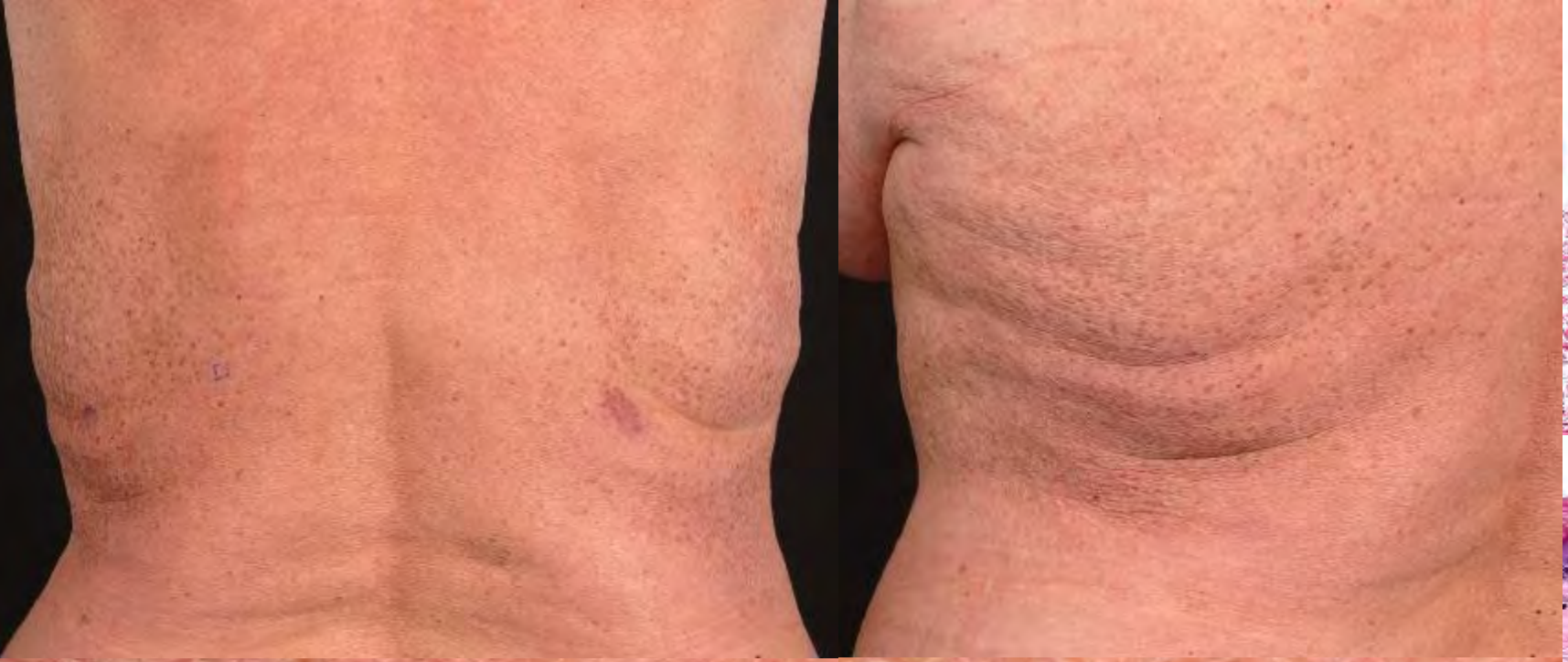
JEADV

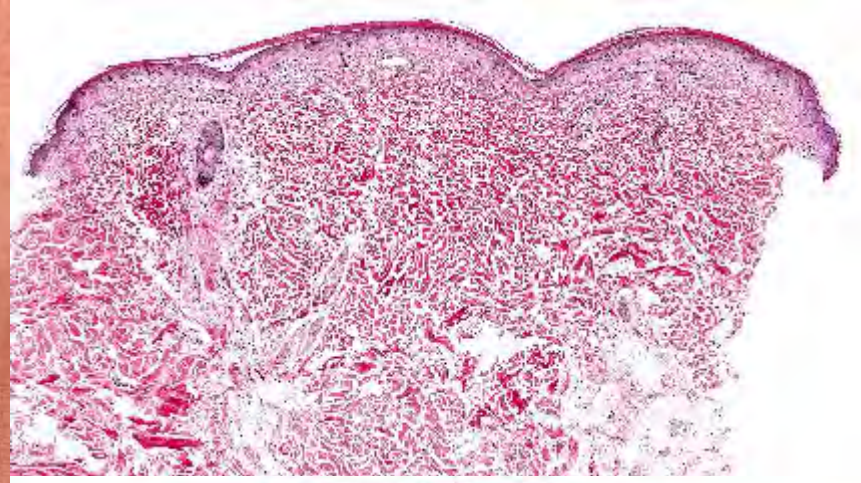
Acquired ichthyosis, asteatotic dermatitis or xerosis? An update on pathoetiology and drug-induced associations

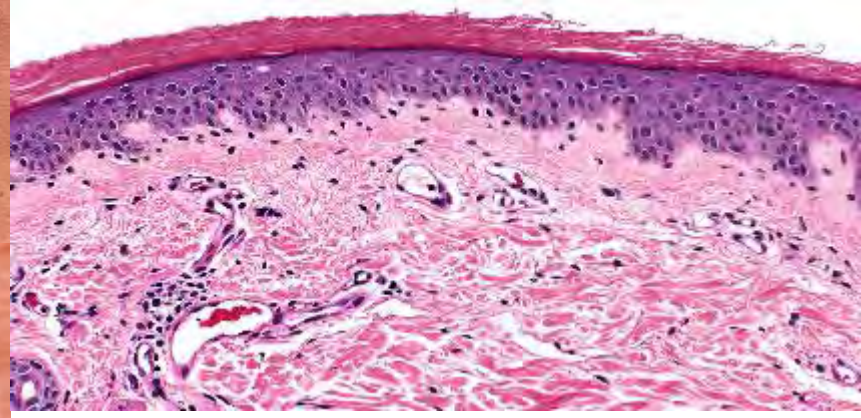
Jason S. Park[1,2,3] | Amir H. Saeidian[4] | Leila Youssefian[1,2] | Sylvia Hsu[5] | Hassan Vahidnezhad[1,2] | Jouni Uitto[1,2]

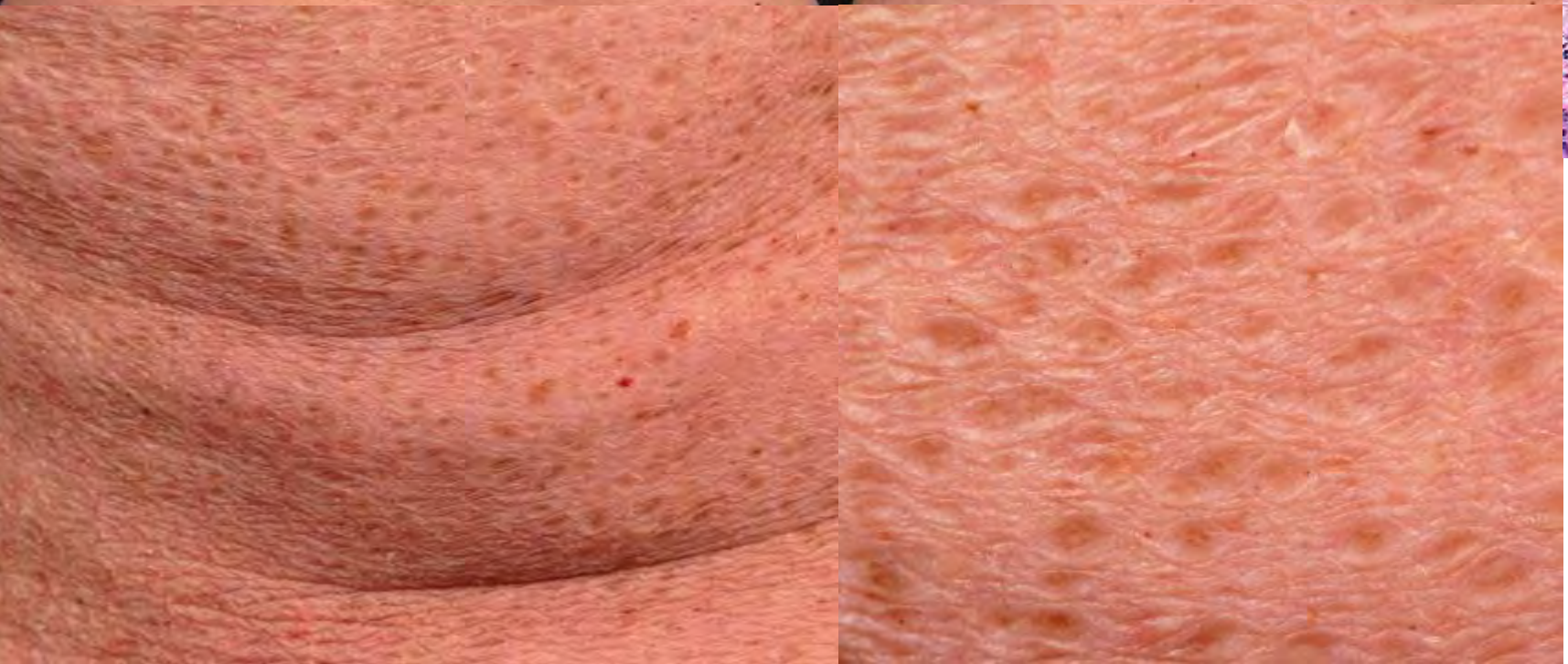
cutaneous entity characterized by keratinization of the skin and the presence or absence of family history of ichthyoses. The disease can range from the mild, white-to-brown (WI) to the more prominent dark brown, ichthyosis. The disease can wax progressive nature. Pathogenesis of AI systemic conditions in patients but can, in some cases, include malignancies. In some cases, AI can be an adverse effect of a toxic exposure. Other conditions present with clinical findings similar to true cases of AI are sporadic throughout a wide variety of medical settings. Due to misdiagnosis of this disease, differentiation and treatment of the underlying, which can include topical emollients, in rare cases, oral retinoids.

...ften associated with severe cases of xerosis or ...).[1] AI usually shows varying degrees of ... a uniformly diminished or absent granular layer of dermal inflammation.[6] In patients ... a detailed investigation into the clinical ... does not yield personal or family history ... keratinocytes pilaris or other keratinocytic ... types seen with the heritable ichthyoses.[1,5] ... we provide an up-to-date overview of AI ... mechanisms suggested in the literature. While ... clinical features in many cases of AI are unspecific, examples are provided for the medical conditions and exposures with clinical importance. In









Ichthyosis vulgaris is present in ~15% of patients with atopic dermatitis; >50% of patients with ichthyosis vulgaris have also atopic dermatitis

Pediatric Dermatology Vol. 28 No. 5 494–501 2011

Skin Manifestations in Primary Immunodeficient Children

Waleed Al-Herz, M.D.,* and Arti Nanda, M.D., D.N.B.E.†

*Department of Pediatrics, Allergy and Clinical Immunology Unit, Al-Sabah Hospital, Kuwait.
†Pediatric Dermatology Unit, Asad Al-Hamad Dermatology Center, Al-Sabah Hospital, Kuwait

Abstract: Skin manifestations are prevalent in primary immunodeficiency disorders (PID). In a large proportion of patients, they manifest as presenting signs and serve as important factors for the early diagnosis of PID. Only a few studies describing the spectrum of skin disorders in PID are available. The objective of the current study was to determine the prevalence and characteristics of skin manifestations in children with PID. Participants were 128 pediatric patients with PID (aged <16 years) registered prospectively over 6 years. Skin manifestations were observed in 61 patients (48%), and those manifestations were the presenting features in 50 (39% of total PID and 82% of those with skin lesions). Skin infections were the most prevalent manifestations, seen in 39 patients (30%), followed by eczemas in 24 (19%). Skin infections were significantly more prevalent in those with congenital defects in phagocyte number, function, or both, as well as in those with well-defined immunodeficiencies. Although widely present in all participants with PID, eczema was a consistent feature (100%) in patients with hyper IgE syndrome and Wiskott-Aldrich syndrome (WAS). Erythroderma of infancy with diffuse alopecia was seen exclusively in patients with severe combined immunodeficiency disorders, telangiectasia in patients with ataxia telangiectasia, and partial albinism with silvery gray hair in those with Chediak-Higashi syndrome. Autoimmune skin manifestations were observed in 6% of reported cases of PID. This study highlights the importance of awareness of skin manifestations of PID to assist in the early diagnosis and management of these disorders.

Primary immunodeficiency disorders (PID) are rare inborn errors of the immune system. In the last two decades, advances in molecular genetics and immunology have resulted in the identification of a growing number of genes that cause PID in human subjects, providing a better understanding of the pathophysiology of these disorders (1). Despite major advances in the recent past, many patients remain undiagnosed or are diagnosed too late, resulting in severe consequences. The skin is an important organ affected in most PID, and in a significant number, skin manifestations are the presenting features before the diagnosis of PID is reached. Thus, a dermatologist may be the first clinician to suspect PID (2). Awareness of various cutaneous manifestations associated with PID can lead to early suspicion and diagnosis, which can result in early treatment (2). Only a

Address Correspondence to Arti Nanda, M.D., D.N.B.E., PO Box 5779, 22058 Safat, Kuwait, or e-mail: artinanda@hotmail.com

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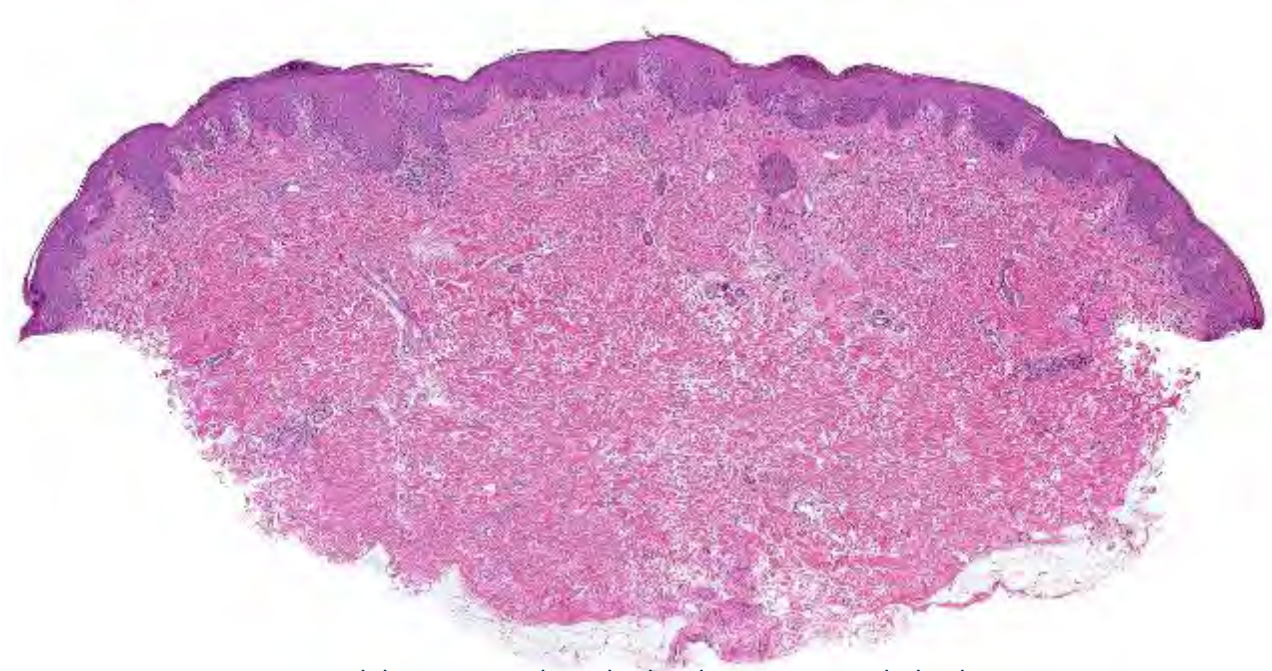
TABLE 2. *Distribution of Various Skin Disorders in 128 Patients with Primary Immunodeficiency Disorders*

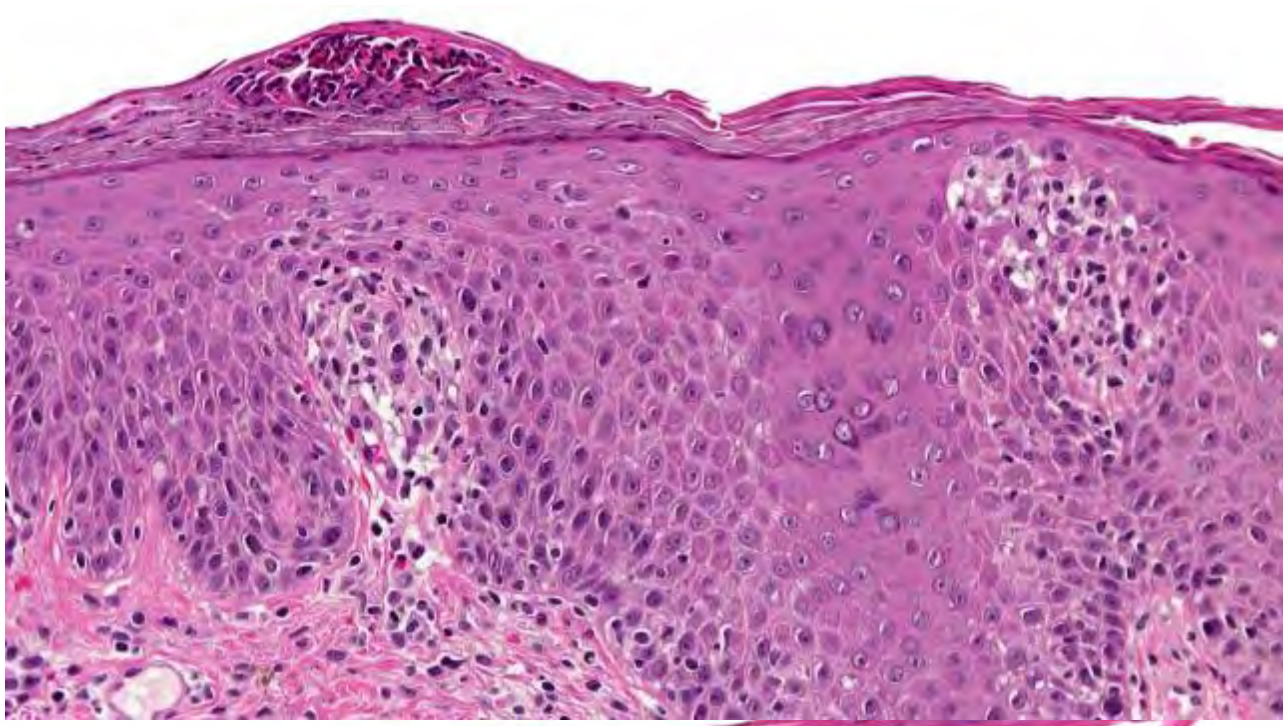
Skin lesions	Presenting as a primary manifestation, *N* (%)	Presenting as a secondary manifestation, *N* (%)	Total, *N* (%)
Skin infections	24 (19)	15 (12)	39* (30)
Bacterial	21 (16)	1 (0.8)	22 (17)
Viral	3 (2)	8 (6)	11 (9)
Fungal	0	6 (5)	6 (5)
Eczema	22 (17)	2 (1.6)	24 (19)
Erythroderma	9 (7)	0	9 (7)
Diffuse alopecia	9 (7)	0	9 (7)
Telangiectasia	7 (5)	1 (0.8)	8 (6)
Autoimmune disorders	2 (1.6)	6 (5)	8 (6)
Urticaria and angioedema	2 (1.6)	2 (1.6)	4 (3)
Partial albinism and silvery gray hair	2 (1.6)	0	2 (1.6)
Langerhans cell histiocytosis	2 (1.6)	0	2 (1.6)
Congenital hypotrichosis	1 (0.8)	0	1 (0.8)
Miscellaneous	6 (5)	9 (7)	15 (12)

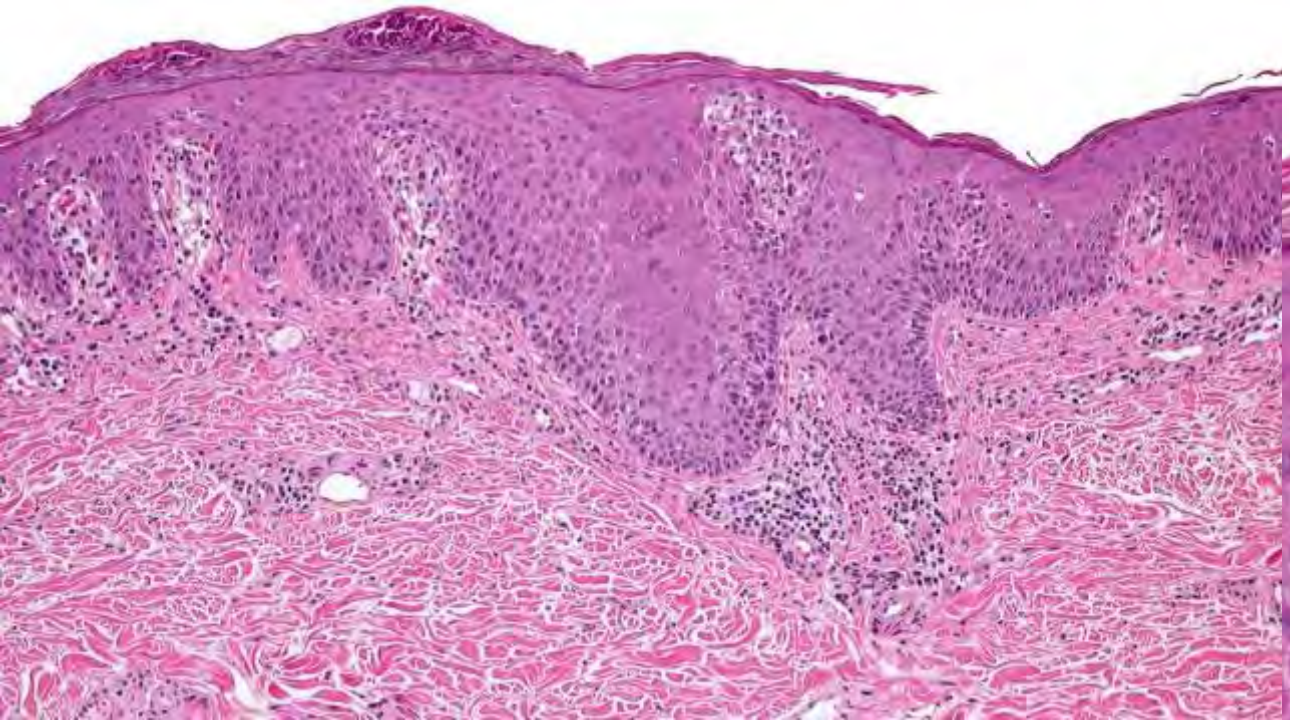
*Six patients had more than one type of skin infection.

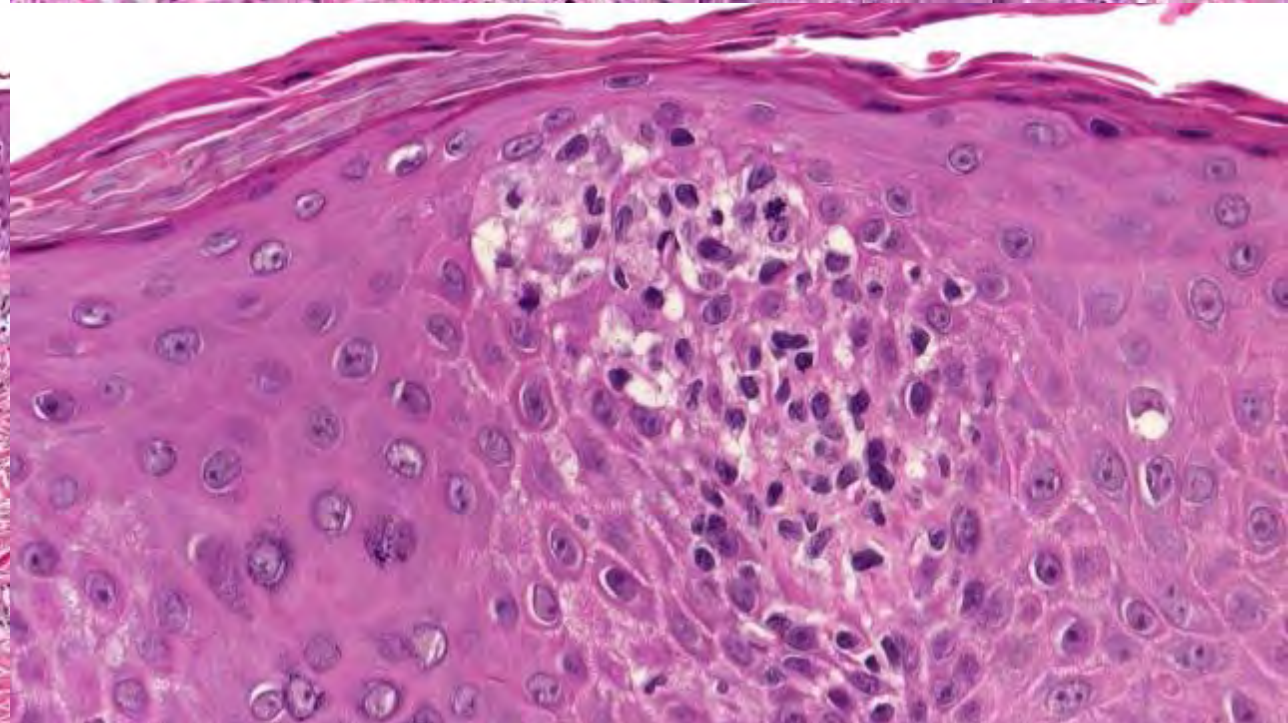
Eczema (atopic dermatitis) is present in 100% of patients with hyper IgE syndrome and Wiskott-Aldrich syndrome.

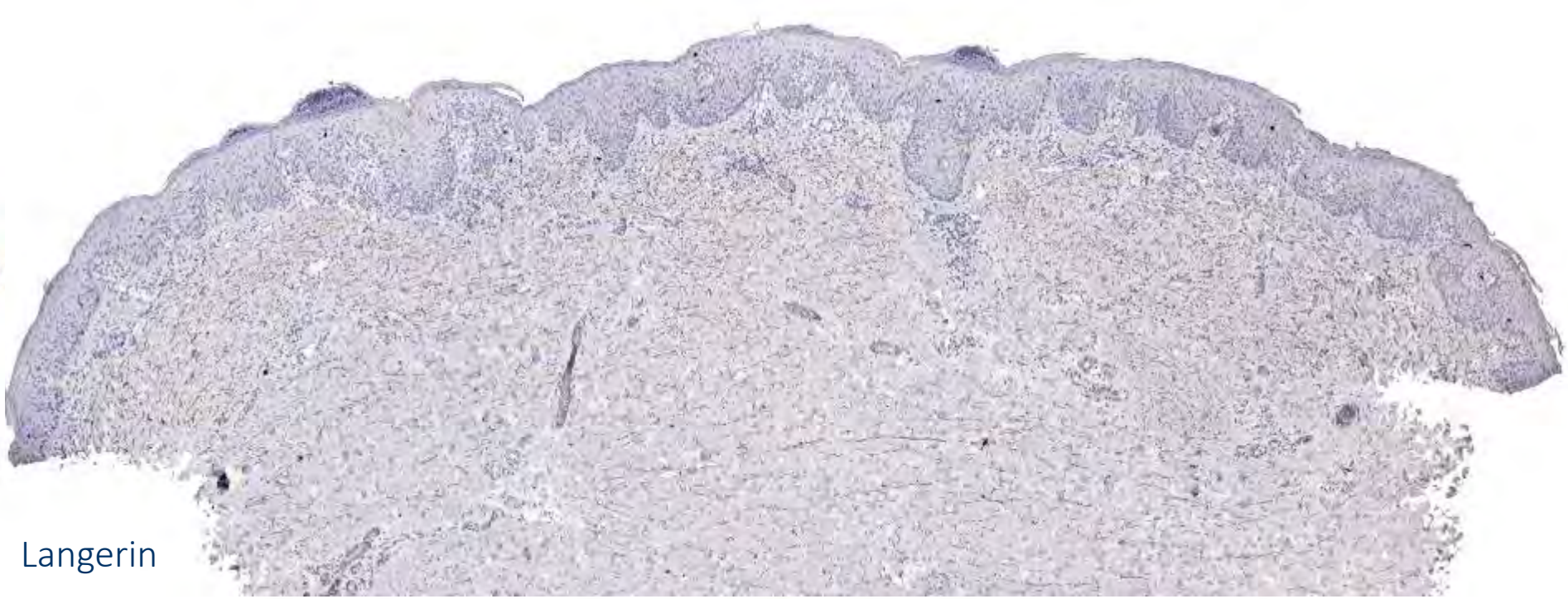


38-year-old man with X-linked agammaglobulinemia

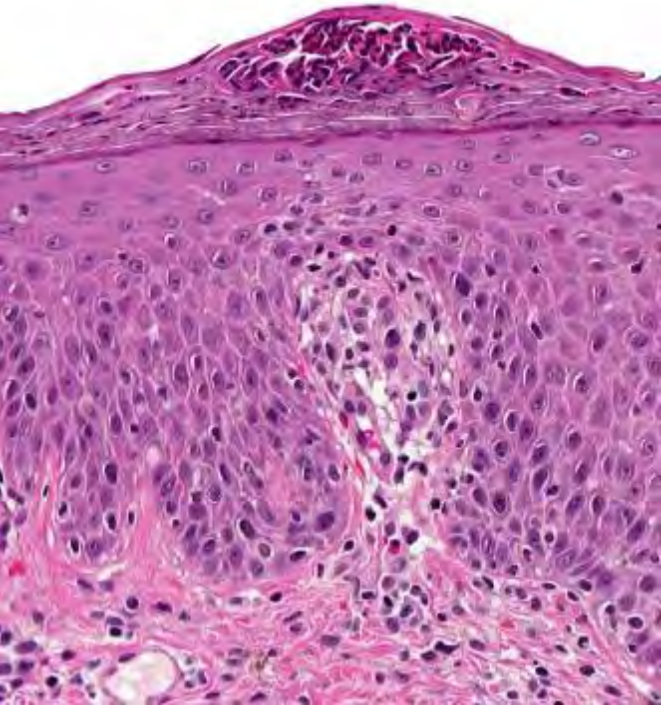


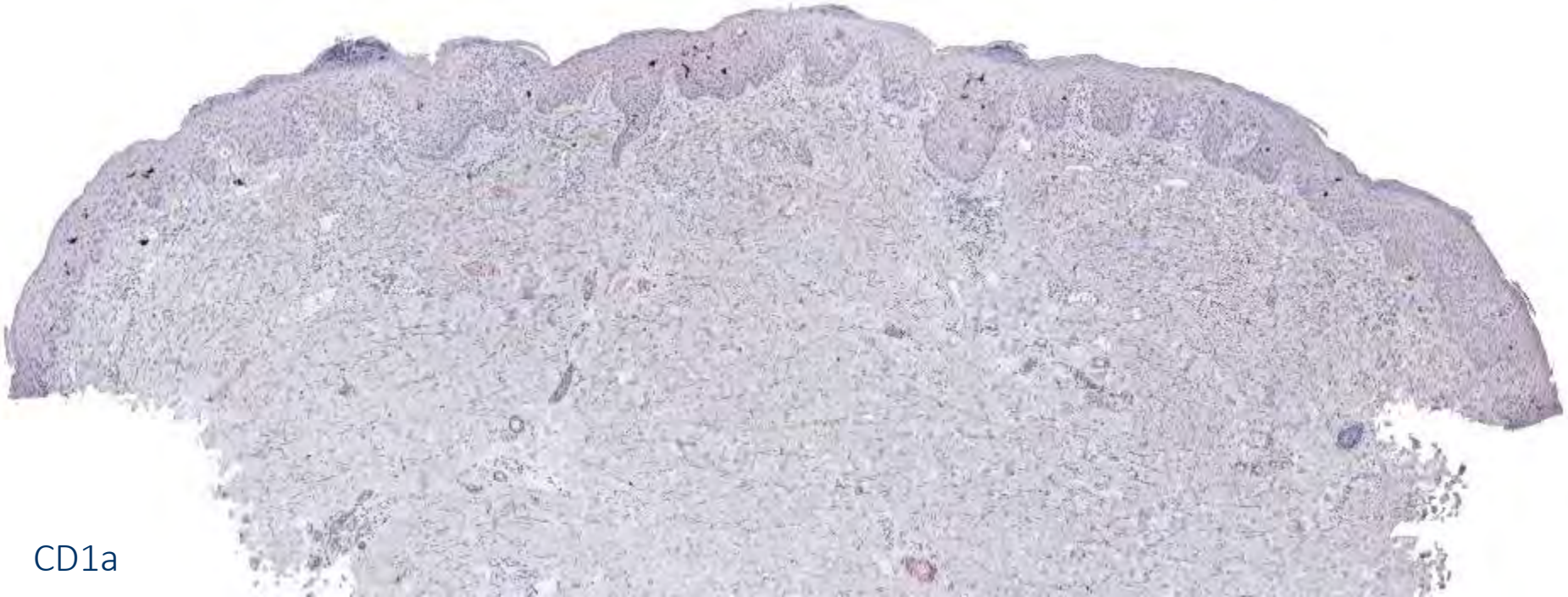






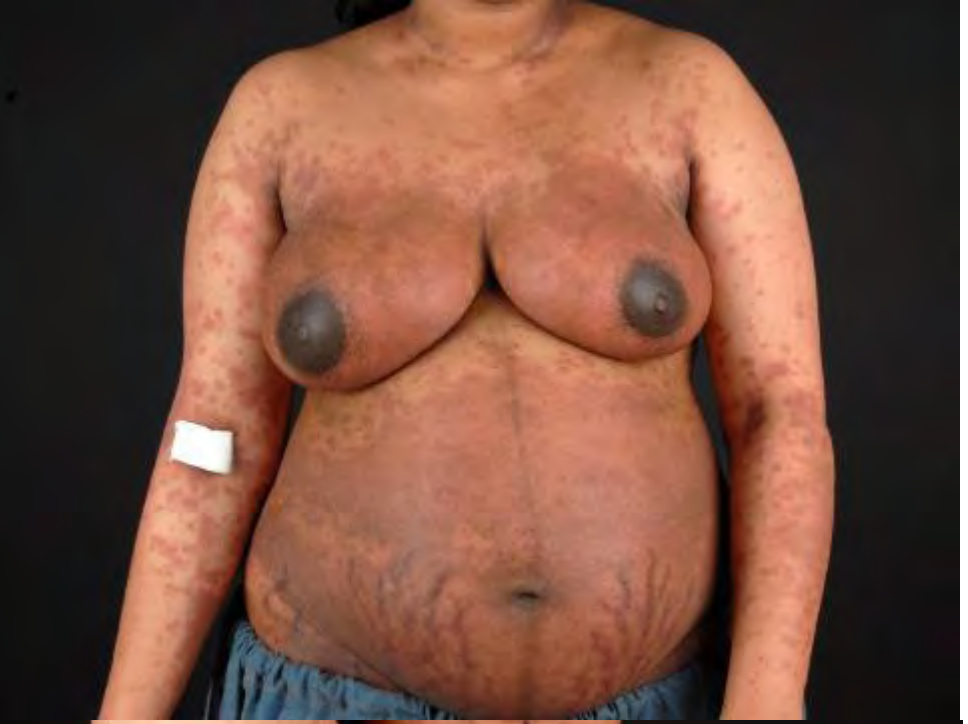
Langerin

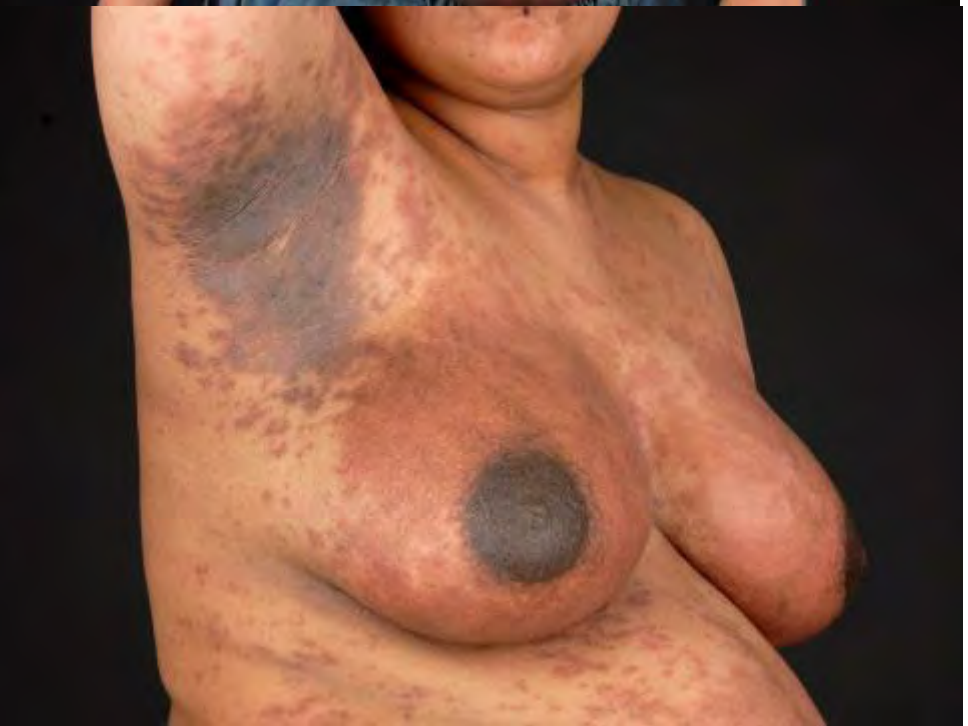


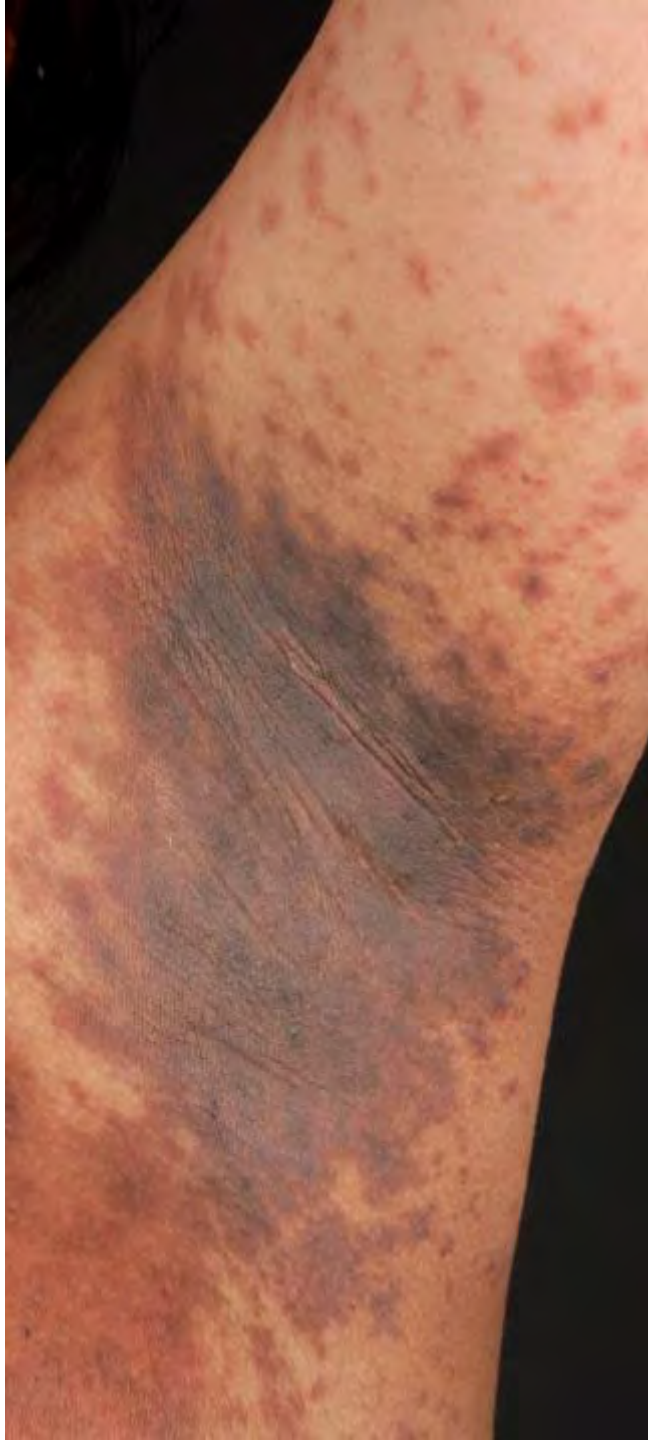


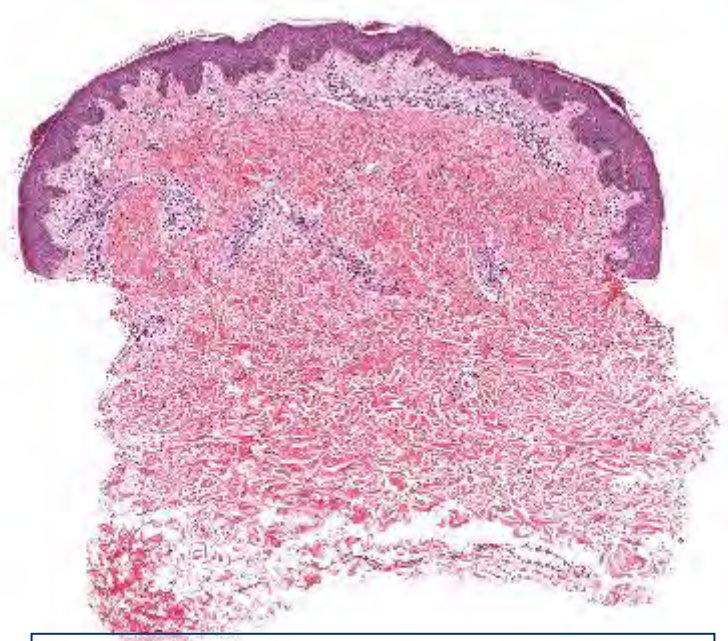
CD1a

F, 26, pregnant

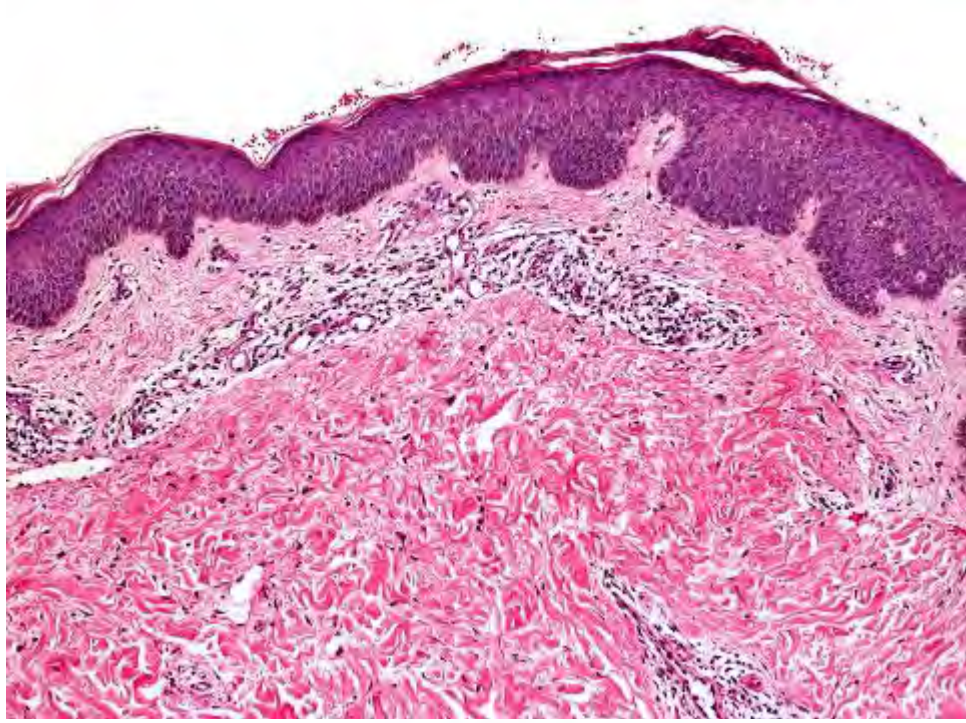


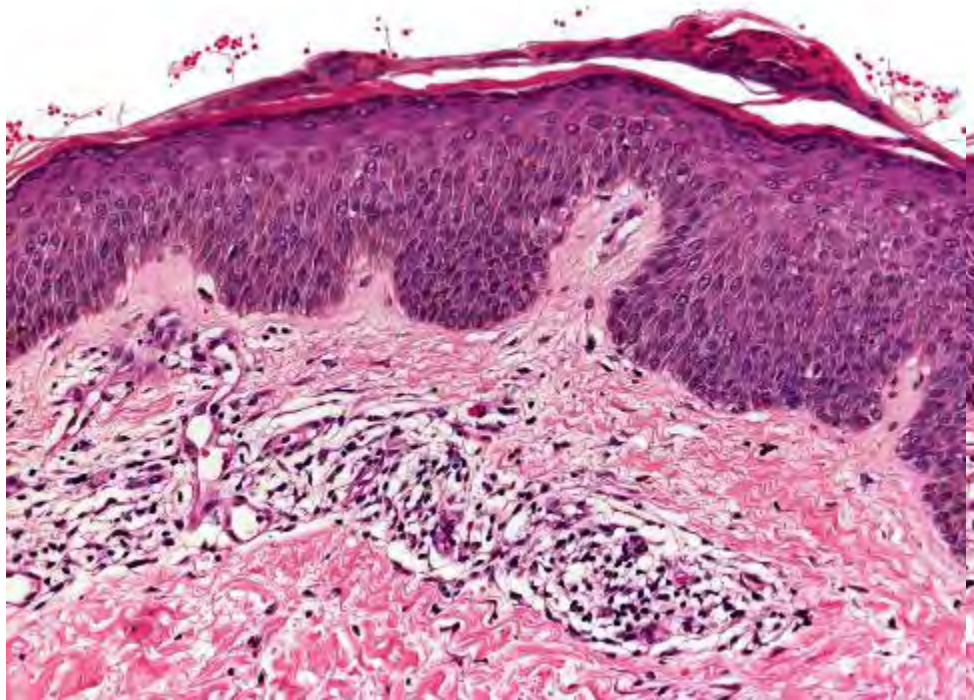


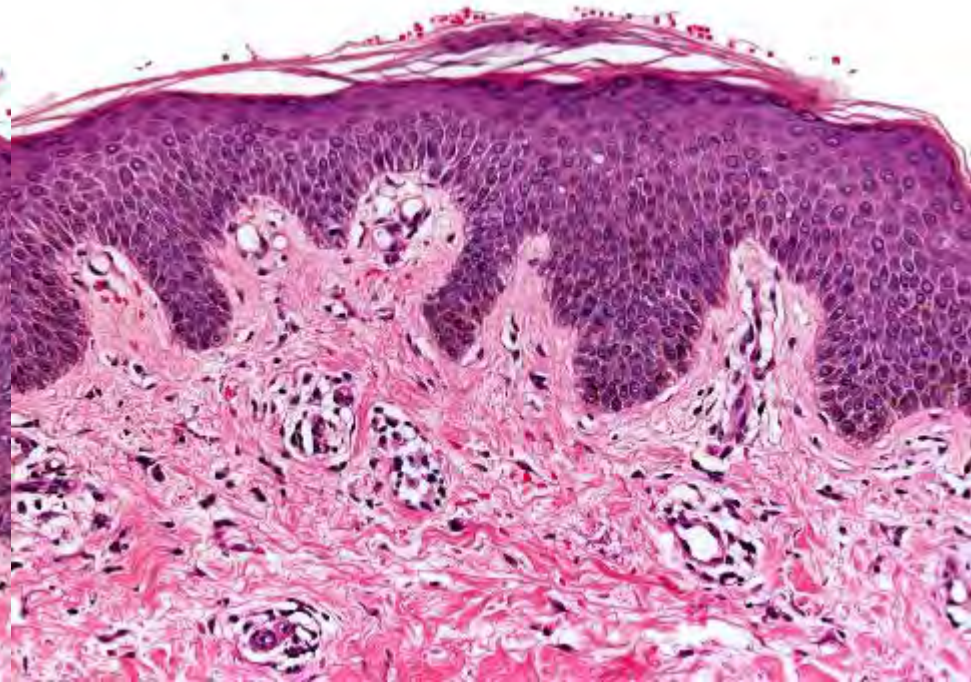


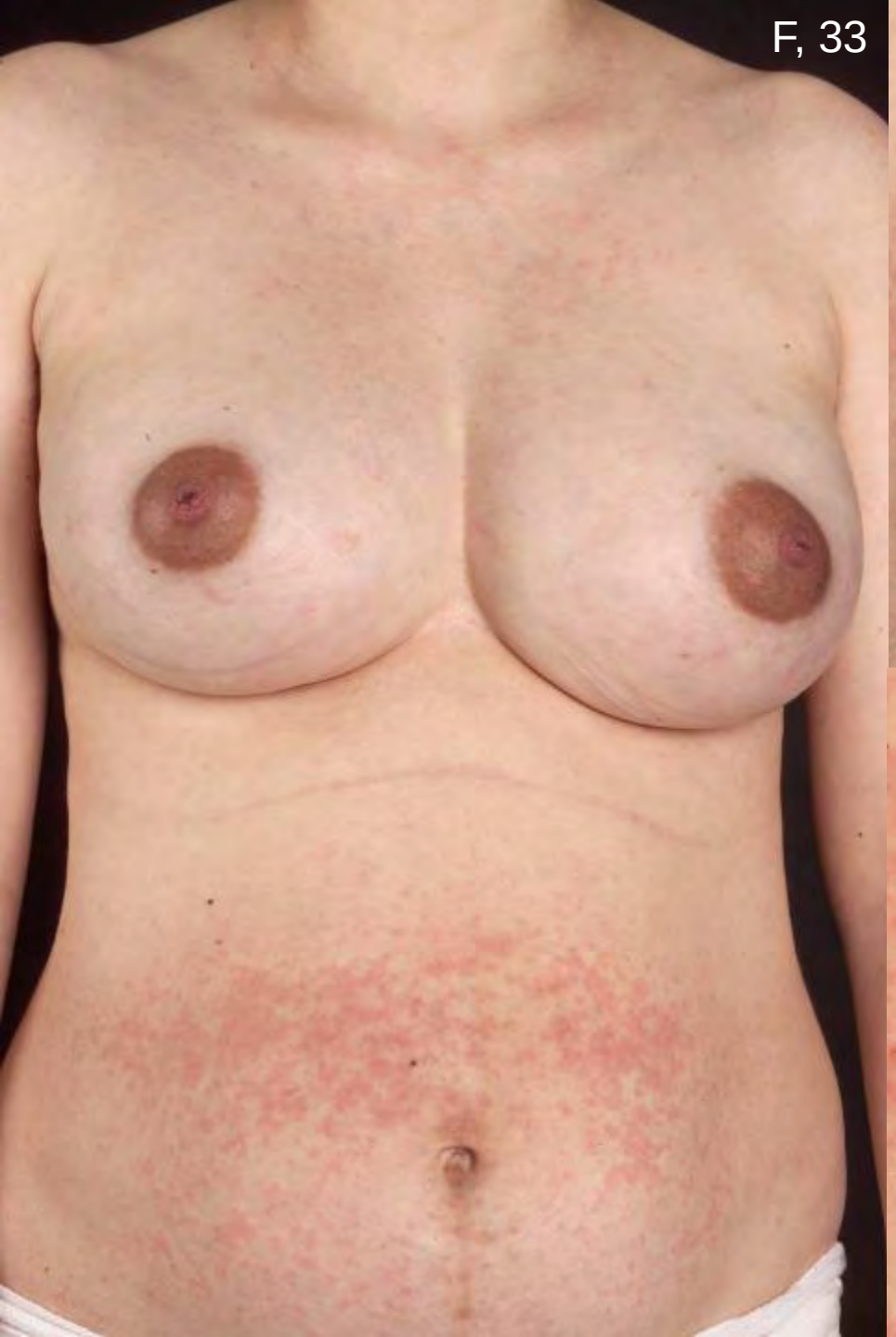


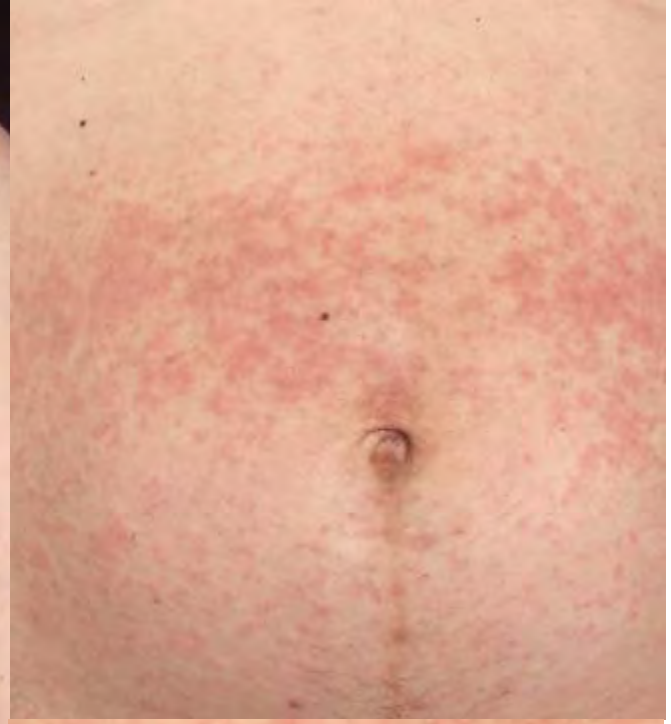
Atopic eruption of pregnancy

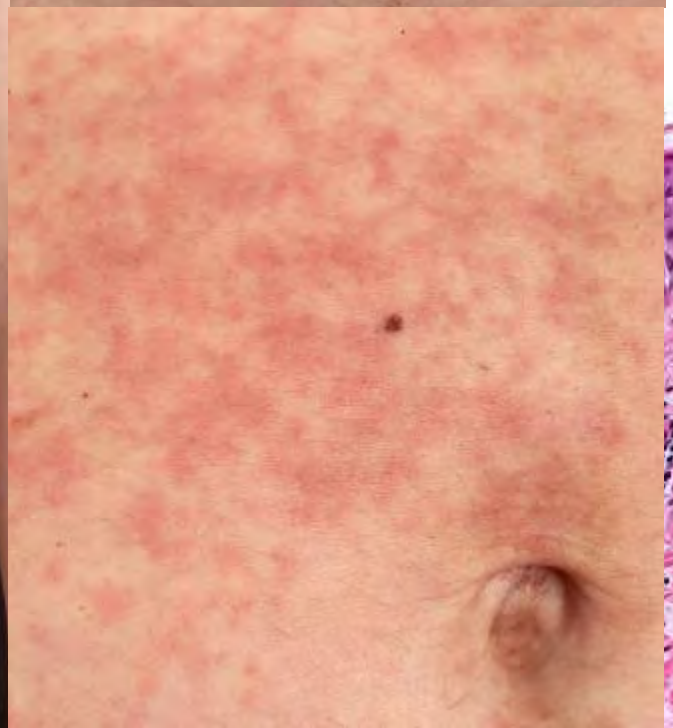


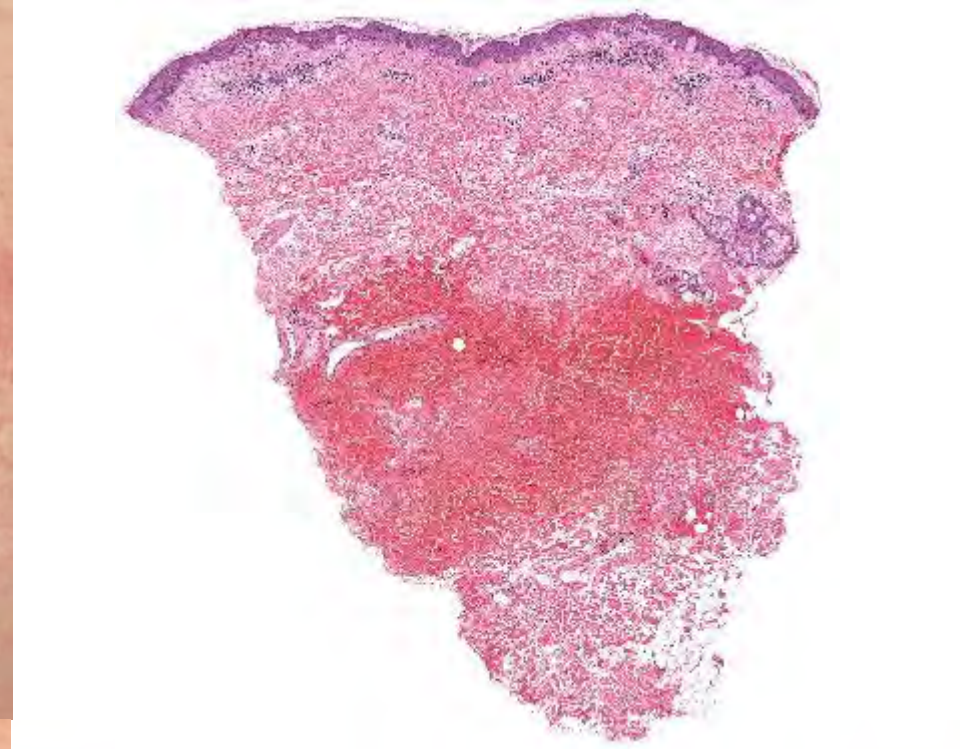


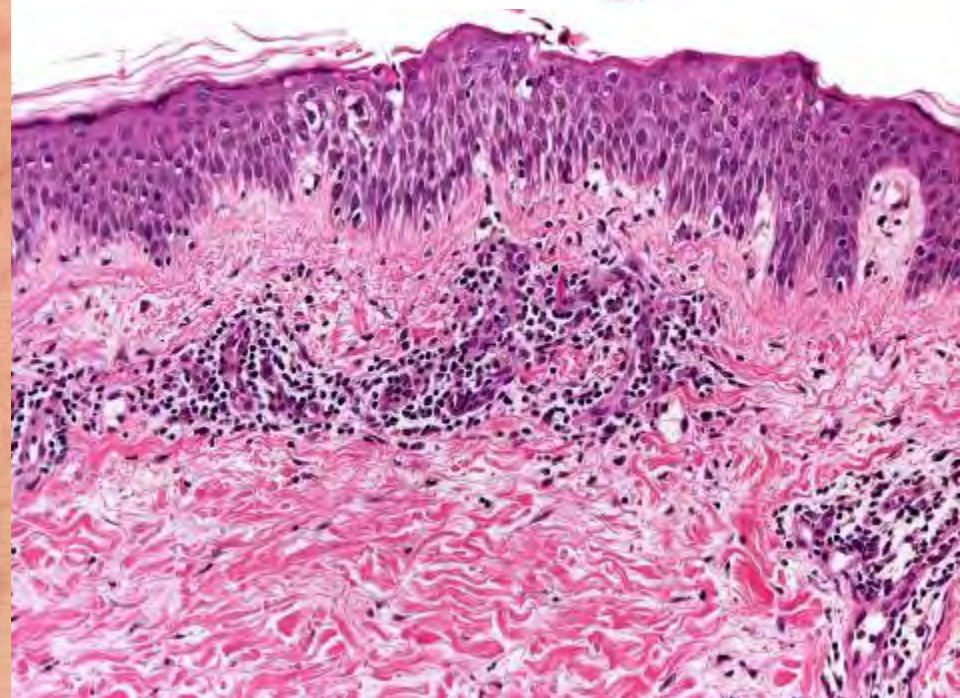


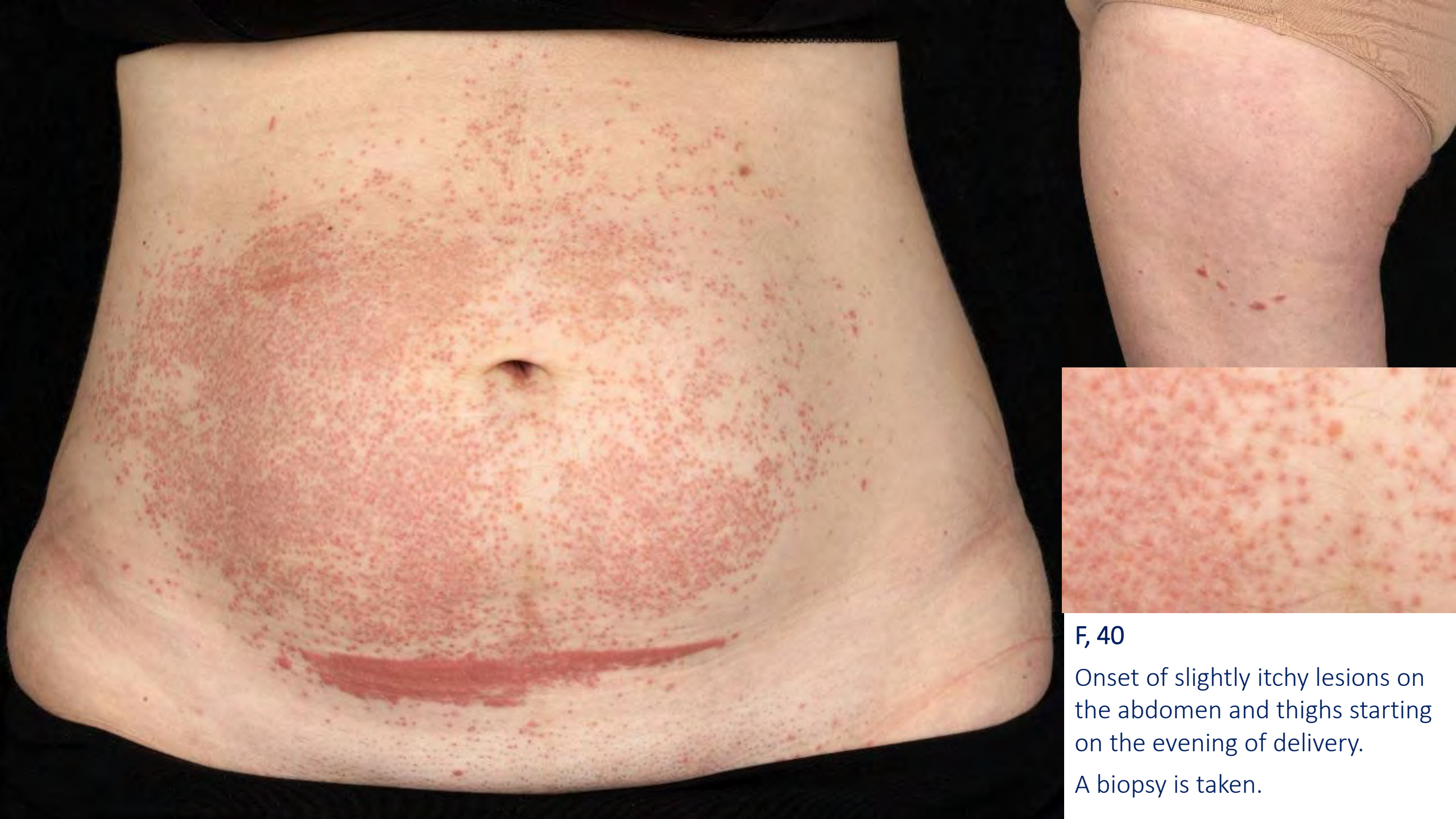

F, 33







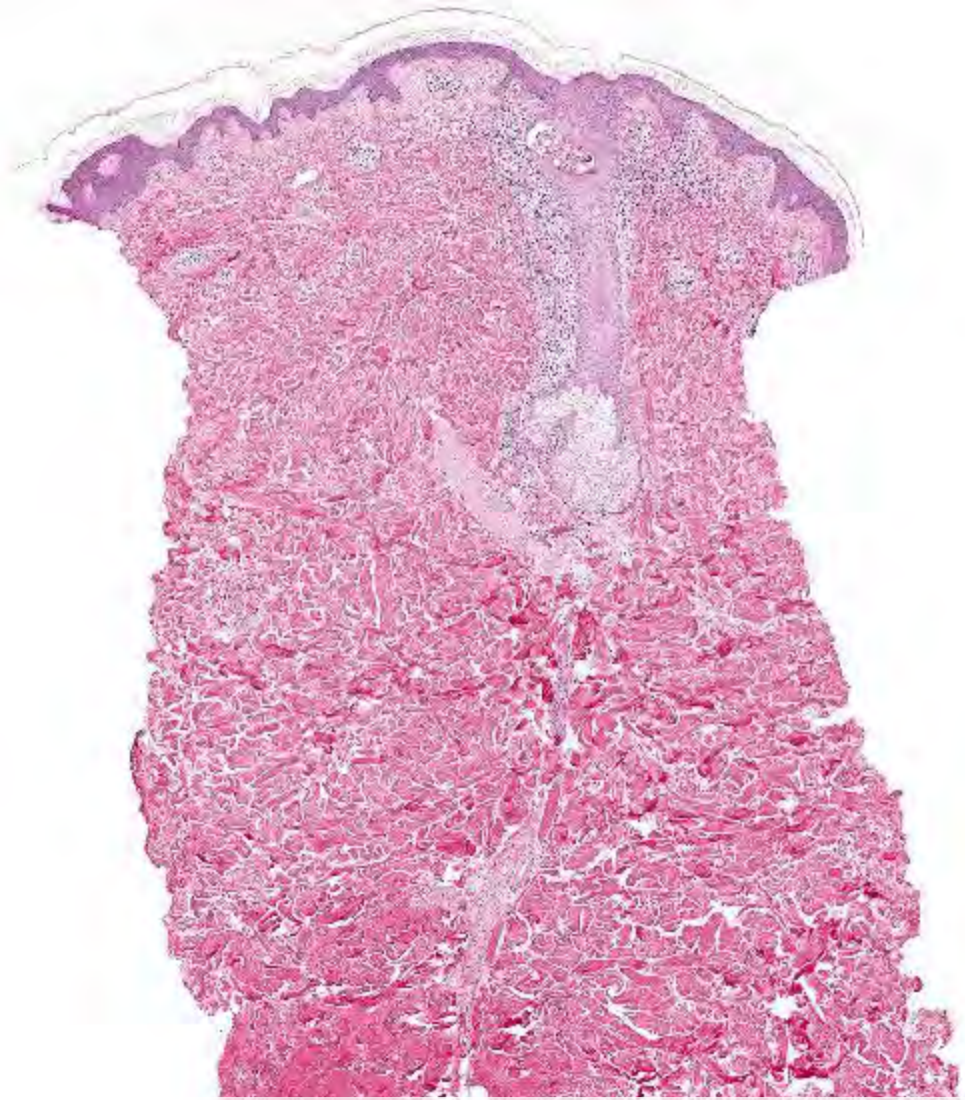


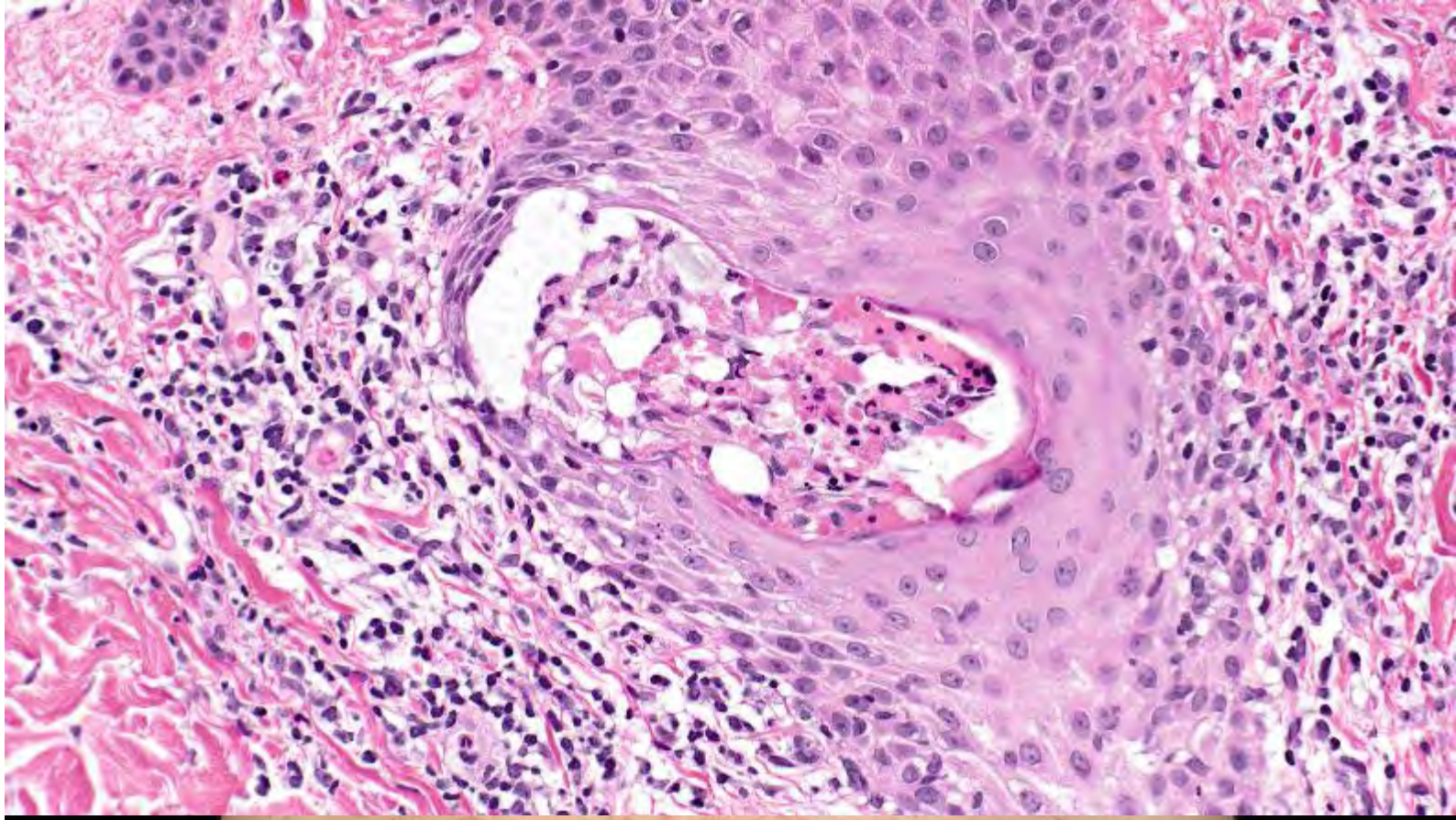


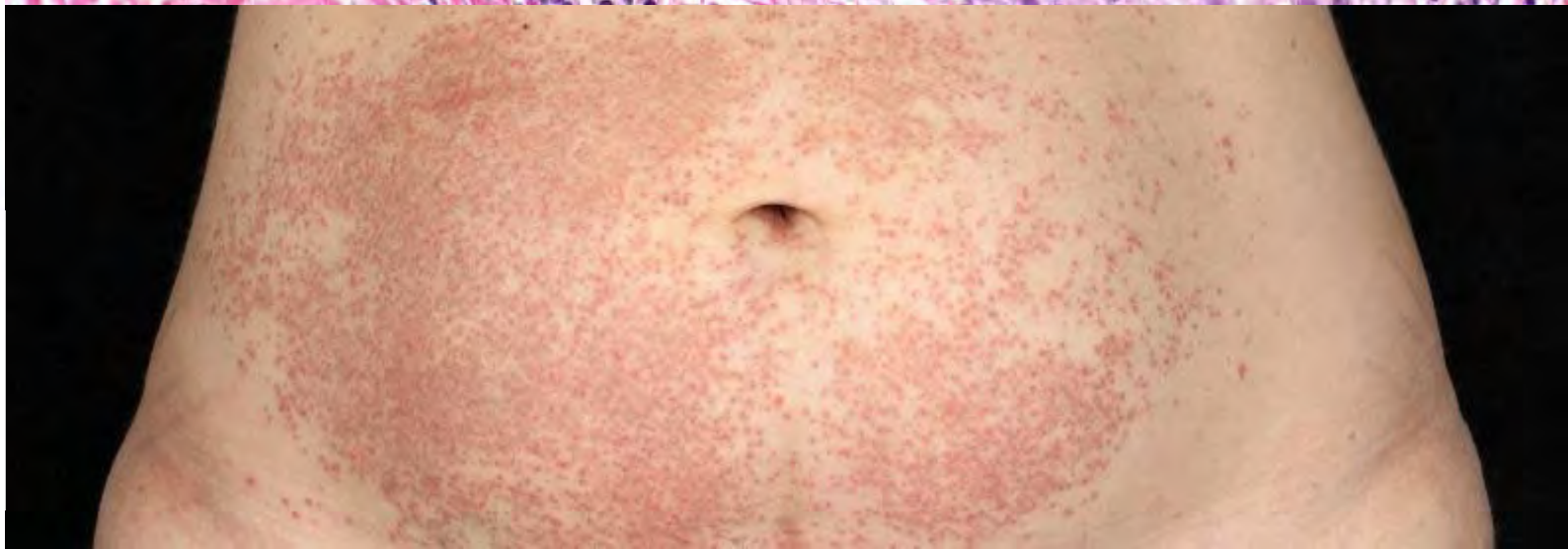
F, 40

Onset of slightly itchy lesions on the abdomen and thighs starting on the evening of delivery.

A biopsy is taken.







Pruritic folliculitis of pregnancy

Pruritic Folliculitis of Pregnancy

Regina Zboralske, MD; Kevin B. Farmer, MD

• We studied the clinical and pathologic features of a pruritic, erythematous, papular eruption occurring in six pregnant women between the fourth and ninth months of gestation. All patients were in good health and without symptoms associated with the eruption. The lesions were generalized except in one patient. The clinical diagnosis at each case was papular dermatitis of pregnancy. The histopathologic feature of acute folliculitis was observed in five of the six women. The sixth patient demonstrated parakeratosis limited to the acrotrichium. No microorganisms were found in the six patients, and direct immunofluorescence microscopy was negative for deposition of immunoreactants in the four patients that were observed. Deliveries were normal, and all infants were healthy. The lesions cleared spontaneously at delivery or in the postpartum period. We believe that papular skin lesions in pregnant women should undergo biopsy to obtain further data regarding the dermatitis and its natural history.

(*Arch Dermatol* 117:20-22, 1981)

Papular dermatitis of pregnancy was first described by Spangler et al[1] in 1962 as a generalized eruption of small, erythematous, pruritic papules occurring any time during pregnancy. It was associated with increased human chorionic gonadotropic levels, decreased plasma levels of hydrocortisone,[2] and decreased urinary estriol levels. The dermatitis was thought to occur rarely, with an incidence estimated at one in 2,000 pregnancies and with an associated increase in fetal mortality approaching 30%. The eruption often cleared after delivery. Though prednisolone or estrogen therapy was advocated for severe cases. The process frequently recurred in subsequent pregnancies.

Recently, Lawley et al[3] described another type of lesion that they termed "pruritic, urticarial papules and plaques of pregnancy." This process occurred during the third trimester of pregnancy in seven patients and was not definitely associated with fetal complications.

We have observed six pregnant patients with a pruritic papular eruption. Five of the six patients demonstrated a pattern of folliculitis that has not been described in the other dermatoses occurring in pregnancy.

Accepted for publication March 4, 1980.

From the Department of Dermatology, Johns Hopkins Medical Institutions, Baltimore. Dr Zboralske is now with the Department of Pediatrics, New York University, New York.

Reprint requests to the Department of Dermatology, Johns Hopkins Medical Institutions, Baltimore, MD 21205 (Dr Farmer).

METHODS

The clinical data are summarized in the Table. The patients' ages ranged from 18 to 33 years. Three were white and three black; one was Oriental. All were in good health; one complained of constitutional symptoms associated with the eruption. Except for prenatal multivitamins, including vitamin A and ascorbic acid at the minimum dose levels recommended for pregnancy, only patient 5 was taking any oral medications, and these were prescribed for a urinary tract infection. She was treated with a combination of sulfamerazole and phenazopyridine hydrochloride followed by nitrofurantoin.

The time of onset of the dermatitis ranged from the fourth to ninth month of gestation. All of the lesions were described as 3- to 5-mm, erythematous papules (Fig 1). One woman was believed to have early vesicle formation, while two others had an urticarial component. Five patients had a generalized distribution of the eruption; the sixth patient had lesions limited to the arms and abdomen.

Treatment modalities included topical 0.25% triamcinolone acetonide, topical 0.05% fluocinonide, topical gamma benzene hexachloride (lindane), systemic hydroxyzine hydrochloride, and systemic diphenhydramine hydrochloride. Following these treatments, there were no objective changes in the lesions, and there was only mild relief of the pruritus. In one patient, the eruption recurred in the fourth month of pregnancy, lasting only one week and clearing spontaneously. In two patients, the lesions cleared on delivery while in two other patients, the dermatosis cleared one month after delivery. One patient had lesions two weeks postpartum but was unavailable for follow-up. Follow-up information was supplied by the referring dermatologists and the patients themselves, when possible. Labor and deliveries were unremarkable, and all infants seemed to be in good health.

Two patients had had abortions with previous pregnancies; however, neither patient had had any lesions associated with a pregnancy occurring between the previous one and the present, affected pregnancies. The other patient reported a similar eruption while taking dermoz.

No serum or urinary human chorionic gonadotropin, hydrocortisone, or estriol levels were obtained in this retrospective study.

HISTOPATHOLOGIC FINDINGS

Punch biopsy specimens of representative lesions from six patients were obtained during 15 months. Serial sections were cut and stained with hematoxylin-eosin. Selected sections were also stained with PAS, Brown-Brenn, or Giemsa. Four cases were studied with direct

Summary of Clinical Data

Patient/Age, yr	Onset of Skin Lesions, Months of Gestation	Resolution of Skin Lesions	Distribution of Papules	Miscellaneous
1/23	4	1 wk after onset	Generalized	None
2/28	5	1 mo post partum	Generalized	Similar eruption occurred during one of two previous pregnancies
3/19	6	—	Generalized	Lesions present 2 wk post partum; patient unavailable for follow-up
4/33	6	1 mo post partum	Generalized	Similar eruption occurred with previous pregnancy and with danazol therapy
5/18	9	After delivery	Generalized	None
6/26	9	After delivery	Arms and abdomen	Unavailable for further follow-up

The specific dermatoses of pregnancy revisited and reclassified: Results of a retrospective two-center study on 505 pregnant patients

Christina M. Ambros-Rudolph, MD,[a] Robert R. Müllegger, MD,[a] Samantha A. Vaughan-Jones, MD,[b] Helmut Kerl, MD,[a] and Martin M. Black, MD, FRCP, FRCPath[b]
Graz, Austria, and London, United Kingdom

Objectives: We sought to evaluate the frequency and clinical characteristics of pruritic dermatoses of pregnancy and to derive a rational and simplified classification.

Methods: A total of 505 pregnant patients seen at two university-based dermatologic hospitals (1991-2004) were retrospectively studied.

Results: Diagnoses included eczema in pregnancy (48.7%), polymorphic eruption of pregnancy (PEP) (30.6%), pemphigoid gestationis (PG) (4.2%), intrahepatic cholestasis of pregnancy (ICP) (3.4%), prurigo of pregnancy (0.6%), pruritic folliculitis of pregnancy (0.2%), and miscellaneous dermatoses (20.6%). Eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy showed considerable overlap and were summarized as atopic eruption of pregnancy (AEP). While PEP, PG, and ICP presented in late pregnancy, AEP started significantly earlier. Primigravidae and multiple gestations were characteristic for PEP, abdominal involvement for PEP and PG, and a history of affected pregnancies for ICP.

Limitations: This was a retrospective study.

Conclusion: We propose classifying the dermatoses of pregnancy as PG, PEP, AEP, and ICP. Stereotypic immunofluorescence and laboratory findings are diagnostic of PG and ICP, whereas distinct clinical characteristics facilitate discrimination between PEP and AEP. (J Am Acad Dermatol 2006;54:395-404.)

The specific dermatoses of pregnancy represent a heterogeneous group of ill-defined pruritic skin diseases unique to pregnancy. With the exception of pemphigoid gestationis (PG), the pathogenesis of these diseases is not understood and there is limited literature on their clinical characteristics. This lack of data is a result in part of the infrequency with which these dermatoses are seen at any one institution. As a consequence, their terminology has been confusing and misleading, and their classification is still the subject of ongoing controversy. Currently, two main classification schemes are used. The first, proposed by Holmes and Black[1] in 1983, includes PG (syn., herpes gestationis), polymorphic eruption of pregnancy (PEP) (syn., pruritic urticarial papules and plaques of pregnancy [PUPPP]), prurigo of pregnancy (PP), and pruritic folliculitis of pregnancy (PF). The second, proposed by Ni Cormack[2] in 1998 as a further simplification, consists of PG, PEP, PP, and intrahepatic cholestasis of pregnancy (ICP). He suggested that PF belonged with the group of PP, but all patients with PF in the original report[1] were thought to have papular eczematitis clinically and were separately described, leading

Abbreviations used:

AEP: atopic eruption of pregnancy
ICP: intrahepatic cholestasis of pregnancy
PEP: polymorphic eruption of pregnancy
PF: pruritic folliculitis of pregnancy
PG: pemphigoid gestationis
PP: prurigo of pregnancy

From the Department of Dermatology, Medical University Graz,[a] and St John's Institute of Dermatology, Guy's Hospital and St Thomas' School of Medicine, St Thomas' Hospital, London.[b]
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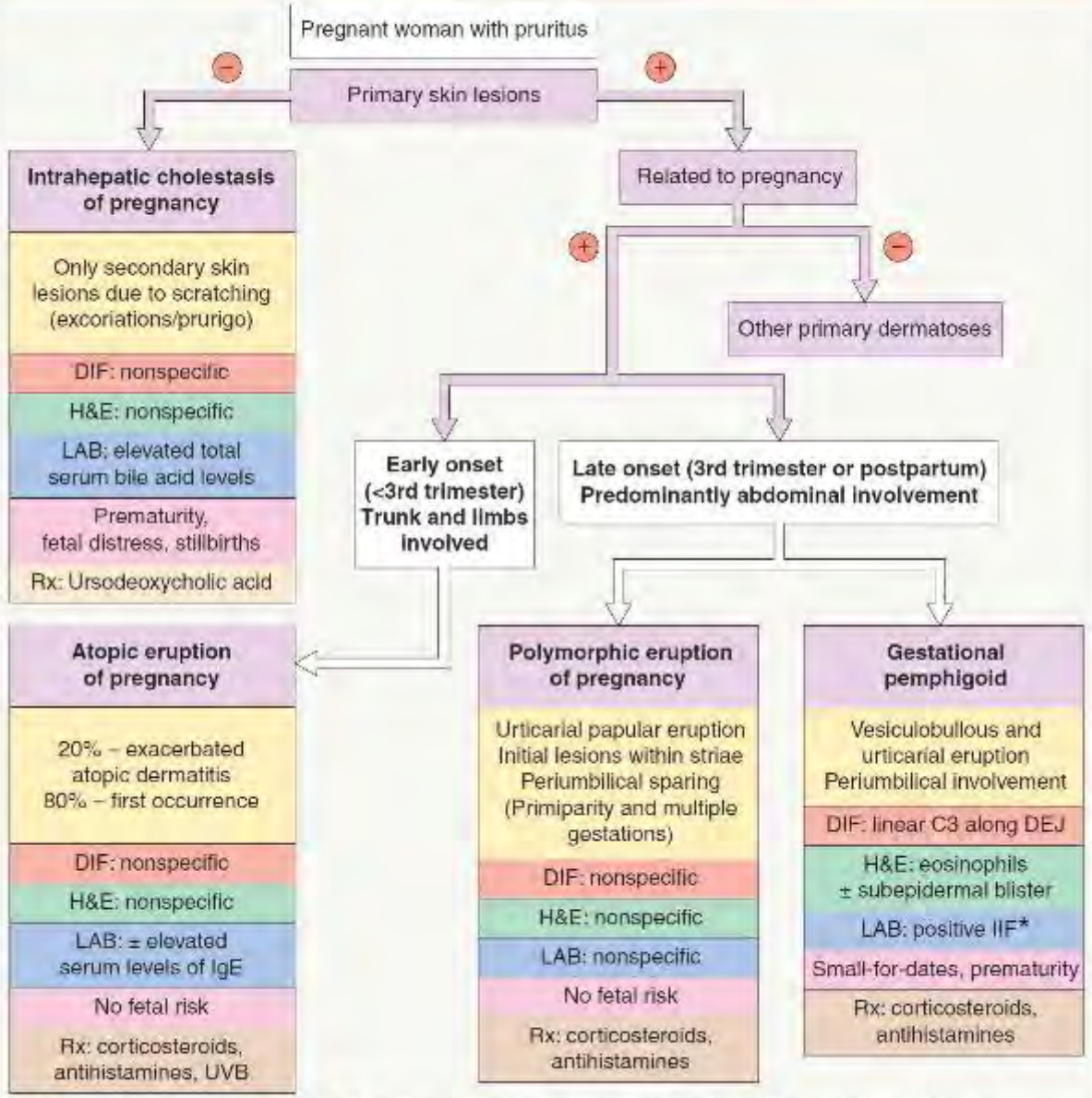
Reprint requests: Christina M. Ambros-Rudolph, MD, Department of Dermatology, Medical University Graz, Auenbruggerplatz 8, 8036 Graz, Austria. E-mail: christina.ambros-rudolph@medunigraz.at.
0190-9622/$32.00

doi:10.1016/j.jaad.2005.12.030

"Eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy showed considerable overlap and were summarized as atopic eruption of pregnancy (AEP)."

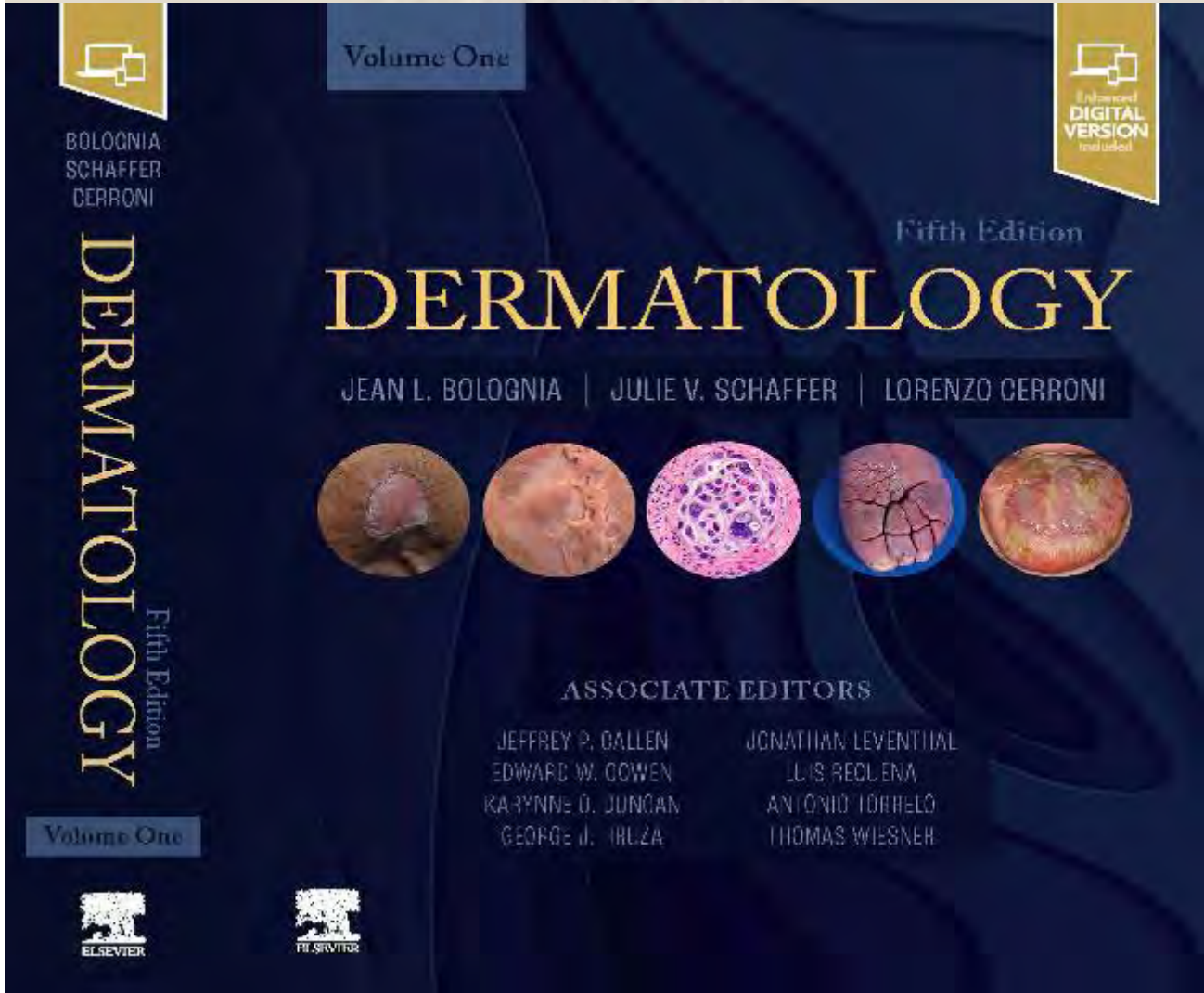
APPROACH TO THE PREGNANT WOMAN WITH PRURITUS



DEJ, dermal–epidermal junction; DIF, direct immunofluorescence; H&E, hematoxylin and eosin-stained histologic sections; IIF, indirect immunofluorescence; LAB, laboratory findings.
*Conventional – 30%; complement-added – nearly all.

Pregnancy Dermatoses 27

Christina M. Ambros-Rudolph



"Conventional" itchy pregnancy dermatoses

- **Gestational pemphigoid:** classically 3rd trimester or post-partum (but may occur in any trimester); commonly recurs (induced also by oral contraception in 25-50% of cases)
- **Polymorphic eruption of pregnancy – PEP (PUPPP):** last part of 3rd trimester or immediately post-partum; usually does not recur; begins typically within striae distensae with sparing of the navel
- **Intrahepatic cholestasis of pregnancy:** 3rd trimester; recurrence in 45-70% of subsequent pregnancies (may be induced also by oral contraception)
- **Atopic eruption of pregnancy** *(includes eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy)*: early onset, mostly during the 1st trimester (<3rd trimester); commonly recurs
- *Eosinophils may be seen in many pregnancy dermatoses; histopathological features mimic oft those of hypersensitivity reactions*

Arch Dermatol Res (1987) 279:348–351

Dermatological Research

Contrasting disease patterns in psoriasis and atopic dermatitis*

P. Christophers and T. Henseler

Department of Dermatology, University of Kiel, D-2300 Kiel, Federal Republic of Germany

Summary. In this report we investigate the simultaneous occurrence of psoriasis and atopic dermatitis (AD) as well as the association with infectious skin diseases. Among 29,159 patients hospitalized between 1953 and 1983, 8.5% (2,467 patients) were treated for psoriasis, while 1.6% (470 patients) were hospitalized for AD treatment. On the basis of incidence rates for both diseases, 36 patients (0.14%) with both psoriasis and AD were expected to be seen. However, the two conditions were simultaneously present in 2 patients only.

Approximately 30% of the AD patients were suffering from either bacterial or viral infection, while this complication occurred in 6.7% of psoriatics. In addition, among 48 patients hospitalized for eczema herpeticatum 39 were atopics and none was psoriatic. The data demonstrate that the occurrence of psoriasis and AD in one and the same patient is quite rare and this may be related to conflicting immune defense patterns. Thus, increased sensitization against foreign procein together with high susceptibility to cutaneous infection present in AD is in contrast to high phagocyte responsiveness in psoriasis, where concurrent infections are rare.

Key words: Psoriasis — Atopic dermatitis — Infection

Psoriasis and atopic dermatitis (AD) are among the most common diseases of the skin. Within the caucasian population the incidence of psoriasis is estimated to be near 2% [2, 6], while the incidence rates of AD are reported to be nearly 5% in younger age groups [10, 19].

Since both psoriasis and AD occur with such marked frequency, it would appear reasonable to assume that there is a possibility of patients in whom both skin disorders may be seen simultaneously. Because the coexistence of both conditions could reveal important pathophysiologic aspects, we investigated in detail the question of simultaneous occurrence of psoriasis and atopic dermatitis. The results indicate that psoriasis and AD occur rarely within the same patient. In addition, the conditions represent mutually exclusive disease patterns associated with a distinct set of diseases.

* Supported by Deutsche Forschungsgemeinschaft (Ch 85/2)

Offprint requests to: Peter Christophers, M.D. (address as above)

Materials and methods

A computerized file was analyzed of 29,159 hospitalized patients of the Department of Dermatology, University of Kiel, containing clinical disease data, e.g., diagnosis, associated disorders, age at onset, laboratory findings, as well as treatment results. From these files data pertinent to psoriasis and atopic dermatitis were retrieved. The period of investigation covered the years from 1953 to 1983. Diseases presenting simultaneously, and in cases of hospitalizations were evaluated, so as entering the separate frequencies of both disease in one period we used to elaborate statistical theorem: in independent events the product of observed frequencies, each of them with one special attribute, is the frequency of subjects showing both attributes simultaneously. Data shown here are only from patients for whom their skin condition was so severe, that inpatient hospital treatment was necessary.

Chi-square analysis was used to calculate differences in patient and incidence of psoriasis and AD patients. The minimal significance level accepted is $p = 0.05$.

Results

Among a total of 29,159 hospitalized patients, 2,467 patients (8.5%) suffered from psoriasis (first diagnosis) and 470 patients (1.6%) were hospitalized for AD treatment. The ratio of sex is nearly the same in psoriatics (57.1% males) AD patients (52.8% males). The average age at the time of admission was 38 years in psoriasis and 17 years in AD. Two patients presented with both diseases at the same time (Table 1).

Table 3. Number of patients with psoriasis ($n = 2,375$) or atopic dermatitis ($n = 473$) showing concurrent infections

Type of infection	Psoriasis patients		Atopic dermatitis patients		Significance p
	(n)	(%)	(n)	(%)	
Viral[a] (total)	80	3.3	62	13.0	≤ 0.001
Herpes simplex	20	0.8	3	0.6	n.s.
Eczema herpeticatum	0	0	38	8.0	≤ 0.001
Bacterial[b]	61	2.6	41	8.7	≤ 0.001
Fungal[c]	159	6.8	7	1.5	≤ 0.001
Tonsillitis	43	1.8	0	1.1	n.s.
Rhinitis allergica	2	0.2	9	1.9	n.s.

[a] Includes verrucae, condyloma acuminata, mollusca contagiosa, varizella zoster, herpes simplex

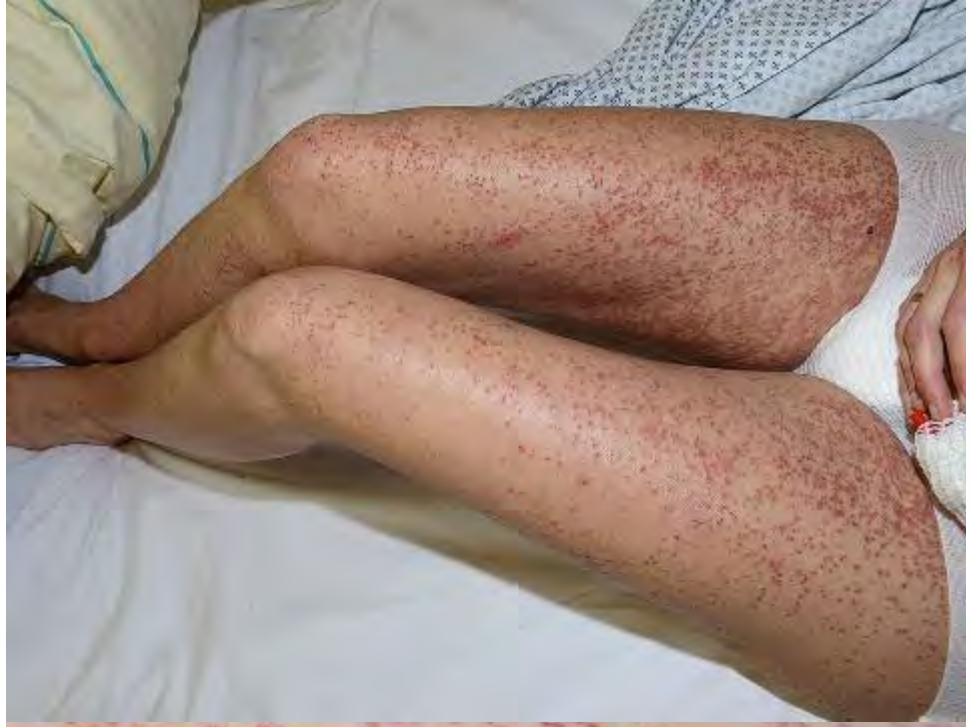
[b] Includes pyoderma, folliculitis, furuncles, deep cutaneous abscesses, erysipelas

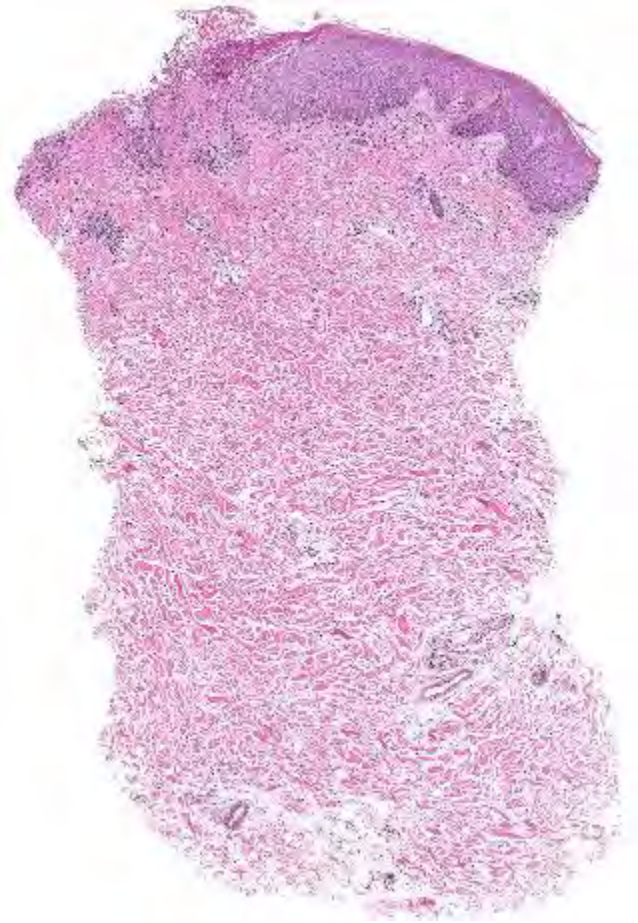
[c] Includes pityriasis versicolor, *Candida albicans* infections, and other forms of nontopical cutaneous mycoses

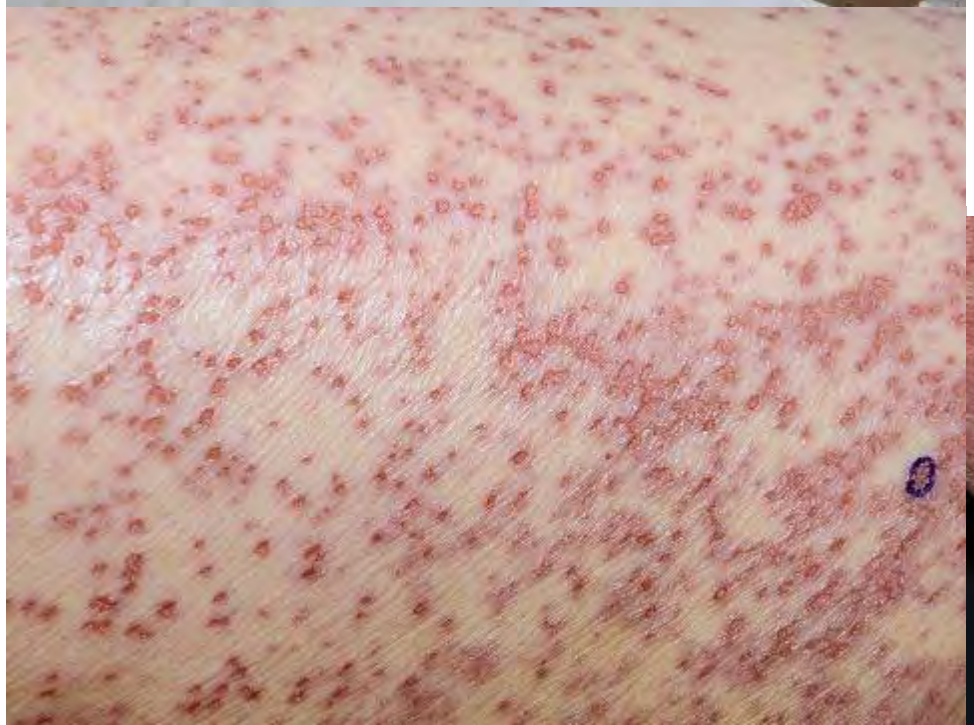
Table 4. Patients (n) with eczema herpeticatum (EH) in association with psoriasis or atopic dermatitis (AD)

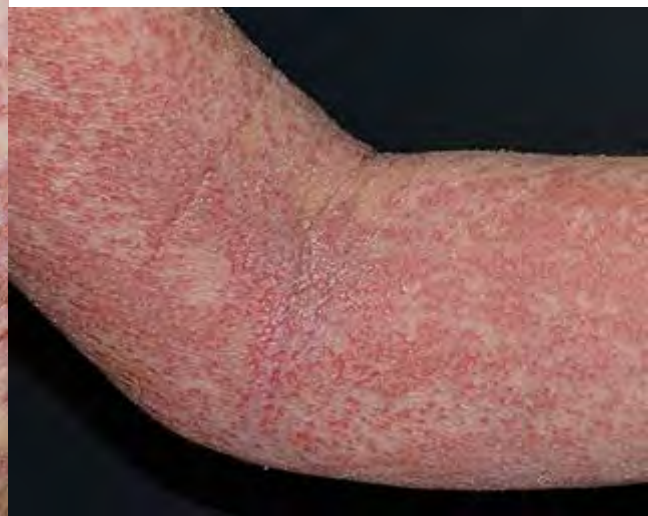
Patients hospitalized	In association with	
	AD	Psoriasis
48	39	0

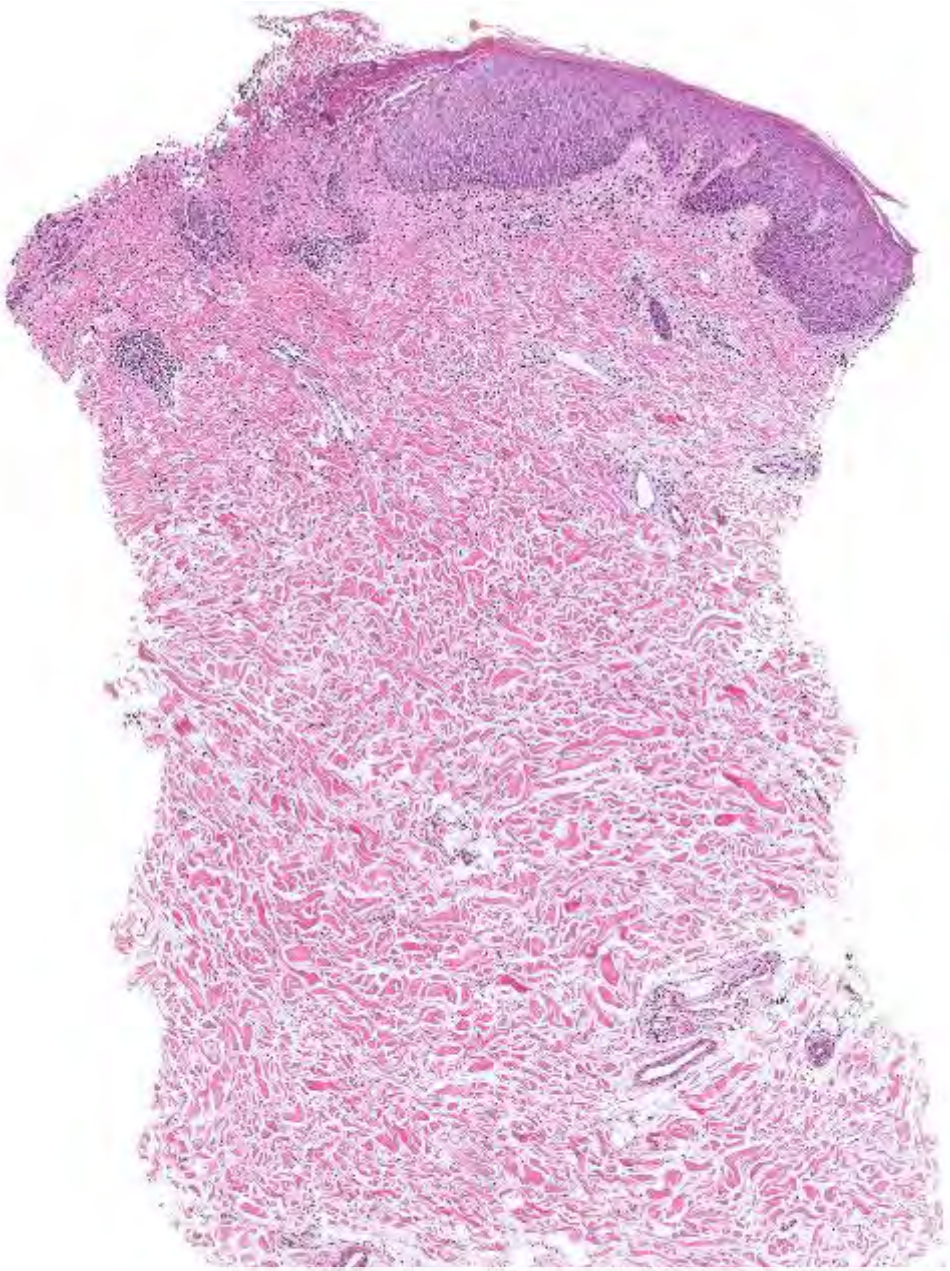
F, 44

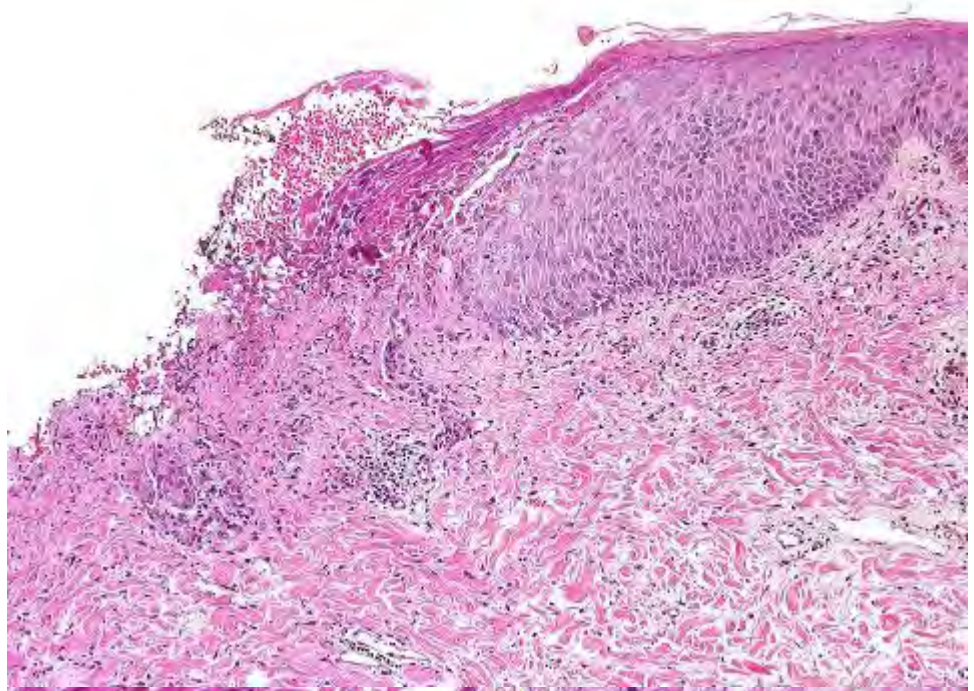


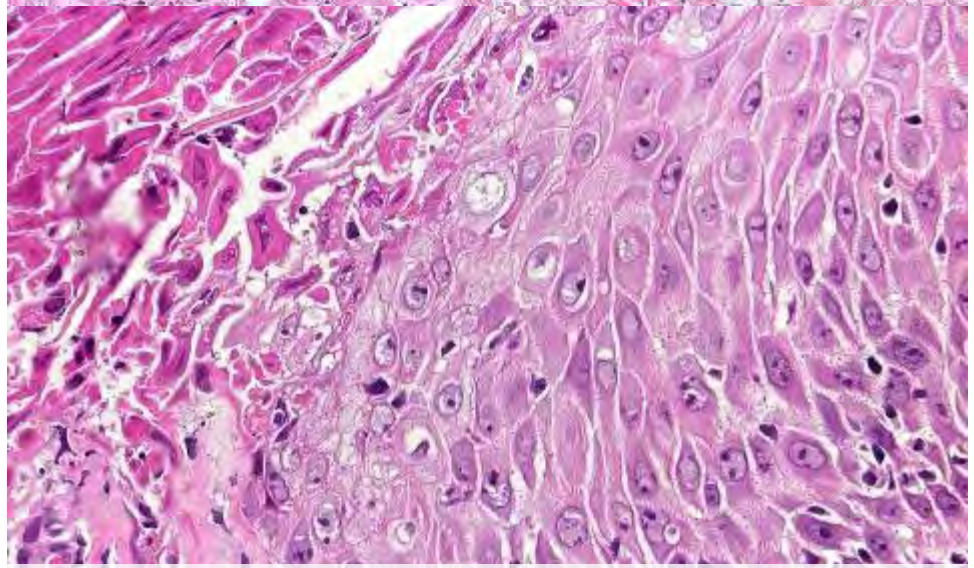




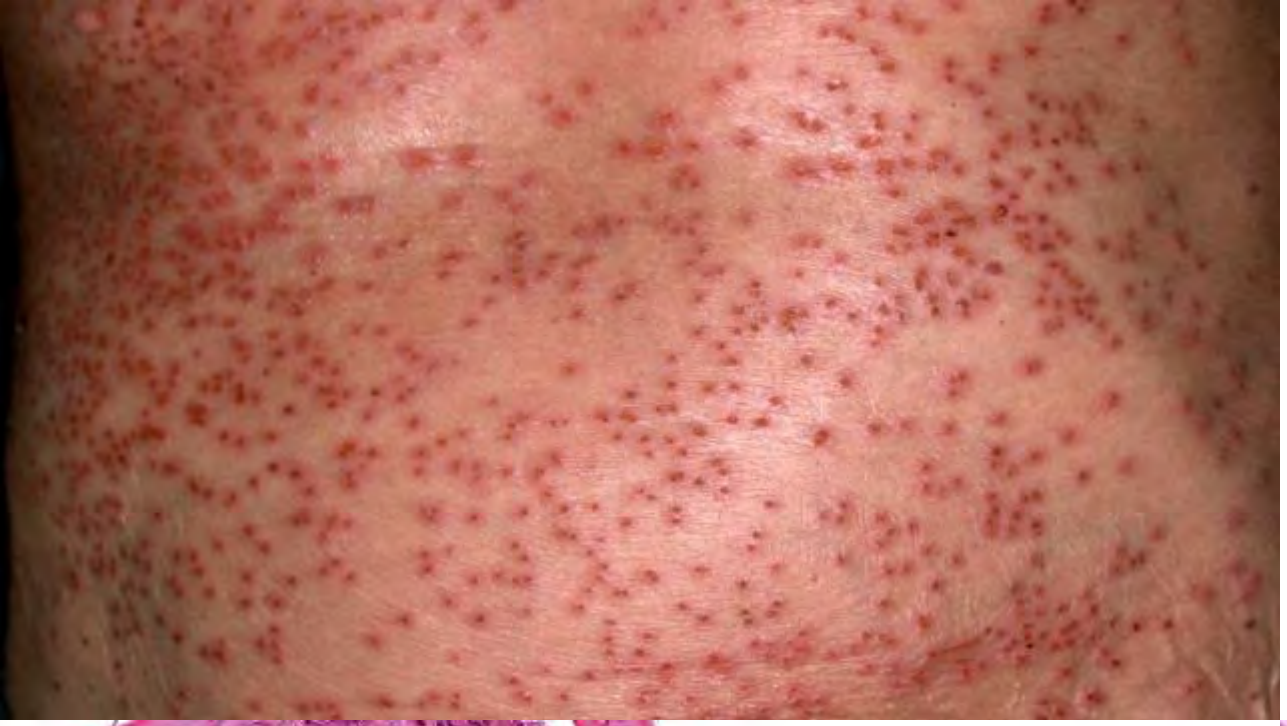


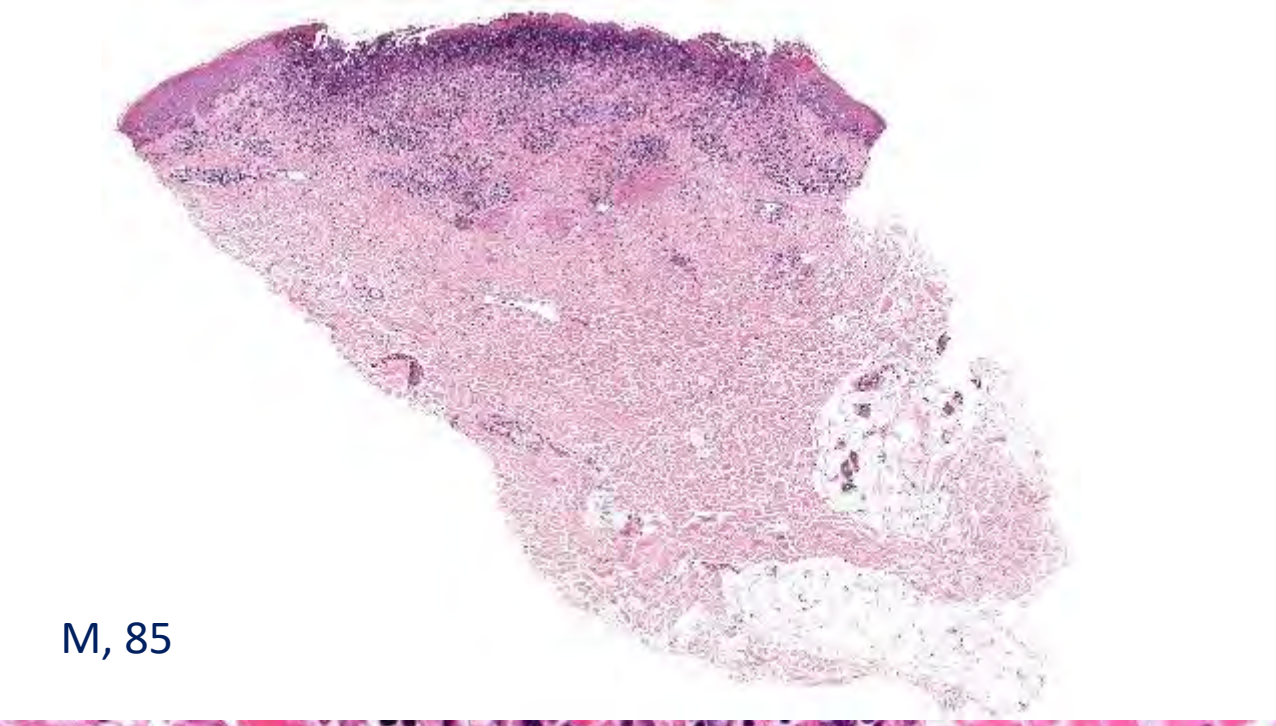






Eczema herpeticum in atopic dermatitis





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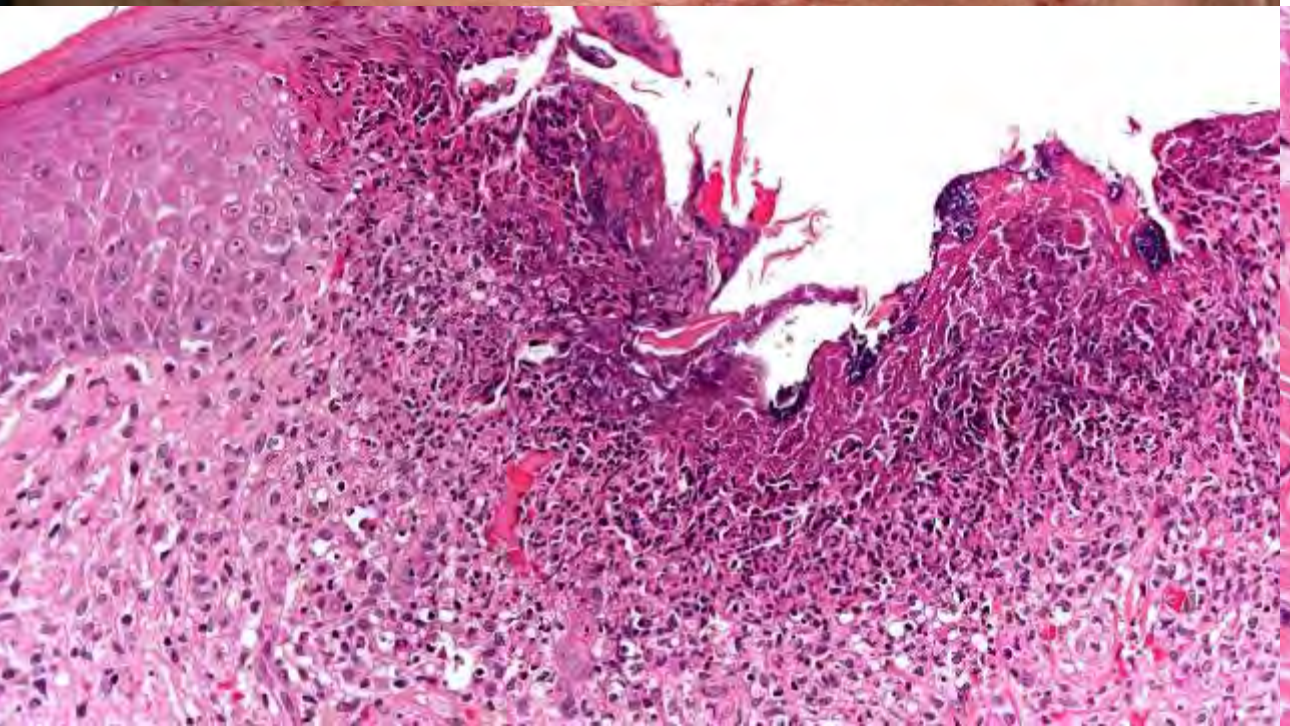

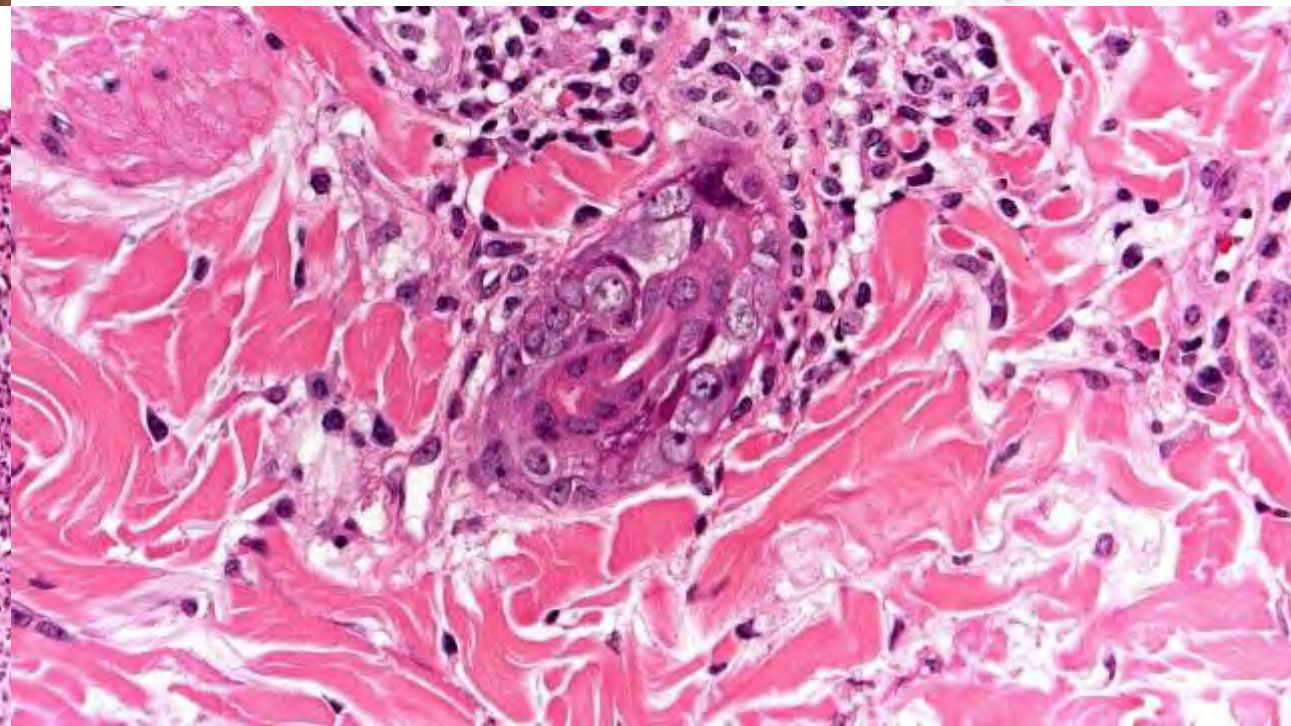

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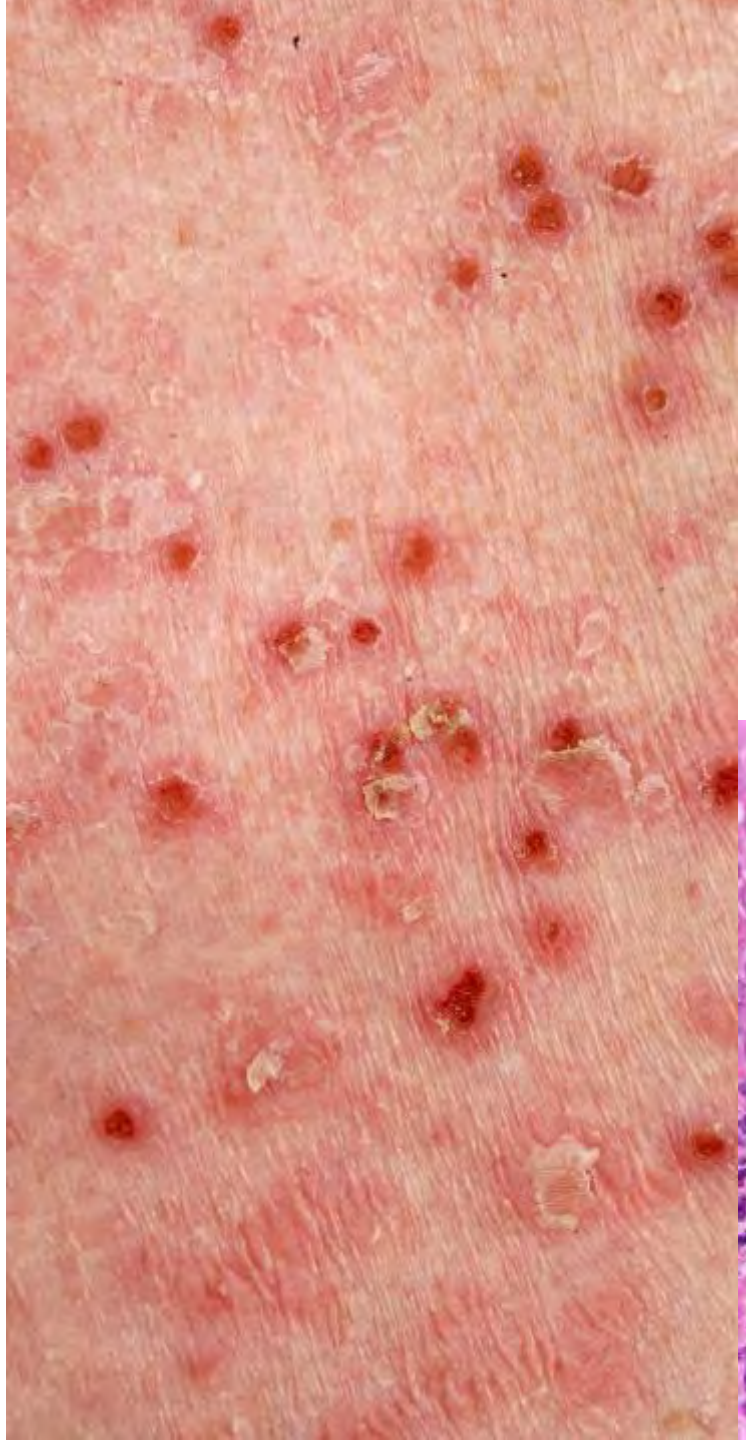
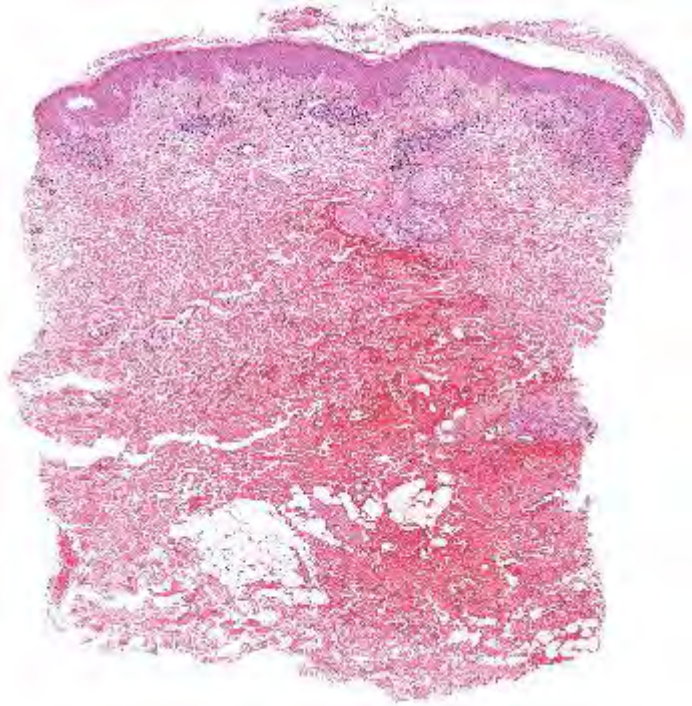
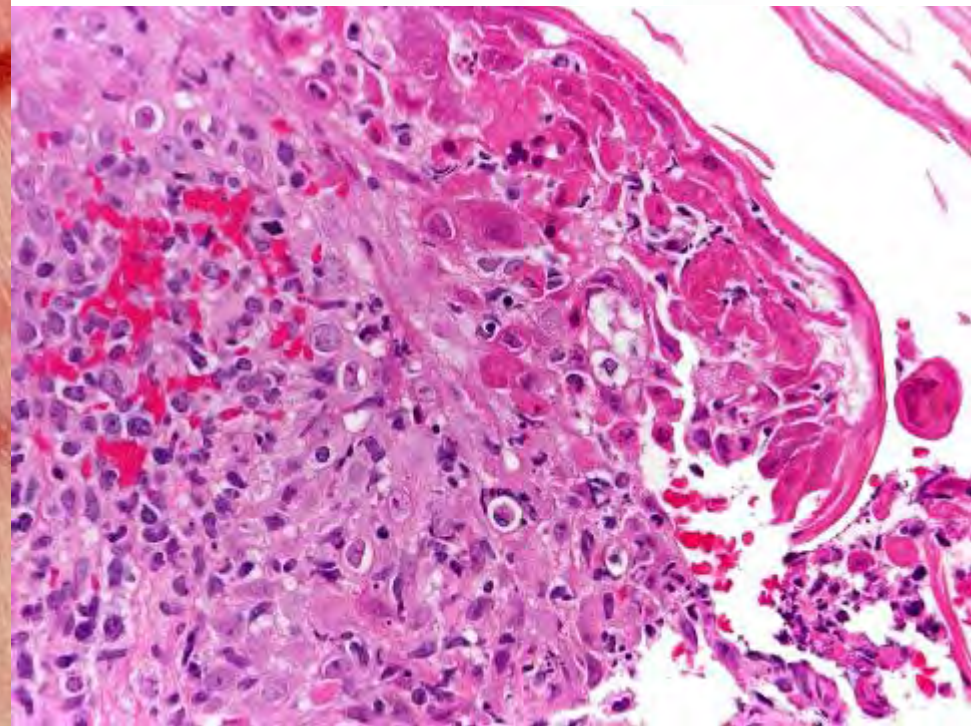


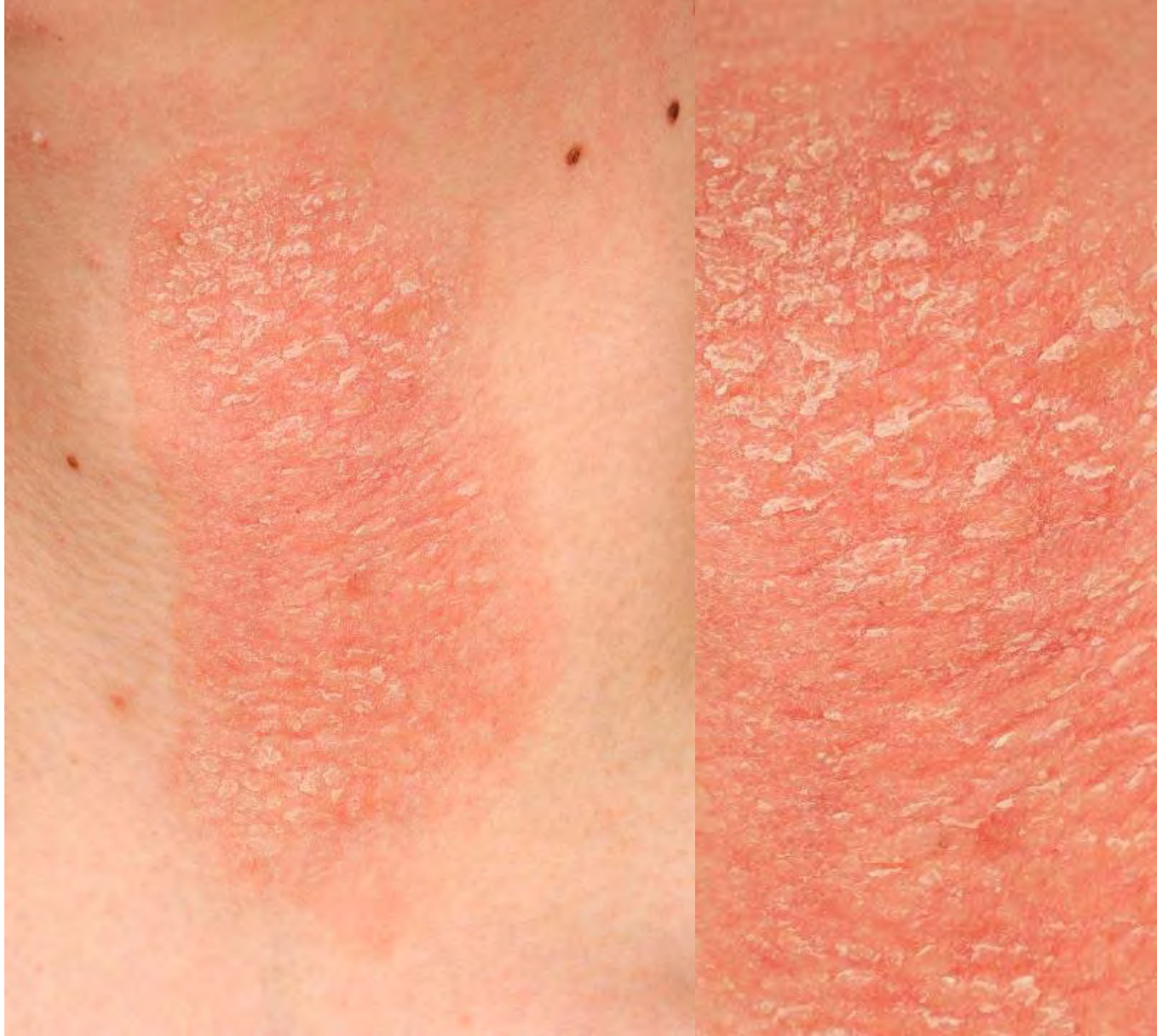


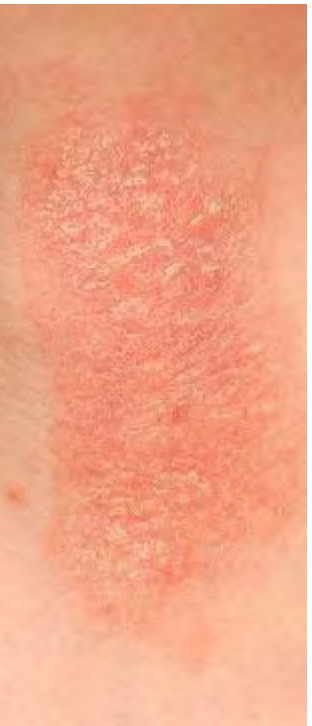


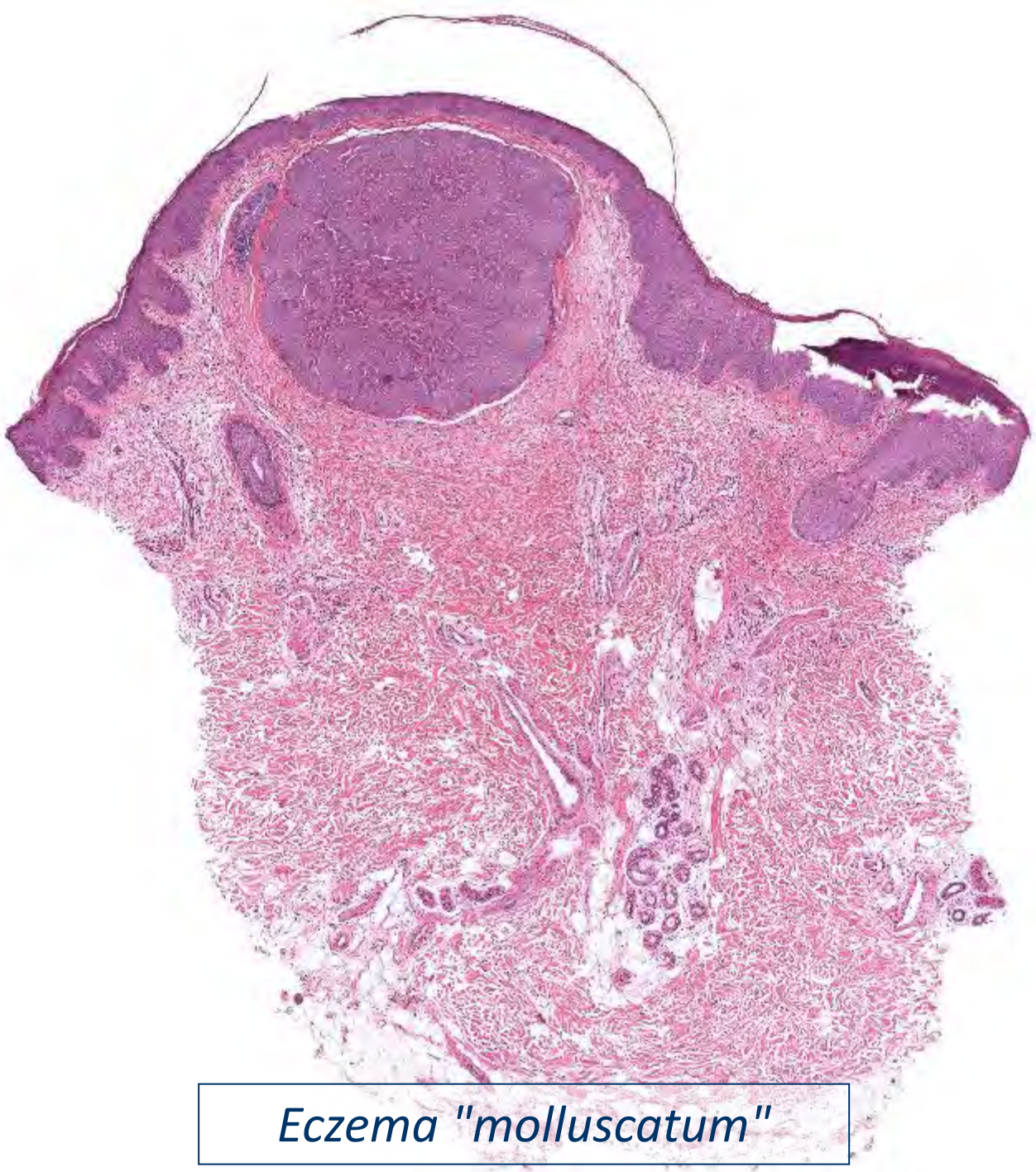
Eczema herpeticum

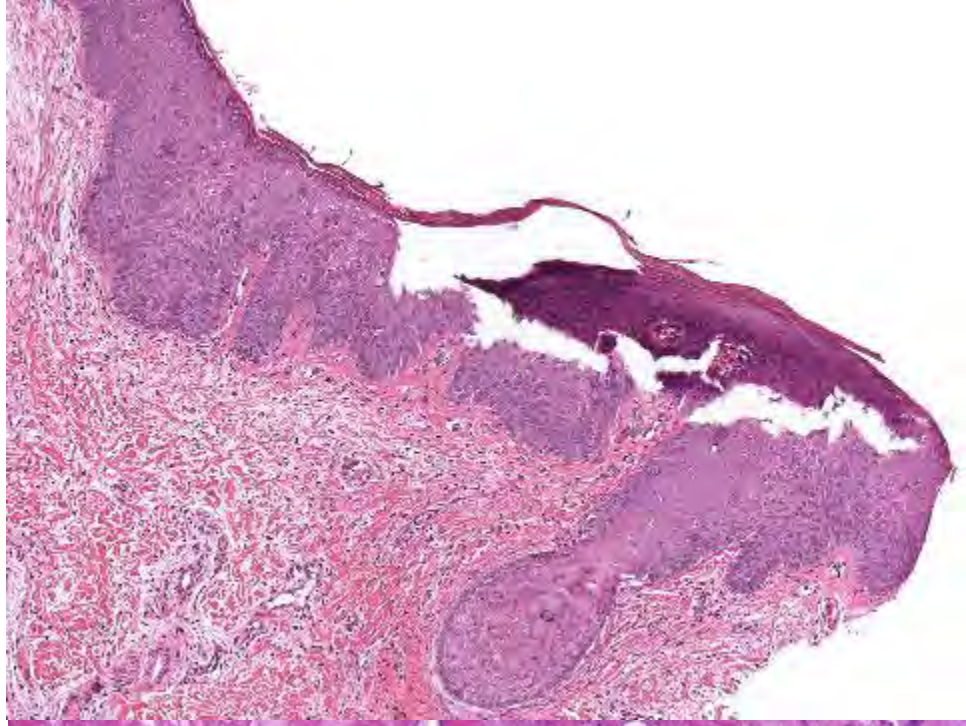
- In patients with atopic dermatitis, Darier disease, Hailey-Hailey disease, pityriasis rubra pilaris, pemphigus foliaceus, seborrheic dermatitis, ichthyosis, mycosis fungoides / Sézary syndrome, other generalized dermatoses
- Possible complications (spread to internal organs); may be lethal
- Biopsy usually not performed; when done, may show only very subtle features

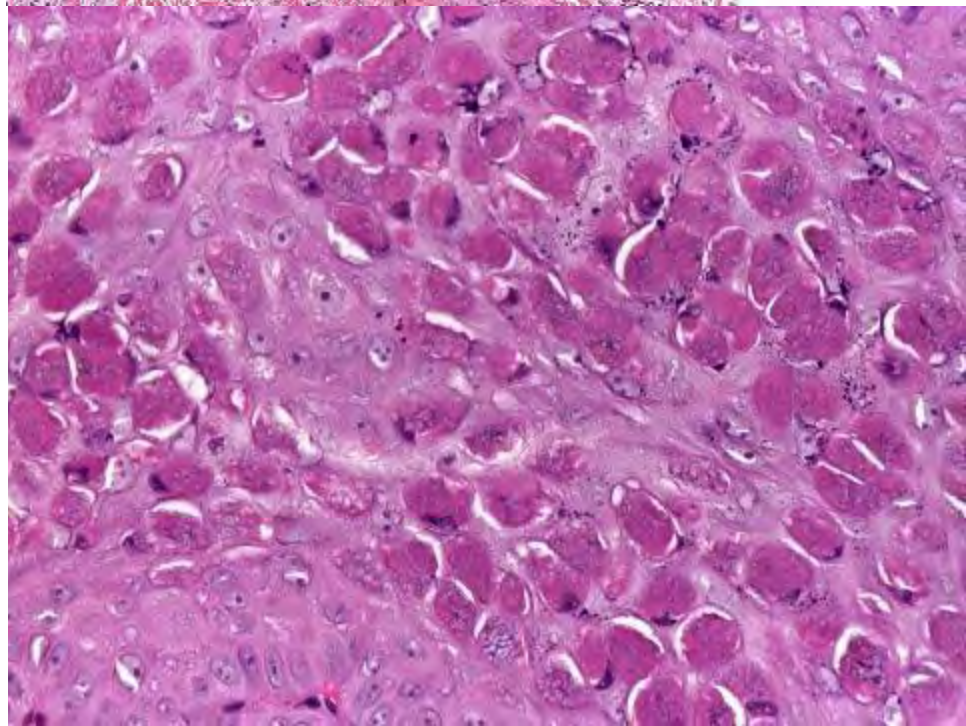
M, 13. Atopic diathesis.





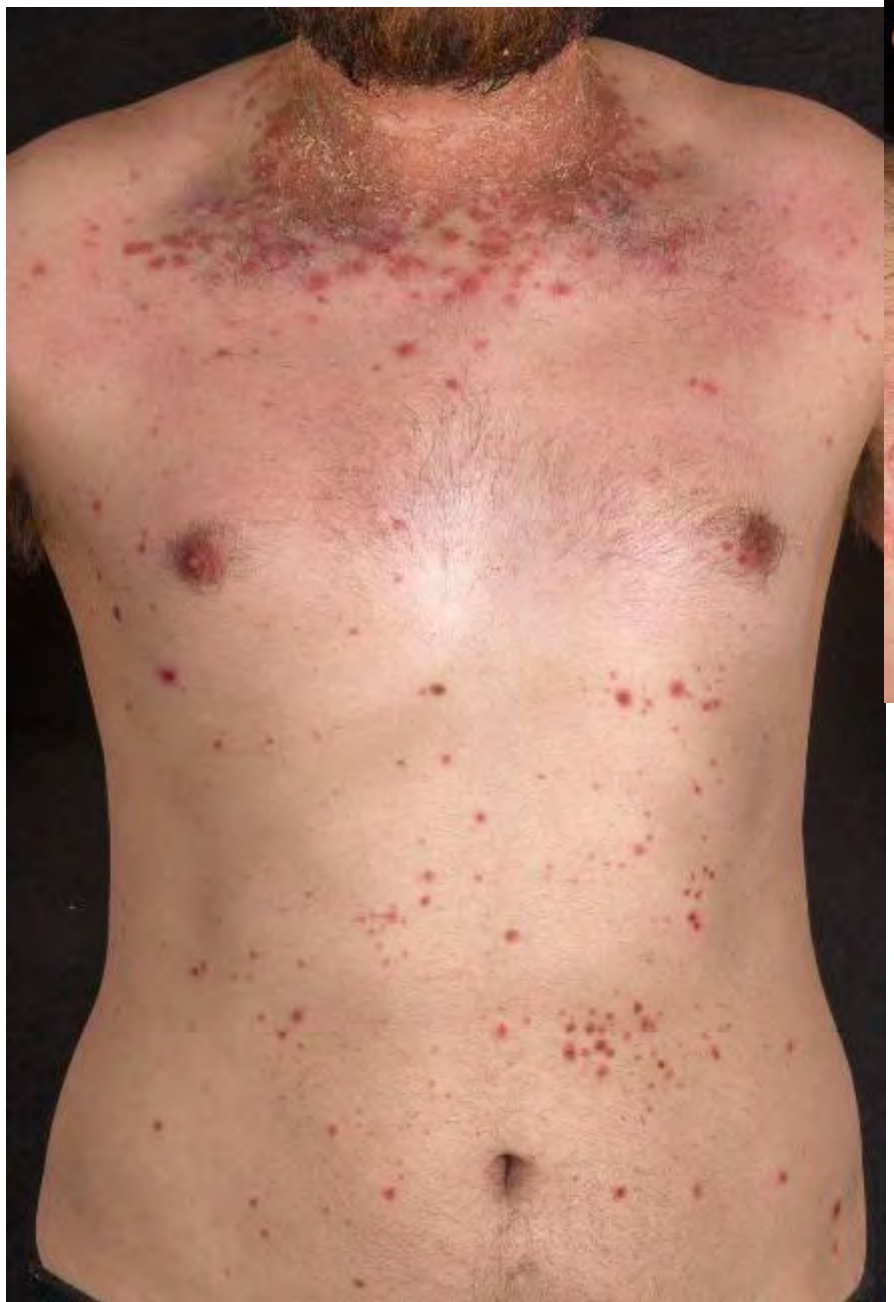


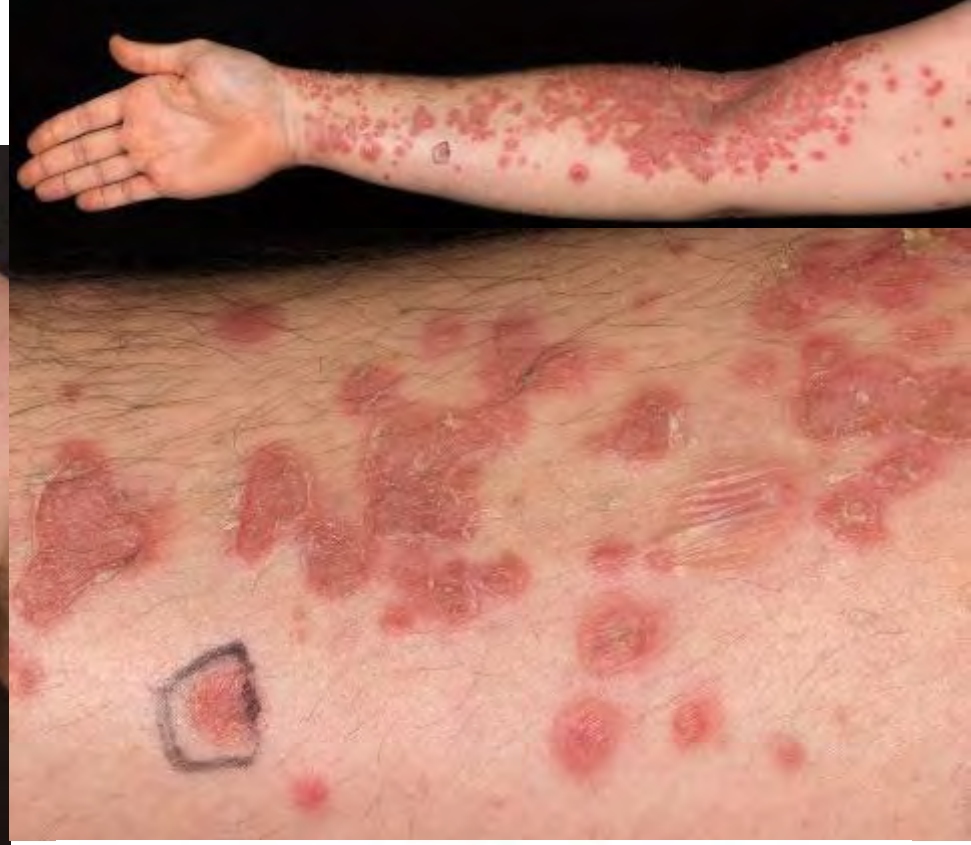


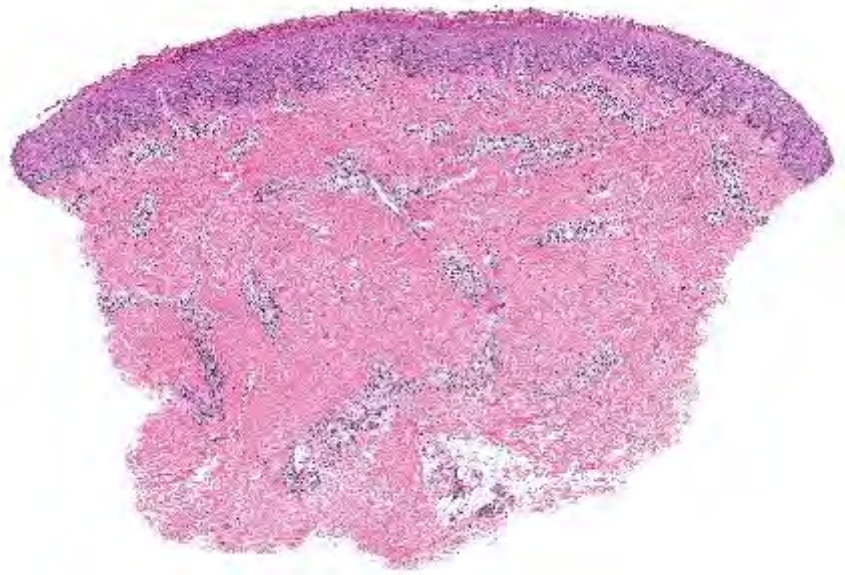


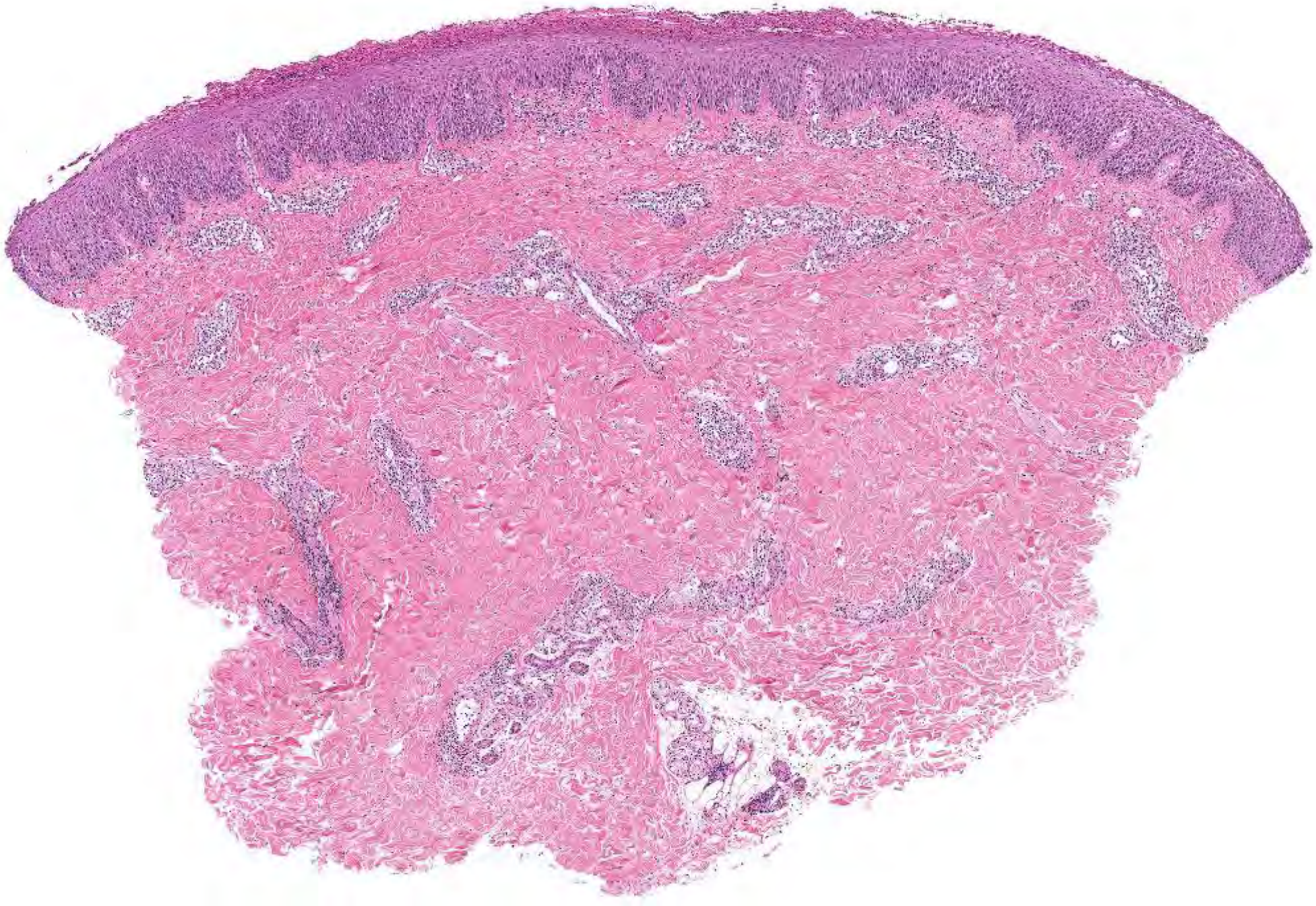
Eczema "molluscatum"

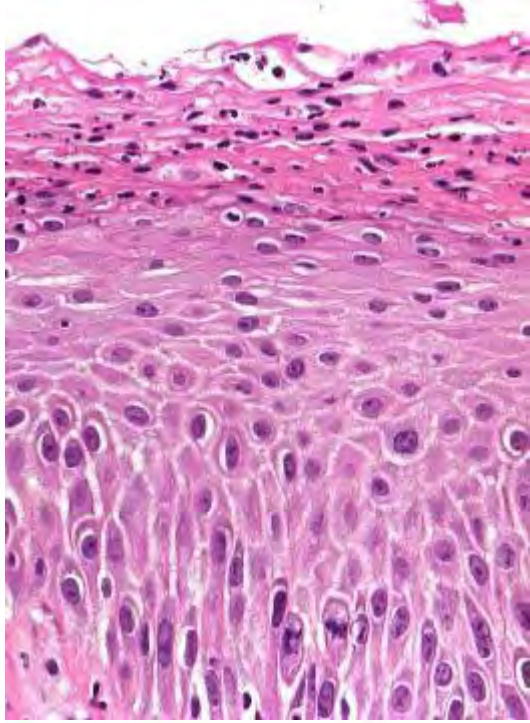
M, 24. Atopic dermatitis.

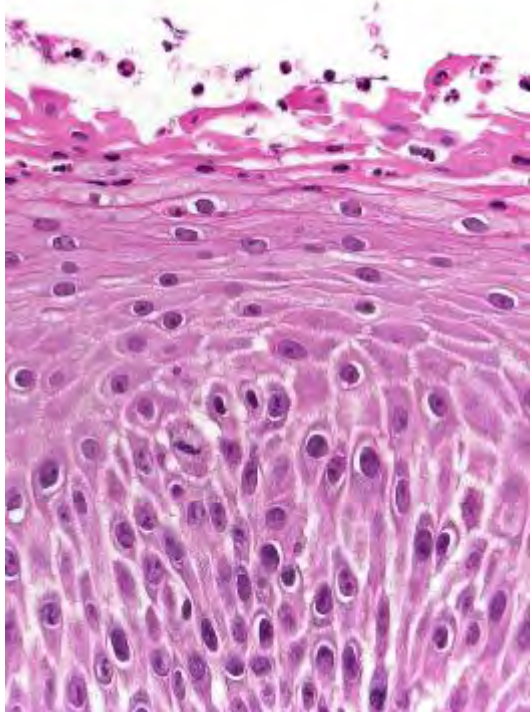


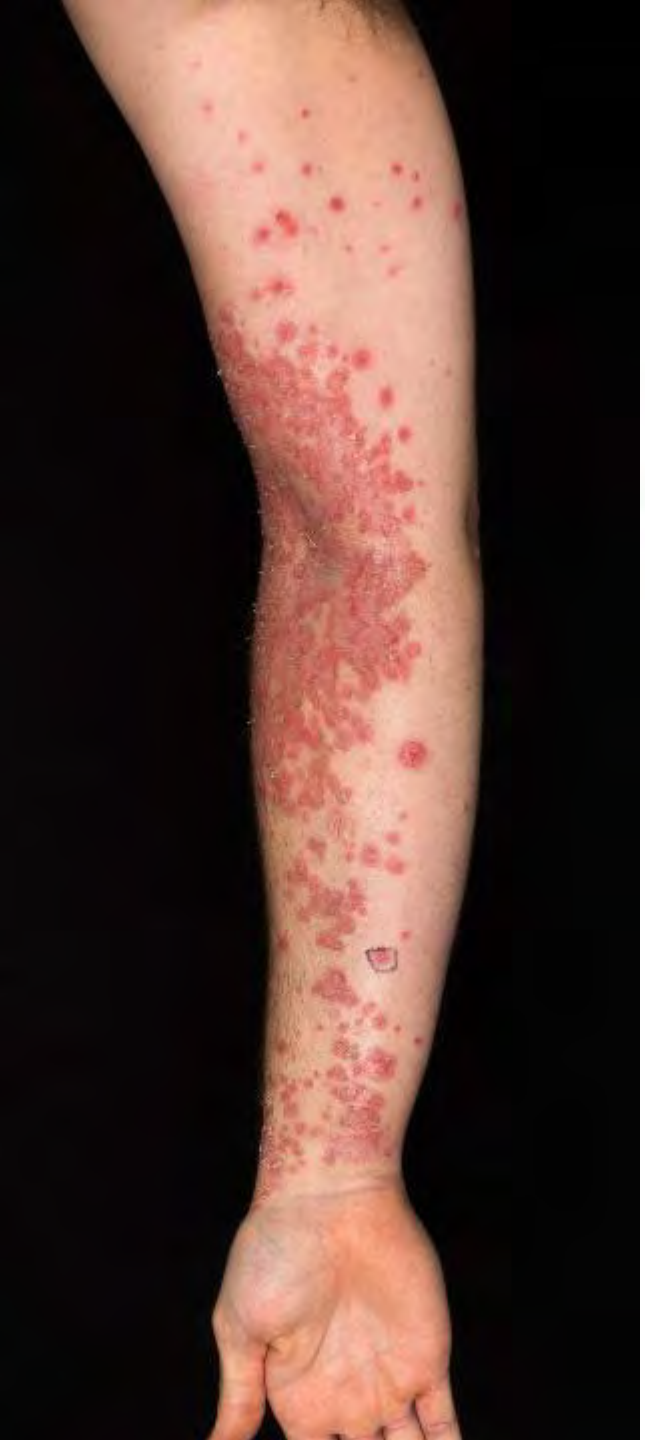


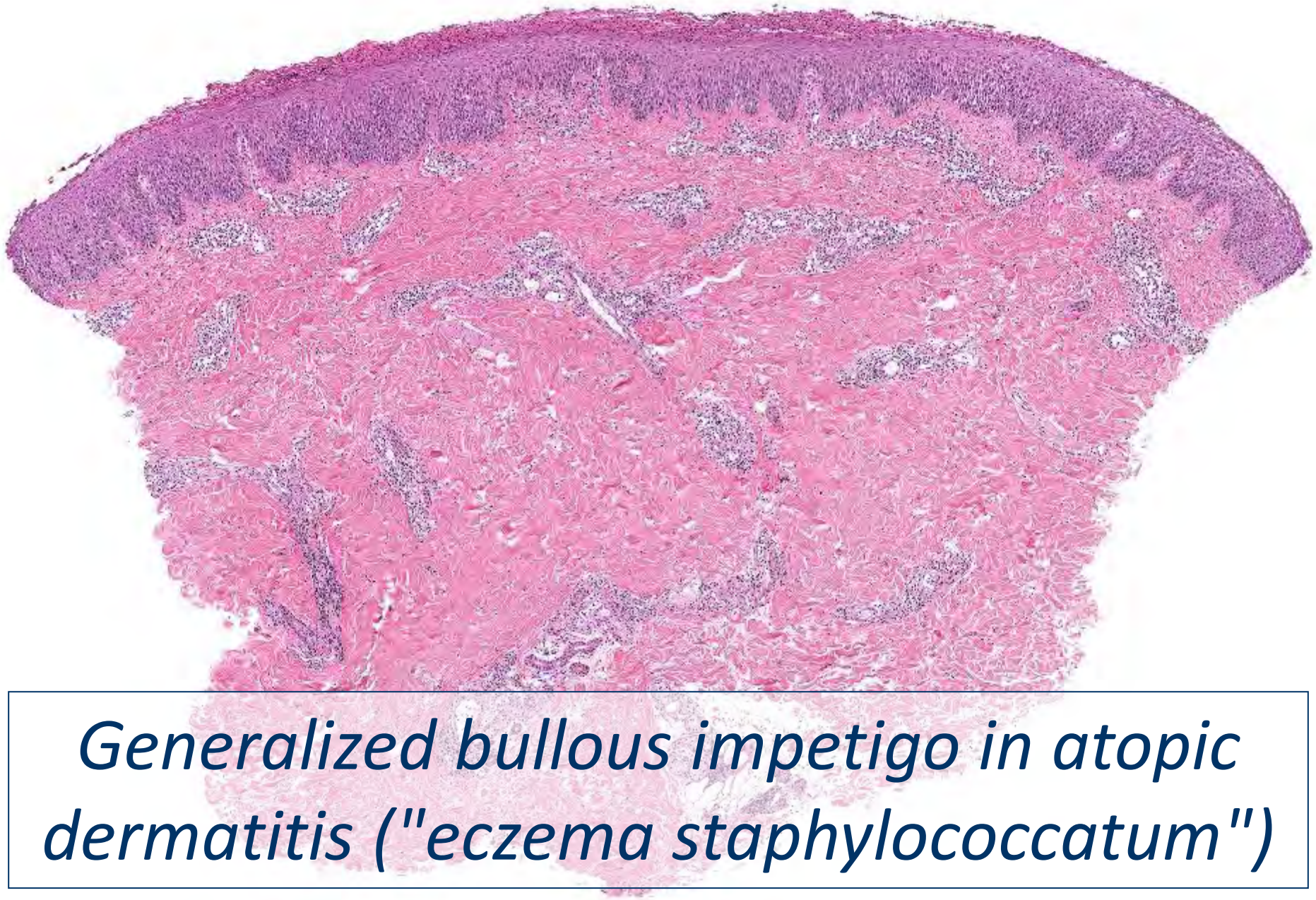












Generalized bullous impetigo in atopic dermatitis ("eczema staphylococcatum")

DOI: 10.1111/jdv.17566

Disseminated bullous impetigo in atopic dermatitis ('eczema staphylococcatum')

Editor

Atopic dermatitis (AD) is a common inflammatory skin disease, with a prevalence of up to 20% in children with wide regional variability.[1] Affected patients are at risk of developing a variety of viral and bacterial infections.[2] Disseminated viral infections, such as eczema herpeticum, eczema vaccinatum, eczema molluscatum or eczema coxsackium, are named after their causative virus and have been frequently reported in AD patients. In contrast, bacterial skin infections, particularly with *Staphylococcus aureus*, have been mainly described as localized infections or impetiginization, and reports of disseminated rashes are rare. Recently, we have noticed several cases of disseminated bullous staphylococcal impetigo in AD patients. In analogy to the disseminated viral infections in atopic skin, the term 'eczema staphylococcatum' could be used.

Patient 1: A 10 year old boy with a history of atopic dermatitis presented with acute onset of a bullous rash. Clinical examination showed generalized erosions and yellow crusts with extensive involvement of the nape and the left antecubital area (Fig. 1, left). Apart from eosinophilia (15%), laboratory tests were normal. PCR was negative for herpes simplex virus 1 and 2. A bacterial smear was positive for *S. aureus*.

Patient 2: A 24 year old patient with a history of atopic dermatitis reported progressive skin changes over one week without any systemic symptoms. Skin examination revealed an eruption of flaccid superficial bullae, some of which had ruptured leaving moist, erythematous erosions with collarette scaling and yellow crusts. The lesions started acral and accentuated on the face, neck and both antecubital areas but did rapidly disseminate to the trunk and both extremities (Fig. 1, right). Laboratory examination was normal except for a slightly elevated CRP value (12.2 mg/L) and a positive ANA titre (1:320).

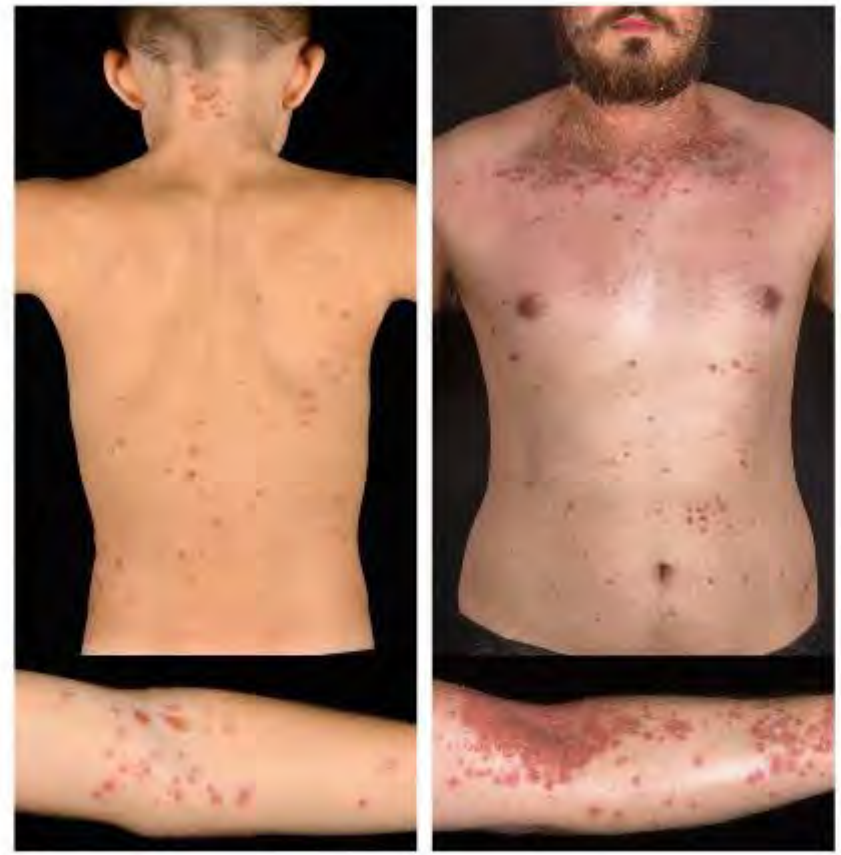


Fig. 1 Clinical finding on the trunk (top) and left antecubital area (bottom) in a 10-year-old boy showing disseminated erosions and yellow crusts (left side) and in a 24-year-old man showing an eruption of flaccid superficial bullae, which have denuded to erythematous erosions with collarette scaling and yellow crusts (right side).

1 Nenoff P, Krüger-Corcovilos M, Gebhart W. Epidemiology of cutaneous mycoses in refugees arriving in Germany. *J Dtsch Dermatol Ges* 2016; **14**: 749–57.

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None.

Conflict of interest

None declared.

I. Papadimitriou, K. Rekatz, N. Sirbiris, F. Pasmou, F. Vrani, F. Vakirlis, A. Lallas, D. Ioannides, E. Sotiriou

First Department of Dermatology-Venereology, Aristotle University of Thessaloniki, Thessaloniki, Greece

*Correspondence: e-mail: [illegible]

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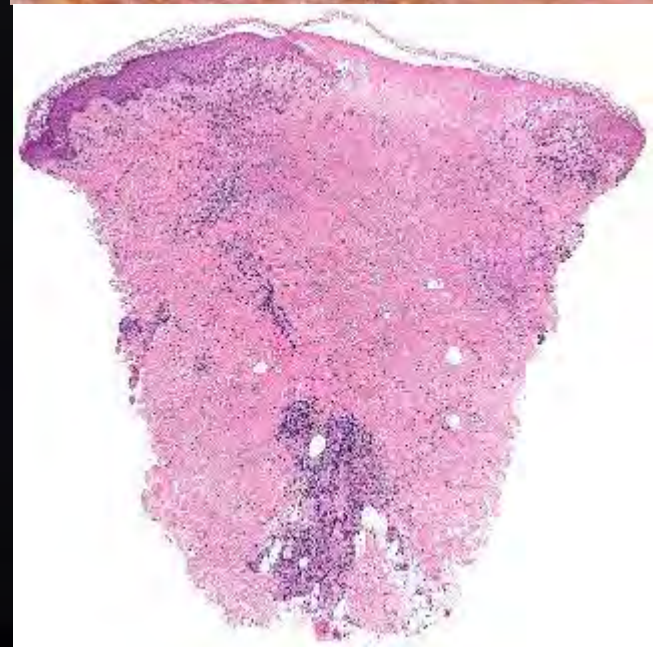
Generalized folliculitis + local steroids on atopic skin
(→ "necrotizing follicular eczema staphylococcatum")

M, 8

1st presentation

8 days later



Staphylococcus aureus colonization in atopic eczema and its association with filaggrin gene mutations

M.-L. Clausen,[1] S.M. Edslev,[2] L.S. Andersen,[1,2] K. Clemmensen,[1] K.A. Krogfelt[2] and T. Agner[3]

[1]Department of Dermatology, Bispebjerg University Hospital, Copenhagen, Denmark
[2]Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark
[3]Institute of Veterinary Science Biology, University of Copenhagen, Copenhagen, Denmark

Linked Comments: Early, Wolf. Commentary. Br J Dermatol 2016; 175:[illegible]

Summary

Background Atopic dermatitis (AD) is a prevalent disease with significant impact on physical health and quality of life. *Staphylococcus aureus* has been directly correlated to disease severity, and may also be a contributing causal factor in the pathogenesis of AD.

Objectives The primary aim was to assess differences in *S. aureus* colonization in patients with AD with and without filaggrin gene mutations. The secondary aim was to assess disease severity in relation to *S. aureus* colonization. Exploratory analyses were performed to investigate *S. aureus* genetic lineages in relation to filaggrin gene (FLG) mutations and disease severity.

Methods Adult patients with AD ($n = 101$) were included in the study. Bacteria swabs were taken from lesional skin, nonlesional skin and the nose. Swabs positive for *S. aureus* were characterized by spa and the respective clonal complex (CC) type assigned. Patients were characterized with respect to disease severity (Scoring Atopic Dermatitis) and FLG mutations ($n = 88$). Fisher's exact test was used to analyse differences in *S. aureus* colonization in relation to FLG mutations.

Results Of the 101 patients included, 74 (73%) were colonized with *S. aureus*. Of the colonized patients, 70 (95%) carried only one CC type in all three different sampling sites. In lesional skin, *S. aureus* was found in 24 of 31 patients with FLG mutations vs. 24 of 54 wild-type patients ($P = 0{\cdot}0004$). Staphylococcus aureus CC1 clonal lineage was more prevalent in patients with FLG mutations ($n = 13$) than in wild-type patients ($n = 2$) ($P = 0{\cdot}003$). No specific bacterial lineage was linked to disease severity.

Conclusions Increased *S. aureus* colonization in patients with AD with FLG mutations, and increased prevalence of CC1 in patients with FLG mutations, suggest that host–microbe interactions and clonal differences in *S. aureus* are important for colonization of AD skin.

What's already known about this topic?

- Staphylococcus aureus is a colonizing and a worsening factor in the pathogenesis of atopic dermatitis (AD).
- Staphylococcus aureus [illegible] and specific clonal lineages [illegible] in AD and other diseases.

What does this study add?

- Staphylococcus aureus colonization of the nose and lesional skin is increased in patients with AD with FLG mutations.
- The *S. aureus* clonal lineage was identical in isolates from three distinct sample sites in patients with AD.
- Staphylococcus aureus CC1 is associated with FLG mutations in patients with AD.

Correspondence
Maja-Lis Clausen
E-mail: mlclausen@dadlnet.dk

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Conflicts of interest
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The role of the skin microbiome in atopic dermatitis: a systematic review*

R.D. Bjerre,[1] J. Bandier,[2] L. Skov,[2] L. Engstrand[3] and J.D. Johansen[1]

[1]National Allergy Research Centre and [2]Department of Dermatology and Allergy Centre and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[3]Department of Microbiology, Tumor and Cell Biology and Center for Translational Microbiome Research, Karolinska Institutet and Science for Life Laboratory, Stockholm, Sweden

Summary

Dysbiosis is a hallmark of atopic dermatitis (AD). The composition of skin microbiome communities and the causality of dysbiosis in eczema have not been well established. The objective of this review is to describe the skin microbiome profile in AD and address whether there is a causal relationship between dysbiosis and AD. The protocol is registered in PROSPERO (CRD42016035813). We searched PubMed, Embase, Scopus and ClinicalTrials.gov for primary research studies applying culture independent analysis on the microbiome on AD skin of humans and animal models. Two authors independently screened the full text of studies for eligibility and assessed risk of bias. Because of heterogeneity no quantitative synthesis was done. Of 5735 hits, 32 met the inclusion criteria (19 published 13 human and six animal studies). The studies varied in quality and applied different methodology. The skin in AD had 'low bacterial' diversity (lowest at eczematous-involved sites) and three studies showed depletion of Malassezia spp. and high non-Malassezia fungal diversity. The relative abundance of Staphylococcus aureus and Staphylococcus epidermidis were greater and other genera were reduced, including Propionibacterium. A mouse survey indicated that dysbiosis is a driving factor in eczema pathogenesis. The data are not sufficiently robust for good characterization; however, dysbiosis in AD not only implicates Staphylococcus spp., but also microbes such as Propionibacterium and Malassezia. A causal role of dysbiosis in eczema in mice should encourage future studies to investigate if this also applies to humans. Other important aspects are temporal dynamics and the influence of methodology on microbiome data.

What's already known about this topic?

- Dysbiosis is a hallmark of atopic eczema (AD). Staphylococcus aureus colonization is associated with disease severity currently.
- Recent availability of culture independent methods to profile microorganisms has enabled studies of the microbiome on AD skin and other skin diseases.

What does this study add?

- AD skin has 'low' bacterial diversity, high non-Malassezia fungal diversity, high abundance of *S. aureus* and *Staphylococcus epidermidis* and reduced abundance of other genera.
- An animal study indicates that dysbiosis is a driving factor in eczema.
- A role for the microbiome in AD and the influence of methodological approaches needs to be resolved.

Correspondence
R.D. Bjerre
E-mail: rasmus.bjerre@regionh.dk

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Conflicts of interest
None declared.

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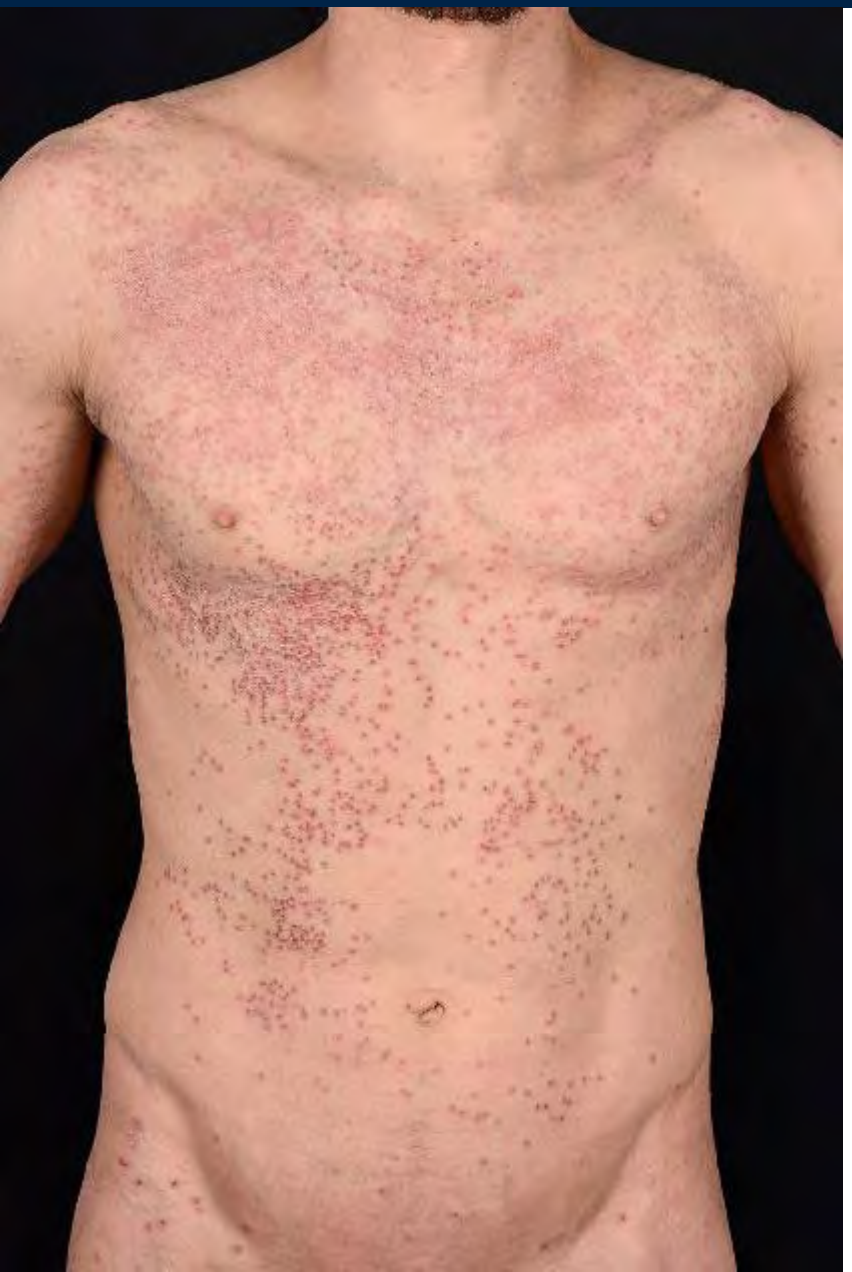
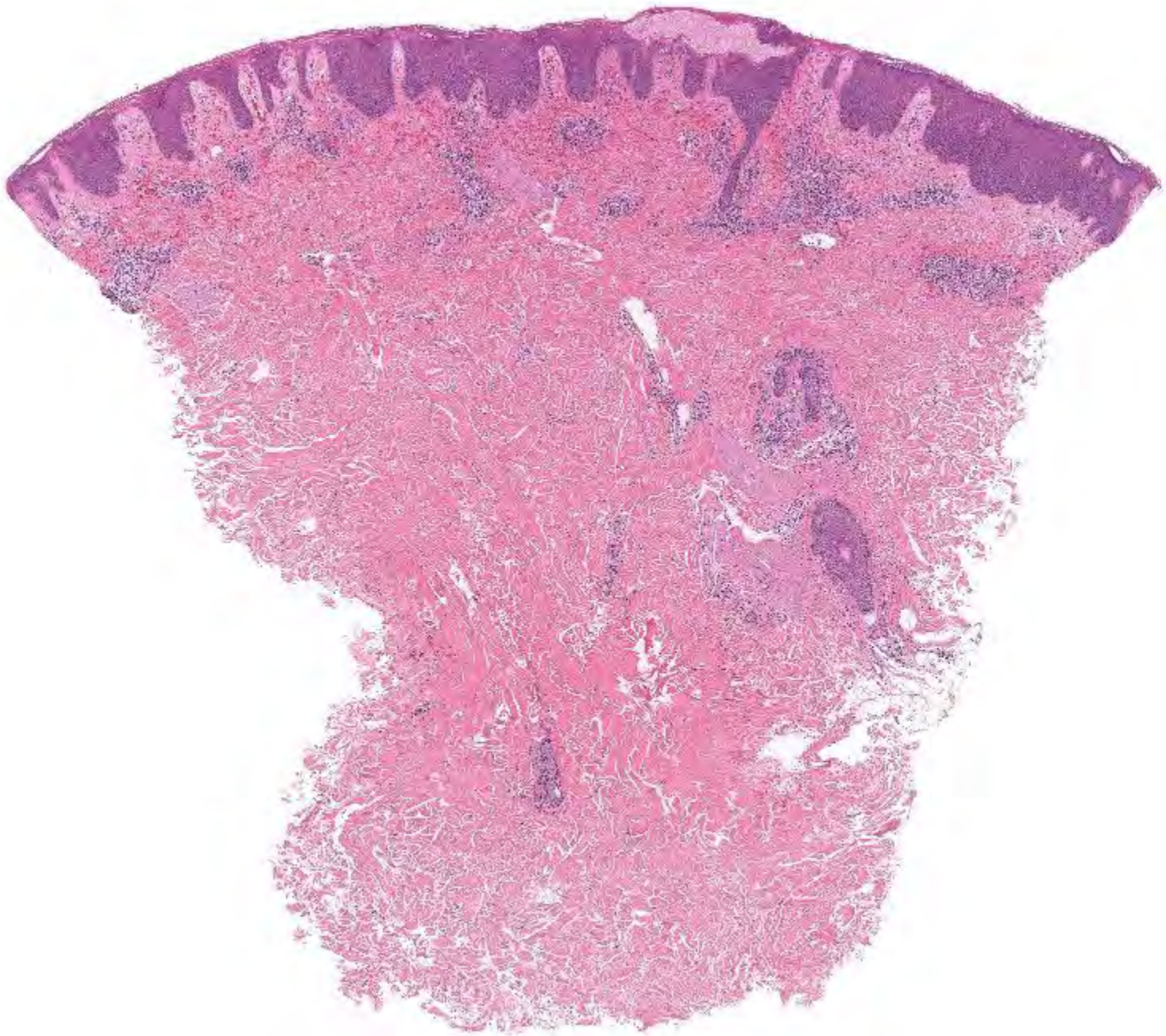
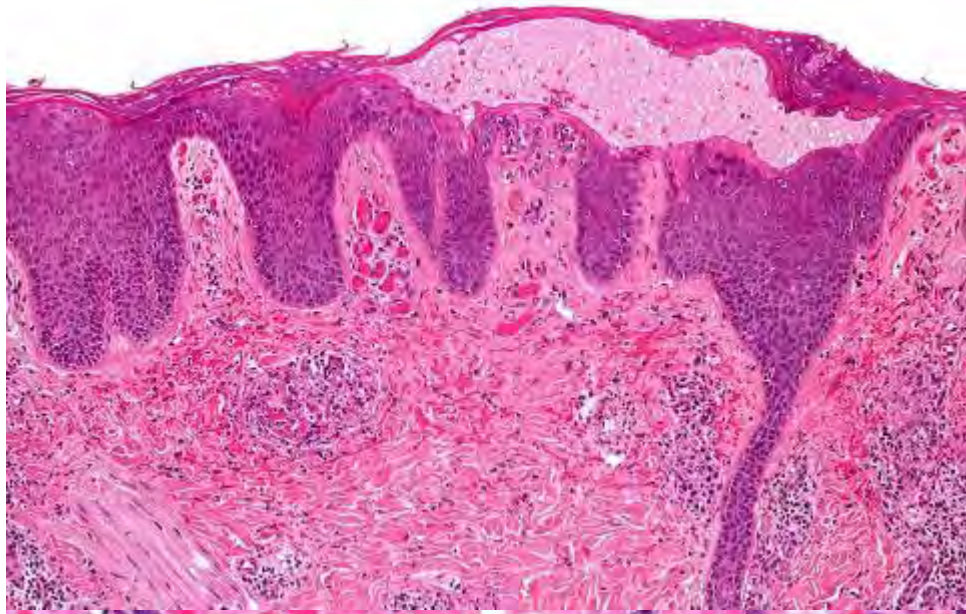
Atopic dermatitis & skin infections

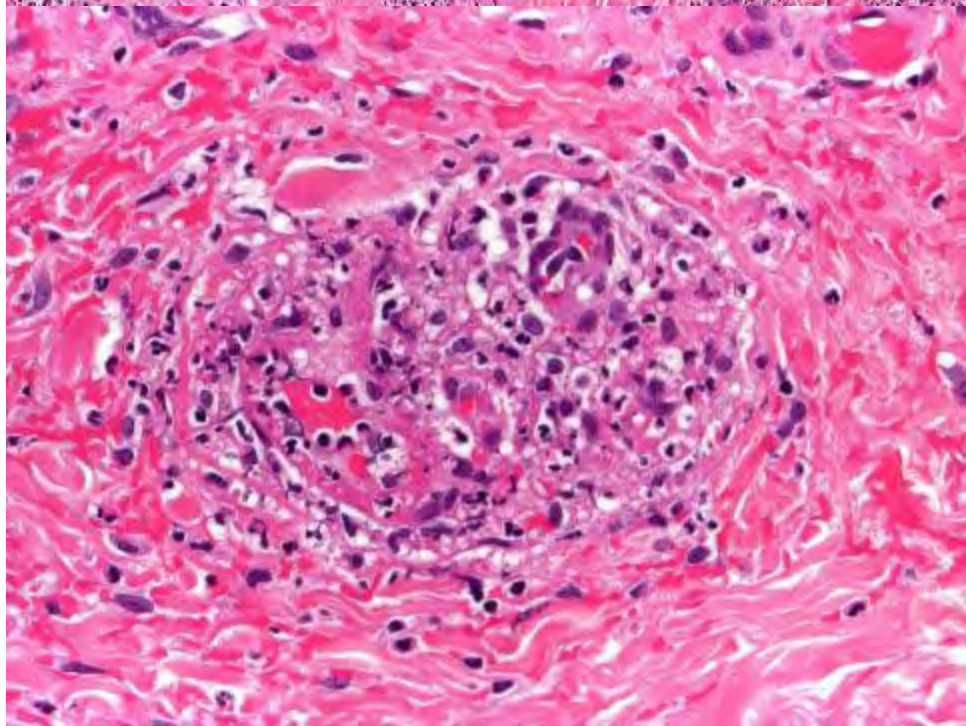


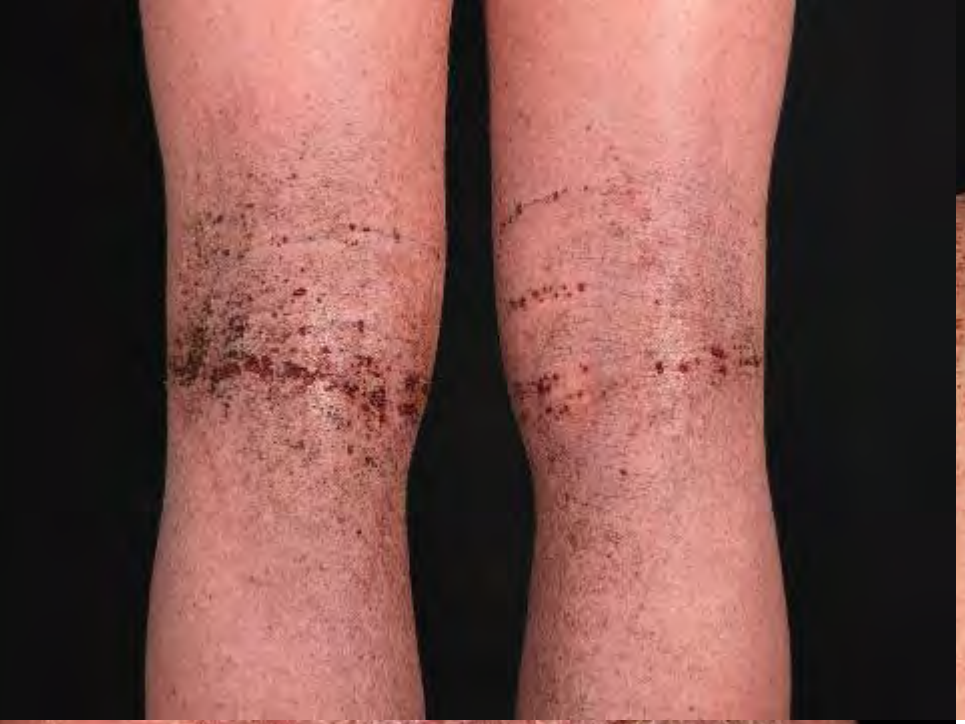
- Eczema herpeticum
- Eczema vaccinatum
- Eczema molluscatum
- Eczema coxsackium
- Eczema staphylococcatum
- *Histopathological features of ezema herpeticum may be very subtle and without clear-cut aspects of herpes infection*

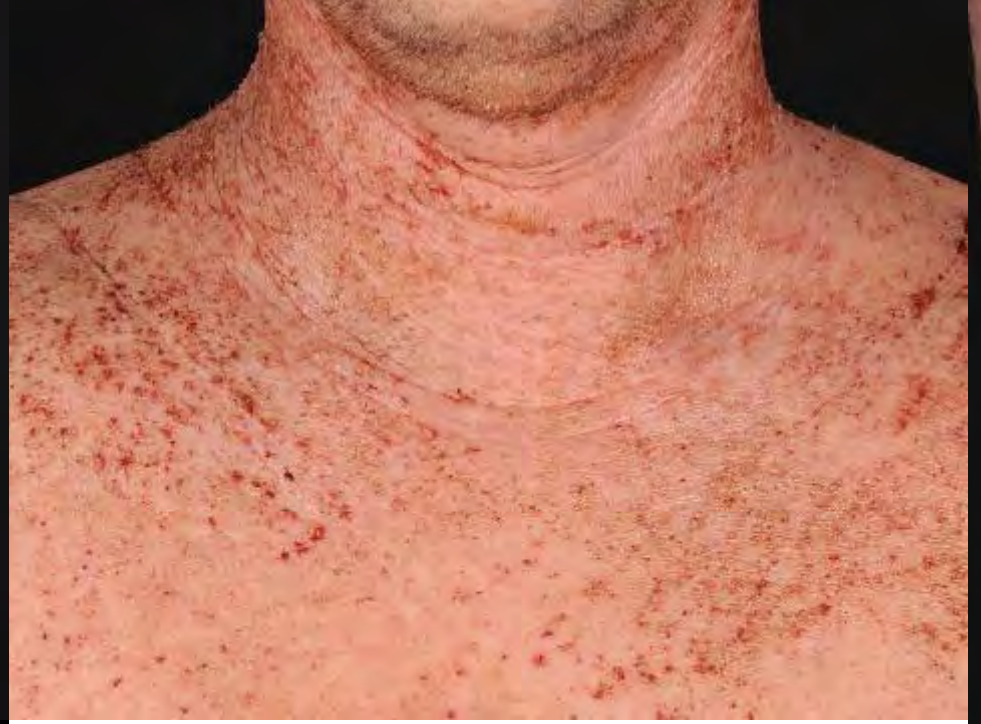
M, 33. Long history of atopic dermatitis. Sudden development of crusted, hemorrhagic lesions on the entire body.

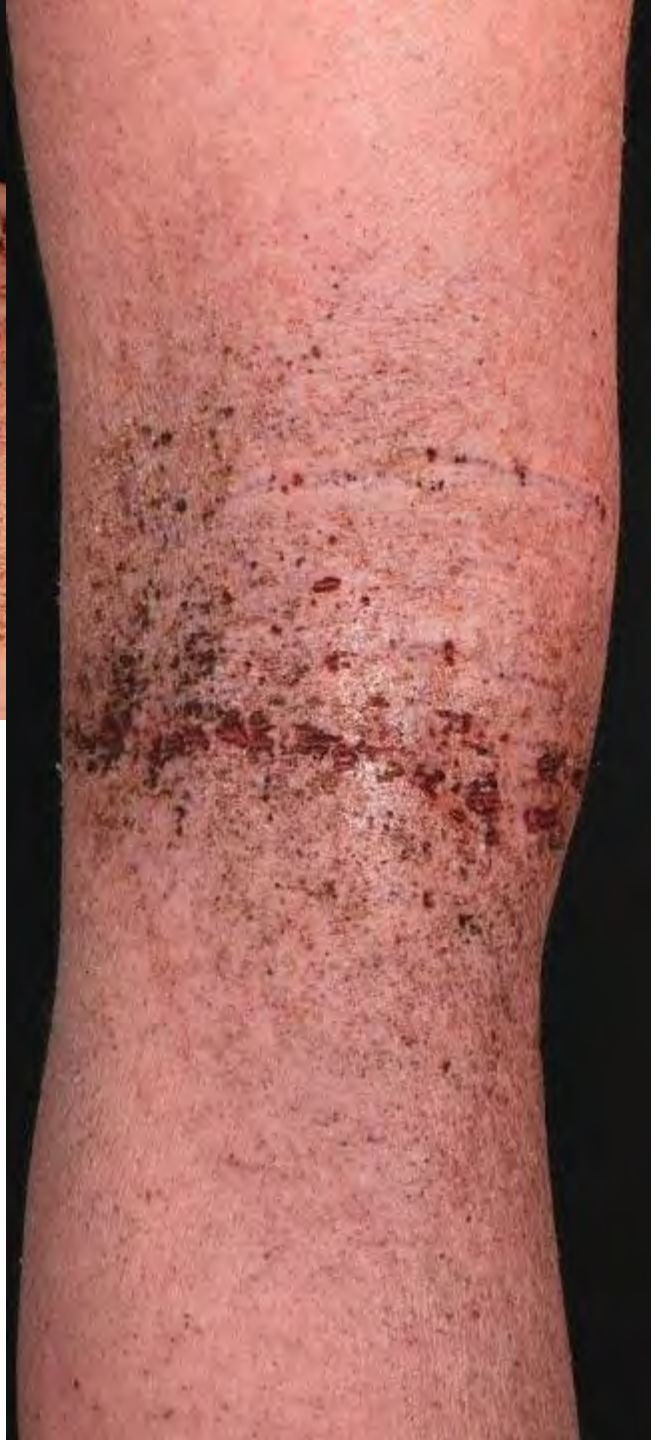


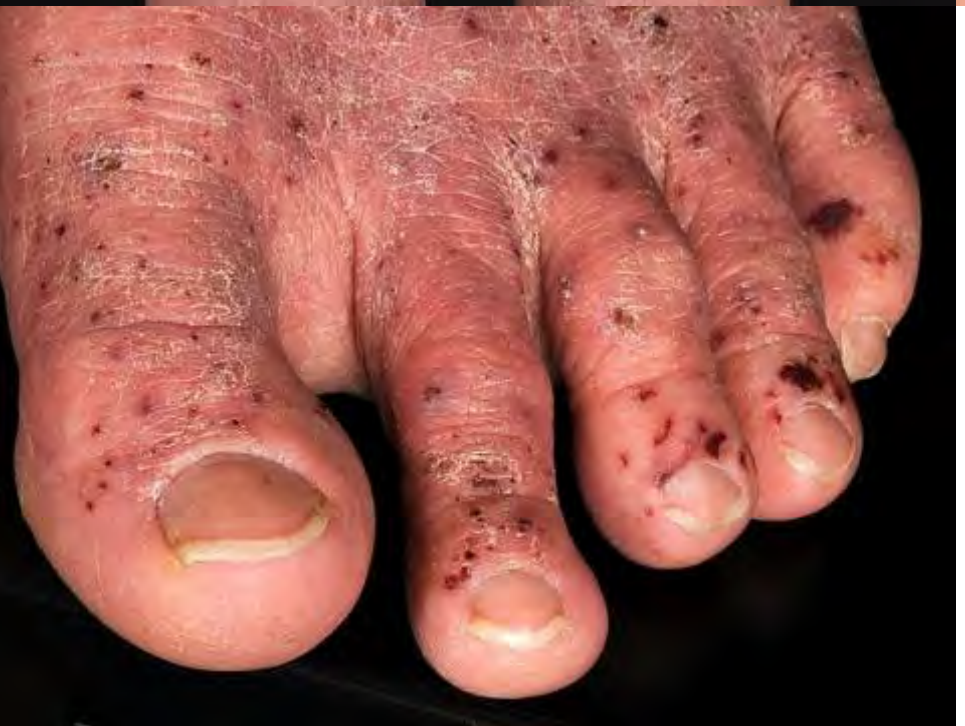


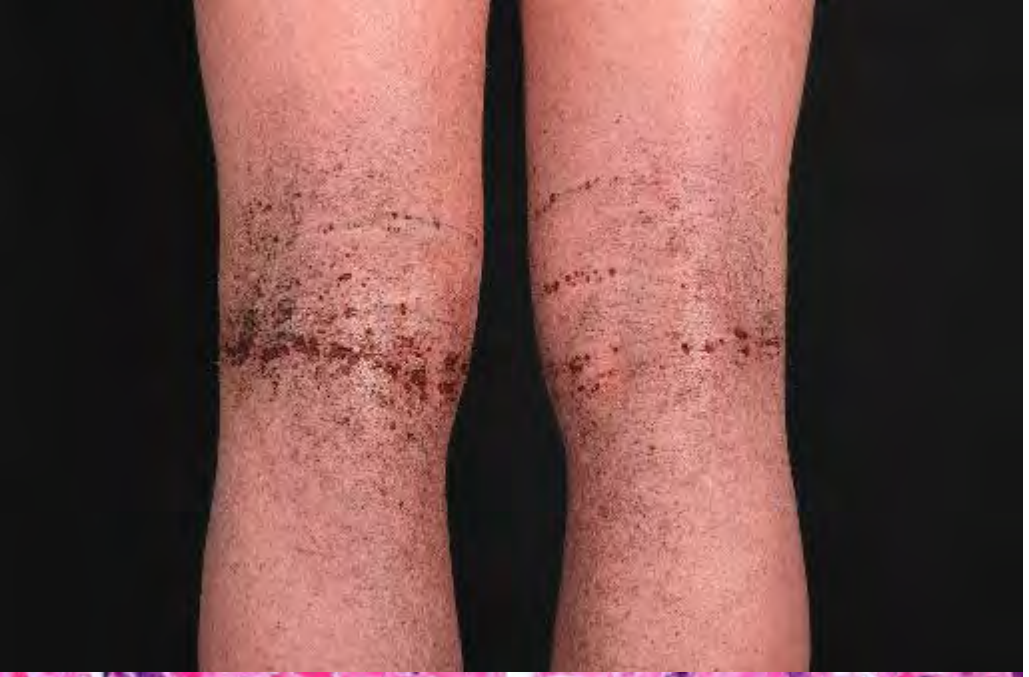


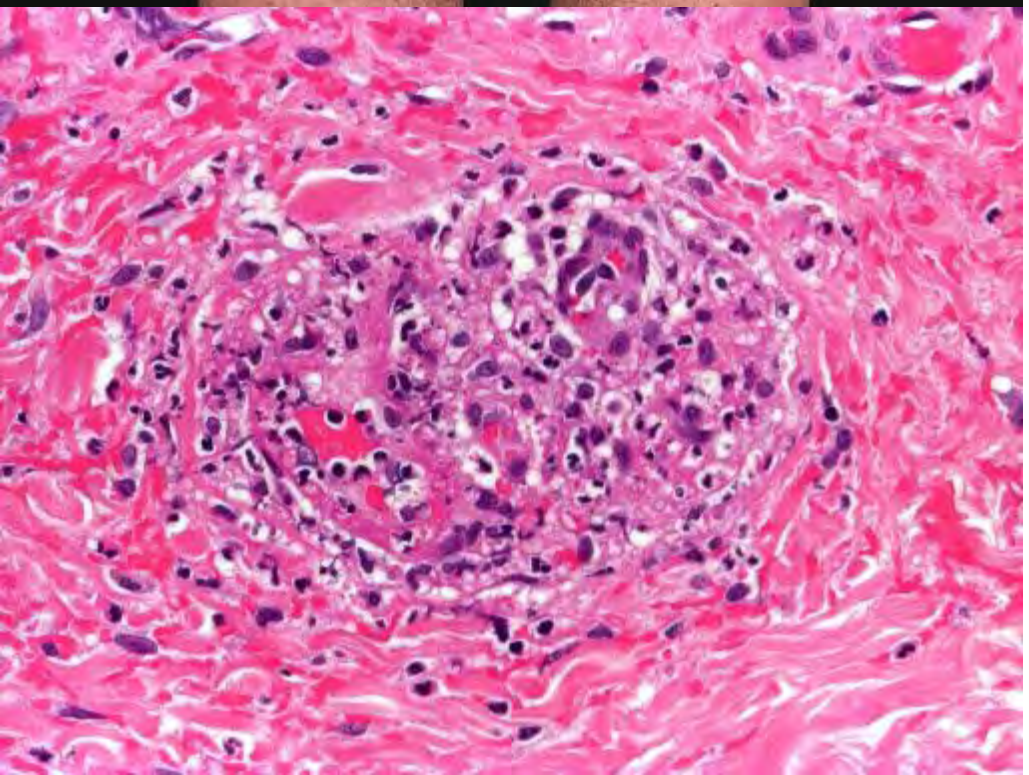


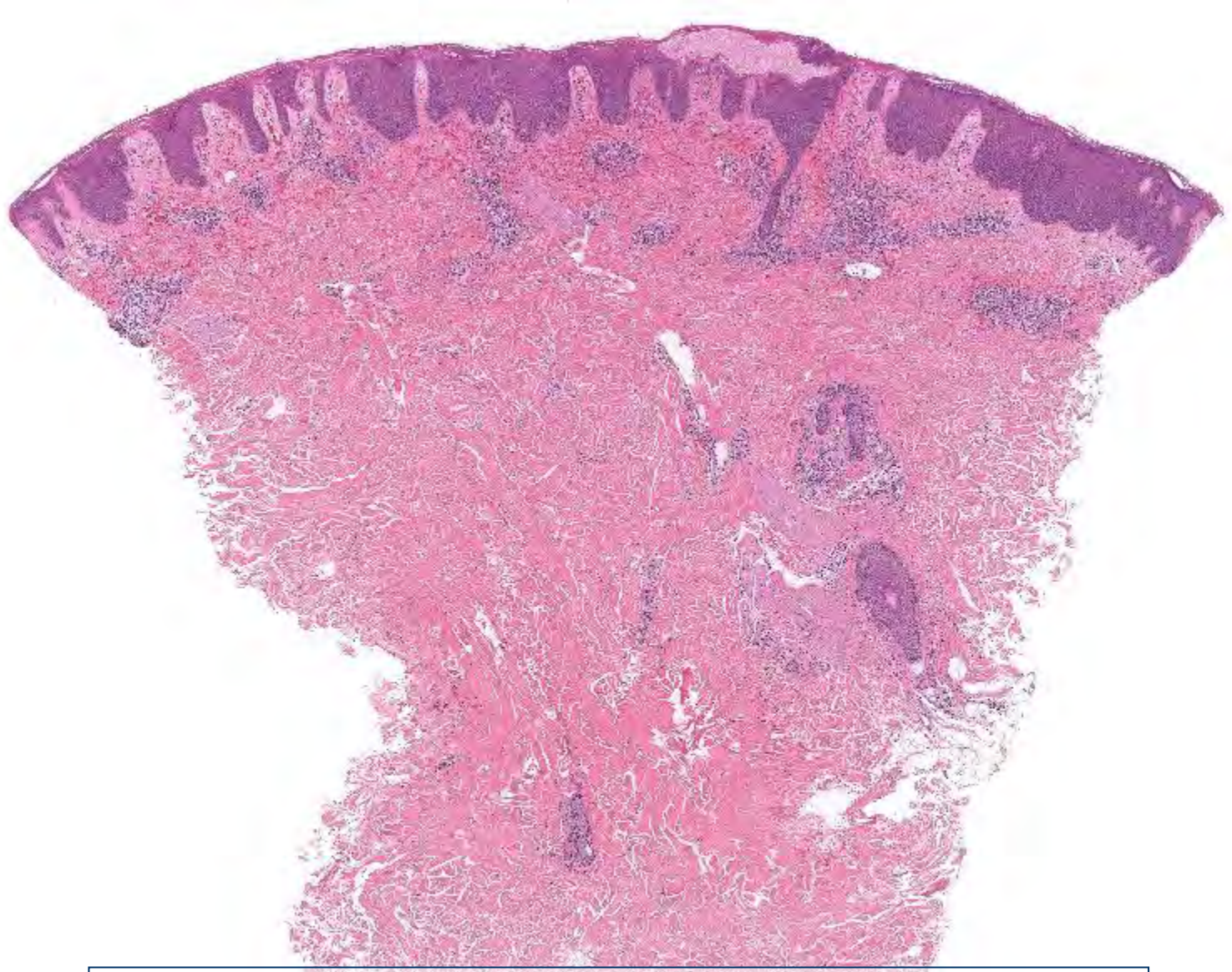




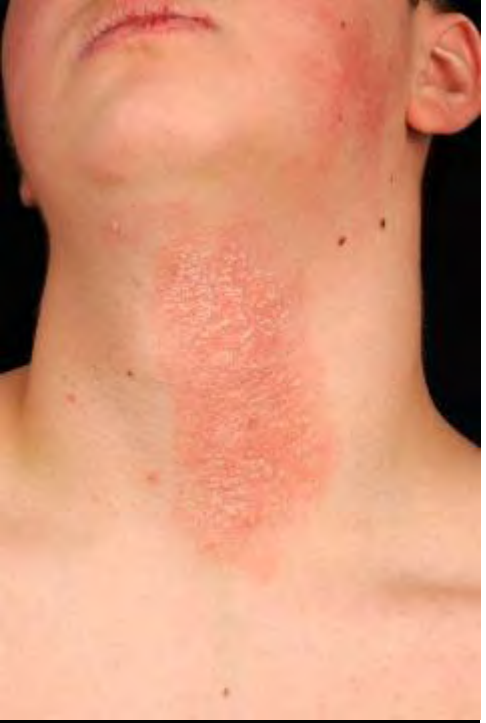


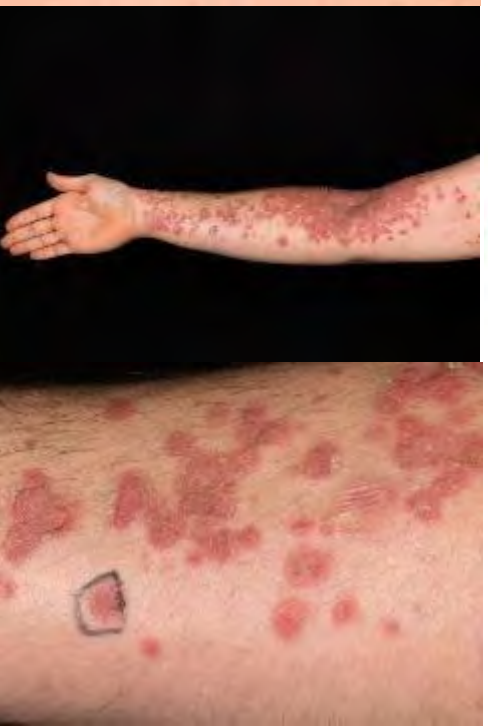


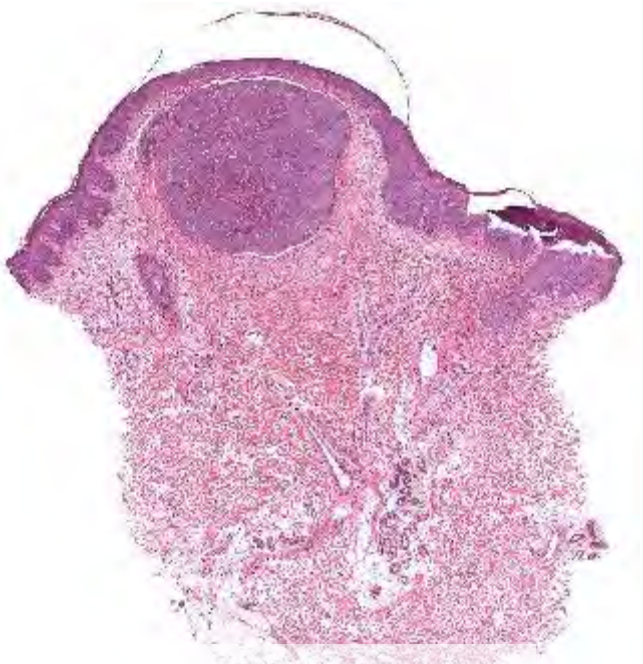




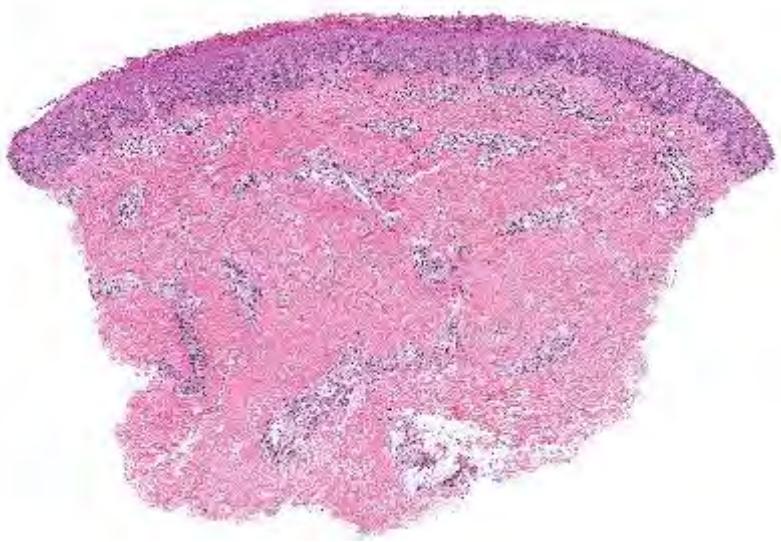
Generalized leukocytoclastic vasculitis in atopic dermatitis



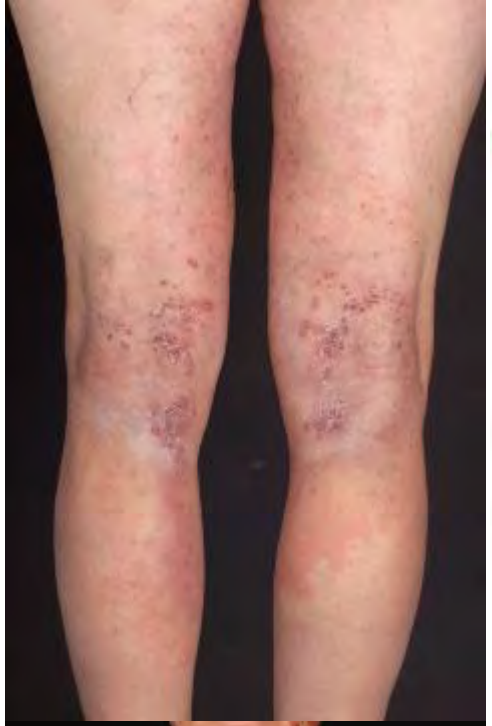


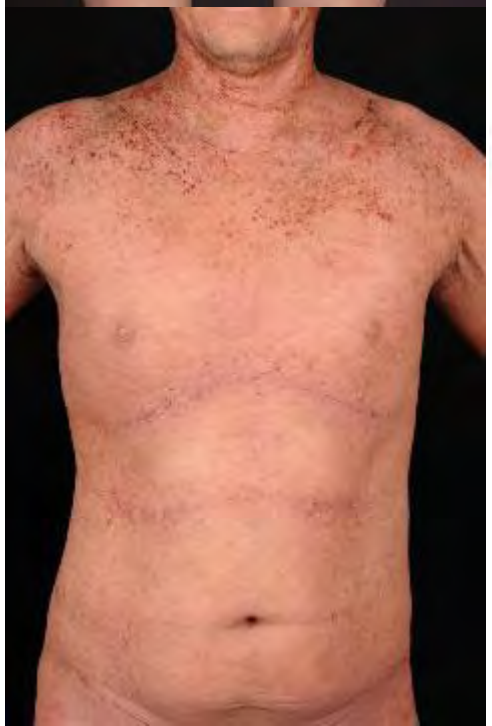


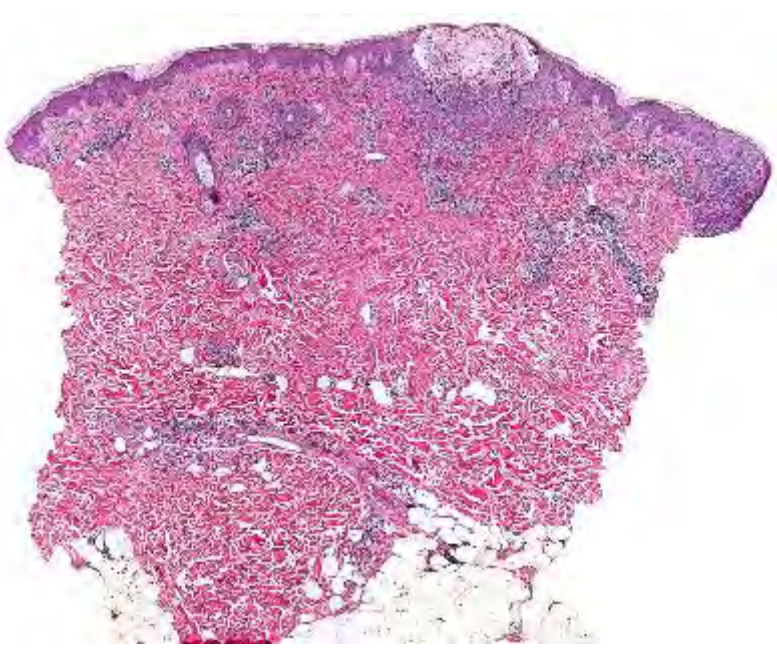
Eczema "molluscatum"



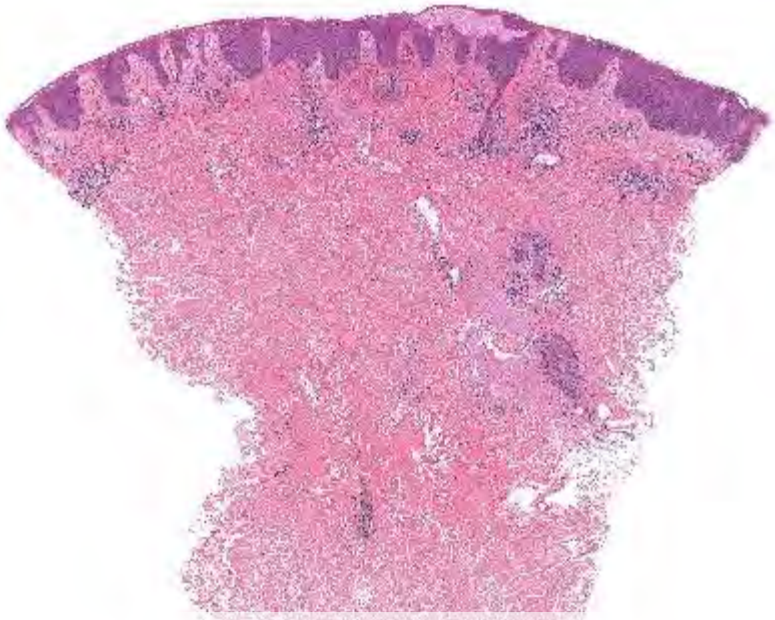
Eczema "staphylococcatum"



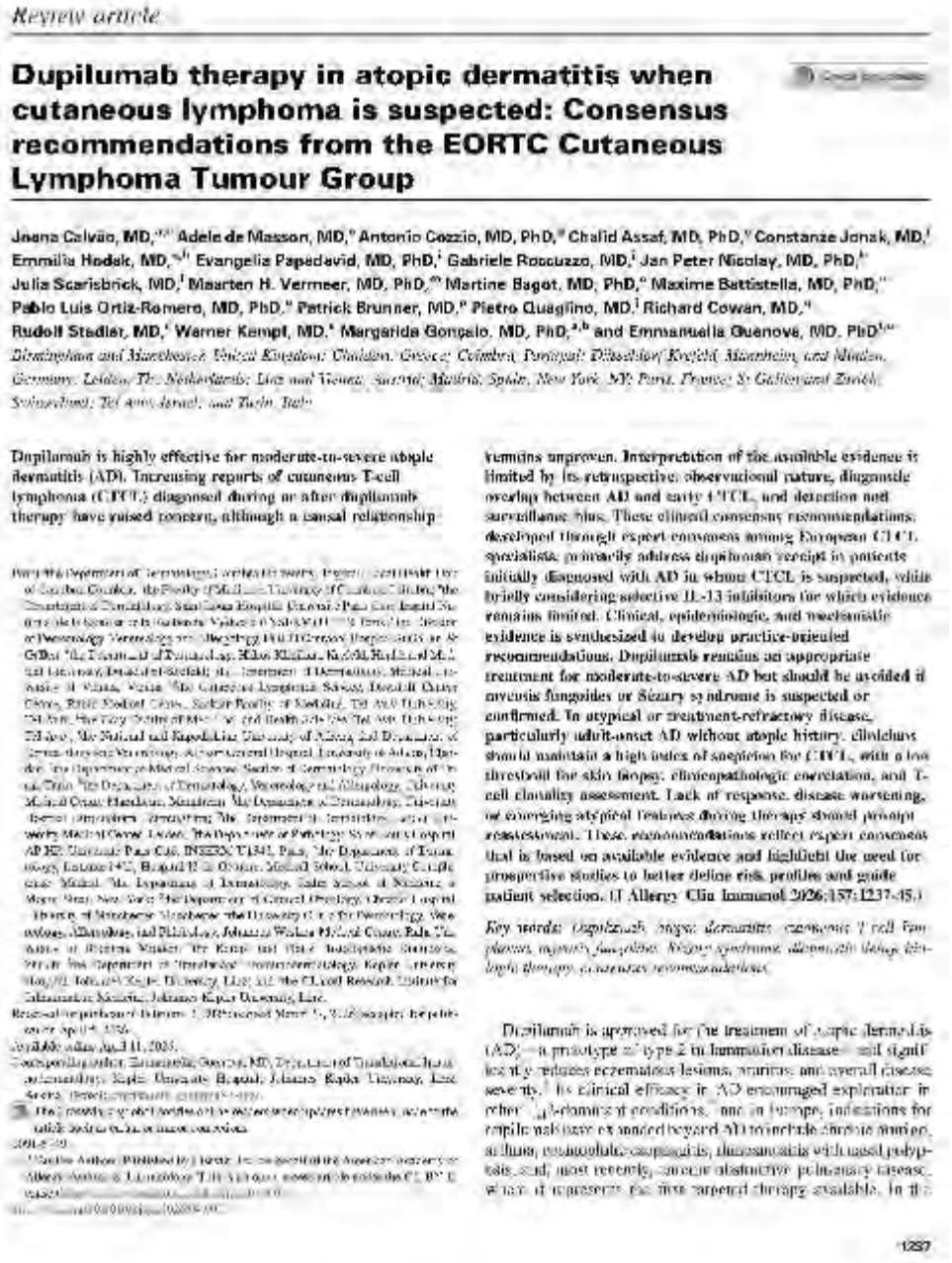




Eczema "herpeticum"



Eczema "vasculiticum"



Review article

Dupilumab therapy in atopic dermatitis when cutaneous lymphoma is suspected: Consensus recommendations from the EORTC Cutaneous Lymphoma Tumour Group

Joana Calvão, MD,[a,b] Adele de Masson, MD,[c] Antonio Cozzio, MD, PhD,[d] Chalid Assaf, MD, PhD,[e] Constanze Jonak, MD,[f] Emmilia Hodak, MD,[g,h] Evangelia Papadavid, MD, PhD,[i] Gabriele Roccuzzo, MD,[j] Jan Peter Nicolay, MD, PhD,[k] Julia Scarisbrick, MD,[l] Maarten H. Vermeer, MD, PhD,[m] Martine Bagot, MD, PhD,[n] Maxime Battistella, MD, PhD,[o] Pablo Luis Ortiz-Romero, MD, PhD,[p] Patrick Brunner, MD,[q] Pietro Quaglino, MD,[r] Richard Cowan, MD,[s] Rudolf Stadler, MD,[t] Werner Kempf, MD,[u] Margarida Gonçalo, MD, PhD,[a,b] and Emmanuella Guenova, MD, PhD[v,w]

Birmingham and Manchester, United Kingdom; Chaidari, Greece; Coimbra, Portugal; Düsseldorf, Krefeld, Mannheim, and Minden, Germany; Leiden, The Netherlands; Linz and Vienna, Austria; Madrid, Spain; New York, NY; Paris, France; St Gallen and Zurich, Switzerland; Tel Aviv-Jaffa, Israel; and Turin, Italy

Dupilumab is highly effective for moderate-to-severe atopic dermatitis (AD). Increasing reports of cutaneous T-cell lymphoma (CTCL) diagnosed during or after dupilumab therapy have raised concern, although a causal relationship remains unproven. Interpretation of the available evidence is limited by its retrospective observational nature, diagnostic overlap between AD and early CTCL, and detection and surveillance bias. These clinical consensus recommendations, developed through expert consensus among European CTCL specialists, primarily address dupilumab receipt in patients initially diagnosed with AD in whom CTCL is suspected, while briefly considering selective IL-13 inhibitors for which evidence remains limited. Clinical, epidemiologic, and mechanistic evidence is synthesized to develop practice-oriented recommendations. Dupilumab remains an appropriate treatment for moderate-to-severe AD but should be avoided if mycosis fungoides or Sézary syndrome is suspected or confirmed. In atypical or treatment-refractory disease, particularly adult-onset AD without atopic history, clinicians should maintain a high index of suspicion for CTCL, with a low threshold for skin biopsy, clinicopathologic correlation, and T-cell clonality assessment. Lack of response, disease worsening, or emerging atypical features during therapy should prompt reassessment. These recommendations reflect expert consensus that is based on available evidence and highlight the need for prospective studies to better define risk profiles and guide patient selection. (J Allergy Clin Immunol 2026;157:1237-45.)

Key words: Dupilumab; atopic dermatitis; cutaneous T cell lymphoma; mycosis fungoides; Sézary syndrome; alternative biologic therapy; consensus recommendations

Dupilumab is approved for the treatment of atopic dermatitis (AD)—a prototype of type 2 inflammatory disease—and significantly reduces eczematous lesions, pruritus, and overall disease severity.[1] Its clinical efficacy in AD encouraged exploration in other [illegible] conditions, and in Europe, indications for [illegible] have expanded beyond AD to include chronic rhinosinusitis with nasal polyposis and, most recently, chronic obstructive pulmonary disease, where it represents the first approved therapy available. In the

"CTCL diagnoses occurring during dupilumab therapy have generated debate regarding whether these cases primarily represent unmasking of previously unrecognized lymphoma or true disease acceleration. These observations can be interpreted in at least 3 non–mutually exclusive ways. First, many cases likely represent unmasking of previously unrecognized CTCL (…). Second, confounding by indication may contribute, as patients with severe or treatment-refractory AD are more likely to receive dupilumab and have been reported to have a higher baseline risk of lymphoma, including CTCL. Third, a smaller subset of cases characterized by rapid clinical deterioration after treatment initiation has raised concern for disease acceleration, although causality remains unproven. Taken together, current evidence suggests that unmasking and diagnostic delay account for many reported cases, while a contributory role of dupilumab in rare cases cannot be definitively excluded."

Review article

Dupilumab therapy in atopic dermatitis when cutaneous lymphoma is suspected: Consensus recommendations from the EORTC Cutaneous Lymphoma Tumour Group

Joana Calvão, MD,[a,b] Adele de Masson, MD,[c] Antonio Cozzio, MD, PhD,[d] Chalid Assaf, MD, PhD,[e] Constanze Jonak, MD,[f] Emmilia Hodak, MD,[g,h] Evangelia Papadavid, MD, PhD,[i] Gabriele Roccuzzo, MD,[j] Jan Peter Nicolay, MD, PhD,[k] Julia Scarisbrick, MD,[l] Maarten H. Vermeer, MD, PhD,[m] Martine Bagot, MD, PhD,[n] Maxime Battistella, MD, PhD,[o] Pablo Luis Ortiz-Romero, MD, PhD,[p] Patrick Brunner, MD,[q] Pietro Quaglino, MD,[r] Richard Cowan, MD,[s] Rudolf Stadler, MD,[t] Werner Kempf, MD,[u] Margarida Gonçalo, MD, PhD,[a,b] and Emmanuella Guenova, MD, PhD[v,w]

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		Recommendation	Agreement / Comment
Clinical scenario warranting caution	3	Clinicians should maintain a high index of suspicion for CTCL in atypical cases of AD, particularly in new-onset AD in adults aged >40 years, especially without personal or family history of atopy and/or with atypical clinical features.	100%	Clinical features suggestive of CTCL may include asymmetrical patches/plaques, predilection for bathing-trunk area, follicular lesions (particularly with alopecia), or erythroderma.
	6	In patients with suspected or confirmed CTCL, dupilumab should be avoided.	94%	Decisions should be individualized.
	7	Its use may be considered in exceptional circumstances, for example for management of refractory pruritus in palliative setting, and only after thorough discussion of potential risks and benefits with patient.	82%	Where available, alternative agents (eg, nemolizumab) may be considered.
	9	In patients with confirmed coexisting AD and CTCL, dupilumab should generally be avoided.	88%	Avoid if possible; see recommendation 7 for exceptions.

Possible interpretations of the onset of CTCL in patients who receive dupilumab:

1) Wrong baseline diagnosis: dupilumab unmasks previously unrecognized CTCL.
2) Pseudo-association: dupilumab is given mostly to patients with severe AD, who also have a higher risk of lymphoma, including CTCL.
3) Dupilumab causes CTCL acceleration.

Atopic dermatitis & other skin disorders

- Cutaneous infections (*herpes*, bacteria, molluscum contagiosum) more common in patients with AD (impaired barrier function); eczema herpeticum may be lethal; possible dissemination of other cutaneous disorders (e.g., vasculitis)
- Ichthyosis vulgaris in ~15% of patients with AD (and AD in ~50% of patients with ichthyosis vulgaris)
- Usually not concomitant with psoriasis (but both diseases may be present simultaneously in a given patient, particularly in the elderly)
- Association with CTCL still debated (but ↑risk of developing CTCL in severe AD); high index of suspicion in unclear cases; biopsy, clonality study in skin and blood
- Role of dupilumab unclear (unmasking undiagnosed CTCL? Causing acceleration of secondary CTCL?); Individualized decision re. dupilumab use in severe AD

Atopic & "atopic-like" dermatitis

- Atopic dermatitis (allergen-specific IgE Abs in serum, typical clinical manifestations, asthma, rhinitis – atopic diathesis)
- Mutations in the filaggrin gene (*FLG*) are responsible for ichthyosis vulgaris and represent a major predisposing factor for atopic dermatitis; early postzygotic loss of heterozygosity may be responsible for linear forms (superimposed AD)
- Great variation in clinical presentation; corresponding variation in histopathologic features
- *Broad spectrum of atopic-like dermatitis* (e.g., xerosis in the elderly, side-effects of some treatment, etc.)