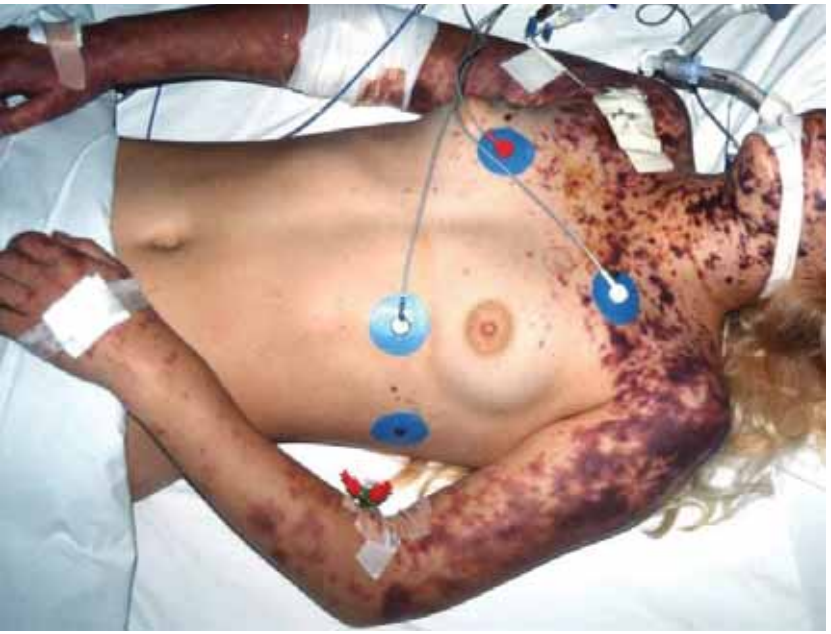

17th Summer Academy of Dermatopathology
Graz, June 30 – July 4, 2025
Unusual presentations of cutaneous infections
Lorenzo Cerroni, Europe



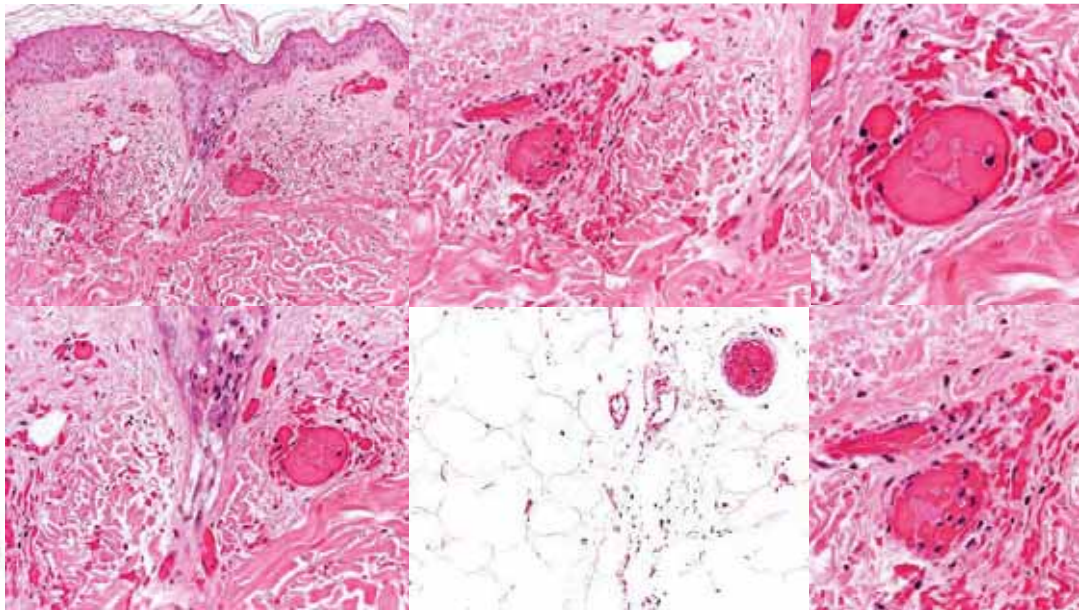
Purpura fulminans

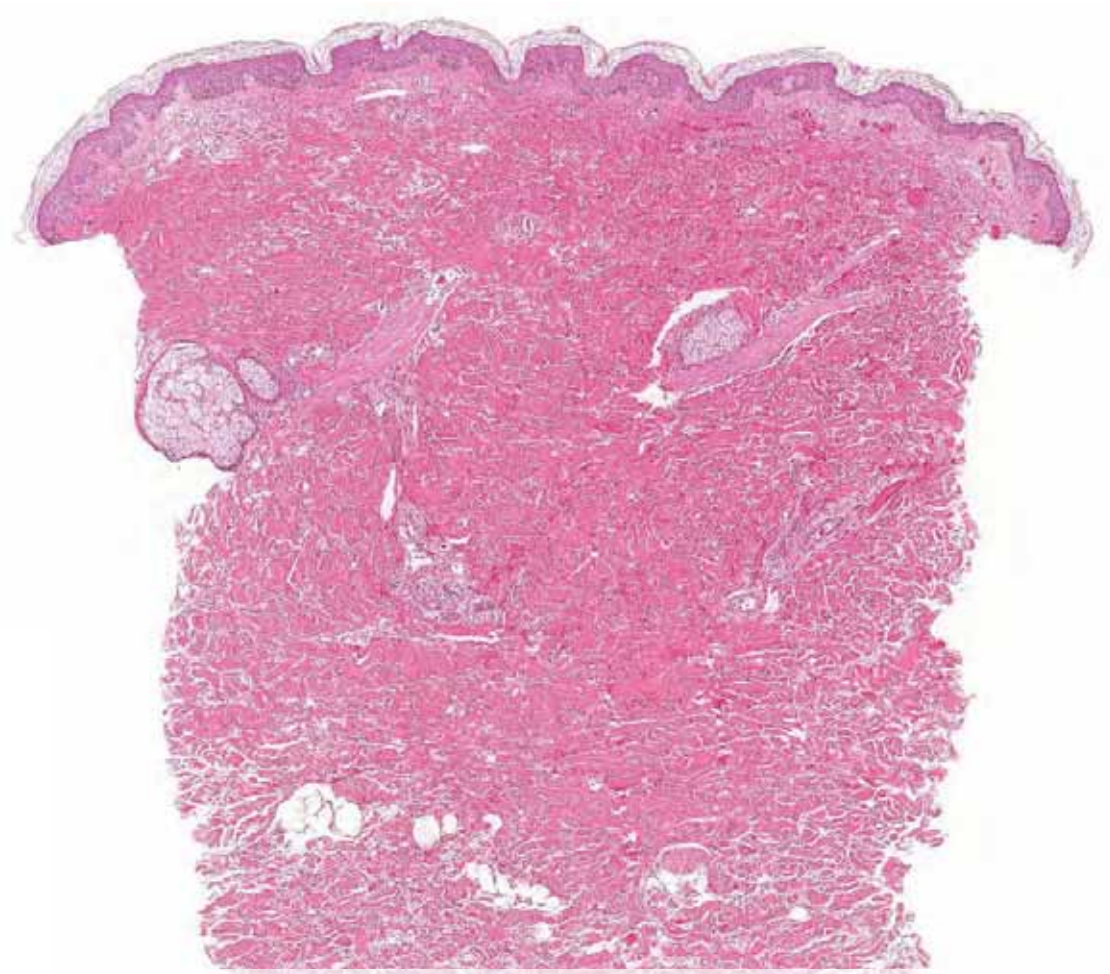
(disseminated intravascular coagulation)

(liquor: 2x negative; blood culture: 6x negative)

F, 16

Two days after influenza vaccination onset of flue-like symptoms managed with acetylsalicylic acid. One day later rapid deterioration of the conditions with shock and purpura fulminans. An emergency doctor administers i.v. antibiotics and sends her to the hospital. Admitted in the intensive care unit with a differential diagnosis of purpura fulminans due to influenza vaccine or drug-related. Two biopsies are taken.





Purpura fulminans due to meningococcal sepsis

Discharged as purpura fulminans due to influenza vaccination.

Amputations of the right leg, left foot and several fingers.

Three years later invited to a television debate on pro and contra of vaccinations.

A pediatrician following the program from home is not convinced of the diagnosis and investigates the case; two skin biopsies and one frozen liquor sample are still available.

PCR analyses performed on all 3 samples show positivity for *Neisseria meningitidis.*

Onset of symptoms after influenza vaccination and intake of acetylsalicylic acid was just by chance and represented a confounding factor.

Injection of antibiotics by the emergency doctor likely saved her life, but at the same time was probably responsible for the negative results of liquor and blood culture.

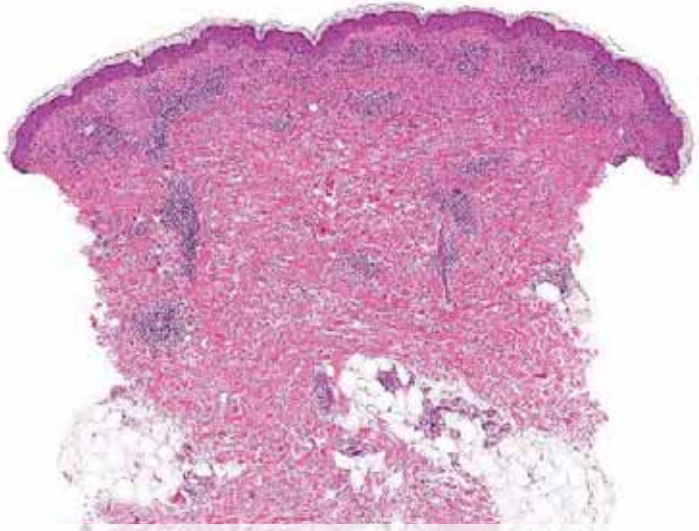
Admitted as in-patient at the emergency department for ***adult*** patients (meningococcal sepsis exceedingly rare in adults).

Unlike in adults, purpura fulminans in children considered as a manifestation of sepsis by ***Neisseria meningitidis*** irrespective of laboratory results.

No harm to the patient – the severe sequelae were not related to the wrong diagnosis, yet huge harm to the community by presenting in television this dramatic case as a side-effect of a vaccination.

F, 13

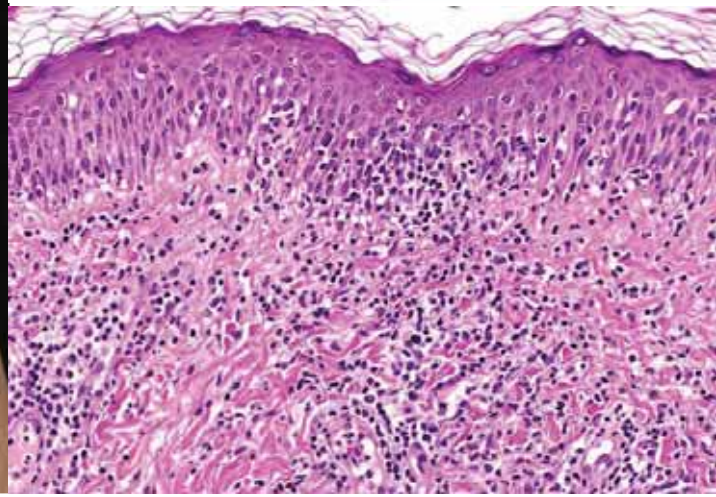
According to the mother lesions present "for 2 years", "onset at the site of a vaccination" and then progressive "descent".



Erythema migrans

PCR positive for ***Borrelia*** DNA.

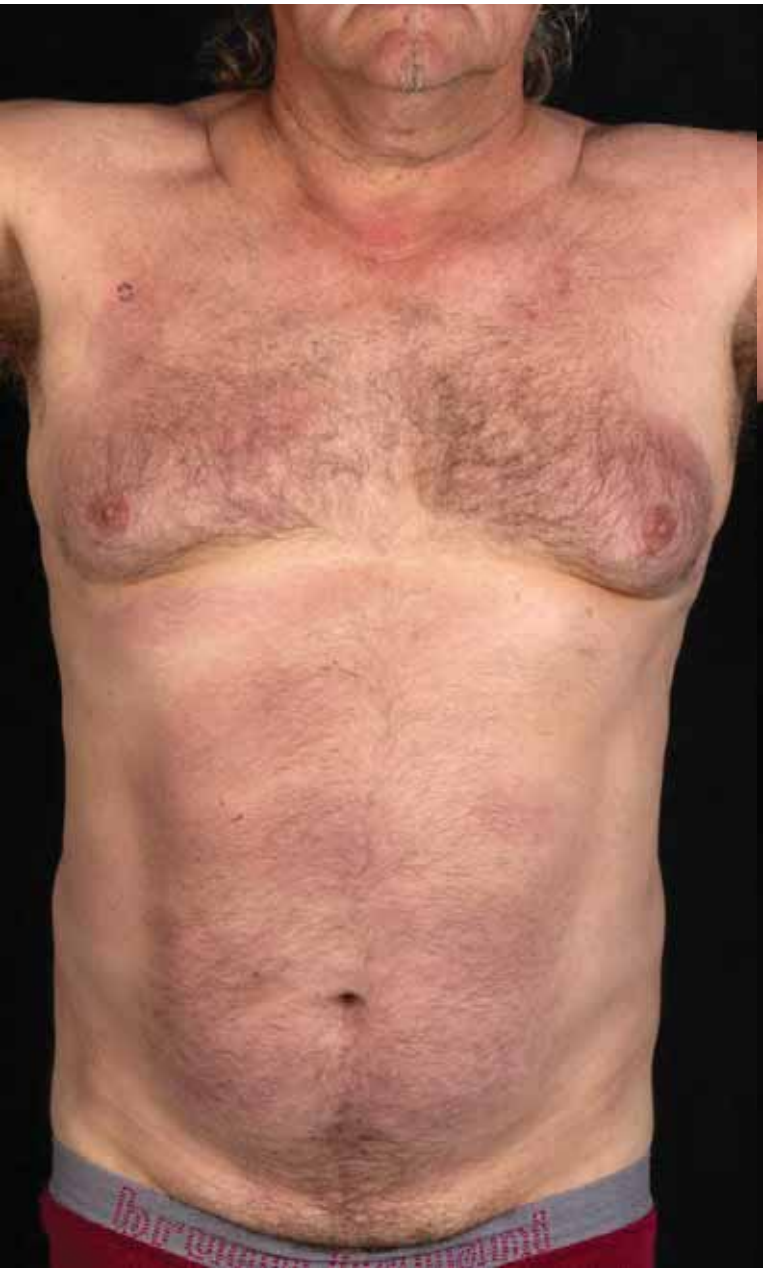
Complete resolution upon antibiotic treatment for 3 weeks.

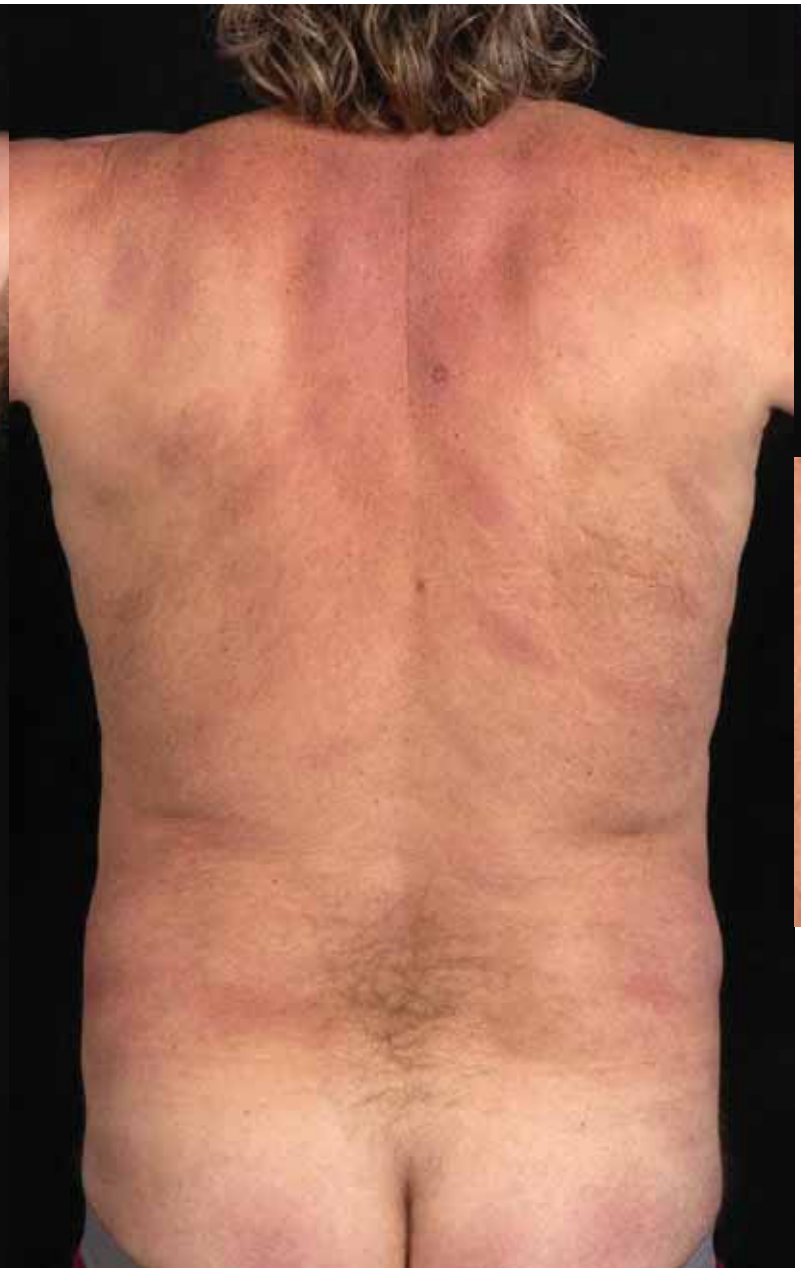


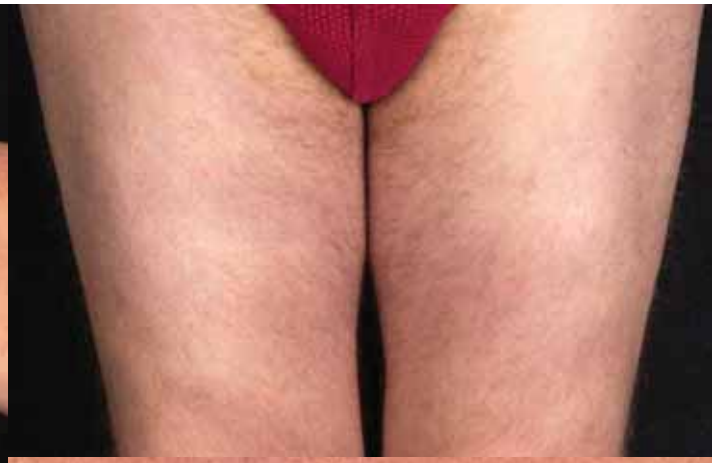
Diagnosis (or misdiagnosis) of an infectious disorder is more than just a diagnosis. It may have a huge social impact on the patient and the community, sometimes directly (e.g., Covid-19 infection at the time of lock-down and personal restrictions), other times indirectly (e.g., "vaccine-related purpura fulminans").

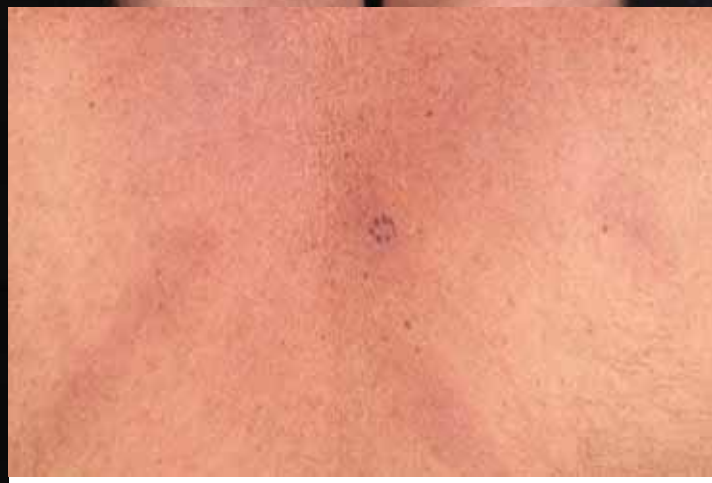
Infectious disorders & arthropod-induced diseases

- Viral infections
  (herpes virus infections; HPV infections; parvovirus B19; hand, foot & mouth disease; milker's nodule & orf; molluscum contagiosum; cowpox; monkeypox; other)
- Bacterial and rickettsial infections
  (impetigo; ecthyma; furuncles; erysipelas; staphylococcal scalded-skin syndrome; TBC; atypical mycobacteriosis; leprosy; rickettsial infections; other)
- Mycoses
  (dermatomycoses; candidiasis; pityriasis versicolor; cryptococcosis; systemic mycoses; other)
- Spirochetal infections
  (syphilis; borreliosis; other)
- Protozoal infections
  (leishmaniasis; other)
- Cutaneous infestations
  (scabies; cercarial dermatitis; larva migrans; myiasis; tungiasis; other)





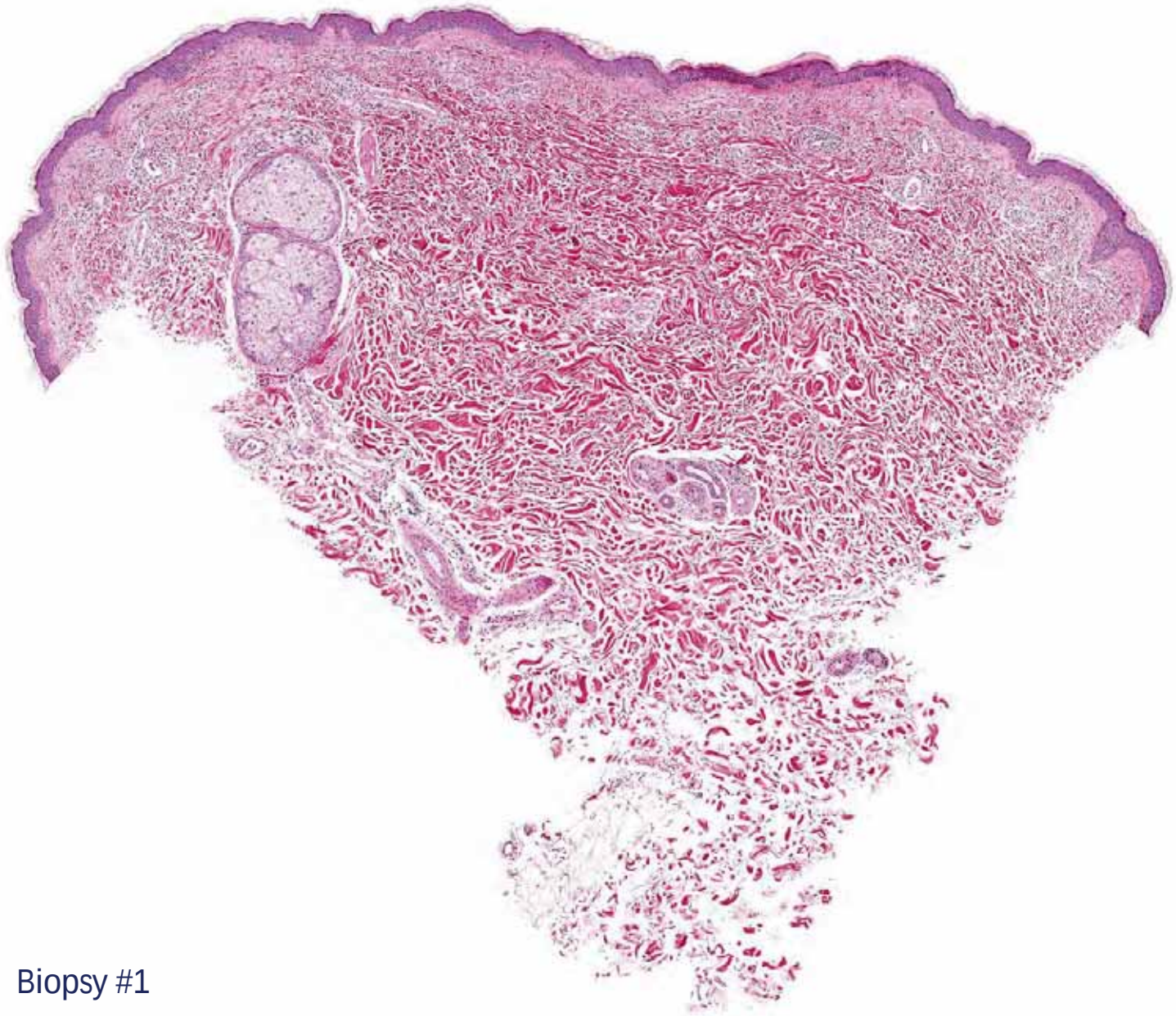




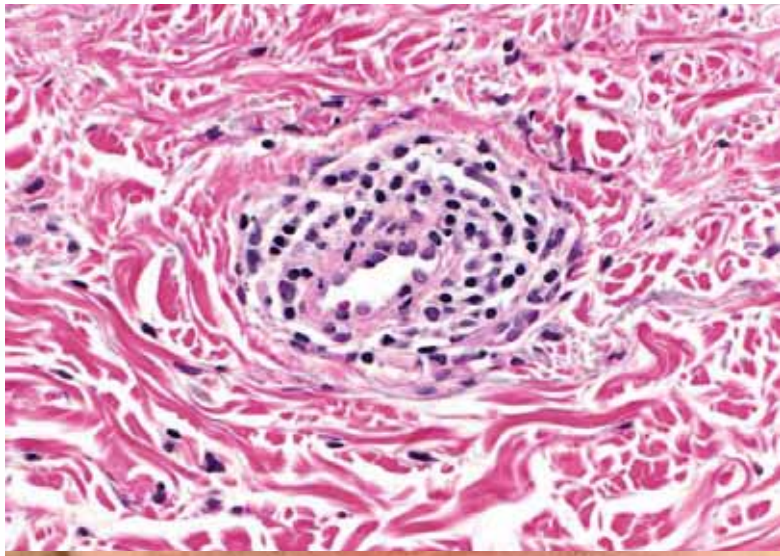
M, 52

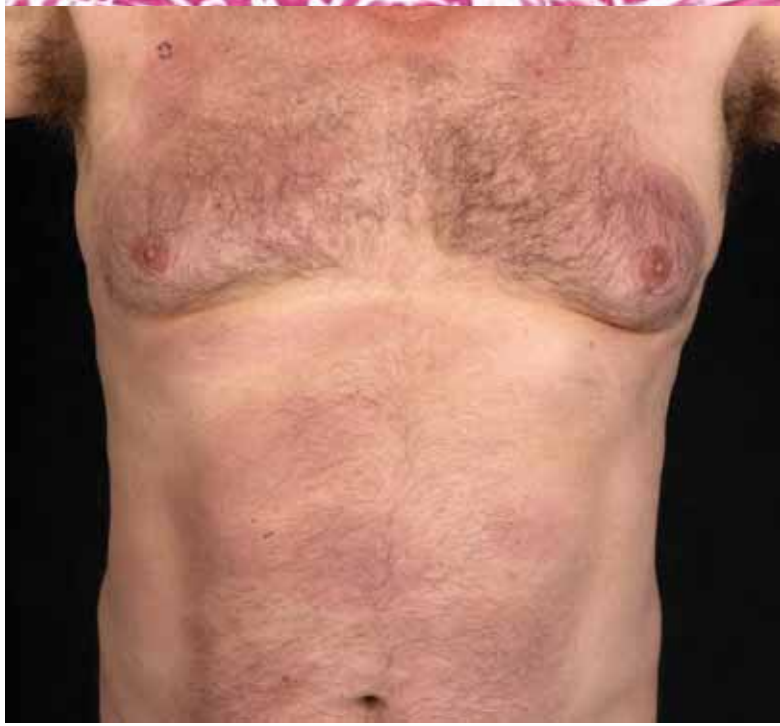
According to the patient generalized skin lesions for 2-3 weeks, starting with shiver and a single lesion on the abdomen.

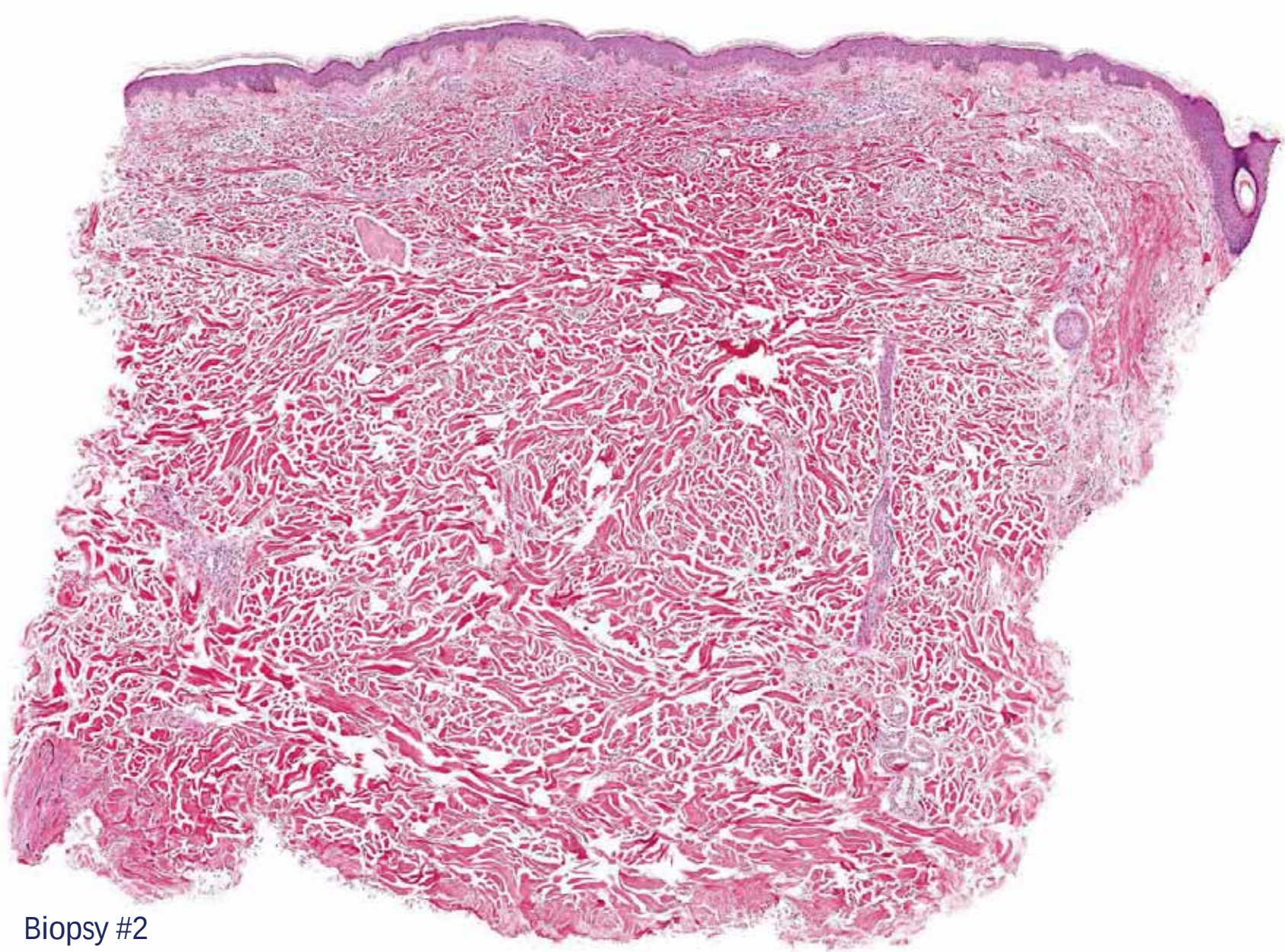
Two biopsies are taken.



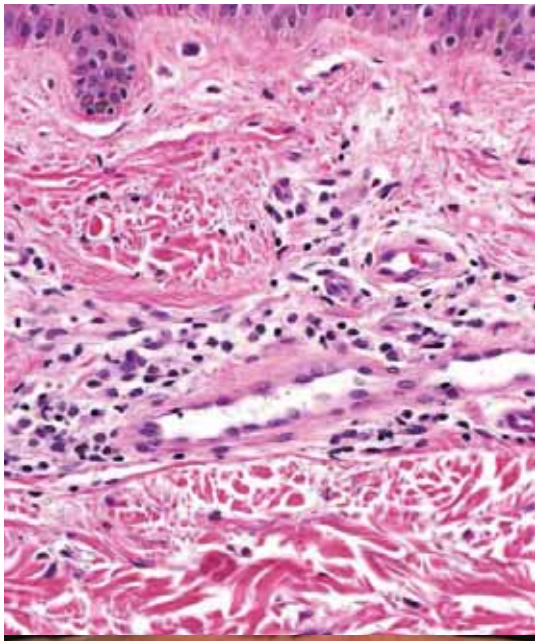
Biopsy #1

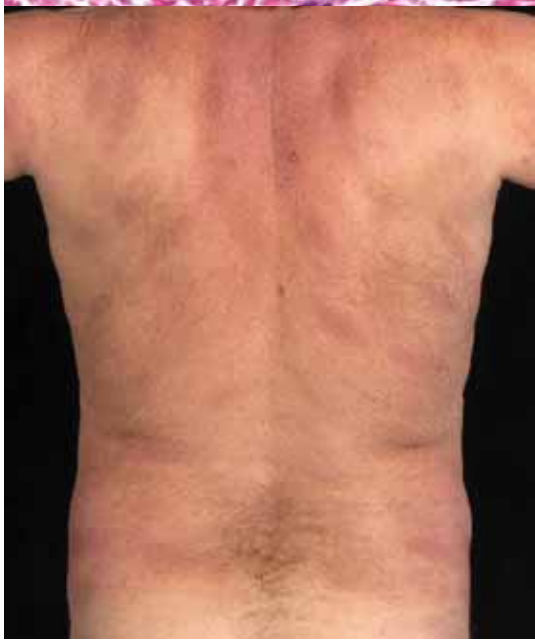


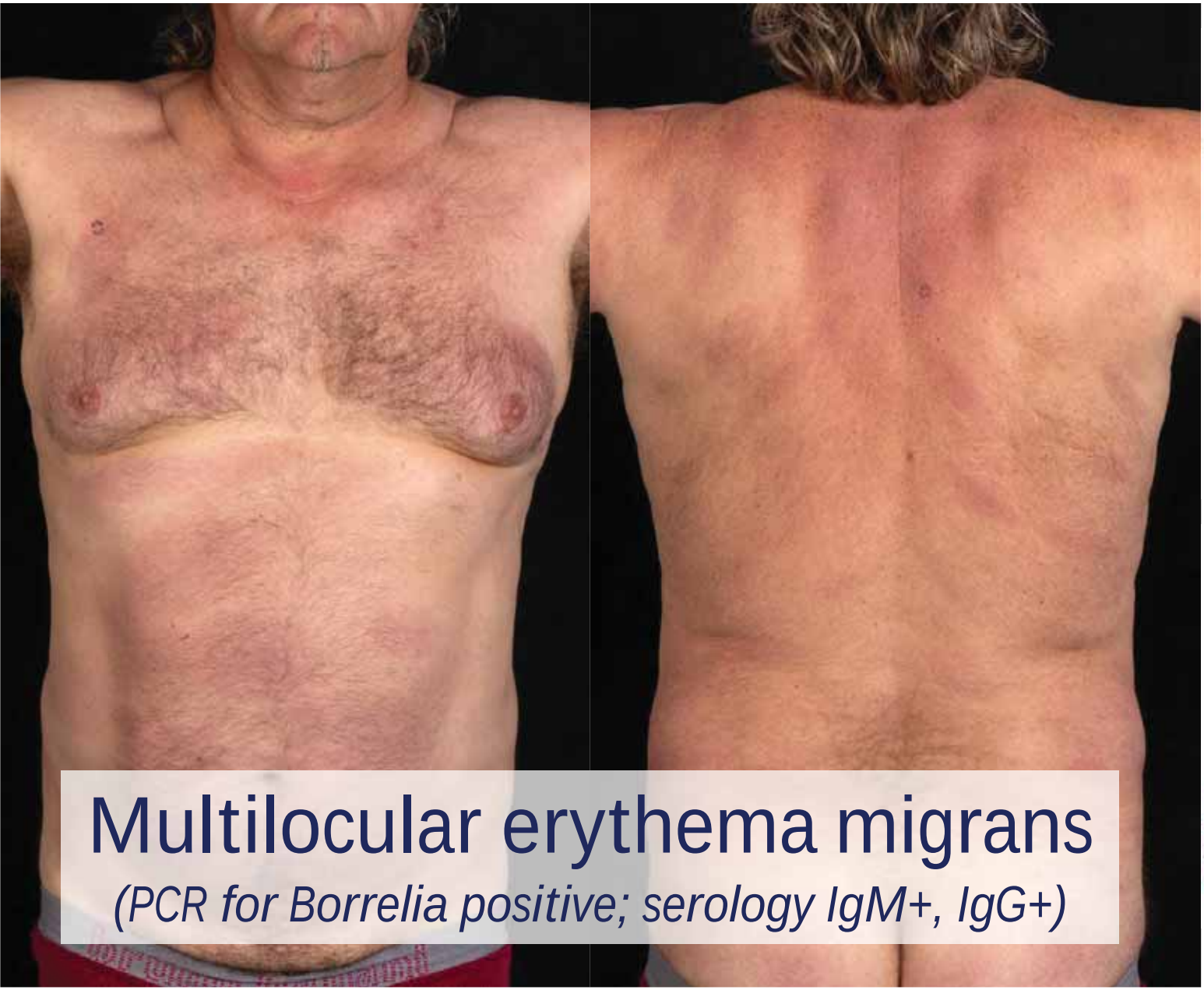




Biopsy #2

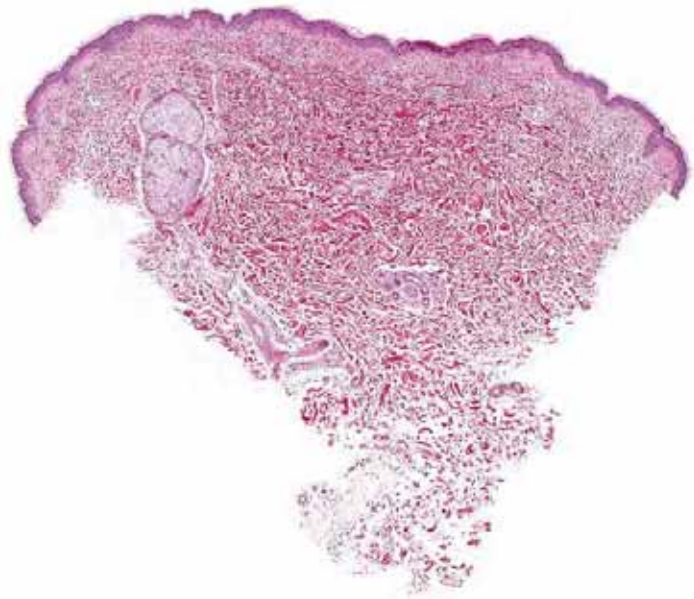


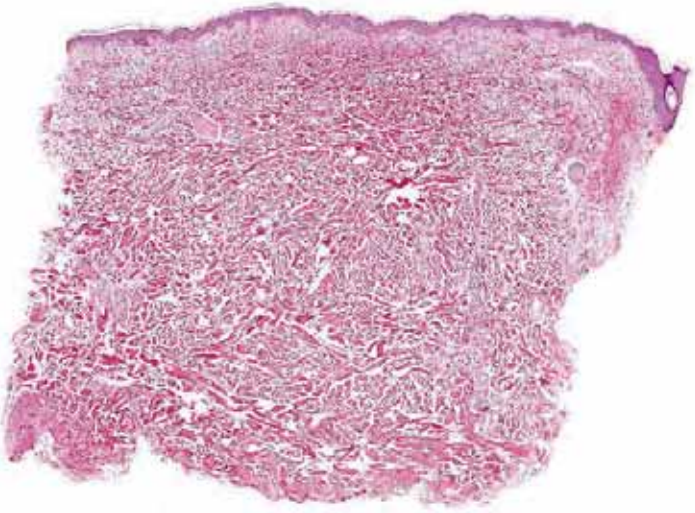


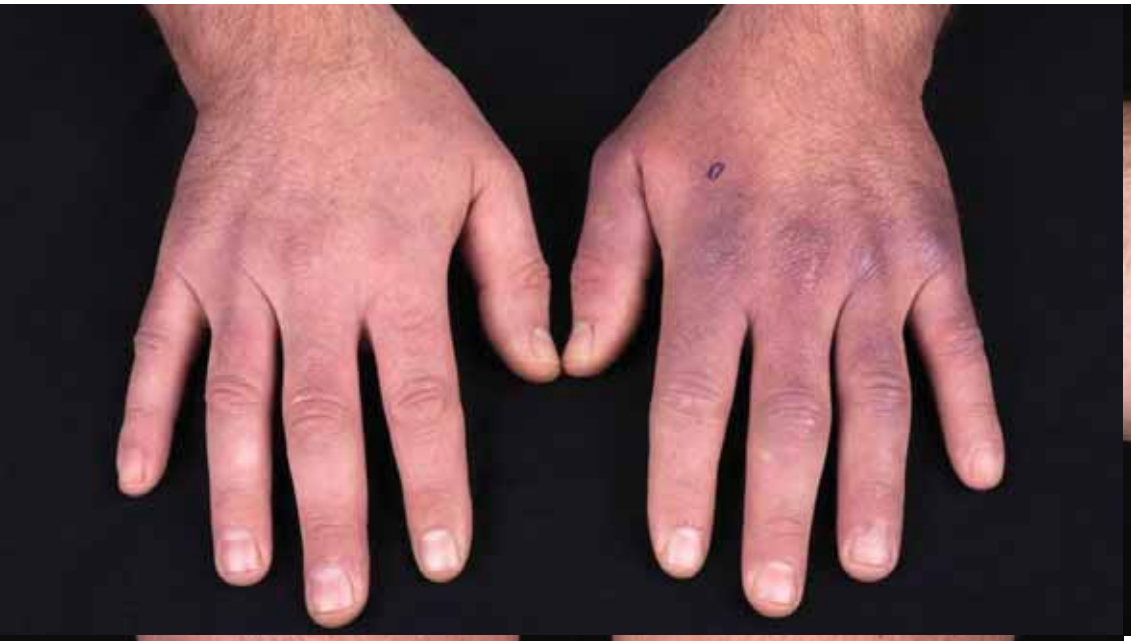


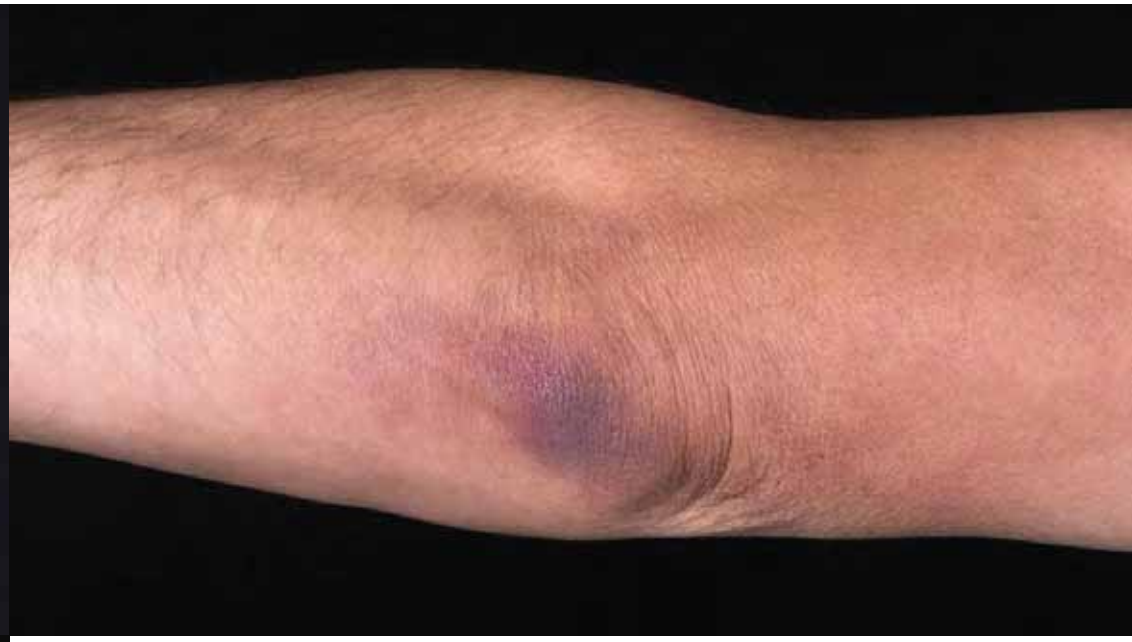
Multilocular erythema migrans

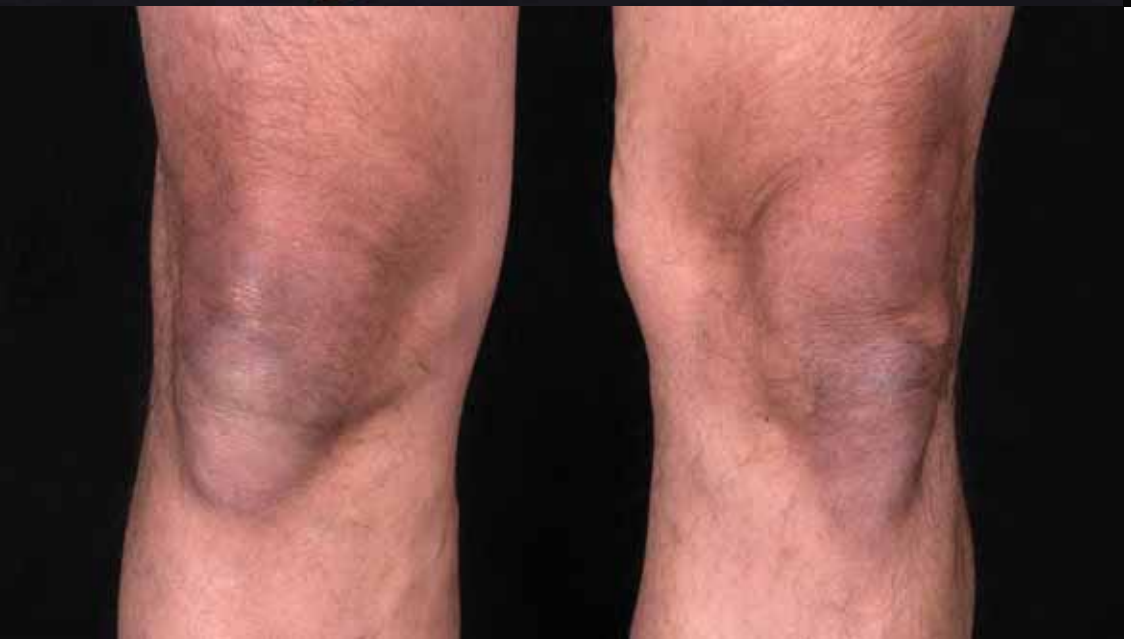
(PCR for Borrelia positive; serology IgM+, IgG+)





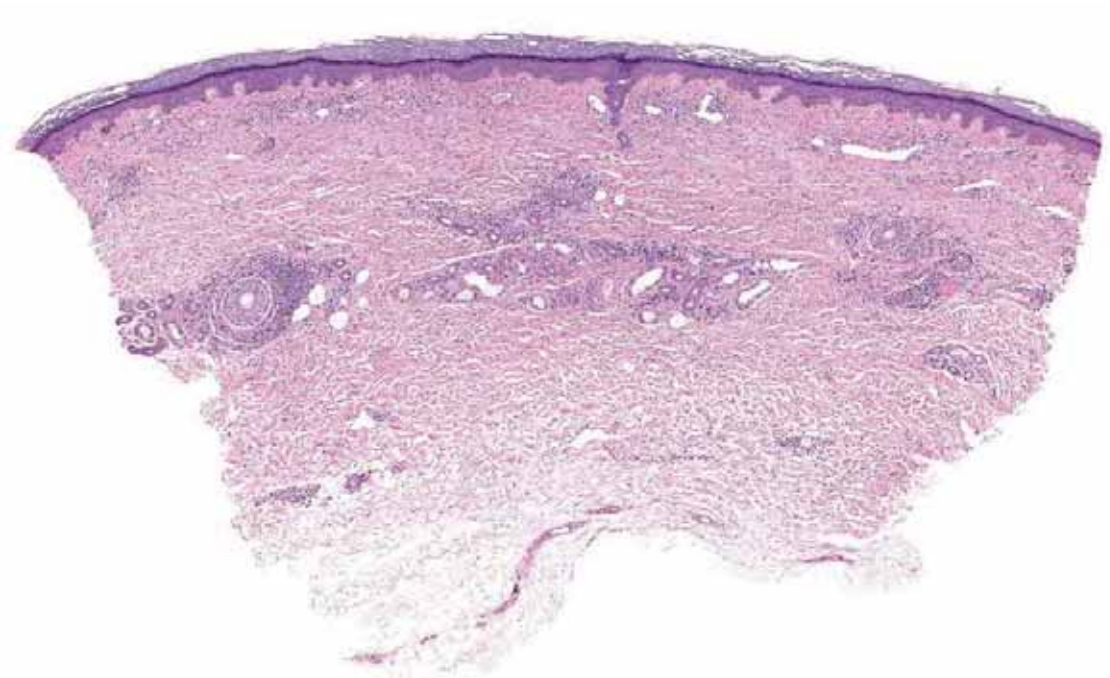


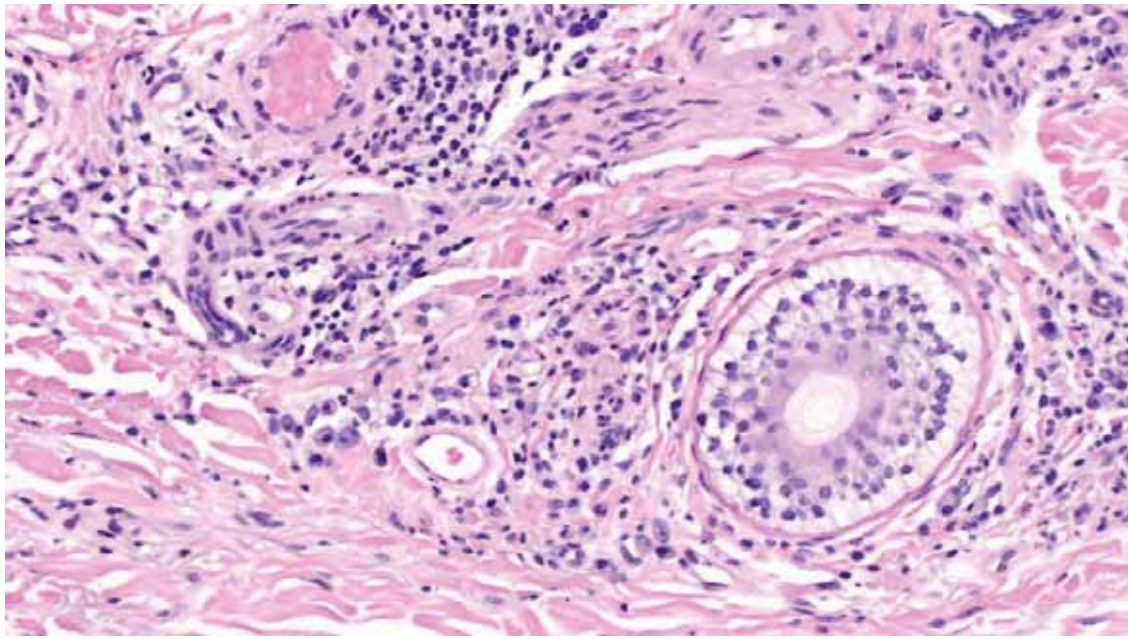




M, 54

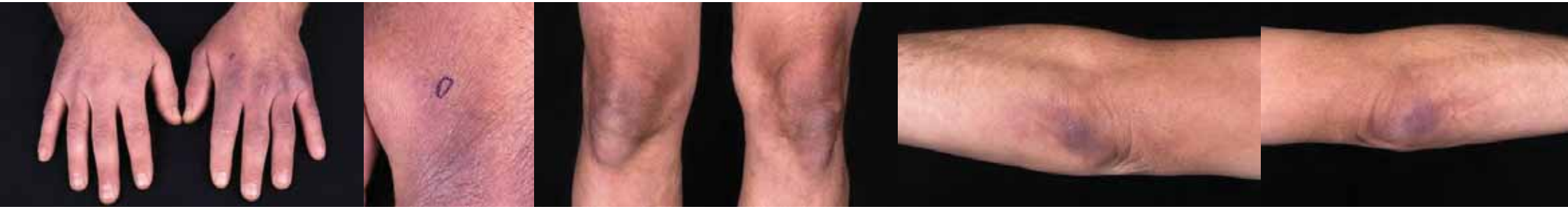
"Swelling" of the right leg for the last several months.
In the last days livid discoloration of the hands and elbows.
No muscle pain; no systemic symptoms.
Myositis-Abs negative.
No history of tick bite.

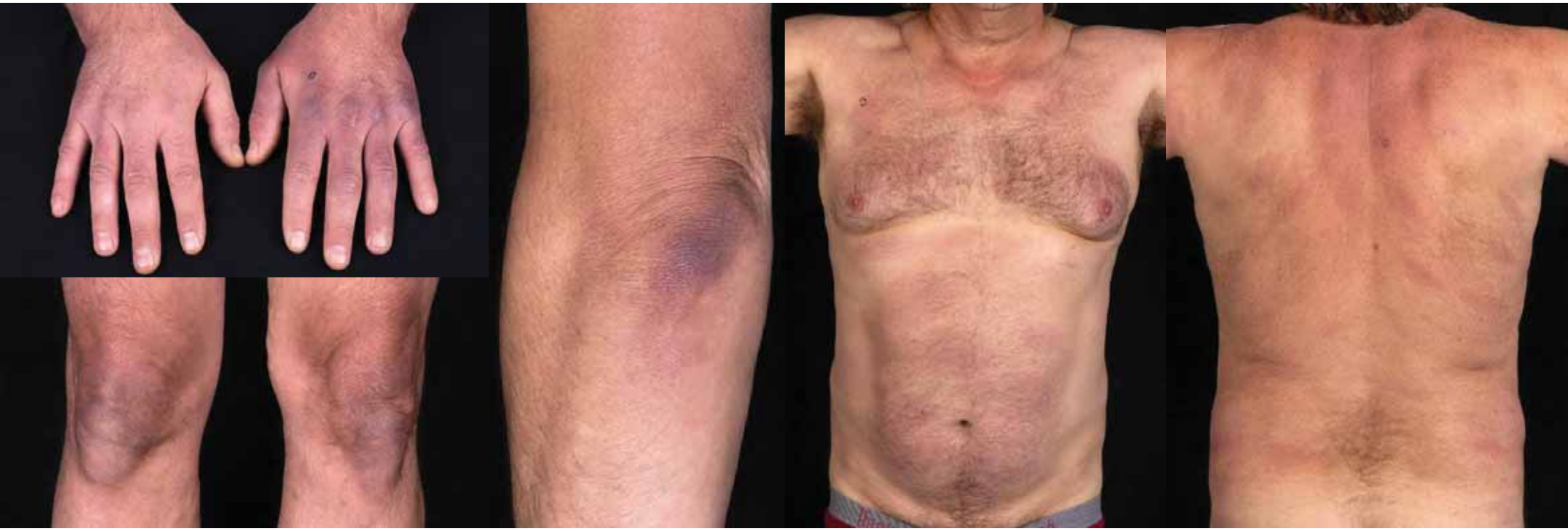




"Multilocular" acrodermatitis chronica atrophicans

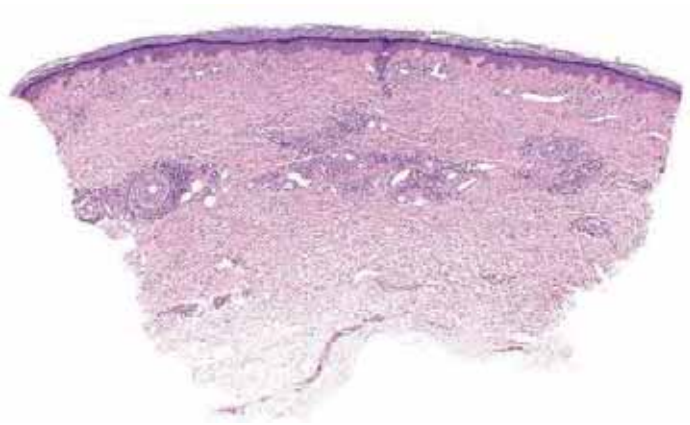
Borrelia-Abs: IgM+ (64 U/ml); IgG+ (>100 U/ml); IgG immunoblot + (20 points)

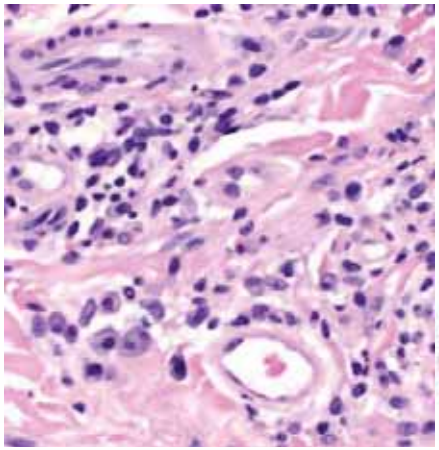


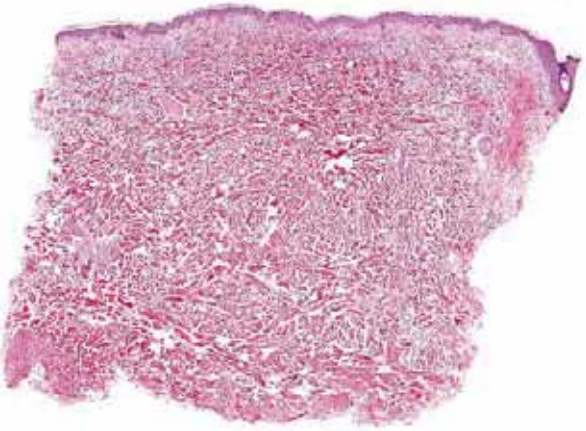


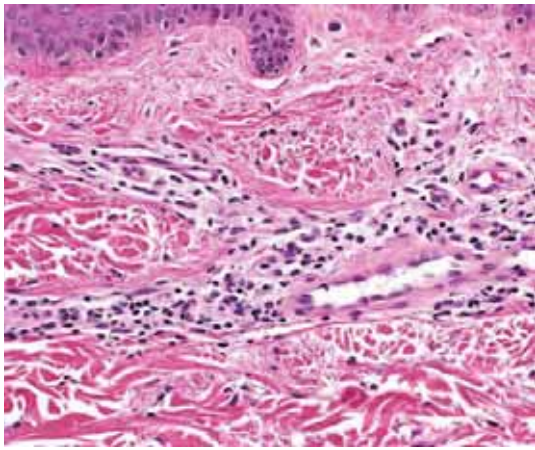
Multilocular acrodermatitis chronica atrophicans

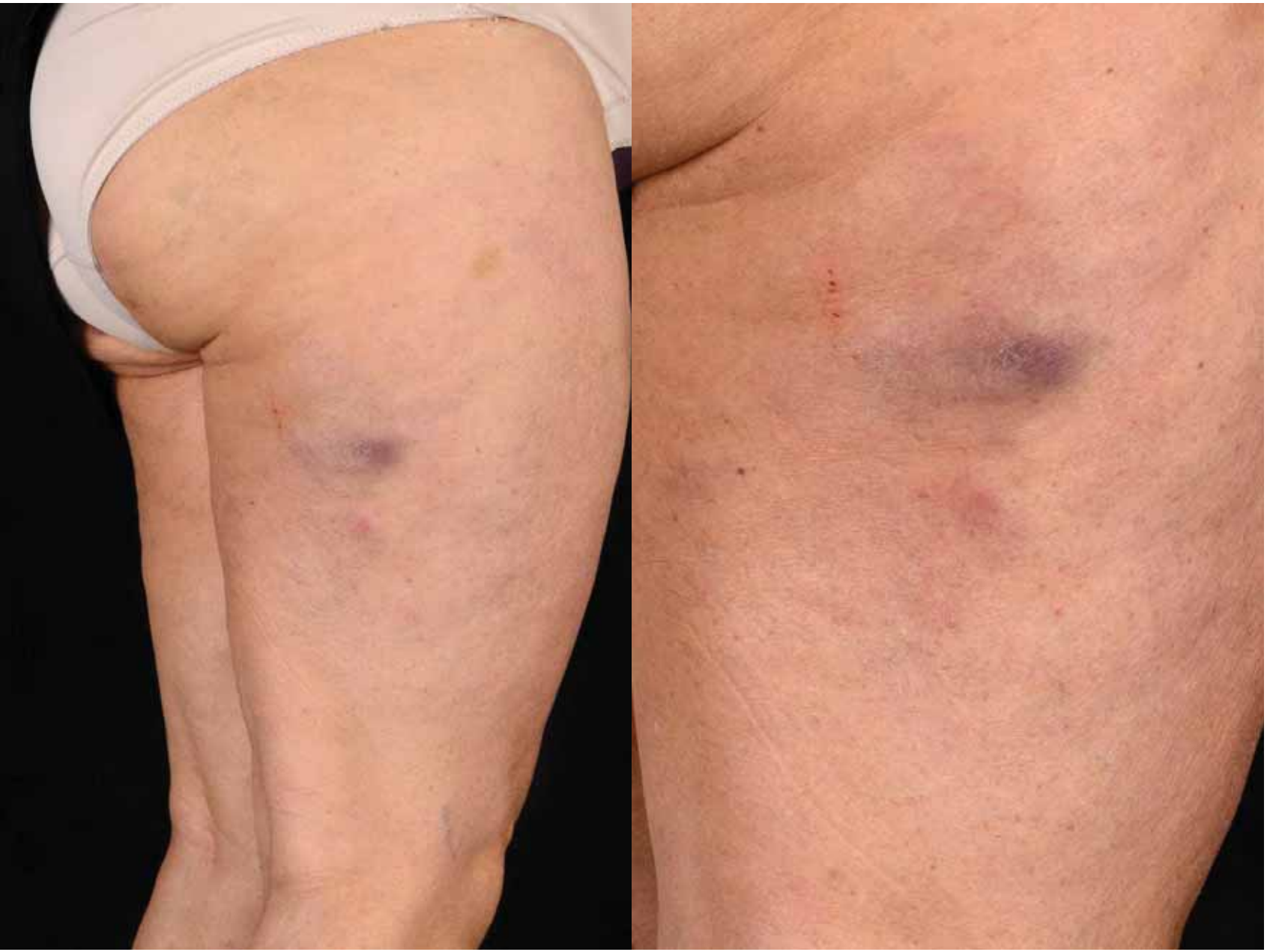
Generalized multilocular erythema migrans









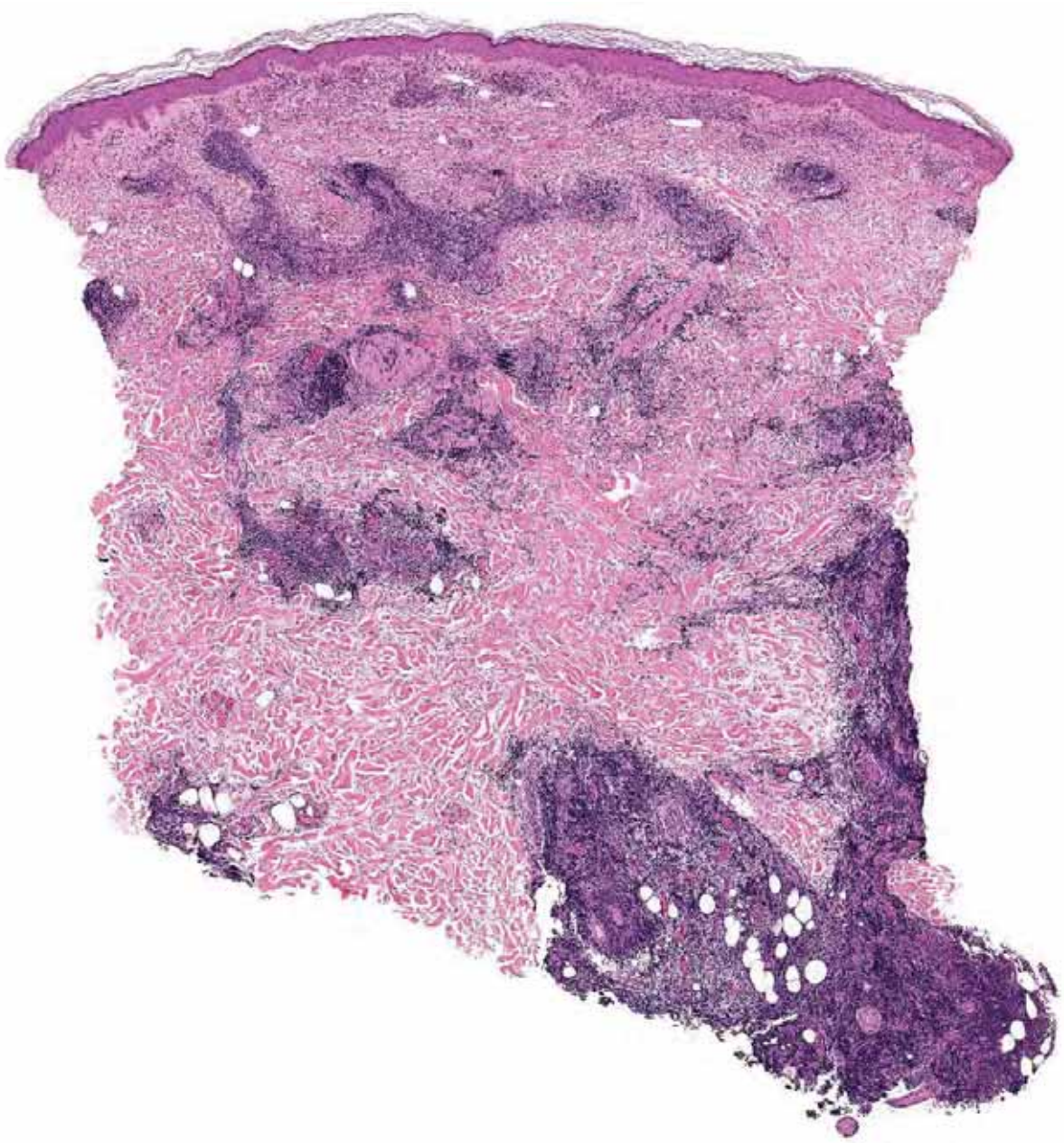


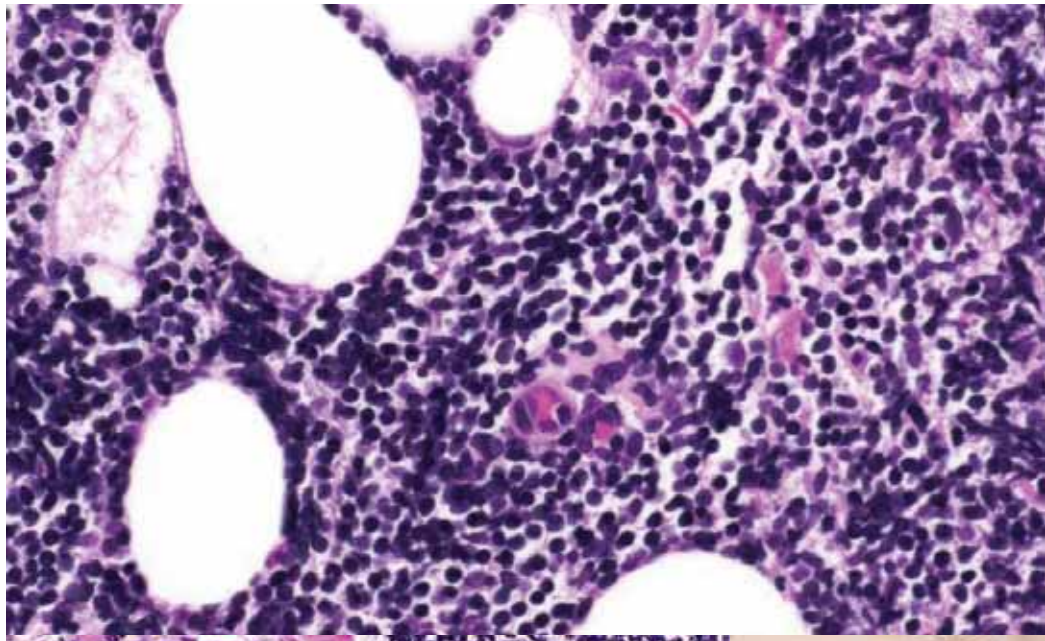
F, 62

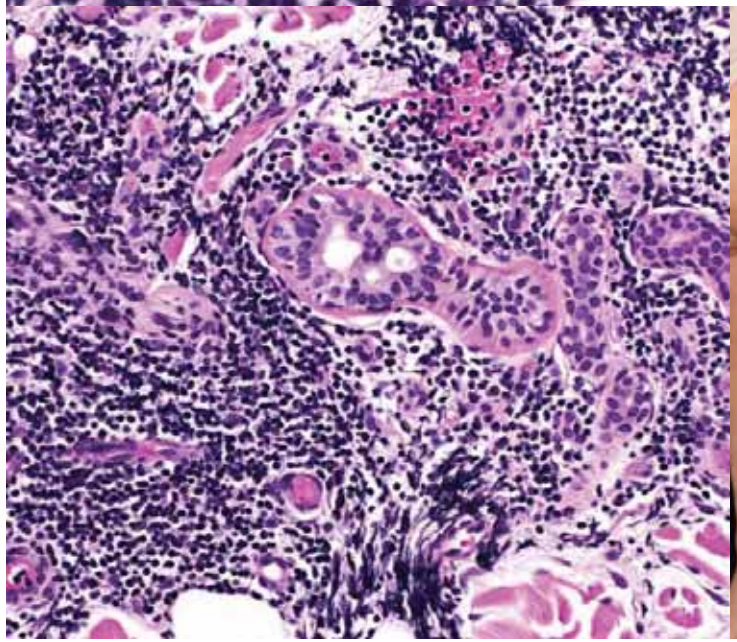
A private dermatologist made a biopsy under the clinical diagnosis of "infiltration on the right thigh", reported externally as atypical lymphoid proliferation, consistent with specific manifestation of B-CLL.

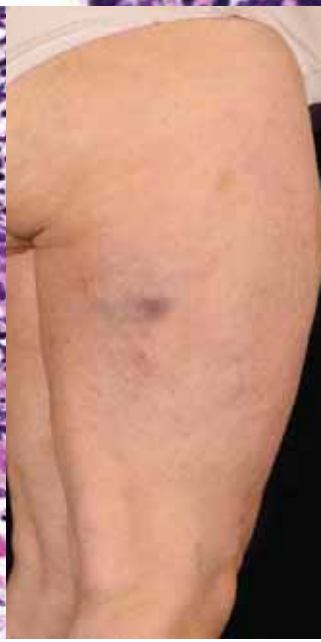
History of B-CLL (1st diagnosis 4 years before presentation, stage Binet A / Rai 1, del 13q14, IgHV mutated (no treatment needed).

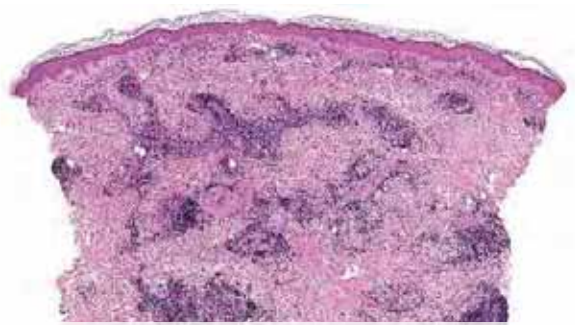
A new biopsy is taken.

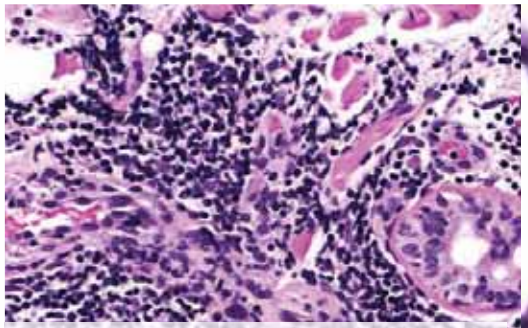


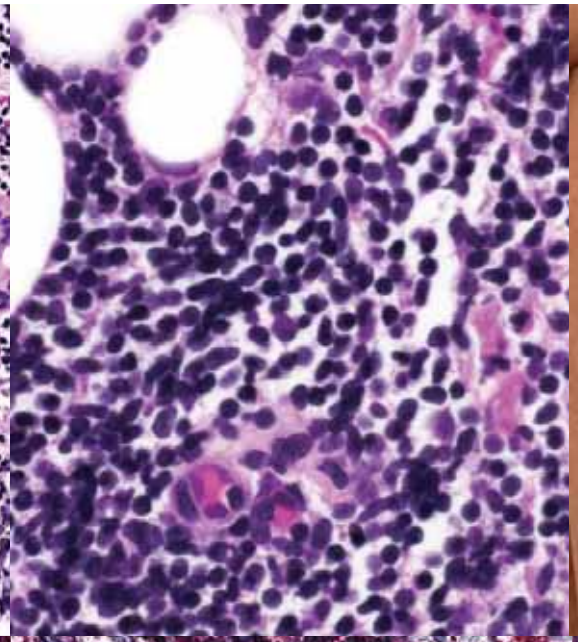


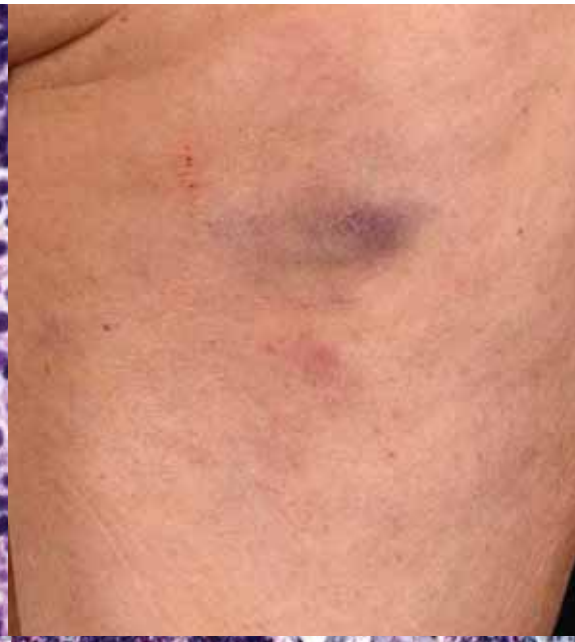






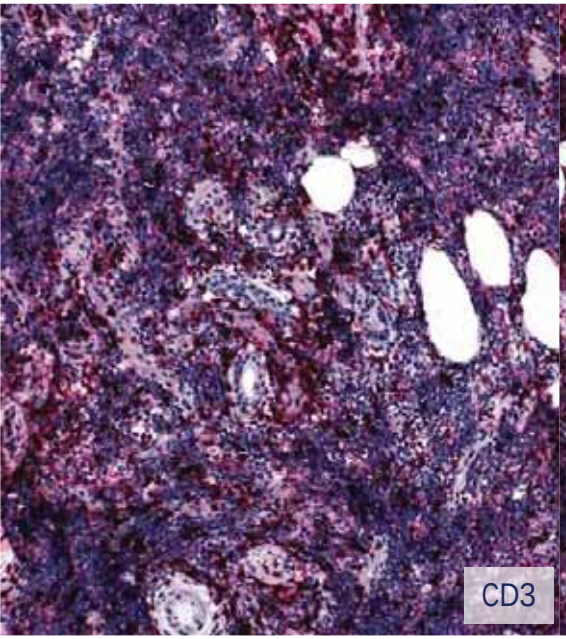


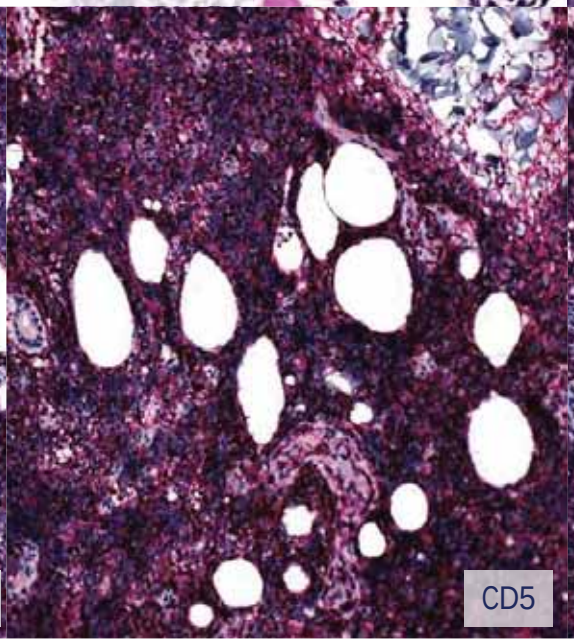


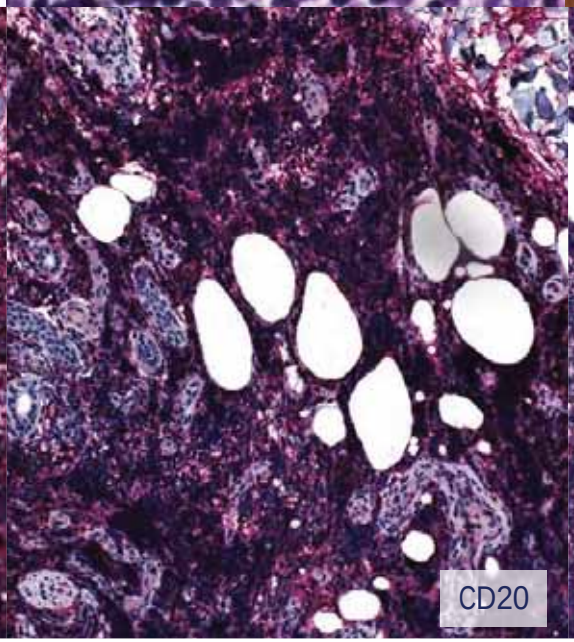


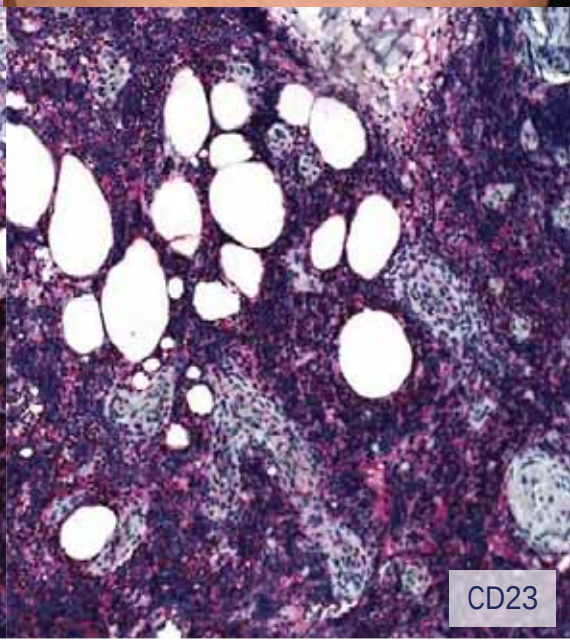
Erythema migrans
with specific infiltrate of B-CLL

PCR on lesional tissue positive for ***Borrelia***









Journal of
Cutaneous Pathology

Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) at sites typical for *Borrelia burgdorferi* infection

Lorenzo Cerroni, Gerald Höfler,[1] Barbara Bäck, Peter Wolf, Gerlinde Maier and Helmut Kerl

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Background: Cutaneous manifestations of B-cell chronic lymphocytic leukemia (B-CLL) comprise a wide spectrum of clinicopathologic presentations. In some cases, onset of skin lesions is triggered by antigenic stimulation, and specific skin infiltrates at sites of previous herpes simplex or herpes zoster infection have been well documented. Specific skin manifestations of B-CLL can also be observed at sites typical for lymphadenosis benigna cutis (nipple, scrotum, earlobe), a *Borrelia burgdorferi*-associated cutaneous B-cell pseudolymphoma.

Methods: We studied specific skin manifestations of B-CLL arising at sites typical for *B. burgdorferi*-induced lymphadenosis benigna cutis, analyzing tissues for presence of *B. burgdorferi* DNA using the polymerase chain reaction (PCR) technique. Six patients with B-CLL (M : F = 4 : 2; mean age: 67.8) presented with specific skin lesions located on the nipple (four cases) and scrotum (two cases).

Results: Clinically there were solitary erythematous plaques or nodules. Histology revealed in all cases a dense, monomorphous infiltrate of small lymphocytes showing an aberrant $CD20^+/CD43^+$ phenotype. In all cases monoclonality was demonstrated by PCR analysis of the J_H gene rearrangement. PCR analysis showed in four of the six cases the presence of DNA sequences specific for *B. burgdorferi*.

Conclusions: Our study demonstrates that infection with *B. burgdorferi* can trigger the development of specific cutaneous infiltrates in patients with B-CLL.

Cerroni L, Höfler G, Bäck B, Wolf P, Maier G, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) at sites typical for *Borrelia burgdorferi* infection.
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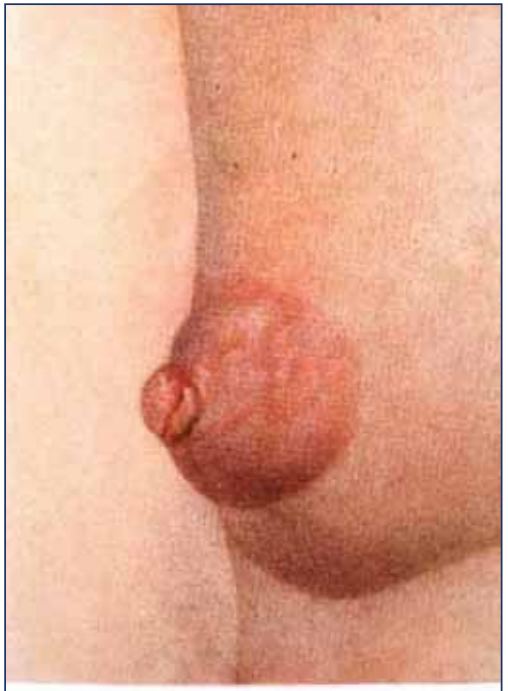
Cutaneous manifestations of B-cell chronic lymphocytic leukemia (B-CLL) comprise a wide spectrum of clinicopathologic presentations.[1,2] In some cases skin lesions are induced by antigenic stimulation; in this context, specific skin infiltrates of B-CLL at sites of previous herpes simplex or herpes zoster infection have been well documented.[3] In some patients, specific skin manifestations of B-CLL arise at sites typical for *Borrelia burgdorferi*-associated diseases such as lymphadenosis benigna cutis (lymphocytoma cutis). The association between these lesions and *B. burgdorferi* infection has not been investigated thus far.

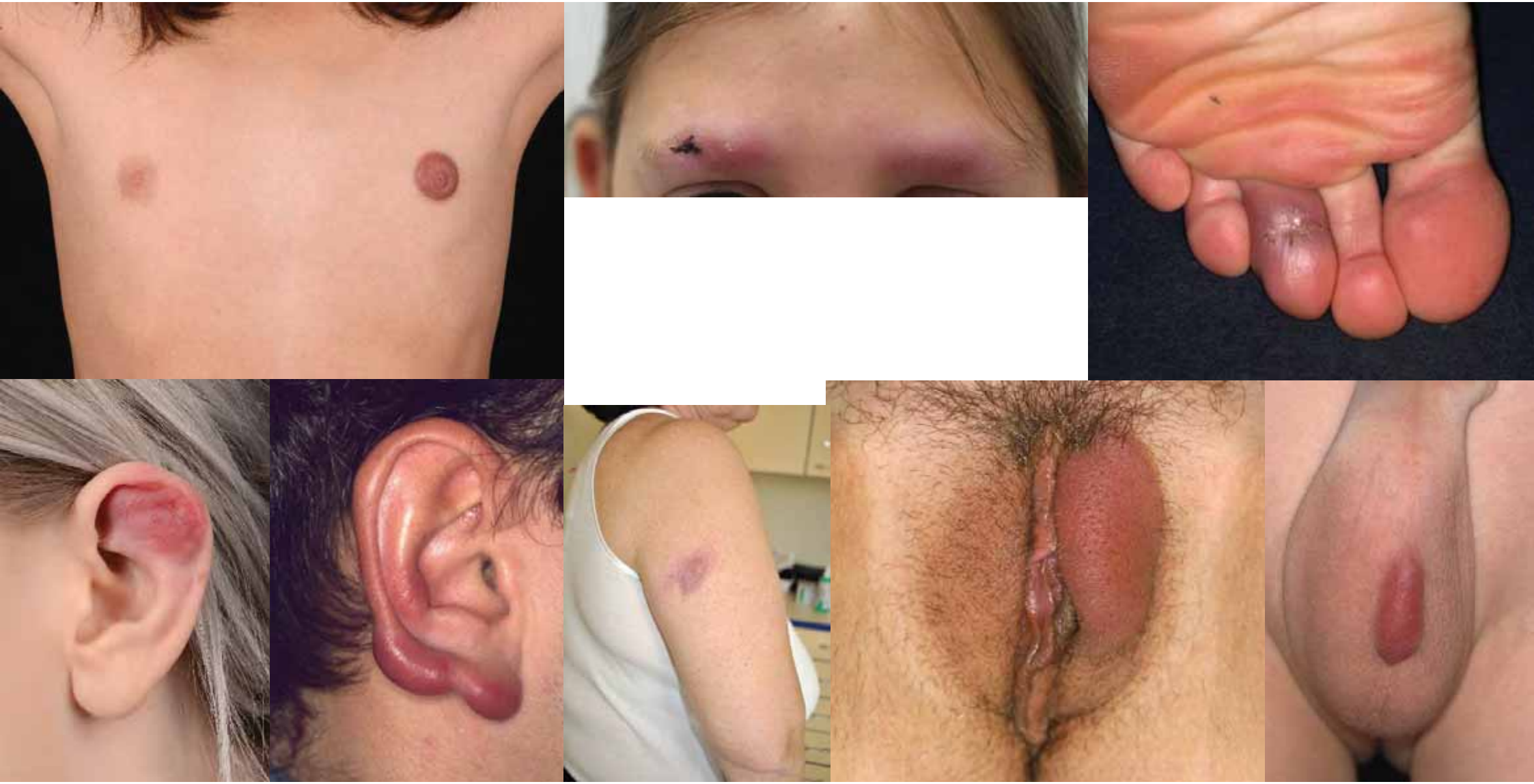
Nipple: 4 cases
Scrotum: 2 cases

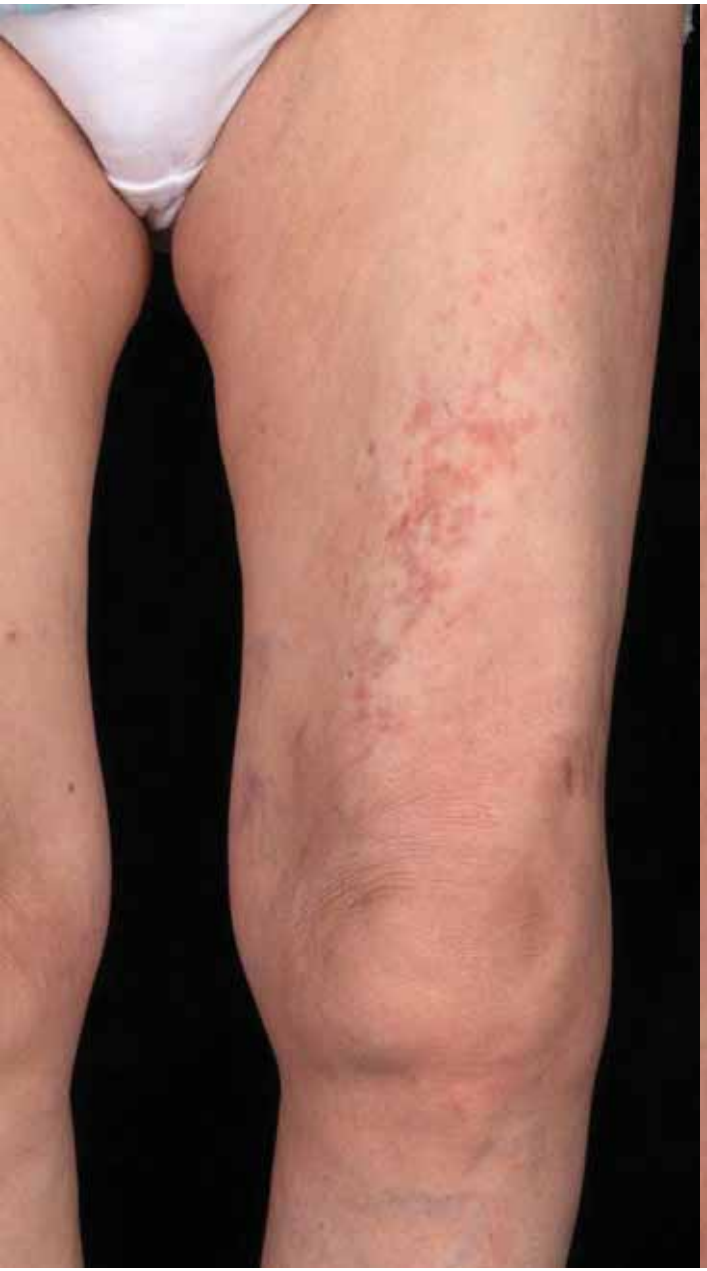
(at present: 18 cases)

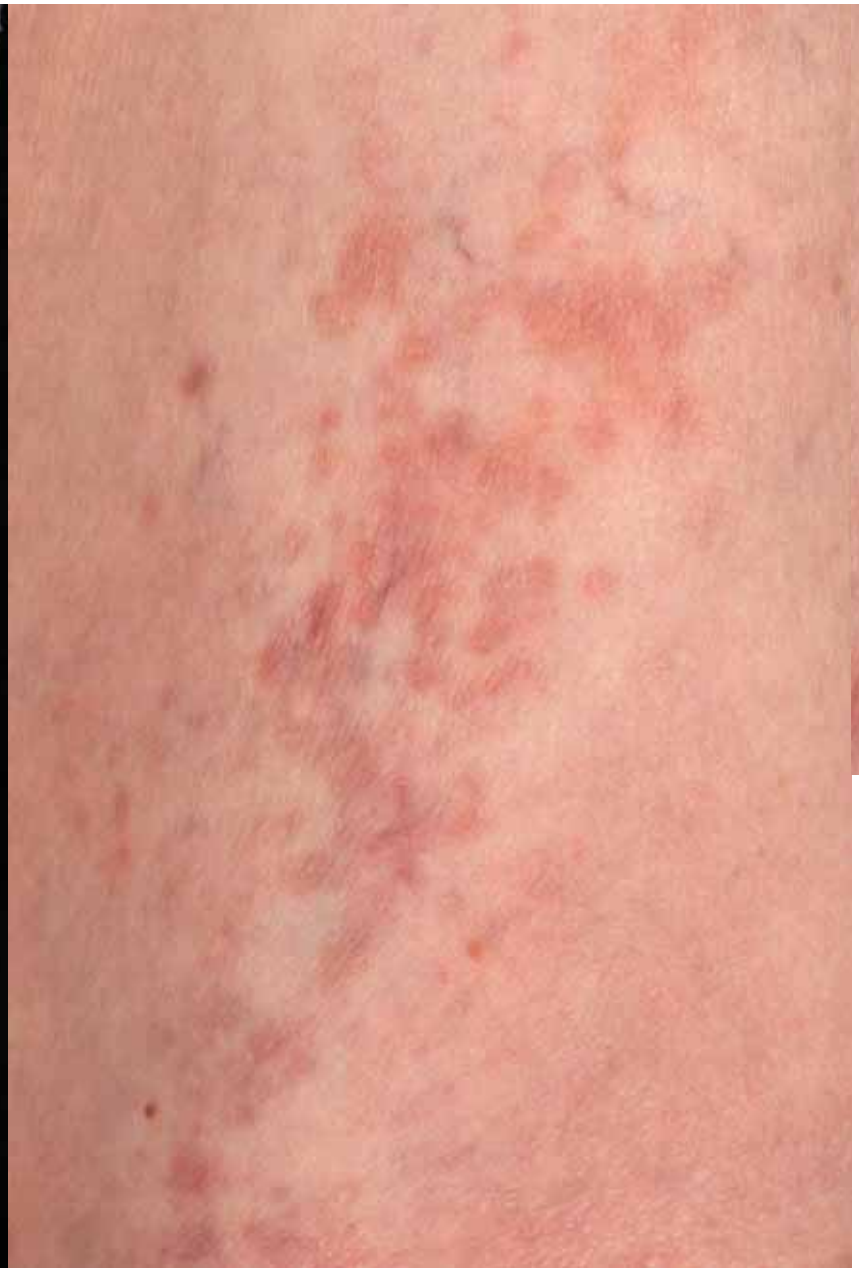


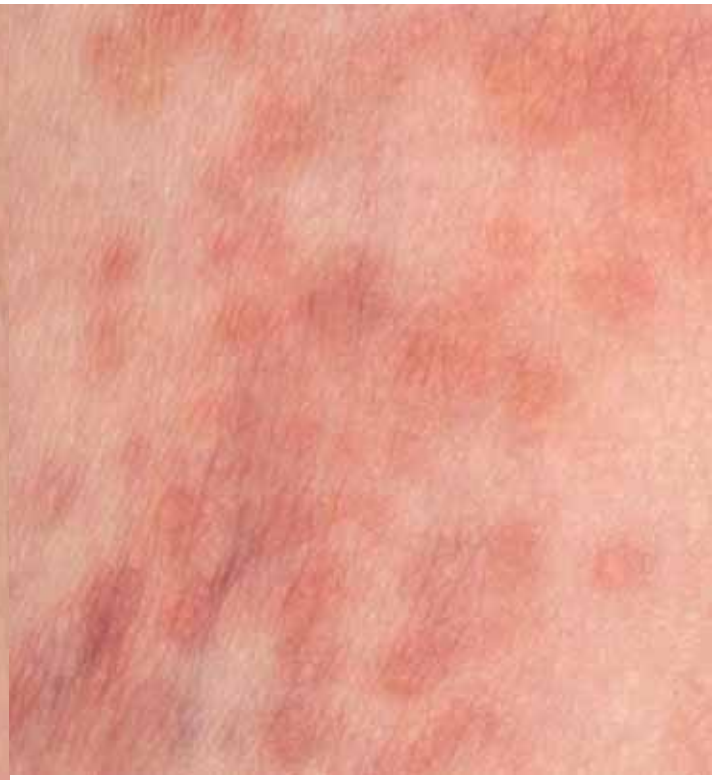
b Leukaemia lymphatica mamillae

Clinical presentations of *Borrelia* lymphocytoma





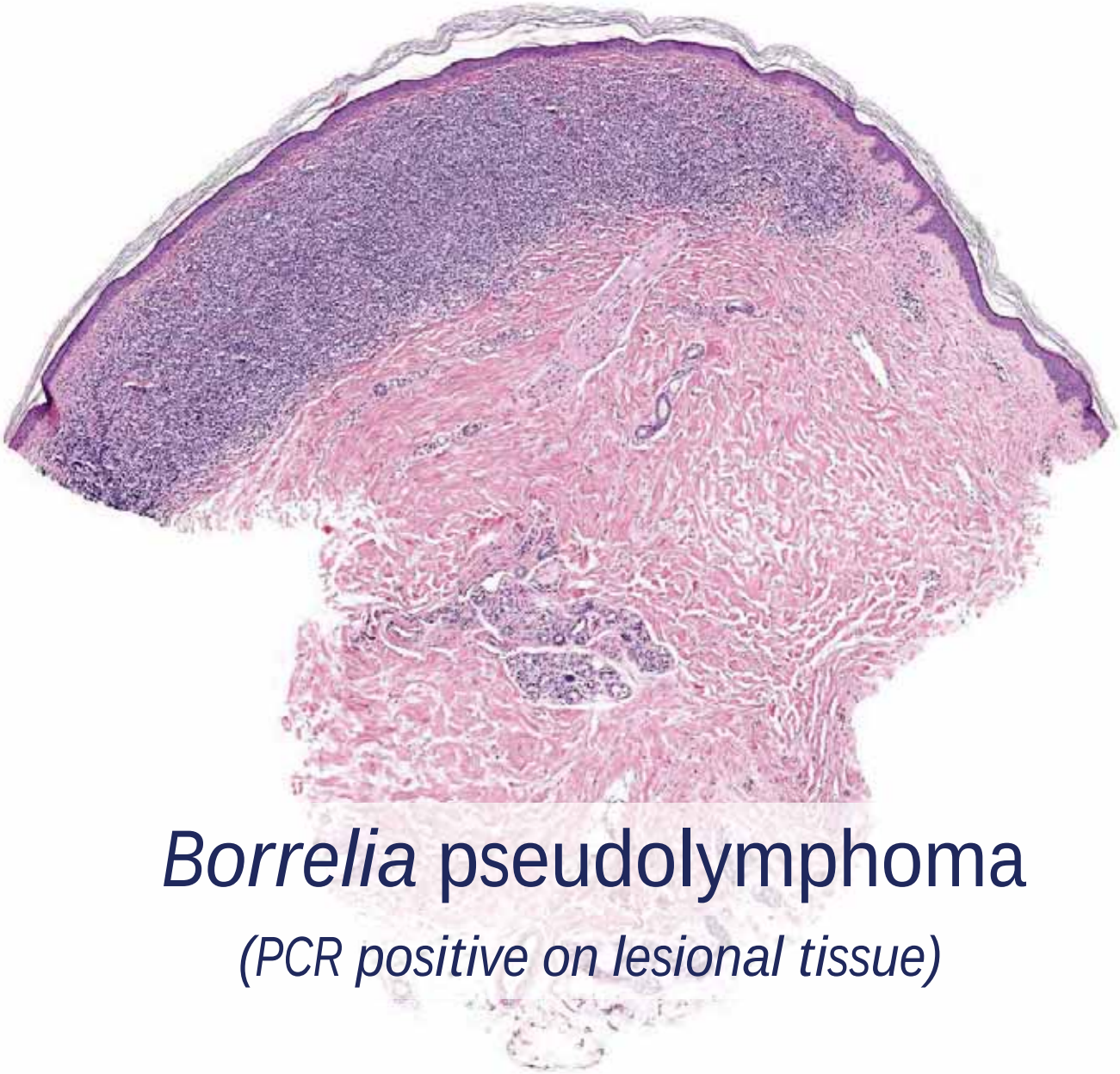


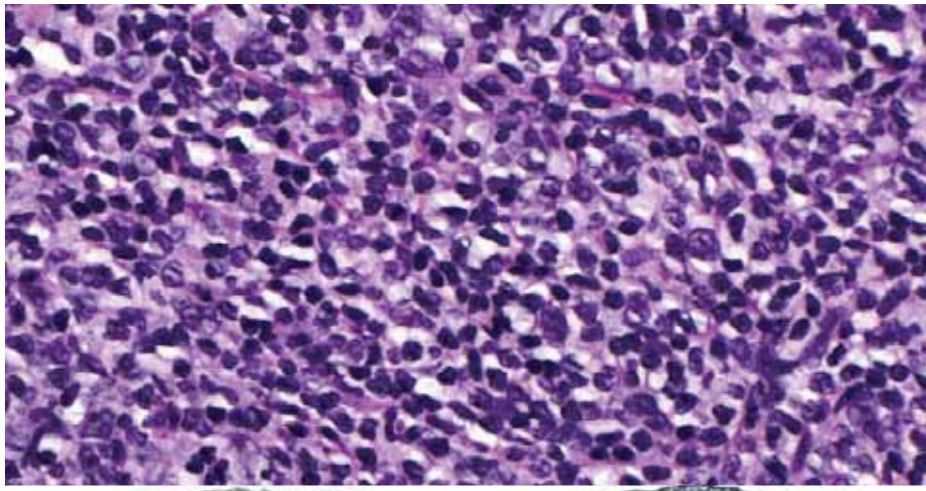


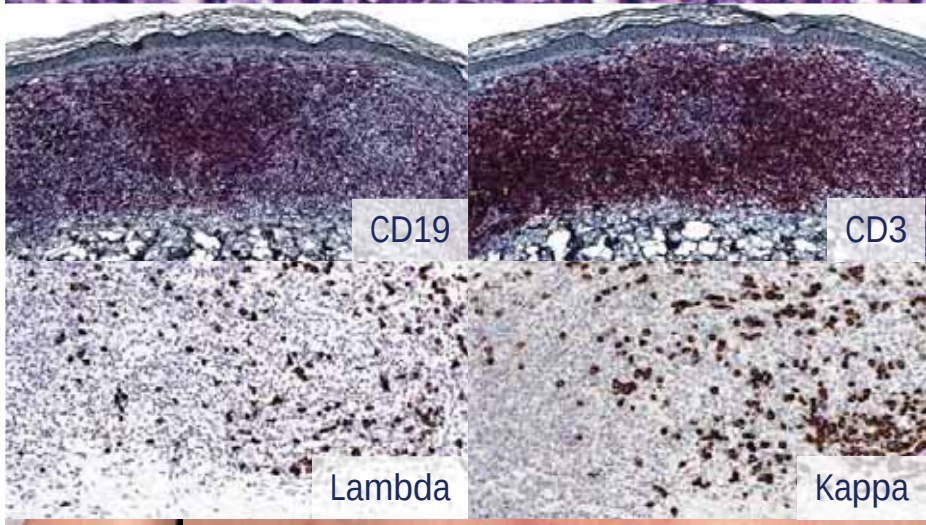
F, 83

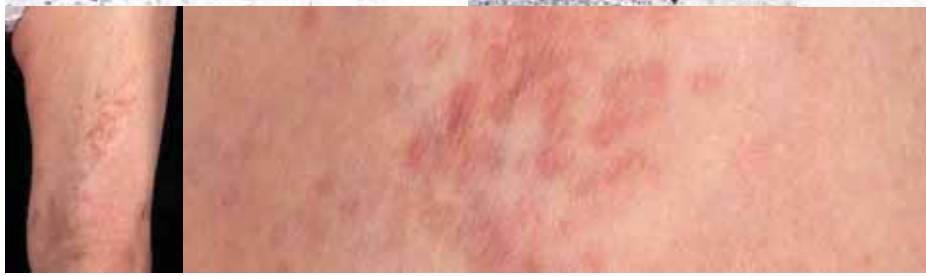
Since approximately 5 months skin lesions on the left thigh. An external biopsy was reported as "lichenoid inflammation, suspect for peripheral T-cell lymphoma, NOS".

A new biopsy is taken.









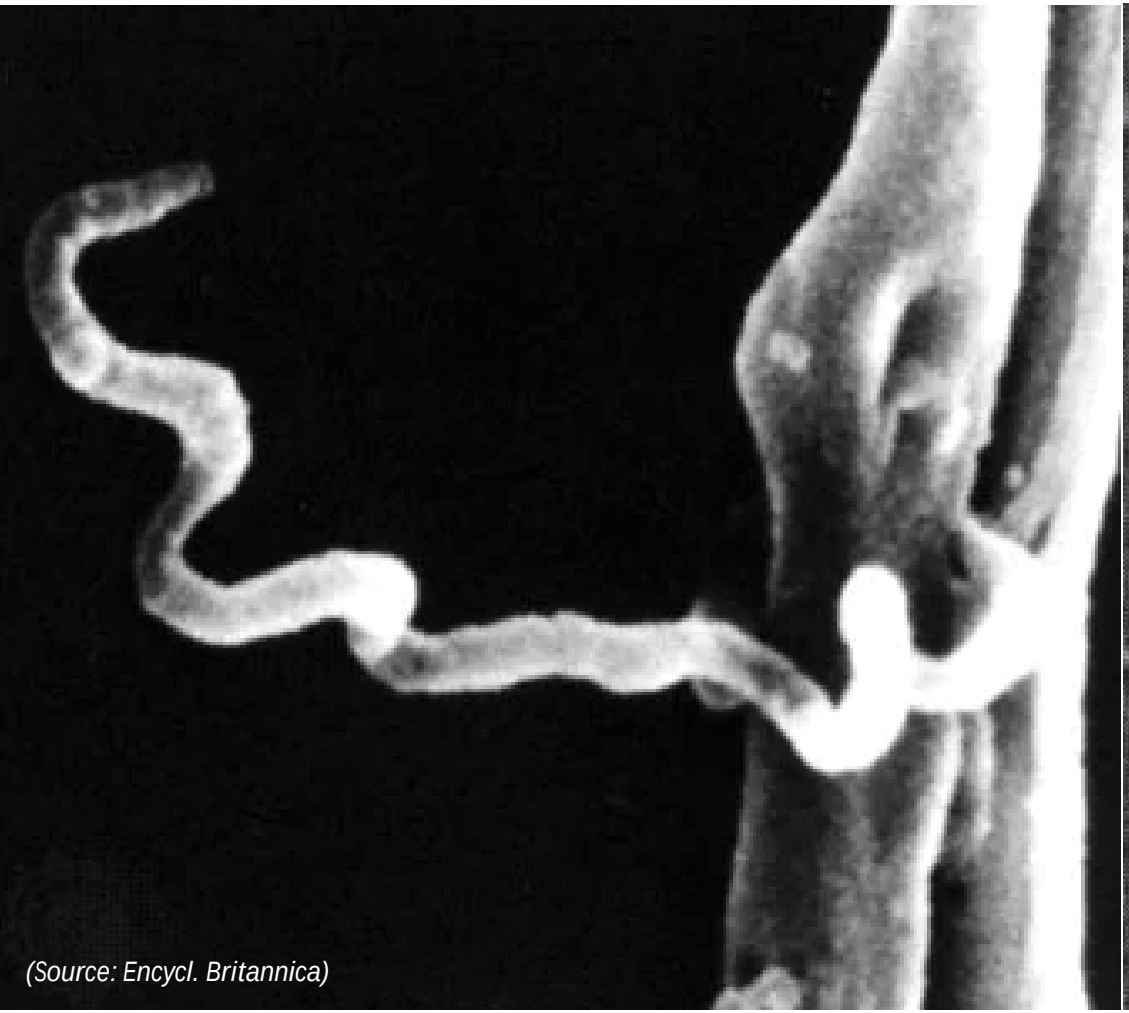
Borrelia pseudolymphoma

(PCR positive on lesional tissue)

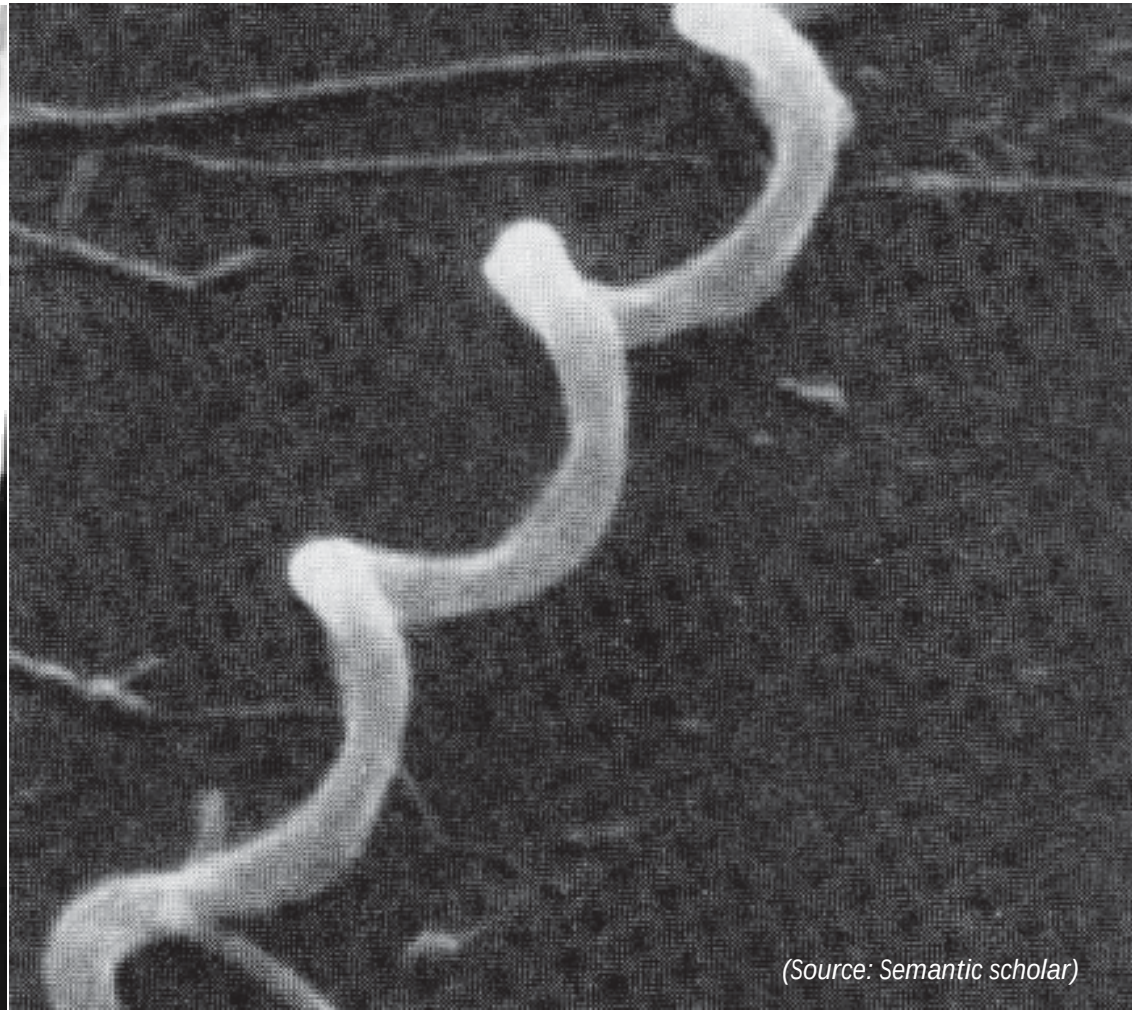
Borrelia infections

- Different clinical presentations are associated with different species of *Borrelia*; some presentations observed in Europe are not seen in American patients
- Conventional Lyme disease (*B. burgdorferi*) is characterized by erythema migrans at the site of tick bite, malaise, muscle and joint pain; later symptoms include neuroborreliosis, arthritis, involvement of other internal organs
- The most common presentation in Europe is erythema migrans, often uncomplicated; *Borrelia* lymphocytoma represents an unusual early *Borreliosis*; acrodermatitis chronic atrophicans and "fibroid nodule" are a manifestation of late *Borreliosis*; both are caused by *B. afzelii* and *B. garinii*

Spirochetal infections



Syphilis (*Treponema pallidum*)

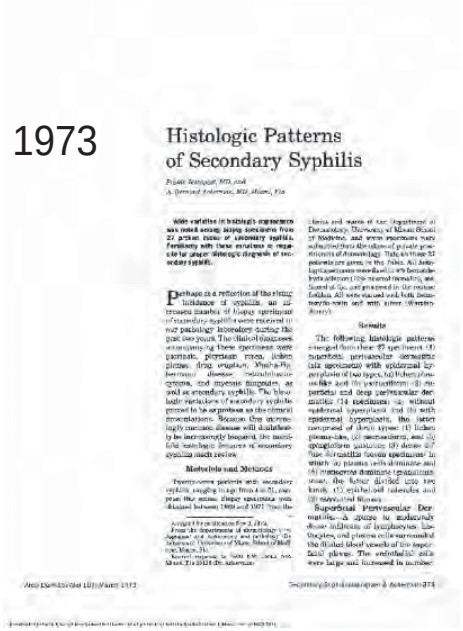


Lyme disease (*Borrelia*, several species)

Syphilis – Histopathological features

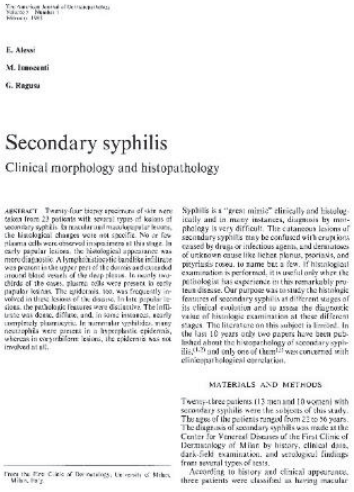
- *Primary syphilis:* ulceration and diffuse dermal infiltrate of lymphocytes, histiocytes, and plasma cells. Endothelial swelling. Large numbers of *Treponema pallidum* spirochetes detected by immunohistochemical staining.
- *Secondary syphilis:* great variability in the histopathological pattern, reflecting the variable clinical appearance of the disease. The epidermis may be normal, psoriasiform, necrotic or ulcerated. The infiltrate can be perivascular, lichenoid, nodular, or diffuse, and is composed of lymphocytes, histiocytes, and plasma cells. Older lesions of secondary syphilis may be granulomatous and can resemble granulomatous dermatoses. Endothelial swelling and vascular proliferation can be seen. Spirochetes are identified by immunohistology in the majority of cases (sometimes only a few microorganisms visible).
- *Lues maligna:* pattern(s) similar to secondary syphilis.
- *Tertiary syphilis:* tuberculoid granulomas (with or without caseation) together with plasma cells. Endothelial swelling is evident. Spirochetes may be difficult to identify.

1973



Histologic Patterns of Secondary Syphilis

1983



E. Alessi
M. Innocenti
G. Ragusa

Secondary syphilis

Clinical morphology and histopathology

2020

Histopathologic features distinguishing secondary syphilis from its mimickers

The following histologic patterns emerged from these 27 specimens: (1) superficial perivascular dermatitis (six specimens) with epidermal hyperplasia of two types, (*a*) lichen planus-like and (*b*) psoriasiform; (2) superficial and deep perivascular dermatitis (14 specimens) (*a*) without epidermal hyperplasia and (*b*) with epidermal hyperplasia, the latter comprised of three types: (1) lichen planus-like, (2) psoriasiform, and (3) spongioform pustular; (3) dense diffuse dermatitis (seven specimens) in which (*a*) plasma cells dominate and (*b*) histiocytes dominate (granulomatous), the latter divided into two kinds: (1) epithelioid tubercles and (2) associated fibrosis.

TABLE 1.

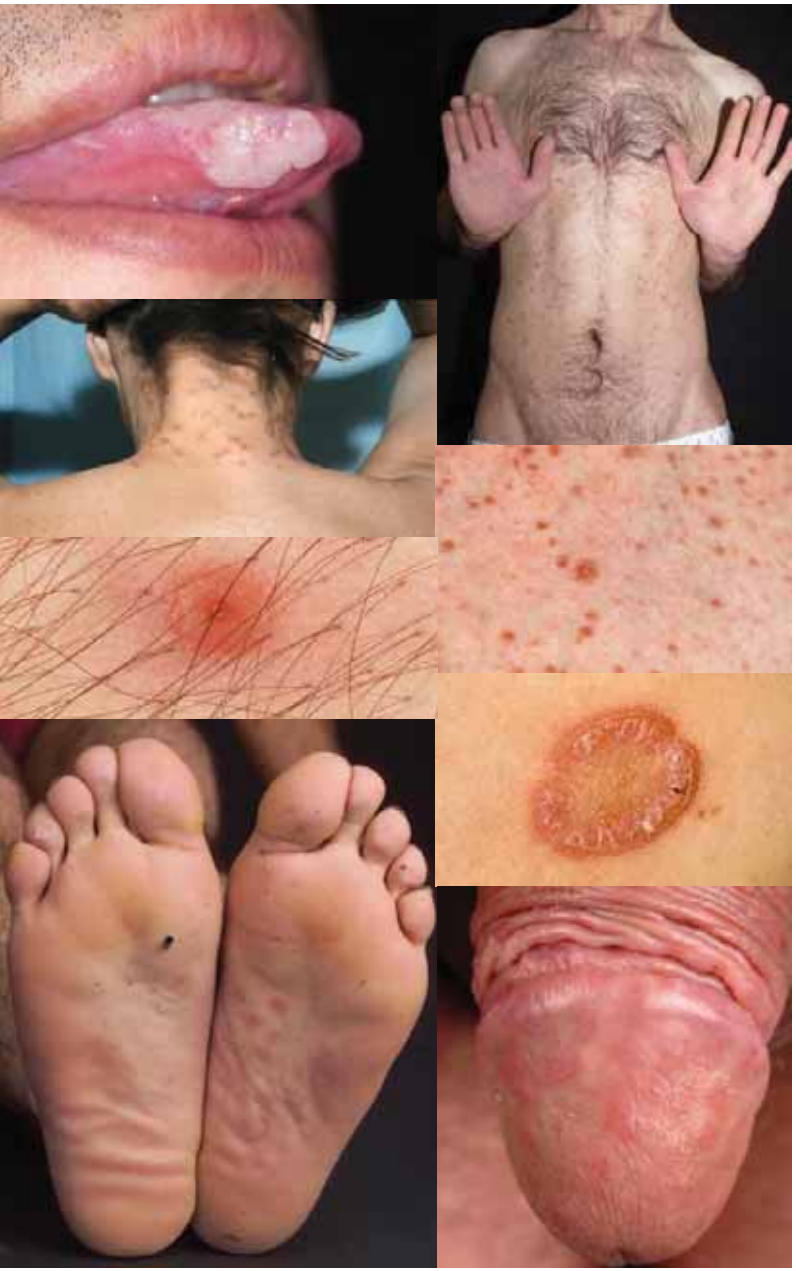
Salient Histological Findings

Clinical morphology of secondary syphilides	Macular	Maculopapular	Early papular	Late papular	Later papular
Days from the infection	70–90	90–120	90–120	120–180	>180
Number of specimens	3	4	7	5	5
Patterns of dermal infiltrate					
Superficial perivascular dermatitis	3	—	—	—	—
Superficial and deep perivascular dermatitis	—	4	—	—	—
Superficial, bandlike, and deep perivascular dermatitis	—	—	7	5	3
Dense diffuse dermatitis	—	—	—	—	2
Plasma cells	—	2	4	5	5
Giant cells	—	—	—	—	1
Epidermal changes					
Parakeratosis	—	—	1	4	2
Spongiosis	—	4	5	4	3
Exocytosis	—	1	5	4	3
Vascular changes					
Thick-walled dilated blood vessels	3	4	7	5	5
Plump endothelial cells	3	4	7	5	5

Table 1. Histopathologic features of syphilis, pityriasis lichenoides, pityriasis rosea, and mycosis fungoides

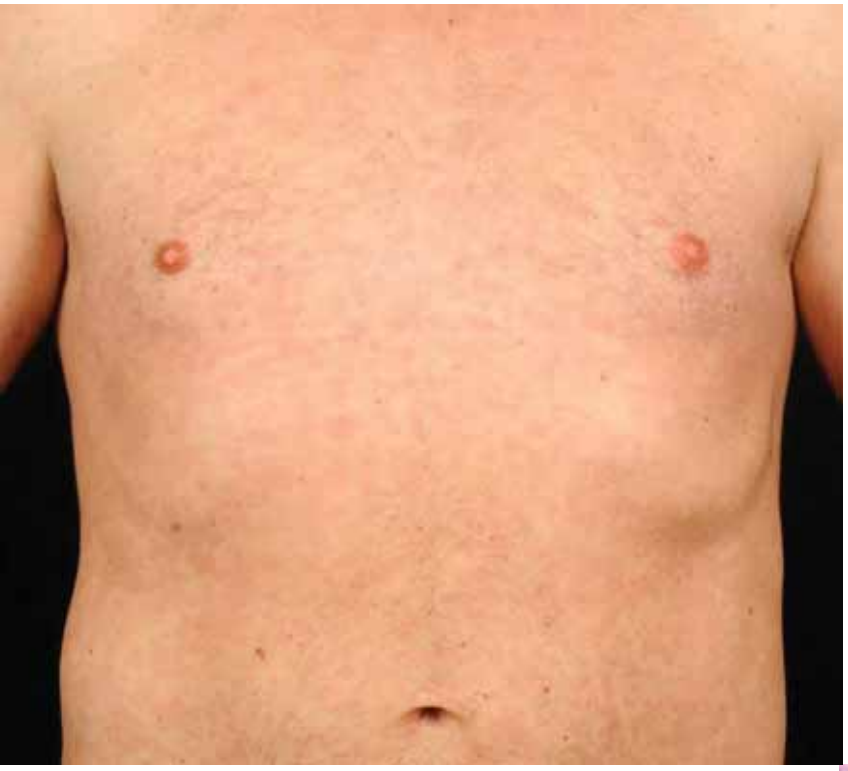
Features	Syphilis, n = 150, n (%)	Pityriasis lichenoides, n = 110, n (%)	Pityriasis rosea, n = 92, n (%)	Mycosis fungoides, n = 104, n (%)
Neutrophils in the stratum corneum	29 (29)	60 (54.55)	1 (1.39)*	8 (7.92)
Presence of plasma cells	71 (71)	62 (56.36)	2 (2.78)*	7 (6.93)
Endothelial swelling	66 (66)	53 (48.18)	14 (19.44)*	12 (11.88)
Effacement of the rete ridges	20 (20)	66 (60.0)	6 (8.37)*	31 (30.69)
Irregular acanthosis	77 (77)	53 (48.18)	29 (40.28)*	34 (33.66)
Psoriasiform acanthosis	3 (3)	78 (70.91)	2 (2.78)*	3 (2.78)
Elongated rete ridges	75 (75)	24 (21.82)	29 (77.36)*	35 (36.36)
Vacuolar interface with vacuolar predominance	11 (11)	60 (54.55)	2 (2.78)*	4 (3.96)
Vacuolar interface with equal numbers of lymphocytes and vacuoles	73 (73)	54 (49.09)	1 (1.39)*	88 (87.13)
Interstitial inflammation	94 (94)	38 (34.55)	16 (22.22)*	64 (63.37)
Lymphocytes with ample cytoplasm	57 (57.00)	58 (52.73)	2 (2.78)*	3 (4.95)

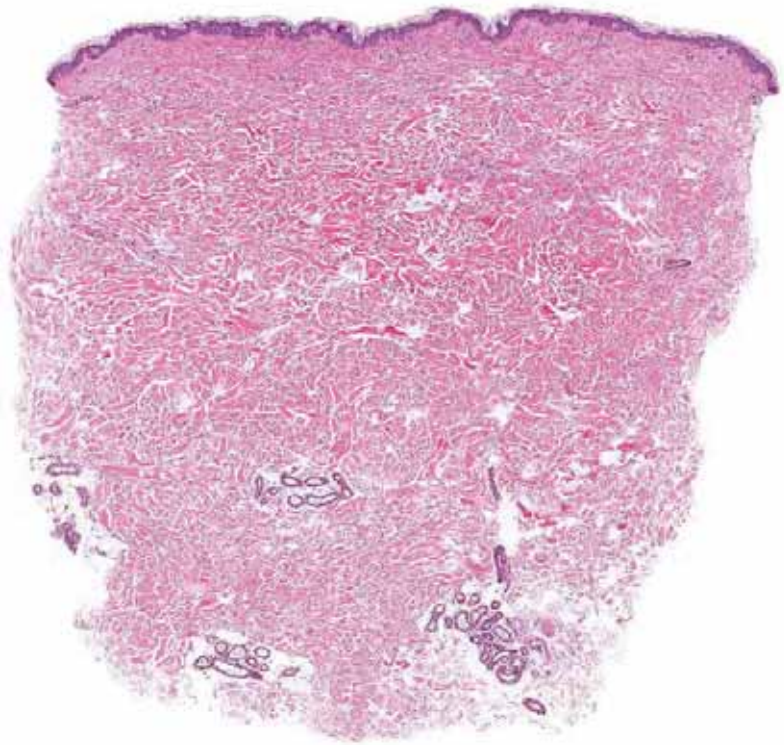
*$P < .0001$ with χ^2 test.

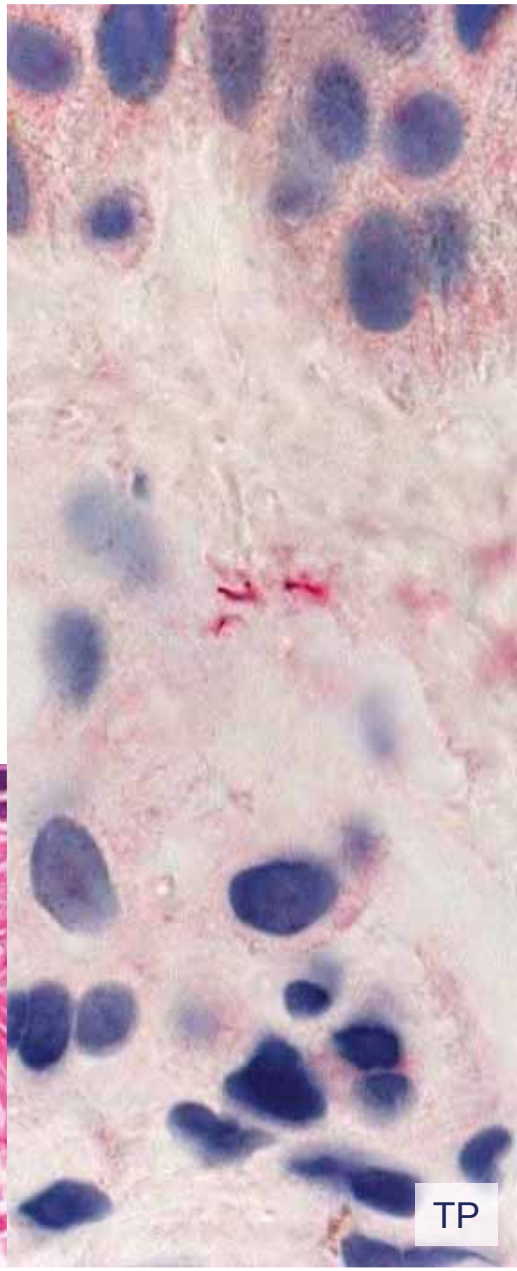


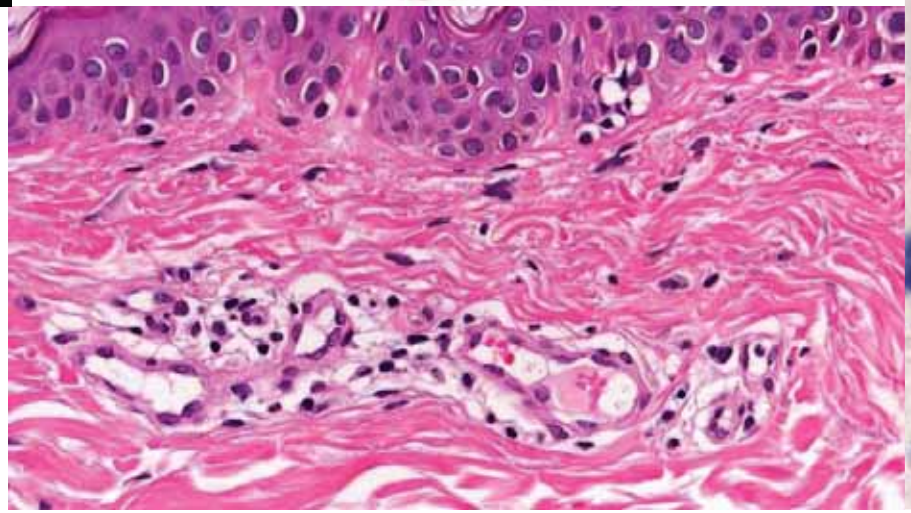
Secondary syphilis - The Great Mime

- Psoriasis-like
- Pityriasis rosea-like
- Pityriasis lichenoides-like
- Viral exanthemas-like
- Drug eruptions-like
- Lichen planus-like (lichenoid syphilis)
- Figurate erythema-like
- Disseminated granuloma annulare-like
- Palmoplantar syphilid
- Condyloma acuminatum-like (condylomata lata) / Mucous patches
- Mycotic infections-like
- Alopecia syphilitica (non-scarring alopecia)
- Atopic dermatitis / diaper dermatitis (congenital syphilis)
- Acquired cutis laxa
- Anetoderma
- Hypomelanosis (leukoderma syphiliticum)
- Necklace of Venus
- Corona veneris along the hairline
- Pseudolymphomatous syphilis







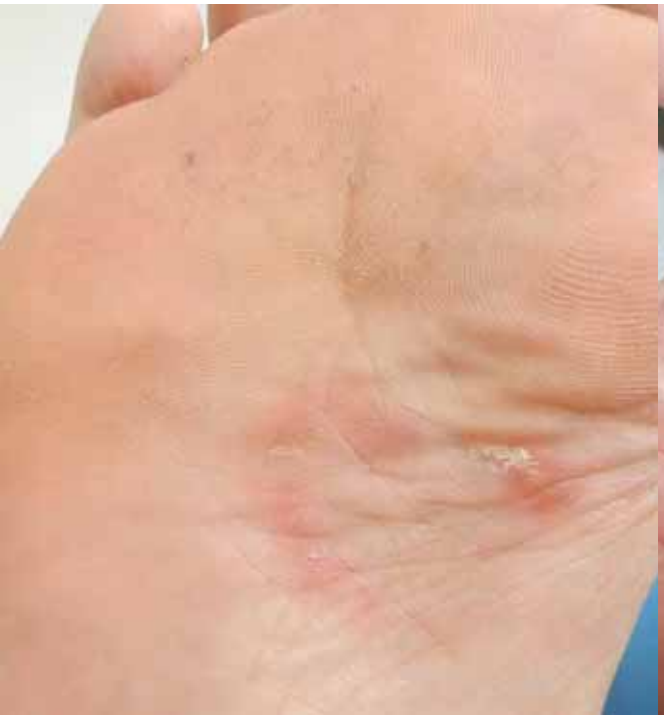


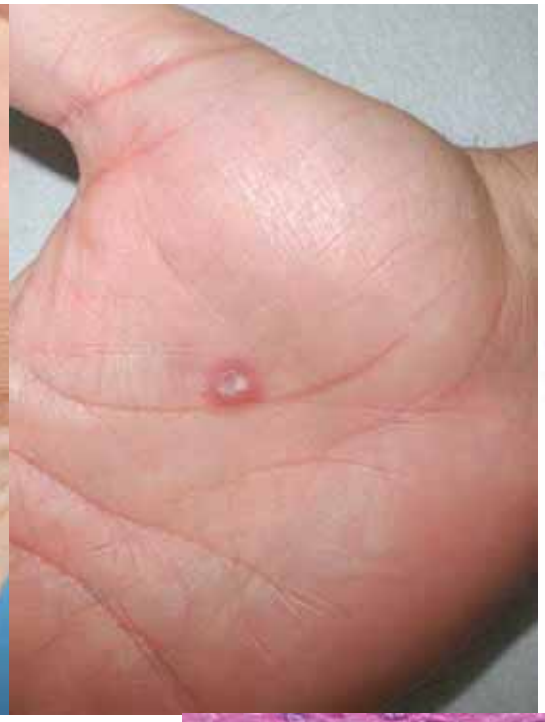
Secondary syphilis – Exanthema

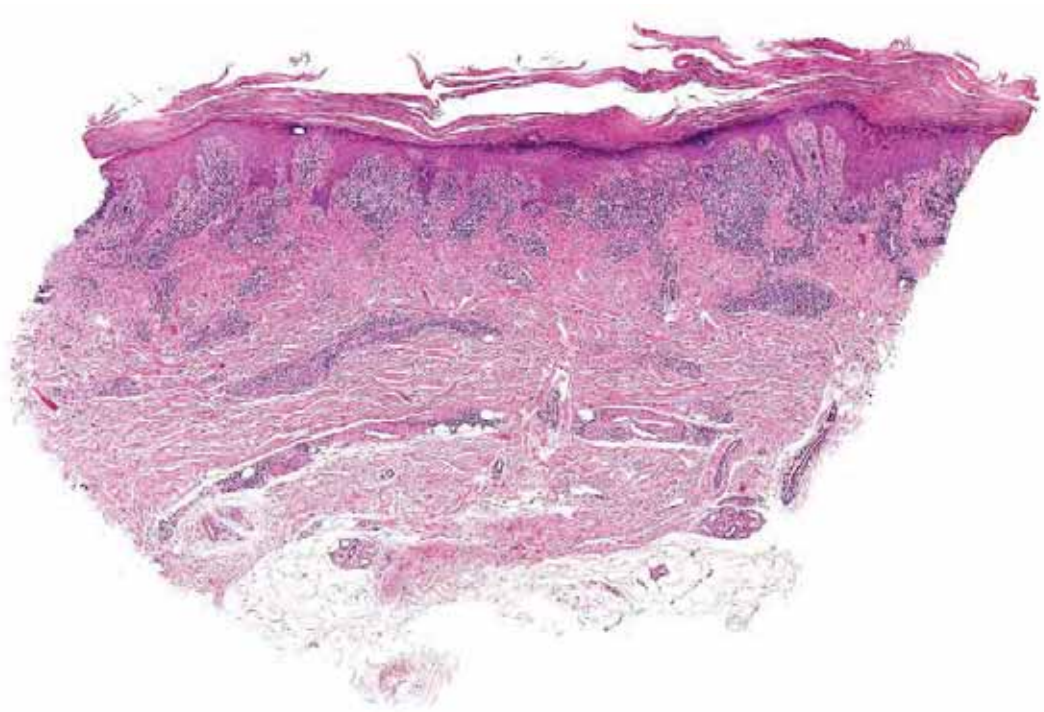
Asymptomatic viral exanthema-like clinical presentation.

The inflammatory infiltrate may be very sparse; plasma cells may be only a few (or absent).

Number of spirochetes detected by immunohistology variable; may be only a few.



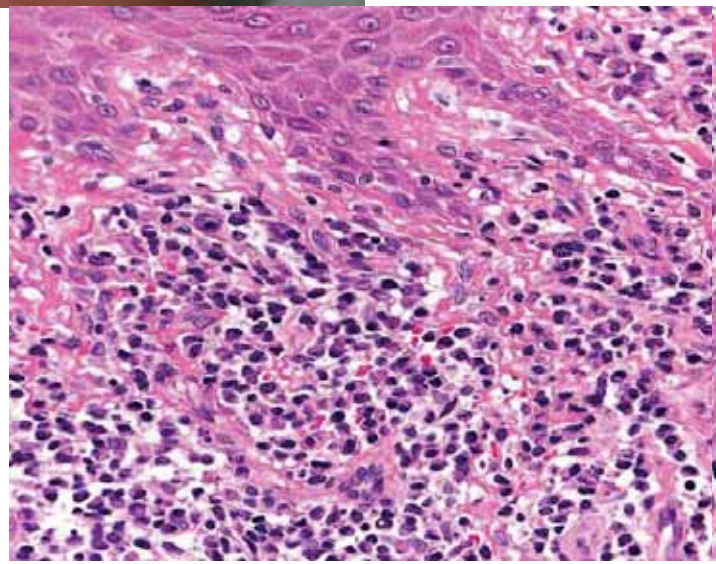


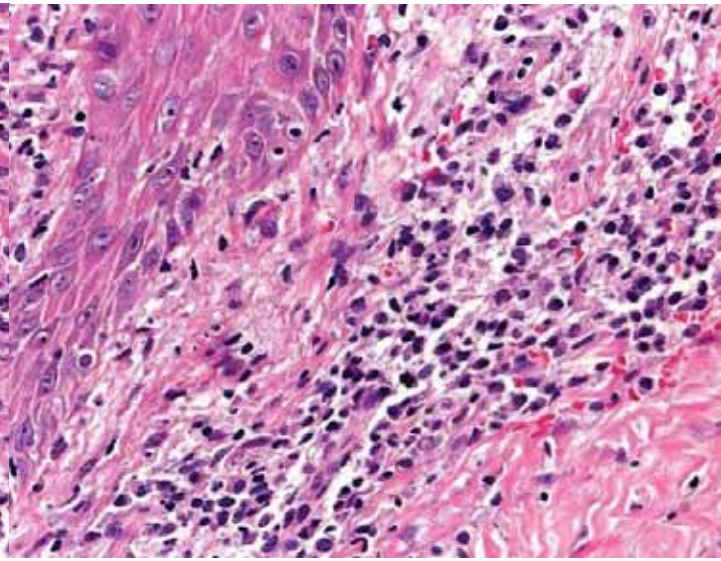


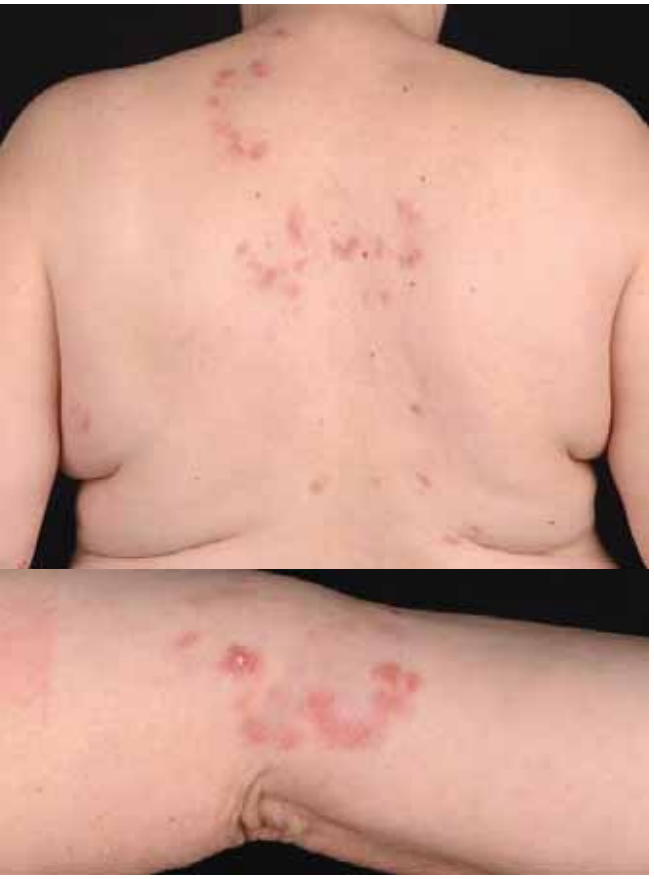
Secondary syphilis – Psoriasiform/Lichenoid

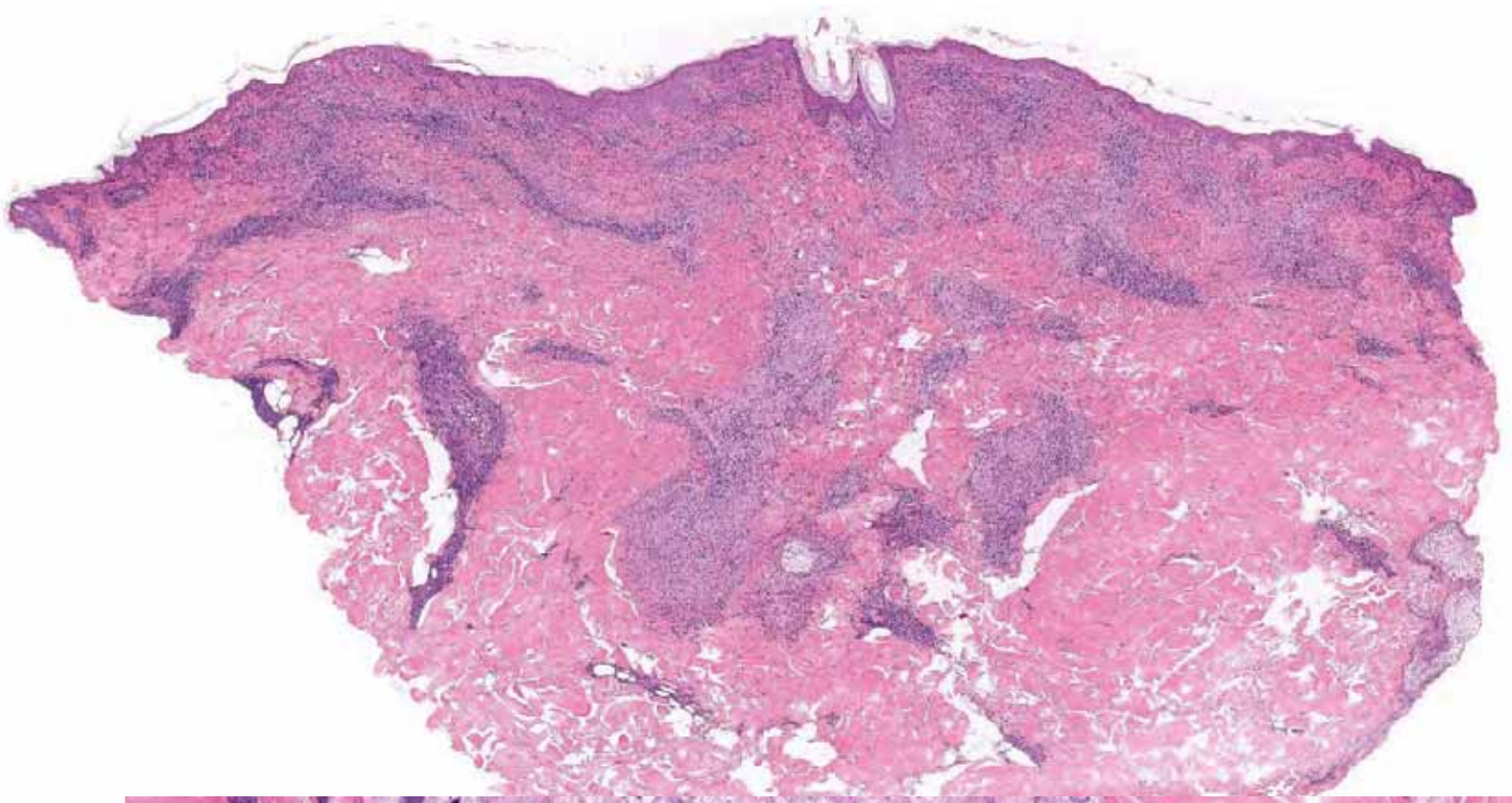
Superficial or superficial and deep, sometimes partly granulomatous.

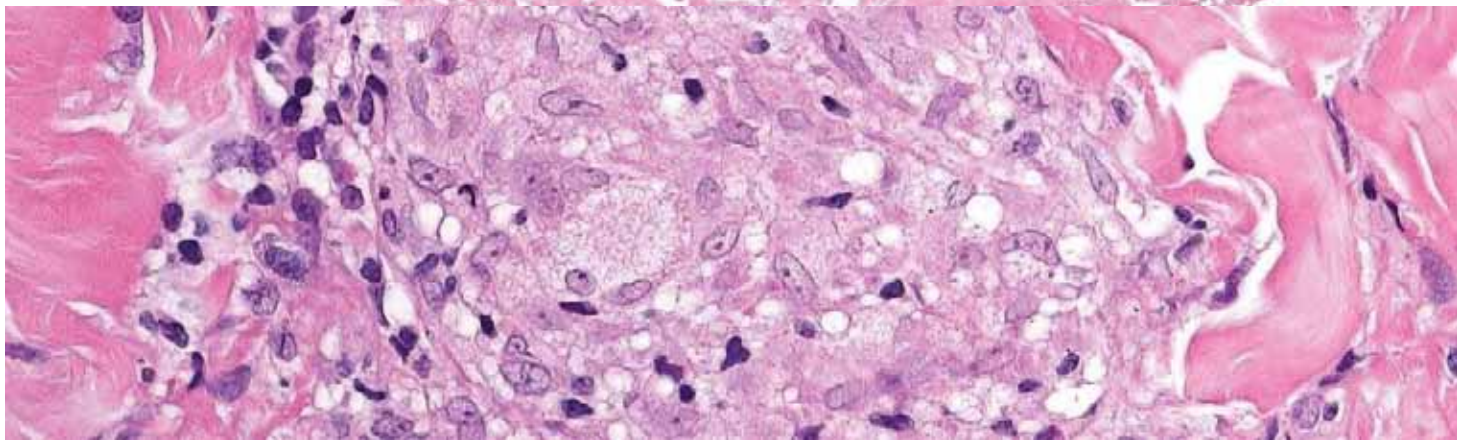
When superficial, it may mimic the histopathological features of mycosis fungoides; presence of plasma cells represents a clue (but they may be just a few or even missing, particularly in HIV+ patients).











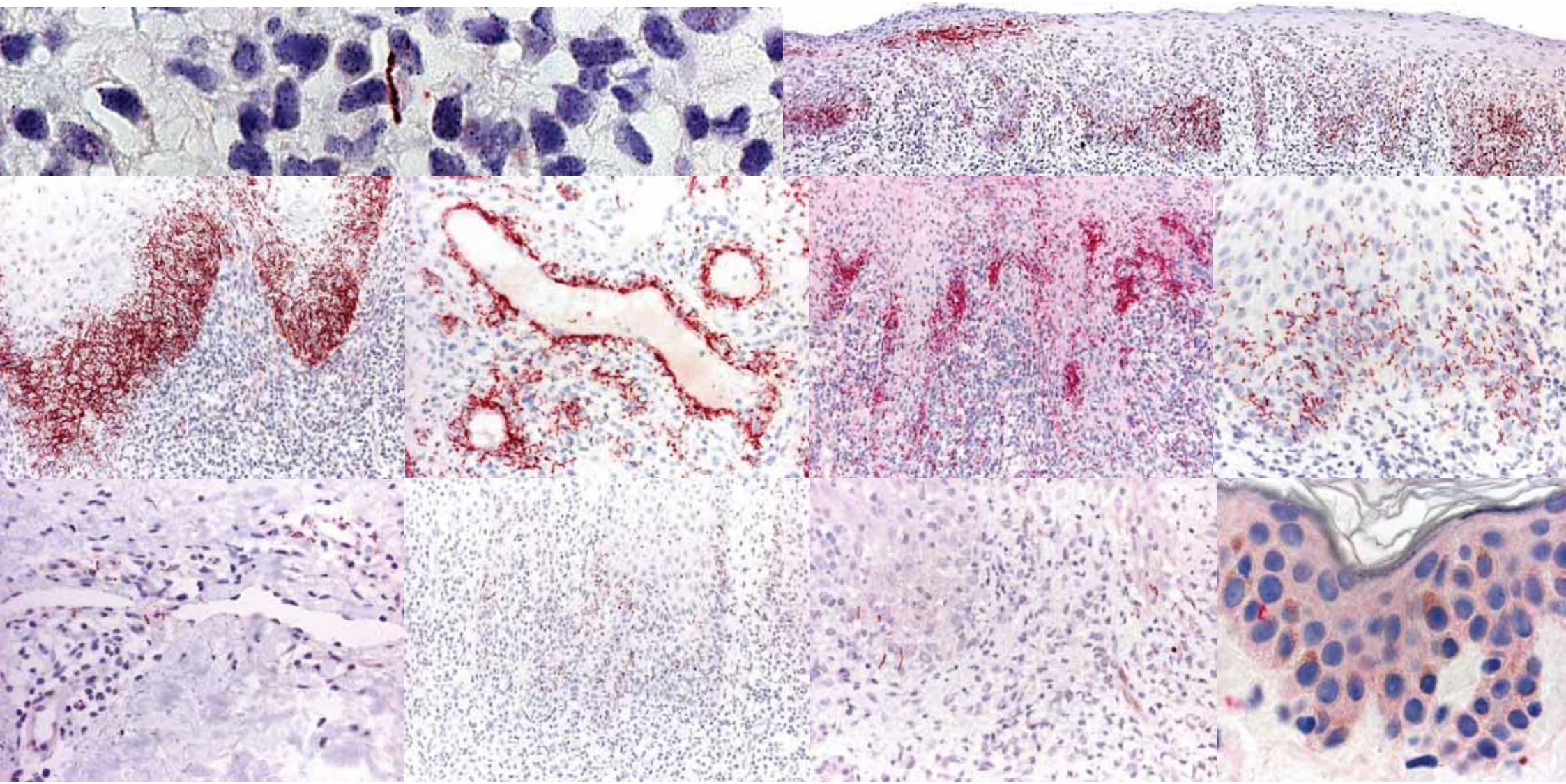
Secondary syphilis – Granulomatous

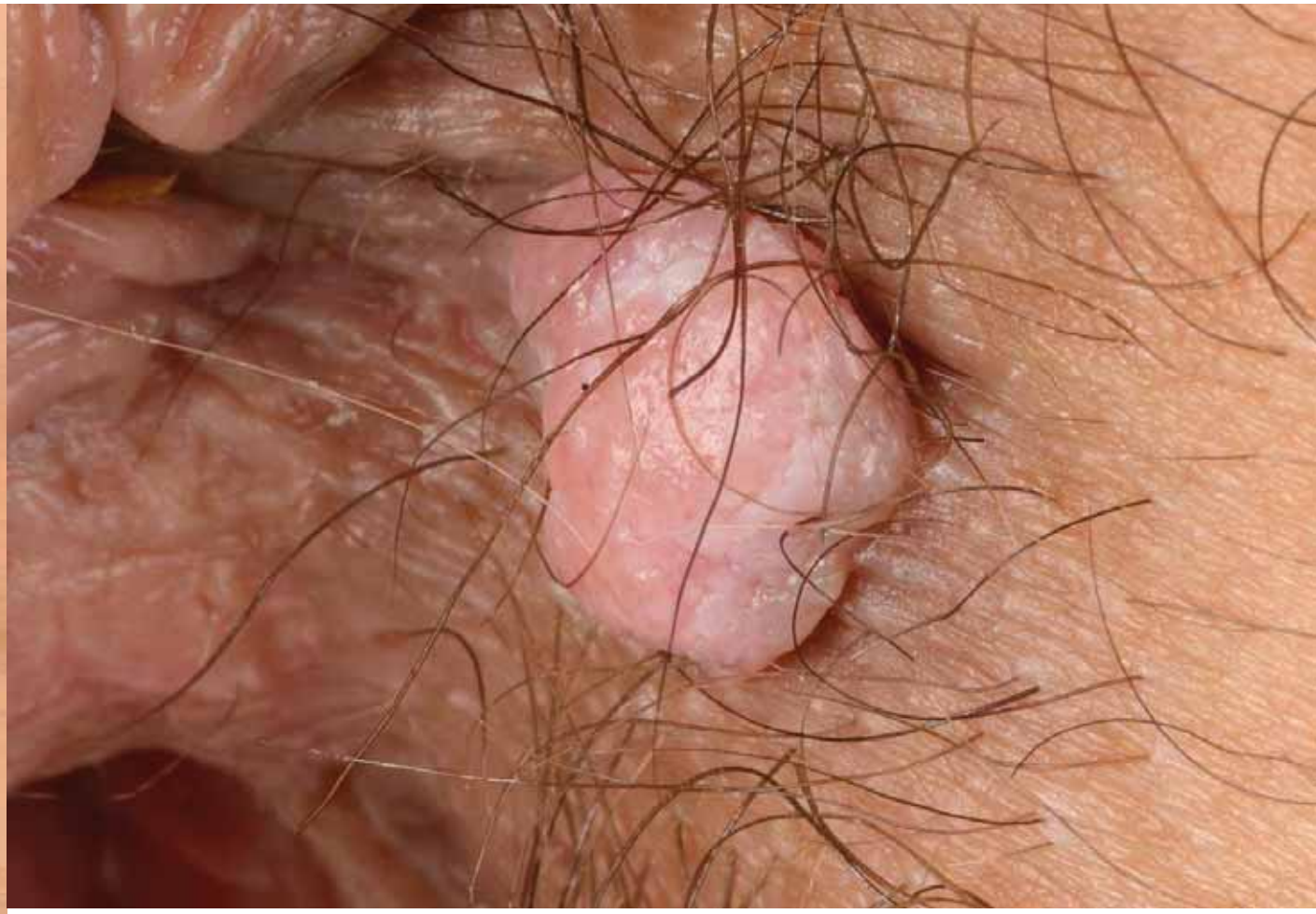
Granulomas (mostly epithelioid) may be observed in almost any type of secondary syphilis.

Variable numbers of plasma cells.

Spirochetae may be only a few.

Secondary syphilis – Patterns of staining for *T. pallidum*

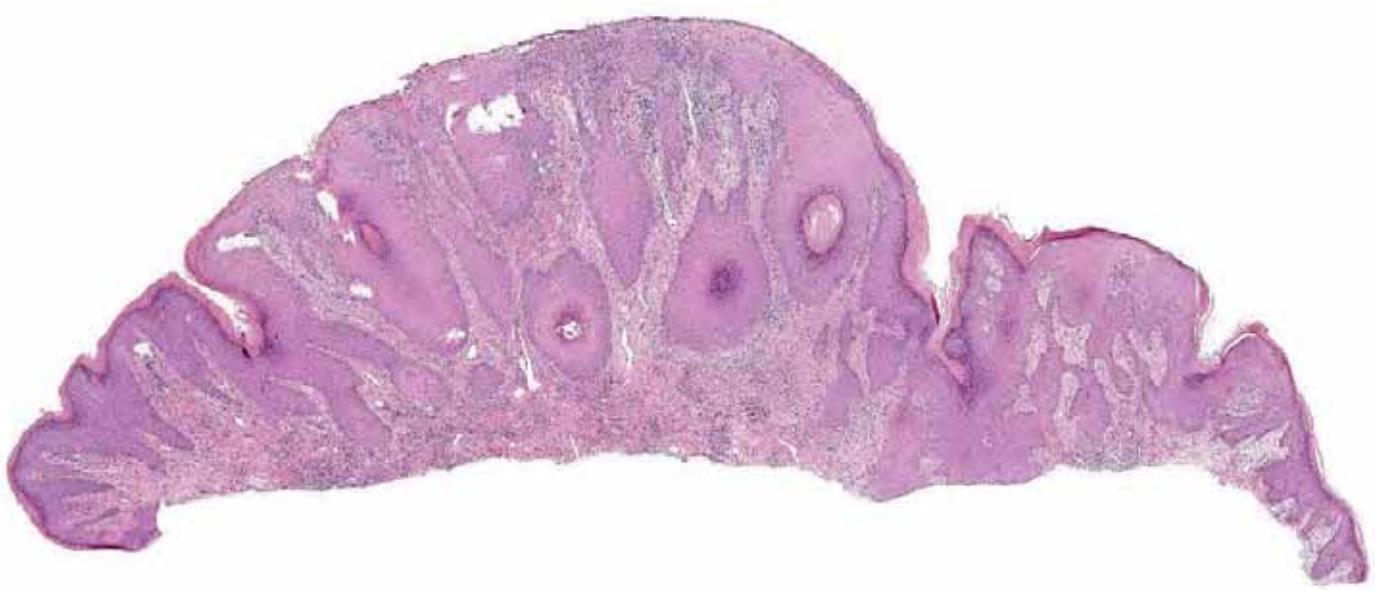


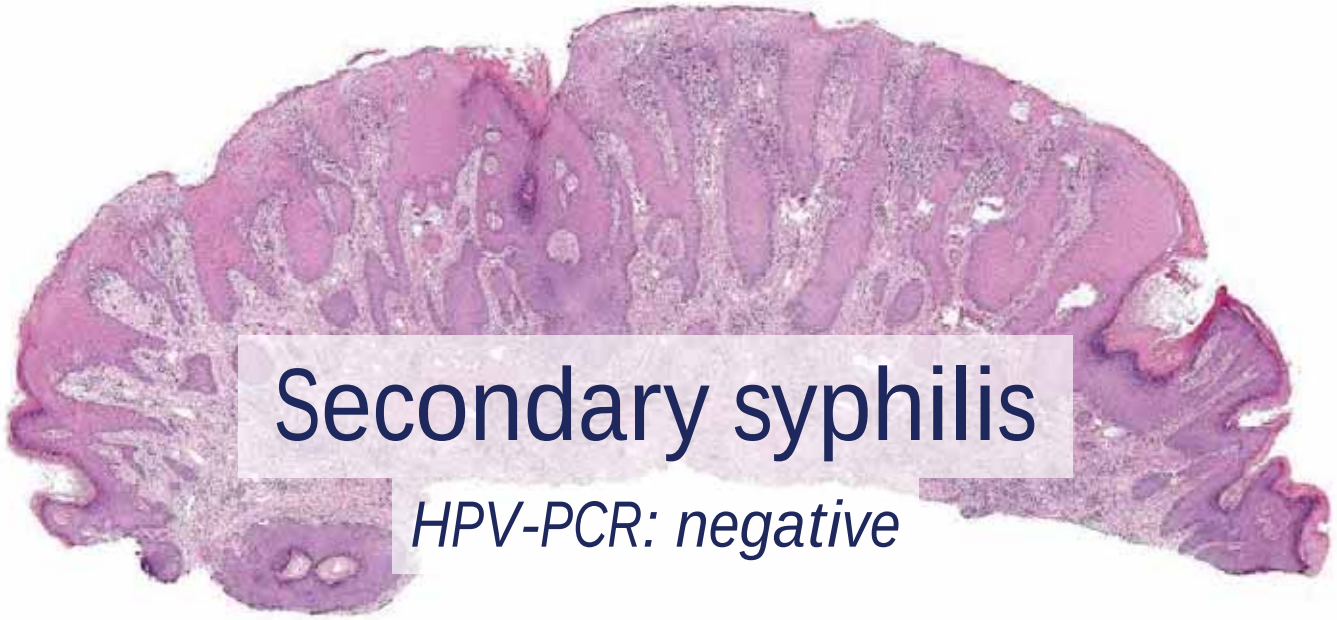


F, 25

Verrucous perianal tumor of unknown duration. No other skin lesions; no other complaints.

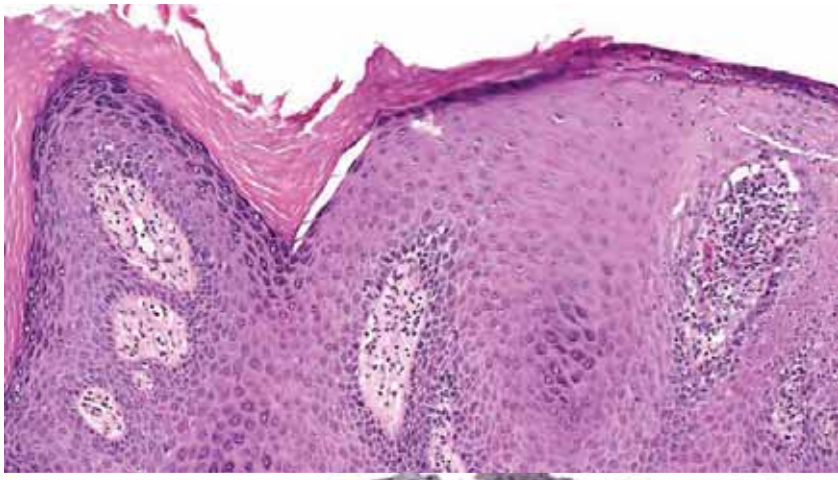
The lesion is removed surgically.

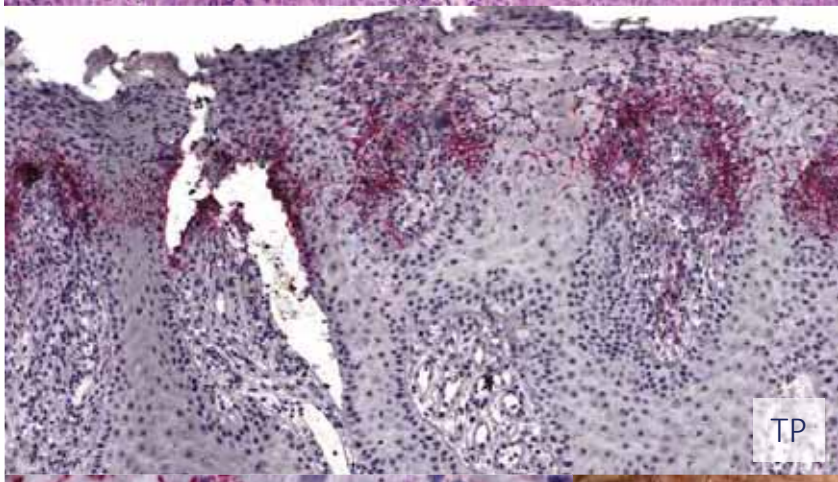


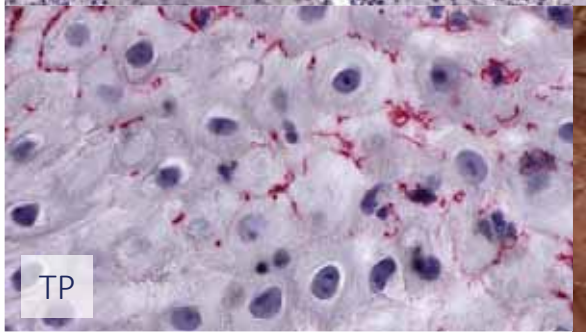


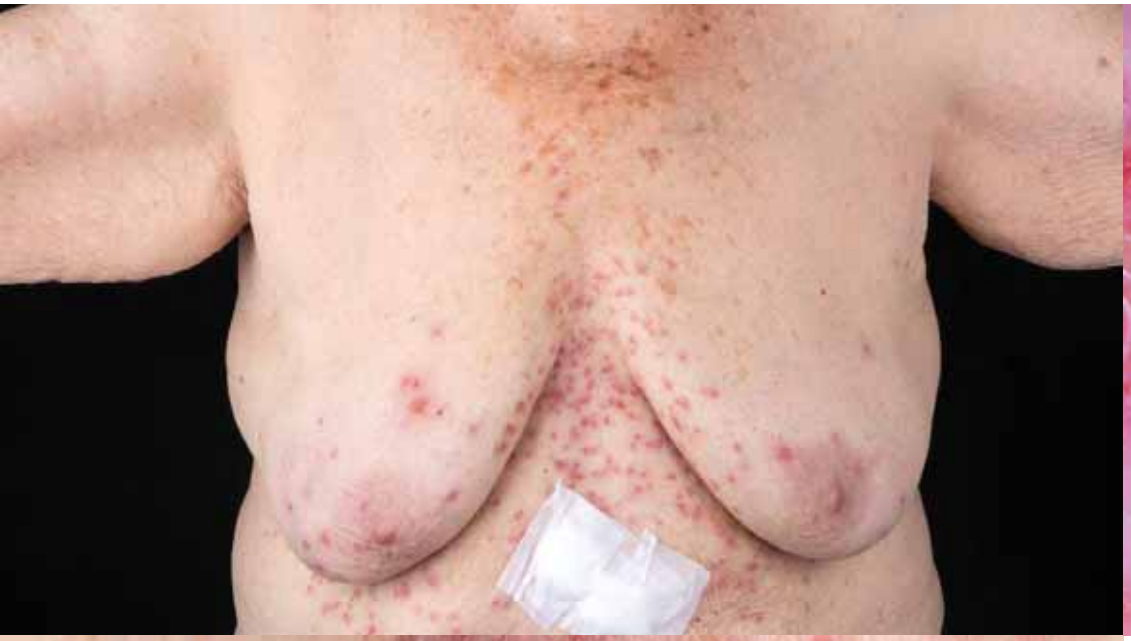
Secondary syphilis

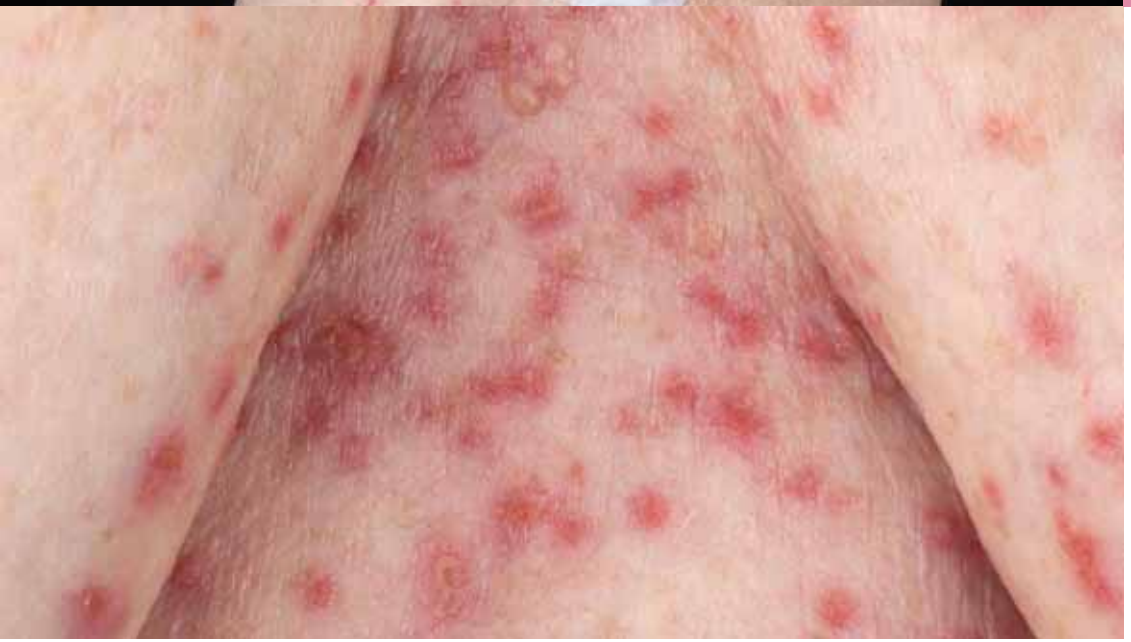
HPV-PCR: negative









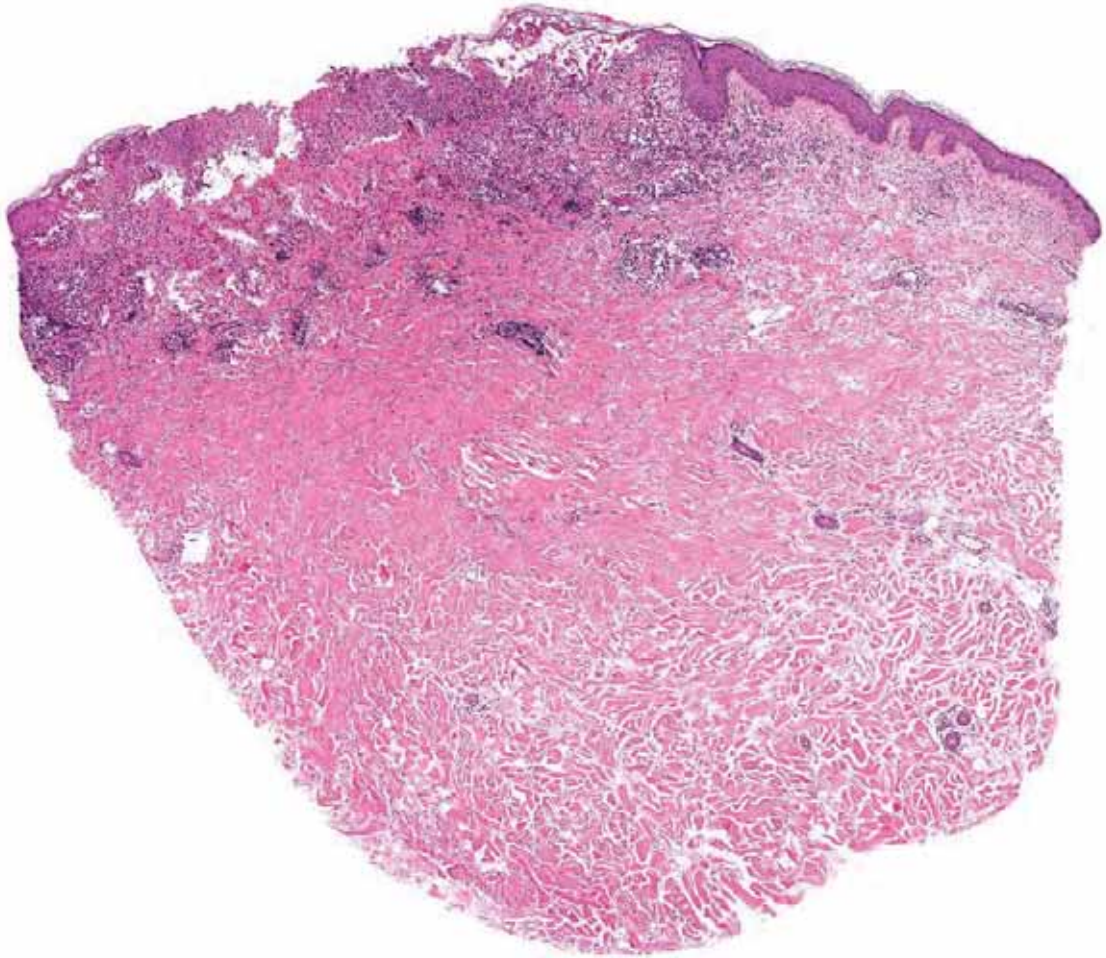


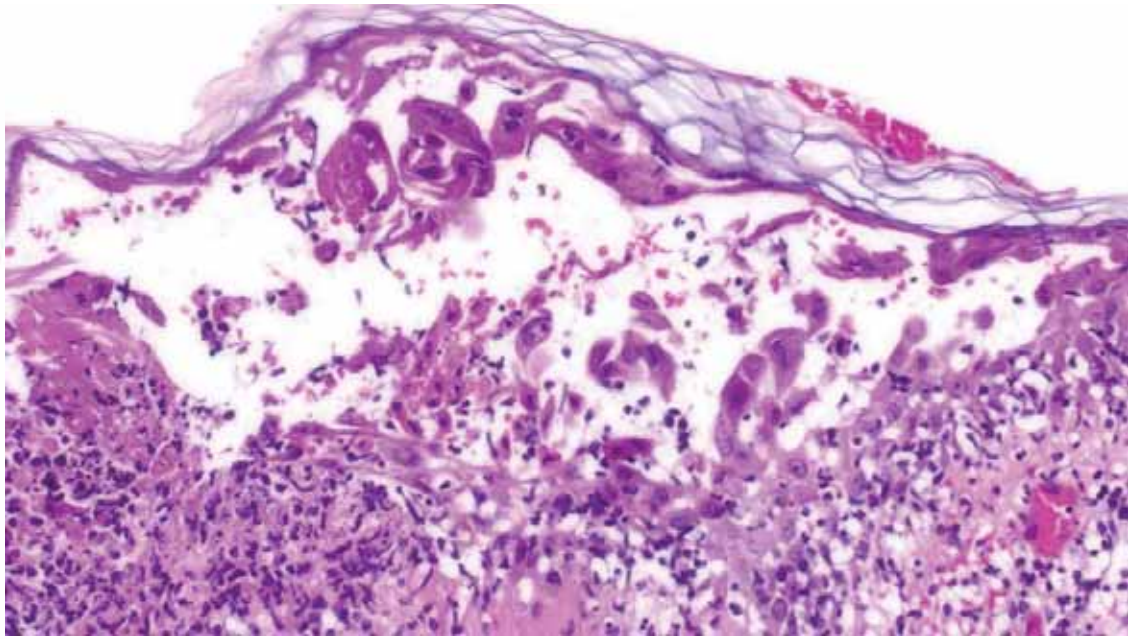
F, 86

Itchy lesions on the trunk present for 2 weeks.

DIF positive at the dermo-epidermal junction (IgG).
BP180 & BP230: 1 (normal).

ANA negative; Ro52-Abs+ .





Widespread herpes simplex-1 infection

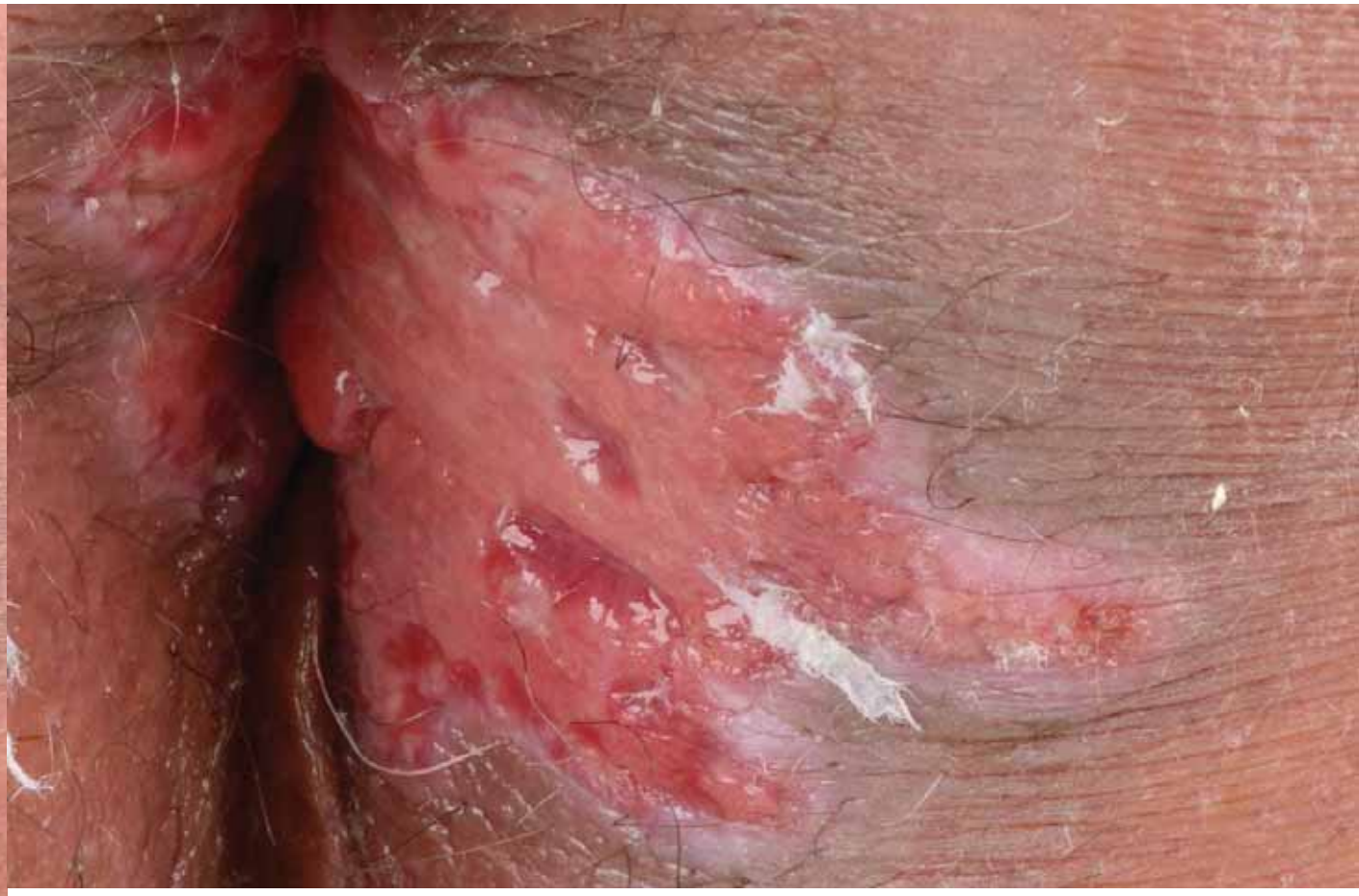
PCR positive for HSV-1.

Within 17 days almost CR with symptomatic local treatment.

No onset of new cutaneous lesions.

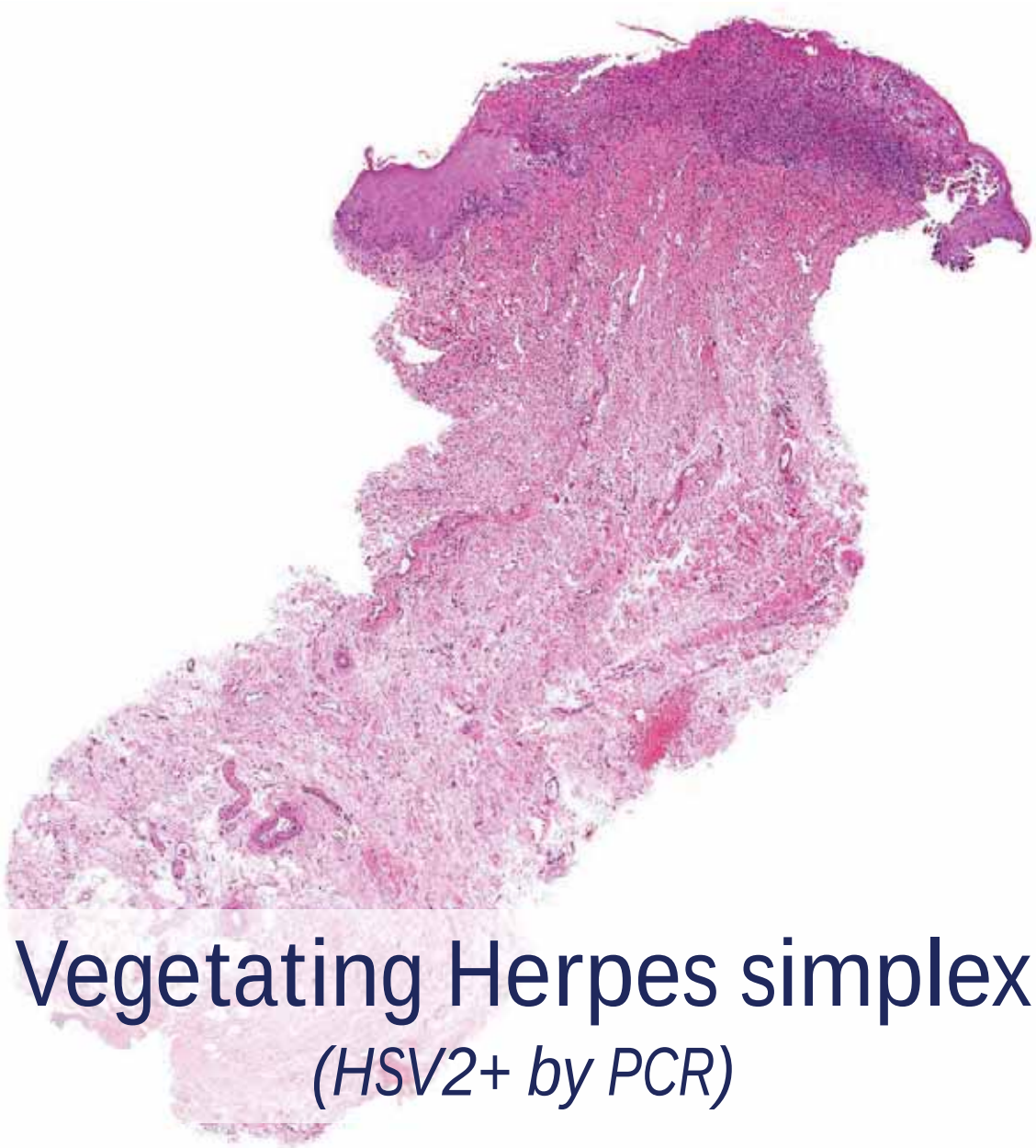
In this case positive DIF and Ro-52 Abs represent a non-specific, yet confounding factor – ***any laboratory report (positive or negative) should always sbe put into clinical perspective.***

Herpes simplex infection in the elderly and immunosuppressed individuals presents oft with unusual/persistent clinical features.



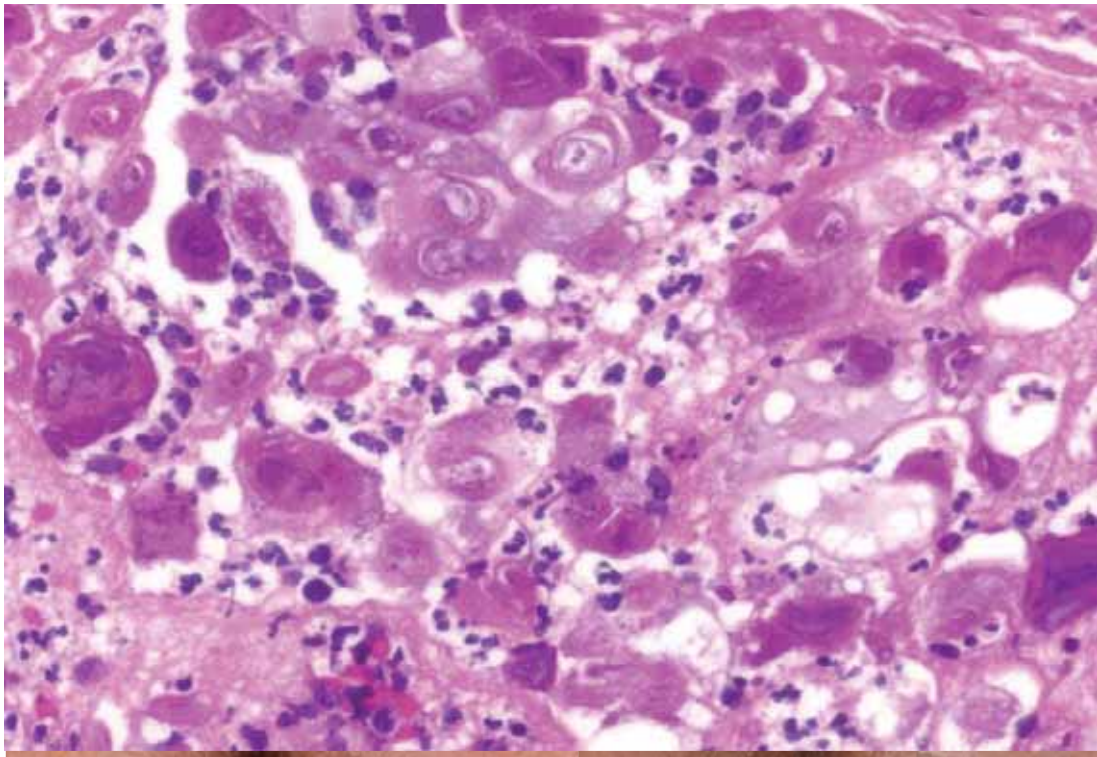
M, 63

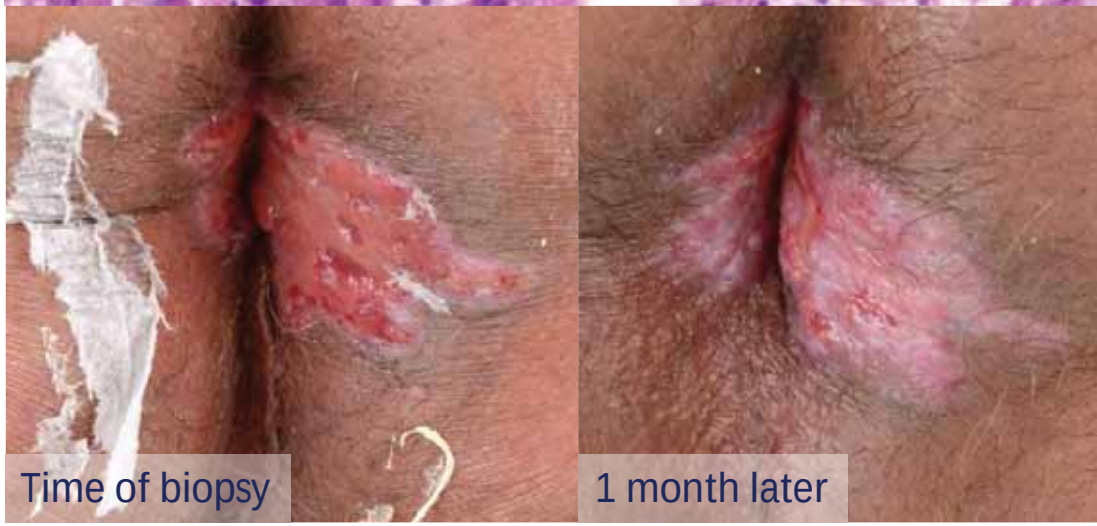
History of stem cell transplantation 3 months before presentation (essential thrombocythemia with post-ETH myelofibrosis), and of cutaneous GVHD (grade 1, CR after local steroids). Immunosuppression with cyclosporin. Perianal lesion detected during hospitalization (duration unknown) and biopsied under a suspect clinical diagnosis of SCC.



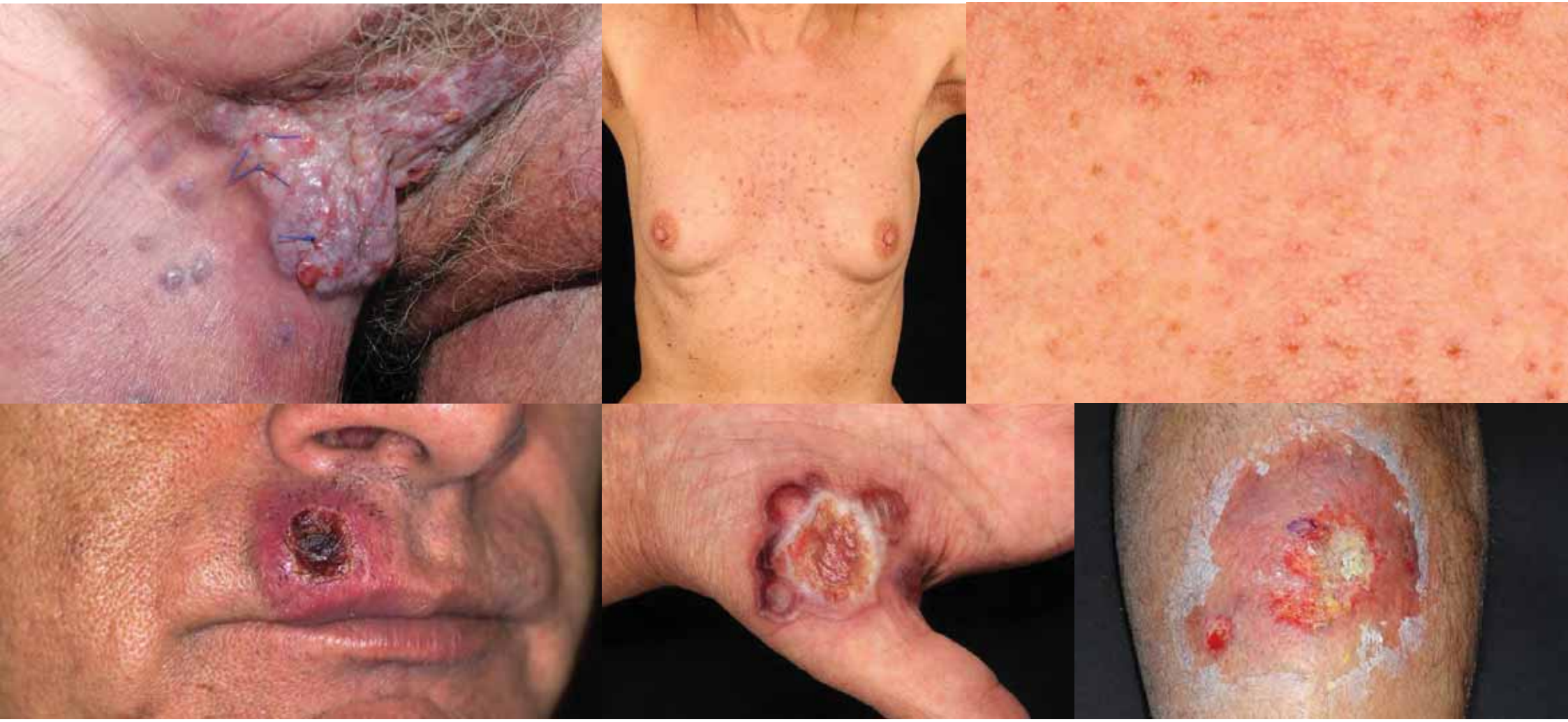
Vegetating Herpes simplex

(HSV2+ by PCR)

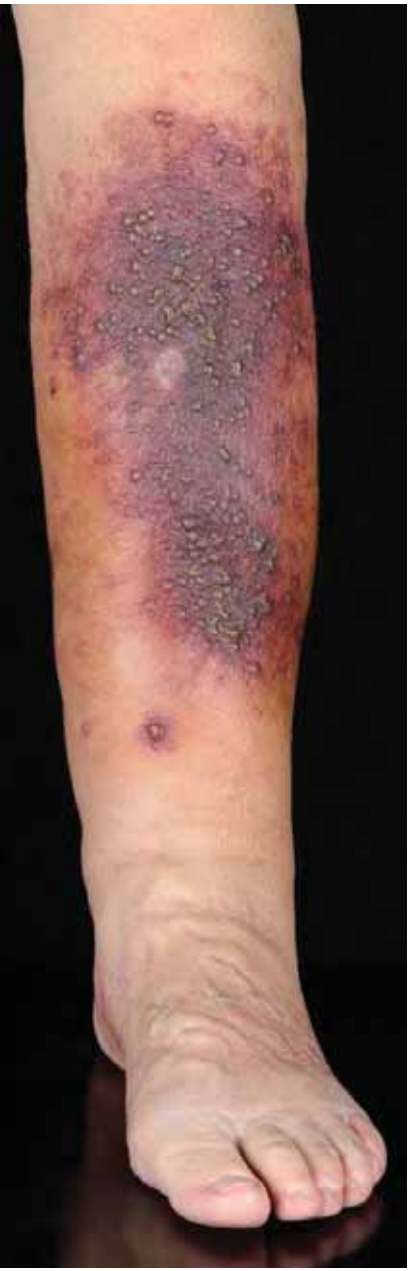


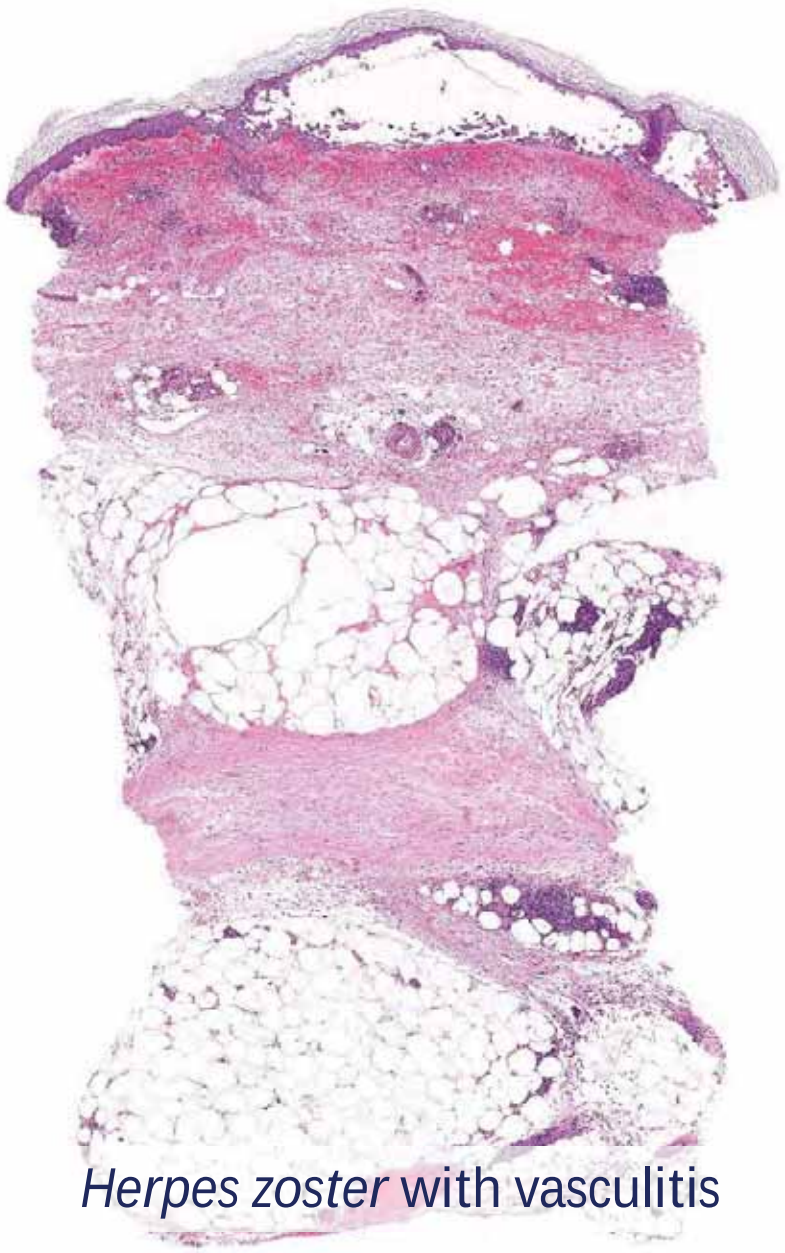


Herpes simplex infection – atypical presentations

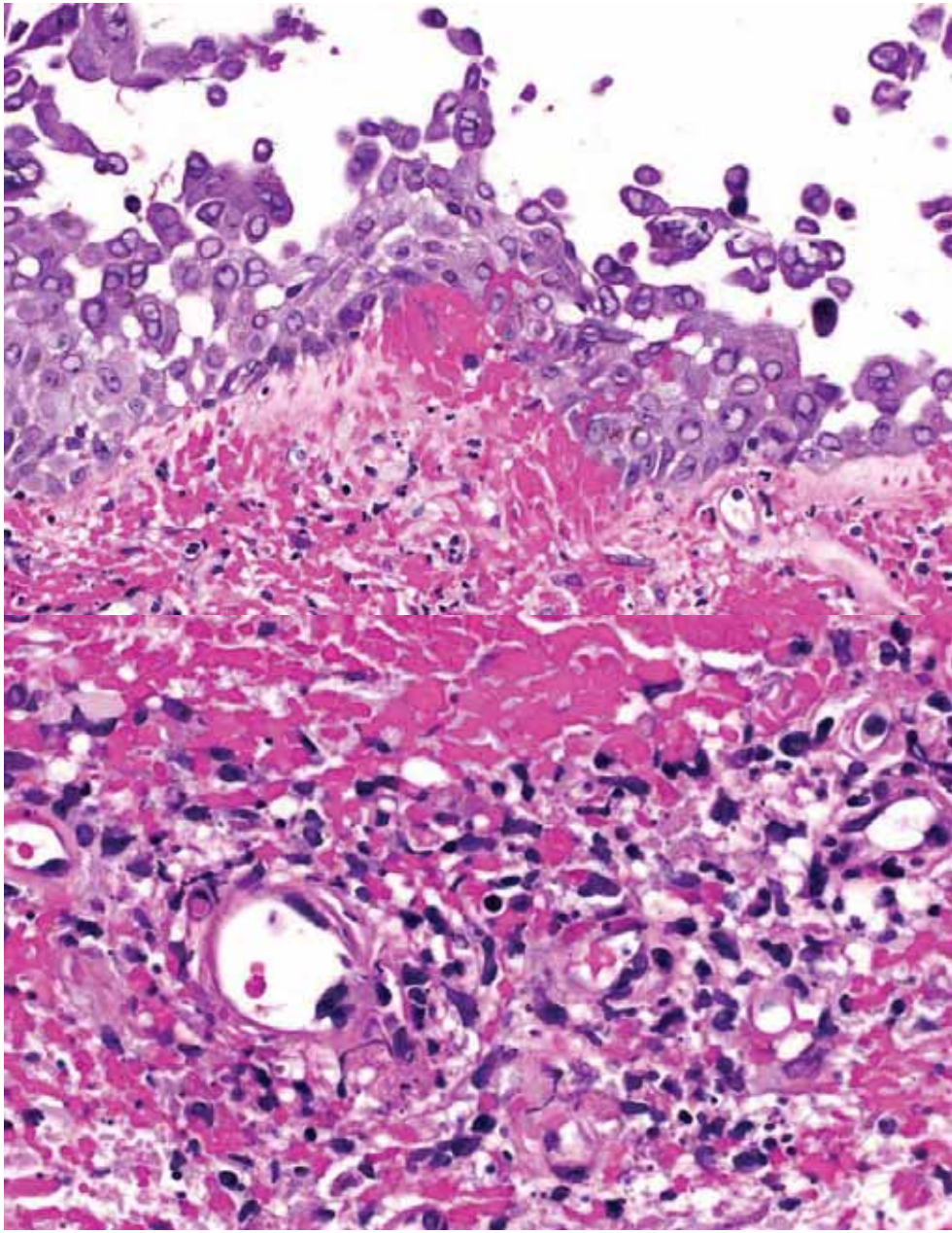


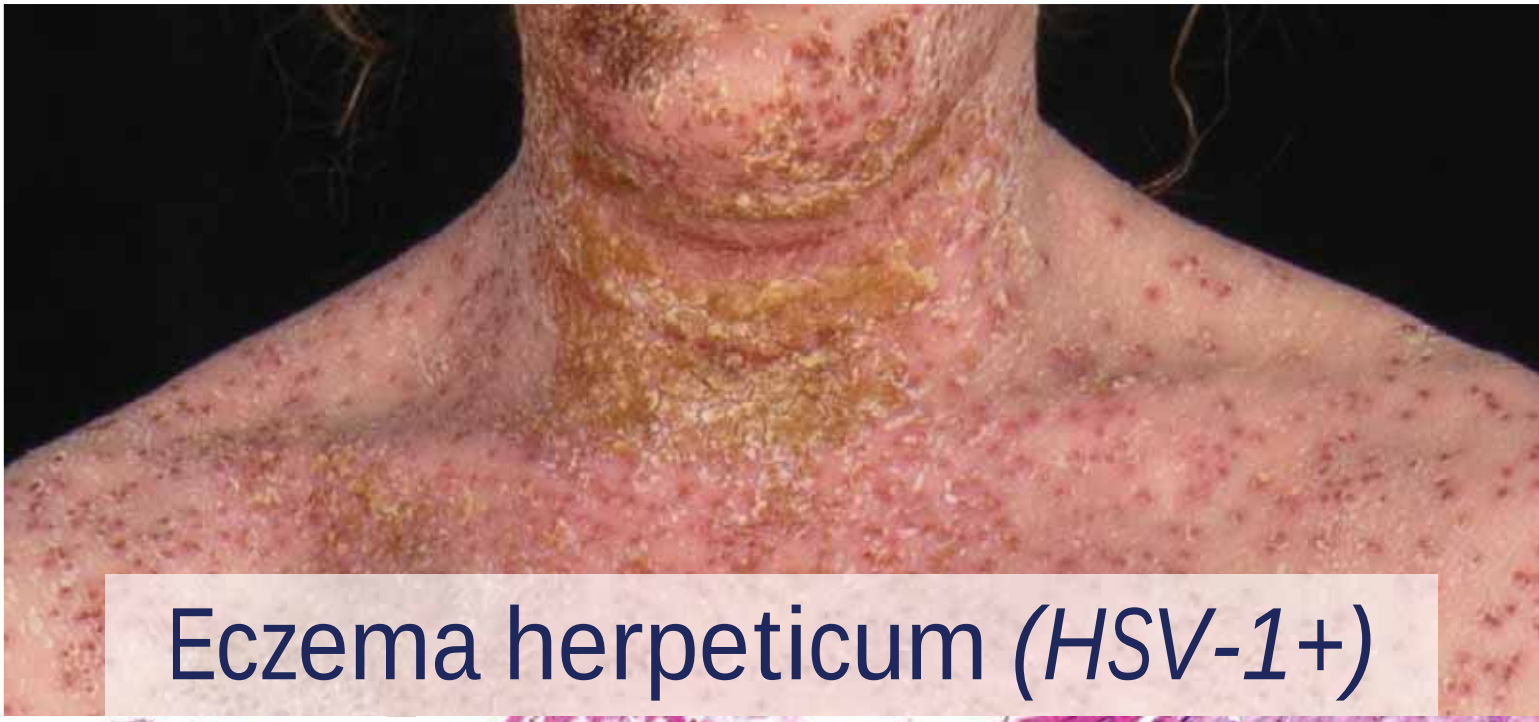
Usually in immunocompromised patients or in the elderly ("immune senescence"). May persist for long time and/or respond poorly to treatment. Often biopsied; histopathological features may be deceptive.



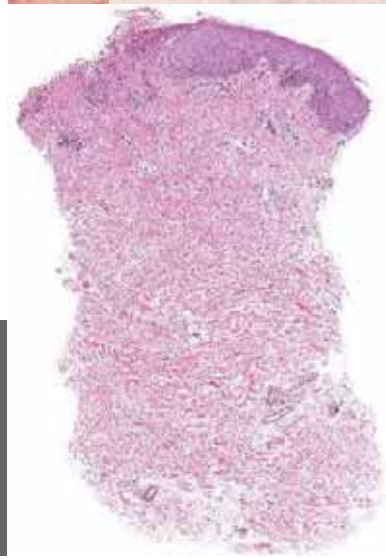


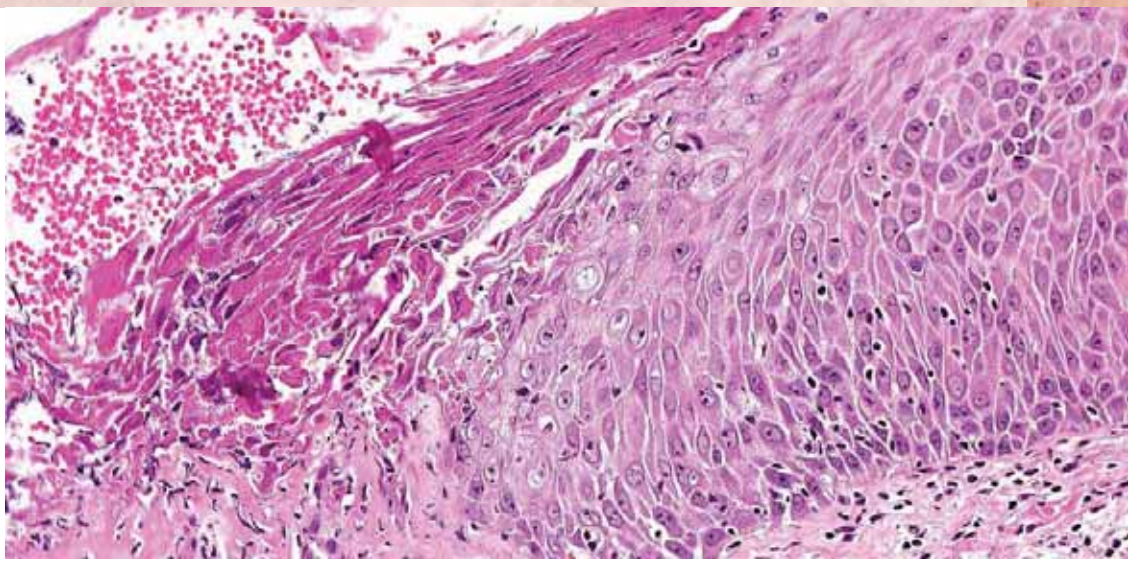
Herpes zoster with vasculitis





Eczema herpeticum *(HSV-1+)*





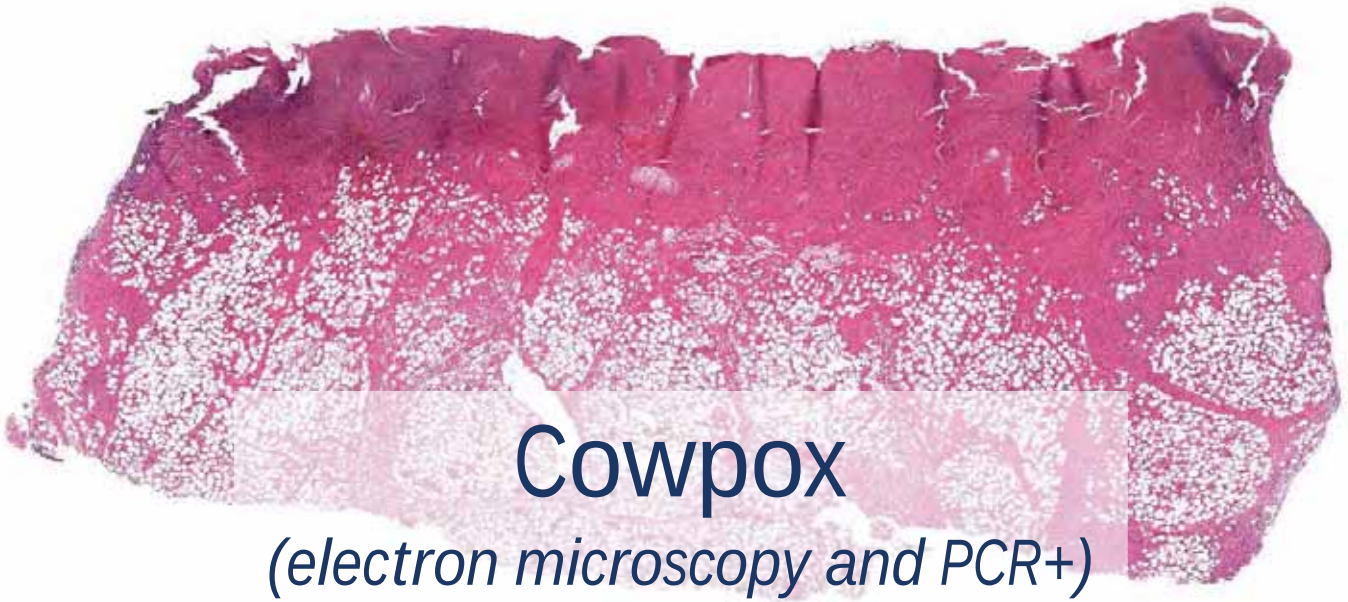
F, 31

History of atopic dermatitis since childhood with multiple recurrences during the last 2 years. Sudden onset of rapidly expanding, partly crusted lesions on the face, neck and upper trunk.

Main poxvirus infections

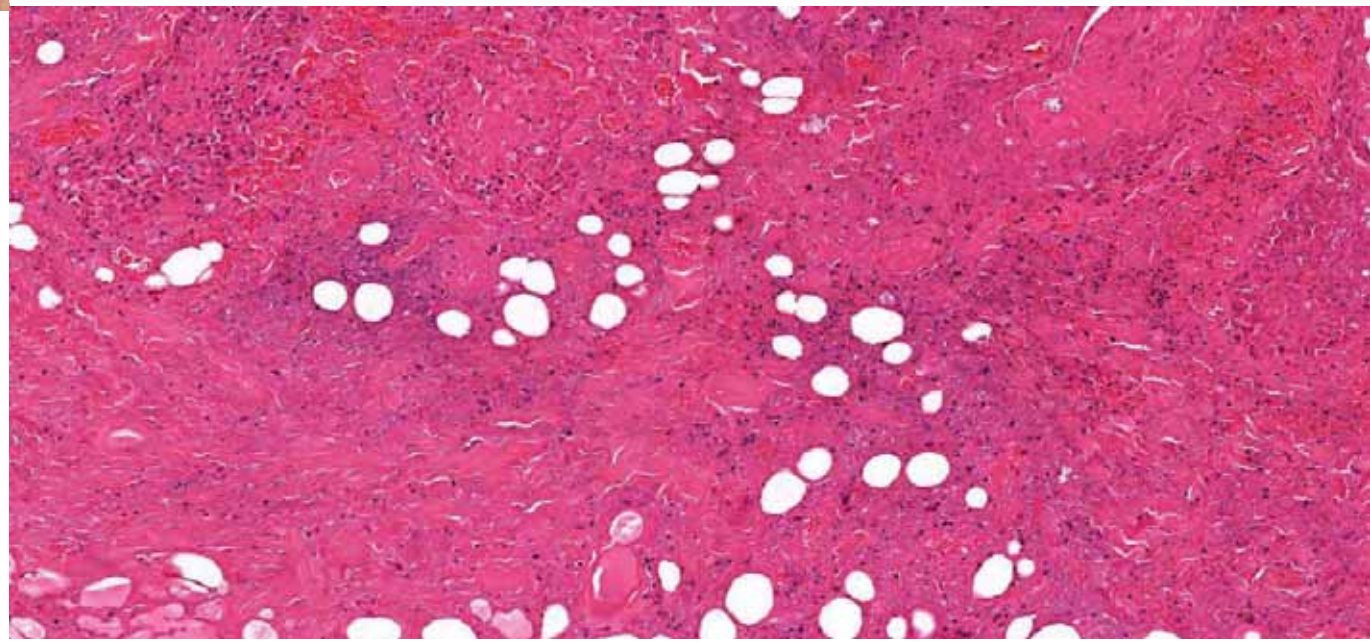
- *Smallpox* (variola orthopoxvirus): theoretically eradicated (two reference collections remain in the US and Russia)
- *Vaccinia* (vaccinia orthopoxvirus): used for smallpox vaccination
- *Monkeypox (mpox)* (monkeypox orthopoxvirus): systemic symptoms, a few to many papulo-pustules; smallpox vaccination protective
- *Cowpox* (cowpox orthopoxvirus): papule rapidly progressing to large ulcer; skin lesion arise after contact with infected animals (nowadays mostly cats)
- *Orf* (orf parapoxvirus): infection from sheep and goats; papule progressing to large erosive lesions
- *Milker's nodules* (paravaccinia parapoxvirus): clinically identical to orf, but infection from cattle (e.g., cows)
- *Molluscum contagiosum* (molluscipox): only in humans (akin to smallpox); common in children; in adults represents a type of STD

Day +14 (surgical debridement)



Cowpox

(electron microscopy and PCR+)



Cowpox – Historical perspective

- First "vaccination" *(name deriving from latin vaccinus: of or related to cows)*
- Farmers and people working regularly with cows who had contracted cowpox were spared during deadly smallpox outbreaks
- In 1774 the English farmer Benjamin Jesty inoculated his wife and two sons with cowpox during a smallpox epidemic (all survived)
- 20 years later Dr. Jenner inoculated people in a similar manner and took credit for the discovery

Pediatr Nephrol (2017) 32:533–536
DOI 10.1007/s00467-016-3534-y

BRIEF REPORT

Fatal disseminated cowpox virus infection in an adolescent renal transplant recipient

Paul Gazzani[1] · Joanna E Gach[1] · Isabel Colmenero[2] · Jeff Martin[3] · Hugh Morton[4] · Kevin Brown[5] · David V Milford[6]

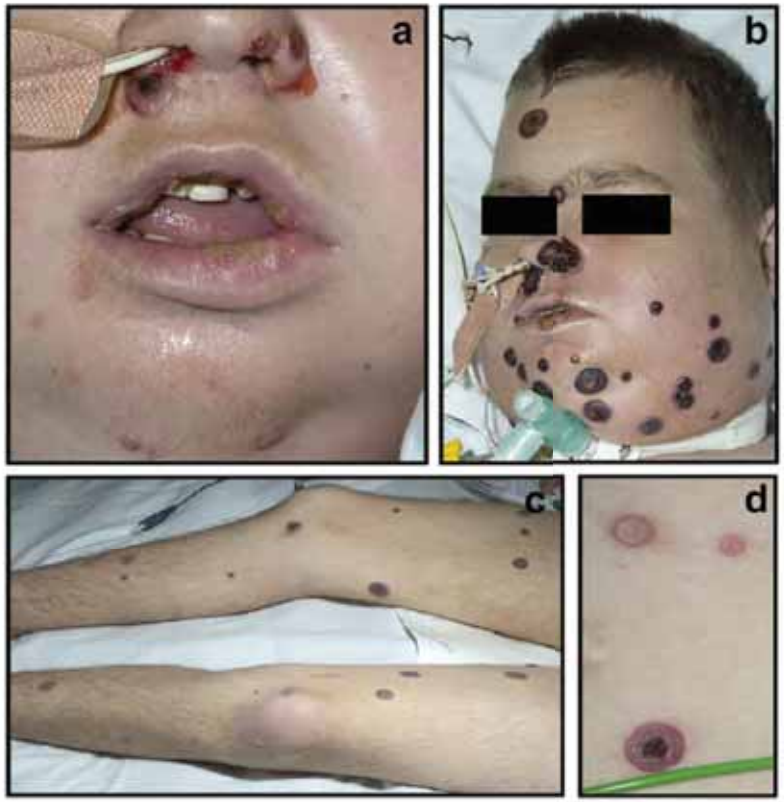


Fig. 1 Clinical images of skin lesions: **a** Papules, vesicles and erosions around the mouth and nose. **b, c** Widespread necrotic lesions several days after disease onset. **d** Progression of skin lesion development from a papule through a vesicopapule to a necrotic ulcerated nodule

Hautarzt (1991) 42:293–297 © Springer-Verlag 1991

Letale Tierpockeninfektion bei einem Atopiker unter dem Bild einer Variola vera

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[3] Institut für Medizinische Mikrobiologie, Infektions- und Seuchenmedizin (Vorstand: Prof. Dr. Dr.h.c.mult. A. Mayr) der Tierärztlichen Fakultät der Universität München

Zusammenfassung

Ein 18jähriger Patient mit schwerem Glukokortikoid-bedürftigem endogenem Ekzem erkrankte an einer von der Hauskatze akquirierten generalisierten, der Variola vera gleichenden Infektion durch ein Kuhpocken-ähnliches Virus. Trotz intensivmedizinischer Behandlung mit kontrollierter Beatmung und Einsatzes des letzten verfügbaren Vaccinia-Hyperimmunglobulins verstarb der Patient nach Beherrschung der Pockenaussaat an Lungenembolie.

Schlüsselwörter: Kuhpocken-ähnliches Virus – Atopiker – Katzen-Poxvirus-Infektion – Vaccinia-Hyperimmunglobulin

Summary

An 18-year-old patient requiring steroid treatment for severe bronchial asthma and with atopic dermatitis acquired a cowpox-like virus infection clinically similar to smallpox from a domestic cat as carrier. In spite of intensive care, with controlled pressure breathing and the last available vaccinia hyperimmunoglobulin, the patient died of pulmonary embolism although viral spread had ceased some days before.

Key words: Cowpox-like virus – Atopic patient – Cat pox virus infection – Vaccinia hyperimmunoglobulin

Die Einstellung der gesetzlichen Pockenschutzimpfung mit dem Vaccinia-Virus führt in zunehmendem Umfang zur Verminderung des Individual- und auch des Populationsschutzes [8] gegenüber den eng verwandten Orthopockenviren (OPV), (s. Tabelle 1). Verschiedentlich wurde bereits aus theoretischen Erwägungen eine zunehmende Gefährdung des Menschen durch Tierpocken in Betracht gezogen und sporadisch wurden auch Fälle einer zumeist lokal verlaufenden Infektion mit Kuhpocken oder Kuhpocken-verwandten Viren publiziert [1, 5, 7, 9, 12, 15].

Wir berichten über einen 18jährigen Patienten mit Glukokortikoidbedürftigem Asthma bronchiale und schwerem endogenem Ekzem, der an einer von der Hauskatze akquirierten Infektion mit einem Kuhpocken-ähnlichen Virus unter einem generalisierten Variola-vera-artigen Bild erkrankte und an deren Folgen trotz Einsatzes des letzten verfügbaren Vaccinia-Hyperimmunglobulins verstarb.

Tabelle 1. Orthopoxviren (nach [11])

Opv. commune (Vaccinia-Virus, Impfpockenvirus mit Varianten beim Pferd, Kaninchen, Elefanten, Waschbären u.a.)
Opv. variolae (Variolavirus, Variola-major-V.)
Opv. alastrim (Alastrimvirus, Variola-minor-V.)
Opv. bovis (Kuhpockenvirus) mit Varianten bei Feliden und Nagern
Opv. muris (Mäusepockenvirus, Ektromelievirus)
Opv. simiae 1 (Affenpocken-, Affenvariolav.)
Opv. cameli (Kamelpockenvirus)
Opv. bubali (Büffelpockenvirus)

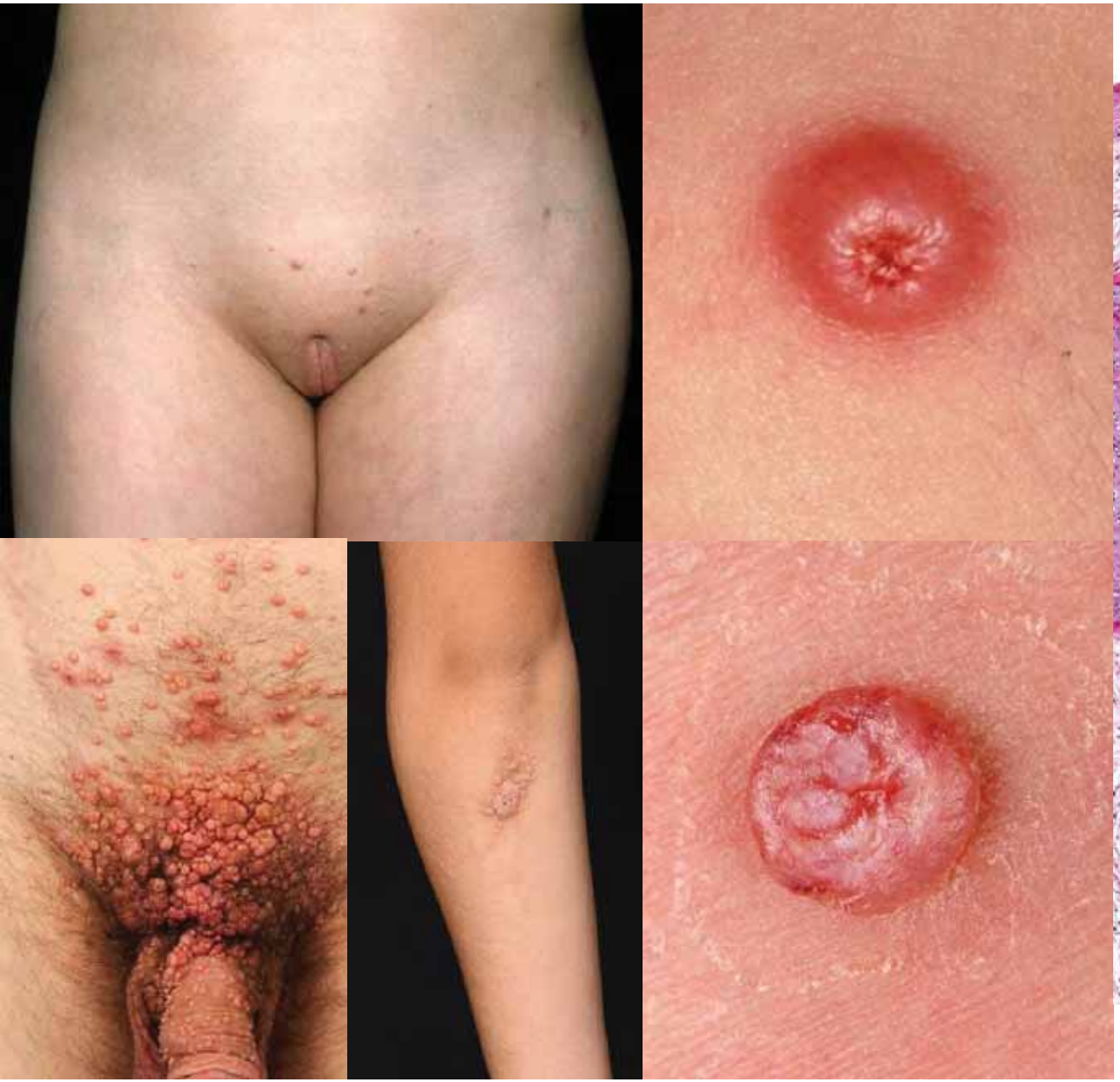
Fallbericht

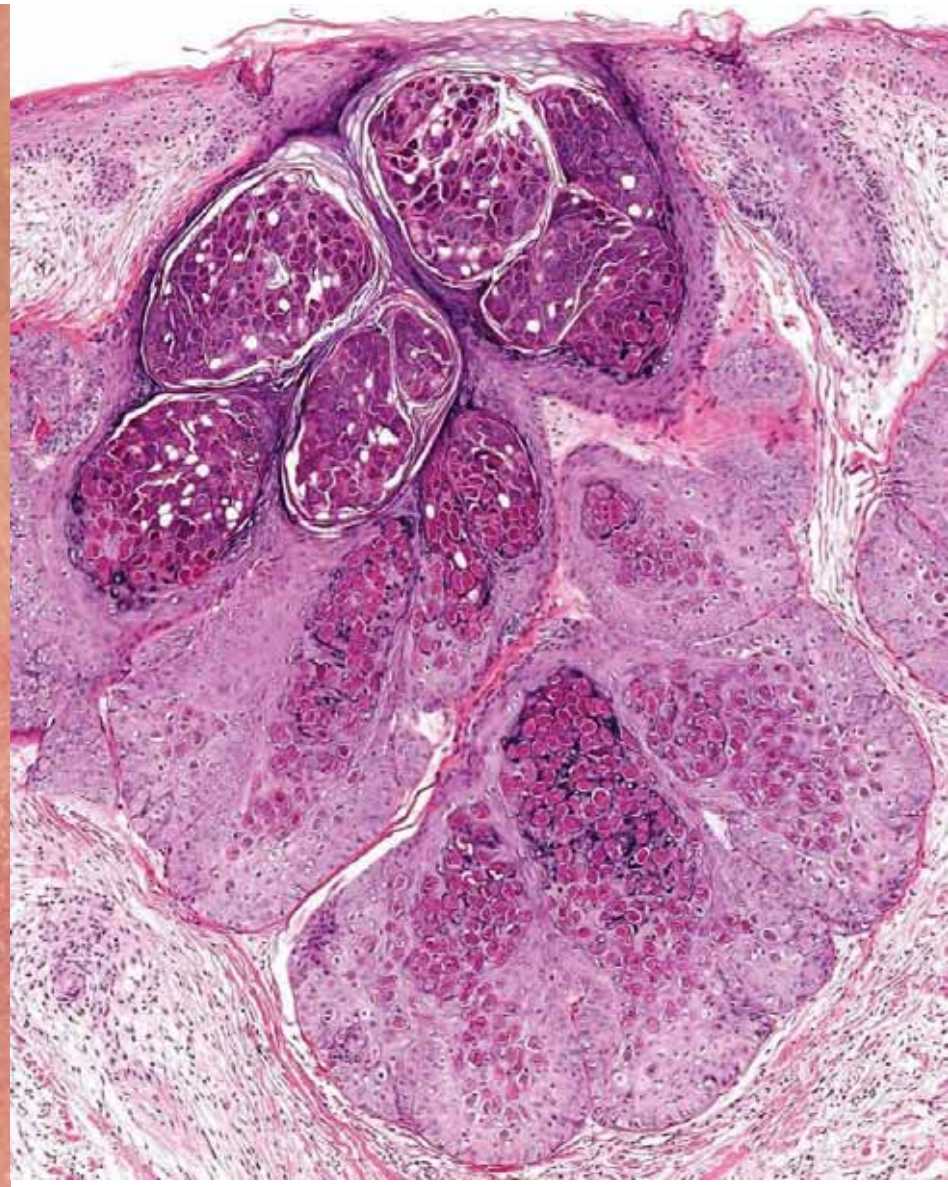
Patient M.S., 18 Jahre.

Anamnese. Seit dem Säuglingsalter besteht bei dem Patienten ein schweres endogenes Ekzem mit allergischem Asthma bronchiale bei Sensibilisierung auf Gräser, Tierepithelien, Haustaubmilben und Schimmelpilze. Bei Gesamt-IgE-Werten bis 9000 KU/l erfolgten vielfache stationäre Aufenthalte wegen erythrodermatischer Exazerbationen des endogenen Ekzems, mehrfach wegen Status asthmaticus sowie dreimal wegen eines Ekzema herpeticatum. Eine Pockenschutzimpfung war angesichts der bestehenden Atopie nicht durchgeführt worden. Antiasthmatische Dauertherapie mit ß2-Sympathikomimetika, Theophyllinpräparaten, Cromoglicinsäure, Mukolytika, einem oralen Antihistaminikum sowie Glukokortikoidinhalaten und systemisch mit 10 mg Prednisolonäquivalent/die.

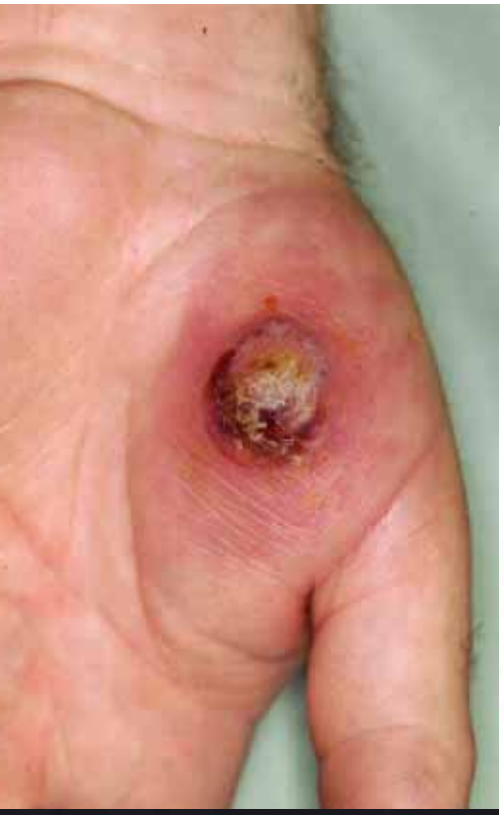
Noch kurz vor der stationären Aufnahme bei uns war eine 3wöchige stationäre Behandlung in Norderney erfolgt.

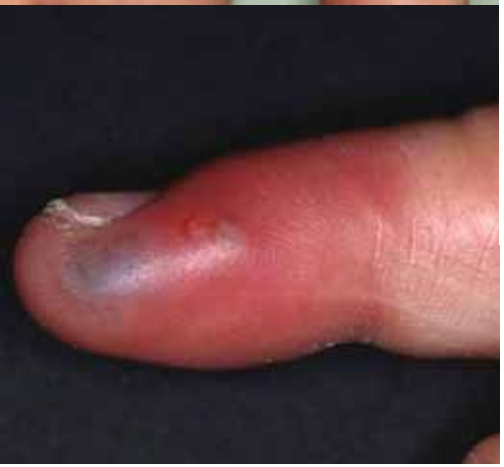
Retrospektiv stellte sich heraus, daß der Patient nach der Rückkehr engen Kontakt zu einer Hauskatze mit Freigang gehabt hatte, die ca. 10 Tage vor der Erkrankung des Patienten wegen einer phlegmonösen Entzündung an der rechten Vorderpfote von ihm in tierärztliche Behandlung gebracht wurde.

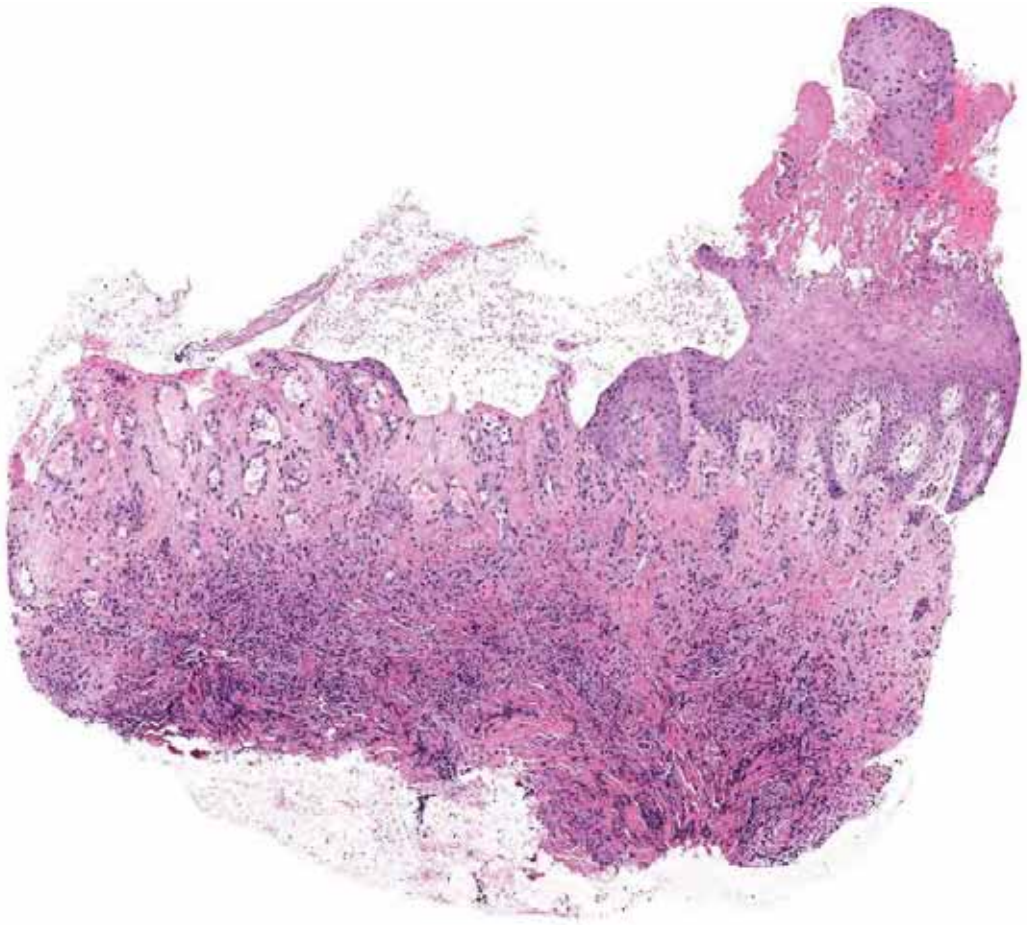


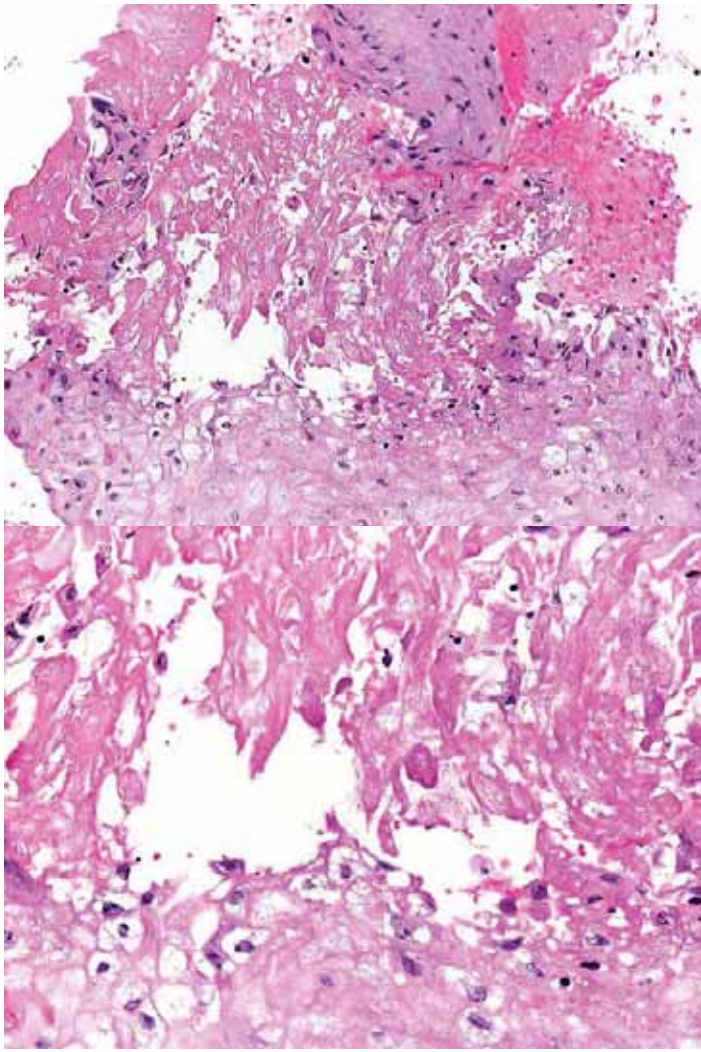


Molluscum contagiosum

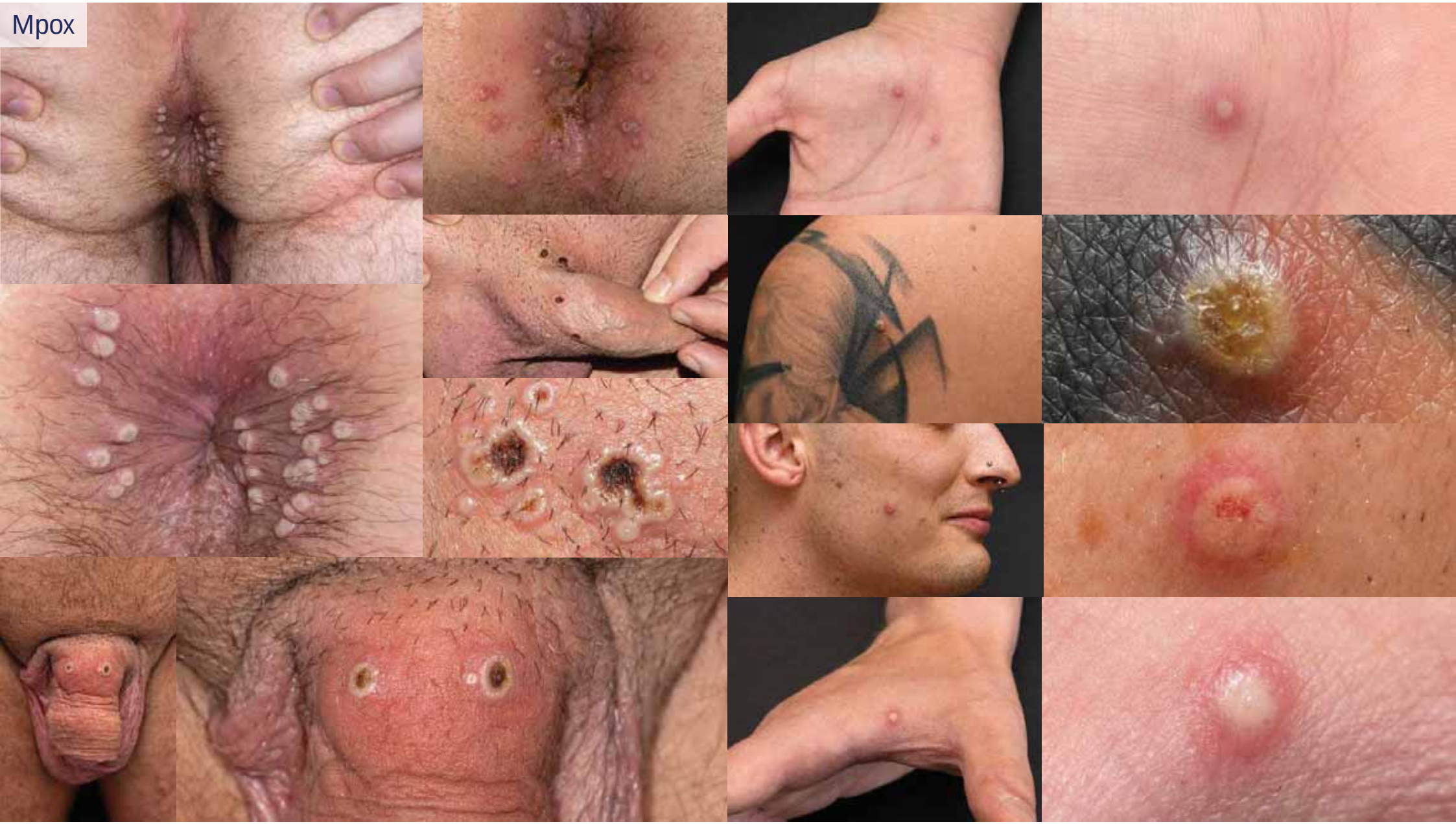


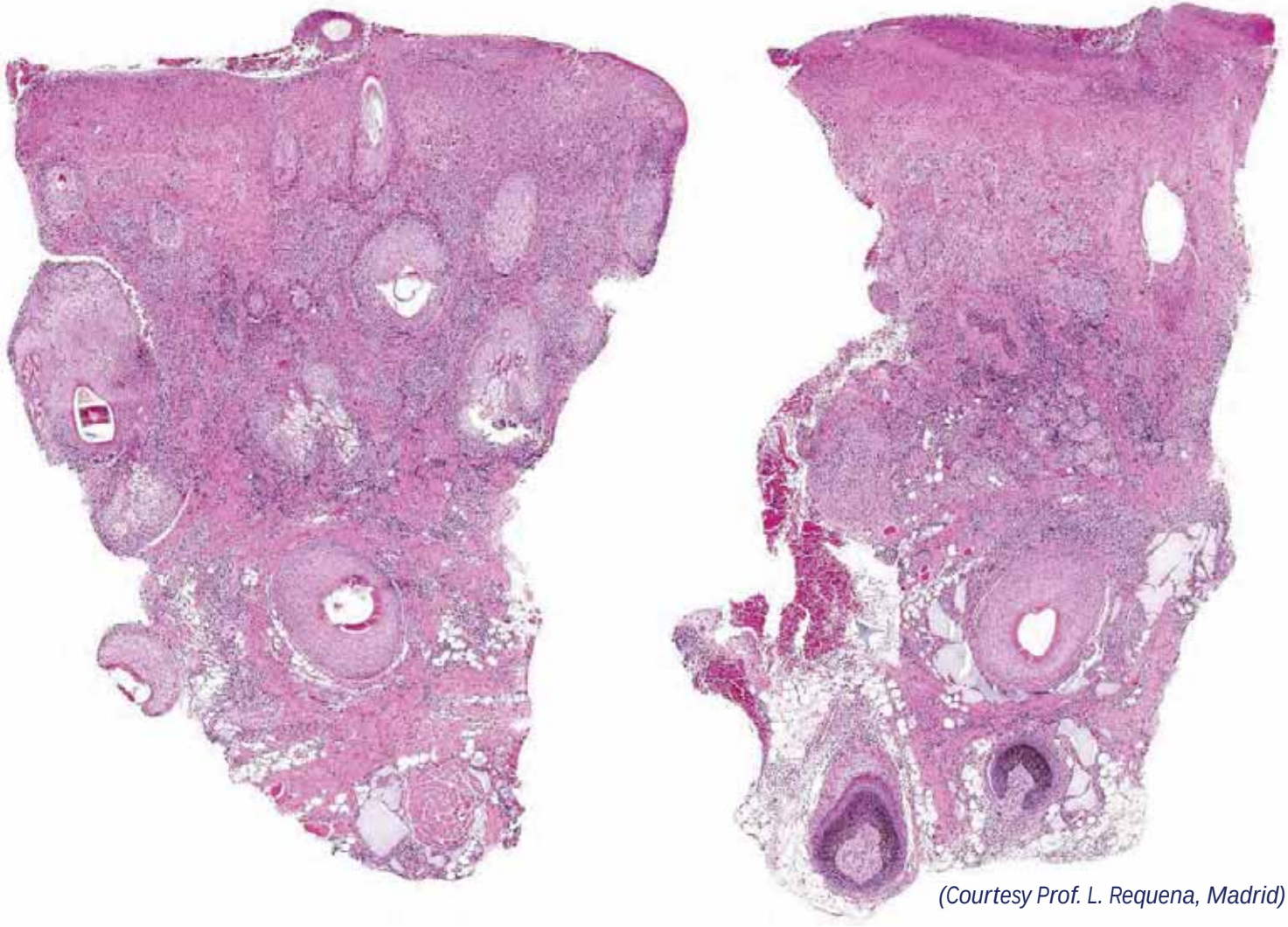




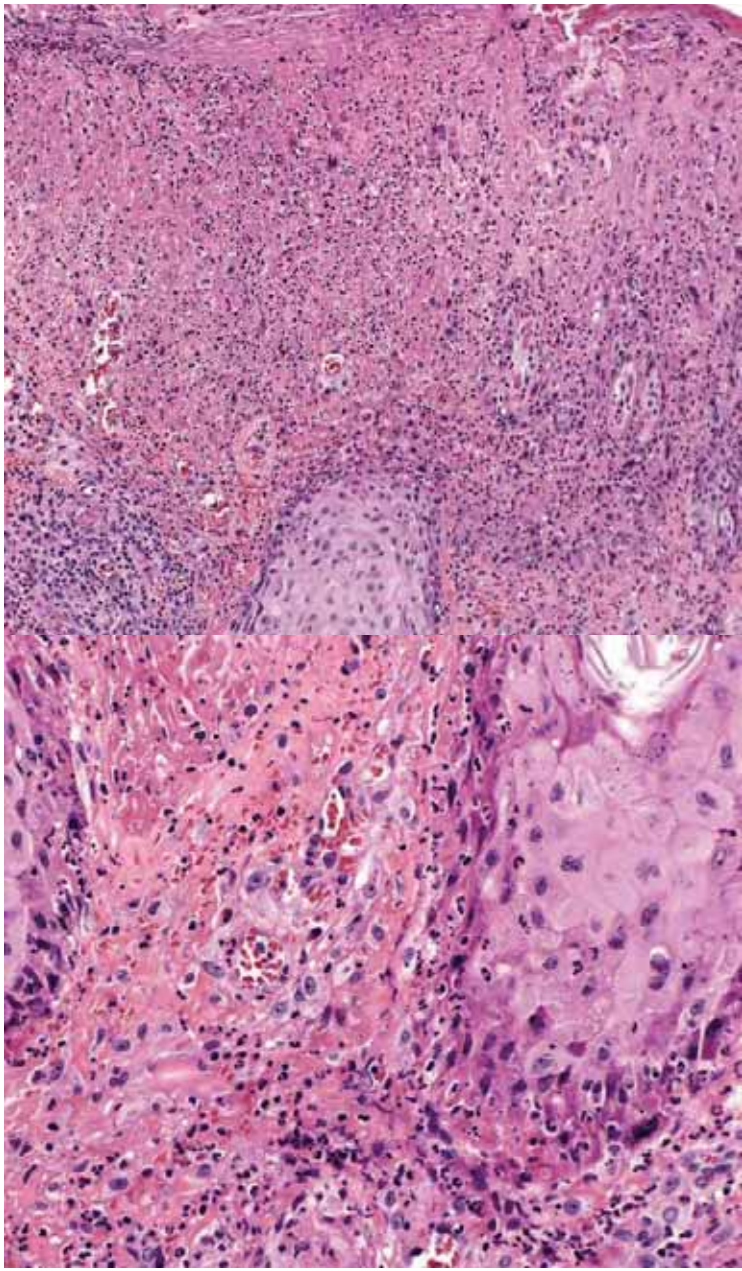


Milker's nodule and orf show identical histopathological findings (epithelial hyperplasia, ballooning degeneration of keratinocytes); in early lesions intracytoplasmic eosinophilic inclusions may be seen.


Mpox



(Courtesy Prof. L. Requena, Madrid)



Monkeypox (mpox) shows ballooning of keratinocytes with subsequent necrotic features of the epidermis and adnexal structures.

BJD
British Journal of Dermatology

Monkeypox outbreak in Spain: clinical and epidemiological findings in a prospective cross-sectional study of 185 cases*

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22 July 2022

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A.C., P.C.E., J.R.M., G.M.E. and P.F.G. contributed equally to this article as lead authors.

*This study received external funding.

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Abstract

Table 1 Demographics of the patients

Number of patients	185
Age (years), mean (SD)	38·7 (8·2)
Gender	
Male	185 (100)
Female	0
Transsexual male	0
Transsexual female	0
Other	0
Previous history of smallpox vaccination	
Unknown	20 (11)
No	145 (78)
Yes (scar/other evidence)	20 (11)
Born before 1972 (large decrease in smallpox vaccination since then)	19 (10)
HIV infection	
Yes	78 (42)
CD4 count (cells/mm^3), median (p25–p75)	698 (549–930)
C4 nadir (cells/mm^3), median (p25–p75)	396 (249–575)
Detectable viral load (*n* = 63)	6 (10)
Required hospitalization	4 (2)
Required intensive care	0
Death	0

The data are presented as *n* (%) unless stated otherwise.
Percentile 25-percentile 75, interquartile range.

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

Francisco José Rodríguez-Cuadrado, MD,[1] Laura Nájera, MD,[2] Dolores Suárez, MD,[3] Gala Silvestre, MD,[3] Diego García-Fresnadillo, Pathology Technician,[3] Gaston Roustan, MD,[4] Laura Sánchez-Vázquez, MD,[5] Margarita Jo, MD,[5] Carlos Santonja, MD,[5] María Concepción Garrido-Ruiz, MD,[6] Ana María Vicente-Montaña, MD,[7] José Luis Rodríguez-Peralto, MD,[7] and Luis Requena, MD[1]

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

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

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

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

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

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

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

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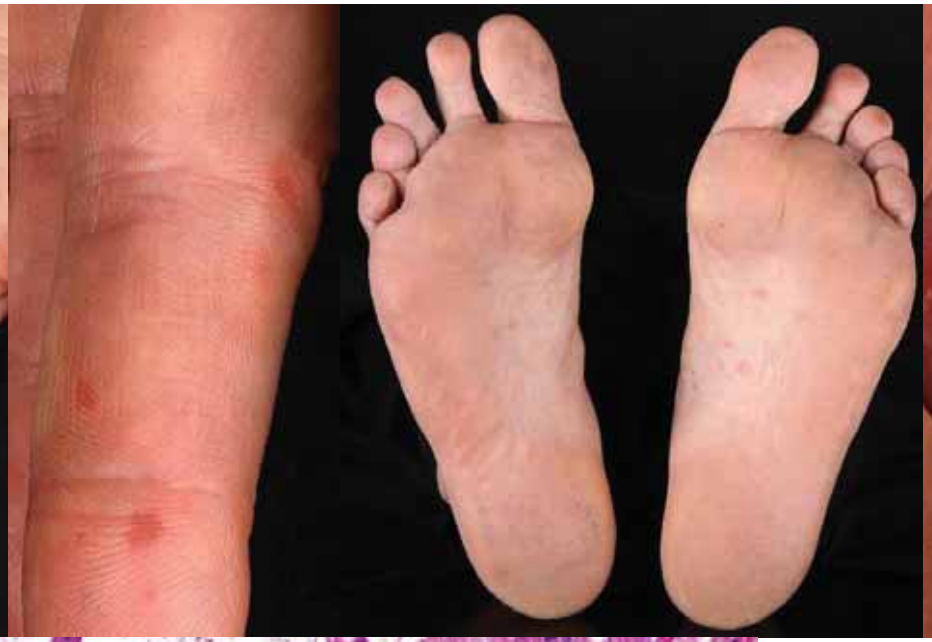
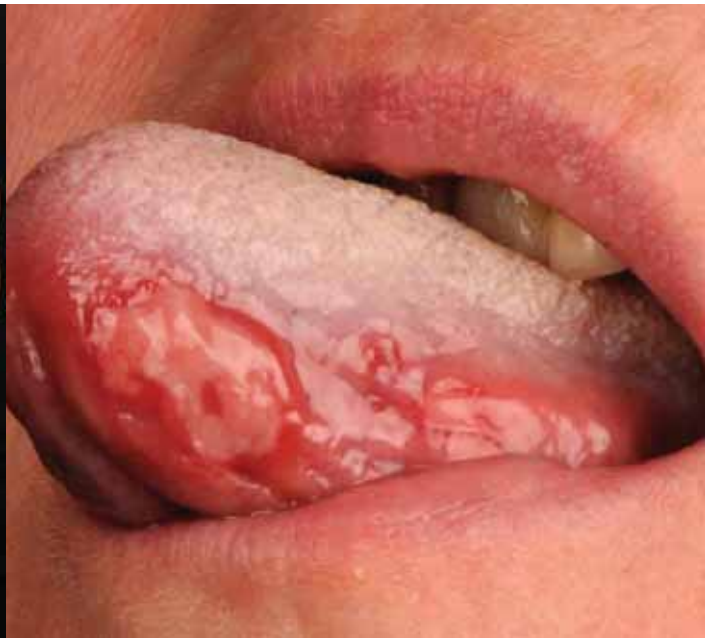
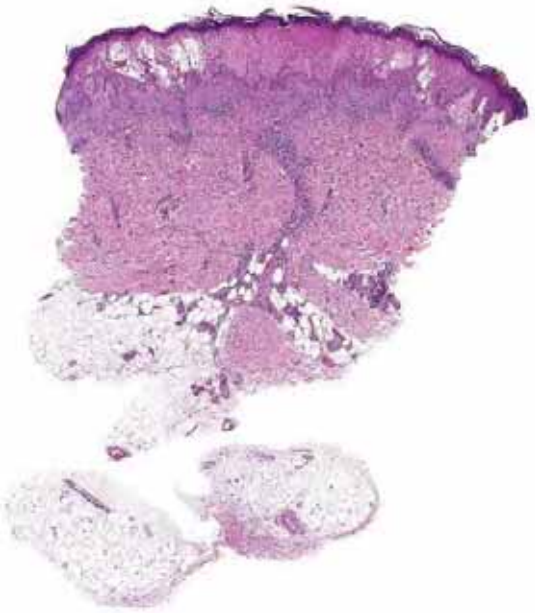
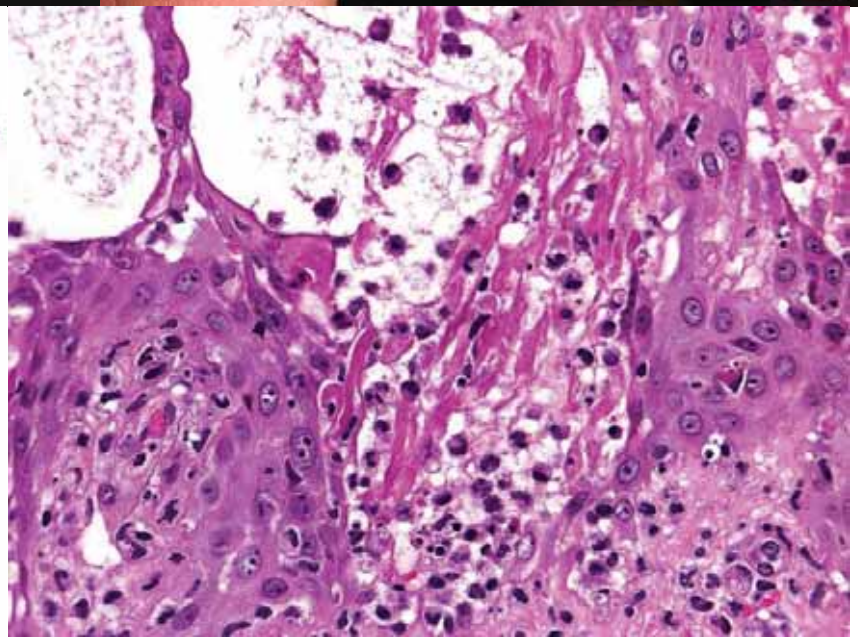


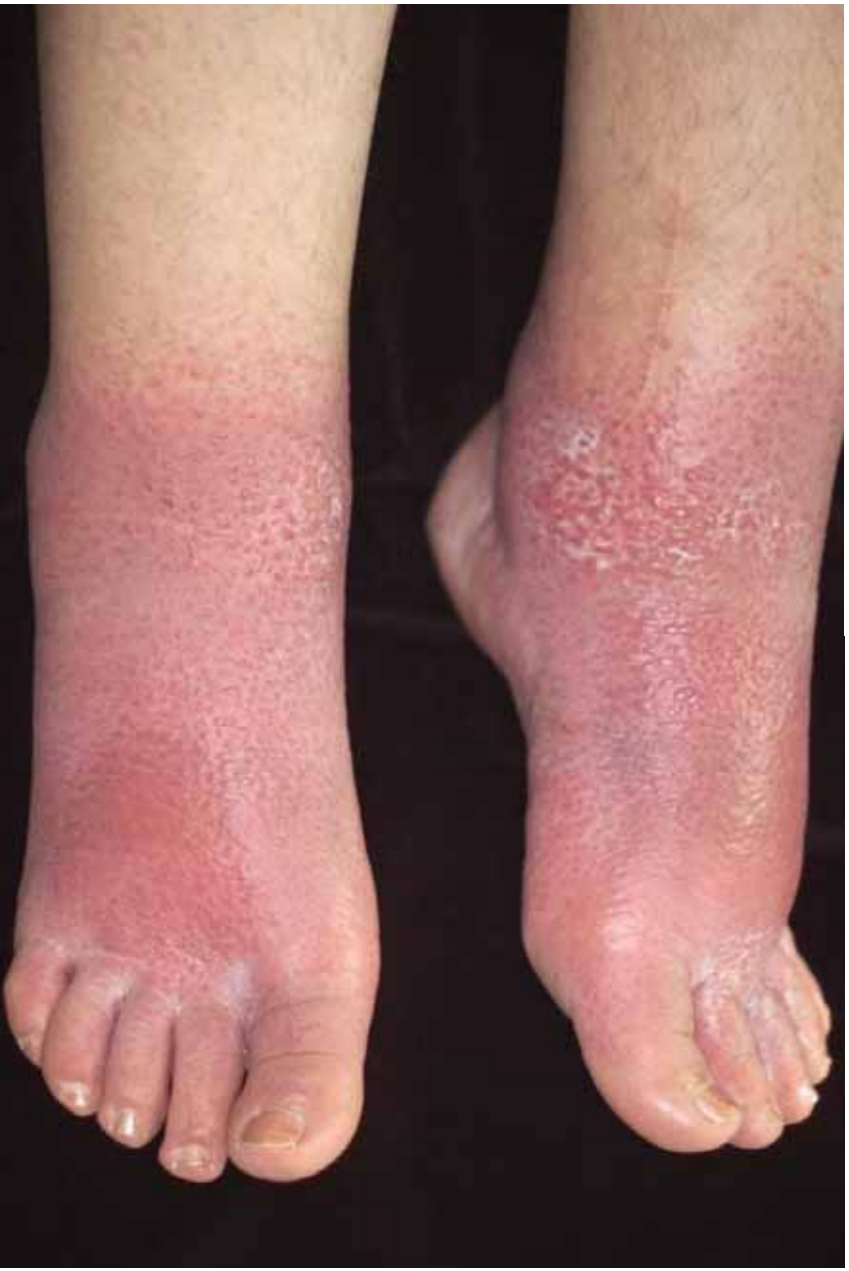


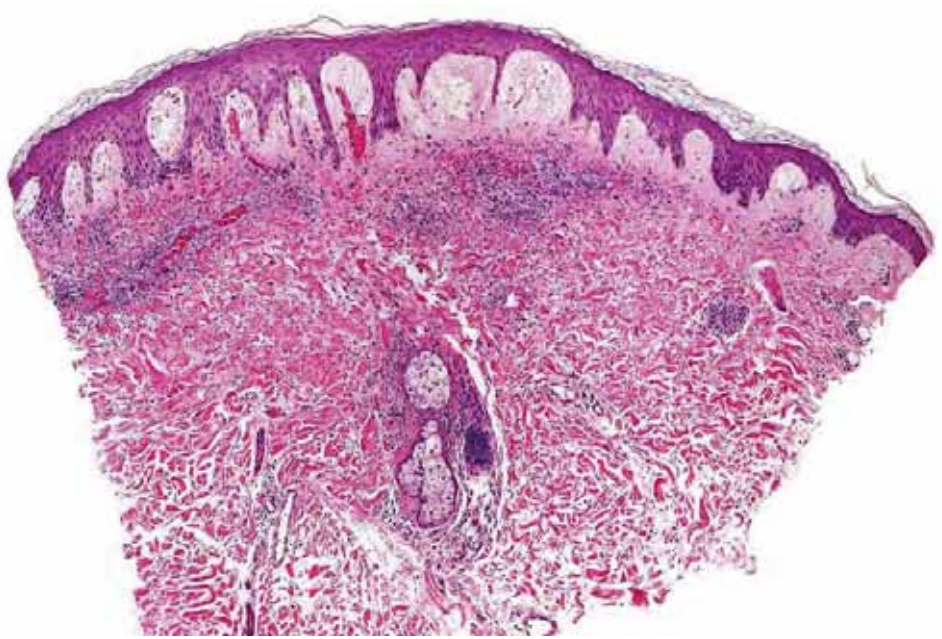


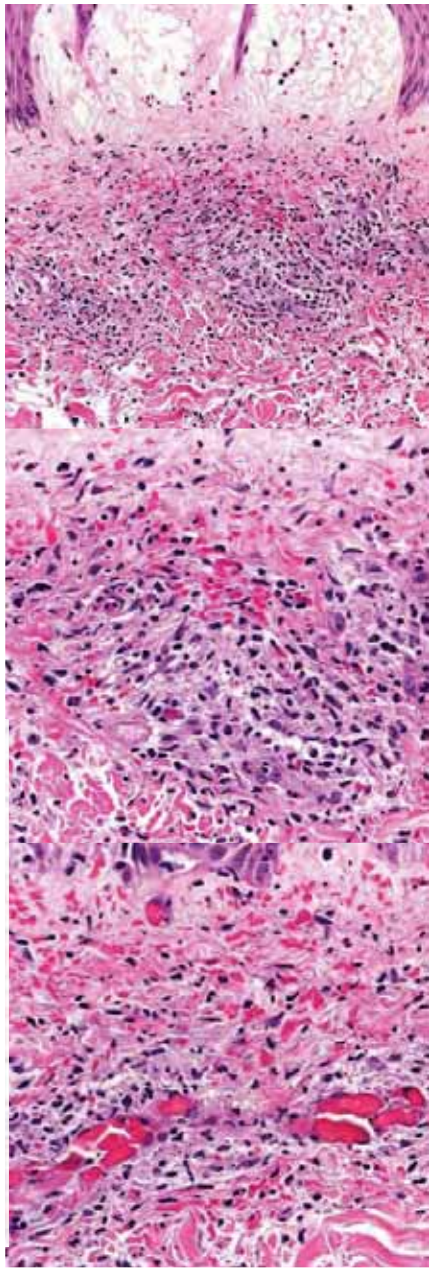


Hand-foot-mouth disease

Enterovirus infection (mostly coxsackievirus A10, A16, A6); Self-limited (beware of risk groups such as neonates or immune suppressed individuals – it may cause life-threatening complications, particularly when caused by enterovirus 71; aseptic meningitis may be observed also in infections with coxsackievirus A16).
Intraepidermal blisters with marked inter- and intracellular edema; the inflammatory infiltrate may contain numerous neutrophils.



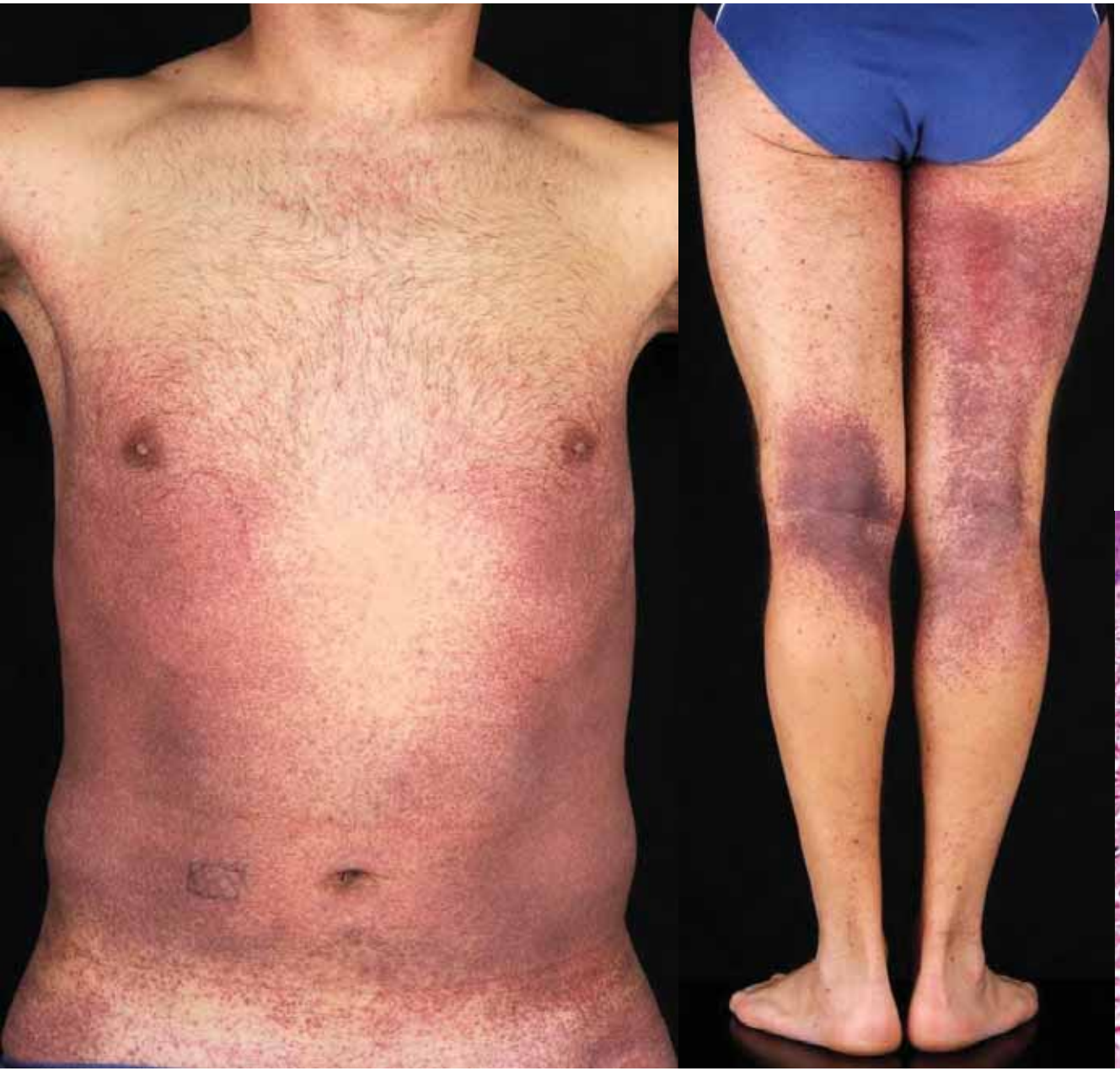




Purpuric gloves and socks syndrome

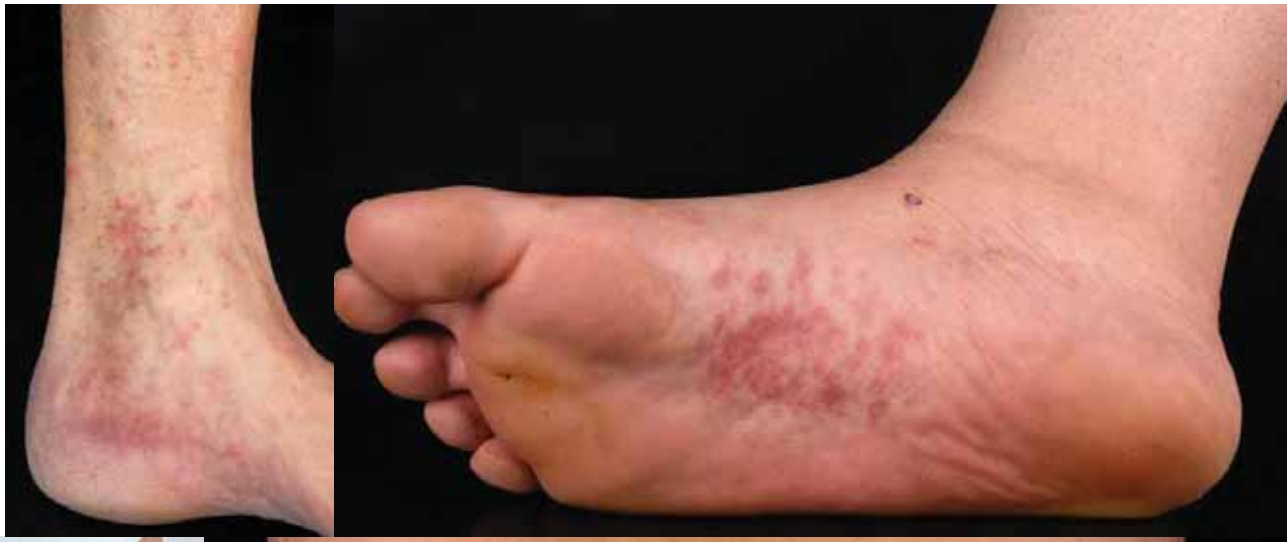
Mostly due to infection with human parvovirus B19; caused also by coxsackievirus B6, HHV-6 and EBV. Edema and erythema of the hands and feet, especially the palms and soles, in association with petechiae and purpura. Self-limited; symptomatic treatment.

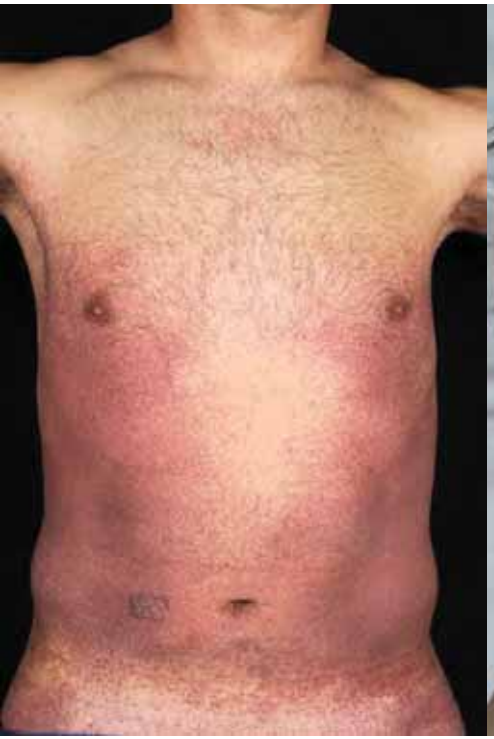
Histology shows dermal inflammatory infiltrates with hemorrhages, corresponding to the purpuric clinical appearance. No evidence of a leucocytoclastic vasculitis.

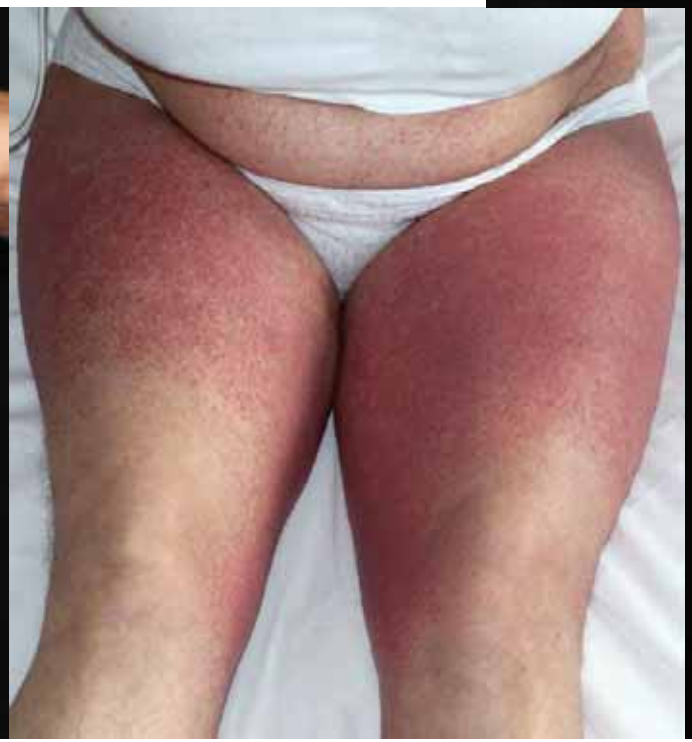


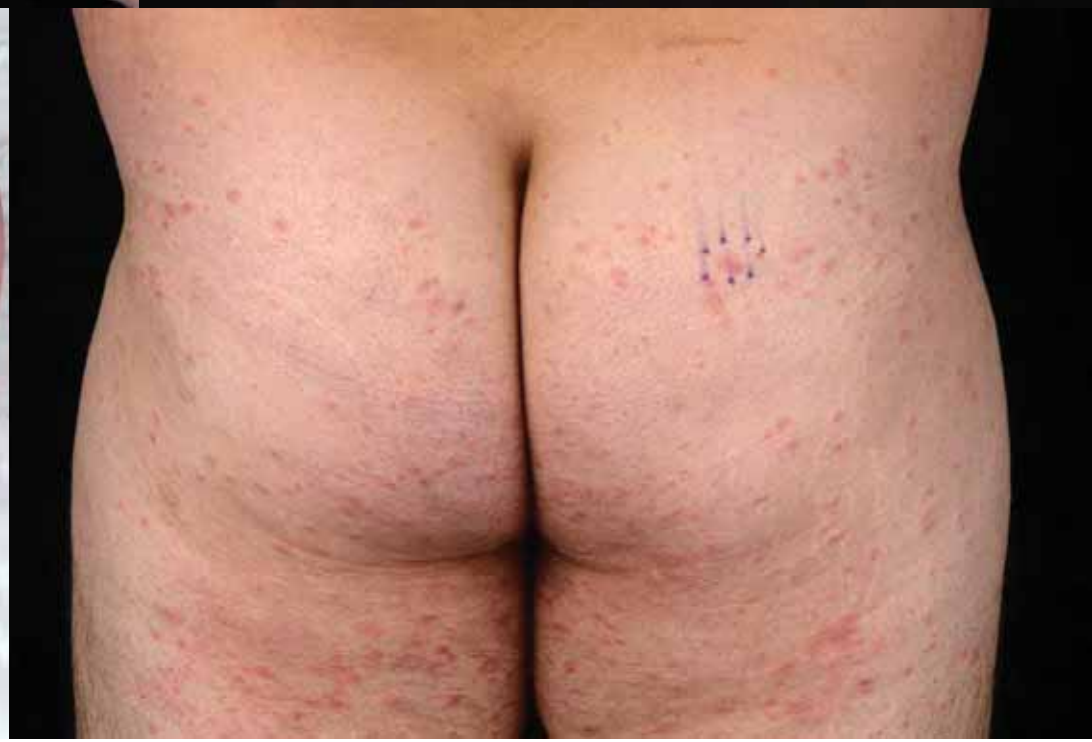
Parvovirus B19 infection

Clinically more than the "socks and gloves" pattern



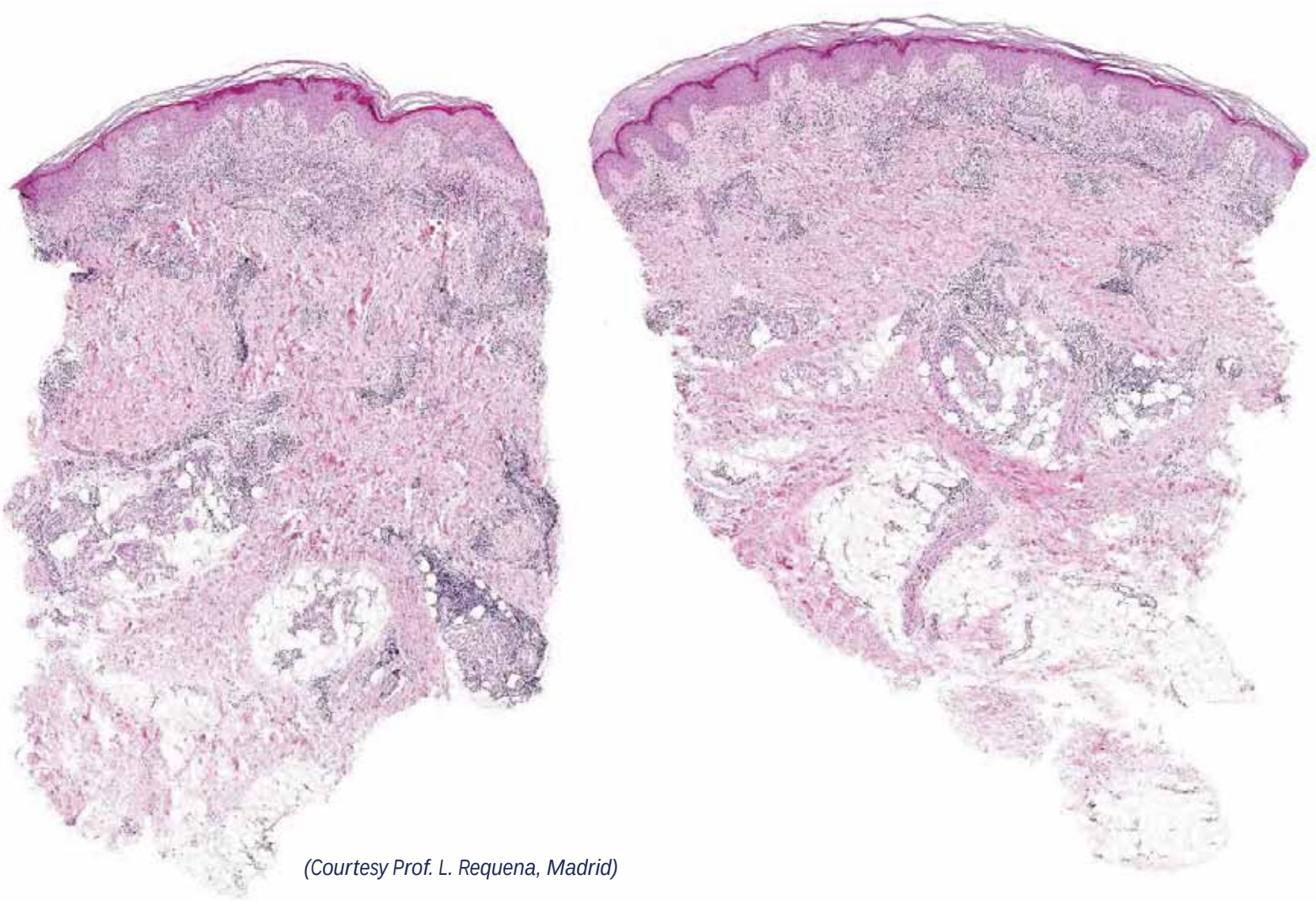




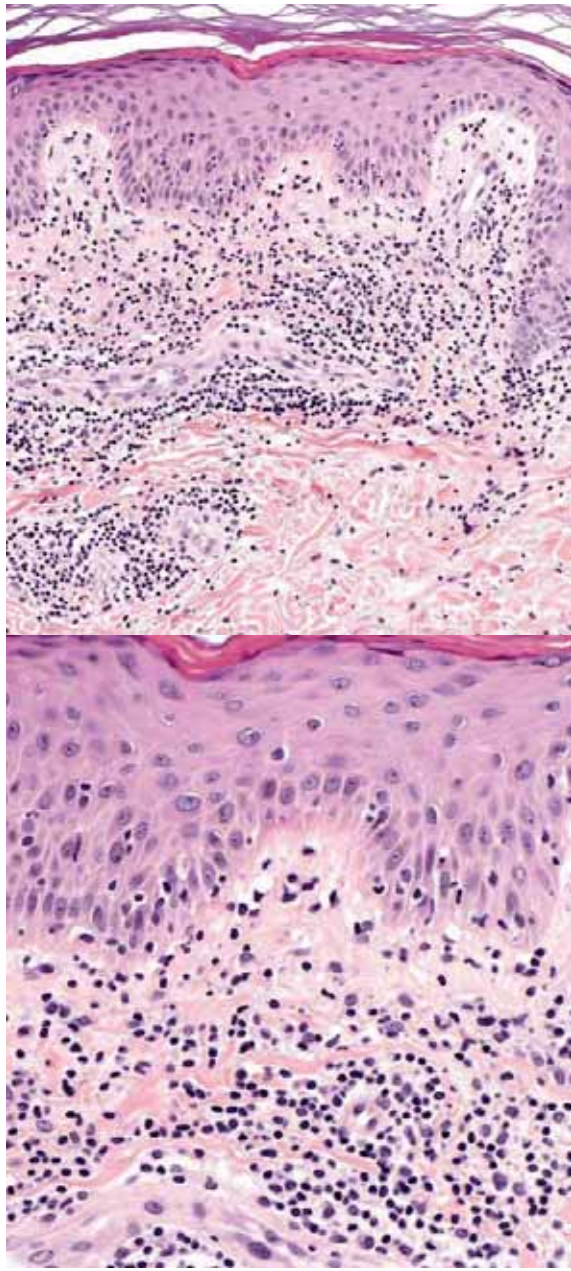


Covid-19 infection and Covid-19 vaccination

- *Covid-19 infection:* chilblain-like lesions, palpable purpura, exathema, urticarial eruptions, other; remarkably, in one study 4 of 5 cases with positive electron microscopy were negative for the nasopharyngeal RT-PCR test for COVID-19
- *Covid-19 vaccination:* spongiotic reactions ("vaccine-related eruption of papules and plaques"), lichenoid dermatitis, urticarial reactions, bullous reactions, neutrophilic dermatosis, leukocytoclastic vasculitis, chilblain-like lesions, hypersensitivity reaction, disseminated intravascular coagulation (rare), other
- *Histopathology:* broad spectrum of presentations related in part to the clinical aspects



(Courtesy Prof. L. Requena, Madrid)



Chilblain-like lesions in Covid-19 infection show similar histopathological findings as conventional chilblain (and chilblain LE).

PAEDIATRIC DERMATOLOGY

BJD
British Journal of Dermatology

SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases*

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Conflicts of interest
The authors declare they have no conflicts of interest.

*This article is accompanied by an editorial.

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Summary

Background Chilblains ('COVID toes') are being seen with increasing frequency in children and young adults during the COVID-19 pandemic. Detailed histopathological descriptions of COVID-19 chilblains have not been reported, and causality of SARS CoV-2 has not yet been established.

Objectives To describe the histopathological features of COVID-19 chilblains and to explore the presence of SARS-CoV-2 in the tissue.

Methods We examined skin biopsies from seven paediatric patients presenting with chilblains during the COVID-19 pandemic. Immunohistochemistry for SARS-CoV-2 was performed in all cases and electron microscopy in one.

Results Histopathology showed variable degrees of lymphocytic vasculitis ranging from endothelial swelling and endothelitis to fibrinoid necrosis and thrombosis. Purpura, superficial and deep perivascular lymphocytic inflammation with perieccrine accentuation, oedema, and mild vacuolar interface damage were also seen. SARS CoV 2 immunohistochemistry was positive in endothelial cells and epithelial cells of eccrine glands. Coronavirus particles were found in the cytoplasm of endothelial cells on electron microscopy.

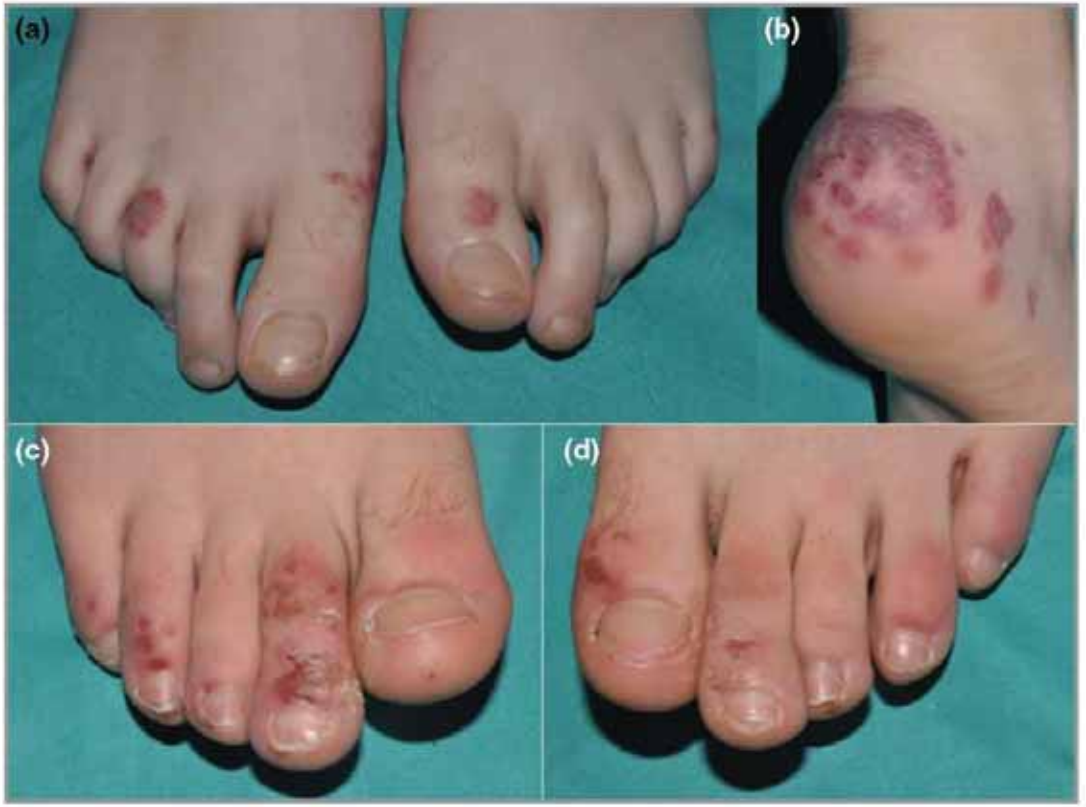
Conclusions Although the clinical and histopathological features were similar to other forms of chilblains, the presence of viral particles in the endothelium and the histological evidence of vascular damage support a causal relation of the lesions with SARS-CoV-2. Endothelial damage induced by the virus could be the key mechanism in the pathogenesis of COVID-19 chilblains and perhaps also in a group of patients severely affected by COVID-19 presenting with features of microangiopathic damage.

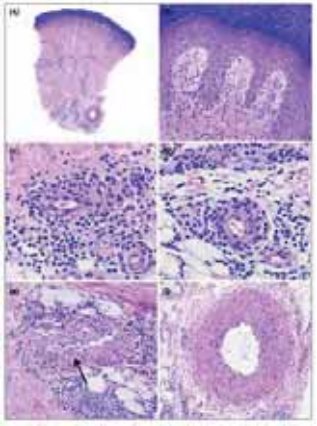
What is already known about this topic?

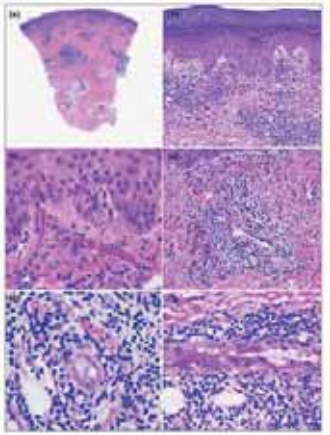
- Despite the high number of cases of chilblains seen during the COVID-19 pandemic, a definite causative role for SARS-CoV-2 has not yet been proven.
- Different pathogenetic hypotheses have been proposed, including coagulation anomalies, interferon release and external factors.

What does this study add?

- The demonstration of SARS-CoV-2 in endothelial cells of skin biopsies by immunohistochemistry and electron microscopy confirms that these lesions are part of the spectrum of COVID-19.







Spectrum of Clinicopathologic Findings in COVID-19-induced Skin Lesions

Demonstration of Direct Viral Infection of the Endothelial Cells

María C. Garrido Ruiz, MD, PhD, Ángel Santos-Briz, MD, PhD,†‡ Alba Sánchez, MD,§ Marina Alonso-Riaño, MD,* Juan Burgos, MD,* Mario Medina-Miguelañez, MD,|| Laura Puebla, MD,|| Concepción Román-Curto, MD, PhD,|| Mónica Roncero-Riesco, MD, PhD,|| Rosa García, PhD,* Pablo L. Ortiz, MD, PhD,§ and José-Luis Rodríguez-Peralto, PhD**

Abstract: The novel coronavirus disease (COVID-19) is a rapidly spreading pandemic, secondary to severe acute respiratory syndrome coronavirus 2. The severity and the little knowledge that we have of the disease have made us focus mostly on the respiratory symptoms. As we bend the curve, other findings reported in association with COVID-19 become of importance for specialists to recognize. We describe the spectrum of clinicopathologic lesions in the skin that can be the only symptom or the first manifestation of COVID-19 and demonstrate the origin of the virus. We collected 25 patients with skin lesions in this context. We recognized 5 types of cutaneous manifestations including acute acroischemic or chilblain-like lesions (11), purpura palpable (2), exanthemas (9), urticarial eruptions (1), and other lesions (2) that might appear with more unspecific pictures. Chilblain-like lesions were the most common form of presentation, which tend to appear as self-healing, erythematous-necrotic plaques mostly on the feet, in young patients with no systemic symptoms associated. Importantly, we visualized viral particles with electron microscopy in 5 of 13 cases analyzed. In this study, we seek to draw a picture of the spectrum of clinicopathologic lesions that may appear in the skin in the context of COVID-19. Although apparently skin lesions are not correlated with disease severity, it may help in some cases to recognize and control the spread of the infection sooner.

Key Words: COVID-19, coronavirus, acroischemic lesions, viral electron microscopy

(*Am J Surg Pathol* 2021;45:293–303)

The novel coronavirus disease (COVID-19) is a rapidly spreading pandemic,[1] secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has claimed 407,000 lives worldwide so far, although likely more than what official numbers show. The severity of pulmonary symptoms, which usually correlate with age and presence of comorbidities, has brought all types of specialists to play a major role against the virus trying to save lives.

Despite the limitations, as the pandemic becomes more still, we start to pay more attention to the many other clinical manifestations of the virus outside the respiratory disease. Thus, anosmia and ageusia are recent otorhinolaryngology-reported manifestations, which may appear as the first or only symptoms of the condition.[2] Skin manifestations are also being reported in the setting of COVID-19-positive patients,[3,4] although the prevalence and patterns of cutaneous involvement are still unclear. In the beginning of the pandemic, Guan et al[3] described a "skin rash" in 2 of 1099 patients (0.2%) presenting with coronavirus disease 2019 in China. A month later, Recalcati[4] reported 18 of 88 patients (20.4%) with confirmed COVID-19 with skin manifestations in Italy. In an attempt to be aware of other possible presentations of the disease, several series and isolated cases are being rapidly reported, with no categorical confirmation of coronavirus infection in most of them. However, it seems that the most common forms of presentations of skin lesions in the context of COVID-19 include erythematous rash,[4,5] urticariform rash,[4–7] acute acroischemic lesions,[5,8–10] and varicella-like exanthema.[11] Despite the profuse characterization of clinical lesions, histopathologic descriptions are still scarce, and there is no definitive proof of the virus in many cases.

In this study, we demonstrate for the first time the presence of viral particles in the skin with electron microscopy (EM) and we describe the wide spectrum of clinicopathologic findings in cutaneous lesions associated with COVID-19, which might be important for the specialists to recognize, as they can be the only symptom or the first manifestation of the disease.

PATIENTS AND METHODS

The retrospective study included 25 patients with dermatologic lesions, 14 from the 12 de Octubre University Hospital in Madrid and 11 from the University Hospital of Salamanca from March 20 to April 25, 2020, in the context of the devastating worldwide pandemic (documented by the

From the Departments of *Pathology; §Dermatology, 12 de Octubre University Hospital, Complutense University of Madrid, Investigation Institute i+12, CIBERONC, Madrid; Departments of †Pathology; ||Dermatology, University Hospital of Salamanca; and ‡Institute for Biomedical Research (IBSAL), Salamanca, Spain.

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

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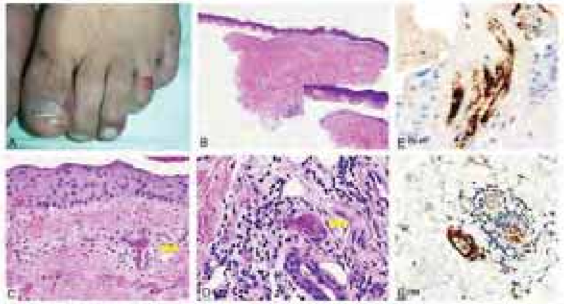

FIGURE 1. Clinical and histopathologic findings of acroischemic lesions in case 2. A, Erythematous edematous macules were observed on the back of the toes, some of them with erosive lesions and crusts. B–D, Light microscopy of the skin biopsy showed marked necrosis of the epidermis (B and inset), and a mild perivascular lymphocytic infiltrate in the reticular dermis. Remarkably intravascular thrombus was identified in several capillaries (C, D; arrows). E and F, IHC showed extensive deposition of C3d and C4d within the microvasculature.

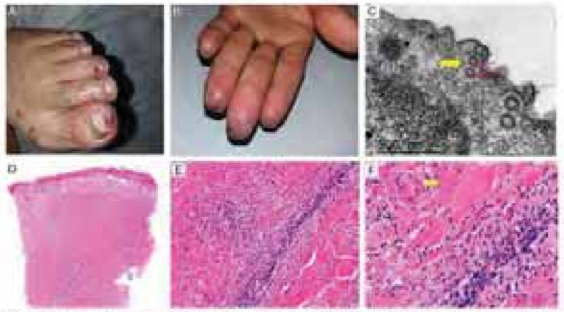

FIGURE 2. Clinical and histopathologic findings of acroischemic lesions in case 2. A and B, Erythematous-purpuric macules were observed on the fingertips of the hands, some of them with a whitish central area, and more residual lesions on the feet, whereas ... C, EM of the skin tissue ... showed viral inclusion particles in endothelial cells of the dermis (arrow). D–F, The biopsy from the fingertip of the third finger of the right hand showed thrombogenic vasculitis (F, arrow) with neutrophils, leukocytoclasia, and remarkable endothelitis and extensive necrosis of the epidermis.

FIGURE 6. A and B, Case 24 presented with erythematous-purpuric lesions on the ball of the first toe of the right foot and fingers of both hands. C and D, Histopathology only showed marked superficial telangiectasias, with no hematic extravasation and no inflammatory infiltrate.

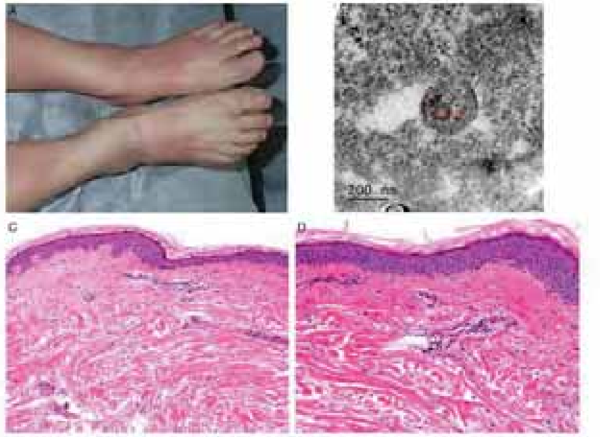

FIGURE 5. A, Case 23 presented with a 3-days long widespread pruritic erythematous exanthema, more intense in the lower limbs. B, EM of the skin tissue showed viral inclusions in the endothelial cells of the capillaries. C and D, Skin biopsy only showed mild perivascular superficial dermatitis with neutrophils and eosinophils.

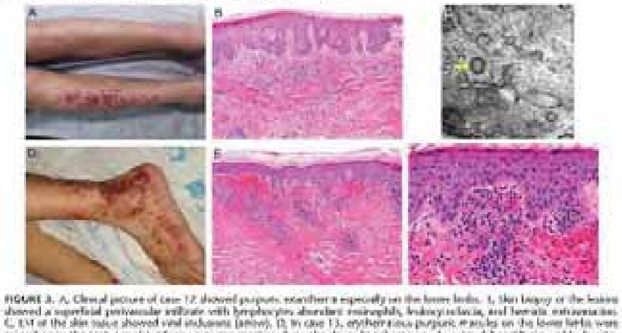

FIGURE 3. A, Clinical picture of case 12 showed purpuric exanthema especially on the lower limbs. B, Skin biopsy of the lesions showed a superficial perivascular infiltrate with lymphocytes, abundant neutrophils, leukocytoclasia, and hematic extravasation. C, EM of the skin tissue showed viral inclusions (arrow). D, In case 13, erythematous-purpuric macules on the lower limbs were extending to the foot. E and F, Microscopic examination showed a dense lymphocytic and neutrophilic infiltrate and leukocytoclasia around the vessels with abundant blood extravasation, endothelial swelling but no fibrinoid necrosis.

FIGURE 4. A, Case 15 presented with widespread confluent small erythematous papules on the trunk. B and C, Skin biopsy showed a superficial perivascular lymphocytic infiltrate with dermal eosinophilia, associated with histiocytes between the collagen bundles. D, Case 19 presented with a confluent maculopapular exanthema initially involving the trunk, and extending to the limbs, several of them with targetoid morphology. E and F, Skin biopsy of the right flank showed erythema multiforme-like lesions with dense lymphocytic perivascular dermatitis and interface dermatitis with isolated necrotic keratinocytes.

MEDICAL DERMATOLOGY

BJD
British Journal of Dermatology

Cutaneous reactions after SARS-CoV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases*

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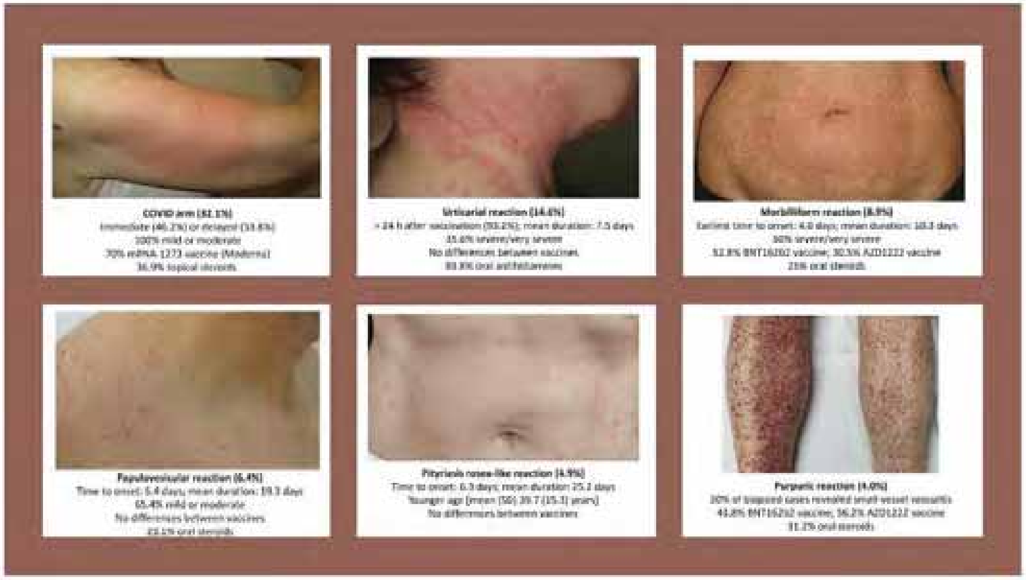


Correspondence
Cristina Muñoz-Santos

Accepted for publication
18 May 2021

Summary

Background Cutaneous reactions after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are poorly characterized.
Objectives To describe and classify cutaneous reactions after SARS-CoV-2 vaccination.
Methods A nationwide Spanish cross-sectional study was conducted. We included patients with cutaneous reactions within 21 days of any dose of the approved vaccines at the time of the study. After a face-to-face visit with a dermatologist, information on cutaneous reactions was collected via an online professional

Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: A registry-based study

Devon E. McMahon, MD,[a] Carrie L. Kovarik, MD,[b] William Damsky, MD, PhD,[c] Misha Rosenbach, MD,[b] Jules B. Lipoff, MD,[b] Aanisha Tyagi, BA,[a] Grace Chamberlin, BA,[a] Ramie Fathy, AB,[b] Rosalynn M. Nazarian, MD,[e] Seemal R. Desai, MD,[f,g] Henry W. Lim, MD,[h] Bruce H. Thiers, MD,[i] George J. Hruza, MD, MBA,[j] Lars E. French, MD,[k,l] Kimberly Blumenthal, MD, MSc,[m] Lindy P. Fox, MD,[n] and Esther E. Freeman, MD, PhD[a,o]

Boston, Massachusetts; Philadelphia, Pennsylvania; New Haven, Connecticut; Dallas and Plano, Texas; Detroit, Michigan; Charleston, South Carolina; St. Louis, Missouri; Munich, Germany; Miami, Florida; and San Francisco, California

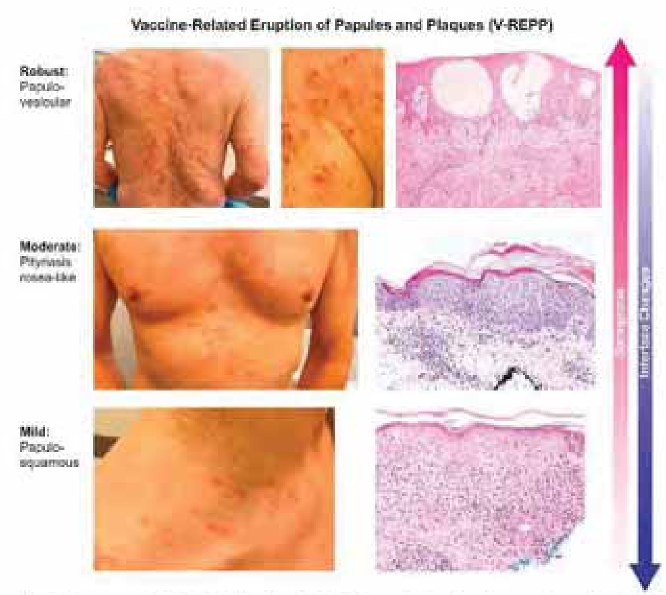
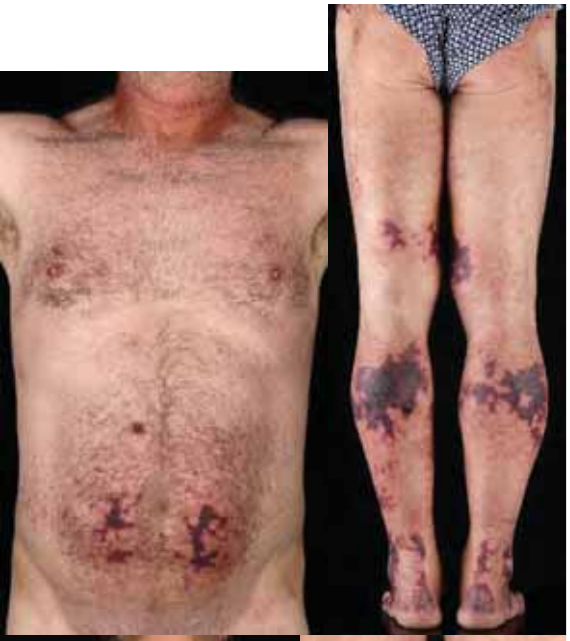
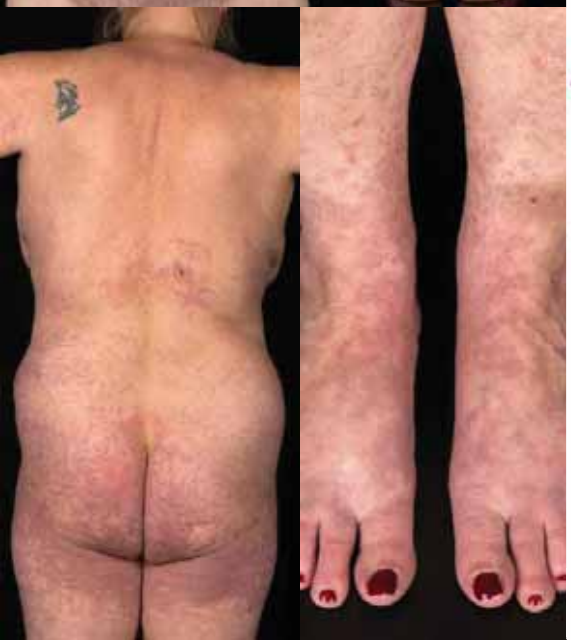
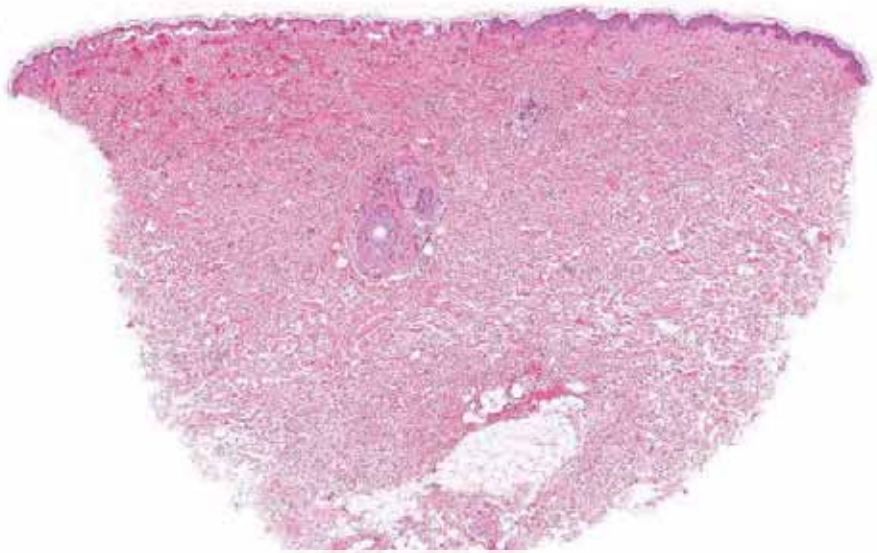


Fig 1. Spectrum of V-REPP following COVID-19 vaccination by degree of spongiosis and interface changes present on histopathology. *V-REPP,* Vaccine-related eruption of papules and plaques.

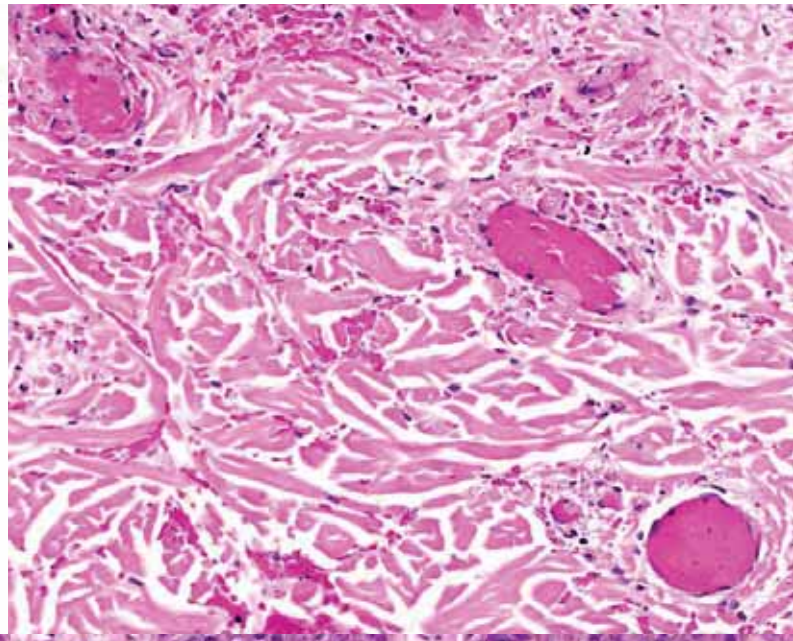
Cutaneous Surgery, University of Miami Miller School of Medicine, Miami[k]; Division of Rheumatology, Allergy, Immunology, Department of Medicine, Massachusetts General Hospital, Boston[m]; and Department of Dermatology, University of California San Francisco, San Francisco.[n]

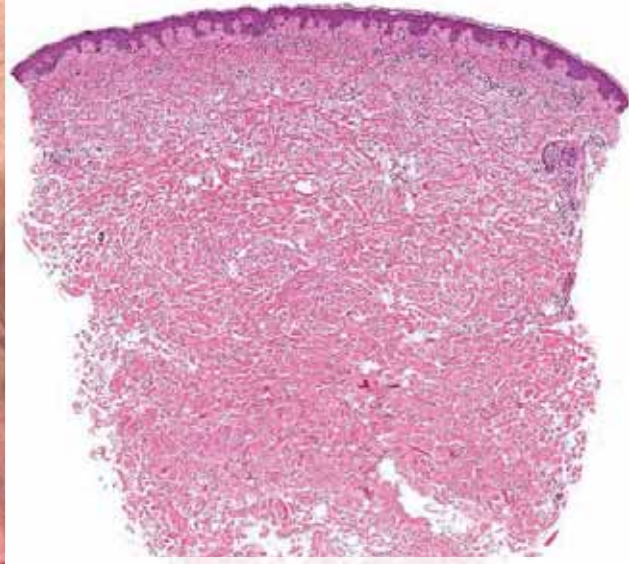




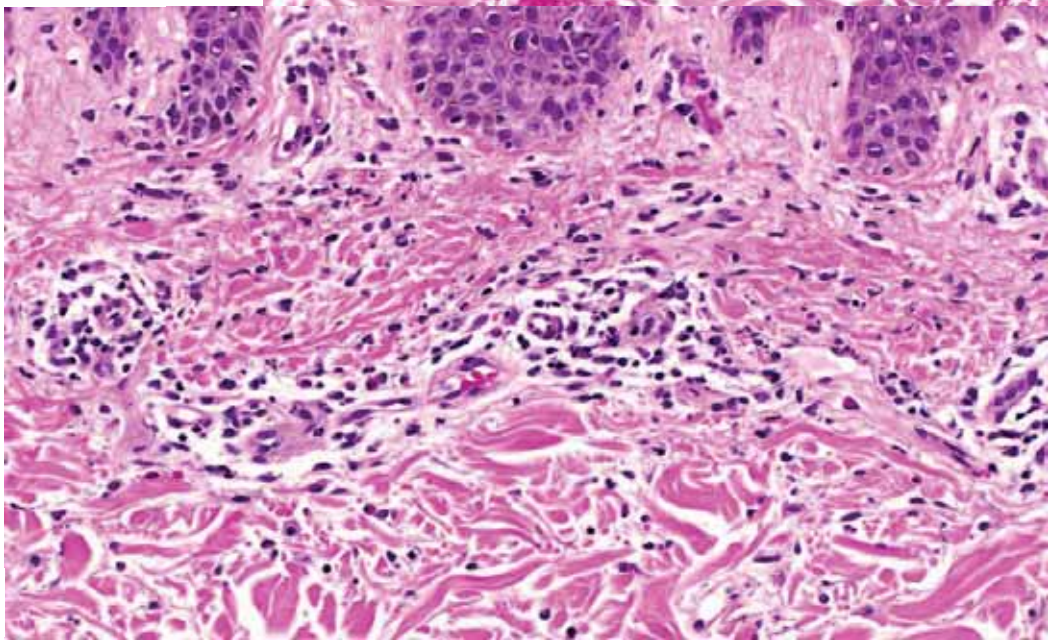


Disseminated intravascular coagulation



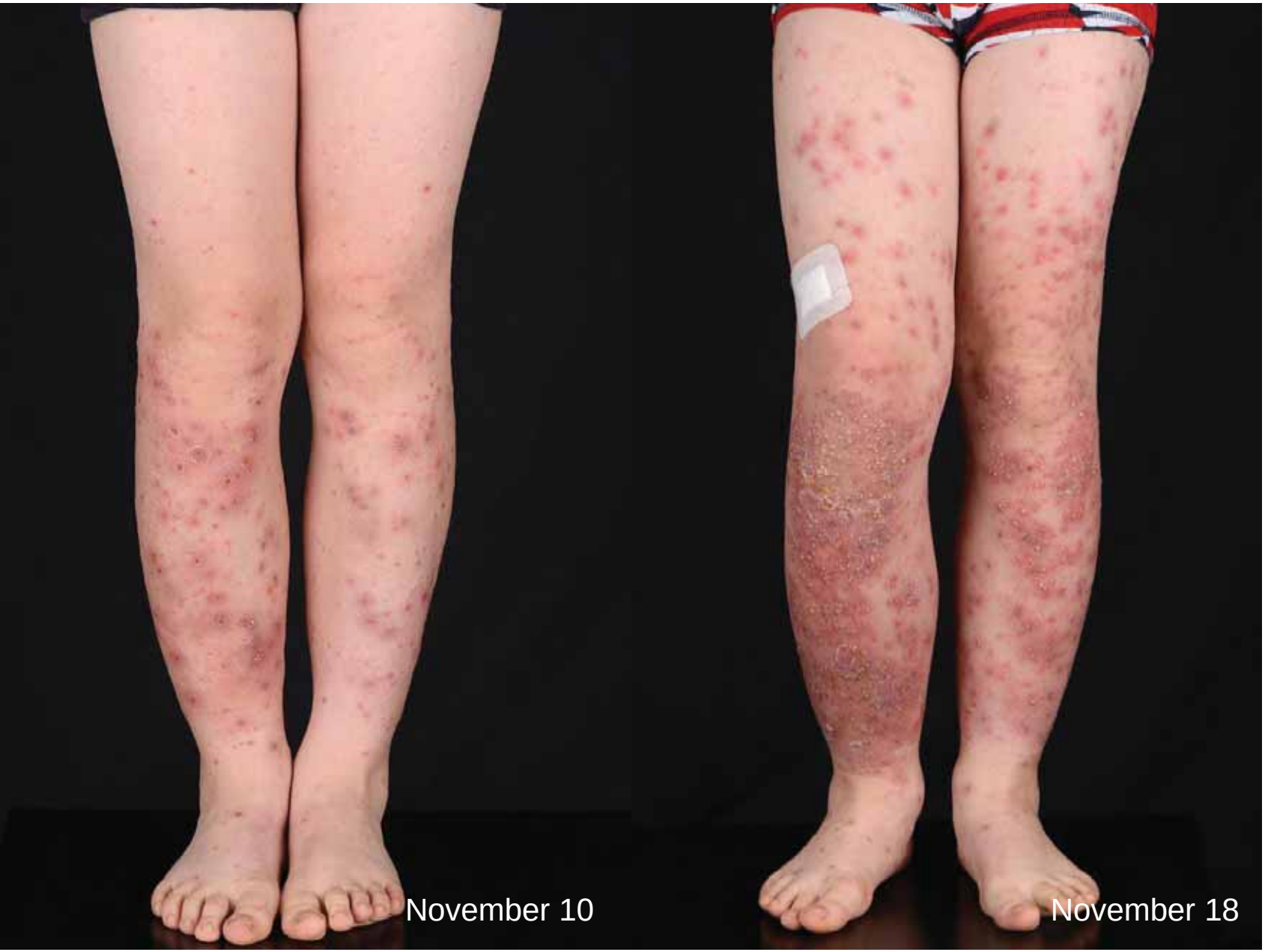


Hypersensitivity reaction



Superficial bacterial infections

- *Folliculitis and furuncles:* infection starting in a hair follicle, subsequently eventually forming an abscess; histology shows a follicular and perifollicular suppurative reaction (the hair follicle may be completely destroyed by the inflammation in late lesions)
- *Impetigo:* solitary, localized or generalized lesions with yellowish crust; lesions may become more widespread in bullous impetigo (due to *S. aureus* phage group II, responsible also for SSSS); histology shows subcorneal collections of neutrophils; bacteria may be visible
- *Ecthyma:* similar to impetigo but with superficial necrosis resulting in a hemorrhagic crust; histology non-specific (presence of bacteria over a necrotic area may suggest the diagnosis)



On control visit further worsening; fever (39°).

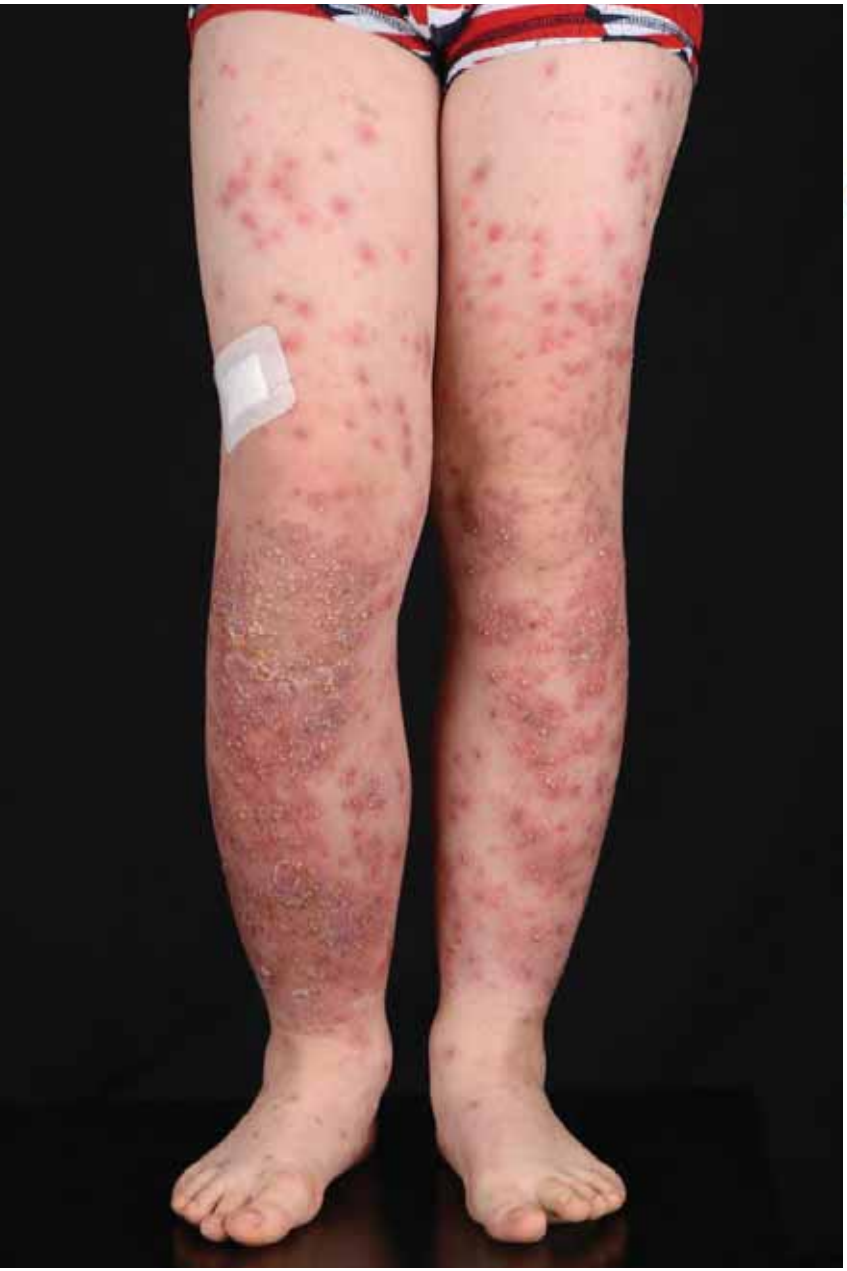
Herpes simplex and varicella/zoster virus PCR negative.

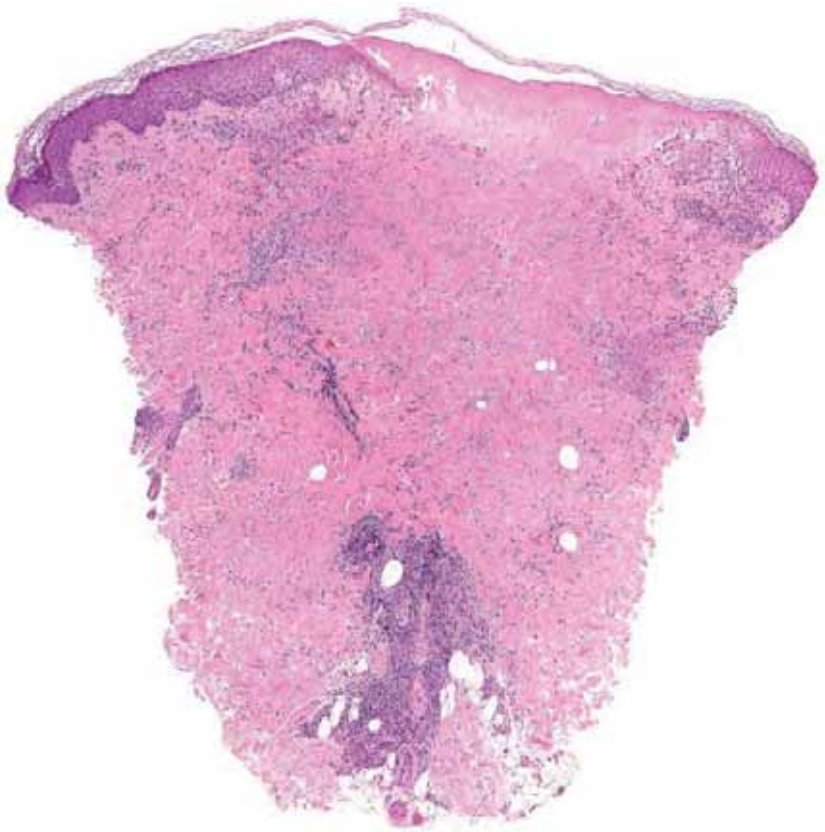
Bacterial smear: staphylococcus aureus.

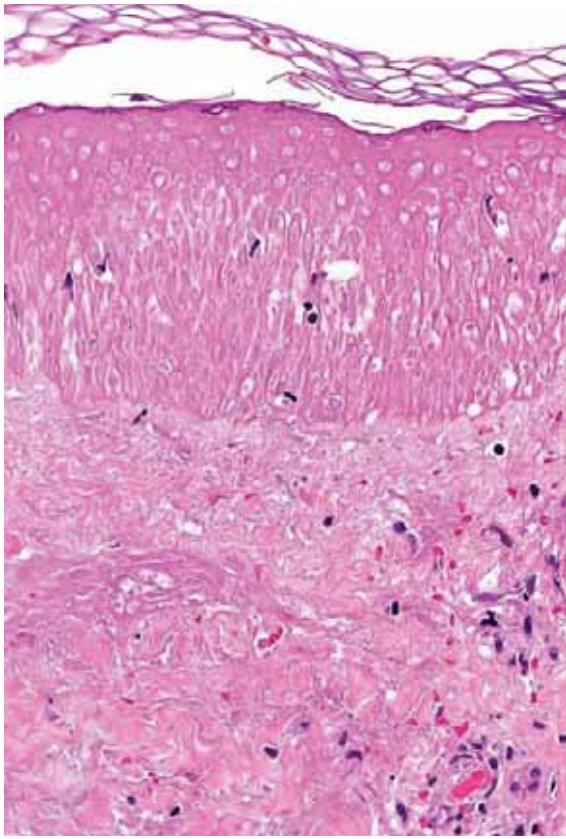
Sent to the pediatric department; admitted as in-patient.

Antibiotic treatment (i.v. cefuroxim) and i.v. antihistamines.

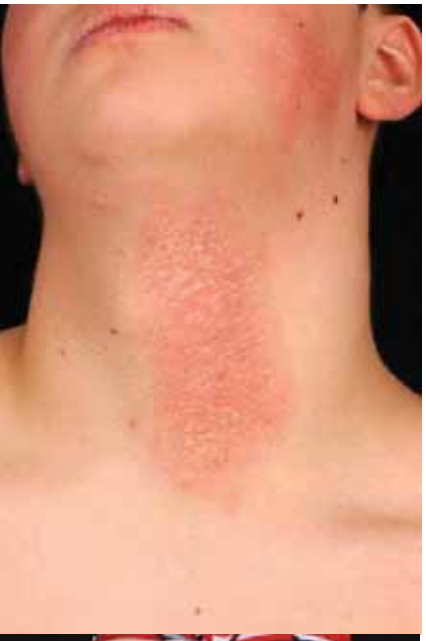
Rapid improvement, discharged from the ward after 6 days with oral antibiotics for further 4 days.

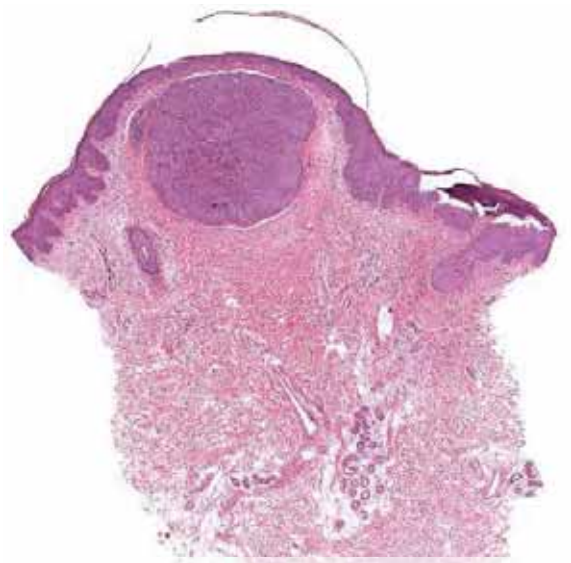




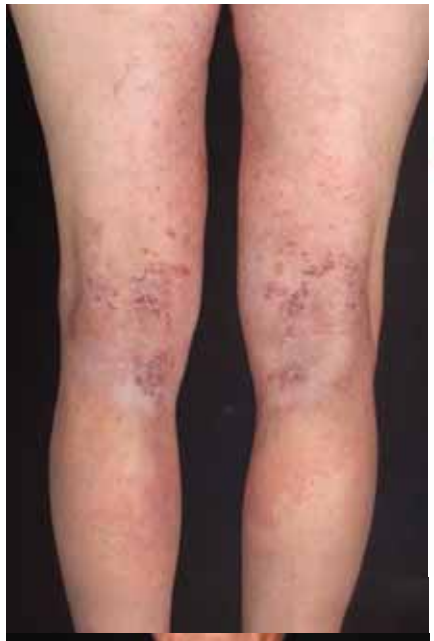


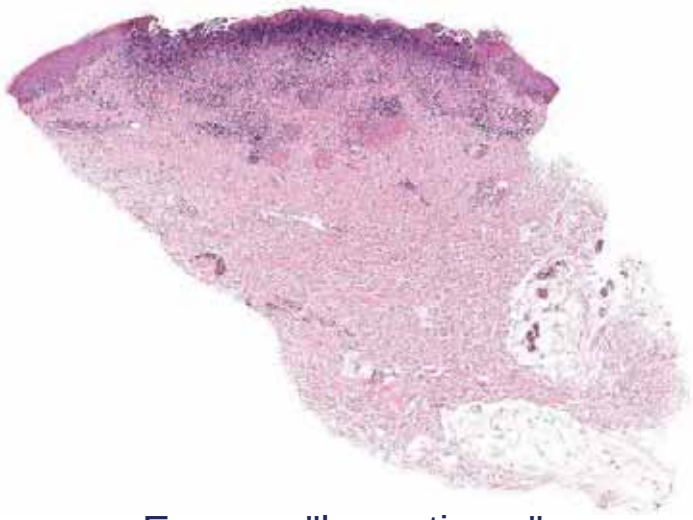
Generalized necrotizing folliculitis
("eczema staphylococcatum")



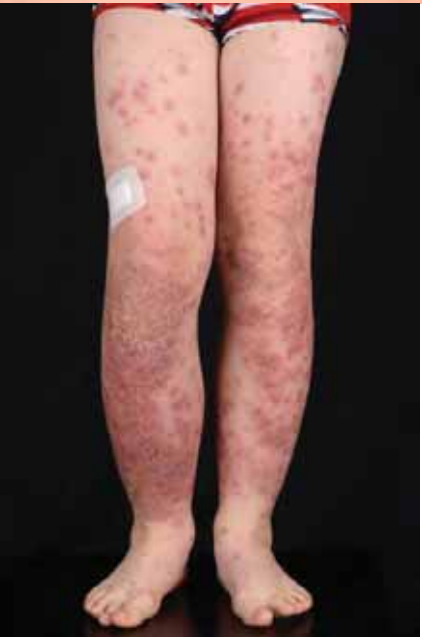


Eczema "molluscatum"

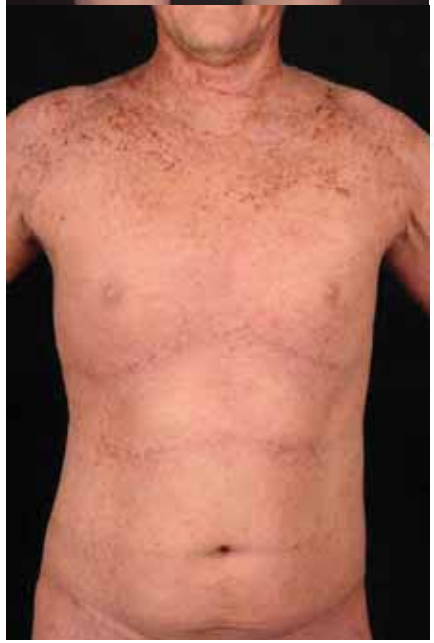


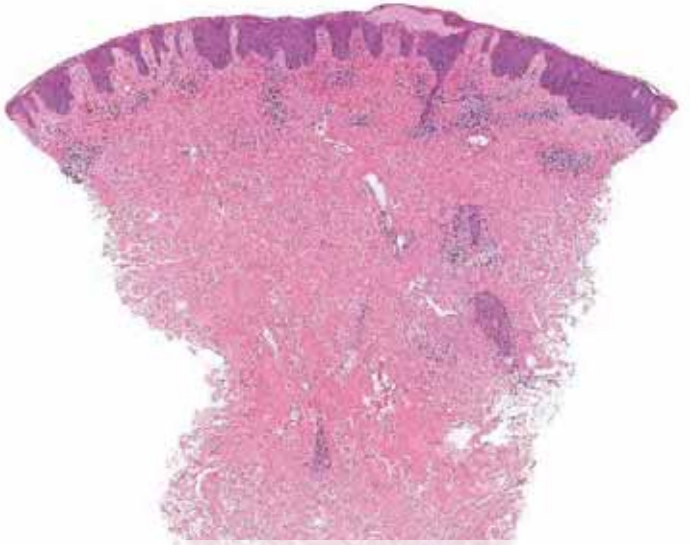


Eczema "herpeticum"



Eczema "staphylococcatum"

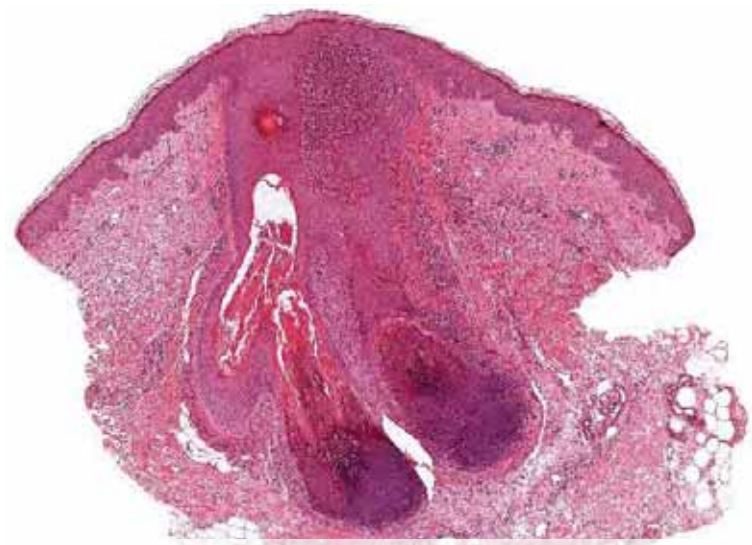


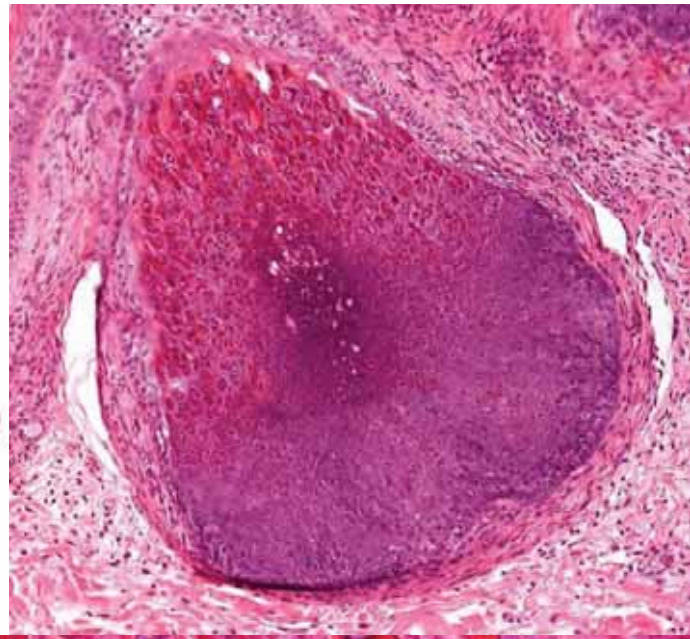


Eczema "vasculiticum"

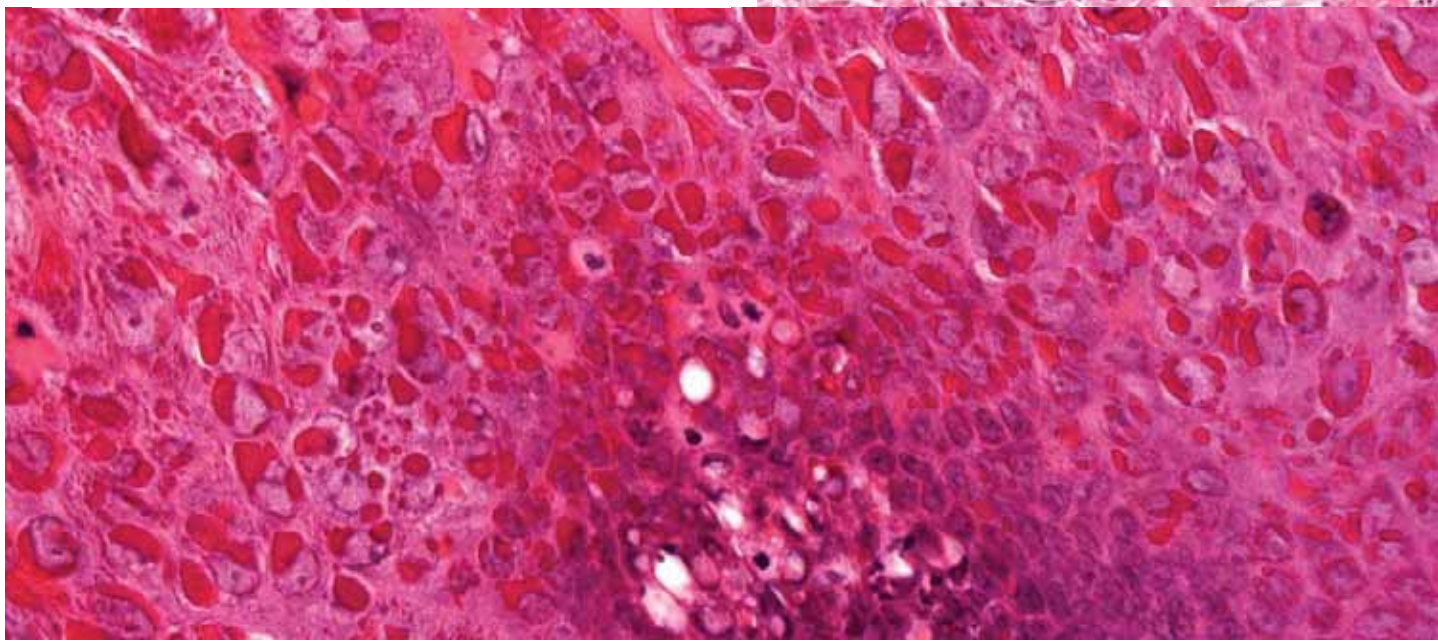
M, 72 with B-CLL

(Consultation Dr. Spaun, Aalborg, Denmark)





Trichodysplasia spinulosa



OBSERVATION

Viral-Associated Trichodysplasia

Characterization of a Novel Polyomavirus Infection With Therapeutic Insights

Karolyn A. Wanat, MD; Phillip D. Holler, MD, PhD; Tzvete Dentchev, MS; Kenneth Simbiri, MS, MRIPH, PhD; Eric Robertson, PhD; John T. Seykora, MD, PhD; Misha Rosenbach, MD

Background: Viral-associated trichodysplasia of immunosuppression is a rare cutaneous eruption that is characterized by follicularly based shiny papules and alopecia with characteristic histopathologic findings of abnormally anagen follicles with excessive inner root sheath differentiation. Prior reports have described the histopathologic characteristics on vertical sections; however, to our knowledge, immunohistochemical analysis of polyomavirus proteins has not been previously performed.

Observations: We discuss the thorough diagnostic evaluation and therapy of an unusual case of viral-associated trichodysplasia due to a newly described human polyomavirus that occurred in a patient with post-treatment chronic lymphocytic leukemia and intermittent white blood cell count. Unique to our study is the immunohistochemical staining for the polyomavirus middle T antigen, which demonstrated positive staining of cellular inclusions within keratinocytes that compose the inner root sheath. Further evaluation with scanning electron microscopy and polymerase chain reaction analysis of viral DNA confirmed the presence of the virus. Treatment with topical cidofovir resulted in dramatic clinical improvement and hair regrowth.

Conclusions: Several tools, including immunohistochemical staining for the polyomavirus middle T antigen, can be used to identify the pathogenic virus associated with viral-associated trichodysplasia. This case highlights the utility of multiple diagnostic modalities and a robust response to a topical therapeutic agent, cidofovir.

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VIRAL-ASSOCIATED TRICHODysplasia (VAT) of immunosuppression (also known as trichodysplasia spinulosa, pilomatrix dysplasia, cyclosporine-induced folliculodystrophy, and trichodysplasia of immunosuppression) is a rare cutaneous eruption that is characterized by erythematous to skin-colored follicularly based spiny papules that predominantly affect the central face as well as by the histopathologic findings of abnormally maturing anagen follicles with excessive inner root sheath differentiation. Variable amounts of alopecia also have been reported, especially involving the eyebrows, eyelashes, and other hair-bearing parts of the face.

We report an exceptional case of VAT that was confirmed by the results of immunohistologic analysis, histopathologic examination, electron microscopy, and polymerase chain reaction (PCR) assay. We also describe the patient's dramatic response to topical cidofovir therapy.

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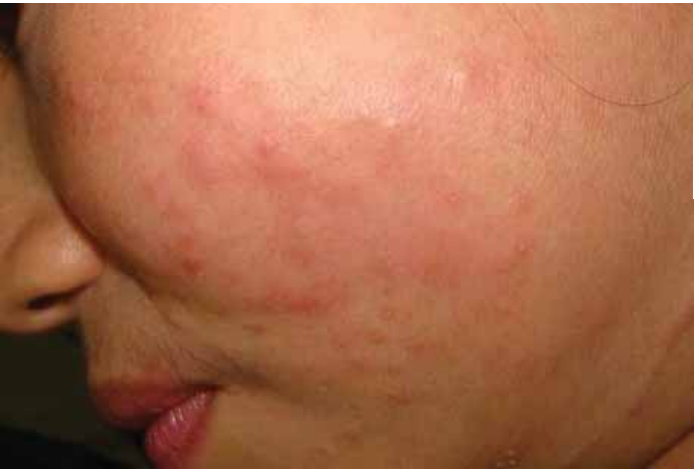
REPORT OF A CASE

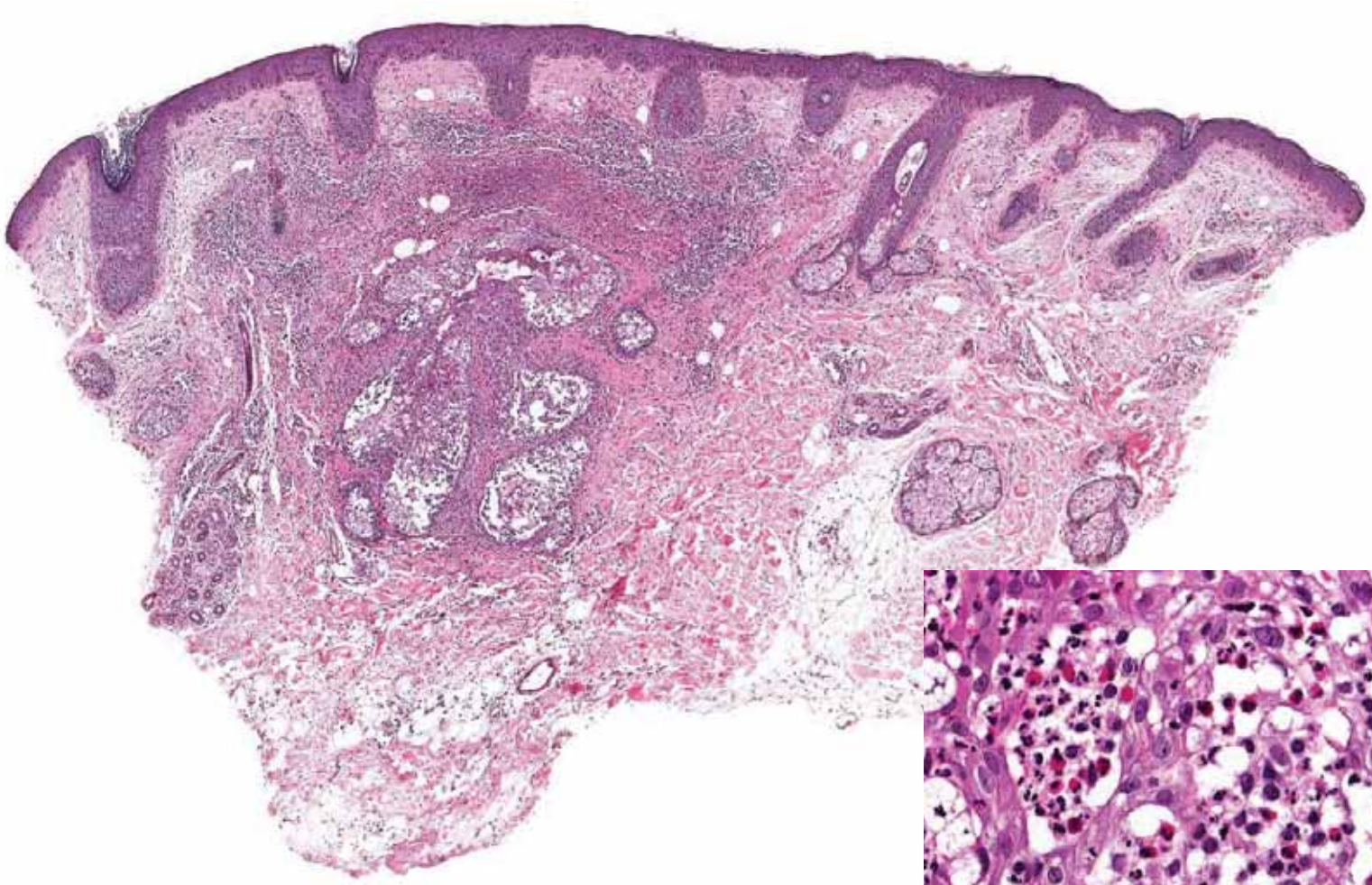
A 57-year-old woman with a history of chronic lymphocytic leukemia presented with a new rash that started 6 months after she completed chemotherapy with rituximab, cyclophosphamide, and cytarabine. She remained on maintenance therapy with monthly intravenous immunoglobulin therapy. Dry skin on her nose and forehead developed into more distinctive skin-colored and erythematous papules that in turn coalesced into plaques. She had a rough texture to her skin as well as alopecia of her eyebrows and eyelashes and the frontal aspect of her scalp. The skin-colored papules subsequently spread to her chest, arms, and legs. She was initially treated with cimetidine, topical imiquimod, salicylic acid, and hydrocortisone for presumed verruca vulgaris at an outside institution, with limited benefit. She was taking no other medications.

Physical examination revealed skin-colored papules that were nearly confluo-

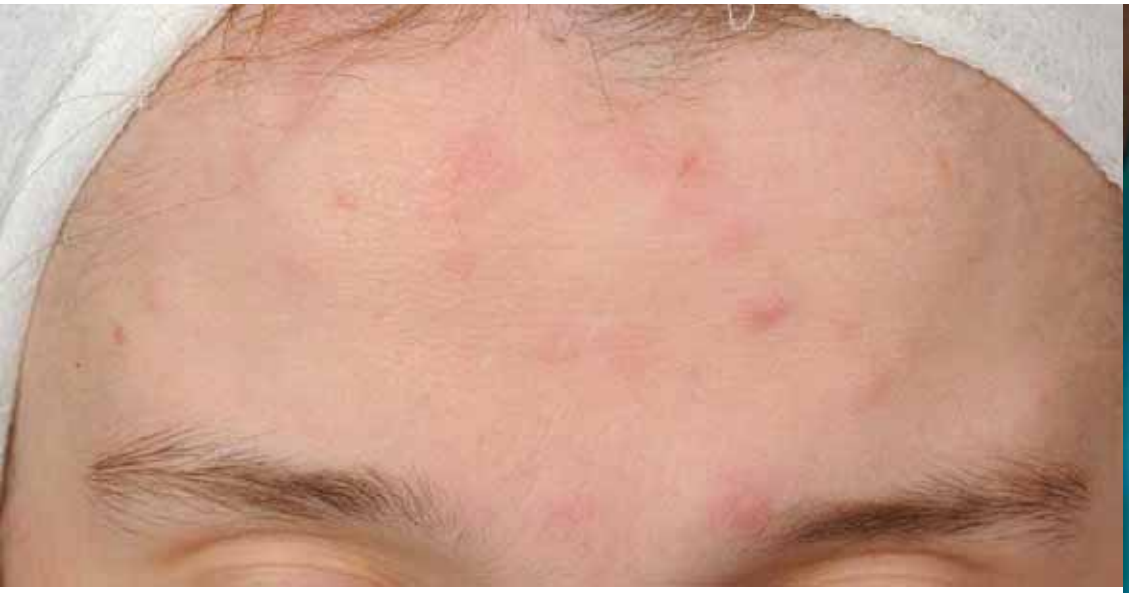
In immunocompromised patients; caused by trichodysplasia spinulosa polyomavirus (TSPyV) / human polyomavirus 8

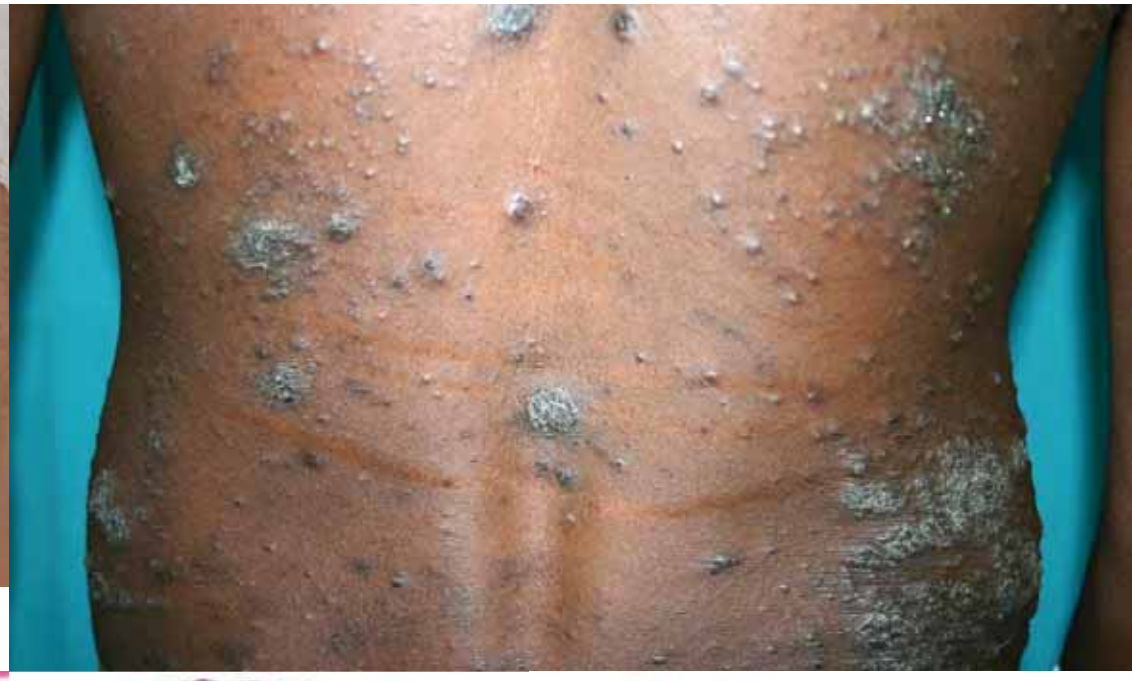
F, 36
HIV infection (CD4+ cell count: 132)

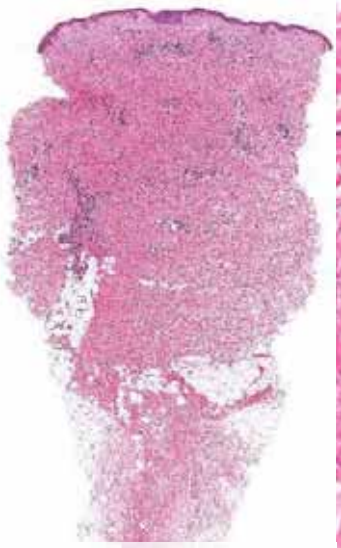


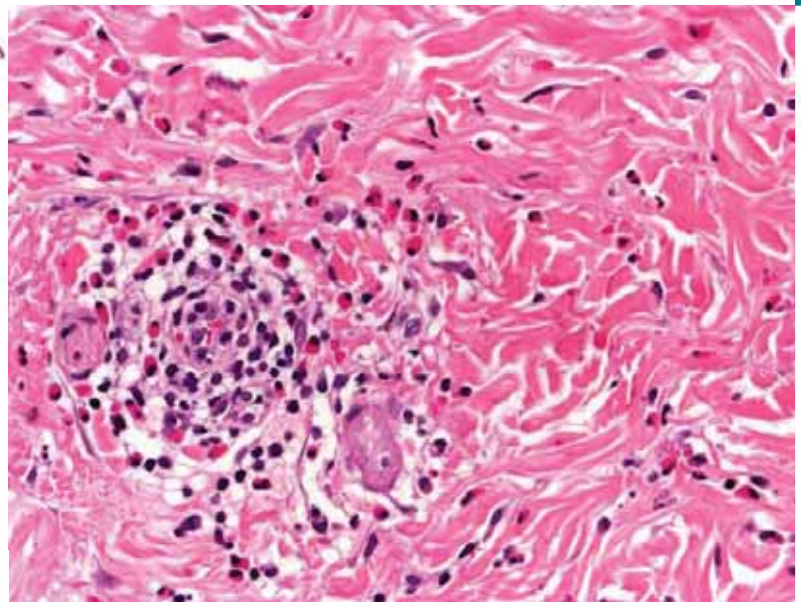


HIV-associated eosinophilic folliculitis

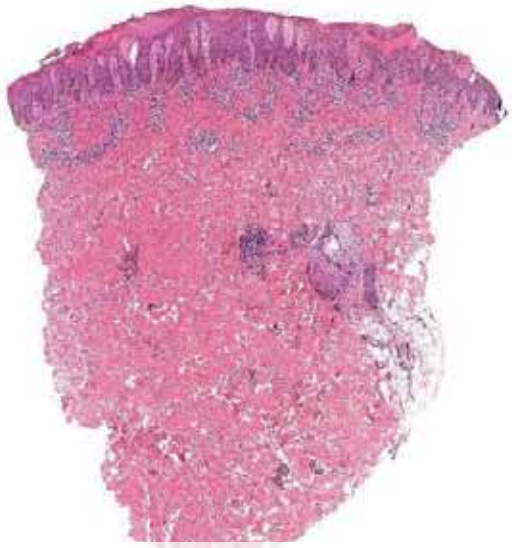


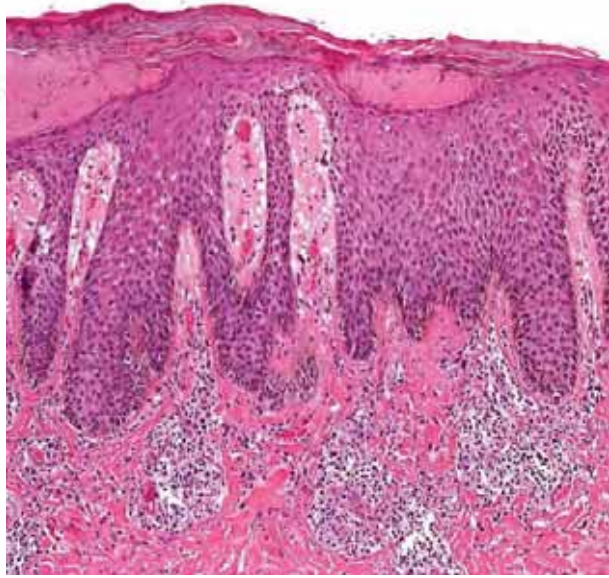




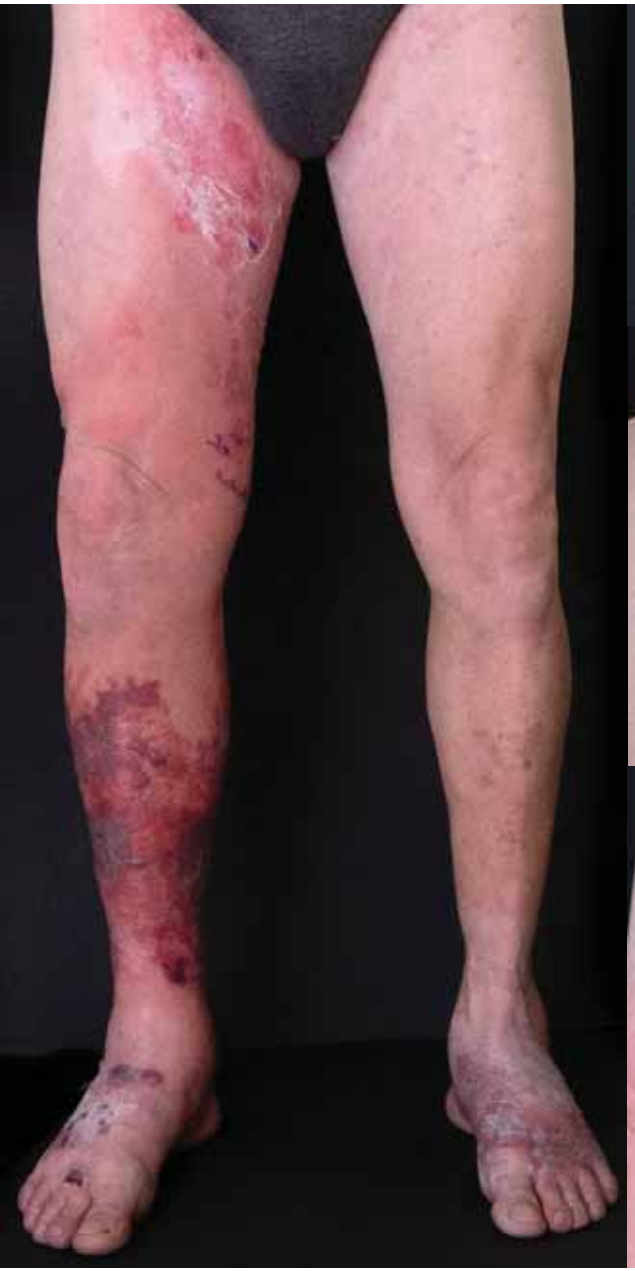


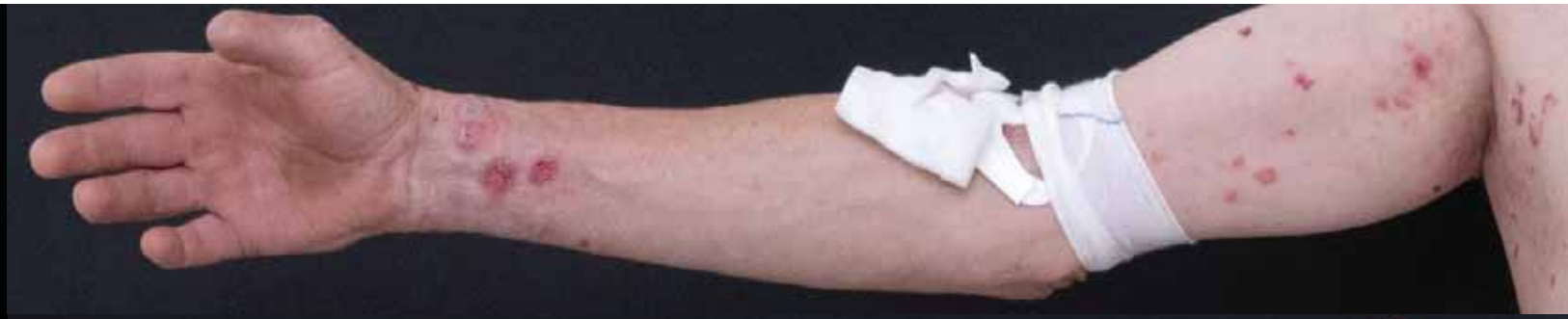
Papular dermatitis of AIDS

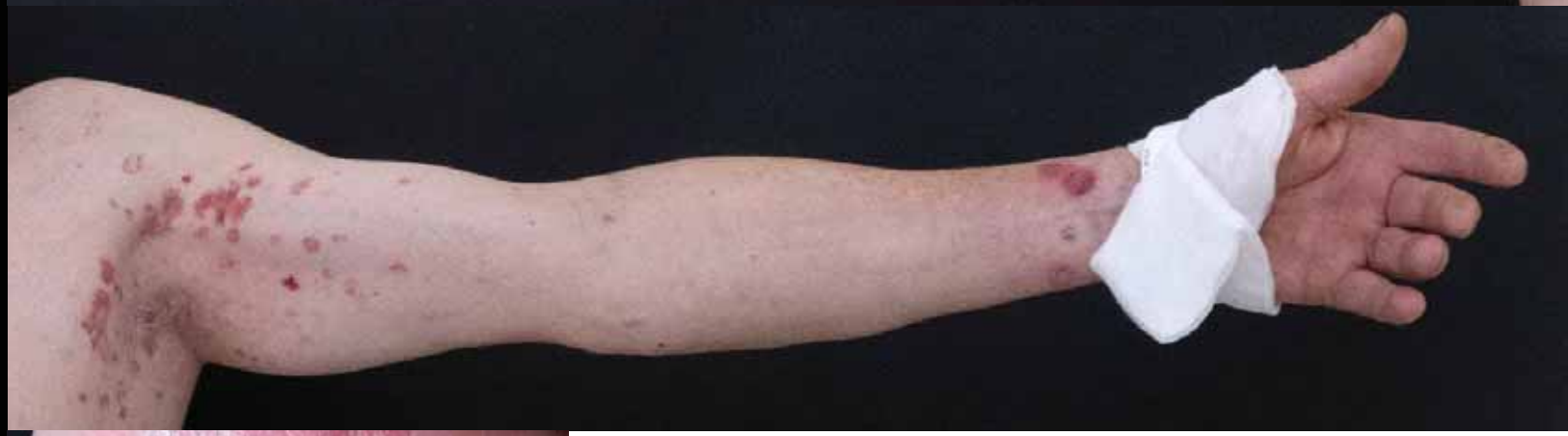


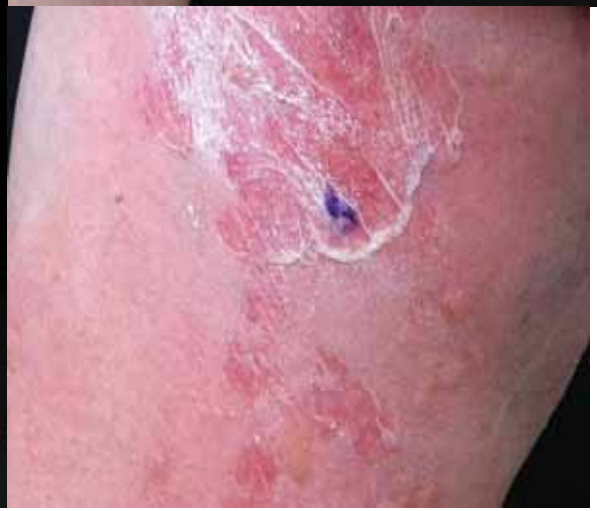


Psoriasiform dermatitis of AIDS







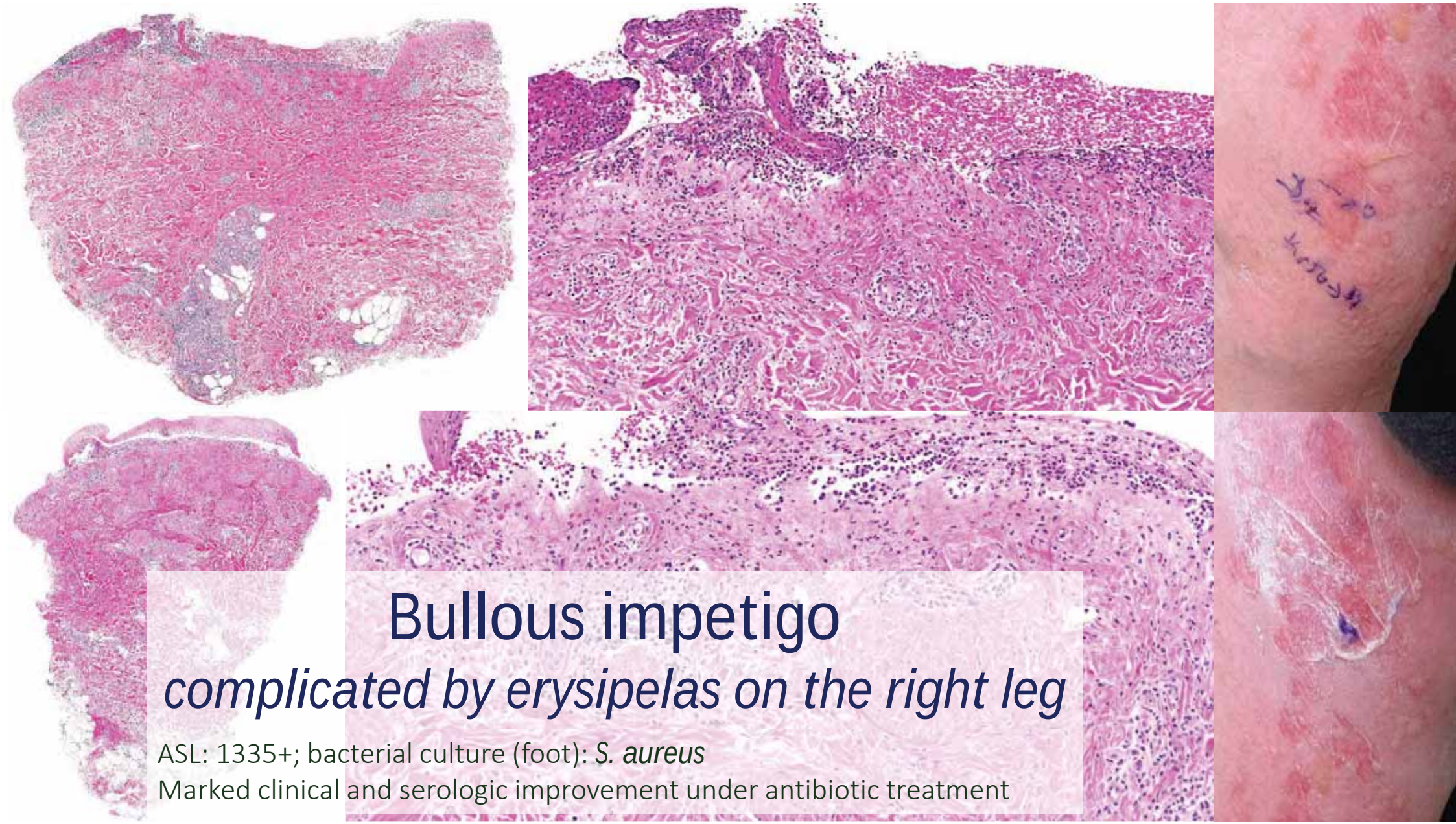


M, 53

Skin lesions progressively enlarging for the last 6 days, starting on both feet. One day fever (39,7°), subsequentely normal body temperature. Managed by the GP with prednisone 100mg/d for 3 days.

Leucocytes 22.39++; CRP 271,9++

Admitted as in-patient; two biopsies are taken.

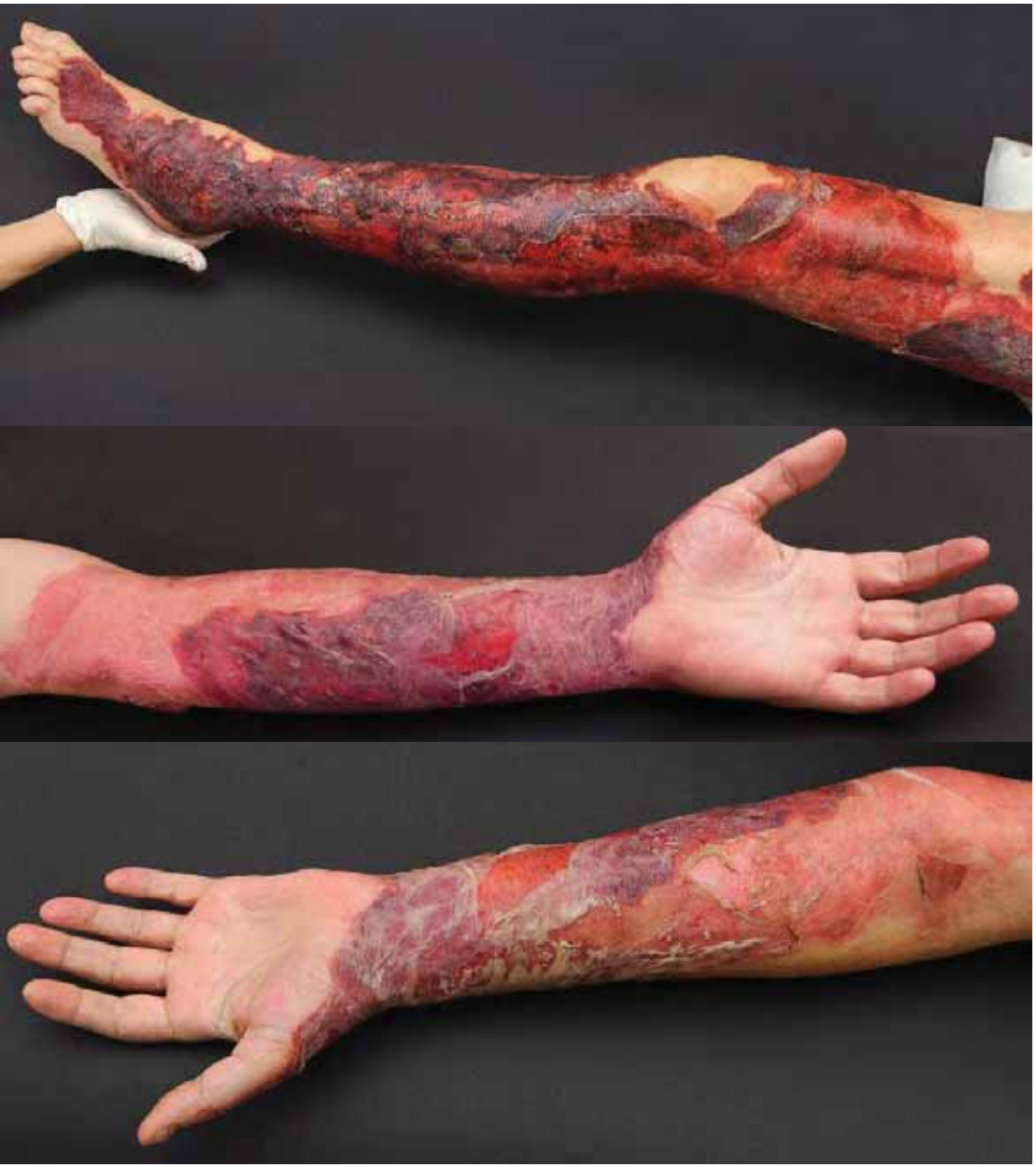


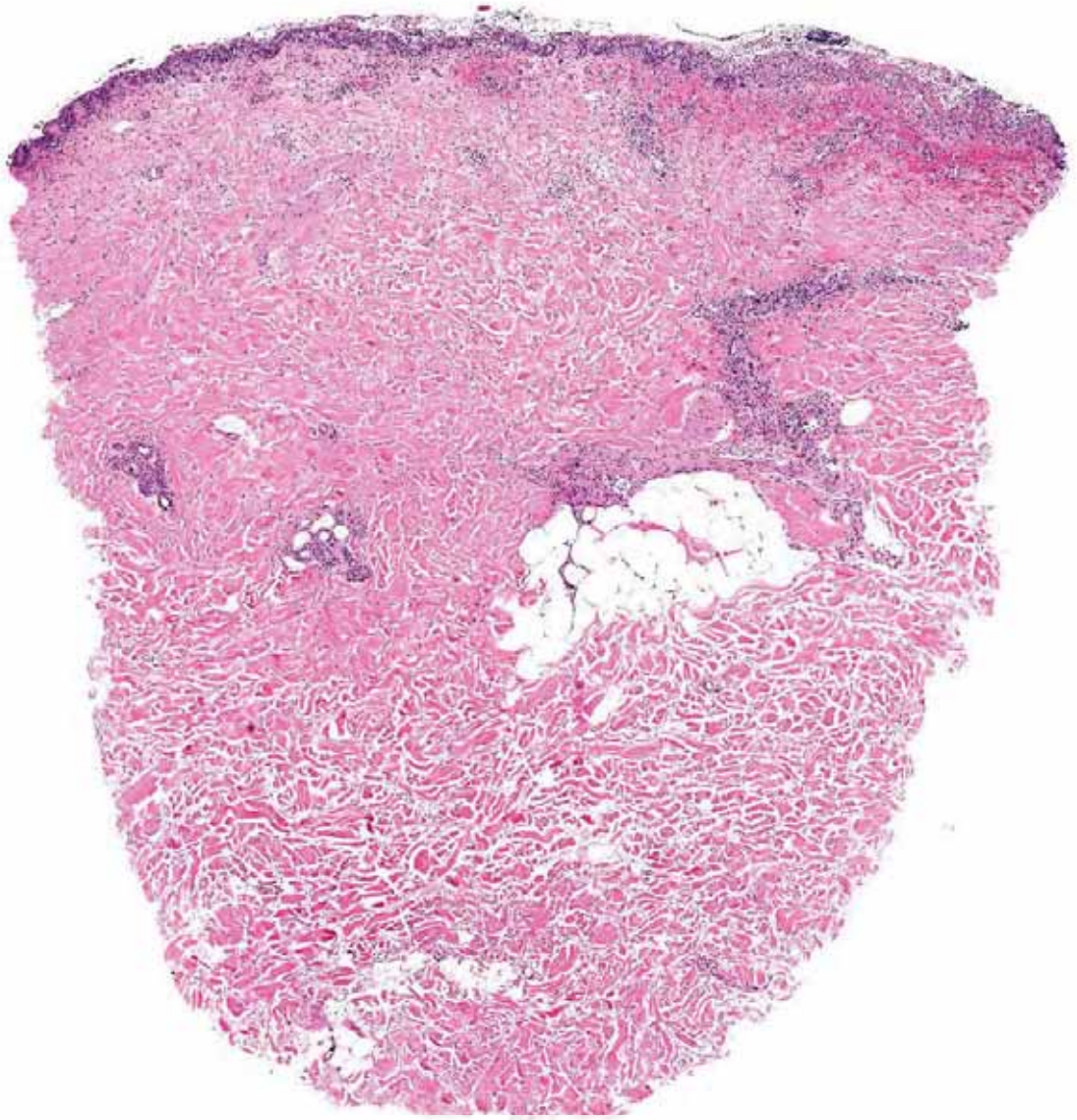
Bullous impetigo

complicated by erysipelas on the right leg

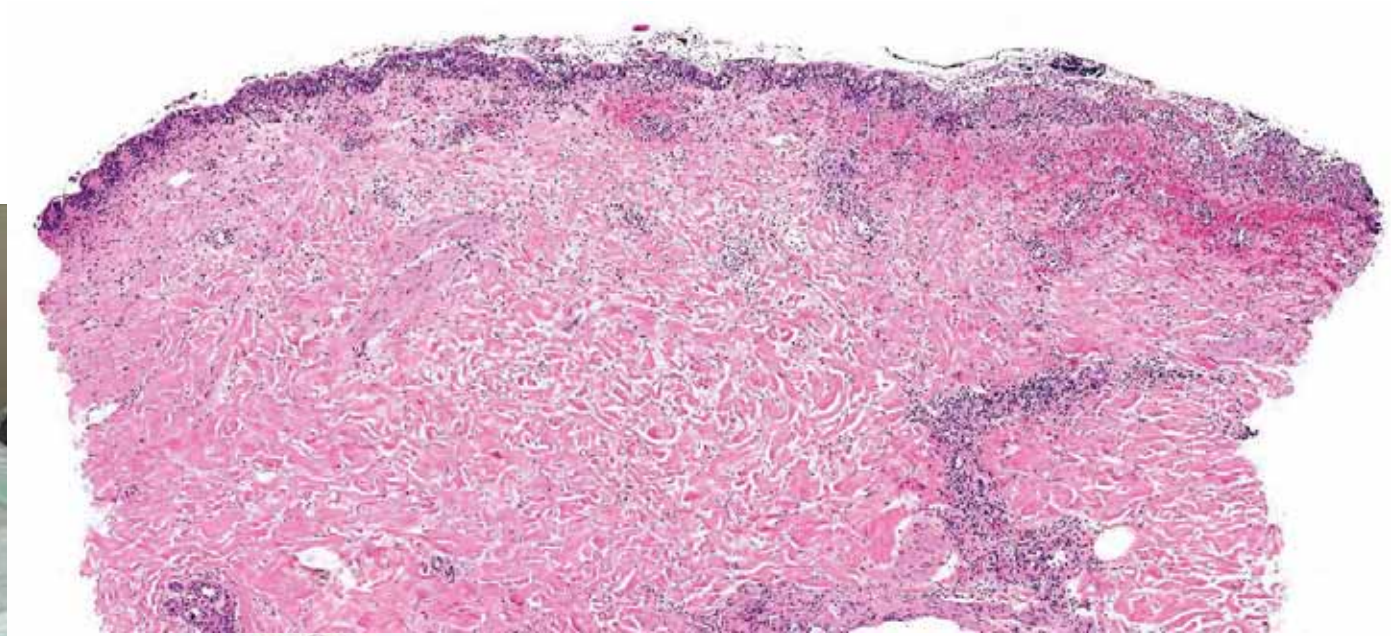
ASL: 1335+; bacterial culture (foot): *S. aureus*

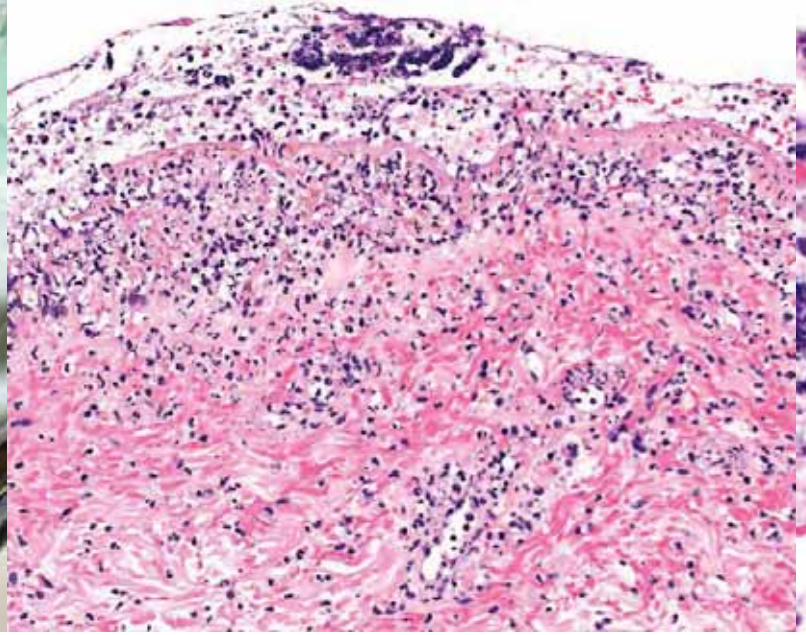
Marked clinical and serologic improvement under antibiotic treatment

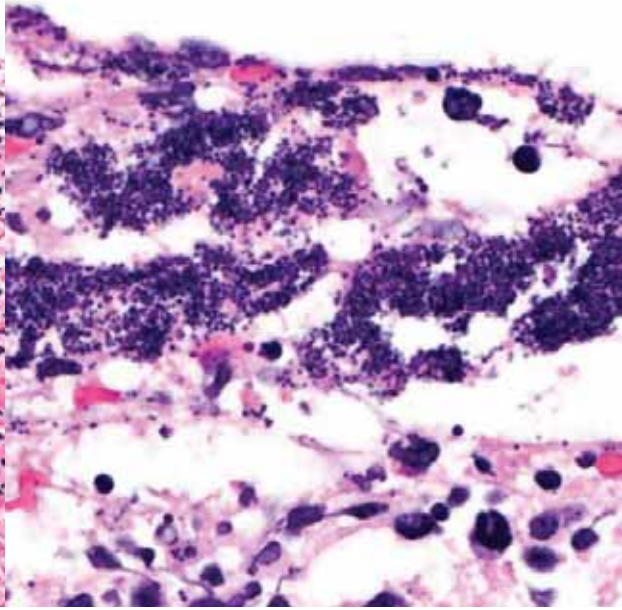


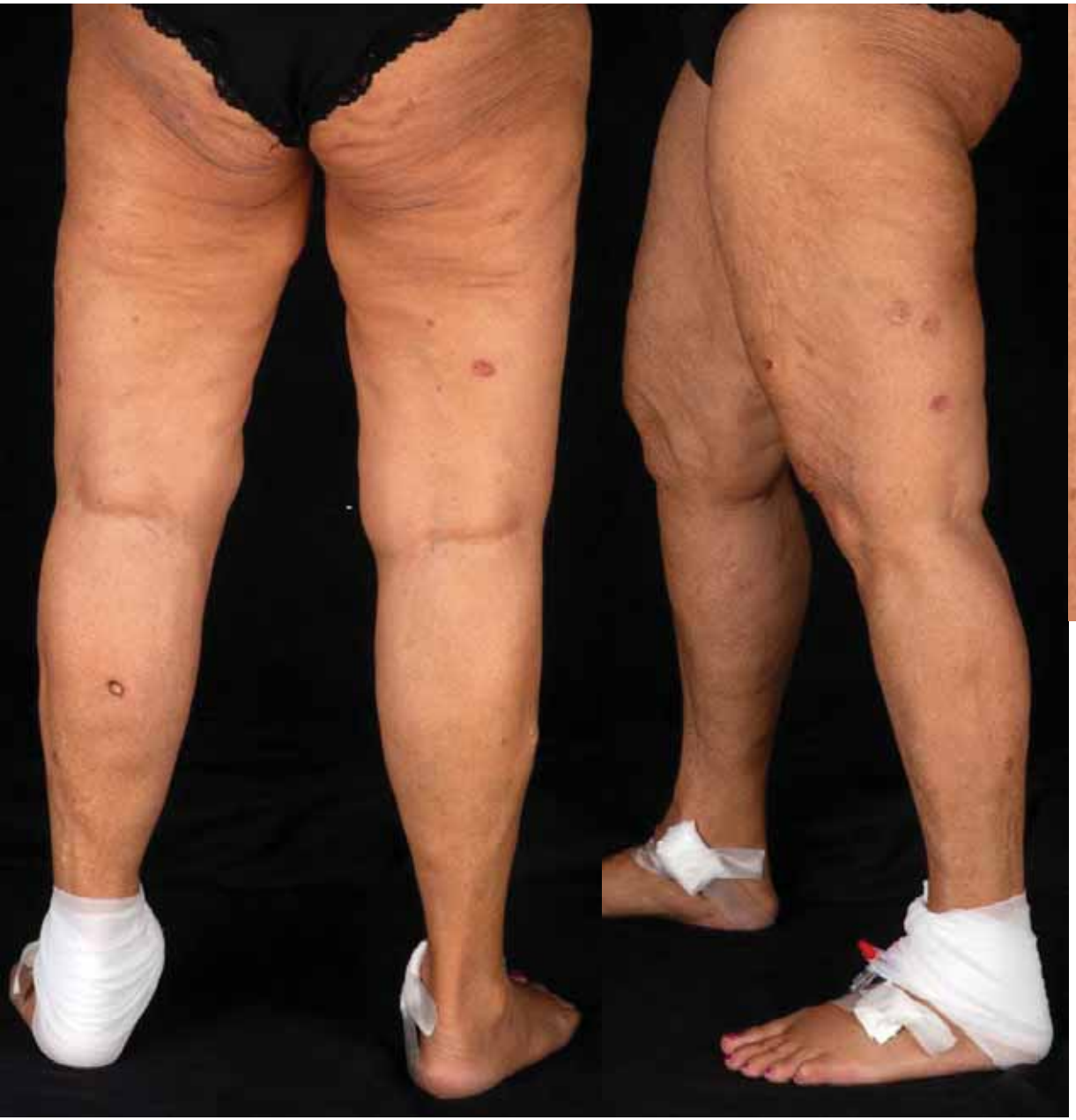


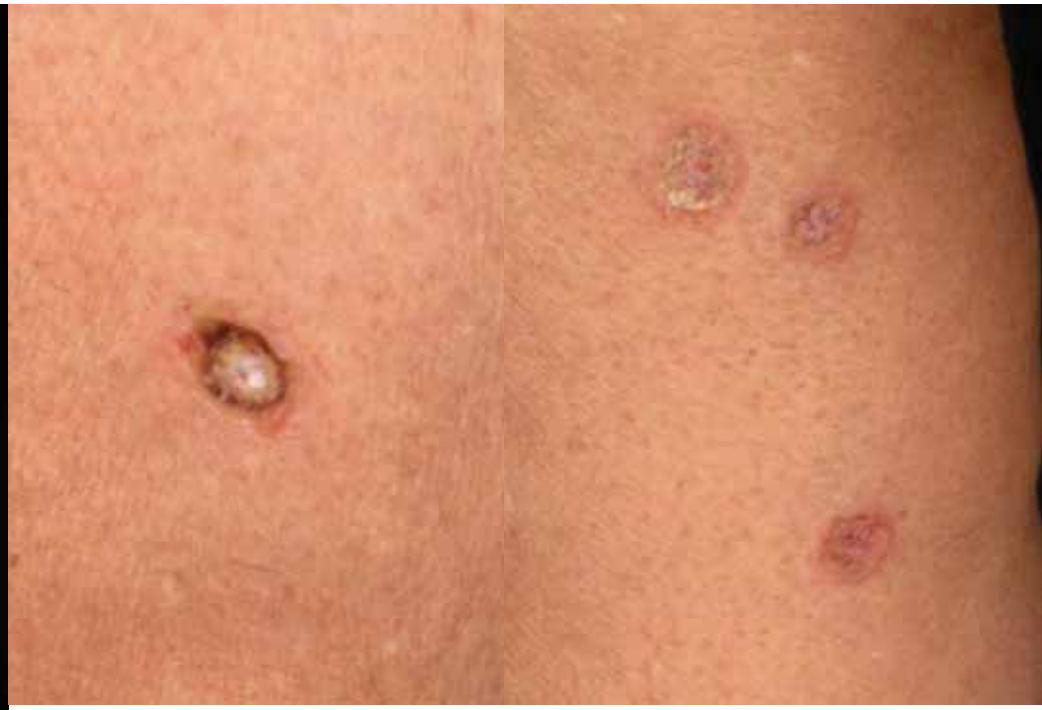
Widespread bullous impetigo









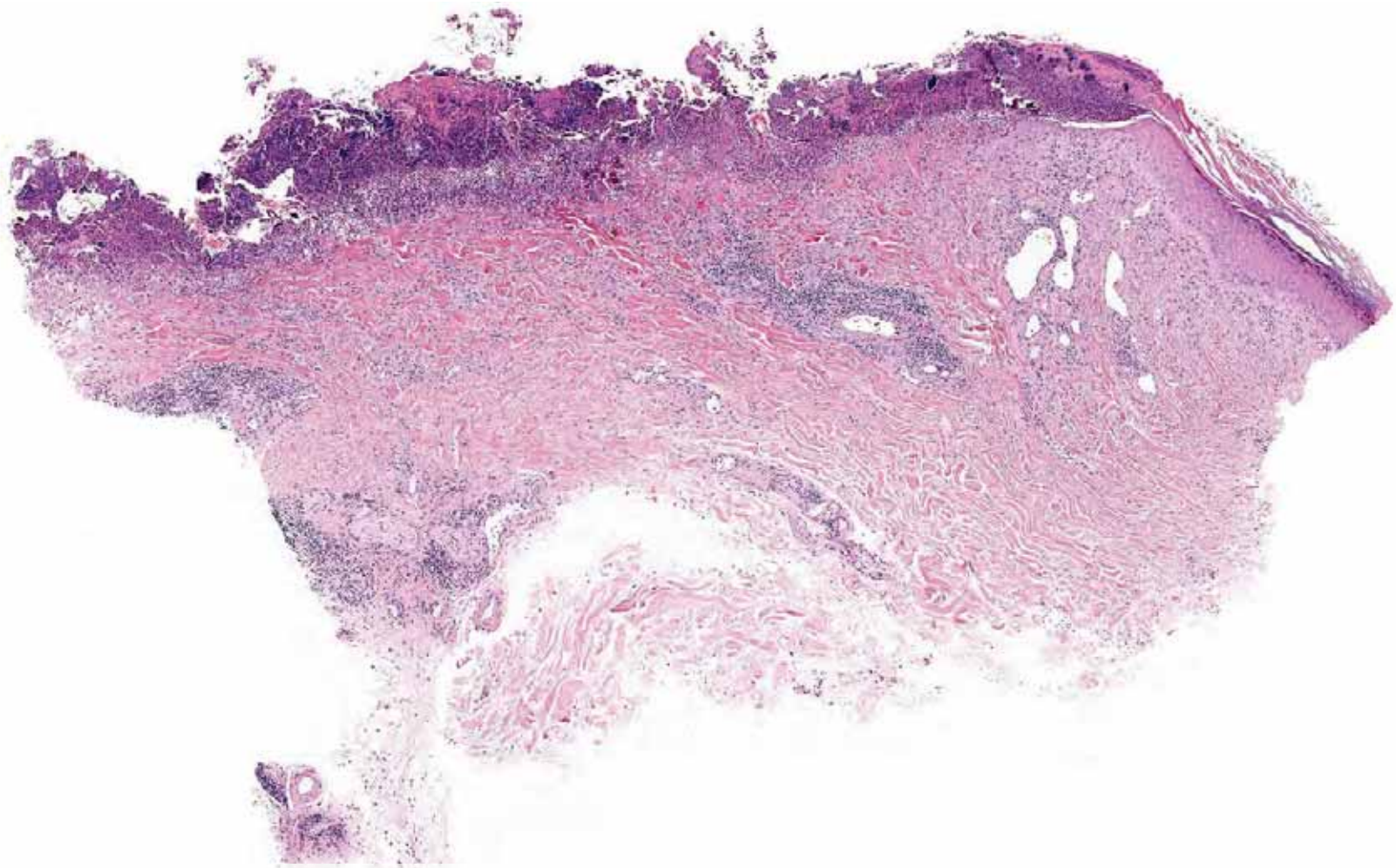


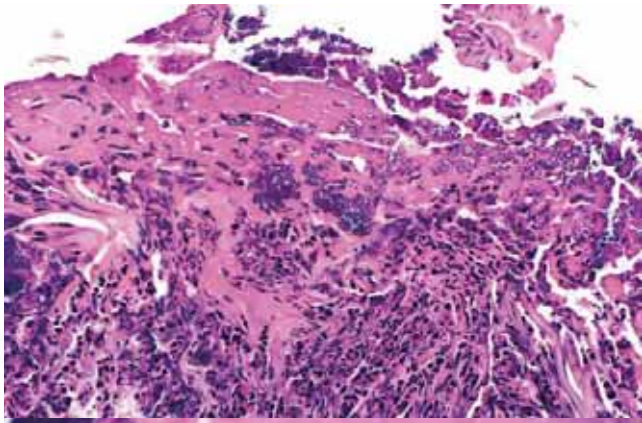
F, 69

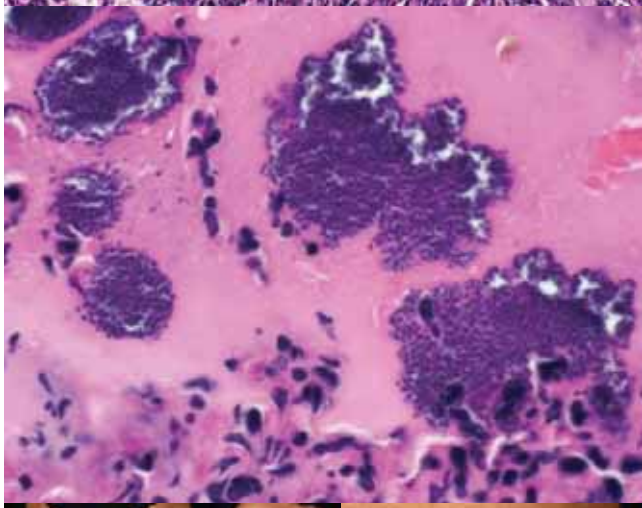
In-patient at another hospital for renal transplant rejection, managed during the last 1 ½ weeks with systemic steroids.

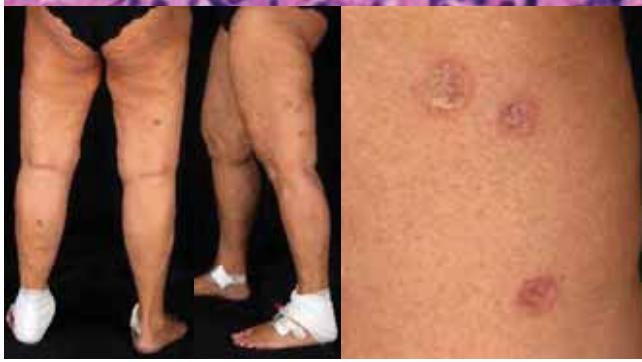
Onset of ulcerated lesions on the lower extremities soon after starting treatment.

A biopsy is taken.





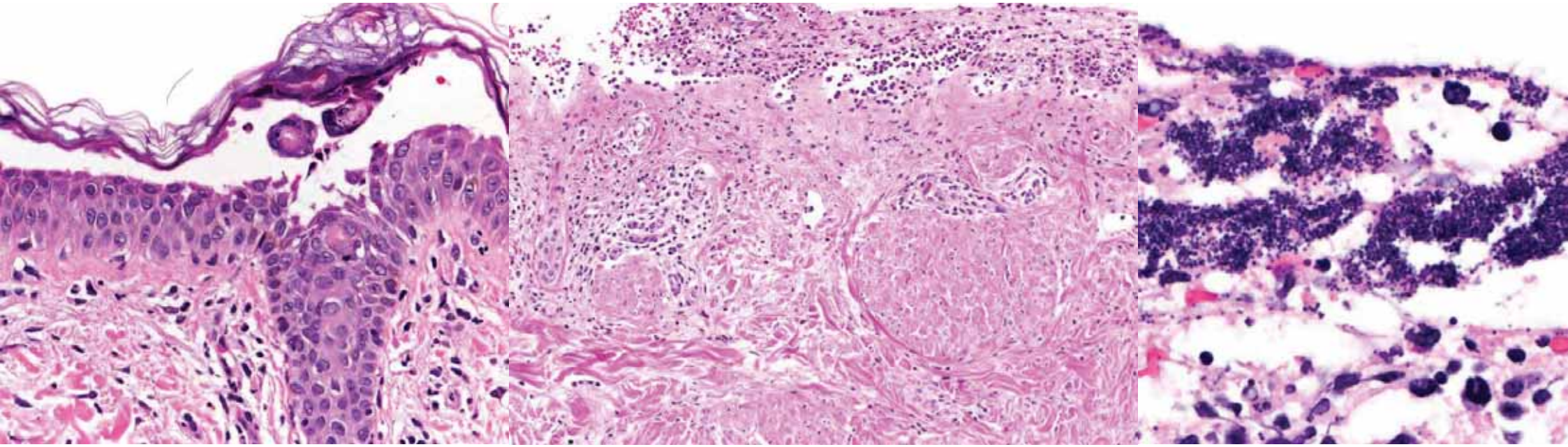




Overlap impetigo / ecthyma

Bacterial culture: S. aureus

Impetigo, overlap impetigo/ecthyma, and ecthyma – one disease



Impetigo, bullous impetigo & ecthyma

Variable clinical presentation; widespread bullous impetigo may be misinterpreted as TEN.

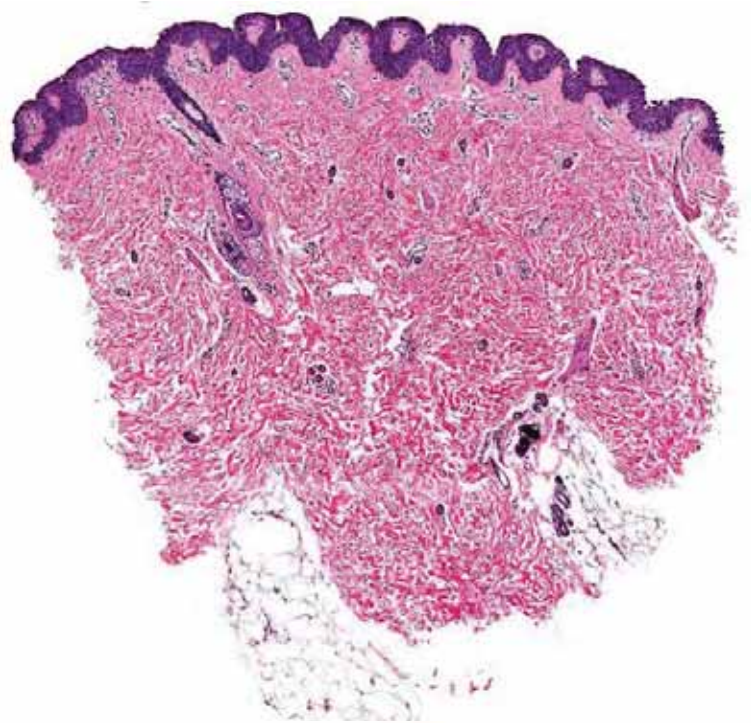
Neutrophil-induced acantholysis visible only (and not always) in intact blisters.

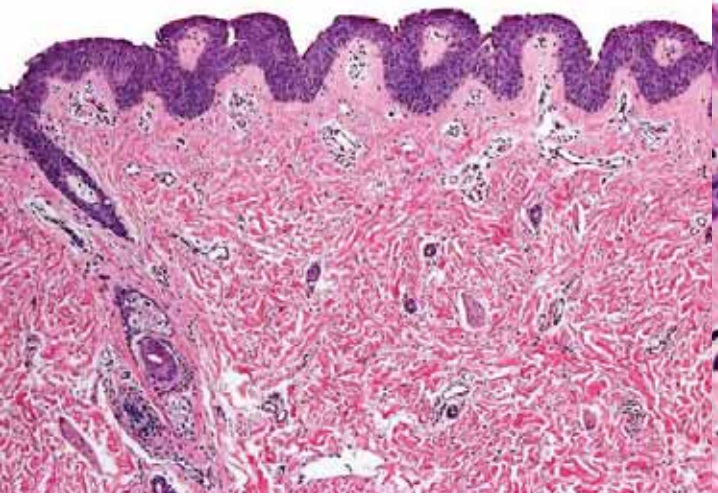
Number of bacteria on H&E highly variable (from none evident to masses).

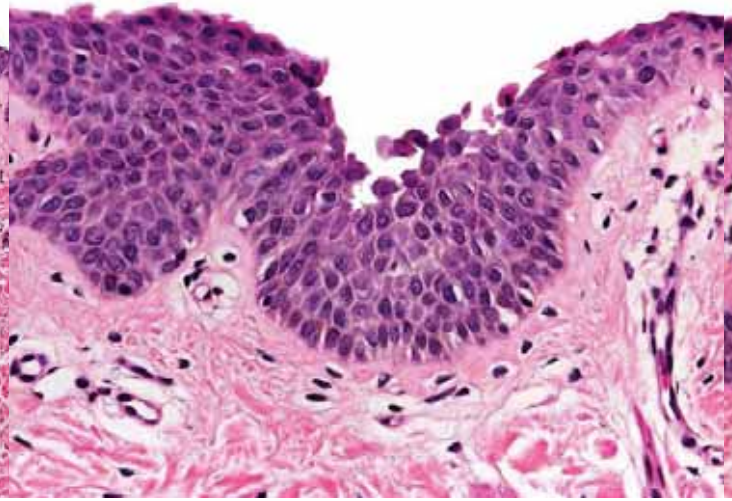
Ecthyma represents a necrotic variant of impetigo.

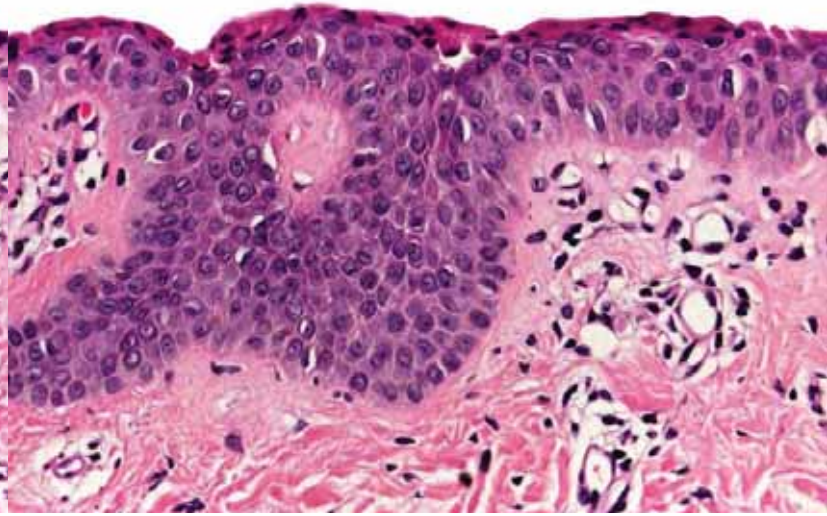
Staphylococcal scalded-skin syndrome

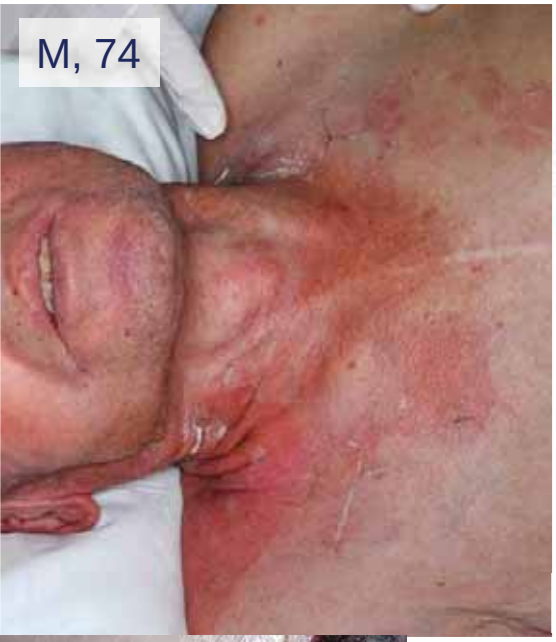
- Due to *S. aureus* phage group II producing exfoliative toxins (A and B) targeting desmoglein 1
- In infections of mucosae or surgical wounds toxins enter the circulation (toxemia), resulting in SSSS; in superficial skin infections local production of toxins results in bullous impetigo
- SSSS rare in adults; usually immunosuppressed patients and/or patients with renal insufficiency; staphylococcal septicemia may occur in adults and may be fatal (risk of death for SSSS: <5% in children, >60% in adults)
- Histology of SSSS; subcorneal blister without inflammatory cells; few acantholytic cells, sparse or absent dermal inflammatory infiltrate; negative immunfluorescence
- In adult patients with septicemia concomitant features of septic vasculitis

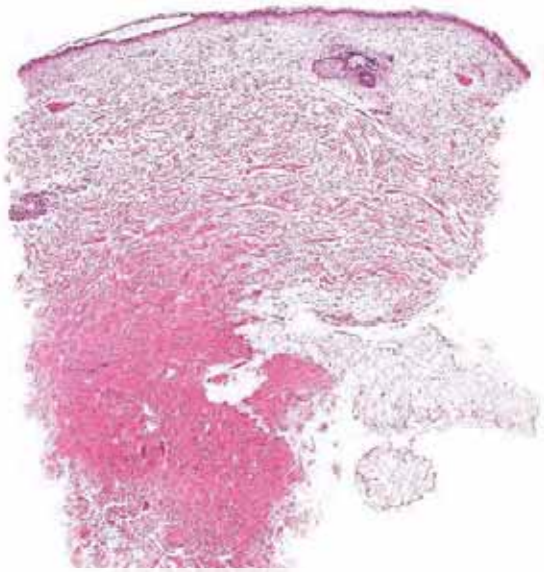




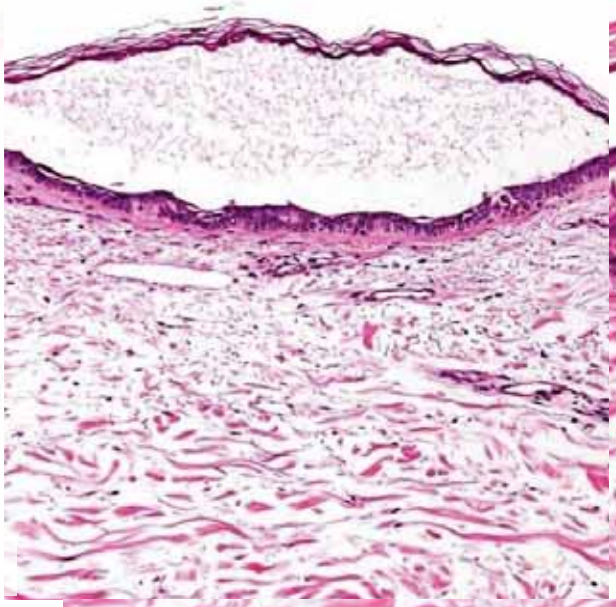


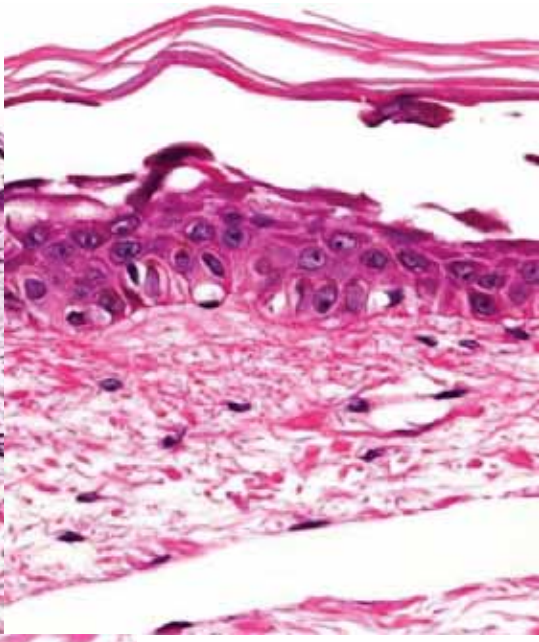


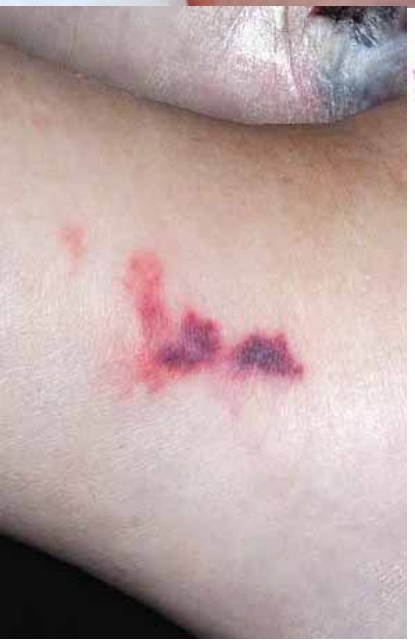


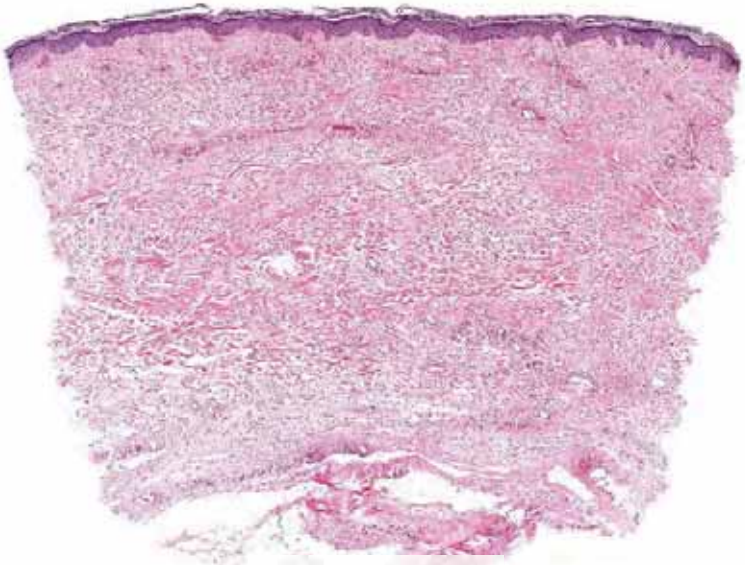


Staphilococcal scalded skin syndrome

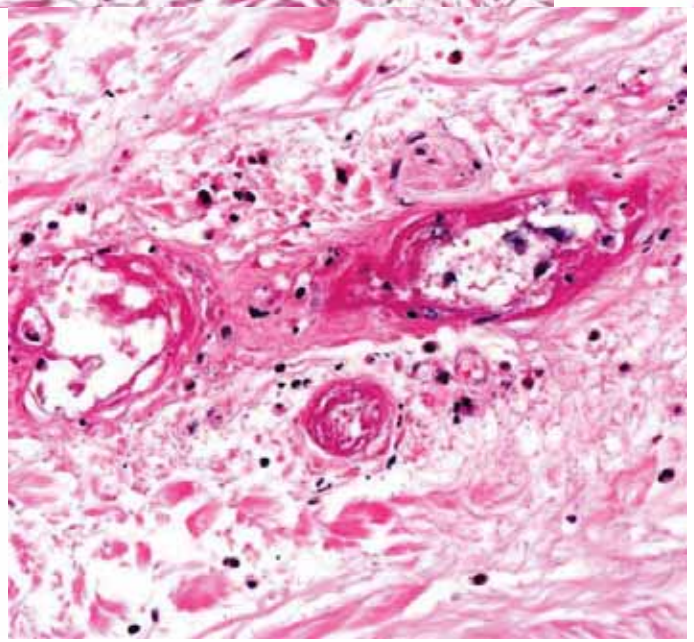








Septic vasculitis



Blood culture: ***Staphylococcus aureus.***

Transferred to the intensive care unit; surgical revision, wound care, systemic support.

Died three days after presentation.

REVIEW ARTICLE

MECHANISMS OF DISEASE

Pemphigus, Bullous Impetigo, and the Staphylococcal Scalded-Skin Syndrome

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PEMPHIGUS, WHICH IS CAUSED BY AUTOANTIBODIES, AND BULLOUS IMPETIGO (including its generalized form, the staphylococcal scalded-skin syndrome), which is caused by *Staphylococcus aureus*, are seemingly unrelated diseases. However, 200 years ago, astute clinicians realized that these diseases had enough clinical similarities to call bullous impetigo and the scalded-skin syndrome in infants "pemphigus neonatorum."[1,2] In this review we explain how a common mechanism accounts for the clinical overlap of these blistering diseases of the skin, and how the unraveling of the molecular pathophysiology of pemphigus provided the clues that were necessary to determine the mechanism of the formation of blisters in bullous impetigo and the staphylococcal scalded-skin syndrome. We also discuss how this new understanding of the pathophysiology of pemphigus could improve the diagnosis and treatment of this potentially life-threatening disease.

PEMPHIGUS

There are two major types of pemphigus, pemphigus vulgaris and pemphigus foliaceus.[3] Patients with pemphigus vulgaris present with blisters and erosions of mucous membranes and skin. There are two subtypes of pemphigus vulgaris: the mucosal-dominant type, with mucosal lesions but minimal skin involvement, and the mucocutaneous type, with extensive skin blisters and erosions in addition to mucosal involvement (Fig. 1A). Patients with pemphigus foliaceus have scaly and crusted superficial erosions of the skin but not of mucous membranes (Fig. 1B).

The blisters of pemphigus vulgaris are characterized by a loss of cell adhesion in the deep epidermis, just above the basal layer (Fig. 1C), whereas in pemphigus foliaceus, the loss of cell adhesion is in the more superficial epidermis, just below the stratum corneum, which is the layer of dead keratinocytes that forms the barrier of the skin (Fig. 1D).

The blood of patients with pemphigus contains IgG antibodies that bind to the surface of normal keratinocytes; this binding is shown with the use of immunofluorescence (Fig. 1E and 1F). Immunofluorescence staining also shows IgG antibodies on the surface of the keratinocytes in biopsy specimens of the skin from patients with pemphigus.

These antibodies, which are autoantibodies because they react with the patient's own cells, are directly pathogenic — that is, they can cause loss of adhesion between keratinocytes, which results in blistering. When injected into neonatal mice, human IgG from patients with pemphigus vulgaris or pemphigus foliaceus binds to the surface of the epidermal keratinocytes (Fig. 1I) and causes blisters (Fig. 1G) with the typical histologic features of pemphigus vulgaris (Fig. 1H) or pemphigus foliaceus (Fig. 2D).[4,5]

Therefore, pemphigus vulgaris and pemphigus foliaceus are related in that they

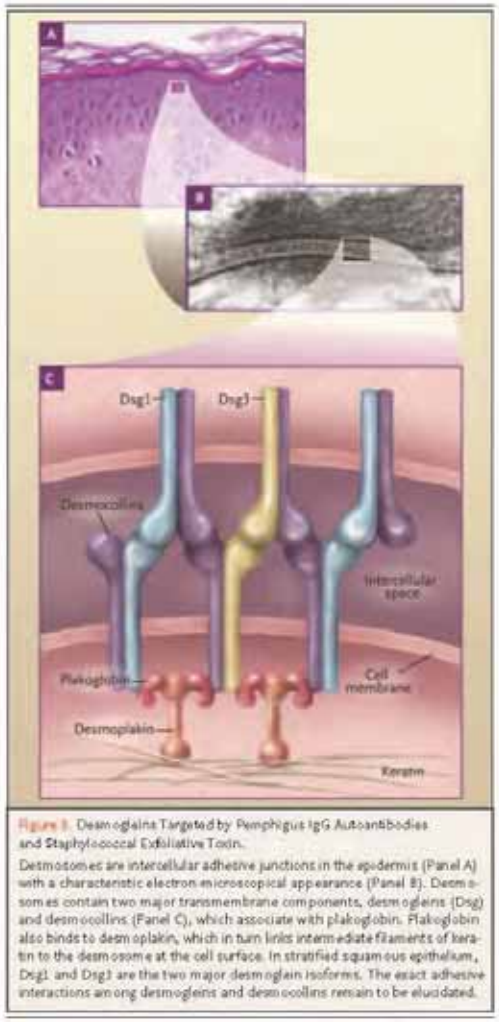


Figure 3. Desmoglein Targeted by Pemphigus IgG Autoantibodies and Staphylococcal Exfoliative Toxin.

Desmosomes are intercellular adhesive junctions in the epidermis (Panel A) with a characteristic electron-microscopical appearance (Panel B). Desmosomes contain two major transmembrane components, desmogleins (Dsg) and desmocollins (Panel C), which associate with plakoglobin. Plakoglobin also binds to desmoplakin, which in turn links intermediate filaments of keratin to the desmosome at the cell surface. In stratified squamous epithelium, Dsg1 and Dsg3 are the two major desmoglein isoforms. The exact adhesive interactions among desmogleins and desmocollins remain to be elucidated.

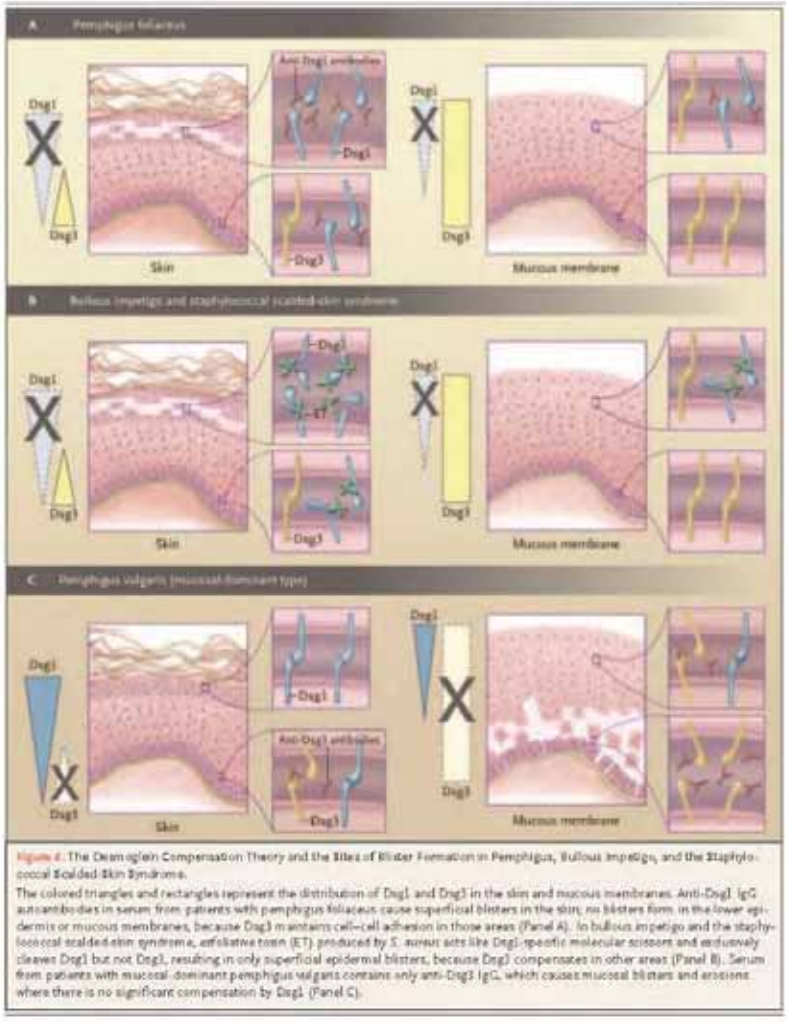
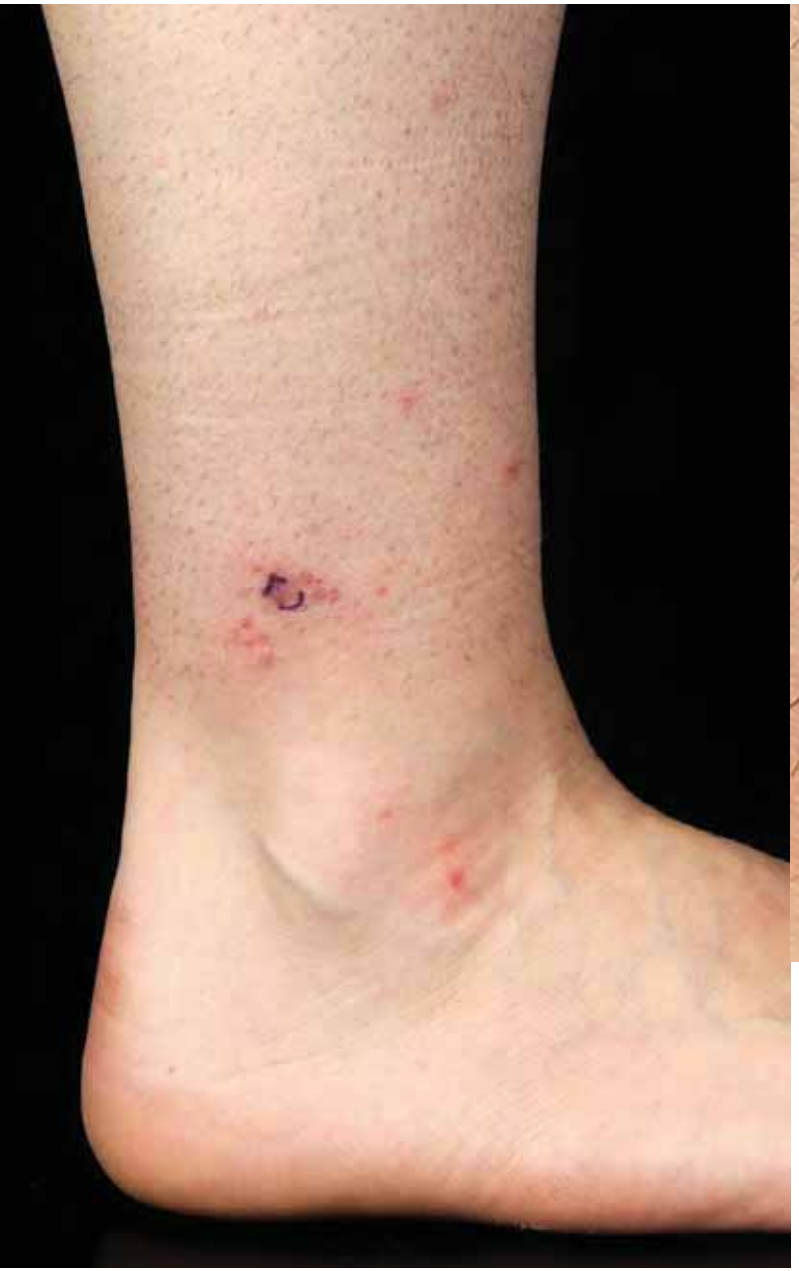
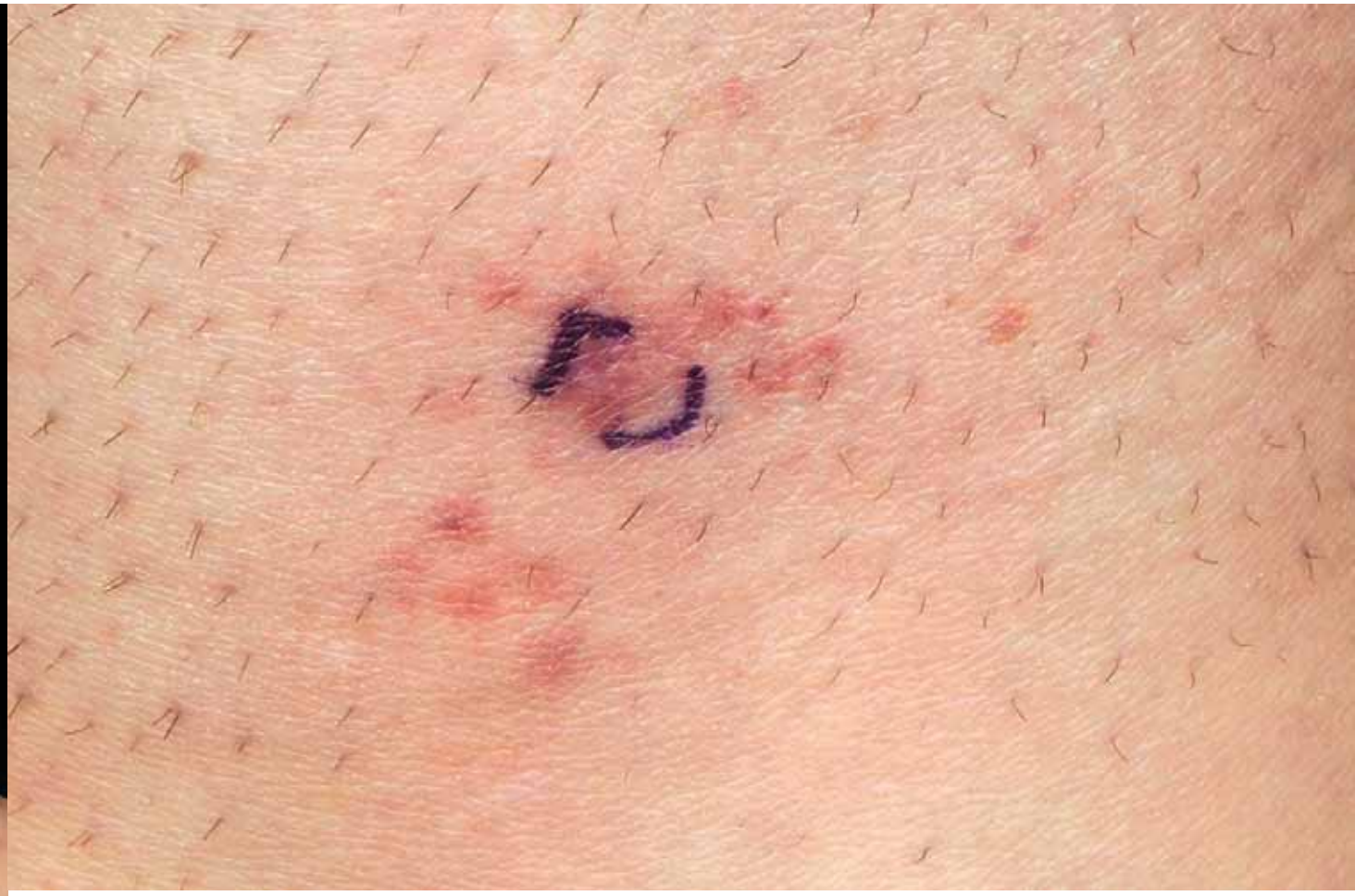


Figure 4. The Desmoglein Compensation Theory and the Sites of Blister Formation in Pemphigus, Bullous Impetigo, and the Staphylococcal Scalded-Skin Syndrome.

The colored triangles and rectangles represent the distribution of Dsg1 and Dsg3 in the skin and mucous membranes. Anti-Dsg1 IgG autoantibodies in serum from patients with pemphigus foliaceus cause superficial blisters in the skin; no blisters form in the lower epidermis or mucous membranes, because Dsg3 maintains cell–cell adhesion in those areas (Panel A). In bullous impetigo and the staphylococcal scalded-skin syndrome, exfoliative toxin (ET) produced by *S. aureus* acts like Dsg1-specific molecular scissors and exclusively cleaves Dsg1 but not Dsg3, resulting in only superficial epidermal blisters, because Dsg3 compensates in other areas (Panel B). Serum from patients with mucosal-dominant pemphigus vulgaris contains only anti-Dsg3 IgG, which causes mucosal blisters and erosions where there is no significant compensation by Dsg1 (Panel C).





F, 26

According to the patient onset of localized skin lesions on the right ankle one day after intake of salicylic acid and mefenamic acid.

A biopsy is taken.

Day 1: The patient presents to the out-patient service. Skin changes on the right ankle one day after intake of salicylic acid and mefenamic acid.

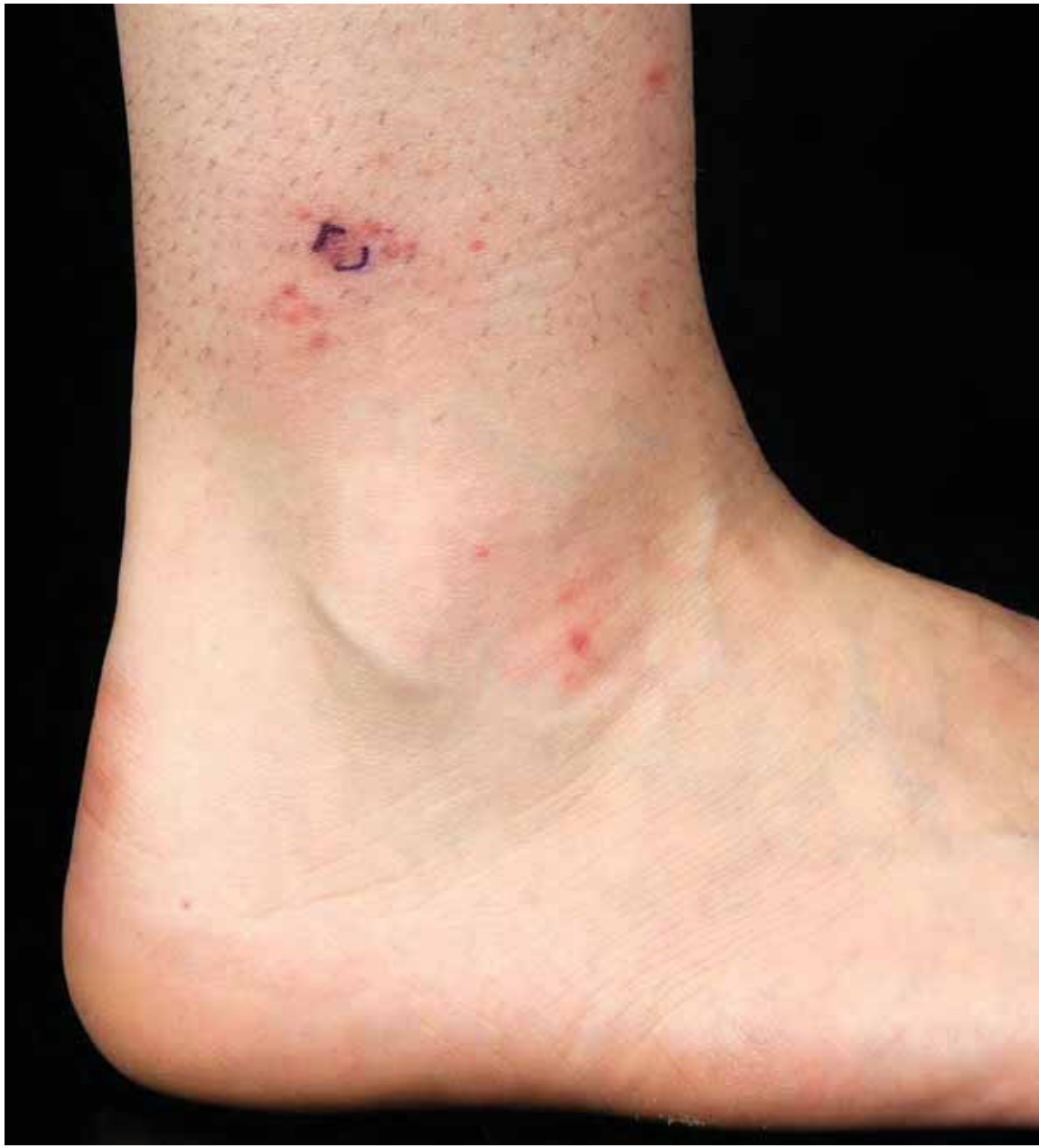
Clinical diagnosis: Drug eruption; ddx: arthropod bite reaction.

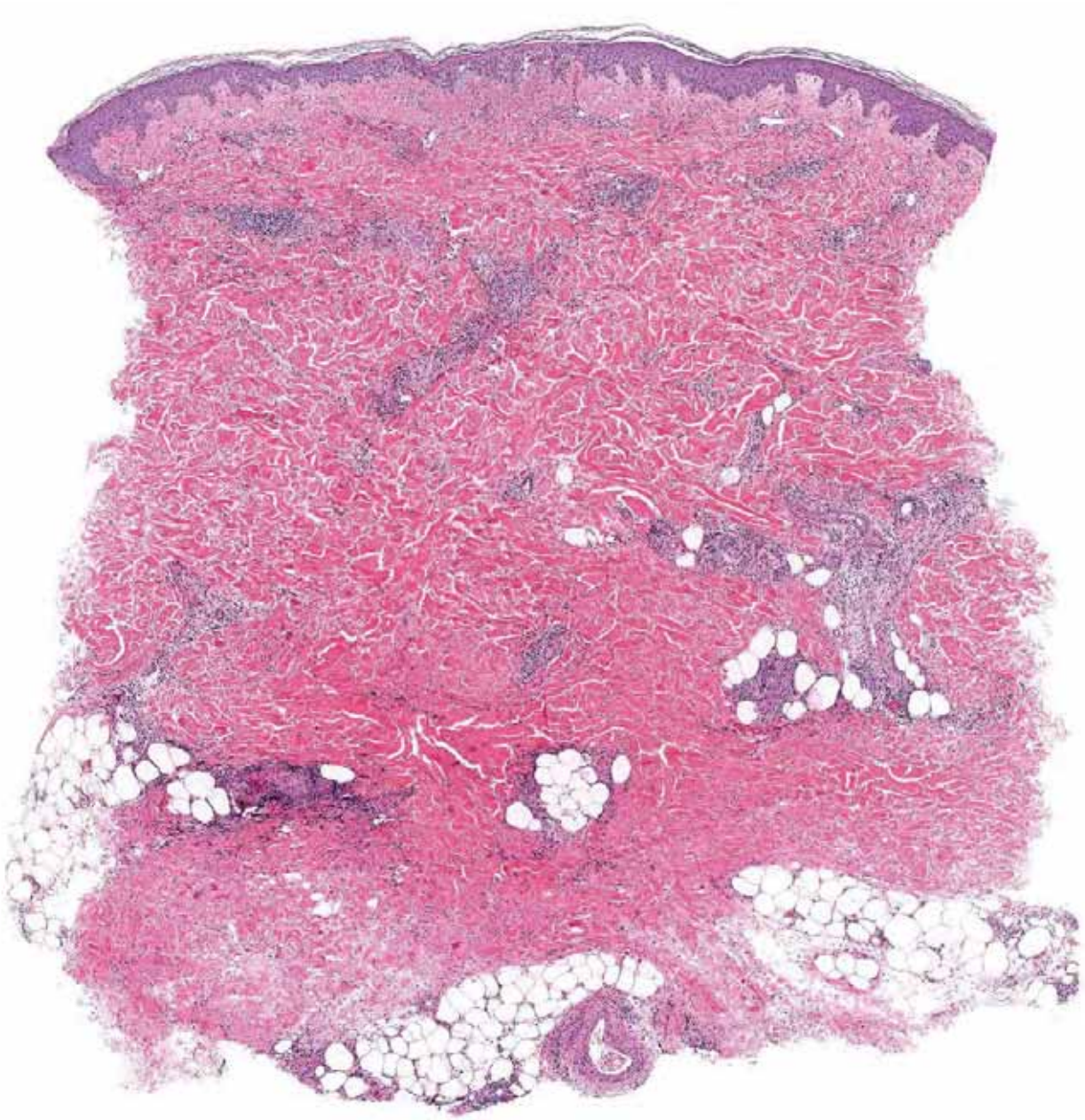
Salicylic acid and mefenamic acid are substituted with paracetamol; treatment with anti-histaminic (loratadin); appointment for allergy tests two months later.

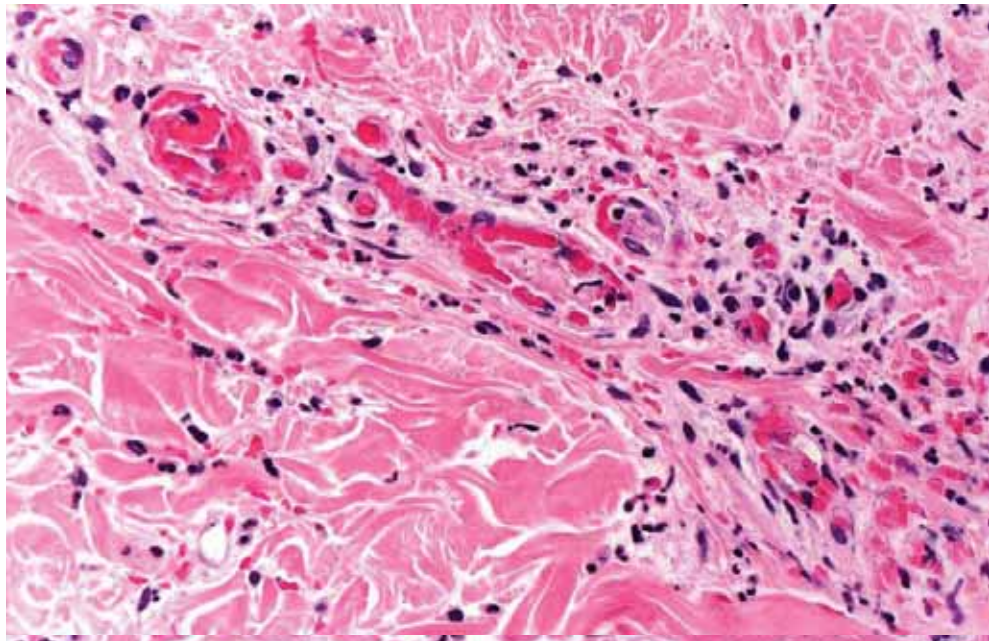
The patient gets an appointment next day for a punch biopsy and a picture (operating room and photographic laboratory already closed).

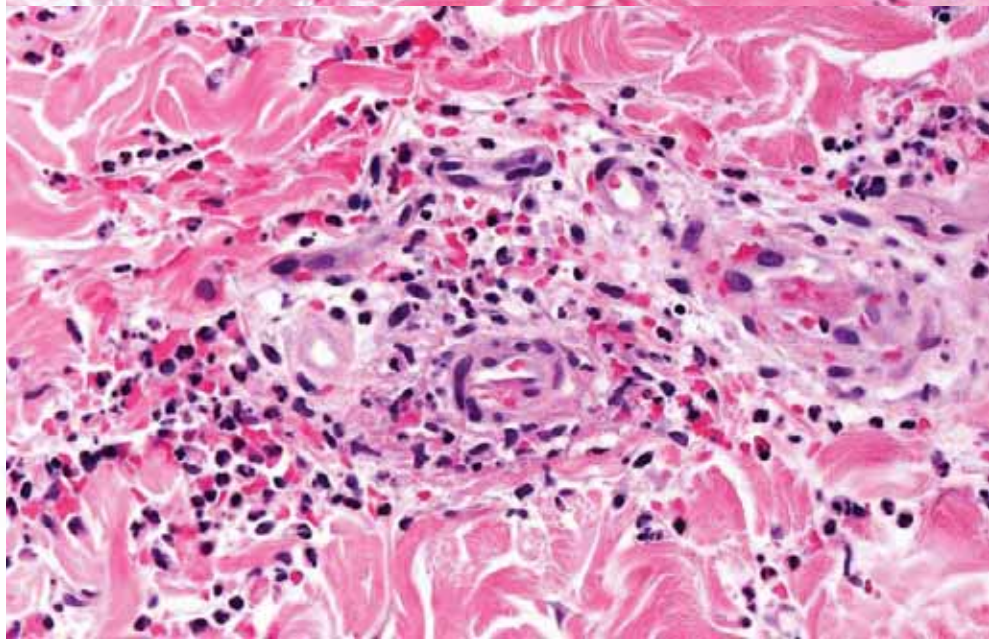
Day 2: Punch biopsy & picture taken.

Histological diagnosis (day 7): consistent with an arthropod bite with intravascular thrombi (venomous bite).

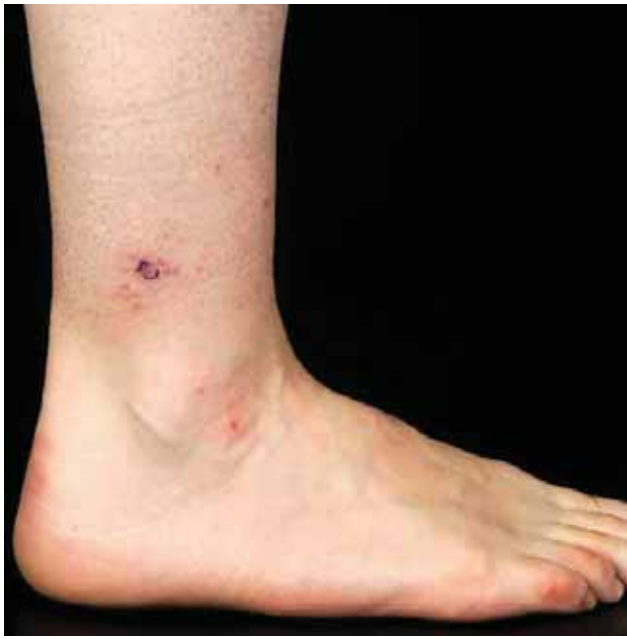




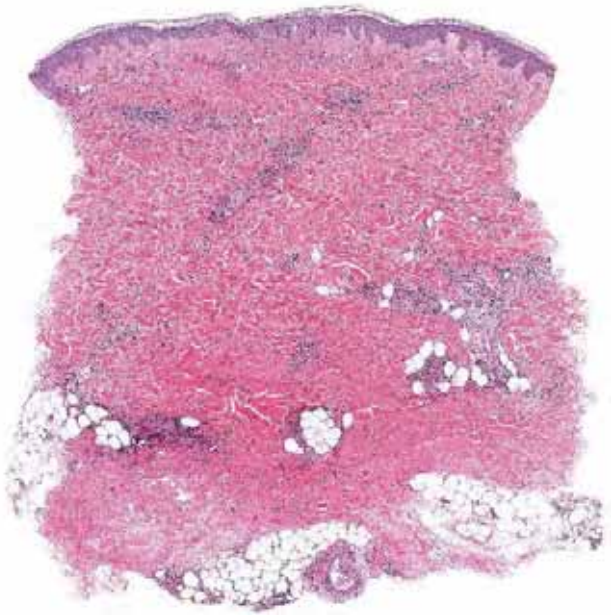




Day 1: The patient presents to the out-patient service. Skin changes on the right ankle one day after intake of salicylic acid and mefenamic acid.
Clinical diagnosis: Drug eruption; ddx: arthropod bite reaction.
Salicylic acid and mefenamic acid are substituted with paracetamol; treatment with anti-histaminic (loratadin); appointment for allergy tests two months later.
The patient gets an appointment next day for a punch biopsy and a picture (operating room and photographic laboratory already closed).
Day 2: Punch biopsy & picture taken.
Histological diagnosis (day 7): consistent with an arthropod bite with intravascular thrombi (venomous bite).



Day 14: The patient presents again to the hospital (general admission) with fever.
Diagnosis: fever of unclear cause (salicylic acid and mefenamic acid had been taken because of fever and headache, now persisting for >3 weeks). The patient says that the skin lesions became worse on paracetamol and there was no improvement with anti-histaminic. Treatment with changed to metamizole, and admission to another hospital (no free beds).



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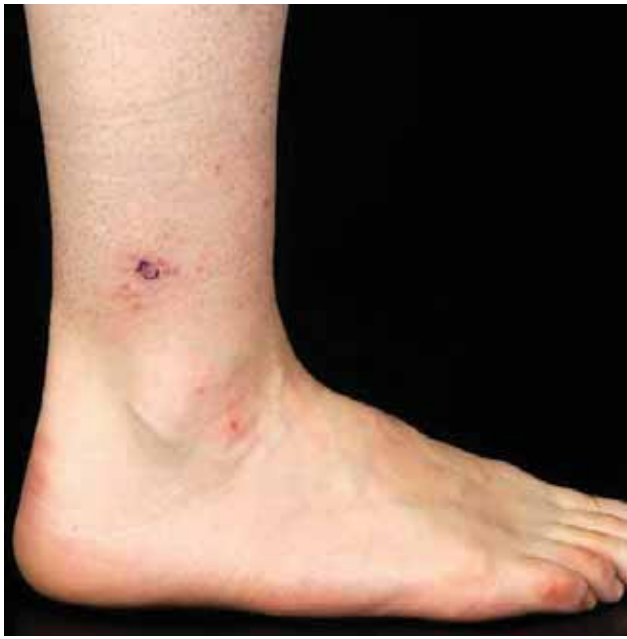

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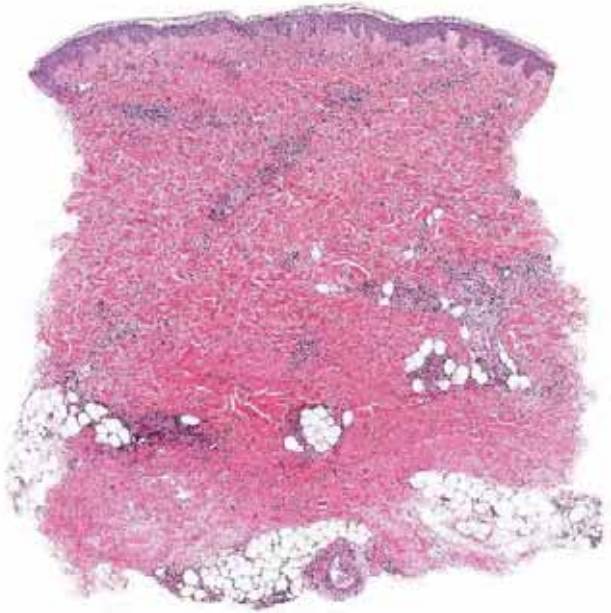
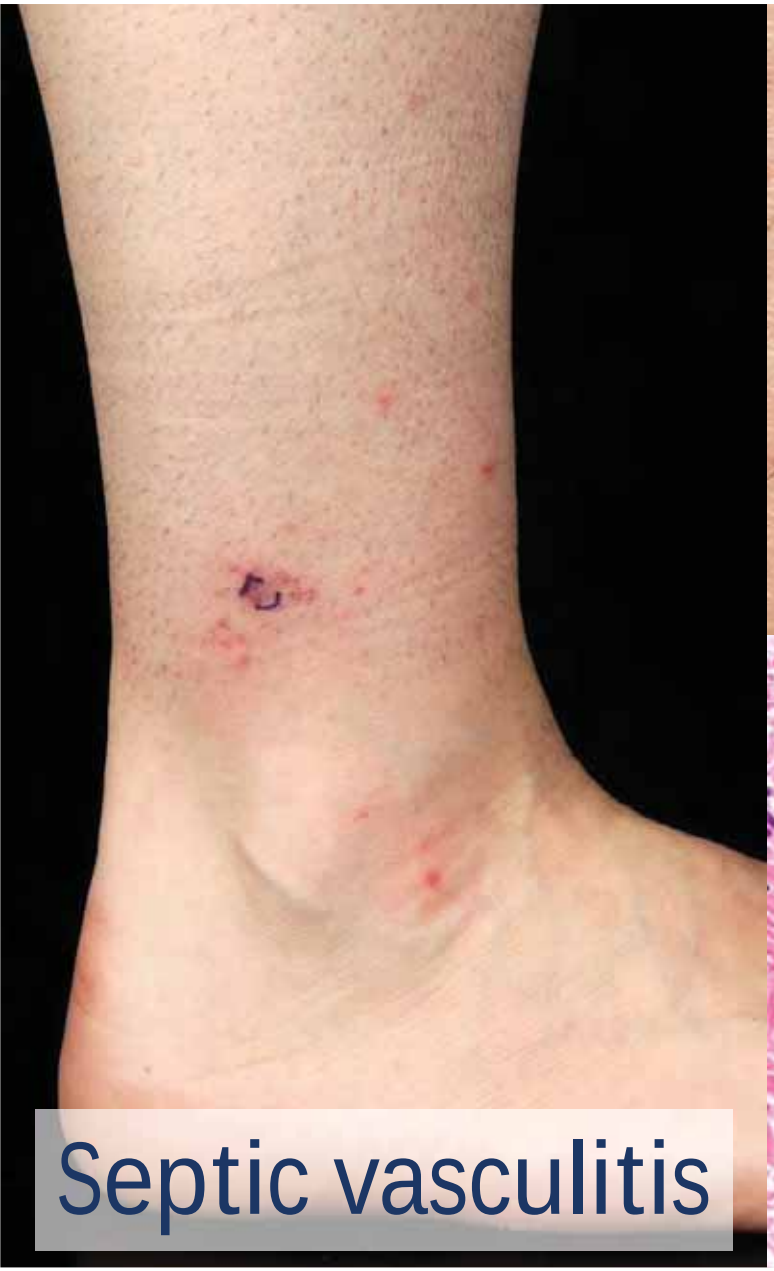
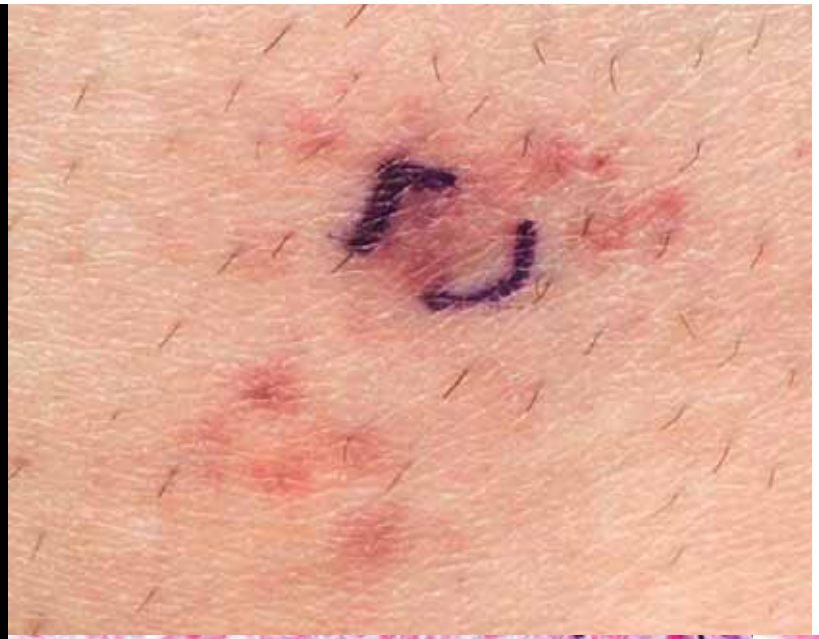
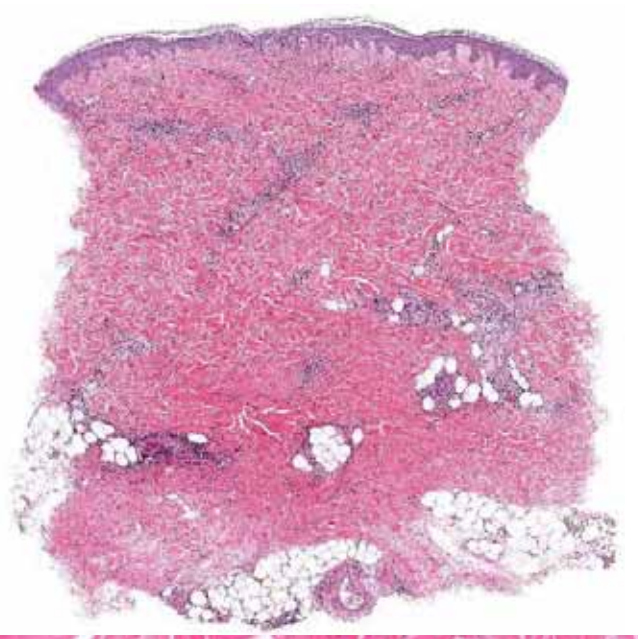
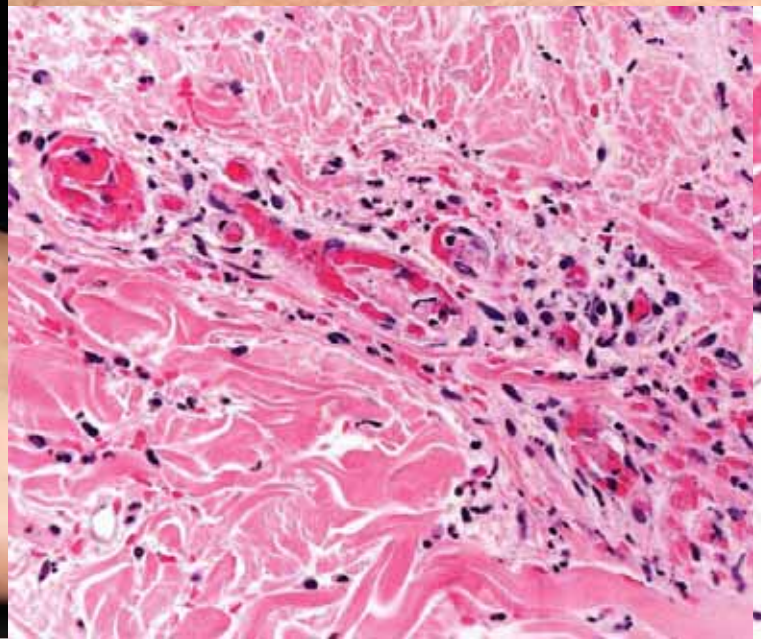


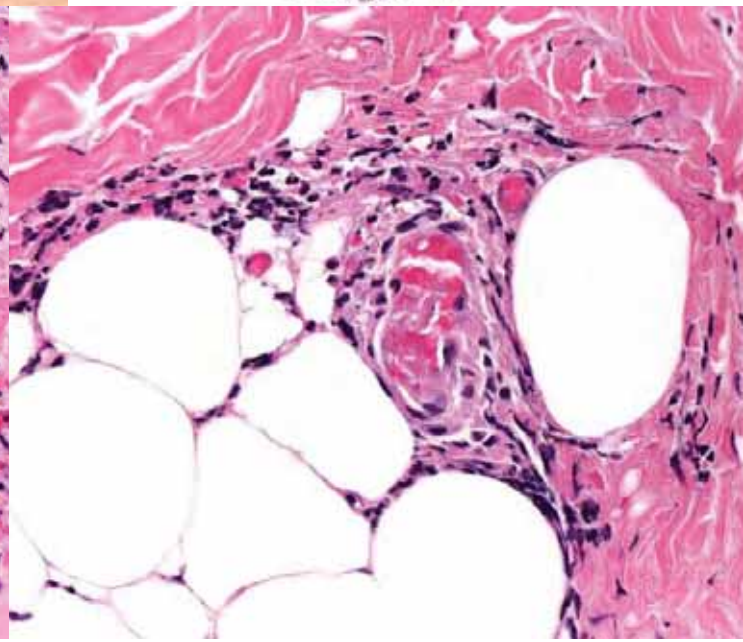
Day 15: Neisseria meningiditis detected in blood culture; therapy changed to ceftriaxone 2x2g i.v.
Request of post-exposition prophylaxis with ciprofloxacin 1x500mg for everybody who had contact with the patient.





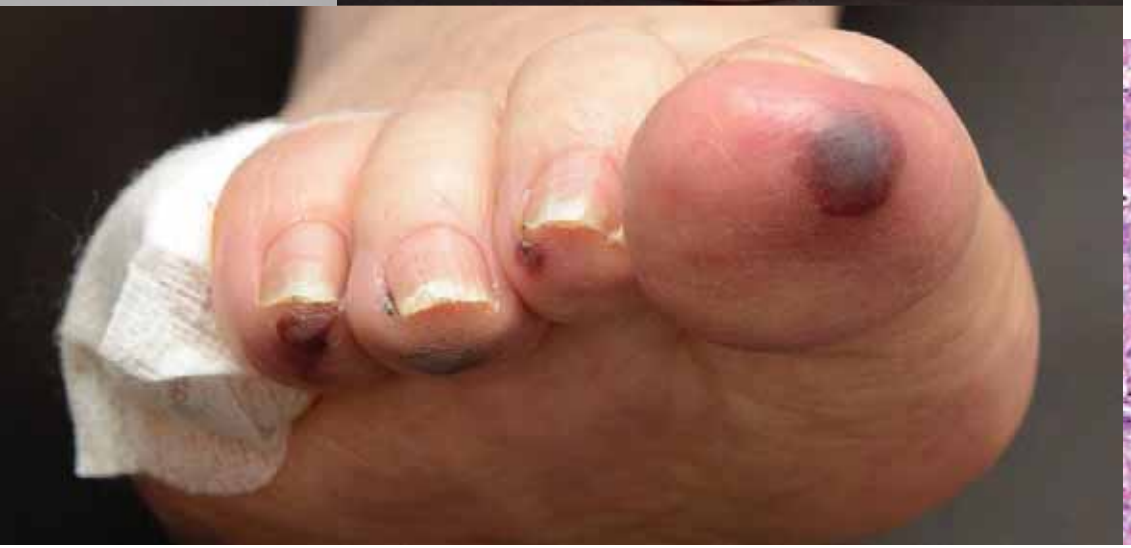


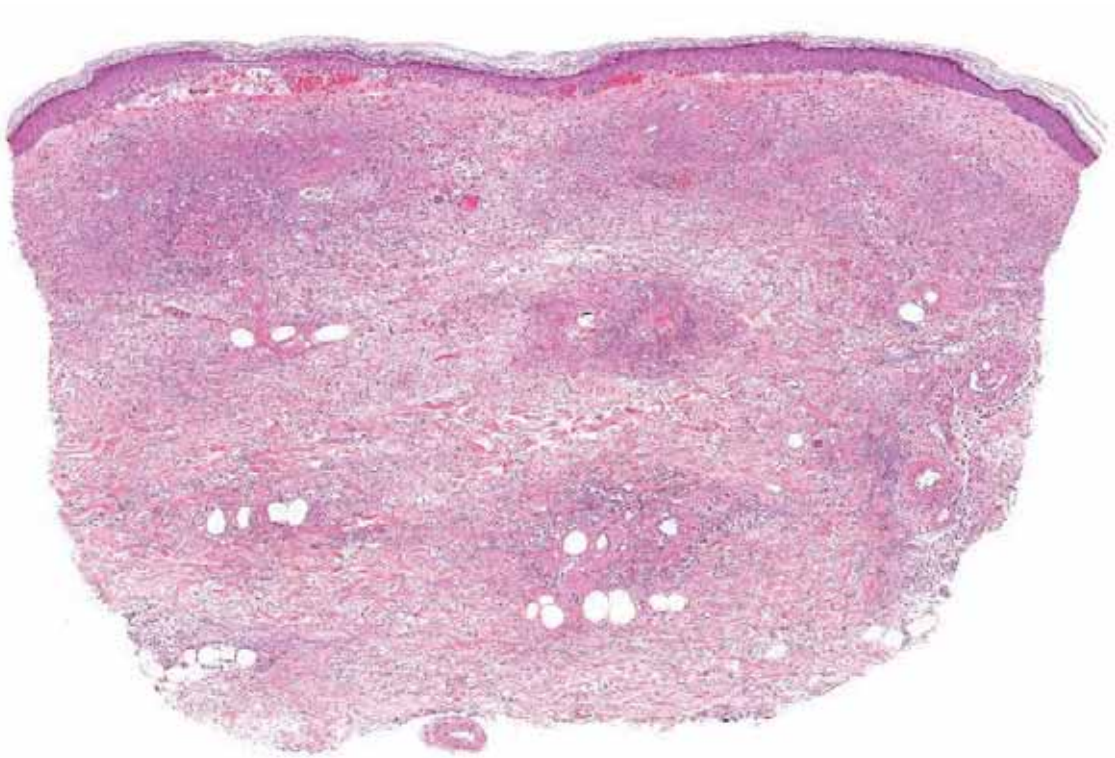


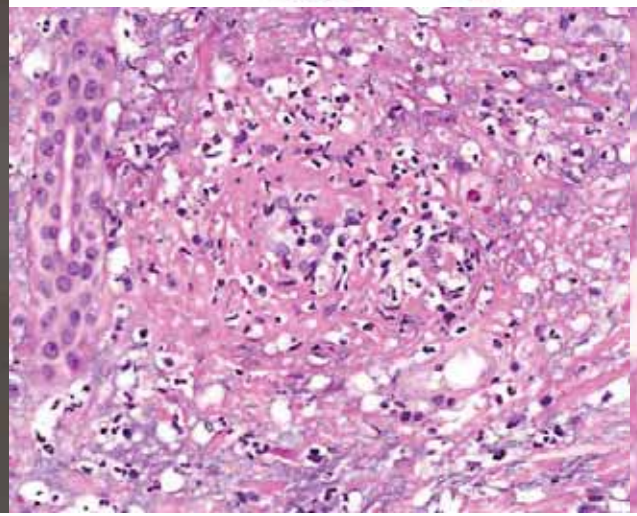


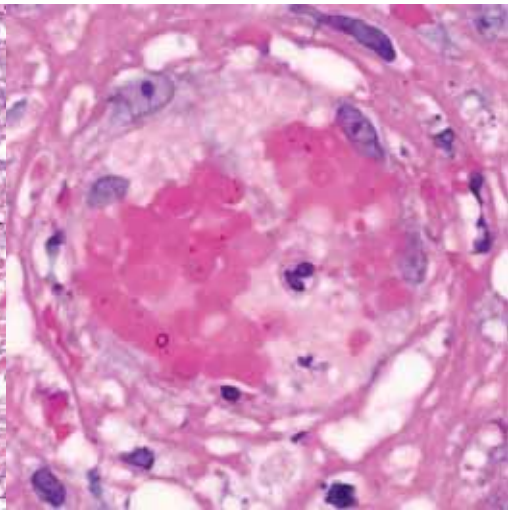
Septic vasculitis

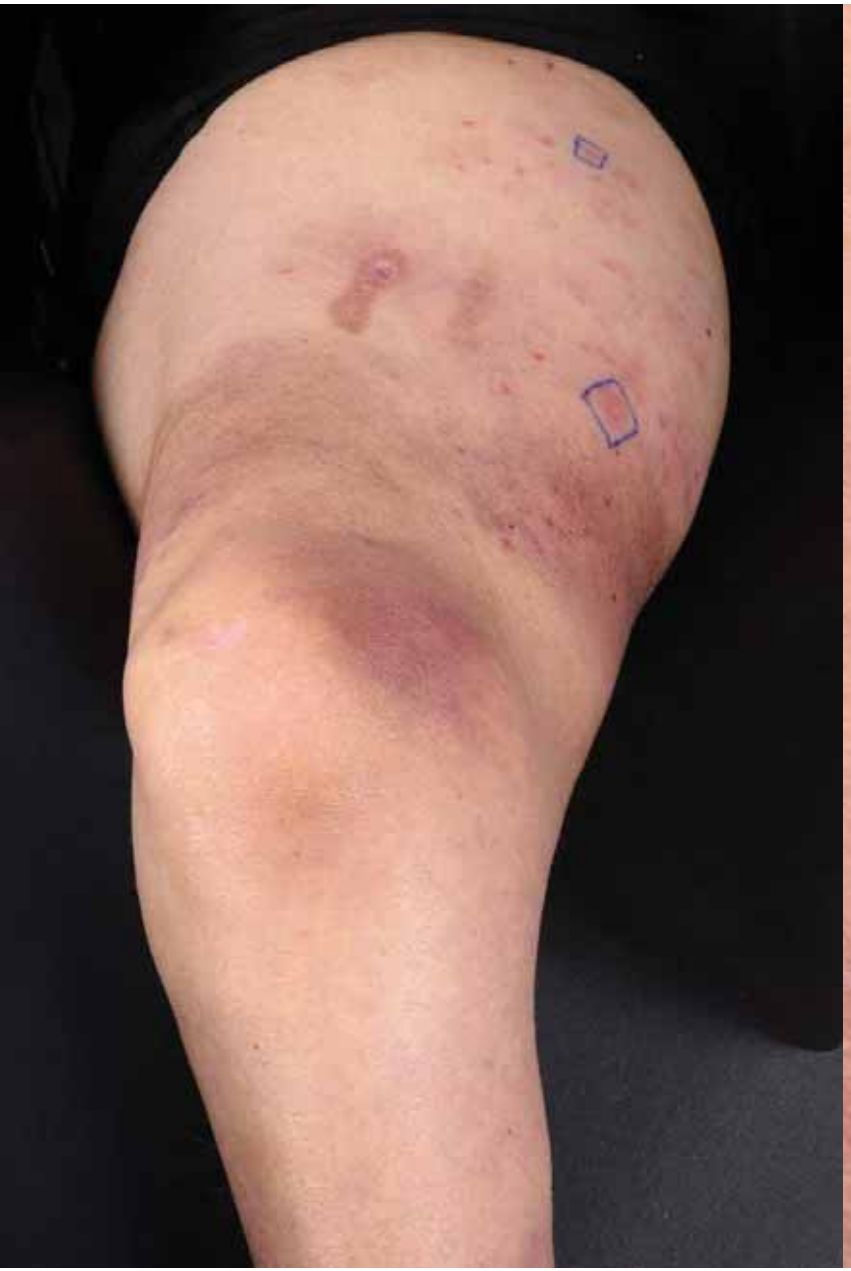
Septic vasculitis

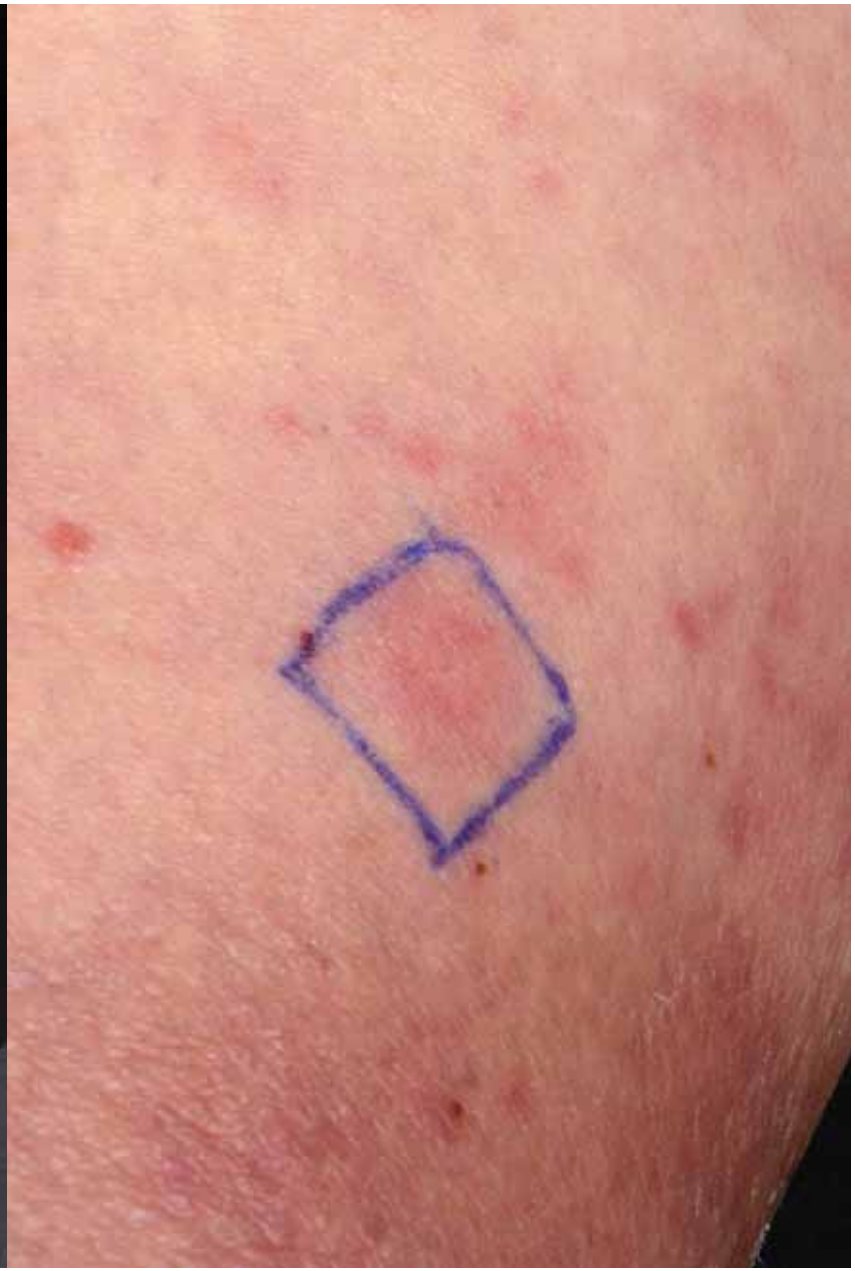












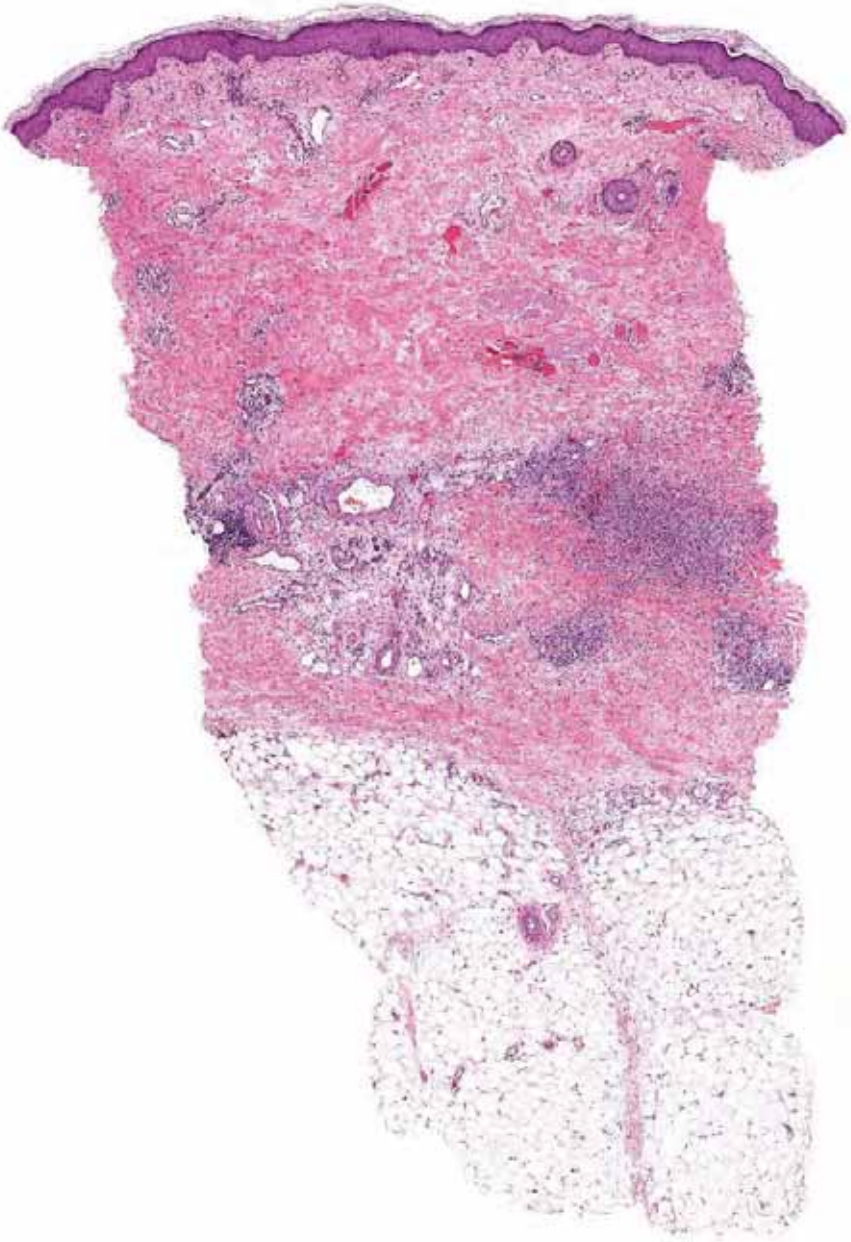
F, 55

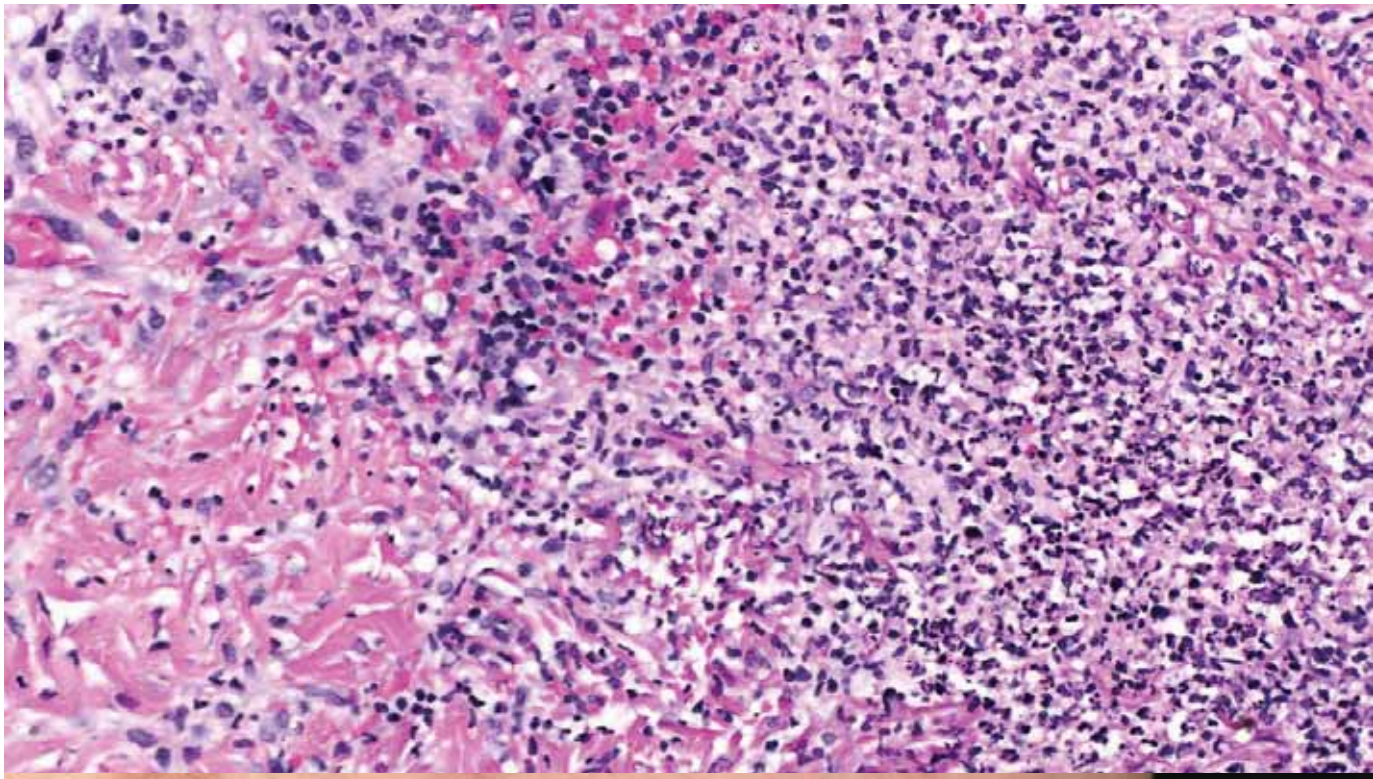
History of monophasic synovial sarcoma of the right foot 31 months before presentation (amputation of the distal right lower leg). Metastases in the lung, right tibia, right inguinal lymph nodes.

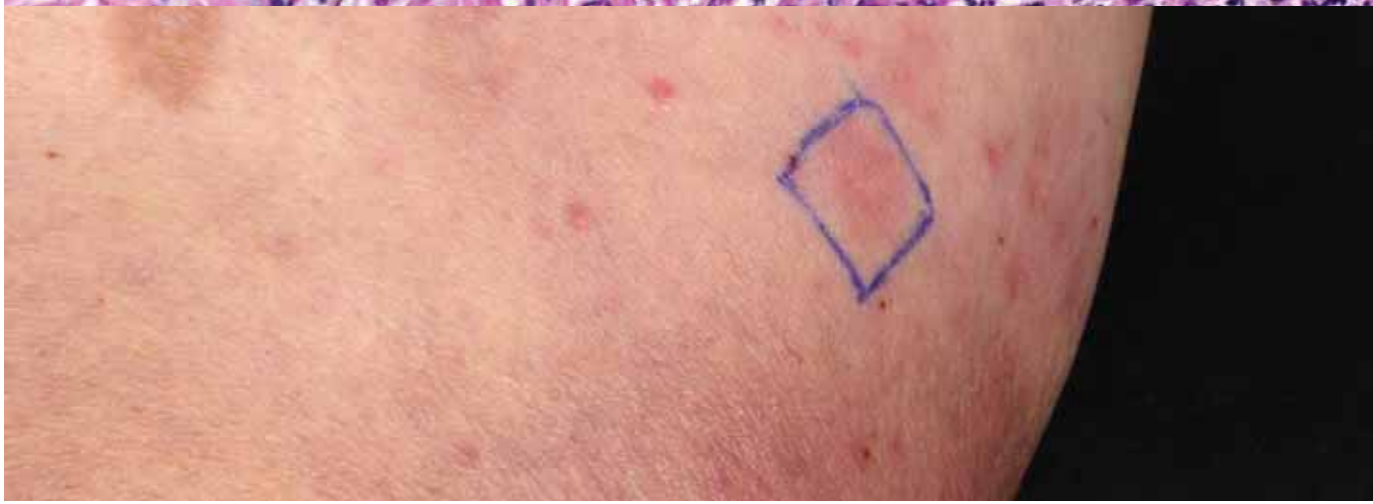
At present treated with ifosfamide.

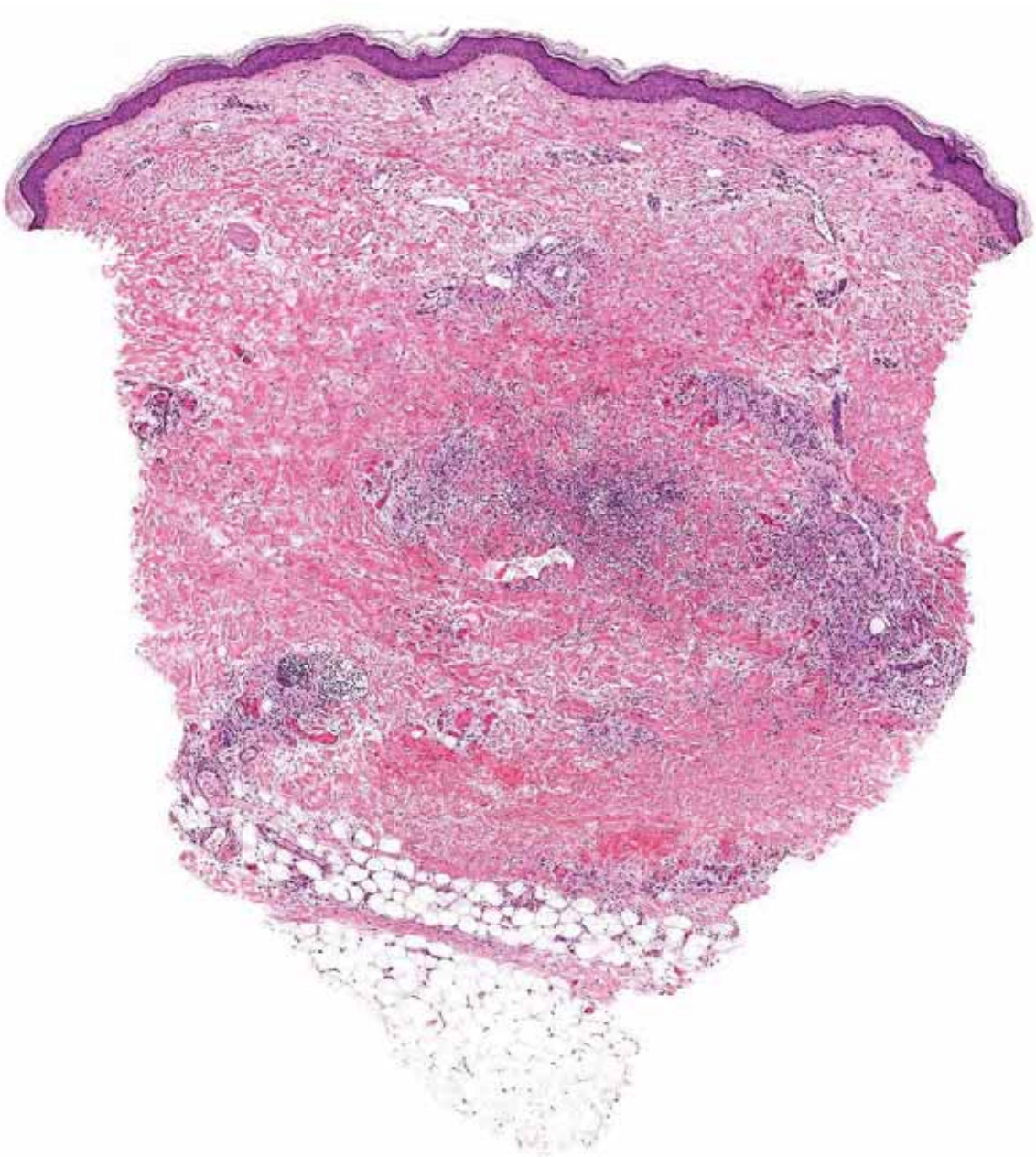
Sudden onset of erythematous lesions on the right upper leg. Fever, neutropenia. CRP: 104.3 mg/L (-5); Leukocytes: 0.30 10^9/L (4.4-11.3).

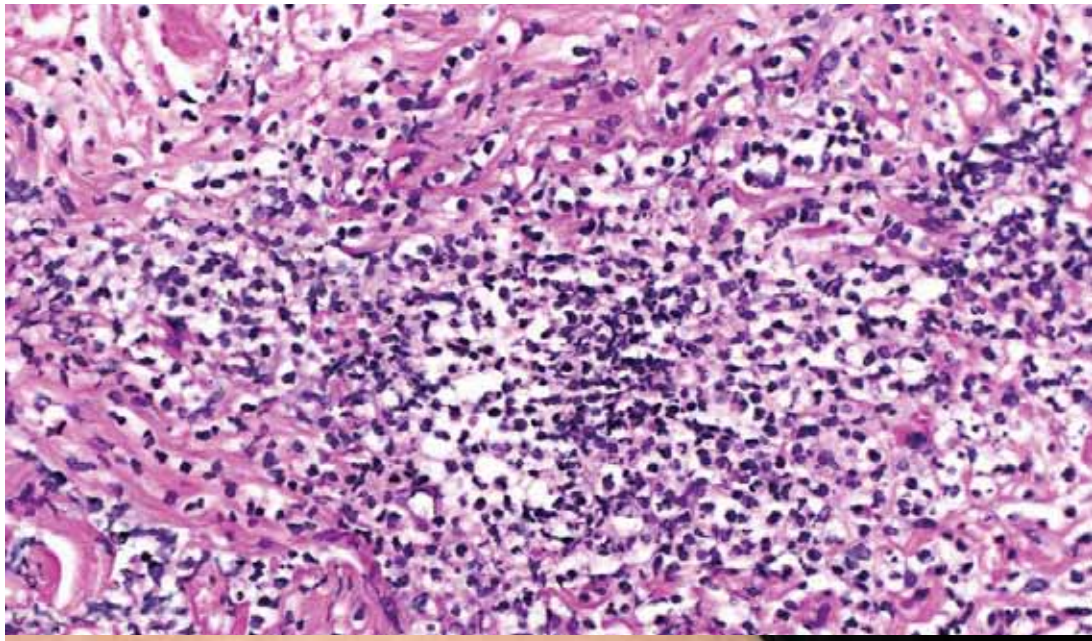
Two biopsies are taken to rule out a cutaneous metastasis of synovial sarcoma.

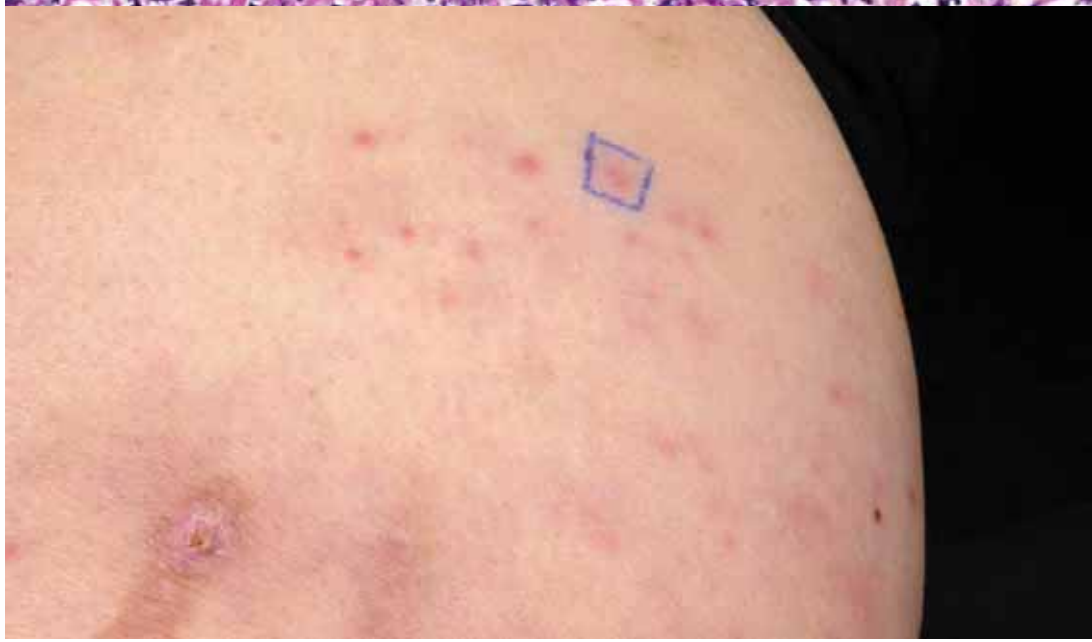


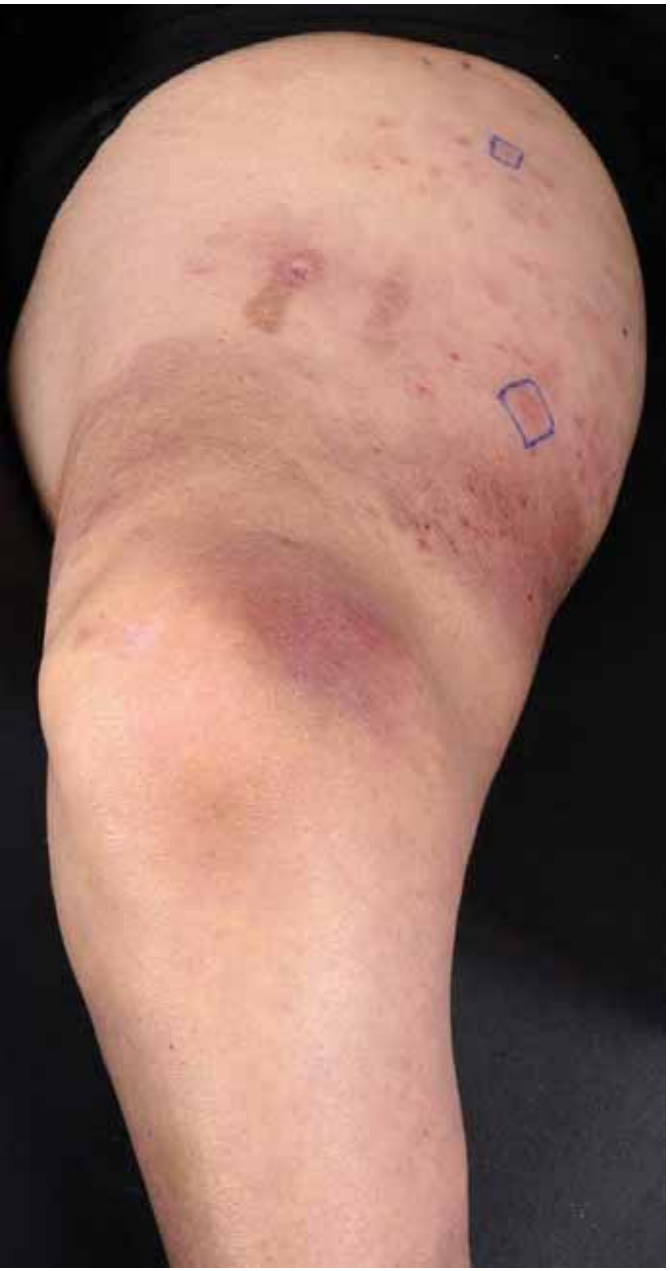


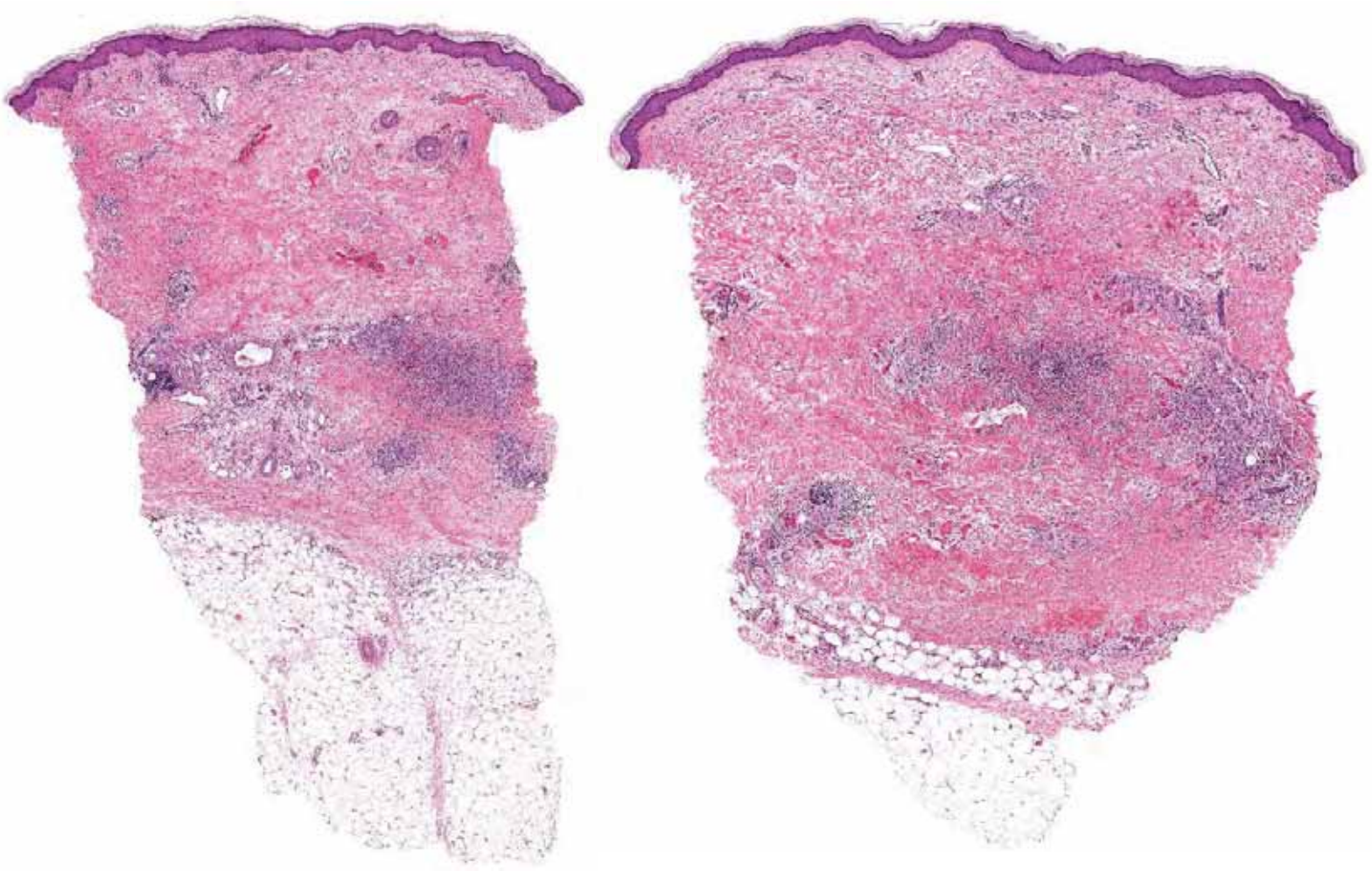






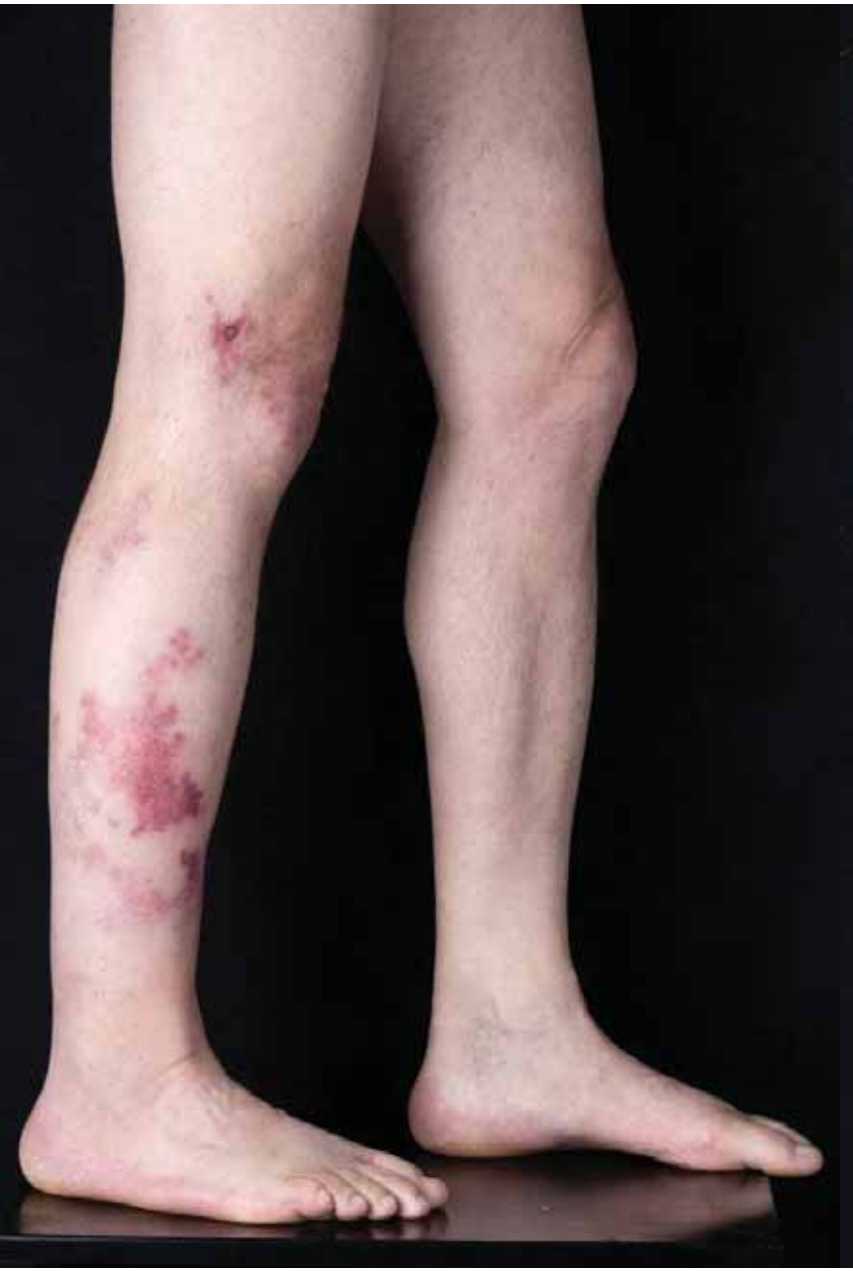


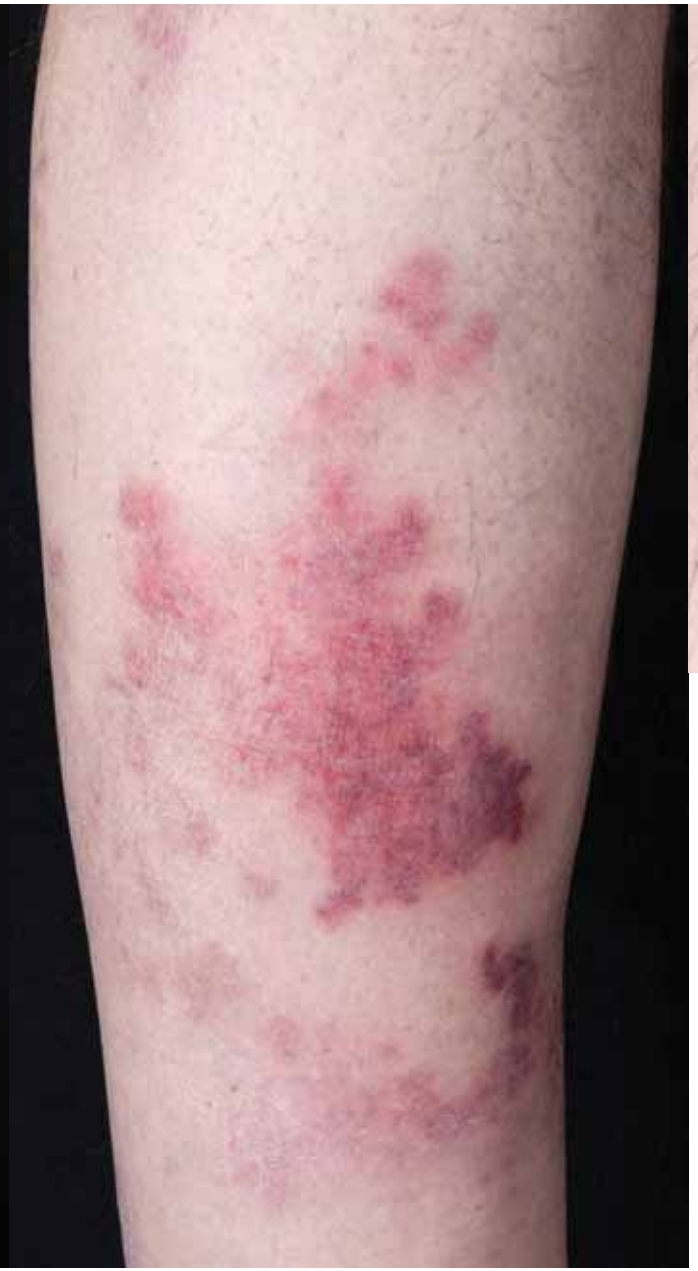


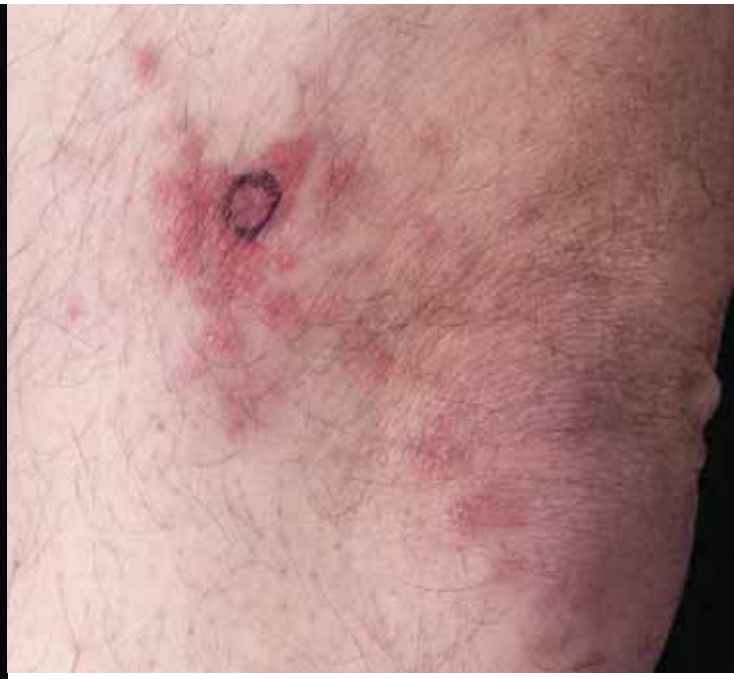


Erysipelas

complete remission after piperacillin/tazobactam therapy





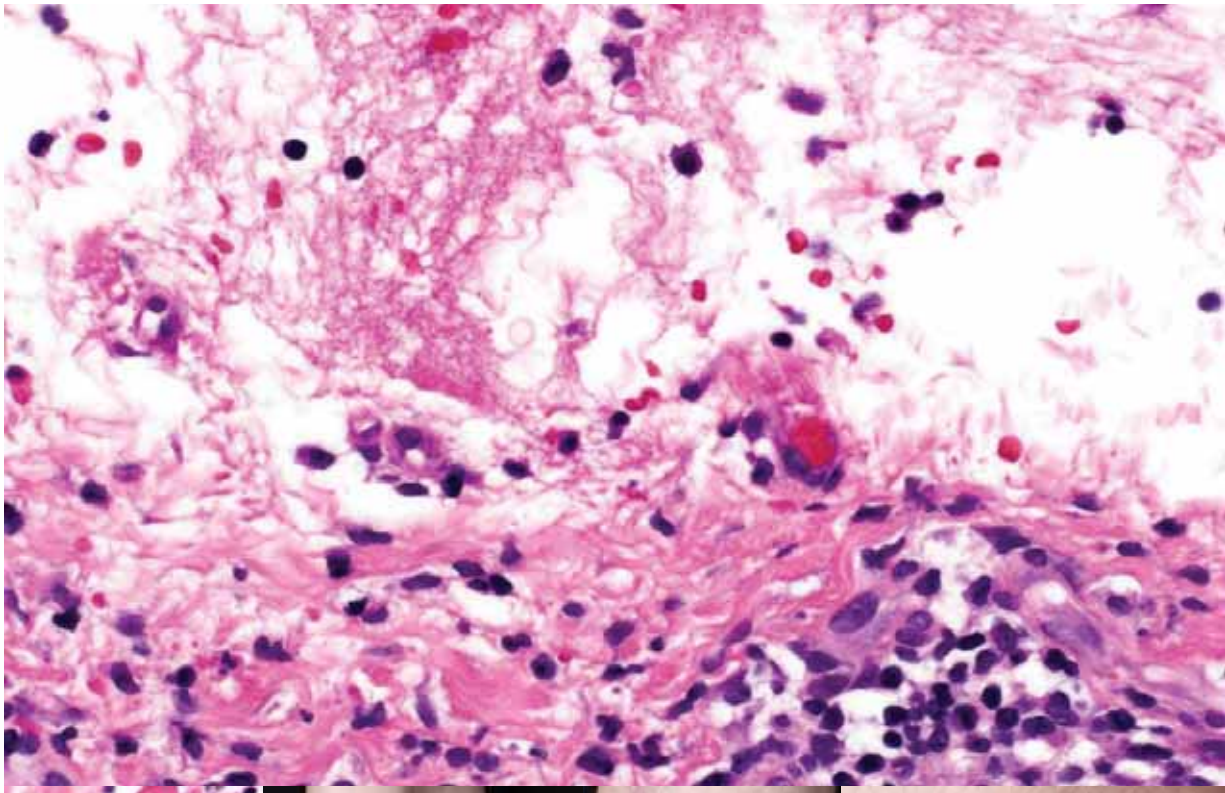


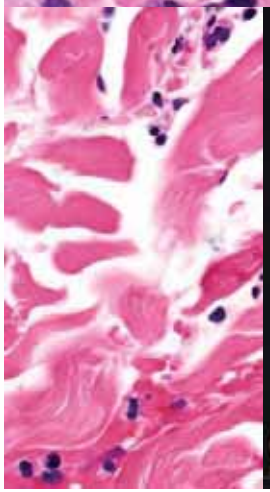
M, 63

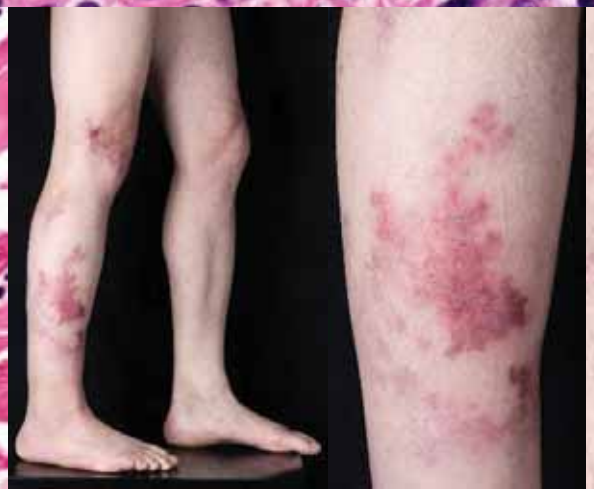
According to the patient recurrent skin lesions on the right leg for approximately 10 years (3x/year), accompanied by fever, diarrhea and malaise.

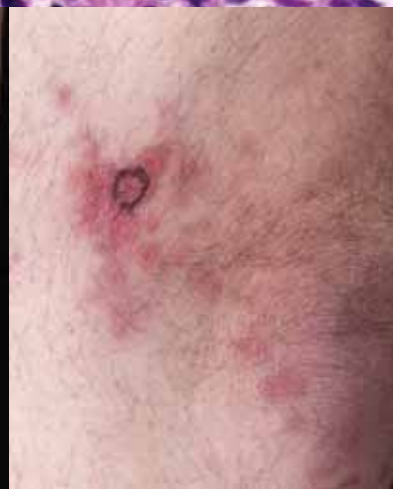
A biopsy is taken.

Recurrent erysipelas









BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Recurrent erysipelas - risk factors and clinical presentation

Malin Inghammar*, Magnus Rasmussen and Adam Linder

Abstract

Background: Erysipelas is a common infection that often recurs, but the impact of specific risk factors for recurrence remains elusive. In the present study we aimed at clarifying predisposing conditions for recurrence.

Methods: Medical records were reviewed from all patients ≥18 years of age diagnosed with erysipelas at the Department of Infectious Diseases at Skåne University Hospital, Sweden, from January 2007 to February 2011. 502 patients were included, of which 357 were single episode erysipelas and 145 had recurrent erysipelas. These two groups were compared regarding underlying conditions and clinical presentation.

Results: Erysipelas in the lower limbs had the greatest propensity of recurrence. The association between underlying conditions and recurrence were largely depending on the site of erysipelas. Overall, the most prominent risk factor for recurrence was lymphedema and other conditions causing a chronic impairment of the defence against microbes. Conditions temporally disrupting the skin barrier (e.g. a focal wound or "cat-web" interdigital, although likely being risk factors for erysipelas per se, did not seem to predispose to repeated episodes. Individuals with recurrent erysipelas tended to seek medical attention earlier and were less likely to be hospitalized or receive intravenous antibiotics, but there was no evidence of any difference in inflammatory reaction when taking confounding factors into account.

Conclusions: In this large cross-sectional study of over 500 patients with erysipelas, lymphedema was the most prominent risk factors for recurrence although the distribution of predisposing conditions varies depending on the site of erysipelas.

Keywords: Erysipelas, Skin infection, Recurrent, Risk factor

Background

Erysipelas is a common infection of the superficial layer of the skin, in contrast to cellulitis and necrotizing fasci-

group A and group G β-hemolytic streptococci. Whether erysipelas also can be caused by *Staphylococcus aureus* or gram-negative bacteria is debated [5-7]. The most com-

502 patients with erysipelas (357 single episode; 145 recurrent erysipelas).
Erysipelas in the lower limbs had the greatest propensity of recurrence. Lymphedema was the most prominent risk factor for recurrence.

CASE REPORT

Pitfall of modern genetics: recurrent erysipelas masquerading as autoinflammatory disease

E.J.W. Spierings, J.W.M. van der Meer, A. Simon*

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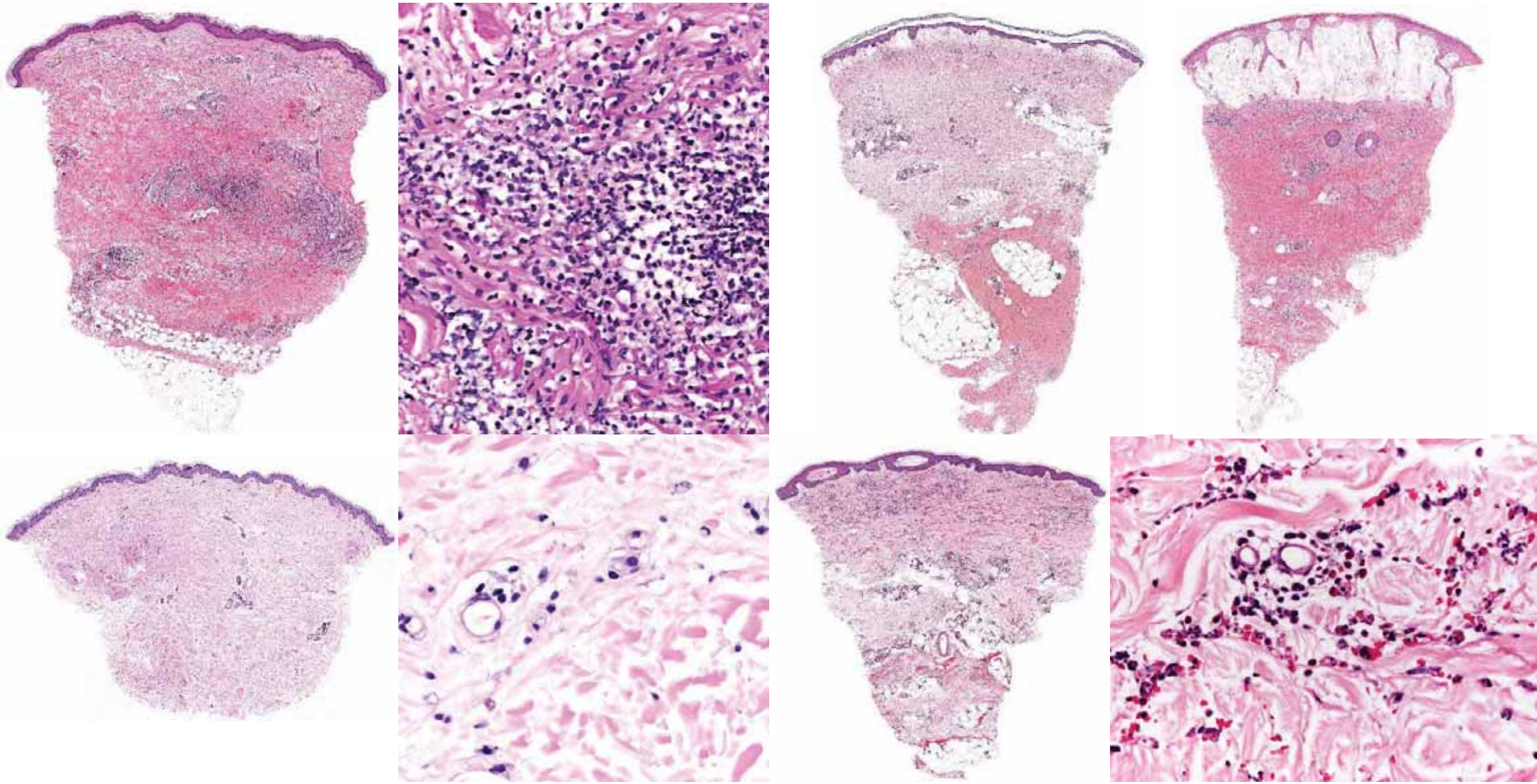
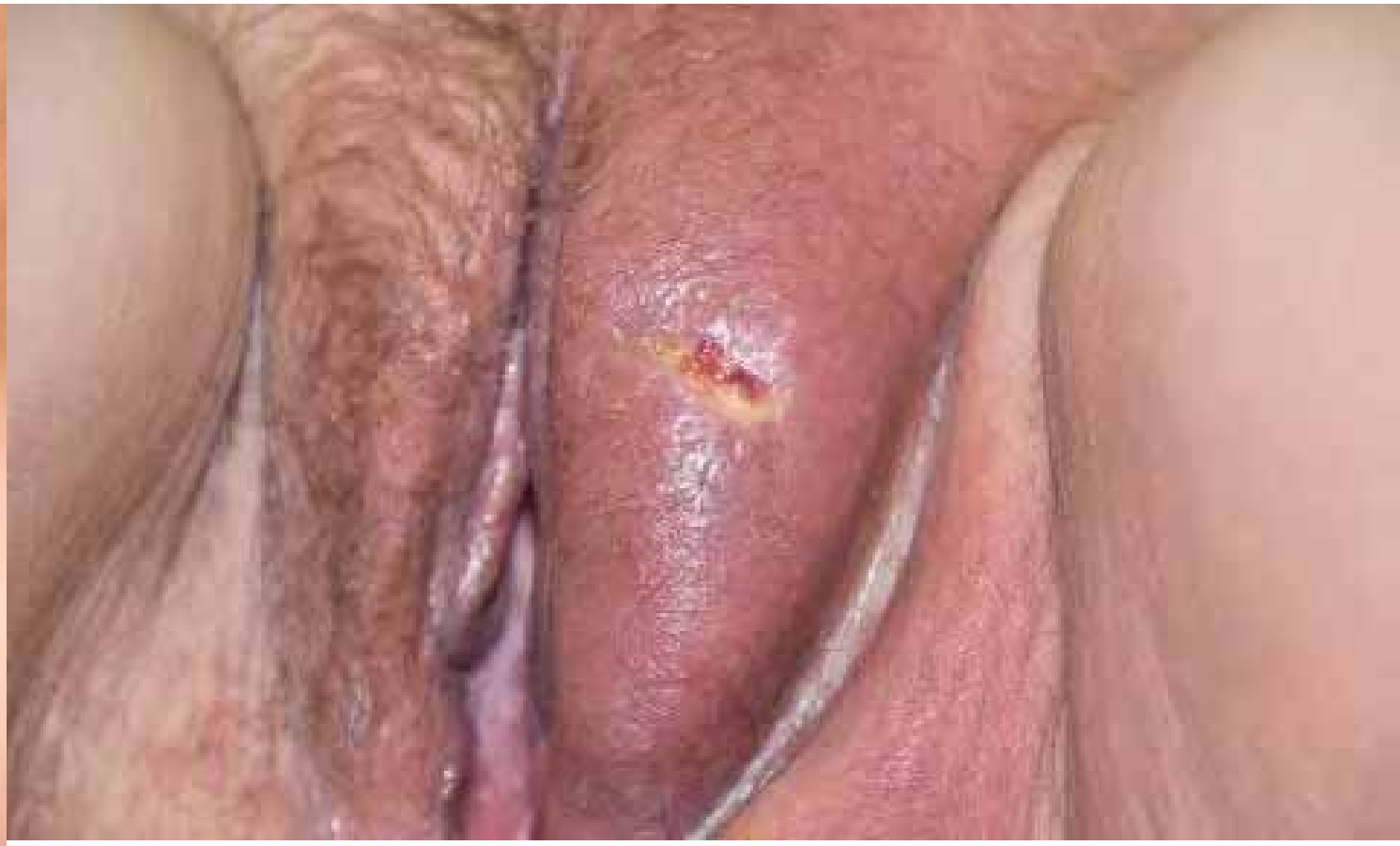
M, 35 with recurrent episodes of itching skin rash over the buttocks accompanied by fever (≥40 °C), general malaise, back pain and bilateral inguinal lymphadenopathy. The attacks had occurred 3-4 times/year for the last eight years. DNA analysis revealed a missense mutation in the NLRP3 gene (Leu677Pro) (mutations in the NLRP3 gene are linked with cryopyrin-associated periodic syndrome – CAPS). Reassessment of the medical history raised the suspicion of recurrent erysipelas of the buttocks. Culture of the perineum yielded group C haemolytic streptococci. The patient received eradication treatment with 10 days of clindamycin (600 mg three times a day). In the three years following, no new episodes of fever or skin lesions occurred.



Histopathology: Variable amounts of neutrophils, subepidermal edema, extravasated erythrocytes

Erysipelas

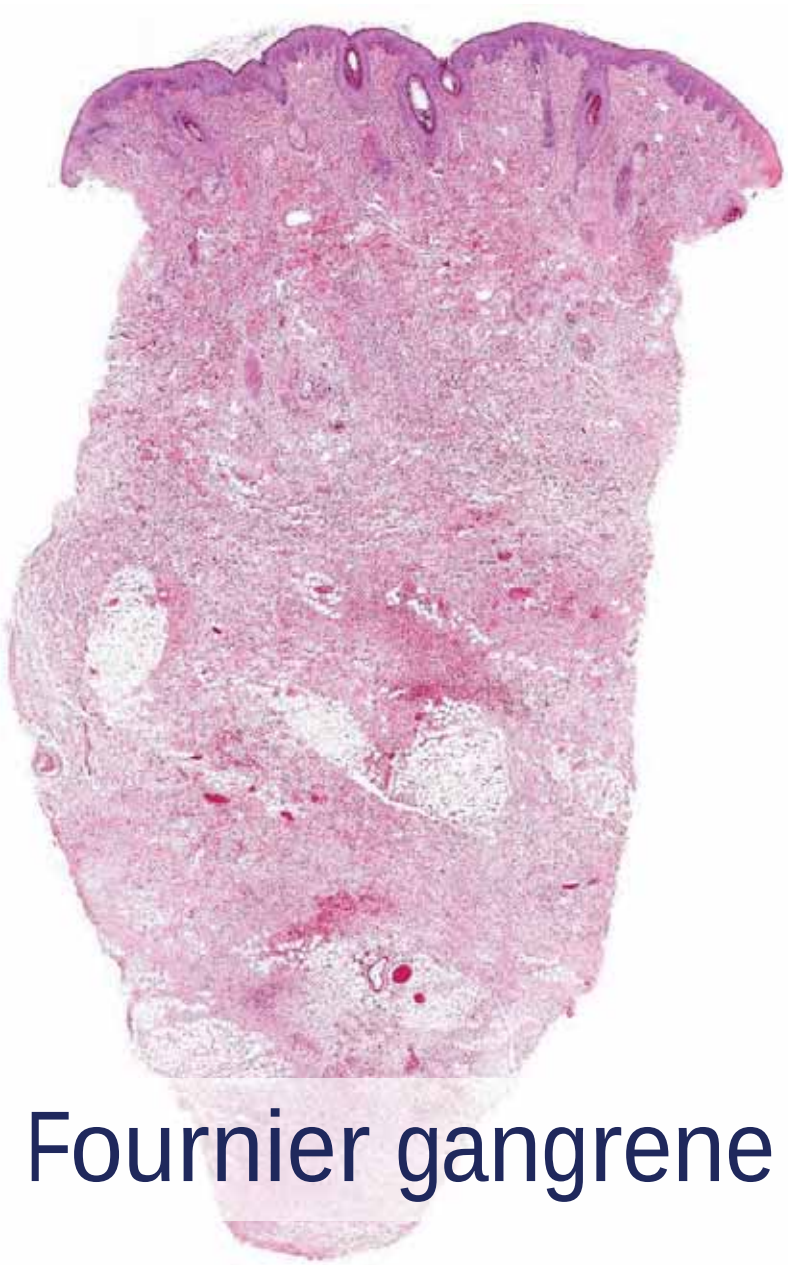
- Bacterial infection of the dermis and subcutaneous fat (streptococcal, sometimes other microorganisms) (the distinction of erysipelas from "cellulitis" in my opinion not meaningful)
- The inflammatory infiltrate is composed mostly of neutrophils in variable number (from sparse to abscess formation); variable edema (when marked may confer a bullous clinical appearance) and hemorrhage (a few extravasated erythrocytes almost always present, may be markedly hemorrhagic in some cases)
- Bacteria are not seen on histopathological sections
- In some cases may progress to necrotizing fasciitis (necrotizing fasciitis and Fournier gangrene begin mostly *de novo*)



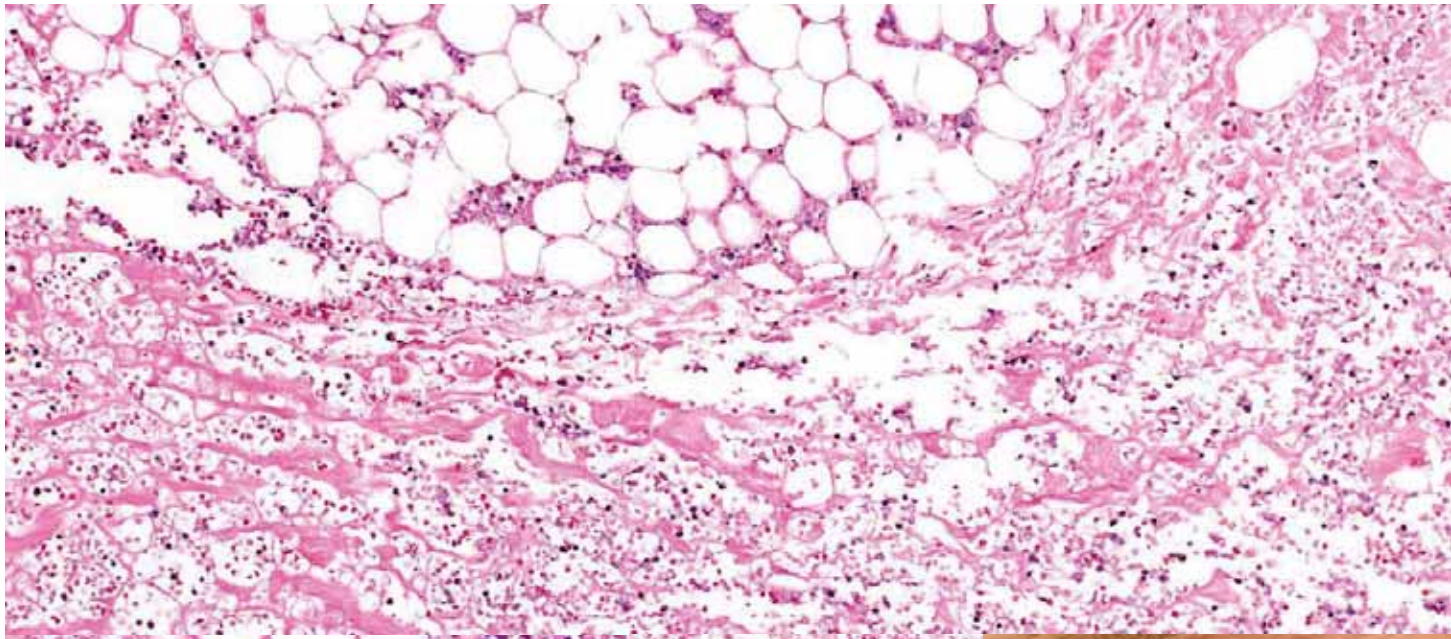
F, 46

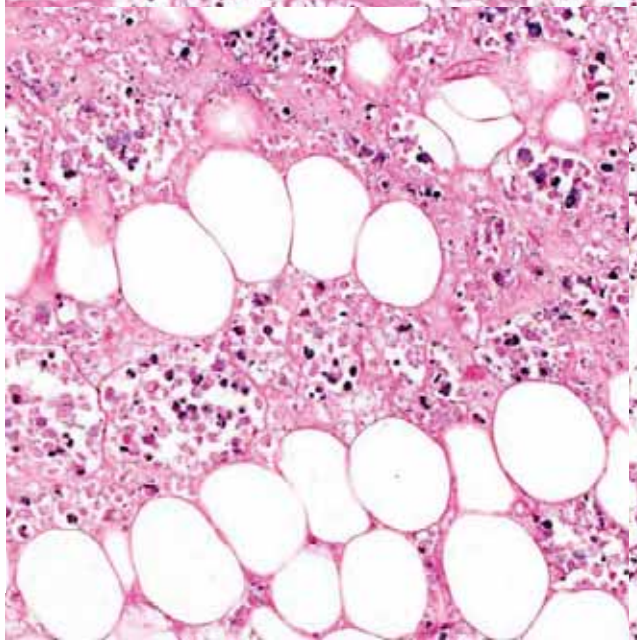
Short after removal of a condyloma by electrocoagulation swelling and redness of the left labium majus, mons pubis and gluteal region. No improvement with antibiotic treatment.

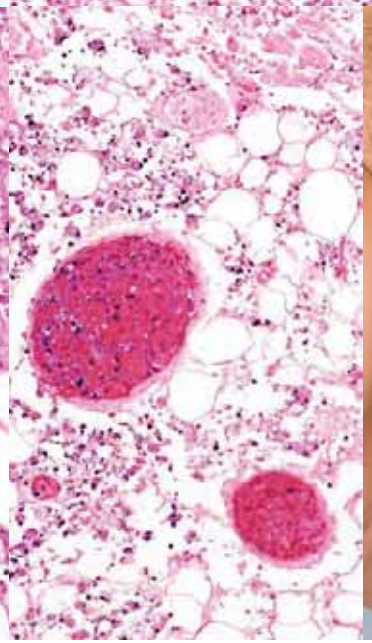
A biopsy is taken.



Fournier gangrene







Cureus

Open Access Review Article

Fournier's Gangrene Diagnosis and Treatment: A Systematic Review

Abstract

Introduction And Background

Review

Methodology

3093 males
131 females

Andrology

BJUI
BJU International

Mortality associated with Fournier's gangrene remains unchanged over 25 years

Robert S. Radcliffe and Masood A. Khan

University Hospitals of Leicester, Leicester, UK

Objectives

To report a case series of Fournier's gangrene (FG) from our institution, and to investigate its mortality over the past 25 years.

Patients and Methods

Case notes of men presenting to our institution from 2013 to 2016 with FG were reviewed. As well as age, diabetic history, length of stay, length of stay in critical care, and mortality; we calculated (where possible) the Uludag Fournier's Gangrene Severity Index (UFGSI).Published studies and cases series reporting the mortality rates for FG were reviewed from 1993 to 2018. The size of the study, country of origin, average age and gender ratio were collected, alongside mortality.

Results

Two of the 11 patients treated for FG at our institution died within 90 days of admission, a mortality rate of 18%. Predicted mortality was significantly higher.A total of 173 publications were identified from the Medical Literature Analysis and Retrieval System Online (MEDLINE) database published between 1993 and 2018, reporting data from 1975 to 2018. Analysis of heterogeneity, by both time and precision, supported exclusion of four retrospective coded database-driven studies from the analysis.From the remaining studies, mortality ranged from 0% to 42%. Of the 6152 reported cases, there were 1220 deaths, giving an overall mortality rate of 19.8%. There was no evidence of a significant change in the mortality rate for FG over time ($P = 0.996$).

Conclusions

In our case series, the mortality rate for FG was 18%, despite a higher predicted mortality (based on UFGSI scores). The treatment of FG remains appropriate resuscitation, aggressive surgical debridement, and critical care management. Perceived high risk of mortality should not deter aggressive management.Mortality due to FG does not appear to have changed over the past 25 years, and is estimated at 19.8%. In studies identifying cases of FG, careful attention should be paid to case definition, particularly when cases are being abstracted retrospectively from large coded databases.

Keywords

mortality, case definition, epidemiology, necrotising soft tissue infections, Fournier's gangrene

Introduction

Despite being the eponym of infective necrotising fasciitis of the perineal, perianal or genital region, Jean Alfred Fournier (1832–1914) was not the first to describe what we now know as Fournier's gangrene (FG). Bourienne had first described the disease in 1764.

FG is typified by an abrupt onset of rapidly progressive painful erythema and tenderness, progressing to swelling, surgical crepitus, and malodorous soft tissue necrosis. Systemic features of worsening sepsis emerge as the disease progresses. Treatment involves aggressive management of the associated sepsis, one or more surgical debridements of necrotic tissue, with later reconstruction as indicated. Over the last 25 years, published mortality rates for FG have varied between 0% and 42% [1]. The majority of publications consist of case series and retrospective analyses of the experiences in single centres.

More recently a number of larger studies using population-based databases have suggested a mortality rate as low as 4.7% [2]. The authors of these studies accept that it is possible that their case definitions over-diagnose FG, and hence under-estimate its mortality.

We present a case series of 11 patients treated for FG at our institution. We also survey the recent published data on mortality rates for FG to look for any trends over time in mortality.

BJU Int 2020; 125: 610–616
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6152 reported cases; 1220 deaths (19.8%)

International Journal of Infectious Diseases

Review

Fournier's gangrene mortality: A 17-year systematic review and meta-analysis

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1990 cases; 249 deaths (12.5%)

Table 2
Meta-analysis of etiologies of death.

Variable	Sample size	Number of studies	Heterogeneity		Model	ER (95% CI)	Publication bias (p-Value)
			p-Value	I^2 (%)			
Sepsis[a]	133/180	19	0.01	49	Random	76% (62–86)	0.001
Multiple organ failure	82 / 67	6	0.004	72		65% (37–87)	–
Renal mortality[b]	11/80	2	0.21	27	Fixed	15% (10–20)	–
Cardiovascular mortality[c]	13/93	9	0.04	0.00		15.7% (9–25)	–
Respiratory mortality[d]	17/103	9	0.37	8		19.4% (12–29)	–
Hepatic mortality[e]	2/44	2	0.79	0.00		5% (1–17)	–
Uncontrolled infection and diabetes[f]	6/8	1	–	–	–	75%	–
Rectal adenocarcinoma[f]	1/2	1	–	–	–	50%	–
Sepsis and multiple organ failure[f]	4/7	1	–	–	–	57%	–
Multi-organ failure and disseminated intravascular thrombosis[f]	8/11	1	–	–	–	73%	–
Diabetes[f]	1/6	1	–	–	–	16.7%	–
Gangrenous infection[f]	5/5	1	–	–	–	100%	–
Intra-abdominal abscess-reduced peristalsis[f]	1/15	1	–	–	–	7%	–
After transition to comfort care measure[f]	2/9	1	–	–	–	11%	–
Disseminated intravascular thrombosis[f]	1/26	1	–	–	–	3.8%	–
Lower gastrointestinal bleeding[f]	1/18	1	–	–	–	5.6%	–
Unknown etiology[f]	1/5	1	–	–	–	20%	–

ER, event rate; CI, confidence interval.
[a] Including septicemia and septic shock.
[b] Including renal failure and chronic kidney disease.
[c] Including heart failure, cardiopulmonary dysfunction, myocardial infarction, cardiac arrest and cardiorespiratory arrest.
[d] Including pneumonia, pulmonary embolism, pulmonary complication and adult respiratory distress syndrome (ARDS).
[e] Including hepatitis and hepatic failure.
[f] Data not subjected to meta-analysis.

ACC Acute and Critical Care

Biomarkers to predict mortality in patients with Fournier's gangrene admitted to the intensive care unit after surgery in South Korea

In Sik Shin, Seong Chan Gong, Sanghyun An, Kwangmin Kim

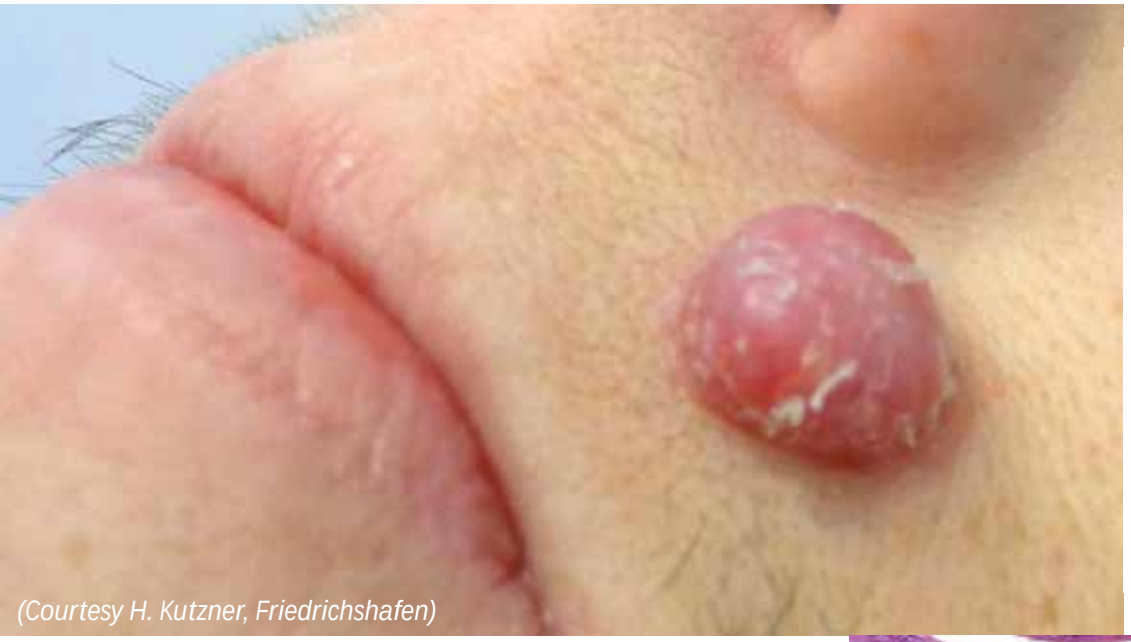
41 cases; 13 deaths (31.7%)

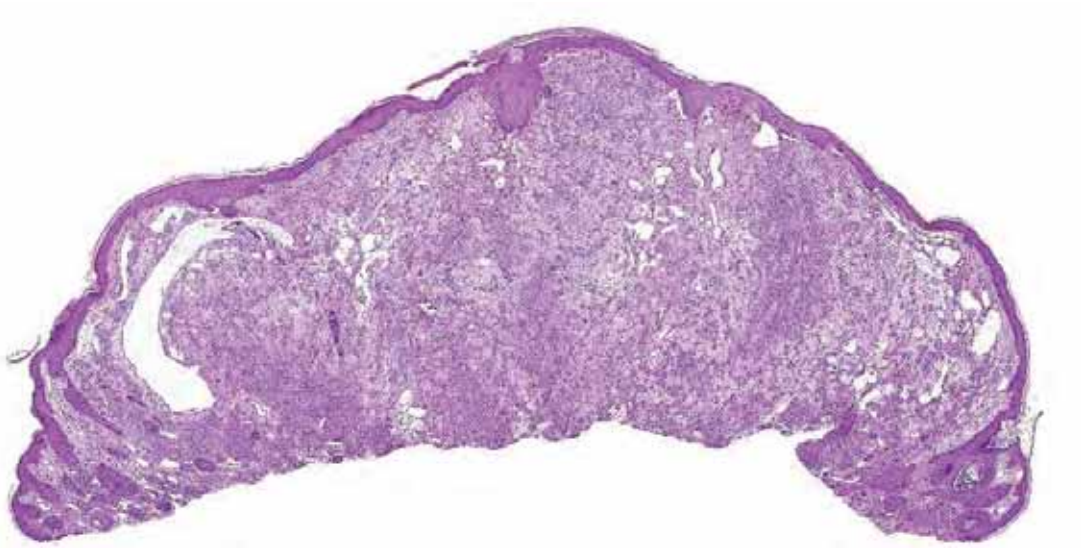
Negative predictive factors:
High postoperative lactate
(survivors: 1.8±0.9; nonsurvivors: 5.8±4.3; p=0.016)
Low initial albumin levels
(survivors: 3.2±0.8; nonsurvivors: 2.4±0.5; p<0.001)

Table 4. Characteristics of postoperative lactate and initial albumin levels

Variable	Optimal cutoff value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Postoperative lactate (mmol/L)	3.00	80.0	95.0	0.877 (0.711–1.000)
Initial albumin (g/dl)	3.05	92.3	57.1	0.827 (0.738–0.997)

AUC: area under the curve; CI: confidence interval.

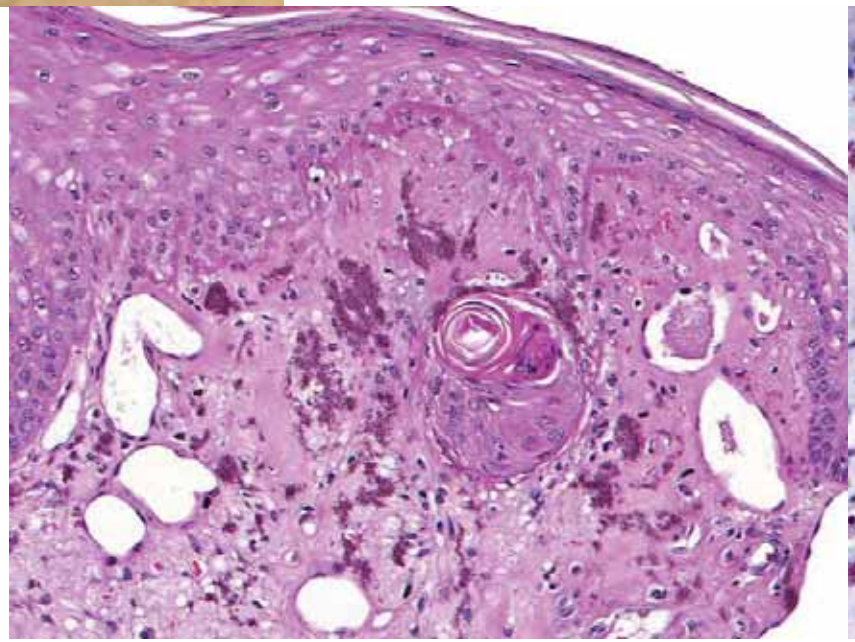

(Courtesy H. Kutzner, Friedrichshafen)

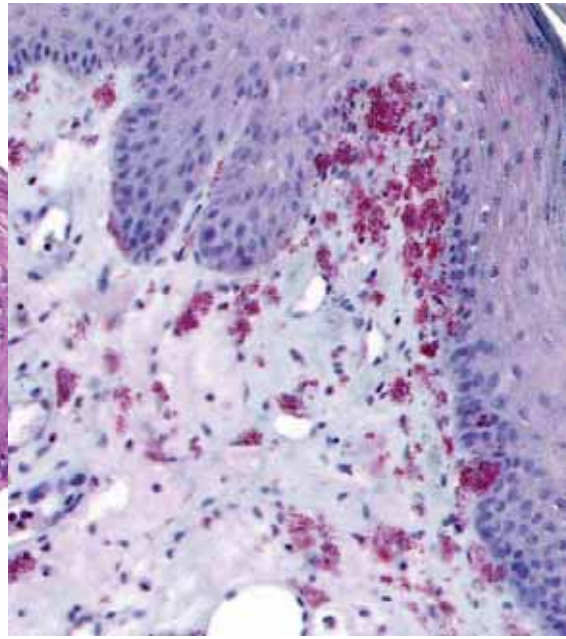


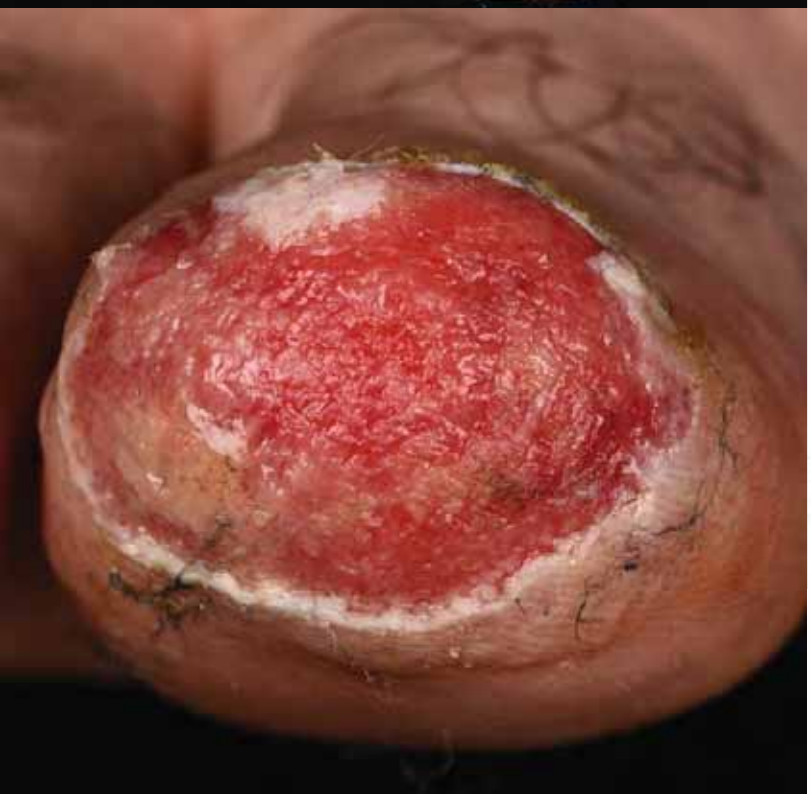
Bacillary angiomatosis

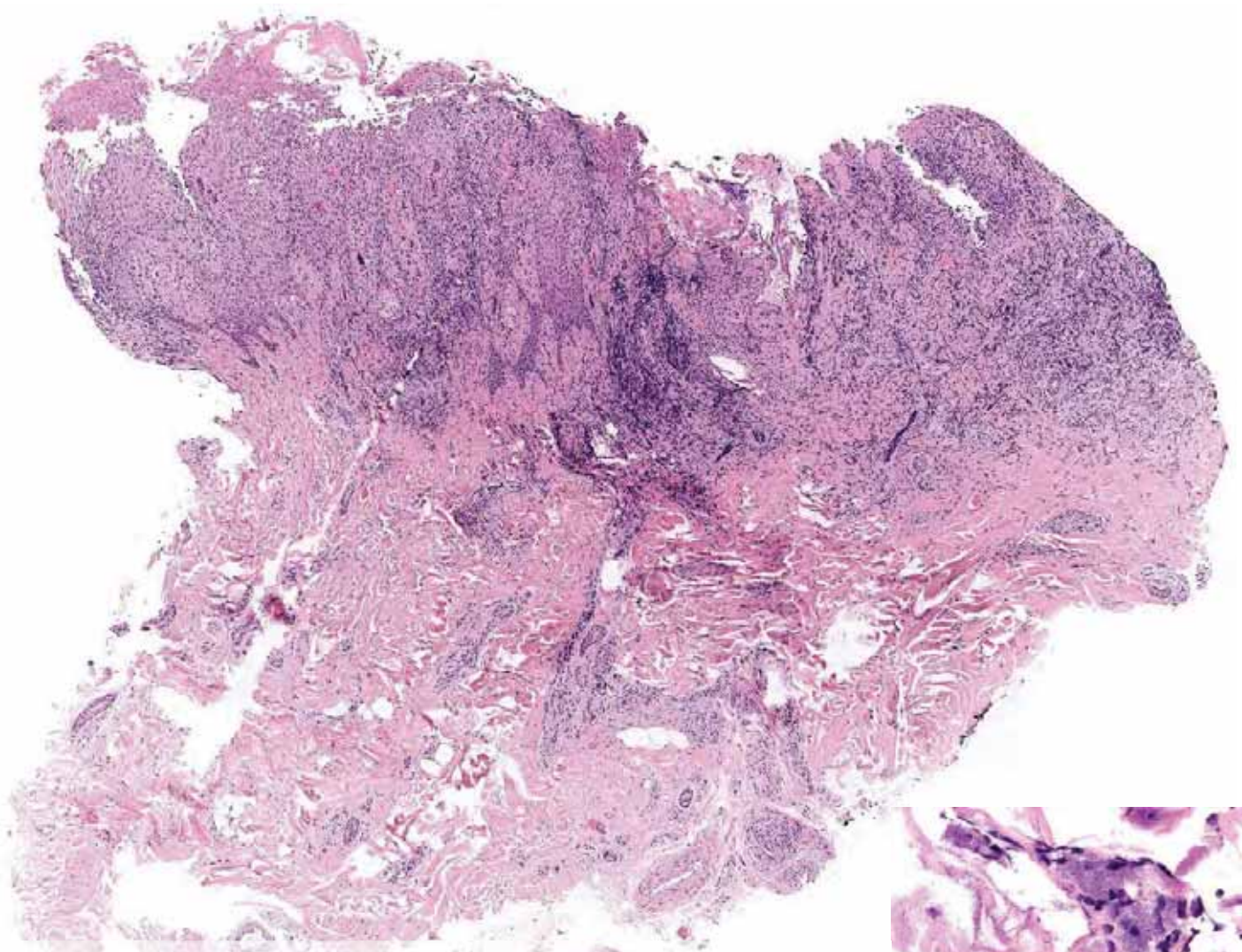
(Bartonella henselae [causing also cat-scratch disease], Bartonella quintana)

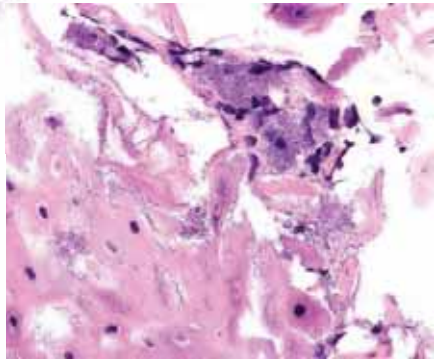
In immunocompromised patients, particularly those infected with HIV. May resemble pyogenic granuloma clinically. Histopathologically, proliferation of vessels admixed with neutrophil-rich inflammatory infiltrate. Bacteria present as clumps of granular material and can be detected by immunohistochemistry. Can be managed by doxycycline plus rifampin.









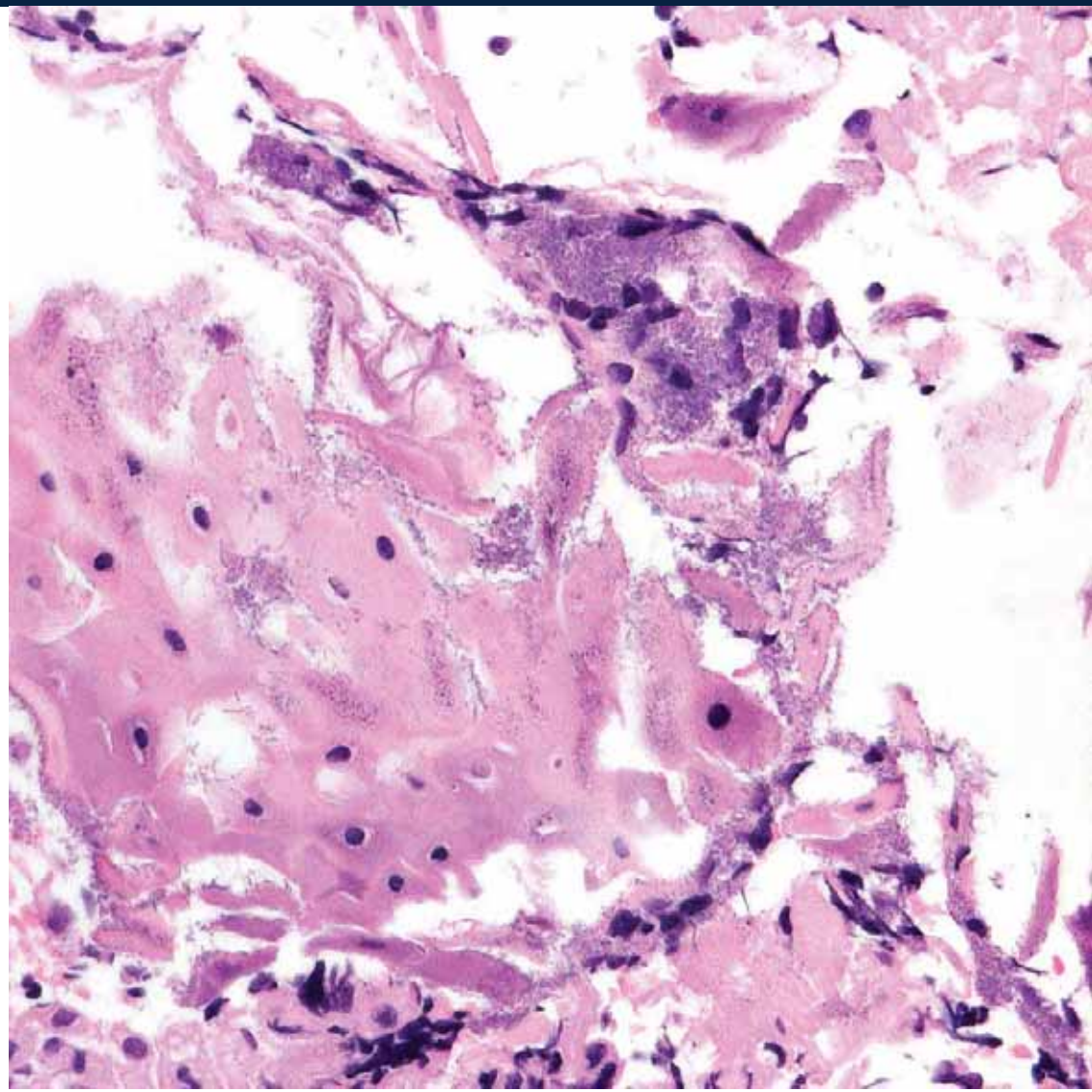


Tropical phagedenic ulcer

(culture: Ps. Aeruginosa)

Tropical phagedenic ulcer

- More common in tropical climate
- Several microorganisms can be responsible for the same clinical presentation
- Usually after minor trauma
- Prolongued antibiotic treatment; Local antiseptics; Surgical debridement, grafting, sometimes amputation
- SCC may develop in long-standing ulcers



Tropical Phagedenic Ulcer *

Evaluation of a New Ambulatory Method of Treatment

GEORGE BLAINE, M.D.

St. Andrew, Jamaica, British West Indies

TROPICAL phagedenic ulcer is a condition ubiquitous in the tropical and subtropical belt. In comparison with other tropical scourges, scant attention has been paid to it in recent years. While other important tropical conditions are "killing," tropical ulcer is merely injurious to health.

Though the condition is not one usually leading to fatalities, the disfigurement, suffering, danger to general hygiene of tropical populations, and its close correlation with the standard of education is a problem to be faced.

In the present study a new ambulatory method of treatment is evaluated, adoption of which might go a long way towards ultimate control of this condition.

The present study was conducted over the past two years in Jamaica, British West Indies. More than 200 cases have been treated and followed.

Definition

Roy's [8] definition is classical: "Tropical ulcer is a rapidly spreading ulcer, occurring usually on the lower extremities of the body, which quickly assumes a phagedenic character and is accompanied by considerable pain, local edema, sloughing, and a serosanguinous and foul-smelling discharge. The edges of the ulcer are undermined and the margins are considerably raised."

Etiology

The disease occurs mostly in sporadic and endemic forms, though outbreaks of almost epidemic proportions have been noted from Assam, Cochin China, Malaya, certain parts of Africa, the Solomon Islands and Melanesia.[3] In the West Indies and the Americas the disease is equally widespread. Most authors agree that the conditon is almost exclusively one of the indigenous populations, but its importance to expeditionary forces must not be overlooked. The condition has been frequent in prisoner of war camps in tropical areas.

An important etiologic factor is the appreciable lack of footwear in underdeveloped and underprivileged areas. Adequate leg cover has also been referred to as a factor by Earle [2] who observed that British troops, in the Mediterranean theatre of war, wearing puttees, were almost free of the condition, while German troops, though campaigning under the best possible hygienic conditions, were greatly affected by tropical ulcer, because of uncovered legs.

The actual onset of ulceration is very rapid and starts from almost any small surface wound. Insect bites, cuts, abrasions, are transformed into a typical, spreading ulcer, within two or three days of the initial trauma.

There is little agreement by previous authors on the correlation of tropical ulcer with deficiency diseases and debilitating conditions, but recently Castellani [1] denied correlation of tropical ulcers with nutritional deficiencies.

Bacteriology and Histopathology

The bacteriologic picture of tropical ulcer is consistently nonspecific. Fusiform bacilli, borelia vincenti, are demonstrable in most

* Submitted for publication November 8, 1957.

Ann Surg 1958

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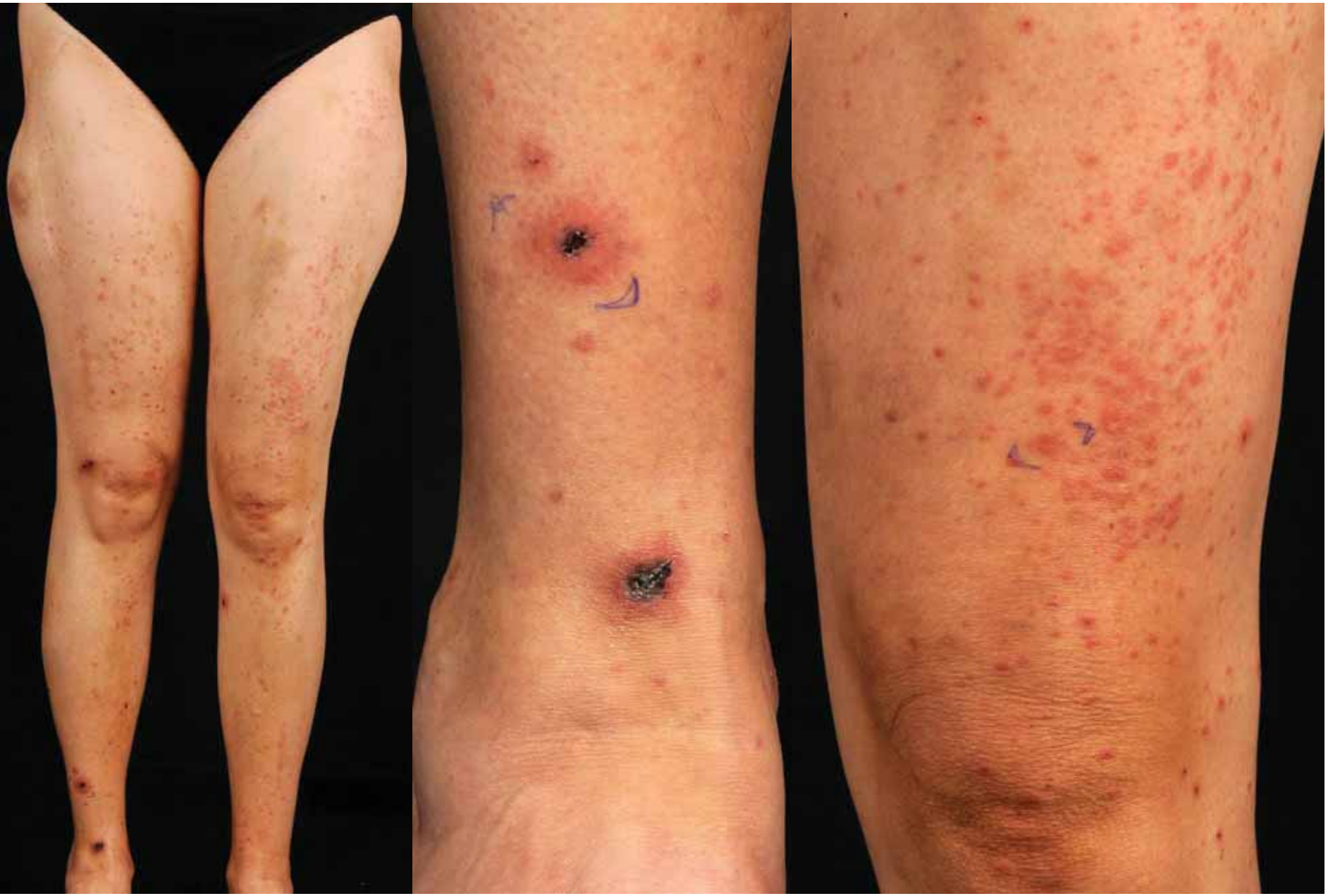
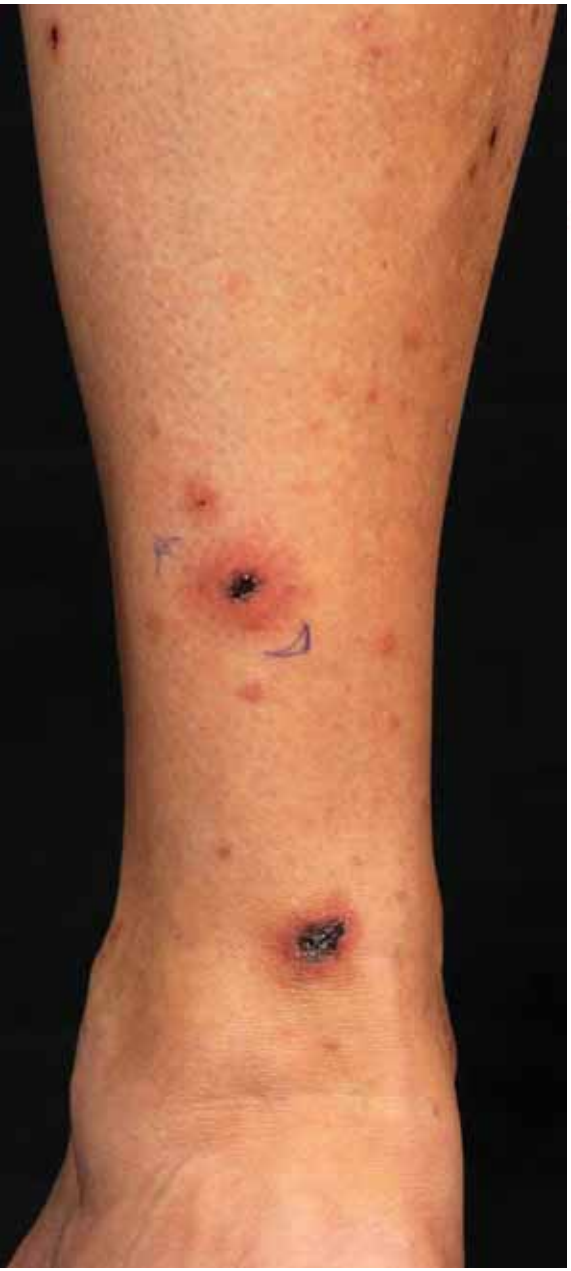


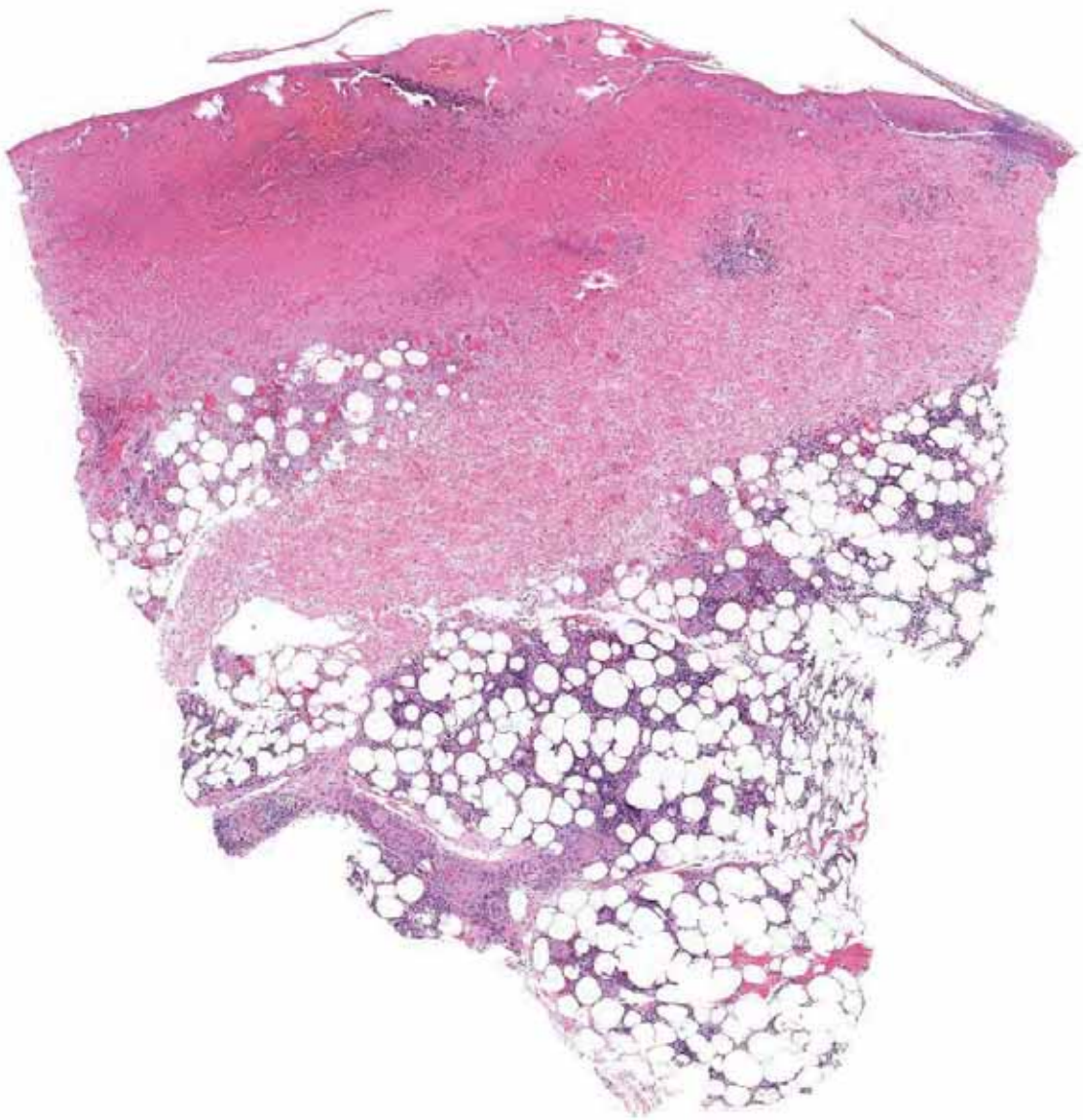
F, 45

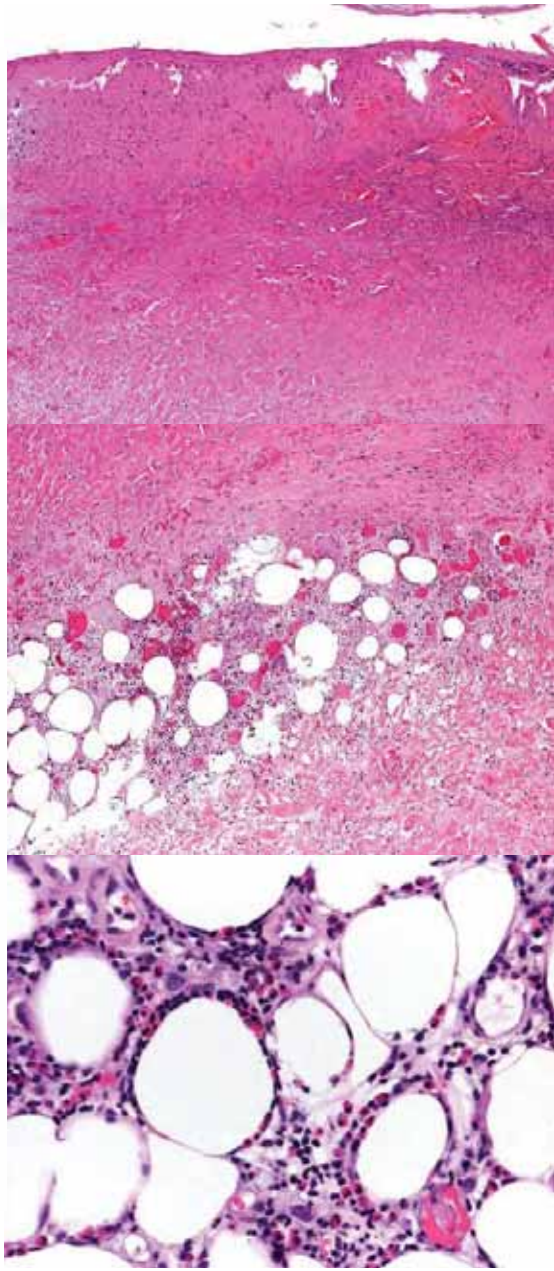
During holiday in Croatia fever, nausea, vomit and diarrhea. Two days later itchy exanthema. Bilateral inguinal and axillary lymphadenopathy.

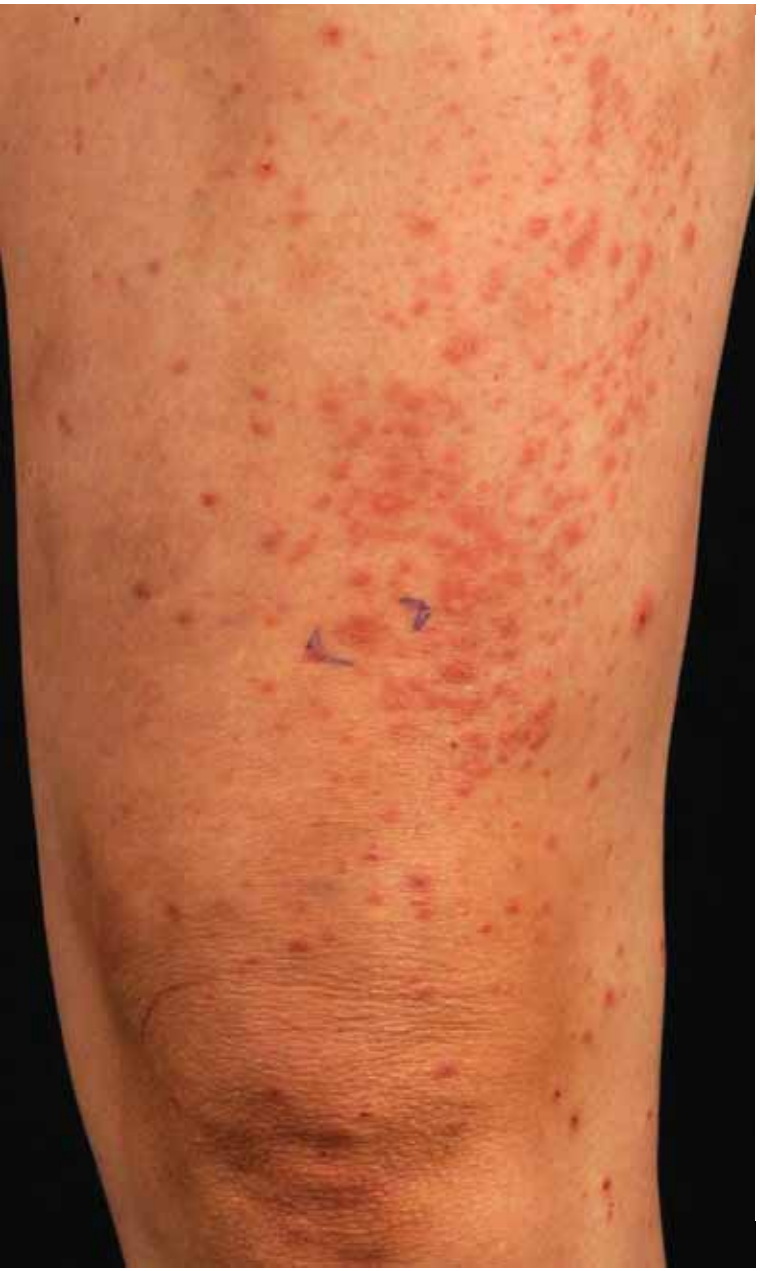
Comes after returning from Croatia with persistent skin lesions (pictures taken 9 days after onset of first symptoms).

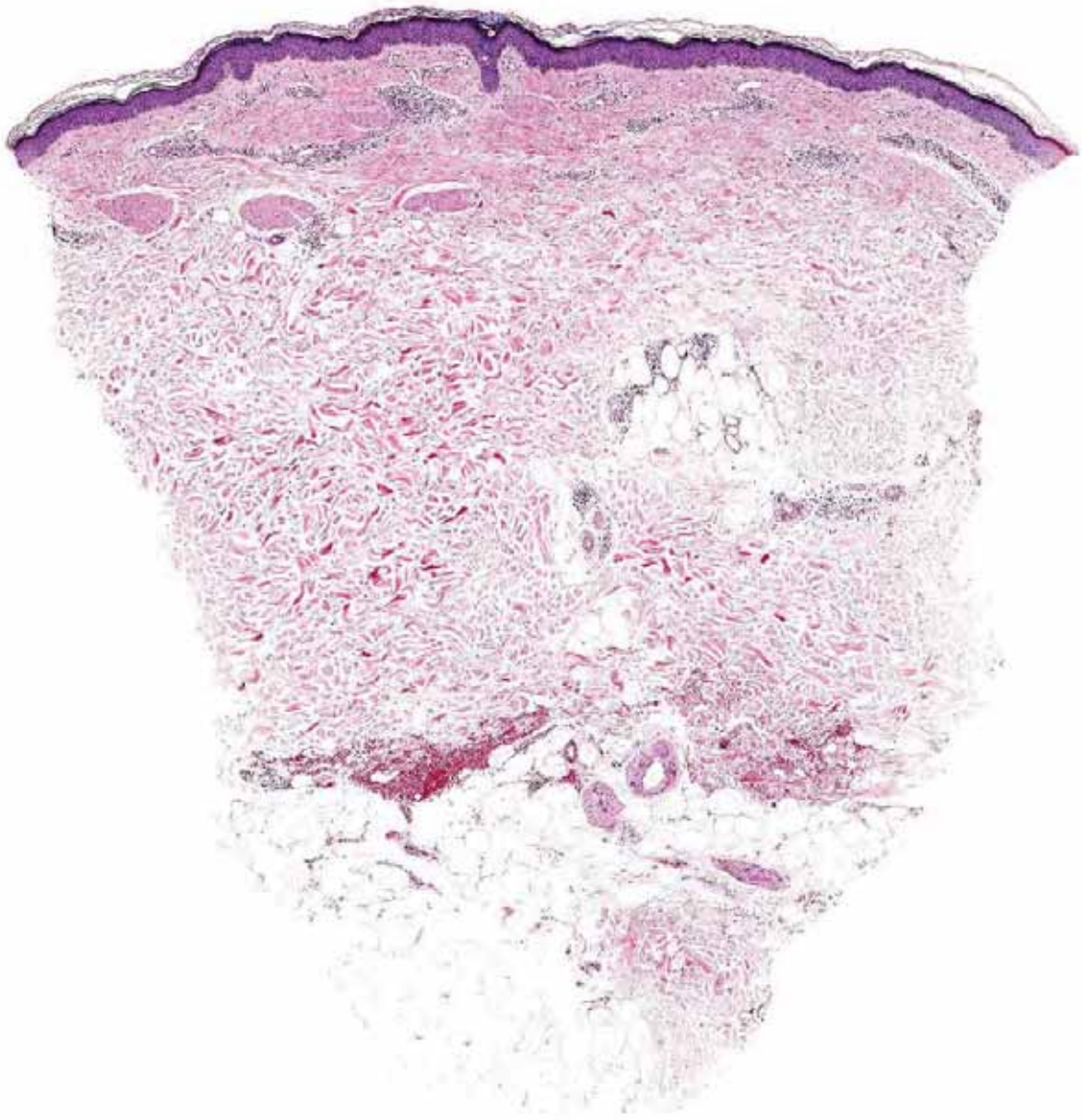
Two biopsies are taken (one from a necrotic and one from a papular lesion).

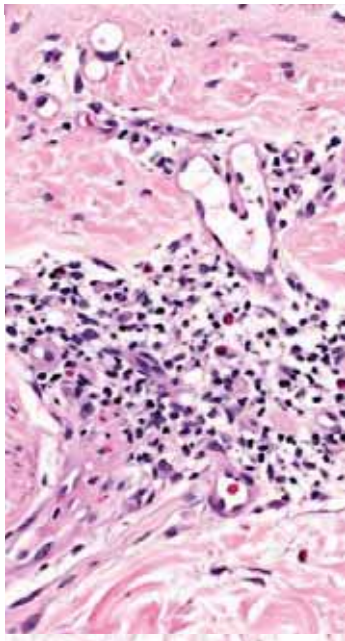


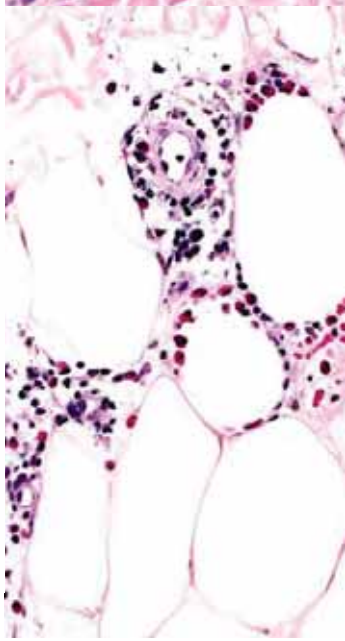


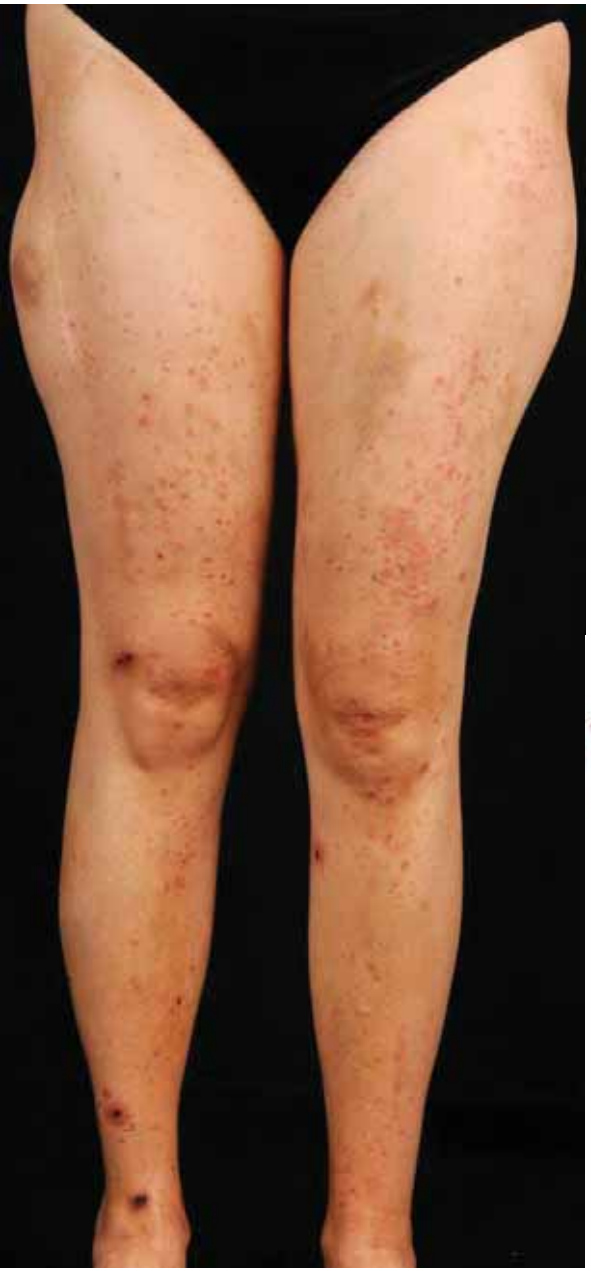


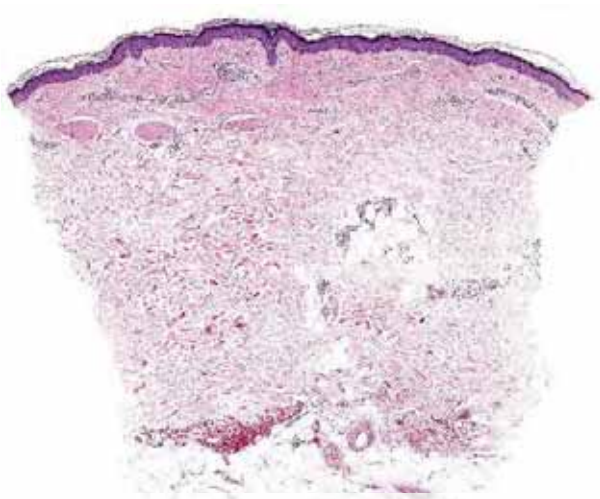




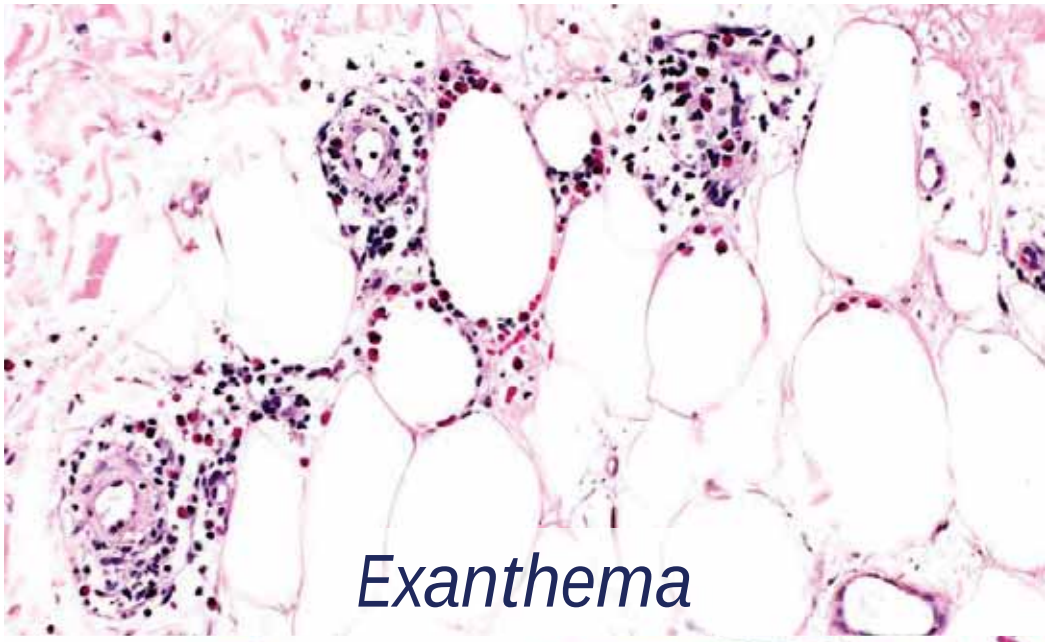




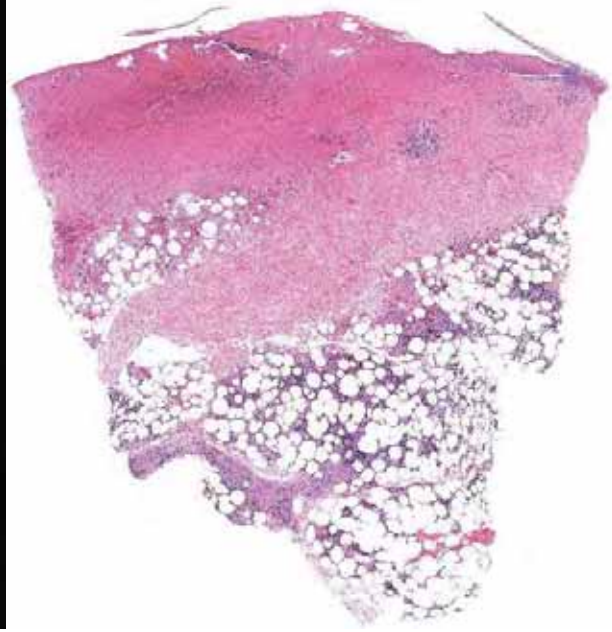


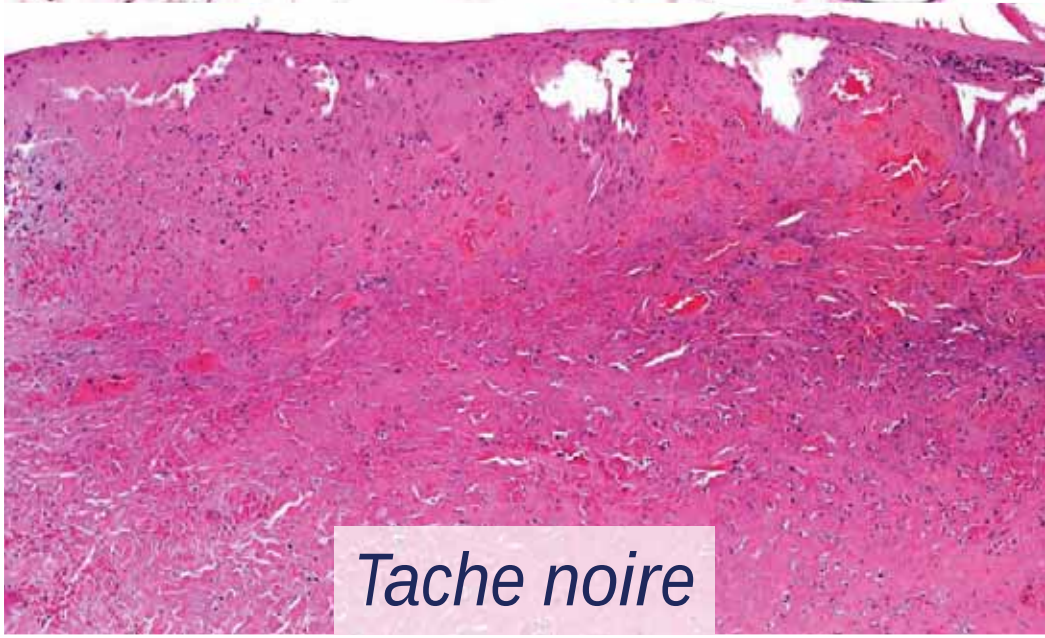


Rickettsiosis



Exanthema





Tache noire

Rickettsial infections (spotted fever group)

- Tache noir at bite site(s) (can be multiple)
- Flu-like symptoms including fever, chills, weakness, vomit, diarrhea and achy muscles
- Subsequent maculo-papulo-(vesicular) rash on the entire body
- Mild course (resolves in 2-3 weeks if untreated); excellent prognosis
- Tache noire: superficial coagulative necrosis with variable inflammation (necrosis may be absent in early lesions)
- Maculopapular lesions: usually features of small vessel vasculitis (hypersensitivity-like reaction in my limited experience)

Mycobacterial infections

- Cutaneous lesions seen mostly in atypical mycobacteriosis (mycobacteria other than TBC – MOTT)
- Cutaneous lesions of TBC nowadays rare in wealthy countries; leprosy still common in endemic countries
- Mostly characterized by granulomatous inflammation with or without caseotic areas; epithelioid (sarcoidal) granulomas typical of tuberculoid leprosy
- Fite-Fandango enzymatic stain highlights the microorganisms in purple and is superior to Ziehl-Neelsen; on the other hand, particularly in MOTT infections the number of microorganisms is often too low to be visible – molecular tests represent the standard for precise characterization

Cutaneous tubercolosis

- Direct inoculation (tuberculous chancre, tuberculosis verrucosa cutis) – neutrophilic abscess surrounded by a granulomatous infiltrate
- Secondary TBC (orificial TBC; scrofuloderma over infected tissues, usually lymph nodes or bones) – extensive caseation necrosis, comparatively few histiocytes
- Lupus vulgaris (hematogenous dissemination) – tuberculoid granulomas with little or no caseation; lymphocytes, plasma cells
- "Tubercolids" (cutaneous immunologic reaction to TBC elsewhere in the body; circulating antigens or small numbers of embolizing dead microorganisms); papulo-necrotic; lichen scrofulosorum; erythema induratum Bazin (in several cases not related to TBC) – vasculitic changes with variable necrosis; (periadnexal) tuberculoid granulomas in lichen scrofulosorum
- Complication at the site of vaccination (local infection causing tuberculoid granulomas with minimal caseation necrosis)

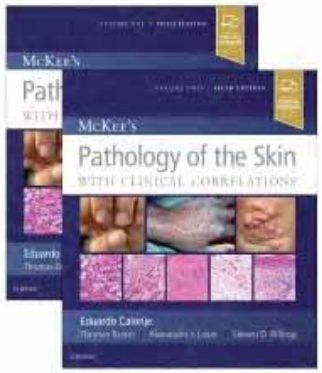
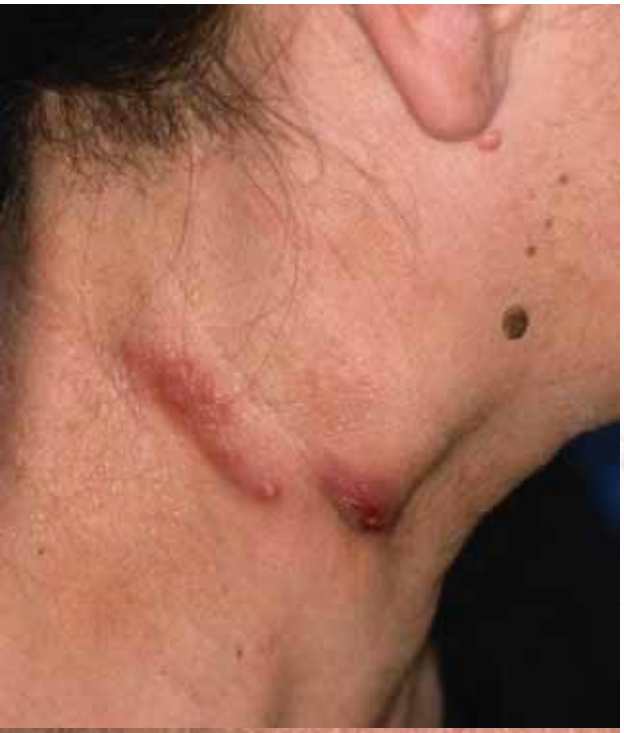
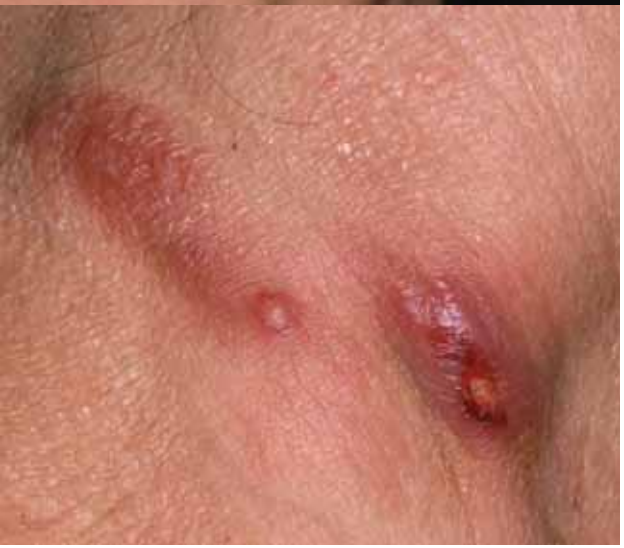
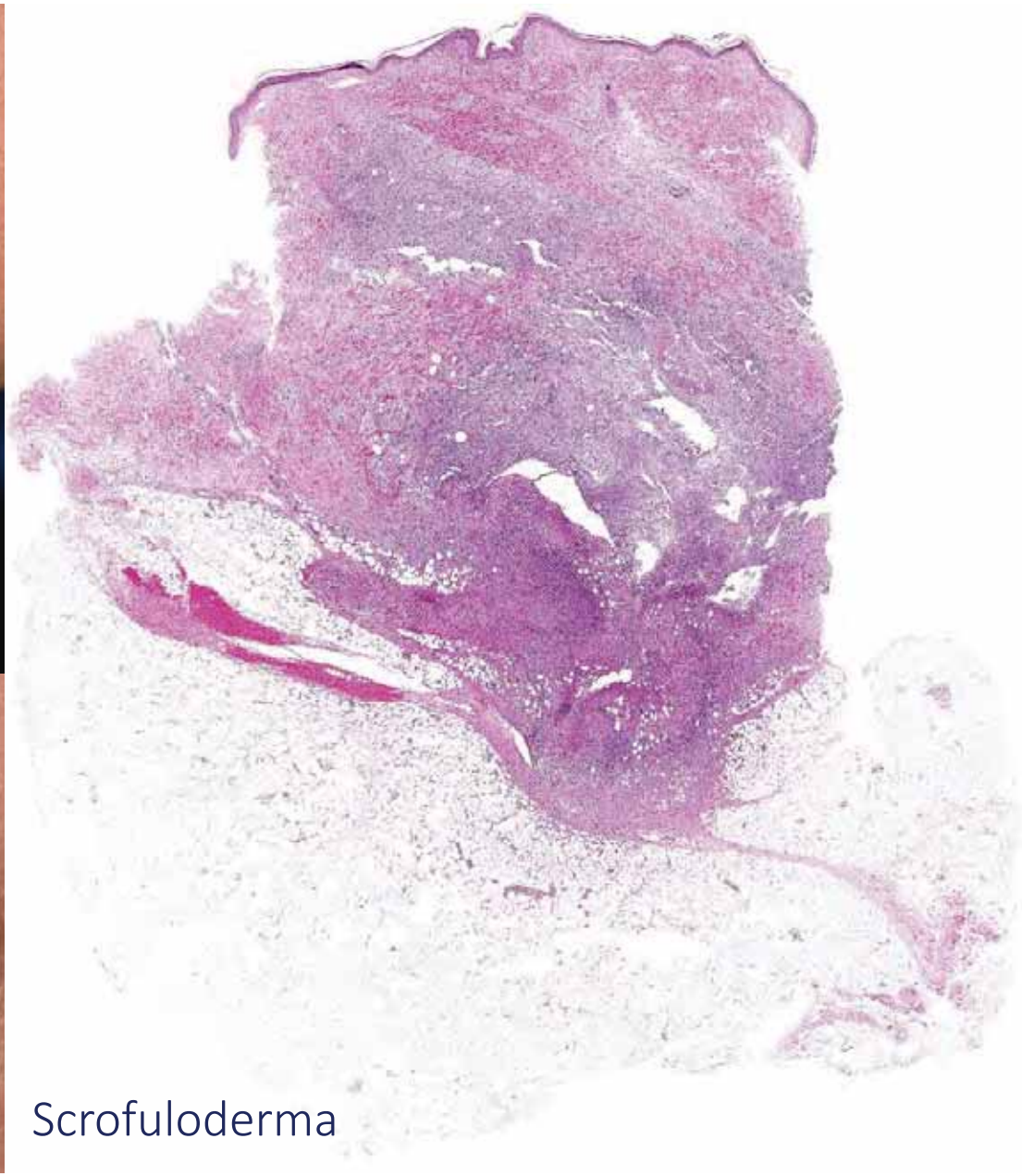


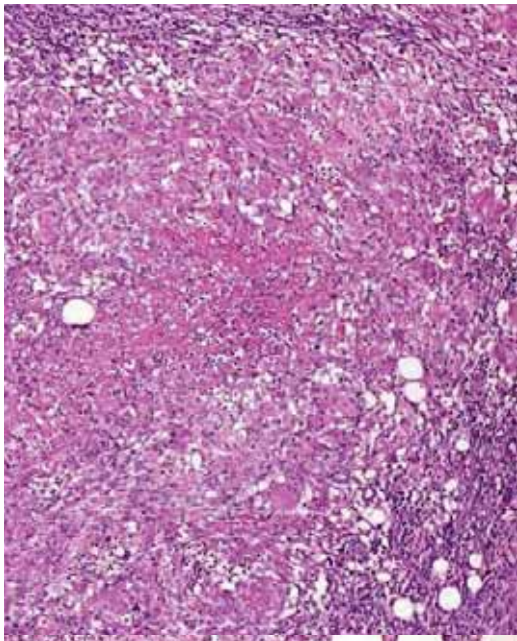
Table 18.2
Variants of cutaneous tuberculosis

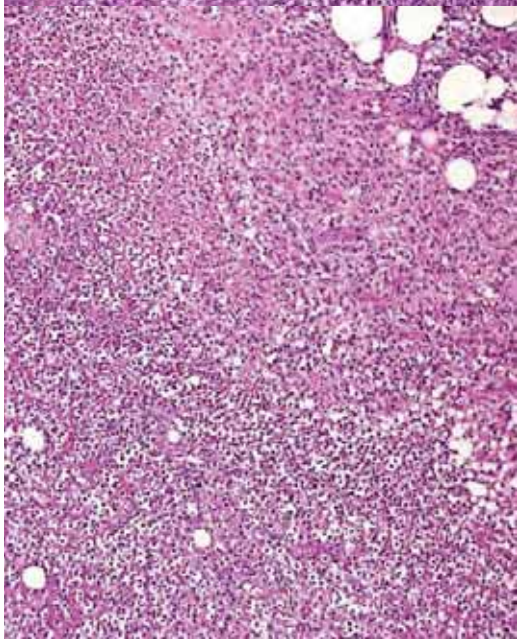
Variant	Route of infection	Association with other TB	Level of infection	Histologic features	Presence of bacilli
Tuberculous chancre	Inoculation	None	Dermis	Neutrophil abscess → caseating granuloma, lymphadenopathy	Present
Warty lupus	Inoculation	Previous or current infection	Dermis	Scanty granulomata, papillomatous acanthosis	Absent or very scanty
Orificial ulcers	Autoinoculation	Active infection in associated organs	Submucosa dermis	Mixed inflammation, few granulomata, necrosis	Numerous
Lupus vulgaris	Inoculation and/or hematogenous	Previous or current, often occult, infection	Superficial dermis	Variable but granulomata, little caseation prominent	May be seen in deep aspect
Scrofuloderma	Extension from underlying infection	Active infection	Subcutaneous and dermal	Mixed inflammation, granuloma, marked fibrosis	May be seen in deep aspect
Tuberculous gumma	Hematogenous	Systemic infection	Subcutaneous	Much caseation, granulomatous fibrosis	Scanty
Miliary tuberculosis	Hematogenous	Systemic infection	Dermis	Central abscess, with surrounding histiocytic infiltrate	Absent or scanty in benign form; present in aggressive form



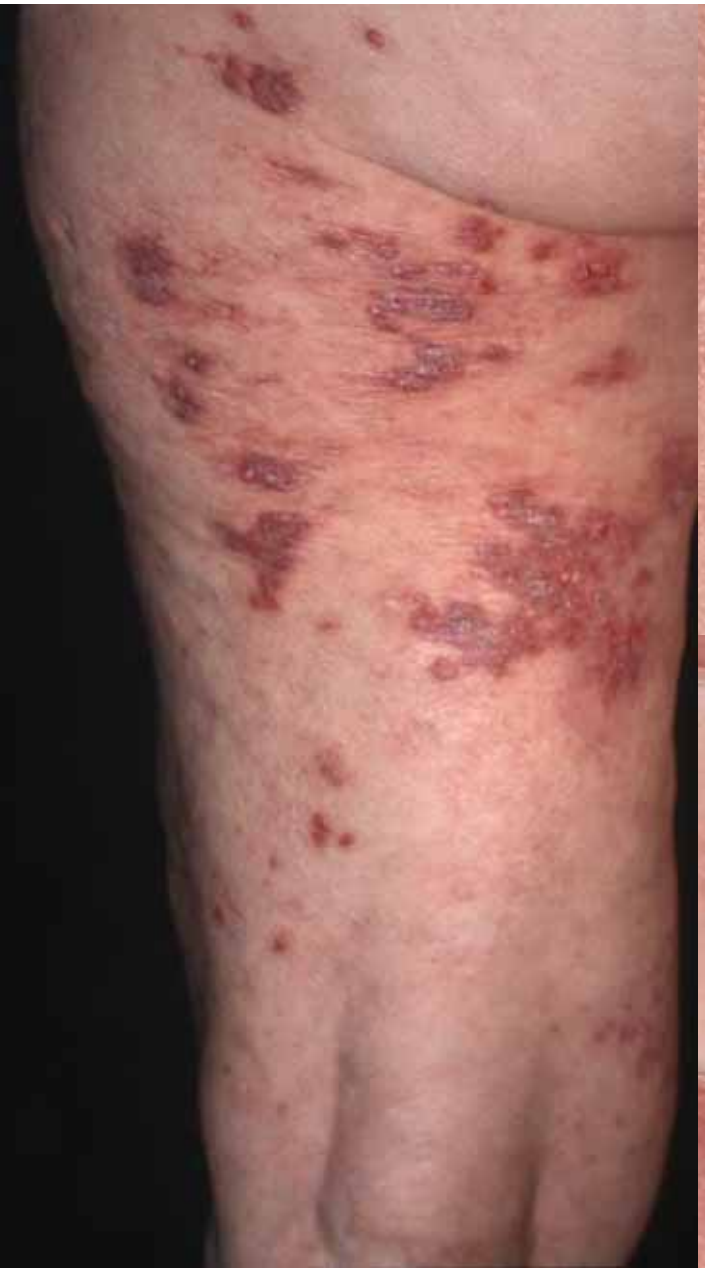


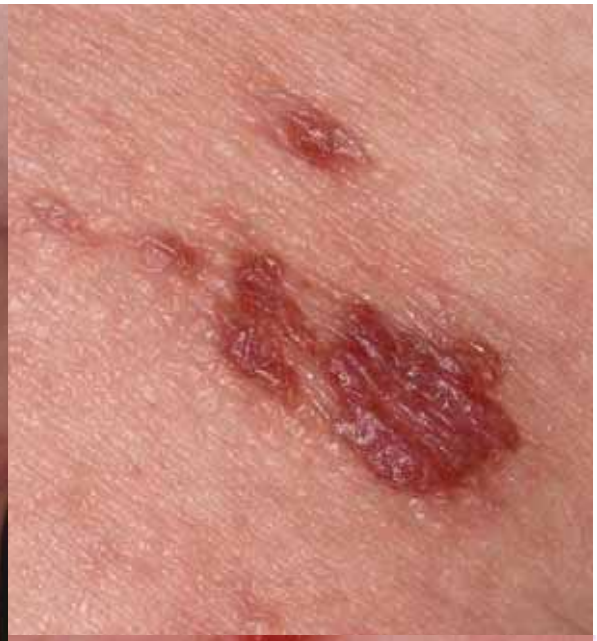


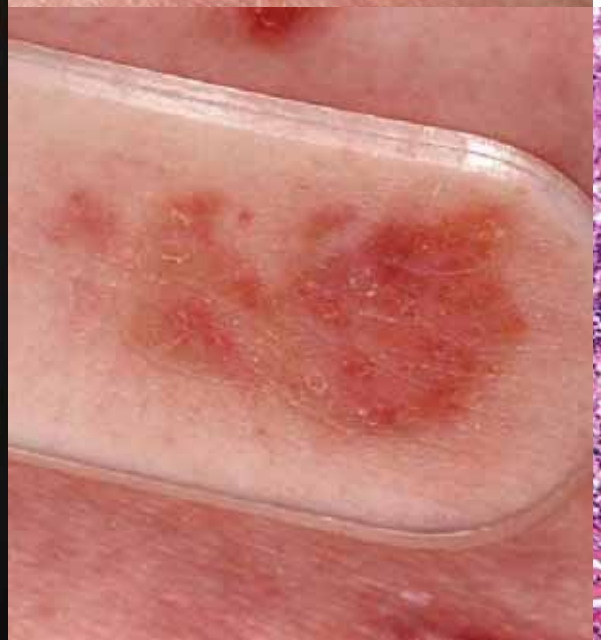


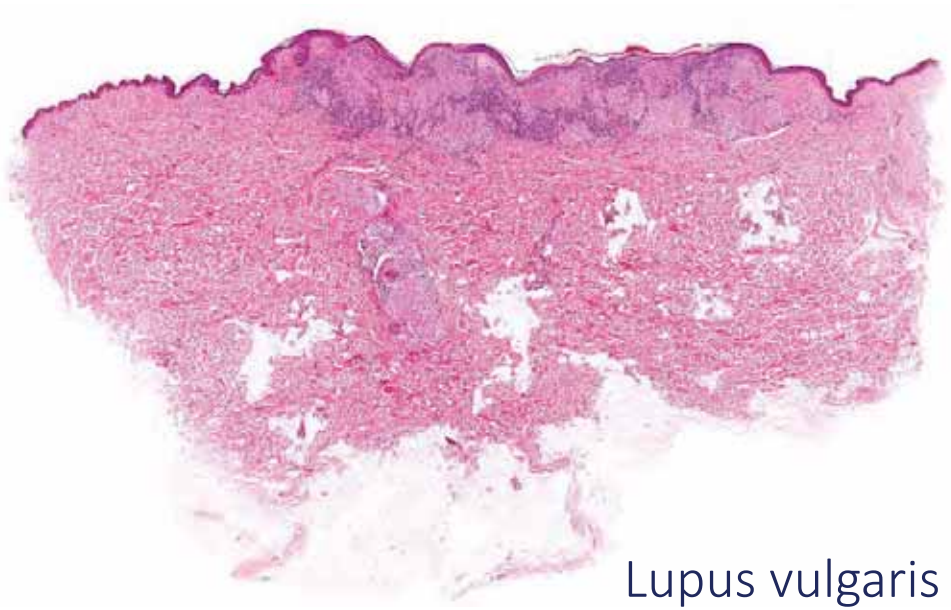


Scrofuloderma

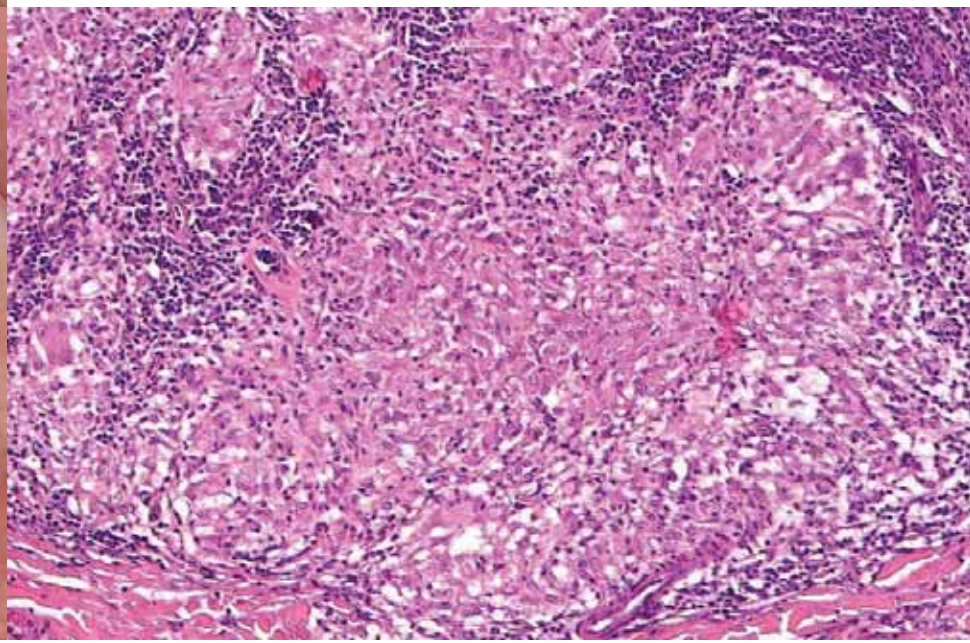


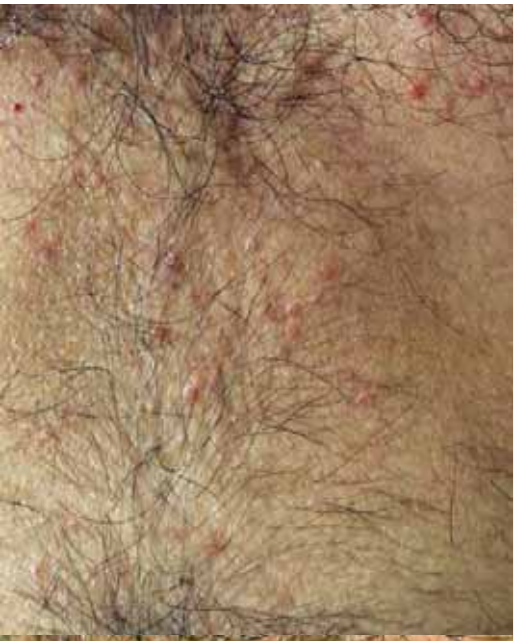


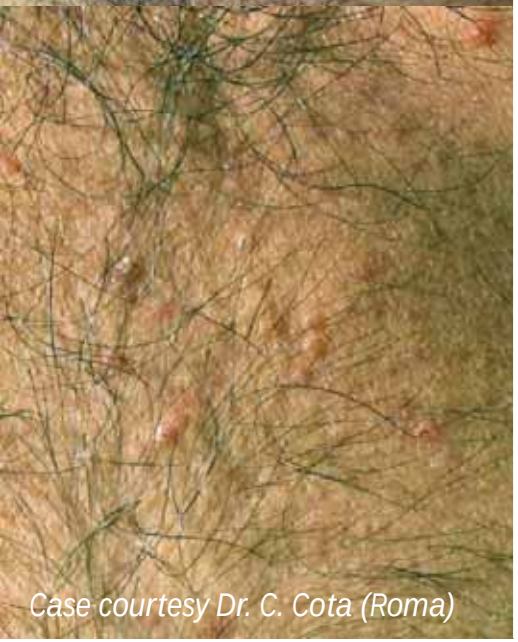




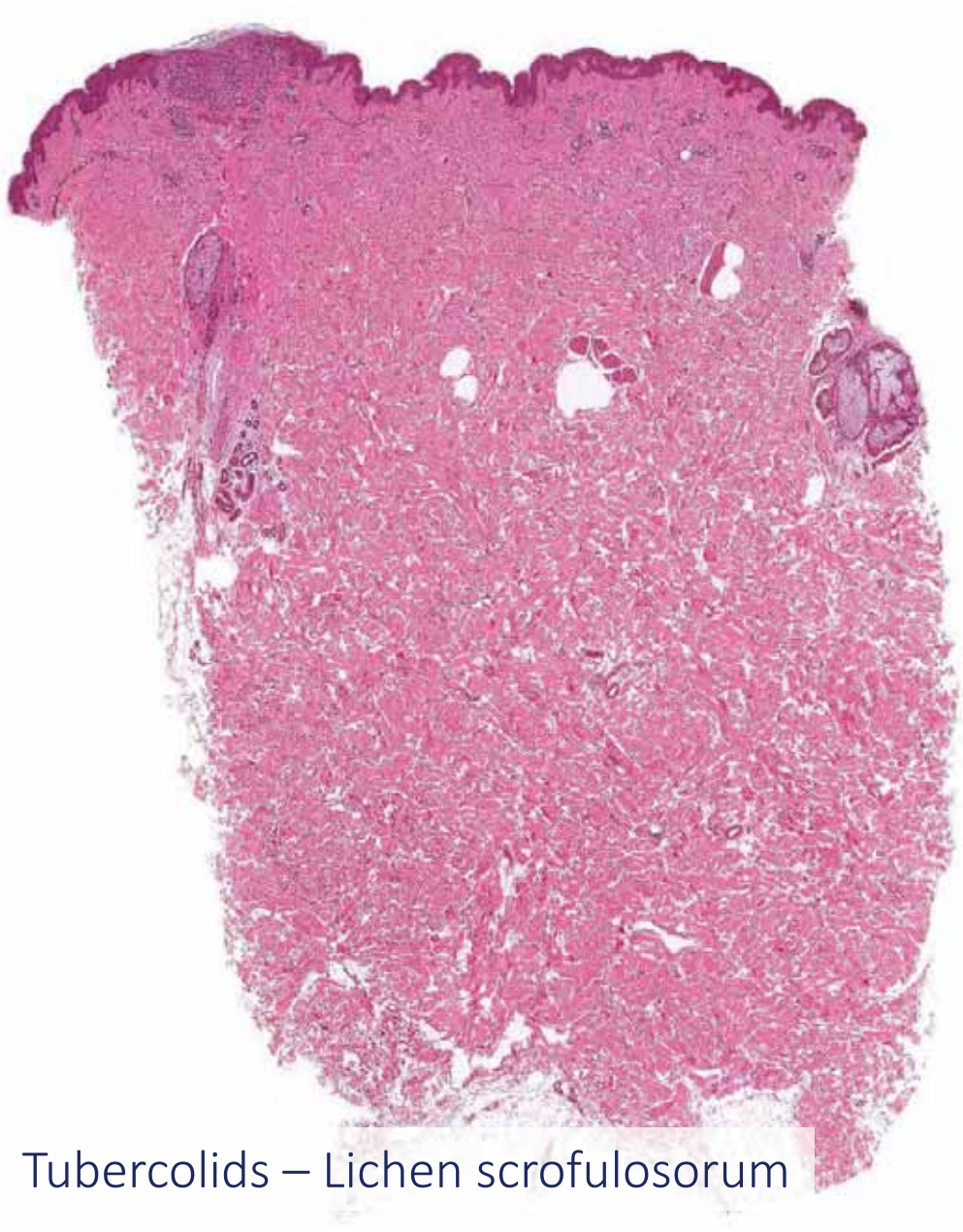
Lupus vulgaris

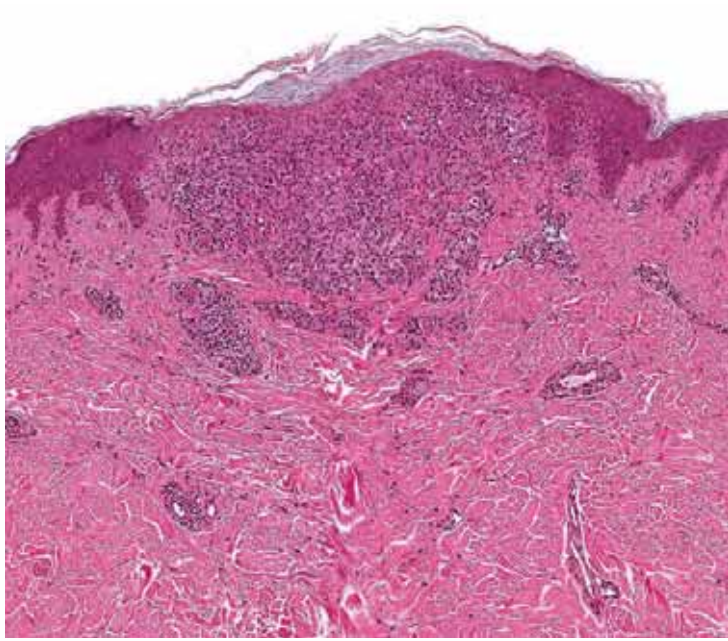


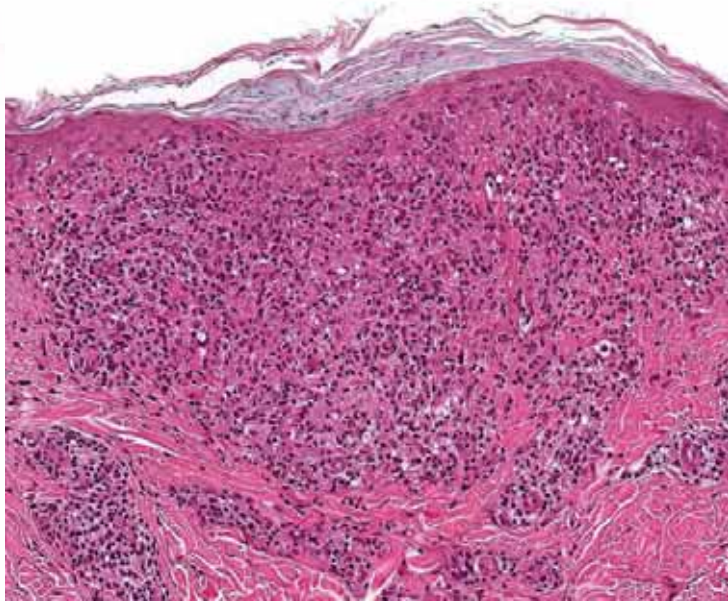




Case courtesy Dr. C. Cota (Roma)







Tubercolids – Lichen scrofulosorum

Lichen Scrofulosorum Mimicking Lichen Planus

Diana Camacho, MD, Úrsula Pielacinski, MD,* Juan María Revelles, MD,* Miguel Górgolas, MD,† Félix Manzarbeitia, MD,‡ Heinz Kutzner, MD,§ and Luis Requena, MD**

Abstract: Lichen scrofulosorum is the most uncommon clinicopathologic variant of the tuberculids. Usually, the eruption appears in children and adolescents with strong immune sensitivity to *Mycobacterium tuberculosis* and consists of tiny follicular papules, closely resembling lichen nitidus. We report a case of lichen scrofulosorum in an adult male with active cervical scrofuloderma who developed lesions of lichen scrofulosorum mimicking clinically lichen planus. Histopathologic study demonstrated granulomas around the hair follicles, although acid-fast bacilli stains, immunohistochemical stain for mycobacteria, polymerase chain reaction investigations and cultures failed to demonstrate *Mycobacterium tuberculosis* in the cutaneous lesions. The most striking features of the reported case were the onset of the eruption in an adult patient and the clinical appearance of the lesions, resembling lichen planus.

Key Words: cutaneous tuberculosis, immunohistochemistry, lichen scrofulosorum, *Mycobacterium tuberculosis*, PCR, tuberculids

(*Am J Dermatopathol* 2011;33:186–191)

Tuberculids comprise a heterogeneous group of cutaneous disorders, which occur in association with internal tuberculosis in patients with a high degree of hypersensitivity response against *Mycobacterium tuberculosis*. Currently, within the spectrum of tuberculids, there are disorders in which *M. tuberculosis* seems to play a significant role, such as lichen scrofulosorum and papulonecrotic tuberculid, and other facultative tuberculids, in which *Mycobacterium tuberculosis* may be one of several pathogenic factors. This latter group of facultative tuberculids includes the panniculitic processes erythema induratum of Bazin and tuberculous erythema nodosum.[1] Recently, nodular granulomatous phlebitis of the skin has been added as an additional clinicopathologic variant of tuberculid.[2]

Lichen scrofulosorum is the most uncommon tuberculid, which is considered the result of hematogenous spread of mycobacteria in a patient strongly sensitive to *M. tuberculosis*. In most cases, it is associated with active chronic tuberculosis of the lymph nodes, bones, or pleura. Clinically, cutaneous lesions of lichen scrofulosorum consist of small follicular or perifollicular, flat-topped erythematous, or yellowish papules, preferably located on the trunk. The process occurs most often in children and adolescents, and usually the lesions resemble clinically to those of lichen nitidus. We present a case of lichen scrofulosorum in an adult male with active cervical scrofuloderma, who developed lichen scrofulosorum mimicking clinically lichen planus.

CASE REPORT

A previously healthy 67-year-old male presented with a mass draining purulent material on the right supraclavicular region. This mass had appeared 2 weeks earlier, and there were no systemic signs or symptoms. Physical examination of the respiratory, cardiovascular, and central nervous systems did not demonstrate abnormalities. Laboratory anomalies included discrete anemia (hemoglobin, 11.5 g/dL) and raised erythrocyte sedimentation rate (57 mm in the first hour). Blood biochemistry and urinalysis yielded normal or negative results. Serologic tests for HIV, hepatitis B, and C viruses and for syphilis also resulted negative. However, Mantoux test was strongly positive, with an induration of 20 mm at 48 hours and Quantiferon test (a serological test that measures specific antigen-driven interferon-γ synthesis by whole blood cells against *M. tuberculosis*) was also positive. Xray of the chest showed no anomalies, but a computed tomography of the chest demonstrated a soft-tissue mass adjacent to the right sternocleidomastoid muscle. A fine needle aspiration of that mass evidenced no malignant cells and the acid-fast bacilli stains (Ziehl-Neelsen and Auramine-Rhodamine) failed to demonstrate mycobacteria. A presumptive diagnosis of scrofuloderma was established, and the patient was discharged home with a triple-drug antituberculous therapy, including isoniazid, rifampicin, and pyrazinamide. However, after 8 weeks of incubation of the aspirated material in Lowenstein-Jensen medium, a positive culture for isoniazid-resistant *M. tuberculosis* was obtained. Then, isoniazid was withdrawn, and ethambutol was added to the therapeutic regimen.

Three months later, the patient returned with healed lesions of cervical scrofuloderma, but an asymptomatic papular eruption had appeared over the trunk and extremities. The eruption had started 2 weeks after introducing the last antituberculous drug regimen. Dermatologic examination revealed flat-topped, polygonal and sharply defined erythematous and violaceous papules with shiny surface grouped on the lower back (Fig. 1). The size of the lesions ranged from 5 to 10 mm in diameter. Although most lesions grouped on the lower back, there were also a few lesions with similar morphology scattered on the anterior chest (Fig. 2), upper and lower extremities. Interestingly, confluent erythematous papules developed on the anterior aspect of the left forearm at the site where the Mantoux test had been performed 3 months earlier (Fig. 2). After 4 months of tuberculostatic drug regimen treatment, the cutaneous lesions have decreased in number and size.

Histopathologic study of a papule from the lower back demonstrated normal epidermis and multiple granulomas involving the upper and mid dermis, which were mostly arranged around the

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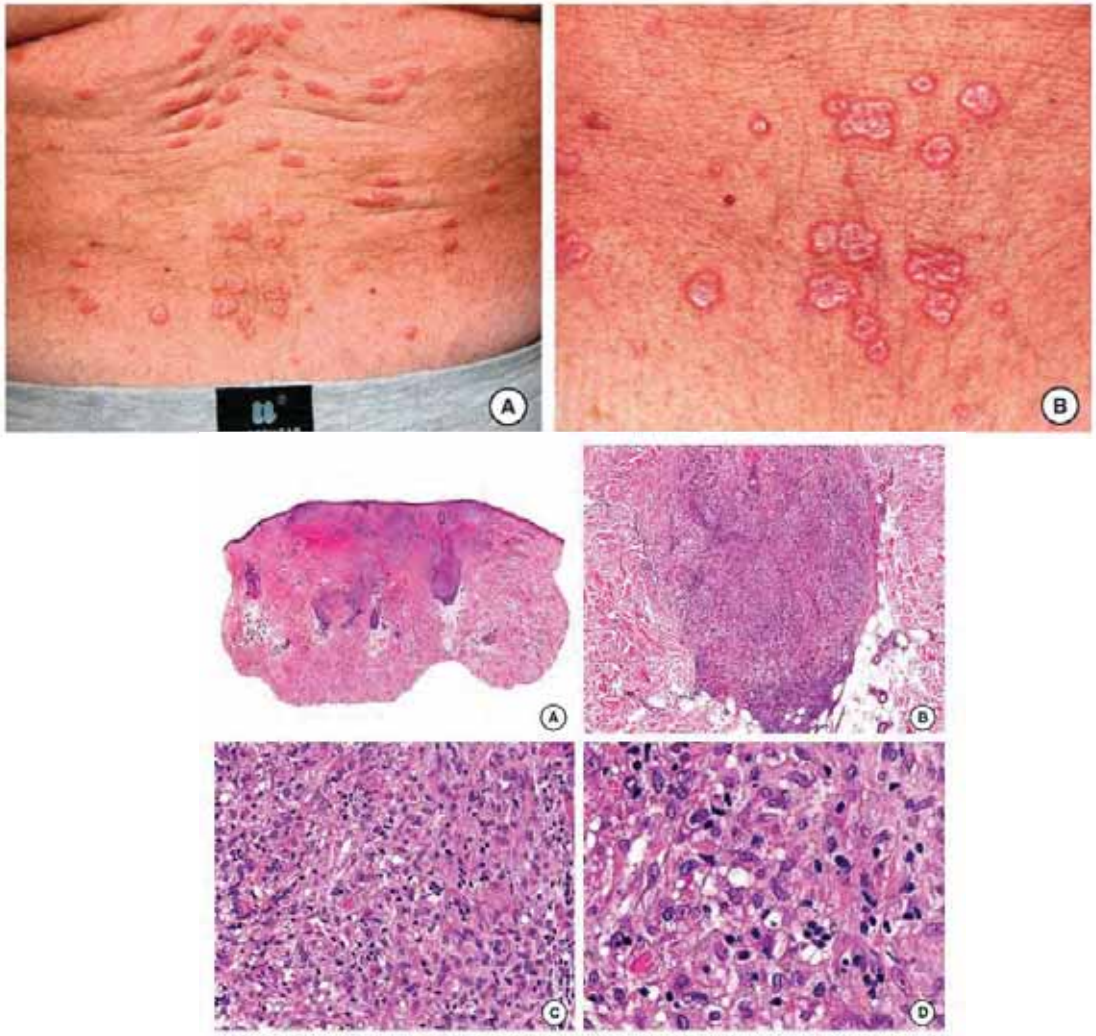
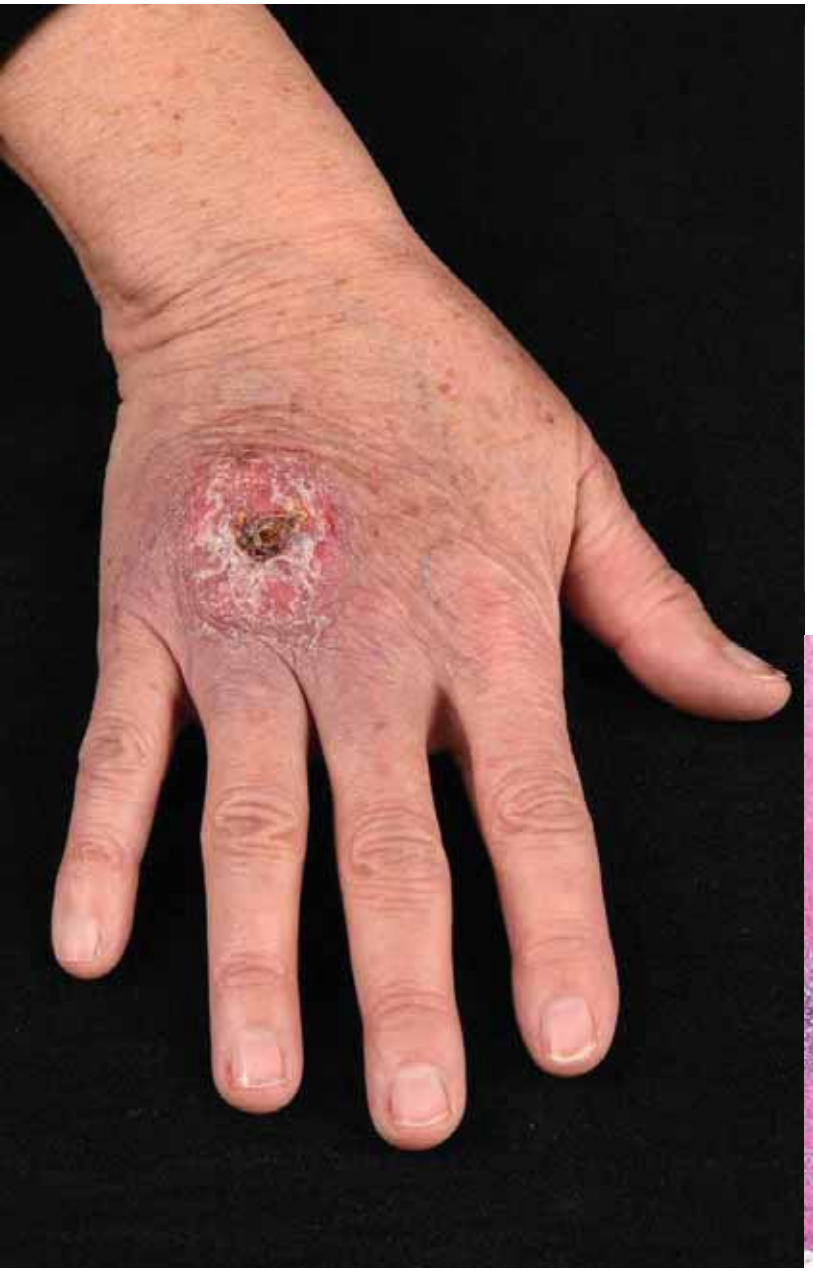
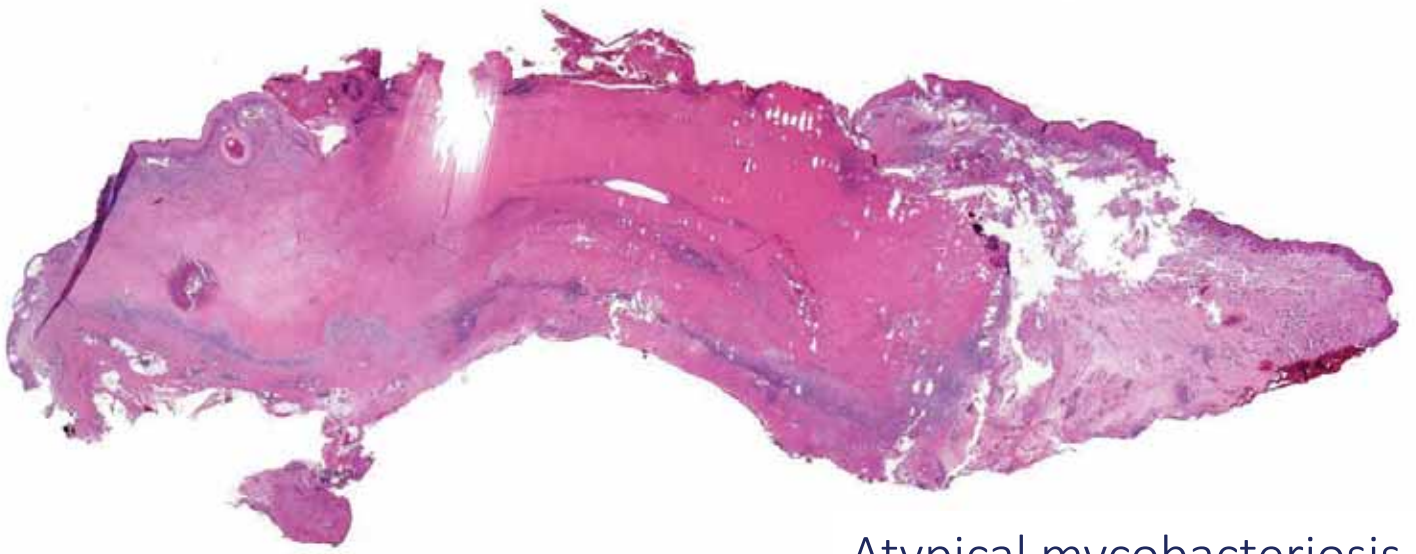


FIGURE 3. Histopathologic features. A, Scanning power view showing nodular infiltrates involving superficial and mid dermis. B, The nodules of the infiltrate were mostly arranged around the hair follicles. C, Higher magnification demonstrated the granulomatous nature of the infiltrate, mostly composed of epithelioid histiocytes. D, Still higher magnification demonstrated that the histiocytes showed vesicular nuclei and large eosinophilic cytoplasm with some vacuolization.

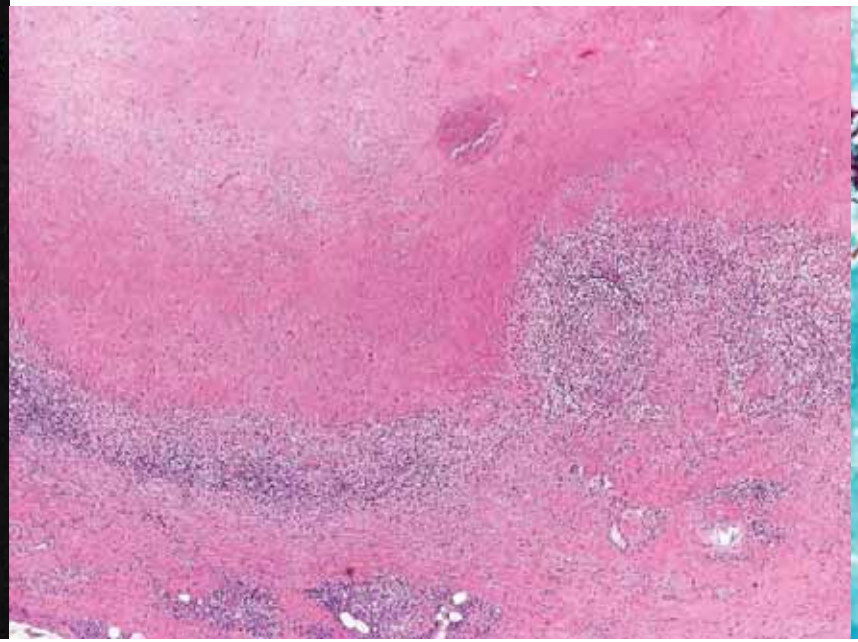
Atypical mycobacteriosis

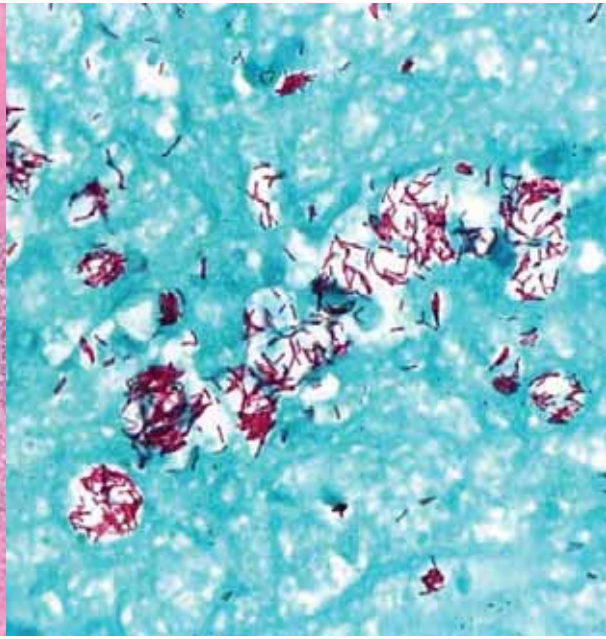
- Usually granulomatous infiltrates without prominent necrosis; extensive necrosis observed in Buruli ulcer *(M. ulcerans) (encountered in Central and West Africa, New Guinea, Australia, Southeast Asia, Mexico, and Japan)*
- Clinically sometimes sporotrichoid pattern, particularly in *M. marinum*
- Usually few microorganisms (if any) detectable with conventional stainings; more abundant in *M. ulcerans*
- Molecular tests allow to characterize the responsible microorganism with precision





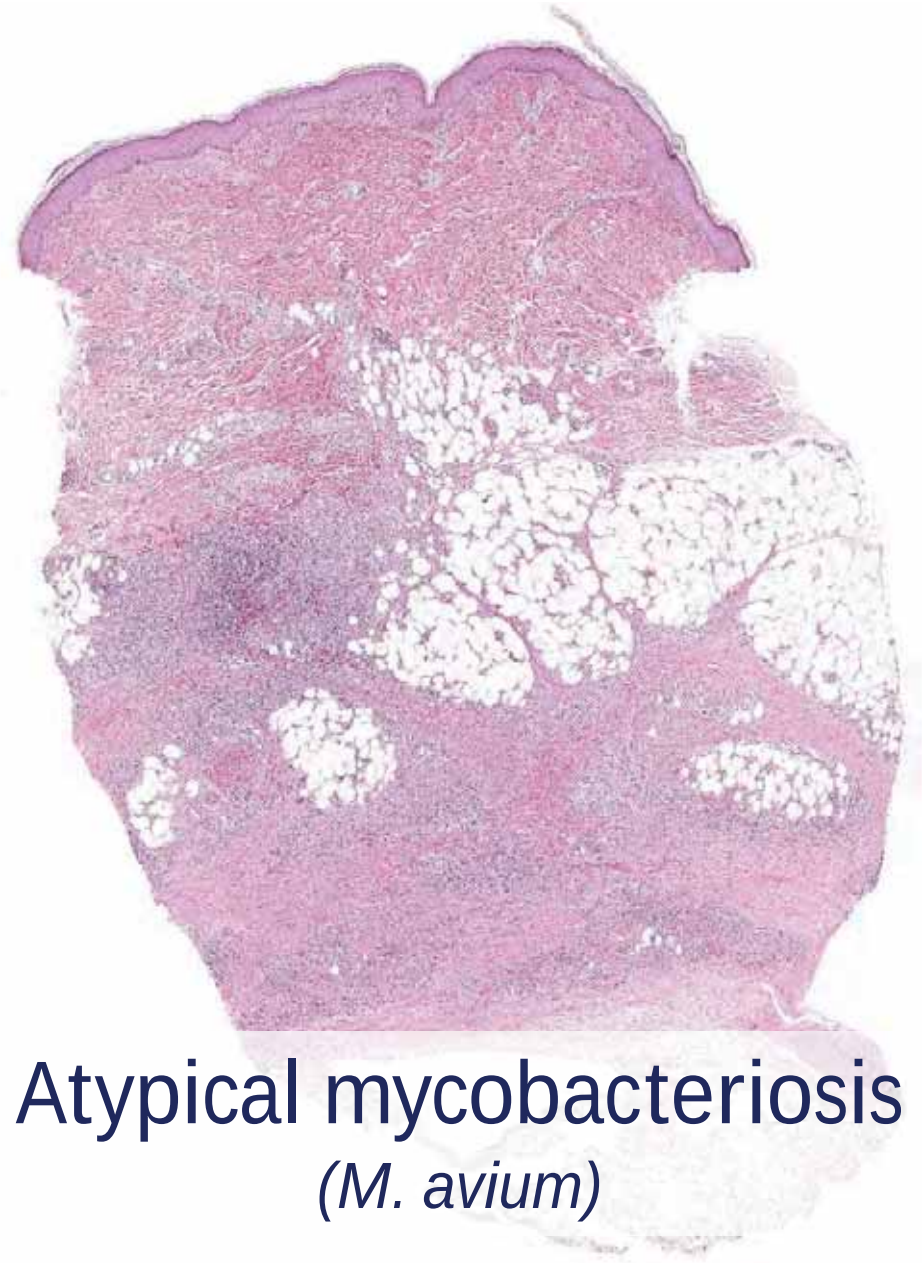
Atypical mycobacteriosis





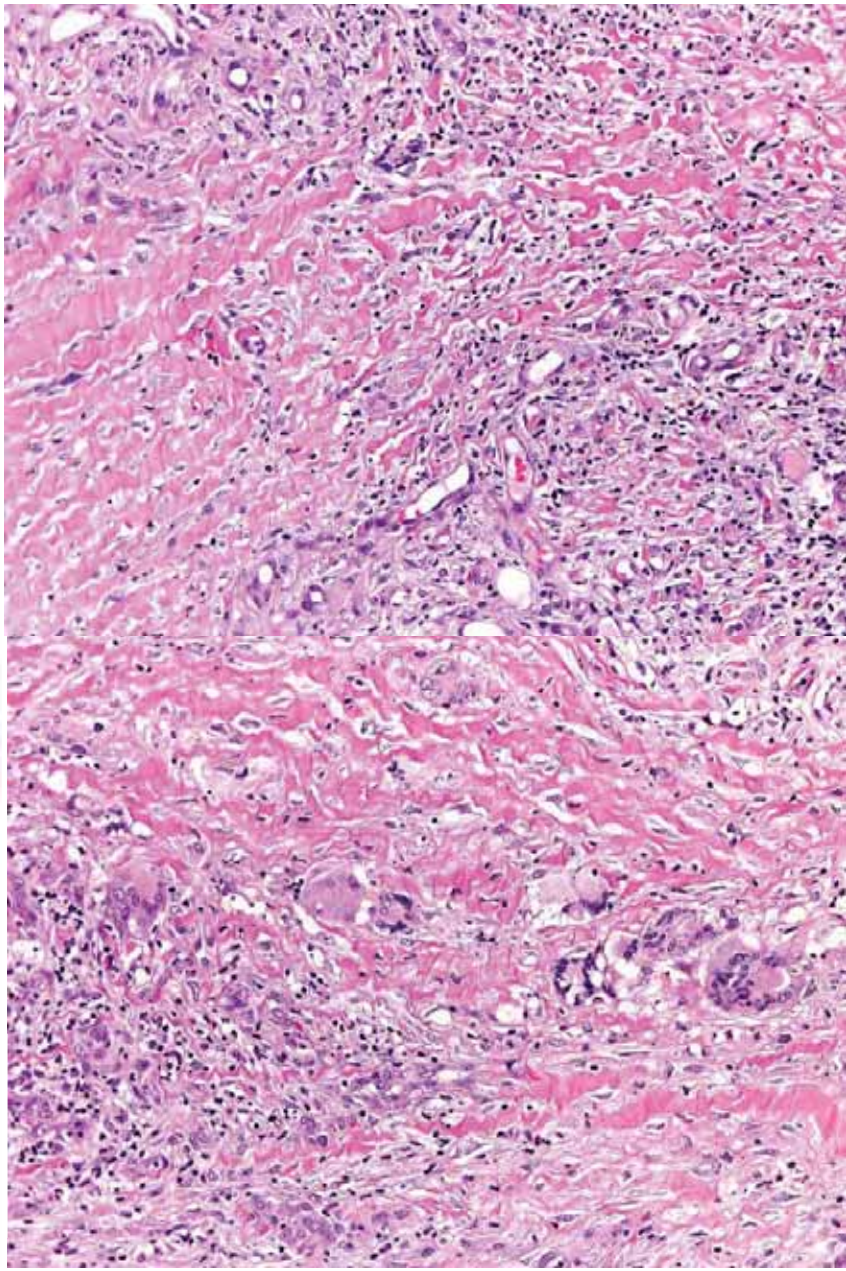
F, 37

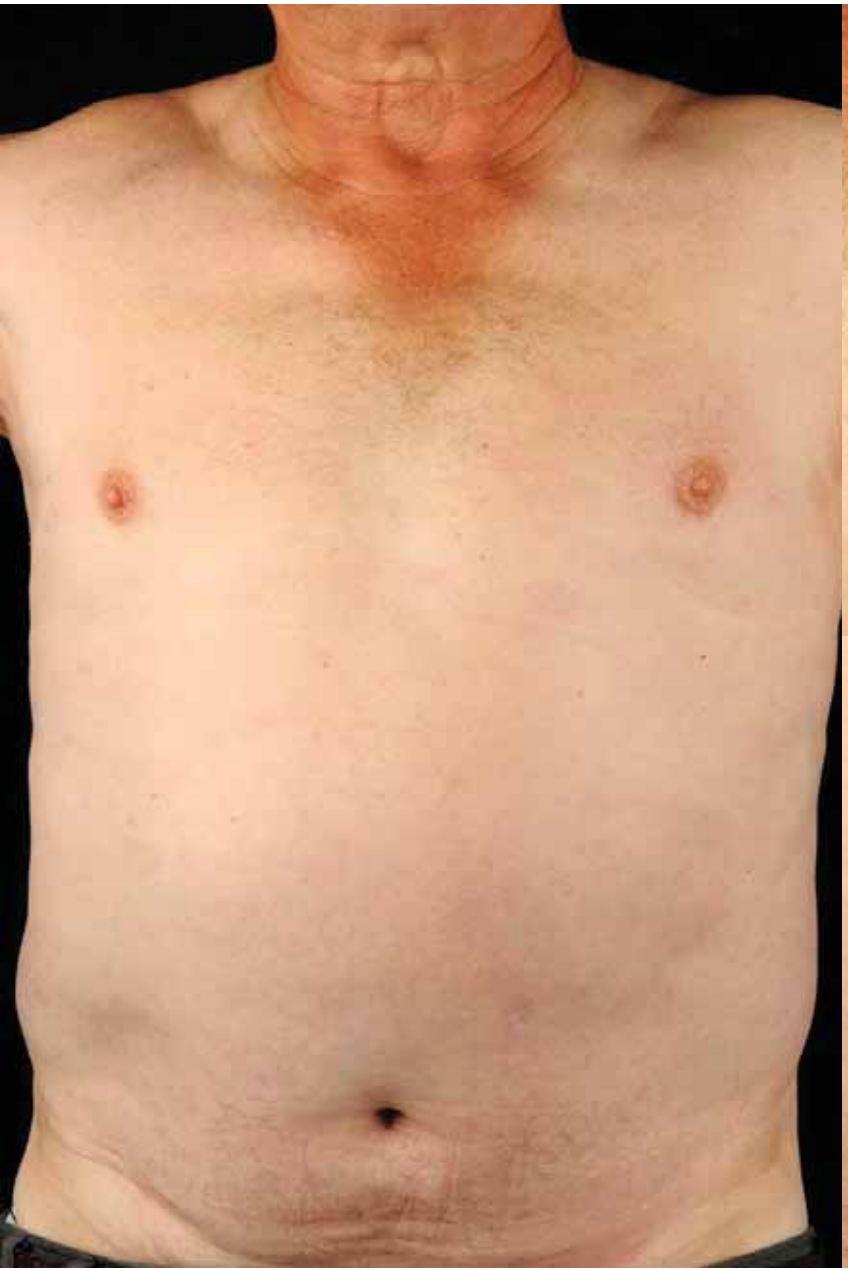
History of tattoo 4 months before presentation. According to the patient onset of skin lesions on and near the tattoo a few weeks afterwards, slowly growing.

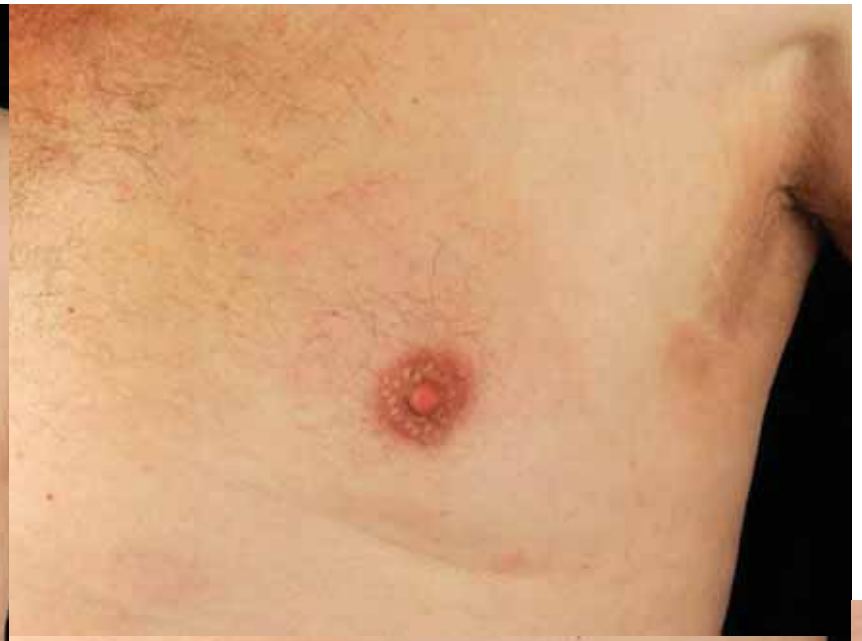


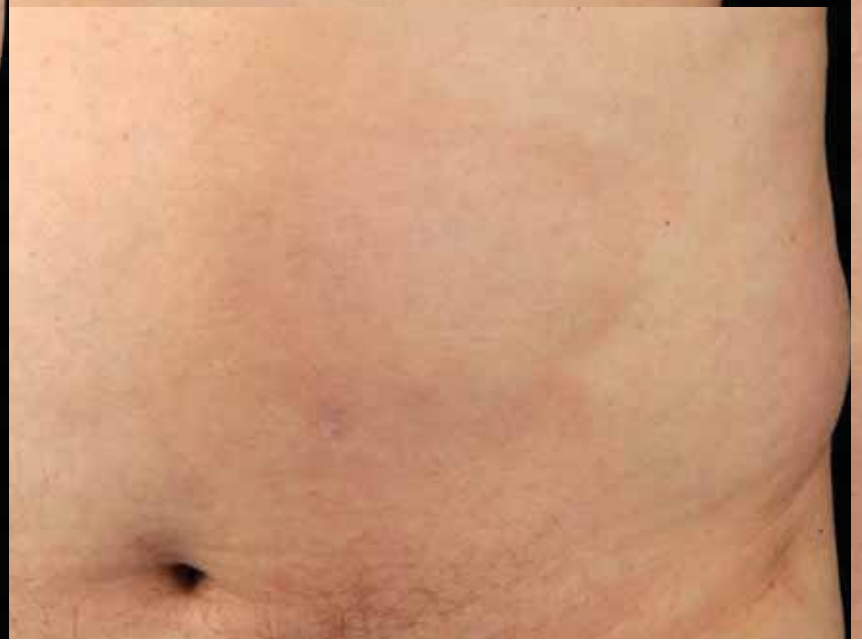
Atypical mycobacteriosis

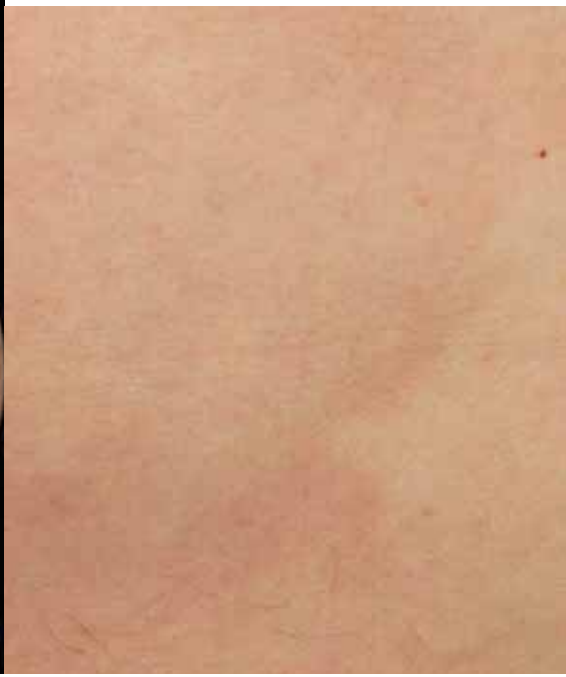
(M. avium)







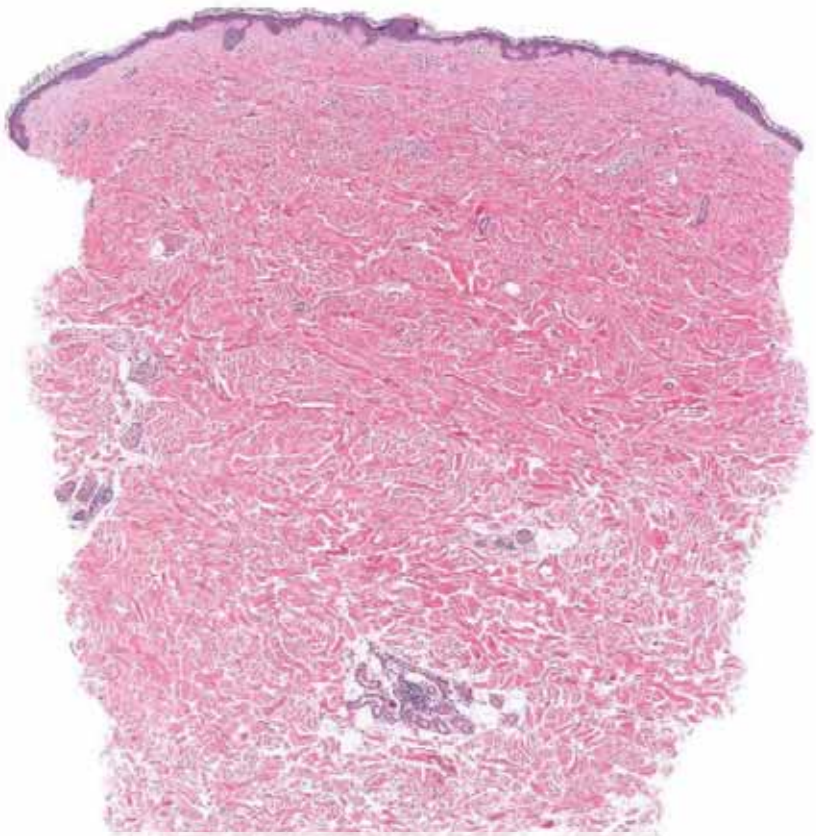




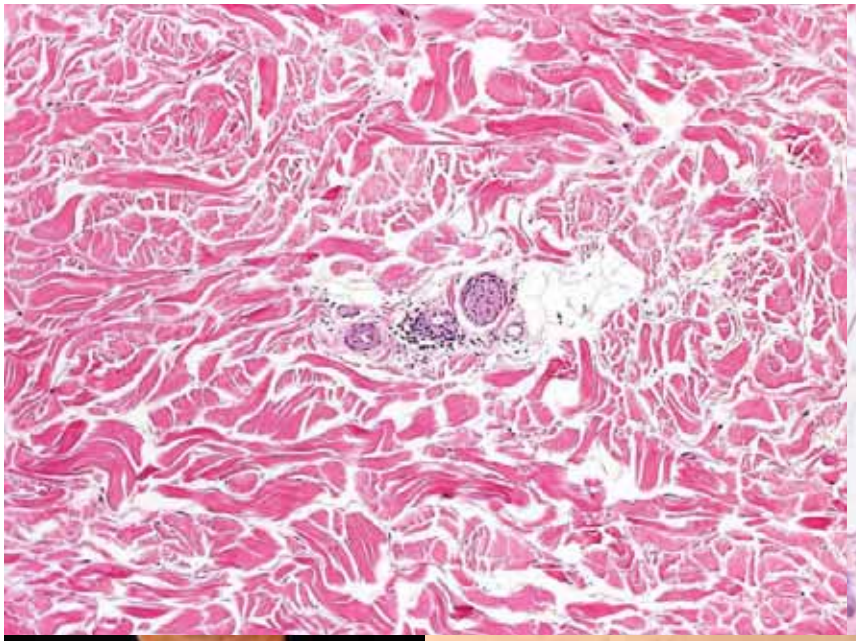
M, 71

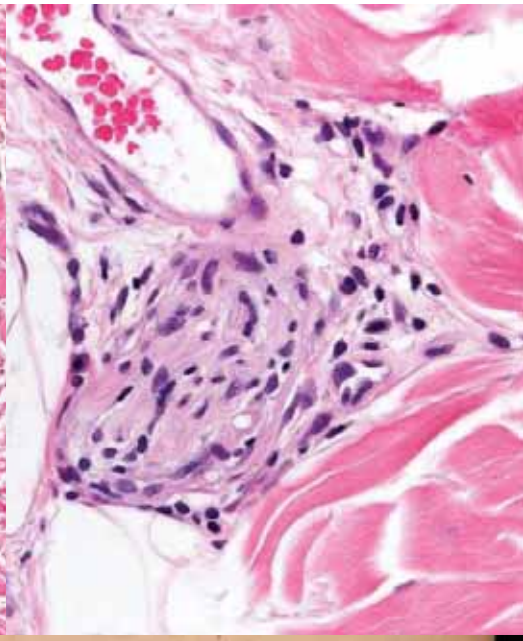
Lesions on the abdomen and pectoral regions ("lilac ring"-like) for 5-6 years. Previously treated with doxycycline for erythema migrans (no improvement).

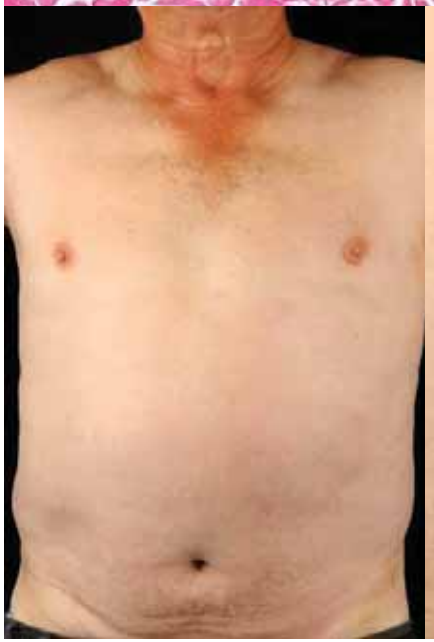
A biopsy is taken under the clinical diagnosis of morphea.

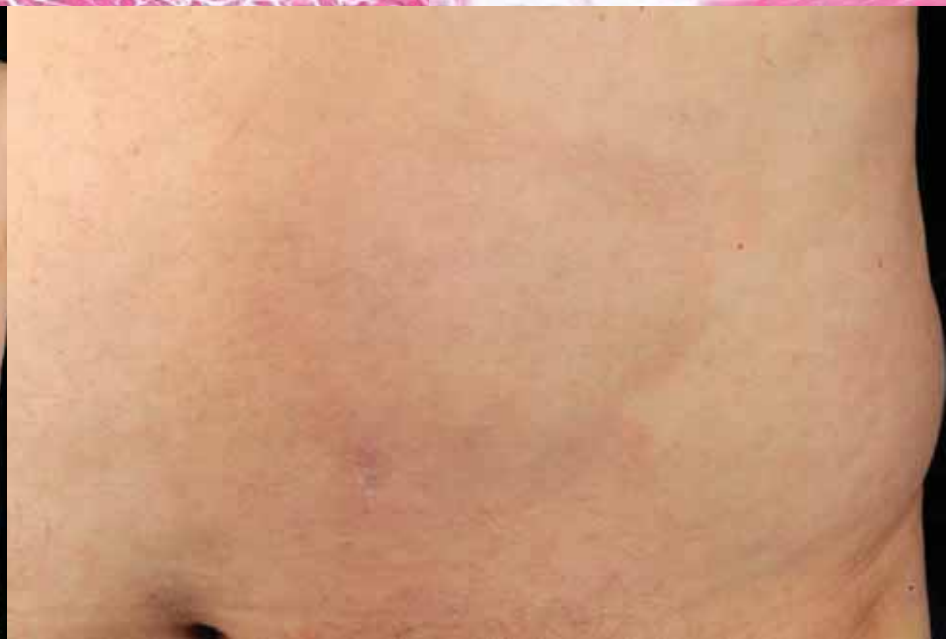


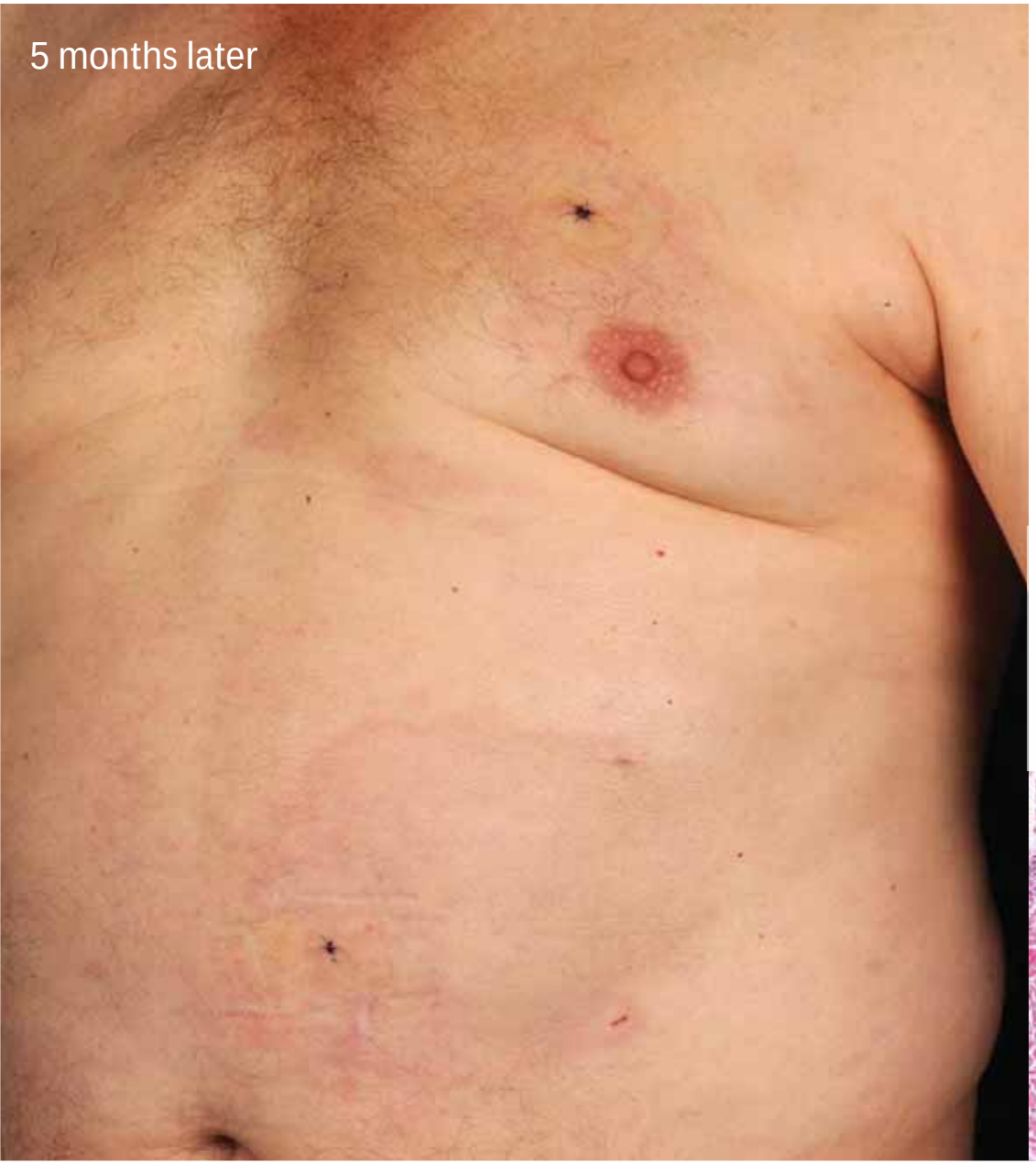
Reported as consistent with morphea

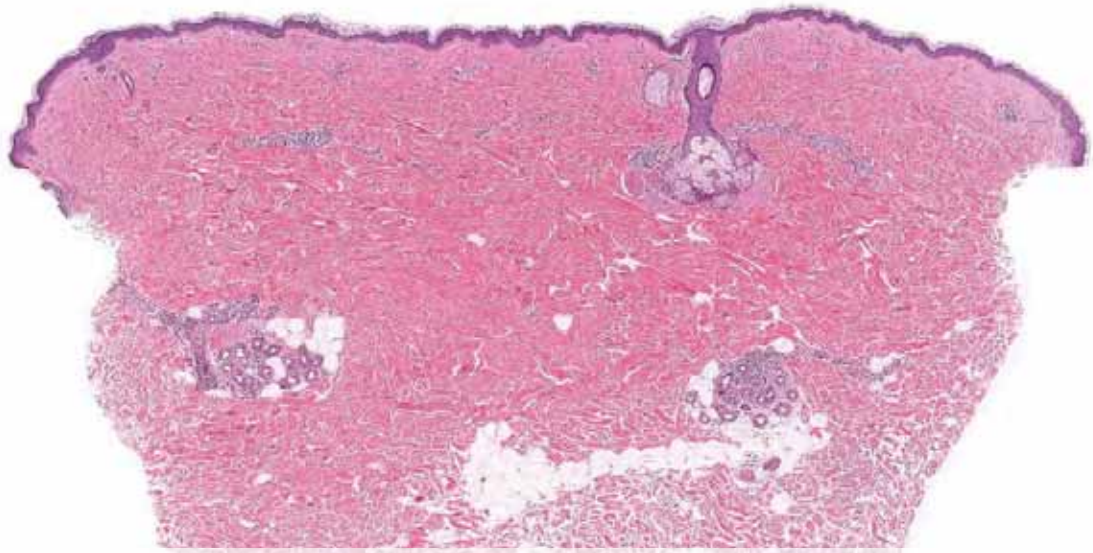












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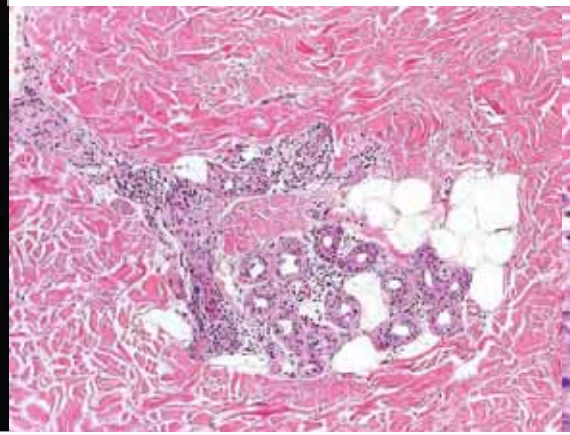
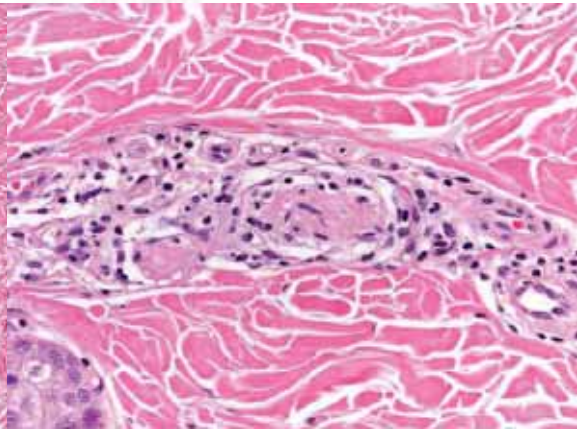
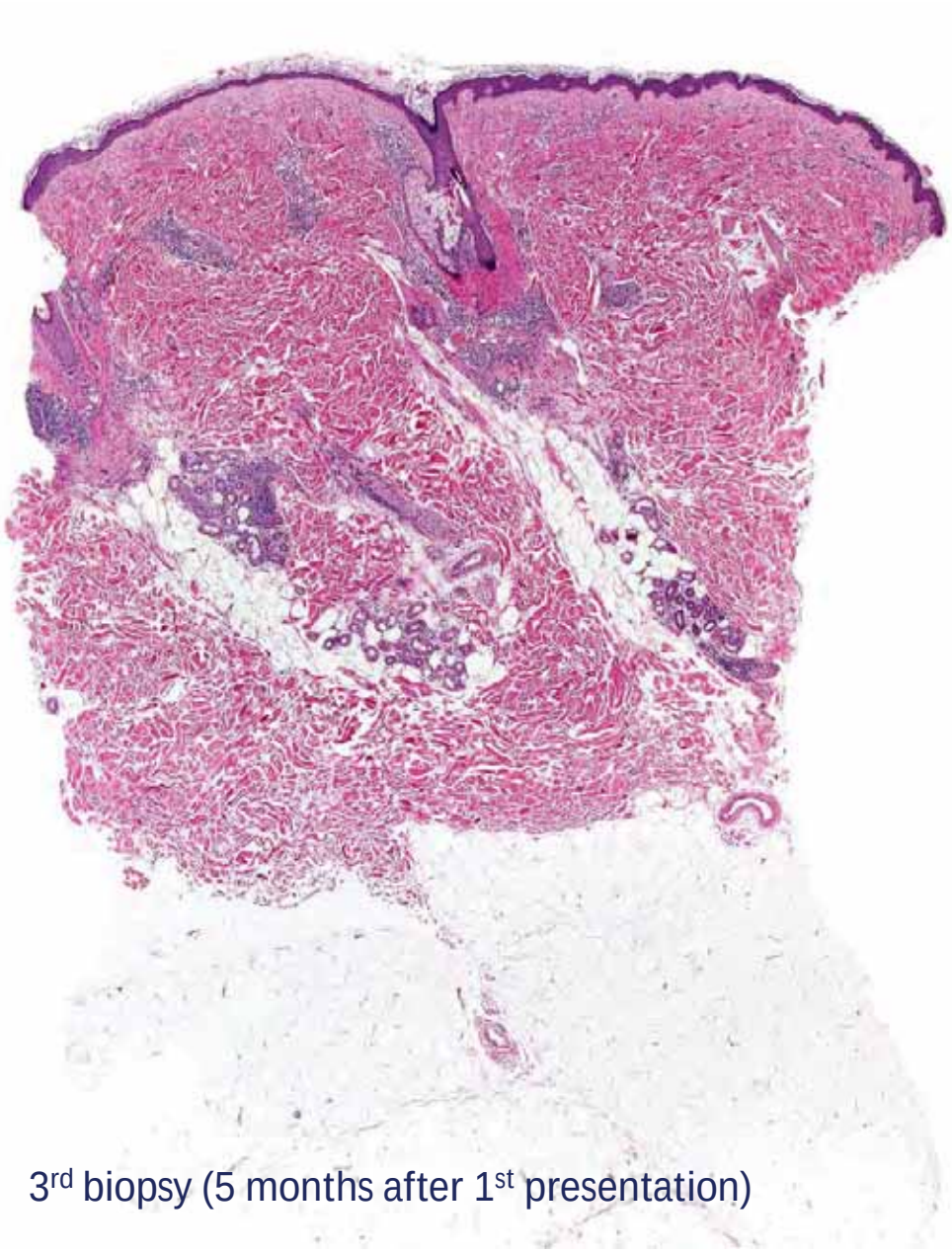
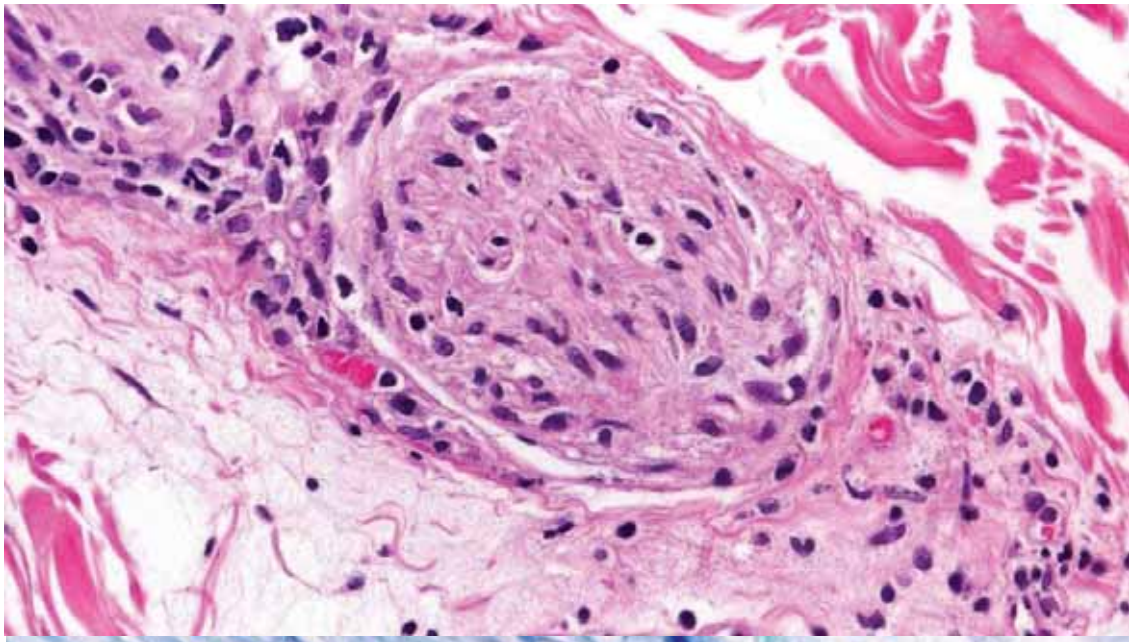
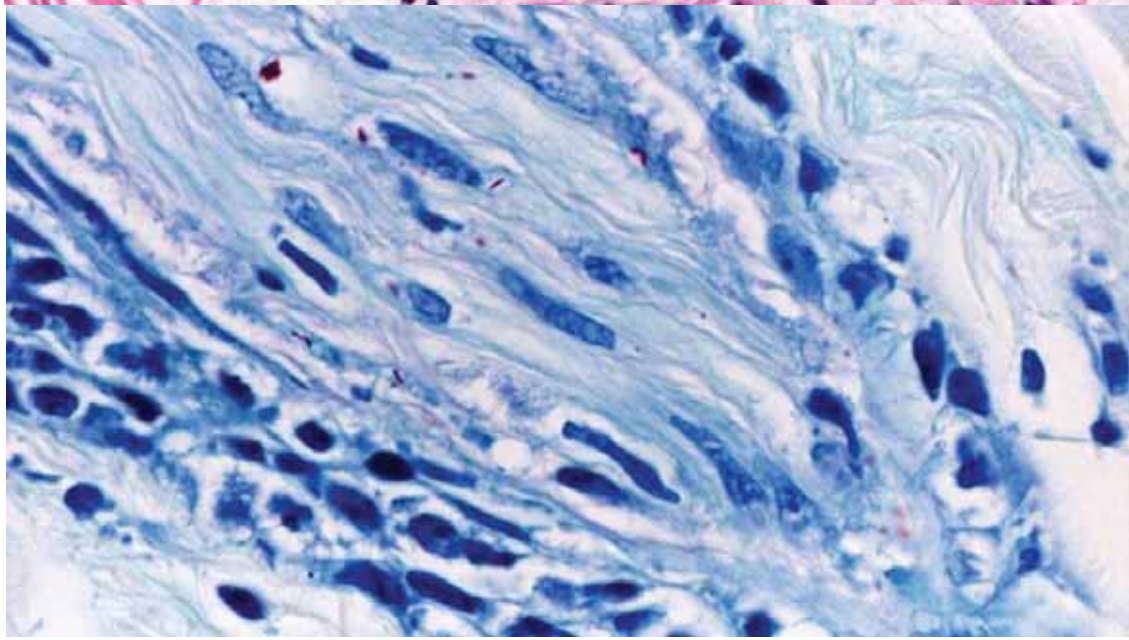


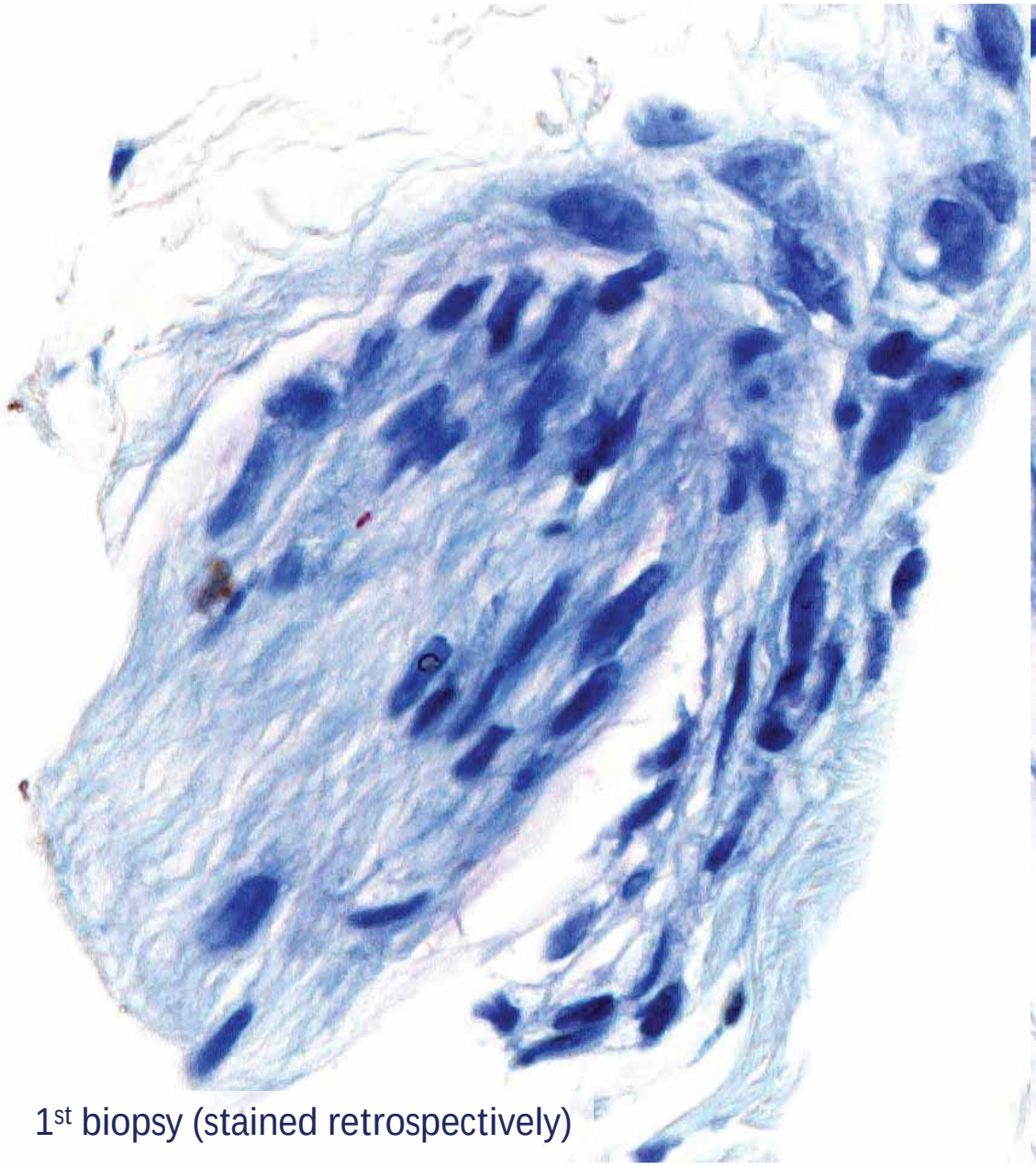




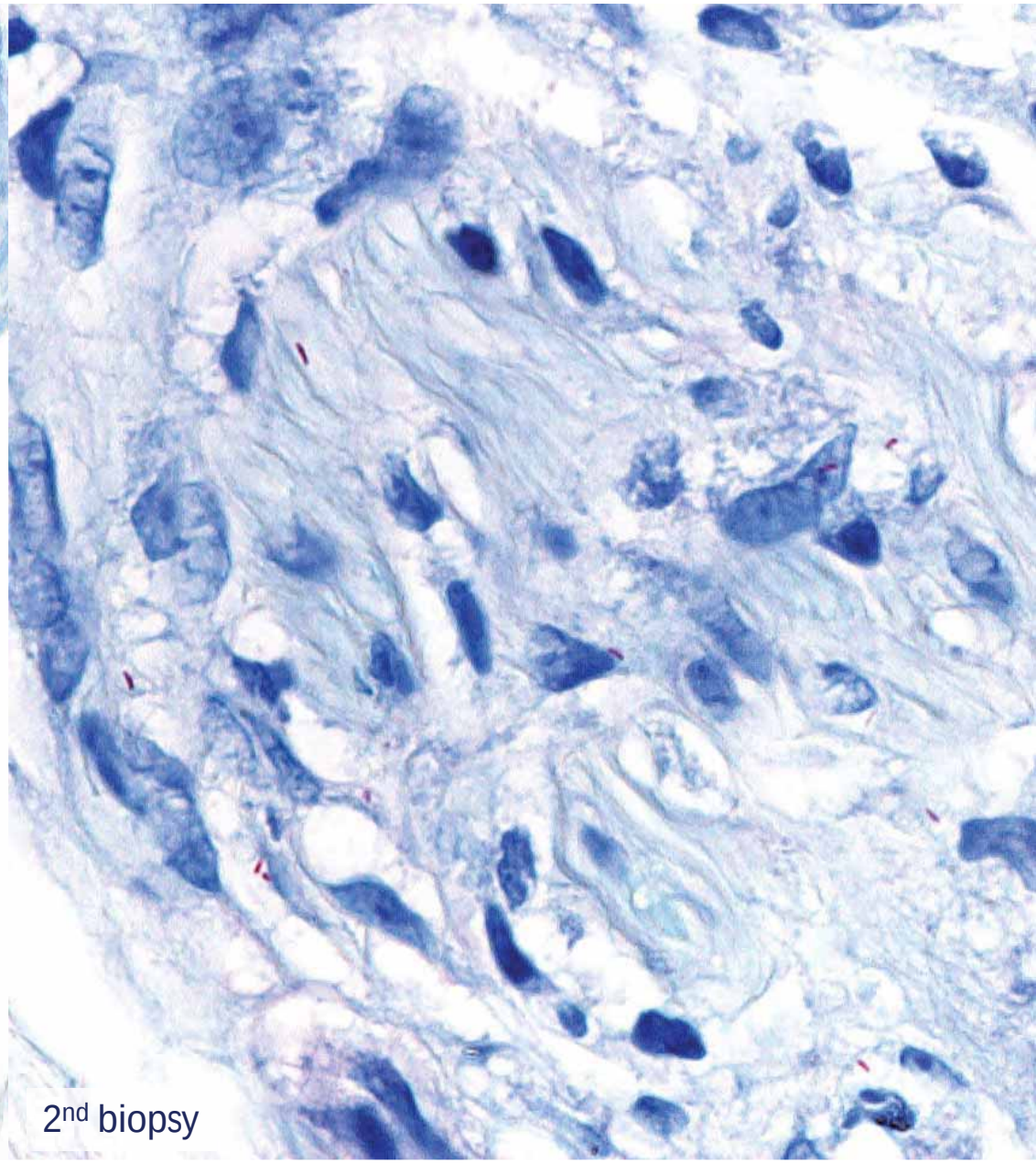
3rd biopsy (5 months after 1st presentation)



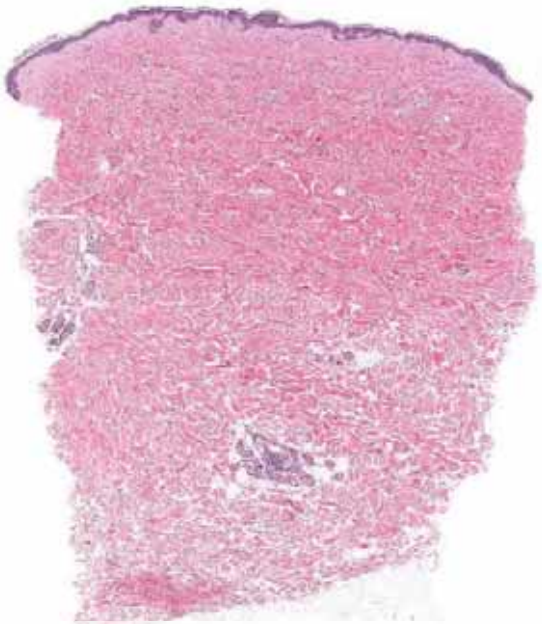
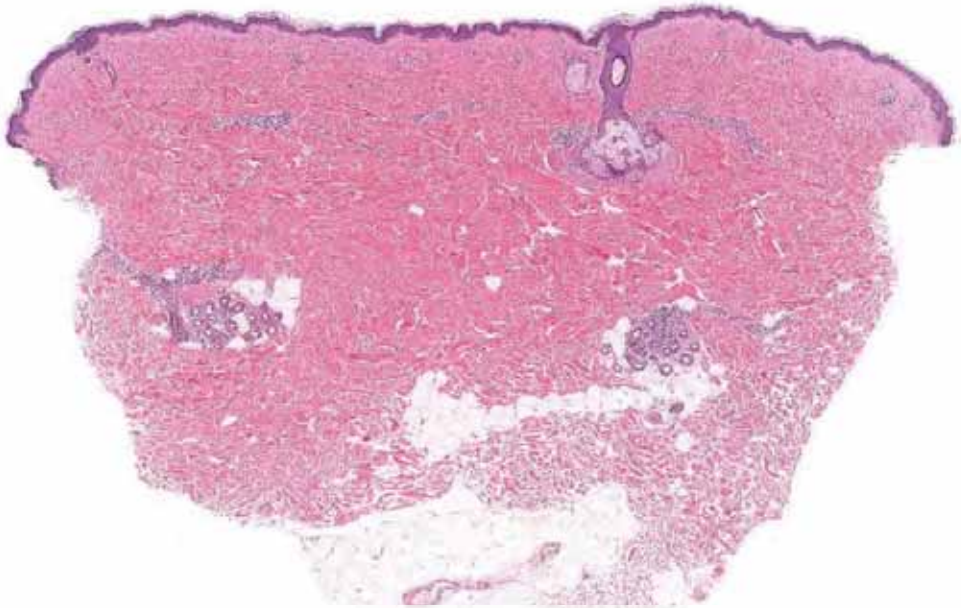
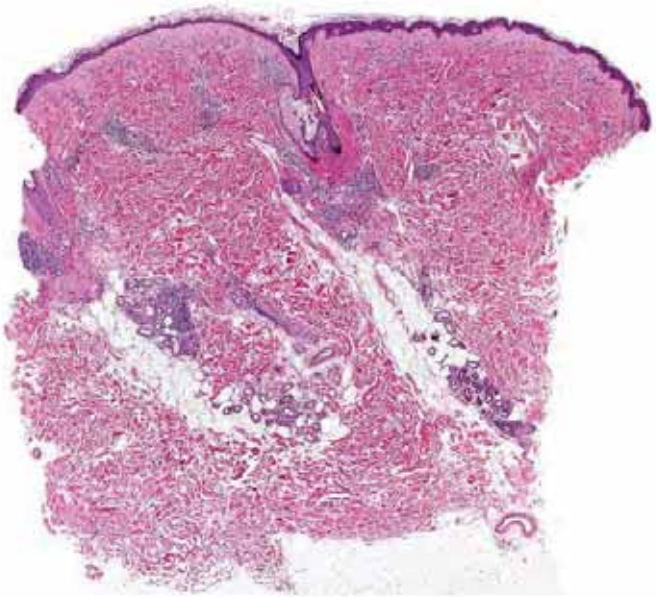




1st biopsy (stained retrospectively)

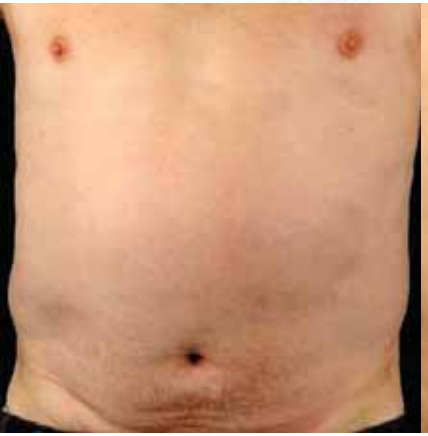
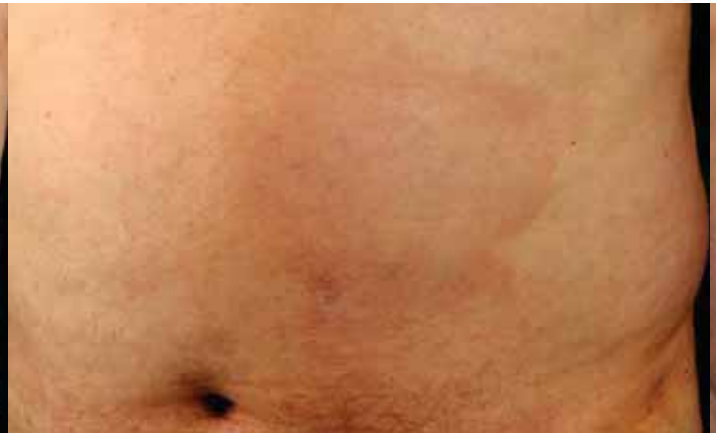
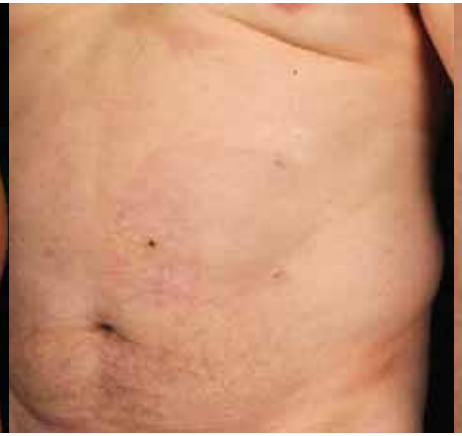
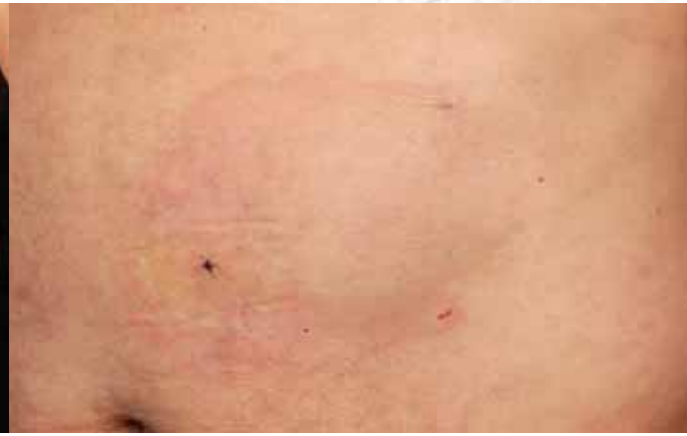


2nd biopsy

Tubercoloid leprosy

On questioning, the patient said that he spent every year several months in South America (Brazil, Paraguay)

CLINICAL PATHOLOGIC CHALLENGE

Annular Lesions in a 70-Year-Old Austrian Man

Herald Reiter, MD, Armin Justich, MD,† and Cesare Massone, MD†*

(*Am J Dermatopathol* 2011;33:861–862)

CHALLENGE

A 70-year-old Austrian man was referred to our Autoimmune Outpatient Clinic in July 2010 for further management and treatment of a morphea diagnosed 3 years earlier. Previous treatments included topical steroids with no improvement. The patient reported the appearance of asymptomatic erythematous annular lesions 3 years earlier. The lesions first appeared on the abdomen and after a few months they spread to the chest and back. Clinical history was negative for other autoimmune diseases. A biopsy performed in 2007 disclosed only a nonspecific perivascular lymphohistiocytic infiltrate. The patient was not taking any drug and has been living for 25 years in Austria, Brazil, and Paraguay and working as a private businessman. Physical examination revealed large asymptomatic annular oval lesions of different diameter, with an erythematous slightly infiltrated border with vague margins symmetrically distributed on the back, chest, and abdomen (Figs. 1–3). The lesions were neither sclerotic nor atrophic. Laboratory test showed normal erythrocyte sedimentation rate, normal red blood cell and white blood cell count, normal liver and renal function, normal glucose, normal serum protein electrophoresis, and negative antinuclear antibodies, borrelia antibodies, and serology for human immunodeficiency virus, syphilis, and hepatitis B and C. A new biopsy on an erythematous border of the lesion of the abdomen was performed (Figs. 4–6).

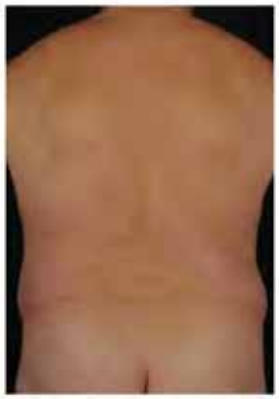


FIGURE 1. Large asymptomatic annular oval lesions of different diameter and with an erythematous slightly infiltrated border with vague margins on the back.

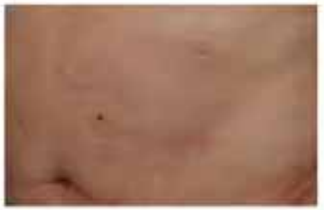


FIGURE 2. Large asymptomatic annular oval lesions of different diameter and with an erythematous slightly infiltrated border with vague margins on the abdomen; please note the suture of the biopsy.

WHAT IS YOUR DIAGNOSIS?

FIGURE 3. Higher magnification of the lesion on the back.

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The authors state that they have no financial or conflicts of interests to disclose.

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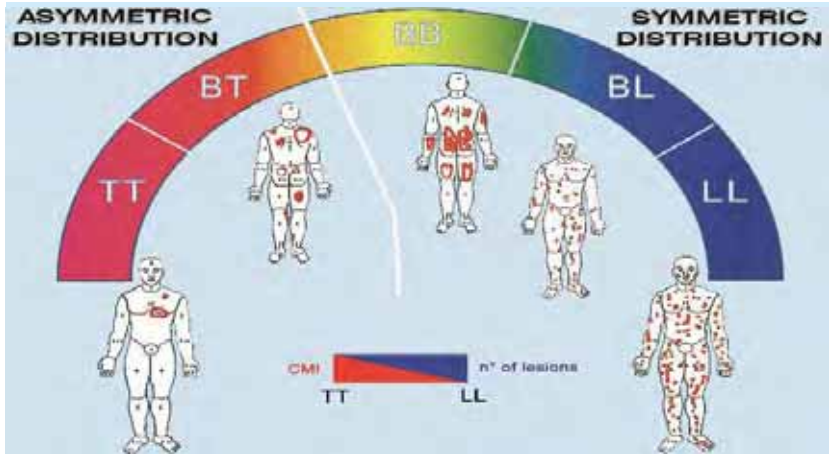
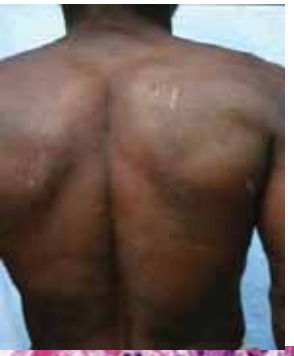
Optimal site for biopsy

Indeterminate leprosy (I)	Centre of the lesions or (better) centre of the anaesthesic area
Tuberculoid leprosy (TT) borderline tuberculoid leprosy (BT)	Infiltrated margin of the lesion
Borderline lepromatous leprosy (BL) and lepromatous leprosy (LL)	Centre of the macule or nodule
Type 1 reaction (T1R)	Most oedematous and infiltrated area
Erythema nodosum leprosum (ENL)	Centre of the nodule; deep biopsy including subcutaneous fat

Ridley and Jopling classification



Tuberculoid leprosy

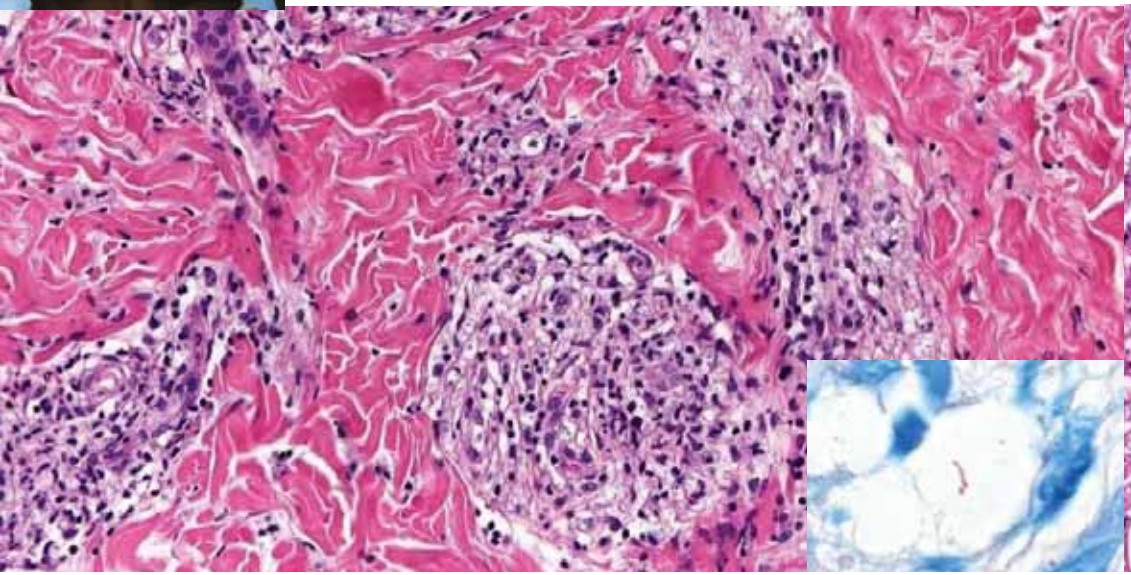


Th1 response

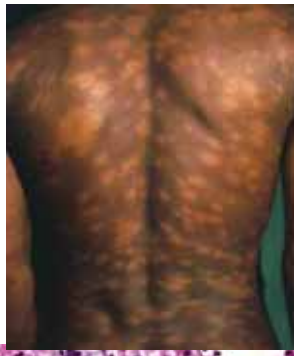
Localized disease

Asymmetric distribution

Epitheliod granulomas (tuberculoid granulomas) with few/no bacilli



Lepromatous leprosy

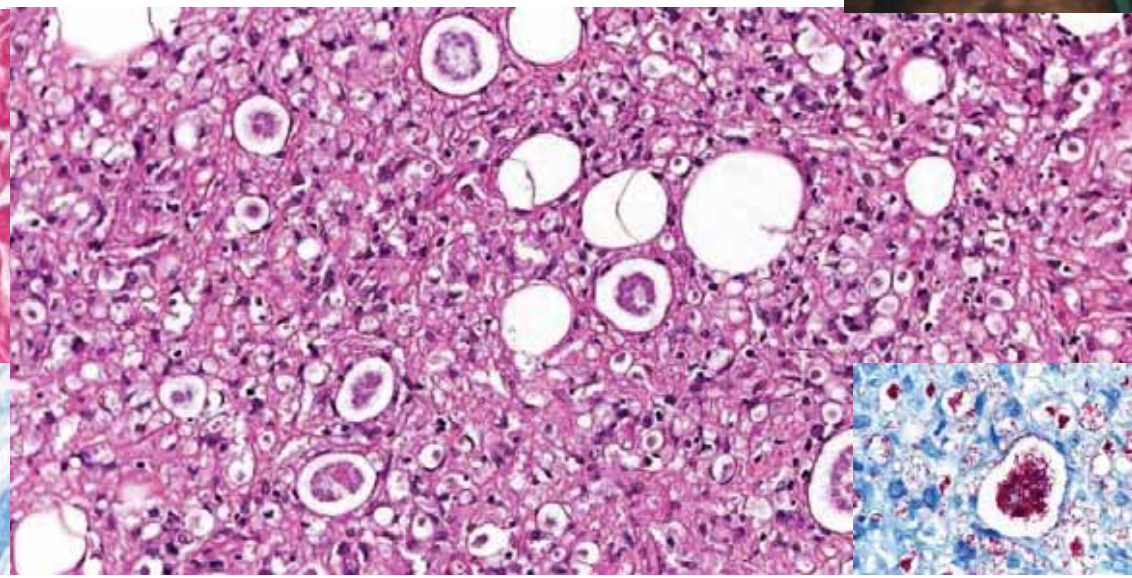


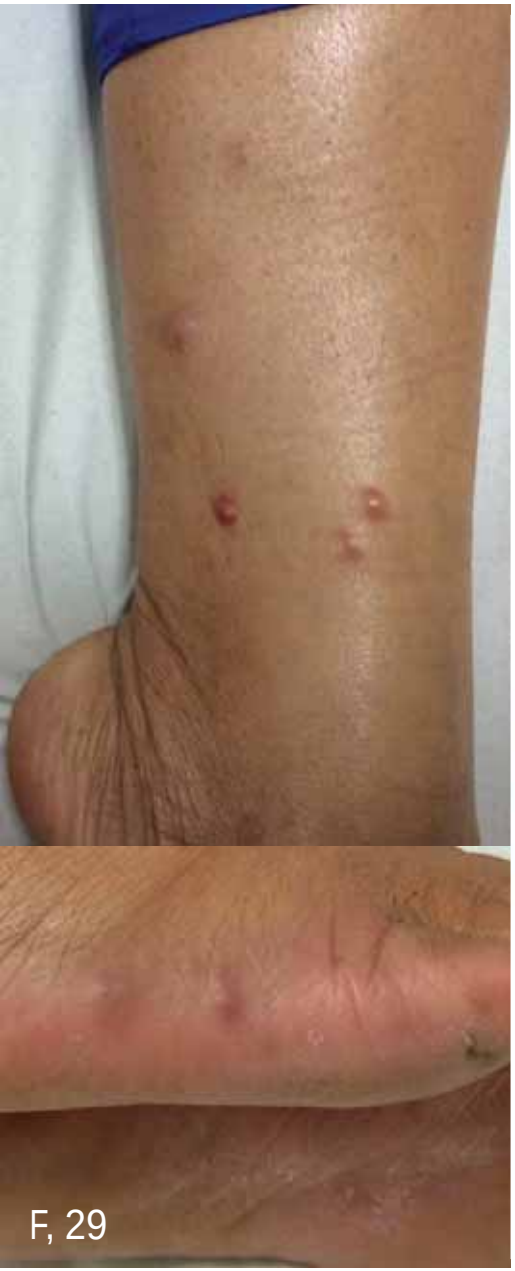
Th2 response

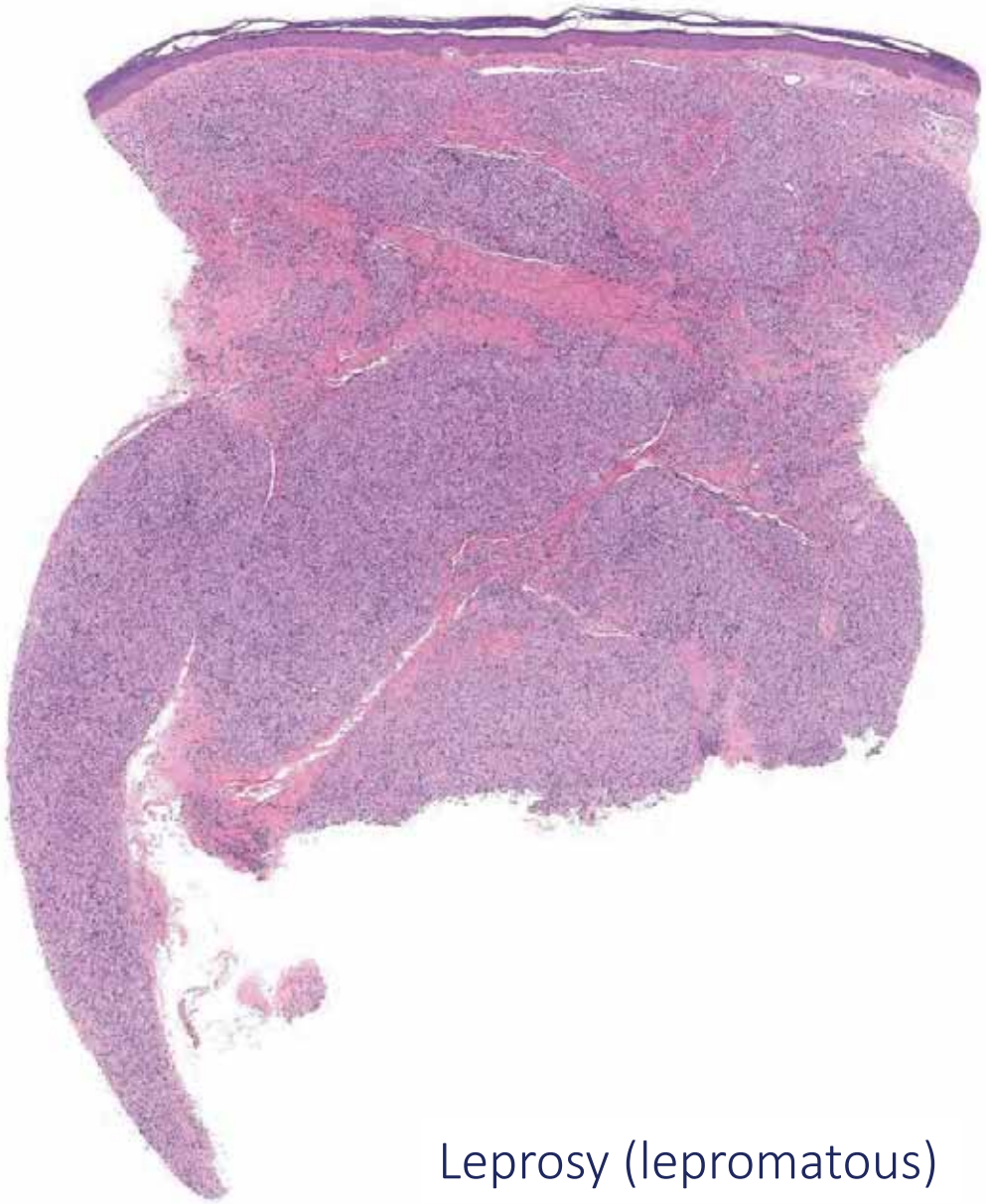
Systemic disease

Symmetric distribution (hematougenous spread)

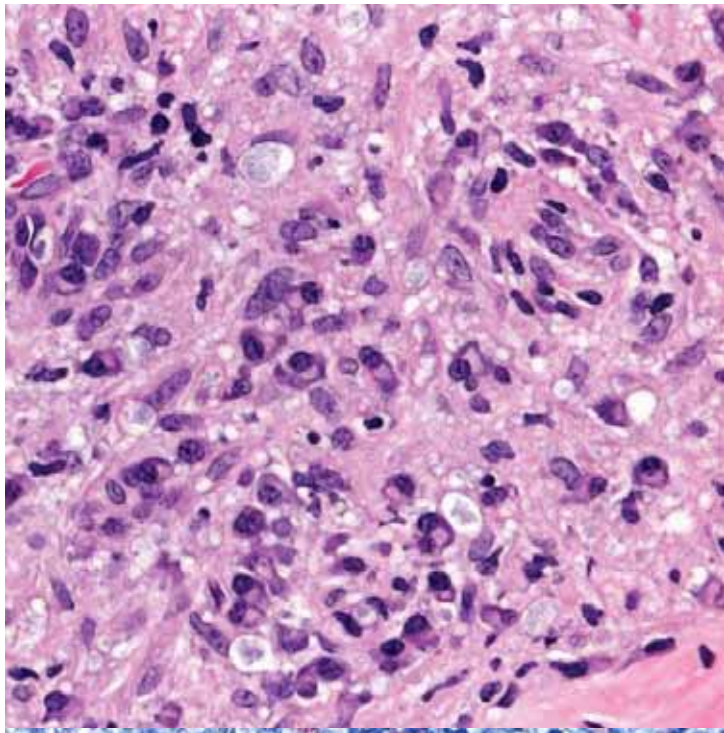
Macrophages & granulomas (lepromatous granulomas) with many bacilli

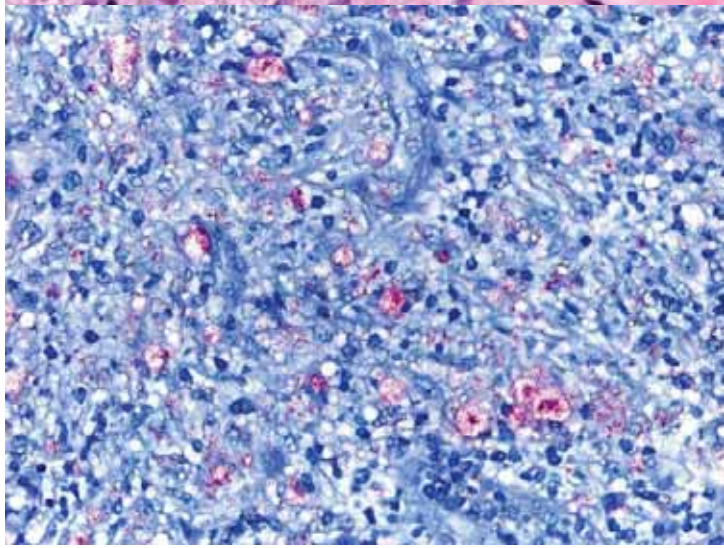


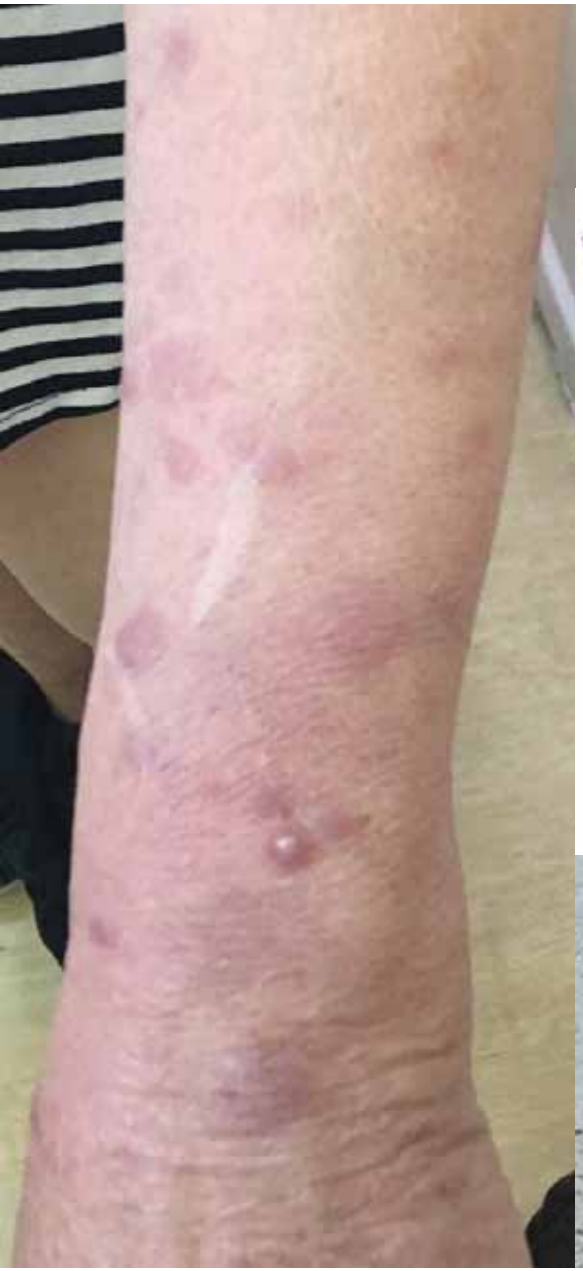




Leprosy (lepromatous)

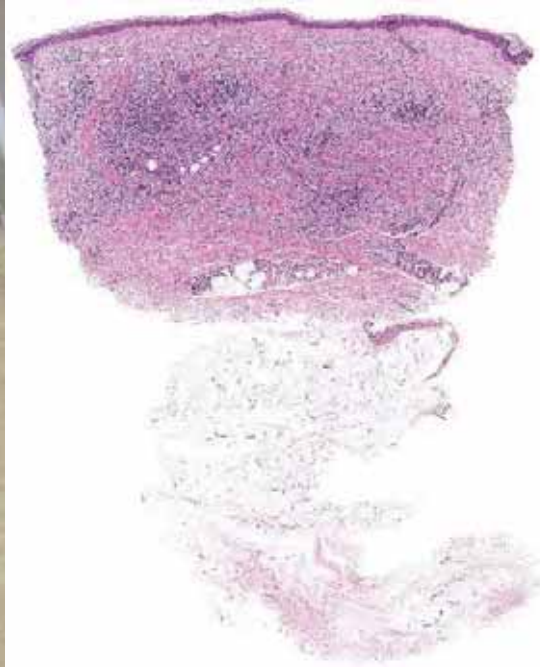


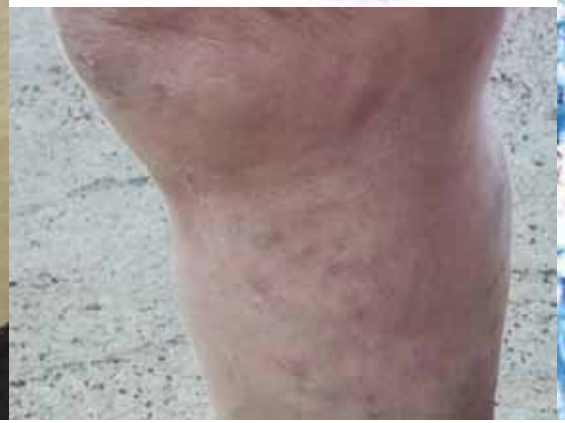


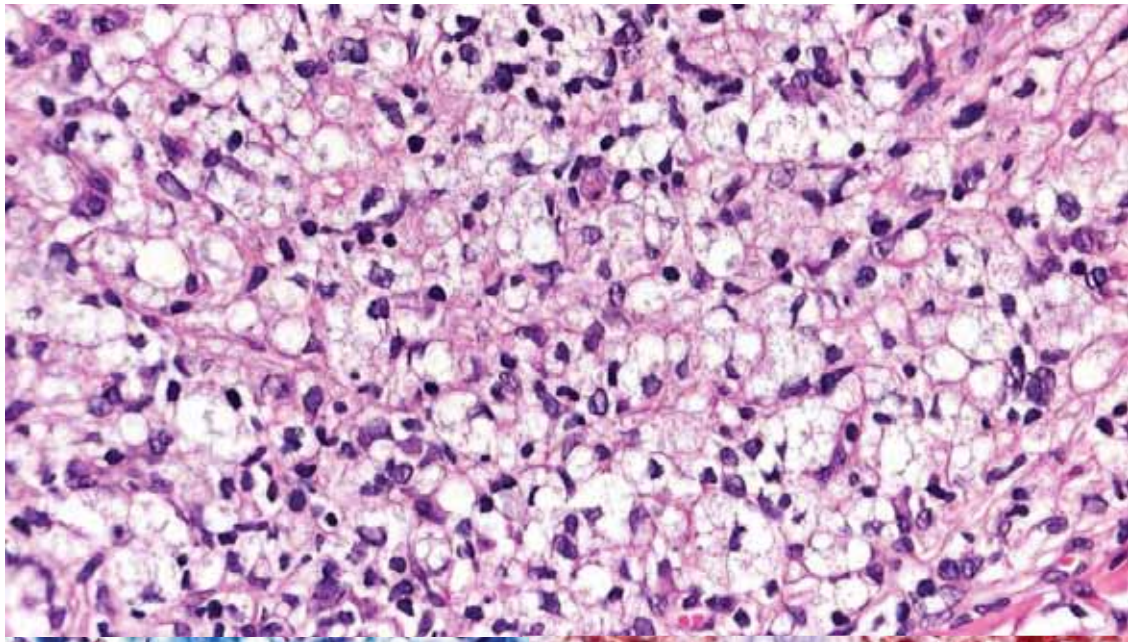


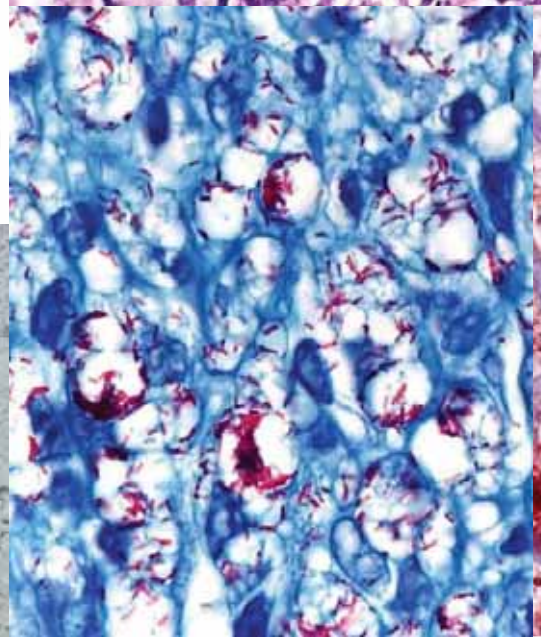
F, 63

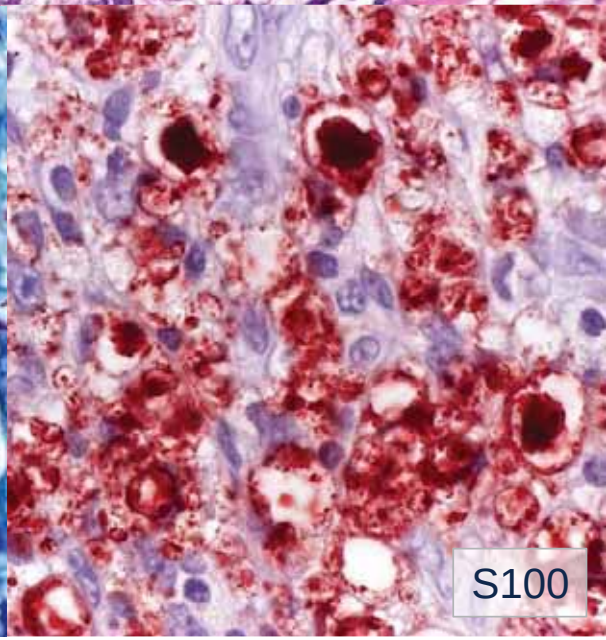
20-year history of itchy skin lesions.











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32(1): 70-71, janeiro-fevereiro, 1990

LETTER TO THE EDITOR

COMMERCIALLY AVAILABLE ANTI-S-100 PROTEIN SERUM STAINS M. LEPRAE IN LEPROSY TISSUES BY IMMUNOHISTOCHEMICAL PROCEDURES.

Demonstration of bacilli and consequently of their antigenic products is easily feasible in multibacillary (LL, BL, BB) forms of leprosy. However, the presence of a non specific chronic inflammatory infiltrate, as seen in indeterminate leprosy, or the persistence of a granuloma in the paucibaccilary (BT, TT) forms of leprosy in the absence of demostrable bacilli, may indicate that free antigenic products are initiating the apparently non-specific inflammation and/or perpetuating the granuloma (9).

Immunohistochemistry proved to be useful to demonstrate infectious organisms and/or their antigens in tissues. Antigenic analysis indicates that there are common antigenic sites among mycobacterial species. On this basis rabbit anti-BCG serum has been widely used as the primary antibody to demonstrate both the bacilli and their antigens in leprosy tissues (5,6). Recently monoclonal antibodies against **M. leprae** have been produced which recognise specific antigens on cell surfaces of leprosy lesions (8).

A phenolic glycolipid with a structure related to mycoside A of **Mycobacterium kansasii** was found in **M. leprae** preparation and had its structure elucidated by HUNTER & BRENNAN (3) and HUNTER, FUJIWARA & BRENNAN (4). A highly specific trisaccharide for serodiagnosis of leprosy was synthesized and proved to be highly sensitive in ELISA (1). This synthetic trisaccharide (ST) is antigenic and anti-serum against it was raised in rabbits by a standard procedure, using incomplete Freund's adjuvant, and was used as primary antibody in an avidin-biotin peroxidase immunohistochemical reaction by us. In multibacillary leprosy, bacilli and/or their antigens were heavily stained in essentially similar manner by anti-BCG and anti-ST sera. In paucibacillary leprosy isolated macrophages in the granuloma were stained by both anti-sera, probably indicating antigenic products which might be relevant in the perpetuation of the granulomatous inflammation.

S-100 is an acidic calcium binding protein so-named because of its solubility in 100% ammonium sulphate solution at neutral pH; it is distributed in the brain of a wide variety of species and is regarded as species non-specific (7). The finding of S-100 antigen in non-nervous tissues and, particularly in antigen-presenting cells of the skin in normal conditions, suggests that S-100 should no longer be considered strictly as a nervous system specific protein. In paucibacillary leprosy S-100 antigen detection was used as a marker to cutaneous nerve branches, since dermal nerves impairment by inflammatory reaction permits the differential diagnosis between paucibacillary leprosy and other skin granulomatosis (2).

A positive staining of **Mycobacterium leprae** and/or its antigens with commercially available (DAKO, Denmark) polyclonal anti S-100 rabbit serum was detected by us in multibacillary leprosy. Essentially similar antigenic sites were demostrated by S-100, anti BCG and anti ST sera. Lepromin absorbed anti S-100 serum failed to stain bacilli but maintened its staining properties as far as antigen presenting cells and dermal nervous branches were concerned. Therefore, the use of non-specifically absorbed commercial anti S-100 protein polyclonal serum in paucibacillary leprosy stains structures known to be usually stained by this anti-serum together with bacillary antigens. The staining properties of **M. leprae** by commercially available (DAKO) polyclonal anti S-100 protein serum is really an artefact. This anti-serum is raised in rabbits using complete Freund's adjuvant, which contain mycobacteria. Consequently different antibodies are present in the anti-serum, some recognizing **M. leprae** and others recognizing S-100 protein.

Therefore, care should be taken when using in immunohistochemical procedures commercially available anti-serum in infectious diseases, chiefly in countries where tuberculosis and leprosy are endemic.

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Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13a

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Departments of Pathology: [1]University Hospital, Cruces, Spain, [2]Hospital "La Paz", Madrid, Spain, [3]New York Presbyterian Hospital – Cornell University Medical Center, New York, NY, USA

In the defense against *Mycobacterium leprae*, macrophages play an essential part in the mechanism of bacterial lysis but require the presence of cytokines such as interleukin 2 and gamma interferon from lymphocytes in order to effectively kill the organisms in any number. While there have been many studies of the lymphocytes in lesions of leprosy, less attention has been given to the immunohistochemical characterization of the macrophage populations. In this study, the cutaneous lesions of 69 patients with leprosy (42 lepromatous, 5 mid-borderline, and 22 tuberculoid) were evaluated by immunohistochemistry for the expression of S100 protein, CD1a, CD68, muramidase, HLA-DR, and Factor 13a. The macrophages from lesions of polar, subpolar, and borderline lepromatous leprosy patients expressed S100 protein intensely and constantly. In contrast, the lesions of polar and subpolar tuberculoid leprosy had very few cells that were immunoreactive for S100 protein ('S100+') in the granulomas in the dermis. The macrophages in all lesions were reactive for CD68 and muramidase. In paraffin sections, macrophages of lepromatous lesions failed to stain for HLA-DR, whereas in tuberculoid lesions, they were strongly positive for HLA-DR. Three patients with histoid leprosy (relapse lesions) had lesions that were strongly positive for Factor 13a and were negative for S100 protein ('S100-'). Given the possible chemotactic and migration inhibition effects of the calcium-binding proteins of the S100 family, these data suggest a possibly important role for S100 protein in the accumulation of macrophages in lepromatous leprosy, and also reveal infection of Factor 13a + dermal dendritic cells in histoid leprosy.

Cuevas-Santos J, Contreras F, McNutt NS. Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13a.
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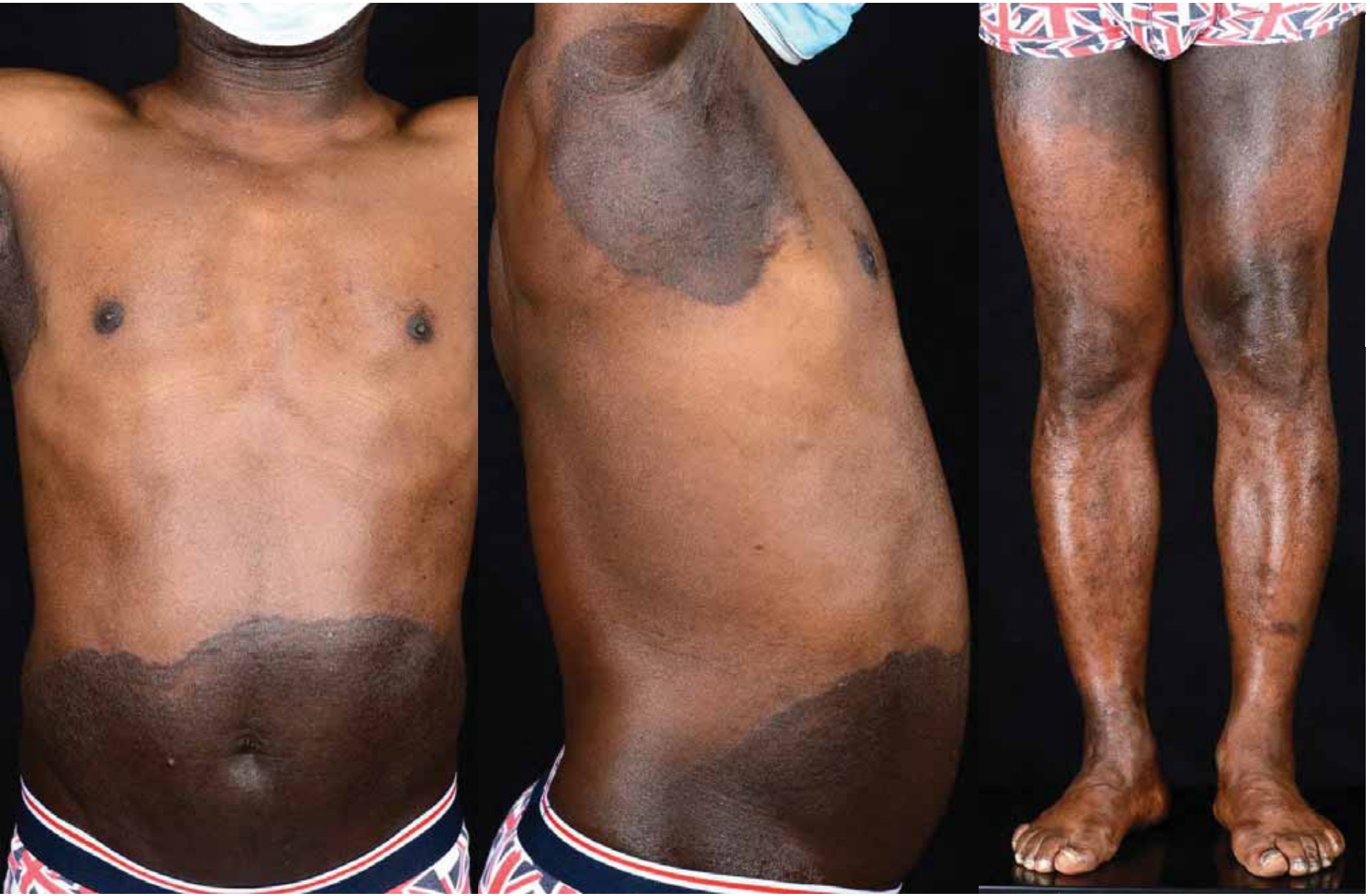
The intracellular residence of *Mycobacterium leprae* makes cytolytic activity of the macrophages essential for the destruction of the organisms. The presence of lymphokines, such as interleukin-2 and gamma interferon, from T-lymphocytes is essential for the activation of cytolytic activity by the macrophages after phagocytosis (2–9). Genetic factors also play a role in the type of lymphocytic response to *M. lepraе* organisms (10–13).

The cutaneous reactions to *M. lepraе* have been divided into histological patterns based on the number and state of aggregation of macrophages, the foamy appearance of the cytoplasm of the

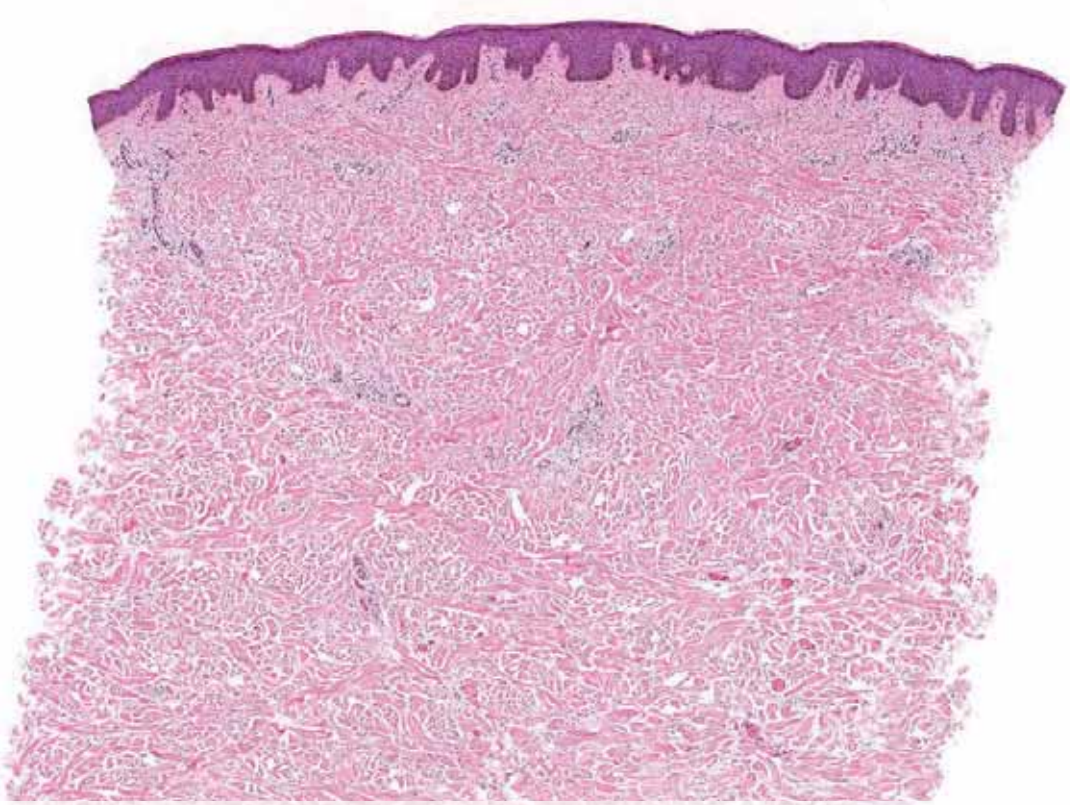
This work is a portion of the doctoral thesis of Dr. Jesús Cuevas-Santos, approved in 1996 by the Facultad de Medicina, University of Alcalá de Henares, Spain, under the direction of Dr. Félix Contreras-Rubio and Dr. José Luis Bardasano-Rubio (1).

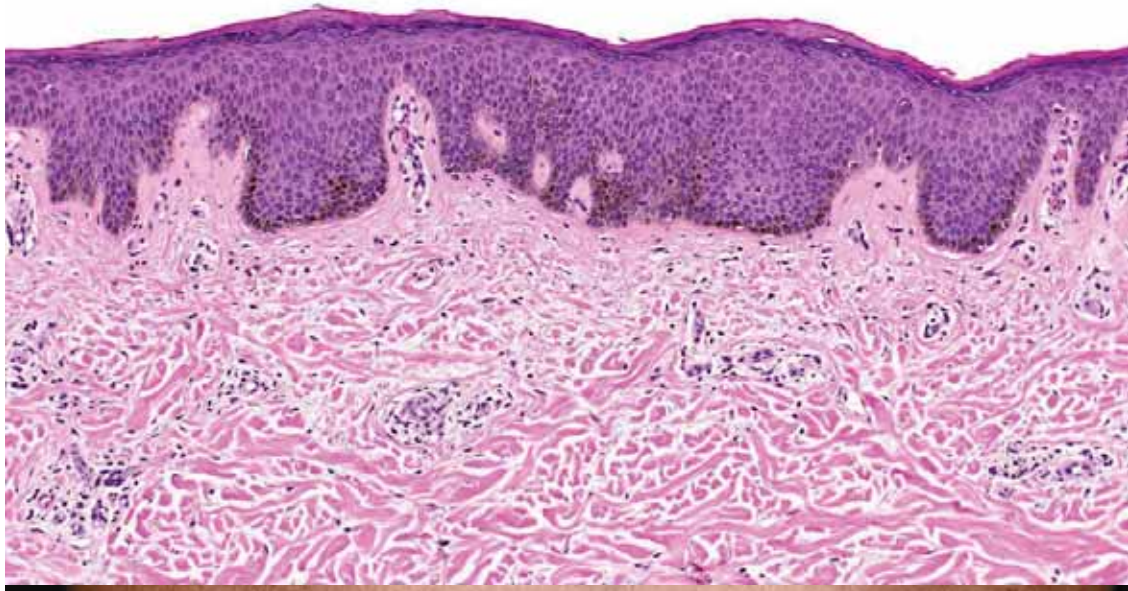


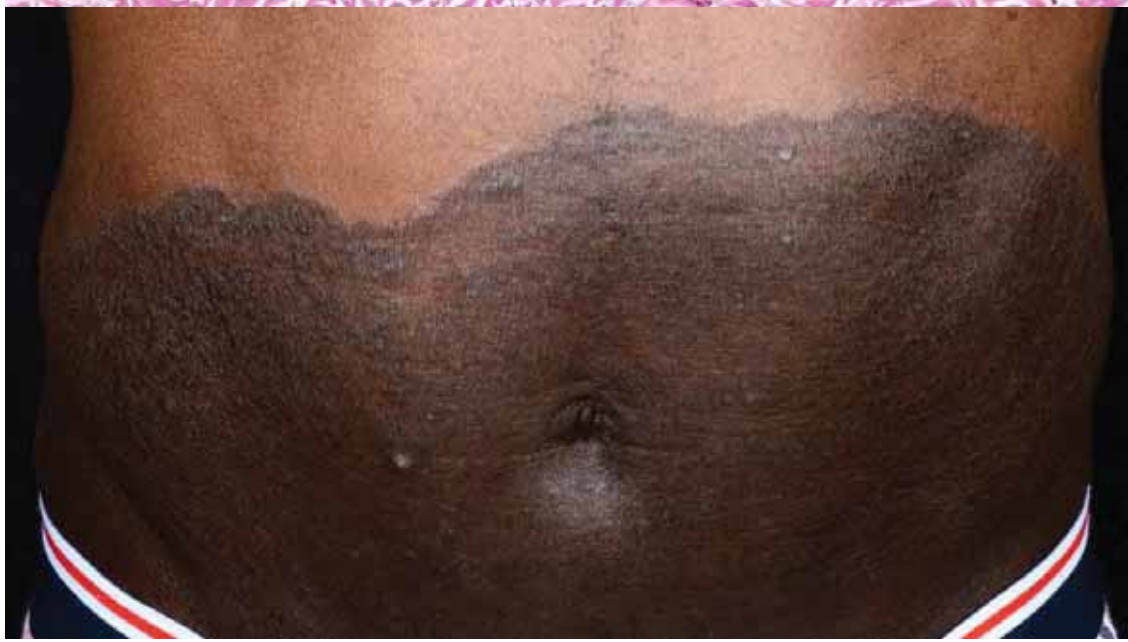
M, 52

Itchy, generalized, slowly growing hyperpigmented lesions for the last 6 months.

A biopsy is taken.







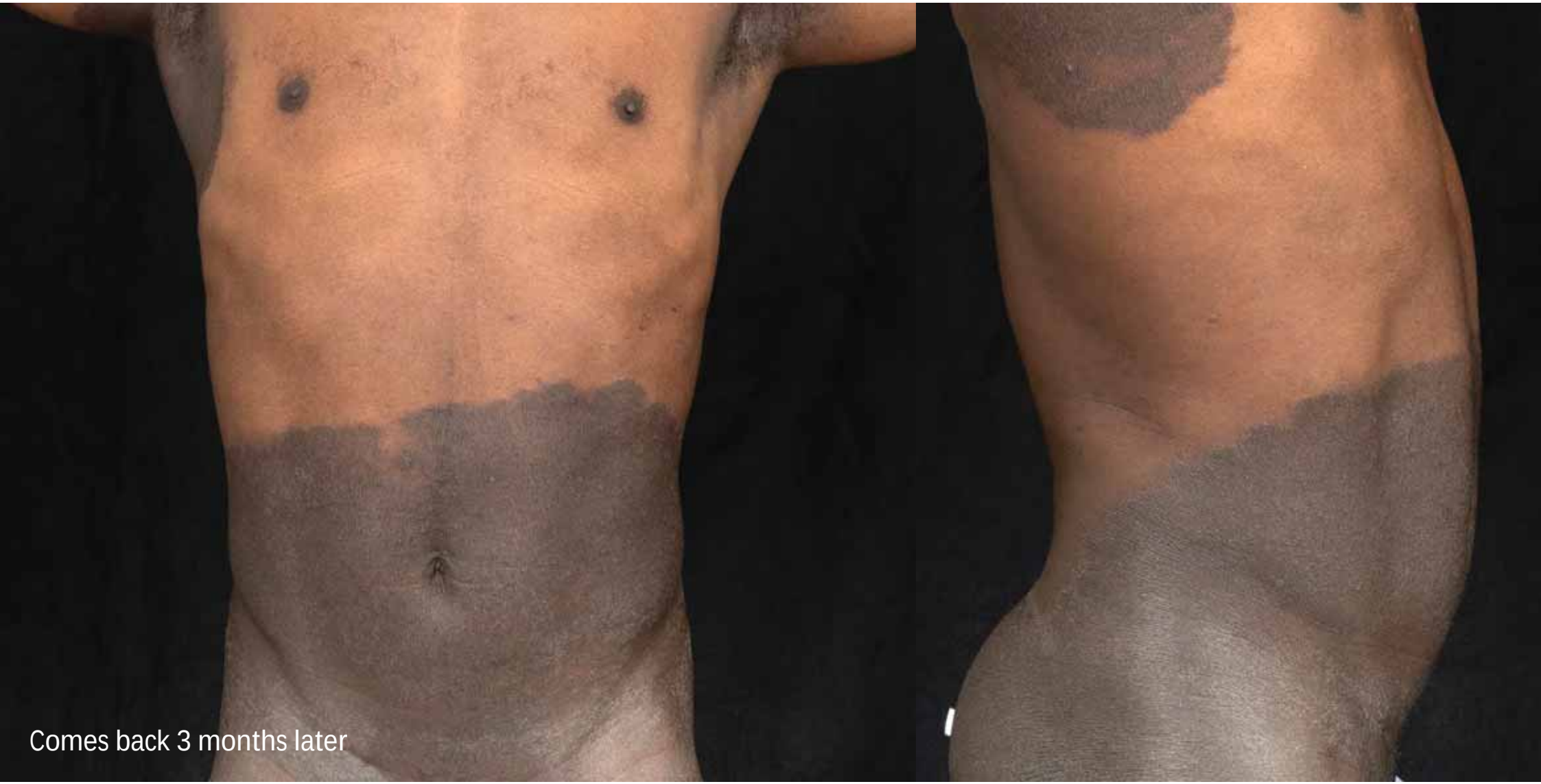
Reported as:

Consistent with a chronic eczematous dermatitis

Mycologic investigation: negative.

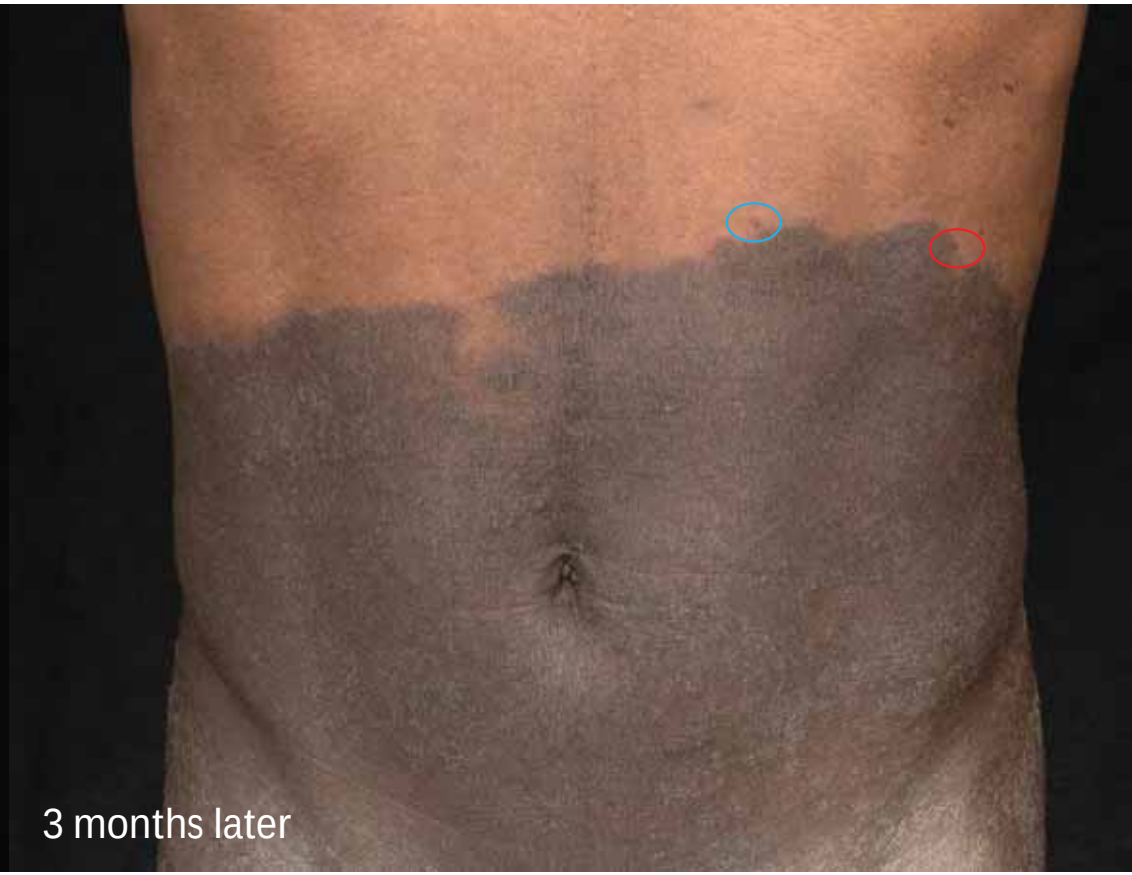
PAS staining on biopsy: negative.

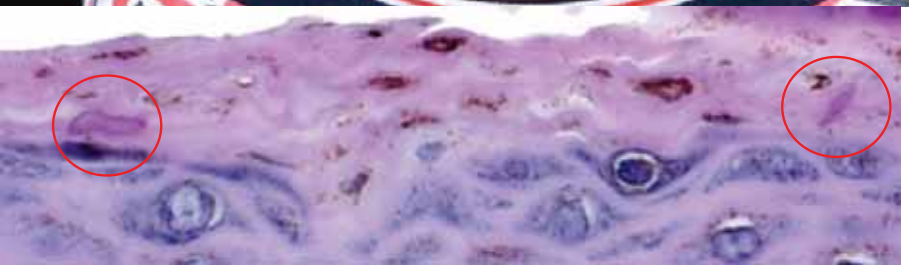
Discharged with the diagnosis of chronic eczematous dermatitis. Treatment with local steroids. No further appointments.



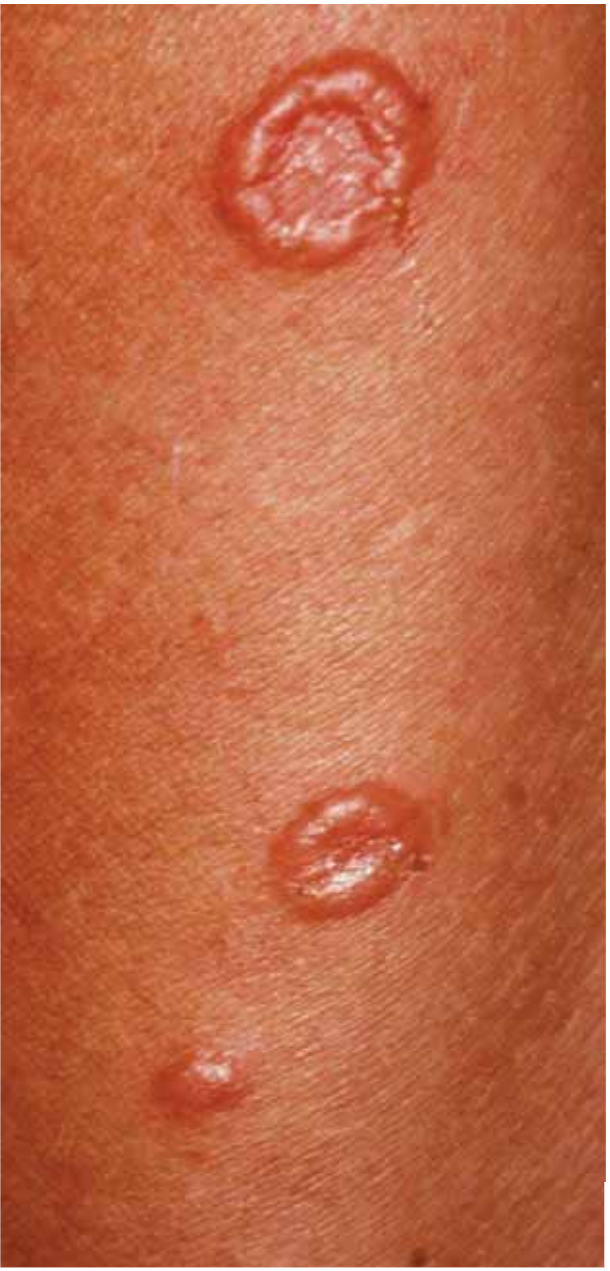
Repeated mycologic investigation: Positive culture for ***Tr. Rubrum***. HIV+.
Treated with terbinafine 250 mg 1x/d; marked improvement at an appointment 2 months later (culture negative).

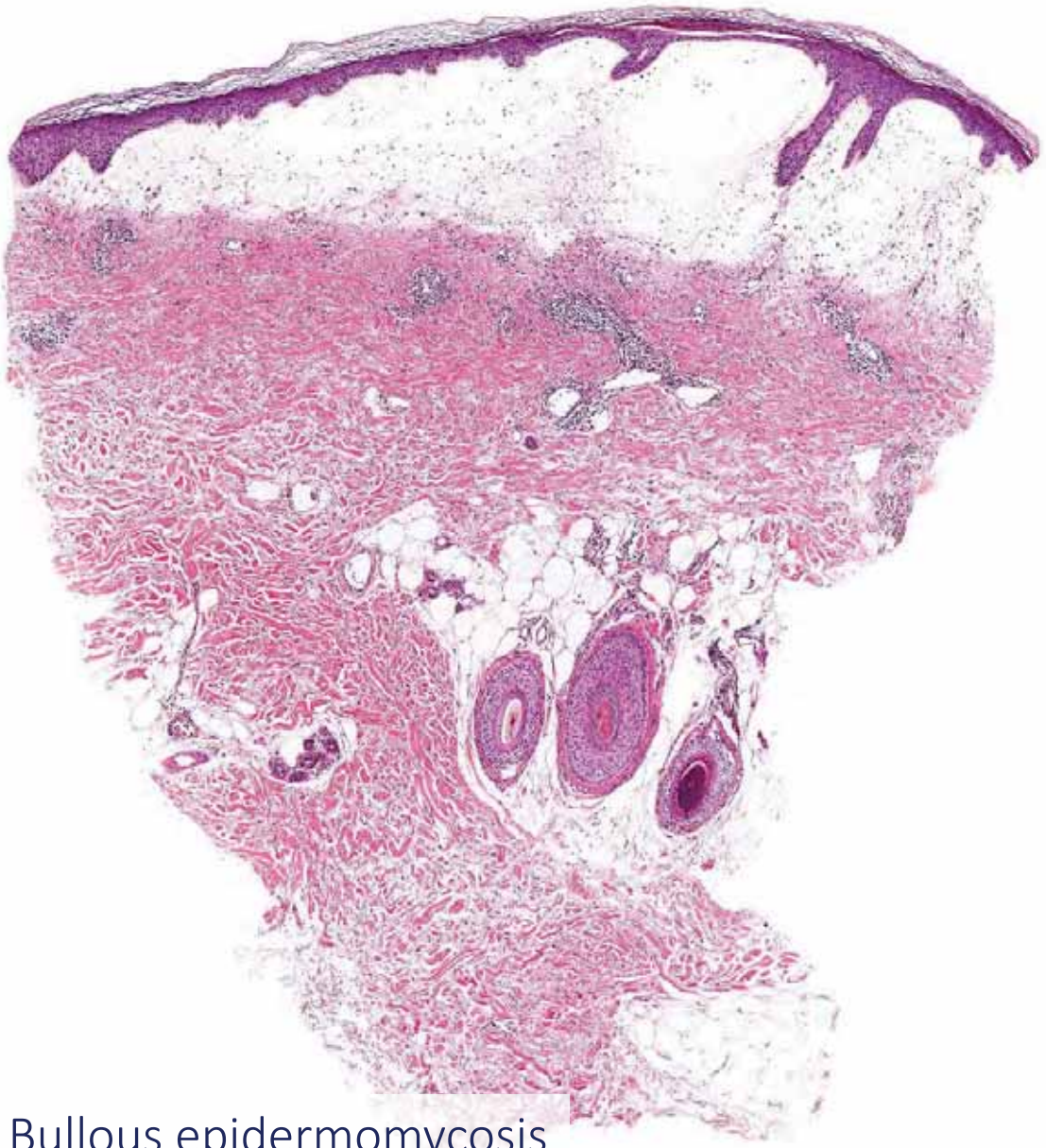
Generalized rubrophytosis

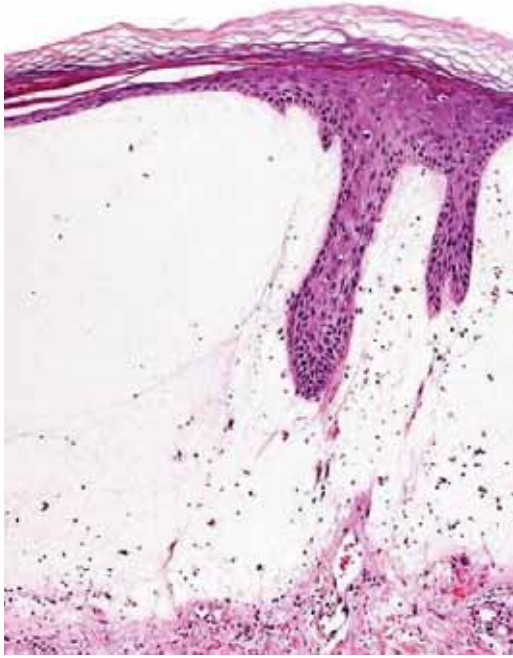


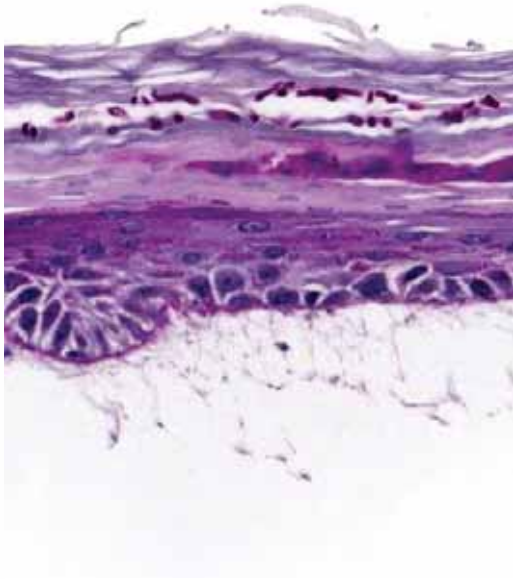


First culture negative.
PAS staining repeated on 16 sections (13 sections stained retrospectively after the result of the positive culture…); only 2 suspicious structures visible on a single section.



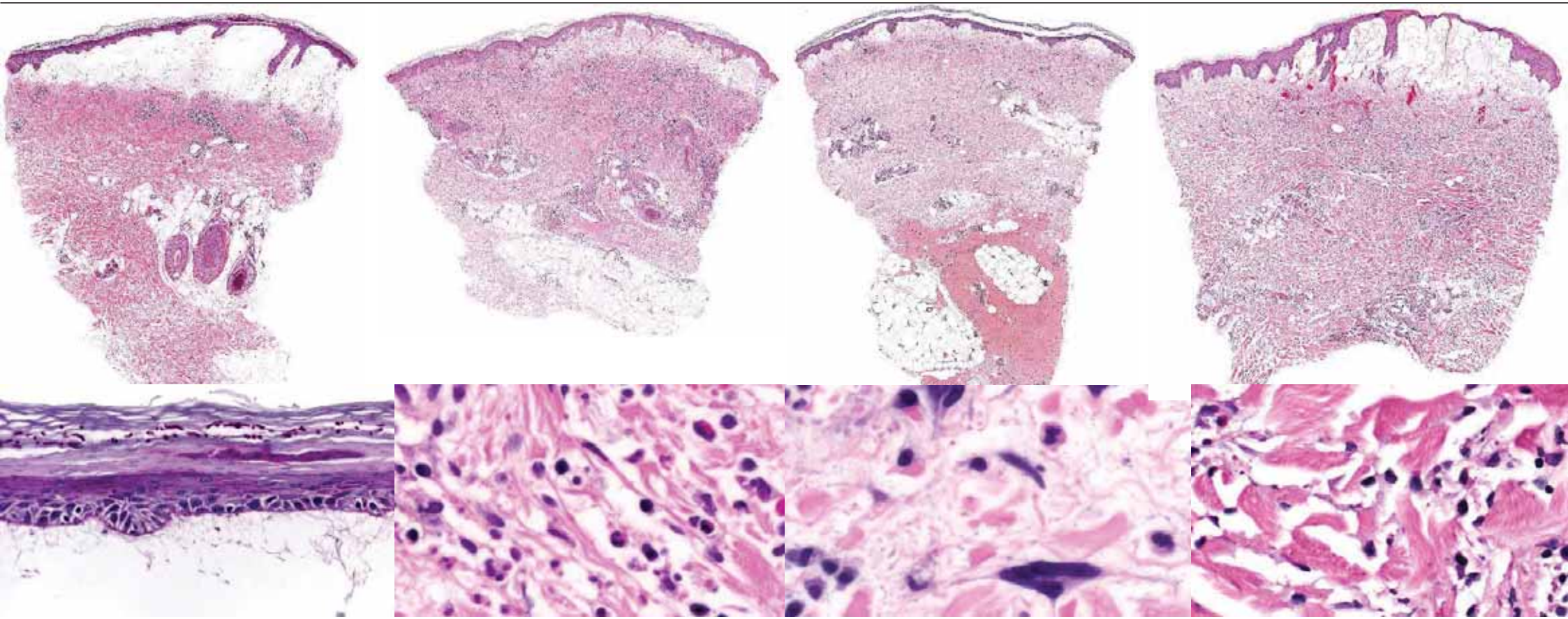






Bullous epidermomycosis

Main vesicular lesions due to pronounced papillary dermal edema



Bullous epidermomycosis

Infiltrate usually superficial; PAS+ hyphae in the horny layer

Bullous arthropod bite reaction

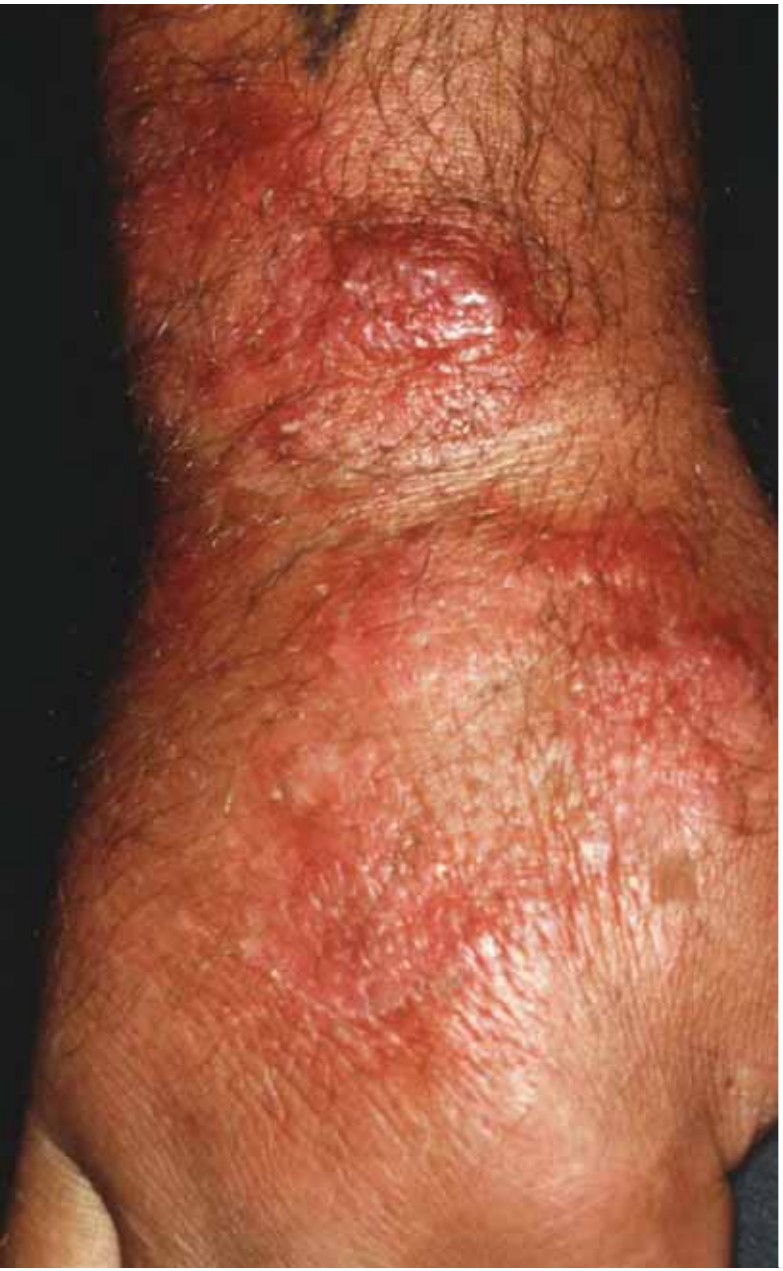
Infiltrate superficial and deep, usually relatively dense; several eosinophils (and neutrophils)

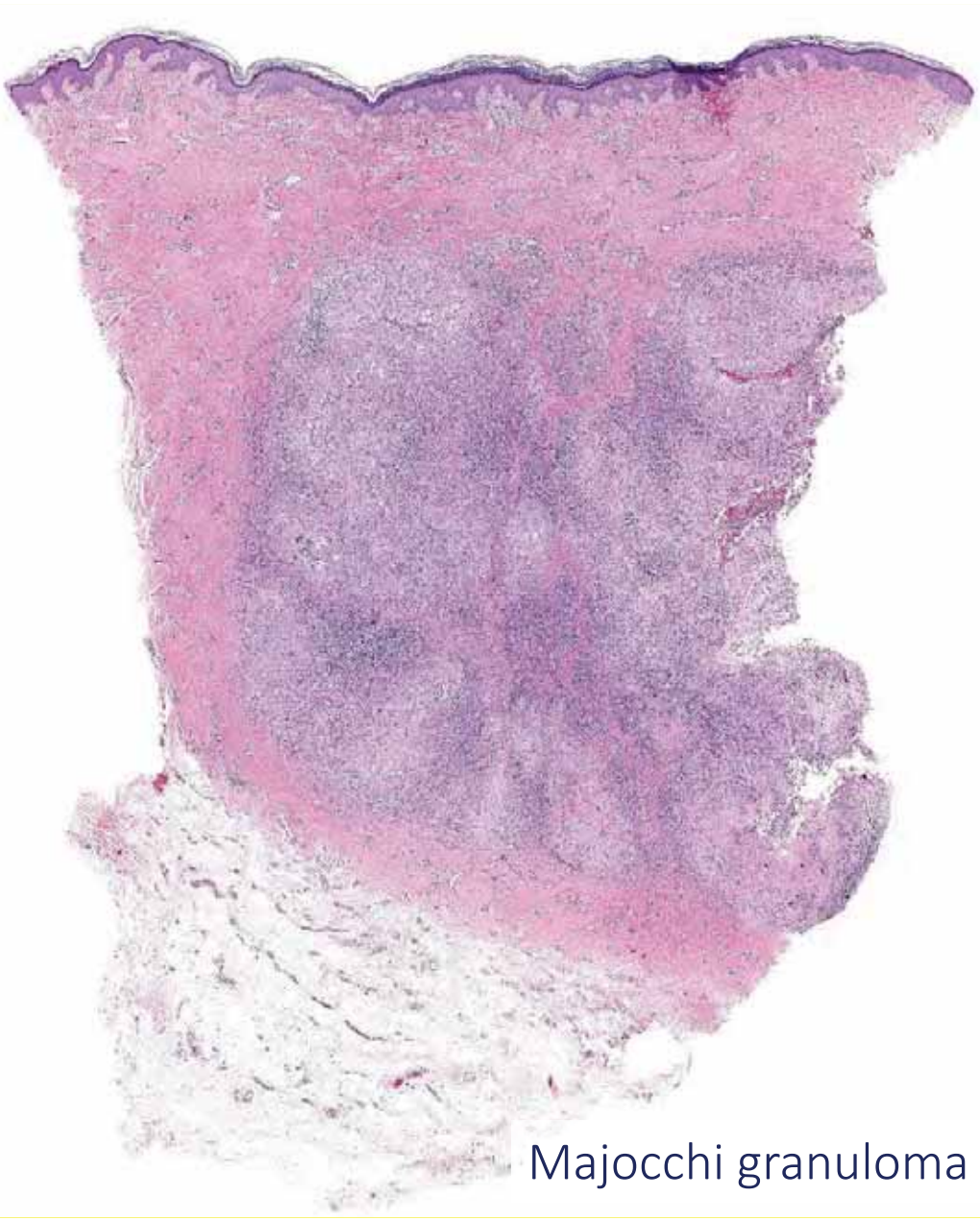
Bullous erysipelas

Infiltrate usually sparse, superficial and deep, with interstitial neutrophils

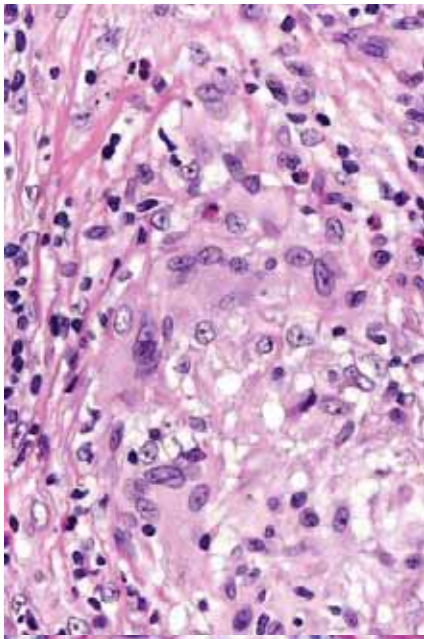
Bullous drug reaction

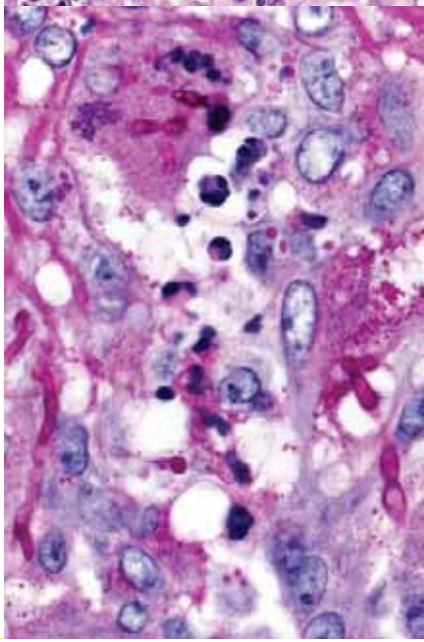
Infiltrate of variable density, may be superficial and deep, with neutrophils and eosinophils

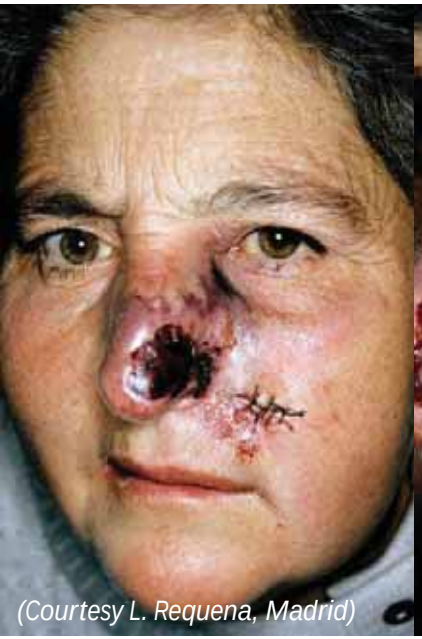


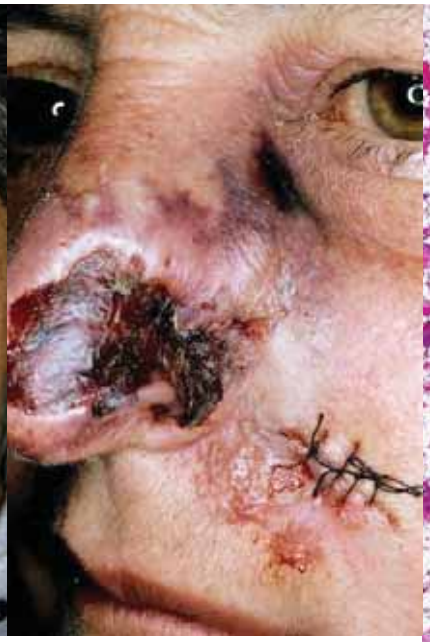


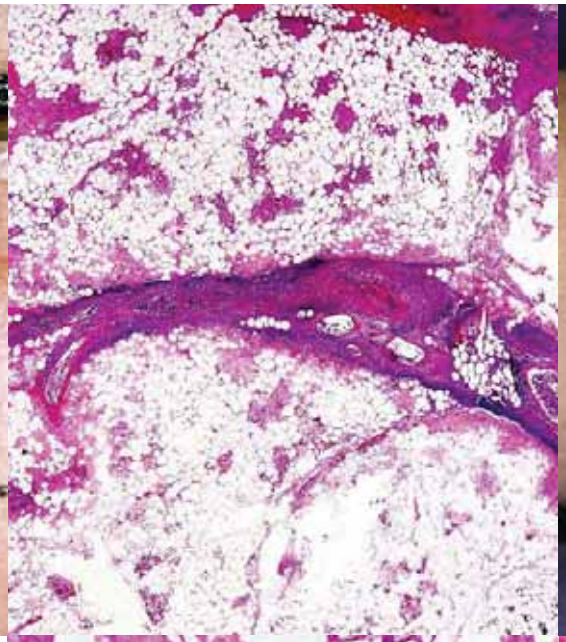
Majocchi granuloma

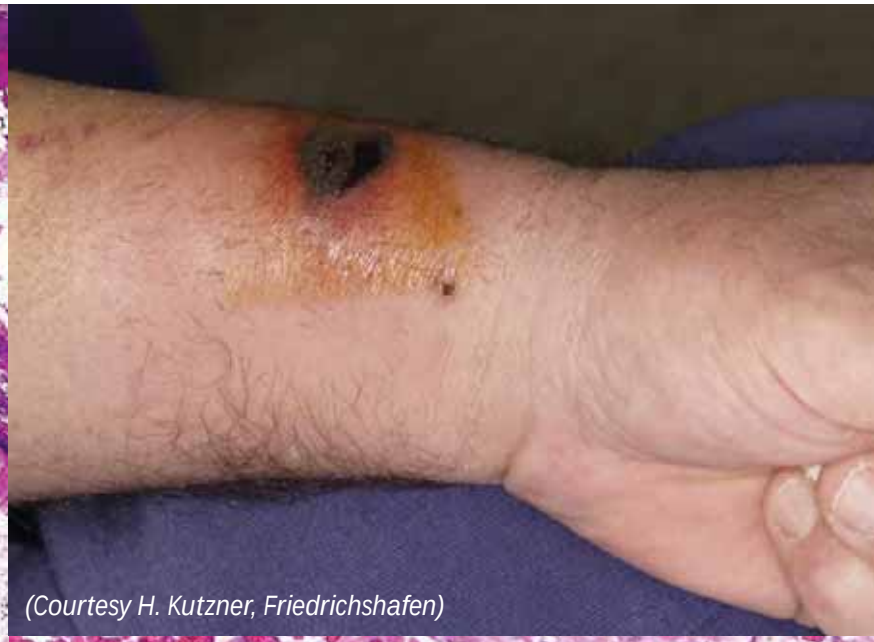








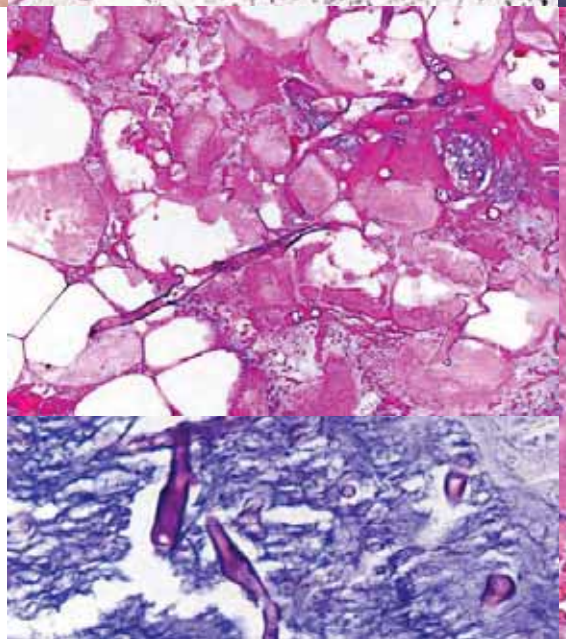


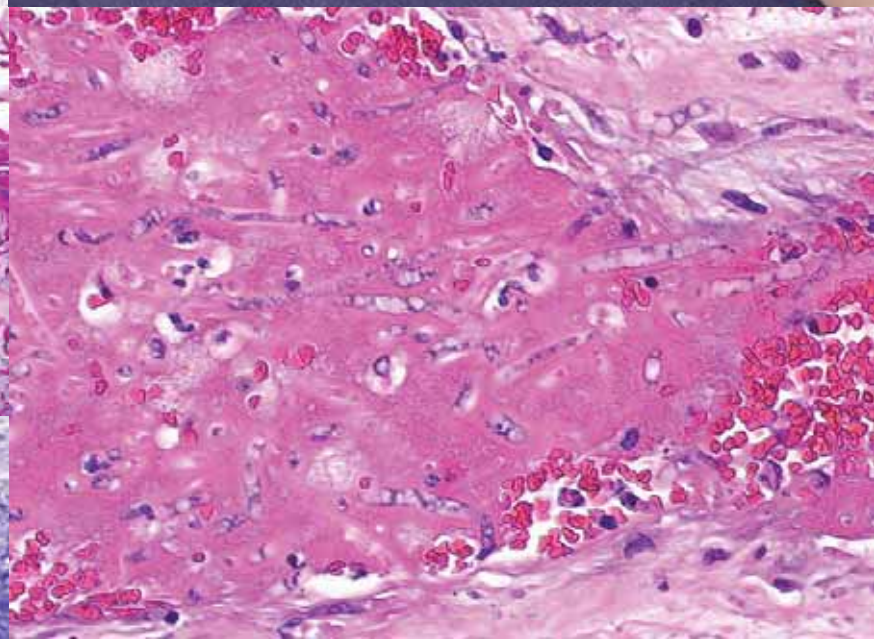


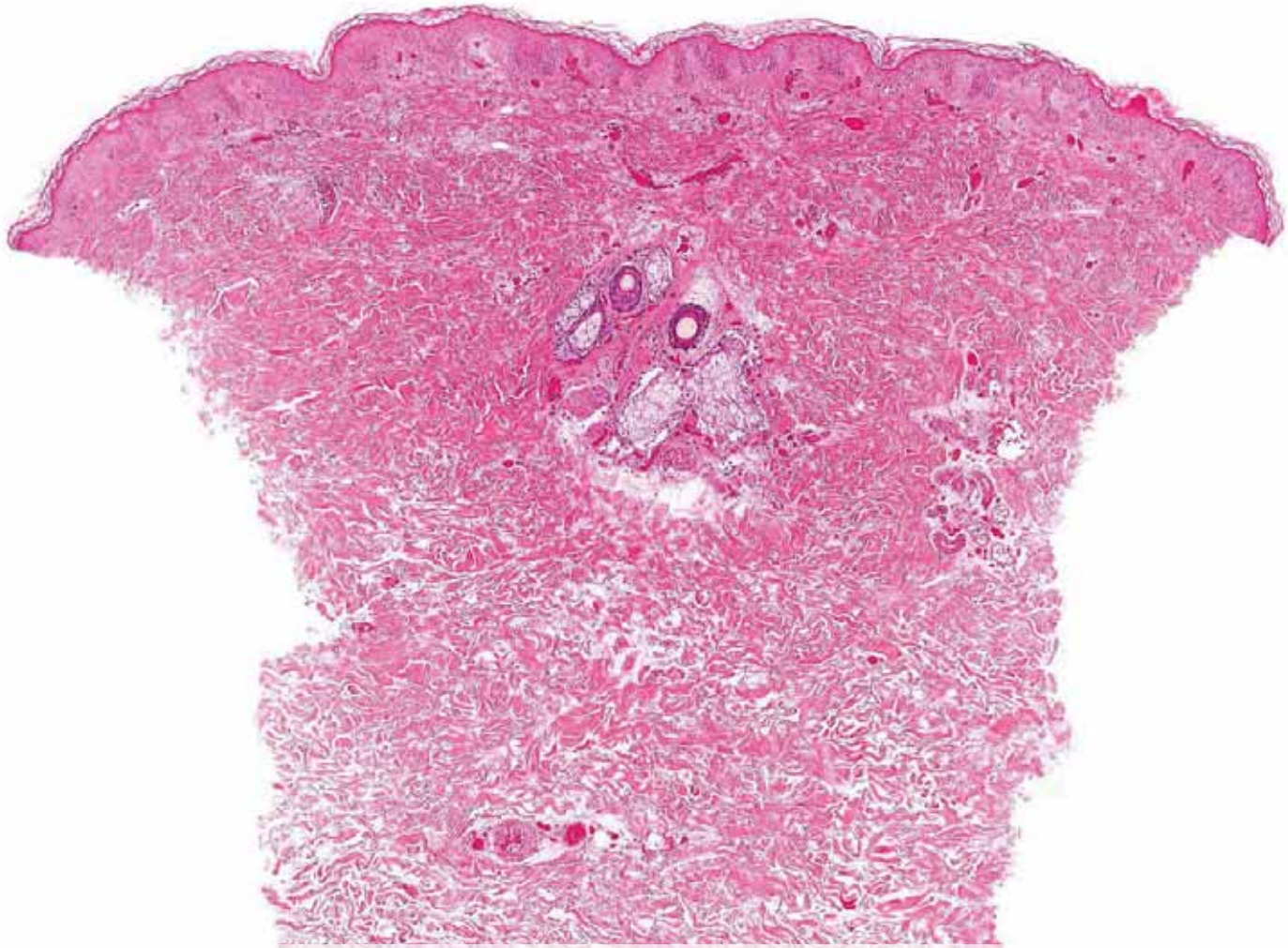
Mucormycosis

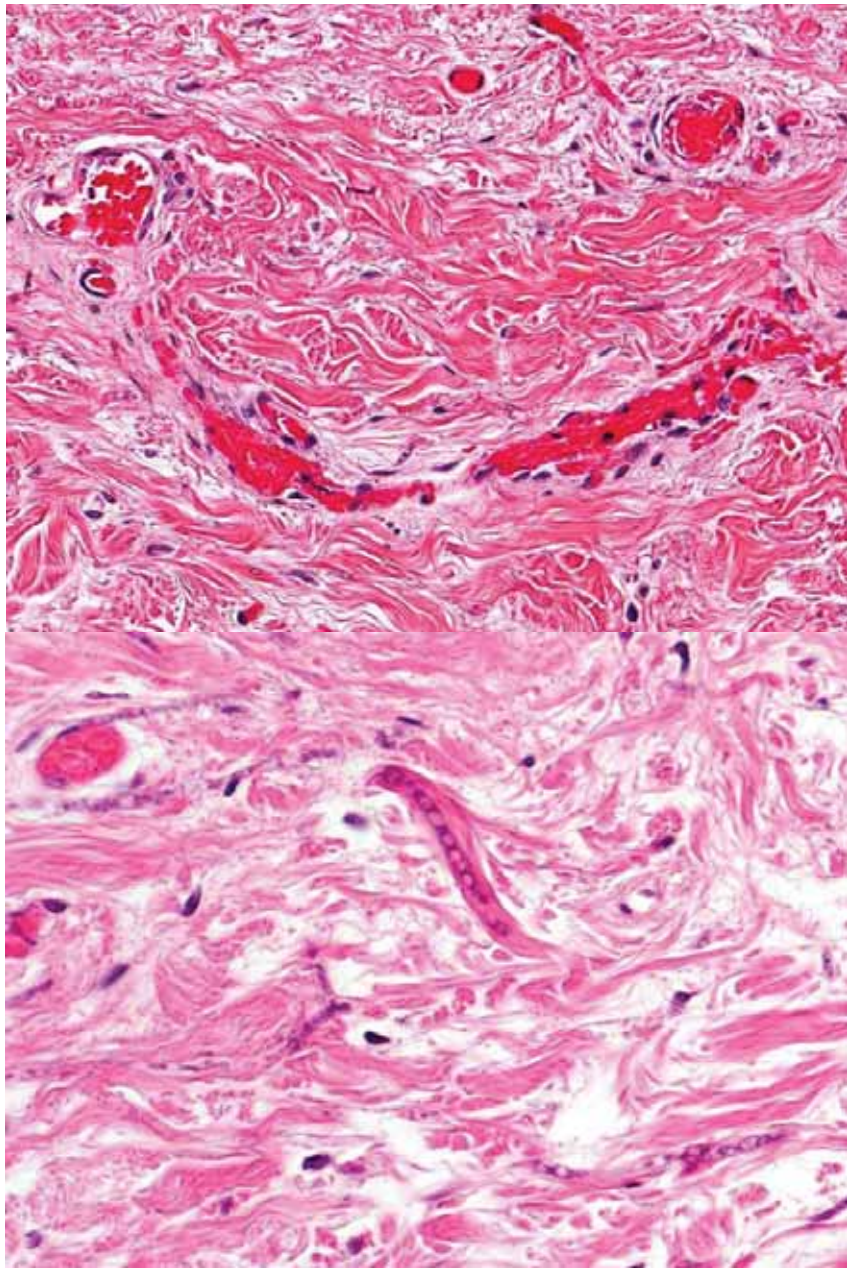
(phycomycosis, zygomycosis)

Rare, aggressive opportunistic fungal infection.
Growth within the lumen and walls of major blood vessels, resulting in thromboembolism with ischemia and necrosis.
Clinical variants: rhino-orbital-cerebral (70-100% mortality), pulmonary, cutaneous (5-10% mortality), gastrointestinal, and disseminated.
Therapy: systemic antifungals and surgical debridement.









Aspergillus sepsis

Aspergillus is a ubiquitous microorganism. Infection mostly in immunocompromised patients. In sepsis microorganisms within the blood vessels and free in the dermis and subcutis.

Mycetomas and botryomycosis

- *Mycetoma:* chronically discharging cutaneous infection with multiple sinus tracks, mostly confined to tropical countries; caused by bacteria (actinomycetoma) or fungi (eumycetoma)
  - *Actinomycetic mycetoma:* skin involvement rare, due to direct inoculation; abscess and colonies (granules) with radiating filamentous bacteria at the border
  - *Eumycetoma:* caused by various fungi; different species show grains of different color
- *Botryomycosis:* basophilic granules composed by nonfilamentous bacteria, usually with a surrounding PAS+ eosinophilic zone, embedded within suppurative inflammation ("bacterial pseudomycosis")
- *Splendore-Hoeppli phenomenon:* eosinophilic fringe around clumps of parasites

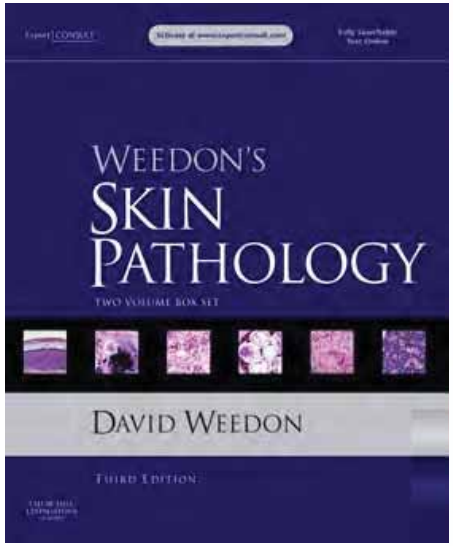
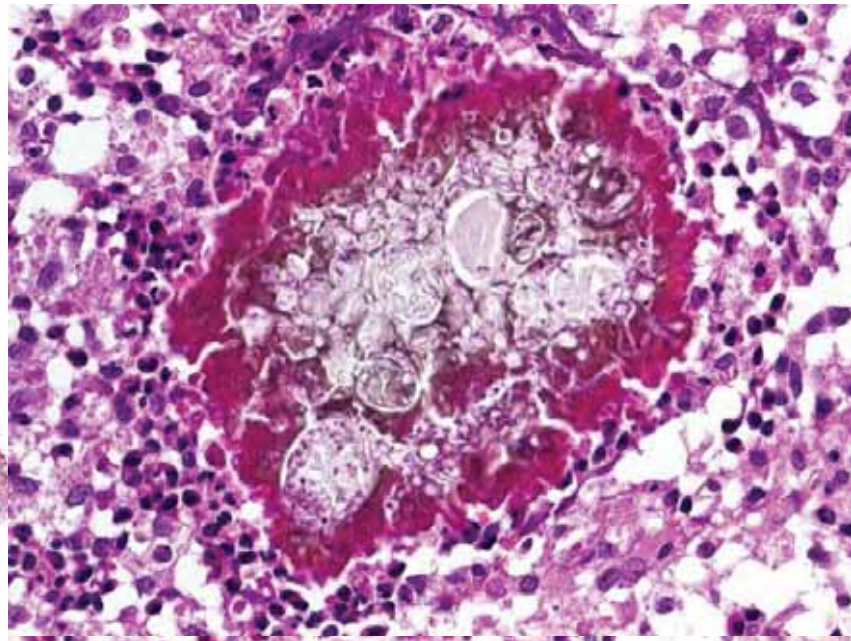
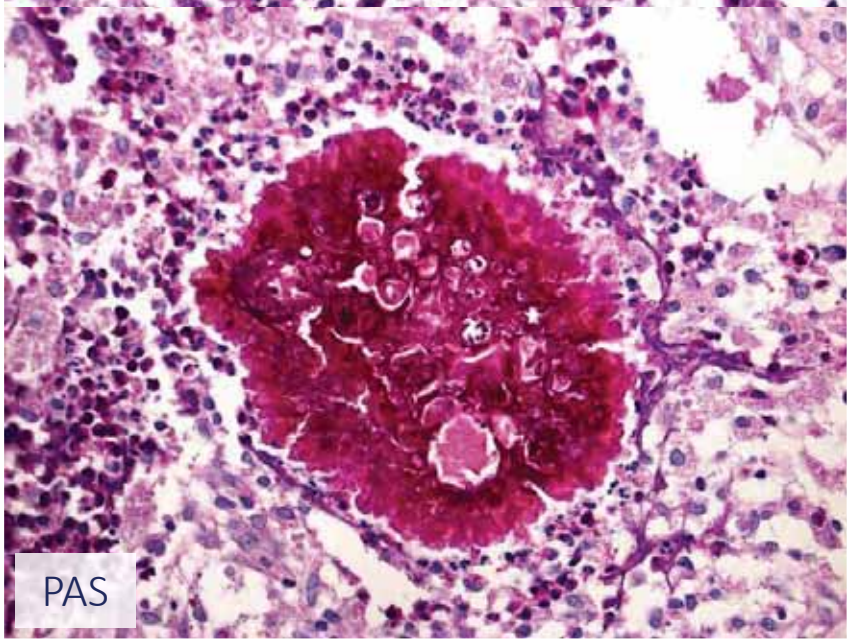


Table 25.1 Color of the grains (granules) in mycetomas

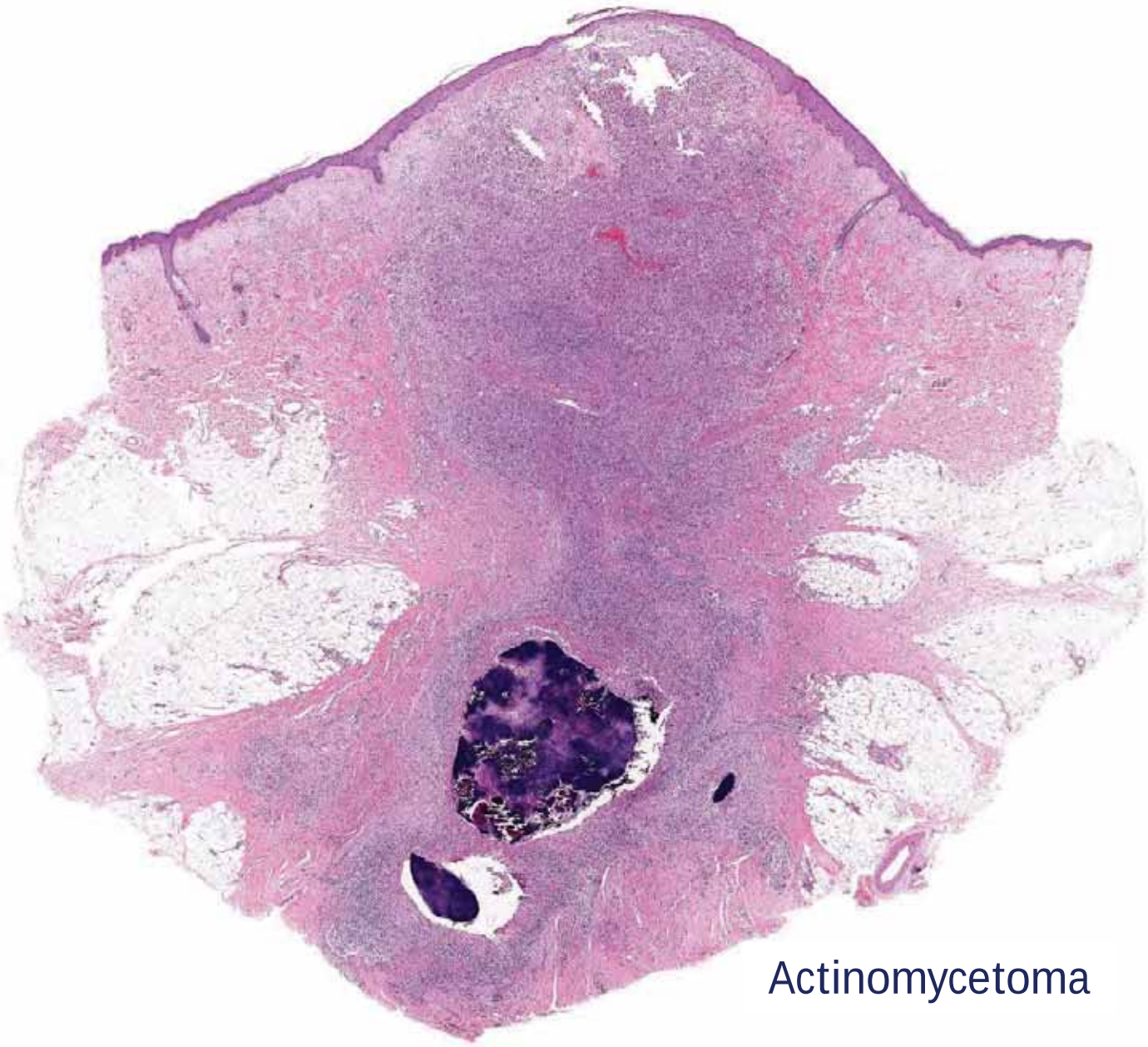
Eumycetomas
Black grains: *Madurella mycetomatis*, *M. grisea*, *Leptosphaeria senegalensis*, *Exophiala jeanselmei*, *Pyrenochaeta romeroi*, *Curvularia lunata*, *Phialophora verrucosa*, *P. parasitica*, *Cladophialophora bantiana*
Pale grains: *Petriellidium boydii*, *Aspergillus nidulans*, *A. flavus*, *Fusarium* sp., *Acremonium* sp., *Neotestudina rosatii*, dermatophytes
Brown grains: *Neoscytalidium dimidiatum*
Actinomycetomas
Red grains: *Actinomadura pelletieri*
Yellow grains: *Streptomyces somaliensis*
Pale grains: *Nocardia brasiliensis*, *N. cavae*, *N. asteroides*, *Actinomadura madurae*

Eumycetoma

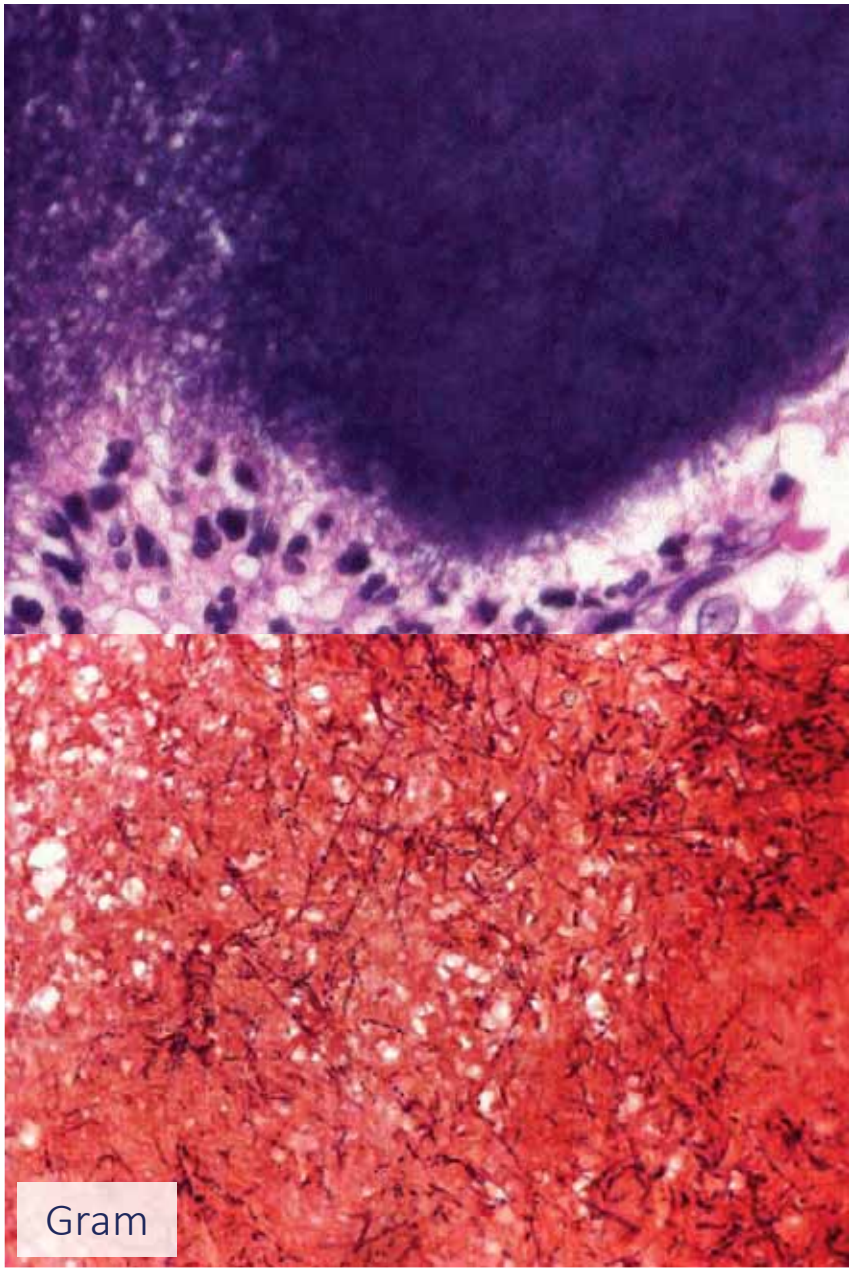




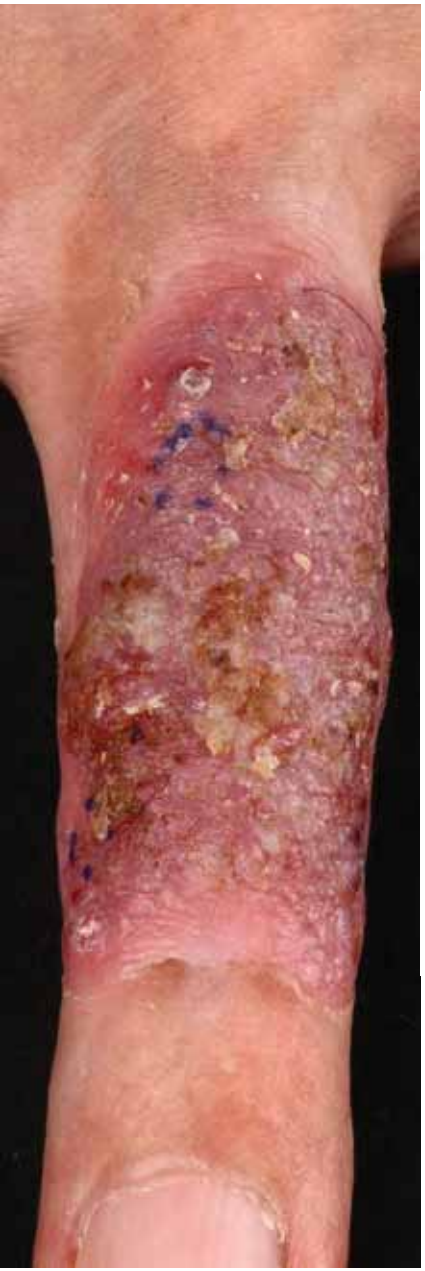
PAS

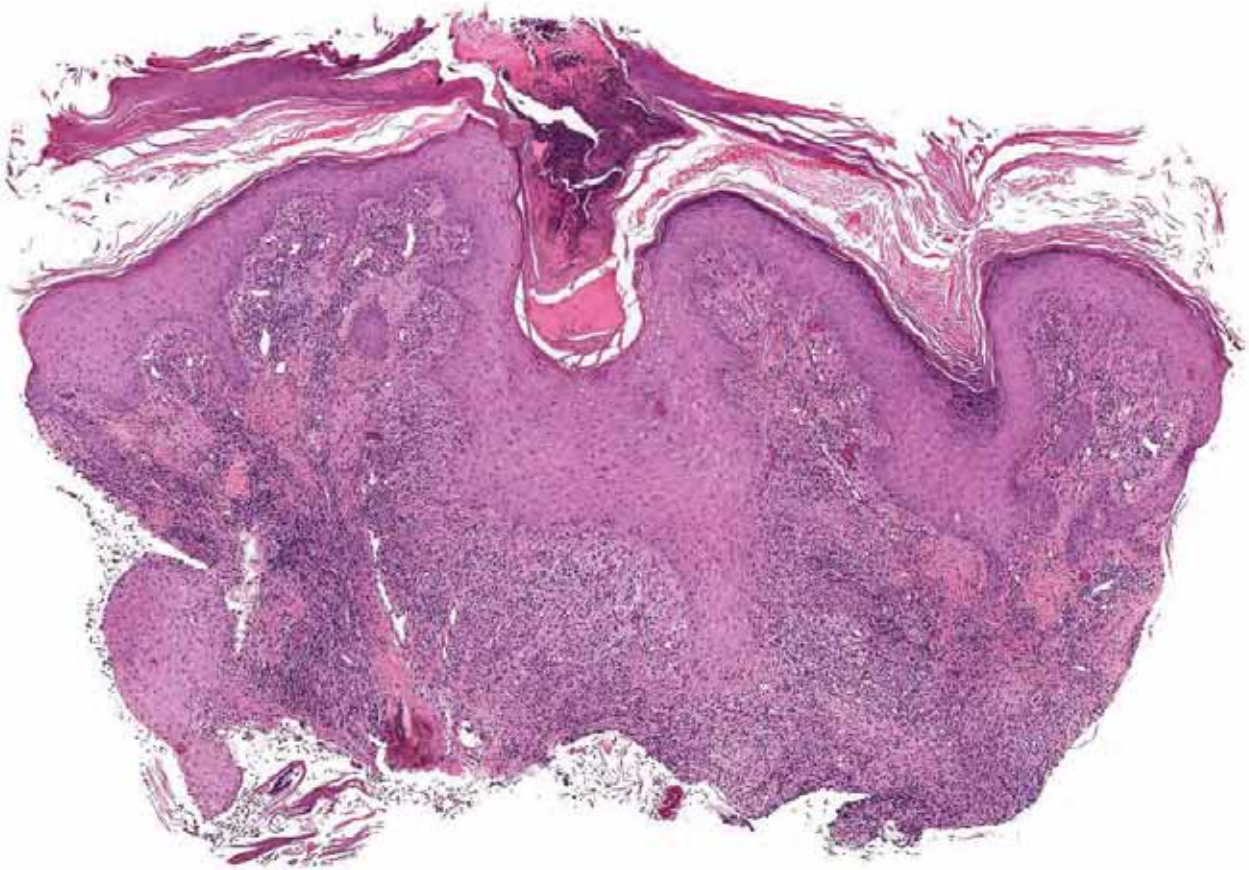


Actinomycetoma

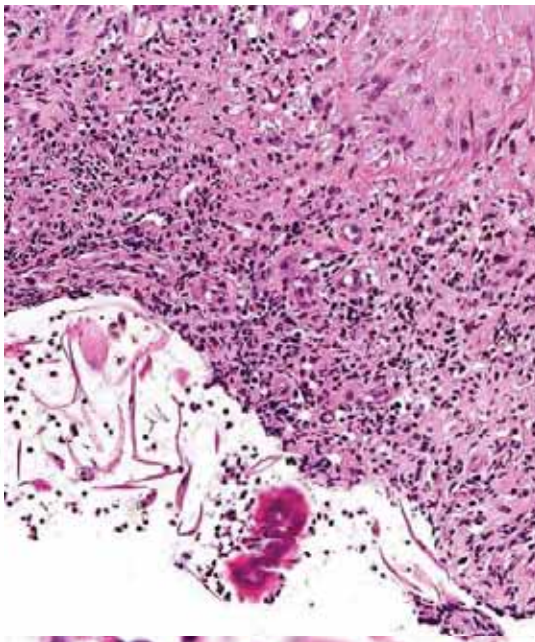


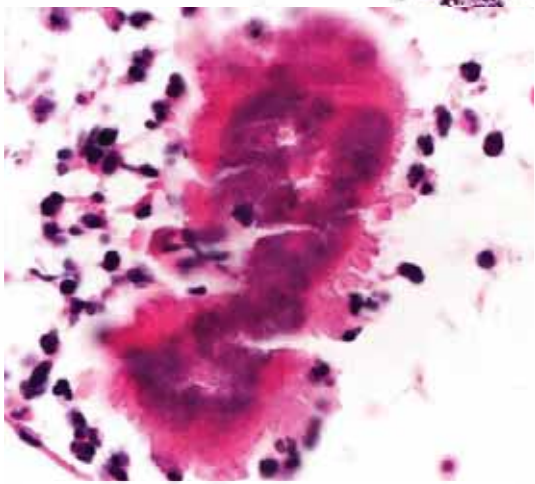
Gram



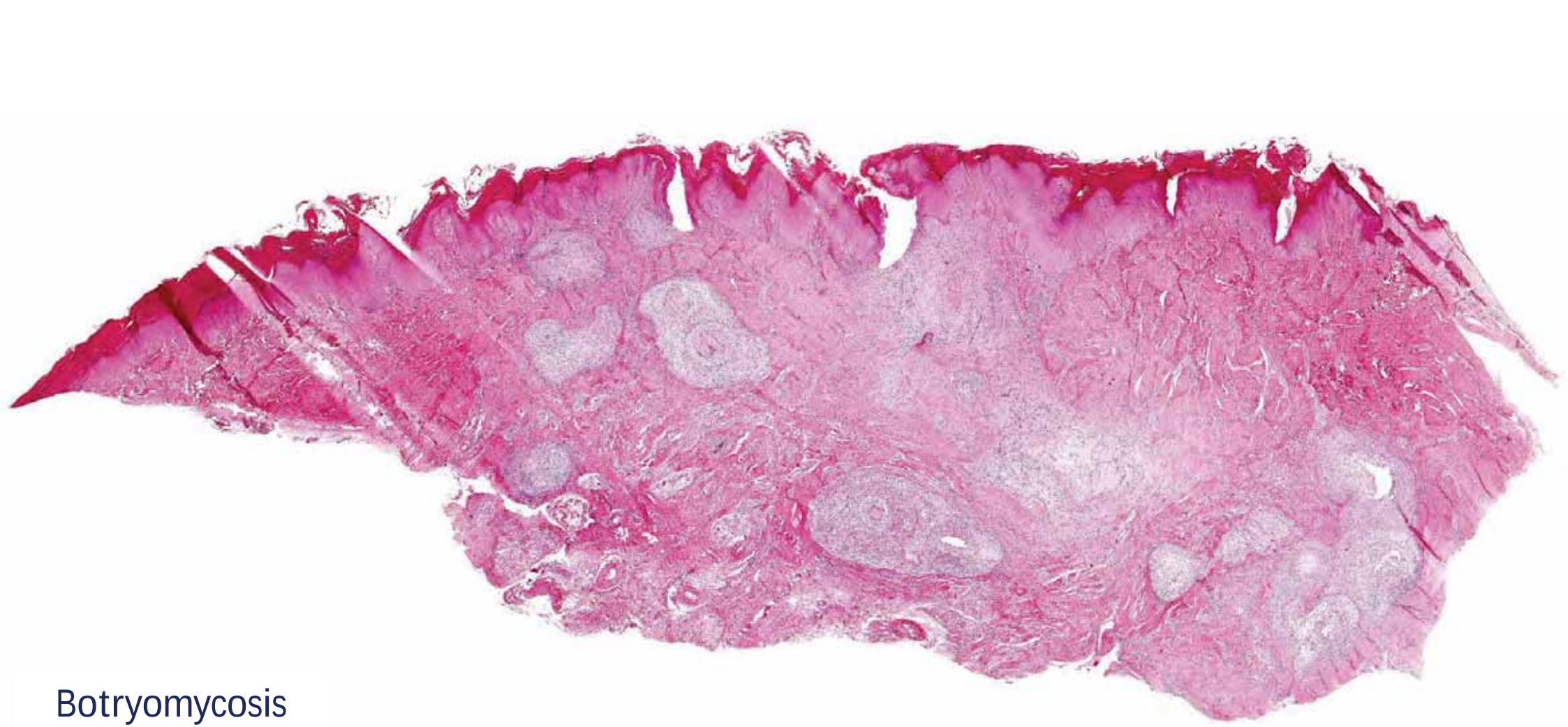


Botryomycosis

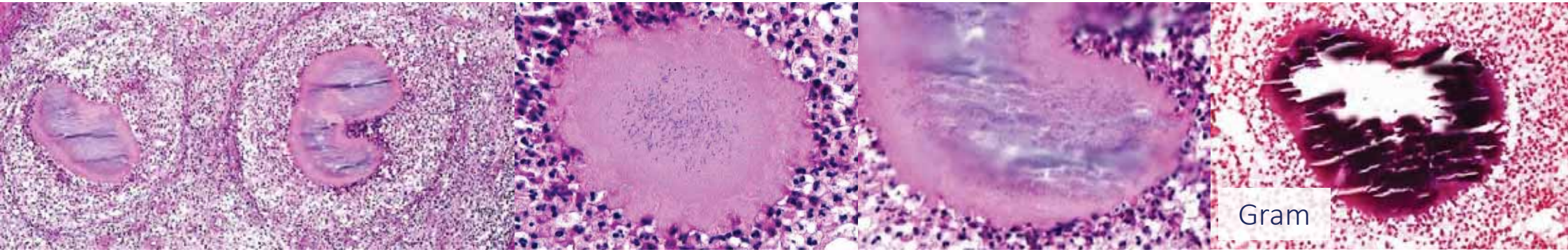




Splendore-Hoeppli phenomenon
(eosinophilic fringe around clumps of parasites)

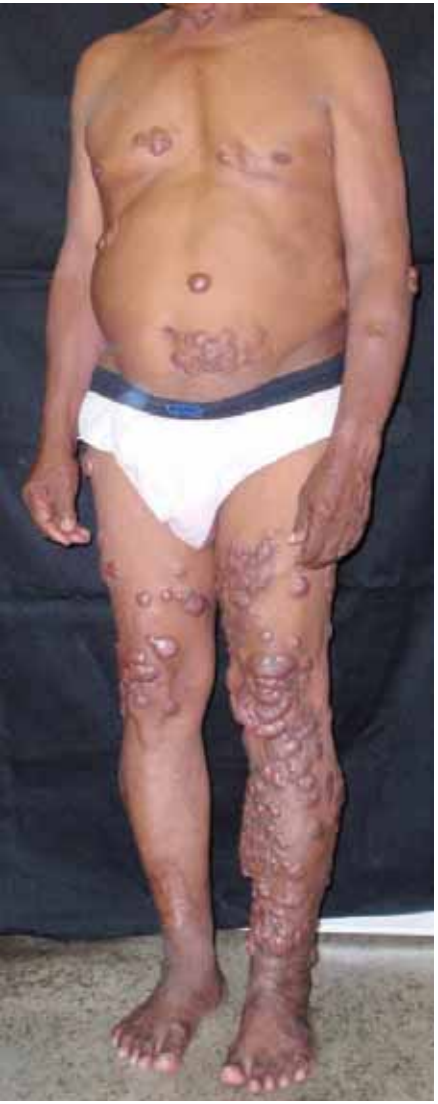


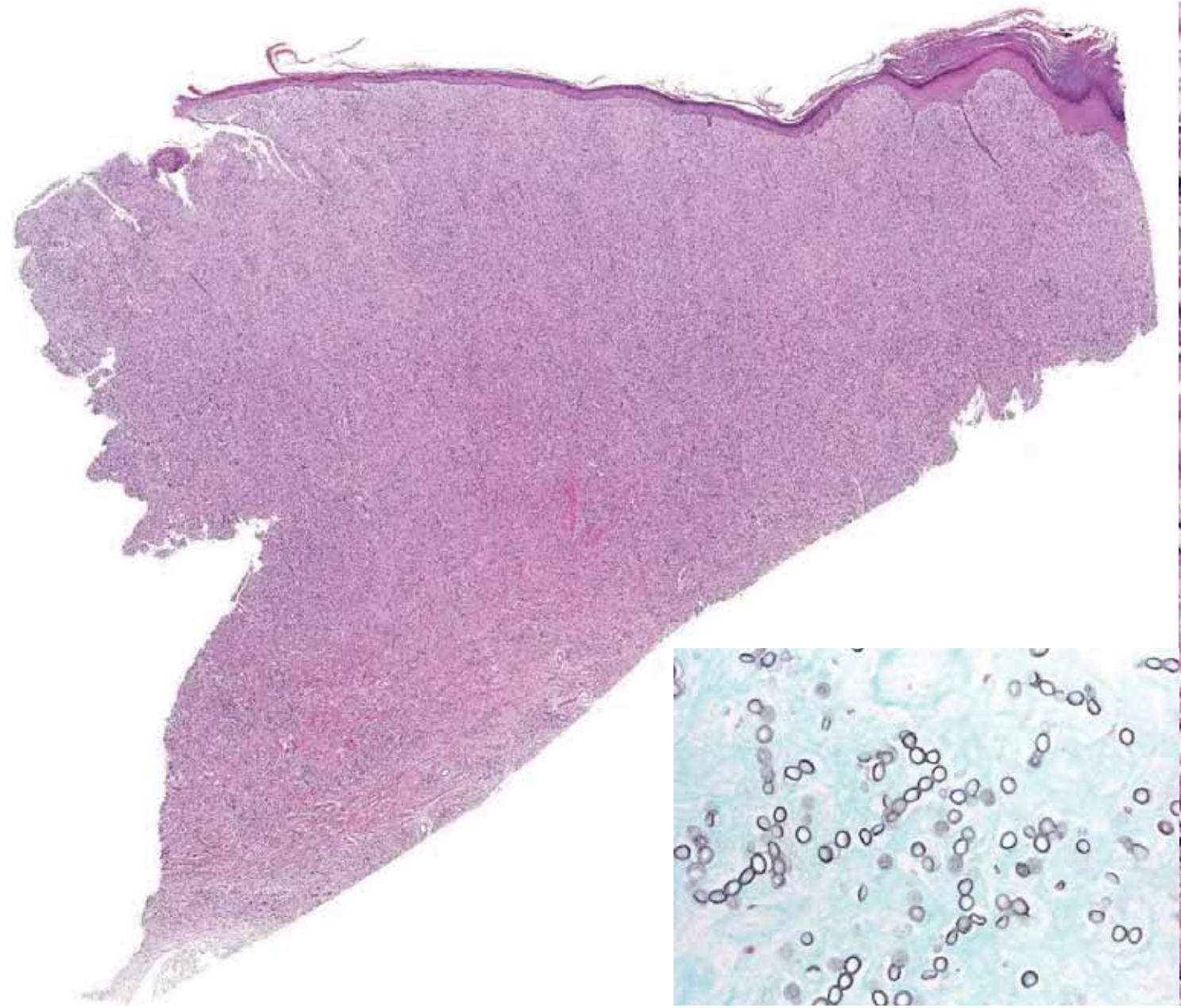
Botryomycosis

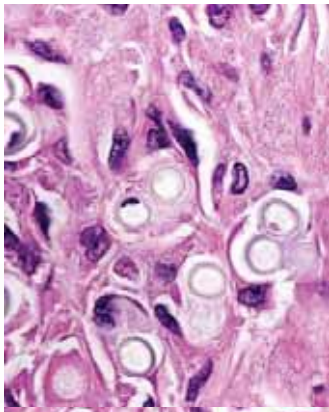


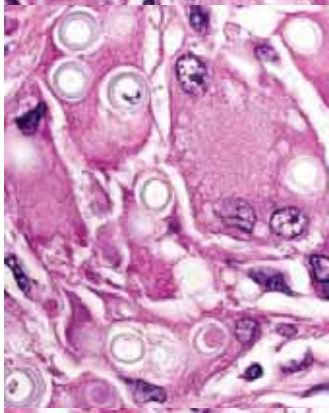
Lobomycosis

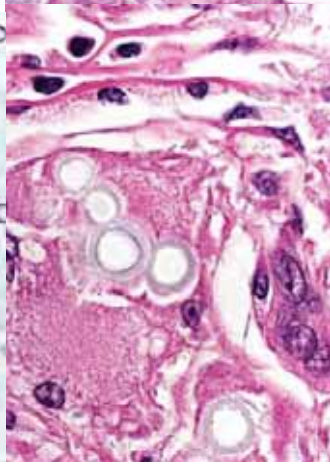
- *Lacazia loboi*, extremely slow-growing fungus endemic in some countries (esp. amazonas regions) and also affecting marine and fresh-water dolphins
- In endemic countries infection from soil and vegetation through skin injuries; reported in travellers to endemic countries or in those who had contacts with affected dolphins; disease in immigrants from endemic Countries may become evident several years after infection
- Prolonged incubation period (months / years)
- Slow-growing papules, nodules, or plaques of various sizes with smooth or verrucous surface; localized and (rarely) disseminated forms
- Round intracellular yeast of 6-12 nm in diameter; occur typically in linear or radiating chains of 2-20 organisms
- *Lacazia loboi* doesn't grow in culture

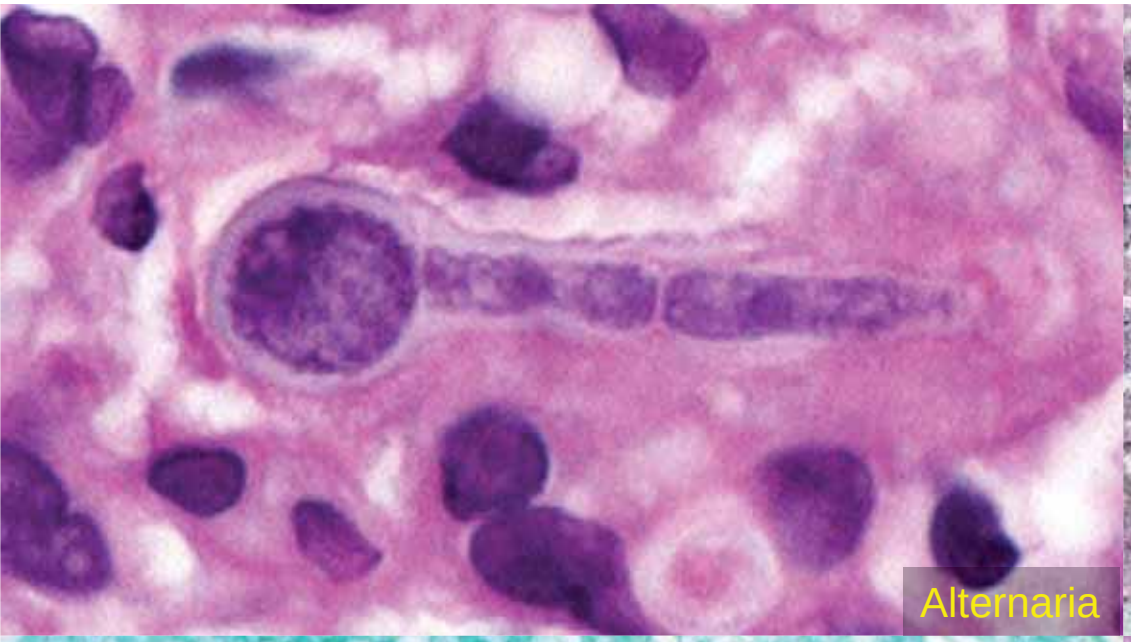


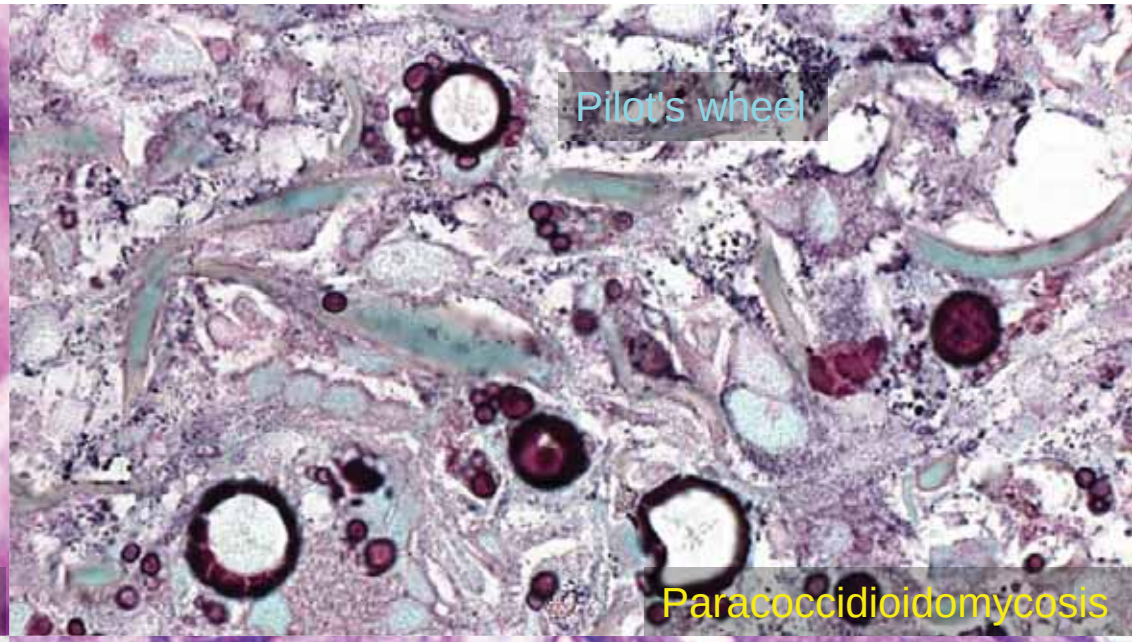


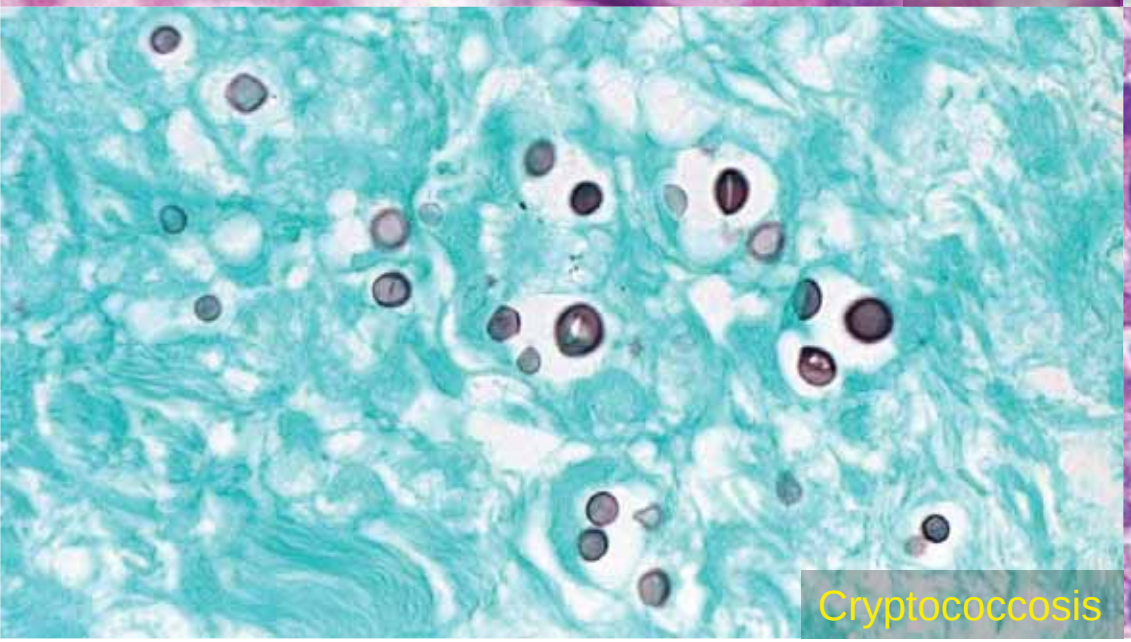


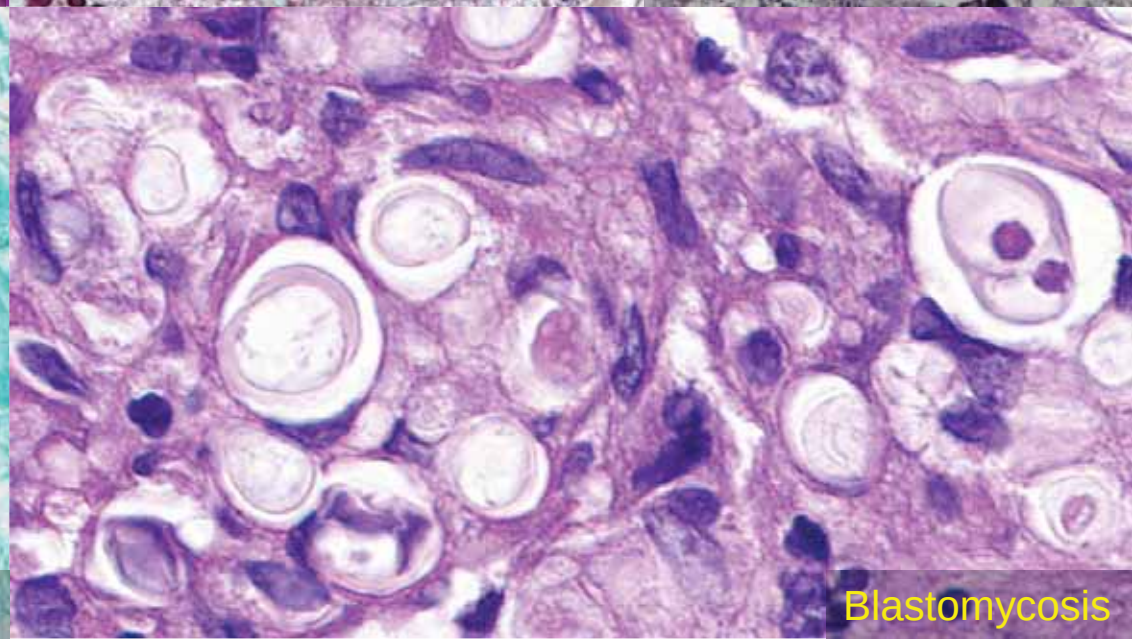


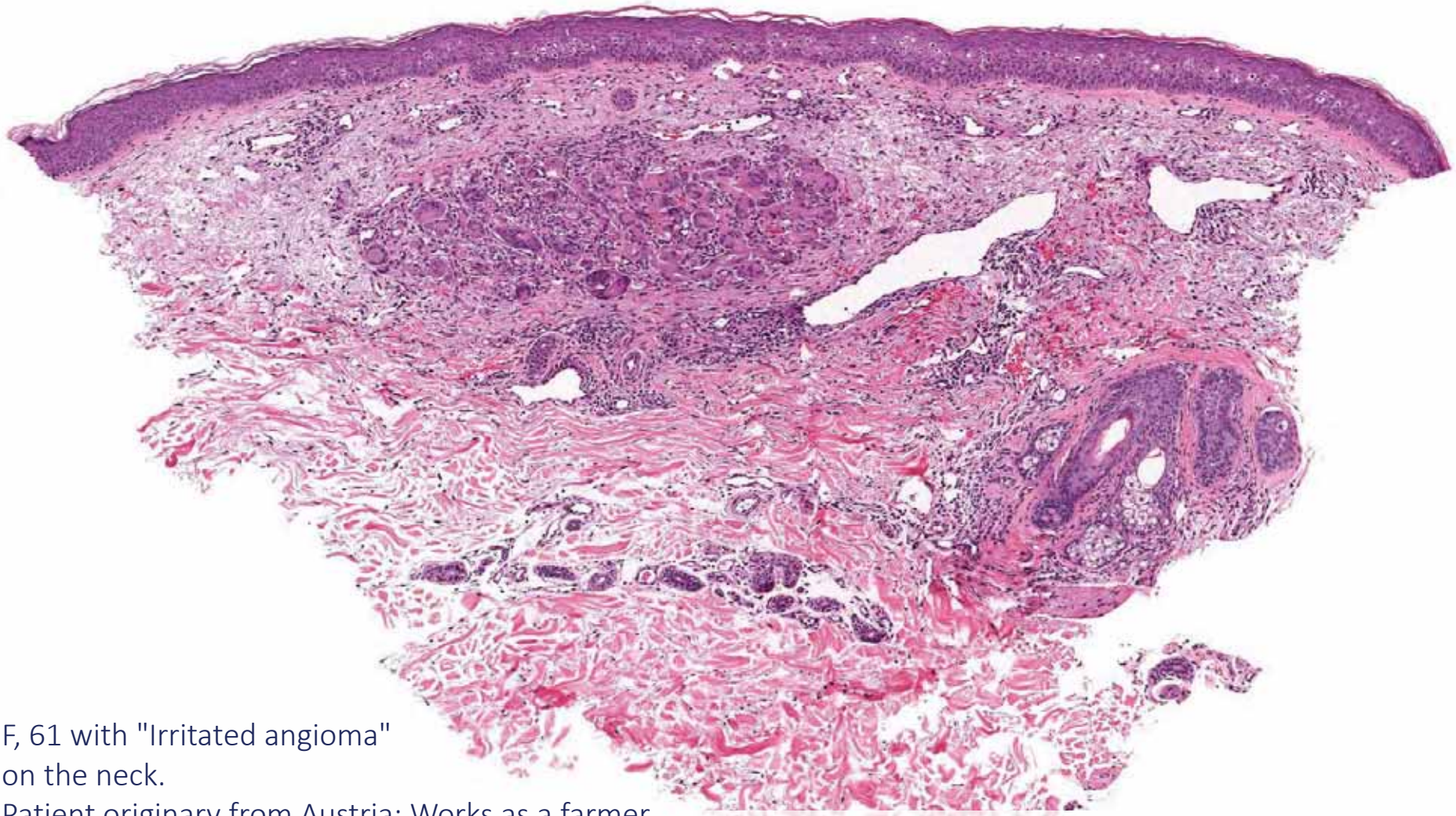


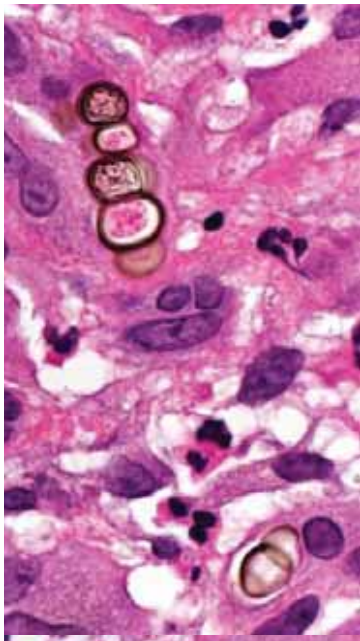

Alternaria

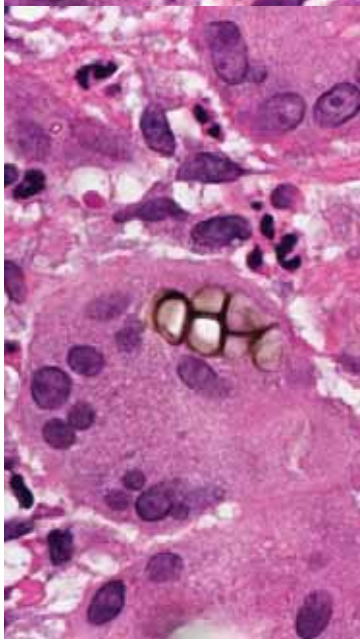

Pilot's wheel
Paracoccidioidomycosis


Cryptococcosis


Blastomycosis







F, 61 with "Irritated angioma"
on the neck.
Patient originary from Austria; Works as a farmer in a rural area; no history of trips in tropical countries (as a matter of fact, no history of any trip in any Country).

Chromoblastomycosis

Chromo(blasto)mycosis

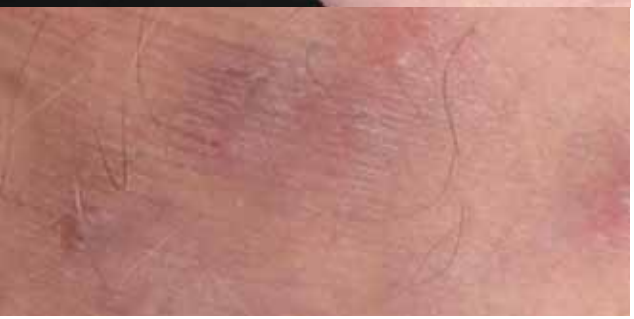
- Mycotic infection of skin and subcutaneous tissues caused by saprophytic, pigmented fungi present in soil and plant debris
- Mostly in tropical or subtropical climates, often in rural areas; Occupational hazard in rural workers in endemic Countries
- Rarely presents as phagedenic ulcer
- Round, thick-walled, 5–12 µm dark golden particles (sclerotic bodies, muriform cells, medlar bodies), mostly within histiocytic giant cells

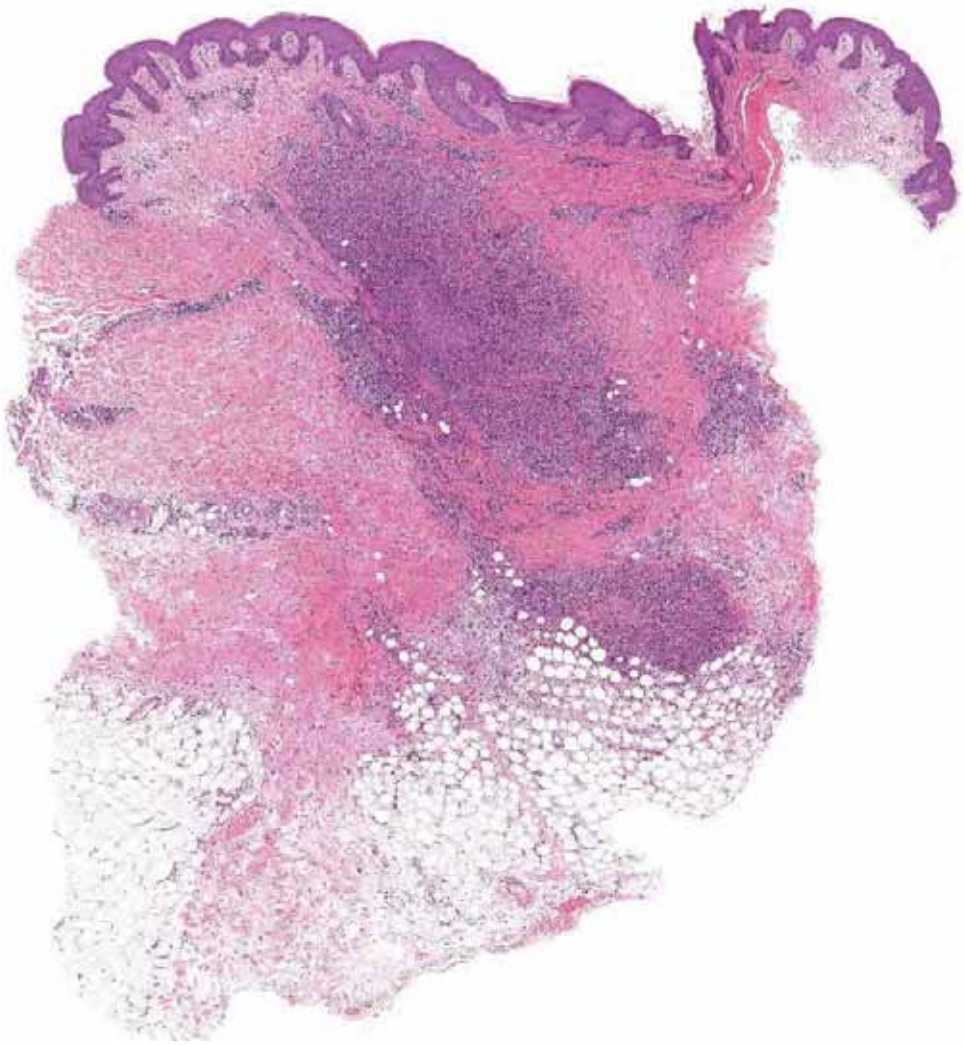
M, 51

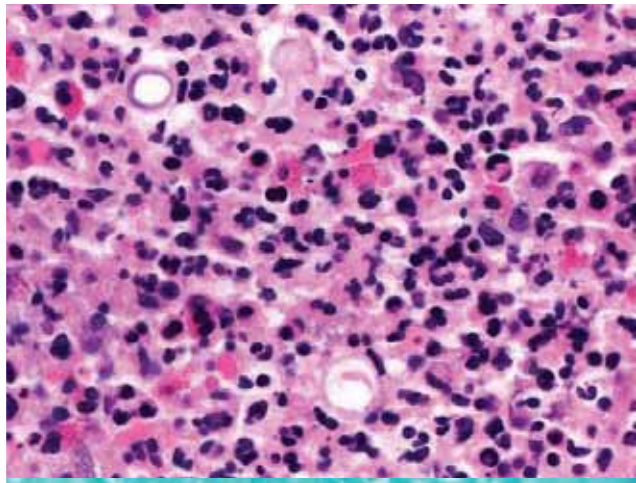
History of melanoma stage IV with multiple metastases in CNS, lymph nodes, liver, lung, pancreas, skin.

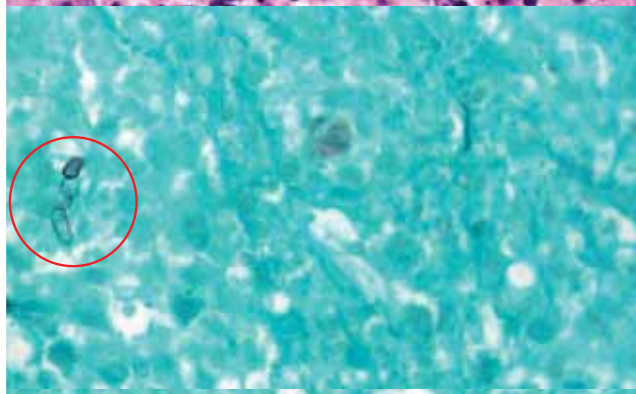
Partly suppurartive lesions on the left groin for some weeks.

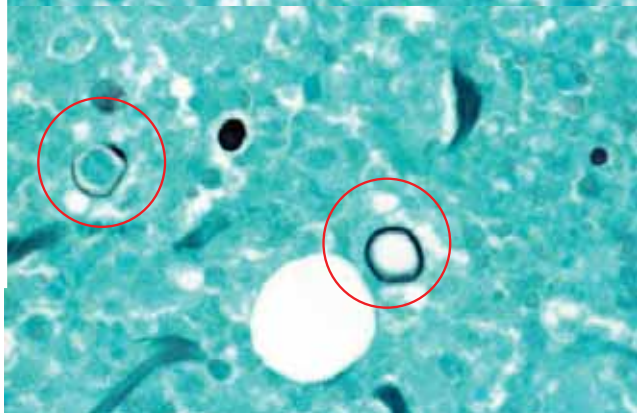
Trip to Dominican Republic 28 years before, no other trips to tropical Countries.











Paracoccidioidomycosis ?

Dear Lorenzo
I agree that, considering all the big ones: para, blasto, lobo and prototheca, this one looks more like paracocci. What I barely see is budding. Budding helps, especially if the neck of the bud is thin. Also, look on the special stains for yeast of all sizes, big ones and small ones: that also favors paracocci. I will show the pictures to my colleagues from path tomorrow.
Best regards, Paco

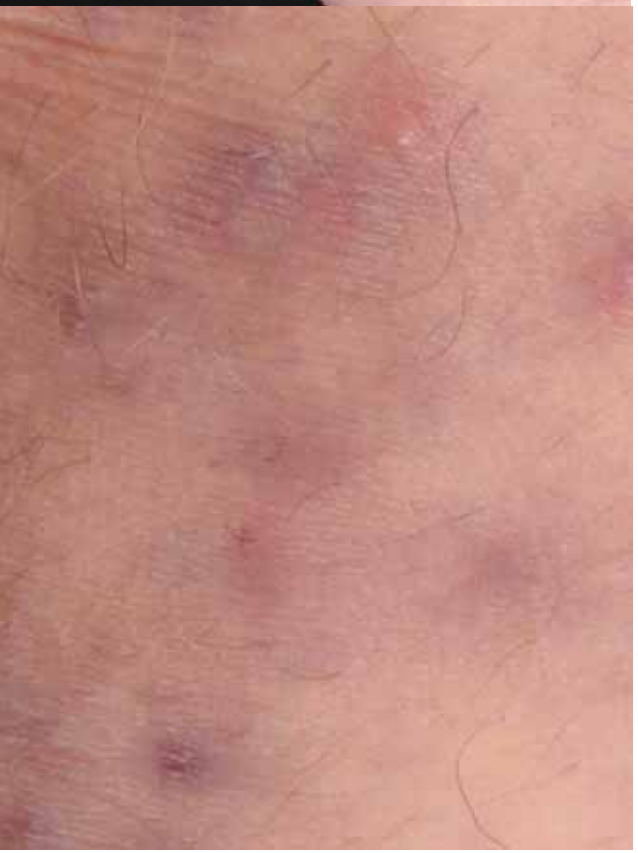
Taking the history we found out that the patient was in the Dominican Republic, but it was 28 years ago.

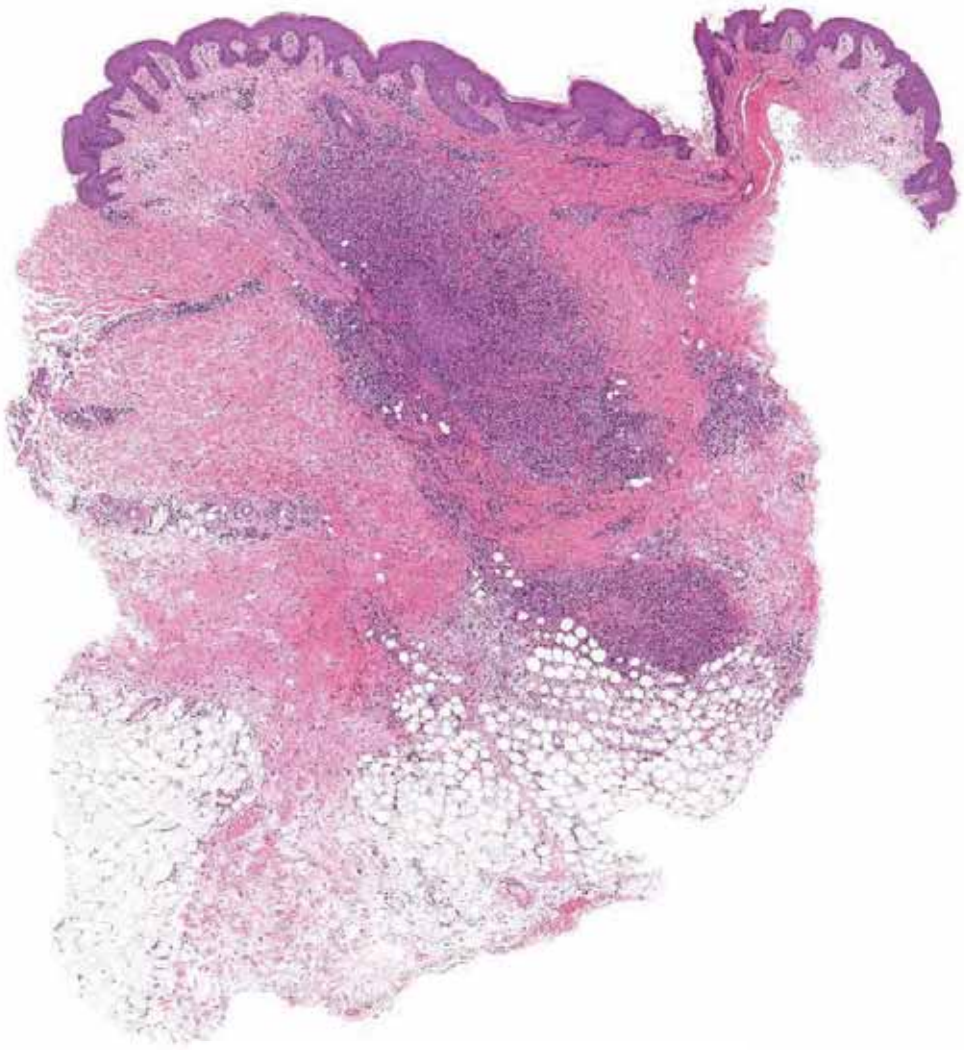
That is very interesting. One infection common in the Dominican Republic is Conidiobolomycosis (common is kind of relative). I thought about it when I saw the eosinophils. Paracocci do not have hyphae. Let me consult with a micologist friend from Mexico. Keep you informed.
Regards, Paco

My Mexican friend says it is rare to have round big cyst in conidiobolomycosis and mostly are big hyphae similar to mucor. Based on morphology, blasto and less likely crypto. He added a fungus I never heard before, Emmonsia crescens or E. parva. I really hope something will grow on culture.
Regards, Paco

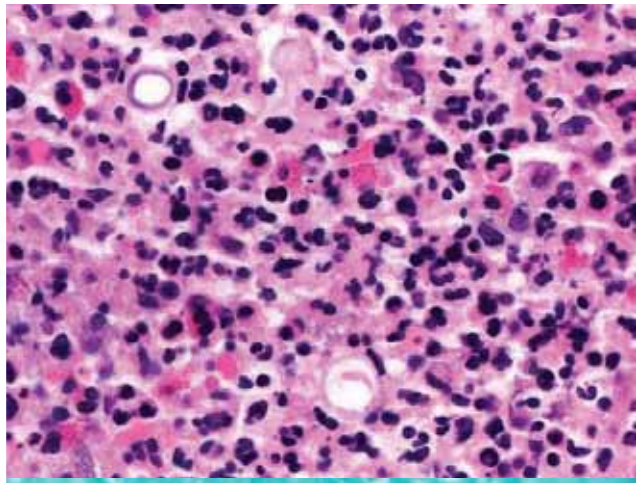
I received the results of culture, which are quite surprising: only *Trichopyton rubrum* was growing. Have you ever seen such a discrepancy - and do you have some kind of explanation?

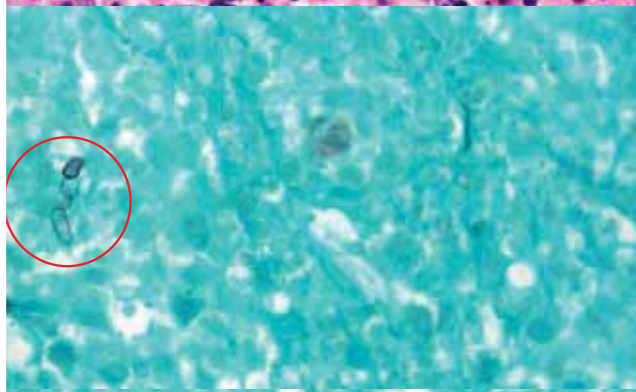
Never, but fungi are a never ending story
Regards, Paco

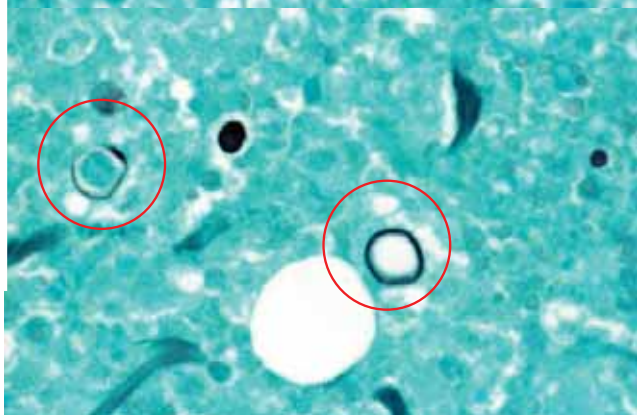




Tr. rubrum







Invasive *Trichophyton rubrum* resembling blastomycosis infection in the immunocompromised host

Robyn F. Squeo, MD,[a] Robert Beer, MD,[a] David Silvers, MD,[a,b] Irene Weitzman, PhD, ABMM,[c] and Marc Grossman, MD, FACP[a] *New York, New York*

A 55-year-old renal transplant recipient with onychomycosis and chronic tinea pedis presented with tender nodules on his left medial heel. He then developed papules and nodules on his right foot and calf. A skin biopsy demonstrated periodic acid-Schiff (PAS) positive, thick walled round cells, 2 to 6 μm in diameter, in the dermis. Skin biopsy culture grew *Trichophyton rubrum*. *T rubrum* has been described as an invasive pathogen in immunocompromised hosts. The clinical presentation, histopathology, and early fungal culture growth suggested *Blastomyces dermatitidis* in the differential diagnosis before the final identification of *T rubrum*. (J Am Acad Dermatol 1998;39:379-80)

Trichophyton rubrum, an anthropophilic ectothrix dermatophyte causes minor skin infection usually confined to the hair, nails, and stratum corneum in healthy persons. In immunocompromised patients, the clinical and histopathologic features of dermatophyte infection may be atypical and the differential diagnosis may include infectious, inflammatory, and neoplastic conditions.[1-4] We describe a renal transplant recipient with chronic onychomycosis, tinea pedis, and multiple lower extremity nodules caused by *T rubrum* that histologically suggested the microform of *Blastomyces dermatitidis*.

CASE REPORT

A 55-year-old renal transplant recipient had multiple, fluctuant, erythematous nodules on his right foot and calf and left foot and heel. The patient had a history of end-stage renal disease caused by chronic hypertensive glomerulonephritis, noninsulin dependent diabetes mellitus, and coronary artery disease. He was treated with hemodialysis until he underwent a cadaveric kidney transplant 11 years ago.

He received a second renal transplant because of chronic rejection 5 months before presentation. Maintenance medications included prednisone (10 mg daily), FK506 (3 mg bid), lanoxin, isosorbide dinitrate, docusate sodium, glyburide, propranolol, and ranitidine.

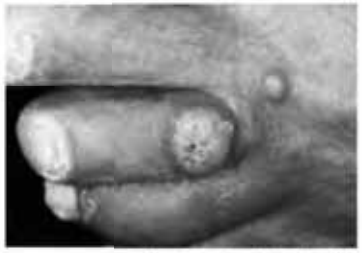


Fig. 1. Crusted, erythematous dome-shaped nodule with minute pustules on dorsum of right third toe caused by *T rubrum*. Chronic onychomycosis was also present.

Examination revealed 2 tender, erythematous nodules on the dorsum of the third toe and heel of left foot. Minute pustules on the side wall of an erythematous crusted nodule were also present on the dorsum of the right third toe (Fig. 1). Two days later, a violaceous nodule developed on his right calf. Interdigital toe web maceration and onychodystrophy were also present.

A biopsy specimen showed scale crust overlying an acanthotic epidermis. Within the dermis, there were pleomorphic organisms that varied from oval to round and ranged in size from 2 to 6 μm in diameter (Fig. 2). Some exhibited germ tubes (Fig. 3) and bizarre hyphal forms. The early development of the culture appeared glabrous and produced spicules on Sabouraud dextrose

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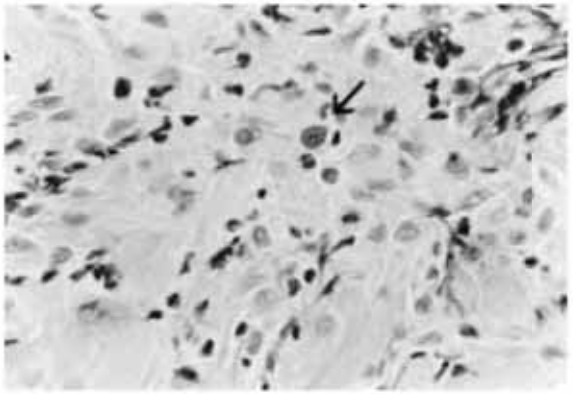

Fig. 2. Pleomorphic spore-like organisms associated

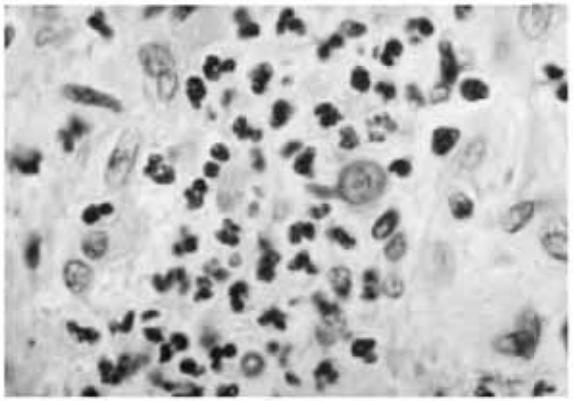

Fig. 3. Fungal structures demonstrate germ tube morphology. (PAS ×650.)

The skin biopsy specimen from this patient demonstrated many thick walled, small, round cells in the dermis with a few single buds and bizarre hyphae

Cutaneous leishmaniasis

- Leishmaniasis is becoming more frequent in non-endemic Countries due to travelers, refugees, troops stationed in endemic areas
- Europe: "old-world" leishmaniasis (*L. tropica*)
- Acute ("oriental boil", "Aleppo boil"), chronic (may mimic a variety of skin conditions), disseminated (anergic hosts)
- Lesions usually solitary on exposed surfaces
- Histopathological features may be partially overlapping with those of syphilis (granulomatous infiltrate with plasma cells)
- Intracytoplasmatic microorganisms usually easily found, but may be present only focally (check especially the subepidermal histiocytes in the center of the infiltrate)
- Must be differentiated from other intracytoplasmatic microorganisms (e.g., histoplasmosis – different clinical setting)

Cutaneous leishmaniasis

- Endemic in many countries in four continents
- Several cases in immigrant patients
- Transmission requires presence of infected sandflies

Source: https://www.researchgate.net/figure/a-Status-of-visceral-leishmaniasis-in-the-world-b-Status-of-cutaneous-leishmaniasis_fig2_350687464

An Epidemic Outbreak of Cutaneous Leishmaniasis Presenting as Suppurative Folliculitis: A Study of 6 Cases

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Abstract: Folliculitis is defined as the inflammation of the follicles. The most common cause of folliculitis is infection. Here, we report an unusual cause of suppurative infundibulitis—which had not yet been described in the literature—due to *Leishmania* infection and exemplified by 6 cases that occurred in the setting of an epidemic outbreak. The 6 individuals were immigrants from Morocco. Most of them were men (4 men and 2 women), and most of them were less than 30 years old (apart from one 40-year-old woman). In all cases, a cutaneous biopsy was performed. There was a granulomatous folliculitis with suppurative granulomas in all the cases. All cases showed prominence of plasma cells in the inflammatory infiltrate, and leishmanias were found in all cases. They were mainly seen in the abscessified central areas. The amount of organisms varied from a few to a moderate amount. They were stained by the anti-CD1a antibody (Novocastra) and by a polyclonal homemade anti-leishmania antibody. In addition, in 1 case, microbiological culture was performed, and *Leishmania major* was demonstrated as the causative agent of the infection.

Key Words: folliculitis, leishmanias, leishmaniasis, outbreak, *L. major*

(*Am J Dermatopathol* 2017;39:363–366)

INTRODUCTION

Folliculitis is defined as the inflammation of the follicles, although at early stages, the inflammation often involves only the infundibulum, which is considered part of the epidermis.

The most common cause of folliculitis is infection. Among the causative microorganisms, the most frequent are bacteria, such as *Staphylococcus aureus*, Gram-negative microorganisms (*Enterobacter*, *Klebsiella*, *Escherichia*, *Serratia*, *Proteus*, or *Pseudomonas*), dermatophytes, *Malassezia*, parasites such as *Demodex*, and viruses such as Herpes or varicella zoster.

In this study, we report an unusual cause of suppurative infundibulitis—which had not yet been described in the literature—due to *Leishmania* infection and exemplified by 6 cases that occurred in the setting of an epidemic outbreak.

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The authors declare no conflicts of interest.

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REPORT OF THE CASES

Six cases were diagnosed and treated in the Spanish National Health System in 6 individuals who were immigrants from Morocco. The 6 individuals had entered Spain between 2009 and 2010, and they were all originally from the city of Erradichia (الرشيدية, *ar-Rachidiya*).

Table 1 shows the clinical data of the 6 individuals. All cases presented with single nodular lesions. In 5 cases, the lesions were located on the extremities, whereas in 1 case the lesion was located on the nape of the neck (Fig. 1). Most of them were men (4 men and 2 women), and most of them were less than 30 years old (apart from one 40-year-old woman). They were part of the same family, but the exact relationships between them could not be precisely established.

In all cases, a cutaneous biopsy was performed. In all cases, similar features were found in the biopsies (Fig. 2), including a granulomatous folliculitis with suppurative granulomas (Fig. 3A, B).Table 2 shows the main histopathological features identified. All cases showed prominence of plasma cells in the inflammatory infiltrate (Fig. 3C). The epidermis was hyperkeratotic and hyperplastic in all cases.

Gram staining was performed to rule out a bacterial infection, and no bacteria were found in any of the cases.

Leishmanias were found in all cases (Fig. 3D). They were mainly seen in the abscessified central areas. The amount of organisms varied from a few to a moderate amount. They were stained by the anti-CD1a antibody (Novocastra) (Fig. 3E). They were also stained by a polyclonal homemade antibody, which was obtained by immunization of rabbits with a suspension of sonicated promastigotes of an *L. infantum* strain (zymodeme MON-1) at a concentration of 1 mg/mL (Fig. 3F). In addition, in 1 case, microbiological culture was performed, and *L. major* was identified as the causative agent of the infection.

DISCUSSION

Leishmaniasis can manifest in many histopathological presentations. However, to the best of our knowledge, suppurative folliculitis in humans has not yet been described in the literature as one of these presentations. This is surprising in light of 2 facts: first, the follicle is one of the areas where insects prefer to sting,[5] because infundibula (as

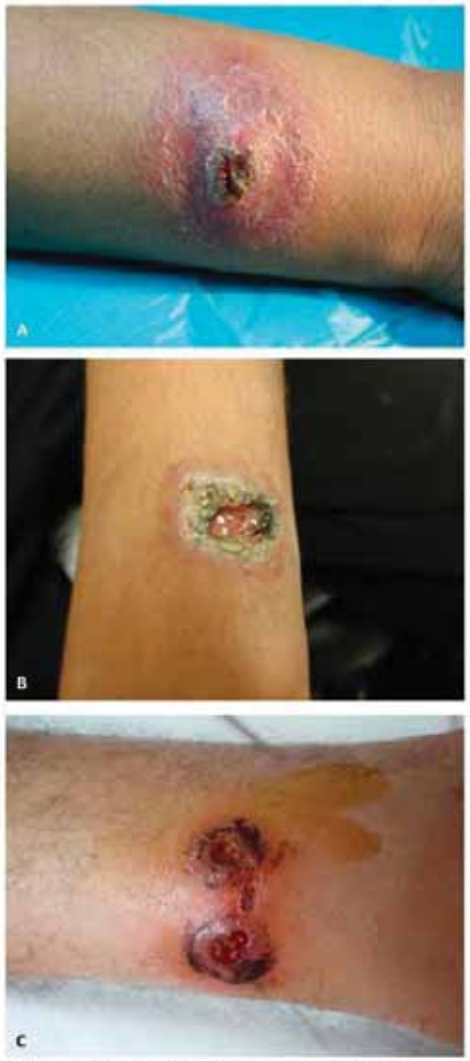


FIGURE 1. Clinical appearance of ulcerative and suppurative lesions from cases 1 (A), 5 (B), and 6 (C).

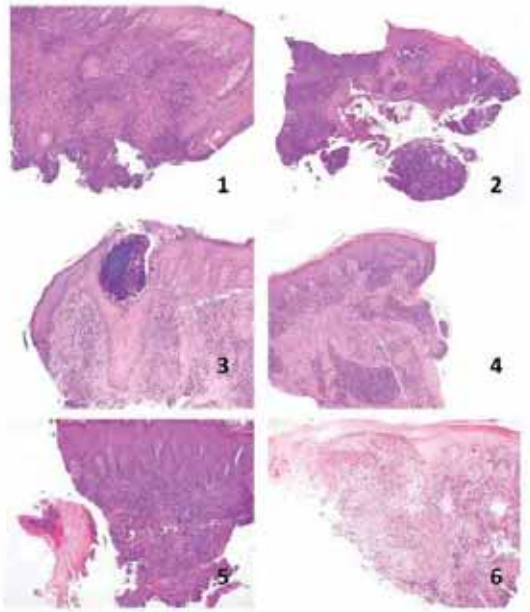
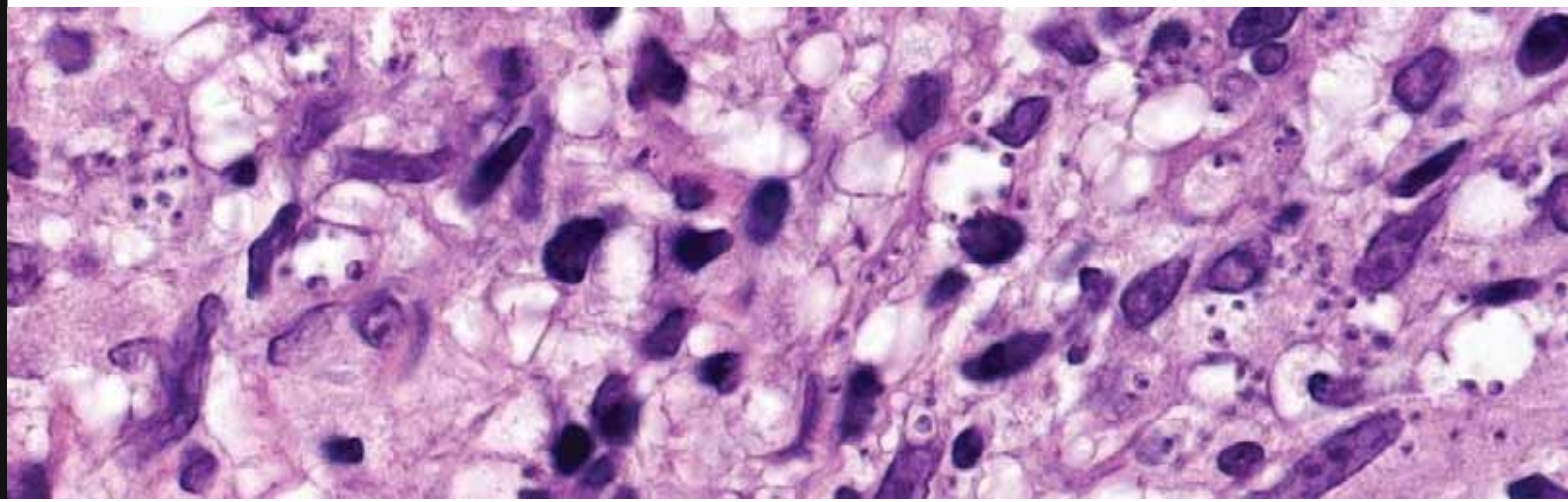
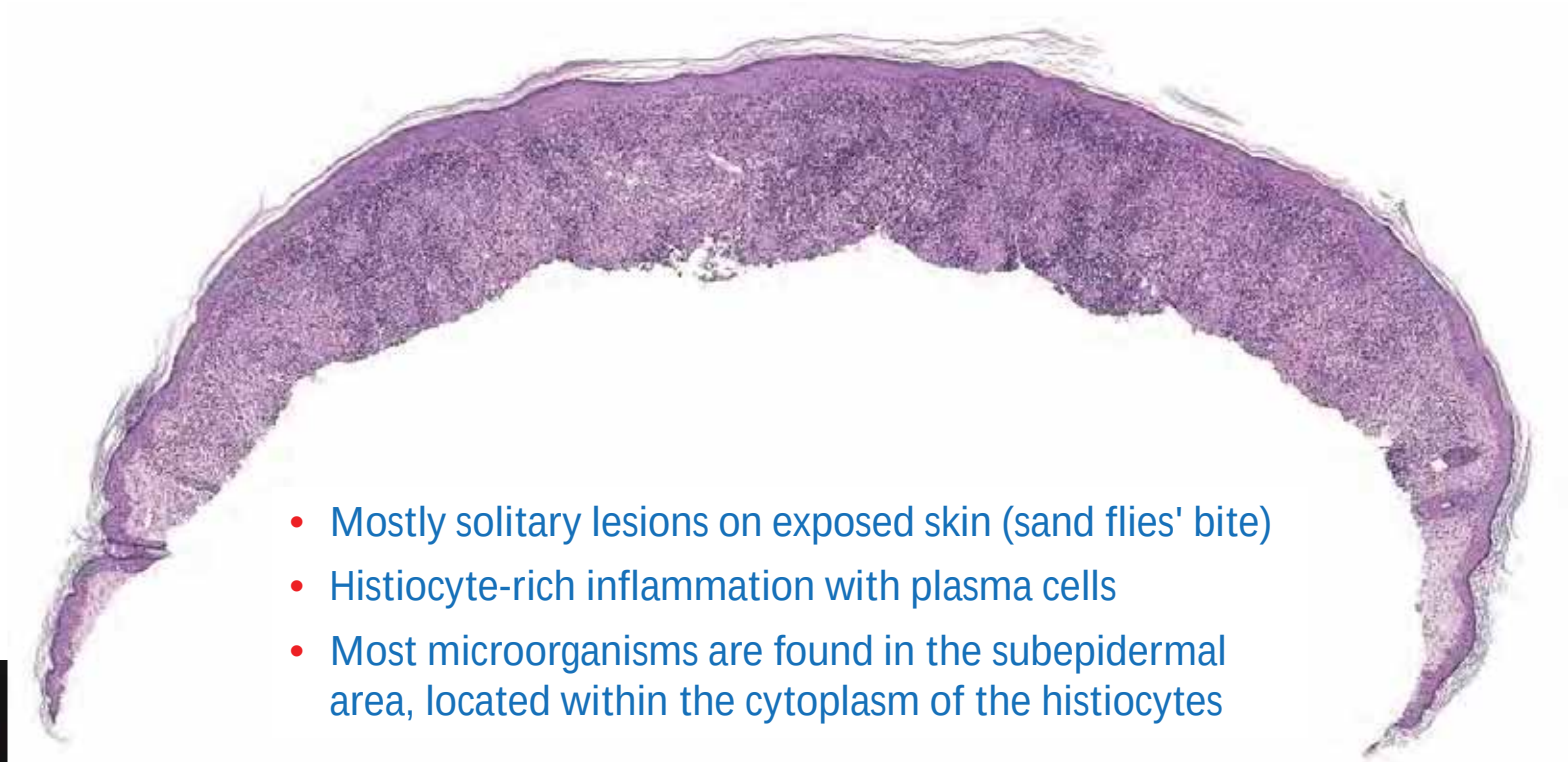
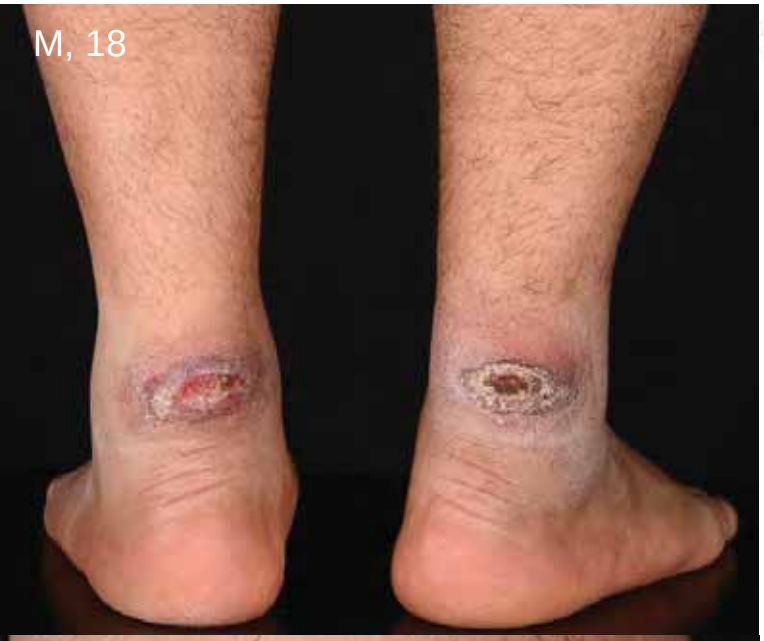


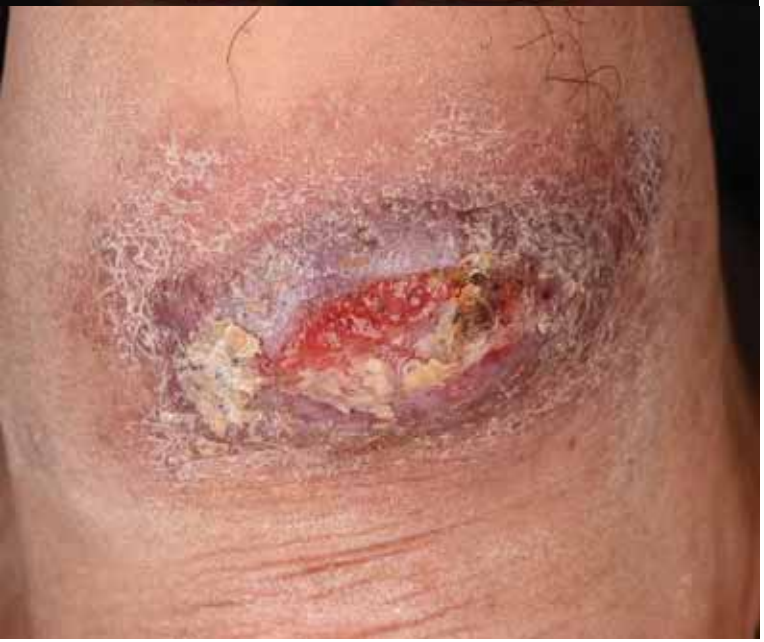
FIGURE 2. Numbered biopsies of the 6 cases. All cases showed an ulcerative granulomatous suppurative folliculitis.

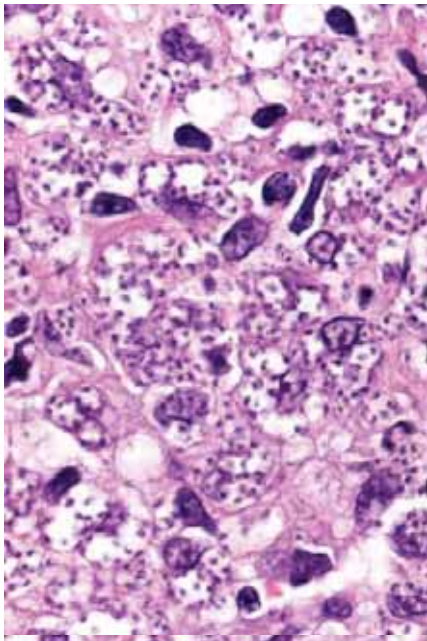


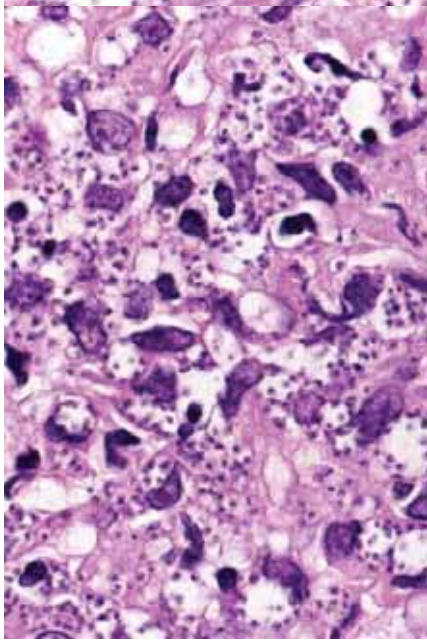


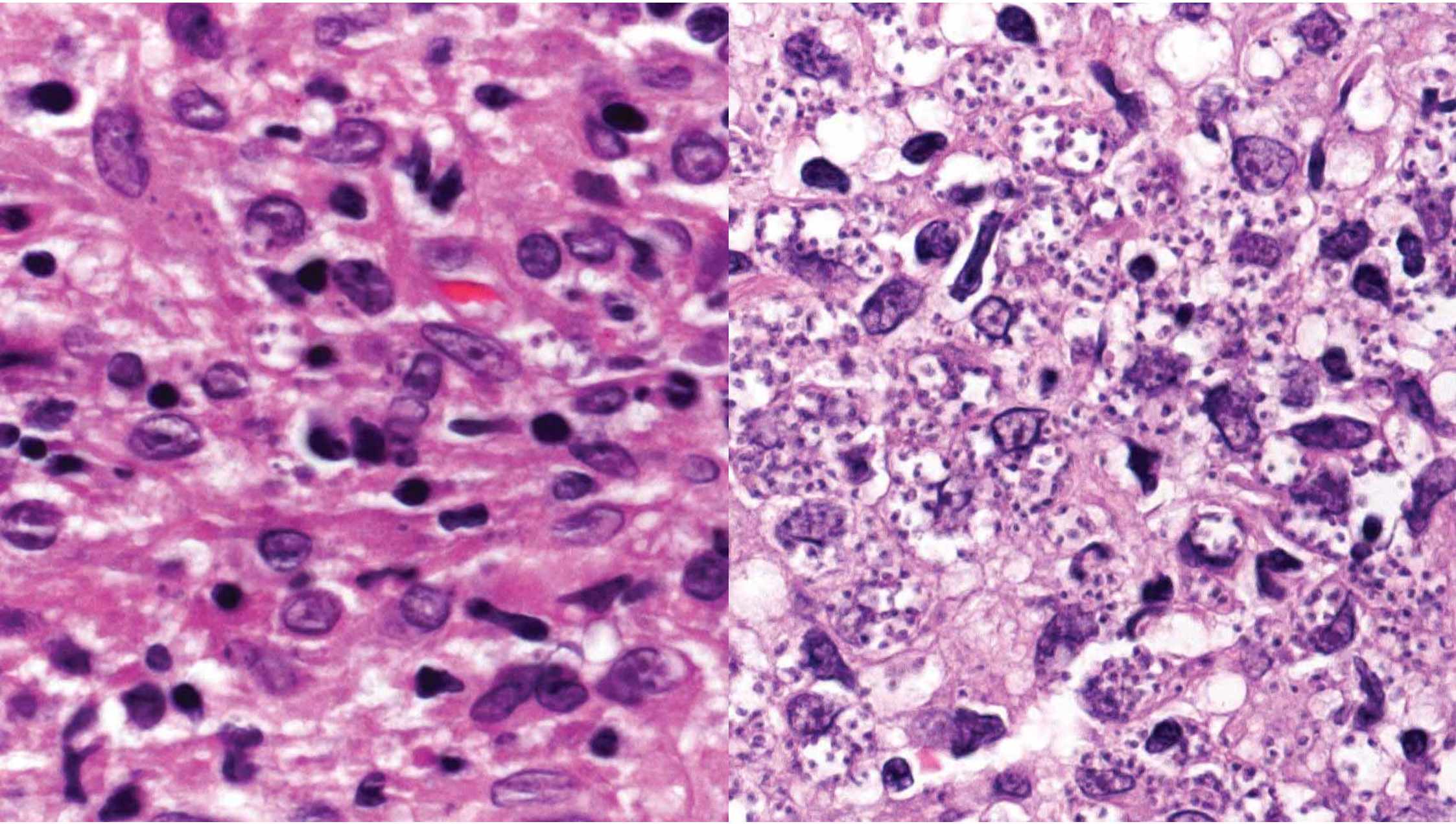
- Mostly solitary lesions on exposed skin (sand flies' bite)
- Histiocyte-rich inflammation with plasma cells
- Most microorganisms are found in the subepidermal area, located within the cytoplasm of the histiocytes


M, 18

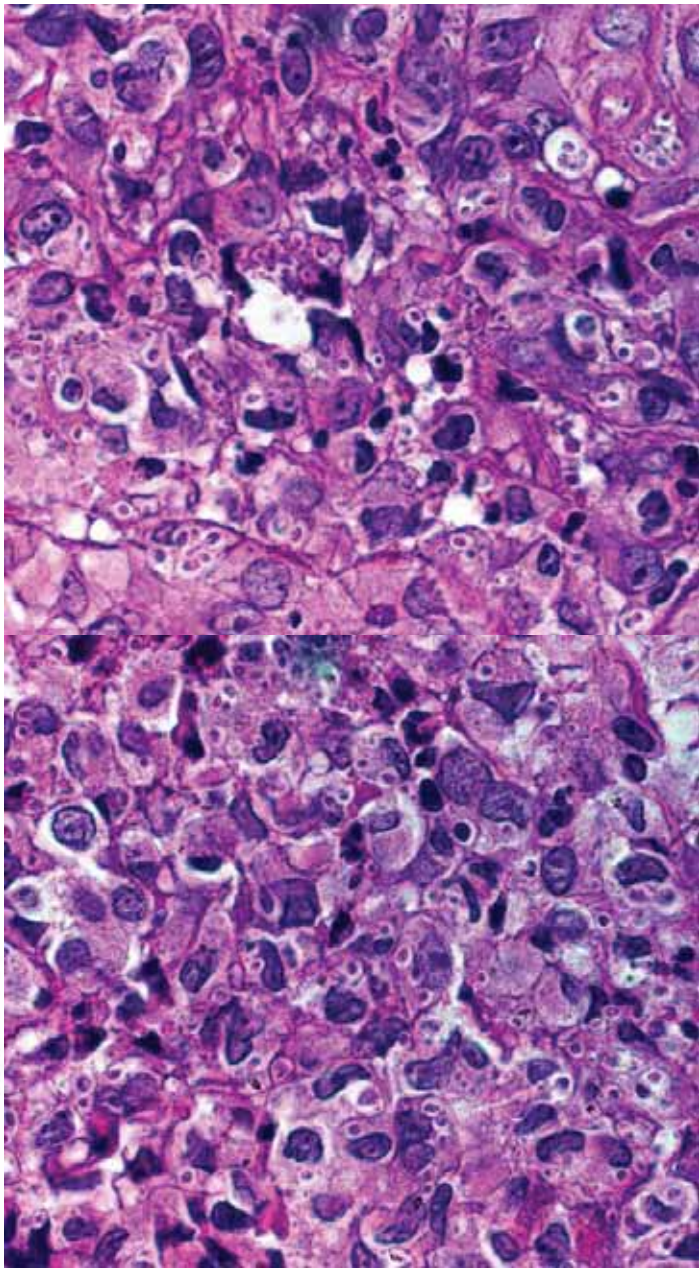


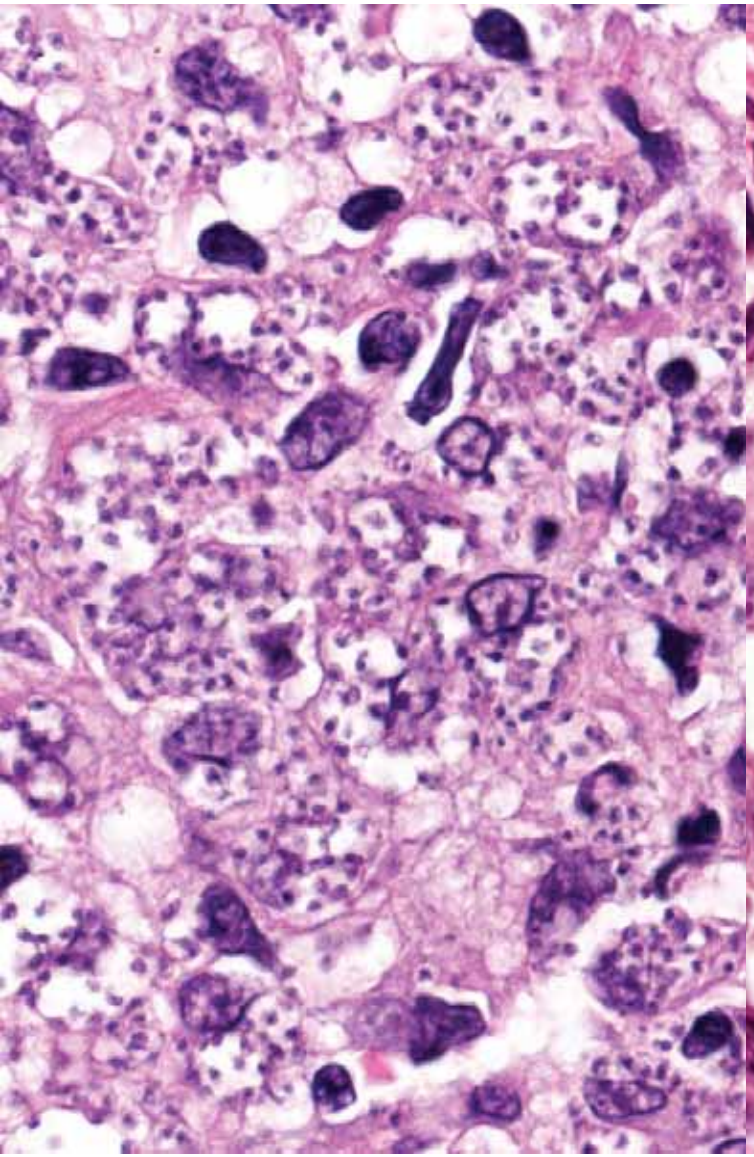




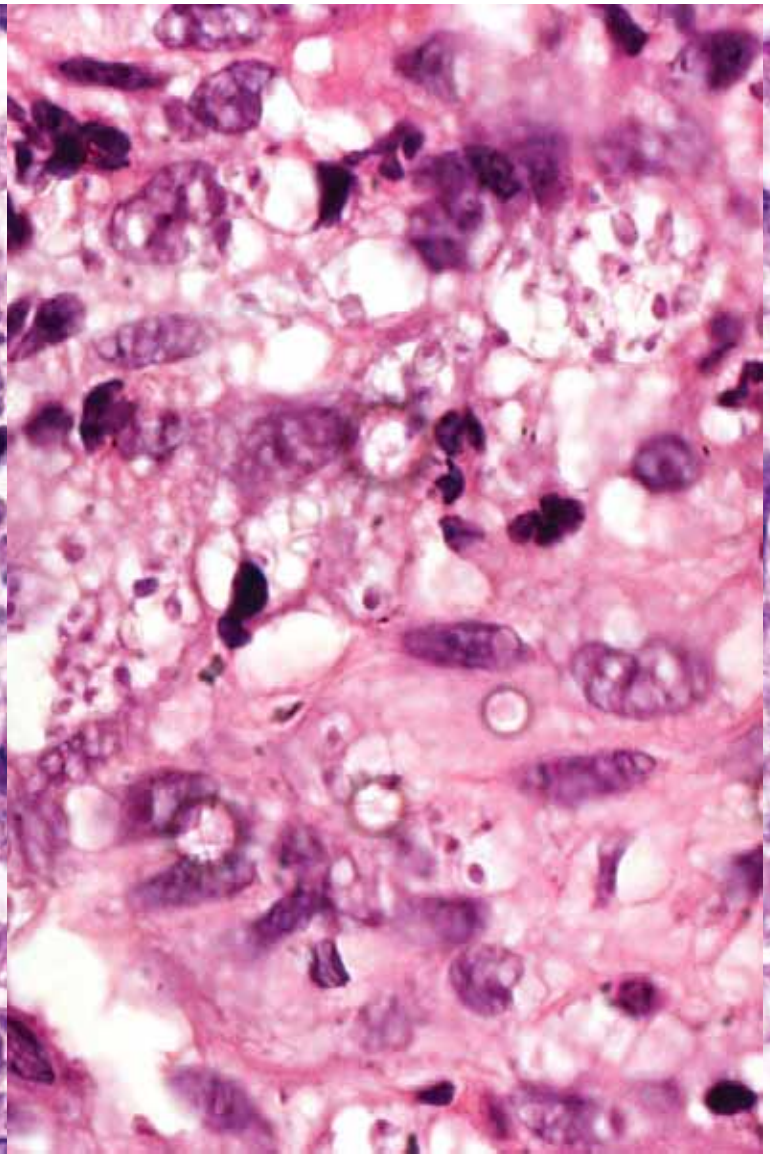


Histoplasmosis

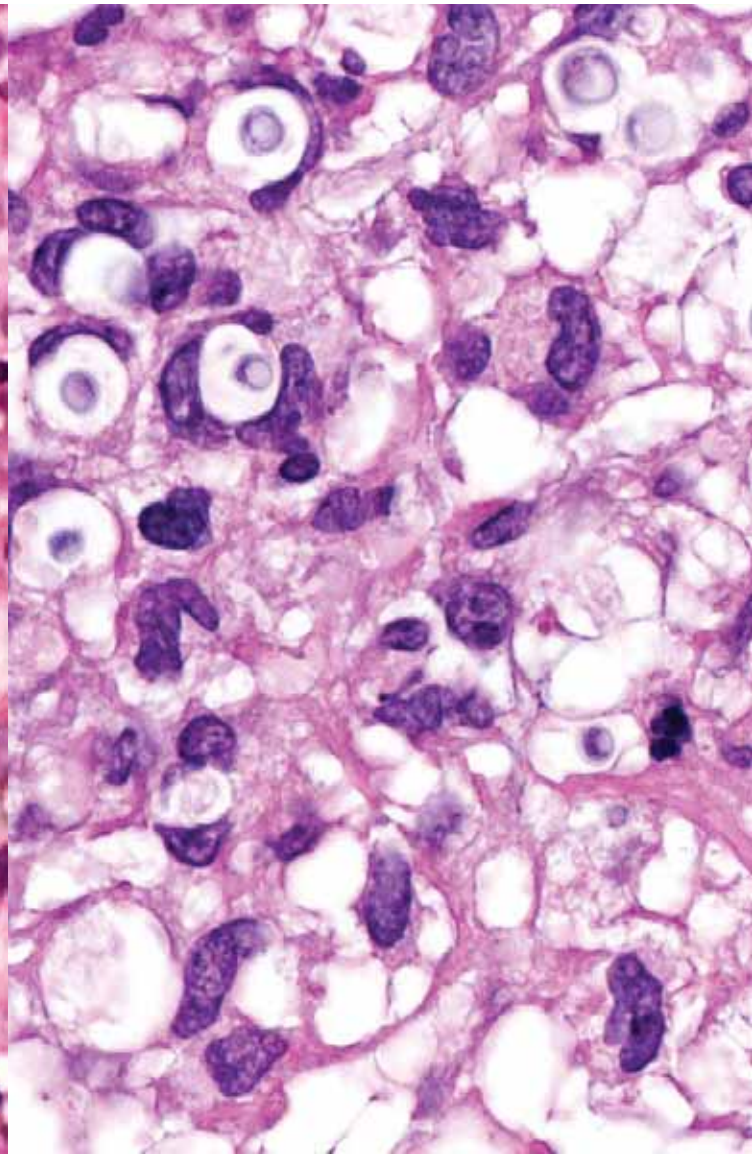




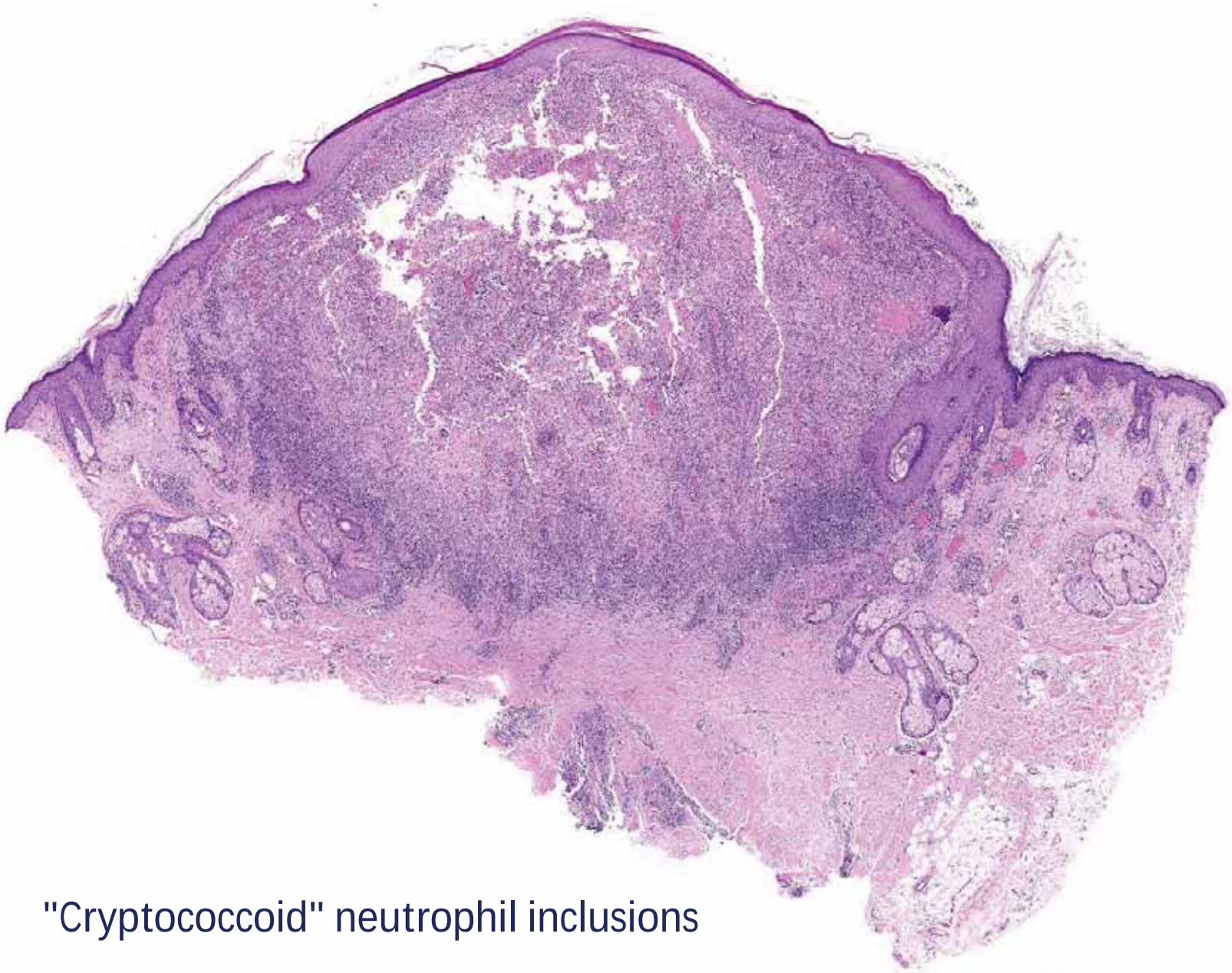
Leishmaniasis

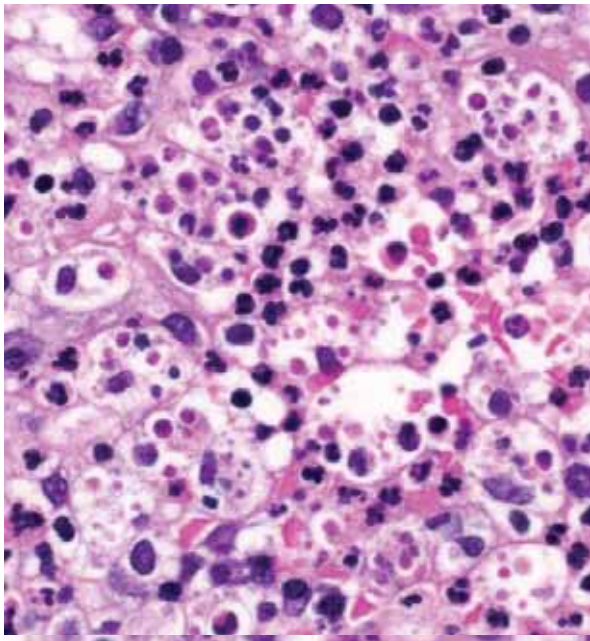


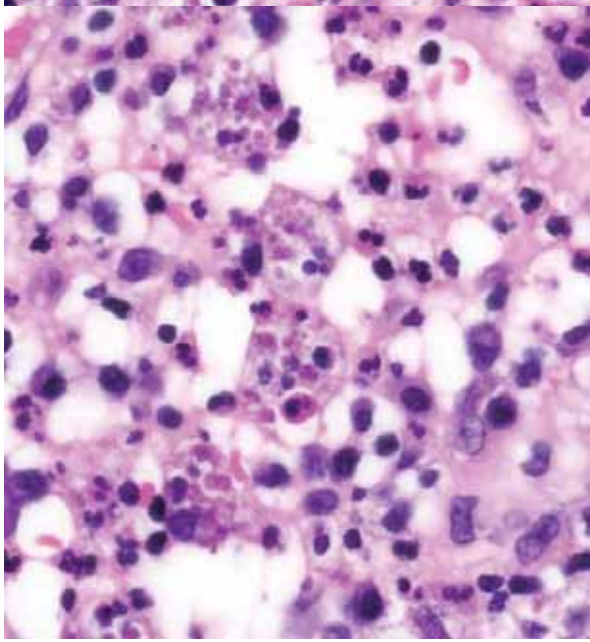
Histoplasmosis



Cryptococcosis







"Cryptococcoid" neutrophil inclusions

Cryptococcoid Sweet's syndrome: Two reports of Sweet's syndrome mimicking cutaneous cryptococcosis

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KEYWORDS: mimic, Sweet's syndrome, neutrophilic dermatosis

1 | INTRODUCTION

Sweet's syndrome, or acute febrile neutrophilic dermatosis, can mimic other conditions both clinically and histopathologically, creating challenges for clinicians and pathologists alike. Recently, a unique histological presentation of Sweet's syndrome has been described which mimics cutaneous cryptococcosis. Only six cases have been reported to date in the literature.[1–4] We report two further cases of neutrophilic dermatosis that were initially histopathologically concerning for cryptococcosis.

2 | CASE PRESENTATION

2.1 | Case 1

A 48-year old woman with past medical history of undefined anemia on no outpatient medications was admitted for a one day history of fever, arthralgias, and an acute onset of skin lesions. On examination, tender erythematous papules and plaques were found on the neck (Figure 1). Laboratory findings revealed leukopenia with mild lymphopenia, normocytic anemia with low reticulocyte count, and elevated erythrocyte sedimentation rate and C-reactive protein.

Biopsy revealed a superficial to mid dermal infiltrate with many conspicuous vacuolated spaces, scattered neutrophils, and large mononuclear cells resembling histiocytes. There was moderate papillary dermal edema, but the diffuse dense neutrophilic infiltrate characteristic of Sweet's syndrome was not present. Examination on higher power revealed basophilic yeast-like bodies within the spaces, concerning for disseminated cryptococcal infection (Figure 6). The patient was started on empiric therapy with amphotericin B while further studies were pending. However, the patient's cutaneous lesions continued to progress, while testing of serum and cerebrospinal fluid were negative for cryptococcal antigen, and Periodic-acid Schiff staining of the cutaneous specimen showed no fungal elements. Culture of lesions for herpes simplex and varicella zoster viruses was negative as well.

Further history revealed that the patient had experienced two previous episodes of an urticarial rash with unknown trigger that resolved spontaneously. She also admitted to frequent cocaine use. Infectious workup was negative for human immunodeficiency virus, hepatitis B, hepatitis C, syphilis, leptospirosis and coccidiosis. Serologic testing did reveal positive anti-nuclear antibody (ANA, 1:160) and positive perinuclear anti-neutrophil cytoplasmic antibodies (pANCA, 1:2560). Further autoimmune studies were positive for anti-ssA antibody, but negative for anti-ssB, anti-RNP, anti-Smith, anti-dsDNA, and anti-CCP antibodies. Both C3 and C4 complement were decreased.

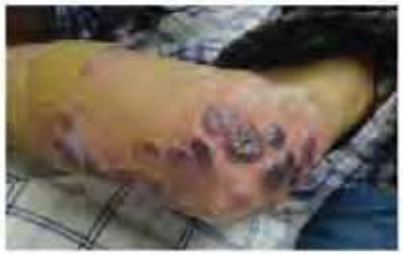

FIGURE 1 Edematous purpuric papules (patient 2). These were painful, and distributed widely over the face, trunk, and extremities.

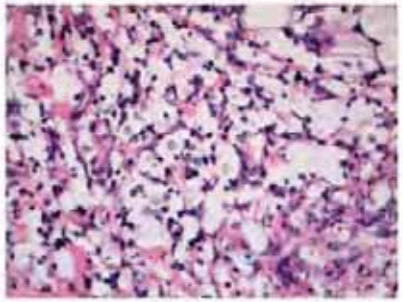

FIGURE 2 Pseudocapsular spaces and basophilic bodies mimicking yeast forms (patient 2). H&E, 200x.

CASE SERIES

Bullous hemorrhagic Sweet syndrome with cryptococcoid neutrophils in patients positive for antineutrophil cytoplasmic antibody without primary vasculitis

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Philadelphia, Pennsylvania and Newark, Delaware

Key words: clinical research; cryptococcoid neutrophils; general dermatology; hemorrhagic bullae; medical dermatology; neutrophilic dermatoses; p-ANCA; Sweet syndrome; vasculitis.

INTRODUCTION

Sweet syndrome (SS) is a febrile neutrophilic dermatosis characterized by pyrexia, peripheral leukocytosis, and an abrupt onset of painful erythematous plaques and nodules.[1,2] Lesions are typically found in an asymmetric distribution on the face, neck, and upper extremities and are often associated with an underlying malignancy, a systemic inflammatory condition, or a preceding infection.[1,2] Histopathologic examination reveals a dense neutrophilic infiltrate with papillary dermal edema, and serum laboratory tests show leukocytosis, an elevated erythrocyte sedimentation rate, or both.[1,2] Atypical bullous or hemorrhagic presentations have been described in the literature, with the majority in a setting of hematologic malignancy.[3] Twenty percent of patients with SS have an underlying malignancy that can manifest with atypical bullae.[3]

Herein, we describe 3 patients with hemorrhagic SS and cryptococcoid-appearing neutrophils on histopathologic examination, all of whom were found to be positive for antineutrophil cytoplasmic antibodies (ANCA) and negative for malignancy. This constellation of findings has rarely been described in the literature and raises new diagnostic and prognostic considerations for SS patients presenting with a hemorrhagic or bullous morphology.

Abbreviations used:
ANCA: antineutrophil cytoplasmic antibody
SS: Sweet syndrome

CASE DESCRIPTIONS

Case 1

A 70-year-old Caucasian woman with end-stage renal disease, diabetes, and chronic obstructive pulmonary disease presented to an outside hospital with fever, nausea, vomiting, and abdominal pain. Head computed tomography demonstrated a soft tissue swelling of the subcutaneous layer along the right parotid and submandibular glands, consistent with a subcutaneous infection, while chest X-ray revealed bilateral infiltrates. A culture of bronchial washings was positive for *Pseudomonas*. She was diagnosed with bilateral pneumonia complicated by septic shock and an infection of the parotid and submandibular glands before the development of hemorrhagic bullae on her face and arms. Subsequently, respiratory distress requiring intubation developed, and she was transferred to our hospital. She received multiple antibiotics, including vancomycin, cefepime, doxycycline, cephalexin, ceftaroline, and piperacillin/tazobactam, prior to the transfer. Physical examination showed erythematous to violaceous tense hemorrhagic bullae on her face, neck, upper portion of

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IRB approval status: Not applicable.

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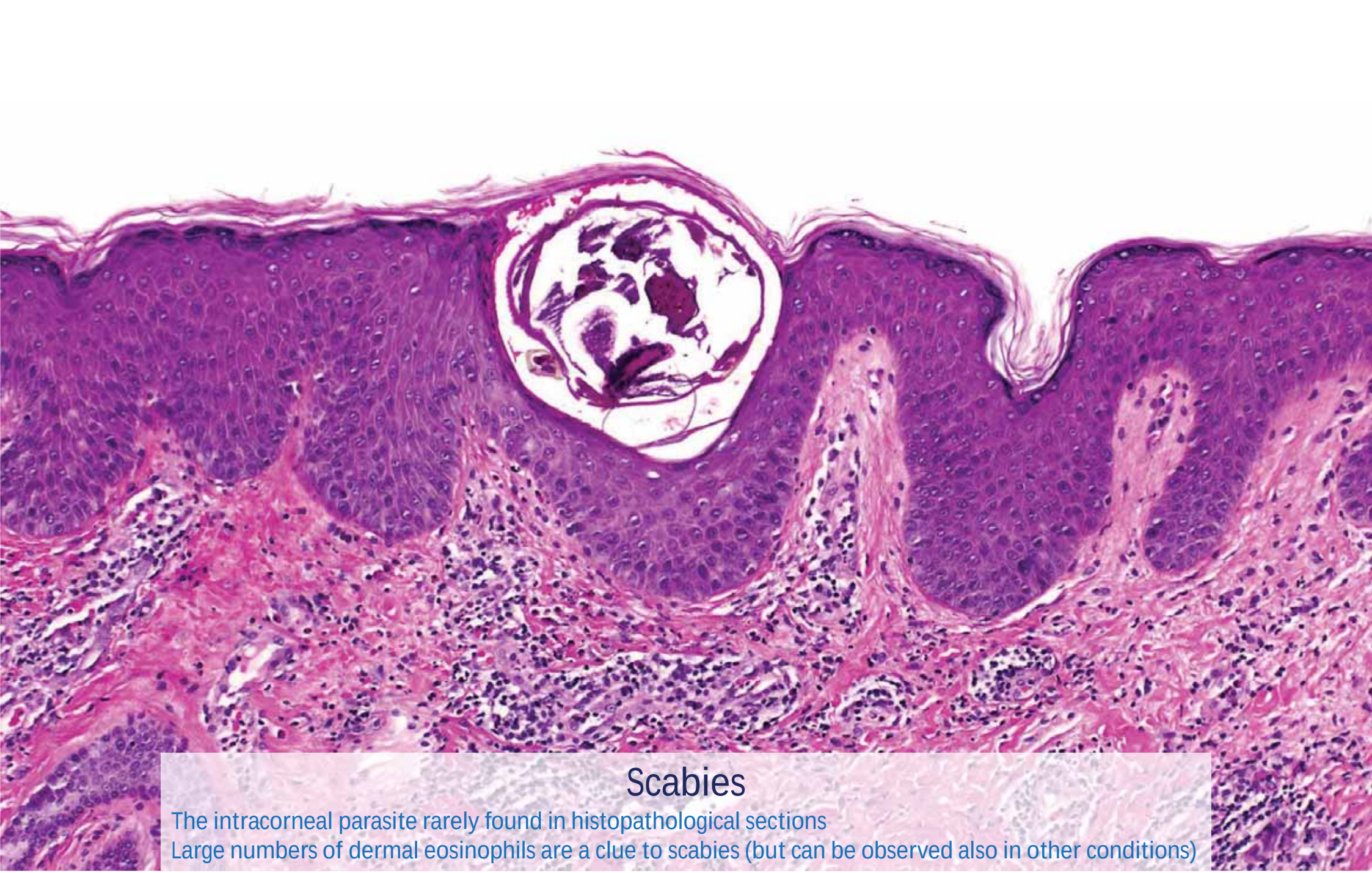
Arthropod-induced diseases & infestations

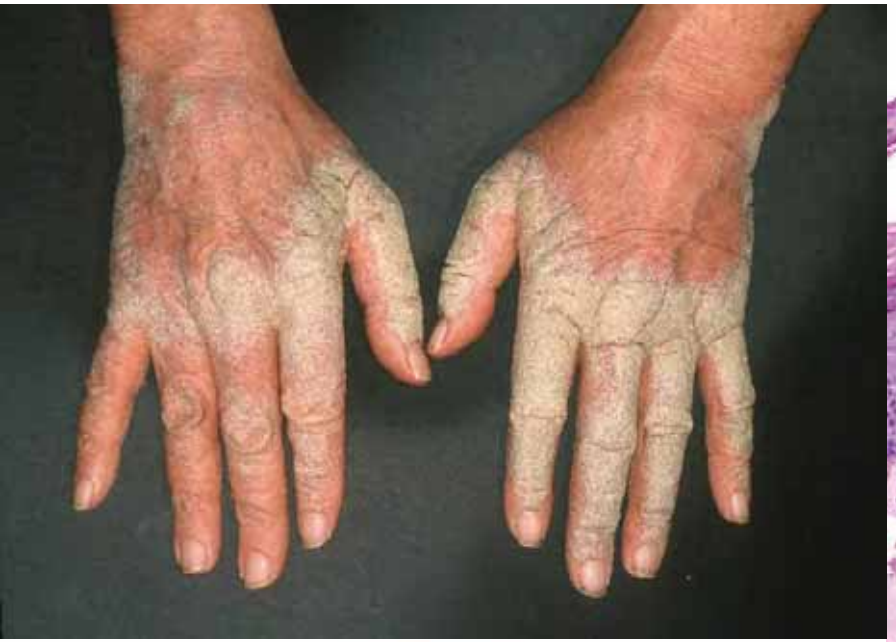
- *Arthropod bites:* one of the most common skin conditions with protean clinical presentation, rarely biopsied if not clinically atypical / therapy-resistant
- *Scabies:* the finding of intracorneal material of *sarcoptes scabiei* is pathognomonic, but the parasite is rarely found in biopsies
- *Larva migrans:* acquired mostly on sandy beaches; cases described recently in non-tropical countries (including Austria); parasites almost never found in biopsies
- *Tungiasis:* parasites enter the skin from the soil, mostly at acral sites; in marginalized, resource-poor populations in the Caribbean, South America and sub-Saharan Africa, and in travelers from endemic countries
- *Myiasis:* fly larvae that grow inside the host; mostly in tropical regions
- *Sparganosis:* endemic in many countries, particularly in Southeast Asia and Eastern Africa; infection by ingesting raw or undercooked meat of infected animals (e.g., snakes, frogs), or by drinking untreated water
- *Filariasis:* particularly in Southeast Asia; transmitted by infected mosquitoes
- *Cercarial dermatitis:* ***swimmer's itch:*** cercariae do not survive in the skin and die; ***schistosomiasis:*** cercarial dermatitis followed by hematogenous infection of urinary tract and/or intestine with deposition of eggs

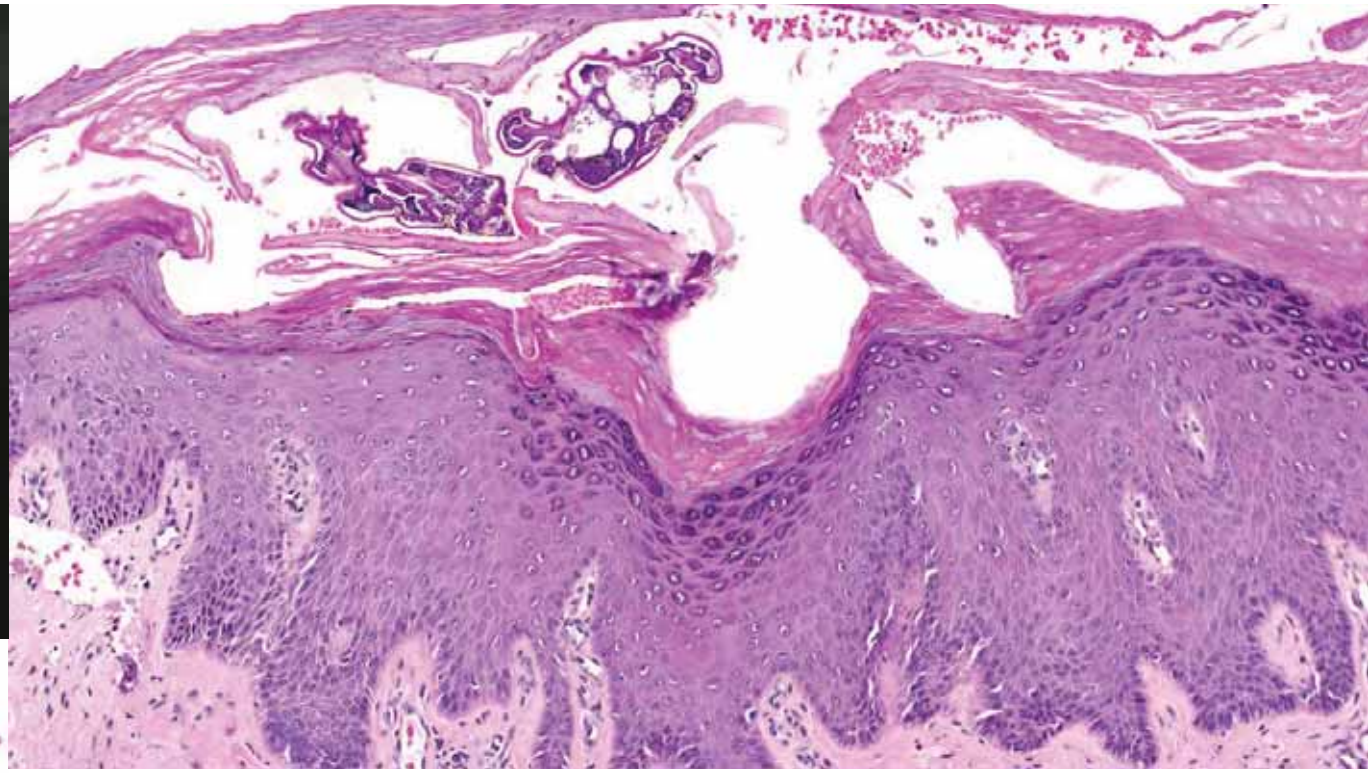


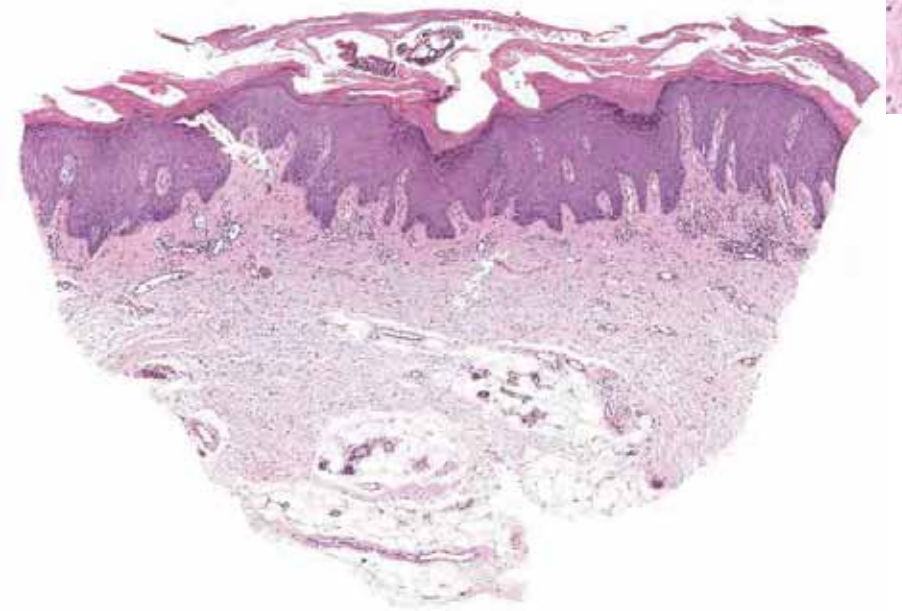
Scabies

The intracorneal parasite rarely found in histopathological sections

Large numbers of dermal eosinophils are a clue to scabies (but can be observed also in other conditions)



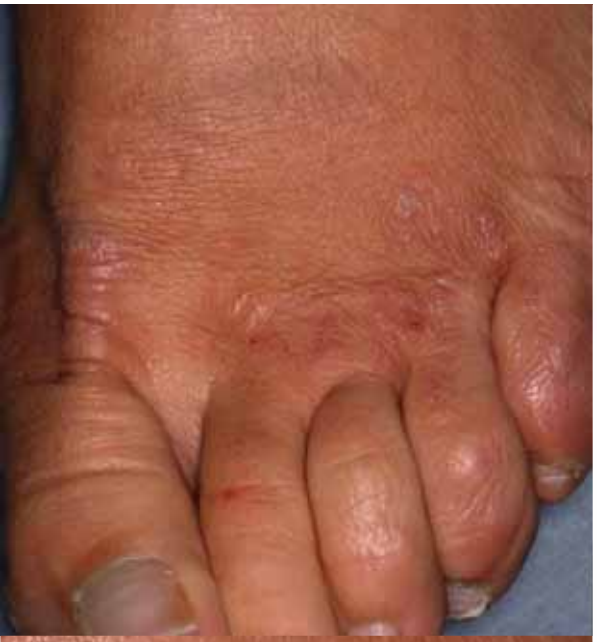


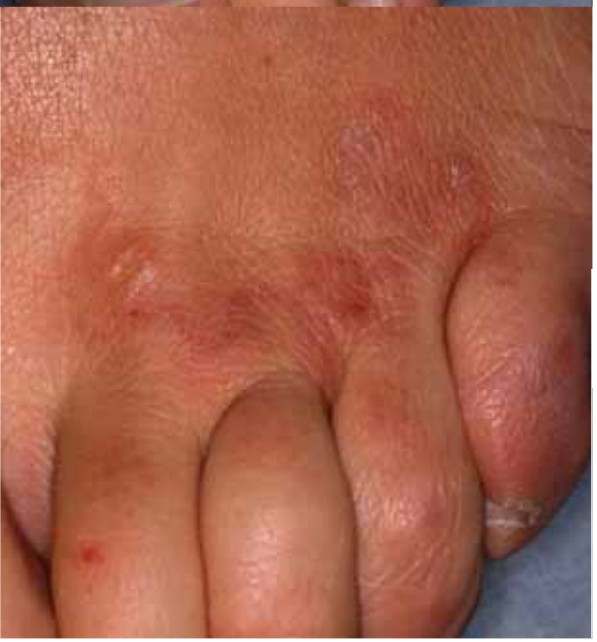


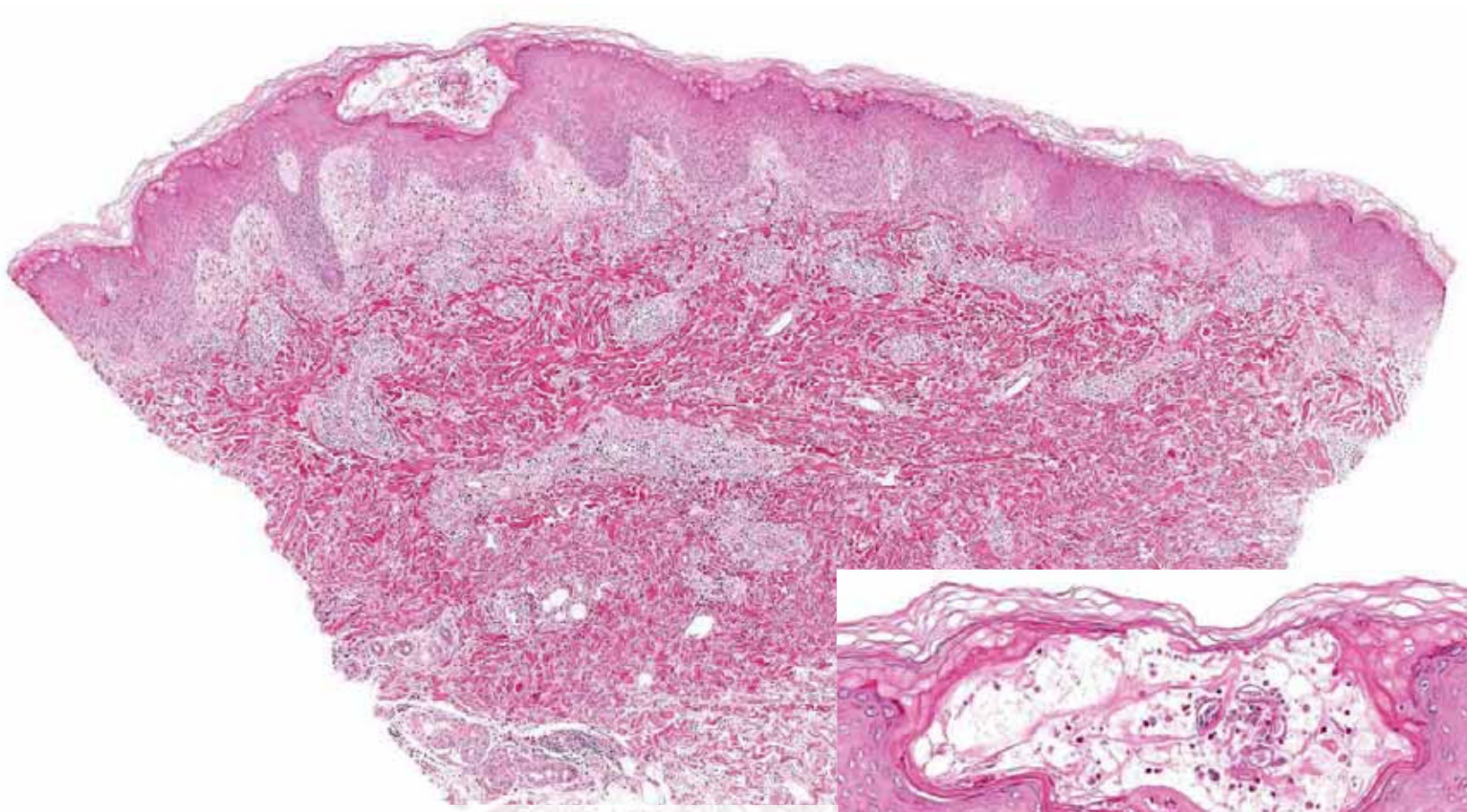
Norwegian scabies

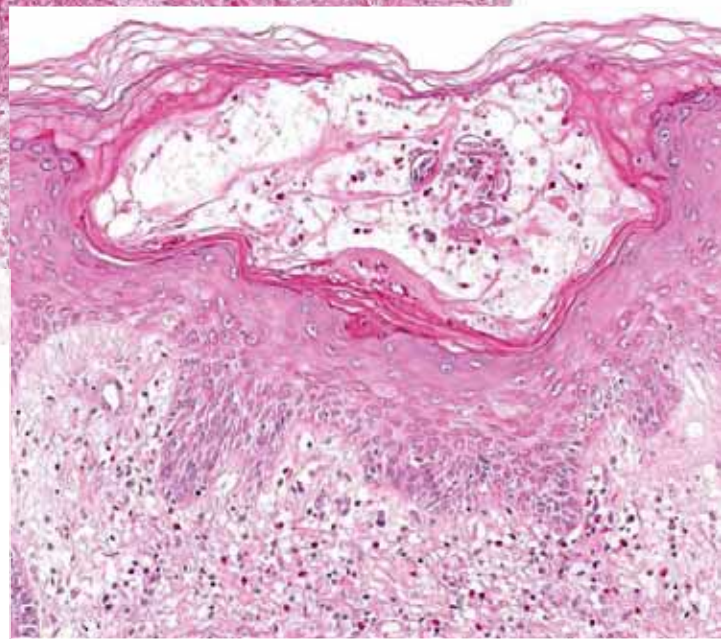
Epidermal features of lichen simplex chronicus; focal parakeratosis.

Mites invariably present, usually in large numbers.





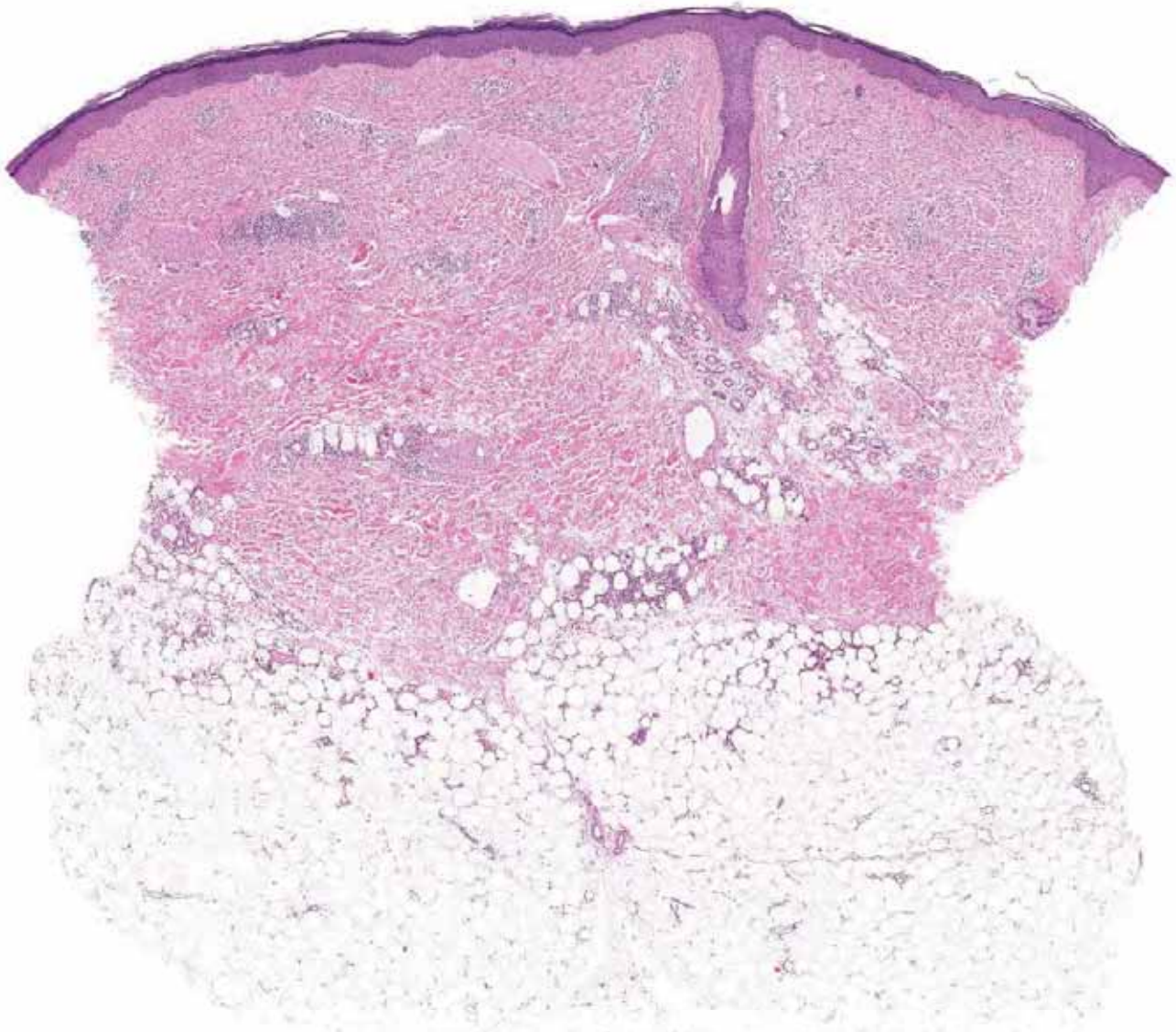


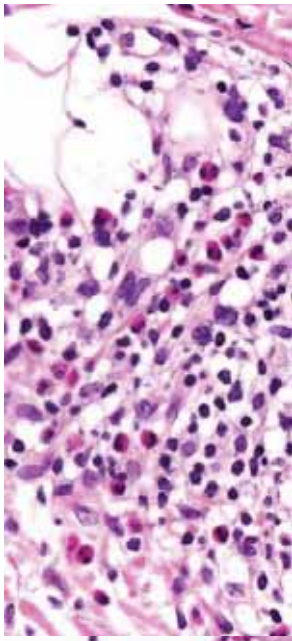


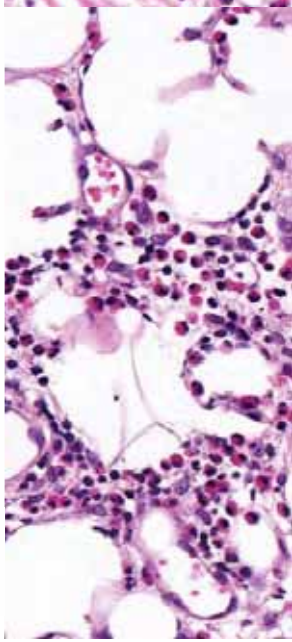
Larva migrans

The intracorneal larva almost never found in histopathological sections (it is somewhere beyond clinically visible lesions – erratic path of the larvae)

In the dermis features of a local hypersensitivity reaction (arthropod bite-like)







Autochthonous (Austrian) larva migrans

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Cutaneous larva migrans, welcome to a warmer Europe

A creeping eruption (CE) is a general term that means serpiginous, itching and moving cutaneous lesion due to the presence of larvae of a helminth or insect.[1] By far the most frequent cause of CE is cutaneous larva migrans (CLM), mostly caused by *Ancylostoma braziliense*, a hookworm of cats and dogs endemic in tropical and subtropical areas. Its diagnosis is essentially clinical,[2] in this way it differs from other aetiologies by a *non-evanescent lesion* with a *slow progression* (some millimetres per day) and also a *typical acral localization*, although it is changing because of nude sunbathing. Transmission occurs when the hookworm's eggs passed in the faeces of an infected animal onto the soil, where under favourable conditions of warm, shady and moist conditions, hatch and mature into infectious larvae. They penetrate the host's naked skin and after an incubation period of about 1 week, start migrating. It is considered a self-limiting disease since its parasites are non-human nematodes, unable to go deeper into the skin. In consequence, no systemic symptoms or severe eosinophilia are found.

The other causes of creeping eruption that we have to keep in mind are:

1 Human nematodes[3]:
   - I Intestinal hookworms (*A. duodenale, Necator americanus*) produce a transient CE called 'ground itch' where the larva penetrates.
   - II *Strongyloides stercoralis* typically originates urticarial CE with a migration of several centimetres per hour (larva currens).
   - III Loa-loa produces also a very fast CE, but usually associated with other symptoms: oedema de Calabar, ocular infestation…
2 Non-human nematodes: *Gnathostoma*[4] is almost restricted to Asia and its characteristic sign is migratory eosinophilic panniculitis.
3 Others: fasciola (*Trematodes*), myiasis linearis migrans (*Gasterophilus* and *Hypoderma*) and creeping hair.[5]

Over the last decades, reports of CLM in Europe have become more and more common, probably because of the frequent journeys to endemic areas. But the most striking fact is the rise, in the last years, of autochthonous cases in southern Europe (Table 1). We present two cases of creeping eruptions that illustrate the history and course of autochthonous CLM. They are the first cases reported in central regions of the Iberian Peninsula. Both cases were infants of 14 and 4 years old, who came in summer to our emergency room with a creeping eruption, localized respectively to his ankle and foot (Fig. 1). The lesions were progressively developed in the course of 3–4 days. No one revealed travel anywhere abroad. The 4-year-old boy was playing barefoot the last weeks in his home yard in Madrid, where cats usually come in. However, the 14-year-old girl was in natural swimming pool in Burgos 1 week before, where animals were permitted. The blood and faeces tests were all negative. No biopsy was performed. We treated both with Albendazole, with a successful response and disappearance of the cutaneous lesions only few days later.

Table 1 European autochthonous cases of cutaneous Larva migrans

Author	Year	Country	Cases	Gender	Age	Risk factor	Serpiginous lesions	Eosinophilia	Treatment
A Di Carlo	1989	Italy (Rome)	1	F	76	Meadow	Hand	Yes	Cryotherapy
M. Nicol	1990	Spain (Malaga)	1	F	17	Botanical garden	Foot		Topic Thiabendazole
J. Colomina	1994	Spain (Valencia)	1	M	13	Cats	Foot	Yes	Oral Thiabendazole
R. Zimmermann	1995	France (Lyon)	1	M	21	Rural	Leg	Yes	Oral Thiabendazole
C Klose	1996	Germany (Berlin)	3	M	38	River	Foot		Topic Thiabendazole
				M	44	River	Foot		Topic Thiabendazole
				F	7	River	Hand		Topic Thiabendazole
L Obanda	1997	Spain (Córdoba)	1	F	Nursing	Rural	?	Yes	Oral Thiabendazole
B. Galanti	2002	Italy (Naples)	5		Adults	Rower's sand + cats/dogs	Limbs		Albendazole 400 mg, 1 day
M. Sibat	2002	Spain (Barcelona)	1	M	22	?	Hand	Yes	Oral Thiabendazole
CR. Patterson	2003	England	1	M	10	Dogs	Foot		Topic Thiabendazole
M. Fernández	2003	Spain (Oviedo)	1	M	3	Rural	Foot	Yes	Topic Thiabendazole
A. Morrone	2008	Italy (Roma)	1	M	3	Beach	Perianal*		Albendazole 400 mg, 1 day
S. Veraldi	2012	France (Brittany coast)	2	F	23	Beach	Ankle*		Albendazole 400 mg, ×3d
				M	28	Beach	Foot*		Albendazole 400 mg, ×3d
Our case	2012	Spain (Burgos)	1	F	14	Swimming pool + cats	Foot	Yes	Albendazole 400 mg, ×3d
J. Castro	2014	Spain (Mediterranean coast)	1	M	28	Beach – Ferret	Shoulder		Albendazole 400 mg, ×3d
E. De canale	2015	Italy (Venice)	1	M	42	Rural	Arm*	Yes	Albendazole 400 mg, ×3d
N Ropars	2015	France (Bretagne)	1	M	69	Lake	Trunk		Ivermectin 200 mg/kg, 1 day
Our case	2015	Spain (Madrid)	1	M	4	Home yard + cats	Ankle	No	Mebendazole 200 mg, ×3d
			24				*Multiple lesions		

Most common cause of creeping eruption (CE):
Ancylostoma braziliense

Other causes of creeping eruption:

Human nematodes

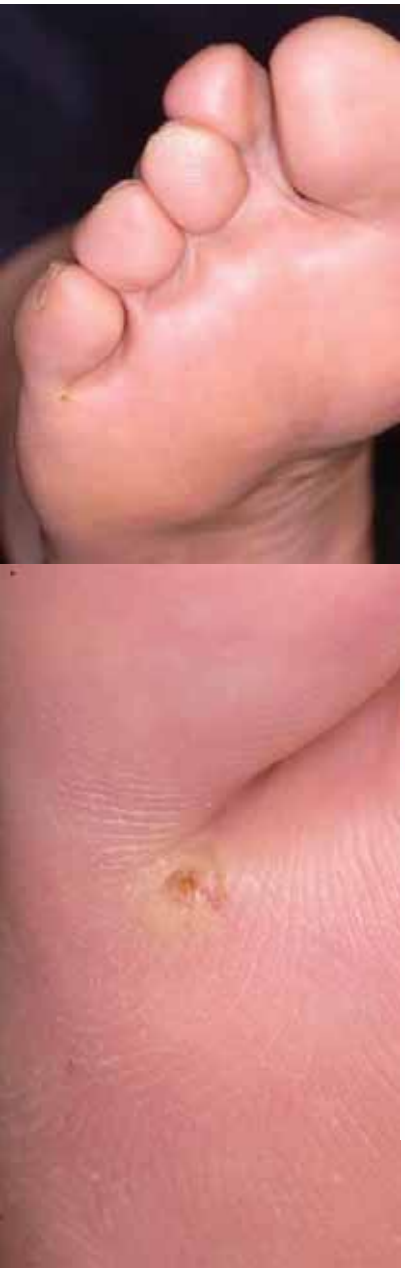
- Intestinal hookworms (*A. duodenale, Necator americanus*), transient CE called 'ground itch' where the larva penetrates
- Strongyloides stercoralis: urticarial CE with a migration of several centimeters per hour (larva currens).
- Loa-loa: very fast CE, usually associated with other symptoms: oedema de Calabar, ocular infestation

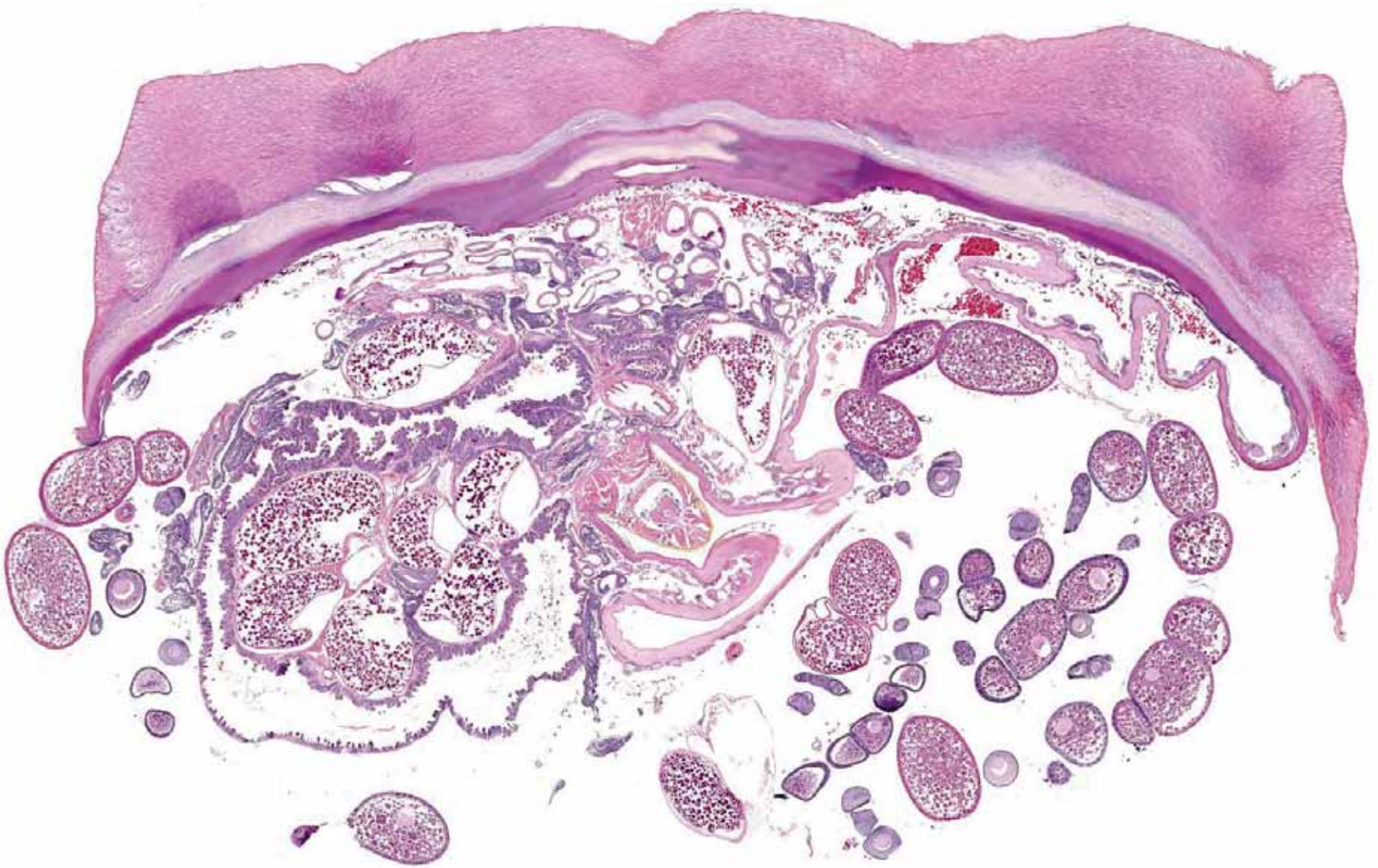
Non-human nematodes

Gnathostoma is almost restricted to Asia and its characteristic sign is migratory eosinophilic panniculitis

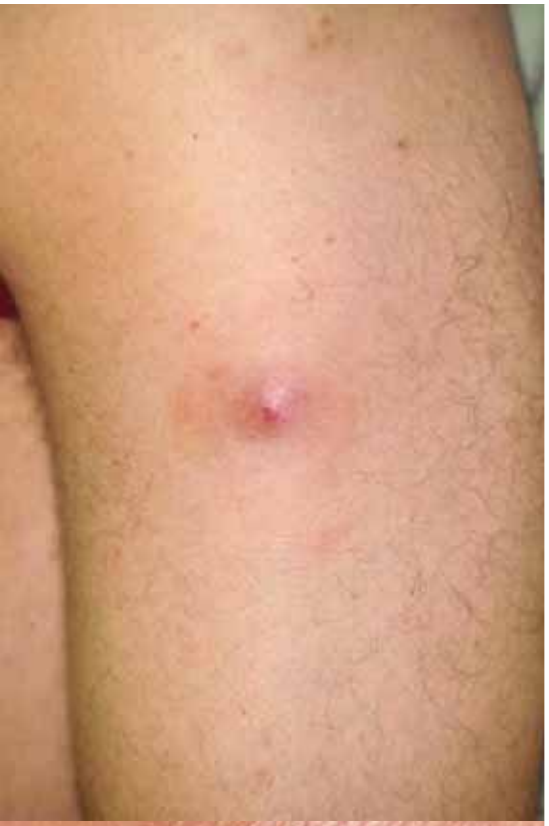
Others

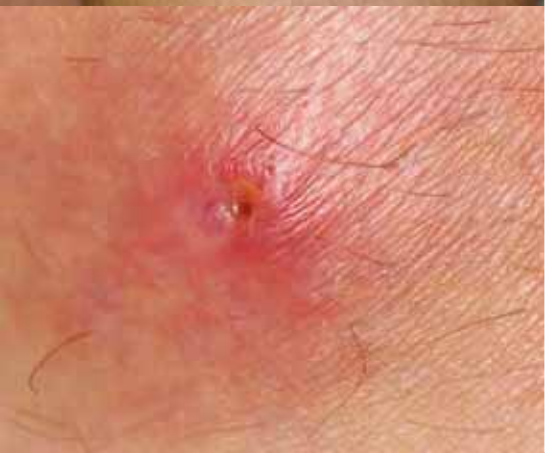
fasciola (*Trematodes*), myiasis linearis migrans (*Gasterophilus* and *Hypoderma*) and creeping hair

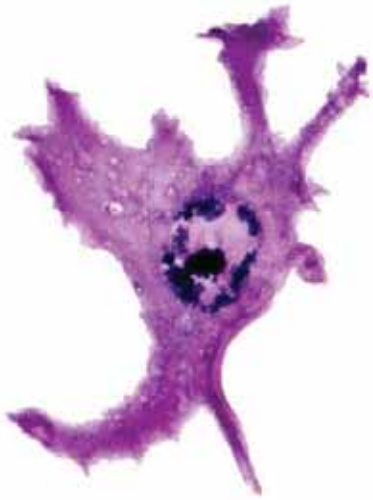




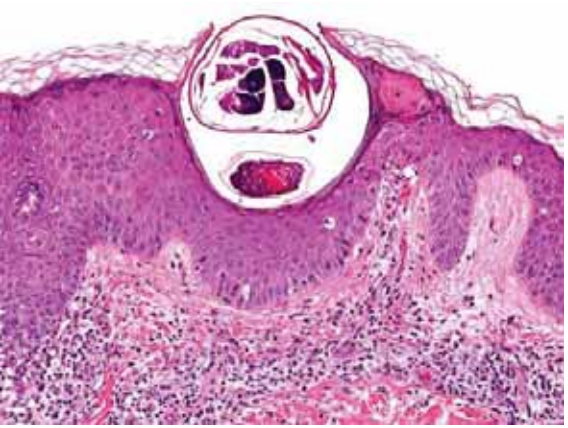
Tungiasis



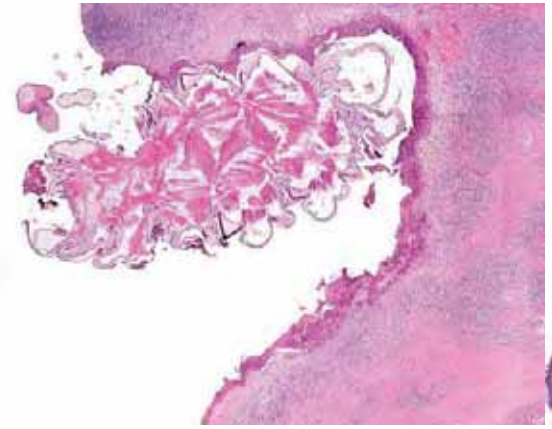




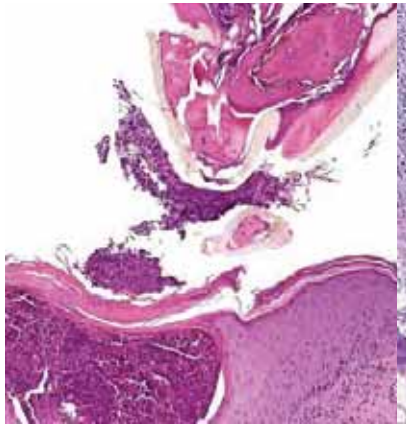
Myiasis



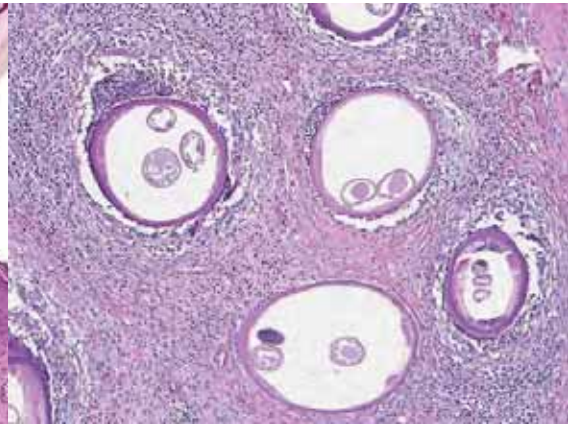
Scabies



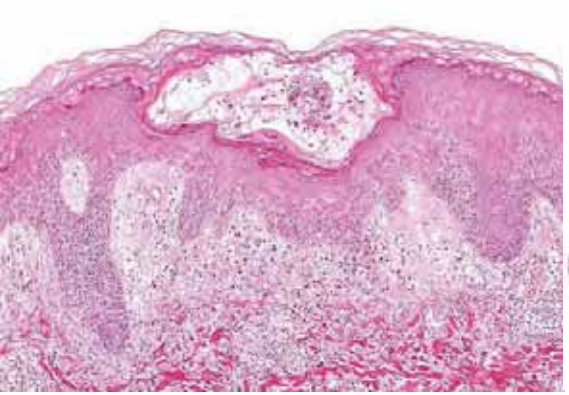
Myiasis



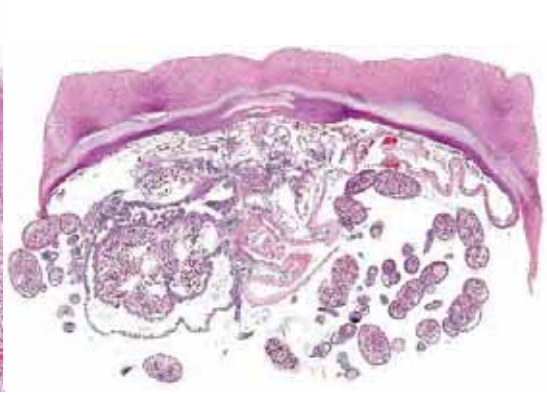
Tick



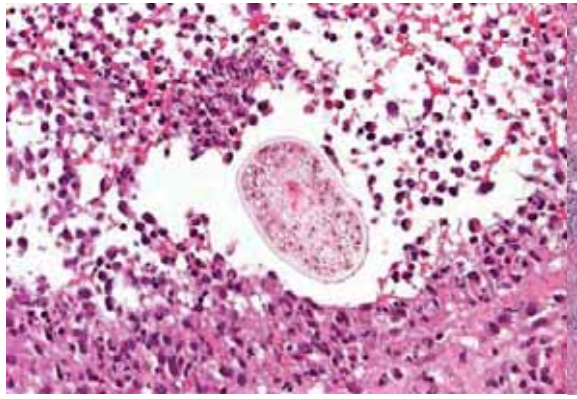
Onchocerciasis



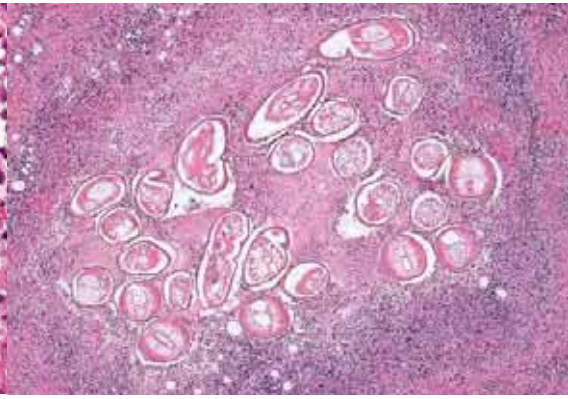
Larva migrans



Tungiasis



Sparganosis



Filariasis

Some arthropods and parasites found in the human skin

Scabies and larva migrans show rarely intracorneal material (eggs, feci and/or parts of the organism). Tungiasis may be intraepidermal, intradermal or both. Ticks are rarely encountered on histopathological sections and may be attached to the skin or show intradermal remnants of the arthropod. Onchocerciasis shows parasites within subcutaneous abscesses. Myiasis shows larvae in the dermis and/or subcutis. Sparganosis shows portions of worms within abscesses. Filariasis presents with degenerating filaria surrounded by inflammation.

Diagnostic Features of Zoonotic Filariae in Tissue Sections

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The diagnostic features in tissue sections from patients with zoonotic filarid infections are reviewed. In general, two types of infections are recognized: 1) those presenting radiologically in healthy patients as coin lesions, which are usually removed because a clinical diagnosis of carcinoma of the lung is made and infarcts containing *Dirofilaria immitis* parasites in pulmonary arteries are found; and 2) those presenting as subcutaneous nodules, in which *D. tenuis*, a parasite from raccoons, *D. repens*, from dogs and cats, *D. ursi*, from bears, and Onchocerca spp, from horses or cattle, require delineation. Moreover, nodules that on microscopic examination are seen to be lymph nodes may harbor Brugia spp. The geographic distribution of these infections, with emphasis on the United States, is discussed. HUM PATHOL 15:514–525, 1984.

Several species of filarial parasites from wild and domestic animals may accidentally infect humans. These zoonotic infections are being recognized more frequently, especially in areas free from human filariasis.[1–3] The numbers are comparatively low, and the infections are regarded as medical curiosities, but there is a need for their recognition and identification since they augment our understanding of the basic biology of filarial infections in general.

The diagnosis of zoonotic filarial infections rests on the recovery and specific identification of the parasite in question, a task not often accomplished. Usually, the organism is seen first by a pathologist, who is often confronted with sections containing dead, poorly preserved worms. Recognition of morphologic features is difficult, and the diagnosis of a parasitic infection may not be made. The benignity of the anatomic lesion, consisting of an inflammatory reaction, is the most important feature, and the parasite becomes a secondary object that needs no further study. Moreover, if a diagnosis and a correct identification are made, they are often based on circumstantial evidence, not on the anatomic characteristics of the parasite.

Zoonotic filarial infections can be divided into two groups: 1) those caused by filariae capable of reaching adulthood and becoming patent in humans (i.e., produce microfilariae), such as *Brugia malayi* and *Dipetalonema perstans*[4]; and 2) those caused by filariae that do not mature under normal conditions and are found in humans in larval stages or as young adults, usually unfertilized. The first group consists of parasites known to be endemic to certain areas that are described in standard books and reviews.[4] The second group is discussed in the present review, which collates data concerning the recognition and diagnosis of the better known zoonotic filarial infections, emphasizing filariae found in the United States, for use by the anatomic pathologist.

GENERAL DESCRIPTION

Filarial worms have been found in almost all tissues of the definitive host, including subcutaneous tissues, lymph nodes, heart and blood vessels, and serosal cavities. The parasites reproduce in these sites and release embryos known as microfilariae, which are found in the peripheral blood or in the skin, according to the species. The life cycle requires an intermediate host, an arthropod, often a mosquito. In the vector, the microfilariae become infective and enter the new host, where the filarid develops to adulthood. Development is sometimes a long process, requiring up to eight months. *Dirofilaria immitis*, for example, requires a two- to three-month maturation period in the subcutaneous tissues before reaching the right heart and pulmonary vessels of its normal host, the dog.[5]

The morphologic features used for the taxonomy of filarial parasites are not considered here, and only the basic characteristics needed for diagnosis in tissues (cross sections of the parasite) are reviewed. In general, the internal anatomic features of all filarial parasites are similar, as schematically illustrated in figures 1 and 2.

There are two separate sexes with the females usually larger than the males. The females have double sex organs, consisting of two tubular structures (fig. 1). These tubes begin in the posterior body as ovaries, become oviducts, loop several times before continuing with the seminal receptacles and uteri, and terminate in the anterior body as a single vagina, which also loops several times before ending in the vulva (fig. 1). The sex organs in the male are composed of a single tube, beginning with a looped testis in the anterior body, continuing posteriorly as the seminal vesicle, and terminating in the vas deferens and ejaculatory duct in the cloaca (fig. 1). Since the sex organs are anchored at only one point (vagina in females, cloaca in males), they are often dislodged when the surgical specimen is cut for histologic processing.

In cross sections, filarial worms are composed of a cuticle and a muscle layer, which limit a general cavity known as the pseudocoel, which contains the intestine, the excretory and nervous systems, and the

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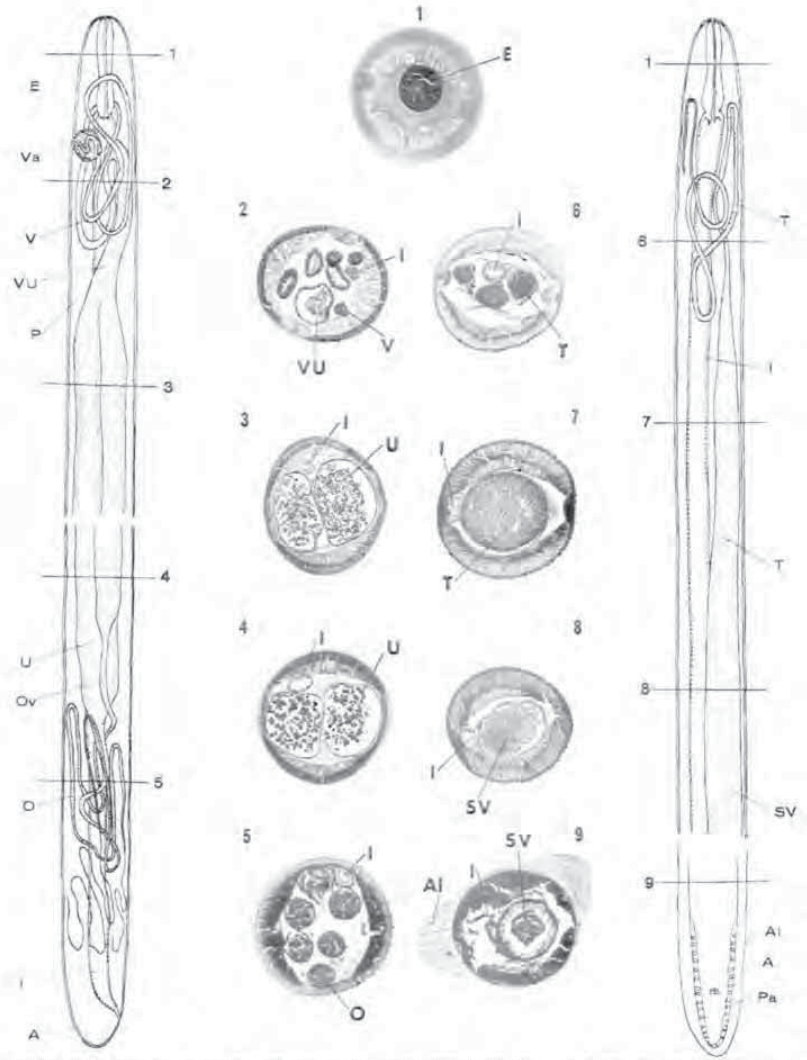
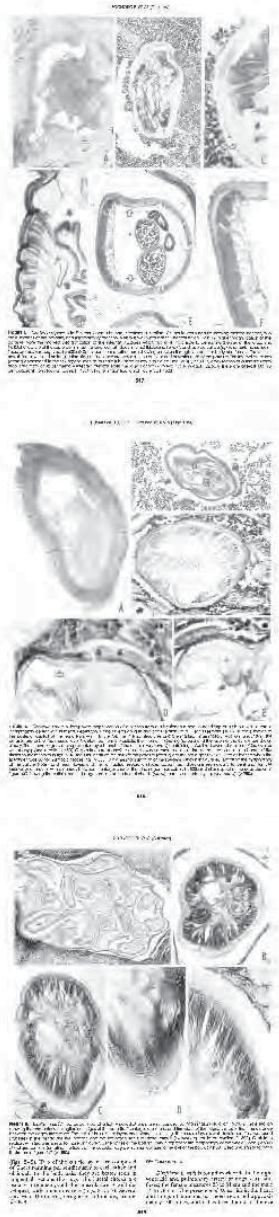
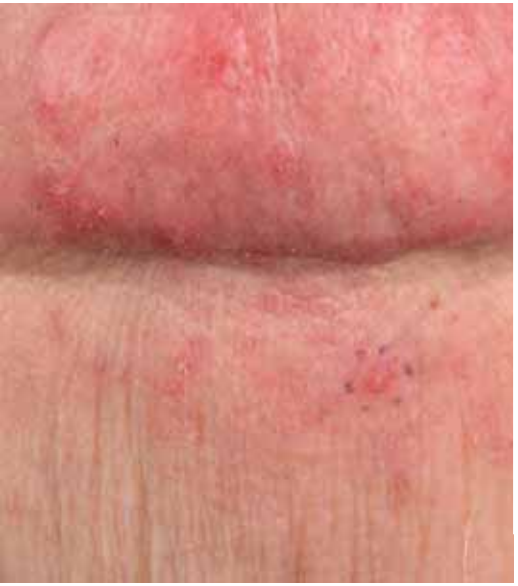
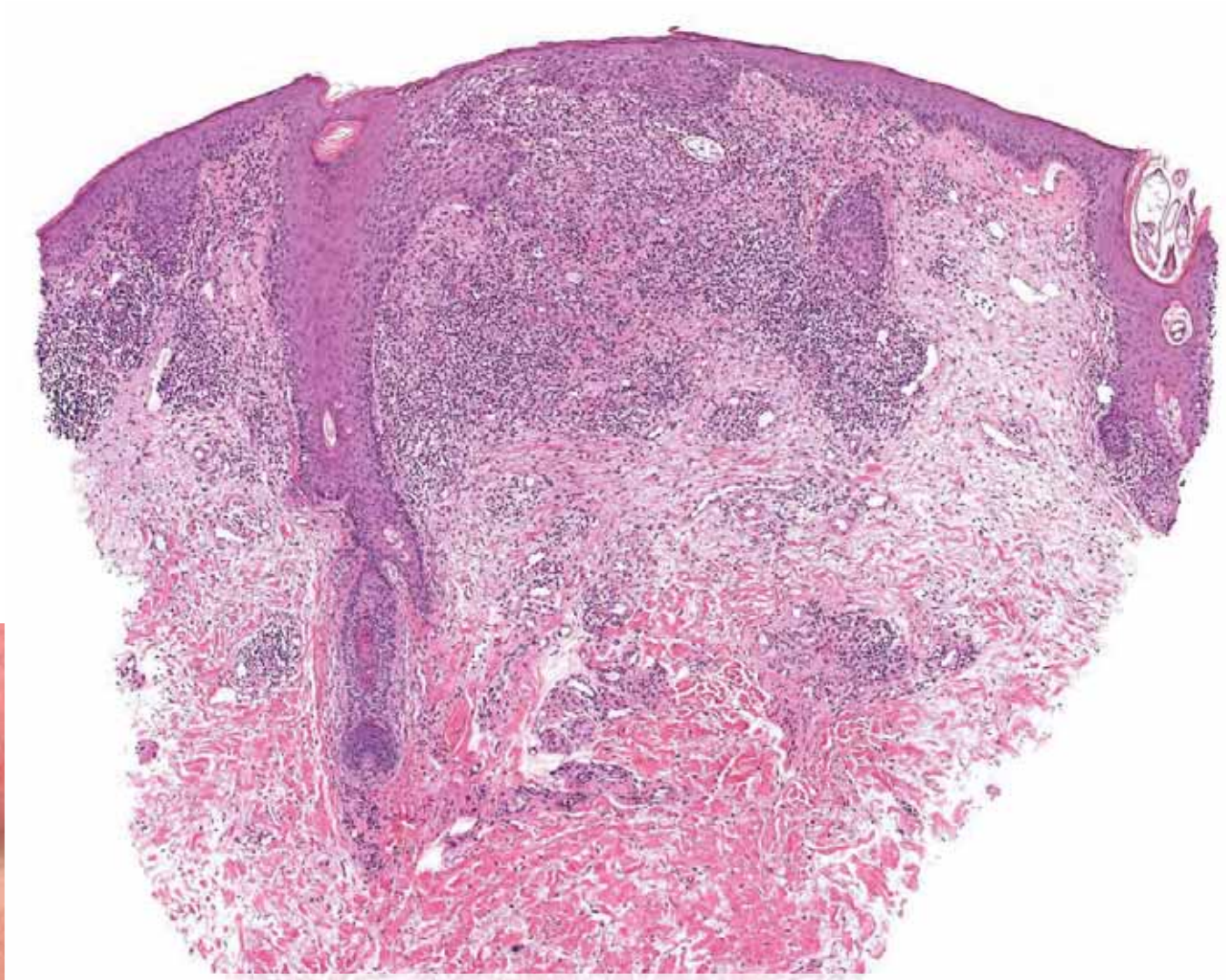
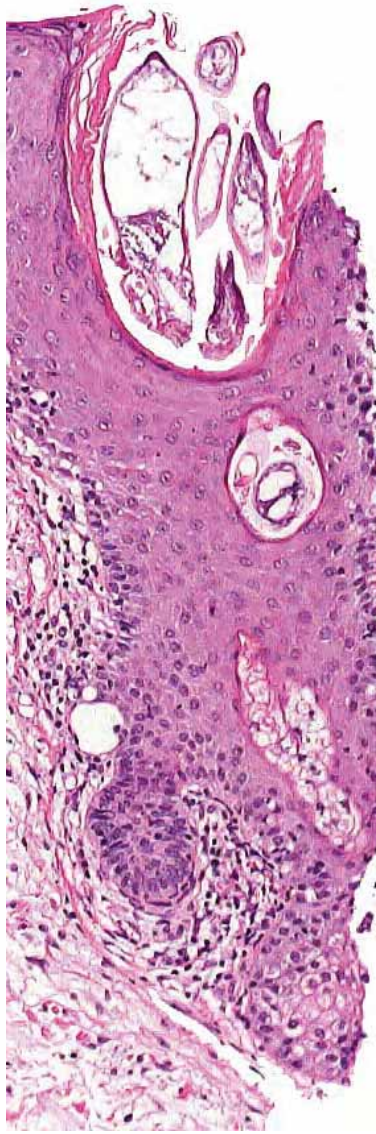


FIGURE 1. Highly schematic representation of the topographic anatomy of a typical filarial parasite. *Left*, female; *right*, male. The numbers on the horizontal lines indicate the level of the cross sections illustrated by photographs of Dirofilaria spp. The posterior end of the male is represented as if it were straight and shows the external features. The sex organ runs parallel to the intestine, and both end in the anus. In Dirofilaria spp the posterior end of the male is curved on its axis several times. Details of structures in cross section are shown in figure 2. A, anus; Al, alae (found in the posterior end of males); E, esophagus; I, intestine; O, ovary; Ov, oviduct; P, pseudocoelum (body cavity); Pa, papillae (sensory organs on the posterior end of the male); SV, seminal vesicle; T, testes; U, uterus; V, vagina; Va, vulva; VU, vagina uterina.

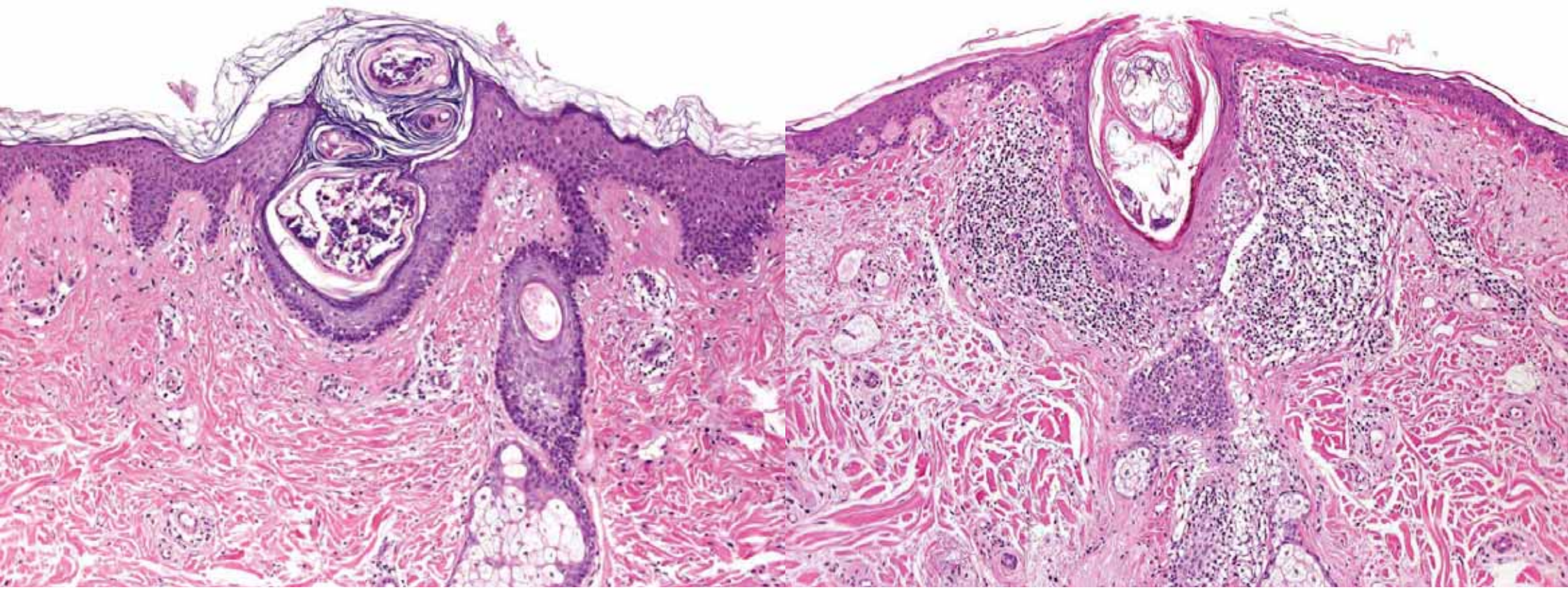




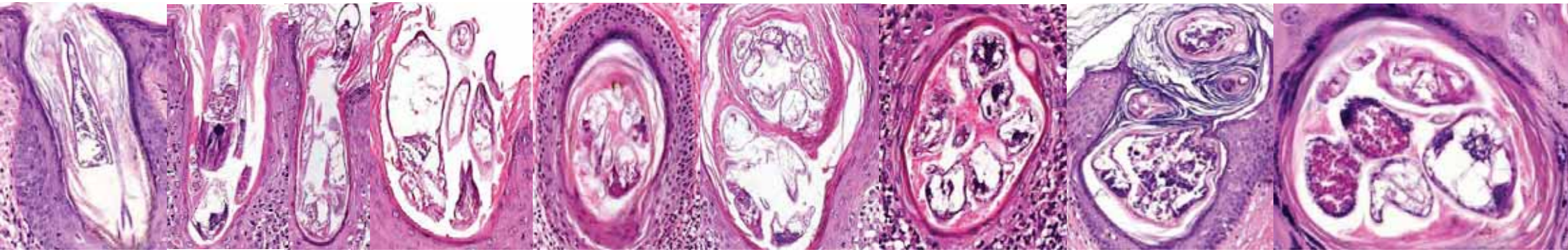




Demodex folliculorum – an ubiquitous organism
To my eyes not associated with a specific disease in immune competent patients, but may "trigger" cutaneous inflammation in given patients

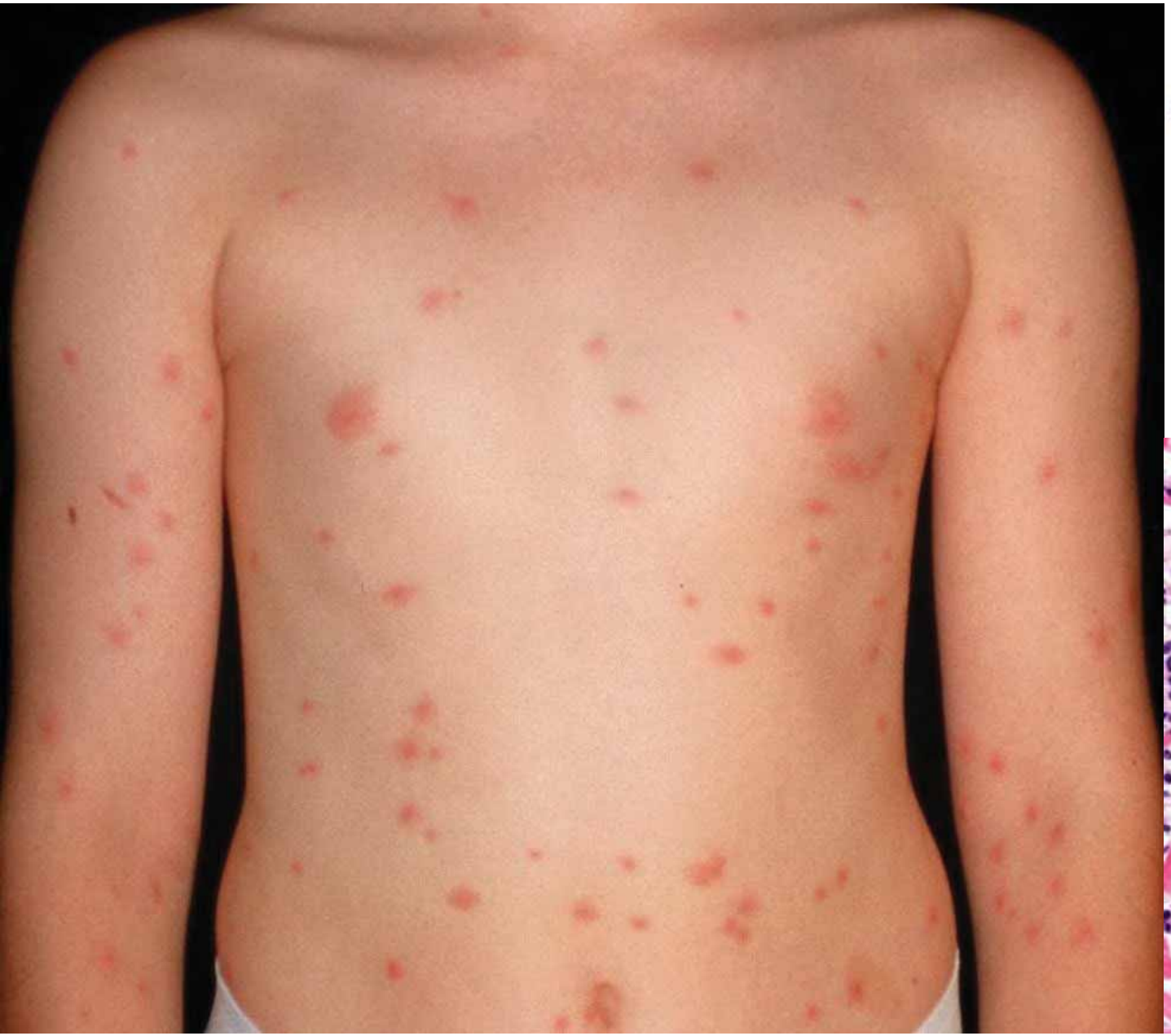


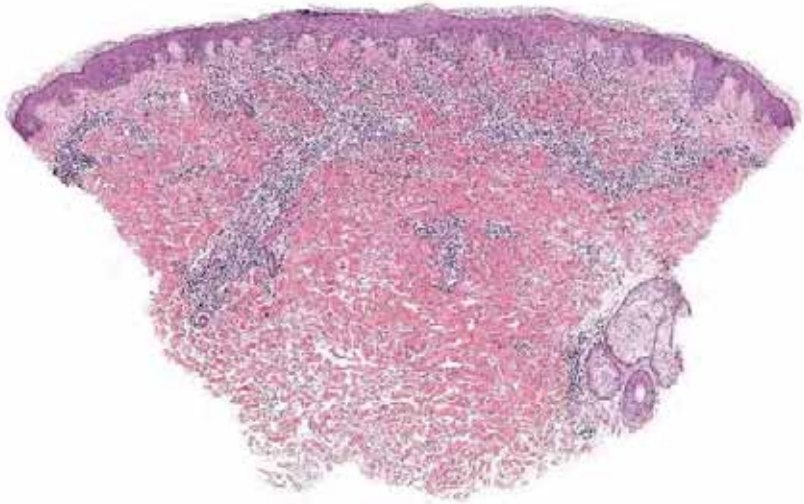
Often a chance finding without inflammation; sometimes with variably dense inflammation of hair follicles

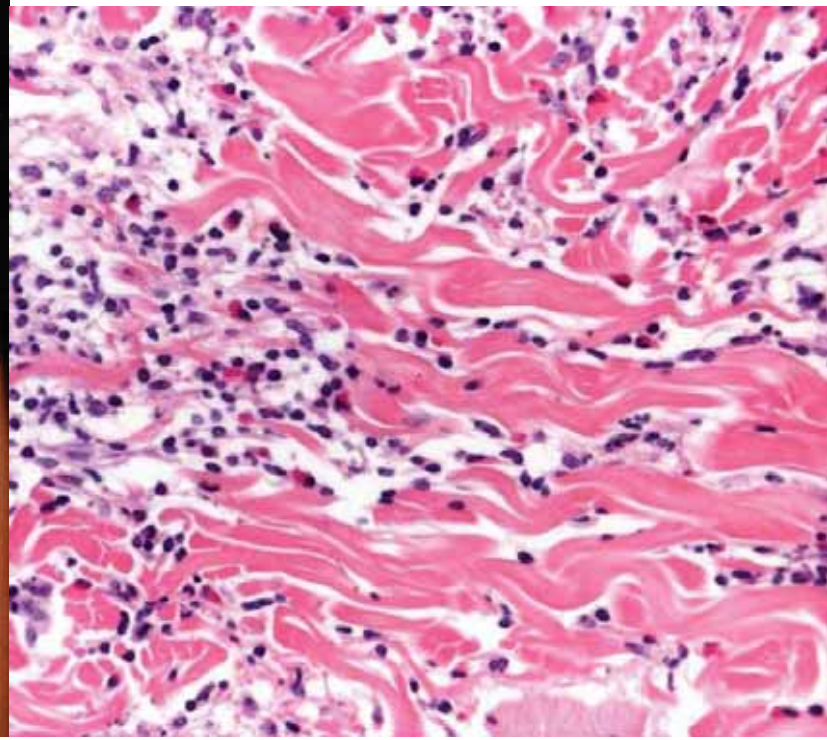


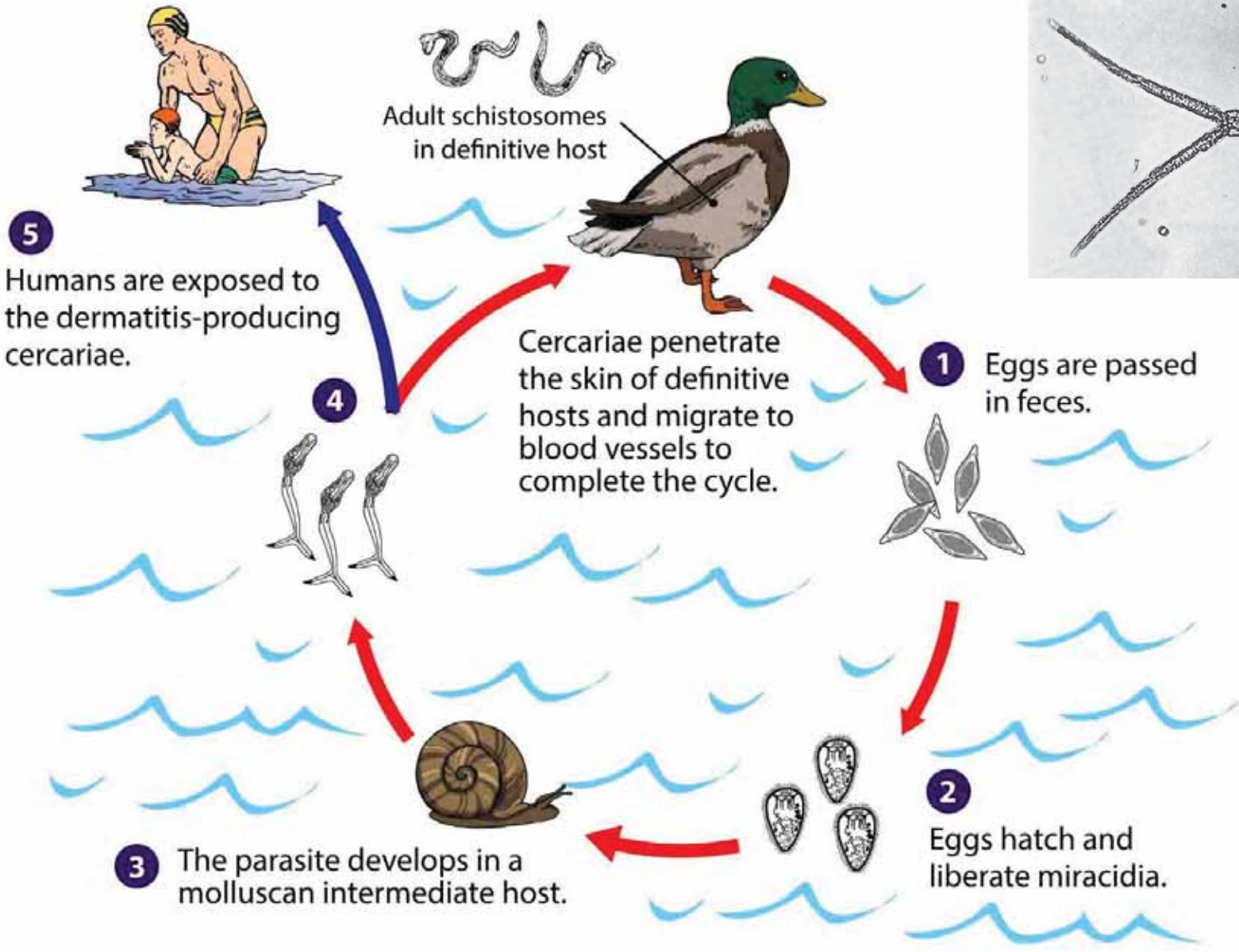
Cercarial dermatitis (swimmer's itch)

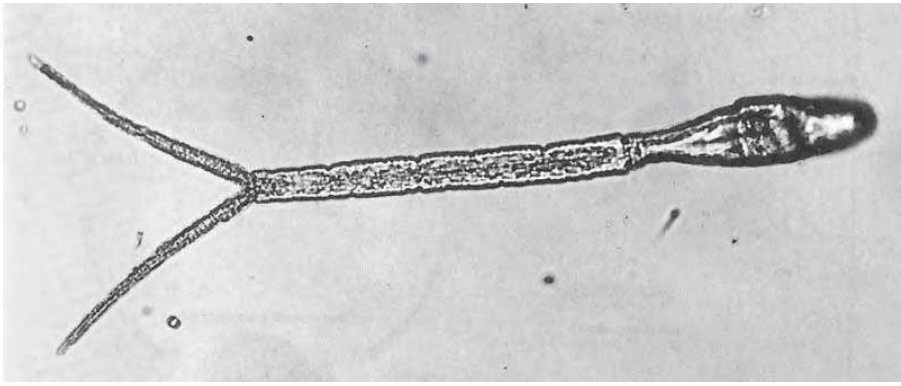
- Penetration of the cercariae into the skin (in search of a place to mature…)
- Some cercariae do not survive in humans and die in the skin (swimmer's itch – not a disease of tropical countries only!)
- In tropical Countries *schistosomiasis* (several types of *Schistosoma*): cercarial dermatitis is followed by hematogenous infection of urinary tract and/or intestine with deposition of eggs (found in urine and stools); chronic infection may be lethal
- Estimated number of affected persons: >230 $x10^6$











Trichobilharzia ocellata

Zerkarien-Dermatitis in der Steiermark *

Within a few days >50 patients attended the outpatient service of the Department of Dermatology because of an itchy dermatitis arising soon after swimming in Styrian lakes.
Cercariae of *Trichobilharzia ocellata* found in 7/33 lakes around Graz.

Infectious diseases & infestations

- A broad spectrum of diseases caused by viruses, bacteria, rickettsiae, spirochetae, fungi, algae, protozoa, helminths or other microorganisms / parasites, ranging from local cutaneous infection to generalized, life-threatening disorders
- Several histopathological patterns including different types of granulomatous inflammation, suppurative infiltrates, vasculitis and obstructive vasculopathy, and/or inflammatory infiltrates reach in plasma cells, neutrophils and/or eosinophils
- Sometimes "invisible" dermatosis (e.g., erythrasma, pityriasis versicolor, some dermatophytoses, pitted keratolysis)
- Sometimes fibrosing "pseudotumors" (e.g., fibroid nodules in acrodermatitis chronica atrophicans)
- Immunohistology available for some microorganisms, molecular tests for many - yet not widely available, expensive, and often not necessary