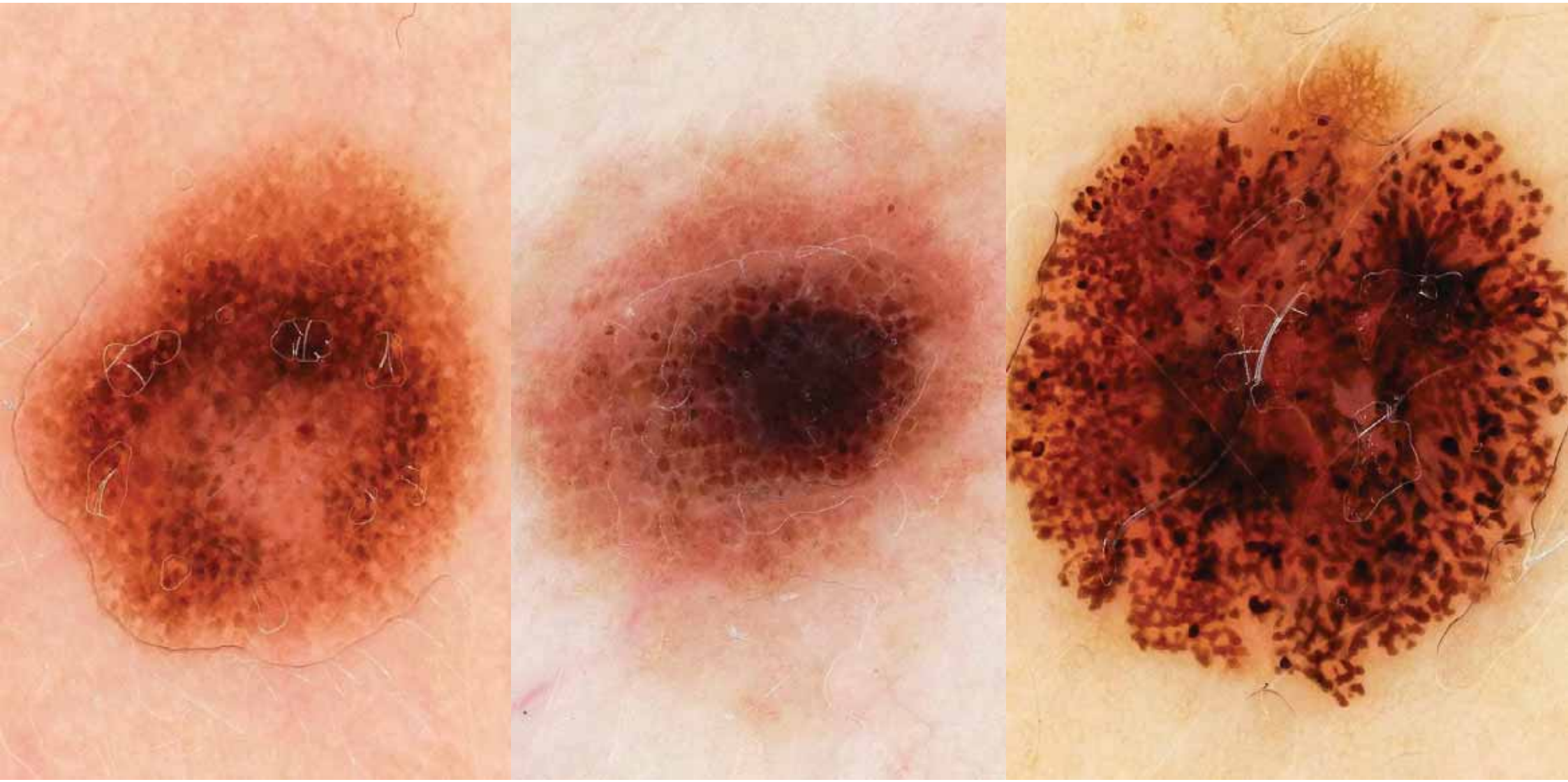
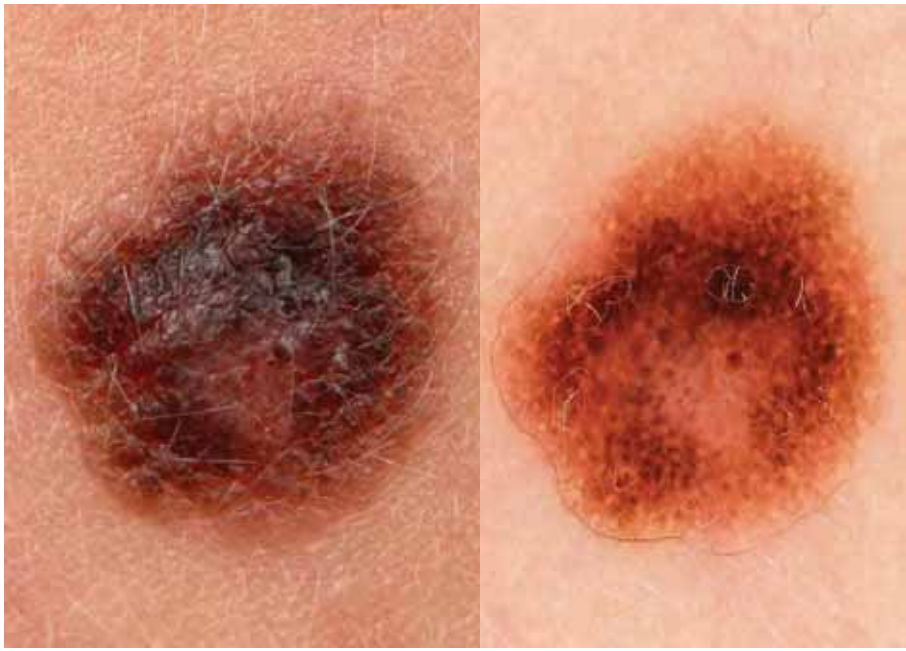

17th Summer Academy of Dermatopathology
Graz, June 30 – July 4, 2025
Clinicopathologic Conference



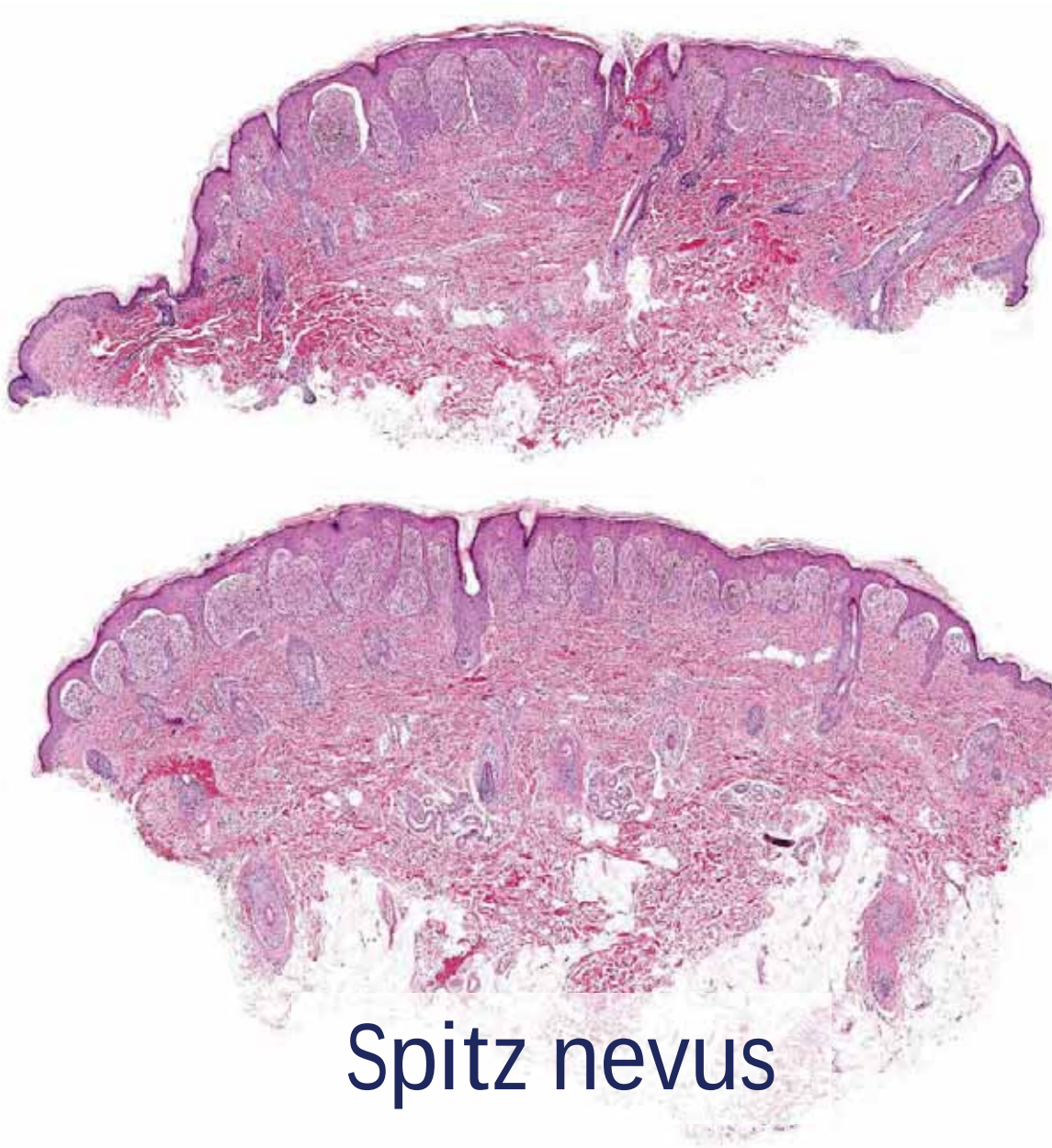
Globules

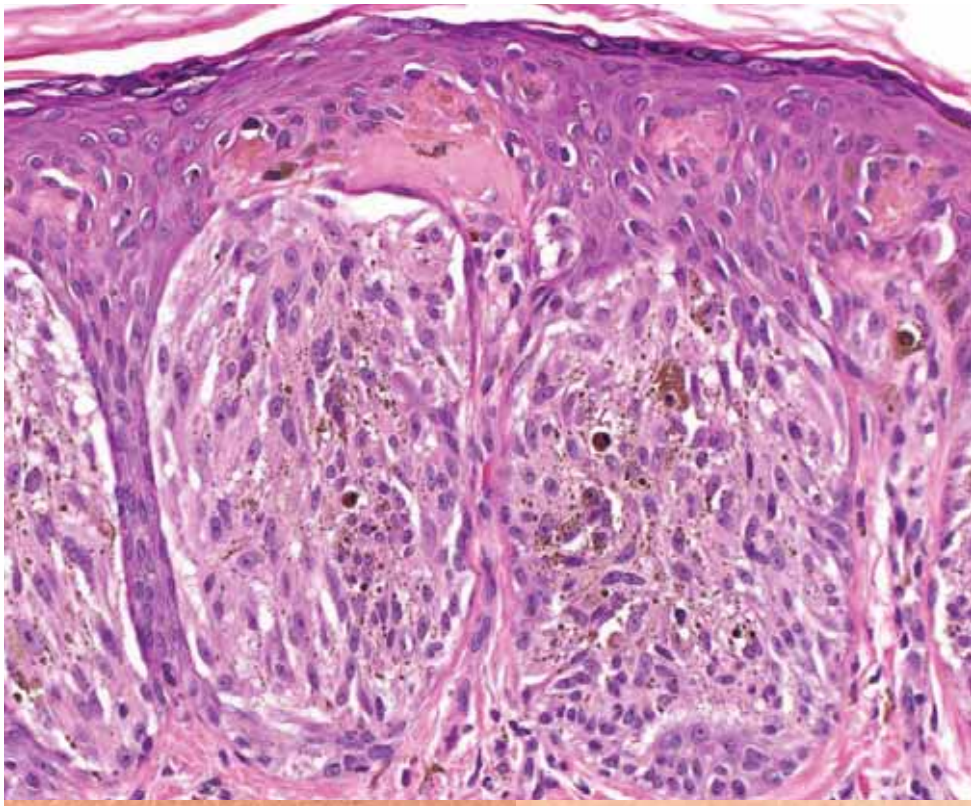


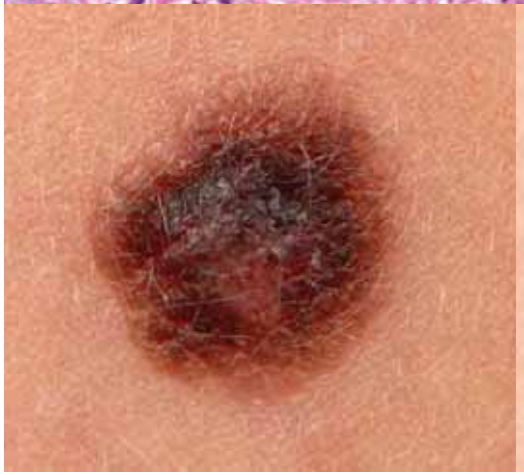
M, 7

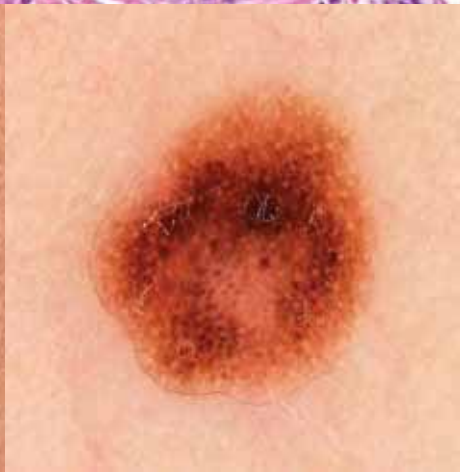
According to the parents pigmented lesion on the left cheek for approximately 1,5 years. At onset rapid growth.

The lesion is excised surgically.

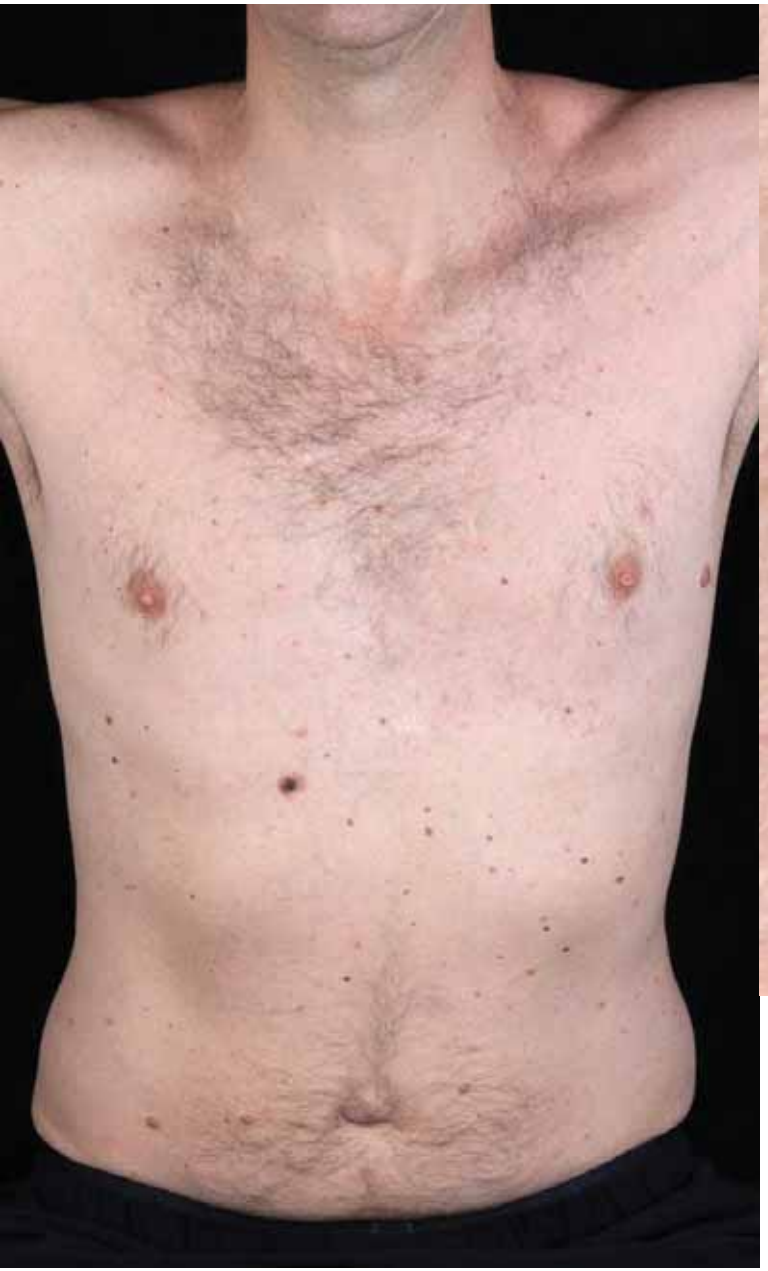


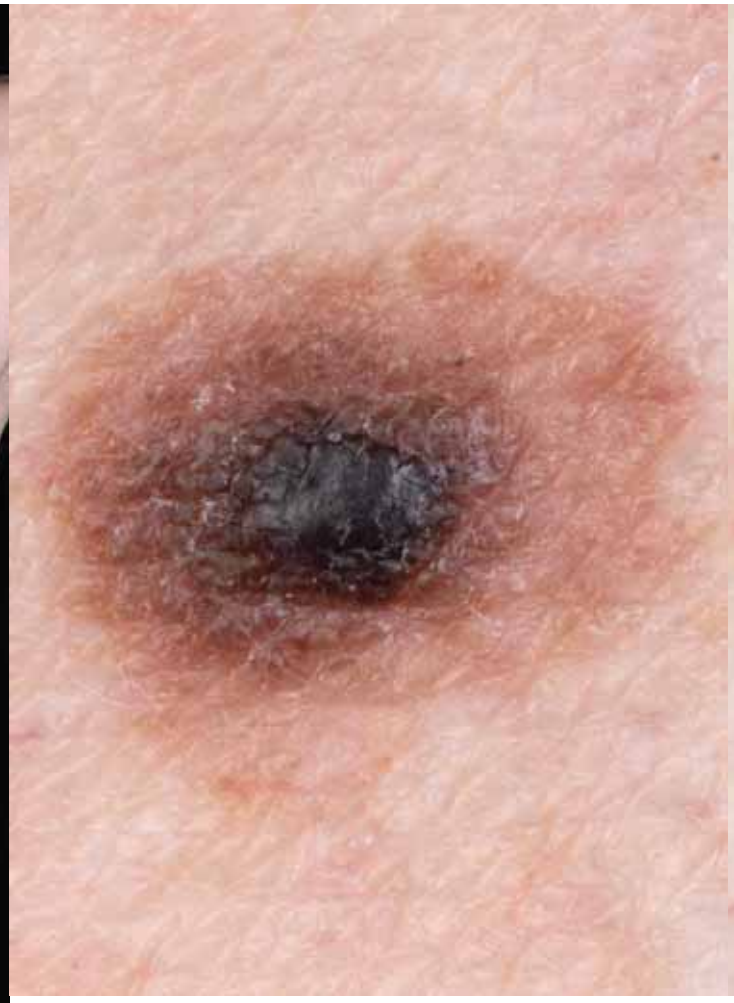


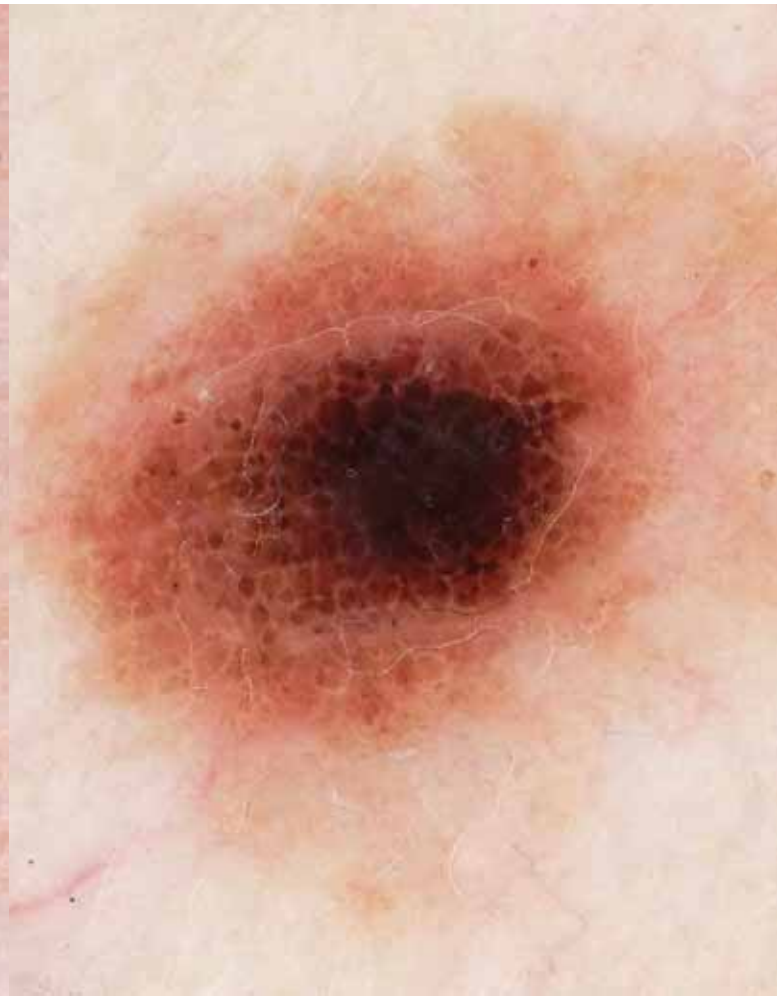




Spitz nevus



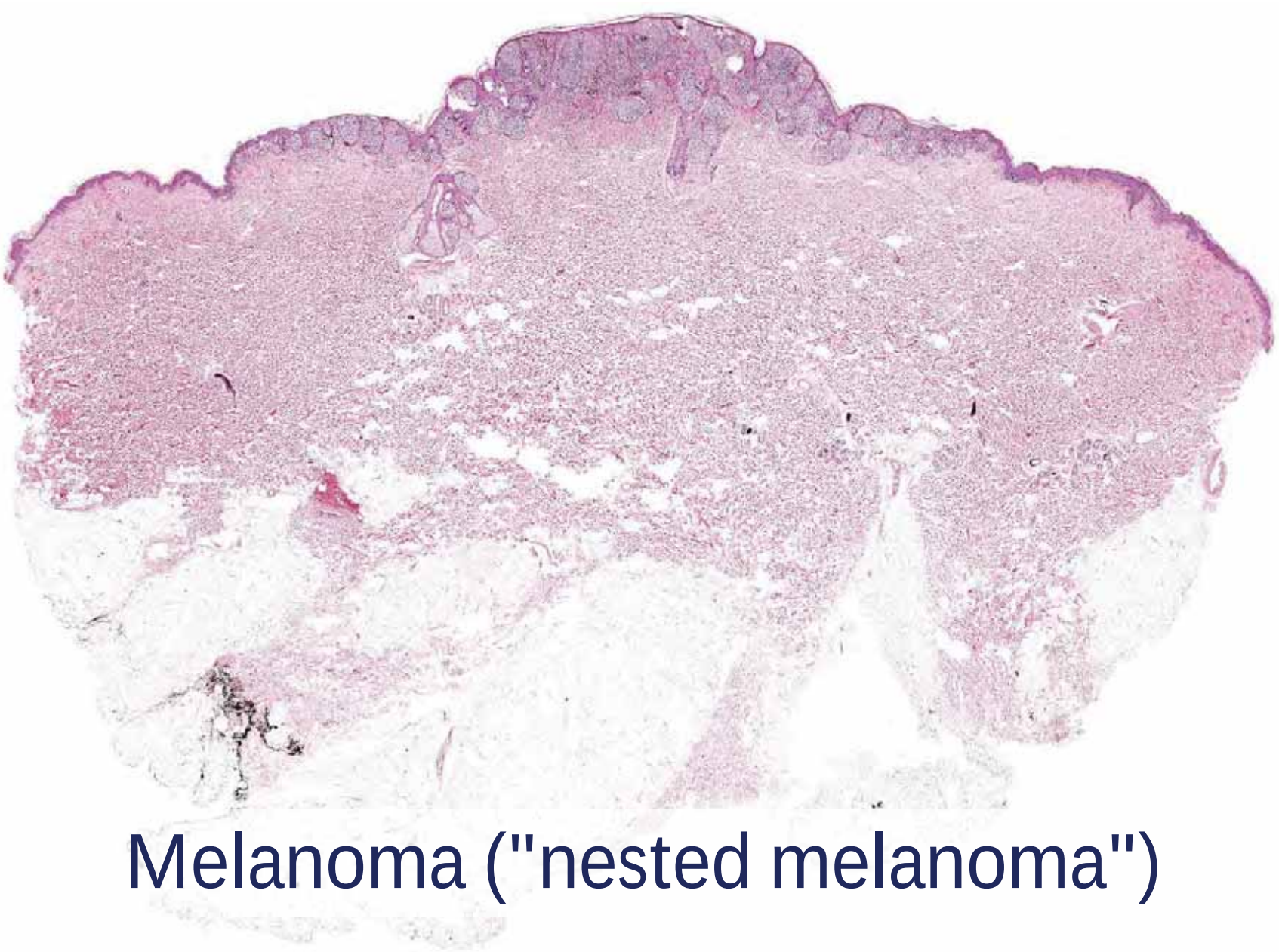


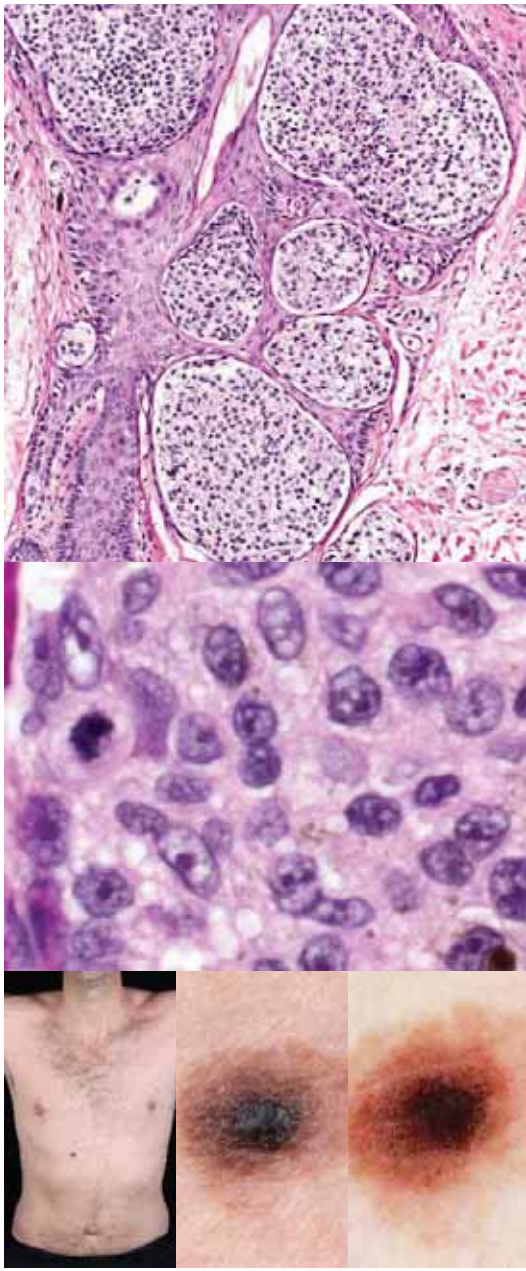


M, 45

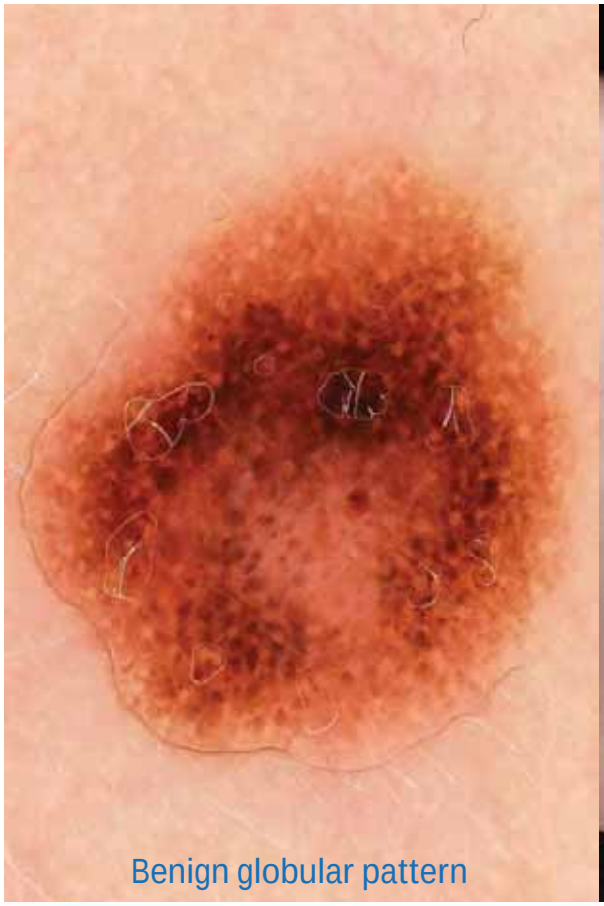
The patient is in regular control with the FotoFinder®. An abdominal lesion is growing compared to the last control (14 months previously).

The lesion is excised surgically.

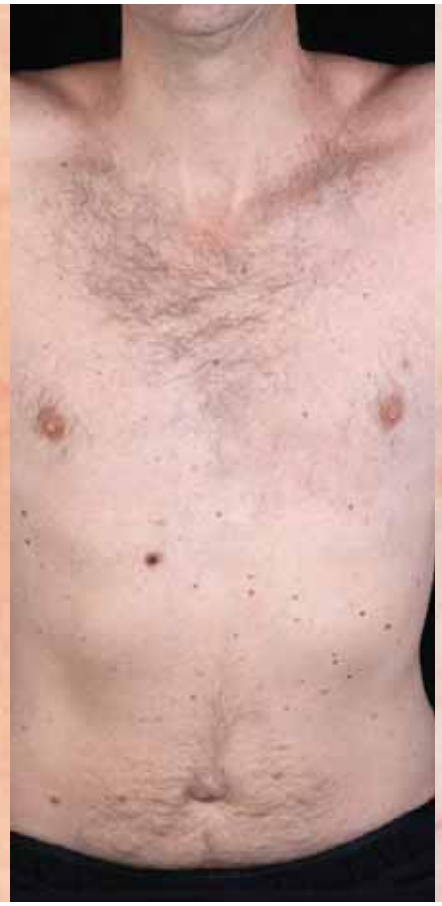


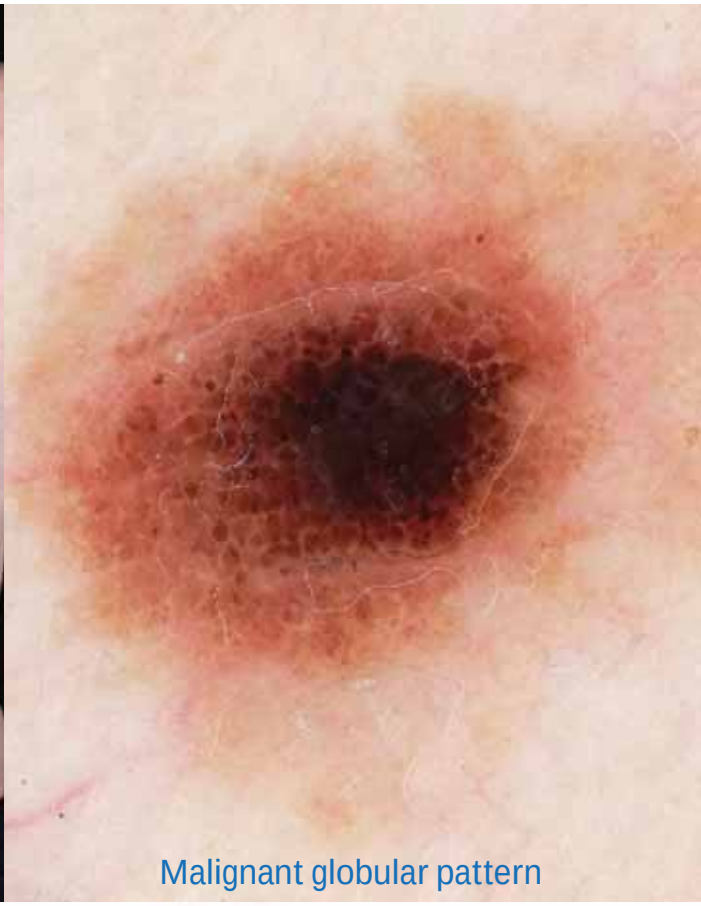


Melanoma ("nested melanoma")

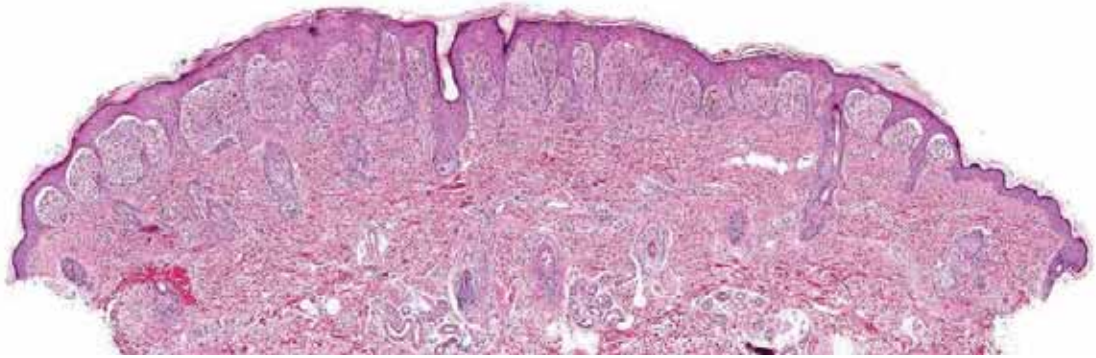


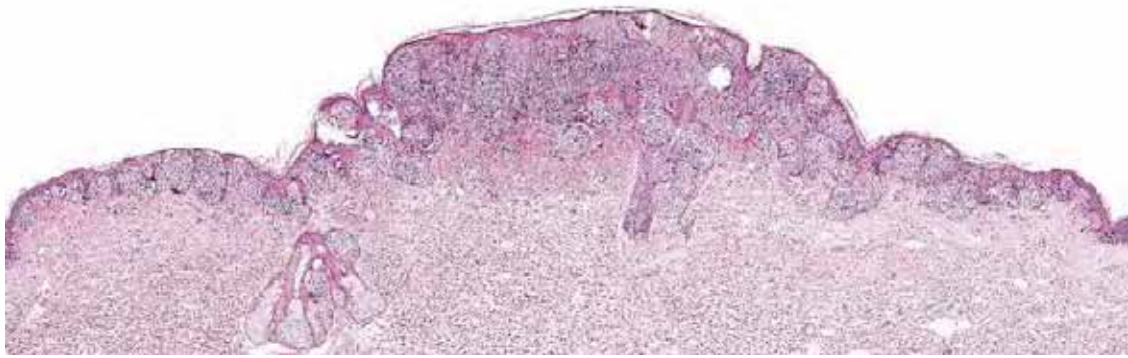
Benign globular pattern

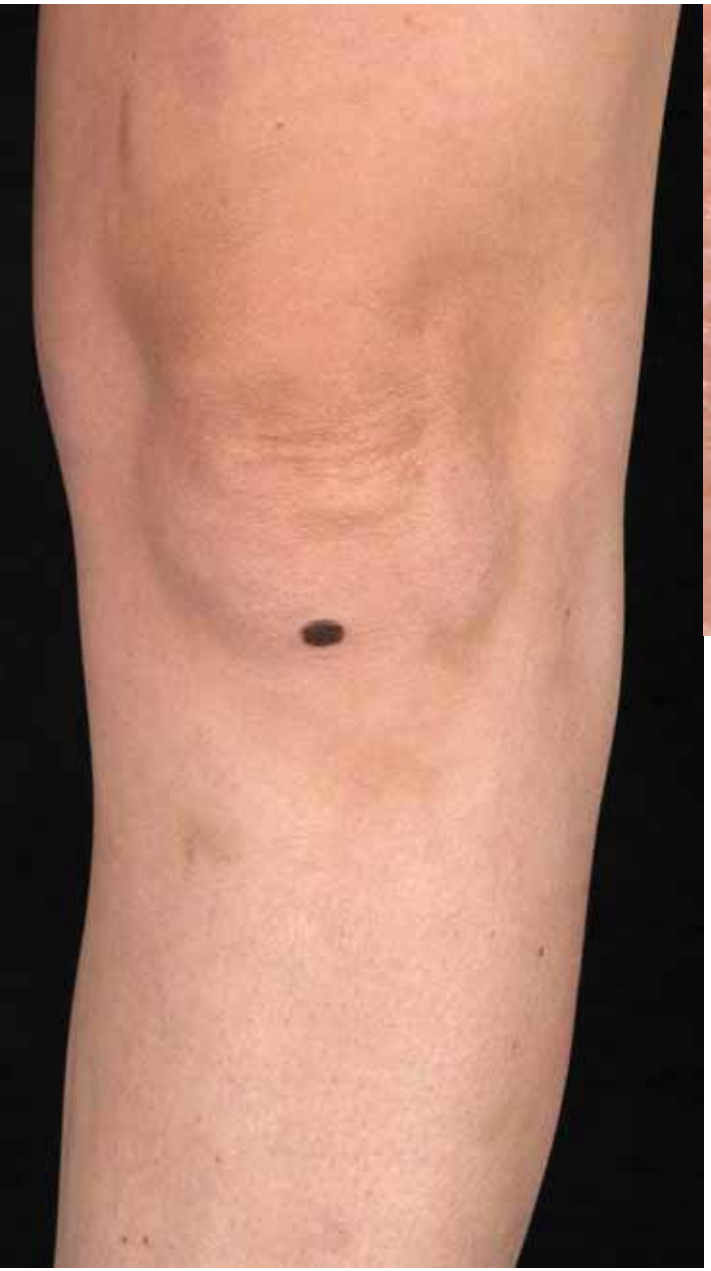


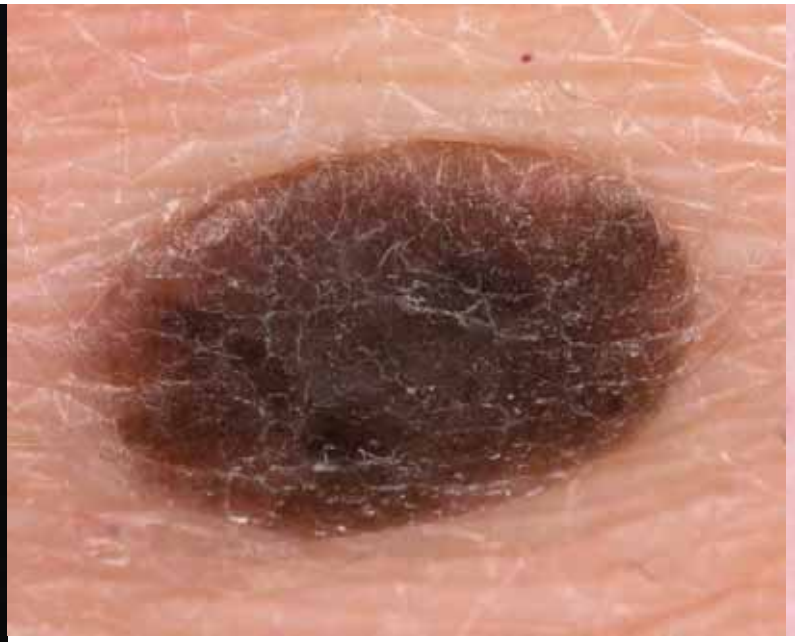


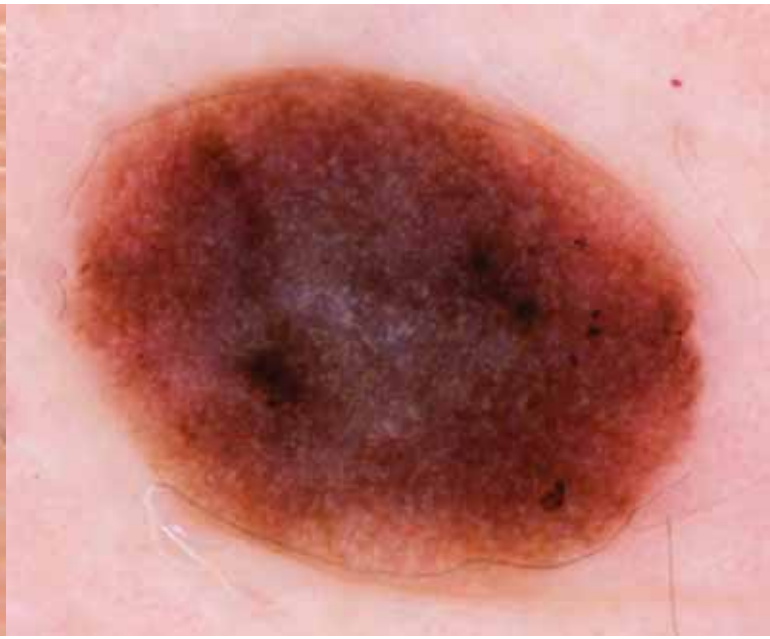
Malignant globular pattern





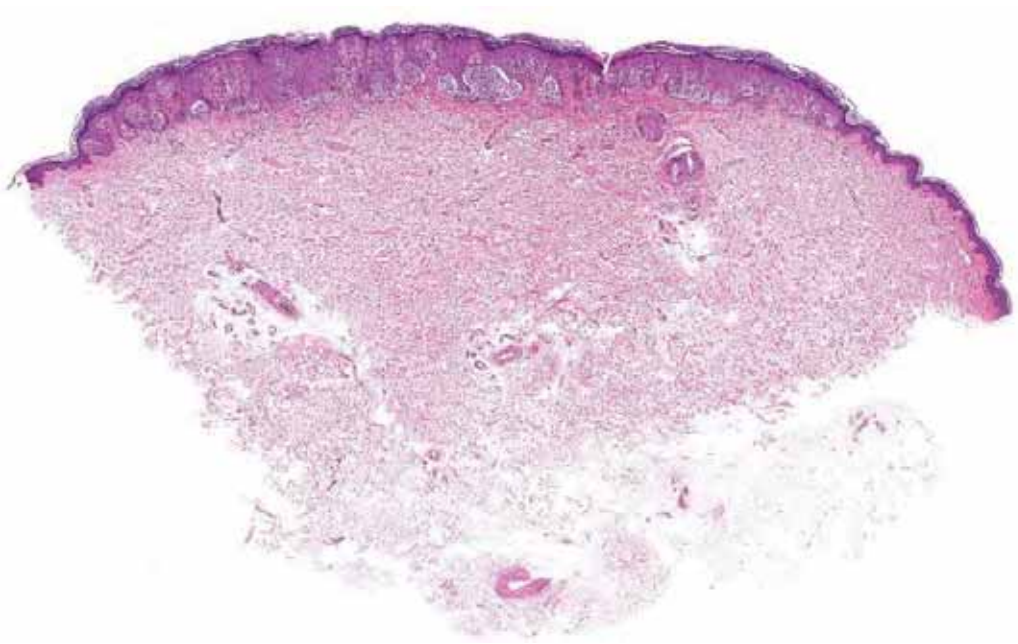


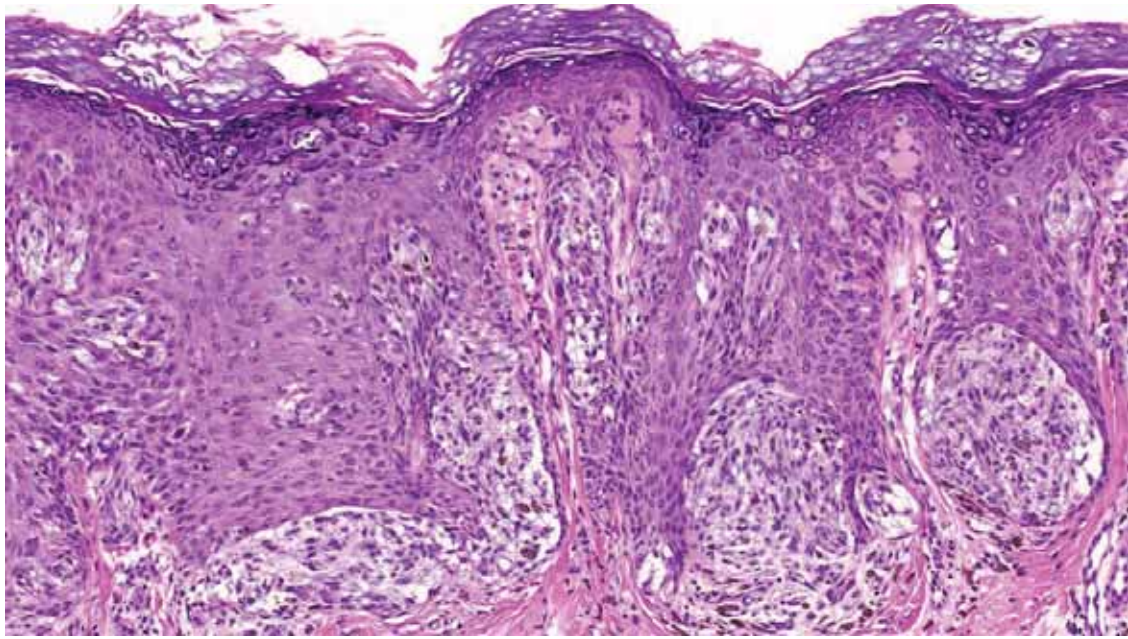




F, 34

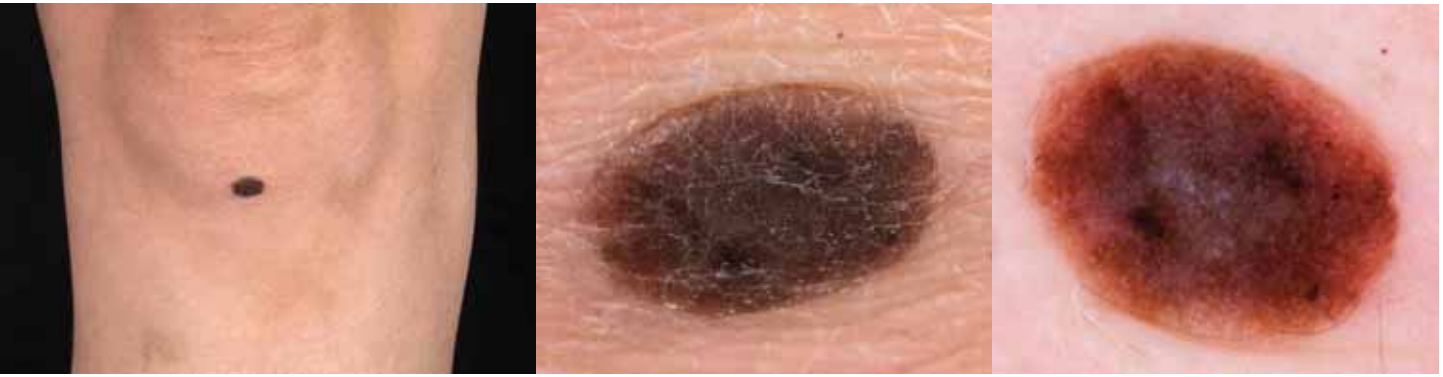
According to the patient pigmented lesion on the left knee, present and slowly growing for approximately 2 years.





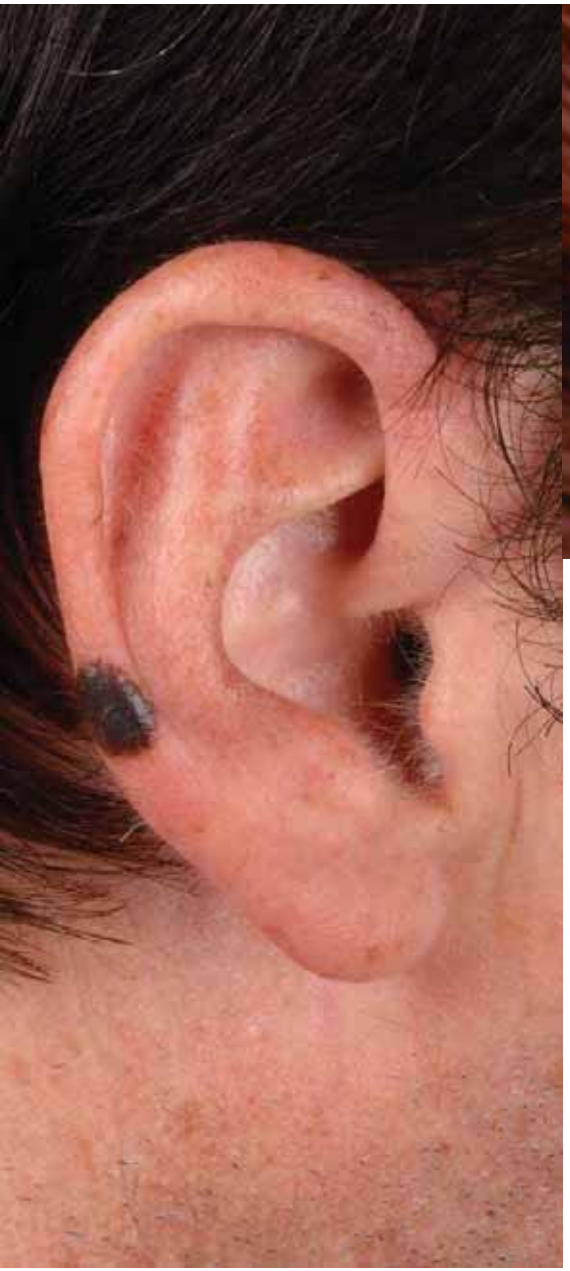
Spitz nevus

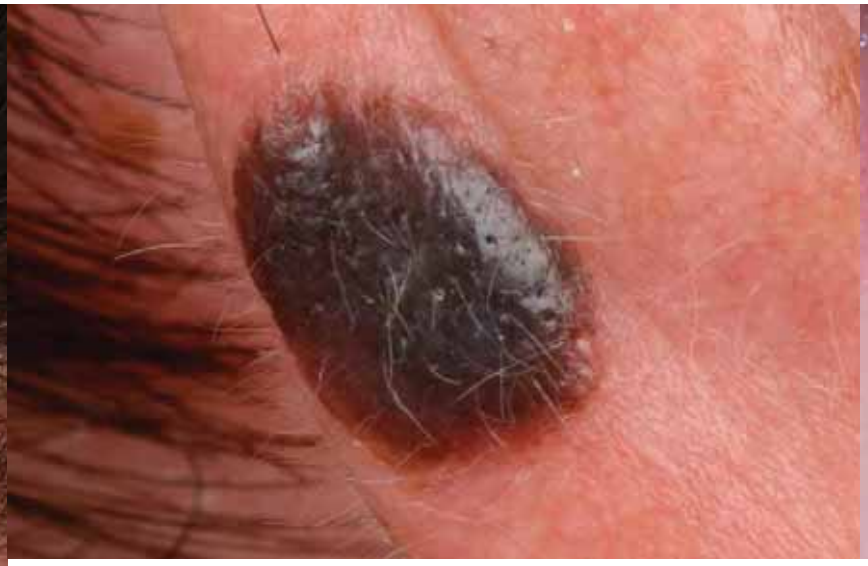
Over the last several years, the original concept of "Spitz nevus" has changed drastically (it was also not described as a "nevus" by Sophie Spitz, but as a juvenile melanoma). Personally, I retain the name "Spitz nevus" *histologically* for those lesions that are:

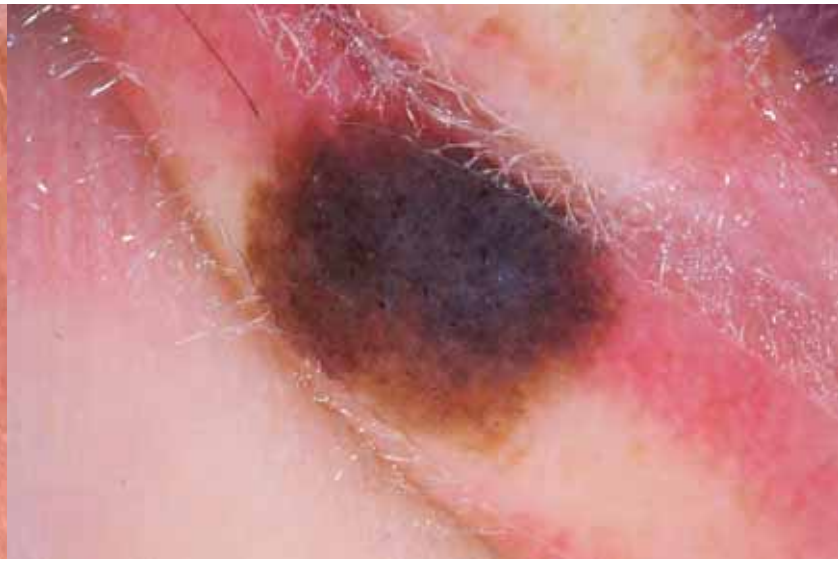


- *Dome shaped, symmetrical, well circumscribed, mainly junctional*
- *Composed predominantly of spindled and epithelioid melanocytes*

Mainly dermal, deeper tumors represent other "spitzoid" melanocytic tumors.

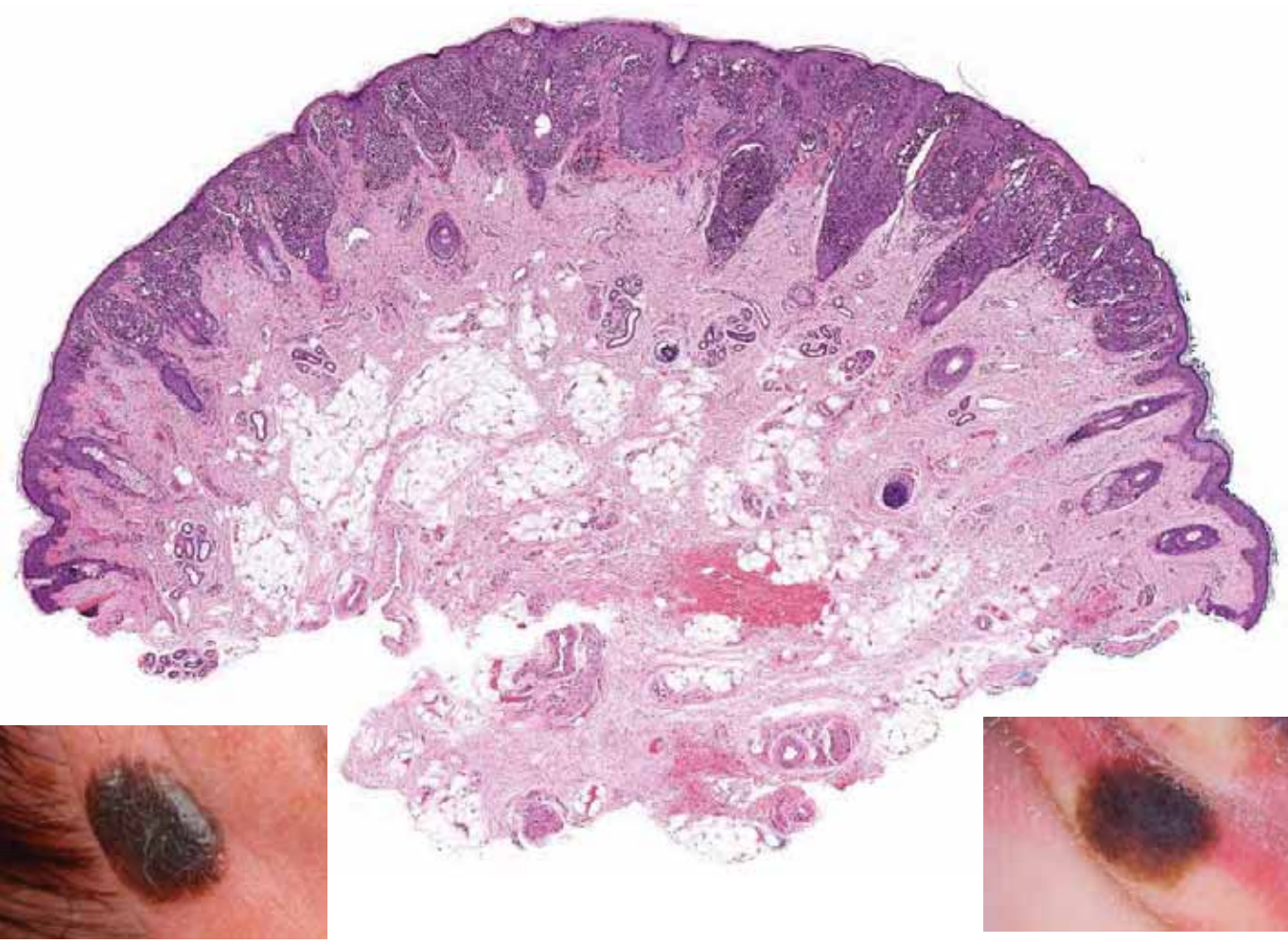


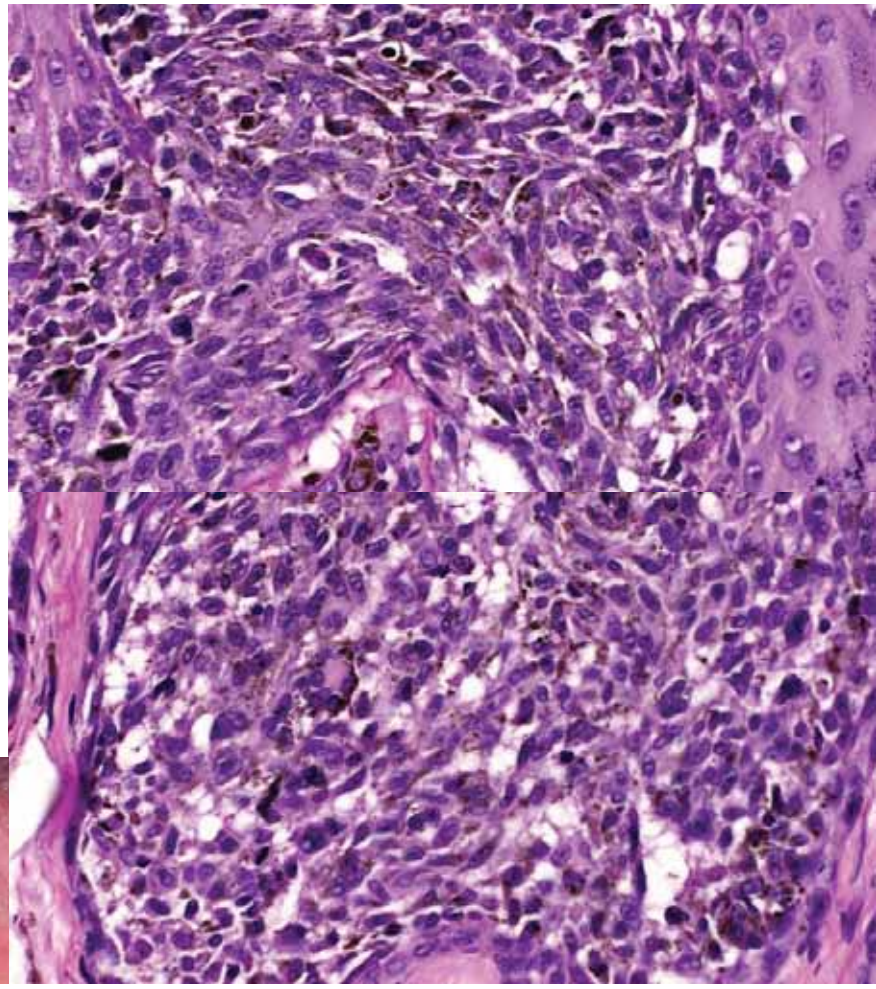




M, 50

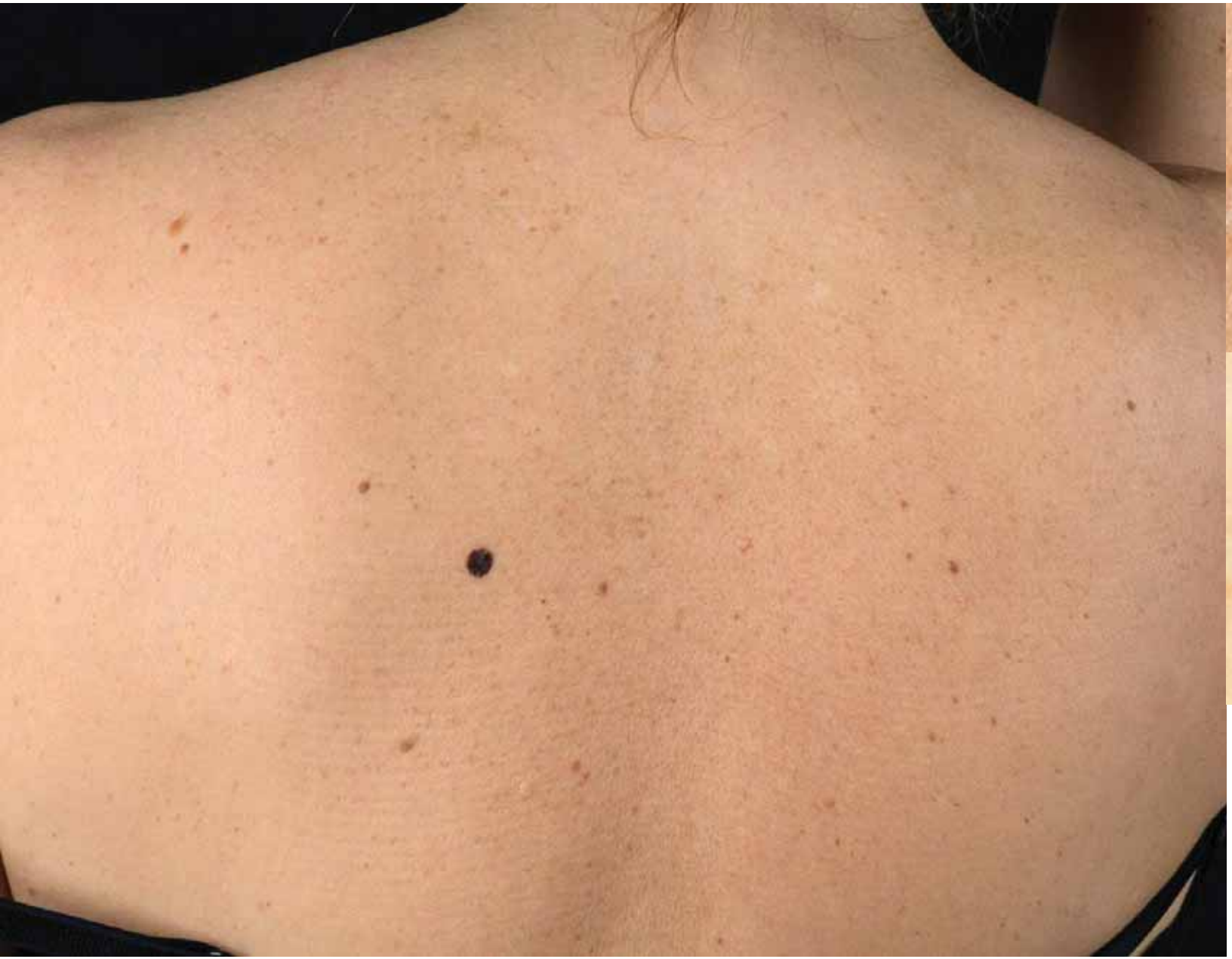
According to the patient pigmented lesion on the right ear of long-standing duration; in the last 6 months the lesion did change markedly.

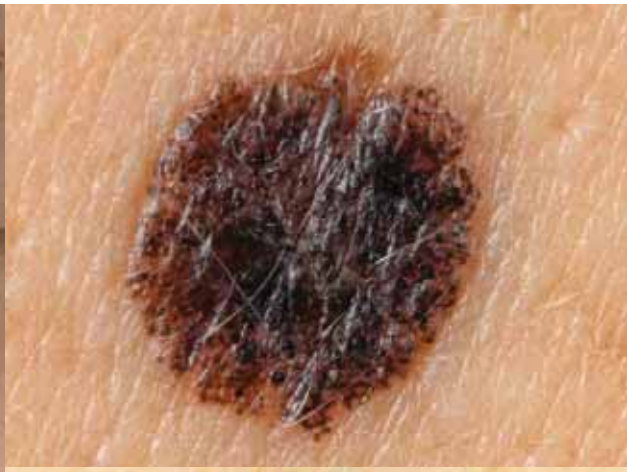


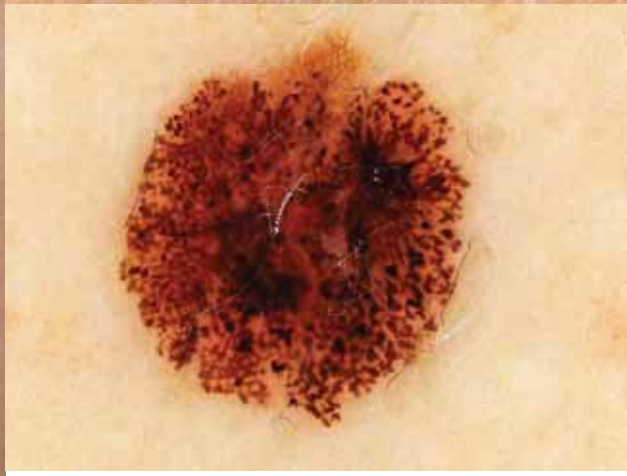


Melanoma *("nested melanoma")*

Main diagnostic features (in spite of overall symmetry and good circumscription): Very large, irregular nests; Many pigmented dendritic (rather than spindled) melanocytes; Rare mitoses; Sun-damage; Prominent involvement of adnexal structures; (History of recent change).



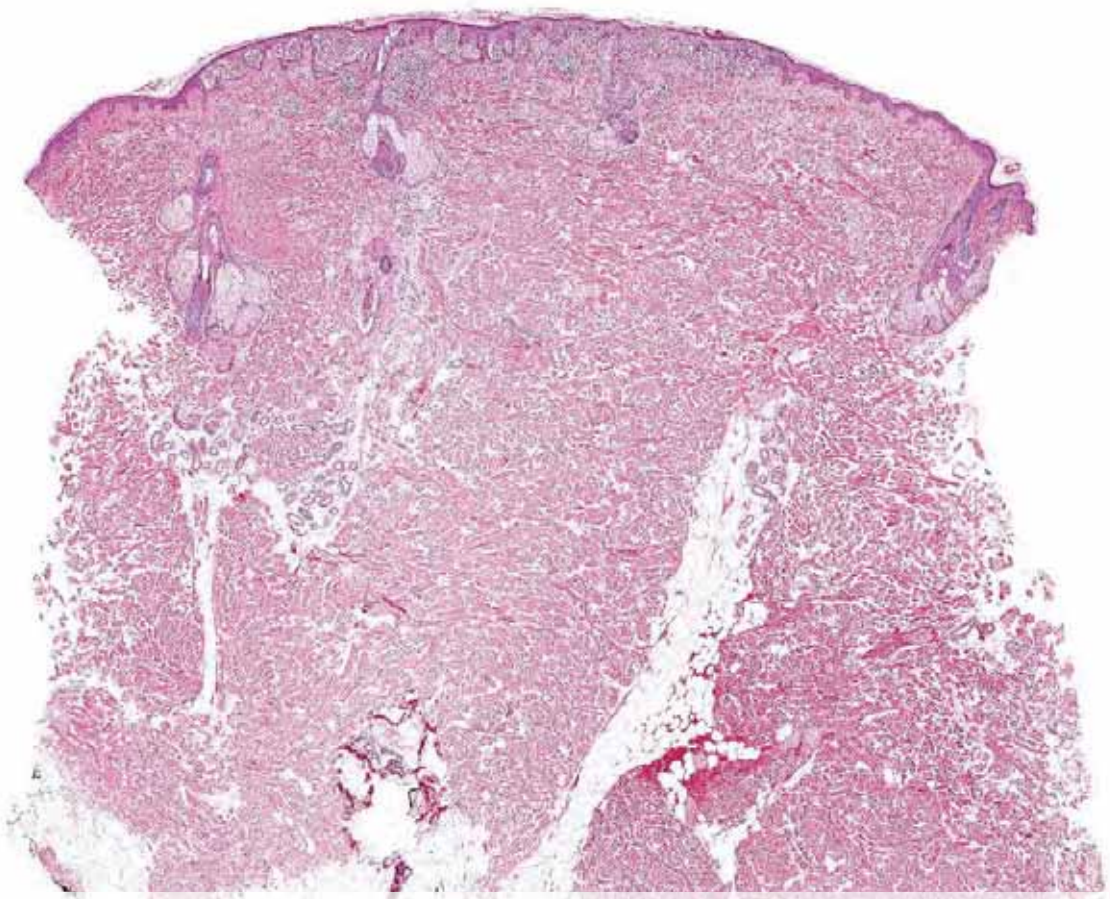


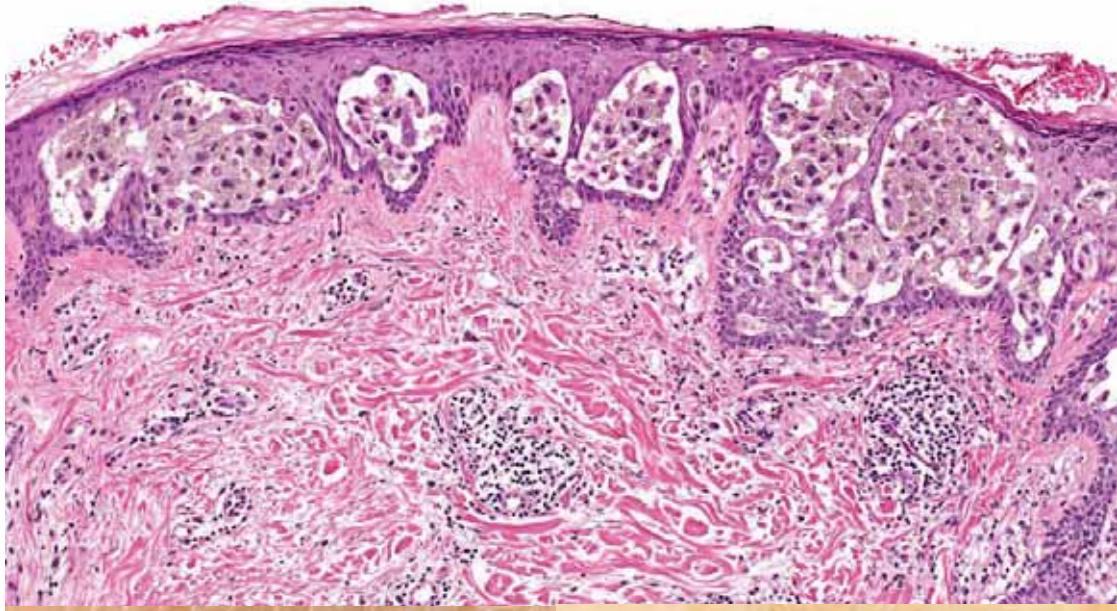


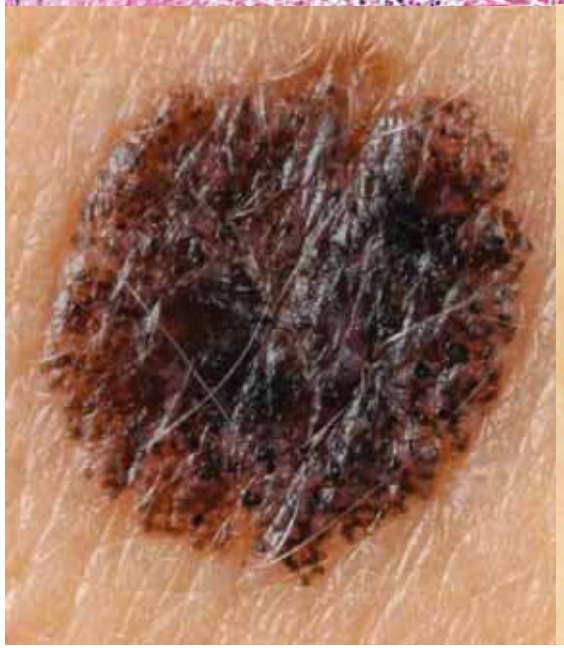
F, 41

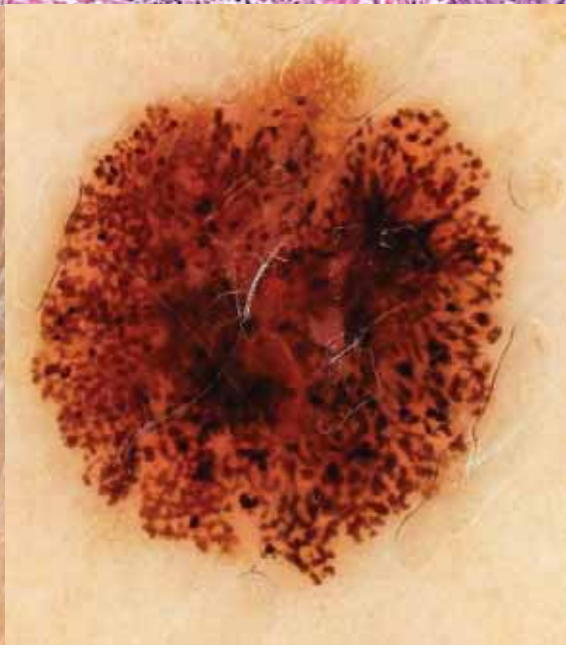
According to the patient recent onset of a pigmented lesion on the back (not noticed 3 years previously during a control by a private dermatologist).

A biopsy is taken.









"Nested" melanoma

with irregular globular pattern

and "pagetoid" (not "spitzoid") melanocytes

Case Report/Case Series

Dermoscopy and Confocal Microscopy of Nested Melanoma of the Elderly
Recognizing a Newly Defined Entity

Caterina Longo, MD; Iris Zalaudek, MD; Simonetta Piana, MD; Giovanni Pellacani, MD; Aimilios Lallas, MD; Camilla Reggiani, MD; Giuseppe Argenziano, MD

Editorial page 905

IMPORTANCE Nested melanoma of the elderly is a newly identified histopathologic variant of superficial spreading melanoma, characterized by intraepidermal large nests. However, the clinical, dermoscopic, and confocal aspects have been depicted only partially.

OBSERVATIONS In our cases series, nested melanoma was a flat, irregularly shaped lesion with variably pigmented and irregularly distributed globules on dermoscopic examination. Confocal microscopy revealed the presence of a "clod" pattern made of large compact nests with variable atypia. These findings correlated well with histopathologic features.

CONCLUSIONS AND RELEVANCE Nested melanoma of the elderly should be included in the differential diagnosis when a flat pigmented lesion, showing dermoscopically an irregular globular pattern, is seen in a patient older than 60 years.

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Nested melanoma of the elderly represents a distinct morphologic variant of superficial spreading melanoma, typified by the presence of large intraepidermal nests. Recently, specific histopathologic criteria of this melanoma subtype have been identified, allowing its differentiation from conventional superficial spreading melanoma.[1,2] However, the clinical, dermoscopic, and confocal features of this newly identified histopathologic entity have been depicted only partially. In this case series, we aimed to describe the distinctive dermoscopic and confocal features of nested melanoma of the elderly to guide clinicians in recognizing this melanoma subtype.

Report of Cases

Case 1

A 65-year-old woman with a history of melanoma was referred for her periodic skin examination. A suspicious pigmented lesion was noticed on her back. Clinically, the lesion differed from the neighboring nevi because of the large size (1.4 cm) and irregular shape and color. Dermoscopically, the lesion was asymmetric and characterized by a prevalent globular pattern with pigmented globules varying in size and color (**Figure 1**).

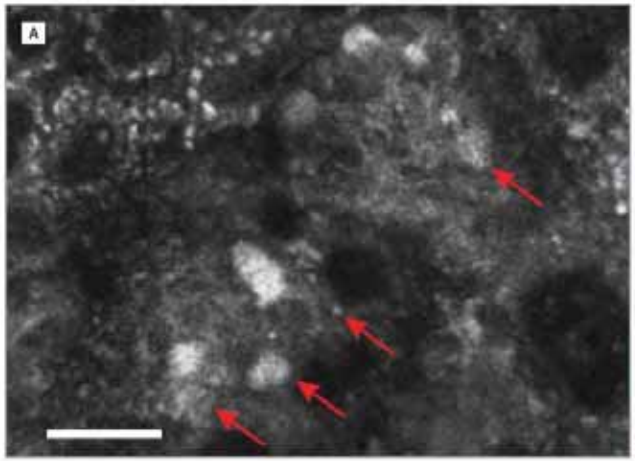
Confocal microscopy revealed the presence of a predominant "clod" pattern at the dermoepidermal junction. The clod pattern was made by large and compact dense nests that filled the interpapillary space while distorting and enlarging it (**Figure 2**). On close examination, cytologic atypia was found within the nests (**Figure 3**).

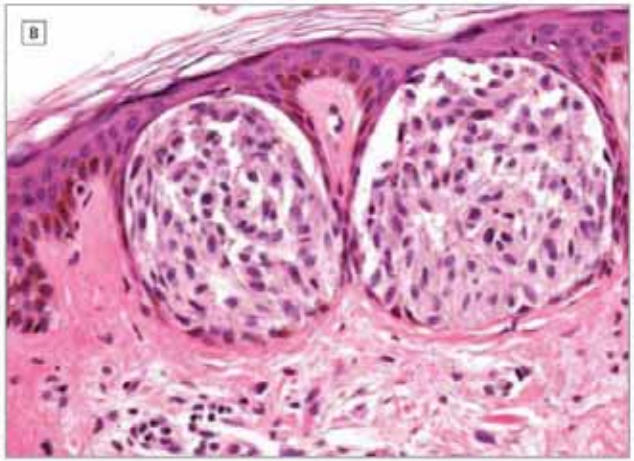
The lesion was excised and subsequent histopathologic examination revealed a junctional melanocytic proliferation with a predominant nested pattern. This was typified by striking, mostly roundish nests of regular size and shape along the dermoepidermal junction. Cytologic atypia within the nests also was evident, together with a minor single cell growth pattern and focal epidermotropism. With the combined clinical, dermoscopic, confocal, and histopathologic features, a final diagnosis of melanoma in situ was made.

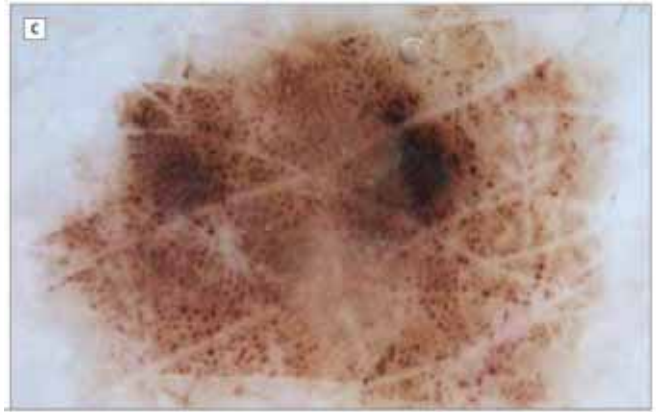
Case 2

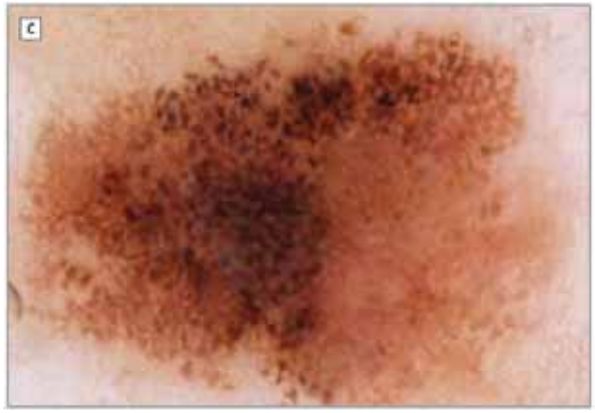
A 70-year-old woman sought consultation for the presence of a solitary growing lesion on her right calf. Clinically, the variegated lesion was 2.5 × 2 cm (**Figure 4**).

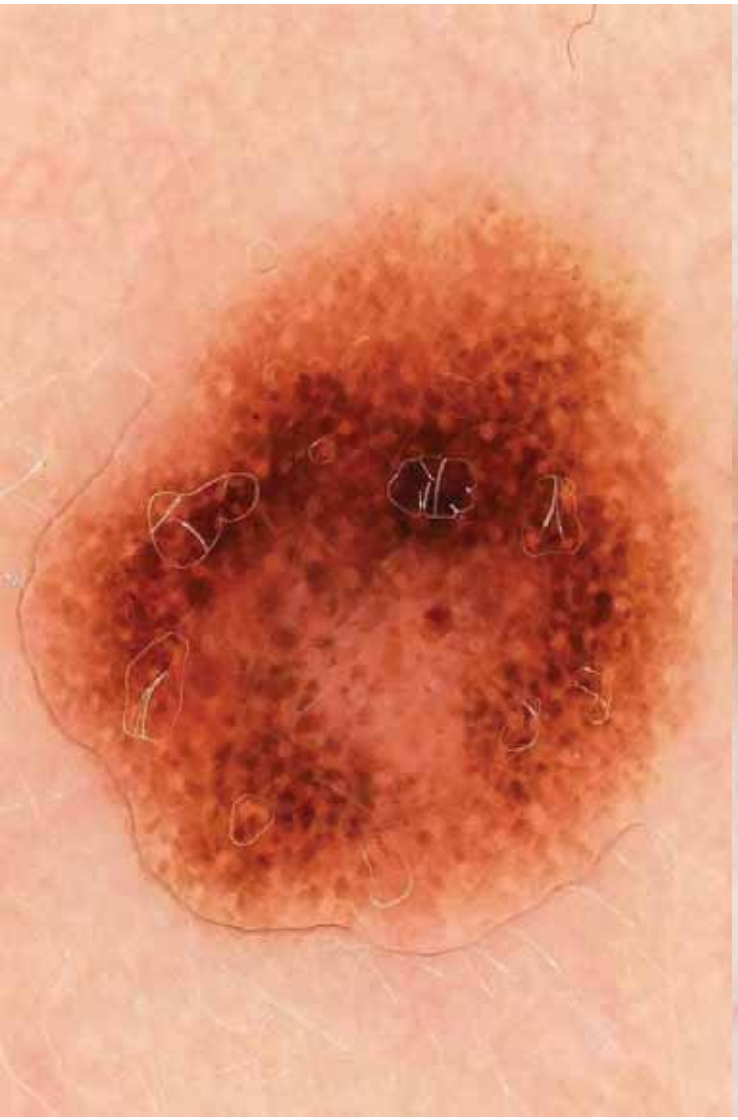
Dermoscopically, the pattern was predominantly globular, with pigmented globules showing striking variation for color and distribution within the lesion. On confocal microscopy, the lesion exhibited a prevalent clod pattern with large nests. Pagetoid spread was focally present along with cytologic atypia at the dermoepidermal junction (**Figure 5**). Histopathologic examination revealed an early invasive melanoma (Breslow thickness of 0.4 mm) with a striking nested pattern of growth. The nests were composed of monomorphous, small, pigmented cells alternating with occasional single atypical, larger melanocytes.



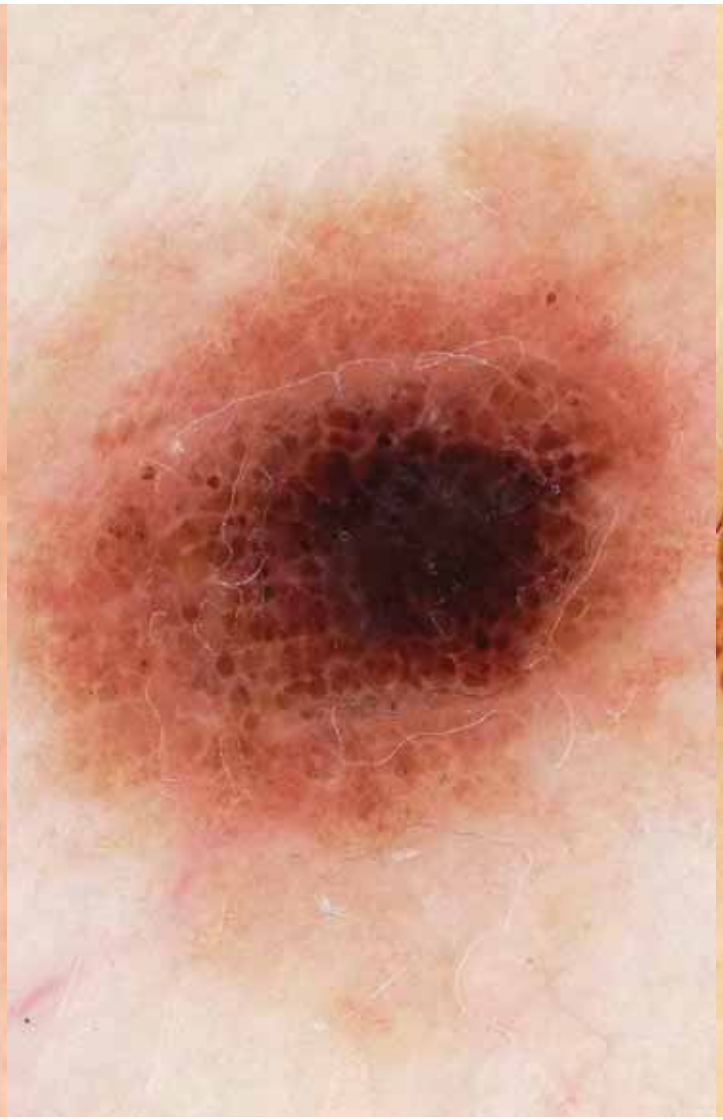




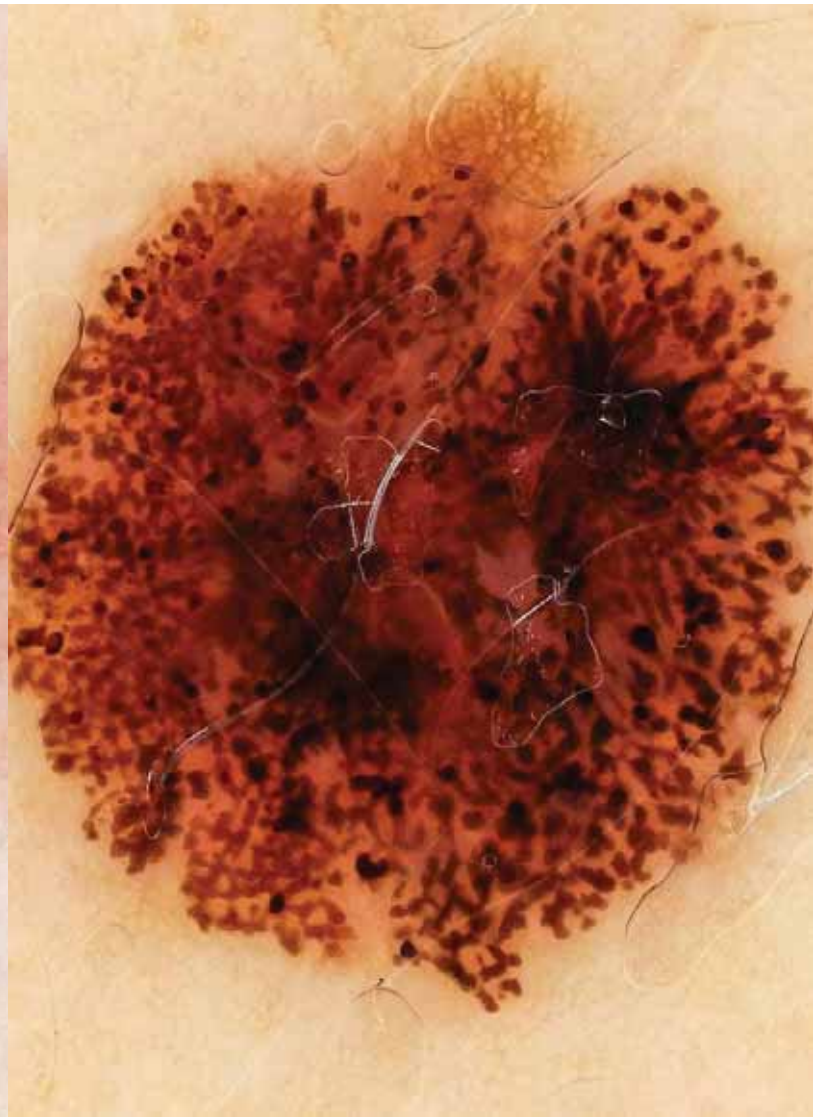




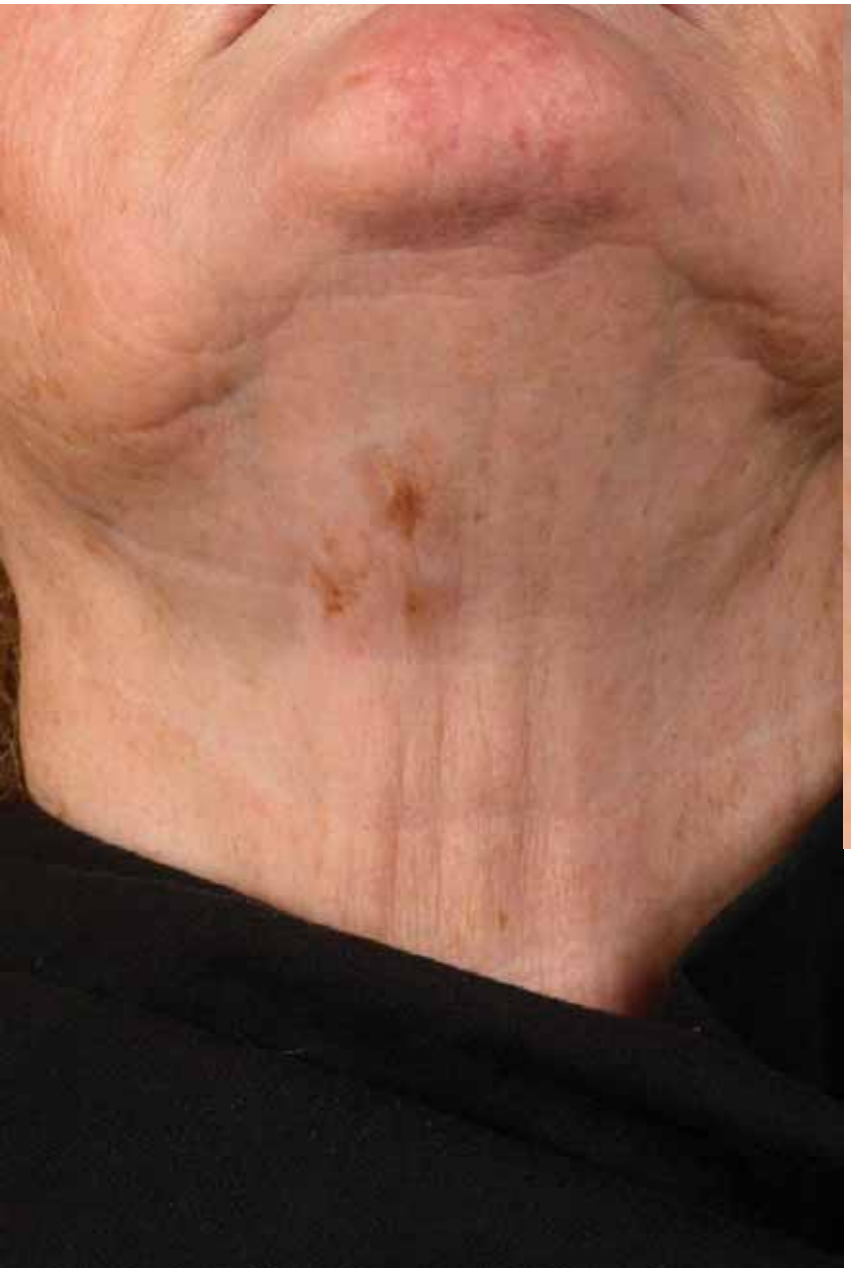
Spitz nevus

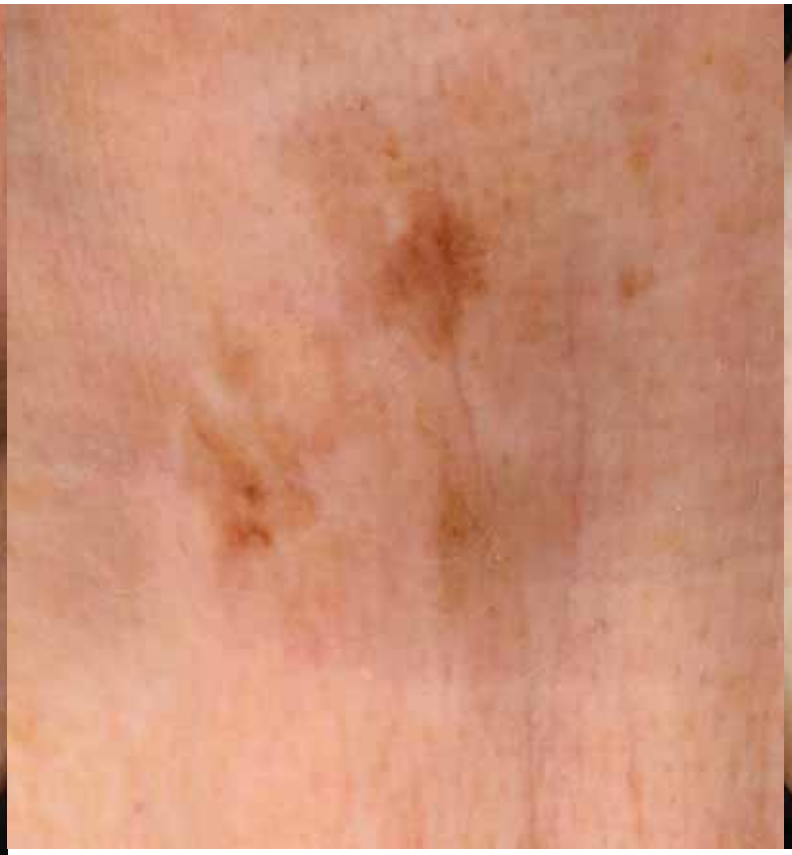


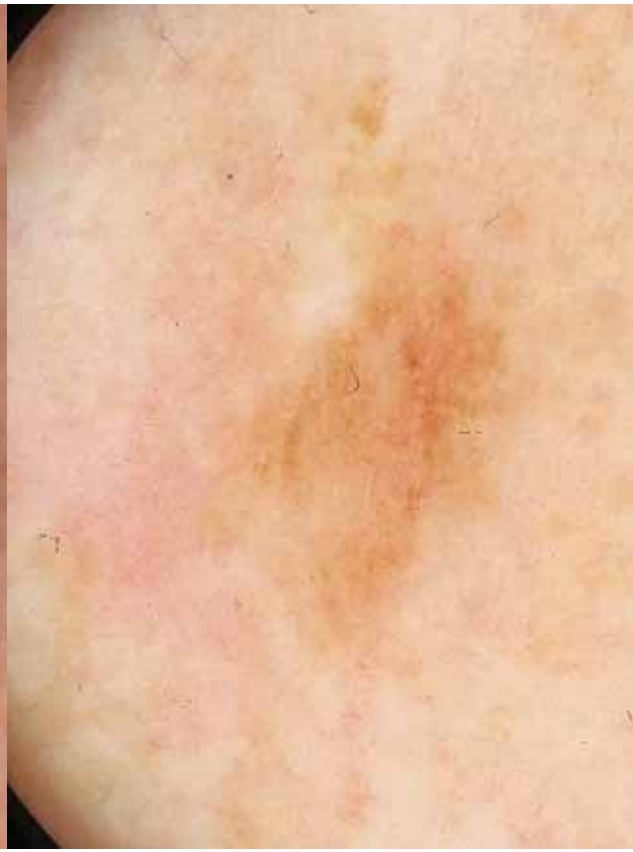
Melanoma



Melanoma



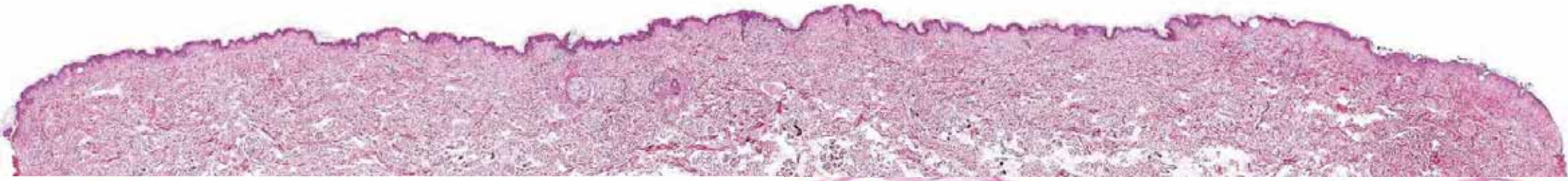


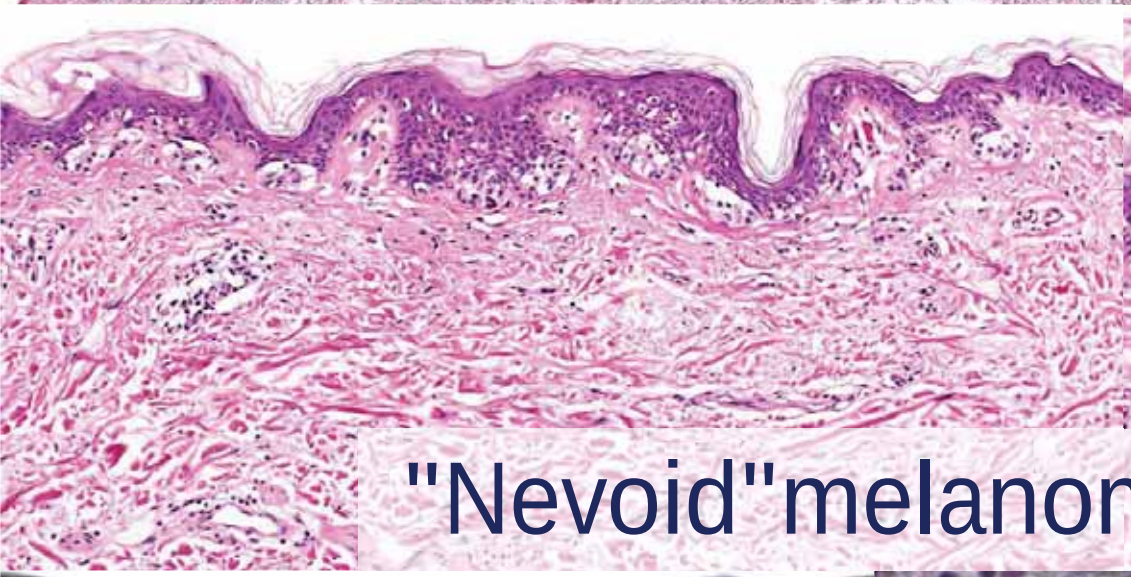


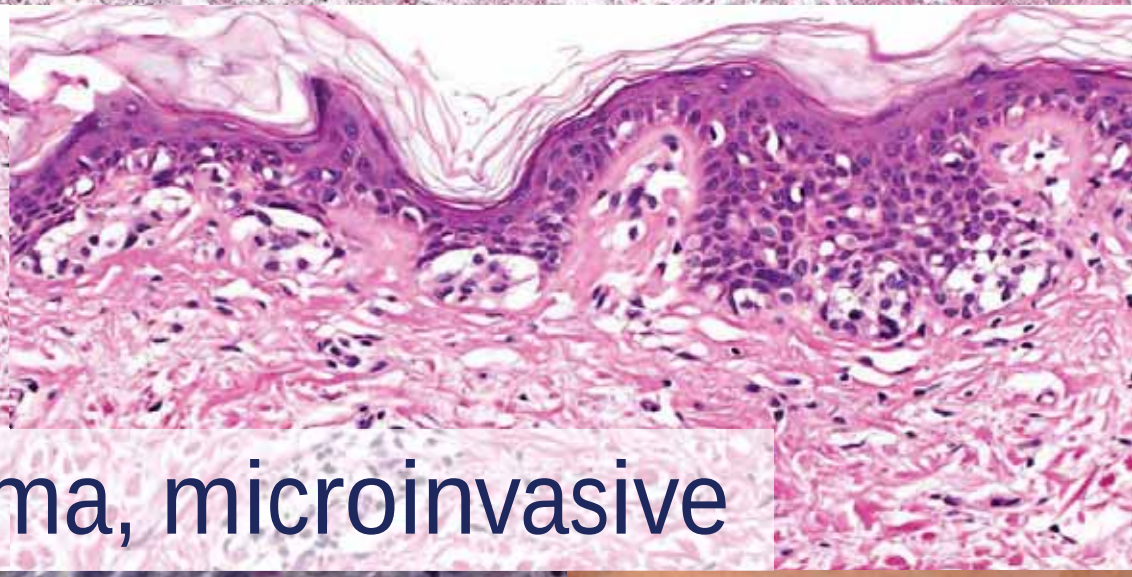
F, 79

Previous shaving biopsy from the anterior part of the neck diagnosed as melanoma in situ. Sent by a private dermatologist for further management.

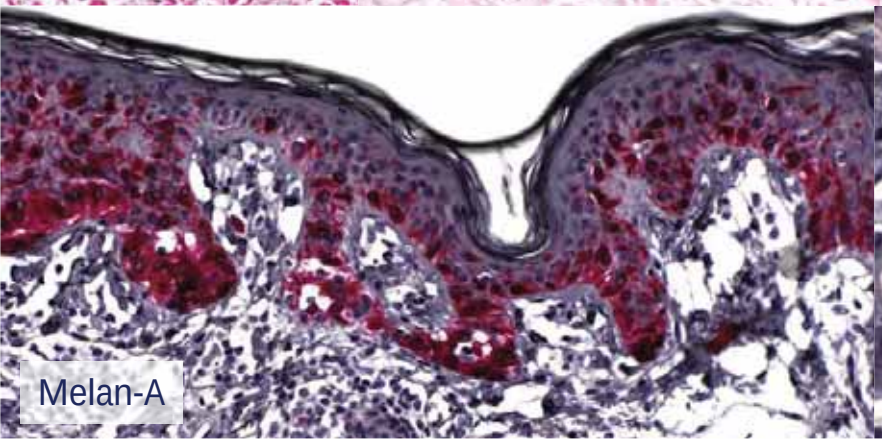
The lesion is excised surgically.

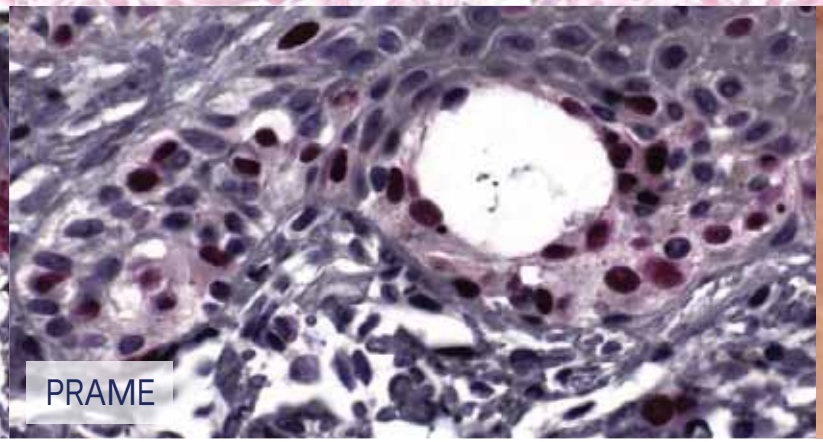


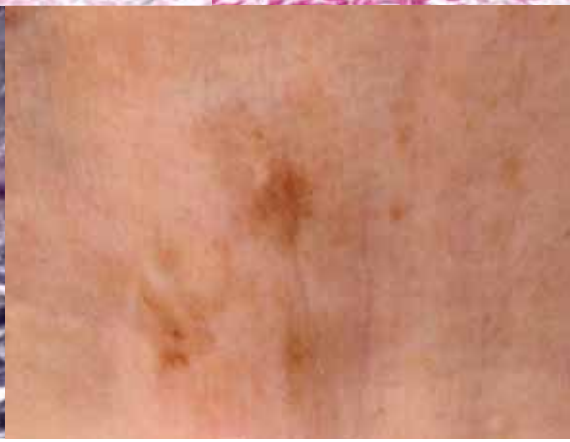


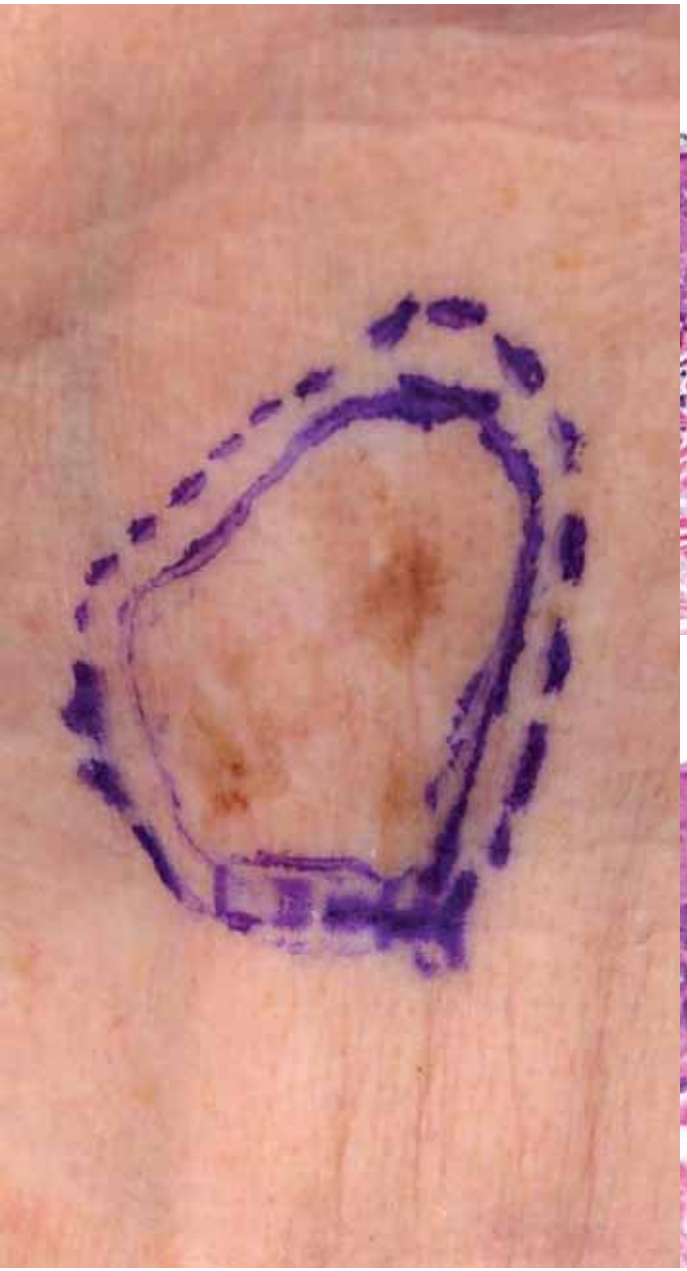


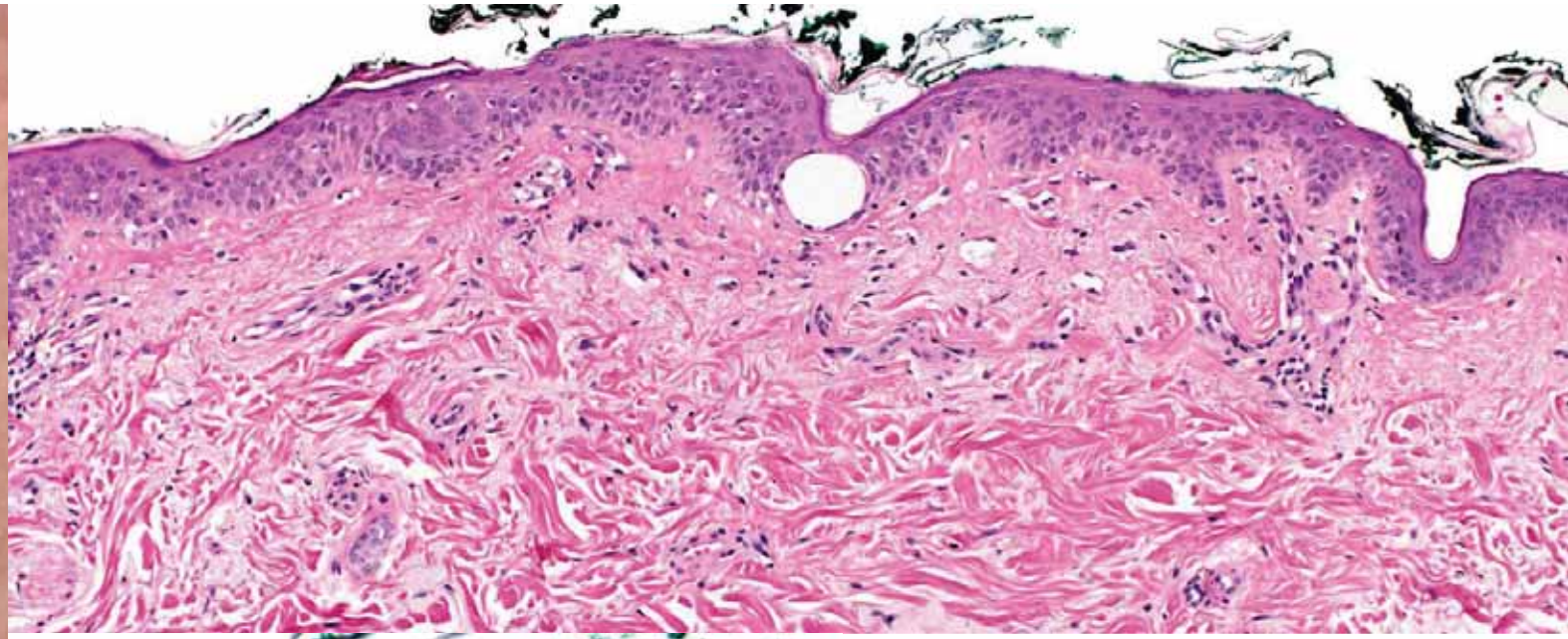
"Nevoid"melanoma, microinvasive

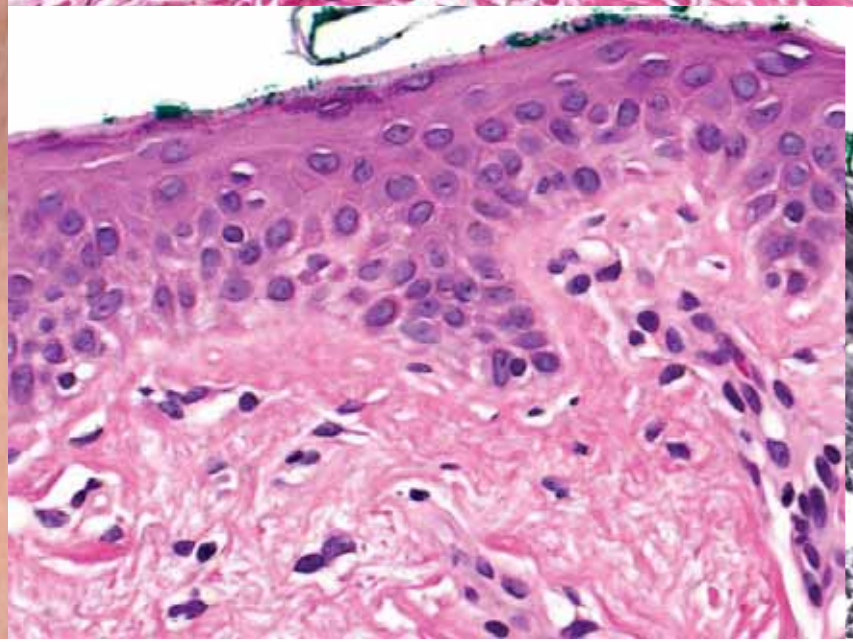


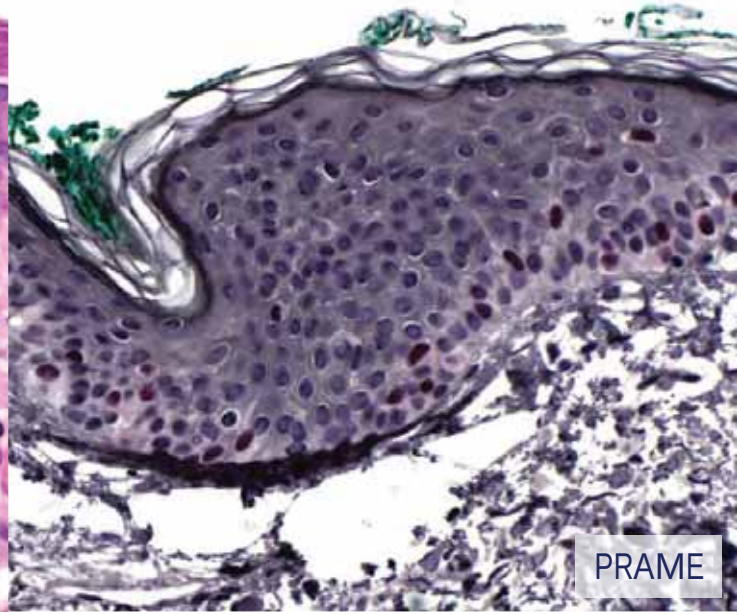











PRAME

JAMA Dermatology | Review

Impact of Clinical Information on Melanocytic Skin Lesion Pathology Diagnosis
A Scoping Review

Belinda Lai, MD; H. Peter Soyer, MD; Lin Zhu, PhD; Peter M. Ferguson, PhD; Blake O'Brien, MBBS; Tristan Dodds, MBBS; Richard A. Scolyer, MD; Gerardo Ferrara, MD; Giuseppe Argenziano, PhD; Katy J. L. Bell, PhD

IMPORTANCE There is poor accuracy and reproducibility for the histopathologic diagnosis of melanocytic skin lesions, and the provision of clinical information may improve this.

OBJECTIVE To examine the impact of clinical information on the histopathologic diagnosis of melanocytic skin lesions.

EVIDENCE REVIEW PubMed, Embase, and Cochrane Library were searched for new records published from January 2018 to January 2024. References included in the 2018 Cancer Council Australia evidence review were also screened, and forward and backward citation searches were conducted.

FINDINGS From 2224 records screened, 162 full-text studies were assessed, and 7 studies were included. Studies included pathologists from Austria, Germany, the US, Italy, the UK, and Australia. Patient populations had a mean age of 43 to 55 years and a proportion of female participants of 23% to 63%. The risk of bias assessment demonstrated that all studies had domains at unclear or high risk of bias. Clinical images increased diagnostic certainty (3 studies) and agreement between pathologists (2 studies) led to diagnostic upgrades in 7.6% to 16.7% of interpretations. Clinical diagnosis on the pathology requisition form reduced the odds of missing a melanoma with progression (1 study), while more clinical elements on the form correlated with higher re-excision rates (1 study). Among patients with distant metastases on long-term follow-up, a prior consensus diagnosis of melanoma was established on histopathology alone.

CONCLUSIONS AND RELEVANCE Providing clinical information to pathologists may improve diagnostic confidence and interobserver agreement and result in upgrading of the histopathologic diagnosis. While providing the clinical diagnosis may prevent missing a progressive melanoma, more research is needed to determine the appropriateness of histopathology upgrading when clinical images are provided and the impacts on patient outcomes.

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Supplemental content
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Melanoma is the most common fatal type of skin cancer and is an important threat to health in many countries.[1] Excluding keratinocyte cancers, cutaneous melanoma was the third most commonly diagnosed cancer and tenth most common cause of cancer death in Australia in 2022.[2] Significant advances have been made in risk assessment, diagnostic technology, and treatment.[3] The accuracy and reproducibility of histopathologic diagnosis remains challenging, however, and ways to improve this remain an active area of research.[3]

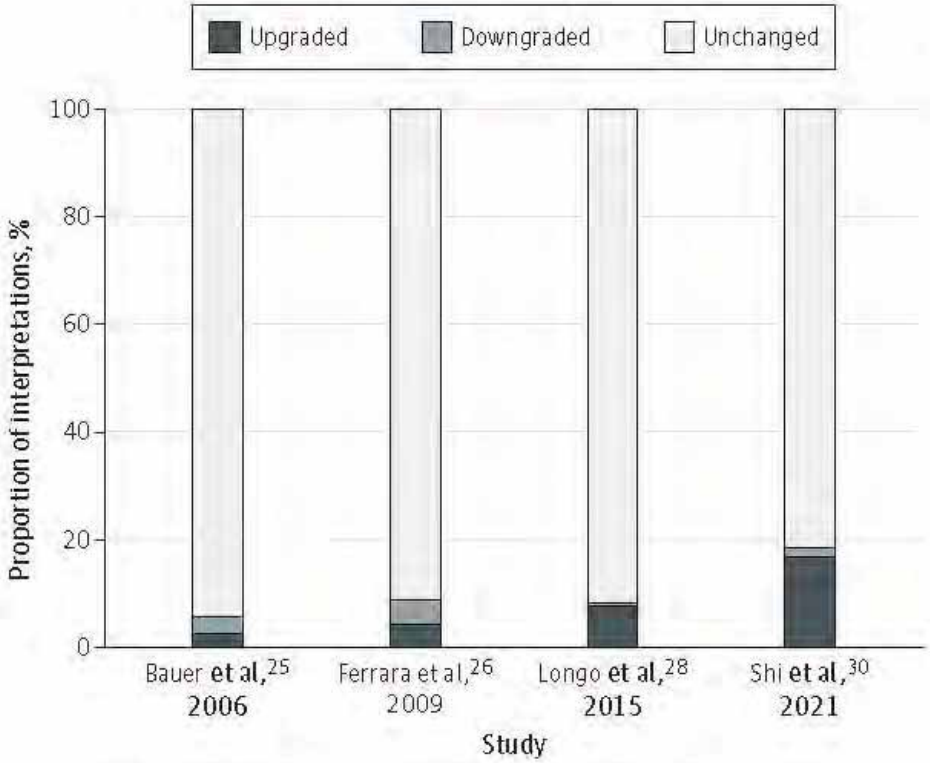
Histopathologic examination of melanoma is the clinical reference standard; however, inherent subjectivity in interpretations results in suboptimal accuracy and reproducibility,[4-9] particularly for borderline melanocytic lesions. To prevent underdiagnosis and overdiagnosis of melanoma, strategies to improve accuracy and reproducibility are required.[10-12] Providing detailed clinical information (including patient demographic characteristics, lesion location and history of change, clinical and dermoscopic images, and prior diagnoses) has been proposed as one such strategy.[13-15]

The 2018 Cancer Council Australia clinical guidelines included evidence identified through systematic database searches (PubMed, Embase, and Cochrane Library) to address the question, "What information should the clinician give the pathologist to aid the diagnosis of melanoma?"[16] To inform the current update of these guidelines, we aimed to identify, collate, and synthesize all available evidence on the impact of providing clinical information to pathologists assessing melanocytic skin lesions.

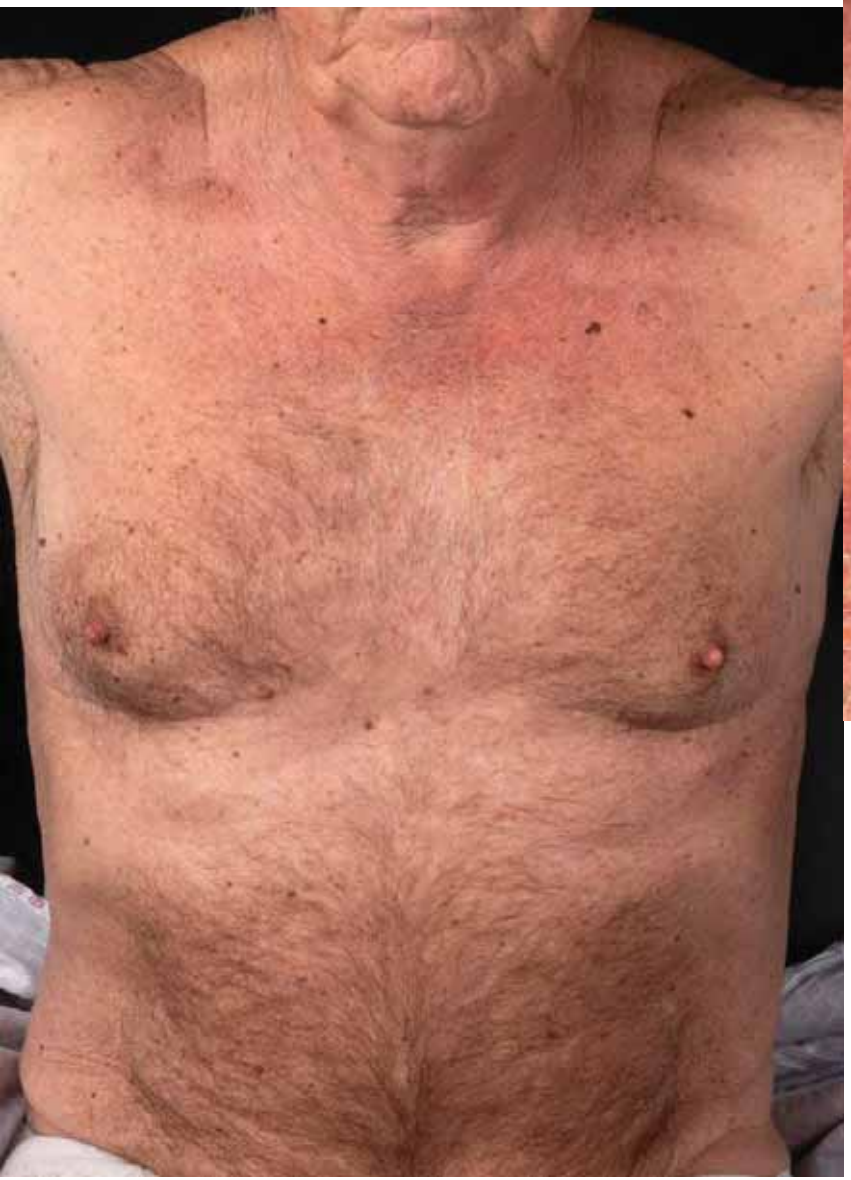
Methods

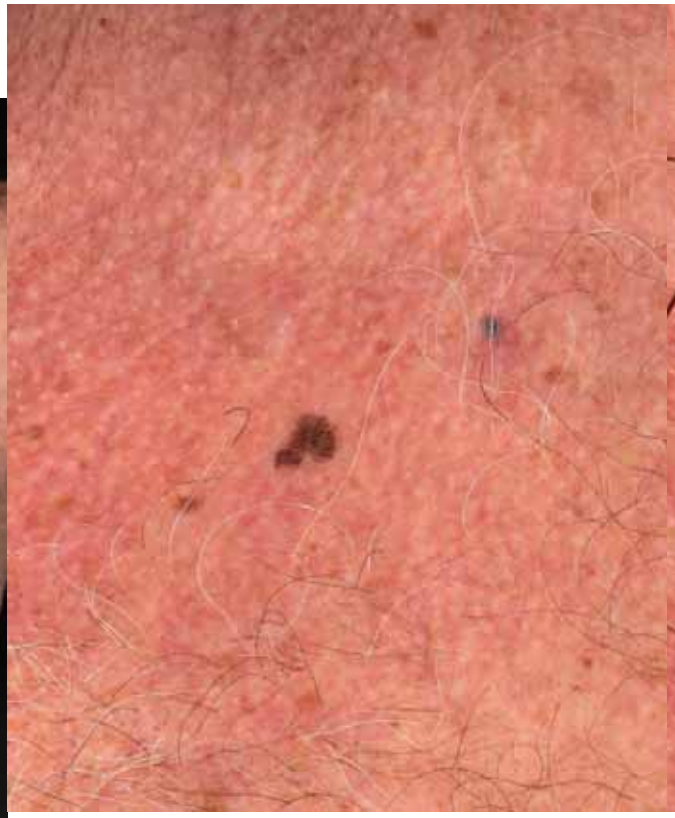
A detailed description of the prespecified study protocol is provided elsewhere,[17] and a summary is provided here. We

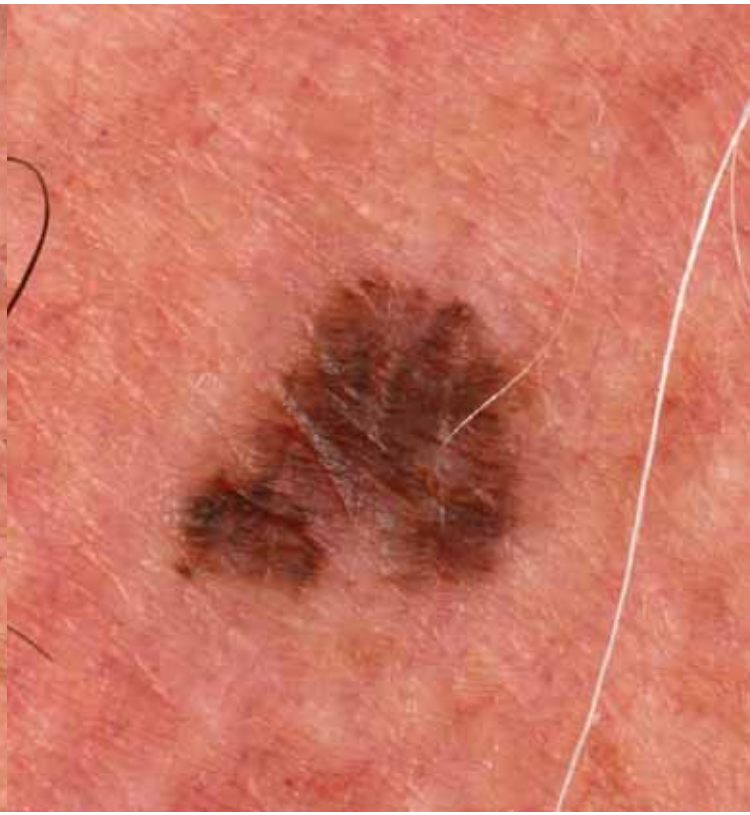
Figure 3. Changes in Histopathologic Diagnosis After Provision of Clinical Information



There were a total of 301 interpretations in the study by Bauer et al[25]; 990 in the study by Ferrara et al[26]; 158 in the study by Longo et al[28]; and 408 in the study by Shi et al.[30]





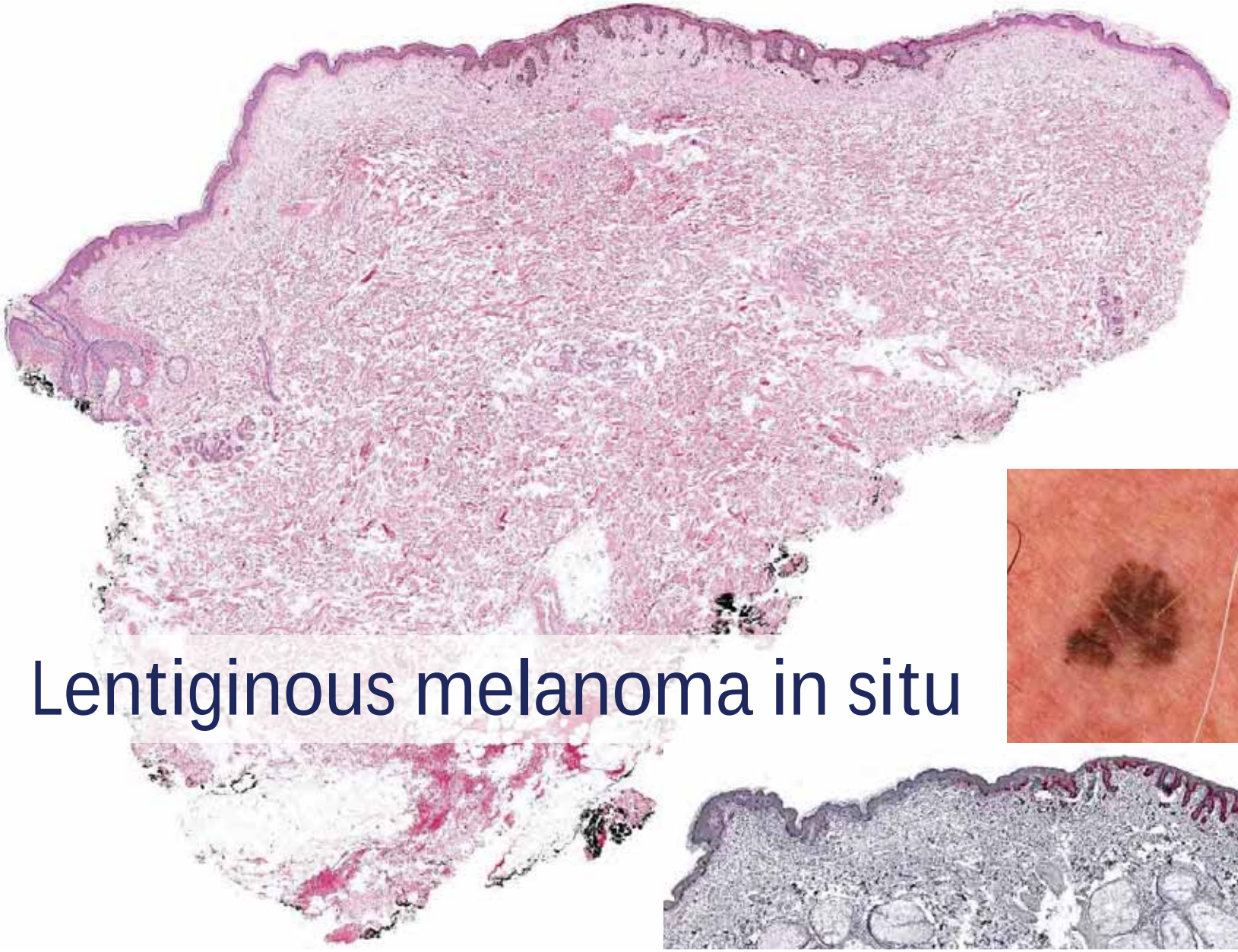


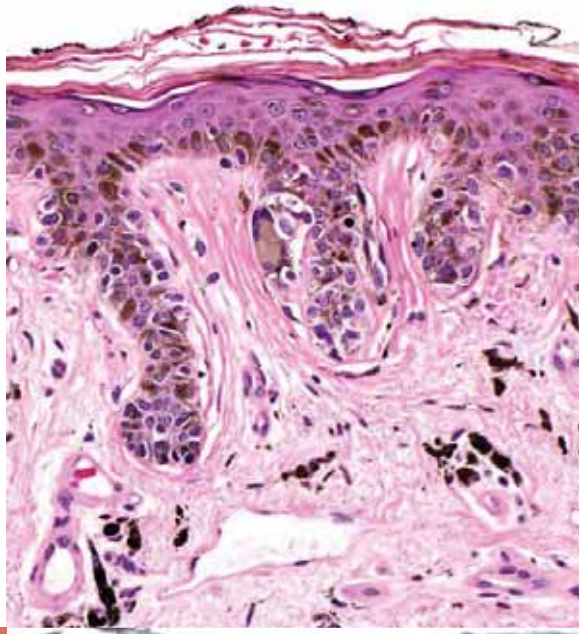
M, 76

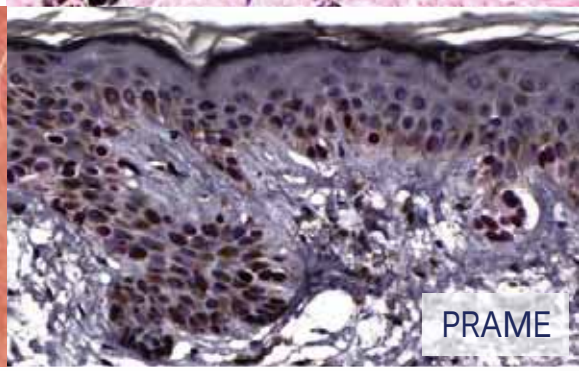
Pigmented lesion on the left subclavicular area of unknown duration.

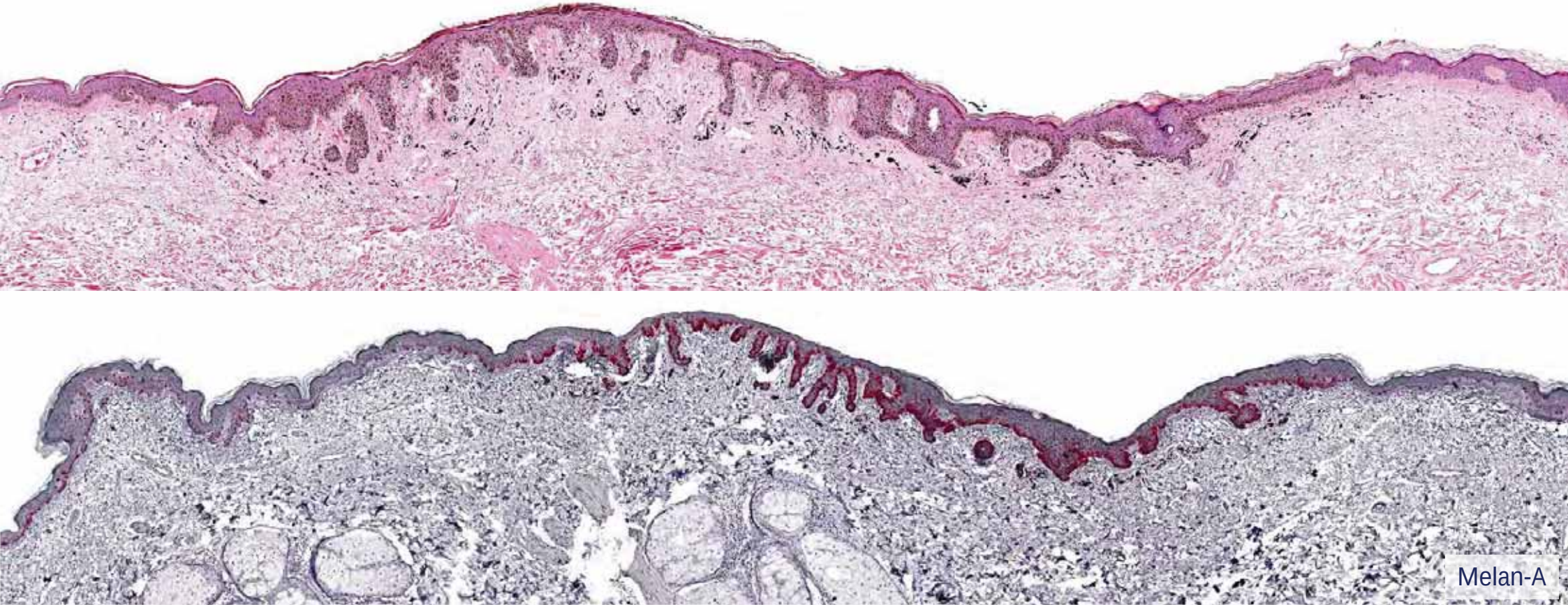
The lesion is excised surgically.

Lentiginous melanoma in situ

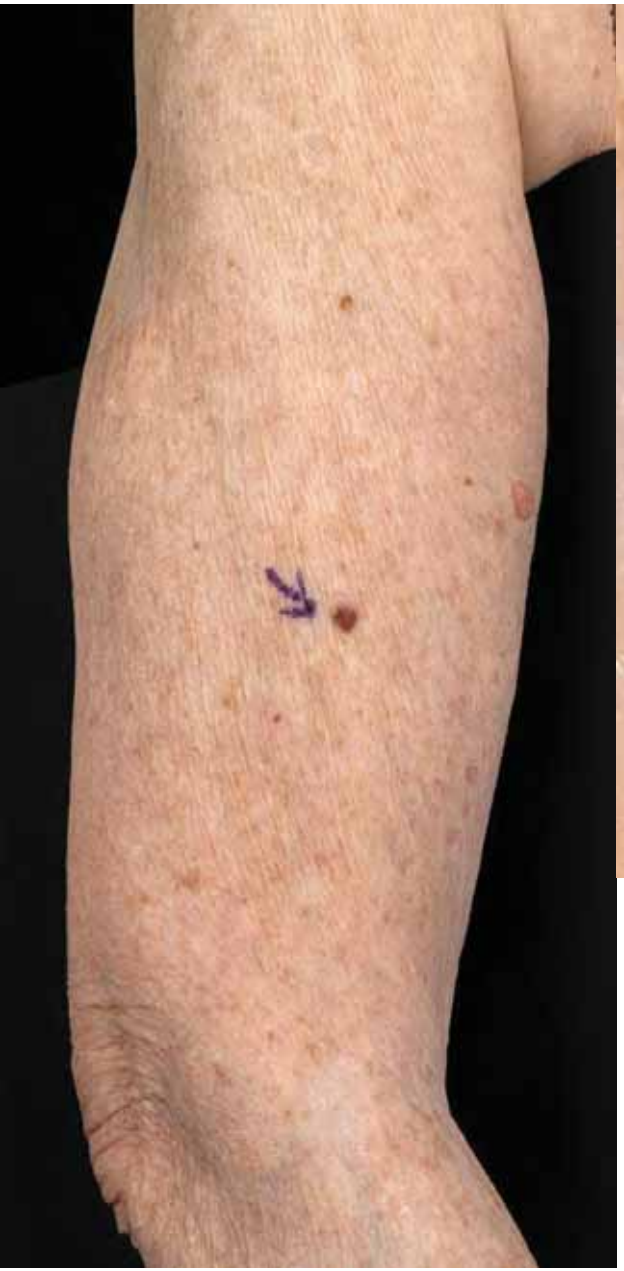


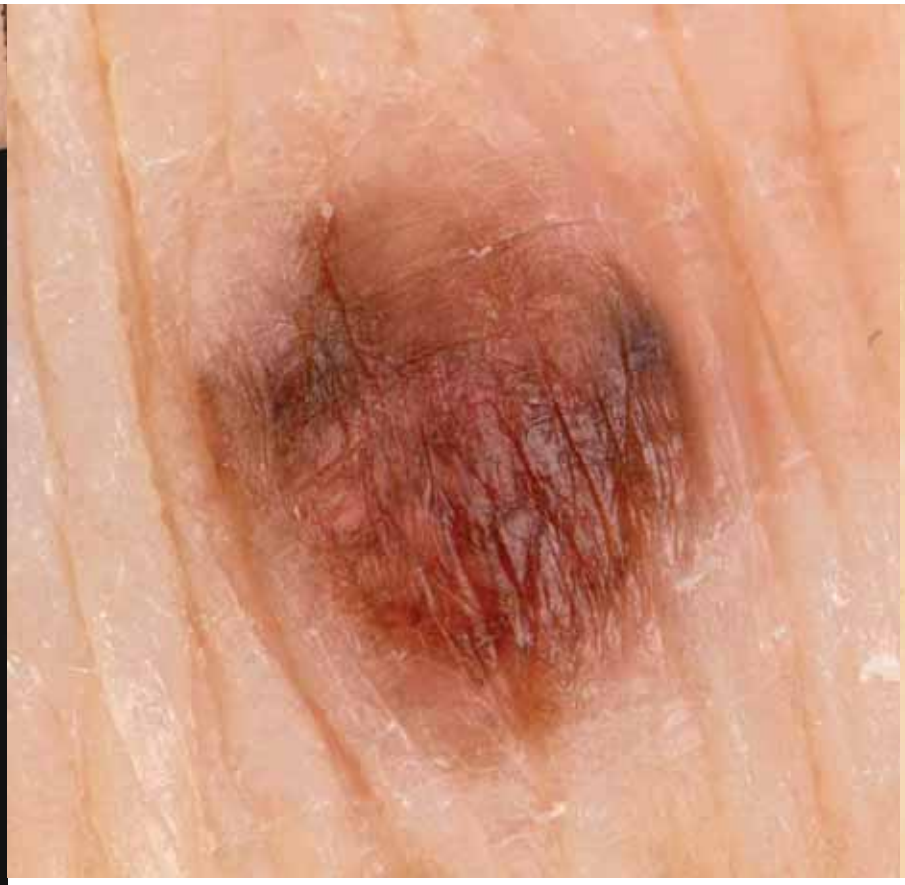


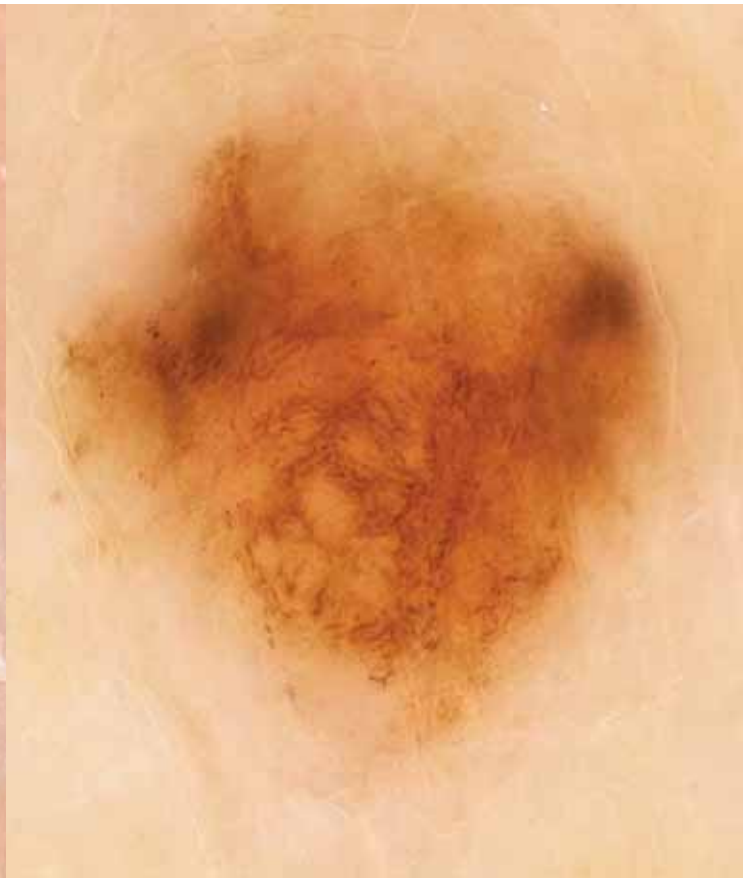




A histopathological diagnosis that can be made with confidence *morphologically* (and confirmed also by correlation with clinical picture and positivity for PRAME).
Histopathological criteria: Broad, flat lesion on sun-damaged skin, composed almost entirely of solitary melanocytes; markedly irregular architecture of the epidermis.



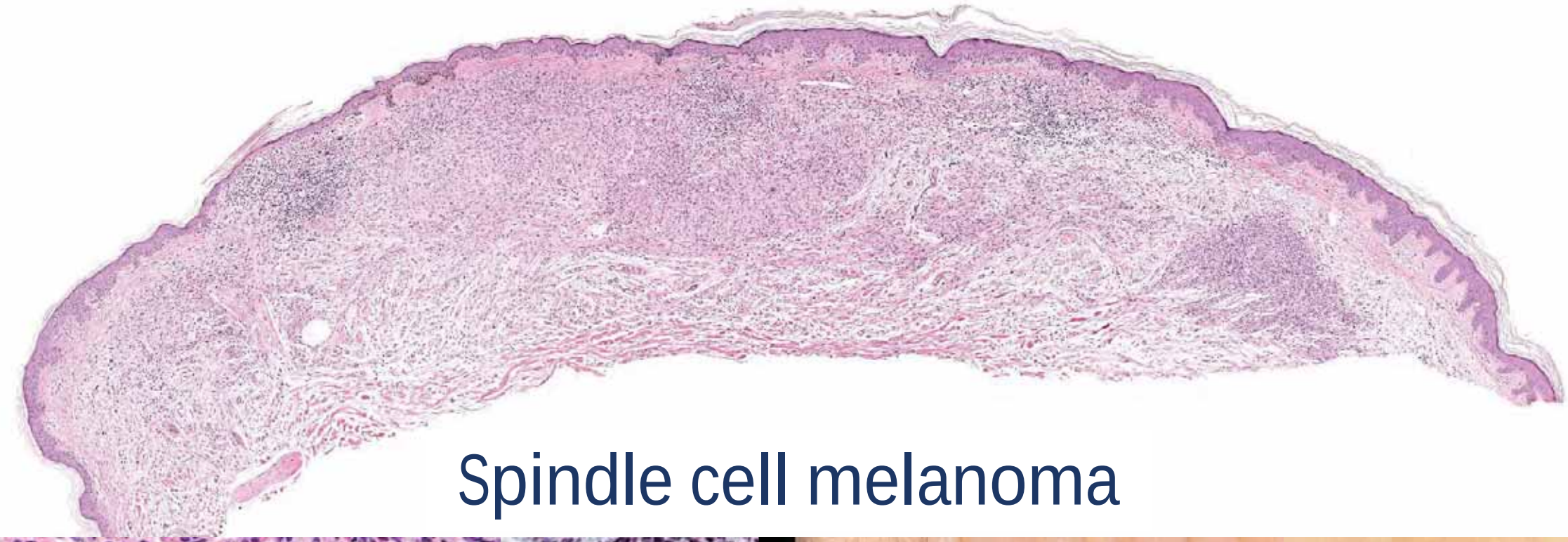




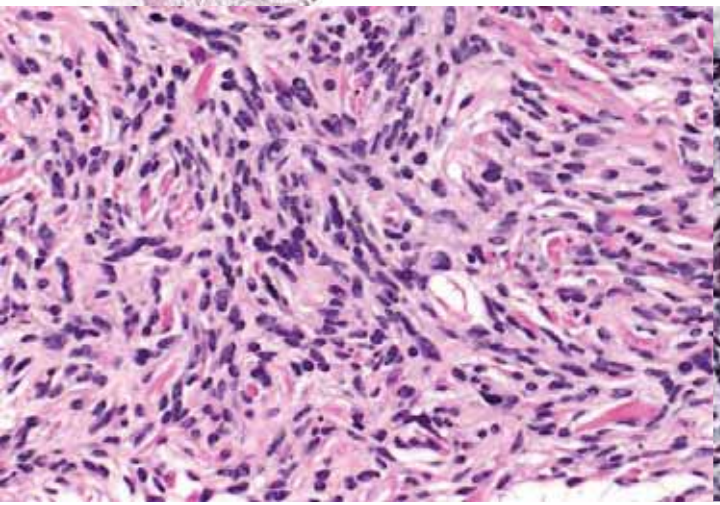
F, 70

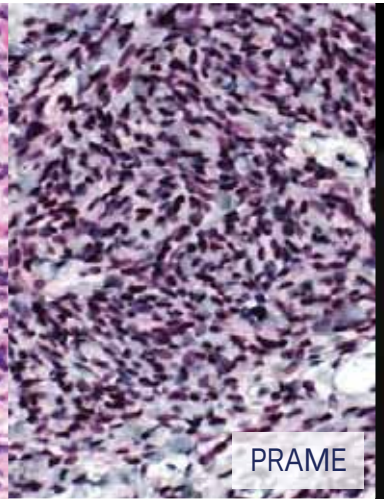
History of melanoma on the left upper arm 5 years before this presentation. During a follow-up visit a pigmented lesion on the right upper arm is noticed (duration not documented in the chart).

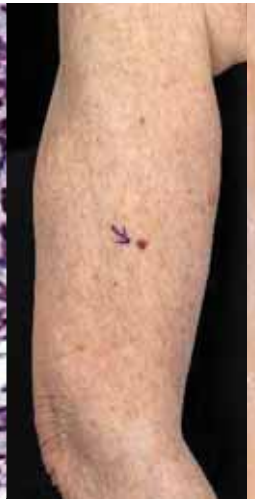
The lesion is excised surgically.

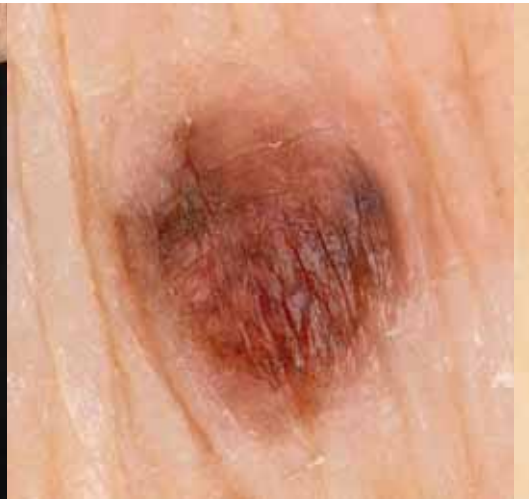


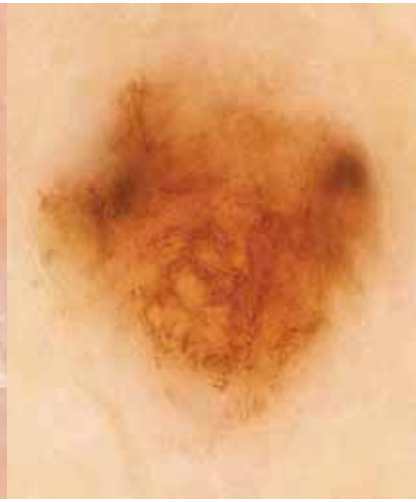
Spindle cell melanoma

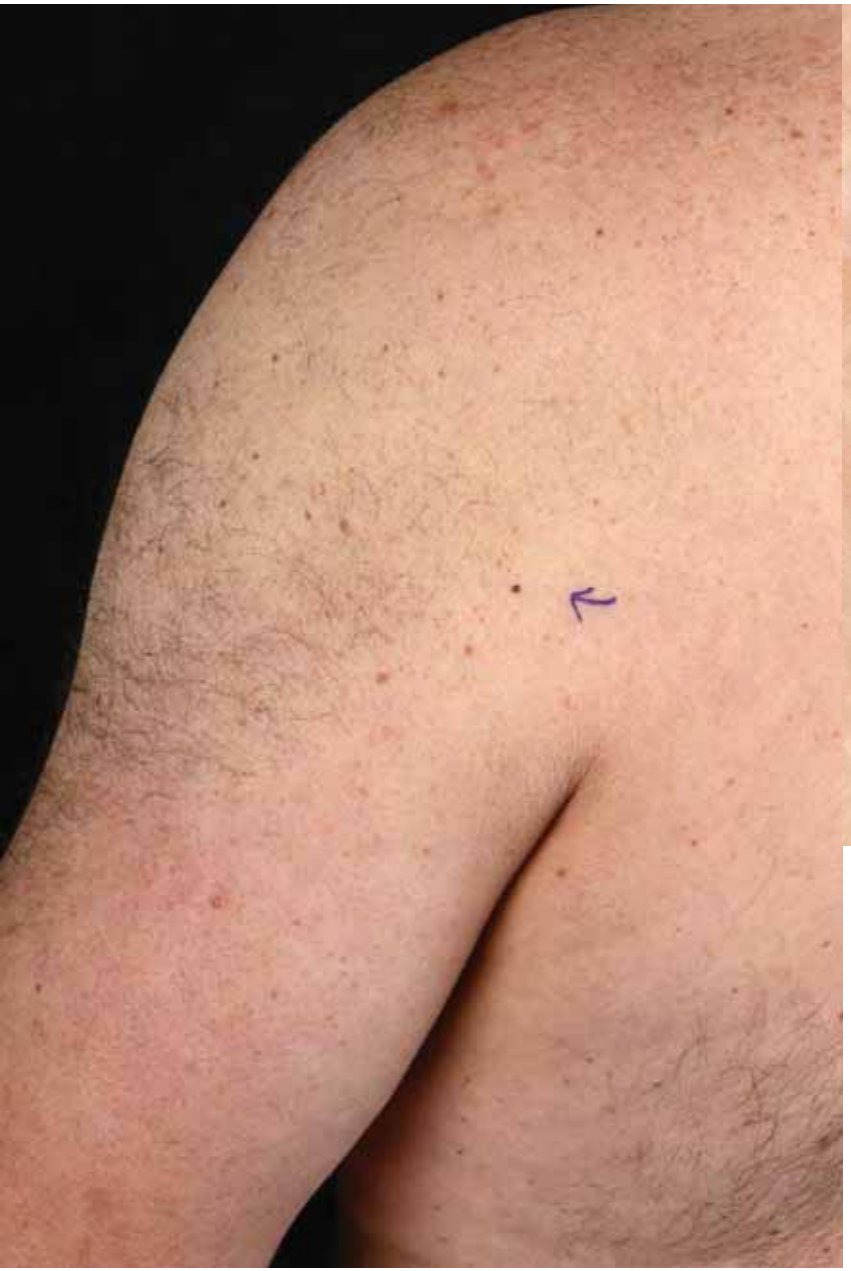


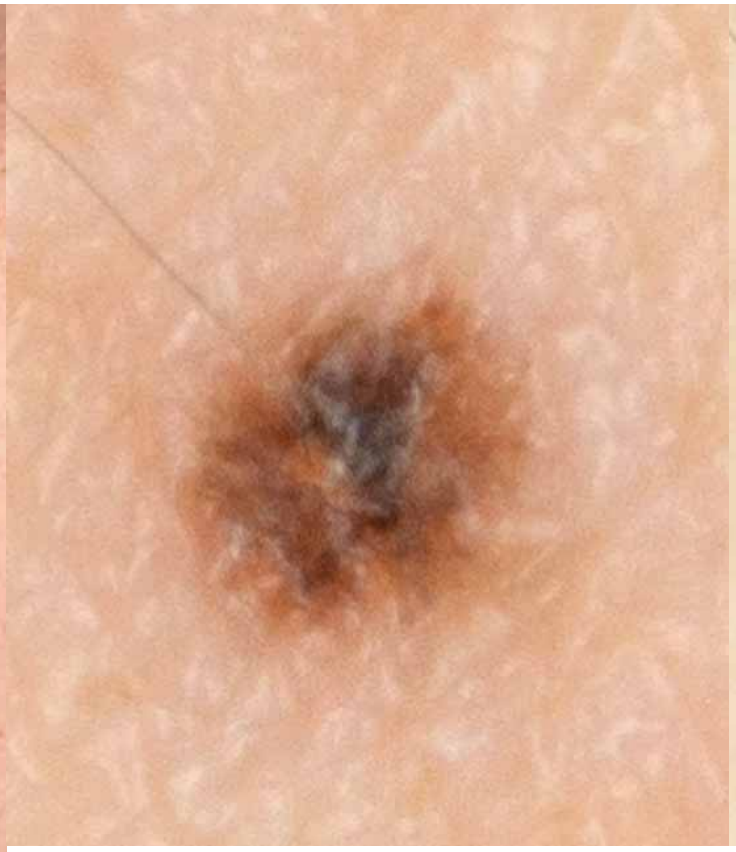


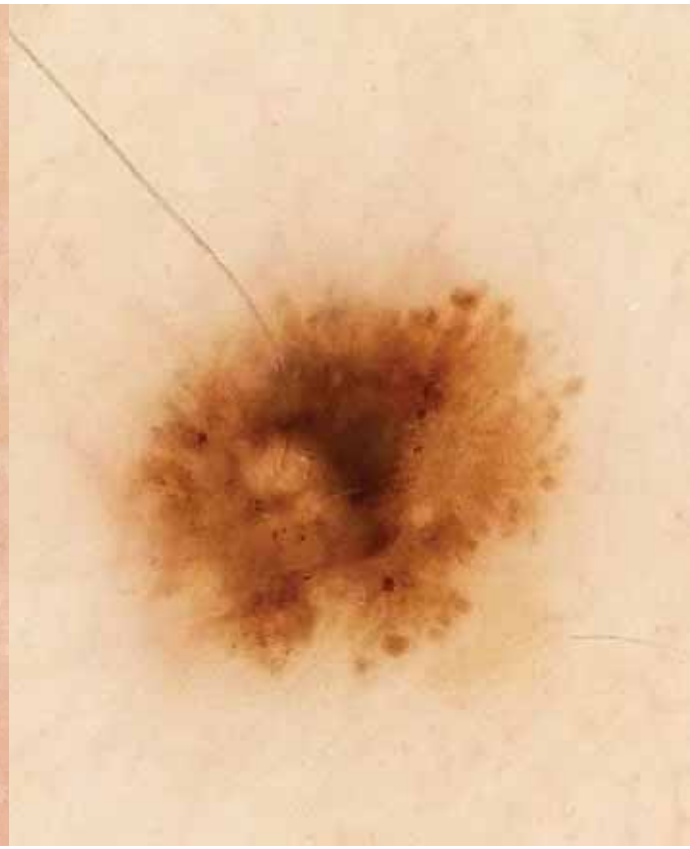








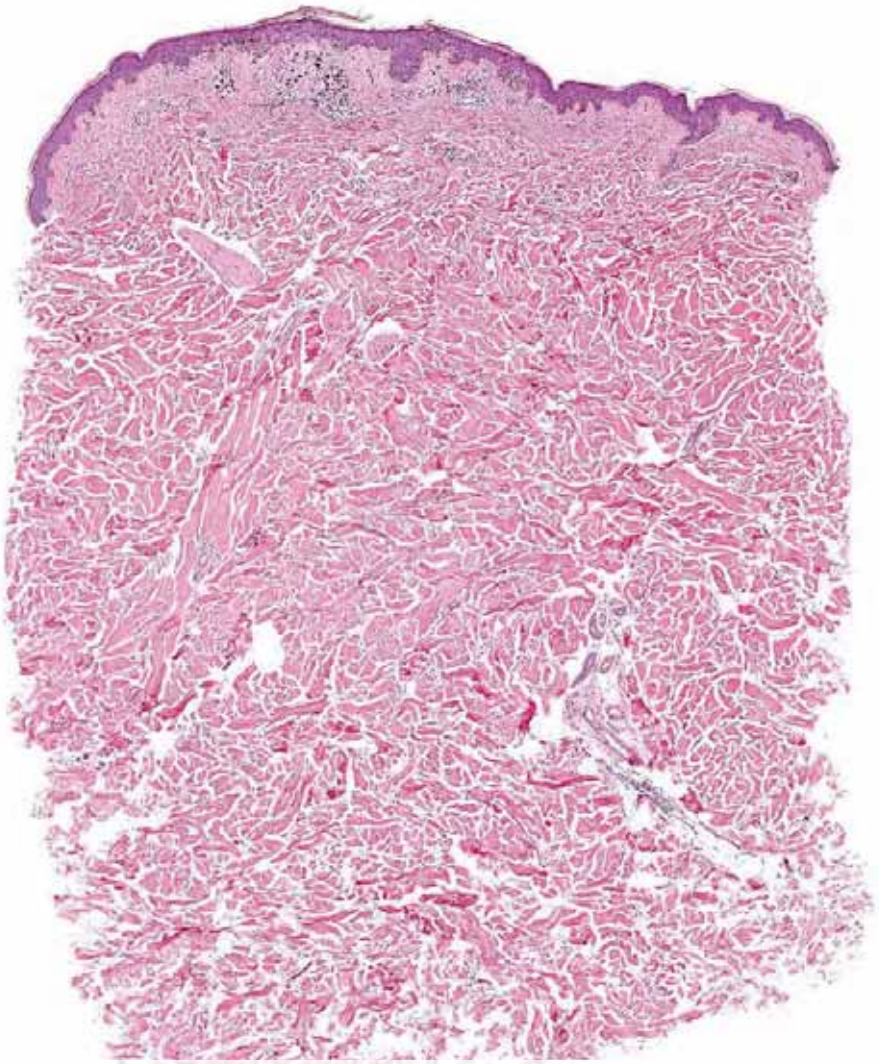




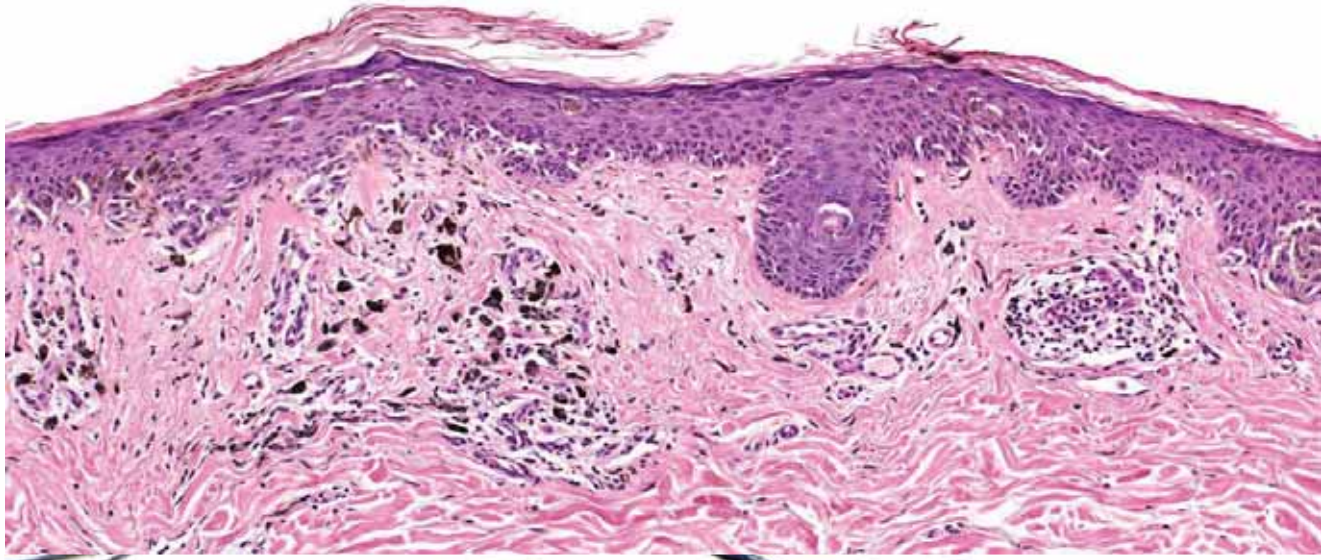
M, 47

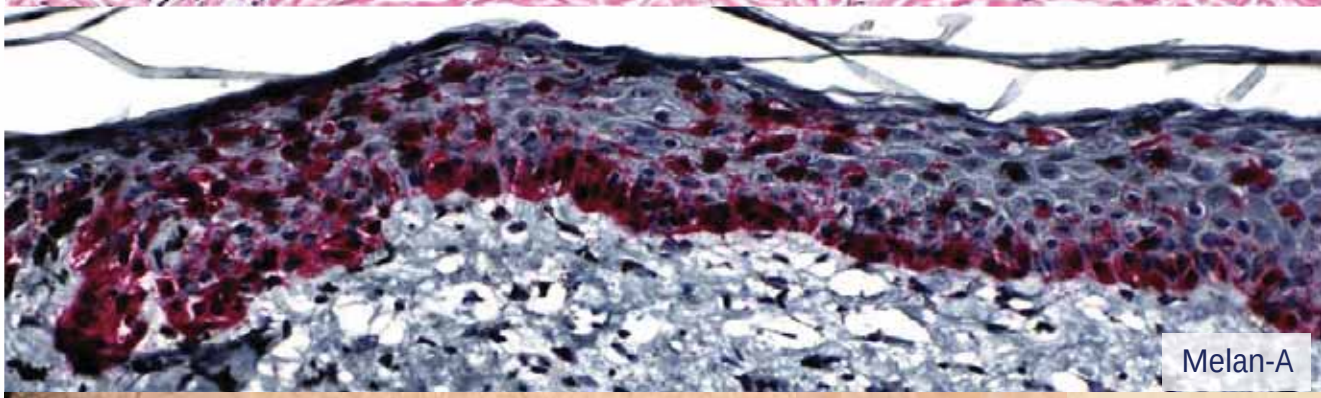
History of melanoma on the back 4 years before this presentation. A pigmented lesion on the left shoulder is noticed (duration not documented in the chart).

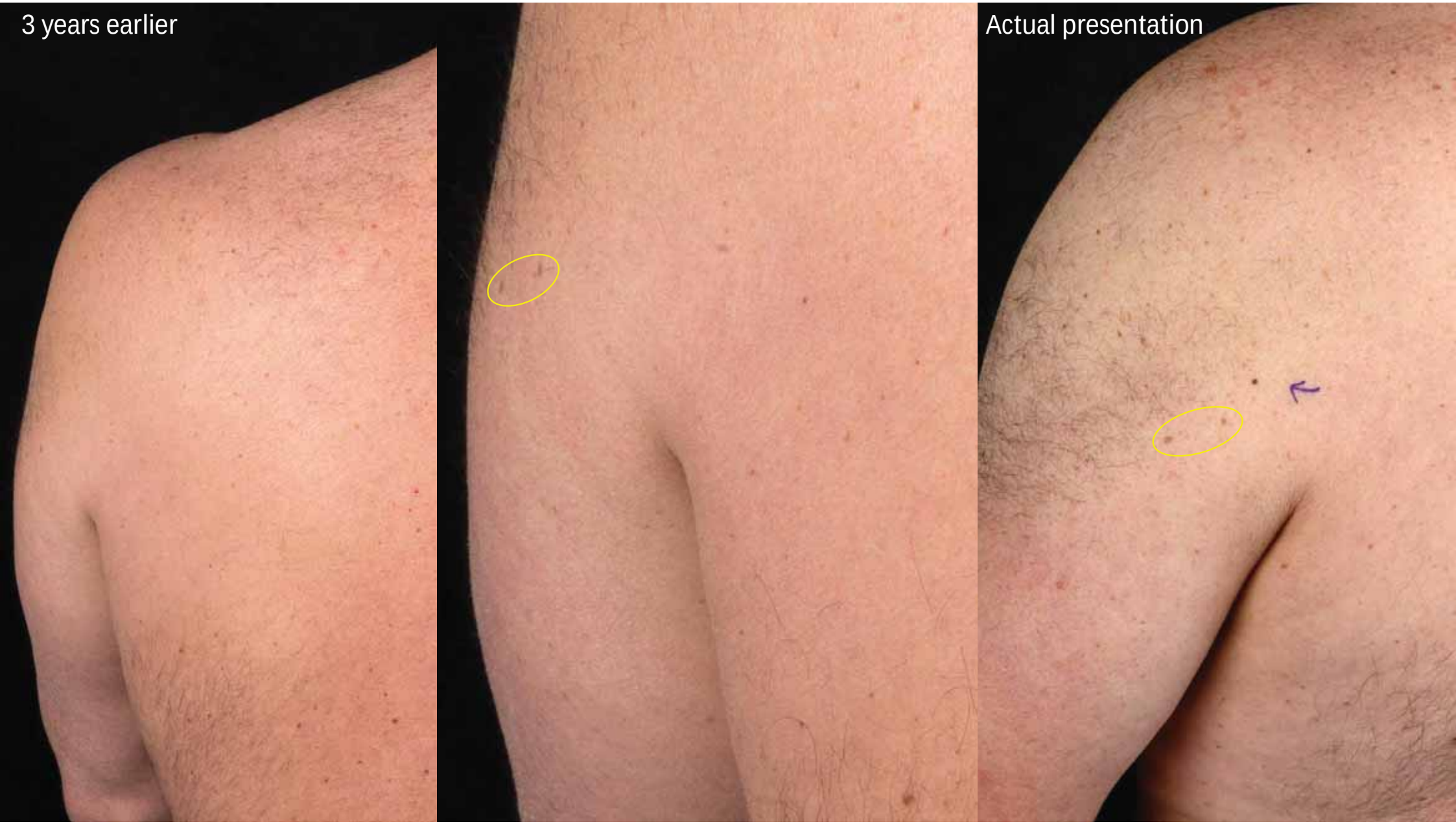
The lesion is excised surgically.

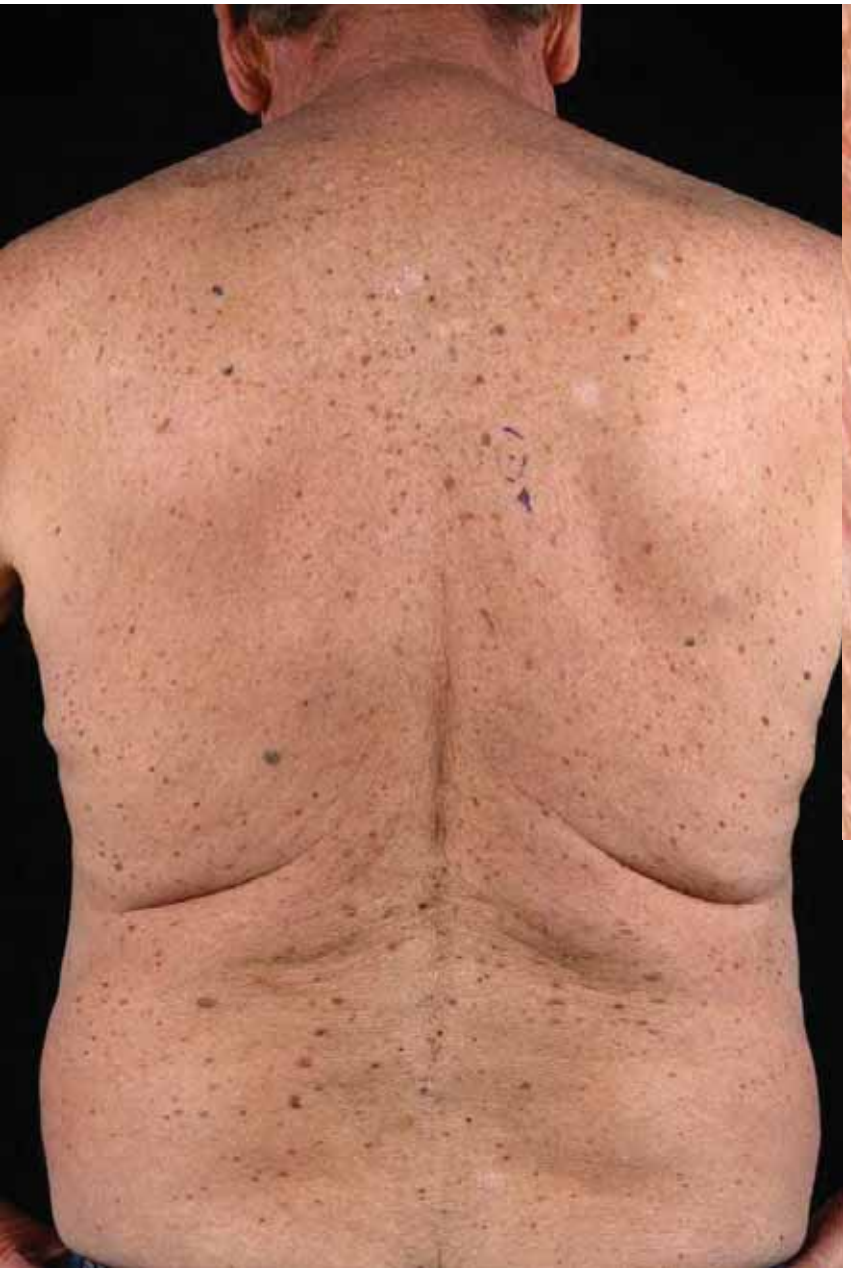


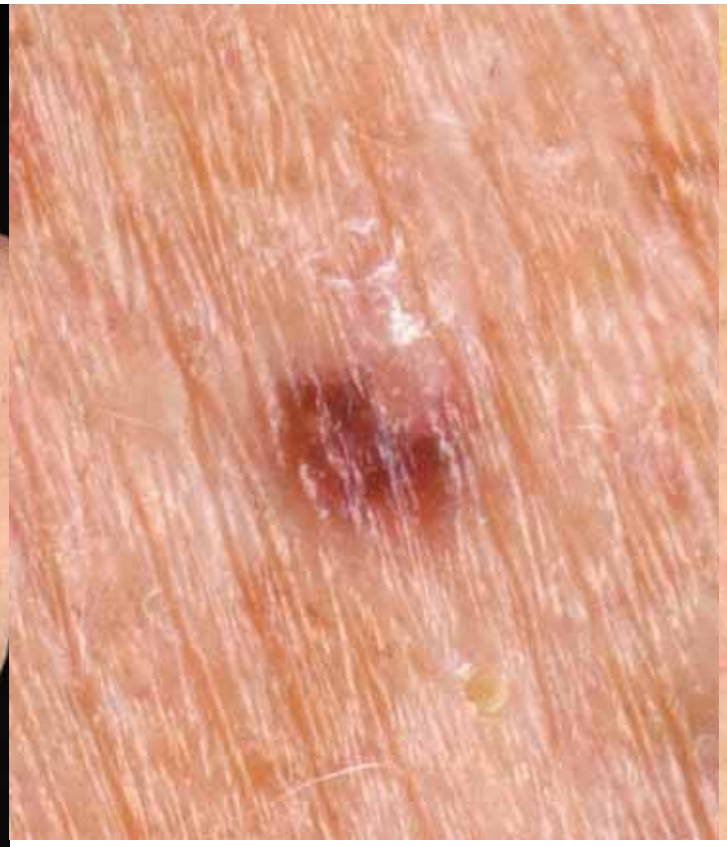
Small melanoma

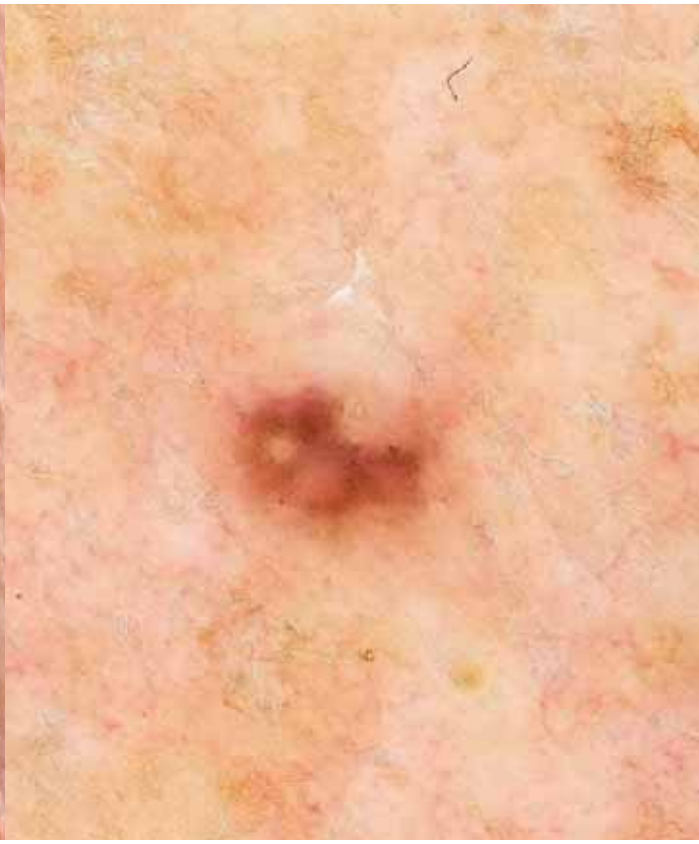





3 years earlier
Actual presentation





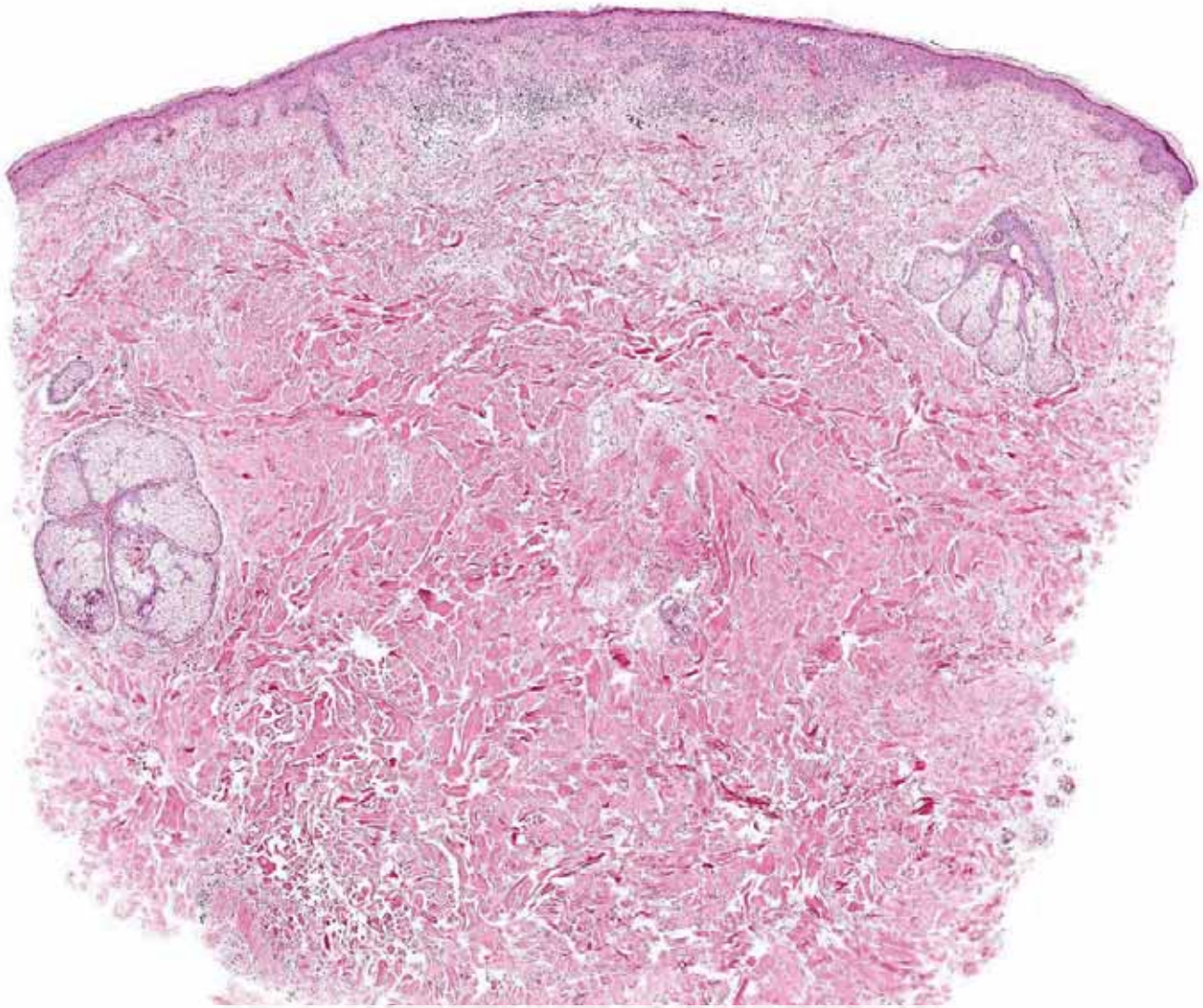


M, 61

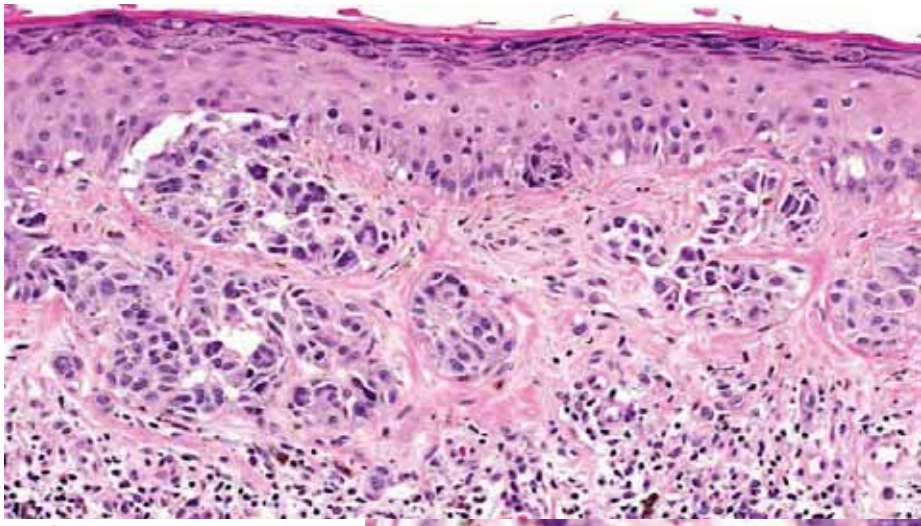
History of 2 melanomas (left shoulder, right upper arm) 15 and 8 years before presentation, respectively.

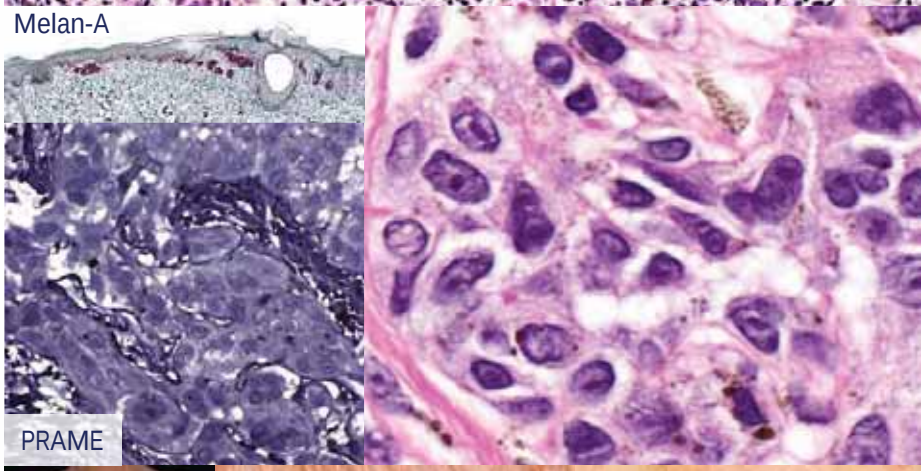
During a follow-up visit an "atypical pigmented lesion" on the right paravertebral area is noticed.

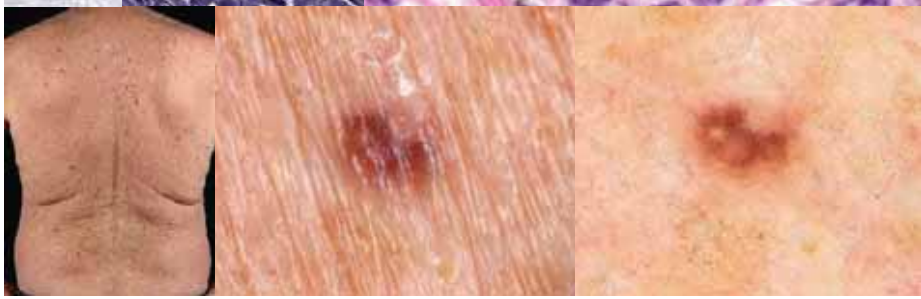
The lesion is excised surgically 7 weeks later.

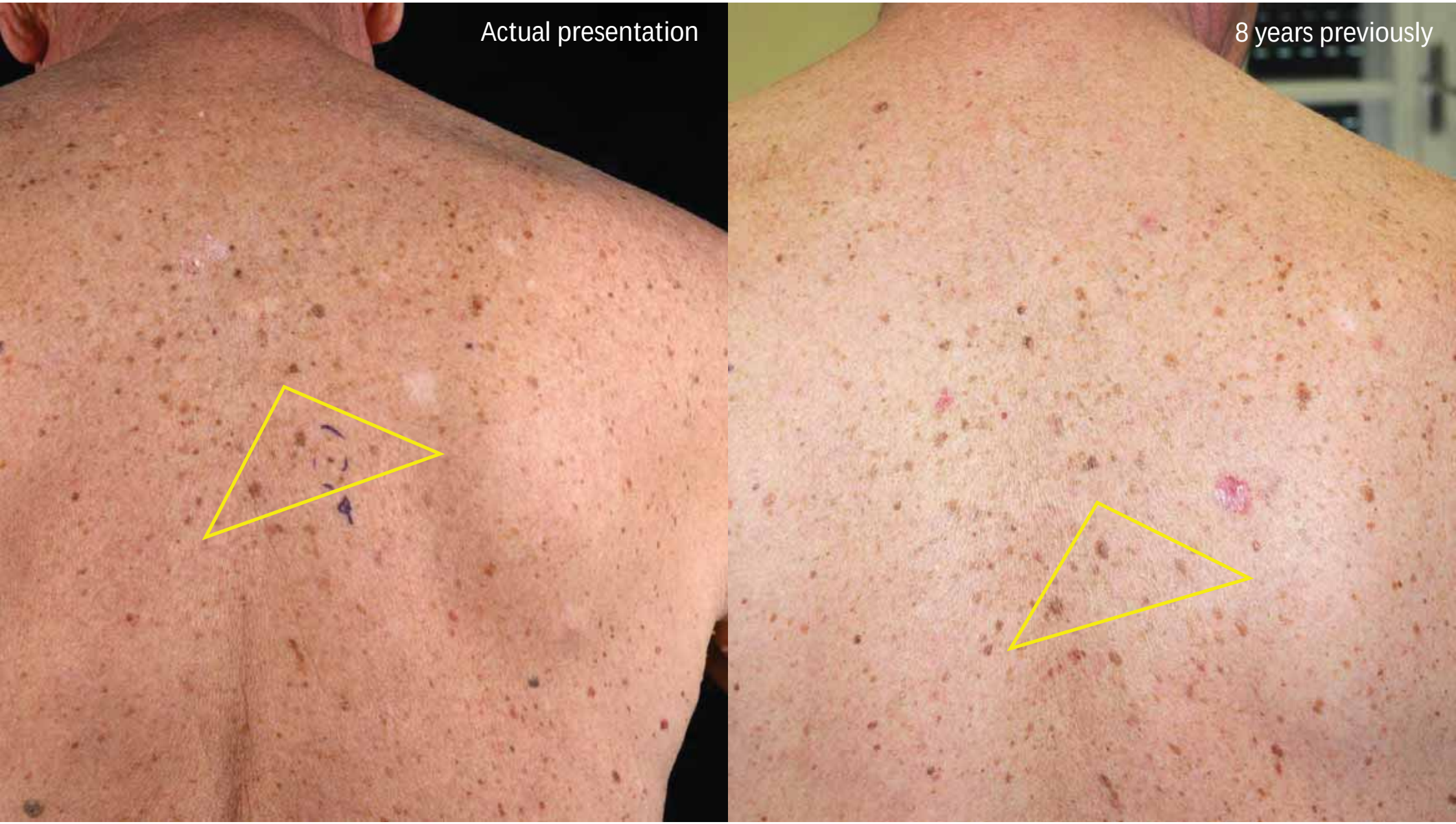


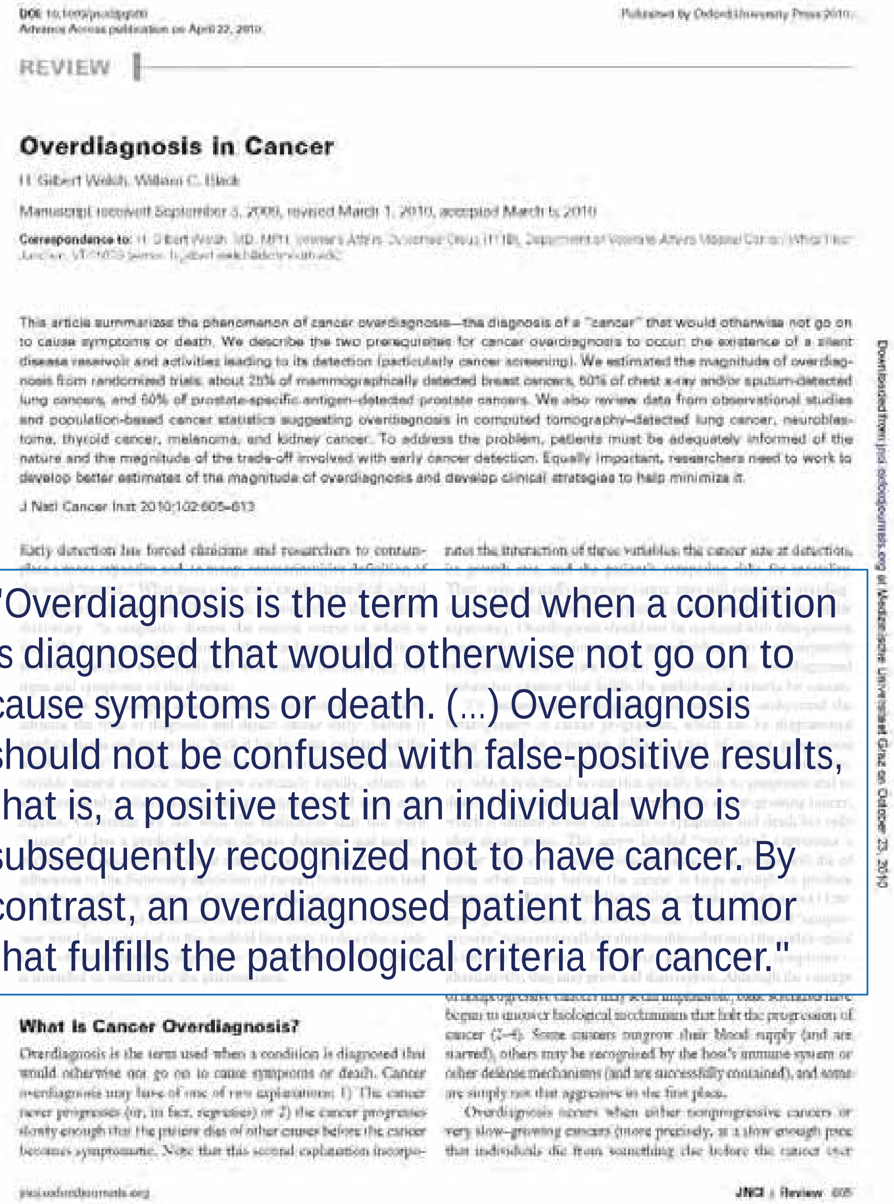
Small melanoma








Actual presentation
8 years previously



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REVIEW

Overdiagnosis in Cancer

H. Gilbert Welch, William C. Black

Manuscript received September 3, 2009; revised March 1, 2010; accepted March 5, 2010.

Correspondence to: H. Gilbert Welch, MD, MPH, ...

This article summarizes the phenomenon of cancer overdiagnosis—the diagnosis of a "cancer" that would otherwise not go on to cause symptoms or death. We describe the two prerequisites for cancer overdiagnosis to occur: the existence of a silent disease reservoir and activities leading to its detection (particularly cancer screening). We estimated the magnitude of overdiagnosis from randomized trials: about 25% of mammographically detected breast cancers, 50% of chest x-ray and/or sputum-detected lung cancers, and 60% of prostate-specific antigen–detected prostate cancers. We also review data from observational studies and population-based cancer statistics suggesting overdiagnosis in computed tomography–detected lung cancer, neuroblastoma, thyroid cancer, melanoma, and kidney cancer. To address the problem, patients must be adequately informed of the nature and the magnitude of the trade-off involved with early cancer detection. Equally important, researchers need to work to develop better estimates of the magnitude of overdiagnosis and develop clinical strategies to help minimize it.

J Natl Cancer Inst 2010;102:605–613

Early detection has forced clinicians and researchers to contem- ... rates the interaction of three variables: the cancer size at detection, ...

What Is Cancer Overdiagnosis?

Overdiagnosis is the term used when a condition is diagnosed that would otherwise not go on to cause symptoms or death. Cancer overdiagnosis may have one of two explanations: 1) The cancer never progresses (or, in fact, regresses) or 2) the cancer progresses slowly enough that the patient dies of other causes before the cancer becomes symptomatic. Note that this second explanation incorpo-

... begun to uncover biological mechanisms that halt the progression of cancer (2–4). Some cancers outgrow their blood supply (and are starved), others may be recognized by the host's immune system or other defense mechanisms (and are successfully contained), and some are simply not that aggressive in the first place.

Overdiagnosis occurs when either nonprogressive cancers or very slow-growing cancers (more precisely, at a slow enough pace that individuals die from something else before the cancer ever

"Overdiagnosis is the term used when a condition is diagnosed that would otherwise not go on to cause symptoms or death. (...) Overdiagnosis should not be confused with false-positive results, that is, a positive test in an individual who is subsequently recognized not to have cancer. By contrast, an overdiagnosed patient has a tumor that fulfills the pathological criteria for cancer."

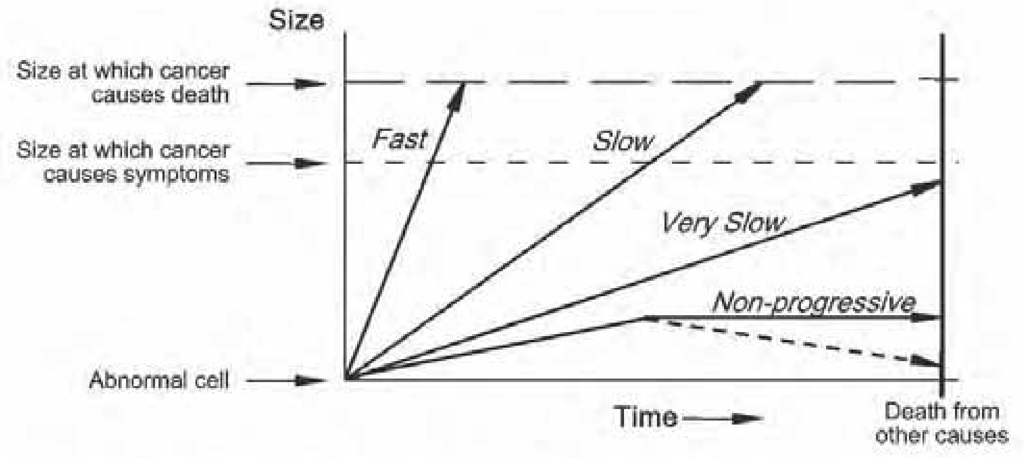
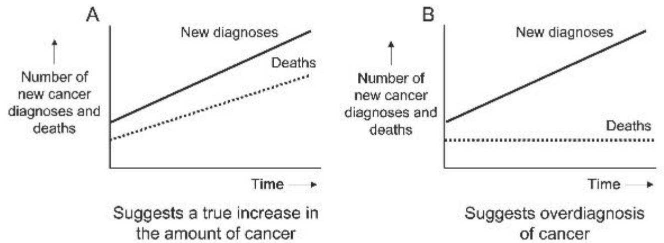
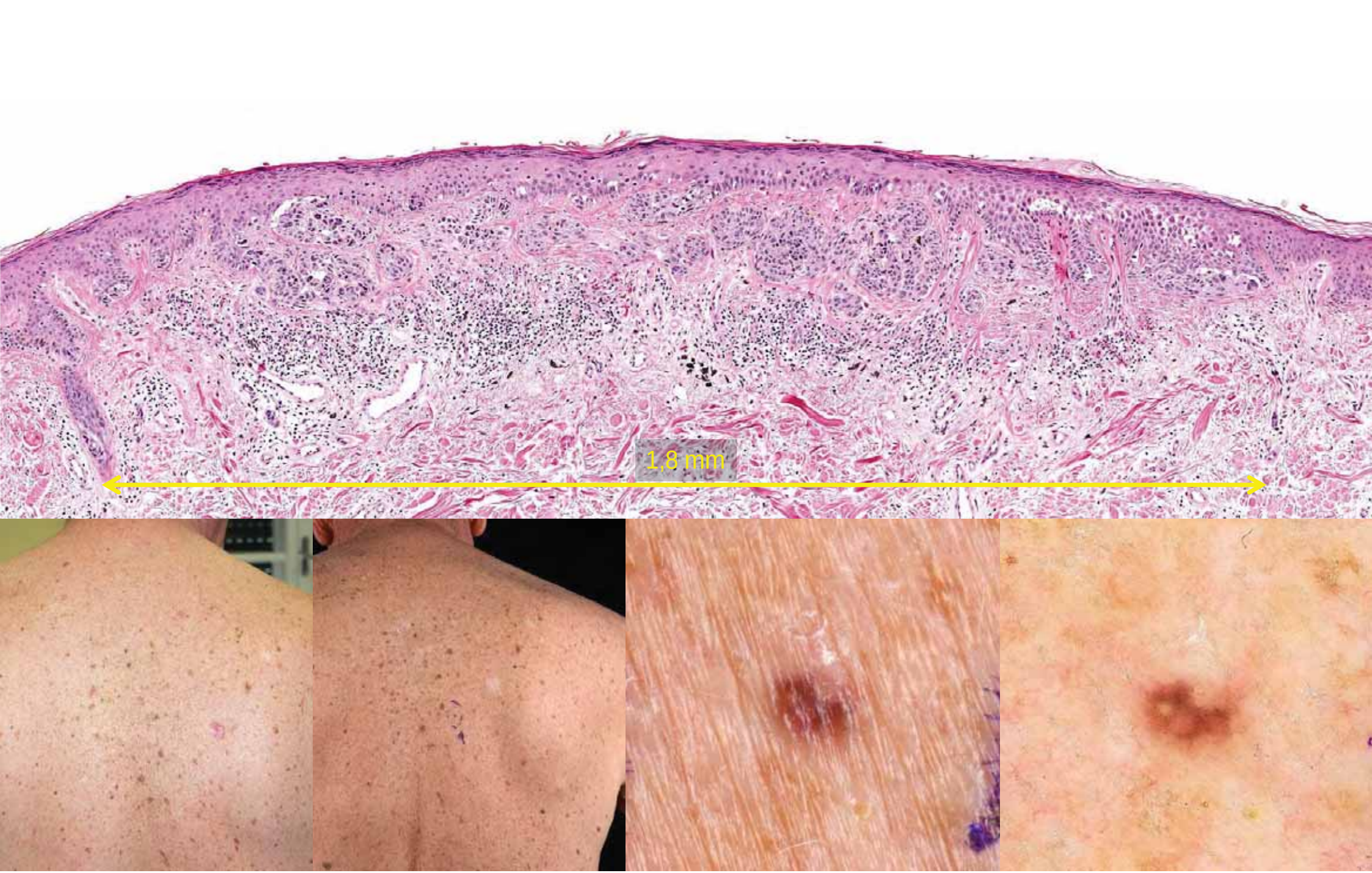


Figure 1. Heterogeneity of cancer progression. The arrow labeled "fast" represents a fast-growing cancer, one that quickly leads to symptoms and to death. The arrow labeled "slow" represents a slow-growing cancer, one that leads to symptoms and death but only after many years. The arrow labeled "very slow" represents a cancer that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms. The arrow labeled "nonprogressive" represents cellular abnormalities that meet the pathological definition of cancer but never grow to cause symptoms—Alternatively, they may grow and then regress (**dotted line**). (Figure 1 was previously supplied by the authors to Wikipedia.)

Figure 6. Two distinct patterns of rapid rises in the rate of diagnosis. **A)** Population data that suggest a true increase in the amount of cancer; **B)** population data that suggest overdiagnosis of cancer.

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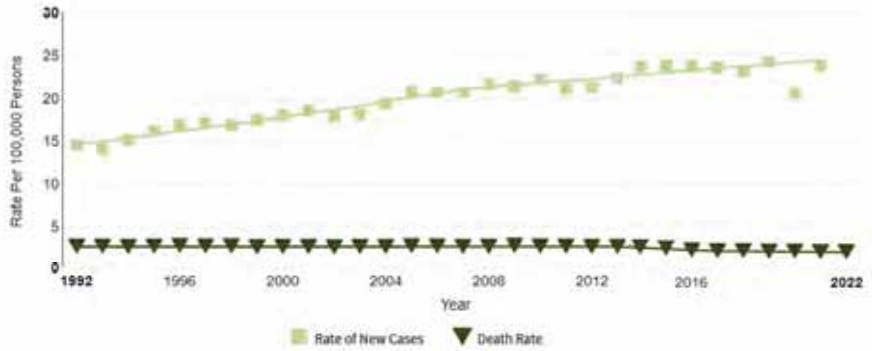
- Cancer Statistics Review +
- Preliminary Cancer Incidence Rates and Trends +
- SEER Publications +

Statistics at a Glance —

At a Glance

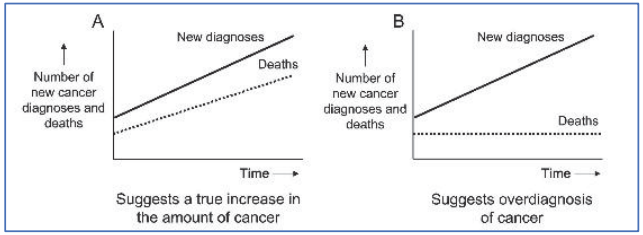
Estimated New Cases in 2024	100,640
% of All New Cancer Cases	5.0%
Estimated Deaths in 2024	8,290
% of All Cancer Deaths	1.4%

5-Year Relative Survival
94.1%
2014-2020

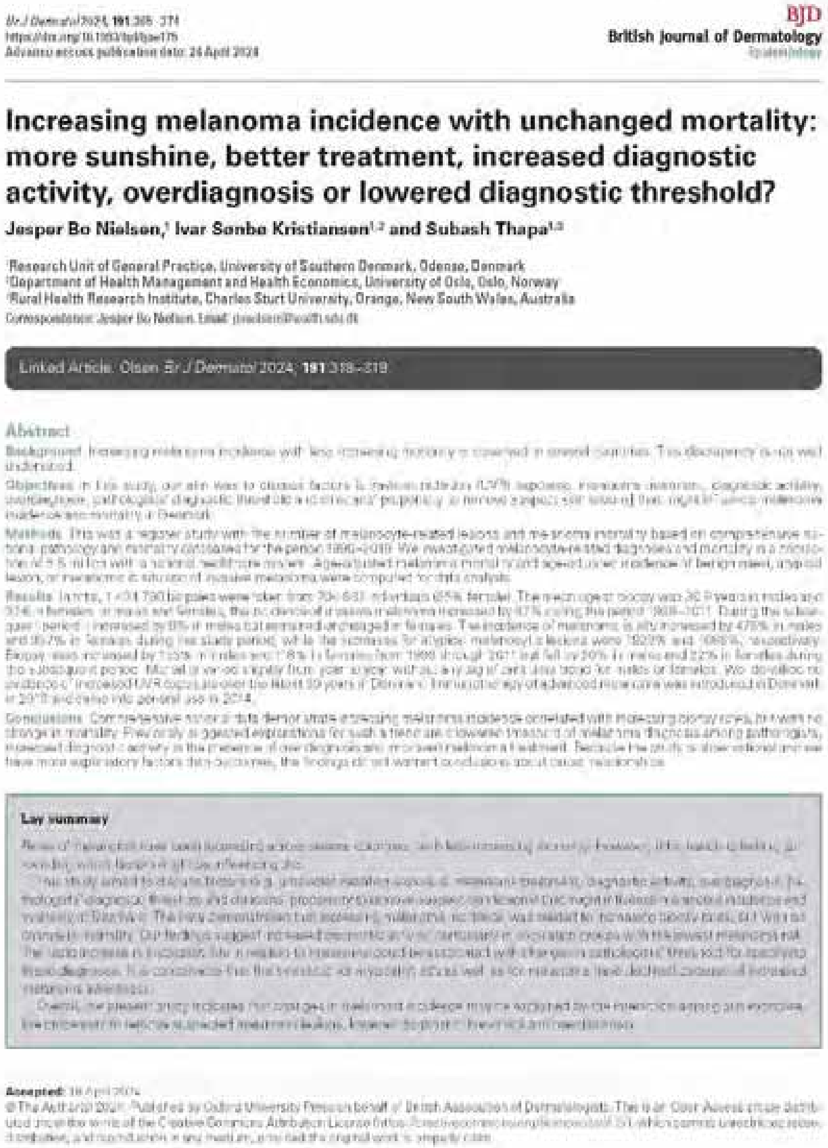


New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.
The 2020 incidence rate is displayed but not used in the fit of the trend line(s). Impact of COVID on SEER Cancer Incidence 2020 data

New cases are also referred to as incident cases in other publications. Rates of new cases are also refered to as incidence rates.



February 7, 2025


BJD
British Journal of Dermatology

Increasing melanoma incidence with unchanged mortality: more sunshine, better treatment, increased diagnostic activity, overdiagnosis or lowered diagnostic threshold?

Jesper Bo Nielsen,[1] Ivar Sønbø Kristiansen[1,2] and Subash Thapa[1,3]

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[2]Department of Health Management and Health Economics, University of Oslo, Oslo, Norway
[3]Rural Health Research Institute, Charles Sturt University, Orange, New South Wales, Australia

Linked Article: Olsen *Br J Dermatol* 2024; **191**

Abstract

Lay summary

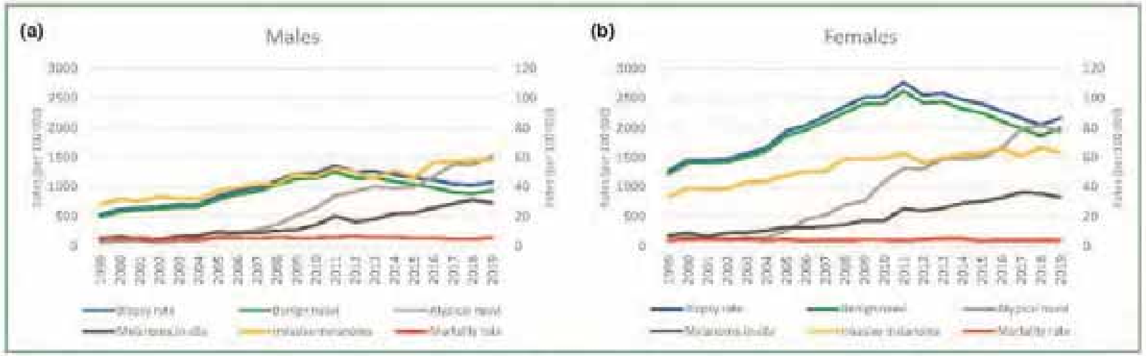
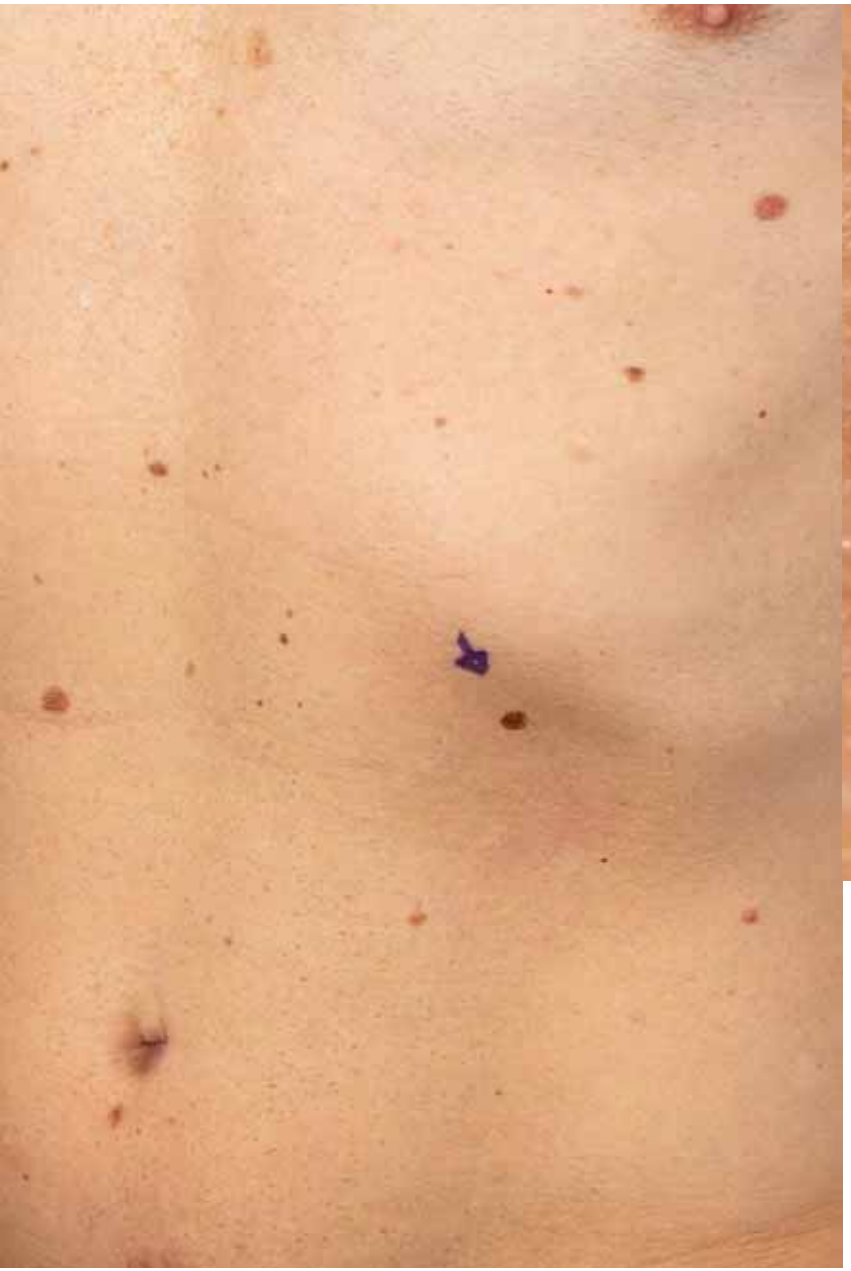
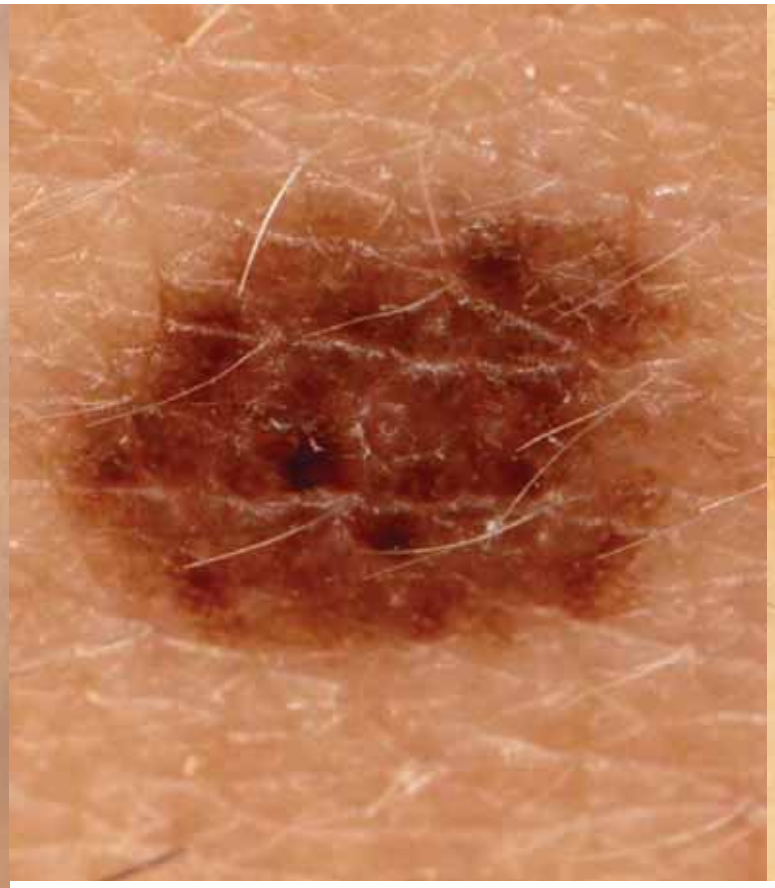
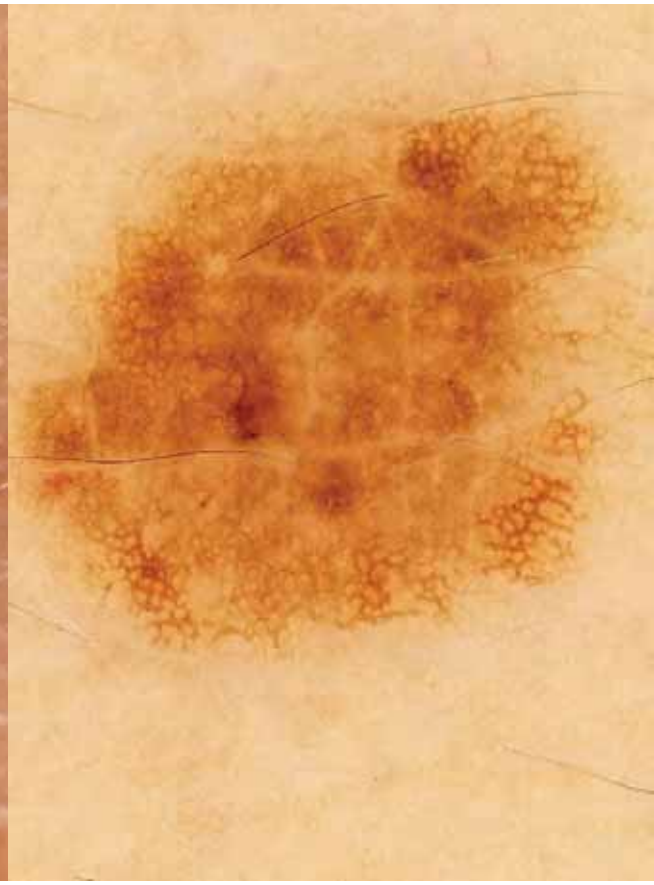


Figure 1 All ages: age-standardized rates for males (a) and females (b) of melanocyte-related skin biopsies, invasive melanoma incidence, atypical naevi, melanoma *in situ* and benign naevi and melanoma mortality. All rates per 100 000 population per year. Scales (y-axis): left: biopsy rate and benign naevi; right: invasive melanoma, atypical naevi, melanoma *in situ* and mortality. Source: Danish Pathology Data Bank and NORDCAN.

"Overall, the present study indicates that changes in melanoma incidence may be explained by the interaction among sun exposure, the propensity to remove suspected melanoma lesions, lowered diagnostic thresholds and overdiagnosis."





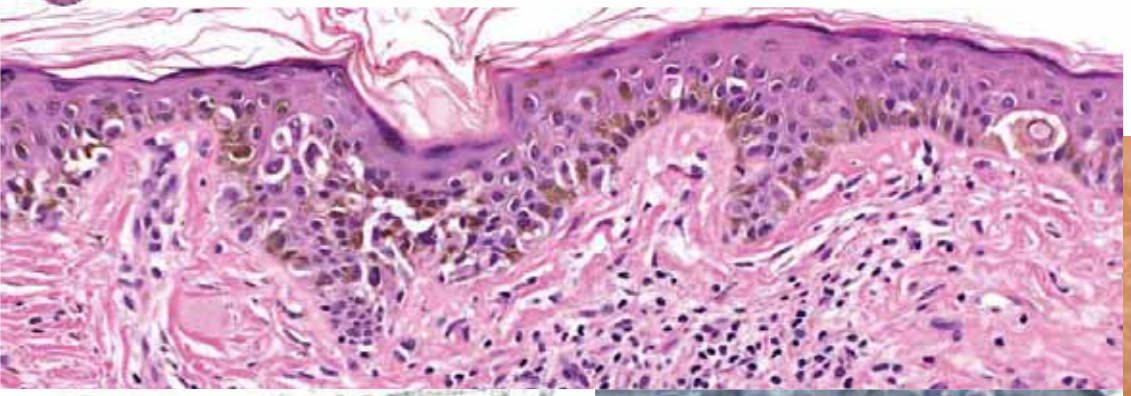


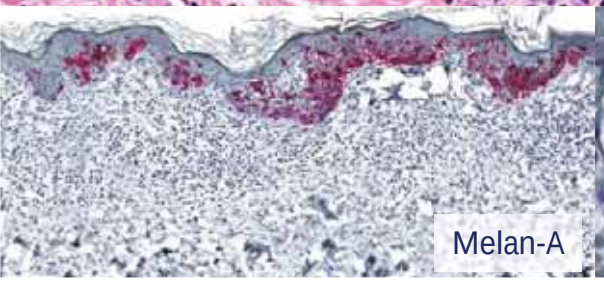
M, 40

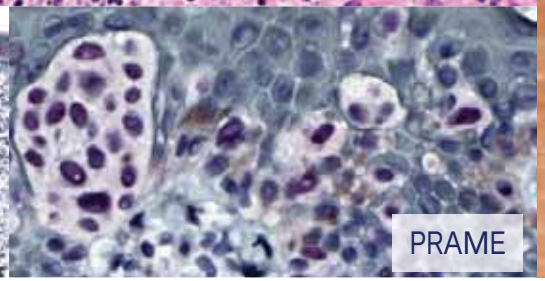
The patient attends regular controls for multiple nevi; one lesion on the left upper abdomen is found to show a slightly thicker network than in previous visits.

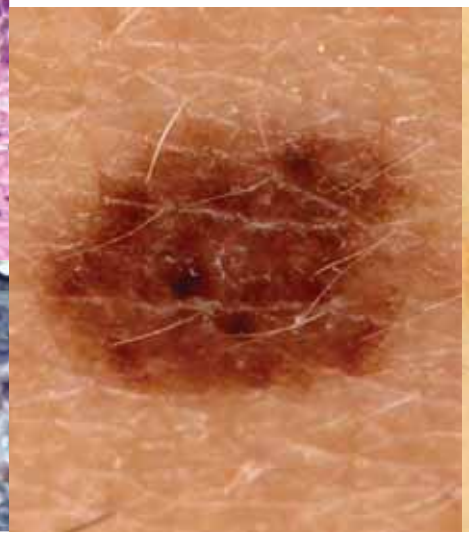
The lesion is excised surgically.

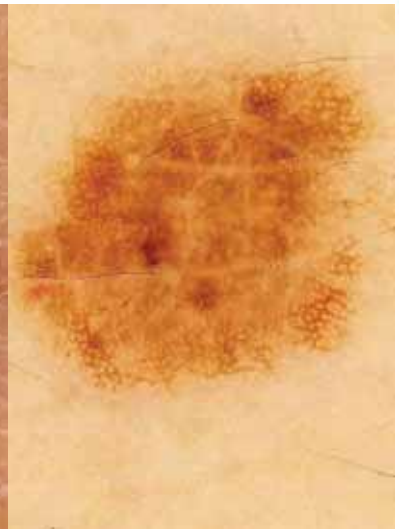
Melanoma

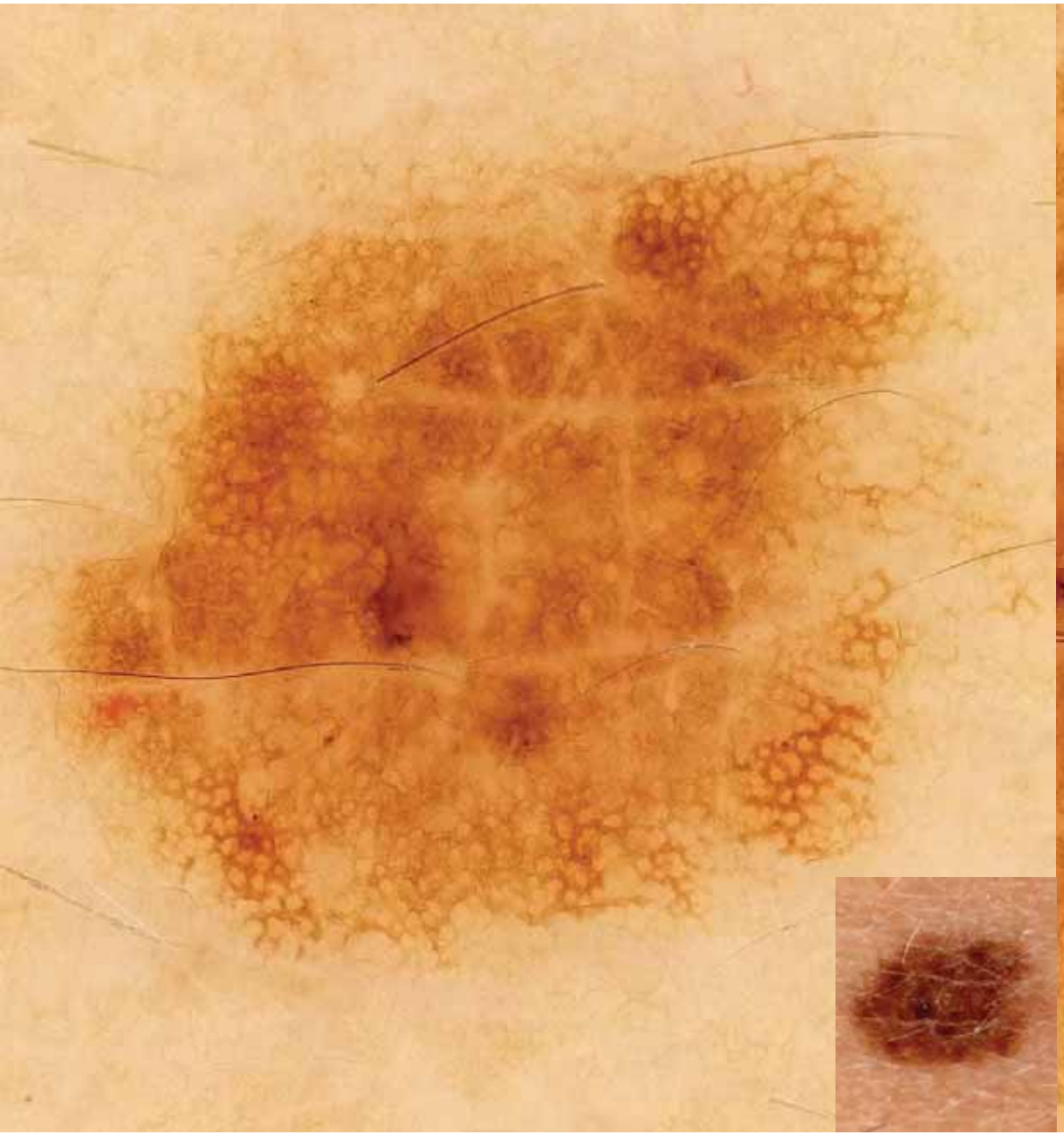


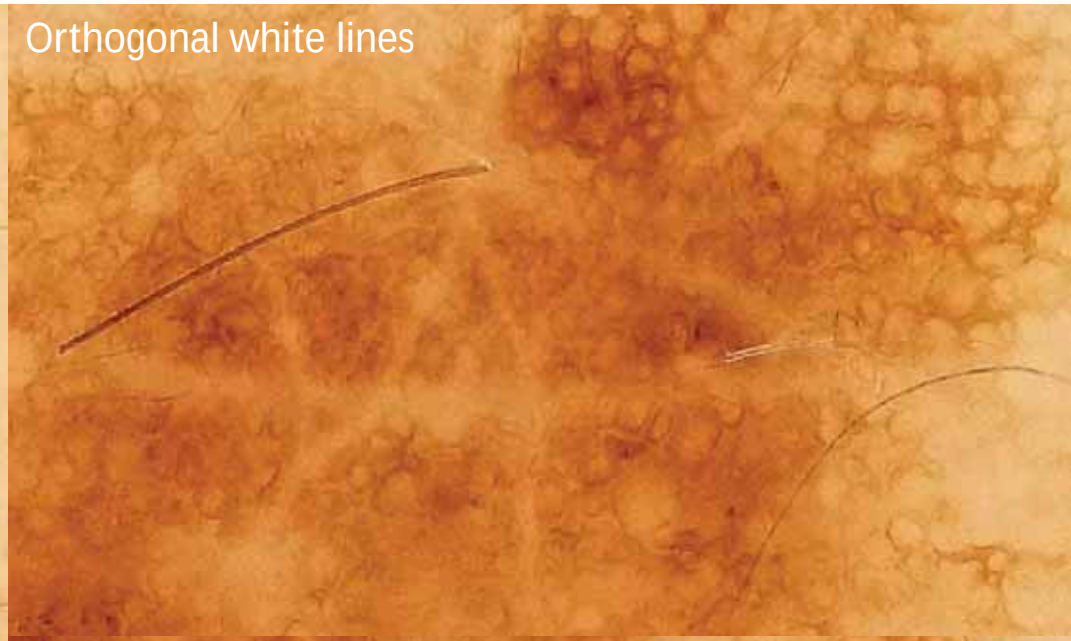


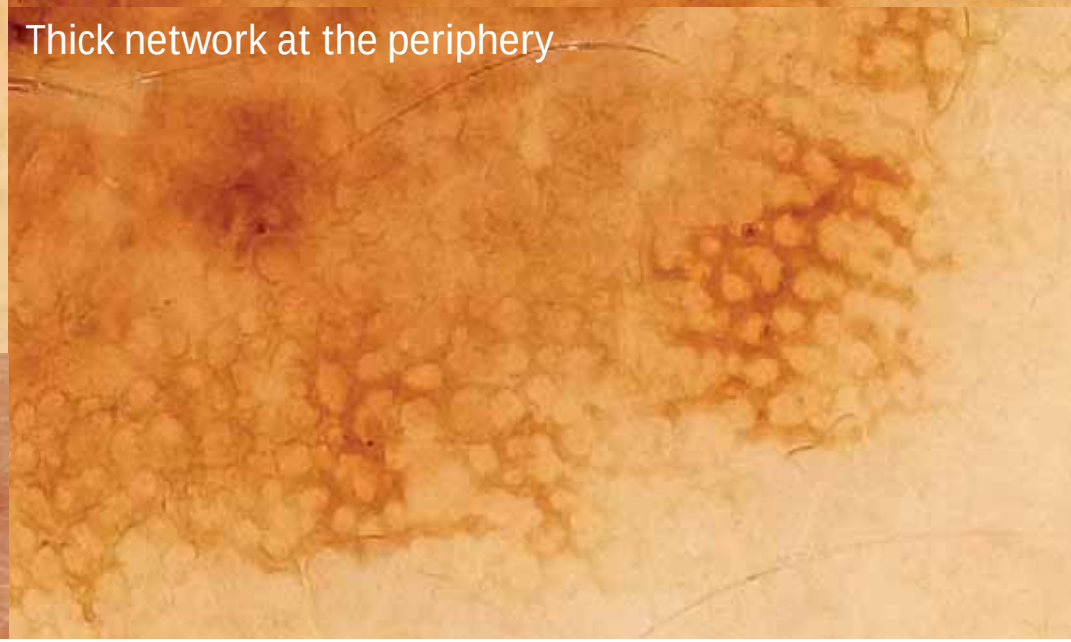


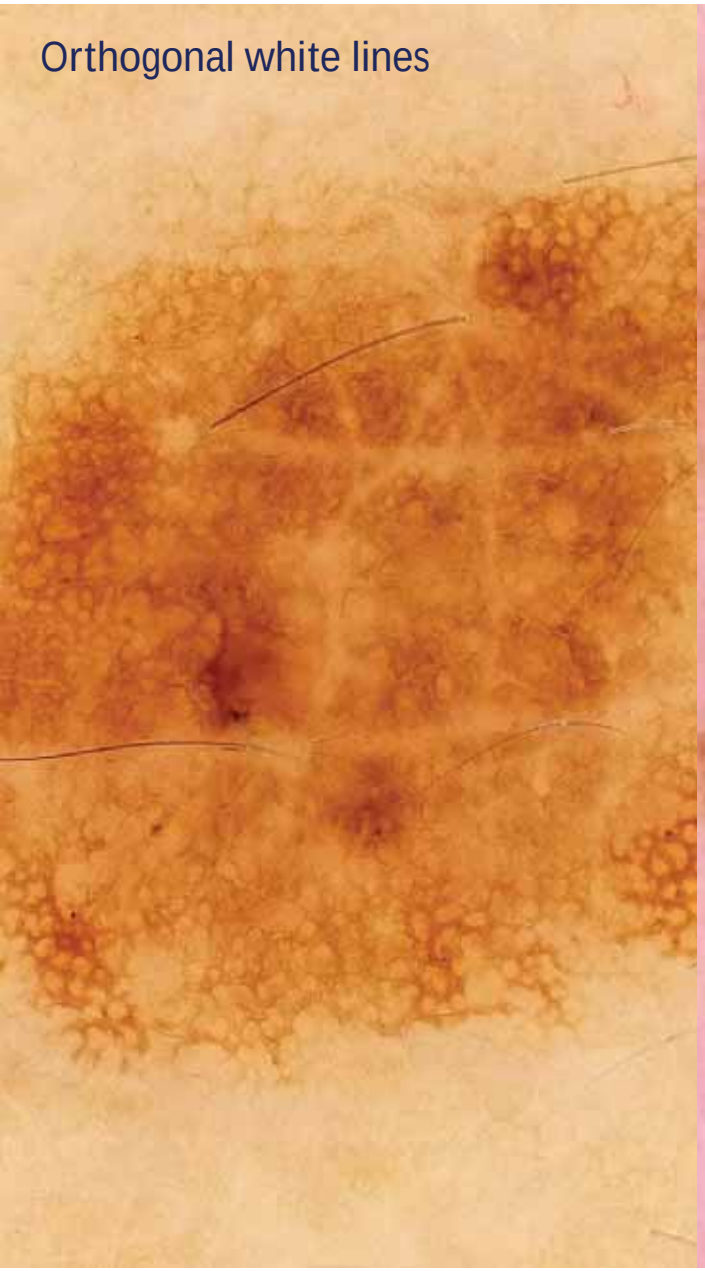




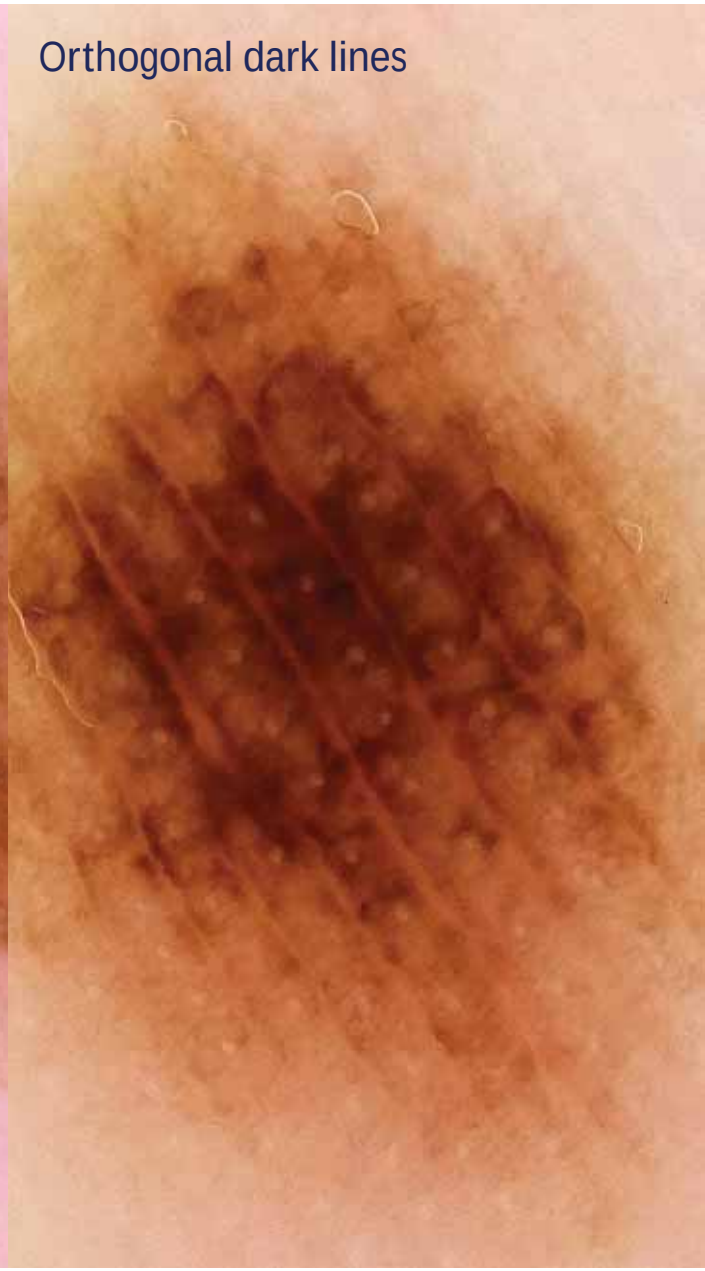


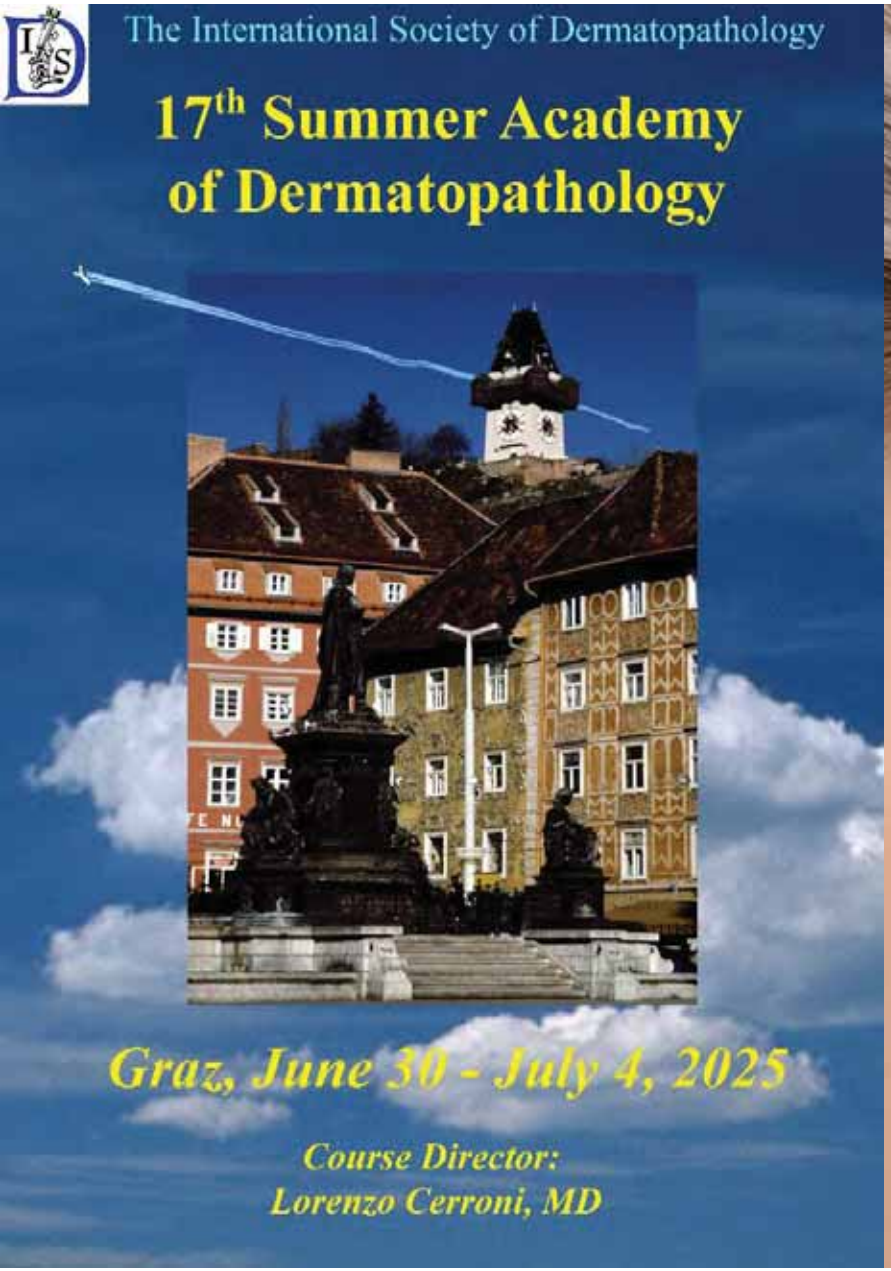

Orthogonal white lines

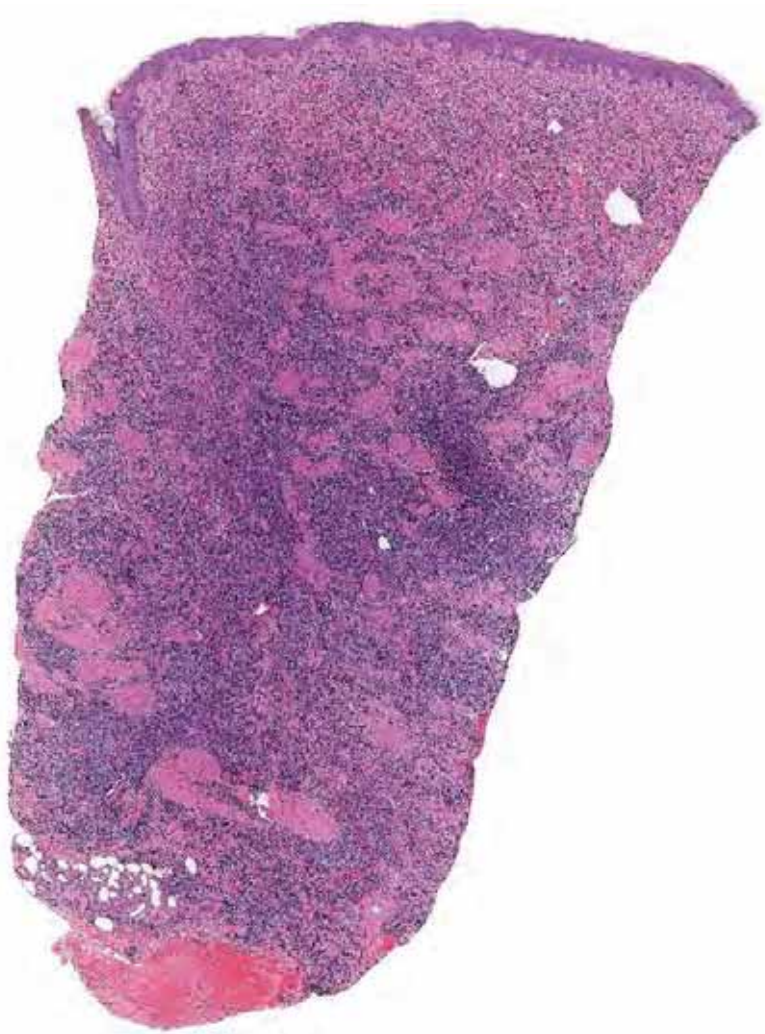

Thick network at the periphery


Orthogonal white lines

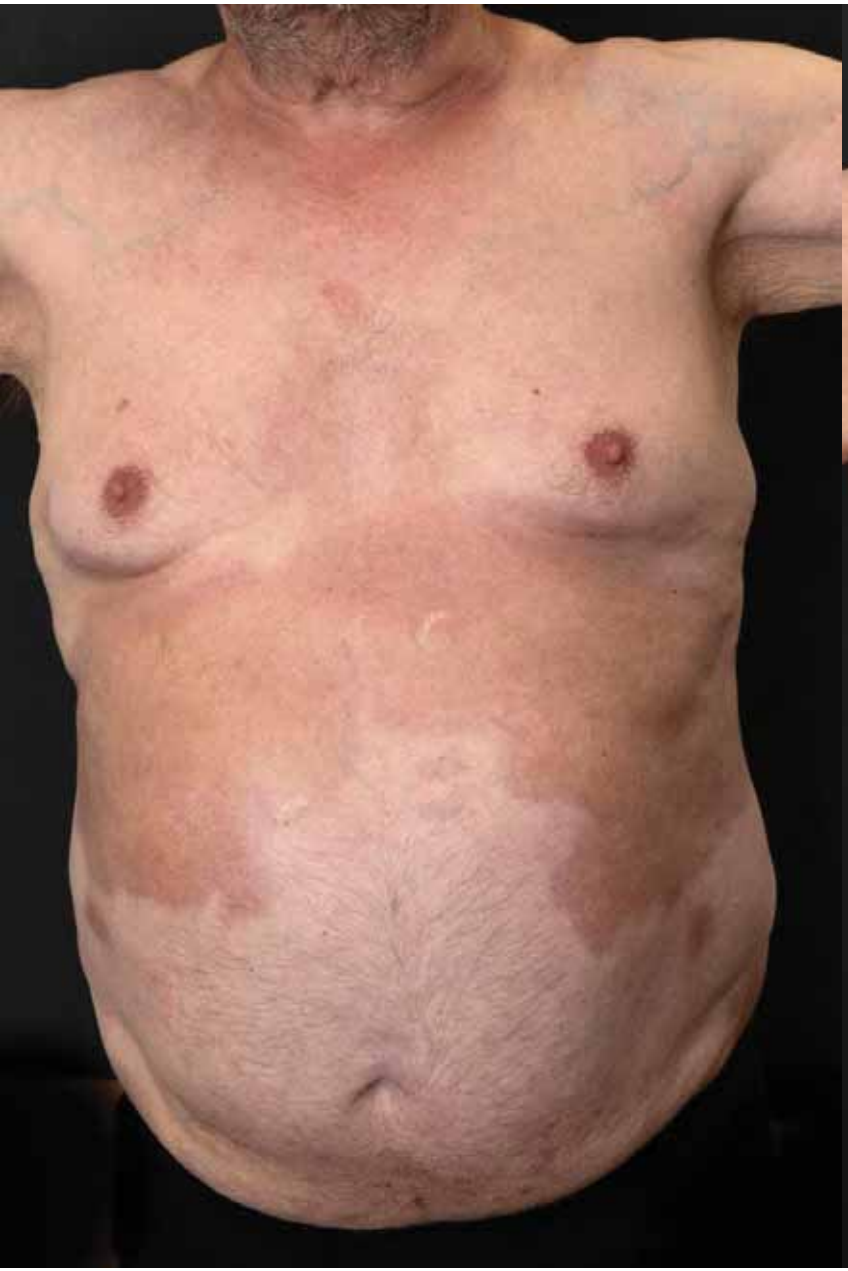

Mikado sign

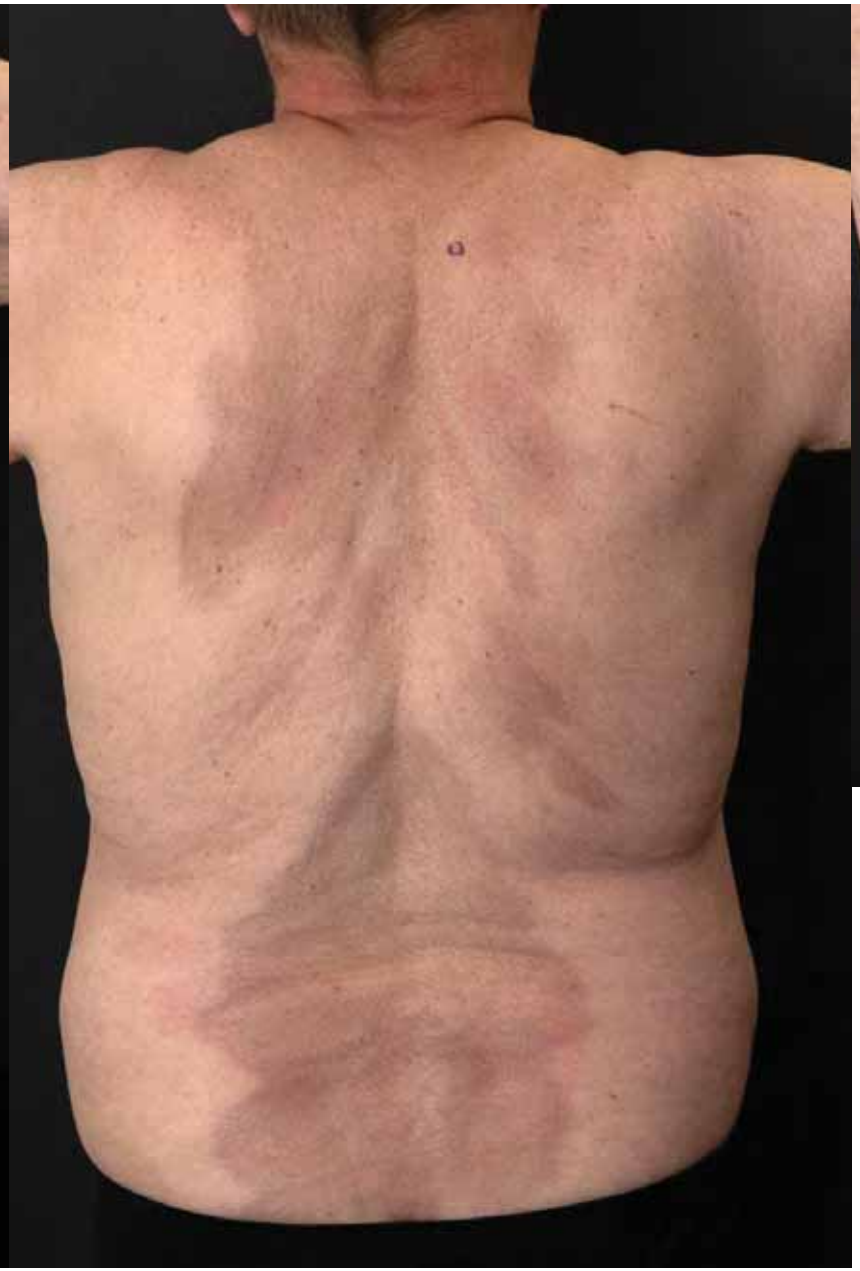

Orthogonal dark lines

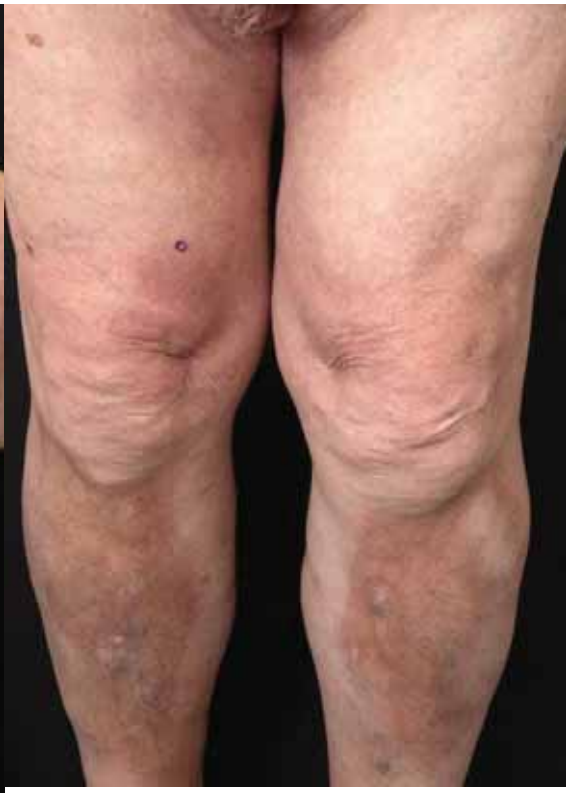




Cutaneous infections & pseudolymphomas: An overlapping world





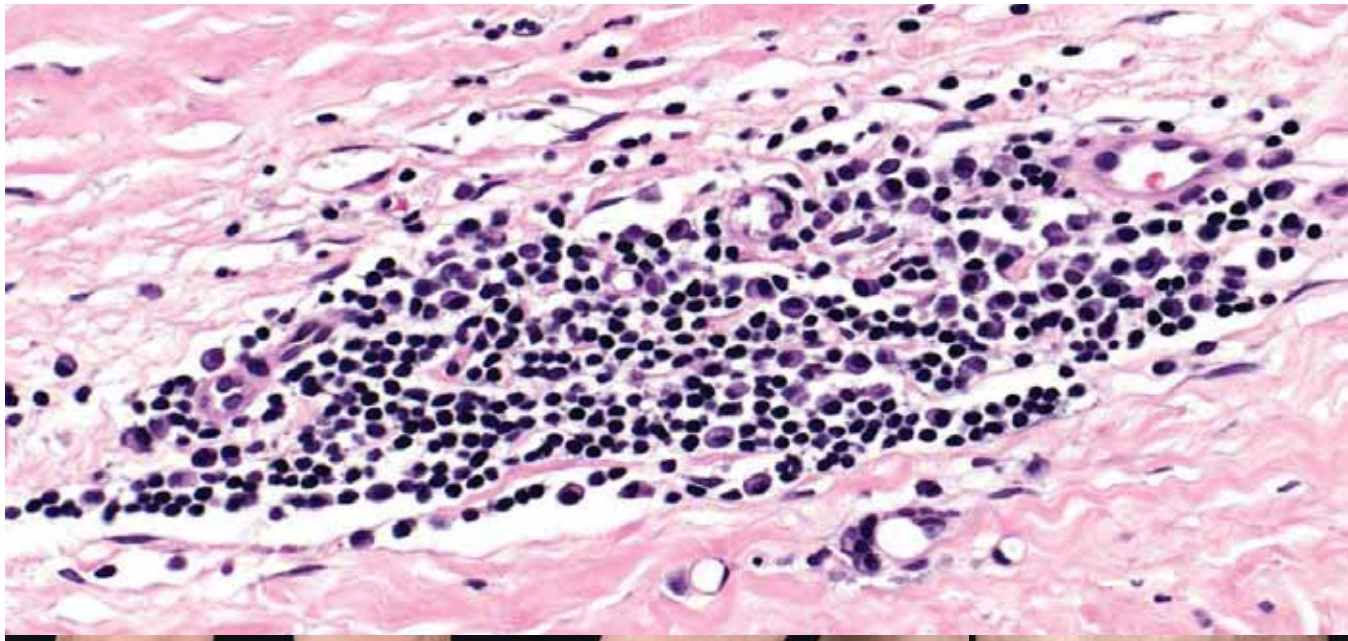


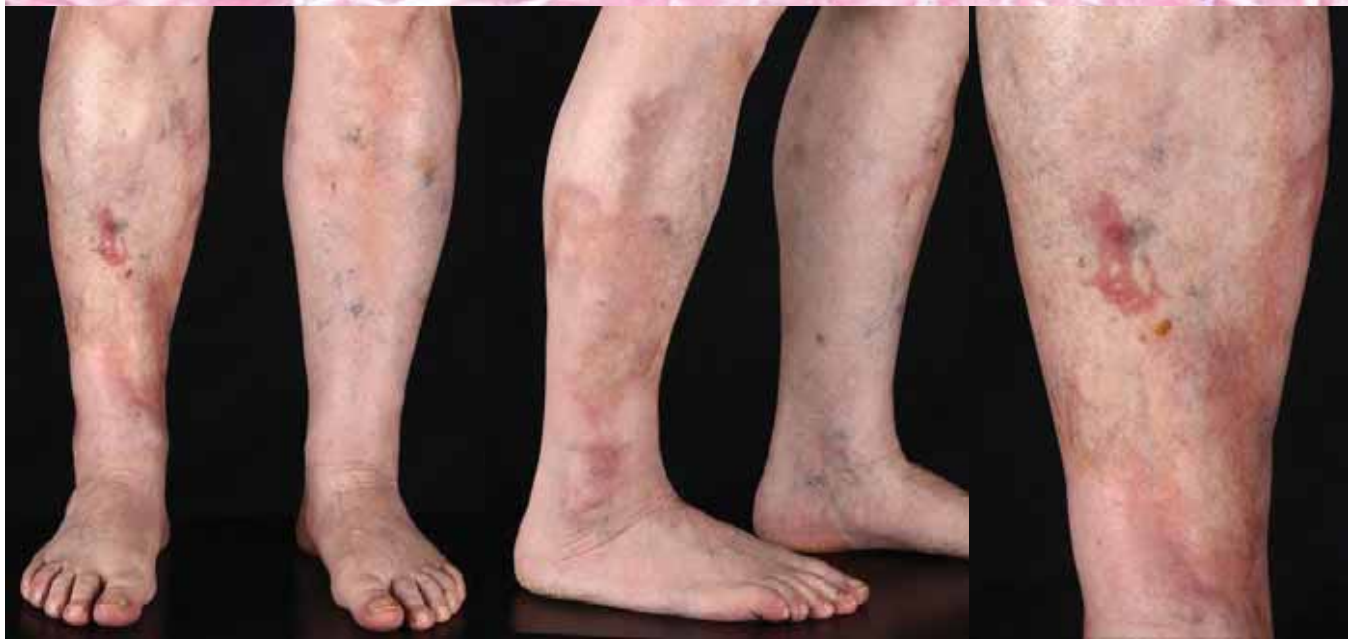
M, 70

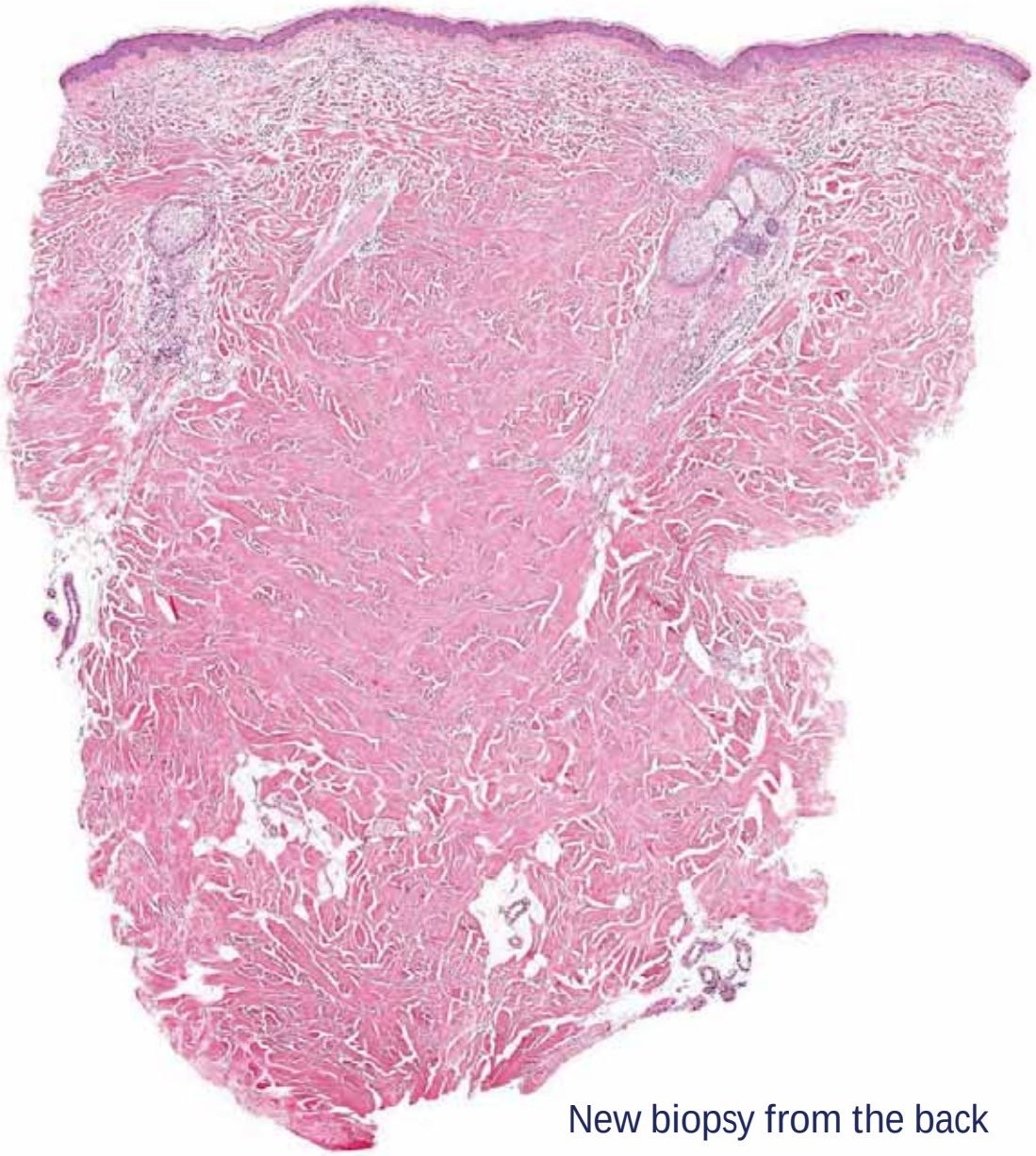
Diagnosis of "necrobiosis lipoidica" on both legs 13 years previously ("verified histologically"); new lesions on the trunk in the following years. According to the patient new erythematous lesions on the trunk and thighs for several days.

Two biopsies are taken (back, right thigh).

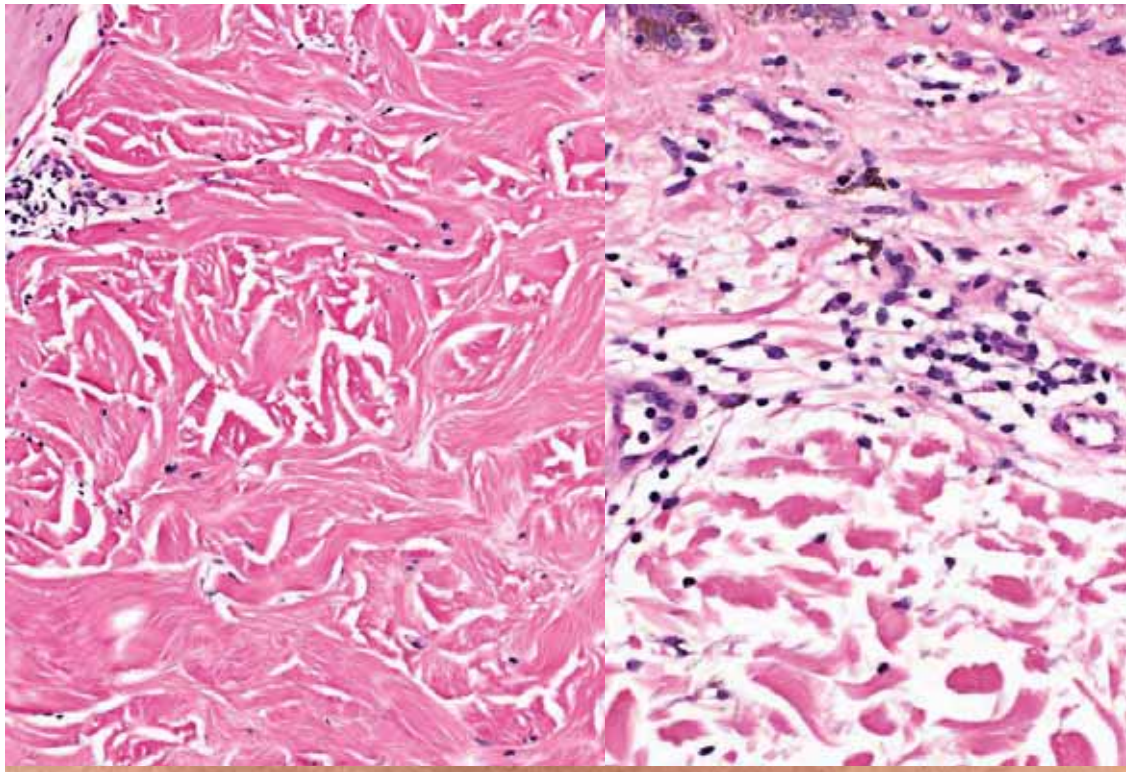
10 years previously

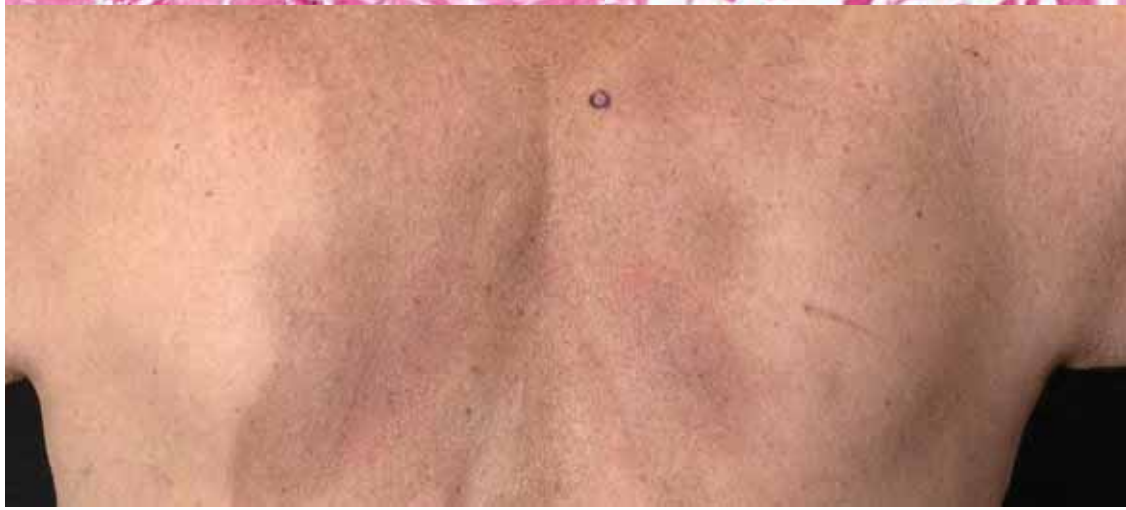


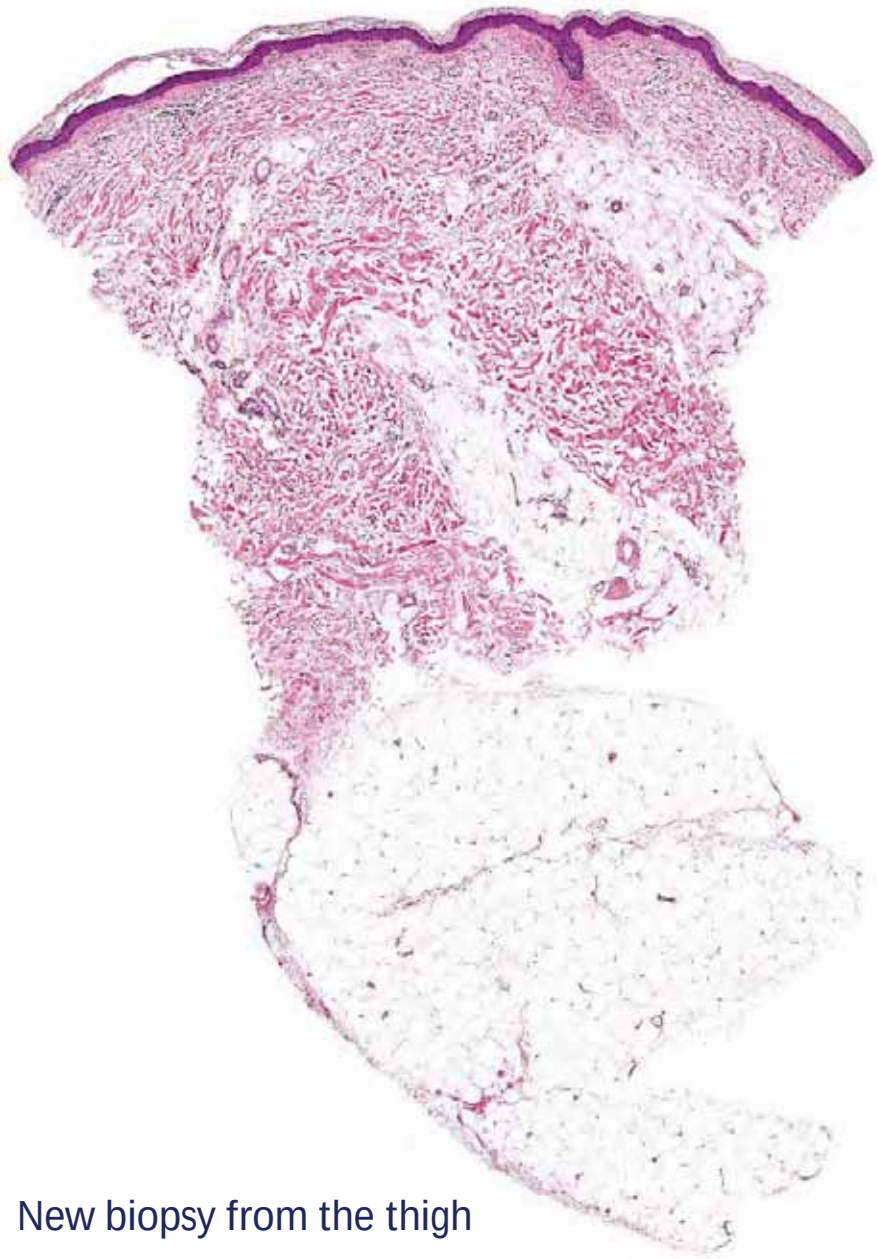




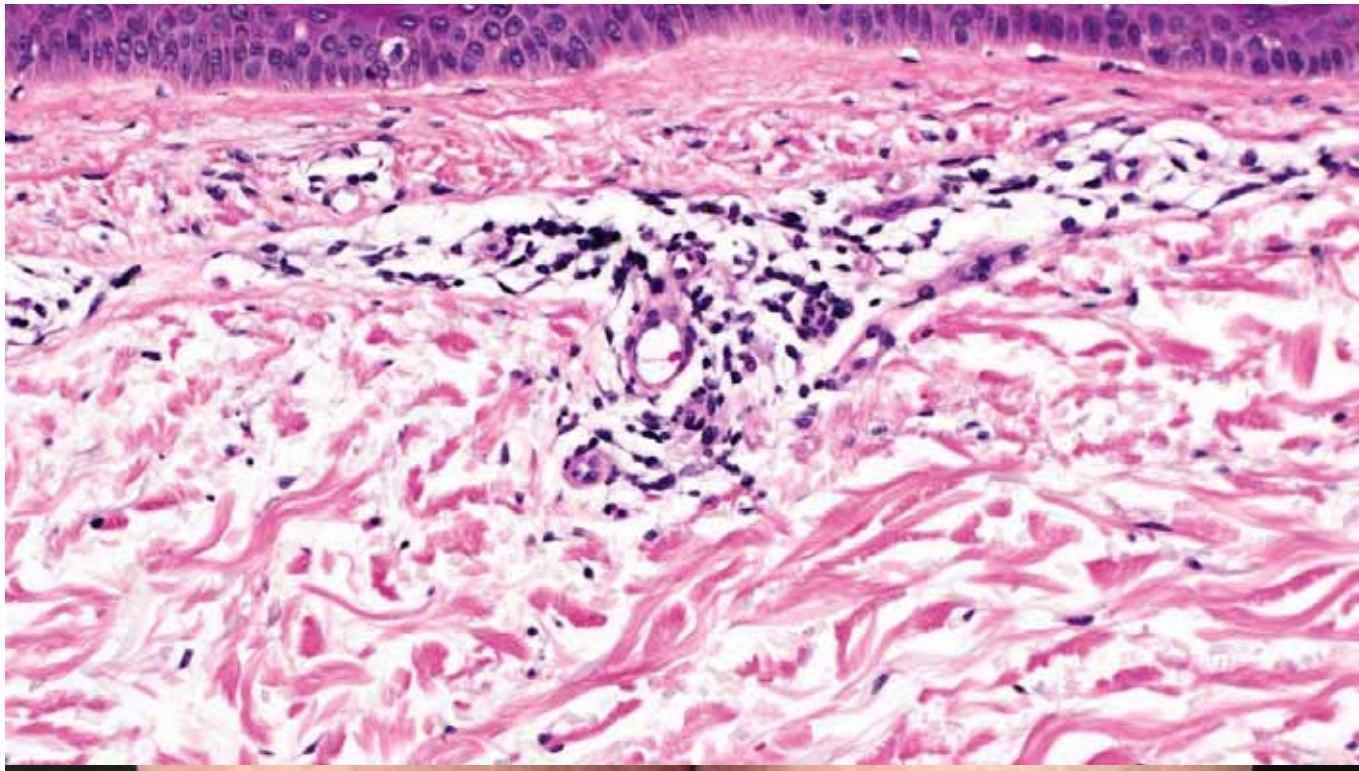
New biopsy from the back

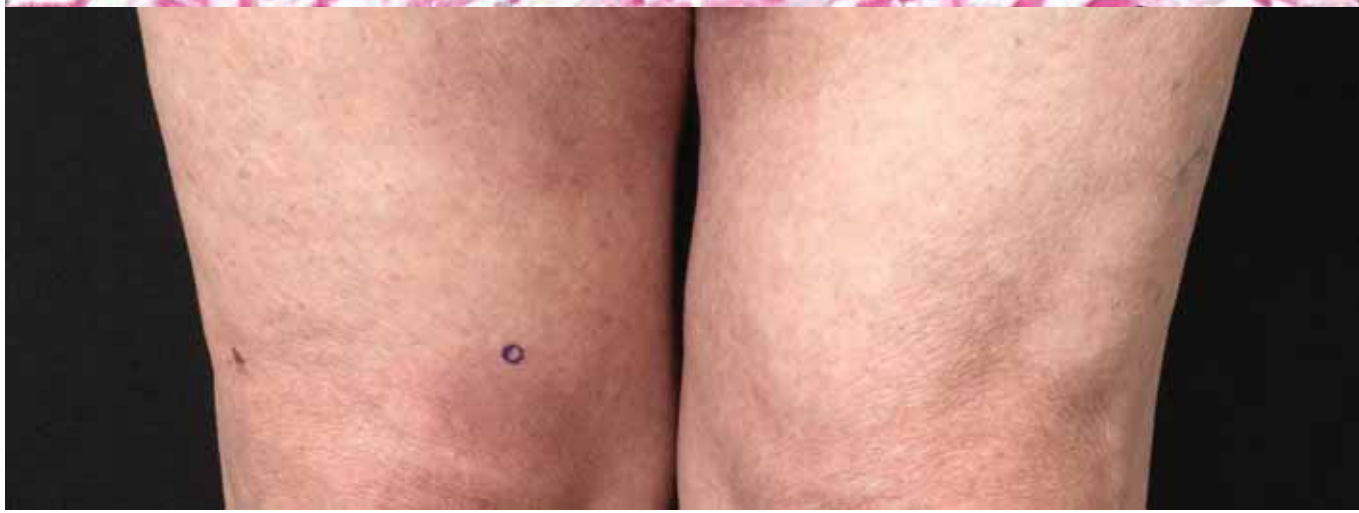


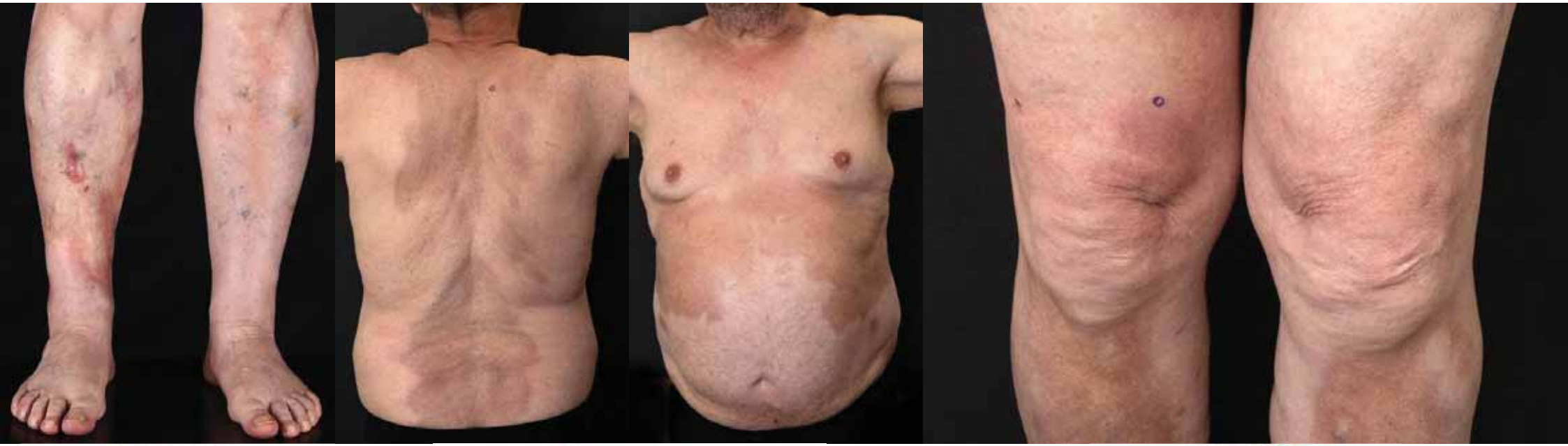


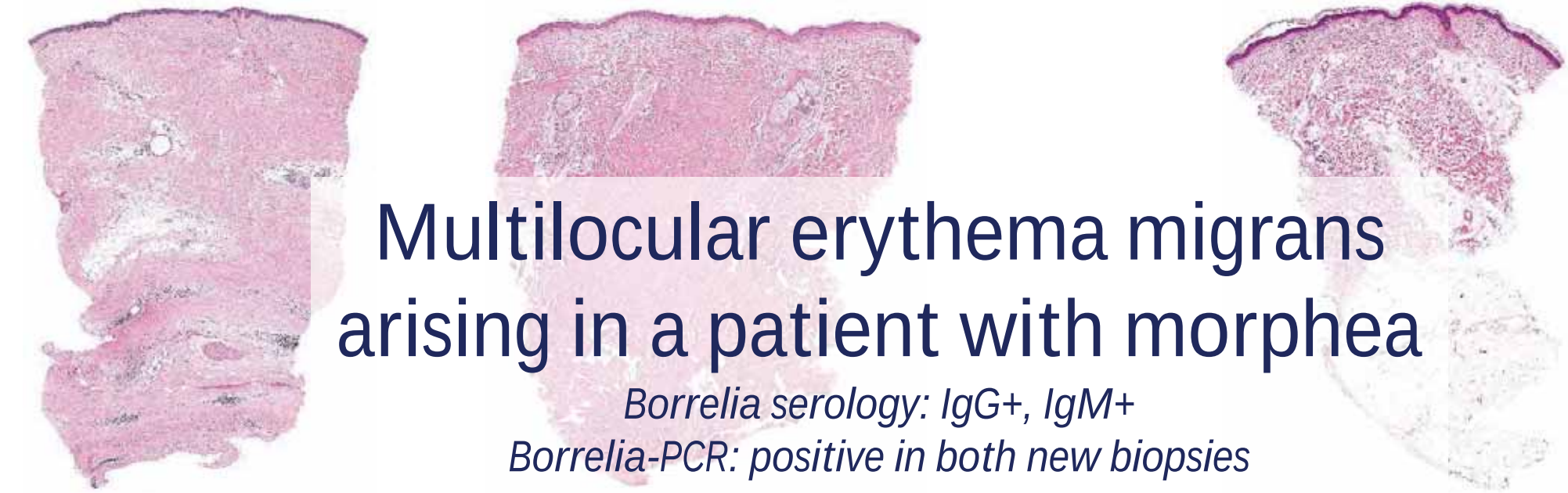


New biopsy from the thigh





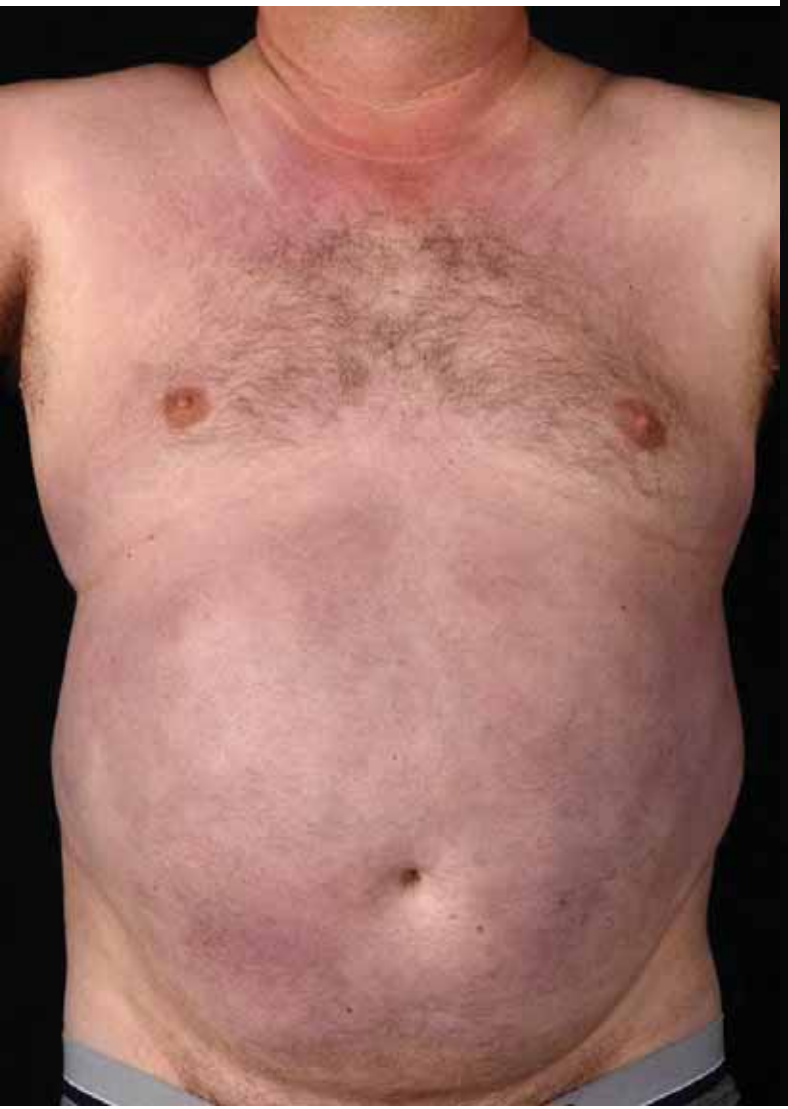


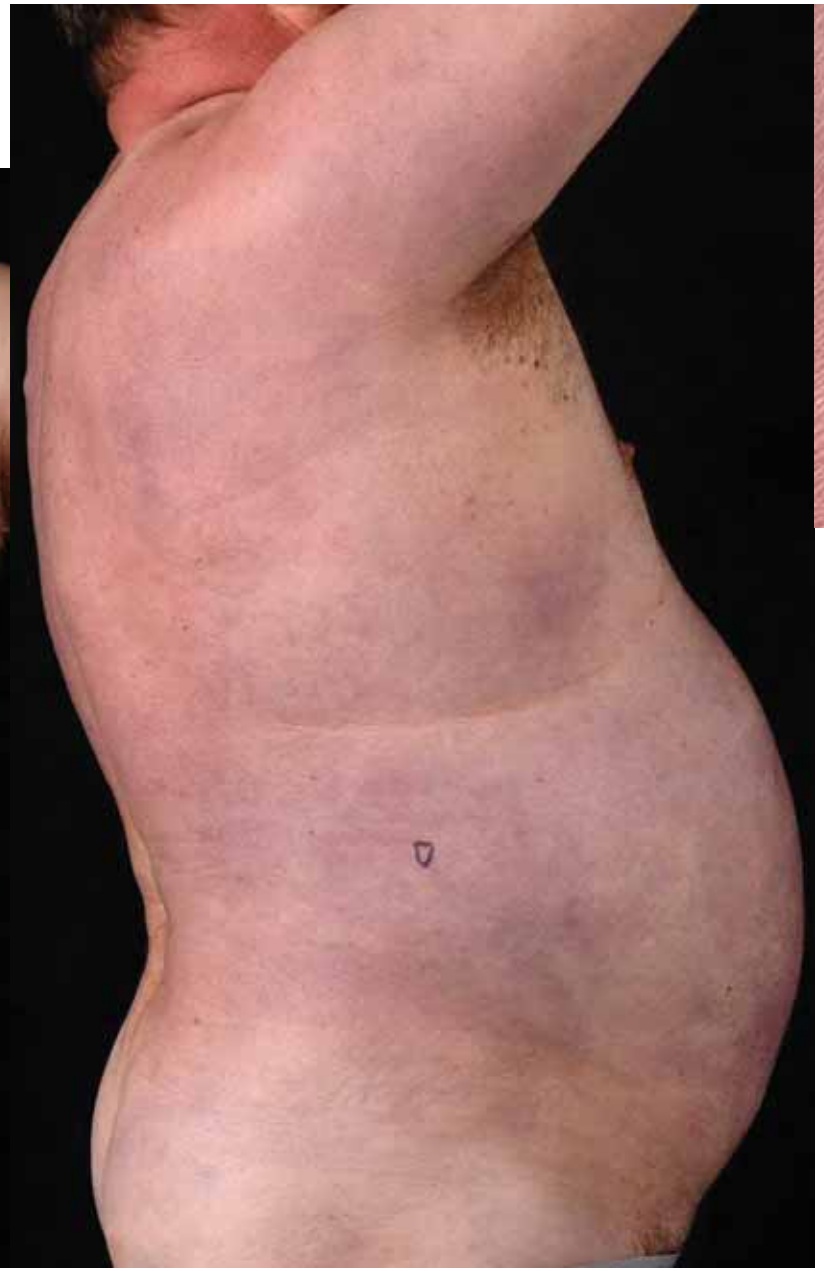


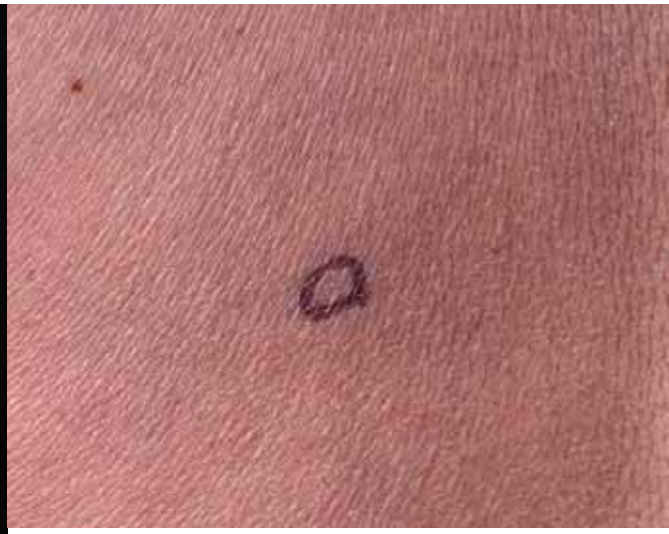
Multilocular erythema migrans arising in a patient with morphea

Borrelia serology: IgG+, IgM+

Borrelia-PCR: positive in both new biopsies





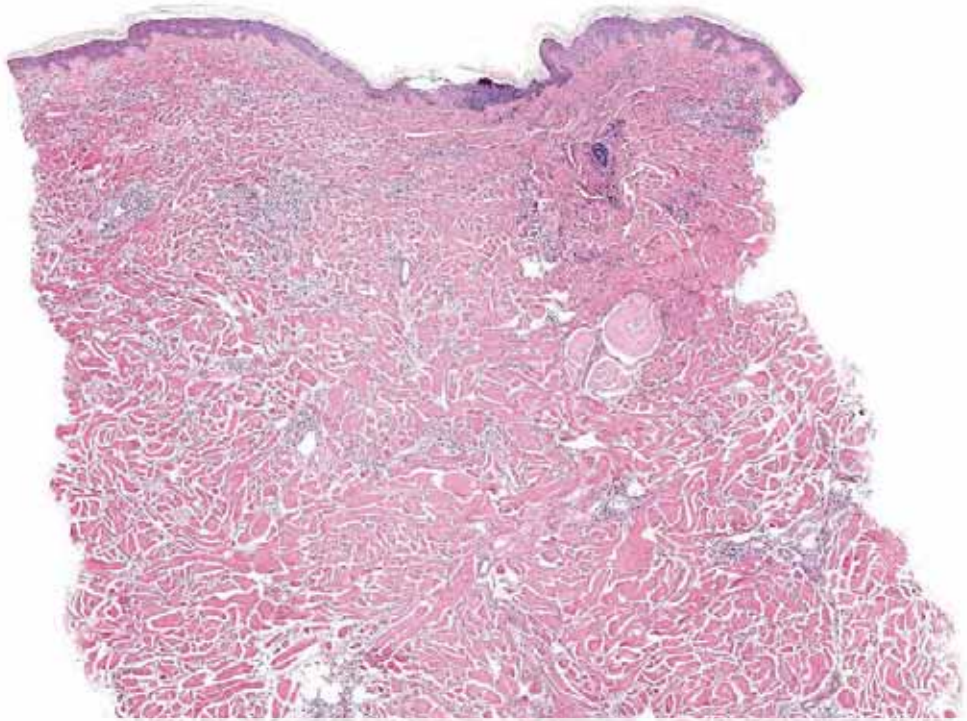


M, 59

According to the patient livid discoloration of the skin on the trunk and upper extremities for approximately 6 months. Does not remind of a tick bite in the last years.

Currently evaluated by hematologists for MGUS and elevation of ferritin.

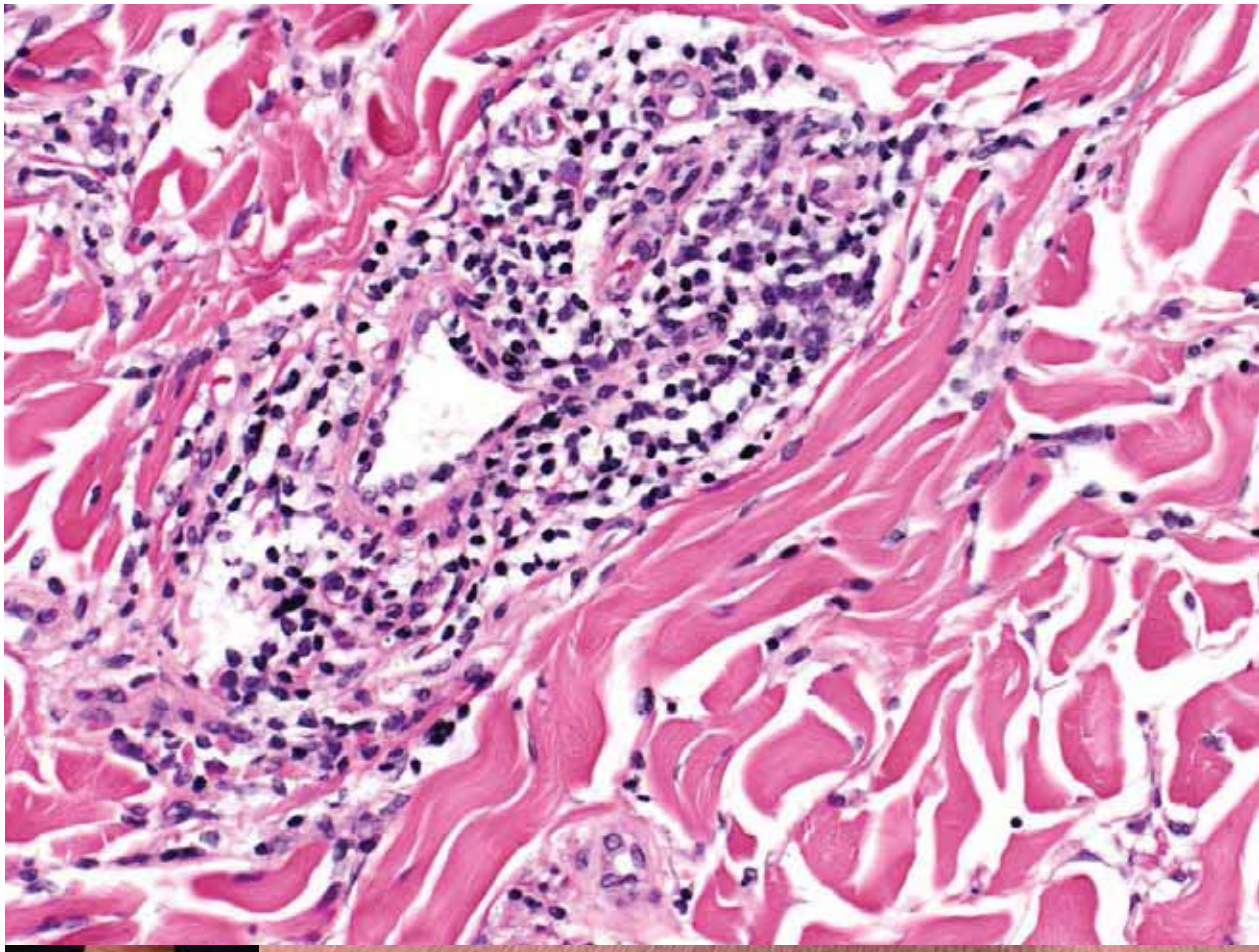
Two biopsies are taken (right flank, left abdomen).

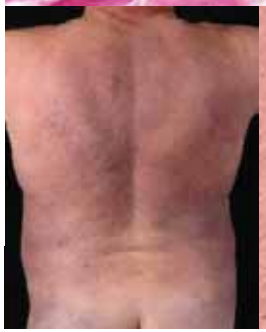


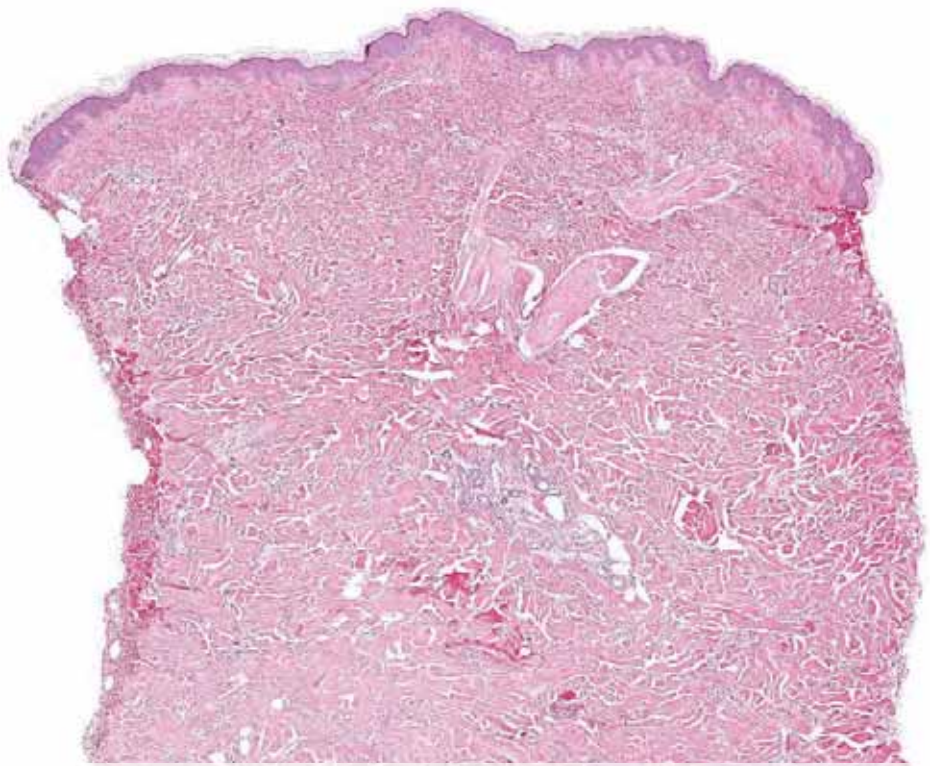
Acrodermatitis chronica atrophicans...

(Borrelia PCR: positive; serology: IgM+, IgG+)

Biopsy from the back



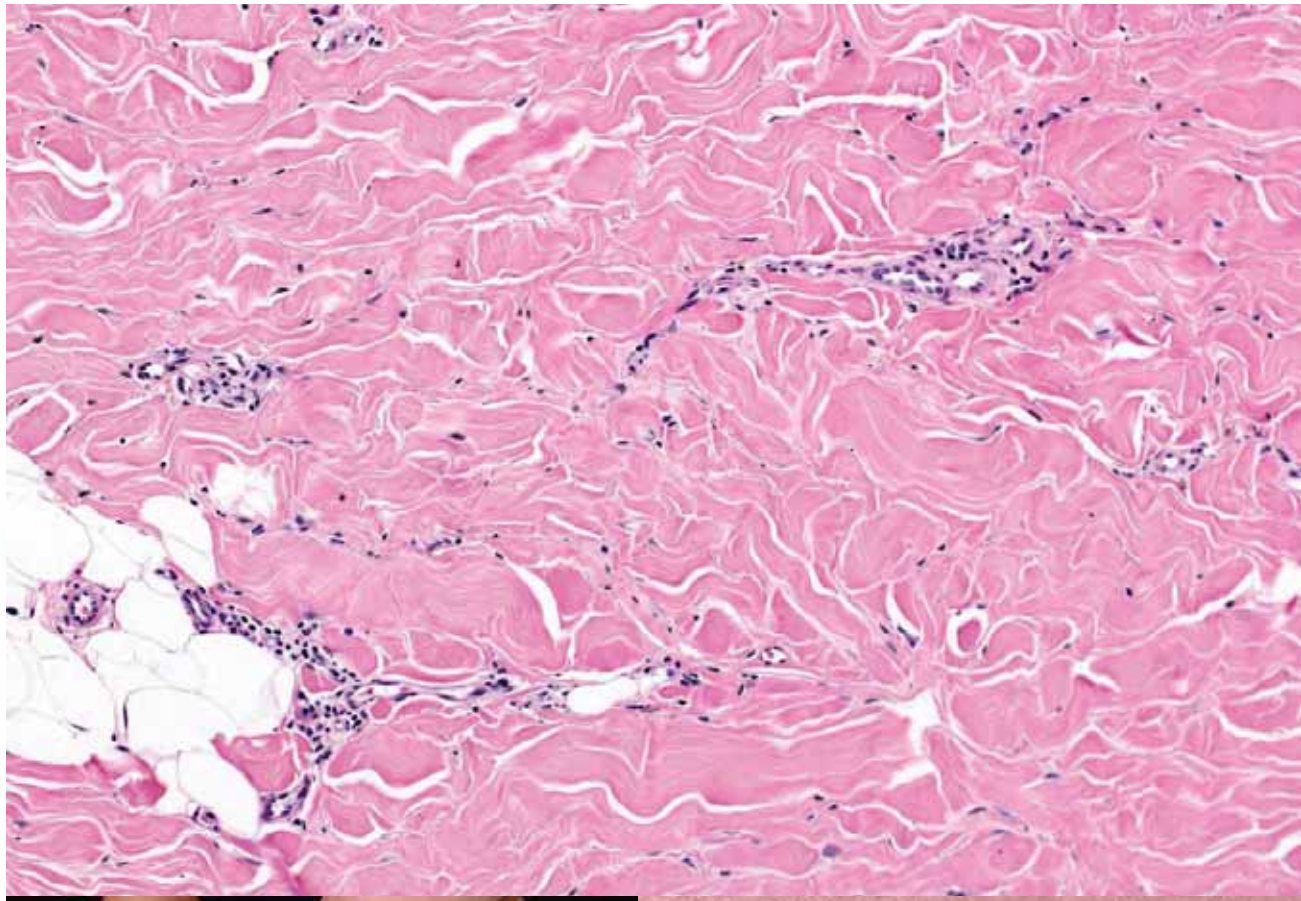


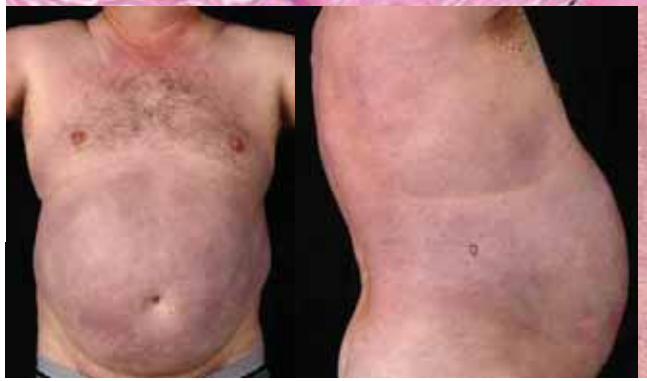


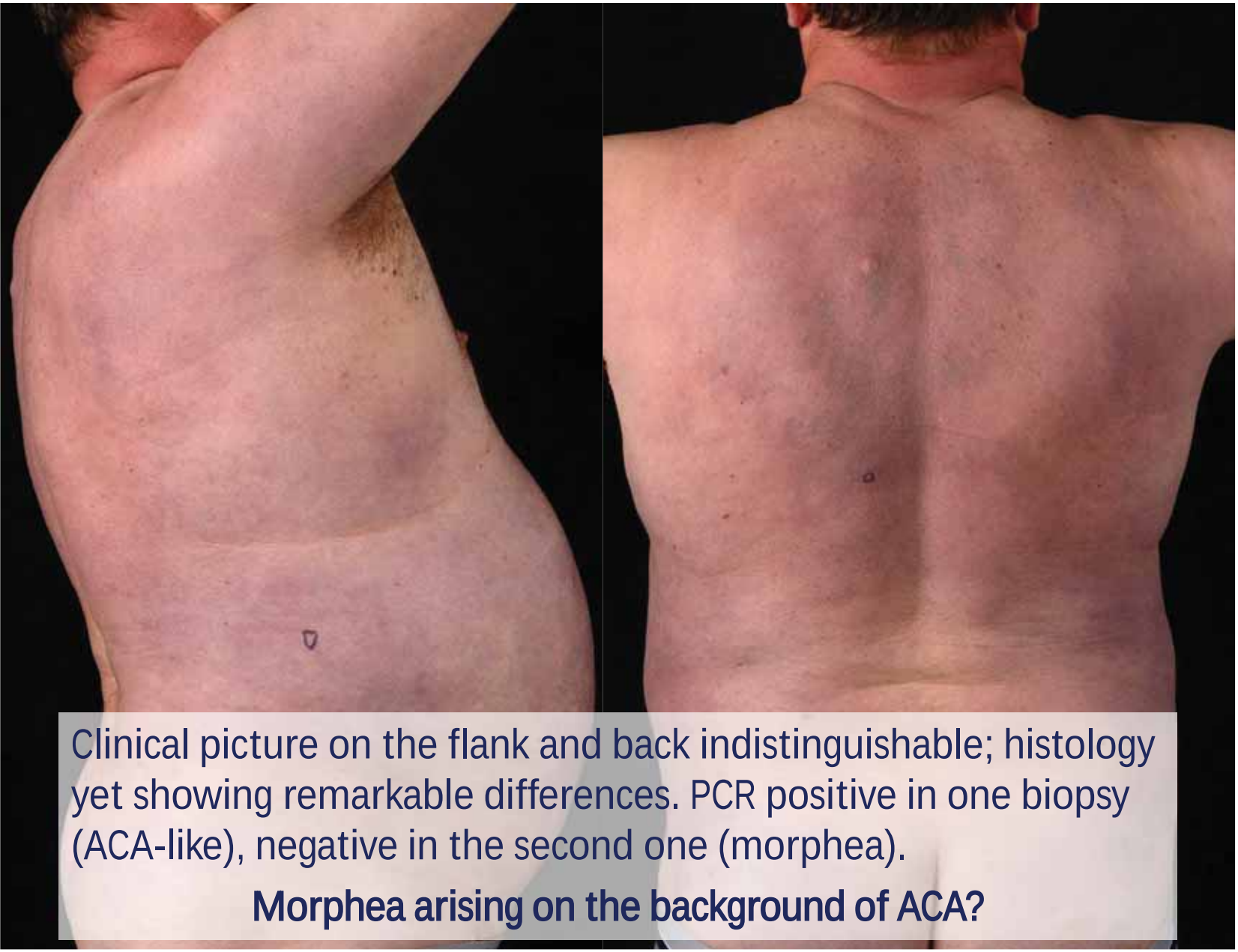
...localized scleroderma

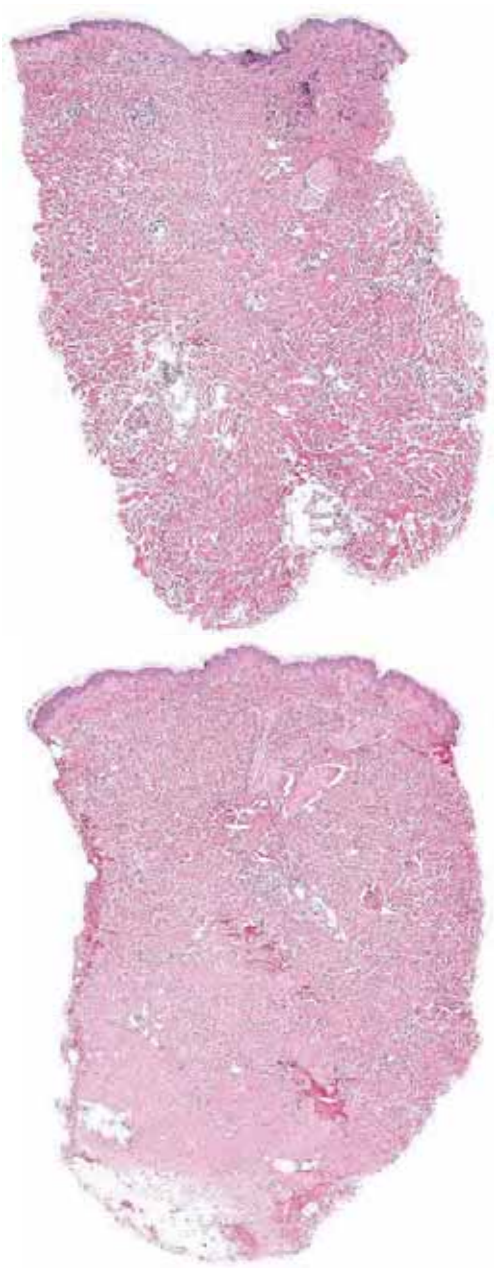
(Borrelia PCR: negative)

Biopsy from the right flank



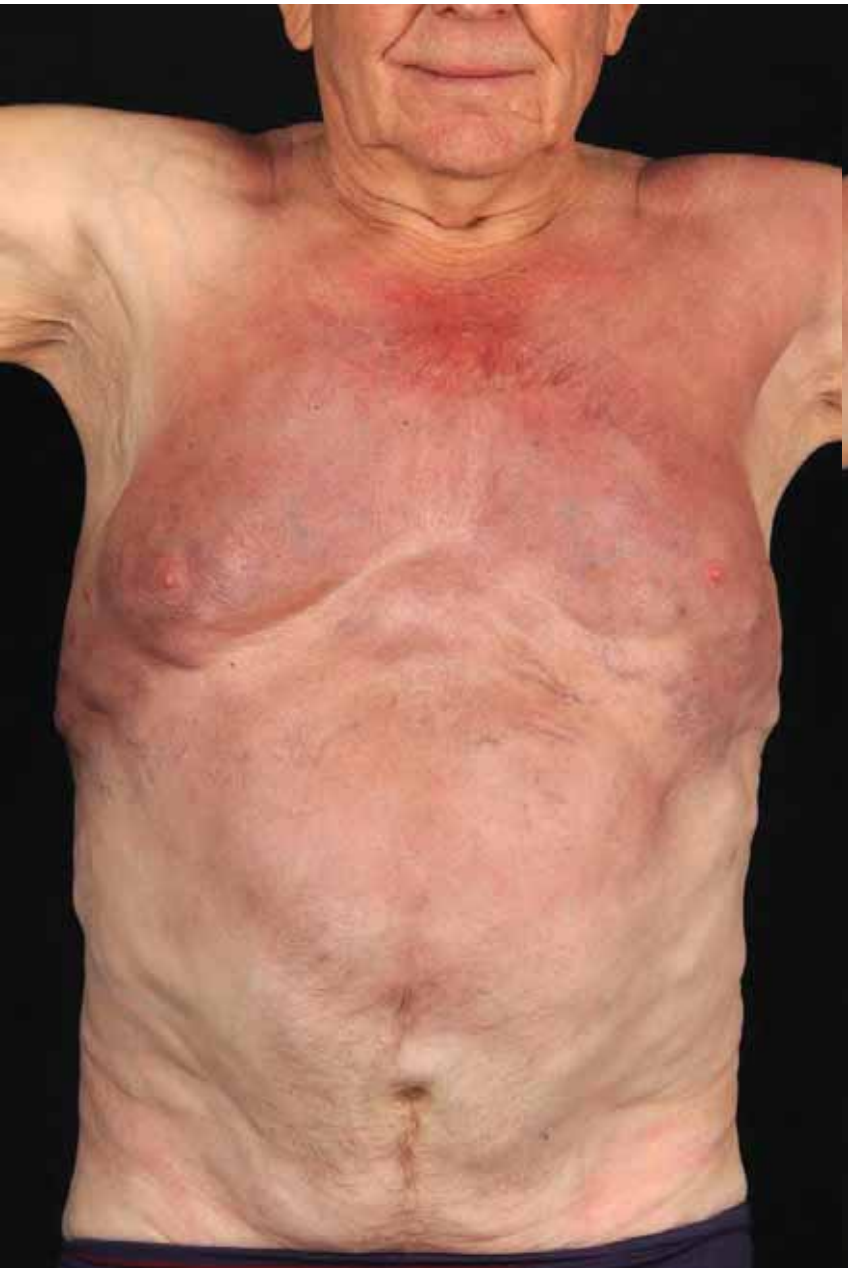


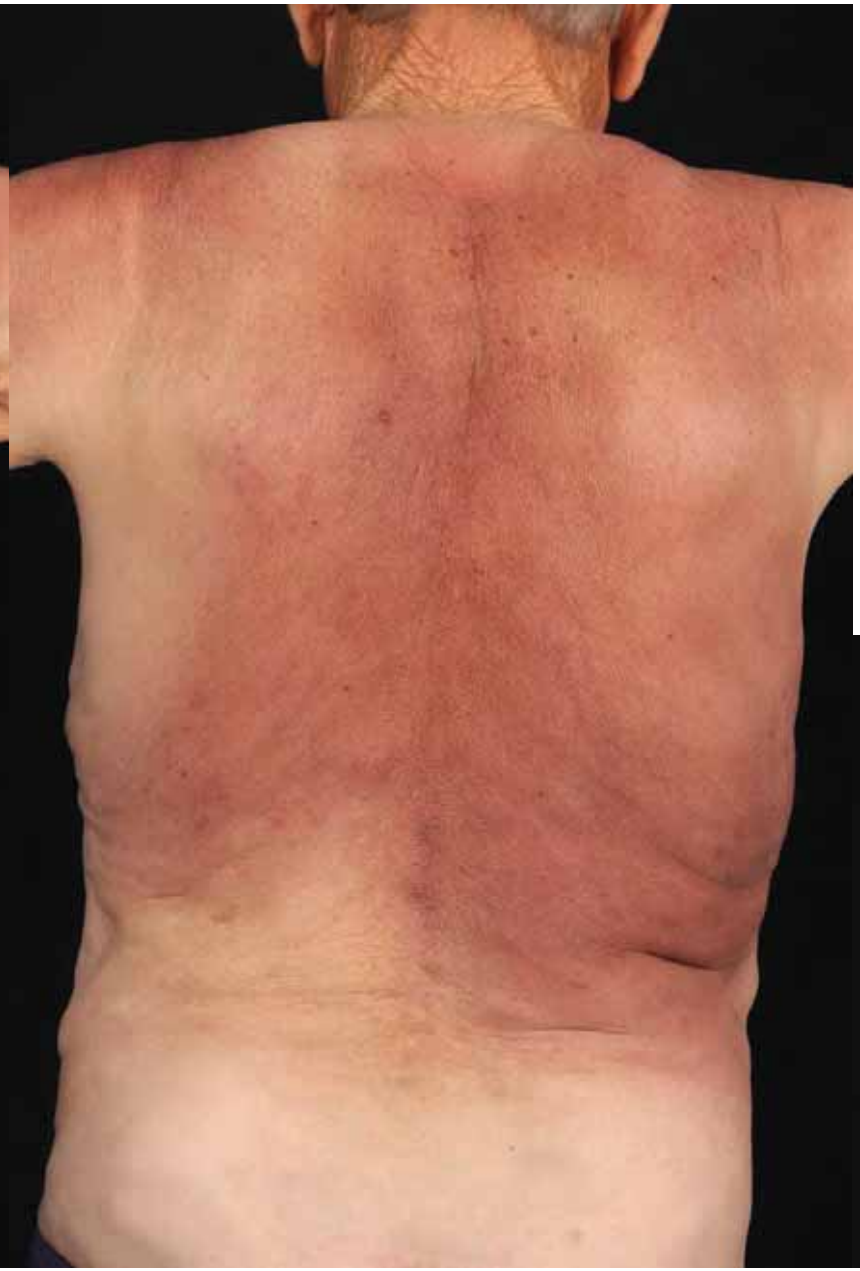


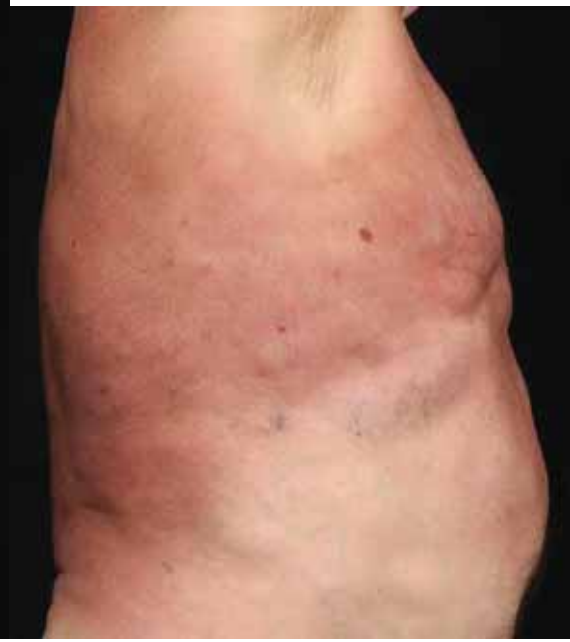


Clinical picture on the flank and back indistinguishable; histology yet showing remarkable differences. PCR positive in one biopsy (ACA-like), negative in the second one (morphea).

Morphea arising on the background of ACA?





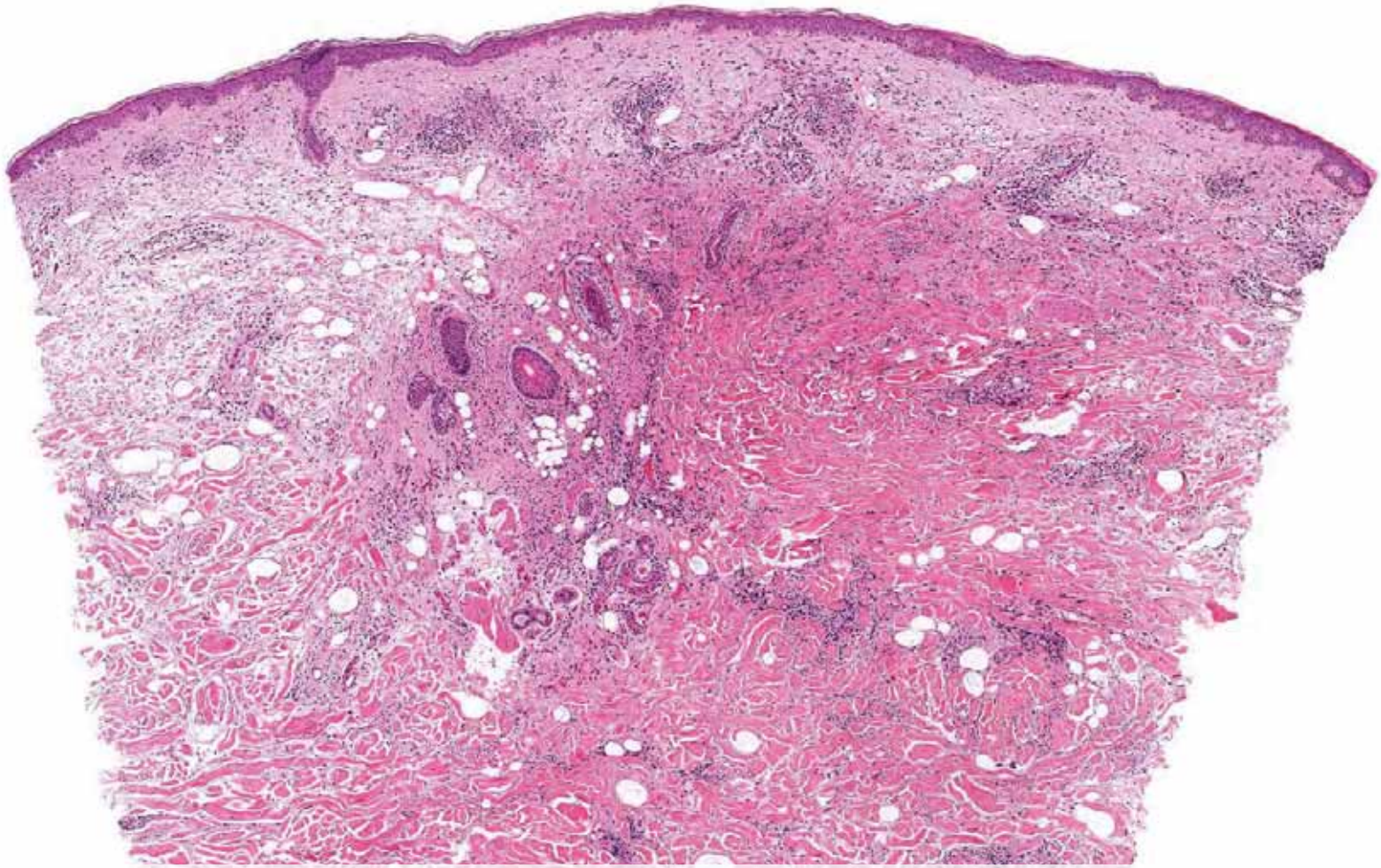


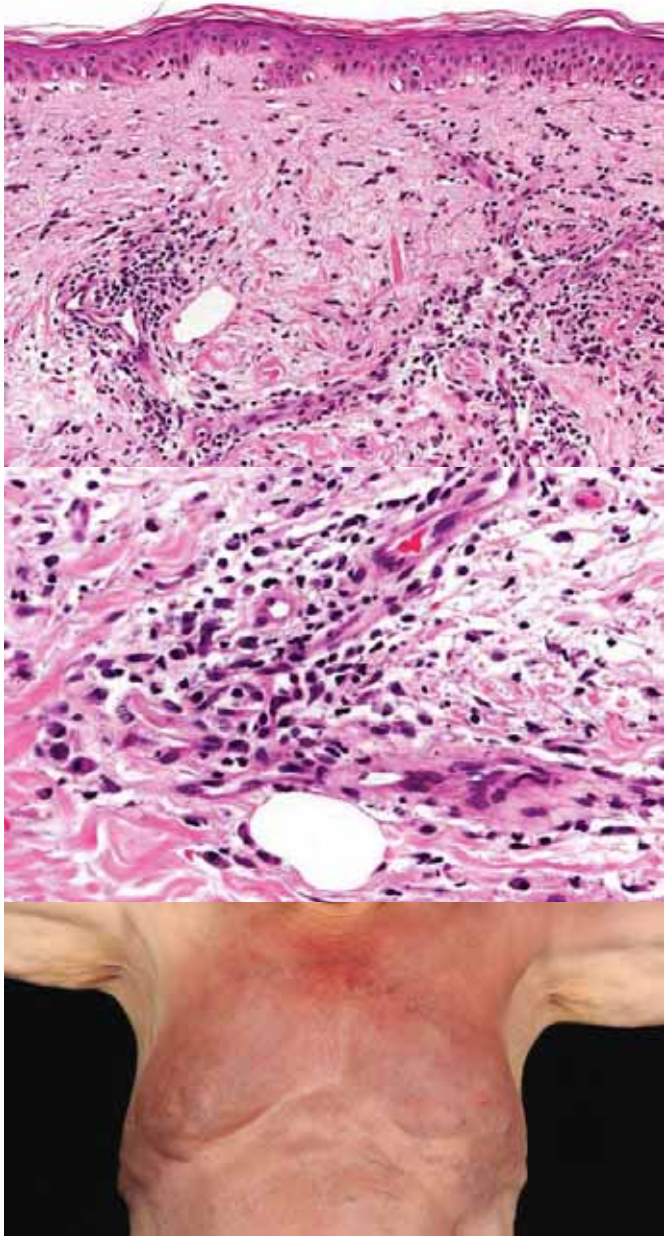
M, 79

History of essential thrombocythemia diagnosed 4 years before presentation (mutation V617F in the JAK-2 kinase), managed with hydroxyurea.

According to the patient skin changes for more than 1 year.

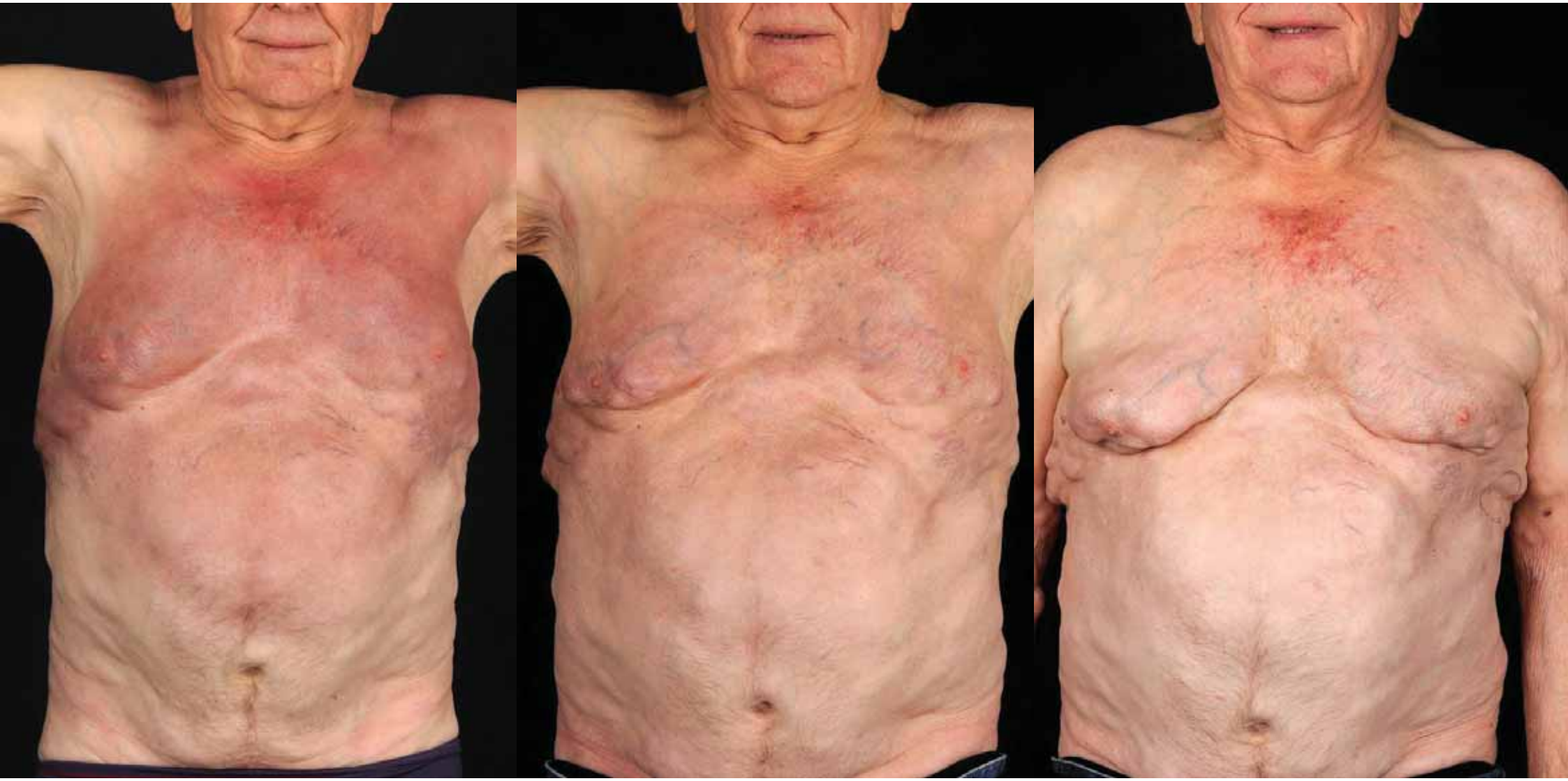
A biopsy is taken.





Acrodermatitis chronica atrophicans

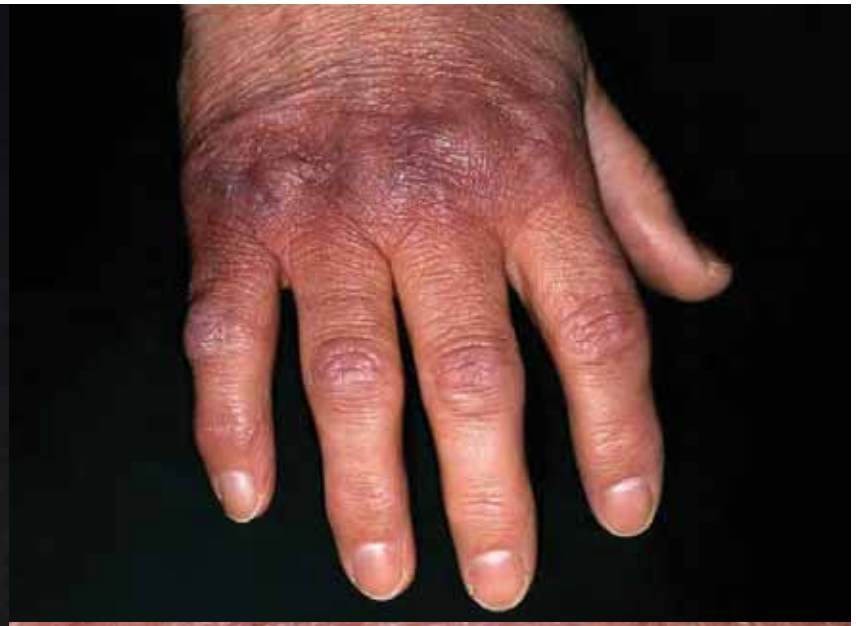
(PCR for Borrelia positive; serology: IgM+, IgG+)

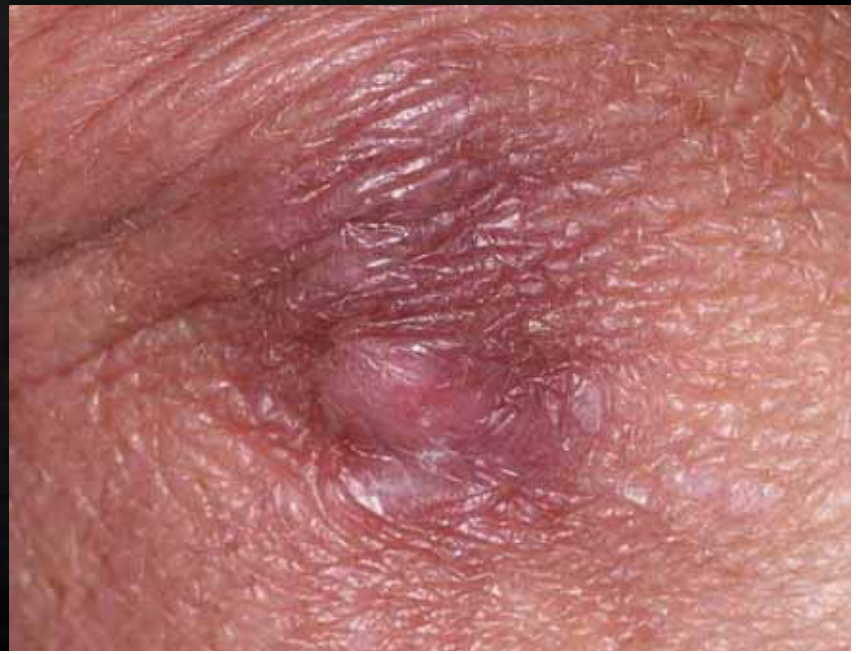


1st presentation
(started on doxycycline for 30 days)

5 months later

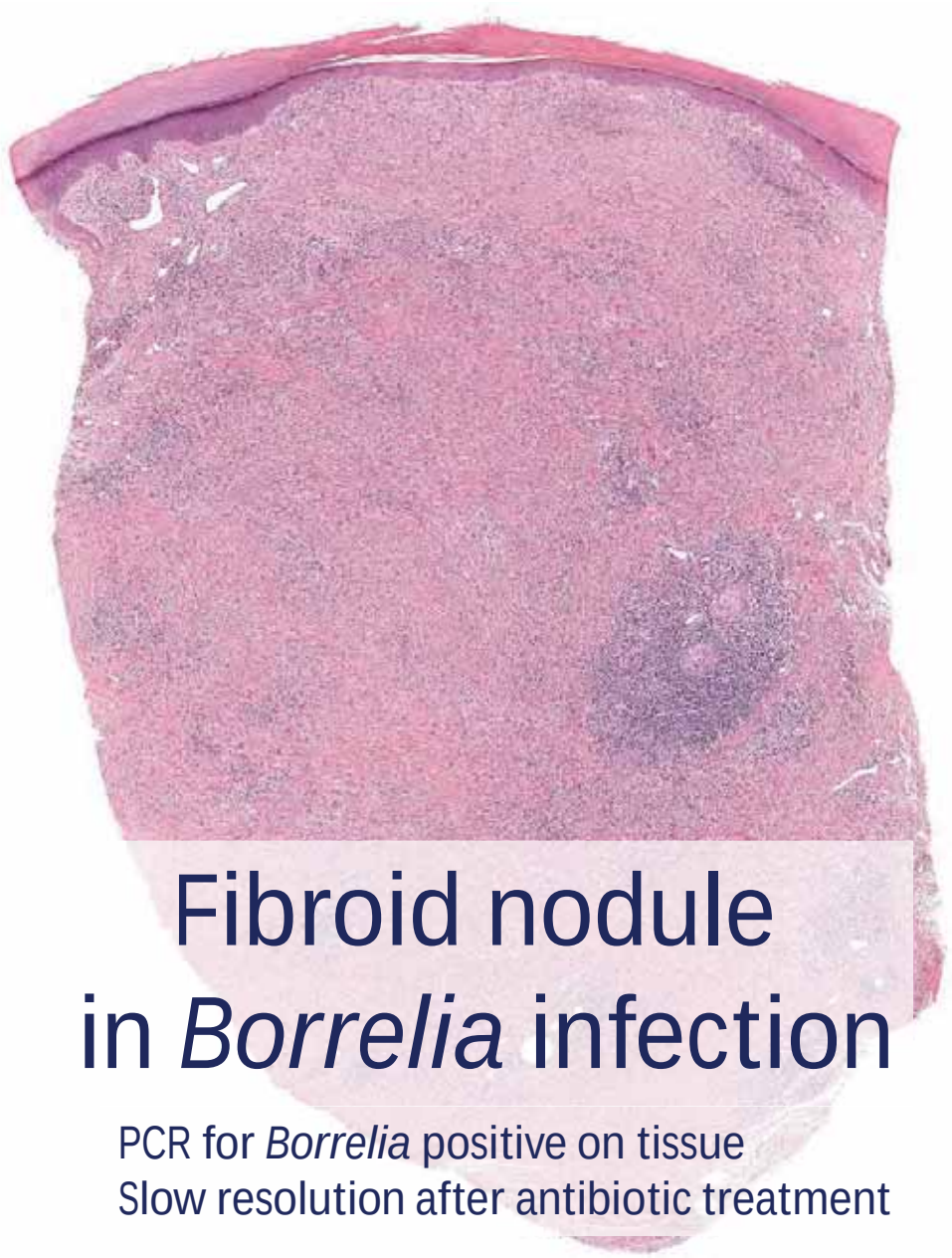
1 year later





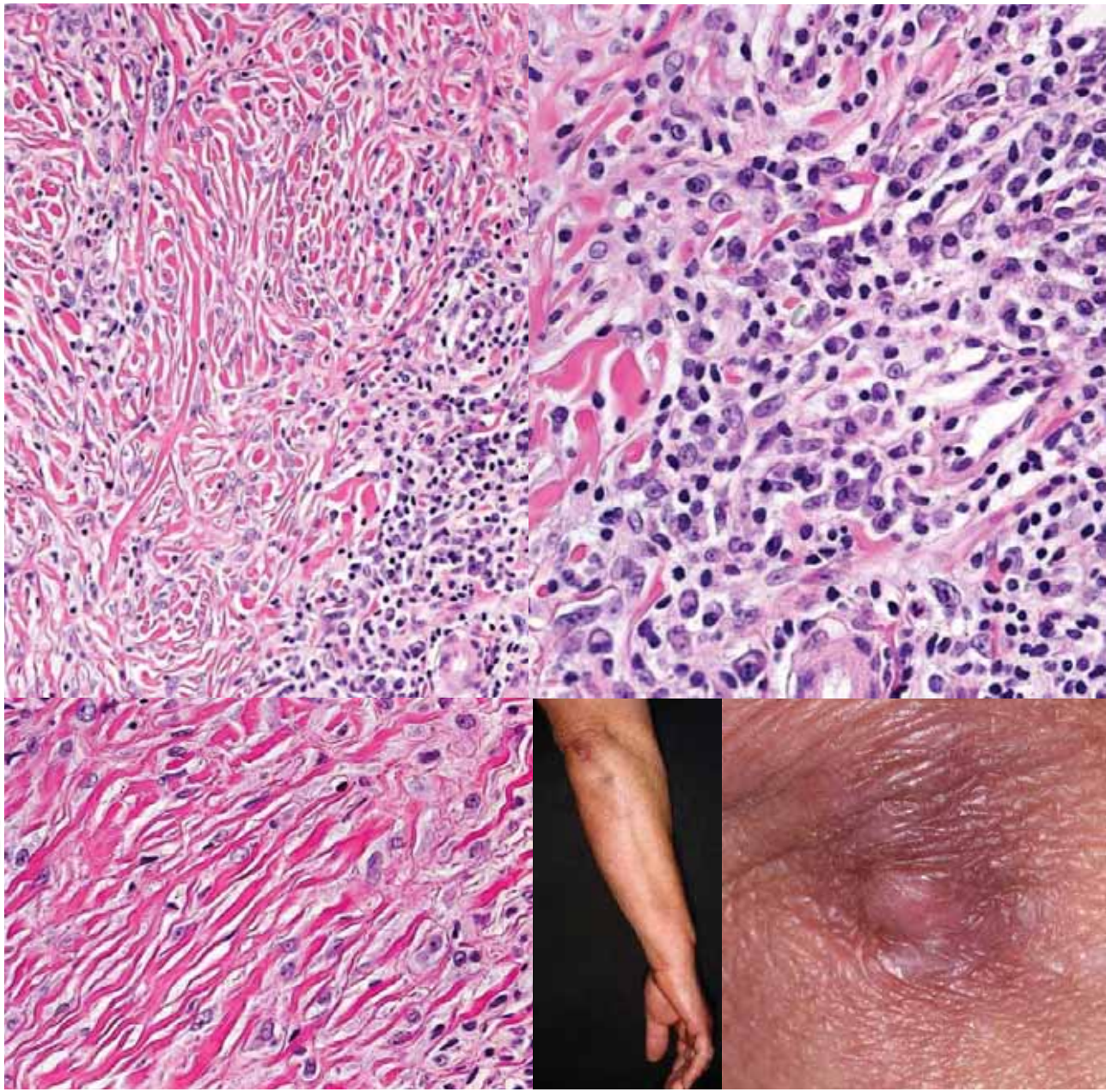
F, 60

Red-brown patches on the dorsum of the right hand with small indurations on the extensor surface of the joints and small nodules on the extensor surface of the right elbow.



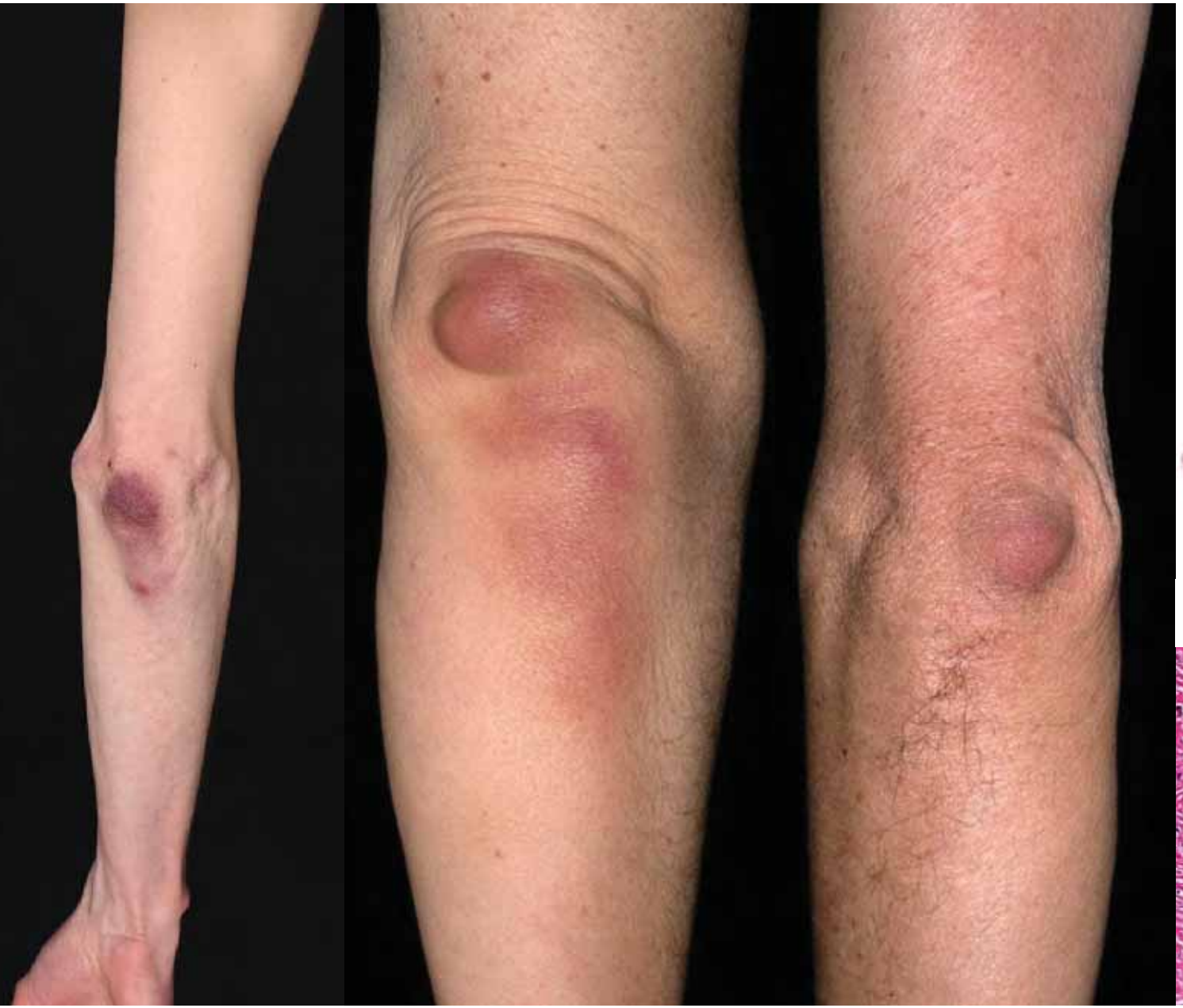
Fibroid nodule in *Borrelia* infection

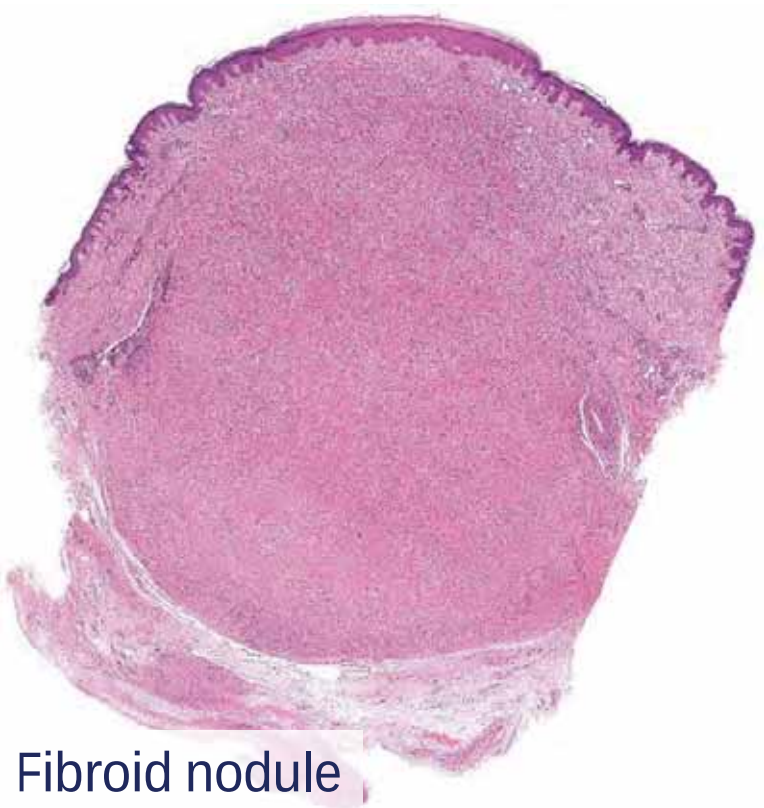
PCR for *Borrelia* positive on tissue
Slow resolution after antibiotic treatment



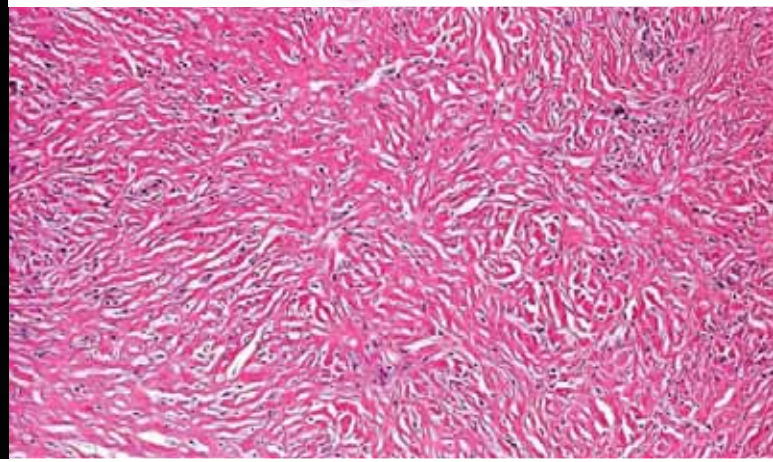
Fibroid nodules in *Borrelia* infection

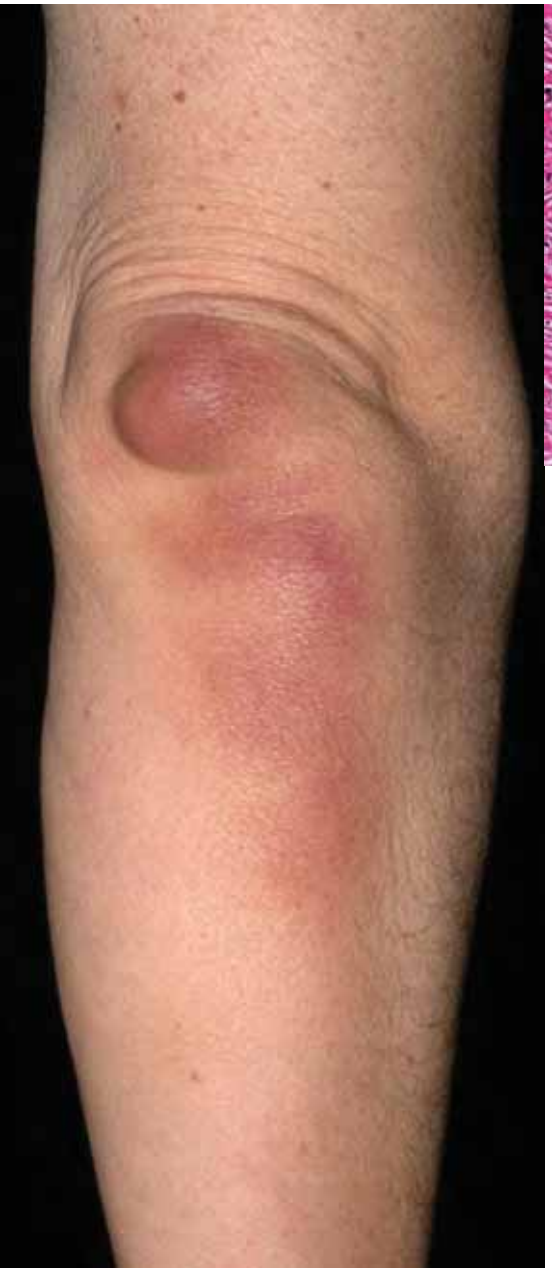
- Unusual manifestation of acrodermatitis chronica atrophicans, mostly associated with *Borrelia afzelii* infection
- Extensor surfaces of joints (particularly elbows)
- Fibrosis and sclerosis of collagen with variably dense infiltrates of lymphocytes and plasma cells
- Should be distinguished histologically from late stages of erythema elevatum et diutinum

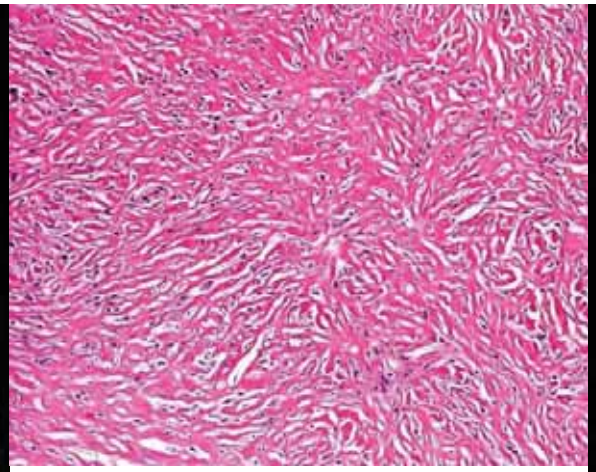




Fibroid nodule

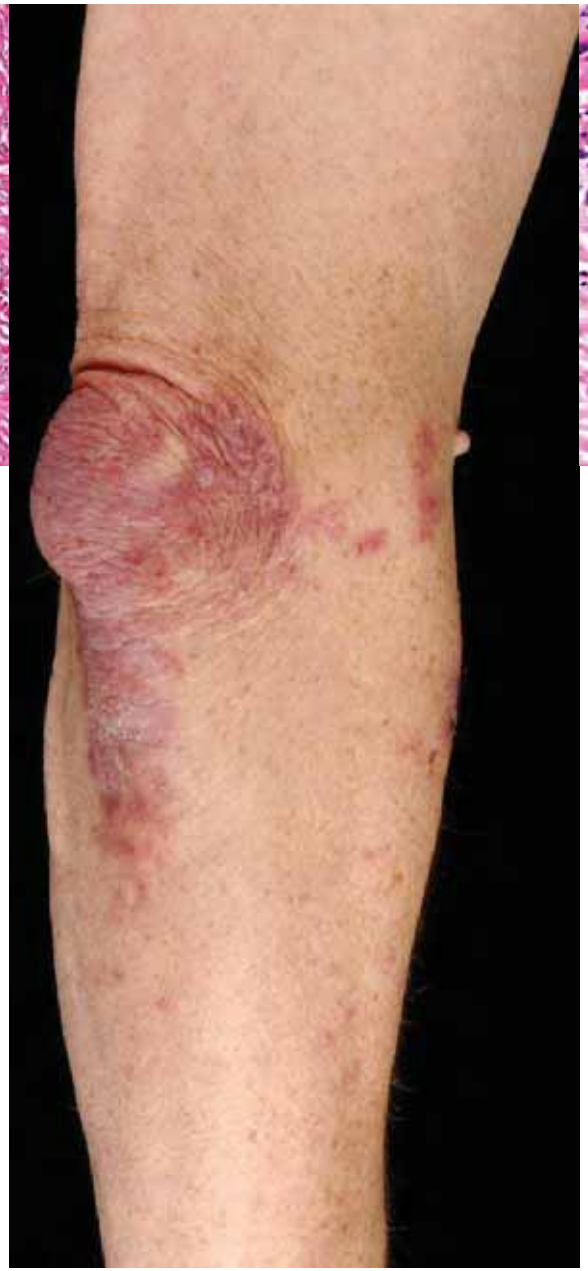


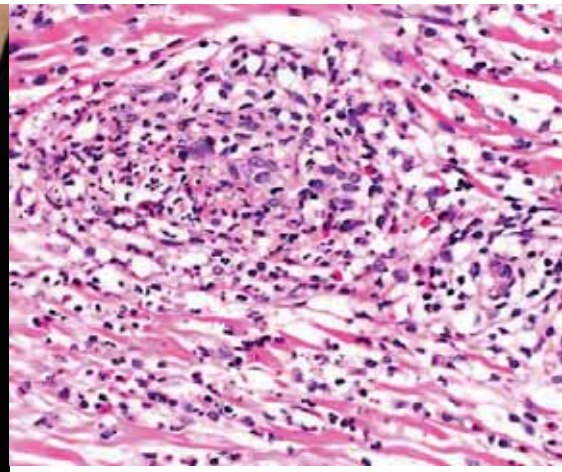




Fibroid nodule in *Borrelia* infection

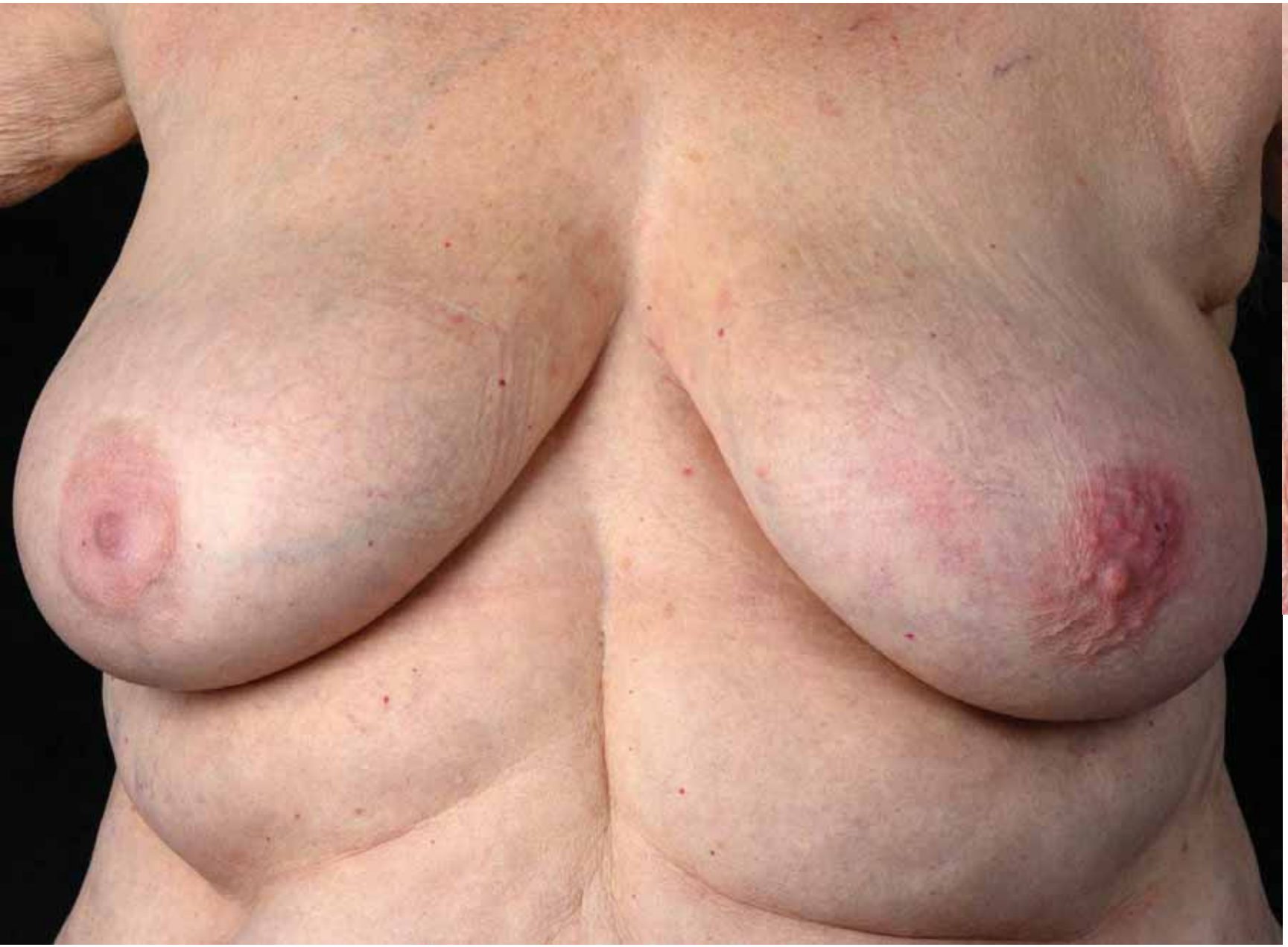
Chronic manifestation of *Borrelia* infection.
Fibrosis and sclerosis accompanied by infiltrates of lymphocytes and plasma cells.

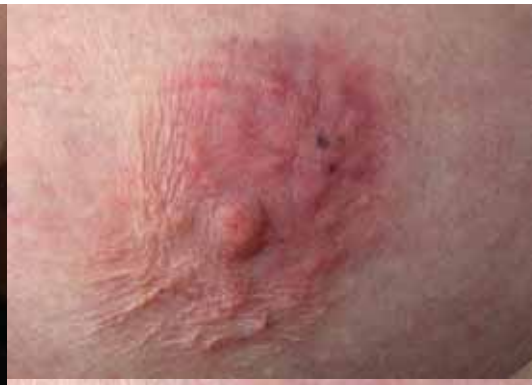


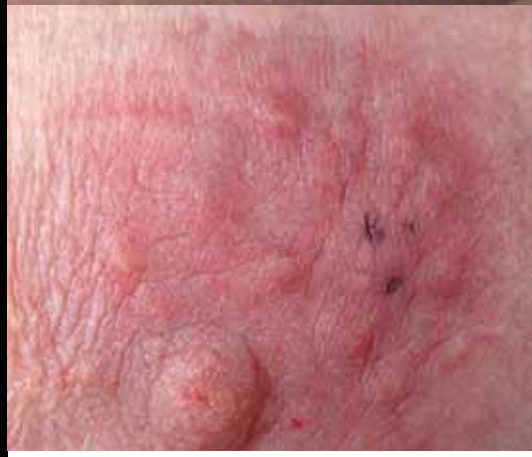


Erythema elevatum et diutinum

Chronic relapsing vasculitis.
Inflammatory infiltrate admixed with neutrophils and eosinophils; focal vasculitis. Fibrosis in late stages.



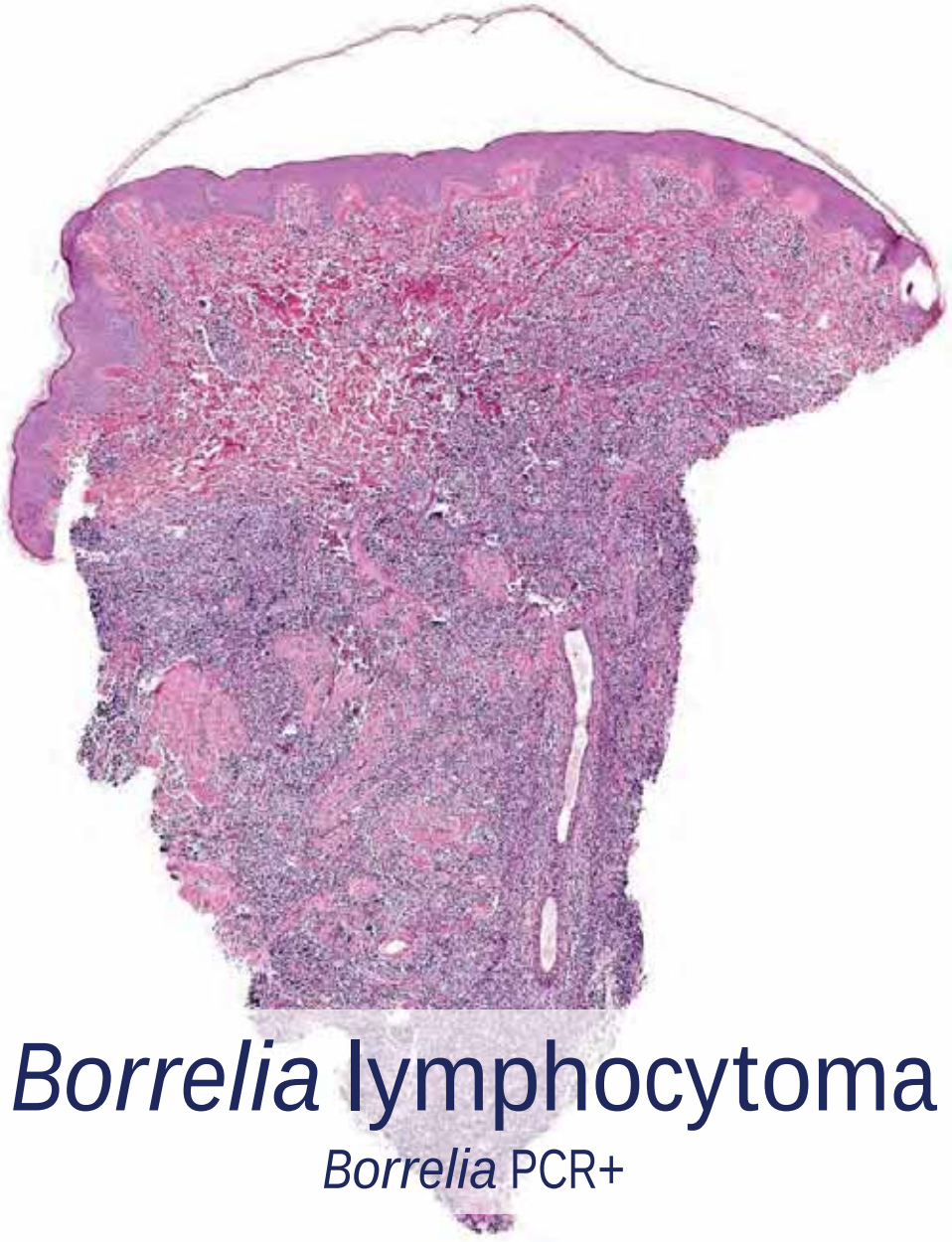




F, 72

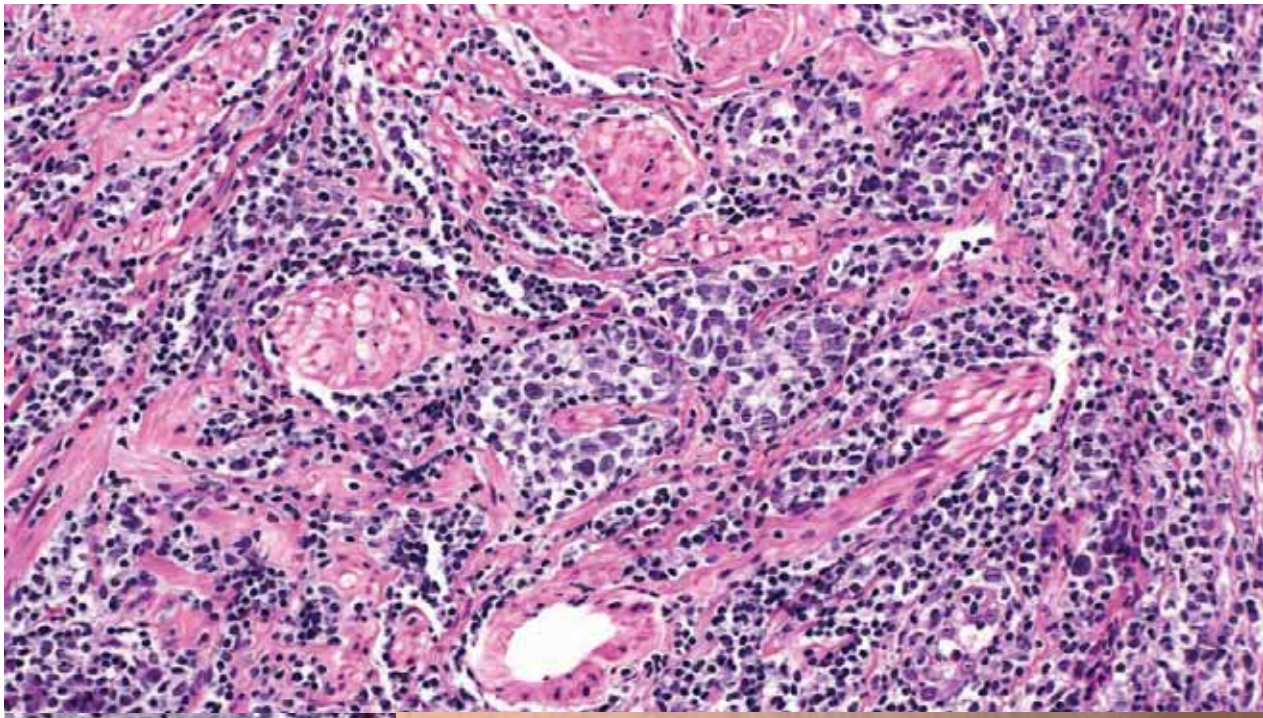
According to the patient skin lesion on the left nipple for approximately 1 month, starting in the intermammary cleft, becoming "a line" from the upper left breast to the left nipple, and finally taking the actual shape.

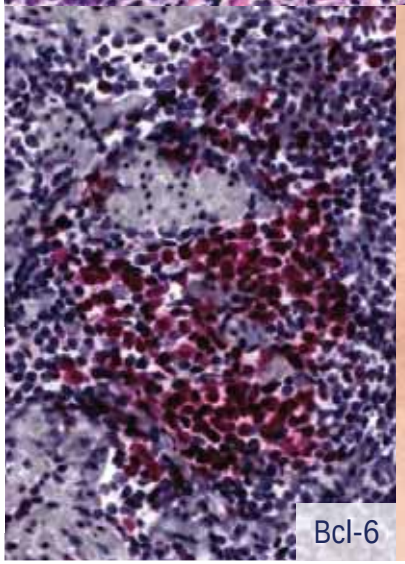
A biopsy is taken.

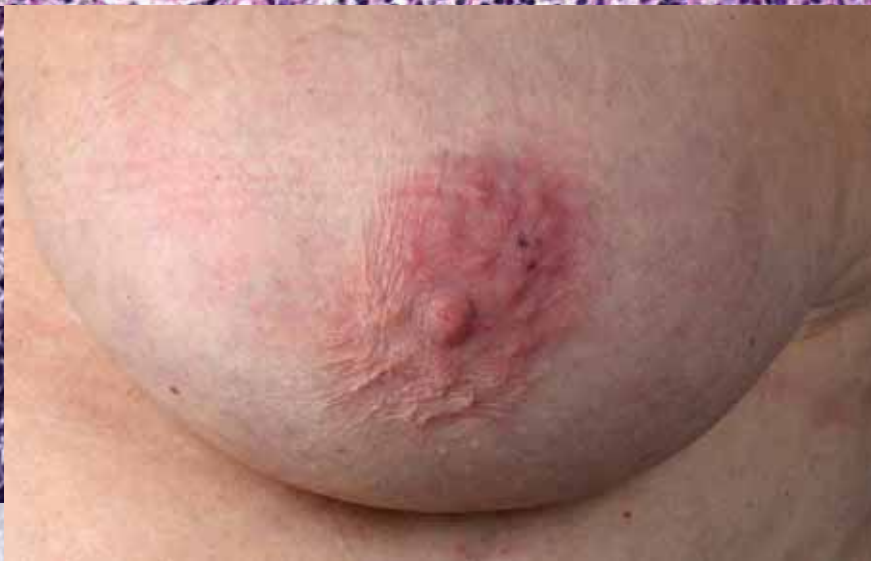


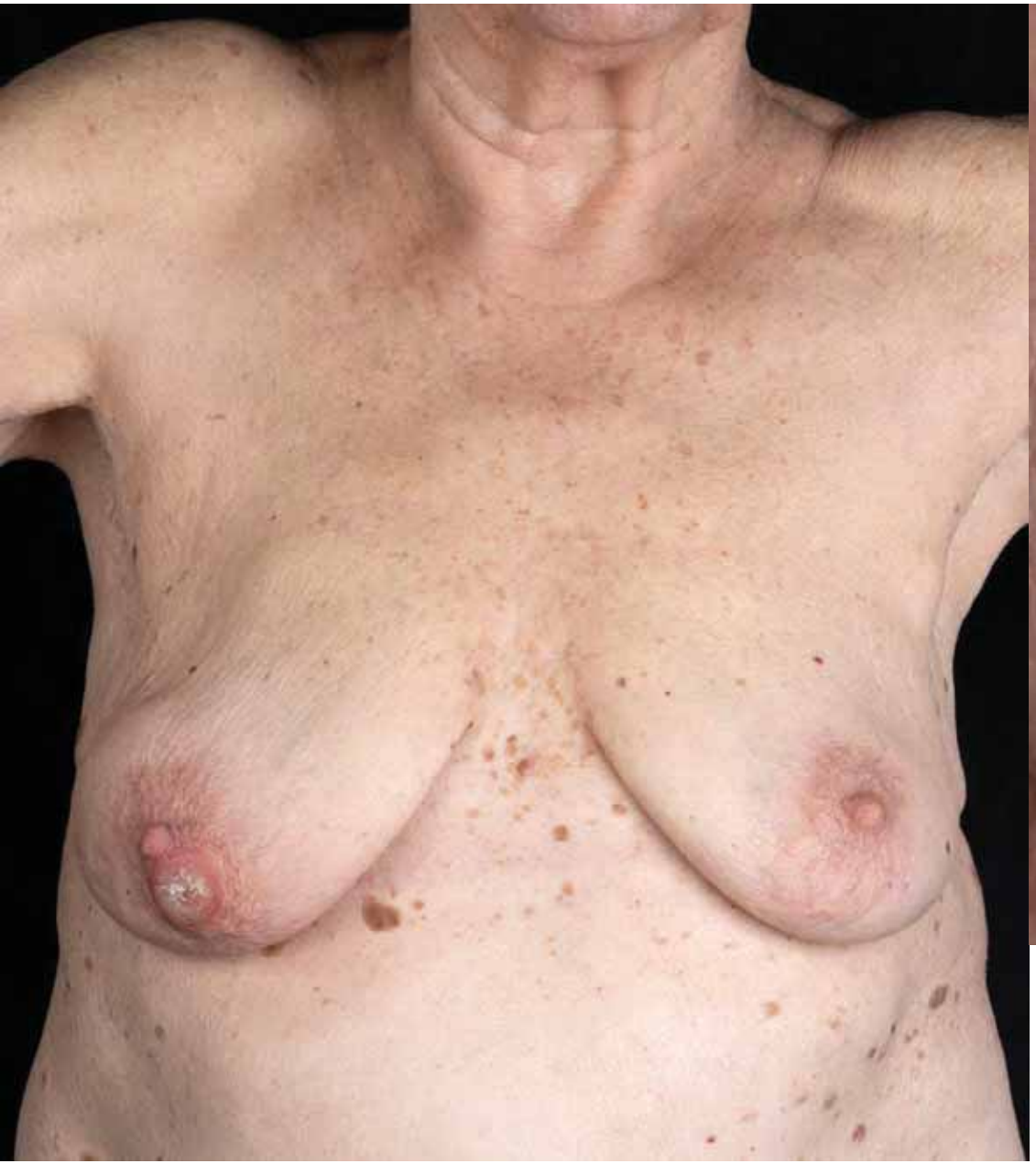
Borrelia lymphocytoma

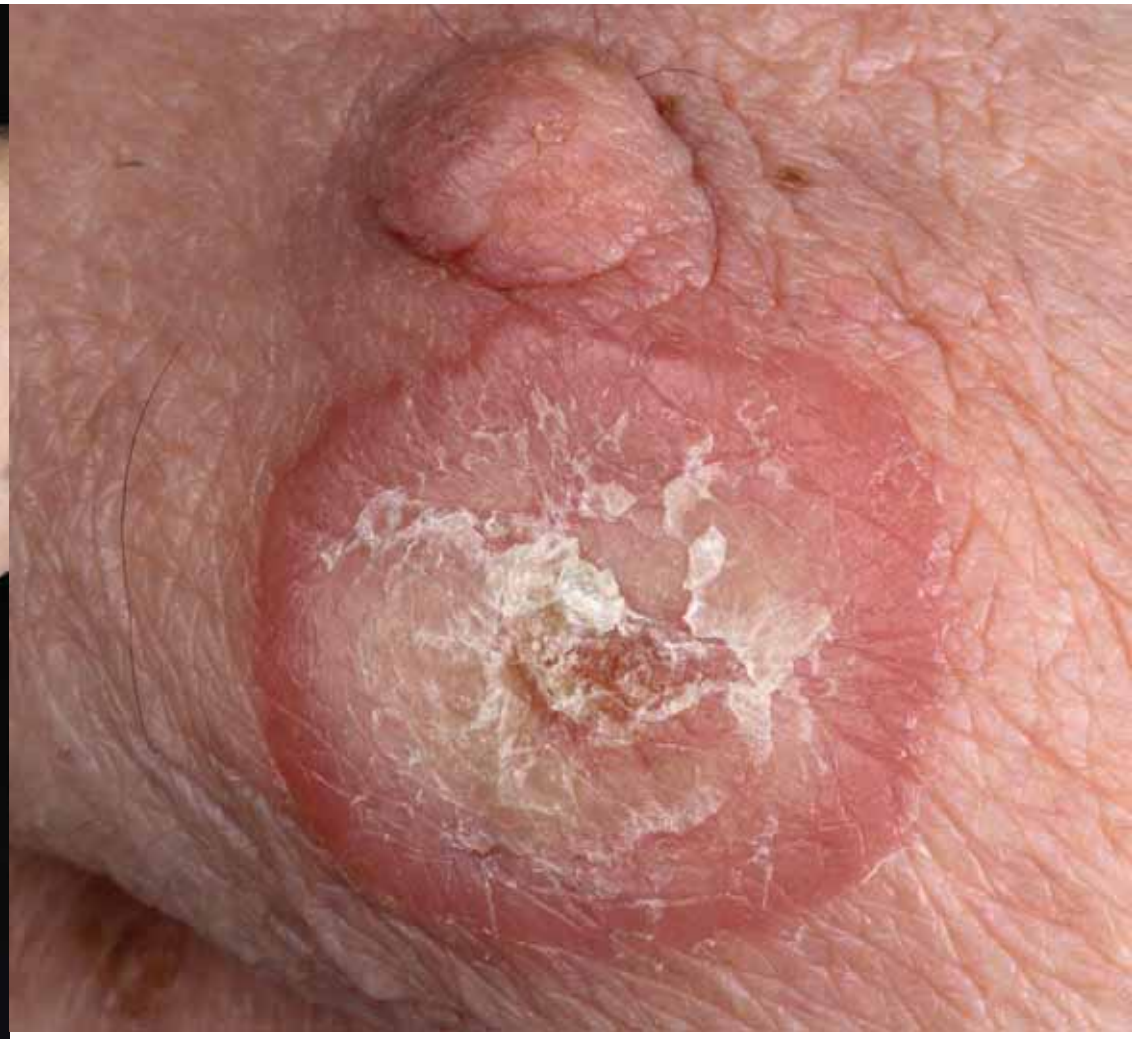
Borrelia PCR+







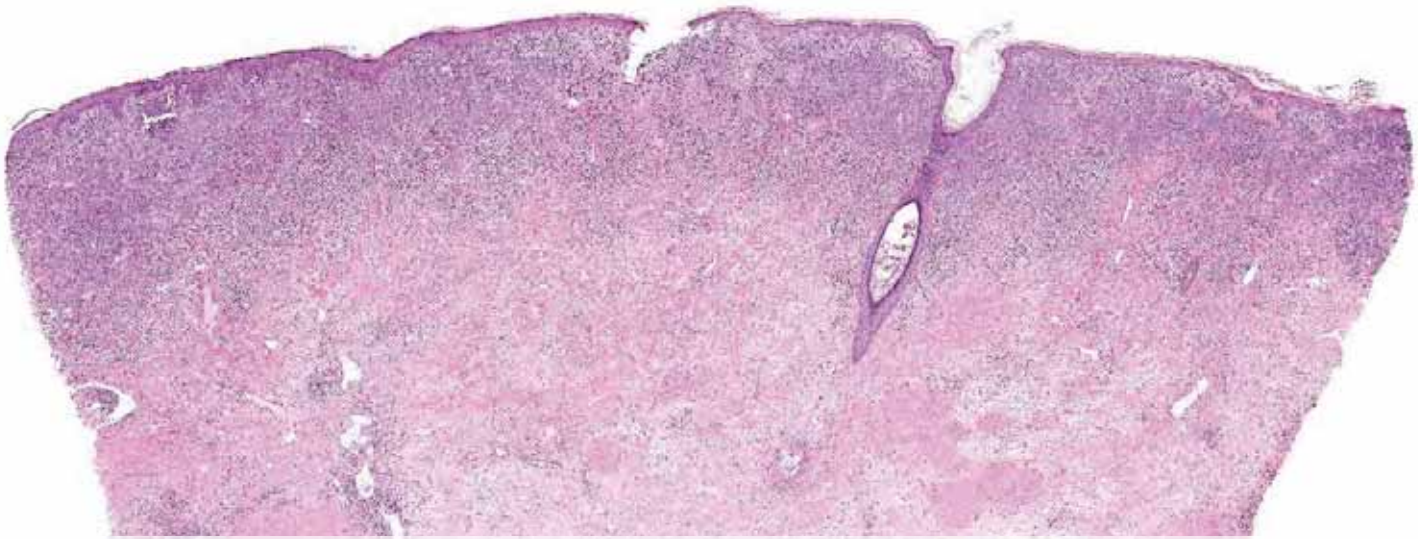




F, 84

Nodule on the right breast of unknown duration.

A biopsy is taken.

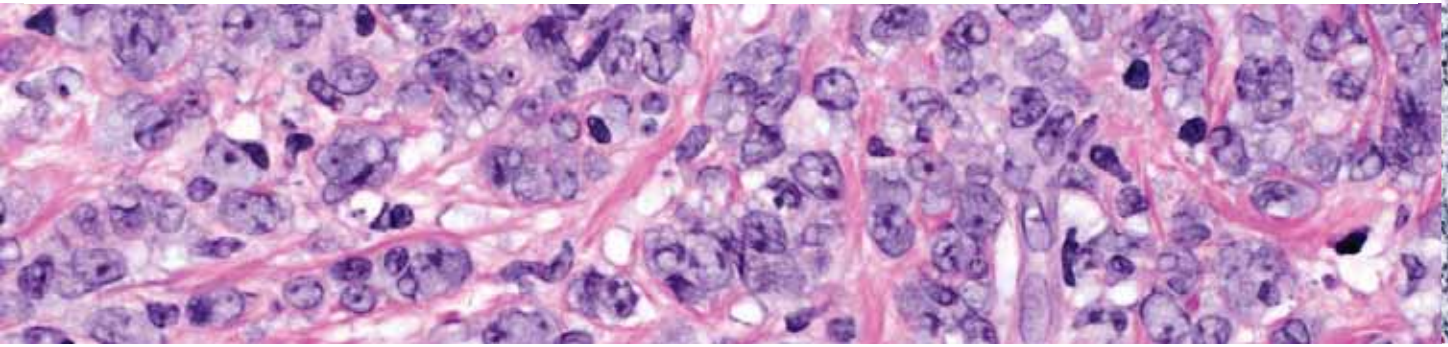


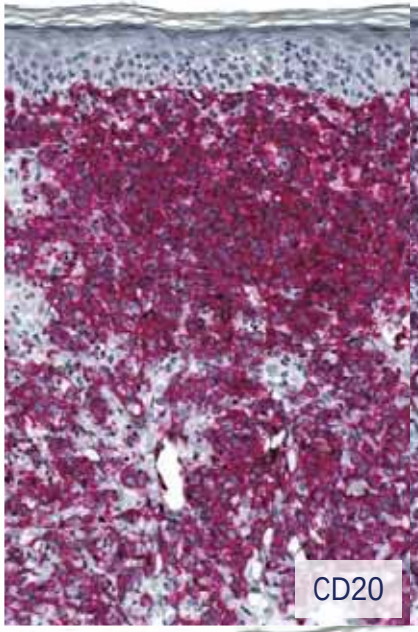
Diffuse large B-cell lymphoma

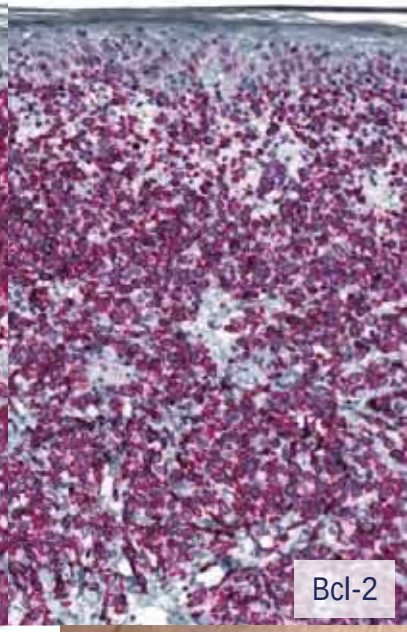
PCR for Borrelia: negative

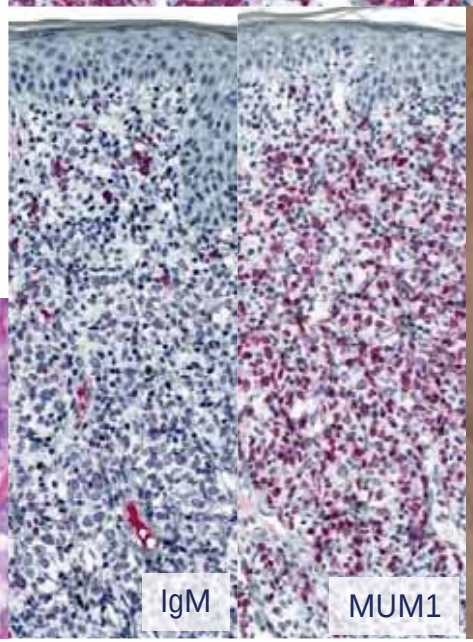
FACS: atypical population of B lymphocytes in blood

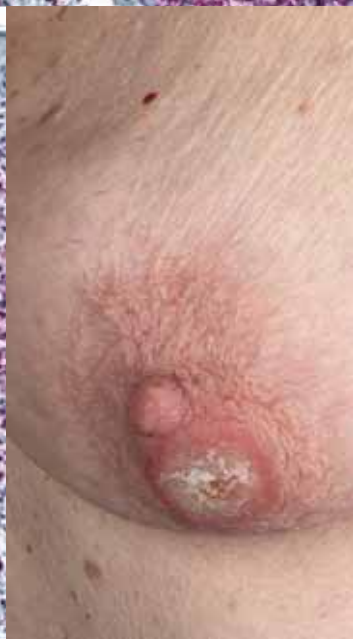
Right axillary LN: DLBCL

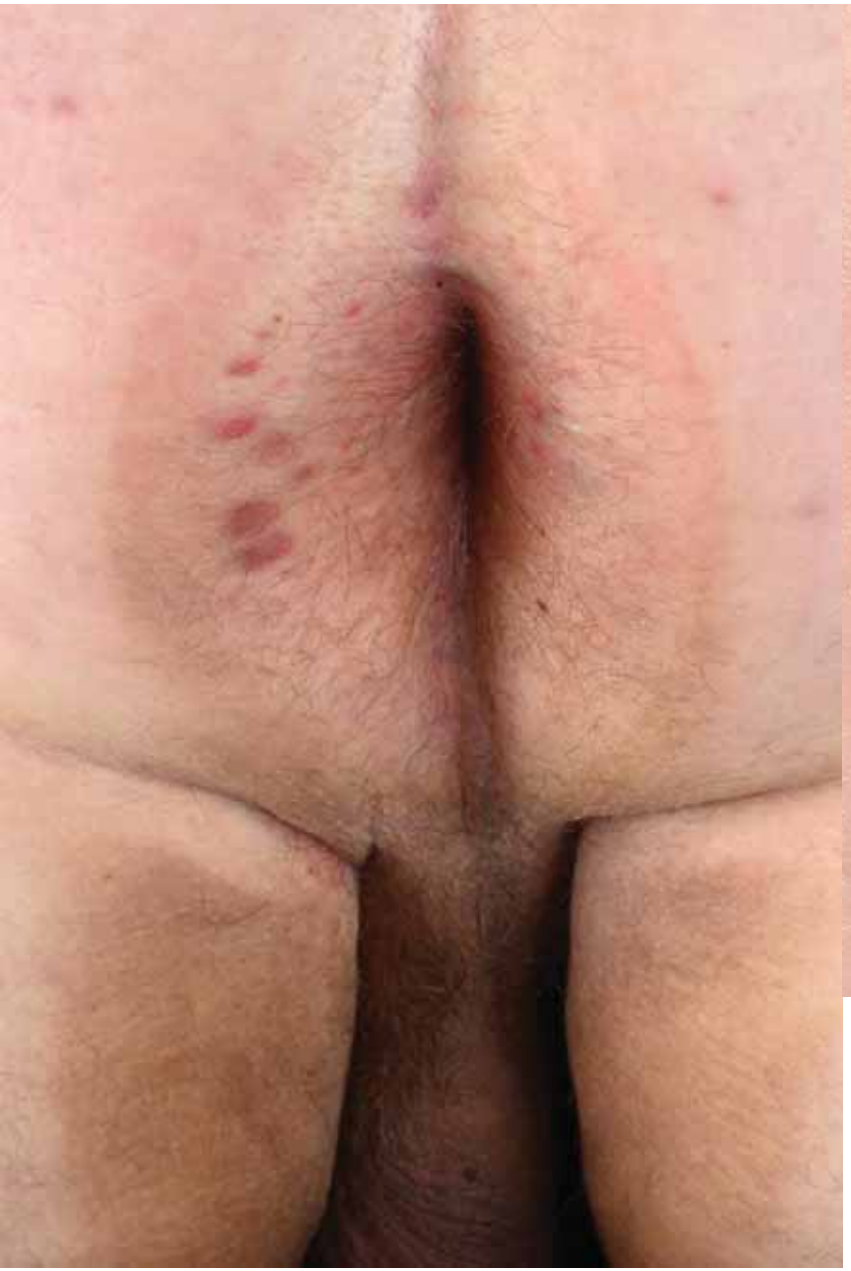


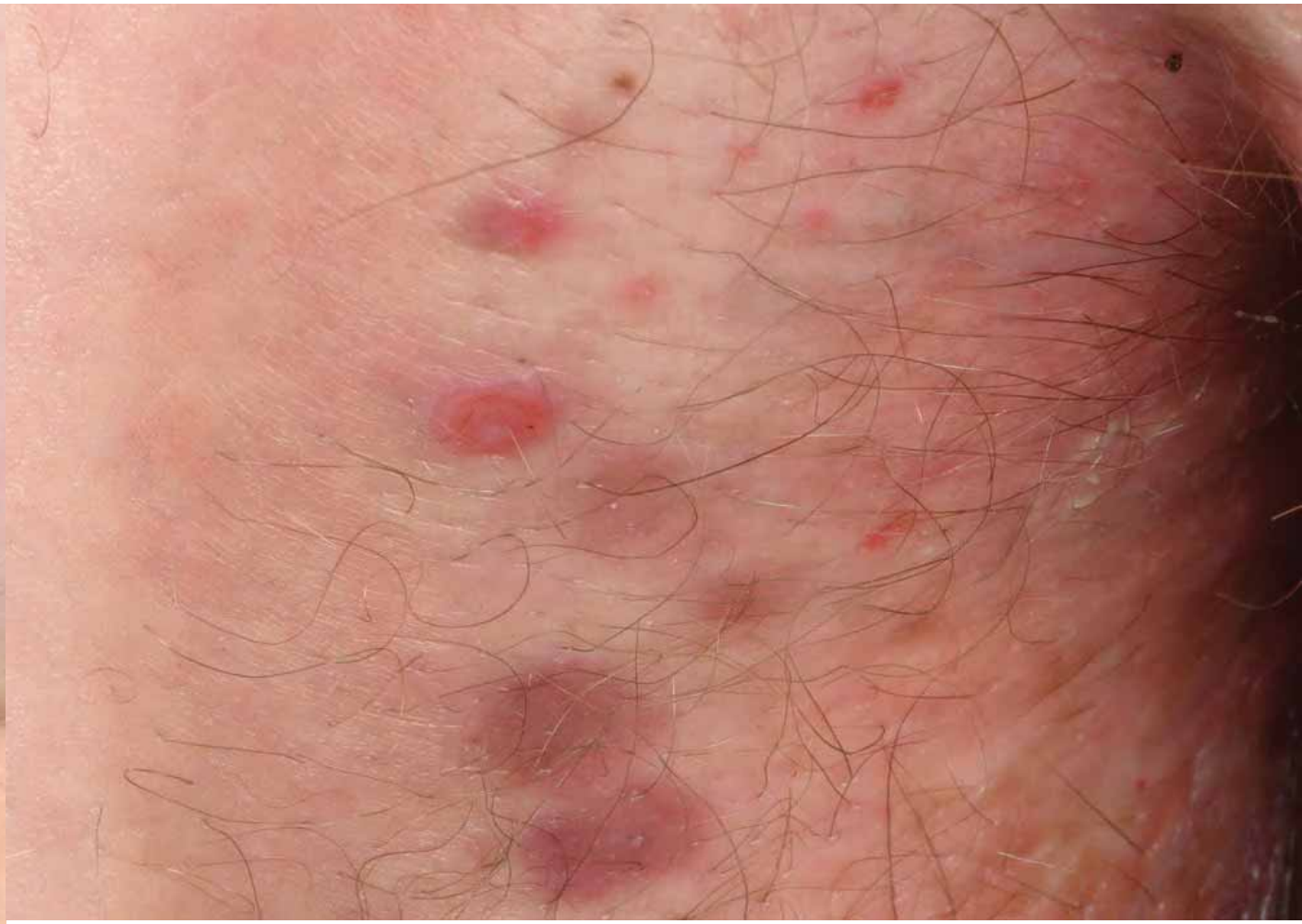








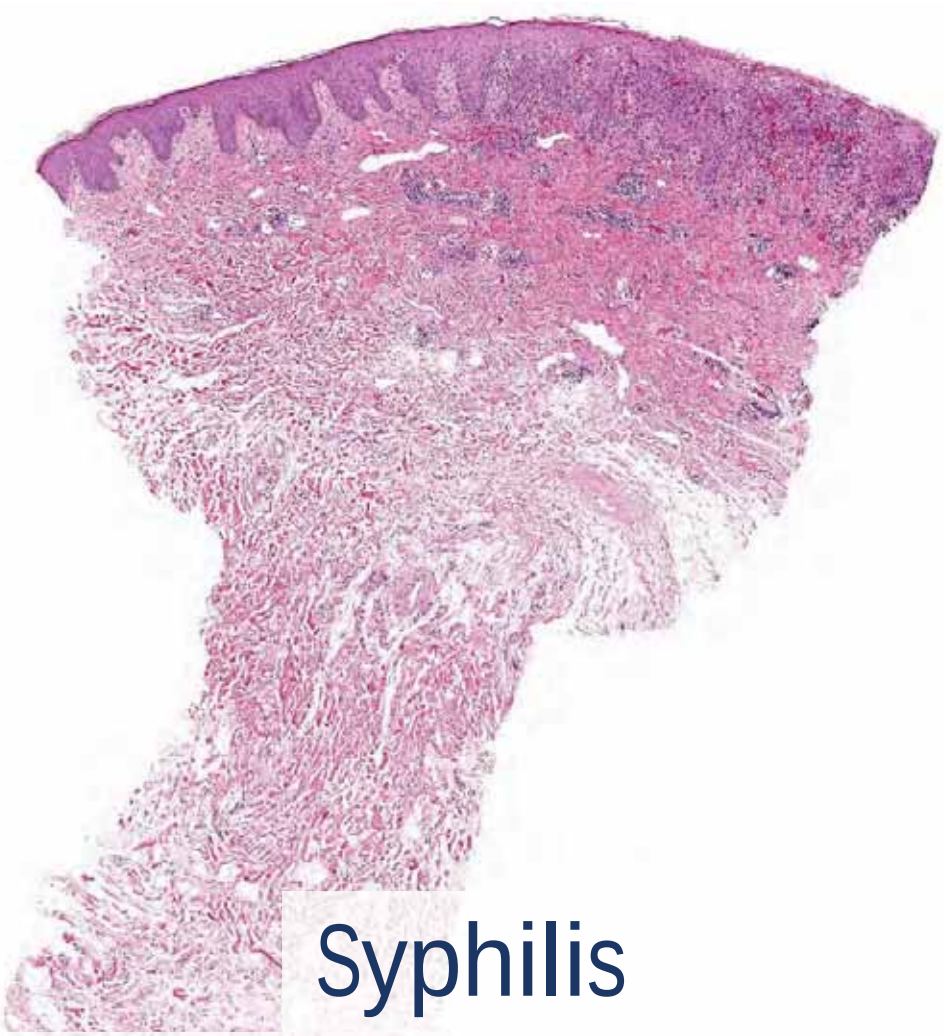




M, 50

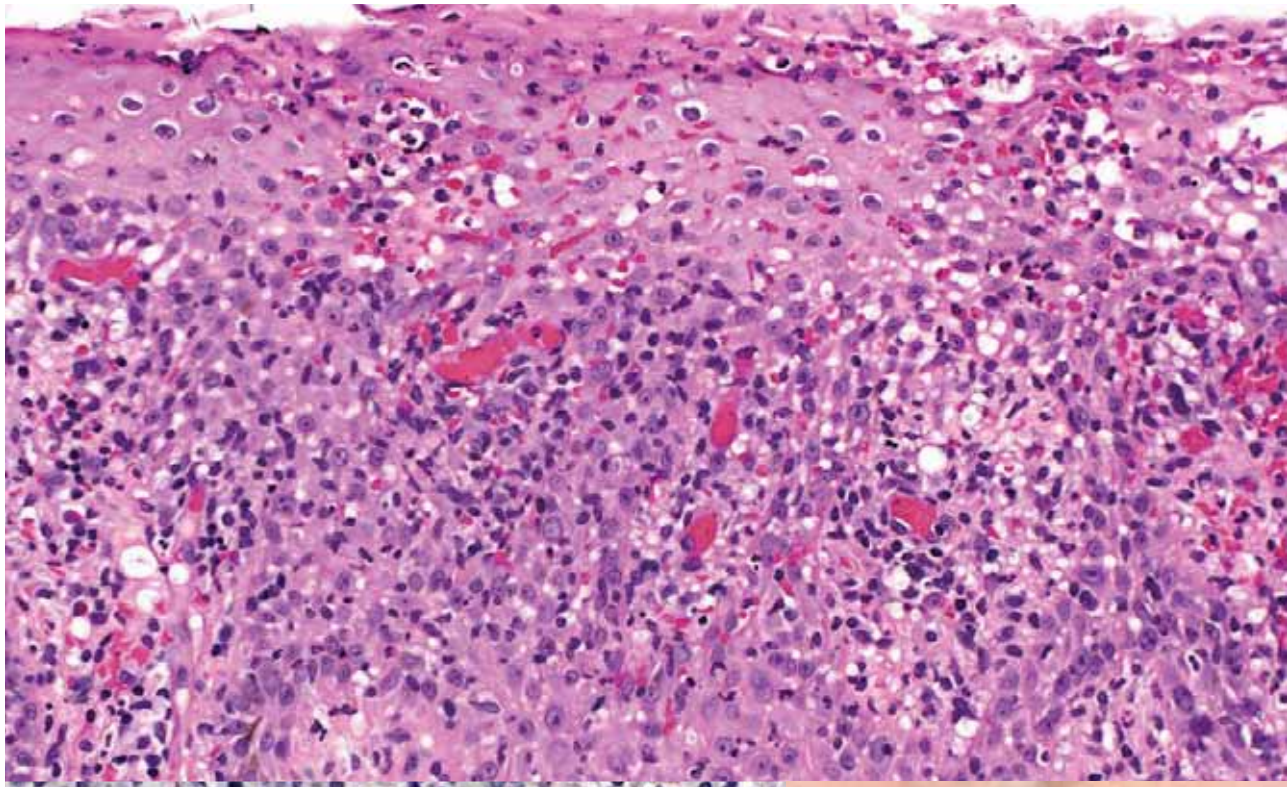
According to the patient slightly itchy perianal lesions for 2 months. No improvement with local steroids.

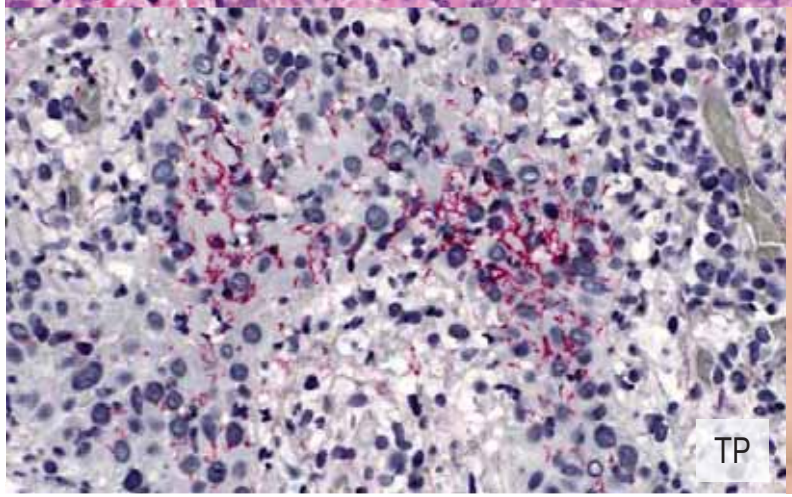
A biopsy is taken.

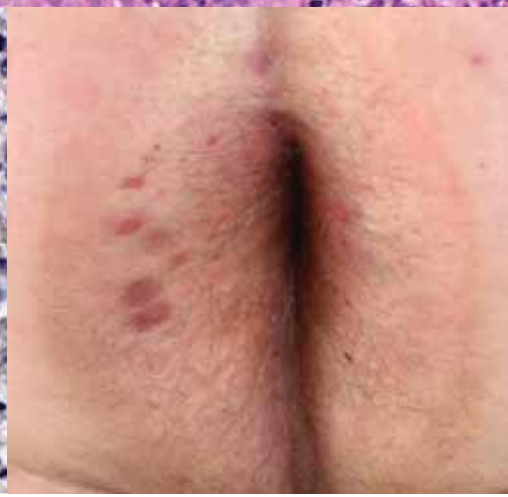


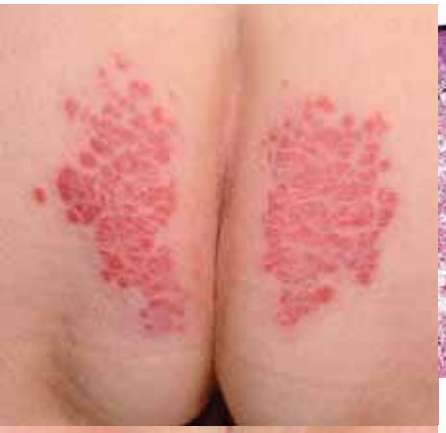
Syphilis

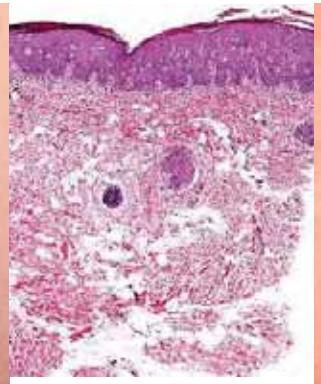
1st infection serologically in 2021, managed only 2 years later with one injection of benzathine benzylpenicillin. VDLR increase in the last 5 months (consistent with a second, recent infection).



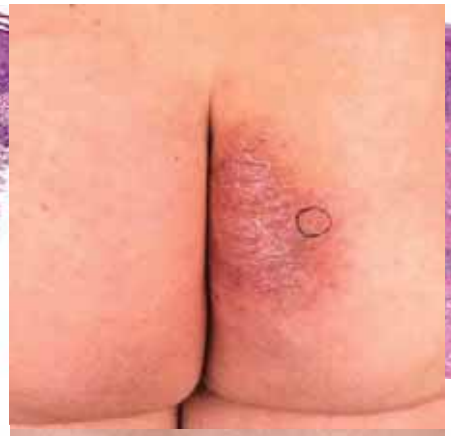


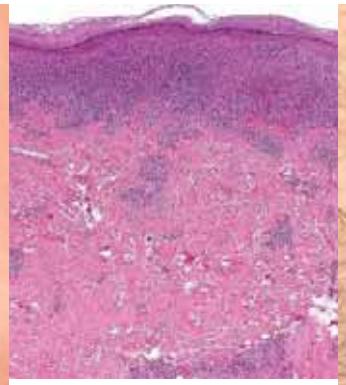




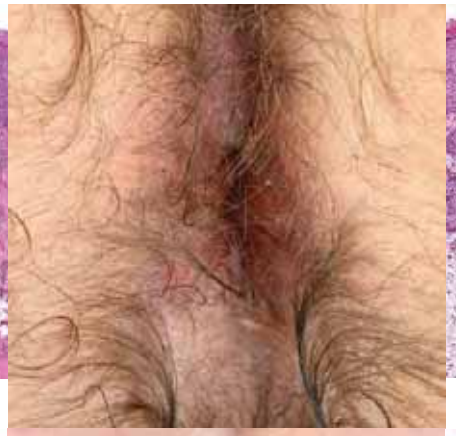


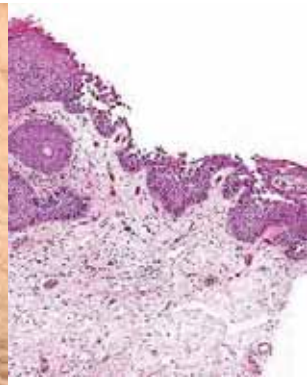
Psoriasis



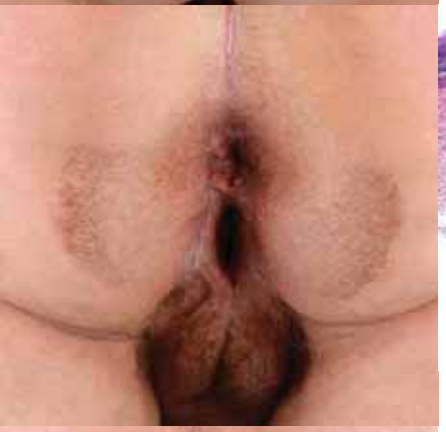


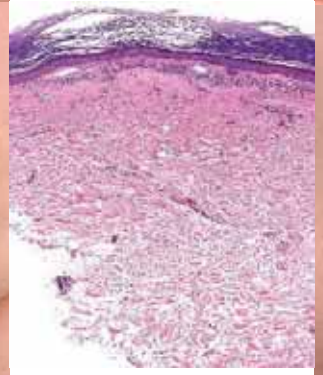
Mycosis fungoides



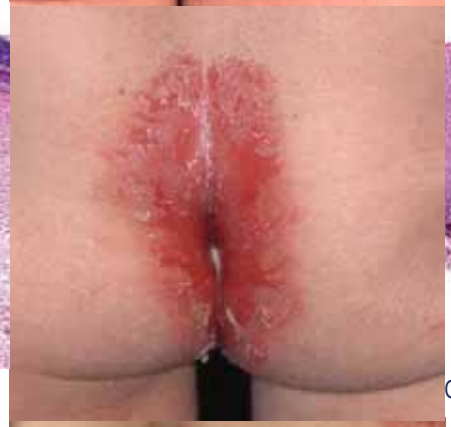


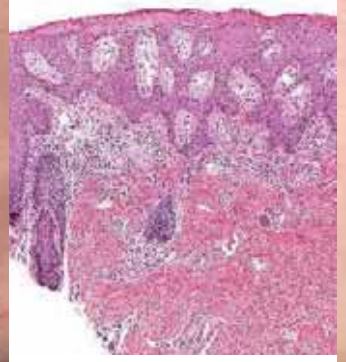
Hailey-Hailey disease



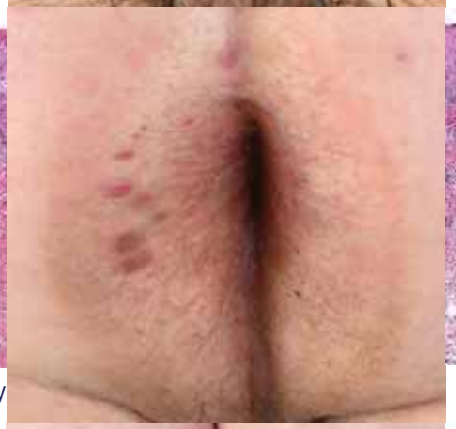


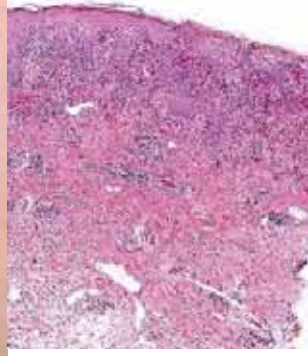
Lichen sclerosus



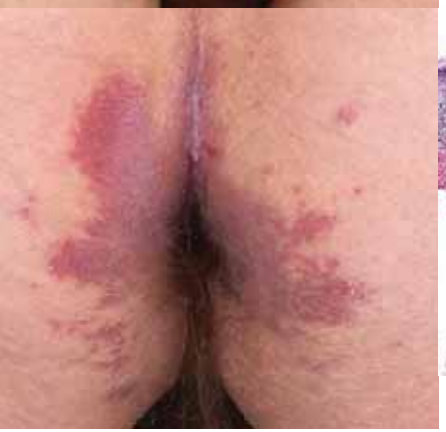


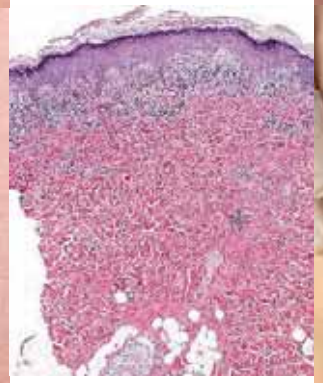
Crohn disease & zinc deficiency



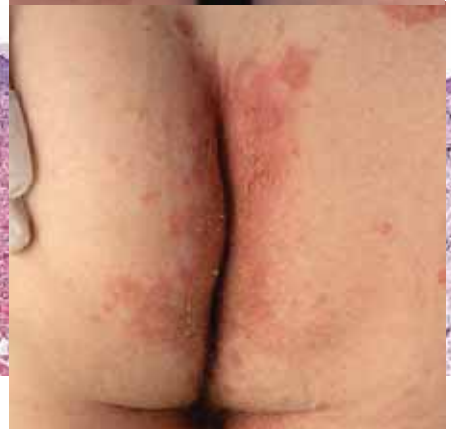


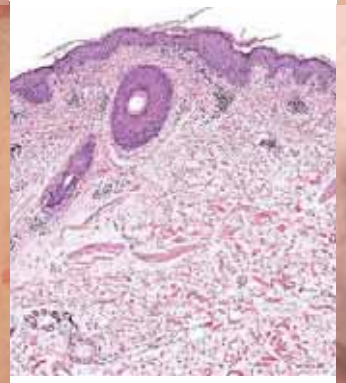
Syphilis



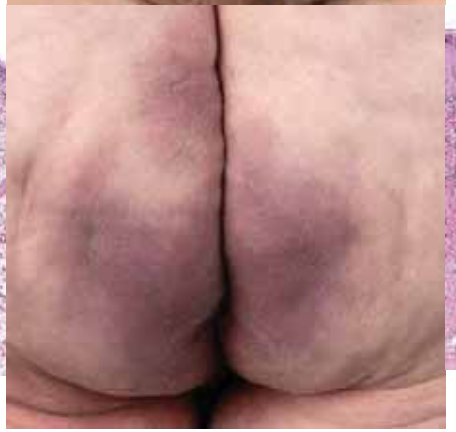


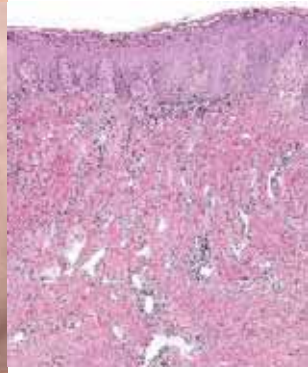
Lichen planus



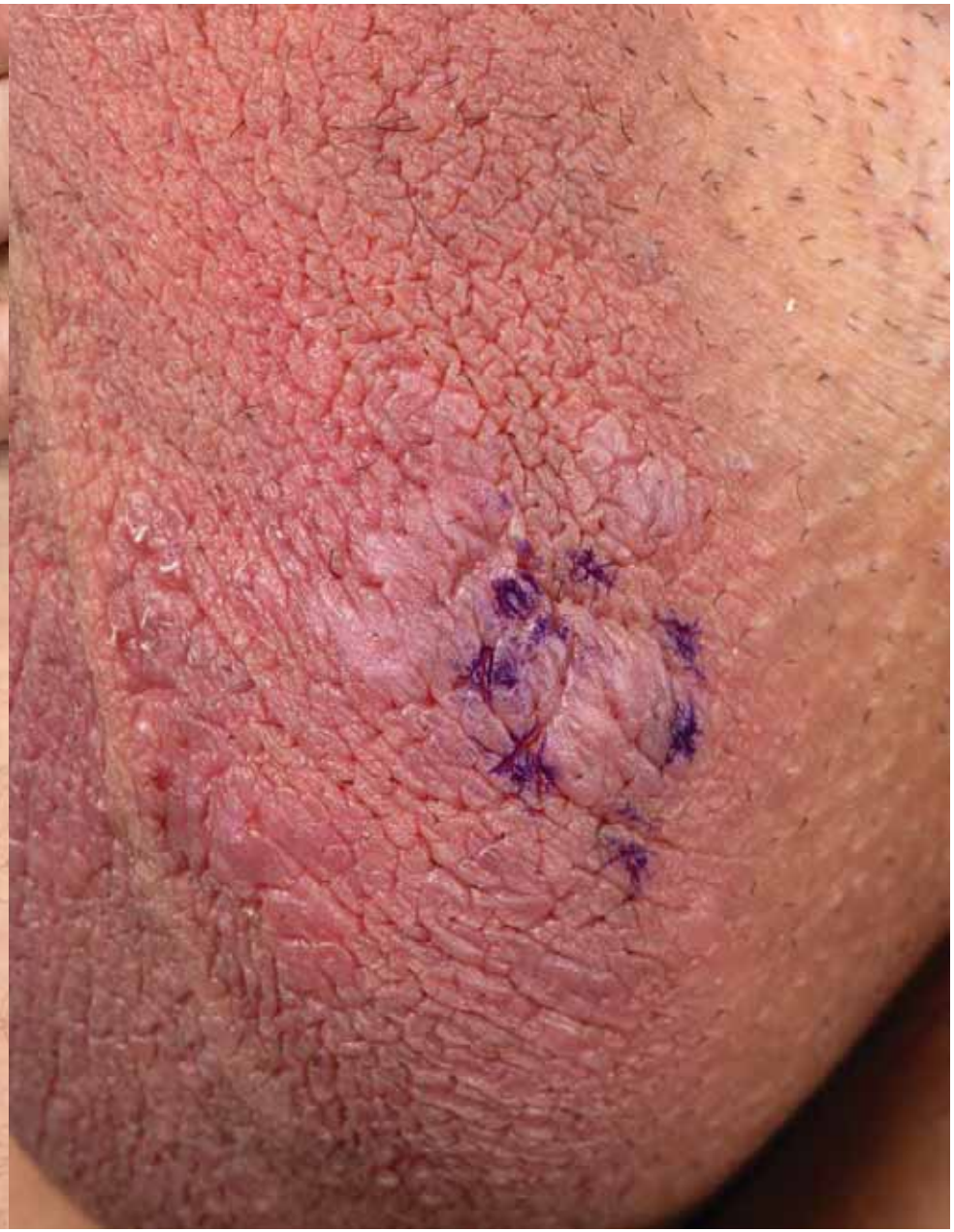


Acrodermatitis enteropathica





Lichen simplex chronicus

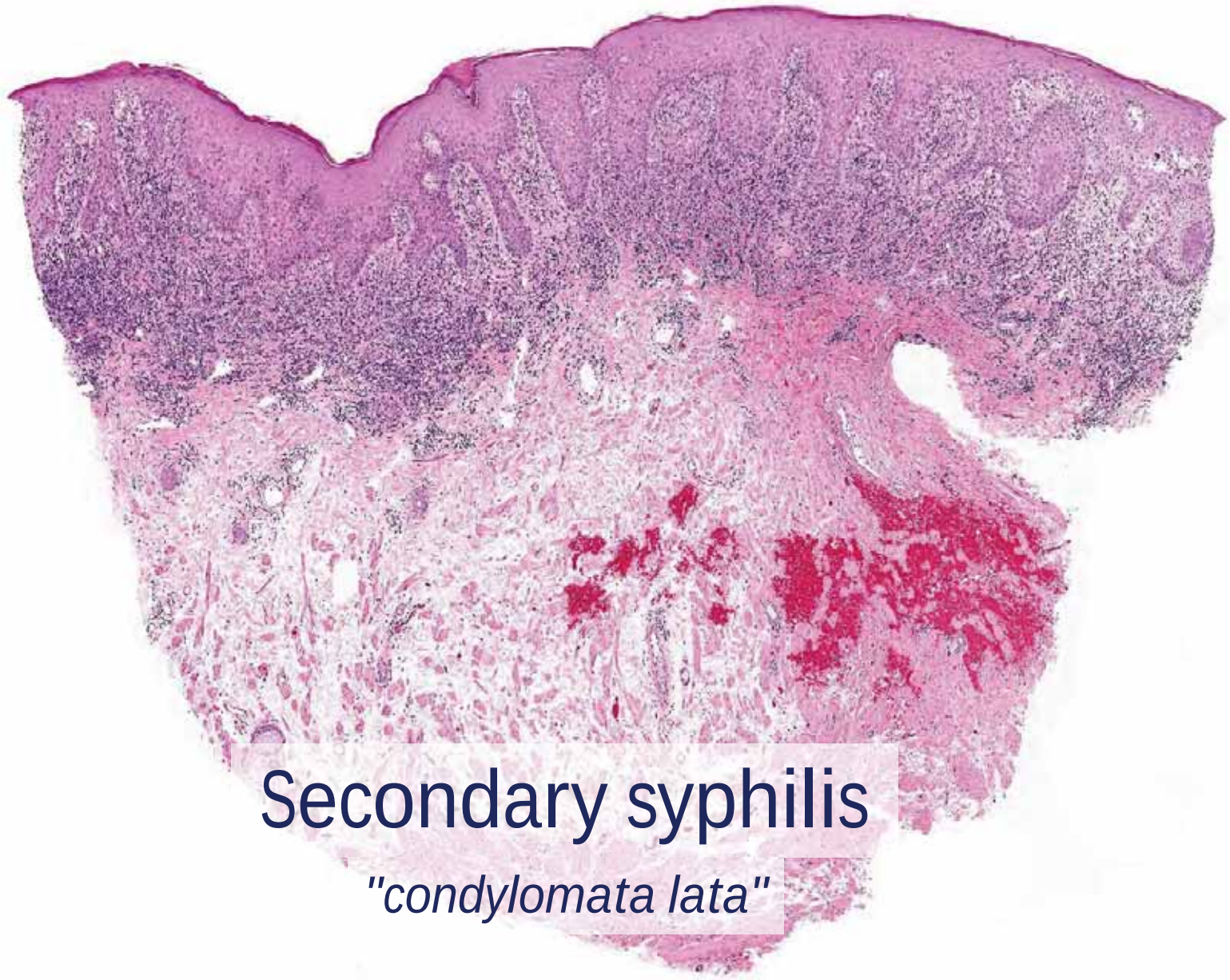


M, 37

According to the patient "scrotal infection" 2 years previously. Itchy scrotal lesions waxing and waning since that time.

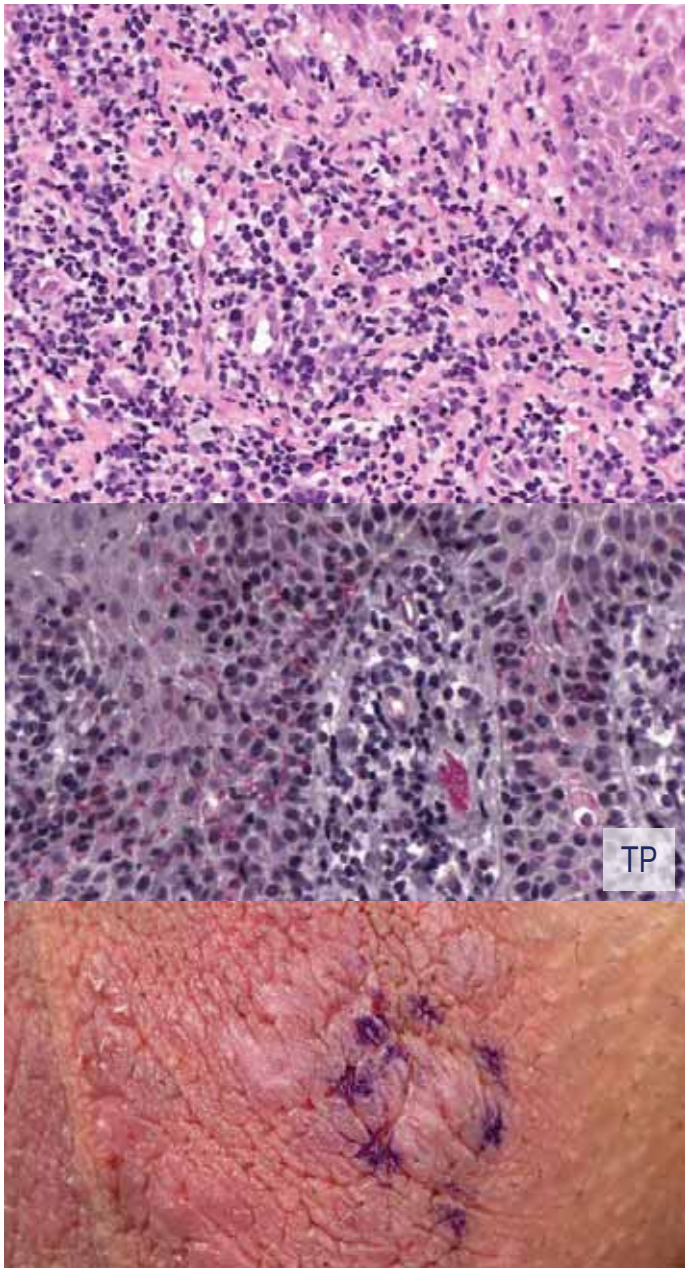
No other skin lesions; no other complaints.

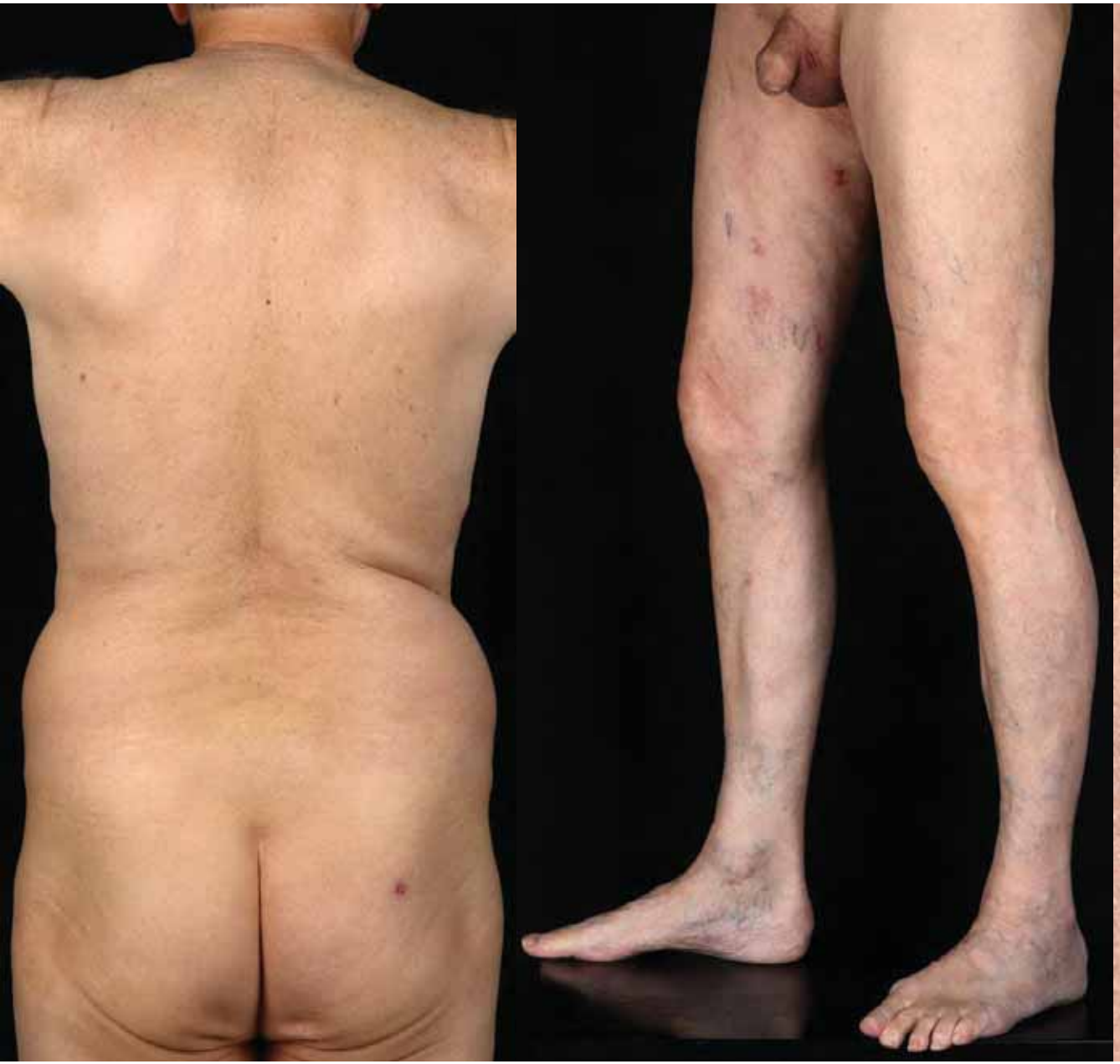
A biopsy is taken under the clinical diagnosis of psoriasis inversa vs. lichen planus.

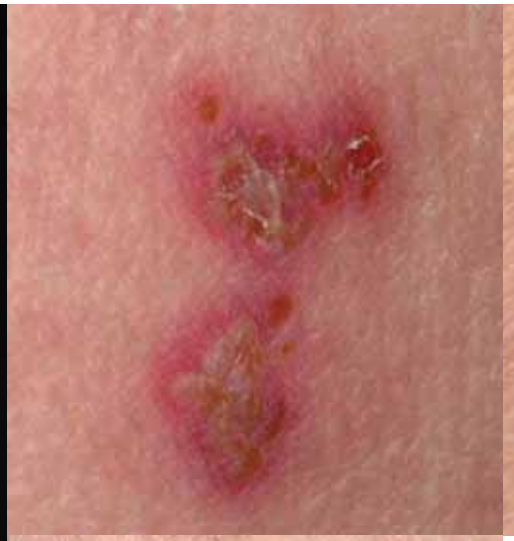


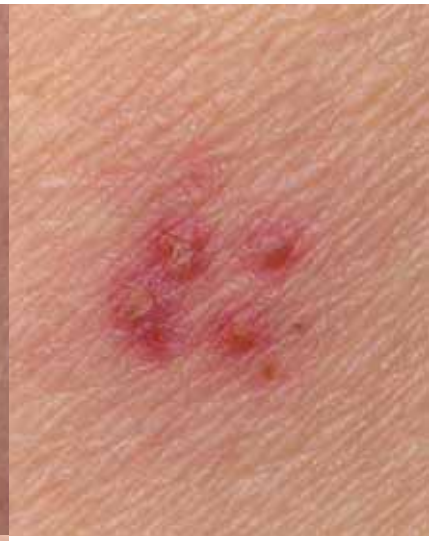
Secondary syphilis

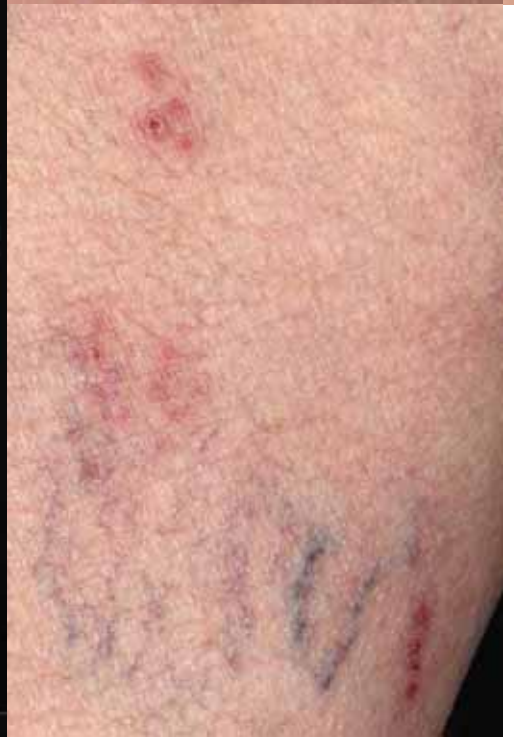
"condylomata lata"









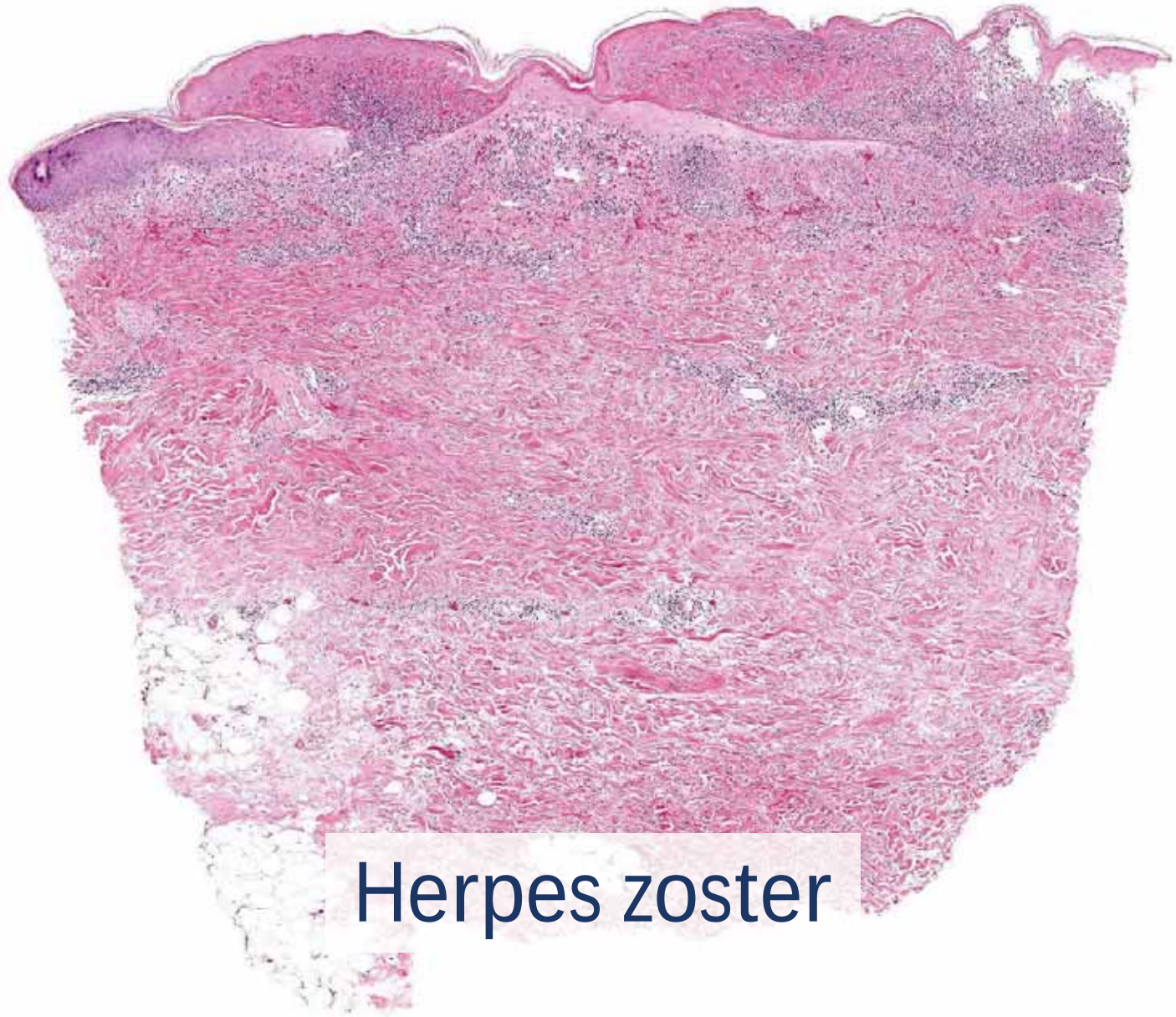


M, 75

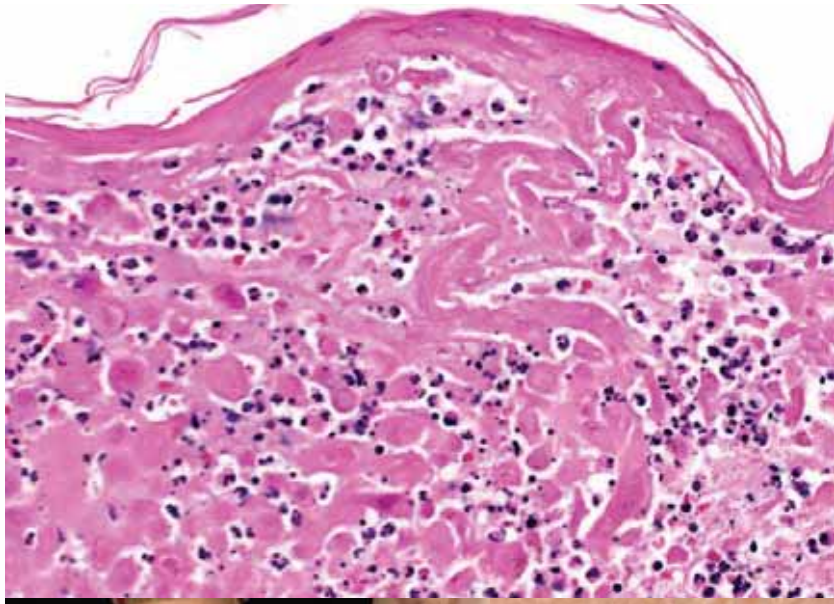
History of PEP / early mycosis fungoides (1st diagnosis 10 years earlier; at present in CR after UVB therapy).

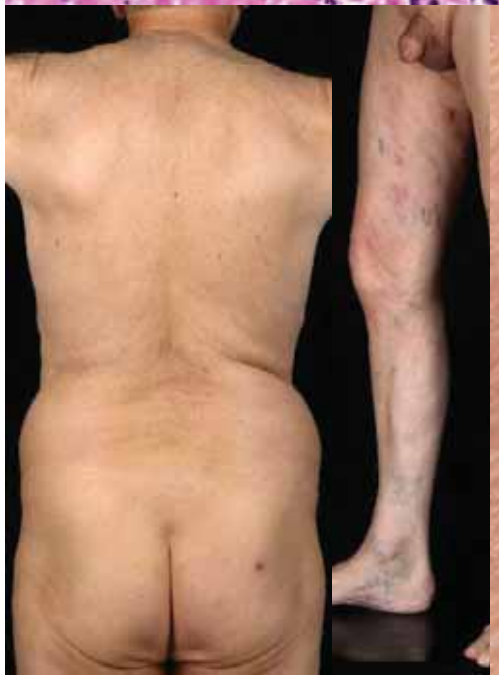
According to the patient new lesions on the right thigh for 1 month; worsening after treatment with local steroids.

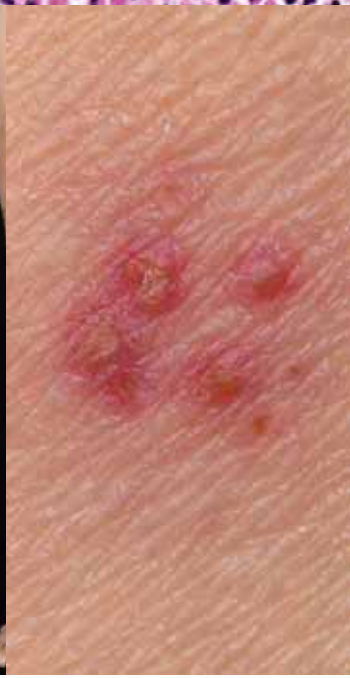
A biopsy is taken.

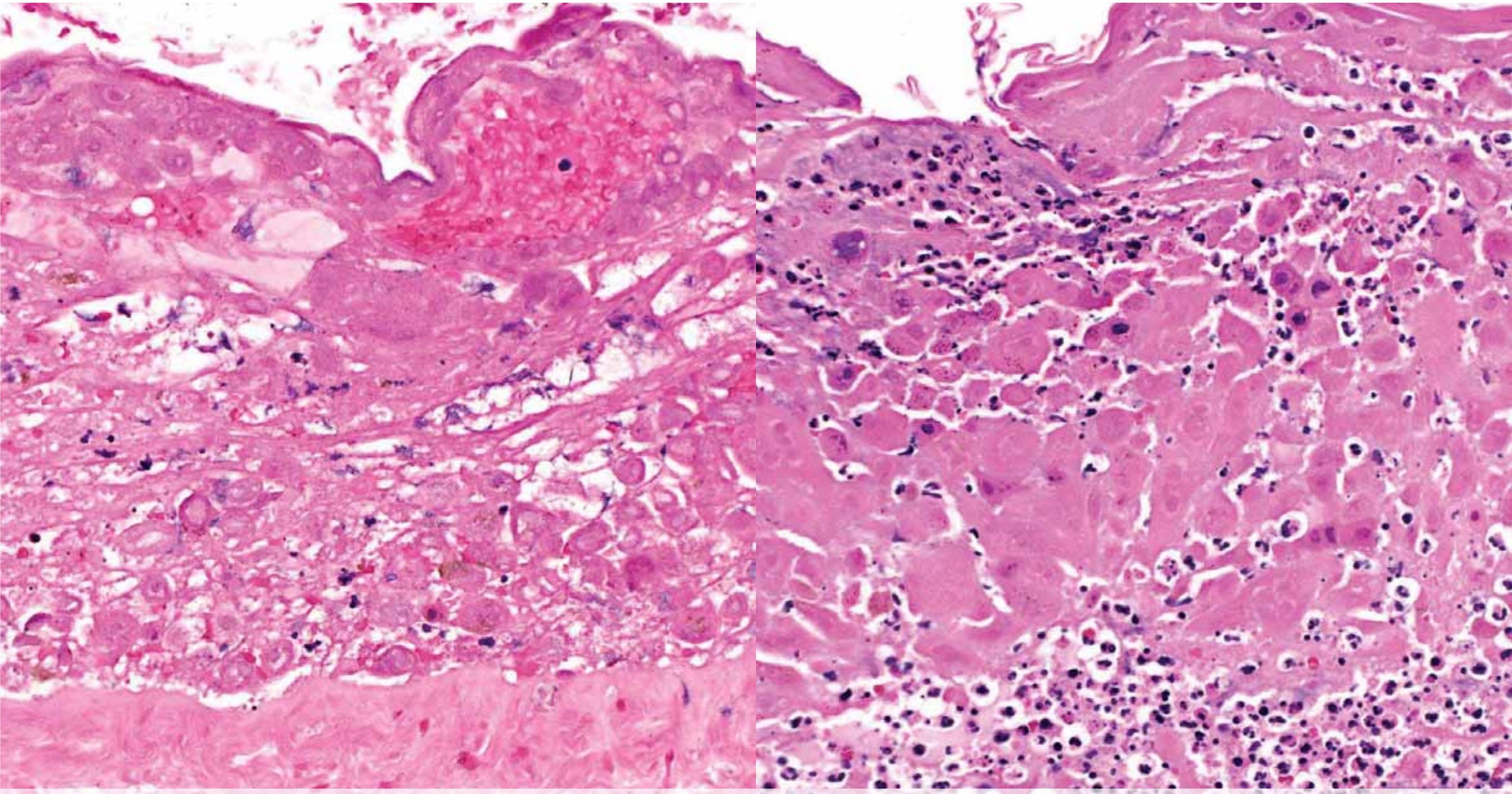


Herpes zoster

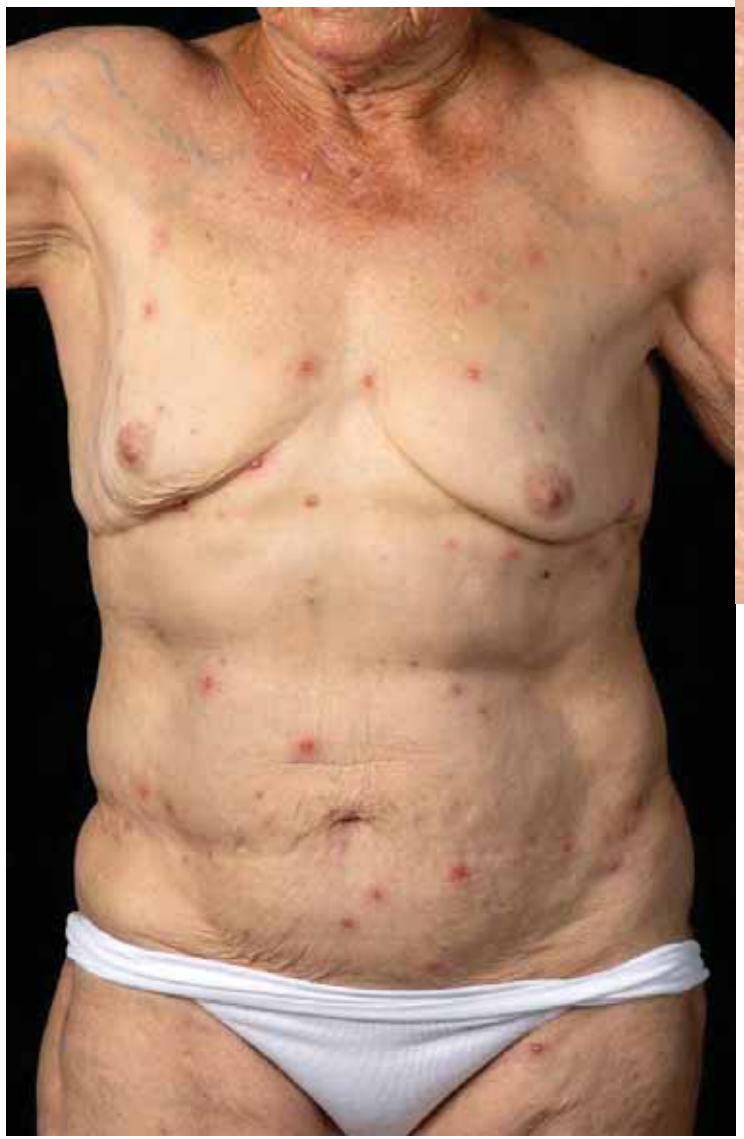


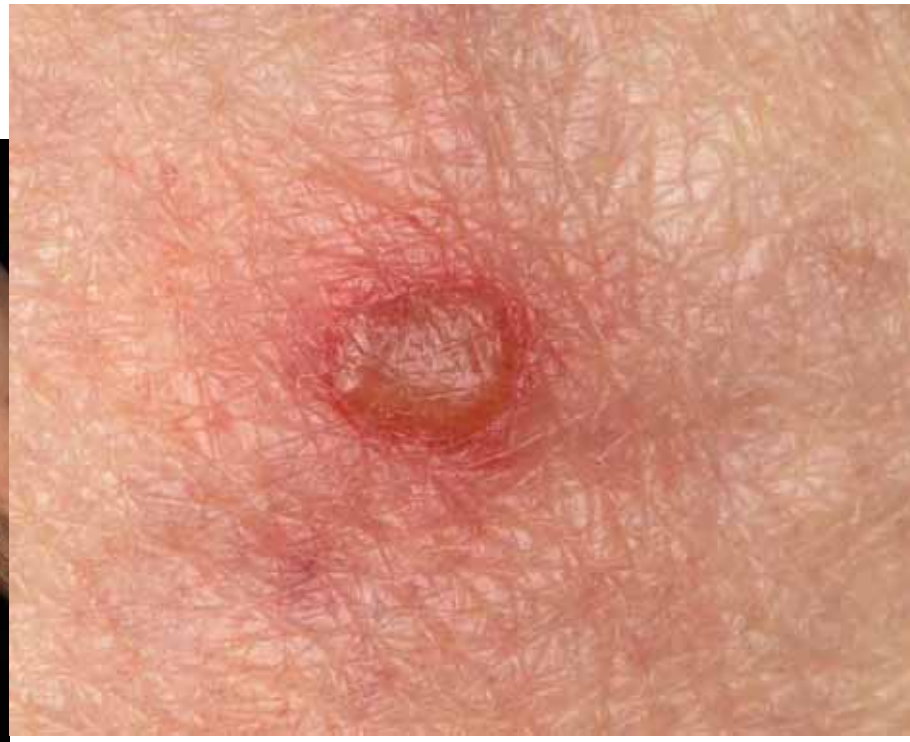






Sometimes only necrotic "ghosts" of ballonized keratinocytes are visible

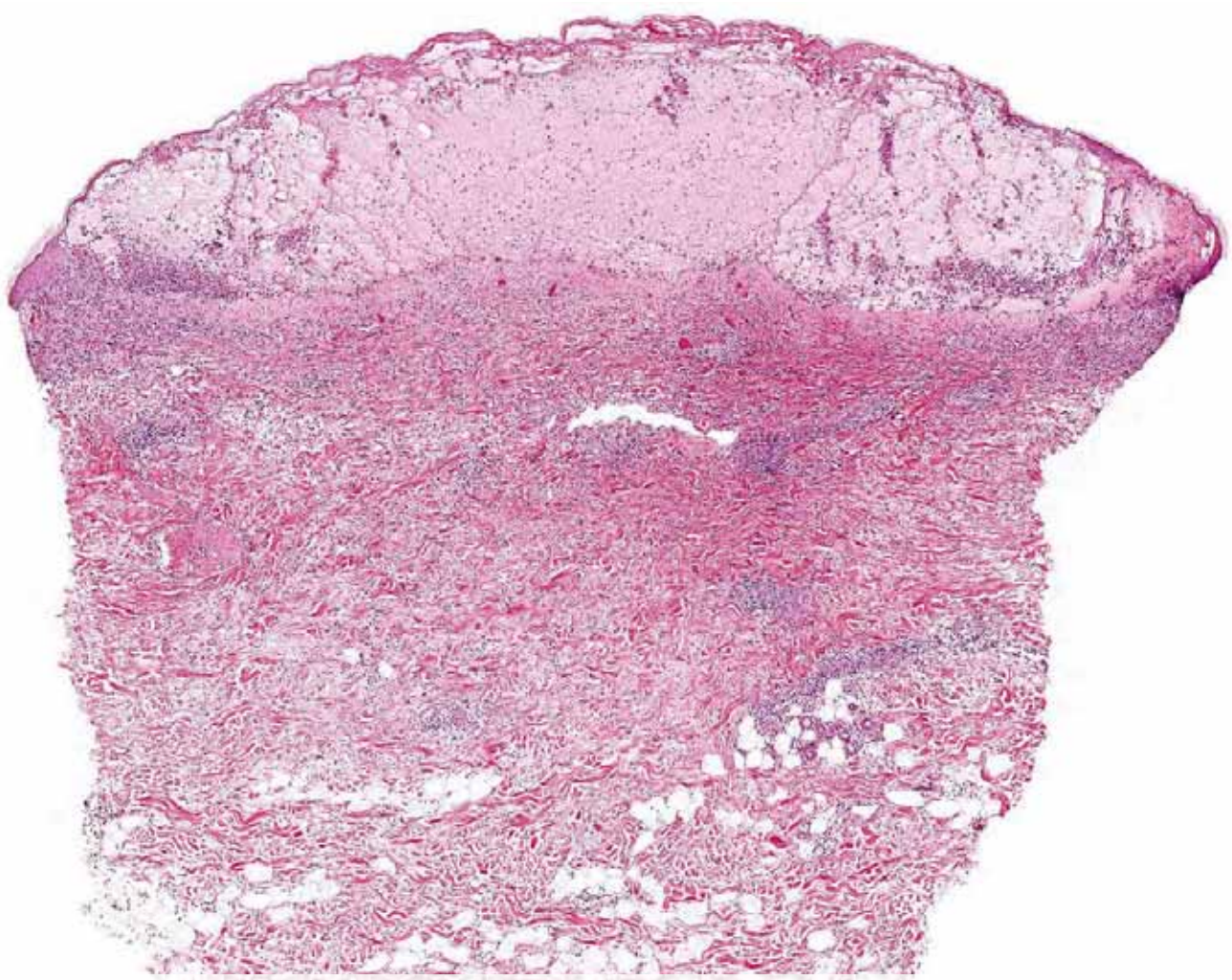


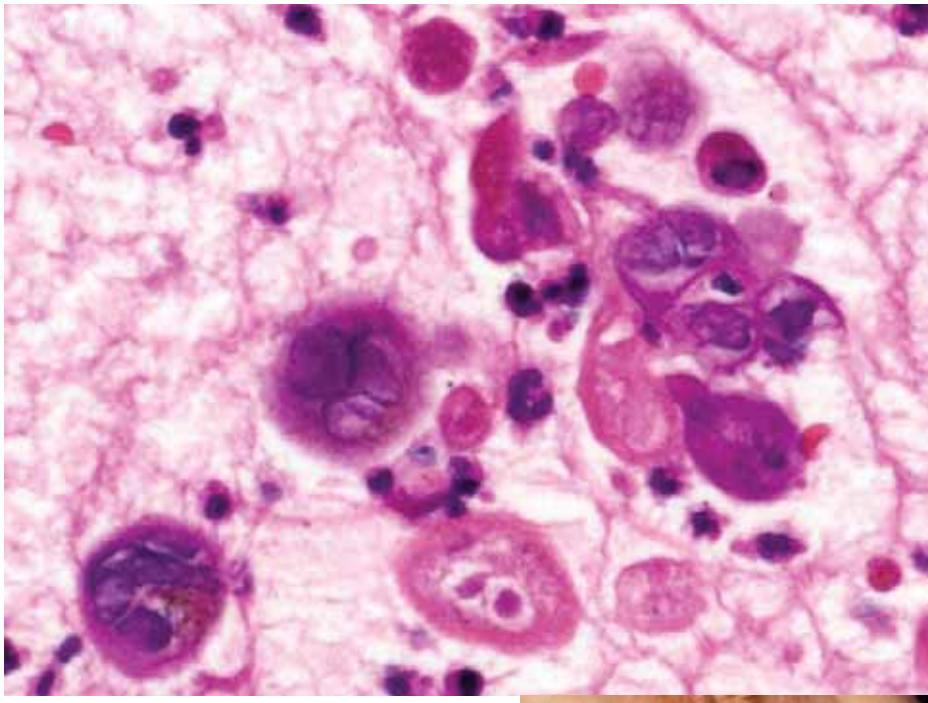


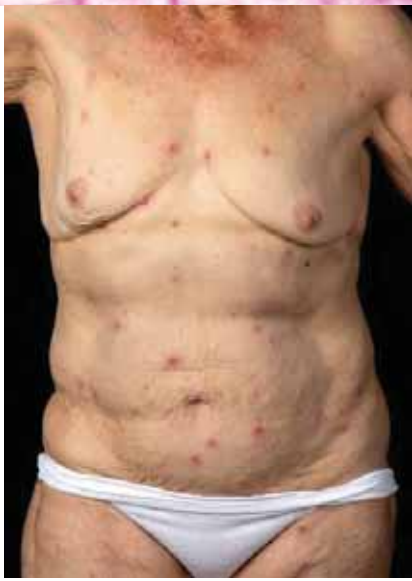
F, 85

According to the patient onset of lesion on the forehead after visiting a hairdresser, in the next days followed by scattered lesions on the entire body.

A biopsy is taken.

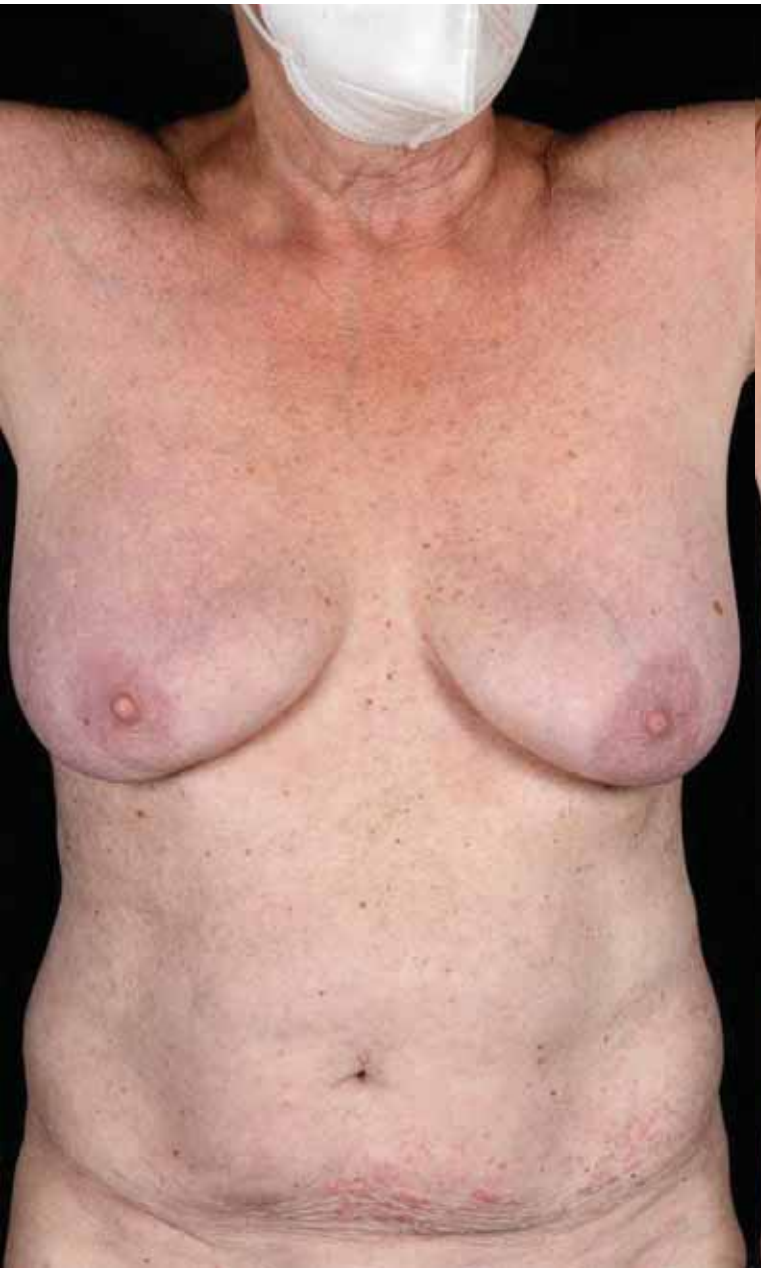


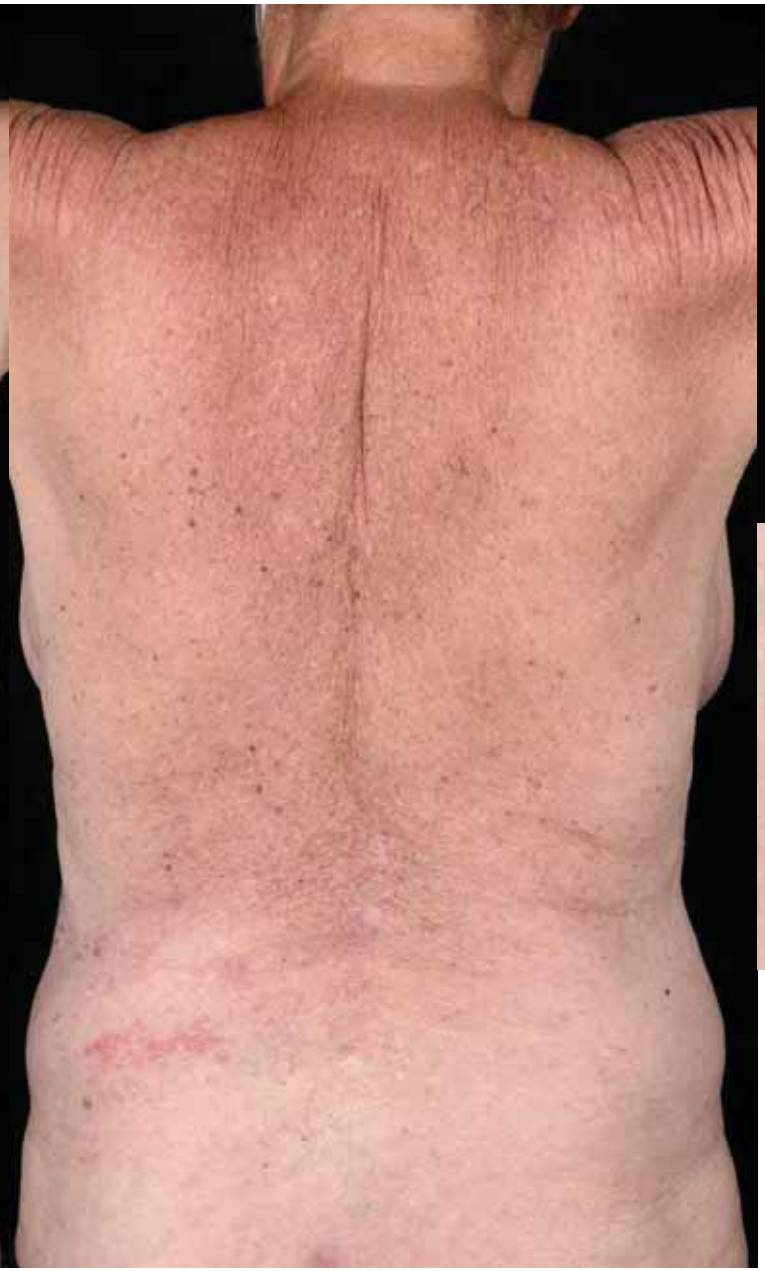


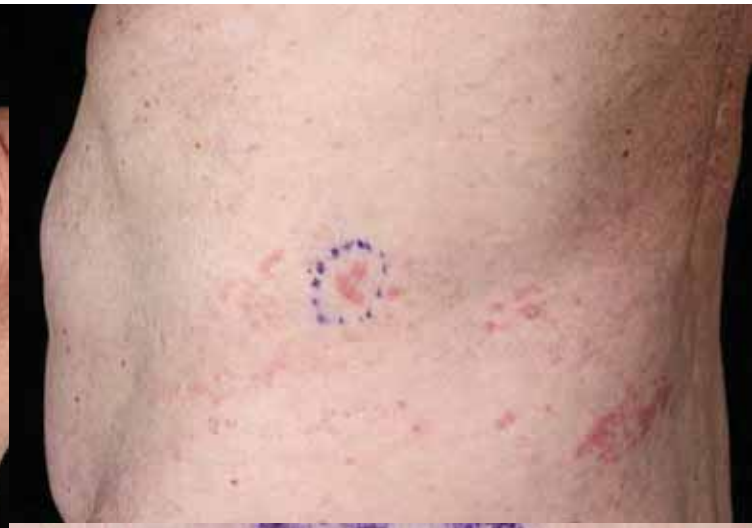


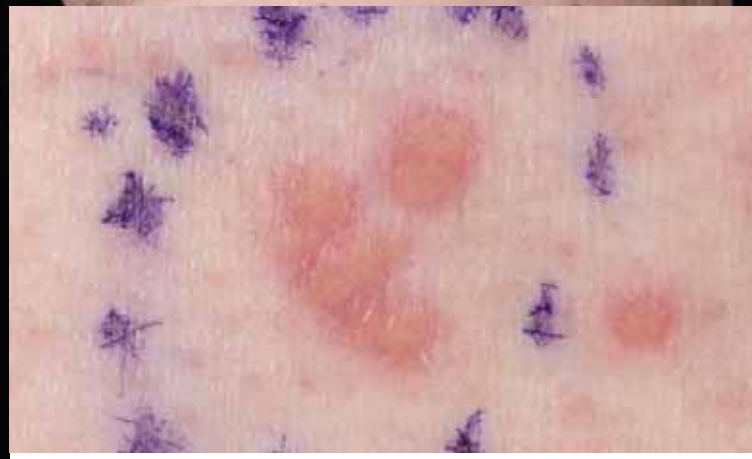
Generalized herpes zoster

PCR+ for VZV







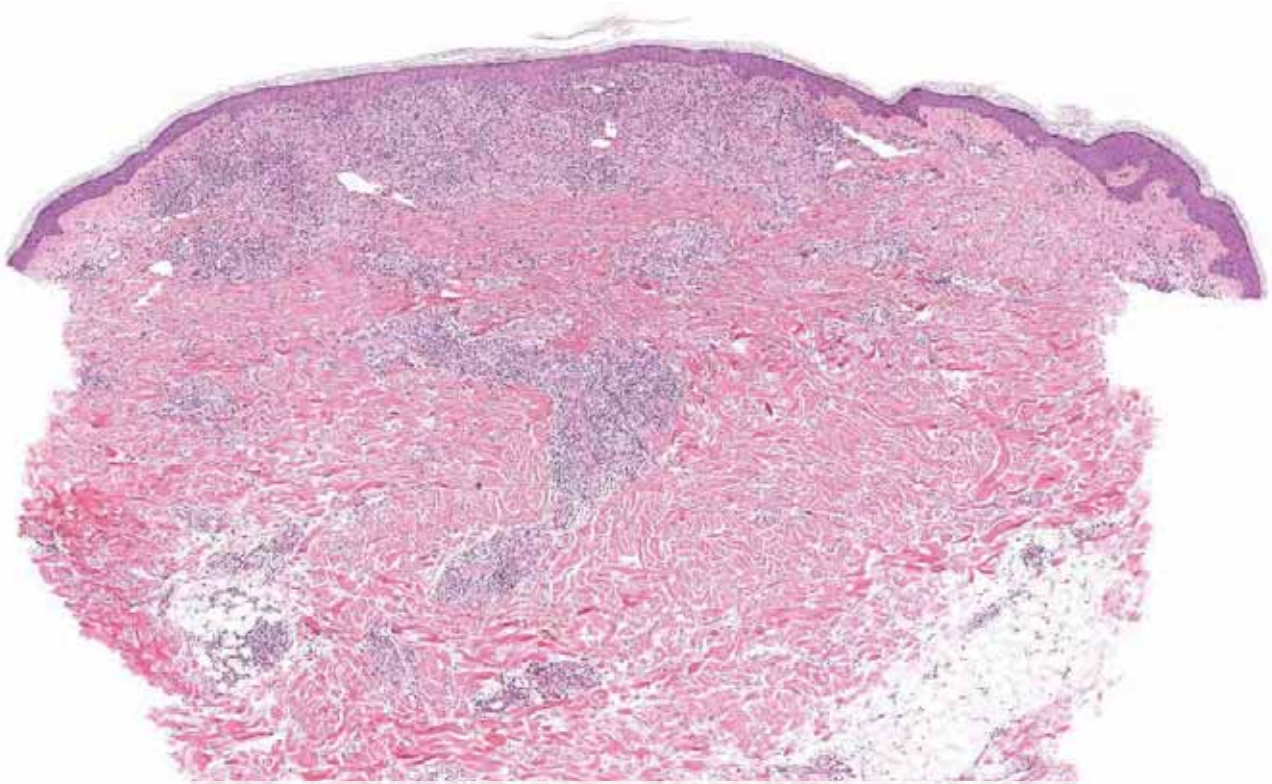


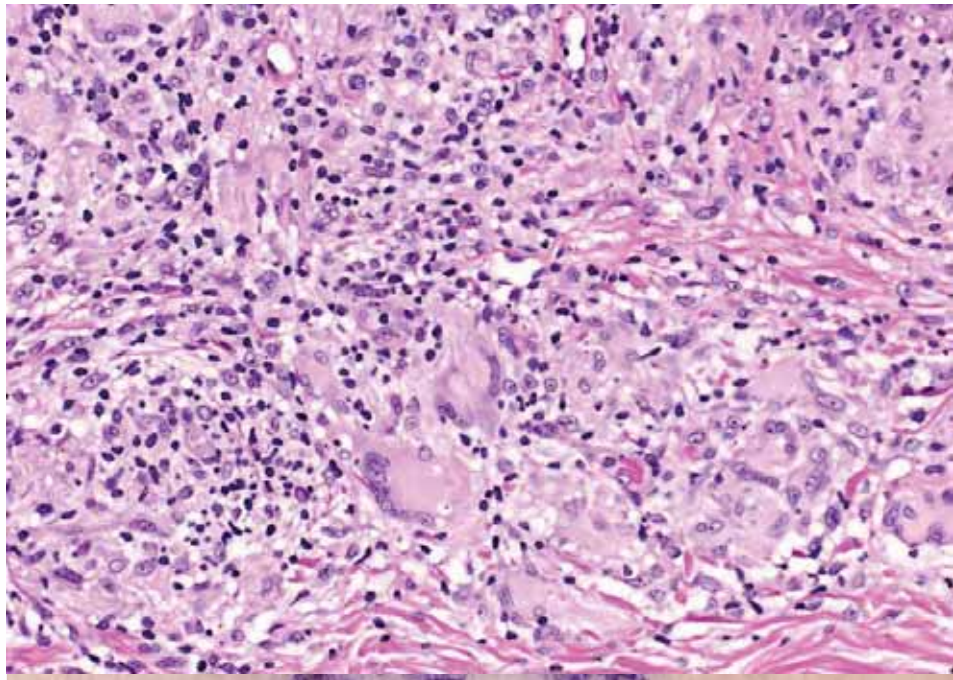
F, 72

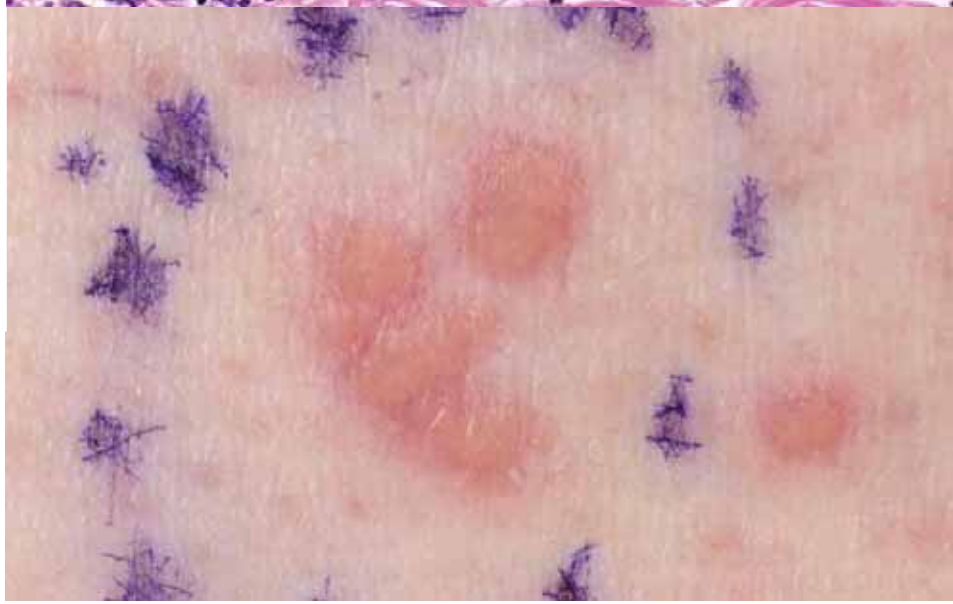
History of melanoma stage IV (1st diagnosis 3 years before observation).

History of herpes zoster (left thoracal 11/12) 3 months prior to observation.

New lesions in the area of the previous zoster; neuralgia.







Post-zoster granulomatous dermatitis

PCR positive for *Herpes zoster*

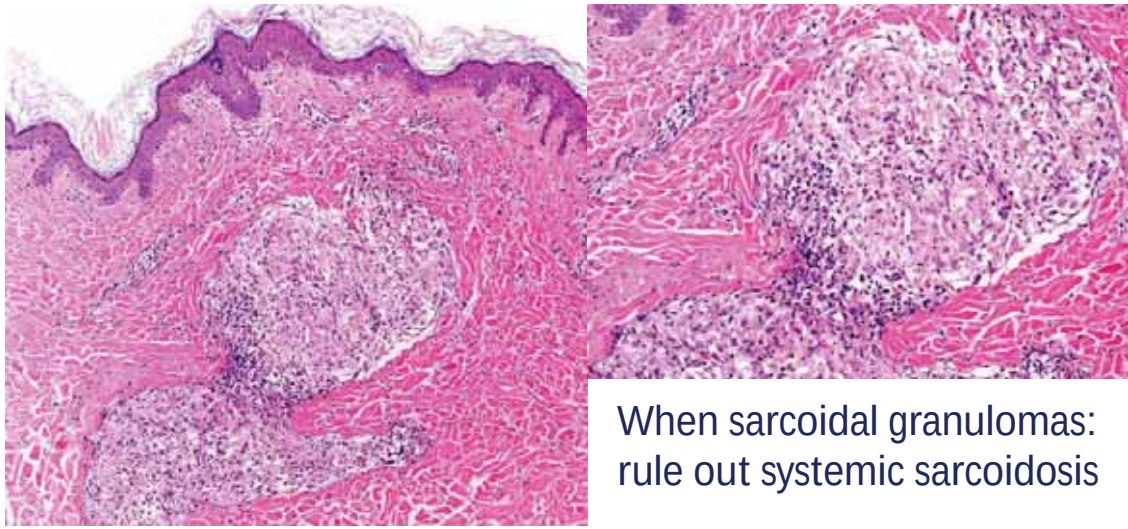
Treated with a second course of high-dose aciclovir (10mg/kg BW for 7 days) with marked improvement.

Post-Zoster skin conditions

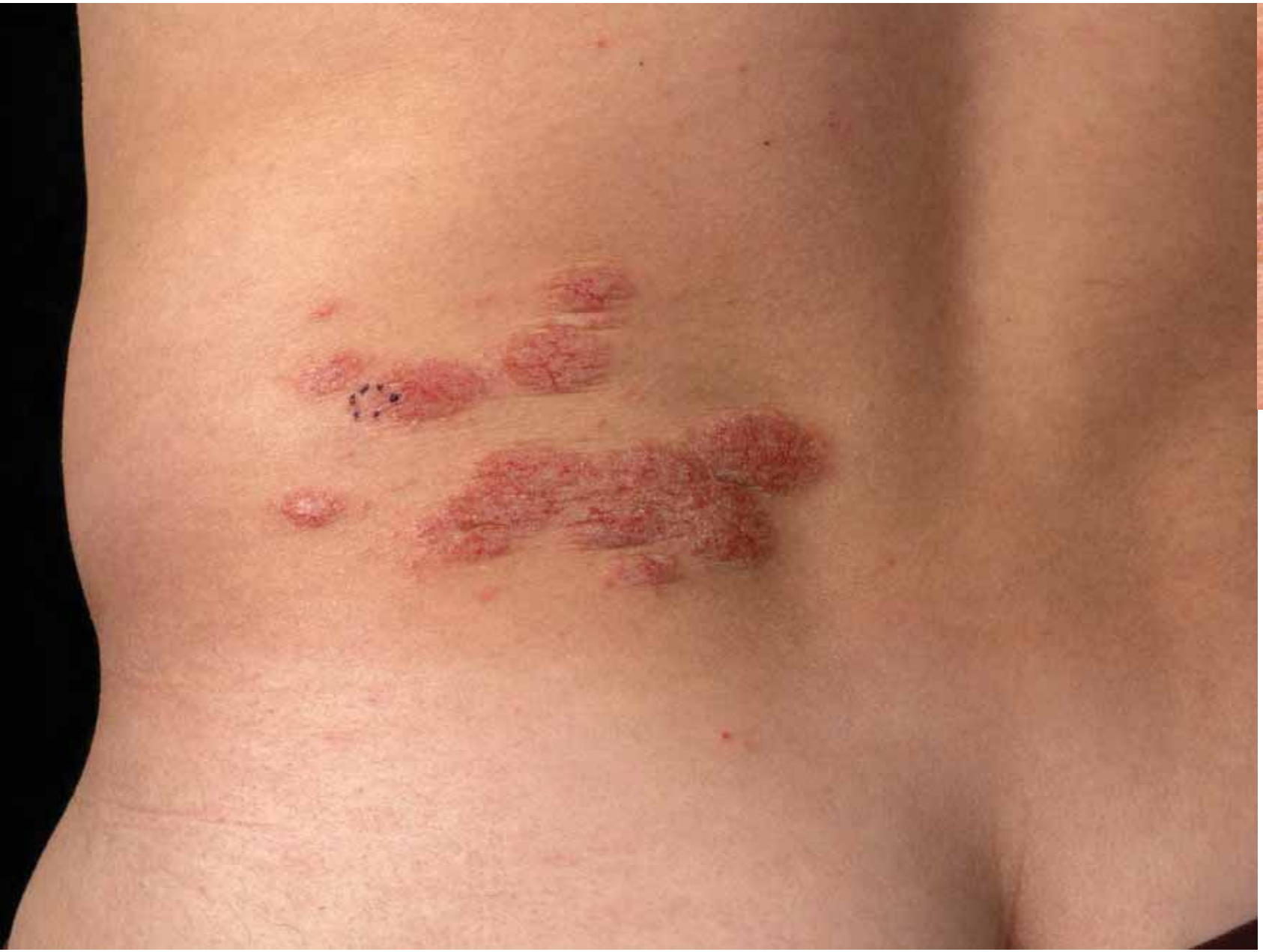
- Granulomas (several types)
- Pseudolymphomas
- Specific infiltrates of several lymphomas & leukemias (esp. B-CLL)
- Lichenoid graft-versus-host disease
- Lichen sclerosus
- Rosai–Dorfman-like reaction
- Eosinophilic dermatosis
- Reactive perforating collagenosis
- Morphea
- Kaposi sarcoma
- *Candida* infection
- Dermatophytosis

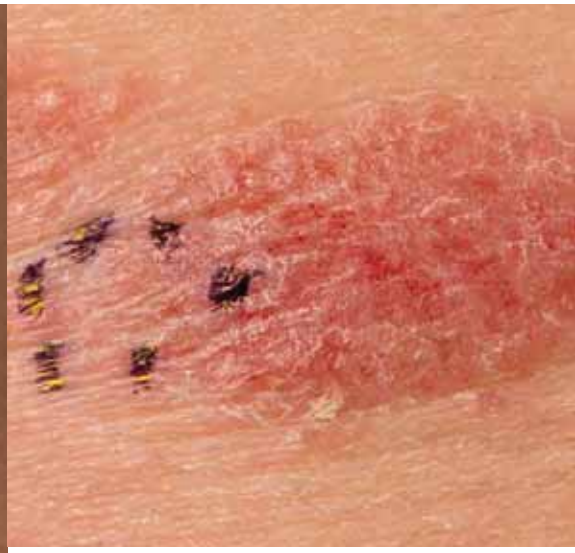
Post-Zoster granulomas

- Granuloma annulare
- Sarcoidal granulomas
- Tubercoloid granulomas
- Interstitial granulomatous dermatitis
- Elastophagic granulomas
- Periadnexal granulomas (including perineural)
- "Pseudolymphomatous" granulomas



When sarcoidal granulomas: rule out systemic sarcoidosis

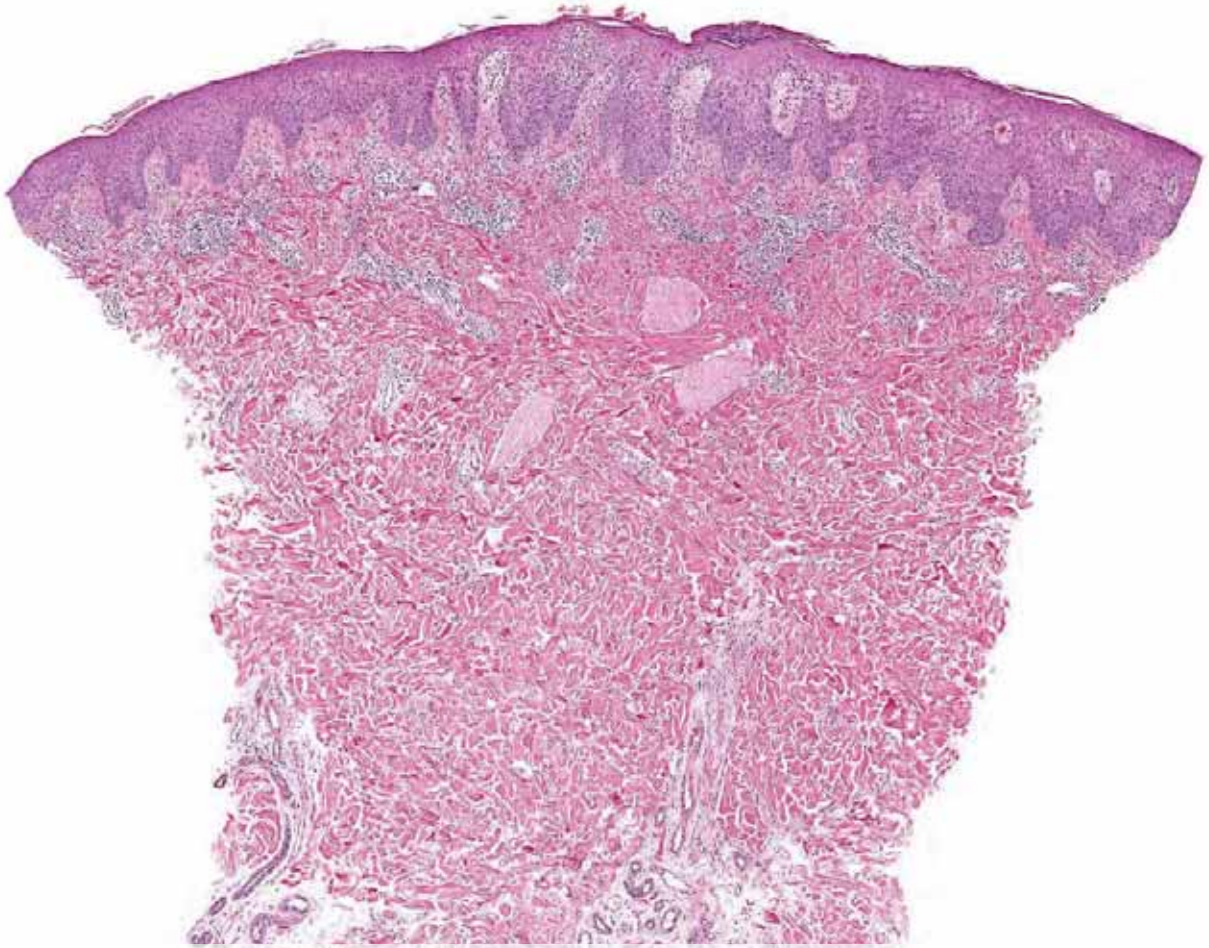


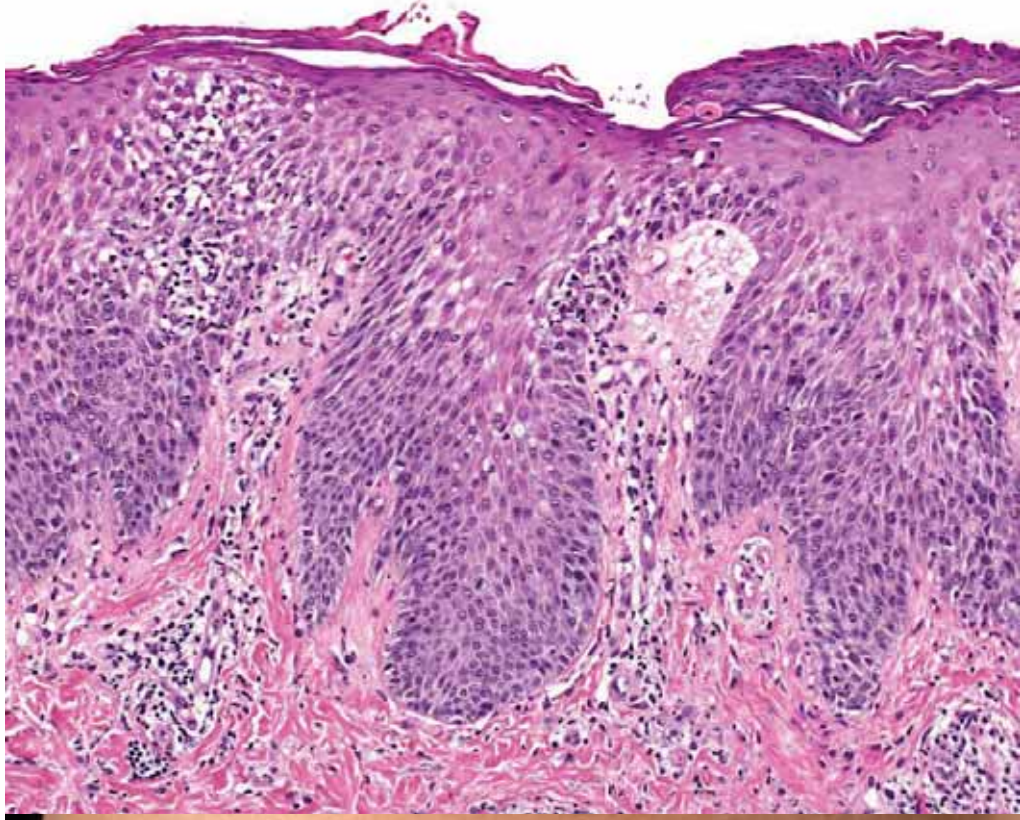


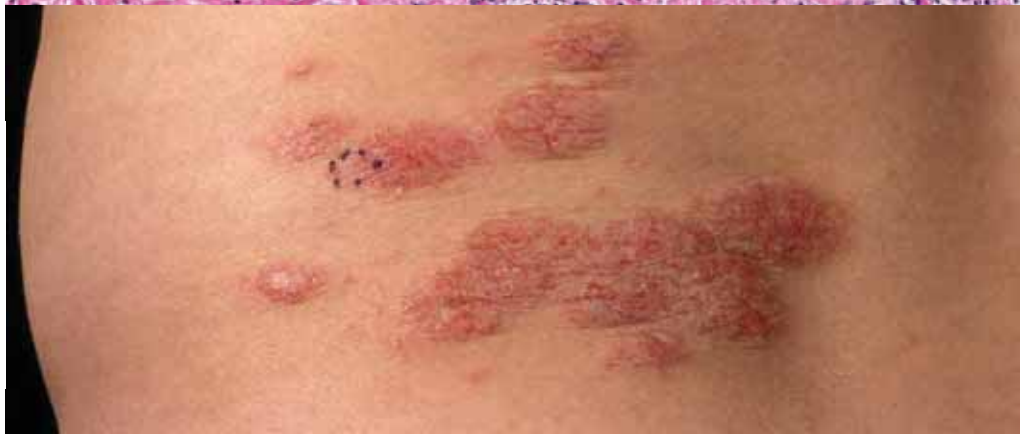
M, 23

Onset of elevated, slightly itchy, erythematous, scaly and crusted lesions at the site of a *herpes zoster* infection (5 weeks previously, managed with valaciclovir and brivudin). According to the patient the skin lesions of *herpes zoster* "never healed" and became progressively more infiltrated.

A biopsy is taken.



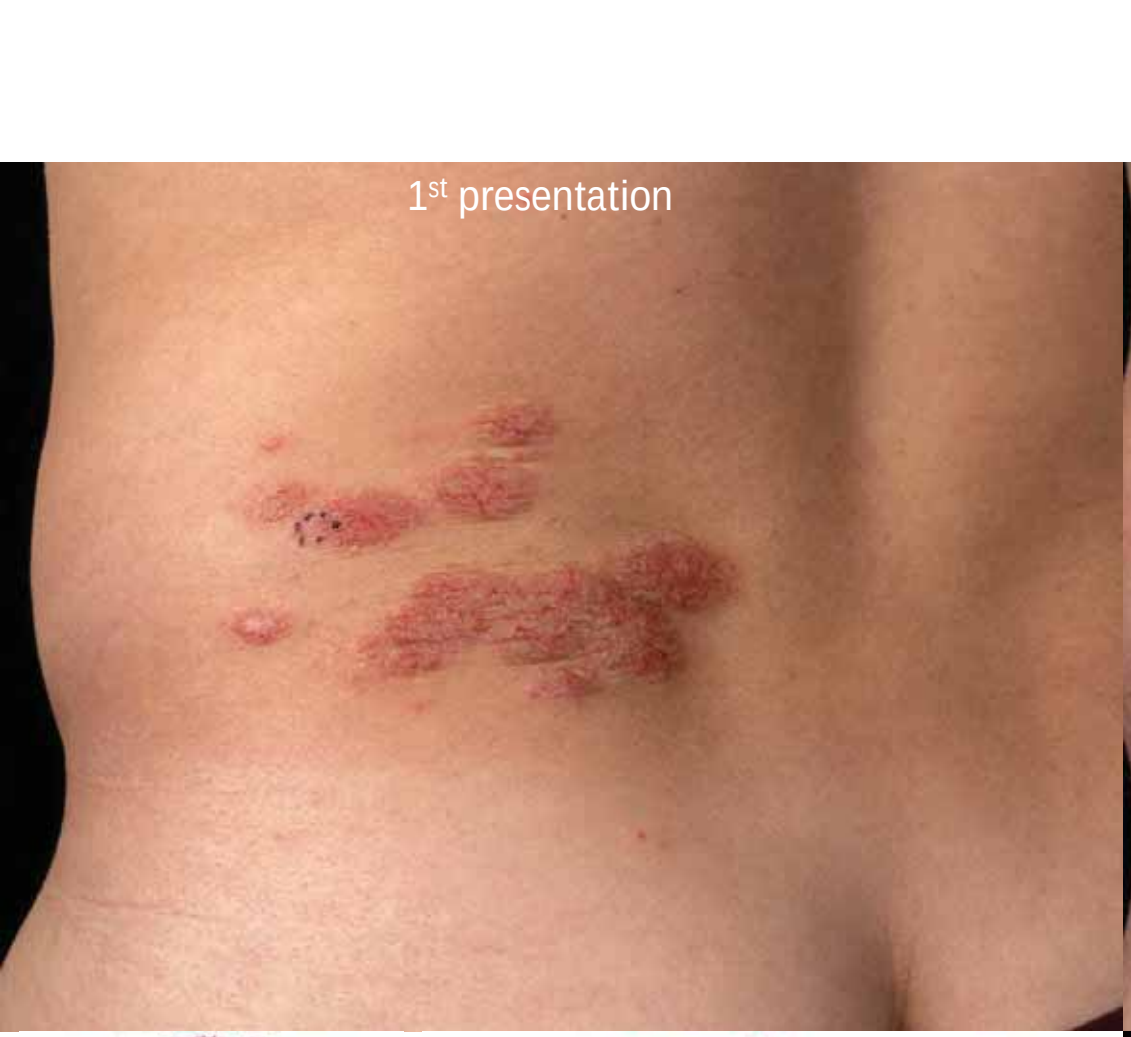


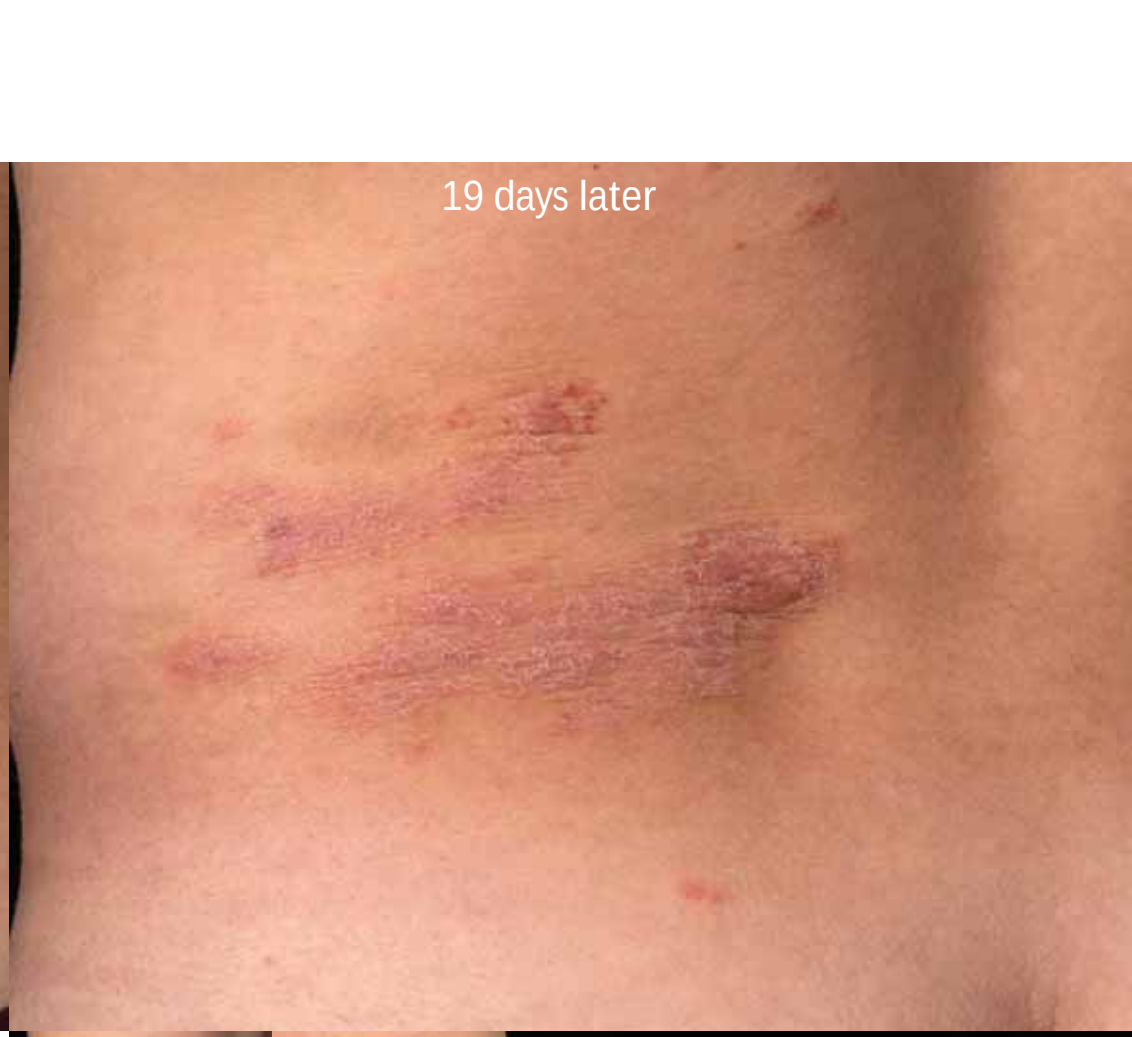


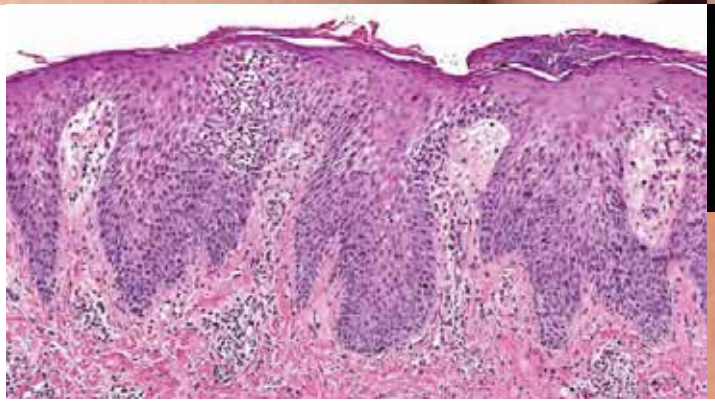
Psoriasis at the site of a *herpes zoster* scar

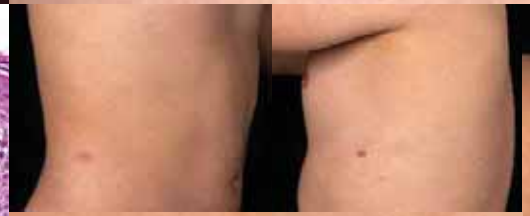
1st presentation

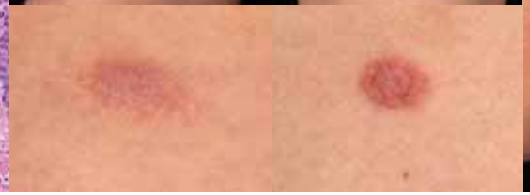
19 days later

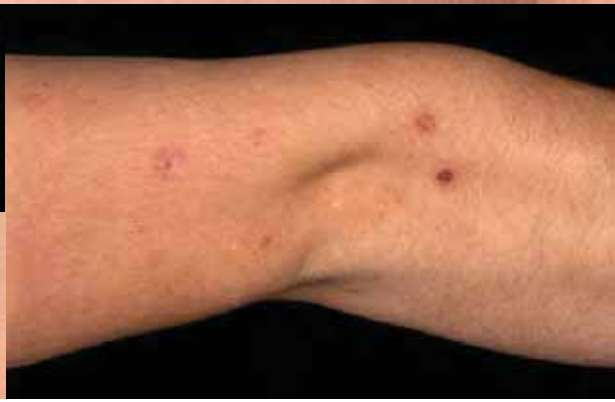












These tumors show a normal analytical profile, although 1 incidental case with elevated carcinoembryonic antigen has been published.[1]

Pathology studies have shown an epithelial growth in the upper half of the reticular dermis consisting of cells with a pale eosinophilic cytoplasm arranged in nests or tubules and surrounded by a sclerotic stroma. The tubular areas contain basophilic granular cells and ductal differentiation with central lumens lined with a compact eosinophilic cuticle. Epithelial growths in the form of a "tadpole's tail" or "comma" is characteristic.[2] The variant known as clear-cell syringoma is more common among diabetics and is characterized by glycogen laden cells.

Immunohistochemical studies of this tumor show positivity for EKH-6, which would support the eccrine ductal origin. The description of eczematous lesions that leave eruptive syringomas as sequelae would raise the hypothesis that the classic eruptive form is actually a reactive hyperplasia against inflammatory processes in the sweat gland ducts.[3]

The histological differential diagnosis should be done with nevus, microcystic adnexal carcinoma, and desmoplastic trichoepithelioma.

These tumors may benefit from physical treatments such as superficial cryotherapy, fulguration, and electrodesiccation, or from chemical agents such as isotretinoin, tretinoin, adapalene, or a 1% aqueous topical solution of atropine. At present, the best treatment is considered to be ablation with ultrapulsed CO_2 laser and preliminary treatment with trichloroacetic acid to minimize scarring. "None of these treatments are considered satisfactory or prevent recurrences.

Because of the age at onset, the fact that the condition did not always appear in outbreaks, and that it affected various skin areas, including the eyelid, we considered our patient to present a form of multifocal generalized syringomas that started on the eyelid.

Acknowledgements

We would like to thank Dr JJ Ríos-Martín of the Anatomical Pathology Department at Hospital Universitario Virgen Macarena de Sevilla in Seville, Spain.

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Psoriasis at the Site of Healed Herpes Zoster: Wolf's Isotopic Response

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To the Editor:

A wide variety of dermatological processes can occur at the site of healed herpes zoster, mainly granulomatous processes, lymphomas, pseudolymphomas, and primary skin tumors or metastasis.[1] These conditions occasionally appear in immunosuppressed patients with neoplasms or human immunodeficiency virus infection, but in other patients there may be no underlying disease. The interval between viral infection and second disease is extremely variable, from days to years.[2] We describe a patient with paroxysmal nocturnal hemoglobinuria who developed guttate psoriasis lesions on the site of previous herpes zoster.

A 41 year-old man who had undergone allogeneic transplantation of bone marrow for paroxysmal nocturnal hemoglobinuria and received

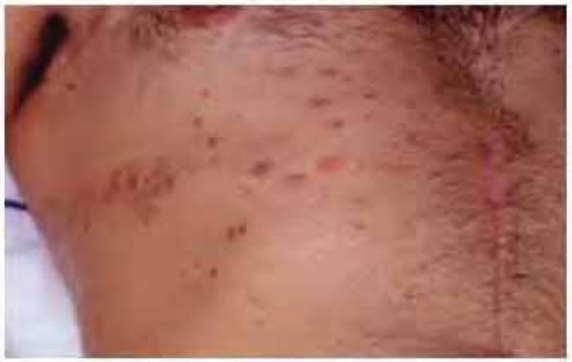

Figure 1. Cluster of erythematous-desquamative lesions with a zosteriform distribution.

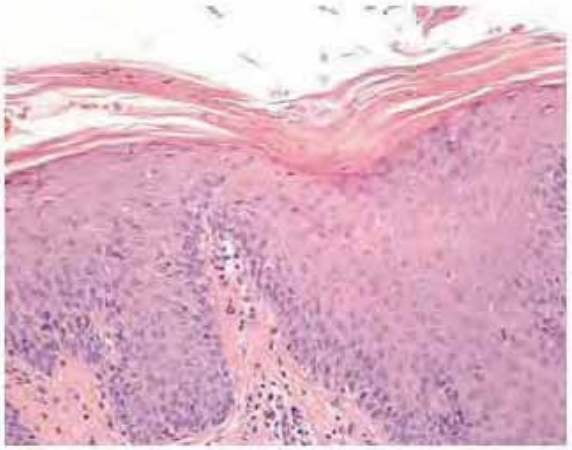

Figure 2. Epidermal hyperplasia and neutrophil clusters in areas of parakeratosis (hematoxylin-eosin, x40).

British Journal of Dermatology 1998; 138: 161–168

Cutaneous reactions at sites of herpes zoster scars: an expanded spectrum

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Summary Several types of cutaneous lesions have previously been described at the sites of herpes zoster scars. We describe 16 patients with cutaneous lesions which had developed on herpes zoster scars. Biopsies were taken from these lesions, and a polymerase chain reaction assay was used to detect the viral genome in paraffin-embedded specimens. Histopathological findings enabled diagnosis of nonspecific granulomatous dermatitis in five patients, granulomatous vasculitis in two patients, lichen sclerosus in two patients, and pseudolymphoma, keloid, sarcoidal granuloma, granuloma annulare, granulomatous folliculitis, lichen planus and cutaneous Rosai–Dorfman disease, each in one patient. Varicella-zoster virus DNA was not identified in any of the patients. Granulomatous folliculitis, lichen sclerosus and cutaneous Rosai–Dorfman disease have not previously been described in herpes zoster scars, but they are three new cutaneous reaction patterns that may have developed within these scars. Our investigations indicate that the cutaneous reactions appearing in herpes zoster scars are not due to the persistence of varicella-zoster virus DNA within the lesions.

Several types of cutaneous lesions have been described developing within resolved cutaneous herpes zoster lesions. These include comedones,[1] xanthomatous changes,[2] granuloma annulare,[3–11] sarcoidal granulomas,[12,13] tuberculoid granulomas,[14,15] granulomatous vasculitis,[16,17] unclassified granulomatous dermatitis,[18–21] tinea,[22] acneiform eruption,[23] furunculosis,[24] contact dermatitis,[24] nodular solar degeneration,[25] pseudolymphoma,[26–28] psoriasis,[29,30] lichen planus,[31–33] morphoea,[34] lichenoid chronic graft-versus-host disease,[35] eosinophilic dermatosis,[36] acquired reactive perforating collagenosis,[37] lymphoma,[38,39] leukaemia,[40–44] Kaposi's sarcoma,[45] angiosarcoma,[46] basal cell carcinoma,[47] squamous cell carcinoma[47] and cutaneous metastases from internal carcinoma.[48] Immunohistochemical studies by Cerroni *et al.*[45] have demonstrated that those cases reported as pseudolymphomas occurring in herpes zoster scars of patients with chronic lymphocytic leukaemia are actually specific cutaneous infiltrates by leukaemia cells.

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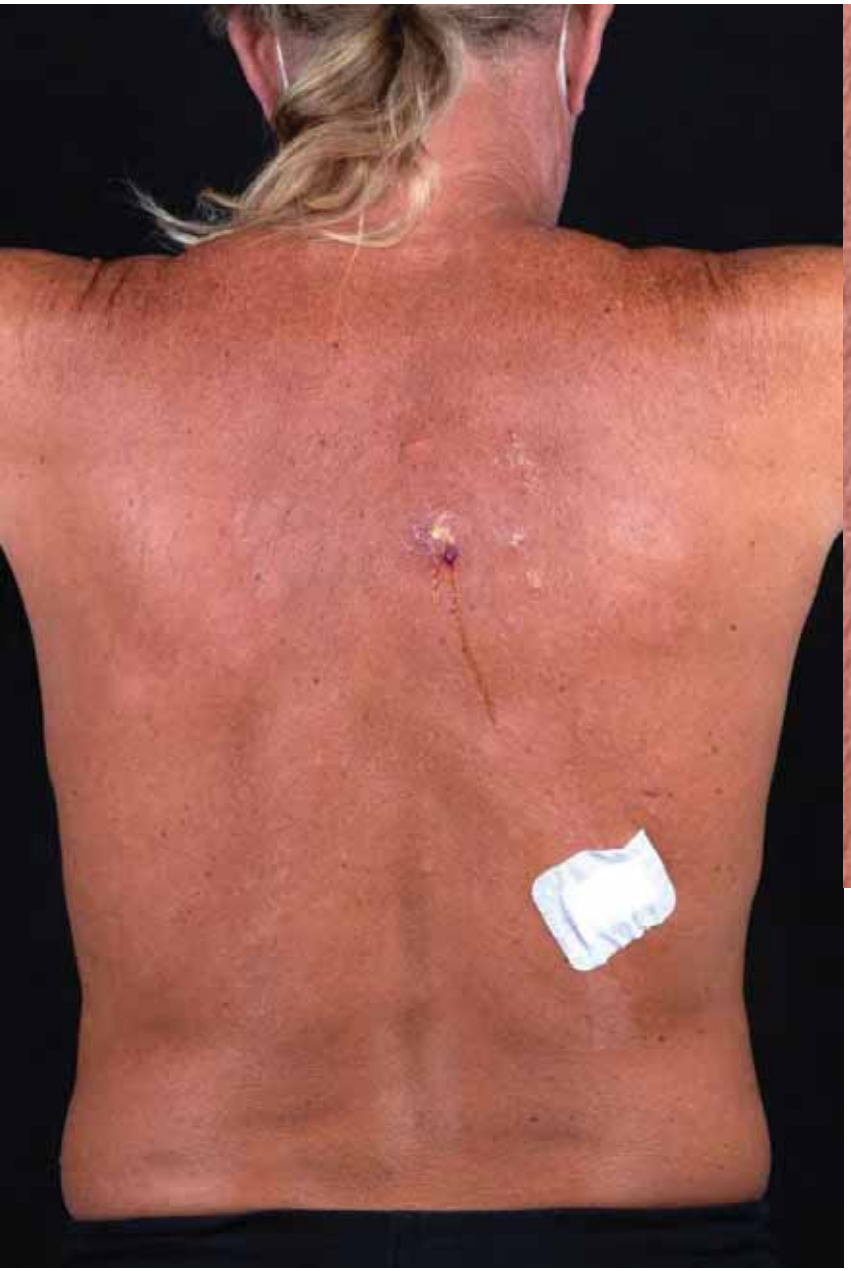
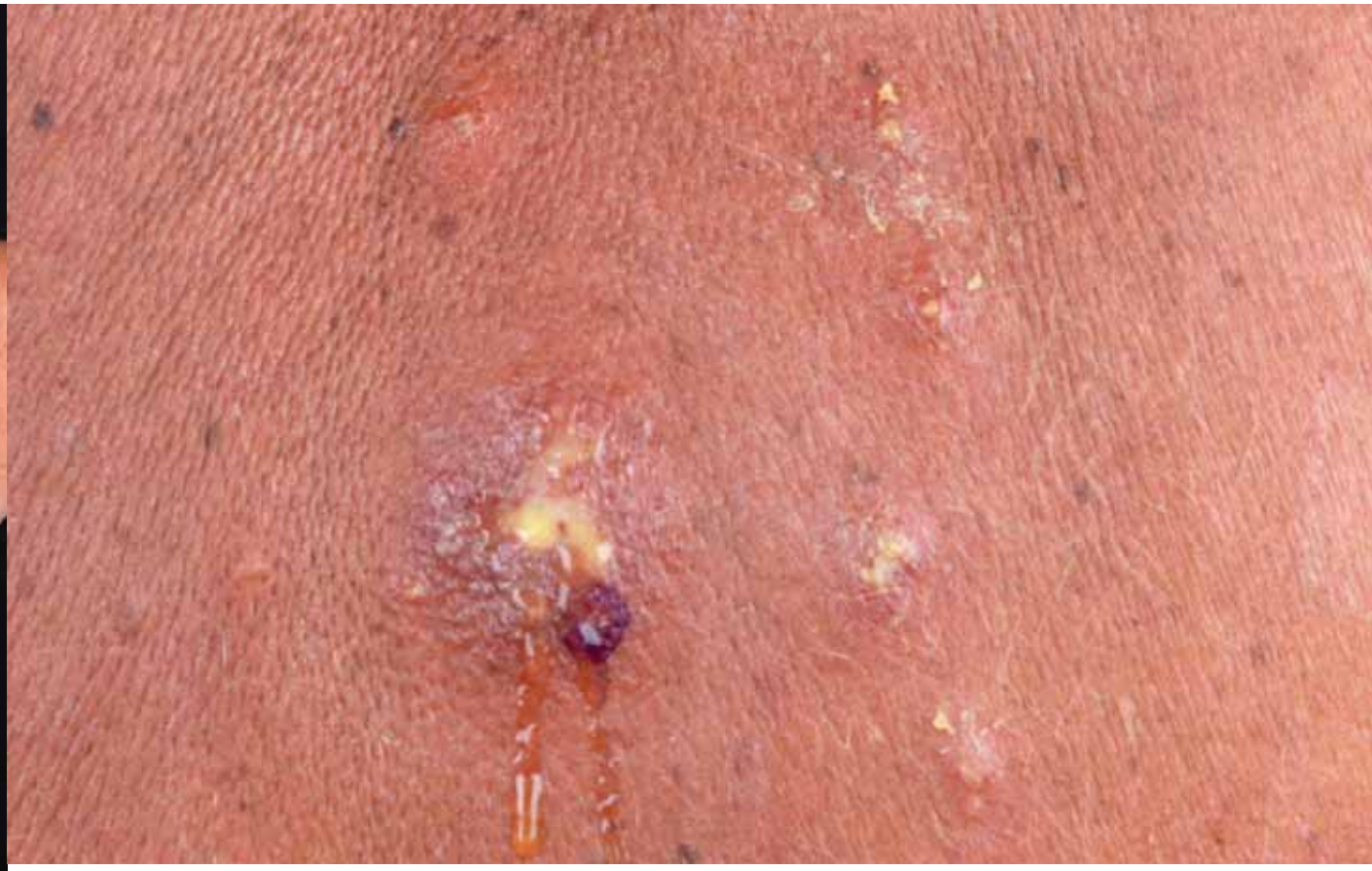
These cutaneous lesions may appear immediately in resolving vesicular lesions or at varying times after the acute eruption. The pathogenesis of the cutaneous reactions following resolved lesions of herpes zoster remains to be elucidated, and in the literature, type III or type IV hypersensitivity reactions[4,14] and Koebner's phenomenon[3,4,12,31–33,45] have been proposed as provoking factors. The polymerase chain reaction (PCR) technique has been used to investigate the presence of varicella-zoster virus (VZV) DNA within these cutaneous reactions. Langenberg *et al.*[16] failed to detect VZV-DNA in lesions of granulomatous vasculitis of an HIV-infected homosexual man which developed 7 weeks after thoracic herpes zoster. Serfling *et al.*[18] detected VZV-DNA in one case of a granulomatous cutaneous reaction occurring 4 weeks after the acute herpes zoster episode, but this investigation gave negative results in granulomatous lesions which developed 2 and 4 years after the acute infection. Using PCR, Gibney *et al.*[10] detected VZV-DNA in granulomatous lesions which developed 4 weeks after the acute herpes zoster infection, but not in lesions occurring 8 and 14 months after resolving herpes zoster. Basciga *et al.*[25] failed to detect

Table 1. Clinical, histopathological and PCR results in patients with cutaneous reactions at the sites of herpes zoster scars

Patient	Age/sex	Interval (weeks)	Location	Histopathological findings
1	64/M	12	Trunk	Nonspecific granulomatous dermatitis
2	77/F	17	Forehead	Pseudolymphoma
3	75/F	4	Trunk	Nonspecific granulomatous dermatitis
4	57/M	7	Face	Granulomatous vasculitis
5	65/F	27	Shoulder	Keloid
6	51/F	9	Back	Sarcoidal granuloma
7	57/F	12	Back	Granuloma annulare
8	46/M	12	Back	Nonspecific granulomatous dermatitis
9	78/F	7	Back	Granulomatous folliculitis
10	67/F	12	Forehead	Nonspecific granulomatous dermatitis
11	73/F	100	Trunk	Lichen sclerosus
12	72/F	20	Face	Nonspecific granulomatous dermatitis
13	73/F	30	Trunk	Lichen sclerosus
14	65/F	8	Face	Granulomatous vasculitis
15	30/M	4	Trunk	Lichen planus
16	77/M	100	Trunk	Cutaneous Rosai–Dorfman disease

NA, none apparent; CLL, chronic lymphocytic leukaemia; AIDS, acquired immunodeficiency syndrome.



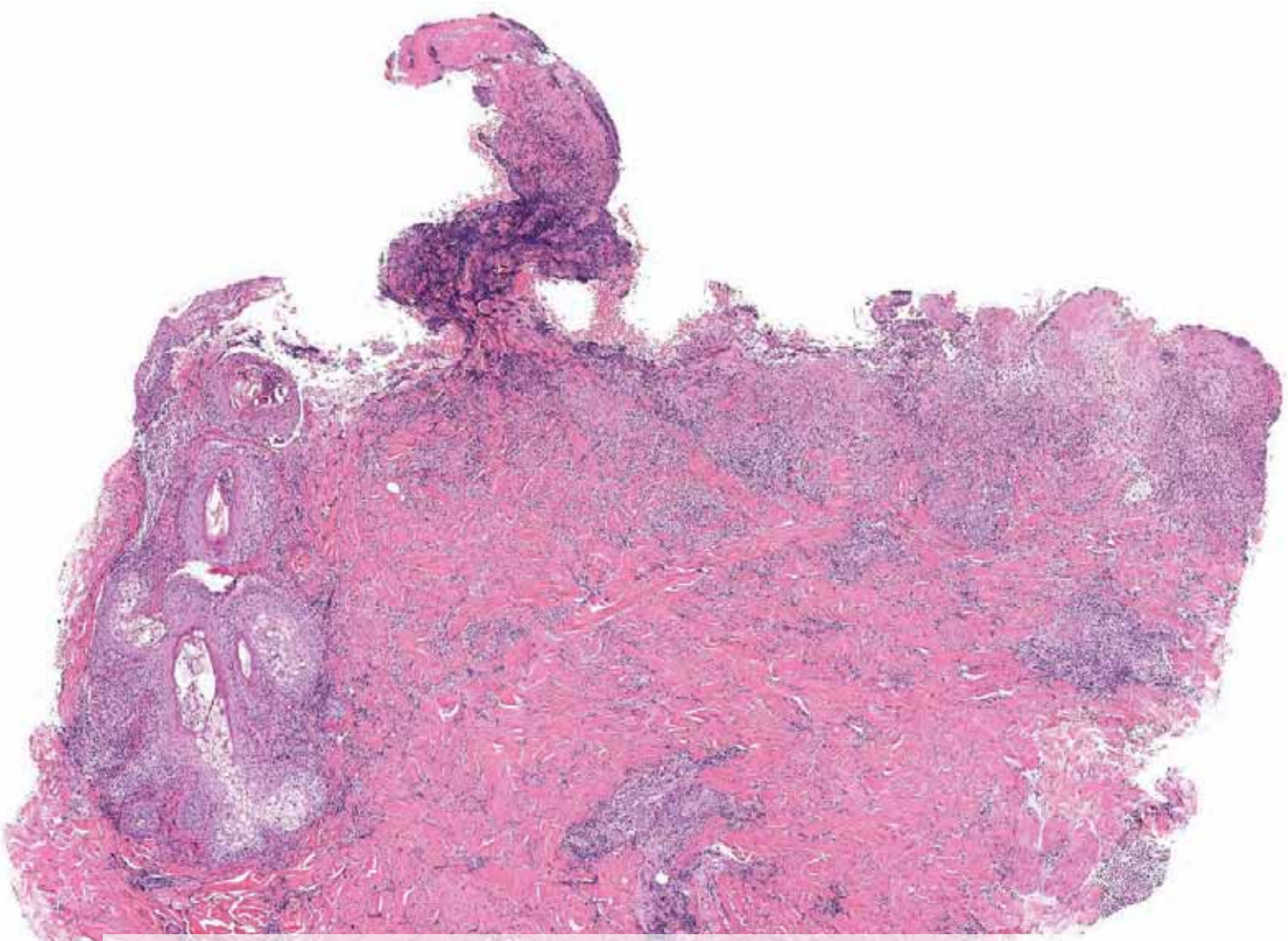


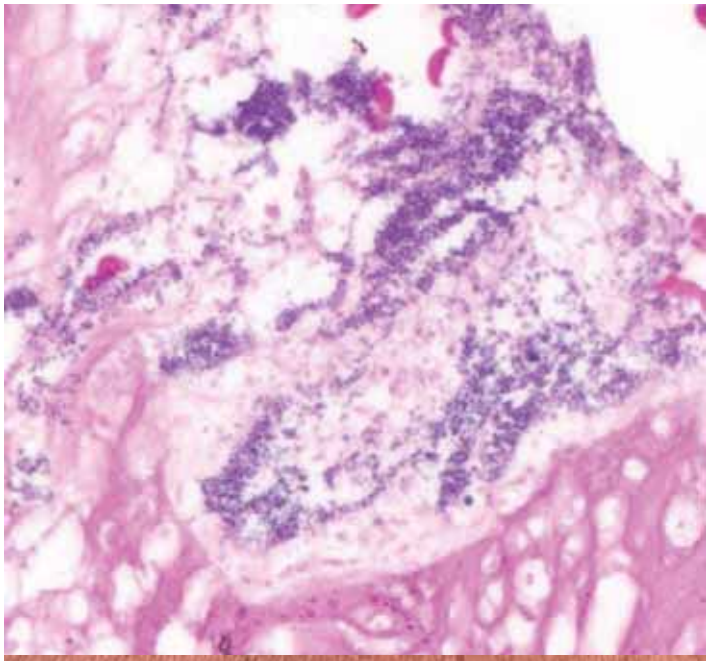
M, 54

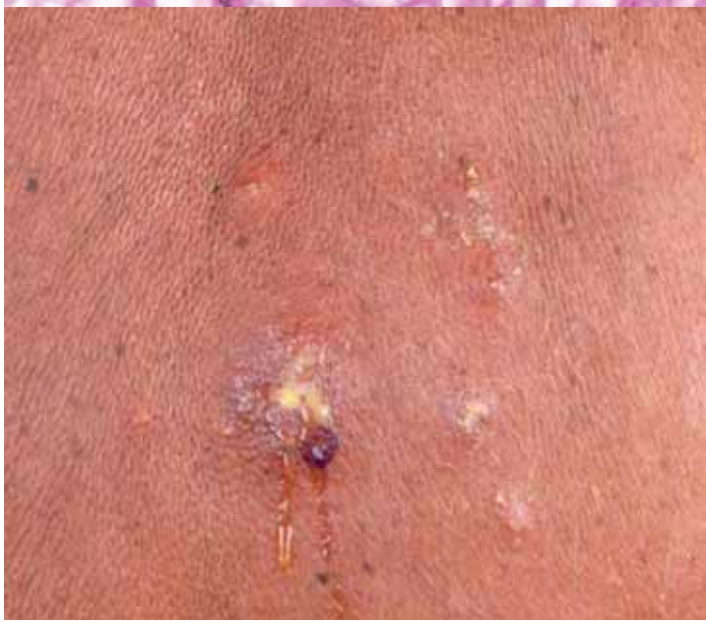
Onset of purulent, localized lesions on the back a few days after returning from a holiday in Egypt. No fever or generalized symptoms at presentation.

PCR for *herpes simplex* and VZV negative.

A biopsy is taken.

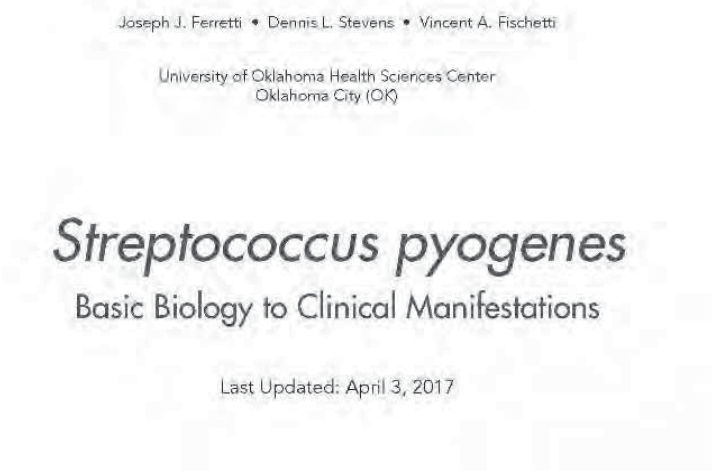






Multiple, localized furuncles

Developed toxic shock syndrome;
Skin culture positive for *Streptococcus pyogenes*

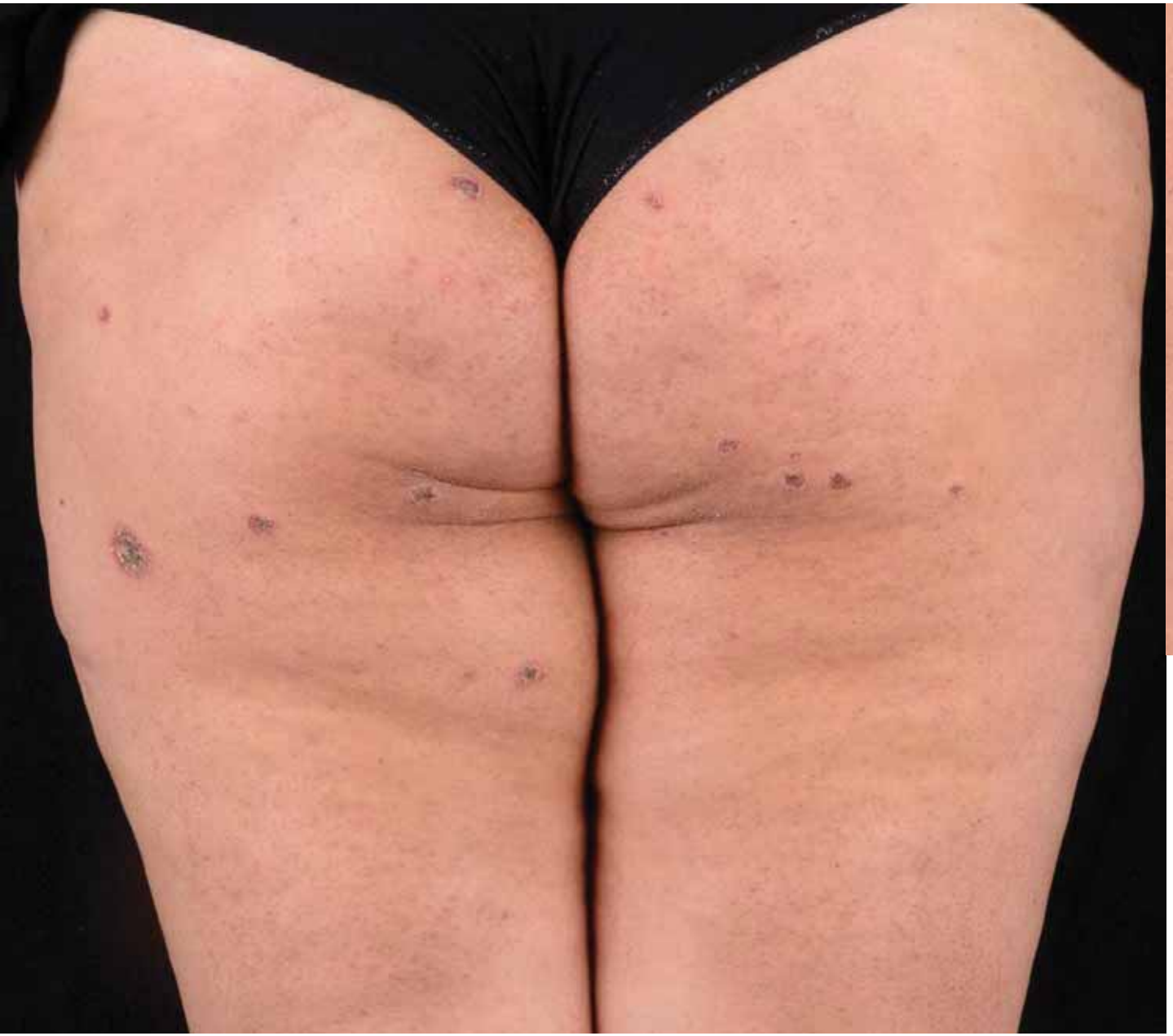


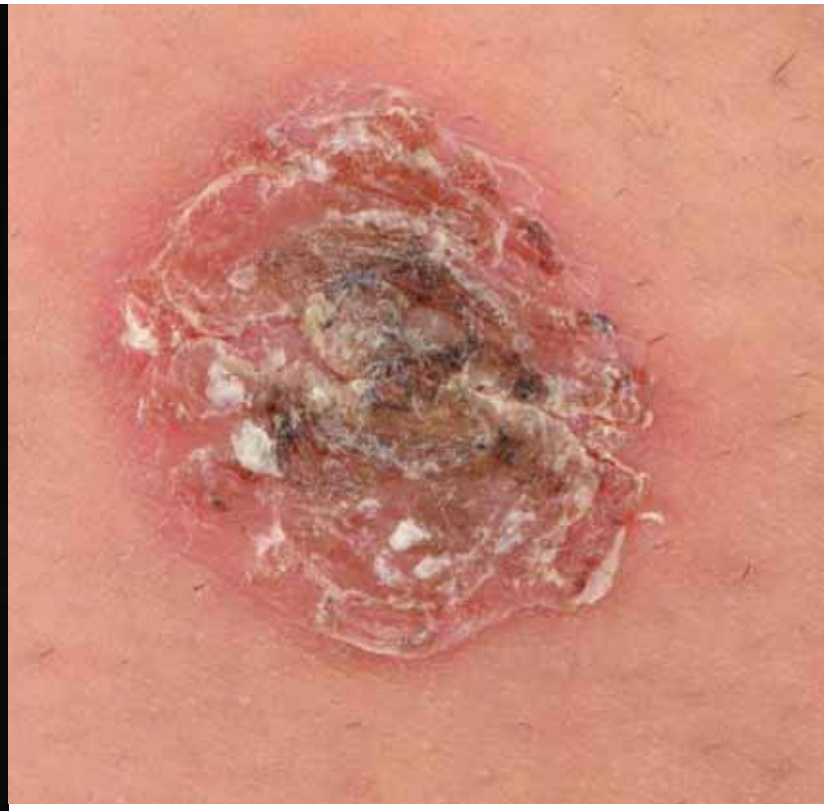
Invasive *S. pyogenes* diseases: scarlet fever, bacteremia, pneumonia, necrotizing fasciitis / myonecrosis, streptococcal toxic shock syndrome; less common invasive diseases include septic arthritis, puerperal sepsis, meningitis, abscess, osteomyelitis, endocarditis, and peritonitis.

The common portals of entry for streptococci in streptococcal toxic shock syndrome include the vagina, pharynx, mucosa, and skin.

Globally, in 2005 it was estimated that at least 663,000 cases of invasive *S. pyogenes* disease occurred each year, which resulted in 163,000 deaths.

Development of severe invasive infections is associated with strains that produce streptococcal pyrogenic exotoxins (Spe)—a family of bacterial superantigens that includes the classical scarlatina toxins SpeA and SpeC, the cysteine proteinase SpeB, and a number of more recently described superantigens (such as mitogenic factor [MF, SpeF] and streptococcal superantigen [SSA]). Superantigens are potent immunostimulators that cause clonal proliferation of T cells and watershed production of pro-inflammatory cytokines that mediate shock and organ failure.

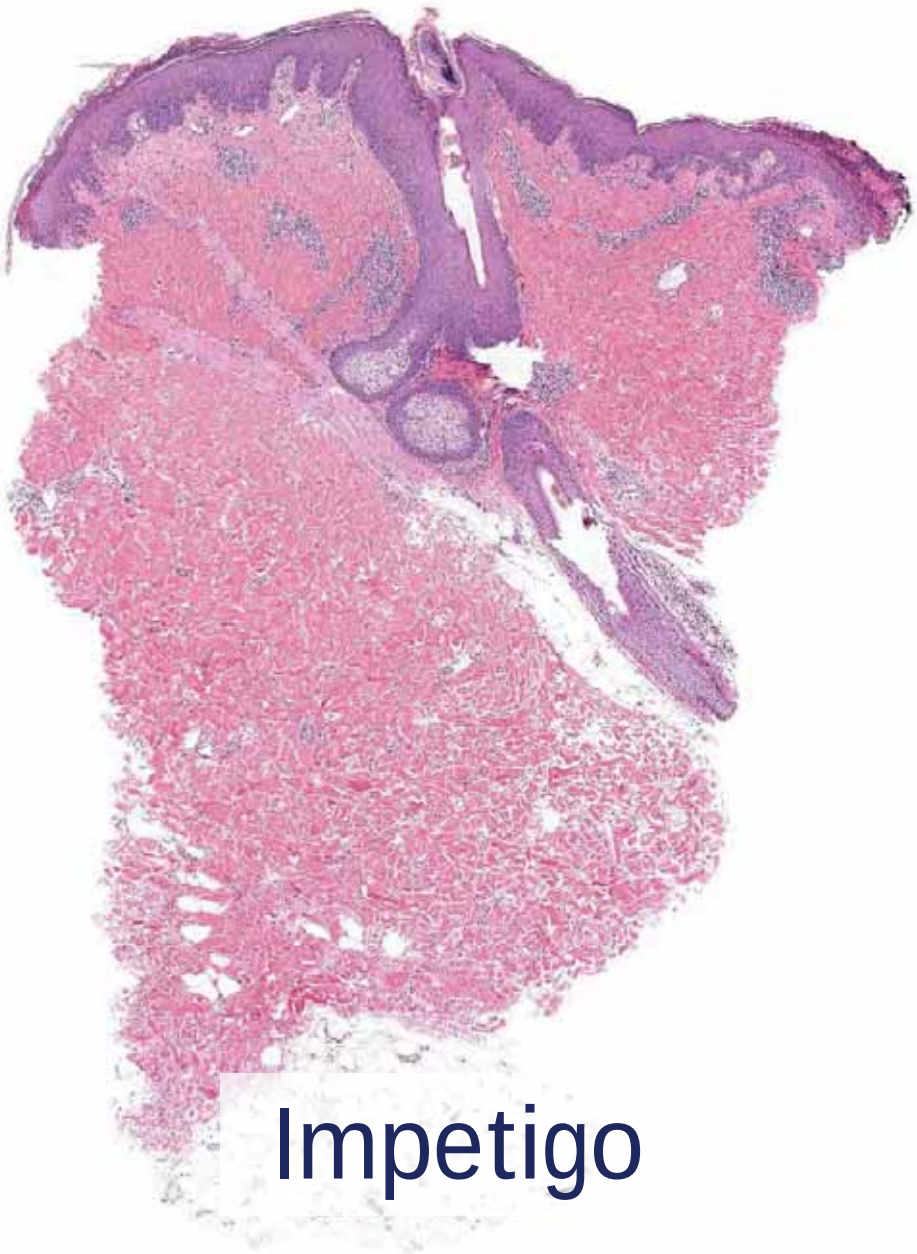




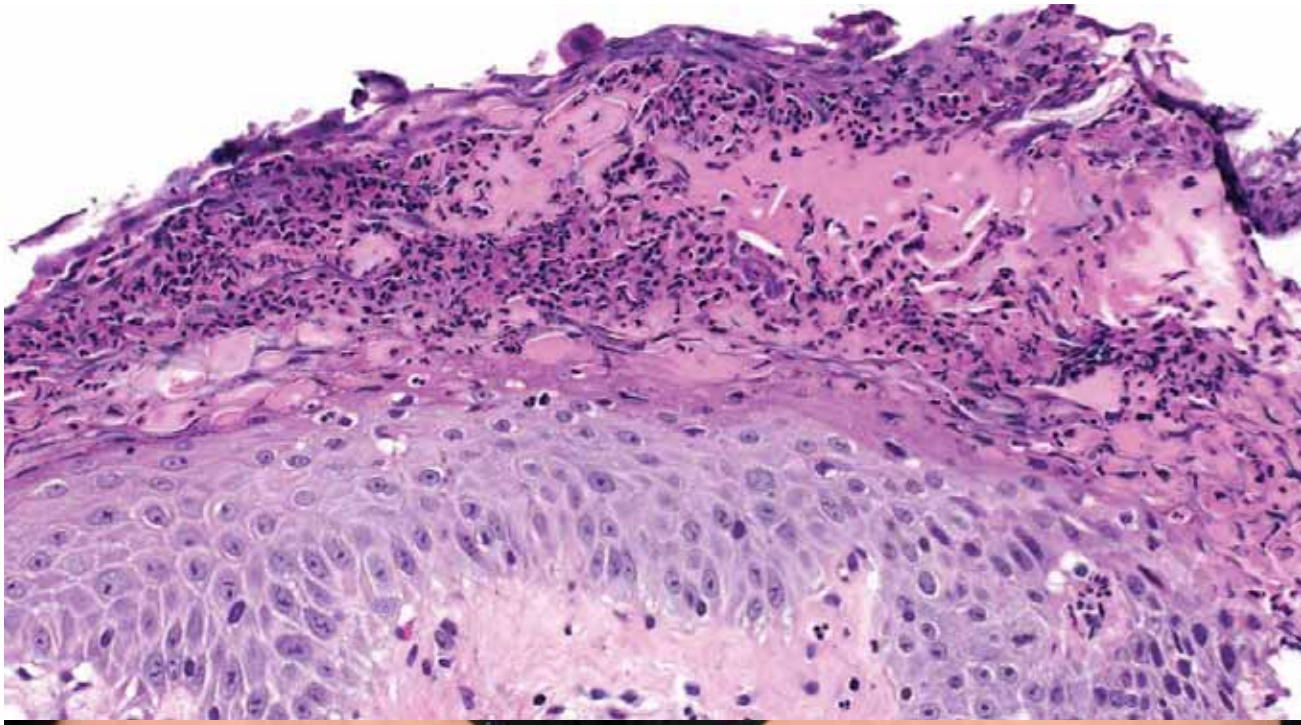
F, 21

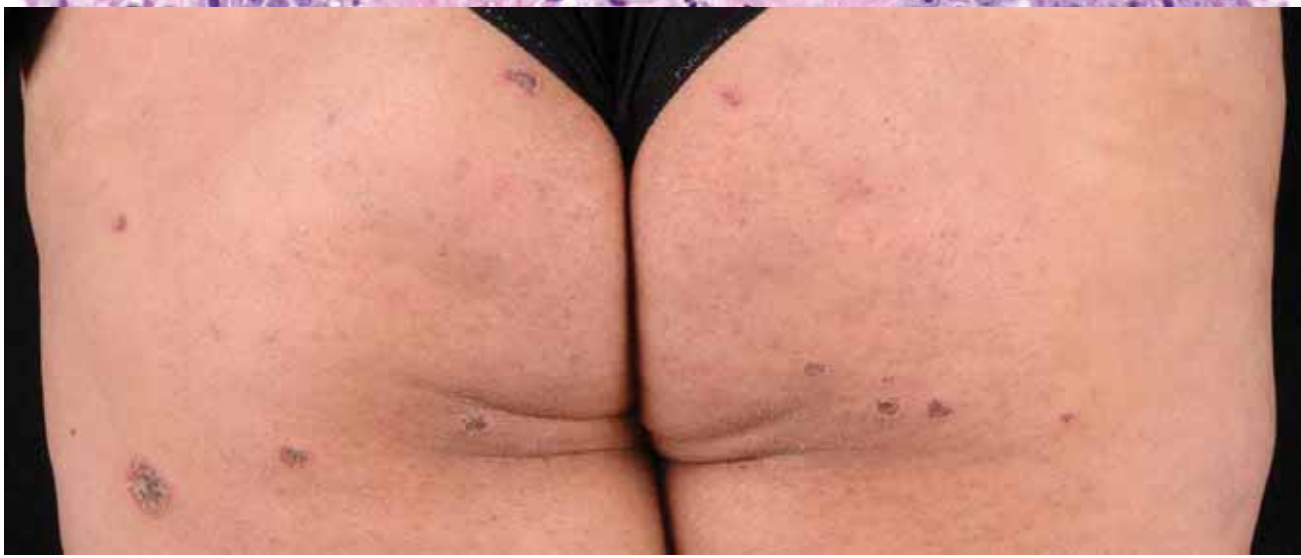
According to the patient asymptomatic "bullous" lesions for one week.

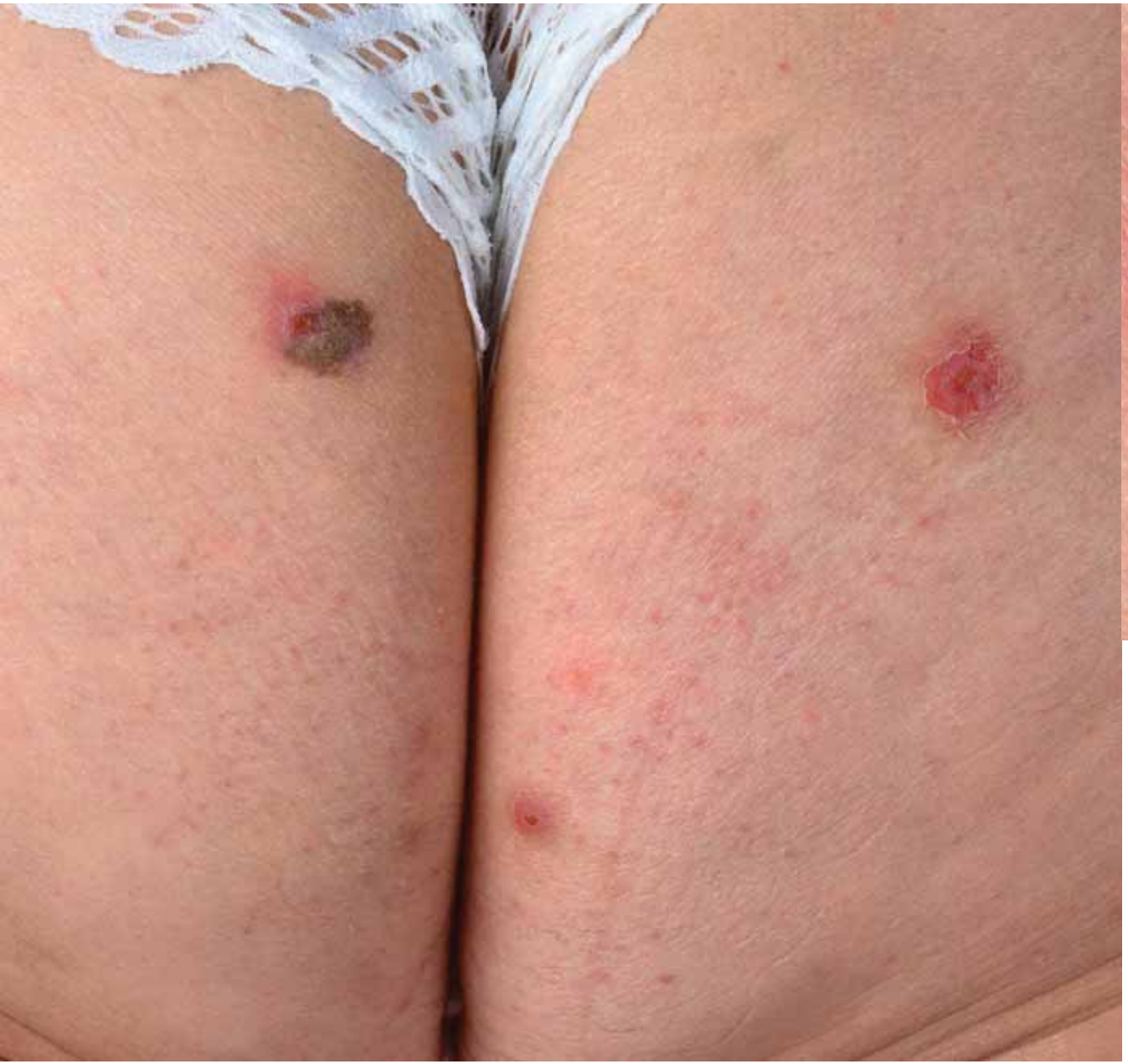
A biopsy is taken.

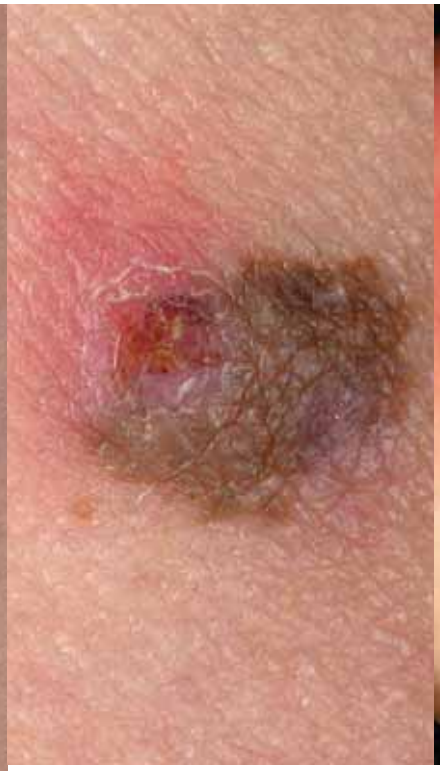


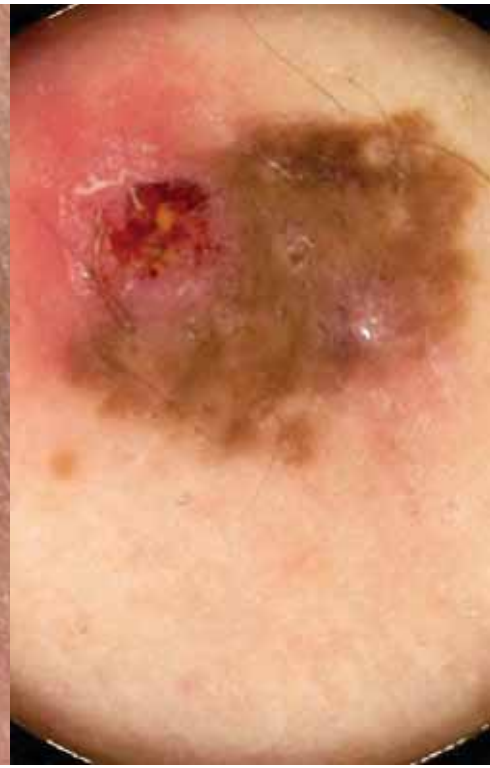
Impetigo









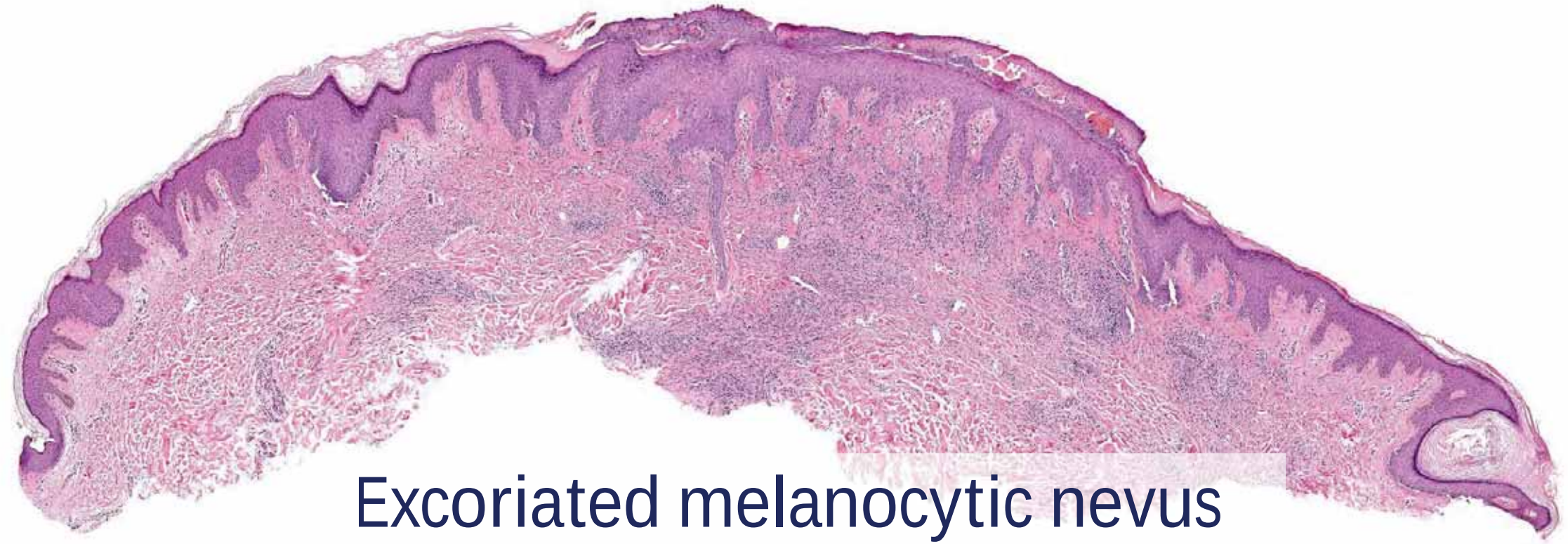


F, 60

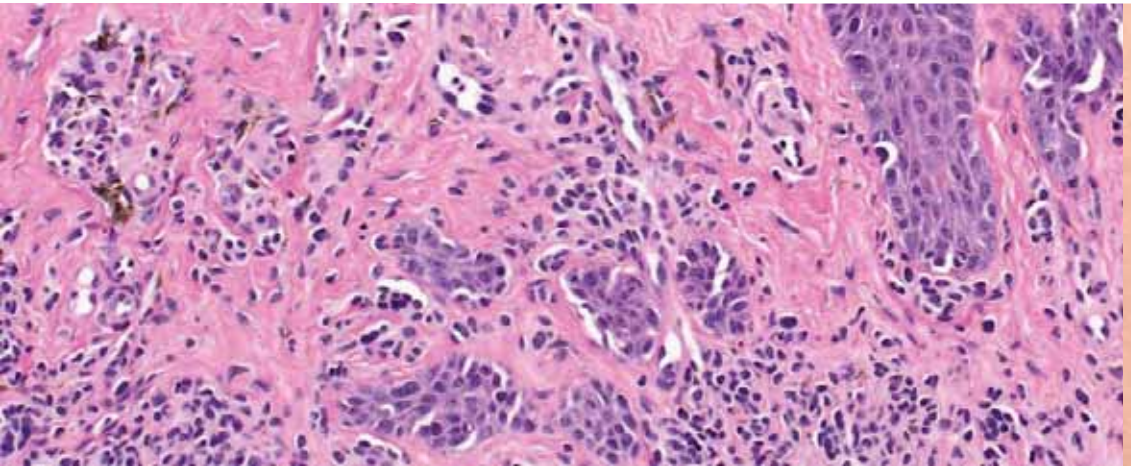
History of prurigo nodularis and of psoriasis (several treatments), and of rosacea.

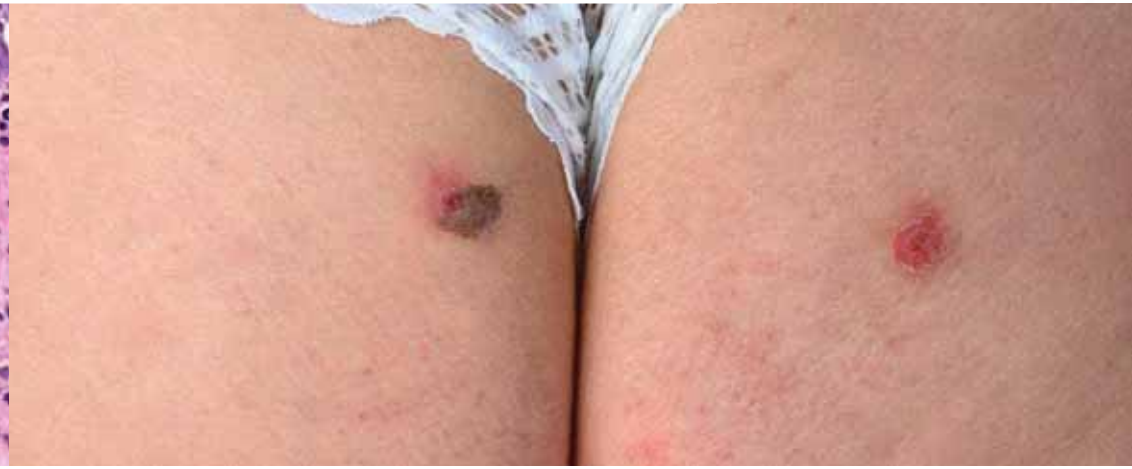
According to the patient modification of a mole on the left buttock since the begin of the UVB treatment.

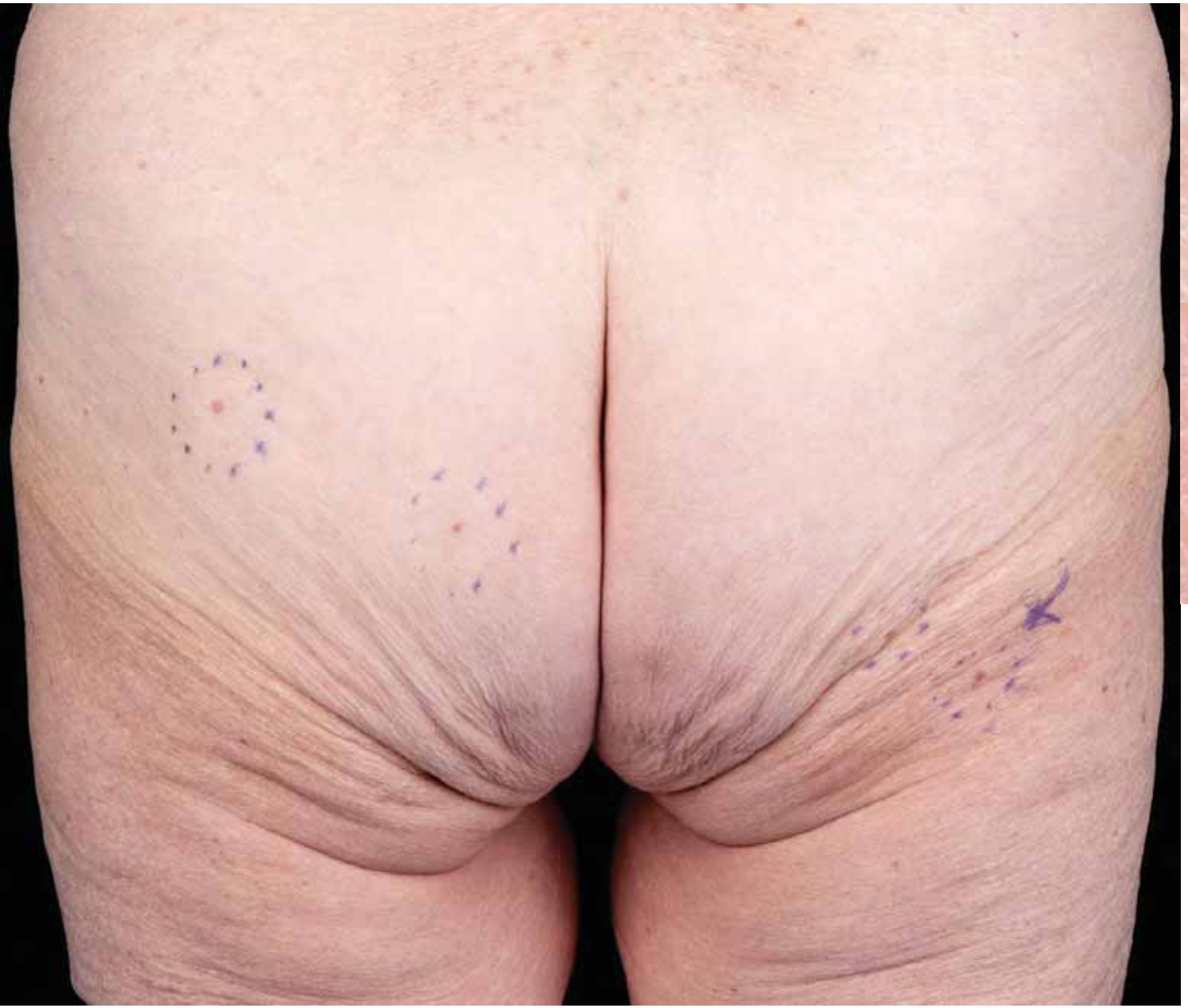
A biopsy is taken.

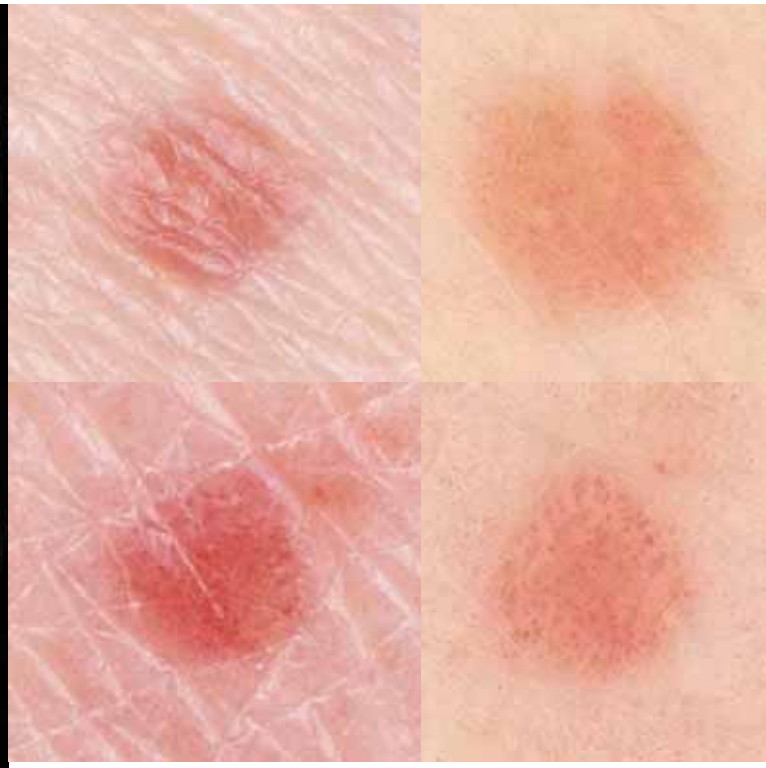


Excoriated melanocytic nevus







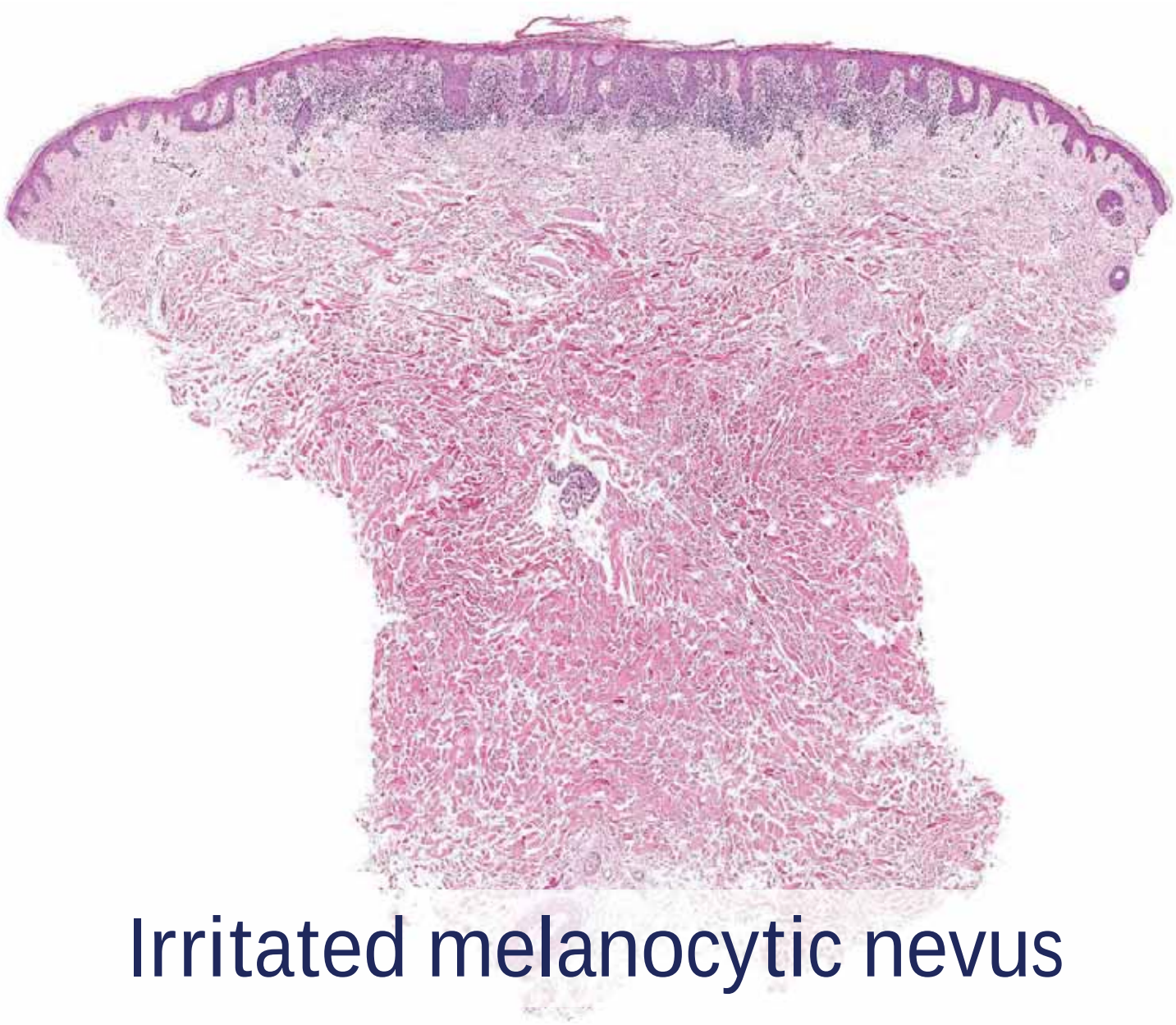


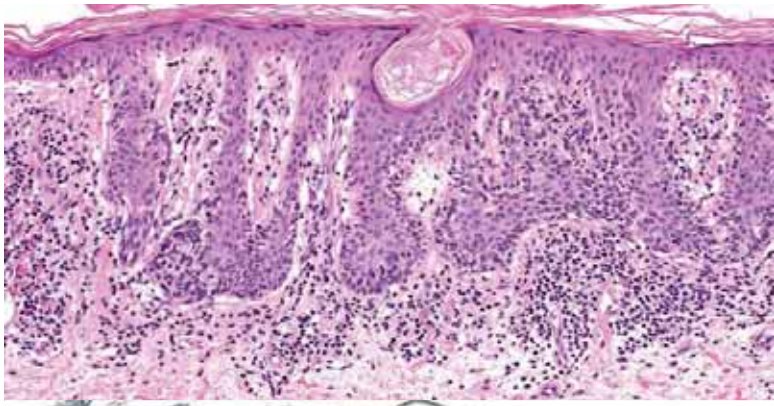
F, 85

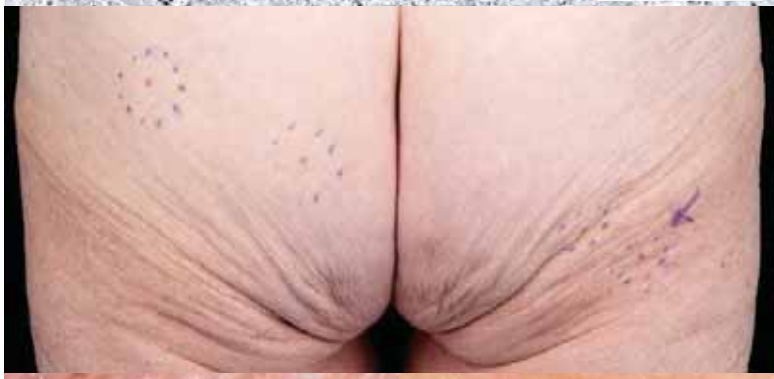
History of 2 MMs 8 and 4 years previously (back, thorax). Diagnosis of angiosarcoma of the liver 1 month before presentation.

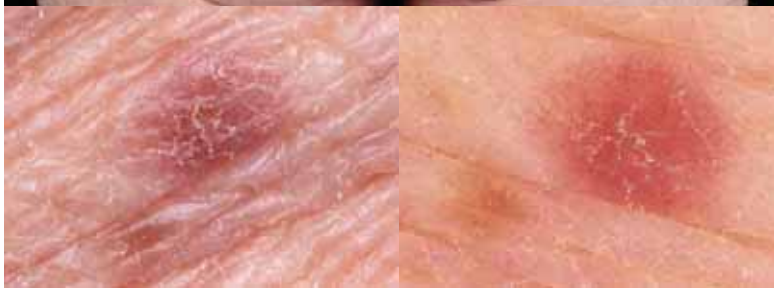
Comes for evaluation of 4 small papules on the buttocks.

A biopsy is taken.

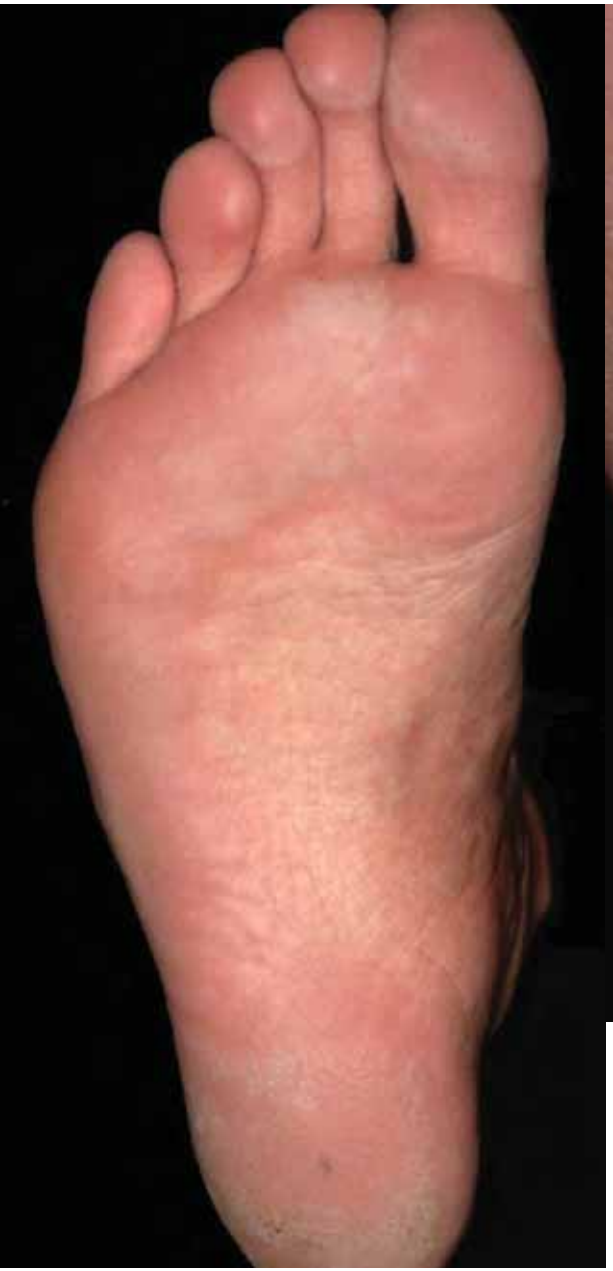


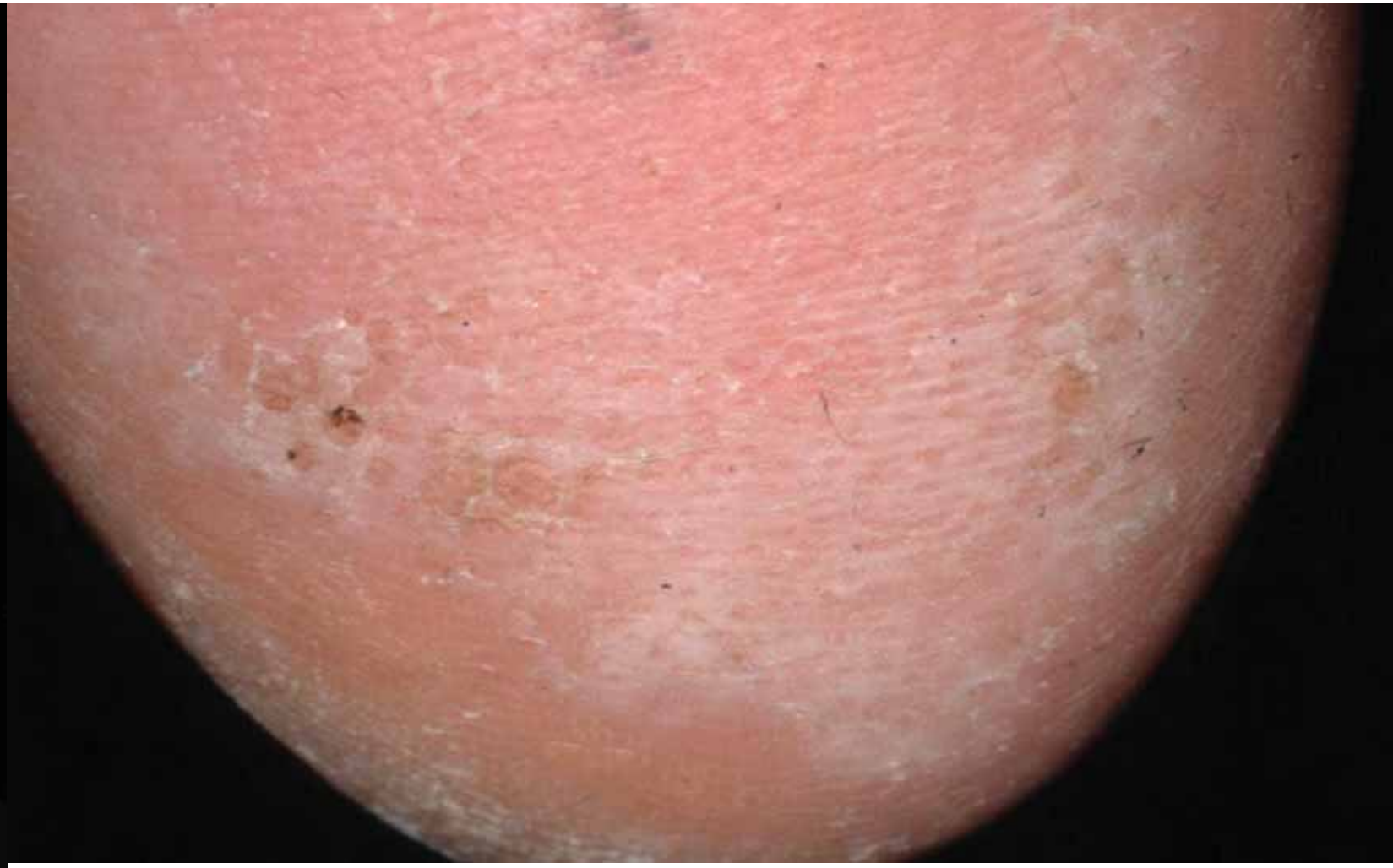






Irritated melanocytic nevus

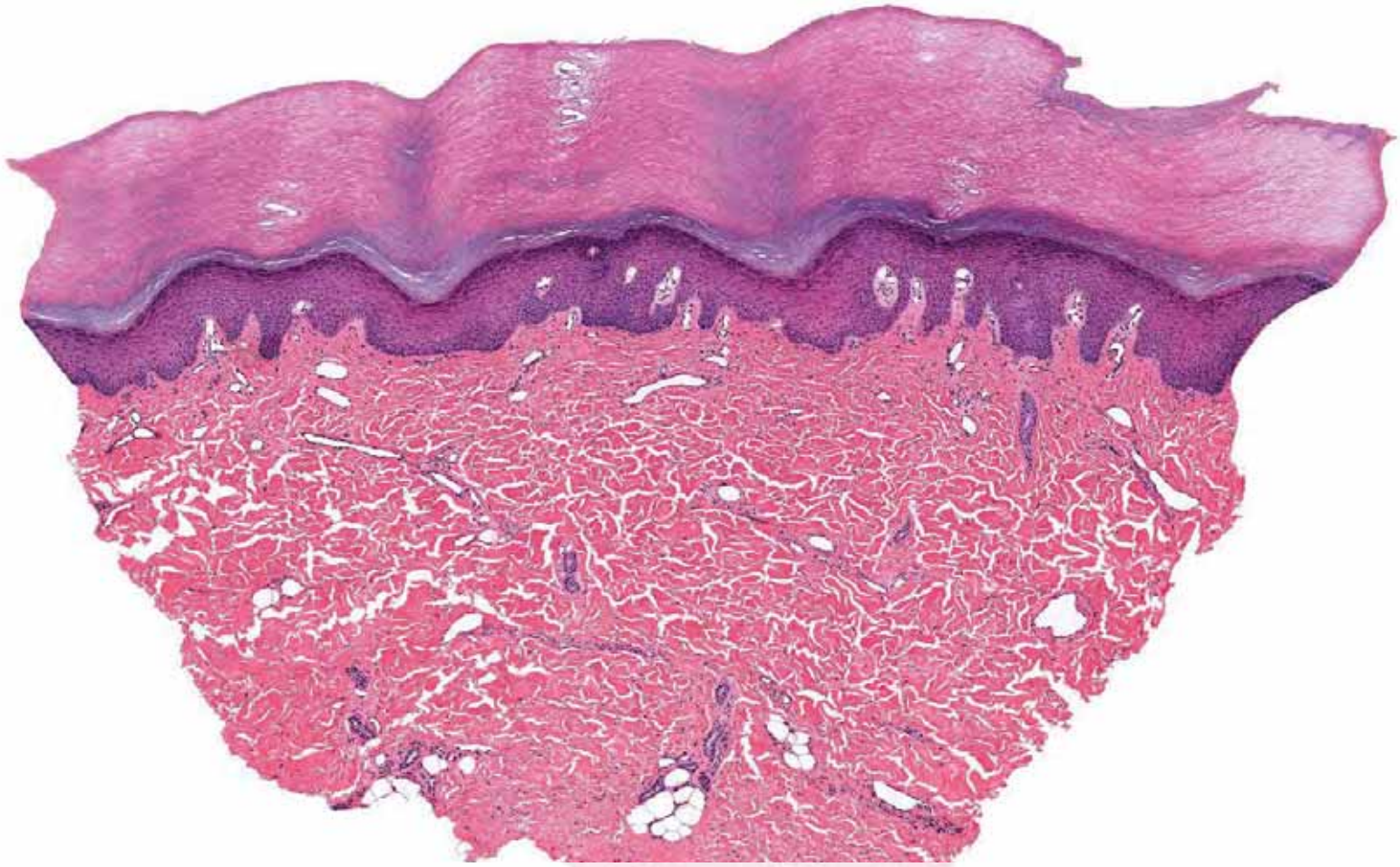


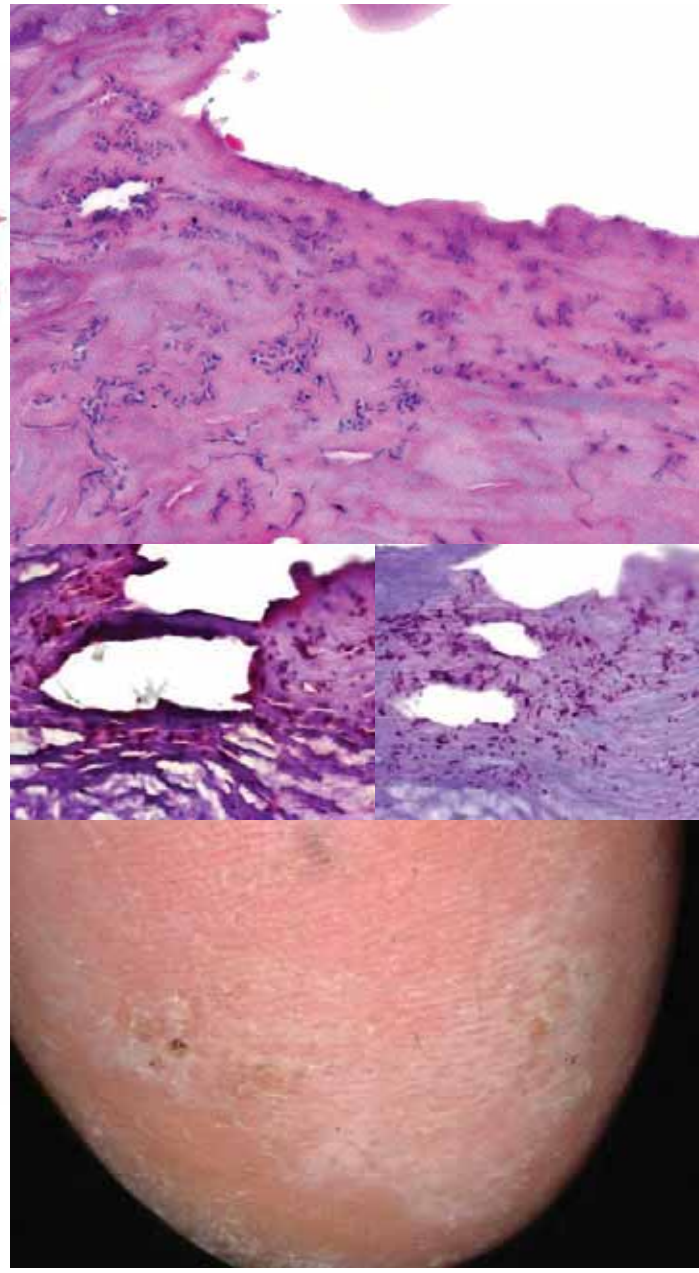


M, 32

Partly macerated lesions on both soles for several weeks.

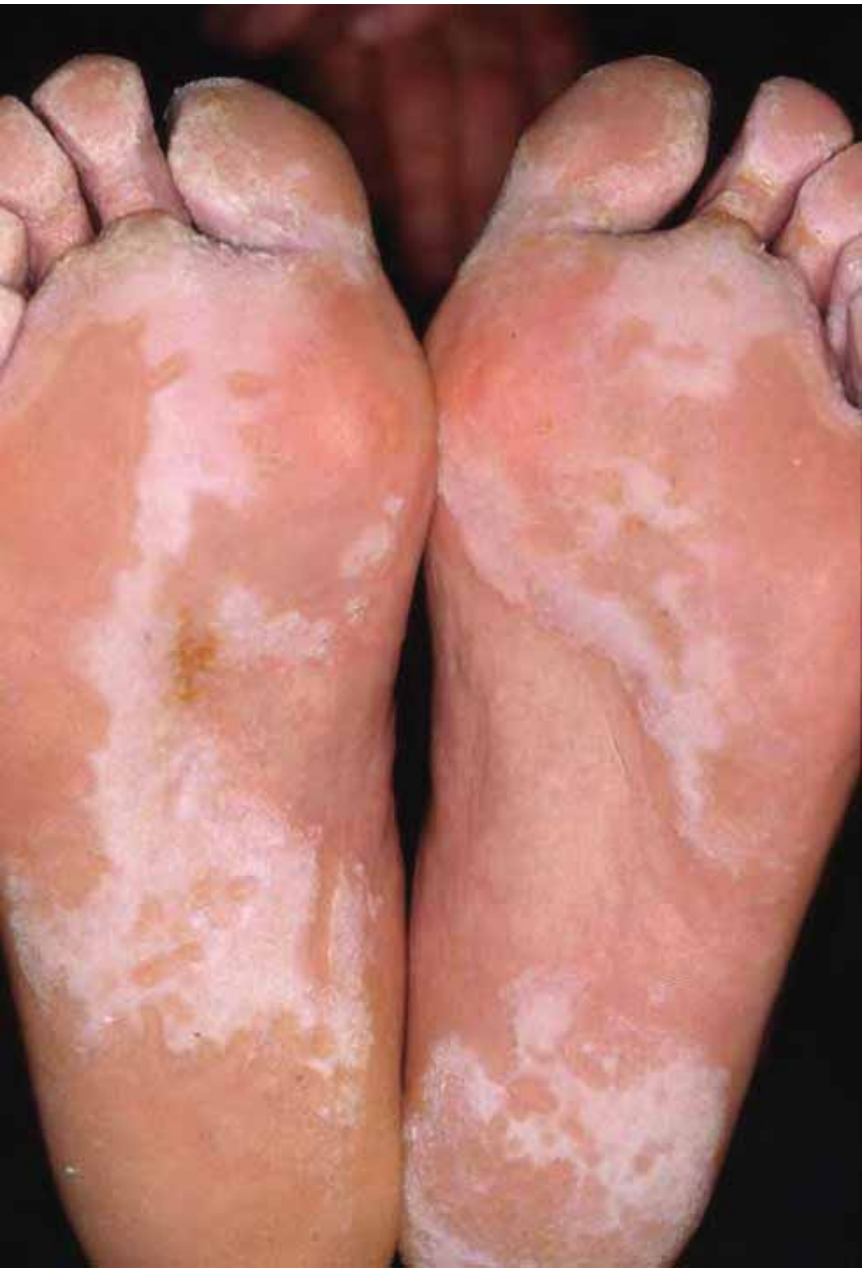
A biopsy is taken.





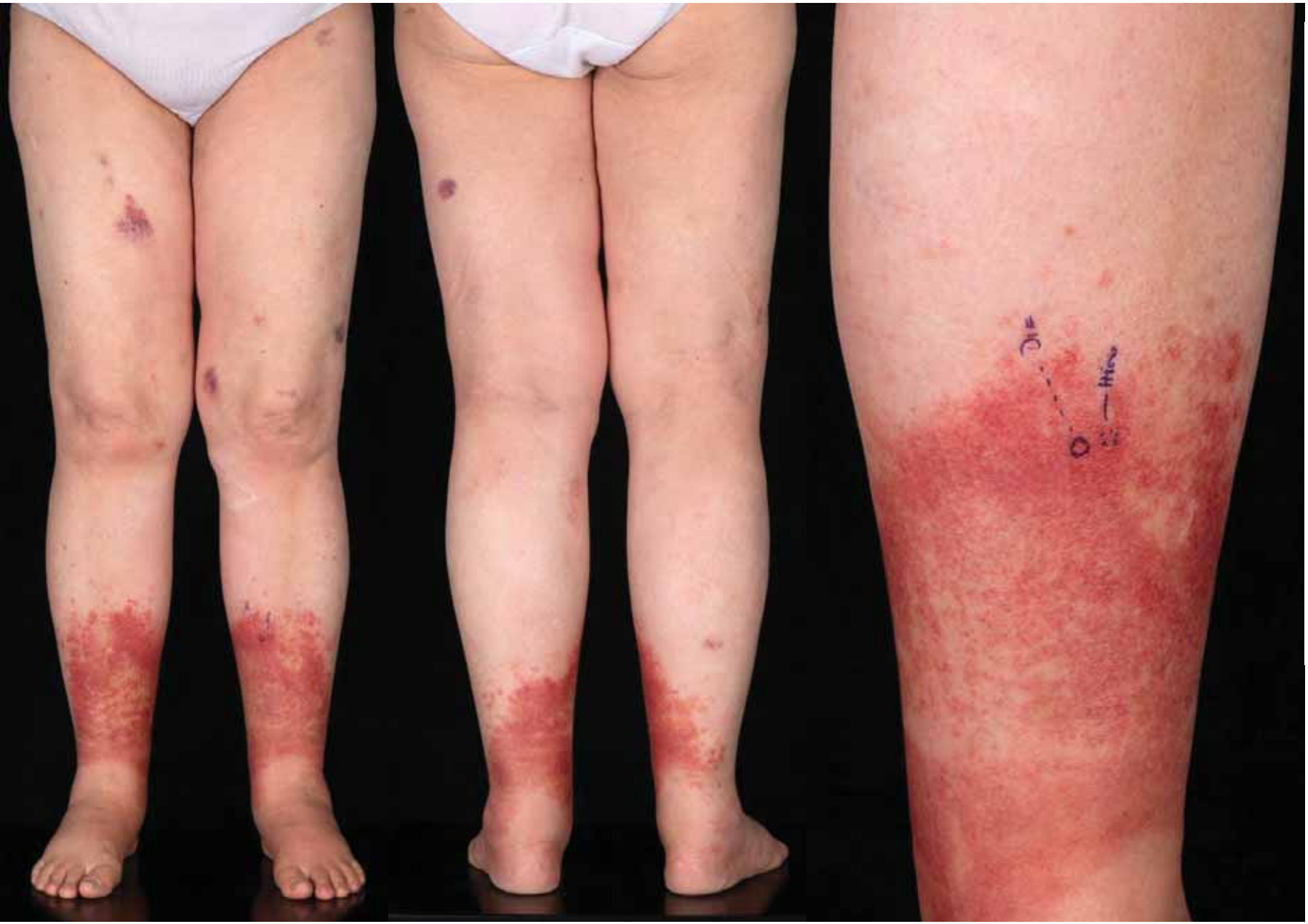
Pitted keratolysis

(Keratoma sulcatum)



Pitted keratolysis
(keratoma sulcatum)

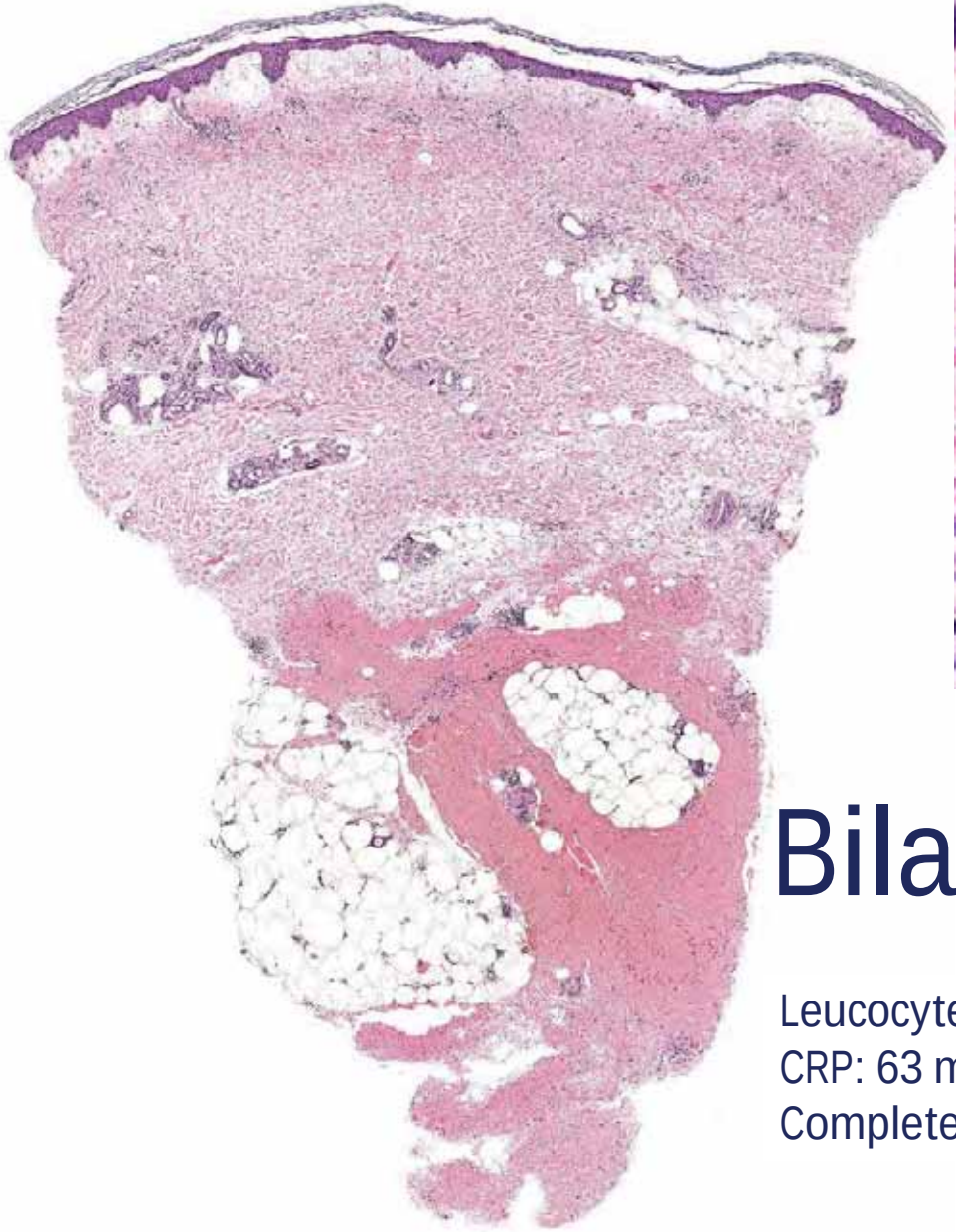
- Bacterial infection of the feet (*Micrococcus sedentarius* or *Corynebacterium* species producing a proteolytic enzyme that digests the horny layer)
- Small crater-like depressions in the stratum corneum on the soles; sometimes confluence to large areas with erosions
- Common hyperhidrosis
- Filamentous and coccoid microorganisms in stratum corneum *(Gram, methenamine silver stain)*

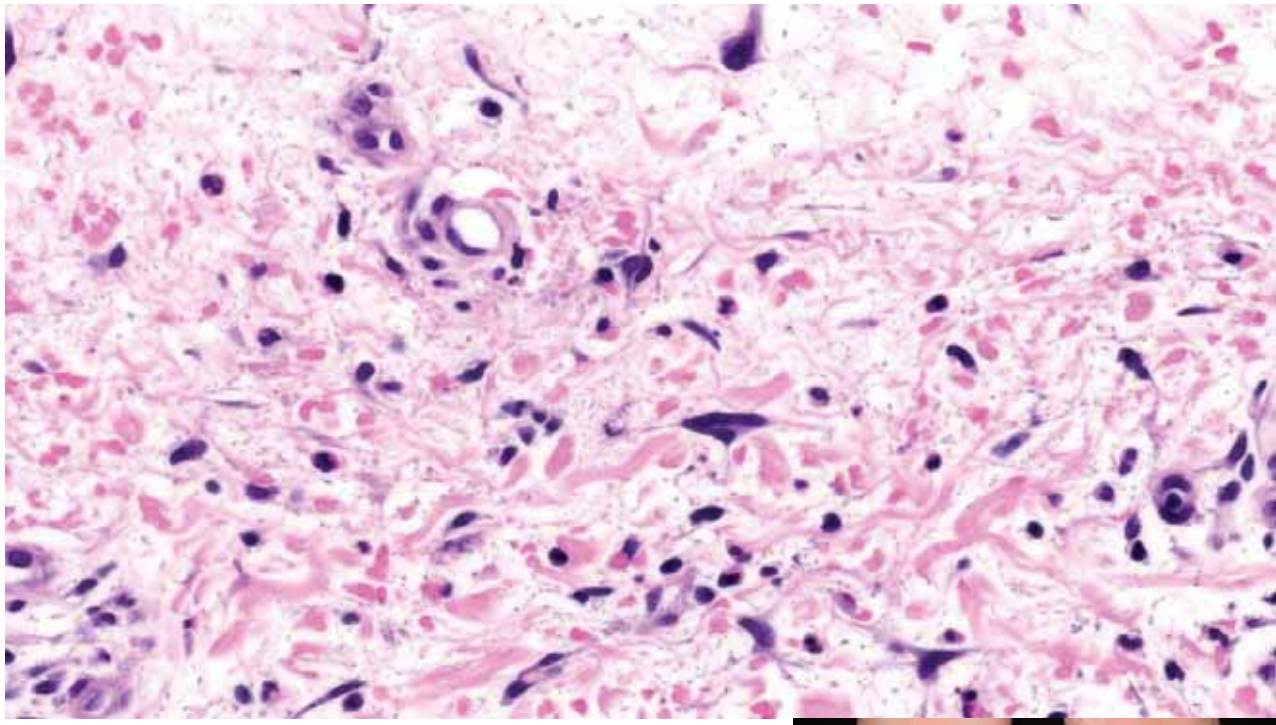


F, 60

History of acute renal insufficiency with dialysis since 3 weeks. Growing erythematous lesions on both lower extremities for some days; treated with oral antibiotics under the diagnosis of erysipelas (ampicillin/sulbactam).

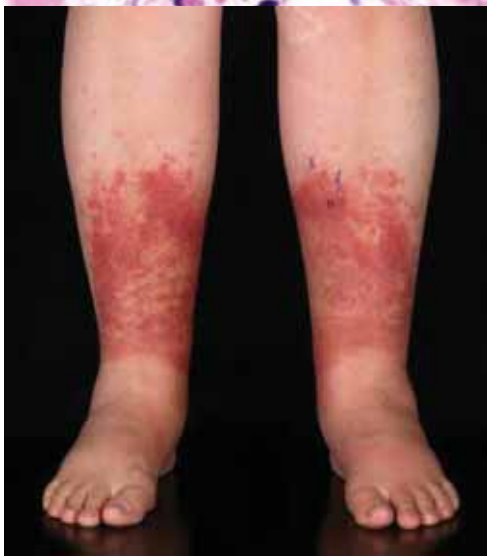
A biopsy is taken because of the unusual (bilateral) clinical presentation.

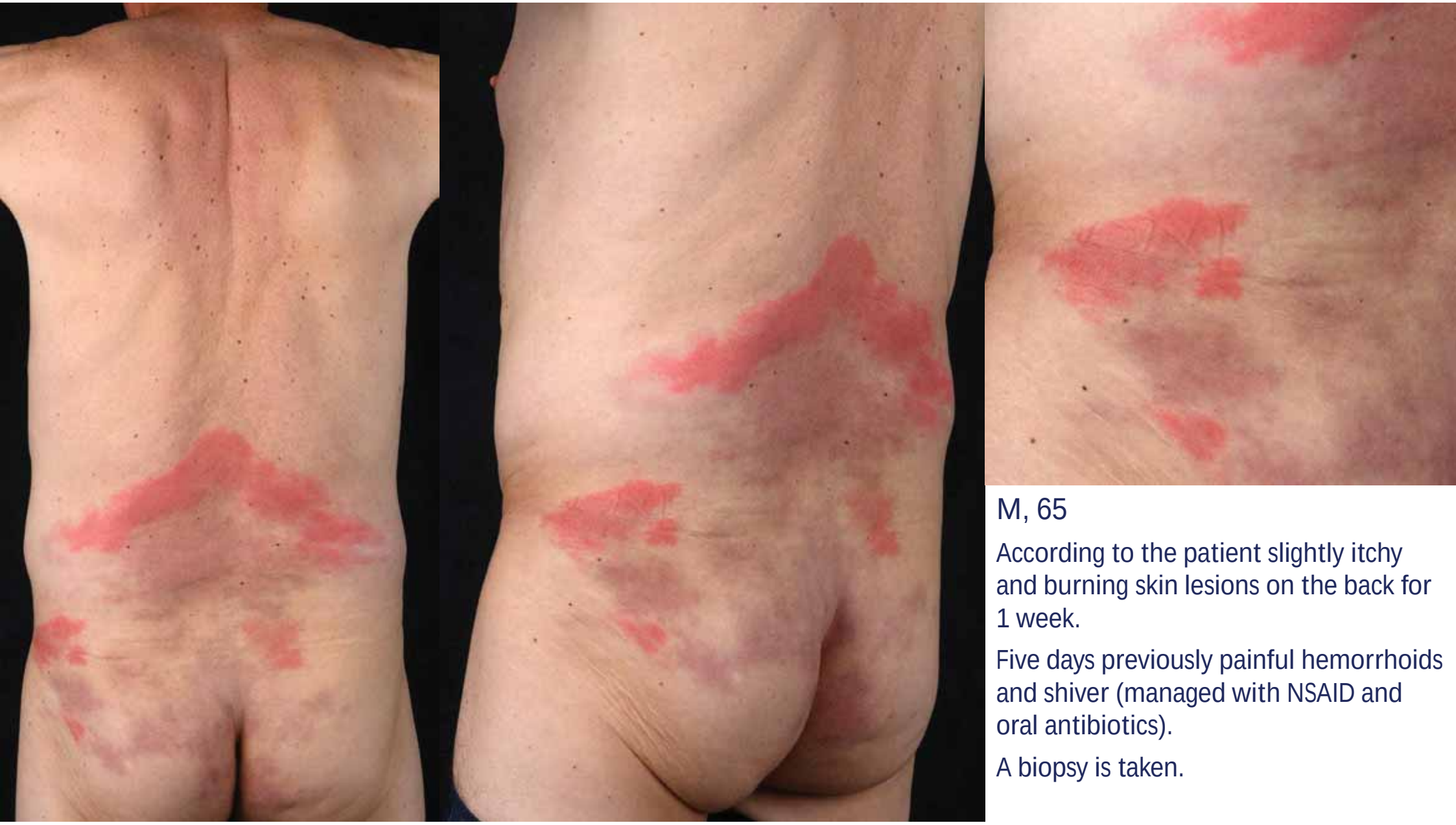




Bilateral erysipelas

Leucocytes: 16.000 (-11.3)
CRP: 63 mg/L (-5)
Complete resolution with antibiotic treatment.



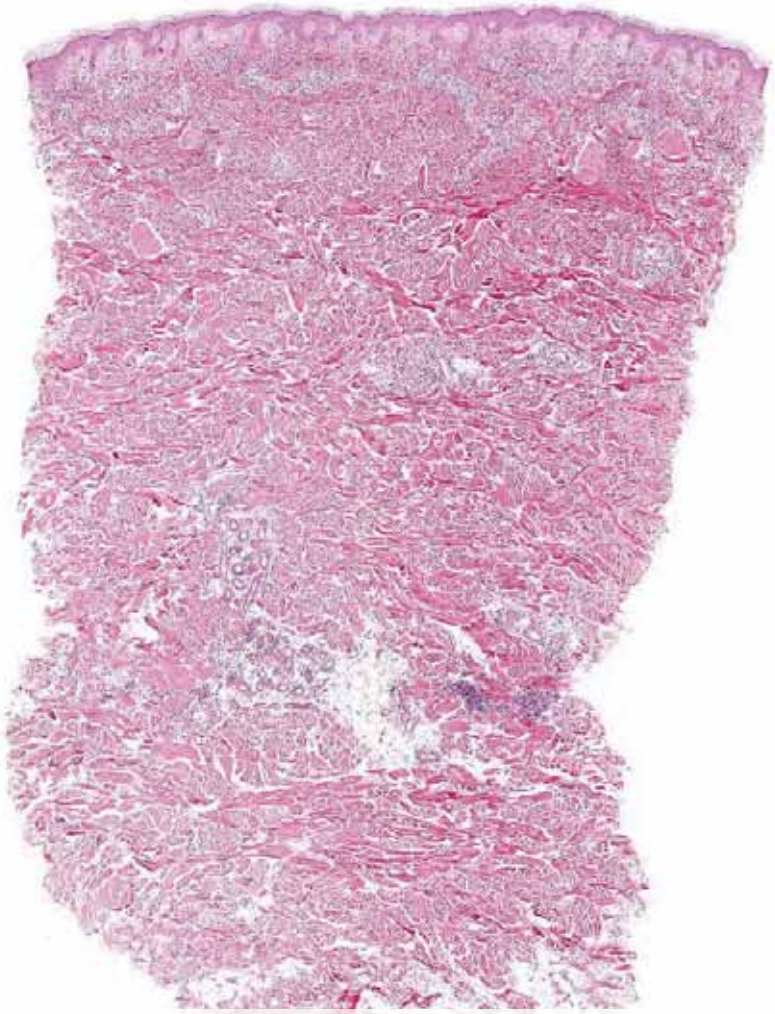


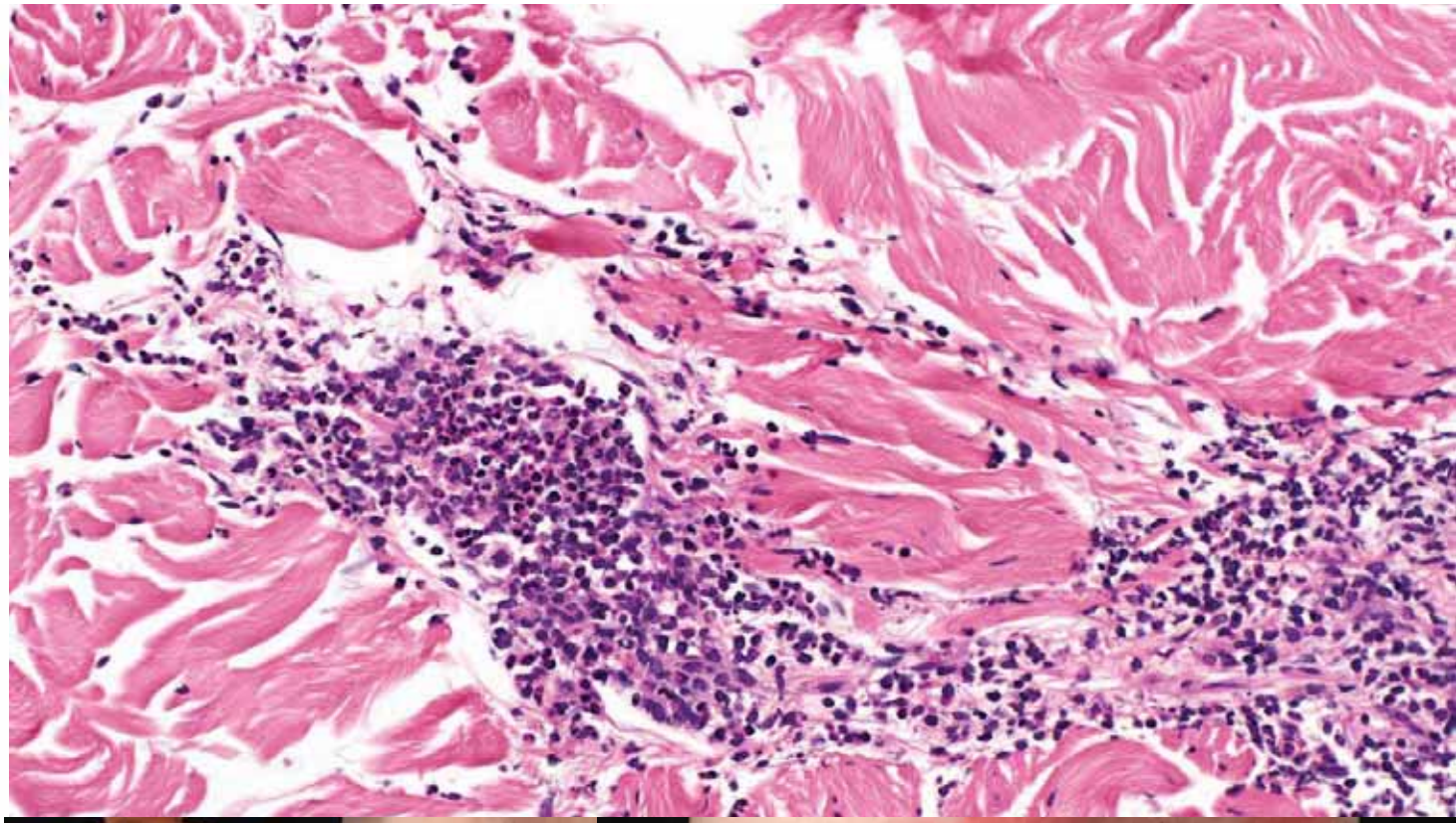
M, 65

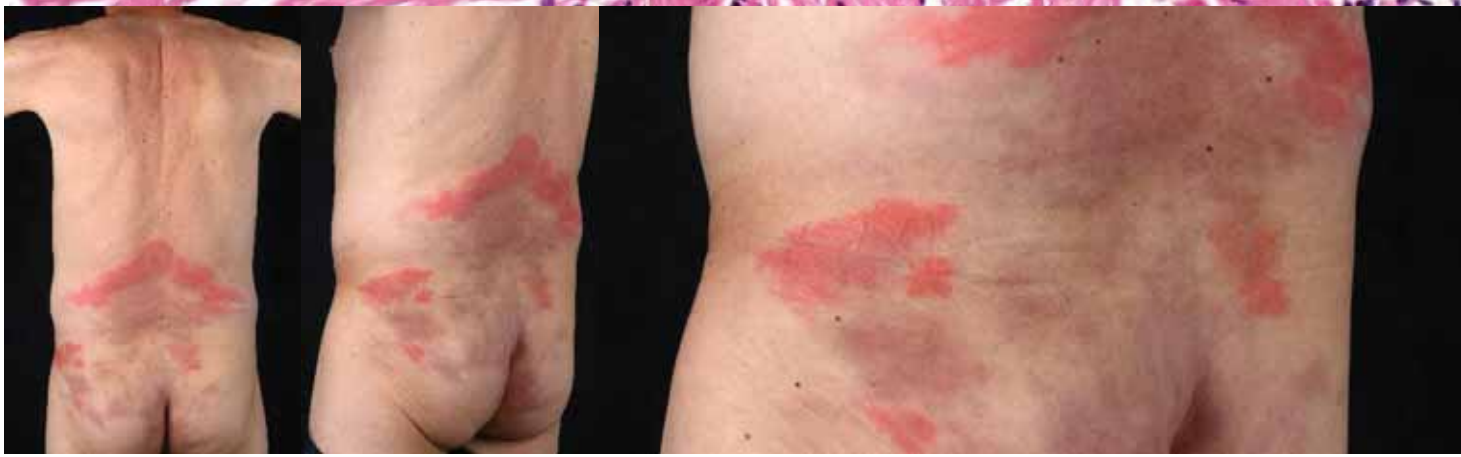
According to the patient slightly itchy and burning skin lesions on the back for 1 week.

Five days previously painful hemorrhoids and shiver (managed with NSAID and oral antibiotics).

A biopsy is taken.



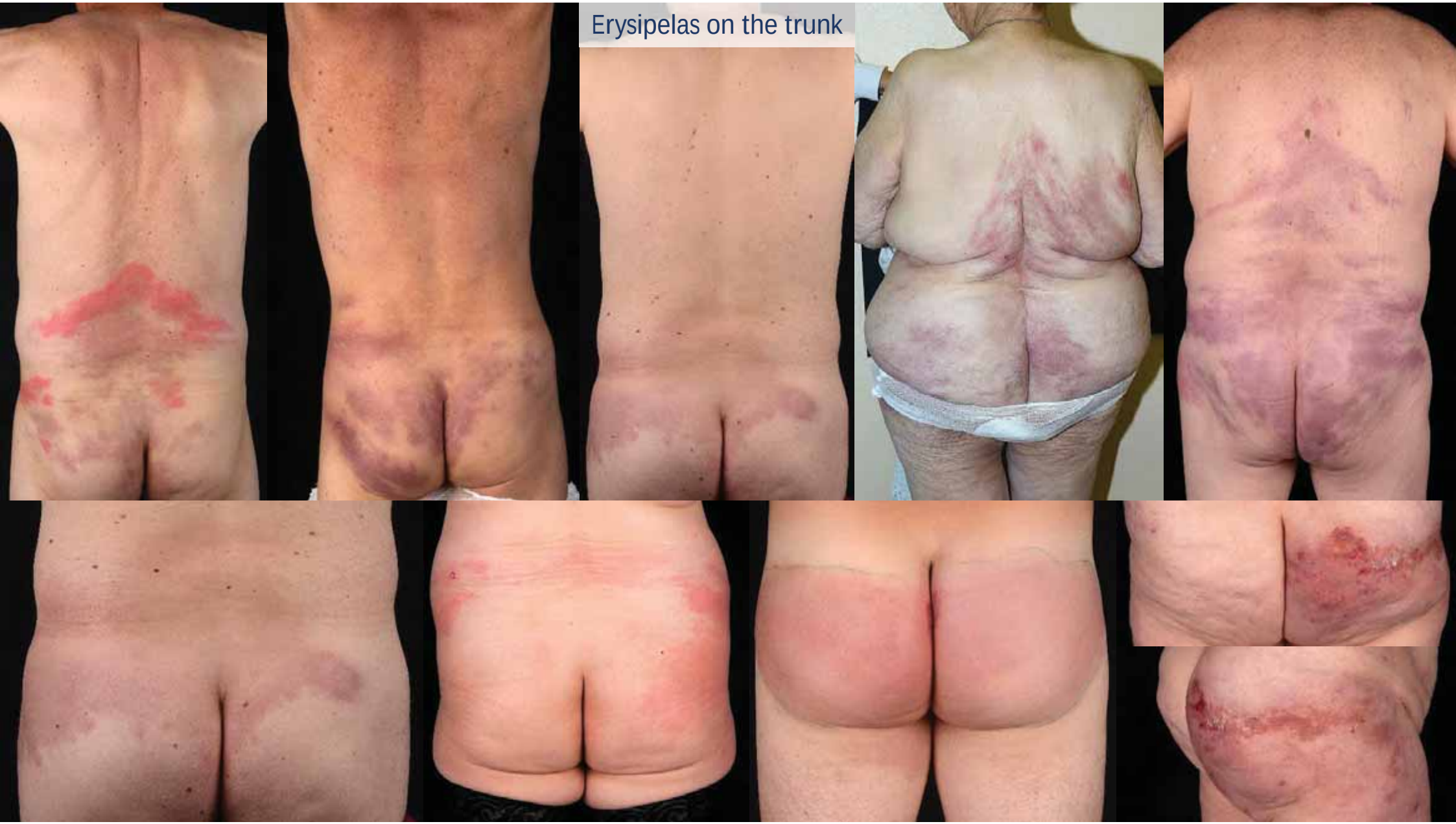


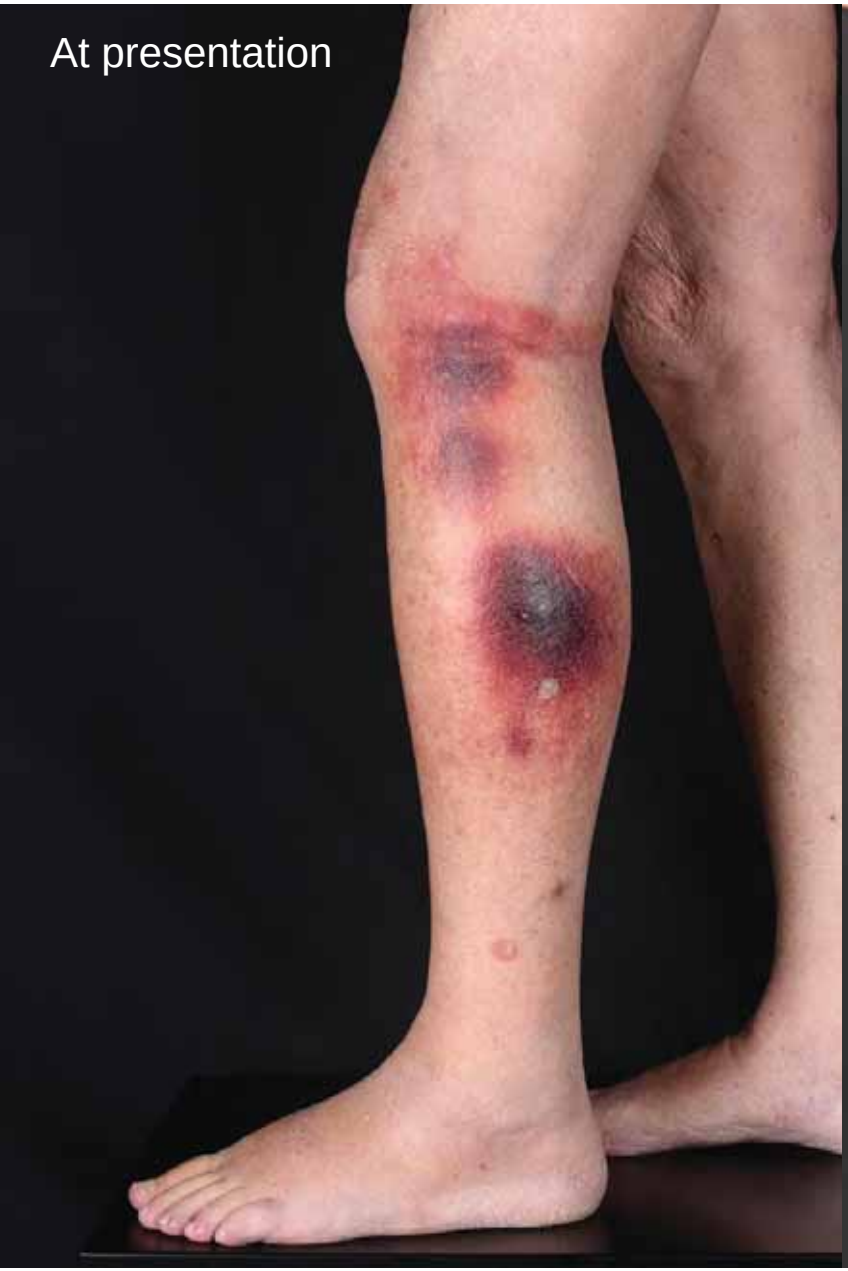


Erysipelas

(Leukocytes: 10.300; CRP: 27,6)

Erysipelas on the trunk





M, 88

According to the patient sudden onset of purpuric lesions on the left leg.

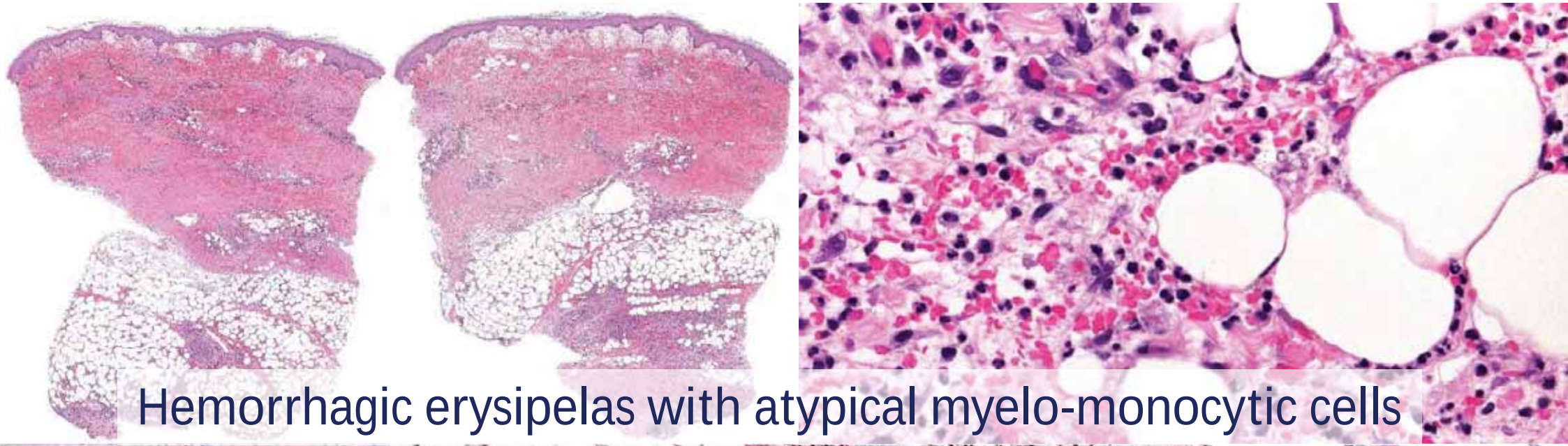
Fever, malaise.

Pancytopenia, LDH 420 (120-240), CRP 16,1 (0-5).

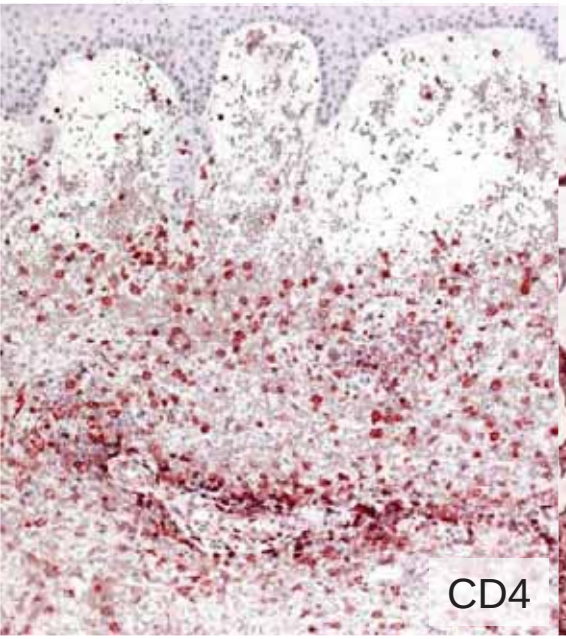
Platelets: 19 g/l (140-400).

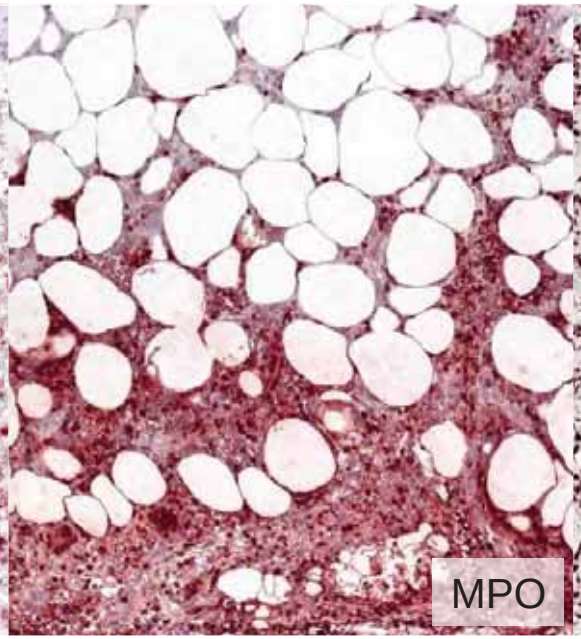
Bacterial smear: *St. aureus.*

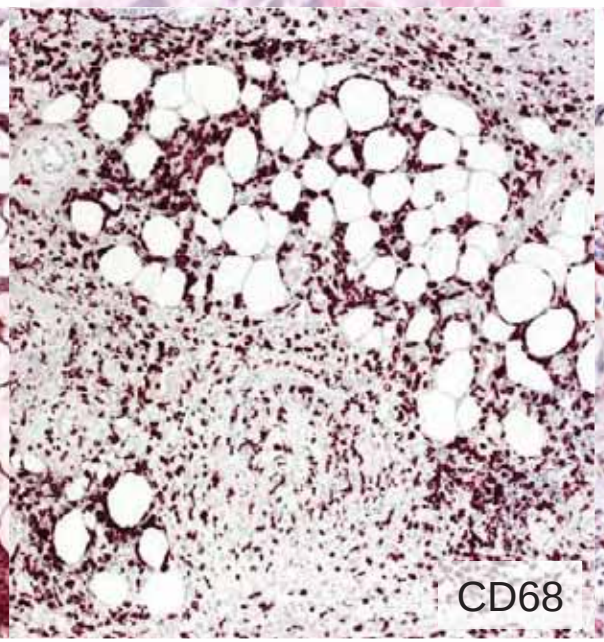
Two biopsies are taken.

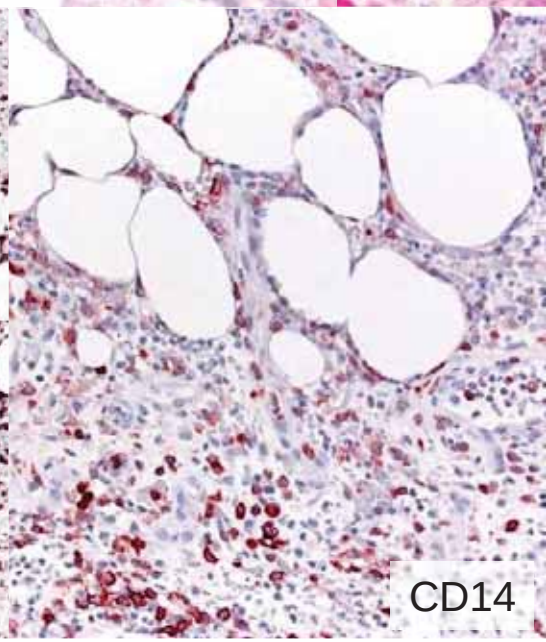


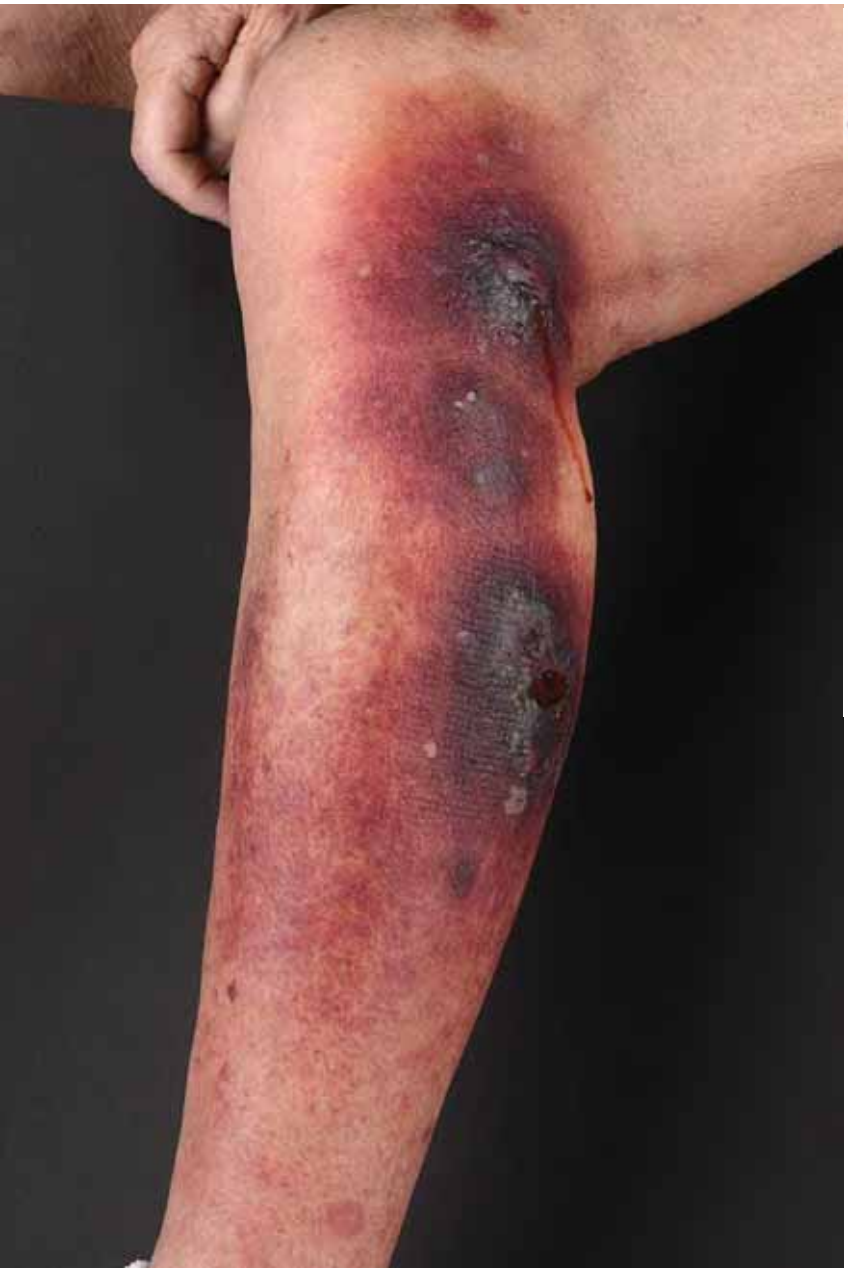
Hemorrhagic erysipelas with atypical myelo-monocytic cells

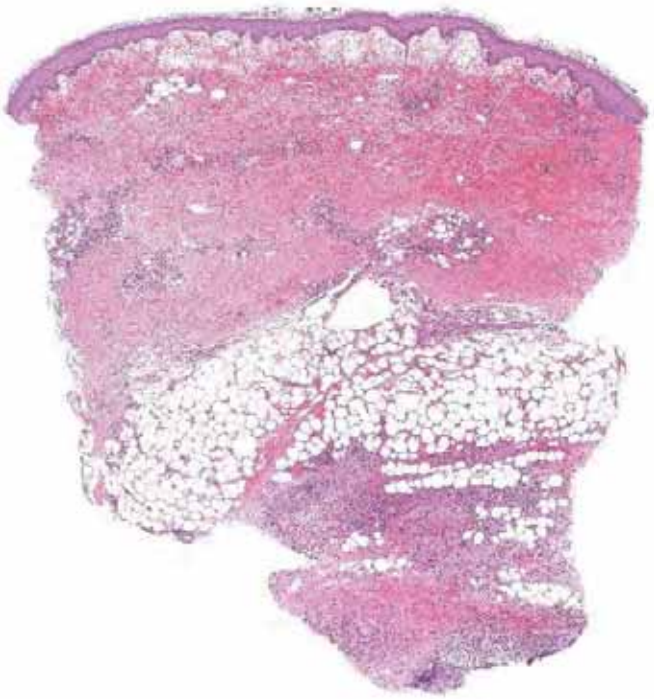


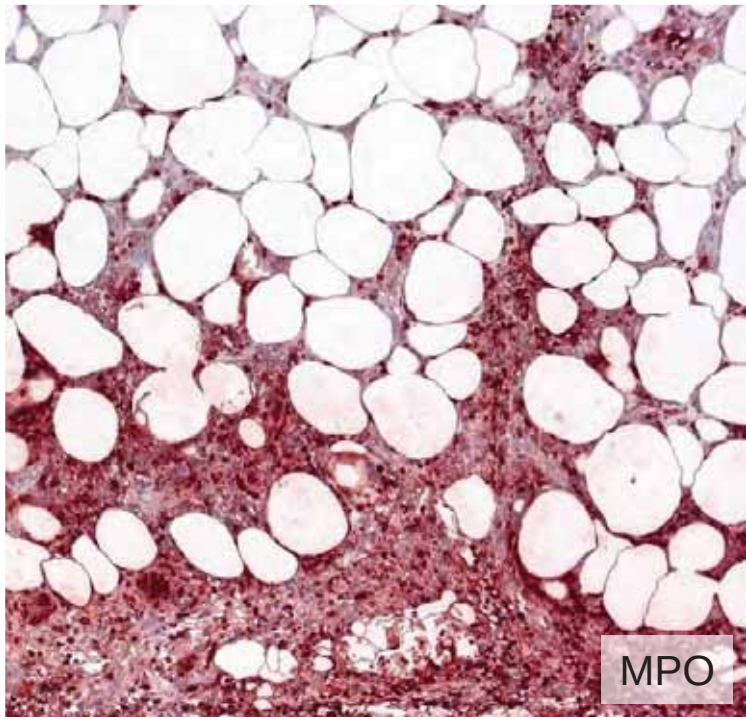










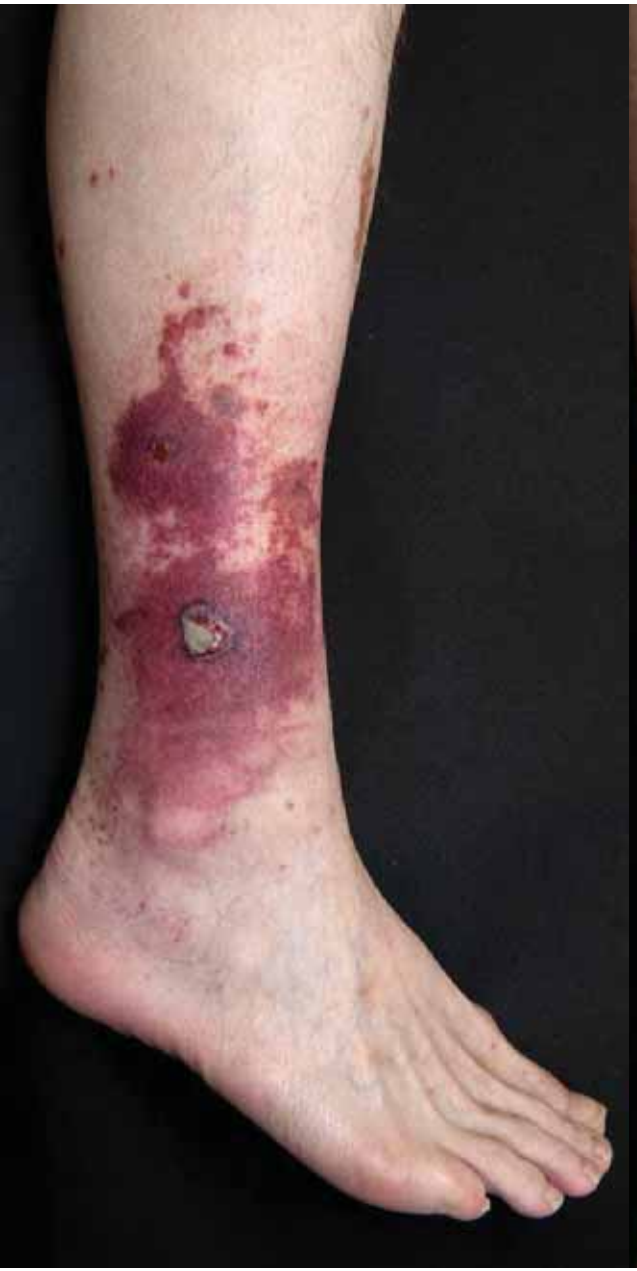


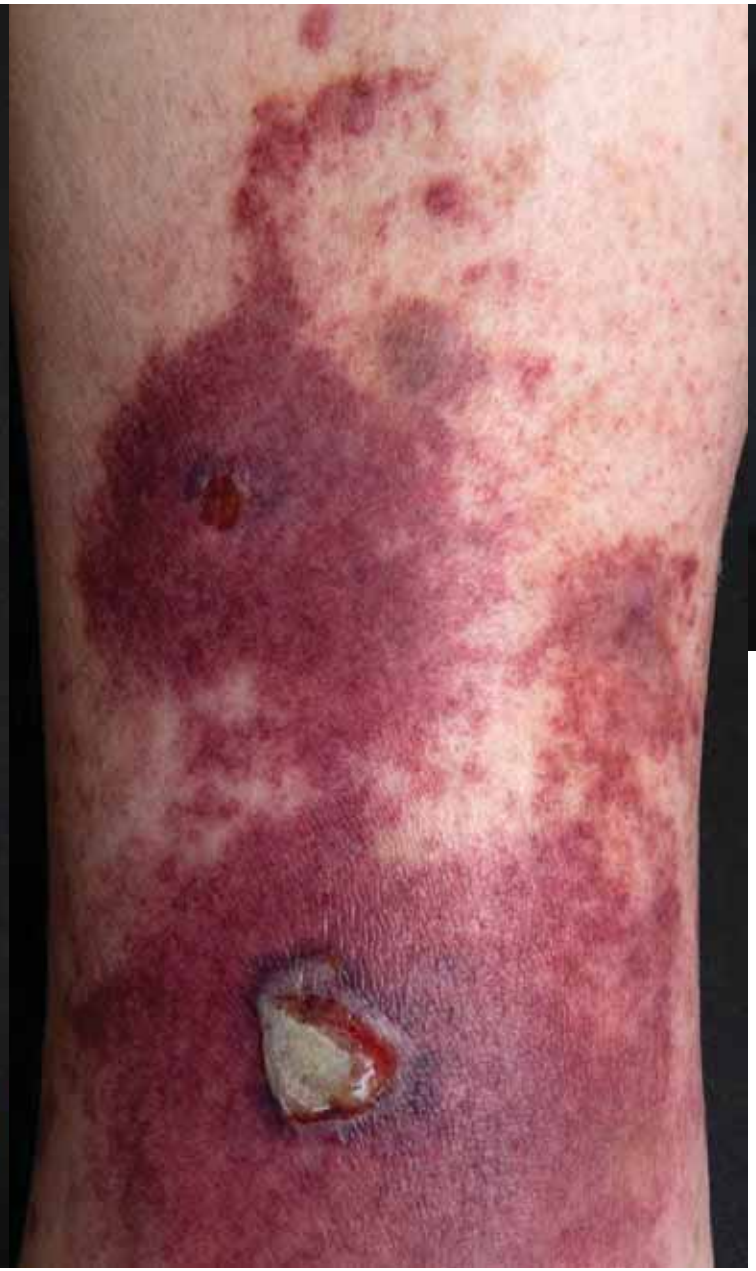
5 months later:

Myelodysplastic syndrome with evolution in acute myeloid leukemia.

Multiorgan failure.

Death 5 months after first presentation.



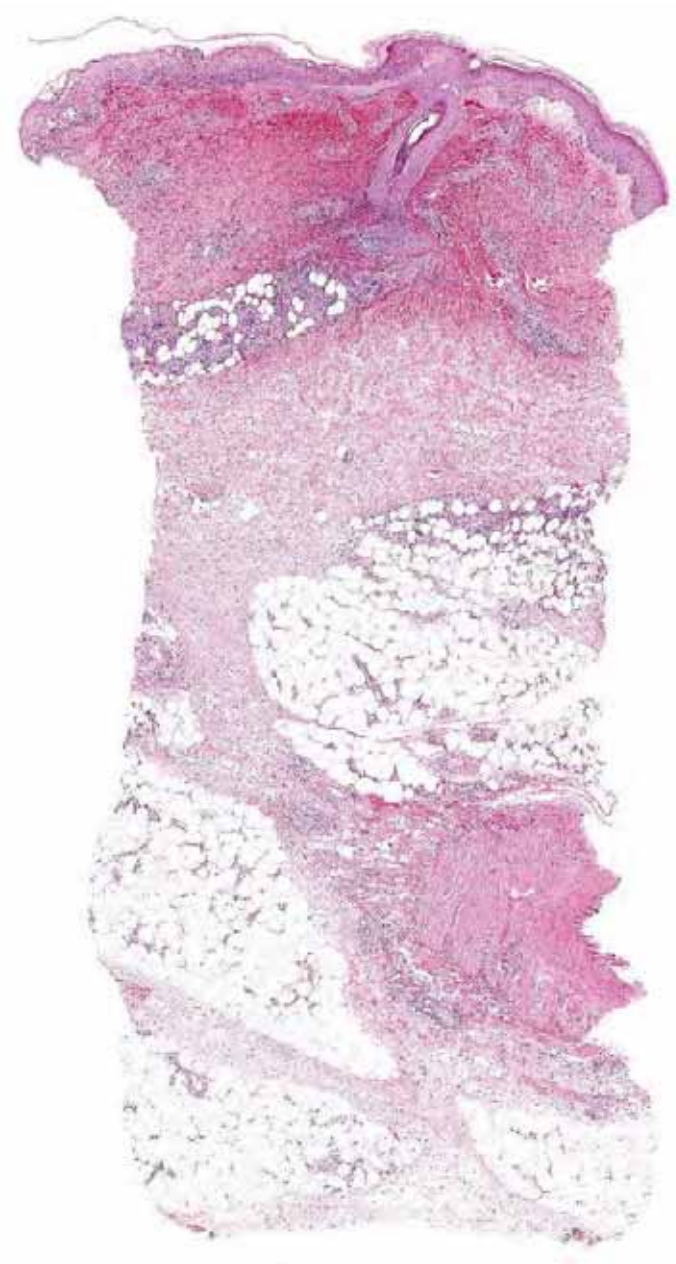


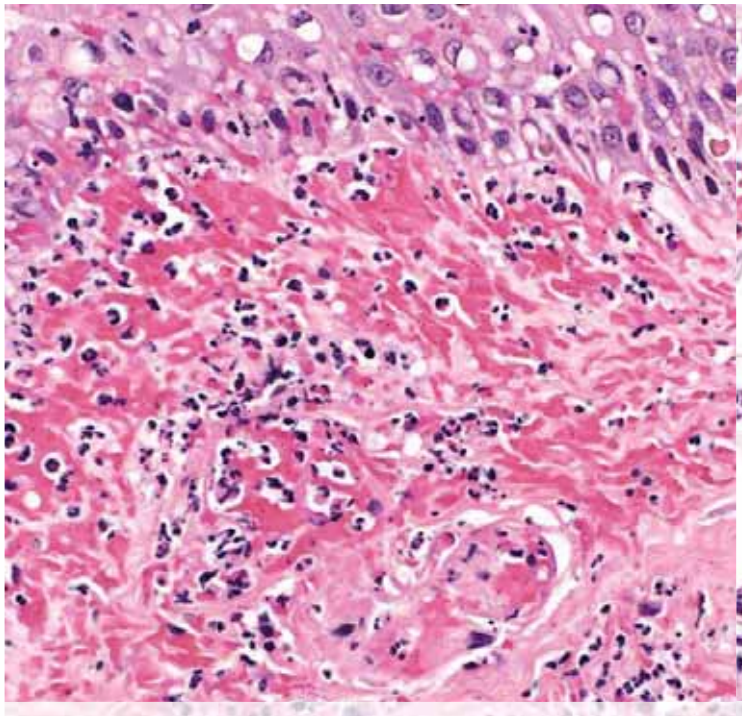
M, 50

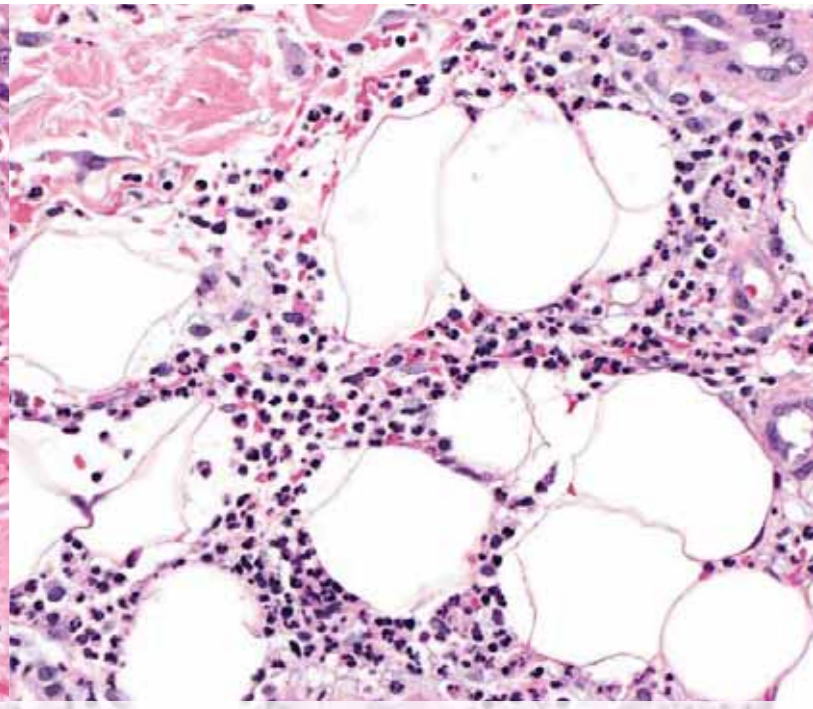
According to the patient skin lesions on both lower extremities for 3 weeks. Visited the GP 2 days before presentation (prescribed doxycycline 200mg/d). Leukocytes: 19.46; CRP: 38.9.

Admitted as in-patient.

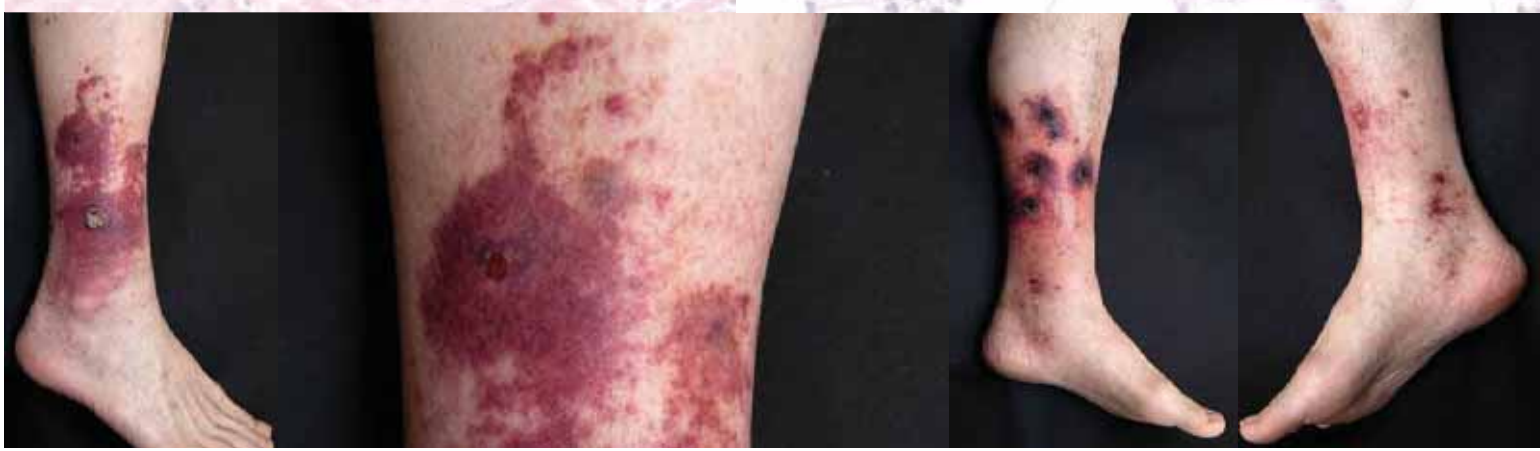
A biopsy is taken.

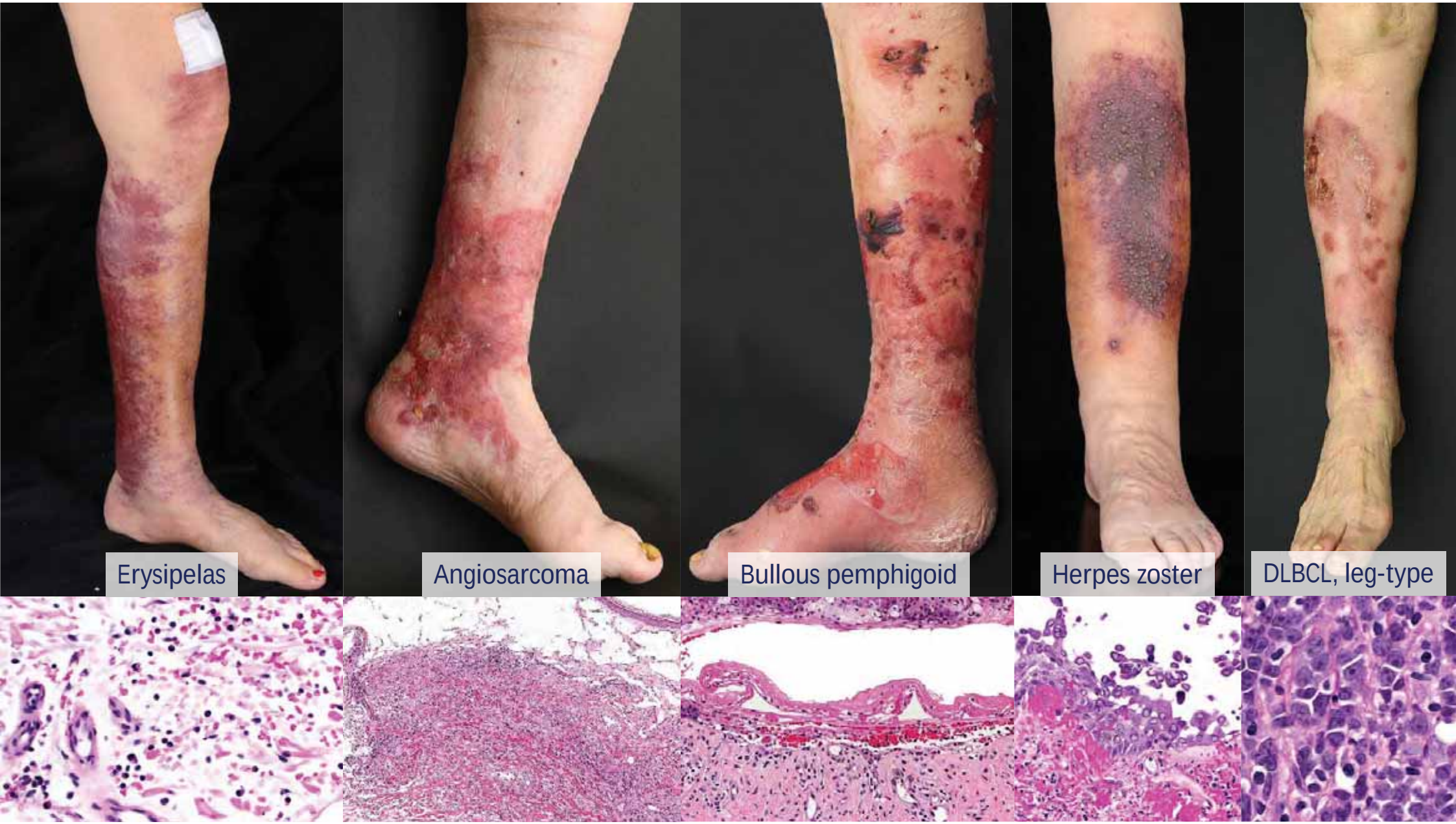


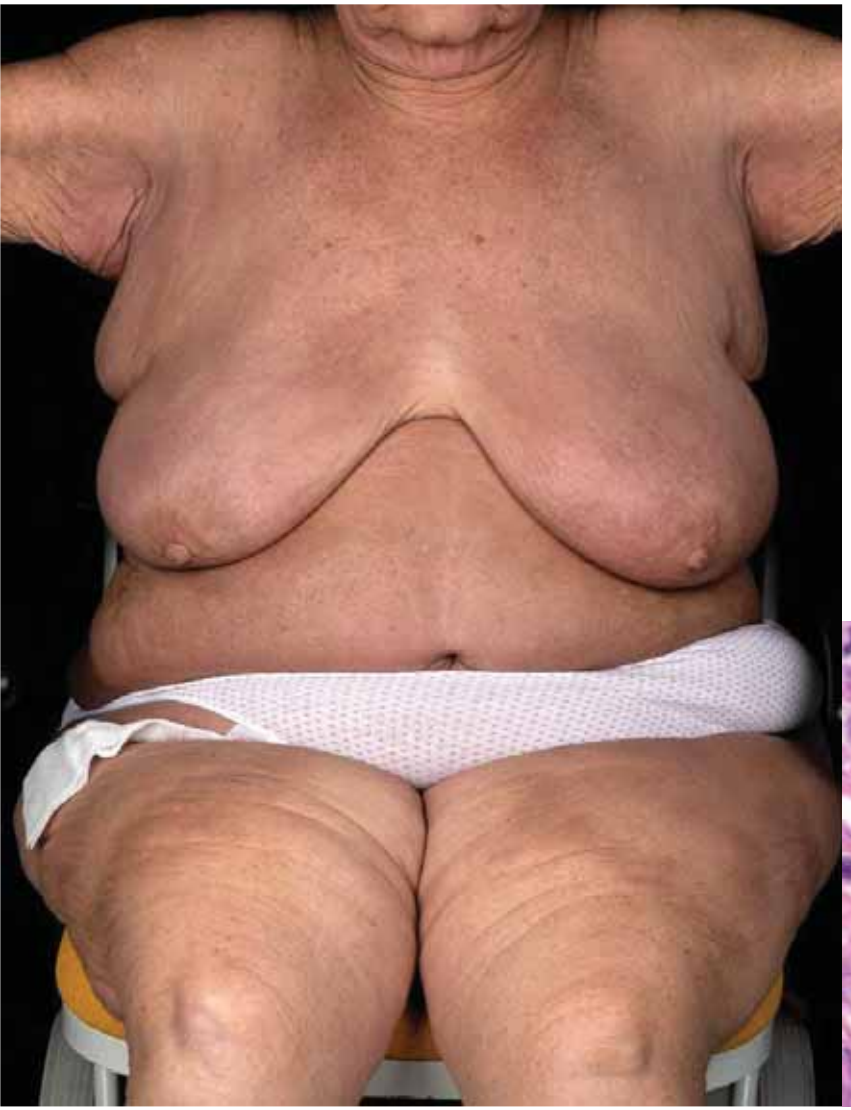


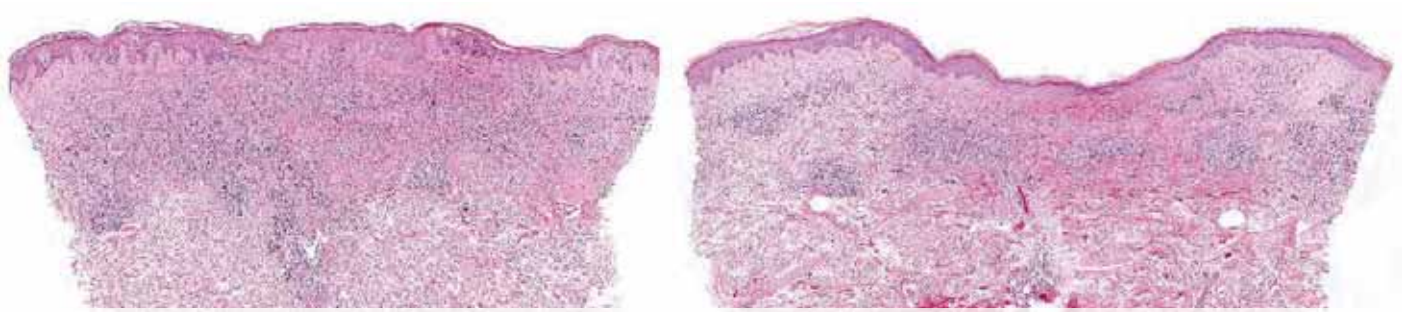


Erysipelas & leukocytoclastic vasculitis




Erysipelas
Angiosarcoma
Bullous pemphigoid
Herpes zoster
DLBCL, leg-type





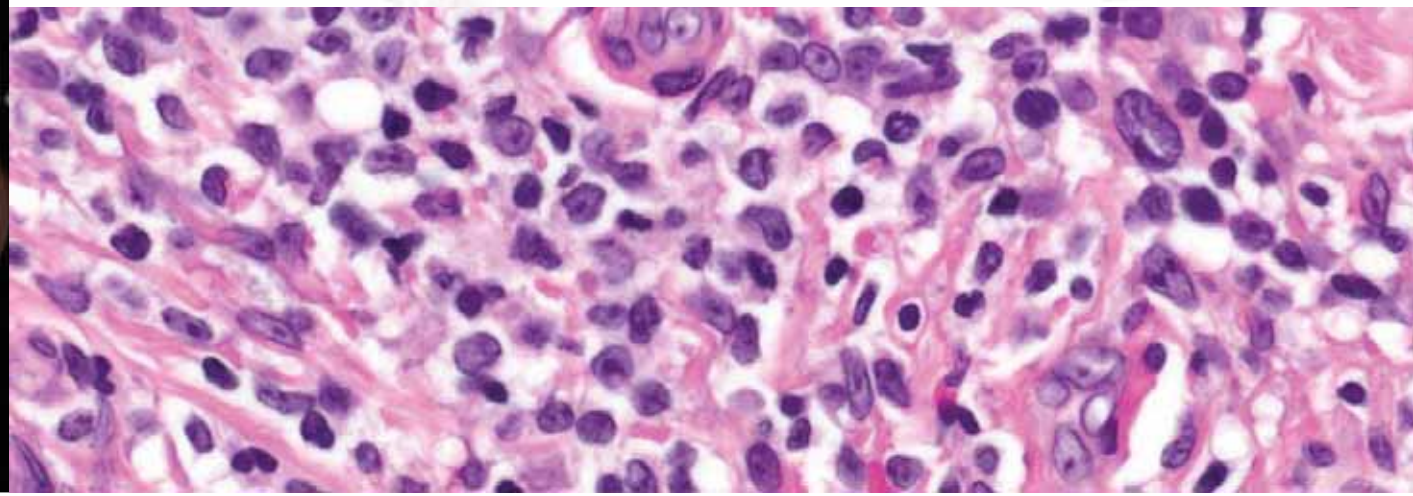
Sézary syndrome with large cell transformation

FACS of peripheral blood: 72% of 3+/4+/7dim-/26- cells; Bone marrow: negative

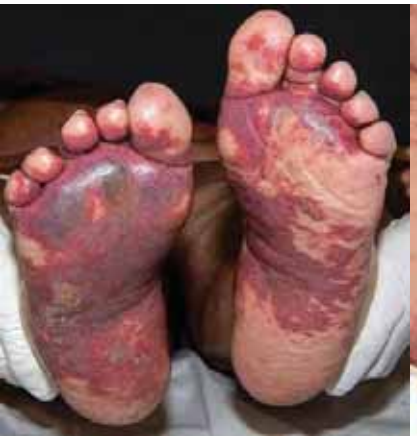
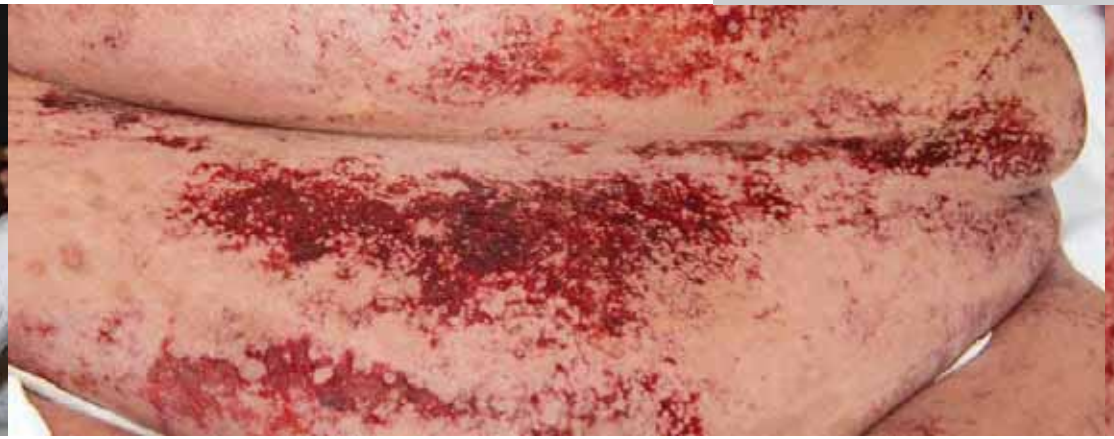
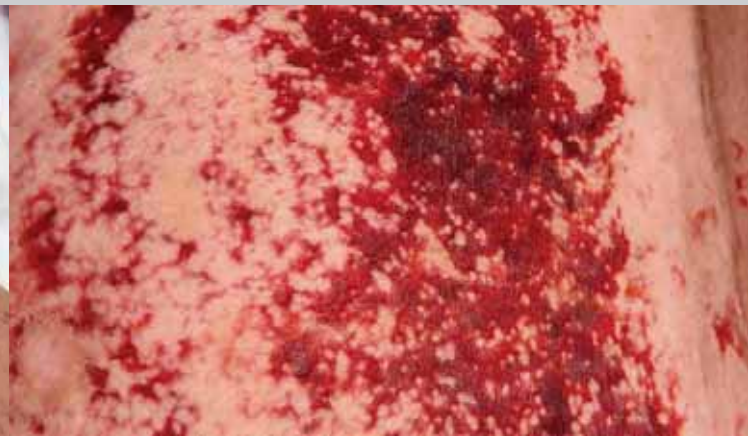
PET: multiple pathological LNs

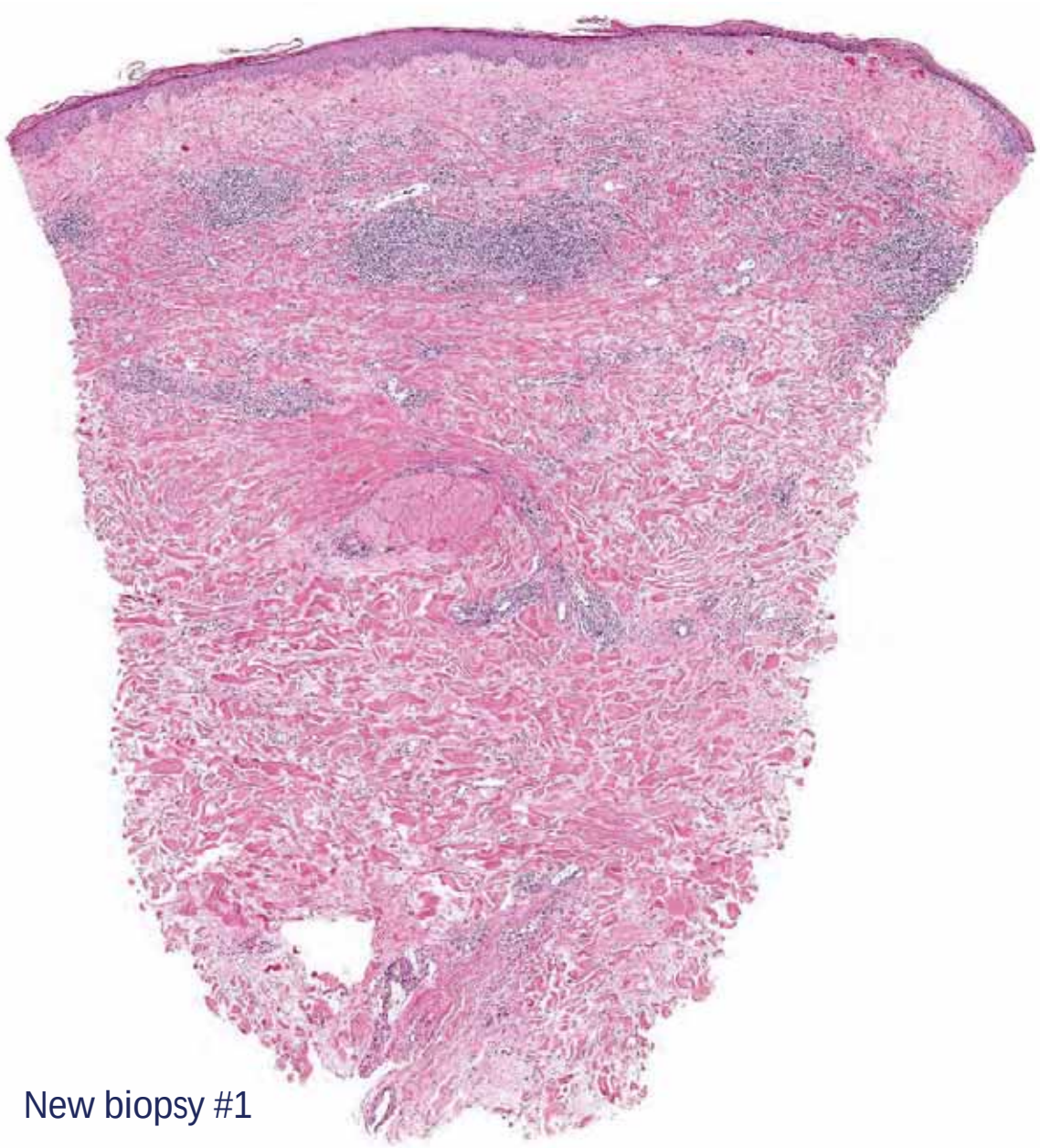
Started on extracorporeal photopheresis 1 month after presentation

Started on mogamulizumab 2 months after presentation

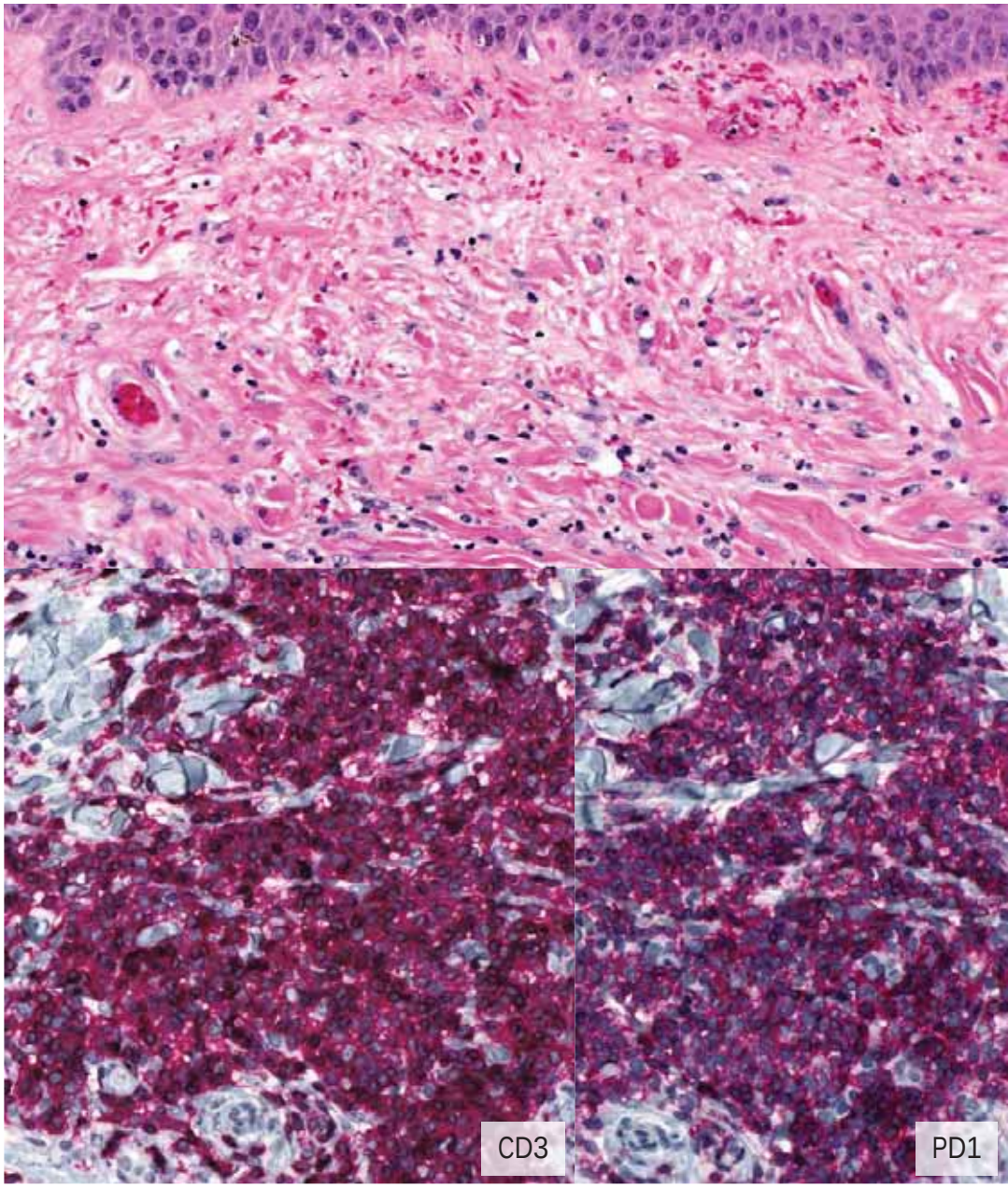


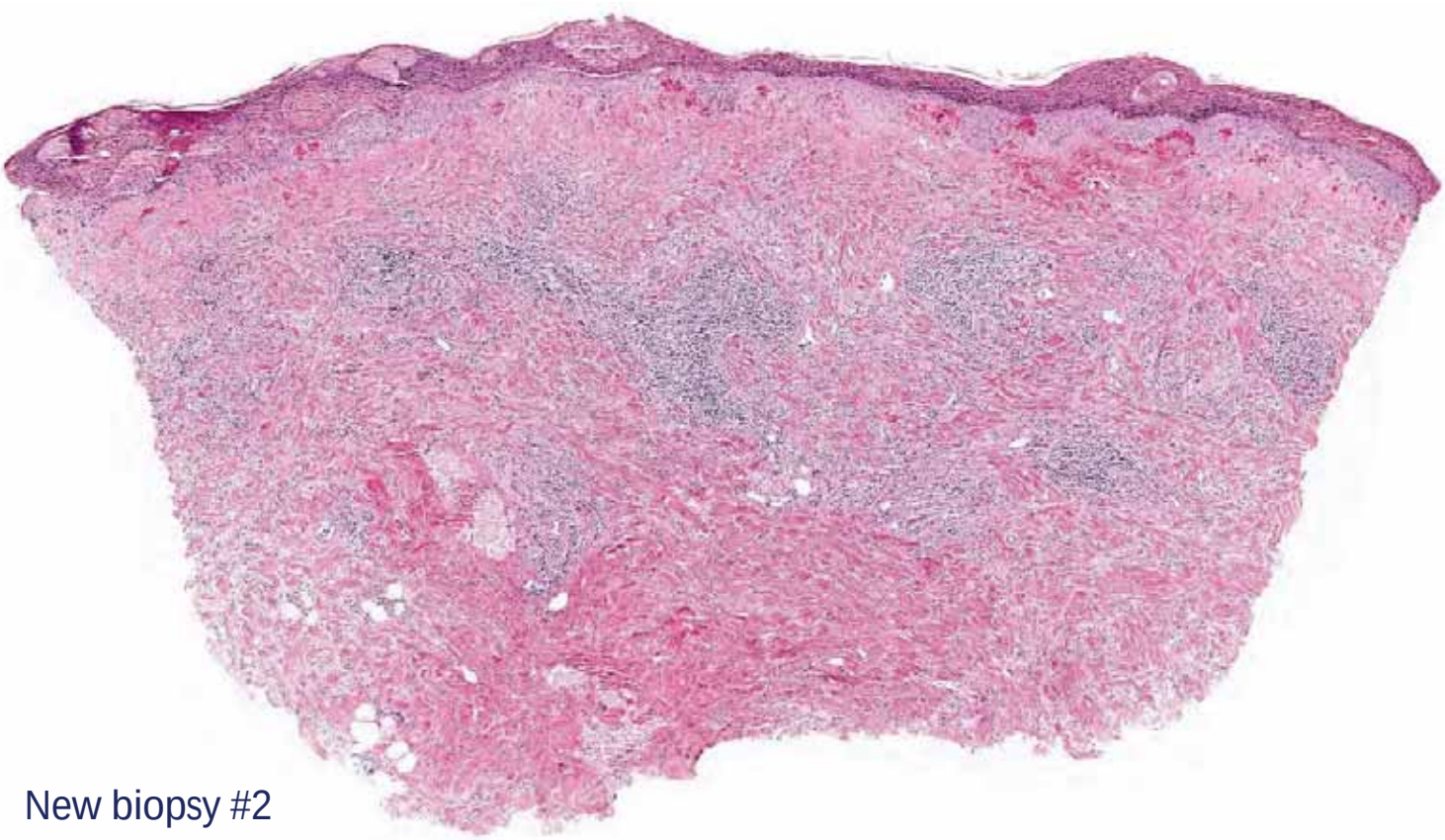
4 days after the first dose of mogamulizumab
Thrombocytopenia (43) (present already before administration)
CRP: 140,6; Procalcitonin: 18,40 (0-0,5)
2 new biopsies are taken



New biopsy #1





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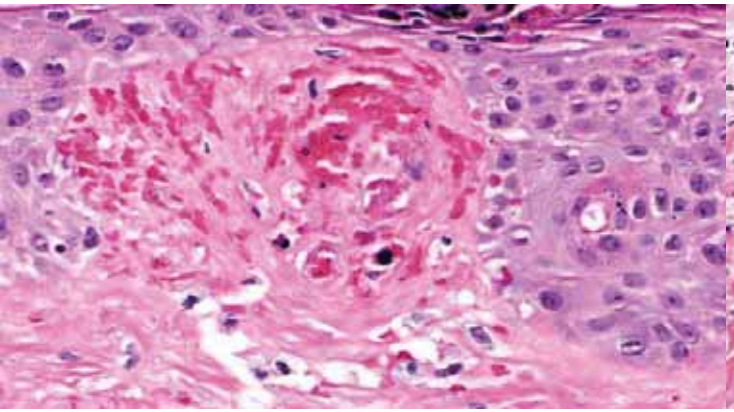

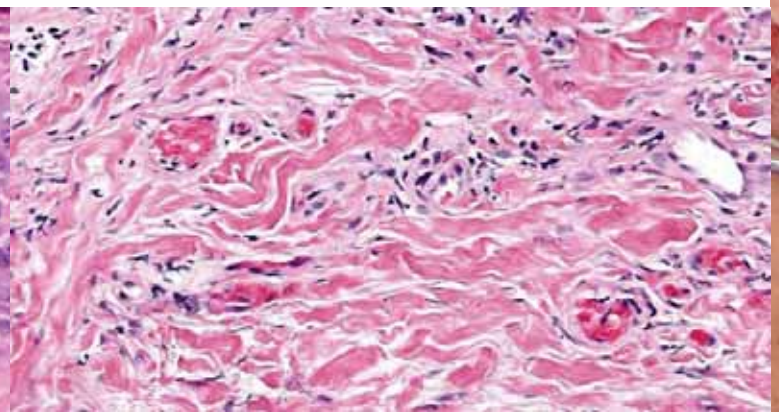

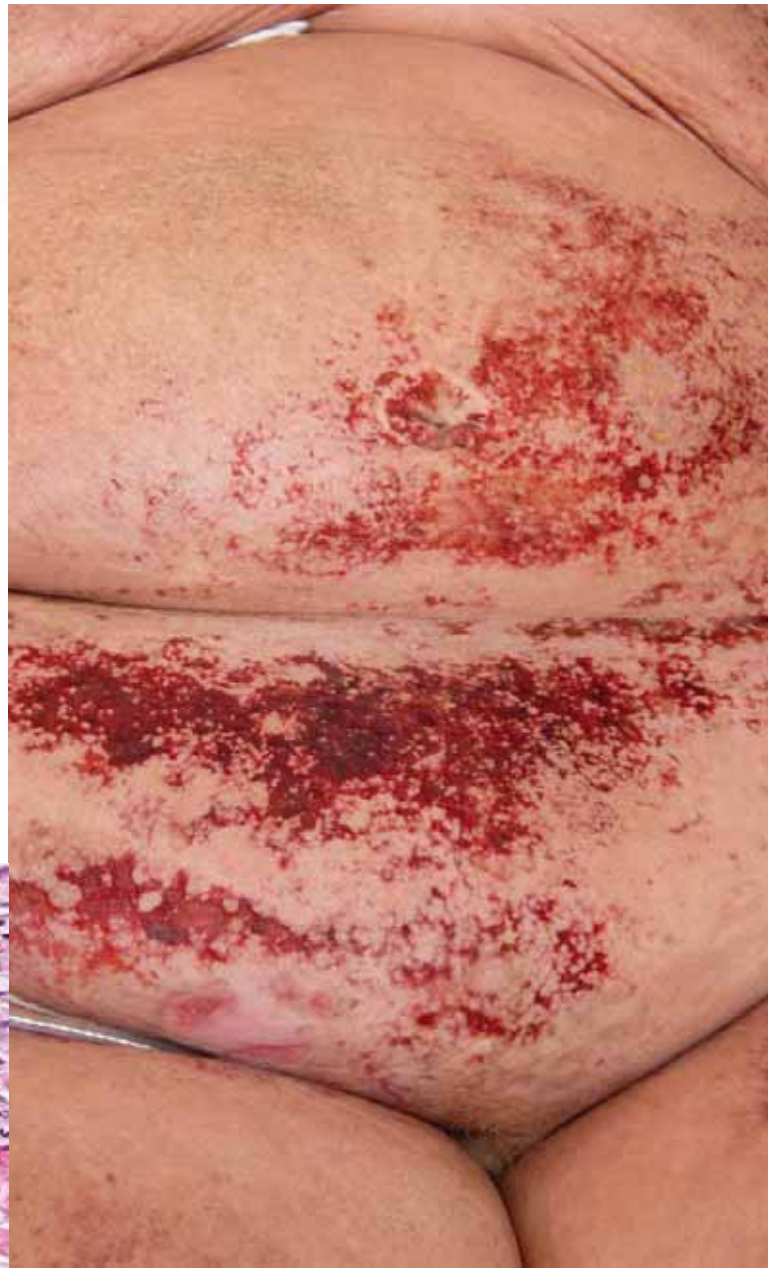

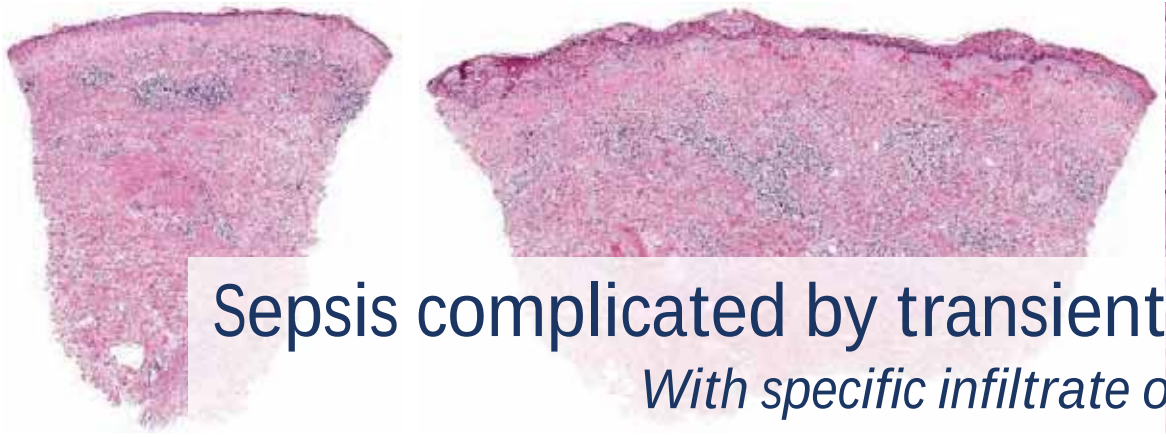

Sepsis complicated by transient DIC and thrombocytopenia

With specific infiltrate of Sézary syndrome

Cancer Medicine

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Cancer Medicine

RESEARCH ARTICLE

Mogamulizumab-Associated Autoimmune Diseases: Insights From FAERS Database Analysis

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Keywords: adverse events | disproportionality analysis | Food and Drug Administration Adverse Event Reporting System | mogamulizumab

ABSTRACT

Background: Mogamulizumab is a monoclonal antibody targeting the C-C chemokine receptor 4, used to treat T-cell malignancies such as cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma, and peripheral T-cell lymphoma. However, real-world studies on mogamulizumab-associated adverse events (AEs) are limited.

Methods: Disproportionality analysis were performed to assess the safety profile of mogamulizumab based on data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database for the period spanning from October 2018 to December 2023. The research investigated demographic characteristics, the onset timing of AEs, and the safety implications associated with mogamulizumab use.

Results: A total of 1182 significant preferred terms were identified among the 3661 mogamulizumab-associated AE reports collected from the FAERS database. The frequently reported AEs including rash, infusion-related reaction, and pyrexia were in line with drug instruction. Notably, several unexpectedly significant AEs were also found, including pemphigoid (ROR = 5.69 [95% CI 1.83–17.66]), unstable angina (ROR = 20.56 [95% CI 8.54–49.5]), bulbar palsy (ROR = 238.36 [95% CI 75.22–755.31]), myositis (ROR = 12.65 [95% CI 5.67–28.19]), and various autoimmune diseases such as autoimmune hepatitis (ROR = 21.35 [95% CI 11.08–41.07]), myocarditis (ROR = 15.29 [95% CI 8.67–26.97]), glomerulonephritis (ROR = 22.49 [95% CI 7.24–69.9]), nephrotic syndrome (ROR = 7.63 [95% CI 2.46–23.67]), myasthenia gravis (ROR = 8.54 [95% CI 3.2–22.77]), and autoimmune thyroiditis (ROR = 11.81 [95% CI 3.8–36.68]).

Conclusion: This study reiterated previously identified AEs associated with mogamulizumab and uncovered additional signals of AEs, particularly emphasizing the risks associated with autoimmune diseases. It is essential to exercise vigilance in monitoring the occurrence of these AEs during the use of mogamulizumab in clinical practice.

PT	Number of Cases	ROR(95% CI)	TTO
Graft versus host disease	21	55.42(36.02, 85.27)	0.00(0.00,0.00)
Myocarditis	12	15.29(8.67, 26.97)	NA
Graft versus host disease in gastrointestinal tract	10	54.73(29.34, 102.08)	133.50(93.00,143.75)
Vitiligo	10	68.41(35.58, 123.93)	58.00(58.00,58.00)
Autoimmune hepatitis	9	21.72(11.28, 41.82)	119.00(86.50,160.00)
Dermatitis exfoliative generalised	9	27.56(14.31, 53.09)	112.50(79.25,153.50)
Graft versus host disease in skin	8	45.1(22.48, 90.47)	NA
Myositis	6	12.65(5.67, 28.19)	NA
Alopecia areata	6	40.1(17.96, 89.54)	547.50(345.25,749.75)
Acute graft versus host disease	5	20.02(8.32, 48.21)	67.00(65.00,76.25)
Myasthenia gravis	4	8.37(3.14, 22.32)	NA
Autoimmune disorder	4	6.29(2.36, 16.77)	NA
Acute graft versus host disease in skin	4	25.08(9.38, 66.95)	88.00(88.00,88.00)
Psoriasiform dermatitis	4	30.48(11.41, 81.44)	0.00(0.00,0.00)
Autoimmune thyroiditis	3	12.05(3.88, 37.41)	NA
Glomerulonephritis	3	22.63(7.28, 70.35)	373.00(373.00,373.00)
Immune thrombocytopenia	3	6.79(2.19, 21.08)	1259.00(1259.00,1259.00)
Autoimmune haemolytic anaemia	3	11.66(3.75, 36.2)	288.00(288.00,288.00)

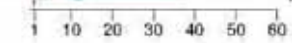
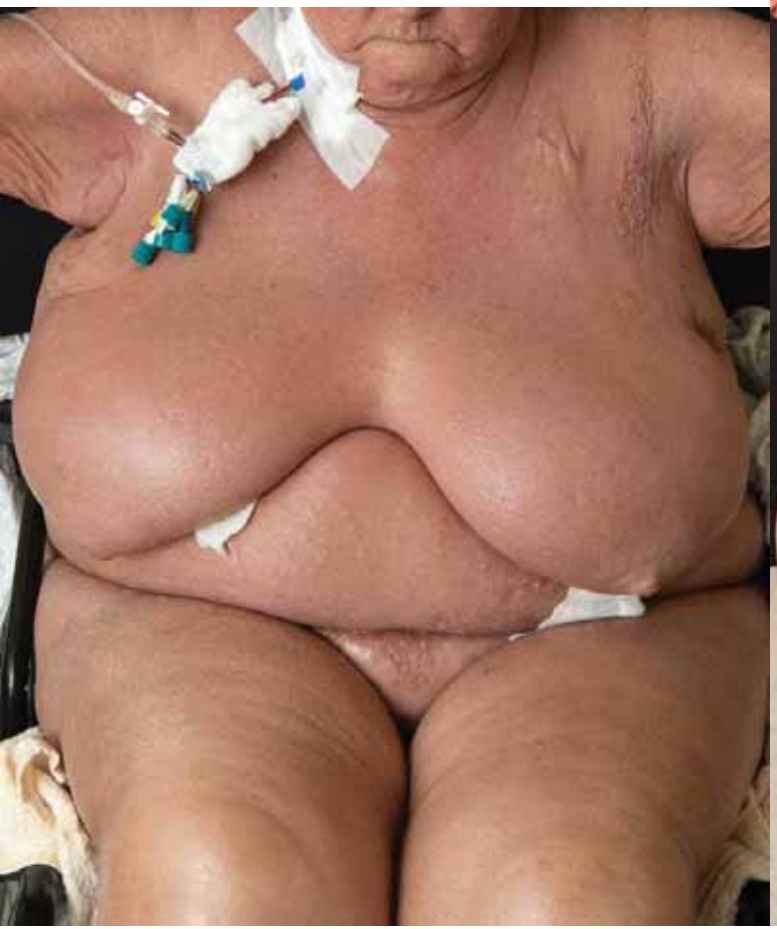
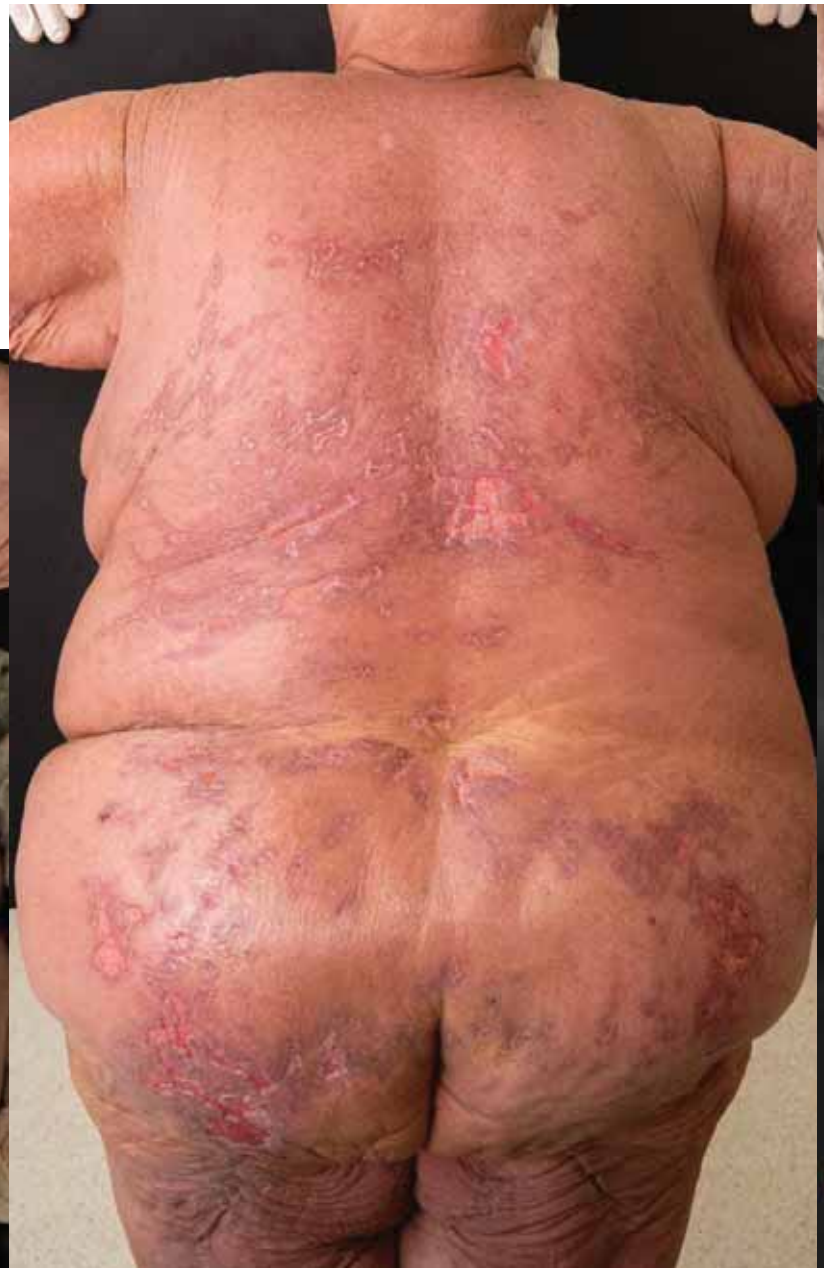


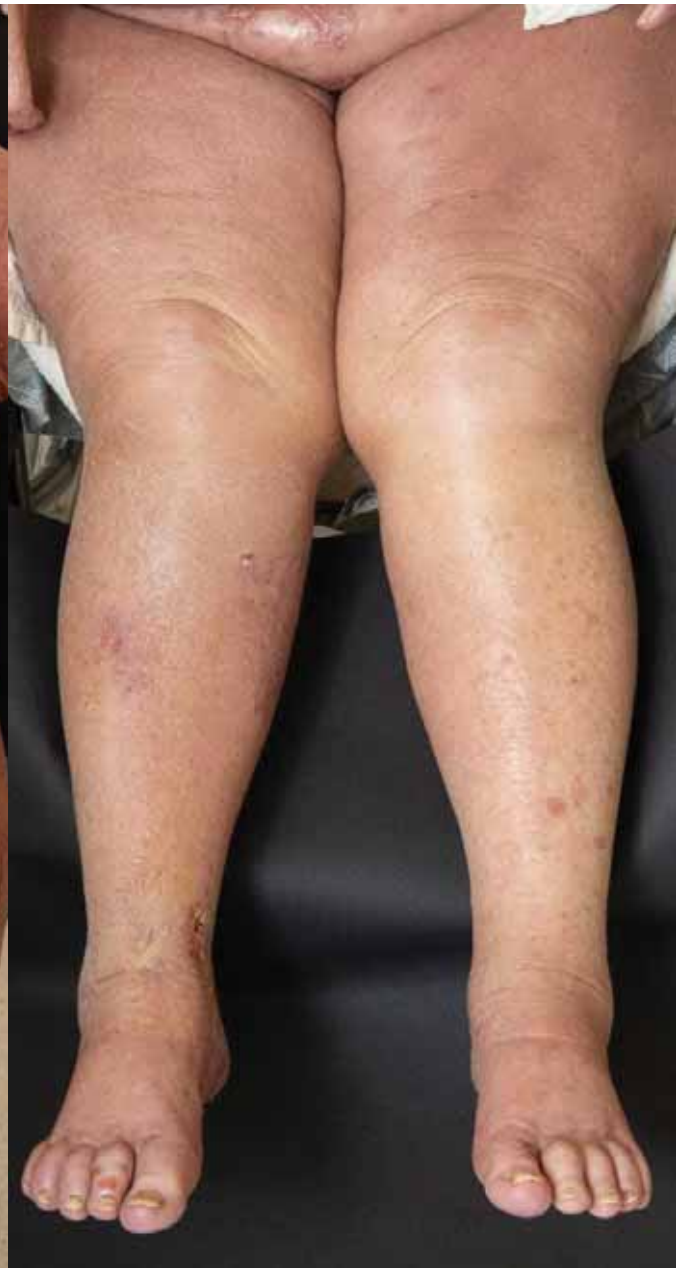
FIGURE 2 | The signal strength of adverse events for mogamulizumab-associated autoimmune diseases. PT, preferred term; ROR, reporting odds ratio; TTO, time to onset.

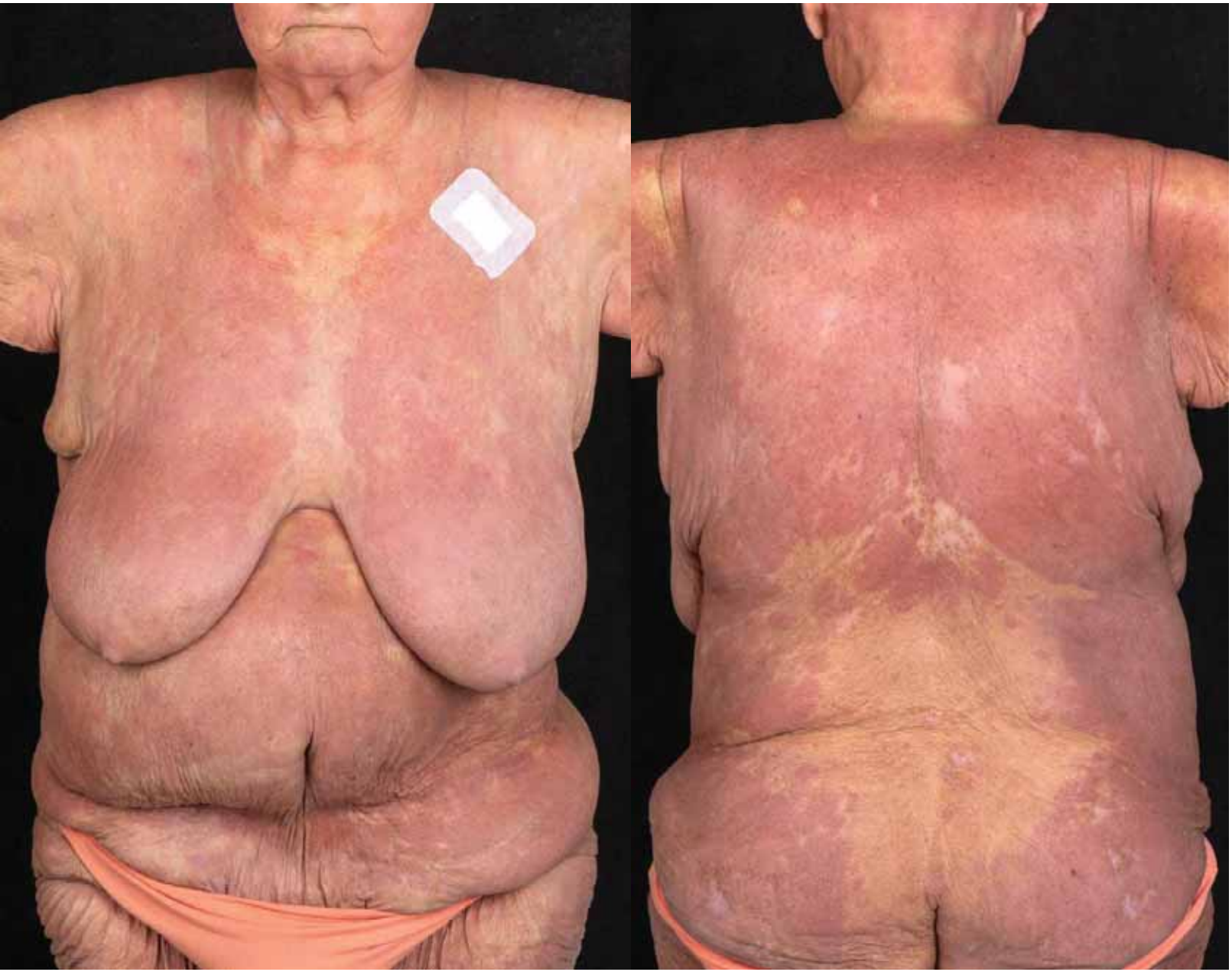
According to the data, the median onset time for adverse events was 21 days, with an interquartile range of 2–107 days. 33.73% of patients experienced adverse reactions within the first week of using mogamulizumab.

Managed successfully with intensive care;
20 days later







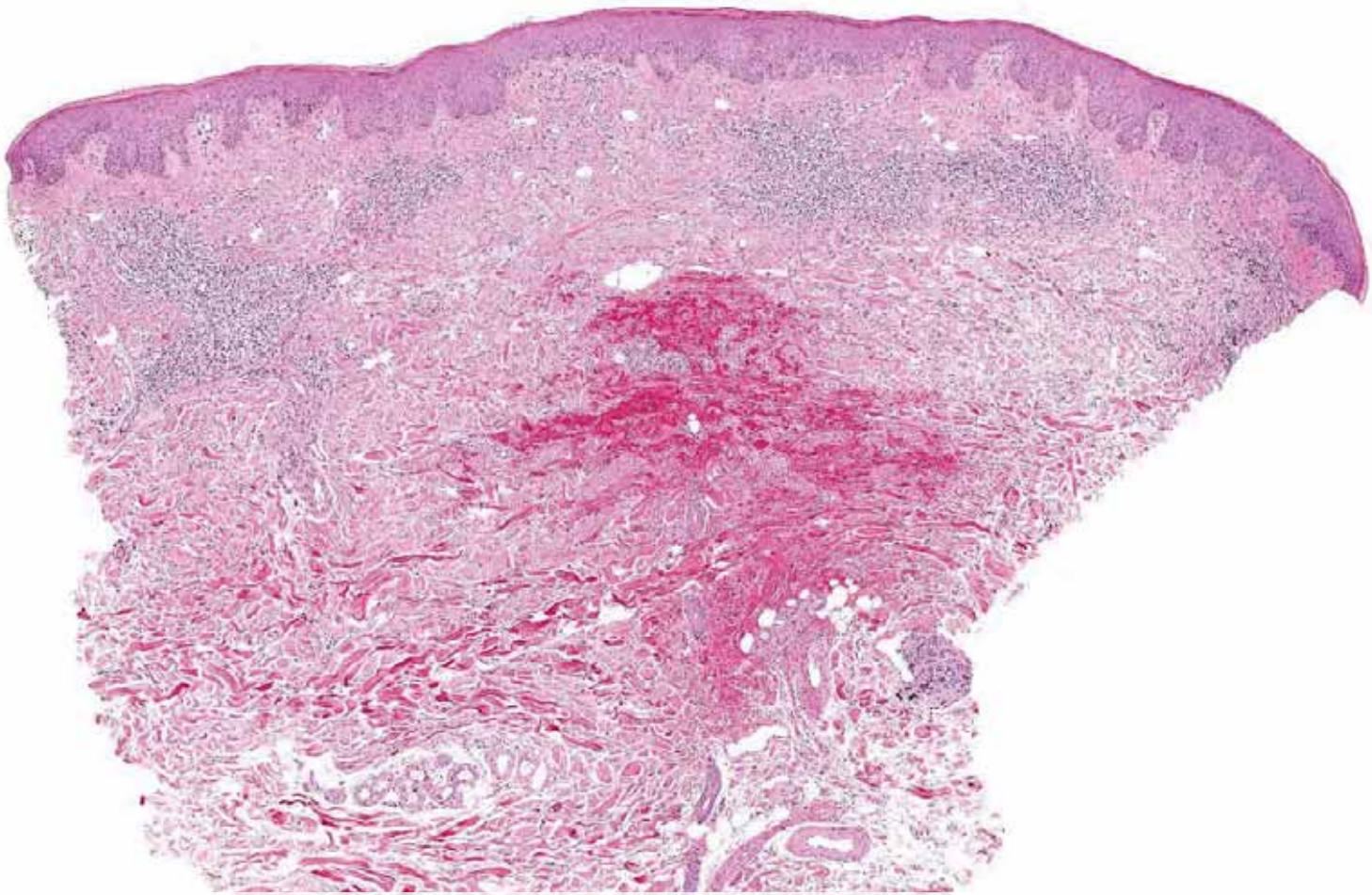


Pictures taken 6 months after first presentation (4 months after sepsis).

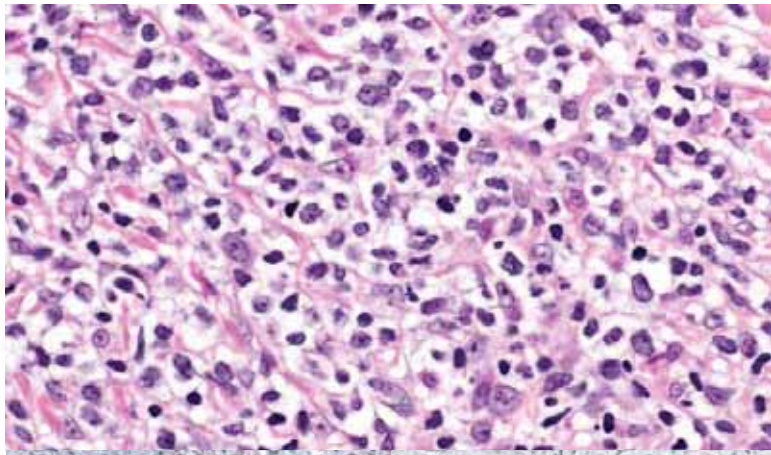
The 2nd mogamulizumab administration was given 2 months after the first one; at present a total of 6 administrations (+ 8 cycles of ECP): no adverse reaction; thrombocytes in normal range (284).

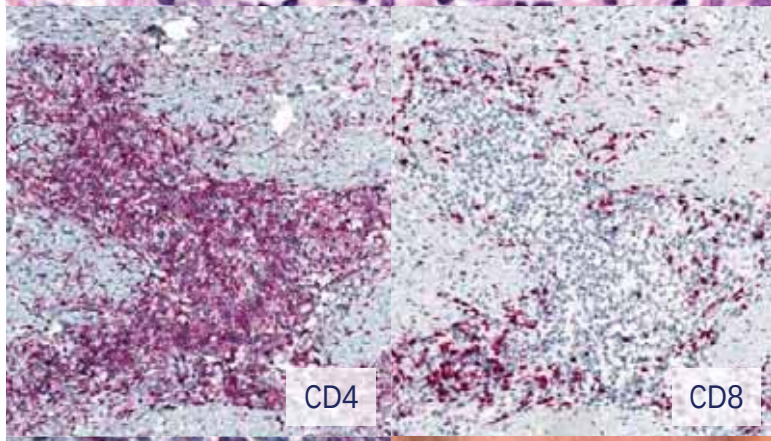
3,5% Sézary cells in blood; PET: clear reduction of pathologic LNs.

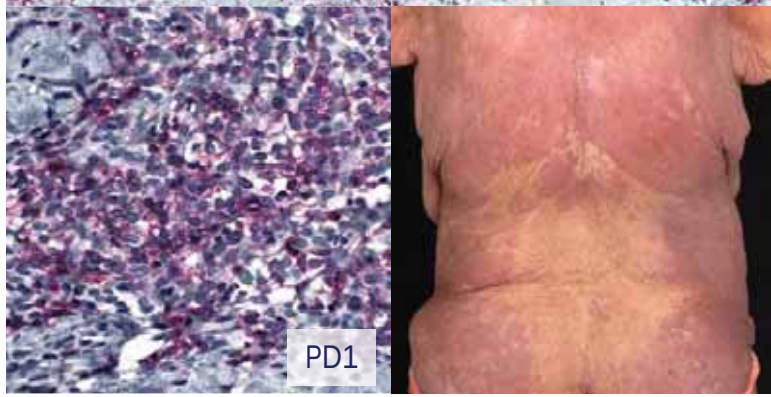
A new biopsy is taken with the clinical query: mogamulizumab-associated rash vs. persistent Sézary syndrome.



Persistent Sézary syndrome (medium/large cells)







Research

JAMA Dermatology | Original Investigation

Clinical Characterization of Mogamulizumab-Associated Rash During Treatment of Mycosis Fungoides or Sézary Syndrome

Kelsey E. Hirotsu, MD; Tatiana M. Neal, BA; Michael S. Khodadoust, MD, PhD; Jennifer Y. Wang, MD; Karin E. Fleger, MD, PhD; Jenna Straus, PhD; Eric Hong, BS; Youn H. Kim, MD; Bernice Y. Kwong, MD

IMPORTANCE Mogamulizumab is a monoclonal antibody against CCR4 approved for treatment for mycosis fungoides (MF) and Sézary syndrome (SS). Mogamulizumab-associated rash (MAR) is difficult to differentiate from cutaneous MF or SS, which can lead to unnecessary discontinuation of drug use because of concern for severe drug reaction or incorrect presumption of disease relapse or progression in the skin.

OBJECTIVE To examine the most common clinical presentations of MAR in patients with MF or SS and the diagnostic and management challenges.

DESIGN, SETTING, AND PARTICIPANTS This retrospective case series assessed patients from a multidisciplinary cutaneous lymphoma clinic and supportive oncodermatology clinic at a major academic referral center who had a diagnosis of MF or SS and received mogamulizumab from January 1, 2013, to January 1, 2020. Treatment was followed by new or worsening rash with skin biopsy results compatible with drug eruption determined by clinicopathologic correlation and molecular testing to exclude active malignant disease.

EXPOSURES At least 1 dose of mogamulizumab.

MAIN OUTCOMES AND MEASURES Mogamulizumab-associated rash was characterized by clinical features, including time to onset, clinical presentation, histopathologic features, and management approach.

RESULTS The study included 19 patients with MF or SS who developed MAR (median age, 65 years; age range, 38-82 years; 10 [52.6%] male). Median time to MAR onset was 119 days (range, 56 days to 3.8 years). Patients with MAR exhibited 4 predominant clinical presentations: (1) folliculotropic MF-like scalp plaques with alopecia, (2) papules and/or plaques, (3) photoaccentuated dermatitis, and (4) morbilliform or erythrodermic dermatitis. The most common anatomical region involved was the head and neck, including the scalp. Histopathologic findings were variable and did not correspond to primary clinical morphologic findings. Immunohistochemistry and T-cell clonality ancillary testing were helpful to distinguish MAR from disease. Most patients with MAR (14 of 19) discontinued mogamulizumab treatment; however, no life-threatening severe cutaneous adverse drug reactions occurred, and the decision for drug therapy cessation was usually multifactorial. Four patients were treated again with mogamulizumab with no life-threatening drug-related events. Approaches to management of MAR include topical corticosteroids, systemic corticosteroids, and/or methotrexate.

CONCLUSIONS AND RELEVANCE This case series found that mogamulizumab-associated rash had a heterogeneous clinical presentation with variable and delayed onset in patients with MF or SS. Mogamulizumab-associated rash exhibited a predilection for the head and neck and was difficult to clinically distinguish from relapse or progression of disease. Recognition of the most common clinical presentations can help prevent unnecessary discontinuation of mogamulizumab treatment. The presence of MAR does not necessitate permanent discontinuation of or avoidance of retreatment with mogamulizumab.

Author Affiliations: Department of Dermatology, Stanford University School of Medicine, Palo Alto, California (Hirotsu, Neal, Wang, Fleger, Straus, Hong, Kim, Kwong); Department of Pathology, Stanford University School of Medicine, Stanford, California (Wang, Fleger); Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, California (Khodadoust, Kim).

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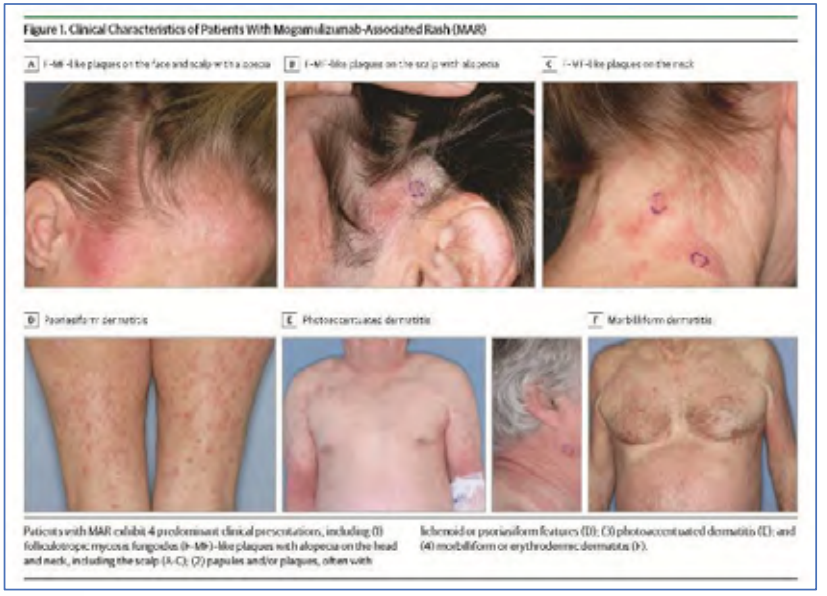
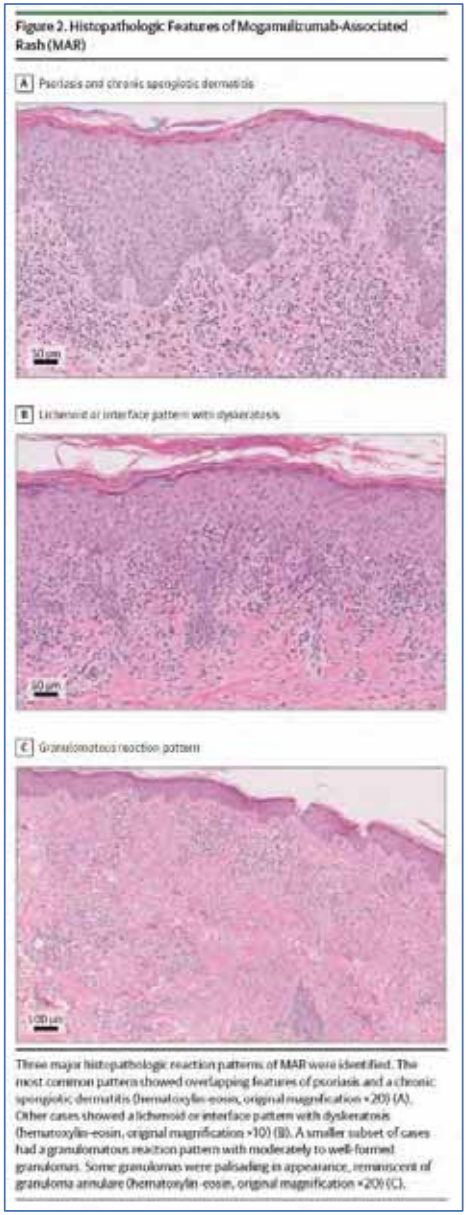
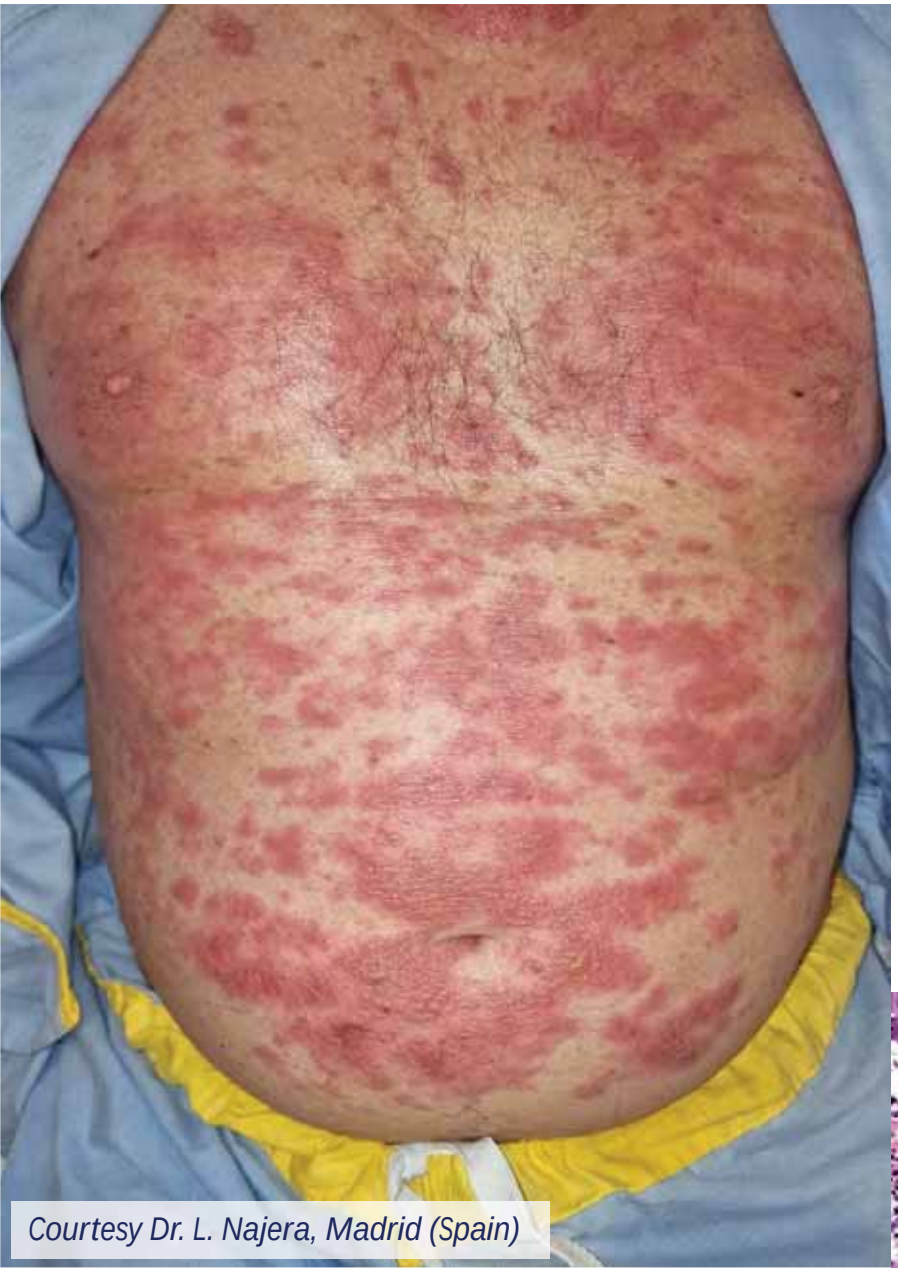


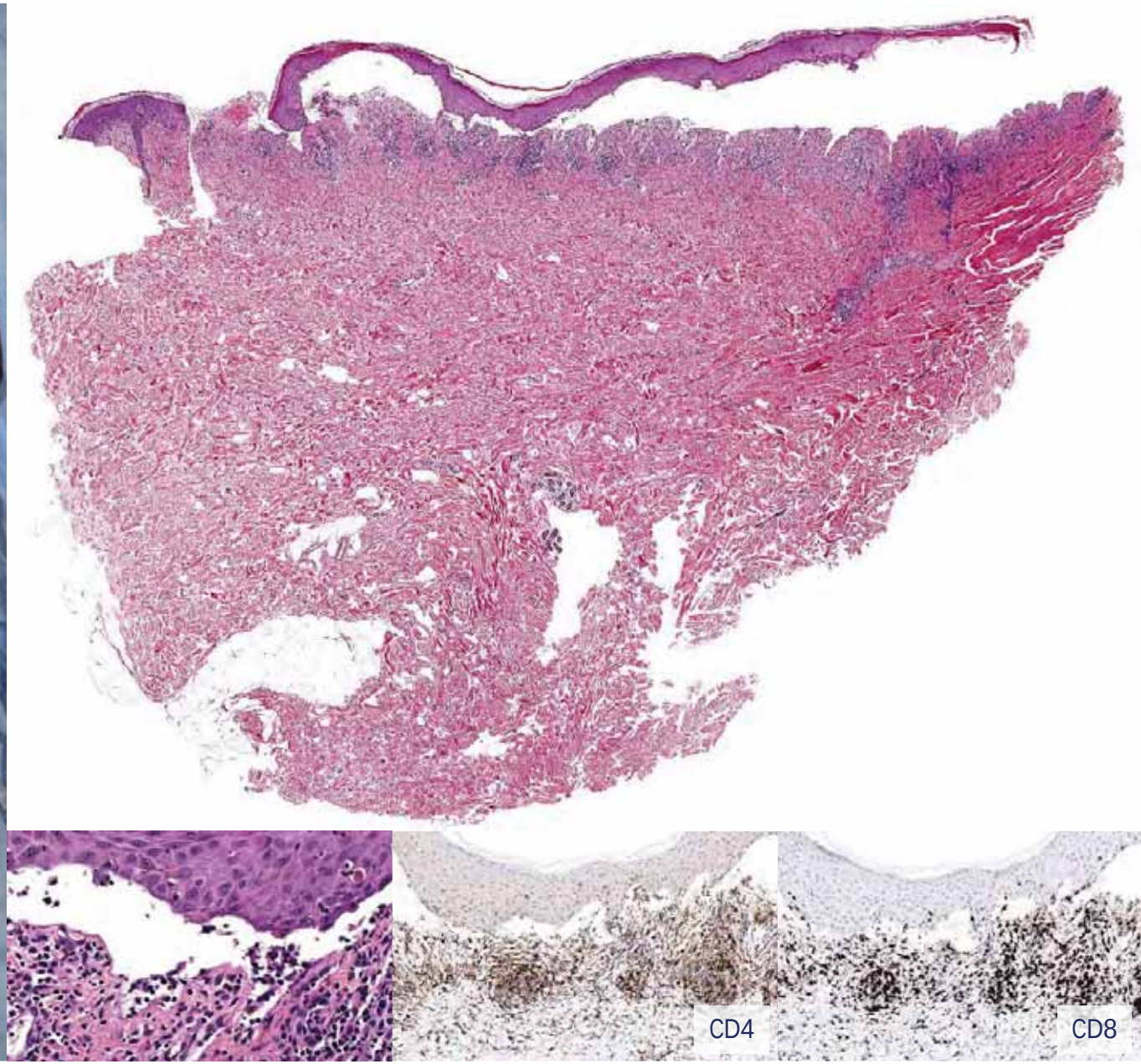
19 patients (MF: 1; Sézary: 18)

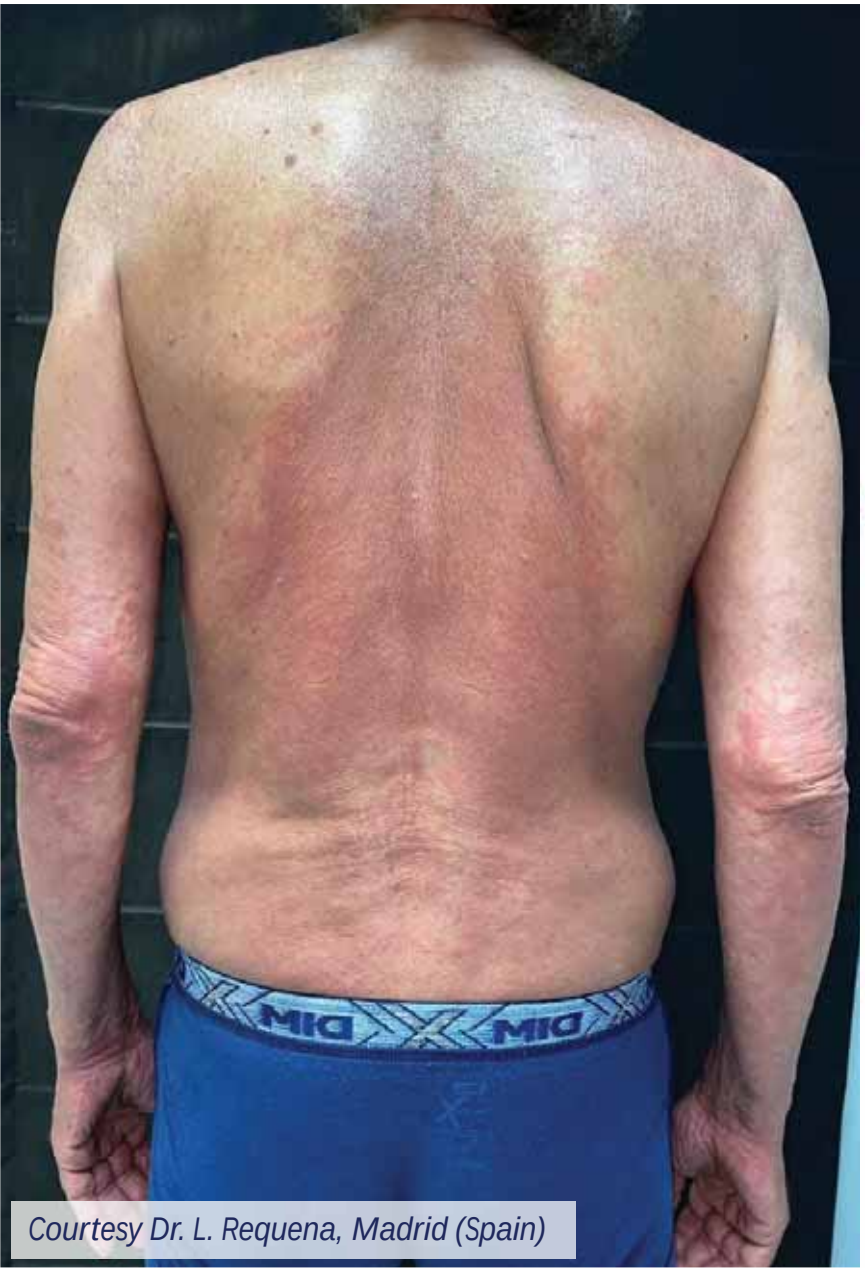
"In contrast to the CD4-predominant T cell populations observed in biopsy specimens from the patients' MF or SS, most MAR biopsy specimens demonstrated exocytosis of CD8-positive T cells and a normal ratio of CD4- to CD8-positive T cells in the dermis, compatible with a reactive process."

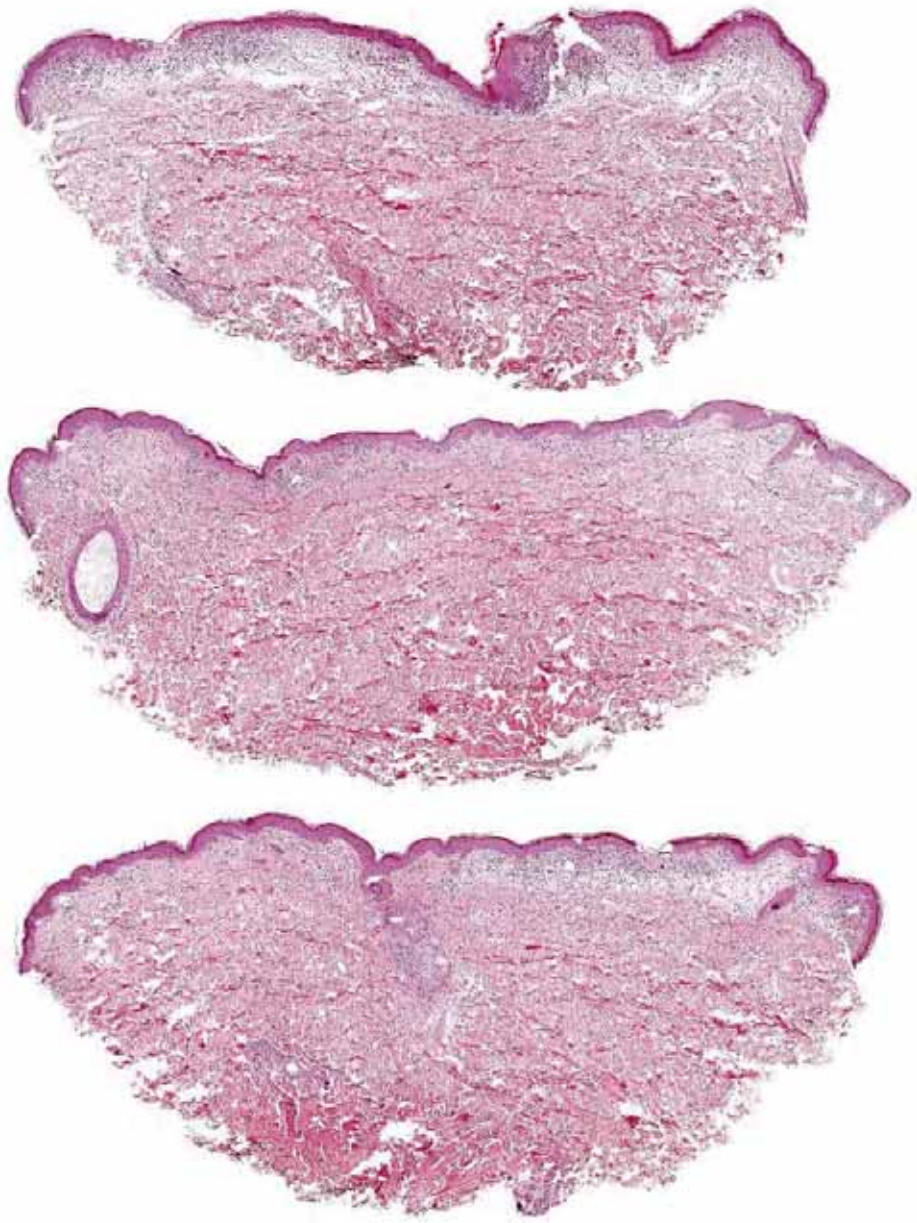


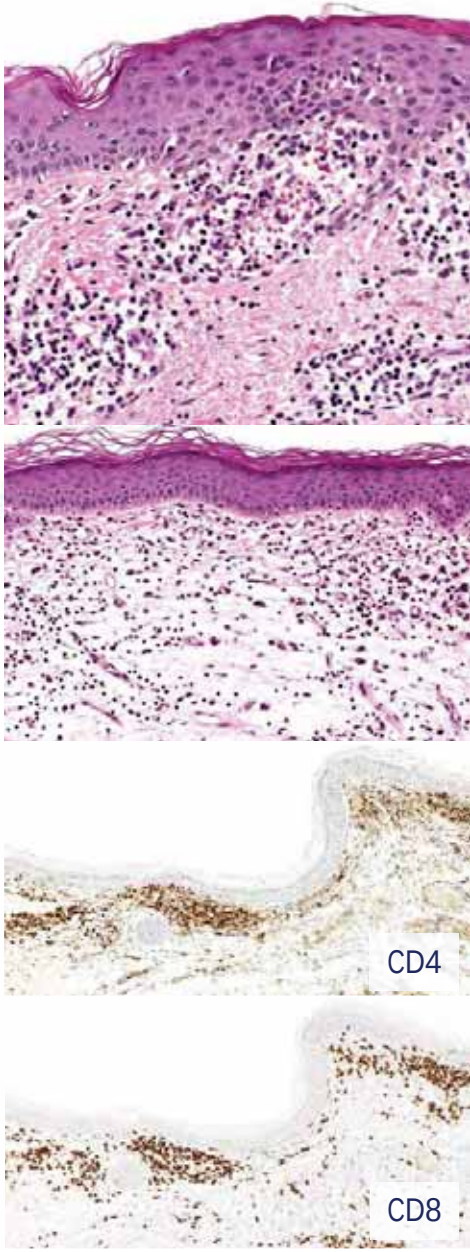


Courtesy Dr. L. Najera, Madrid (Spain)




Courtesy Dr. L. Requena, Madrid (Spain)




CD4
CD8

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MINIREVIEW

Mogamulizumab-associated rash – Case series and review of the literature

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Summary

Mogamulizumab, a monoclonal antibody directed against CC chemokine receptor 4, is approved as a second-line treatment of mycosis fungoides and Sézary syndrome.

One of the most common side effects is mogamulizumab-associated rash (MAR), which can present in a variety of clinical and histological types. Clinically, it can be difficult to differentiate between MAR and progression of the underlying disease, so histological examination is crucial for clinicopathological correlation. Current data analyses suggest that MAR is more common in patients with Sézary syndrome and is associated with a significantly better response to treatment, making the distinction from disease progression particularly important. The management of MAR depends on its severity, and therapy may need to be paused.

This article presents three cases from our clinic and reviews the current literature on MAR. It emphasizes the importance of understanding MAR in the management of patients with cutaneous lymphomas.

KEYWORDS

cutaneous T cell lymphoma, mogamulizumab, mogamulizumab-associated rash, mycosis fungoides, Sézary syndrome

INTRODUCTION

Mogamulizumab is a humanized monoclonal antibody directed against the CC chemokine receptor 4 (CCR4) and is approved for the second-line treatment of the most common cutaneous T-cell lymphomas (CTCL), mycosis fungoides (MF), and Sézary syndrome (SS).[1,2] The approval was based on the randomized, controlled phase III study *Mogamulizumab versus Vorinostat in previously treated cutaneous T-cell lymphoma* (MAVORIC).[3] The study showed significant superiority of mogamulizumab in terms of progression-free survival (PFS) and overall response rate (ORR).[3] Mogamulizumab leads to the destruction of antibody-loaded tumor cells via antibody-dependent cell-mediated cytotoxicity (ADCC).[2] After mogamulizumab binds to the CCR4 receptor, an NK cell binds to the cell-bound mogamulizumab with its Fc receptor and subsequently destroys the tumor cell.[2] In addition to tumor cells, CCR4-expressing cells also include regulatory T cells (Treg), which are depleted by mogamulizumab therapy.[4] In this context, there have been anecdotal reports of immune responses that occur when Th2 cells are suppressed, with a possible Th1 shift and associated increased activity of $CD8^+$ T cells, which can manifest in the skin (e.g., psoriasis) or in solid organs (e.g., hepatitis or colitis).[5–7]

In the pivotal study, mogamulizumab-associated rash (MAR) was observed in 24% of patients in the mogamulizumab arm.[3] MAR is highly variable in its clinical manifestation and was the most common adverse event leading to treatment discontinuation in the MAVORIC study.[3,8]

Due to the heterogeneous clinical presentation of CTCL, differentiation from the underlying disease is often difficult, leading to diagnostic and therapeutic challenges.[9] Identifying skin changes as MAR is important to avoid

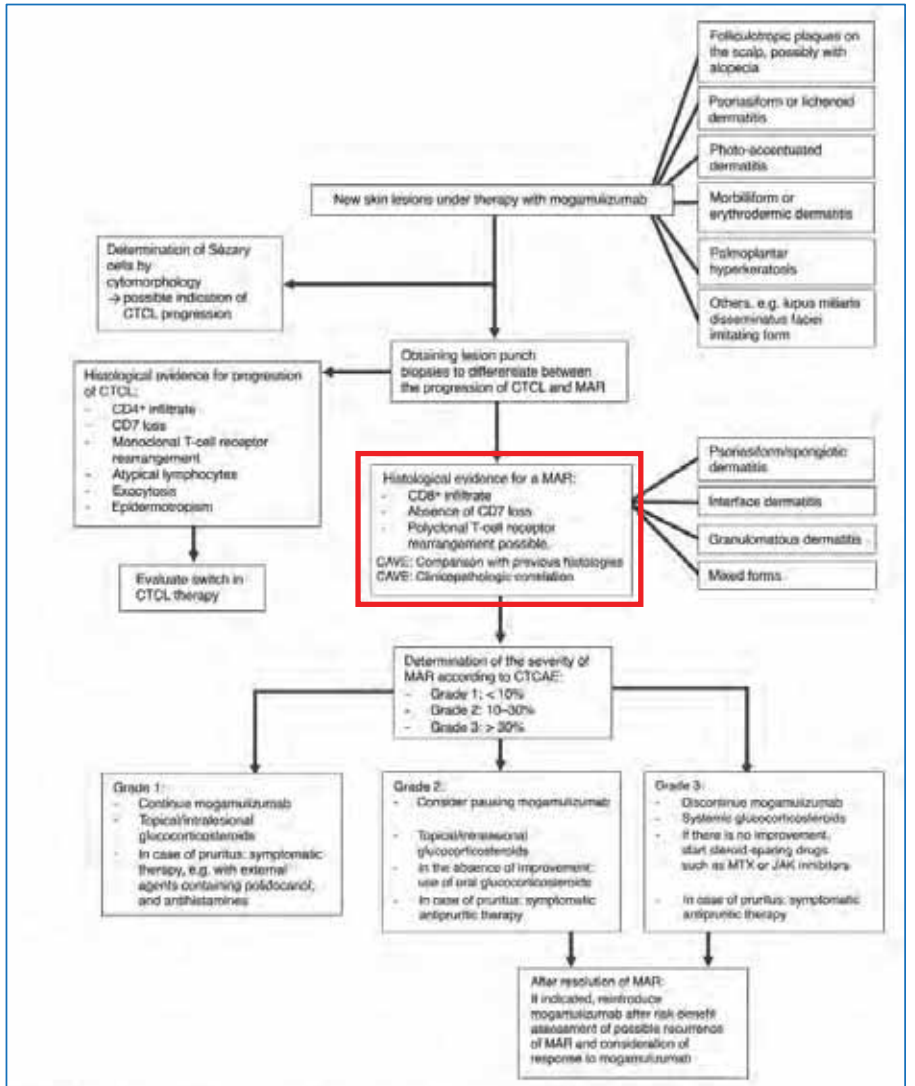
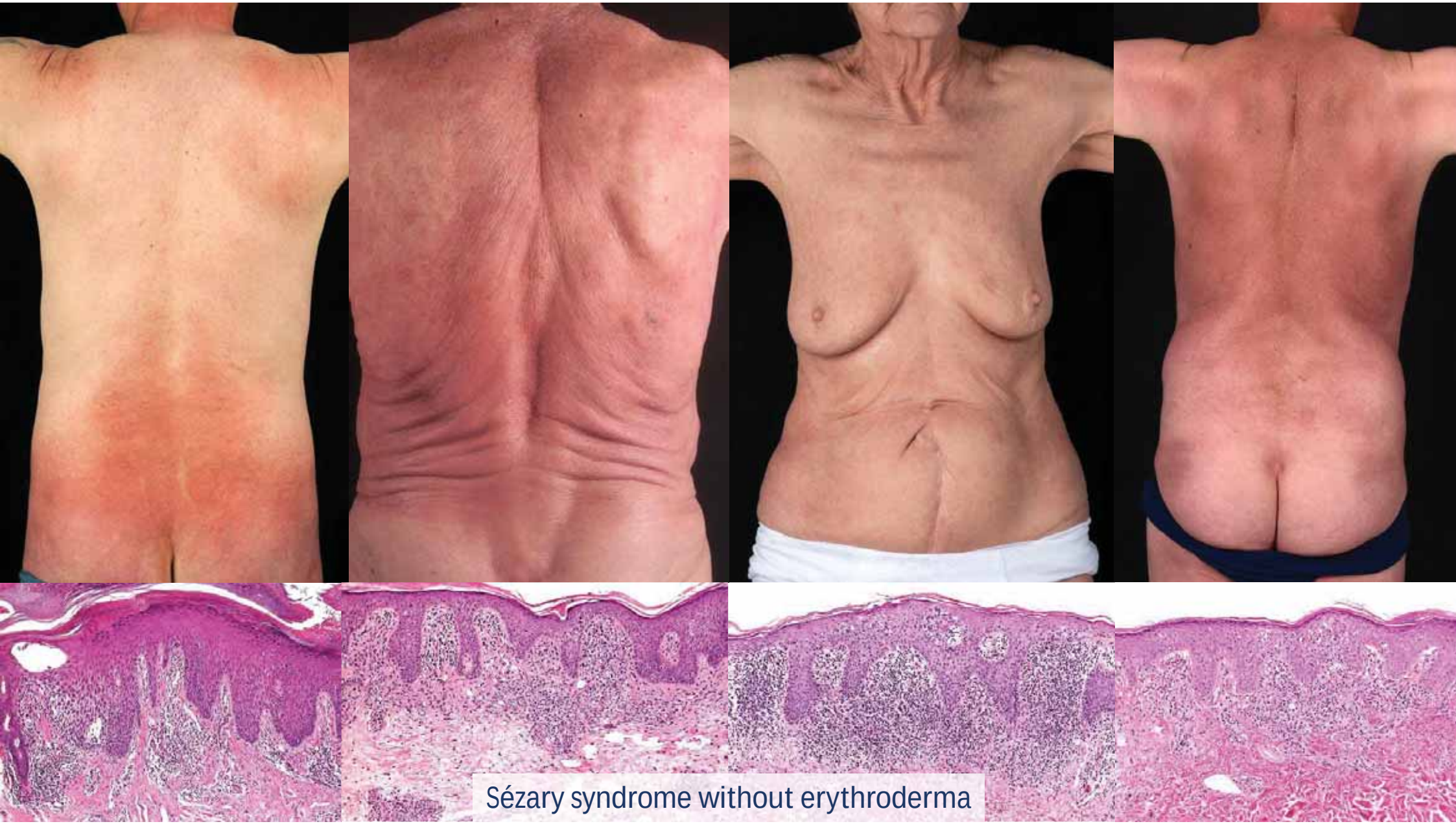
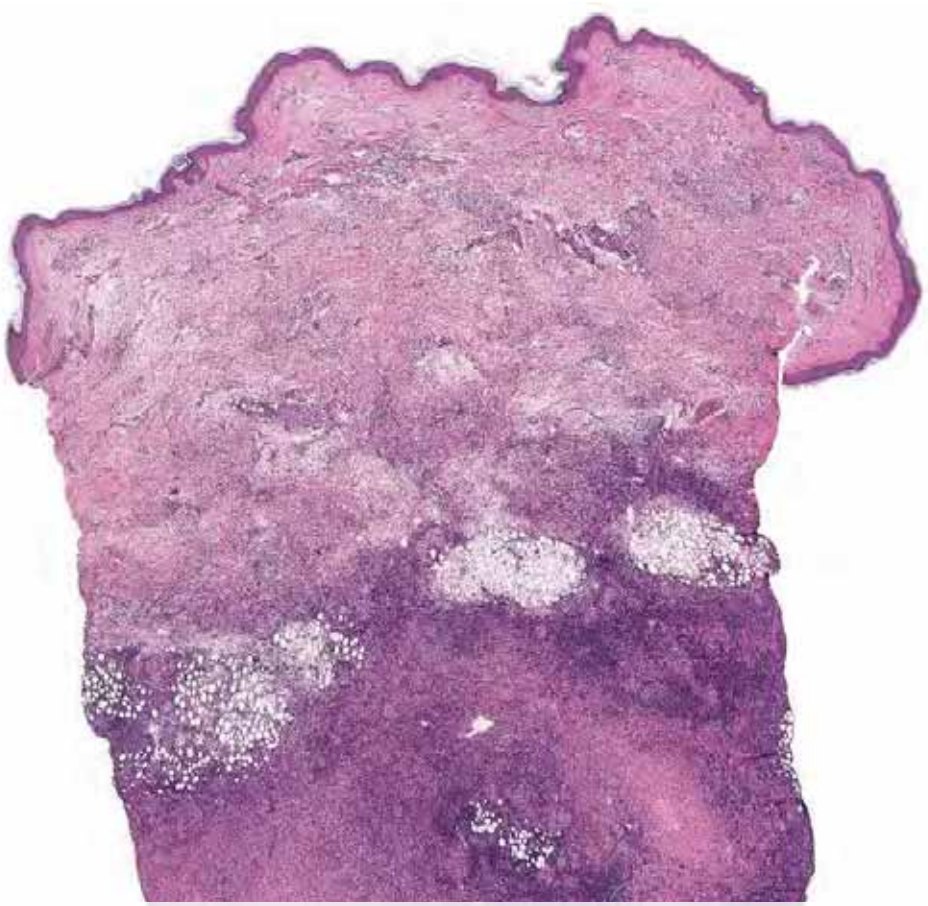


FIGURE 4 Step chart for management of suspected mogamulizumab-associated rash, based on Musiek et al.[9]

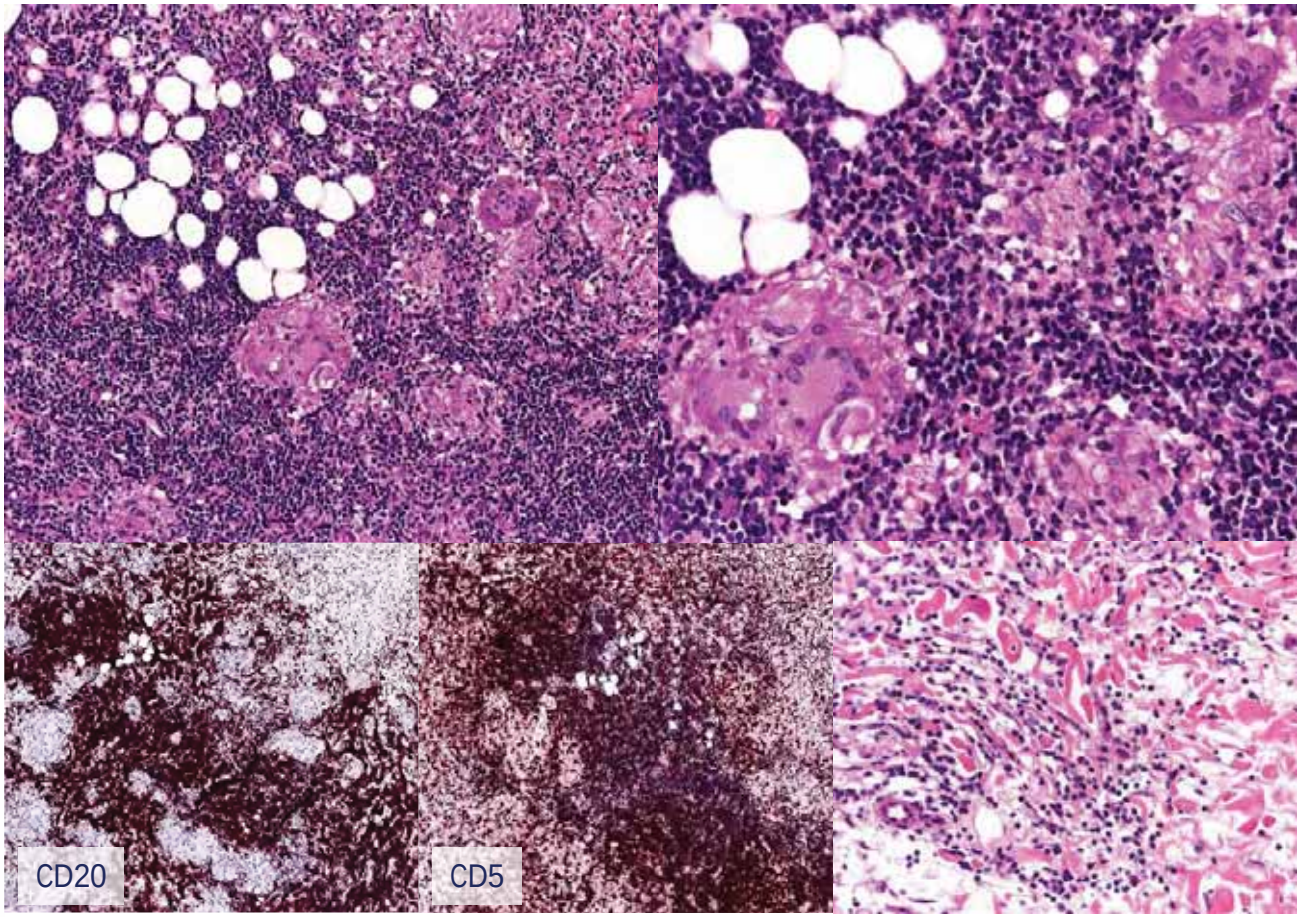


Sézary syndrome without erythroderma



Borreliosis

Acrodermatitis chronica atrophicans with granulomatous panniculitis PCR+ on lesional tissue



F, 93
According to the patient skin lesions on the left hand and elbow for approximately 1 year, accompanied by paresthesia and pain.
No relevant medical history. Axillary lymph nodes not palpable. Sonography of the left elbow: chronic bursitis.
A biopsy is taken from the elbow under the clinical diagnosis of cutaneous lymphoma.
The case is sent in consultation by Dr. Würtz (Klagenfurt, Austria).

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WILEY JCP

CASE REPORT

Septolobular panniculitis in disseminated Lyme borreliosis

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Lyme disease classically evolves through clinical manifestations according to the stage of illness. Because many of the systemic symptoms are non-specific, and because serology may yield false negative results, cutaneous findings merit even greater importance to diagnosis. The pruriginous skin lesion, erythema migrans (EM), occurs early and is the only independent diagnostic clinical feature according to the guidelines of the Infectious Diseases Society of America. EM itself has protean guises, being, at times, vesicular, indurated, necrotic, purpuric, solid, or targetoid, but it is not the sole Borrelia associated skin lesion. Acrodermatitis chronica atrophicans and borrelial lymphocytoma cutis are other well-known skin manifestations. A rare cutaneous manifestation that is increasingly reported in Lyme patients is panniculitis, which develops after dissemination of the spirochete. We present such a case in a patient who was initially treated for cellulitis as well as neck and radicular leg pain, thereby expanding the cutaneous spectrum of Lyme disease.

KEYWORDS
erythema migrans, Lyme disease, panniculitis

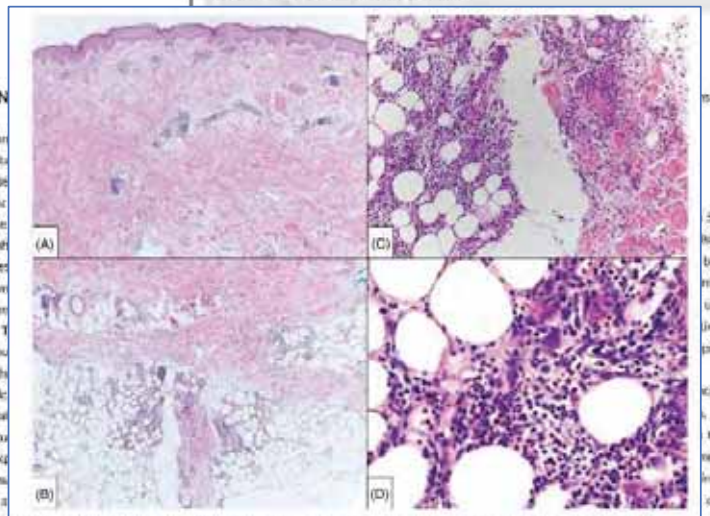

FIGURE 2 Sections from the thigh punch biopsy show a perivascular and interstitial, superficial and deep dermatitis with associated perilobular lobular panniculitis. The dermal infiltrate was mainly lymphocytic but included plasma cells, neutrophils and eosinophils. H&E x40 (A). The subcutis showed prominent infiltration by both neutrophils and lymphocytes, involving mainly the lobular fat with extension to fibrous septa, H&E x40 (B). Detail of the subcutaneous infiltrate, H&E x100 (C) and x500 (D)

Septal Panniculitis as a Manifestation of Lyme Disease

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and
Newark, New Jersey

A 22-year-old woman presented with fever, chills, photophobia, and headaches, followed by a centrally clearing erythematous skin eruption, migratory polyarthralgias, conjunctivitis, and subsequently, tender, nodular skin lesions. Antibodies to Borrelia burgdorferi were consistent with acute Lyme disease. Skin biopsy revealed acute septal panniculitis. This dermatologic manifestation has not been previously described in Lyme disease.

Lyme disease, initially described by Steere et al [1] in 1977, is a multisystem disease, usually beginning in summer with a characteristic skin lesion, erythema chronicum migrans. The lesion is often associated with symptoms suggesting a viral-type illness, including myalgias, arthralgias, fatigue, headache, stiff neck, and lymphadenopathy. After several weeks to months, neurologic or cardiac abnormalities may develop. Subsequently, many patients have intermittent or chronic arthritis, which can be associated with destructive articular changes. In the last few years, it has been determined that the disease is caused by a spirochete, Borrelia burgdorferi [2], which has been successfully isolated from skin, blood, cerebrospinal fluid, and synovium of infected patients [3], and is transmitted by the bite of the Ixodes dammini or other related ticks. Antibiotic therapy, in particular with tetracycline for erythema chronicum migrans and the associated symptoms and high-dose intravenous penicillin for the later findings, appears to be highly effective [4].

Erythema chronicum migrans is the hallmark skin lesion of Lyme disease, serving as a distinctive clinical marker for the diagnosis. Typical-
herna chronicum migrans begins as a red macule or papule that
ds centrifugally to form an annular lesion, often with central clear-
casionally with an indurated center [1]. In its absence or when it
ts in an atypical fashion, the diagnosis of Lyme disease may be
t because of the nonspecific nature of the early manifestations.
present herein a case of Lyme disease in which the skin manifes-
was highly unusual, initially presenting with typical erythema chron-
migrans, but followed by multiple painful nodular lesions with
gic evidence of septal panniculitis.

REPORT

iously healthy 22-year-old white woman had acute pain over the
of the left foot and swelling in the left popliteal fossa on August 20.
The following day, she had fever to 38.5°C, chills, and for two days
enced photophobic headaches, along with nuchal rigidity. On August
sed, confluent erythema developed over her anterior chest, which
from the center and resolved completely in 24 hours. By August 26,
s experiencing severe, migratory polyarthralgias of the knees, left

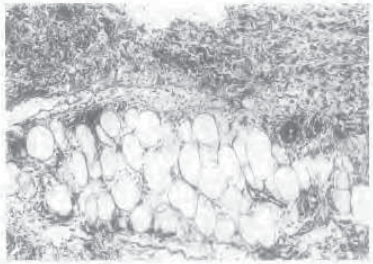

Figure 2. Subcutaneous fat lobule and fibrous septums with perivascular and septal inflammation (hematoxylin and eosin stain; original magnification × 500, reduced by 35 percent).

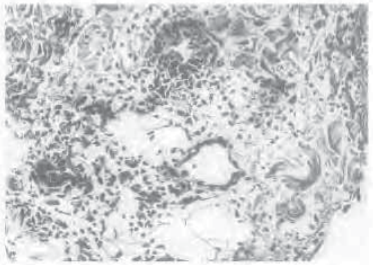

Figure 3. Subcutaneous fat with dense perivascular inflammation involving small vessels (hematoxylin and eosin stain; original magnification × 1,285, reduced by 35 percent).

Lobular Panniculitis due to *Borrelia burgdorferi* Infection Mimicking Subcutaneous Panniculitis-Like T-Cell Lymphoma

Werner Kempf, MD, Dmitry V. Kazakov, MD, PhD,† and Heinz Kutzner, MD*‡*

Abstract: The authors present an unusual case of lobular panniculitis caused by *Borrelia burgdorferi* sensu lato infection in a 56-year-old man. It presented clinically as a solitary subcutaneous nodule. Histopathologically, the lesion resembled subcutaneous panniculitis-like T-cell lymphoma by manifesting atypically appearing lymphocytes with cytotoxic phenotype. *B. burgdorferi* etiology was proven by positive polymerase chain reaction and serology and positive response to antibiotics.

Key Words: lymphoma, skin, pseudolymphoma, panniculitis, plasma cells, plasmacytoid dendritic cells, CD123, lupus profundus

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Borreliosis or Lyme disease is a multifocal worldwide disease caused by a group of related spirochetes *Borrelia burgdorferi* sensu lato that are transmitted by specific *Ixodes* spp ticks.[1] Lyme disease is the most common tick-borne infectious disease in North America, where it is caused only by the species of *Borrelia*, namely *B. burgdorferi* sensu stricto. In contrast, in Europe, at least 5 species of *Borrelia* (*B. burgdorferi* sensu stricto, *Borrelia afzelii*, *Borrelia garinii*, *Borrelia spielmanii*, and *Borrelia bavariensis*) can cause the human disease, leading to a wider variety of possible clinical presentations, of which the most common ones include erythema migrans, lymphocytoma cutis, and acrodermatitis chronica atrophicans.[2–6] Panniculitis is an extremely rare presentation of borreliosis, described to date only in a handful of cases.[4,11] We present a patient with Borreliosis in whom an initial biopsy revealed lobular panniculitis with a dense infiltrate containing atypically appearing cells with cytotoxic phenotype thus closely mimicking subcutaneous panniculitis-like T-cell lymphoma (SPTCL), a manifestation not previously reported to our knowledge.

CLINICAL CASE REPORT, TREATMENT, AND FOLLOW-UP

A 56-year-old man presented with a subcutaneous infiltration on the right chest wall and an erythematous lesion on the right arm that had appeared before occurrence of the subcutaneous nodule. He was otherwise healthy, and, specifically no B symptoms were reported. After the diagnosis of borreliosis (vide infra), the patient was administered 100 mg of doxycycline twice a day for 3 weeks with complete remission. The patient is alive with no evidence of the disease

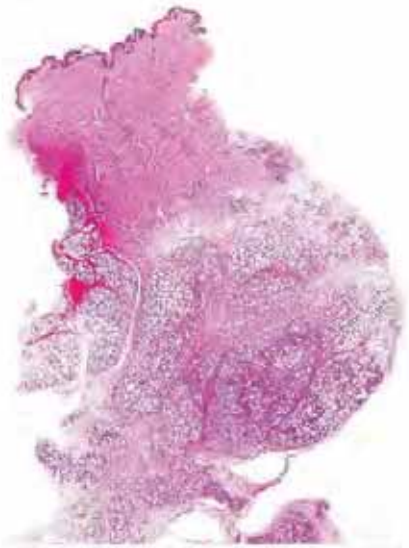

FIGURE 1. Biopsy specimen from the subcutaneous nodule. At scanning magnification, a dense subcutaneous infiltrate with predominant involvement of the lobules can be recognized.

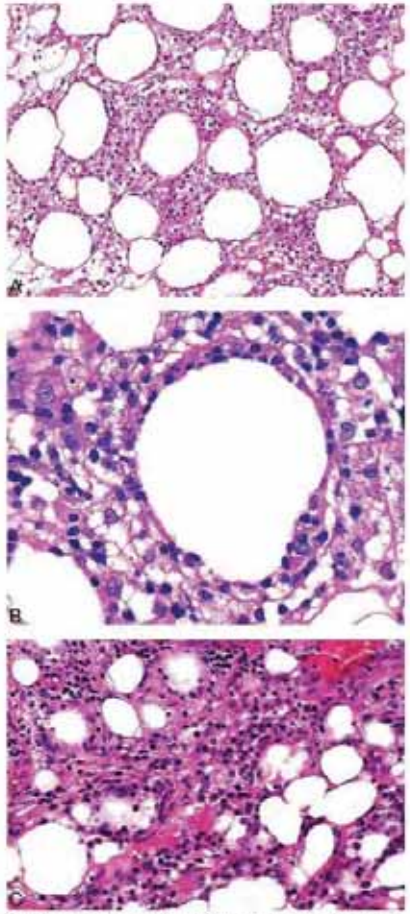

FIGURE 2. Biopsy specimen from the subcutaneous nodule. Lymphocytes are small, with occasional medium-sized cells showing mild nuclear pleomorphism. Note rimming of lymphocytes around adipocytes (A, B). Admixture of plasma cells in the infiltrate can be seen (C).

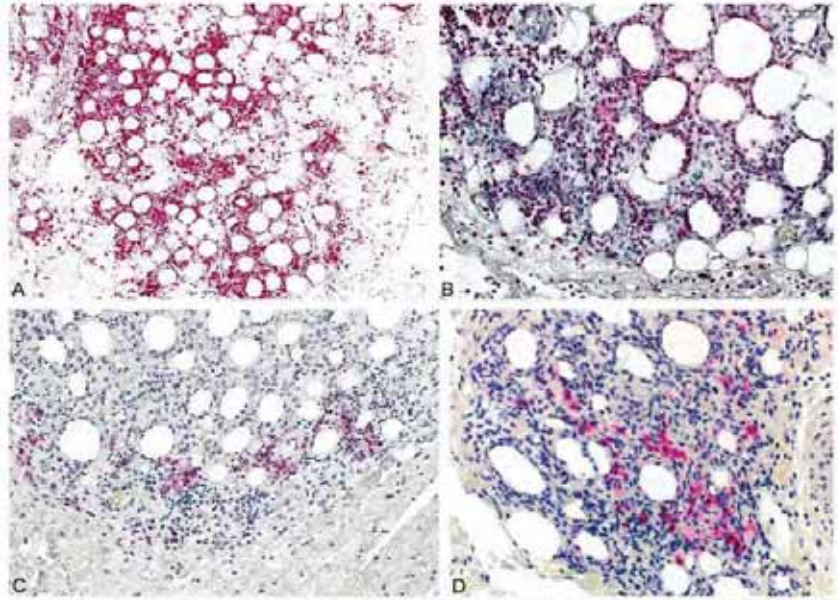

FIGURE 3. Biopsy specimen from the subcutaneous nodule. Immunohistochemical staining for CD8 (A), beta F1 (B), CD138 (C), and CD123 (D).

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The authors have no funding or conflicts of interests to declare.

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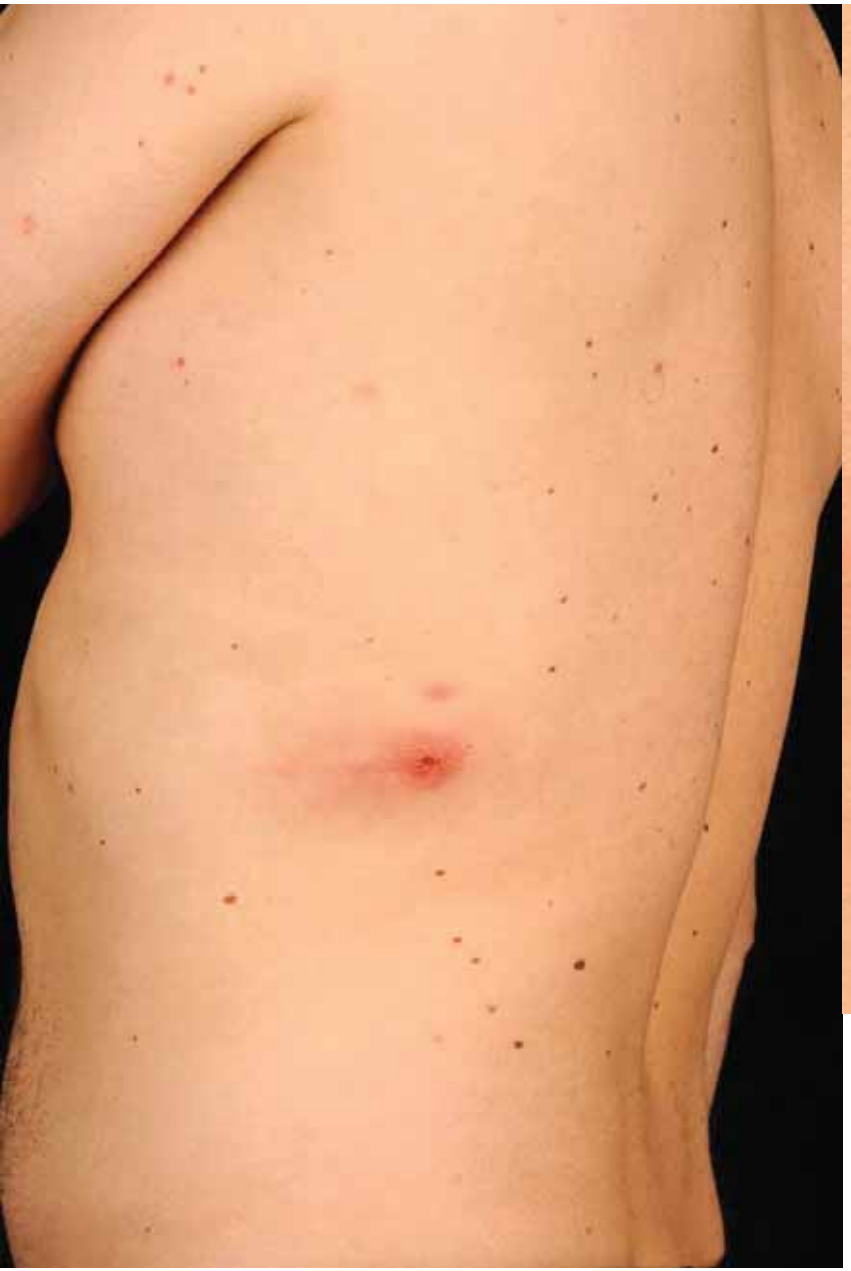
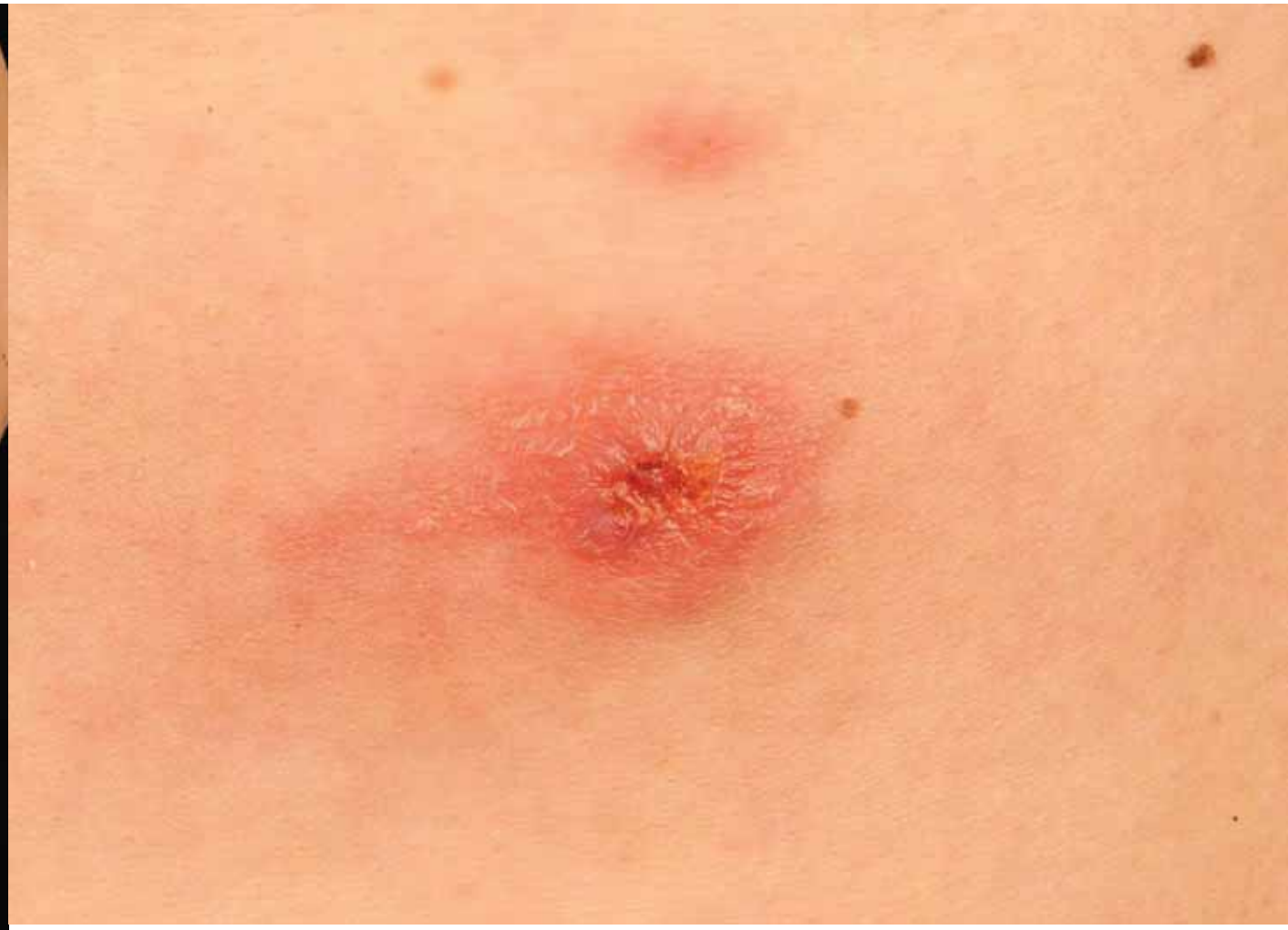
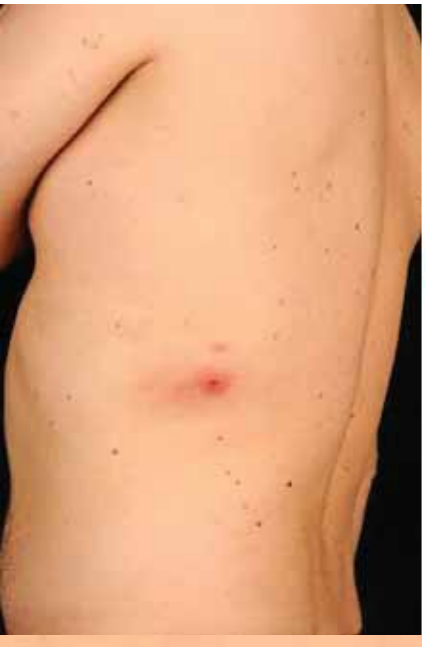


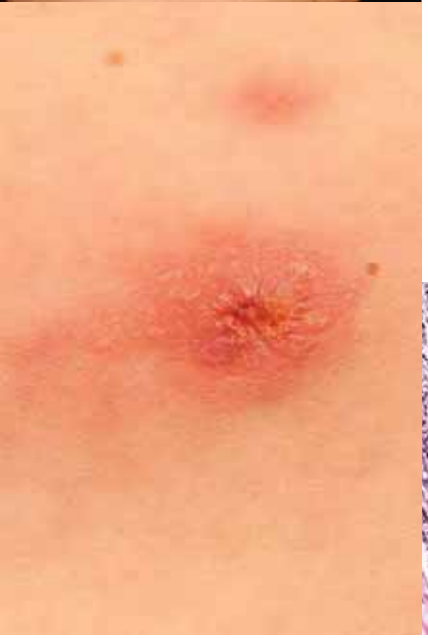


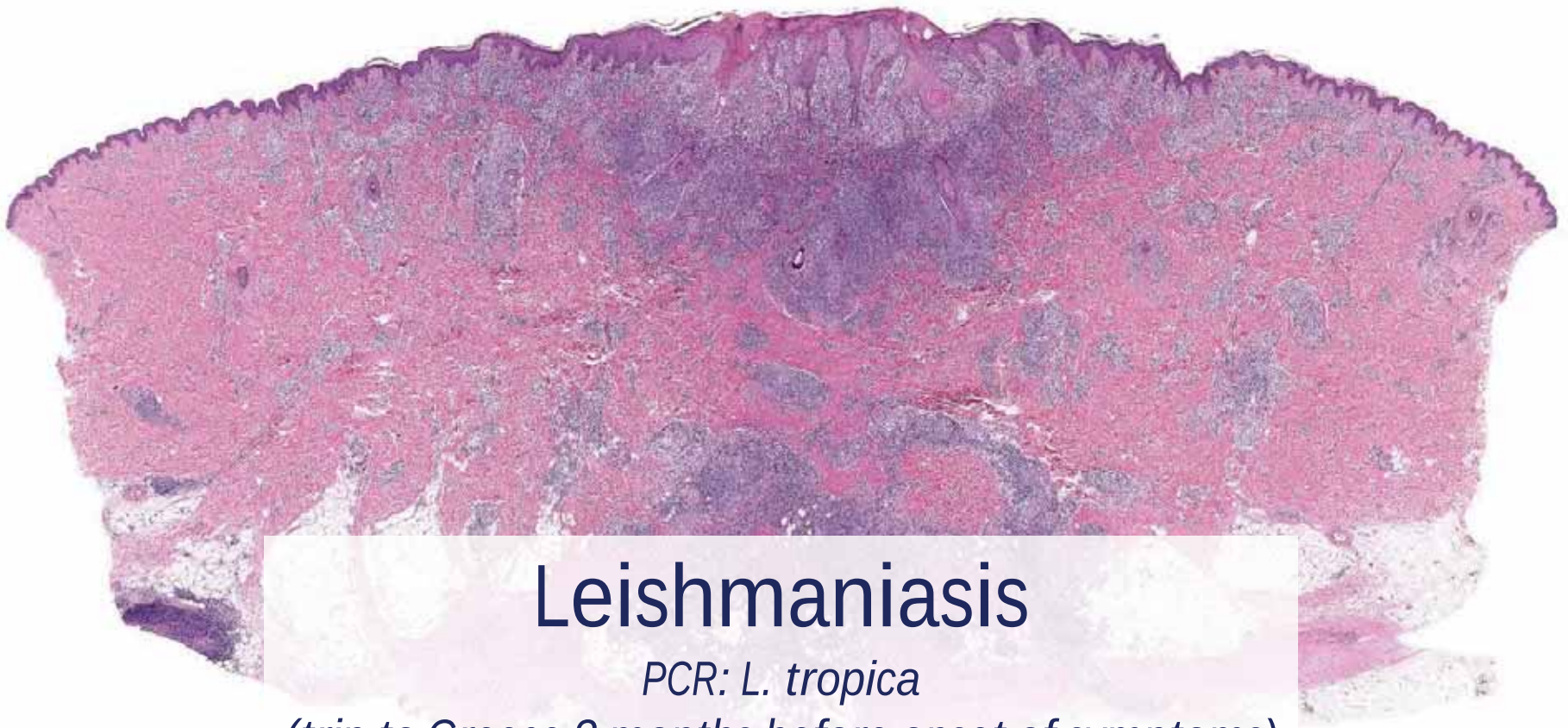
M, 37

According to the patient solitary skin lesion on the trunk for 3 months. A previous punch biopsy was reported as pseudolymphoma.

The lesion is excised surgically.



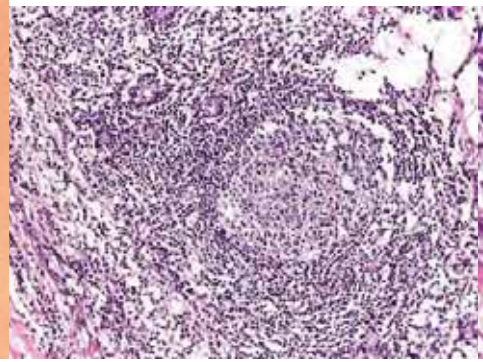


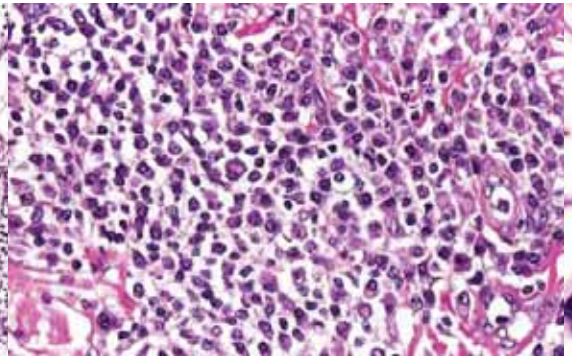


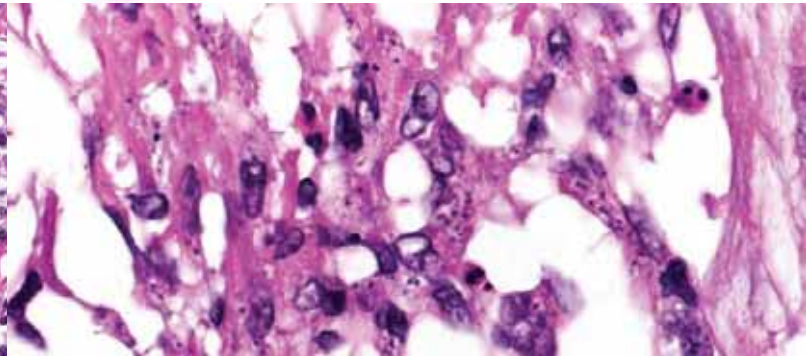
Leishmaniasis

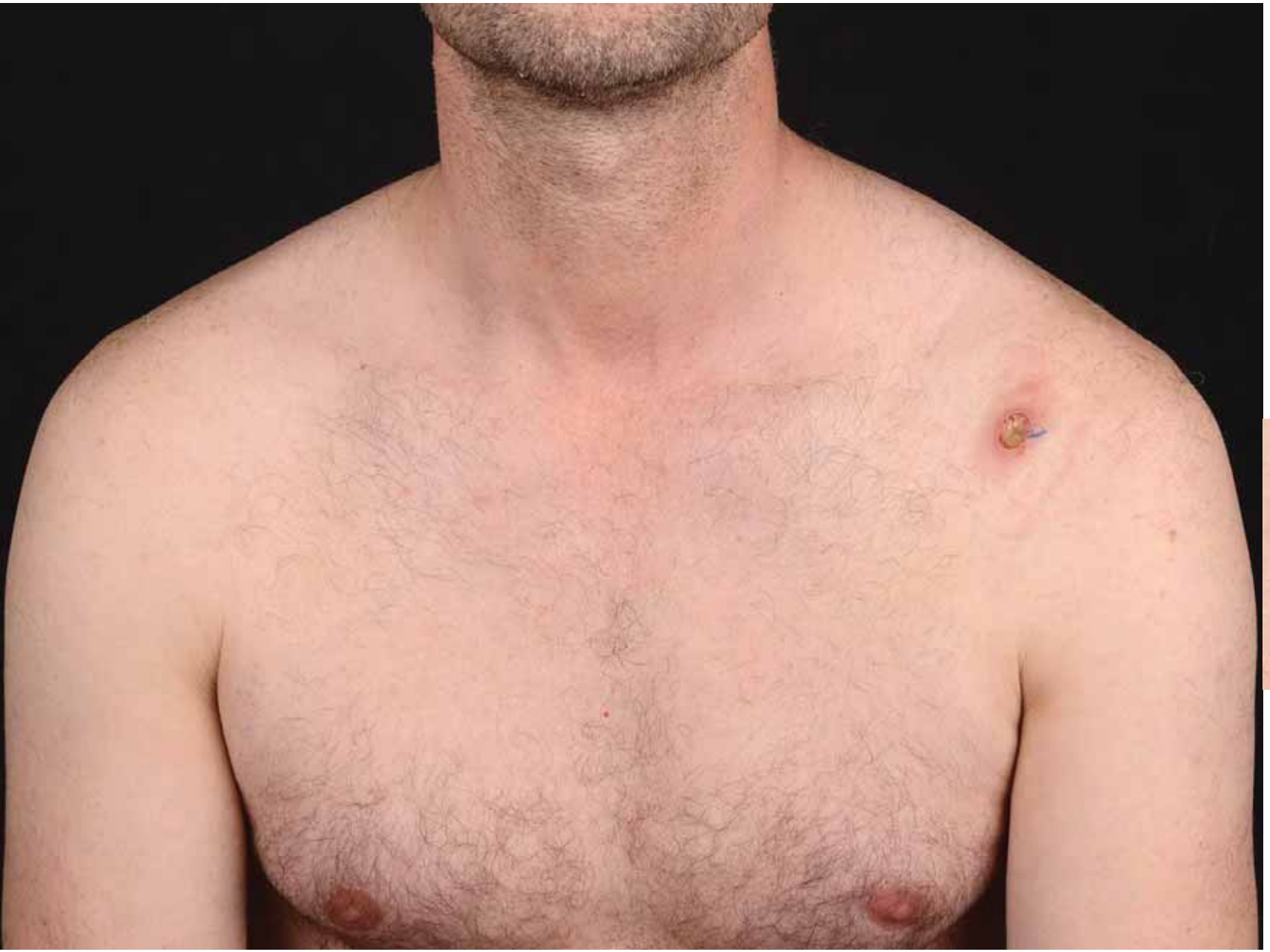
PCR: L. tropica

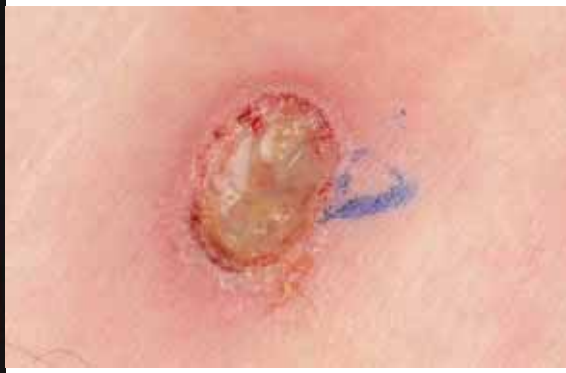
(trip to Greece 3 months before onset of symptoms)







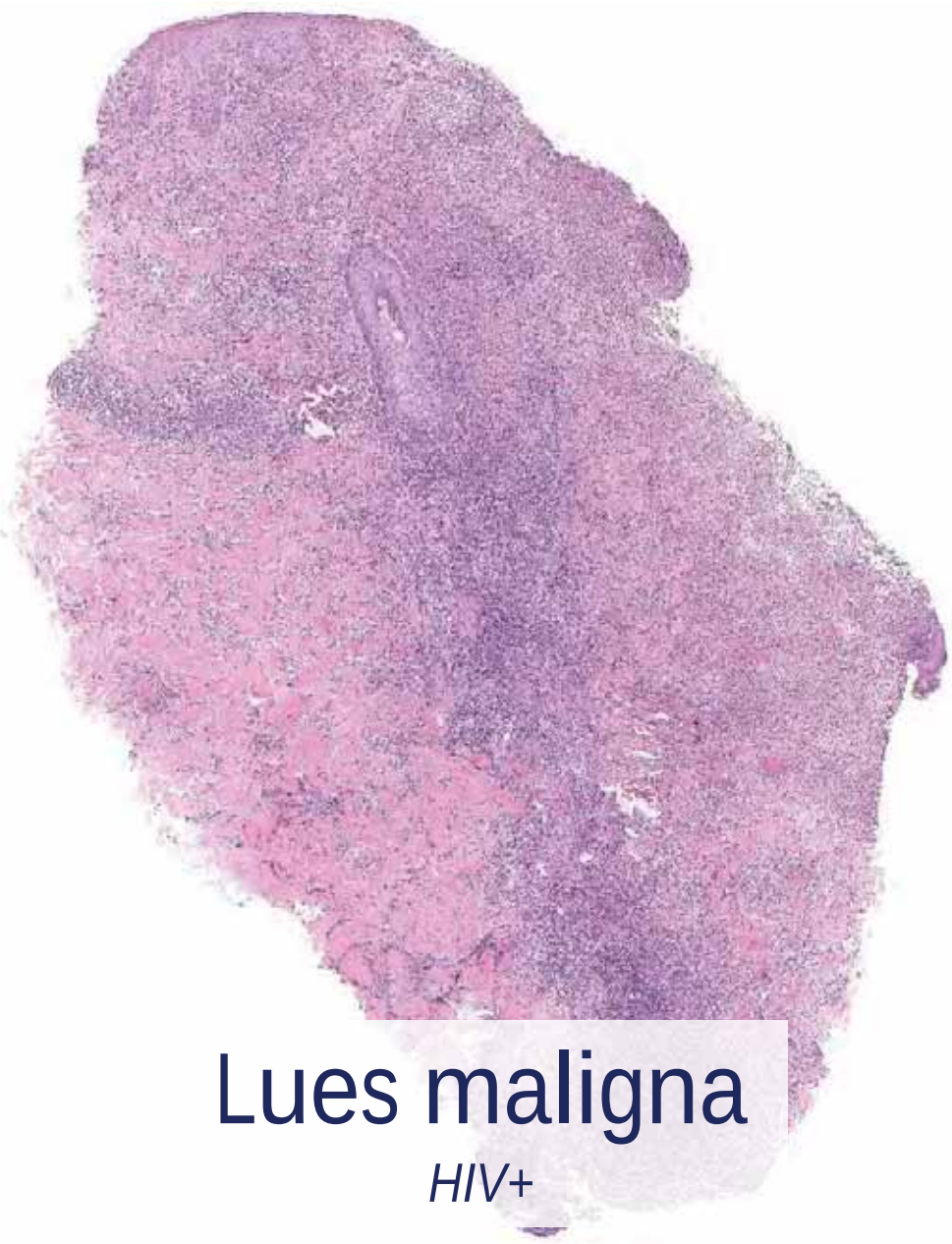




M, 44

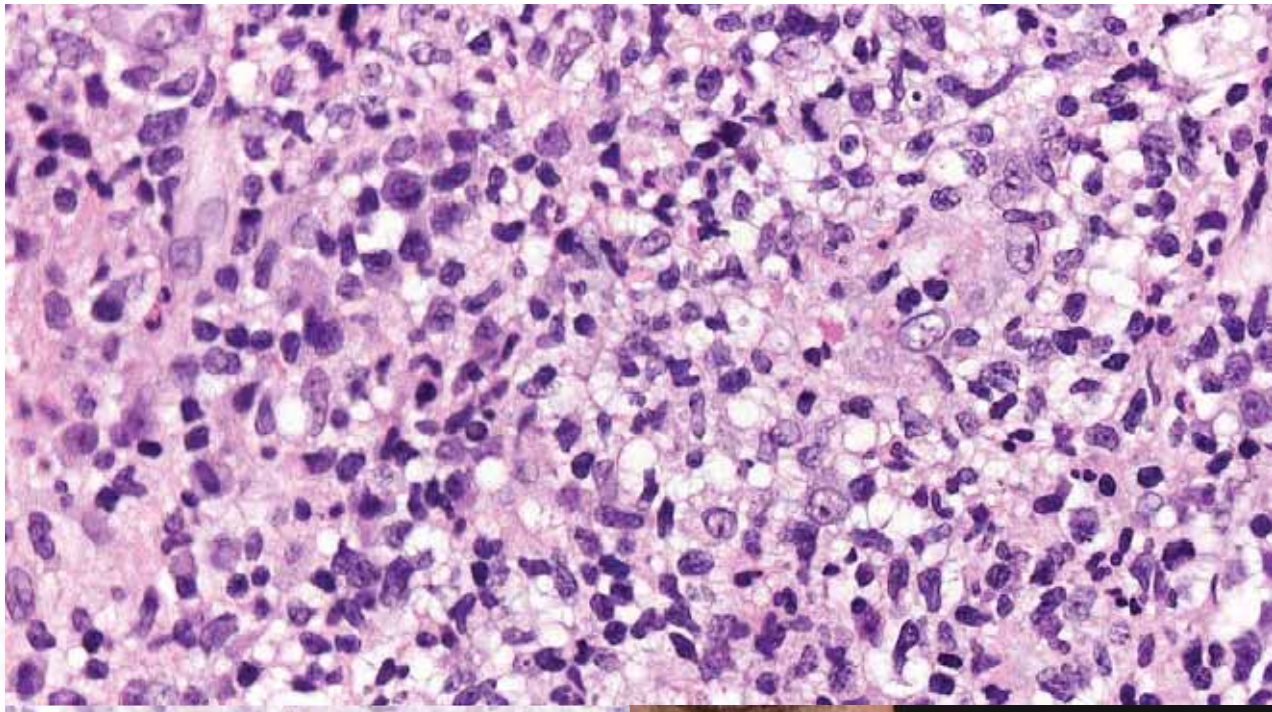
According to the patient two ulcerated nodules on the left temple and left shoulder for 2 months; malaise.

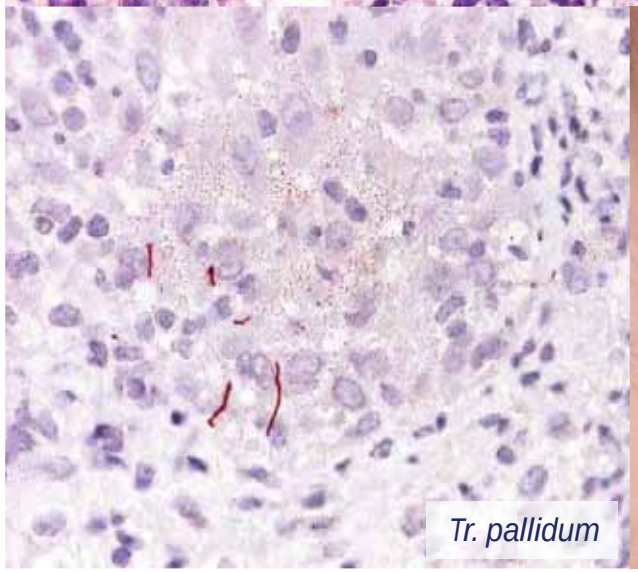
A biopsy is taken.



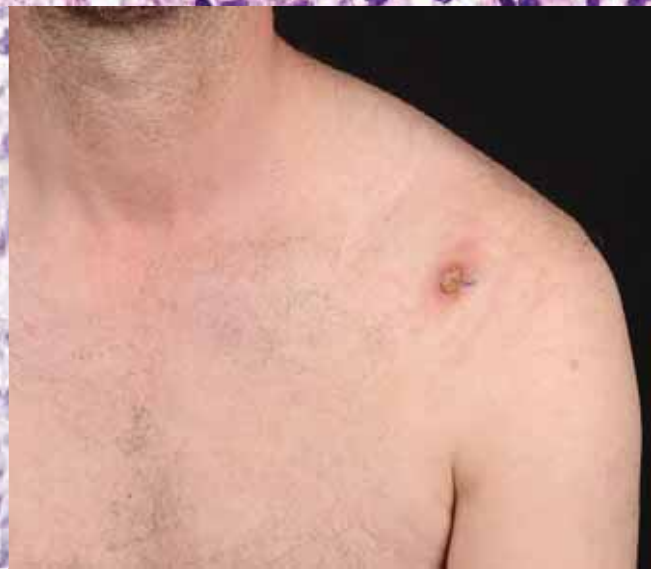
Lues maligna

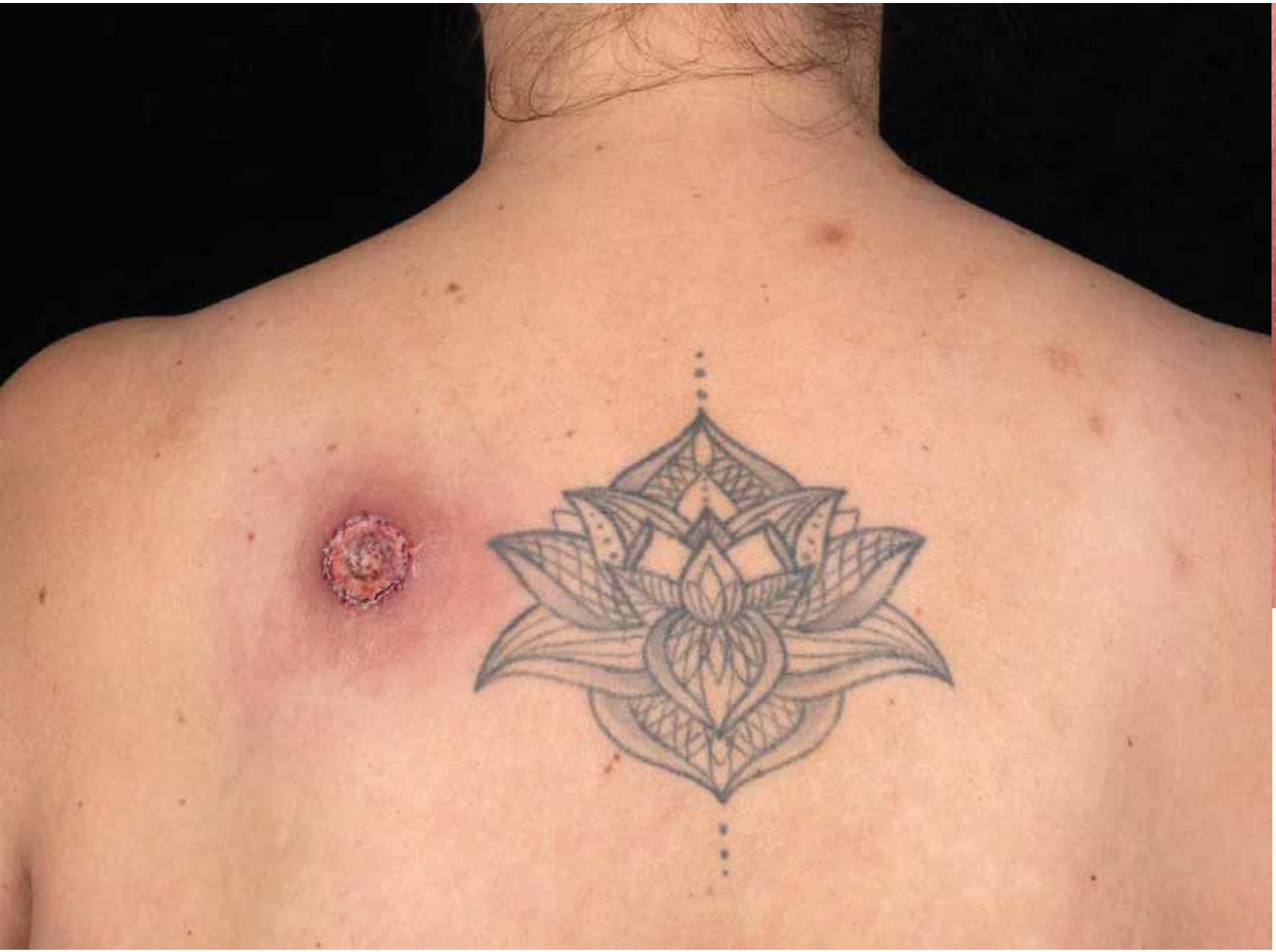
HIV+

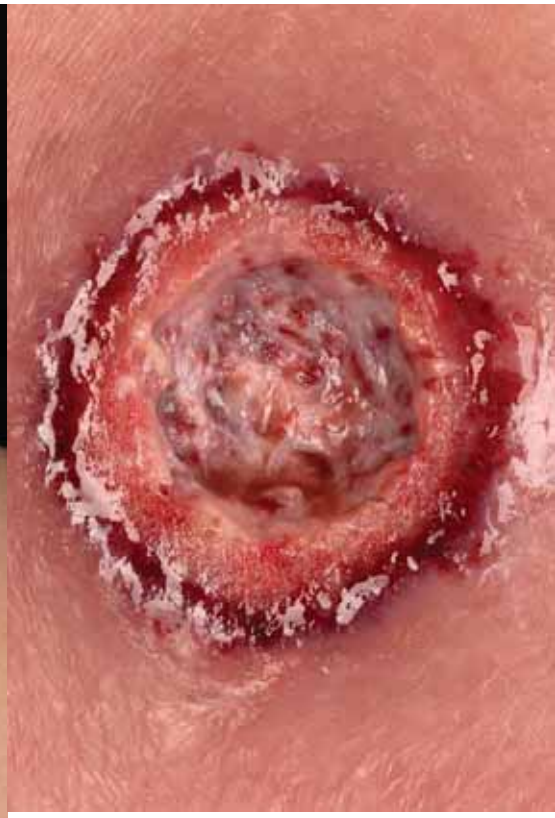




Tr. pallidum



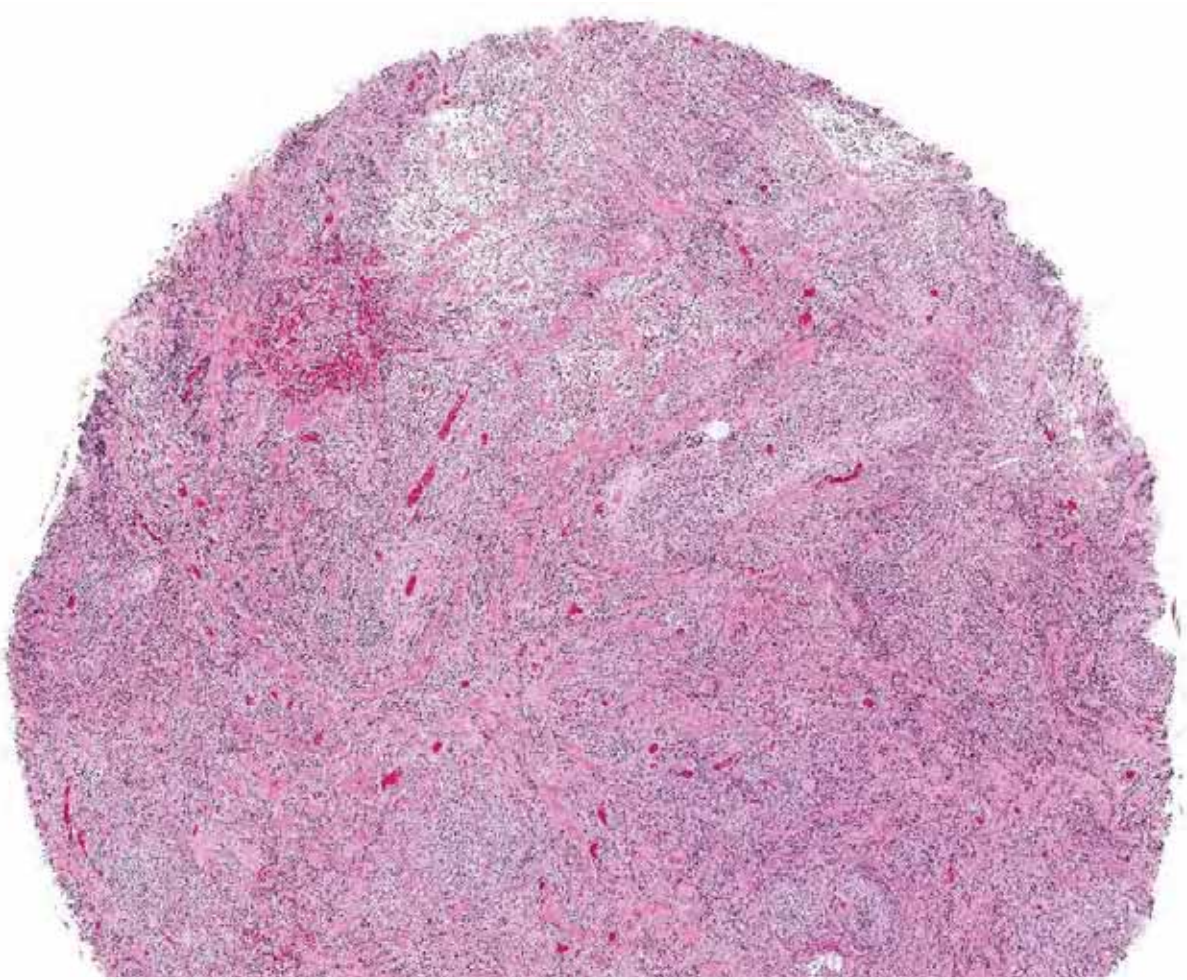




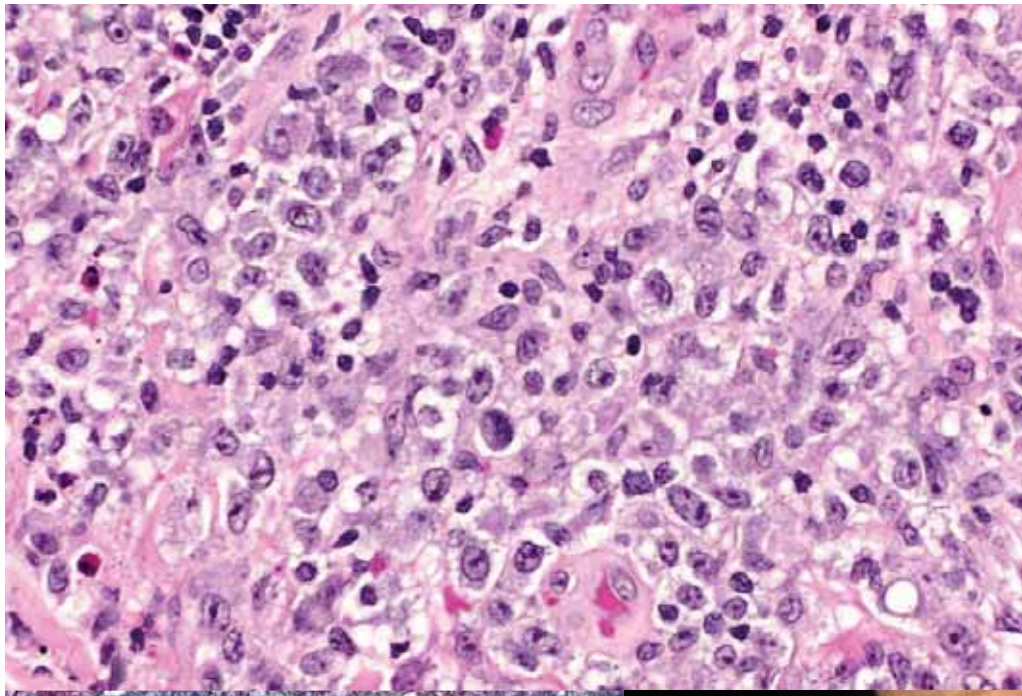
F, 47

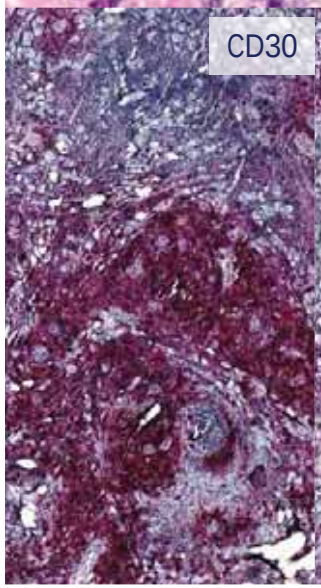
According to the patient ulcerated lesion on the back for 3 months; no improvement with systemic antibiotics.

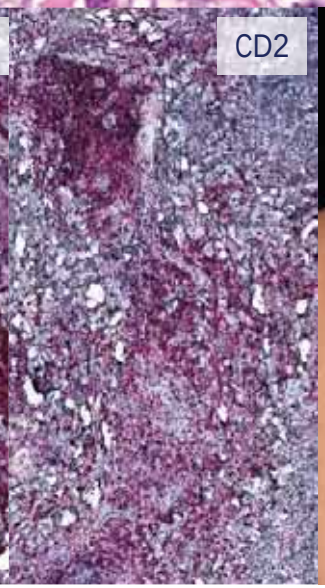
A biopsy is taken.

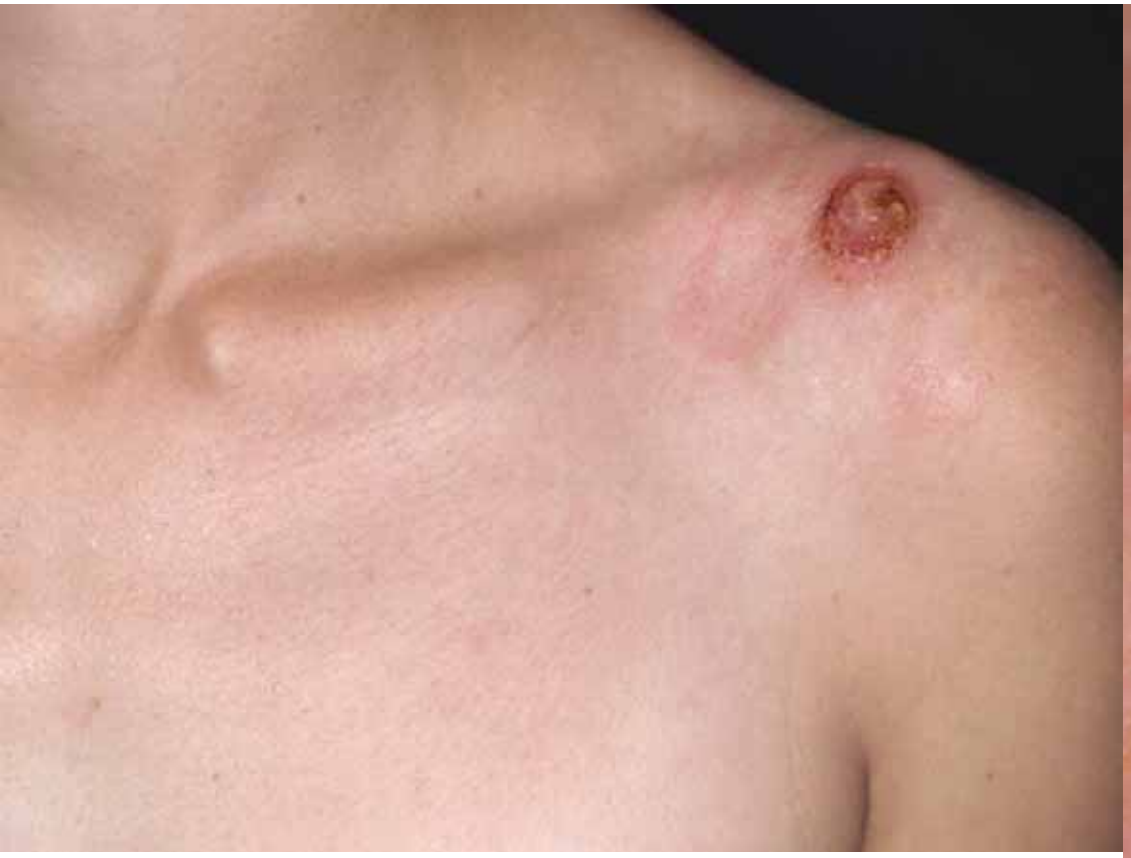


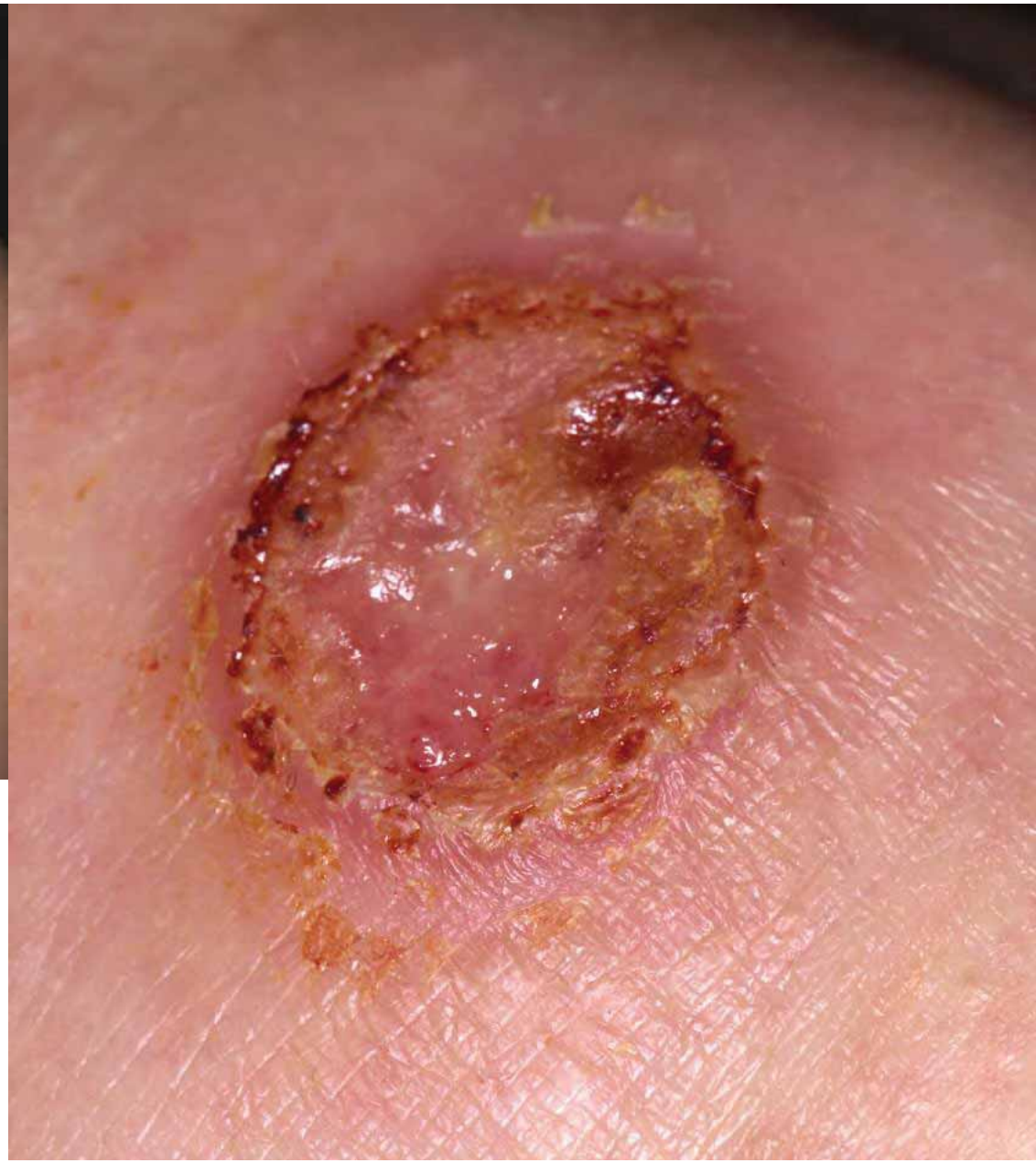
Cutaneous anaplastic large cell lymphoma











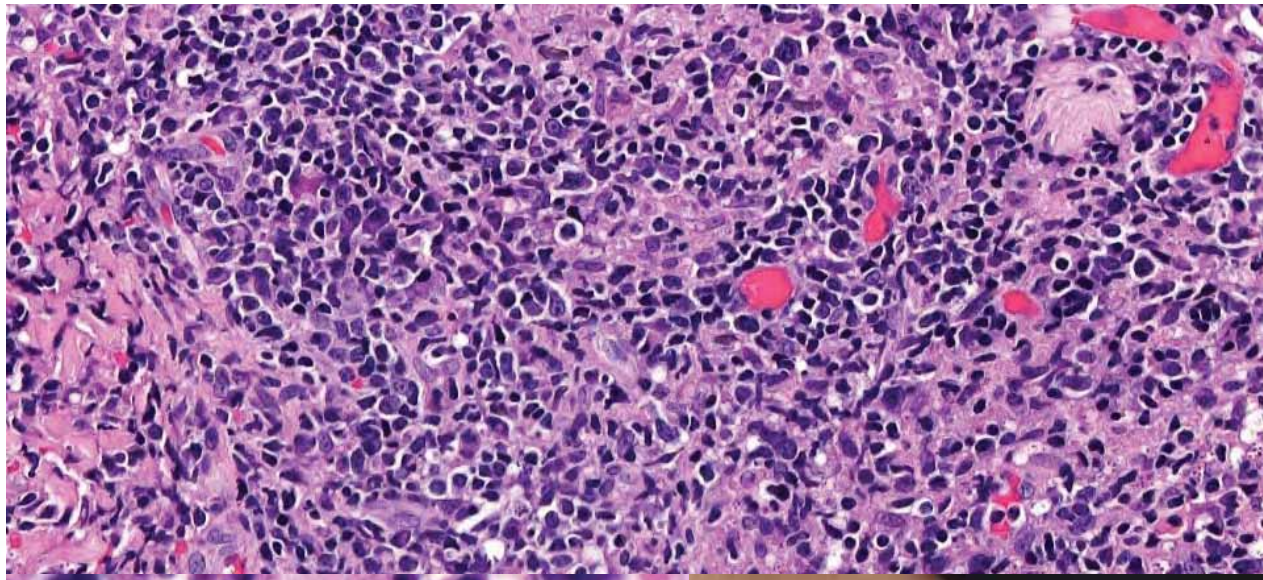
F, 24

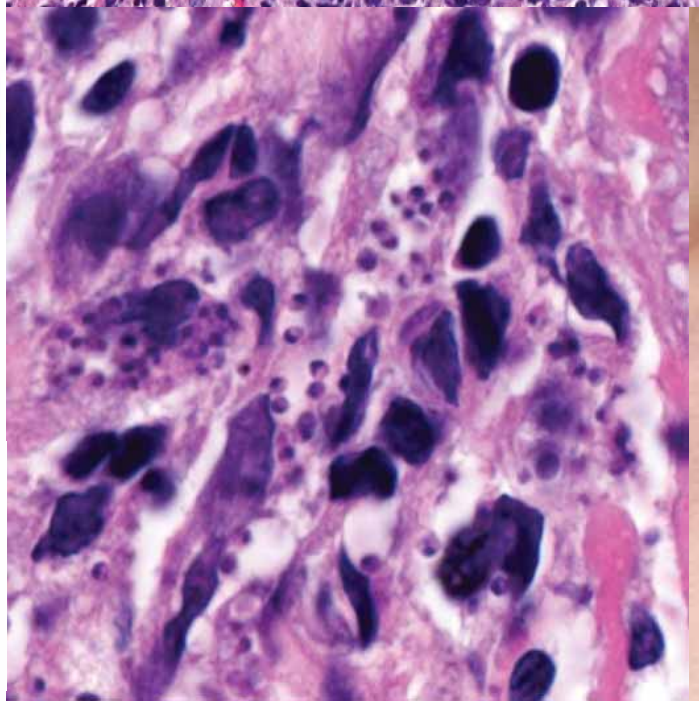
According to the patient ulcerated lesion on the left shoulder for the last 5 weeks. No improvement with systemic antibiotics. Trip to Venezuela 3 months previously.

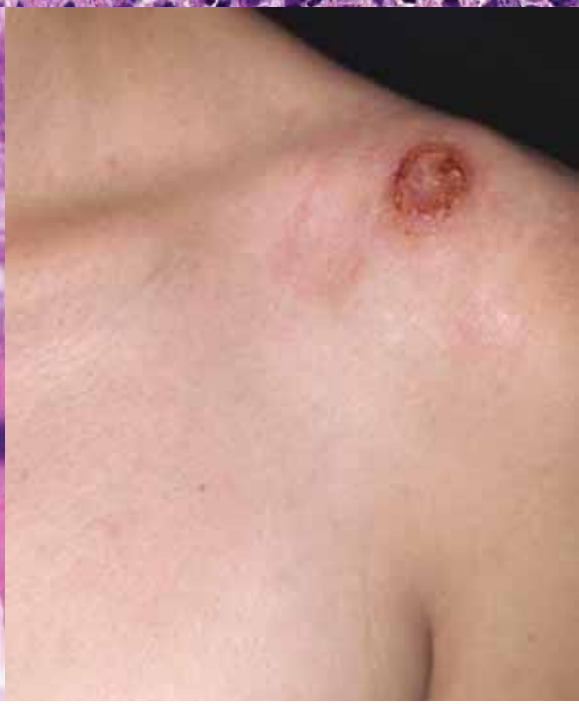
A biopsy is taken.

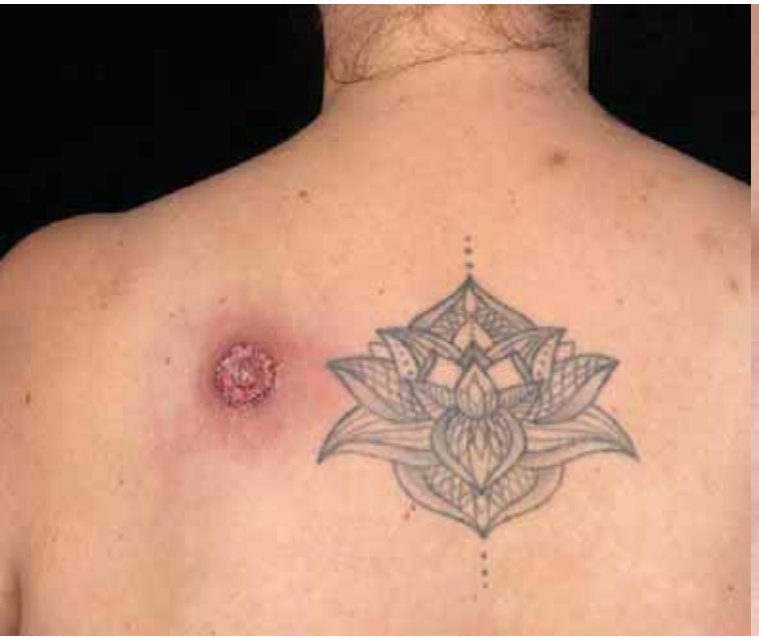
Leishmaniasis

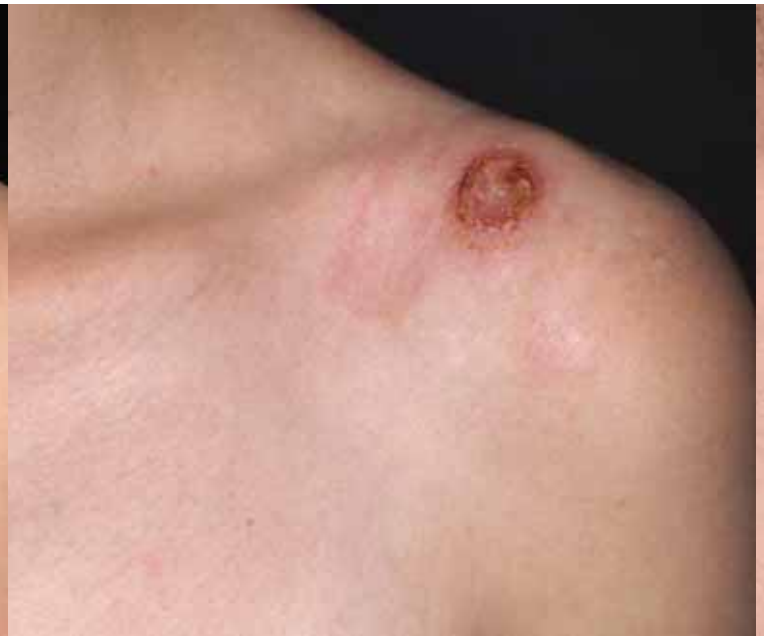
(new world leishmaniasis, not responding to topical treatment and requiring systemic management)

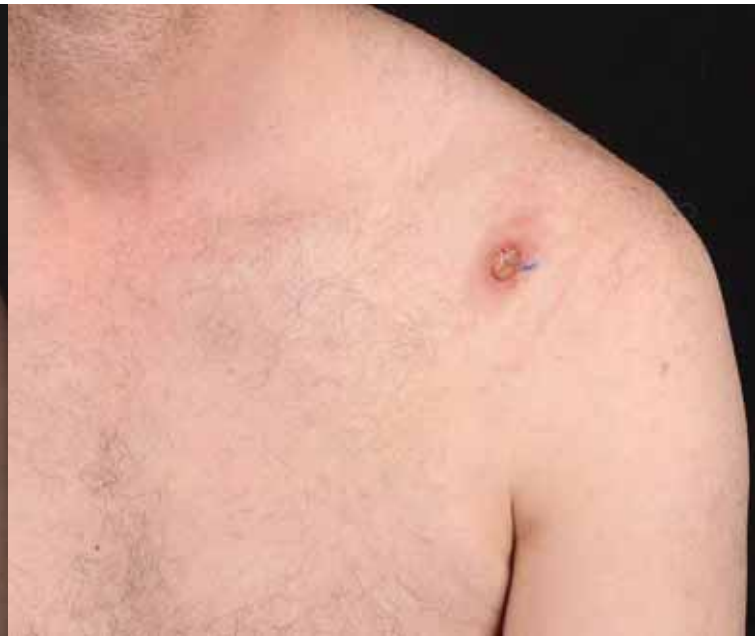




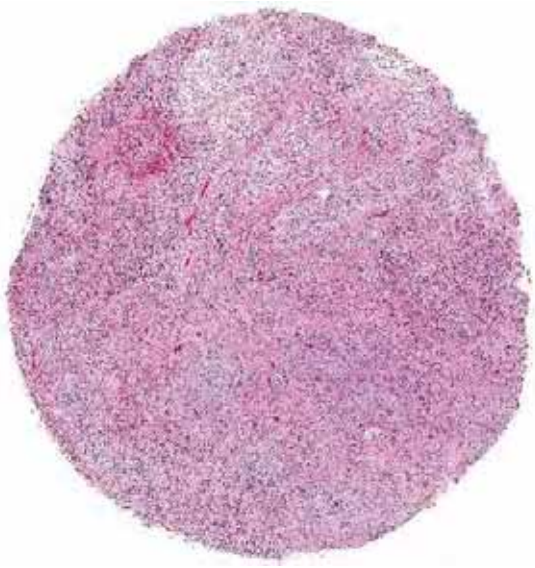


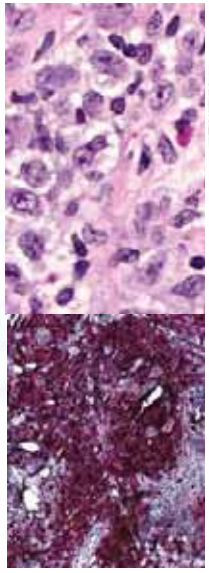




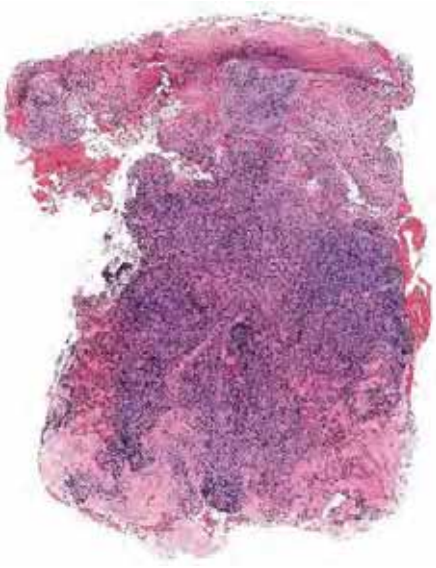


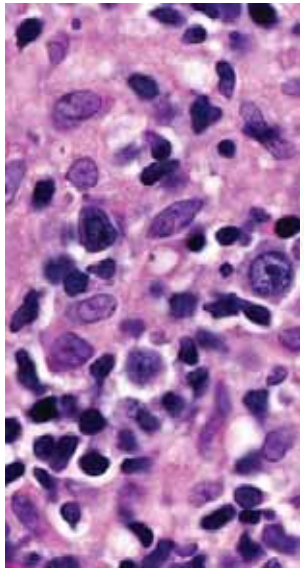
Anaplastic large cell lymphoma



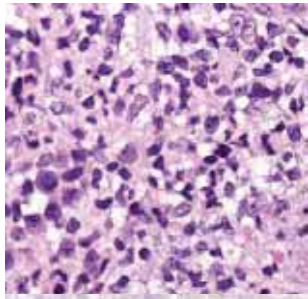


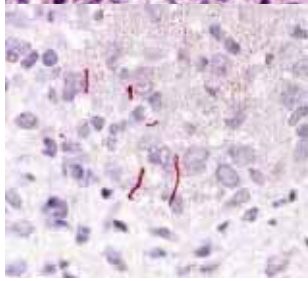
Leishmaniasis

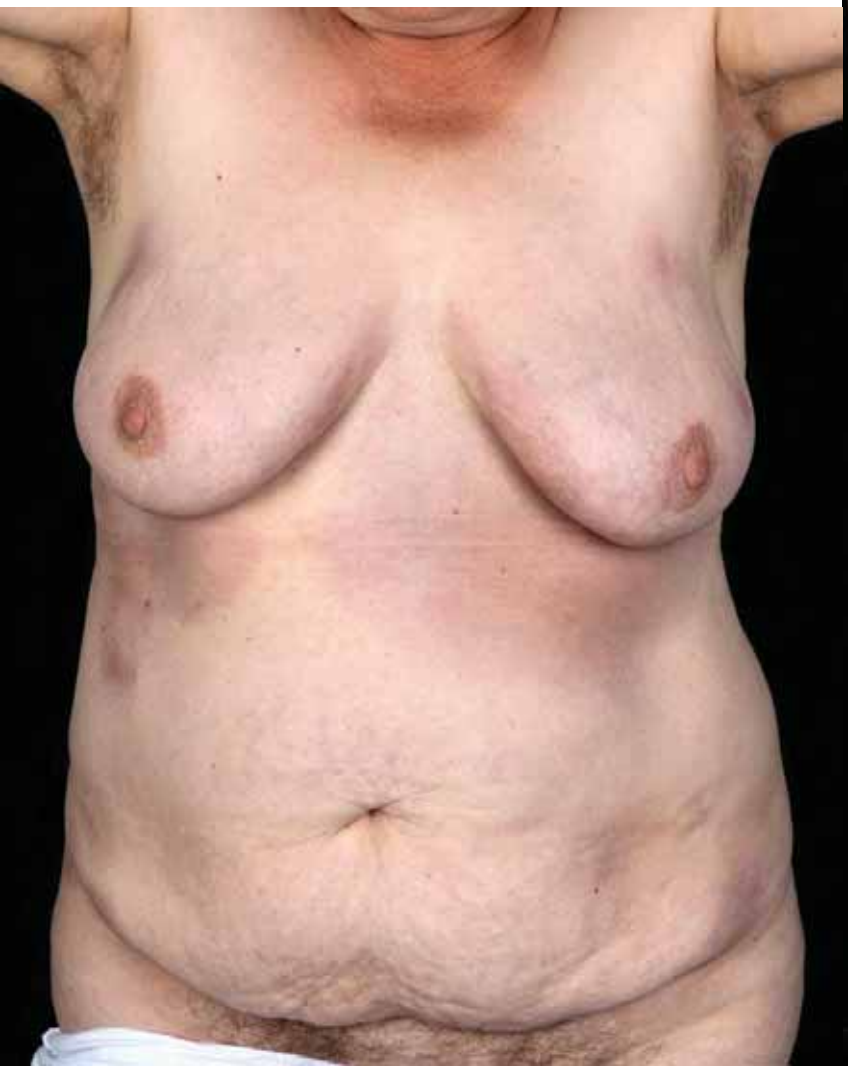


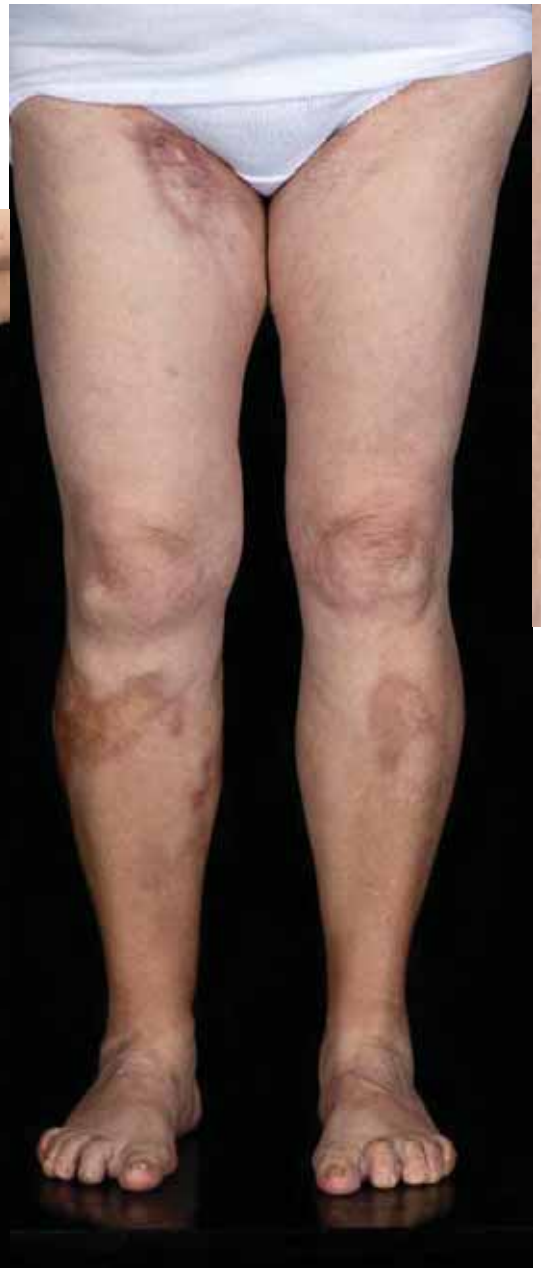


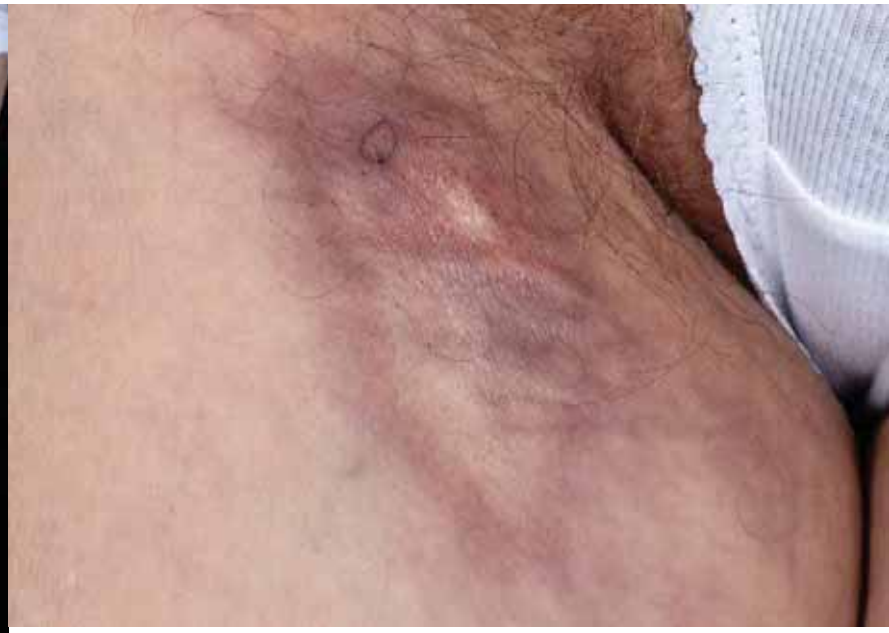
Lues maligna









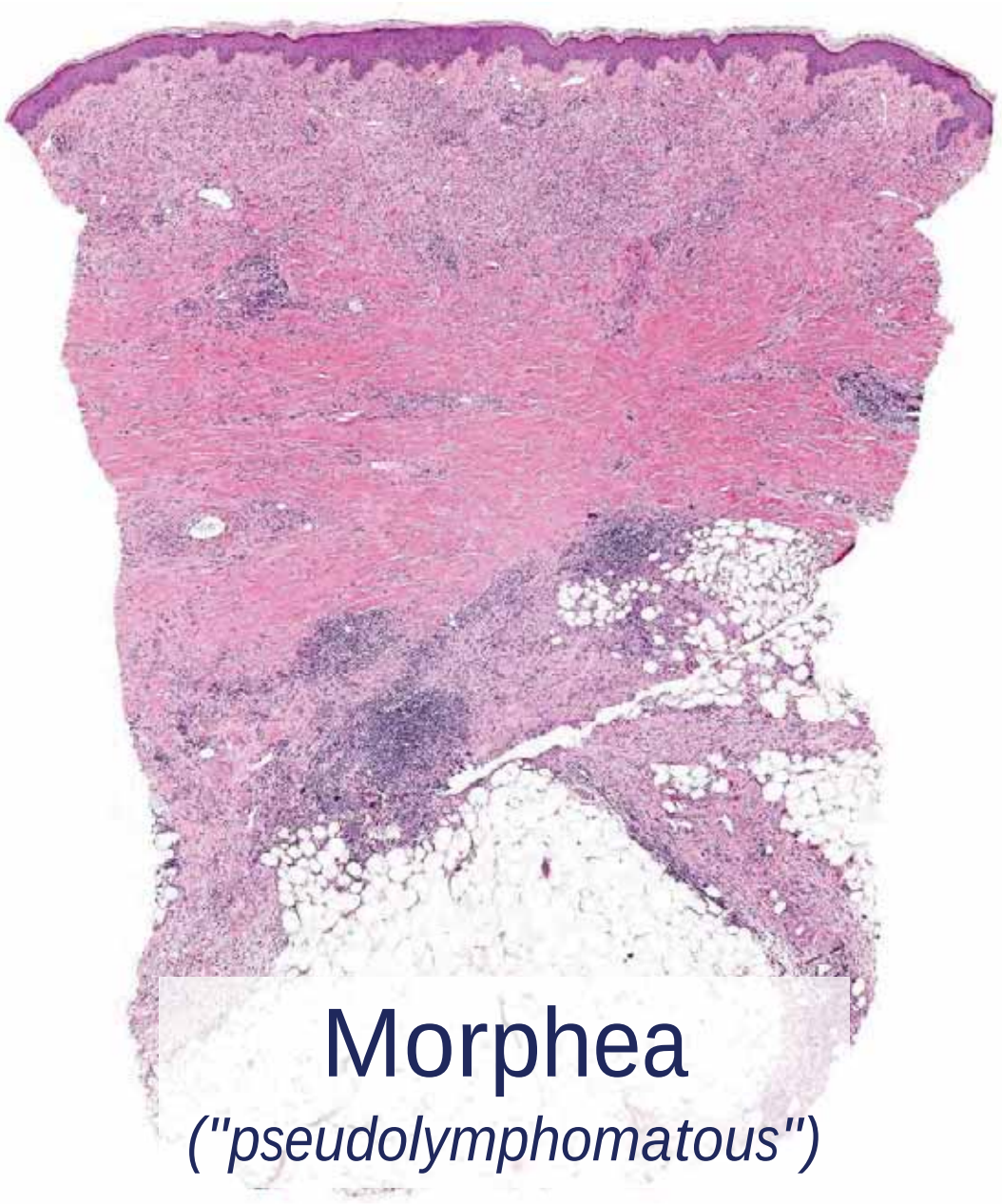


F, 64

History of morphea for the last 9 years, managed several times with UV irradiation.

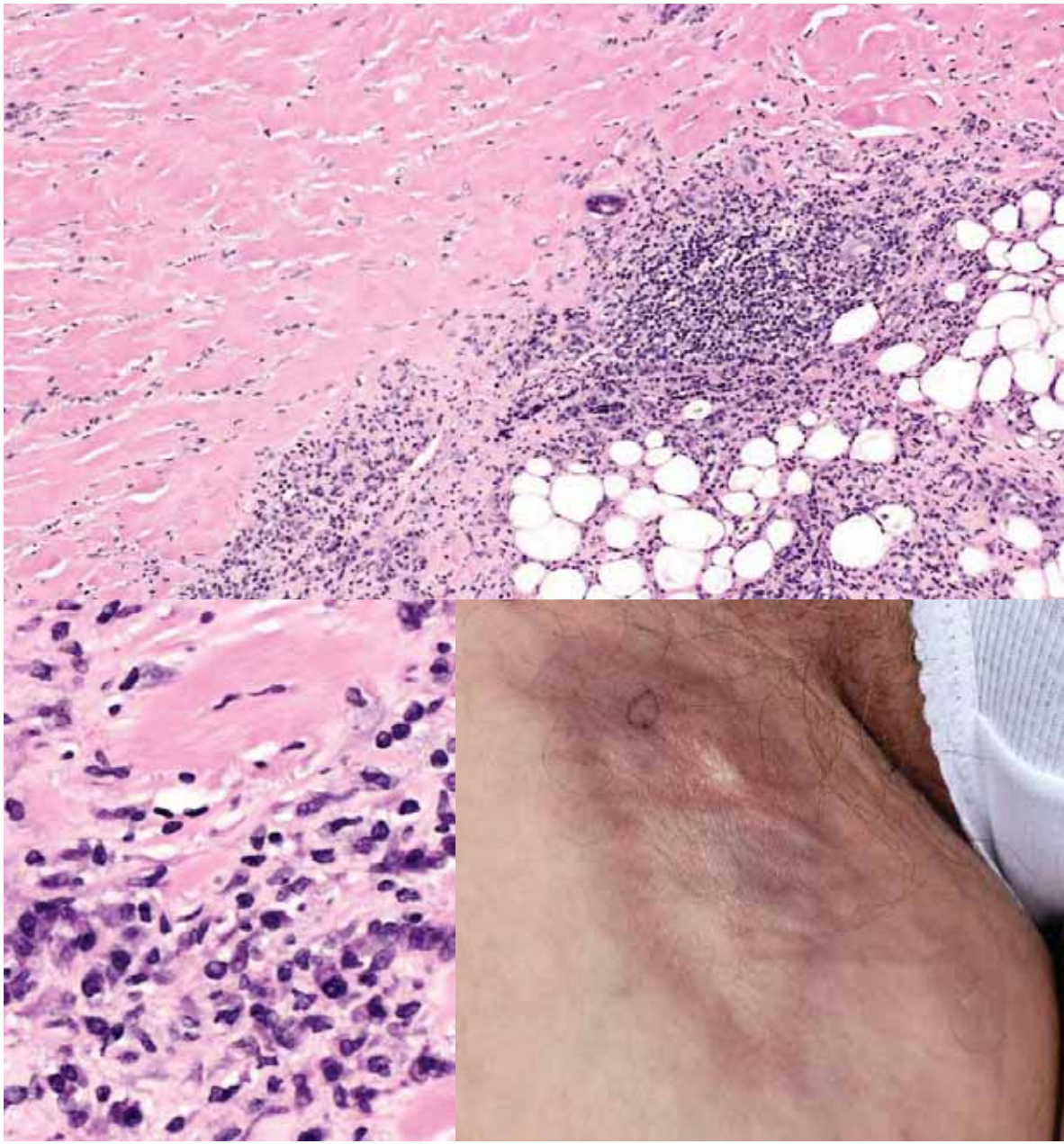
According to the patient new lesion on the proximal right thigh / groin for the last 5 months; an external biopsy (not available for review) has been reported as necrobiosis lipoidica.

A biopsy is taken.



Morphea

("pseudolymphomatous")

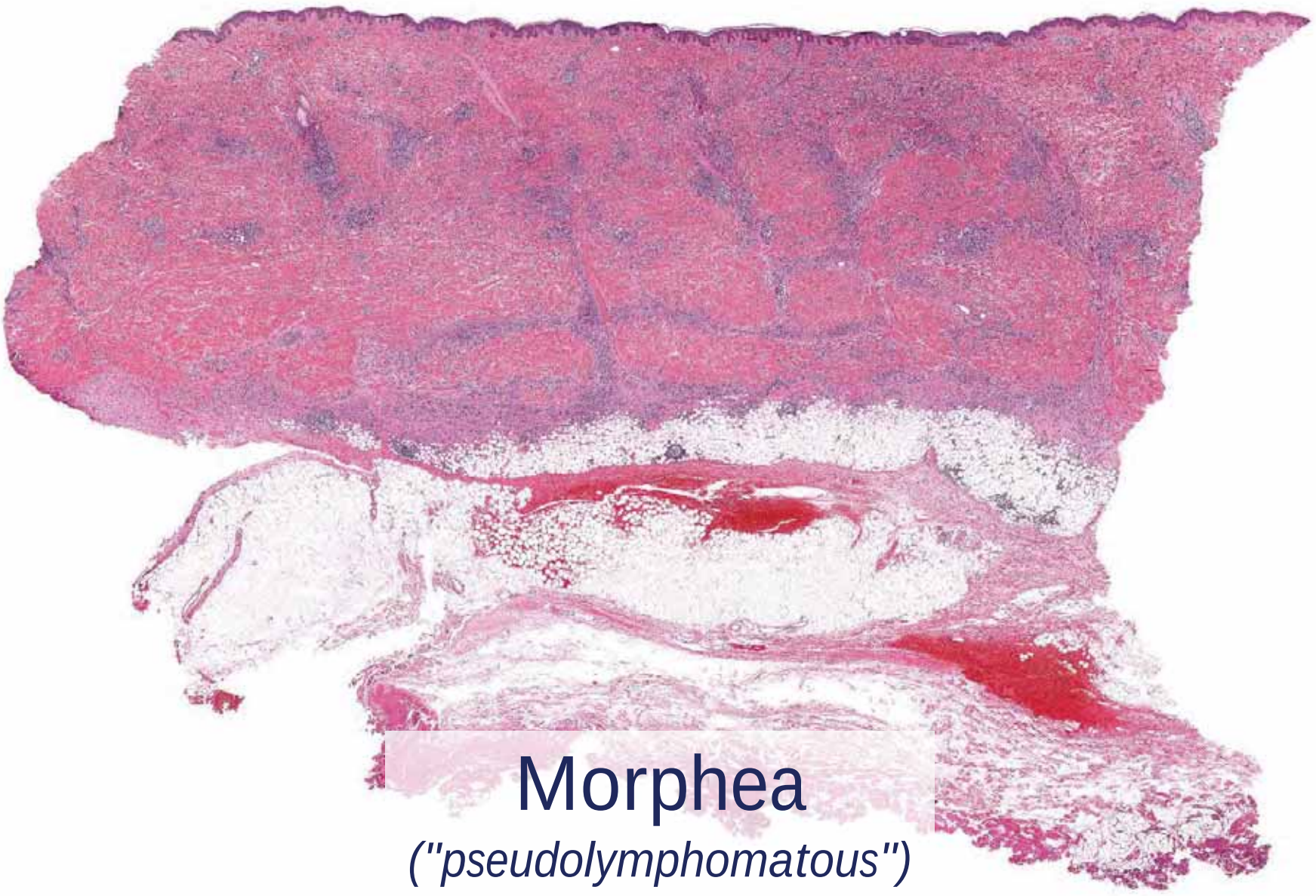


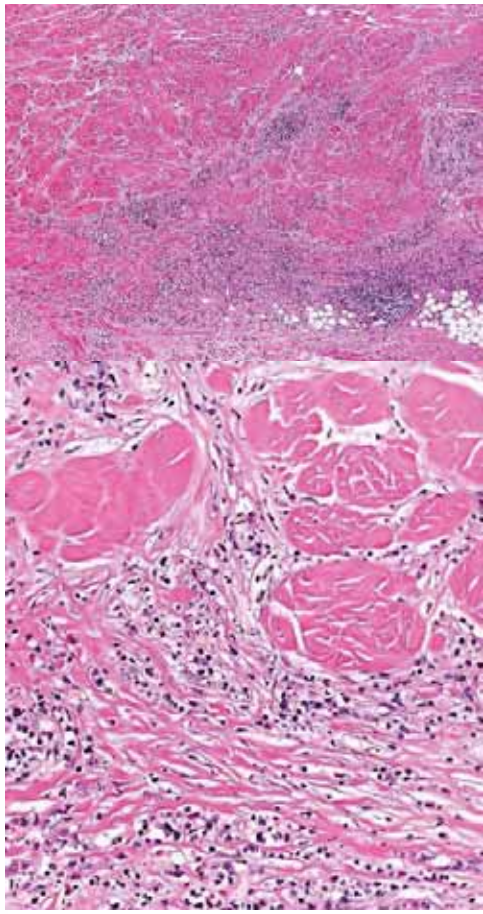
M, 33

According to the patient on the right part of the back rapid confluence and growth of "papules", to form the actual lesion, which is indurated and asymptomatic.

A biopsy is taken.

(Consultation Dr. De Rosa, Napoli, Italy)





Morphea

("pseudolymphomatous")

CASE REPORT

Cutaneous lymphoid hyperplasia arising in pre-existing morphea plaques treated with methotrexate

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Key words: cutaneous lymphoid hyperplasia; localized scleroderma; lymphoma; methotrexate; morphea; pseudolymphoma.

INTRODUCTION

Morphea, also known as *localized scleroderma*, is characterized clinically by indurated skin and fibrosis of the dermis or subcutaneous tissue. Its etiology is unknown.[1] Based on clinical presentation, morphea is classified into plaque, generalized, bullous, linear, and deep morphea types. Several types of morphea may be present in the same patient.[2] Cutaneous lymphoid hyperplasia (CLH) is defined as cutaneous B-cell infiltrates that resemble B-cell lymphoma clinically and histologically.[3] Herein we report a case of CLH arising in pre-existing morphea plaques treated with methotrexate.

CASE REPORT

A 69-year-old white woman presented with multiple indurated skin lesions over the trunk for 6 months. Medical history was unremarkable, notably negative for Raynaud phenomenon or systemic symptoms. Physical examination found multiple large indurated symmetrical plaques, with violet-colored borders, on the chest, flanks, and back (Fig. 1).

Laboratory investigations were all within the normal range, including autoantibody profile (antinuclear antibodies, anti–ds-DNA, anti–sel-70, anticentromere, antihistone, antiphospholipid antibodies, rheumatoid factor, antithyroid antibodies). A skin biopsy found dermal thickening by dense collagen bundles with focal and moderate interstitial lymphocytic infiltrate. This histologic aspect was compatible with morphea, and the diagnosis of generalized morphea was established.

The lesions were deemed active because of their increasing numbers and peripheral "lilac rings." The patient was treated with 30 sessions of psoralen ultraviolet A (PUVA) photochemotherapy without improvement. During this time, the patient had multiple painful nodules over morphea plaques. There were no clinical signs of infection, and the patient denied trauma, scratching, or any new medications. Clinical examination found multiple infiltrated erythematous nodules over the chest and the scapular regions (Fig. 2). There were no palpable lymph nodes or enlarged liver or spleen.

A skin biopsy of the nodular lesion showed thickening and hyalinization of the reticular dermis, consistent with previously diagnosed underlying morphea, associated with dermal and subdermal dense lymphocytic infiltrates with the formation of several lymphoid follicles with germinal centers, containing tingible body macrophages. The biopsy also found a diffuse infiltrate of plasma cells and eosinophils (Figs. 3, *A* and 4, *A*). There was no cytonuclear atypia.

Abbreviations used:

CLH: cutaneous lymphoid hyperplasia
CTD: connective tissue diseases

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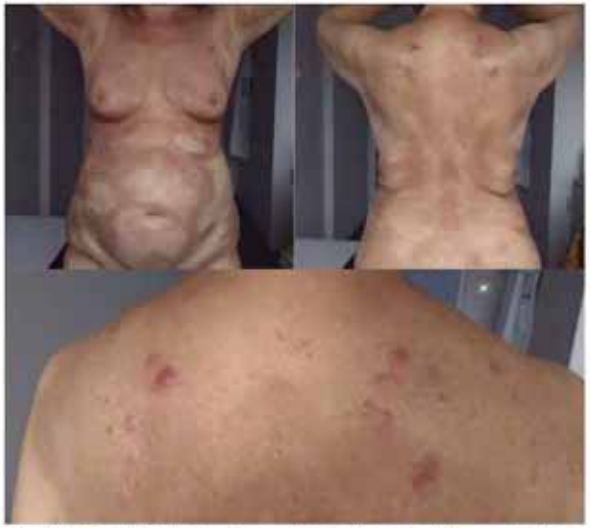


Fig 2. Multiple infiltrated erythematous nodules over the chest and the scapular regions.

Biopsy-proven morphea. Nodular lesions arising after 30 cycles of PUVA. Negative serology for *Borrelia*; no response to doxycycline 200 mg/d for 3 weeks. Apparent regression of the nodules after 6 months of low-dose MTX (25 mg/wk).

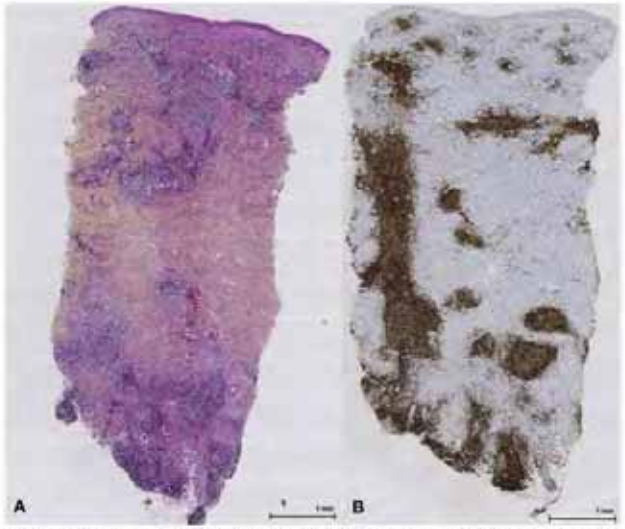


Fig 3. **A**, Skin biopsy shows thickening and hyalinization of the reticular dermis associated with dermal and subdermal dense lymphocytic infiltrates with the formation of several lymphoid follicles/germinal centers. **B**, Immunohistochemistry shows most of the infiltrate represented by $CD20^+$ B cells. ×10. (**A**, Hematoxylin phloxine saffron stain, original magnifications: **A** and **B**, ×10.)

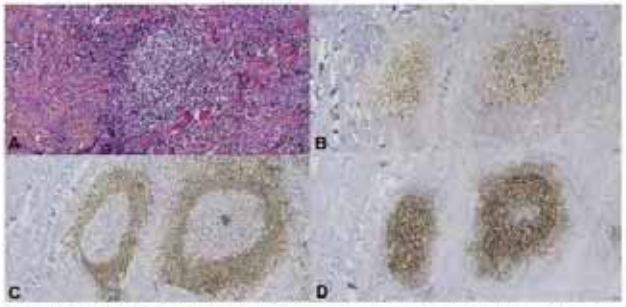
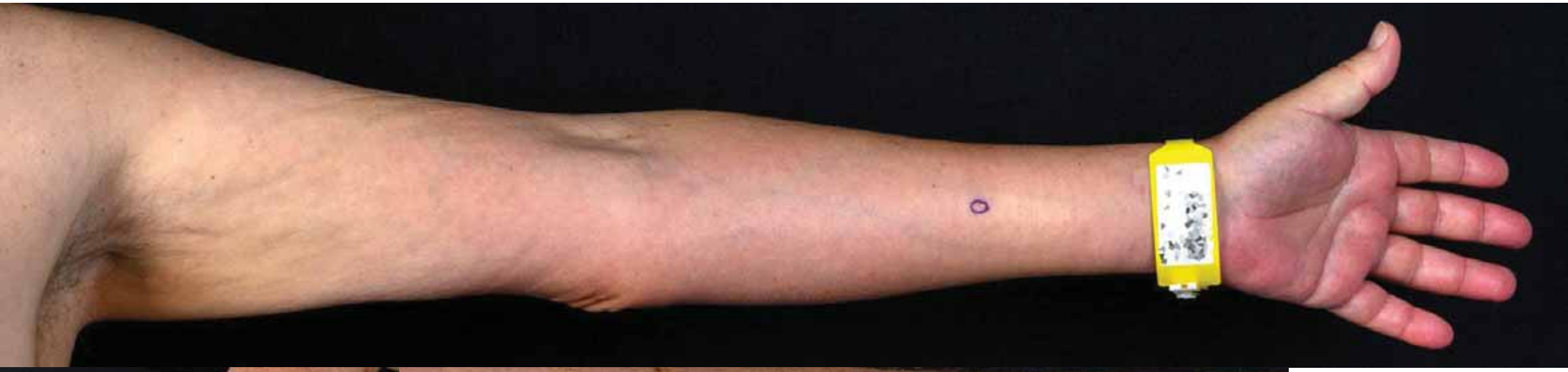
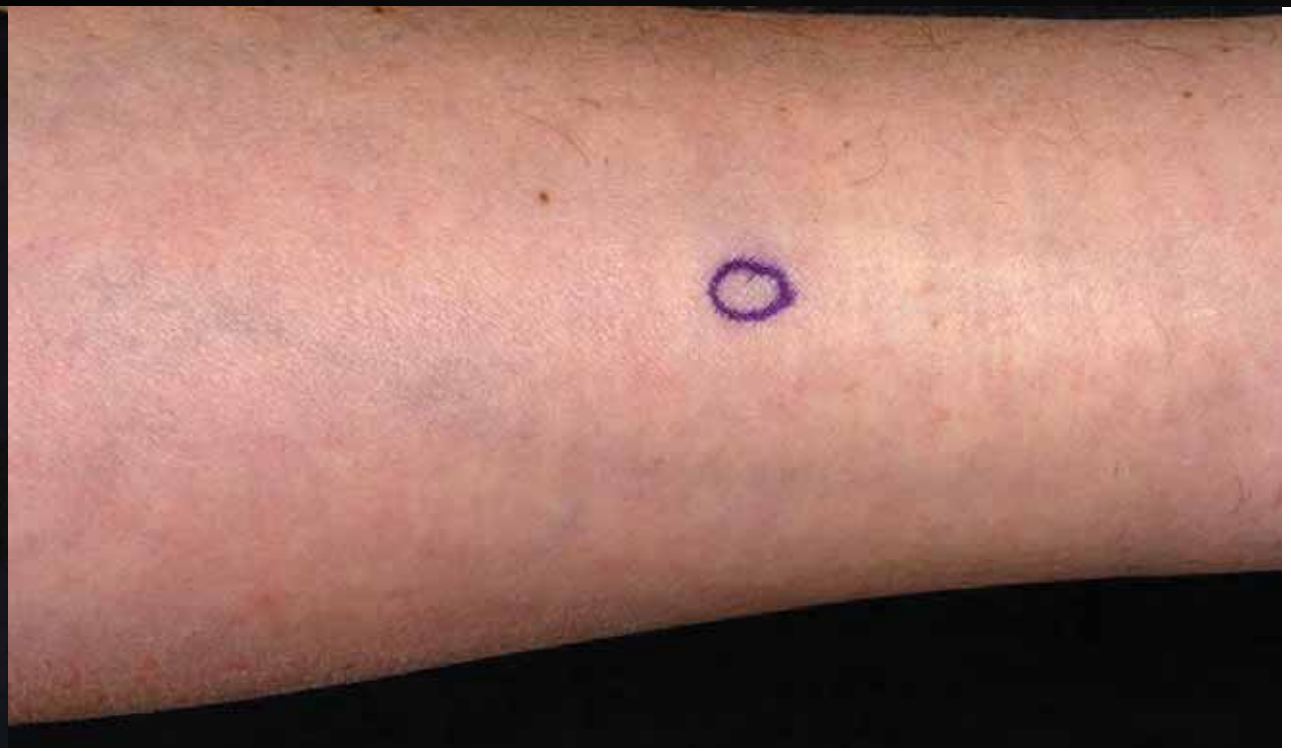


Fig 4. **A**, Lymphoid follicle with germinal center. Note some histiocytes and some eosinophils in the peripheral. **B**, Bcl-6 immunoreactivity inside germinal centers. **C**, Bcl-2 expression is absent inside some germinal centers. **D**, $CD23^+$ follicular dendritic cell network was regularly structured. (**A**, Hematoxylin phloxine saffron stain; **B-D**, immunohistochemistry; original magnifications: **A**, ×170; **B-D**, ×100.)





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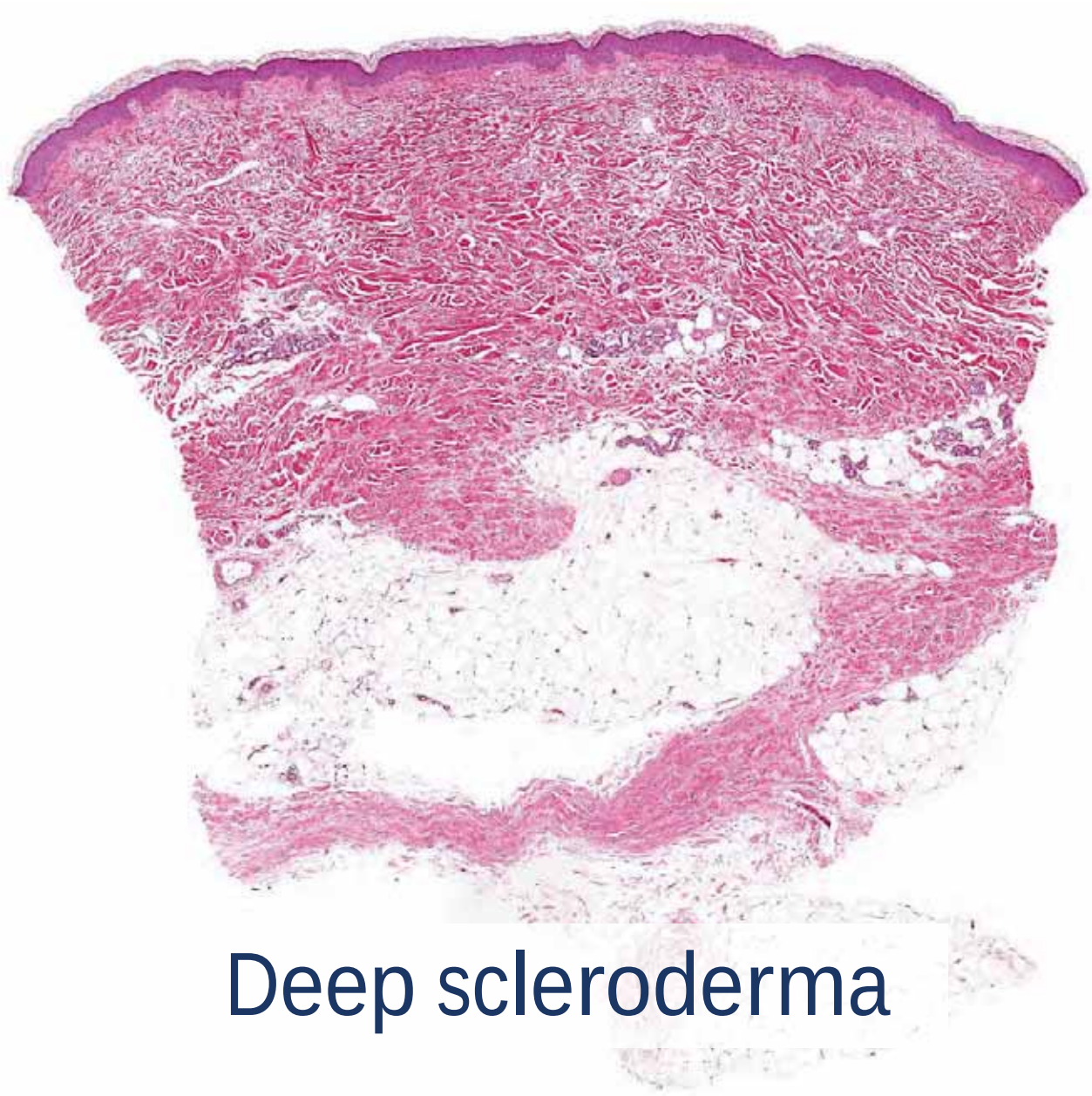
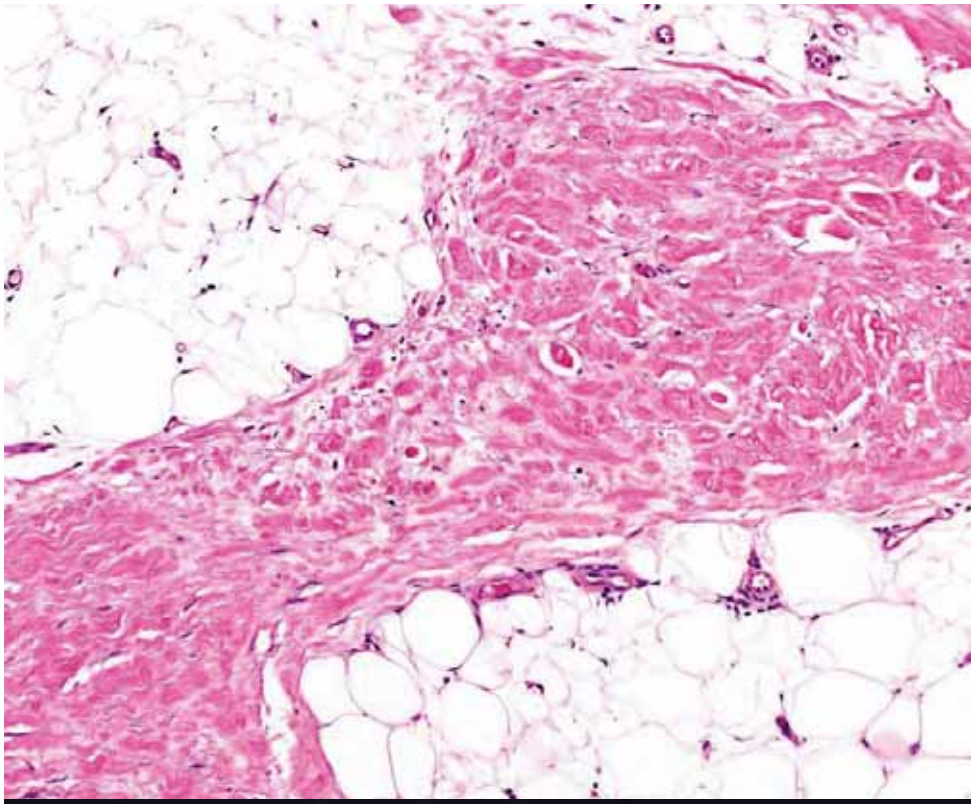
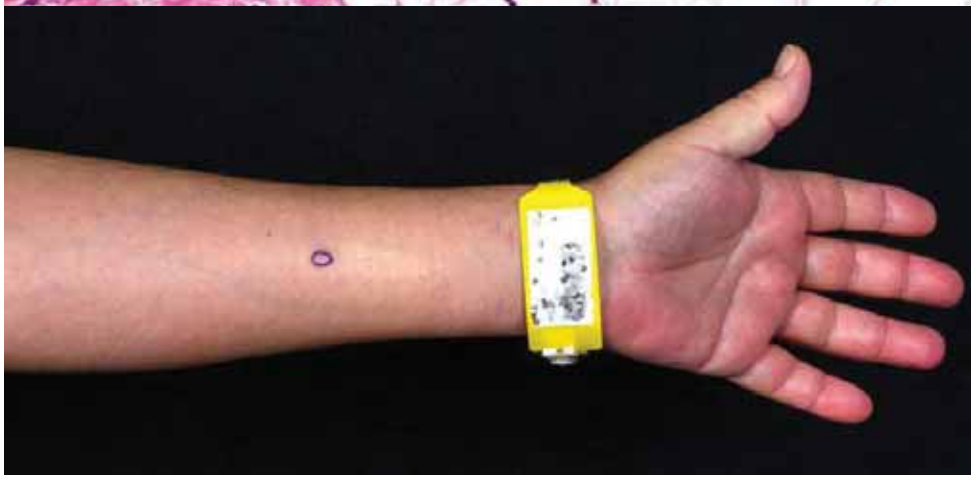
History of HLAB27 positive ankylosing spondylitis (1st diagnosis 11 years before presentation). In-patient in another Hospital for suspicion of systemic scleroderma; sent to our Department in order to take a skin biopsy.

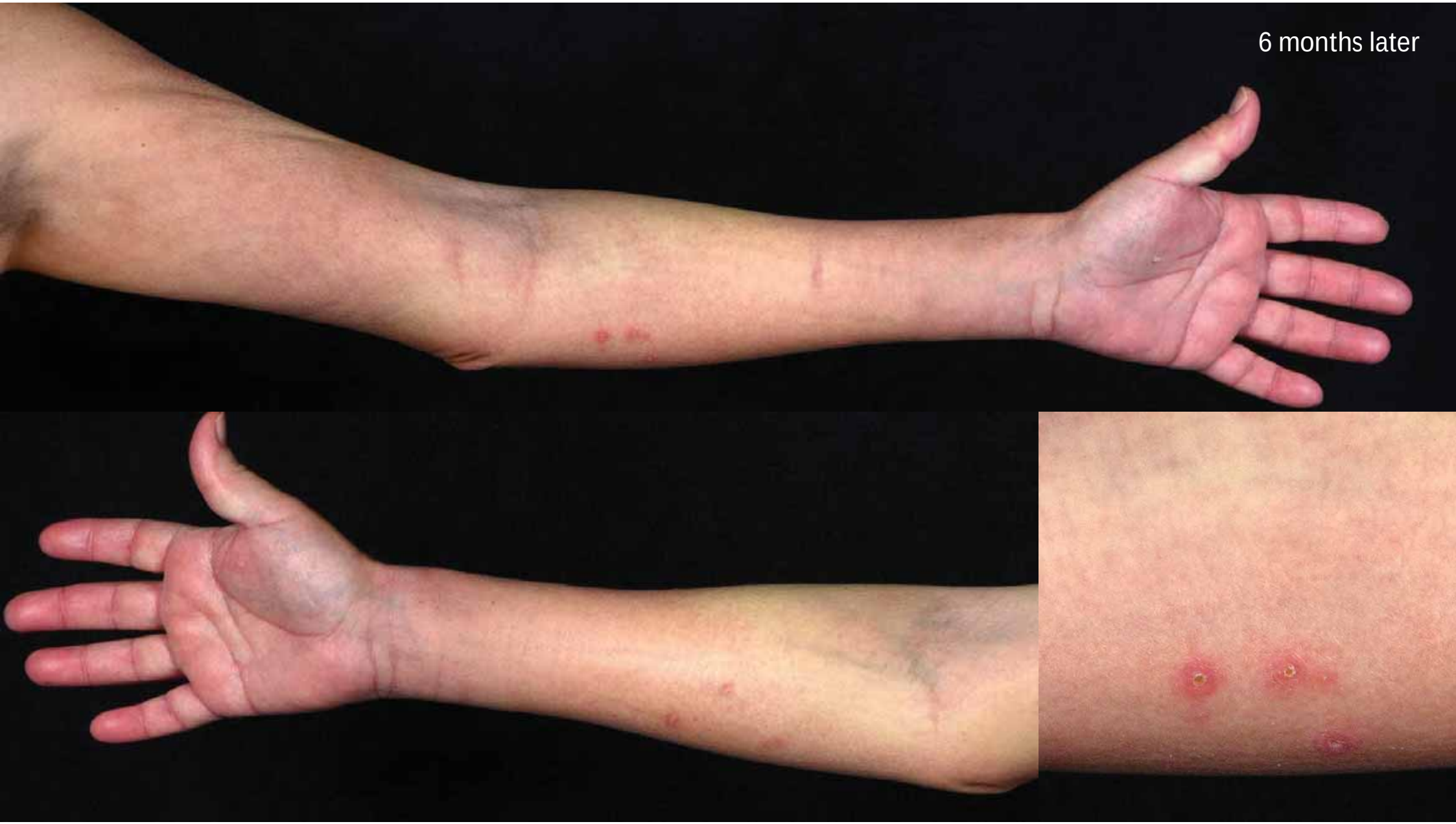
A biopsy is taken.

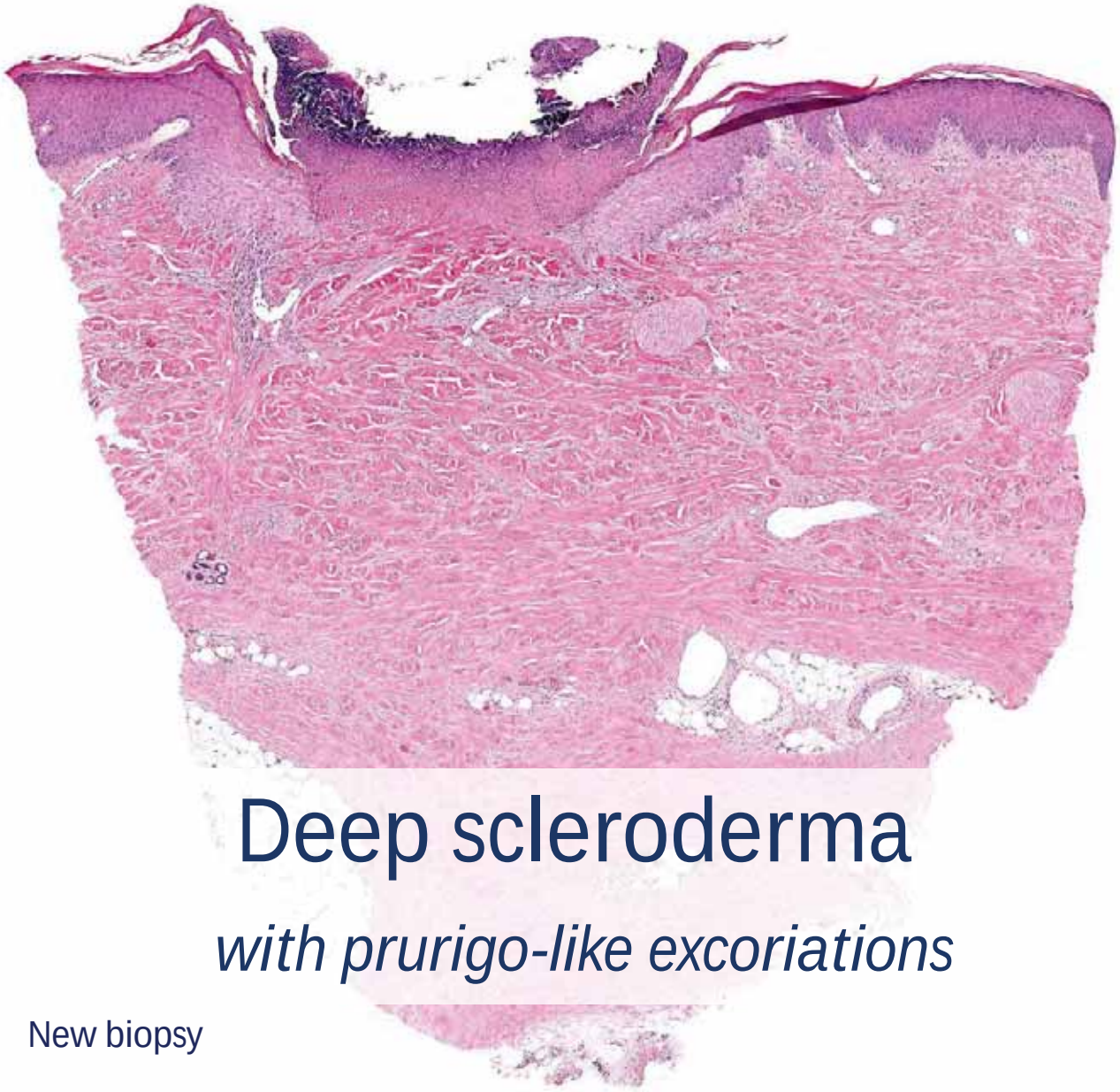


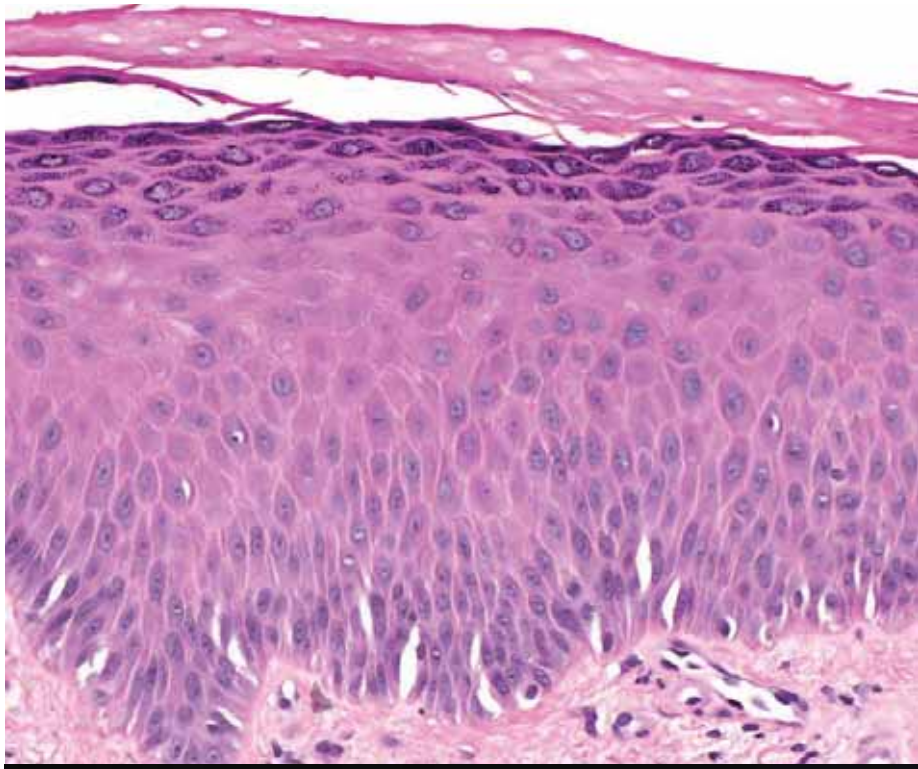
Deep scleroderma

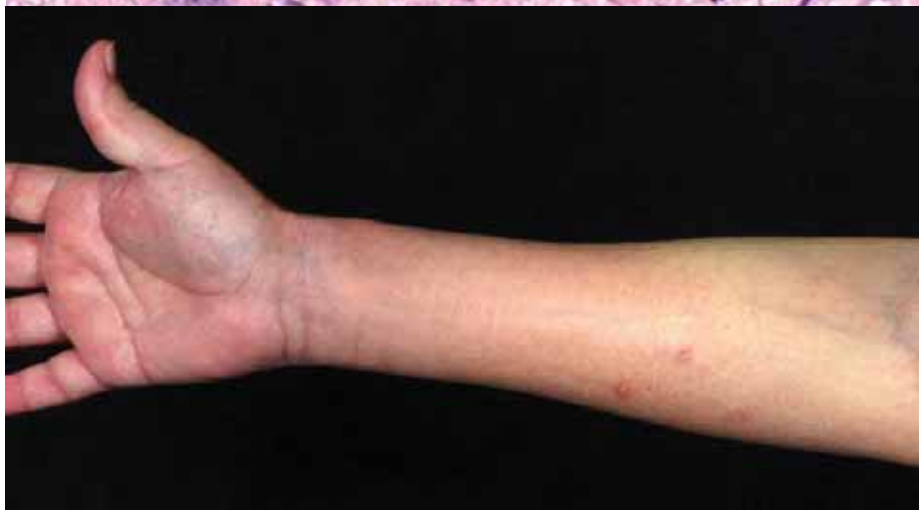





6 months later







Deep scleroderma

with prurigo-like excoriations

New biopsy

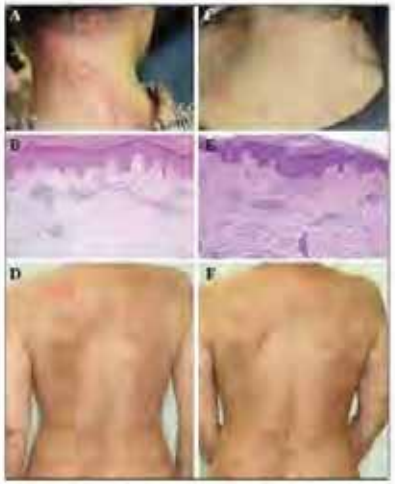


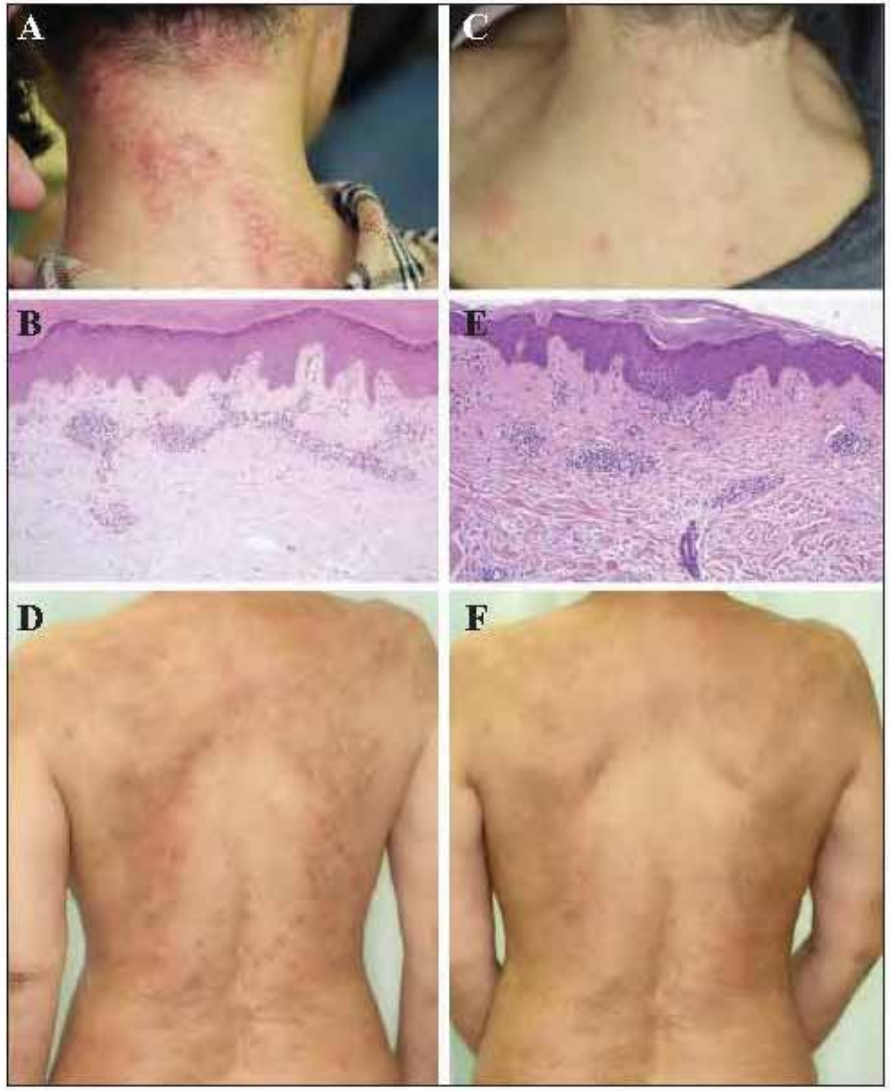
Figure 1. A, B, C) Case1. A) Clinical appearance before treatment, showing pruritic papules on the neck. B) Histopathological findings of lichenoid papules on the elbow, showing a thickened epidermis and perivascular infiltration of lymphocytes in the upper dermis; no eczematous or sclerotic change is seen (hematoxylin and eosin [H&E]; original magnification: x100). C) Clinical appearance on the neck after 12 sessions of ultraviolet phototherapy. Case 2 (D, E, F). D) Clinical appearance at the first visit to our hospital, showing pruritic papules and lichenoid papules on the back. E) Histopathological findings of pruritic papules on the upper arm (H&E; original magnification: x100). F) Clinical appearance of the back after 15 sessions of ultraviolet phototherapy.

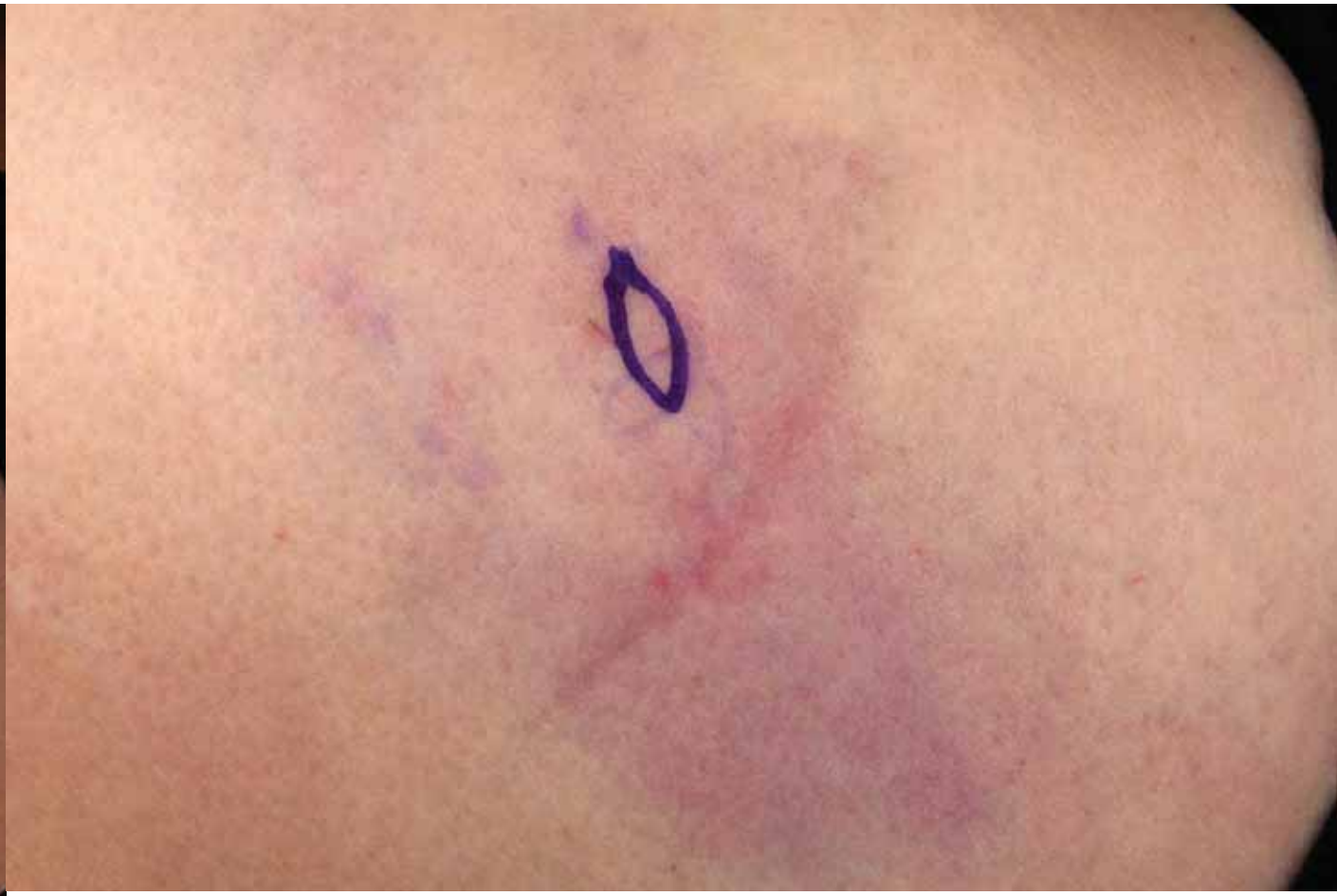
Prurigo with systemic sclerosis successfully treated with narrow-band UVB phototherapy

Chronic prurigo is an umbrella term for a range of clinical manifestations. There are many types of chronic prurigo, such as nodular, papular and plaque types [1]. While the pathogenesis of prurigo remains unknown, various coexisting diseases are well known [2]. We present two cases of prurigo associated with systemic sclerosis.

Case 1 was a 58-year-old Japanese woman who had been suffering from Raynaud's phenomenon and dermal sclerosis of the fingers. She was diagnosed with systemic sclerosis and treated with prostaglandin for the vascular lesions. Seven years after the diagnosis, she complained of pruritic papules on the neck, elbow, and other sites (*figure 1A*). She had no previous history of atopic disease. Laboratory investigations showed a high titre of antinuclear antibody (x640; centromere pattern) and anti-centromere antibody was positive (165 U/mL). No interstitial pneumonia was noted. Histopathological examination of a cutaneous biopsy specimen from the lichenoid papules on the elbow revealed perivascular lymphocytic infiltration in the upper dermis (*figure 1B*). No spongiotic or sclerotic changes were seen. From these results, we diagnosed the pruritic papules as prurigo. Although the prurigo was refractory to topical corticosteroids, once-weekly ultraviolet phototherapy (narrow-band UVB) improved the pruritus and papules within two months (*figure 1C*). She was exposed to 0.7 J/cm^2 at each session. We continued the ultraviolet phototherapy once every two weeks for the following four months, until almost no prurigo was observed. After cessation of phototherapy, the papules slightly recurred at three months.

Case 2 was a 70-year-old Japanese woman who was diagnosed with systemic sclerosis 20 years ago. Since then, she had been suffering from pruritic papules on the trunk and extremities. She had no past history of atopic disease. Although she had been treated with topical corticosteroids at several hospitals, the pruritic papules did not improve. At the initial visit to our hospital, she presented with papules and lichenoid papules with pruritus on the back and extremities (*figure 1D*). Laboratory investigations showed a high titre of antinuclear antibody (x1,280; homo and centromere patterns) and anti-centromere antibody was positive (494 U/mL). No interstitial pneumonia was noted. Histopathological examination of a cutaneous biopsy specimen from the papule on the upper arm revealed perivascular lymphocytic infiltration in the upper dermis (*figure 1E*). No spongiotic or sclerotic changes were seen. From these results, we diagnosed the pruritic papules as prurigo. We initiated treatment with topical corticosteroids and ultraviolet phototherapy (narrow-band UVB) once a week. After eight treatment sessions, the pruritic papules markedly improved (*figure 1F*). She was exposed to 1.0 J/cm^2 at each session.





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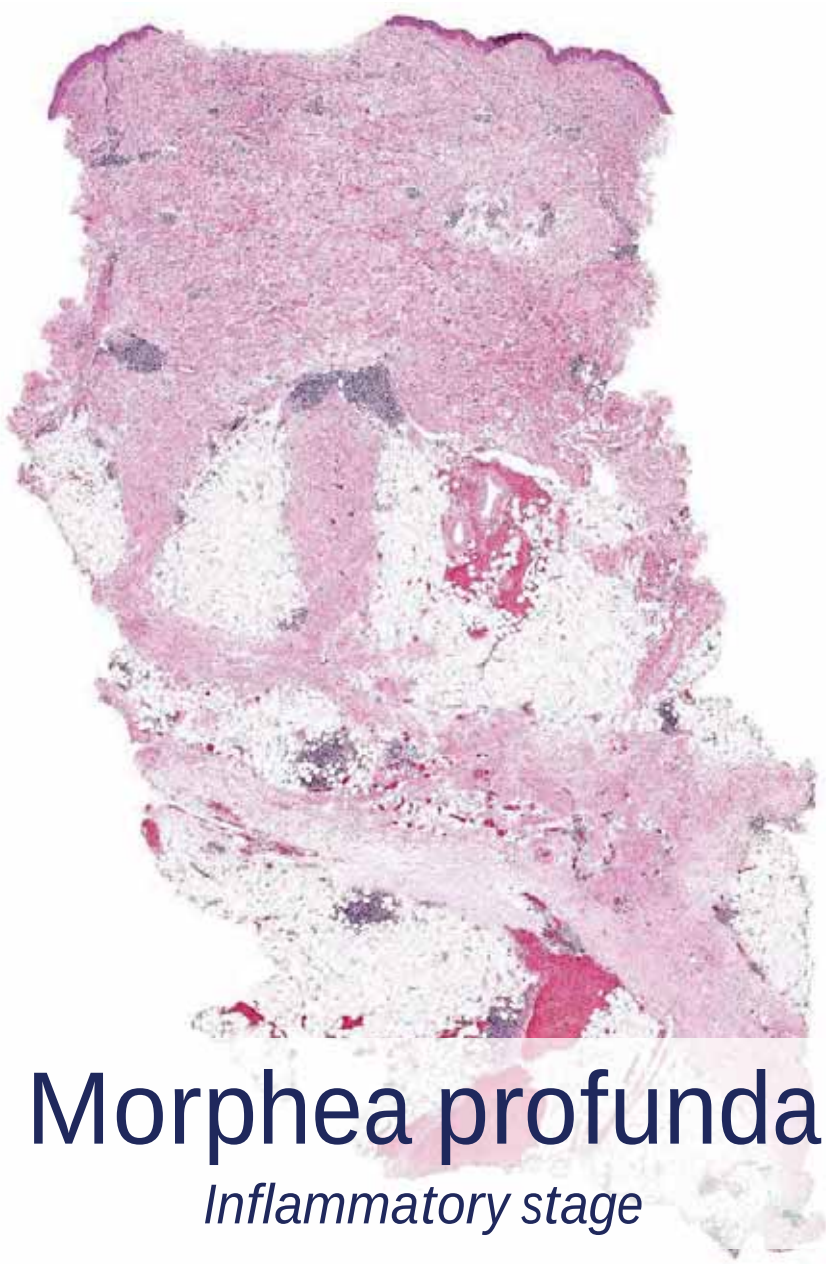
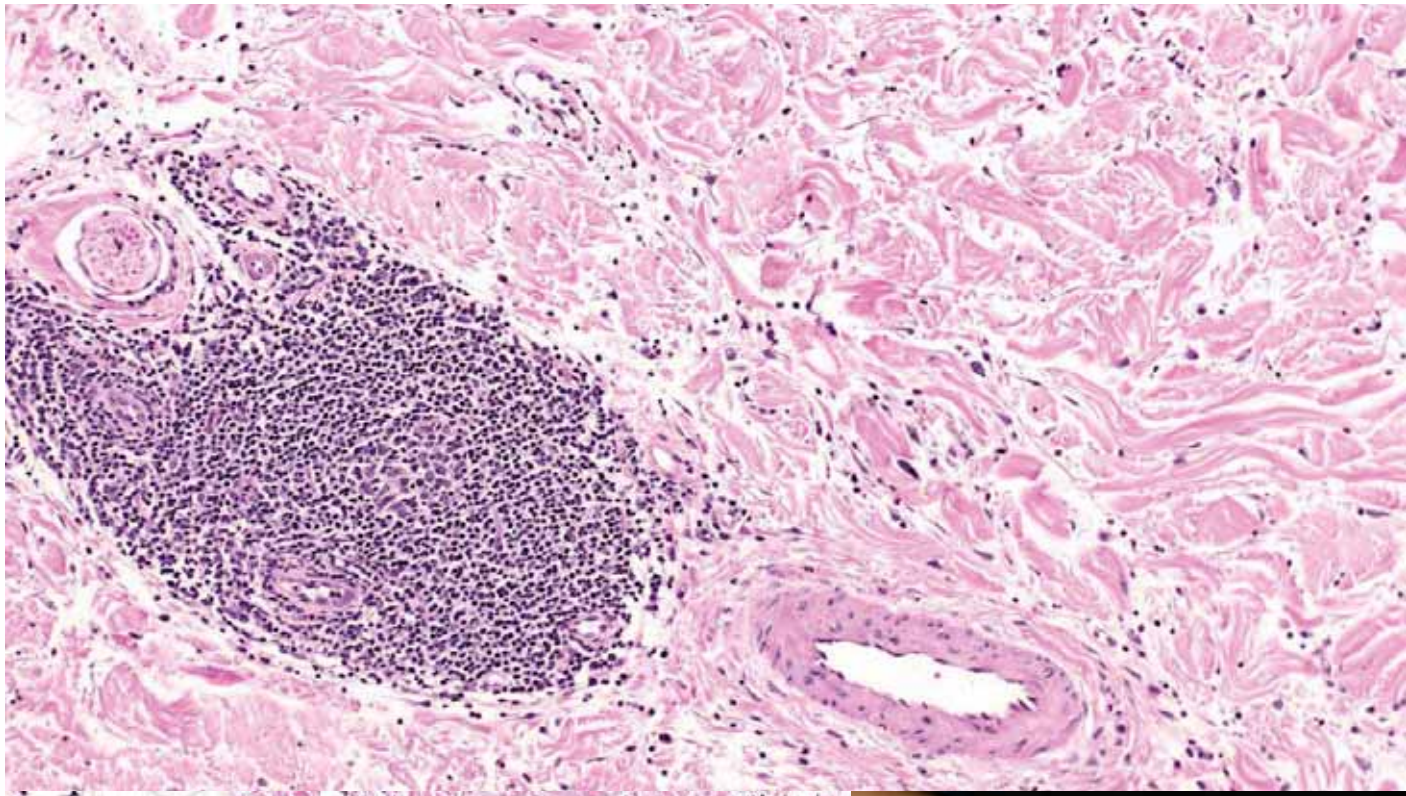
According to the patient pruritic, painful, enlarging lesion on the left thigh for approximately 6 weeks. No previous trauma, no arthropod bite, no fever or systemic symptoms.

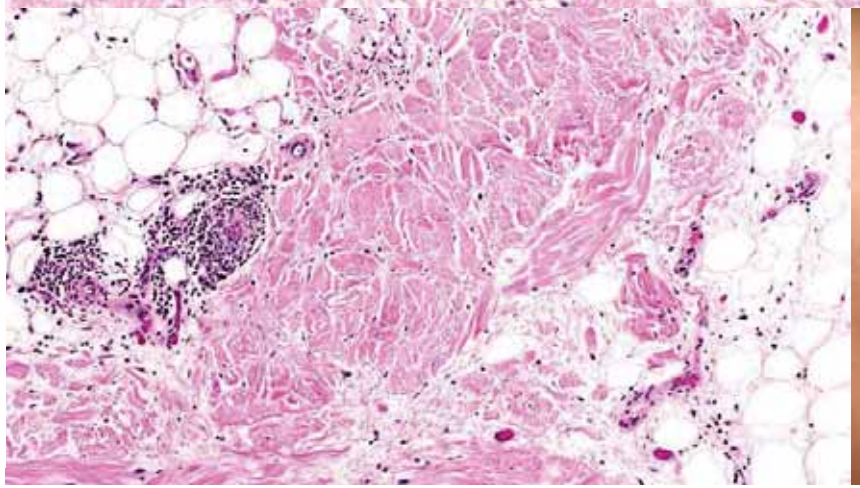
A biopsy is taken.

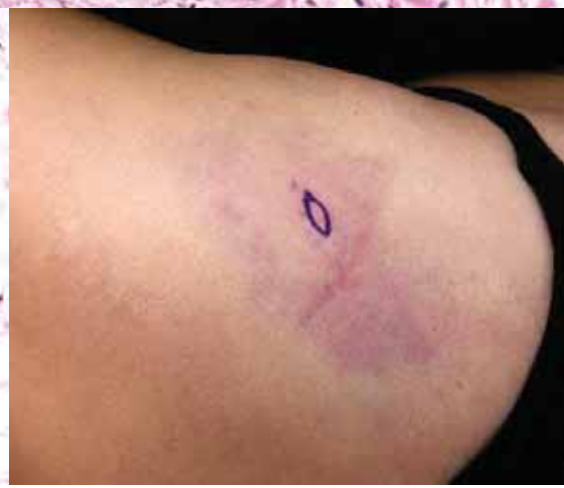


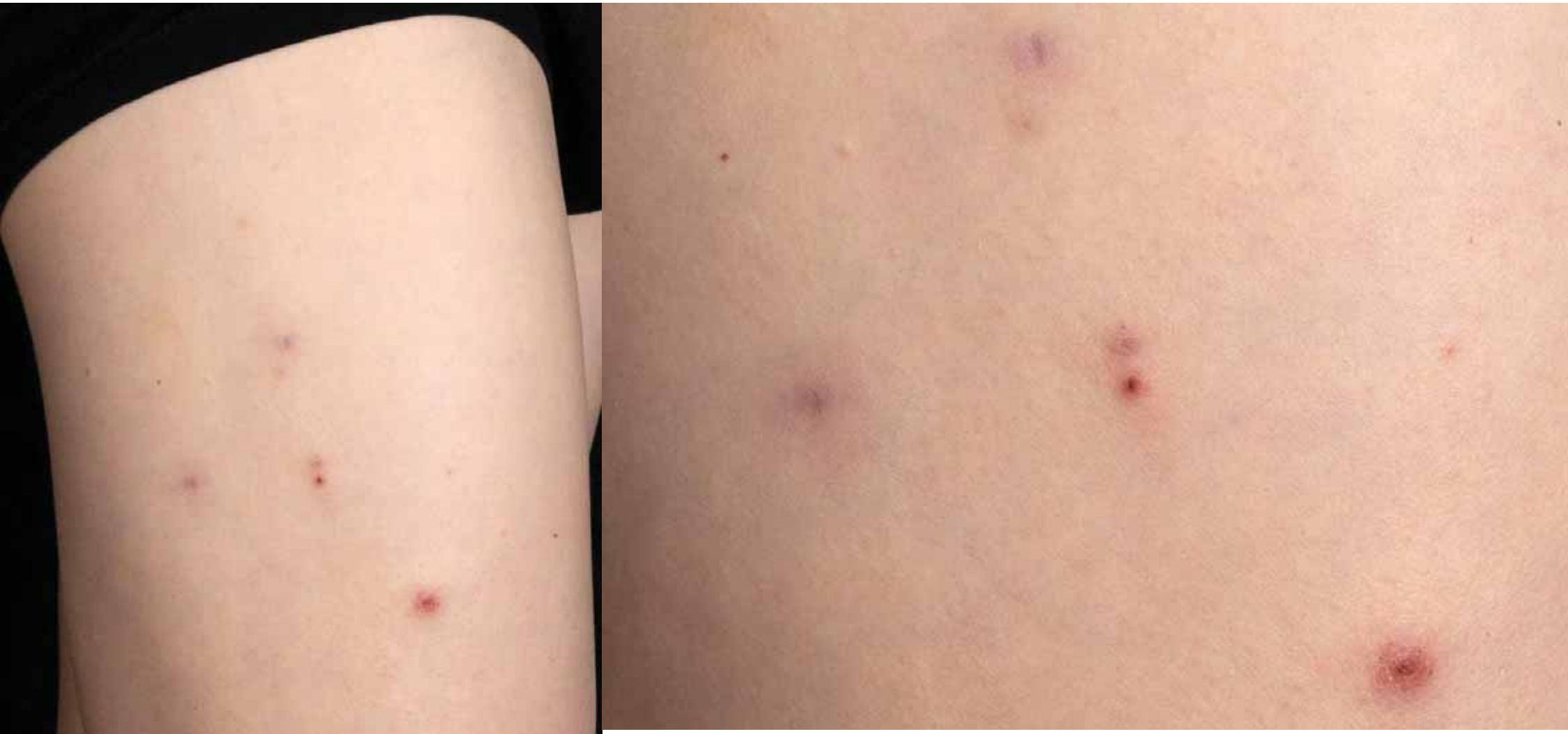
Morphea profunda

Inflammatory stage









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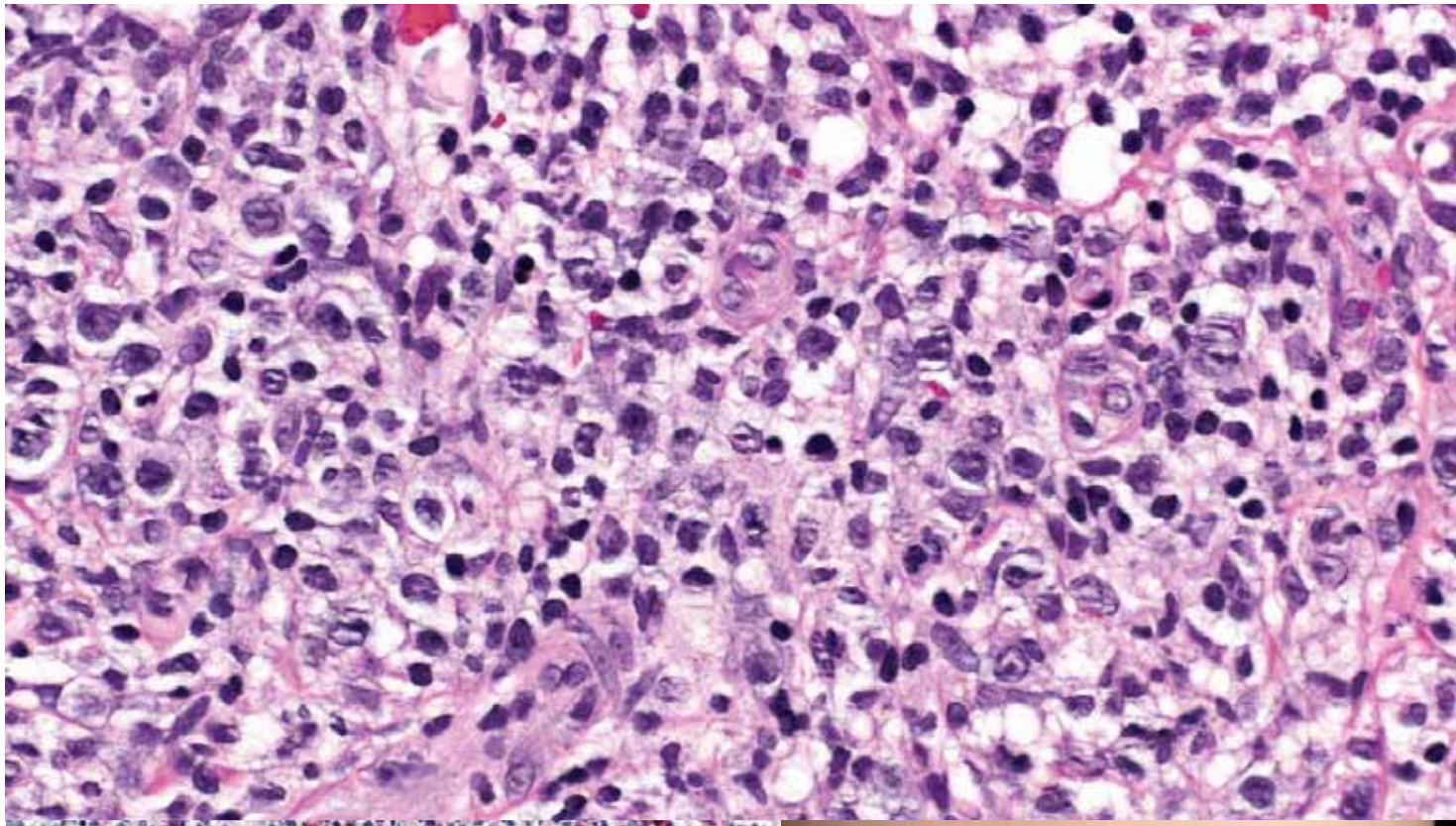
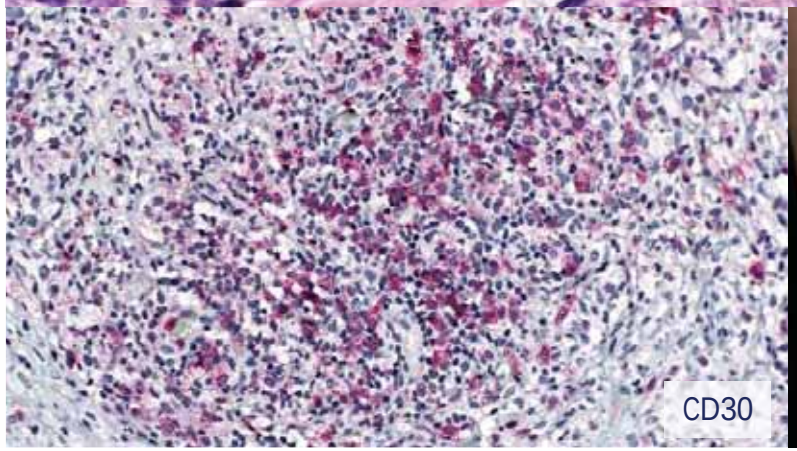
Lesions on the right thigh for 2 months, partly regressing.

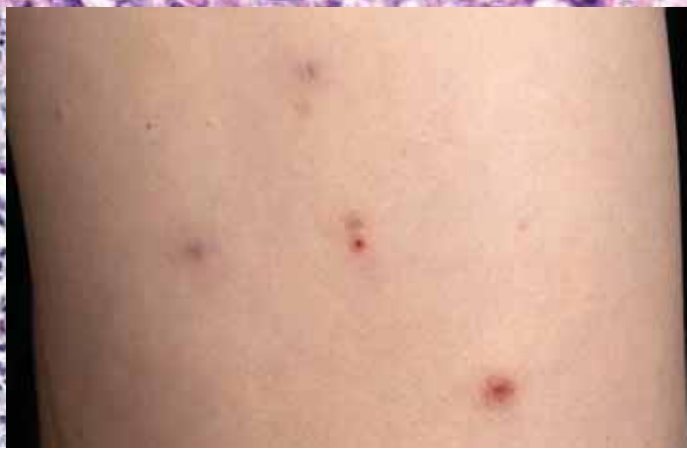
Three biopsies are taken (suspect clinical diagnosis of lymphomatoid papulosis).

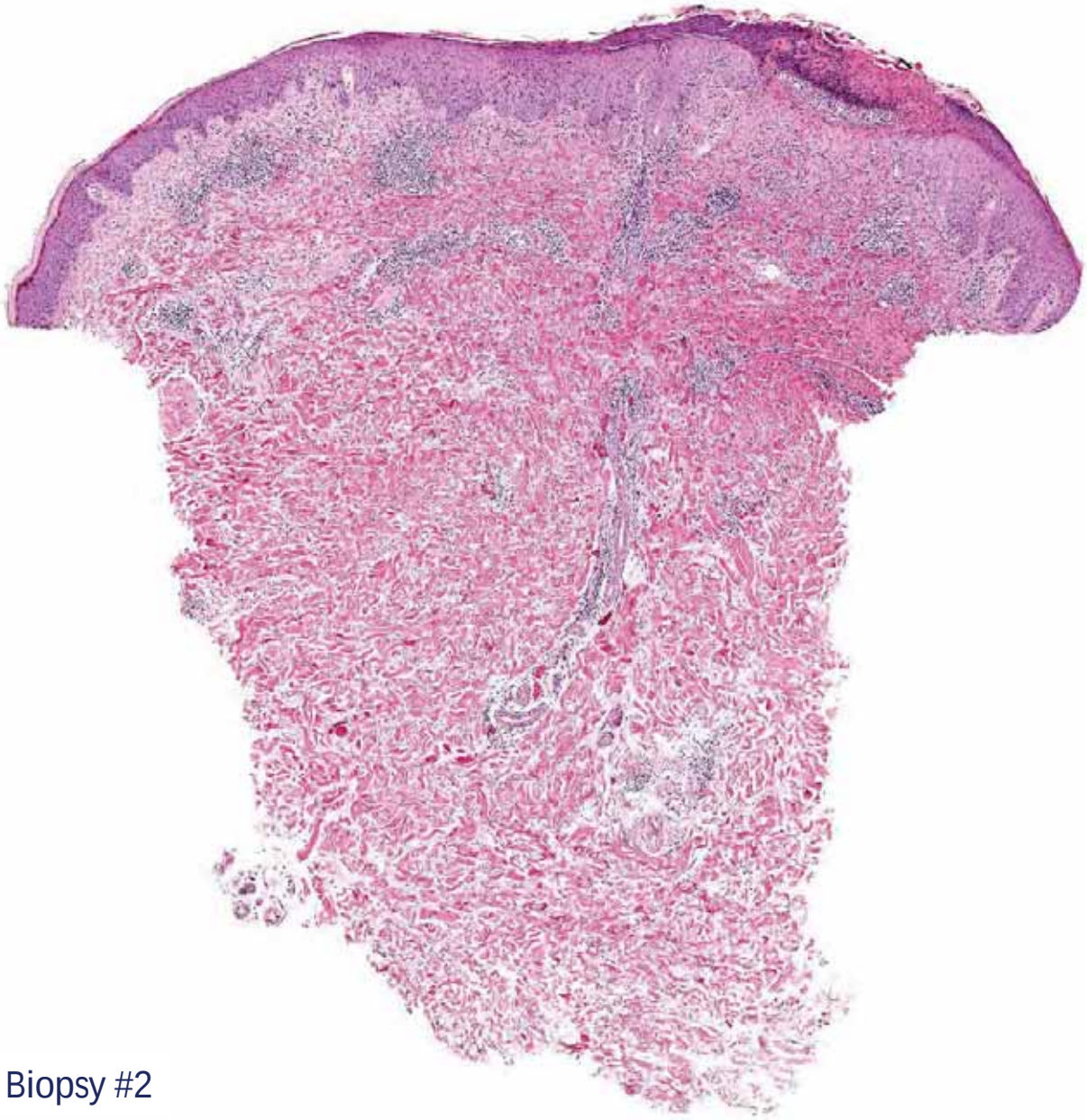
Biopsy #1



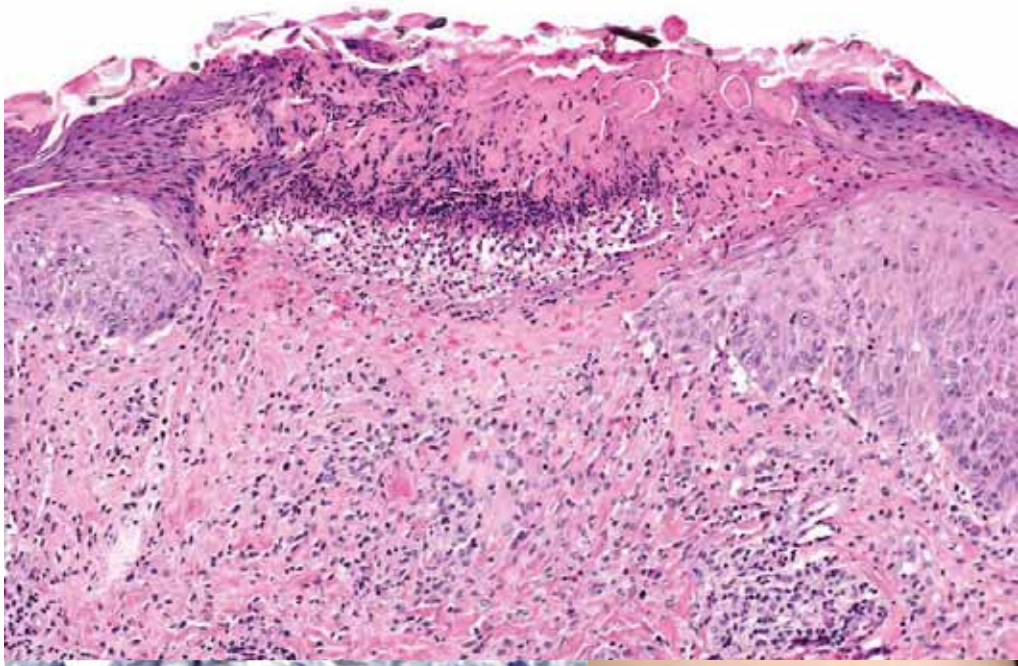


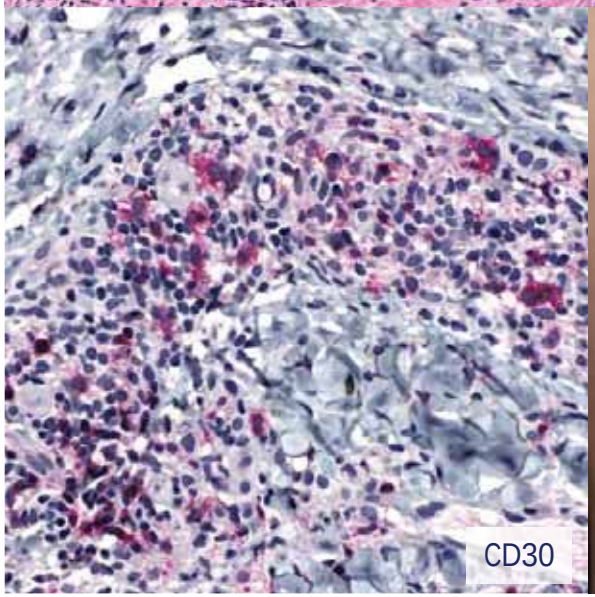
CD30





Biopsy #2





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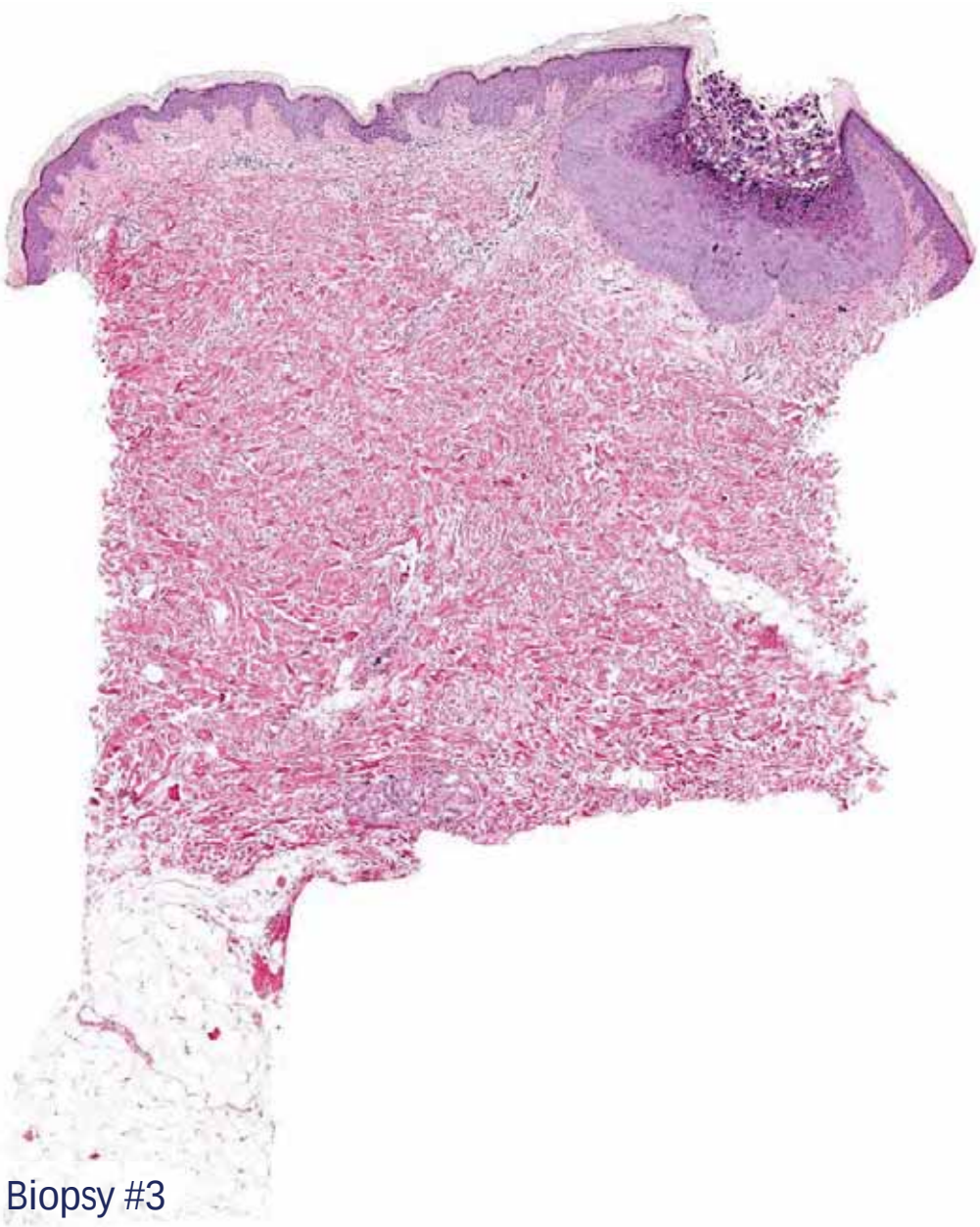
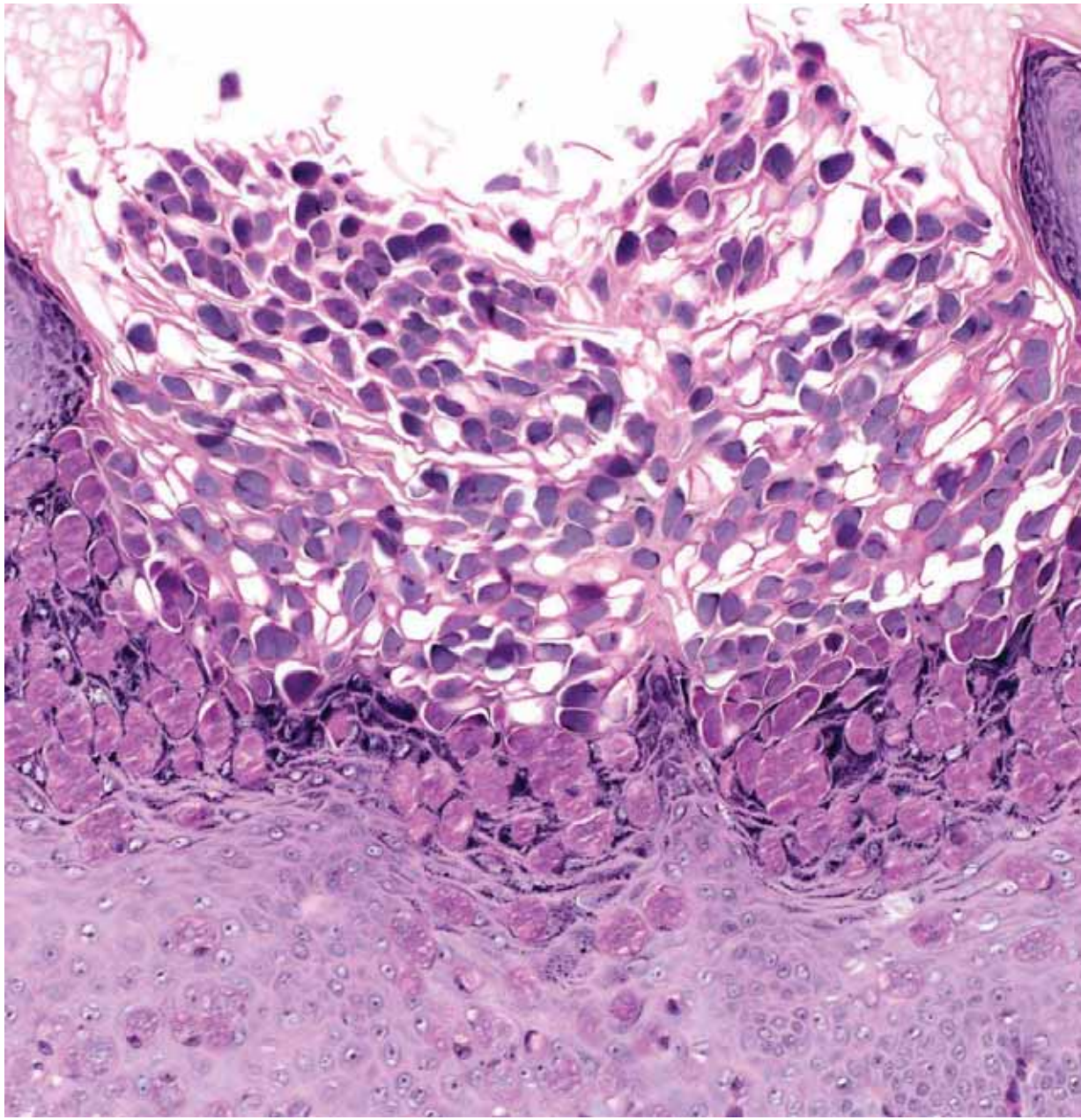
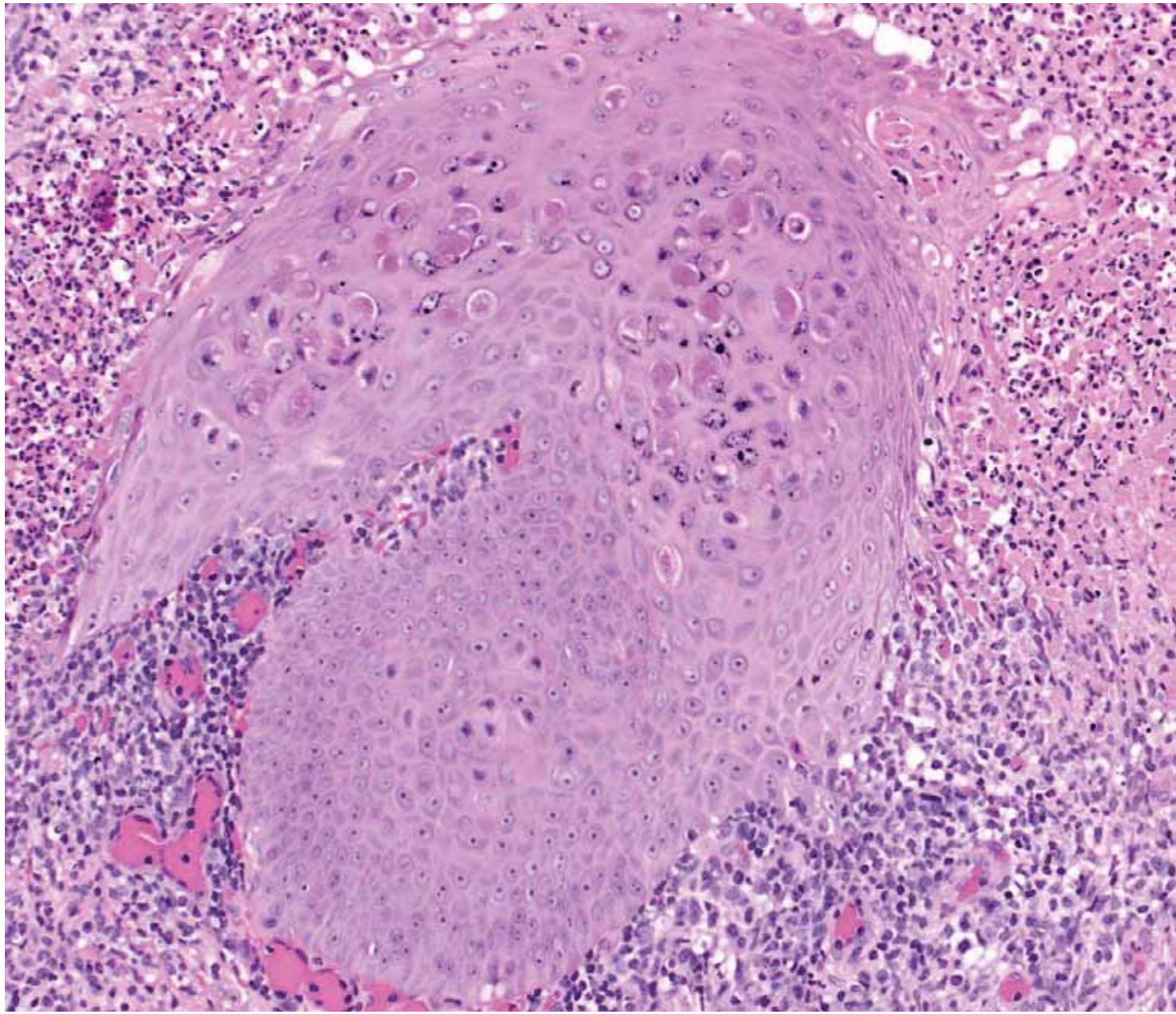
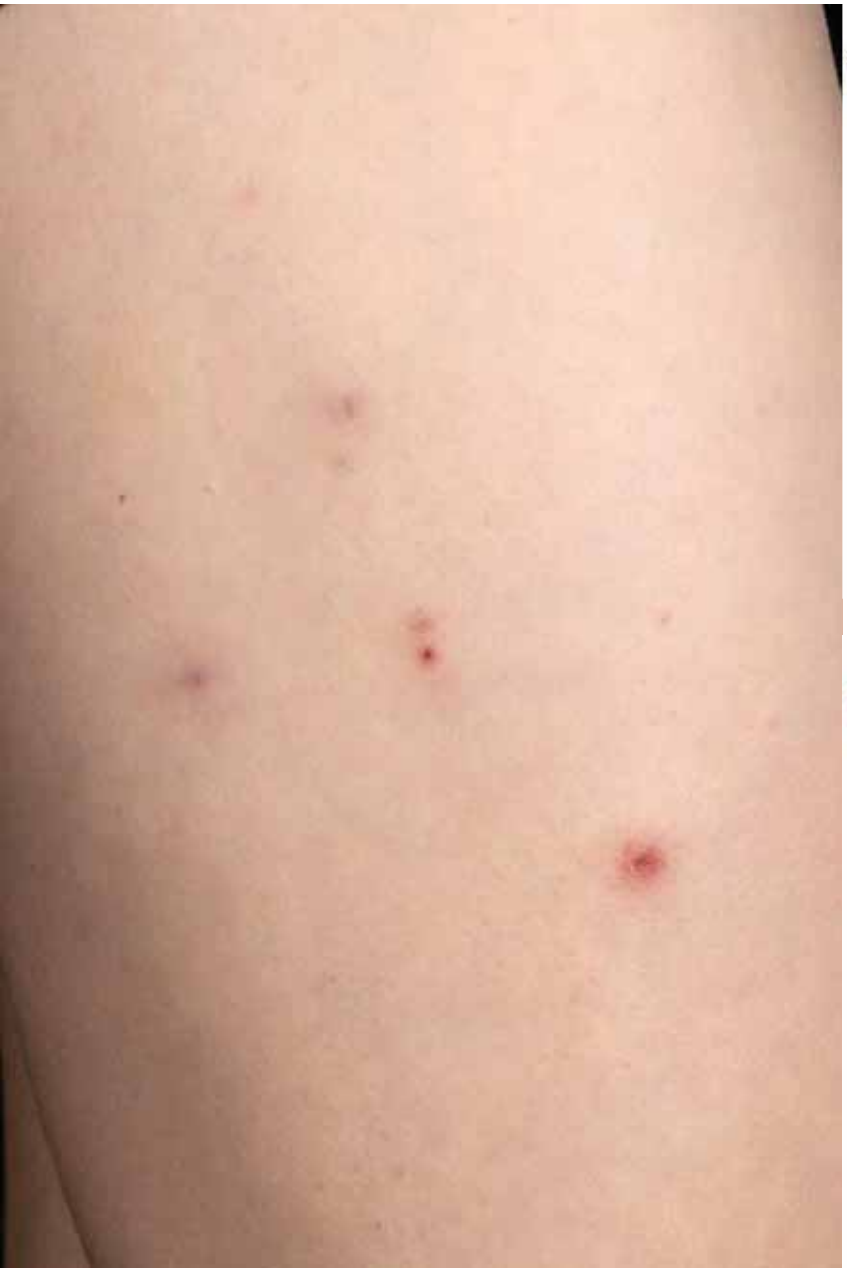


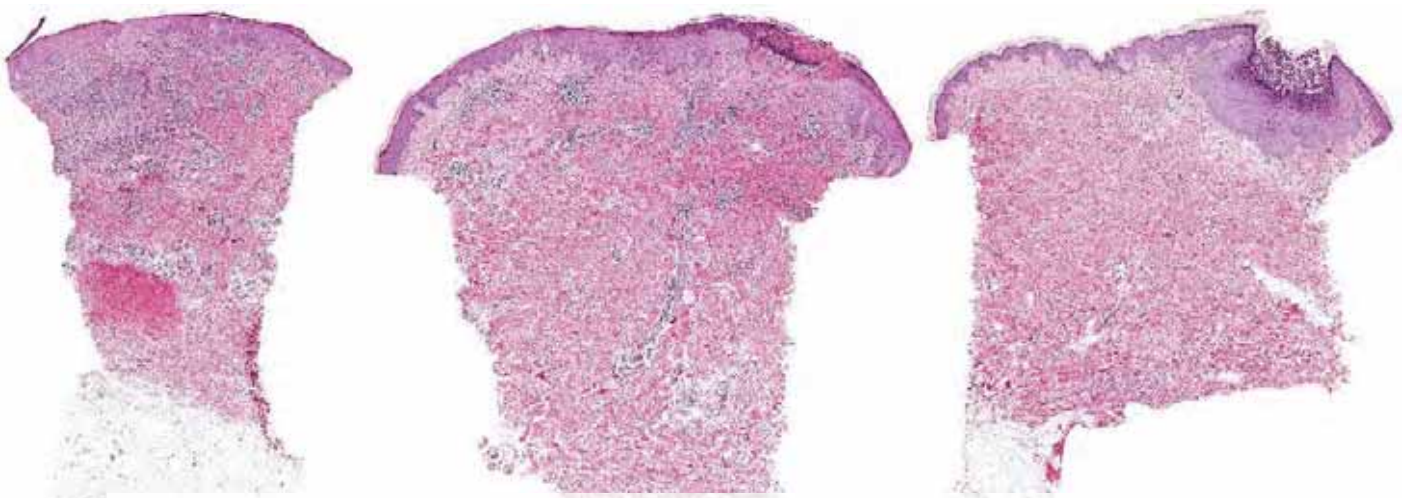
Biopsy #3



Biopsy #1 (deeper levels)







Molluscum contagiosum