GEORG-AUGUST-UNIVERSITÄT GÖTTINGEN IN PUBLICA COMMODA SEIT 1737

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Teaching cases from Göttingen with clinico-pathological correlation

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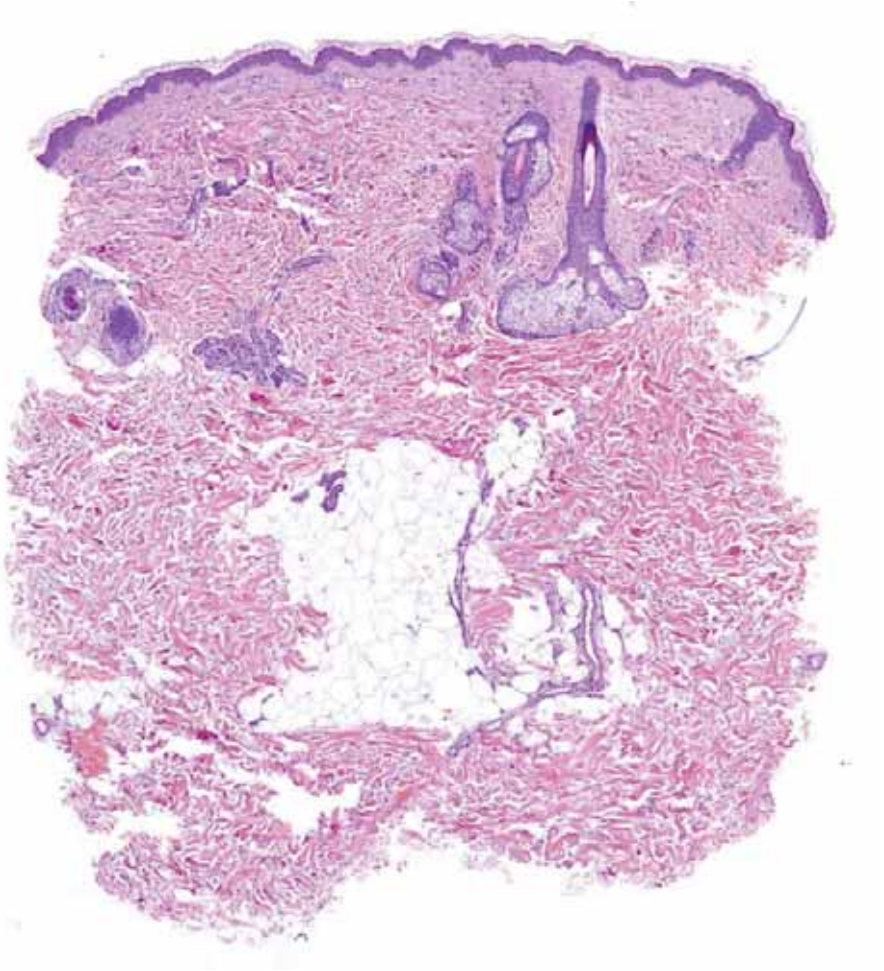
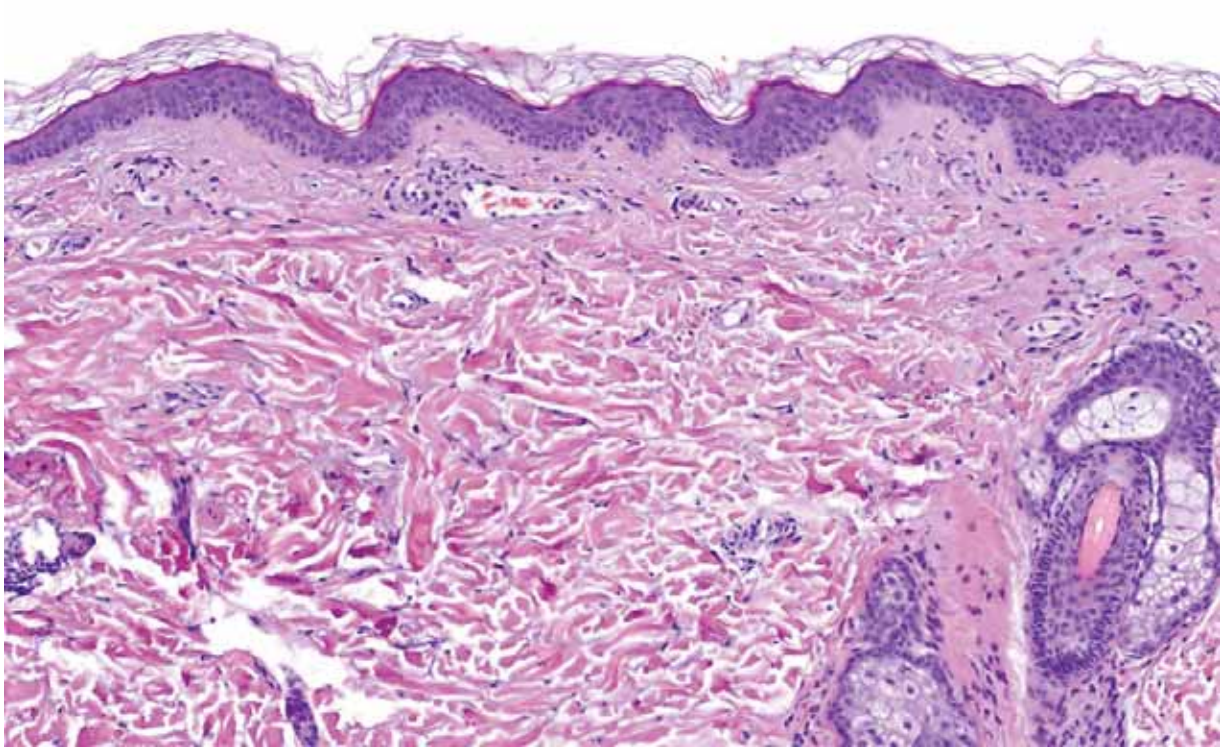
Österreich
Basel
Zürich
Dijon
Innsbruck
Graz
Schweiz
Lausanne
Genf
Slowenien


»Die Wand«

Histology





18-year-old women, circumscribed erythema
Upper trunk and arms

Invisible dermatosis

Invisible dermatosis for dermatopathologist / pathologist refers to skin diseases where no or minimal changes can be detected with standard H&E sections, despite a clear clinical presentation.

Clinical pathologic correlation (CPC)

Helpful special stains:

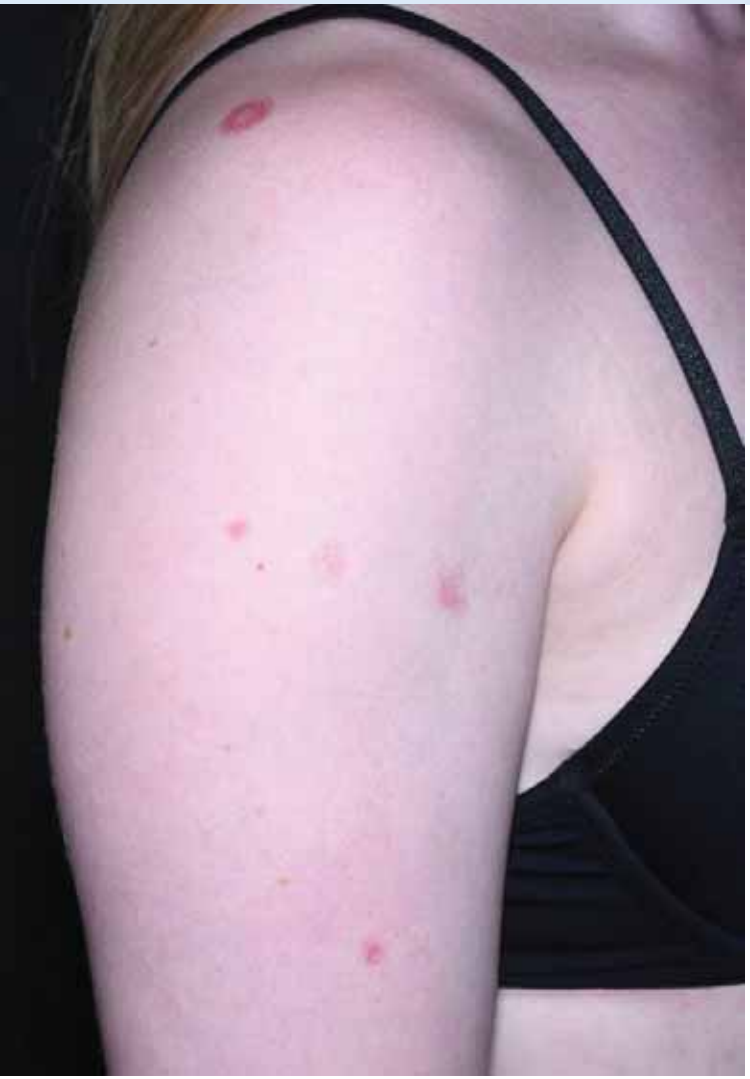
- PAS
- Alcian
- Elastica
- Giemsa
- Step sections
- Immunostains: e.g. CD117

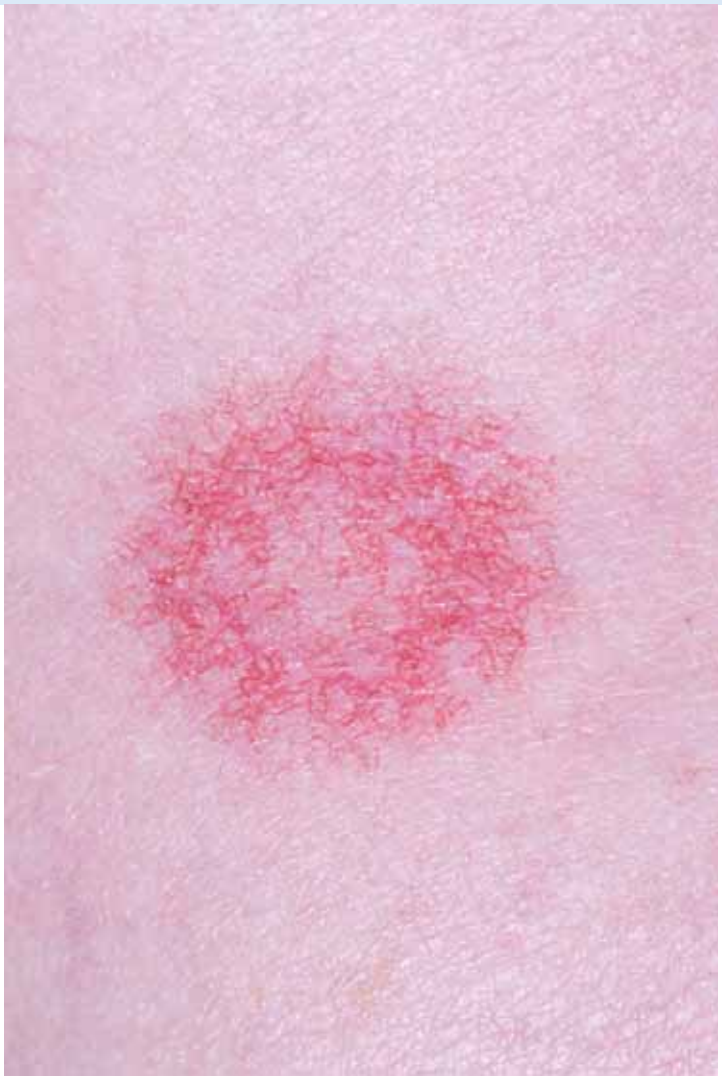
Table 2: Invisible dermatoses of the pathologist

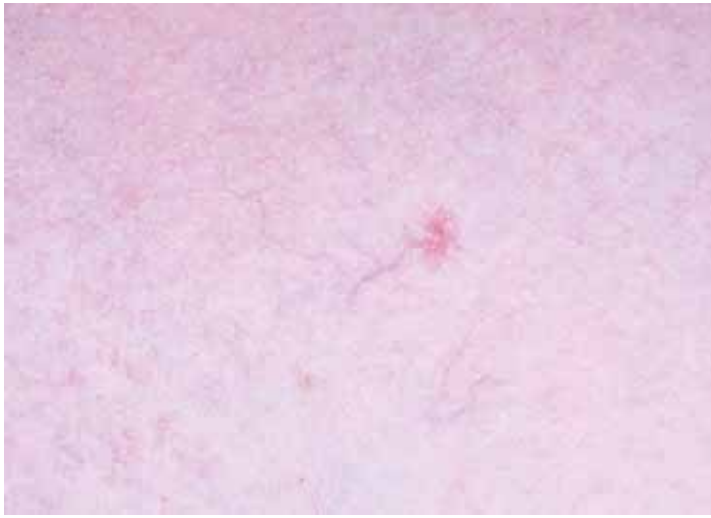
1. Fungal infections (Tinea versicolor, Tinea corporis)
2. Scabies
3. Secondary syphilis
4. Indeterminate leprosy
5. Plane warts
6. Cutaneous leishmaniasis
7. Pityriasis rosea
8. Guttate psoriasis
9. Parapsoriasis both large plaque and small plaque types
10. Granuloma annulare
11. Porokeratosis
12. Mastocytosis
13. Ichthyosis vulgaris
14. Macular amyloidosis
15. Pseudoxanthoma elasticum, anetoderma and nevus elasticus
16. Scleroderma/atrophoderma of Pasini and Pierini lipoatrophy
17. Scleredema Buschke, other mucinoses
18. Argyria
19. Pigmentary lesions such as vitiligo, or cafe au lait spot, dermal melanosis, haemochromatosis, hypomelanosis of Ito, ash leaf macules of tuberous sclerosis.
20. Graft versus host disease
22. Lupus erythematosus
23. Metastatic deposits
24. Blue nevi, Becker's nevus
25. Tumors: Large cell acanthoma, syringoma, atrophic and superficial variants of basal cell epithelioma, some variants of actinic keratosis and Bowen's disease, mycosis fungoides in patch stage
26. Adnexal diseases: anhidrotic ectodermal dysplasia, argyria, mercury pigmentation, alopecia areata

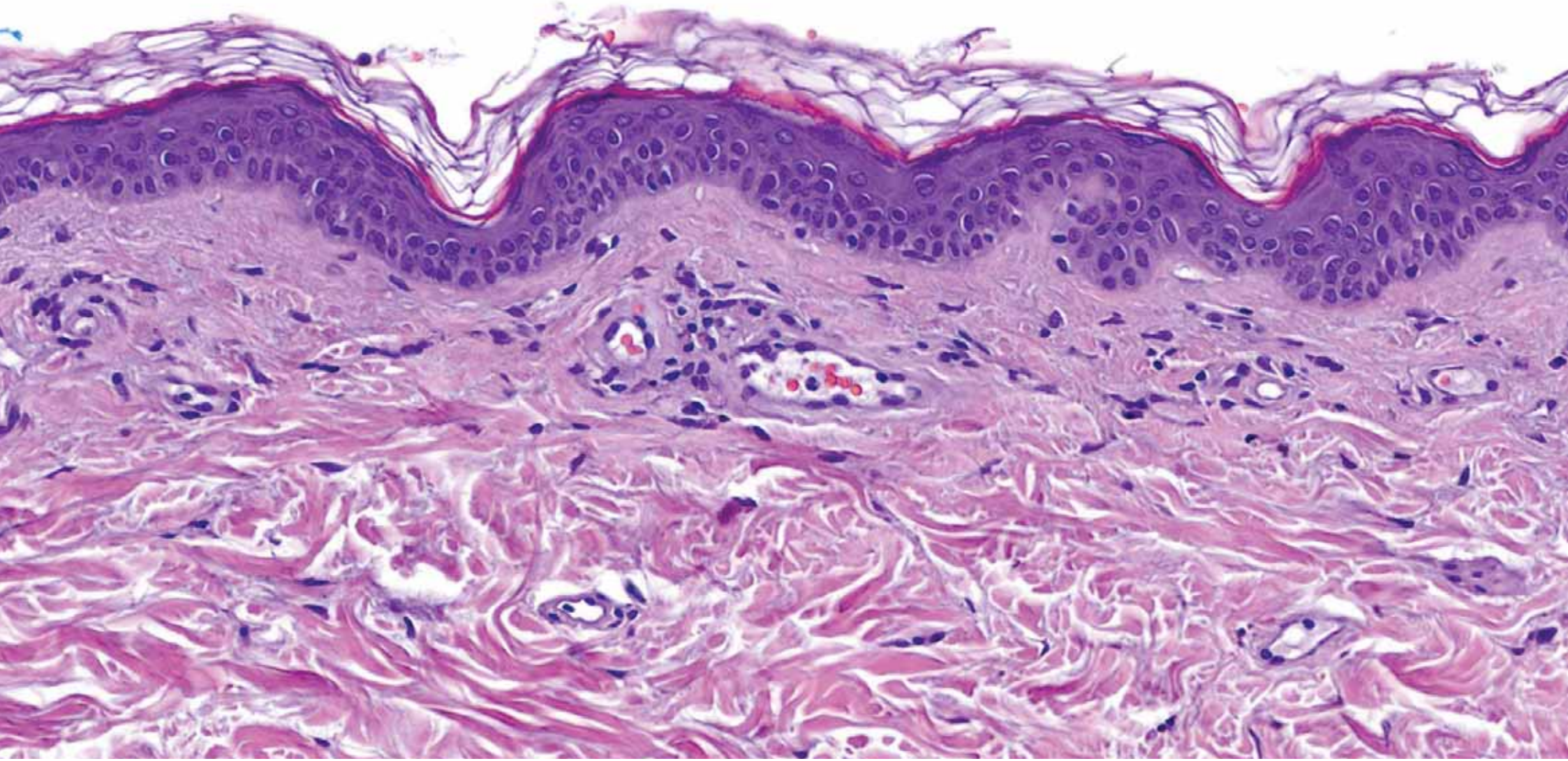
Mysore V. Invisible dermatoses. Indian J Dermatol Venereol Leprol 2010;76:239-48.

Clinical presentation

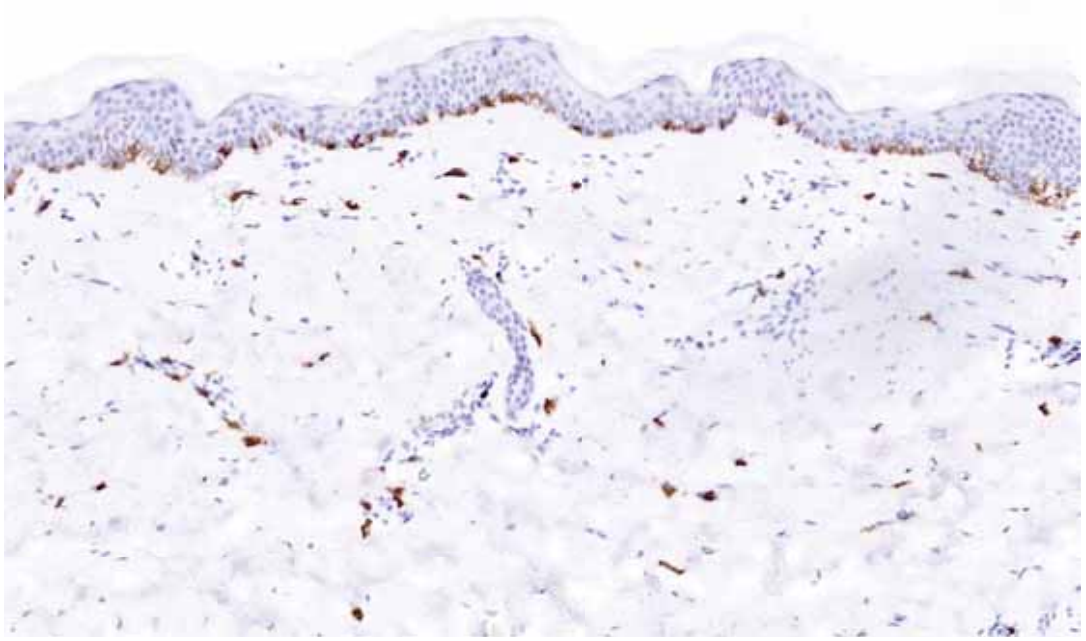




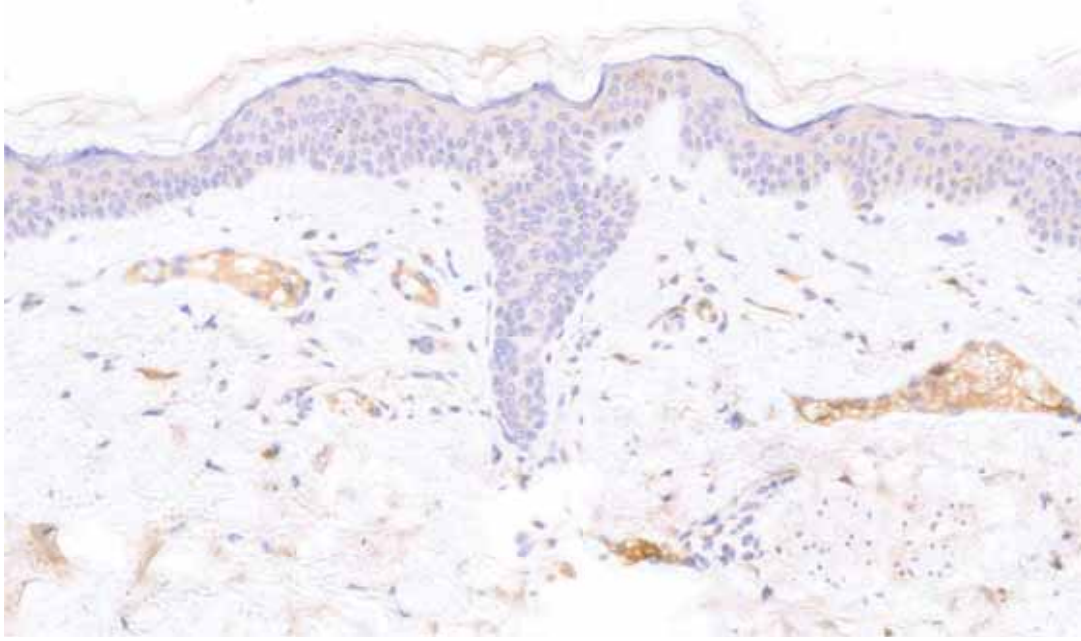




Immunohistochemistry

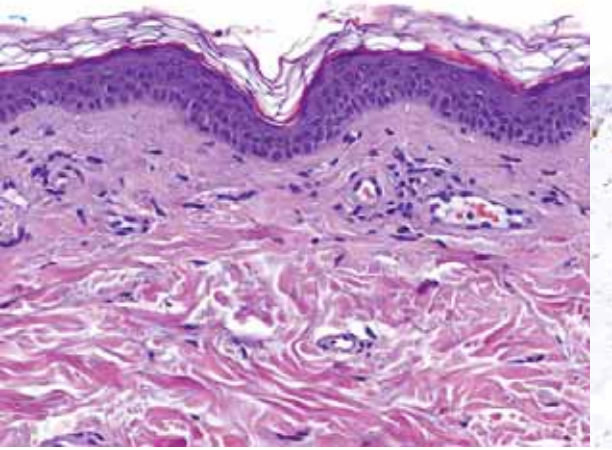


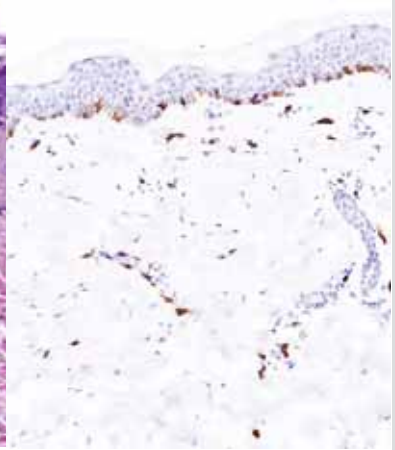
CD117



CD25

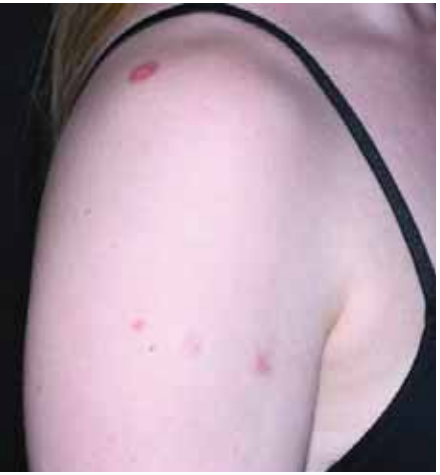
Summary of the findings

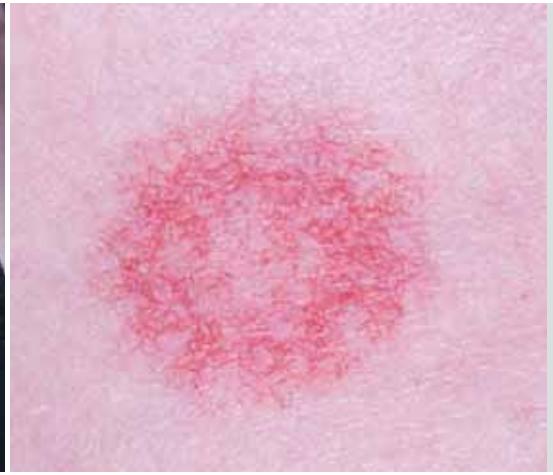




Histology:

Invisible dermatosis!
Special stains are required!
CD117+ CD25- CD30- mast cells





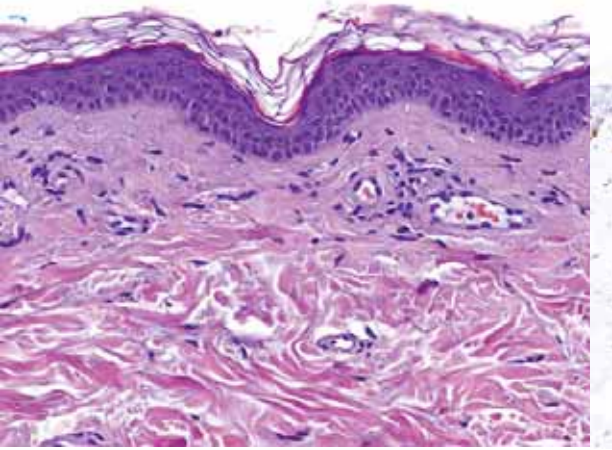
Clinical presentation:

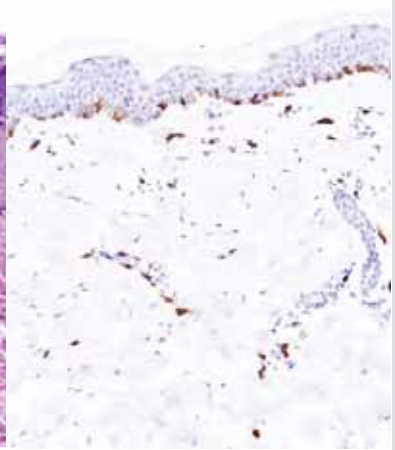
Multiple erythematous maculae with teleangiectasia

diagnosis

?

Summary of the findings





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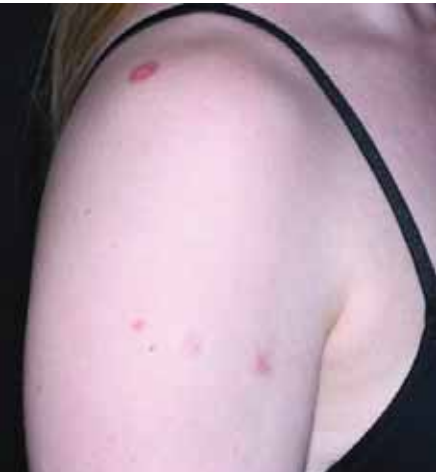
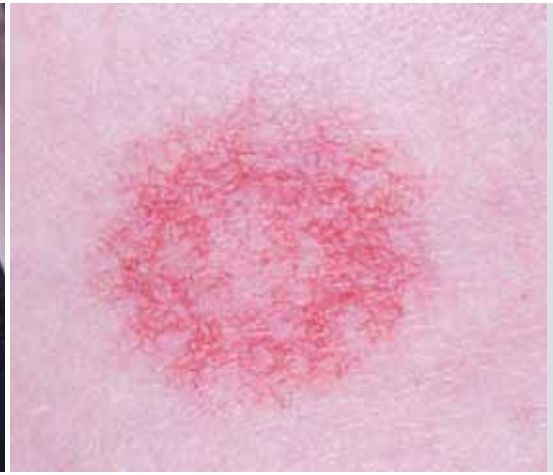


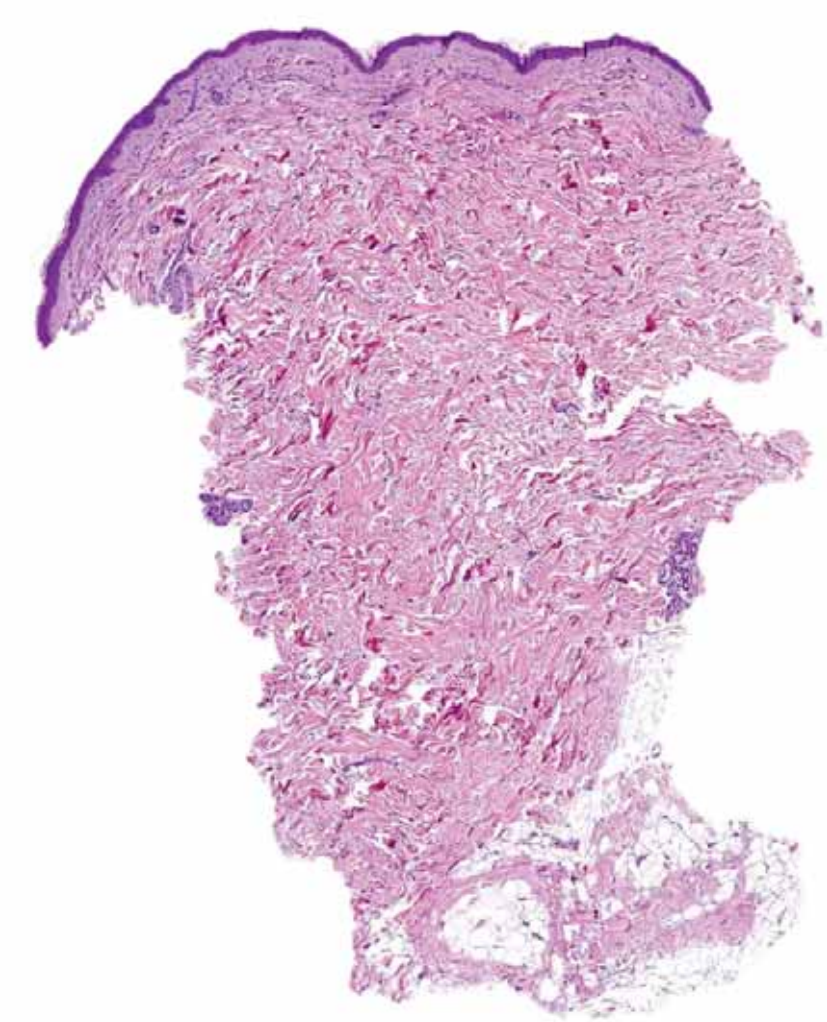


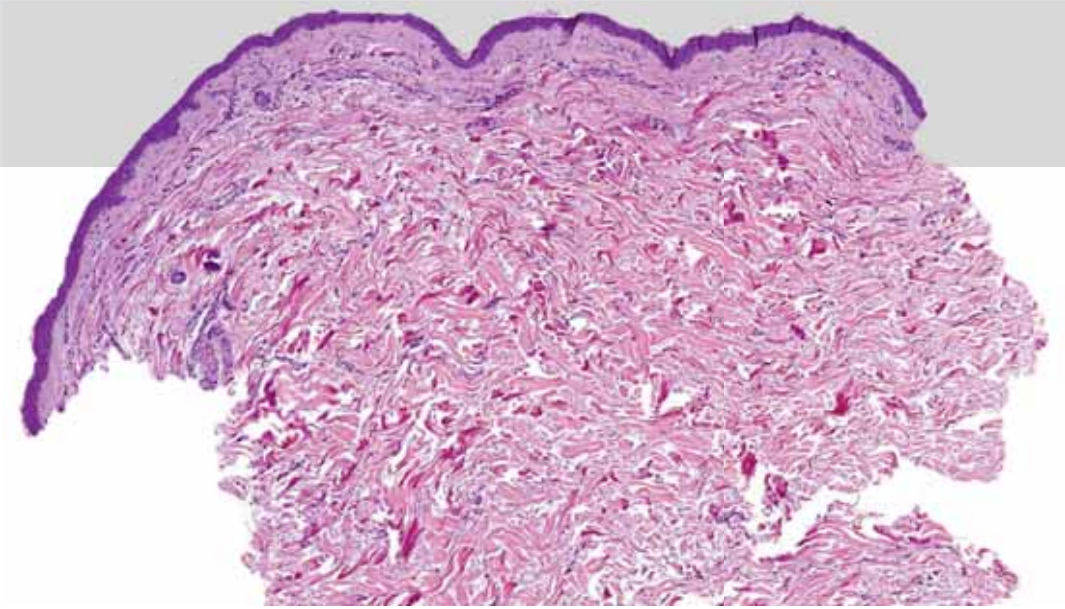
Clinical presentation:

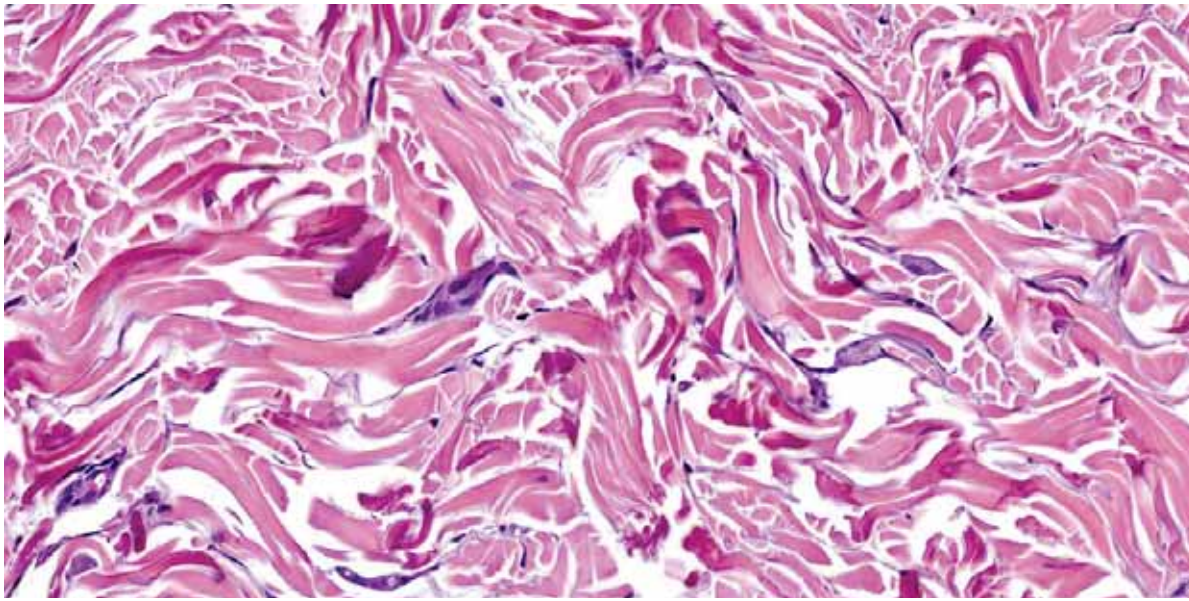
Multiple erythematous maculae with teleangiectasia

TMEP:
Teleangectasia eruptiva macularis perstans

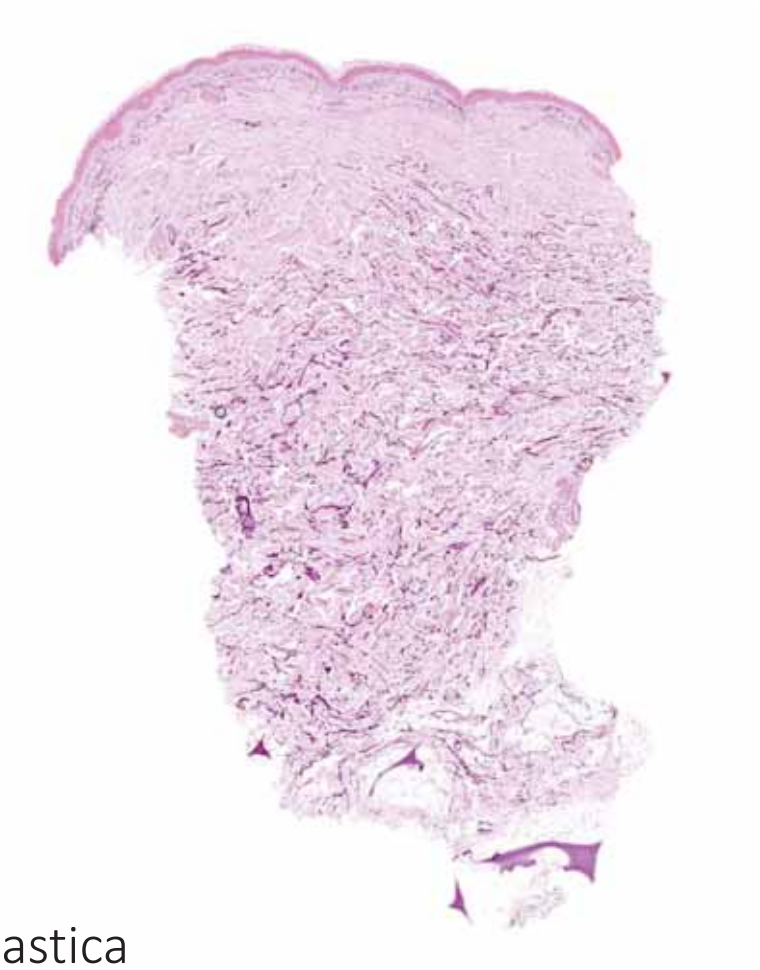
Histology



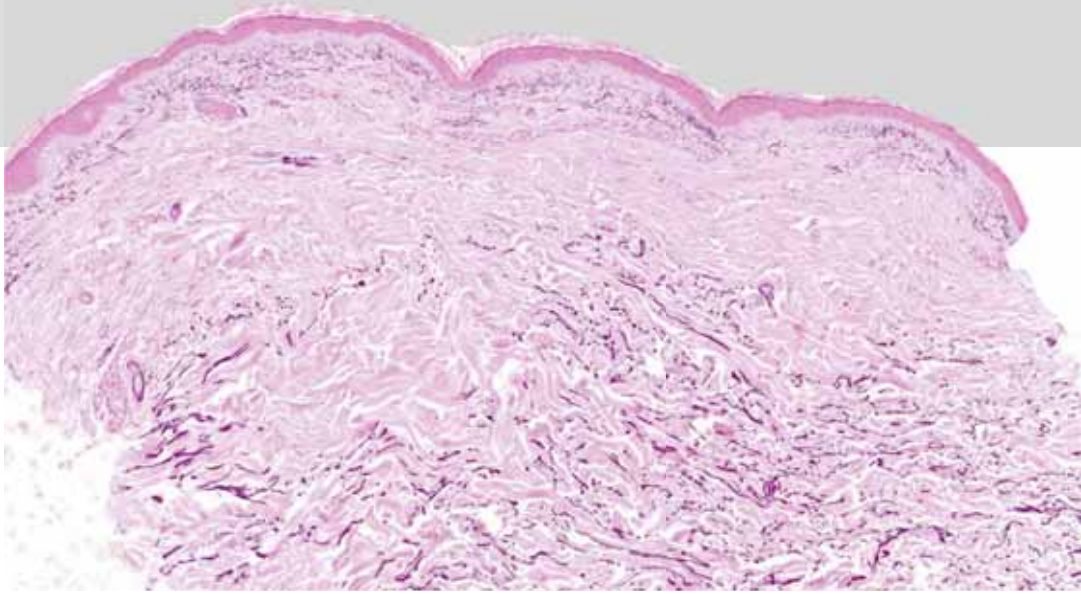


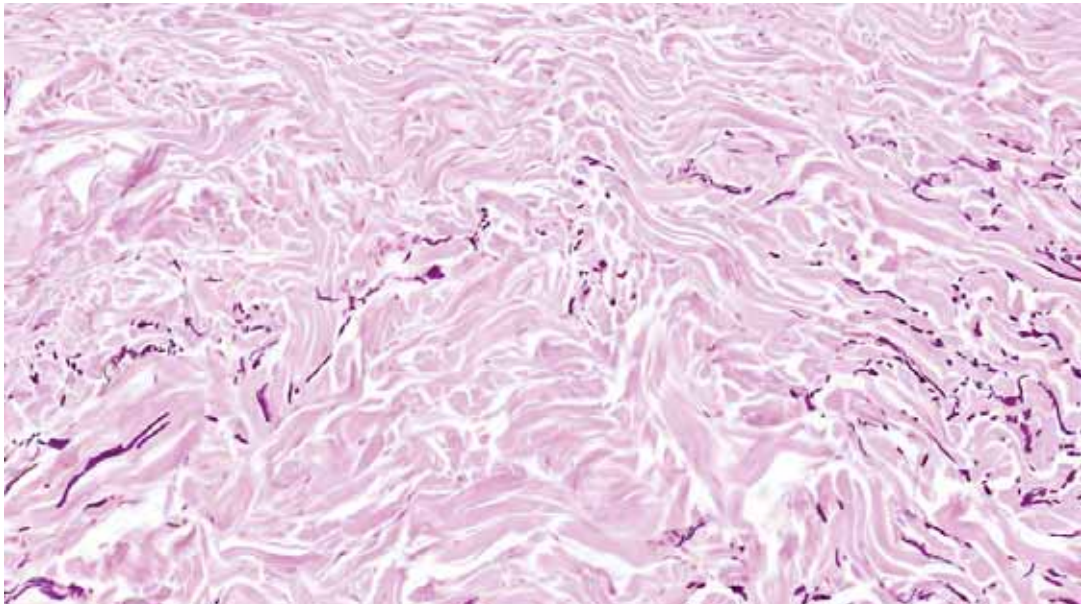


Histology

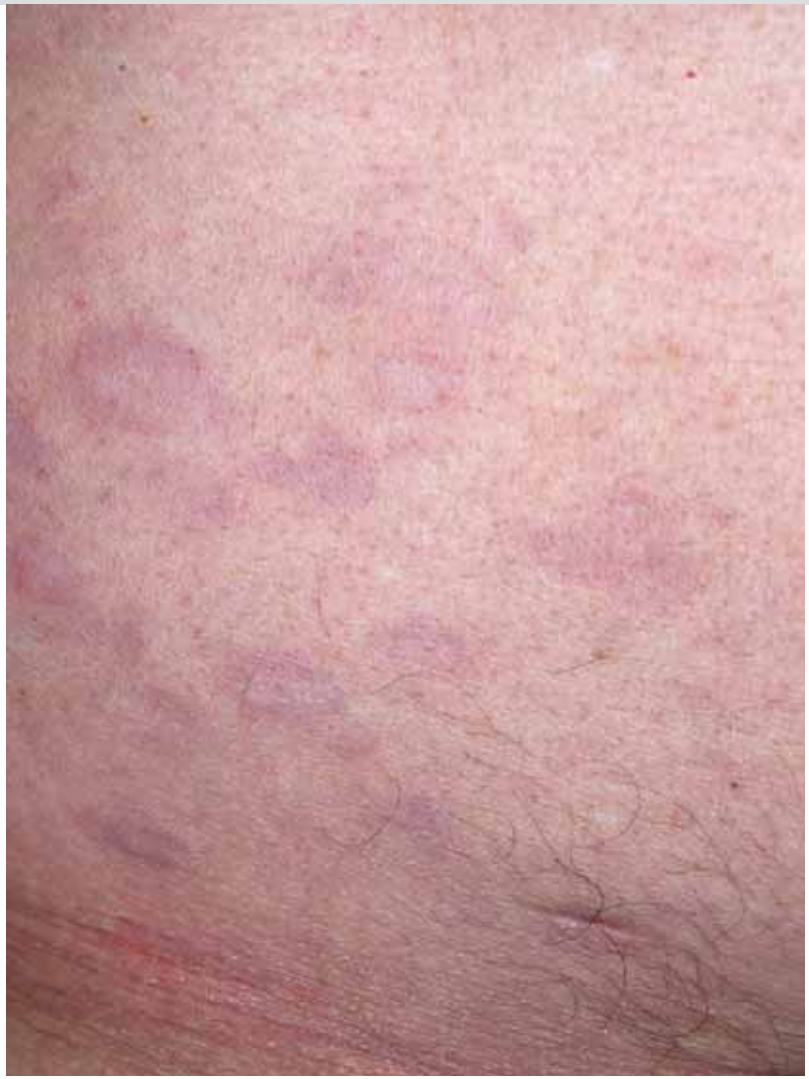


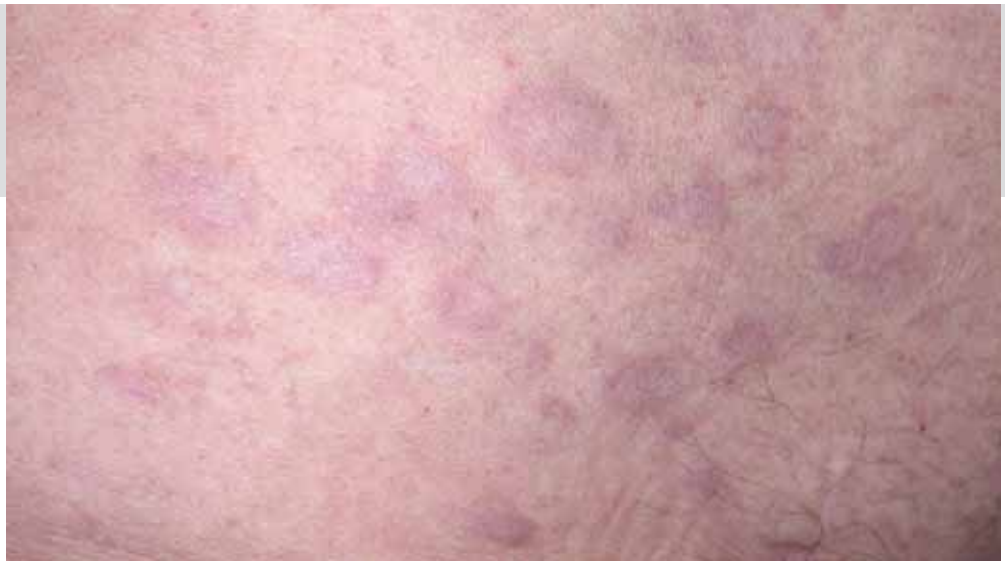
Elastica

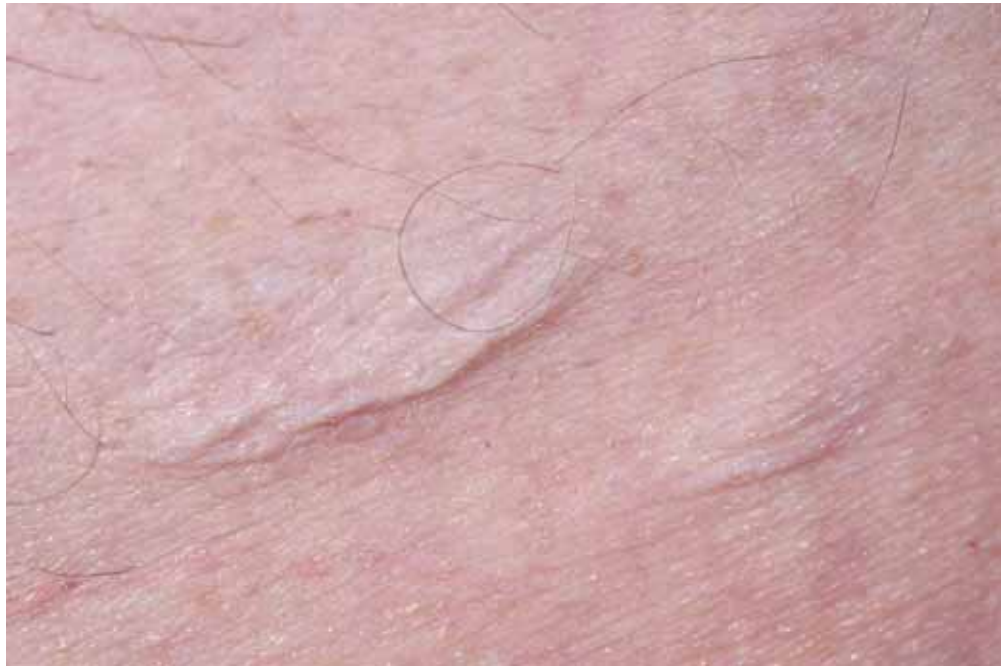




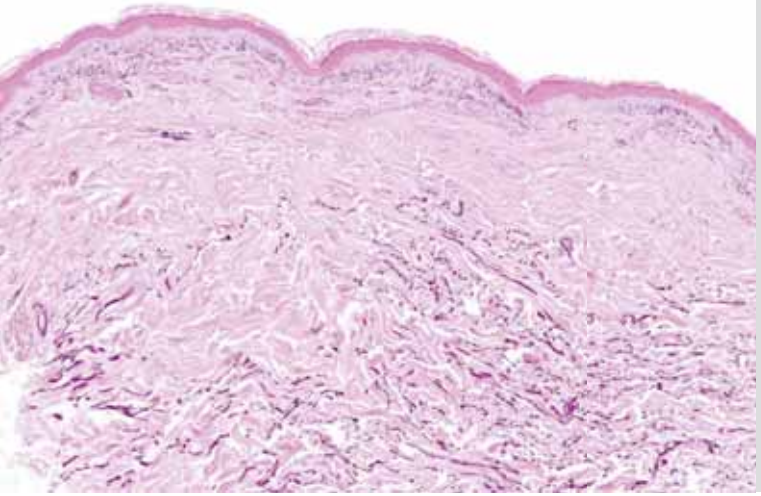
Clinical presentation





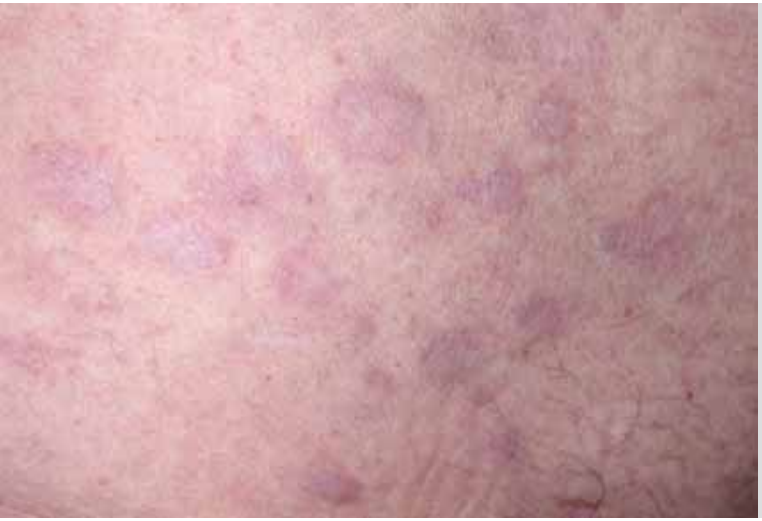


Summary of the findings:



Histology:
Few giant cells in the mid dermis

Elastica: loss of elastic fibers in the mid dermis

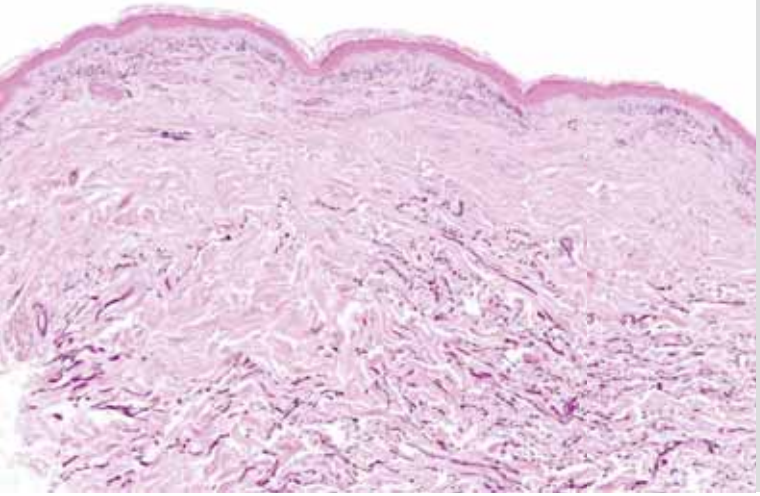


Clinical presentation:
Annular erythema with central paling
Slack skin

diagnosis

?

Summary of the findings:



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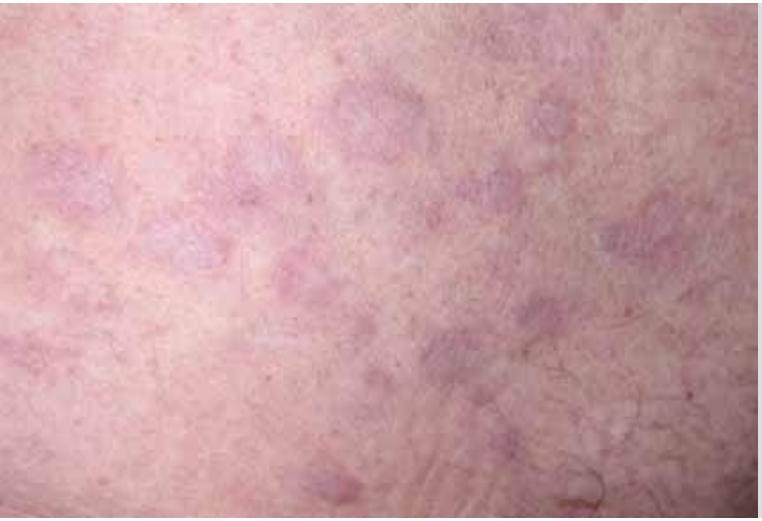
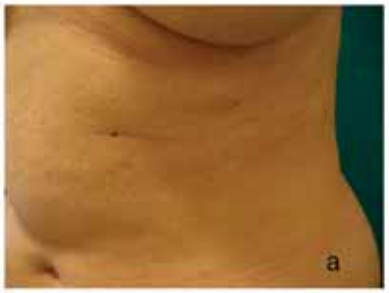


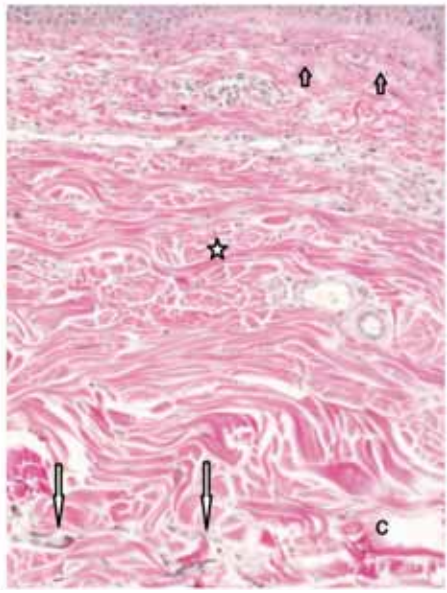
Clinical presentation:
Annular erythema with central paling
Slack skin

mid dermal elastolysis

Mid dermal elastolysis

- Acquired loss of elastic fiber material in the mid-dermis
- Pathogenesis is unclear: sun-exposure, autoimmune process
- No Familial clustering, higher incidence in middle-aged women
- Predominantly affects the trunk and proximal extremities
- Mostly as macular areas of varying sizes with a slightly raised, mildly wrinkled surface
- Therapeutically: difficult to manage, sun protection





From: Tronnier M. et al. JDDG 2018

The **clinical** presentation is classified into **three distinct types**:

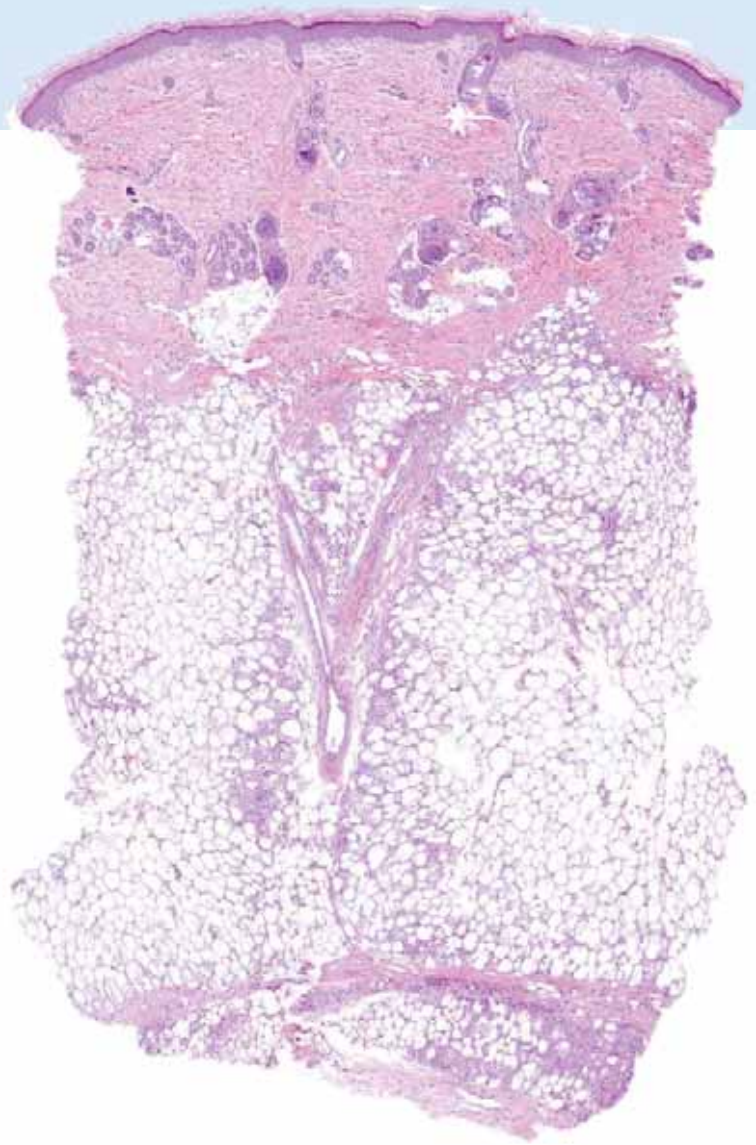
Type 1: localized round or oval lesions with fine wrinkling

Type 2: perifollicular elevation

Type 3 (rare): reticular erythema (frequently overlapping with other types)

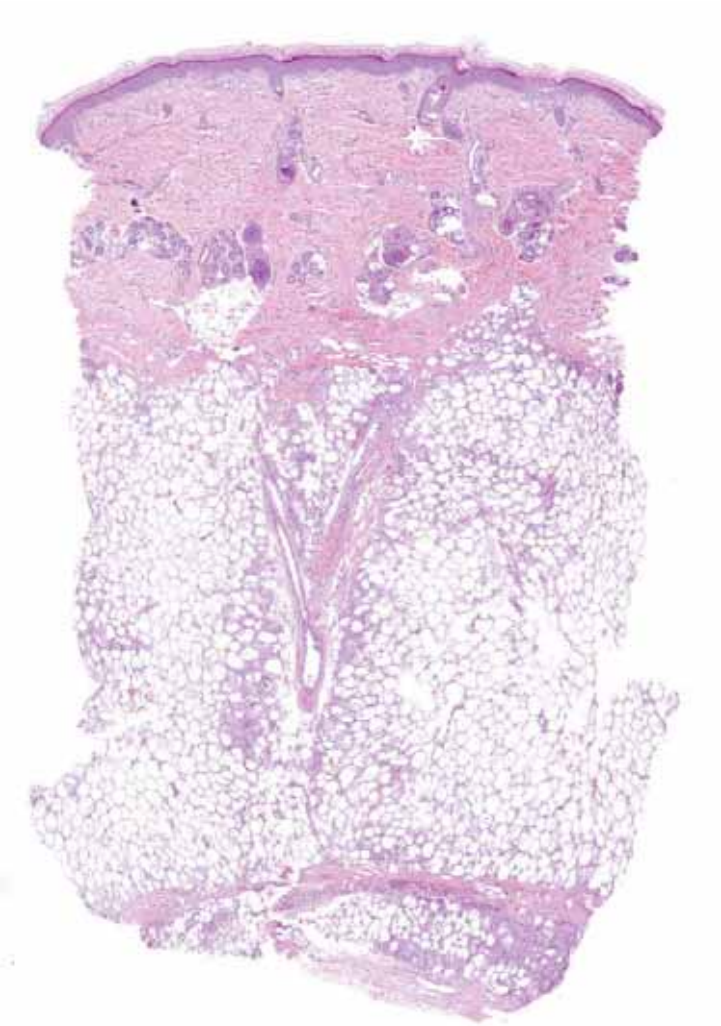
Tronnier M. Cutaneous disorders characterized by elastolysis or loss of elastic tissue. JDDG 2018; 183 -191.
Gambichler T. Mid-dermal elastolysis. Arch Dermatol Res 2010; 302: 85–93.
Hardin J, Dupuis E, Haber RM. Mid-dermal elastolysis: a female-centric disease: case report and updated review of the literature. Int J Wom Dermatol 2015; 1: 126–30.

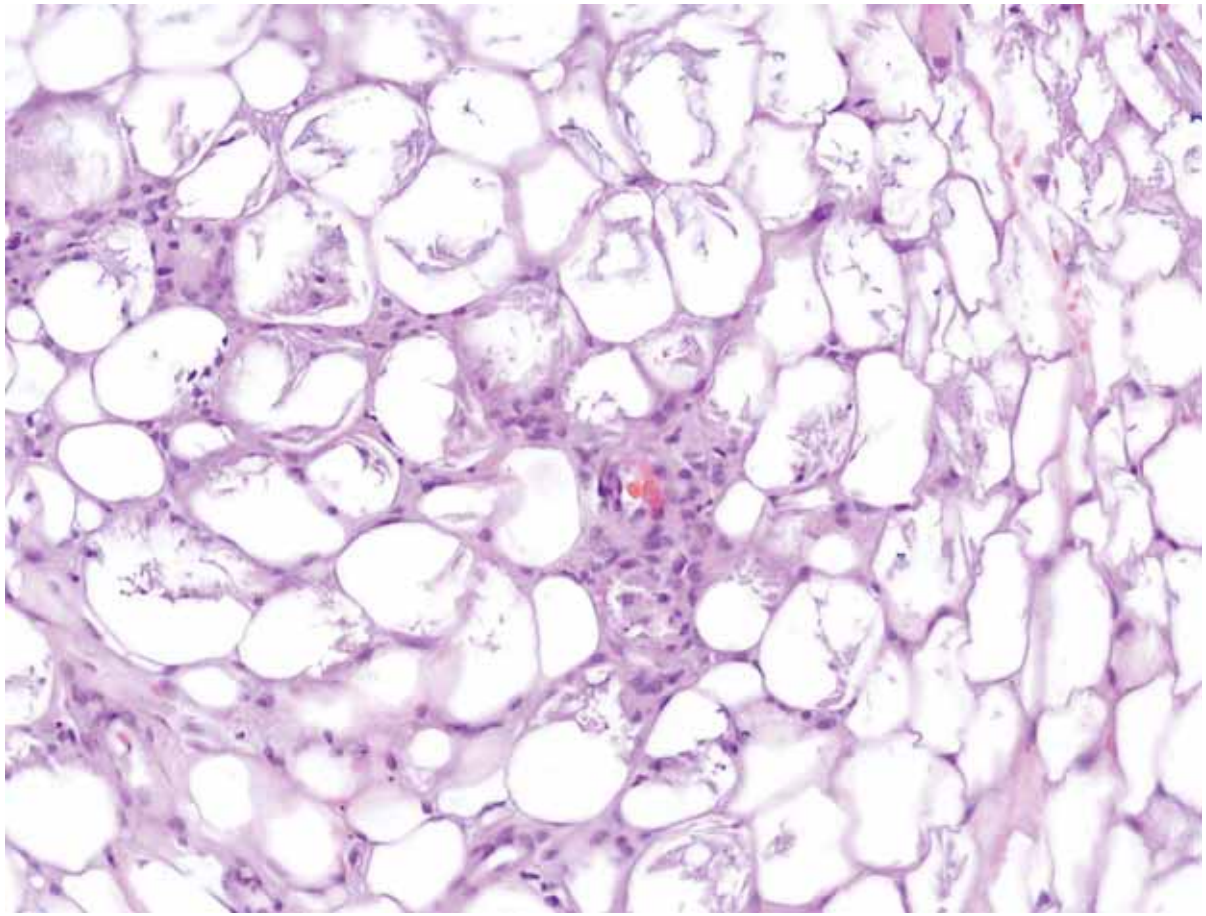
Histology

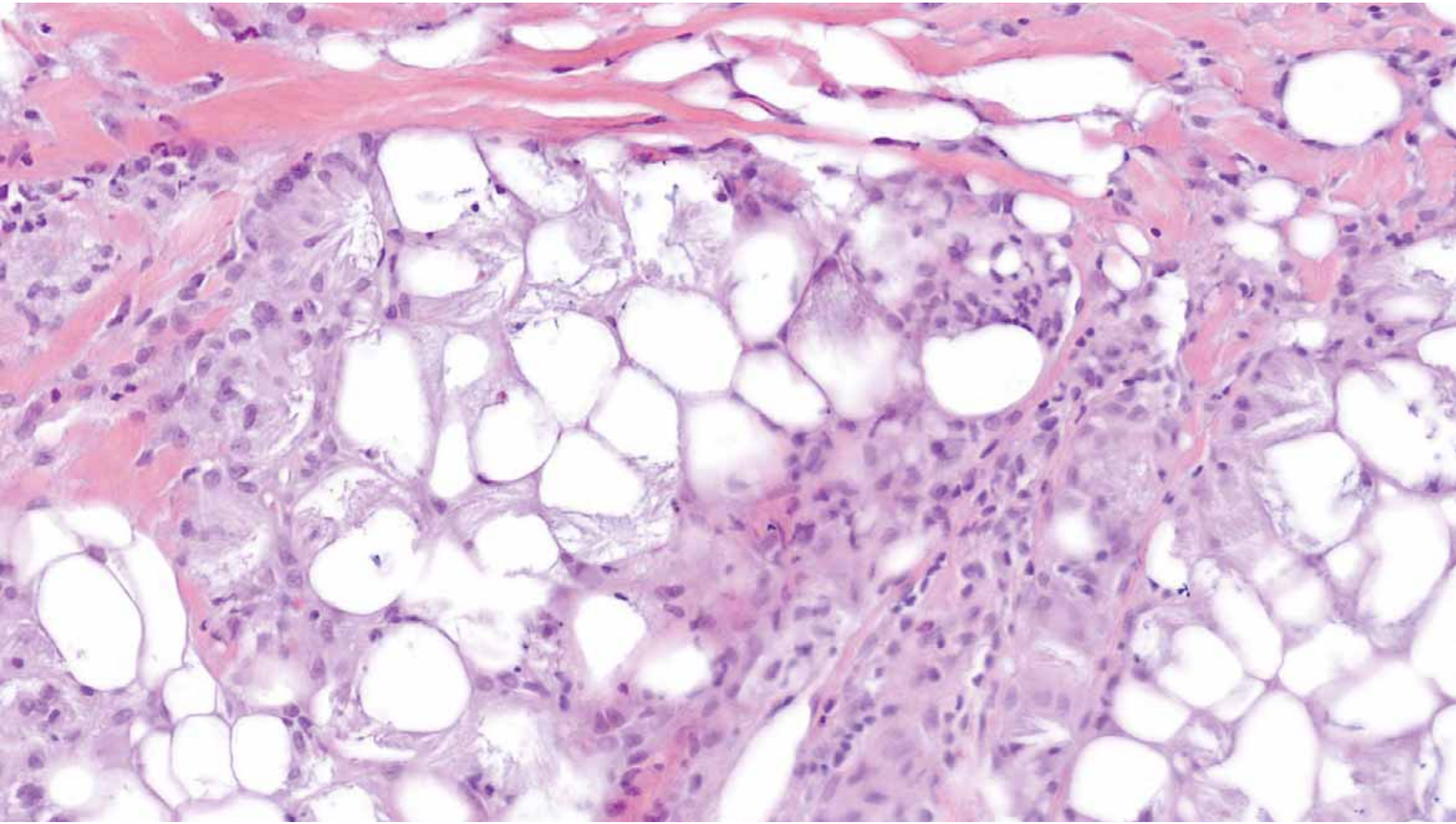


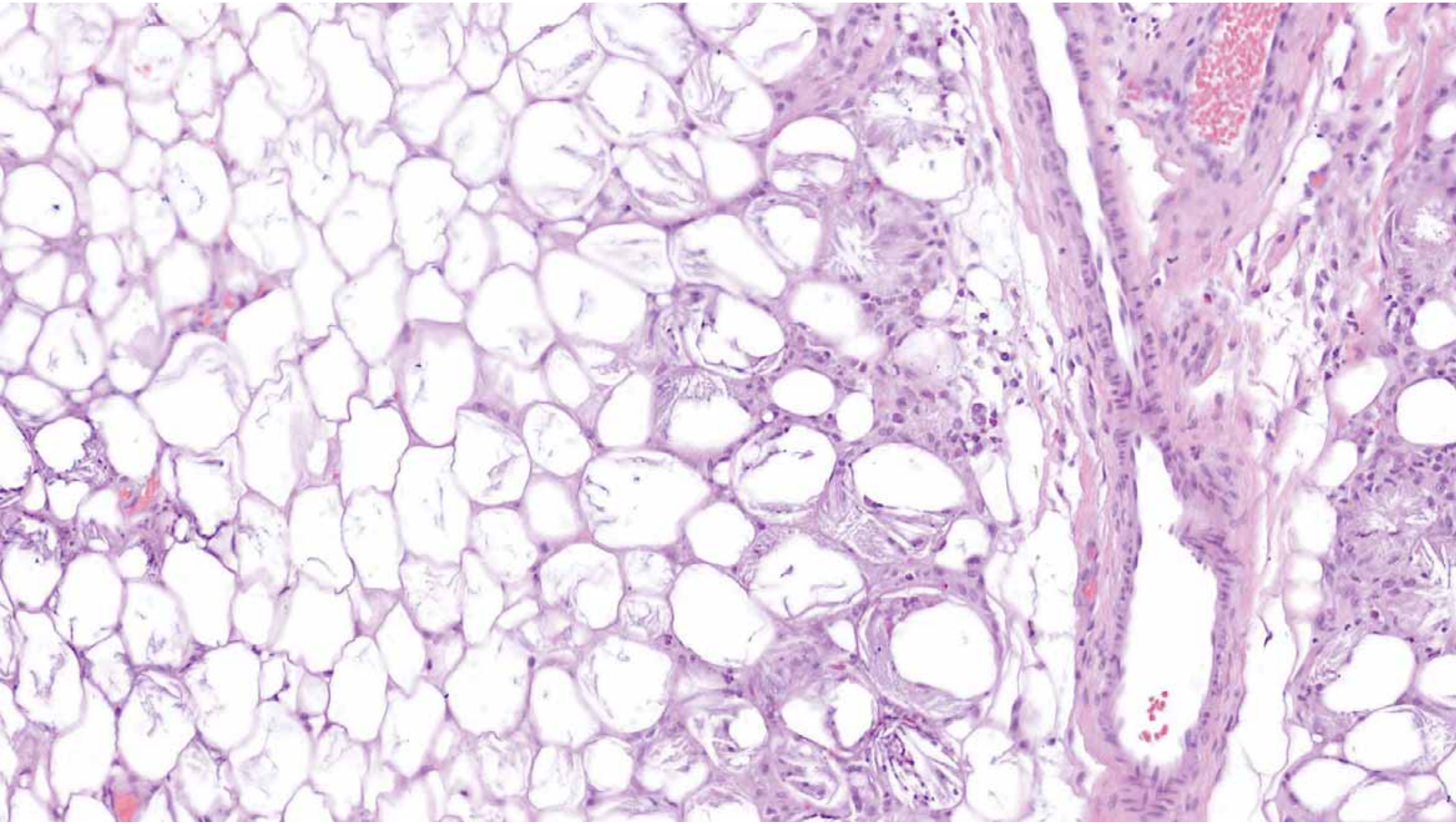
10-day-old full-term newborn boy
Otherwise healthy
Multiple confluent deep red nodules on the back

Histology



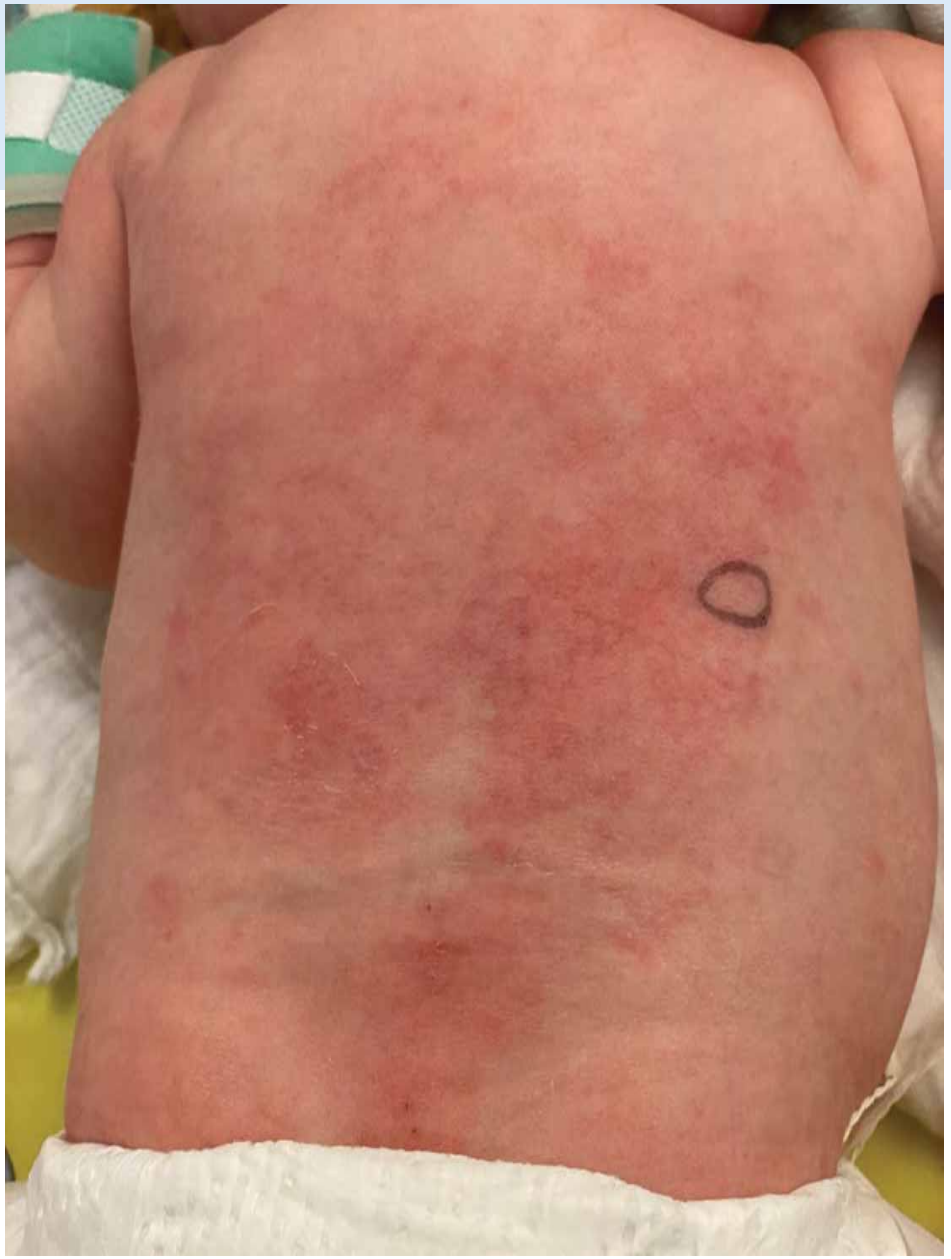




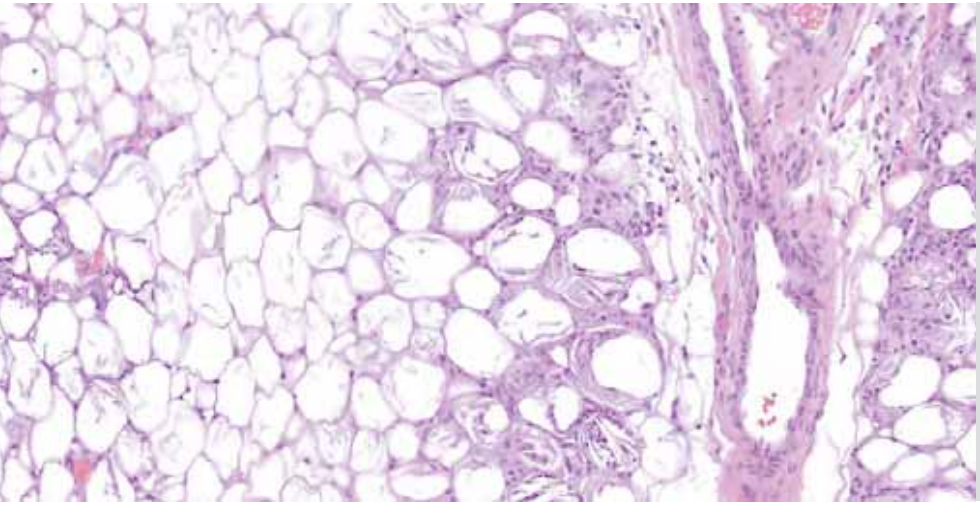


Clinical presentation

10-day-old newborn boy
Full-term neonates with perinatal stress
Otherwise healthy
Indurated nodular net-like erythema on the back

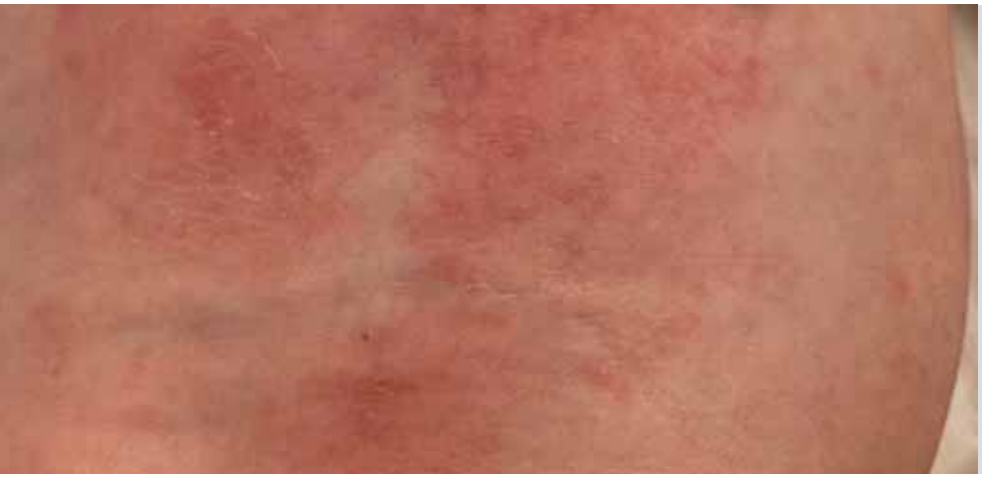


Summary of the findings



Histology:

- Lobular panniculitis
- Necrotic adipocytes, needle-shaped crystals
- Lymphocytes, macrophages, giant cells



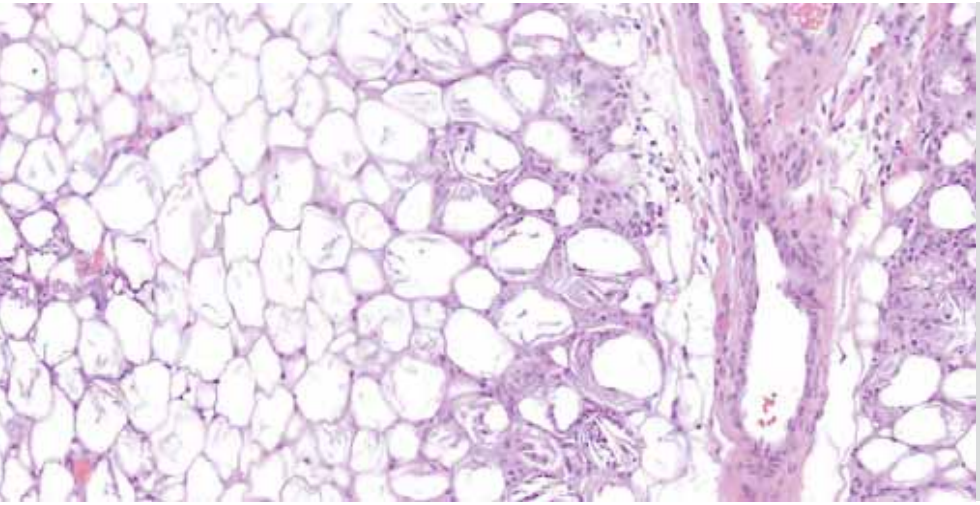
Clinical presentation:

- Full-term neonate with perinatal stress
- Indurated nodular net-like erythema
- Located on the back

diagnosis

?

Summary of the findings



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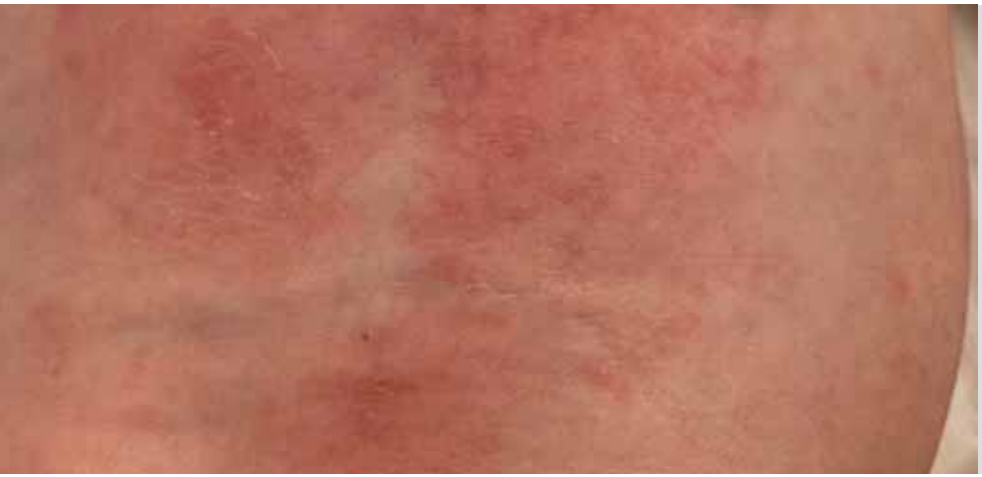


Clinical presentation:

- Full-term neonate with perinatal stress
- Indurated nodular net-like erythema
- Located on the back

Adipo-necrosis neonatorum

Adiponecrosis neonatorum

= subcutaneous fat necrosis of the newborn (SFNN)

- Rare, self-limiting panniculitis
- Full- or post-term neonates
- Associated with perinatal stress: hypoxia, hypothermia, meconium aspiration, birth-trauma
- Onset: first few days or weeks after birth
- Common locations: cheeks, back, buttocks, arms, and thighs
- Systemic complications: hypercalcemia, thrombopenia and hypoglycemia
- Prognosis: excellent, Ca^{2+} monitoring

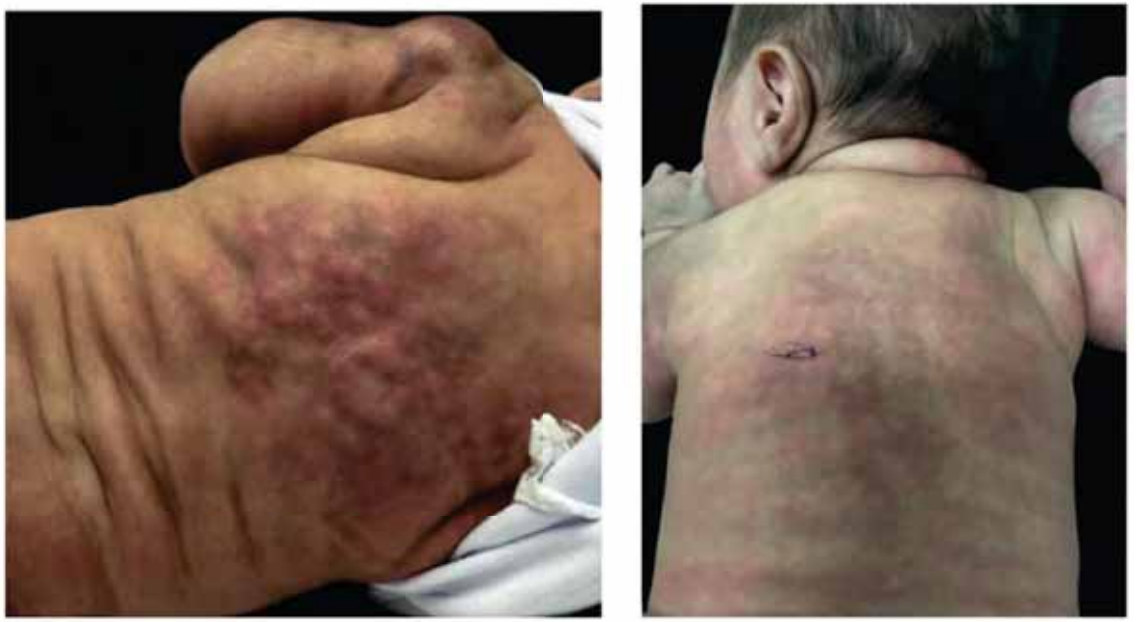


FIGURE 1: Multiple purple-erythematous nodules on the dorsum

From: Muzy G, Mayor SAS, Lellis RF. Subcutaneous fat necrosis of the newborn: clinical and histopathological correlation. An Bras Dermatol. 2018;93(3):412-4

DD of adiponecrosis neonatorum

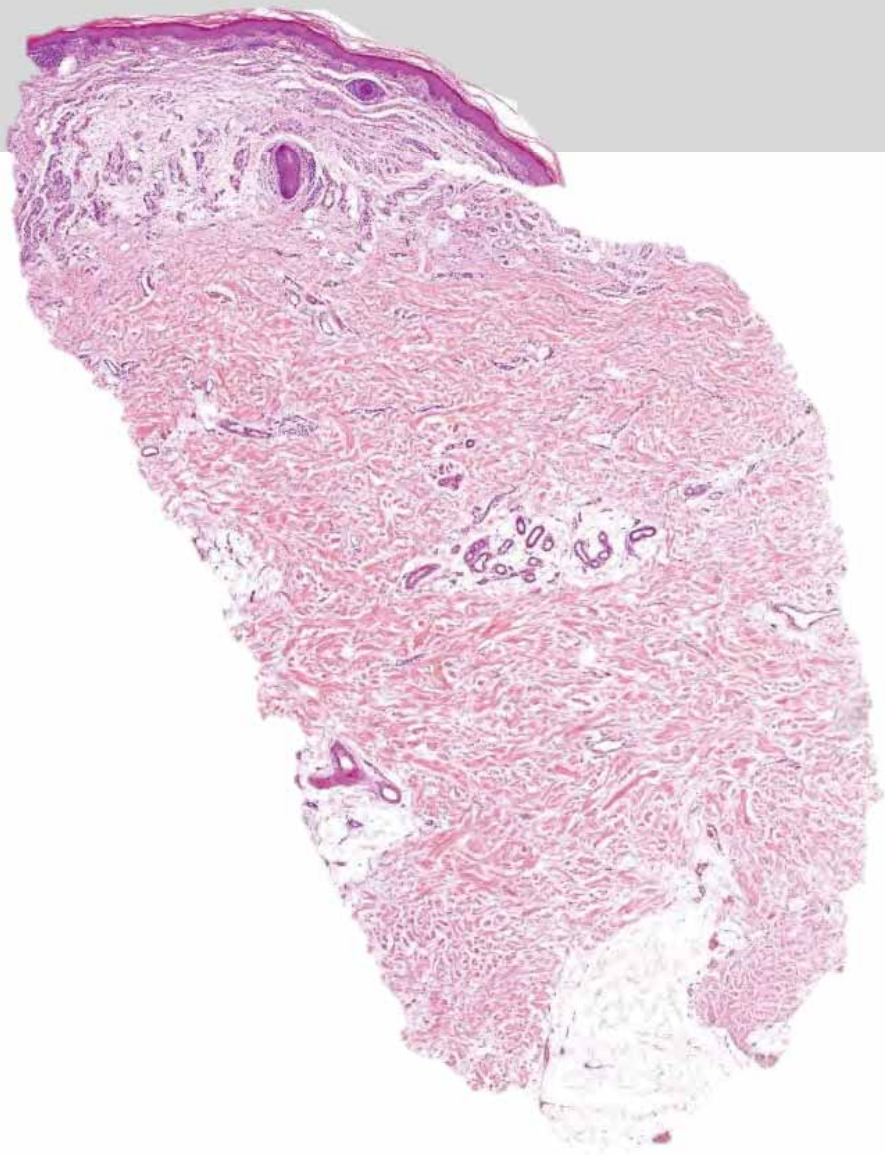
= subcutaneous fat necrosis of the newborn (SFNN)

Chart 1: Clinical and histopathological findings of SFNN and its differential diagnoses

Disease	SFNN	Sclerema neonatorum	Scleredema
Patients	Term or post-term newborns	Premature newborns	Newborns
Prognosis	Self-limited	High mortality	Low mortality
Clinical presentation	Subcutaneous nodules on the back and buttocks of healthy patient	Symmetric sclerosis of the skin and subcutaneous fat on the trunk and limbs of patient with malformations and systemic involvement	Symmetric edema of lower limbs, with positive Godet sign
Histopathology	Granulomatous inflammation with histiocytes containing birefringent crystals and lobular panniculitis	Necrosis of adipocytes without inflammation; fibrosis of the adipocyte septa	Interstitial edema with lobular and panniculitis, without vasculitis

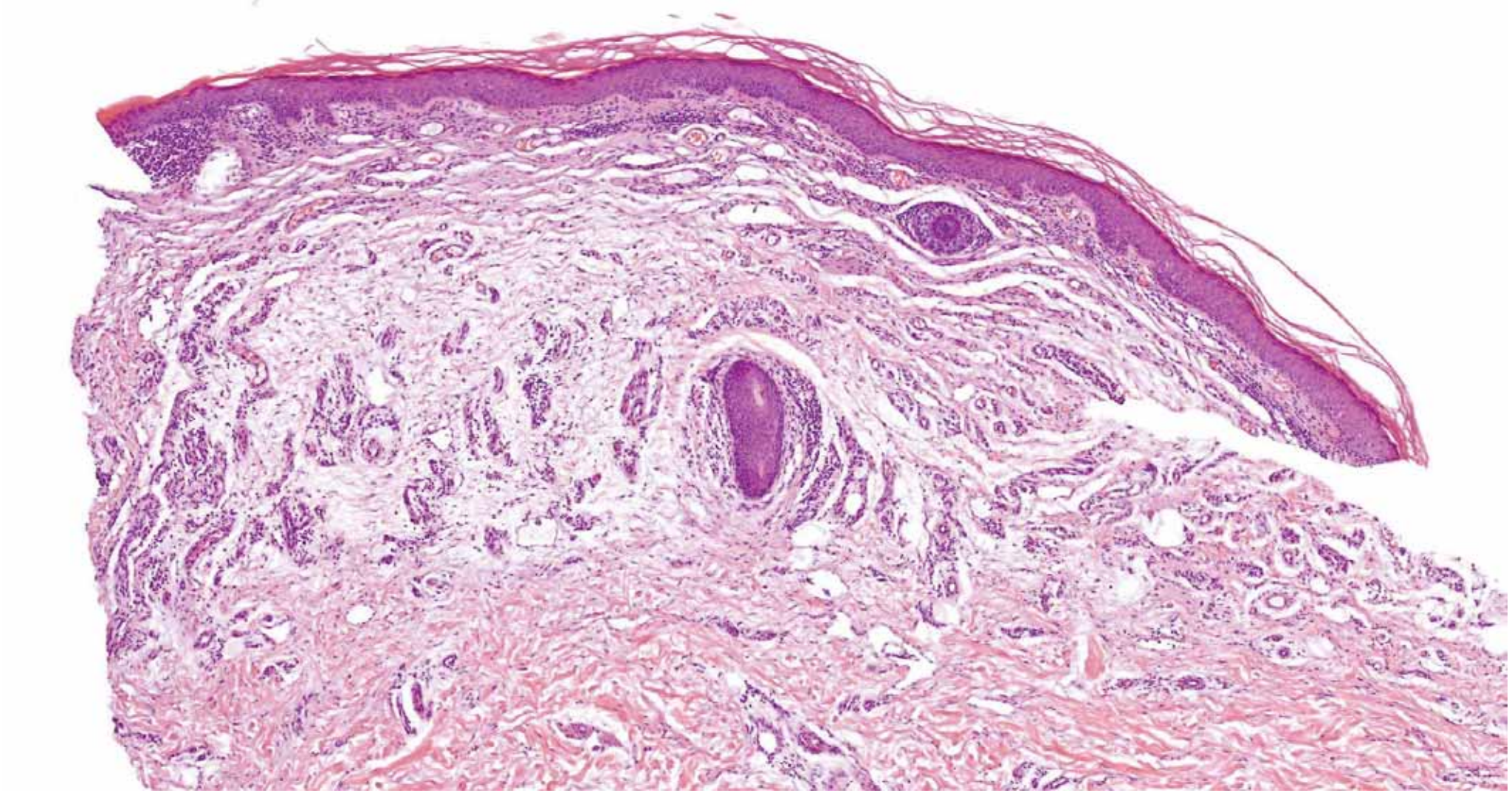
From: Muzy G, Mayor SAS, Lellis RF. Subcutaneous fat necrosis of the newborn: clinical and histopathological correlation. An Bras Dermatol. 2018;93(3):412-4

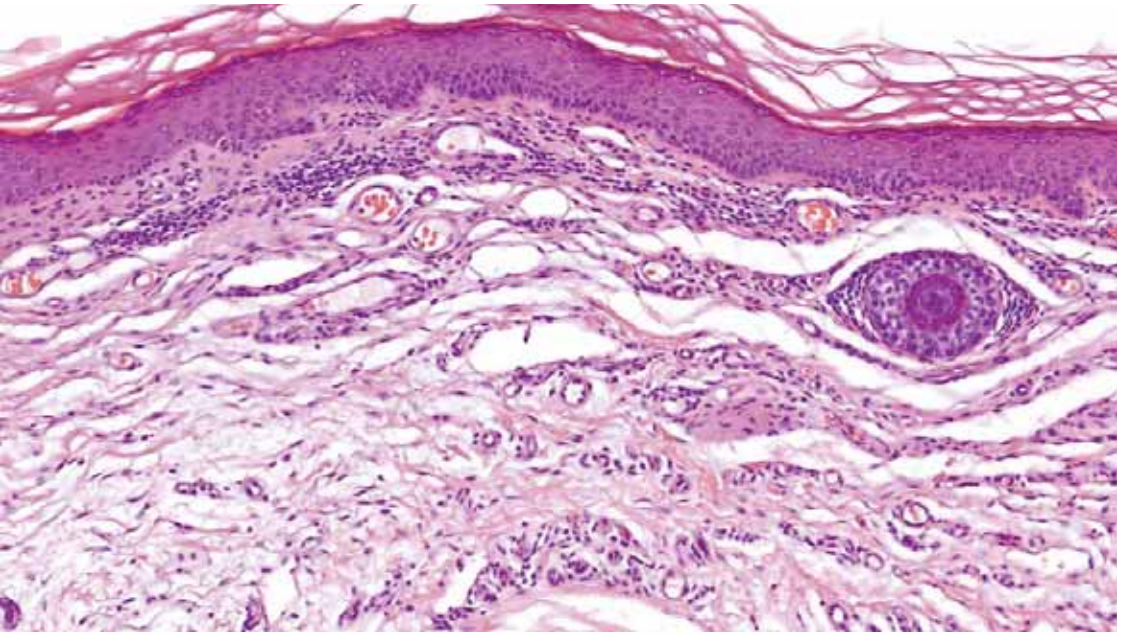
Clinical information

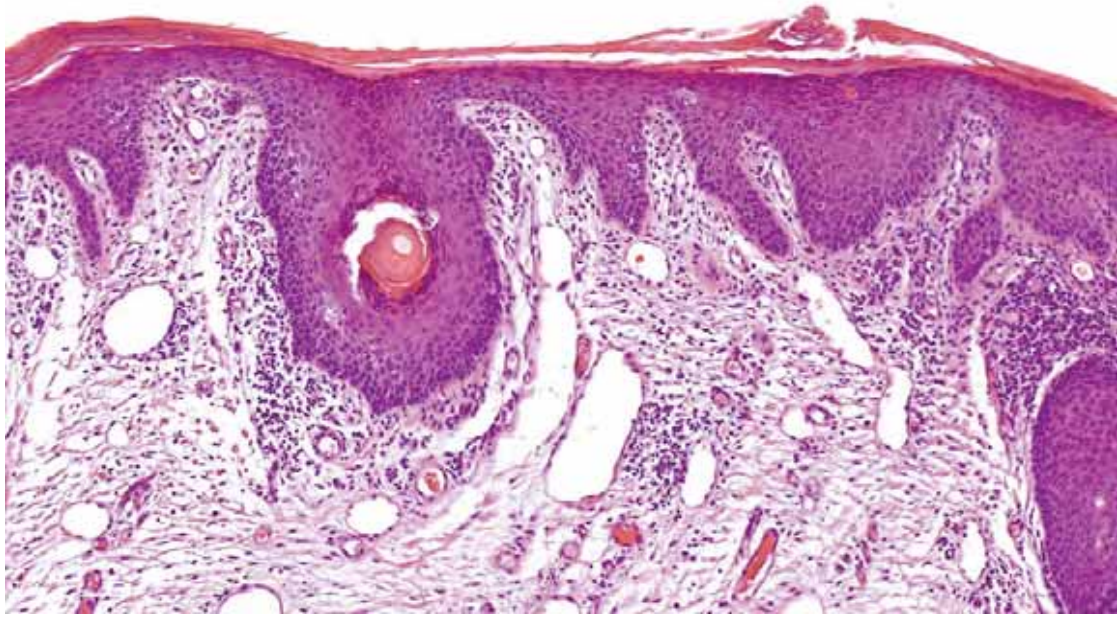


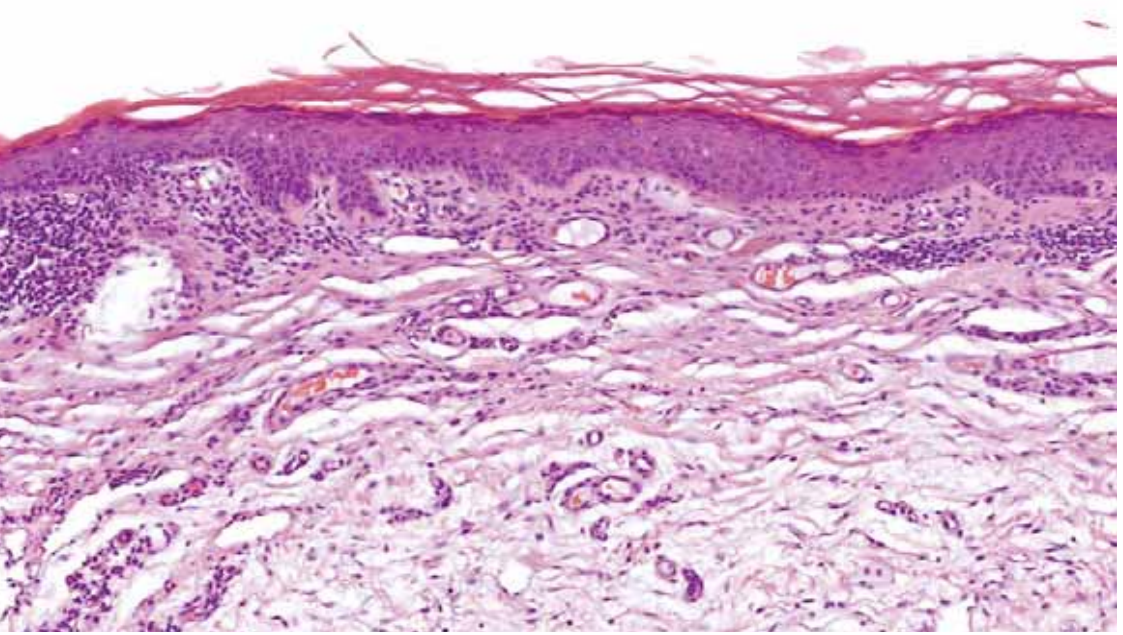
- 84-year-old male patient
- Erythematous to brownish well-demarcated itchy lesion on the lateral hip
- Vascular tumour?

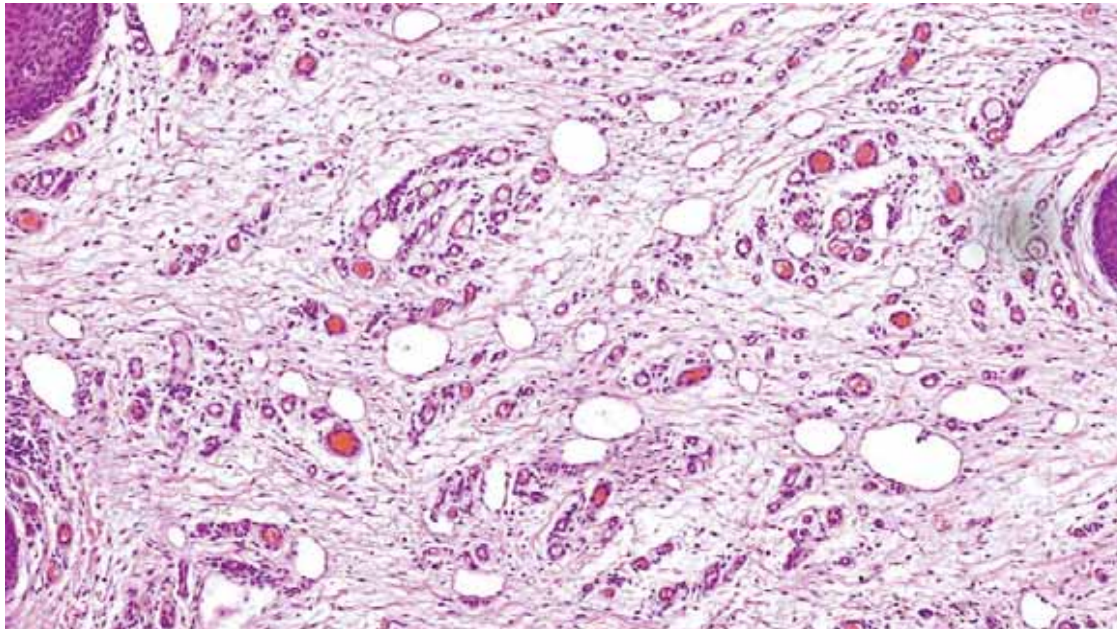
Histology

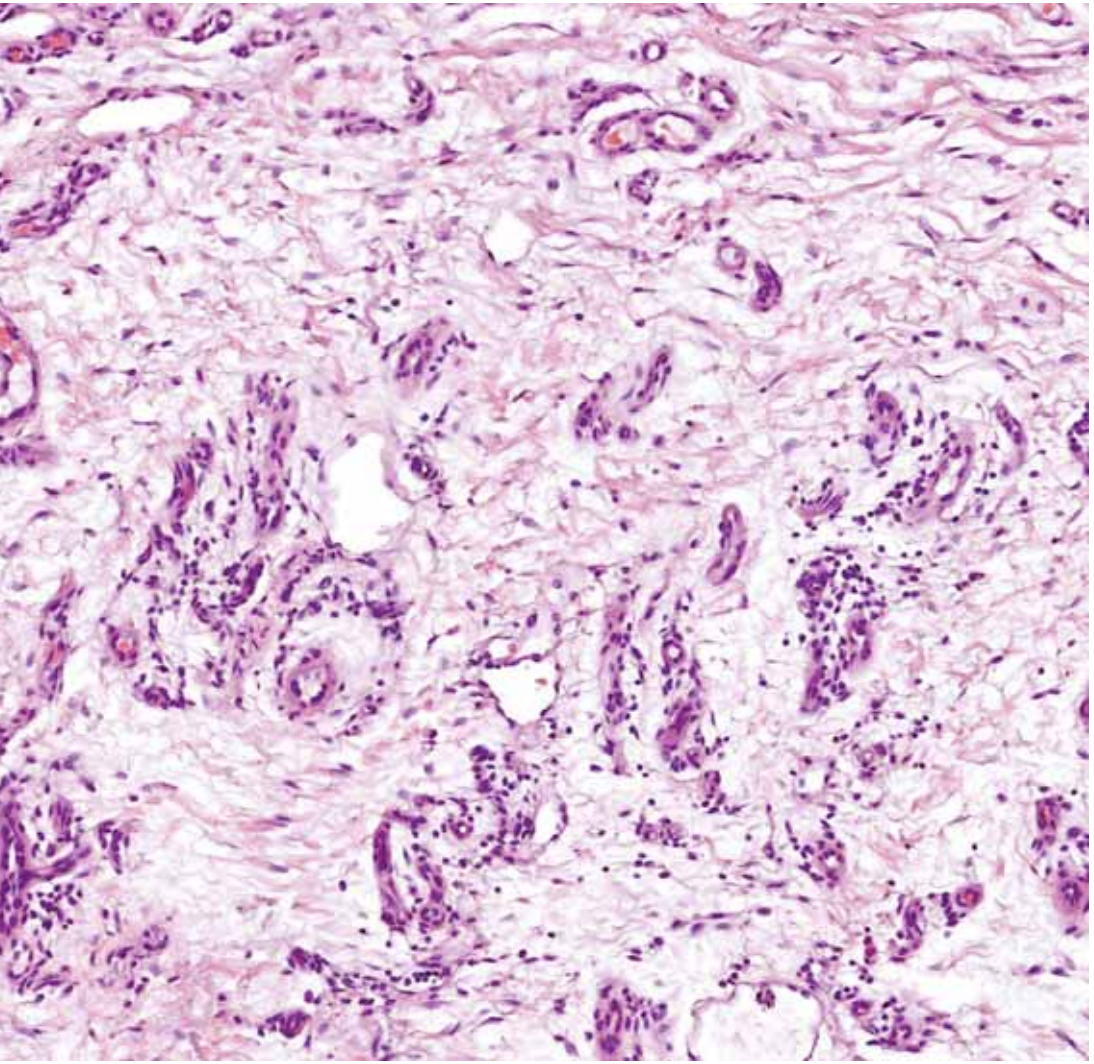


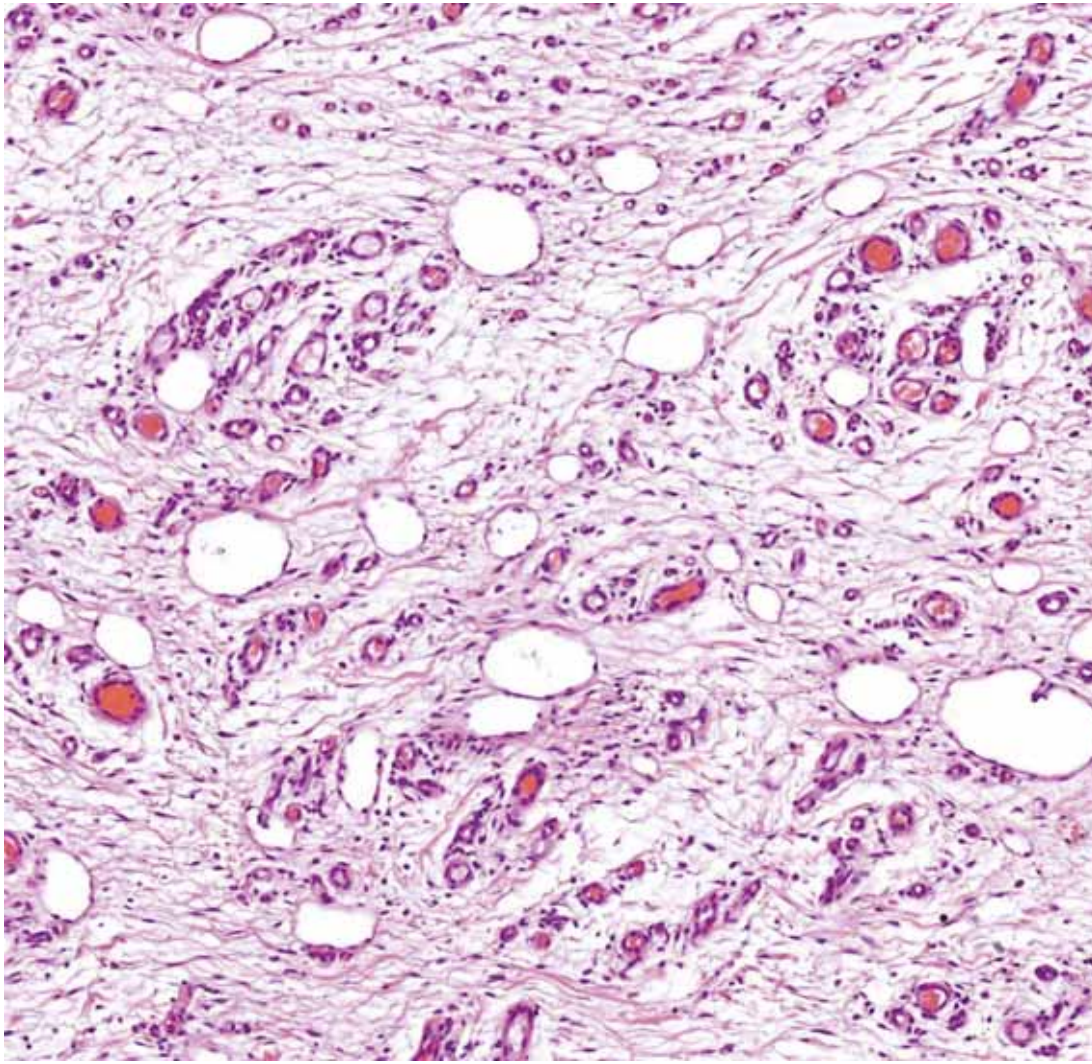




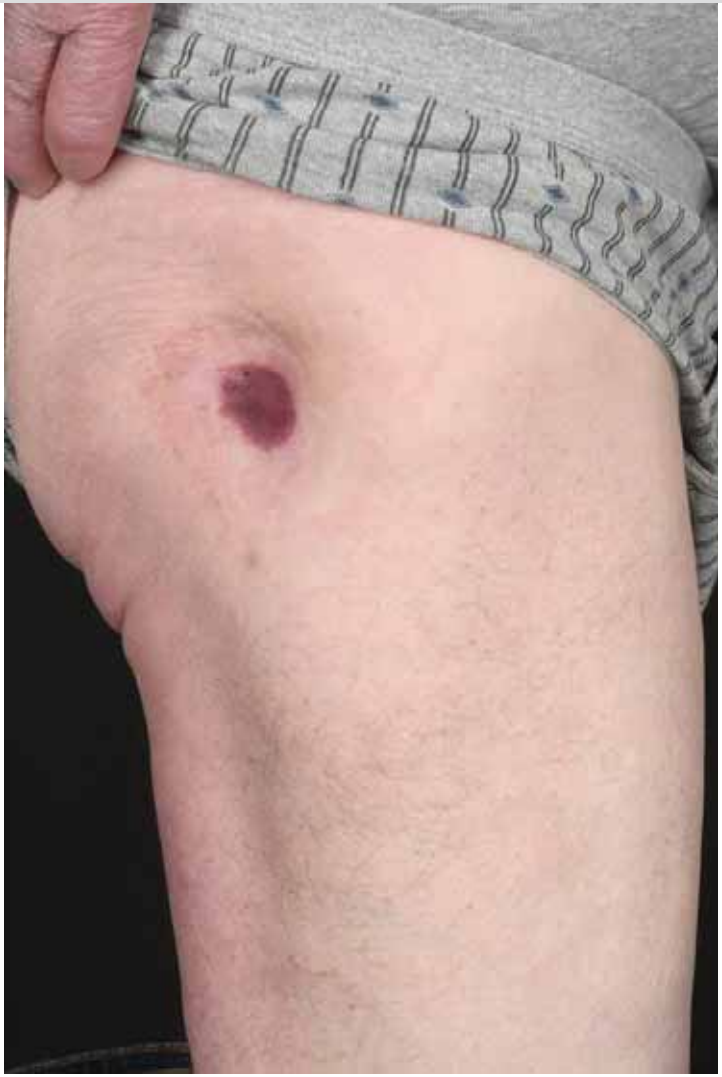


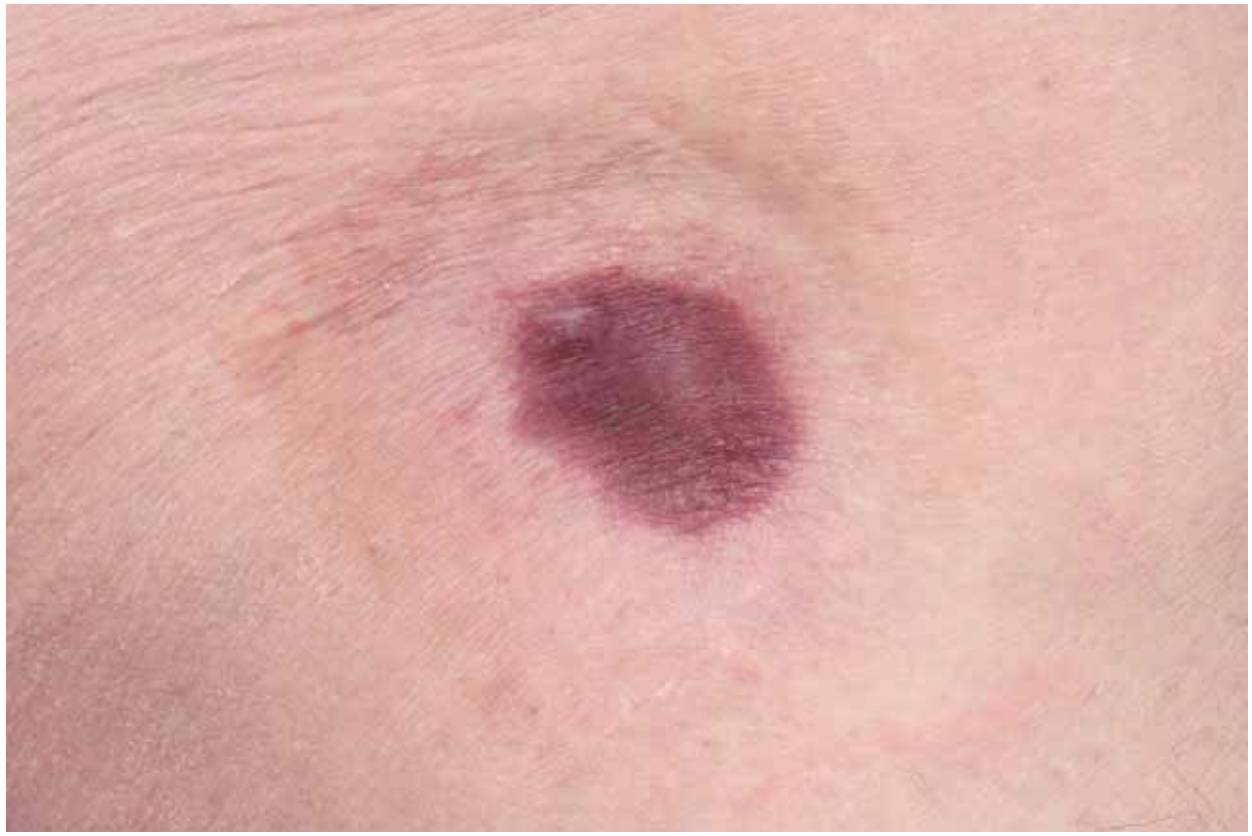




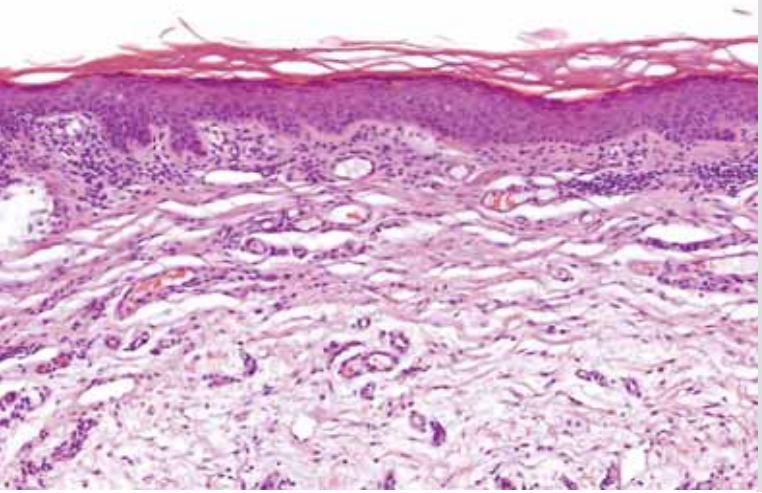


Clinical presentation

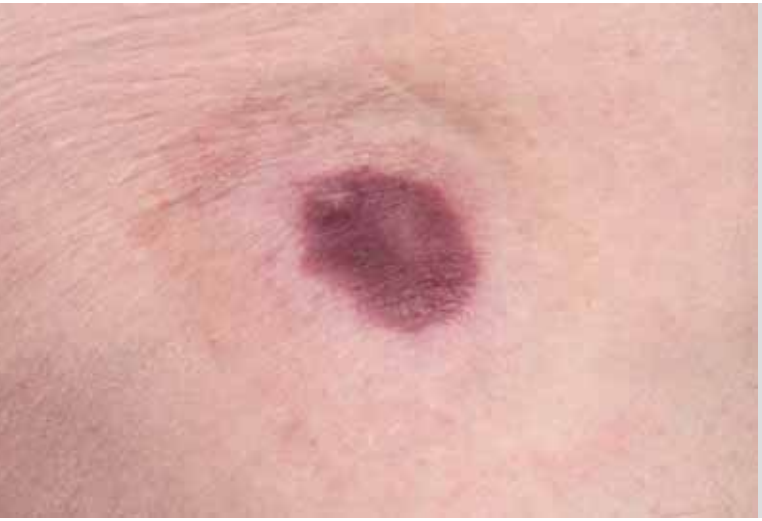




Summary of the findings:



Histology:
Acanthosis and Hyperkeratosis
Lymphocytic infiltrate
Extravasation of erythrocytes
Fibrosis
Capillary proliferation and/or dilation

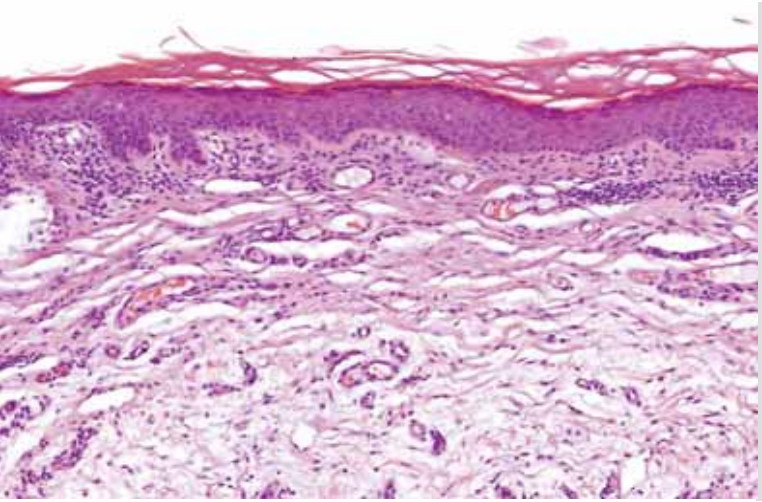


Clinical presentation:
Well-demarcated red to brownish plaque
Often itchy

diagnosis

?

Summary of the findings:



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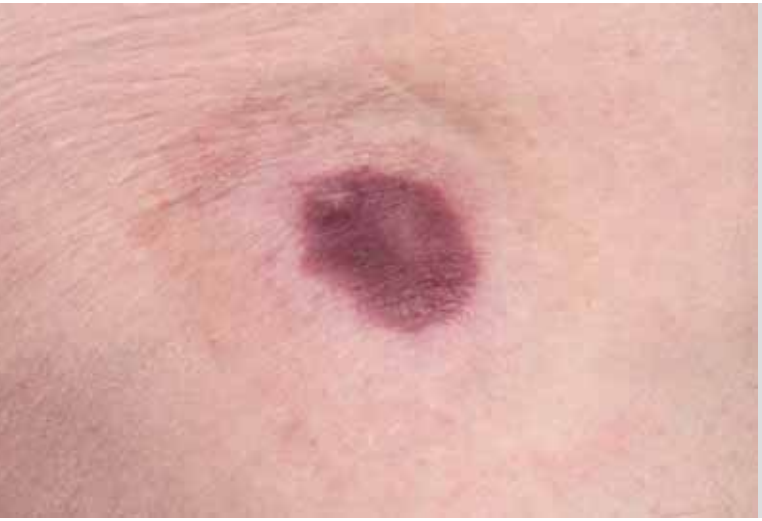


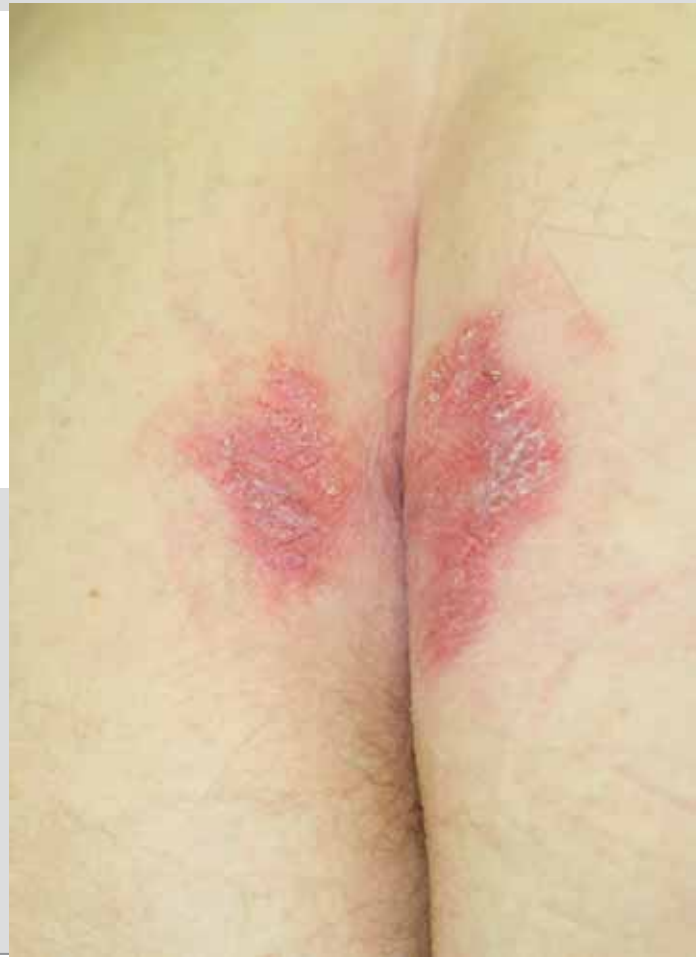
Clinical presentation:
Well-demarcated red to brownish plaque
Often itchy

senile gluteal dermatosis

Senile gluteal dermatosis

= Reactive Epidermal hyperplasia and Angiogenesis of the Rear (REAR)

- First reported in Japan 1979 by Yamamoto et al.
- 13% in elderly patients above 60 years
- Pressure, repetitive friction → angiogenesis

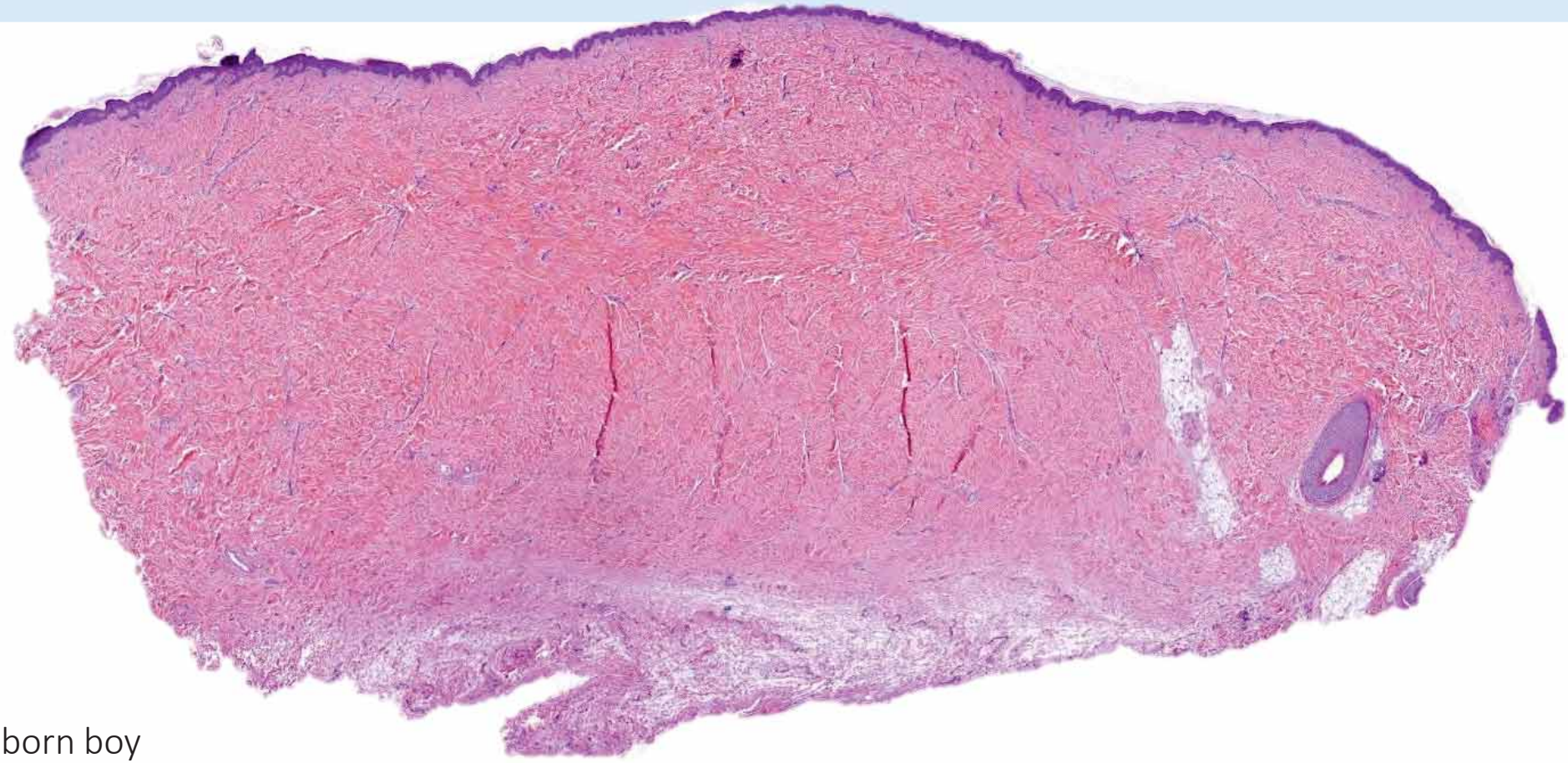


Histology:

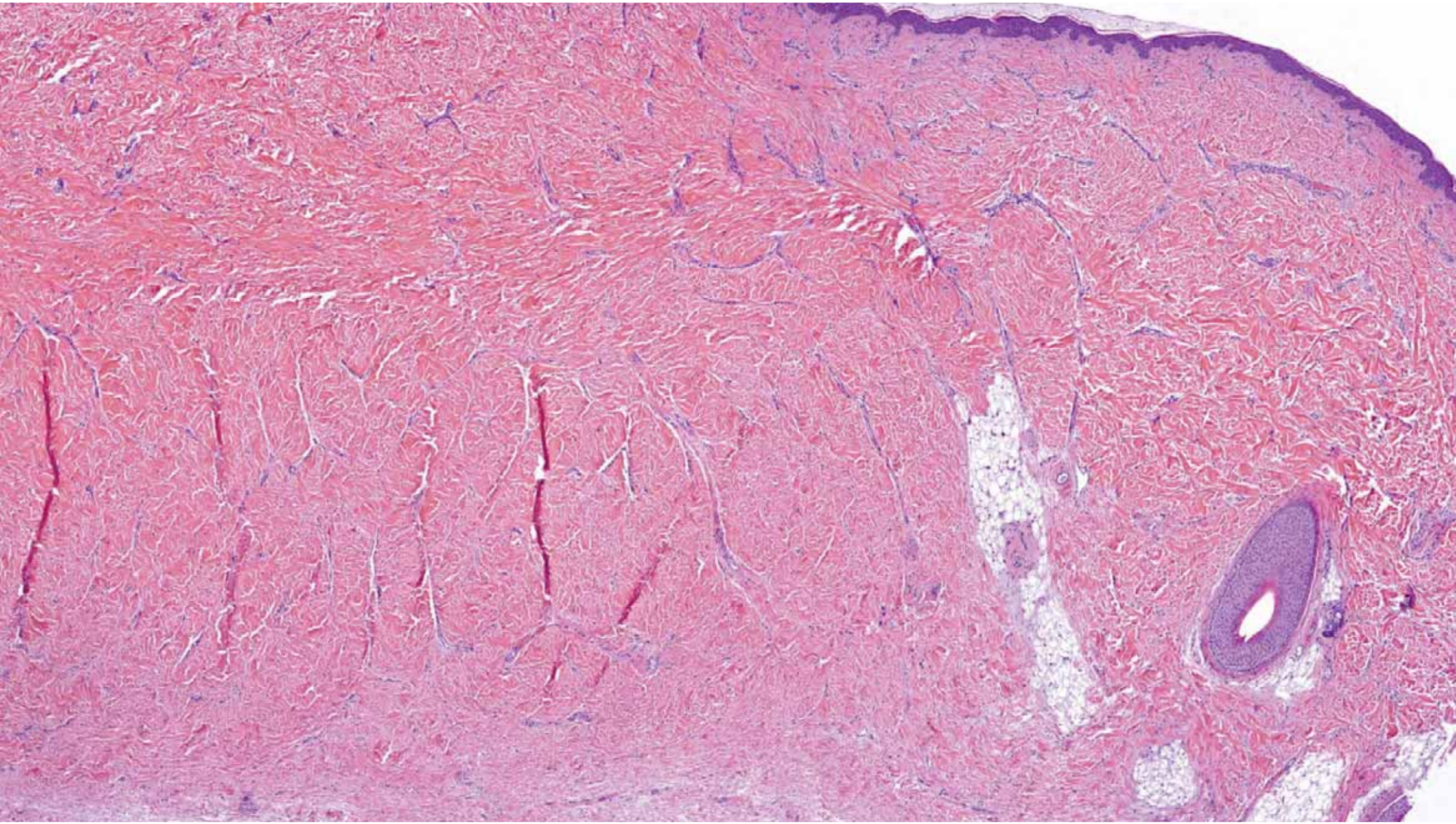
- Hyperkeratosis
- Psoriasiform epidermal hyperplasia, follicular plugging
- Edema
- Separation of collagen fibers
- Capillary vascular dilatation and proliferation

Liang MW et al. Reactive Epidermal Hyperplasia and Angiogenesis of the Rear (REAR): A Proposed Unifying Name for Senile Gluteal Dermatosis and Prurigiform Angiomatosis. Case Reports Dermatopathology. 2022 Oct 13;9(4):343-354.

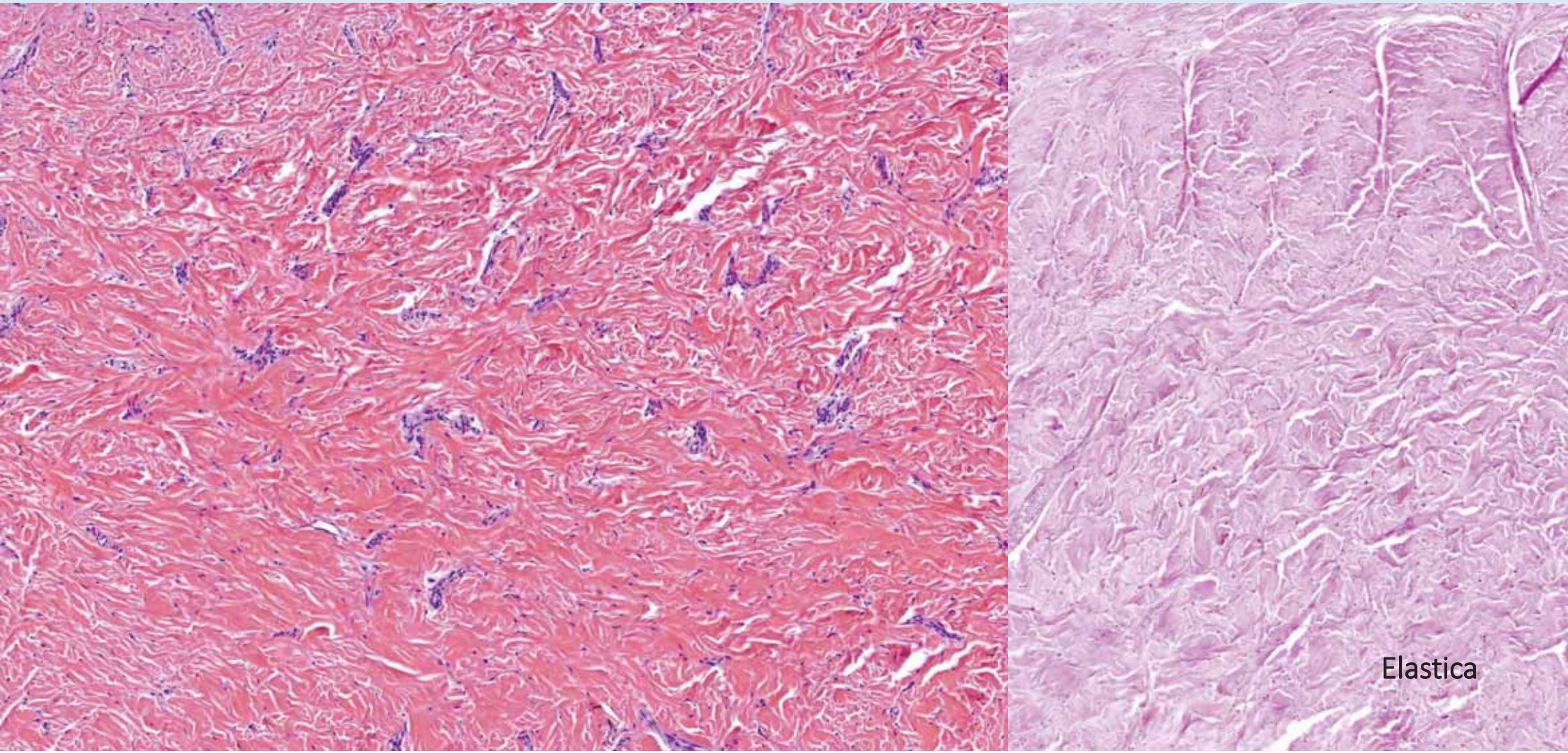
Histology



1-day-old newborn boy
Crust on the scalp, midline, otherwise healthy
Histology taken after surgical excision in the age of 1.5 years



Histology



Clinical presentation

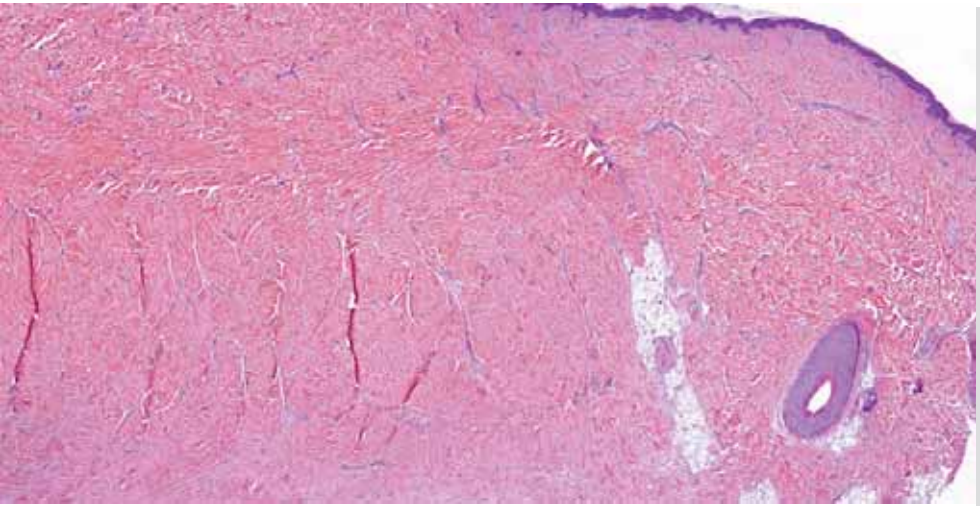
Age: 1.5 years

Hair-less area, scaring

No additional abnormalities

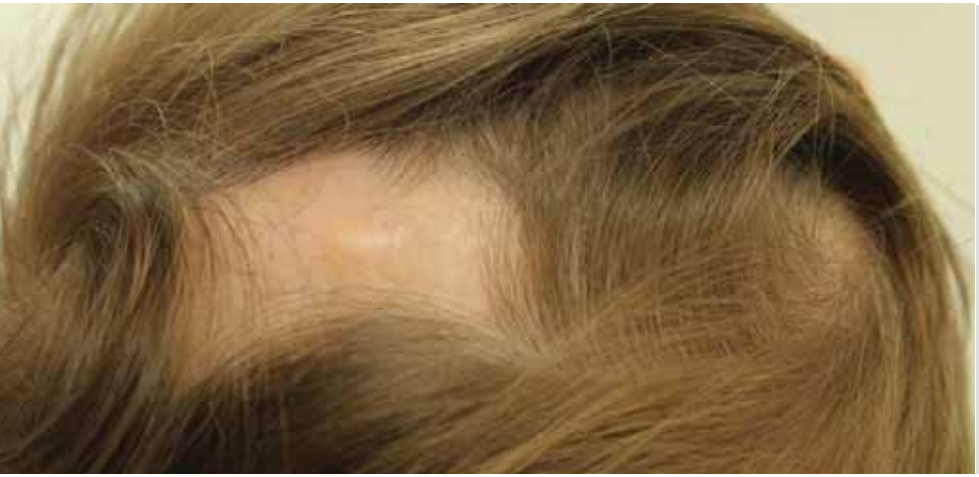
Age-appropriate development

Summary of the findings



Histology:

Fibrosis with loss of adnexal structures and no elastic fibers



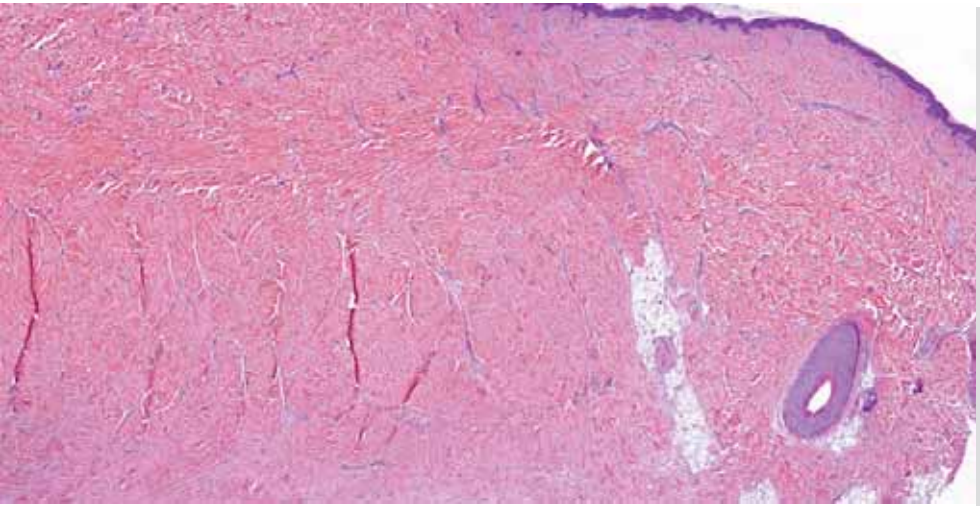
Clinical presentation:

Ulceration and crust in the midline of the scalp after birth
After 1.5 year: circumscribed hair loss

diagnosis

?

Summary of the findings



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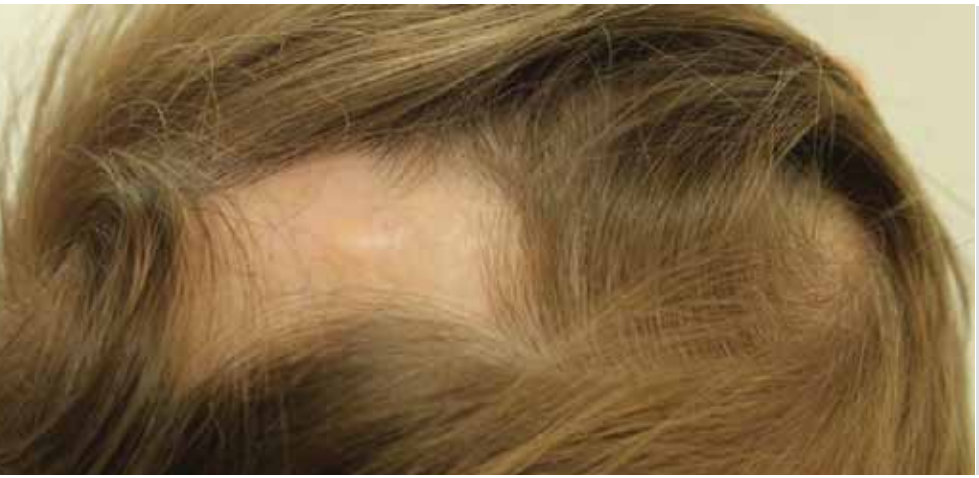


Clinical presentation:

Ulceration and crust in the midline of the scalp after birth
After 1.5 year: circumscribed hair loss

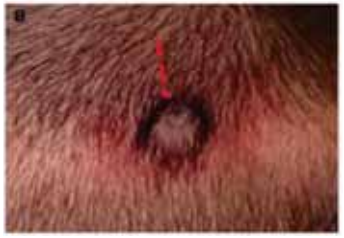
Aplasia cutis congenita

Aplasia cutis congenita (ACC)

- Location:
  - Most common: scalp (especially the vertex), ~70–85% of cases.
  - Can also occur on the trunk, limbs, or in a symmetric pattern (especially in syndromic cases).

- Lesion Characteristics:
  - Varies from a small, superficial erosion or scar-like area to a large full-thickness defect involving skin, subcutaneous tissue, and even skull or dura
  - Lesions may be ulcerated or crusted at birth, membrane-covered (like a thin translucent film) or healed scars if detected later
  - Can be solitary or multiple

- Hair collar sign:
  - A ring of darker or denser hair around the lesion



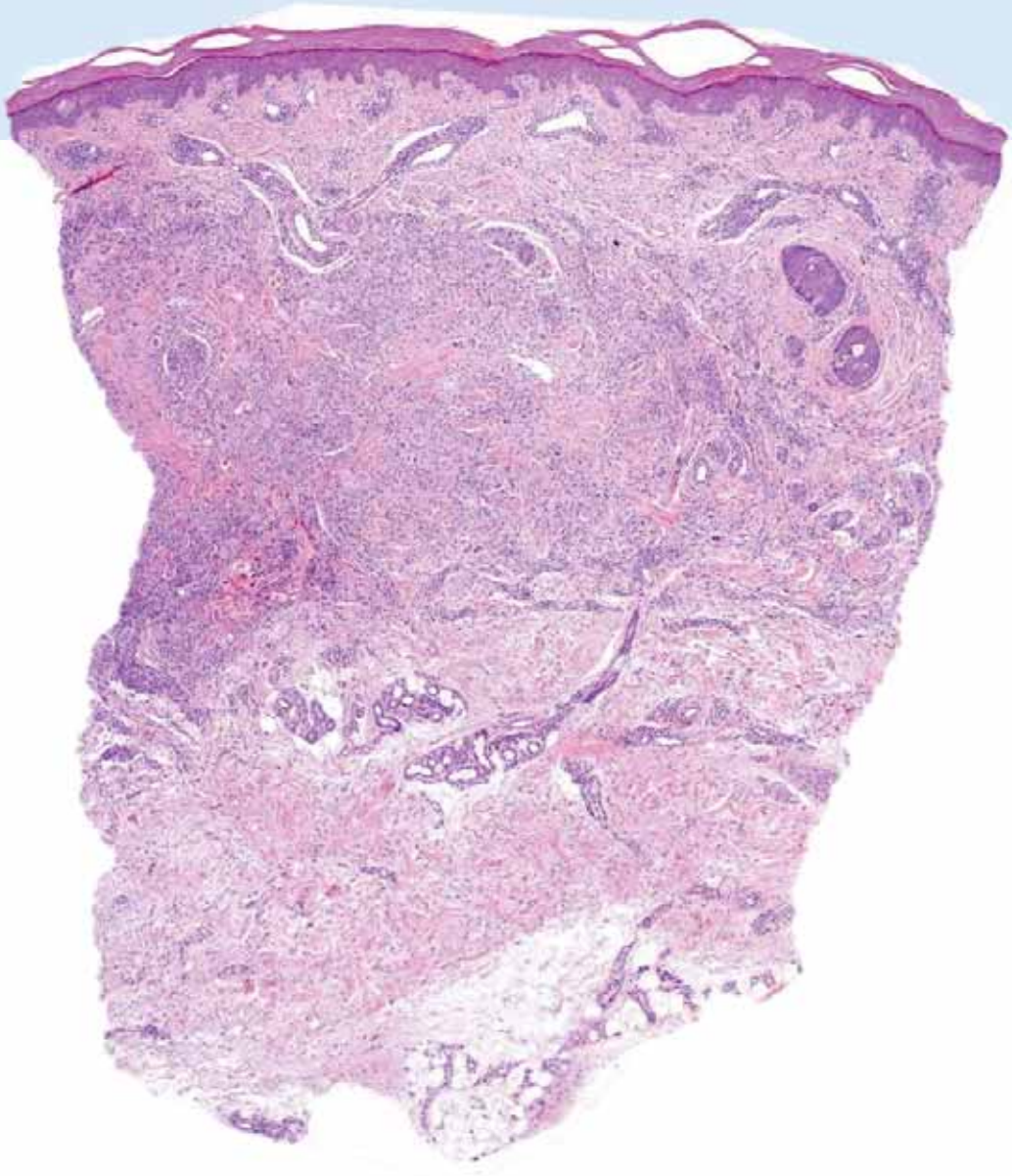
From: Shah S, et al. BMJ Case Rep 2024;17

- Associated Anomalies:
  - In severe cases, especially with larger scalp defects, underlying skull or brain structures can be absent or malformed

Risks and Complications:

- Infections: Open skin lesions are susceptible to bacterial infections (e.g., Staphylococcus aureus, Streptococcus pyogenes)
- Hemorrhage: If underlying vasculature is exposed or eroded
- Dehydration: Especially in large lesions in newborns
- CNS-involvement: With deeper defects, especially over the skull:
  - Meningitis
  - Herniation of brain tissue (encephalocele)
- Cosmetic concerns

Histology

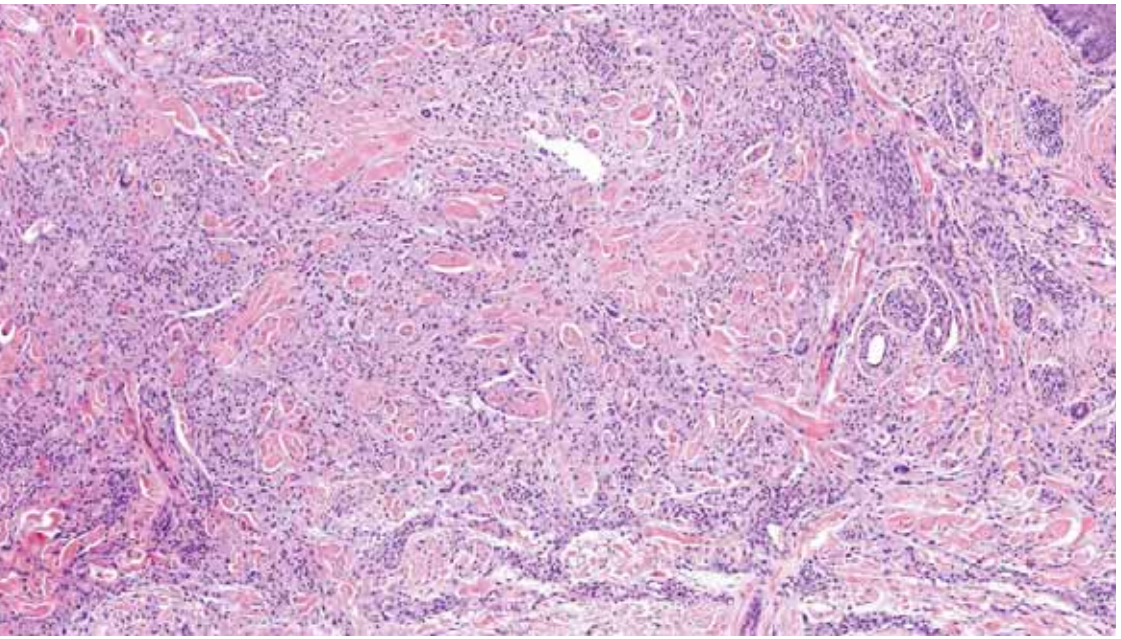


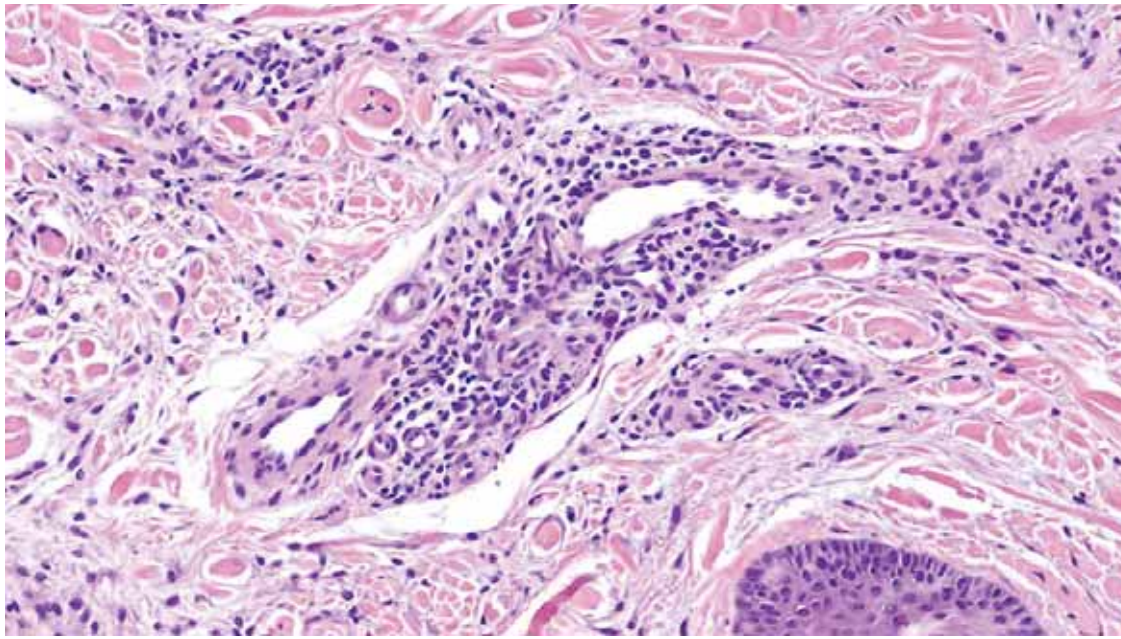
43-year-old man

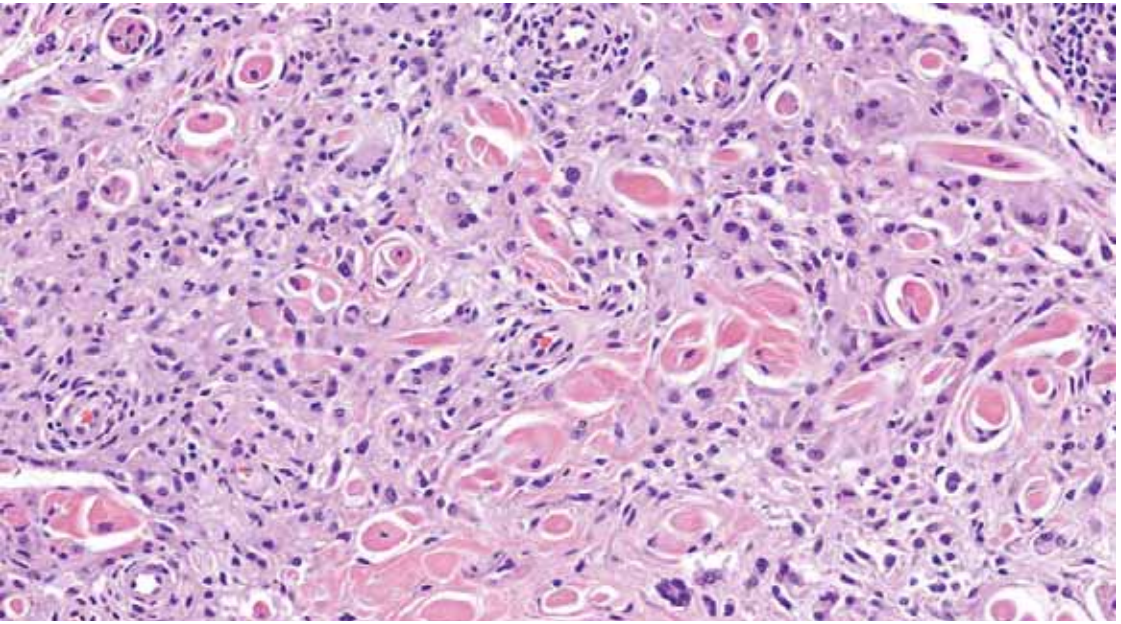
Erythematous lesion on the arm

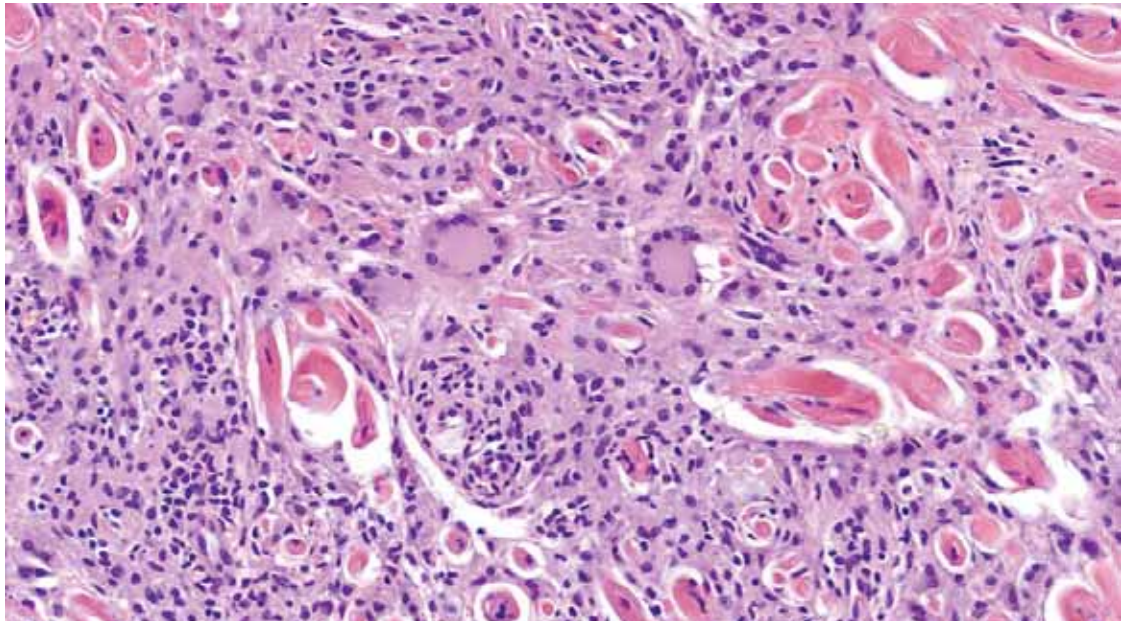
Suspected diagnosis: Granuloma annulare,

nodule related to rheumatism



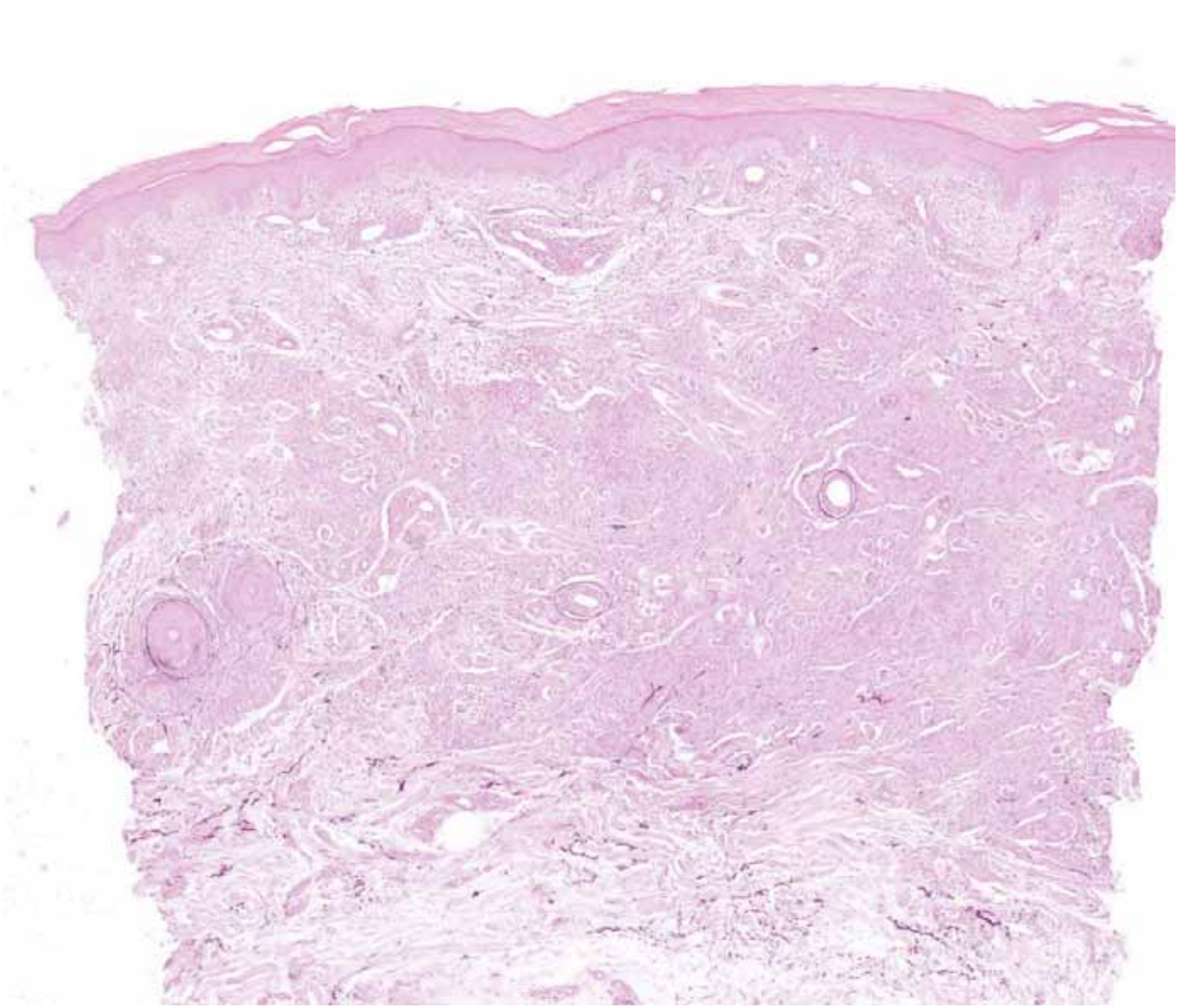




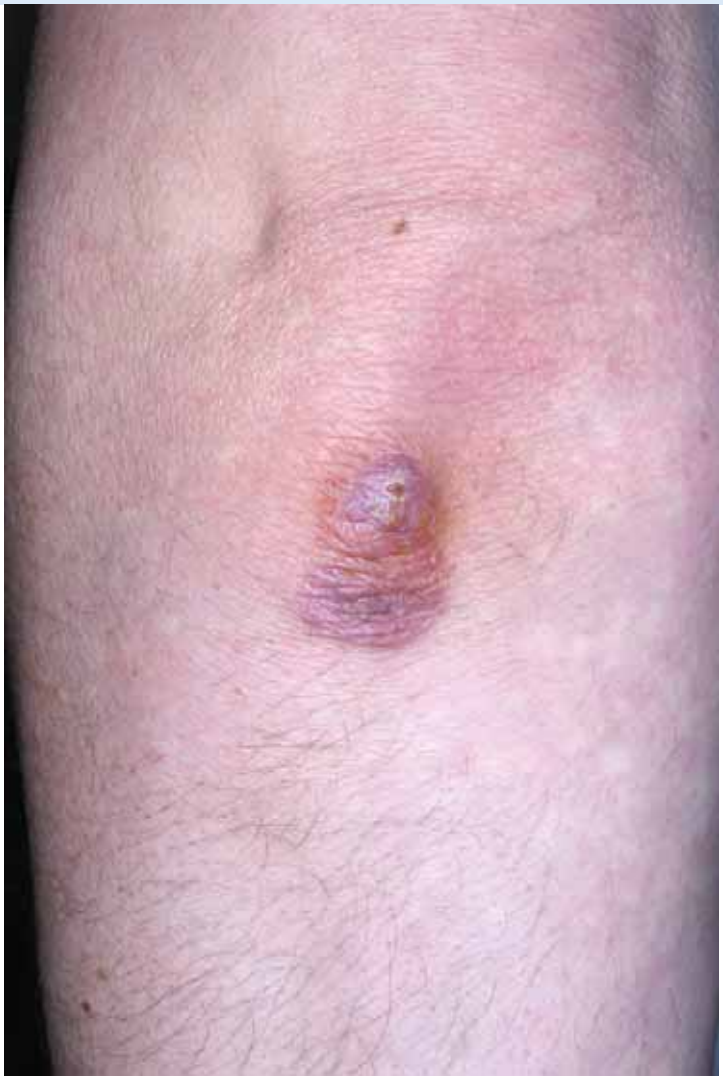


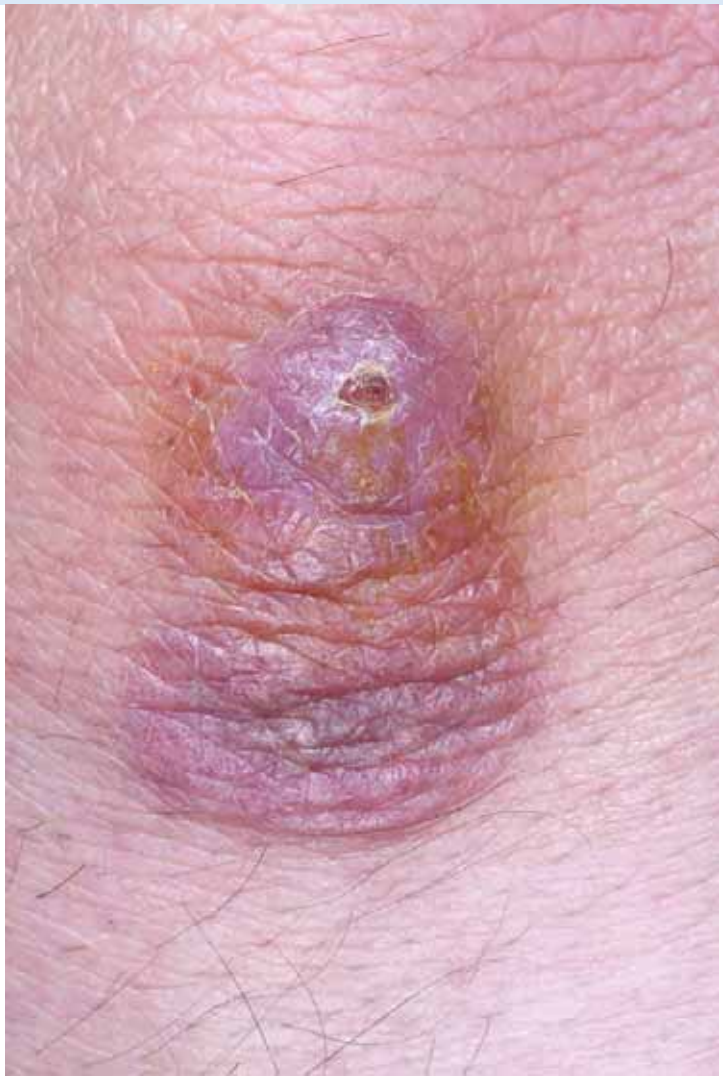
Elastica:

reduced elastic fibers

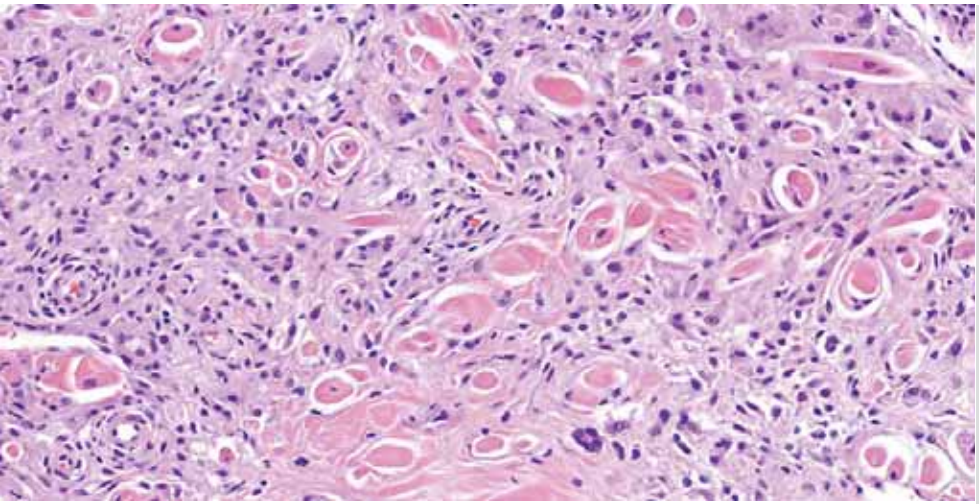


Clinical presentation



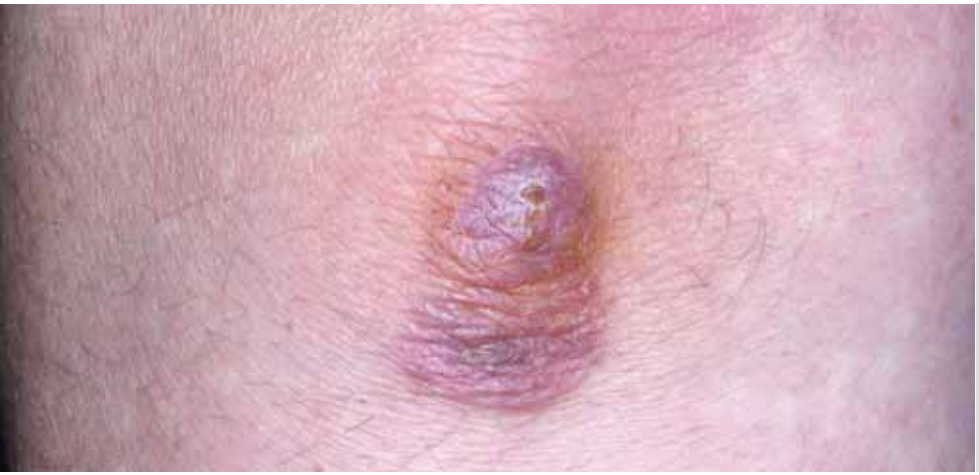


Summary of the findings



Histology:

- Histiocytic interstitial infiltrate with entrapment of the collagen bundles (pseudorosettes)
- Lymphocytes, few plasma cells, giant cells



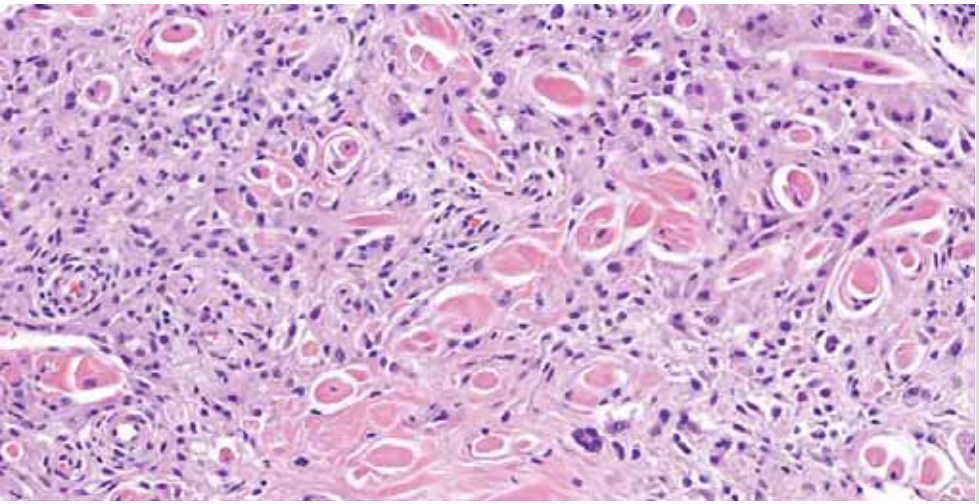
Clinical presentation:

- Brownish-reddish nodule on the elbow, ulceration

diagnosis

?

Summary of the findings



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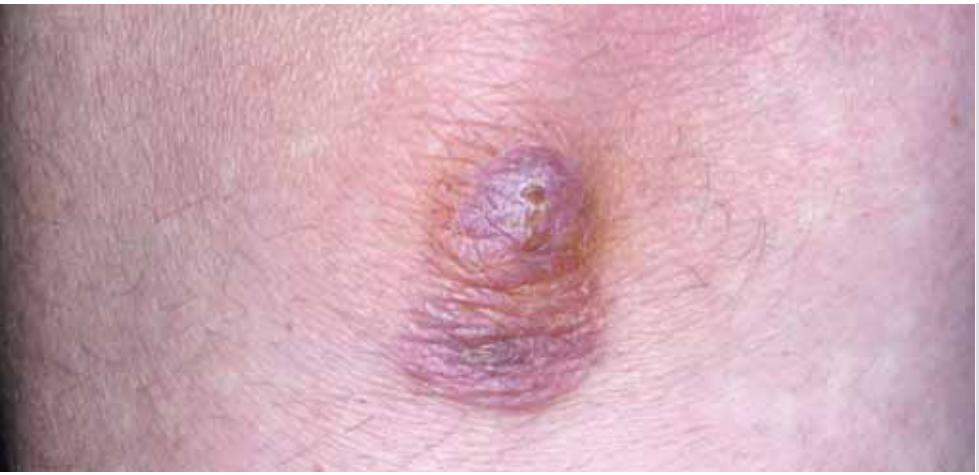


Clinical presentation:

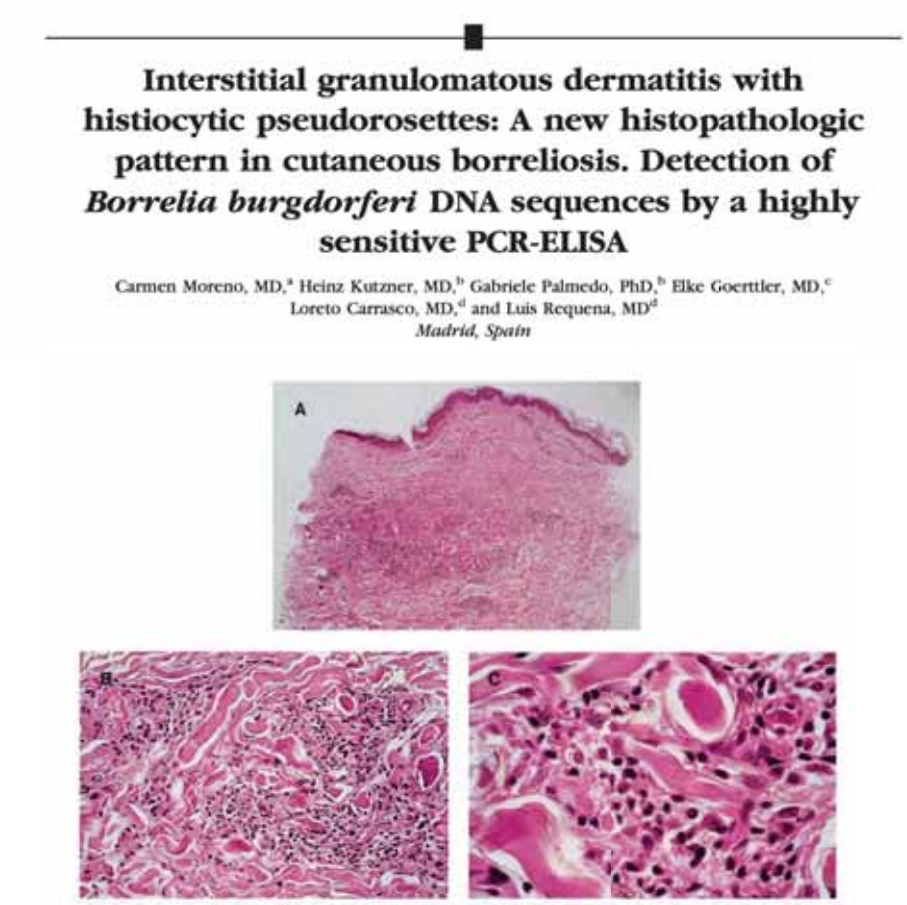
- Brownish-reddish nodule on the elbow, ulceration

borreliosis

Interstitial granulomatous dermatitis with histiocytic pseudorosettes

Histopathologic findings:

- Interstitial inflammatory infiltrate mostly composed of histiocytes
- Dispersed among the collagen bundles of the dermis
- Focal areas of small pseudorosettes (histiocytes radially disposed around thick collagen bundles)
- Few plasma in some cases (2/11 cases)
- Histology closely resembling interstitial type of granuloma annular

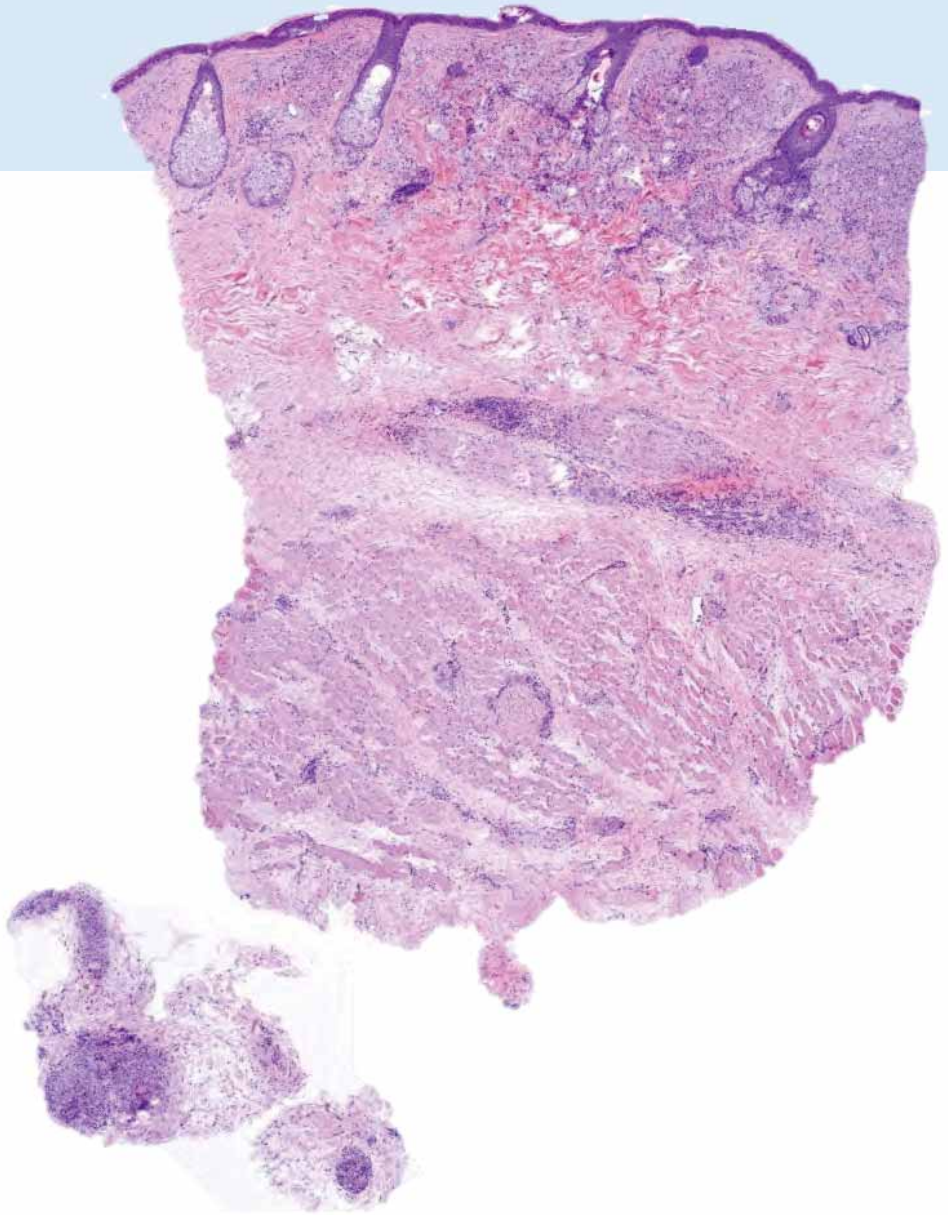


Interstitial granulomatous dermatitis with histiocytic pseudorosettes: A new histopathologic pattern in cutaneous borreliosis. Detection of *Borrelia burgdorferi* DNA sequences by a highly sensitive PCR-ELISA

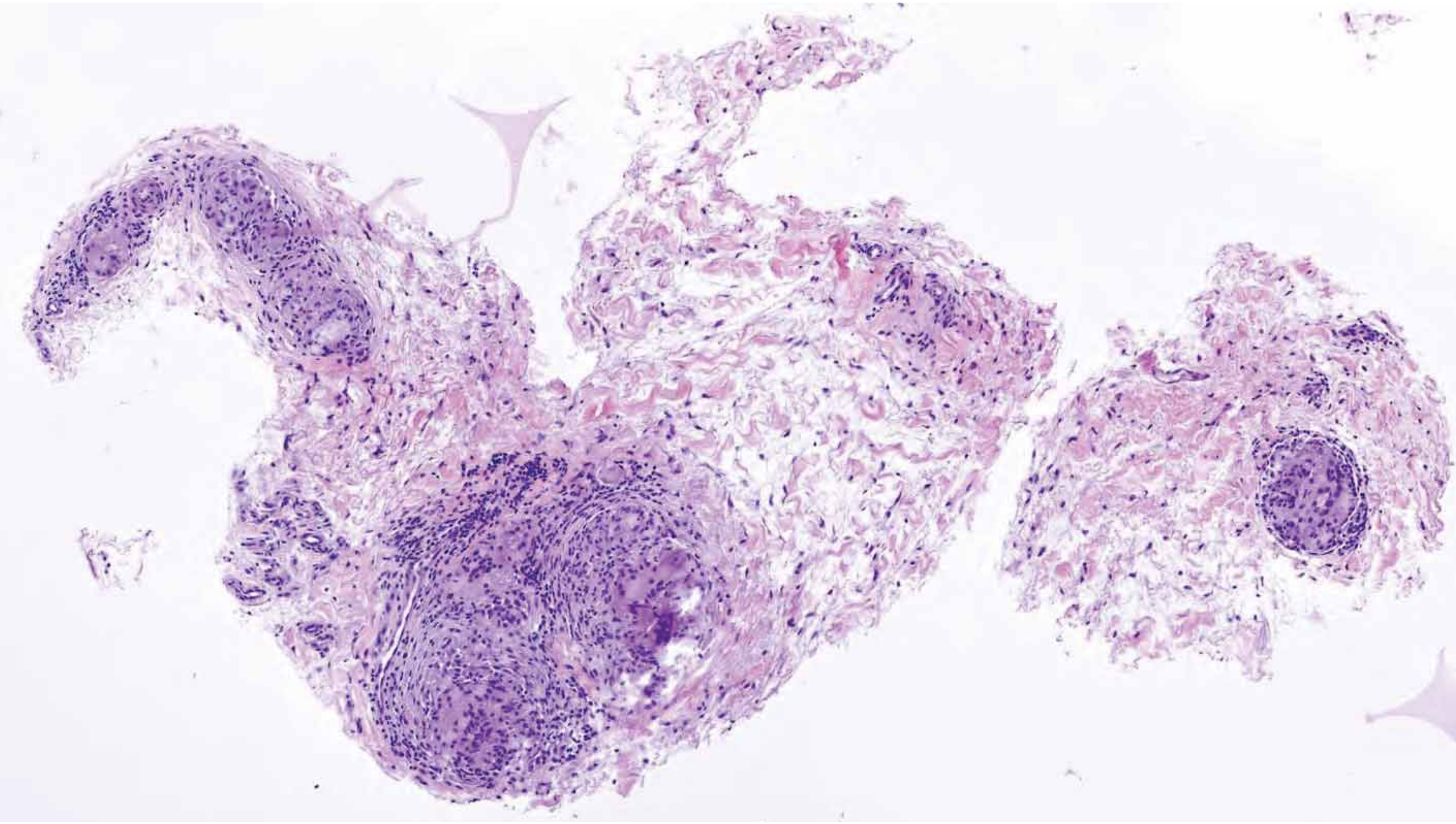
Carmen Moreno, MD,[a] Heinz Kutzner, MD,[b] Gabriele Palmedo, PhD,[b] Elke Goerttler, MD,[c] Loreto Carrasco, MD,[d] and Luis Requena, MD[d]
Madrid, Spain

Moreno C, Kutzner H, Palmedo G, Goerttler E, Carrasco L, Requena L. Interstitial granulomatous dermatitis with histiocytic pseudorosettes: A new histopathologic pattern in cutaneous borreliosis. Detection of Borrelia burgdorferi DNA sequences by a highly sensitive PCR-ELISA . Am Acad Dermatol 2003;48:376-84.

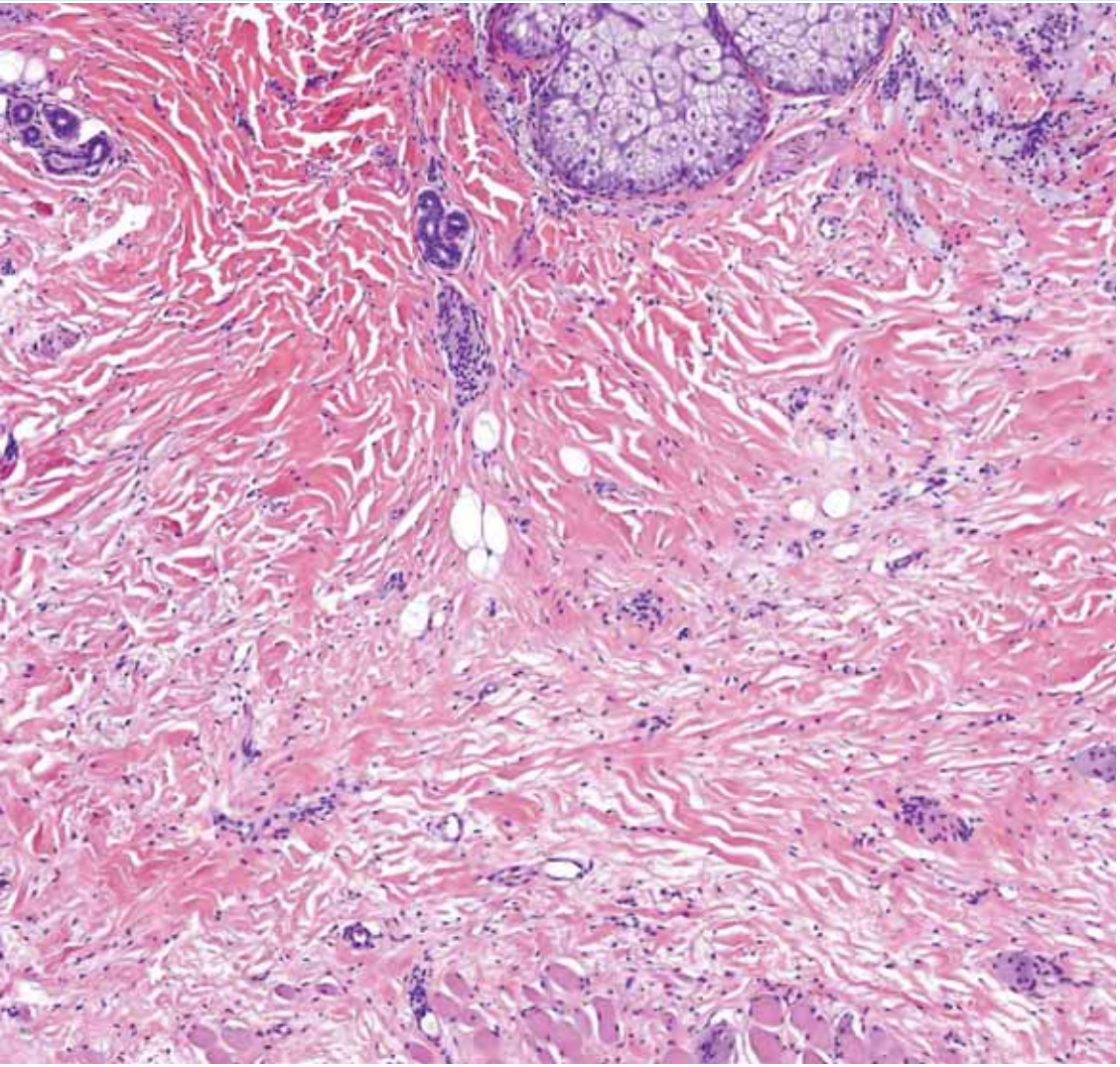
Histology

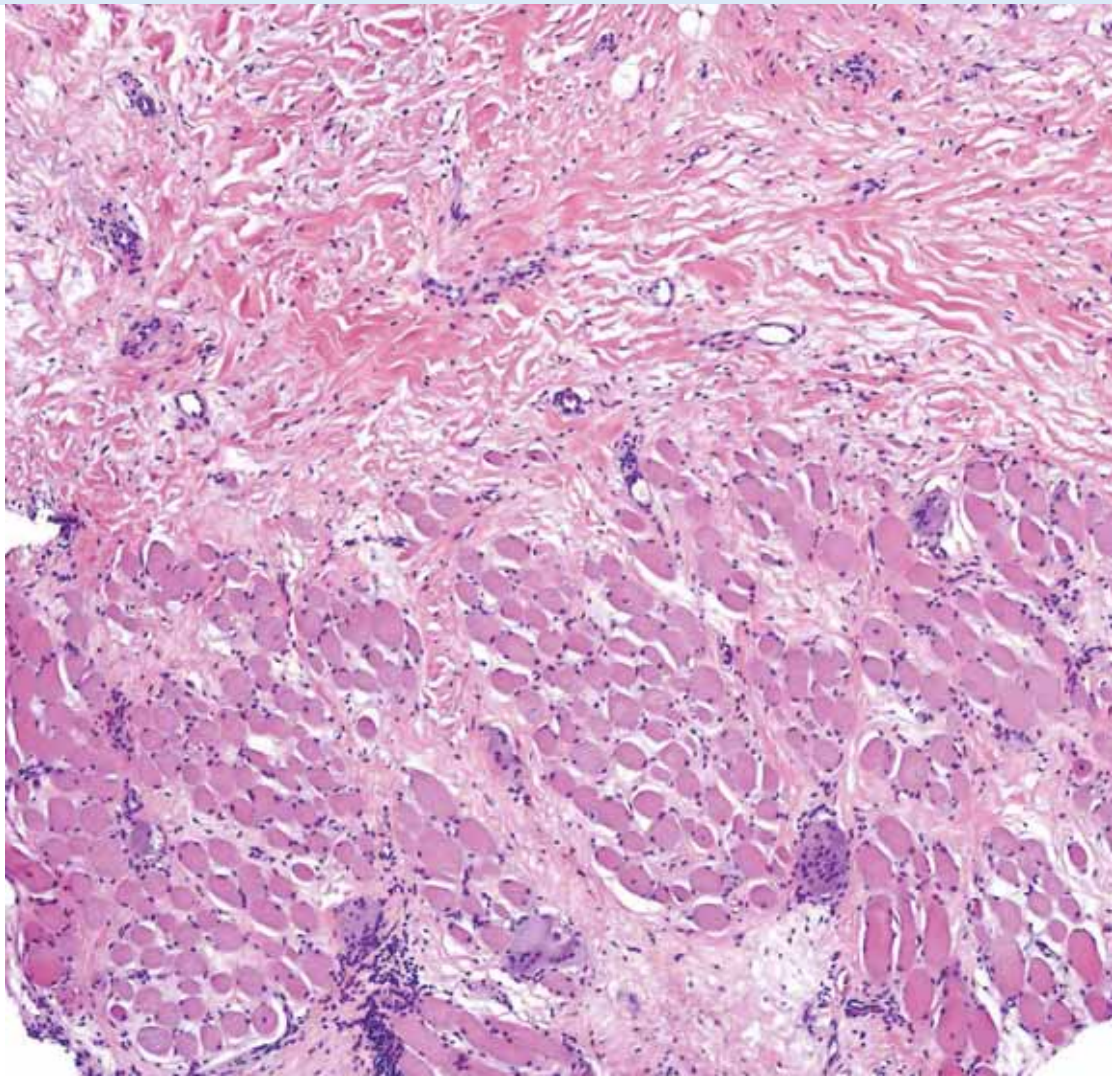


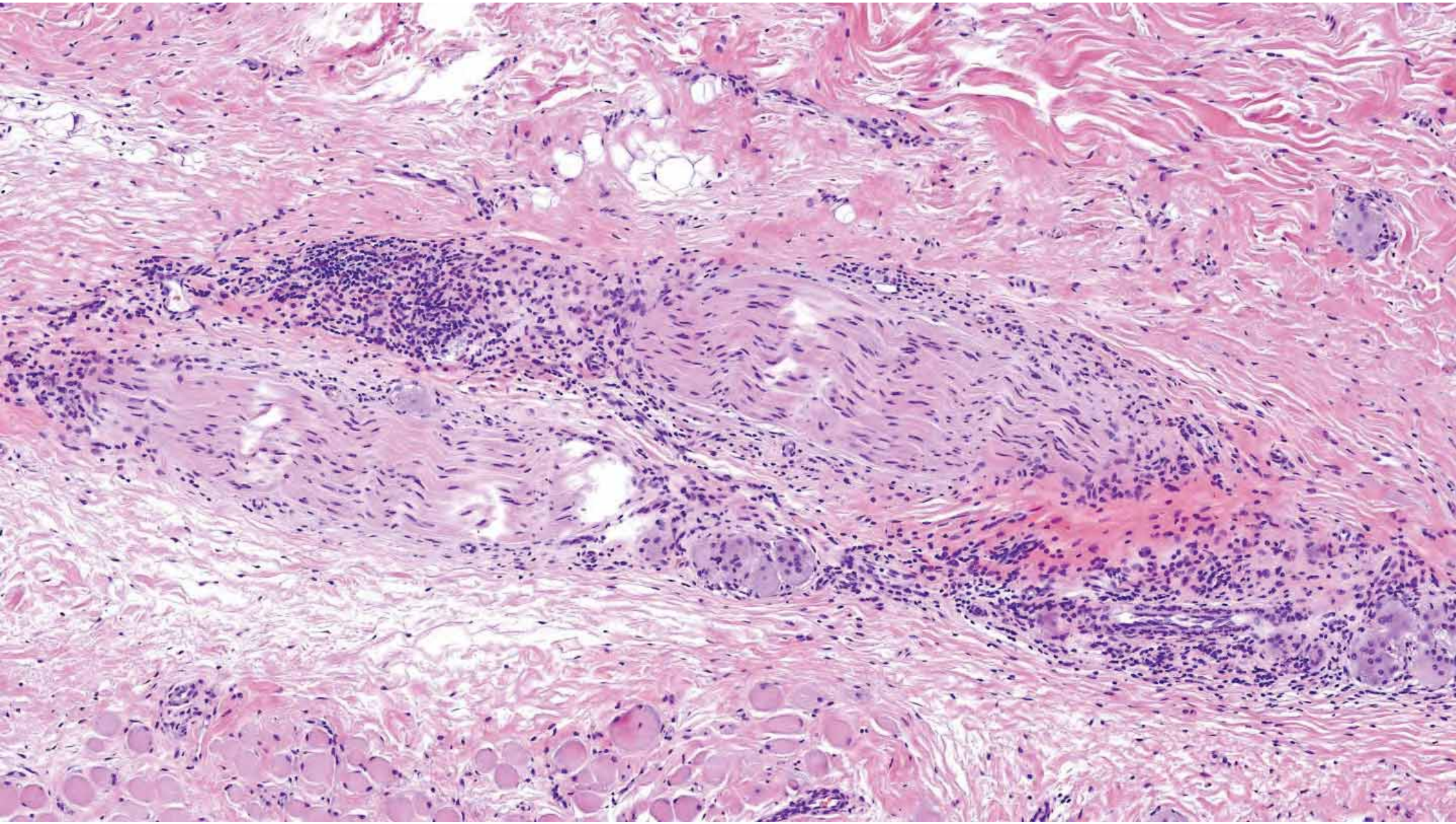
58-year-old women
For 10 years slowly growing atrophic plaque on the forehead
Previous diagnosis: sarcoidosis
No treatment response: confirm diagnosis

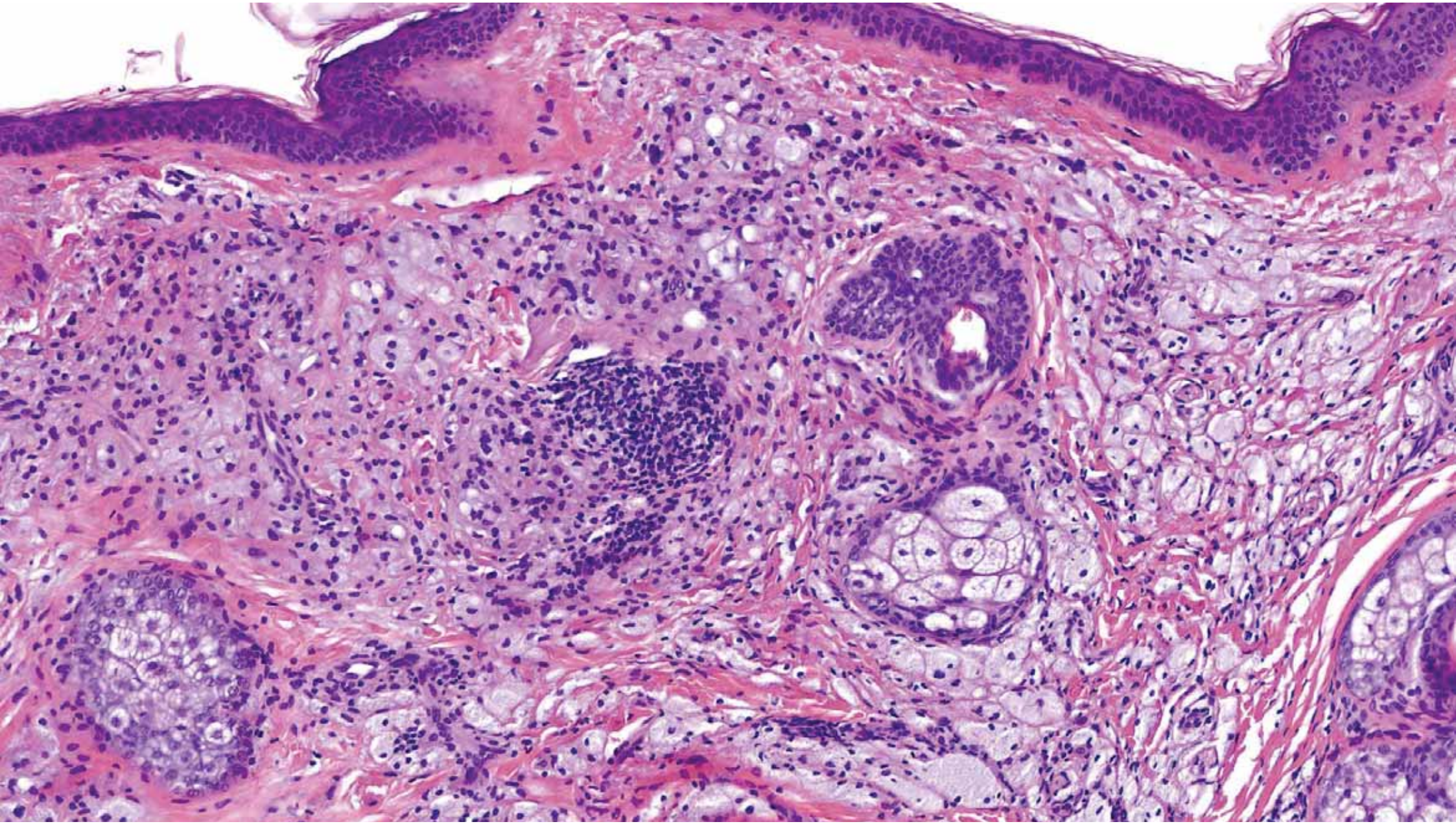


Histology

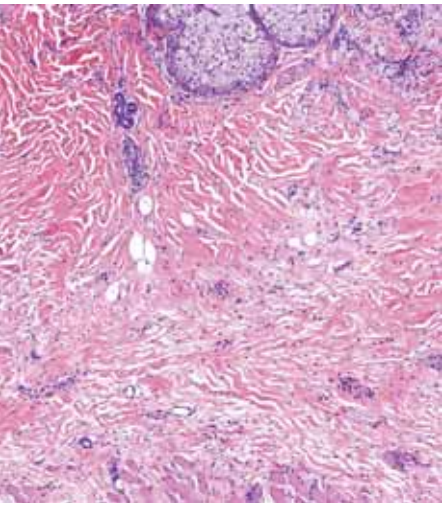


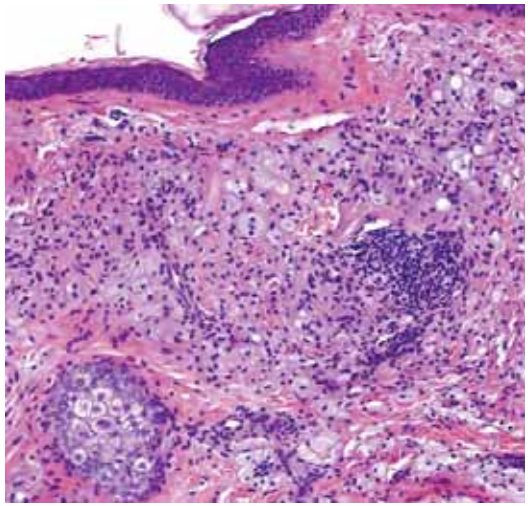






Summary of the findings





Histology:

- Fibrosis, granulomatous infiltrate, giant cells
- Lipid-laden macrophages (foam cells)

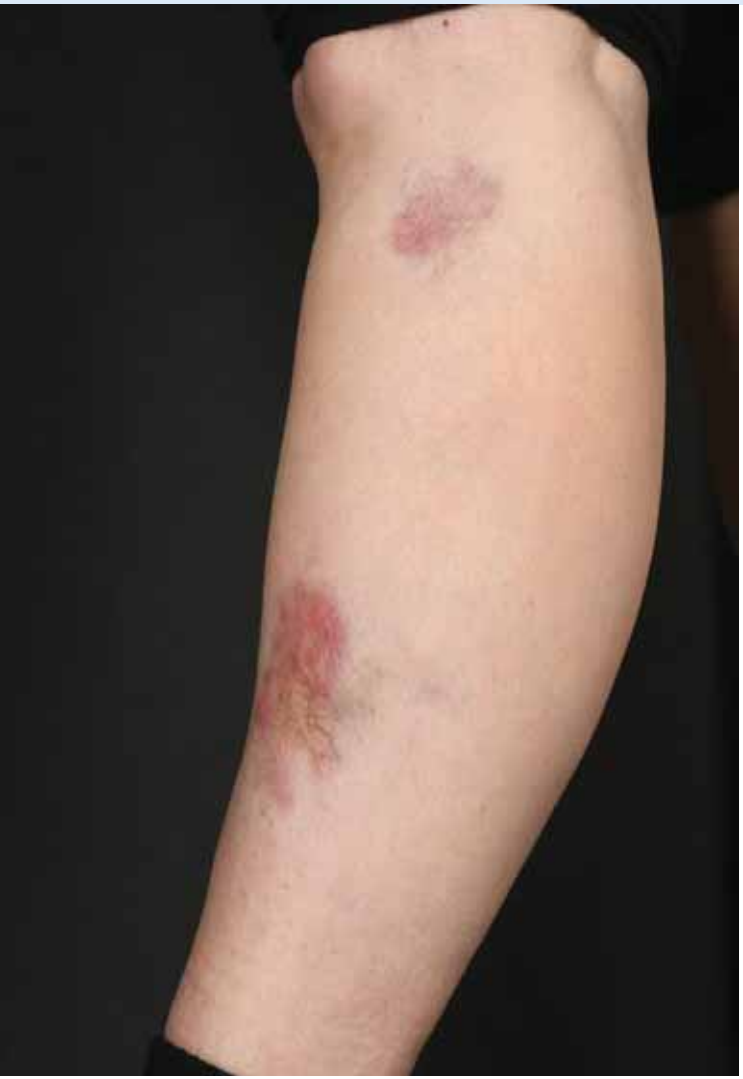
Clinical presentation:

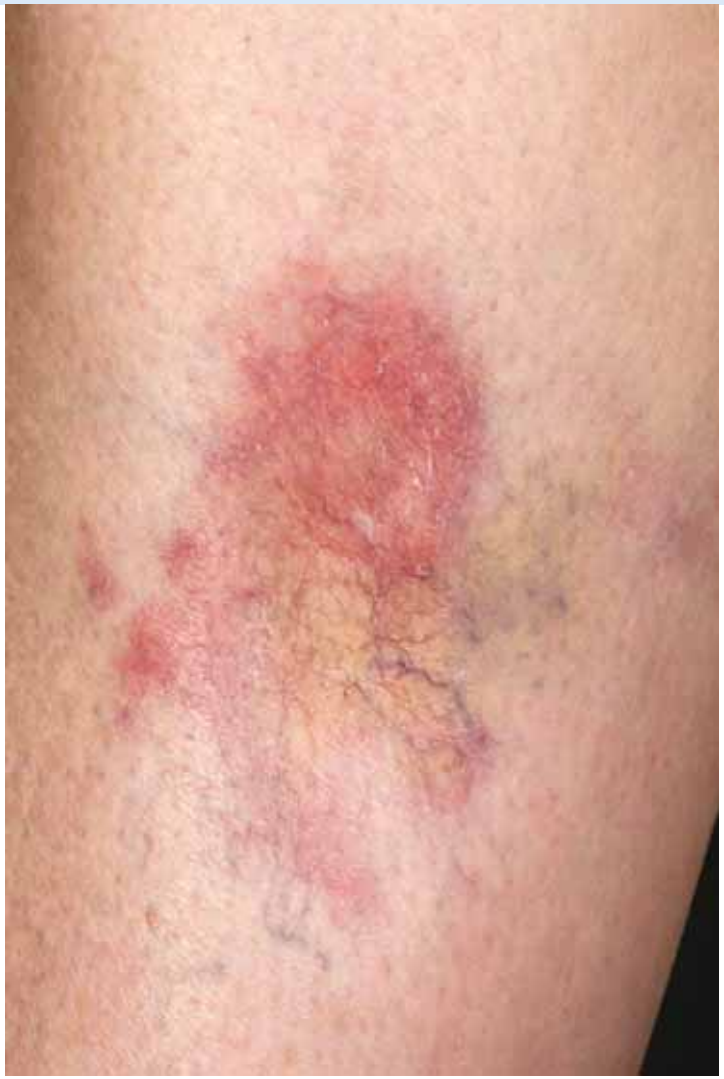
- Central atrophy, teleangiectasia
- Yellow plaques at the edges of the skin lesion

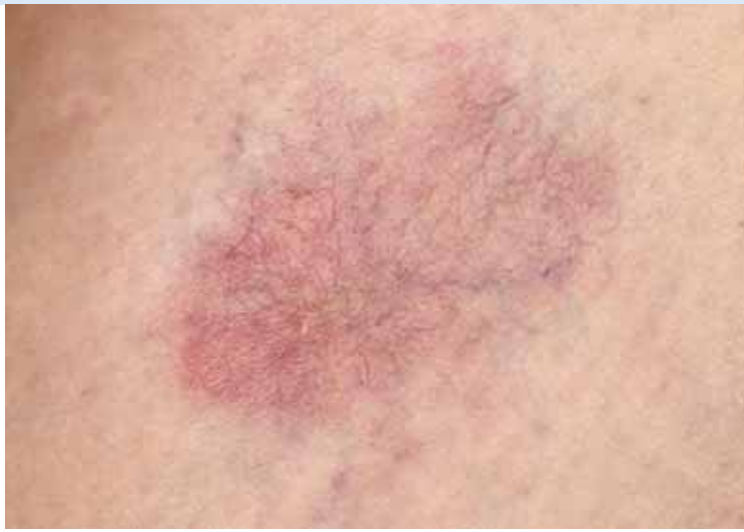
diagnosis

?

Clinical presentation

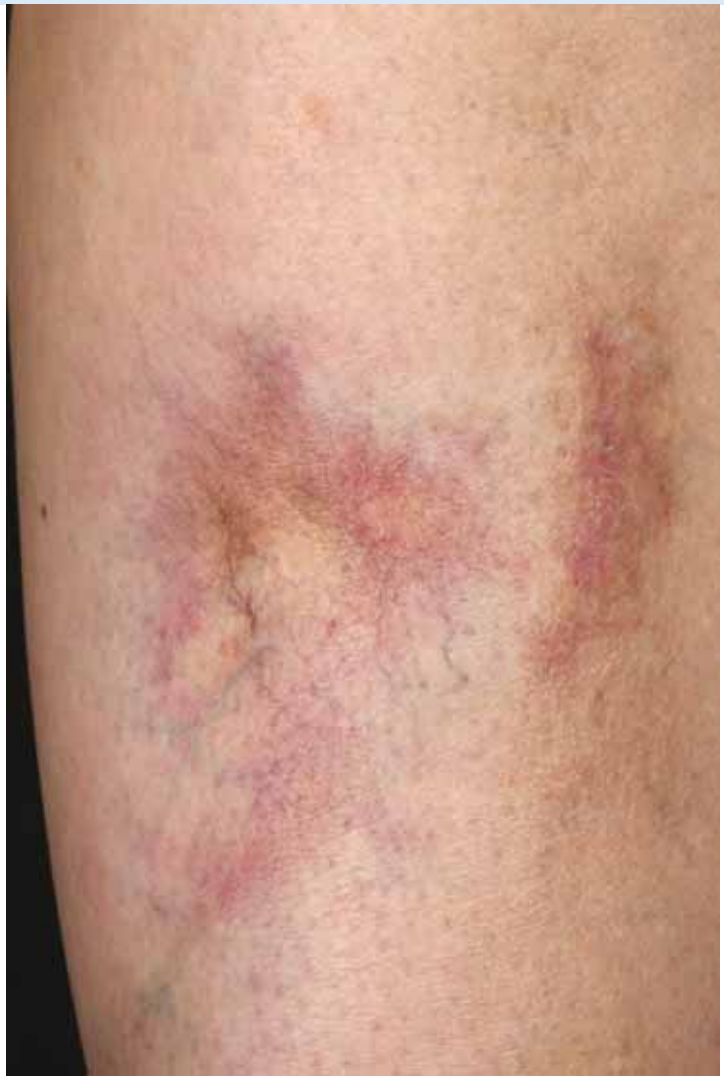


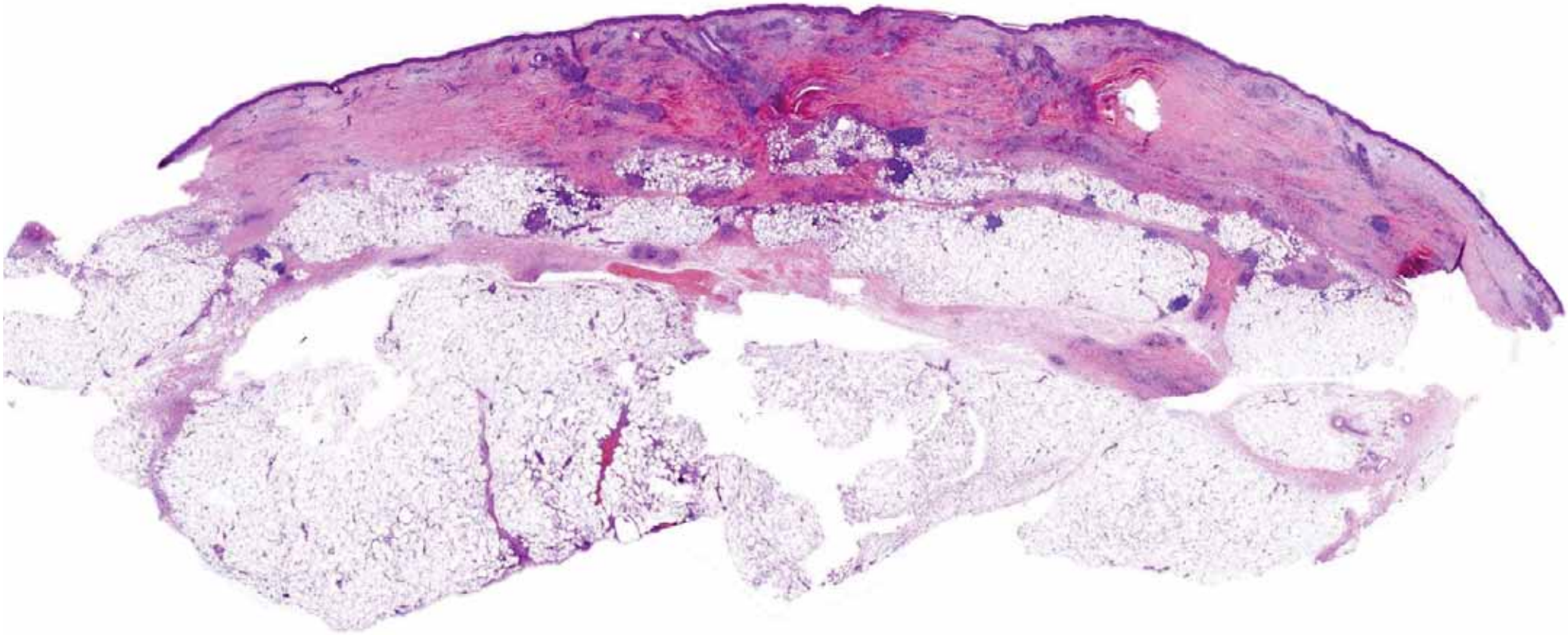


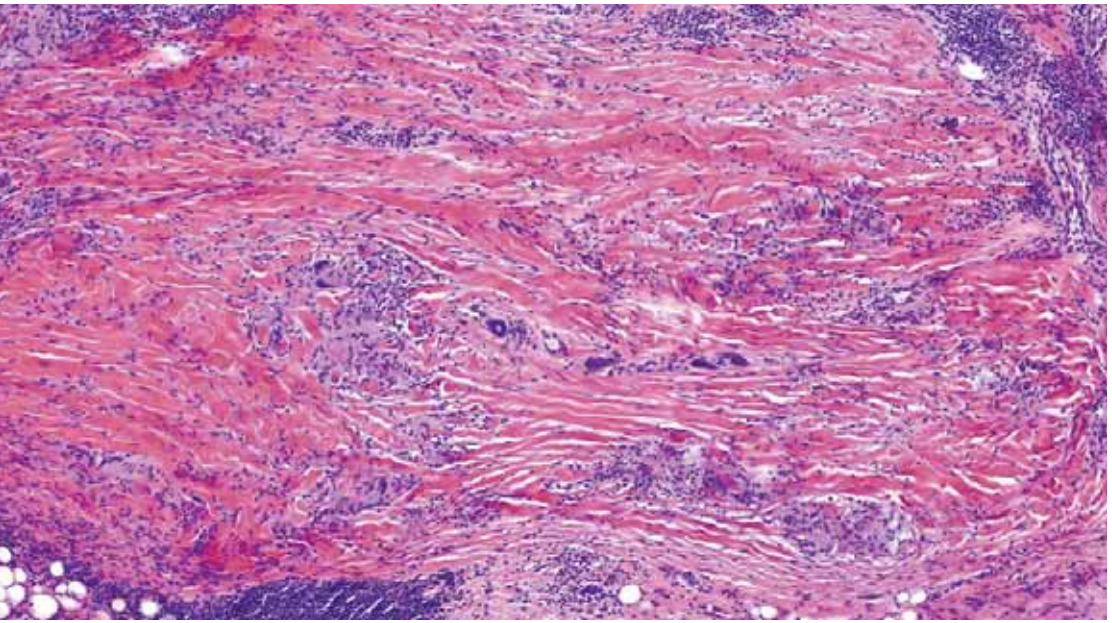


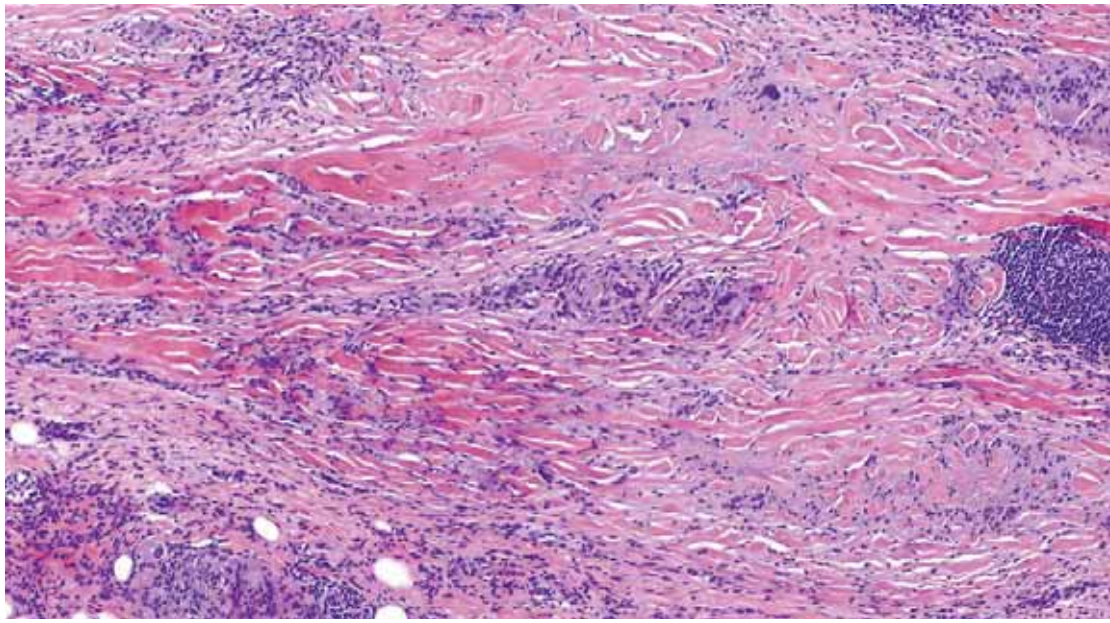
no diabetes
no hematologic disease
no lipid metabolism disorder

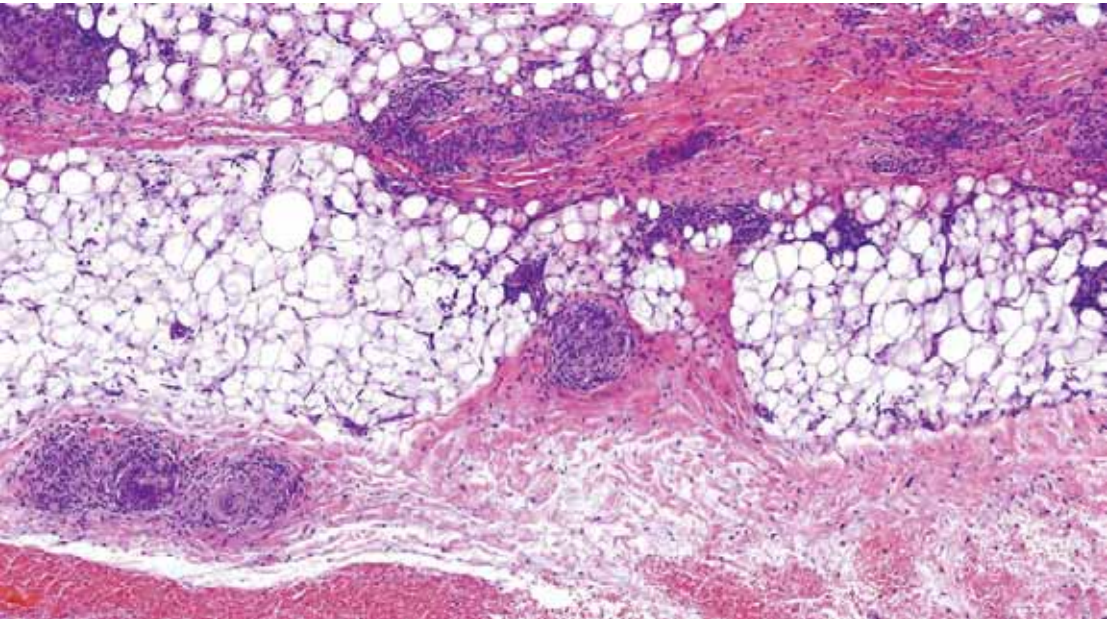
Clinical presentation

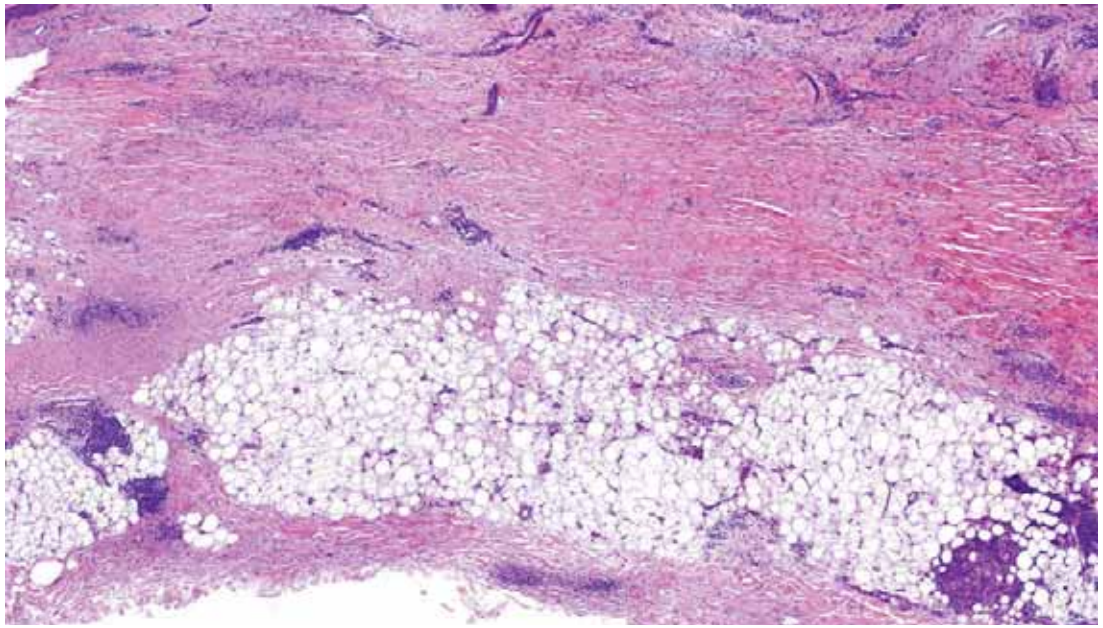




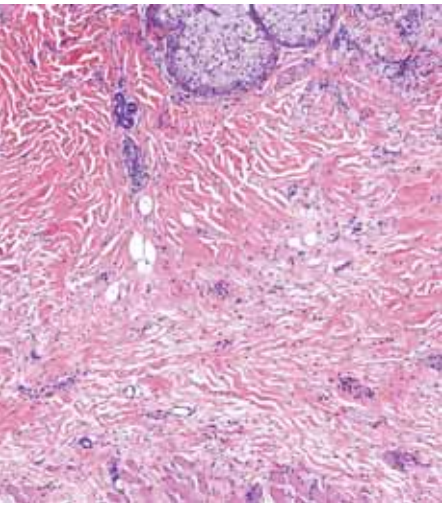


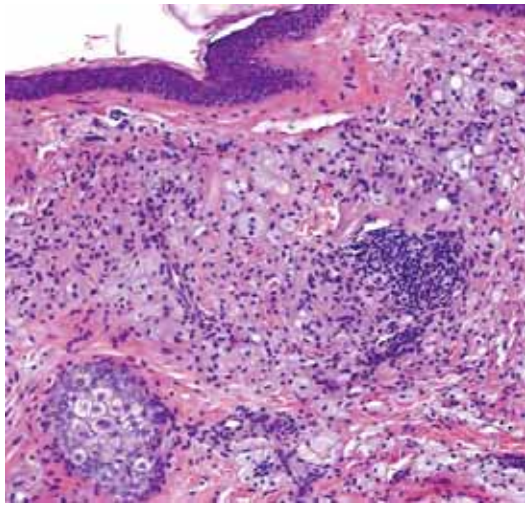






Summary of the findings





Histology:

- Fibrosis, granulomatous infiltrate, giant cells
- Lipid-laden macrophages

Clinical presentation:

- Central atrophy, teleangiectasia
- Yellow plaques at the edges of the skin lesion

Necobiosis lipoidica

Necrobiosis lipoidica

Granulomatosis disciformis chronica et progressiva / Miescher‘s granuloma (Leder et al. 1948):

In Europe:

- Not a separate disease but most probably necrobiosis lipoidica in patients without diabetes mellitus

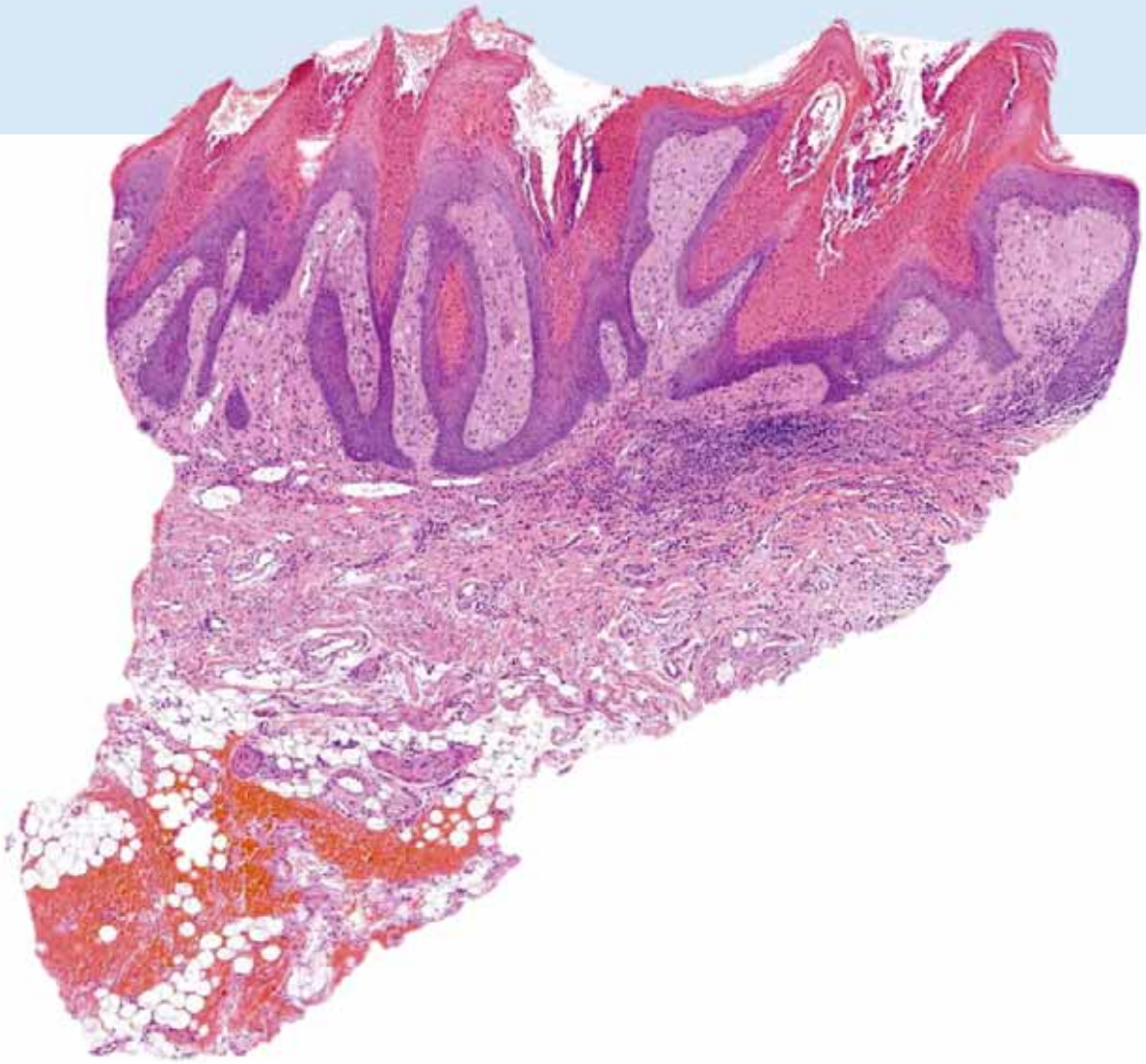
In the USA:

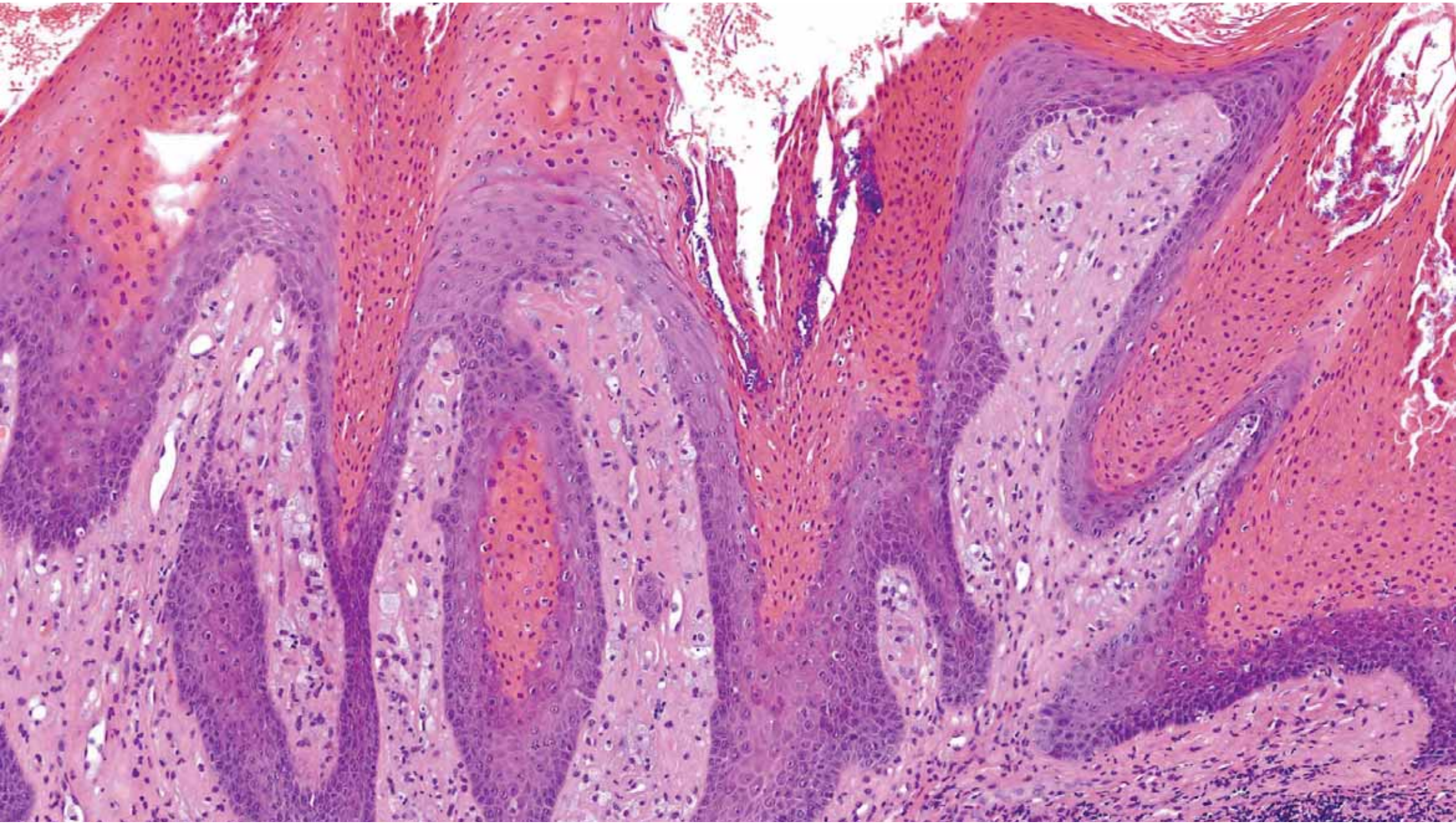
- The term granulomatosis disciformis chronica et progressiva / Miescher’s granuloma of the face is used for necrobiosis lipoidica on the forehead and head
- The changes consist of circulating or more serpiginous lesions with central healing and depigmentation, especially at the hairline.
- Often no associated diabetes mellitus

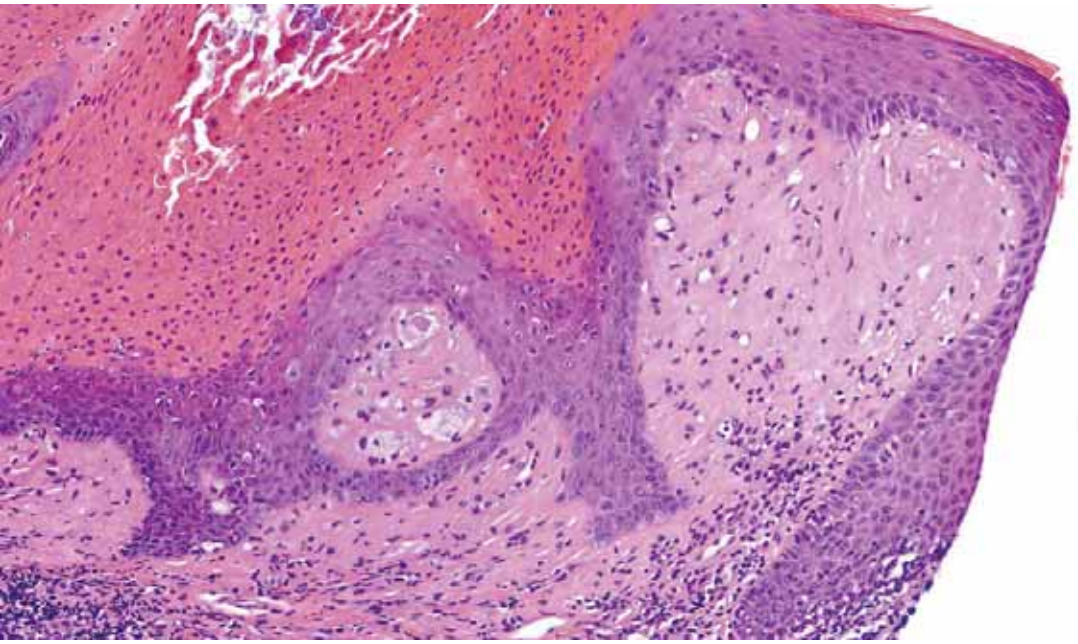
Bergler-Czop B, et al. Mischer`s granulomatosis (granulomatosis disciformis chronica et progressiva) in a non-diabetic patient. Diagnostic Pathology 2009,4:28

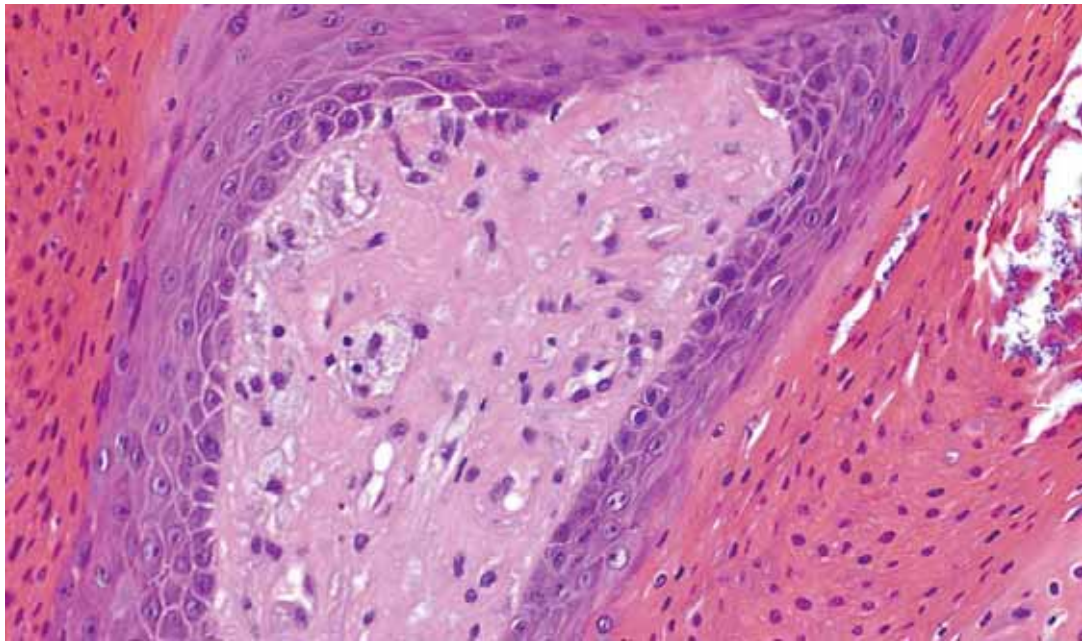
Histology

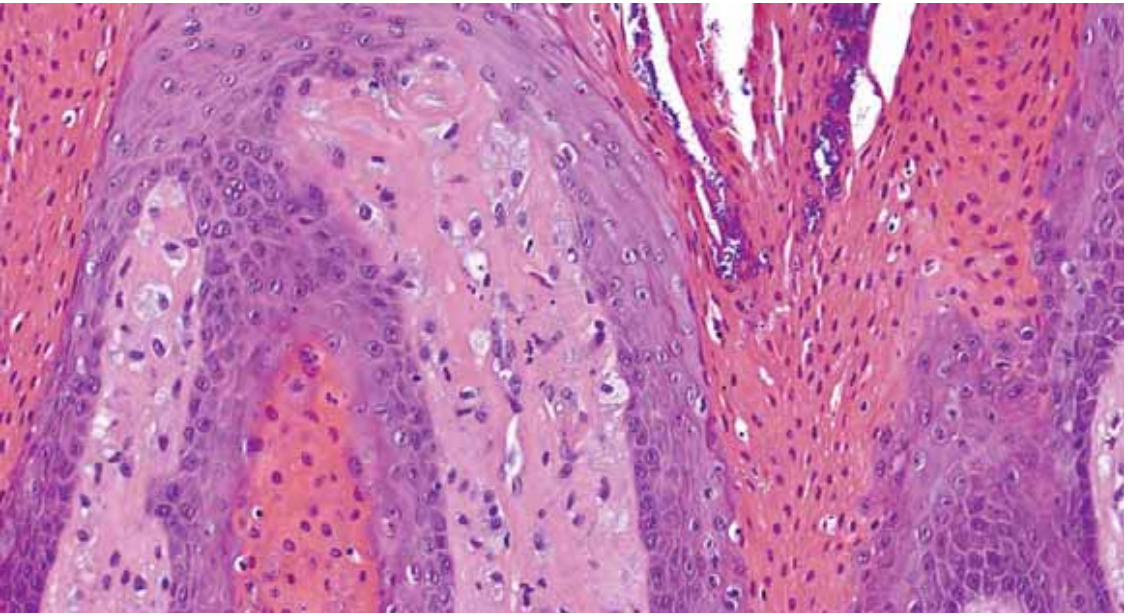
64-year-old male
Lower lip
Suspected diagnosis:
squamous cell carcinoma

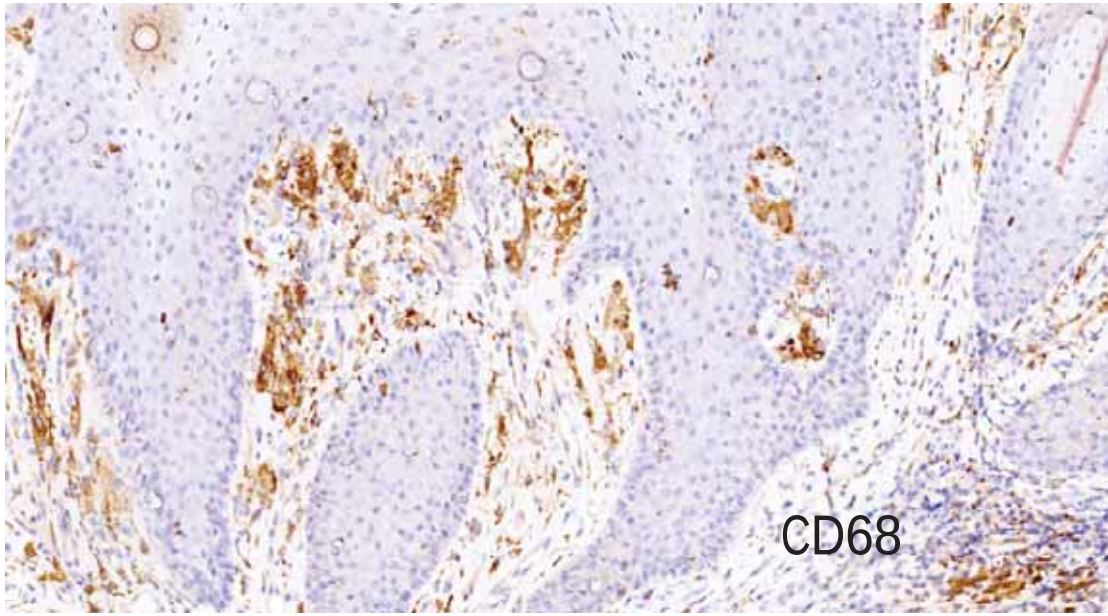




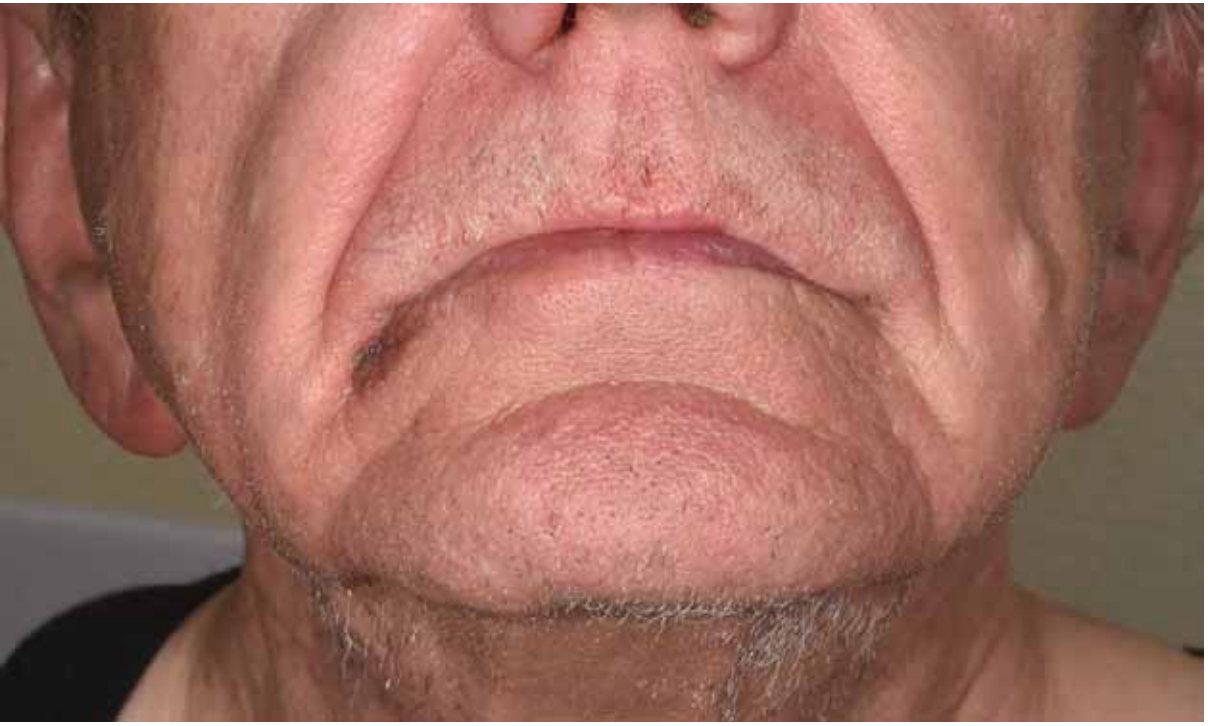


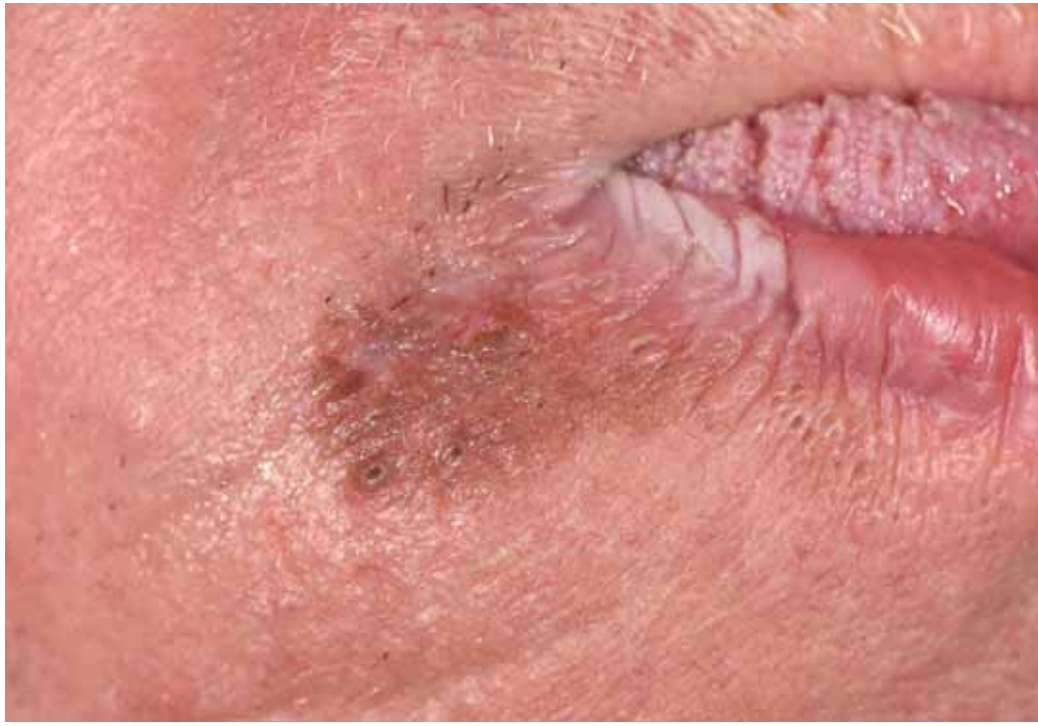




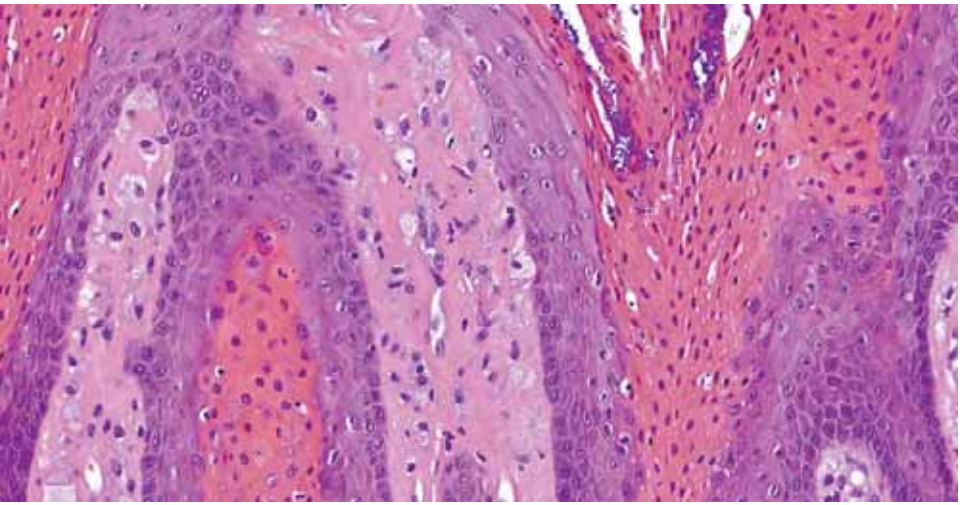

CD68

Clinical presentation



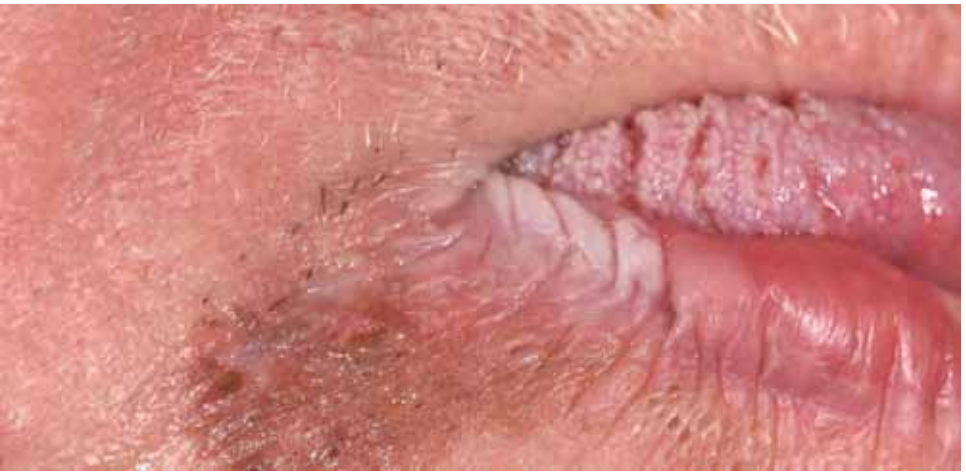


Summary of the findings



Histology:

Verruciform papillomatosis
Parakeratotic hyperkeratosis
Foamy macrophages



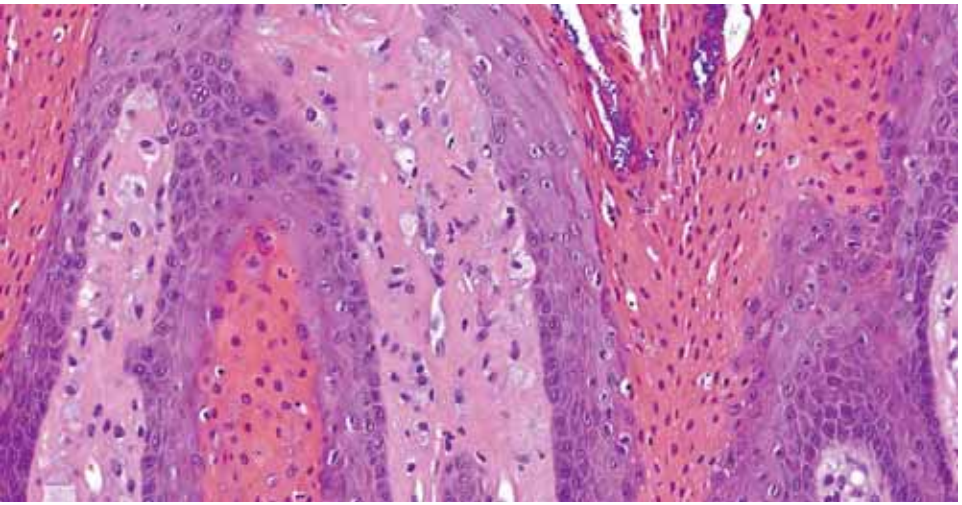
Clinical presentation:

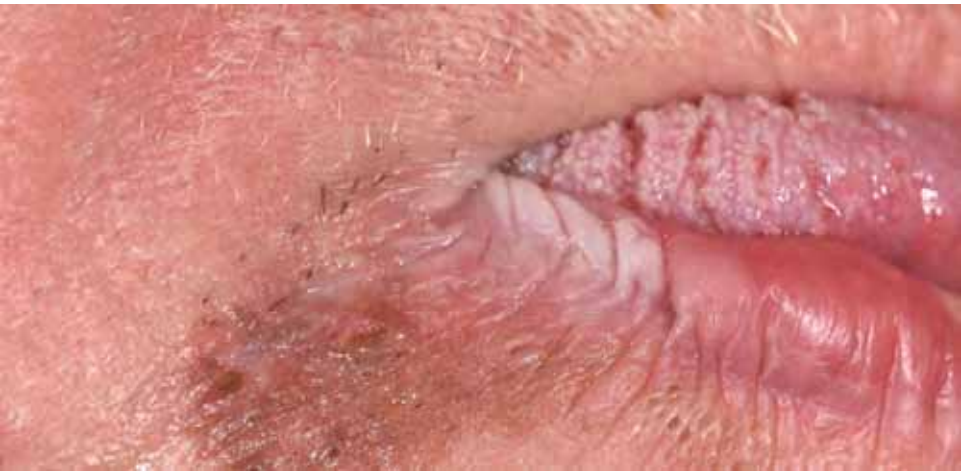
Papillomatous / verruciform whitish plaque on the lower lip

diagnosis

?

Summary of the findings





Histology:

Verruciform papillomatosis
Parakeratotic hyperkeratosis
Foamy macrophages

Clinical presentation:

Papillomatous / verruciform whitish
Plaque on the lip

verruciform xanthoma

Verruciform xanthoma

- Oral cavity: masticatory mucosa and tongue
- Predominantly affects males, mean age 50y
- Can be associated with: e.g. lichen planus, squamous cell carcinoma, leukoplakia
- Can occur in CHILD syndrome
- No relation to human papillomavirus

Suggested pathomechanism:
Mechanical trauma → inflammation → epithelial damage: keratinocyte necrosis → releases intracellular lipids → phagocytized by macrophages → inflammatory response and verruciform epidermal hyperplasia

Journal of Cutaneous Pathology

CHILD syndrome with mild skin lesions: histopathologic clues for the diagnosis

CHILD syndrome is an acronym signifying *congenital hemidysplasia with ichthyosiform nevus and limb defects*. A 27-year-old woman presented with chronic verrucous and hyperkeratotic skin lesions involving the left genital area, left hand and left foot since childhood. The histopathologic findings were consistent with verruciform xanthoma. In correlation with the clinical picture of a linear lesion, the diagnosis of CHILD nevus was made. Subsequent genetic analysis identified a germline c.324C>T (p.A105V) *NSDHL* mutation and confirmed a diagnosis of CHILD syndrome. This syndrome can be associated with only minimal clinical symptoms. The anatomical distribution of the lesions, a static clinical course and the typical histopathologic features of a CHILD nevus can serve as the clue to a diagnosis of CHILD syndrome in such cases.

Susanne Gantner[1], Arno Rütten[2], Luis Requena[3], Gerhard Gassenmaier[4], Michael Landthaler[1] and Christian Hafner[1]

[1]Department of Dermatology, University of Regensburg, Regensburg, Germany, [2]Dermatopathology Friedrichshafen, Friedrichshafen, Germany, [3]Department of Dermatology, Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain, and [4]Dermatology, Passau, Germany

CHILD: congenital hemidysplasia with ichthyosiform nevus and limb defects

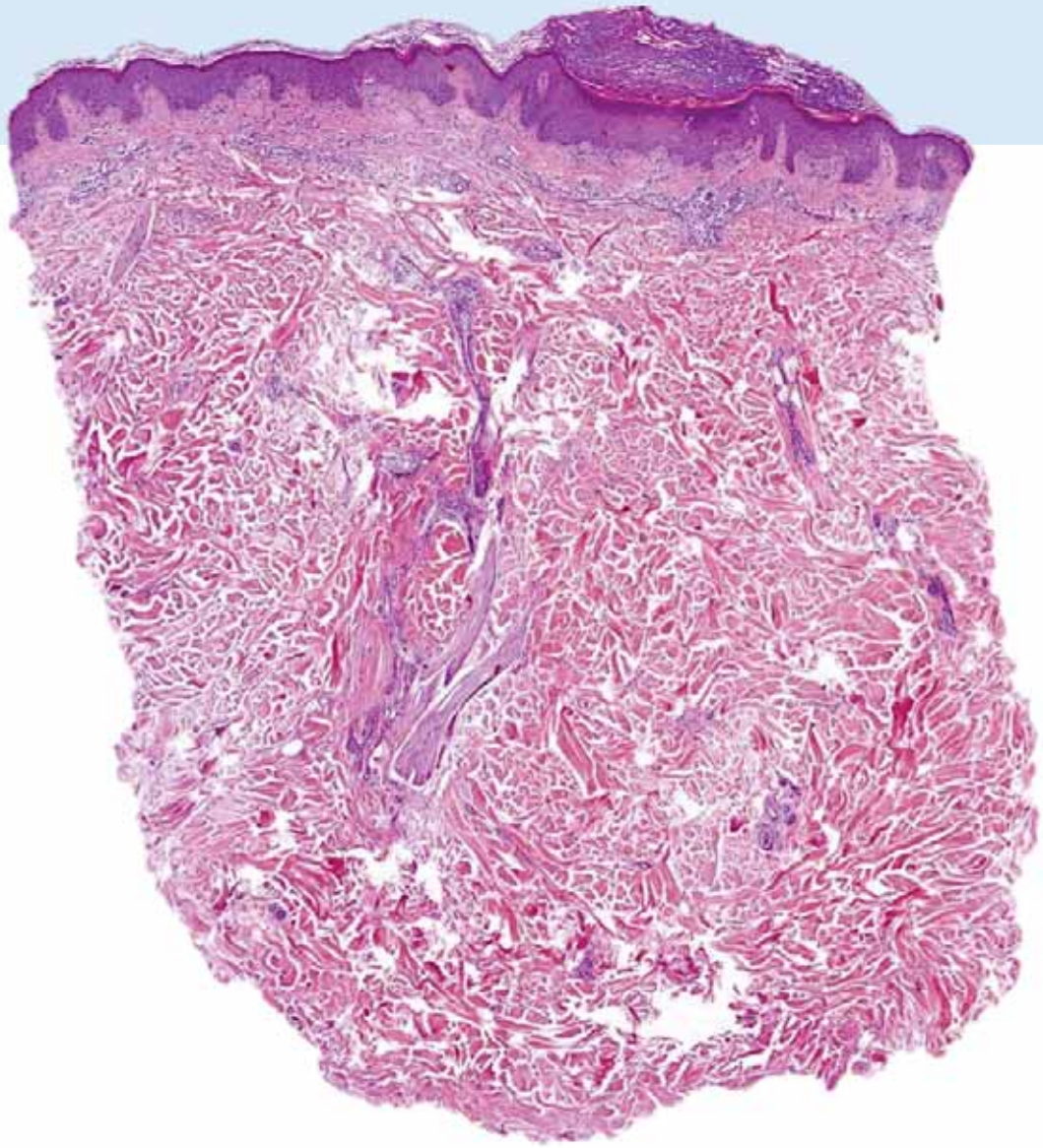
- X-linked dominant, lethal for male embryos
- Verruciform xanthoma in **association with clinical findings** (lateralization, ptychotropism, presence since birth and arrangement along Blaschko lines) is indicating a CHILD syndrome

Chatterjee A, Purkait S K, Banerjee I, et al. (November 09, 2024) Oral Verruciform Xanthoma of the Lower Lip: A Rare Entity. Cureus 16(11): e73352
Gantner S, Rütten A, Requena L, Gassenmaier G, Landthaler M, Hafner C. CHILD syndrome with mild skin lesions: histopathologic clues for the diagnosis. J Cutan Pathol 2014; 41: 787–790.

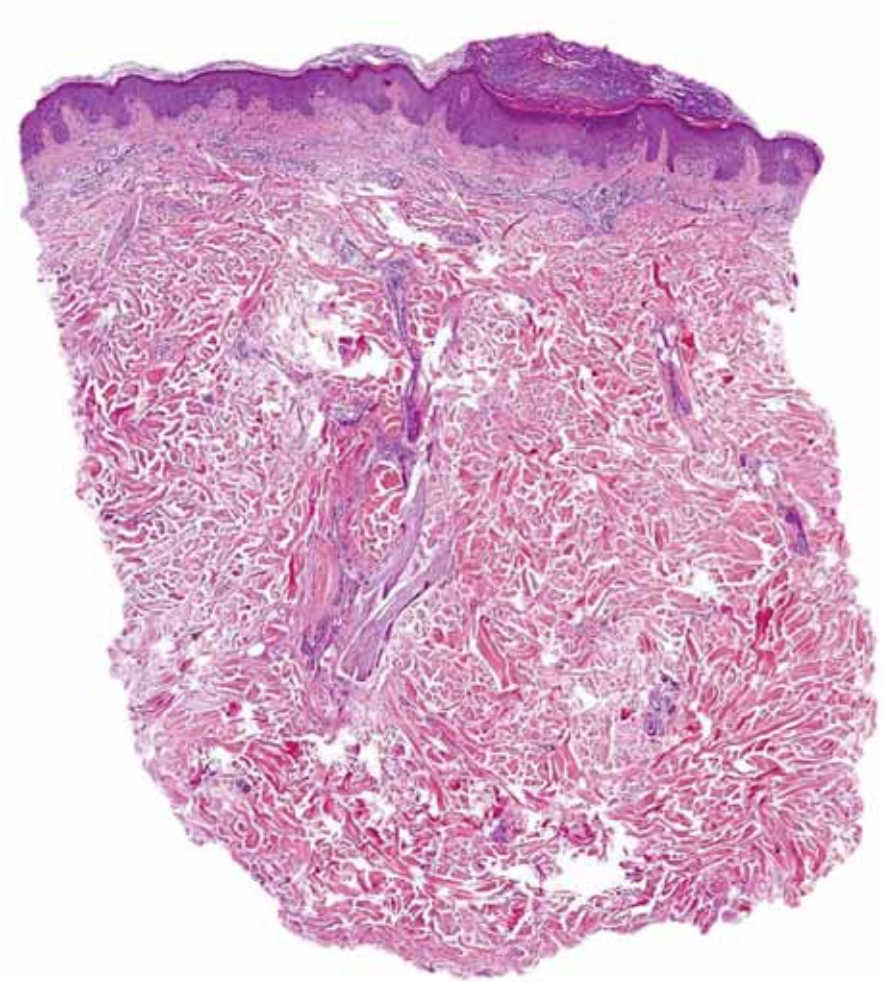
Histology

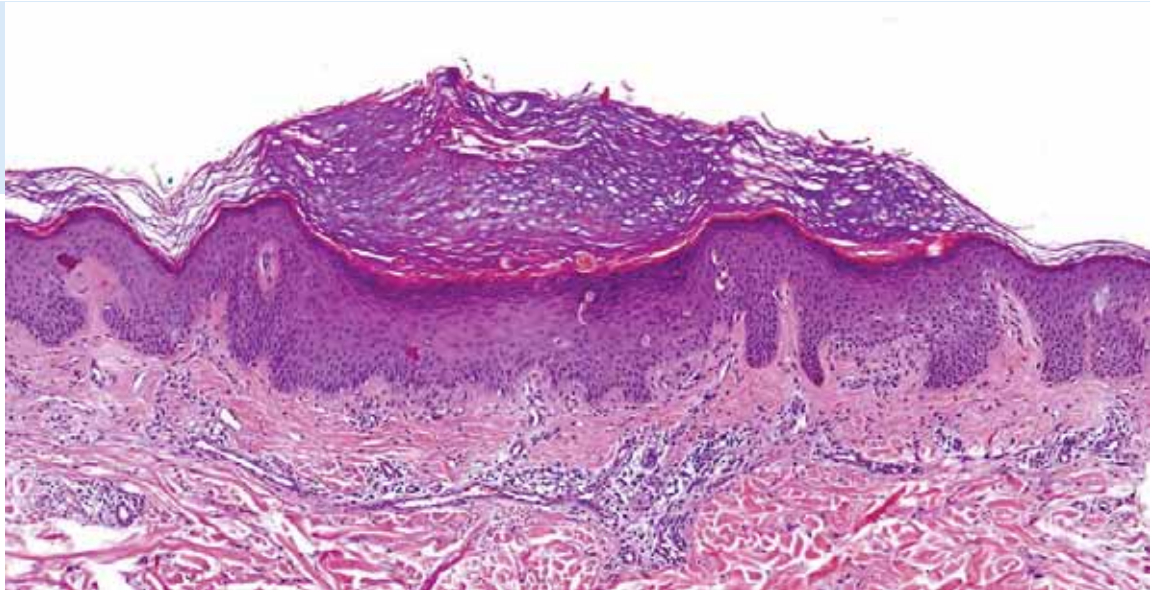
59-year-old male patient
Suspected diagnosis: Atopic dermatitis with significant pruritus
Medical history:

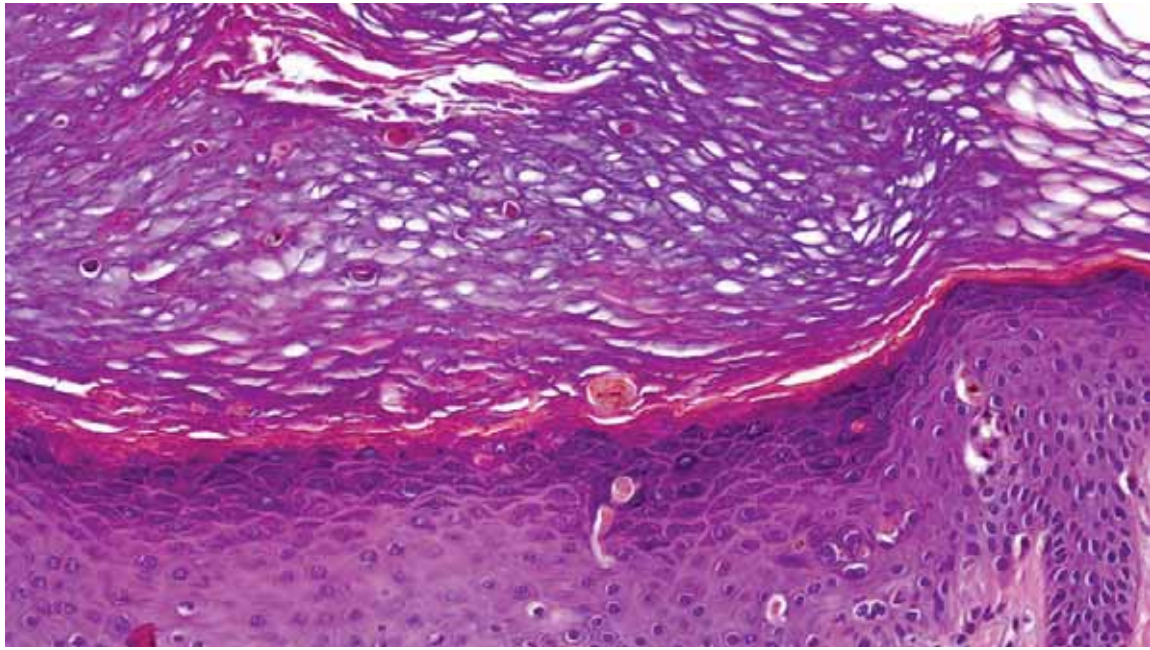
- Diabetes type II
- Chronic hepatitis B
- Hypertension and hypothyroidism



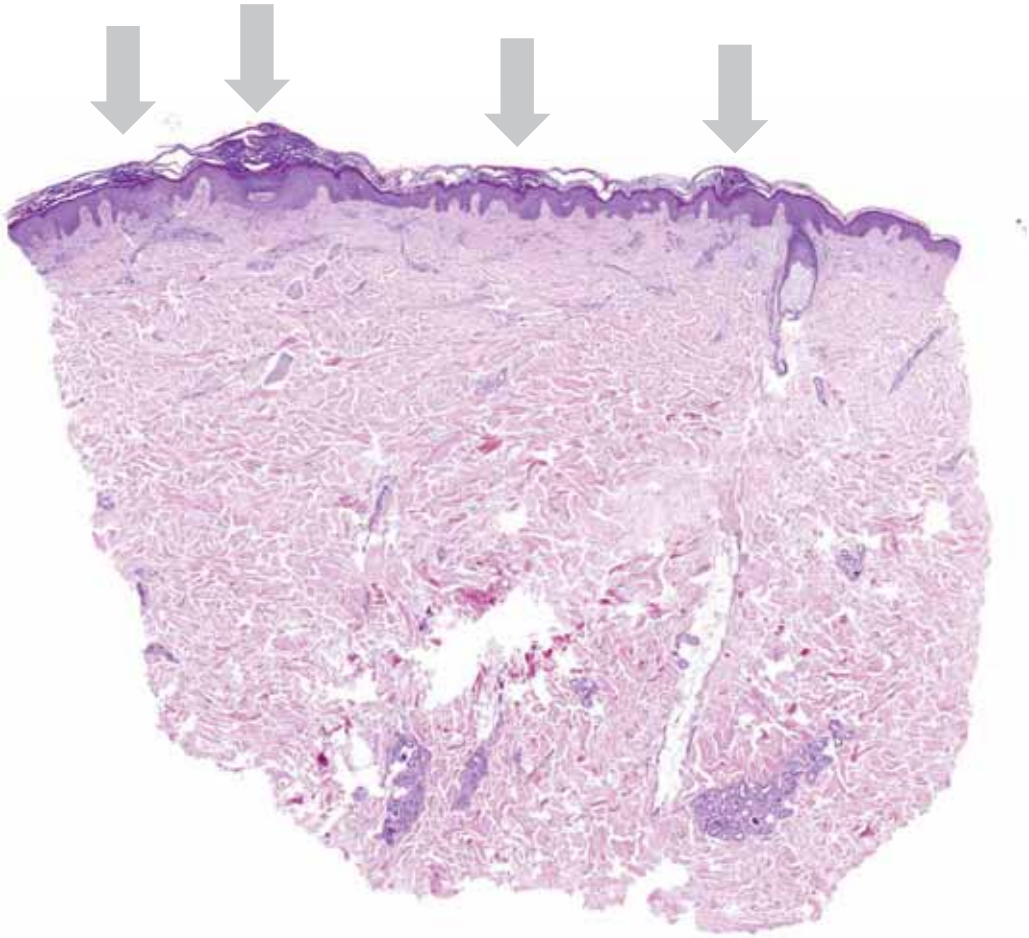
Histology – 1. biopsy

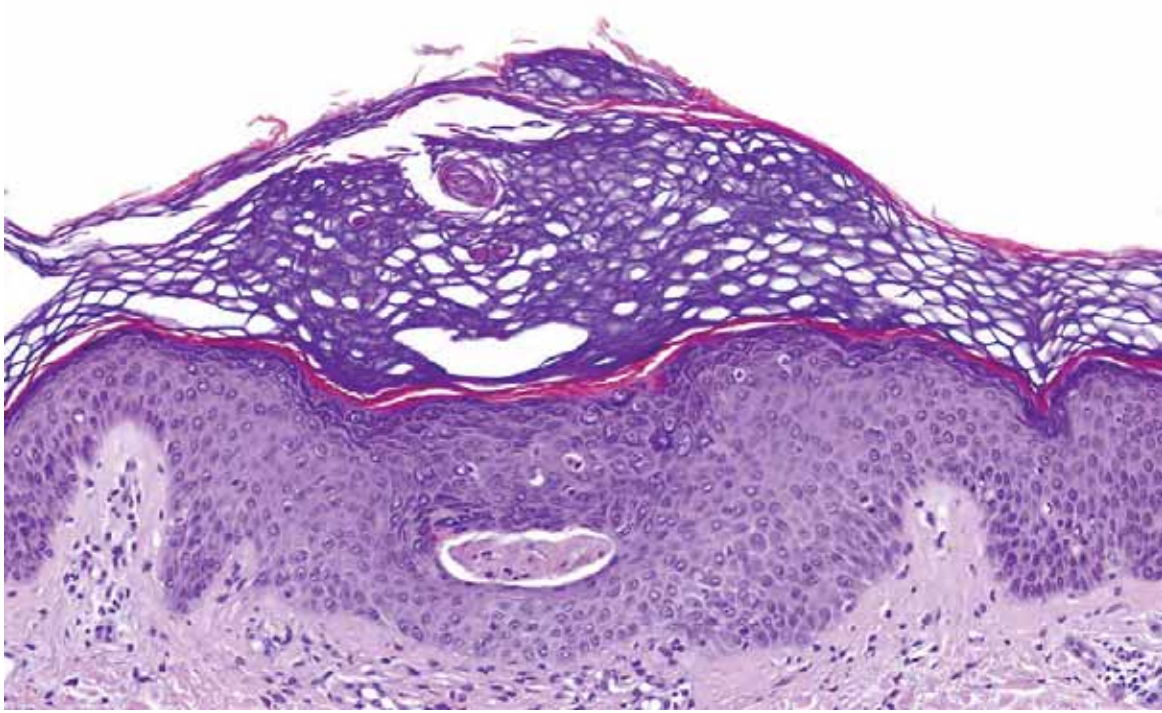




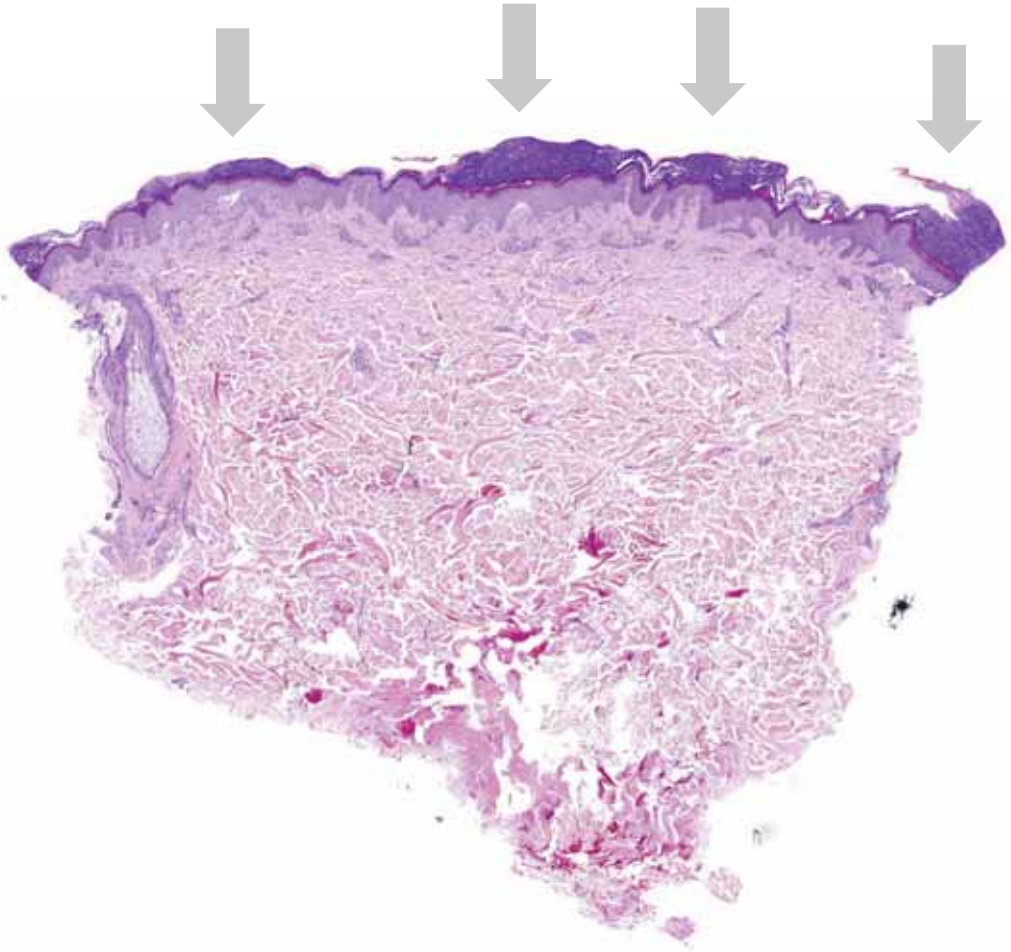


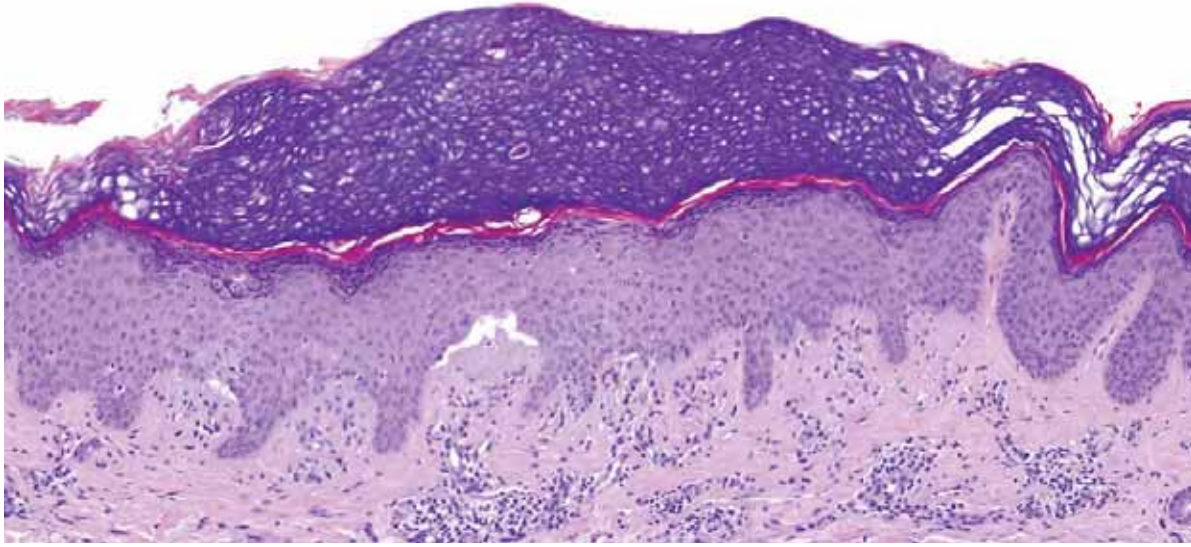
Histology – 2. biopsy



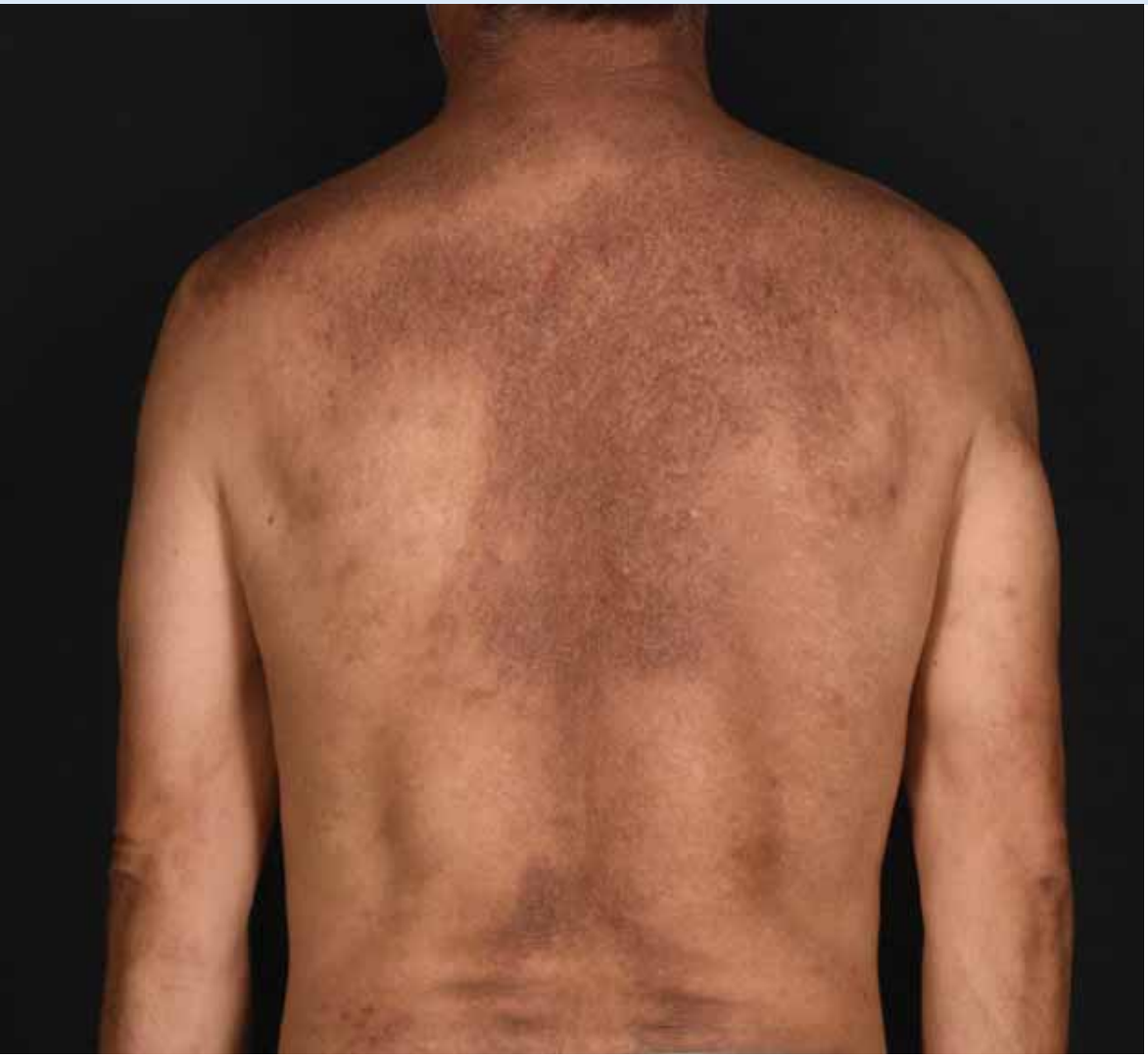


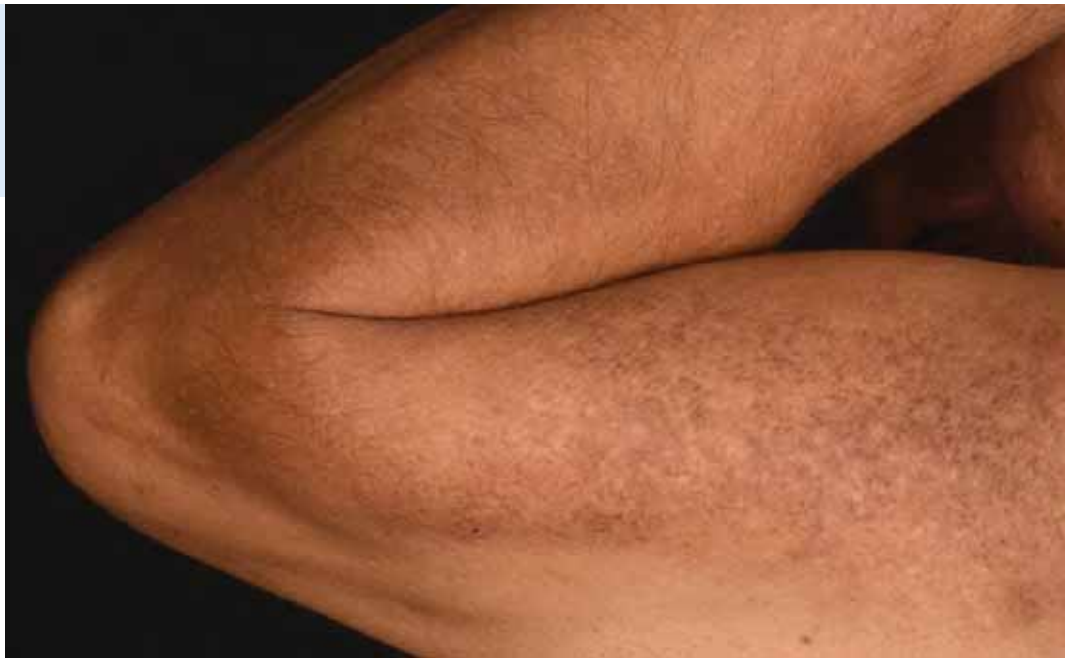
Histology – 3. biopsy

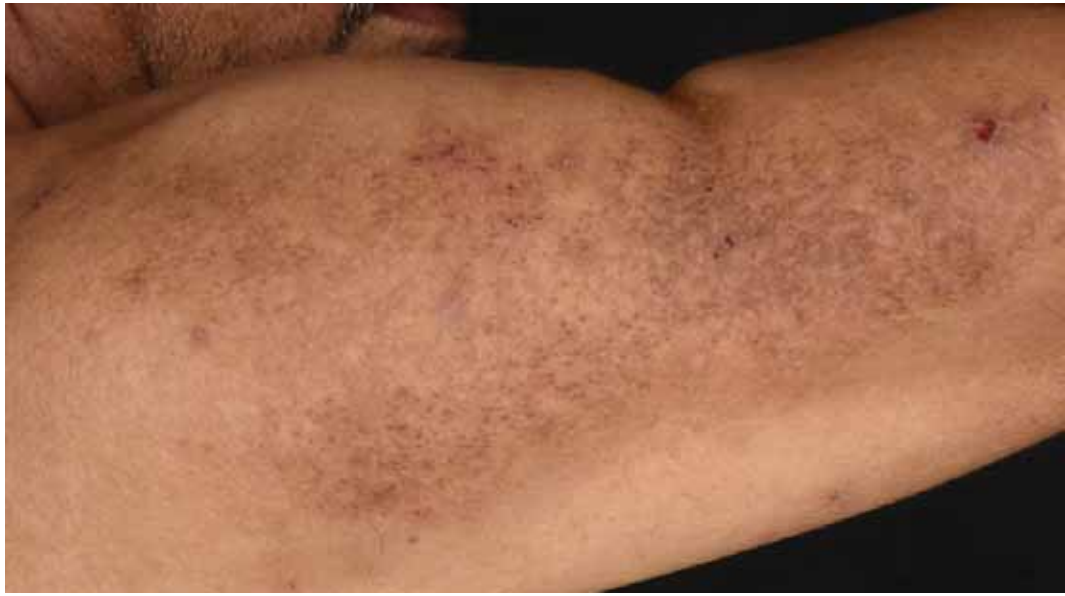




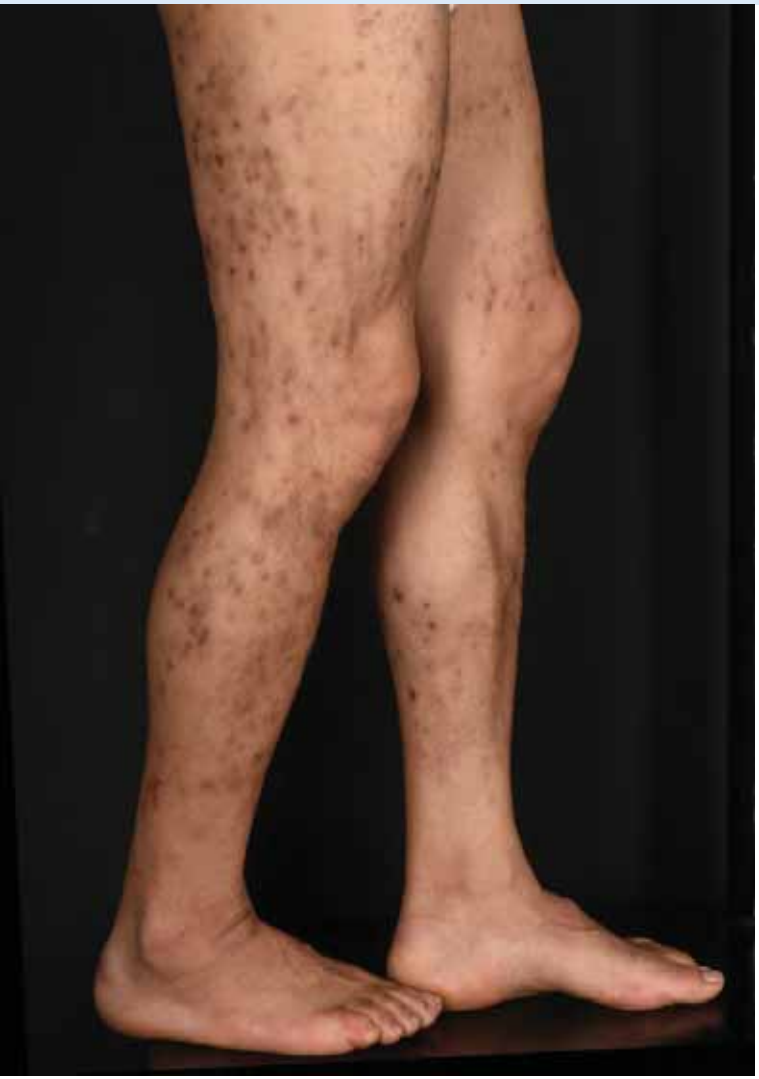
Clinical presentation

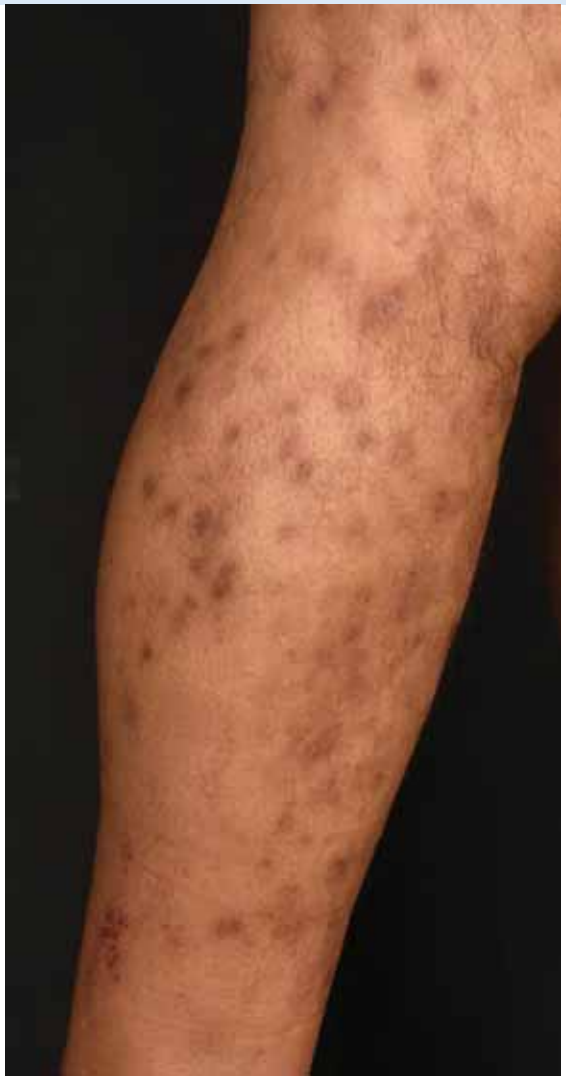


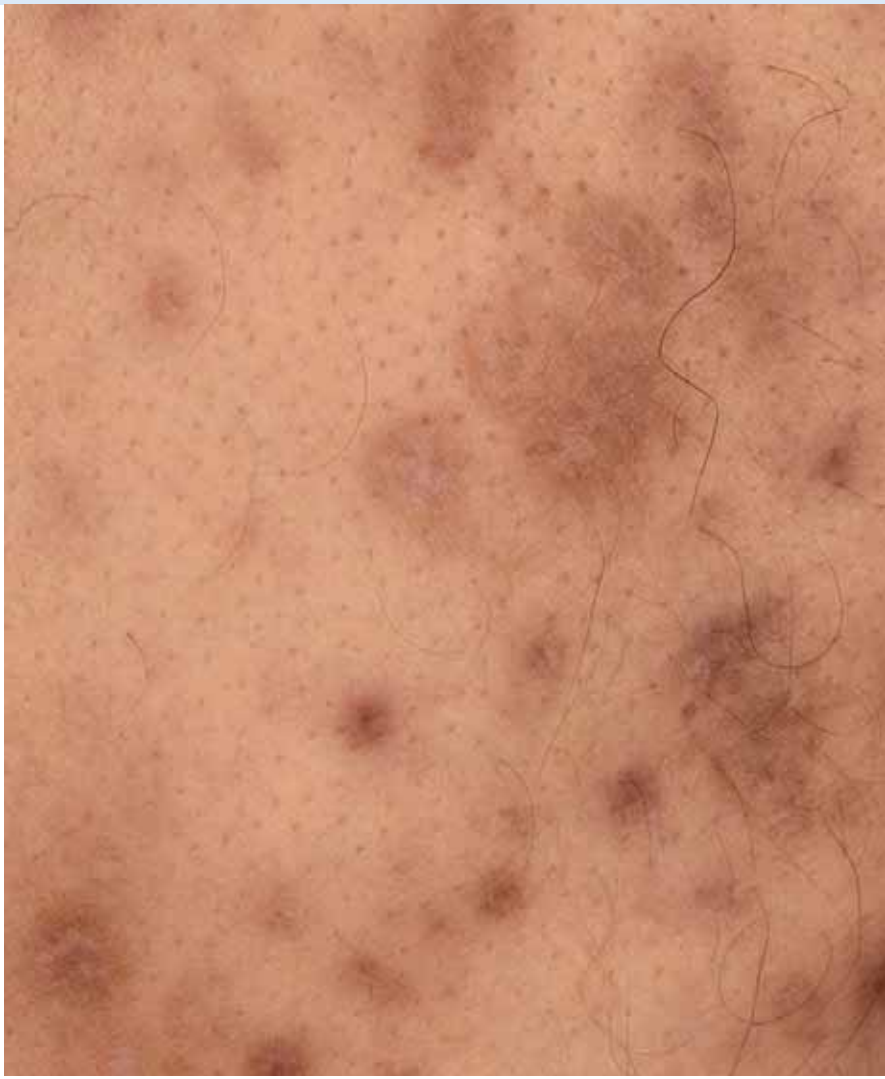




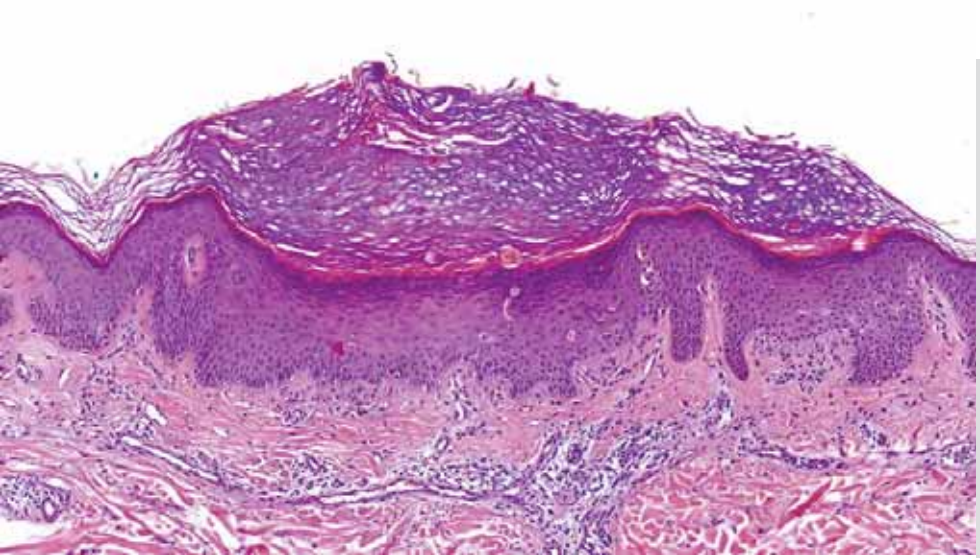
Clinical presentation





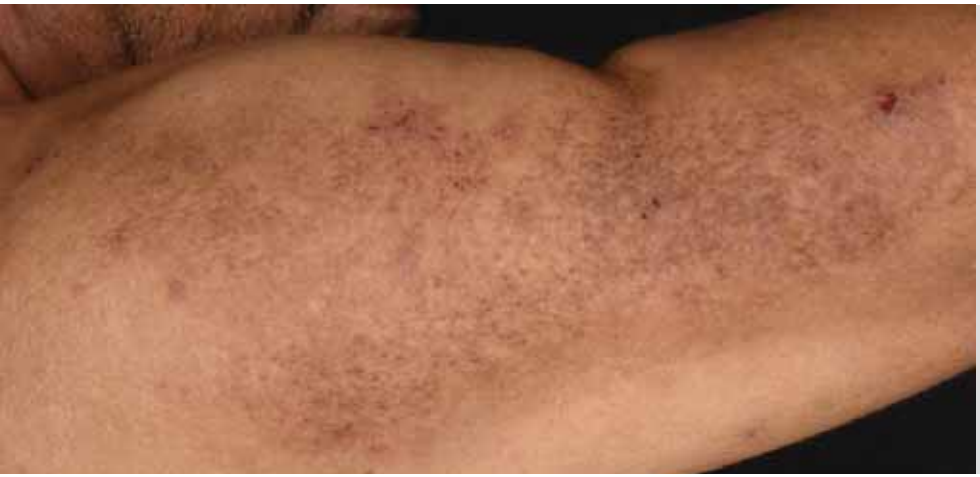


Summary of the findings



Histology:

Dyskeratosis in the epidermis and in basket-wave-like orthokeratosis



Clinical presentation:

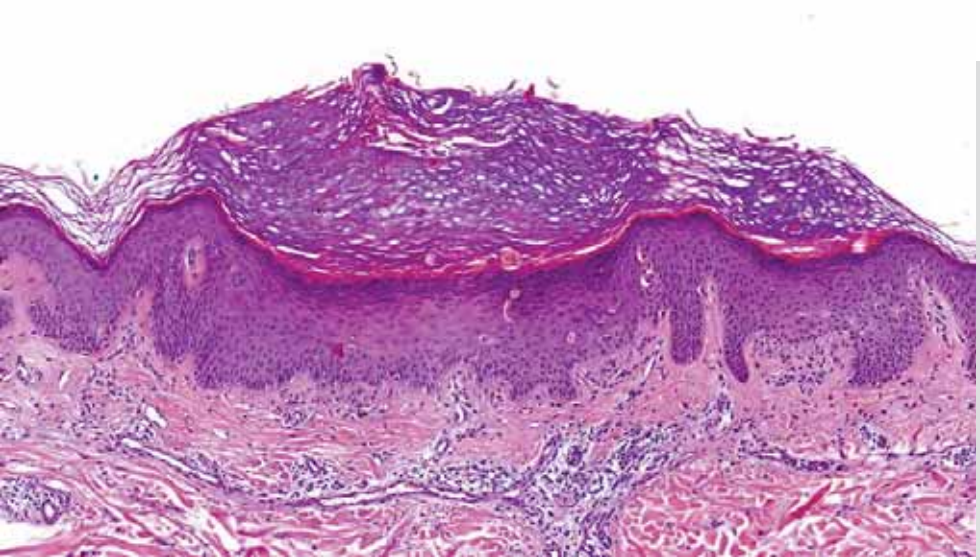
Hyperpigmentations and pigmented papules and plaques with excoriations

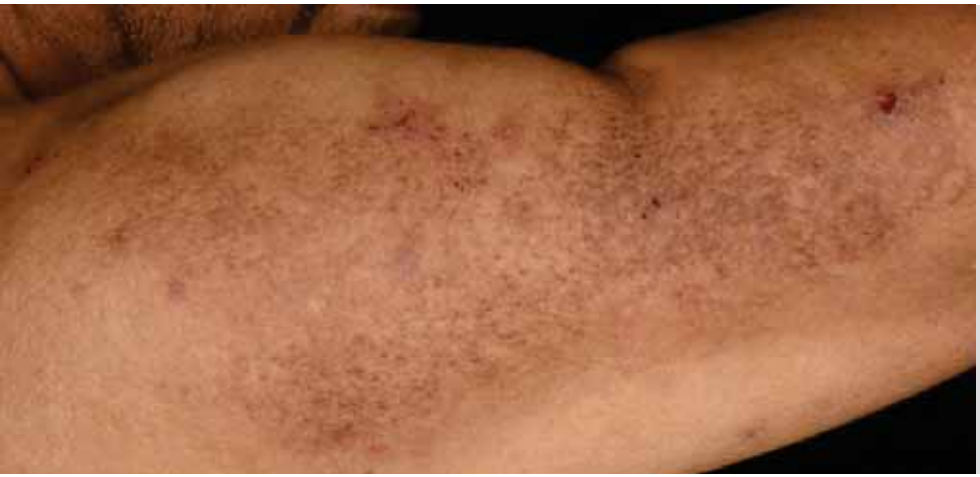
Heavily pruritic

diagnosis

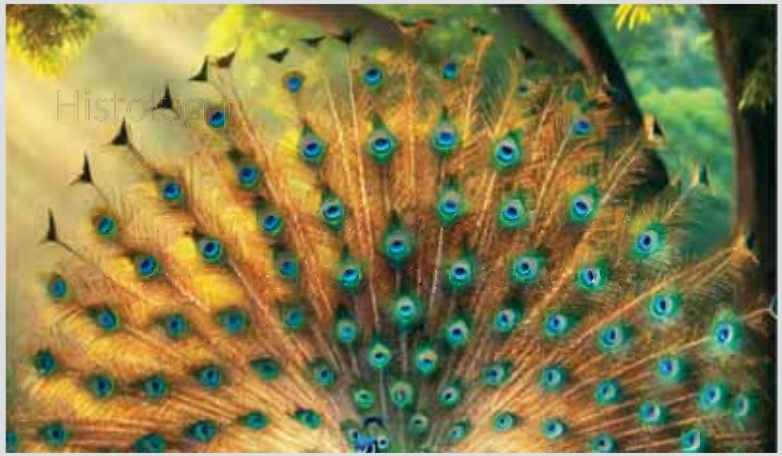
?

Summary of the findings





Clue!



Clinical presentation:

Hyperpigmentations and pigmented papules and plaques with excoriations

Heavily pruritic

Pruritic and dyskeratotic dermatosis

associated with human polyomavirus 6 and 7 (HpyV6/7)

Pruritic and dyskeratotic dermatosis

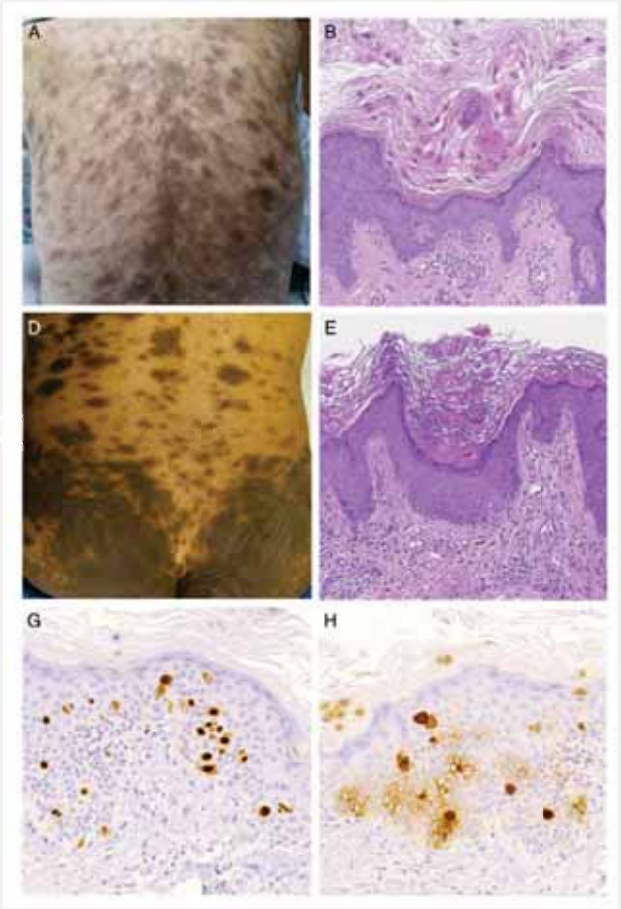
BRIEF REPORT

JID 2015:211, 1560

Human Polyomavirus 7–Associated Pruritic Rash and Viremia in Transplant Recipients

Jonhan Ho,[1,a] Jaroslaw J. Jedrych,[1,a] Huichen Feng,[2] August A. Natalie,[1] Lisa Grandinetti,[1] Ezra Mirvish,[1] Maria M. Crespo,[2] Dhiraj Yadav,[3] Kenneth E. Fasanella,[3] Siobhan Praksell,[3] Shih-Fan Kuan,[4] Diana V. Pastrana,[5] Christopher B. Buck,[5] Yoko Shuda,[5] Patrick S. Moore,[5] and Yuan Chang[5]

[1]Department of Dermatology, [2]Division of Pulmonary, Allergy, and Critical Care, [3]Department of Medicine, and [4]Department of Pathology, School of Medicine, and [5]Cancer Virology Program, Cancer Institute, University of Pittsburgh, Pennsylvania; and [6]Laboratory of Cellular Oncology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

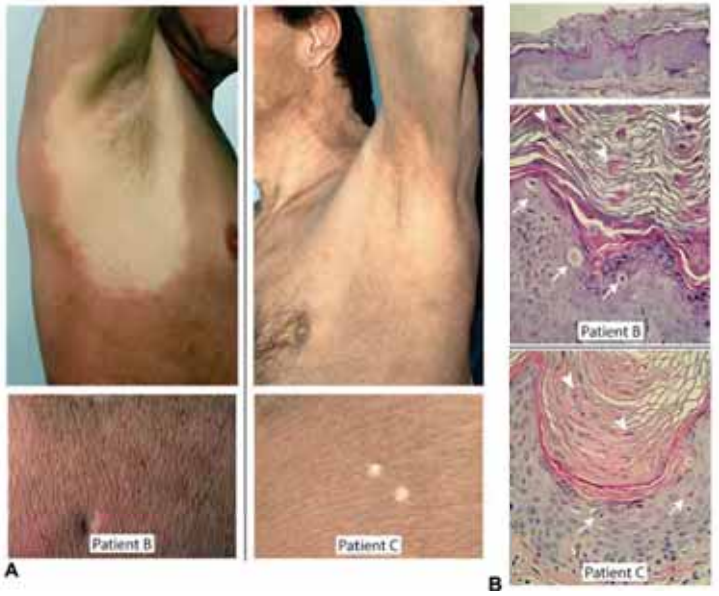


DERMATOPATHOLOGY

Human polyomavirus 6 and 7 are associated with pruritic and dyskeratotic dermatoses

Khang D. Nguyen, MD,[1] Eunice E. Lee, BA,[2] Yangho Yue, PhD,[1] Jiri Stork, MD,[3] Lumir Pock, MD,[3] Jeffrey P. North, MD,[4] Travis Vandeventill, MD,[5] Clay Cockerell, MD,[6,7] Gregory A. Hosler, MD, PhD,[6,7] Diana V. Pastrana, PhD, Christopher B. Buck, PhD,[2] and Richard C. Wang, MD, PhD[1]

Dallas, Texas; Prague and Pilsen, Czech Republic; San Francisco, California; and Bethesda, Maryland

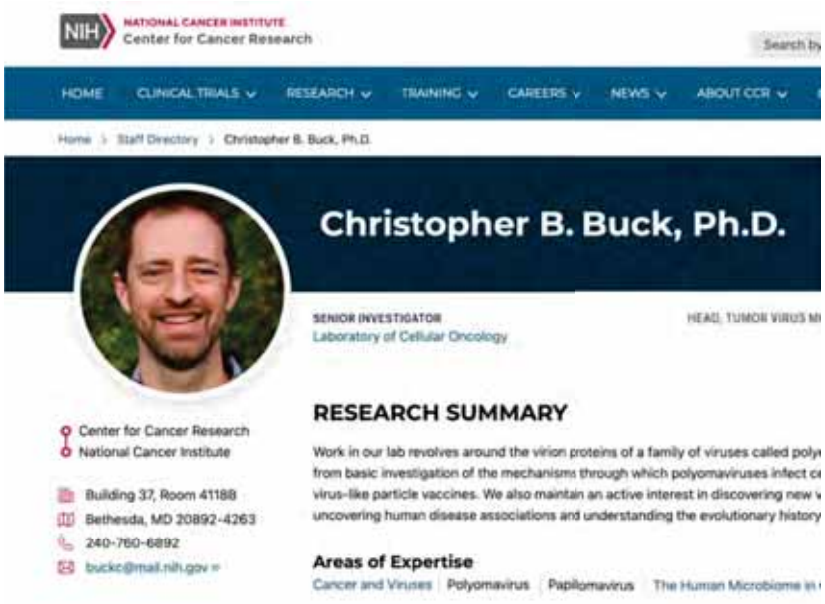


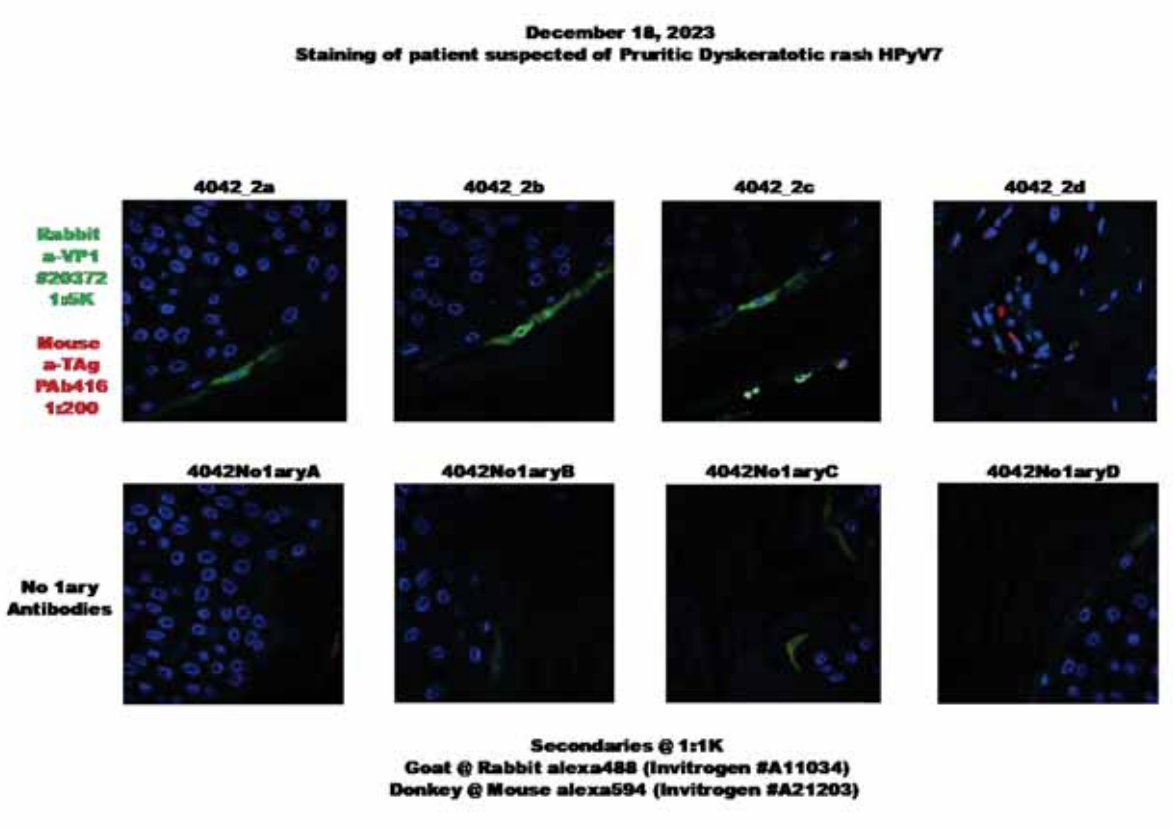
First description in 2015: two immuno-suppressed patients after lung tx

Ho J et al. Human Polyomavirus 7-associated pruritic rash and viremia in transplant recipients. JID 2015; 211: 1560-1565.
Nguyen KD et al. Human polyomavirus 6 and 7 are associated with pruritic and dyskeratotic dermatoses. Dermatopathology 2017; 76: 932-940.
Bartley BR et al. Current treatments and emerging therapies of human polyomavirus-associated skin diseases: a comprehensive review. Int J Dermatol: 2023; 62: 387-396.

Detection of HPyV7

Stains were done by:
Diana Pastrana, Buck's lab





Ho J et al. Human Polyomavirus 7-associated pruritic rash and viremia in transplant recipients. JID 2015; 211: 1560-1565.
Nguyen KD et al. Human polyomavirus 6 and 7 are associated with pruritic and dyskeratotic dermatoses. Dermatopathology 2017; 76: 932-940.
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Pruritic and dyskeratotic dermatosis HPyV7

- Few documented cases in the literature
- Most patients were immunosuppressed:
  - 3 lung transplant
  - 1 heard transplant
  - 2 kidney-pancreas transplant
  - 1 HIV
  - No IS at time of diagnosis

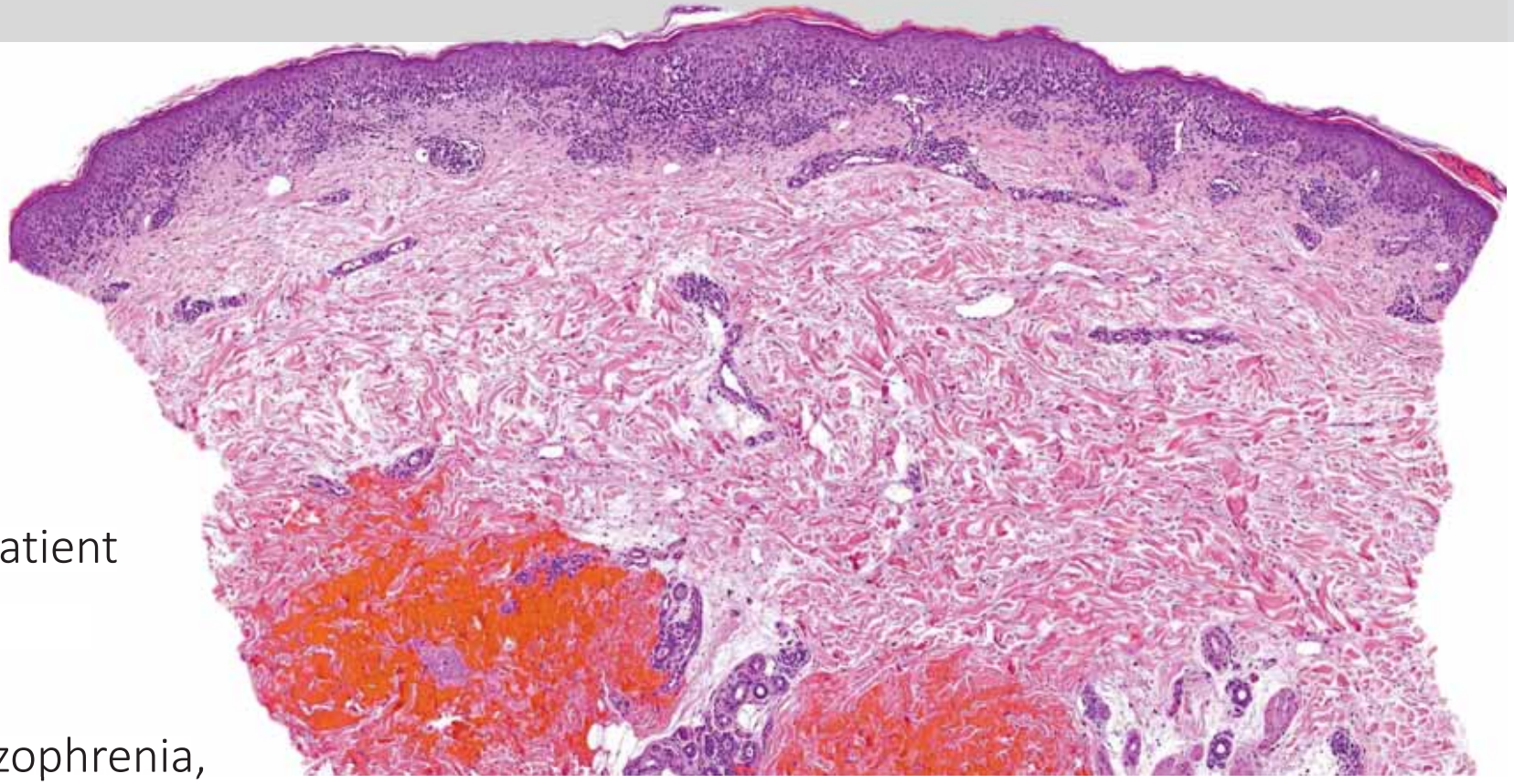
- Therapy: acitretin 25 mg oral
  topical Cidofovir 3%

Our patient:

- Diabetes
- Hepatitis B
- No HIV
- No other immunosuppression

Ho J et al. Human Polyomavirus 7-associated pruritic rash and viremia in transplant recipients. JID 2015; 211: 1560-1565.
Nguyen KD et al. Human polyomavirus 6 and 7 are associated with pruritic and dyskeratotic dermatoses. Dermatopathology 2017; 76: 932-940.
Bartley BR et al. Current treatments and emerging therapies of human polyomavirus-associated skin diseases: a comprehensive review. Int J Dermatol: 2023; 62: 387-396.

Histology

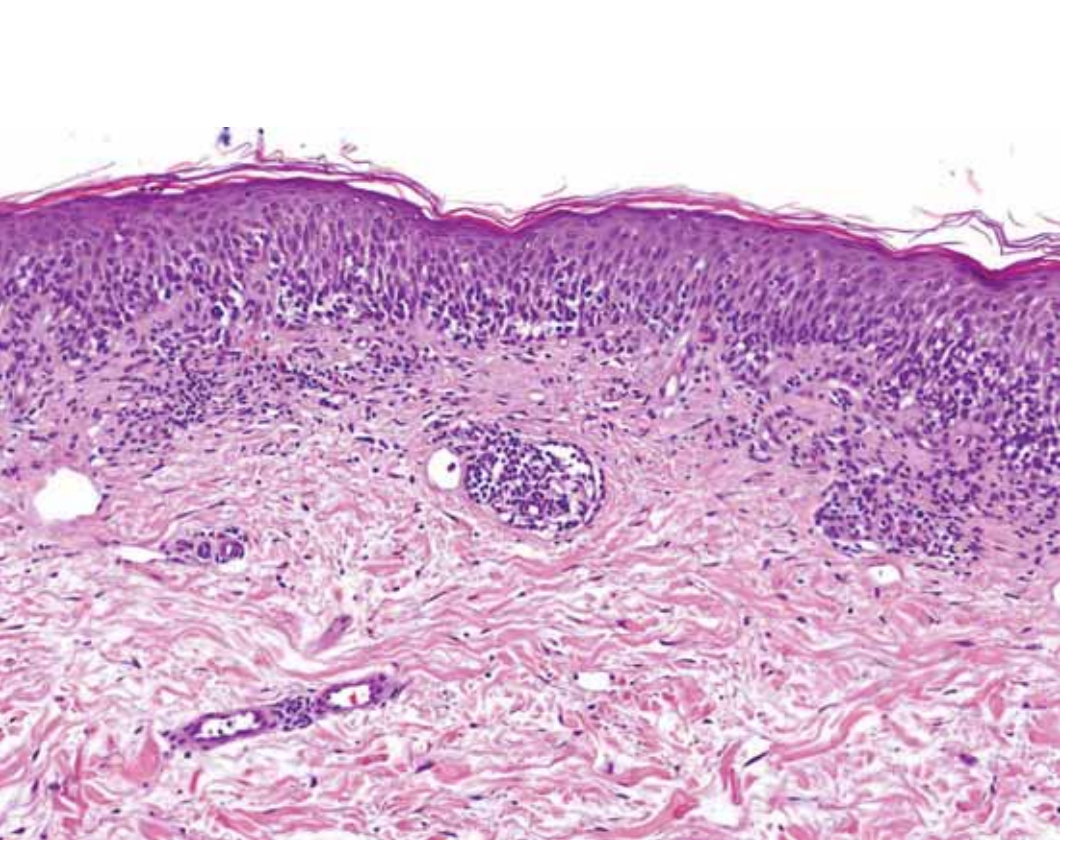


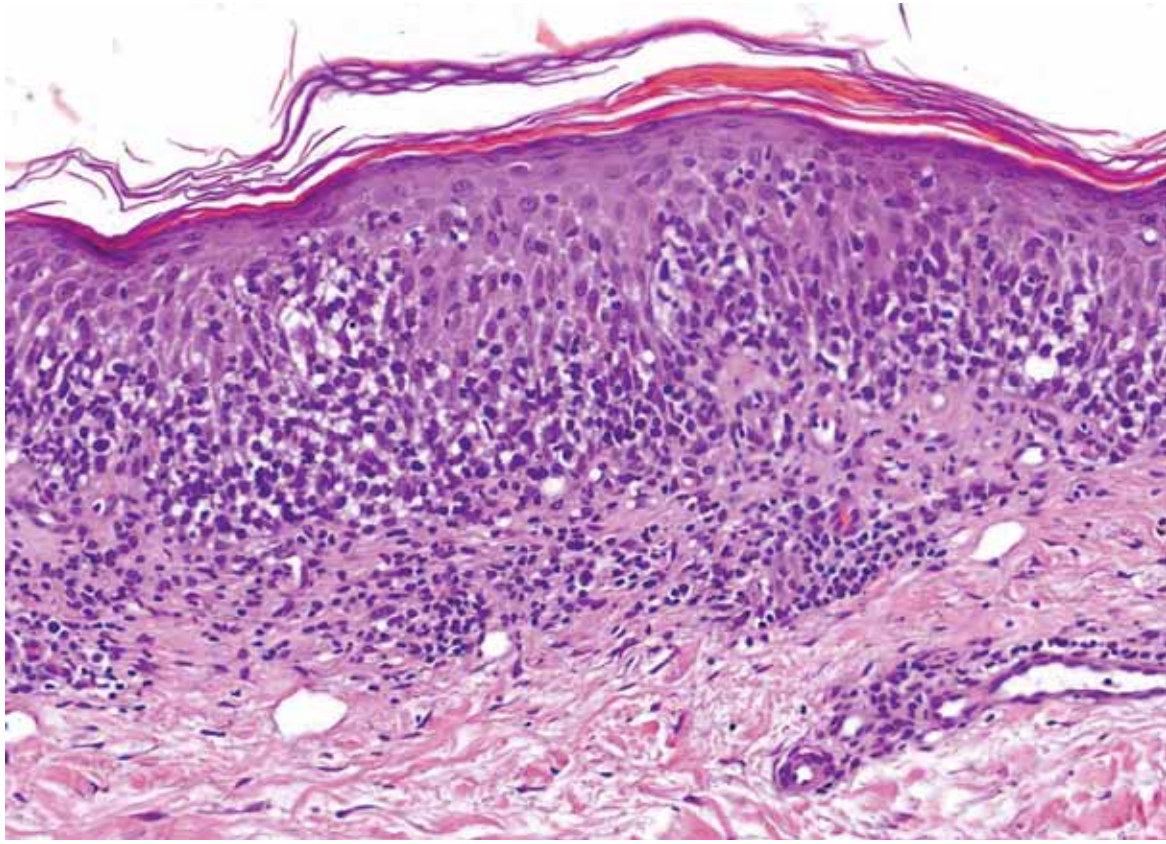
65-year-old female patient

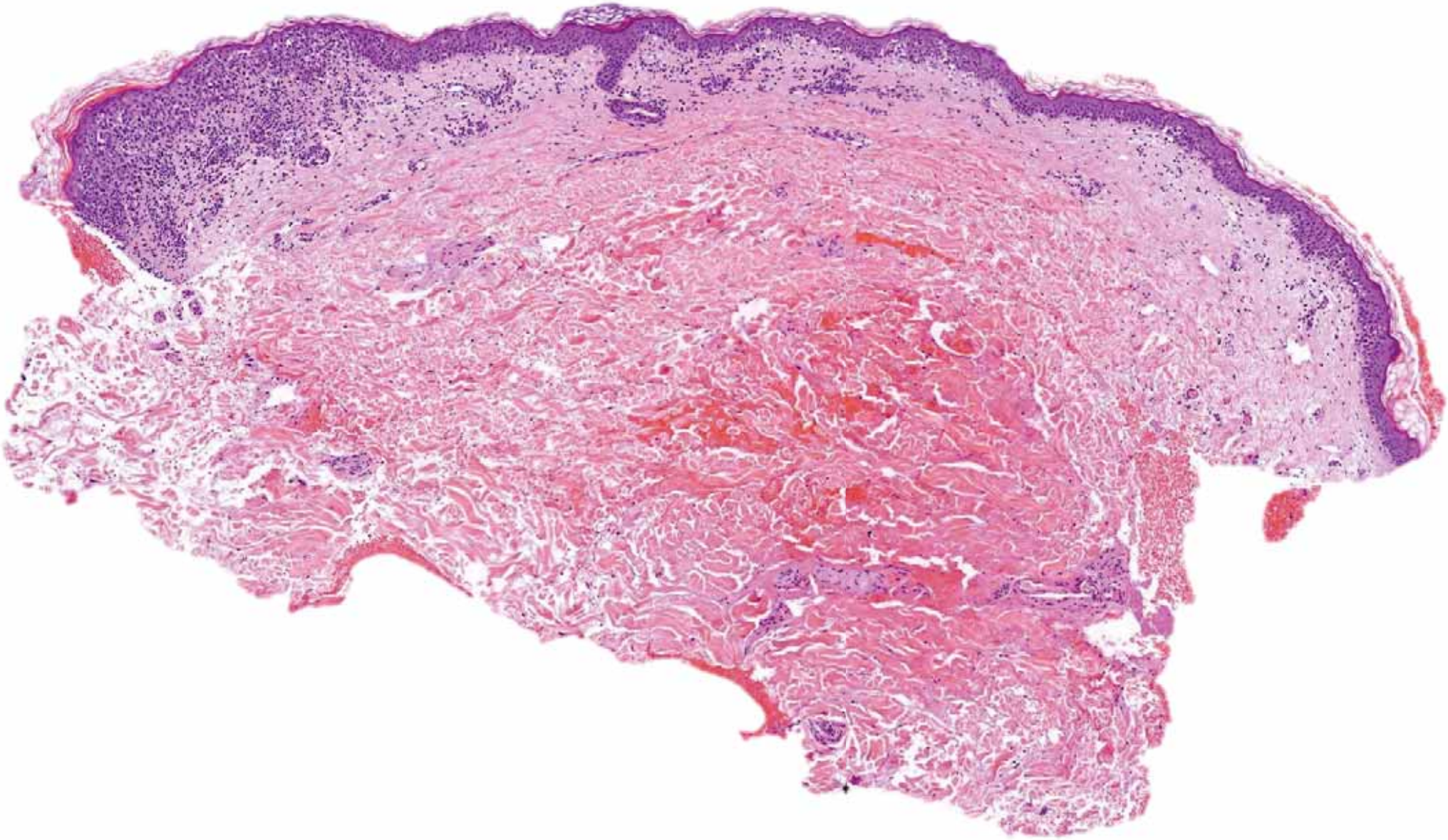
Suspected diagnosis:
mycosis fungoides

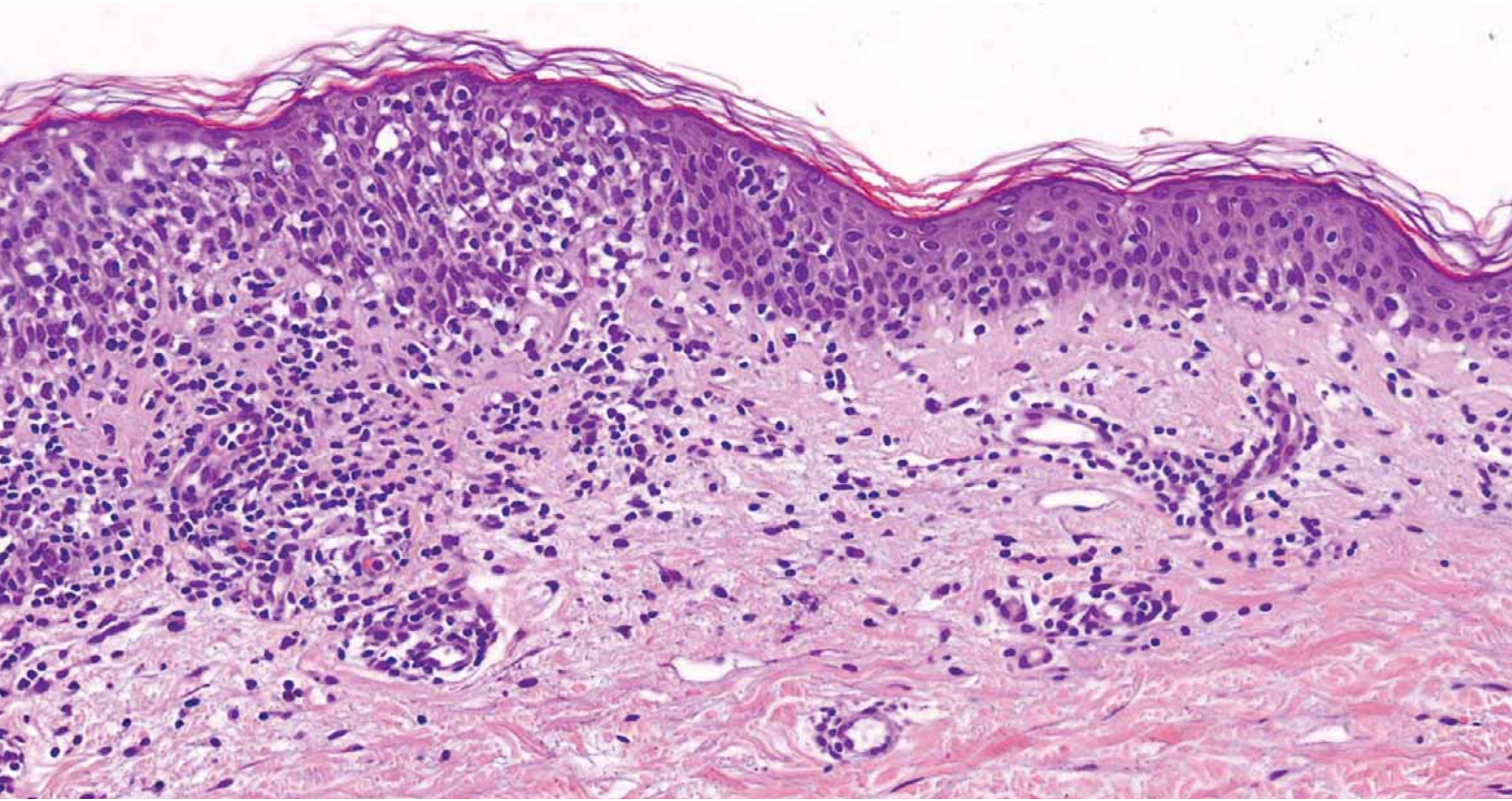
Medical history: schizophrenia, anxiety disorder

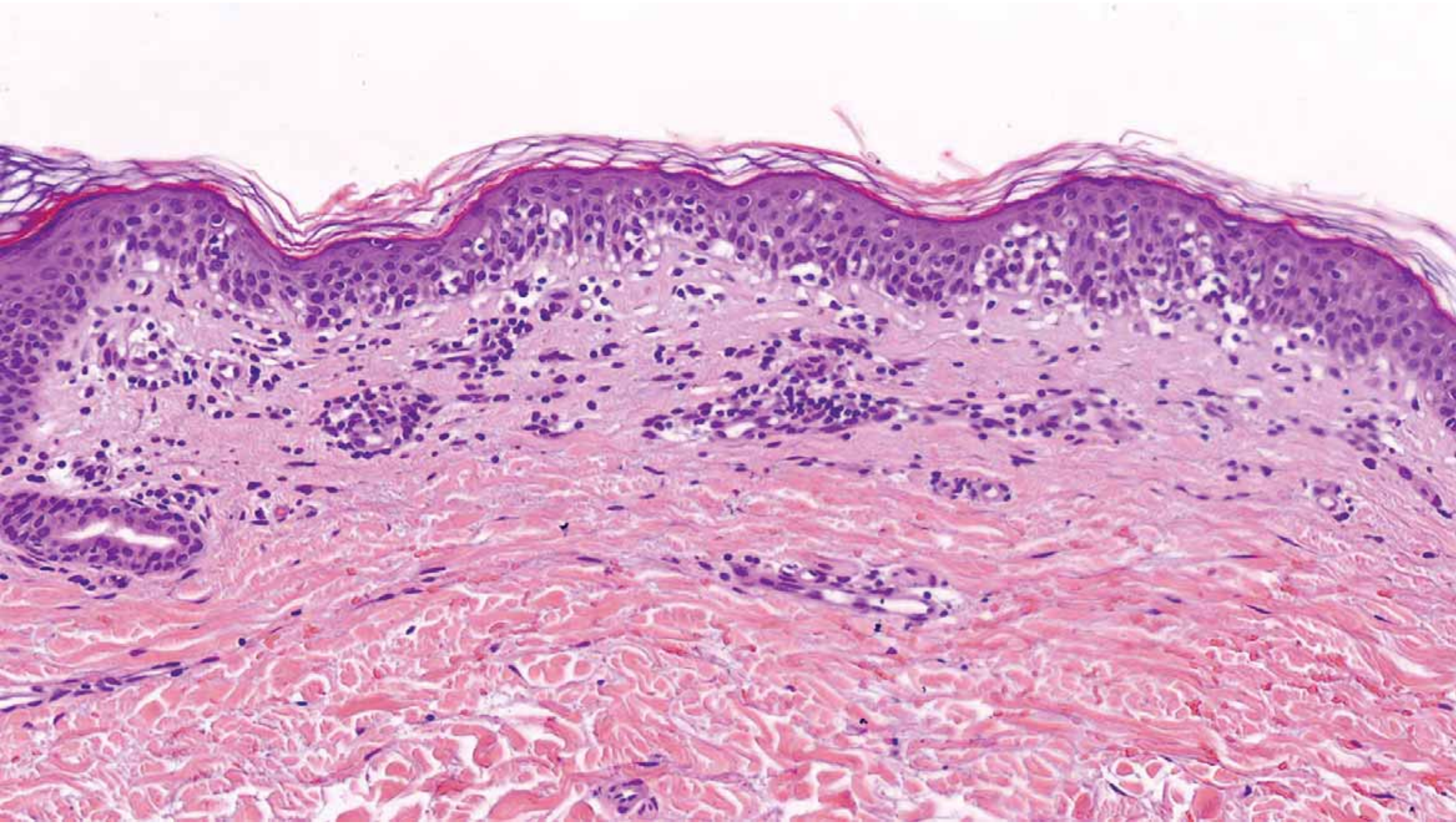
Histology





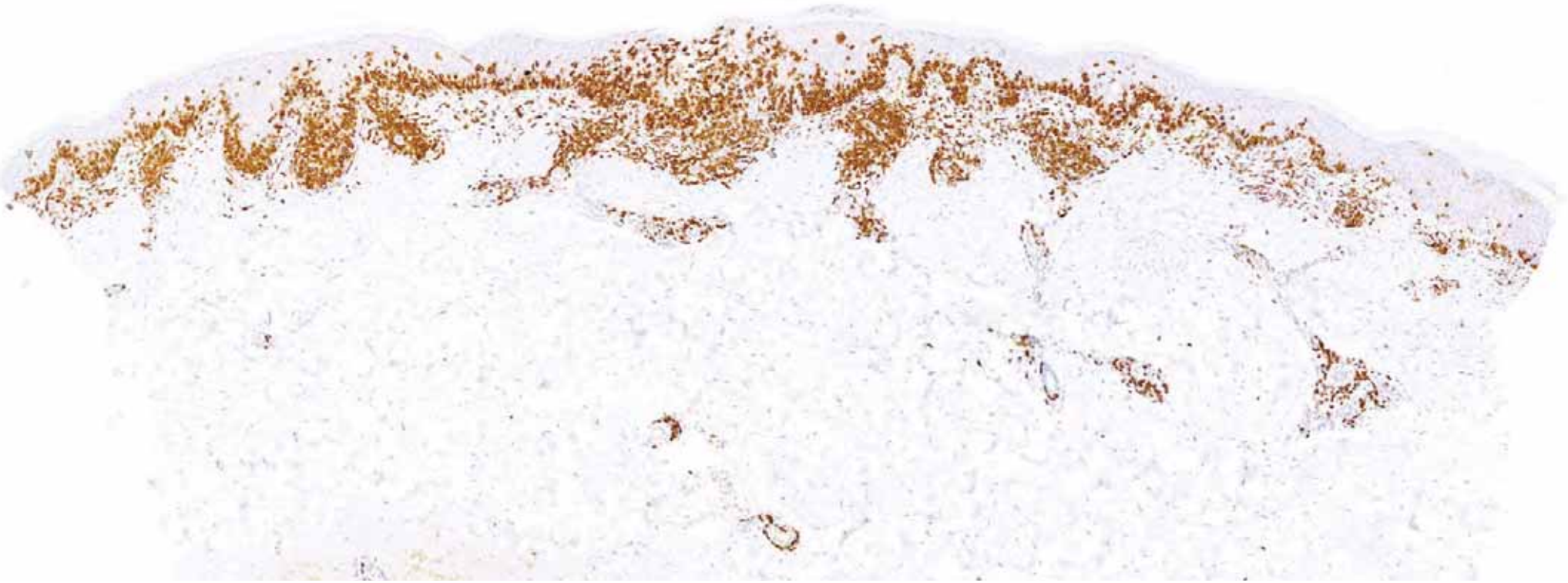






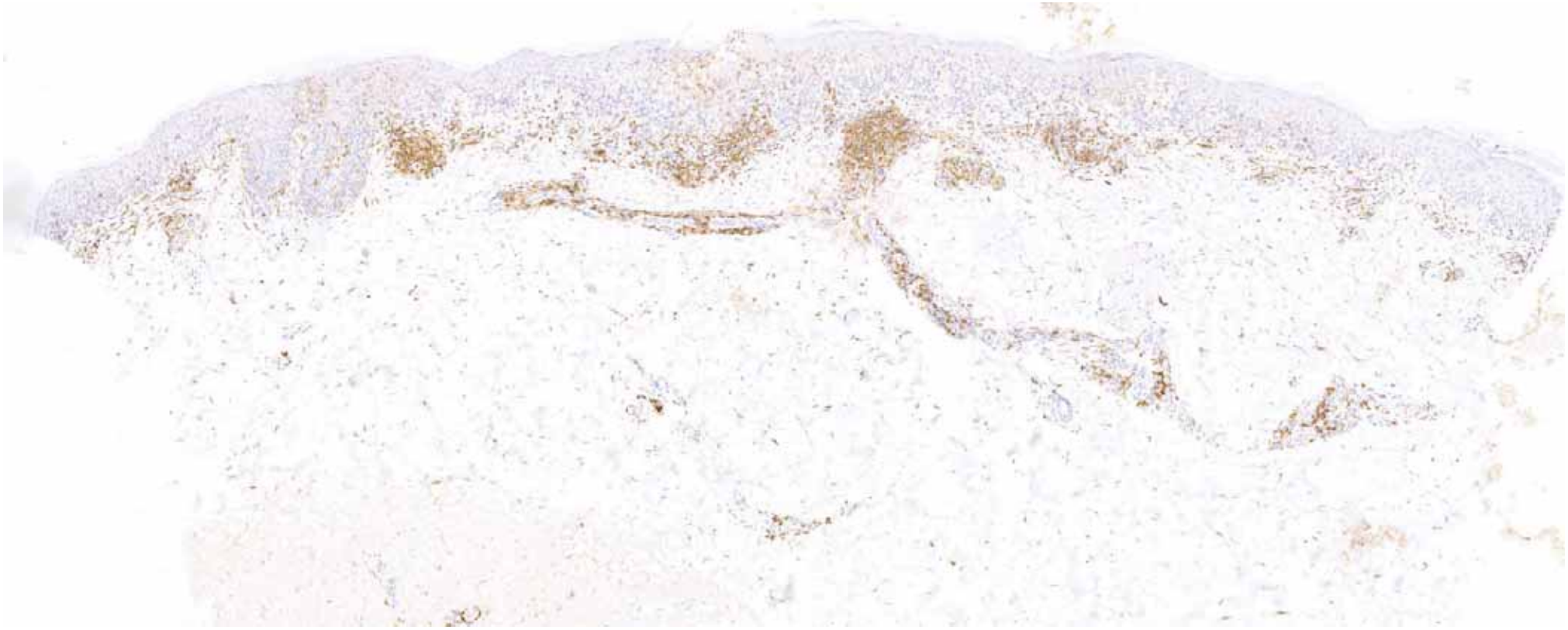
Immunohistochemistry

CD3



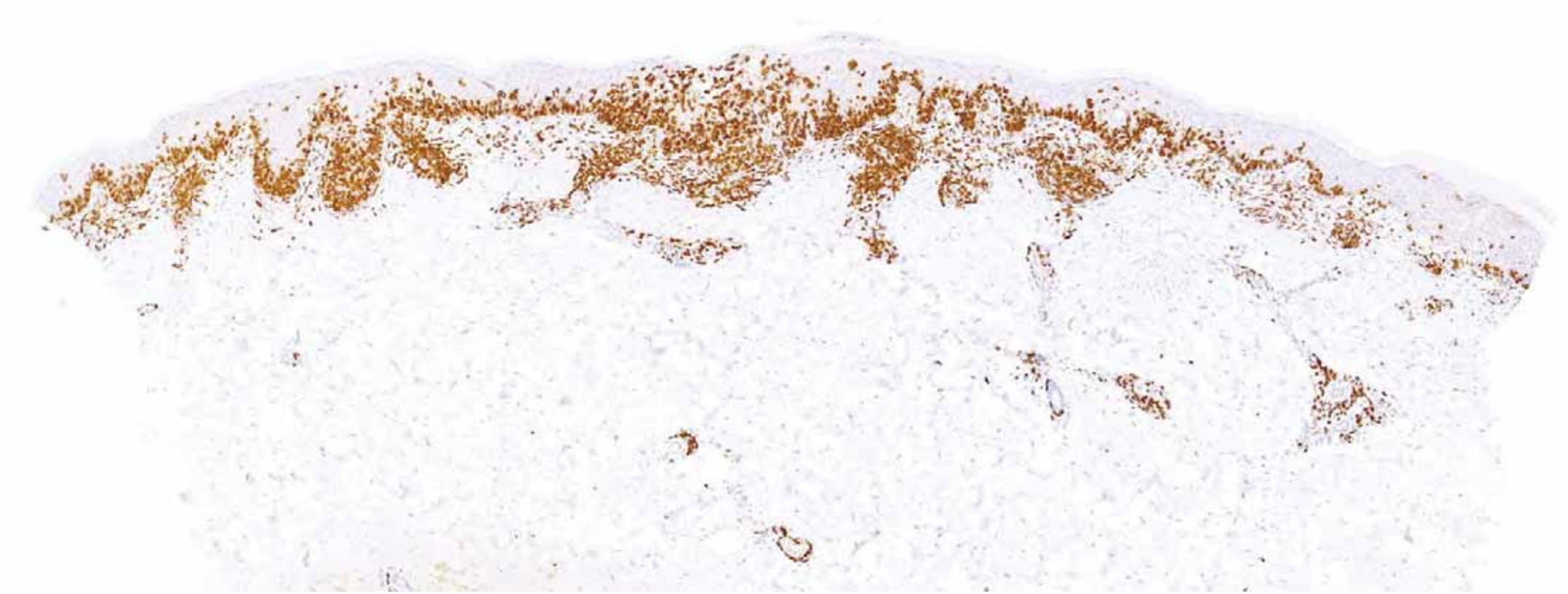
Immunohistochemistry

CD4

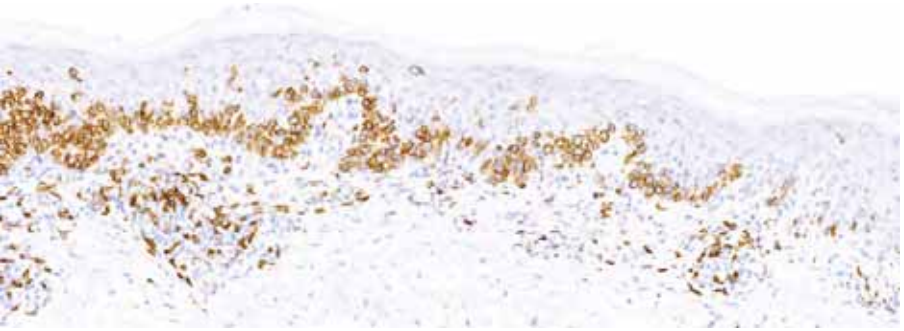


Immunohistochemistry

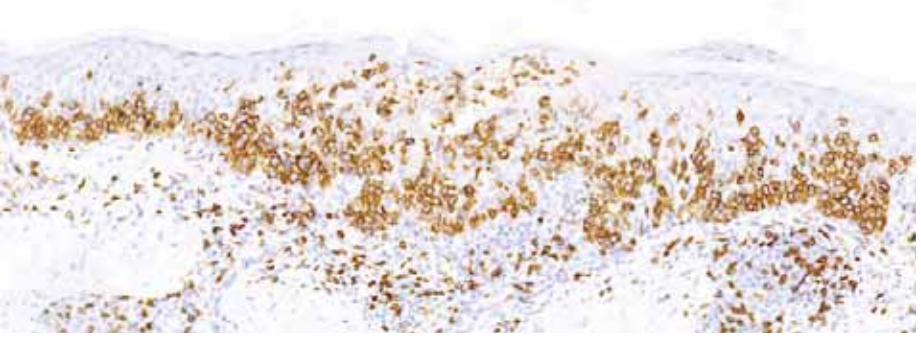
CD8



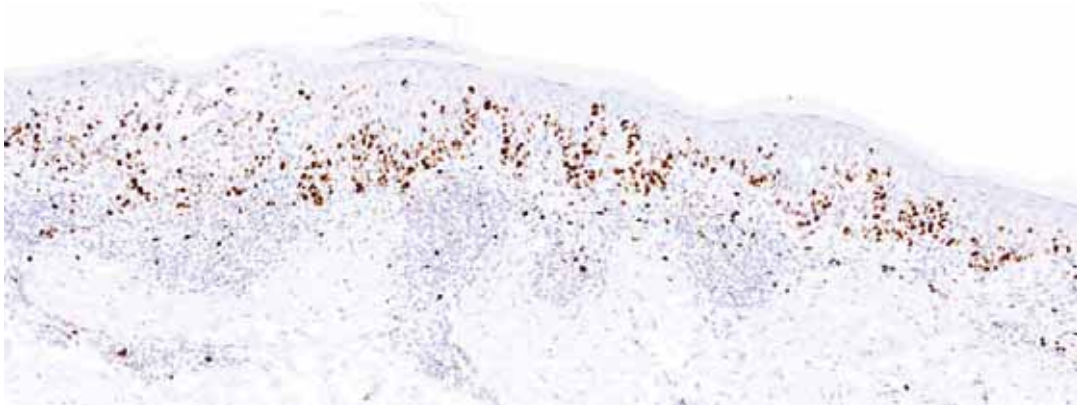
Immunohistochemistry



CD8



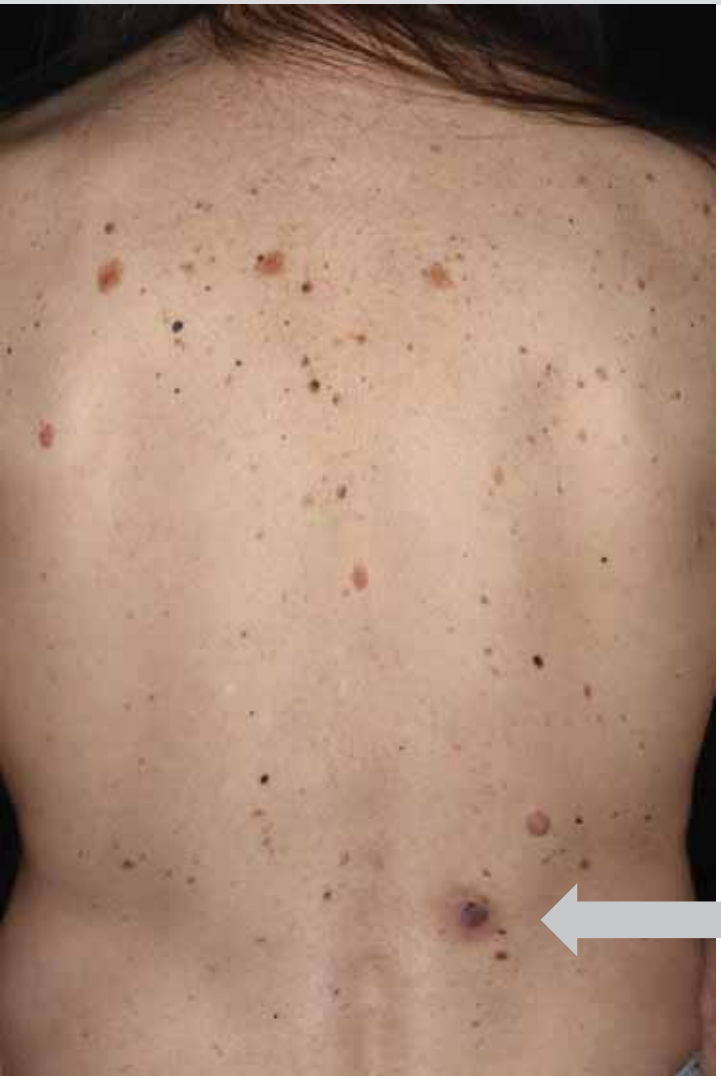
CD8

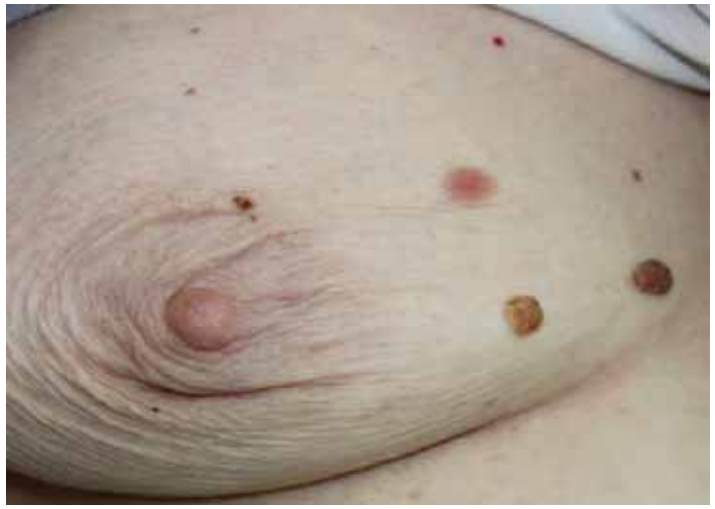


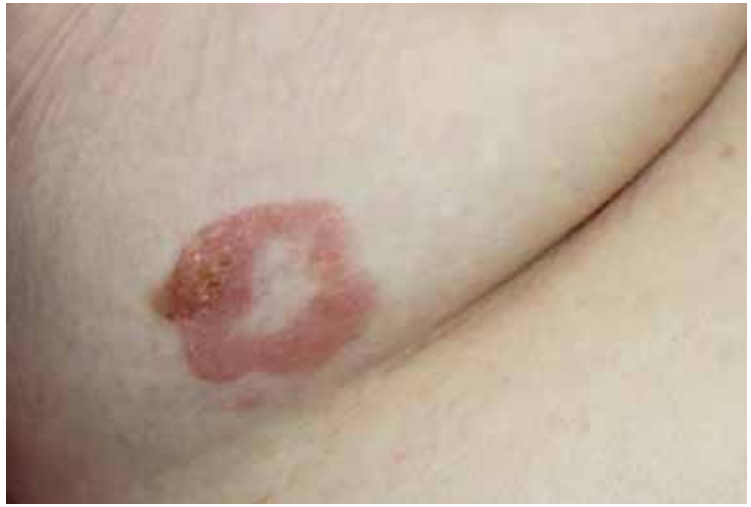
Ki67

CD3+, CD8+, CD4-, Ki67 ↑
TIA 30%, GranzymB 30%, Perforin neg.
CD45RA-, CD45R0+
TCR beta+, TCR gamma-

Clinical presentation



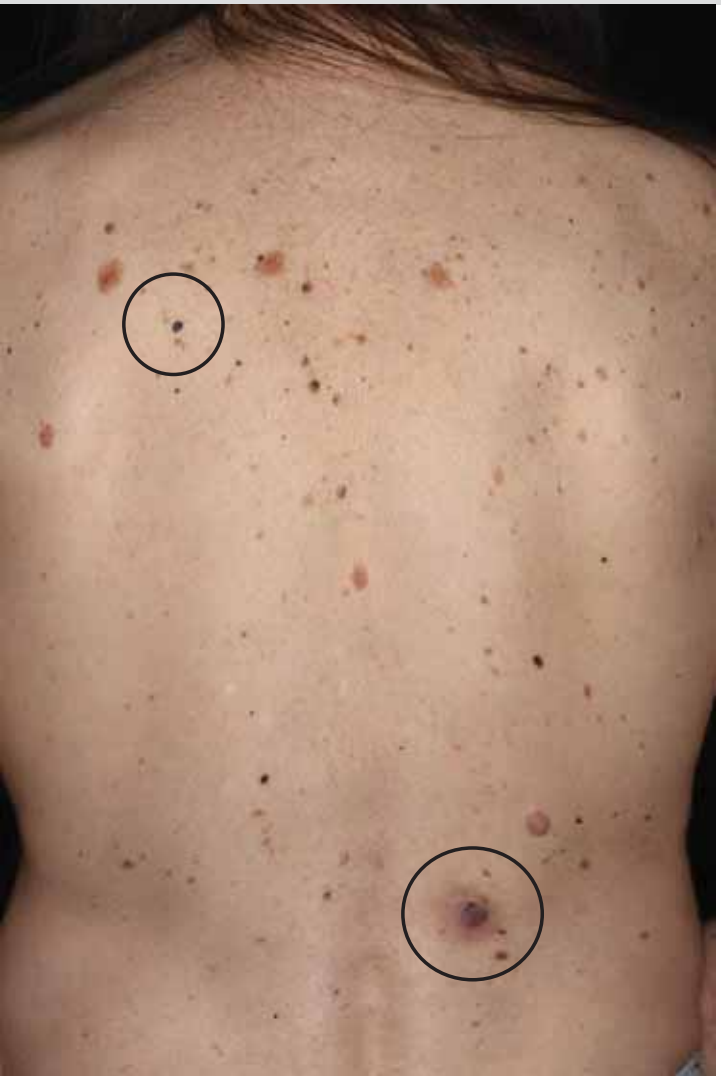


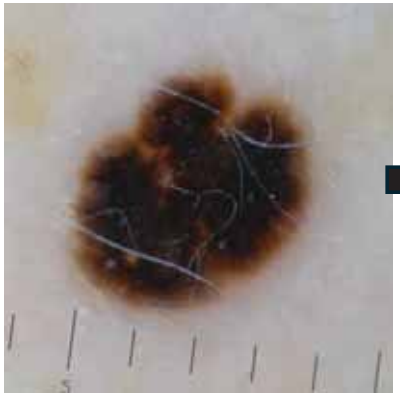


Sudden appearance of two flat plaques on the breast

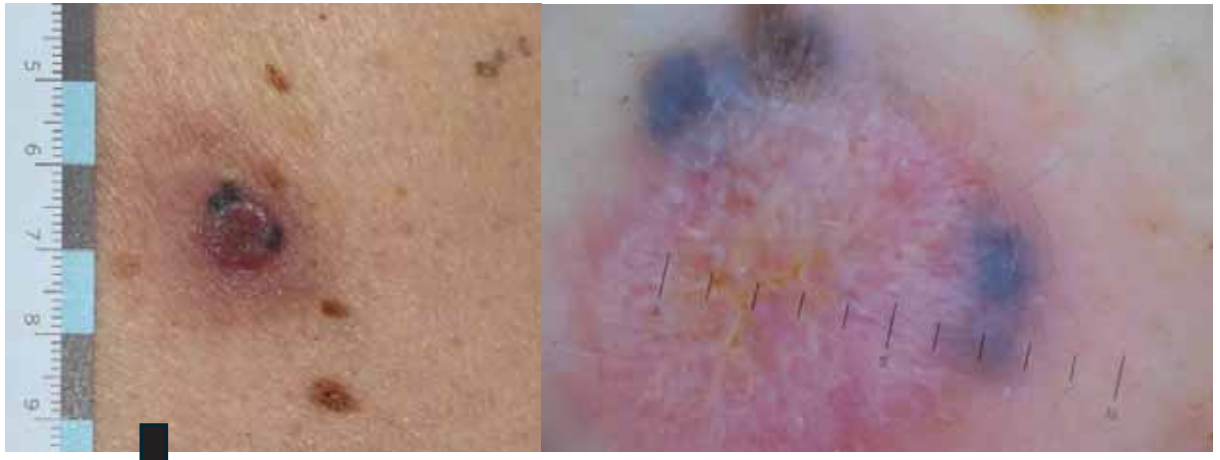
Development of a nodule on the lower right back

Clinical presentation



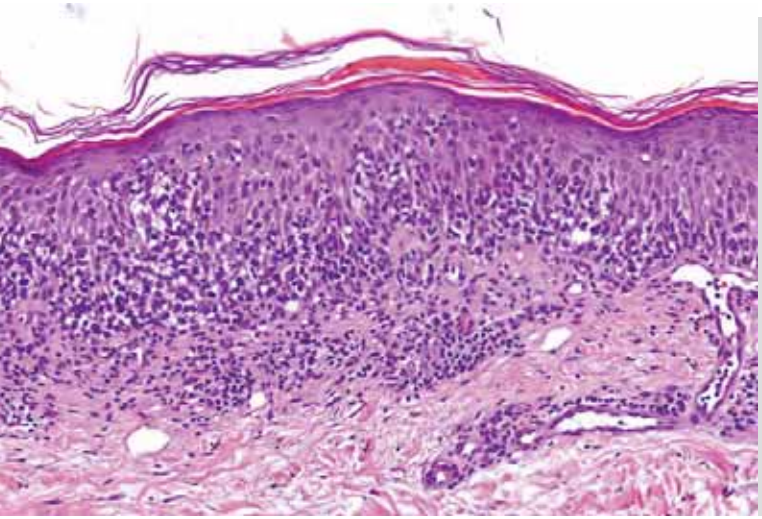


SSM, TD 0.2 mm, pT1a

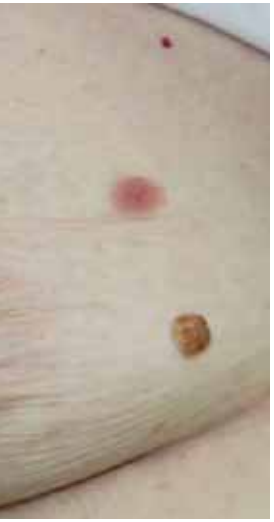


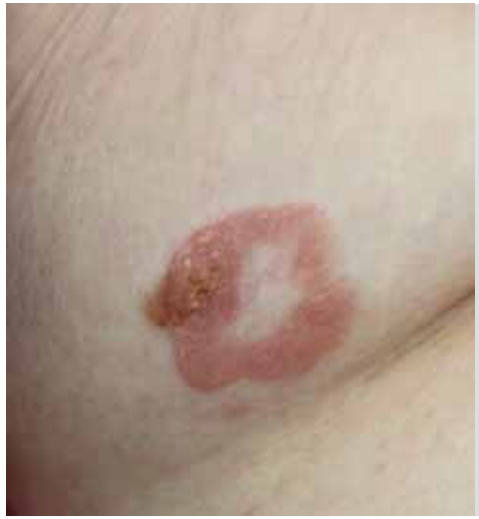
sek. nod. SSM, ulcerated, TD 5.7 mm, pT4b, N0 (0/4), M0

Summary of the findings:



Histology:
Epidermotropic, lining-up + pagetoid spread, small lymphocytes
Immunohistochemistry:
CD3+, CD8+, CD4-, Ki67 ↑
TIA 30%, GranzymB 30%, Perforin neg.
CD45RA-, CD45R0+
TCR beta+, TCR gamma-





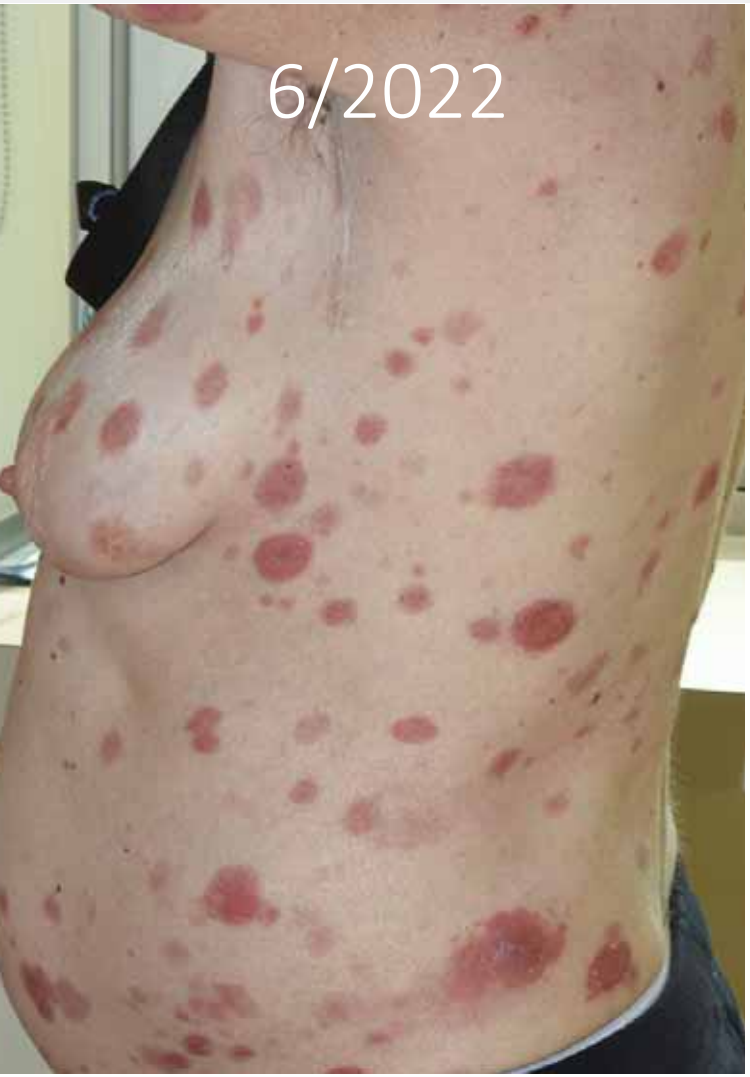
Clinical presentation:
Two isolated flat plaques
Staging:
CT neck-pelvis: no pathologic findings
FACS (peripheral blood): normal

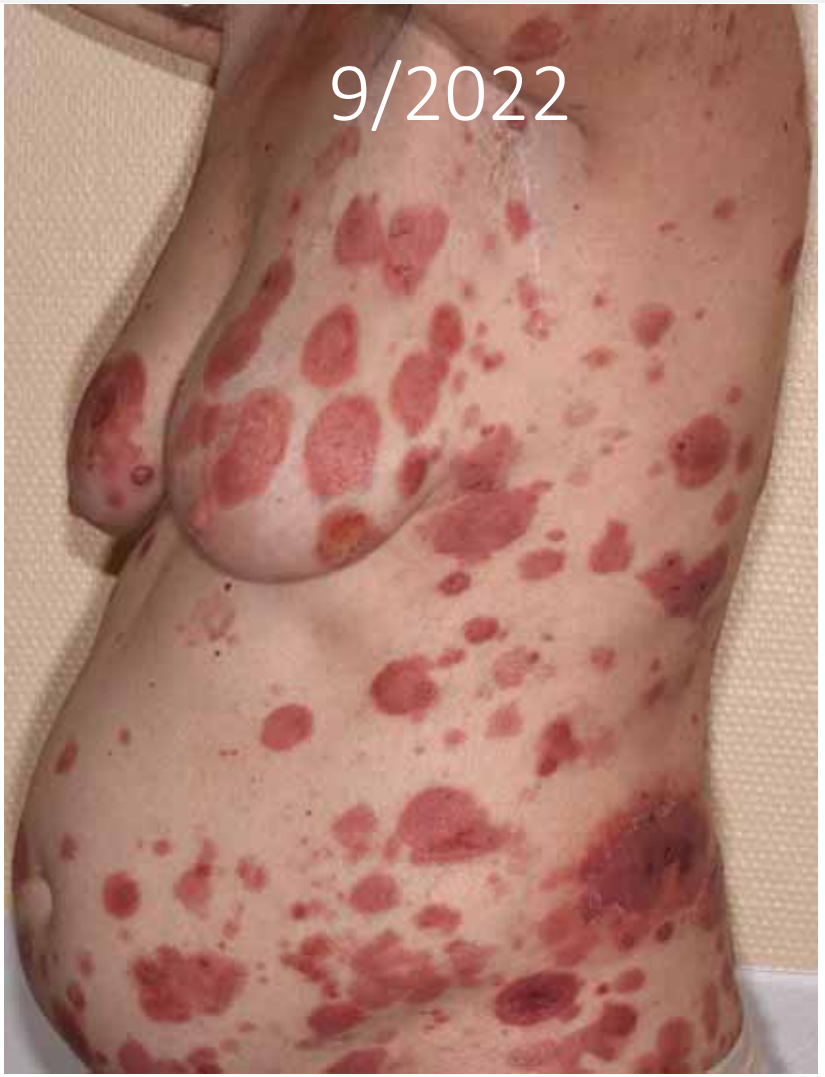
Stage: IA (T1b, N0, M0, B0)

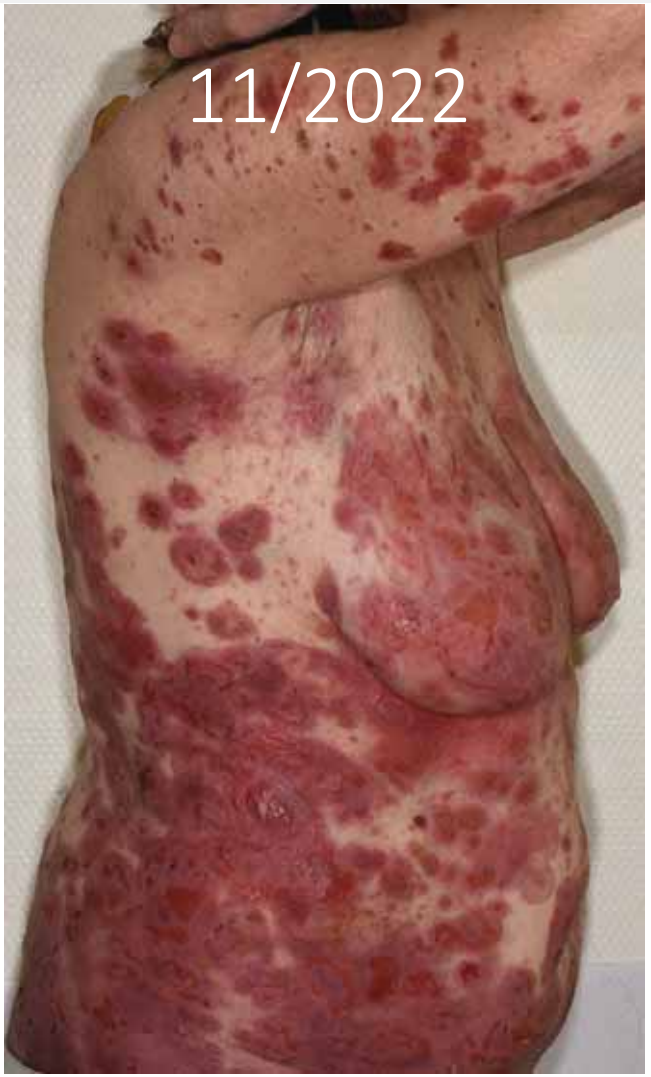
diagnosis

?

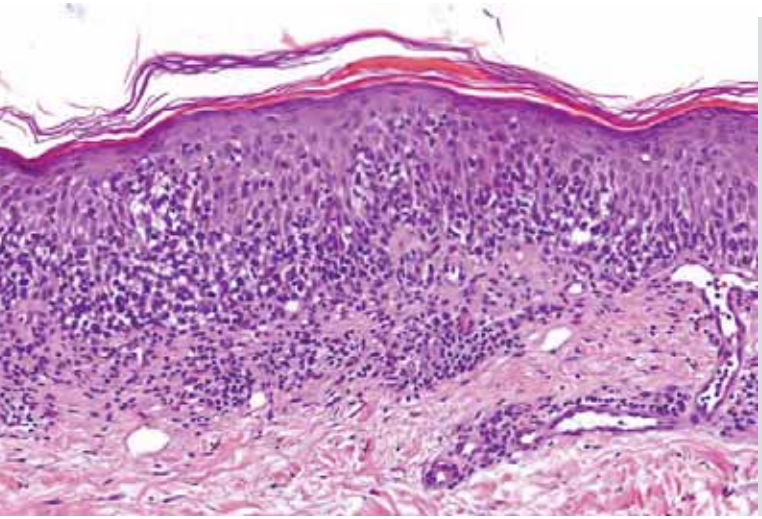
Further course: rapid progression + systemic manifestation

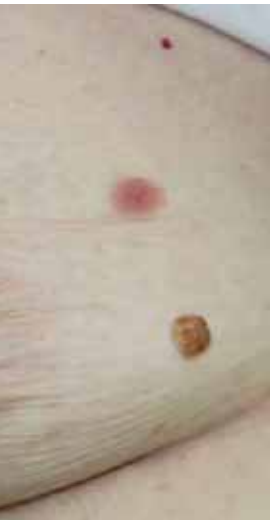


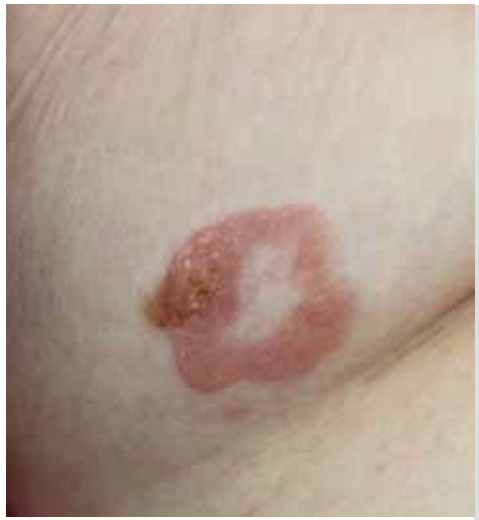




Summary of the findings:







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FACS (peripheral blood): normal

Stage: IA (T1b, N0, M0, B0)

CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8+AECTCL)

CD8+ Mycosis fungoides

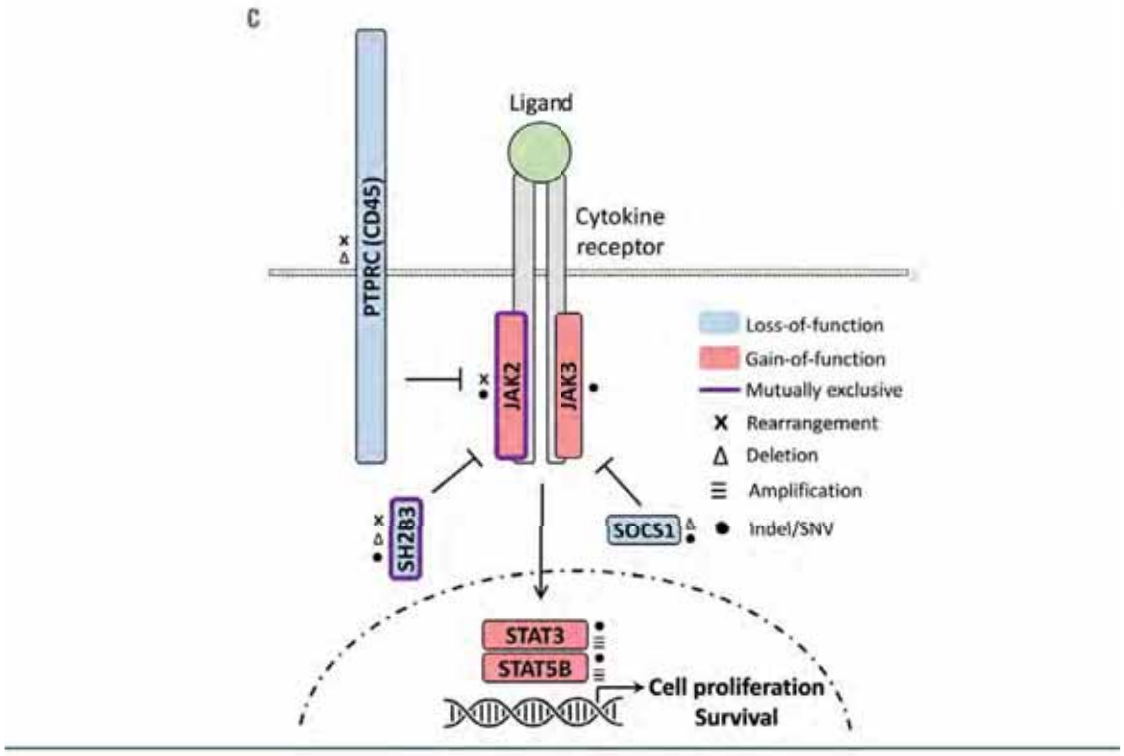
- patches, plaques, tumors
- ulceration in later stages
- mostly indolent course
- extracutaneous manifestation is rare: lymphnodes
- Moderate basal epidermotropism

- CD3+, CD8+, CD45R0+, TCRbeta+, cytotoxic markers+, ki67 low - high
- median 5-year survival: 85%

pc CD8+ AECTCL

- plaques and tumors
- early ulceration is common, necrosis
- rapid progressive
- extracutaneous manifestation is common: CNS, lung, oral, testes)
- Significant epidermotropism, apoptotic keratinocytes
- CD3+, CD8+, CD45RA+, TCRbeta+, at least 1 cytotox. Marker+, ki67 high
- median survival: 2 years

Dysregulation JAK2 signaling pathway




ARTICLE

Non-Hodgkin Lymphoma

Ferrata Storti Foundation

Deregulation of JAK2 signaling underlies primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

Armando N. Bastidas Torres,[1] Davy Cats,[2] Jacoba J. Out-Luiting,[1] Daniele Fanoni,[3] Hailiang Mei,[2] Luigia Venegoni,[3] Rein Willemze,[1] Maarten H. Vermeer,[1] Emilio Berti[4] and Cornelis P. Tensen[1]

[1]Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands; [2]Sequencing Analysis Support Core, Leiden University Medical Center, Leiden, the Netherlands; [3]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy and [4]Department of Dermatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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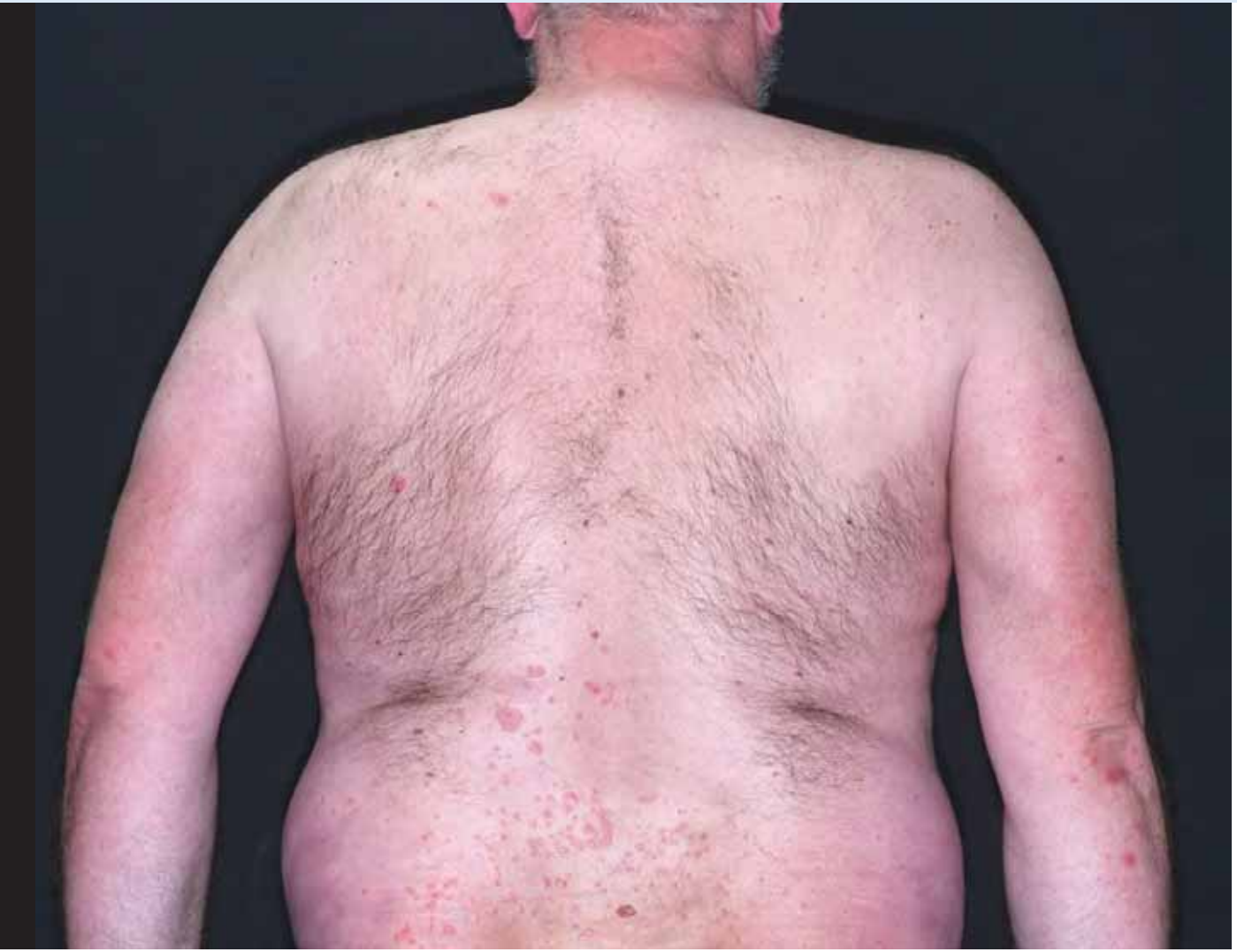
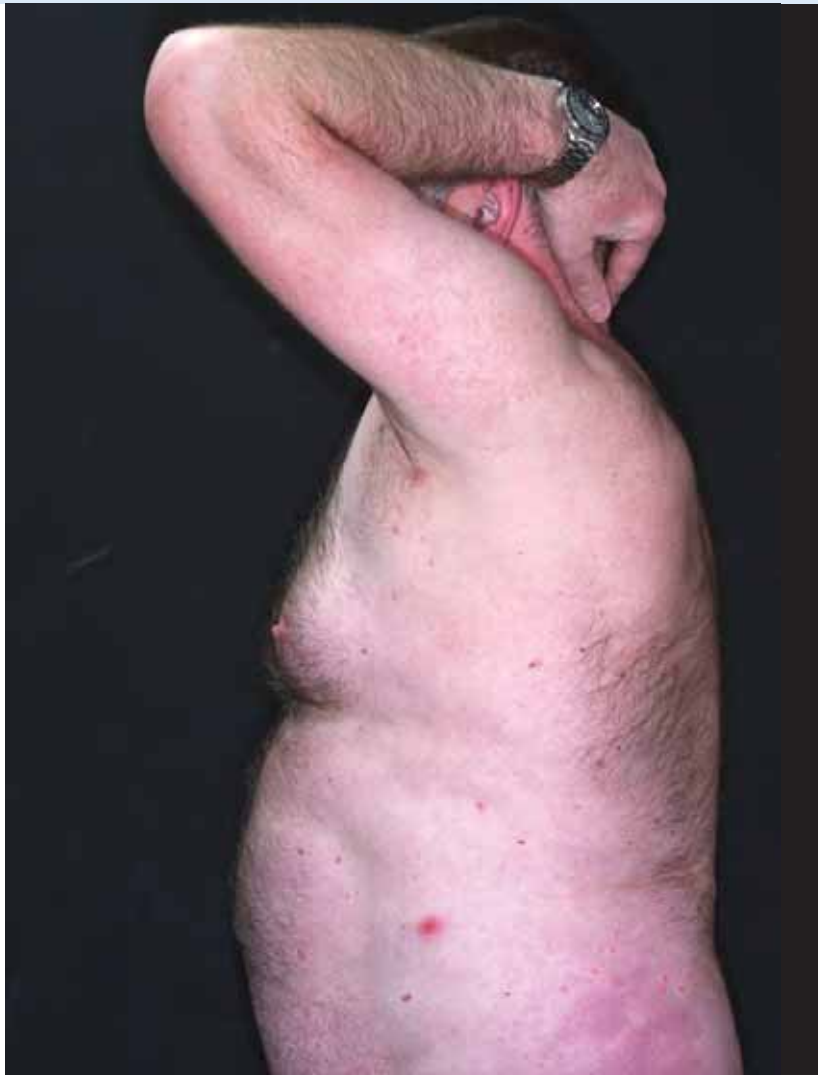
- Alteration of JAK-STAT-pathway (JAK2 Fusion)
- Activation of JAK2 pathway
  → Ruxolitinib
- NFkB activaton
  → Bortezomib, Dimethylfumerat
- Combination therapy? Synergistic effects?

Clinical information

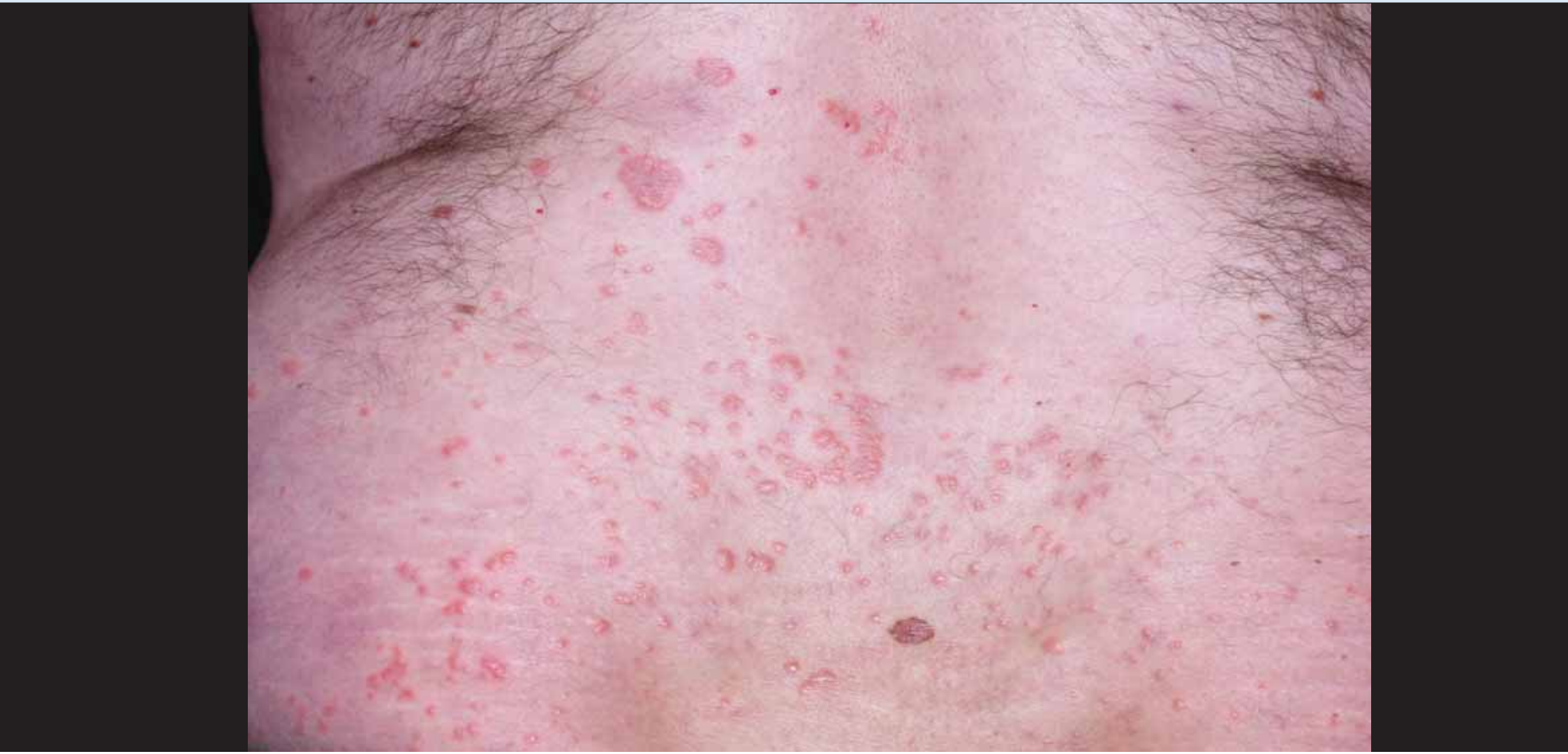
- 48-year-old male patient
- Bad general health condition, night sweat
- Skin eruptions for 6 months, first diagnosed as herpes zoster
- General and skin symptoms responded to systemic steroids
- Histology refereed in a lymphoma reference center
- External diagnosis of Sézary syndrome
- Cutaneous lymphoma clinic for treatment

Clinical presentation

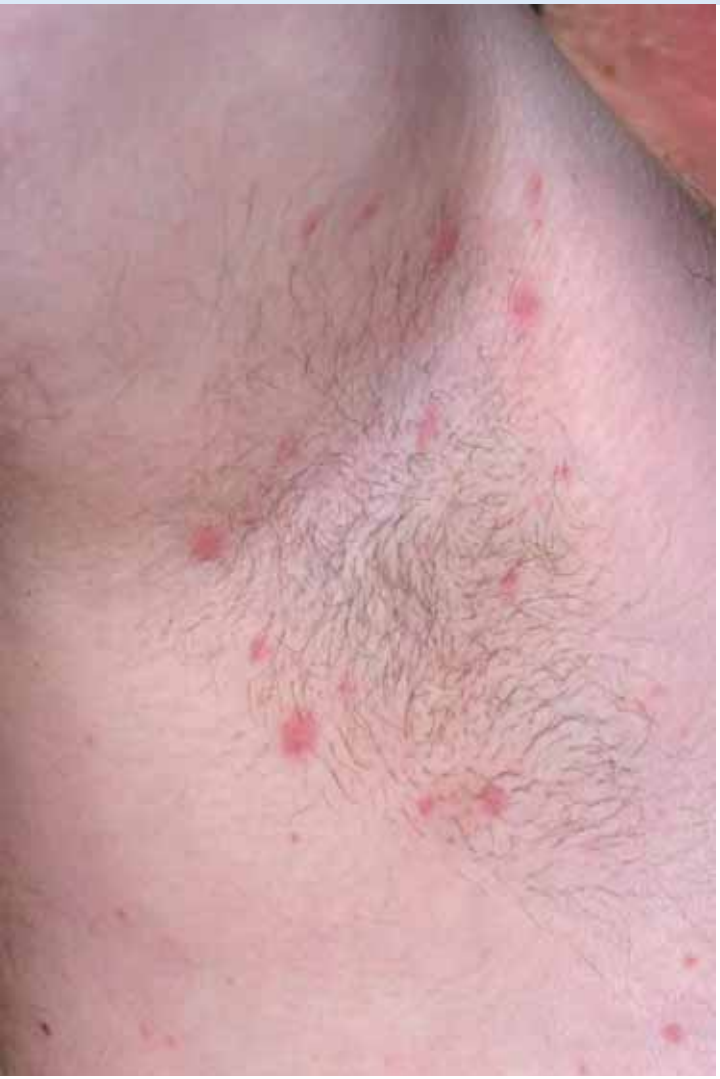


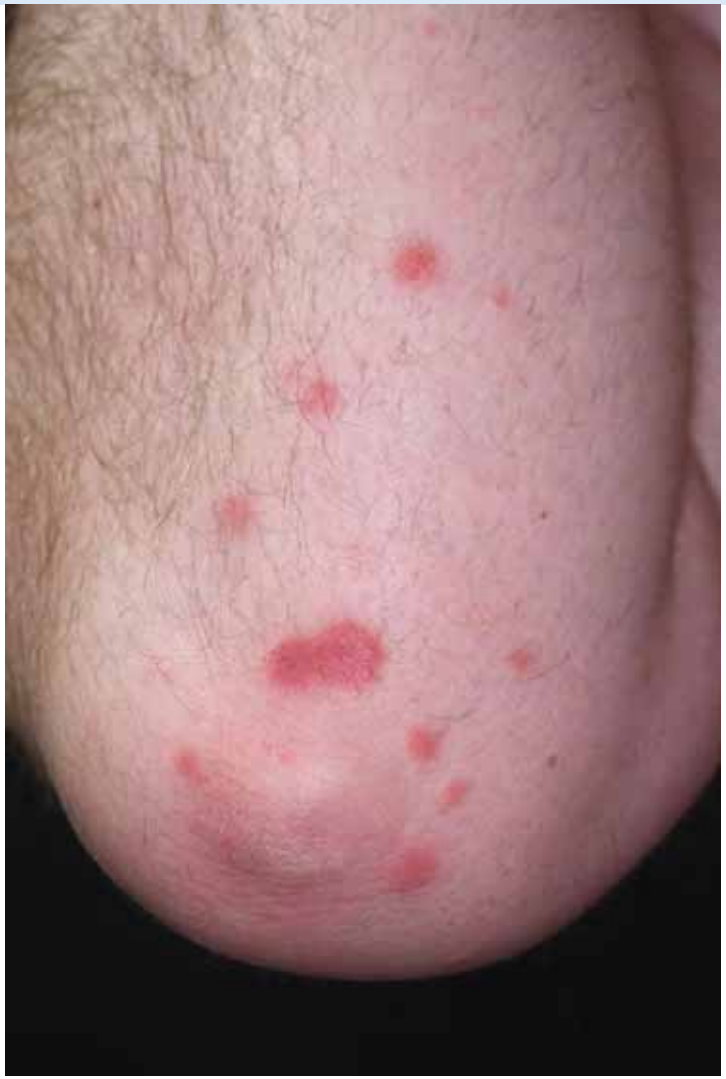


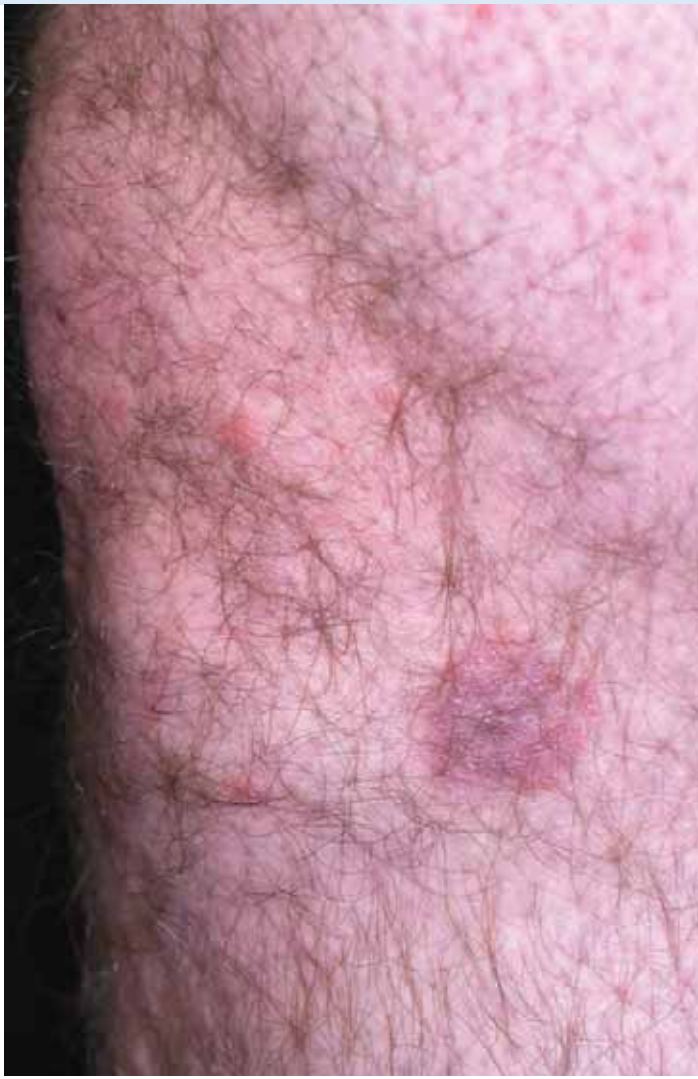
Clinical presentation



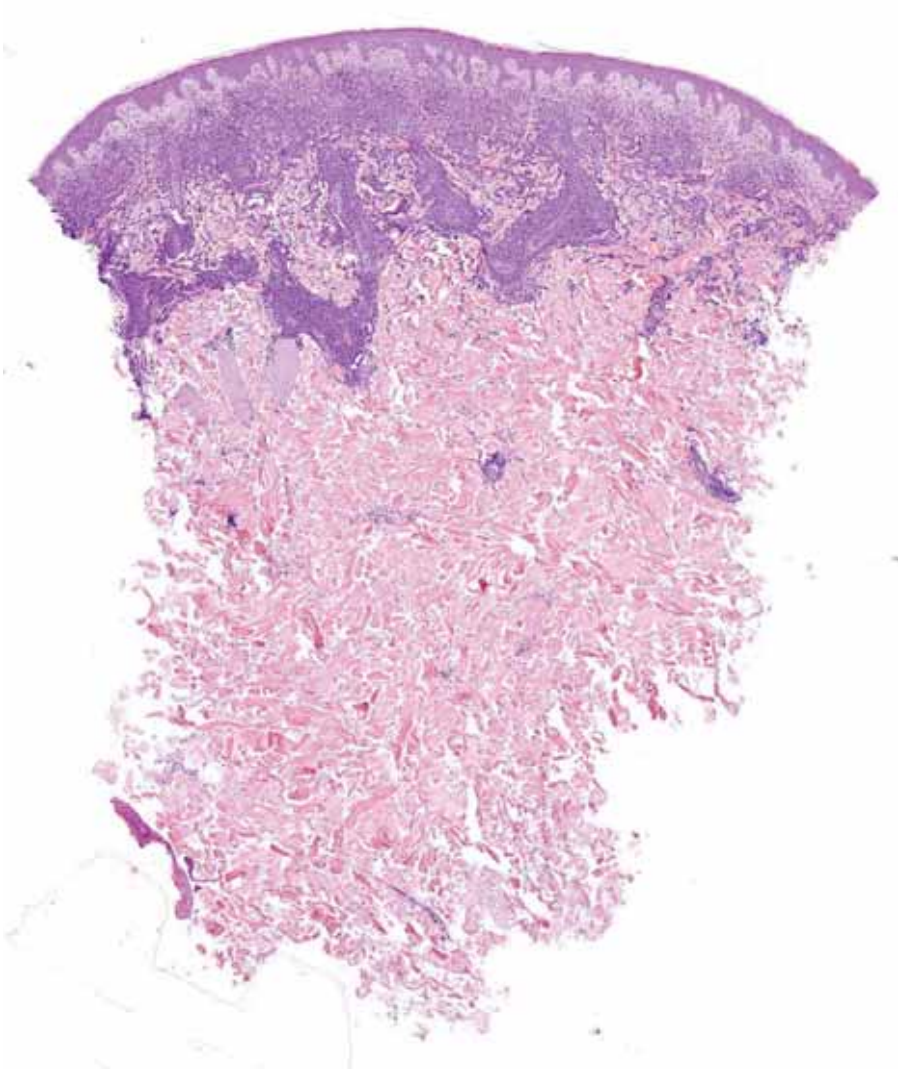
Clinical presentation

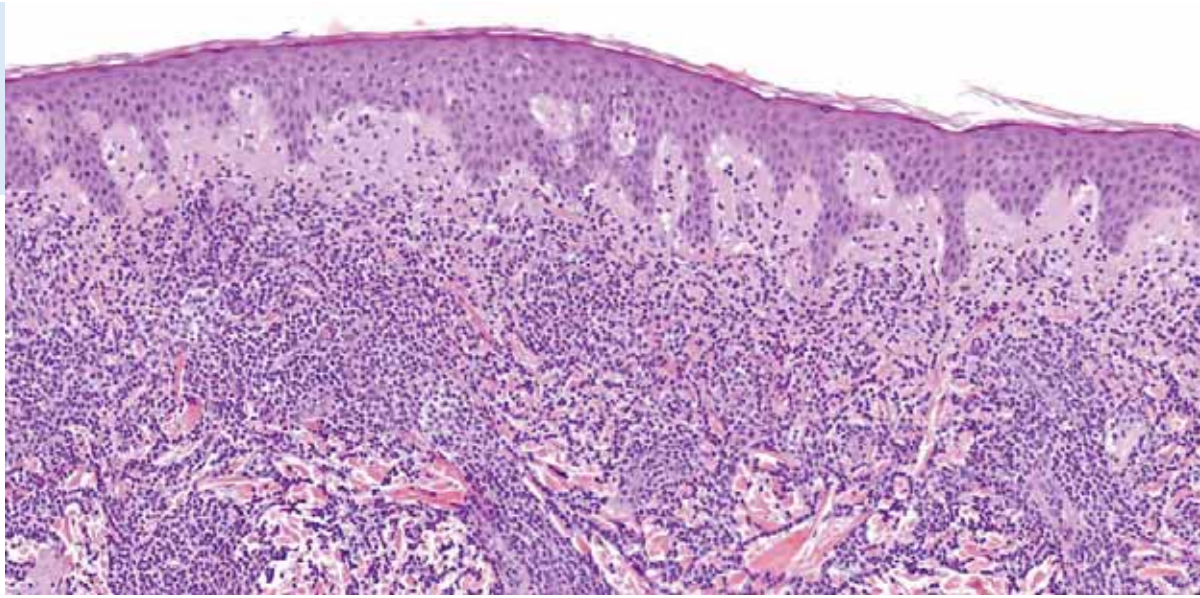


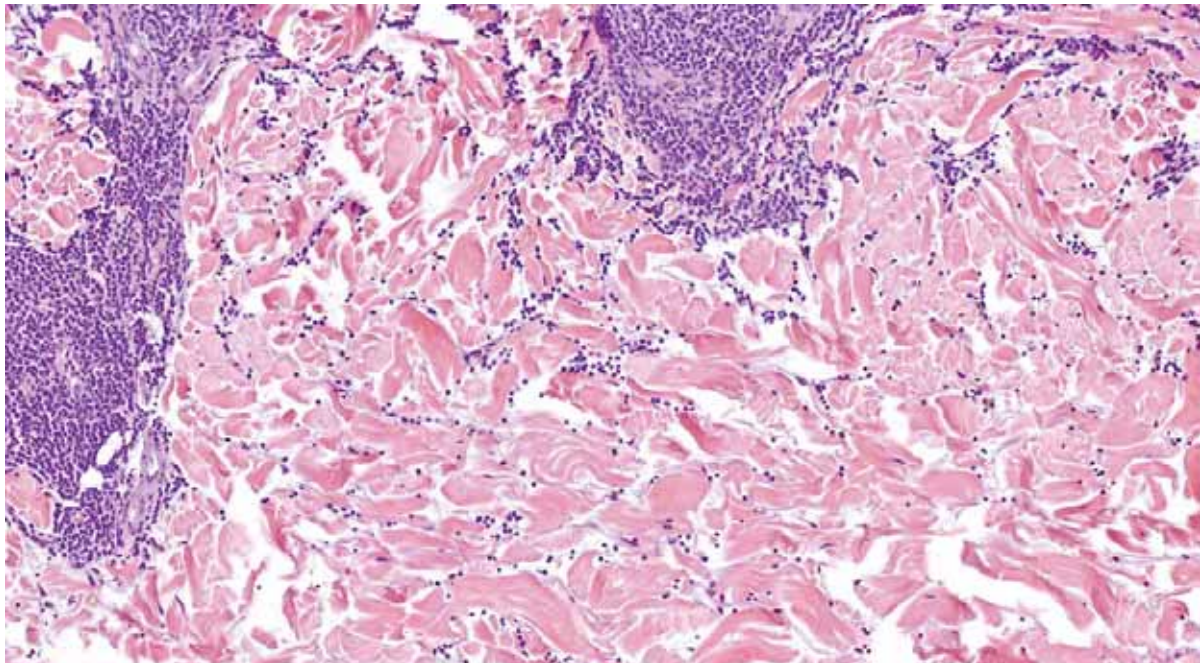


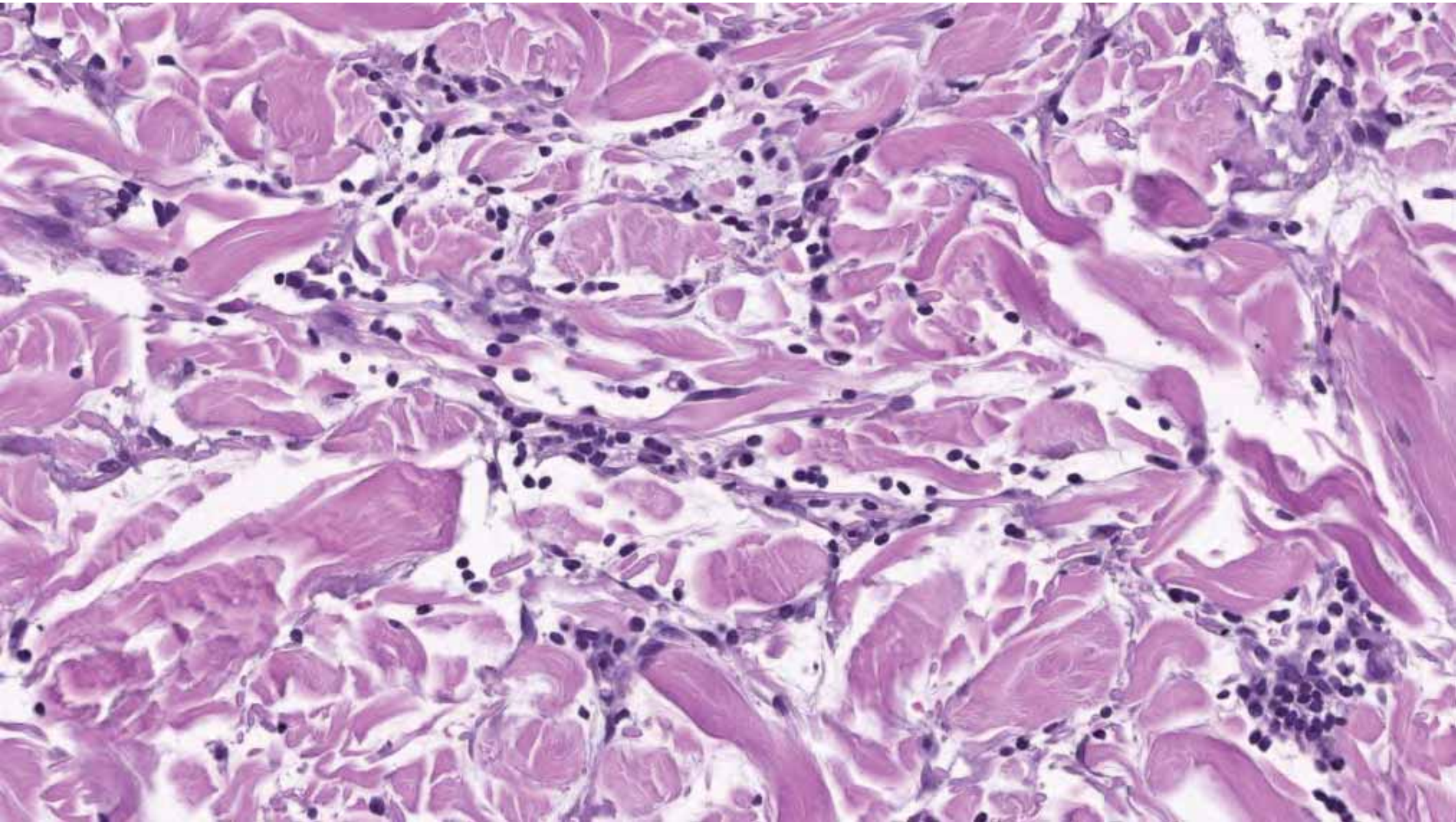


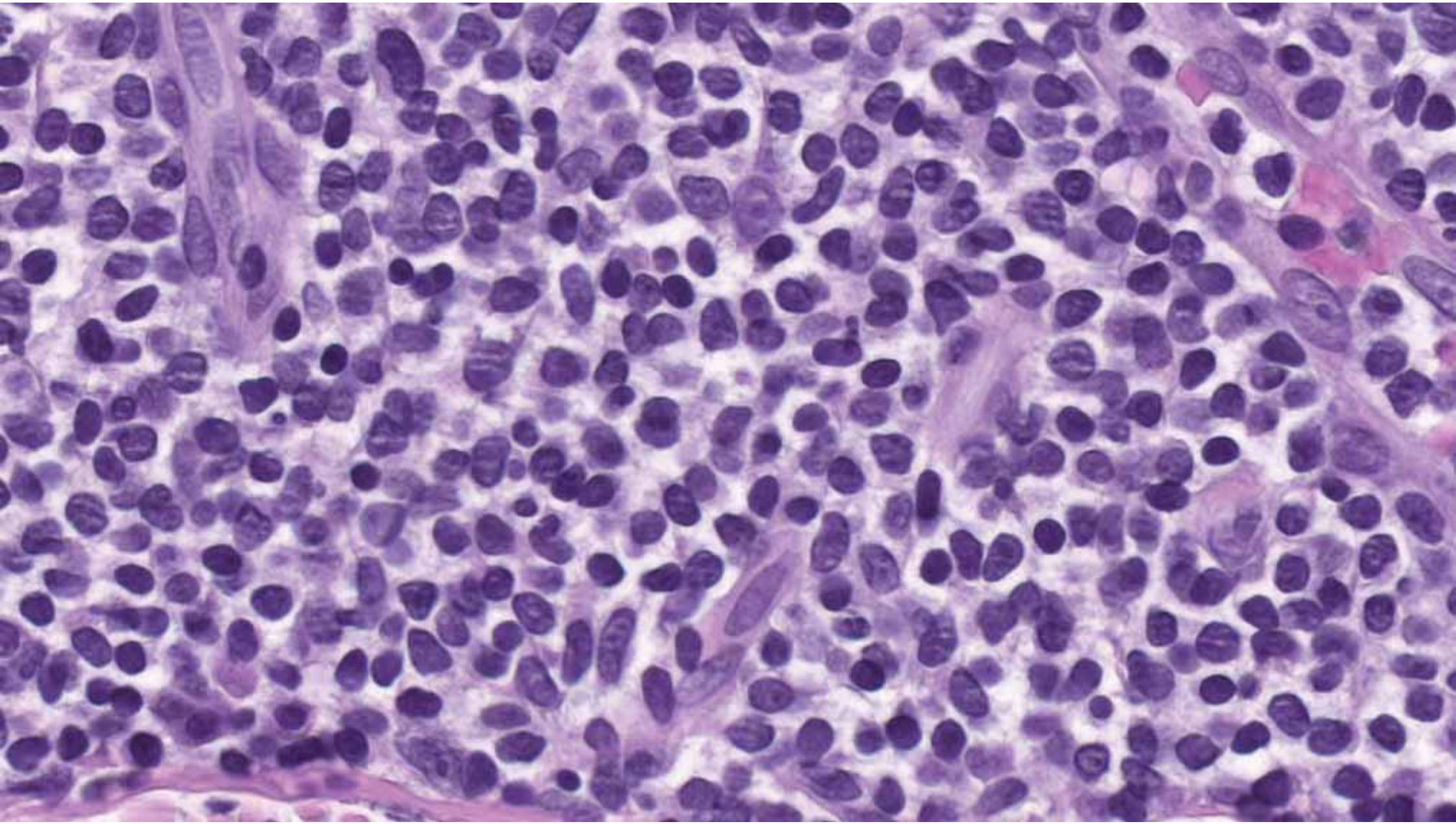
Histology



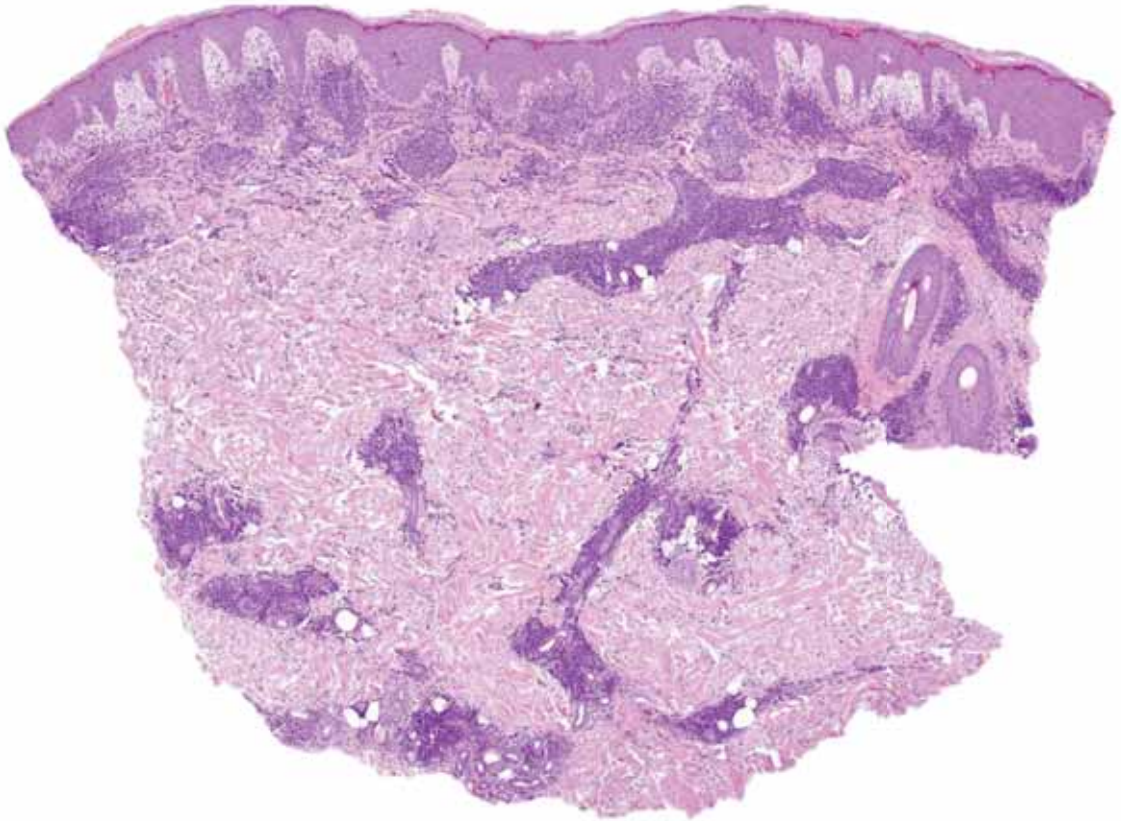


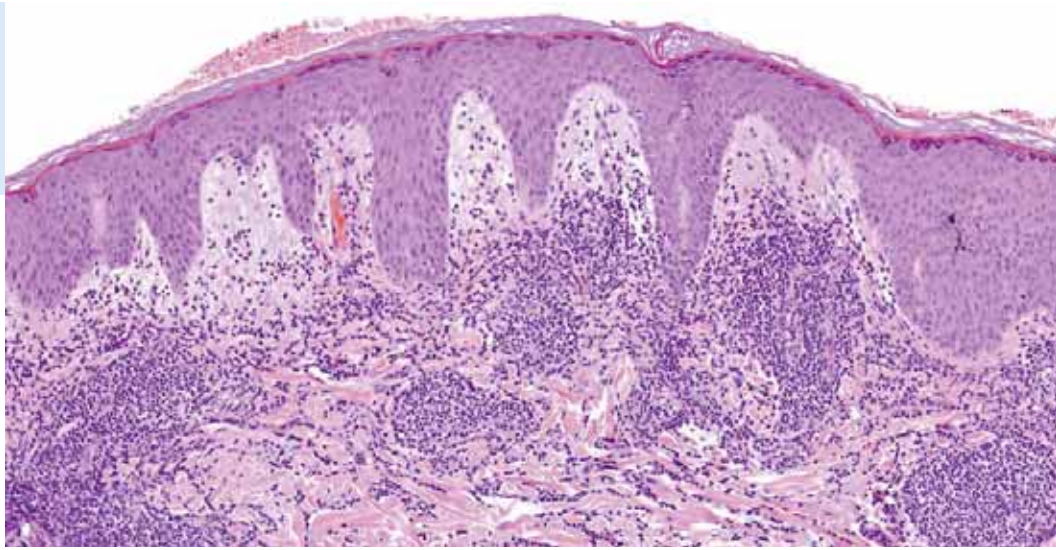


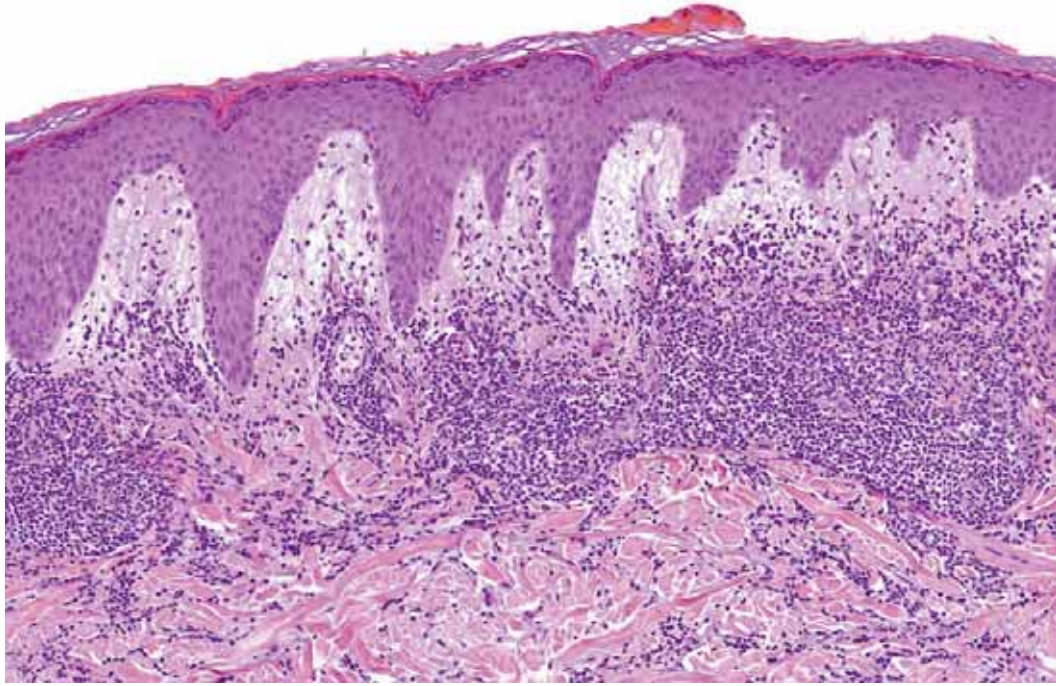


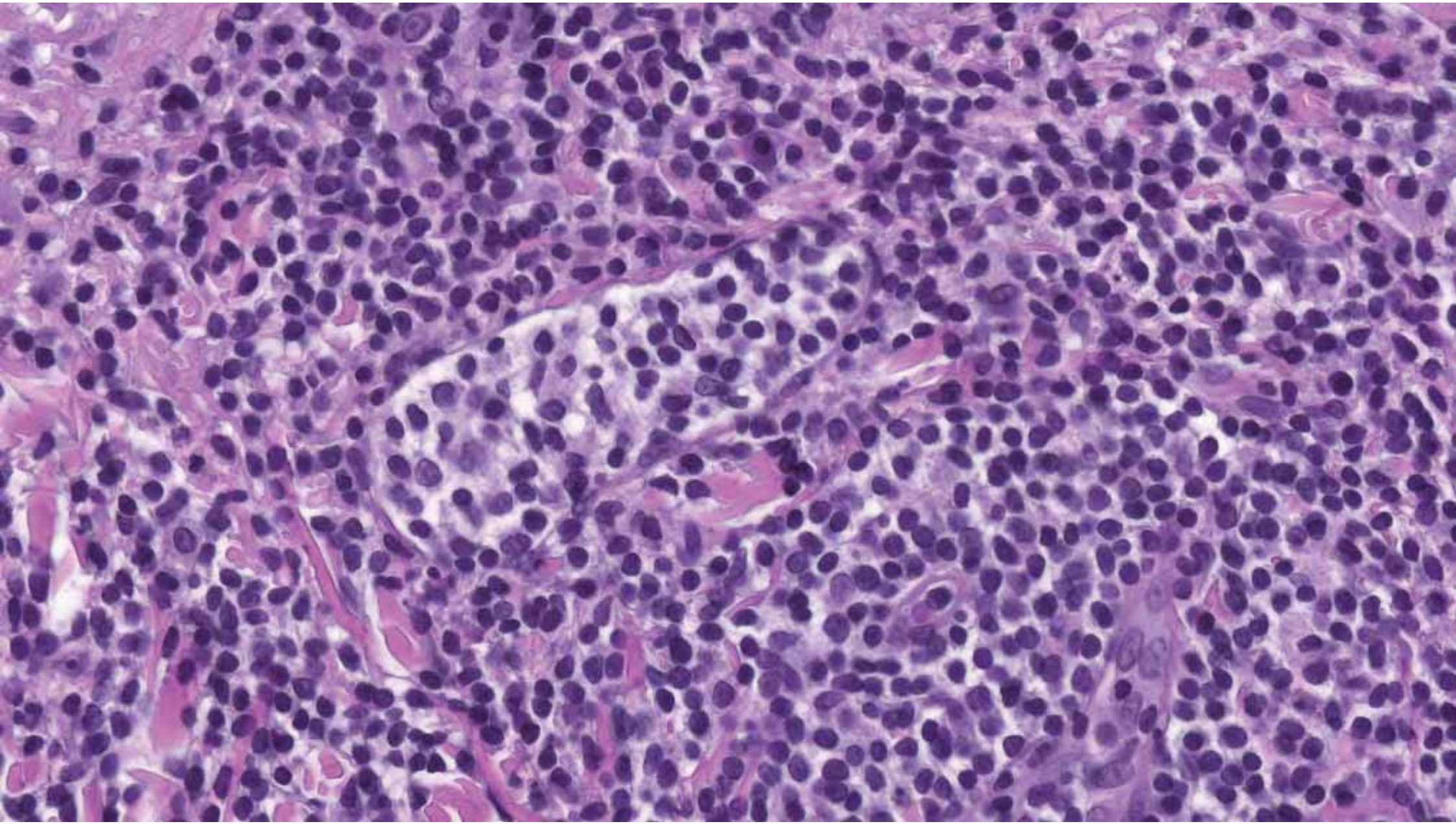


Histology

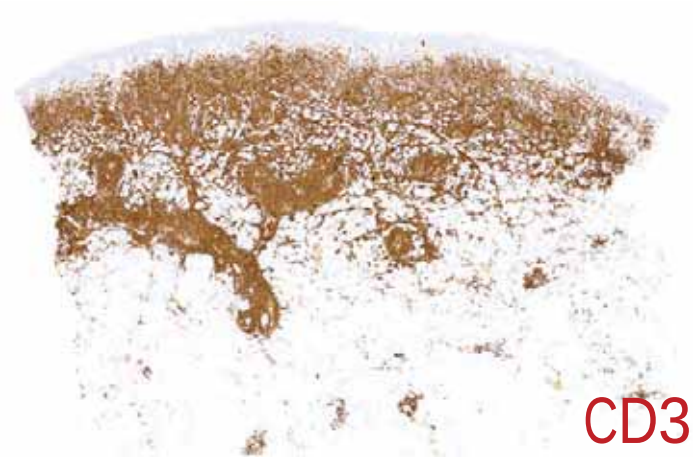


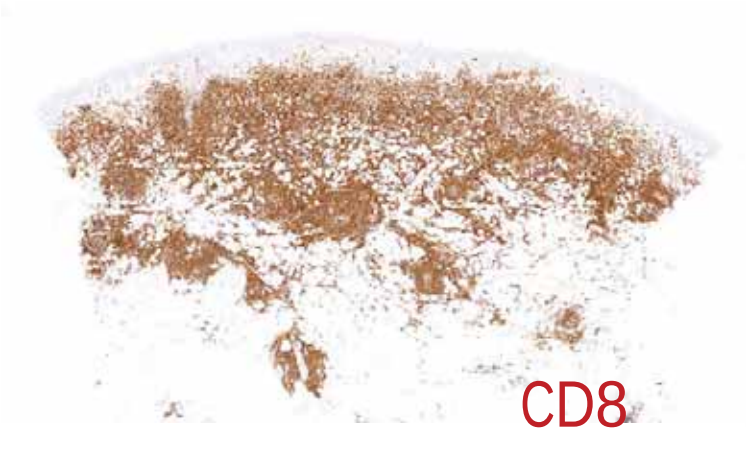




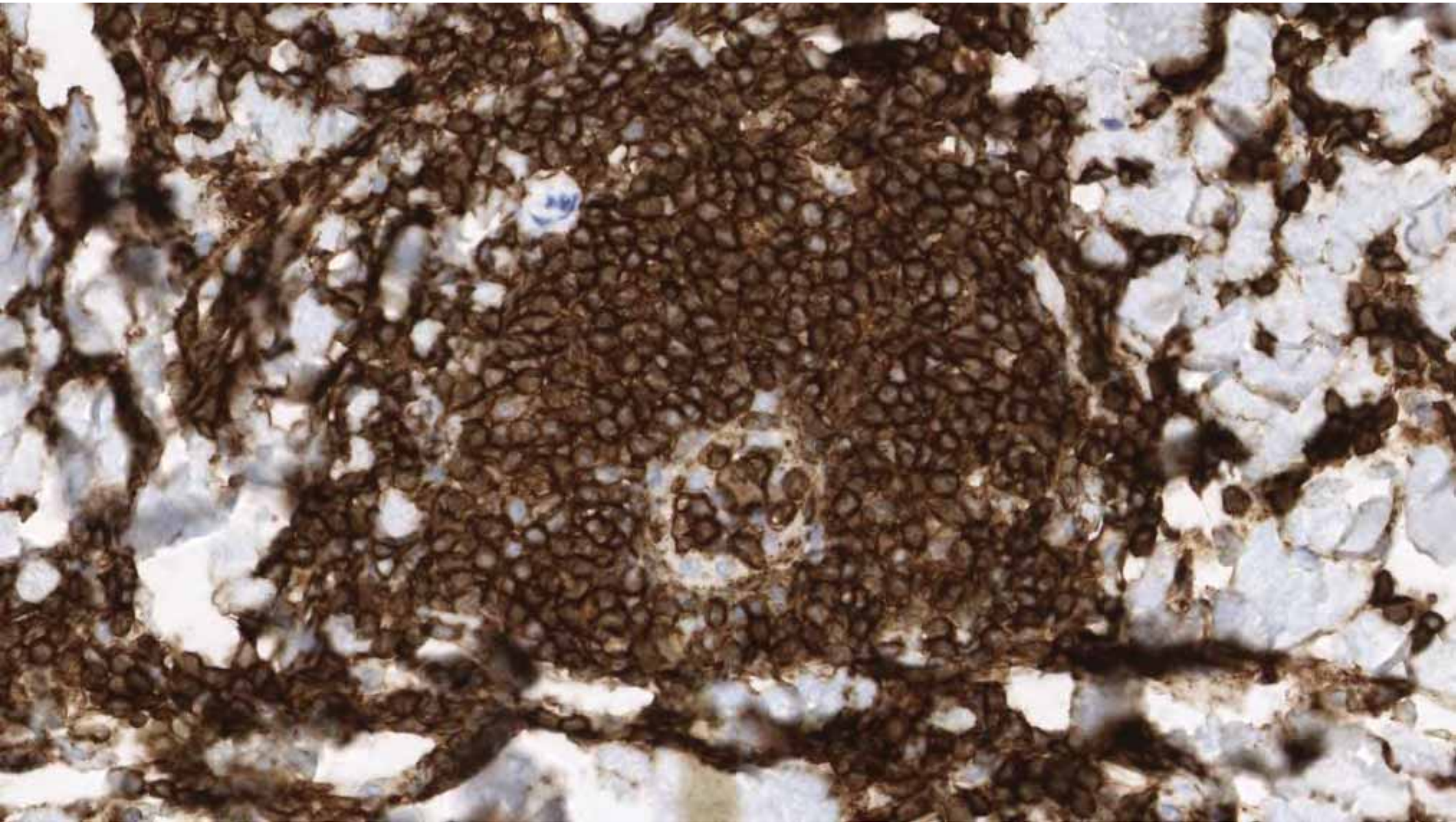


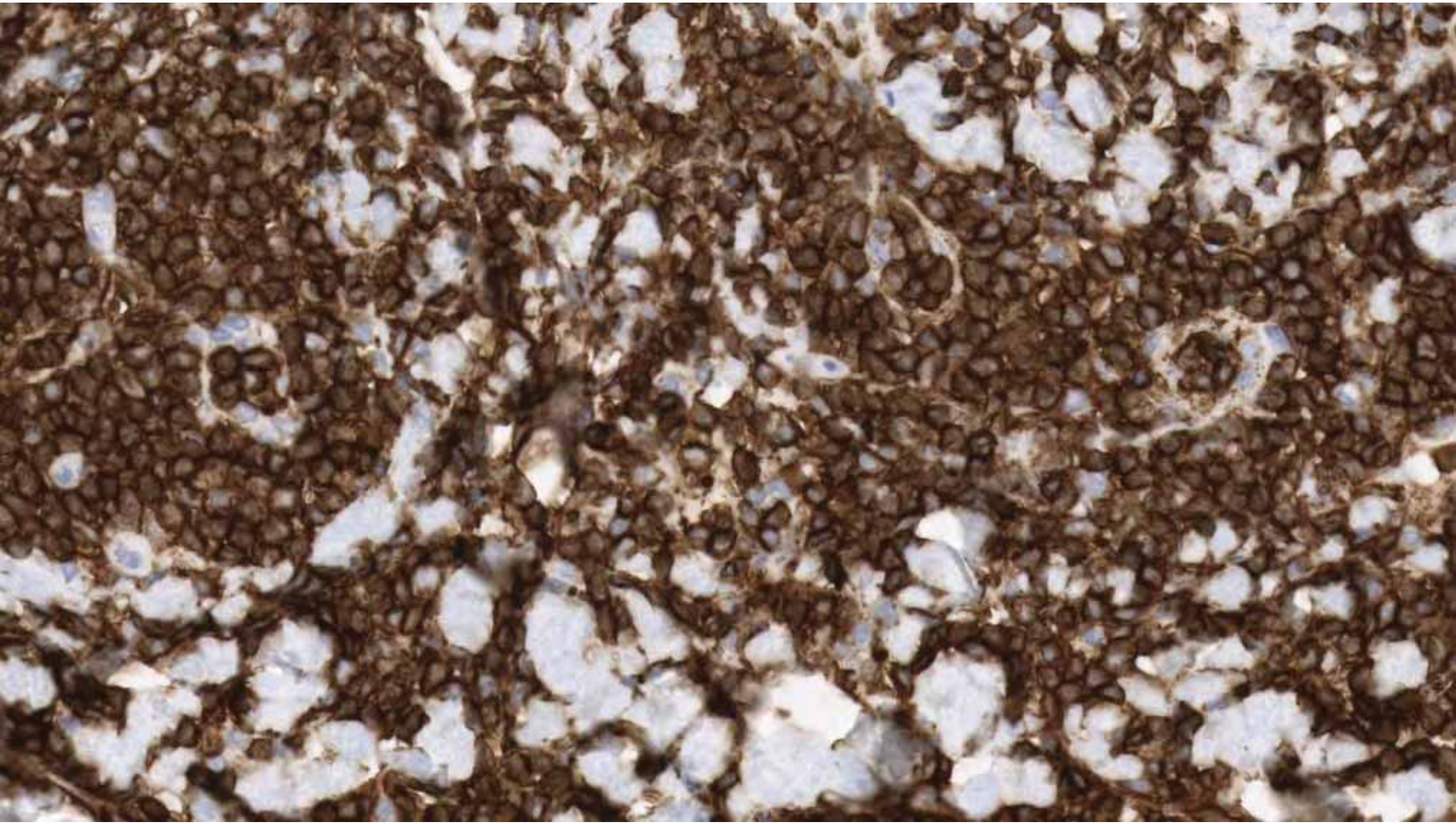
Immunohistochemistry





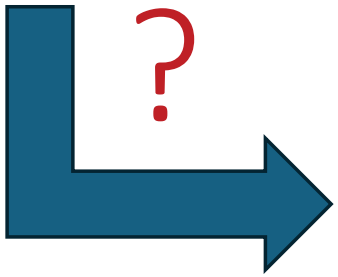
PD1 negative





Additional diagnostic

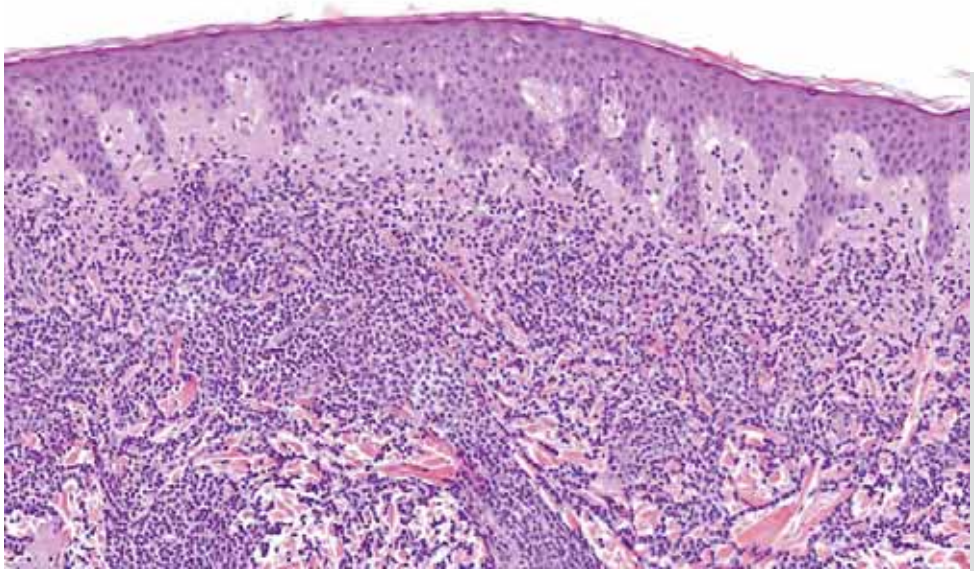
- Enlarged peripheral lymph nodes
- B-symptoms: night sweat and weight loss
- CT head – pelvis: splenomegaly, disseminated enlarged lymphnodes
- Peripheral blood: lymphocytosis >5x10^9/l



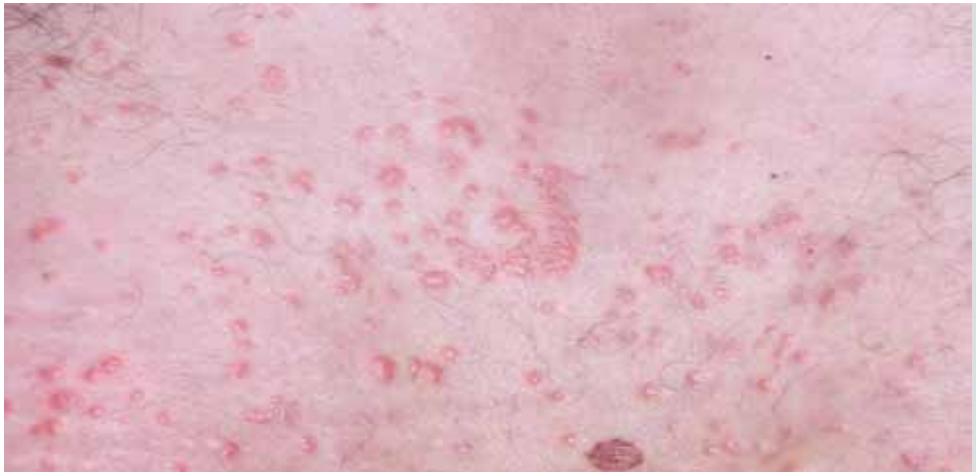
Sézary syndrome?

- Erythrodermic
- Palmo-plantar Hyperkeratosis
- Lymphadenopathy
- CD3+, CD4+, CD8-, PD1+

Summary of the findings



Histology:
Band-like superficial and deep periadnexal and perivascular infiltrate
Vacuolar alteration
Papillary edema
Single-file pattern
CD3+, CD4-, CD7+, CD8+, PD1-, Ki67↑

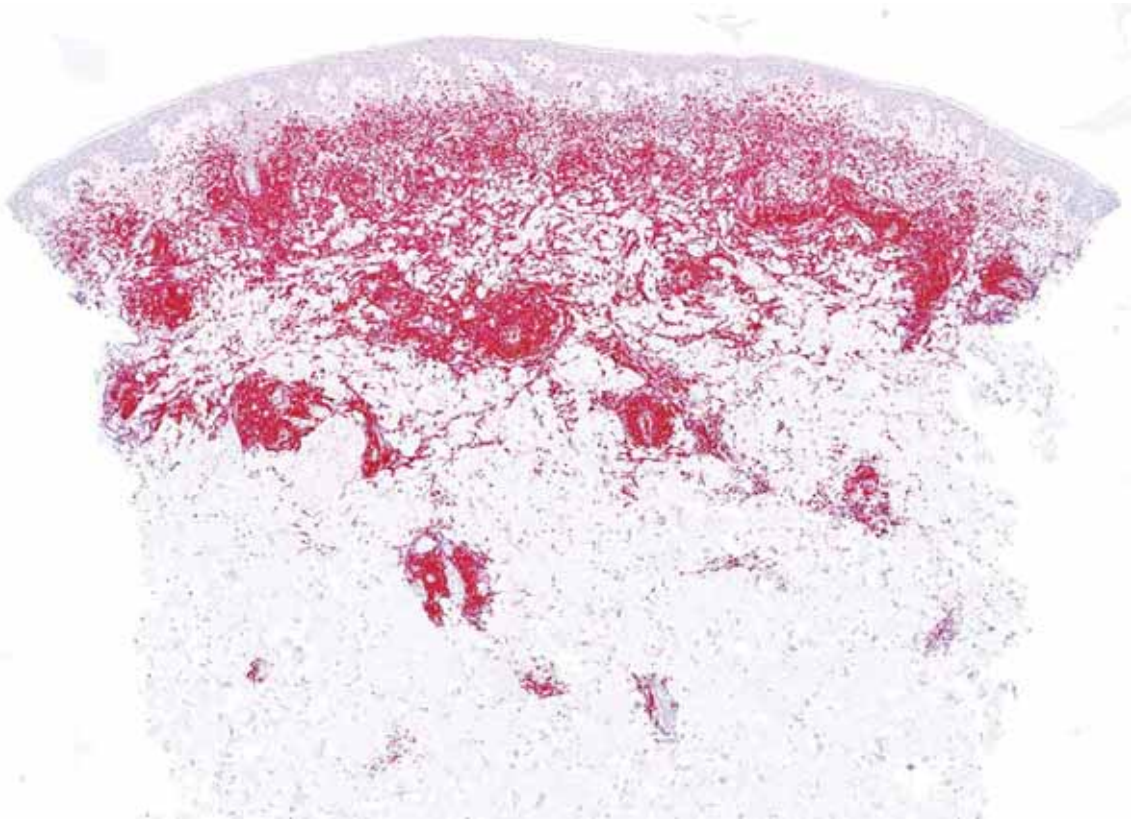


Clinical presentation:
Lichenoid and urticarial plaques
No erythroderma
No palmar/plantar hyperkeratosis
Generalized lymphadenopathy

diagnosis

?

Additional diagnostic



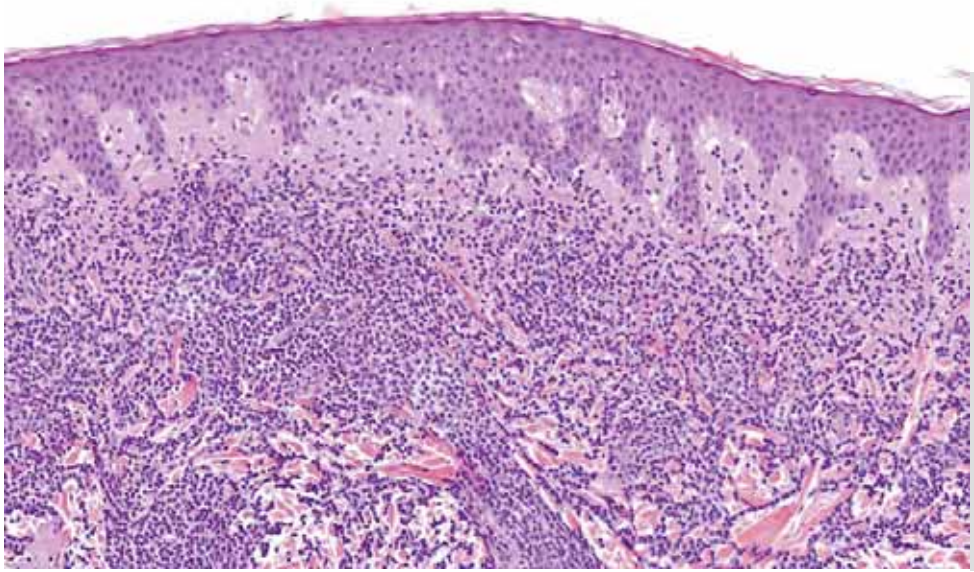
TCL-1*

Genetic diagnostics:

- t(14;14) (q11;q32)
- Activation of TCL1A

*T-Cell Leukemia/Lymphoma 1

Summary of the findings



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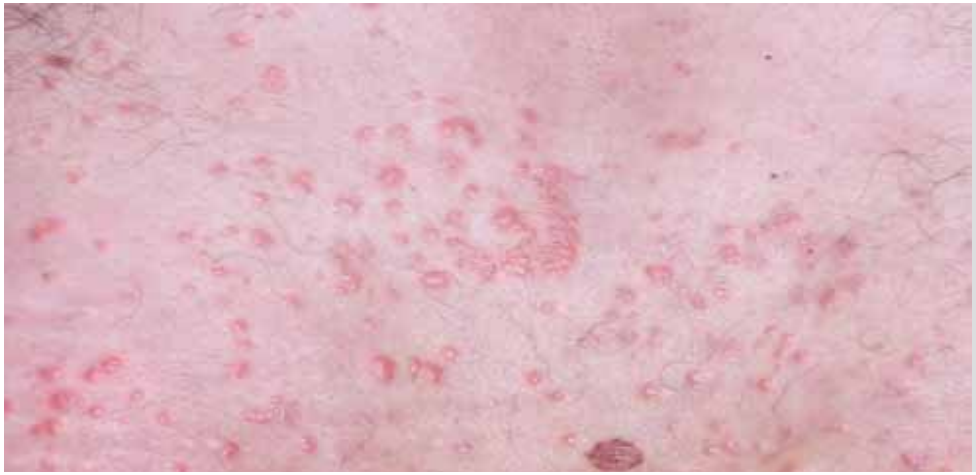
Papillary edema
Single-file pattern
CD3+, CD4-, CD7+, CD8+, PD1-, Ki67↑



Clinical presentation:
Lichenoid and urticarial plaques
No erythroderma
No palmar/plantar hyperkeratosis
Generalized lymphadenopathy

secondary cutaneous infiltrate of a

T-pro-lymphocytic leukemia

T-prolymphocytic leukemia

Histology:
- Small to medium-sized lymphocytes
- Irregular and prominent nucleoli
- Moderately basophilic cytoplasm
- 25% small cell variant

Immunohistochemistry:
- T-cell markers: CD2+, CD3+ (may be weak), CD5+, CD7+
- Coreceptor expression:
  - CD4+, CD8- (40-60%)
  - CD4+, CD8+ (25-41%)
  - CD4-, CD8+ (15%)
- CD52+ (→ alemtuzumab)
- TCL1+

Diagnostic criteria*
according to consensus guidelines and WHO 5th ed.:

Major diagnostic criteria
- Peripheral blood lymphocytosis >5x10^9/l or bone marrow infiltrate with P-TLL phenotype
- Evidence of T-cell monoclonality
- Demonstration of TCL1A (14q32) or MTCP1 (Xq28) or TCL1A protein expression

Minor criteria
- Abnormalities in chromosome 11
- Abnormalities in chromosome 8
- Abnormalities in chromosome 5, 12, 13 or 22 or complex karyotypes
- Involvement of specific sites (e.g. splenomegaly, effusions)

*in 90-95% of cases the diagnosis is established by all three major criteria met.
Caveat: rare TCL-1 negative cases.

T-prolymphocytic leukemia

Epidemiology:

- P-TLL accounts for <2% of all mature lymphoid leukemias
- It is the most common mature T-cell leukemia, but still rare overall
- < 0.1 per 100.000 people per year

Patients' population:

- Median age 61 years (range 30 – 84 years), about 15% occurs in younger patients (<50 years)
- Slightly more common in males (2:1)

Skin involvement:

- Skin involvement is common (20%)
- Nonspecific: exanthema, plaques, nodules, erythroderma, facial edema

Typical clinical findings:

- Splenomegaly (almost always)
- Lymphadenopathy (common)
- Serosal involvement (e.g. pleural effusions, ascites)
- CNS involvement can occur

Highly aggressive course: overall survival approximately 21 months

From: Mustafa Wasifuddin et al.

WHO classification of skin tumours 2022 5ed.
Mustafa Wasifuddin J et al. Recurrence of T-Cell Prolymphocytic Leukemia with a Rare Presentation as Diffuse Generalized Skin Lesion. Investig Med High Impact Case Rep. 2023 May 23;11

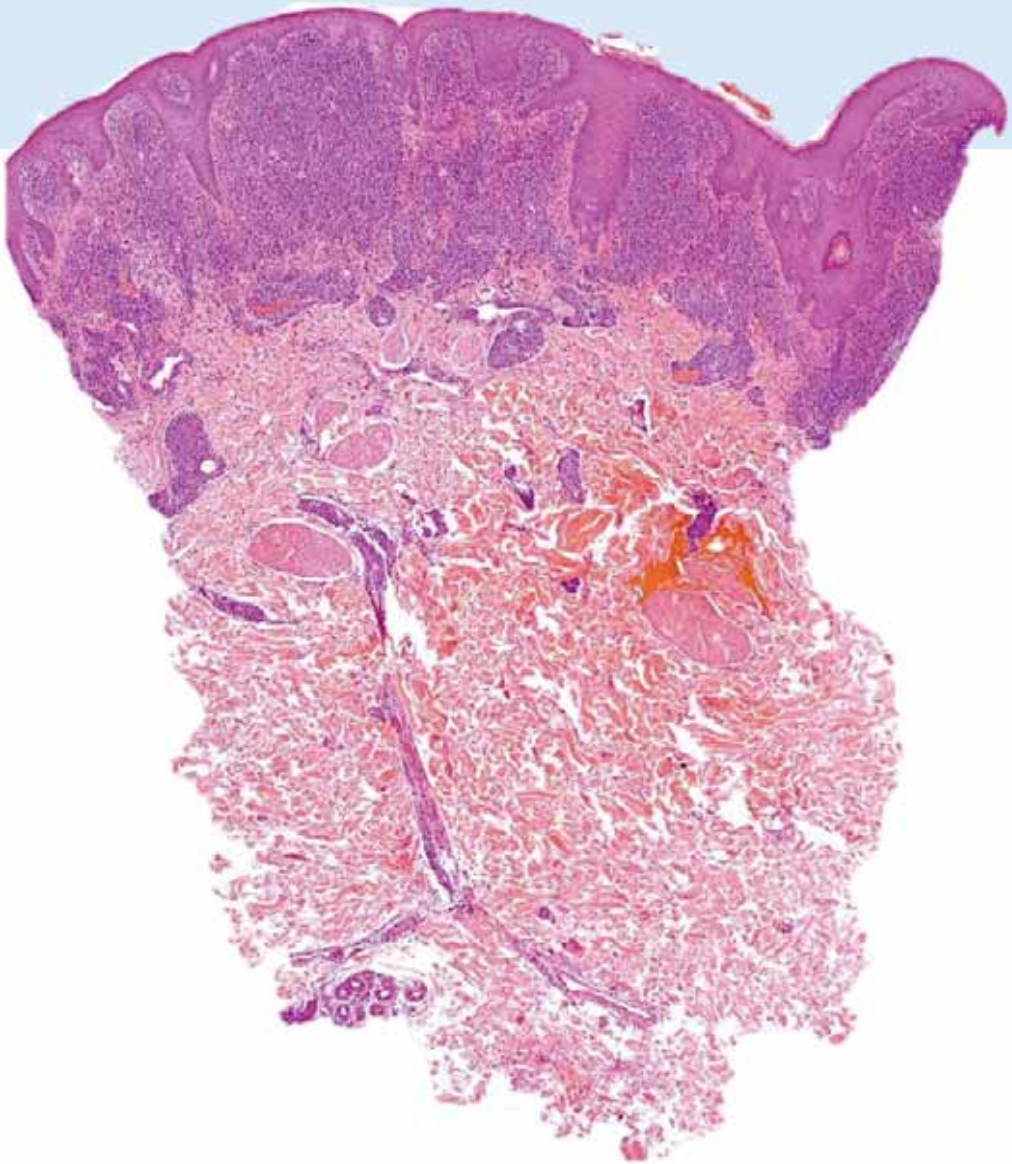
Histology

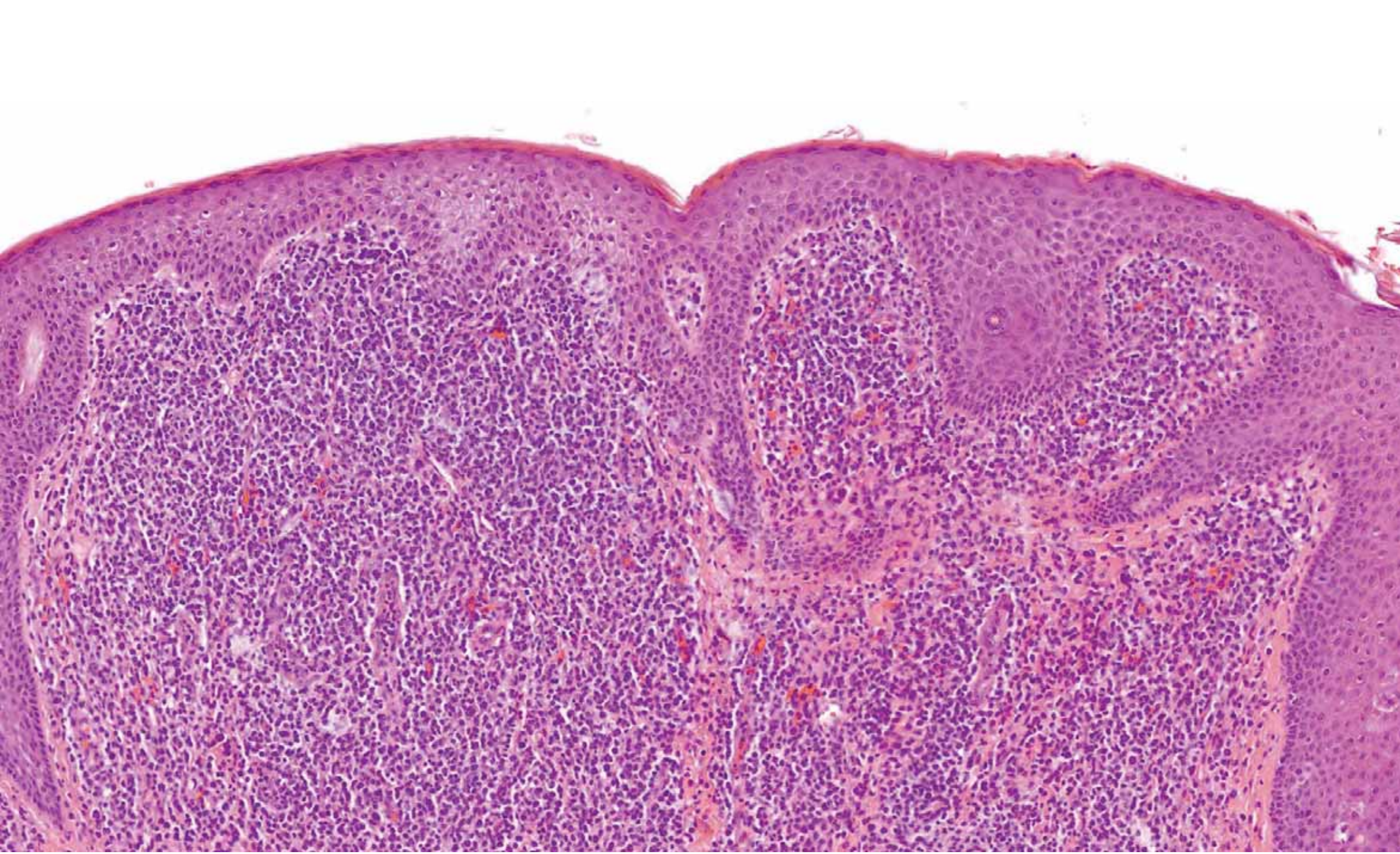
78-year-old male patient

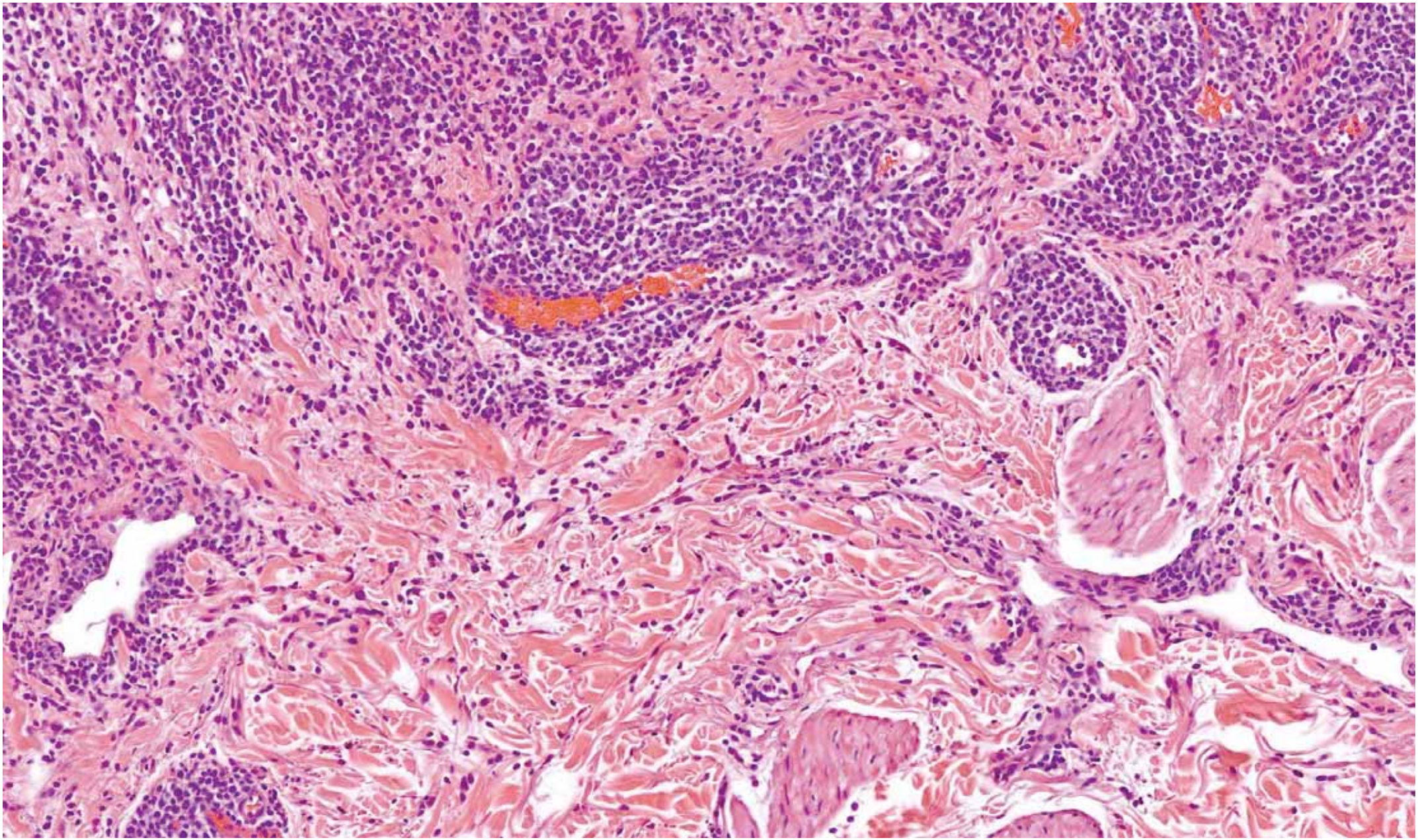
Bad general health condition, generalized lymphadenopathy and pruritus

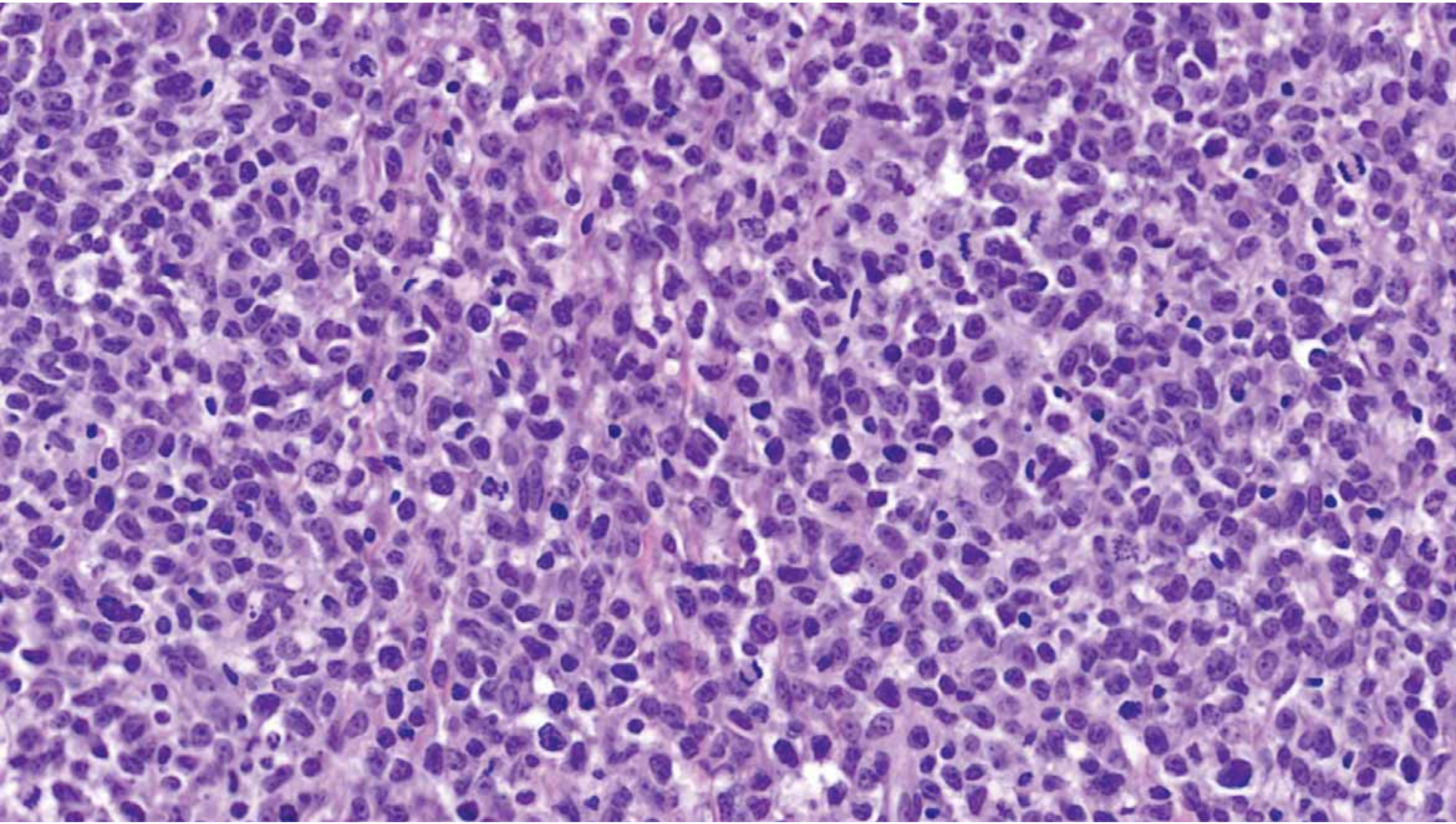
Skin eruptions for 18 months

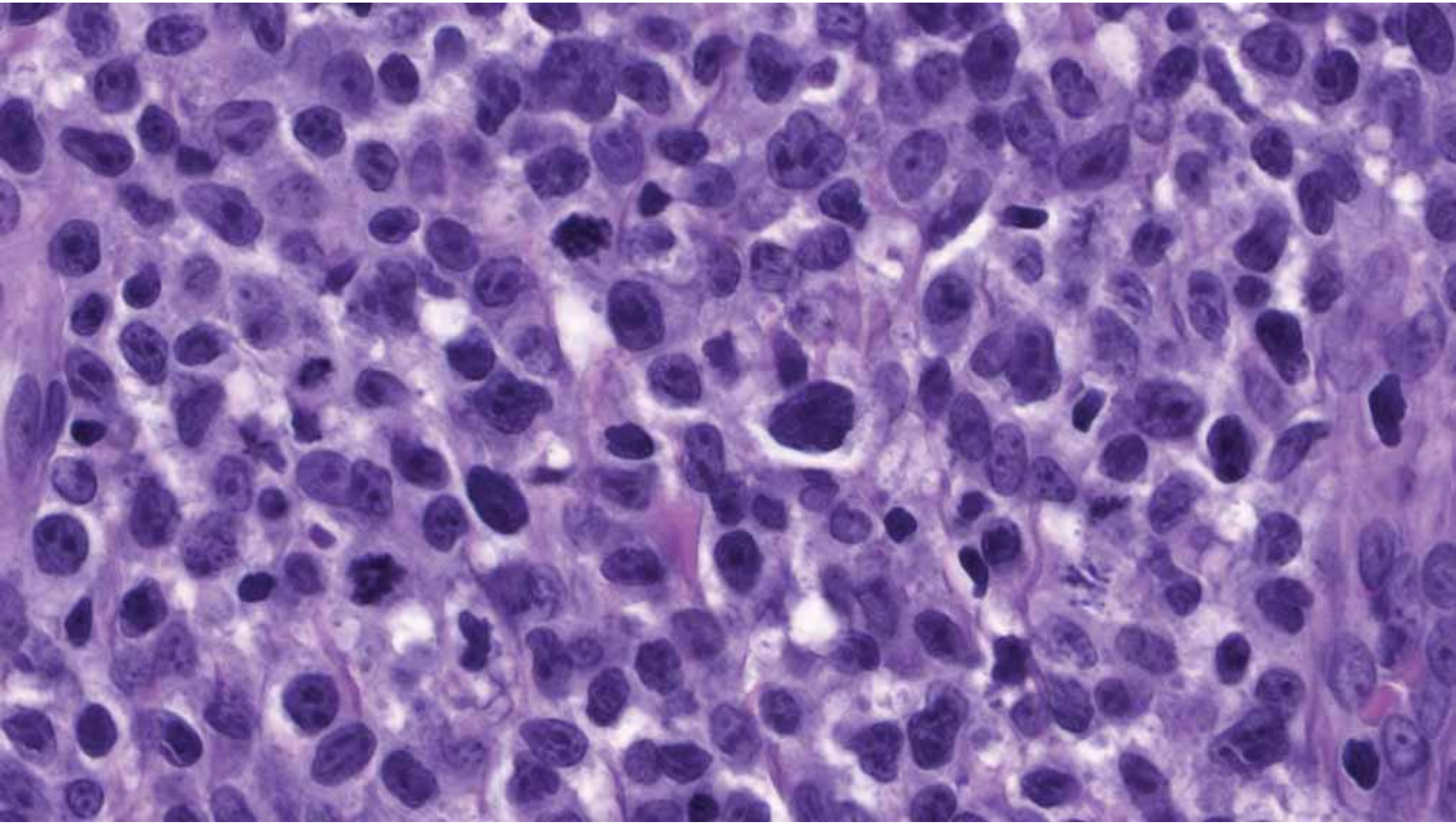
Suspected diagnosis: Sézary syndrome



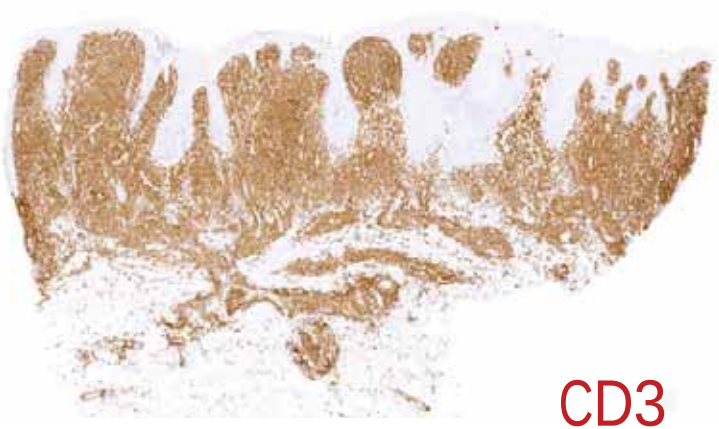




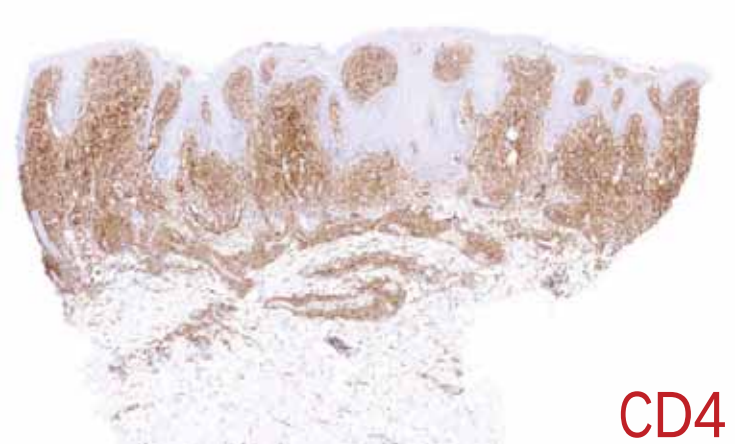




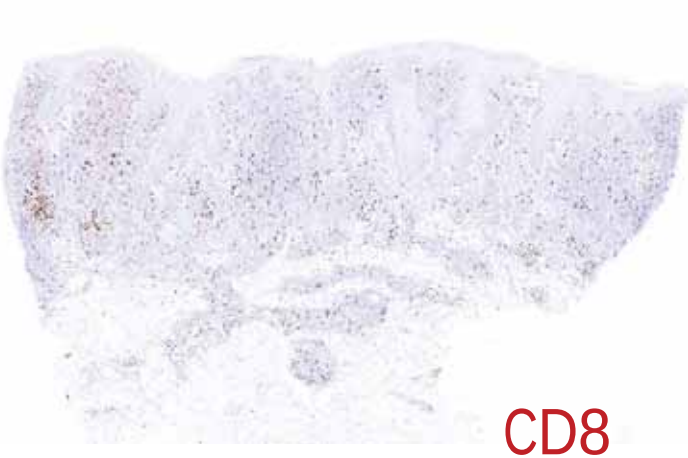
Histology



CD3

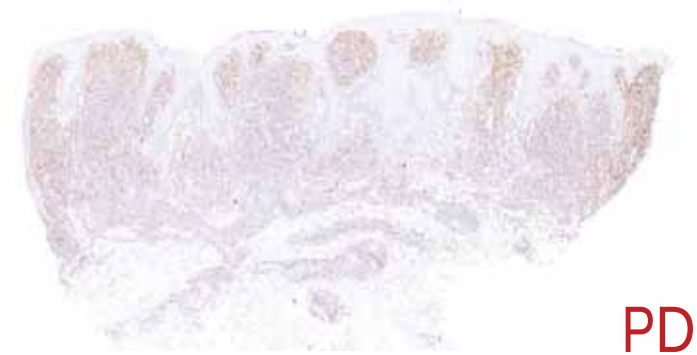


CD4

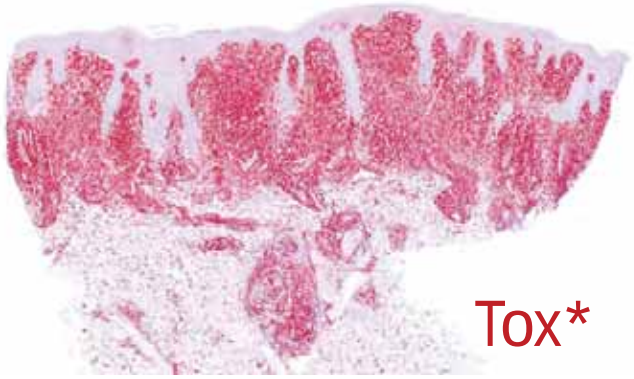


CD8

CD7



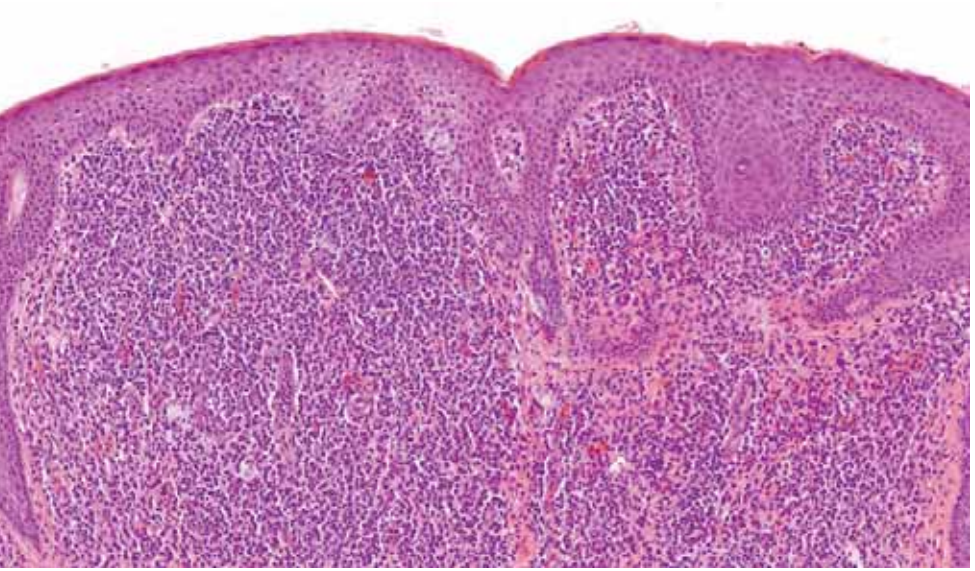
PD1



Tox*

*thymocytes selection associated HMG-box

Summary of the findings



Histology:

Band-like superficial and deep periadnexal and perivascular infiltrate
CD3+, CD4+, CD7-, CD8-, PD1+, Tox+

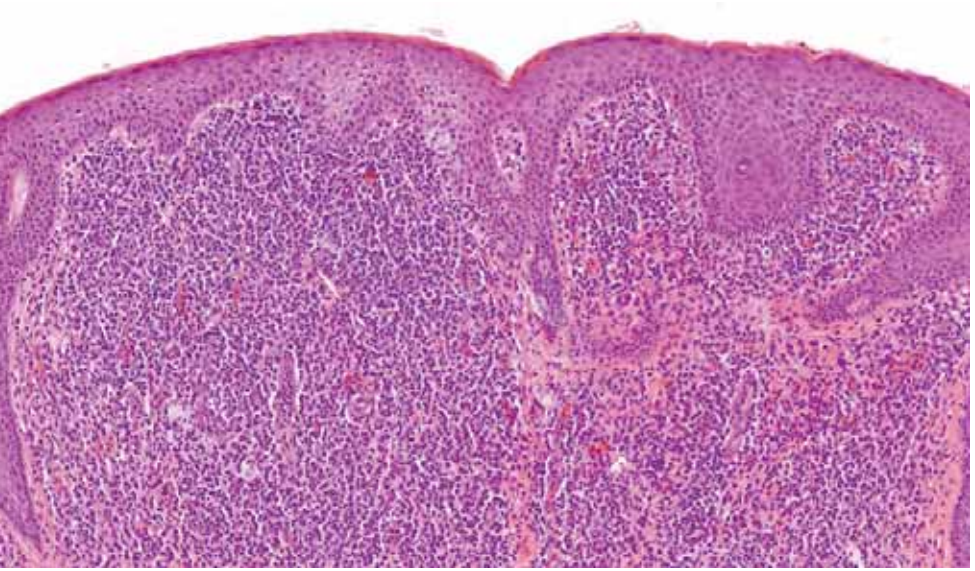
Clinical presentation:

Erythrodermic skin
Lymphadenopathy
Palmo-plantar Hyperkeratosis
Itch

diagnosis

?

Summary of the findings



Histology:

Band-like superficial and deep periadnexal and perivascular infiltrate
CD3+, CD4+, CD7-, CD8-, PD1+, Tox+

Blood: B2

Clinical presentation:

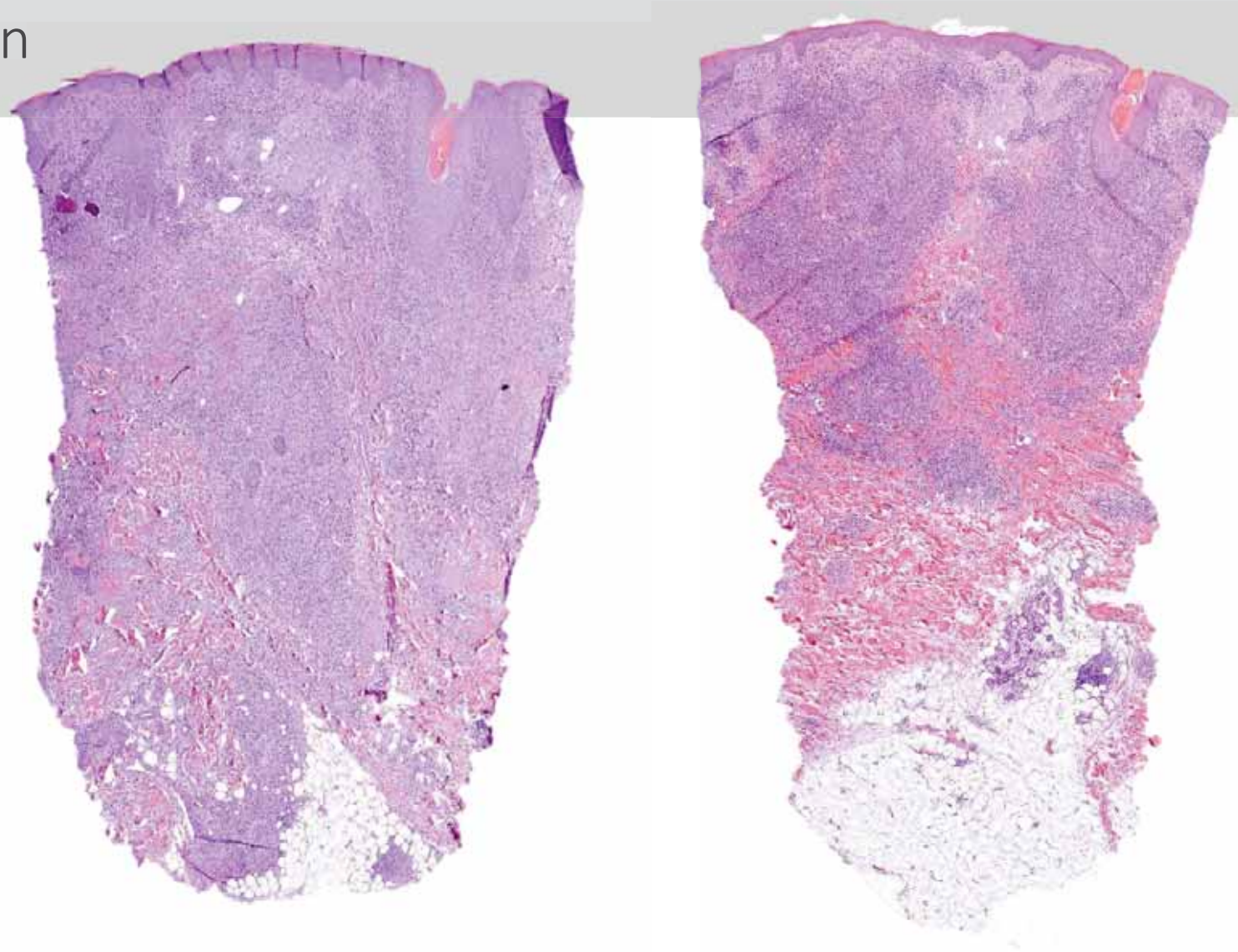
Erythrodermic skin
Lymphadenopathy
Palmo-plantar Hyperkeratosis
Itch

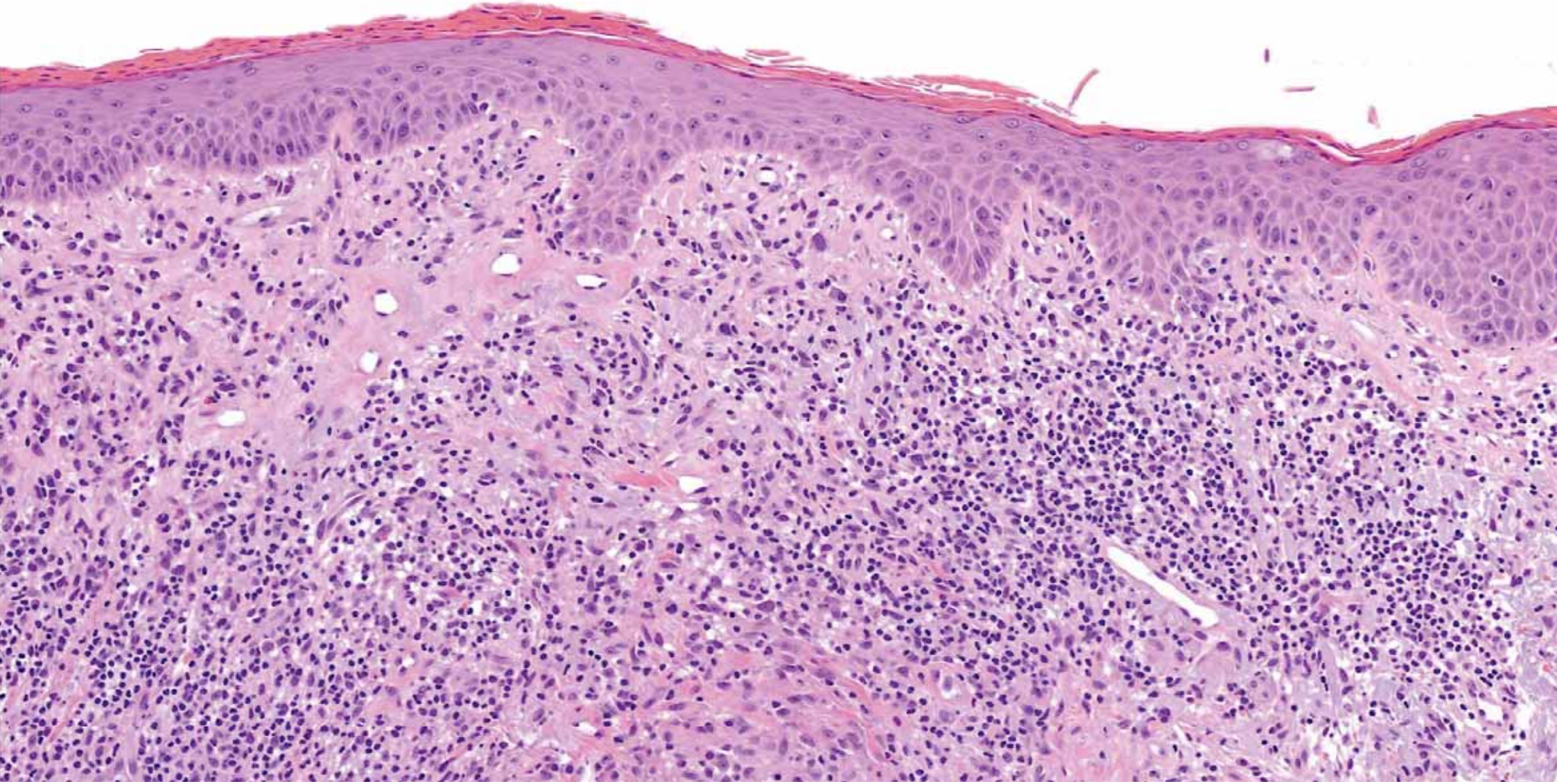
Sézary syndrome

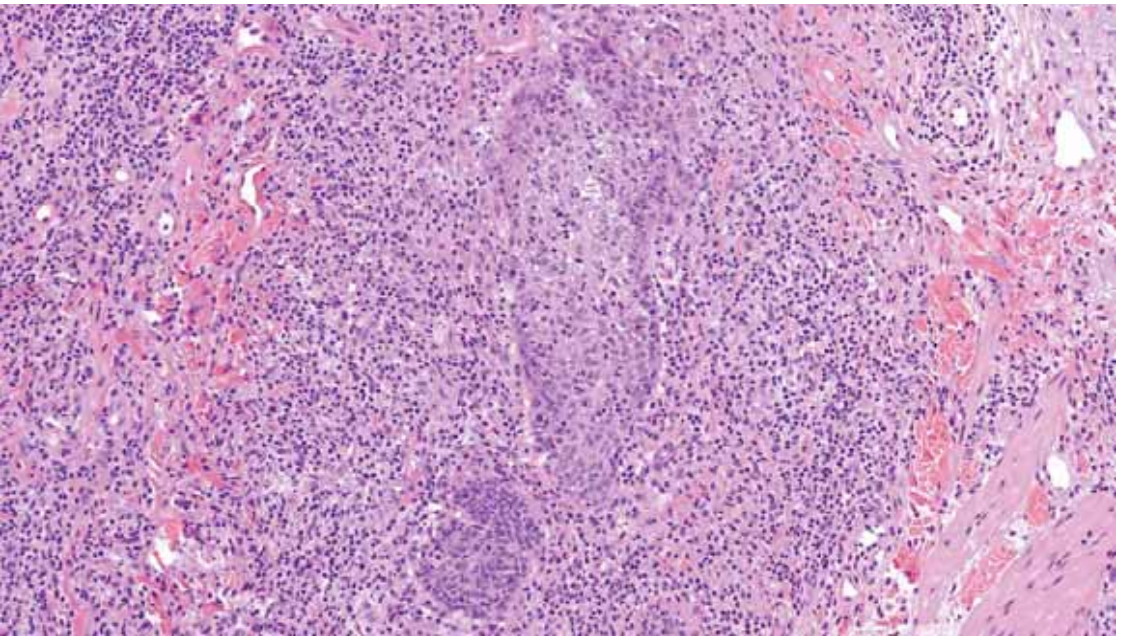
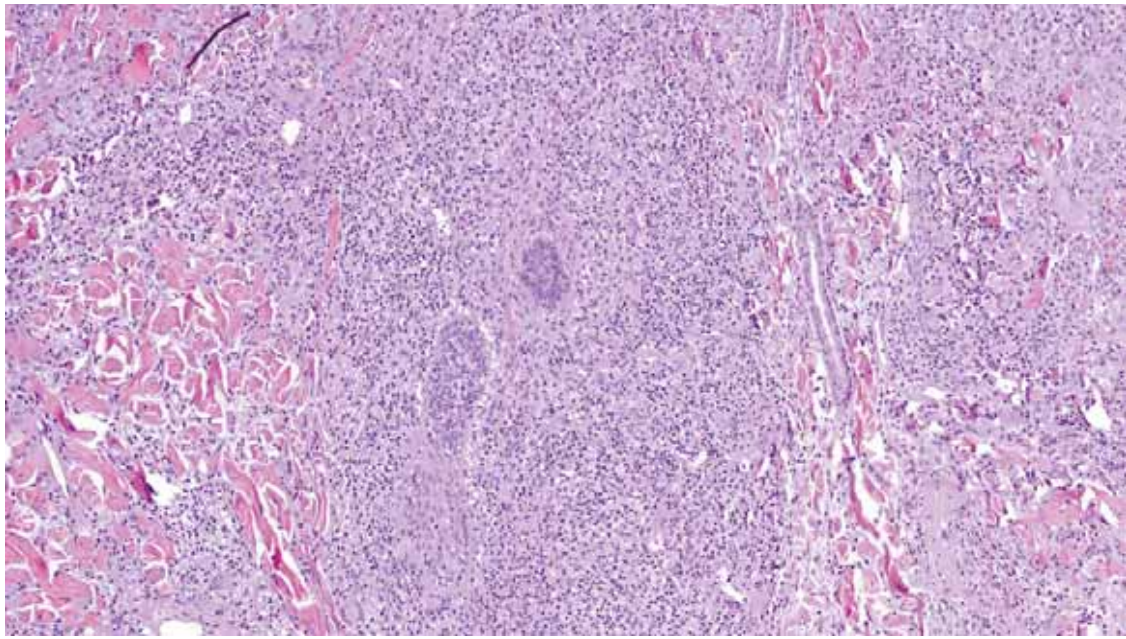
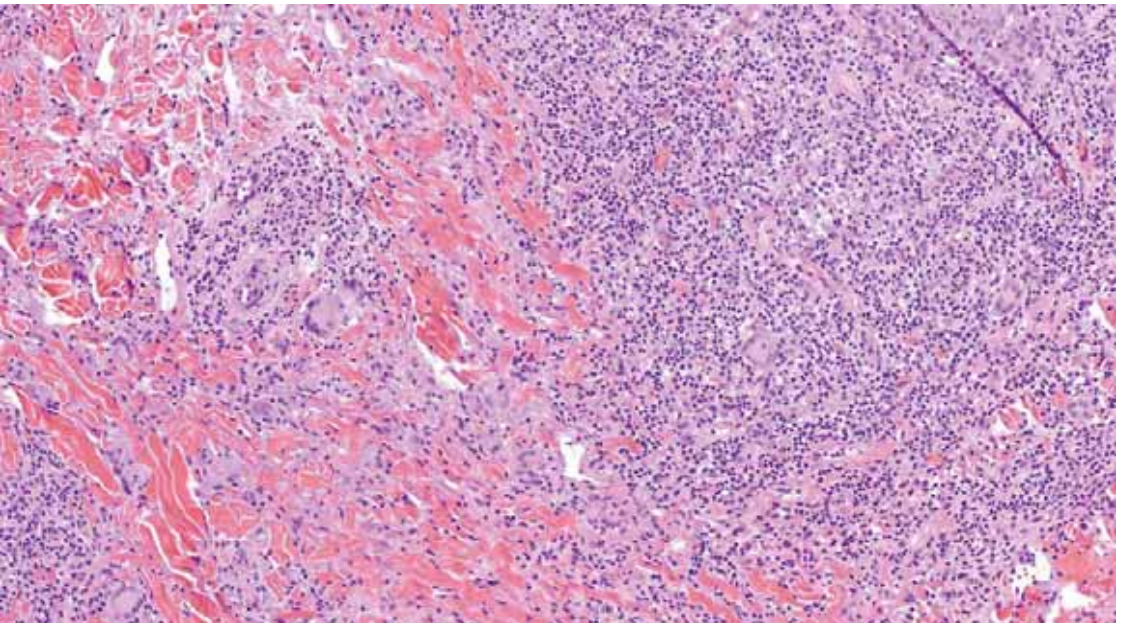
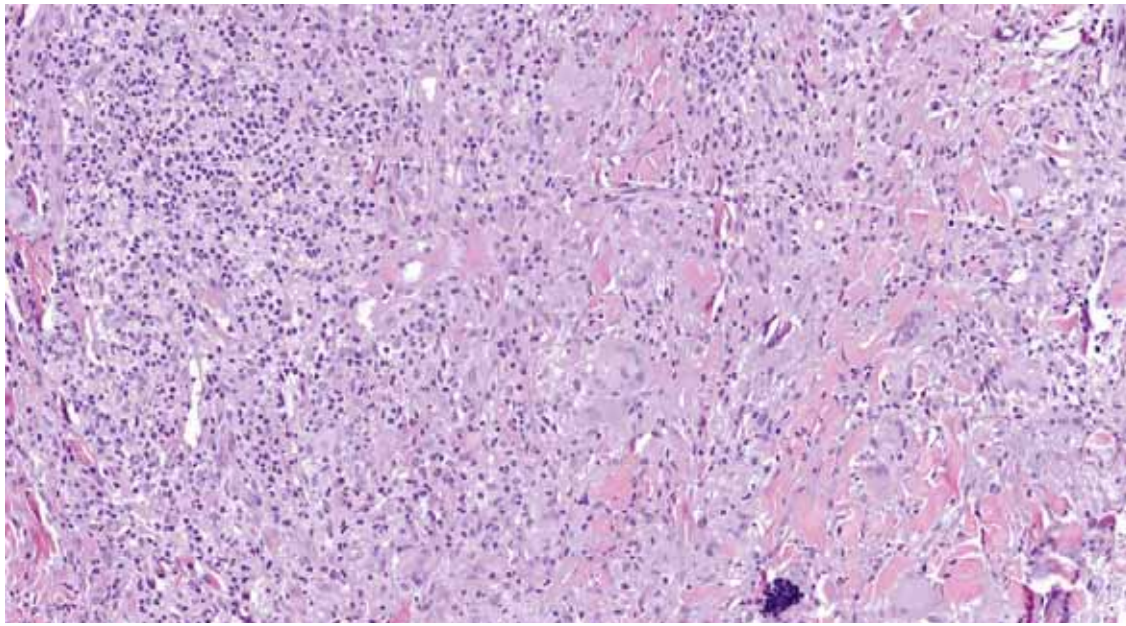
Feature	T-PLL	Sézary syndrome
Age group	60–70 years	>50 years
CD3	Positive	Positive
CD4	Positive	Positive
CD8	+/− (often CD4+/CD8+ or CD4+/CD8-)	Negative
CD7	Strongly positive	Often lost
TCL1A	Positive	Negative
TdT	Negative	Negative
HTLV-1	Negative	Negative
Skin involvement	Common (~20–30%)	Typical (hallmark)
Cytotoxic markers	Negative	Negative
Prognosis	Very poor (months w/o treatment)	Less aggressive

Clinical information

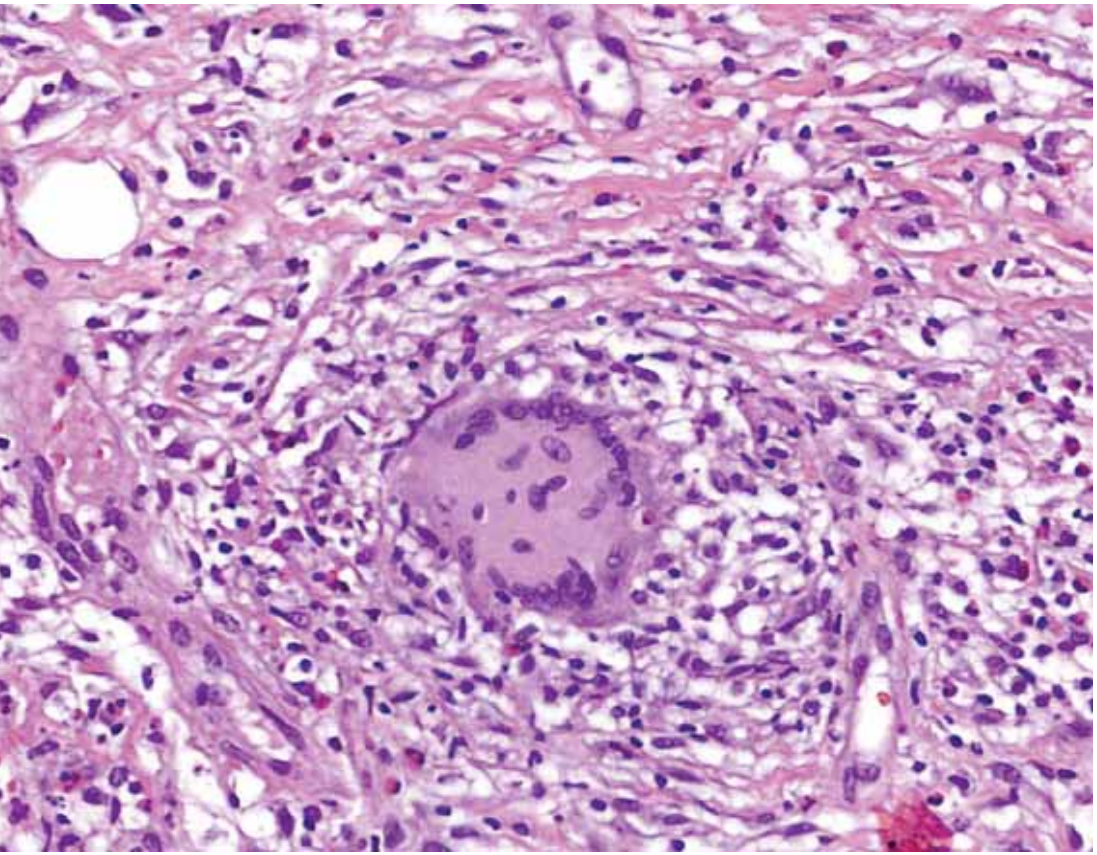
- 64-year-old male patient
- Suffering from CD4+ classical Mycosis fungoides
- Progression under treatment?

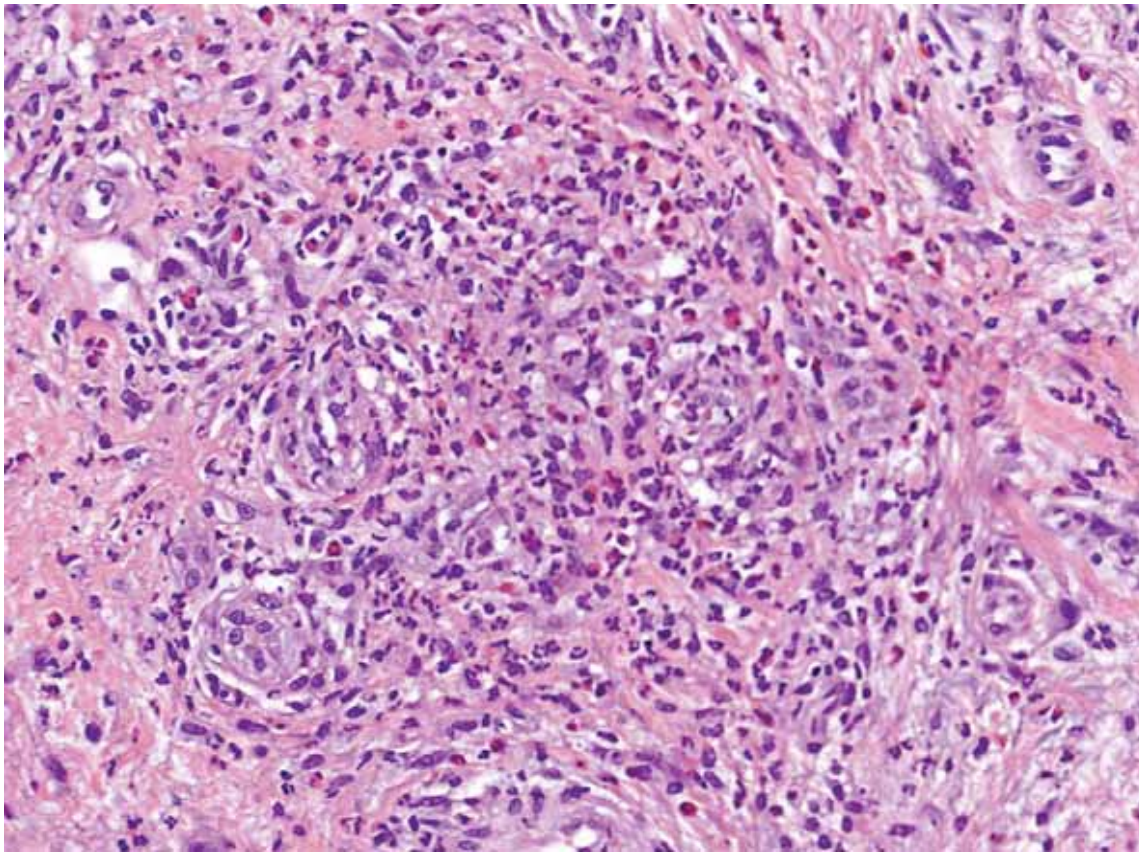




Histology





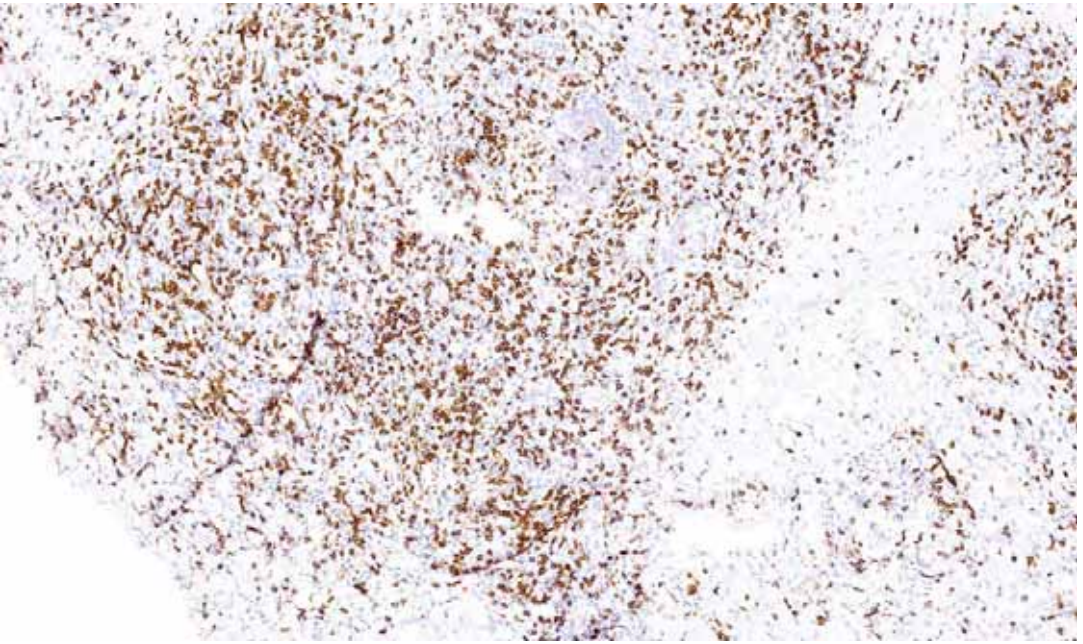
Immunohistochemistry

CD3

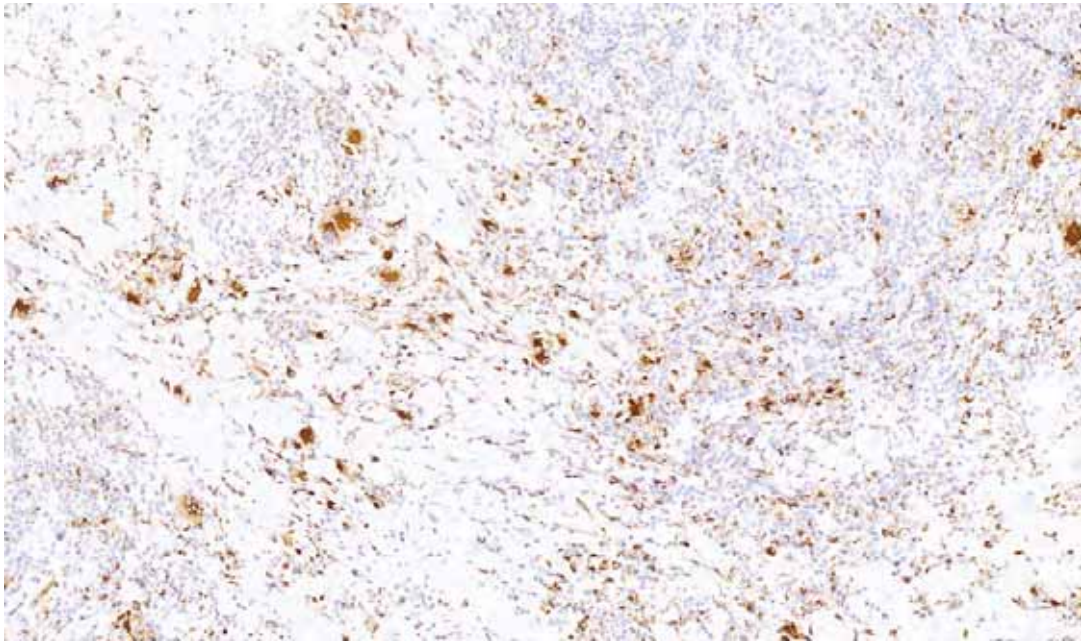
CD4

CD8

Immunohistochemistry

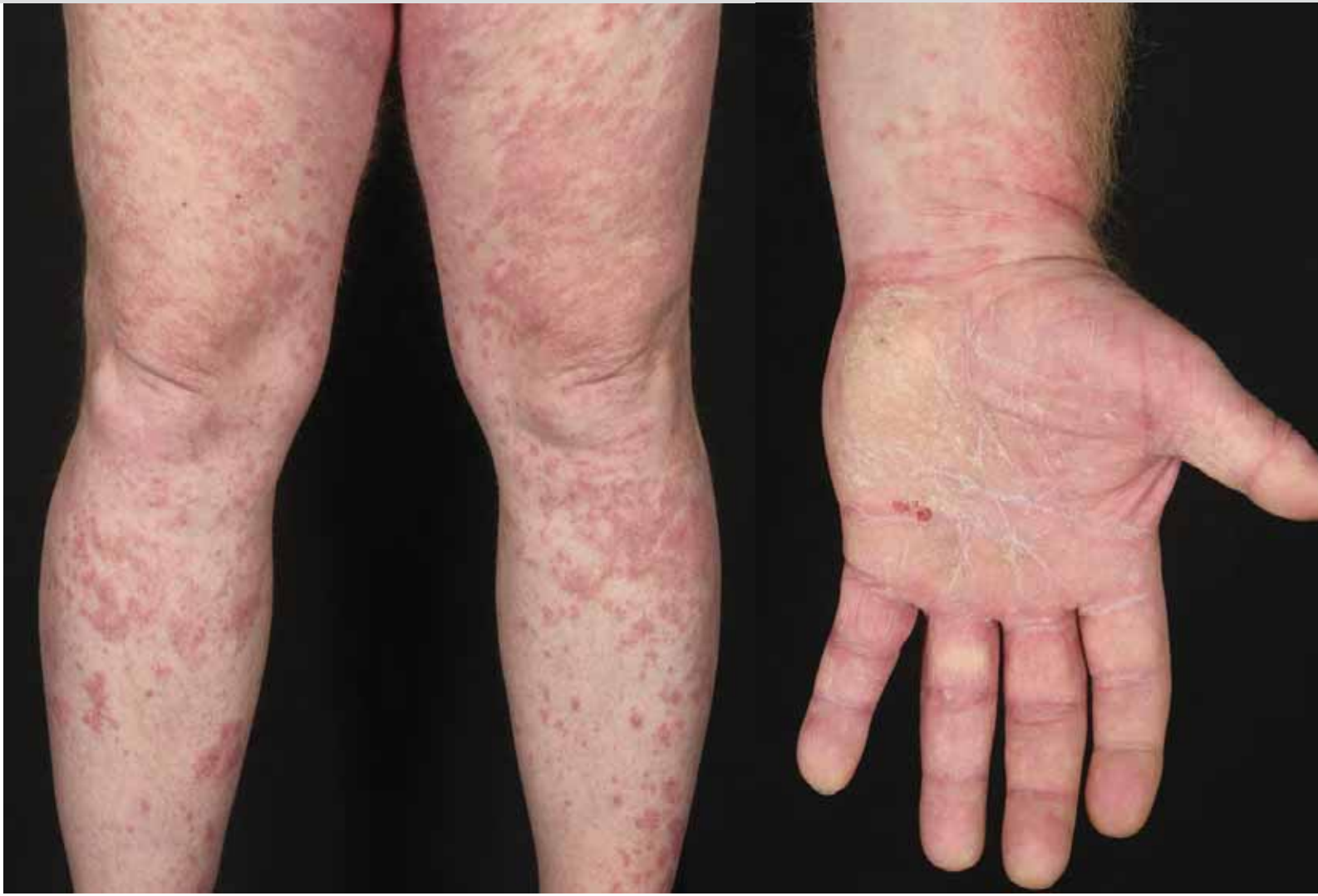


CD8



CD68

Clinical presentation



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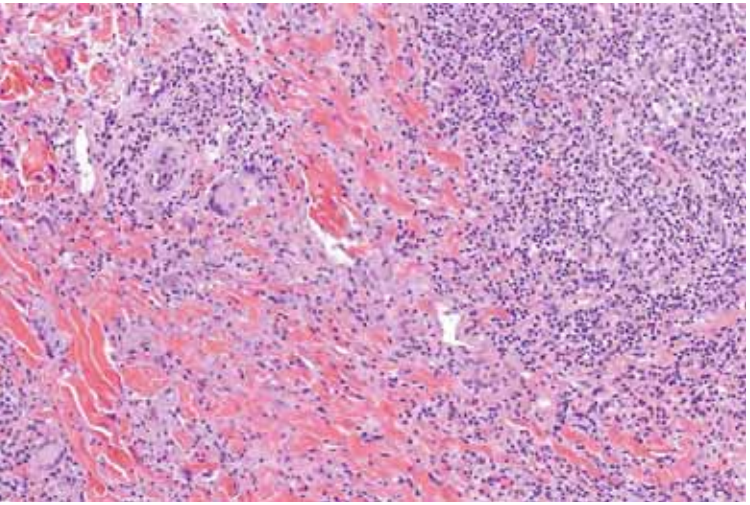


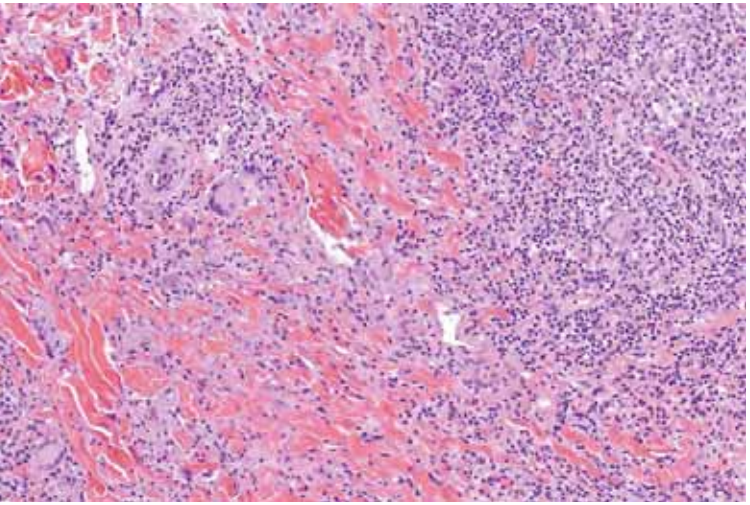
Histology:
Mild interface dermatitis
Granulomatous infiltrate, lymphocytes, eosinophils
CD8 > CD4, CD7 retained
High number of macrophages (CD68+)

Clinical presentation:
Generalized exanthema
Lichenoid aspect
Face involved, präauricular
Palmoplantar hyperkeratosis

diagnosis

?

Summary of the findings:



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Lichenoid aspect
Face involved, präauricular
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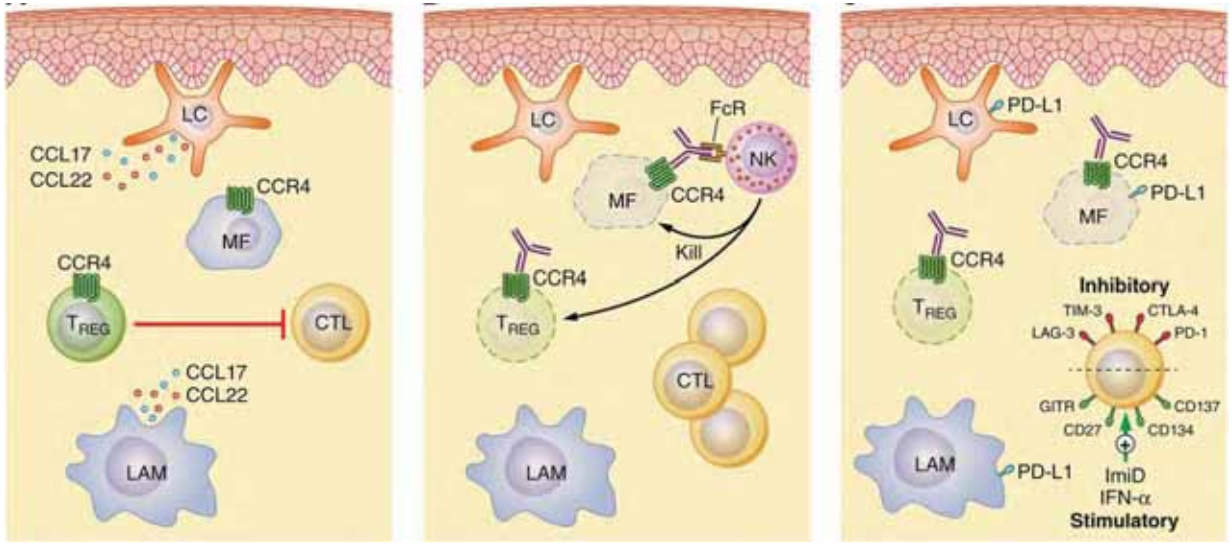
Mogamulizumab-associated rash (MAR)

Mogamulizumab- associated rash (MAR)

- Mogamulizumb is a CCR4-directed antibody approved for second line treatment of mycosis fungoides and Sézary syndrome in adult patients.
- The overall response rates varied between 28% and 59%.
- MAR is a common side effect reported in 23% to 68% of patients treated and presents with a broad spectrum of clinical.

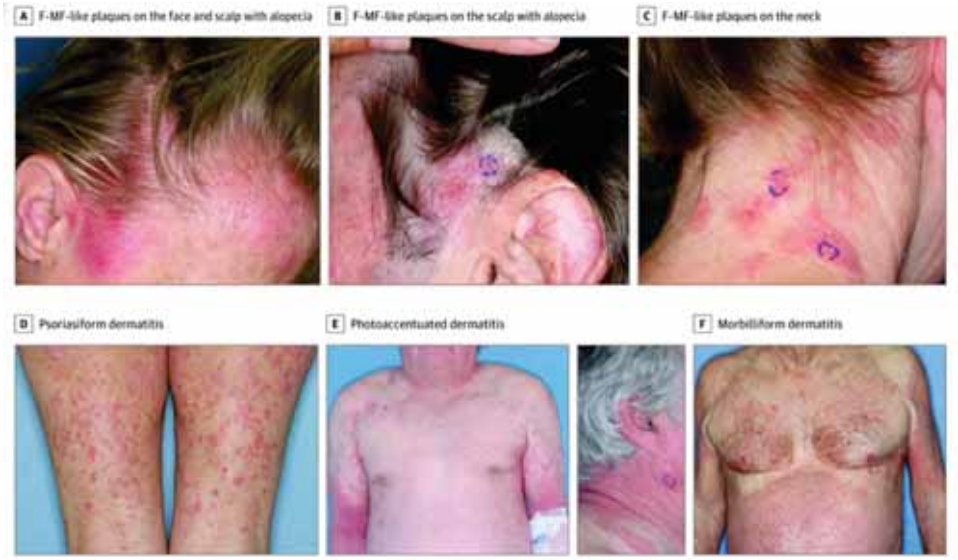


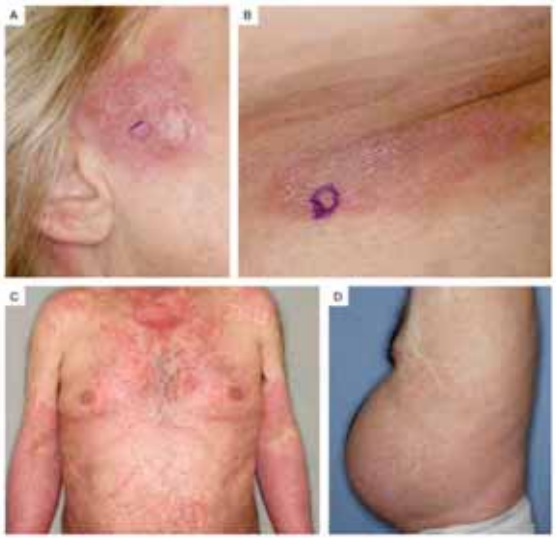
aus R. Wilcox. Inside Blood commentary 2015

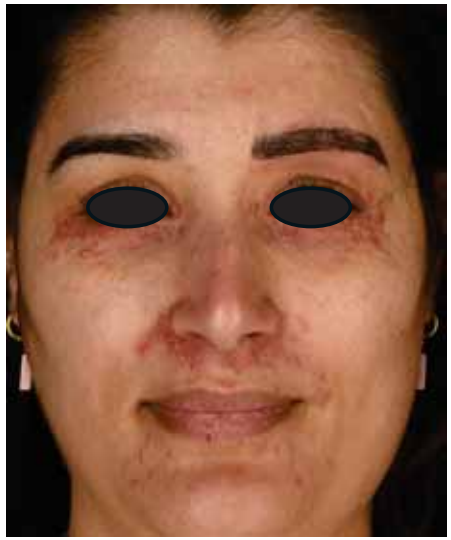
1. Kim YH et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2018;19:1192-1204. 2. Beylot-Barry M et al. Effectiveness of mogamulizumab in patients with Mycosis Fungoides or Sezary syndrome: A multicentre, retrospective, real-world French study. J Eur Acad Dermatol Venereol. 2023;37:1777-1784. 4. Chen L et al. Mogamulizumab-Associated Cutaneous Granulomatous Drug Eruption Mimicking Mycosis Fungoides but Possibly Indicating Durable Clinical Response. JAMA Dermatol. 2019;155:968-971. 6. Hirotsu KE et al. Clinical Characterization of Mogamulizumab-Associated Rash During Treatment of Mycosis Fungoides or Sezary Syndrome. JAMA Dermatol. 2021;157:700-707. 7. Mitteldorf C et al. Mogamulizumab-associated rash simulating lupus miliaris disseminatus faciei. J Eur Acad Dermatol Venereol. 2023;37:e479-e481.

Mogamulizumab- associated rash (MAR)

The clinical spectrum includes:
(1) folliculotropic or plaque mycosis fungoides-like lesion (2) papules and/or plaques, often with lichenoid or psoriasiform features (3) photo-accentuated dermatitis and (4) morbilliform or erythrodermic dermatitis. In addition, other clinical variants, such as Lupus miliaris disseminatus faciei (LMDF) or alopecia-areata-like hair loss, have also been reported.







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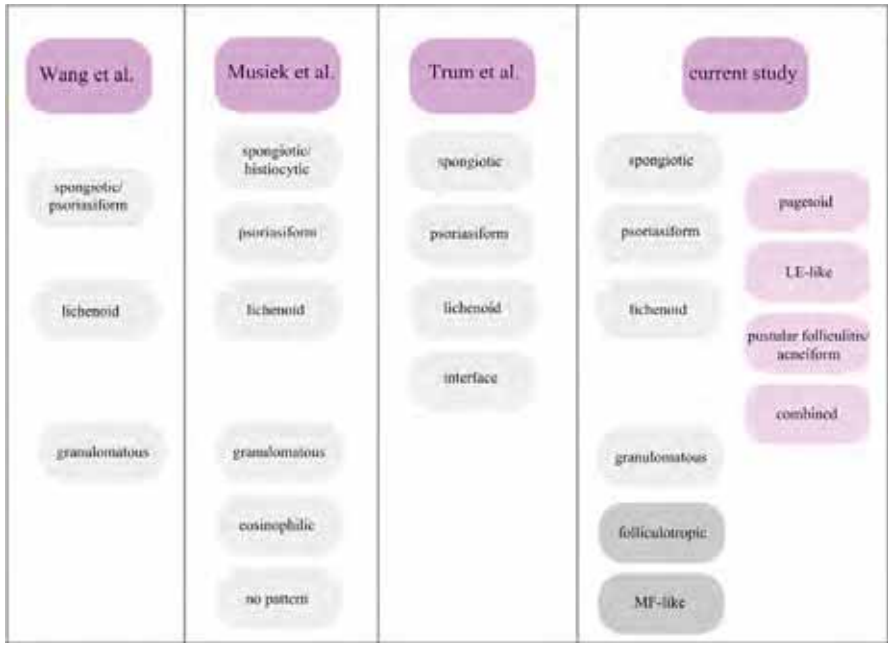
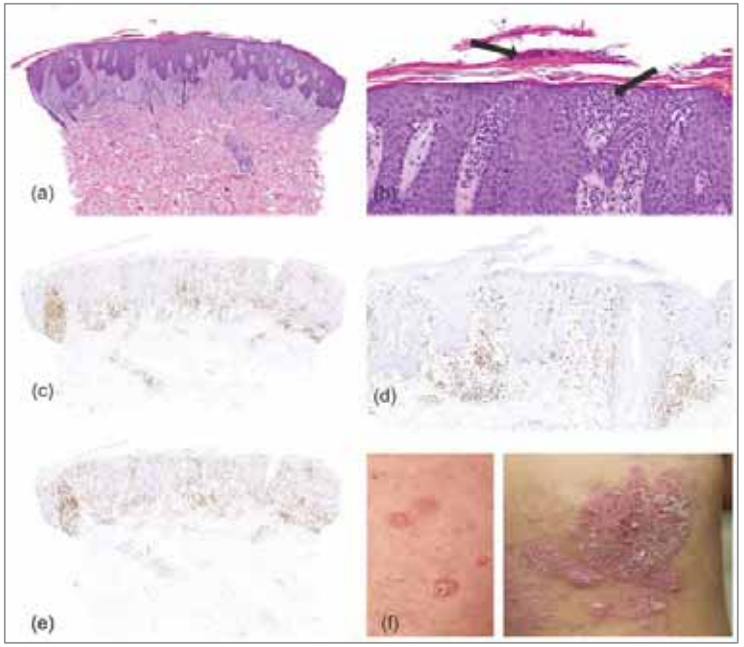
Mogamulizumab- associated rash (MAR)

the histological spectrum includes 10 patterns



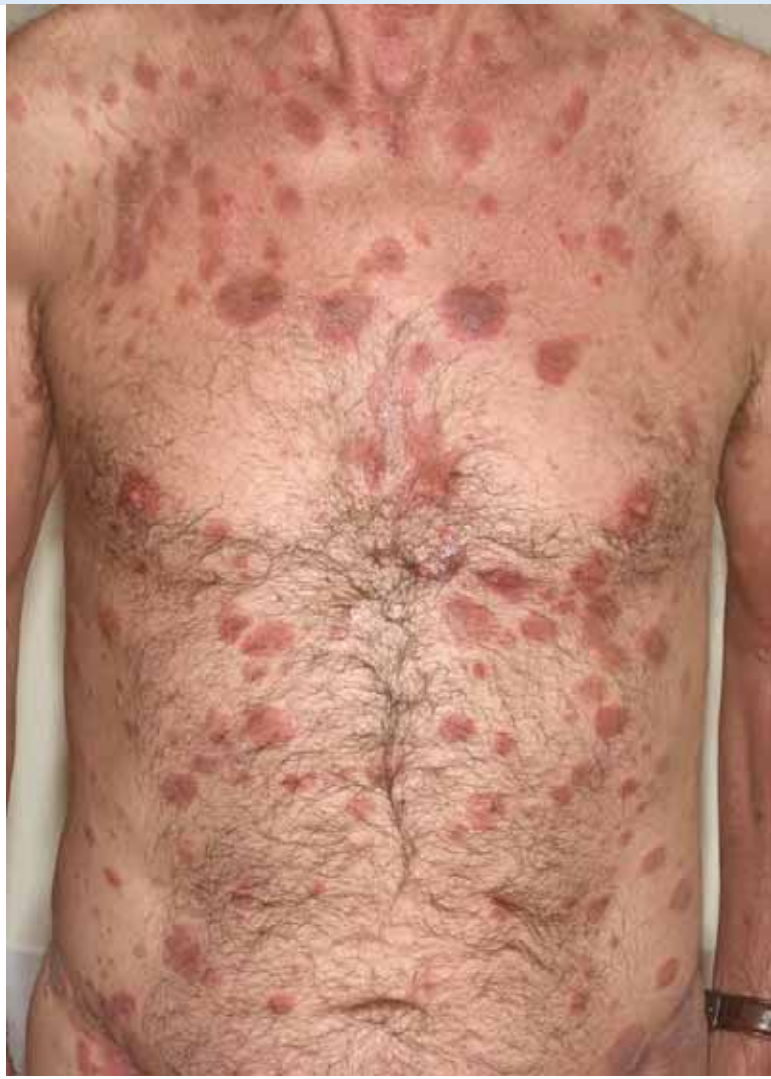
e.g. psoriasiform pattern



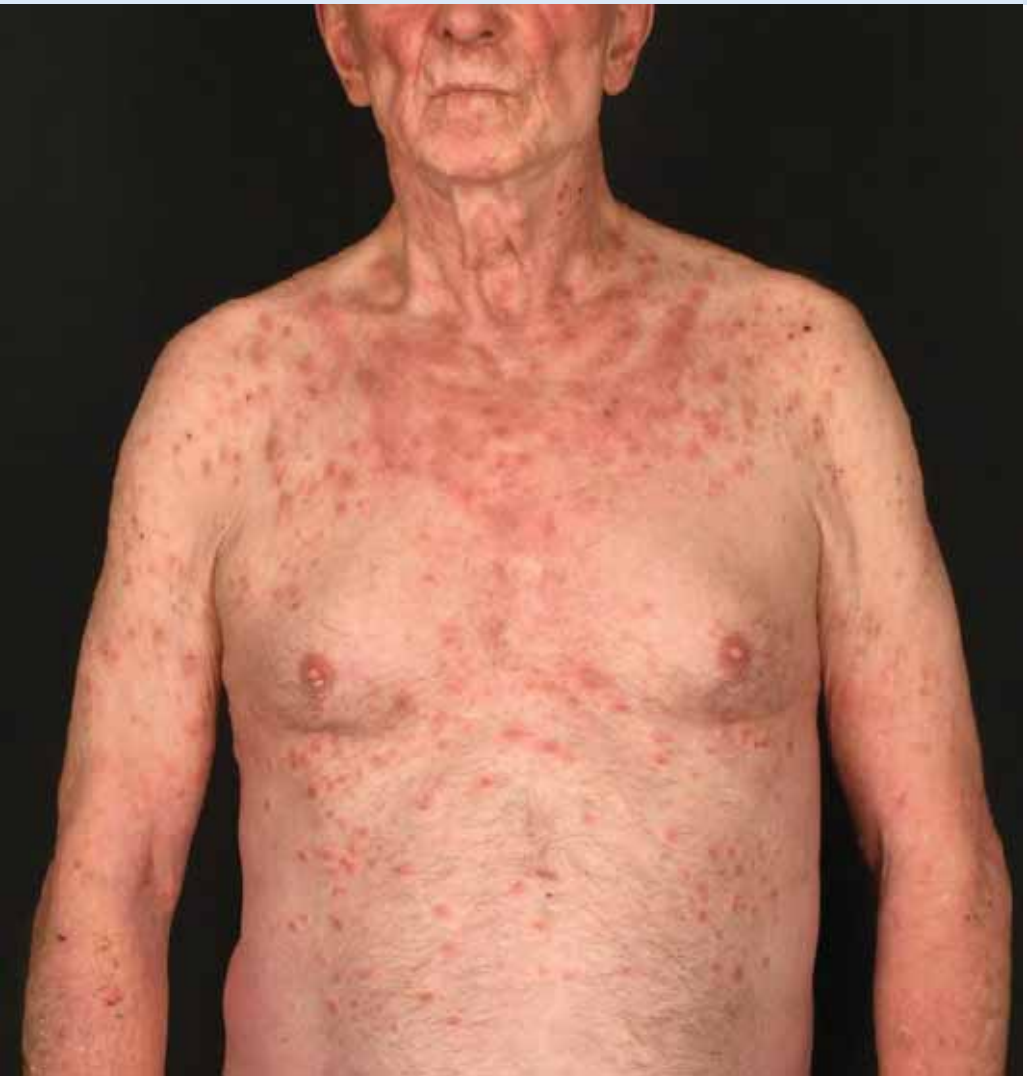
Mitteldorf C. Novel and Recurrent Histopathologic Patterns of Mogamulizumab-Associated Rash: Diagnostic Implications and Insights for Accurate Diagnosis. J Dtsch Dermatol Ges. 2025 May 27. doi: 10.1111/ddg.15773. Online ahead of print.

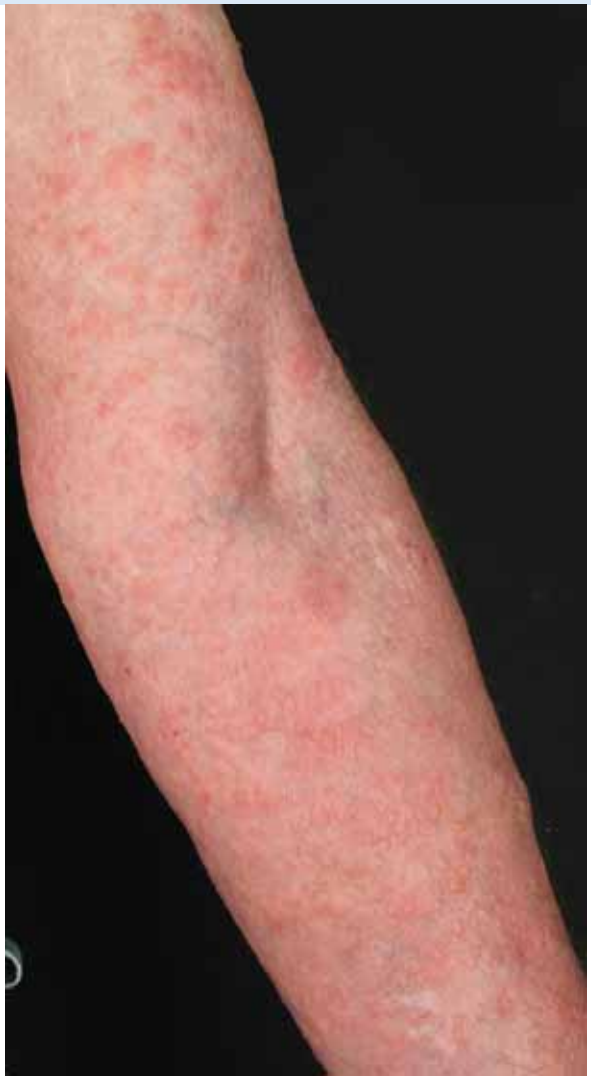
Clinical information

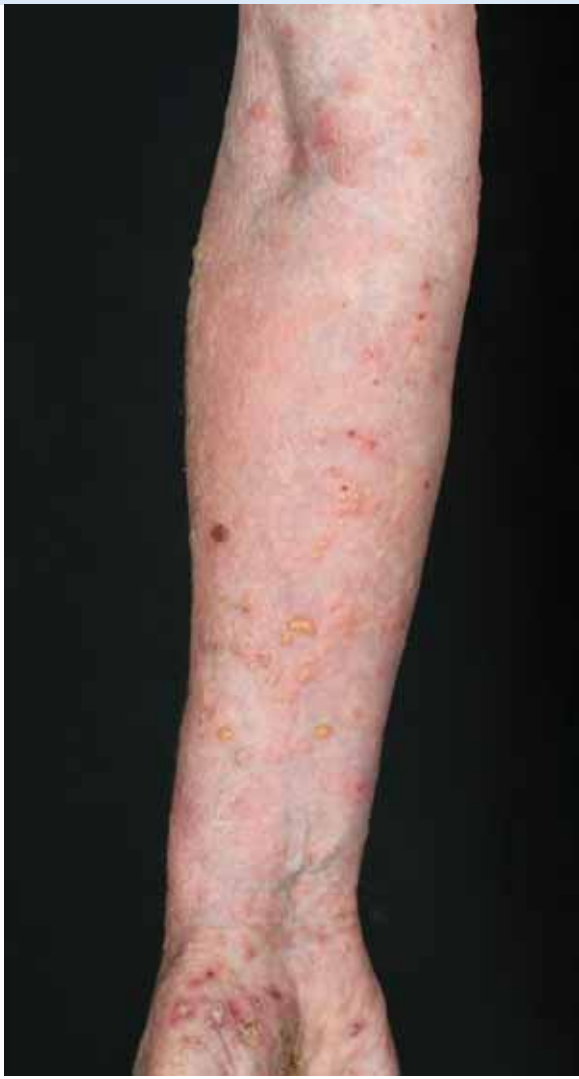
- 83-year-old male patient
- Mycosis fungoides for 35 years
- T3, N0, M0, B0 = stage IIB
- Previous therapies:
  - Topical steroids, chlormethin gel, antisepetic therapies
  - UVB-311, PUVA (systemic, bath)
  - MTX, Interferon, Bexarotene, Mogamulizumab, Brentuximab vedotin, Gemcitabin, Resmain study
  - Local radiotherapy, total skin beam radiation
  - Systemic antibiotics
  - Total skin beam radiation
  - Topical steroids



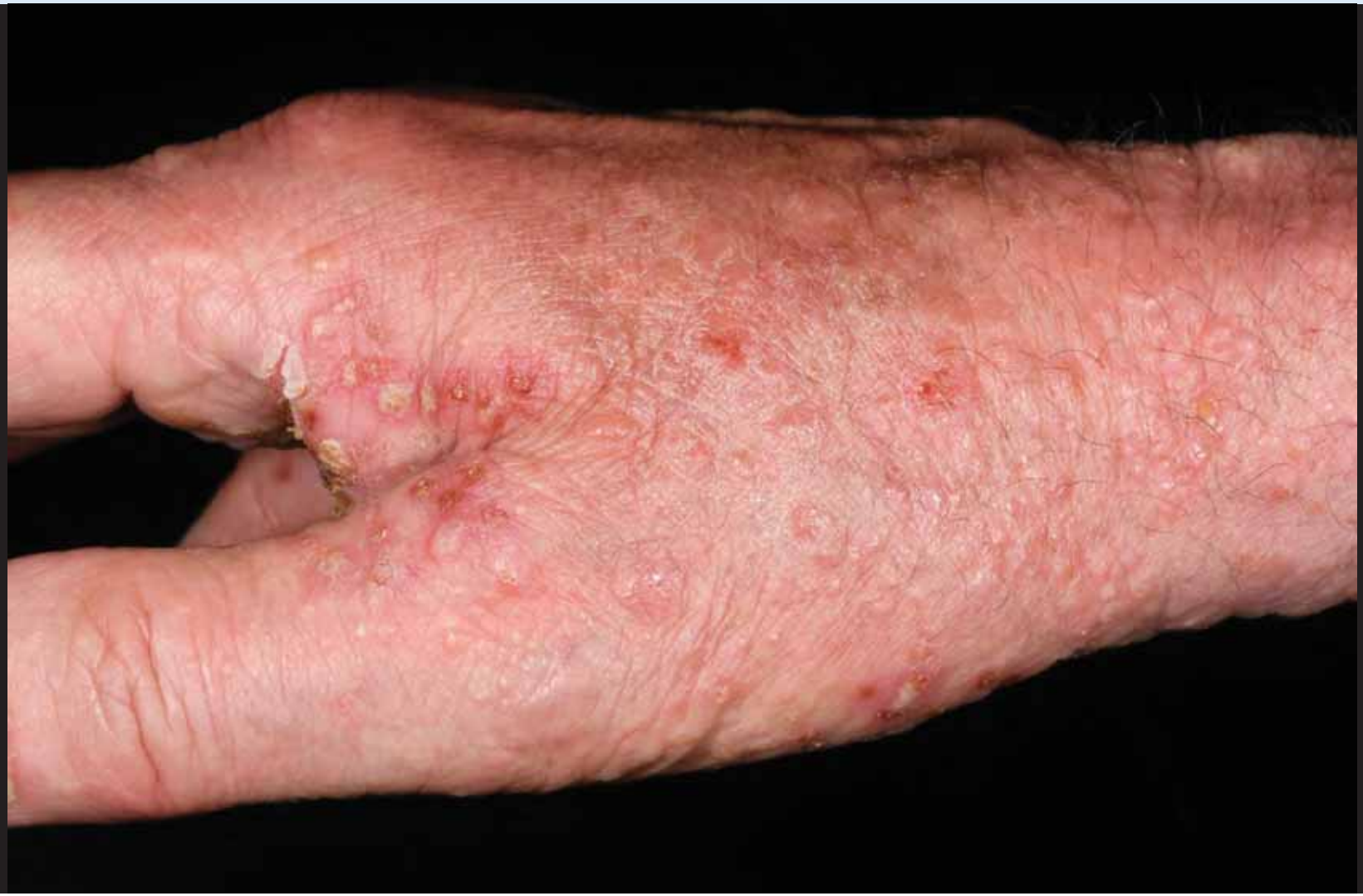
Clinical presentation



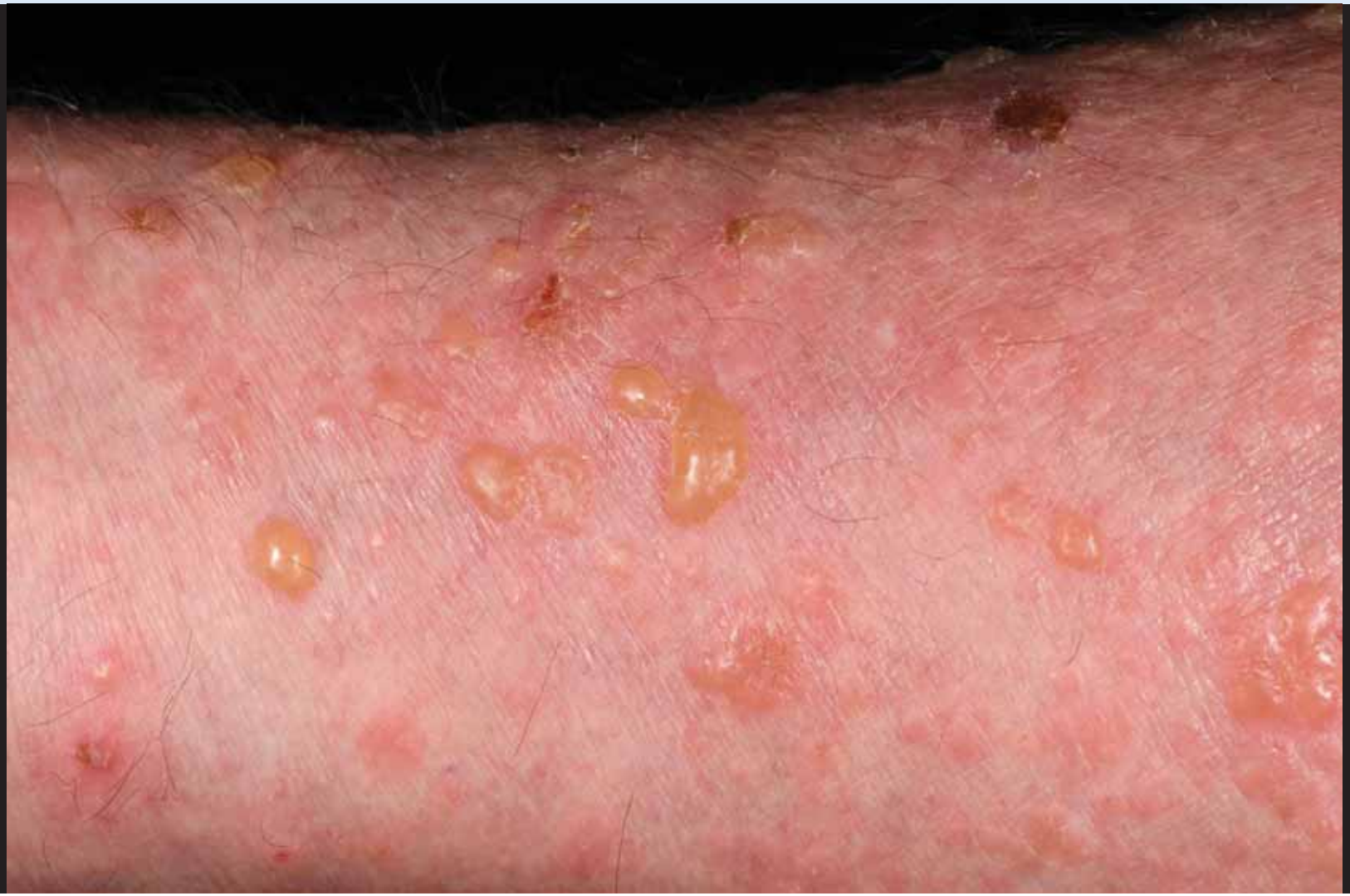




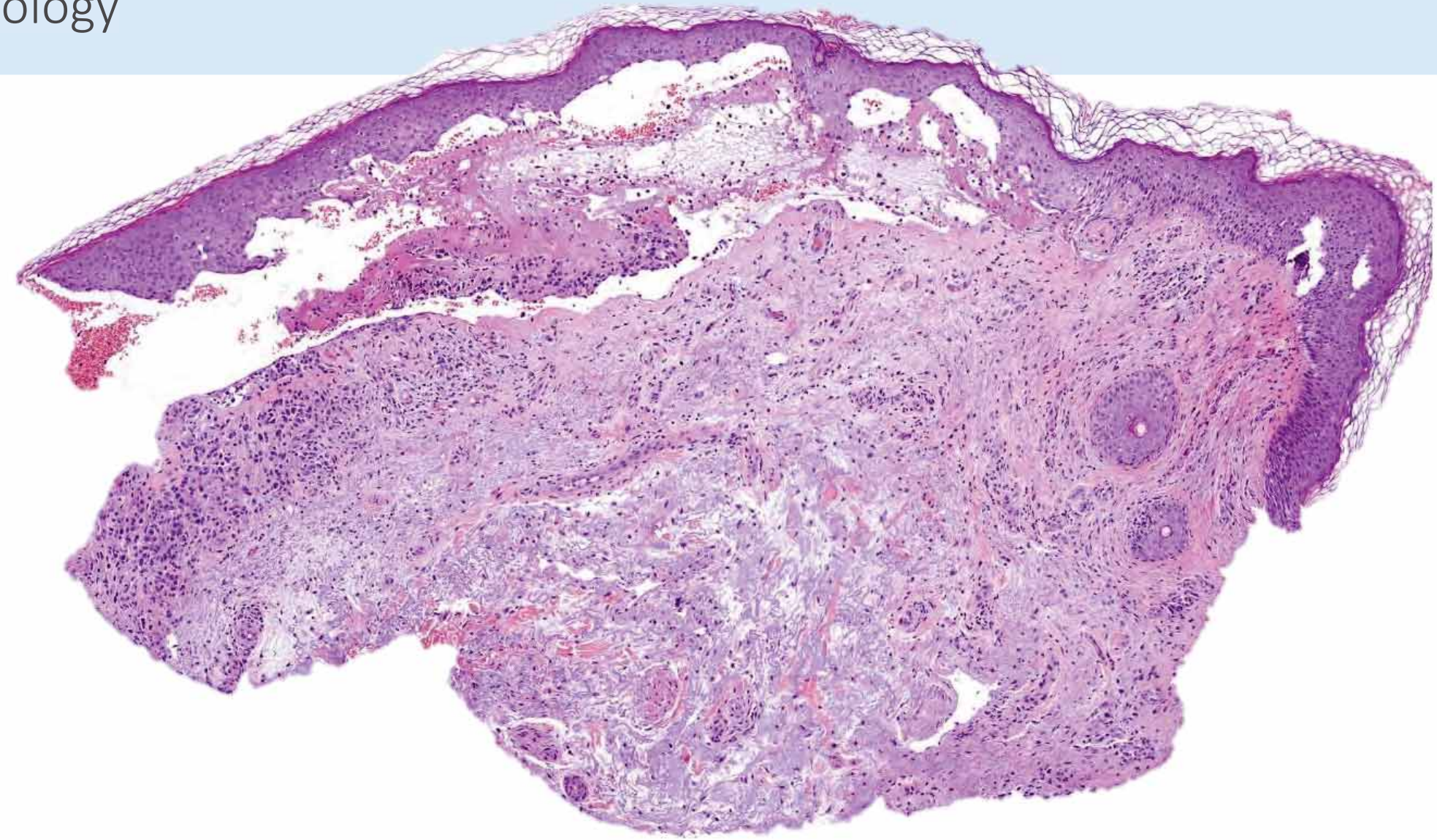
Clinical presentation

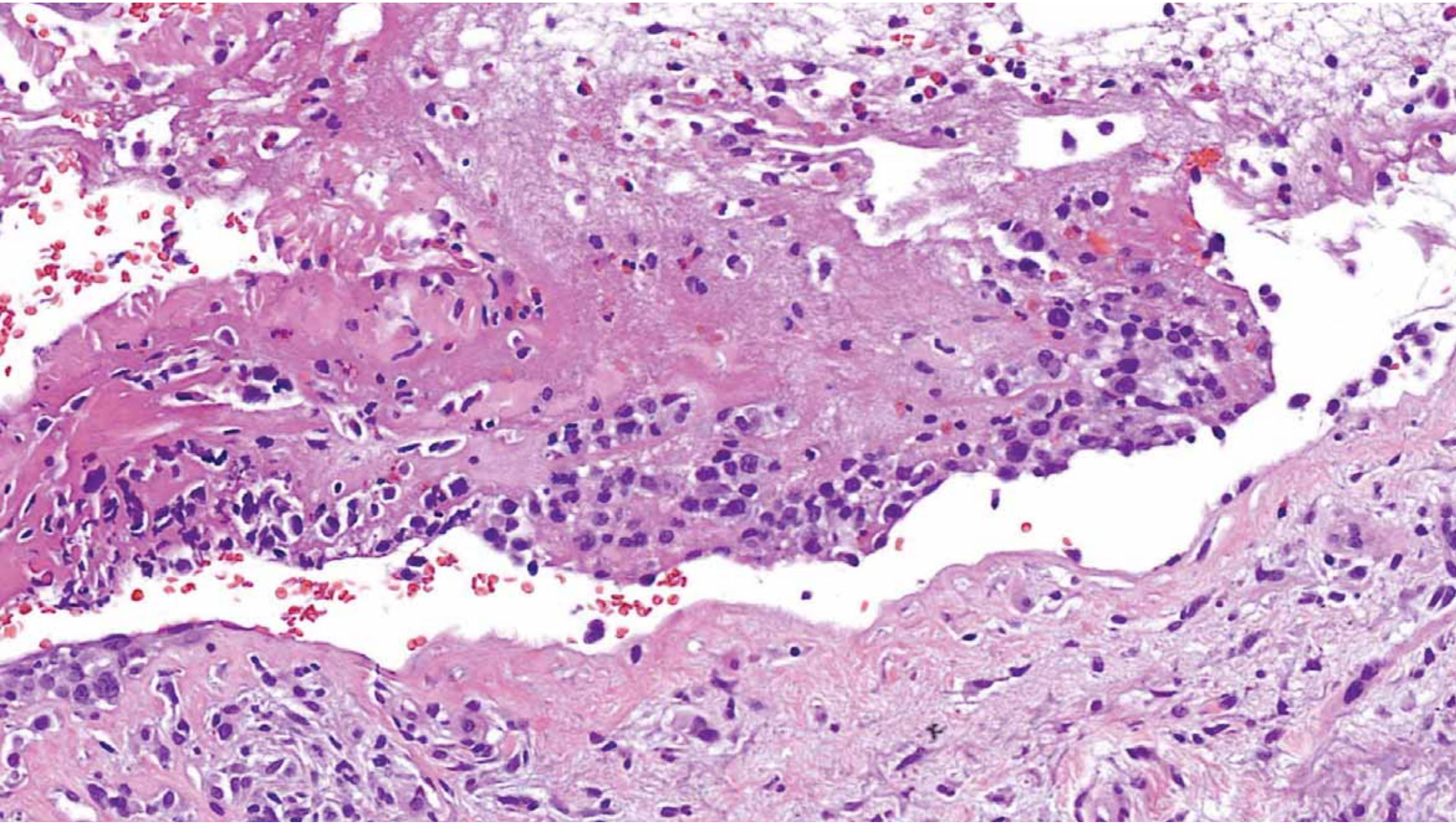


Clinical presentation



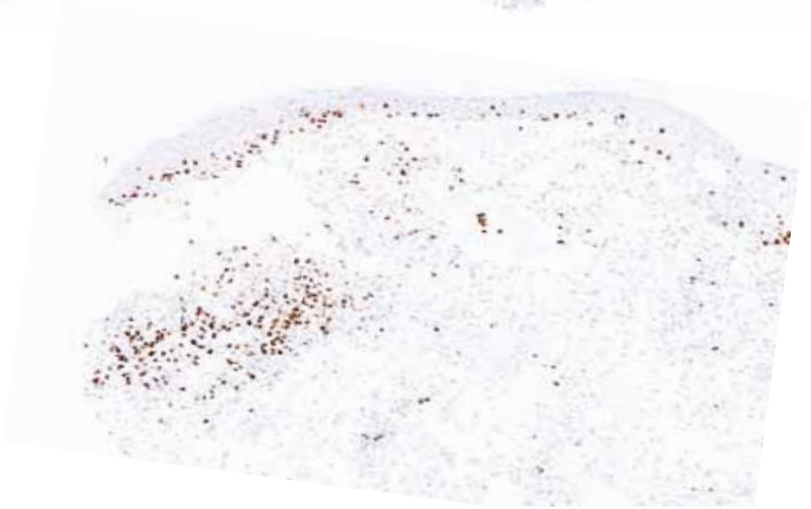
Histology





Immunohistochemistry

CD4



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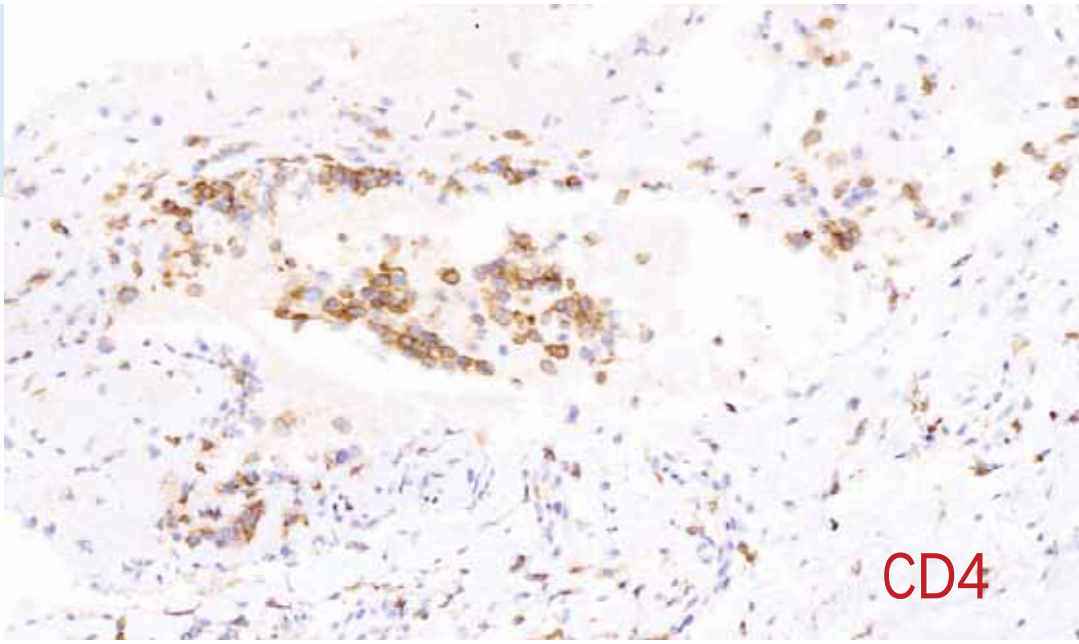
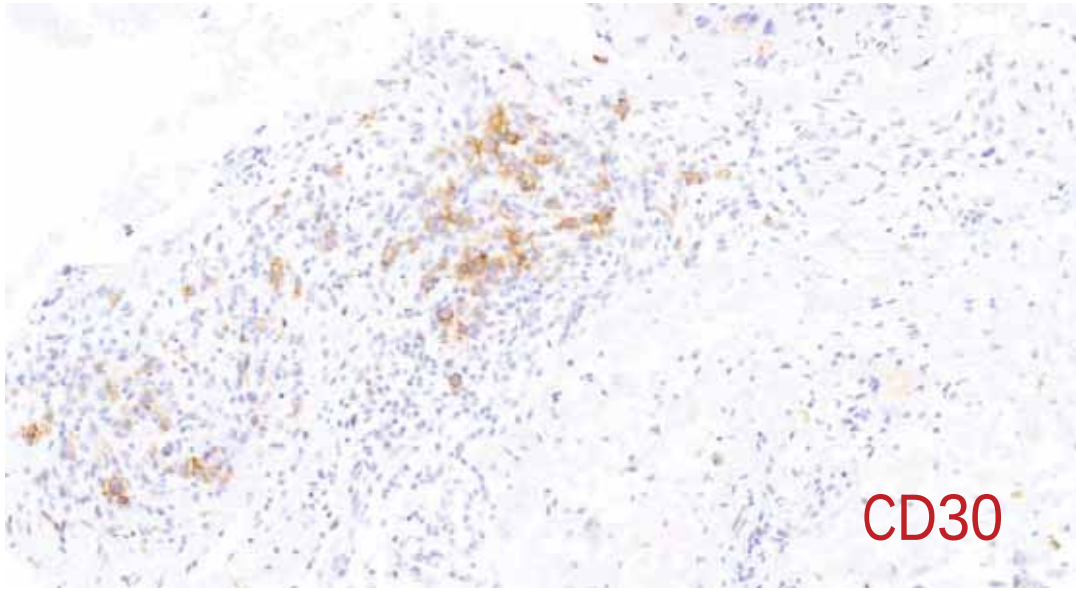
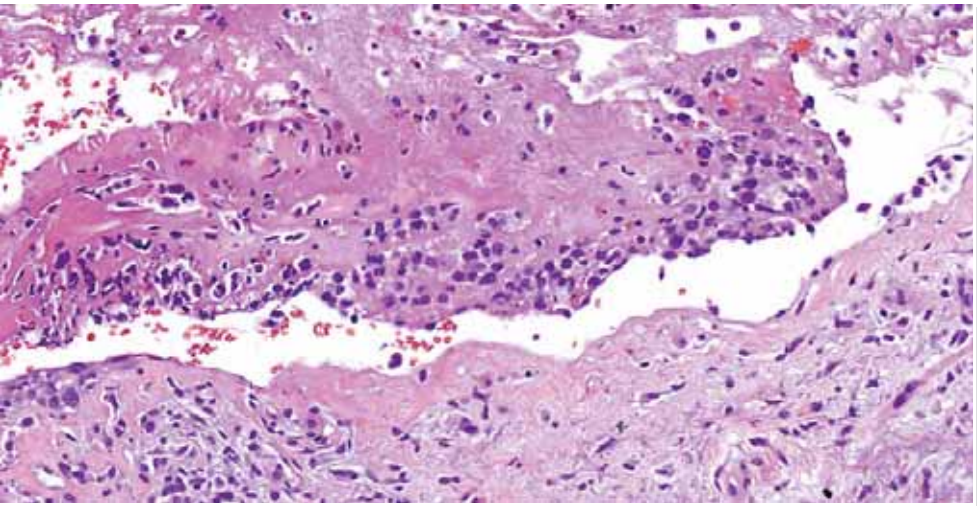


CD4



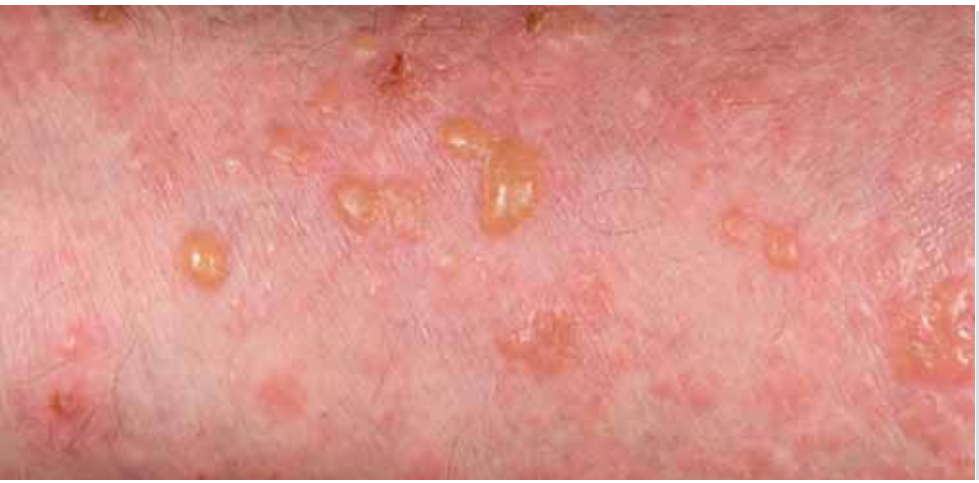
CD30

Summary of the findings



Histology:

Subepidermal blister
Clefts filled with atypical lymphocytes
CD3+, CD4+, CD8-, Ki67↑, CD30 50%



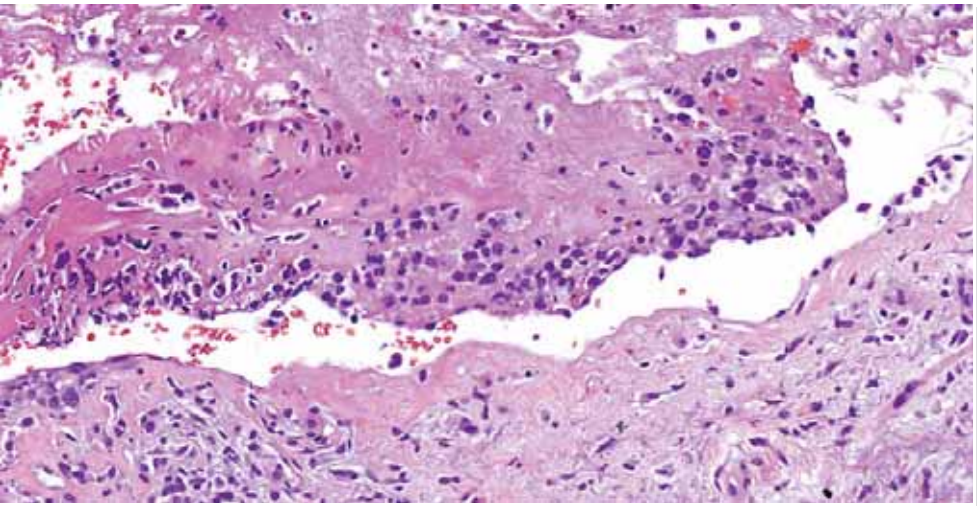
Clinical presentation:

Blisters on erythematous ground,
Patches and plaques
Heavily pruritic
No autoimmune bullous disease
No drug reaction

diagnosis

?

Summary of the findings



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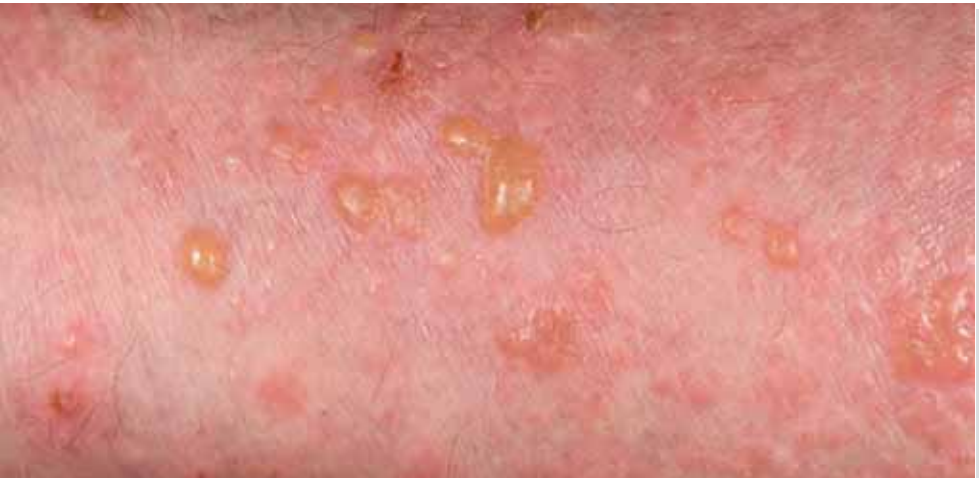


Clinical presentation:

Blisters on erythematous ground,
Patches and plaques
Heavily pruritic
No autoimmune bullous disease
No drug reaction

bullous mycosis fungoides

Bullous mycosis fungoides

- Very rare: approximately 20 cases have been reported
- Mycosis fungoides bullosa is largely restricted to older patients with an more aggressive clinical course
- Vesicles and blisters usually arise in typical plaques and tumours but also in normal-appearing skin.
- The pathological mechanism is unclear.

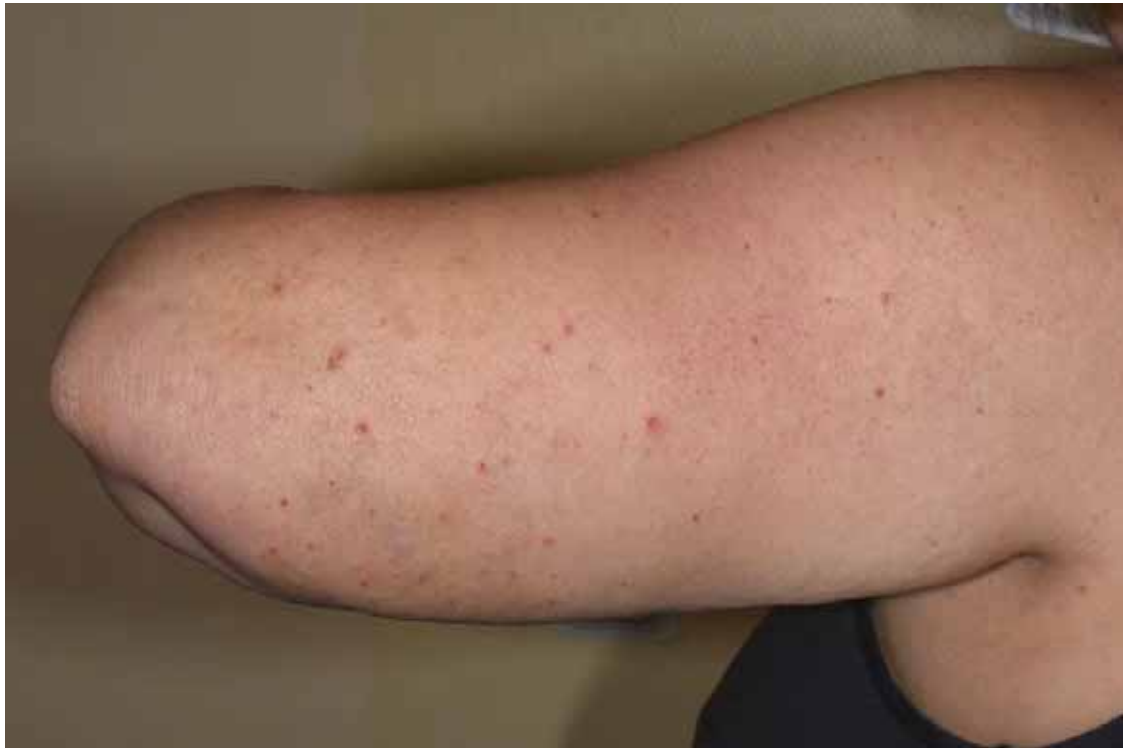
Recommended diagnostic criteria:

(1) Clinically apparent vesiculobullous lesions, with or without typical mycosis fungoides lesions (patches, plaques, tumors)
(2) Typical histologic features of mycosis fungoides (atypical lyphoid cells, epidermotropism, Pautrier's microabscesses) with intraepidermal or subepidermal blisters;
(3) Negative immunofluorescence (both direct and indirect, if possible) to rule out concomitant autoimmune bullous diseases;
(4) Negative evaluation for other possible causes of vesiculobullous lesions (eg, medications, bacterial or viral infection, porphyria, phototherapy).

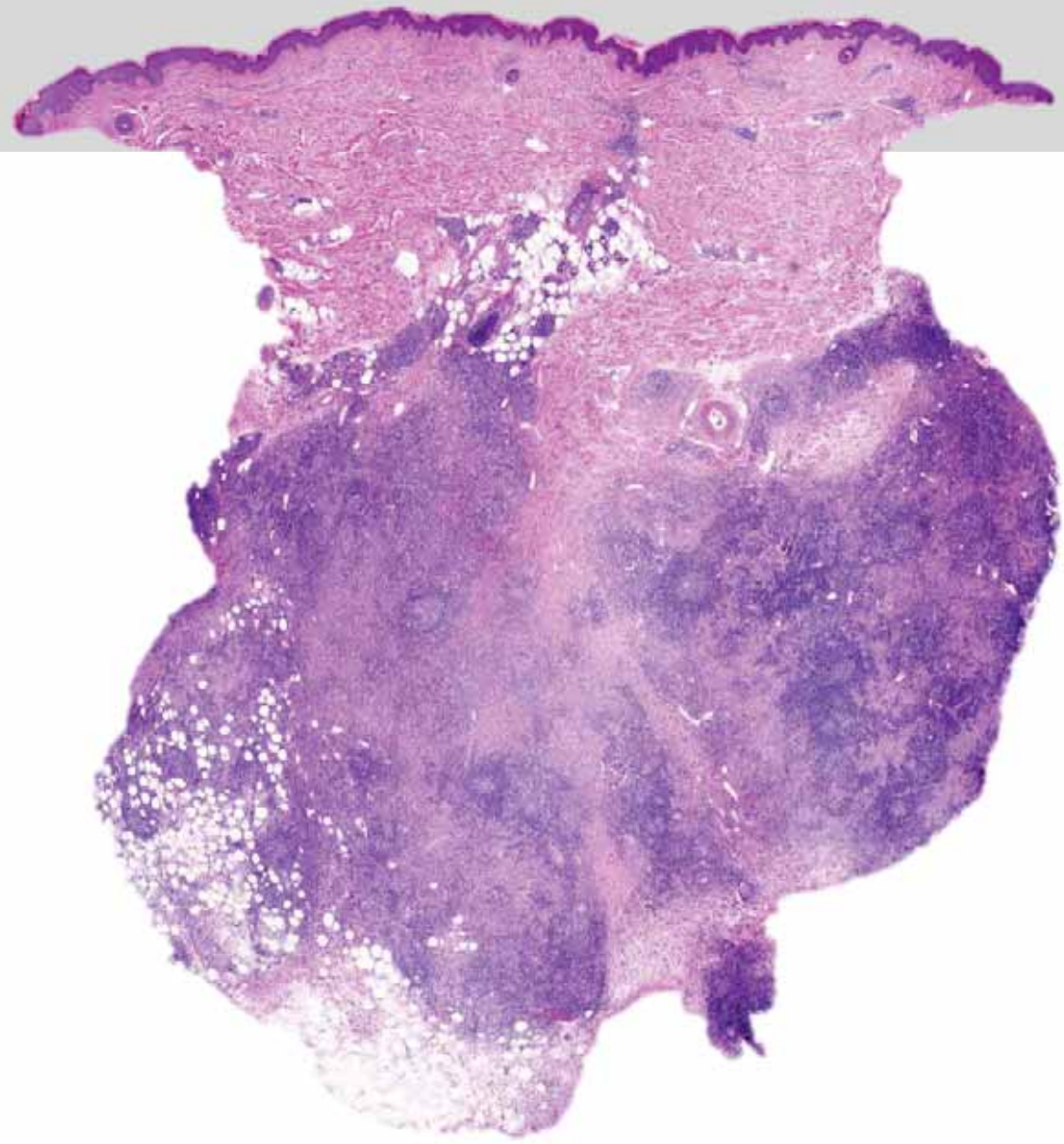
Bowman PH, Hogan DJ, Sanusi ID. Mycosis fungoides bullosa: report of a case and review of the literature. Am Acad Dermatol. 2001;45(6):934-9.
Kneitz H, Bröcker E-V, Becker J. Mycosis fungoides bullosa: a case report and review of the literature. J Med Case Rep . 2010 Mar 3;4:78.

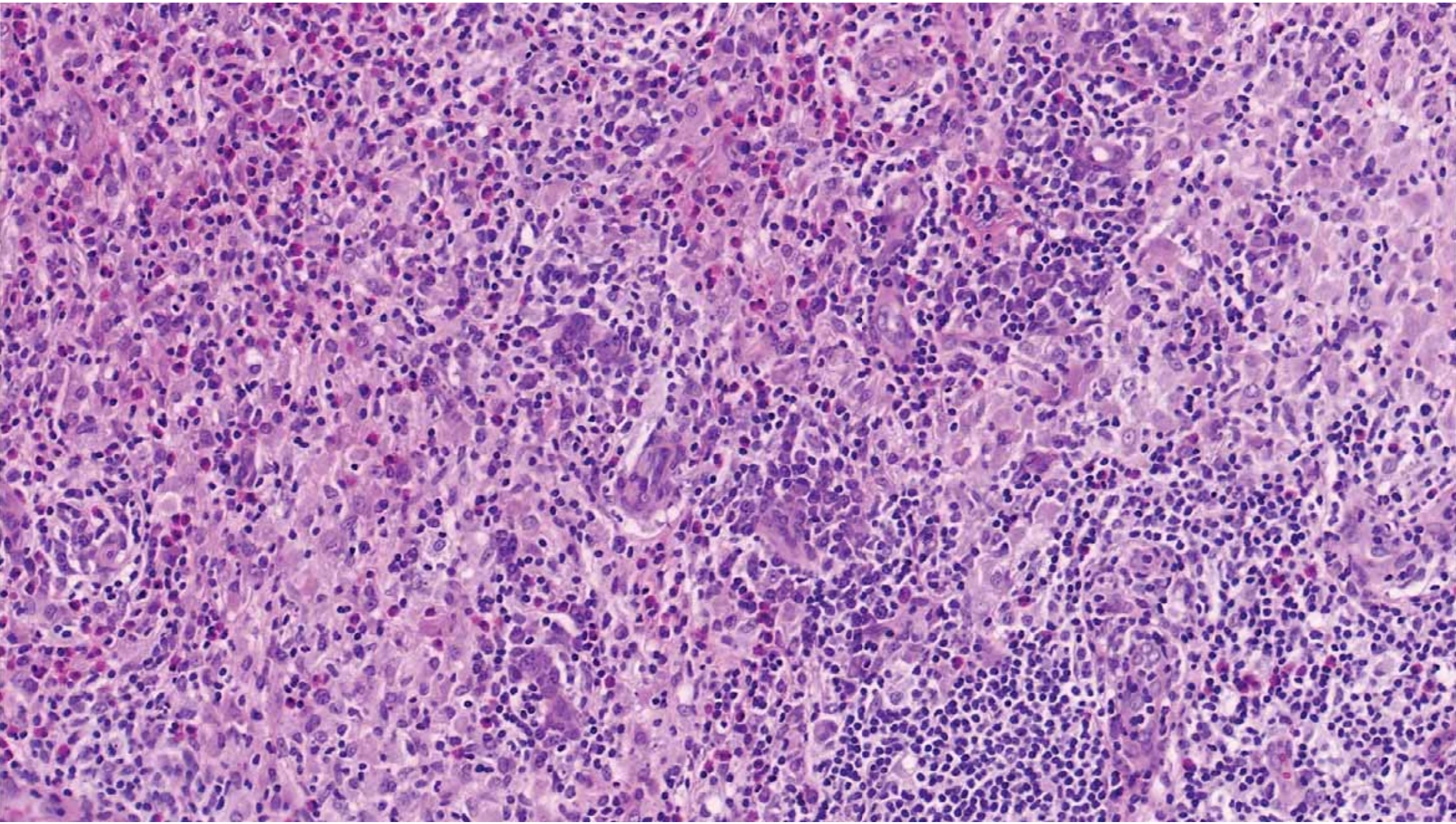
Clinical information

- 49-year-old female
- Deep located itching nodule on her left upper arm for three months
- No pain, no ulceration
- No traumatization
- Clinician suspected: panniculitis, (pseudo-) lymphoma

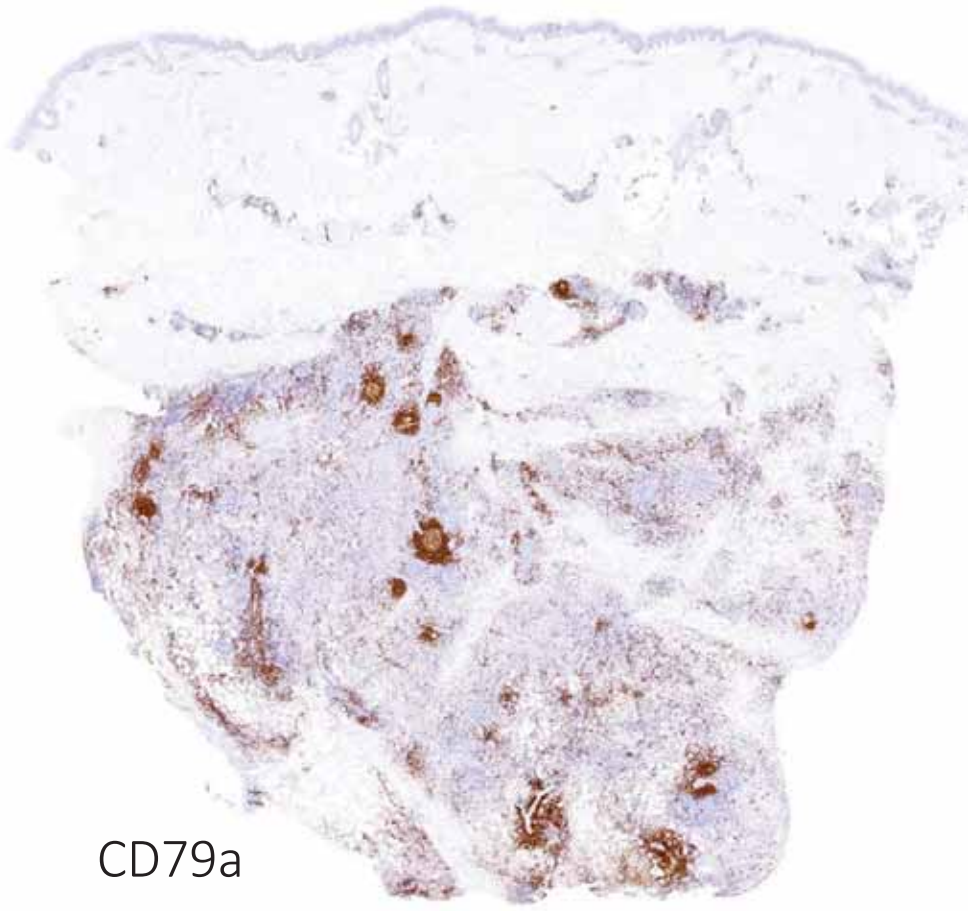


Histology

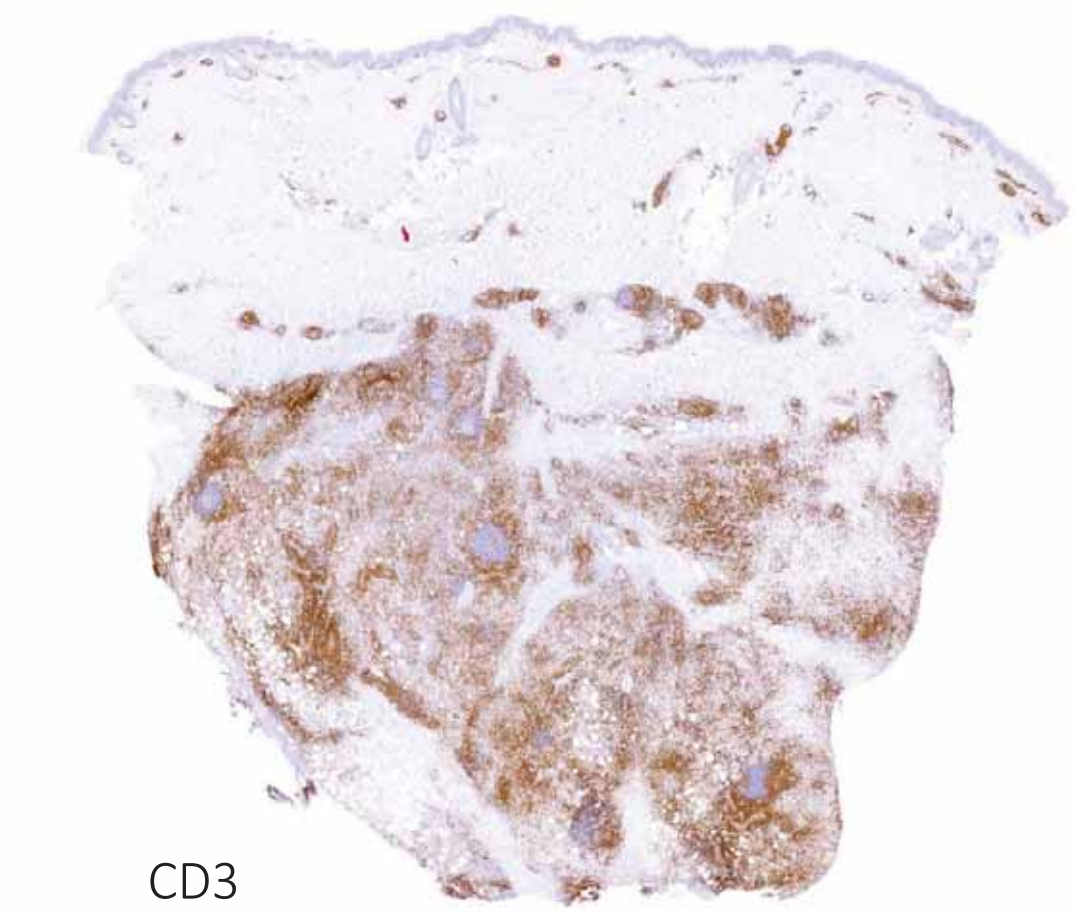




Immunohistochemistry

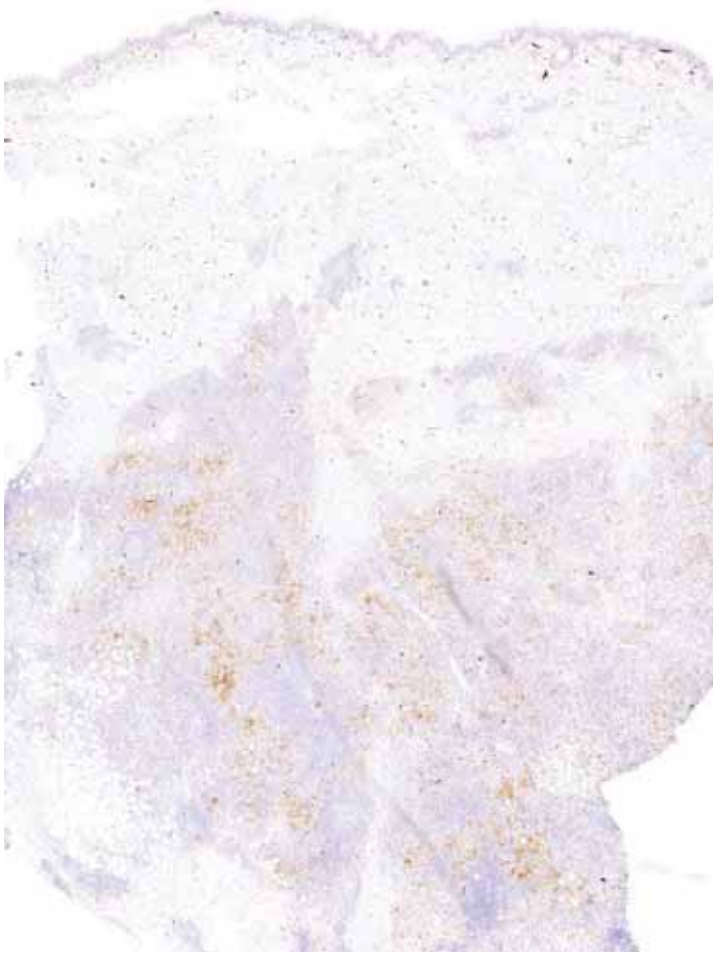


CD79a

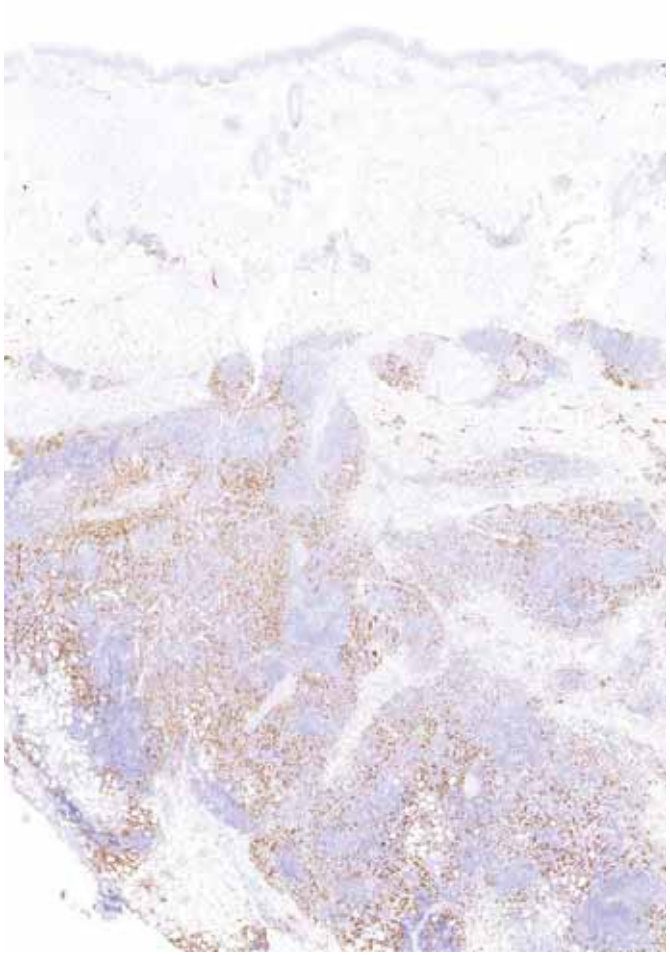


CD3

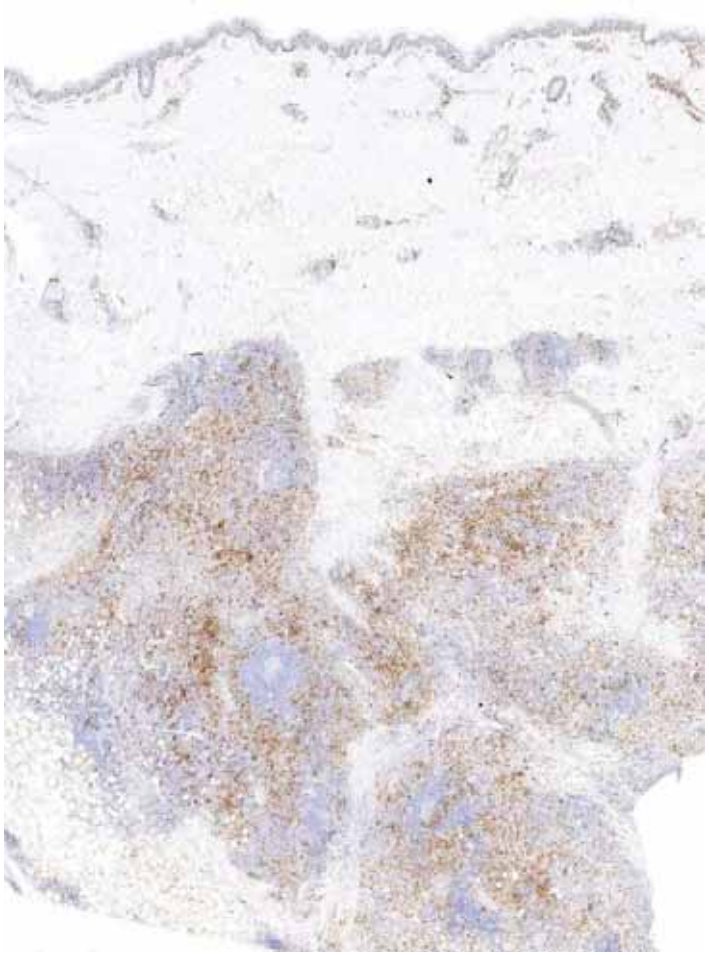
Immunohistochemistry



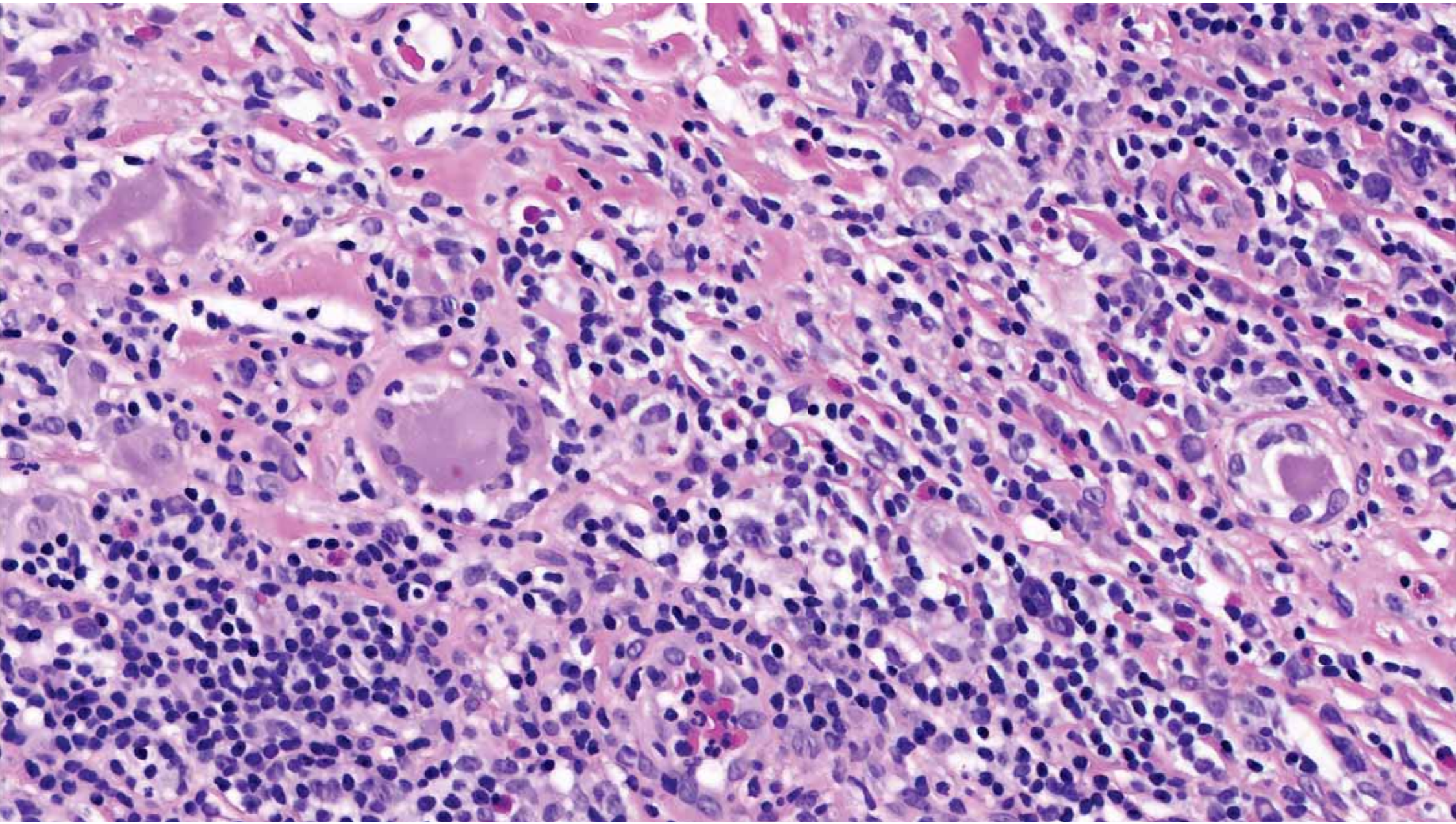
CD68



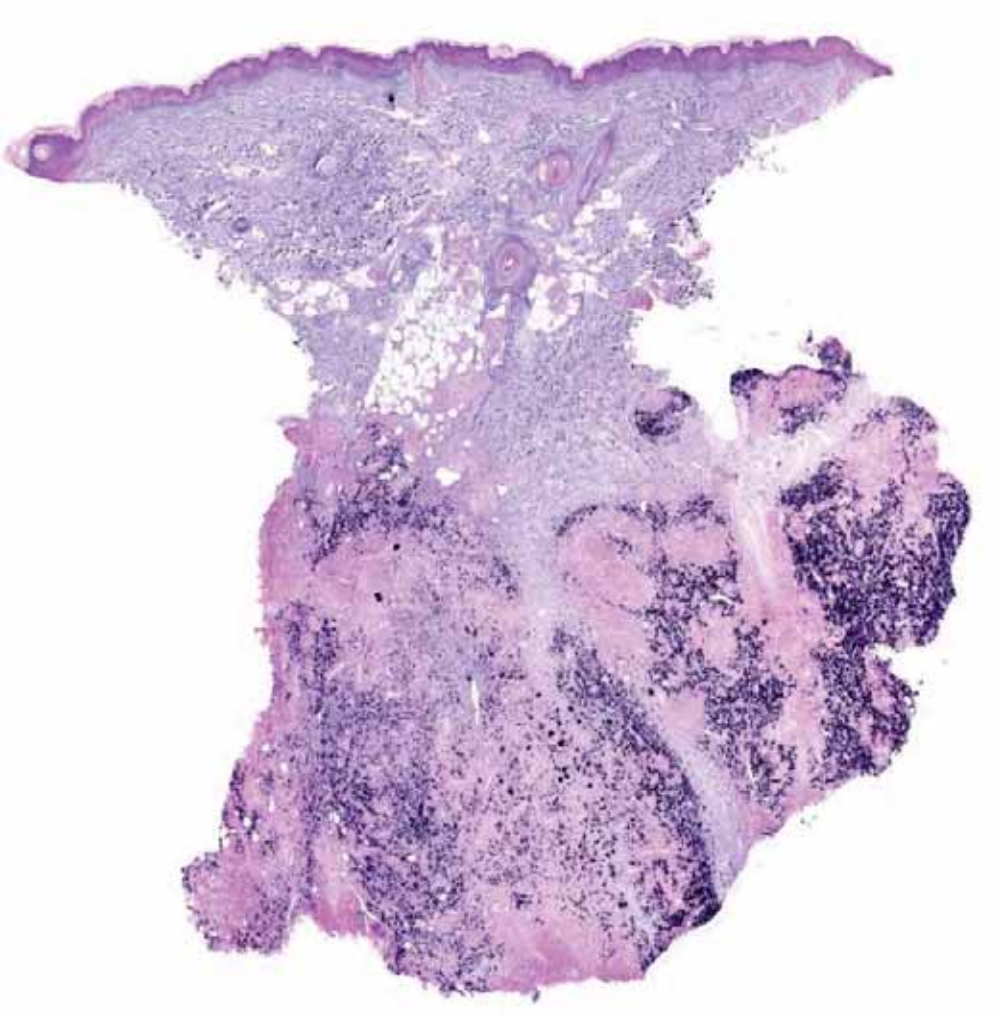
CD1a

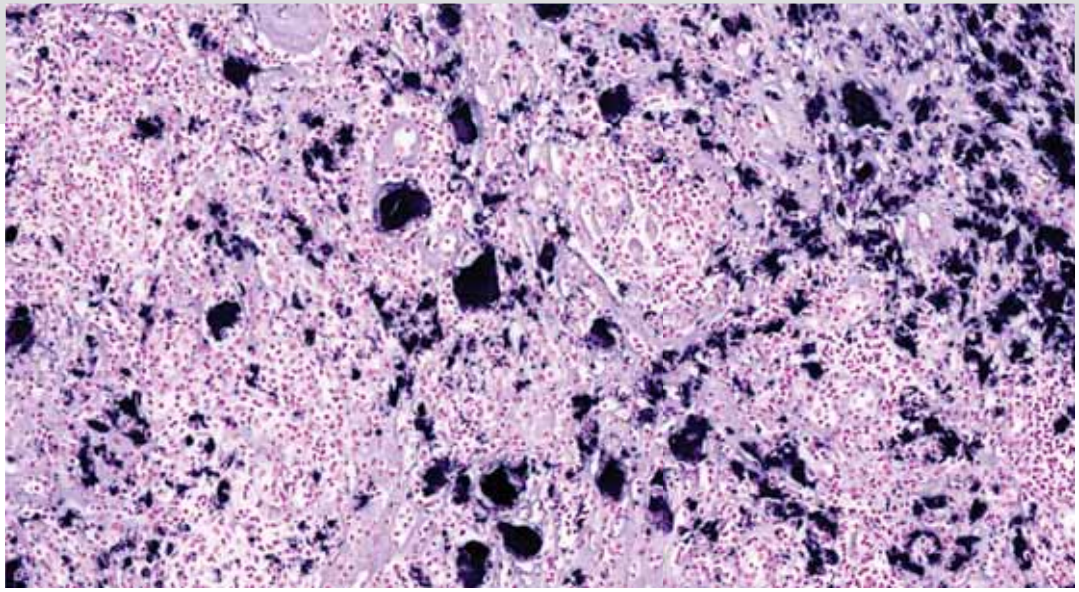


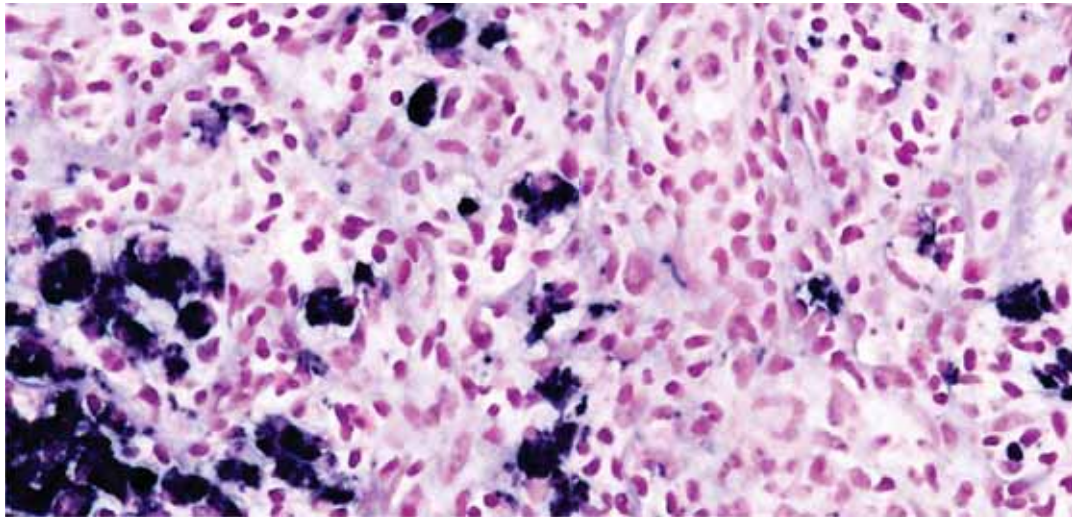
S-100

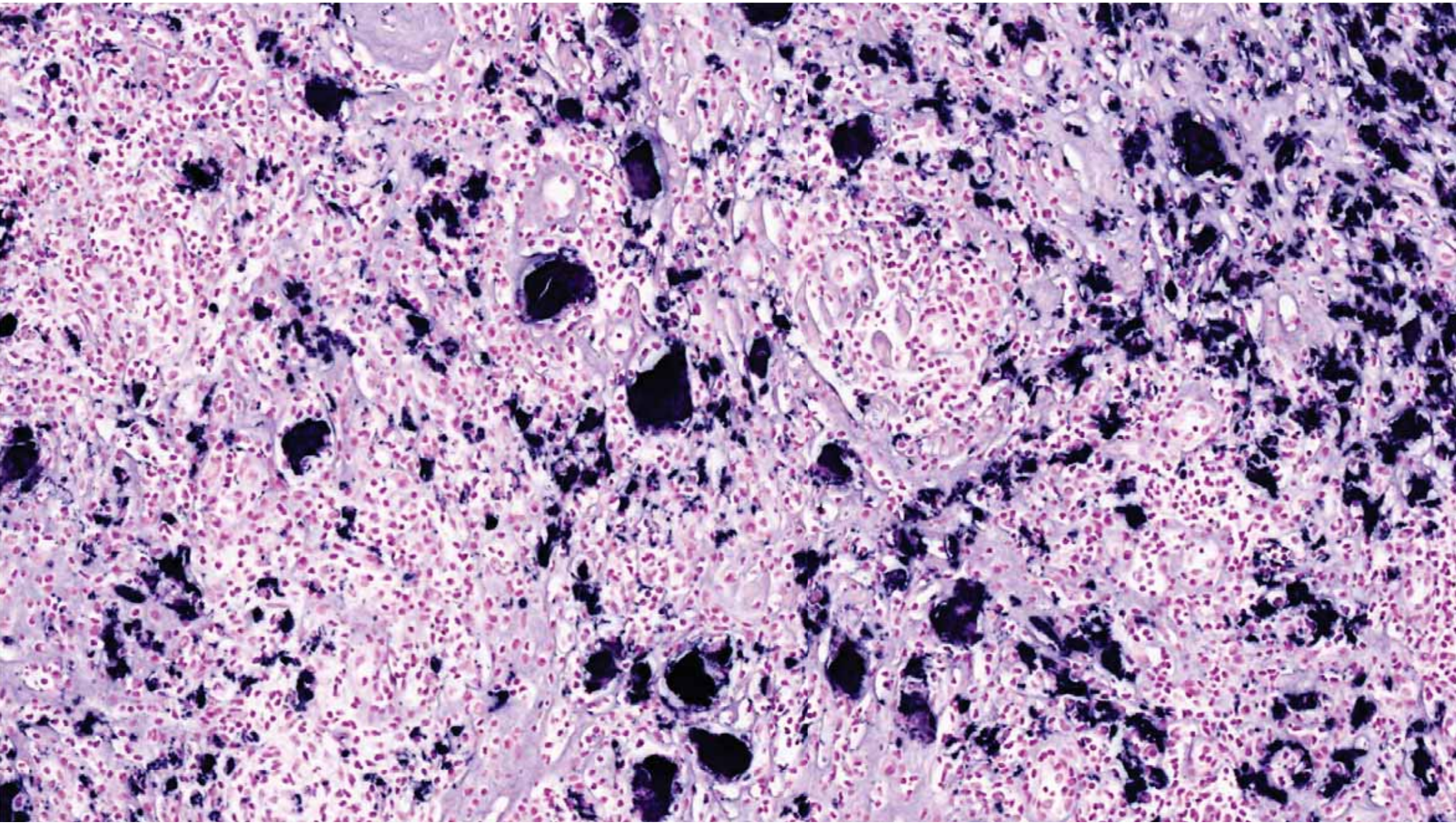


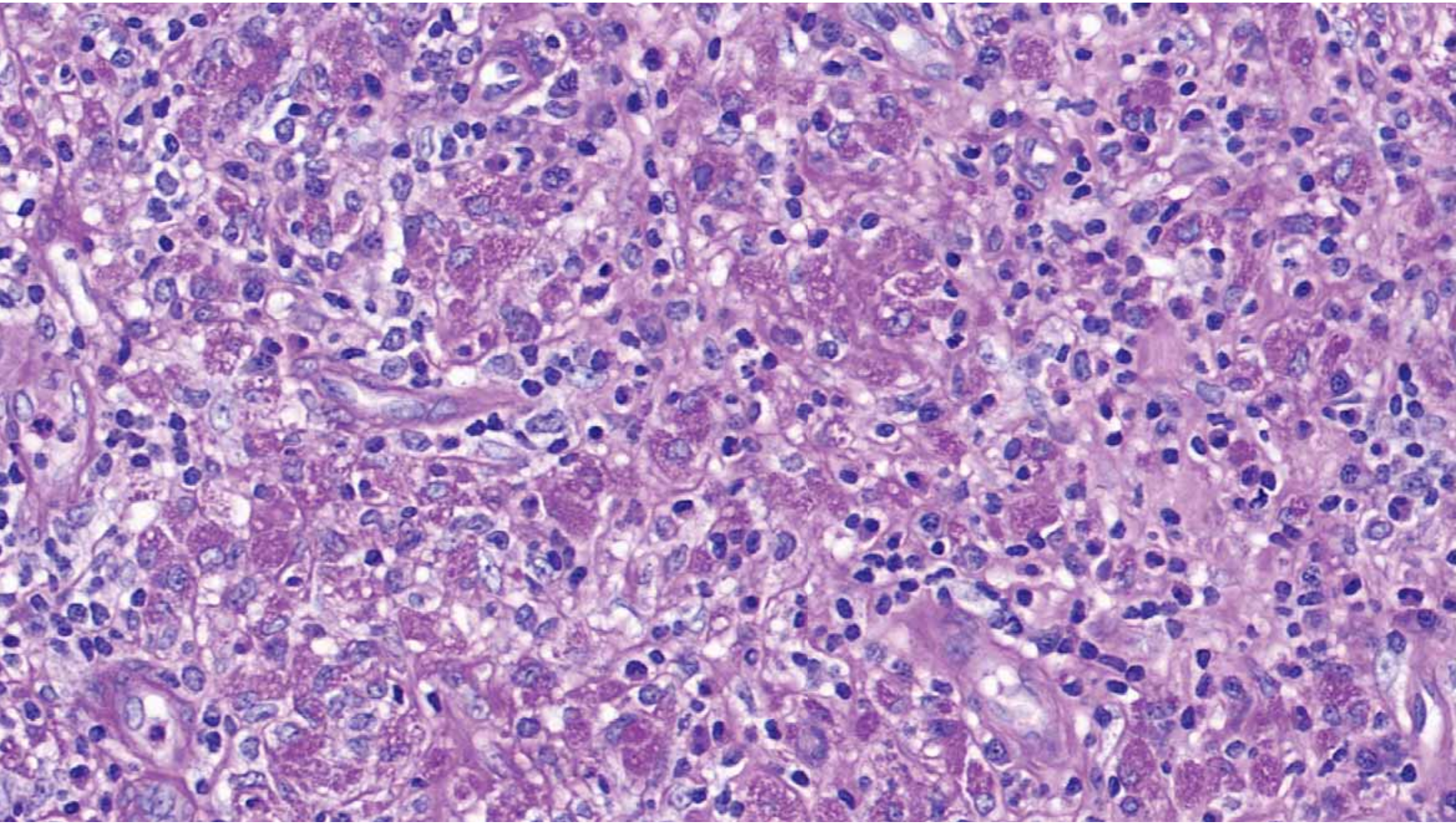
EBV in situ hydridization



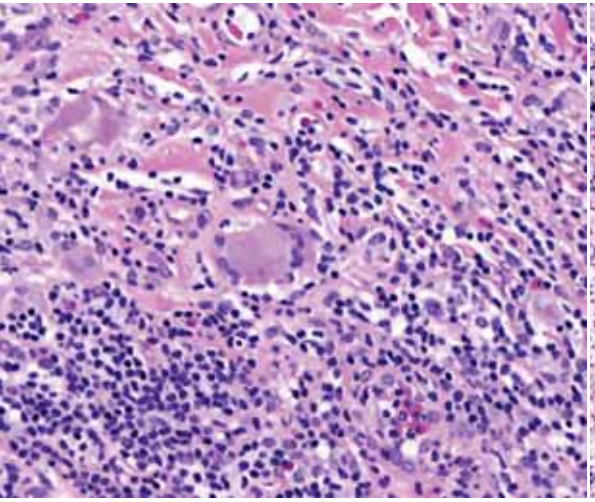


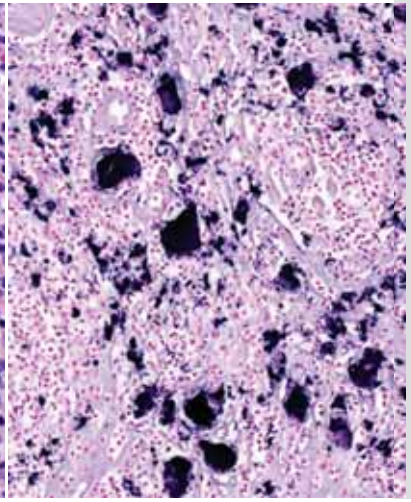






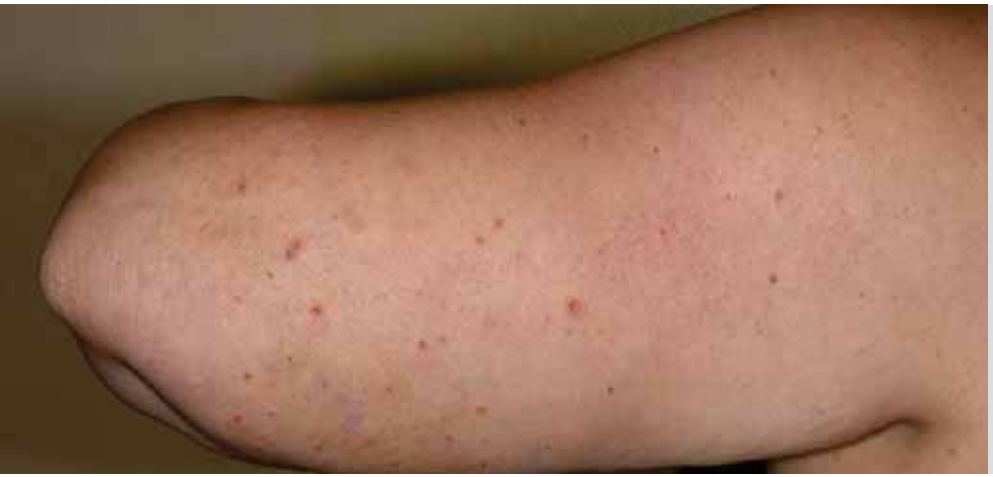
Summary of the findings





Histology:

Deep mixed infiltrate
Reactive germinal centers
Cytoplasm: EBV+ i.s.H. material



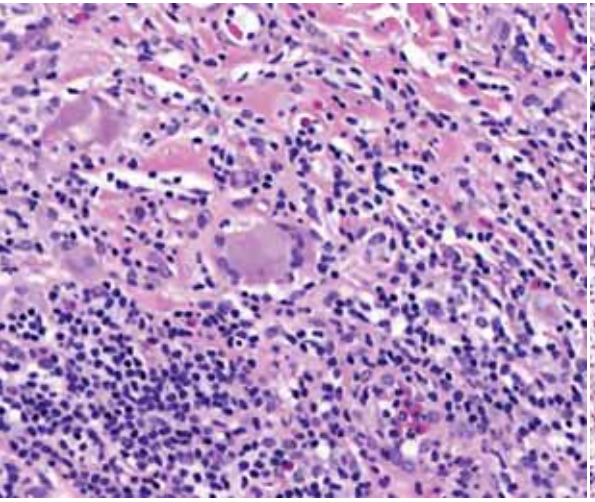
Clinical presentation:

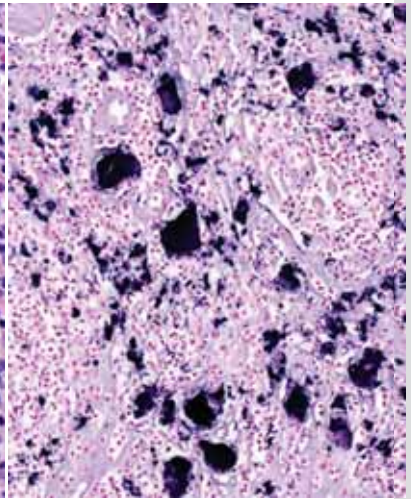
Deep located itching nodule for three months
No traumatization
Desensitization 3 years ago, but the nodule developed 3 month ago

diagnosis

?

Summary of the findings





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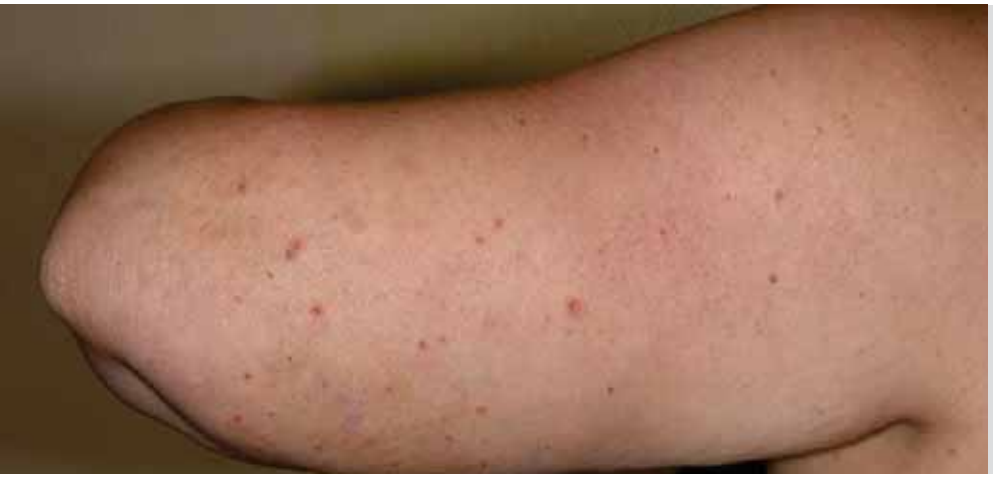


Clinical presentation:

Deep located itching nodule for three months
No traumatization
Desensitization 3 years ago, but the nodule developed 3 month ago

Subcutaneous reactive lympho-proliferation after desensitization
(Aluminium hydroxide granuloma)

Aluminium hydroxide granuloma

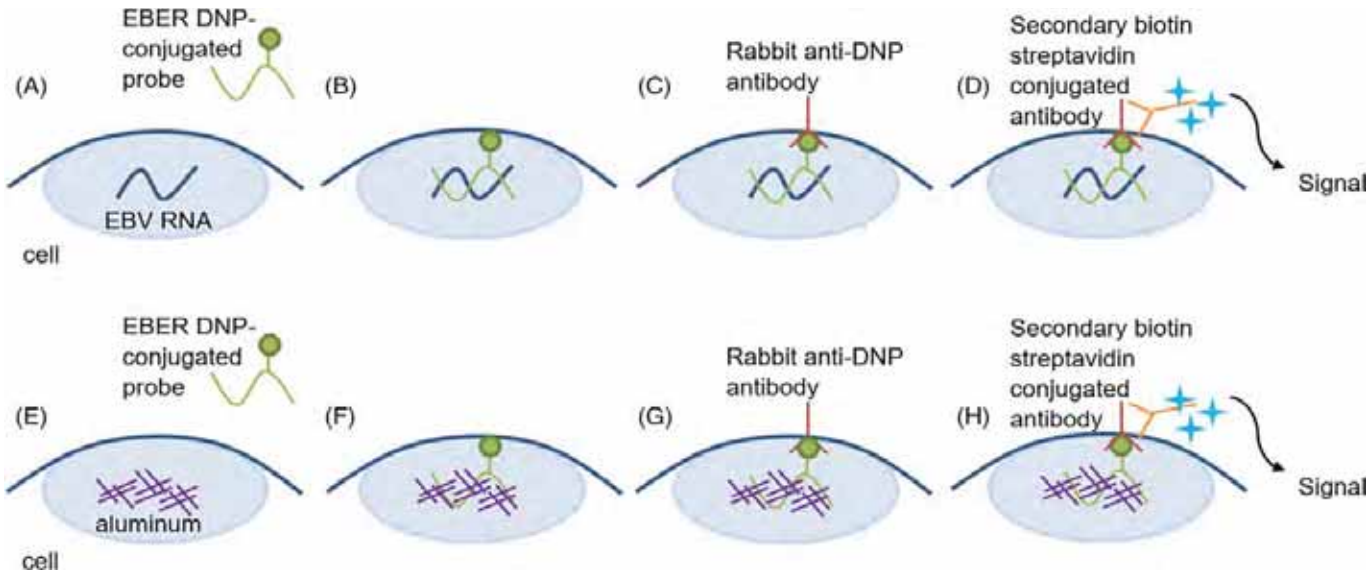
- Desensitization 3 years ago, but the nodule developed 3 month ago.
- Long latency period between the application and the occurrence of skin reactions have been described (up to 8 years).
- Aluminum hydroxide is widely used as an adjuvant in vaccines and desensitization solutions.
- 20 – 30% of the treated patients develop subcutaneous granulomas, persistent for years in 0.5-6%.
- Postulated cause for the persisting immune response:

  perpetuate foreign-body reaction

  delayed hypersensitivity reaction to aluminum hydroxide

- Aluminium hydroxide detection by in-situ-hybridization (e.g. EBV, kappa, lambda,…)

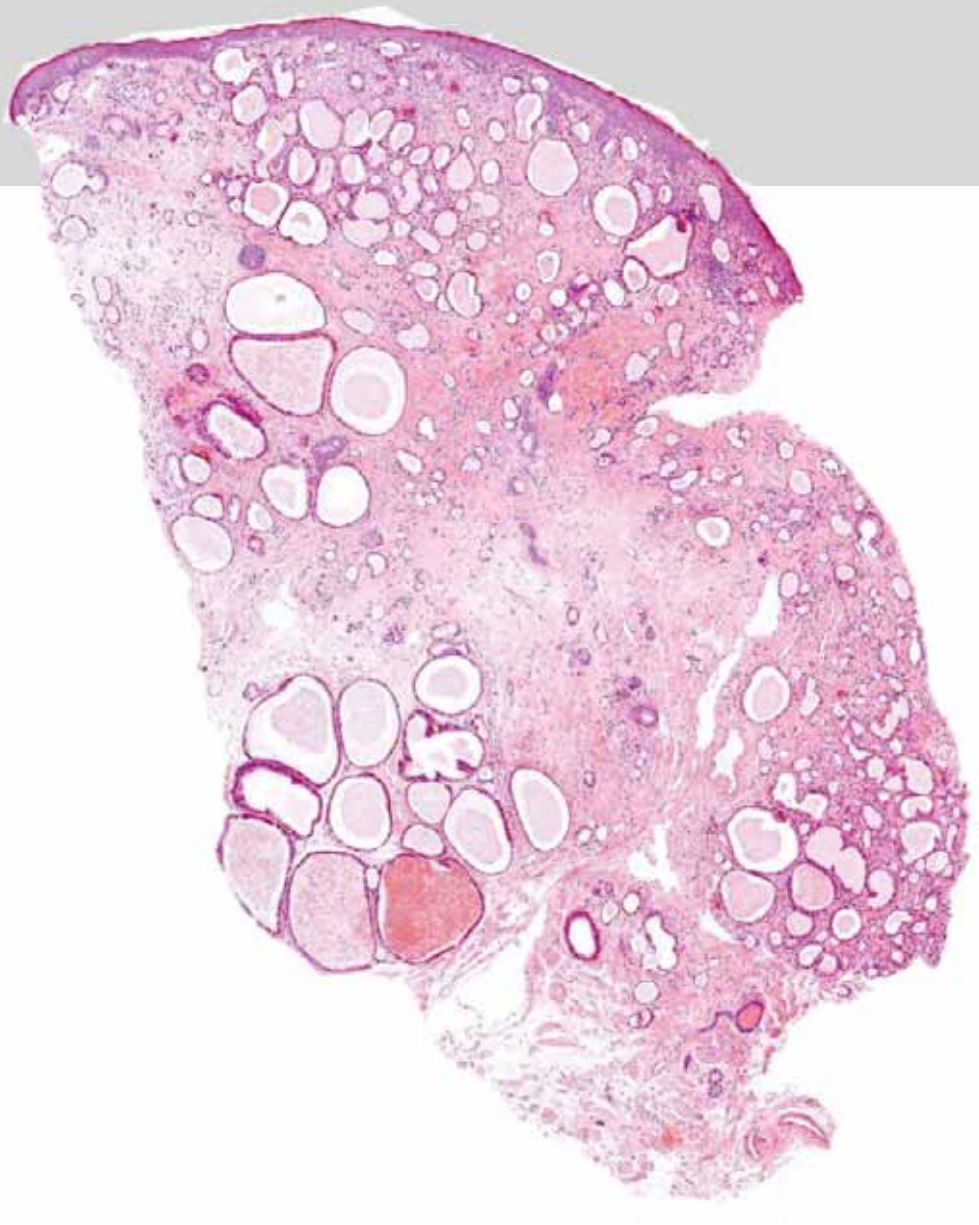
Mechanismen of Al detection by EBV ISH

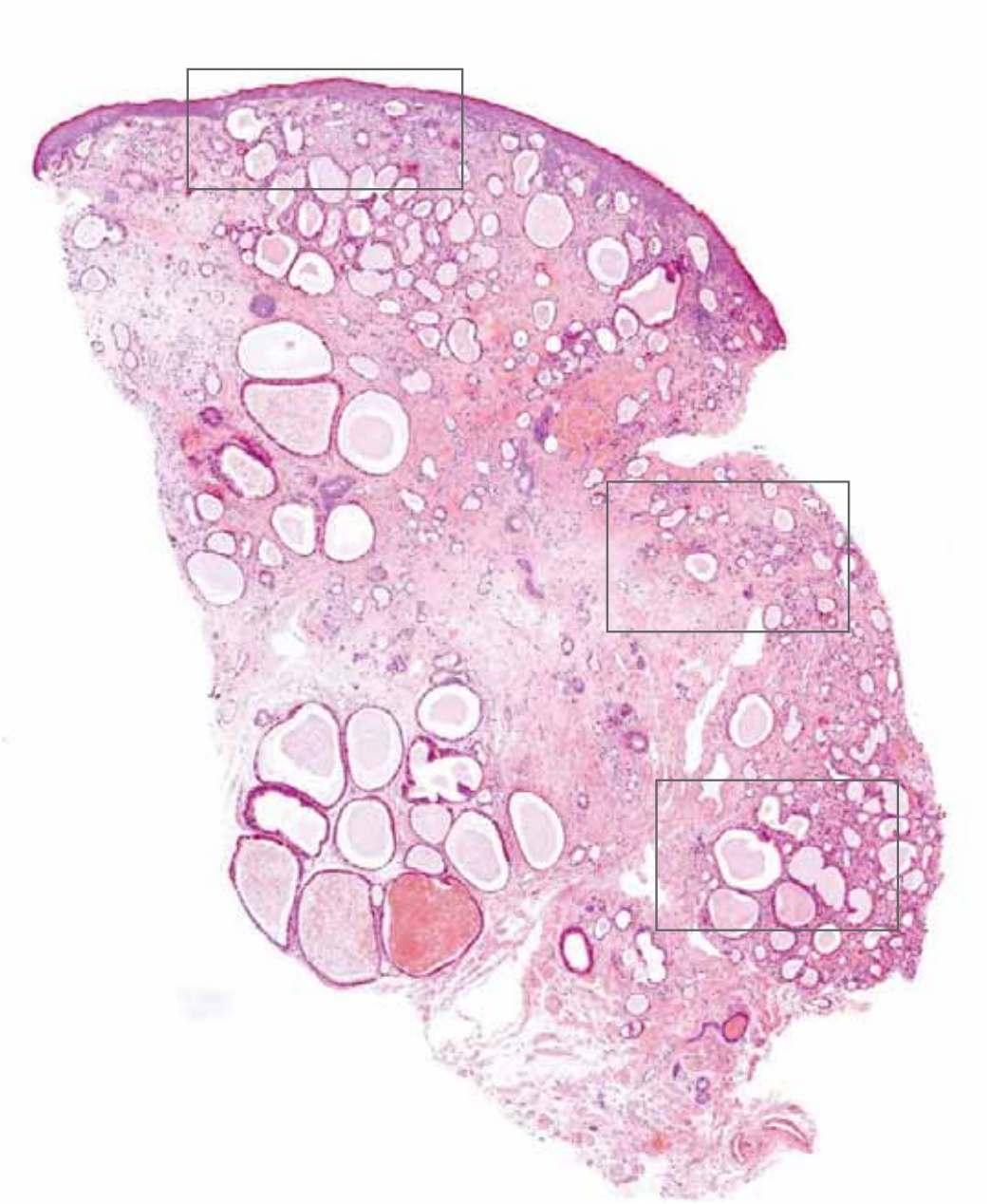


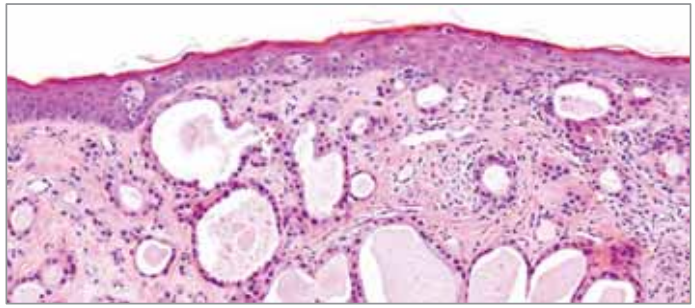
From: Frings V. et al EBER in situ hybridization in subcutaneous aluminium granuloma/lymphoid hyperplasia… J Cutan Pathol 2021.

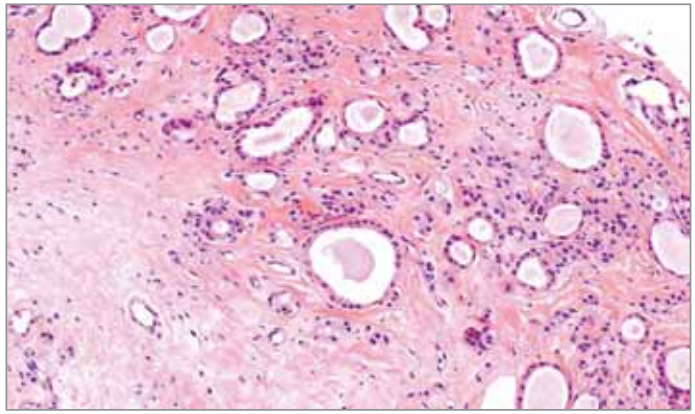
Histology

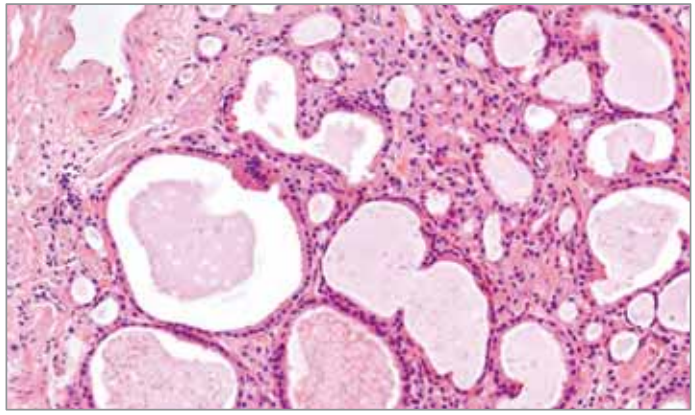
75-year-old male patient
Scrotal erythema with little nodules and cysts
For one year, slowly growing
Suspected diagnosis: M. Paget

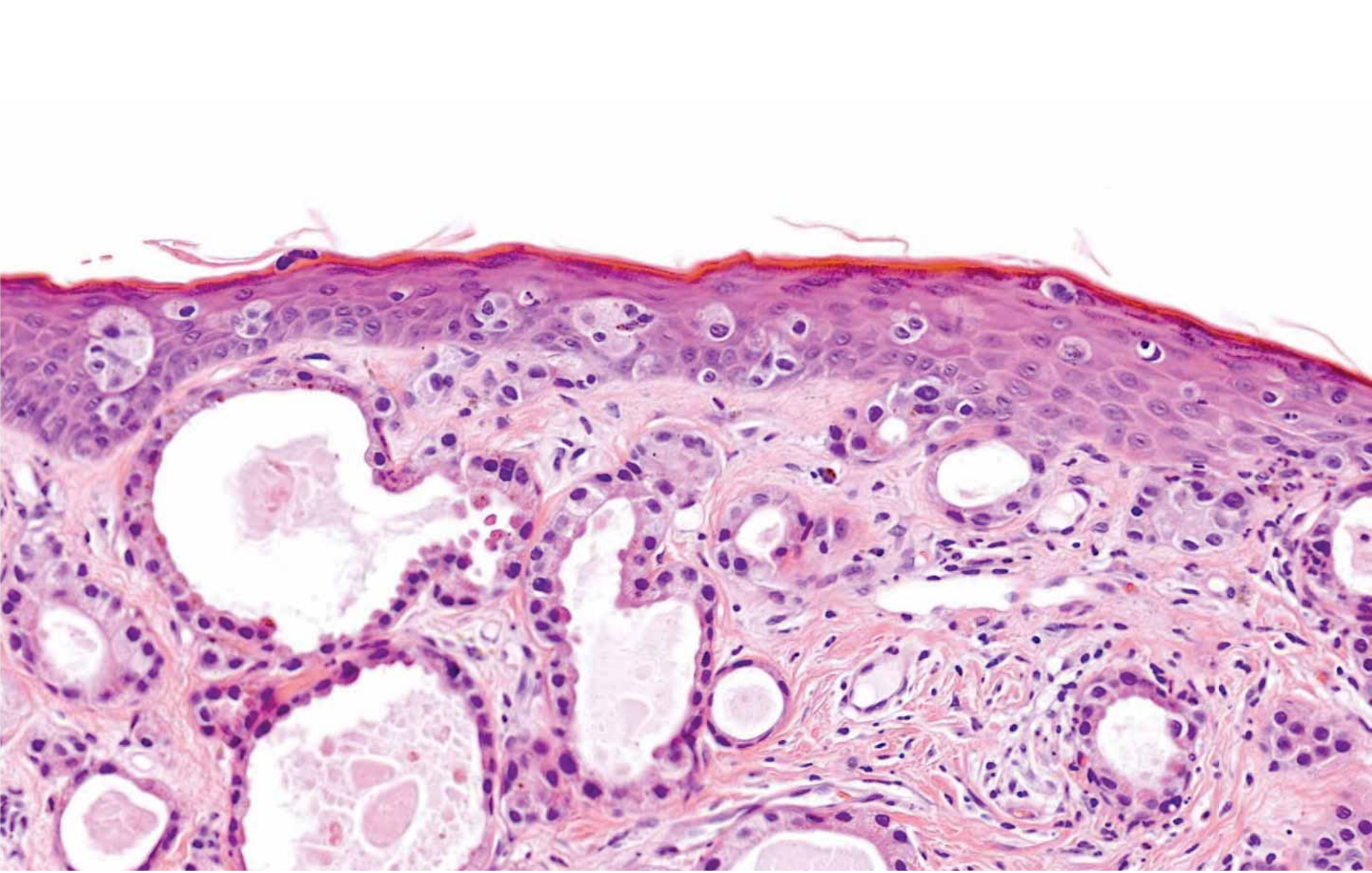






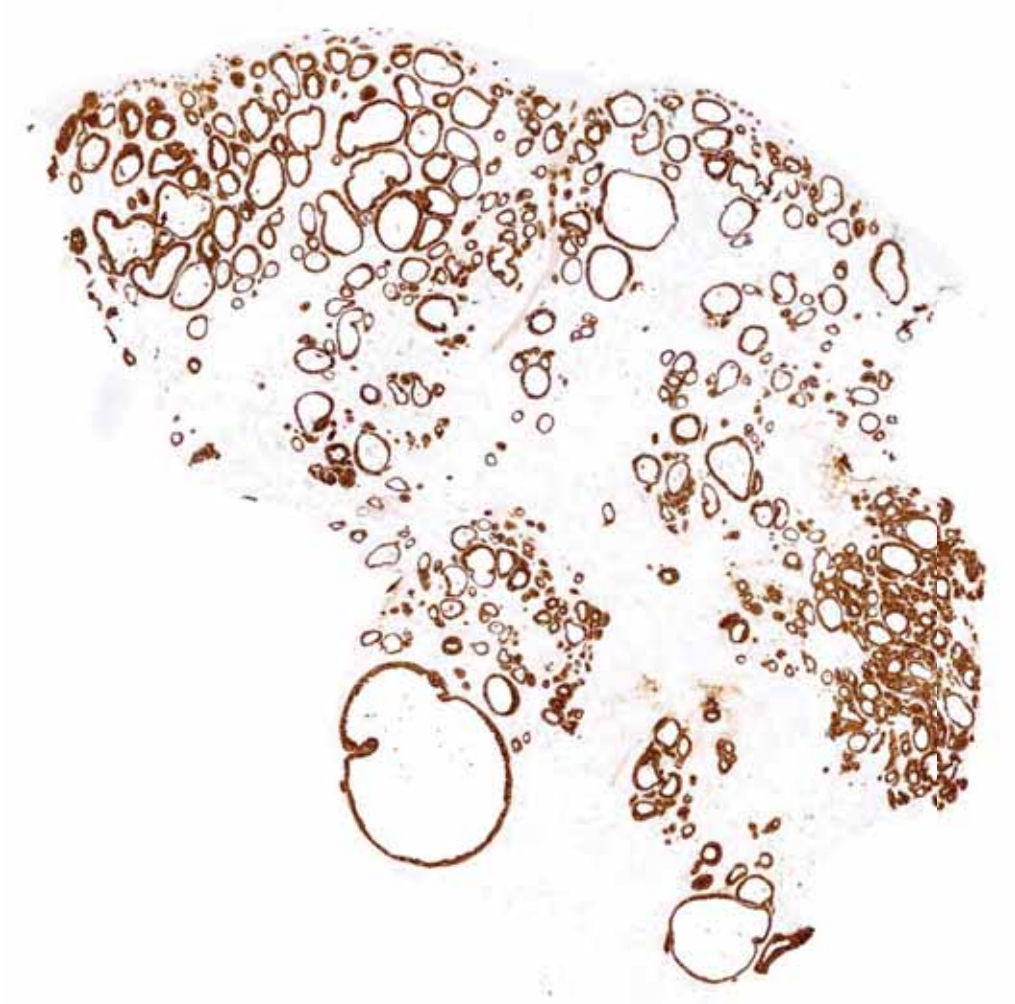


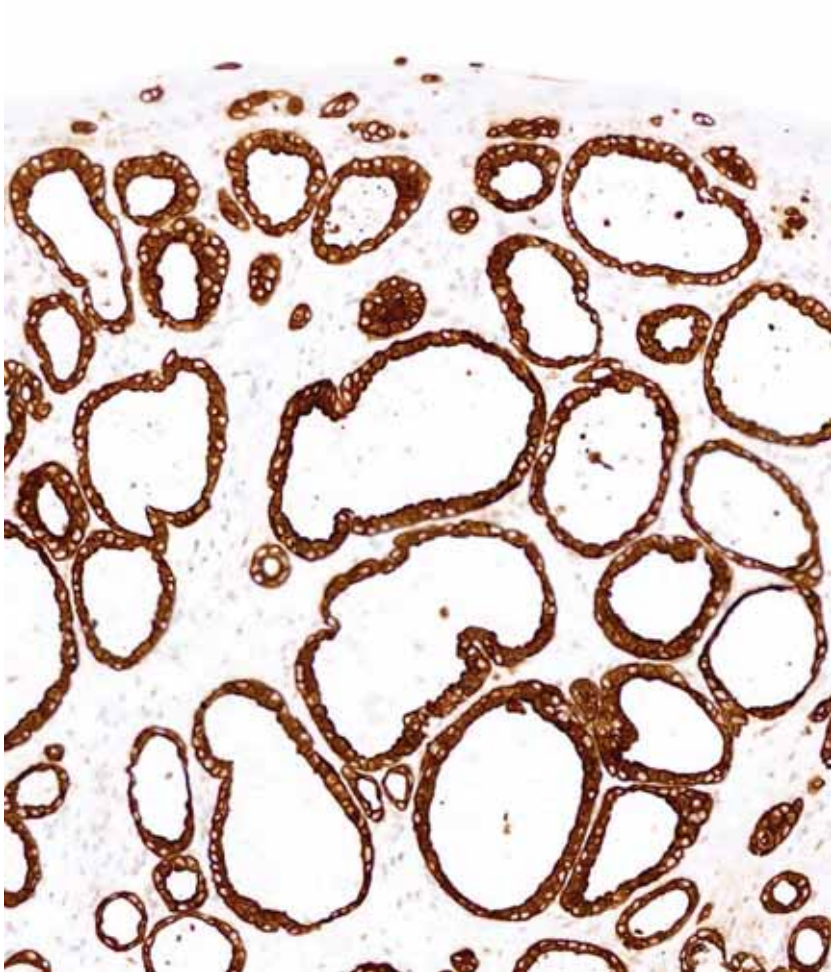


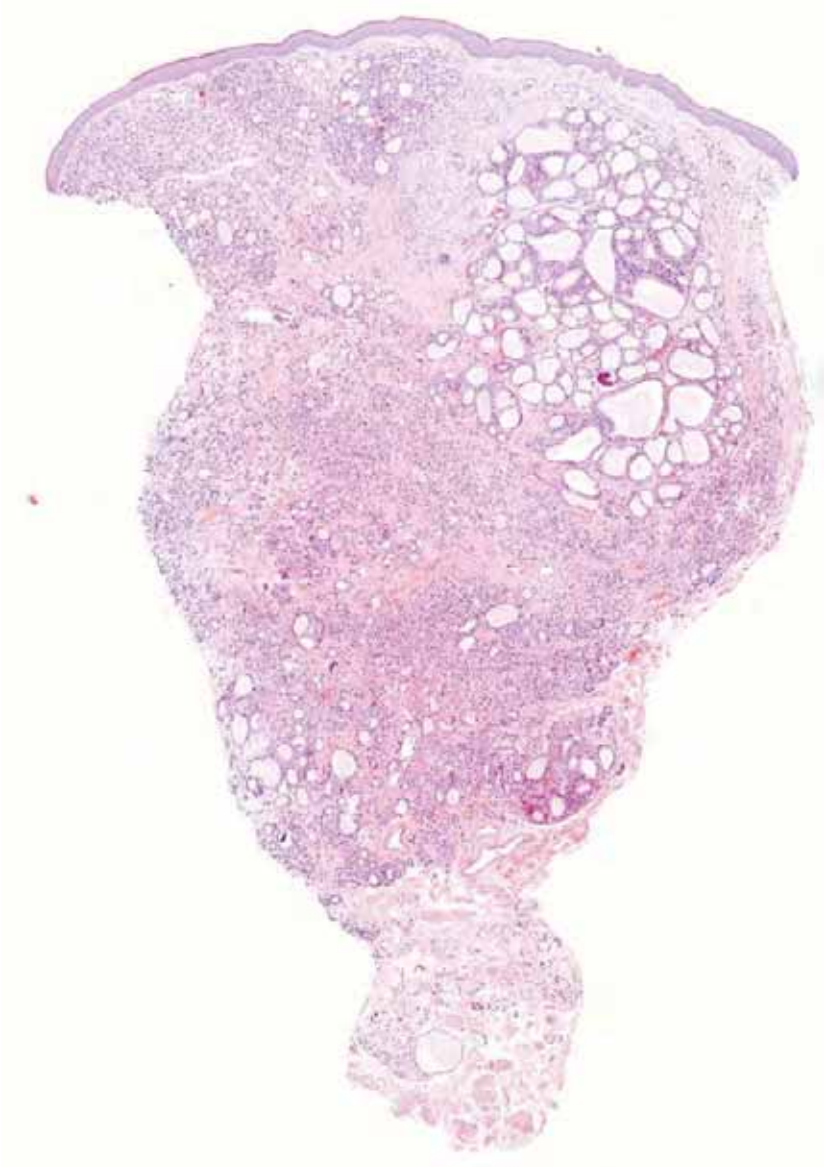


Immunohistochemistry

CK7





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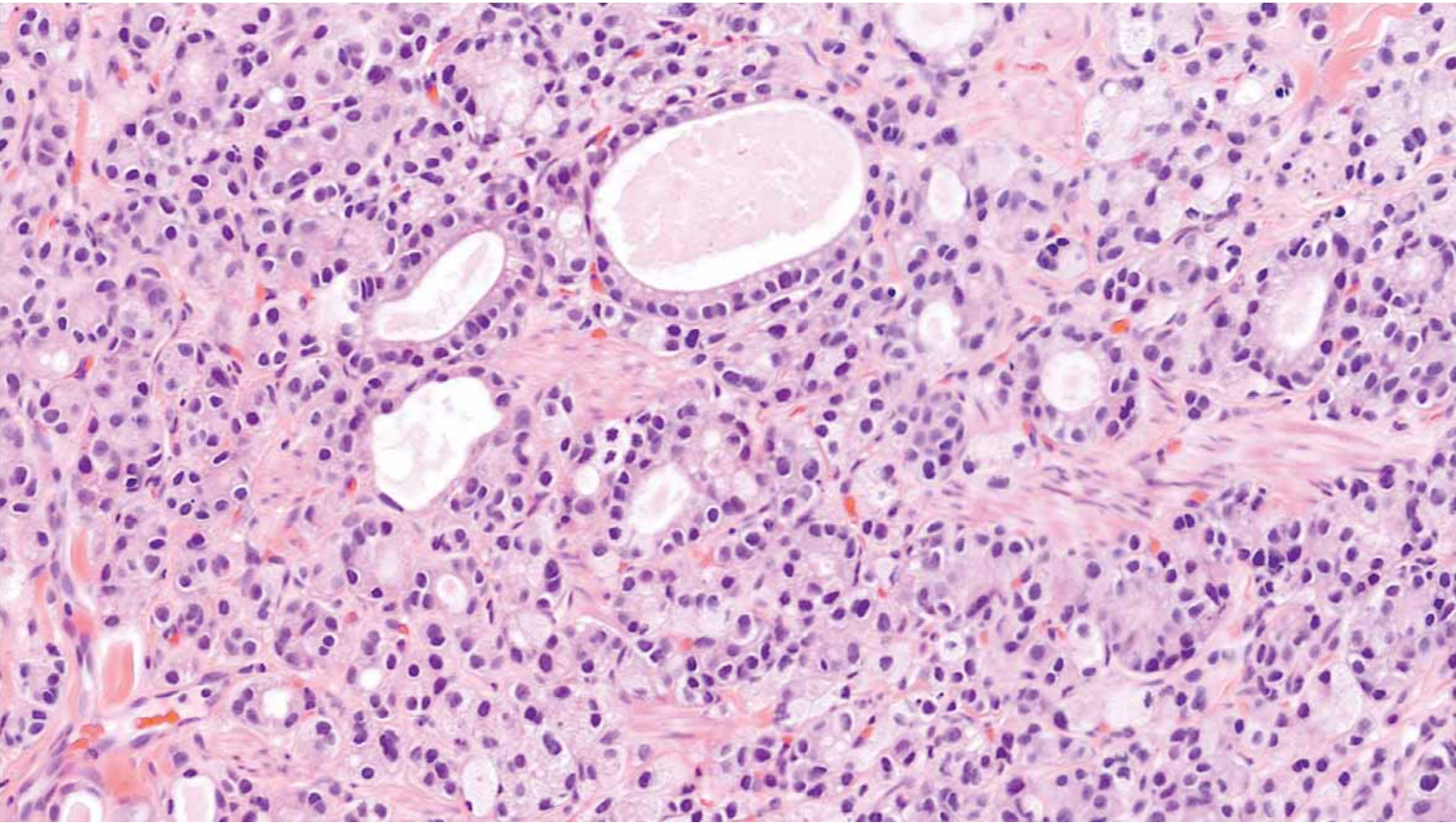
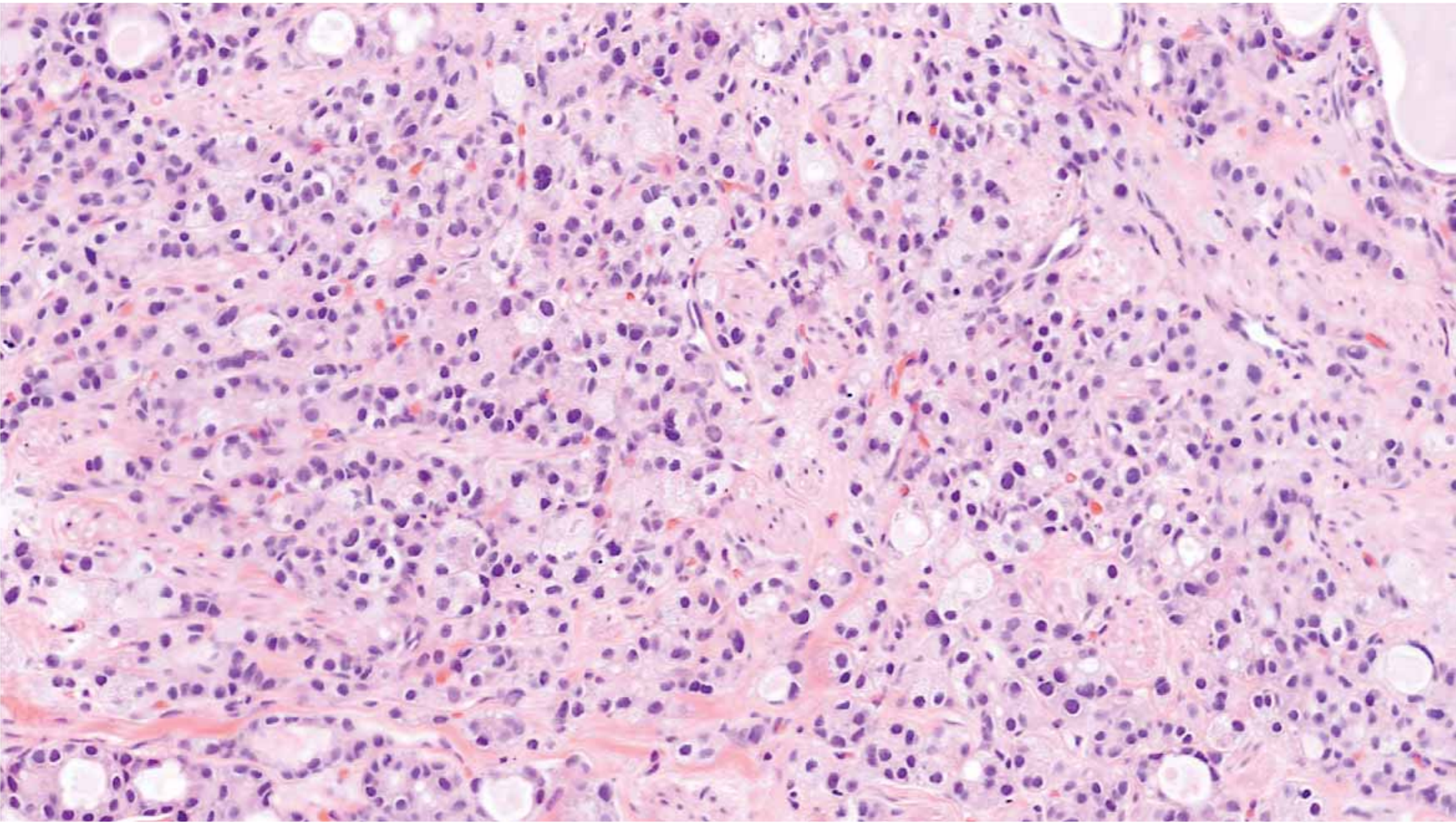
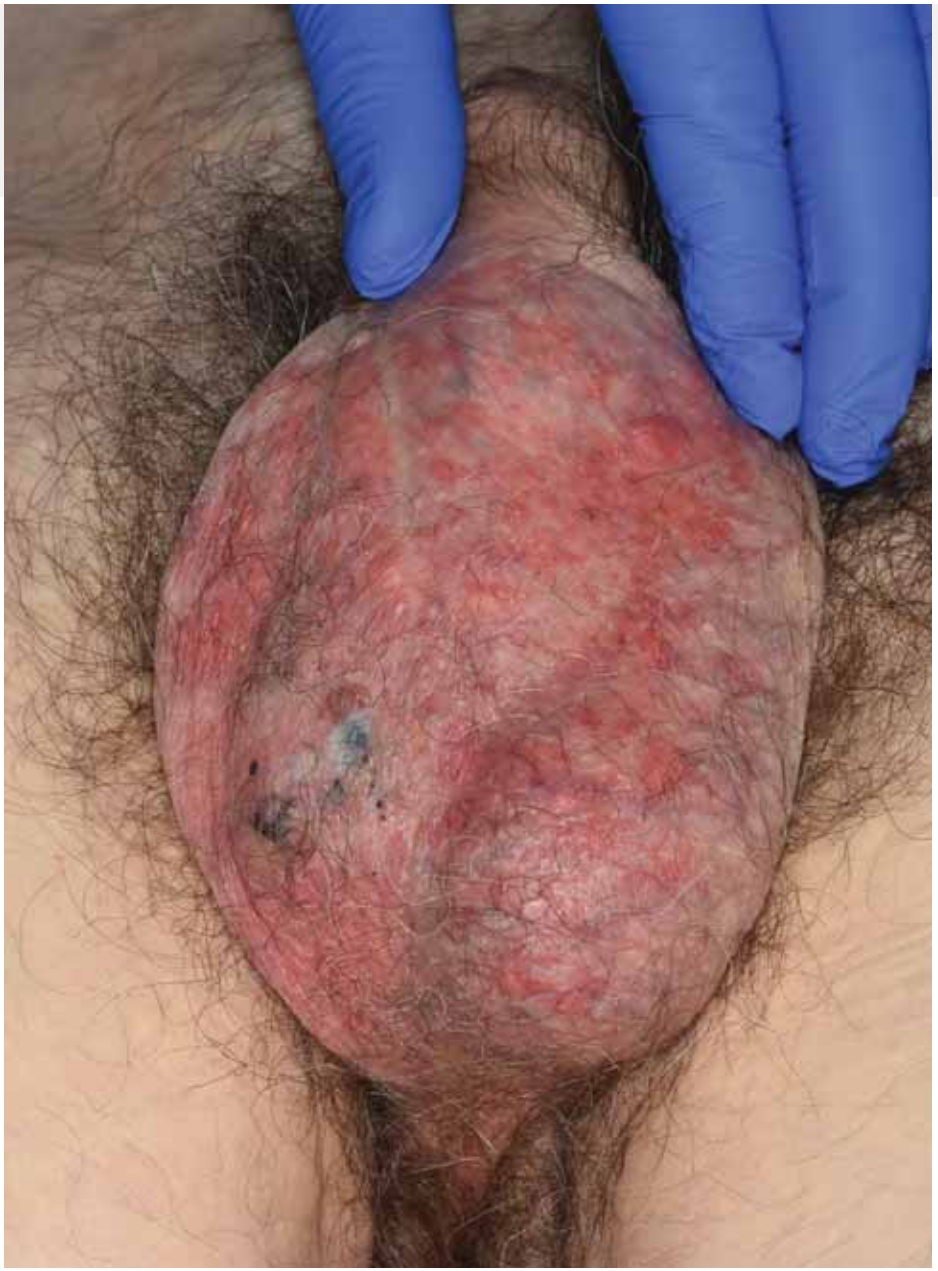
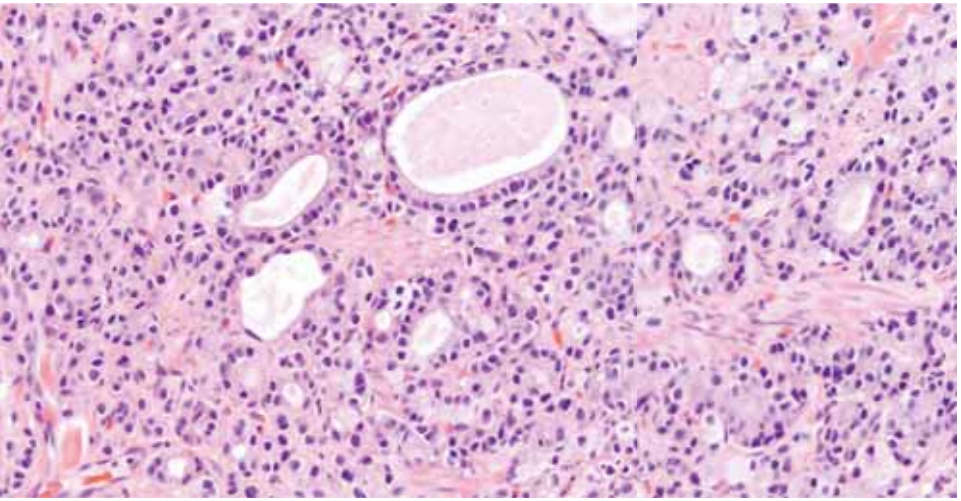


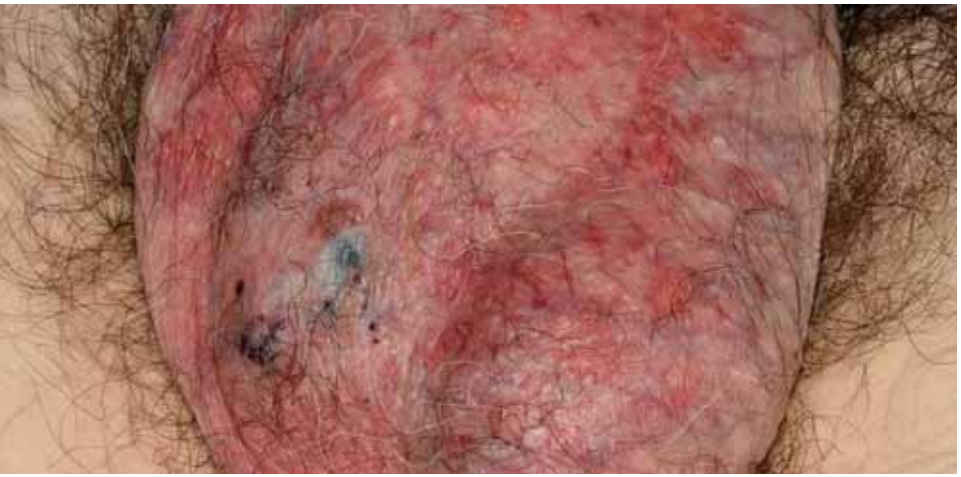


Clinical presentation



Summary of the findings





Histology:

- Non-encapsulated deep infiltrating
- Pagetoid spread
- Tubular, cribriform areas alongside solid, cord-like arrangements
- Apocrine secretion
- Atypia, few mitoses

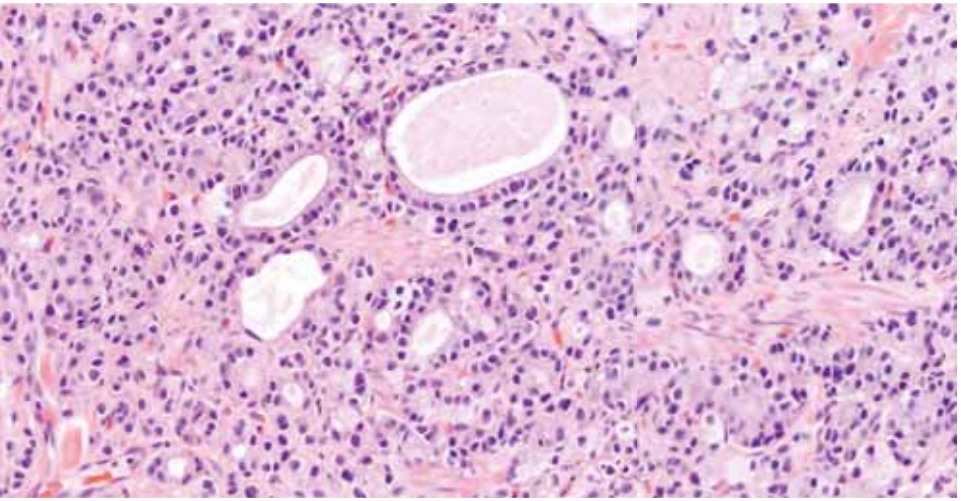
Clinical presentation:

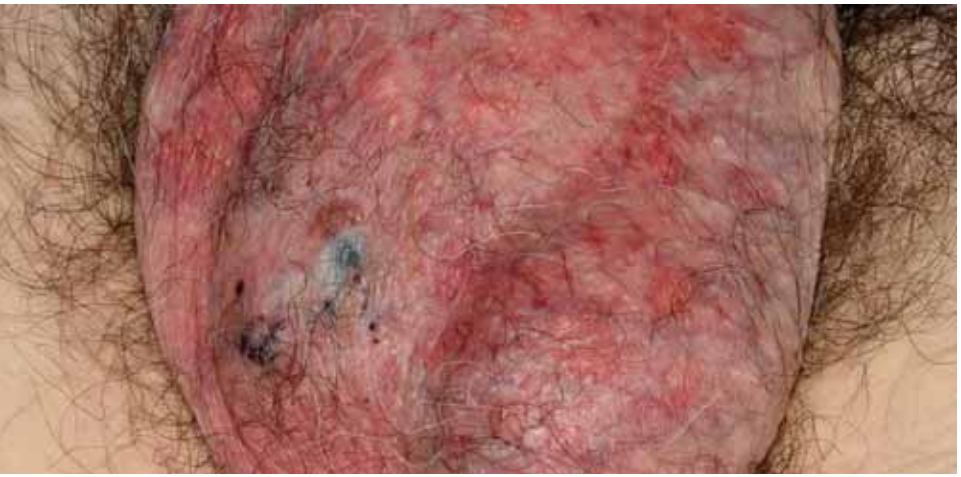
- Scrotal erythema with little nodules, cysts, hemorrhage
- For one year, slowly growing
- No prior history of malignancy

diagnosis

?

Summary of the findings





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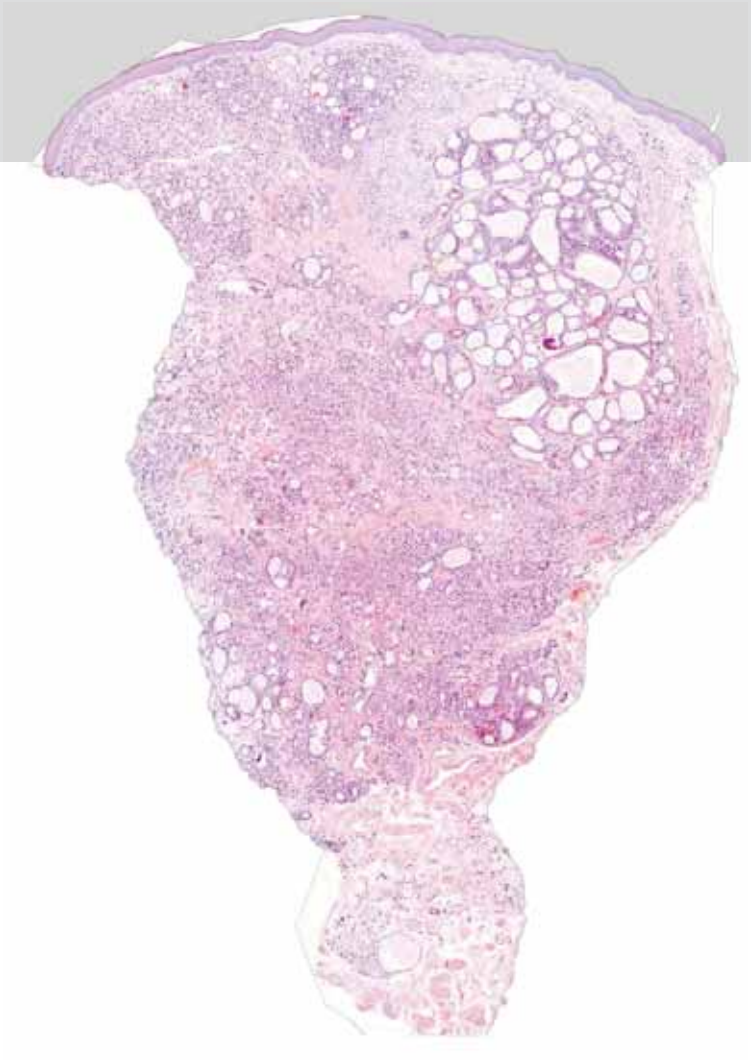
apocrine carcinoma

Apocrine carcinoma



Summary of histological criteria:

- Non-encapsulated tumor with infiltration of the dermis and subcutis.
- Intraepidermal (pagetoid) spread is possible.
- Tubular and cribriform areas alongside solid and cord-like arrangements of tumor cell clusters.
- Apocrine secretion.
- Variable atypia, mostly low to moderate.
- Mitotic activity: low to moderate.
- The tumor cells express: CK7, GATA-3, and GCDFP-15.
- Variable expression of: S-100, EMA, CEA, estrogen, androgen, and progesterone receptors.
- Markers for extracutaneous tumors can be helpful to exclude metastases (e.g., CDX2, PSA).

Kazakov D, Argenyi ZB, Brenn T et al. Apocrine Carcinoma. WHO-classification of skin tumors. Lyon France: IRAC Press; 2018.
Terada T, Kamo M, Sugiura M. Apocrine carcinoma of the scrotum with extramammary Paget's disease. Int J Dermatol. 2013;52: 501-518. PMID: 23451826

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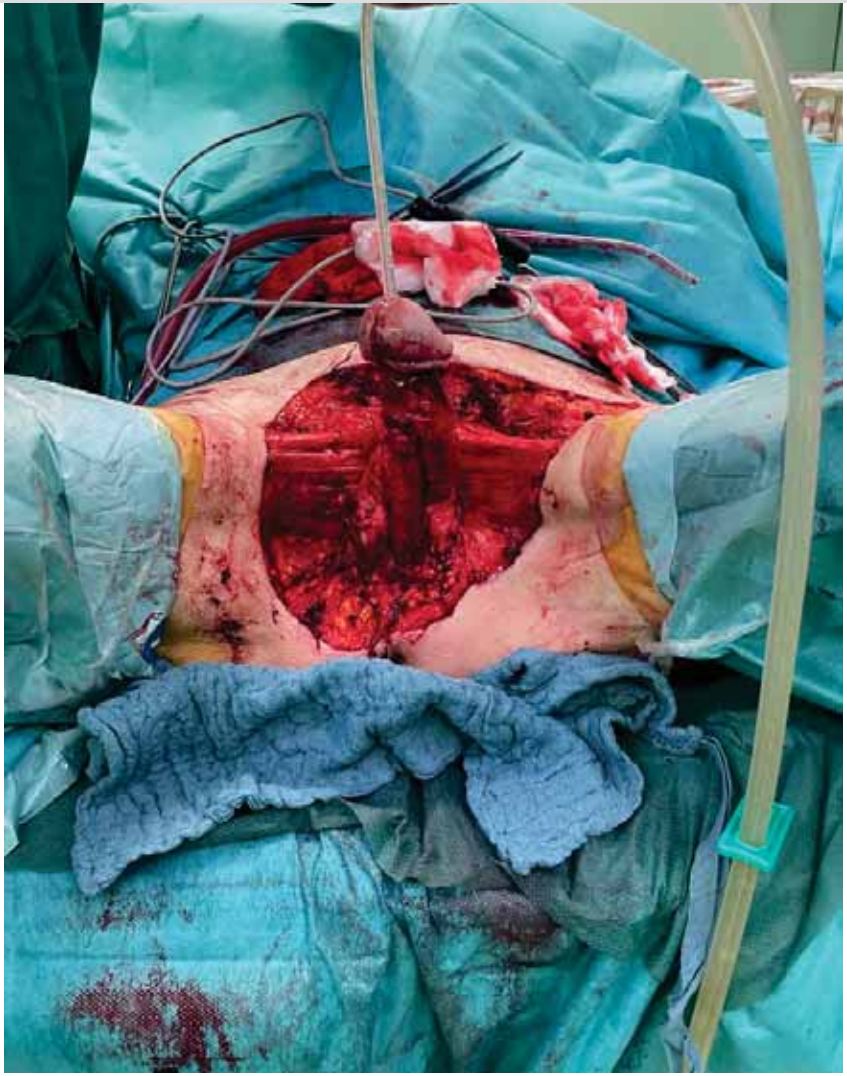
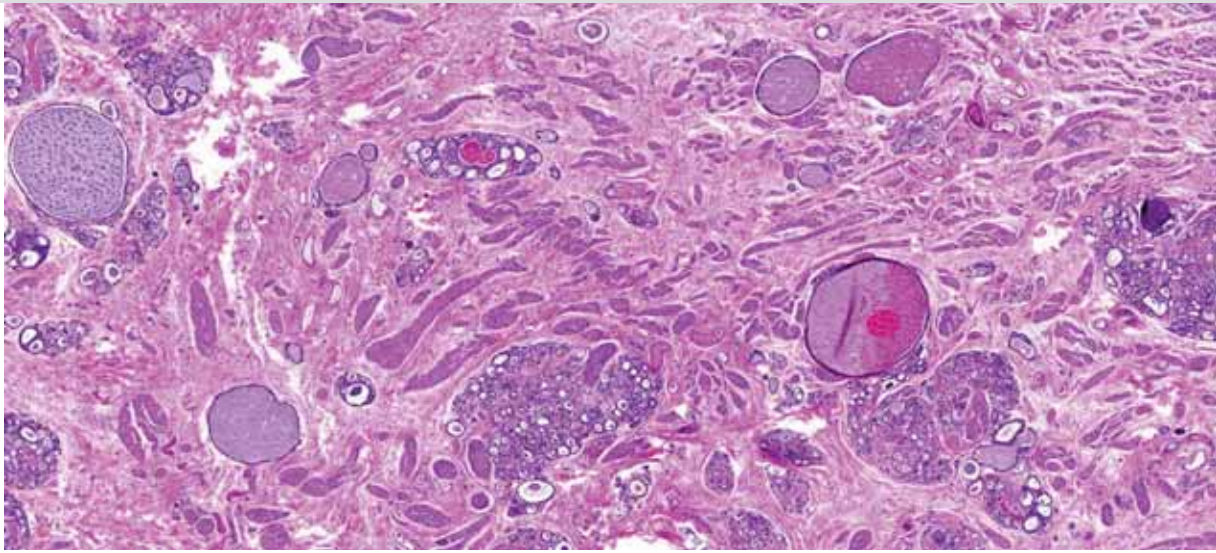
Apocrine carcinoma

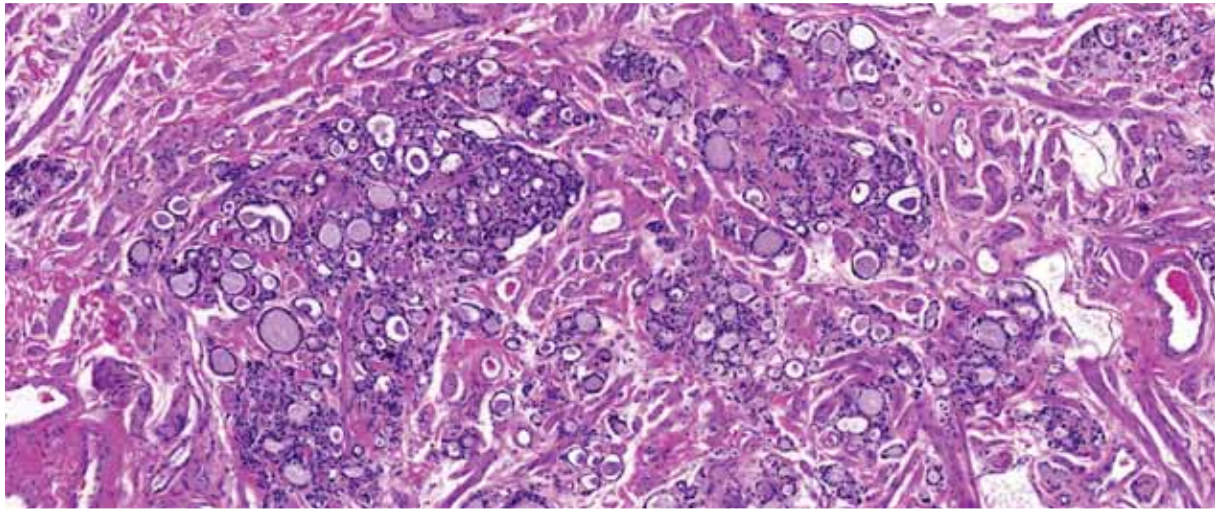
- Extremely rare tumor, most commonly affecting patients in the fifth to sixth decade of life.
- Occurs in areas with a high density of apocrine sweat glands, particularly the axillary region.
- Typically presents as a solitary nodule or as a multinodular lesion.
- Local recurrences occur in approximately 30% of cases, and lymph node metastases in about 40%. Visceral metastases are rare.
- Overall prognosis is unfavorable.
- Staging is required (to assess for metastases and to rule out other possible visceral tumors).
- Treatment: surgical excision, if feasible. Case reports exist on the use of radiation and chemotherapy.

Soe S-H, Shin D-H, Sung H-W. Apocrine carcinoma of the groin possibly associated with extramammary Paget's disease. Ann Dermatol. 2011;23: 519-521. PMID: 22148025
Furudate S, Fujimura T, Tsukada A et al. Successful treatment of advanced primary cutaneous apocrine carcinoma of the scrotum with systemic chemotherapy and radiotherapy followed by Denosumab. Case Report Oncol. 2017;10: 52-56. PMID: 28203164

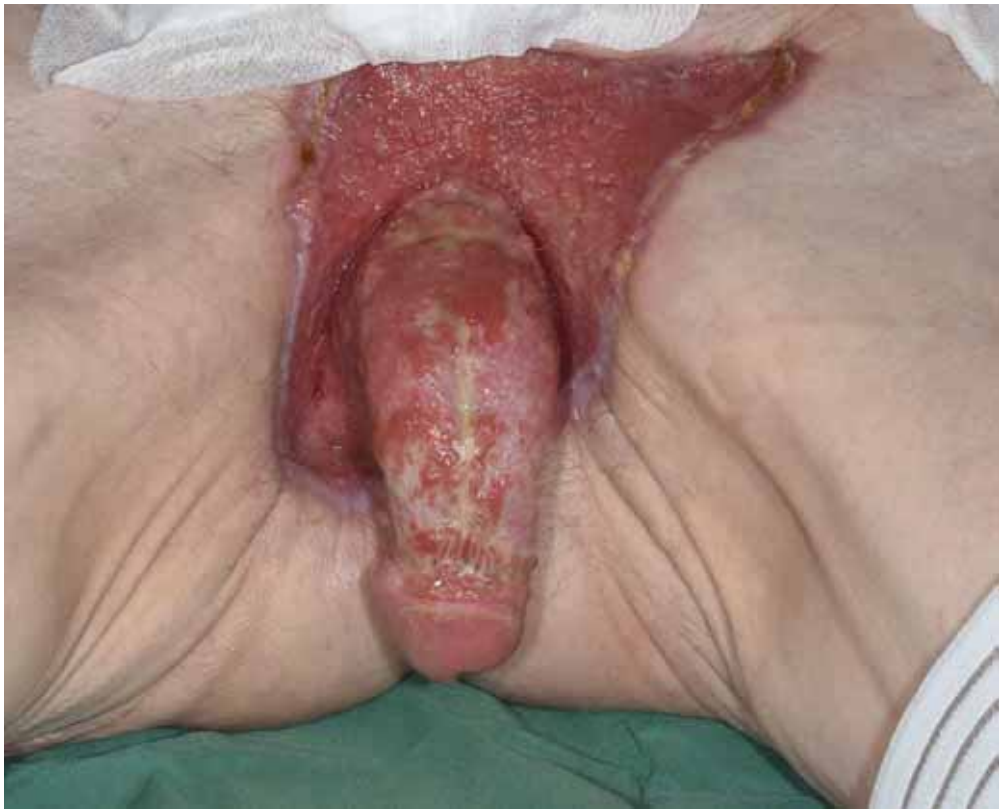
Surgical treatment: resection margins: R1





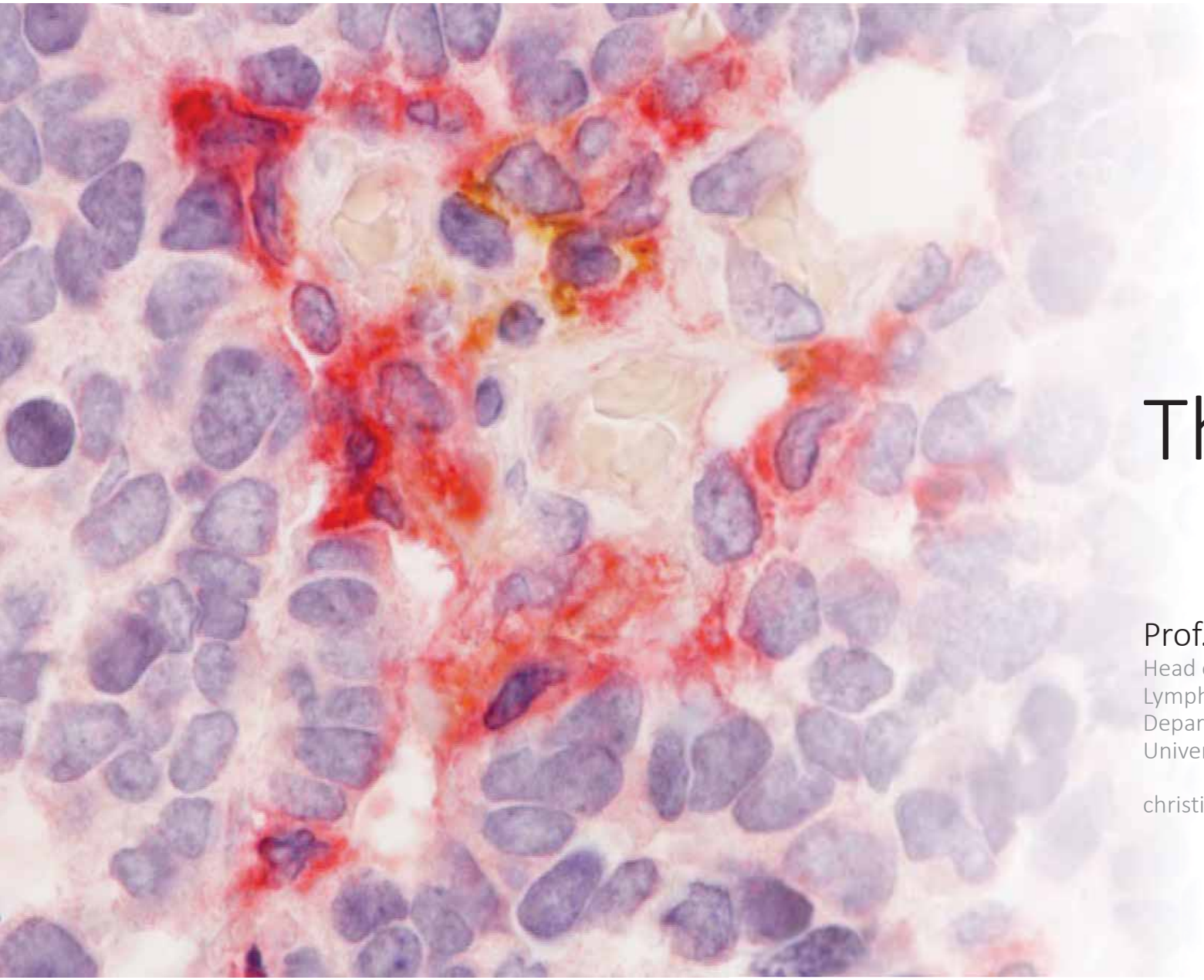


Final result



after granulation

after split-thickness skin graft



Thank you!

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