ATLAS OF DERMATOPATHOLOGY

SMTEBOOKS

PRACTICAL DIFFERENTIAL DIAGNOSIS BY CLINICOPATHOLOGIC PATTERN

Günter Burg
Werner Kempf, Heinz Kutzner
Josef Feit, Laszlo Karai

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Practical Differential Diagnosis by Clinicopathologic Pattern

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To our families and teachers

Contents

Preface

This atlas is addressed to pathologists and dermatologists who intend to become familiar with a practical approach to dermatopathology.

The structure of the book and of its chapters follows a basic approach to morphology. In histomorphology, as in clinical (macro-)morphology, the first step is to identify the localization of the pathological changes which is mostly done at scanning magnification; the second step includes assessing the distribution or pattern of pathologic elements at higher magnification and finally to search for the pathognomic elements – the so-called diagnostic clues.

It is like approaching a painting. In one of the almost 50 cabinets of the Alte Pinakothek in Munich, German paintings of the 14th–17th century are displayed (step 1). Among them one can detect a wonderful painting by Albrecht Altdorfer (1529) (step 2). Looking more closely one will discover between the many details Darius of Persia in flight and Alexander of Greece pursuing him (step 3). This is the clue for the "diagnosis," telling us that the Battle of Issus (333 BC), occident against orient, is the main theme of the painting.

Looking at a microscopic slide, our brain is following the same approach of overall orientation, identifying a prototypic pattern and finding the essential clue(s) for the diagnosis.

Therefore, in this book histo- and cytomorphologic elements should give guidance rather than any pathogenetic parameters we may have in our minds. Starting with the cornified layer of the epidermis, the chapters follow the pathological findings in the various levels of the epidermis, dermis and subcutaneous fat tissue and describe and display prototypes of diagnoses, their variants and the differential diagnoses, which may simulate the prototype. Each diagnosis is shown by its clinical appearance (Cl:) and by its histomorphology (Hi:) at

The Battle of Alexander at Issus 333 BC by Albrecht Altdorfer.
(bpk/Bayerische Staatsgemäldesammlung, München)

scanning magnification and at high power magnification, pointing to special clues.

Descriptions in *italic* are not displayed as pictures in the same chapter, but may be demonstrated in another one.

Many of the histologic images shown are taken from the *Hypertext Atlas of Dermatopathology* (www.atlases.muni.cz).[1]

References are not comprehensive, but may be of some help for getting more detailed information.

[1] *Hypertext Atlas of Dermatopathology* Josef Feit, Hana Jedličková, Zdeněk Vlašín, Günter Burg, Werner Kempf, Leo Schärer, Luděk Matyska (www.atlases.muni.cz)

Abbreviations

Cl	Clinical features
CNS	Central nervous system
DIF	Direct Immunofluorescence
Hi	Histological features
HPF	High power field
PAS	Periodic acid-Schiff
PCR	Polymerase chain reaction

Dermatopathology

Text-Atlas for Practical Differential Diagnosis of Clinicopathologic Pattern of Inflammatory Skin Diseases

Editors: Günter Burg, Werner Kempf, Heinz Kutzner

Co-Editors: Josef Feit and Laszlo Karai

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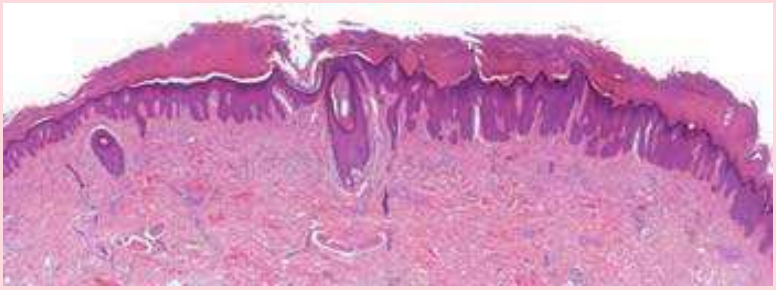
Introduction

Some basic terms in dermatohistology

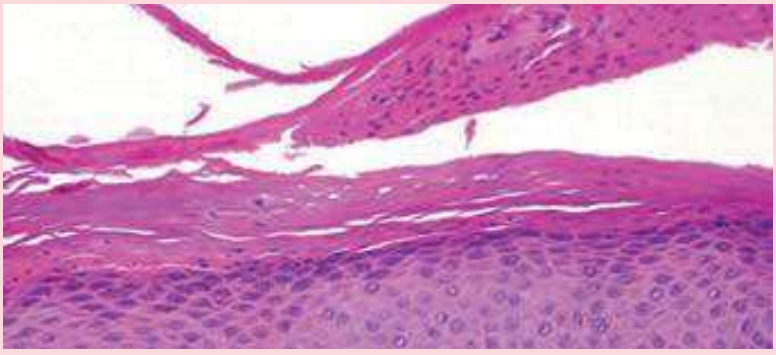
Horny layer

Orthokeratosis: Basket weave stratum corneum

Hyperkeratosis: Thickened stratum corneum

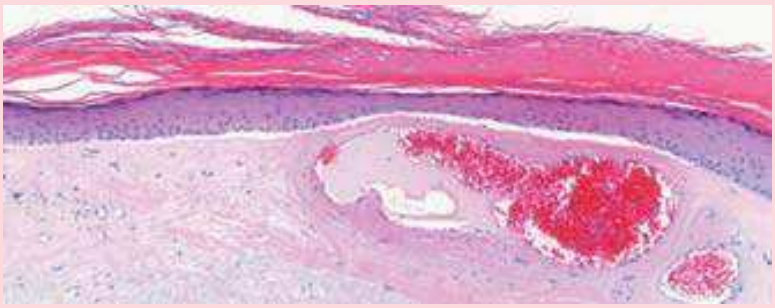


Parakeratosis: Remnants of nuclei in stratum corneum

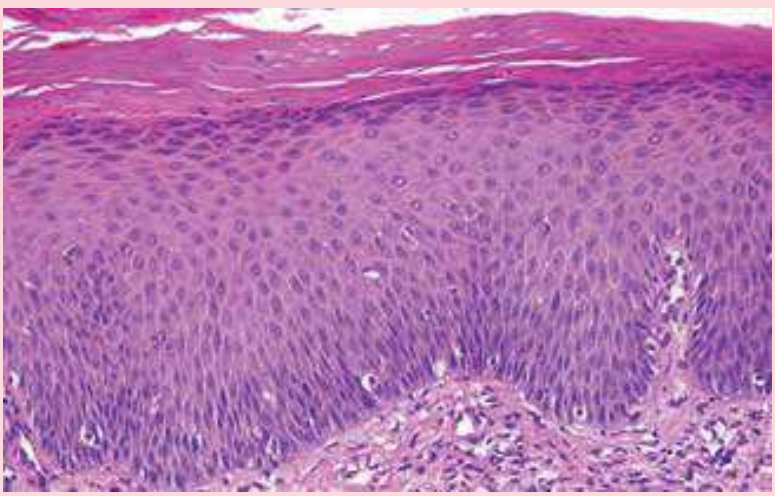


Epidermis

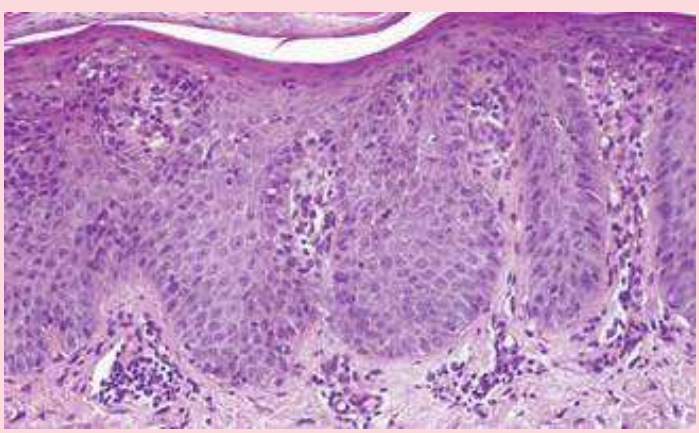
Atrophy



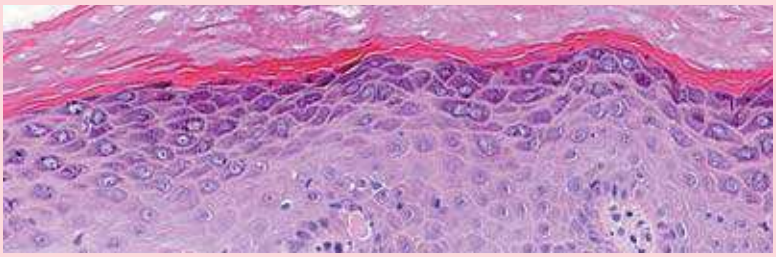
Acanthosis



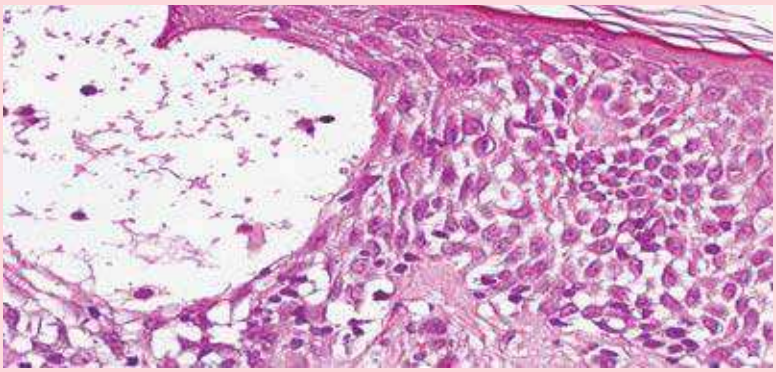
Papillomatosis



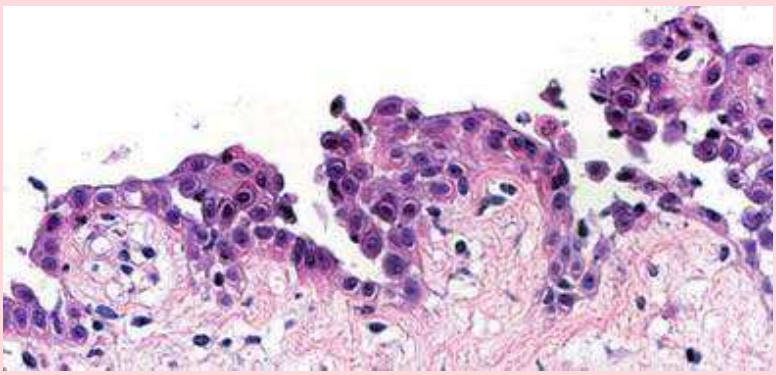
Hypergranulomatosis



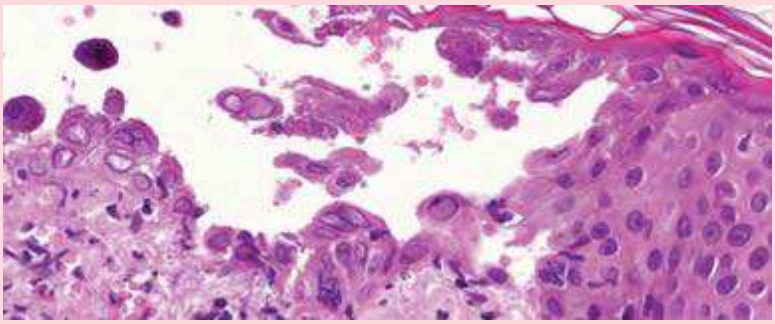
Spongiosis



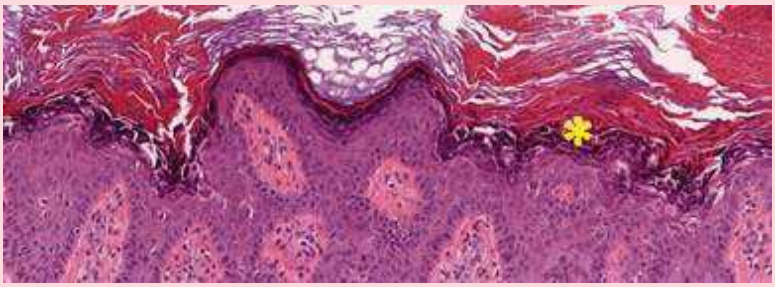
Acantholysis



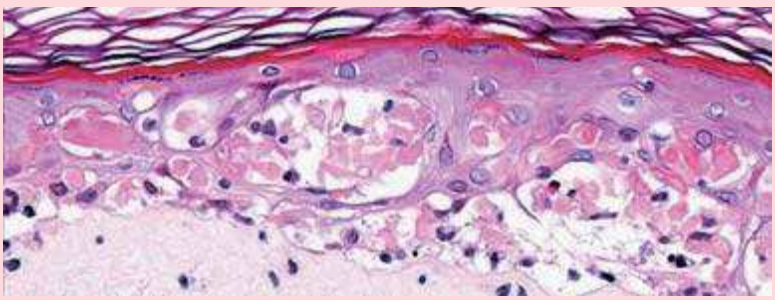
Ballooning



Dyskeratosis(*)

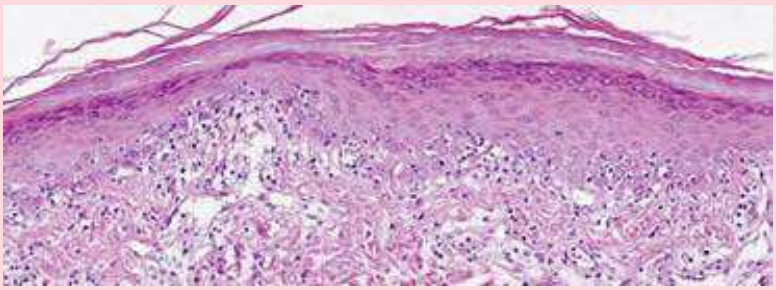


Necrotic keratinocytes

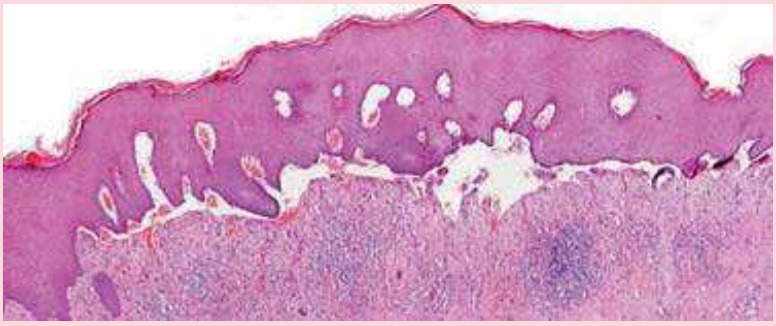


Interface

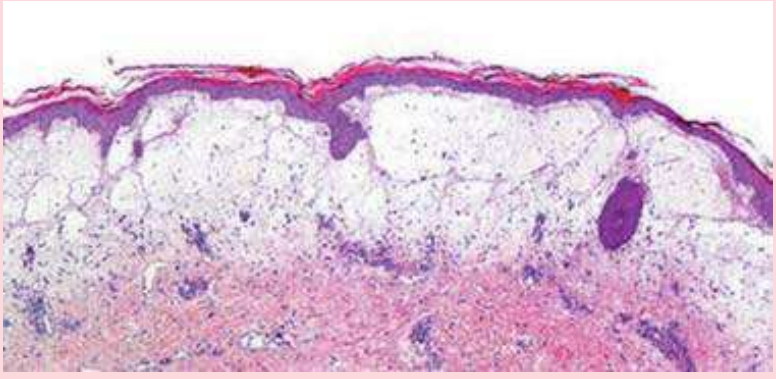
Interface dermatitis



Subepidermal blistering

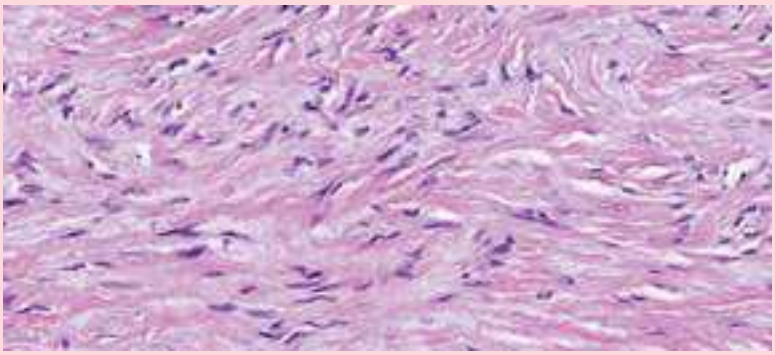


Subepidermal edema

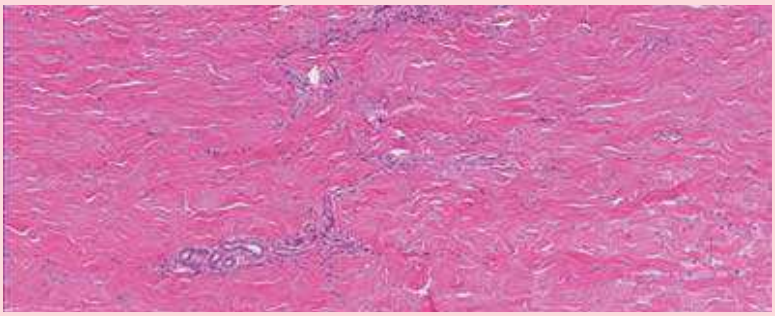


Dermis

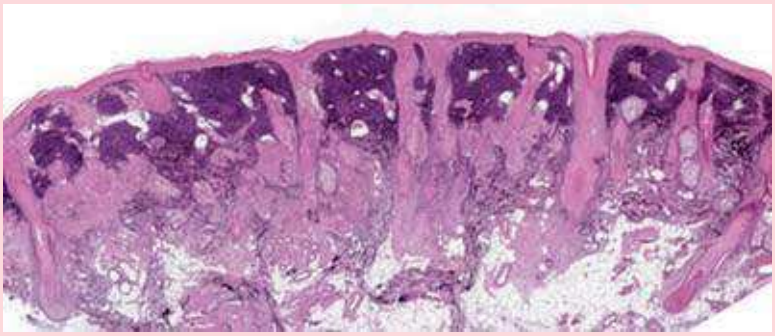
Fibrosis



Sclerosis

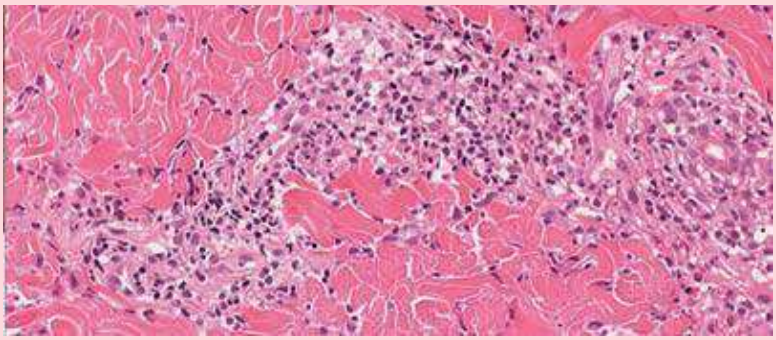


Elastosis, actinic



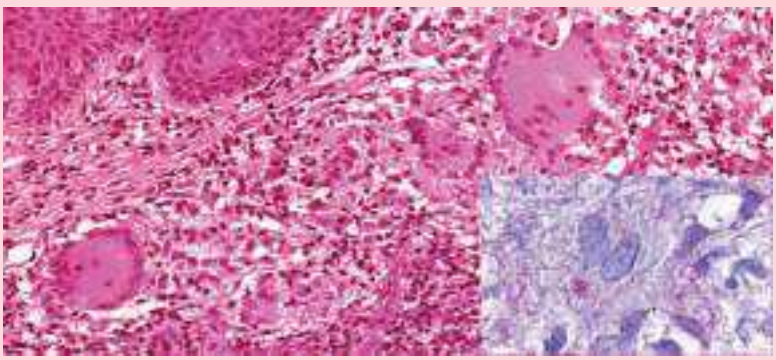
Elastica stain

Vasculitis

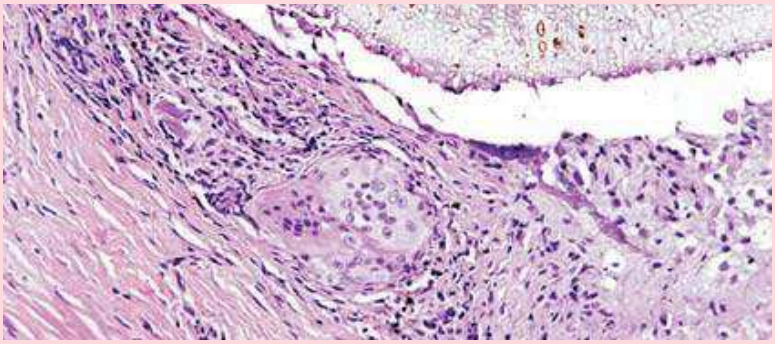


Calcification (vessel wall)

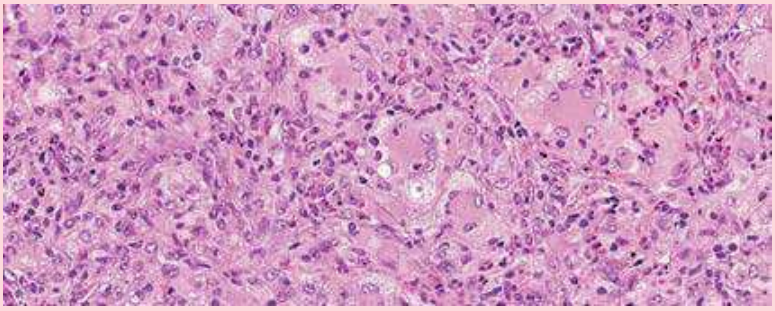
Langhans giant cells with *acid fast bacilli* (inset)



Foreign body giant cells



Touton giant cells

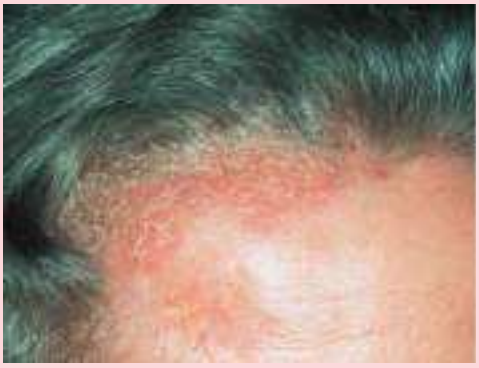


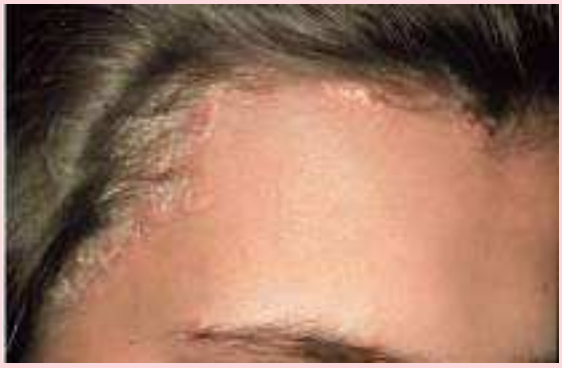
Clinicopathologic Correlation

When considering clinicopathologic correlations in approaching a diagnosis there basically are four scenarios, in which the diagnostic impact of histopathology may be high, moderate, low or none.

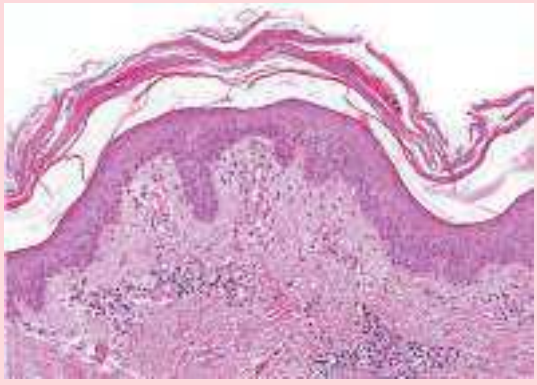
1. High diagnostic impact of histology, when the clinical presentations are almost identical

Psoriasis (left) vs seborrheic dermatitis (right)



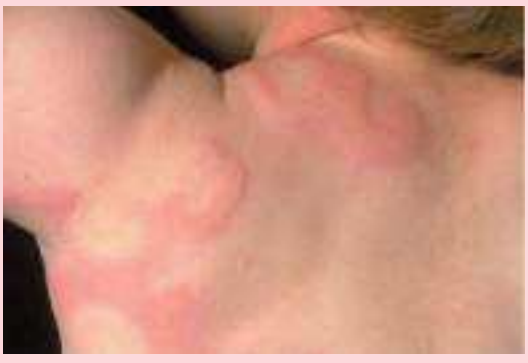


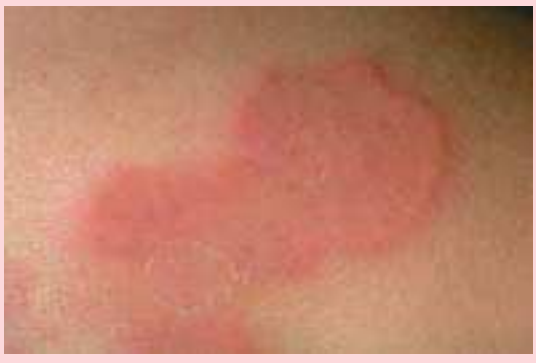
Psoriasiform acanthosis

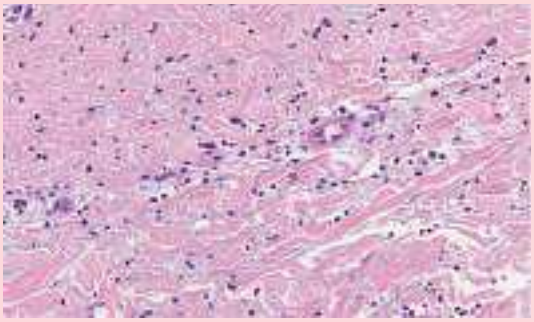


Free floating parakeratotic scale without psoriasiform acanthosis

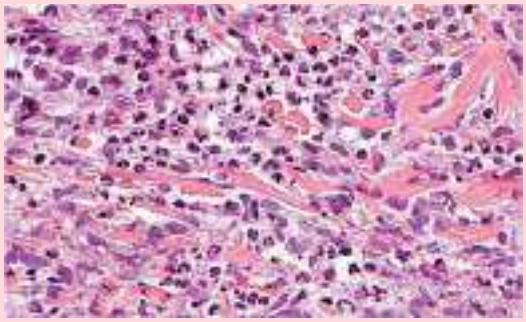
Urticaria (left) vs Sweet's syndrome (right)





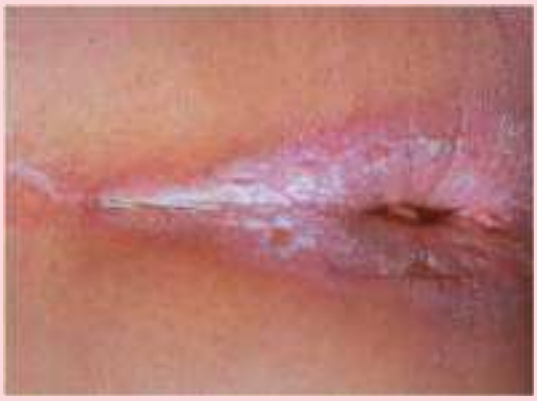


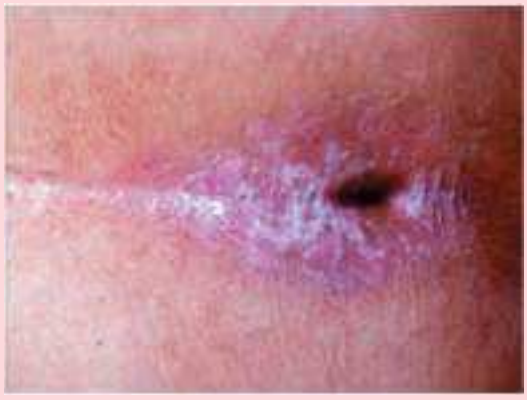
Sparse granulocytic infiltrate

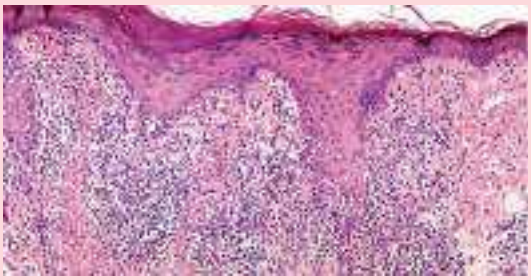


Densely packed sheets of neutrophils

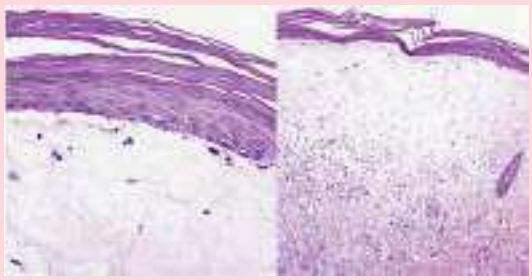
Lichen planus (left) vs lichen sclerosus et atrophicus (right)







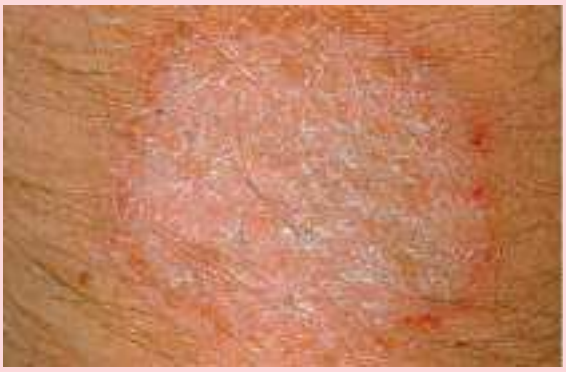
Sawtooth pattern with hypergranulosis and lichenoid interface dermatitis

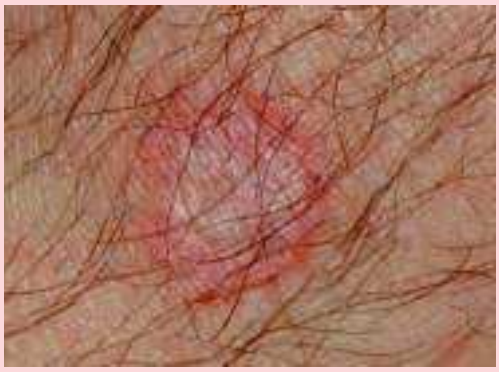


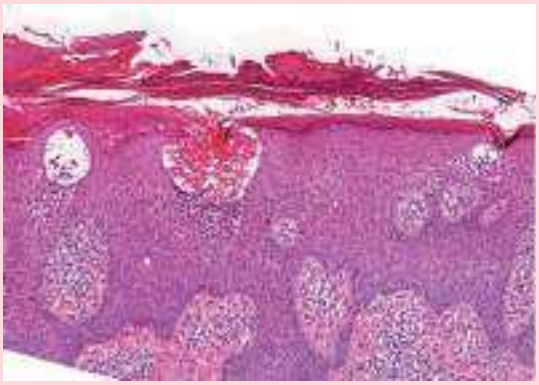
Tricolore pattern with red epidermis, white sclerosis, and blue band-like infiltrate.

2. Moderate diagnostic impact of histology, when the histology is just confirmation of the clinical diagnosis and is not mandatory as such

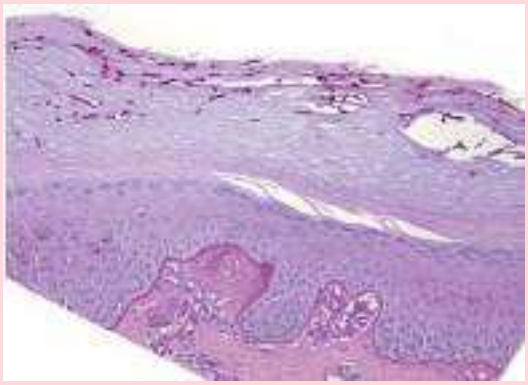
Nummular dermatitis (left) vs fungal infection (tinea) (right)







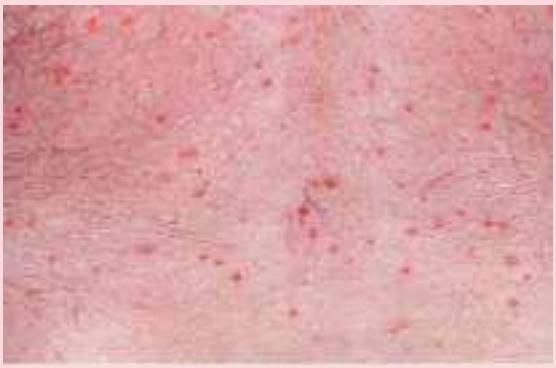
Scale crust without fungal organisms.

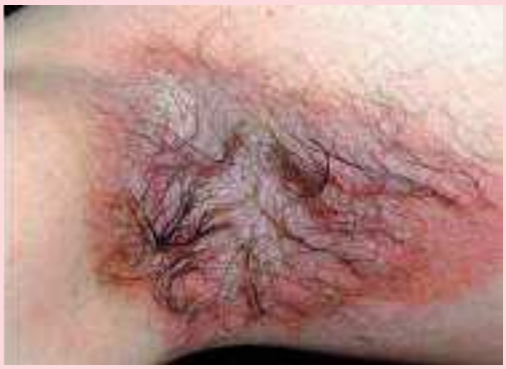


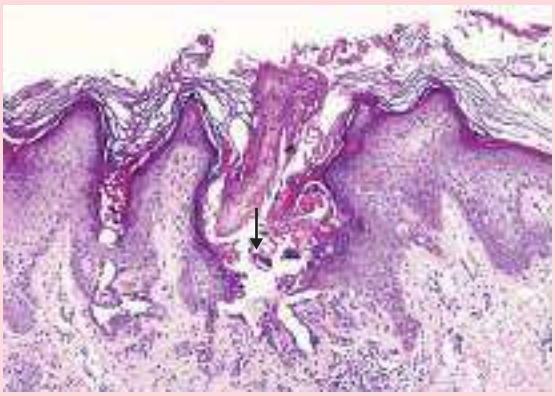
Hyphae and spores within cornified layer.

3. Low diagnostic impact of histology, when the clinician has to make the diagnosis based on the clinical presentation

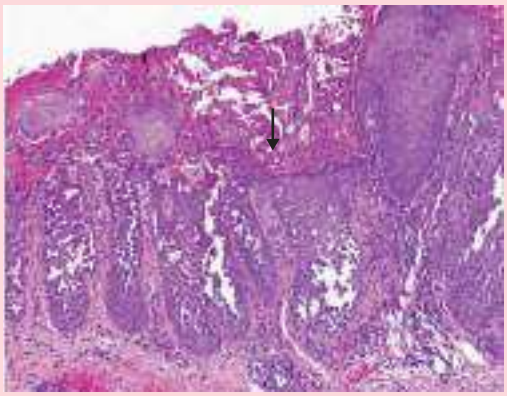
Transient acantholytic dermatosis (Grover's disease) (left) vs benign chronic familial pemphigus (Hailey-Hailey disease) (right)





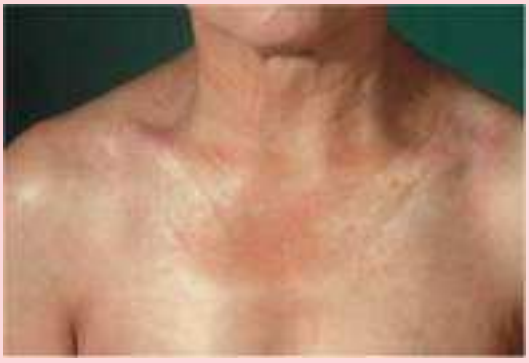


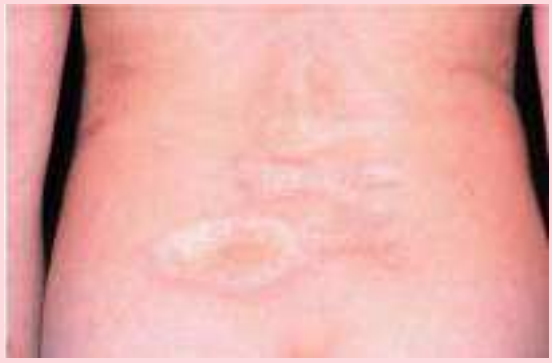
Focal acantholytic dyskeratosis (arrow)

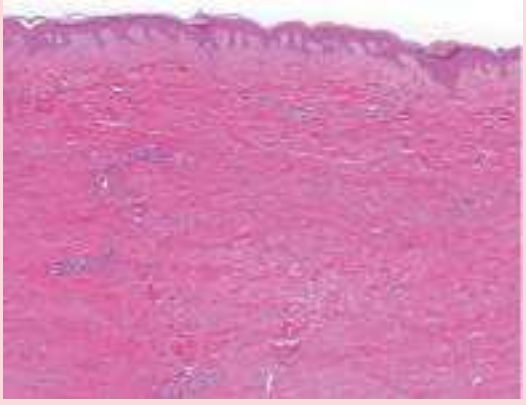


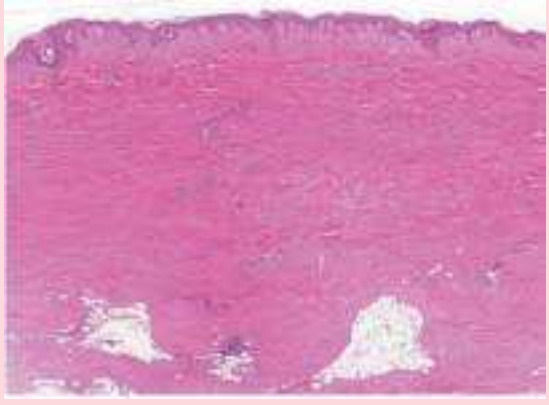
Transepidermal acantholysis (arrow)

Systemic diffuse scleroderma (left) vs circumscribed scleroderma (morphea) (right)

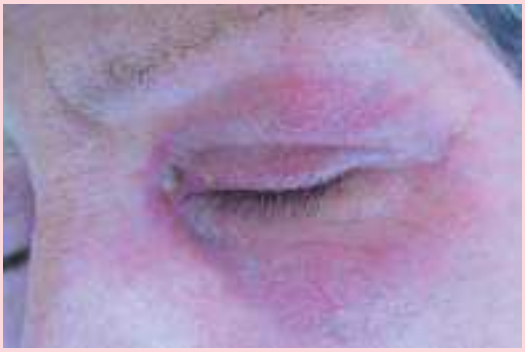


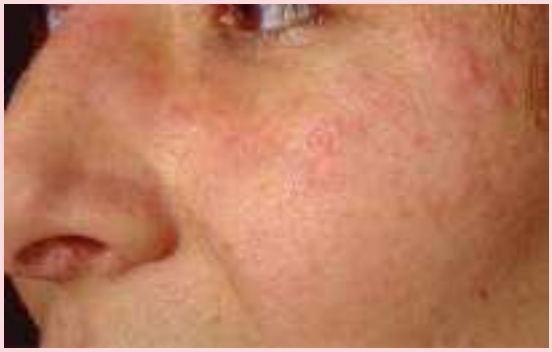


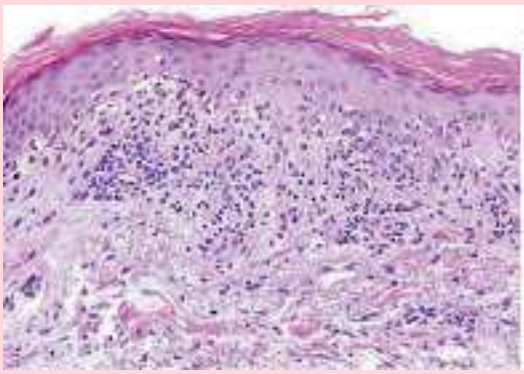




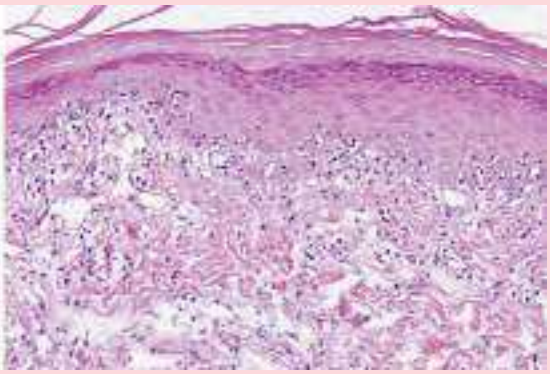
Dermatomyositis (left) vs acute systemic lupus erythematosus (right)







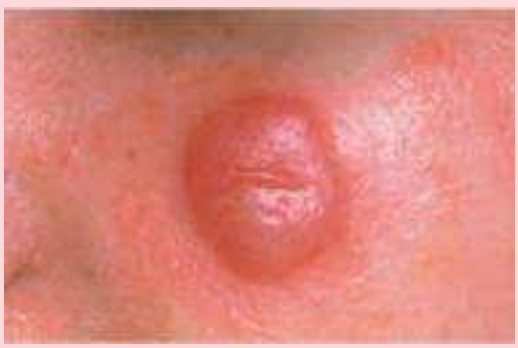
Denser infiltrate.

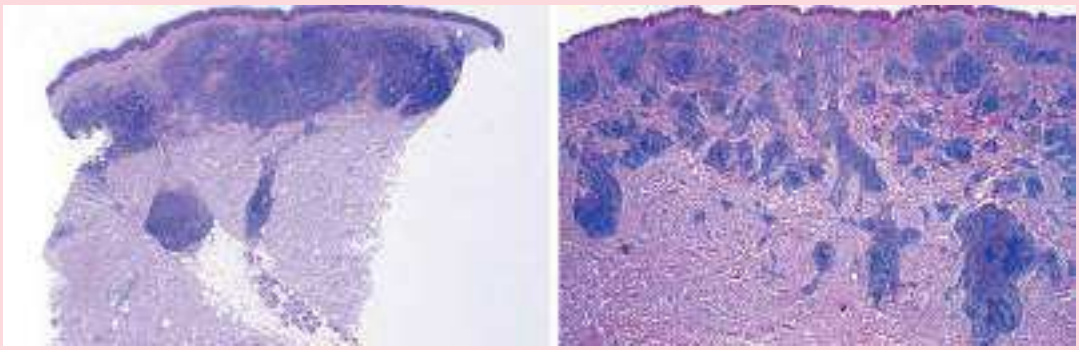


Less round cell infiltrate, more mucin deposits.

4. Little or no diagnostic impact of histology, when neither the clinical nor the histological presentation allows a definite diagnosis, which often is revealed only by the clinical course or the therapeutic susceptibility

Pseudolymphoma (left) vs cutaneous B-cell lymphoma (right)



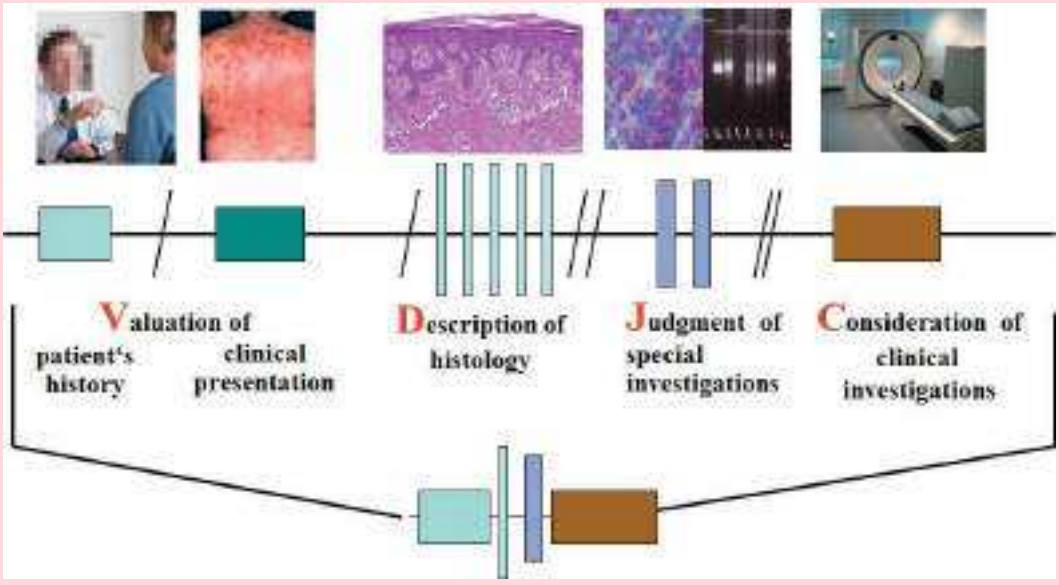


Similar pattern and immunophenotype in both lymphatic infiltrates.

The Diagnostic Puzzle

Even though apart from a thorough history, clinical presentation and histomorphology are the basic elements in reaching a proper diagnosis, additional investigations like immunophenotyping, genotyping and molecular techniques in conjunction with laboratory investigations sometimes are very helpful in completing a complex puzzle by "rearrangements" of various facts.

Stepwise approach to diagnosis
by VDJC rearrangement of information



Final diagnosis

Helpful links

For more information on common skin diseases you can register and login free of charge at DOIT (Dermatology Online with Interactive Technology; www.cyberderm.net).

For guidance through the program have a look on YouTube: https://www.youtube.com/watch?v=3ekhor35w0w&feature=emm-upload_owner#action=share.

A Collection of high resolution histological images are presented free of charge in the Hypertext Atlas of Dermatopathology (www.atlases.muni.cz).

CHAPTER 1
Horny Layer

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.
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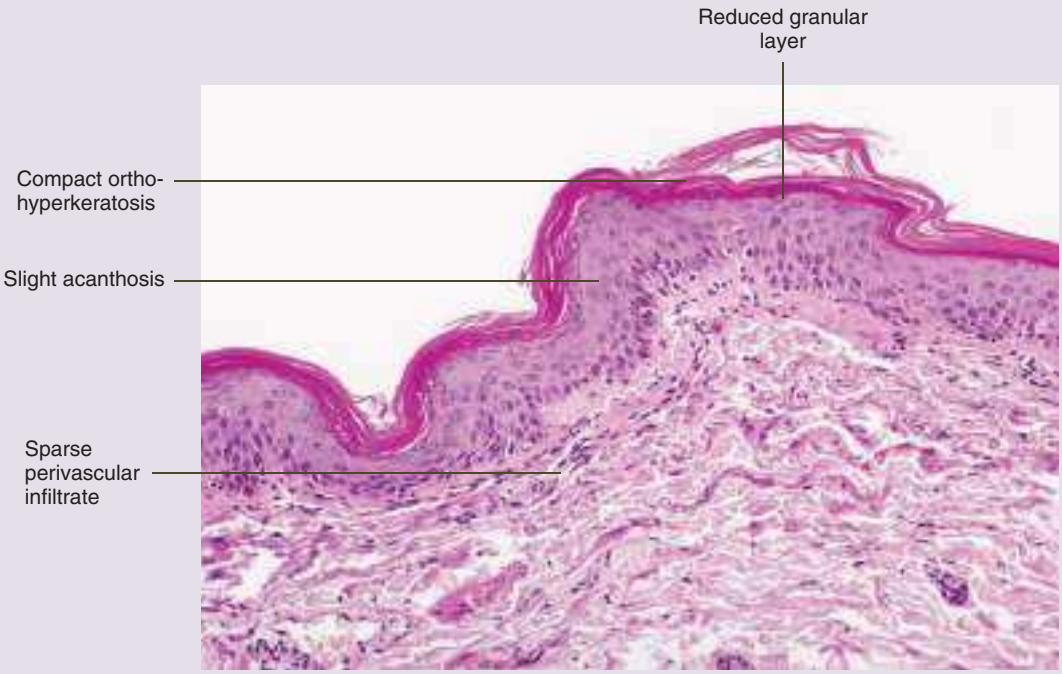
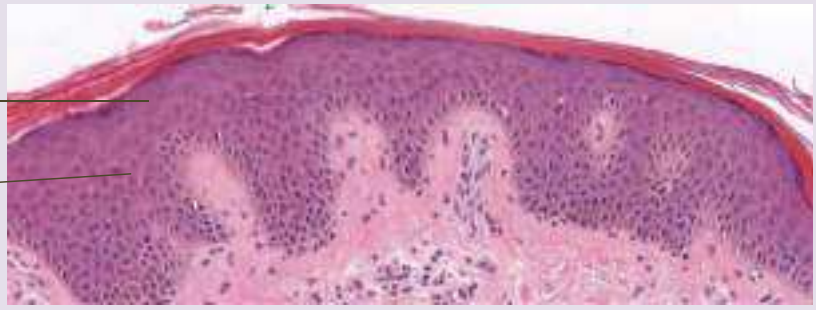
PROTOTYPE: Ichthyosis vulgaris

Gray-white scales

Cl: Starts in first year of life, dry rough scaly skin, gray-white scales are shed, symmetrical sparing of flexural areas, hyperlinear palms and soles, often atopic dermatitis (50%).



Ichthyosis vulgaris

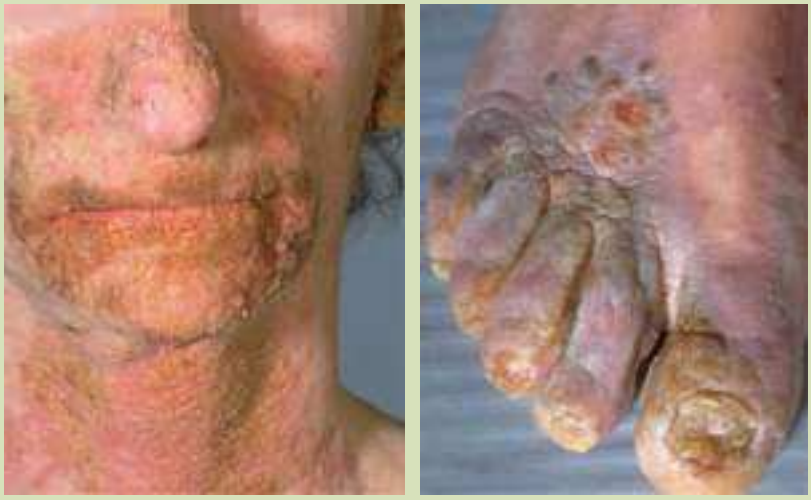


Hi: Compact orthohyperkeratosis, granular layer reduced or absent, lack of parakeratosis, follicular dilatation and hyperkeratosis. Epidermis usually normal, sometimes acanthotic or atrophic. No or sparse perivascular infiltrate in the papillary dermis.

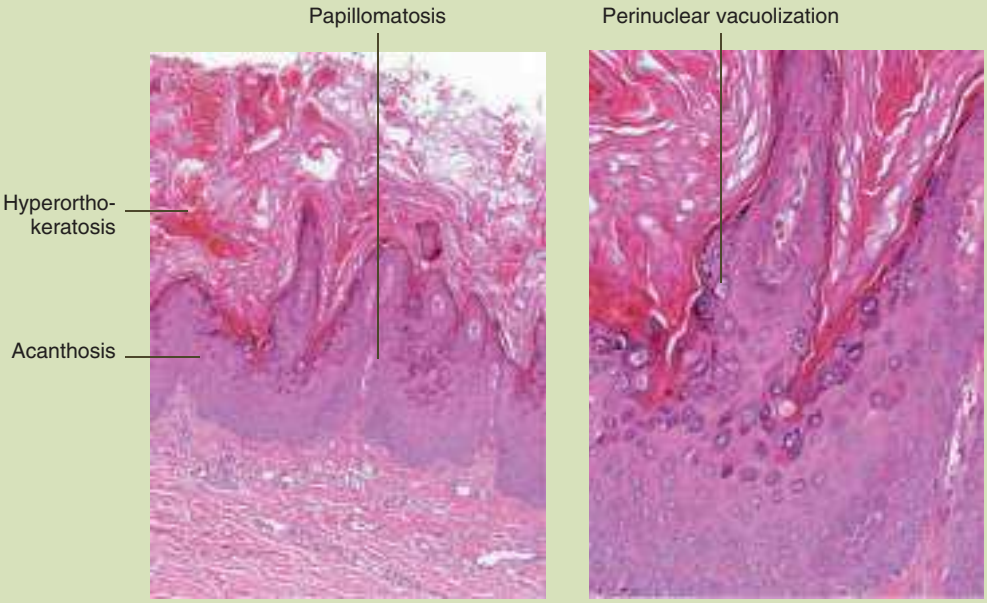
VARIANTS: Acquired ichthyosis vulgaris

Histology is identical to ichthyosis vulgaris.

DIFFERENTIAL DIAGNOSIS: Ichthyosis hystrix



Cl: Massive, dark, sometimes spiny hyperkeratosis. Various genetic forms exist. Flexures, palms and soles are involved.



Hi: Mild hyperorthokeratosis, acanthosis, papillomatosis, elongation of rete ridges. Perinuclear vacuolization of granular and spinous layer keratinocytes, presenting epidermolytic features.

Other Diagnosis

Refsum syndrome (heredopathia atactica polyneuritiformis): *Vacuolization of basal and suprabasal keratinocytes (accumulation of phytanic acid; Sudan red stain)*

X-linked dominant ichthyosis (Harlequin ichthyosis): *Clinical features similar to ichthyosis vulgaris, but flexures are involved, undescended testes in 30%. Vacuolization of basal and suprabasal keratinocytes (accumulation of phytanic acid; Sudan red stain)*

Lamellar ichthyosis: *Genetically heterogeneous disorder, usually present at birth presenting as collodion baby in case of generalized involvement. Erythrodermic and non-erythrodermic forms. Transglutaminase-deficiency in most forms. Histology shows mild to moderate hyperorthokeratosis, stratum granulosum normal or broadened, acanthosis, papillomatosis*

Bullous, epidermolytic ichthyosis (bullous form of erythrodermia ichthyosiformis congenitalis): *Erythroderma at birth with diffuse blistering and erosions, like burned. Histologically the most striking feature is acanthokeratolysis with epidermal thickening leading to superficial blister formation. Tonofilaments can be seen as dark clumps in a shell-like arrangement around the nucleus*

Syndromes of ichthyosis and trichothiodystrophy (Tay syndrome): *Additional clinical symptoms and biochemical findings.*

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de Berker, D., W. A. Branford, S. Soucek, and L. Michaels (1993). "Fatal keratitis ichthyosis and deafness syndrome (KIDS). Aural, ocular, and cutaneous histopathology." *Am J Dermatopathol* **15**(1): 64–9.

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Hoang, M. P., K. R. Carder, A. G. Pandya, and M. J. Bennett (2004). "Ichthyosis and keratotic follicular plugs containing dystrophic calcification in newborns: distinctive histopathologic features of x-linked dominant chondrodysplasia punctata (Conradi-Hunermann-Happle syndrome)." *Am J Dermatopathol* **26**(1): 53–8.

Nabai, H. and A. H. Mehregan (1979). "Ichthyosis linearis circumflexa." *J Cutan Pathol* **6**(2): 148–9.

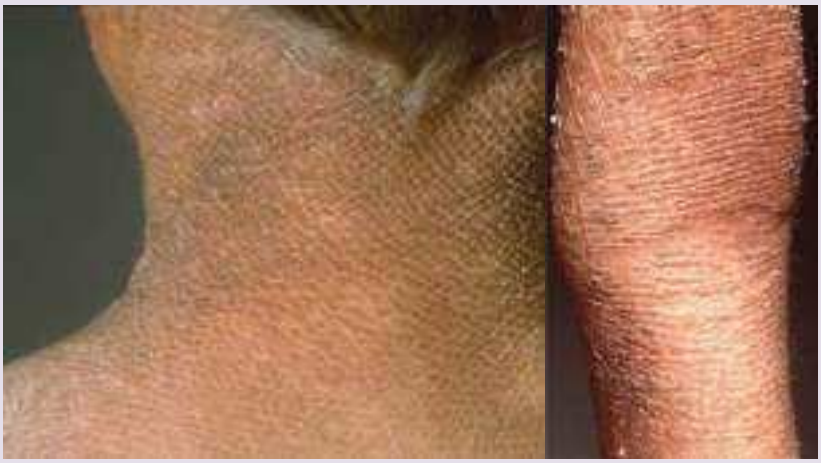
Niemi, K. M. and L. Kanerva (1989). "Ichthyosis with laminated membrane structures." *Am J Dermatopathol* **11**(2): 149–56.

Niemi, K. M., K. Kuokkanen, L. Kanerva, and J. Ignatius (1993). "Recessive ichthyosis congenita type IV." *Am J Dermatopathol* **15**(3): 224–8.

Okulicz, J. F. and R. A. Schwartz (2003). "Hereditary and acquired ichthyosis vulgaris." *Int J Dermatol* **42**(2): 95–8.

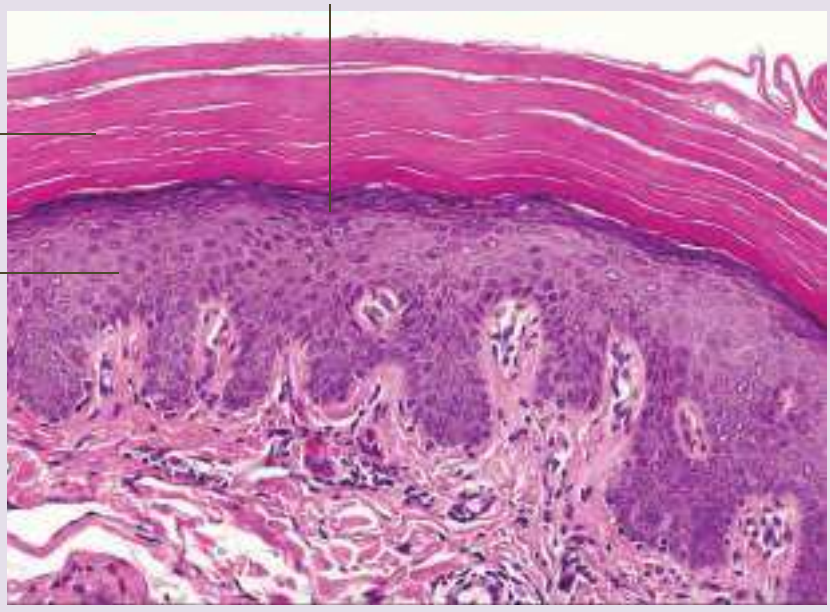
Sandler, B. and K. Hashimoto (1998). "Collodion baby and lamellar ichthyosis." *J Cutan Pathol* **25**(2): 116–21.

PROTOTYPE: Lamellar ichthyosis



Lamellar ichthyosis. Neck and cubital area

Cl: Genetically heterogeneous disorder, usually manifest at birth presenting as collodion baby in case of generalized involvement. Erythrodermic and non-erythrodermic forms. Transglutaminase deficiency in most forms.



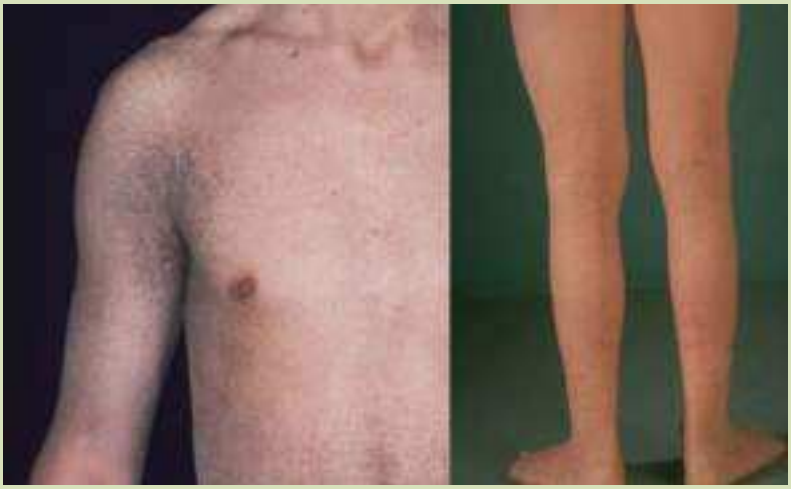
Hi: Mild to moderate hyperorthokeratosis, stratum granulosum normal or broadened, acanthosis, papillomatosis.

DIFFERENTIAL DIAGNOSIS: Congenital ichthyosis group X-linked dominant ichthyosis (Harlequin ichthyosis)

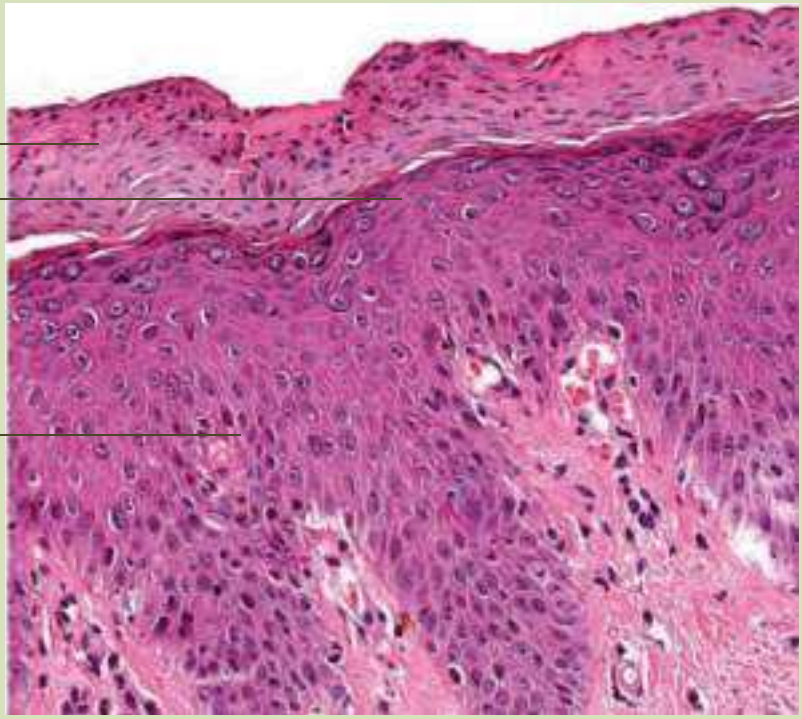
Cl: Similar to ichthyosis vulgaris, but flexures are involved, undescended testes in 30%.

Hi: Vacuolization of basal and suprabasal keratinocytes (accumulation of phytanic acid; Sudan red stain).

DIFFERENTIAL DIAGNOSIS: X-linked recessive ichthyosis



CI: Starts in the first week of life with fine scales and mild erythema, aggravating after a few months. Brown scales giving a dirty appearance cover the whole integument, without sparing of flexural areas.

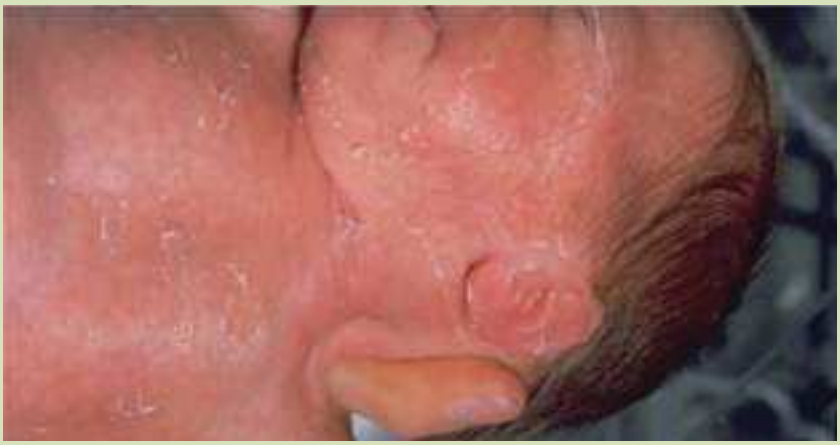


Hi: Marked hyperkeratosis, thickened or normal and sometimes thinned granular layer, spinous layer variably acanthotic and papillomatous, mild to marked perivascular infiltrate in the papillary dermis.

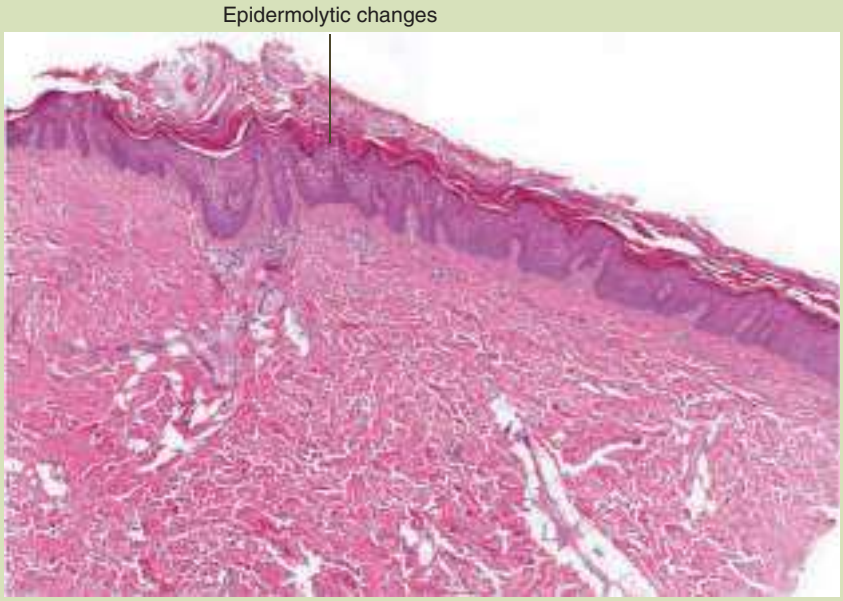
HORNY LAYER

DIFFERENTIAL DIAGNOSIS: Bullous epidermolytic ichthyosis (bullous form of congenital ichthyosiform erythroderma)

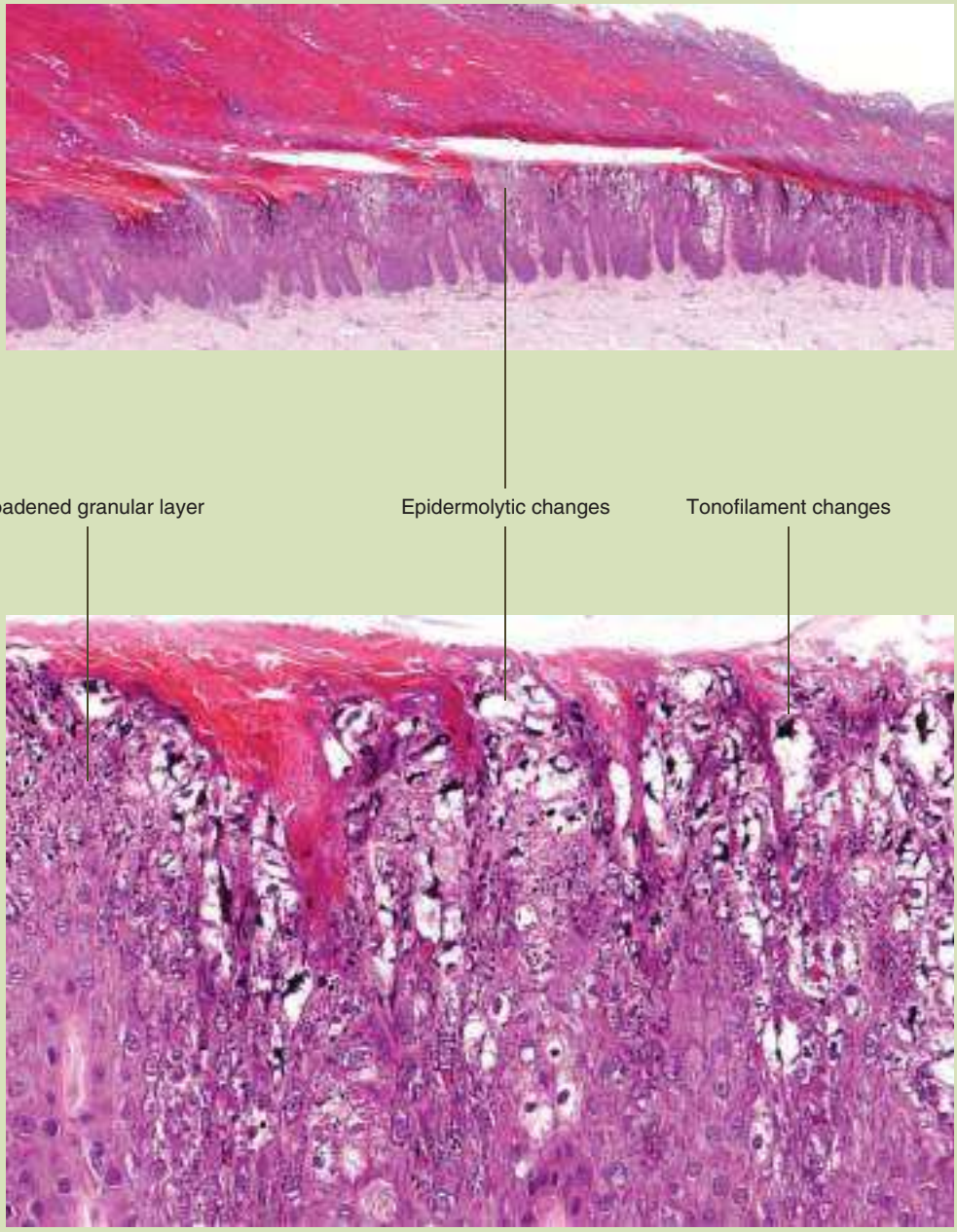
Congenital ichthyosiform erythroderma



CI: Erythroderma at birth with diffuse blistering and erosions, as if burned.



Bullous epidermolytic ichthyosis



Hi: Epidermolytic changes in the upper part of the spinous and the broadened granular layer, which may lead to superficial blister formation. Tonofilaments can be seen as dark clumps in a shell-like arrangement around the nucleus.

Ichthyosis and deafness syndromes: *Additional clinical symptoms and biochemical findings*

- *Ichthyosis and deafness syndromes*
  - *Hystrix-like ichthyosis with deafness (HID)*
  - *Keratitis, ichthyosis-like hyperkeratosis and deafness (KID)*
- *Ichthyosis hystrix Curth-Macklin: epidermolytic changes without bullae*
- *Erythrodermia congenitalis ichthyosiformis*
- *Neutral lipid storage disease with ichthyosiform erythroderma (Dorfman syndrome): foamy cytoplasm of keratinocytes in the basal and the granular layer*

Erythrokeratoderma variabilis, various forms: *Migratory erythema and/or persistent hyperkeratotic plaques. Orthohyperkeratosis over a normal granular layer, acanthosis and papillomatosis. Perivascular lymphocytic infiltrate of variable intensity in the upper dermis*

DIFFERENTIAL DIAGNOSIS: Other Skin Diseases

- ***Acanthosis nigricans****: confined to flexural areas. Hyperpigmentation of epidermal basal layer*
- ***Epidermal nevus*** (*see* Chapter 2, Pruriginous, page 47) *circumscribed lesion with acanthosis and hyperkeratosis*
- ***Palmoplantar keratodermas****: confined to palmoplantar areas*
- ***Chronic eczema*** *(lichen simplex chronicus)* (*see* Chapter 2, Chronic, page 36) *foci of parakeratosis, perivascular lymphocytic infiltrate in the upper dermis*
- ***Pityriasis rubra pilaris*** (*see* Chapter 2, psoriasiform, page 56): *Horizontally and vertically alternating ortho- and hyperparakeratosis (checkerboard sign). Subtle perivascular infiltrate, clinically nappes claires*
- ***Clavus*** (*see* Chapter 2, Pruriginous, page 46): *Circumscribed lesion with acanthosis and hyperkeratosis. No inflammation*

References

Hoang, M. P., K. R. Carder, *et al.* (2004). "Ichthyosis and keratotic follicular plugs containing dystrophic calcification in newborns: distinctive histopathologic features of x-linked dominant chondrodysplasia punctata (Conradi-Hunermann-Happle syndrome)." *Am J Dermatopathol* **26**(1): 53–8.

CHAPTER 2
Epidermis

CHAPTER MENU

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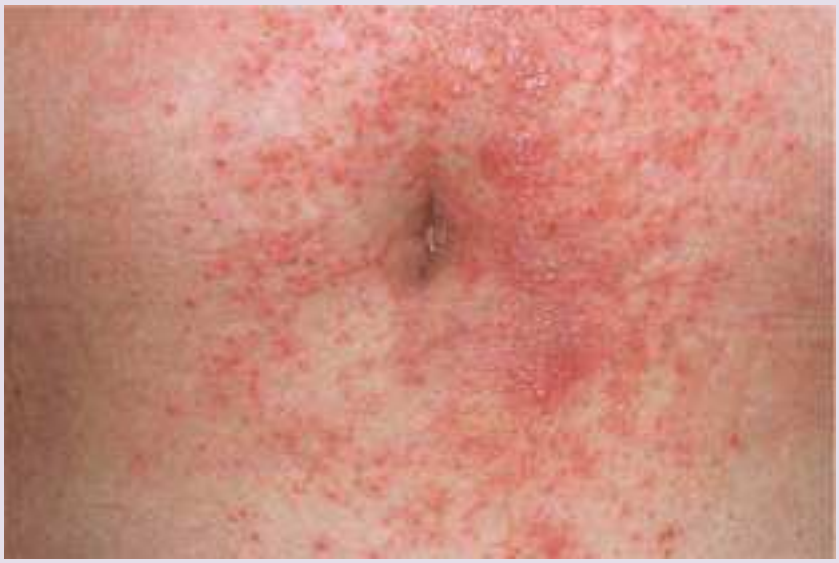
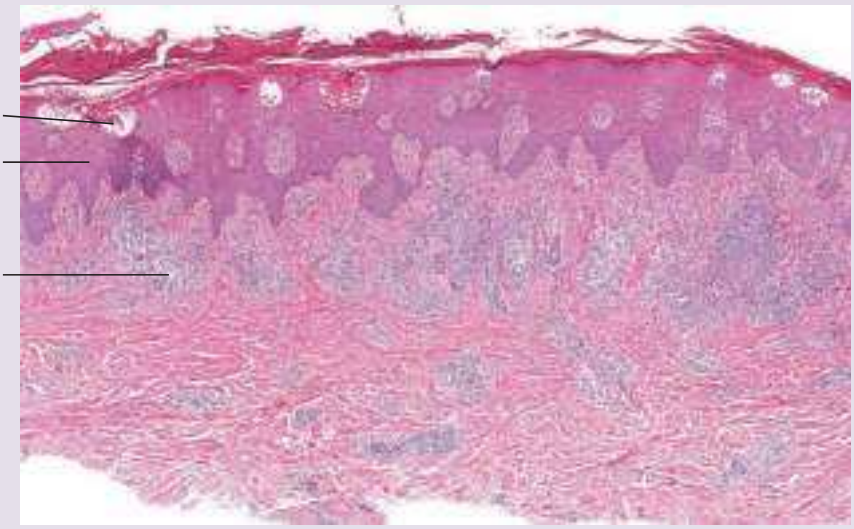
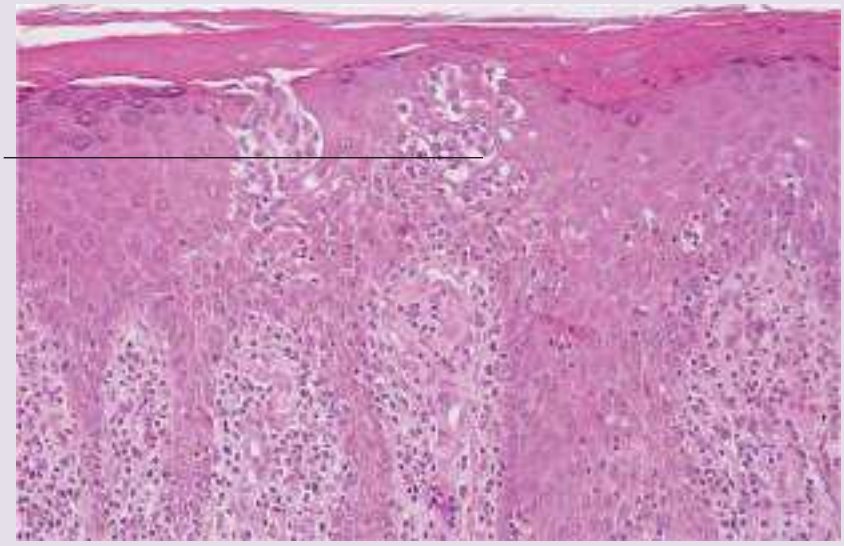
PROTOTYPE: Acute (contact) dermatitis

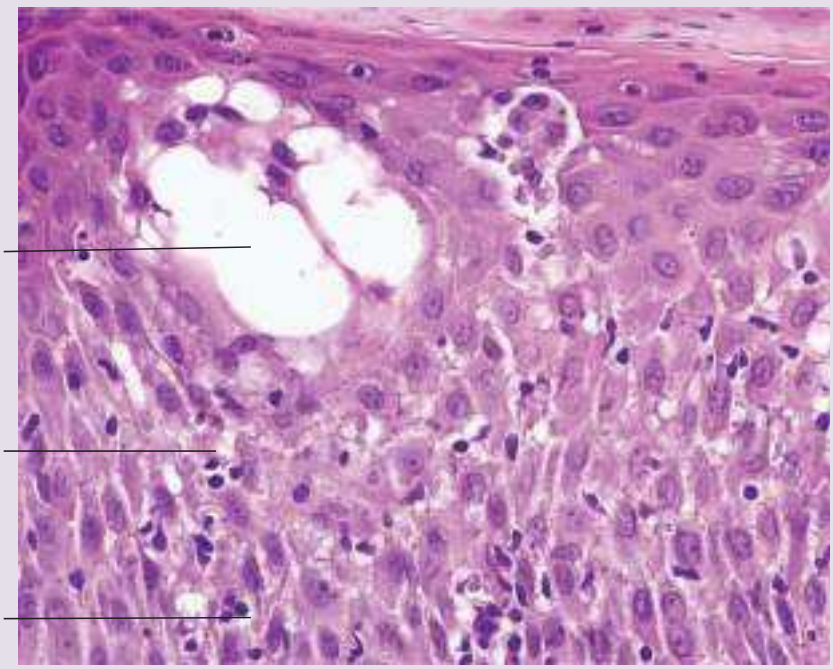


Cl: Erythema, vesicles and crust formation in a fairly circumscribed area.



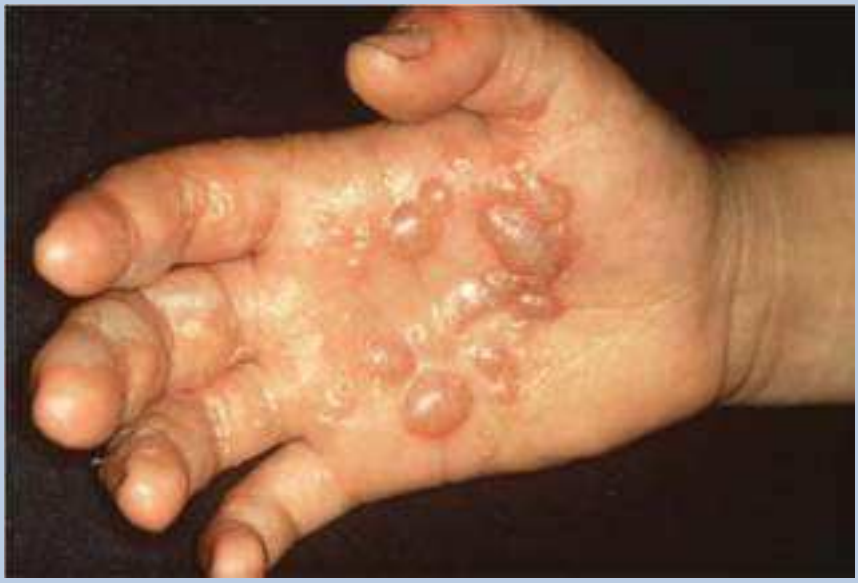
Acute (contact) dermatitis



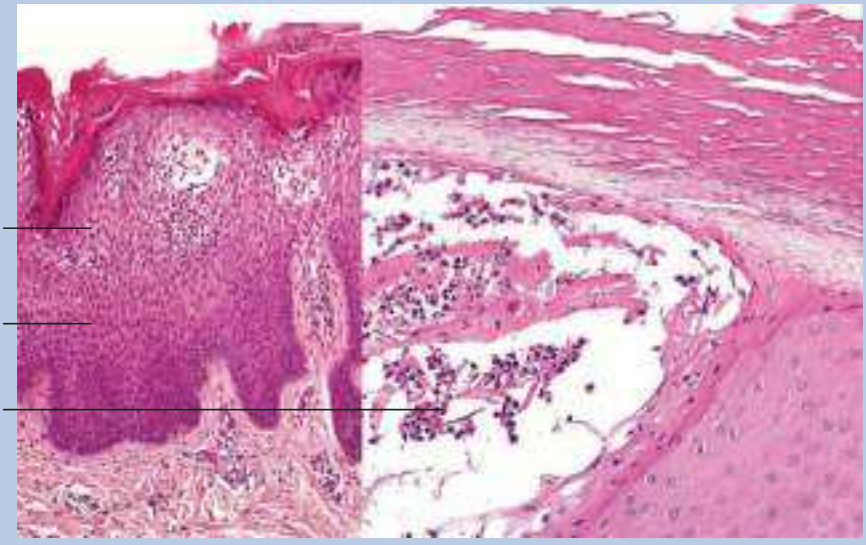


Hi: Spongiosis, acanthosis of variable degree and hyperparakeratosis of variable degree depending on the evolutionary stage, diffuse and perivascular predominantly lymphocytic infiltrate with a few eosinophils or neutrophils, edema of the papillary dermis.

VARIANT: Dyshidrotic eczema



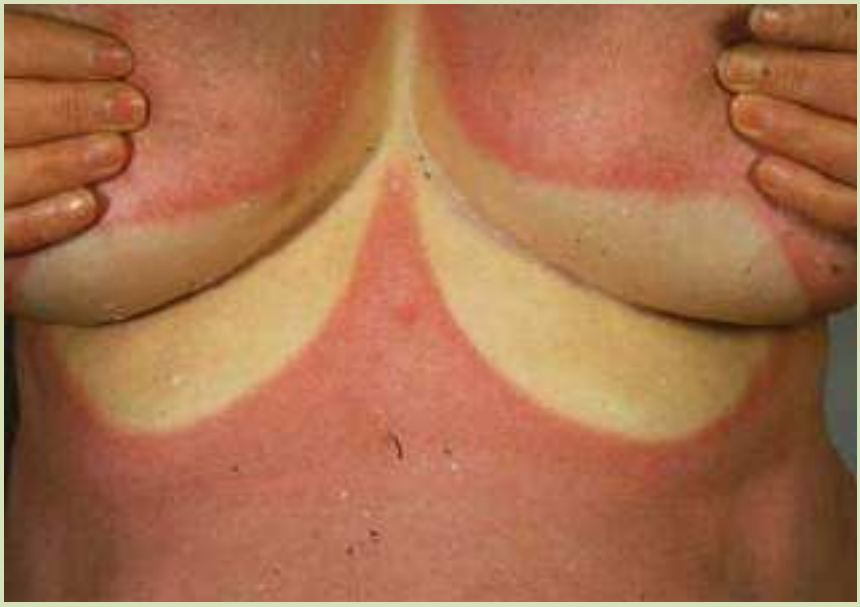
Cl: Small vesicles or larger blisters (pompholyx) on palms and soles.



Hi: Spongiotic vesicles.

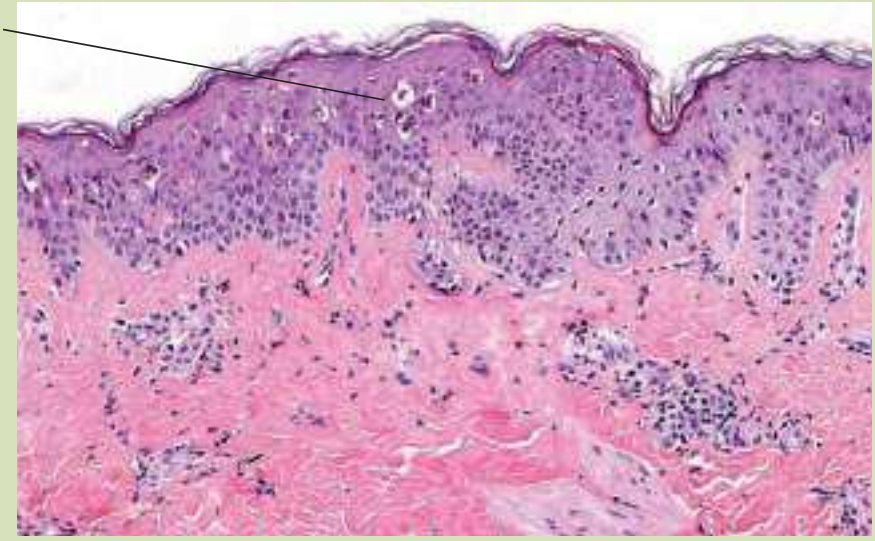
Acute toxic contact dermatitis: *necrotic keratinocytes, admixture of neutrophils.*
Acute allergic contact dermatitis: *prominent number of eosinophils.*

DIFFERENTIAL DIAGNOSIS: Phototoxic and photoallergic dermatitis



Erythema in sunlight exposed areas

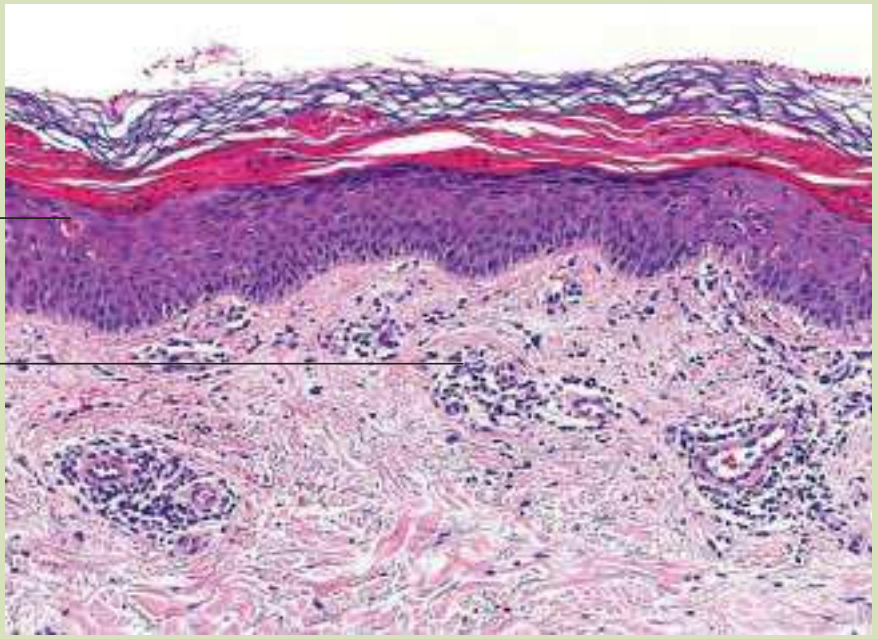
CI: Erythema, vesicles or blisters in sun exposed areas with sharp (toxic) or fairly sharp (allergic) demarcation.

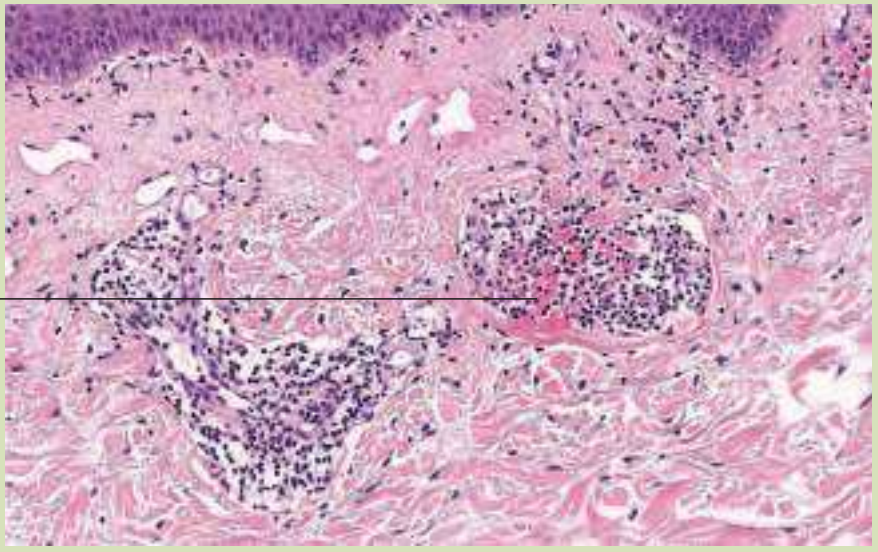


Necrotic keratinocytes: «Sunburn cells»

EPIDERMIS

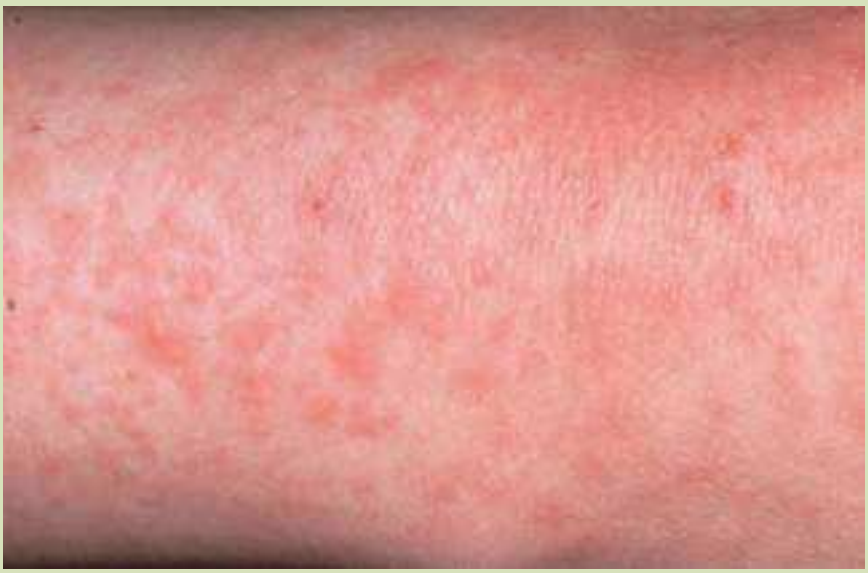
Phototoxic and photoallergic dermatitis



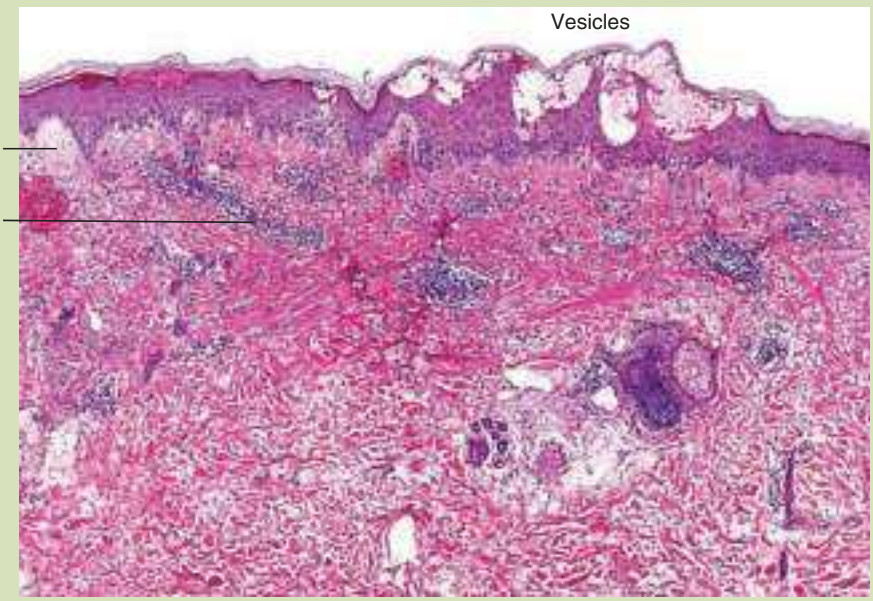


Hi: Variable spongiosis and acanthosis, apoptotic keratinocytes, mixed cellular infiltrate, composed of lymphocytes, eosinophils, few neutrophils; extravasation of erythrocytes; dermal edema in the upper dermis.

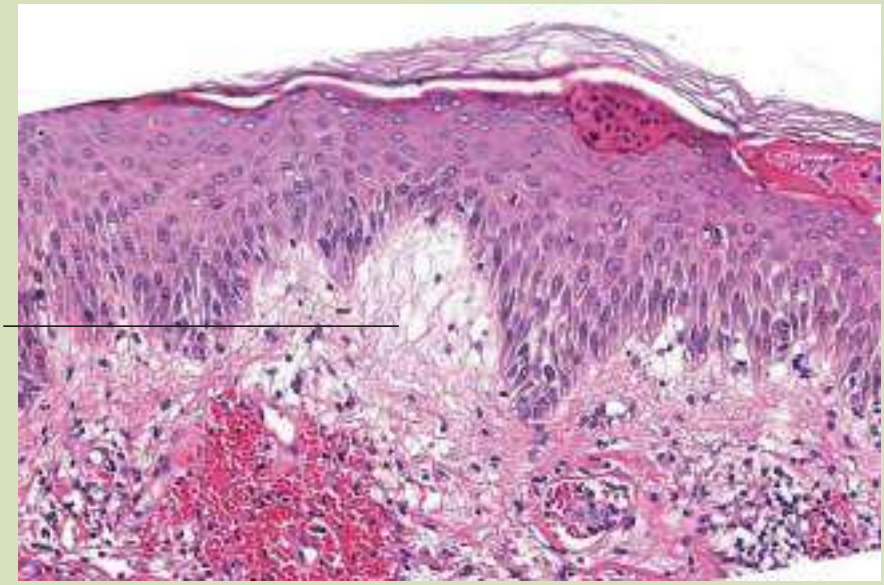
DIFFERENTIAL DIAGNOSIS: Polymorphous light eruption

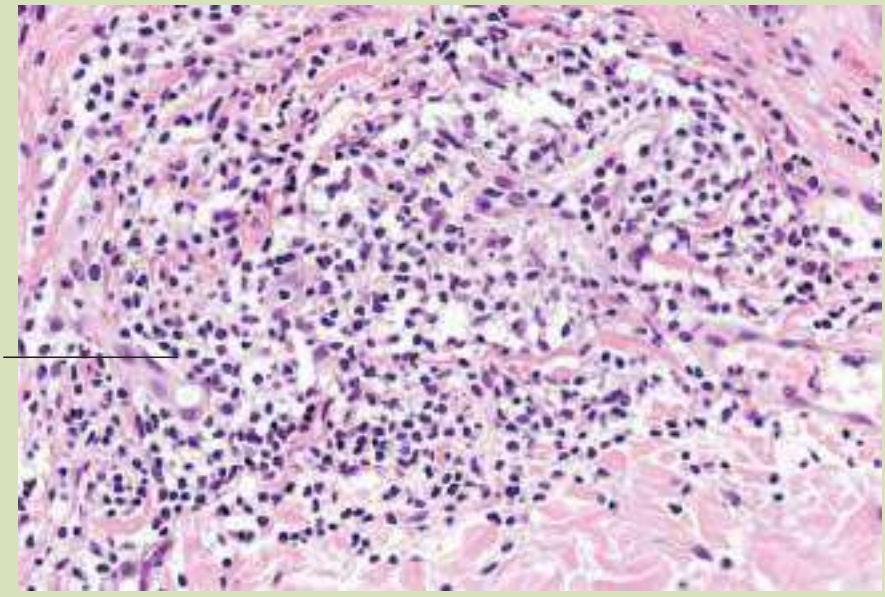


CI: Even though PLE is a monomorphous eruption in the affected individual, there are many different (polymorphous) clinical manifestations between individual patients, ranging from erythematous to papular or papulovesicular lesions, which appear exclusively in sun exposed areas.



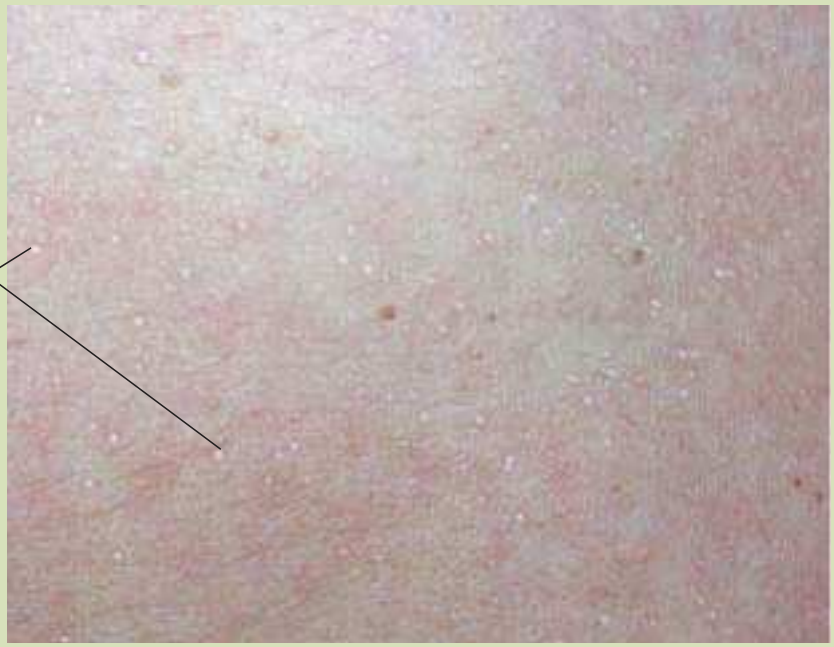
Polymorphous light eruption



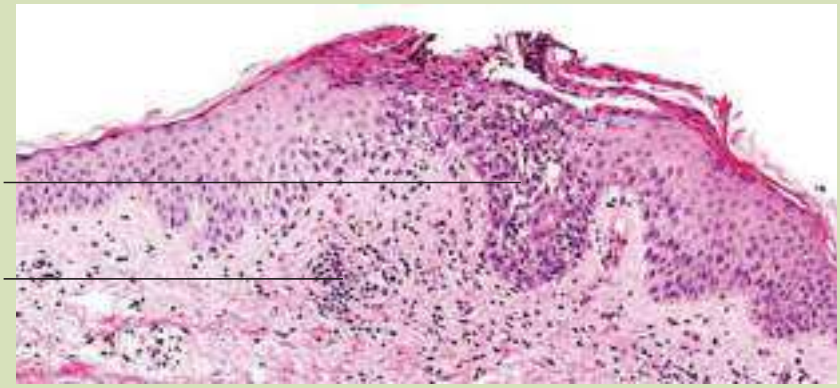


Hi: Epidermal changes with spongiosis and vesicles. Marked papillary dermal edema, blistering of the junctional zone, cuff-like perivascular lymphocytic infiltrates with eosinophils.

DIFFERENTIAL DIAGNOSIS: Miliaria cristallina



Cl: Erythema with crystalline exsudate in the follicular ostia.



Hi: Spongiosis involving the acrosyringium. Miliaria cristallina: subcorneal vesicle, neutrophils. Miliaria rubra: spongiosis of the upper half of the acrosyringium, lymphocytic infiltrate around sweat gland ducts in the papillary dermis.

Other Diagnosis

Acute nummular dermatitis: *Intracorneal inclusions of serum ("wet" stratum corneum), crust formation, intraepidermal vesicles, neutrophils.*

Id-reaction: *Clinical context, admixture of eosinophils, focal epidermal changes.*

Infestation: *Numerous eosinophils, occasionally identifiable organisms, such as scabies or parts of organisms.*

Pemphigus vulgaris, prebullous stage: *Spongiosis, exocytosis of eosinophils (so-called eosinophilic spongiosis); DIF: intercellular intraepidermal deposits of IgG and C3.*

Bullous Pemphigoid: *Prebullous stage: spongiosis, exocytosis of eosinophils; DIF: linear deposits of IgG and C3 at the junctional zone.*

Cutaneous T-cell lymphoma *(spongiotic form): Nuclear atypia and lining-up of lymphocytes at the junctional zone and formation of Pautrier microabscesses.*

Incontinentia pigmenti *(early vesicular stage): Eosinophilic spongiosis, whorls of necrotic keratinocytes.*

Comments

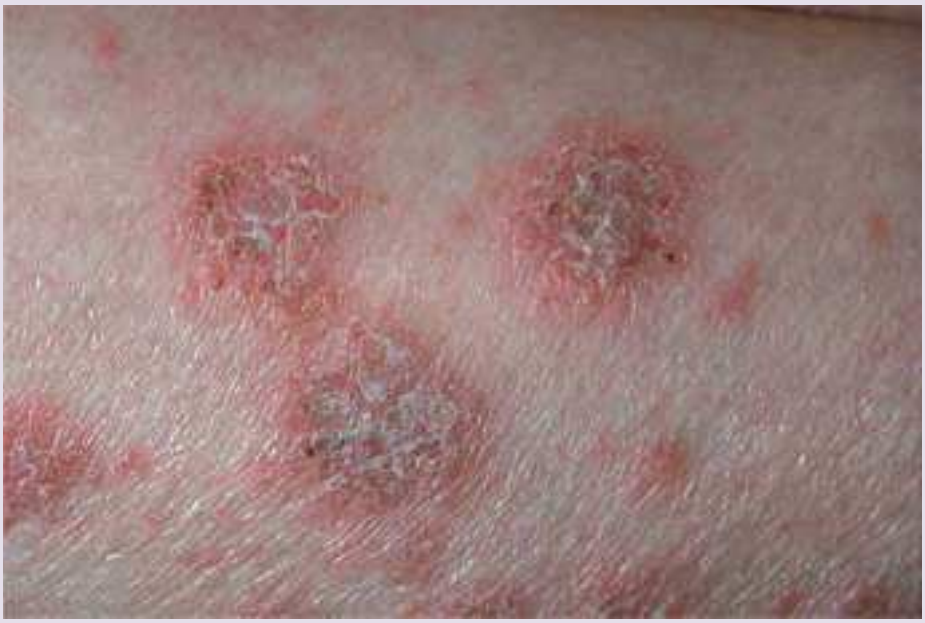
In patients with urticarial and eczematous lesions, which cannot be explained by another cause (contact allergy, atopic dermatitis, eczematous drug eruption), a prebullous phase of pemphigus vulgaris and bullous pemphigoid should be considered as a differential diagnosis. In such patients direct immunofluorescence or immunohistochemical detection of C3d in formalin-fixed biopsies of bullous pemphigoid will be diagnostically very helpful to identify the underlying disease.

References

Aydin, O., B. Engin, O. Oguz, *et al*. (2008). "Non-pustular palmoplantar psoriasis: is histologic differentiation from eczematous dermatitis possible?" *J Cutan Pathol* **35**(2): 169–73.

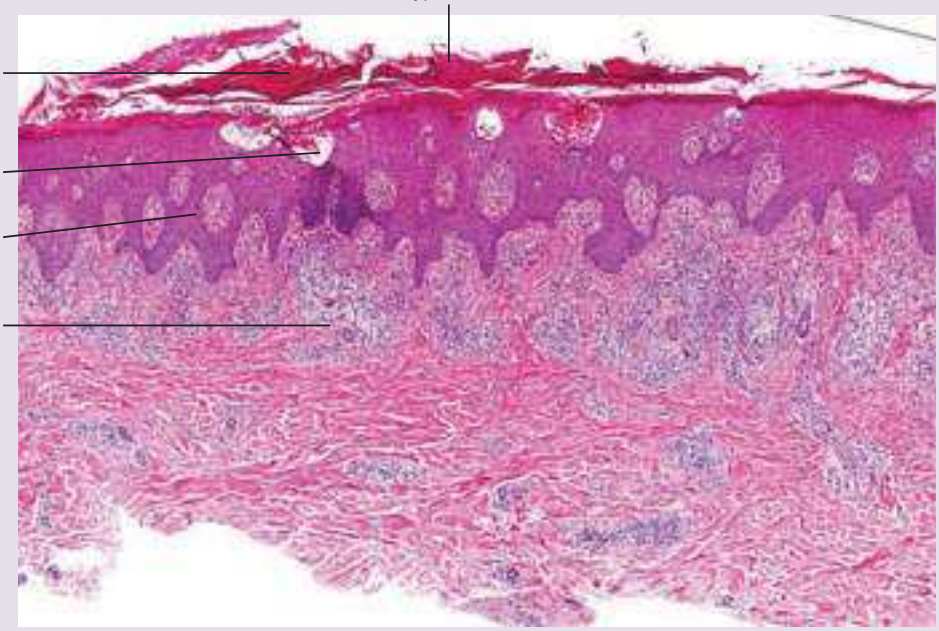
Pfaltz, K., K. Mertz, C. Rose, *et al*. (2010). "C3d immunohistochemistry on formalin-fixed tissue is a valuable tool in the diagnosis of bullous pemphigoid of the skin." *J Cutan Pathol* **37**(6): 654–8.

PROTOTYPE: Nummular dermatitis



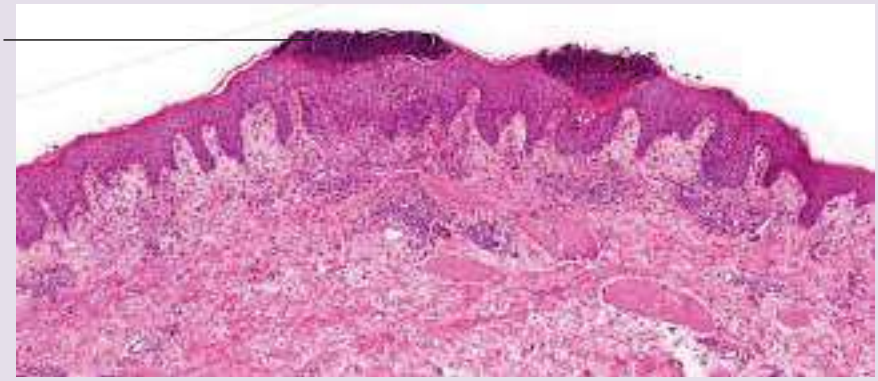
Nummular lesions with erythema and desquamation

Cl: Nummular (coin-shaped), exsudative patches and plaques, often with crusts.

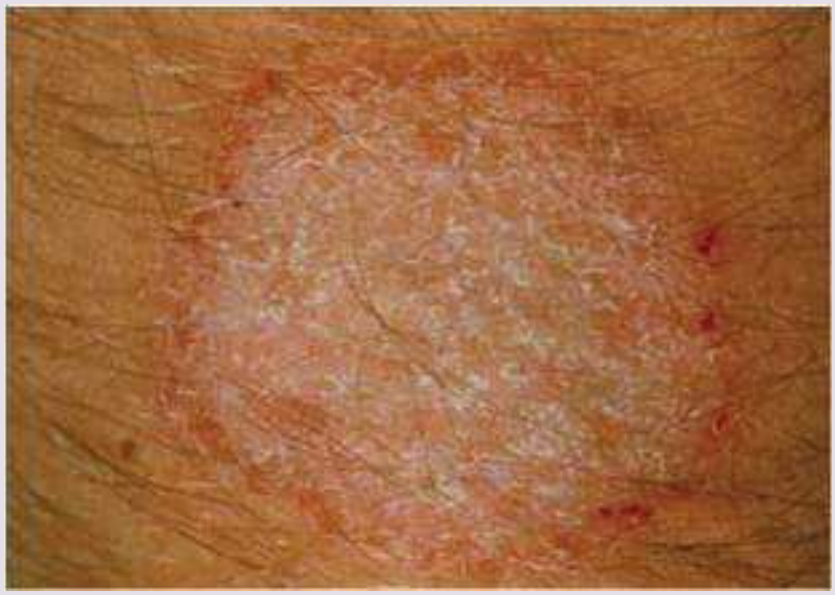


Hi: Intracorneal inclusions of serum ("wet" stratum corneum); scale-crust, acanthosis, hyperparakeratosis, intraepidermal vesicles, diffuse and perivascular infiltrate of lymphocytes and eosinophils and/or neutrophils.

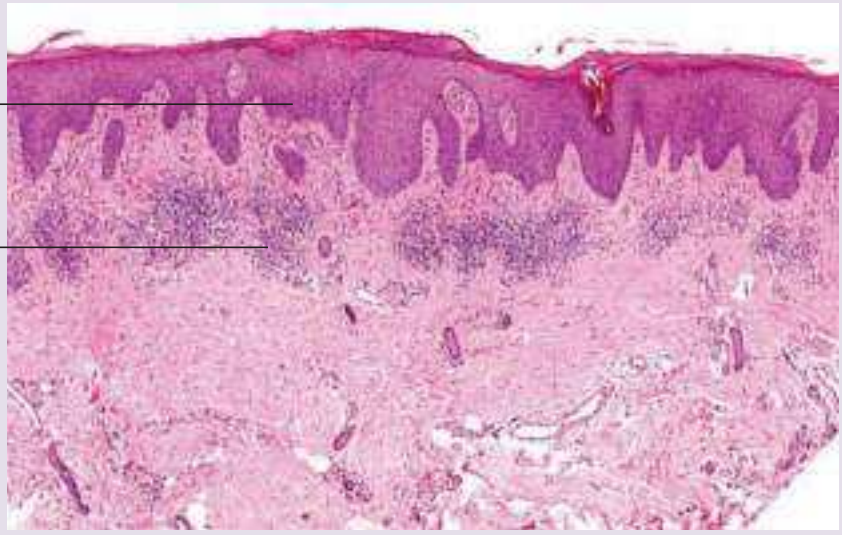
Nummular dermatitis



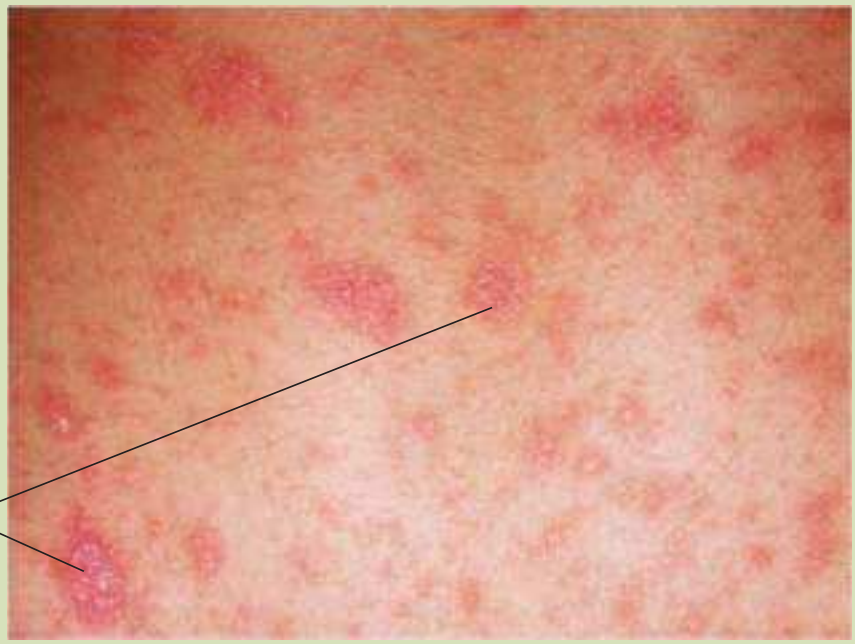
Nummular dermatitis



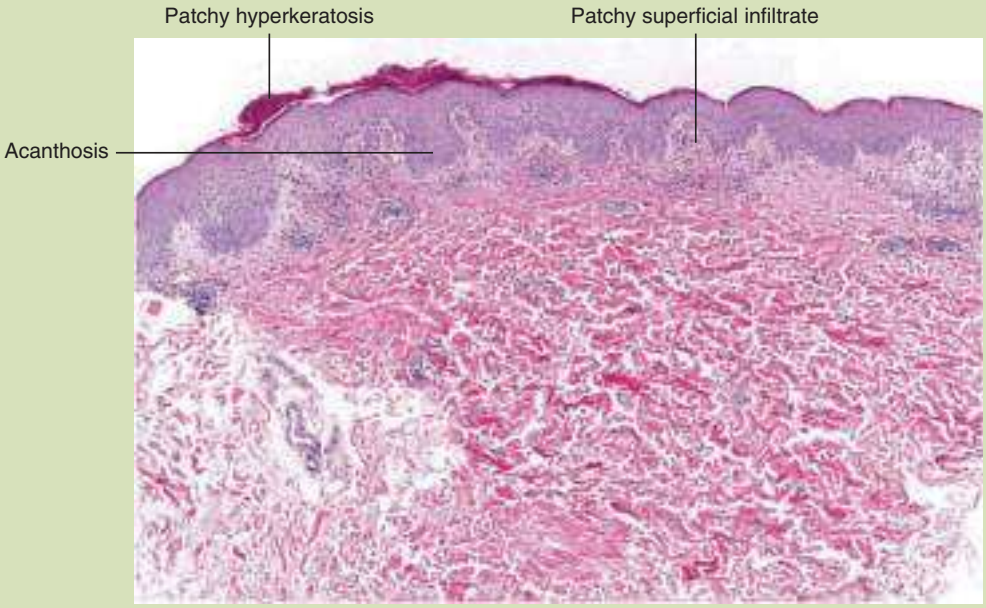
Nummular lesion. Erythema, scaling



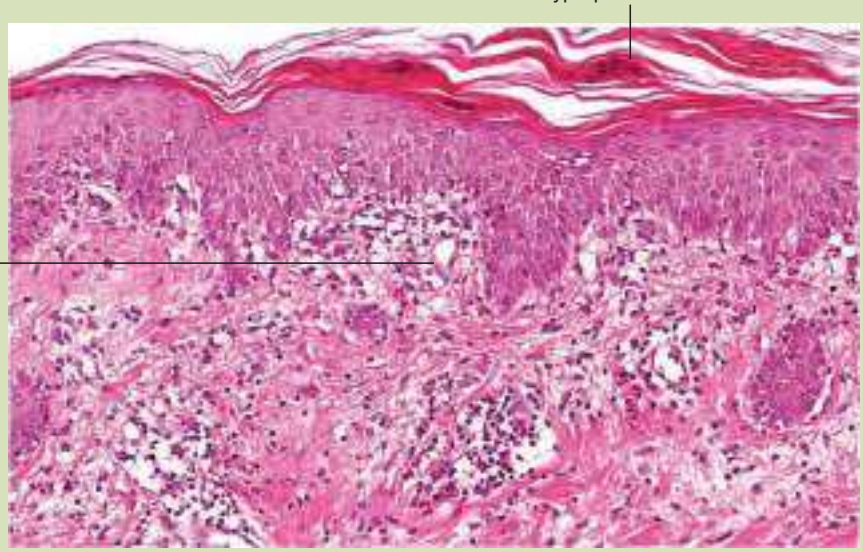
DIFFERENTIAL DIAGNOSIS: Pityriasis rosea

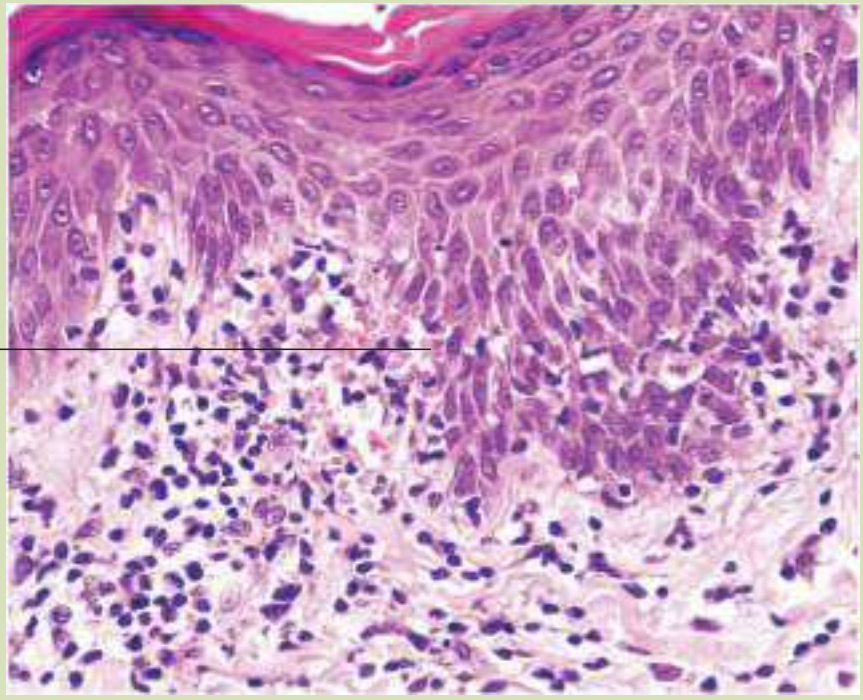


Cl: Disseminated erythematous patches with superficial scaling; process starts with a single oval herald patch.



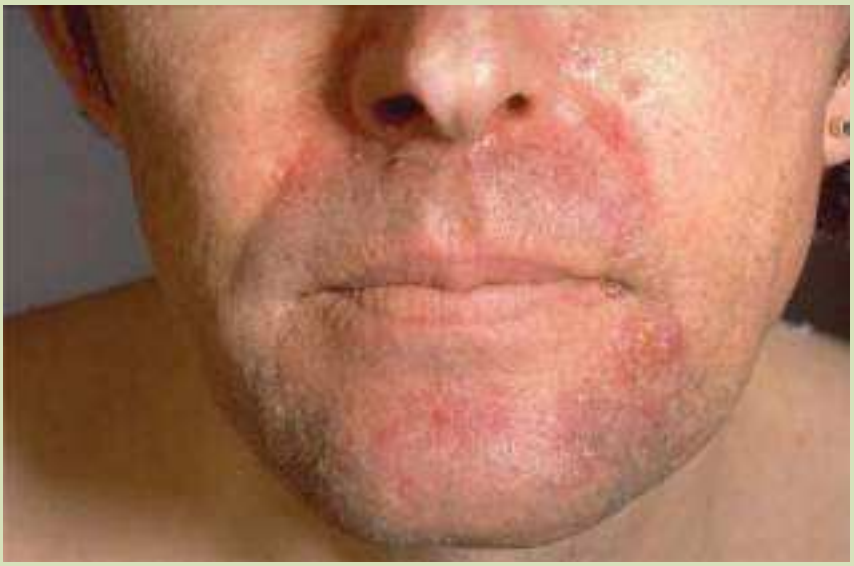
Pityriasis rosea



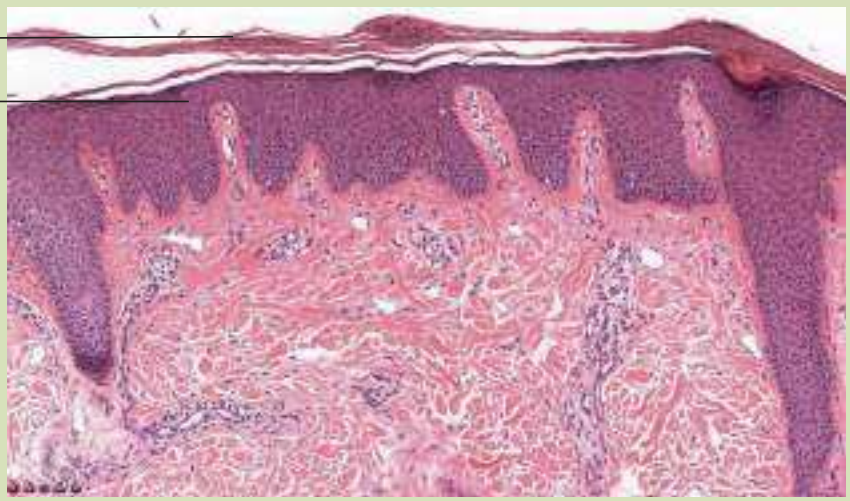


Hi: Focal hyperparakeratosis, slight spongiosis, lymphocytic infiltrate in the upper dermis, intraepidermal erythrocytes.

DIFFERENTIAL DIAGNOSIS: Seborrheic dermatitis

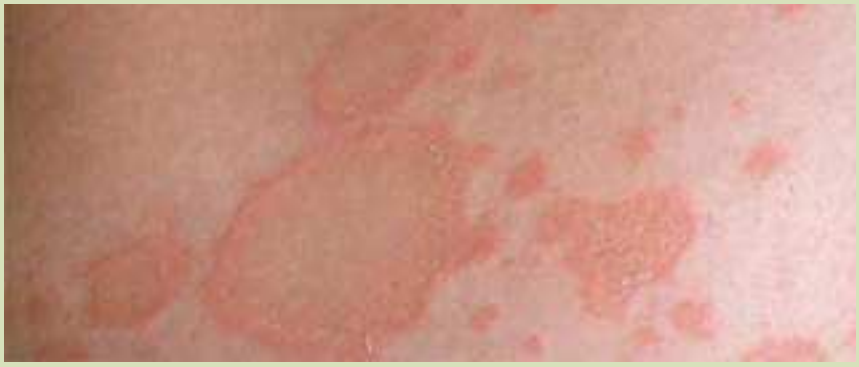


Cl: Erythema and scaling, preferentially in the centro-facial area, breast, scalp.

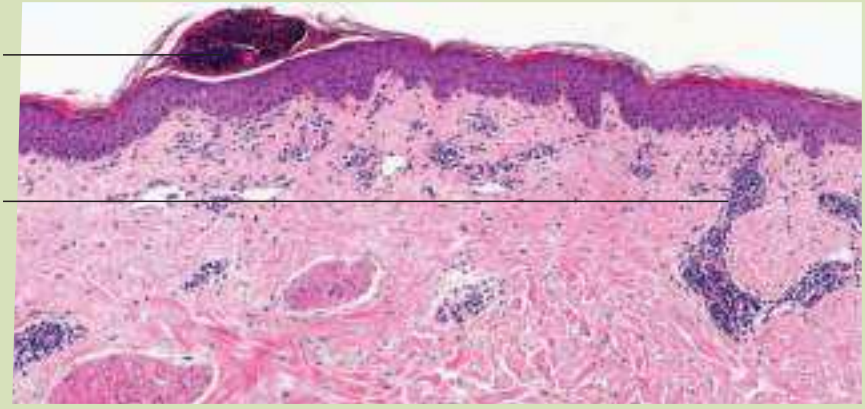


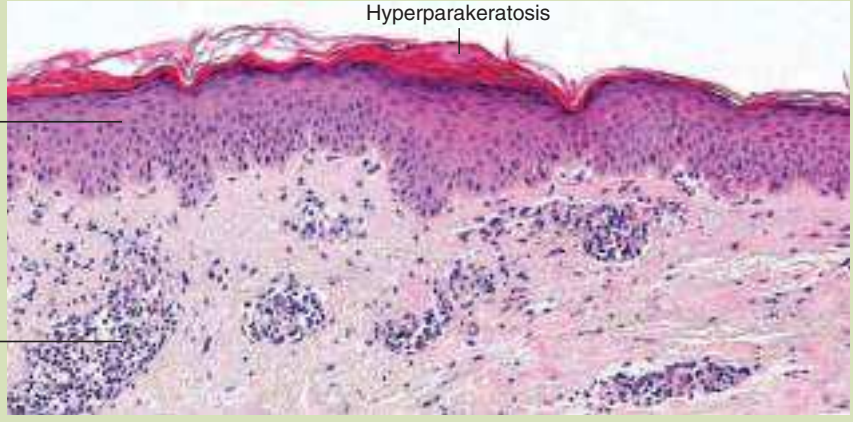
Hi: Psoriasiform acanthosis and hyperparakeratosis overlying hair follicle ostia, exocytosis of neutrophils.

DIFFERENTIAL DIAGNOSIS: Erythema annulare centrifugum



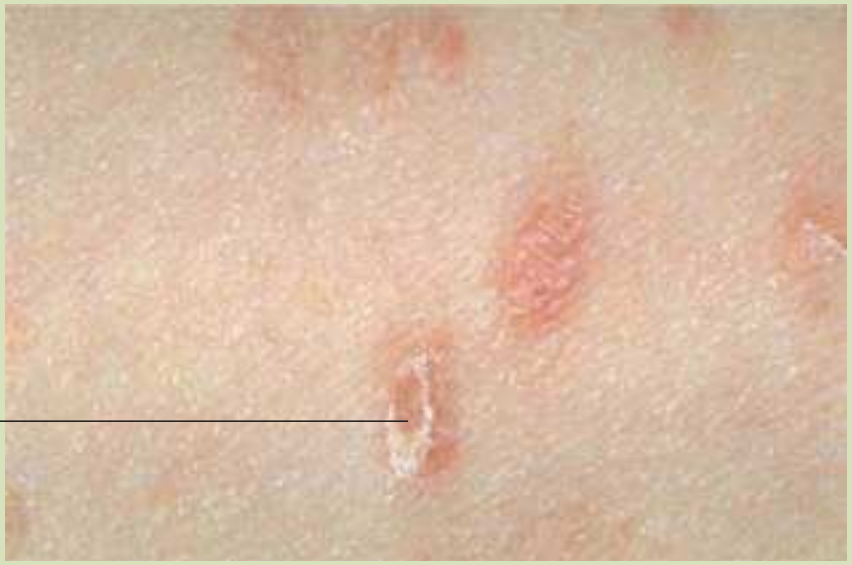
Cl: Centrifugal erythematous rings with slight elevation, scaling and central regression.



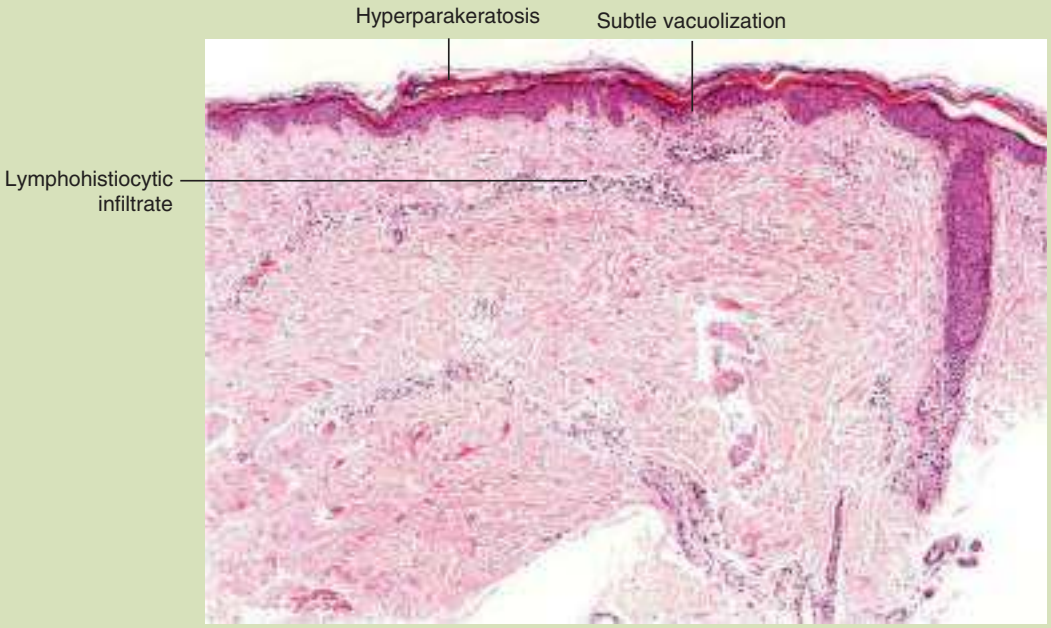


Hi: Spongiosis, parakeratosis, superficial cuff-like perivascular lymphocytic infiltrate; superficial and deep forms, cuff-like lymphocytic perivascular infiltrates in all dermal layers, no or subtle epidermal changes.

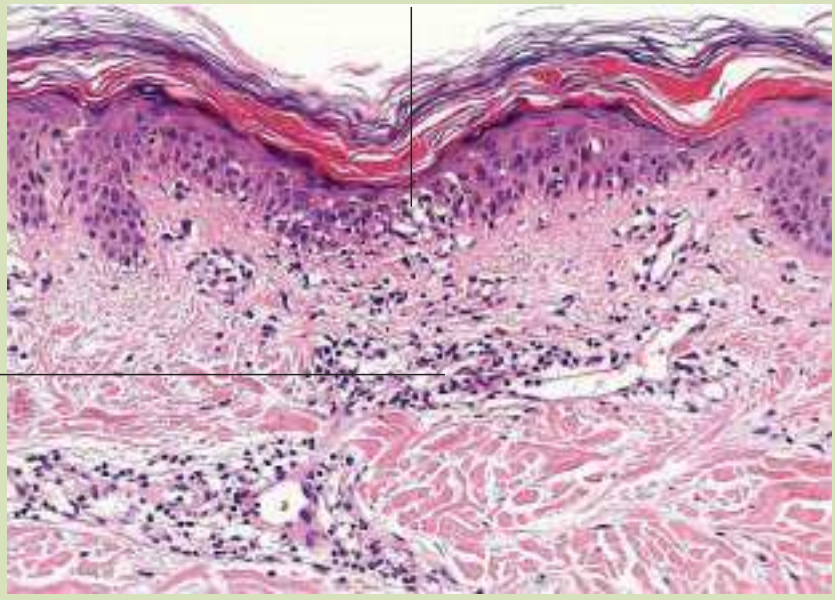
DIFFERENTIAL DIAGNOSIS: Pityriasis lichenoides

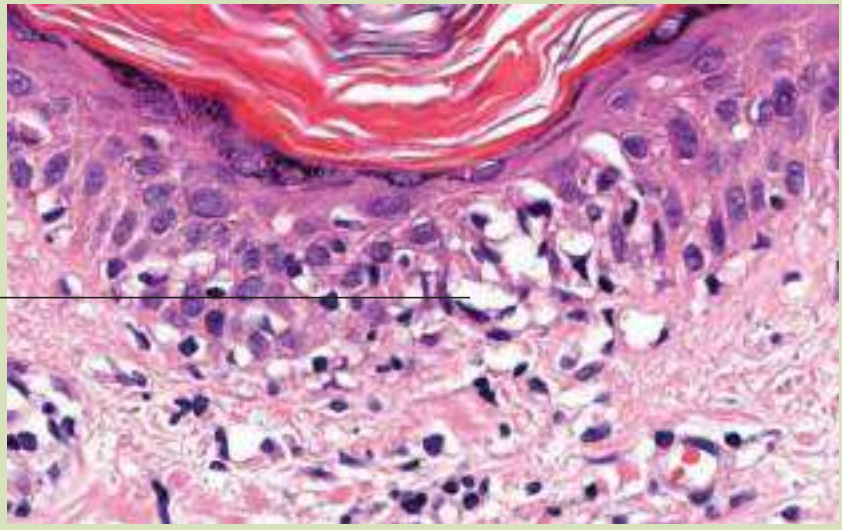


CI: Erythematous small patches or papules with scaling led and subsequent superficial ulceration. Spectrum of diseases includes acute (PLEVA, *see* chapter Necrotic, page 84), subacute and chronic forms.



Pityriasis lichenoides

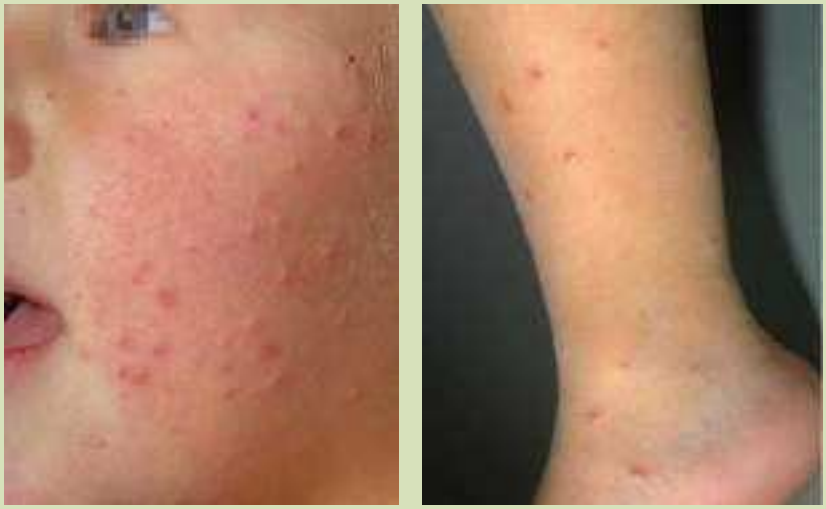




Hi: In the acute form, there is a wedge-shaped, predominantly lymphocytic infiltrate, often band-like at the junction, focal hyperparakeratosis with inclusions of neutrophils, intraepidermal erythrocyte extravasation, focal vacuolization of the dermal–epidermal junction, exocytosis of lymphocytes and single apoptotic keratinocytes. In chronic forms the changes are more subtle, albeit with a subepidermal infiltrate.

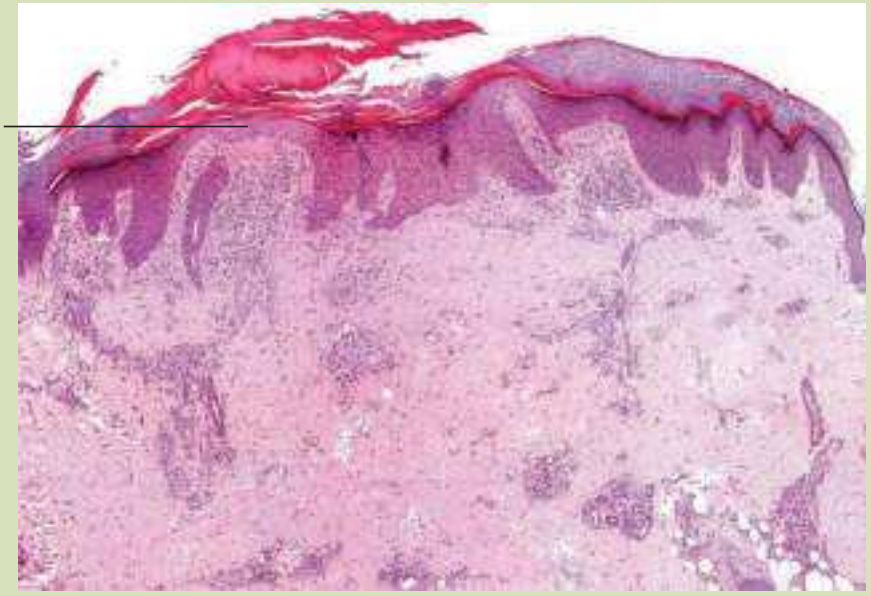
DIFFERENTIAL DIAGNOSIS: Papular acrodermatitis of childhood (Gianotti-Crosti)

Small papules



Cl: Small red papules in the face or on the limbs, fever, systemic involvement possible (hepatitis).

Focal epidermal necrosis



Hi: Early lesions: spongiosis, foci of epidermal necrosis, exocytosis of neutrophils and eosinophils as well as intraepidermal accumulations of Langerhans cells.

Other Diagnosis

***Tinea**: Neutrophils in the horny layer, plasma cells, detection of fungi by PAS- or Grocott stain.*

References

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Clarke, L. E., K. F. Helm, J. Hennessy, *et al*. (2012). "Dermal dendritic cells in psoriasis, nummular dermatitis, and normal-appearing skin." *J Am Acad Dermatol* **66**(1): 98–105.

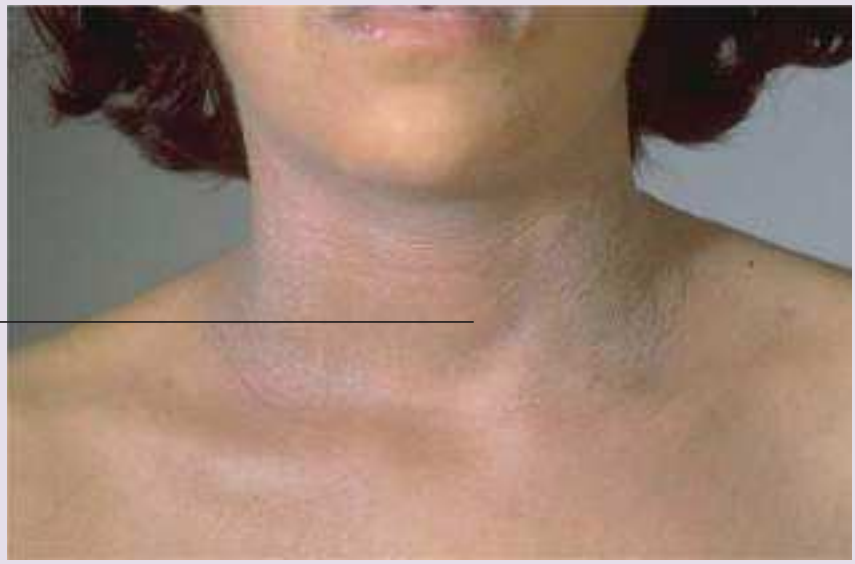
Jarvikallio, A., I. T. Harvima, and A. Naukkannen (2003). "Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema." *Arch Dermatol Res* **295**(1): 2–7.

Maddison, B., A. Parsons, O. Sangueza, *et al*. (2011). "Retrospective study of intraepidermal nerve fiber distribution in biopsies of patients with nummular eczema." *Am J Dermatopathol* **33**(6): 621–3.

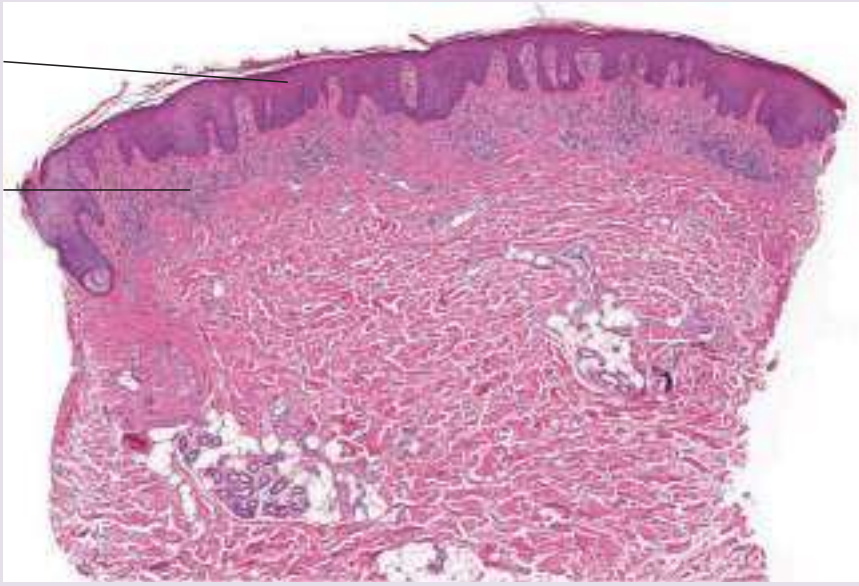
Patel, N., A. Mohammadi, and R. Rhatigan (2012). "A comparative analysis of mast cell quantification in five common dermatoses: lichen simplex chronicus, psoriasis, lichen planus, lupus, and insect bite/allergic contact dermatitis/nummular dermatitis." *ISRN Dermatol* **2012**: 759630.

Stevens, D. M. and A. B. Ackerman (1984). "On the concept of distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger-Garbe). Is it nummular dermatitis?" *Am J Dermatopathol* **6**(4): 387–95.

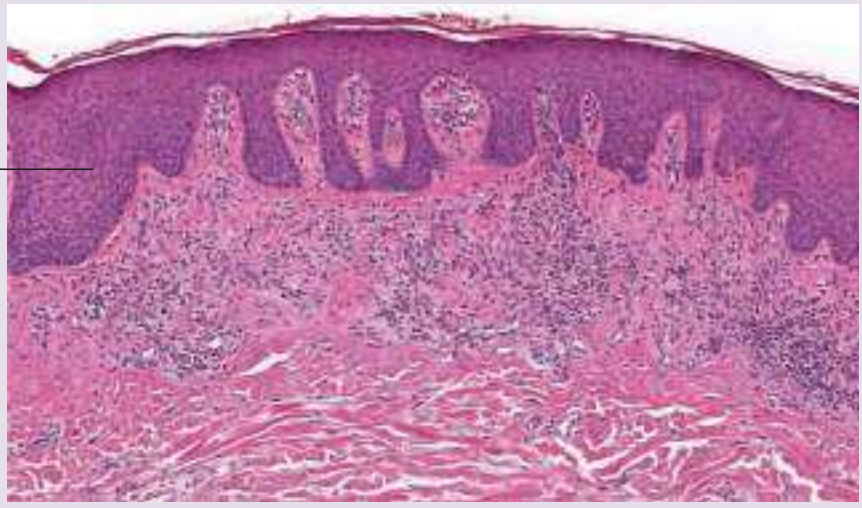
PROTOTYPE: Eczema, chronic: Atopic dermatitis, Lichen simplex chronicus

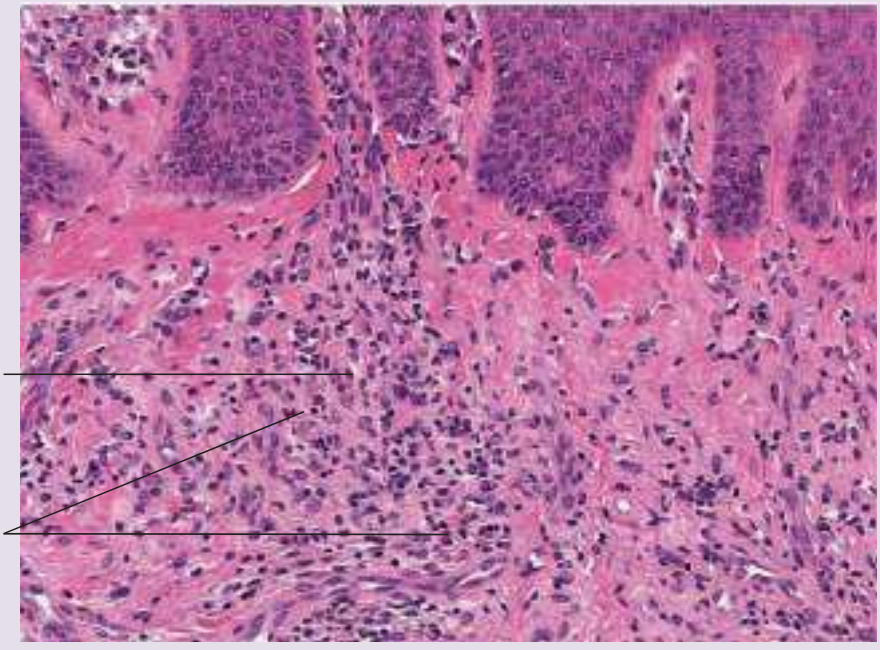


CI: Pruritus, chronic well demarcated plaques, showing lichenification (thickening of skin, prominent skin lines) and hyperpigmentation (variable). Excoriations from scratching.



Atopic dermatitis



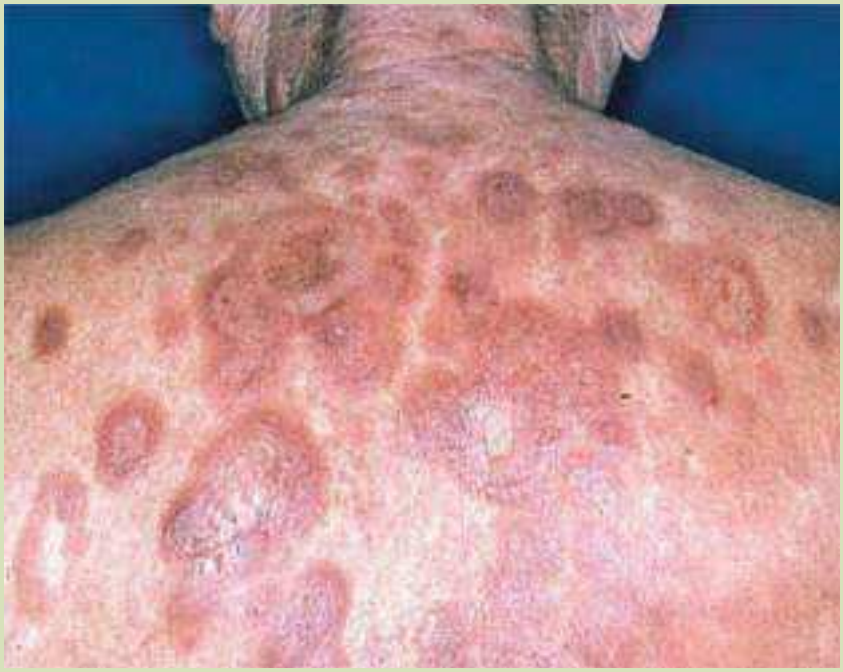


Hi: Acanthosis, hyperparakeratosis, no inclusions of serum, hypergranulosis, reduced or absence of spongiosis, mild perivascular infiltrate of lymphocytes, fibrosis of the papillary dermis. Scattered eosinophils may be present.

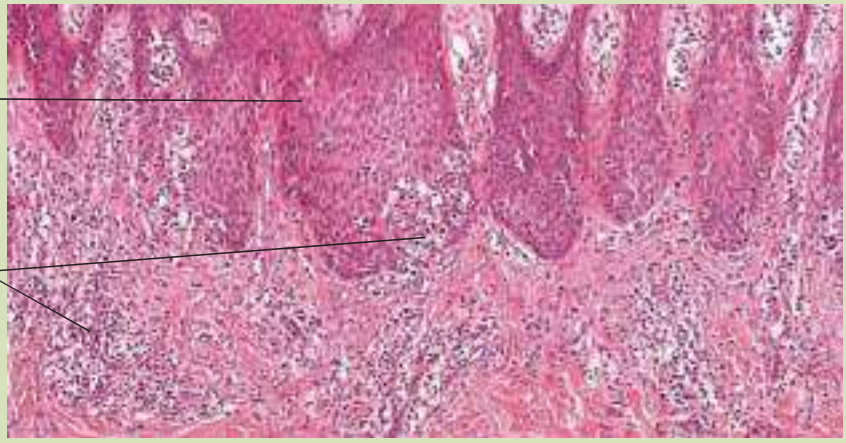
VARIANT: Subacute eczema

Focal and subtle spongiosis.

DIFFERENTIAL DIAGNOSIS: Cutaneous T-cell lymphoma (CTCL)



Cl: Circumscribed patches and plaques with tendency to tumorous transformation.



Hi: Nuclear atypia of lymphocytes which show lining-up at the junctional zone and formation of Pautrier microabscesses.

Other Diagnosis

Psoriasis *(see* Psoriasiform*): Inclusions of neutrophils in hyperparakeratosis, reduced or absent granular layer.*

Prurigo*: Dermal fibrosis (see* Pruriginous, page 42*).*

Parapsoriasis / chronic superficial dermatitis *(see* Psoriasiform, page 54*): Focal parakeratosis and exocytosis of lymphocytes, lack of significant acanthosis or spongiosis, sparse lymphocytic dermal infiltrate.*

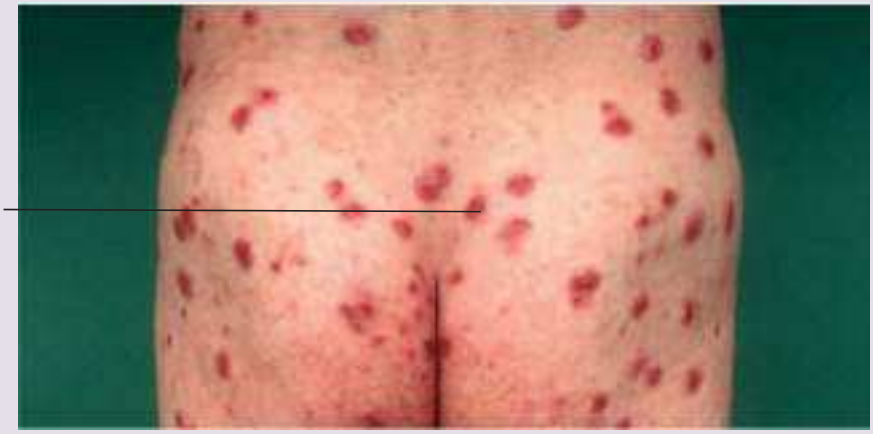
Pityriasis rubra pilaris *(see* Psoriasiform, page 56*): Alternating ortho- and hyperparakeratosis (checkerboard sign), follicular plugging, plump rete ridges, sparse lymphocytic infiltrate.*

References

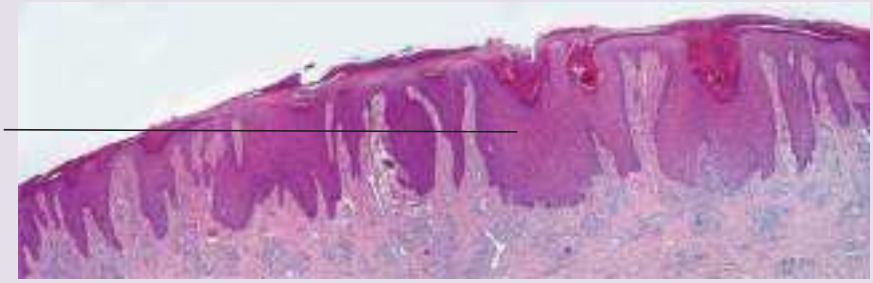
Hurwitz, R. M. and C. DeTrana (1990). "The cutaneous pathology of atopic dermatitis." *Am J Dermatopathol* **12**(6): 544–51.

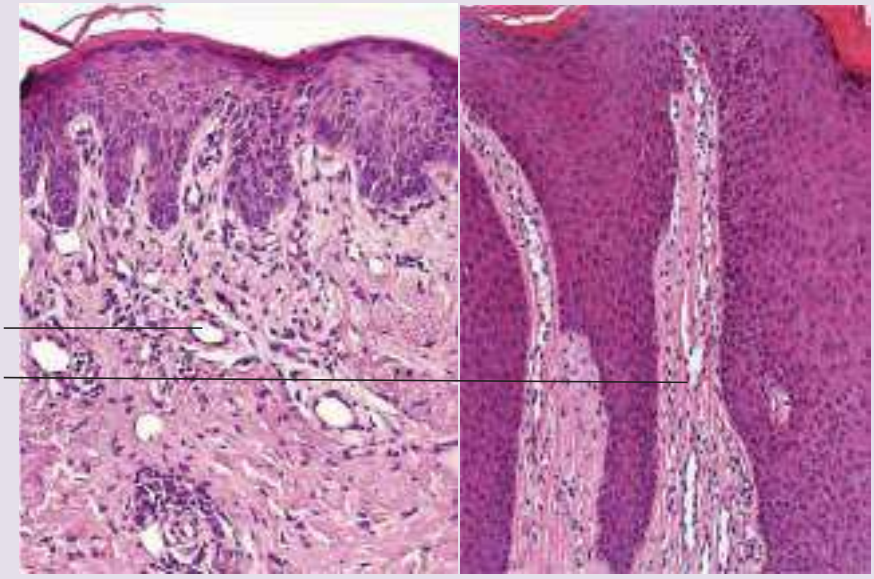
Summey, B. T., S. E. Bowen, and H. B. Allen (2008). "Lichen planus-like atopic dermatitis: expanding the differential diagnosis of spongiotic dermatitis." *J Cutan Pathol* **35**(3): 311–14.

PROTOTYPE: Prurigo simplex subacuta/chronica

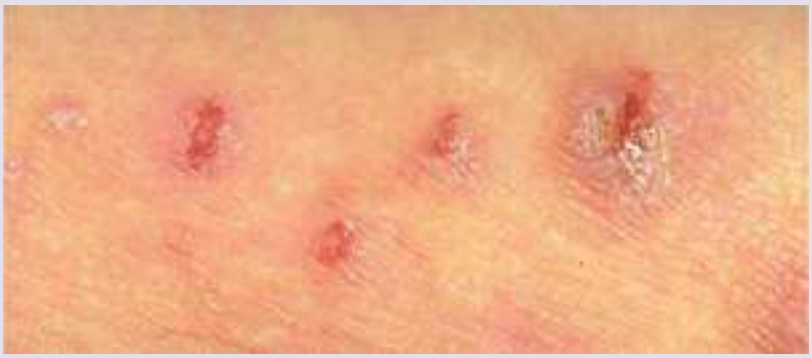


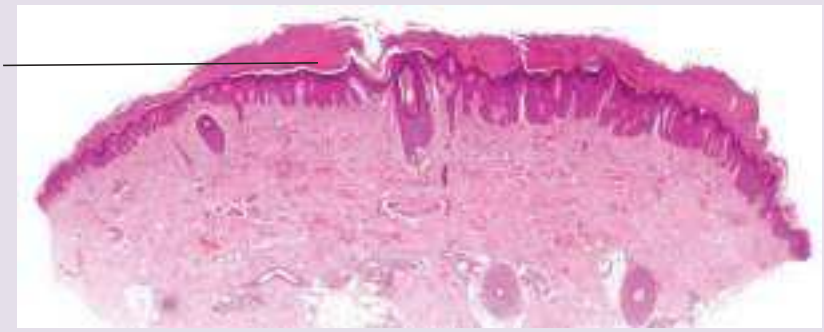
CI: Pruritic papules and nodules, red or hyperpigmented, preferentially on the trunk and extremities. Female>male preponderance.





Prurigo simplex





Hi: Pseudocarcinomatous acanthosis, focal hyperparakeratosis, hypergranulosis, papillomatosis, vertical papillary fibrosis, increased number of fibroblasts and subtle fibrosis, sparse lymphocytic infiltrate. A few eosinophils, plasma cells and ulceration may be present.

Comment

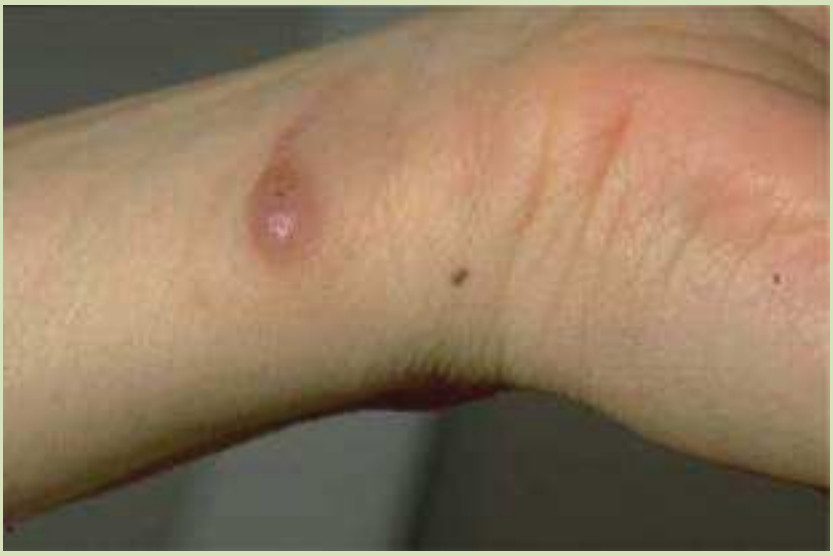
Additional examinations (history, serology) are recommended to search for diabetes mellitus, chronic hepatopathy and nephropathy.

VARIANT: Prurigo nodularis, Hyde-type

Clinical variant showing large nodules.

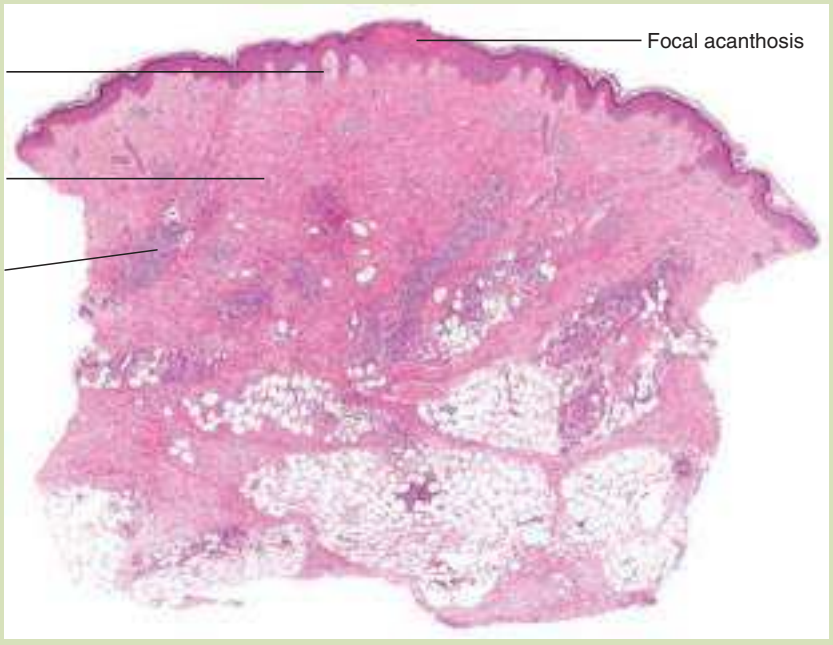
DIFFERENTIAL DIAGNOSIS: Infestation and arthropod bite reaction

Late arthropod bite reaction: fibrotic nodule (histiocytoma)



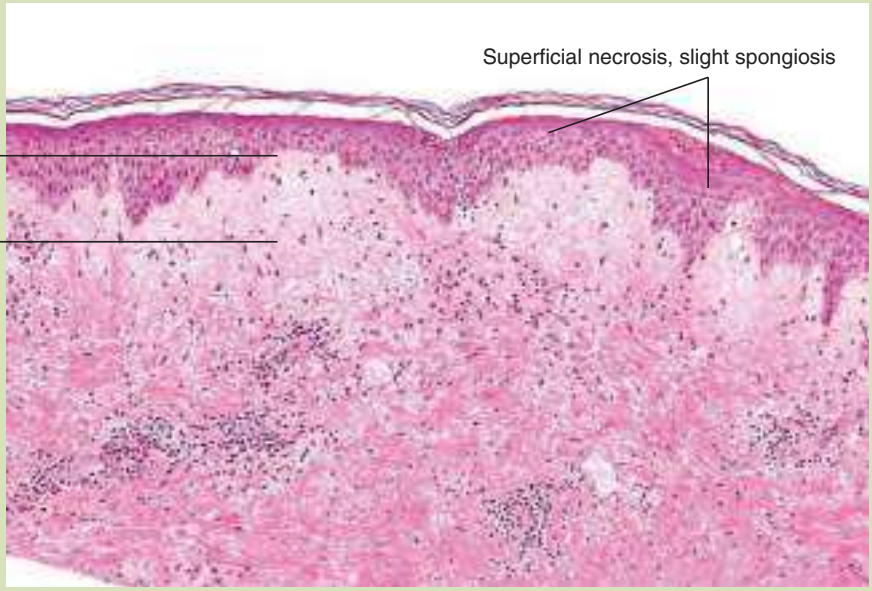
Cl: Firm red nodule, occasionally excoriated.

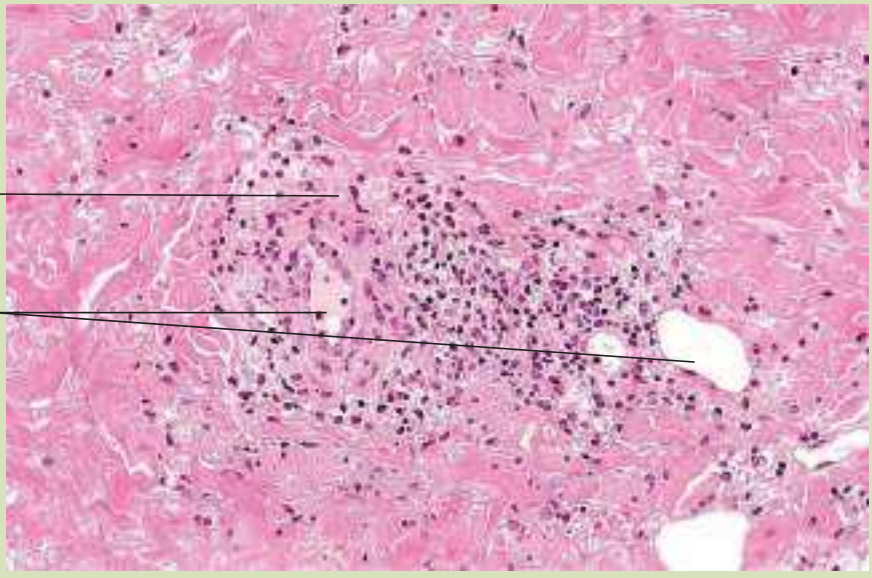
Arthropod bite, early reaction



Hi: Arthropod bite, early reaction.

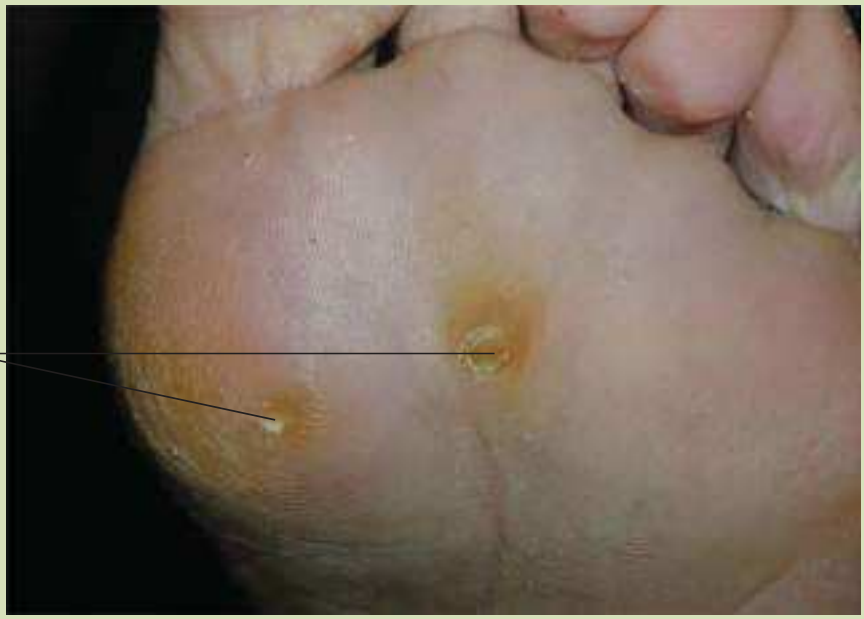
Infestation and arthropod bite reaction



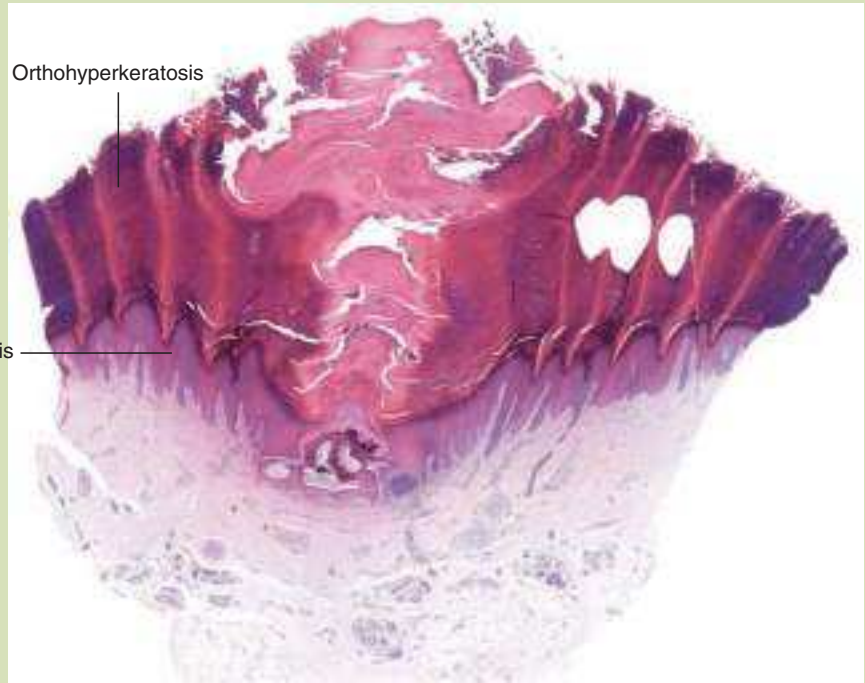


Hi: Focal spongiosis or excoriation, mixed cellular infiltrate (early lesions) with numerous eosinophils. Fibrotic nodule (histiocytoma) is a late stage reaction.

DIFFERENTIAL DIAGNOSIS: Clavus/knuckle pads

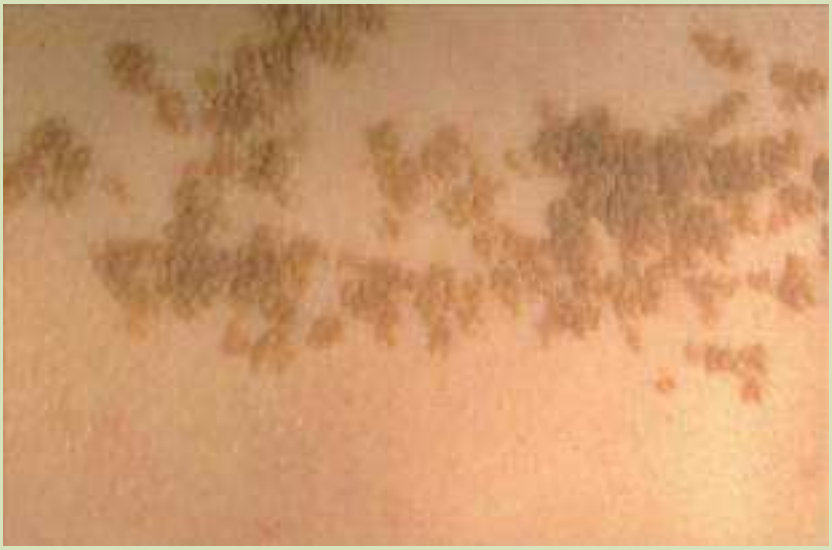


Cl: Circumscribed brownish nodule or hyperkeratotic lesion on the plantar surface (clavus).

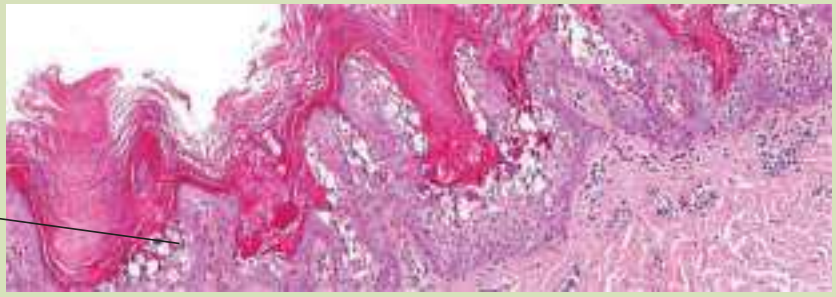


Hi: Acanthosis, fibrosis, lack of inflammatory infiltrate. There may be underlying osteoma cutis in some cases.

DIFFERENTIAL DIAGNOSIS: Epidermal nevus

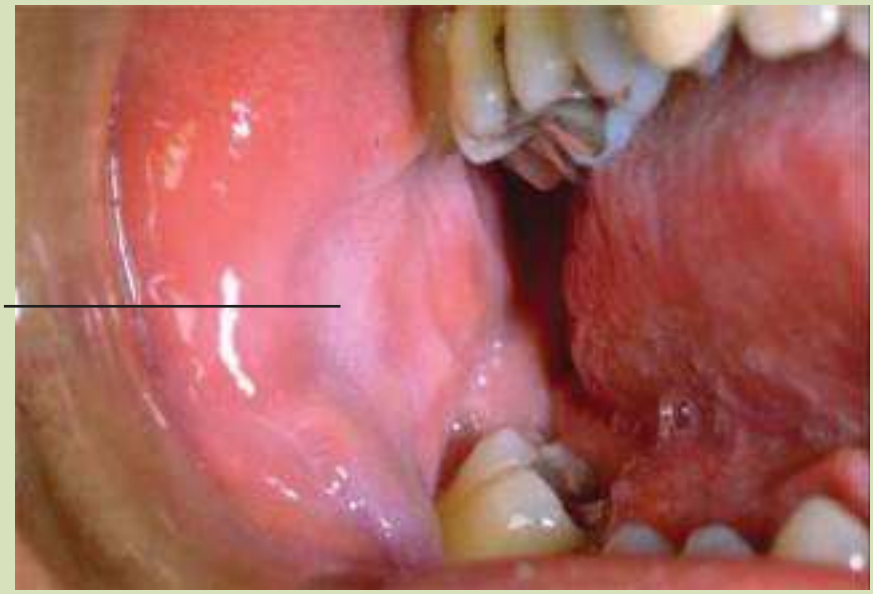


Cl: Brownish hyperkeratosis, sometimes linear or along tension lines.

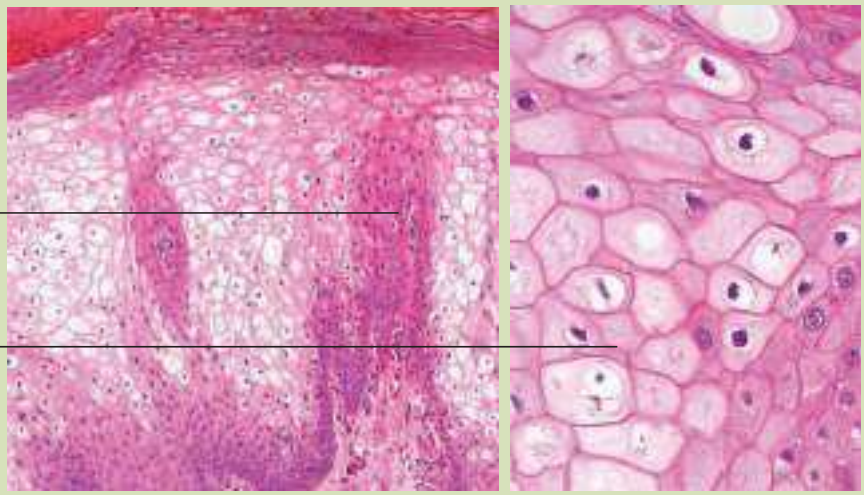


Hi: Circumscibed lesion, orthohyperkeratosis, lack of inflammatory infiltrate.

DIFFERENTIAL DIAGNOSIS: White sponge nevus of the mucous membrane



Cl: White netlike spot on the mucous membrane.



Hi: Epithelial hyperplasia with clear spinous cells, showing perinuclear eosinophilic condensations.

Other Diagnosis

Reactive leukoplakia: *Vacuolated and ballooned epithelial cells in the upper third of the epithelium, focal para- and/or hyperkeratosis, acanthosis.*

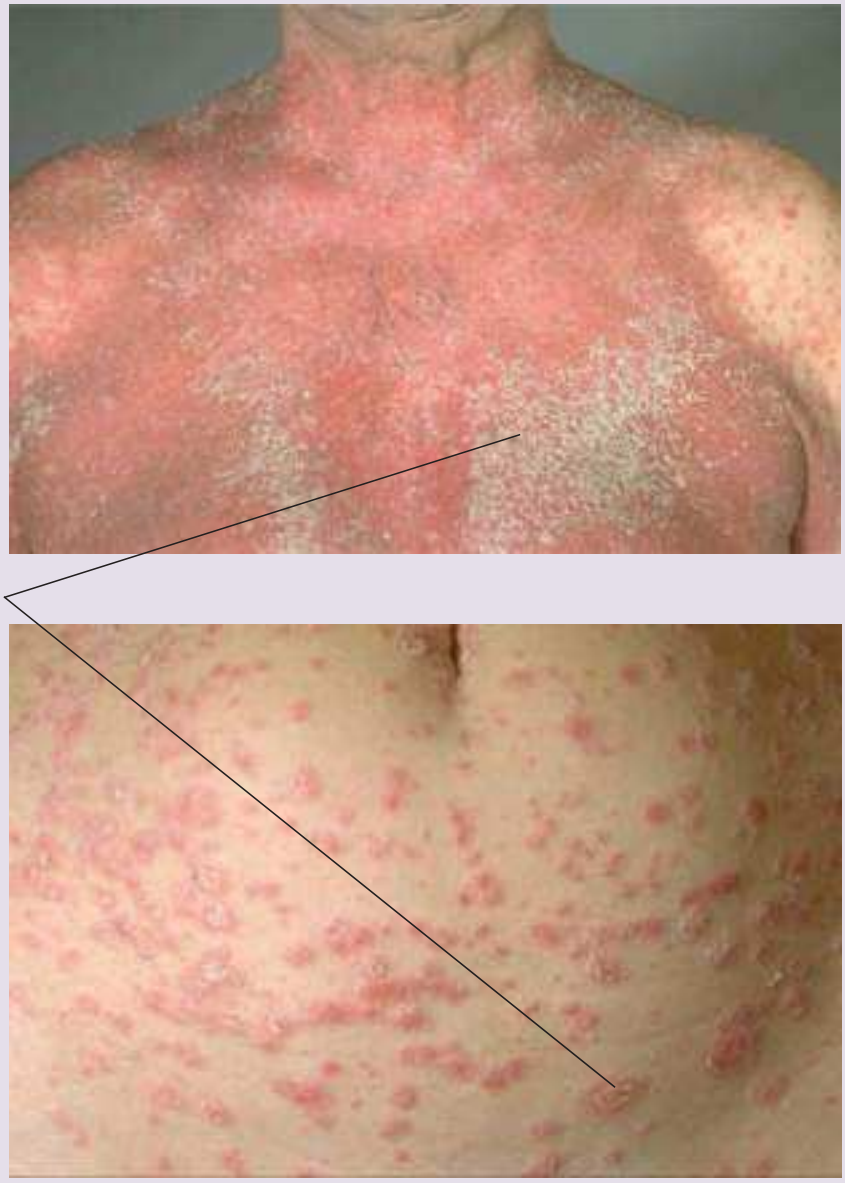
Chronic eczema *(see* Chronic, page 36*)*

References

Lindley, R. P. and C. M. Payne (1989). "Neural hyperplasia is not a diagnostic prerequisite in nodular prurigo. A controlled morphometric microscopic study of 26 biopsy specimens." *J Cutan Pathol* **16**(1): 14–18.

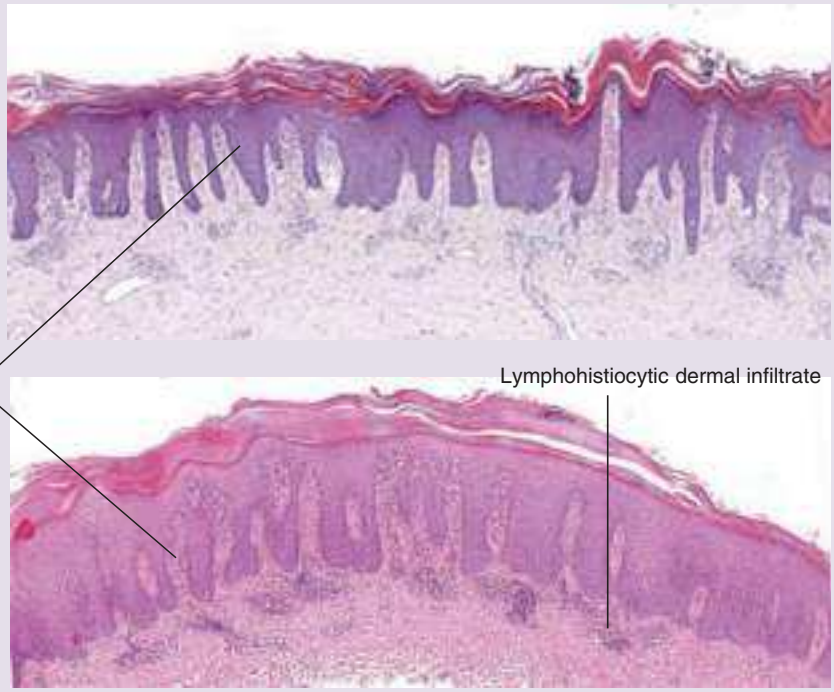
Weigelt, N., D. Metze, and S. Ständer (2010). "Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients." *J Cutan Pathol* **37**(5): 578–86.

PROTOTYPE: Psoriasis vulgaris

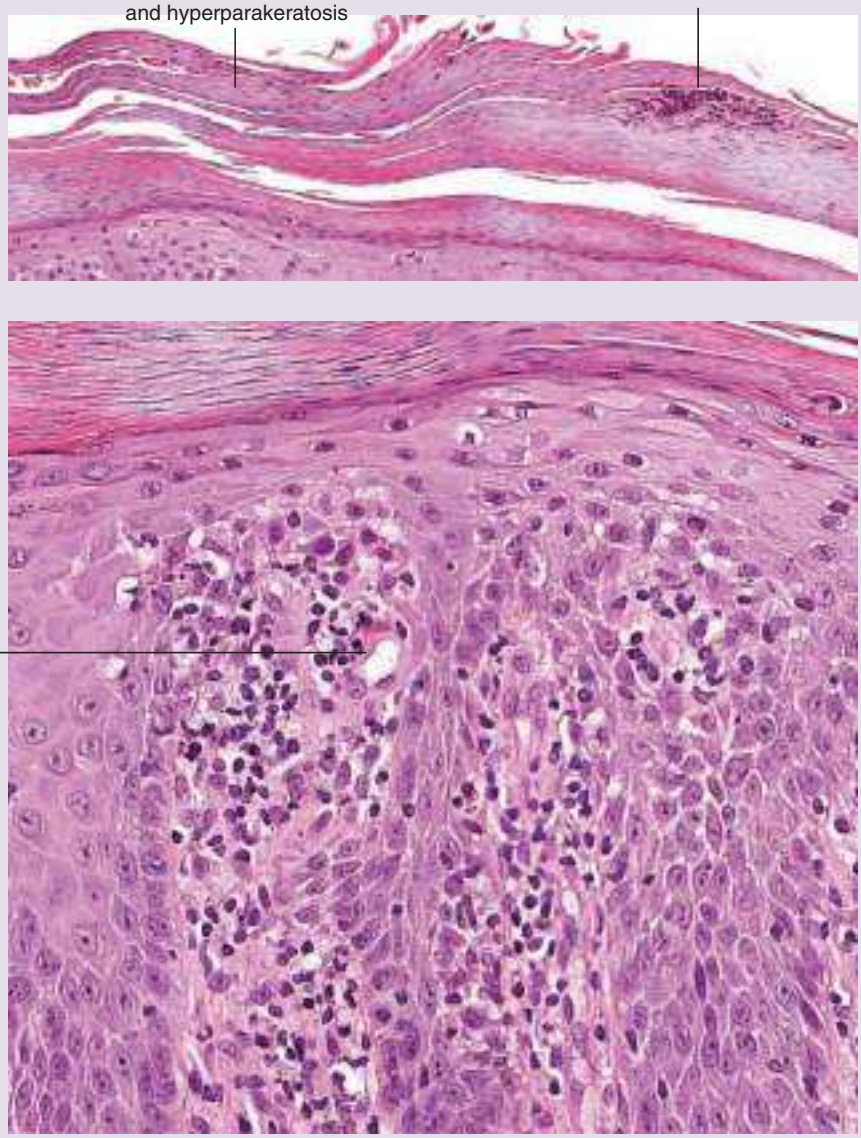


CI: Sharply demarcated scaling and erythematous papules and plaques.

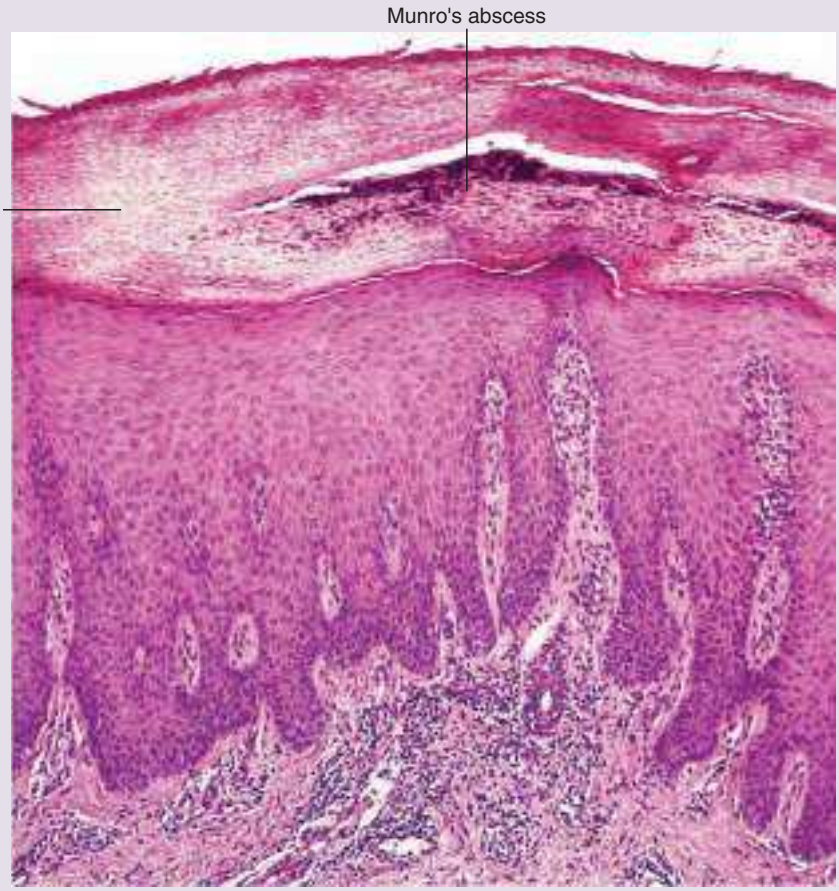
Psoriasis vulgaris



Psoriasis vulgaris



Psoriasis vulgaris

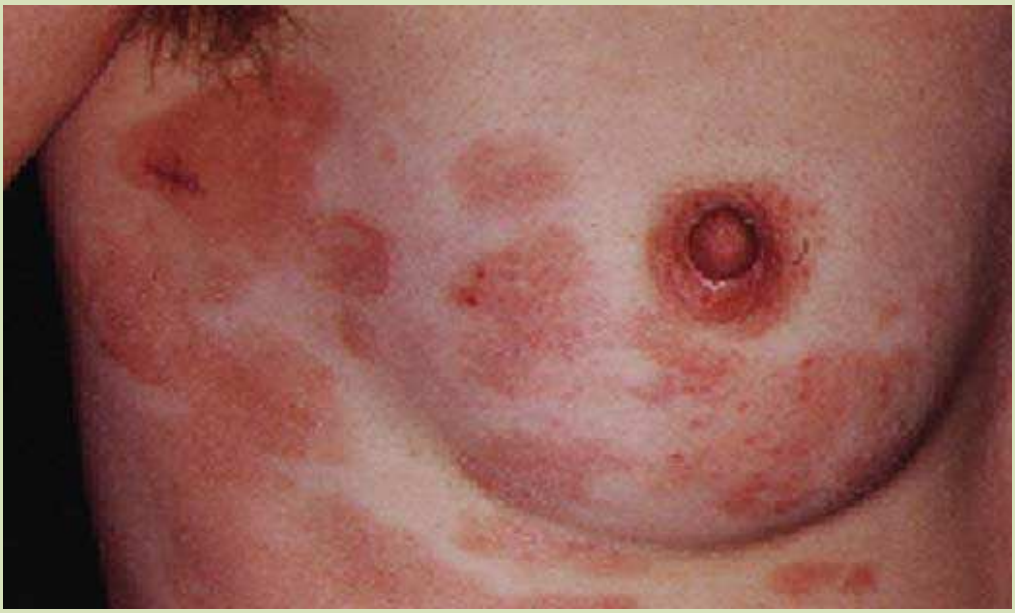


Hi: Hyperortho- and hyperparakeratosis. Acanthosis and papillomatosis. Neutrophilic micro-abscesses in the cornified layer (Munro's micro-abscesses) and in the upper spinous layer (Kogoj's pustules). Focal loss of stratum granulosum. Tortuous elongation and dilatation of papillary capillaries. Thinning of the epidermis above tips of the papillae. Lymphocytic infiltrate in the papillary dermis ("firering" (Grüneberg) or "squirting" (Pinkus) papillae).

VARIANTS

Psoriasis pustulosa generalisata *(von Zumbusch)* *(see* Pustular, page 70*)*
Psoriasis pustulosa palmo-plantaris *(Königsbeck-Barber)* *(see* Pustular, page 70*)*

DIFFERENTIAL DIAGNOSIS: Parapsoriasis, large plaque (mycosis fungoides early stage)



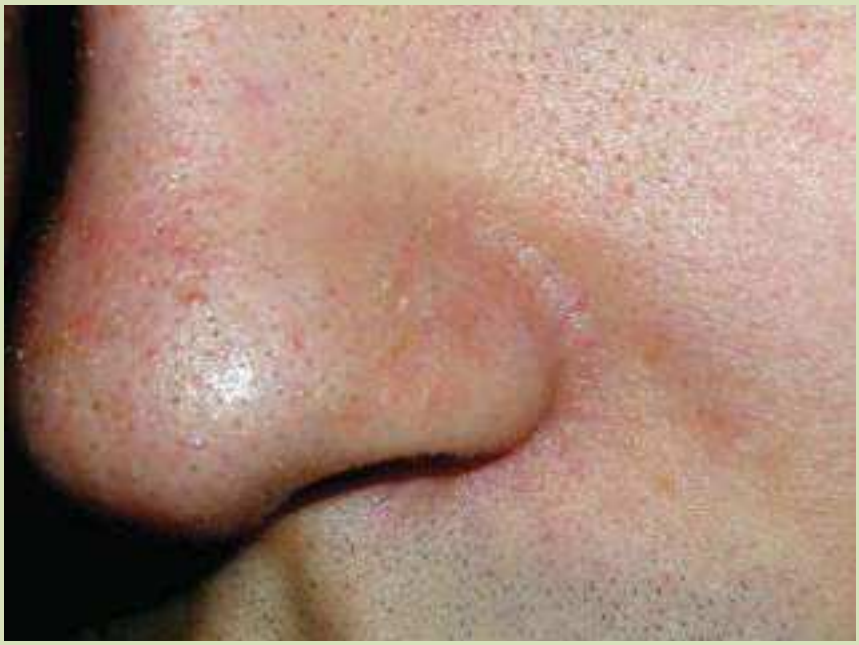
Cl: Confluent, erythematous patches, sometimes slightly scaling.

Hi: Epidermis normal or slightly acanthotic, superficial lymphocytic infiltrate with epidermotropism, preferentially along on the tip of the rete ridges. Edema and slight fibrosis may be present in the papillary dermis.

Comment

Psoriasis and parapsoriasis (PP) are semantic differential diagnoses. Large plaque parapsoriasis is widely considered as early stage of mycosis fungoides and clinically may simulate psoriasis; histologically, however, PP presents completely differently from psoriasis (see Lichenoid, page 120).

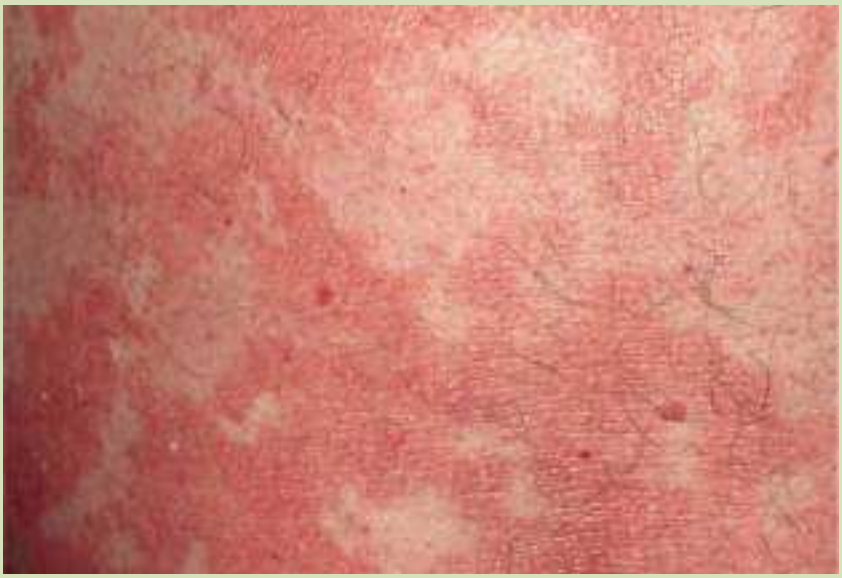
DIFFERENTIAL DIAGNOSIS: Seborrheic dermatitis, subacute dermatitis



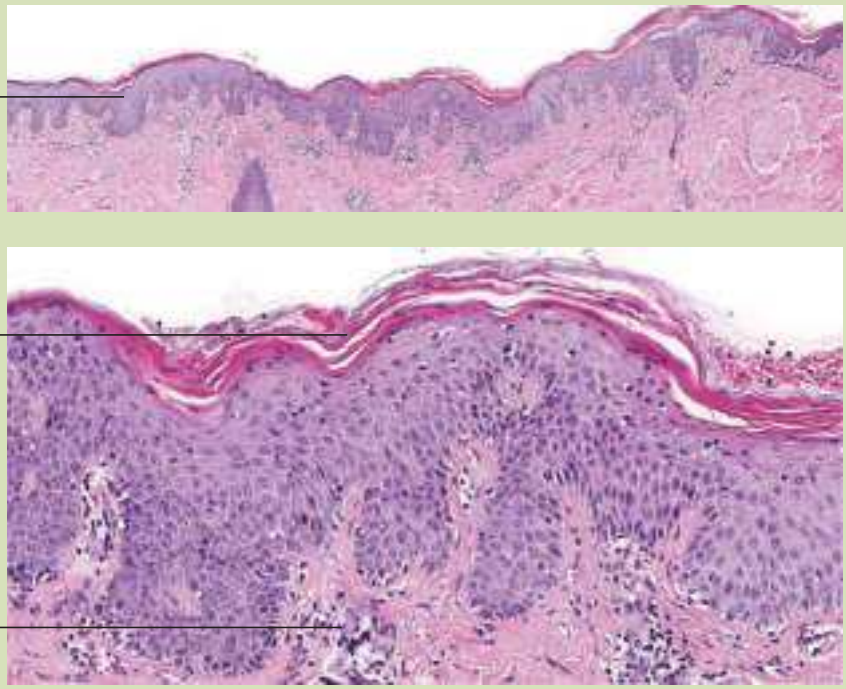
Cl: Erythema and scaling, preferentially in central face and scalp.

Hi: Acanthosis, papillomatosis and parahyperkeratosis, particularly around hair follicle ostia, exocytosis of neutrophils.

DIFFERENTIAL DIAGNOSIS: Pityriasis rubra pilaris



Cl: Psoriasiform erythema, follicularly bound with uninvolved skin in between (nappes claires).



Hi: Plump acanthosis and papillomatosis, horizontally and vertically alternating ortho- and hyperparakeratosis (checkerboard sign), no or rather sparse lymphocytic infiltrate.

Other Diagnosis

***Nummular dermatitis**: Spongiosis, hyperparakeratosis (see* Subacute, page 25*).*

***Chronic atopic dermatitis; lichen simplex chronicus** (see* Chronic, page 36*): No inclusion of neutrophils, broadened granular layer, broad acanthosis.*

***Fungus infection**: Little inflammation, demonstration of hyphae and spores in the stratum corneum by PAS-stain (see* Pustular, page 75*).*

***Epidermal nevus**: Verruciform profile, lack of inflammation, sometimes epidermolytic changes of keratinocytes (see* Koilocytic, page 102*).*

***Reiter's syndrome:** Involvement of genital and oral mucosa. Histology identical to psoriasis.*

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Braun-Falco, O. and G. Burg (1970). "[Histochemistry of capillaries in psoriasis vulgaris]." *Arch Klin Exp Dermatol* **236**(2): 173–89.

Braun-Falco, O. and G. Burg (1970). "[Inflammatory infiltrate in psoriasis vulgaris. A cytochemical study]." *Arch Klin Exp Dermatol* **236**(3): 297–314.

Kouskoukis, C. E., R. K. Scher, and A. B. Ackerman (1983). "What histologic finding distinguishes onychomycosis and psoriasis?" *Am J Dermatopathol* **5**(5): 501–3.

Magro, C. M. and A. N. Crowson (1997). "The clinical and histomorphological features of pityriasis rubra pilaris. A comparative analysis with psoriasis." J Cutan Pathol **24**(7): 416–24.

Mordovtsev, V. N. and V. I. Albanova (1989). "Morphology of skin microvasculature in psoriasis." *Am J Dermatopathol* **11**(1): 33–42.

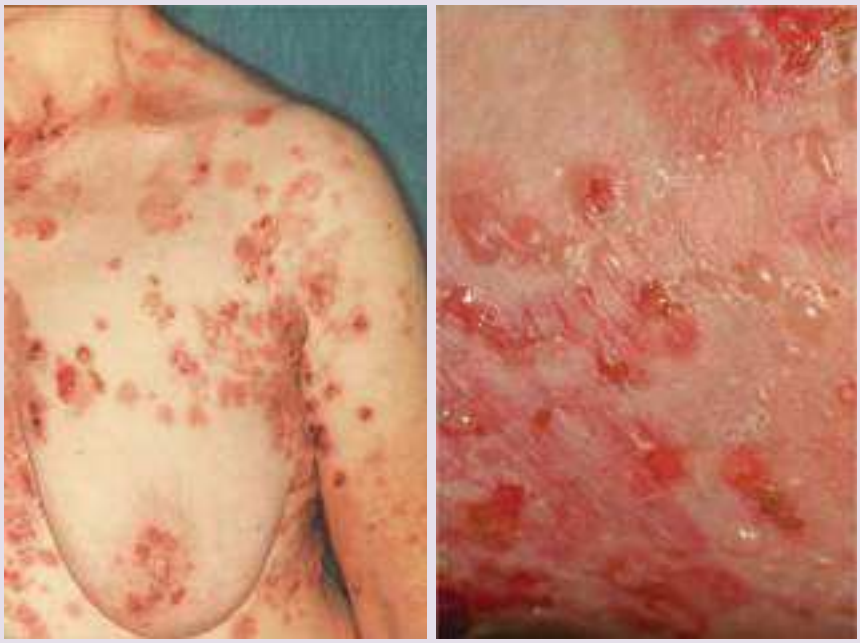
Pinkus, H. and A. H. Mehregan (1980). "On the evolution, maturation, and regression of lesions of psoriasis." *Am J Dermatopathol* **2**(3): 287–8.

Ragaz, A. and A. B. Ackerman (1979). "Evolution, maturation, and regression of lesions of psoriasis. New observations and correlation of clinical and histologic findings." *Am J Dermatopathol* **1**(3): 199–214.

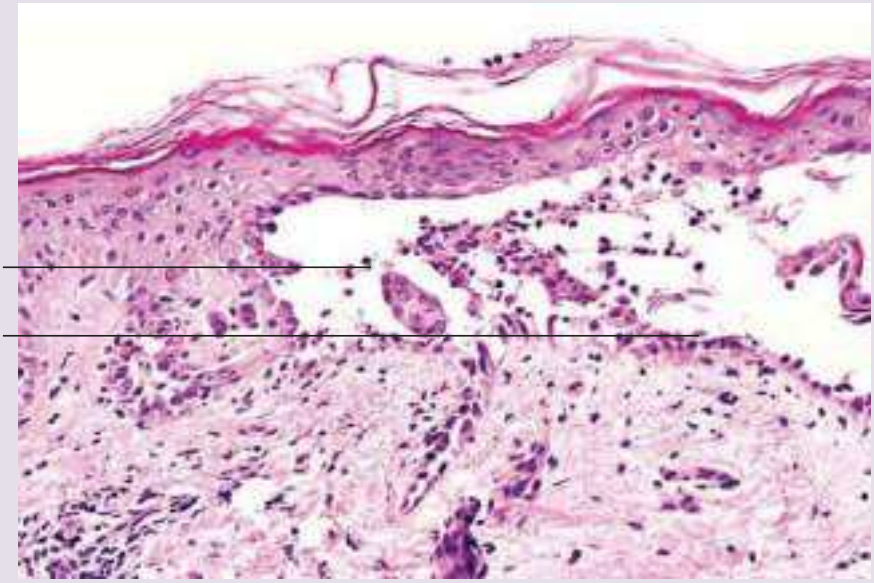
Sweet, W. L. and B. R. Smoller (1997). "Differential proliferation of endothelial cells and keratinocytes in psoriasis and spongiotic dermatitis." *J Cutan Pathol* **24**(6): 356–63.

PROTOTYPE: Pemphigus vulgaris

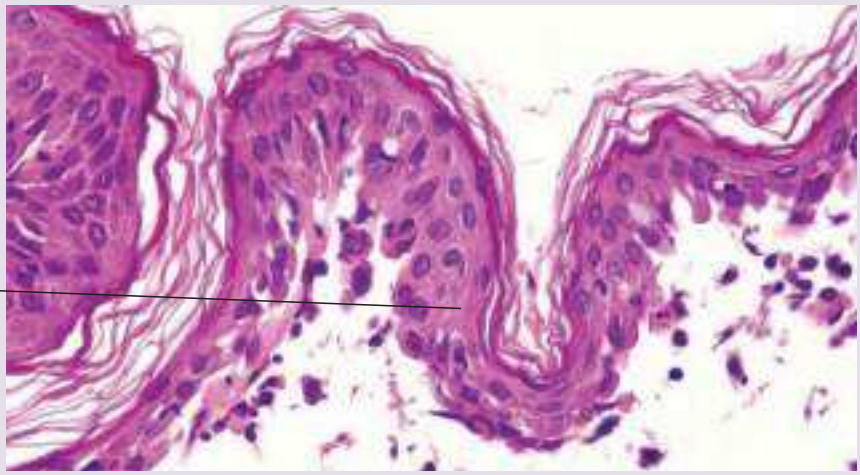
Bullae and erosions

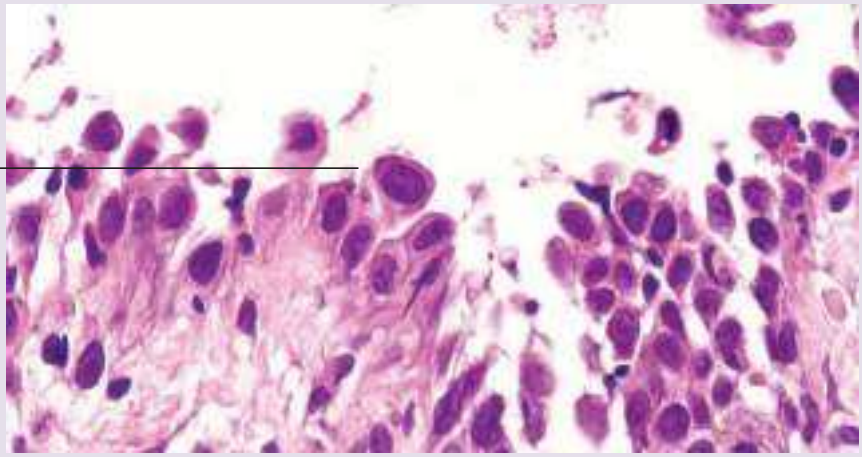


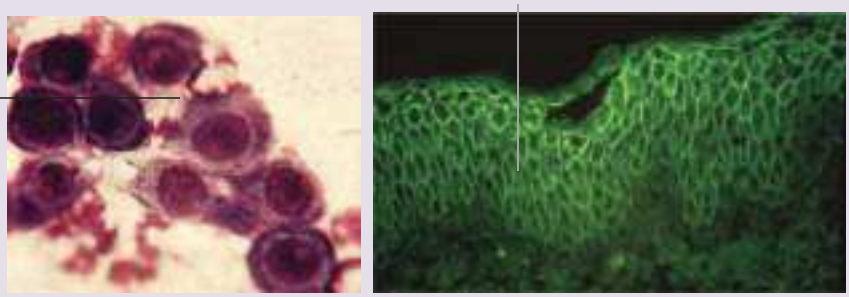
CI: Onset with oral erosions in 50% of cases, later superficial, fragile blisters with rapid transition to crusted erosions.



Pemphigus vulgaris

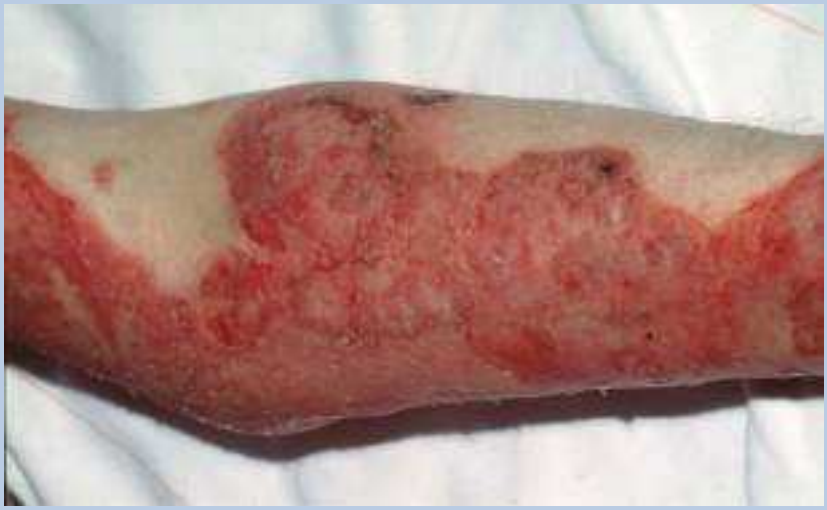




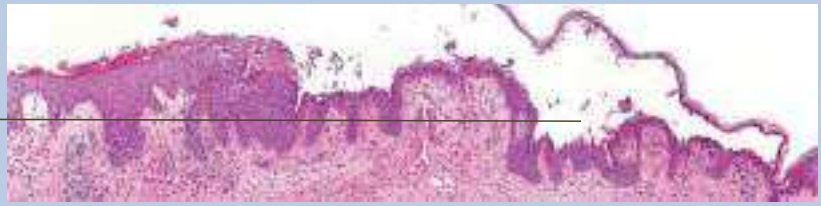


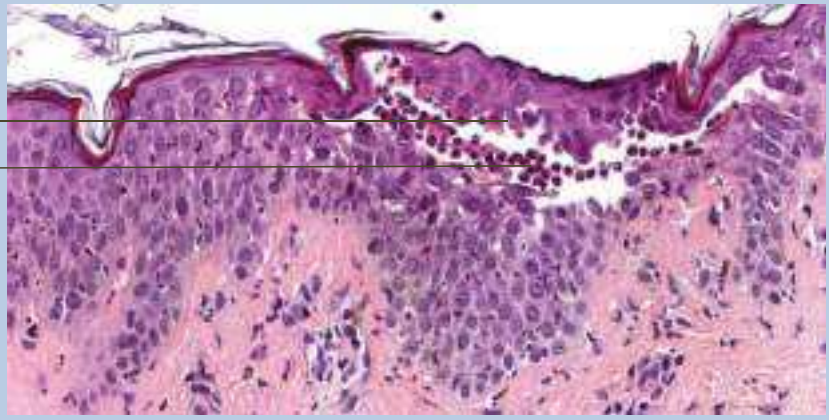
Hi: Intraepidermal suprabasal clefts due to acantholysis. Acantholytic cells floating in the blisters. Tombstone-like arrangement of basal keratinocytes. Labelling of IgG autoantibodies against surface proteins of keratinocytes in the direct immunofluorescence.

VARIANT: Pemphigus foliaceus



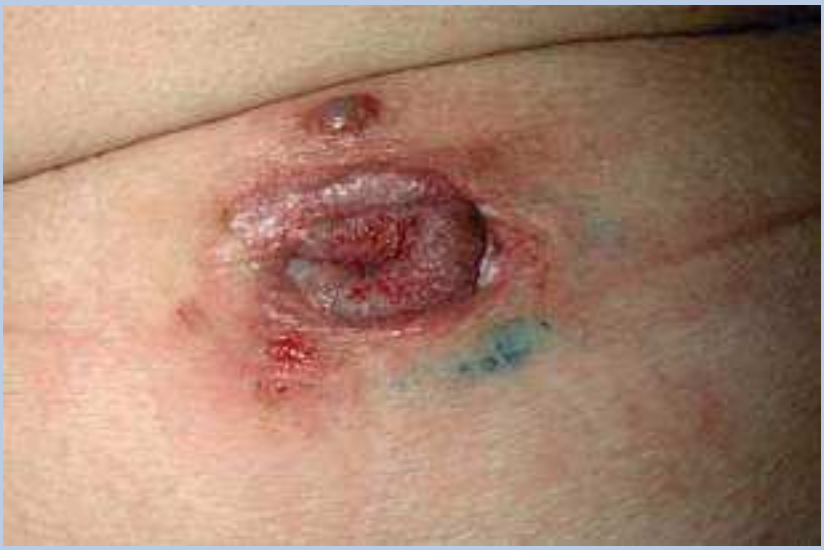
Cl: Superficial erosions and crusts.



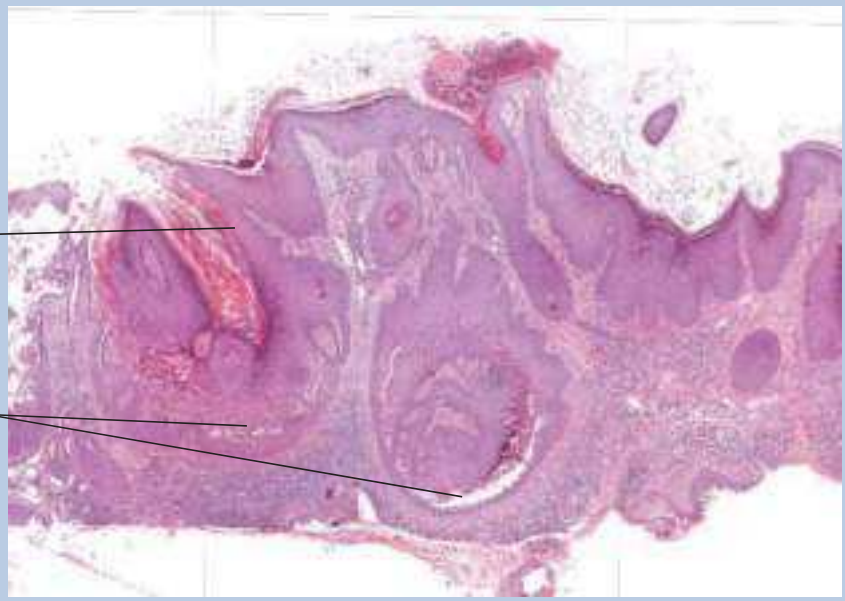


Hi: Acantholysis on the level of granular layer, DIF: IgG and C3 deposits in the upper layers of the epidermis.

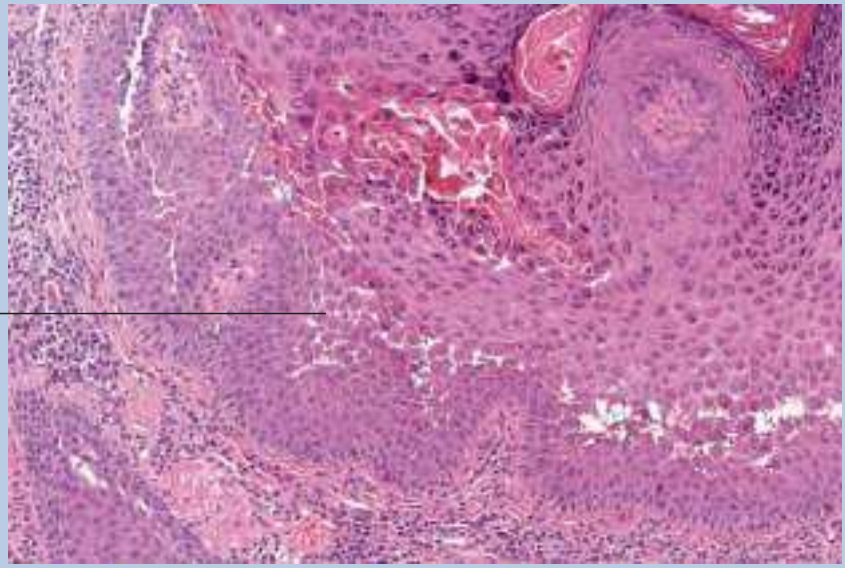
VARIANT: Pemphigus vegetans

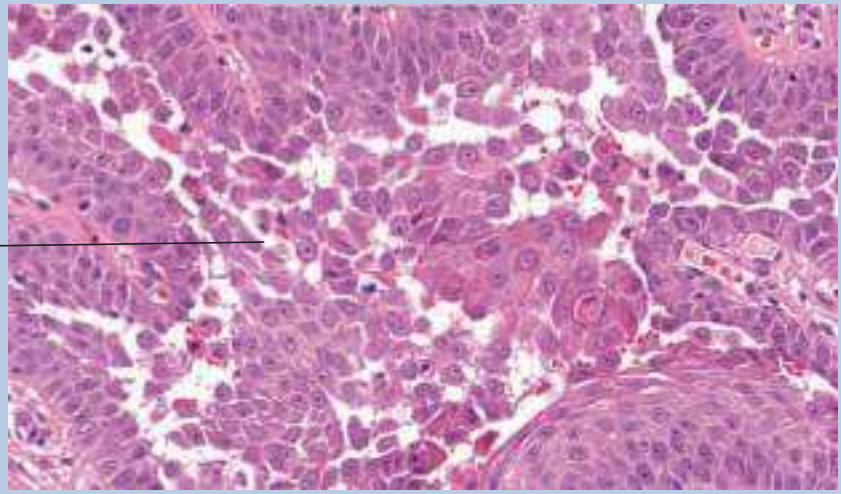


CI: Vesicles, blisters or pustules with papillomatous growth and vegetations.



Pemphigus vegetans

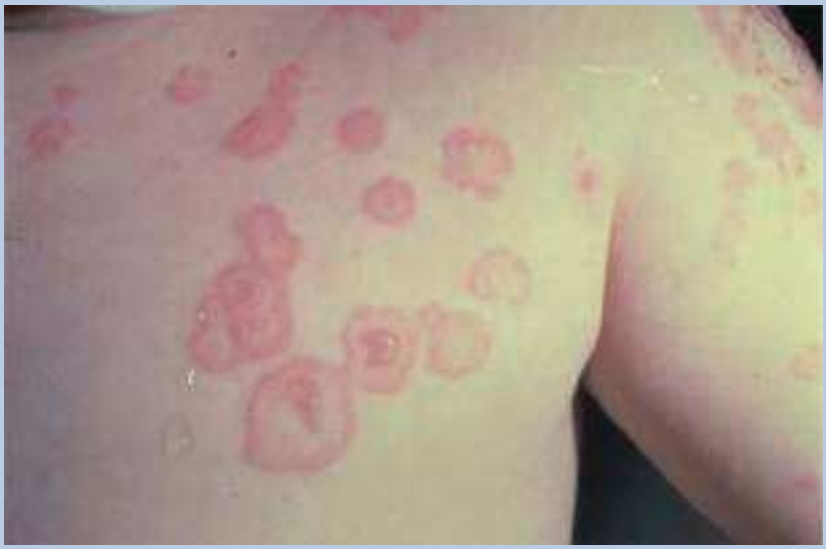




Hi: Suprabasal acantholytic blisters, verrucous epidermal hyperplasia, pustules with eosinophils.

VARIANT: IgA Pemphigus

IgA Pemphigus

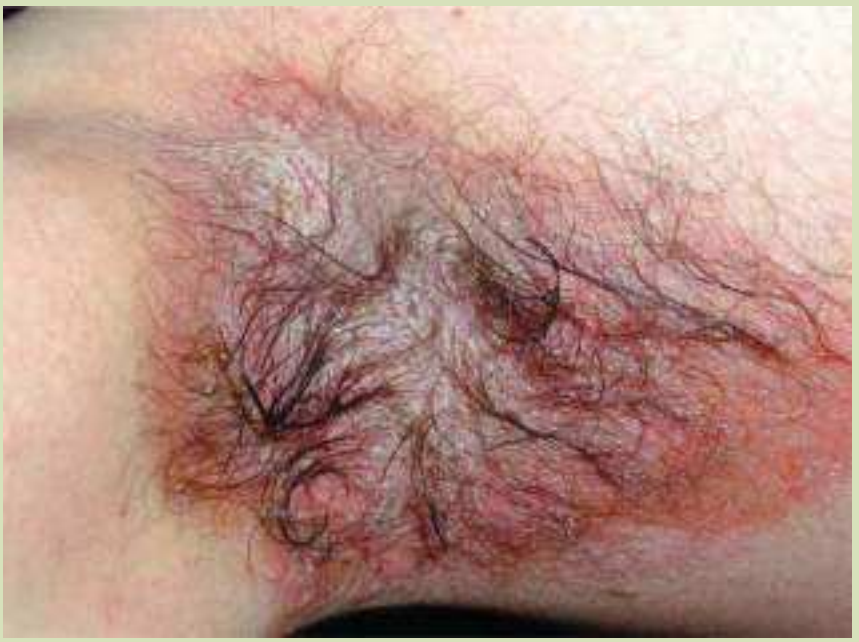


Cl: Vesicles or pustules, annular arrangement.

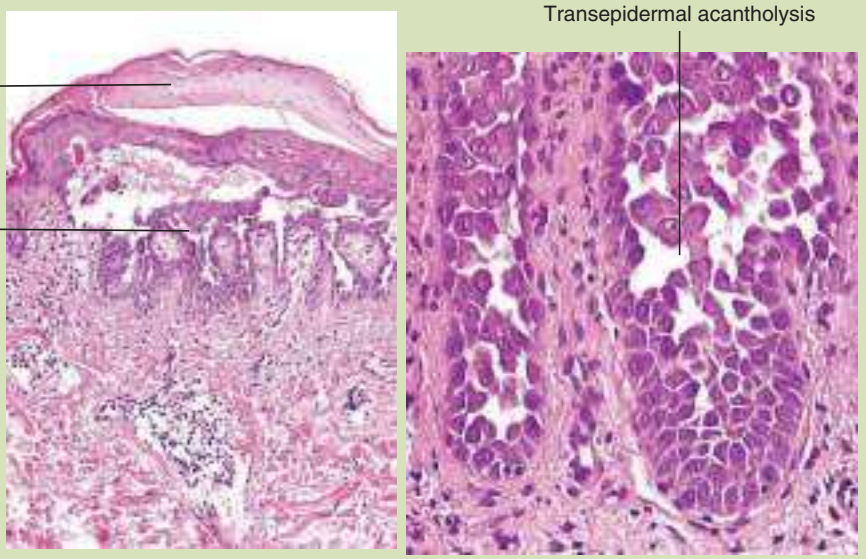
Hi: Subepidermal acantholytic blister. DIF: IgA deposits in the upper layers of the epidermis.

Paraneoplastic pemphigus: *Suprabasal acantholysis, interface dermatitis.*

DIFFERENTIAL DIAGNOSIS: Chronic benign familial pemphigus (Hailey-Hailey's disease)

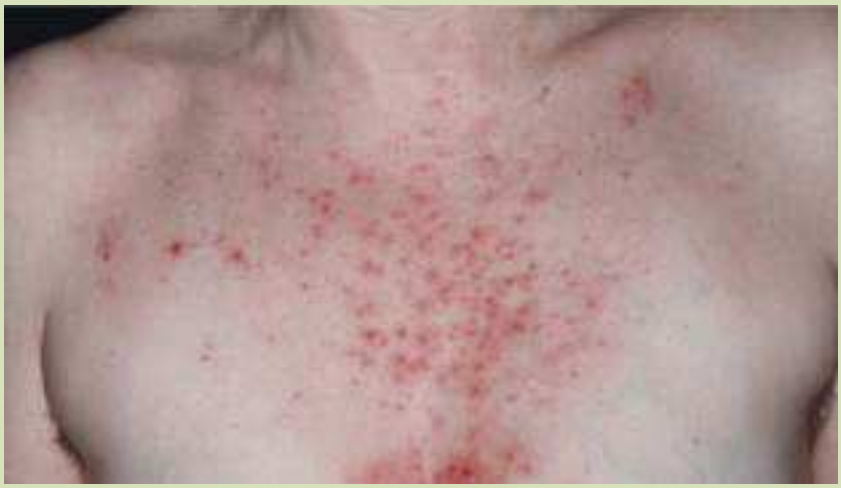


Cl: Maceration and friction, preferentially in the groin, axilla, perianal region, and the neck.

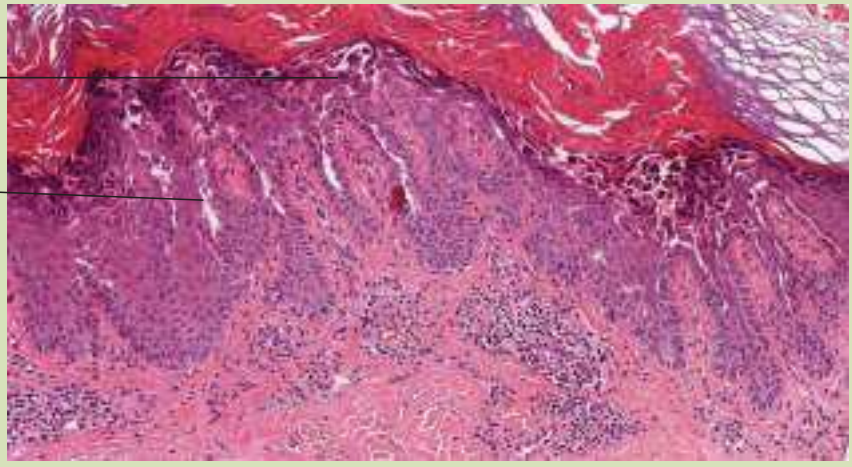


Hi: Suprabasal acantholysis, dyskeratosis, hyperparakeratosis.

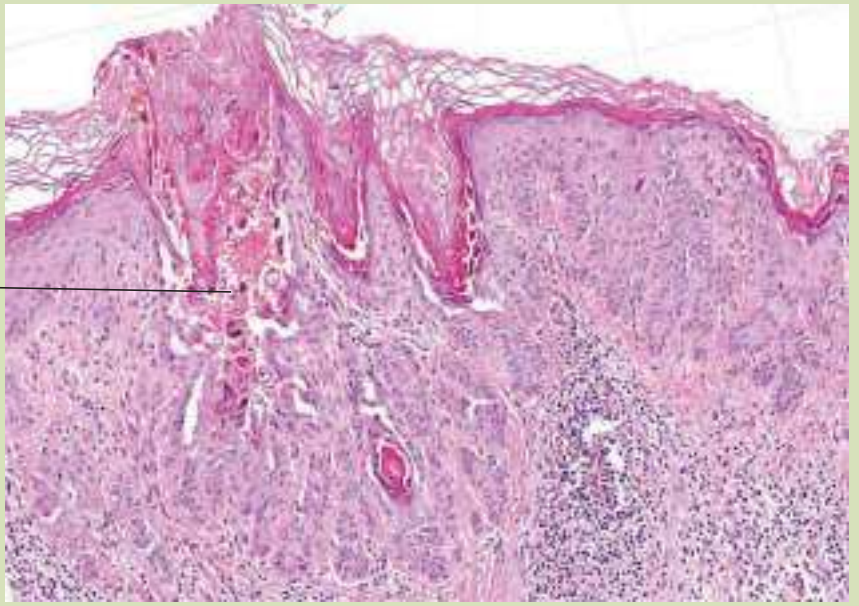
DIFFERENTIAL DIAGNOSIS: Dyskeratosis follicularis (Darier's disease)

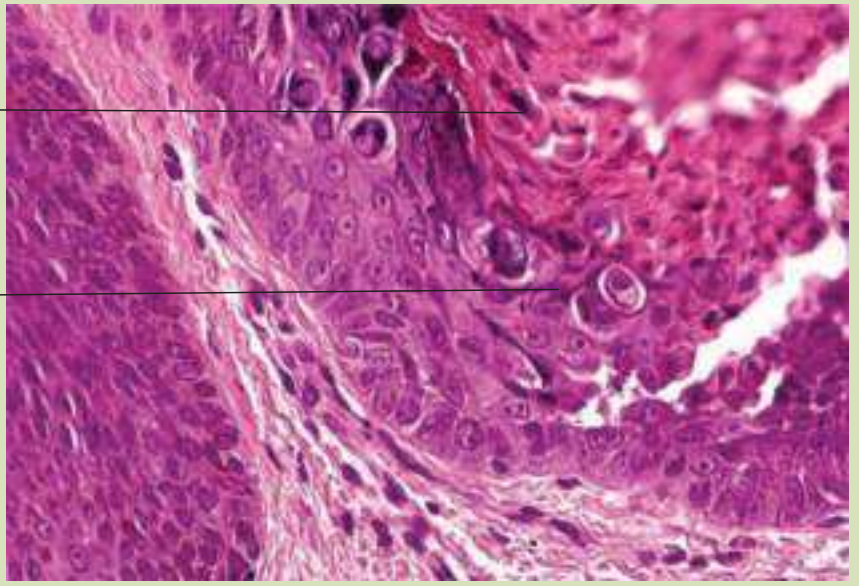


CI: Grayish tiny keratotic papules preferentially in the seborrheic (central axis) areas of the breast and back.



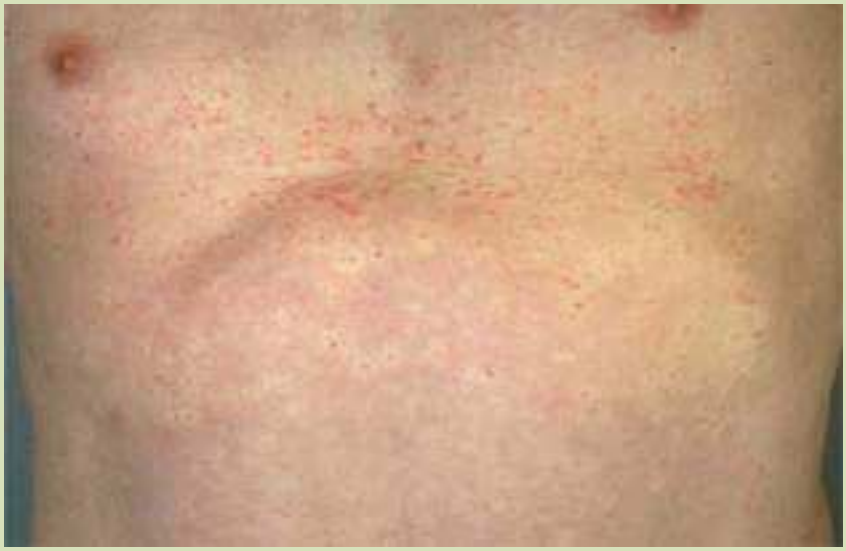
Dyskeratosis follicularis



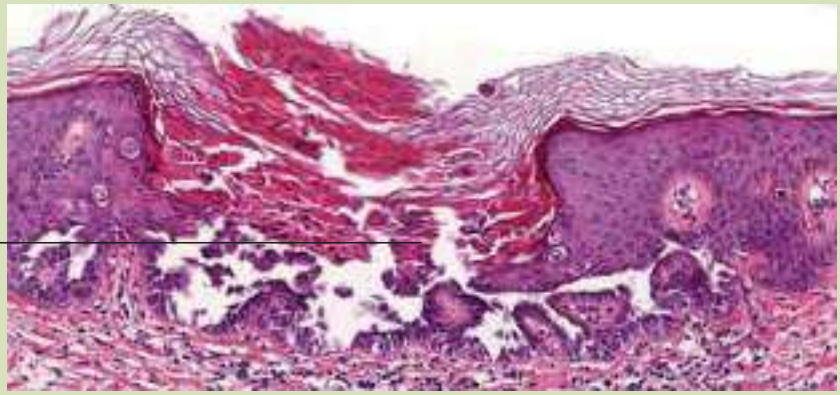


Hi: Acantholytic dyskeratosis, suprabasal cleft, acanthosis, parakeratosis, corps ronds and grains due to dyskeratosis.

DIFFERENTIAL DIAGNOSIS: Transient acantholytic dermatosis (Grover's disease)



Cl: Multiple tiny pruritic papules or vesicles on the trunk.



Hi: Small acantholytic foci with dyskeratosis, seen also in Darier's or Hailey-Hailey's disease.

Other Diagnosis

Bullous pemphigoid: *Subepidermal blister without acantholysis; eosinophils and neutrophils in the blister cavity and in the dermal infiltrate, no necrotic keratinocytes, no significant edema in the dermis, admixture of plasma cells.*

Impetigo contagiosa *(see Pustular, page 73): Subcorneal acantholysis, neutrophils and exsudate in the superficial blister, mixed dermal infiltrate with neutrophils, eosinophils and plasma cells. Bacteria may be detected in the blister.*

Other bullous skin diseases

References

Kouskoukis, C. E. and A. B. Ackerman (1984). "What histologic finding distinguishes superficial pemphigus and bullous impetigo?" *Am J Dermatopathol* **6**(2): 179–81.

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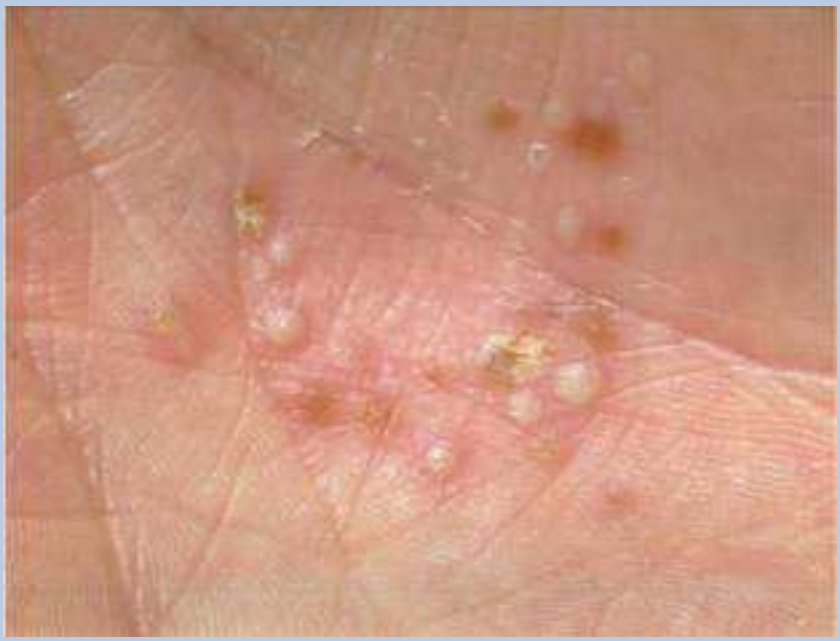
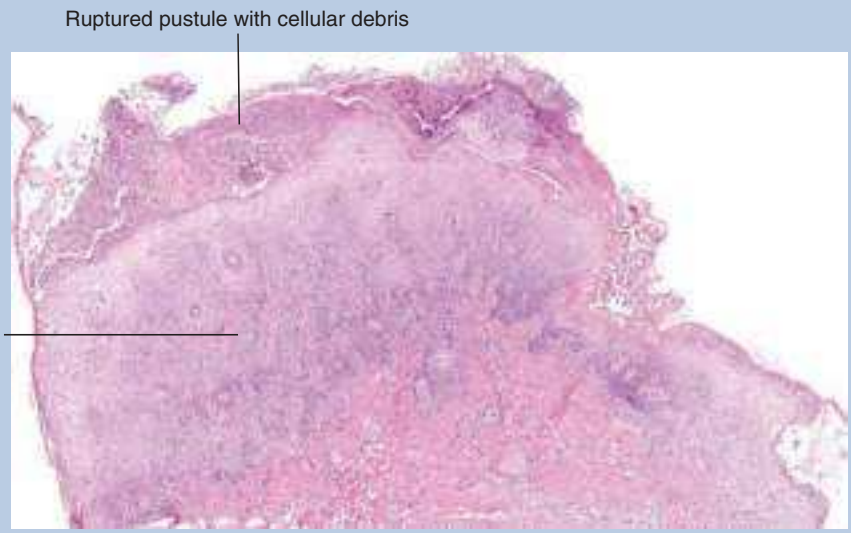
PROTOTYPE: Psoriasis pustulosa

VARIANT: Pustular psoriasis of palms and soles, Königsbeck-Barber-type

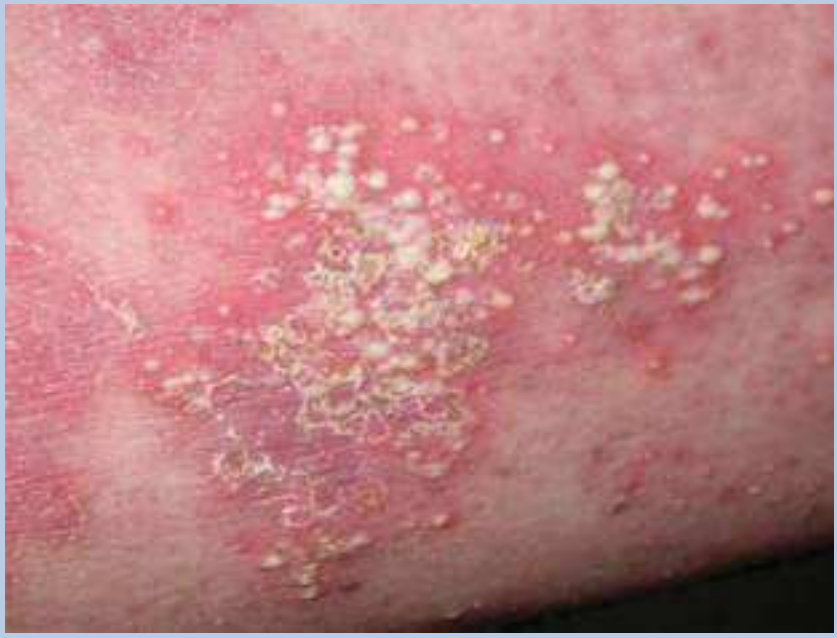


Cl: Pustules on palms and soles (Königsbeck-Barber type) or generalized (von Zumbusch type).

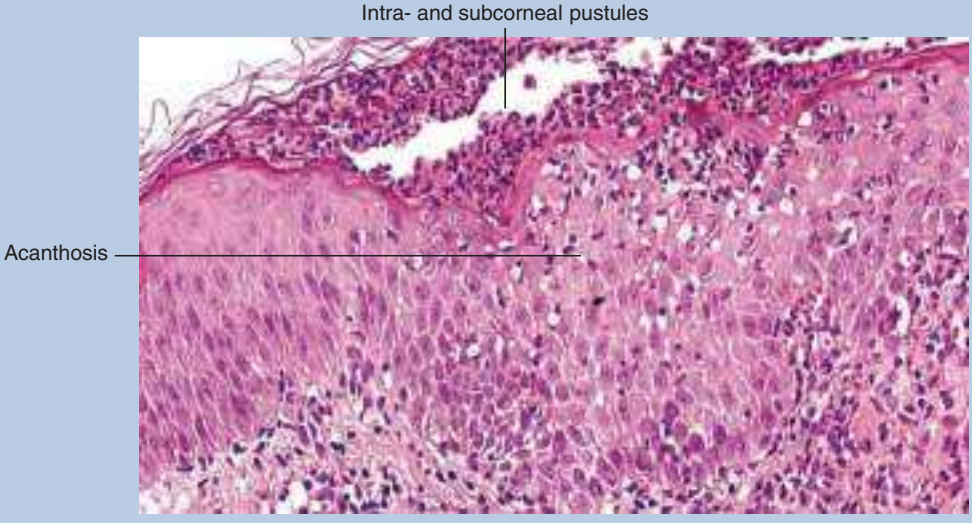


Hi: Intraepidermal neutrophilic pustules (Kogoj pustules and Munro's micro-abscesses), psoriasiform acanthosis, hyperparakeratosis, perivascular lymphohistiocytic infiltrate with a few neutrophils in the upper dermis.

VARIANT: Generalized pustular psoriasis, von Zumbusch-type



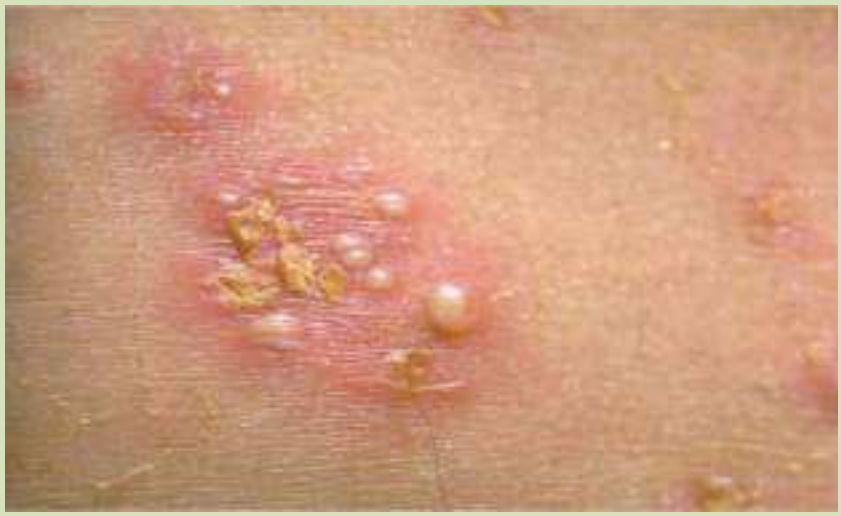
Cl: Clinical variant; generalized pustules.



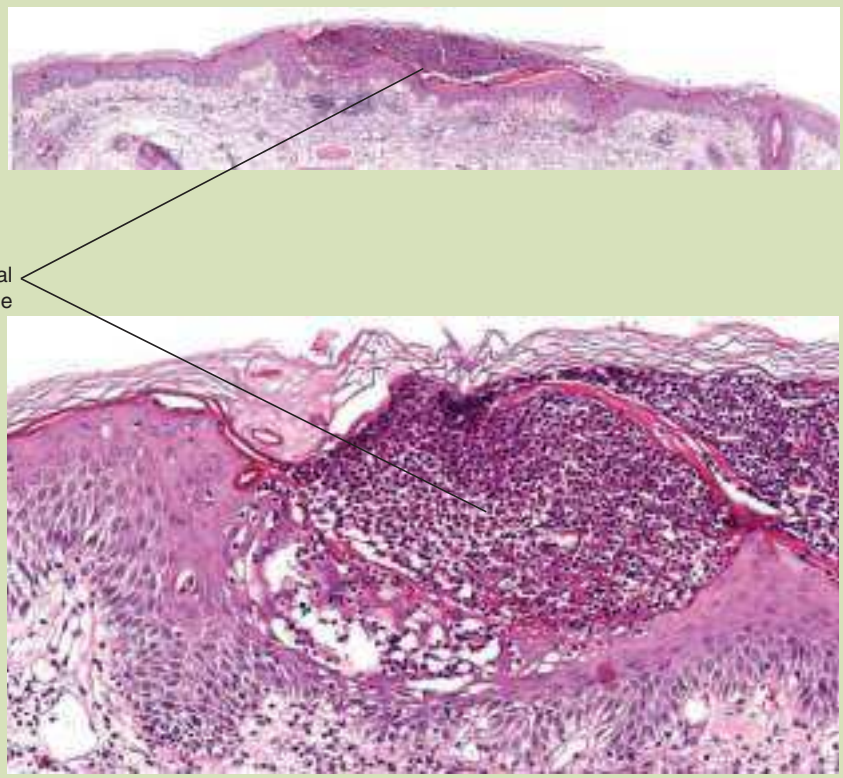
Hi: Similar to palmoplantar pustulosis, discrete acanthosis.

DIFFERENTIAL DIAGNOSIS: Subcorneal pustulosis

Subcorneal pustulosis



Cl: By some experts considered as a variant of pustular psoriasis.

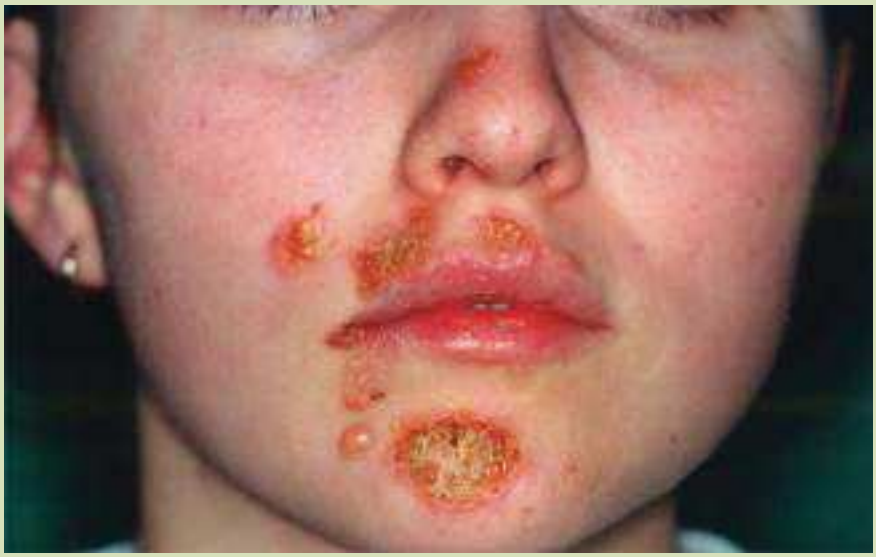


Hi: Subcorneal neutrophil-rich pustules without spongiform features.

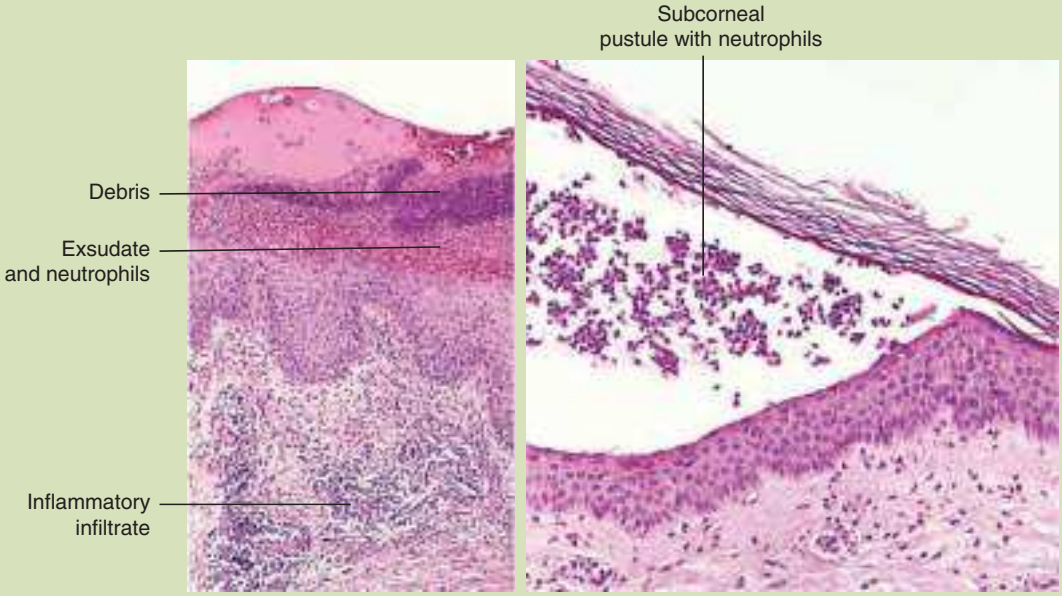
Comment

IgA-pemphigus pattern.

DIFFERENTIAL DIAGNOSIS: Impetigo contagiosa

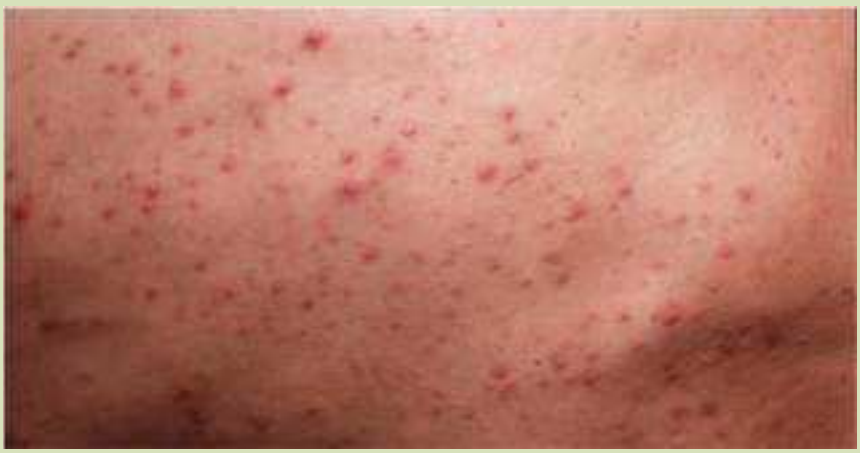


Cl: Superficial erosion following destruction of small pustules, yellow circumscribed crusts.

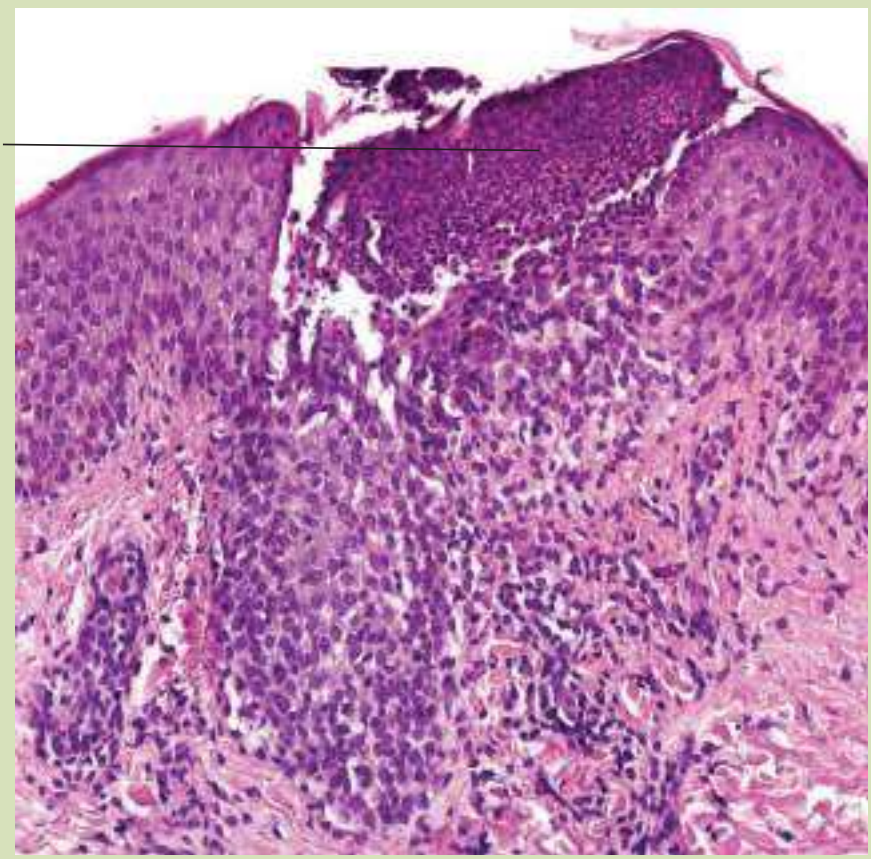


Hi: Subcorneal acantholysis, neutrophils and exsudate in the superficial blister, mixed dermal infiltrate with neutrophils, eosinophils and plasma cells. Bacteria may be detected in the blister.

DIFFERENTIAL DIAGNOSIS: Ostiofolliculitis (pustular)



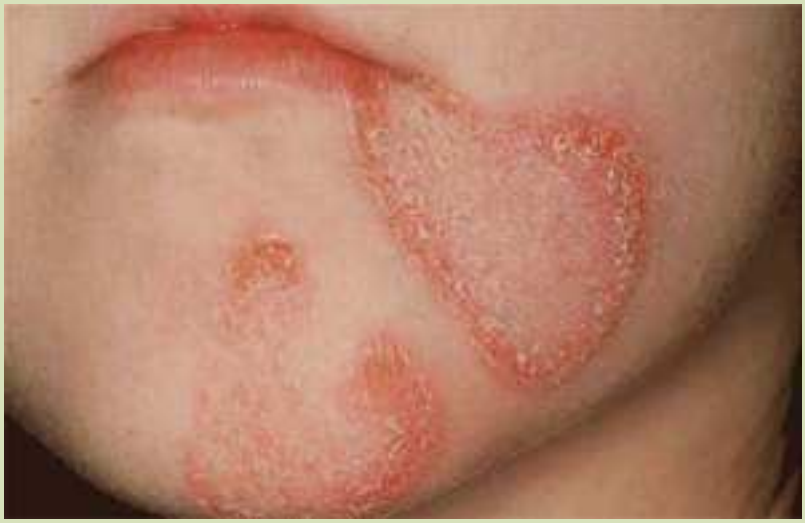
Cl: Follicle-bound small pustules.



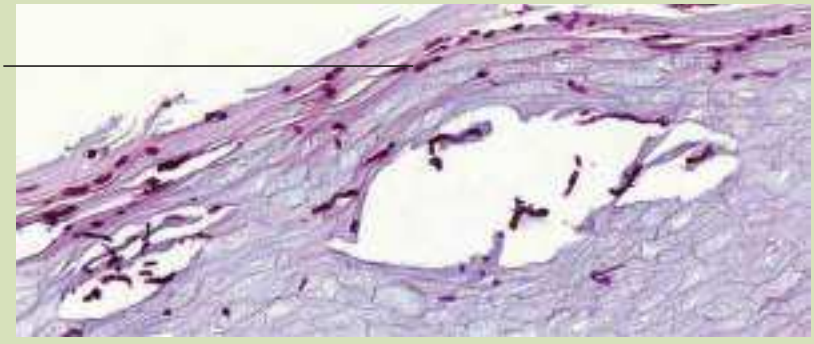
Hi: Involvement of follicular structures. Pustules in the follicular ostia.

DIFFERENTIAL DIAGNOSIS: Tinea

Superficial fungal infection with *dermatophytes*

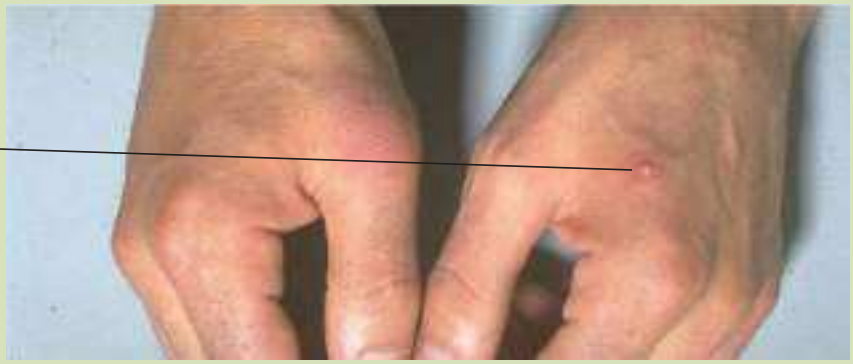


Cl: Small pustules, crusts and scaling with centrifugal growth and tendency to regression in the center of the circumscribed lesions.

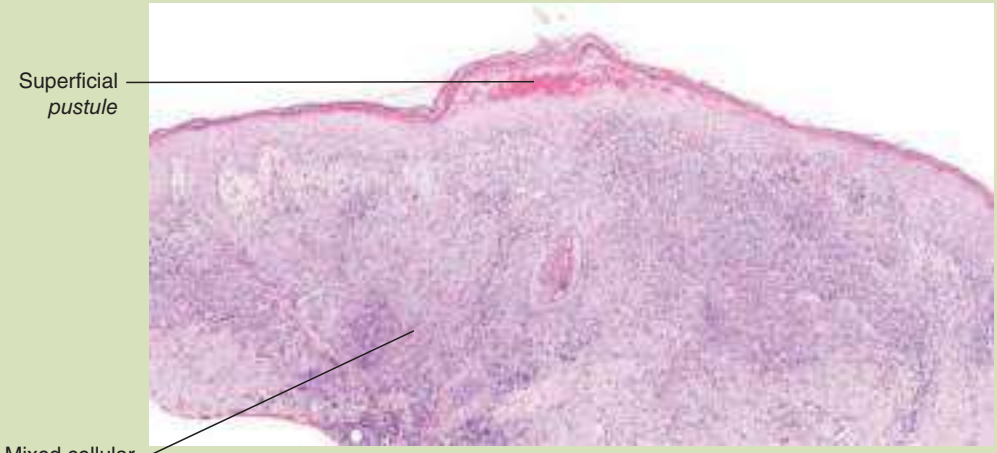


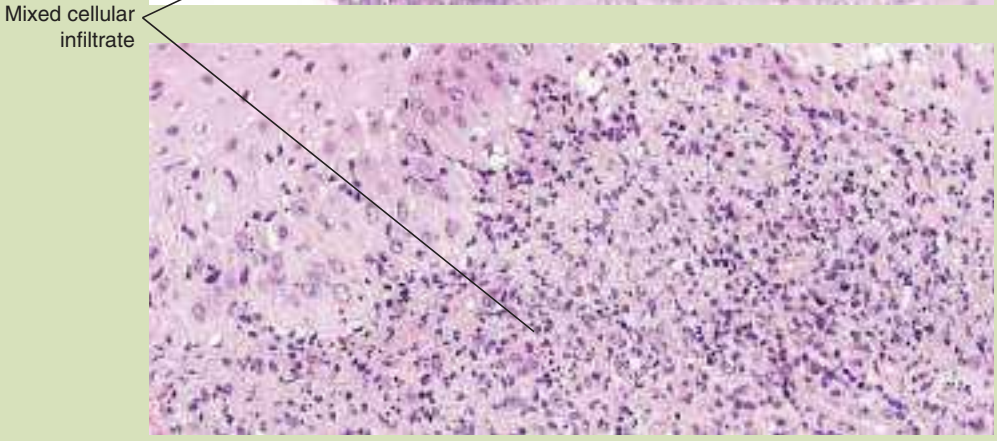
Hi: Focal crust formation, mixed cellular dermal infiltrate of neutrophils, occasionally eosinophils and plasma cells. Detection of fungi by PAS or Grocott stains.

DIFFERENTIAL DIAGNOSIS: Behçet's disease (Behçet-Adamantiades syndrome)



Cl: Disseminated small pustules. Multisystemic disorder with oral and genital aphthae, uveitis, synovitis, thrombophlebitis and cutaneous pustular vasculitis in some cases.





Hi: Superficial pustules. Mixed cellular infiltrate in the dermis. Vasculitis in some cases.

Other Diagnosis

Acute generalized exanthematous pustulosis (AGEP): *Often induced by drugs. Initially often starting in flexural body regions. Overlapping histology with pustular psorasis. Admixture of eosinophils. Discrete acanthosis.*

Infantile acropustulosis*: Early lesions: Spongiosis, foci of epidermal necrosis, exocytosis of neutrophils and eosinophils. Late lesions: subcorneal and intraepidermal pustules.*

Transient neonatal pustular melanosis, early lesions: *Distinct clinical features in a newborn.*

Pemphigus foliaceus *(see* Bullous, acantholytic, page 60*): Acantholysis on the level of granular layer, DIF: IgG and C3 deposits in the upper layers of the epidermis.*

IgA Pemphigus*: Acantholysis, subcorneal pustules with neutrophils. DIF: IgA deposits in the upper layers of the epidermis (see* Bullous, page 63*).*

Miliaria cristallina and rubra *(see Ekzematous,* Acute, page 23*): Involvement of the acrosyringium, spongiosis, mixed cellular infiltrate with numerous neutrophils.*

References

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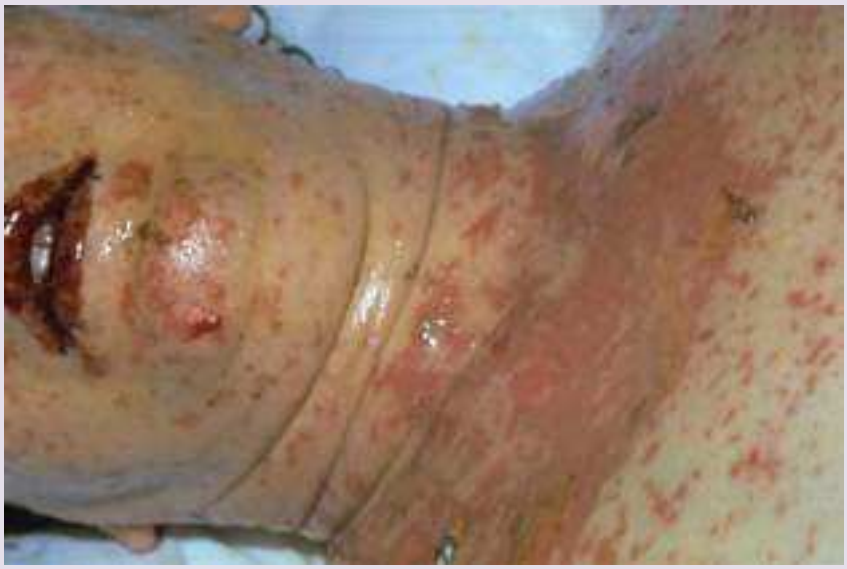
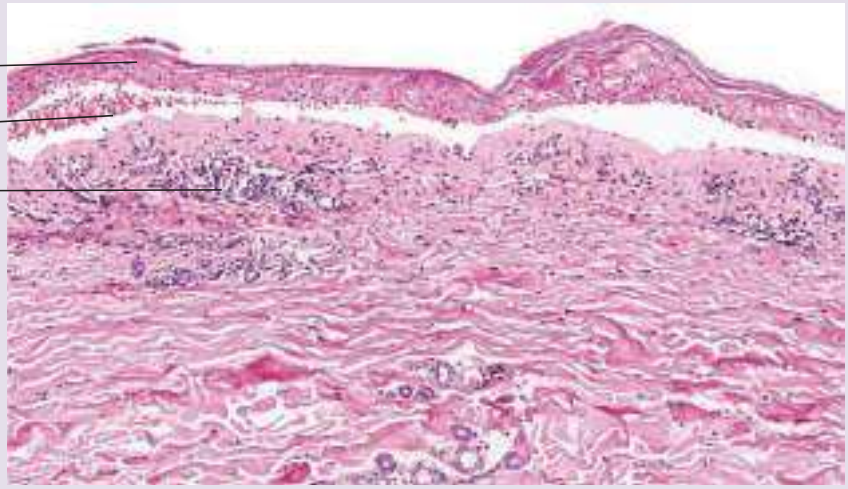
PROTOTYPE: Toxic epidermal necrolysis (TEN, Lyell's syndrome)



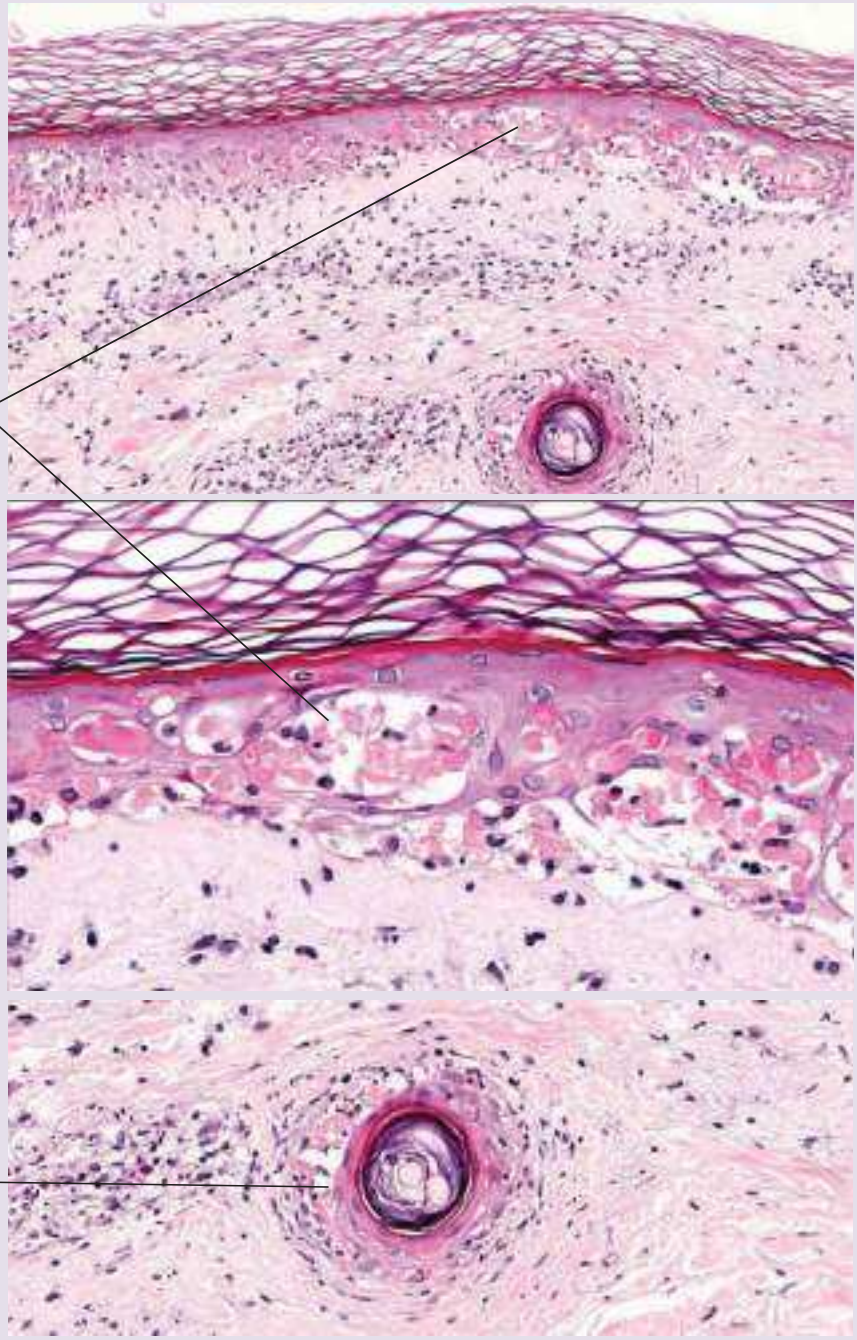
CI: Starting with a confluent grayish, maculopapular exanthema, finally hemorrhagic blisters, epidermal necrosis and erosions due to loss of sheets of epidermis develop. Usually severe periorificial mucosal erosions.



Comment

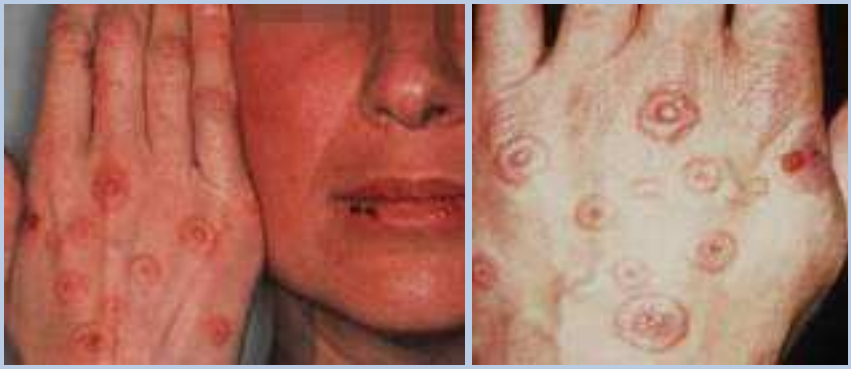
Erythema exsudativum multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are variants of the same disease spectrum but of varying severity.

Toxic epidermal necrolysis

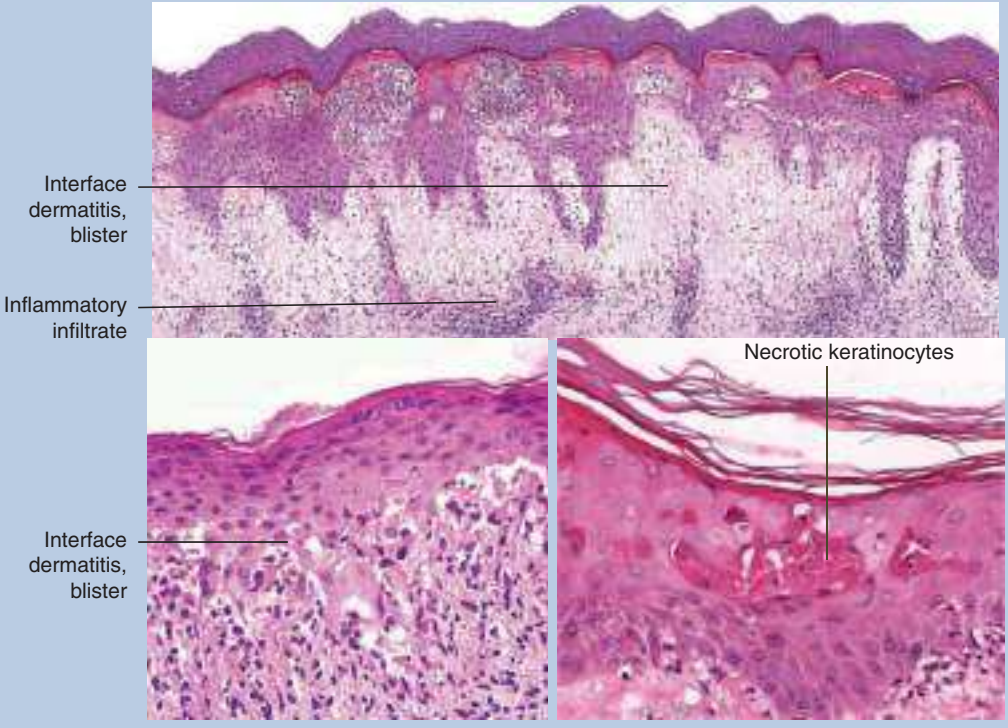


Hi: Full thickness epidermal necrosis, normal basket weave stratum corneum, subepidermal blister formation, dermal papillae intact, minimal inflammation, erythrocyte extravasation.

VARIANT: Erythema multiforme

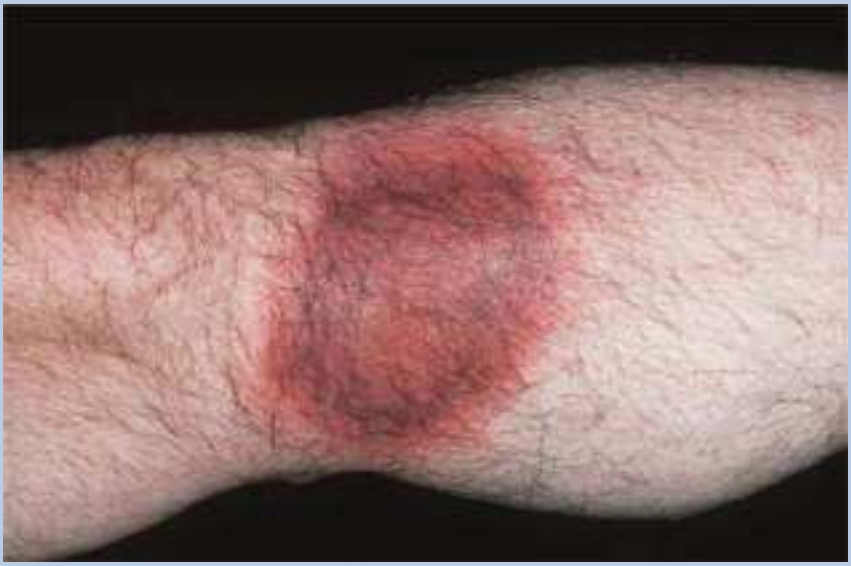


CI: Erythematous blistering target- or iris-shaped lesions, preferentially on the dorsum of the hands.

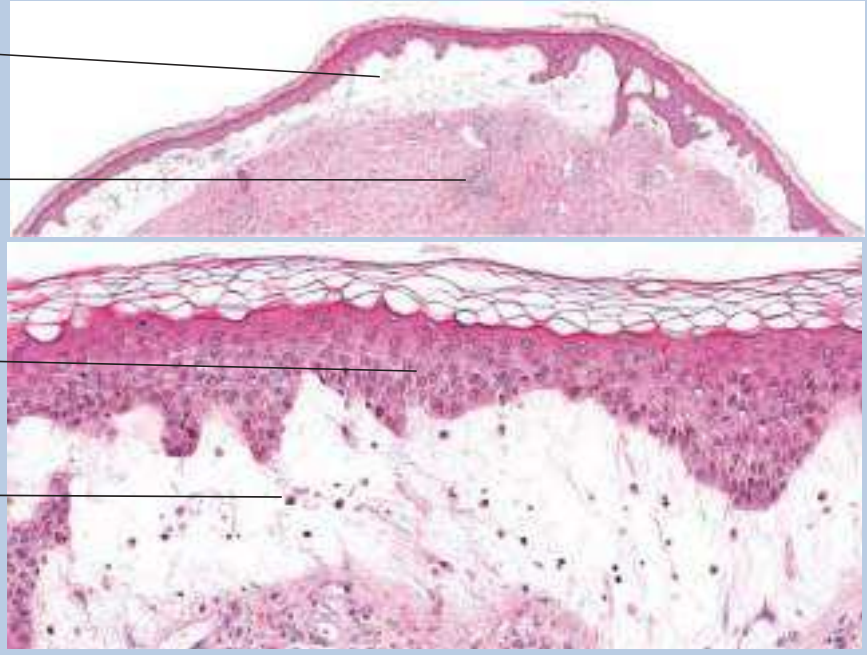


Hi: Interface dermatitis, necrotic keratinocytes in all epidermal layers, lymphocytic infiltrate, edema in the upper dermis.

VARIANT: Fixed drug reaction



Cl: Solitary circumscribed often hemorrhagic erythema in a "fixed" localization.

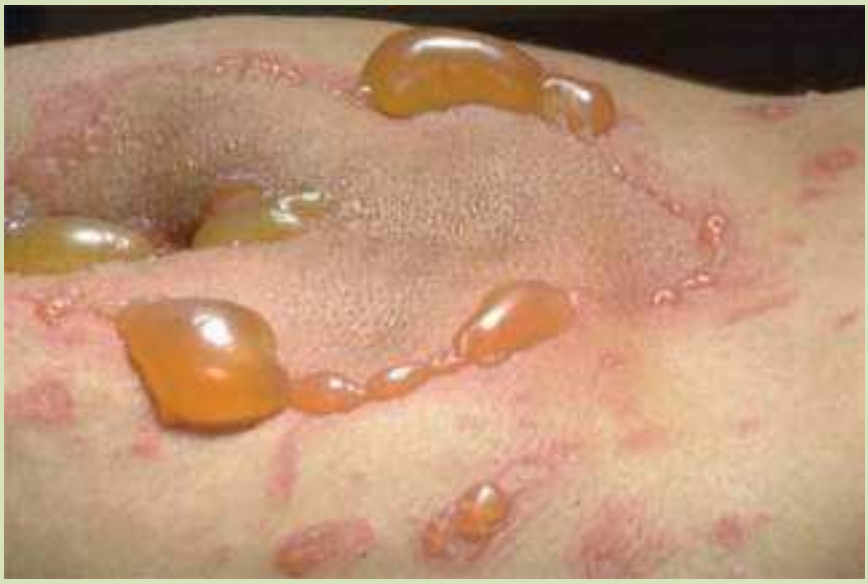


Hi: Single cell necrosis of keratinocytes in all epidermal layers, interface dermatitis, lymphocytic infiltrate with eosinophils, pigment loss.

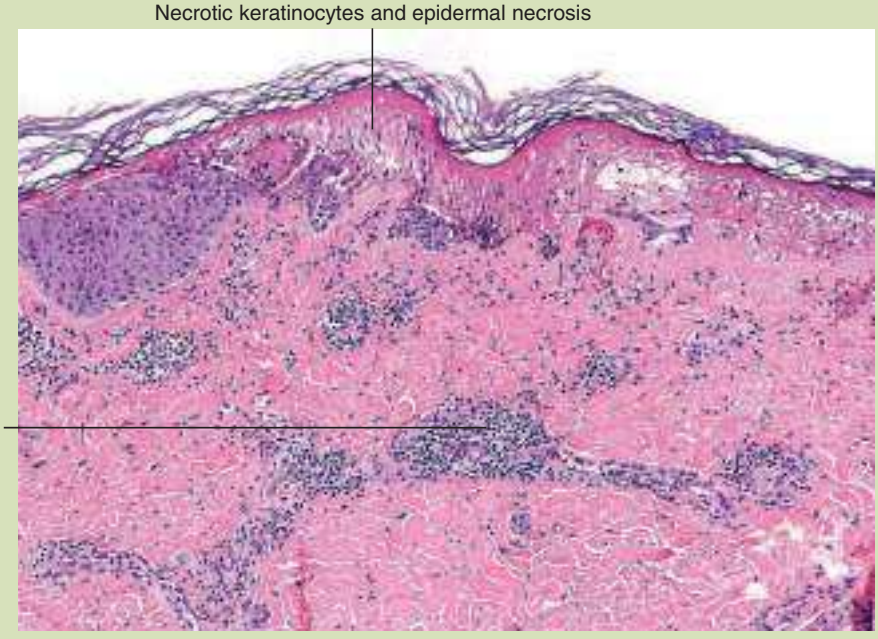
DIFFERENTIAL DIAGNOSIS

Staphylococcal scaled skin syndrome (SSSS): *Following a staphylococcal infection and mediated by bacterial exotoxins, initially erythema resembling scarlet fever followed by unstable large blisters which quickly erode and lead to widespread loss of superficial parts of the epidermis.*
Histology shows subcorneal blistering with few granulocytes, few acantholytic keratinocytes, sparse perivascular infiltrate of neutrophils and lymphocytes.

DIFFERENTIAL DIAGNOSIS: (Phyto-) phototoxic dermatitis

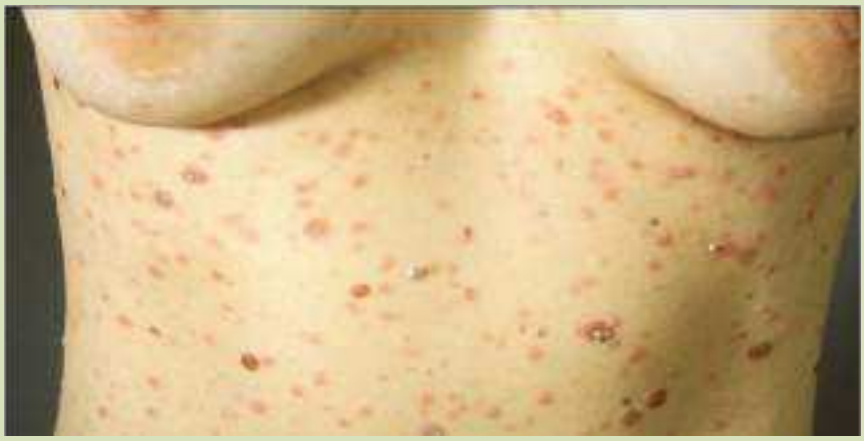


Cl: Erythema and tense blister formation in light exposed area, limited to the site contact of phototoxic agent (furocumarine) exposure.

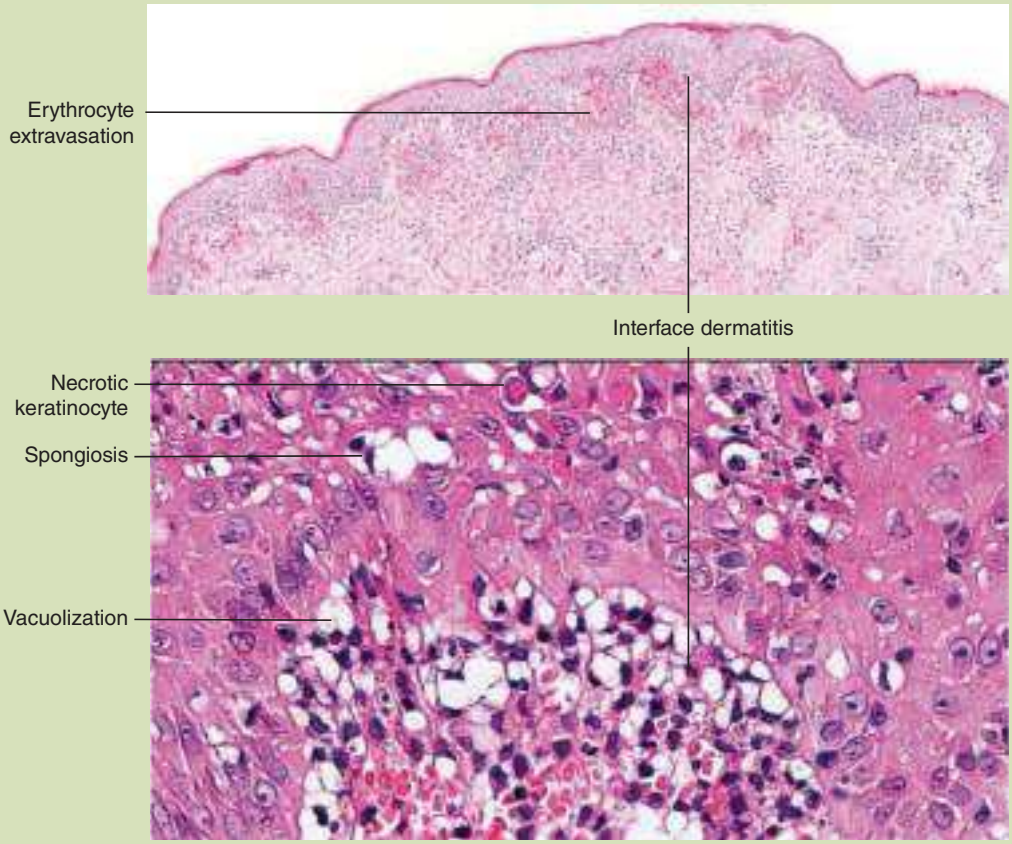


Hi: Necrotic keratinocytes, extensive edema or subepidermal blister formation, sparse infiltrate.

DIFFERENTIAL DIAGNOSIS: Pityriasis lichenoides et varioliformis acuta (PLEVA)

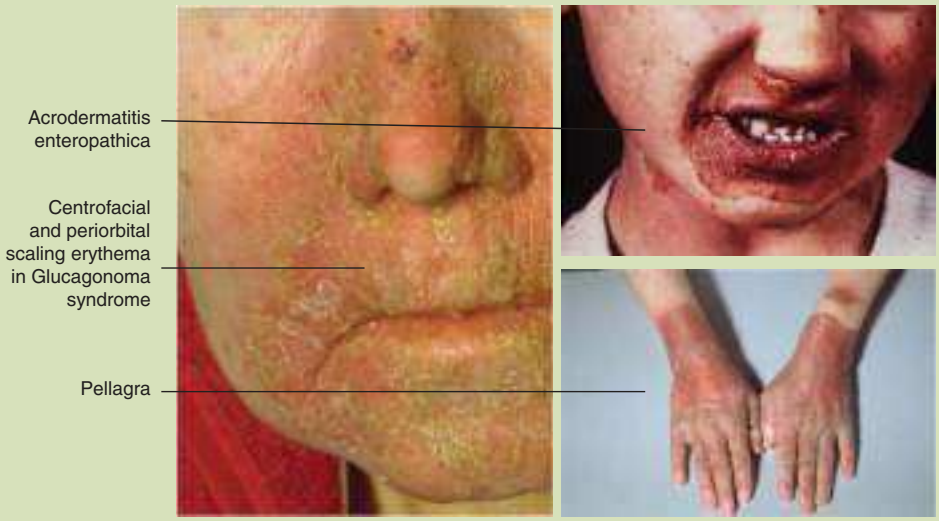


Cl: Small papules and plaques with scaling or superficial crust.

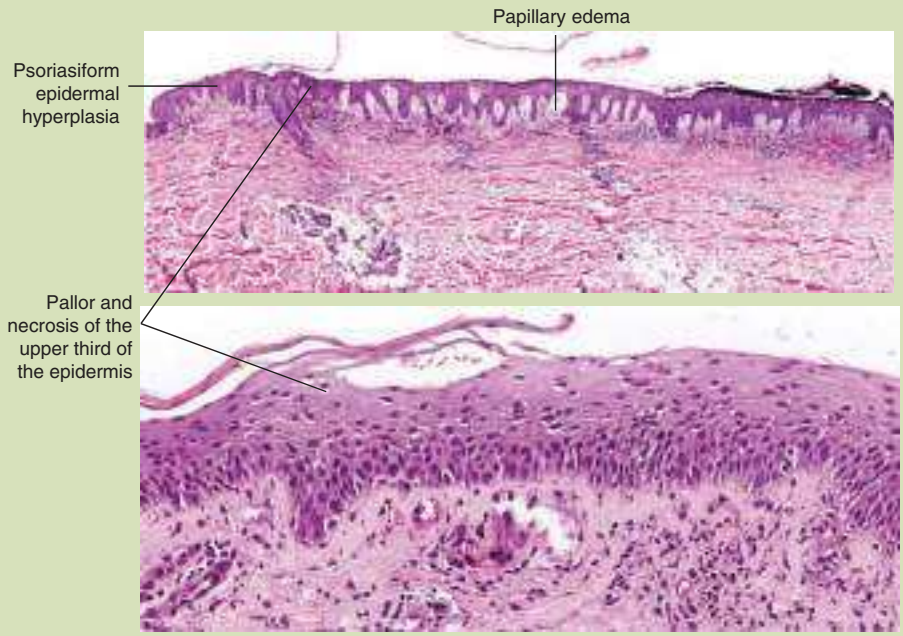


Hi: Focal epidermal changes (vacuolization, spongiosis, exocytosis of lymphocytes), necrotic keratinocytes, focal hyperparakeratosis with inclusions of neutrophils, erythrocyte extravasation.

DIFFERENTIAL DIAGNOSIS: Necrolytic migratory erythema (Glucagonoma-syndrome)



Cl: Eczematous changes periorally and around other orifices.



Hi: Psoriasiform epidermal hyperplasia, confluent parakeratosis, pallor and/or necrosis of the upper third of the epidermis, superficial perivascular infiltrate, papillary edema.

Comment

Superficial necrobiosis of the epidermis with crust formation is the common denominator of these etiologically different disorders.

Other Diagnosis

Acrodermatitis enteropathica (zinc deficiency-syndrome): *Histologic changes similar to necrolytic migratory erythema.*

Pellagra*: Histologic changes similar to necrolytic migratory erythema.*

Viral exanthema, herpes virus*: Acantholysis, ballooning of keratinocytes, multinucleated syncytial epithelial cells, homogenized steel-grey nucleoplasm, marginalized chromatin (see* Ballooning, page 87*).*

Graft-versus-host reaction, acute*: Interface dermatitis, necrotic keratinocytes. Clinical context (see* Chapter Lichenoid, page 116*).*

Combustio and congelatio*: Epidermal necrosis. History, clinical context.*

Porphyria cutanea tarda (*see* Chapter 3, Subepidermal blistering, page 128).

References

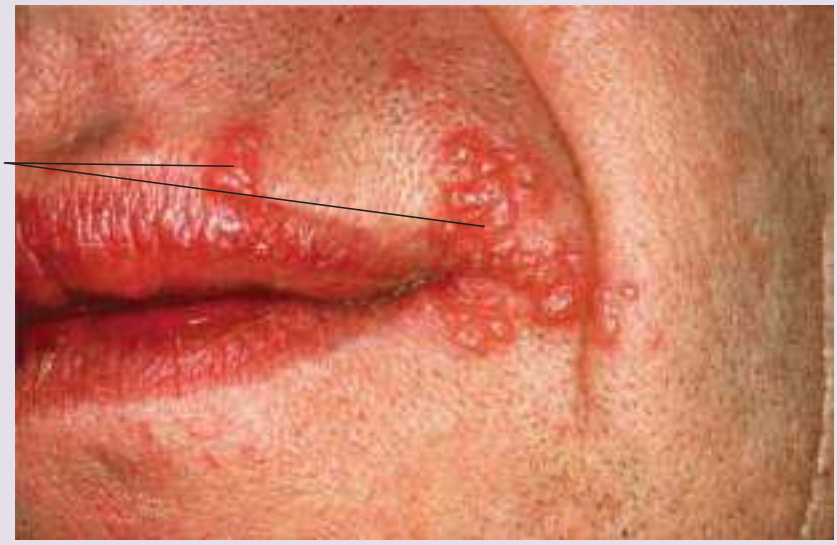
Letko, E., D. N. Papaliodis, G. N. Papaliodism, *et al.* (2005). "Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature." *Ann Allergy Asthma Immunol* **94**(4): 419–36; quiz 436–438, 456.

Lyell, A. (1983). "The staphylococcal scalded skin syndrome in historical perspective: emergence of dermopathic strains of Staphylococcus aureus and discovery of the epidermolytic toxin. A review of events up to 1970." *J Am Acad Dermatol* **9**(2): 285–94.

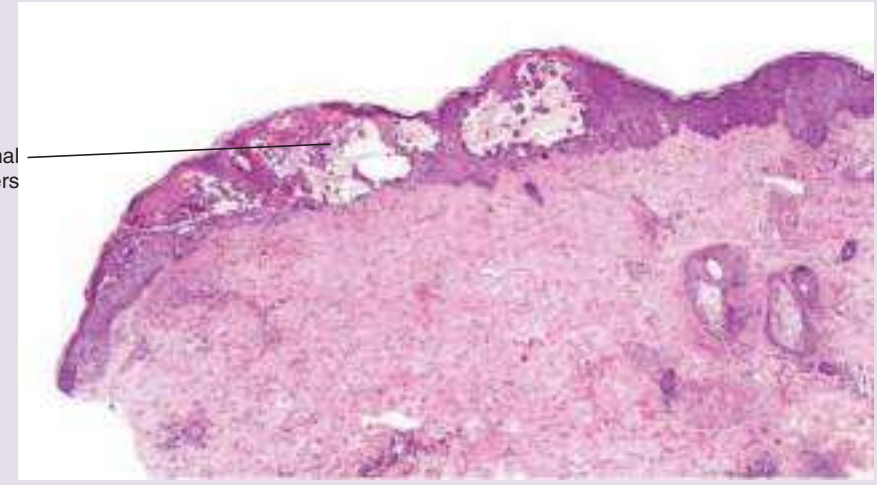
Megahed, M. (2004). *Histopathology of Blistering Diseases: With Clinical, Electron Microscopic, Immunological and Molecular Biological Correlations*. Heidelber, New York, Springer.

Papadopoulos, A. J., R. A. Schwartz, Z. Fekete, *et al.* (2001). "Pseudoporphyria: an atypical variant resembling toxic epidermal necrolysis." *J Cutan Med Surg* **5**(6): 479–85.

PROTOTYPE: Alpha-herpes virus-infections: Herpes simplex

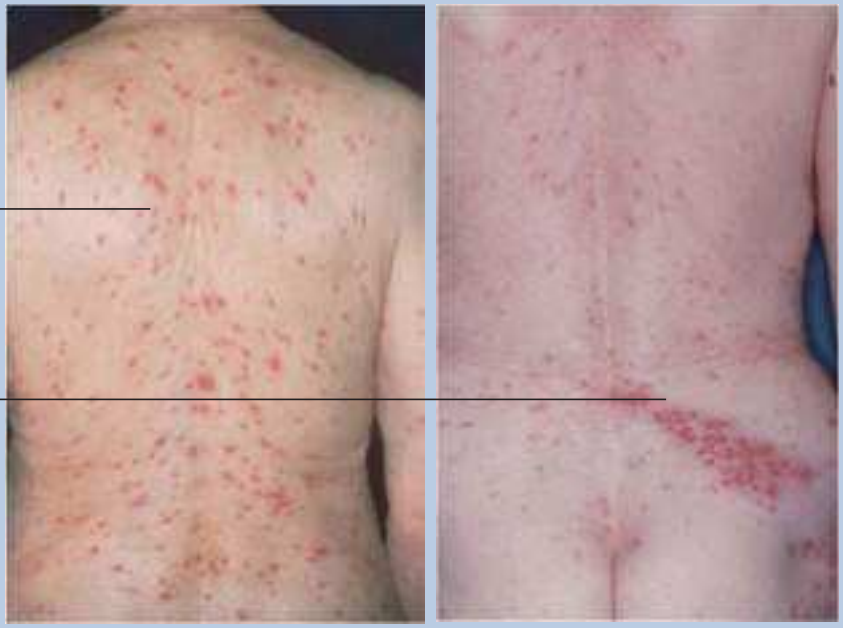


Cl: Erythema with clusters of small vesicles, usually on the lips (type 1) or the genital mucosa (type 2).

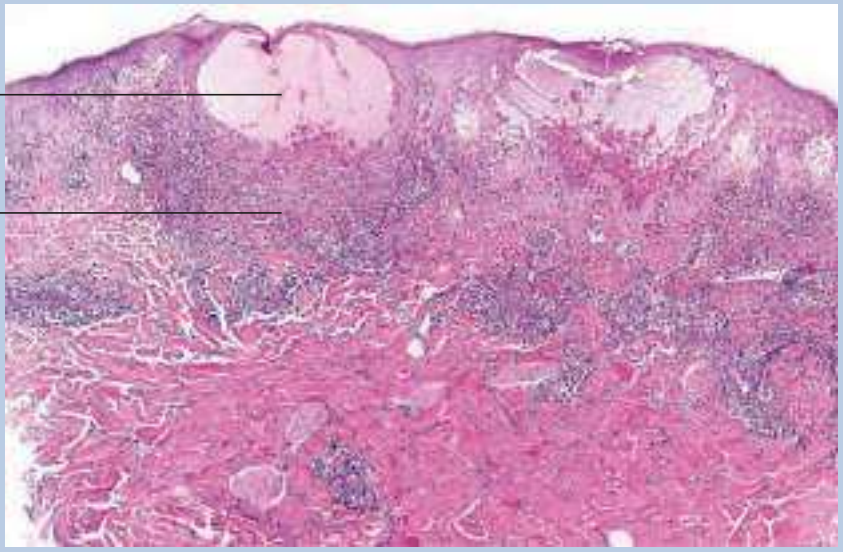


Hi: Acantholysis, ballooning degeneration of keratinocytes, "steel gray" nuclei of keratinocytes, necrotic keratinocytes, multinucleated (syncytial) epithelial cells, inter- and intracellular edema and intraepidermal vesicles. Mixed cellular infiltrate, lymphocytes predominating, dermal edema, occasionally lymphocytic and leukocytoklastic vasculitis.

VARIANTS: Varicella (Chickenpox)/Herpes zoster

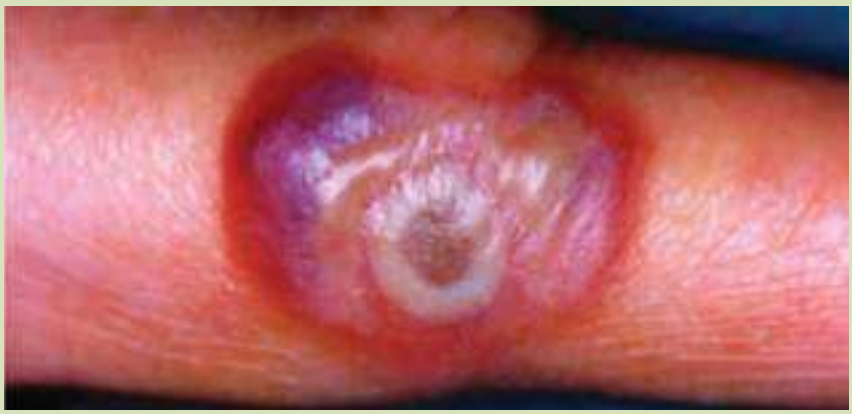


Cl: Generalized papulovesicles and vesicles in different stages of development. Difference between varizella and herpes zoster is due to their clinical presentation.

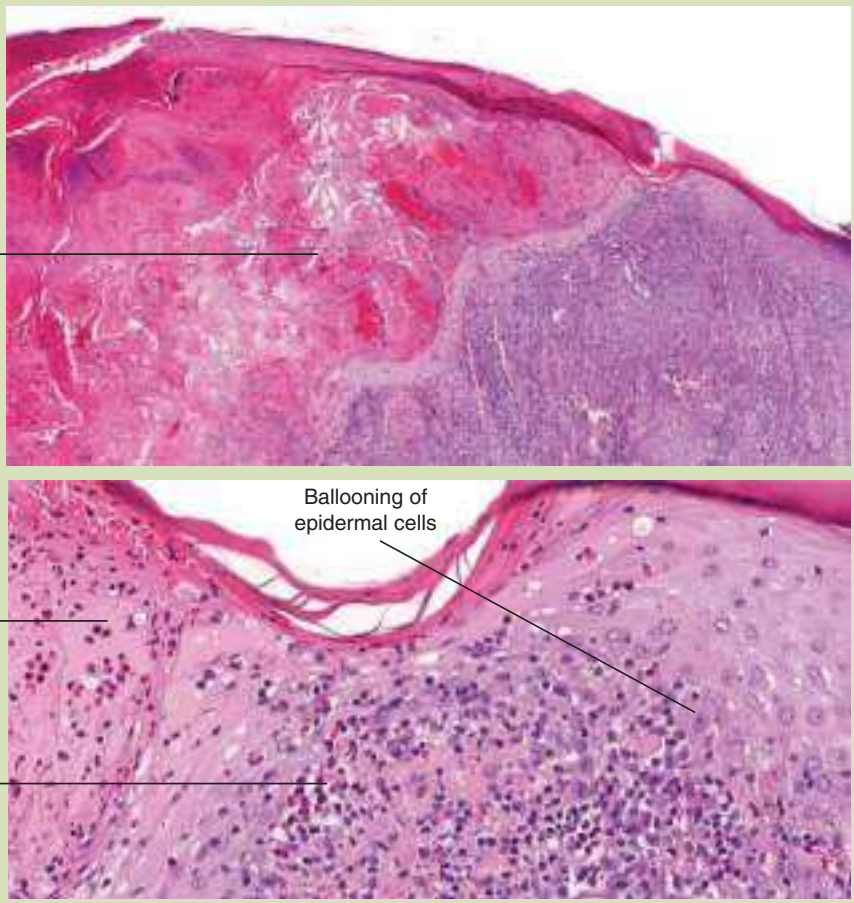


Hi: Like herpes simplex (*see*, page 87).

DIFFERENTIAL DIAGNOSIS: Poxvirus and other viral infections, ecthyma contagiosum (ORF)

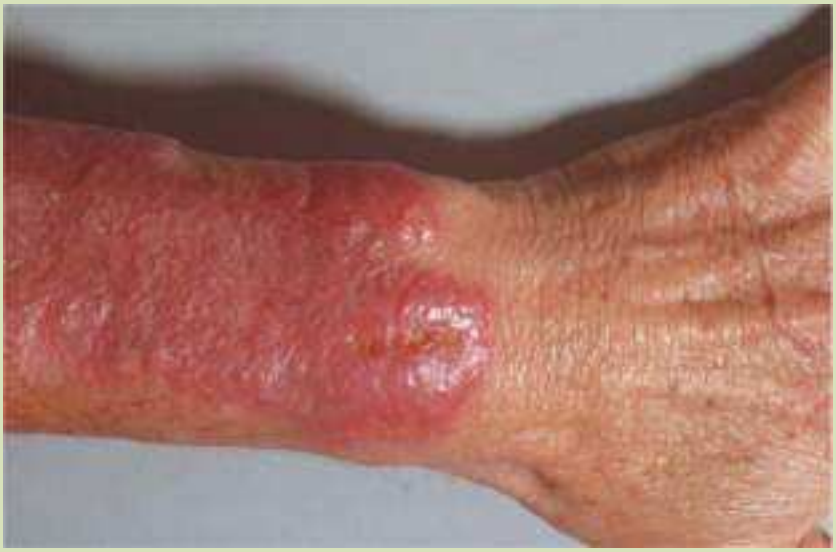


Cl: Solitary hemorrhagic blistering lesion usually on a finger.

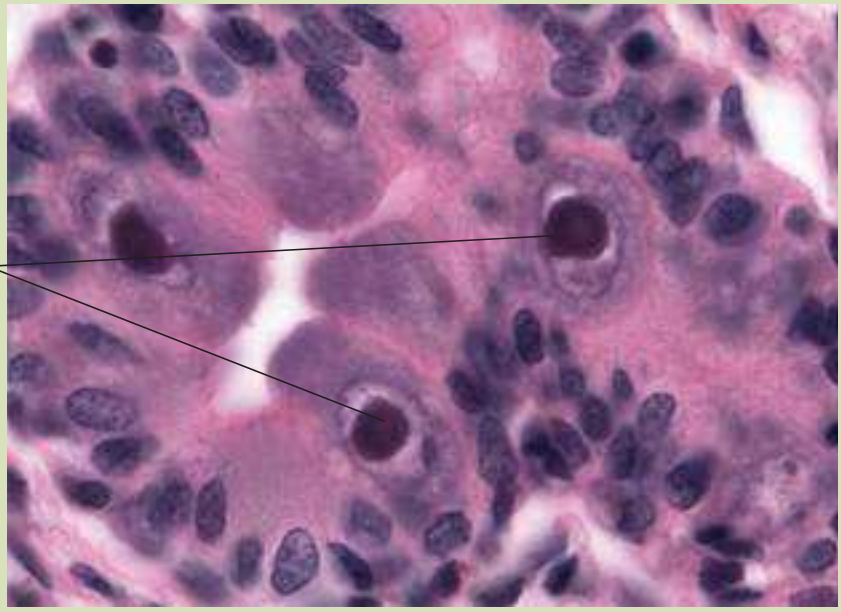


Hi: Epithelial hyperplasia, eosinophilic intracytoplasmic inclusions (Guarnieri bodies), mixed dermal infiltrate.

DIFFERENTIAL DIAGNOSIS: Cytomegalovirus infection

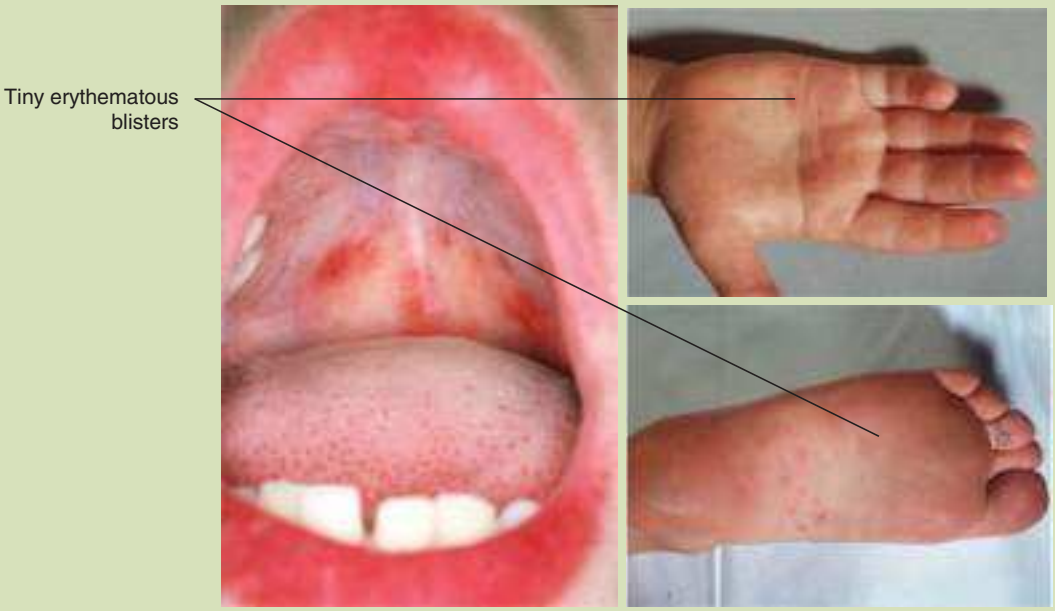


Cl: Variable depending on localization. Vesicular or superficial ulceration with crust.

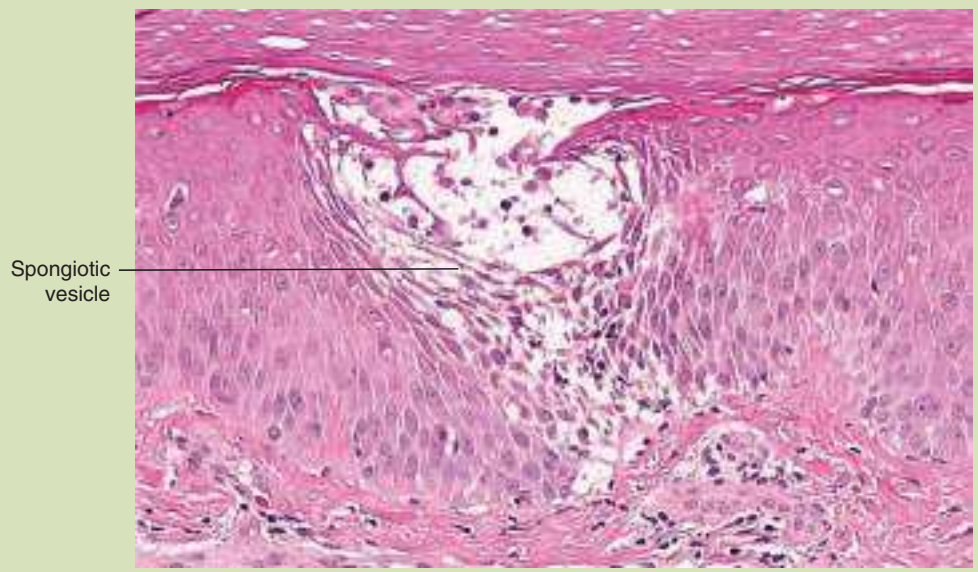


Hi: Endothelial cells with inclusions (owl eye cells) in the small dermal vessels (specimen from lung).

DIFFERENTIAL DIAGNOSIS: Hand, foot and mouth disease (Coxsackievirus)



CI: Tiny papulovesicles on palms and soles and on the palate.



Hi: Reticular epithelial degeneration with blister formation.

Other Diagnosis

Pemphigus vulgaris *(see* Bullous, acantholytic, page 58***):*** *Intraepidermal blister formation due to suprabasal acantholysis. No necrotic keratinocytes. No ballooning.*

Erythema multiforme*: Interface changes, necrotic keratinocytes, edema in the upper dermis, no ballooning (see* Necrotic, page 80*).*

Pityriasis lichenoides, acute: *Interface changes, focal spongiosis, single necrotic keratinocytes and hyperparakeratosis with inclusions of neutrophils, no intraepidermal blister or vesicle formation (see* page 84*).*

Comment

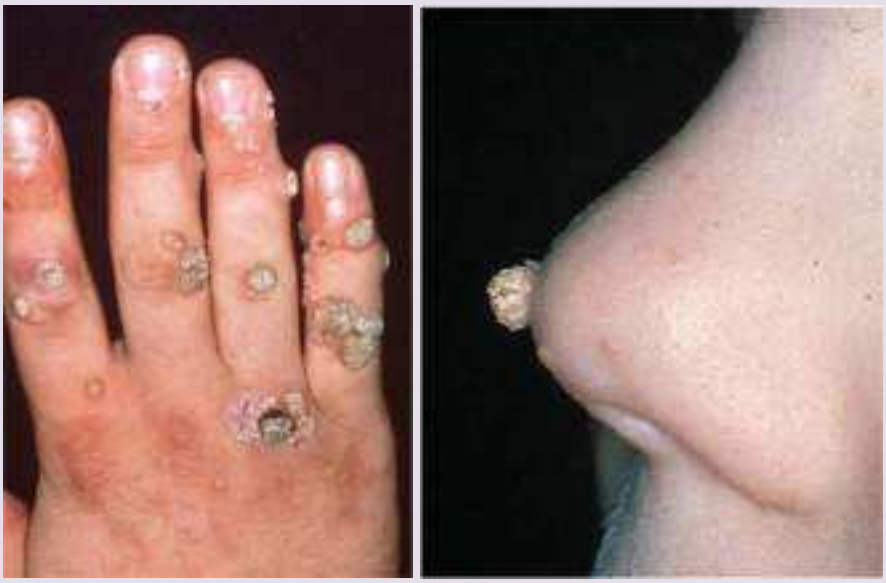
Differentiation between herpes simplex virus and varicella zoster virus is only possible by immunohistochemical, molecularbiologic or virological studies.

References

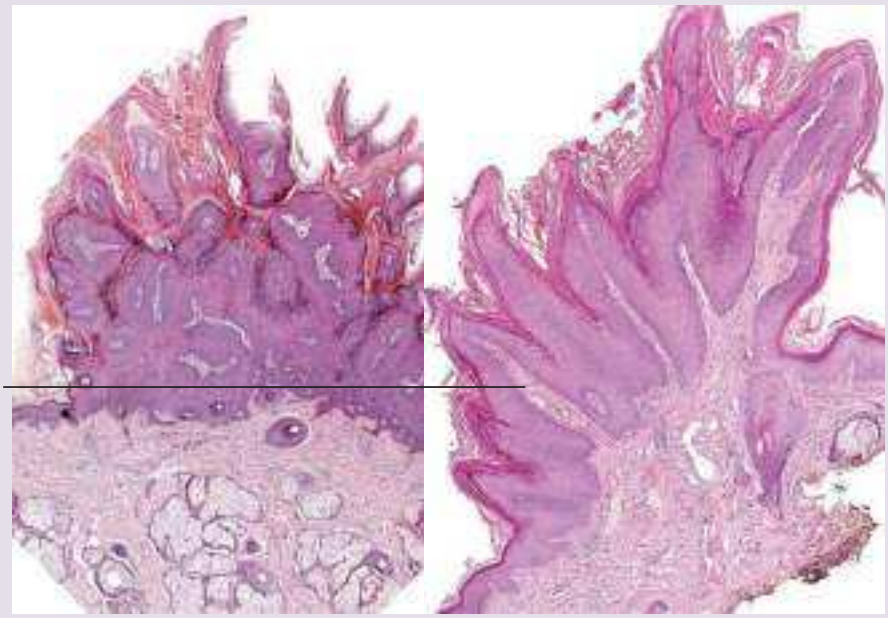
Boyd, A. S., J. P. Zwerner, and J. L. Miller (2012). "Herpes simplex virus-induced plasmacytic atypia." *J Cutan Pathol* **39**(2): 270–3.

Chisholm, C. and L. Lopez (2011). "Cutaneous infections caused by Herpesviridae: a review." *Arch Pathol Lab Med* **135**(10): 1357–62.

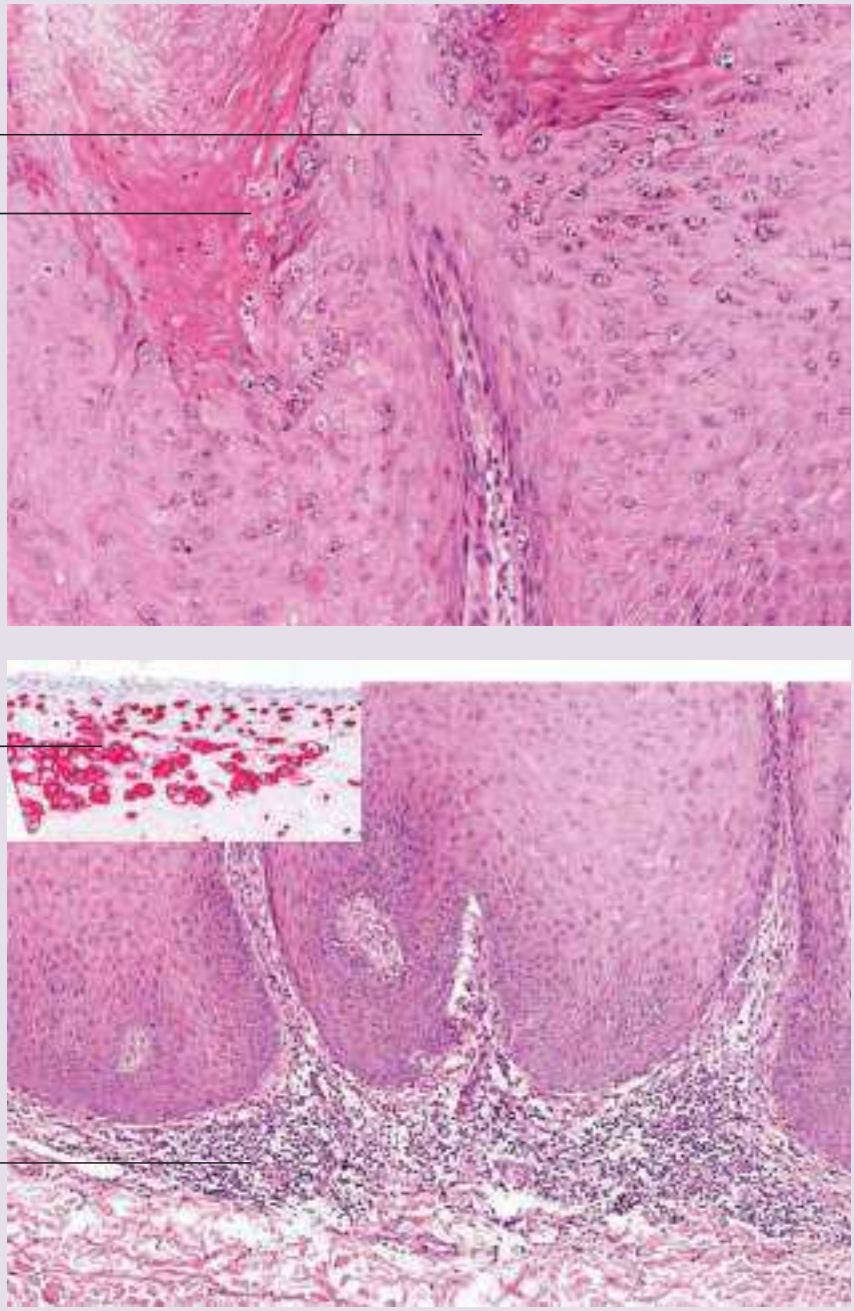
PROTOTYPE: Verruca vulgaris



Cl: Solitary or grouped papules showing massive hyperkeratosis and sometimes significant inflammation.

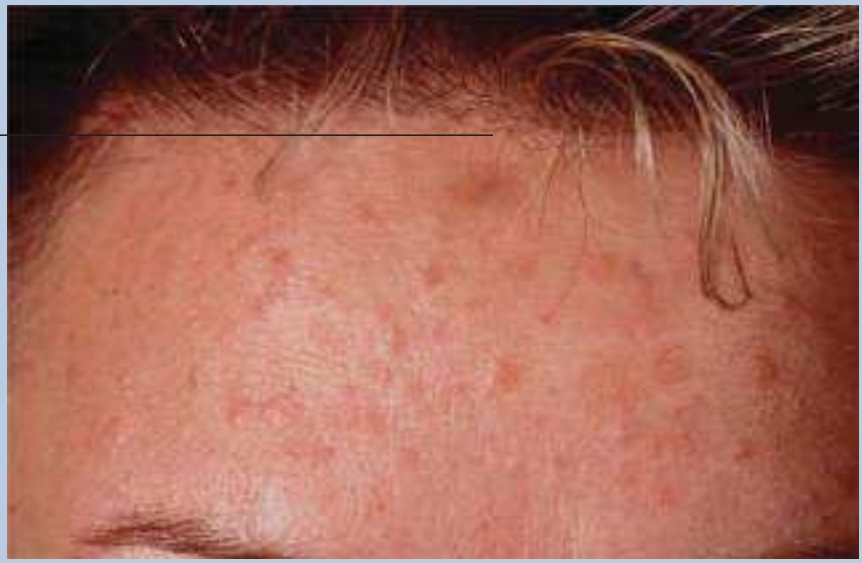


Verruca vulgaris

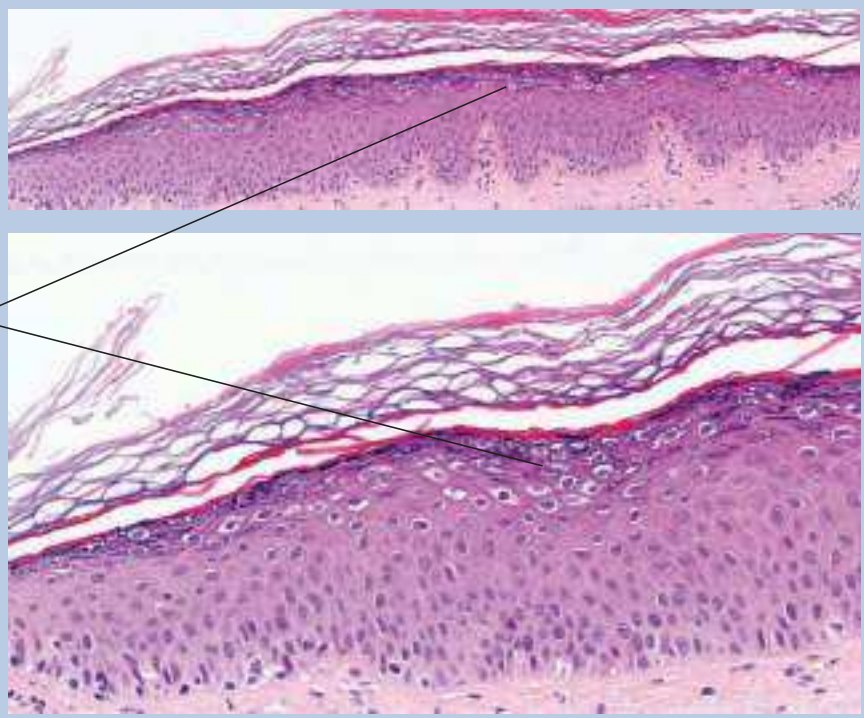


Hi: Hyperkeratosis with focal parakeratosis, intracorneal inclusions of fibrous hemorrhagic exsudate, digitated epidermal hyperplasia with koilocytes and confluent rete ridges, and papillomatosis, hypergranulosis with enlarged keratohyalin granules, dilated vessels in the papillary dermis.

VARIANT: Verruca plana

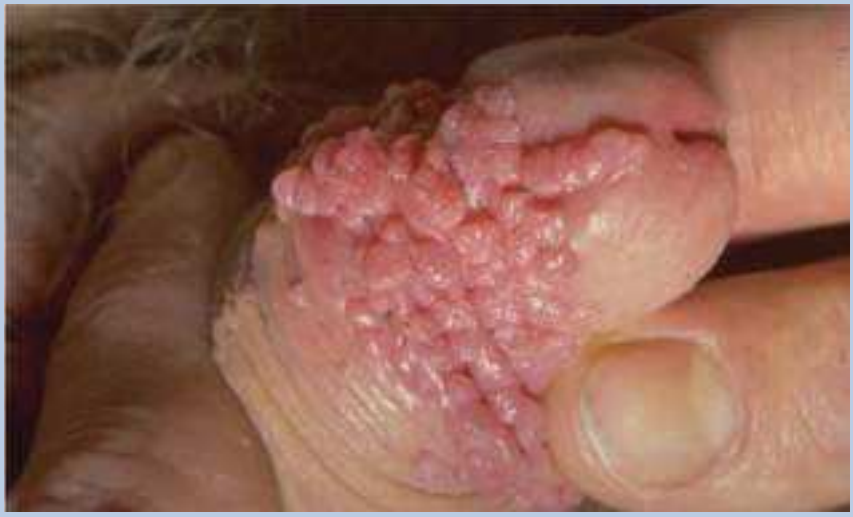


CI: Hyperkeratotic (verruciform) papules.

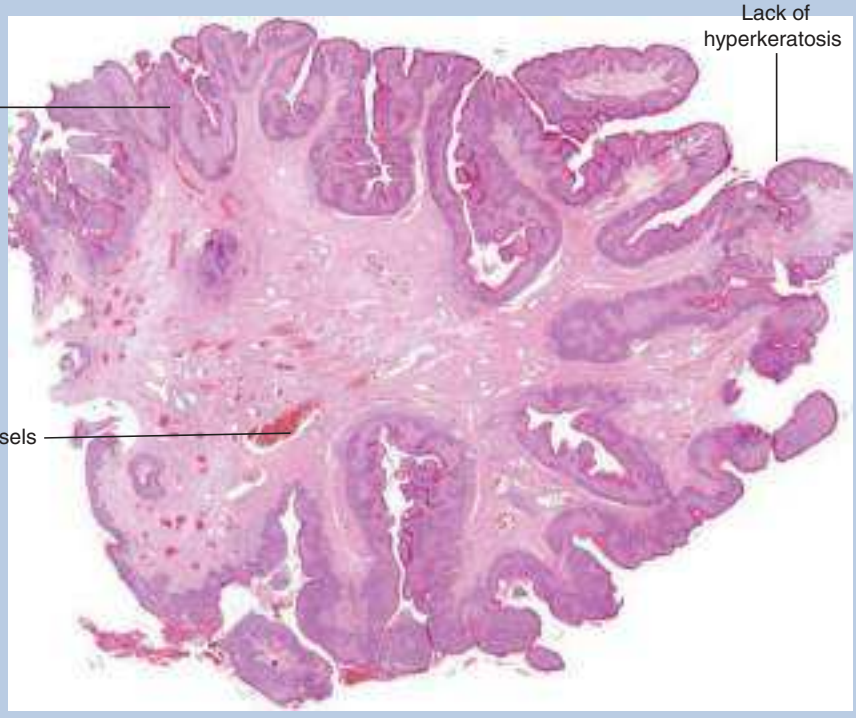


Hi: Hyperkeratosis, slight acanthosis, koilocytes (bird's eye cells) in the granular layer.

VARIANT: Condyloma acuminatum

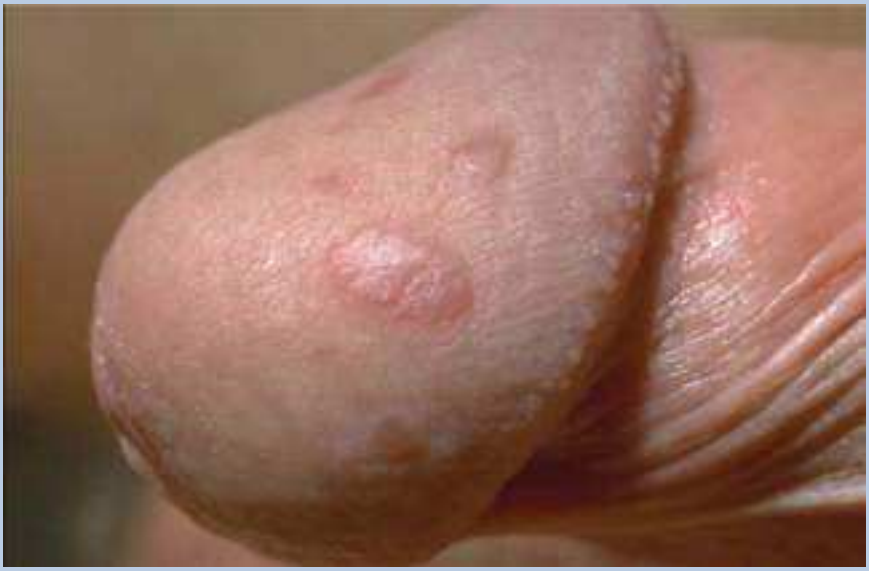


Cl: Papular and verruciforme lesions in anogenital localization.

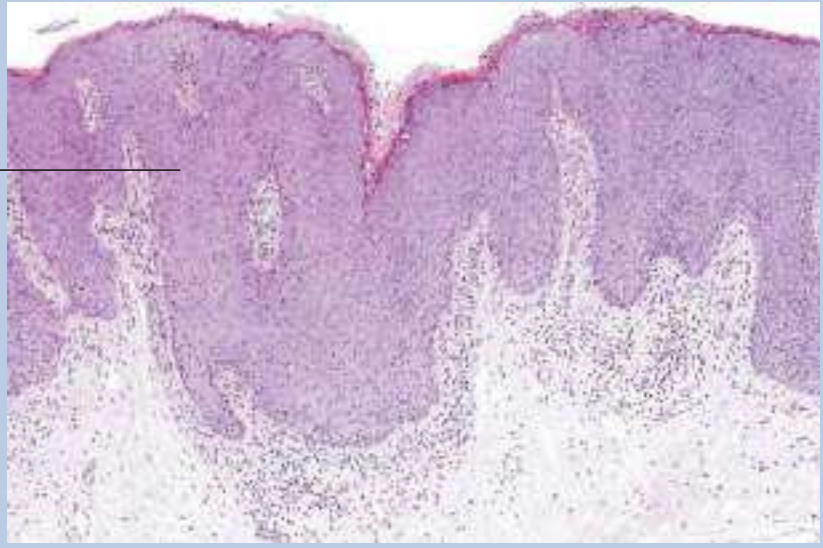


Hi: Acanthopapilloma with only a few koilocytes and focal hyperparakeratosis.

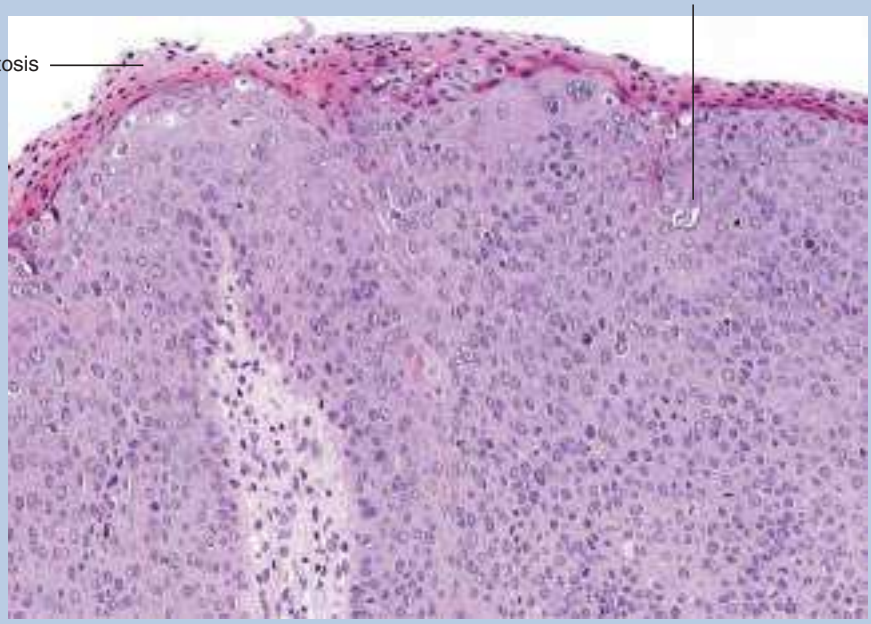
VARIANT: Bowenoid papulosis (Penile or vulvar intraepithelial neoplasia, grade 2 or 3)

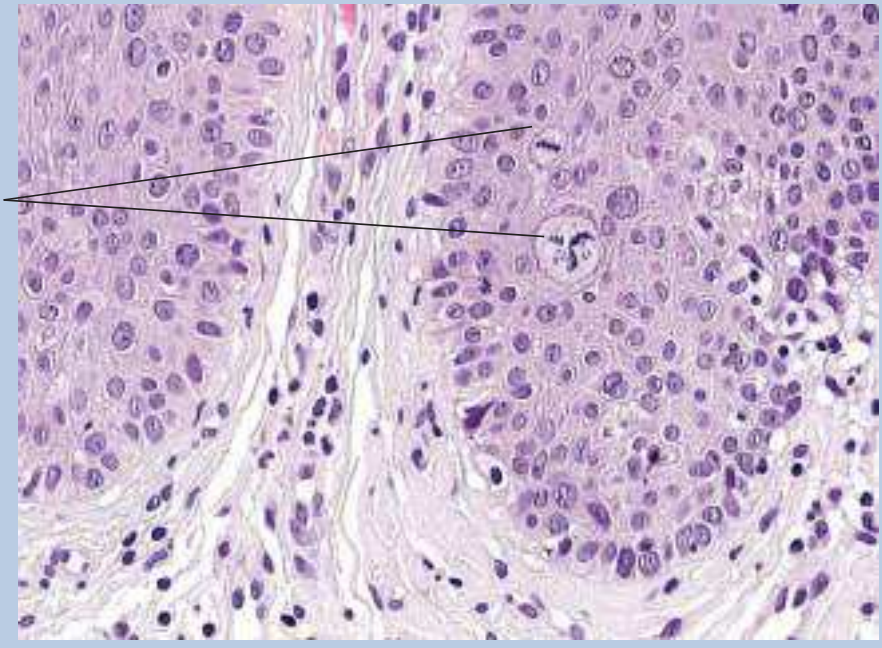


CI: Solitary or confluent flat papular eruptions in anogenital localization.



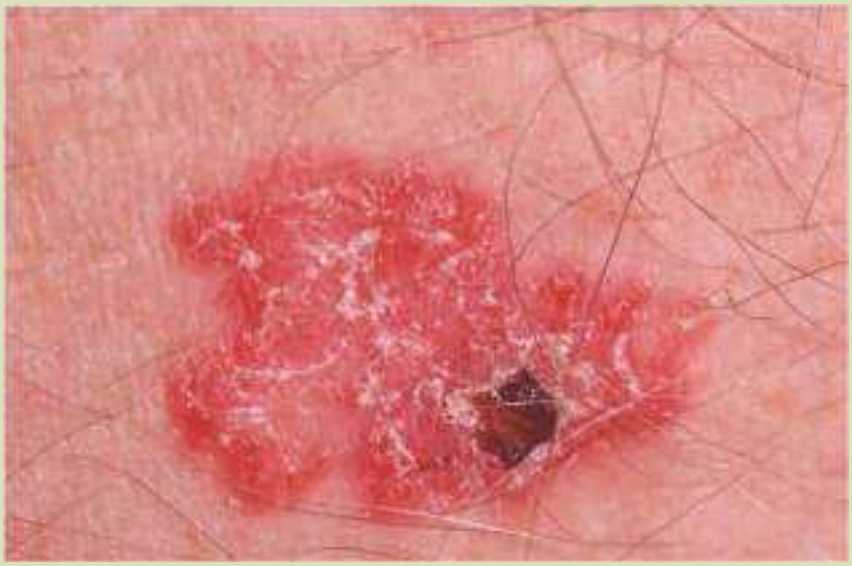
Bowenoid papulosis (Penile or vulvar intraepithelial neoplasia, grade 2 or 3)



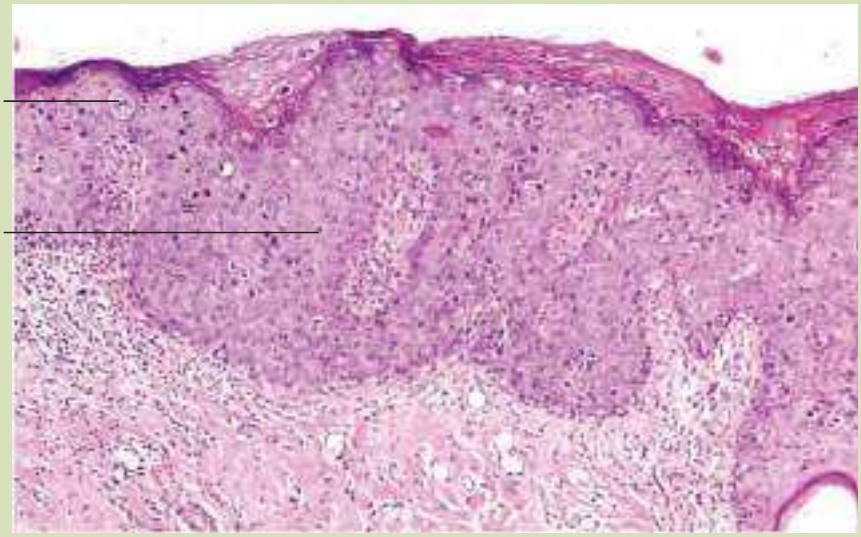


Hi: Atypical epithelial cells with nuclear pleomorphism and mitotic activity.

DIFFERENTIAL DIAGNOSIS: Bowen's disease



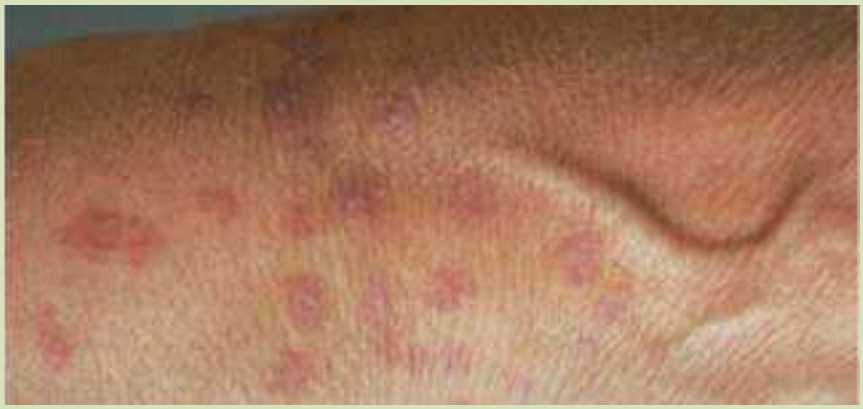
Cl: Circumscribed erythematous plaque with scaling or erosion and crust.



Hi: Full thickness atypia of the epidermis, clumped and pleomorphic nuclei, mitoses. Occasionally associated with HPV infection.

DIFFERENTIAL DIAGNOSIS: Epidermodysplasia verruciformis (Lewandowsky-Lutz)

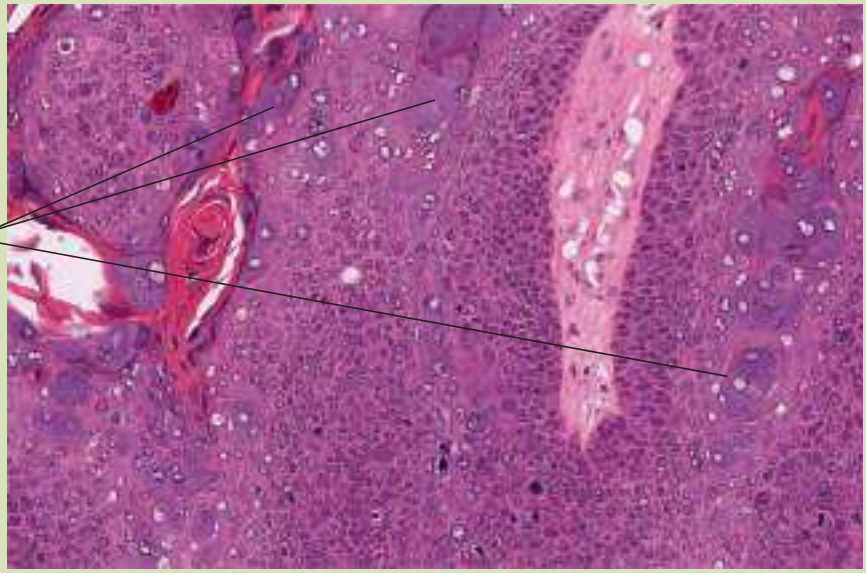
Brownish plaques on the dorsum of one hand



Cl: Genodermatosis, tiny circumscribed lesions, mostly on the extremities.

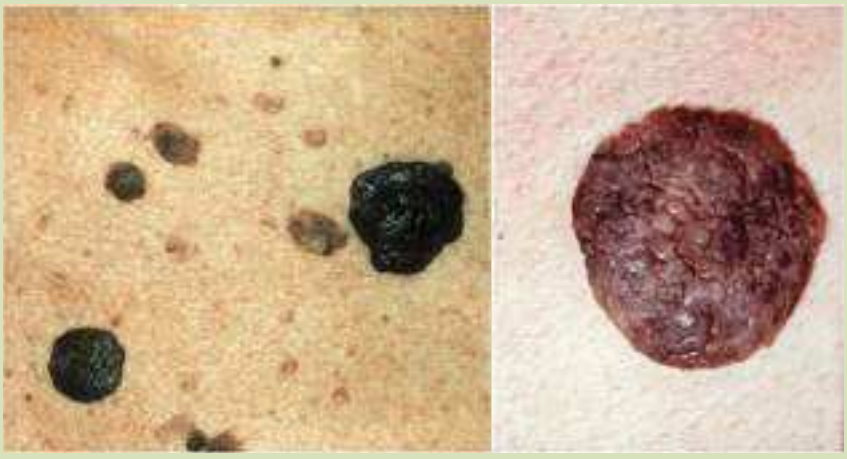
Verruciform acanthosis and papillomatosis

Typical «blue cells»



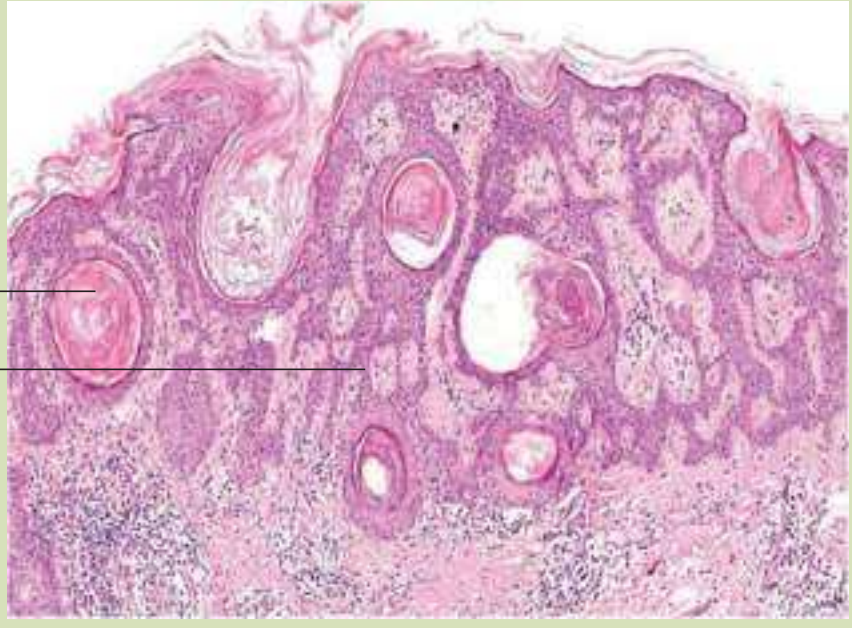
Hi: Intraepidermal enlarged keratinocytes with bluish cytoplasm ("blue cells"). Infection with beta/EV-HPV types.

DIFFERENTIAL DIAGNOSIS: Seborrheic keratosis



Keratotic papules and nodules of variable color

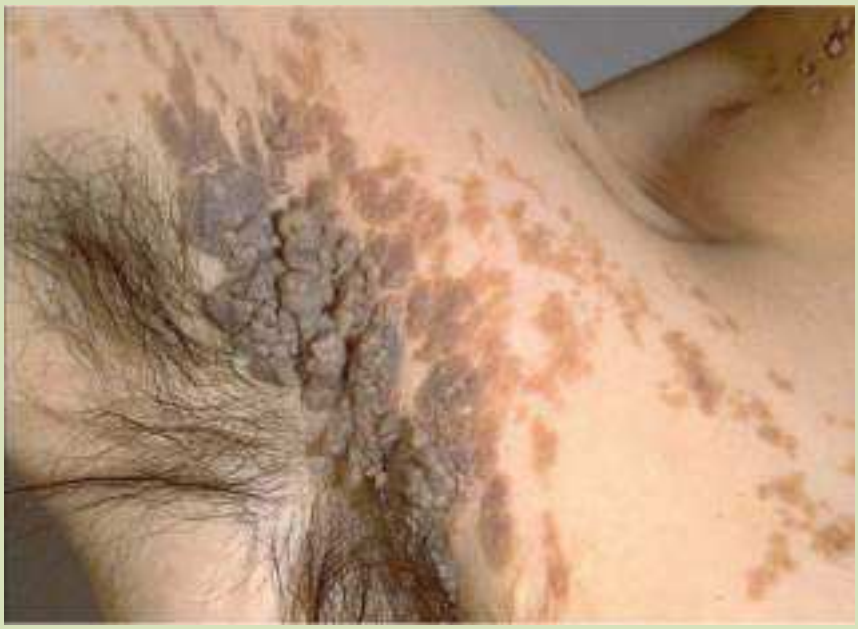
Cl: Various features. Usually brown to black irregularly hyperkeratotic papules or nodules.



Hi: Acanthoma with intraepidermal horn cysts, no koilocytes.

DIFFERENTIAL DIAGNOSIS: Verrucous epidermal nevus

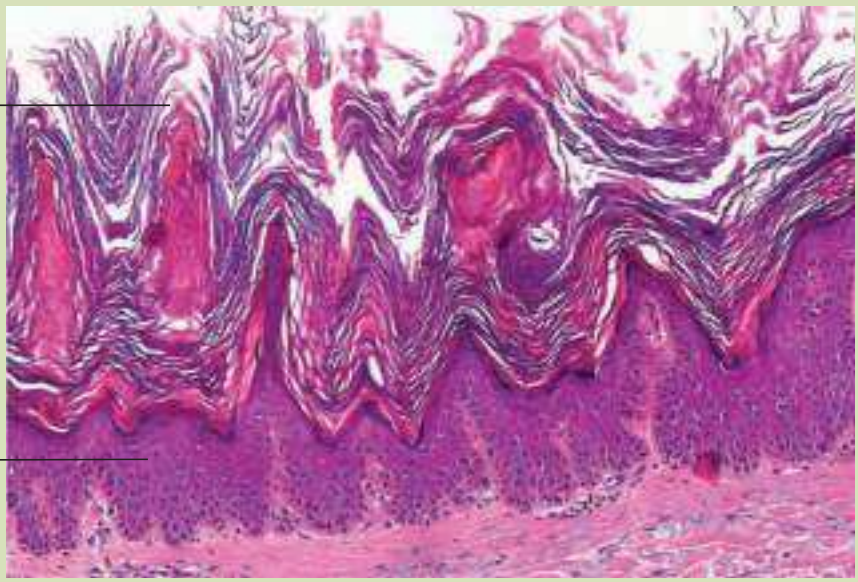
Lesions present since birth or early childhood



Cl: Present since early childhood.

Stratified spires of hyperkeratosis

Acanthosis, papillomatosis; no koilocytes



Hi: Acanthosis, papillomatosis, hyperkeratosis, no koilocytes.

Other Diagnosis

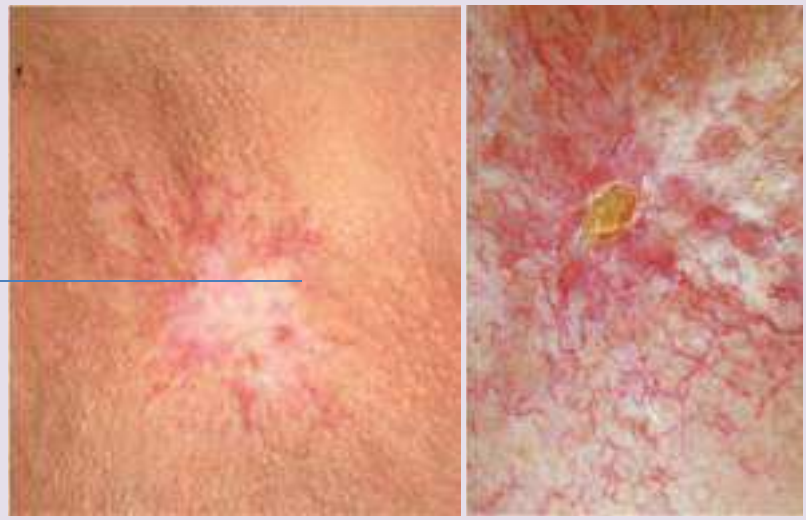
Focal oral hyperplasia (Heck's disease): *large epithelial cells in the upper layers of the oral mucosa. Linked to HPV 13 and 32.*

References

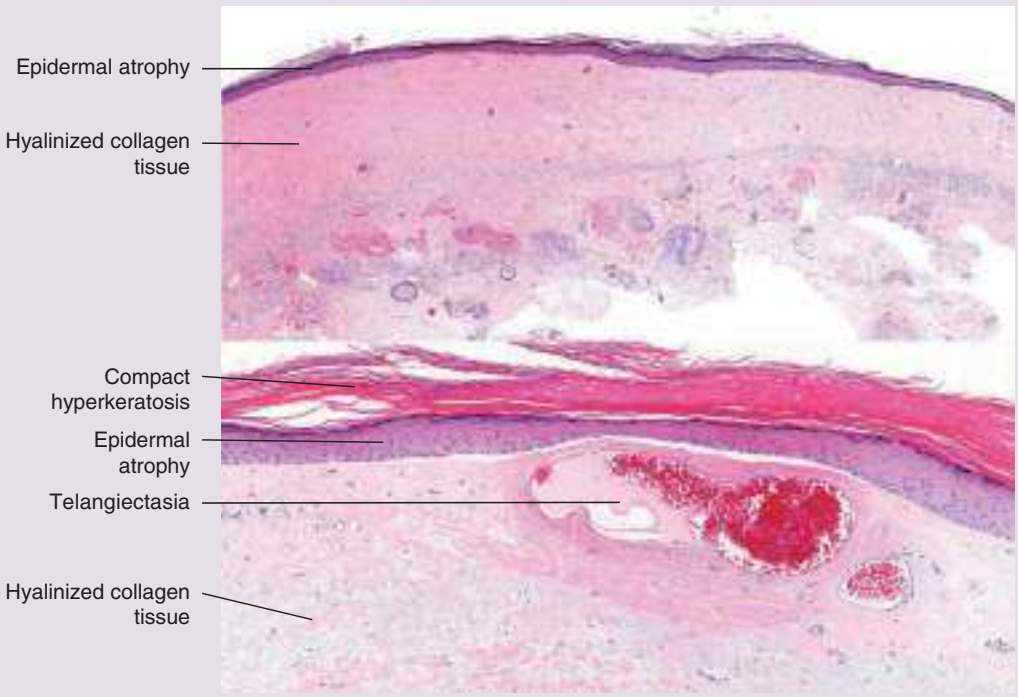
Requena, L. and C. Requena (2010). "[Histopathology of the more common viral skin infections]." *Actas Dermosifiliogr* **101**(3): 201–16.

Spielvogel, R. L., C. Austin, and A. B. Ackerman. (1983). "Inverted follicular keratosis is not a specific keratosis but a verruca vulgaris (or seborrheic keratosis) with squamous eddies." *Am J Dermatopathol* **5**(5): 427–42.

PROTOTYPE: Chronic radiodermatitis

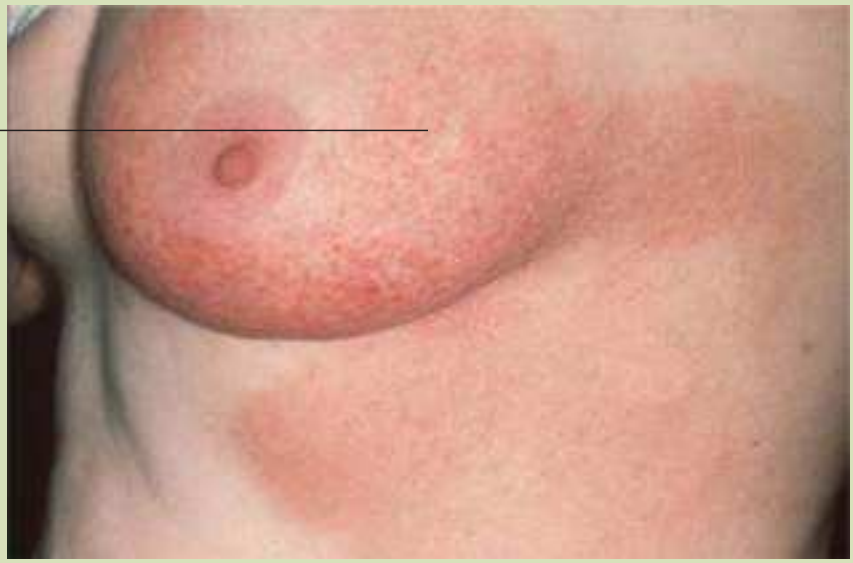


Cl: Years after superficial (soft) or electron beam radiation. The skin shows atrophy with loss of rete ridges, hyper- and depigmentation and telangiectasias. This feature also is referred to as poikiloderma.

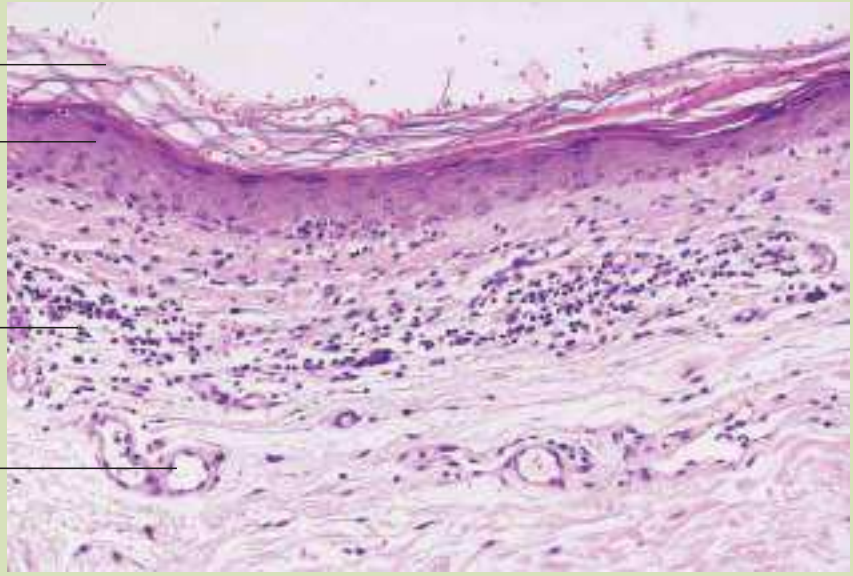


Hi: Atrophy of the epidermis, basal hyperpigmentation, hyalinized collagen tissue, telangiectatic vessels in the upper dermis, and melanophages.

DIFFERENTIAL DIAGNOSIS: Poikiloderma vasculare atrophicans Jacobi

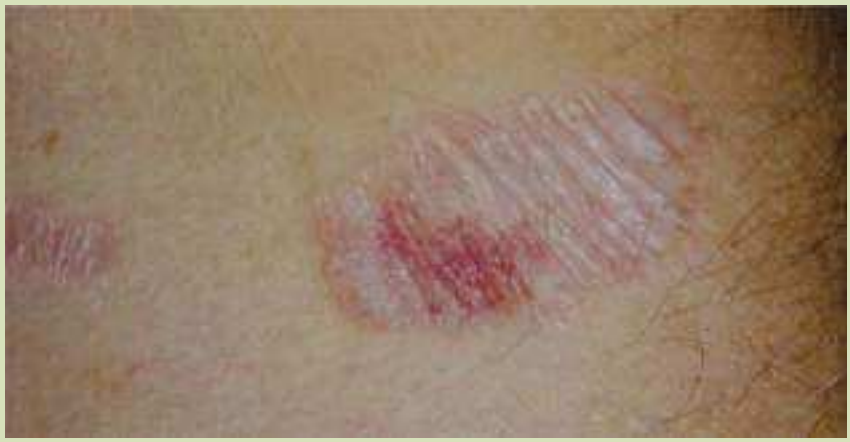


Cl: Mottled slightly scaling erythematous patches.

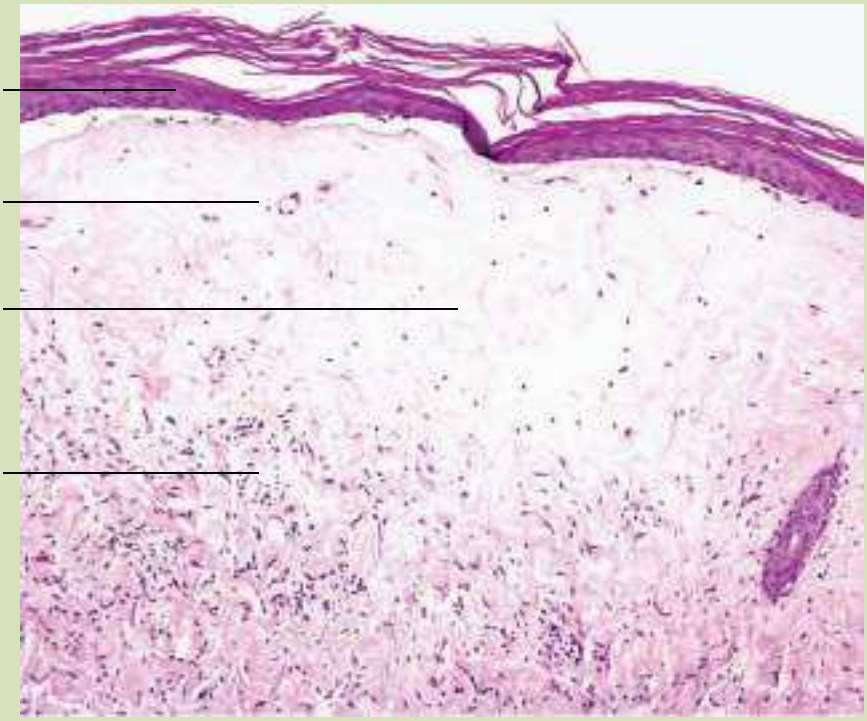


Hi: Subtle lymphocytic infiltrate. No hyalinized dermal collagen tissue.

DIFFERENTIAL DIAGNOSIS: Lichen sclerosus et atrophicus

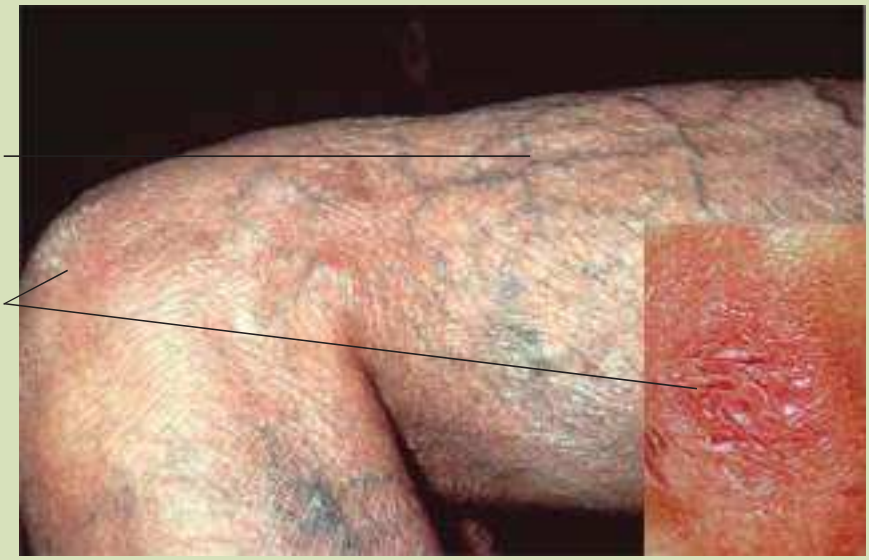


Cl: Whitish atrophic plaques; occasional intracutaneous bleeding, especially in the genital area.

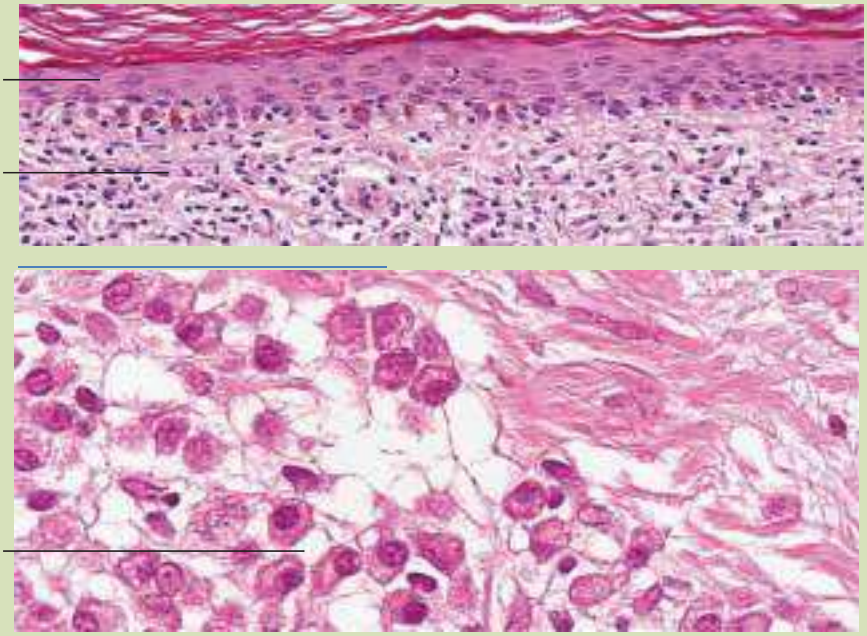


Hi: Initially and at the margins of the lesions there is a band-like lichenoid infiltrate, very similar to lichen planus (*see* page 110). Later there is a tricolor pattern in the center: atrophy of the (red) epidermis with hyperkeratosis, pale (white) hyalinized upper dermis with (blue) band-like infiltrate beneath the hyaline zone.

DIFFERENTIAL DIAGNOSIS: Acrodermatitis chronica atrophicans



CI: Atrophy of the skin with translucent superficial vessels.



Hi: Perivascular infiltrates with numerous plasma cells. Atrophy of the epidermis and dermis in fully developed stage.

Other Diagnosis

Morphea: *Thickened collagen bundles, broadened dermis and subcutaneous septa. Sweat glands engulfed by compact collagen bundles (see* Chapter 4, Sclerosis, page 205*).*

Scar*: Fibrotic collagen tissue with loss of elastic fibers.*

CHAPTER 3
Dermal–epidermal Junction (Interface)

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.
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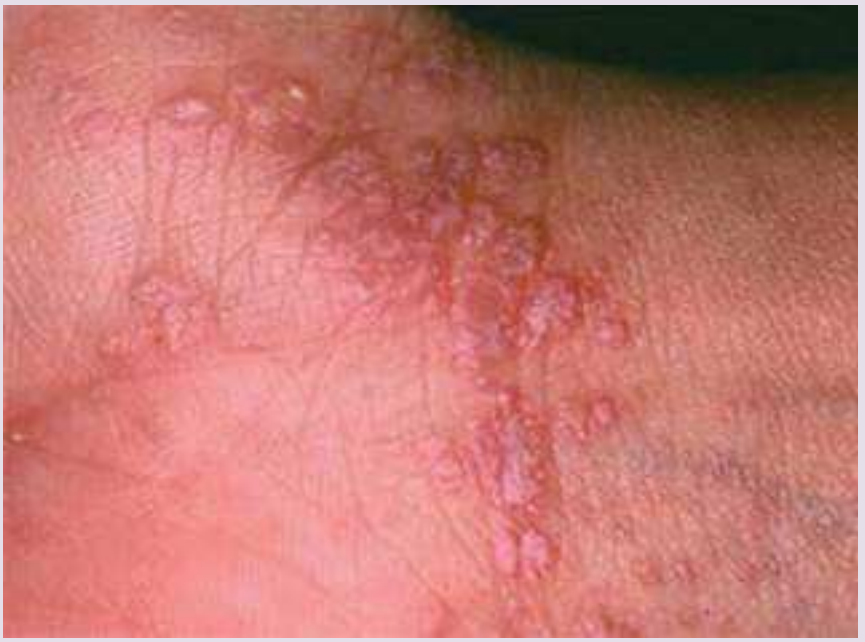
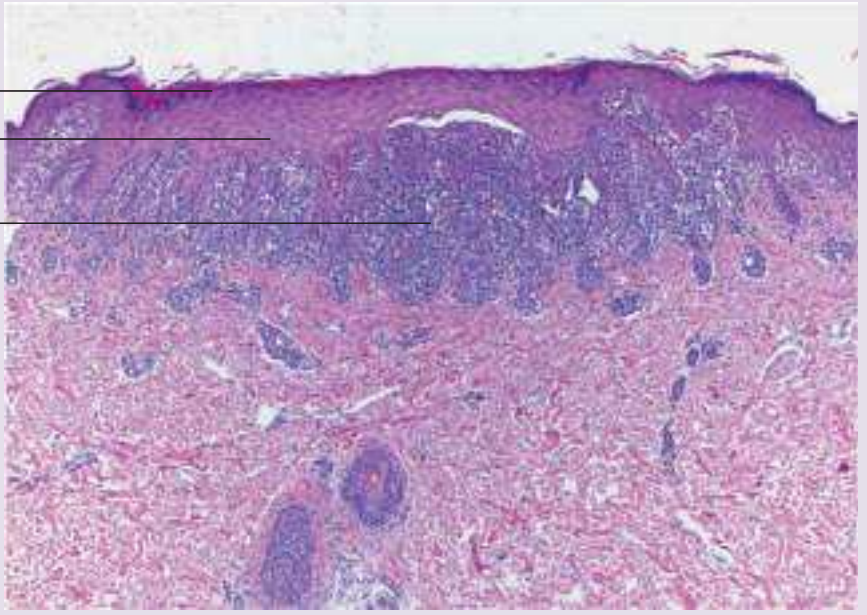
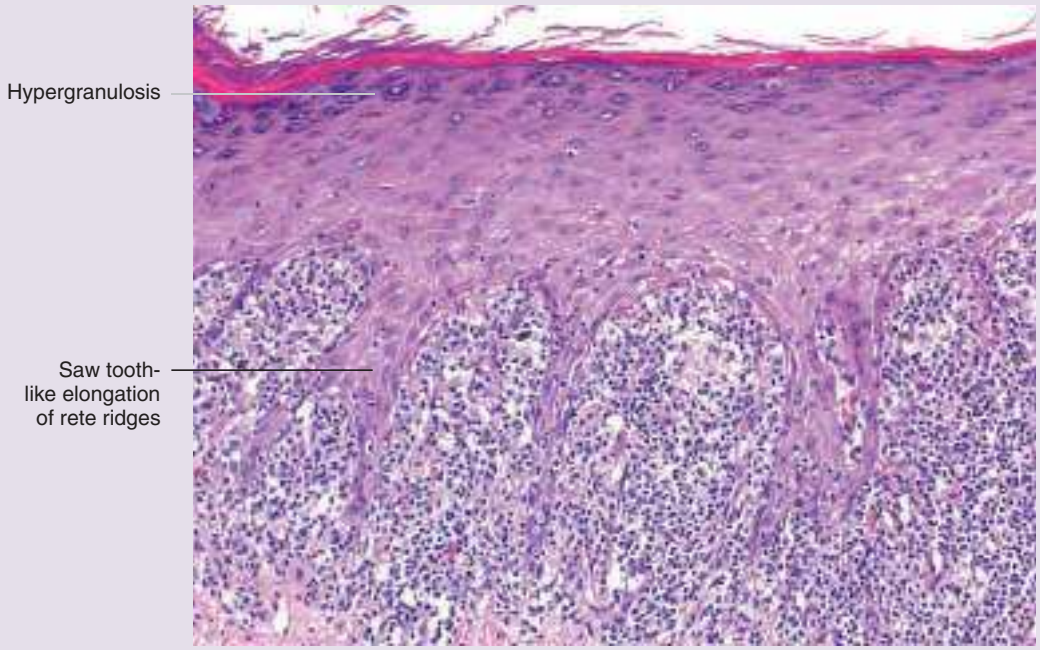
PROTOTYPE: Lichen (ruber) planus

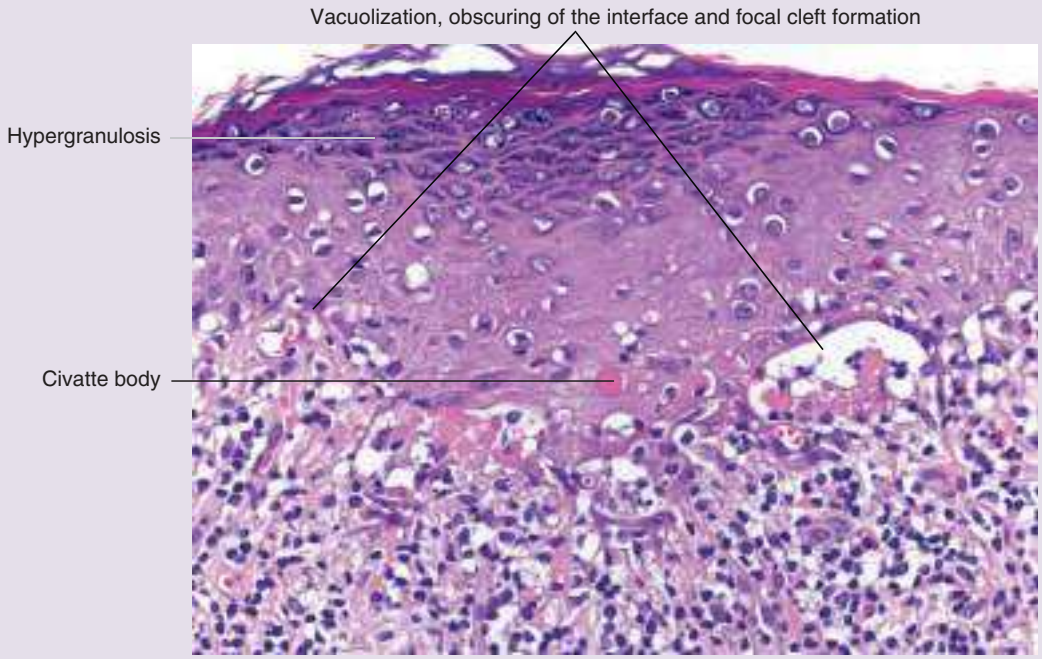


CI: Pruritic polygonal violet papules, mucosa with Wickham striae.



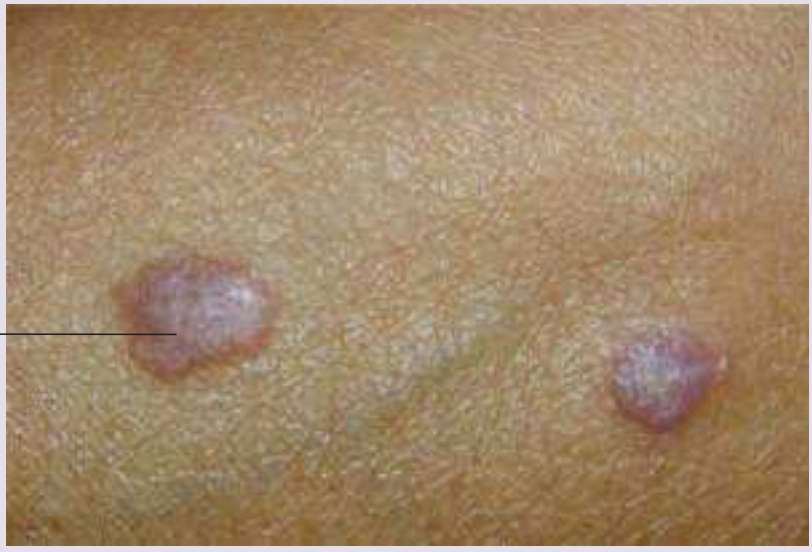
Lichen planus



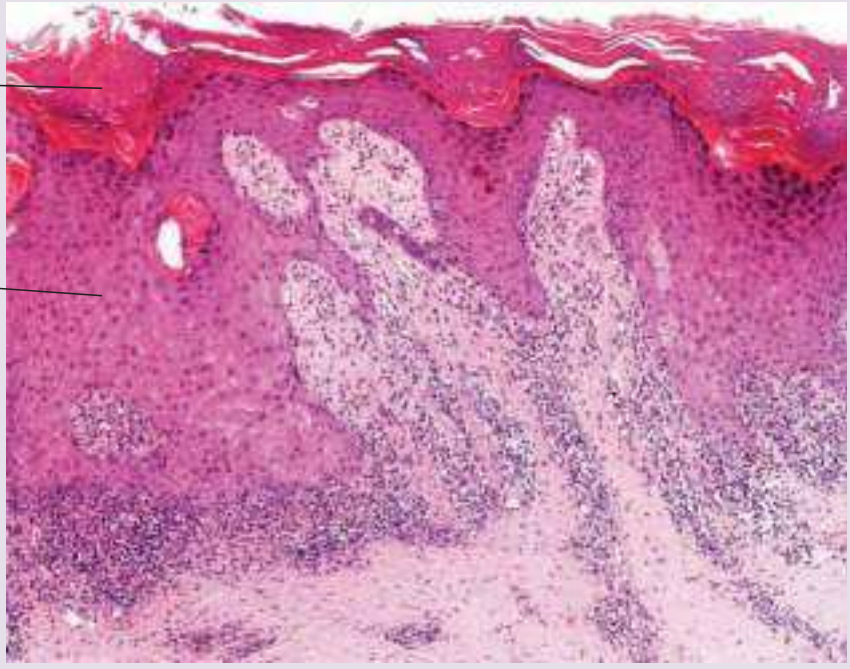


Hi: Interface dermatitis, acanthosis, V-shaped hypergranulosis, hyperkeratosis, subepidermal band-like lymphocytic infiltrate.

VARIANT: Hypertrophic (syn: verrucous) lichen planus

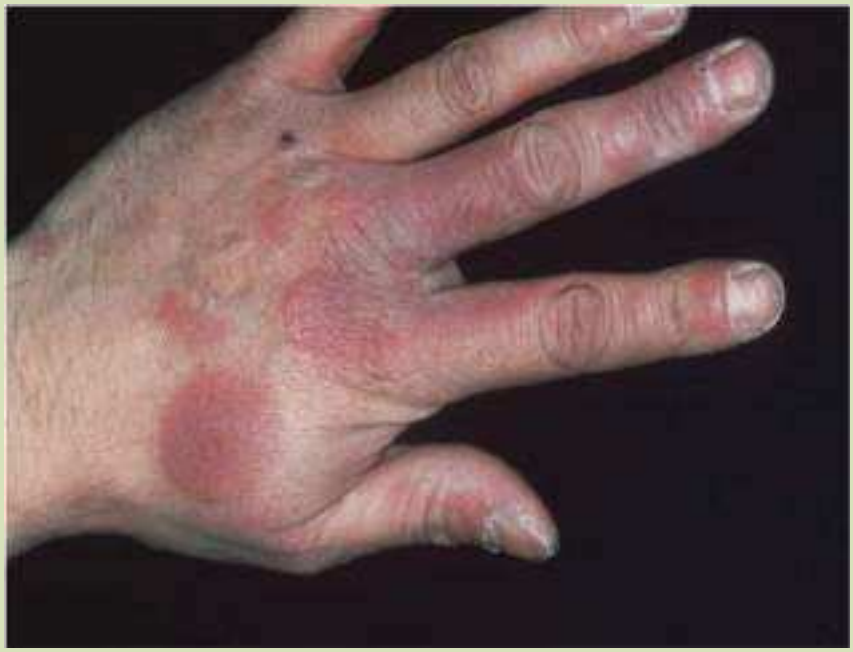


Cl: Verrucous papules.

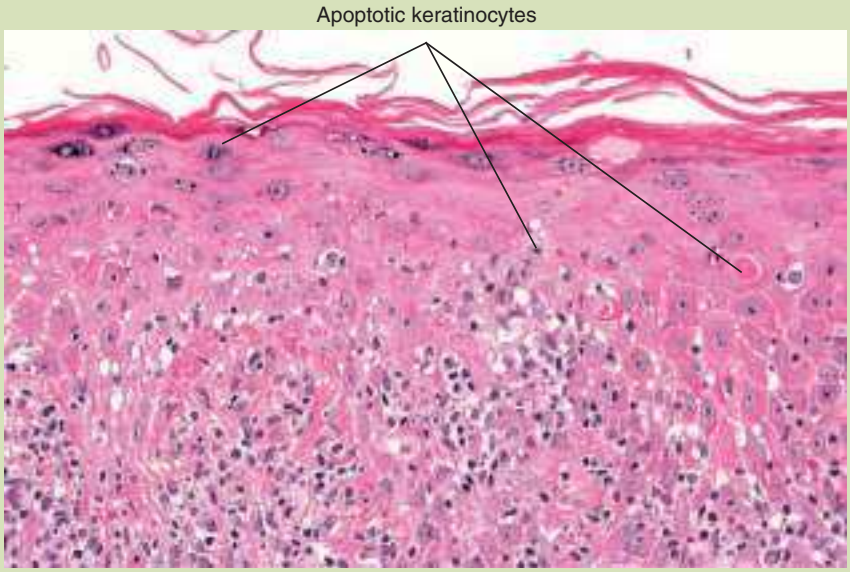


Hi: Orthohyperkeratosis, pseudocarcinomatous hyperplasia, interface lymphocytic infiltrate.

DIFFERENTIAL DIAGNOSIS: Lichenoid drug reaction

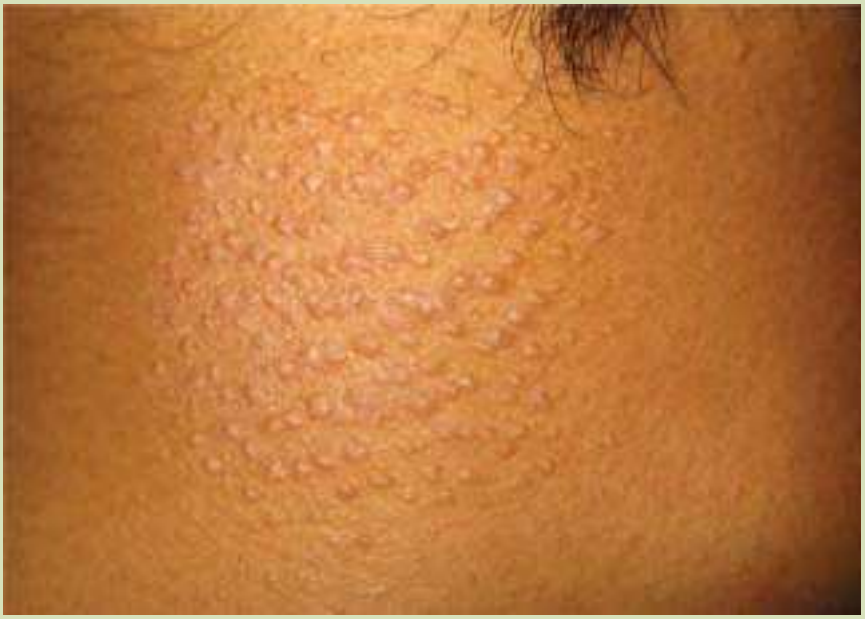


Cl: Disseminated maculo-papular lesions.

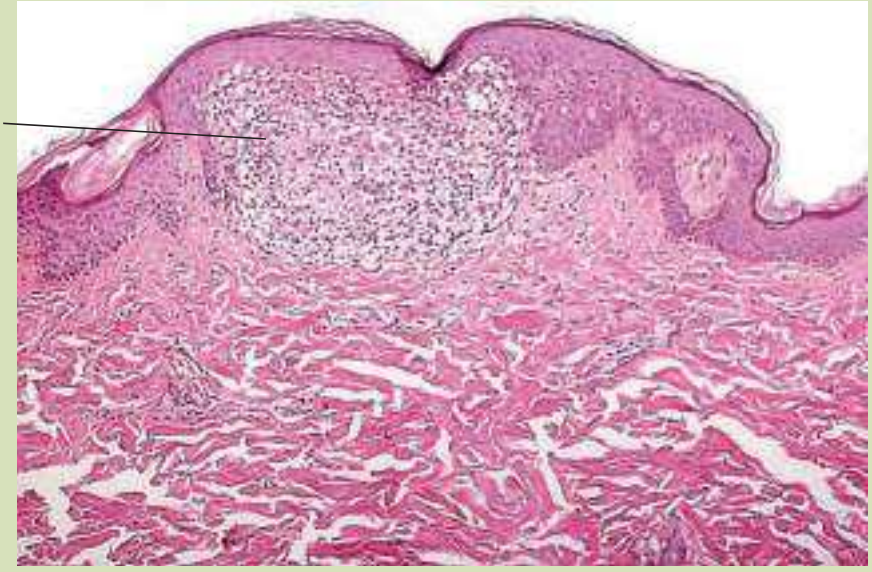


Hi: Very similar to lichen planus, but usually many eosinophils and apoptotic keratinocytes, occasionally parakeratosis.

DIFFERENTIAL DIAGNOSIS: Lichen nitidus

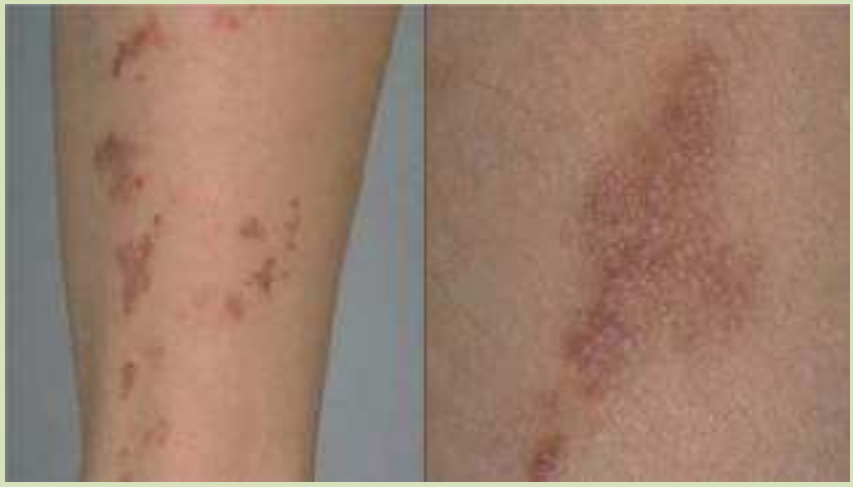


Cl: Group of tiny papules.

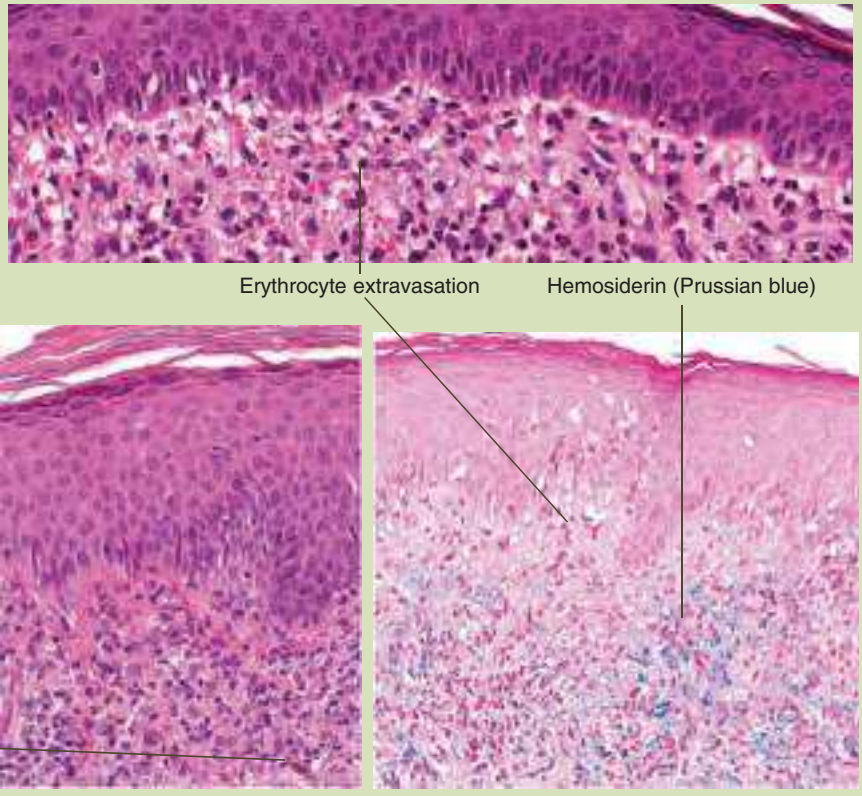


Hi: Circumscribed nodular lymphohistiocytic infiltrate in the upper dermis.

DIFFERENTIAL DIAGNOSIS: Lichen aureus

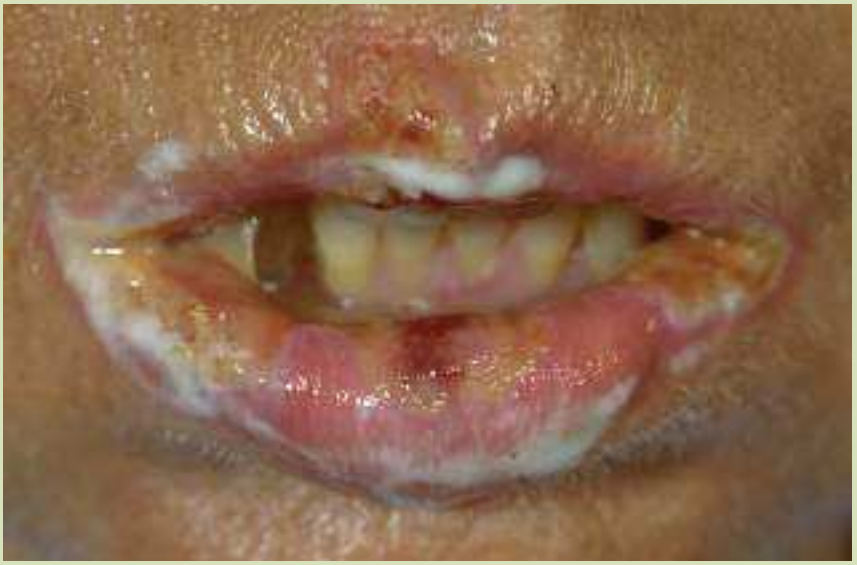


Cl: *Red-brown* circumscribed lesion.

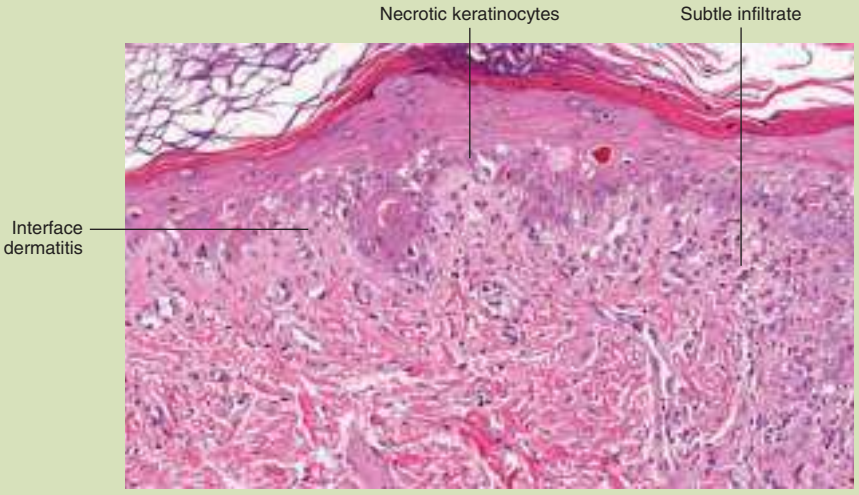


Hi: Band-like infiltrate, less pronounced vacuolization, extravasated erythrocytes, hemosiderin deposits.

DIFFERENTIAL DIAGNOSIS: Acute graft-versus-host reaction

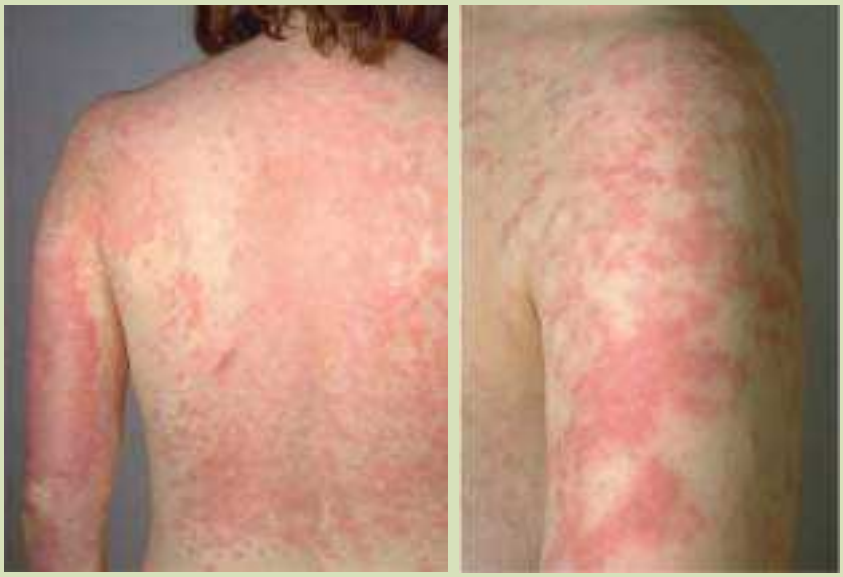


Cl: Massive necrolytic changes of the oral mucosa, similar to drug induced toxic epidermal necrolysis (TEN, *see* page 78) in a patient with prior bone marrow transplantation.

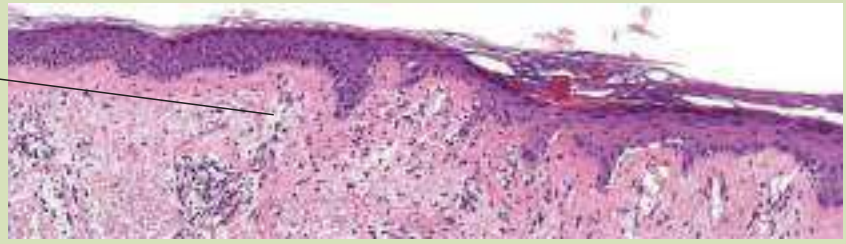


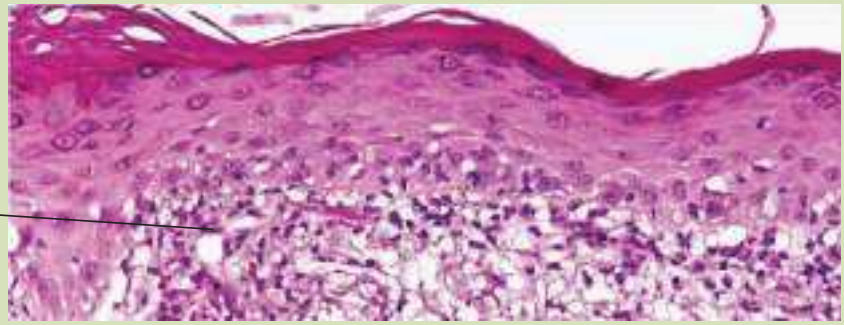
Hi: Thinned epidermis, numerous apoptotic keratinocytes, satellite cell necrosis, vacuolar change at the dermal–epidermal junction, less intense lymphocytic infiltrate.

DIFFERENTIAL DIAGNOSIS: Lupus erythematosus, acute systemic

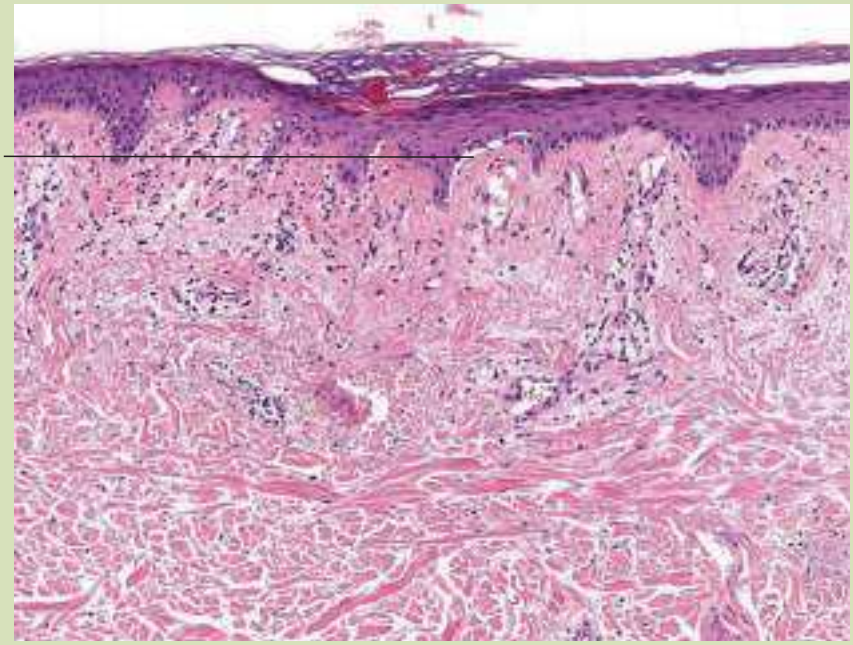


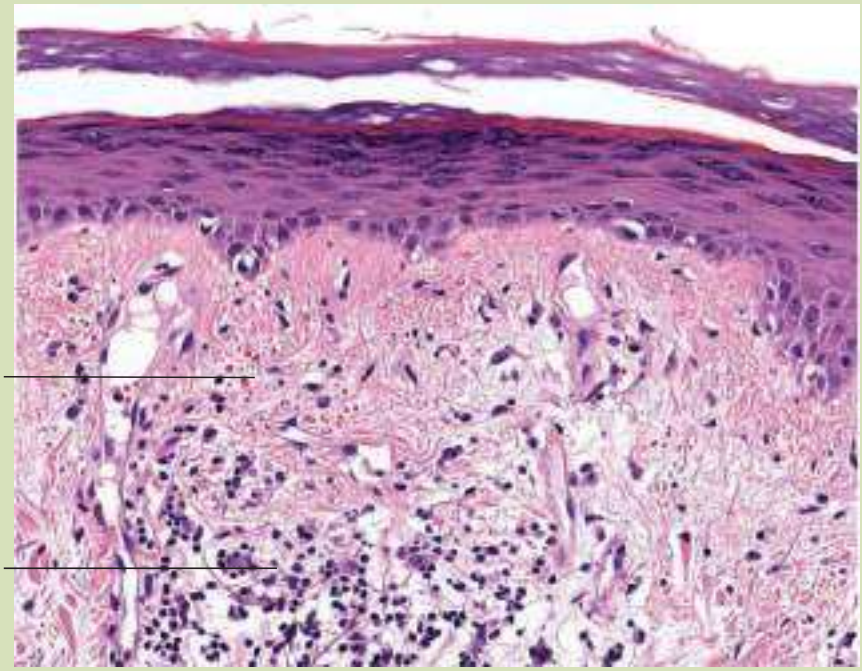
CI: Patchy bizarre and confluent erythemas.





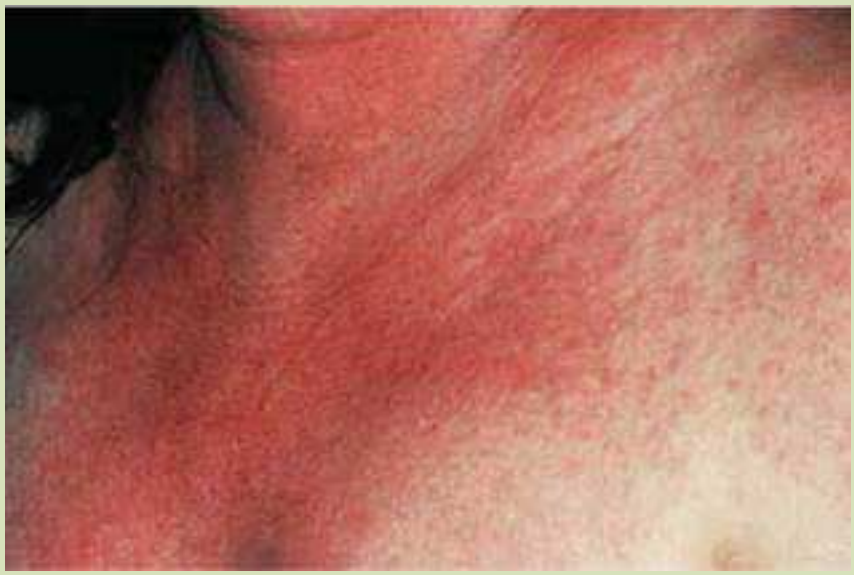
Lupus erythematosus



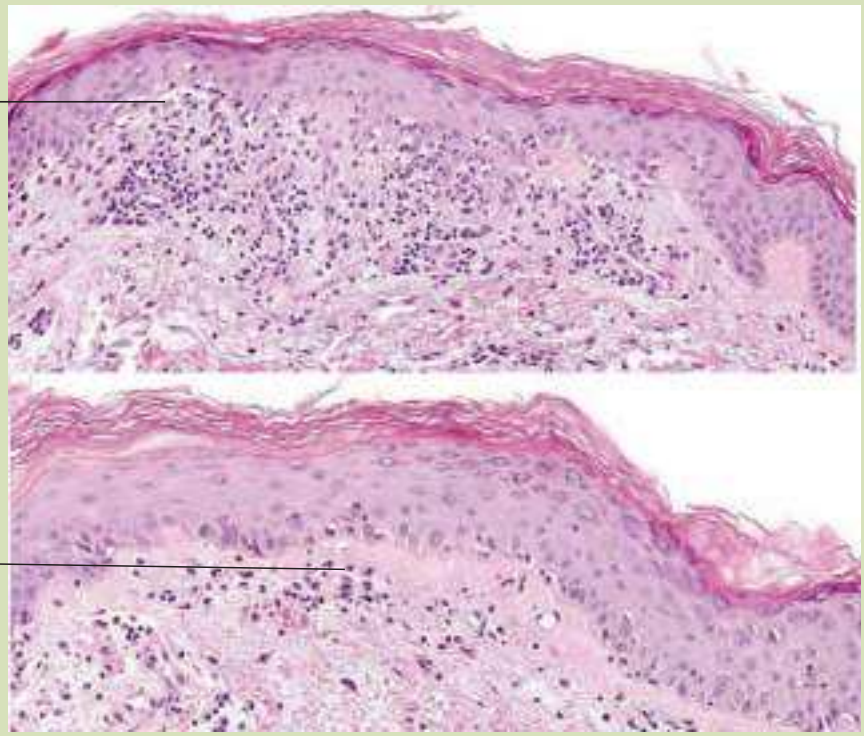


Hi: Lymphocytic interface dermatitis, often with neutrophils, nuclear dust, subtle vasculitis.

DIFFERENTIAL DIAGNOSIS: Dermatomyositis

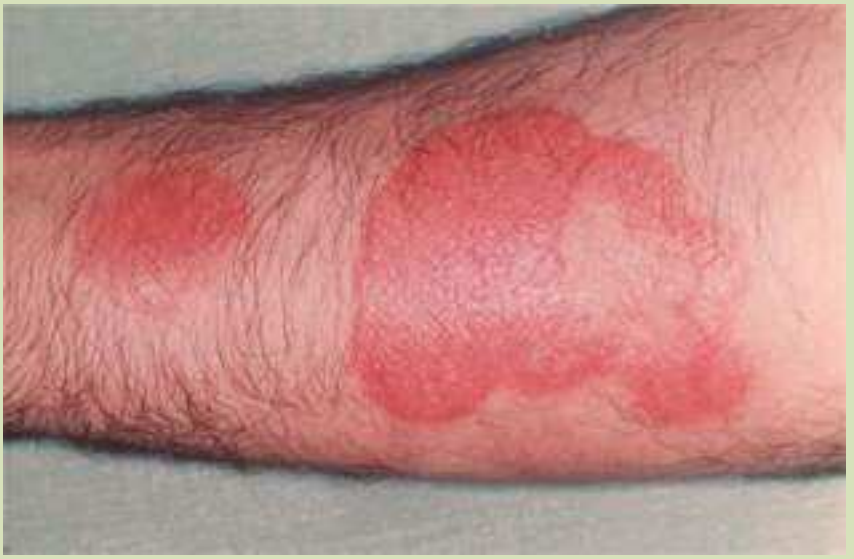


CI: Erythema or poikilodermatic lesions or Gottron papules on fingers.

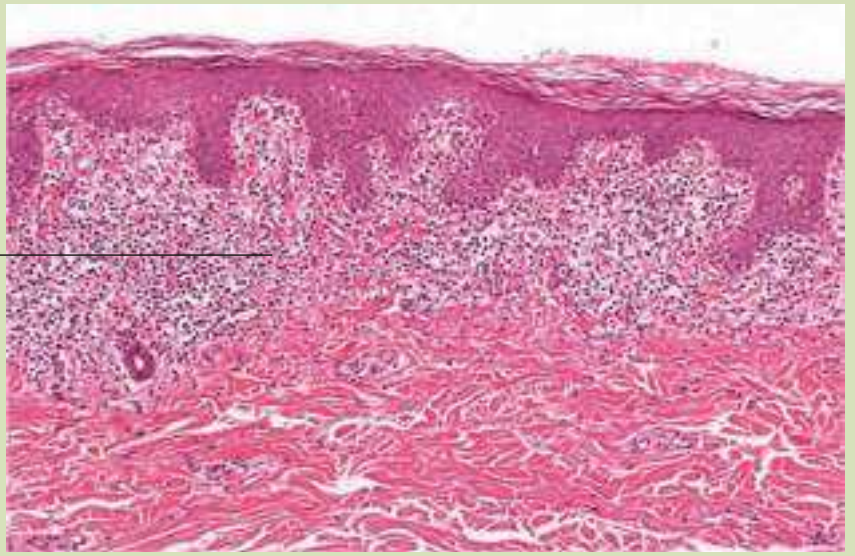


Hi: Interface dermatitis, deposits of mucin in the upper dermis, sparse perivascular infiltrate.

DIFFERENTIAL DIAGNOSIS: Mycosis fungoides (early stage)



Cl: Longstanding patches.



Hi: Lining-up of atypical lymphocytes along the dermal–epidermal junction, rather subtle epidermotropism without spongiosis. Infiltrate may be band-like, but rarely with associated necrotic keratinocytes.

Other Diagnosis

Lichen planus-like keratosis: *Solitary lesion. Predilection site: chest. Histology is identical to lichen planus, in the margins often hyperpigmented elongated rete ridges.*

Keratosis lichenoides chronica*: Hyperkeratotic flat papules, preferentially on the extremities, often in linear arrangement. Histology shows acanthosis, orthohyperkeratosis, interface dermatitis, lichenoid infiltrate in the upper dermis.*

Pityriasis lichenoides et varioliformis acuta (PLEVA): *(see* Chapter 2, Necrotic, page 84*): Disseminated red scaly maculo-papular lesions. Focal vacuolization, spongiosis and hyperparakeratosis with inclusions of neutrophils, wedge-shaped superficial and deep lymphocytic infiltrate.*

Fixed drug eruption **(***see* Chapter 2, Edema, page 81**):** *Usually solitary circumscribed brownish patch, recurrence after intake of the drug. Histologically there is incontinence of pigment. Apoptotic keratinocytes in all epidermal layers, eosinophils and occasionally neutrophils.*

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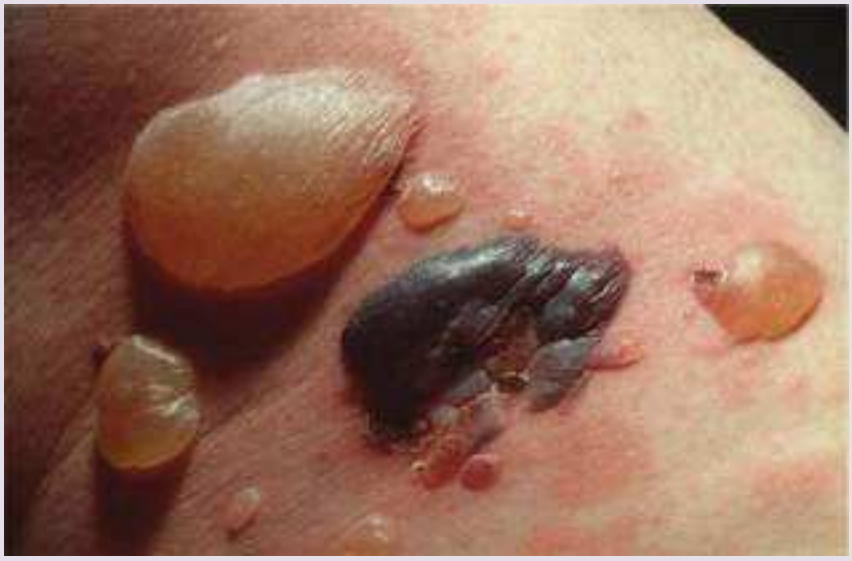
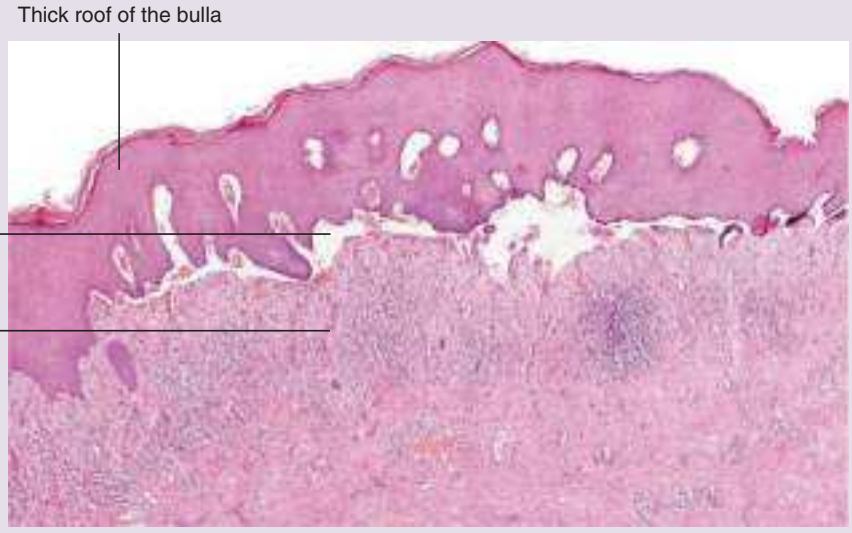
PROTOTYPE: Bullous pemphigoid

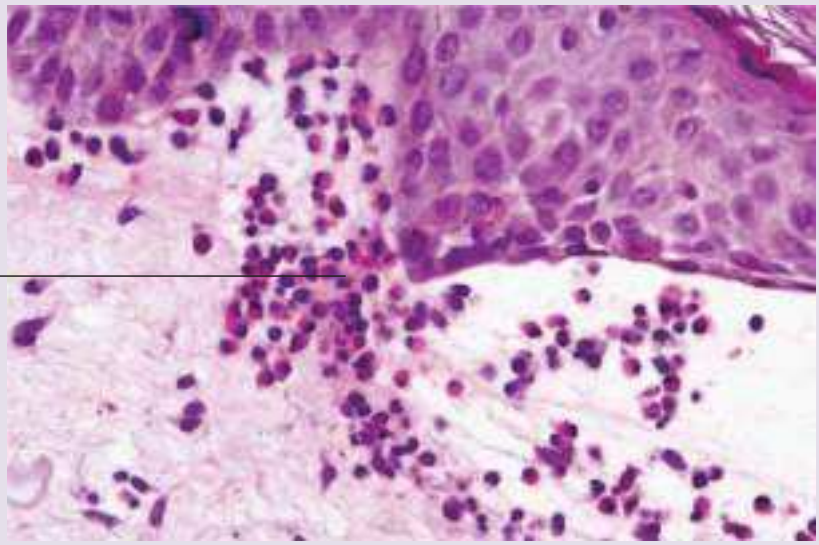


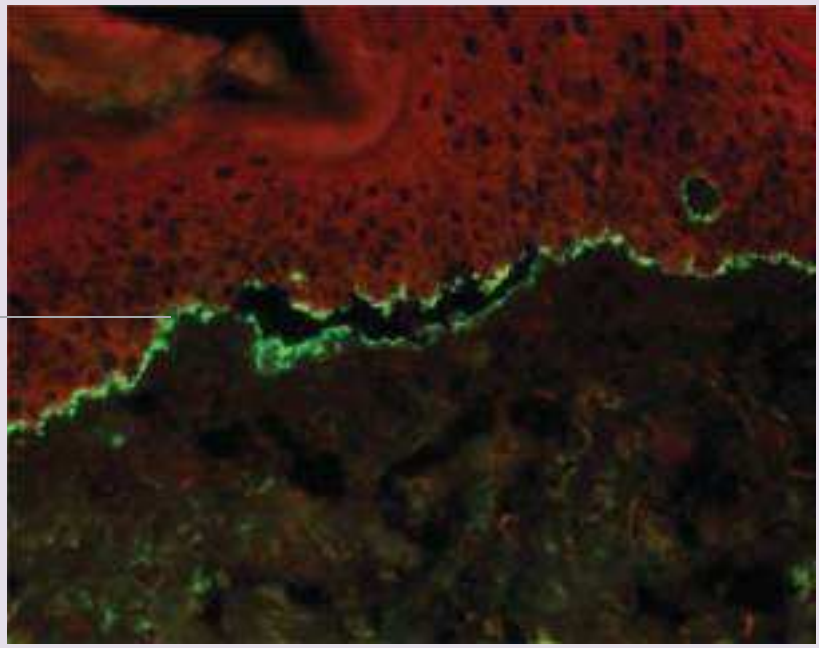
Cl: Initially erythematous and urticarial patches and plaques (prebullous stage), marked pruritus; later tense, sometimes hemorrhagic blisters; mucosal involvement possible.



Hi: Clear-cut cleft or bulla at the dermal-epidermal junction. Associated eosinophilic infiltrate.

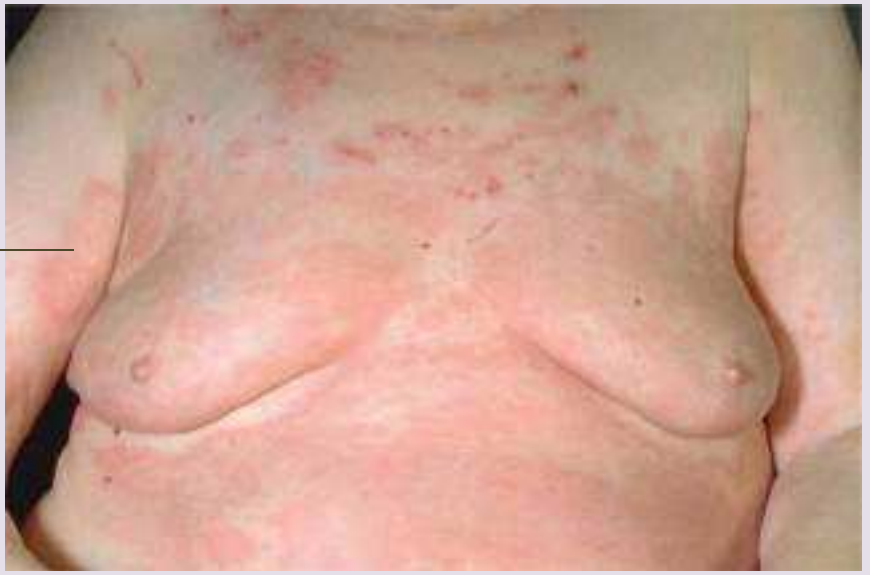
Bullous pemphigoid

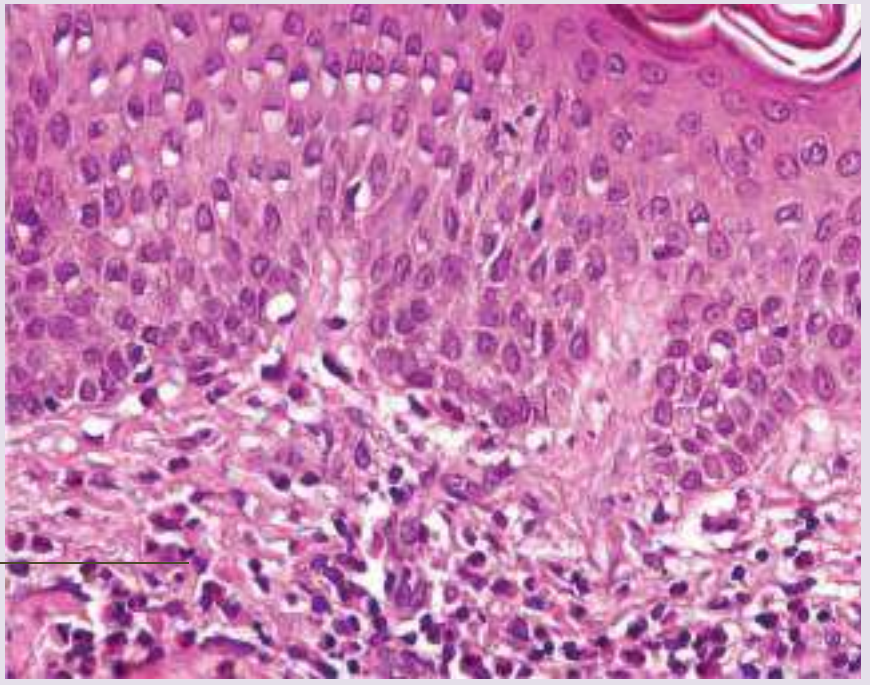




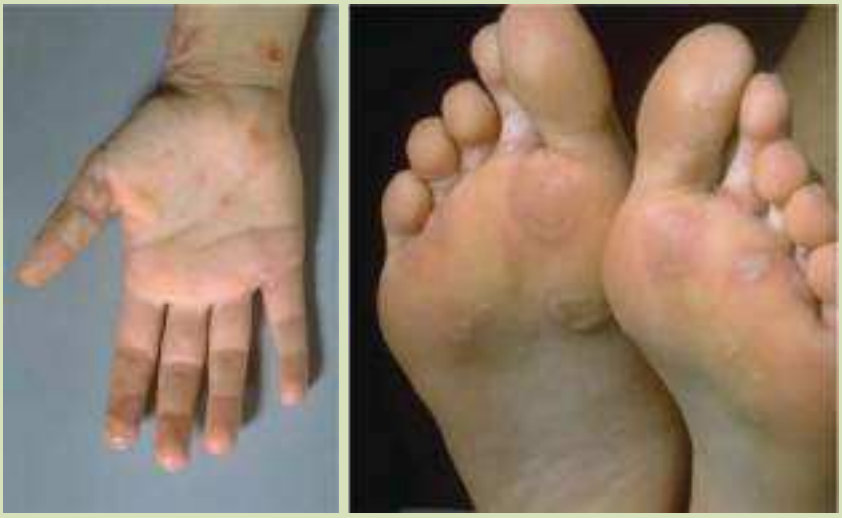
Hi: Subepidermal blister, eosinophils and neutrophils in the blister cavity and in the dermal infiltrate, no necrotic keratinocytes, no significant edema in the dermis, admixture of plasma cells. Subepidermal blistering is lacking in the prebullous state. Immunohistochemistry: Linear deposits of C3d at the junctional zone. Direct immunofluorescence: Linear IgG and C3 deposits at the junctional zone of adjacent non-lesional skin or mucosa.

Bullous pemphigoid, early urticarial stage

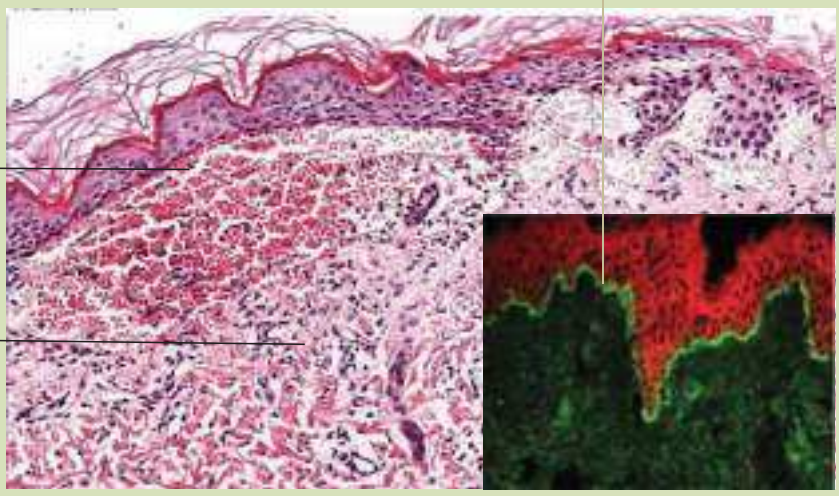




DIFFERENTIAL DIAGNOSIS: Autoimmune bullous disorders: Epidermolysis bullosa

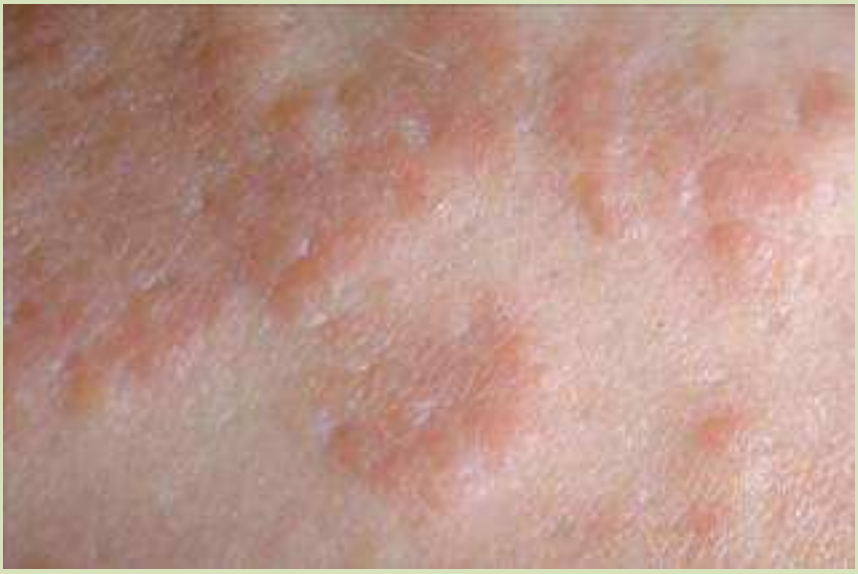


Cl: Epidermolysis bullosa simplex (Weber-Cockayne). Variable clinical features with mechanobullous blister formation.

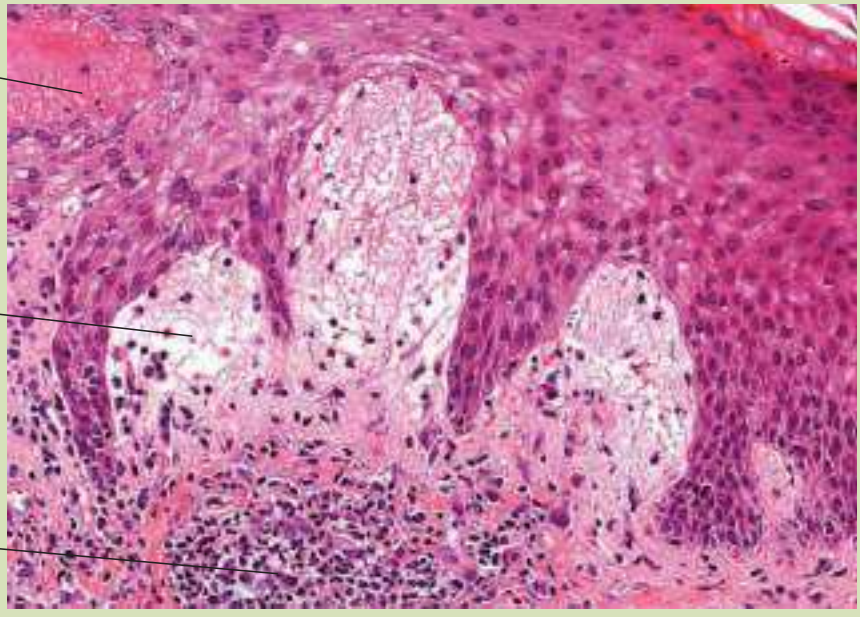


Hi: Epidermolysis bullosa acquisita. Few inflammatory cells, split skin test and collagen IV staining (inset): antibodies on the roof of the blister.

DIFFERENTIAL DIAGNOSIS: Pemphigoid gestationis

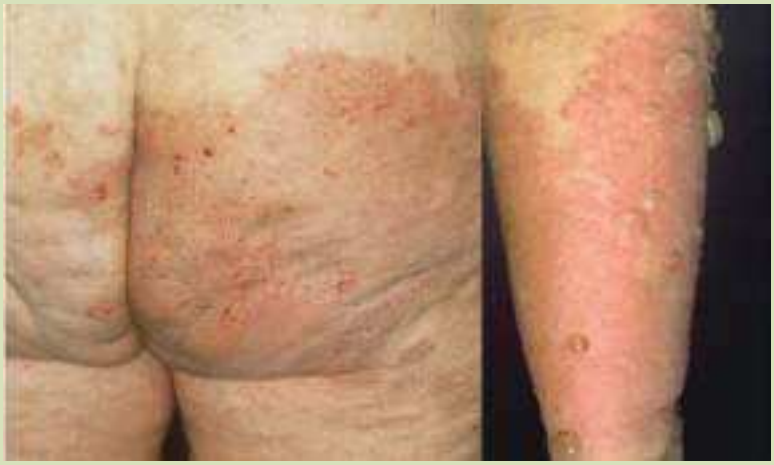


Cl: Pruritic papules and plaques, usually starting in the 3rd trimester of gestation in the abdominal region at any time during pregnancy or thereafter.

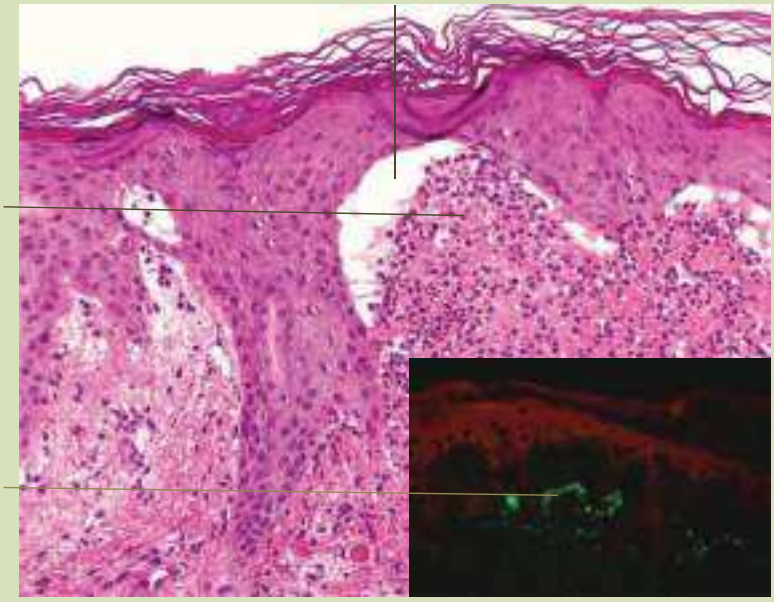


Hi: Histology and DIF identical to bullous pemphigoid.

DIFFERENTIAL DIAGNOSIS: Dermatitis herpetiformis (Duhring's disease)



CI: Polymorphous (eczematous papules, plaques and vesicles) itching lesions, preferentially on elbows, knees and buttocks.



Hi: Papillary microabscesses of neutrophils (and eosinophils). DIF (inset): Granular IgA deposits at the junctional zone.

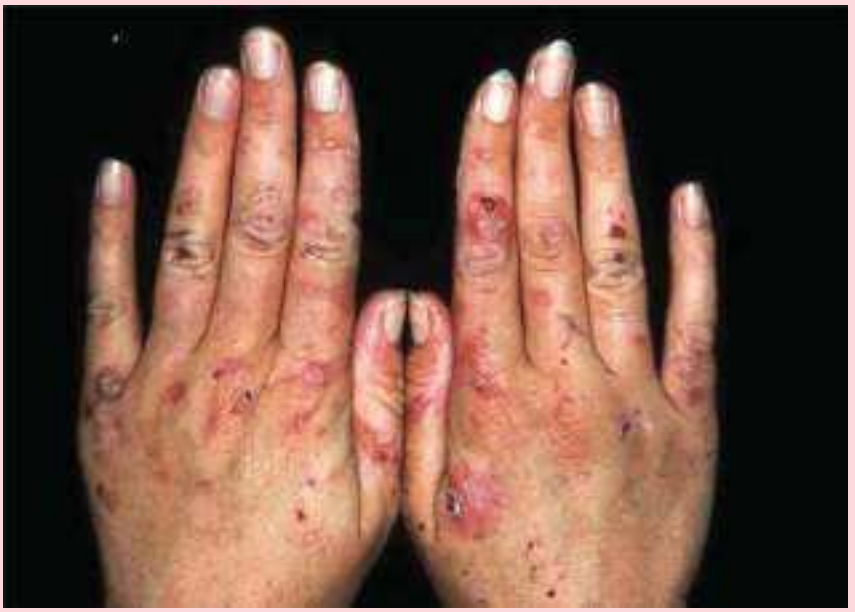
IgA linear bullous dermatosis *(see* Chapter 2, Bullous, acantholytic, page 63*): Pruritic erythematous papules and plaques, transforming into tense blisters in an annular or herpetiform arrangement. Histology shows infiltrates of neutrophils and eosinophils. DIF: linear IgA deposits along the junctional zone.*

Systemic lupus erythematosus*: urticarial lesions with band-like subepidermal neutrophilic infiltrate (see page 117).*

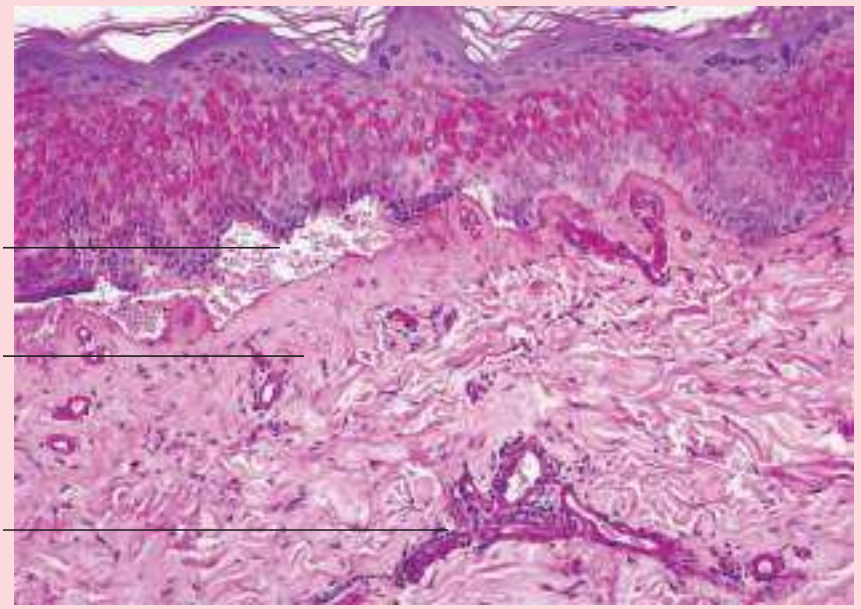
Epidermolysis bullosa acquisita: *bullous lesions with band-like subepidermal neutrophilic infiltrate.*

Vancomycin-induced bullous dermatitis *with band-like subepidermal neutrophilic infiltrate.*

OTHER SKIN DISEASES: Porphyria cutanea tarda

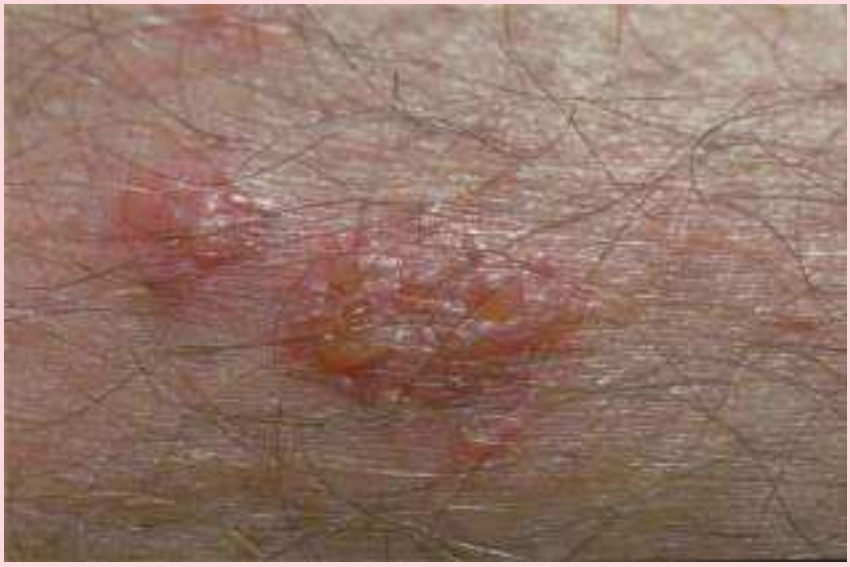


Cl: tense blisters, erosions with crust formation in sun exposed areas, preferentially back of the hands.

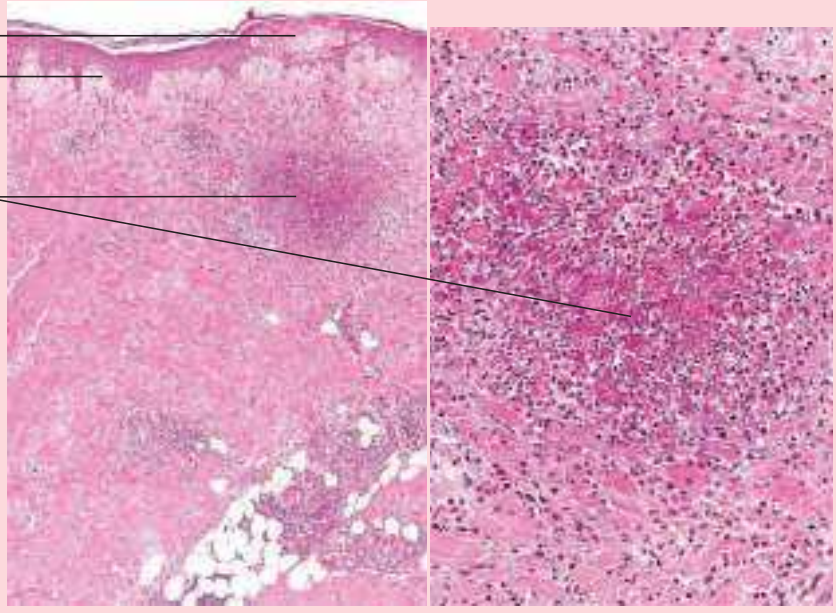


Hi: Subepidermal blister, preserved papillae (festooning), almost no inflammatory infiltrate, thickening of vessel walls (PAS). Fibrosis.

OTHER SKIN DISEASES: Arthropod bite reaction

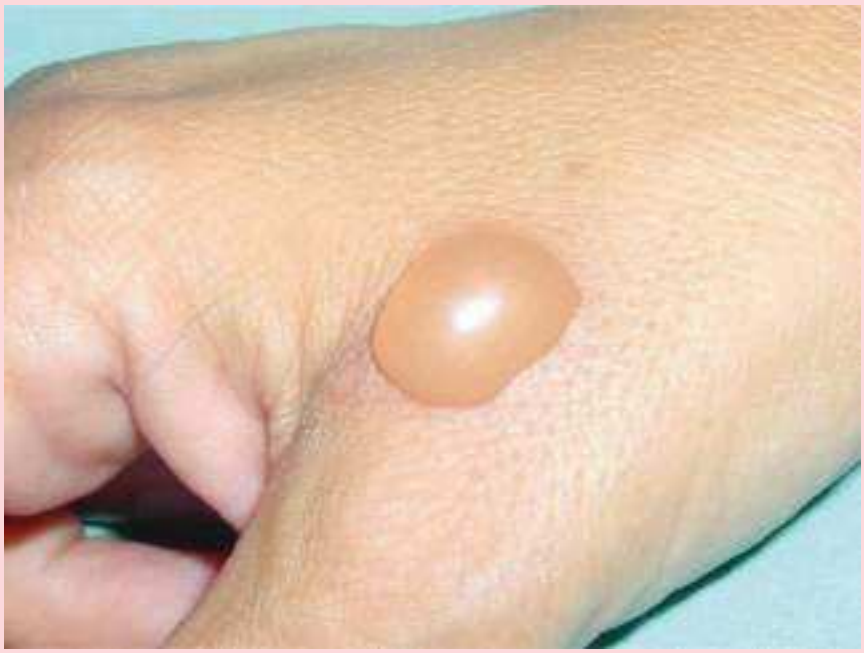


CI: circumscribed urticarial wheal.

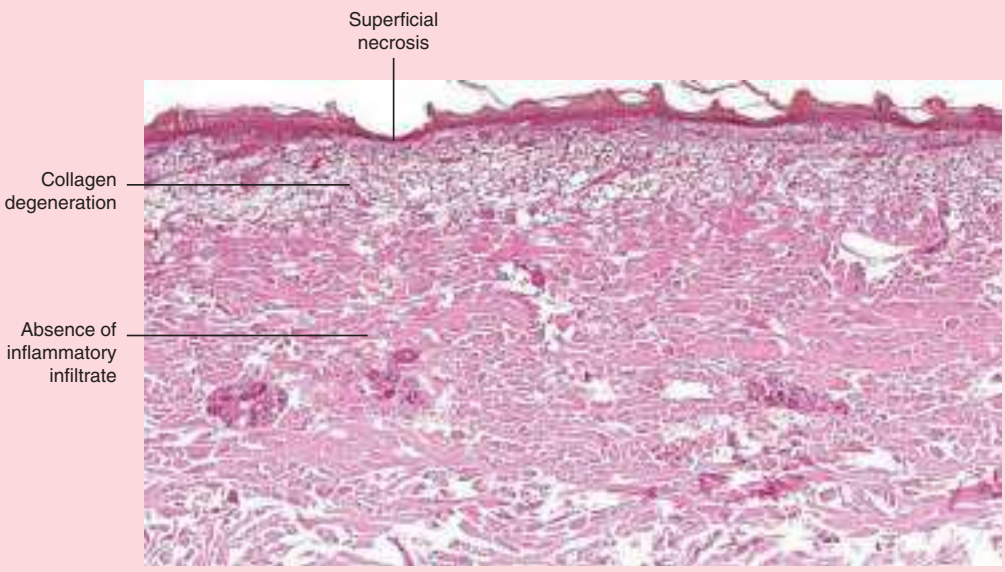


Hi: focal spongiosis, subepidermal edema, wedge-shaped infiltrate with eosinophils and neutrophils.

OTHER SKIN DISEASES: Thermic or mechanical blistering

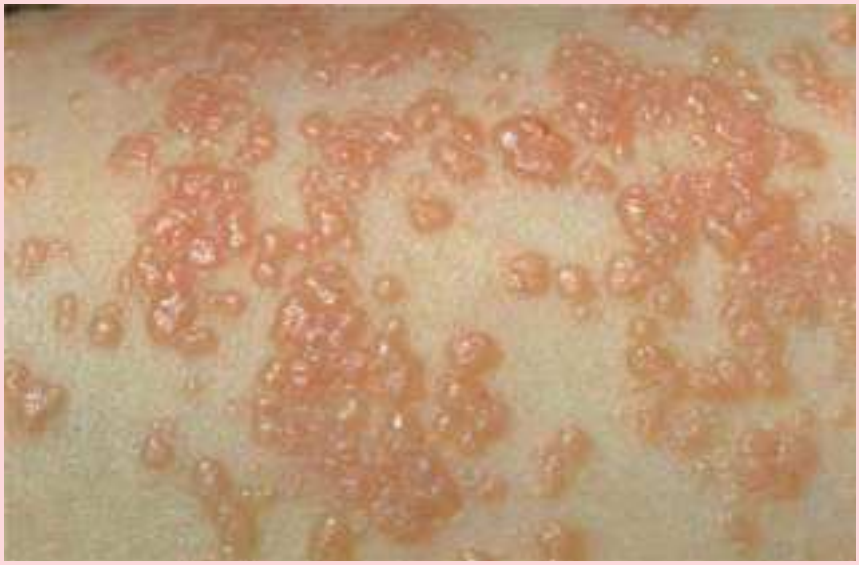


Cl: Tense blister.

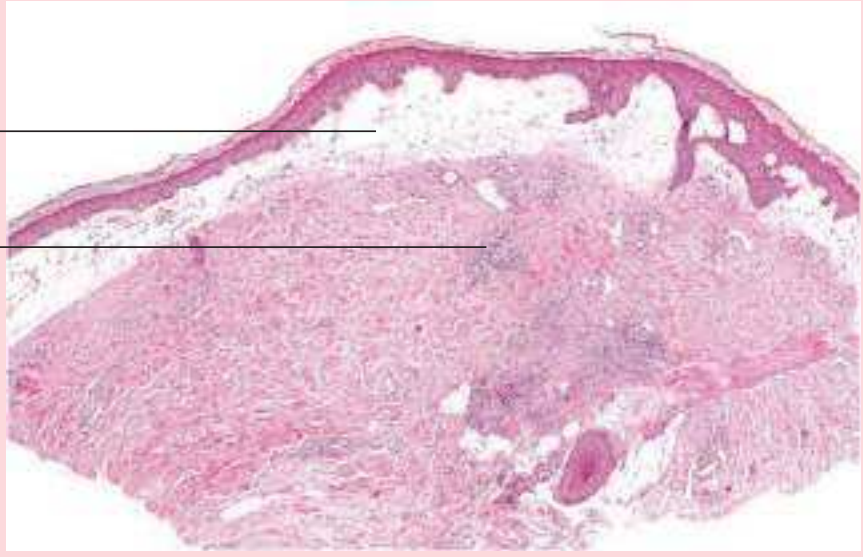


Hi: Lack of infiltrate, prominent necrotic or vacuolated keratinocytes.

OTHER SKIN DISEASES: Bullous drug eruption



Cl: Tense blisters on erythema.



Hi: Subepidermal blister formation, necrotic keratinocytes, lymphocytic infiltrate with eosinophils.

Erythema (exsudativum) multiforme *(see* Chapter 2, Necrobiotic, page 80)**:** *interface dermatitis, necrotic keratinocytes in all epidermal layers. Edema in upper dermis, lymphocytic infiltrate.*

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CHAPTER 4
Dermis

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.

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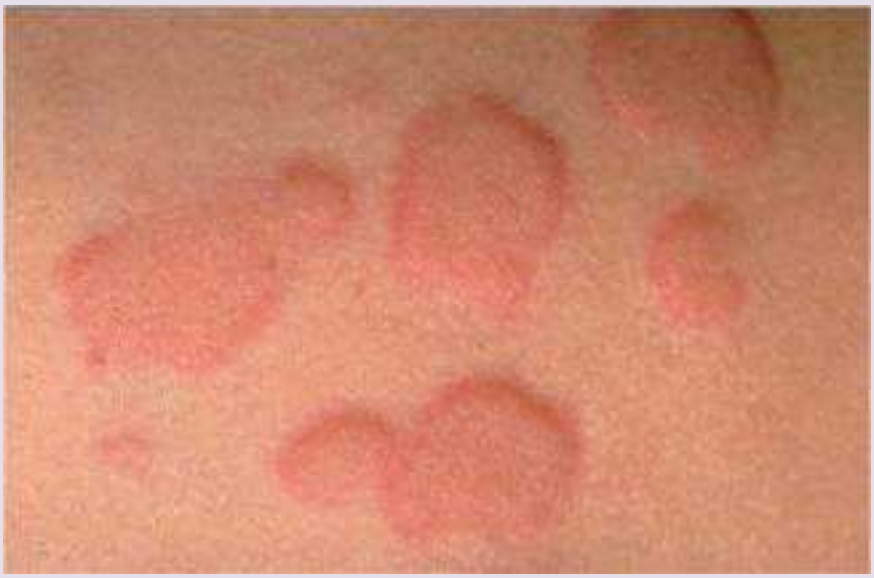
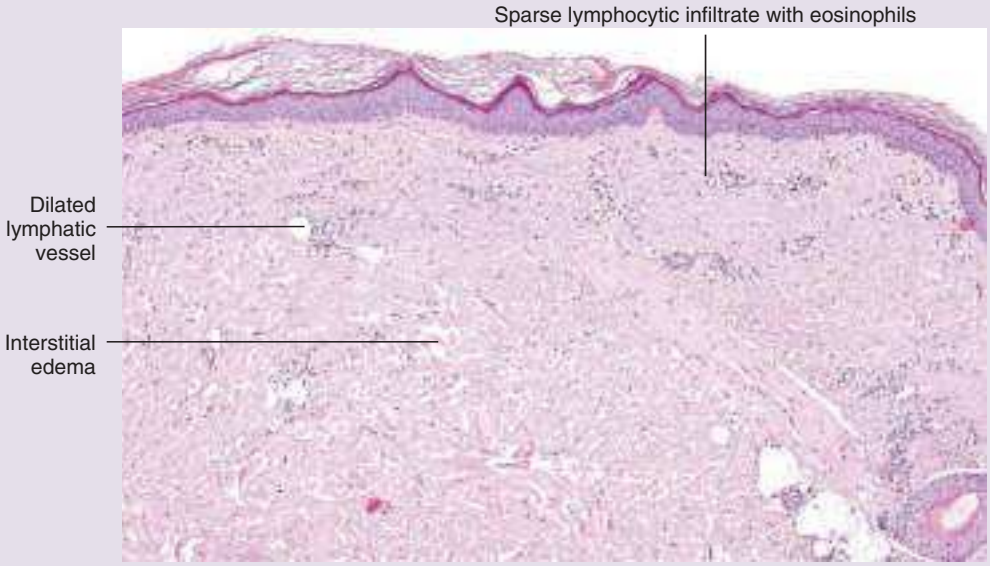
PROTOTYPE: Urticaria

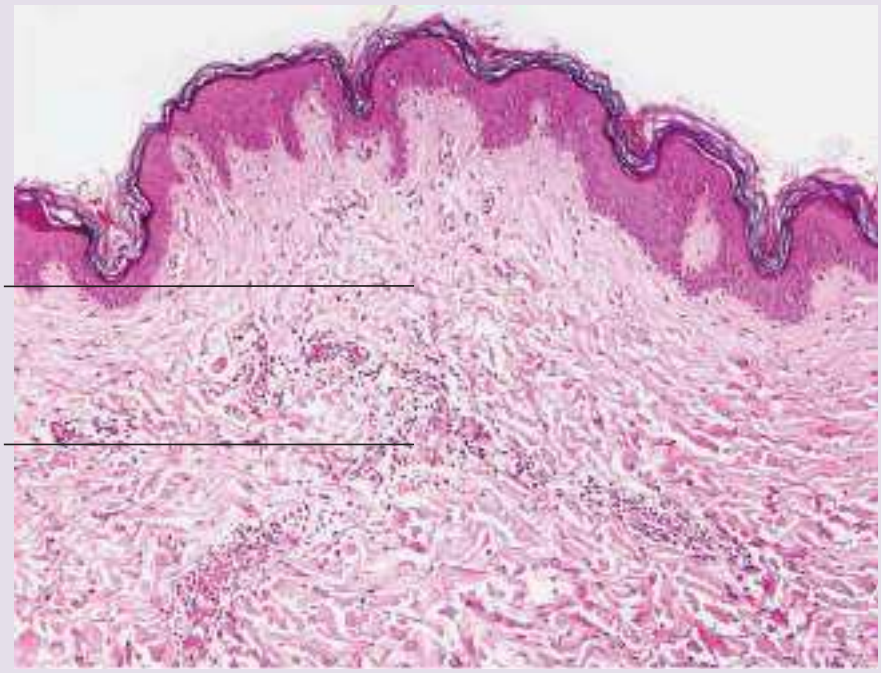


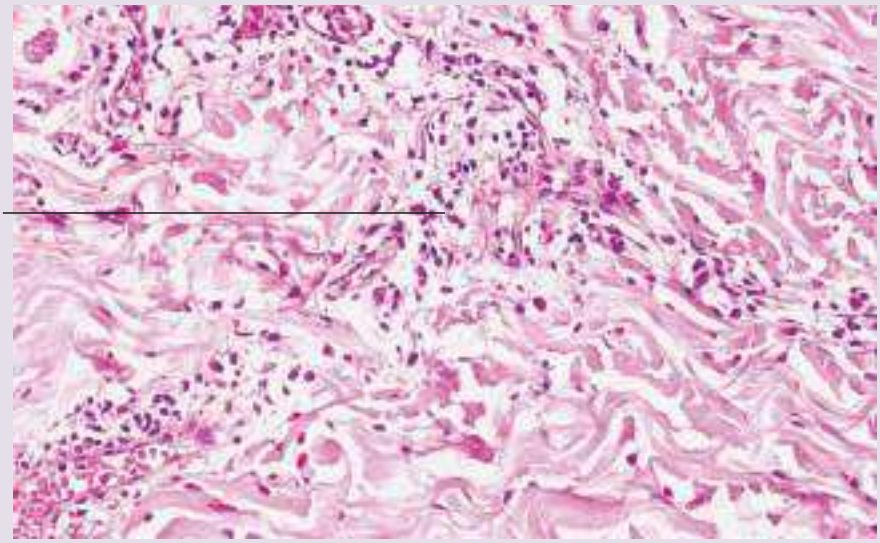
Cl: Pruritic, transitory (usually a few hours), erythematous, slightly elevated plaques and patches with various pathogenetic background.



Hi: Sparse inflammatory infiltrate. Histological clue: few granulocytes within vessel lumina and with interstitial splaying throughout the dermis.

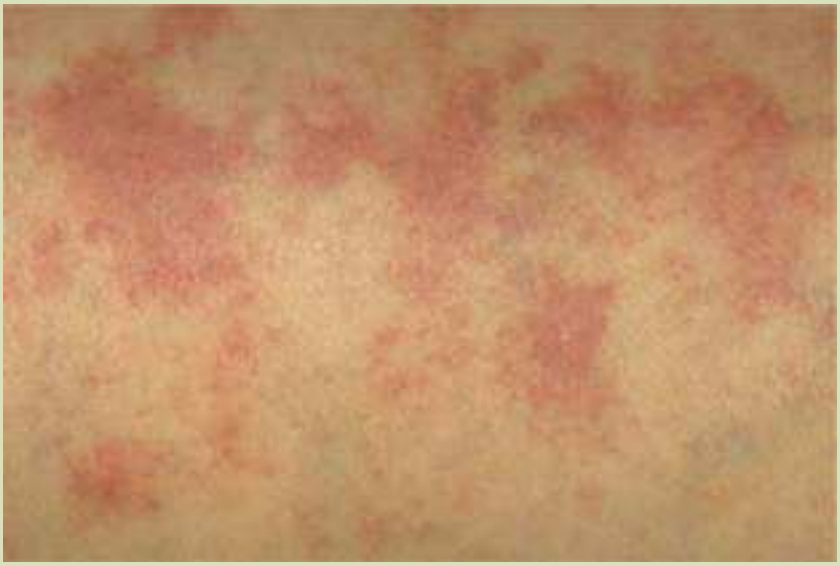
Urticaria



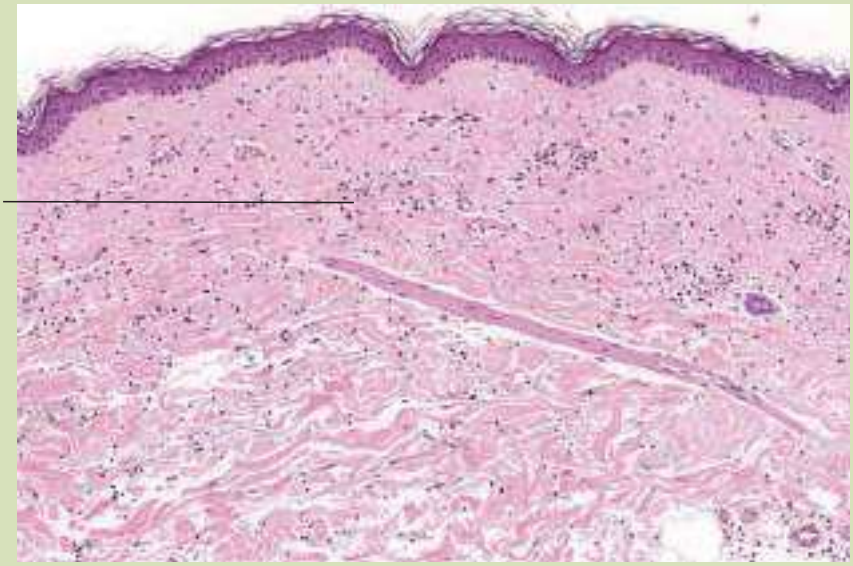


Hi: Edema of the reticular dermis. Dilated blood and lymphatic vessels, sparse perivascular and interstitial inflammatory infiltrate composed of eosinophils, neutrophils and lymphocytes. No epidermal changes.

DIFFERENTIAL DIAGNOSIS: Urticarial vasculitis

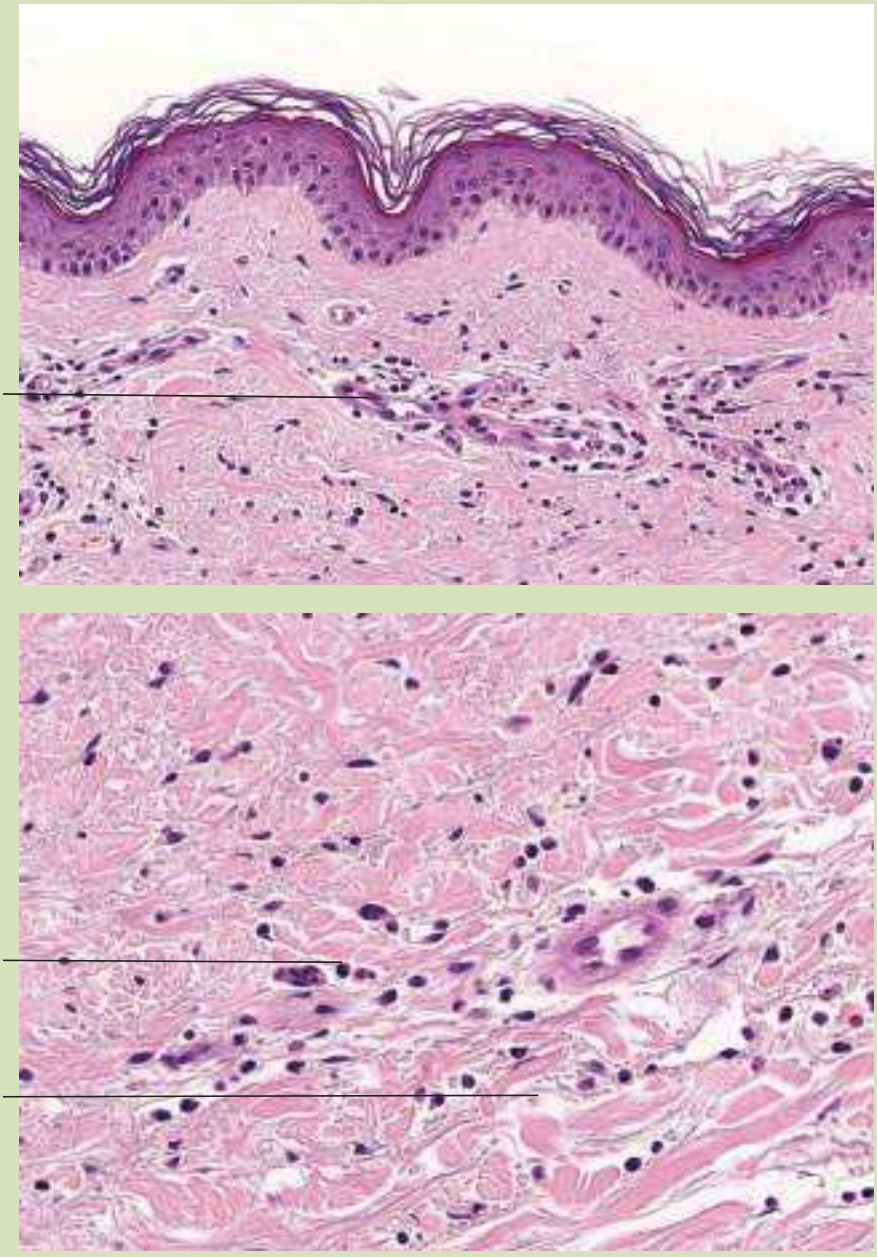


Cl: Urticarial lesions with purpura, which persists longer than 24 hours.



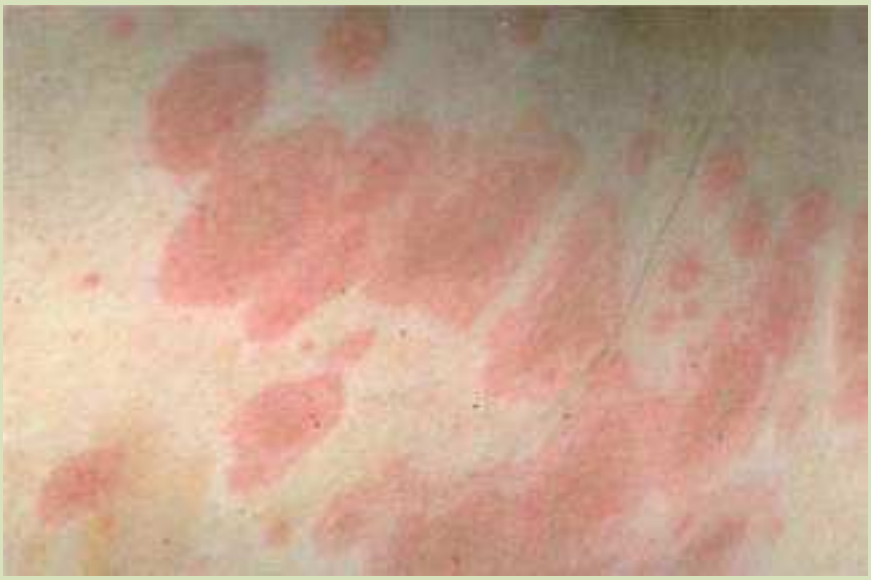
Hi: Sparse neutrophilic vasculitis with urticarial interstitial splaying of granulocytes.

Urticarial vasculitis

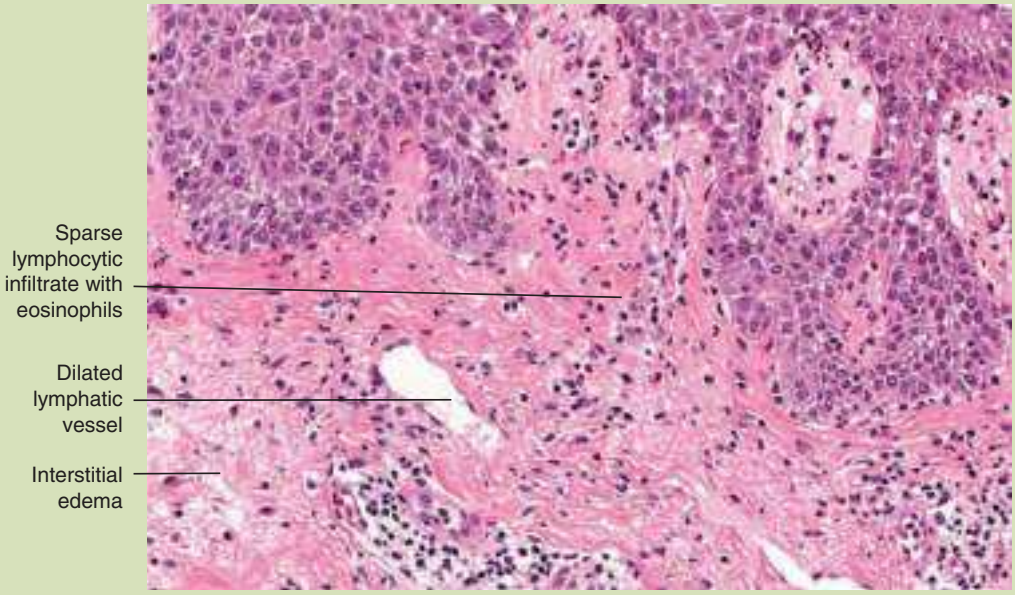


Hi: Infiltration of vessel walls of small dermal vessels by eosinophils and neutrophils, nuclear dust.

DIFFERENTIAL DIAGNOSIS: Drug eruption (*see also* Chapter 2, Necrotic and Chapter 3, Lichenoid)

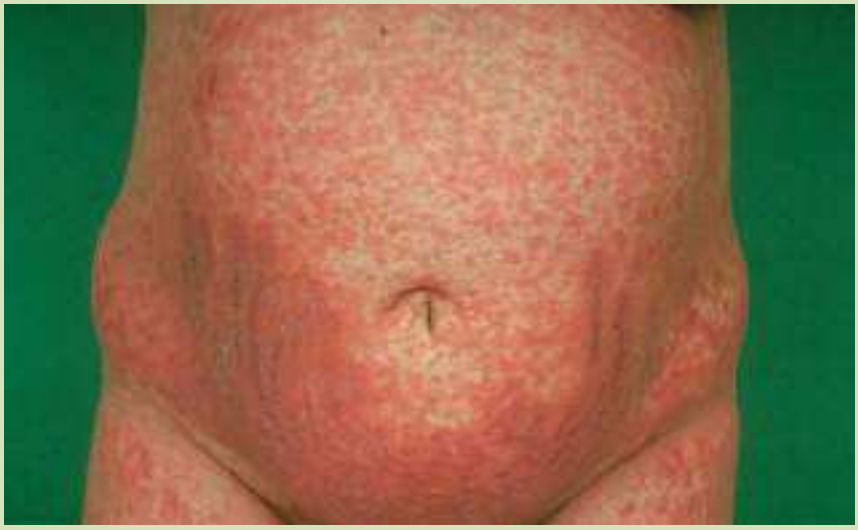


Cl: Erythema and urticarial wheals.

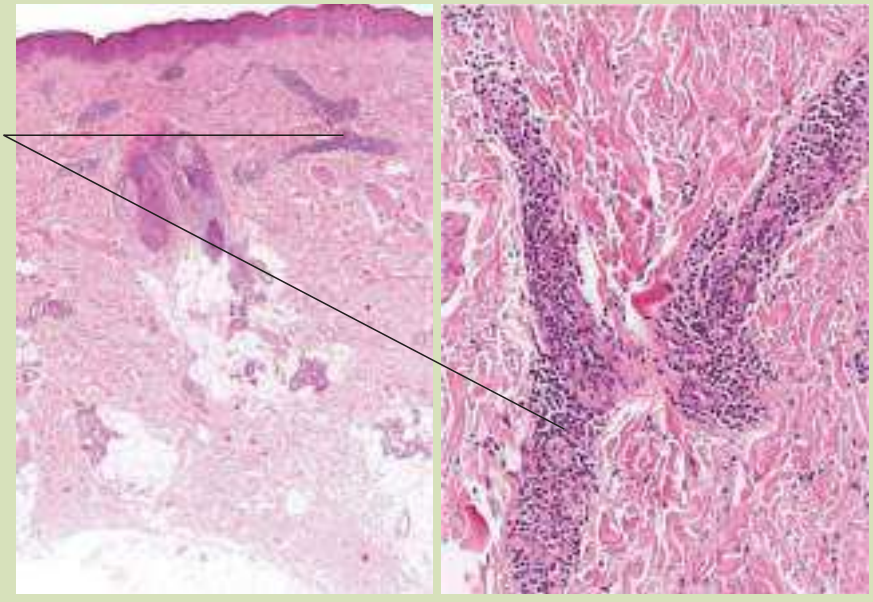


Hi: Histology may be identical to urticaria. Occasionally interface changes. Clinically, mostly exanthema with maculo-papular lesions.

DIFFERENTIAL DIAGNOSIS: Pruritic urticarial papules and plaques of pregnancy



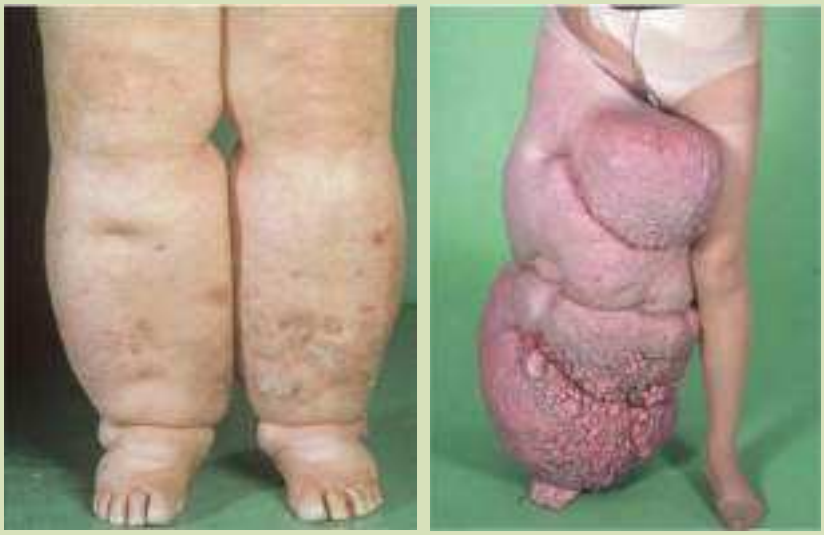
Cl: Pruritic urticarial papules and plaques usually occurring on the abdomen in the last trimester of pregnancy.



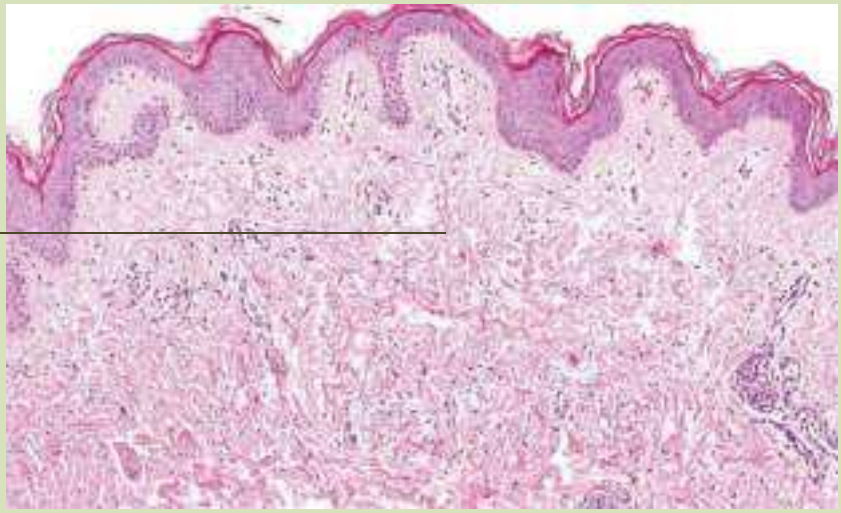
Hi: Perivascular infiltrates of lymphocytes and eosinophils. Epidermal changes with spongiosis may be present.

DIFFERENTIAL DIAGNOSIS: Lymphedema

Massive lymphedema congenital (left) and acquired (right)



Cl: Swelling usually on the lower legs or in areas of blocked lymph drainage.



Hi: Edema without inflammatory infiltrate.

Other Diagnosis

Neutrophilic urticaria: *Perivascular infiltrate in the upper and mid dermis with predominance of neutrophils. May be associated with Schnitzler syndrome (rare multisystem disorder with urticaria and monoclonal gammopathy).*

Mastocytosis (Urticaria pigmentosa): *Subtle perivascular infiltrate with admixture of eosinophils and numerous mast cells (>20 mast cells per HPF).*

Erysipelas (*see* Non-granulomatous, neutrophil- or eosinophil-rich, page 162): *Perivascular and interstitial infiltrate with predominance of neutrophils. Edema. Clinically circumscribed erythema and fever.*

Bullous pemphigoid, prebullous phase (*see* Non-granulomatous, neutrophil- or eosinophil-rich, page 166): *Clinically and histologically simulating urticaria with dermal infiltrates of eosinophils.*

Dermatitis herpetiformis (Duhring) (*see* Chapter 3, Subepidermal blistering, page 127): *Accumulations of neutrophils and vacuolization in the papillae.*

Arthropod bite reaction (*see also* Chapter 3, Subepidermal blistering, page 129): *Wedge-shaped infiltrate with lymphocytes and eosinophils. Epidermis with focal spongiosis.*

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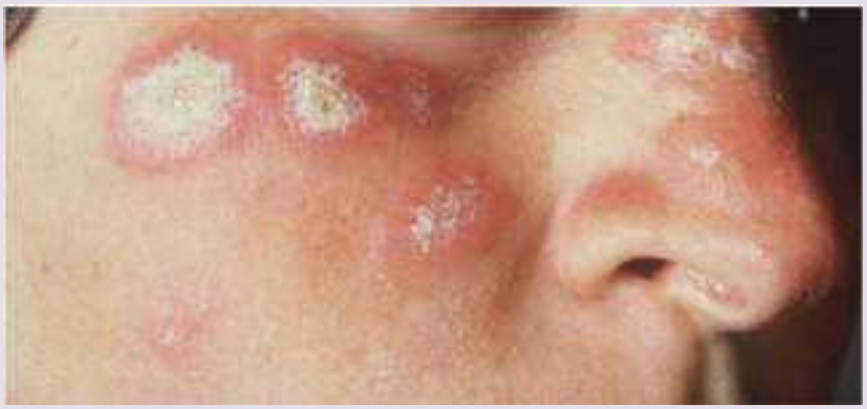
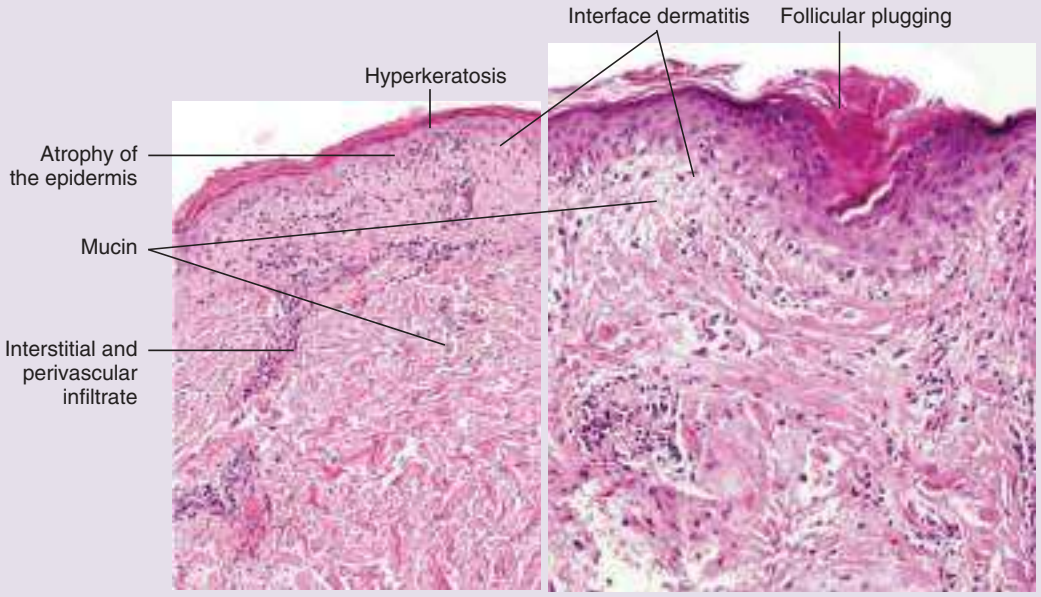
PROTOTYPE: Lupus erythematosus (LE), chronic discoid



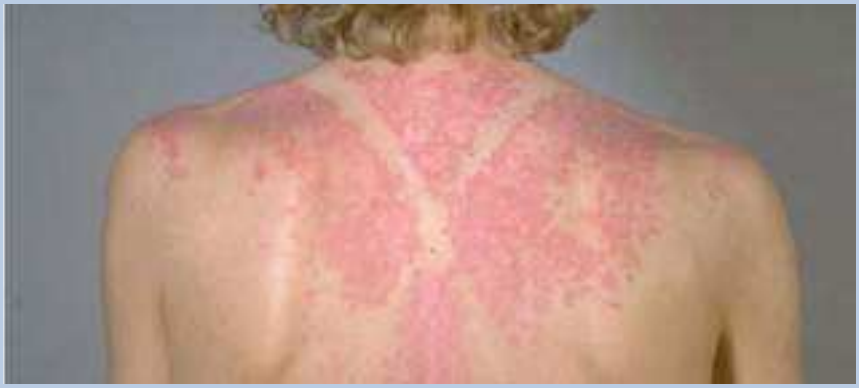
Cl: Coin or disk-shaped erythematous plaques with follicular hyperkeratoses and a tendency to heal with scarring, usually on light-exposed areas.



Hi: Hyperkeratosis, follicular plugs. Atrophy of the epidermis, apoptotic keratinocytes. Vacuolization of the junctional zone (interface dermatitis). Patchy or cuff-like perivascular and periadnexal dense lymphocytic infiltrates. No eosinophils. Interstitial mucin in all levels of the dermis.

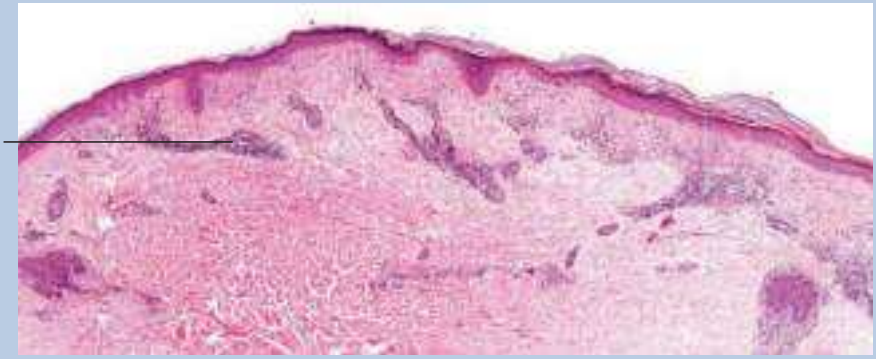
VARIANT: Systemic LE (SLE)

Erythema in sun exposed areas

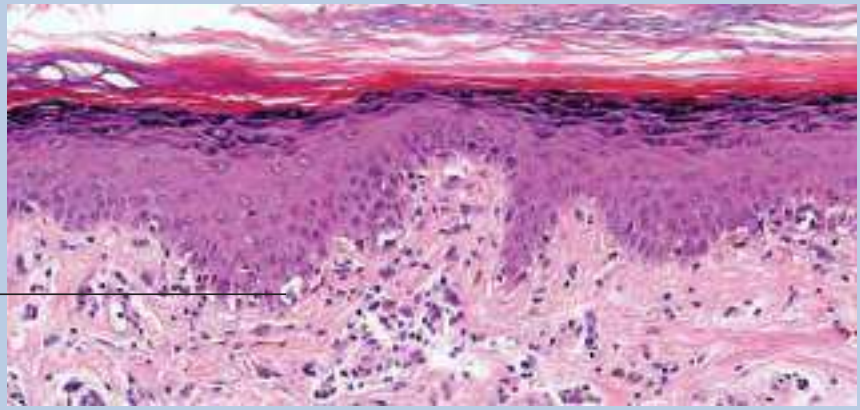


CI: The diagnosis is based on 4 or more ACR (American College of Rheumatology) criteria being fulfilled. These include: "butterfly" erythema of the face, photosensitive erythematous diffuse macules, oral ulcerations.

Sleeve-like perivascular infiltrate

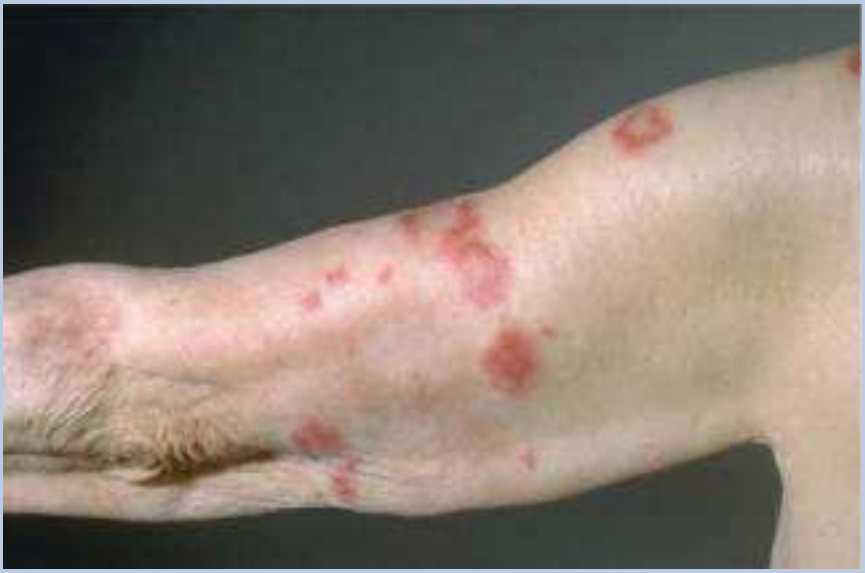


Interface dermatitis

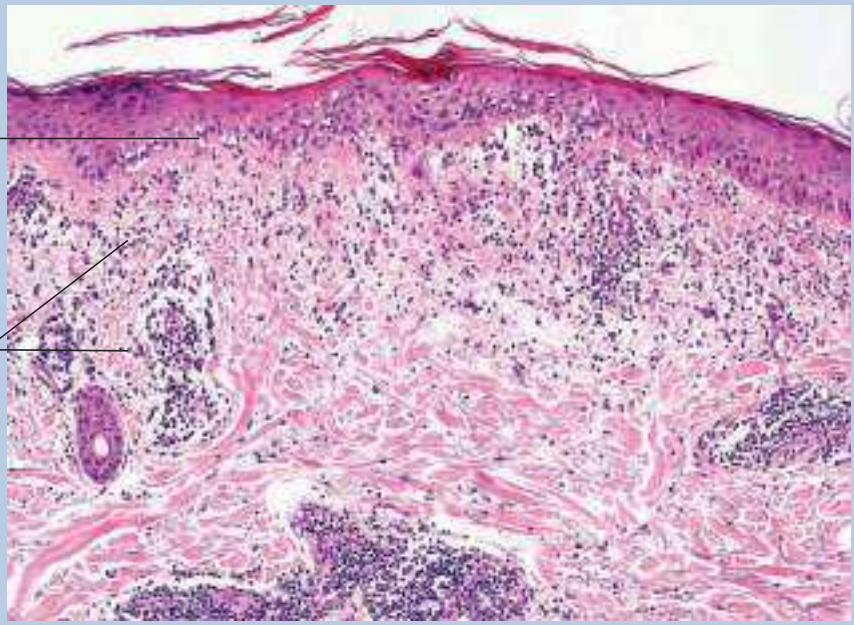


Hi: Interface dermatitis, necrotic keratinocytes, sparse inflammatory infiltrate. Edema and mucin in the upper dermis.

VARIANT: Subacute cutaneous LE (SCLE)



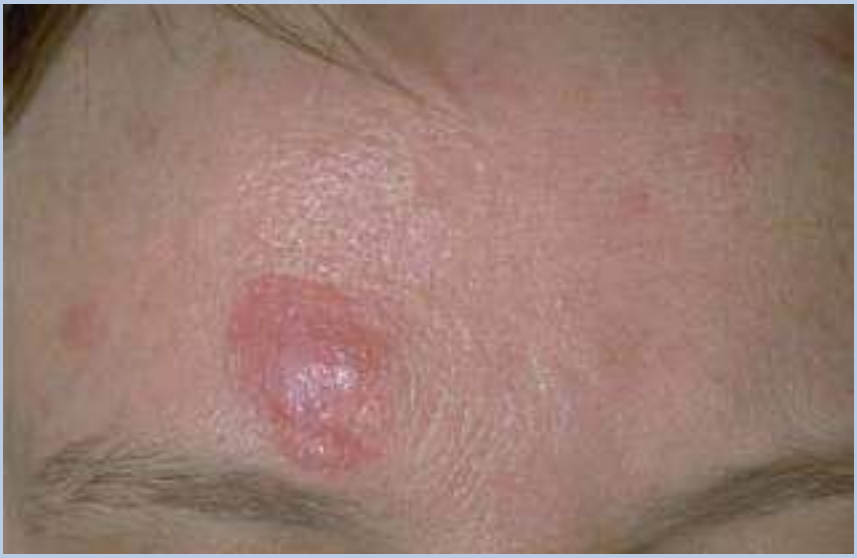
Cl: Non-scarring, polycyclic-annular or papulosquamous (psoriasiform) plaques which usually involve the upper half of the body and are clearly UV light-provoked. If present, systemic symptoms (arthritis, fever, malaise) are milder than in SLE (severe CNS or renal disease rare).



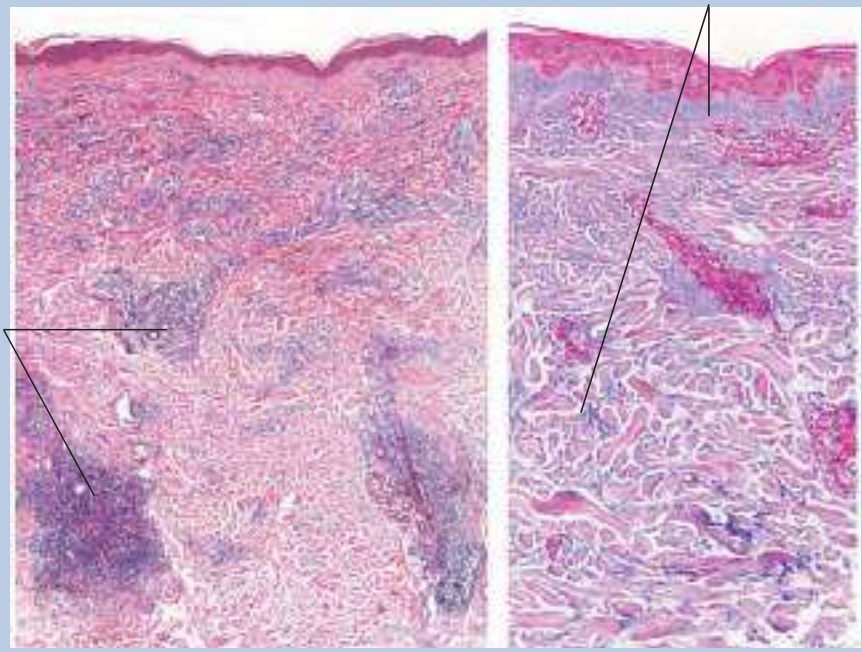
Hi: Interface dermatitis. Necrotic keratinocytes may be present. Perivascular lymphocytic infiltrate in the upper dermis, more prominent than in systemic LE. Dermal mucin.

VARIANT: LE tumidus

Nodular lesions on the forehead

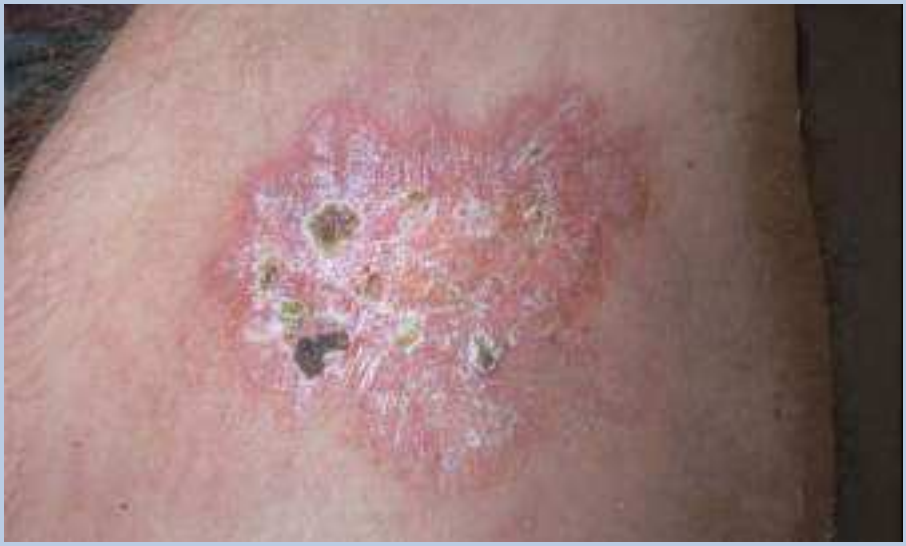


Cl: Papulo-nodular lesions or plaques without scaling. Face and trunk are preferential localizations.

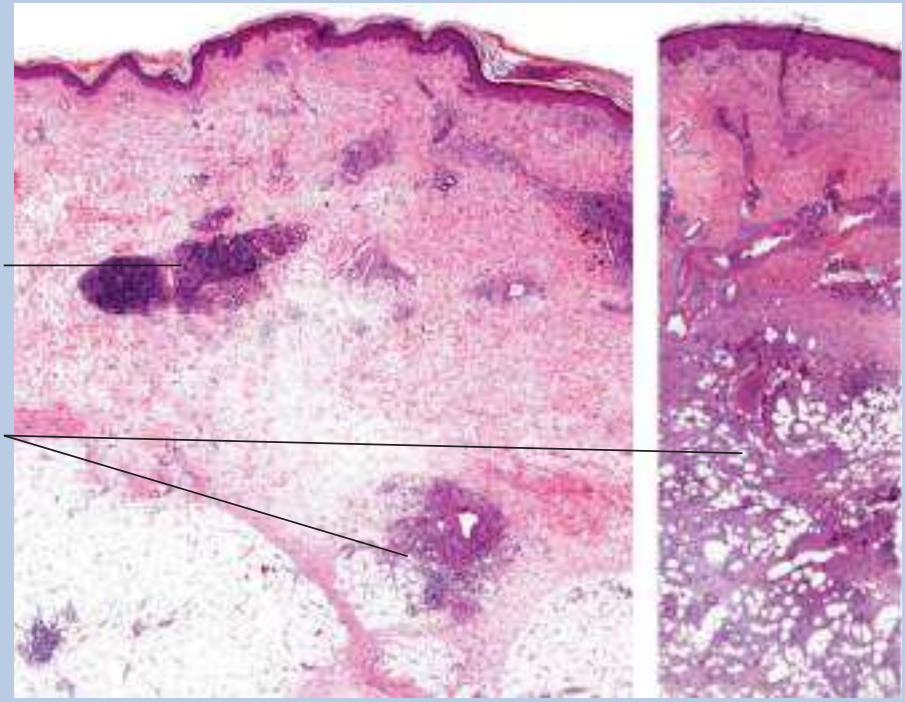


Hi: Superficial and deep perivascular and periadnexal cuff-like lymphocytic infiltrates, interstitial mucin deposits in the dermis, lack of epidermal changes such as junctional vacuolar degeneration or hyperparakeratosis.

VARIANT: LE profundus (lupus panniculitis)

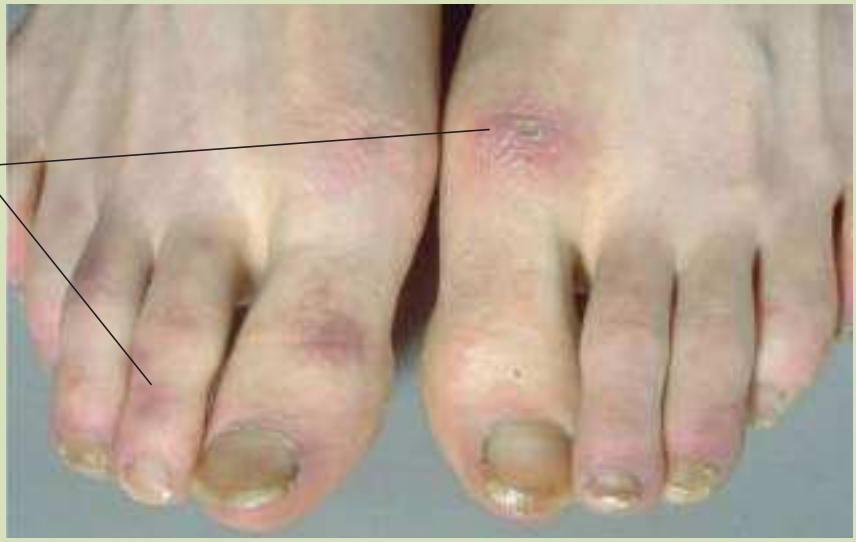


Cl: Slightly elevated subcutaneous nodular lesion. The overlying epidermis is normal or retracted and sometimes may show involvement with erythema and firm hyperkeratosis. Ulcerations may occur.

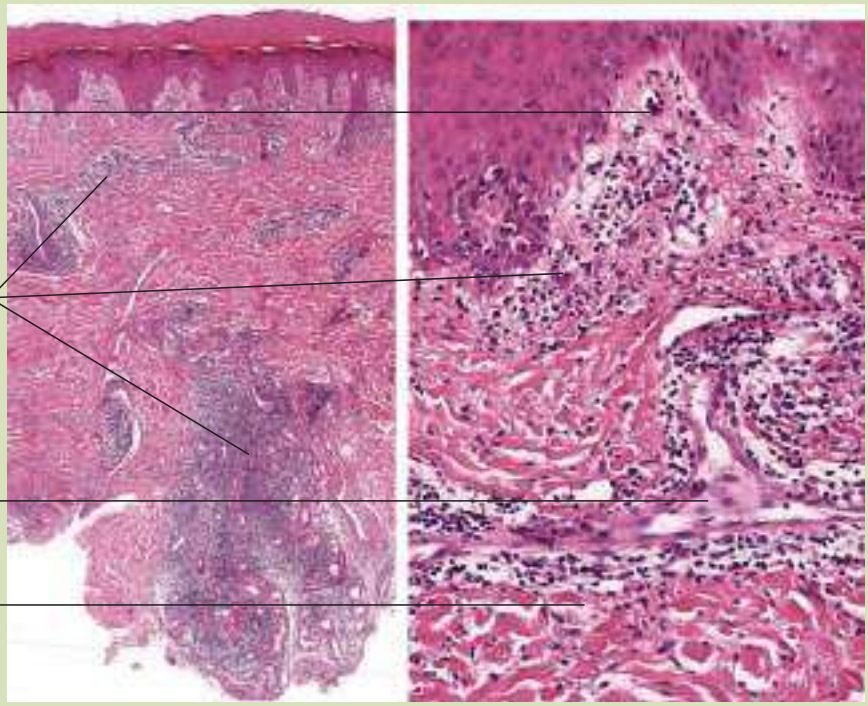


Hi: Infiltrates in the deep dermis and in septae and lobules of the subcutaneous fat tissue. Conspicuous lack of neutrophils within the infiltrat. Admixture of plasma cells may be present.

DIFFERENTIAL DIAGNOSIS: Pernio (chilblains)

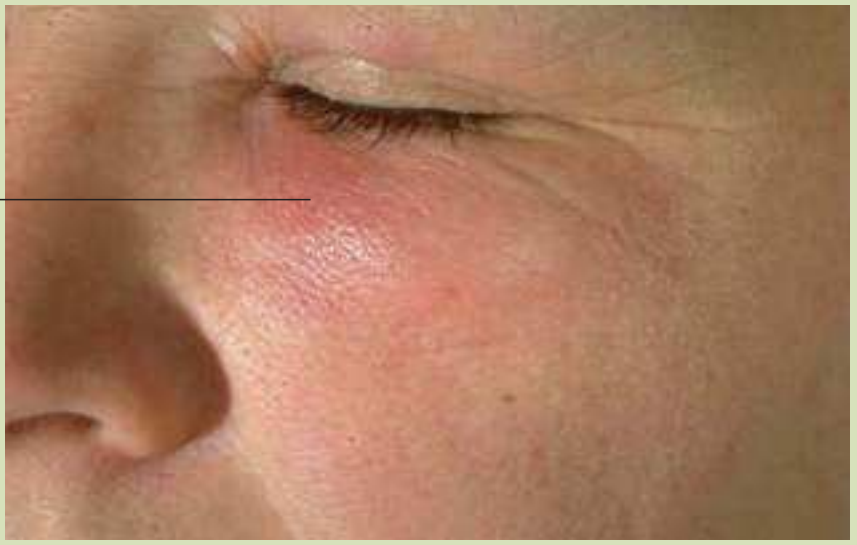


Cl: Blue-red edematous nodular swelling or infiltrates in acral localizations (fingers or toes), frequently associated with hyperhidrosis and acrocyanosis.

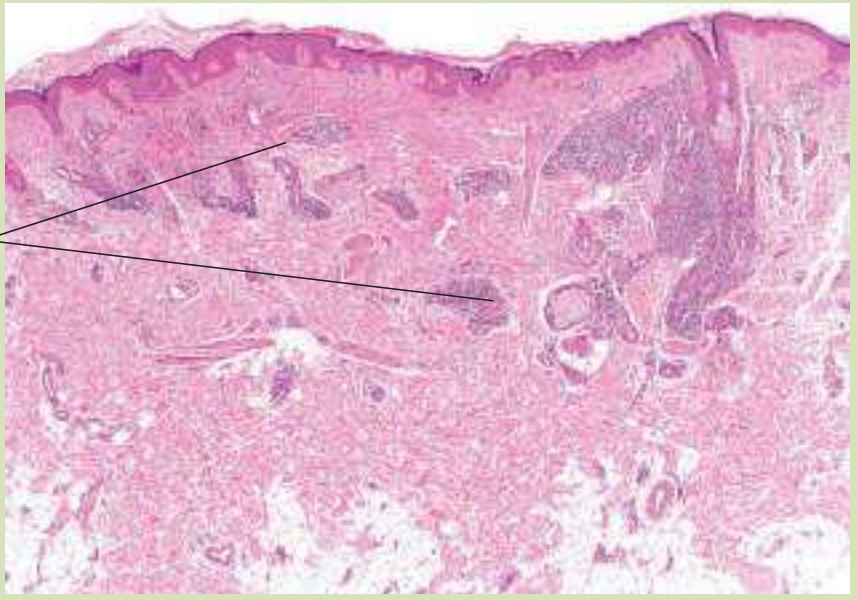


Hi: Similar histological findings, but less prominent junctional vacuolization. Lymphocytes in edematous vessel walls; plasma cells may be present.

DIFFERENTIAL DIAGNOSIS: Lymphocytic infiltration (Jessner-Kanof)

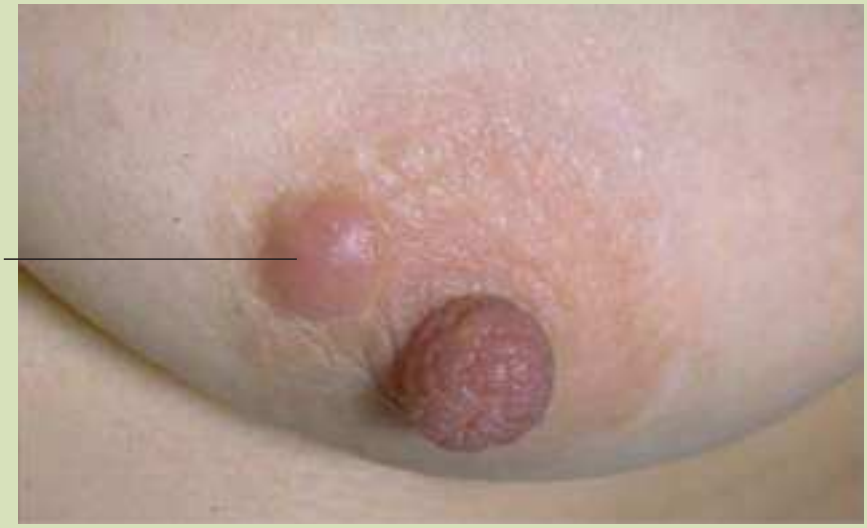


Cl: Circumscribed erythematous plaque-like swelling or infiltrate.

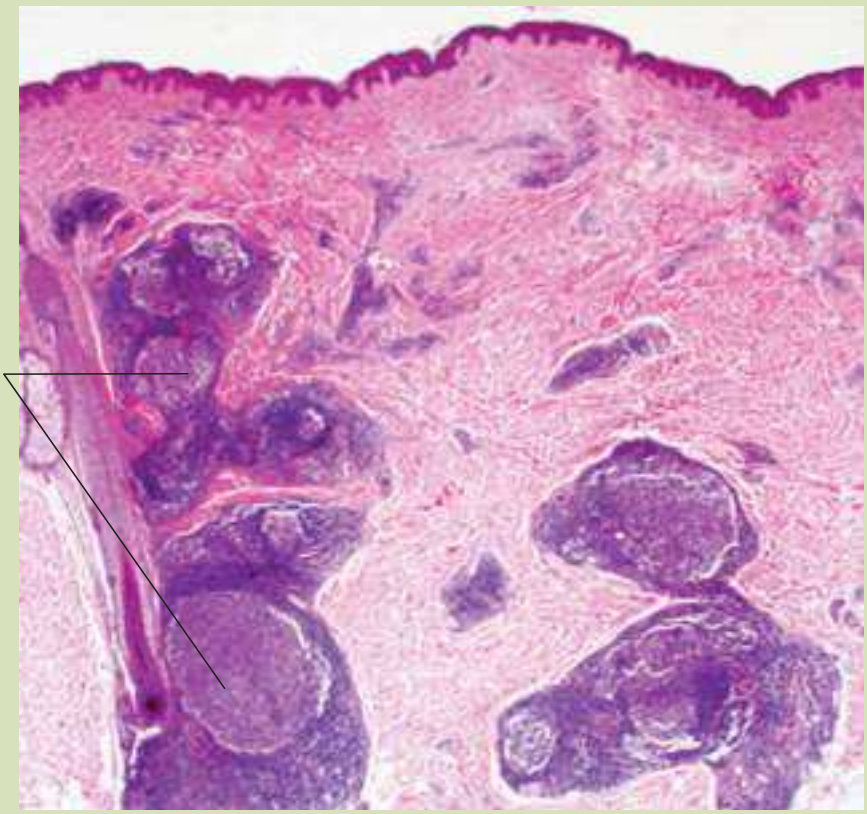


Hi: Perivascular lymphocytic infiltrates in all dermal layers. Sparse interstitial mucin deposits.

DIFFERENTIAL DIAGNOSIS: Pseudolymphoma



Cl: Usually solitary soft papule or nodule.



Hi: Superficial and deep perivascular and interstitial lymphocytic infiltrates with admixture of plasma cells and eosinophils with or without follicular structures (lymphadenosis benigna cutis).

OTHER Diagnosis

Reticular erythematous mucinosis (REM syndrome) (*see* Chapter 7, Mucin, page 302): *Perivascular lymphocytic infiltrates in all dermal layers and sparse interstitial mucin deposits.*

Photoallergic and phototoxic reactions (*see* Chapter 2, Acute, pages 19, 83): *Apoptotic keratinocytes, spongiosis, perivascular infiltrate with eosinophils (especially in photoallergic reaction).*

Polymorphic light eruption (*see* Chapter 2, Acute, page 21): *Even though PLE is a monomorphous eruption in the affected individual, there are many (polymorphous) clinical features between individual patients, ranging from erythematous to papular or papulovesicular lesions, which appear exclusively in irradiated areas. Marked papillary dermal edema, blistering of the junctional zone, sleeve-like perivascular lymphocytic infiltrates with eosinophils. Epidermal changes with spongiosis may be present.*

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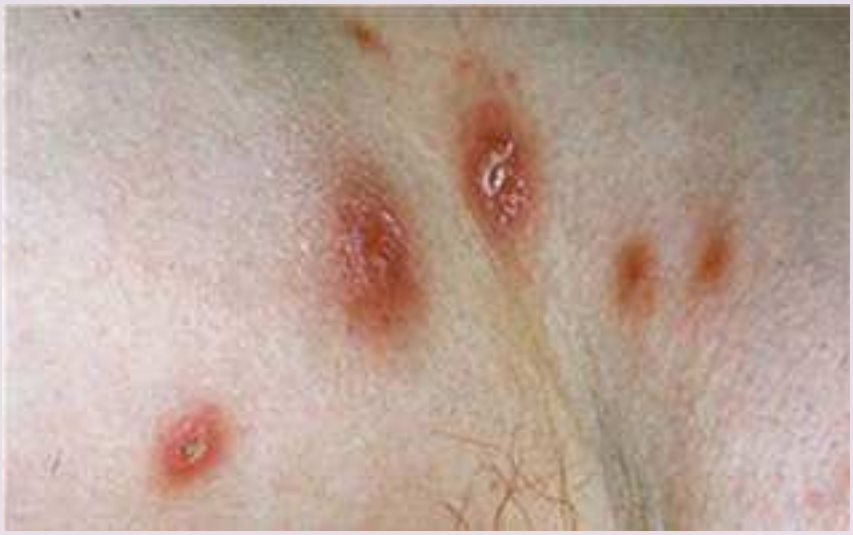
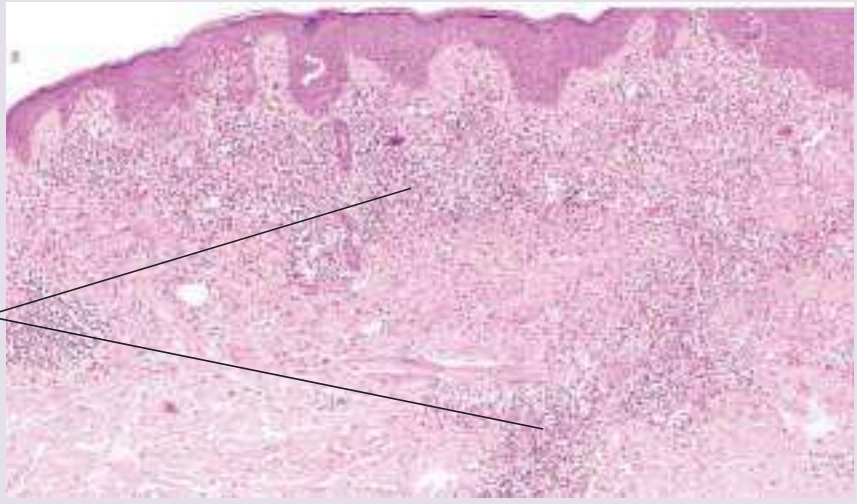
PROTOTYPE: Lymphomatoid papulosis (LYP), type A



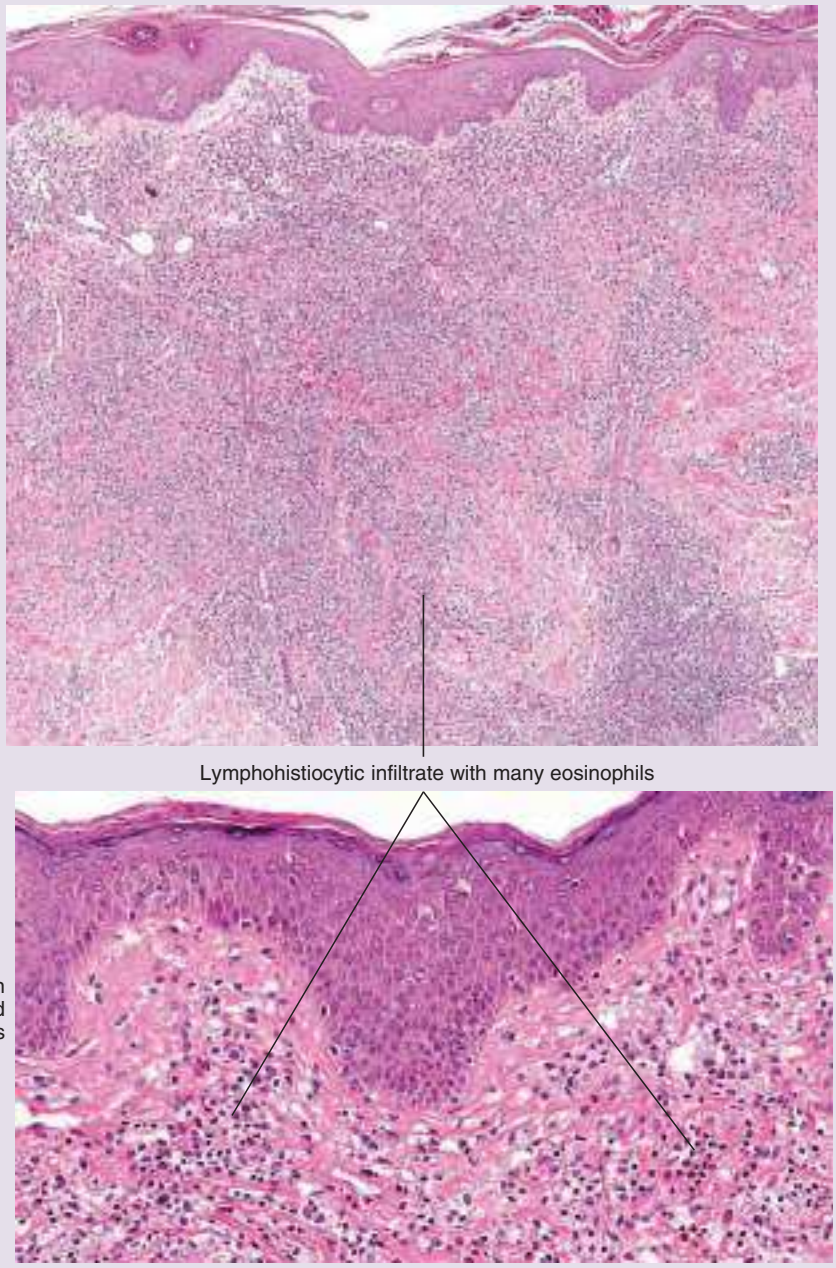
Papules with central necrosis

CI: Disseminated or grouped recurrent, papulonecrotic lesions, which heal spontaneously within a few weeks, sometimes leaving behind varioliform scars.



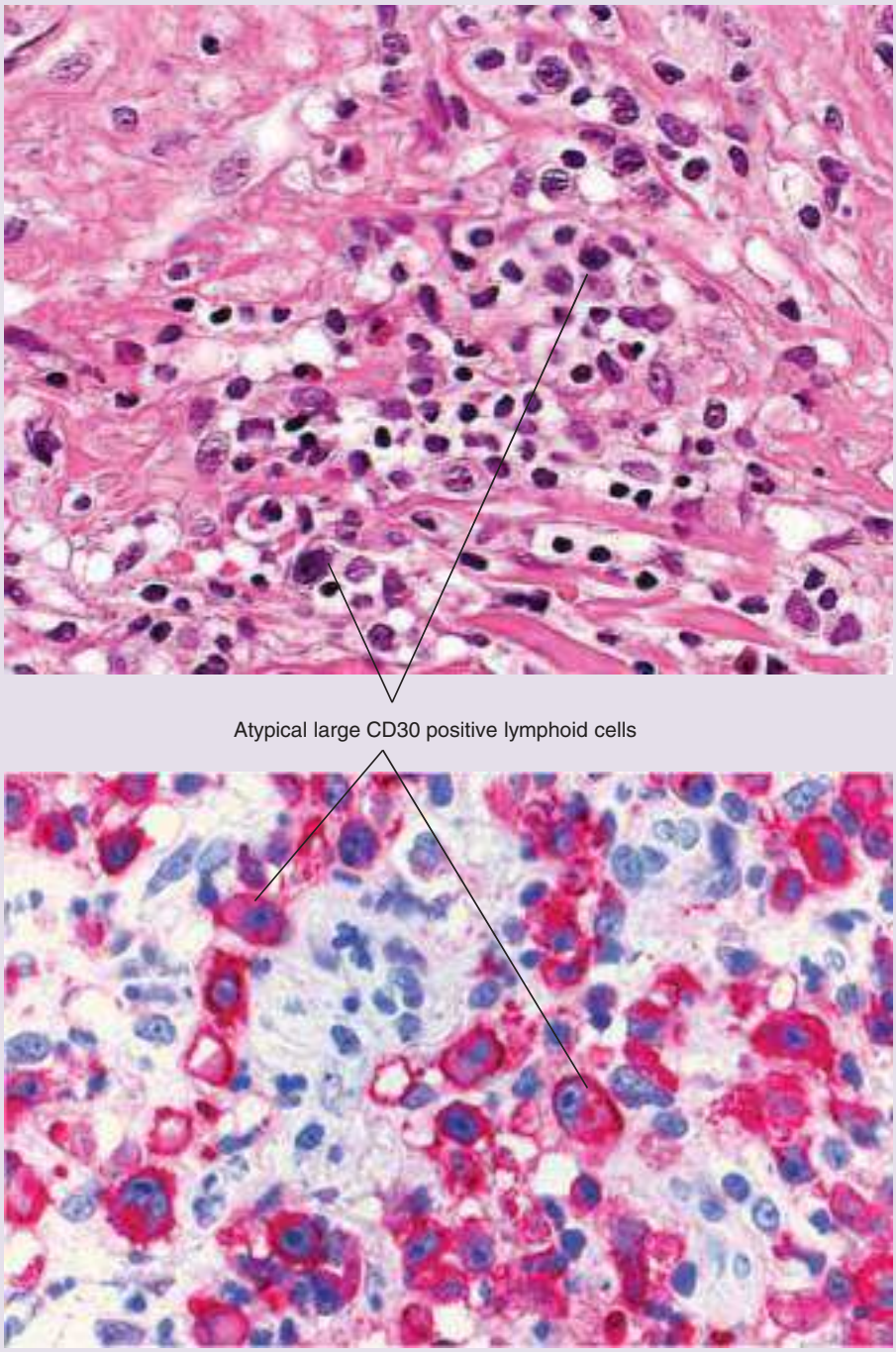
Infiltrate in upper and mid dermis

Lymphomatoid papulosis, type A



Hi: Various histological types (types A-E). Wedge shaped mixed infiltrate containing large atypical lymphocytes, small lymphocytes, histiocytes, neutrophils and eosinophils. Expression of CD30 by the large atypical lymphocytes (except in the MF-like type B), high mitotic activity, damage of blood vessel walls, ulceration, scar formation in regressing lesions.

Lymphomatoid papulosis, type A



Hi: Scattered large CD30+ lymphocytes amongst an infiltrate with eosinophils and histiocytes.

VARIANTS: Types B, C, D, E, 6p25.3

Type B: *Mycosis fungoides-like variant with epidermotropic small to medium-sized atypical lymphocytes with cerebriform nuclei and variable expression of CD30.*

Type C: *Cohesive sheets of large CD30+ lymphocytes with admixture of only a few inflammatory cells.*

Type D: *Epidermotropic infiltrate of small to medium-sized CD8+ and CD30+ atypical lymphocytes. Deeper perivascular infiltrates may be present.*

Type E: *Angiocentric and angiodestructive infiltrates of predominantly medium-sized atypical CD30+ and often CD8+ lymphocytes. Extensive hemorrhage, necrosis and ulceration.*

6p25.3 translocation associated type: *Pagetoid reticulosis-like epidermal involvement with usually prominent dermal nodule. Small to medium-sized atypical cells showing prominent periadnexal involvement. Frequent loss of T-cell markers (double negative for CD4 and CD8, however, beta F1+) with very high proliferative activity and diminished or lost expression of TIA-1. Positive FISH study with the 6p25.3 probe (the only subtype so far with reproducible genetic abnormality).*

DIFFERENTIAL DIAGNOSIS

Primary cutaneous anaplastic large cell lymphoma (ALCL): *Histological features identical to LyP type C with a nodular infiltrate of large CD30+ anaplastic lymphocytes. Expression of CD30 by more than 75% of large cells. Clinically solitary or grouped rapidly growing tumor.*

Systemic anaplastic large cell lymphoma: *Identical histological features to primary cutaneous ALCL and LyP type C, but often expression of ALK/p80 and EMA.*

Mycosis fungoides (see Chapter 2, Psoriasiform and Chapter 3, Lichenoid, page 120): *Patches and plaques are present. MF (patch/plaque) may histologically be indistinguishable from LyP type B and D, MF (transformation or tumor stage) may be similar to LyP C.*

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma: *Histologically similar to LyP type D, but no expression of CD30. Clinically rapidly evolving erosive and necrotic plaques and tumors.*

Extranodal NK/T-cell lymphoma, nasal type and cutaneous gamma/delta lymphoma: *Histologically similar to LyP type E, but clinically erosive and necrotic tumoral lesions, no spontaneous regression. Association with EBV in extranodal NK/T-cell lymphoma.*

Lymphomatoid drug eruption: *Variable features (Mycosis fungoides-like, Pseudolymphoma-like, Lupus erythematosus like, lichenoid, vasculitis-like).*

Lymphomatoid contact dermatitis: *Spongiosis, superficial and dense lymphoid infiltrate, eosinophils.*

Hypersensitivity reaction (arthropod, scabies, infestations): *Wedge-shaped infiltrate, mixed cellularity activated small to medium-sized lymphocytes, some of them with expression of CD30, neutrophils, eosinophils, plasma cells occasionally present, epidermal alterations).*

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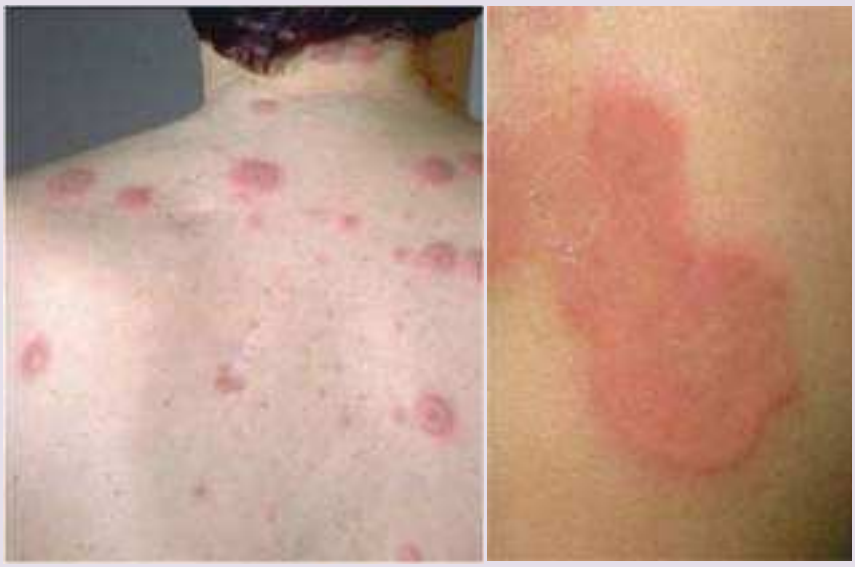
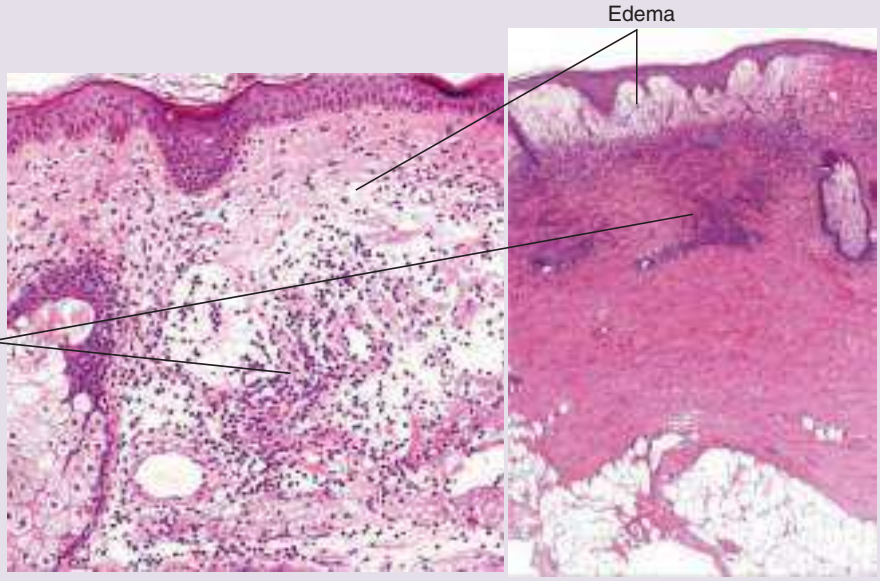
PROTOTYPE: Acute febrile neutrophilic dermatosis (Sweet syndrome)

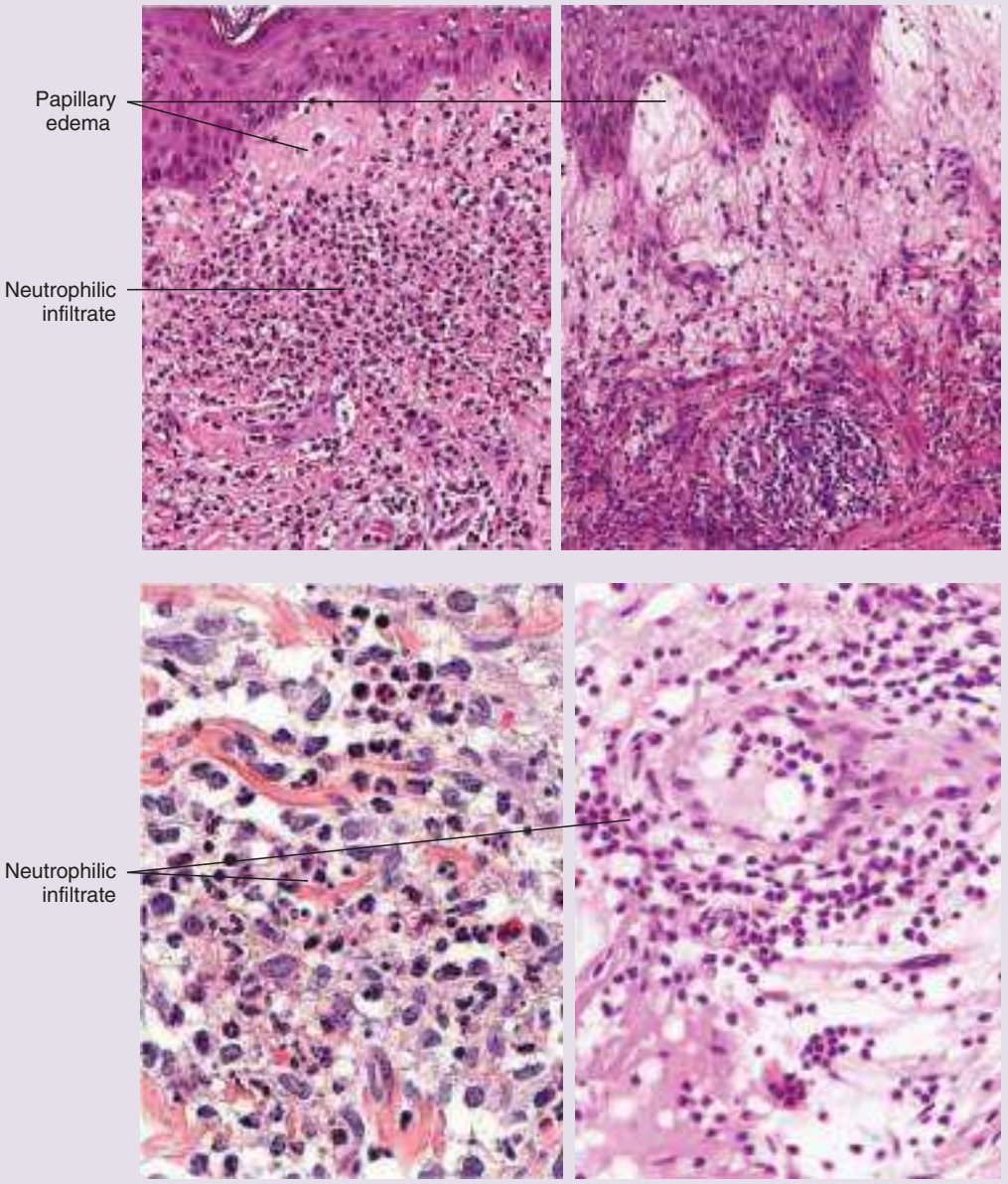
Targetoid erythematous, urticarial and bullous lesions



CI: Succulent, tender, red juicy plaques or nodules, which eventually may get pustular, bullous and hemorrhagic. The patients present with fever and elevated neutrophil counts. Occasional association with myelomonocytic leukemia.

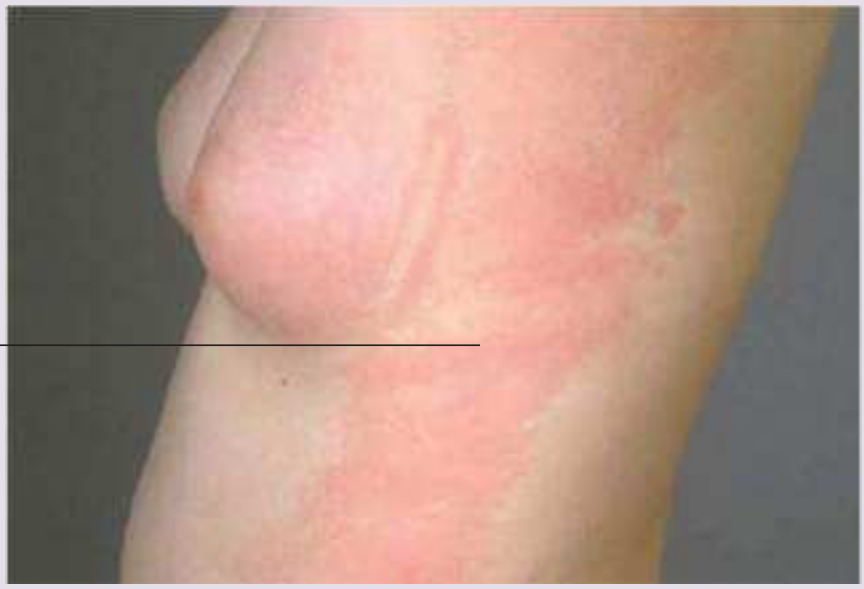


Acute febrile neutrophilic dermatosis (Sweet syndrome)

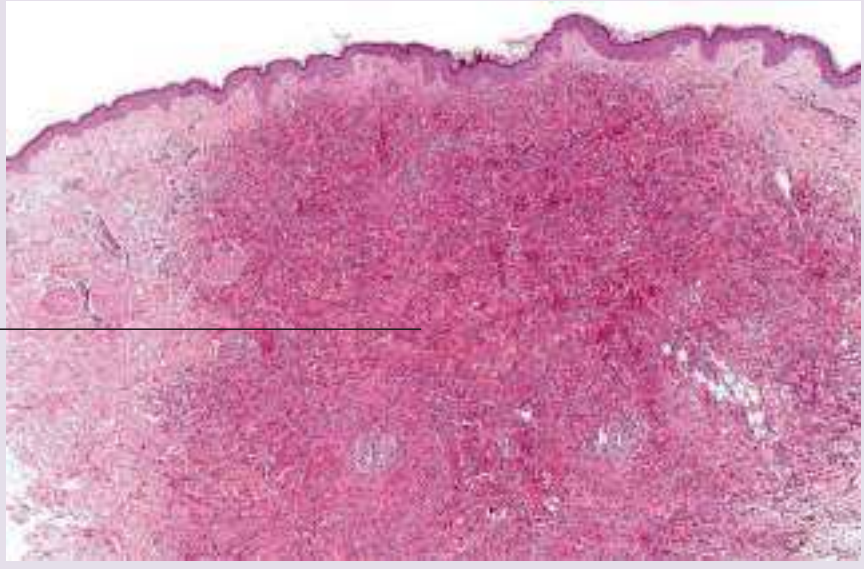


Hi: Diffuse neutrophilic infiltrate extending to the deep dermis, marked papillary edema, leukocytoklasia with nuclear dust, no signs of vasculitis. Subcutaneous (panniculitis-like) Sweet syndrome may occur.

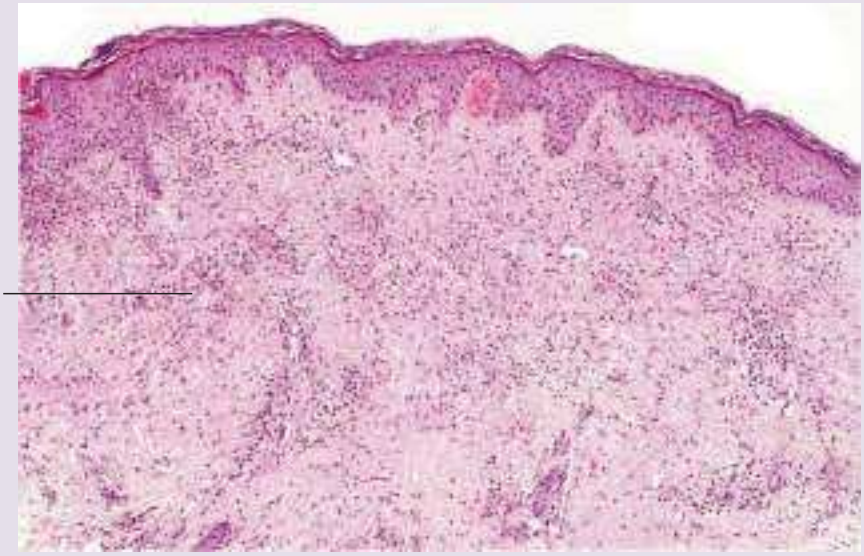
PROTOTYPE: Eosinophilic cellulitis (Wells syndrome)



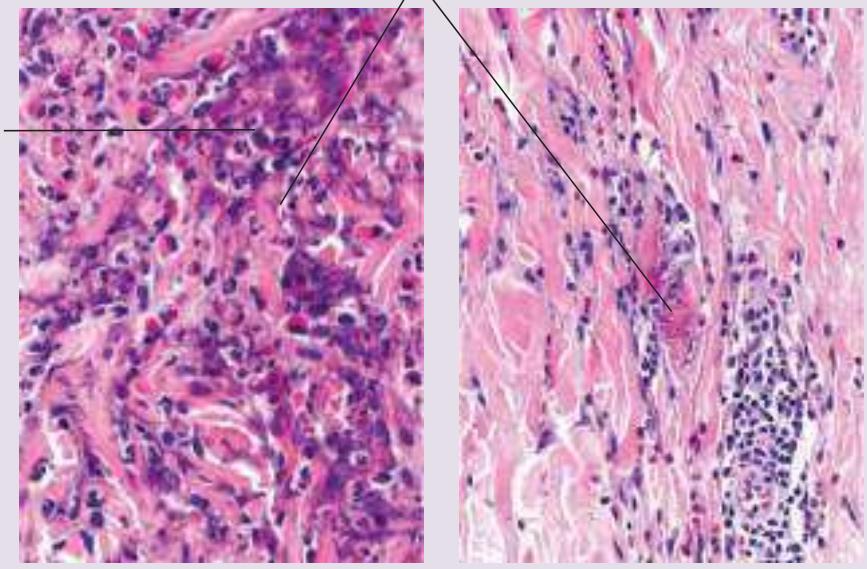
Cl: Multiple circumscribed erythematous or urticarial lesions during the acute phase, which lasts a few days. In exceptional cases, large "geographical" erythemas, imitating erysipelas. Pruritic erythematous infiltrated lesions are typical for the late granulomatous stage.



Eosinophilic cellulitis (Wells syndrome)



Eosinophilic degeneration of collagen («flame figures») with eosinophils and eosinophilic dust



Hi: In the entire dermis, dense perivascular and diffuse interstitial infiltrate composed of eosinophilic granulocytes and few lymphocytes; edema of the papillary dermis; multiple eosinophilic flame figures consisting of eosinophilic degenerate collagenous cores surrounded by eosinophilic granulocytes; granulomatous features in late stages with eosinophilic micro-granulomas consisting of central necrobiotic eosinophilic cores which are surrounded by multiple histiocytes and macrophages ("eosinophilic micro-granulomas").

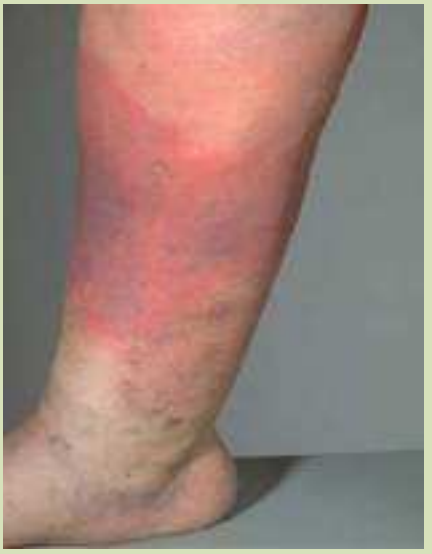
VARIANTS:

Early stage, with edematous urticarial infiltrate consisting mostly of eosinophilic granulocytes and few lymphocytes, rarely resembling erysipelas or classic urticaria.

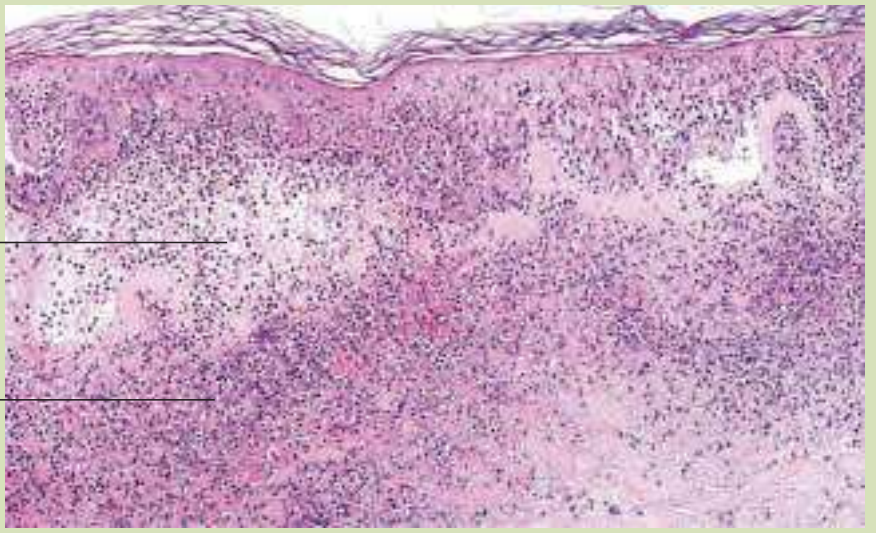
Late stage, granulomatous infiltrations with multiple prominent eosinophilic micro-granulomas.

DIFFERENTIAL DIAGNOSIS: Erysipelas

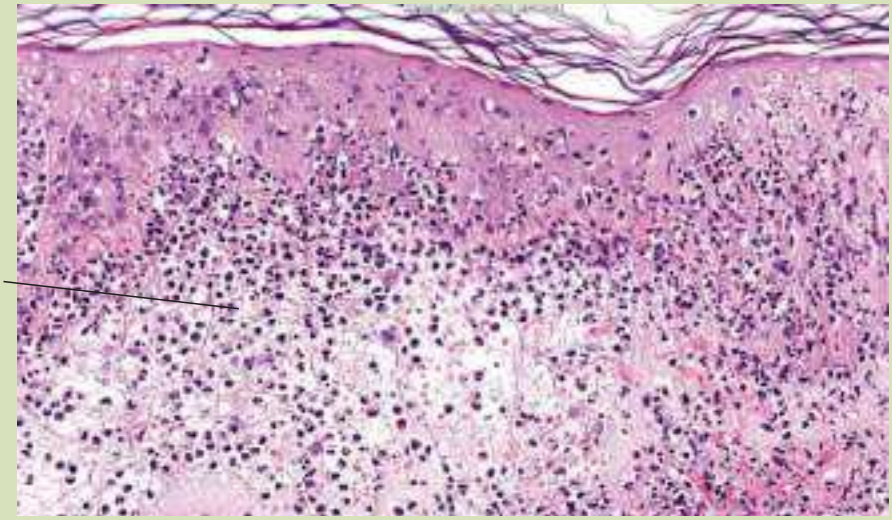
Erysipelas of the leg and face

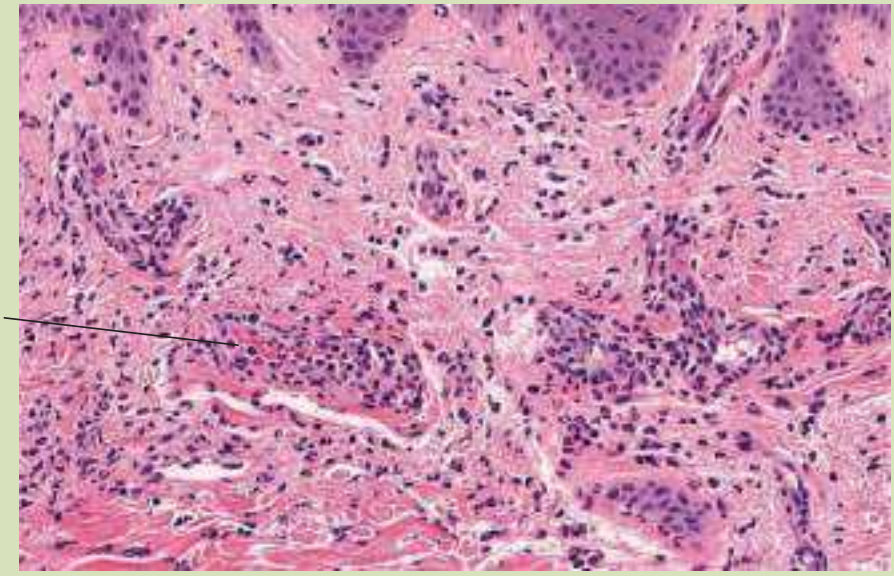


CI: There is a broad spectrum ranging from erythematous to hemorrhagic and bullous. The most typical presentation is a painful swelling and erythema with the tendency to centrifugal spread; due to mostly streptococcal infection of superficial lymph vessels. Preferential localizations are the legs and the face.



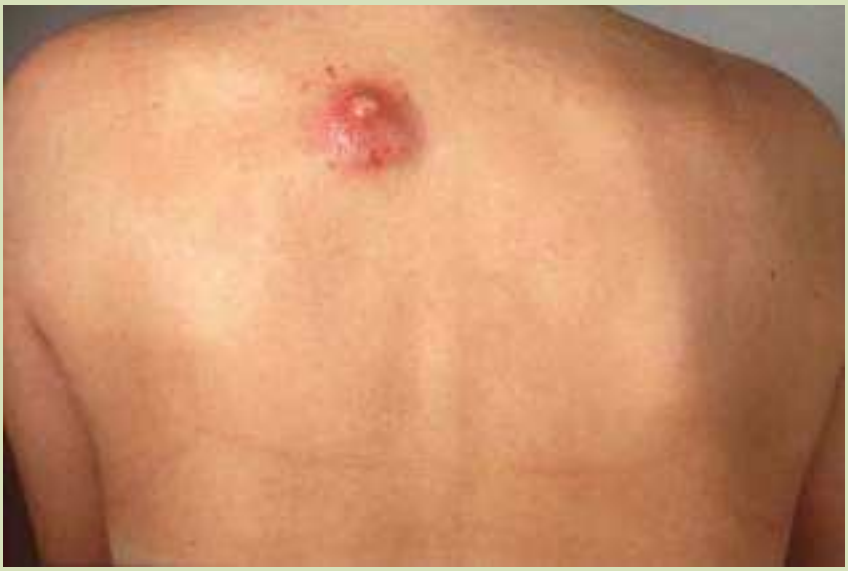
Erysipelas



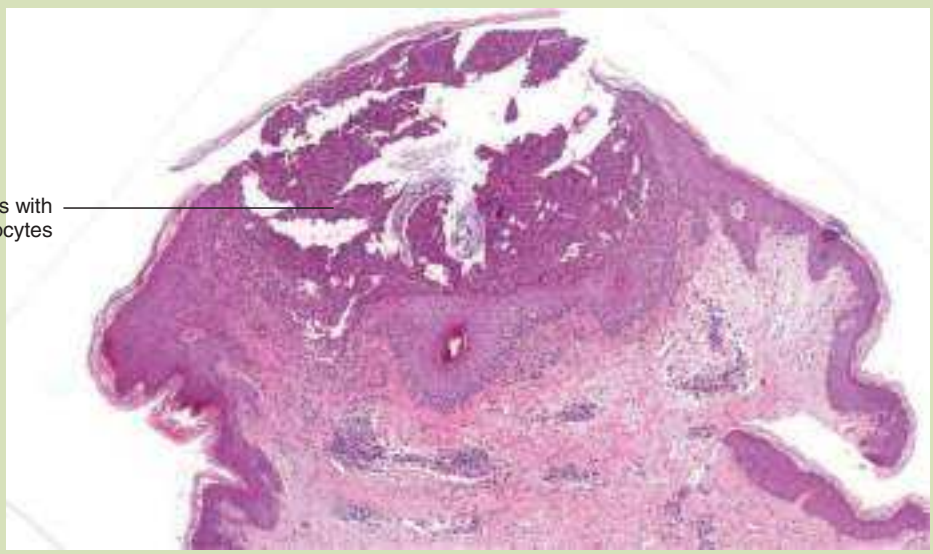


Hi: Edema in the upper dermis, dilatation of vessels, neutrophilic infiltrate of variable density.

DIFFERENTIAL DIAGNOSIS: Abscess

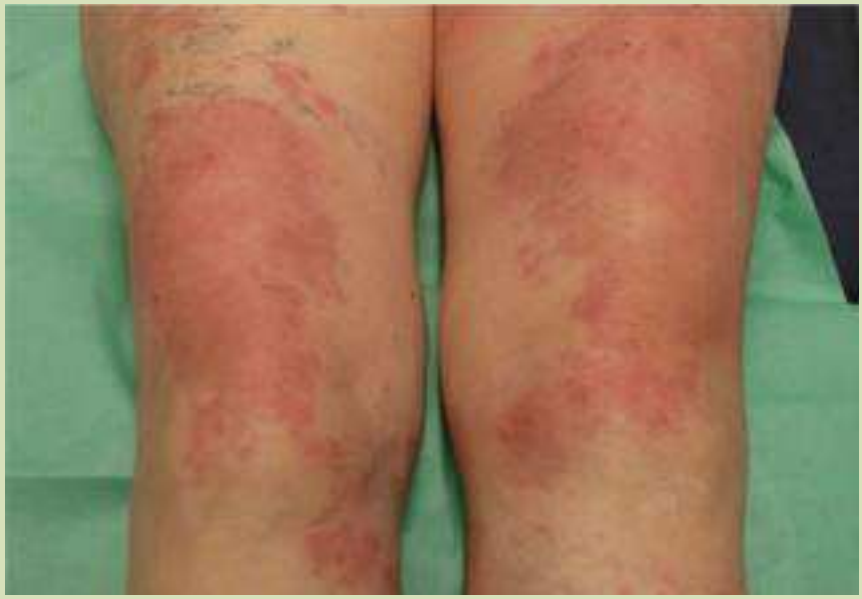


Cl: Circumscribed swelling with pustular core.

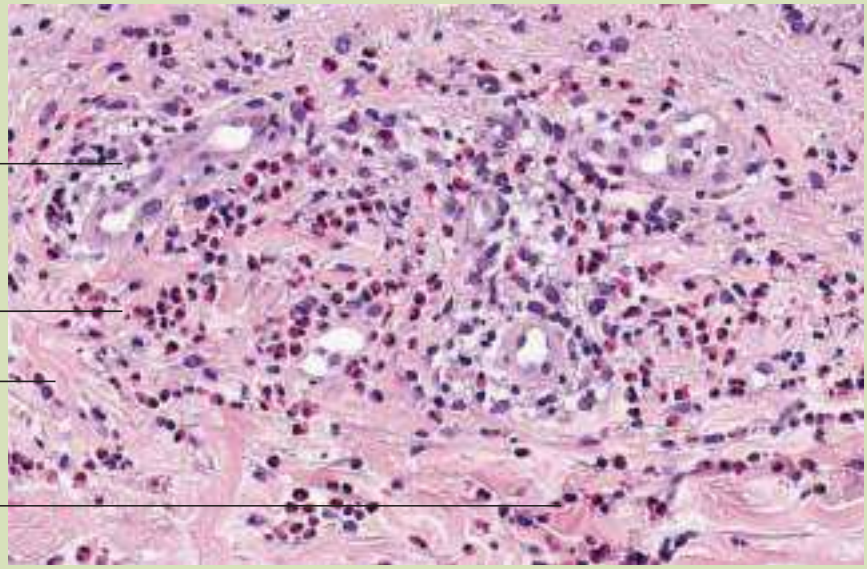


Hi: Purulent neutrophilic infiltrate with necrosis.

DIFFERENTIAL DIAGNOSIS: Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis)

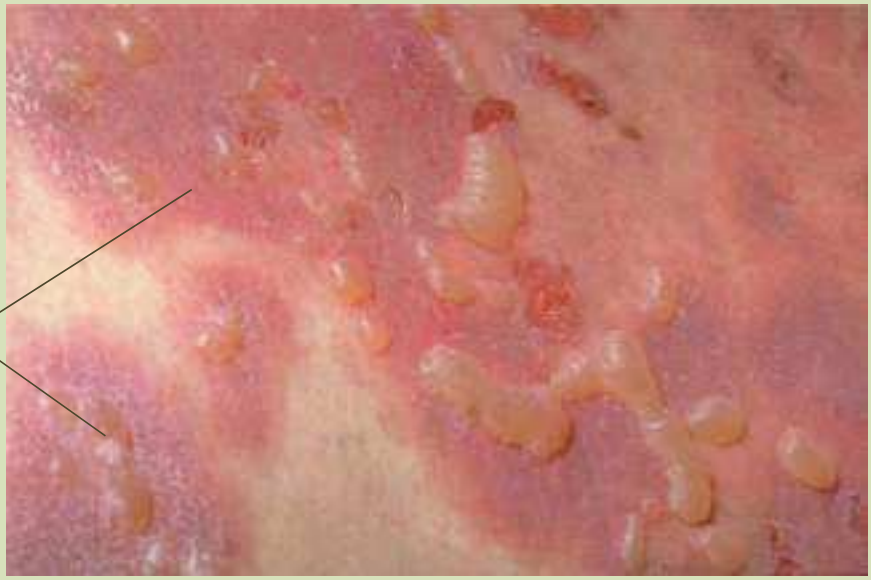


Cl: Purpuric erythema.

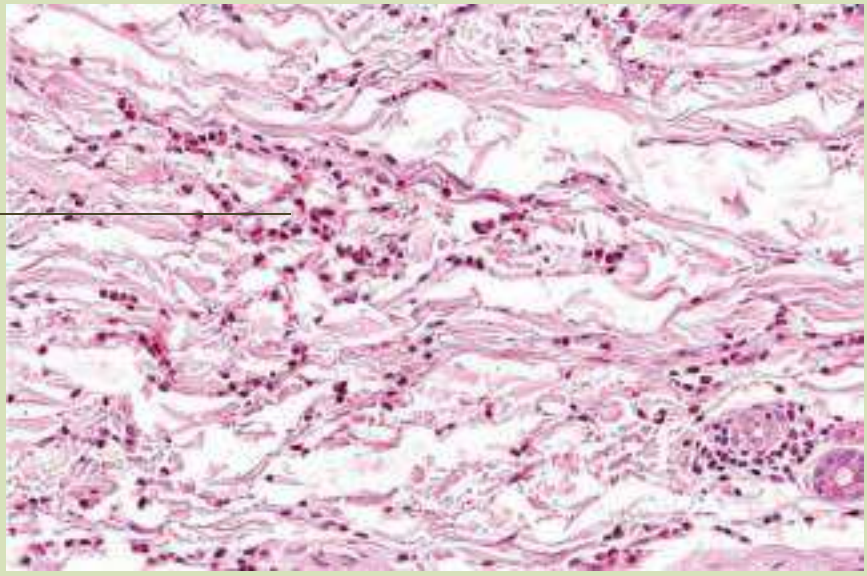


Hi: Eosinophilic vasculitis in conjunction with eosinophilic flame figures and/or eosinophilic palisading micro-granulomas. Eosinophilic vasculitis is paramount for the diagnosis.

DIFFERENTIAL DIAGNOSIS: Bullous pemphigoid

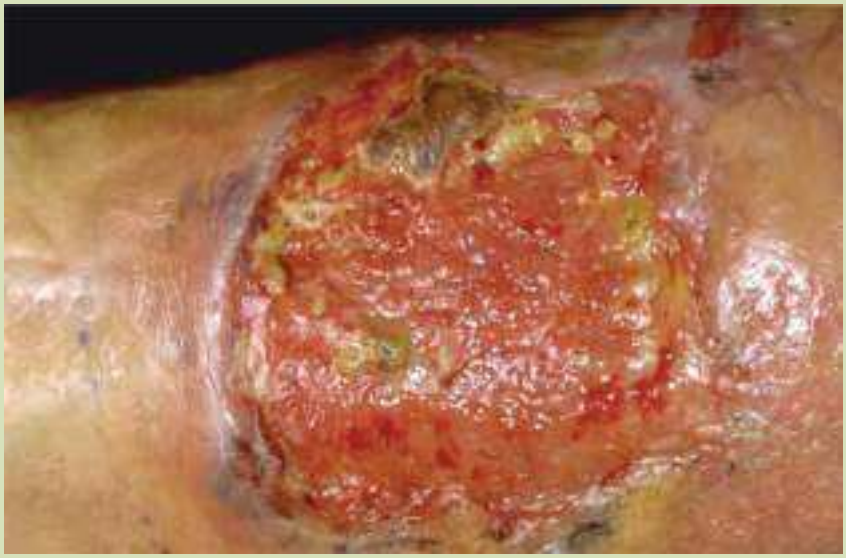


Cl: Erythema and tense bullae, occasionally hemorrhagic.

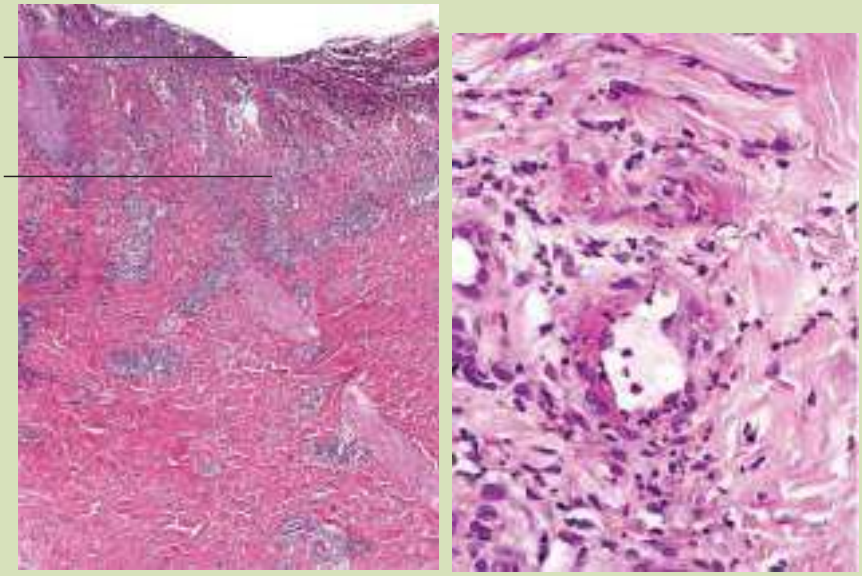


Hi: Classic subepidermal bulla, in conjunction with an adjacent eosinophilic infiltrate, occasionally studded with eosinophilic flame figures.

DIFFERENTIAL DIAGNOSIS: Pyoderma gangraenosum



Cl: Centrifugally expanding ulcer with elevated undermined violaceous border.



Hi: Neutrophil-rich inflammation beyond the ulcer and leukocytoklastic vasculitis with damaged vessel walls, intramural granulocytes, fibrin- and erythrocyte-extravasation.

Other Diagnosis

Arthropod bite reaction (*see* Chapter 3, Subepidermal blistering, page 129): *Circumscribed, wedge-shaped infiltrate, occasionally with flame figures.*

Eosinophilic folliculitis (HIV): *Folliculitis with eosinophilic granulocytes, often spilling over into the adjacent dermis.*

Eosinophilic fasciitis (Shulman syndrome) (*see* Sclerosis page 210): *Superficial and deep infiltrate, extending into the subcutis. Often sparse eosinophilic infiltrate in upper parts of the dermis, and dense infiltrate in the subcutis. Flame figures are not a constant feature.*

Comments

Classic "red" flame figures consist of a degenerate collagenous core surrounded by densely packed eosinophilic granulocytes and karyorrhexis. This type of flame figure may be encountered in all variants of eosinophil-rich inflammatory infiltrates.

Classic "blue" flame figures ("Churg-Strauss granuloma") consist of a rather large, strongly basophilic central necrobiotic collagenous core surrounded by densely packed neutrophilic granulocytes. Basophilic flame figures are most often associated with LE, rheumatoid arthritis and similar autoimmune disorders.

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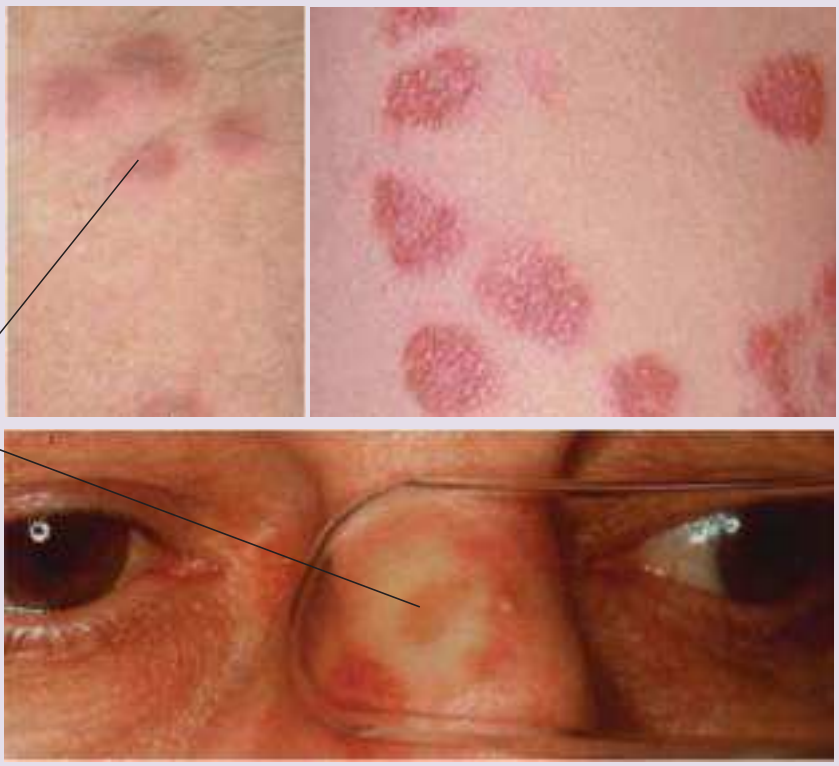
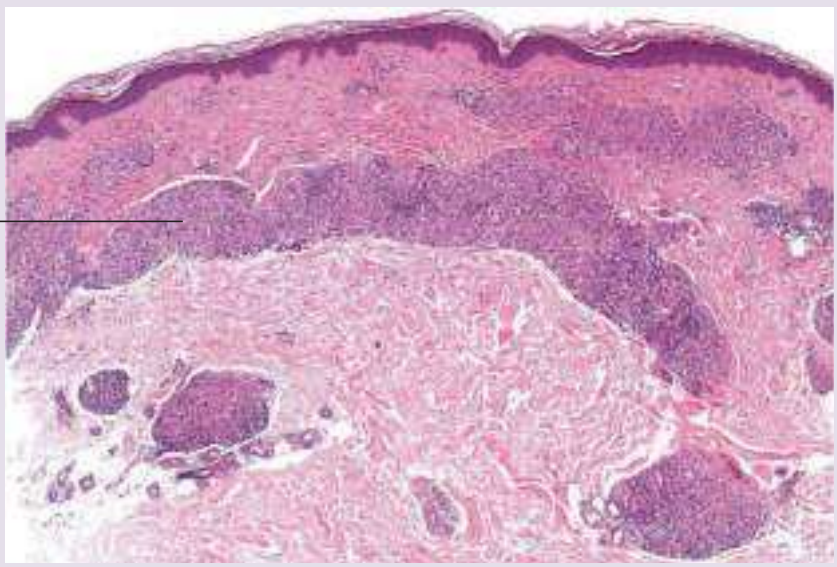
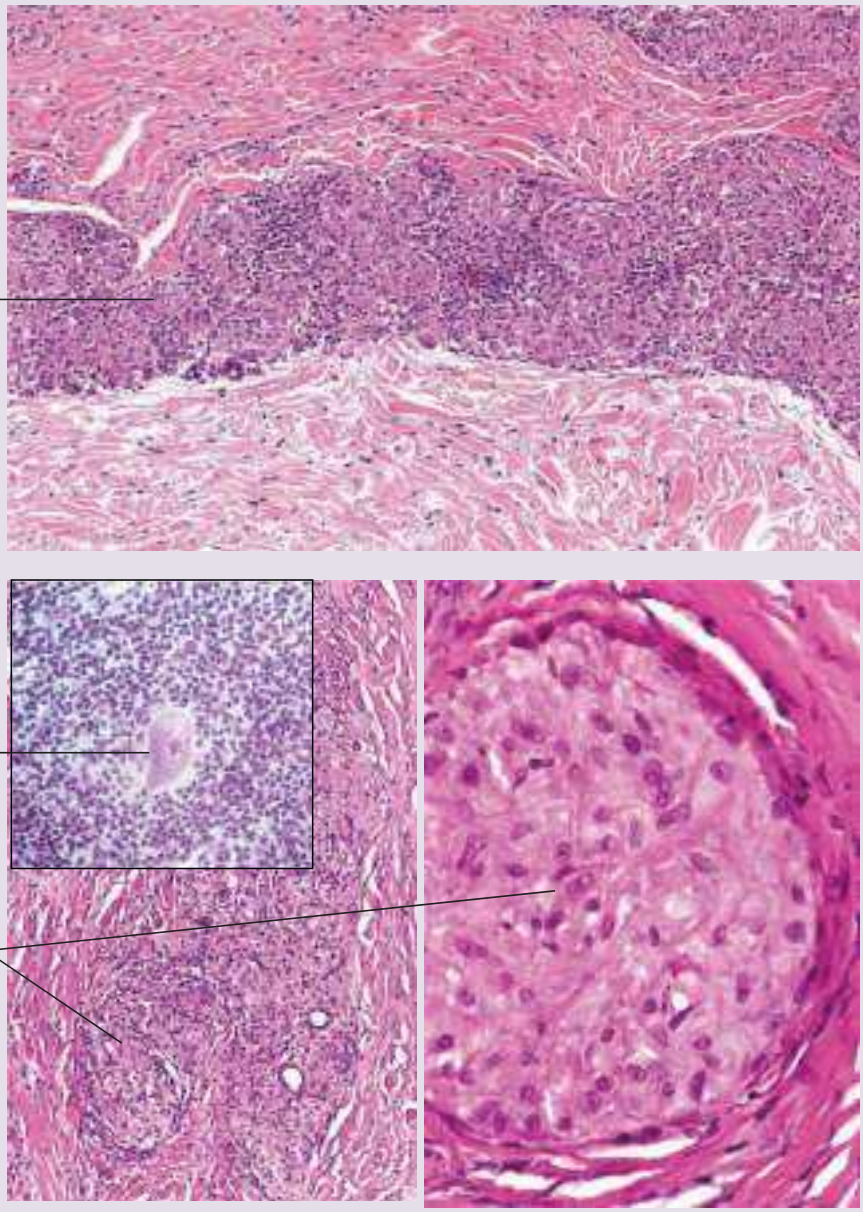
PROTOTYPE: Sarcoidosis



CI: There are many clinical forms of skin manifestations in sarcoidosis, which is basically a systemic disease with manifestations in various organs. Cutaneous lesions may appear as brown-bluish "sarcoid" erythemas, plaques, nodules, circinate lesions, subcutaneous infiltrates or cicatricial lesions.

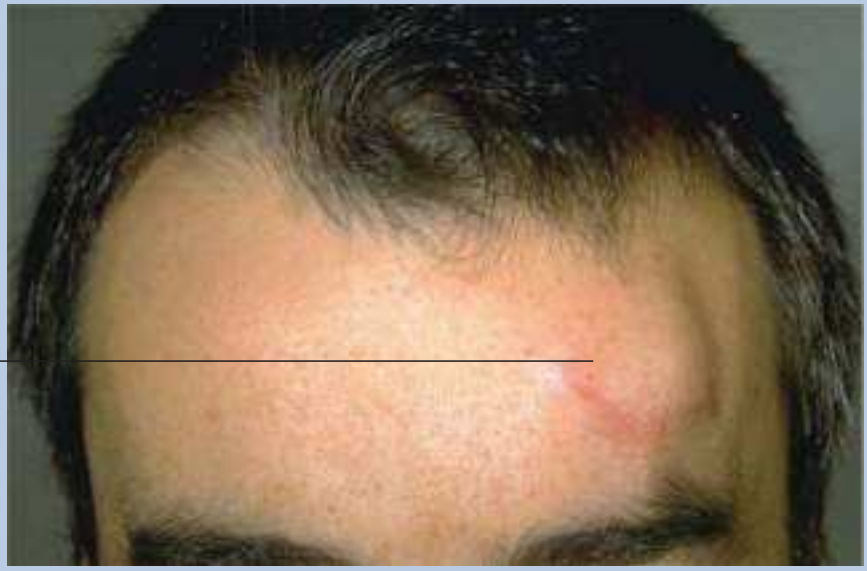


Sarcoidosis

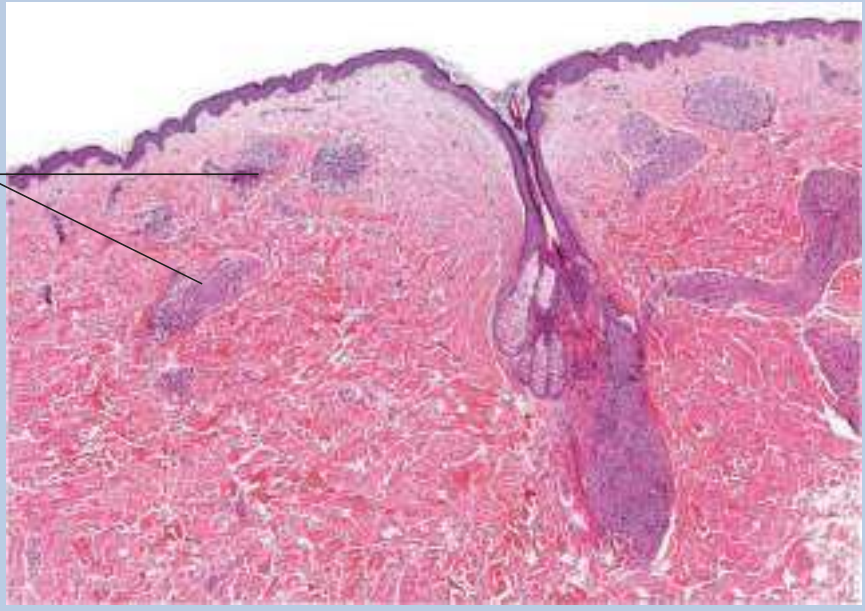


Hi: Dermal nodular infiltrates of non-caseating "naked" (lacking an accompanying lymphocytic infiltrate) epithelioid granulomas; asteroid bodies in the cytoplasm of histiocytic giant cells. Admixture of only a few lymphocytes in most cases. Occasionally birefringent foreign body material is detectable by polarization (sarcoidal foreign body reaction).

VARIANT: Granulomatosis disciformis (Miescher)

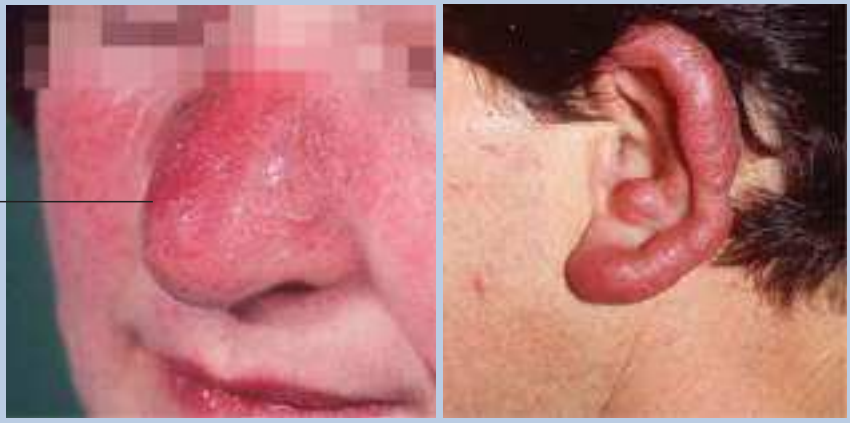


CI: Superficial disk-like or ring-shaped lesion, frequently on the forehead.

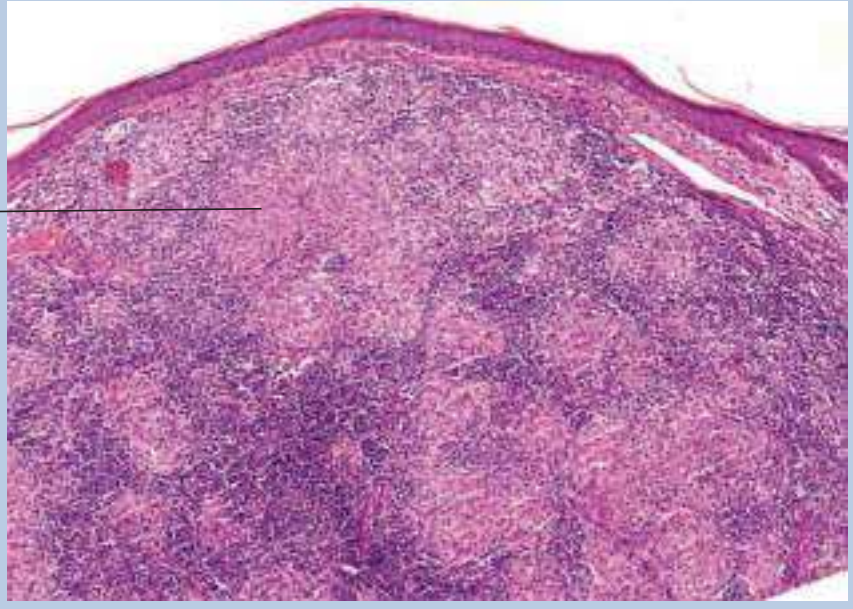


Hi: "Naked" epithelioid cell granulomas in the upper dermis.

VARIANT: Sarcoidosis (Lupus pernio)



Cl: Bluish red infiltrated swelling, mostly in acral localization.

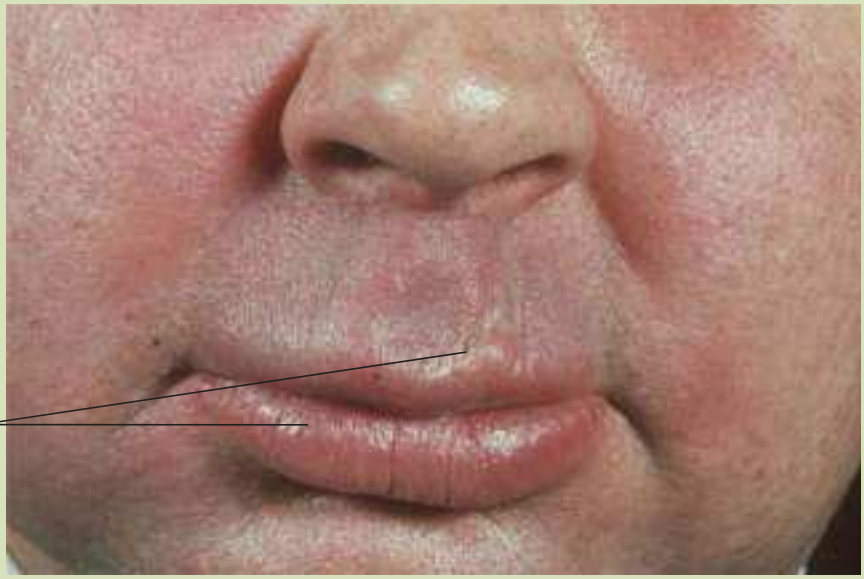


Hi: Epithelioid granulomas accompanied by a dense lymphocytic infiltrate. Mostly located on the face, especially the nose.

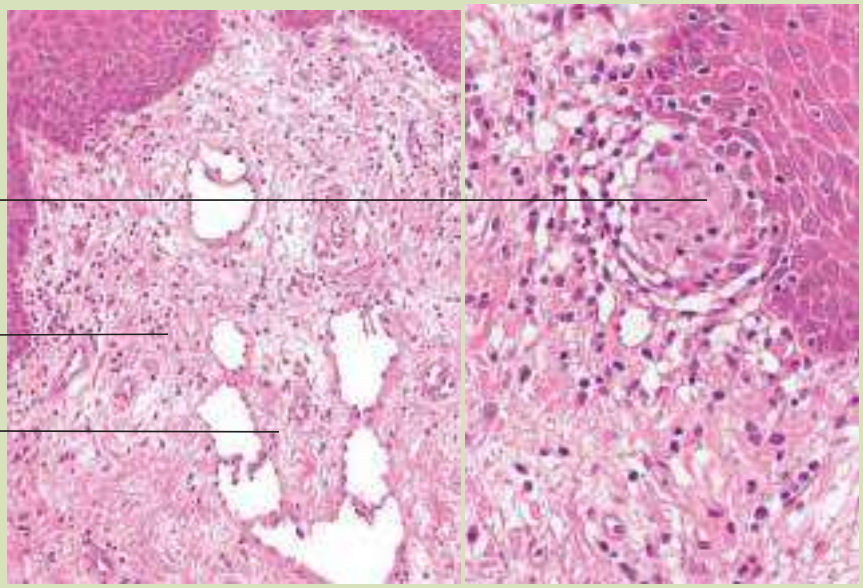
Sarcoidosis associated syndromes

- *Löfgren-syndrome:* *Acute sarcoidosis, involvement of hilar lymph nodes, erythema nodosum, arthritis.*
- *Heerfordt –syndrome:* *Enlargement of parotis gland, uveitis, paresis of the facial nerve, fever.*
- *Ostitis cystica multiplex (Jüngling):* *Chronic fibrosing sarcoidosis, lupus pernio, bone cysts (distal phalanx of digits or toes).*

DIFFERENTIAL DIAGNOSIS: Cheilitis granulomatosa (Miescher)

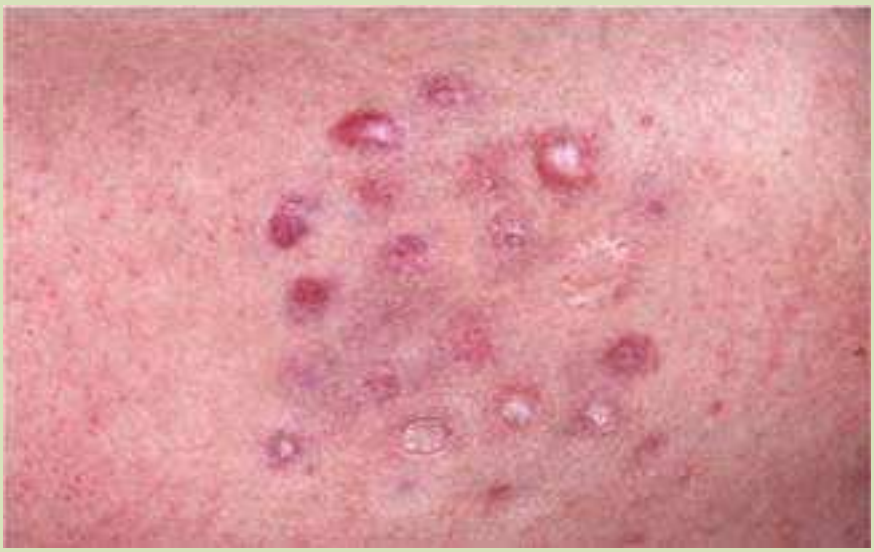


CI: Lip swelling, may be associated with facial paresis and lingua plicata (Miescher-Melkersson-Rosenthal syndrome).

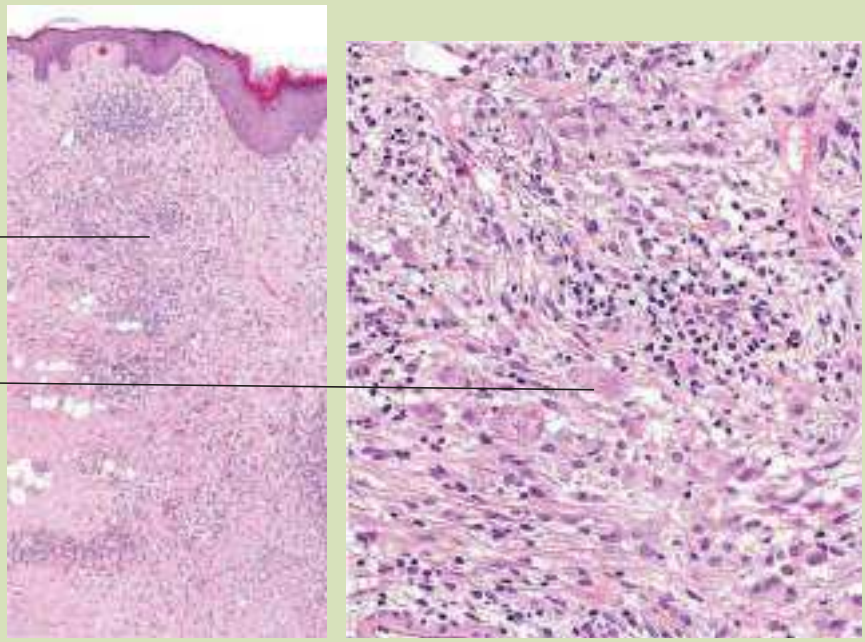


Hi: Edema or fibrosis of the dermis, few "naked" granulomas and dilatation of lymphatic vessels.

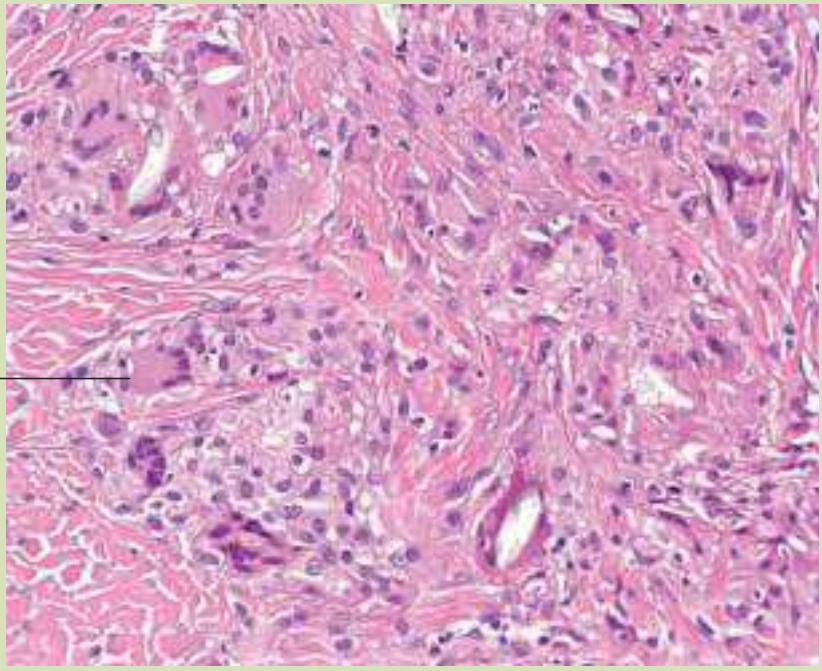
DIFFERENTIAL DIAGNOSIS: Foreign body granuloma

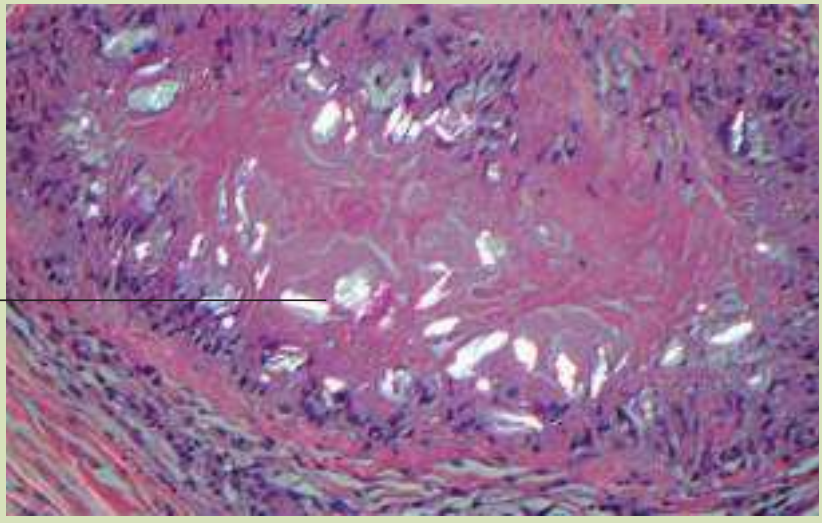


CI: Papules or scars.



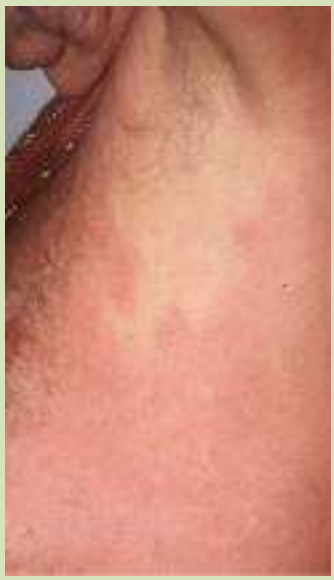
Foreign body granuloma



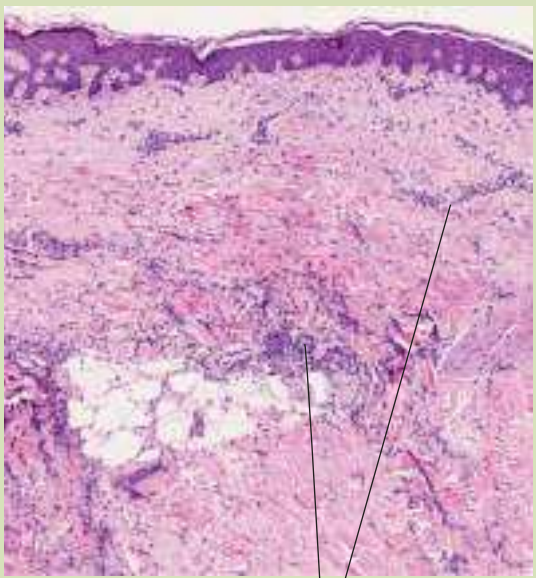


Hi: Detection of foreign bodies of various origin (filler substances, trauma-associated foreign material such as glass etc.).

DIFFERENTIAL DIAGNOSIS: Interstitial granulomatous dermatitis (with arthritis)

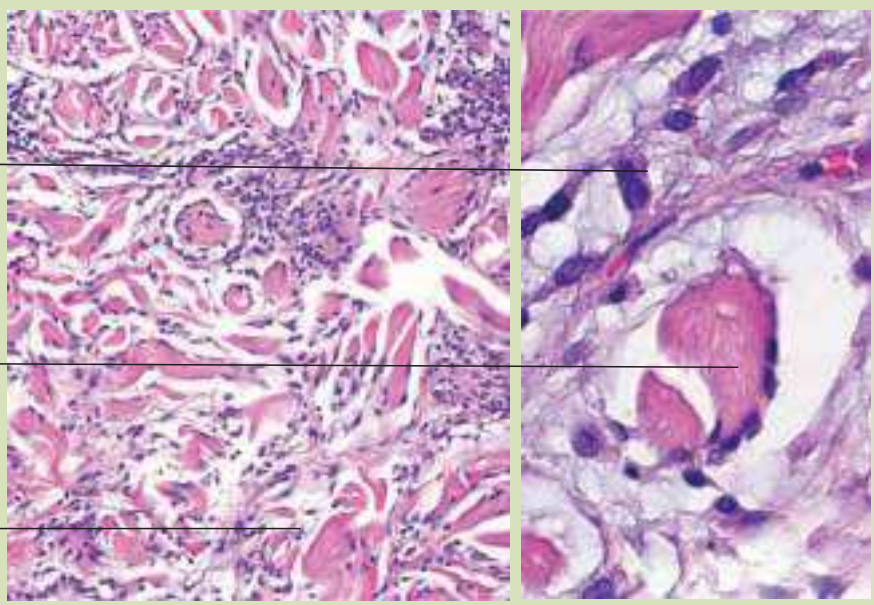


Distinct macular erythema on the left side of the thorax



CI: Patchy confluent erythema associated with arthritis.

Interstitial and perivascular neutrophilic infiltrate



Histiocytes

«Free floating» collagen bundle surrounded by histiocytes

Interstitial histiocyte-rich infiltrate

Hi: Histiocyte-rich infiltrate, eosinophils, entrapment of collagen fibres, no necrobiosis. Typical "free floating" collagen bundles with peripheral rims of histiocytes.

Other Diagnosis

Granulomatous rosacea (*see* Chapter 8, Pilosebaceous unit, page 332): *Erythematous and slightly brownish plaques, papules or pustules in a centrofacial distribution involving the nose and cheeks. Histologically there is a folliculocentric granulomatous dermal infiltrate with epithelioid cells and multinucleated giant cells of the Langhans-type, telangiectasias in the upper dermis, lymphocytes, neutrophils and plasma cells, sebaceous hyperplasia*

Granuloma faciale (*see* Chapter 5, Localized, page 252): *violaceous brown-red infiltrated plaques, preferentially in the face of males. Histologically there is a lymphohistiocytic ("granulomatous") infiltrate with leukocytoklastic vasculitis. Many eosinophils and plasma cells are present.*

Granuloma annulare (*see* Dermis: Infiltrates: Granulomatous, with necrosis, page 187): *Necrobiotic areas containing mucin surrounded by a palisading histiocytic infiltrate or focal interstitial histiocyte-rich infiltrates (interstitial type).*

Crohn's disease: *Non-caseating granulomas, clinical context crucial for diagnosis.*

Mycobacterial infections (*see* Granulomatous, with necrosis, page 179)*: Granulomas with or without necrosis (e.g. atypical mycobacteria) with admixture of neutrophils and lymphocytes. Detection of mycobacteria as acid-fast bacilli in Ziehl Neelsen stain, by PCR or tissue culture.*

Granulomatous cutaneous T-cell lymphoma (mycosis fungoides): *Sarcoidal or granuloma annulare like pattern. Atypical small to medium-sized lymphocytes, epidermotropism in only half of the cases.*

Erythema nodosum (*see* Chapter 6, Panniculitis, septal, page 268): *Multinucleated giant cells and mixed cellular infiltrate in the septa of the subcutaneous fat tissue. Erythema nodosum occurs together with lymphadenopathy and polyarthritis in the context of Loefgren syndrome in patients with acute sarcoidosis.*

Comment

The occurence of sarcoidal infiltrates due to foreign material in a preexisting scar may represent manifestation of systemic sarcoidosis and should be the starting point for further examinations.

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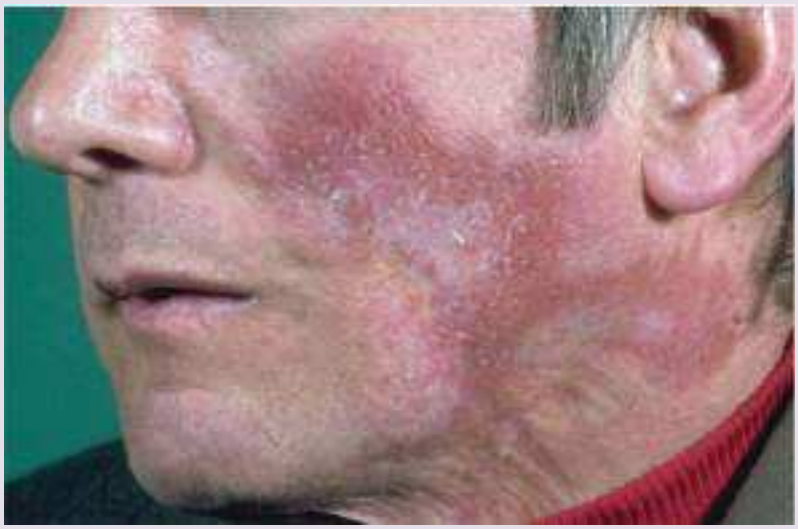
Sanchez, J. L., A. C. Berlingeri-Ramos, et al. (2008). "Granulomatous rosacea." *Am J Dermatopathol* **30**(1): 6–9.

Tchernev, G., J. W. Patterson, *et al.* (2010). "Sarcoidosis of the skin – a dermatological puzzle: important differential diagnostic aspects and guidelines for clinical and histopathological recognition." *J Eur Acad Dermatol Venereol* **24**(2): 125–37.

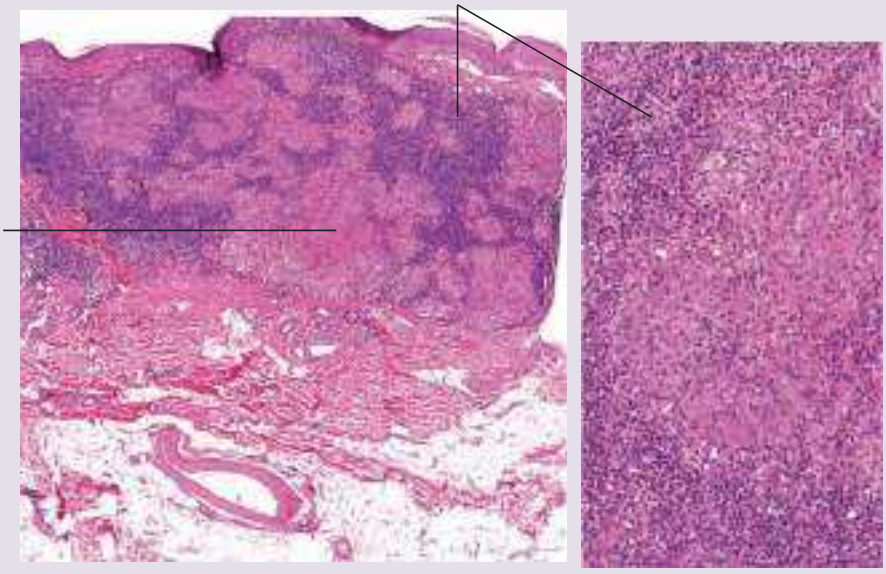
Tomasini, C. and M. Pippione (2002). "Interstitial granulomatous dermatitis with plaques." *J Am Acad Dermatol* **46**(6): 892–9.

PROTOTYPE: Lupus vulgaris

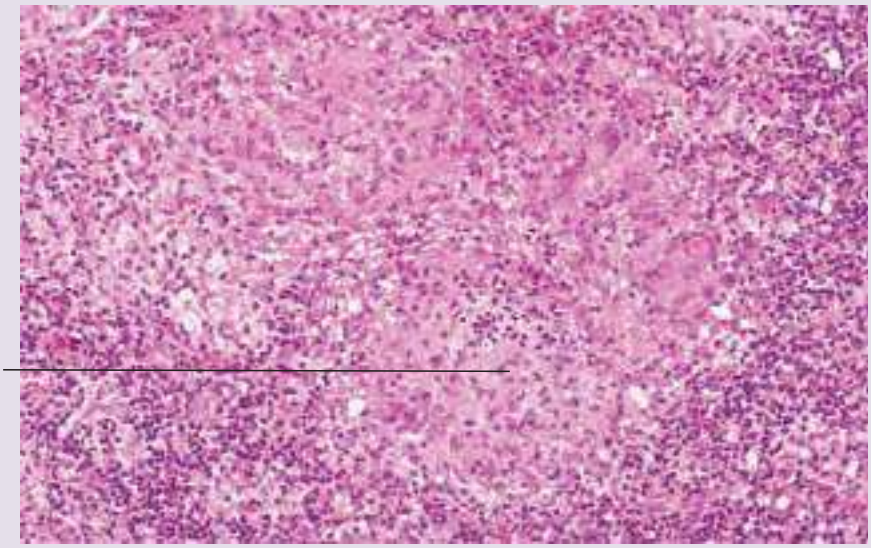


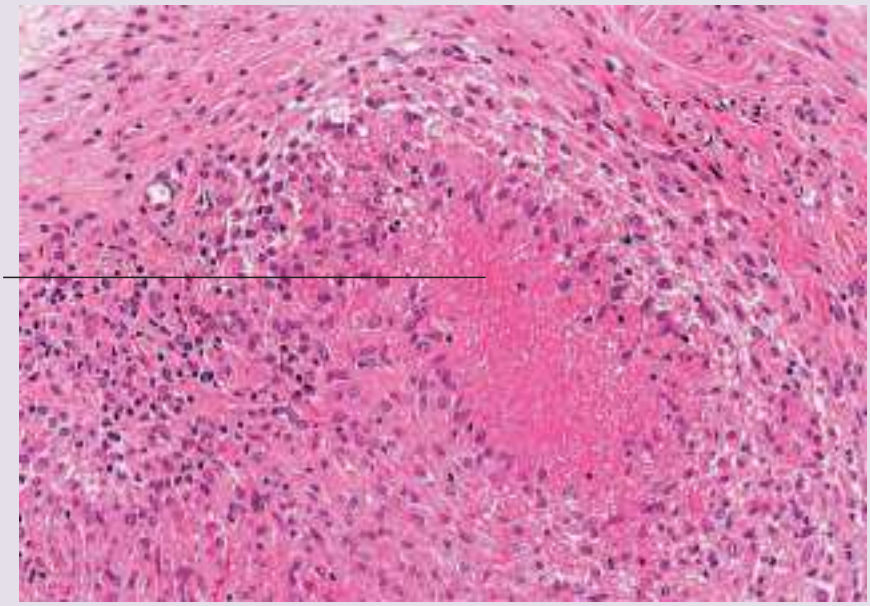
Atrophic slightly scaling red-brown plaque with scarring

CI: Small nodules or atrophic, mutilating plaques. Verrucous variants with hyperkeratosis.



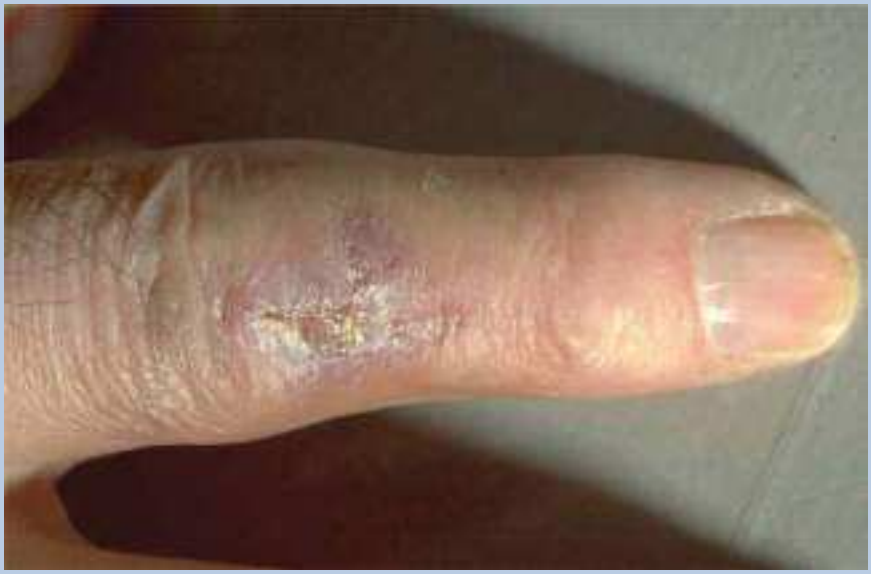
Lupus vulgaris



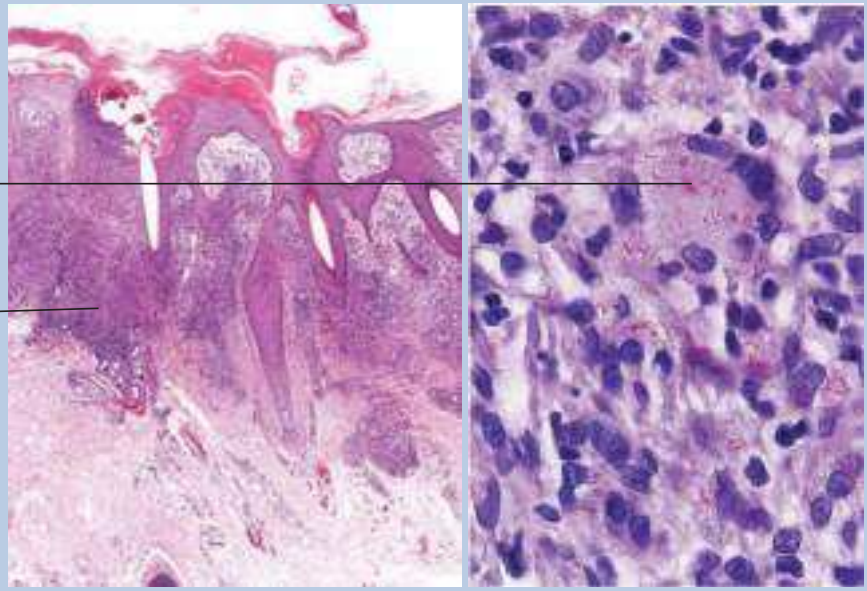


Hi: Small nodular dermal granulomas composed of pale histiocytes, few multinucleated Langhans cells, and a dense outer lymphocytic mantle. Central caseating necrosis may not always be present.

VARIANT: Atypical mycobacteriosis

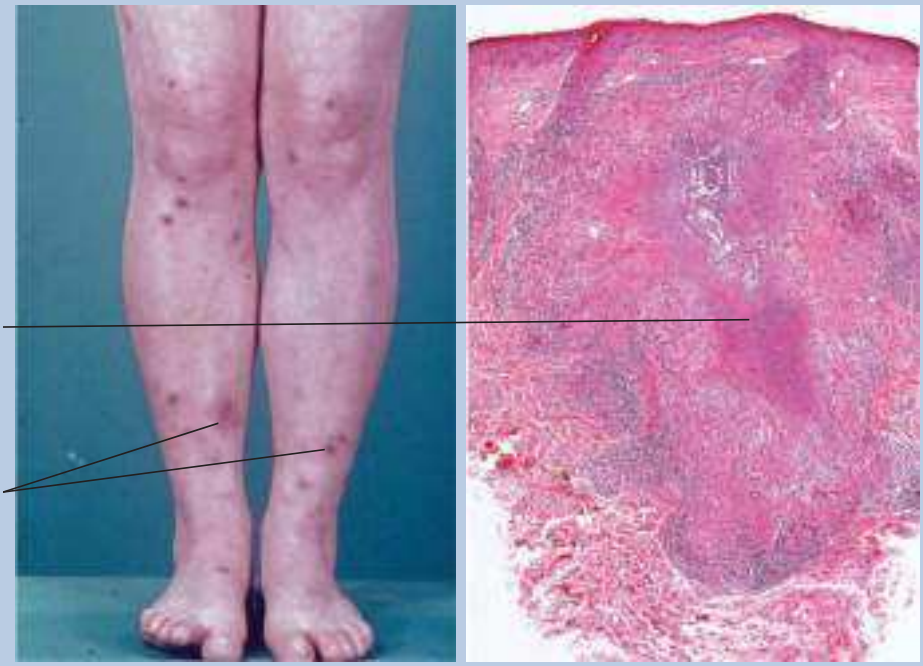


Cl: Brown-bluish, mostly solitary nodular or plaque-like infiltrate with superficial ulceration and crust formation. Preferentially acral localization (hand or finger).

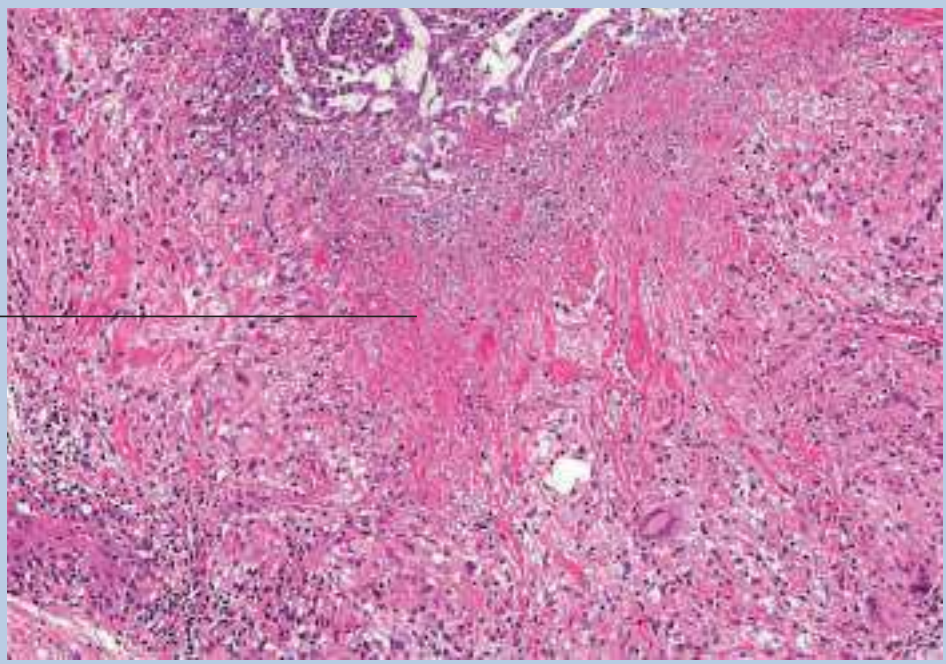


Hi: Neutrophil-rich histiocytic infiltrates and granulomas. Suppurative granulomas. Classic palisading pattern with caseation necrosis often missing. Detection of mycobacteria in some cases.

VARIANT: Papulonecrotic tuberculid

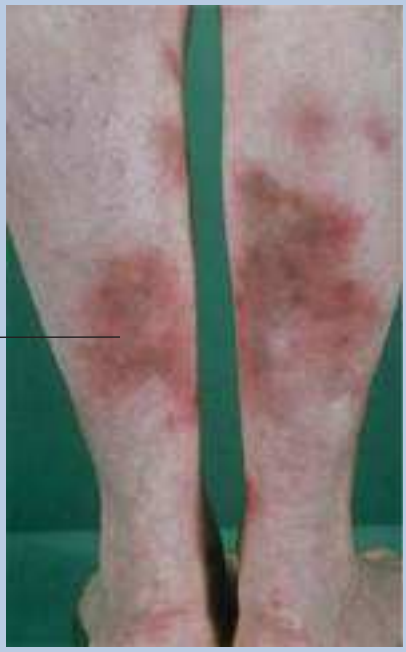


Cl: Papulo-necrotic lesions, mostly in acral localization.



Hi: Nodular or lymphohistiocytic infiltrates with or without caseation. Small granulomas.

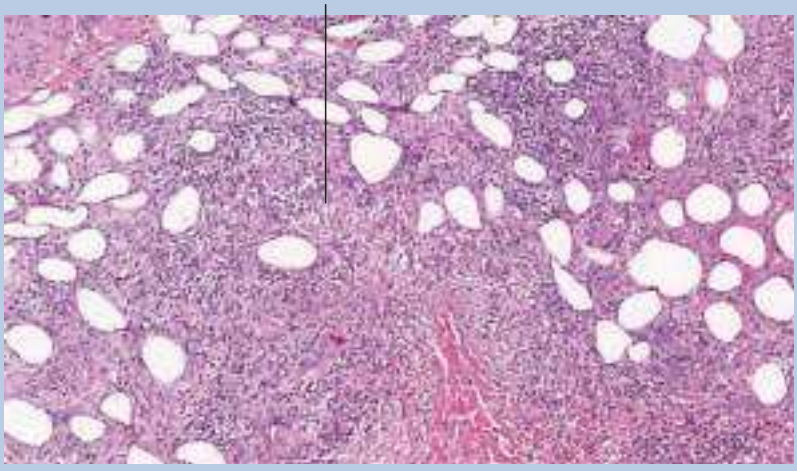
VARIANT: Erythema induratum (Bazin)



Contusiform lesions on the calfs

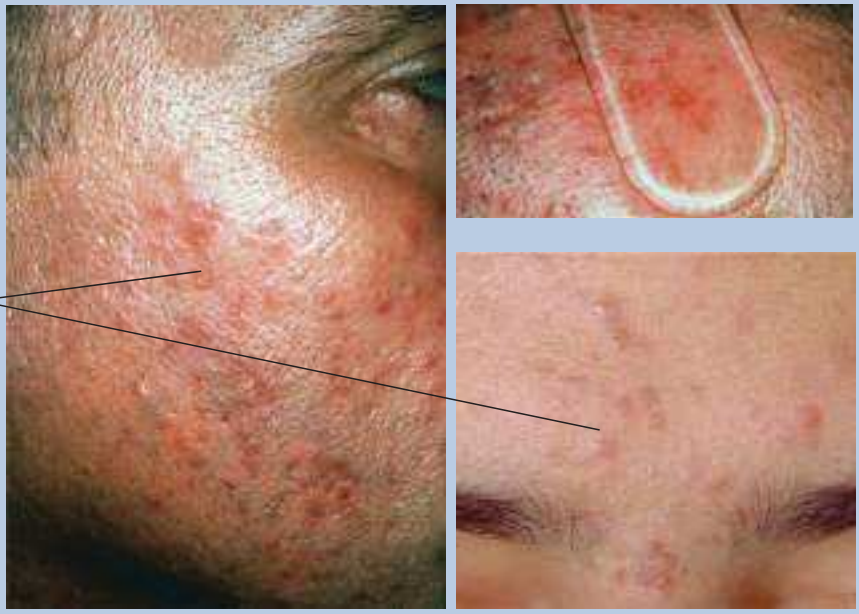
Cl: Contusiform plaques on the calfs, no ulceration.

Lymphohistiocytic infiltrate in the deep dermis and subcutis

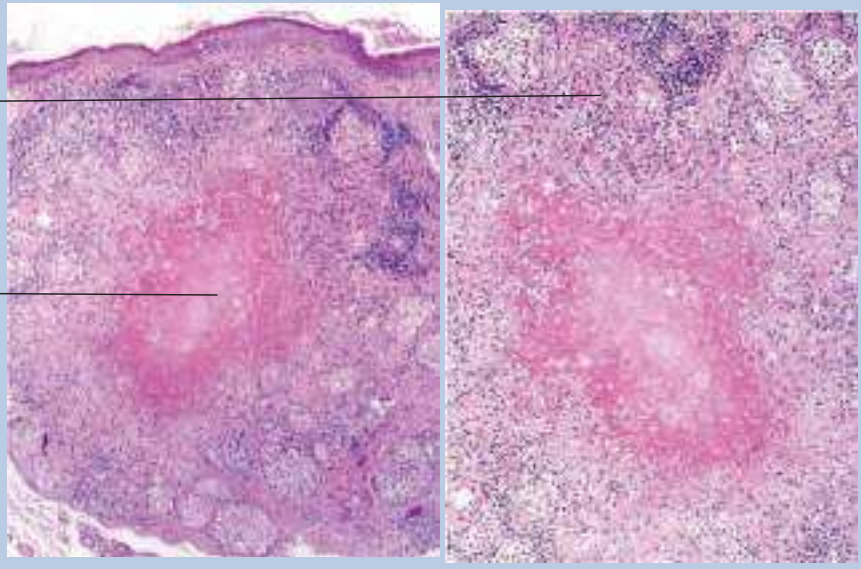


Hi: Suppurative granulomas. Mostly lobular panniculitis with or without accompanying vasculitis. Must be destinguished from nodal vasculitis and deep thrombophlebitis. Molecular detection of mycobacterial DNA in rare cases.

VARIANT: Lupus miliaris disseminatus faciei



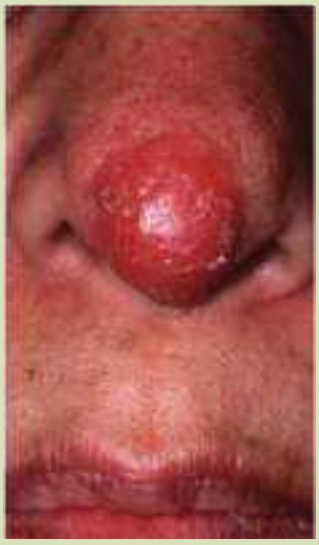
Cl: Tiny red-brown papules, simulating acne.

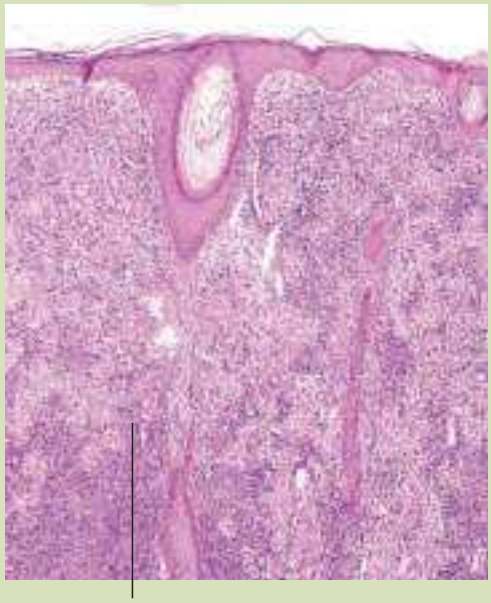


Hi: Classic lupus imitator with different clinical background (acne agminata): marked central necrobiosis surrounded by lymphocytes and predominating histiocytes. No infectious organisms.

Tuberculosis cutis verrucosa: *association of caseating granulomas with overlying verrucous epidermis.*

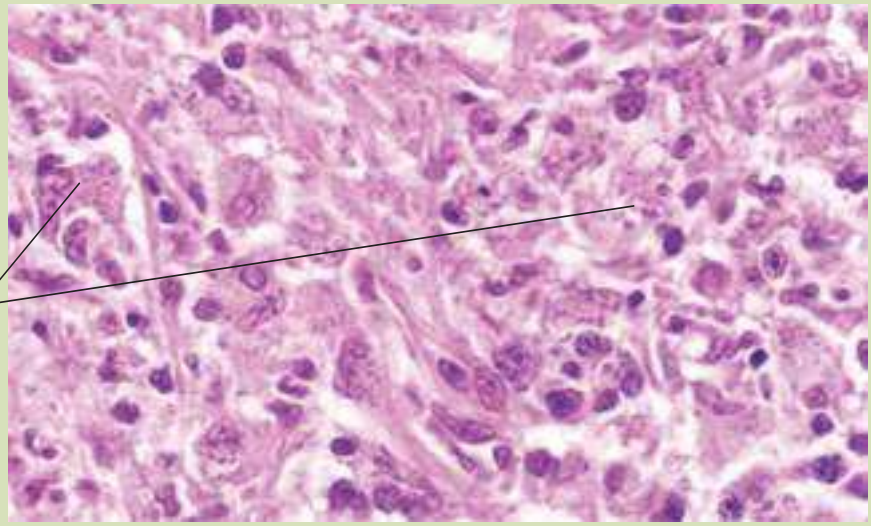
DIFFERENTIAL DIAGNOSIS: Leishmaniasis





Lympho-histiocytic infiltrate with granulomatous features hugging the epidermis.

Cl: Cutaneous form shows a nodular infiltrate with tendency to ulcération.



Amastigotes

Hi: Pale lymphohistiocytic infiltrate, with amastigotes. Plasma cells are typical.

Other Diagnosis

Granuloma annulare (*see* page 187)*: Firm small skin-colored papules arranged in rings or arcs with predilection of the extensor aspects of extremities (especially fingers and backs of hands); in disseminated variant trunk is also involved. Less frequently hard, movable subcutaneous nodules are found. No pruritus. Histology shows palisading granuloma, epitheloid cells, histiocytes, necrobiosis (degeneration of collagen), with deposits of mucin.*

Sarcoidosis (*see* Granulomatous, without necrosis, page 169)*: "Naked granulomas" with subtle or absence of a peripheral lymphocytic mantle. Slight central necrobiosis may be present in exceptional cases. No mycobacteria detectable.*

Necrobiosis lipoidica: *Yellow plaques and patches, frequently on the shins of women, erythematous border, central atrophy. Ulceration may occur. Histologically layers of confluent necrobiosis are seen throughout the dermis, alternating with layers of palisading lymphohistiocytic granulomatous infiltrate with multinucleated giant cells, plasma cells are common.*

Rheumatoid nodules: *Eosinophilic necrobiotic areas surrounded by palisading histiocytic infiltrate.*

Elastolytic giant cell granuloma: *Solitary or annular and confluent lesions, preferentially in light exposed areas. Histology shows annular granulomas with central necrobiosis, simulating granuloma annulare and many giant cells containing inclusions of phagocytized fibers.*

Foreign body granuloma (*see* Granulomatous, with necrosis, page 175)*: Look for birefringent foreign body particles.*

Granulomatous acne/rosacea (*see* Chapter 8, Pilosebaceous unit, page 332)*: Perifollicular infiltrates. No necrobiotic caseating centers amidst granulomas. No typical palisading pattern.*

Granuloma faciale (*see* Chapter 5, Localized, page 252)*: Brownish plaques, frequently in the face or on the forehead. Lymphohistiocytic, granulomatous infiltrate with eosinophils and plasma cells with signs of leukocytoklastic small vessel vasculitis.*

References

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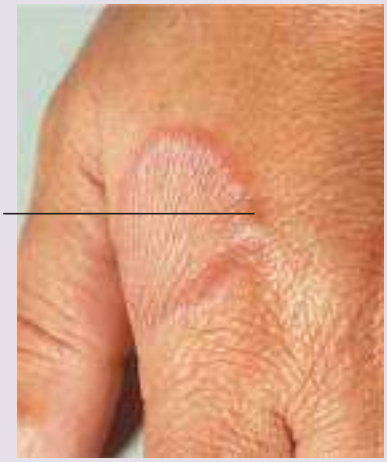
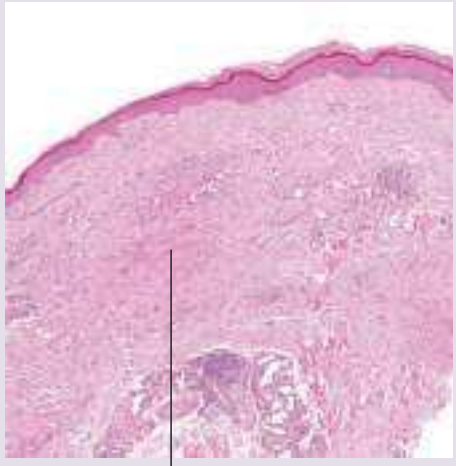
Min, K. W., J. Y. Ko, *et al*. (2012). "Histopathological spectrum of cutaneous tuberculosis and non-tuberculous mycobacterial infections." *J Cutan Pathol* **39**(6): 582–95.

PROTOTYPE: Granuloma annulare

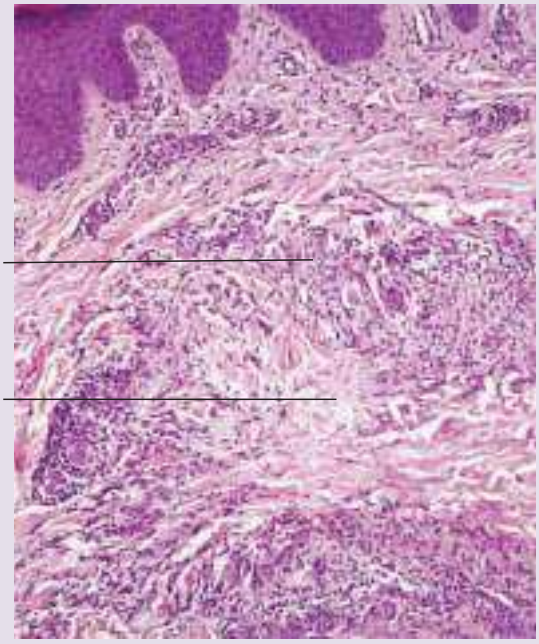


Ring of confluent skin colored papules



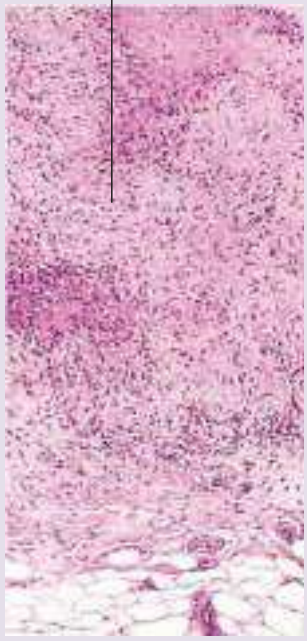
CI: Firm small skin-colored papules arranged in rings or arcs on the extensor aspects of extremities (especially fingers and backs of hands); in disseminated form trunk is also involved. Less frequently hard, movable subcutaneous nodules are found. No pruritus.

Granulomatous infiltrate

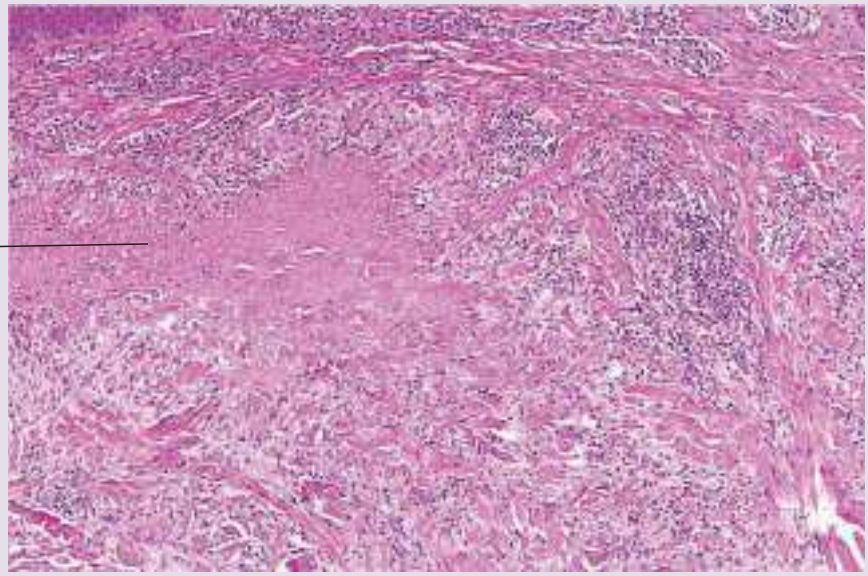


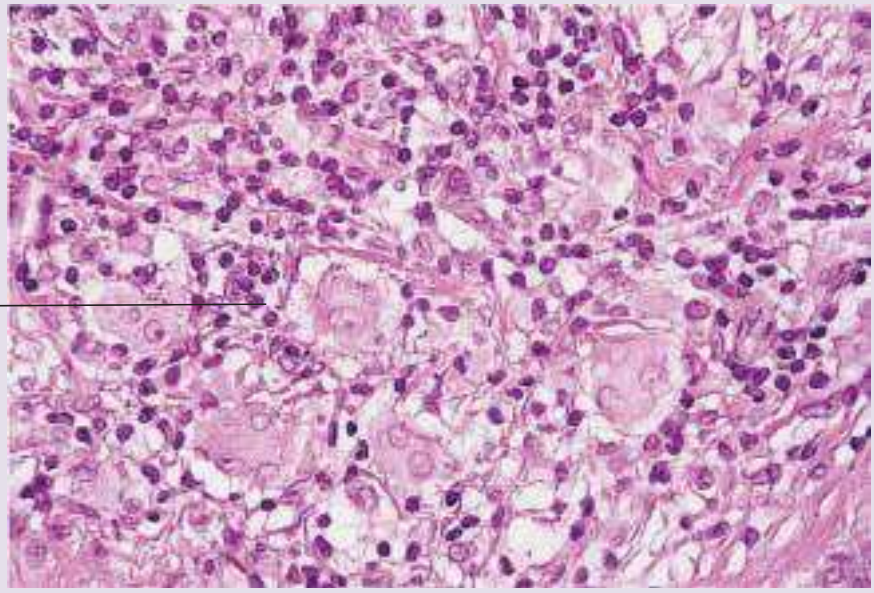
Palisading granuloma

Necrobiosis



Granuloma annulare





Hi: Palisading granuloma, epitheloid cells, histiocytes, necrobiosis (degeneration of collagen), deposits of mucin, a few eosinophils.

VARIANT: Deep granuloma annulare

Interstitial form: *no necrobiosis, interstitial histiocyte-rich infiltrate*

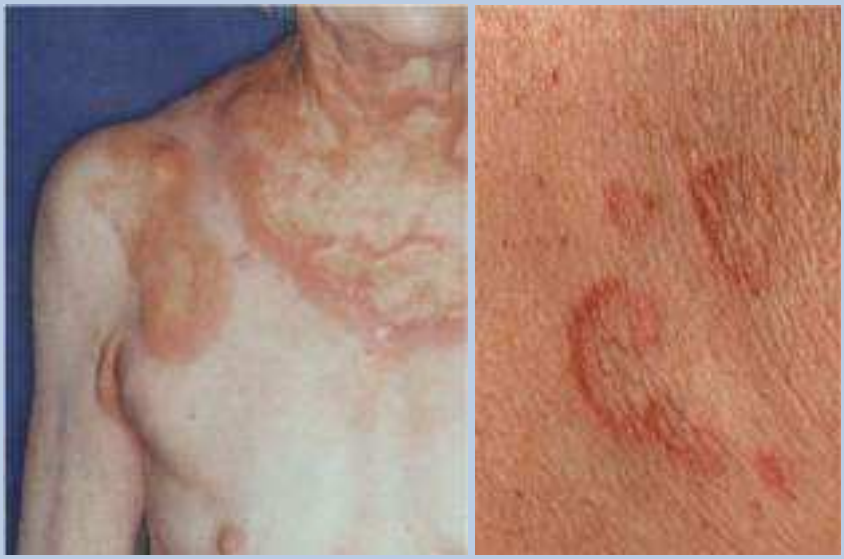
Perforating granuloma annulare

Subcutaneous granuloma annulare

Granuloma annulare in scars (zoster)

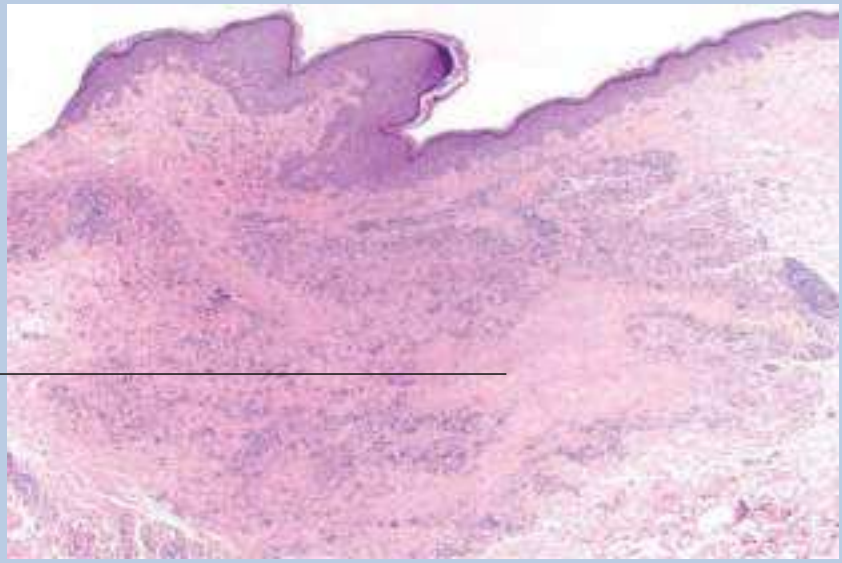
VARIANT: Annular elastolytic giant cell granuloma

Confluent anular lesions with elevated border and central atrophy



Cl: Annular or plaque-like lesions with elevated borders.

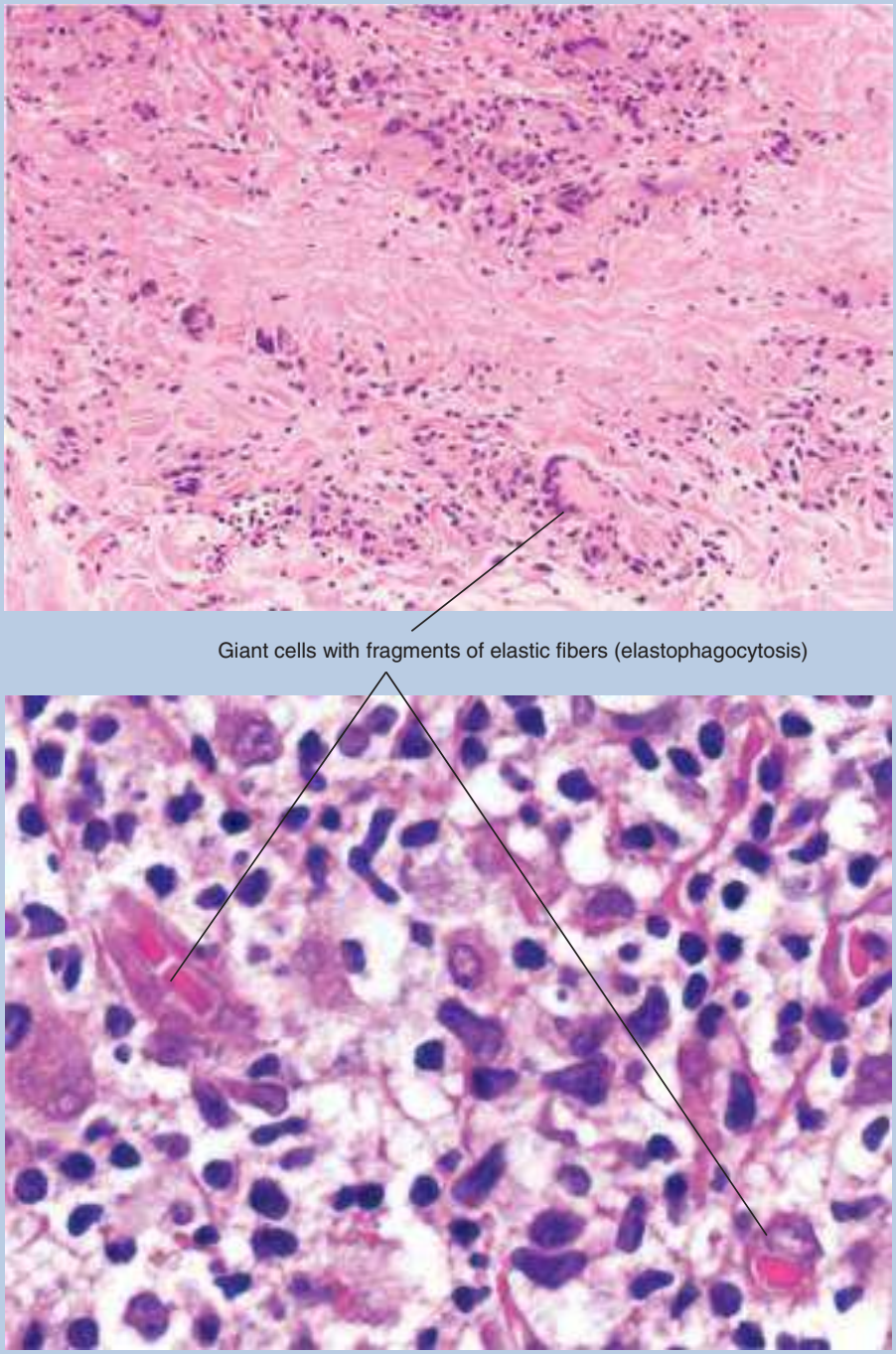
Palisading histiocyte-rich infiltrate with central necrobiosis



Comment

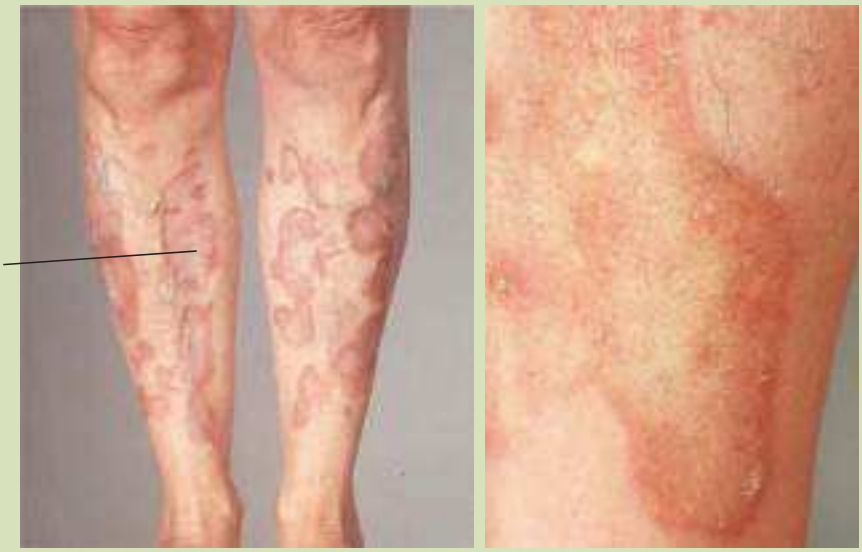
May be identical with necrobiotic xanthogranuloma (*see* DEPOSITION AND STORAGE, Lipids, page 295).

Annular elastolytic giant cell granuloma

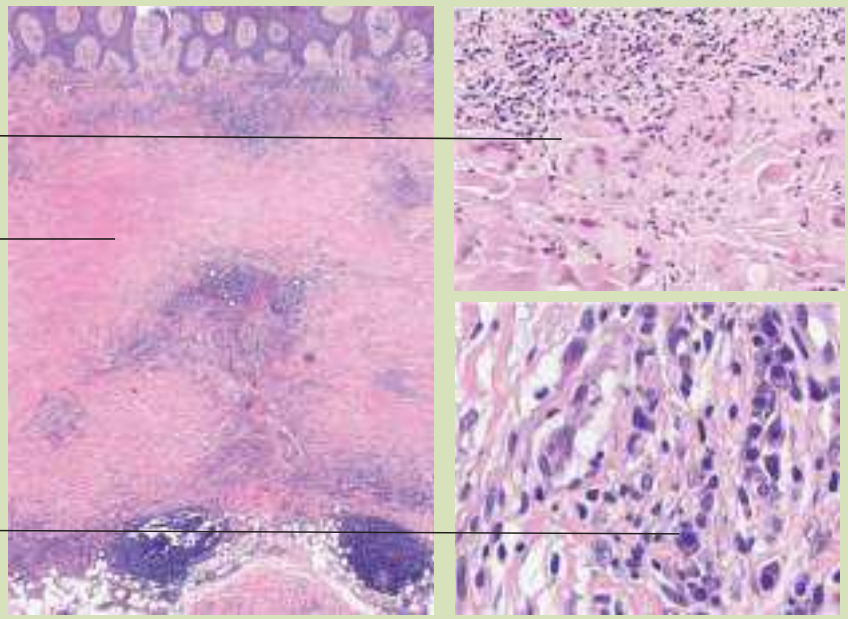


Hi: Palisading granuloma with central necrosis; multinucleated giant cells with inclusions of fibrous material in the periphery.

DIFFERENTIAL DIAGNOSIS: Necrobiosis lipoidica

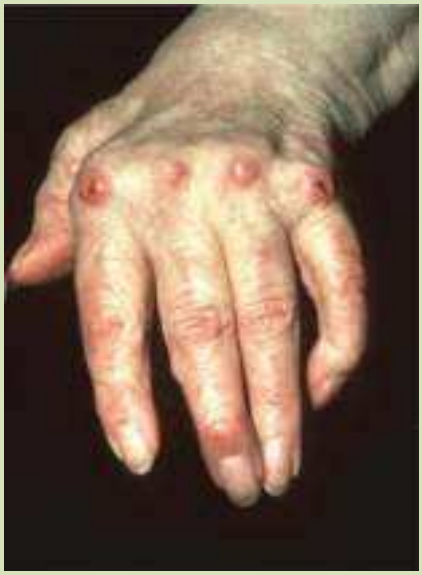


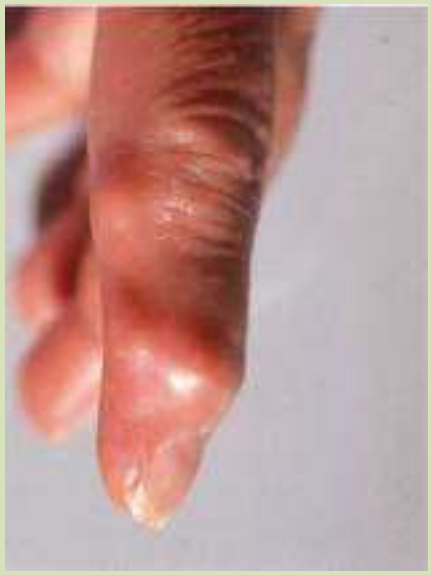
Cl: Brownish and yellowish atrophic plaques with erythematous border, preferentially on the lower extremities; frequent association with diabetes mellitus.



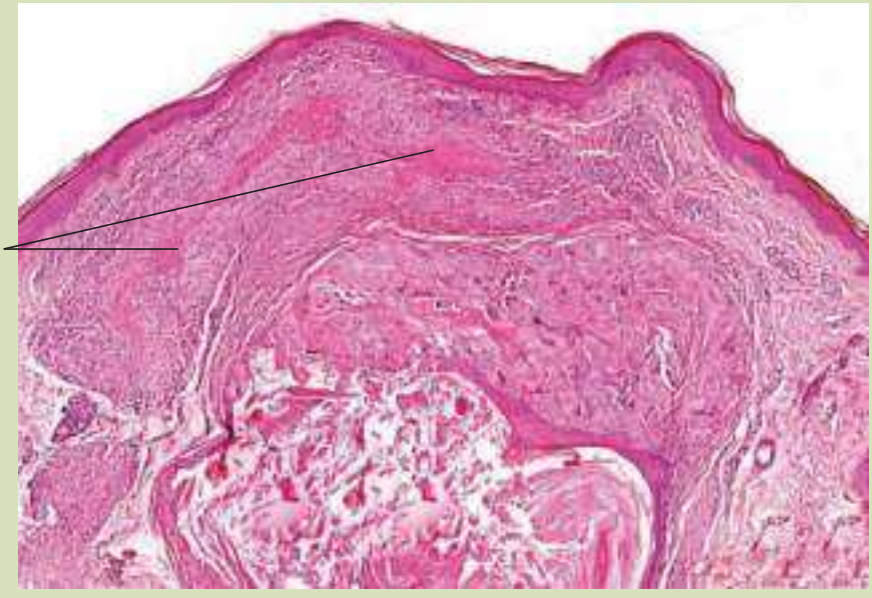
Hi: Alternating horizontal layers of degenerated collagen and granulomatous infiltrate throughout all levels of the dermis.

DIFFERENTIAL DIAGNOSIS: Rheumatoid nodule

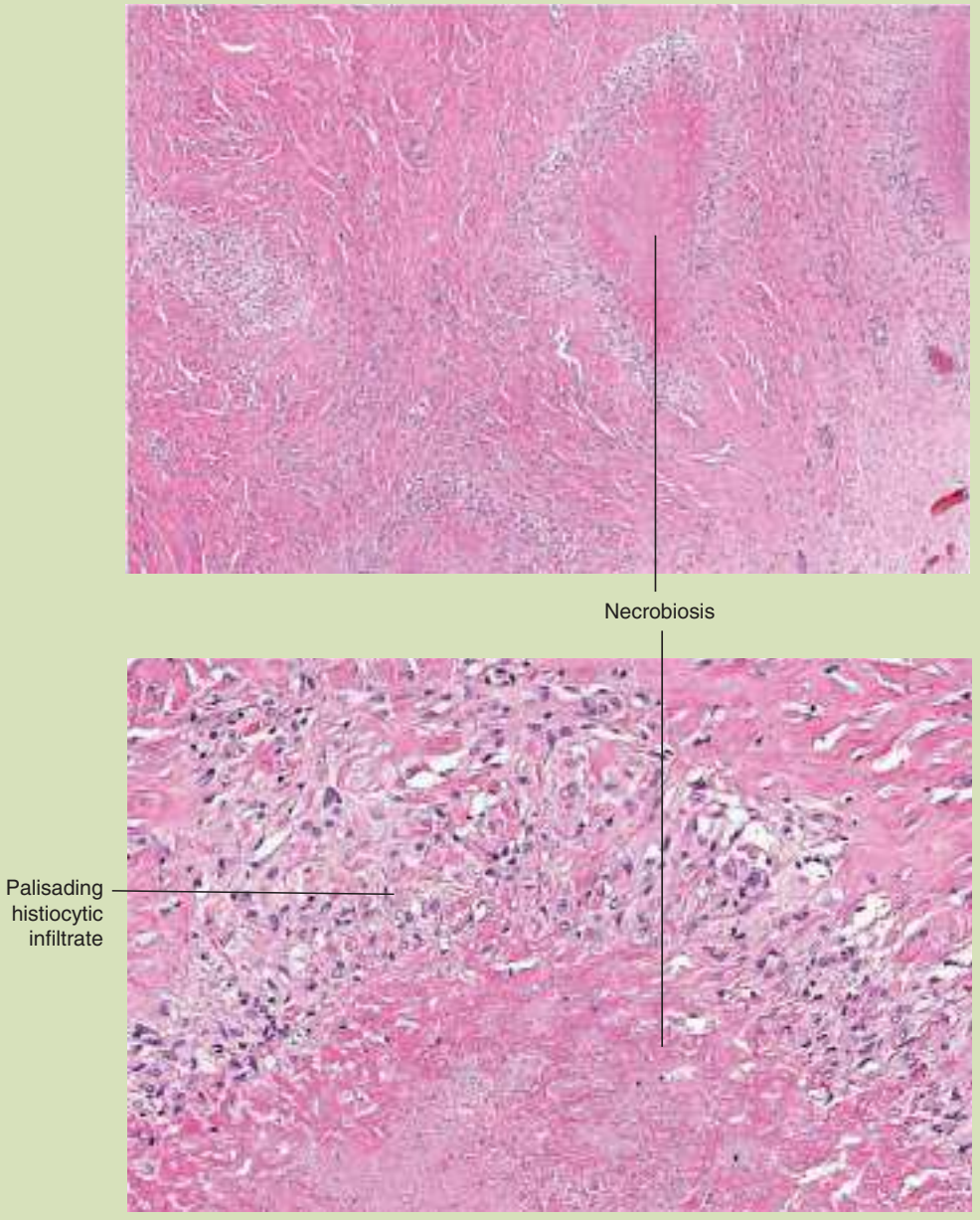




CI: Hard nodules, preferentially on elbows, fingers, feet and knees, in conjunction with rheumatoid arthritis.



Rheumatoid nodule



Hi: Area of eosinophilic degeneration of collagenous and fibrous tissue, surrounded by a palisaded granulomatous infiltrate. Vasculitis is exceptionally rare.

References

Al-Hoqail, I. A., A. M. Al-Ghamdi, *et al*. (2002). "Actinic granuloma is a unique and distinct entity: a comparative study with granuloma annulare." *Am J Dermatopathol* **24**(3): 209–12.

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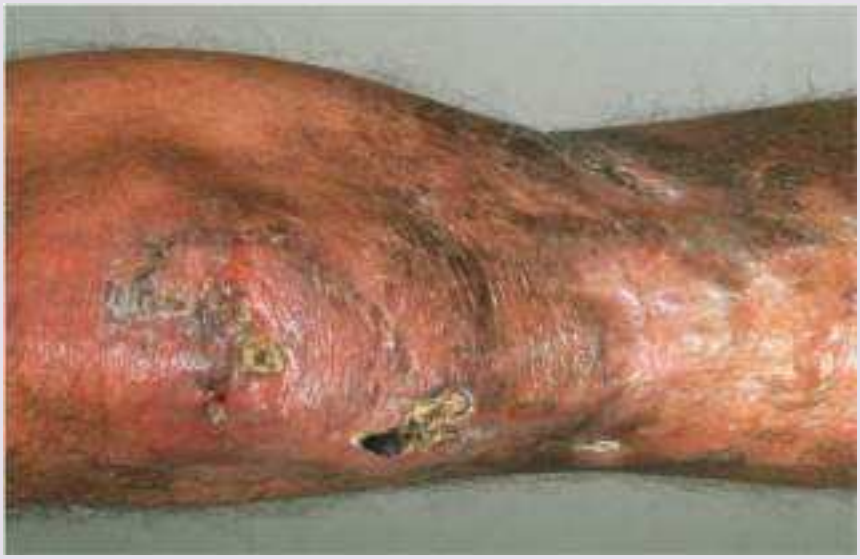
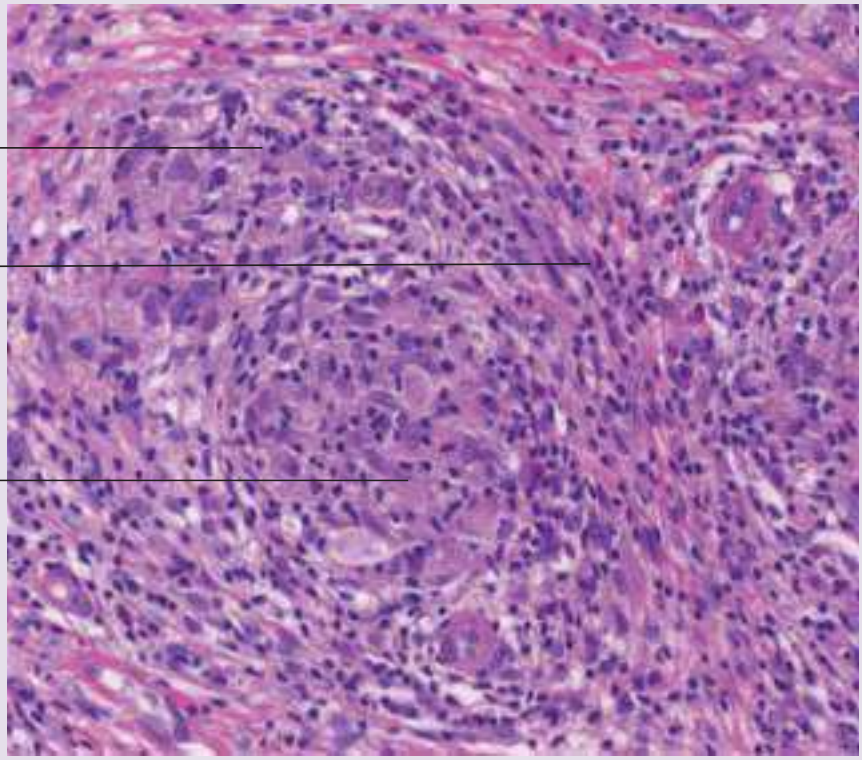
Patterson, J. W. (1988). "Rheumatoid nodule and subcutaneous granuloma annulare. A comparative histologic study." *Am J Dermatopathol* **10**(1): 1–8.

PROTOTYPE: Granulomatous mycosis fungoides

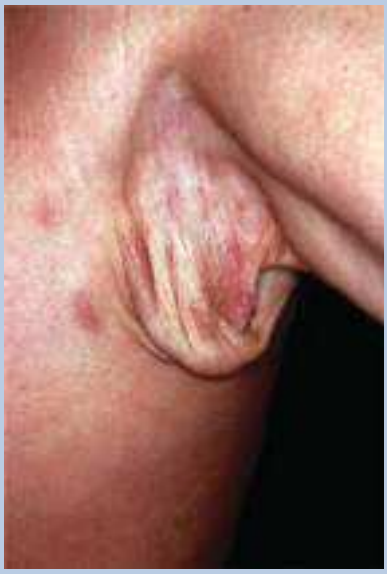


Cl: Patches and plaques.

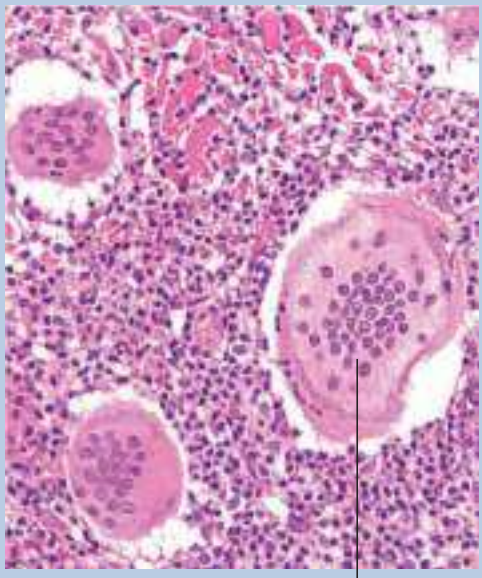


Hi: Lymphocytic infiltrate with prominent accumulations of histiocytes macrophages and giant cells. Epidermotropism in half of the cases only.

VARIANT: Granulomatous slack skin

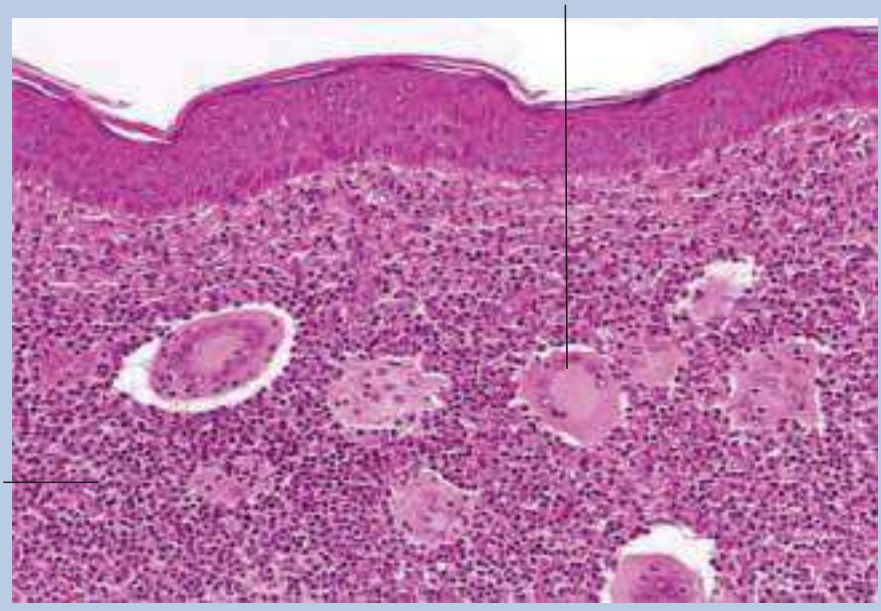


Pendulous skin fold in the axilla



Cl: Areas of slack skin with large skin folds in the axillae and groins.

Scattered large multinucleated giant cells with emperipolesis

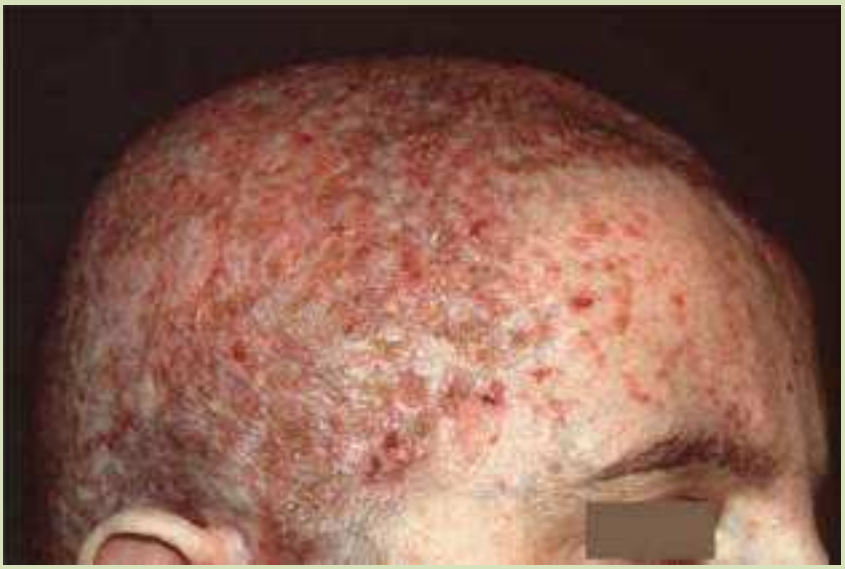


Lymphocytic infiltrate

Hi: Disseminated large multinucleated giant cells with emperipolesis "floating" within the tumorous lymphocytic infiltrate.

DIFFERENTIAL DIAGNOSIS: Langerhans cell histiocytosis (Histiocytosis X)

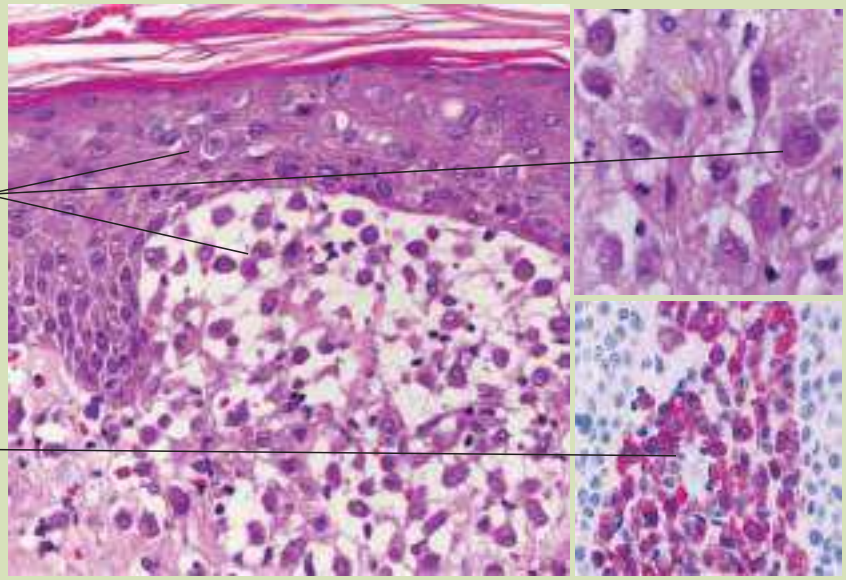
Scaly crusty lesions in a child



Cl: Letterer-Siwe: children, scaly and crusty lesions on the head and at diaper and seborrheic sites. Hand-Schüller-Christian: adults, intertriginous areas. Additional symptoms present in both forms.

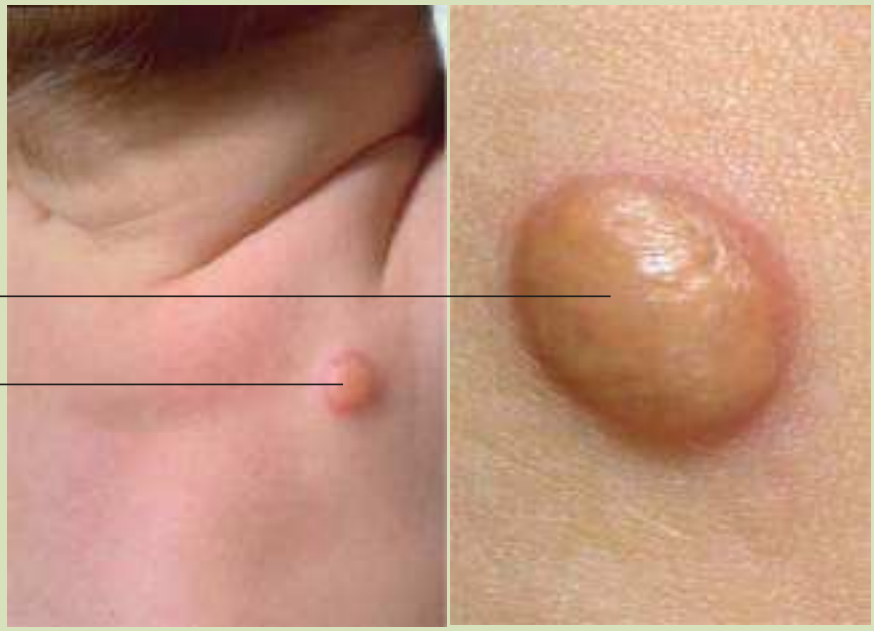
Epidermotropic tumor cells (Langerhans cells)

CD1a positive tumor cells

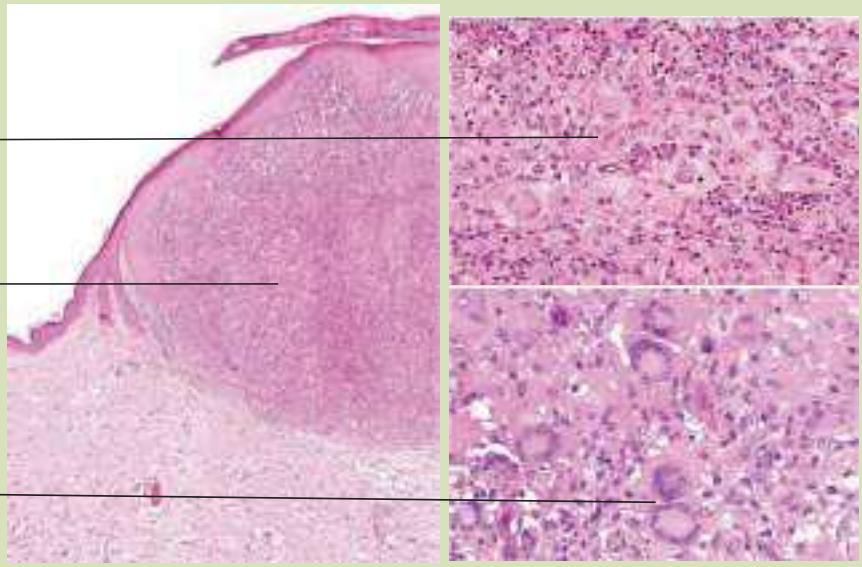


Hi: Histiocyte-rich lesions with epidermotropic proliferations of cells with large, pale, vesicular nucleus and abundant slightly eosinophilic or amphophilic cytoplasm (Langerhans cells).

DIFFERENTIAL DIAGNOSIS: Non-X-histiocytoses : Juvenile xanthogranuloma

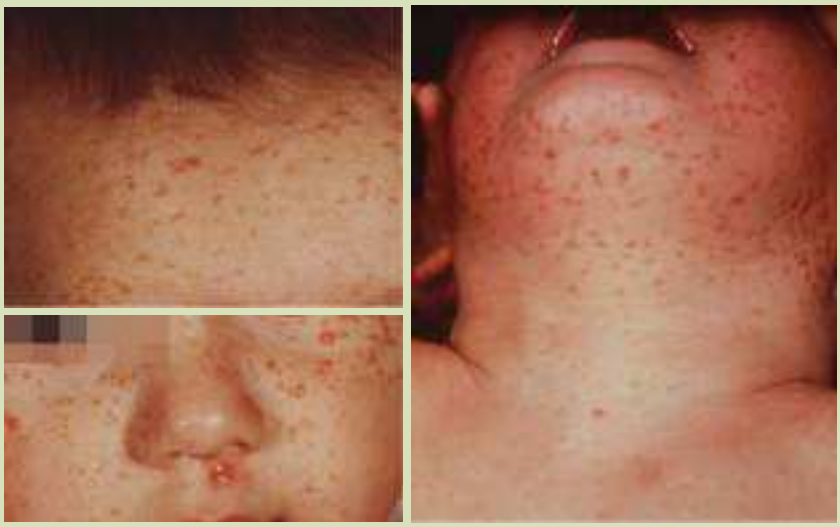


Cl: Solitary or multiple papules.

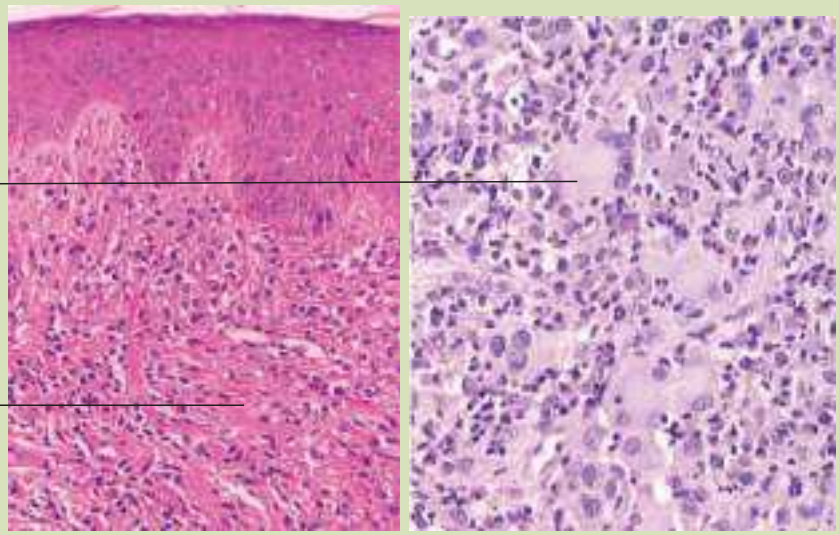


Hi: Histology shows a dense infiltrate of macrophages with abundant slightly eosinophilic cytoplasm in early lesions, whereas in mature lesions foamy cells and Touton giant-cells are seen.

DIFFERENTIAL DIAGNOSIS: Benign cephalic histiocytosis (close relationship to JXG)

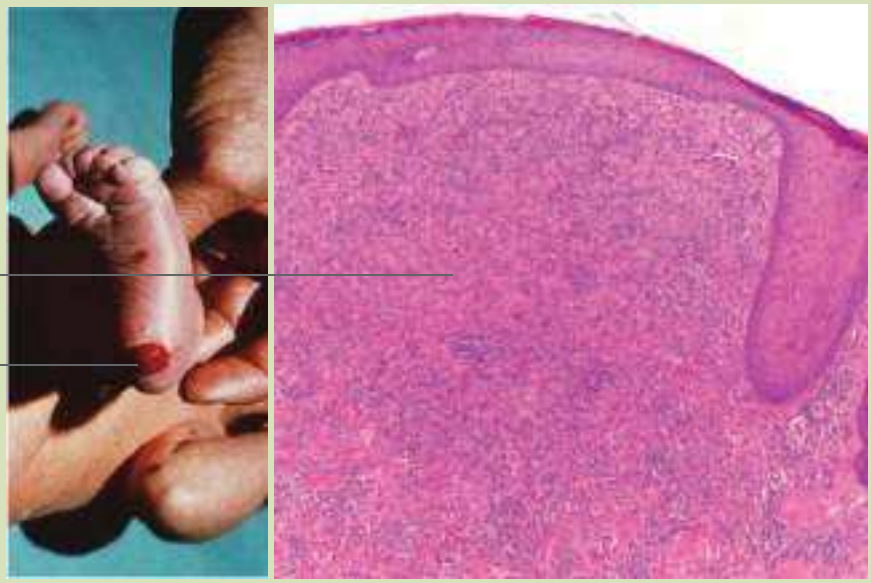


Cl: Slightly raised, small red to yellowish papules, mostly in the head and face area of children.

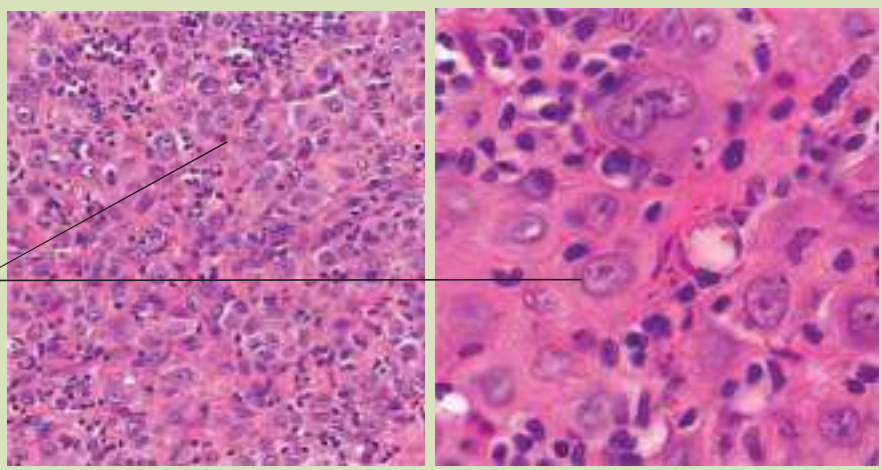


Hi: Histiocytes.

DIFFERENTIAL DIAGNOSIS: Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker)

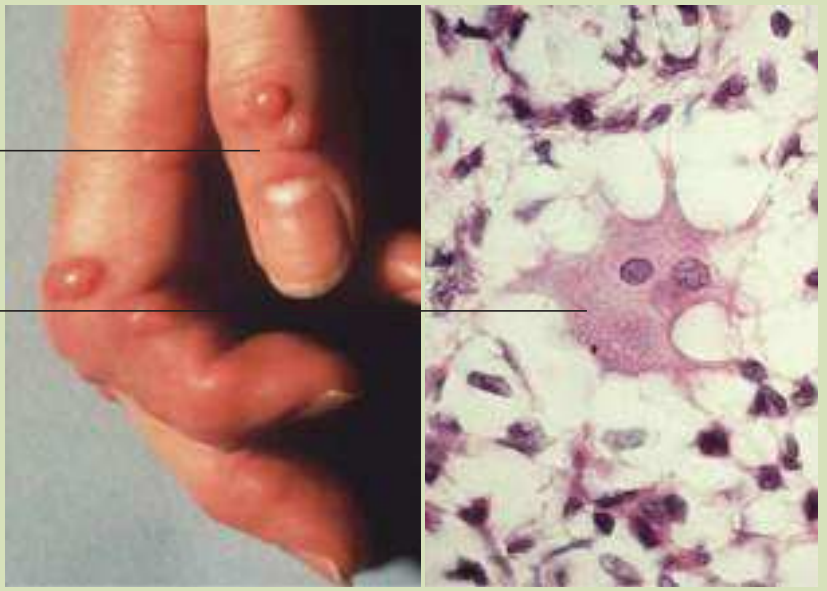


Cl: Congenital small solitary or multiple nodules. No systemic involvement. Spontaneous regression *(Bonifazi et al 1982)*.



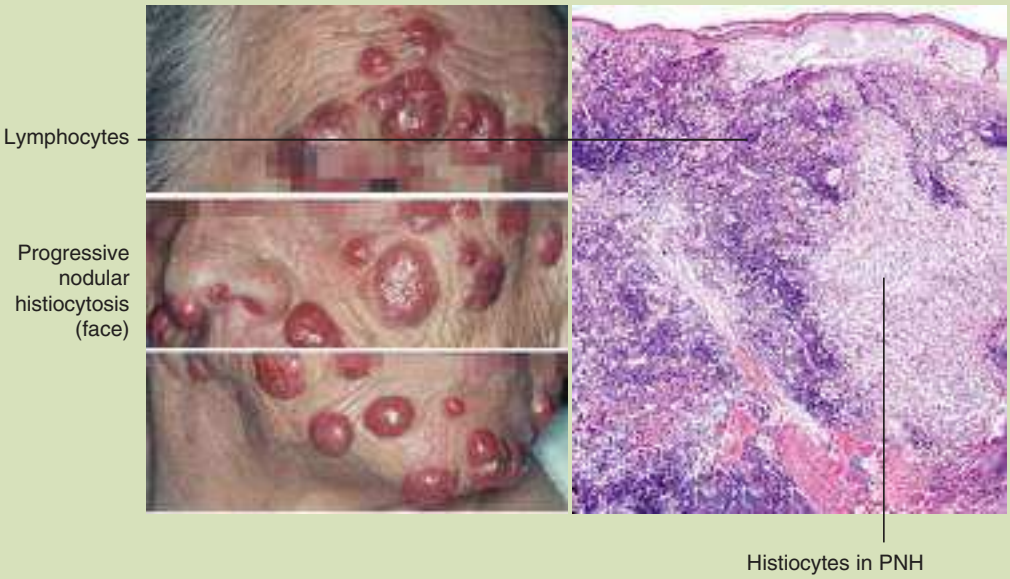
Hi: Large mono-or multinucleated cells with abundant eosinophilic or ground-glass like cytoplasm.

DIFFERENTIAL DIAGNOSIS: Multicentric reticulohistiocytosis (MRH, lipoid dermatoarthritis)



Cl: Systemic disease, predominantly in middle-aged women, showing multiple small firm nodules; may be paraneoplastic.
Hi: Histiocyte-rich infiltrates with PAS-positive multinucleated giant cells.

DIFFERENTIAL DIAGNOSIS: Progressive nodular histiocytosis (PNH)



Cl: Progressive development of widespread nodular and tumorous lesions. Good general health, absence of systemic symptoms.
Hi: Massive infiltrate of histiocytes, intermixed with lymphocytes.

Other Diagnosis

Necrobiotic xanthogranuloma (*see* Chapter 7, Lipids, page 295)*: Mostly in association with IgG paraproteinemia. Yellowish indurated plaques. Histology reveals collagen degeneration, sheets of foamy cells, cholesterol clefts and Touton type giant cells.*

References

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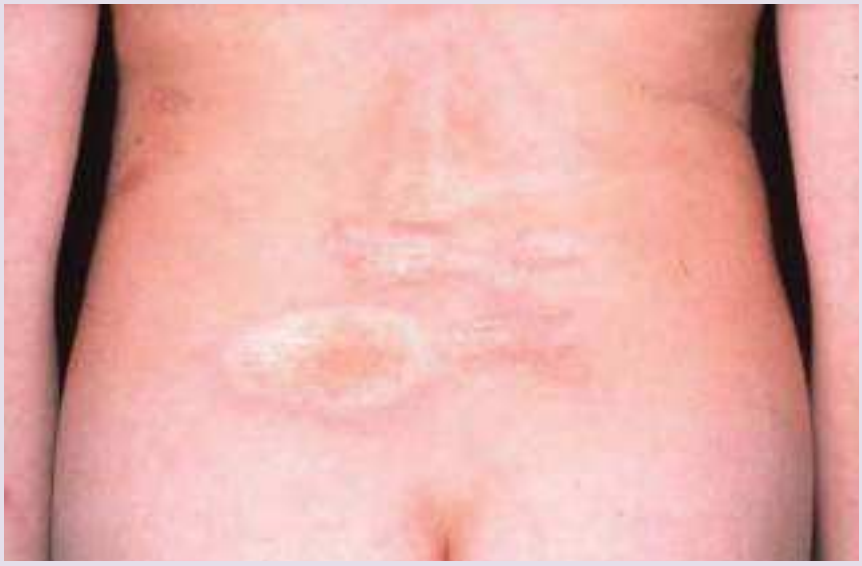
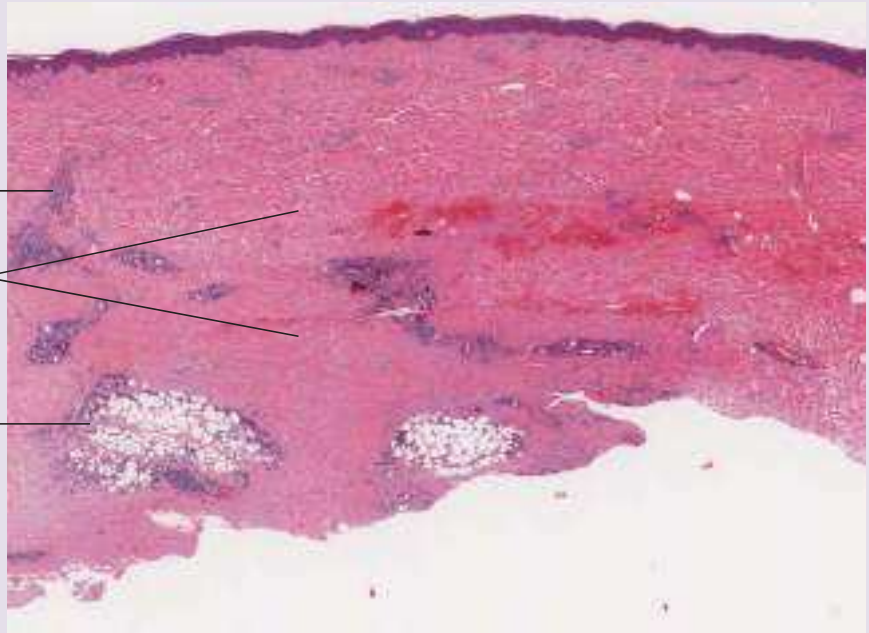
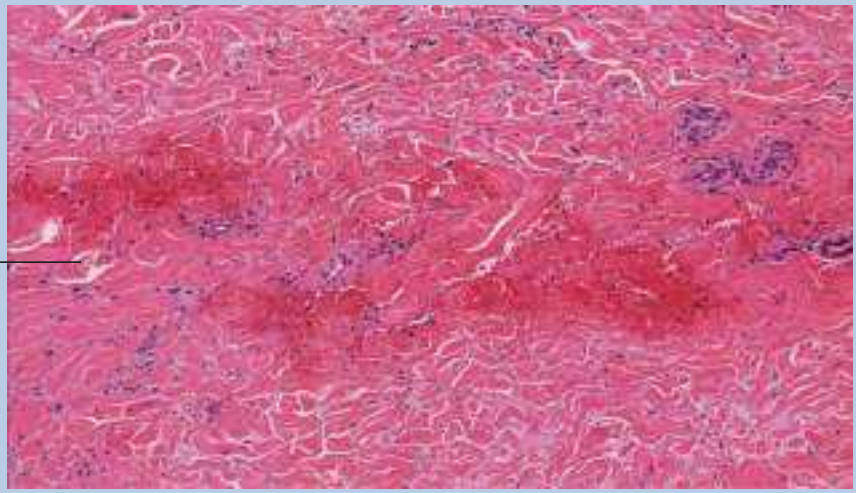
PROTOTYPE: Circumscribed scleroderma (morphea)

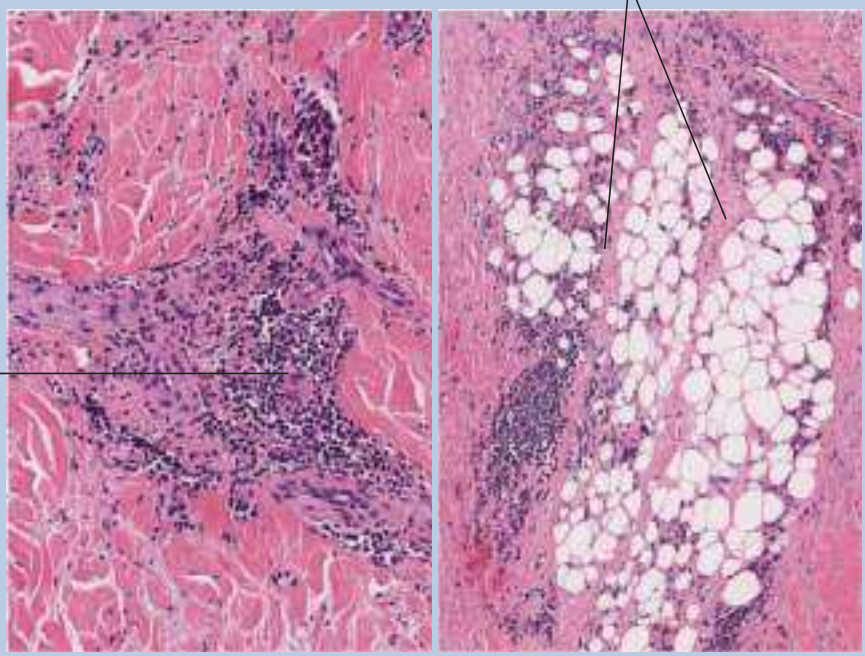


CI: Centrifugally spreading erythema with progressive central white-yellow induration with loss of adnexal structures. Border often with purple tones (lilac ring) as sign of disease activity.



Circumscribed scleroderma (morphea)





Hi: Epidermis normal or atrophic, thickening of the reticular dermis, plump collagen bundles, reduction of elastic fibres, sclerosis of fat septae, scattered lymphocytic infiltrate, occasionally plasma cells, nodular aggregation of lymphocytes at the dermal-subcutis border.

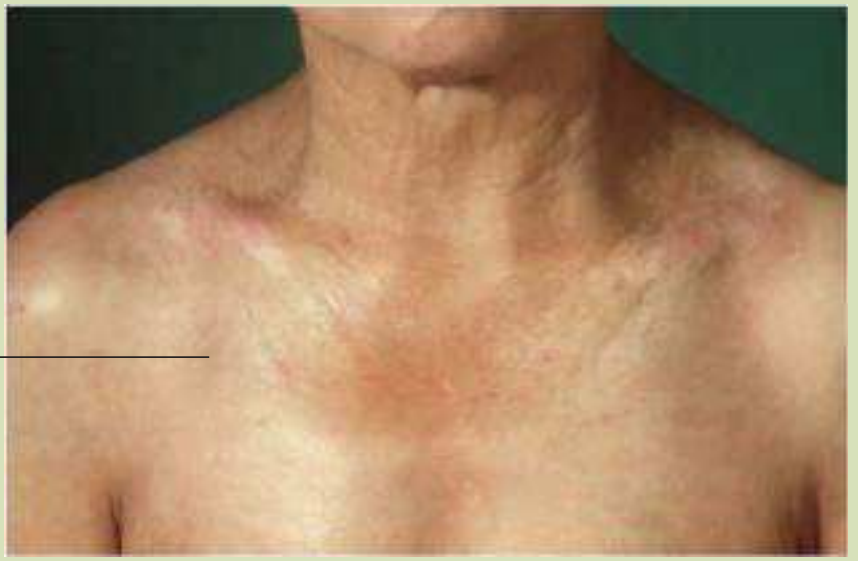
VARIANTS:

Early stage morphea: *edema in the upper dermis, lymphocytic infiltrate, occasional plasma cells and eosinophils*

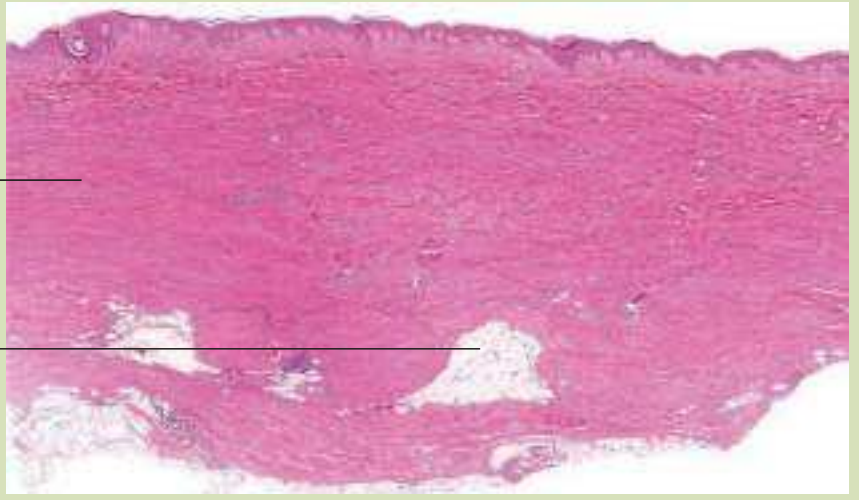
Late stage morphea: *prominent fibrosis and thickening of the reticular dermis, thickening of collagen bundles, dilatation of blood vessels, entrapping of sweat glands and adnexal structures in higher levels of the dermis and embedded in thickened collagen bundles.*

Morphea profunda: *fibrosis extending into the subcutaneous tissue. Sclero-lichen: combination of morphea and histological pattern of lichen sclerosus et atrophicus.*

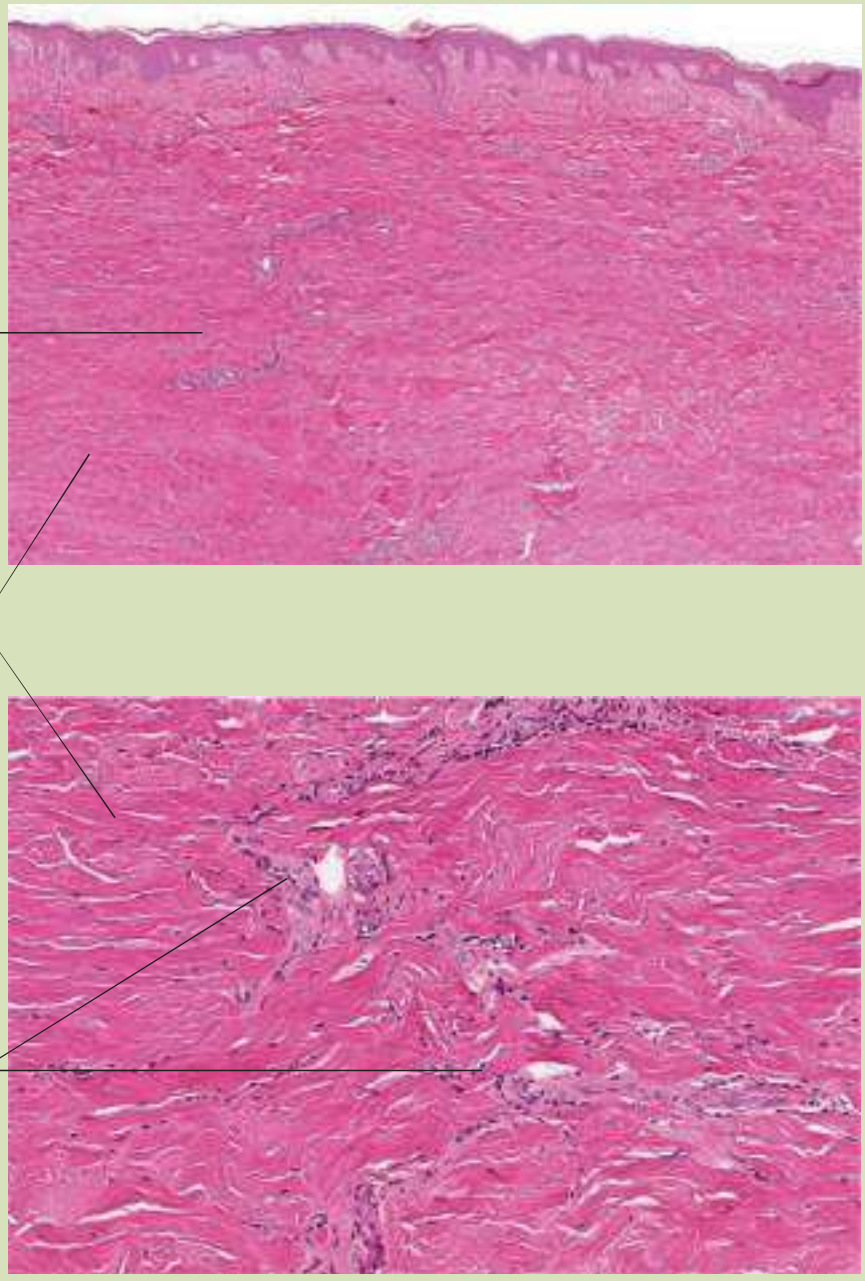
DIFFERENTIAL DIAGNOSIS: Systemic scleroderma



CI: Systemic disorder with potential involvement of internal structures and variable presentation on the skin, which is hardened and thickened; acral forms and generalized forms. Raynaud phenomenon.

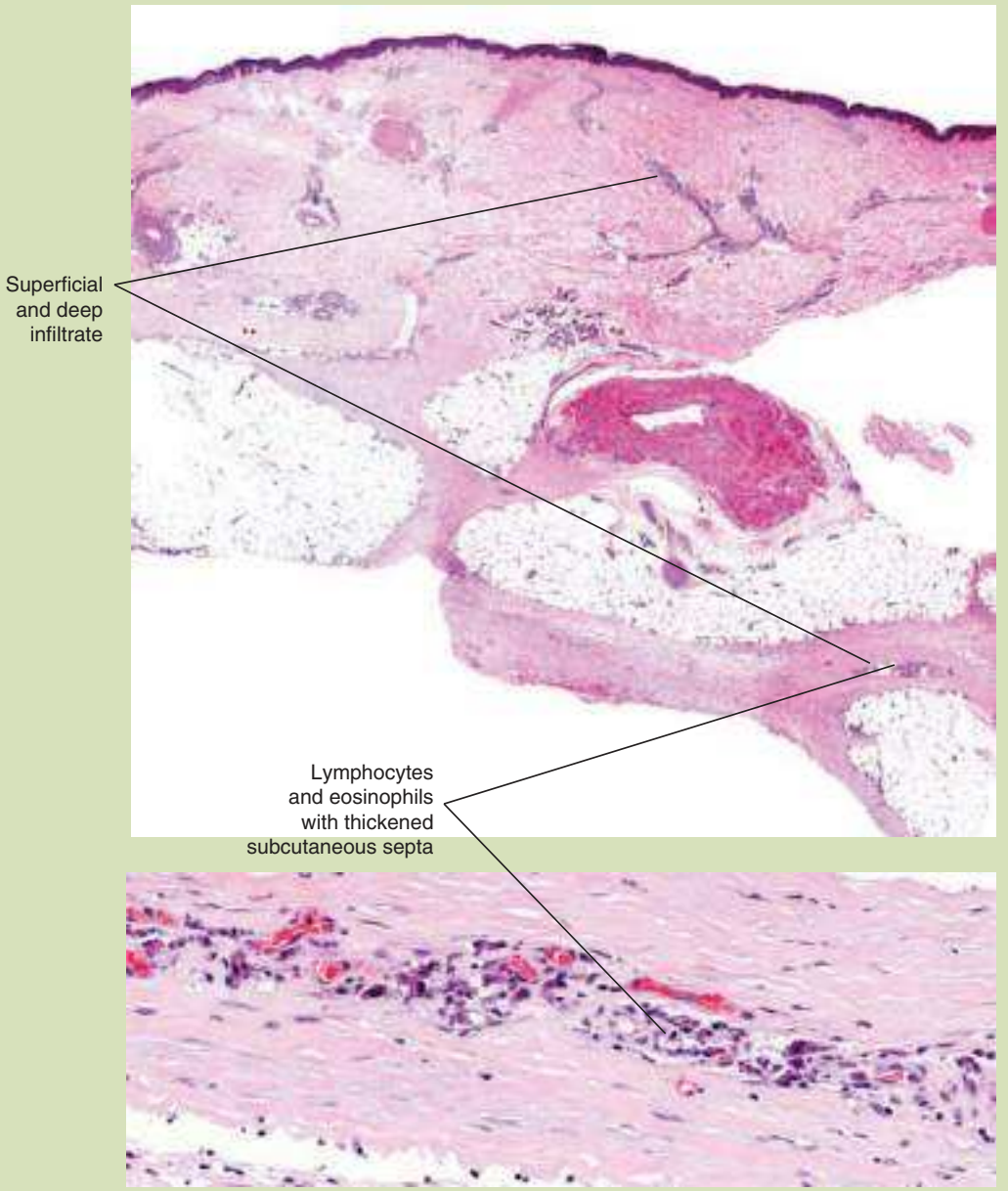


Systemic scleroderma



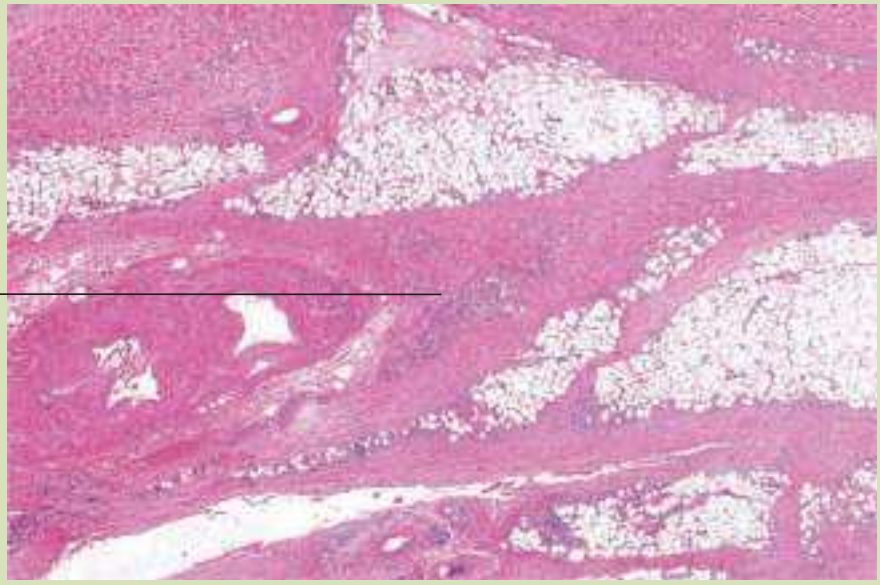
Hi: Identical with morphea (*see* above, page 205).

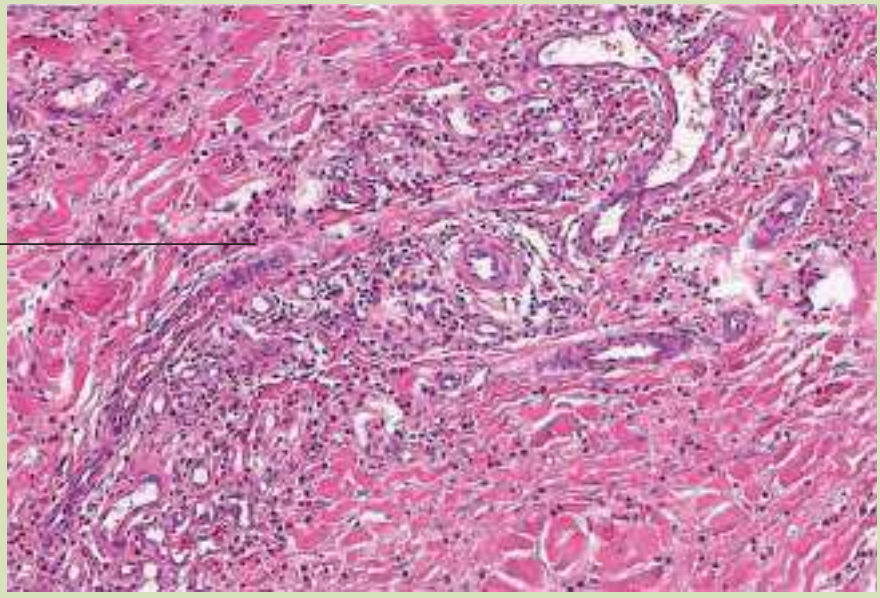
DIFFERENTIAL DIAGNOSIS: Eosinophilic fasciitis (Shulman syndrome)



Cl: Sudden symmetrical hardening of skin, preferentially in young adults, lack of Raynaud phenomenon.
Hi: Deep morphea pattern, involving subcutaneous septa.

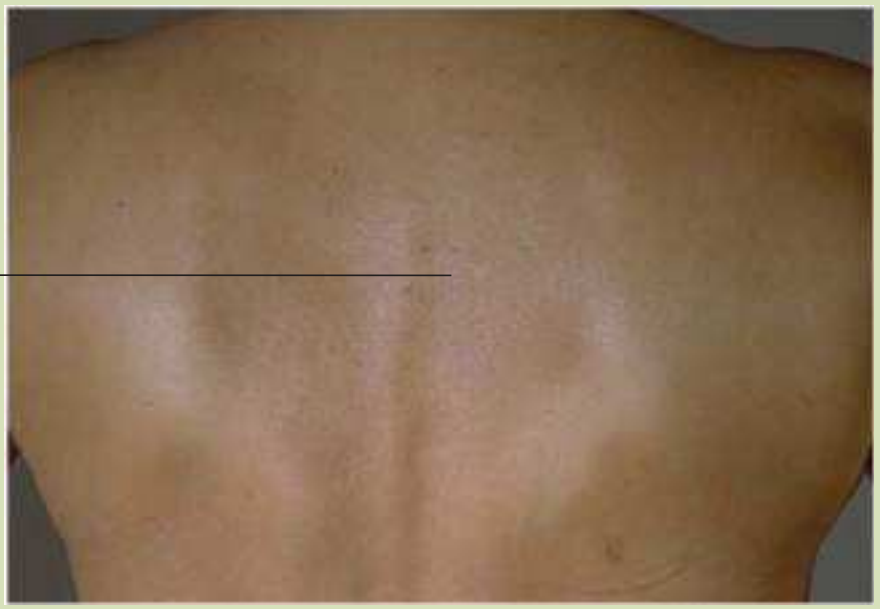
Eosinophilic fasciitis (Shulman syndrome)



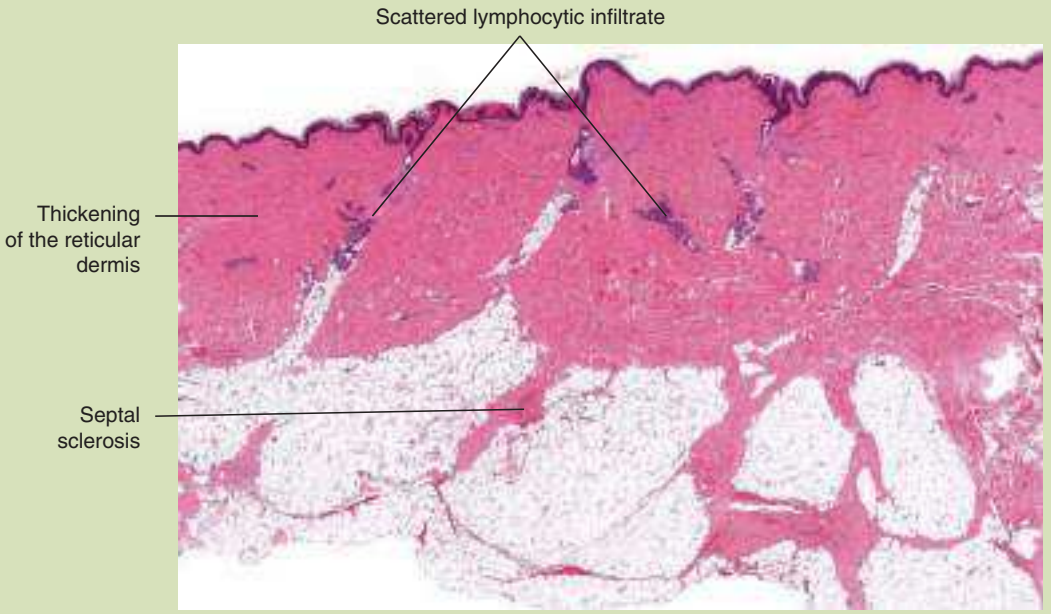


Hi: In addition to sclerosis of the dermis and fat septa, there is conspicuous sclerosis of fascia. Tissue eosinophilia may be present.

DIFFERENTIAL DIAGNOSIS: Chronic graft-versus-host (GvH)- reaction, sclerosing form

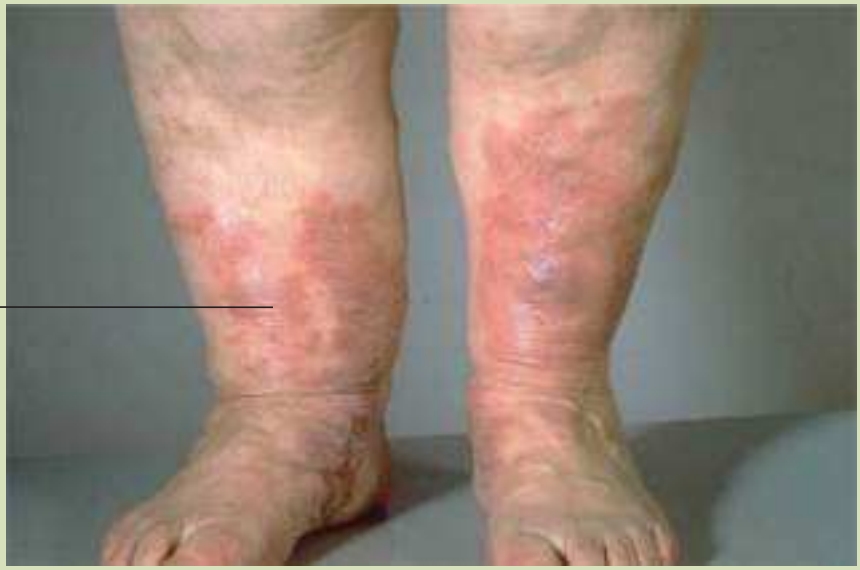


Cl: Hardening of the skin, similar to systemic sclerosis.

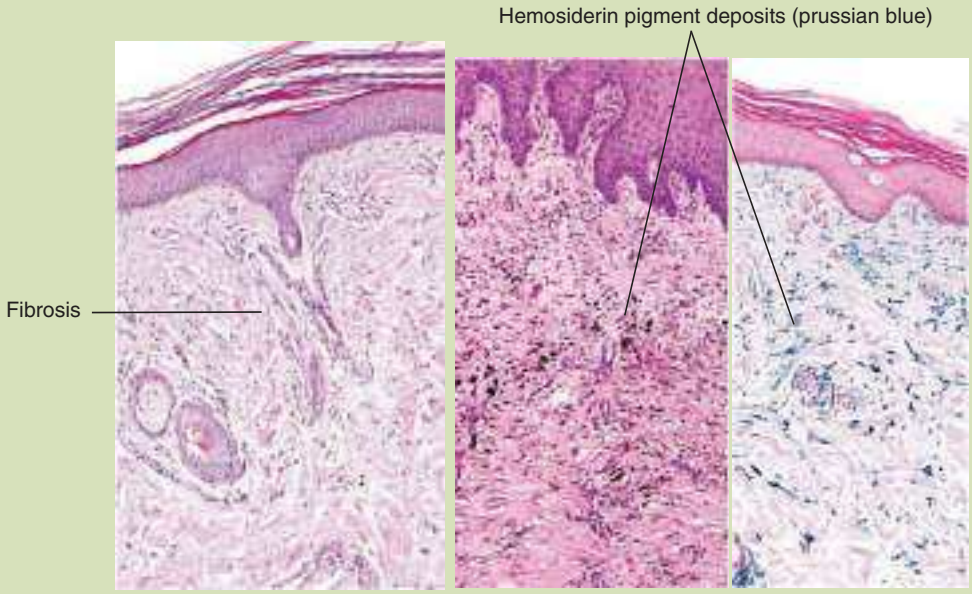


Hi: Sclerosis initially in upper and mid dermis.

DIFFERENTIAL DIAGNOSIS: Stasis dermatitis

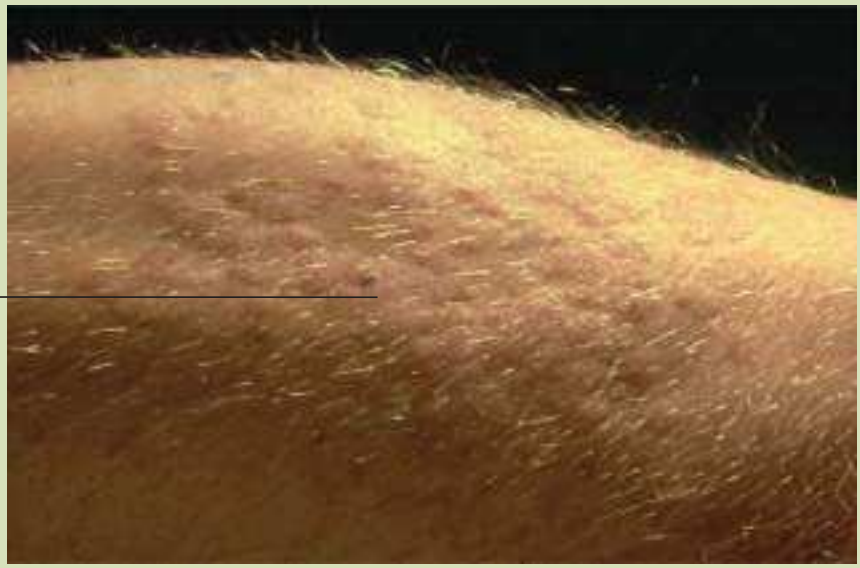


Cl: Pruritic eczematous skin changes with red to brown pigmentation, commonly in conjunction with chronic venous insufficiency and thus preferential localization on the lower legs.

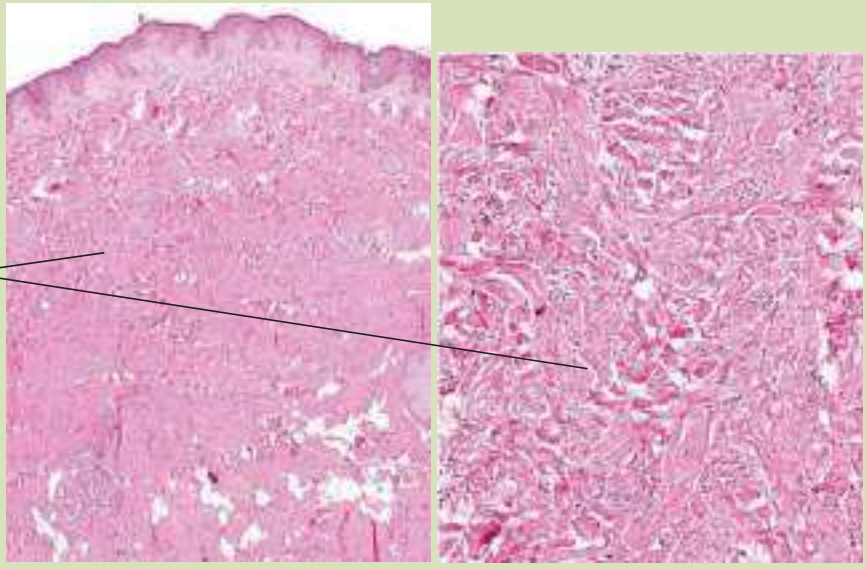


Hi: Acanthosis and variable degree of spongiosis, Erythrocyte extravasation, edema in the upper dermis, sclerosis in the mid and lower dermis may be present, hemosiderin deposits in all dermal layers.

DIFFERENTIAL DIAGNOSIS: Connective tissue nevus



Cl: Soft papules or plaque.



Hi: Thickened and disarranged collagen as well as elastic fibers. No infiltrate.

Other Diagnosis

Lipodermatosclerosis: *Sclerosis and hemosiderin deposits in all dermal layers. Subtle infiltrate.*

Nephrogenic fibrosing dermopathy: *Increased number of (CD34+) fibroblasts, interstitial mucin deposits.*

Scar: *Loss of elastic fibres and adnexal structures.*

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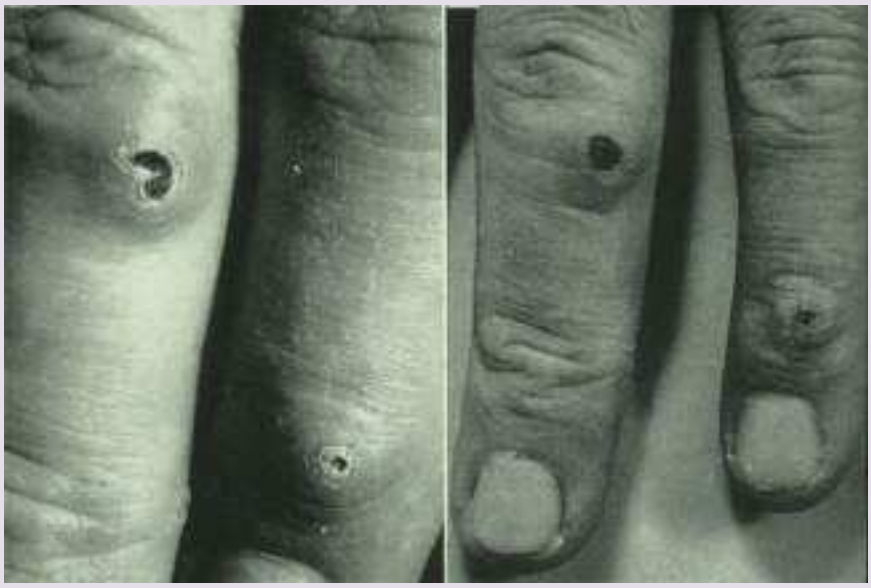
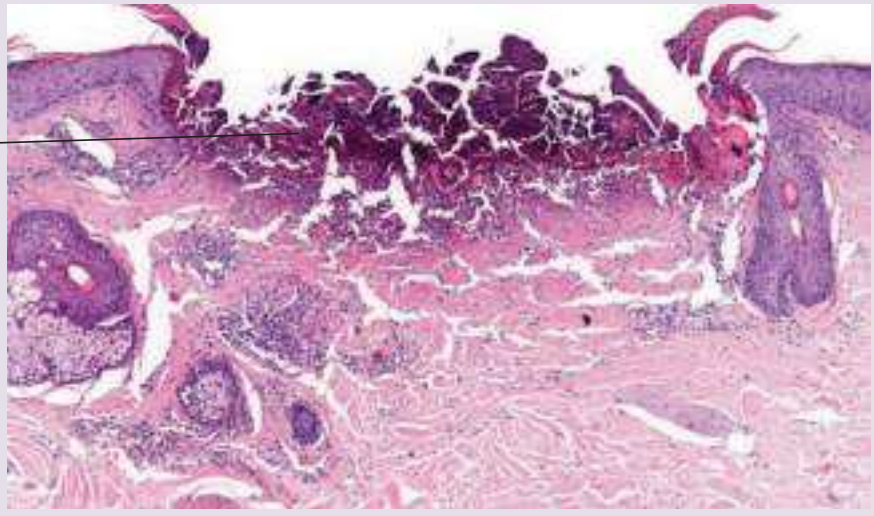
PROTOTYPE: Reactive perforating collagenosis

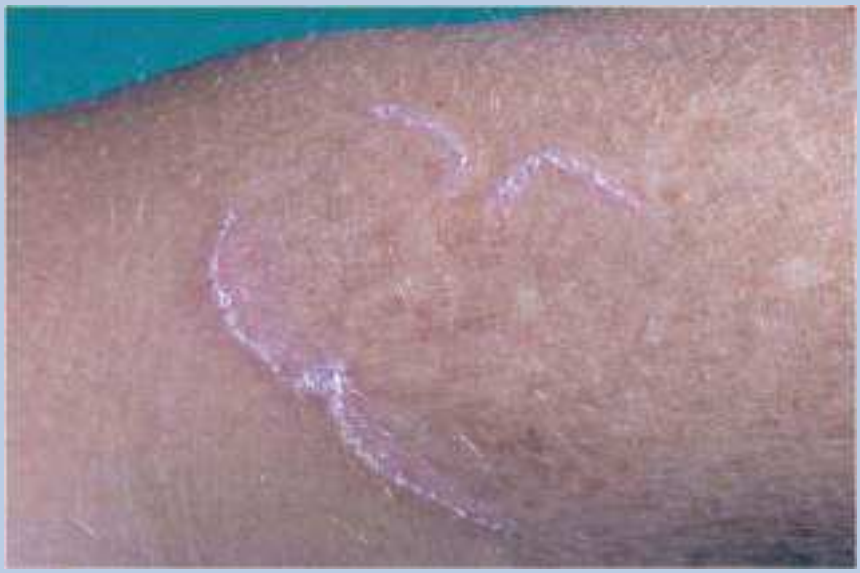


Cl: Pruritic papules with small ulcers with eschar.

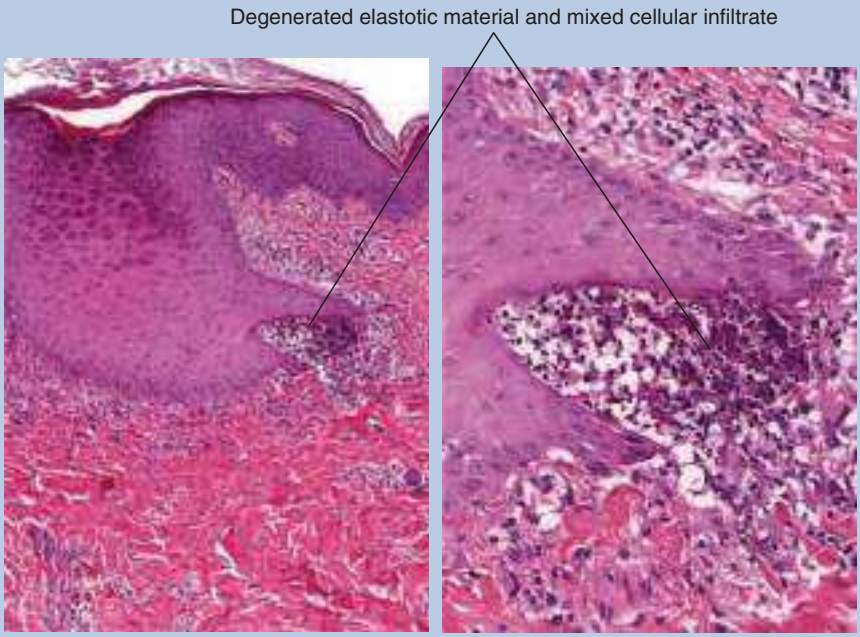


Hi: Sharply demarkated flat ulceration with extrusion of collagen and elastic fibers, covered by debris and neutrophils. Subtle infiltrate mainly of neutrophils in the upper dermis.

VARIANTS: Elastosis perforans serpiginosa (perforating elastosis)



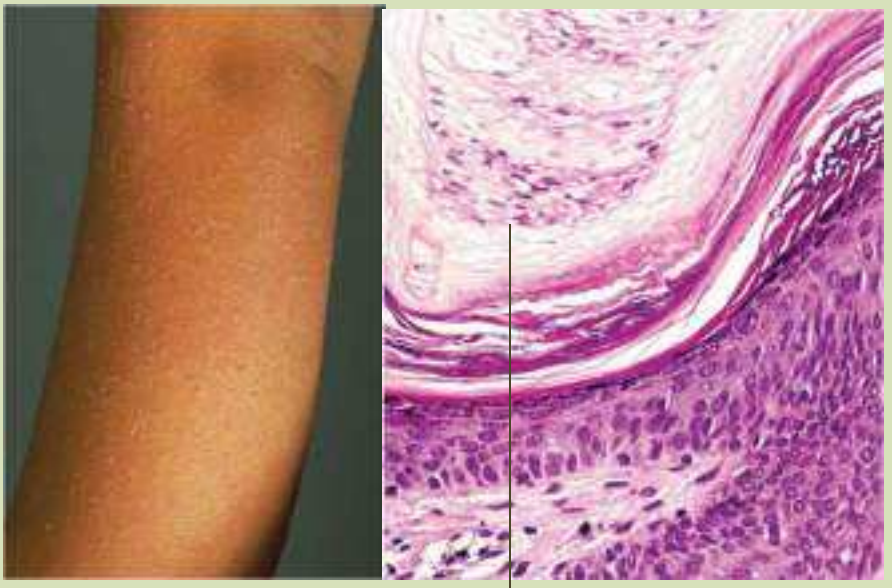
Cl: Tiny keratotic papules forming annular lines.



Hi: Increased number and sizes of elastic fibres in upper dermis; small transepithelial channel with extrusion of elastic fibers; degenerated elastotic material; mixed cellular infiltrate with neutrophils.

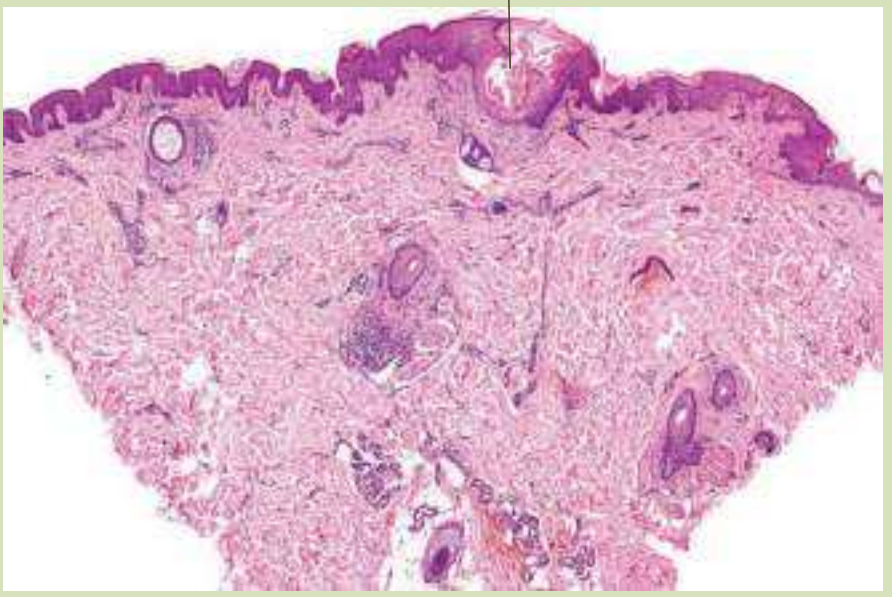
Hyperkeratosis follicularis et parafollicularis in cutem penetrans (Kyrle's disease): *Hyperkeratotic dome-shaped papules with a central plug, sometimes in a linear arrangement. Histology shows an intraepithelial channel; crater filled with parakeratotic horn.*

DIFFERENTIAL DIAGNOSIS: Keratosis pilaris



Cl: Tiny keratotic papules.

Hyperkeratosis in the hair follicular ostium



Hi: Hyperparakeratosis in the hair follicle ostia.

Comment

Reactive perforating collagenosis is considered as variant of prurigo with deep excoriation and subsequent extrusion of collagen and elastic fibers. It is often associated with diabetes mellitus and chronic hepatic or renal failure.

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CHAPTER 5
Vessels

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.

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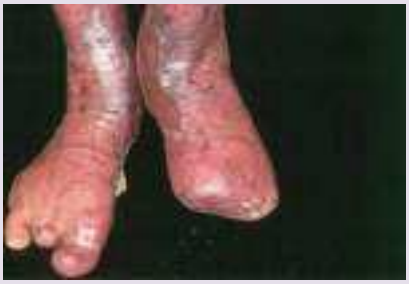
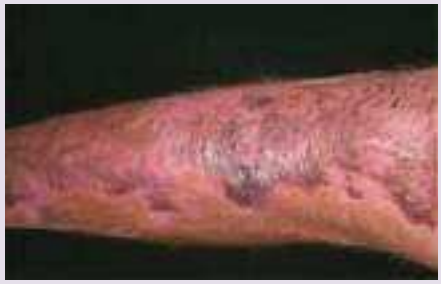
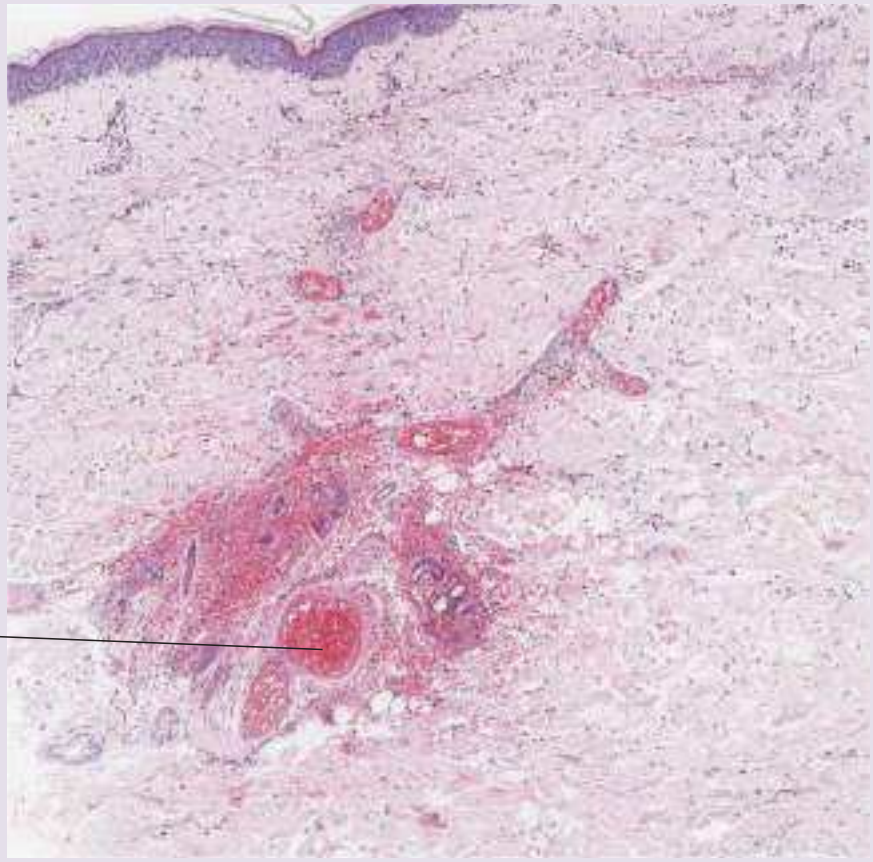
PROTOTYPE: Purpura fulminans

Mutilations following purpura fulminans



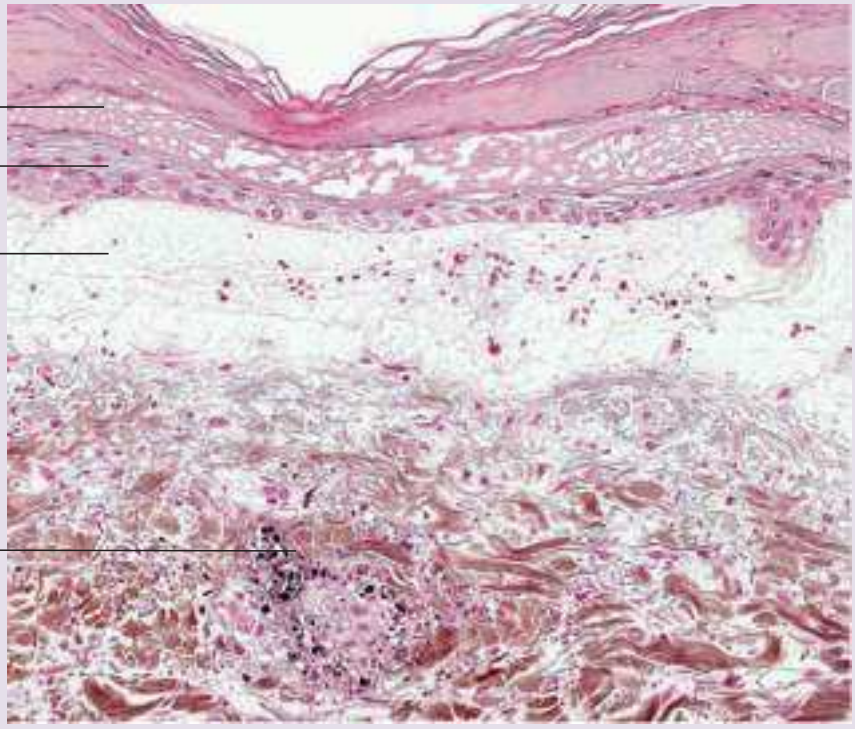


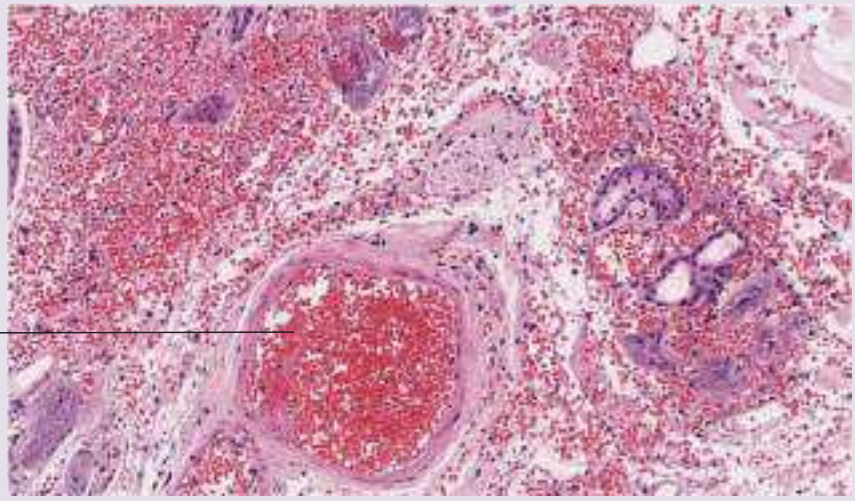
CI: Purpura fulminans is a severe, life-threatening disorder caused by disseminated intravascular coagulation. Due to multiple causes, including meningococcal sepsis, intravascular coagulation leads to widespread cutaneous hemorrhage, preferentially on the extremities with ecchymoses, blistering and necrosis of various degree.



Intravascular occlusion and hemorrhage

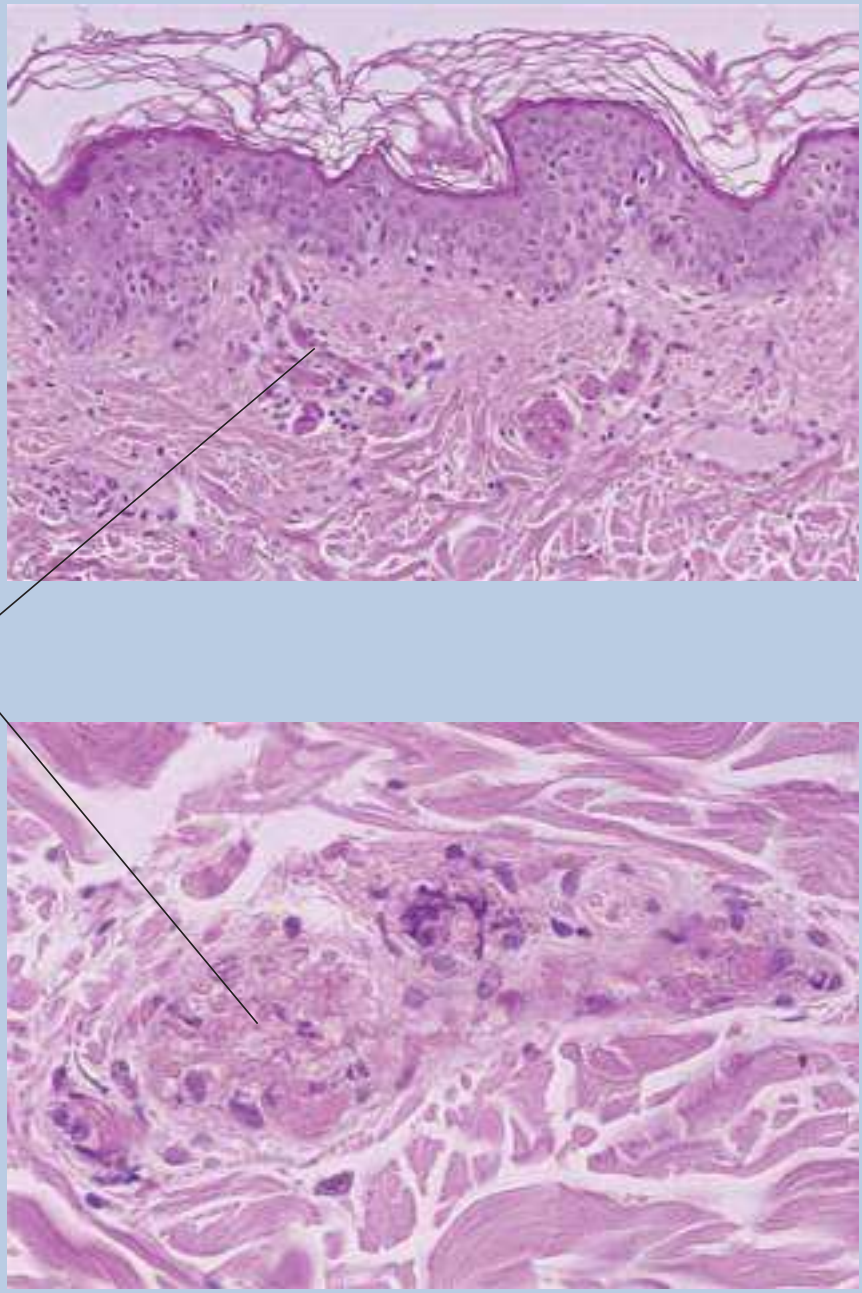
Purpura fulminans





Hi: Occlusion of small vessels by fibrin thrombi, extensive extravasation of erythrocytes, no or sparse inflammation, in advanced stages massive necrosis with ulceration.

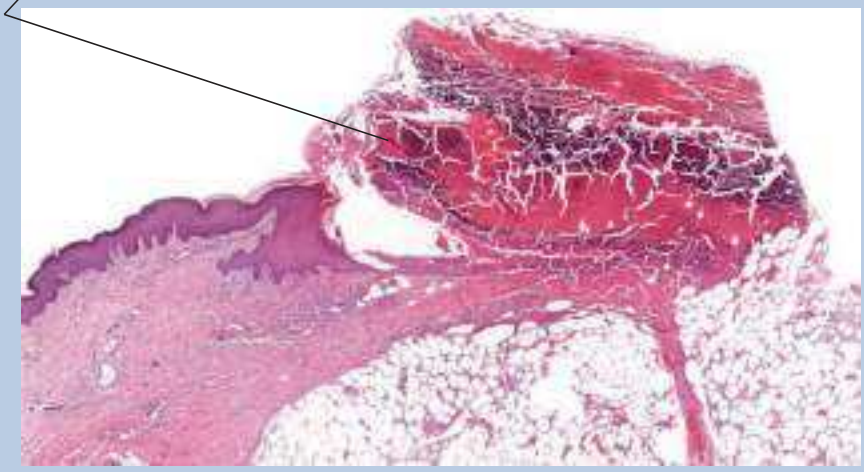
VARIANT: Septic vasculitis

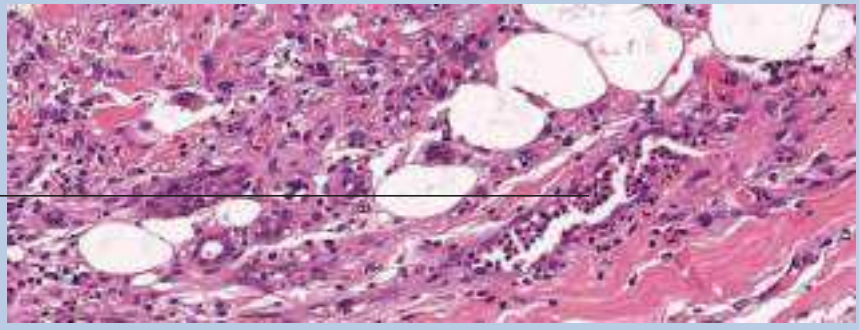


Hi: Leukocytoklastic vasculitis with marked fibrin thrombi, bacteria within the vessel lumen and vessel wall. Neutrophilic infiltrate and karyorrhexis often very discrete.

VARIANT: Coumarin necrosis

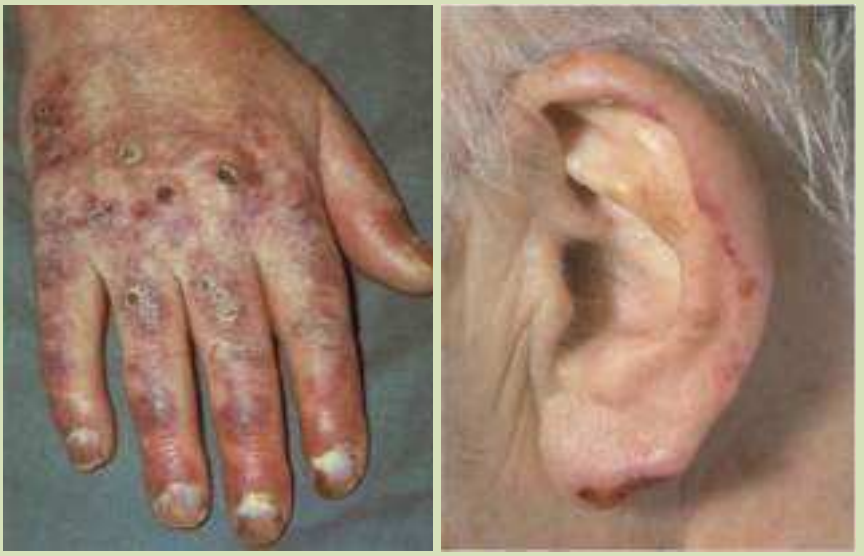
Cl: Hemorrhagic superficial necrosis.



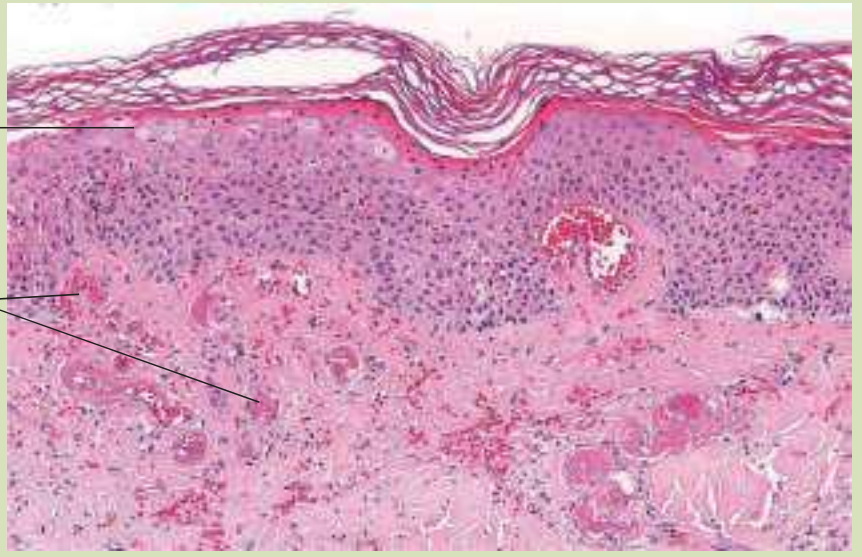


Hi: Fibrin and platelet thrombi. In advanced stages haemorrhage, necrosis en masse and ulceration. No significant vasculitis and inflammation.

DIFFERENTIAL DIAGNOSIS: Cryoglobulinemia type 1 (monoclonal type)

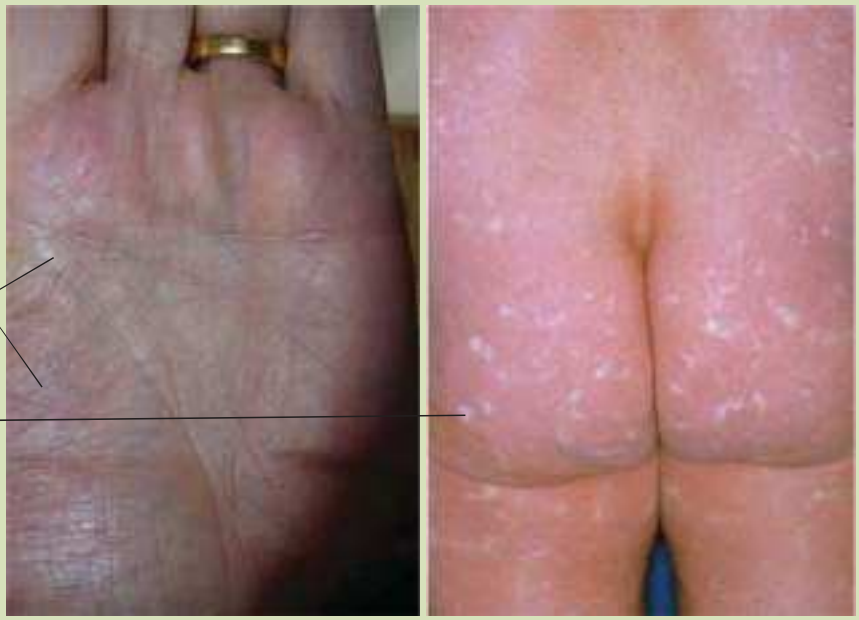


Cl: Acral livid infiltrates with tendency to superficial ulceration.

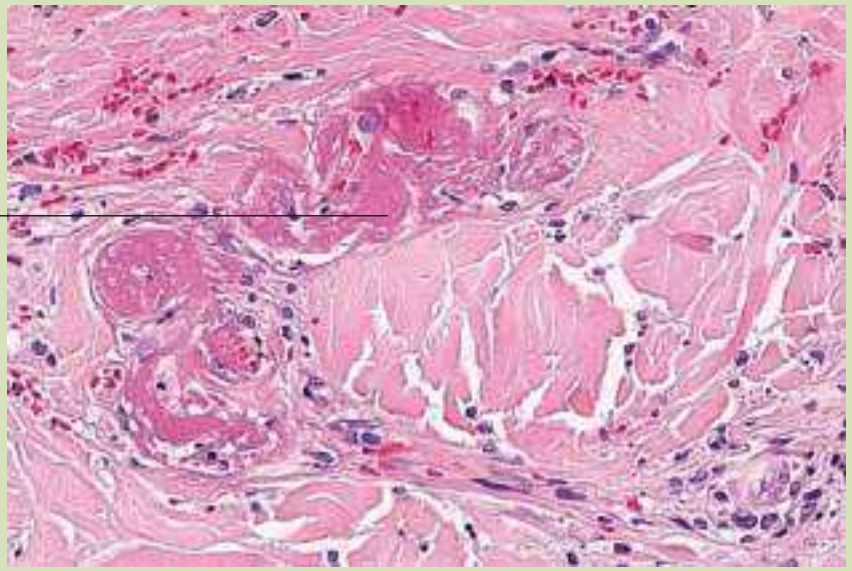


Hi: PAS-positive thrombi. Necrotic keratinocytes. No vasculitic changes.

DIFFERENTIAL DIAGNOSIS: Macroglobulinemia, (Waldenström, IgM)

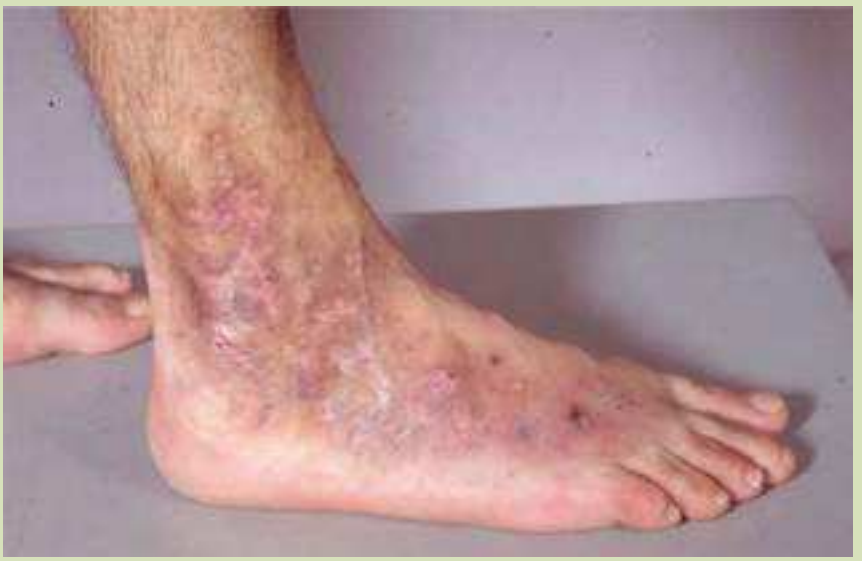


Cl: Palms show white spots ("leukoderma angiospasticum"). Bizarre anemic spots in areas exposed to cold (room temperature).



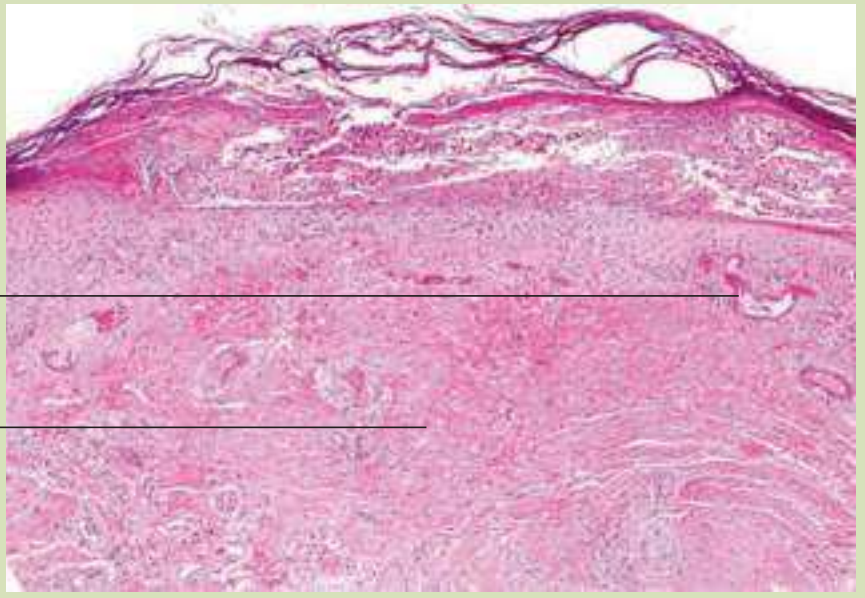
Hi: Occlusion of capillaries in the upper dermis and draining vessels in the mid dermis.

DIFFERENTIAL DIAGNOSIS: Atrophie blanche (capillaritis alba)

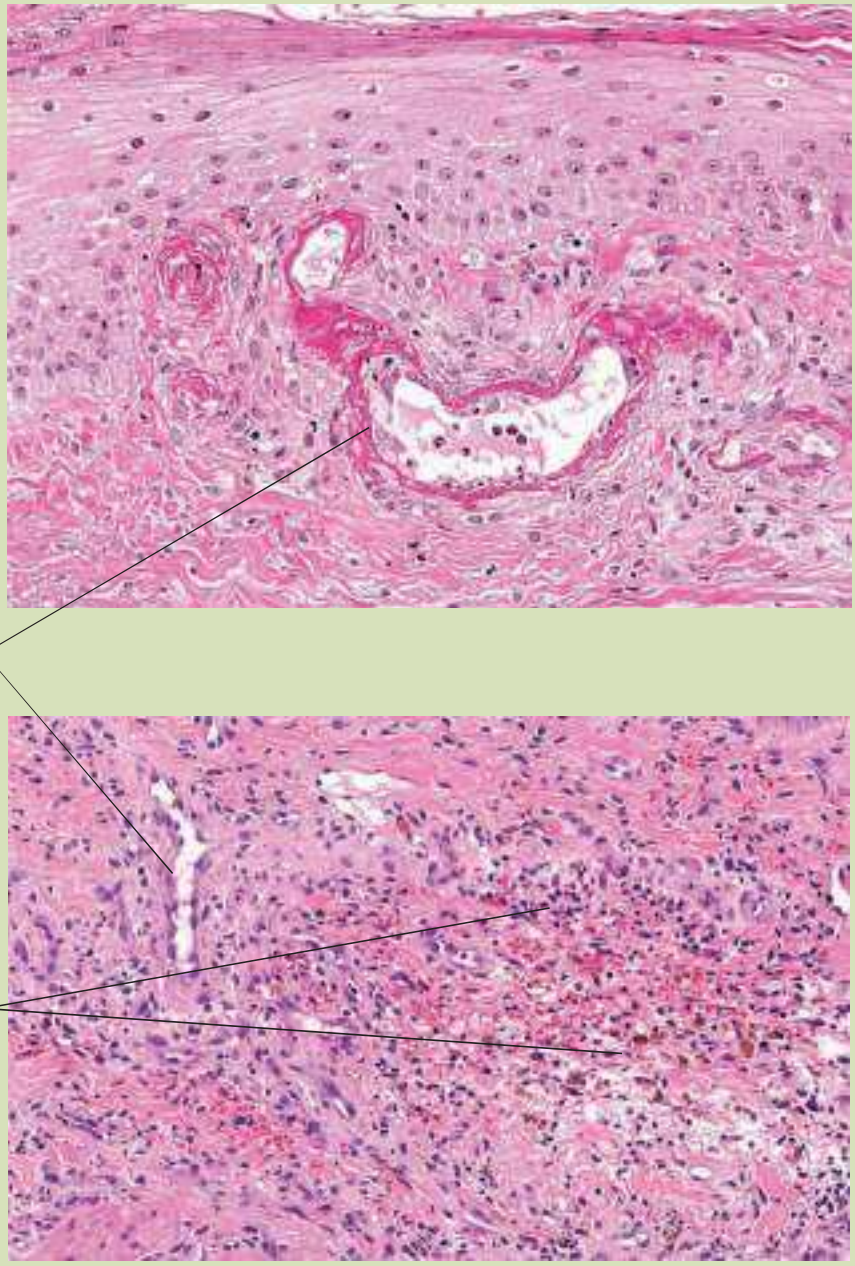


Atrophie blanche. Capillaritis alba

CI: Atrophy, pigmentation due to hemosiderin deposits. Sclerosis, ulceration in advanced stages.

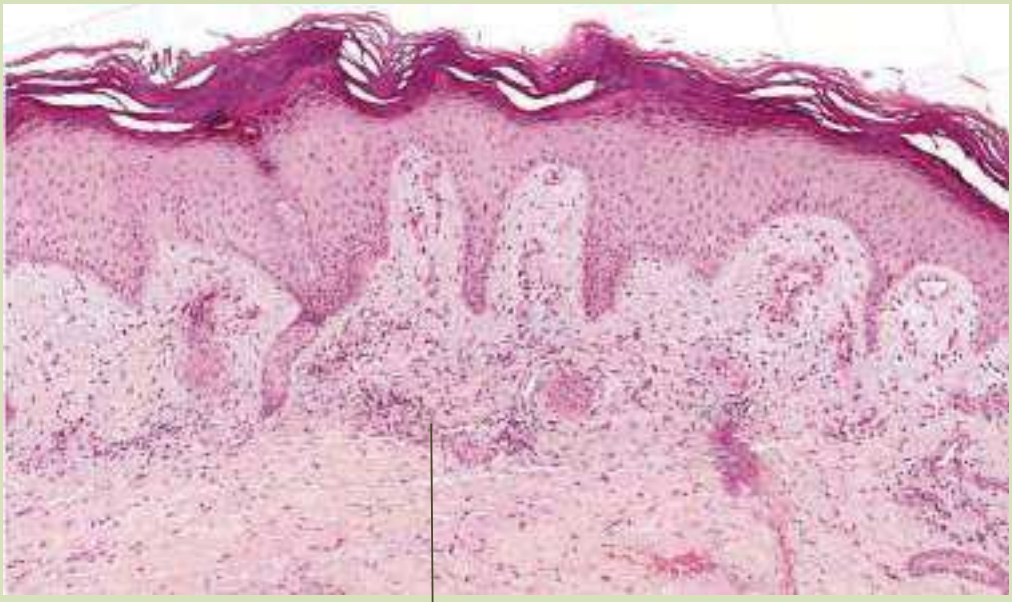


Atrophie blanche (capillaritis alba)

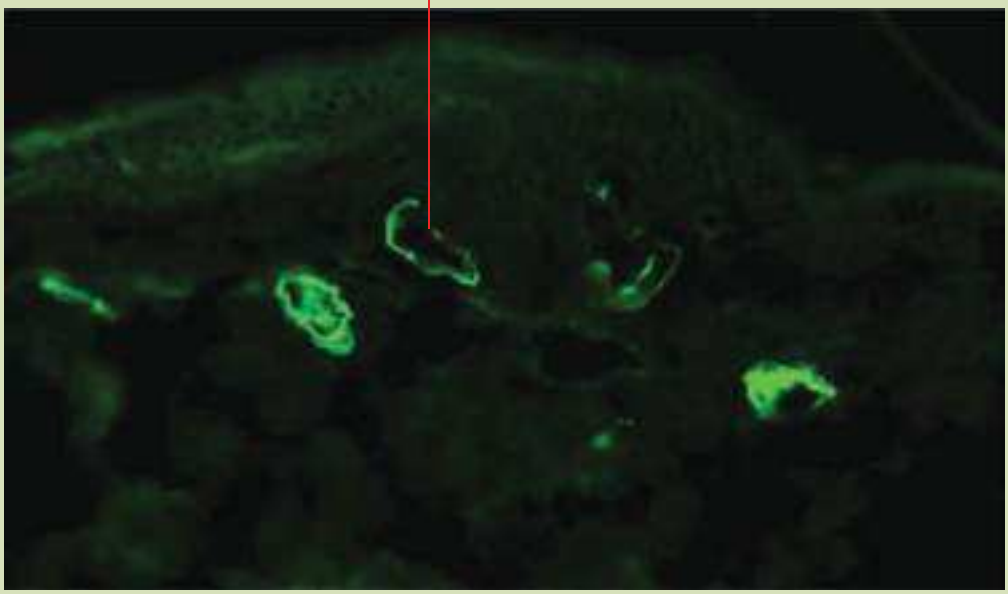


Hi: Fibrin thrombi in conjunction with fibrin rings in the vessel wall. No vasculitis. The combination of intravascular fibrin rings and thrombi is pathognomonic.

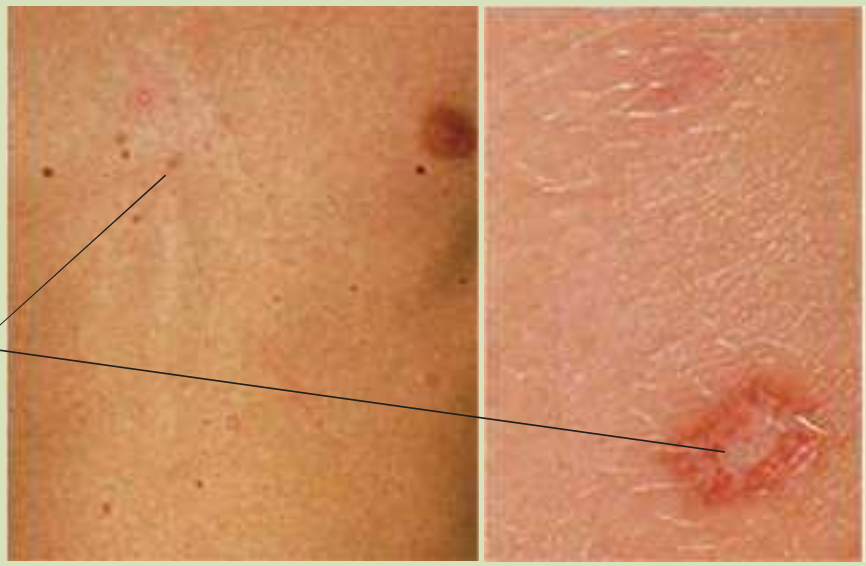
Atrophie blanche (capillaritis alba)



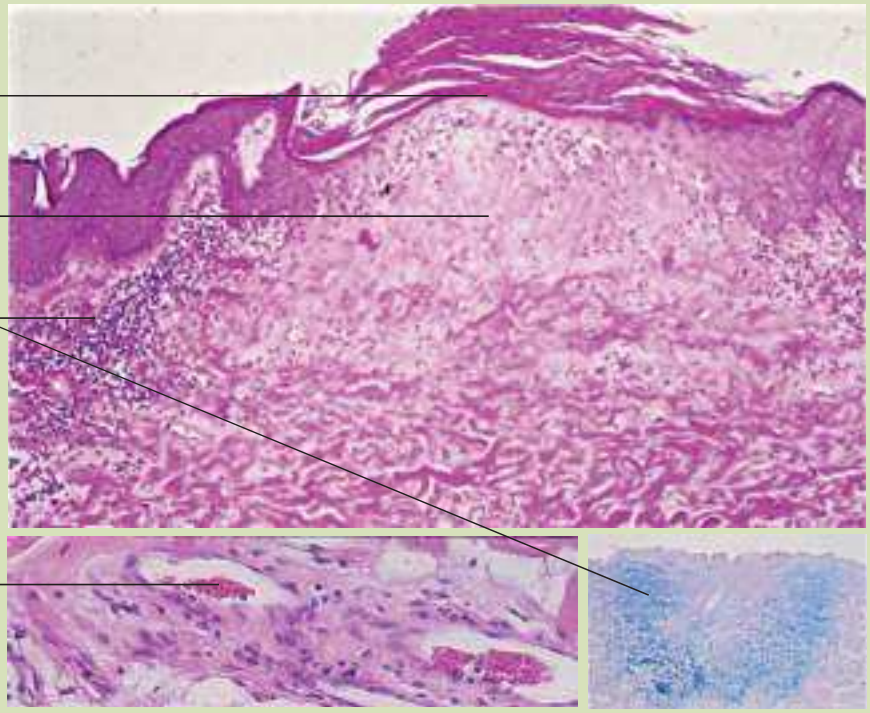
Thickening of vessel walls.
Fibrin rings (FITC, anti-fibrinogen)



DIFFERENTIAL DIAGNOSIS: Malignant atrophic papulosis (Köhlmeier-Degos)



Cl: Systemic disease involving skin, gut and central nervous system. Papules become centrally atrophic resulting in a white scar. No ulceration or crusts.



Hi: Leukocytoklastic vasculitis with vascular occlusion in the deep dermis and wedge-shaped dermal necrosis.

Other Diagnosis

Thrombotic thrombocytopenic purpura *(Werlhof disease): PAS-positive platelet-rich thrombi. No inflammation. No vasculitis. Erythrocyte extravasation of various degrees.*

Antiphospholipid (Hughes) syndrome: *thrombotic occlusion of arteries and veins due to hypercoagulability of the blood, caused by antiphospholipid antibodies.*

Cutaneous cholesterol embolism: *Occlusive vasculopathy with thrombi containing needle shaped cholesterol crystals (wedge-shaped open spaces).*

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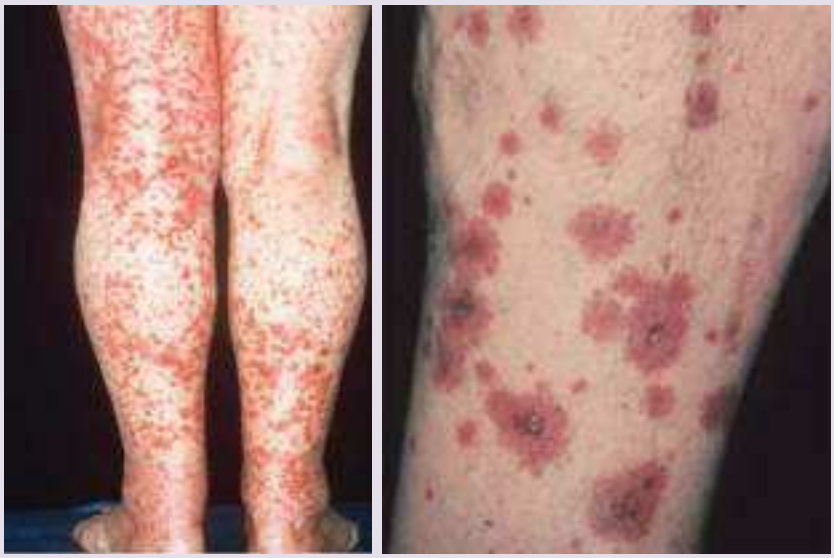
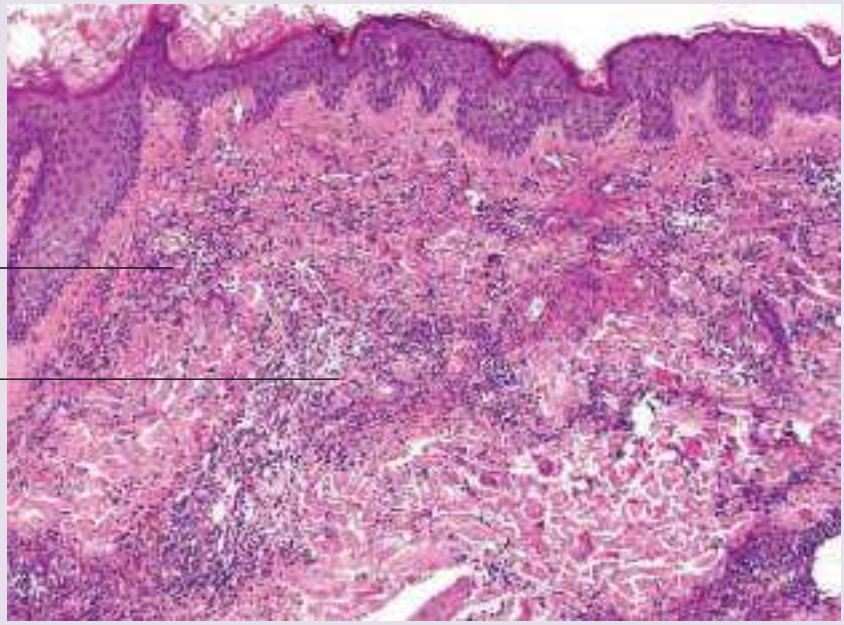
PROTOTYPE: Leukocytoklastic vasculitis

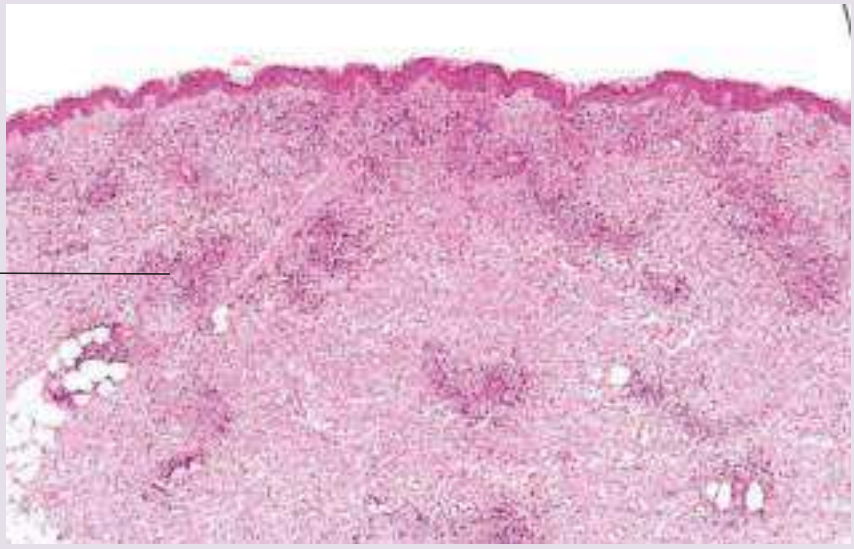


Purpura, hemorrhagic papules, necrosis

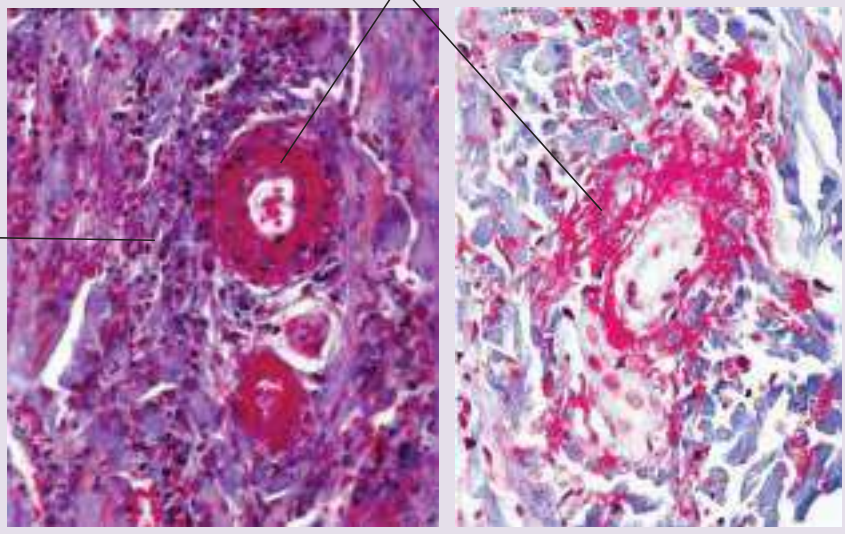
CI: Palpable purpura, hemorrhagic bullae, secondary necrosis; in some patients associated with internal involvement (kidney, GI tract, joints, nervous system) and corresponding symptoms.



Leukocytoklastic vasculitis

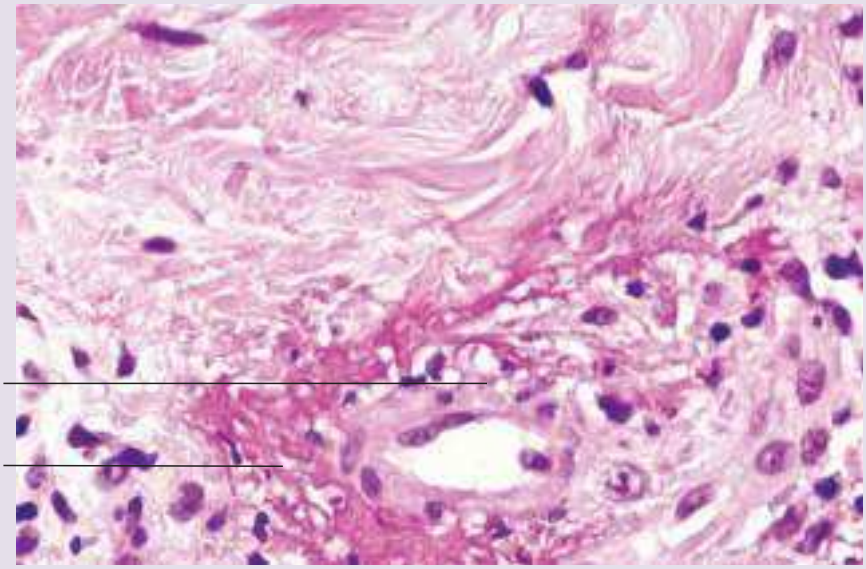


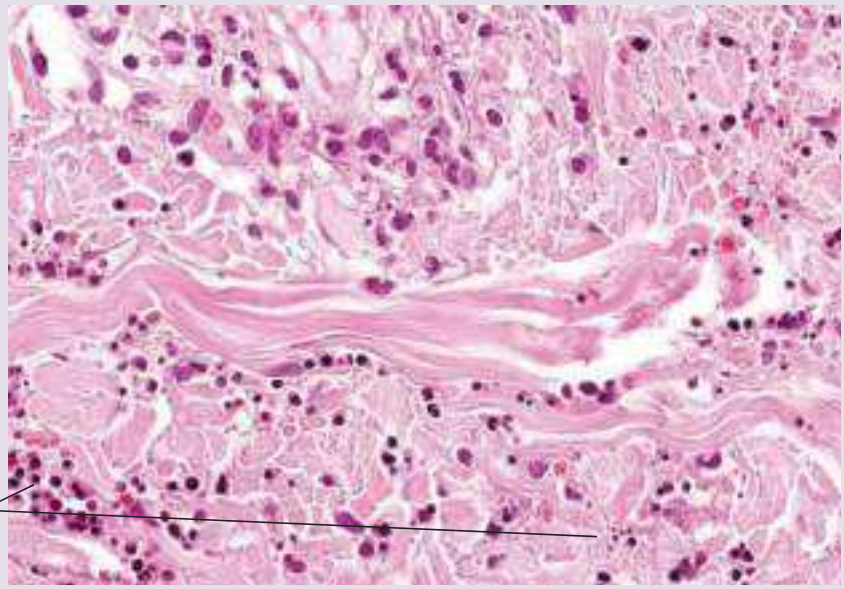
Small vessels with thickened walls (trichrome: fibrin and erythrocytes red)



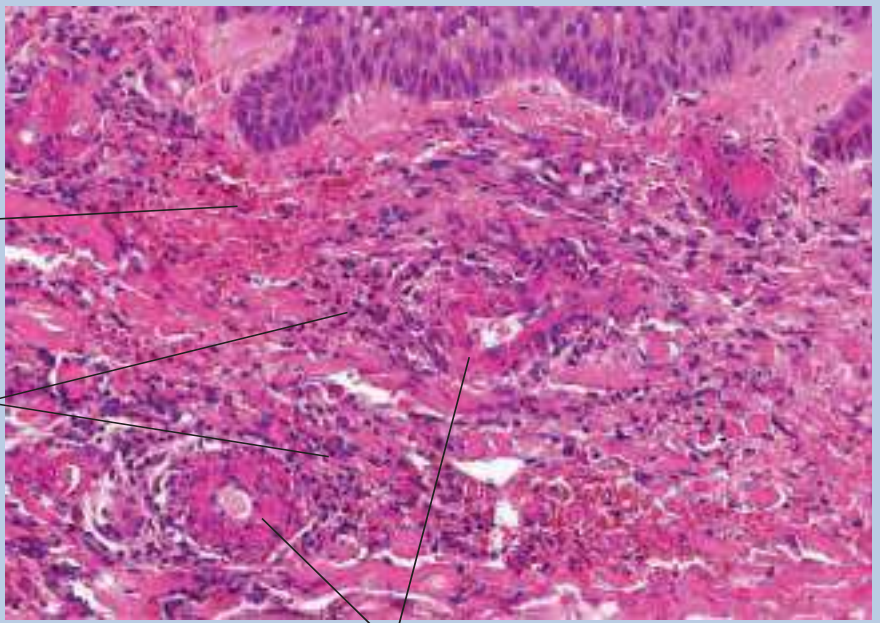
Hi: Damage of postcapillary venules in the dermis, patent lumina, destruction of vessel walls, intramural fibrin deposits, peri- and intravascular infiltrate with neutrophils and eosinophils, karyorrhexis with nuclear debris ("dirty" pattern), extravasation of erythrocytes, marked papillary edema, necrosis of overlying epidermis may occur.

Leukocytoklastic vasculitis

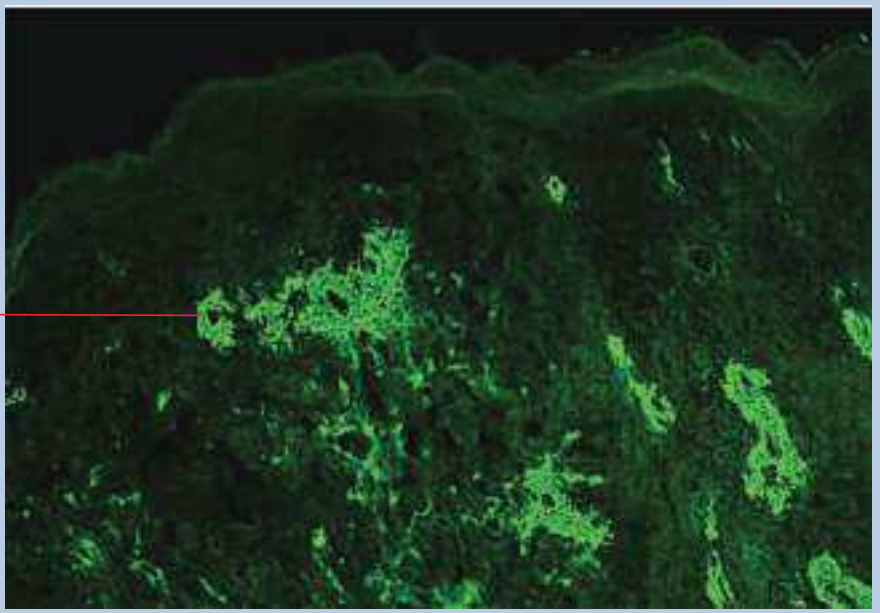




VARIANT: IgA vasculitis (Purpura Schoenlein-Henoch)

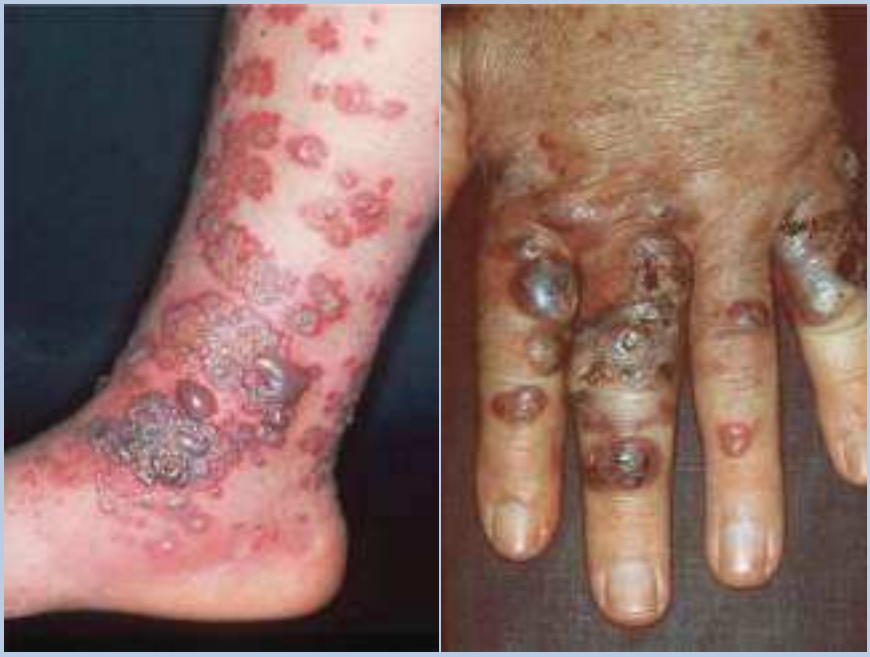


Cl: Purpuric hemorrhagic papules; systemic involvement (kidney, gut, joints).

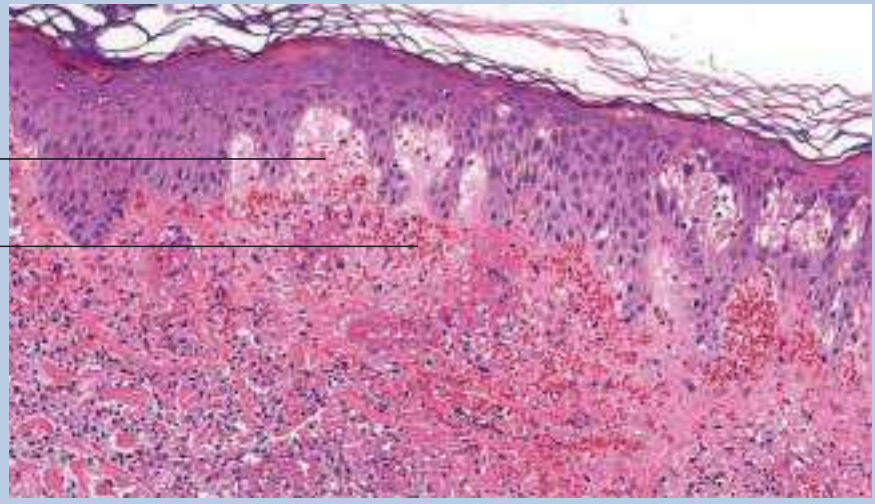


Hi: DIF: deposits of IgA in vessel walls. Involvement of visceral organs, especially GI tract and kidney.

VARIANT: Bullous leukocytoklastic vasculitis



Cl: Hemorrhagic bullae; hint for myelomonocytic and other leukemias.

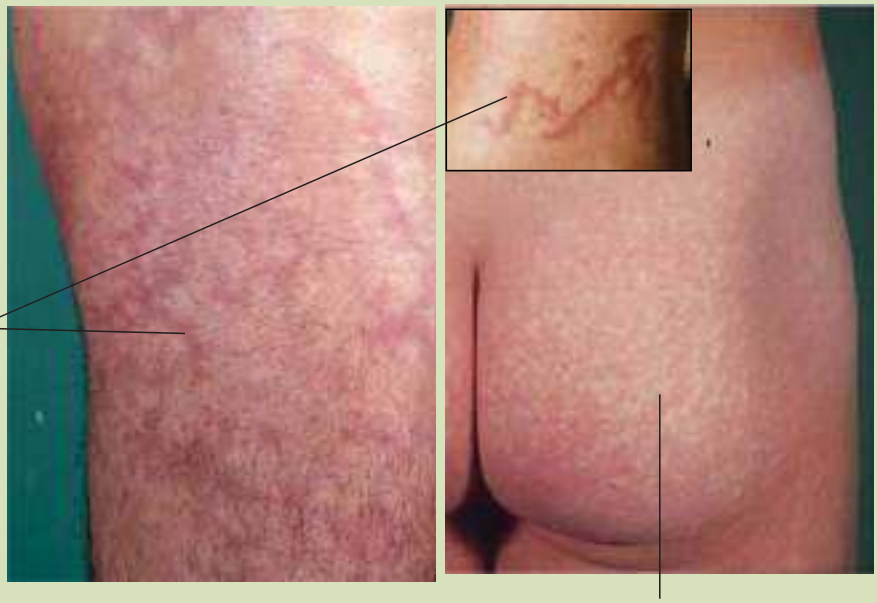


Hi: Marked edema in the papillary dermis.

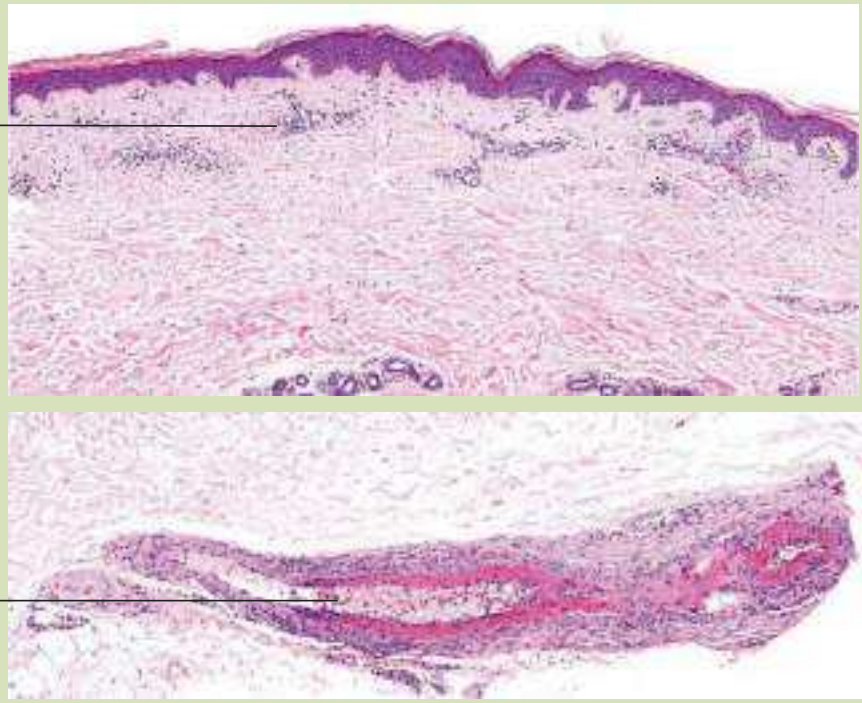
Pustular: *with accumulation of neutrophils in the epidermis*

Ulcerative: *necrosis of the epidermis.*

DIFFERENTIAL DIAGNOSIS: Livedo racemosa



CI: faint net-like and bizarre erythema.



Hi: thickening of vessel walls (corresponding to white anemic spots), often occlusion of vessel lumina in the deep dermis or subcutis.

Other Diagnosis

Urticarial vasculitis *(see* Chapter 4, Edema, page 136*): Edema of the papillary and reticular dermis, perivascular and interstitial infiltrate of eosinophils and neutrophils, mild leukocytoklastic vasculitis, subtle or absent extravasation of erythrocytes.*

Septic vasculitis *(Neisseria meningitidis, Staphylococci) (see* Intravascular coagulation, page 224*): Necrosis of vessel walls, completely occluded, thrombosed lumina, nuclear dust, bacteria, occlusion of blood vessels by fibrin thrombi.*

Cryoglobulinemia *(see* Intravascular coagulation, page 226*): Fibrin thrombi only in type 1, leukocytoklastic vasculitis in type 2.*

Acute systemic lupus erythematosus *(see* Chapter 3, Lichenoid, page 117*): Interface dermatitis, lymphocytic nuclear dust.*

Papulosis maligna *(Köhlmeier-Degos) (see* Intravascular coagulation, page 231*): Leukocytoklastic vasculitis with vascular occlusion and wedge-shaped dermal necrosis.*

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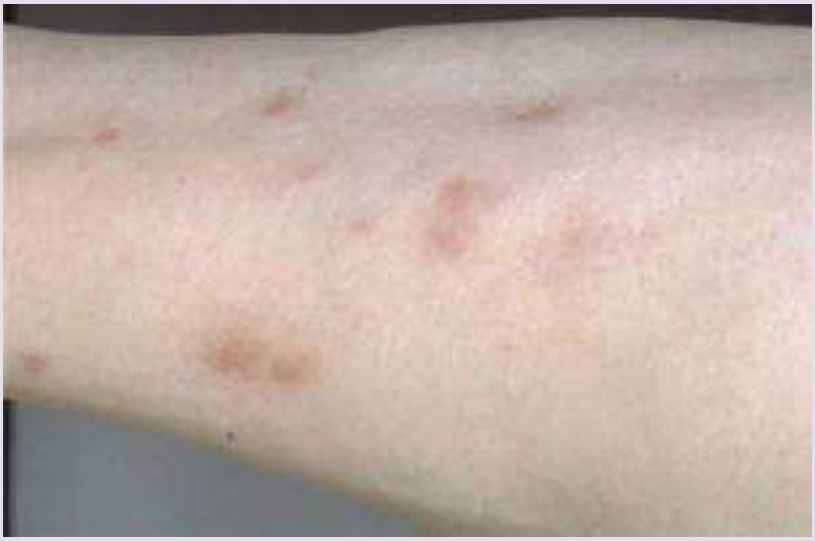
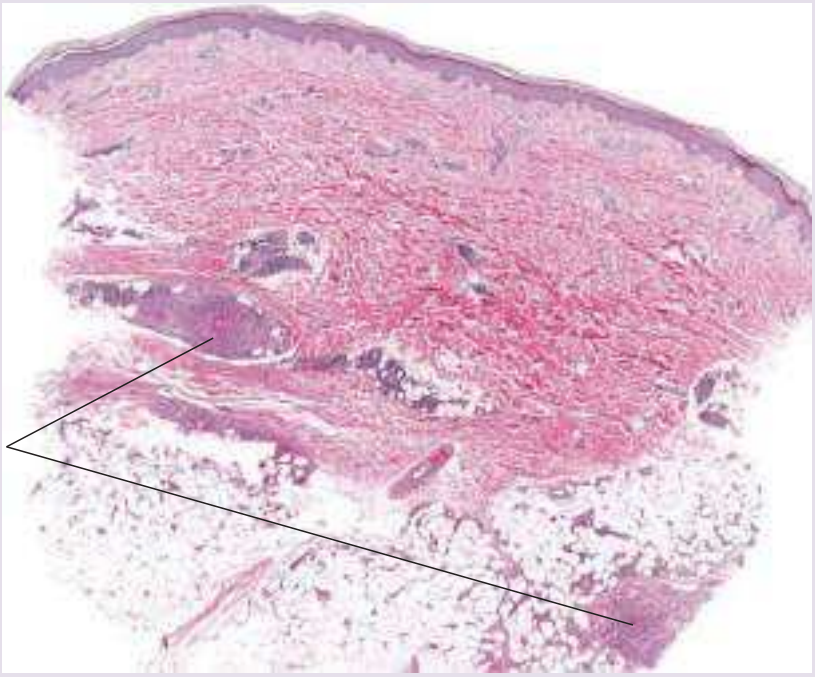
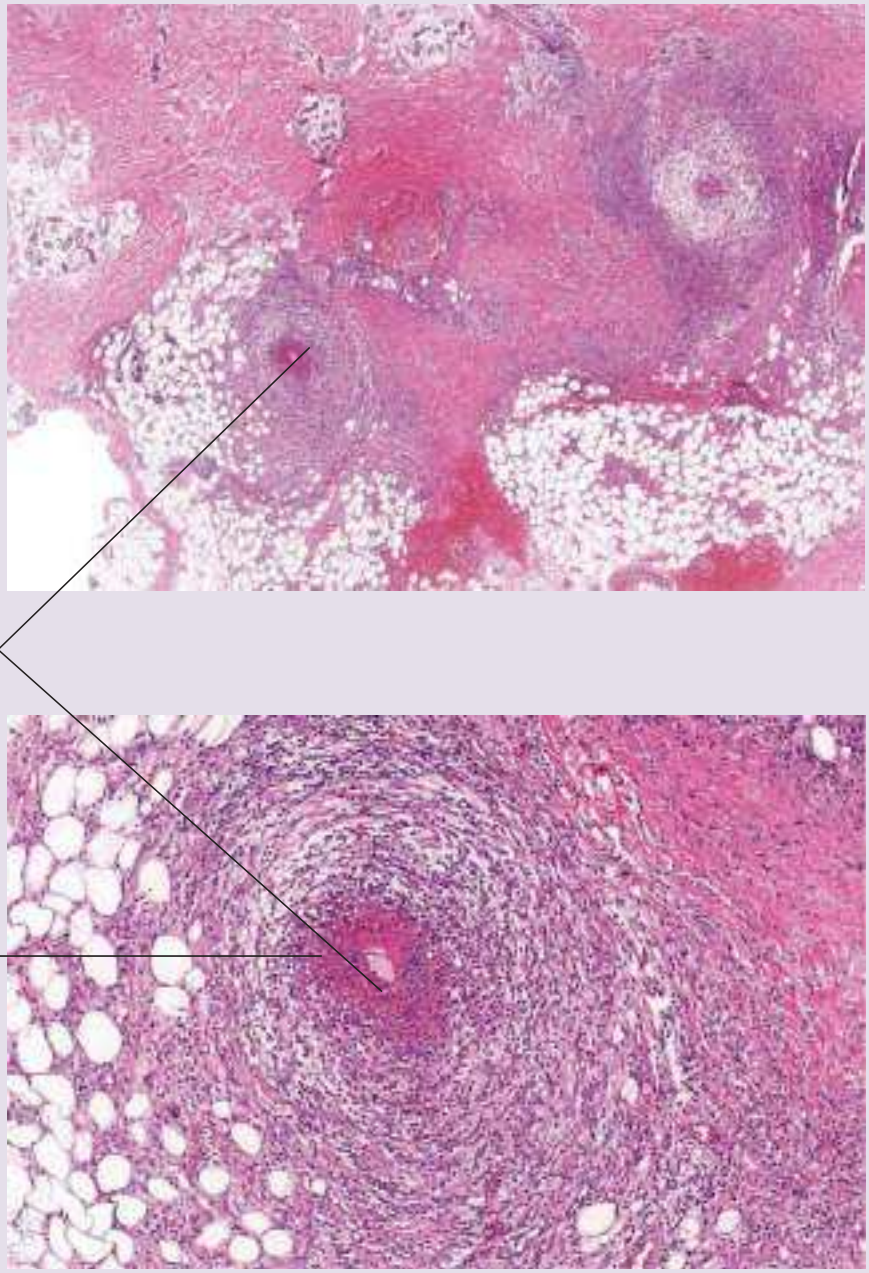
PROTOTYPE: Cutaneous polyarteritis nodosa



CI: There is a broad spectrum of systemic manifestations due to infarction of specific organs, especially kidneys. In the skin painful erythematous nodules or ulcers which may be associated with subtle pattern of livedo reticularis.

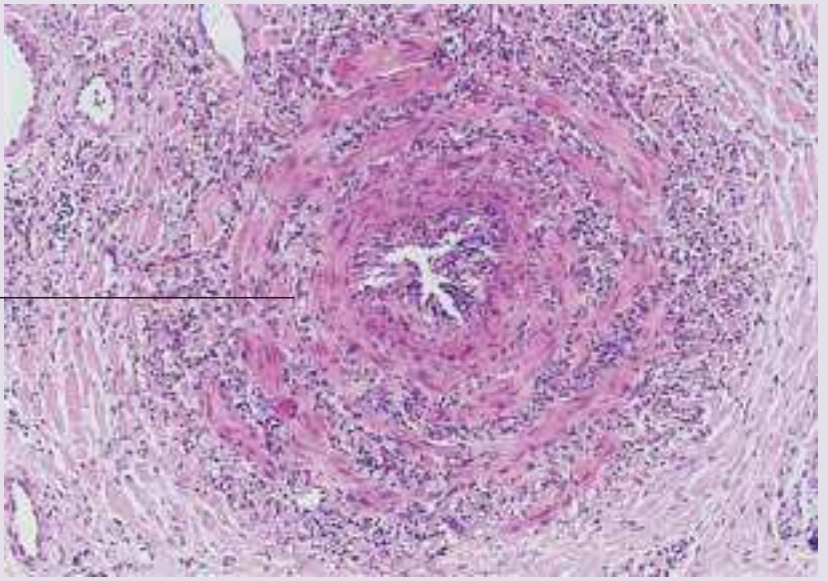


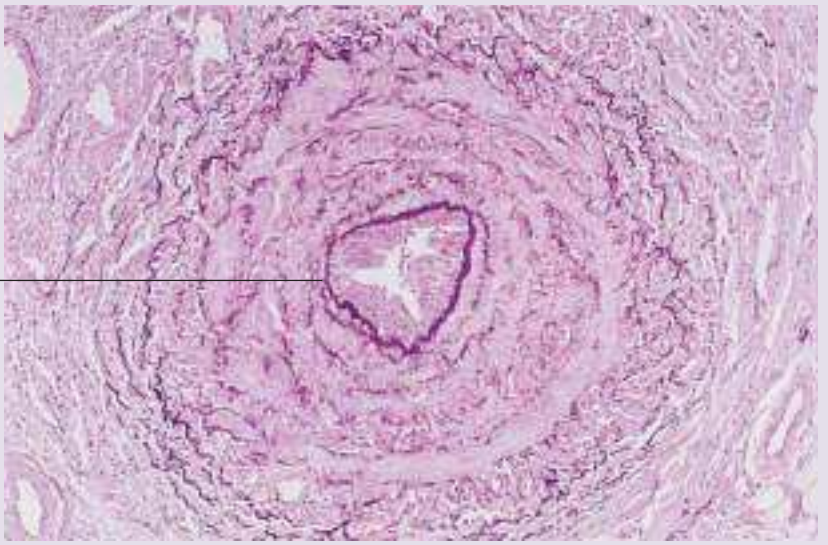
Cutaneous polyarteritis nodosa



Hi: Leukocytoklastic vasculitis of small to medium-sized arteries with neutrophils, eosinophils, nuclear dust, fibrin in the vessel wall, intima proliferation and thrombotic occlusion of the lumen, occasional necrosis with ulceration. Elastica stain highlights the lamina elastica interna of the arterial vessel.

Cutaneous polyarteritis nodosa





VARIANT

Microscopic polyarteritis: *necrotizing vasculitis, anti-neutrophil cytoplasmic autoantibodies (ANCA) frequently positive*

DIFFERENTIAL DIAGNOSIS

Superficial thrombophlebitis: *Similar findings, but involvement of a vein*

Wegener's granulomatosis: *Leukocytoklastic vasculitis with granulomatous infiltrates. Pulmonary involvement in almost all patients.*

Churg-Strauss syndrome *(see* page 165): *Leukocytoklastic vasculitis with eosinophil rich infiltrates.*

Nodular vasculitis: *Lobular panniculitis with leukocytoklastic vasculitis of subcutaneous vessels*

Comment

In individual cases it may be challenging to distinguish panarteritis nodosa from superficial thrombophlebitis on histological grounds alone.

References

Chen, K. R. (2010). "The misdiagnosis of superficial thrombophlebitis as cutaneous polyarteritis nodosa: features of the internal elastic lamina and the compact concentric muscular layer as diagnostic pitfalls." *Am J Dermatopathol* **32**(7): 688–93.

Hall, L. D., S. R. Dalton, *et al.* (2013). "Re-examination of features to distinguish polyarteritis nodosa from superficial thrombophlebitis." *Am J Dermatopathol* **35**(4): 463–71.

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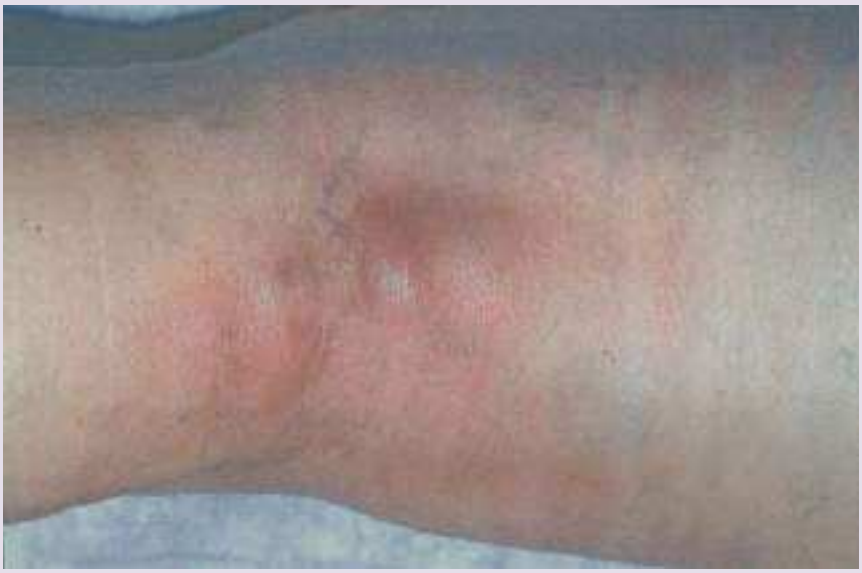
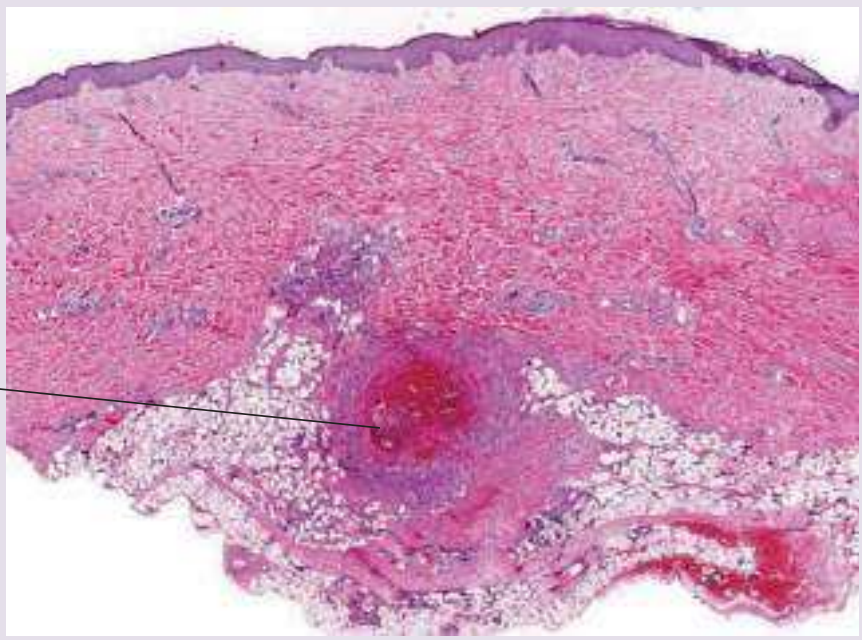
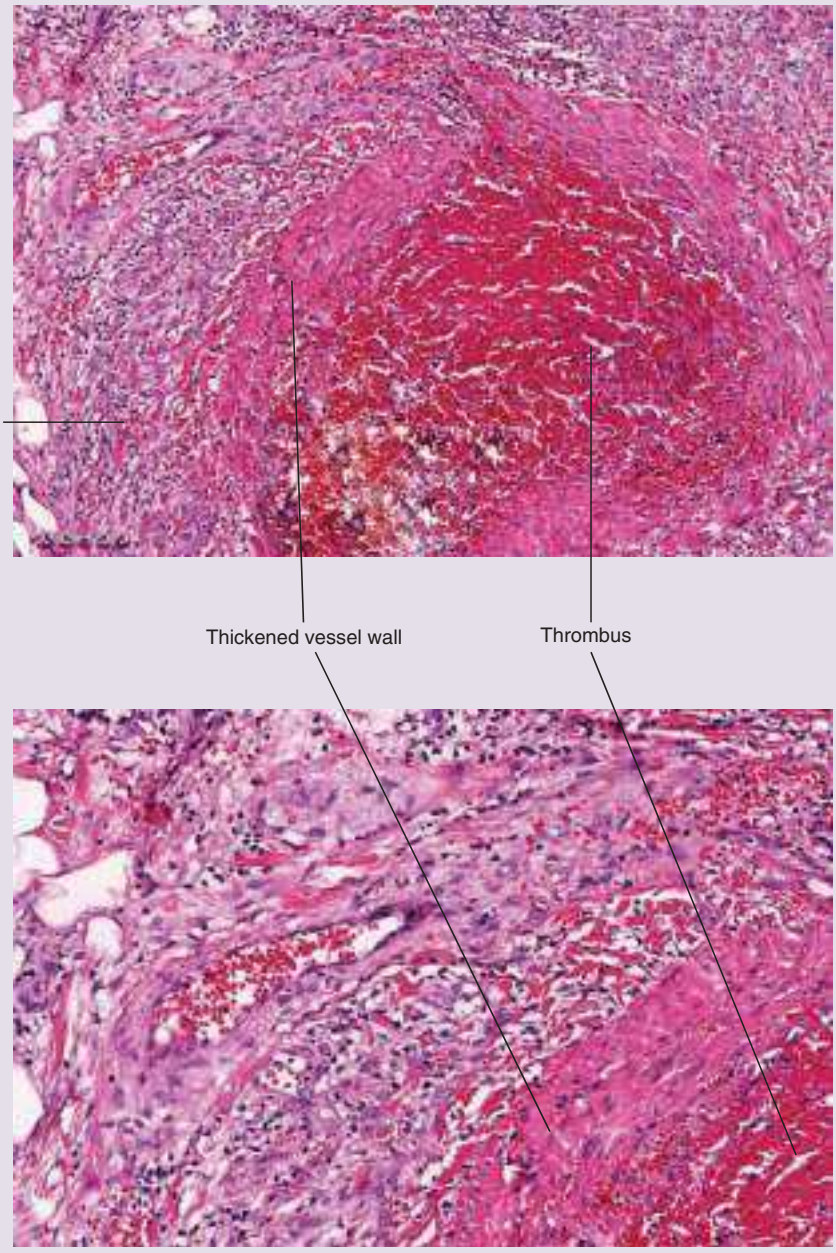
PROTOTYPE: Thrombophlebitis



CI: Distinct painful swelling with erythema and tenderness of the overlying skin, most frequently of the lower extremities. Multiple lesions may occur (so-called migratory thrombophlebitis).



Thrombophlebitis



Hi: Prominent vein in deep dermis or superficial subcutis with a thick muscular media and occluded lumen. Thrombus formation is paramount for the diagnosis of thrombophlebitis. Intramural inflammation may be scant, fibrinoid intramural deposits are absent. Early stages show neutrophil-rich infiltrates, mostly confined to the perivascular layers. Late stages show mixed inflammatory infiltrates surrounding the vessel but not spilling over into adjacent dermal or subcutaneous layers. Marked elastic fibers within thickened vessel wall.

VARIANT

Mondor disease: *distinct clinical features. Cord-like induration on the outer chest wall due to thrombophlebitis of the subcutaneous veins, always in linear arrangement.*

DIFFERENTIAL DIAGNOSIS

Polyarteritis nodosa *(see* Medium-sized vessels, page 240*): Marked intramural inflammation in conjunction with necrosis. Vasculitis mostly confined to arterioles (polyarteriolitis) of the deep dermis and superficial subcutis, but not to medium-sized or thicker arteries; the intramural inflammatory infiltrate widens the medial muscular arteriolar layer, thereby creating the false impression of a medium-sized thick-walled artery. A histopathological hallmark of polyarteritis nodosa is the patent vessel lumen in conjunction with dense intramural inflammation. There are typical intramural fibrinoid deposits forming a thick homogeneous ring between the intima and the lamina elastic interna.*

Nodular vasculitis: *In many cases, deep thrombophlebitis is mistaken for nodular vasculitis, particularly in lesions involving the lower extremities. Classic nodular vasculitis involves medium-sized arteries of the subcutis with a dense infiltrate spilling over into adjacent tissues, e.g. the septa of the subcutaneous fat and the lobular fat.*

Comment

As a *diagnostic clue*, nodular vasculitis presents with a thickened vessel wall devoid of elastic fibers between smooth muscle layers, while thrombophlebitis is characterized by multiple elastic fibers within the muscular vessel wall. Lamina elastica interna may be similar in both thick caliber veins and arteries of the lower limb.

Comments

The most challenging task in pathology of medium-sized vessel vasculitis is to differentiate between superficial thrombophlebitis of the lower extremities and cutaneous polyarteritis nodosa. It is quite remarkable that veins of the lower extremities are thick-walled, sometimes suggesting the pattern of mid-sized arteries. However, the muscular medial layer of thick-walled veins of lower extremities is multi-layered and includes multiple delicate strands of elastic fibers, while in mid-sized arteries there is a thick homogeneous and contiguous muscular layer without interspersed elastic fibers.

Thrombophlebitis is always associated with thrombosed lumina, while in polyarteritis nodosa lumina are patent. The latter shows marked intramural inflammation with widening of the vessel wall and necrosis, while thrombophlebitis mostly is accompanied by a perivascular infiltrate confined to the immediate vicinity of the vessel. Fibrinoid deposits do not occur in vessel walls of thrombophlebitic lesions, but are quite characteristic of polyarteritis nodosa.

References

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Hall, L. D., S. R. Dalton, *et al.* (2013). "Re-examination of features to distinguish polyarteritis nodosa from superficial thrombophlebitis." *Am J Dermatopathol* **35**(4): 463–71.

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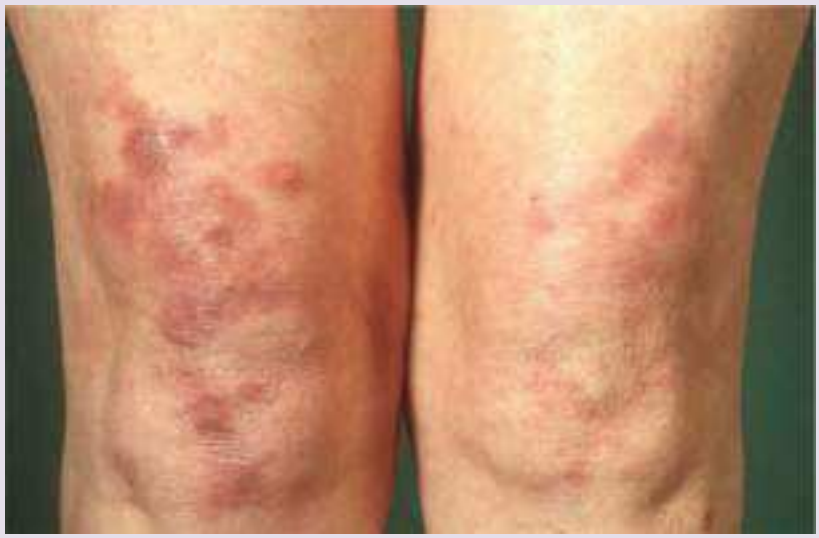
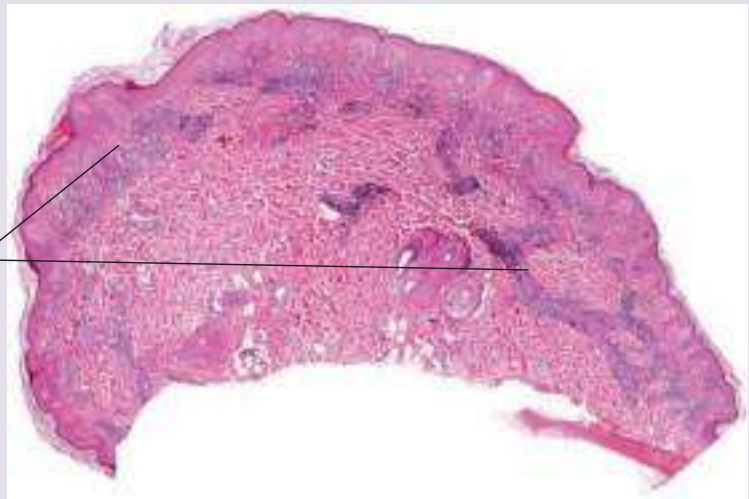
PROTOTYPE: Erythema elevatum diutinum



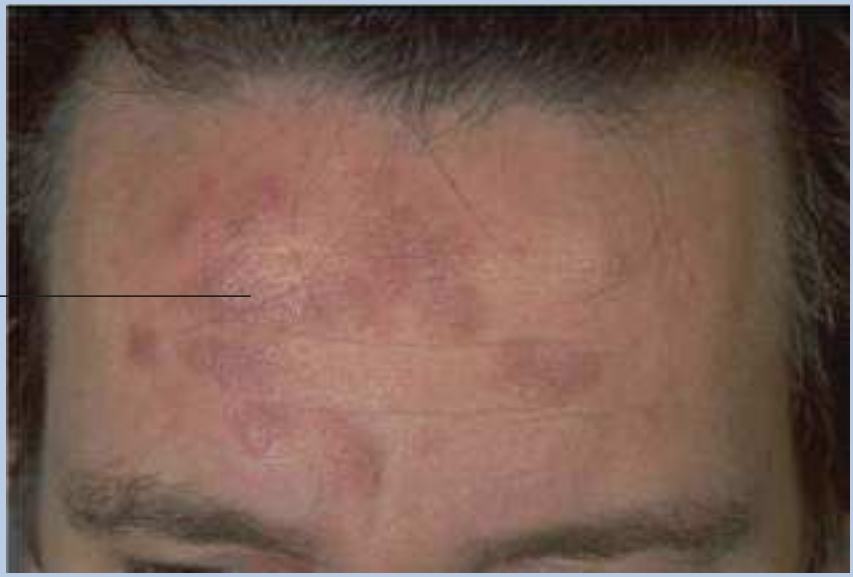
Cl: Persistent, pad-like violaceous papules or plaques, symmetrically on the extensor surface of extremities.



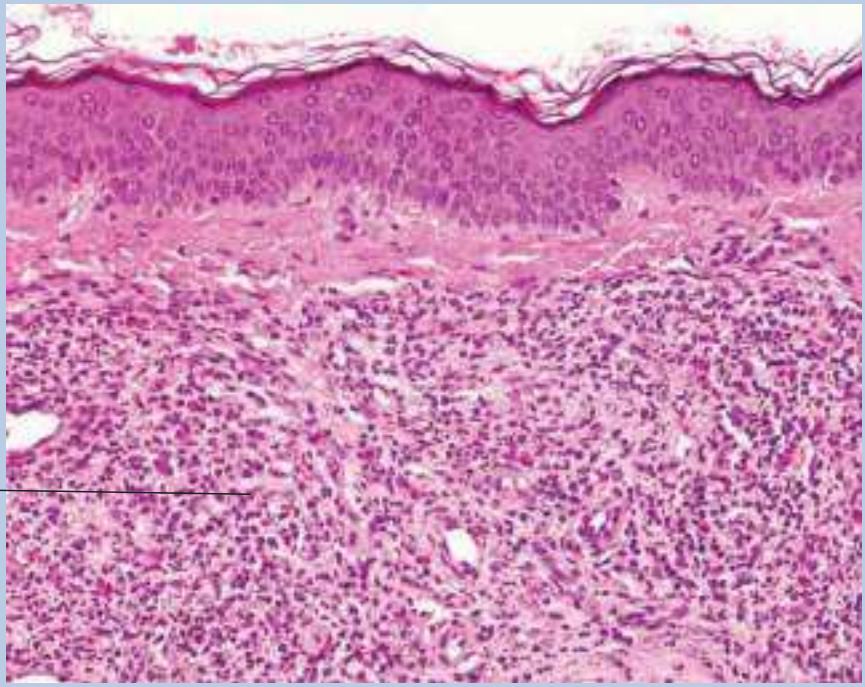
Hi: Leukocytoklastic vasculitis of small vessels in the upper and mid dermis with admixture of eosinophils and plasma cells and variable degrees of concentric fibrosis.

Early stage: Mixed cellular infiltrate. Lymphocytes, neutrophils, eosinophils, nuclear dust and leukocytoklastic vasculitis in the center of the infiltrates
Late stage: Concentric fibrosis, histiocytes and plasma cells.

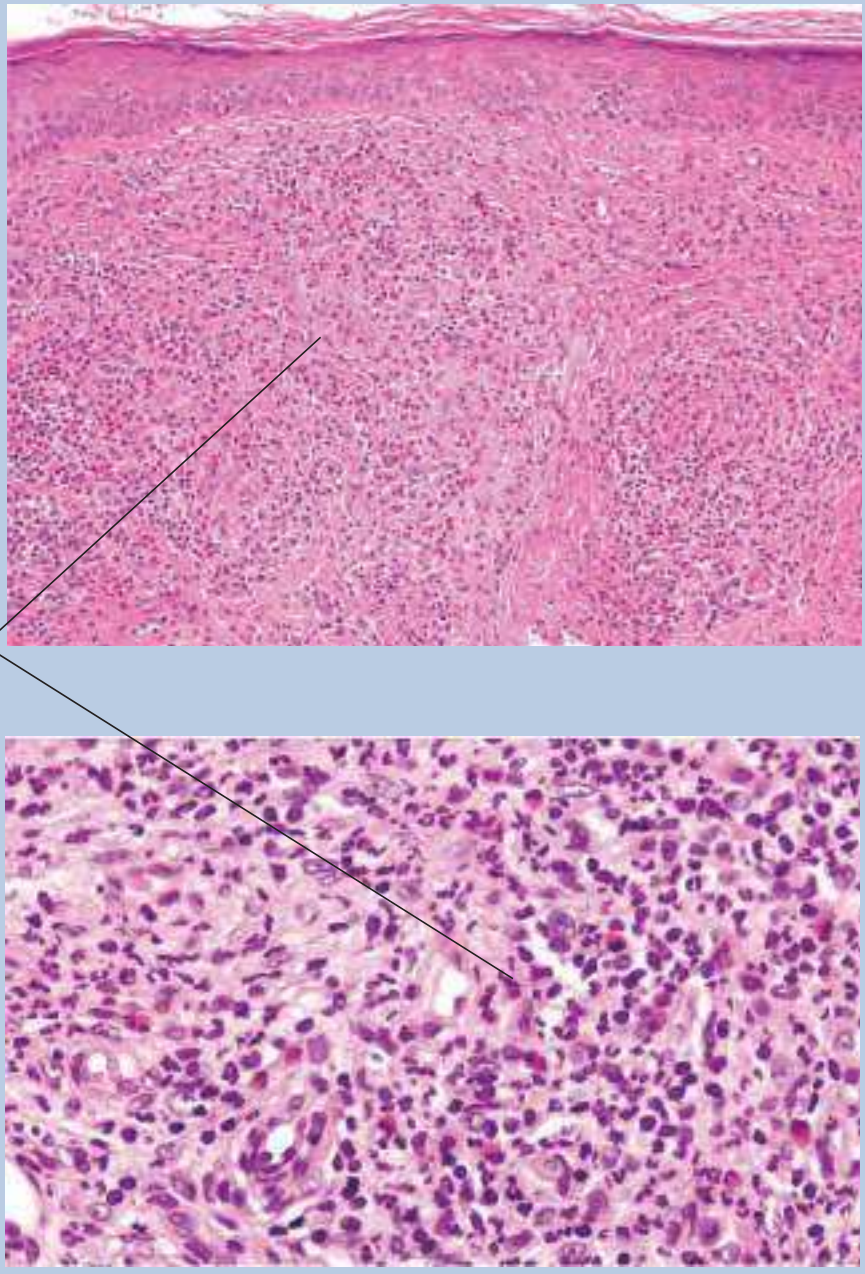
VARIANT: Granuloma faciale



CI: Violaceous brown-red infiltrated plaque, preferentially in men's faces.



Granuloma faciale



Hi: Overlapping with erythema elevatum et diutinum. There is a lymphohistiocytic ("granulomatous") infiltrate with leukocytoklasic vasculitis. Many eosinophils are present. Nuclear dust. Admixture of plasma cells.

DIFFERENTIAL DIAGNOSIS

Interstitial granulomatous dermatitis *(see* page 177*): Clinically shows patchy confluent erythema associated with arthritis. Histologically there is diffuse neutrophilic infiltrate, which tends to accumulate in dermal papillae; plasma cells.*

Sweet's syndrome *(see* Chapter 4, Non-granulomatous infiltrates, neutrophil- or eosinophil-rich, page 157*): Diffuse dermal neutrophilic infiltrate, no admixture of plasma cells, no prominent vasculitic features.*

Eosinophilic cellulitis (Wells syndrome) *(see* Chapter 4, Non-granulomatous infiltrates, eosinophil-rich, page 159*): Diffuse dermal infiltrates of eosinophils, flame figures, no vasculitis.*

Behçet's disease *(see* Chapter 2, Pustular, page 76*): In early stage: necrotizing leukocytoklastic vasculitis (pustules); Late stage: granulomatous reaction*

Comment

Erythema elevatum diutinum and granuloma faciale differ in regard to their clinical presentation, but show overlapping histological features. Therefore some experts consider the two conditions to represent one nosologic entity.

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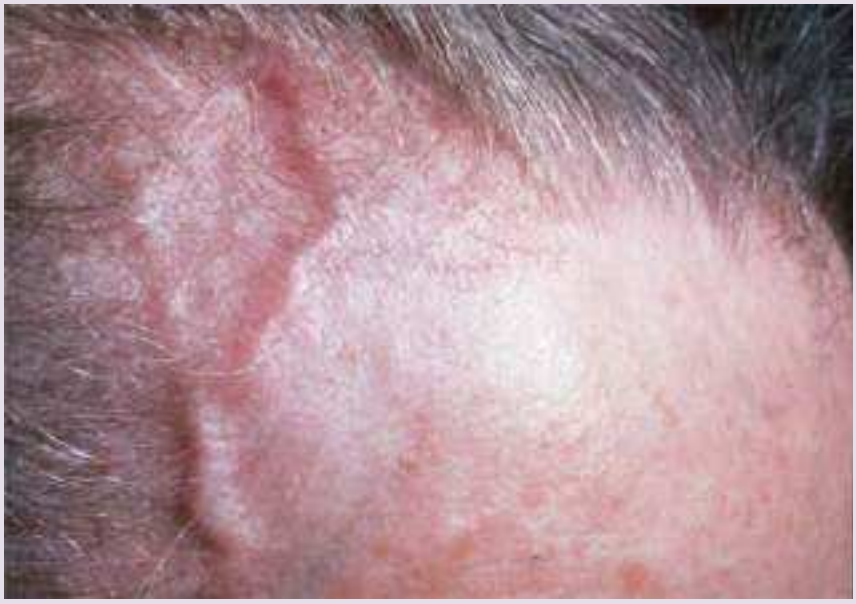
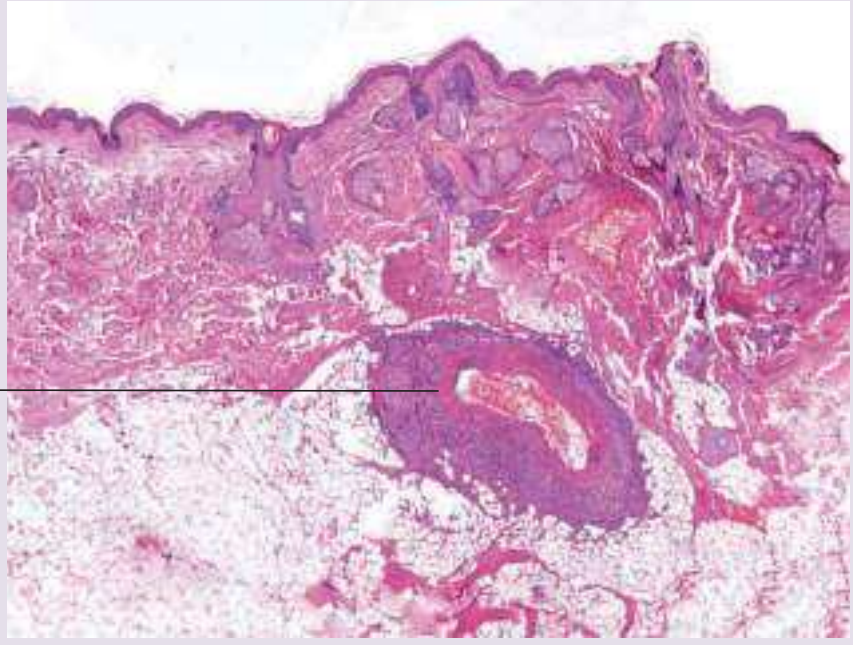
PROTOTYPE: Temporal arteritis



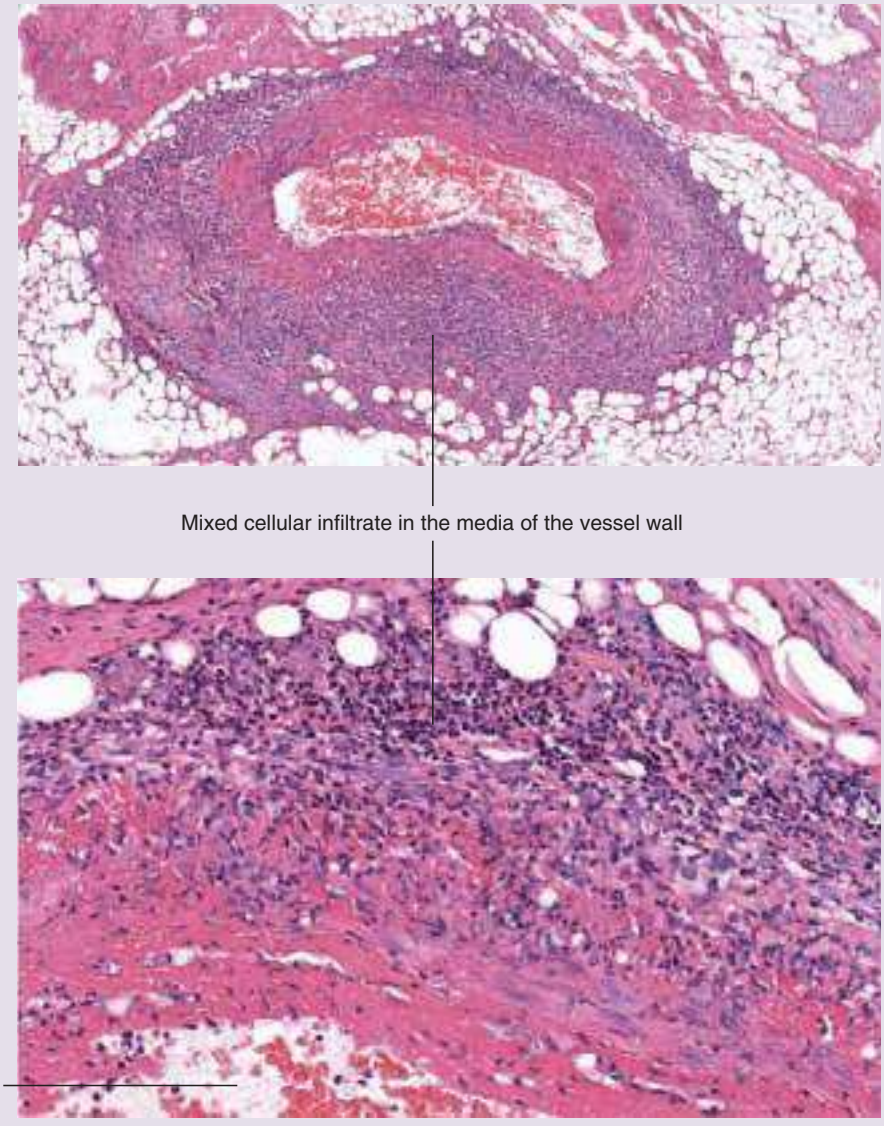
Palpable arteria on the forehead

CI: Mostly in the temporal area erythema and ulceration overlying a palpable arteria. General symptoms include fever, pain and malaise. Sudden visual impairment may occur.



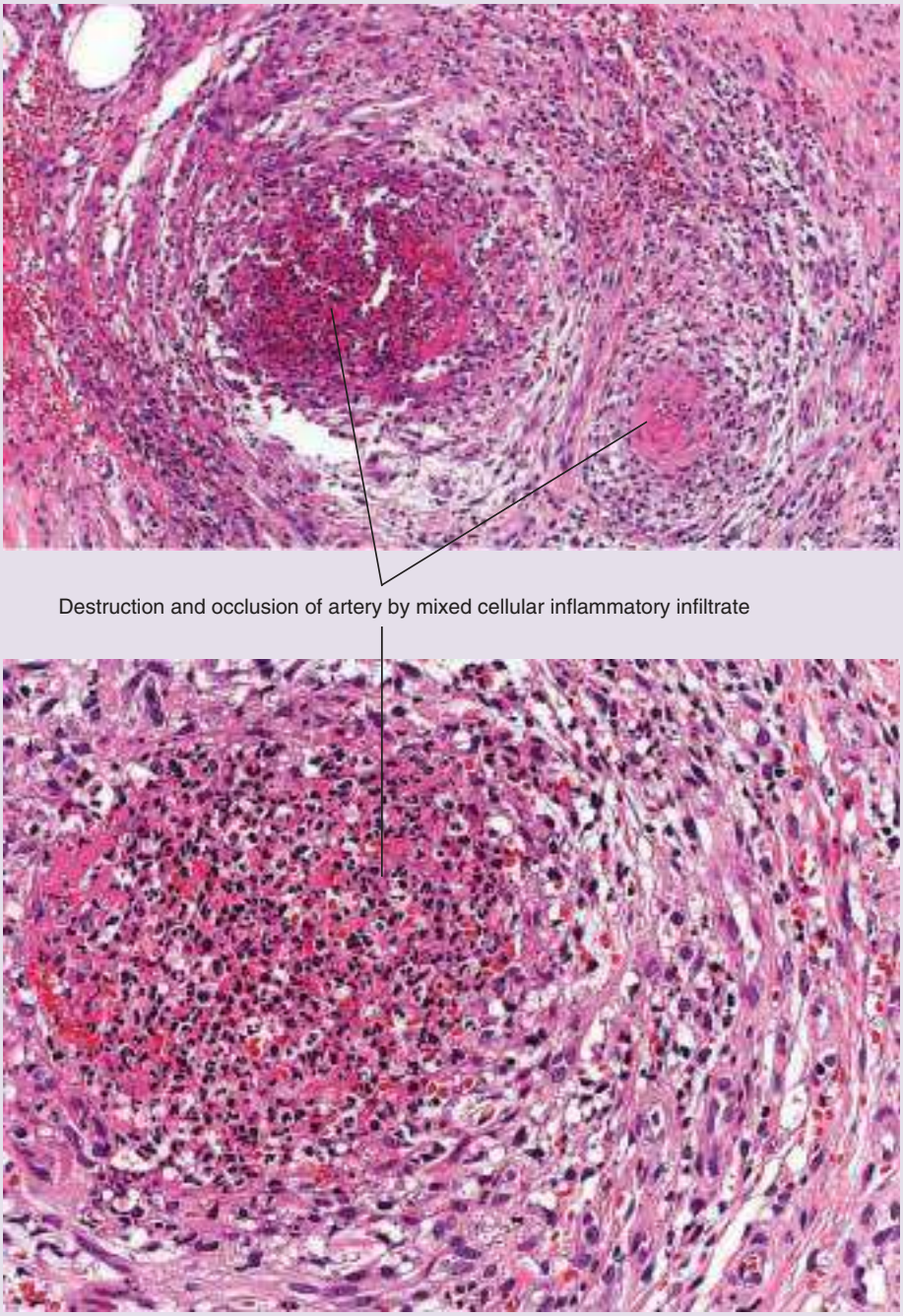
Temporal artery

Temporal arteritis



Hi: Granulomatous vasculitis involving medium to large arteries, with prominent skip areas. Vascular changes predominate in the inner media of the vessel wall with a mixed infiltrate containing multinucleated histiocytes. Destruction of the internal elastic lamina. No extravascular granuloma formation. Inflammatory changes may be restricted to the subintimal compartment of the vessel wall.

Temporal arteritis



Destruction and occlusion of artery by mixed cellular inflammatory infiltrate

VARIANTS

Subintimal inflammatory changes, *sparing the media, without marked multinucleate cells. Focal fragmentation of the internal elastic lamina.*

DIFFERENTIAL DIAGNOSIS

Polyarteritis nodosa *(see* Medium-sized vessel, page 240*): leukocytoklastic vasculitis of small to medium-sized arteries, fibrin deposits, leukocytoklasia, no giant cells within vessel walls.*

Churg-Strauss syndrome *(see* page 165*): Eosinophilic extravascular palisading granulomas in conjunction with eosinophilic vasculitis. Extravascular palisading granulomas may be a prominent feature.*

Wegener's granulomatosis: *Granulomatous vasculitis with extravascular palisading granulomas. Neutrophilic granulocytes may predominate.*

Thrombangitis obliterans *(Buerger's disease): Cellular mixed inflammatory infiltrate within vessel wall. No granulomatous changes. Scant neutrophils.*

Lymphocytic thrombophilic (macular) arteritis: *Medium-sized vessel vasculitis with fibrinoid thrombi or rims within the vessel and vessel wall, lymphocytes and histiocytes.*

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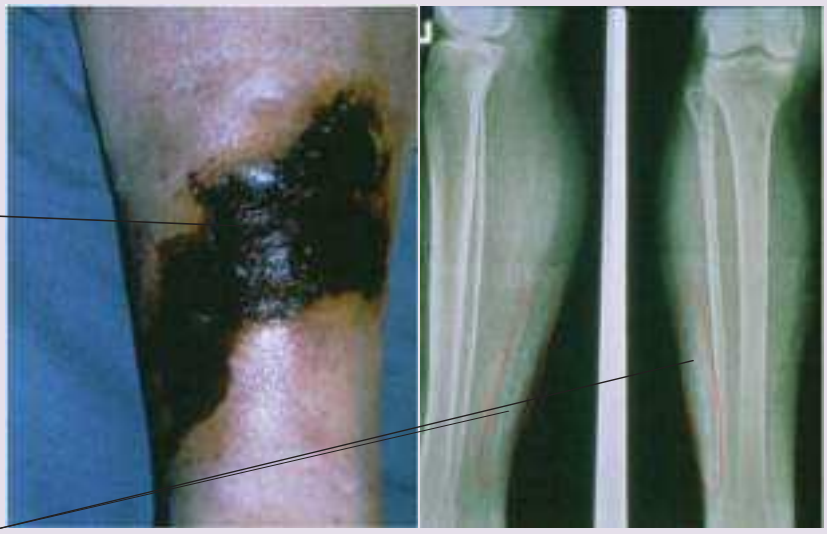
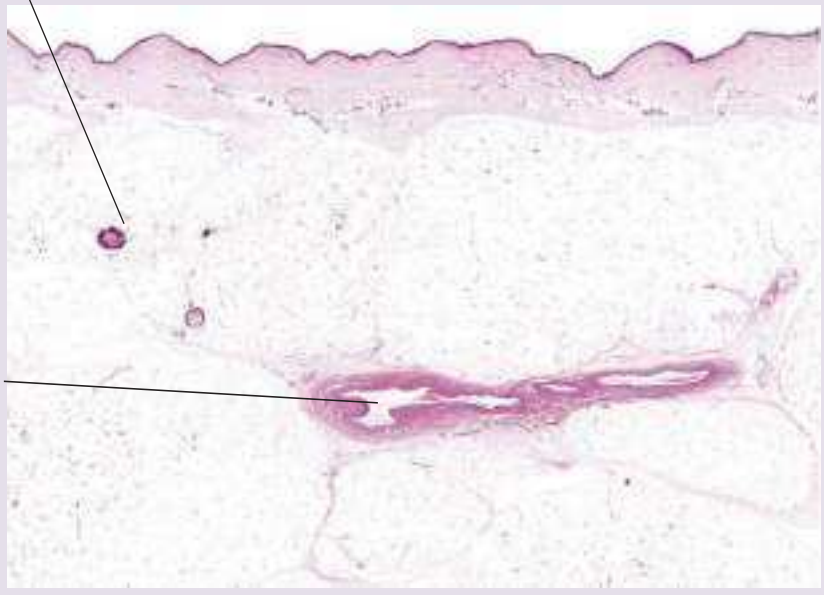
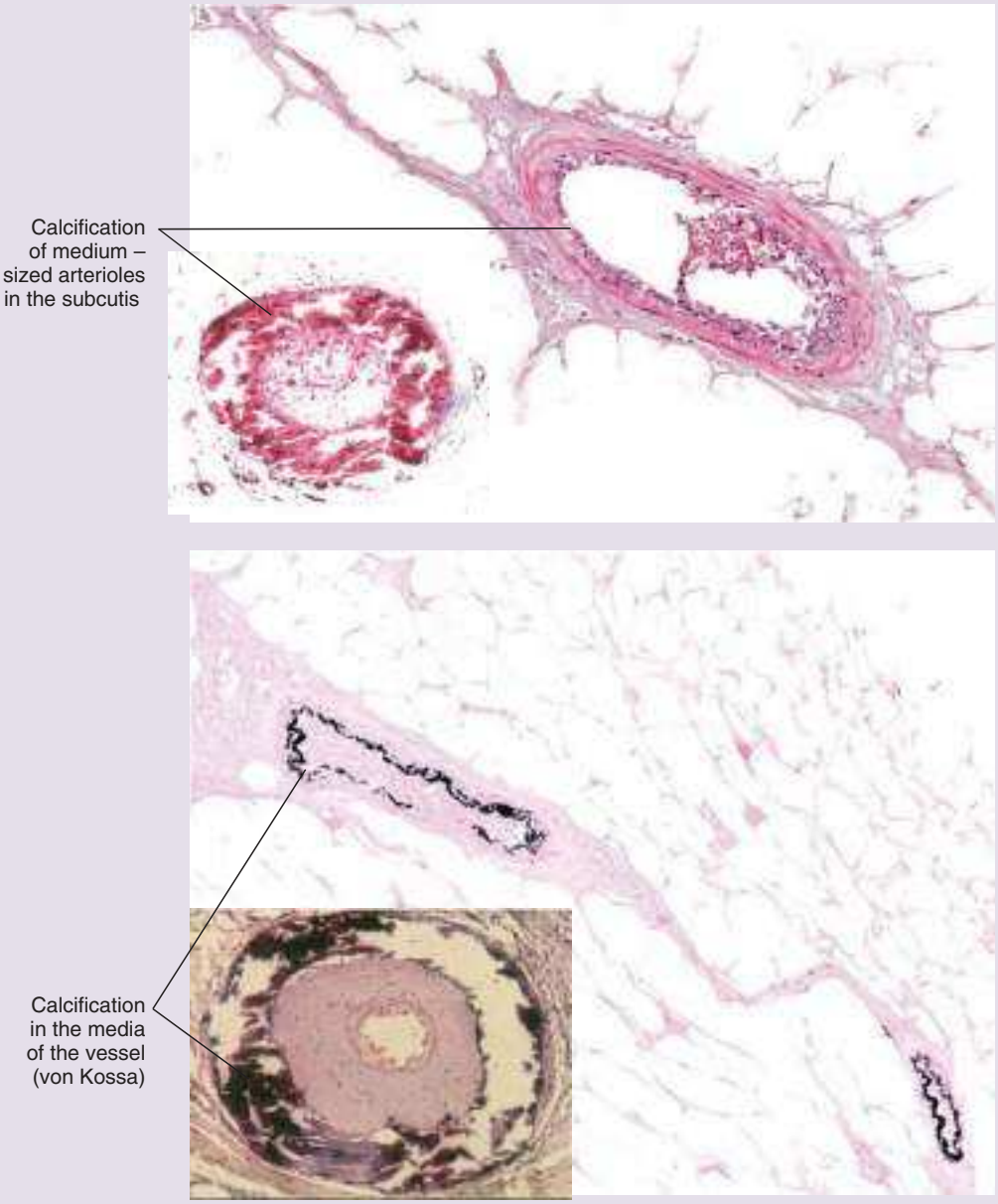
PROTOTYPE: Cutaneous calciphylaxis (calcifying uremic arteriolopathy)



Cli: Superficial necrotic plaques and ulceration, usually on the lower leg in conjunction with chronic renal failure or/and hyperparathyroidism.



Cutaneous calciphylaxis



Hi: cutaneous uremic calciphylaxis. The histopathological hallmarks of this condition are multiple tiny calcification foci within the subcutaneous fat, mostly in association with lobular capillaries and necrotic fat cells. Medial calcification of mid-sized arteries in conjunction with ulceration is common but cannot be used as a discriminating clue against Martorell's hypertensive arteriolosclerosis due to morphological overlap between the two entities.

VARIANTS

Early stage *may show only minimal calcification of vessels.*
Late stages *may be accompanied by massive inflammation and necrosis, simulating panniculitis or pyoderma gangraenosum.*

DIFFERENTIAL DIAGNOSIS

Arteriosclerosis: *Incipient stages without visible clinical symptoms. Advanced stages with painful necrotic skin ulcers on the laterodorsal part of the leg, often with bilateral involvement. Ulcerations show morphological overlap with pyoderma gangraenosum. Systemic alterations include arterial hypertension and diabetes. Histology shows arteriolar changes in the deep dermis or subcutis with stenotic arteriolosclerosis and medial calcification, often in association with overlying ulceration. Arteriolar vessel walls are markedly thickened, with intramural medial calcification indistinguishable from calciphylaxis and other non-uremic variants of calciphylaxis. The ulceration may show undermined borders and a neutrophil-rich infiltrate, similar to histopathological changes in association with pyoderma gangrenosum. The condition is also known as Martorell's hypertensive ischemic leg ulcer.*

Oxalosis: *Birefringent crystalline deposits within lumina of small vessels. No significant vasculitic phenomena, no vessel wall calcification.*

Non-uremic calciphylaxis: *often indistinguishable from uremic calciphylaxis. Clinical investigations are paramount (calcium and phosphate levels, uremic parameters and others).*

Cutaneous calcinosis: *This multifactorial condition mostly affects the extravascular tissues. Significant vascular changes do not occur. Metaplastic calcification is typical of necrotic and tumorous foci.*

Incidental calcification: *Functionally insignificant vascular calcification indistinguishable from calcified arteriolosclerosis may be observed in the vicinity of excised epithelial or mesenchymal tumors from sun-exposed skin of the elderly, e.g. in BCC or SCC of the face.*

Comment

The leading clinical picture with calcified arteriolosclerosis is Martorell's hypertensive ischemic leg ulcer, mostly affecting older patients with arterial hypertension and diabetes. Surprisingly, this condition is commonly confused with pyoderma gangraenosum, due to its massive ulceration. However, mural calcification of mid-sized arterial vessels is not an inherent part of pyoderma gangraenosum. Uremic and non-uremic calciphylaxis may be a significant pitfall in the diagnosis of subcutaneous arteriolosclerosis with vessel wall calcification. Remarkably, calcification of mid-mural myoid layers of arterioles are identical in both uremic/non-uremic calciphylaxis and in Martorell's calcified arteriolosclerosis. However, only the former conditions show conspicuous disseminated calcification in the subcutaneous fat with multiple calcified foci in association with capillaries between fat cells. Von Kossa stain may be necessary to appreciate these distinctive changes.

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CHAPTER 6
Subcutis

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.
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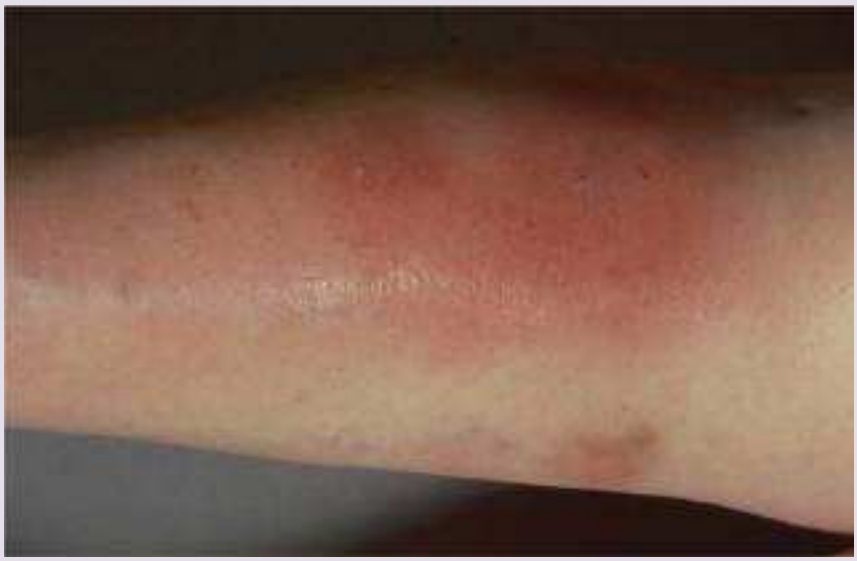
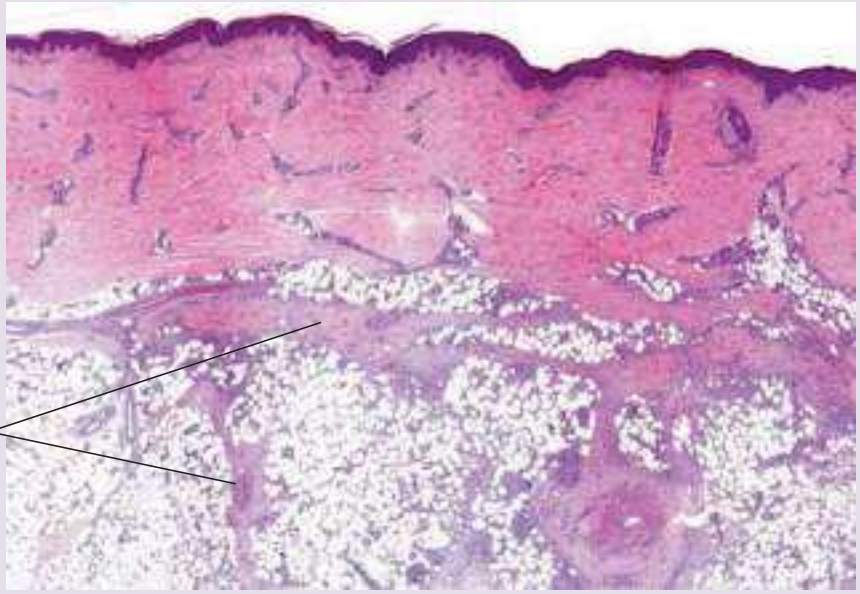
SUBCUTIS

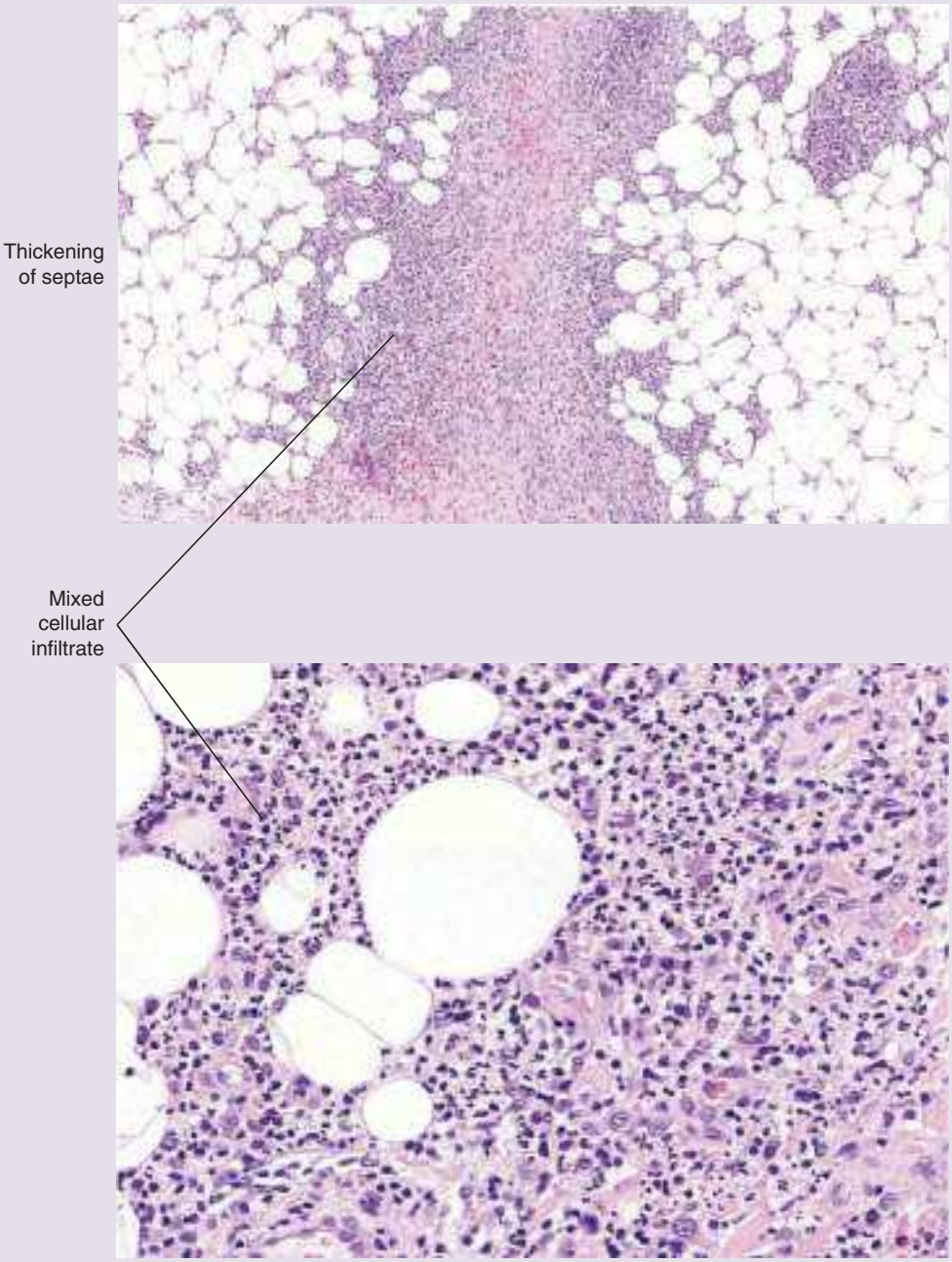
PROTOTYPE: Erythema nodosum (early stage)



CI: Bruise-like red, highly pressure sensitive swelling involving predominantly the ankles, knees and anterior shins of middle-aged women. Ulceration does not occur. Lesions heal within 4-8 weeks with complete regression without scars.

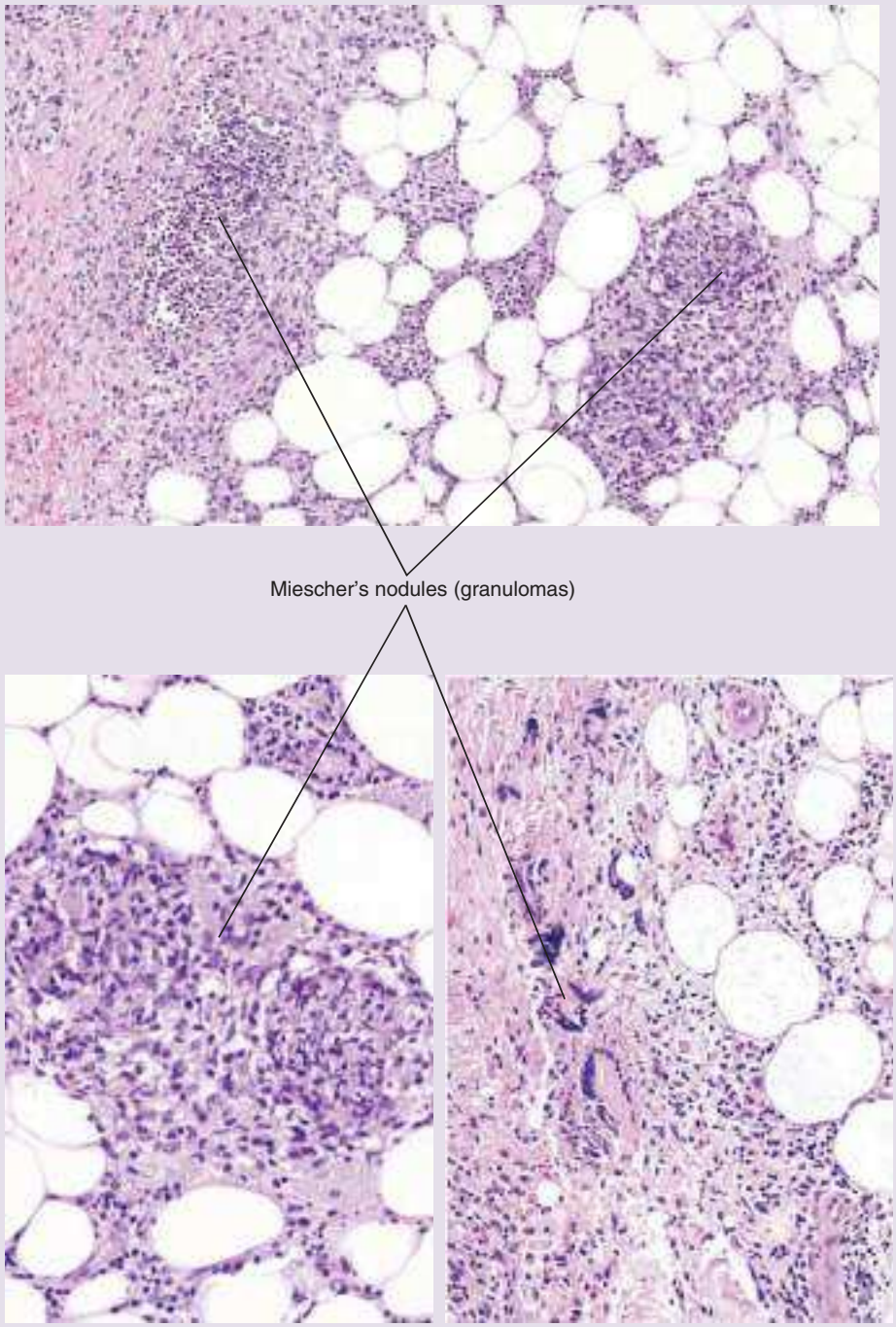


Erythema nodosum



Hi: Thickening of subcutaneous septa, edema, neutrophils, eosinophils and lymphocytes (septal panniculitis), histiocytic granulomas in the periphery of fat lobules (Miescher's granulomas). No vasculitis.

Erythema nodosum



DIFFERENTIAL DIAGNOSIS:

Septal panniculitis

Deep morphea: *Thickened subcutaneous septa, subtle lymphocytic infiltrate with admixture of plasma cells.*

Lobular panniculitis

Nodular vasculitis: *Leukocytoklastic vasculitis involving venous and arterial vessels.*

Erythema induratum Bazin (see Chapter 4, Granulomatous infiltrates, with necrosis)

Posttraumatic panniculitis: *Foamy histiocytes surrounding pseudocystic spaces.*

Factitial panniculitis

Infectious panniculitis: *Septal and lobular mixed infiltrates with neutrophils, eosinophils and plasma cells. Abscess formation.*

Comments

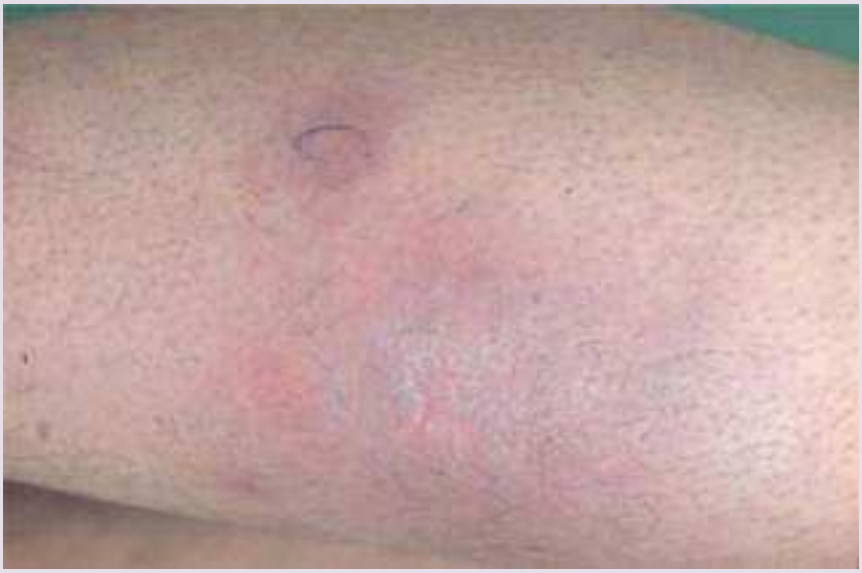
The clinical presentation in the various types of panniculitis uniformly is a more or less erythematous soft cushion-like swelling.
Erythema nodosum may occur in the context of sarcoidosis (Loefgren syndrome with hilar lymphadenopathy, polyarthritis and erythema nodosum).

References

Requena, L. and E. Sanchez Yus (2007). "Erythema nodosum." *Semin Cutan Med Surg* **26**(2): 114–25.

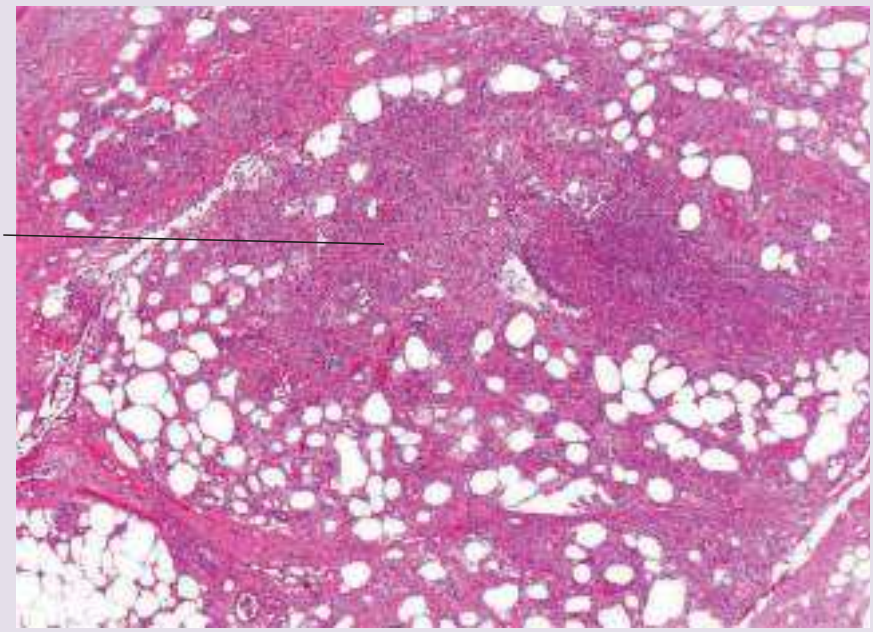
SUBCUTIS

PROTOTYPE: Lupus panniculitis (Syn. Lupus profundus)



Indurated subcutaneous nodules on the leg

Cl: Multiple, subcutaneous indurated, painless nodules or plaques preferentially involving upper arms, shoulders, buttocks and breasts of women.

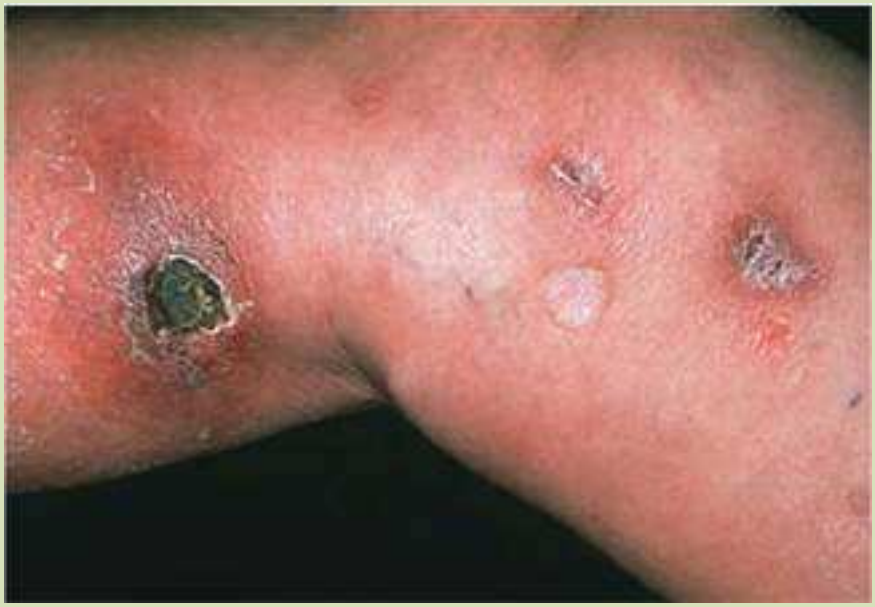


Lobular predominantly lymphocytic infiltrate

Hi: Lobular and paraseptal panniculitis with lymphocytic infiltrates and admixture of plasma cells and macrophages. Karyorrhexis. Mucin deposits in dermis and subcutis. No vasculitis. Rimming of adipocytes by lymphocytes, fat necrosis, plasma cells. No neutrophilic granulocytes.

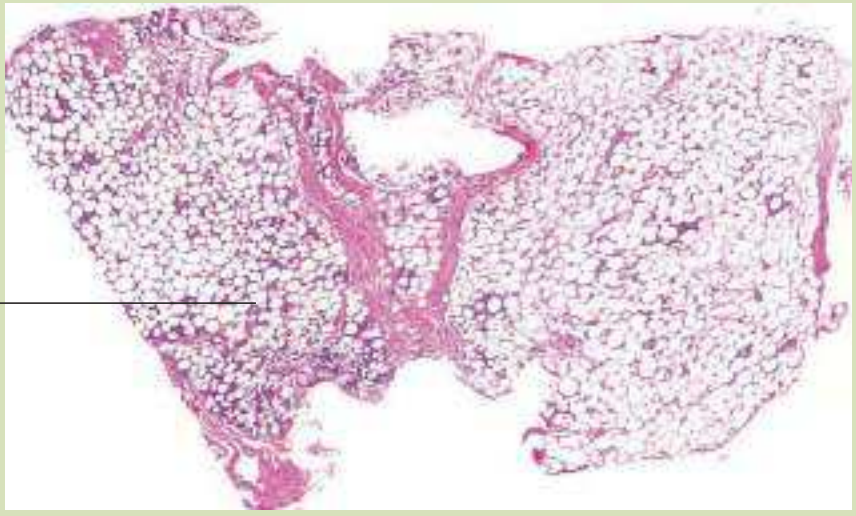
DIFFERENTIAL DIAGNOSIS: Subcutaneous panniculitis-like T-cell lymphoma

Ulcerated subcutaneous nodules



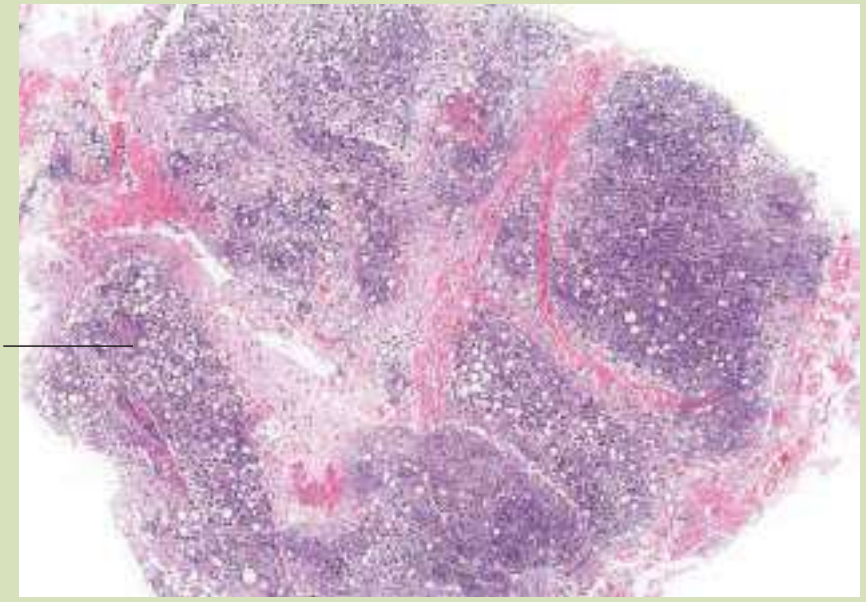
CI: Multiple erythematous swelling and subcutaneous nodules without epidermal involvement except occasional occurrence of ulceration.

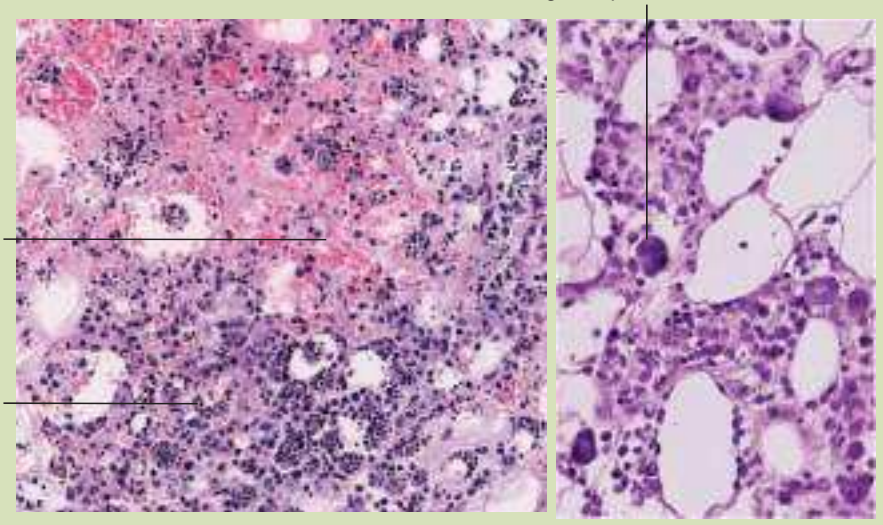
Predominantly lobular infiltrate of tumor cells



SUBCUTIS

Subcutaneous panniculitis-like T-cell lymphoma





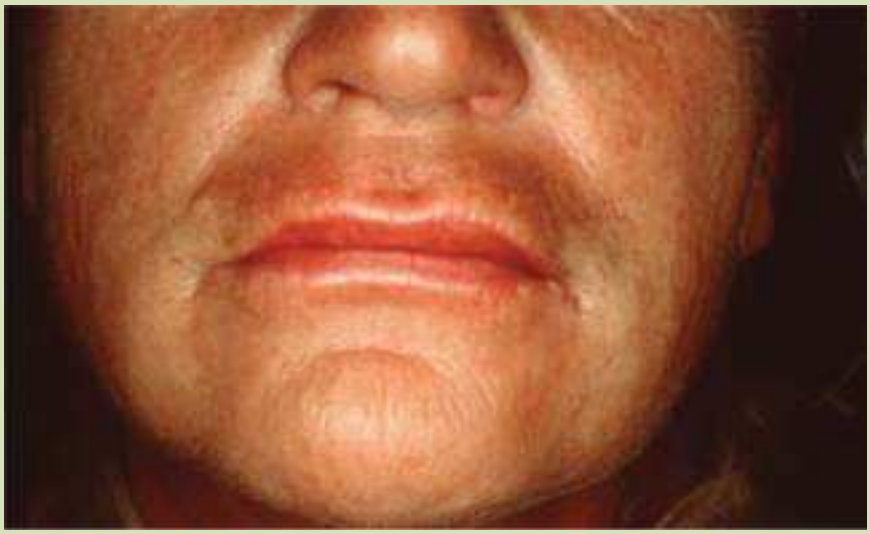
Hi: Lobular infiltrates of small to medium-sized lymphocytes with nuclear atypia which surround adipocytes (rimming). Lymphocytes express betaF1 and are CD8 positive. Large anaplastic tumor cells may occur in advanced stage.

DIFFERENTIAL DIAGNOSIS

Gamma/delta (γ/δ) T-cell lymphoma: *range of lesions from subtle erythema, dermal/subcutaneous induration to (ulcerating) tumors. Histology: usually "three tiered" involvement of epidermis, dermis and panniculus. Tumor cells show similar features to* ***Subcutaneous panniculitis-like T-cell lymphoma*** *with more karyorrhexis, CD56 positive and gamma/delta phenotype (betaF1 is negative).*

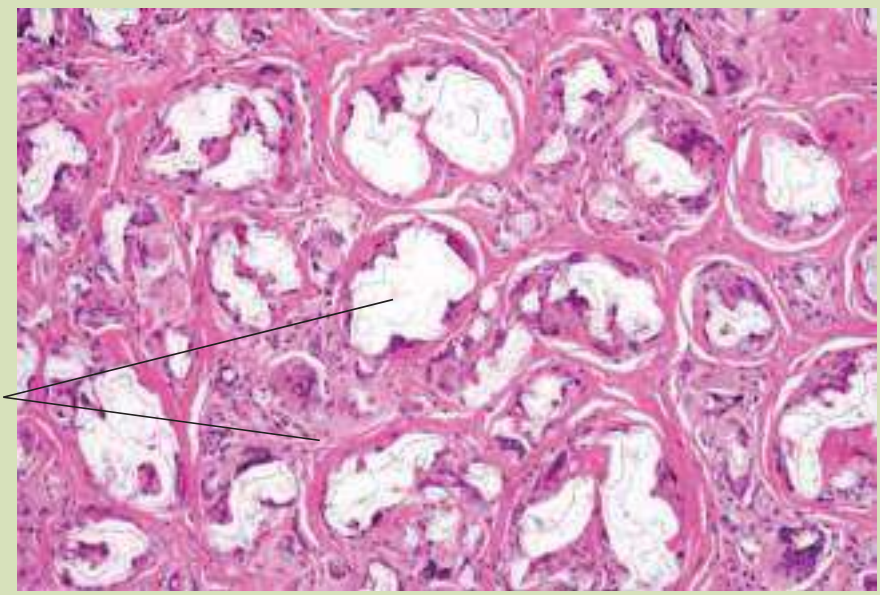
DIFFERENTIAL DIAGNOSIS: Paraffinoma

Swelling of the upper lip



Cl: Swelling due to cutaneous and subcutaneous injections.

Bizarre clear spaces and fibrosis



Hi: Bizarre empty spaces within fibrotic tissue.

Other Diagnosis

Nodular vasculitis: *Leukocytoklastic vasculitis, mostly lobular mixed infiltrate.*

Erythema nodosum **(*see* page 268)*****:*** *Septal infiltrates, mixed cellular in early stage, histiocyte-rich in late stage with granulomas (Miescher nodules).*

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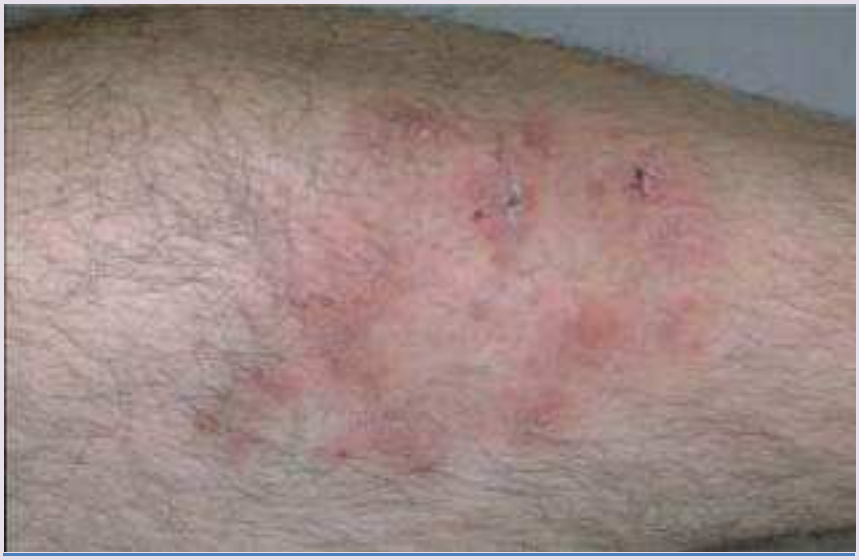
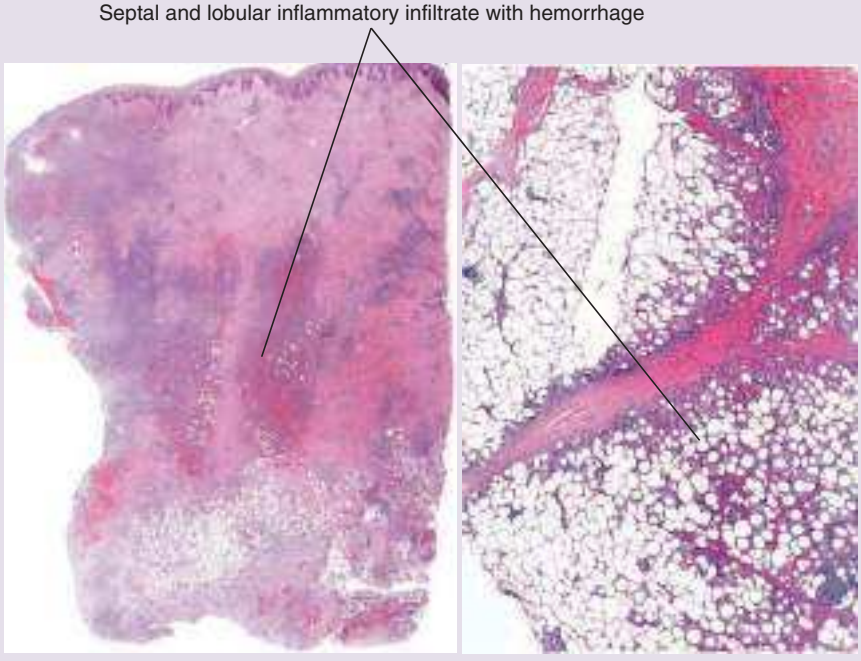
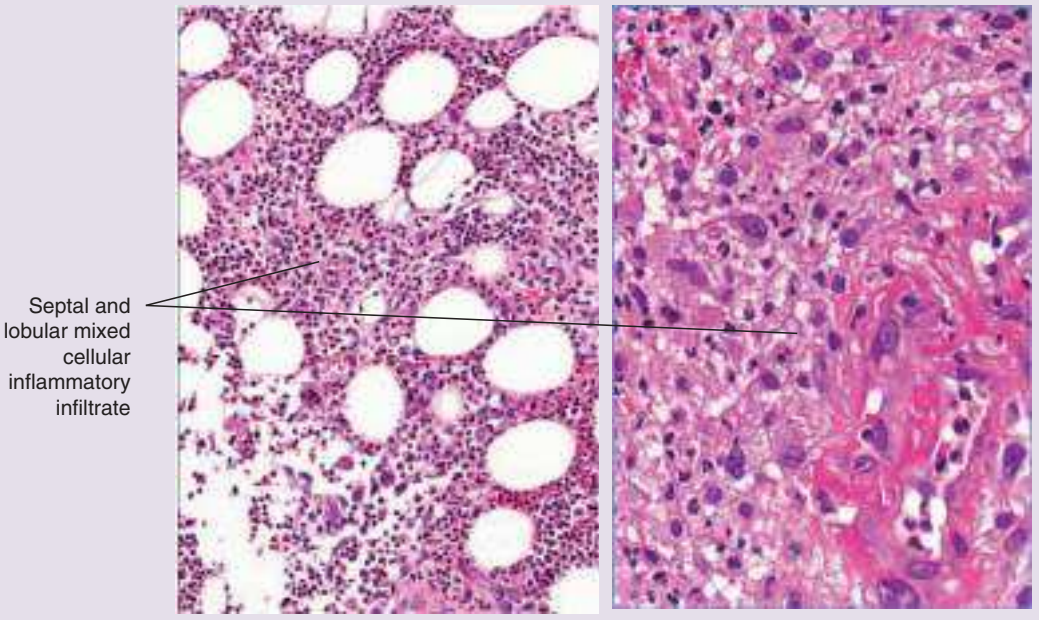
PROTOTYPE: Traumatic and factitious panniculitis

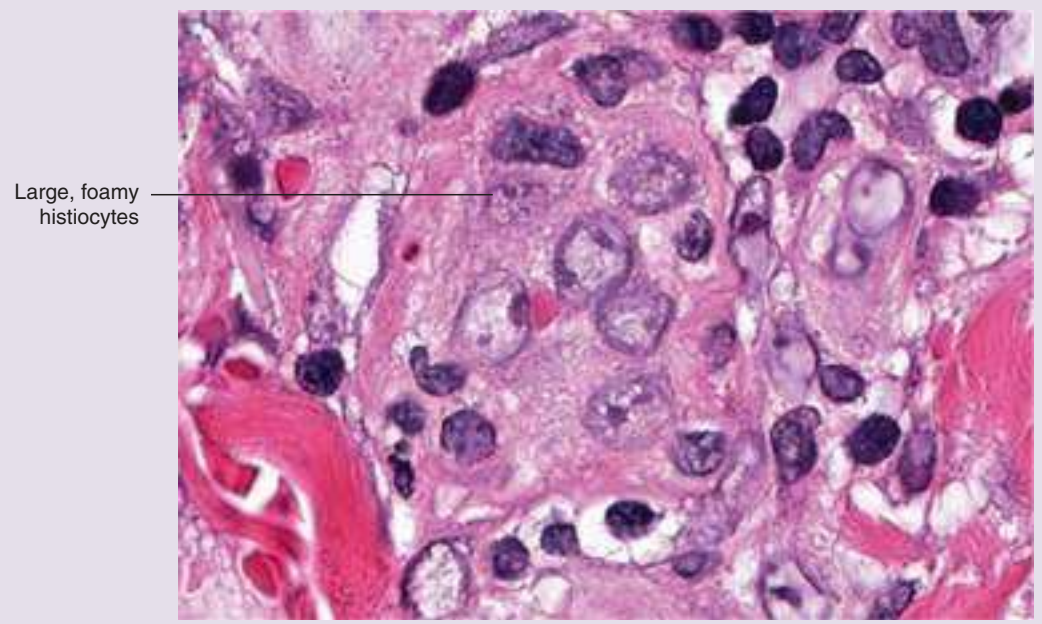


CI: Tender indurated plaques or nodules, after trauma or as a result of self-induced trauma.



Traumatic and factitious panniculitis



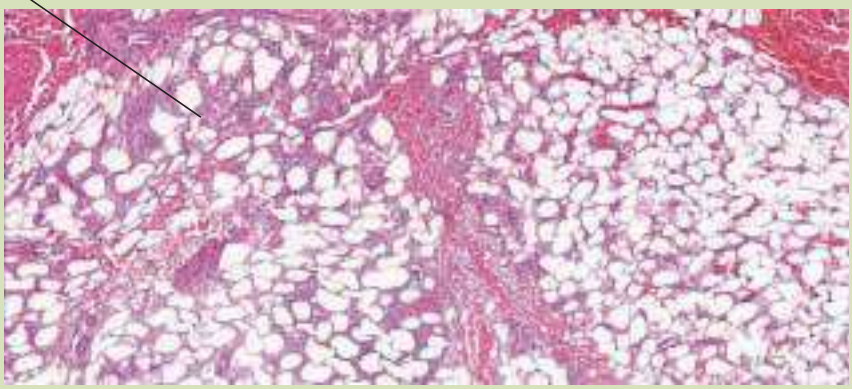


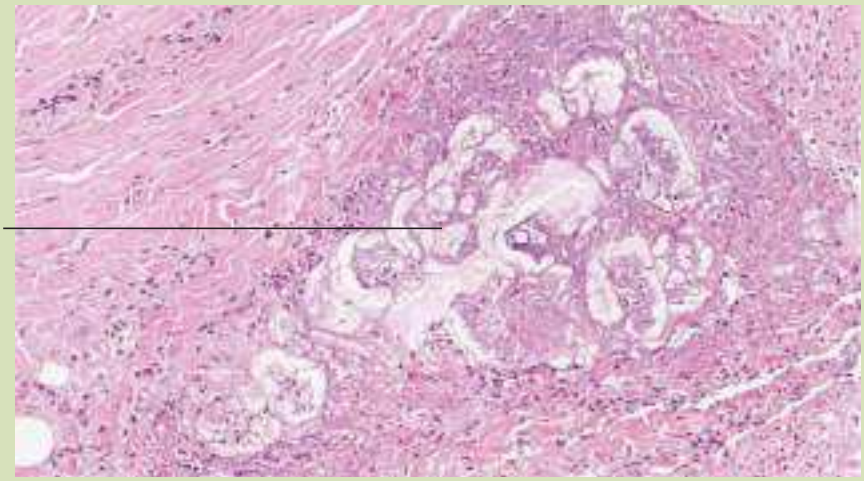
Hi: In the initial phase necrotic adipocytes, neutrophils and hemorrhage. In the later stage, foamy histiocytes within the lobules, pseudocyst formation due to necrosis of fat tissue, fibrosis. If the factitious panniculitis is associated with injection sometimes (polarizable or non-polarizable) foreign material can be identified.

VARIANT

Subcutaneous fat necrosis of newborn: *needle-like clefts*

DIFFERENTIAL DIAGNOSIS: Pancreatic panniculitis





Cl: Erythematous swelling.

Hi: Lobular panniculitis with degeneration of the lipocytes and saponification (basophilic degeneration), infiltrate of neutrophils, lymphocytes and histiocytes surrounding necrotic adipocytes with thickened eosinophilic membranes (ghost cells).

Other Diagnosis

Infectious panniculitis: *Mixed cellular infiltrate with abundant neutrophils in the septa and lobuli. Abscess formation may be present. Detection of microorganisms.*

Alpha-1-antitrypsin deficiency: *Ulcers draining oily material. Initially neutrophilic infiltrates in the reticular dermis, followed by septal and lobular infiltrates and necrosis. Later fibrosis and calcification.*

Subcutaneous Sweet syndrome: *diffuse subcutaneous infiltrates of neutrophils. No abscesses. Association with hematologic malignancies.*

Comment

Many variations due to the various factitial injuries (trauma, injections).

References

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CHAPTER 7
Deposition and Storage

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.

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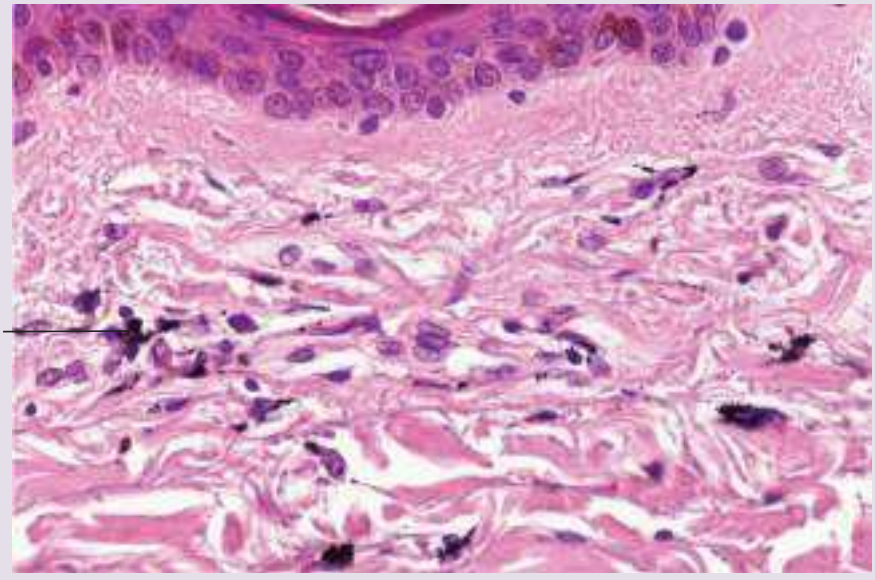
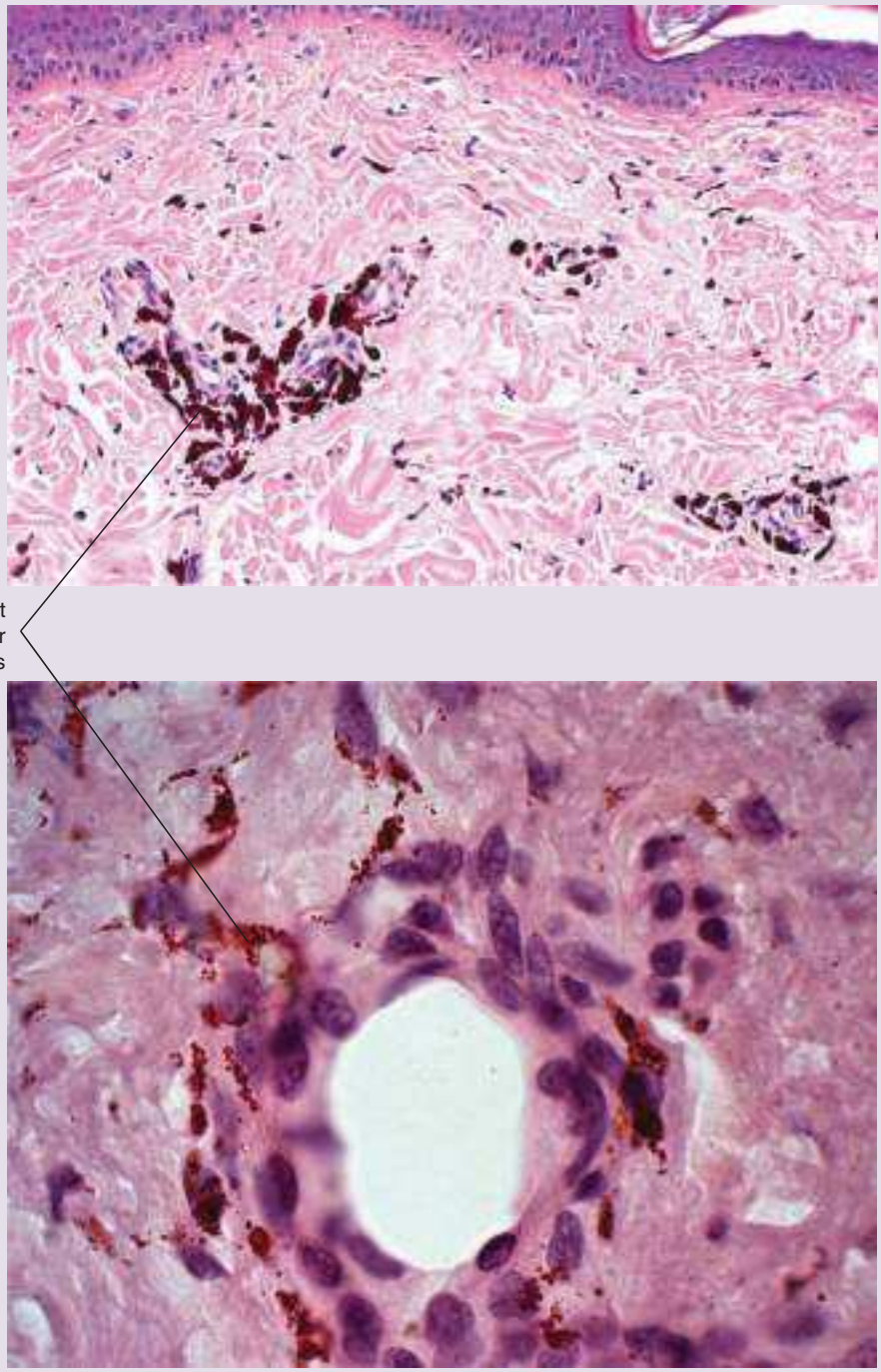
PROTOTYPE: Tattoo

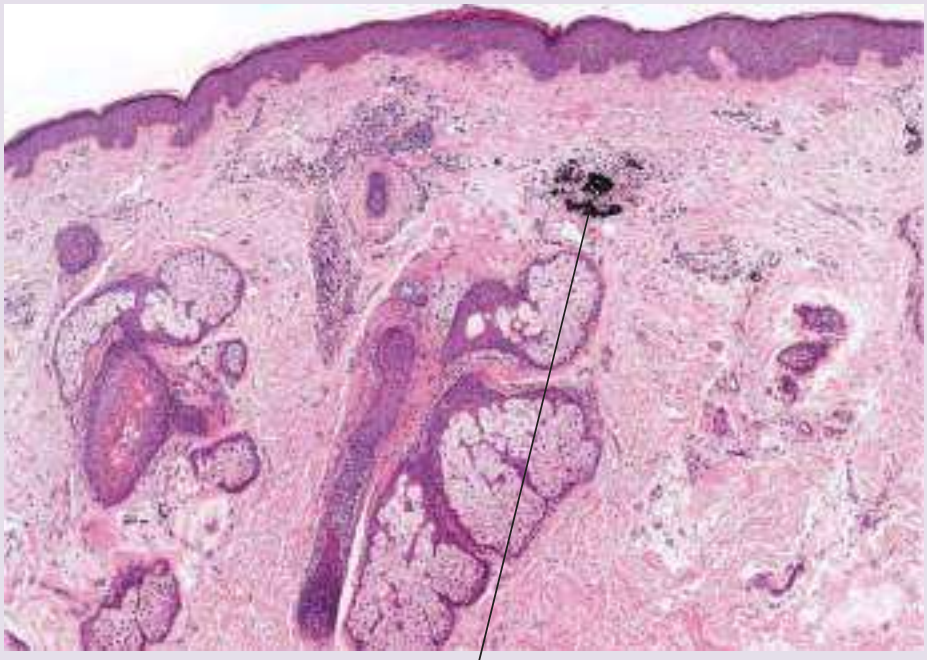
CI: Permanent tattoos are made intentionally for cosmetic reasons or accidently (firecracker) by bringing a wide range of dyes and pigments into the dermal skin. They may lead to allergic reactions.



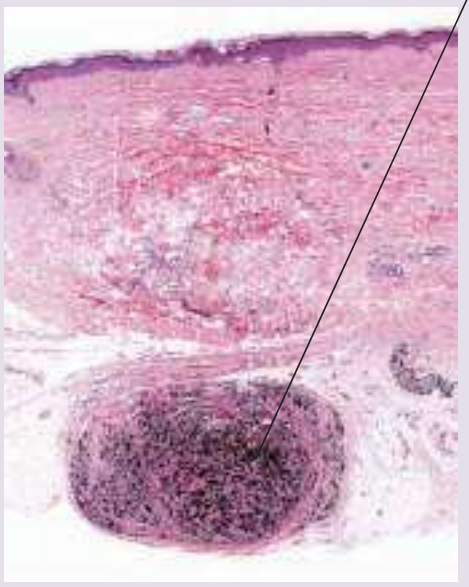
Tattoo

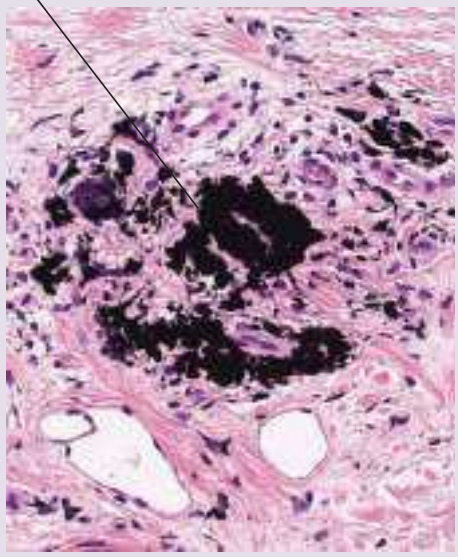


Tattoo



Accidental tattoo from an injury with a pencil (graphite)





Hi: deposition of pigment extracellulary and in histiocytes of the upper and mid dermis, no or little inflammatory infiltrate.

VARIANTS

Eczematous reaction to tattoo dyes: *Spongiosis.*

Psoriasiform reaction.

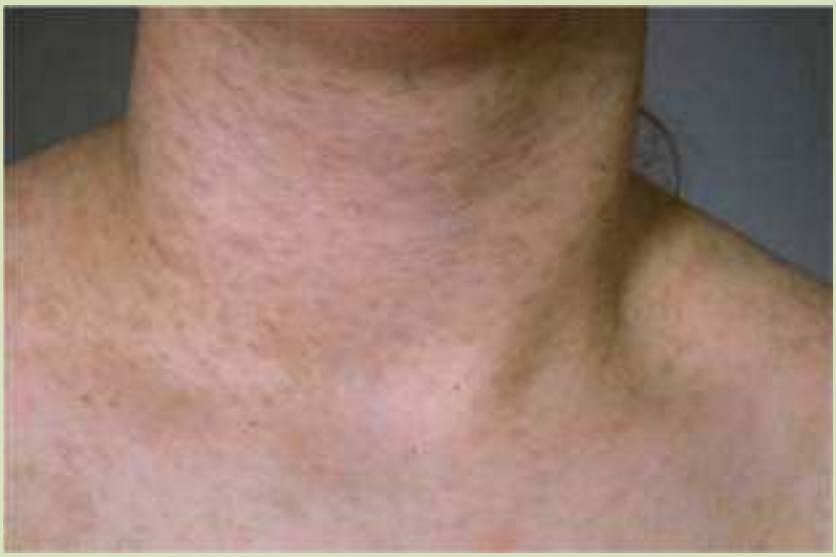
Lichenoid and pseudolymphomatous reaction to tattoo: *Interface dermatitis with band-like lymphocytic infiltrate. In addition, dense lymphocytic infiltrate in the deep dermis.*

Granulomatous reaction: *Sarcoidal granulomas, suppurative granulomas, necrobiotic areas.*

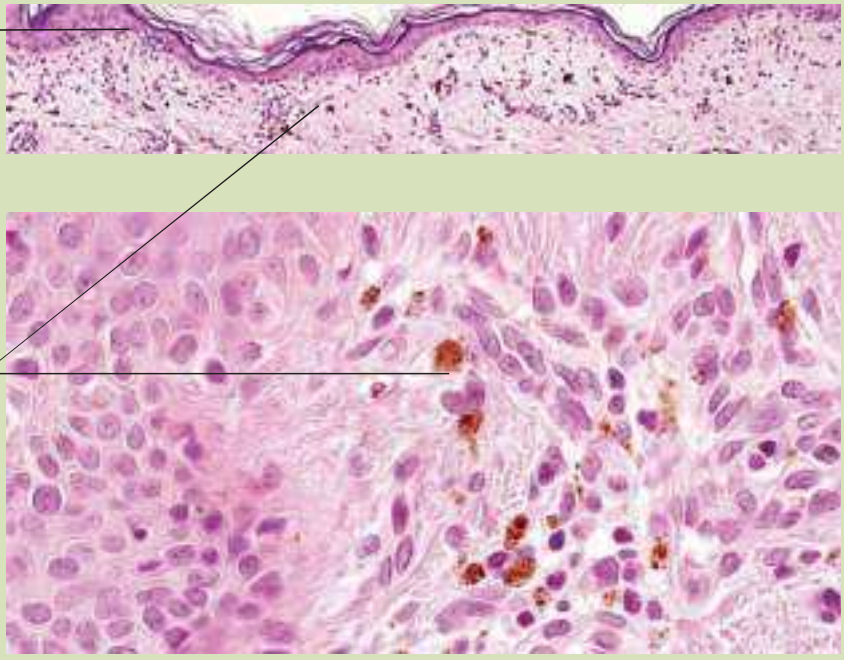
Vasculitis: *Small vessel leukocytoklastic vasculitis.*

Fibrosing reaction*: Histologically mimicking morphea.*

DIFFERENTIAL DIAGNOSIS: Erythema dyschromicum perstans

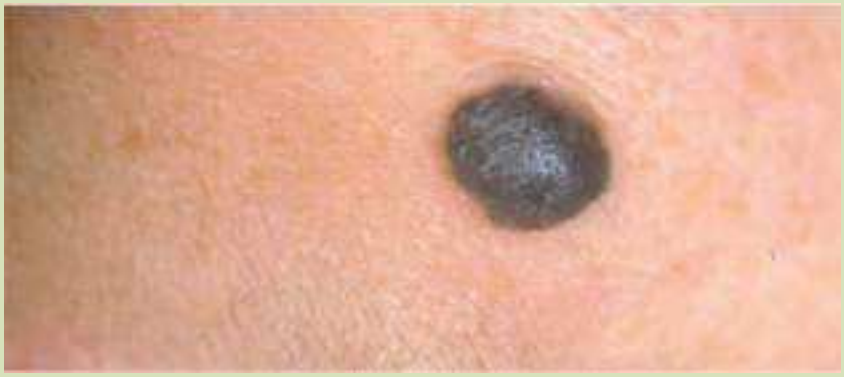


Cl: Brownish small patches.

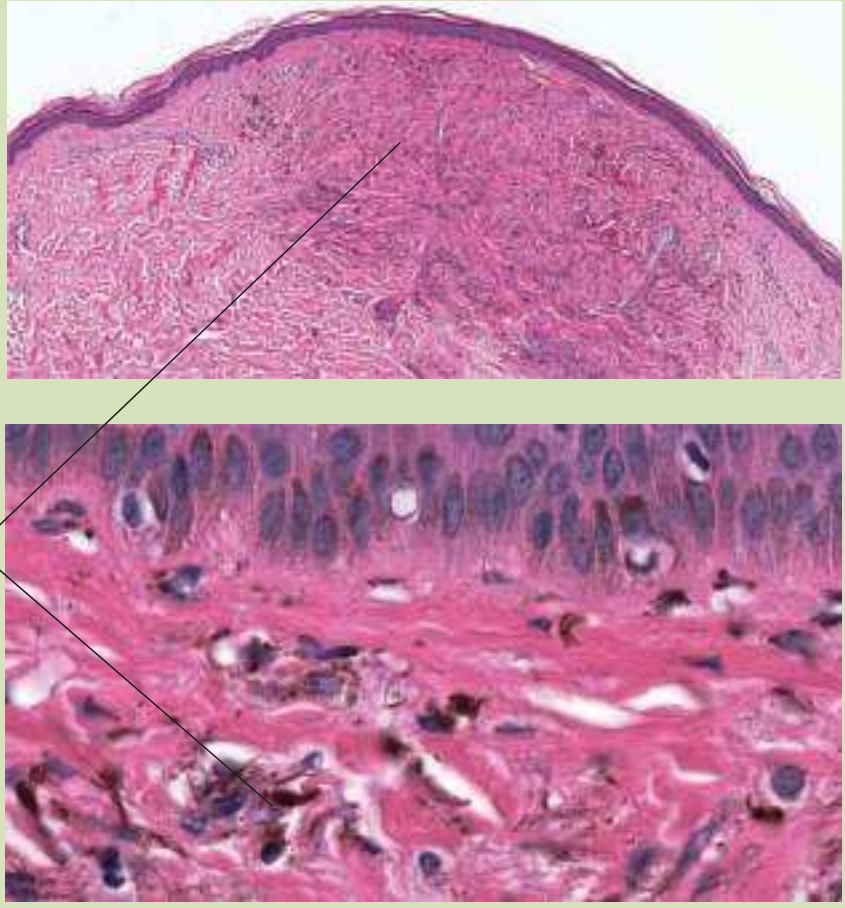


Hi: Vacuolar degeneration of the basal layer, superficial lymphocytic infiltrate; scattered melanophages in the upper dermis.

DIFFERENTIAL DIAGNOSIS: Blue nevus



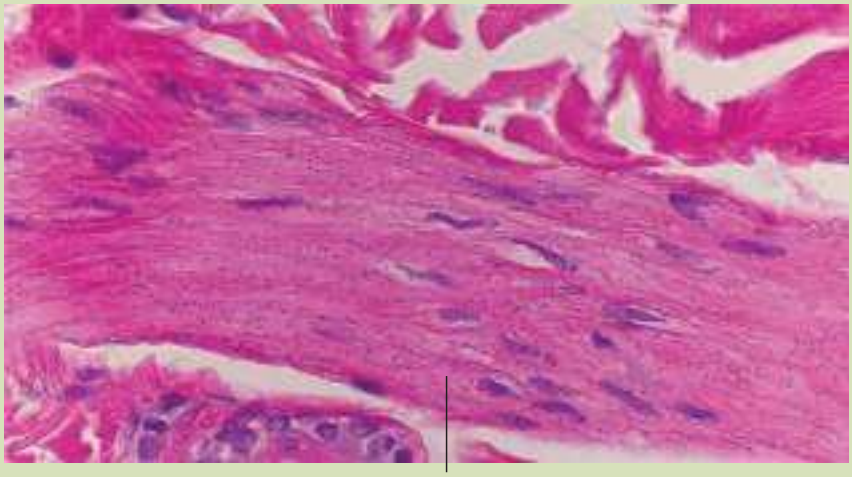
Cl: Black patch or nodule.

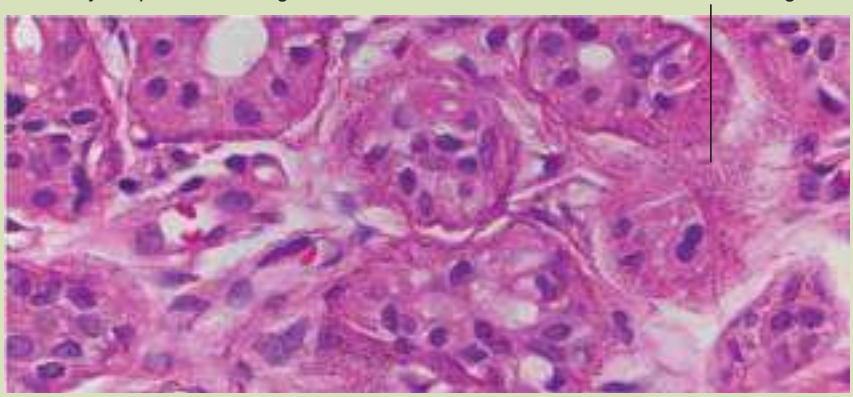


Hi: dendritic melanocytic cells in the dermis, melanophages.

DIFFERENTIAL DIAGNOSIS: Argyria

CI: Diffuse bluish-brown discoloration.





Hi: Deposits of silver at reticular fibers, especially around adnexal structures. No inflammatory infiltrate.

Other Diagnosis

Pigment incontinence *following inflammation, due to friction or* ***t****o melanosis in metastatic melanoma****:*** *granular melanin pigment mostly in macrophages (melanophages).*

Amalgam deposits/Hydrargyrosis*: Accidental amalgam deposits in the oral mucosa.*

Ochronosis.

Comments

Epithelioid granulomas around tattoo may represent a local sarcoid reaction pattern to tattoo or represent cutaneous manifestation of systemic sarcoidosis.
Granulomatous reaction may represent complication by mycobacterial infection: Search for acid-fast bacilli by Ziehl-Neelsen stain or mycobacterial DNA by polymerase chain reaction.

References

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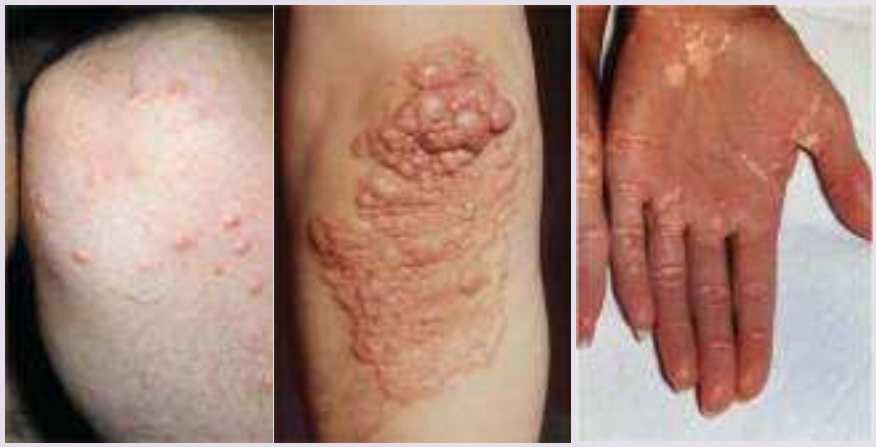
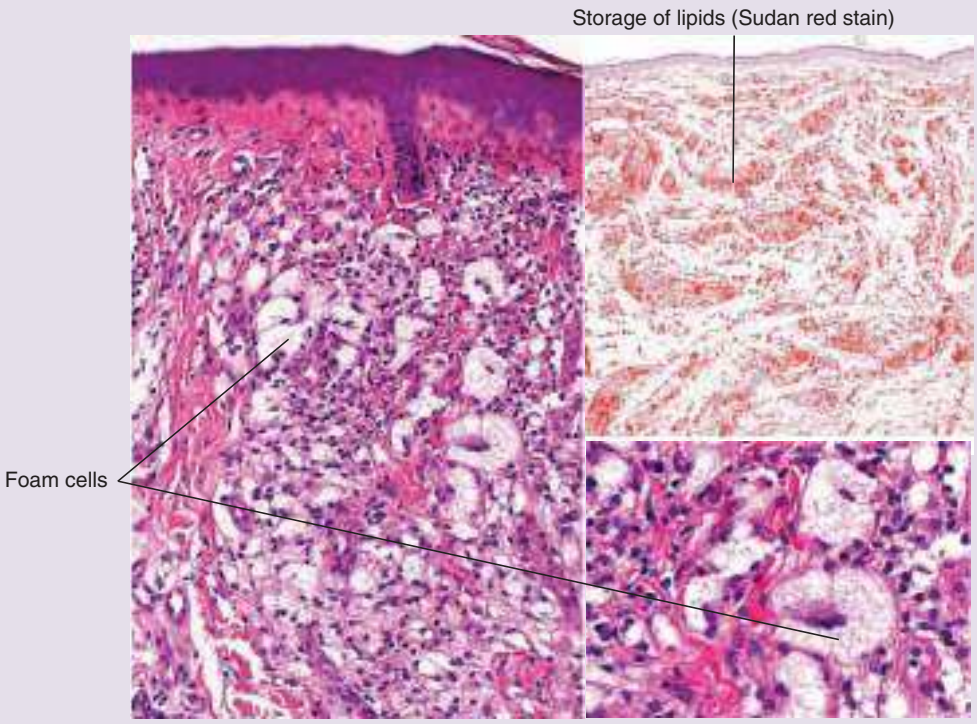
PROTOTYPE: Xanthoma



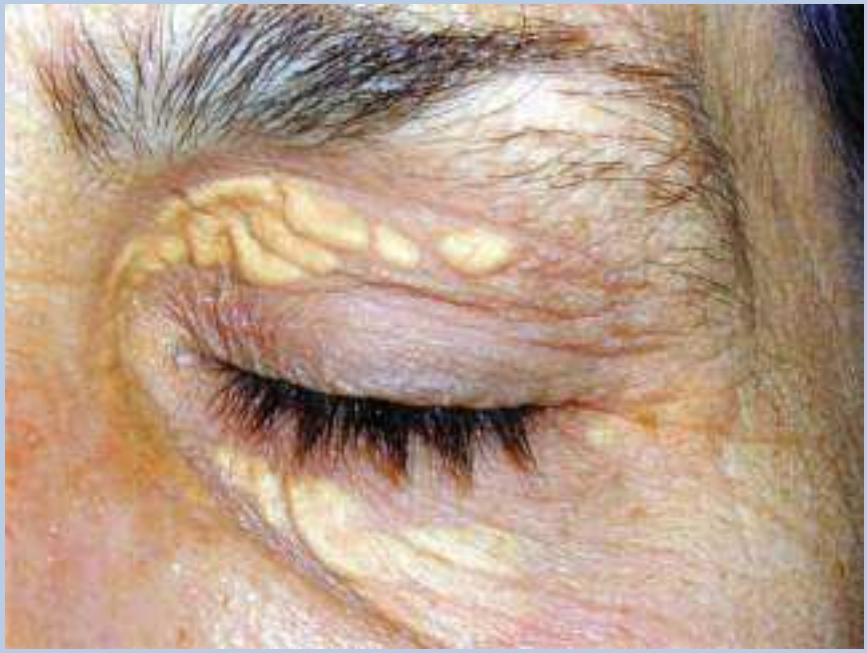
Eruptive xanthomas | Nodular xanthomas | Tendinous xanthomas

CI: There are many different variants of xanthomas, which all show yellowish discoloration of the skin in the area of deposition of lipids. There may be flat lesions like in xanthelasma or nodular lesions of various sizes.

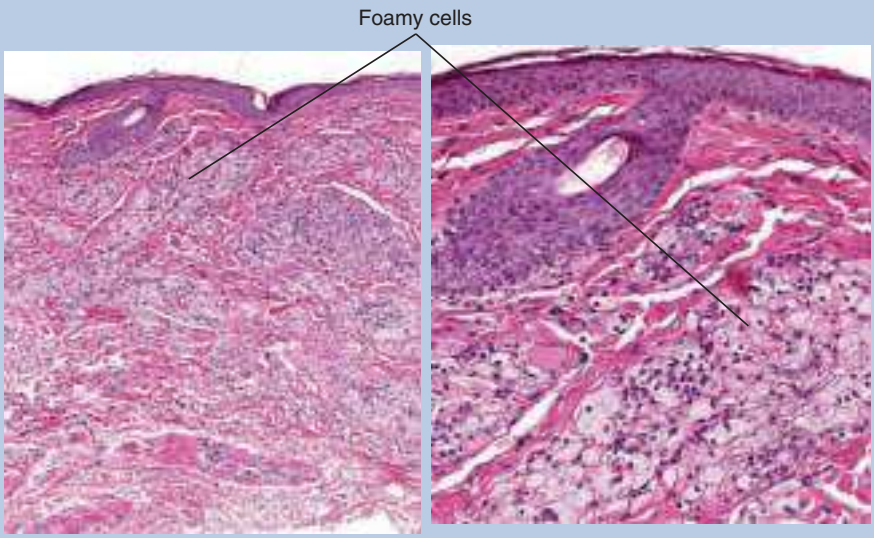


Hi: Clusters of foamy histiocytes; no or little inflammatory infiltrate; occasionally deposits of extracellular lipids.

VARIANTS: Xanthelasma



CI: Yellow plaques periocularly.



Hi: Superficial clusters of foam cells; no inflammation.

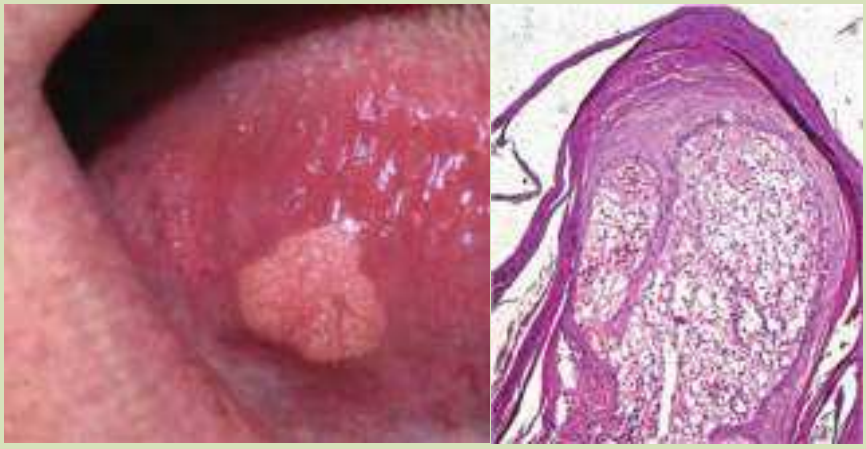
Variants:

Tendinous xanthomas

Eruptive xanthomas

Nodular xanthomas

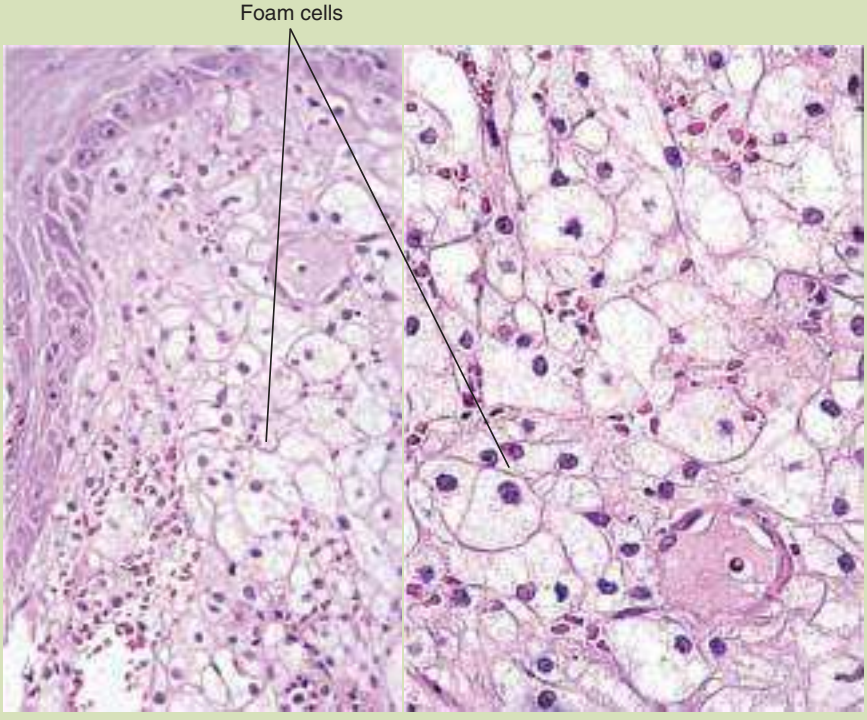
DIFFERENTIAL DIAGNOSIS: Verruciform xanthoma



Nodule on the tongue

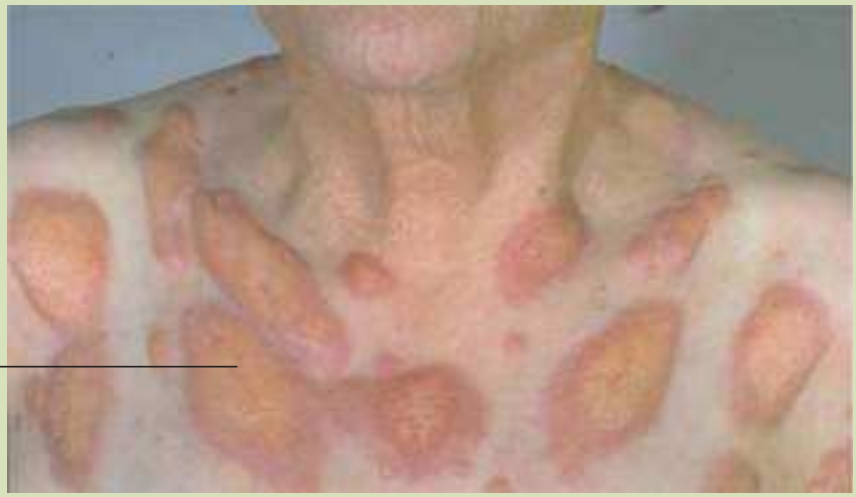
Verruciform lesion (nose)

Cl: Solitary papular lesion, usually on the tongue, occasionally in the nostril.

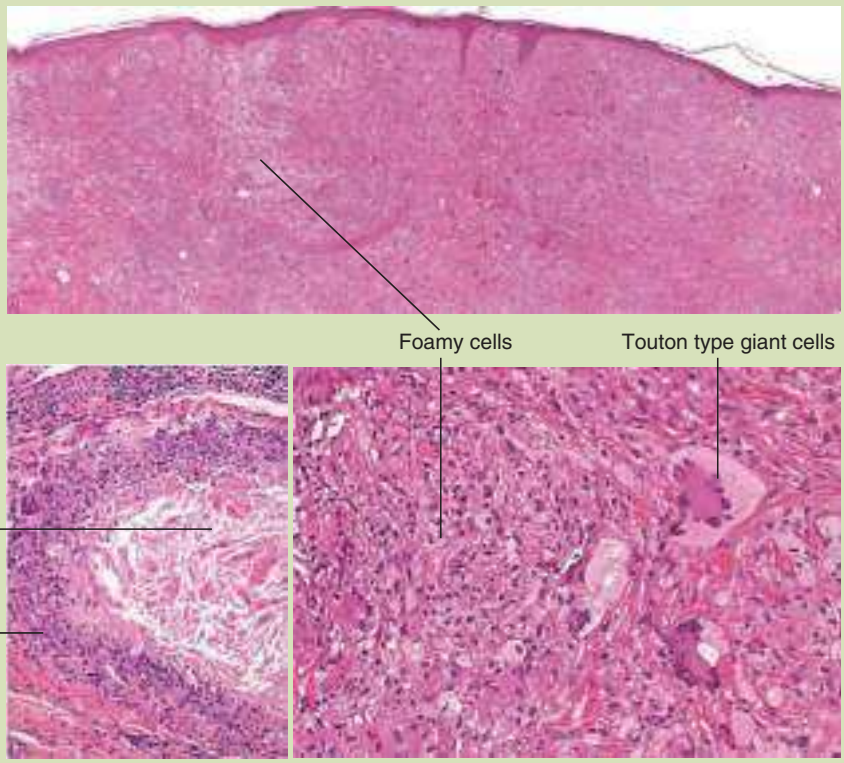


Hi: Densely packed foam cells are seen in the dermis of the verruciform lesion.

DIFFERENTIAL DIAGNOSIS: Necrobiotic xanthogranuloma



Cl: Mostly in association with IgG paraproteinemia. Yellowish indurated plaques.

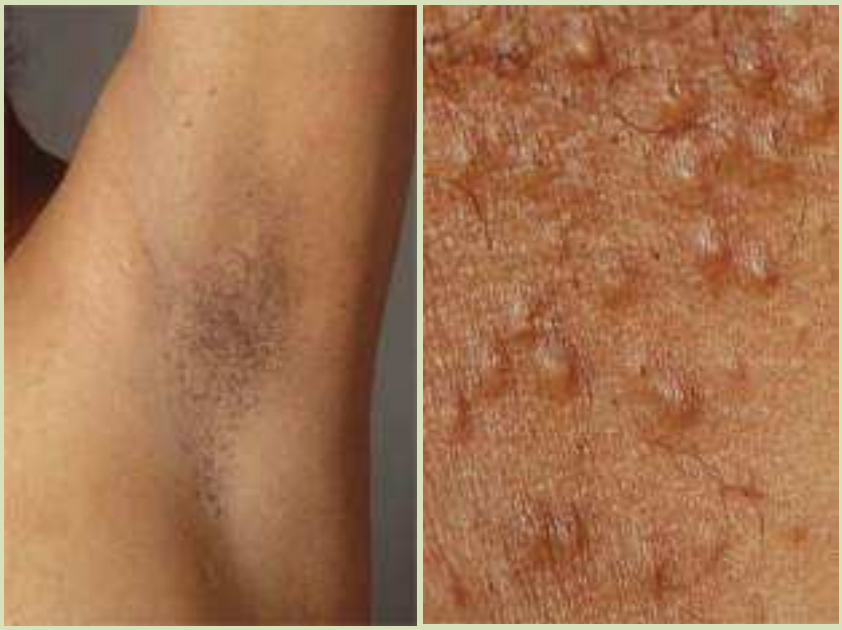


Hi: Large areas of collagen degeneration, sheets of foamy cells, cholesterol clefts and Touton type giant cells. Often prominent palisading.

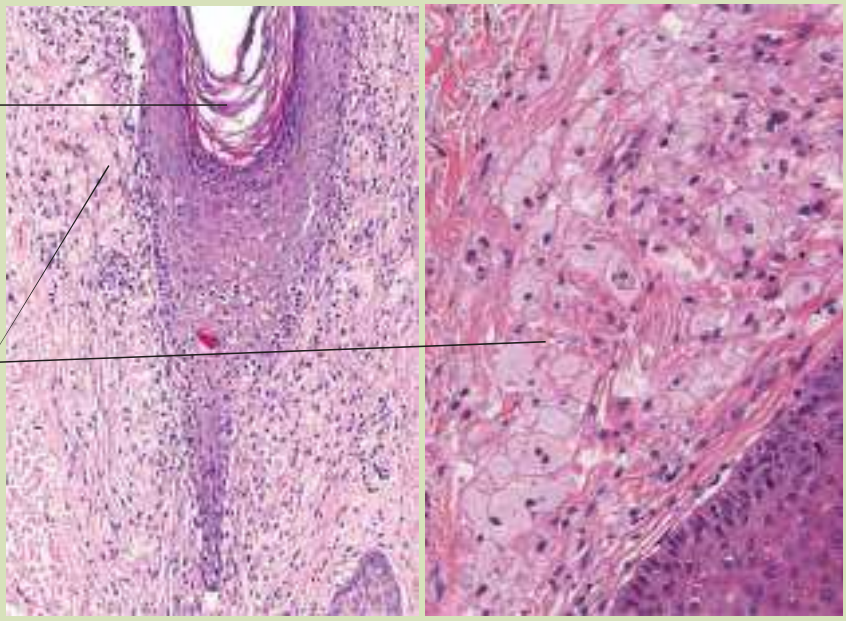
Comment

May be nosologically identical with annular elastolytic giant cell granuloma (see DERMIS, Granulomatous, page 190).

DIFFERENTIAL DIAGNOSIS: Axillary perifollicular xanthomatosis (Fox-Fordyce disease)



Cl: Follicular papular eruptions in the axillae.



Hi: Hyperkeratotic plugging of the follicles, surrounded by inflammatory infiltrate and occasionally xanthomatous features.

Other Diagnosis

Juvenile xanthogranuloma *(see* Chapter 4, Granulomatous infiltrates, Proliferative, page 199*): solitary or multiple papules. Histology shows a dense infiltrate of macrophages with abundant slightly eosinophilic cytoplasm in early lesions, whereas in mature lesions foamy cells and Touton giant-cells are seen. Admixture of eosinophils.*

References

Beham, A. and C. D. Fletcher (1991). "Plexiform xanthoma: an unusual variant." *Histopathology* **19**(6): 565–7.

Bito, T., C. Kawakami, *et al.* (2010). "Generalized eruptive xanthoma with prominent deposition of naked chylomicrons: evidence for chylomicrons as the origin of urate-like crystals." *J Cutan Pathol* **37**(11): 1161–3.

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Mete, O., E. Kurklu, *et al.* (2009). "Flat type verruciform xanthoma of the tongue and its differential diagnosis." *Dermatology Online Journal* **15**(9).

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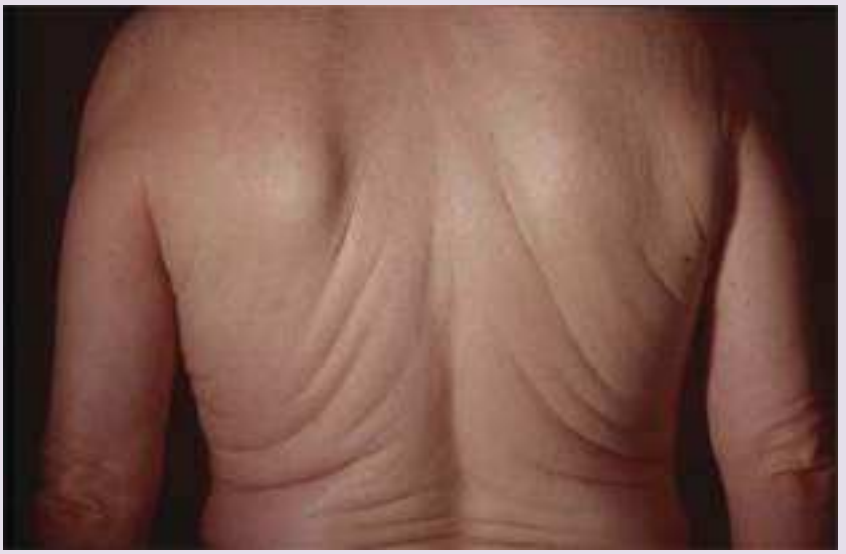
Williford, P. M., W. L. White, *et al.* (1993). "The spectrum of normolipemic plane xanthoma." *Am J Dermatopathol* **15**(6): 572–5.

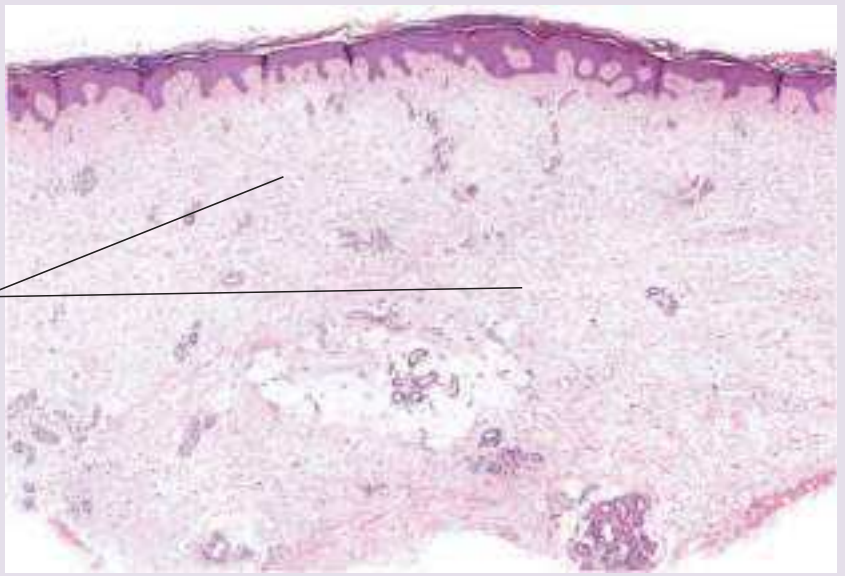
PROTOTYPE: Myxedema, diffuse, generalized

Waxy pale and thickened skin with typical skinfolds

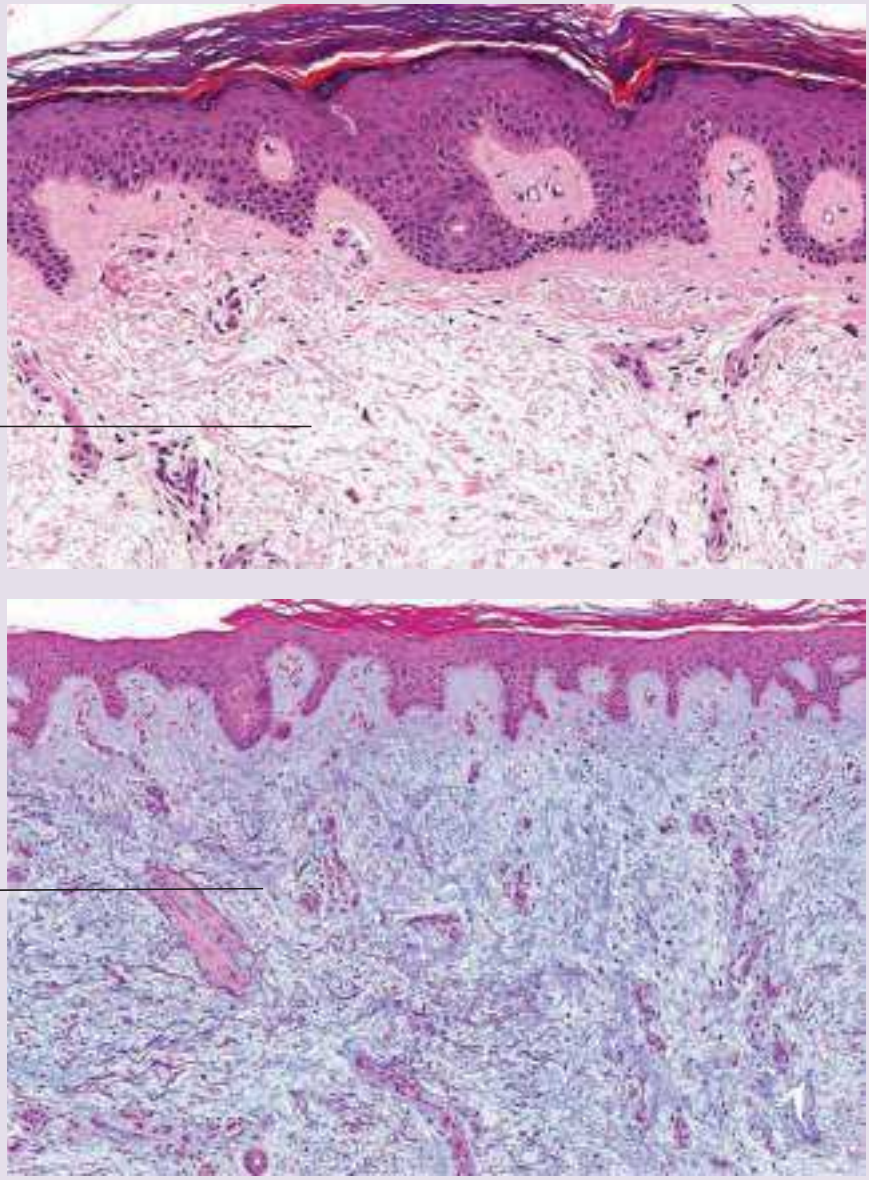


CI: Deposition of mucin in the dermis due to hypothyroidism leads to diffuse swelling and waxy pale and dry skin.

Pale mucin deposits

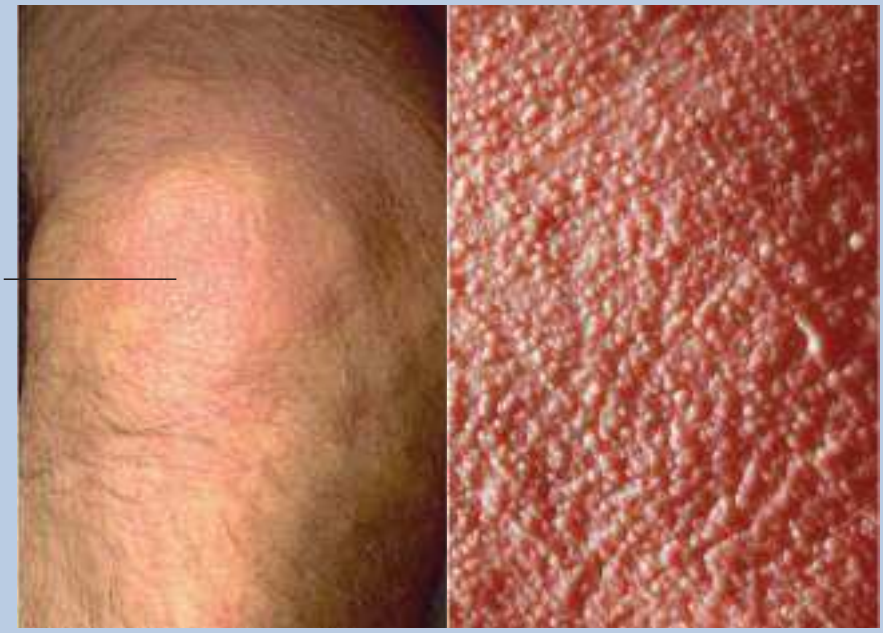


Myxedema

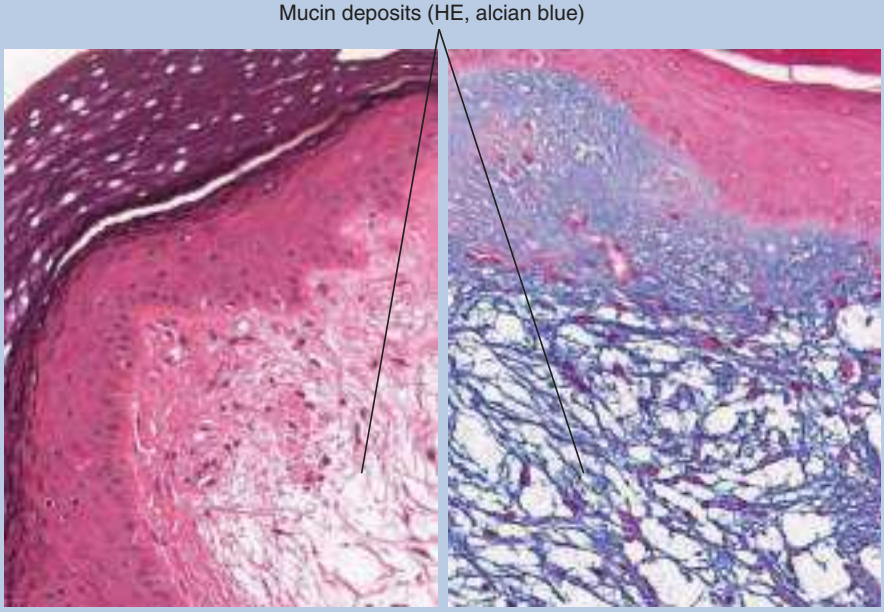


Hi: Hyperkeratosis, slight edema and abundant mucin, fibrosis in deep dermis and subcutis in late stages, simulating scleroderma.

VARIANTS: Lichen myxedematosus (papular mucinosis)



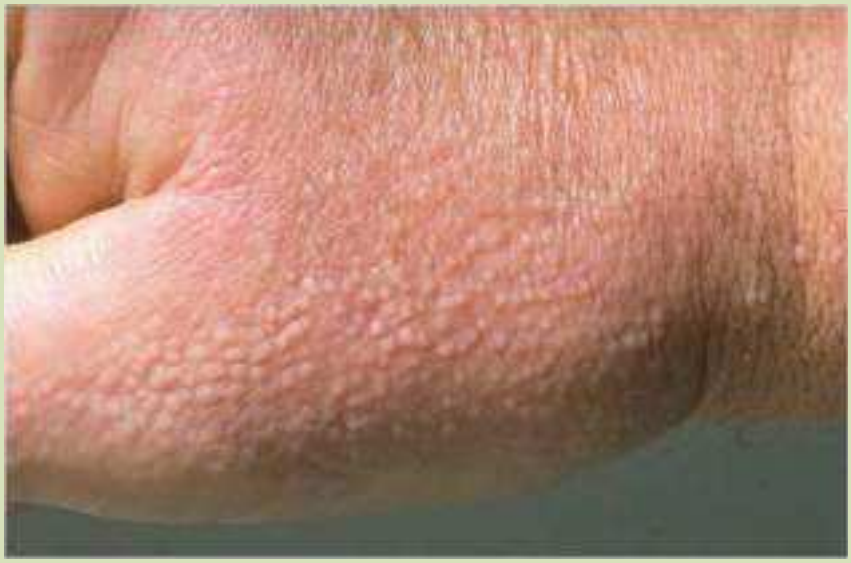
Cl: Disseminated papules on hands or on extensor sites of the extremities.



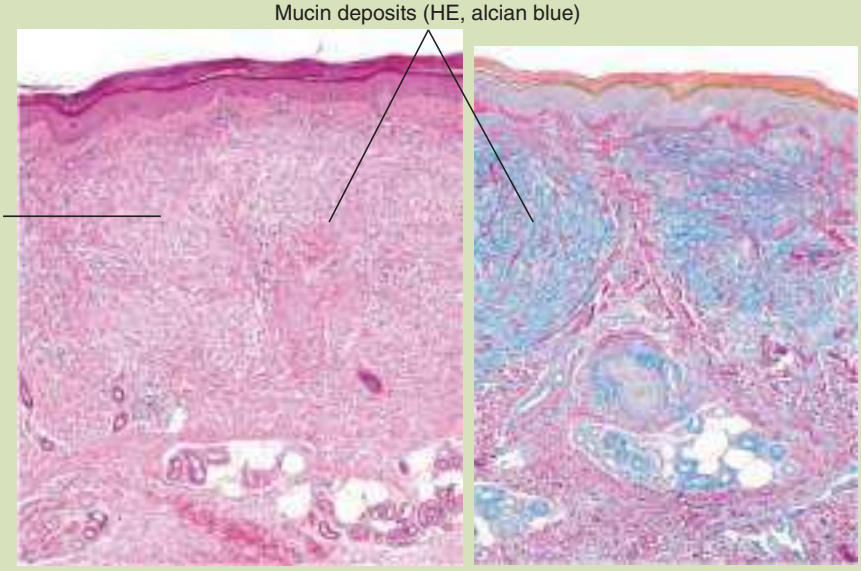
Hi: Thinning of the epidermis, flattening of rete ridges, atrophy of adnexal structures, diffuse deposits of mucin in the upper and mid dermis, dense packing of thickened collagen bundles (fibromucinosis), proliferation of fibroblasts, sparse lymphocytic infiltrate.

Praetibial myxedema: *association with thyroid dysfunction*

DIFFERENTIAL DIAGNOSIS: Scleromyxedema (Arndt-Gottron)



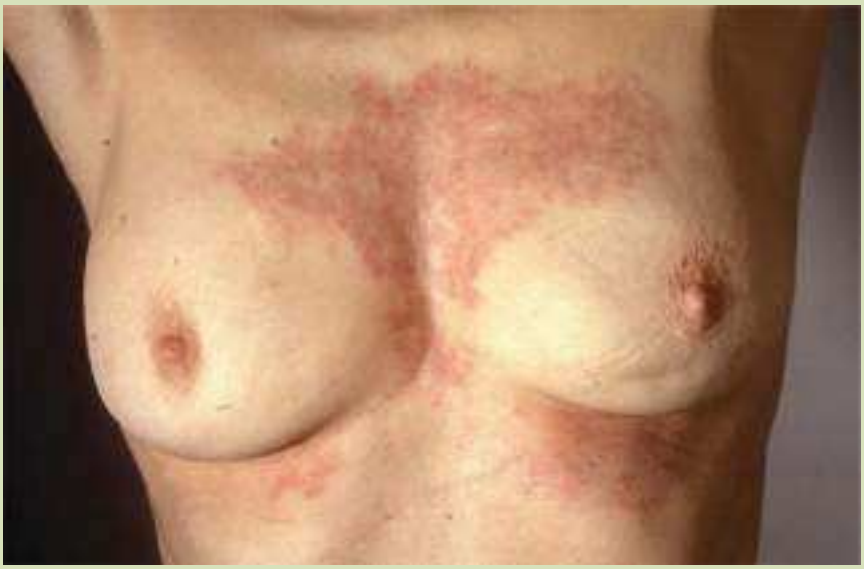
Cl: Lichenoid papules and diffuse elephant skin-like thickening with deep folds in tension lines. Association with underlying monoclonal gammopathy in some patients.



Hi: Deposits of mucin in the dermis, thickened collagen bundles, some plasma cells.

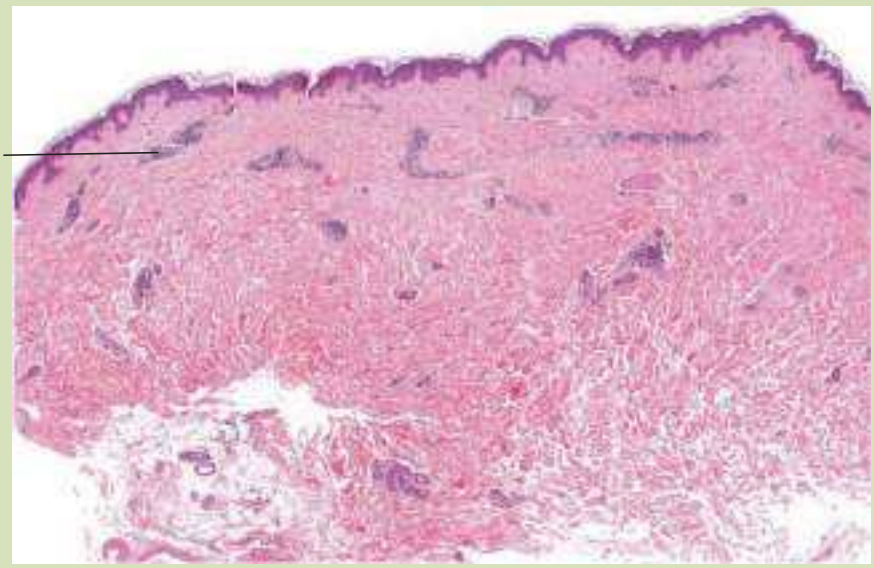
DIFFERENTIAL DIAGNOSIS: Reticular erythematous mucinosis (REM)

Reticular erythema

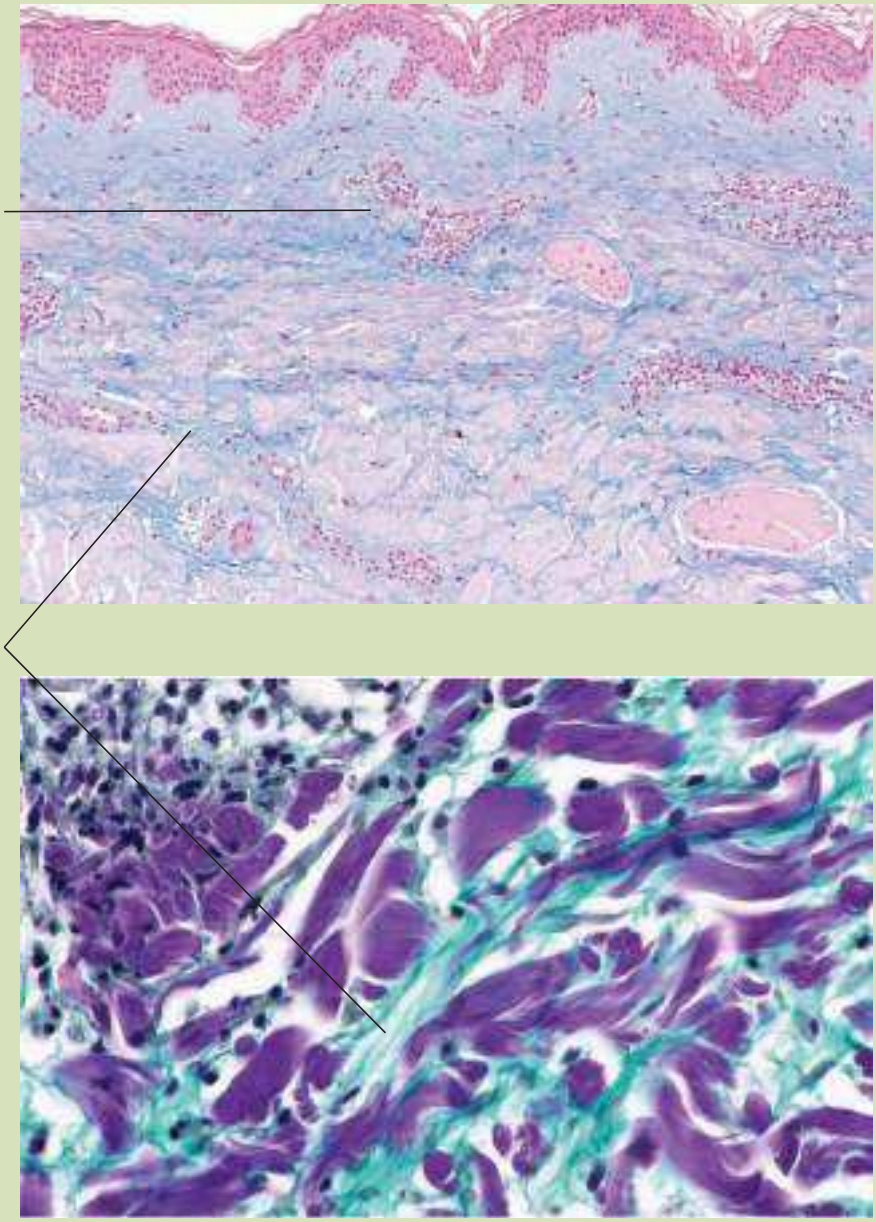


Cl: Fine reticular erythema, preferentially on the chest.

Sparse perivascular infiltrate

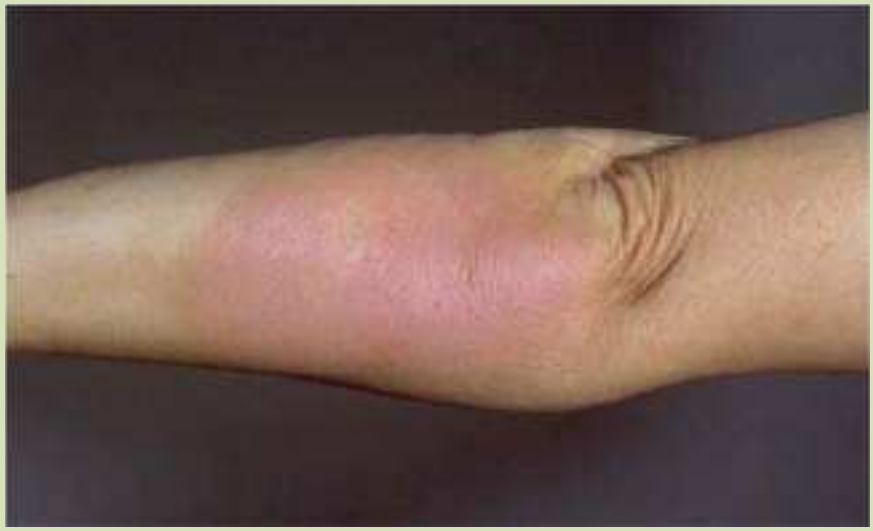


Reticular erythematous mucinosis (REM)

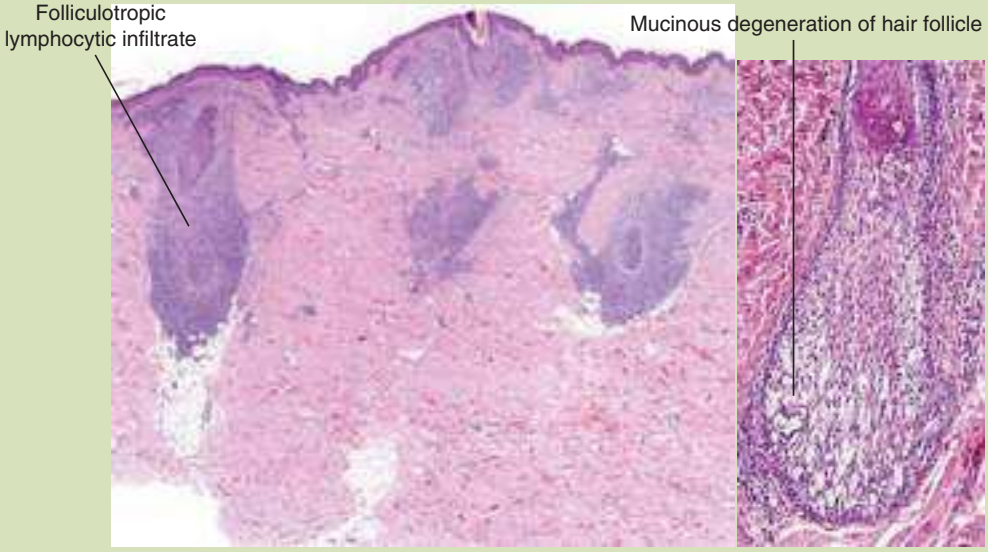


Hi: Normal epidermis, mucin in upper and mid dermis, sparse perivascular and periadnexal lymphocytic infiltrate.

DIFFERENTIAL DIAGNOSIS: Lymphoma associated follicular mucinosis (folliculotropic mycosis fungoides)



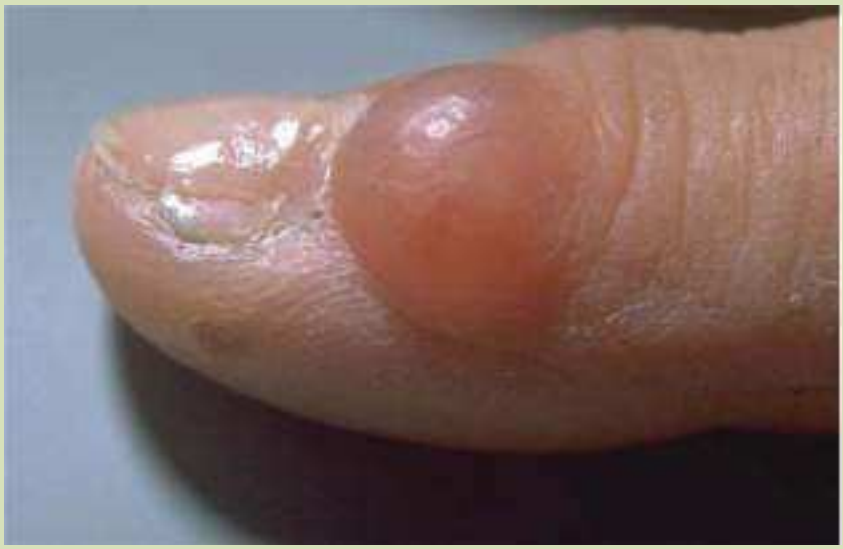
Cl: Infiltrated erythematous plaques.



Hi: Epidermo-and folliculo-tropic lymphocytic infiltrate. Mucinous degeneration of hair follicles.

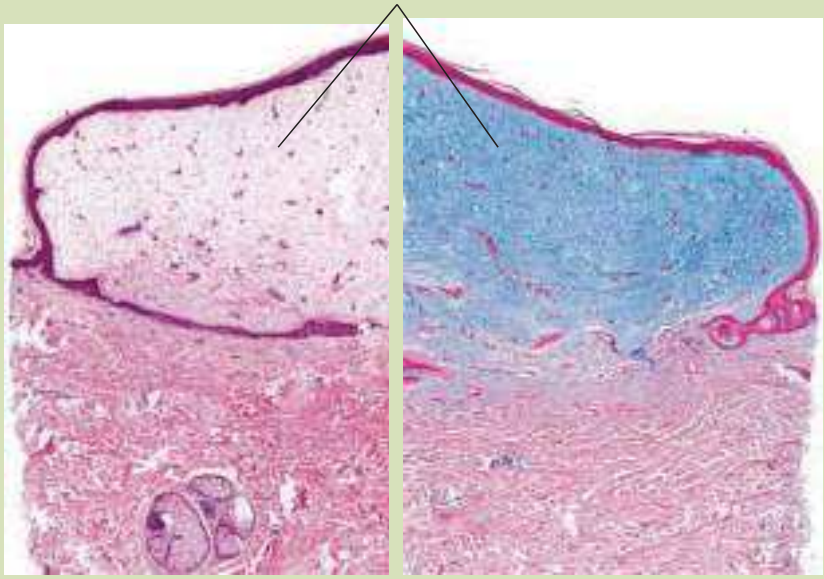
DIFFERENTIAL DIAGNOSIS: Mucoid pseudocyst of the digit or of the lip

Cyst over distal interphalangeal joint

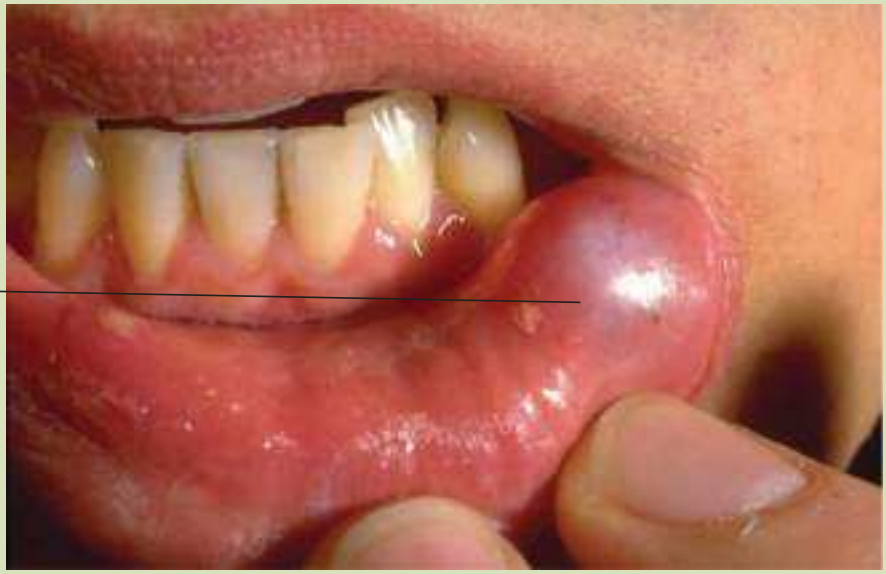


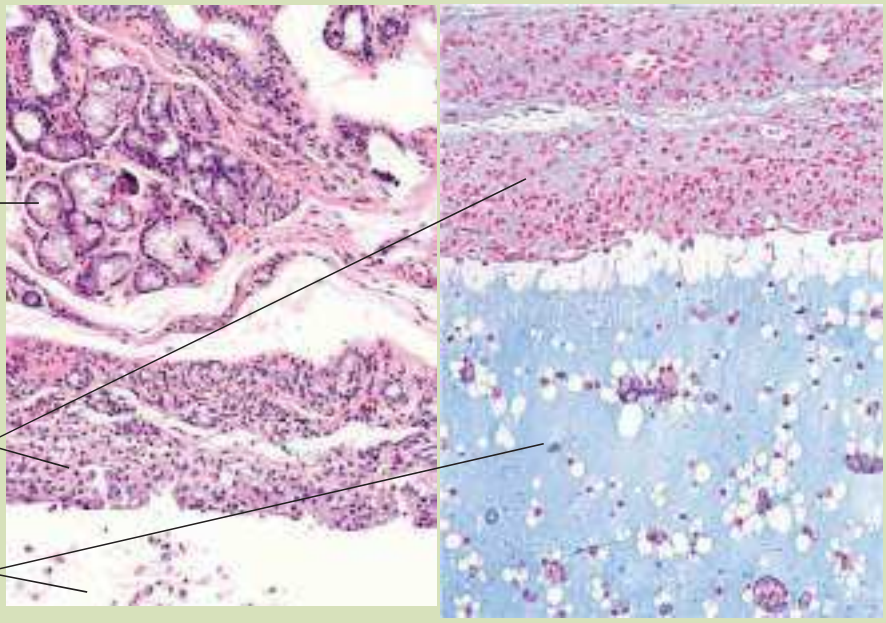
CI: Translucent cystic lesion, frequently following injury.

Mucin deposits (HE, alcian blue)



Mucoid pseudocyst

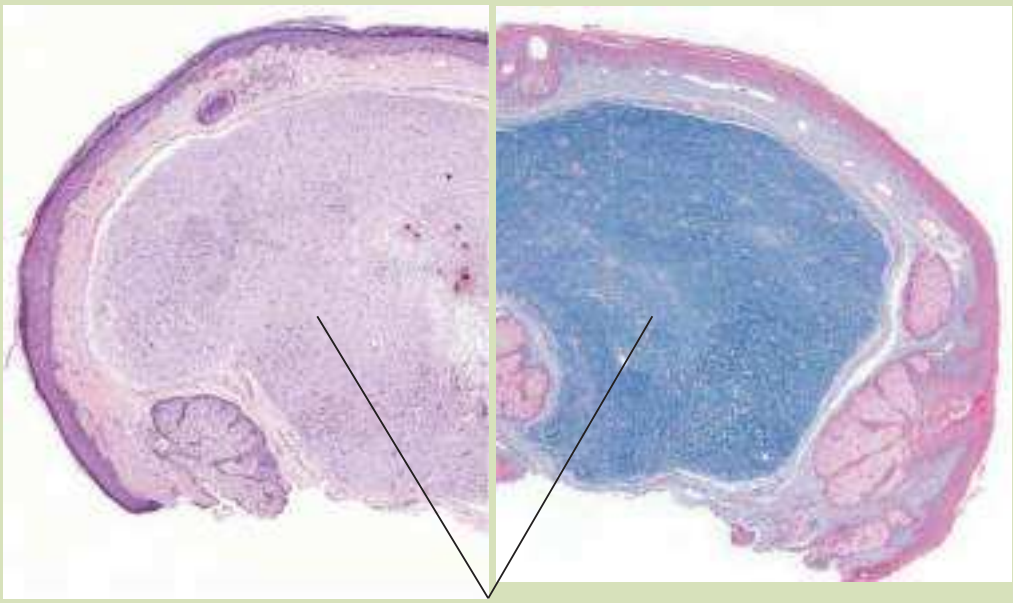




Hi: Cavity filled with loose mucoid material; lack of epithelium; alignment and compression of marginal fibroblasts and collagen bundles forming a fibroconnective wall (pseudocyst).

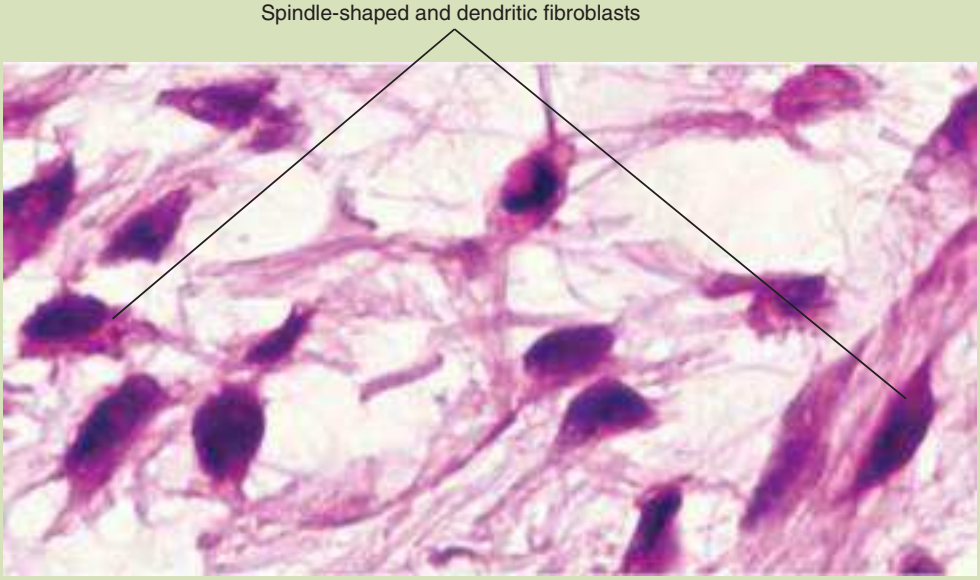
DIFFERENTIAL DIAGNOSIS: Cutaneous myxoma

Cl: Circumscribed, soft nodular lesion.



Well-defined, circumscribed, unencapsulated mucin deposits (HE, alcian blue)

Spindle-shaped and dendritic fibroblasts



Hi: Unencapsulated, well-defined mucin deposition in the dermis and subcutis, increased number of myofibroblasts, smooth muscle-actin positive cells, factor XIII negative.

Other Diagnosis

Cutaneous focal mucinosis: *Ill-defined mucin deposits in the dermis; smooth muscle-actin negative, factor XIIIa positive dendritic cells.*

Scleroderma *(see* Chapter 4, Sclerosis, page 208*): thickened collagen bundles, no macrophages.*

Scleredema adultorum Buschke: *Diffuse thickening of the skin due to deposits of mucopolysaccharides; "peau d'orange"-aspect; no increased number of fibroblasts; frequent association with diabetes.*

Lupus erythematosus *(see* Chapter 4, DERMIS, Infiltrates, non-granulomatous, lymphocytic, page 142*): Sleeve-like perivascular and periadnexal lymphocytic infiltrate.*

Myxoid neurothekeoma*: Well circumscribed lobulated proliferation of S100-positive spindled and epithelioid cells and myxoid stroma.*

Comment

Histologically, ganglion and digital mucoid cyst cannot be distinguished.

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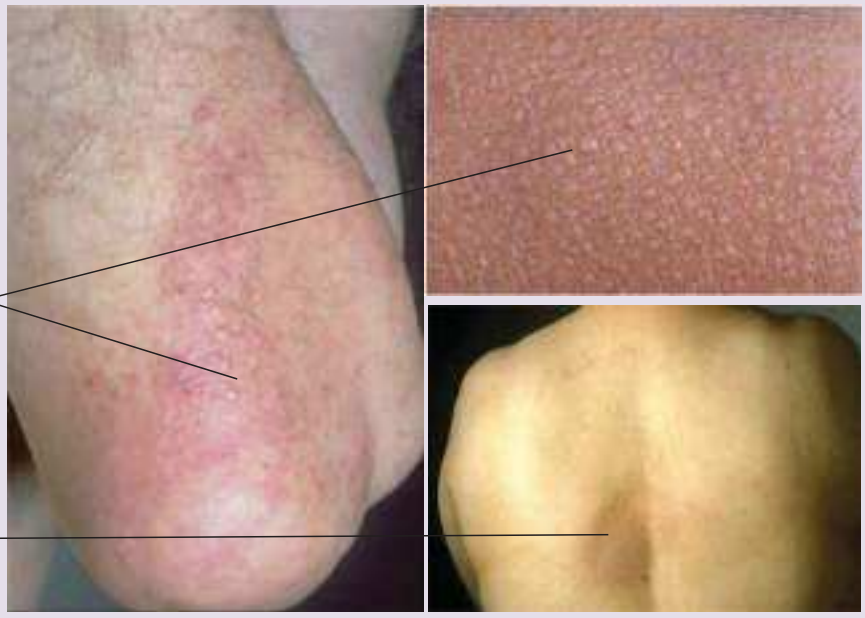
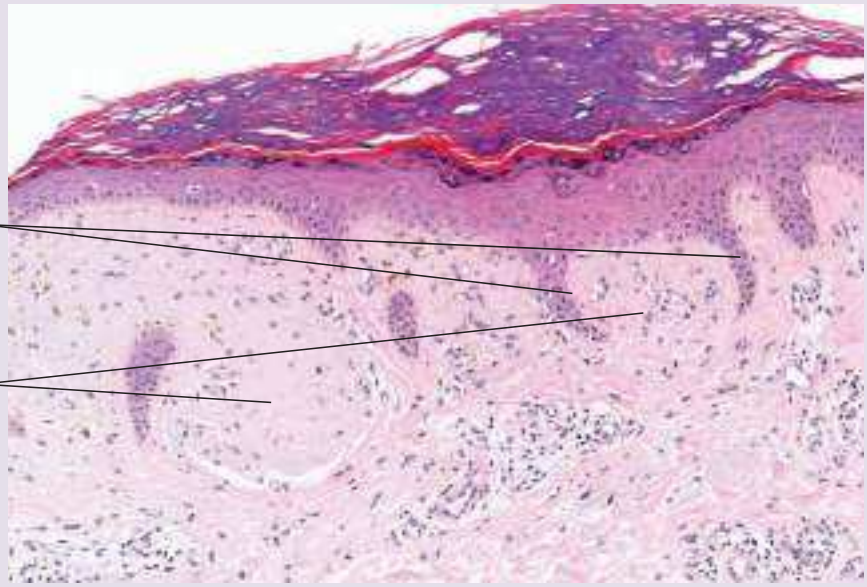
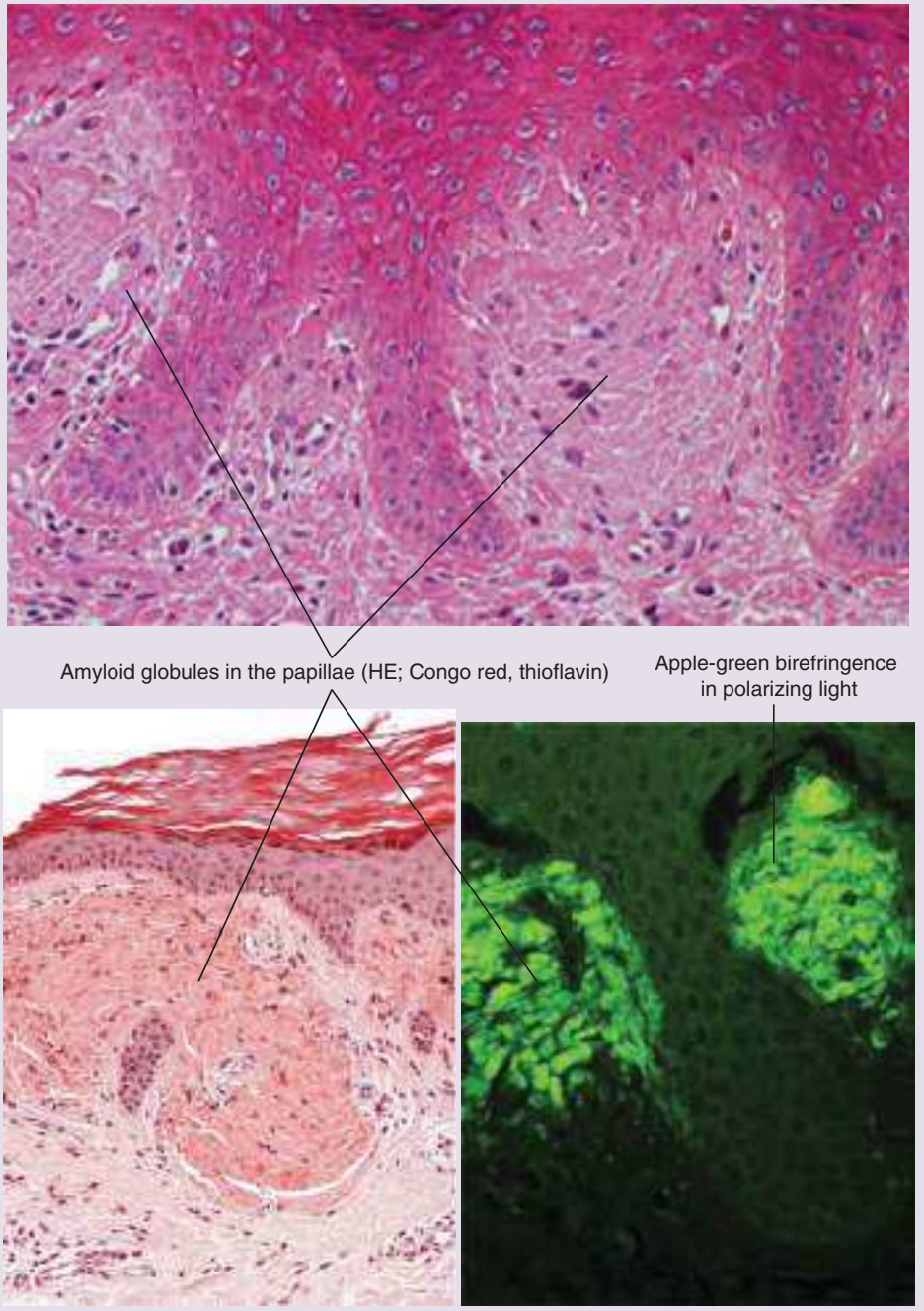
PROTOTYPE: Lichen amyloidosus



CI: Chronic and pruritic disease, showing firm, densely arranged papules with a lichenoid surface mostly on the extensor aspect of the extremities.

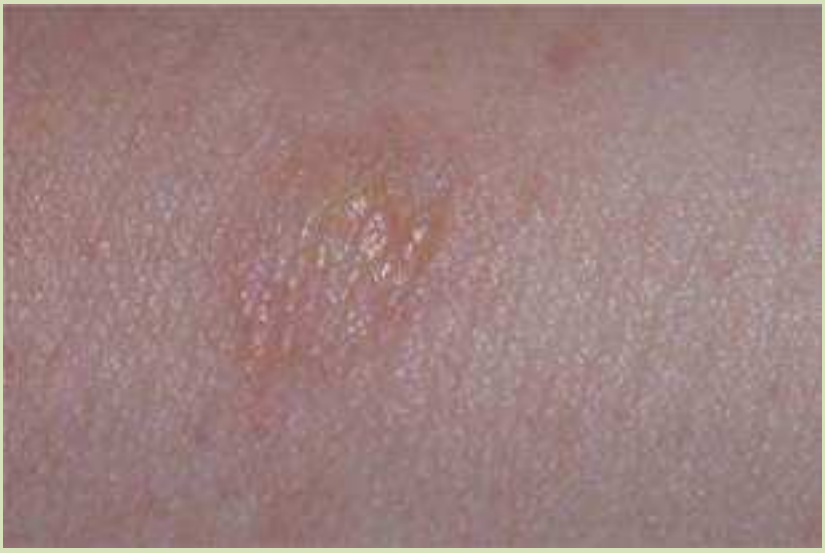


Lichen amyloidosus



Hi: Eosinophilic globular deposits in the papillary dermis; expanding of dermal papillae by large clumps of amyloid in late stages; thinning of rete ridges; acanthosis, hyperkeratosis and hypergranulosis. Amyloid deposits are highlighted by apple-green birefringence under polarizing light in Congo-red or thioflavin stained specimens.

DIFFERENTIAL DIAGNOSIS: Colloid milium



Cl: Yellowish tiny papules or plaques, in light exposed areas.

Hi: Globules of elastotic-staining degenerative collagen material in the upper and papillary dermis.

Other Diagnosis

Hyalinosis cutis et mucosae *(lipoid proteinosis): Genetic disorder with accumulation of glycoproteins affecting skin, nervous system and other organs. Dermal deposits of amorphous eosinophilic hyaline material (PAS positive) with concentric rings around vessel walls and eccrine glands.*

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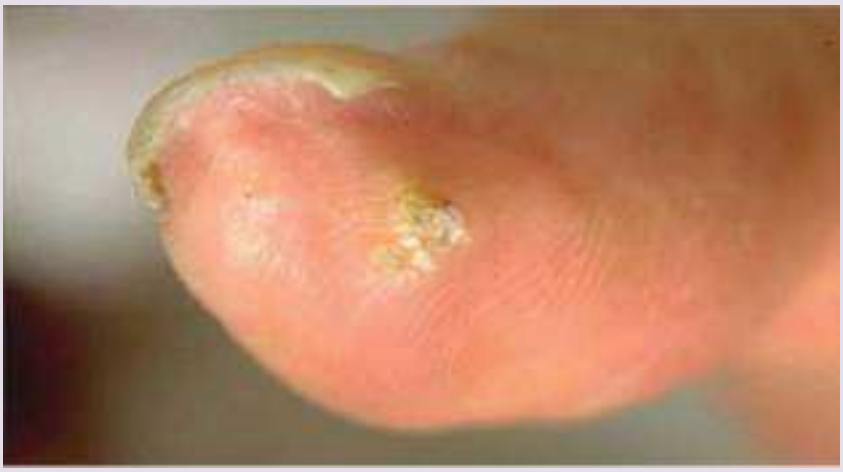
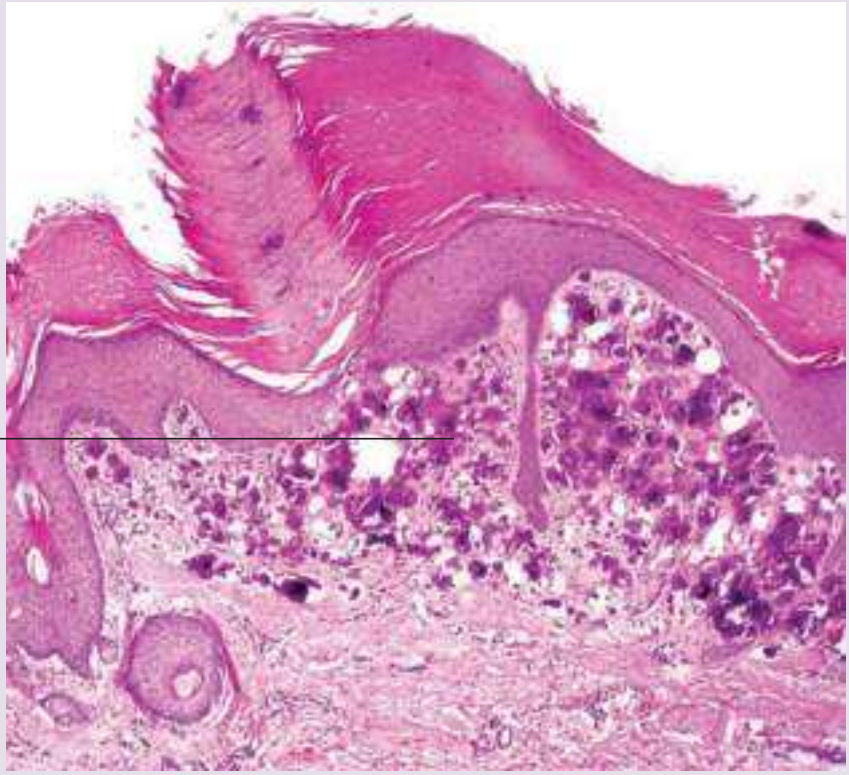
PROTOTYPE: Calcinosis cutis

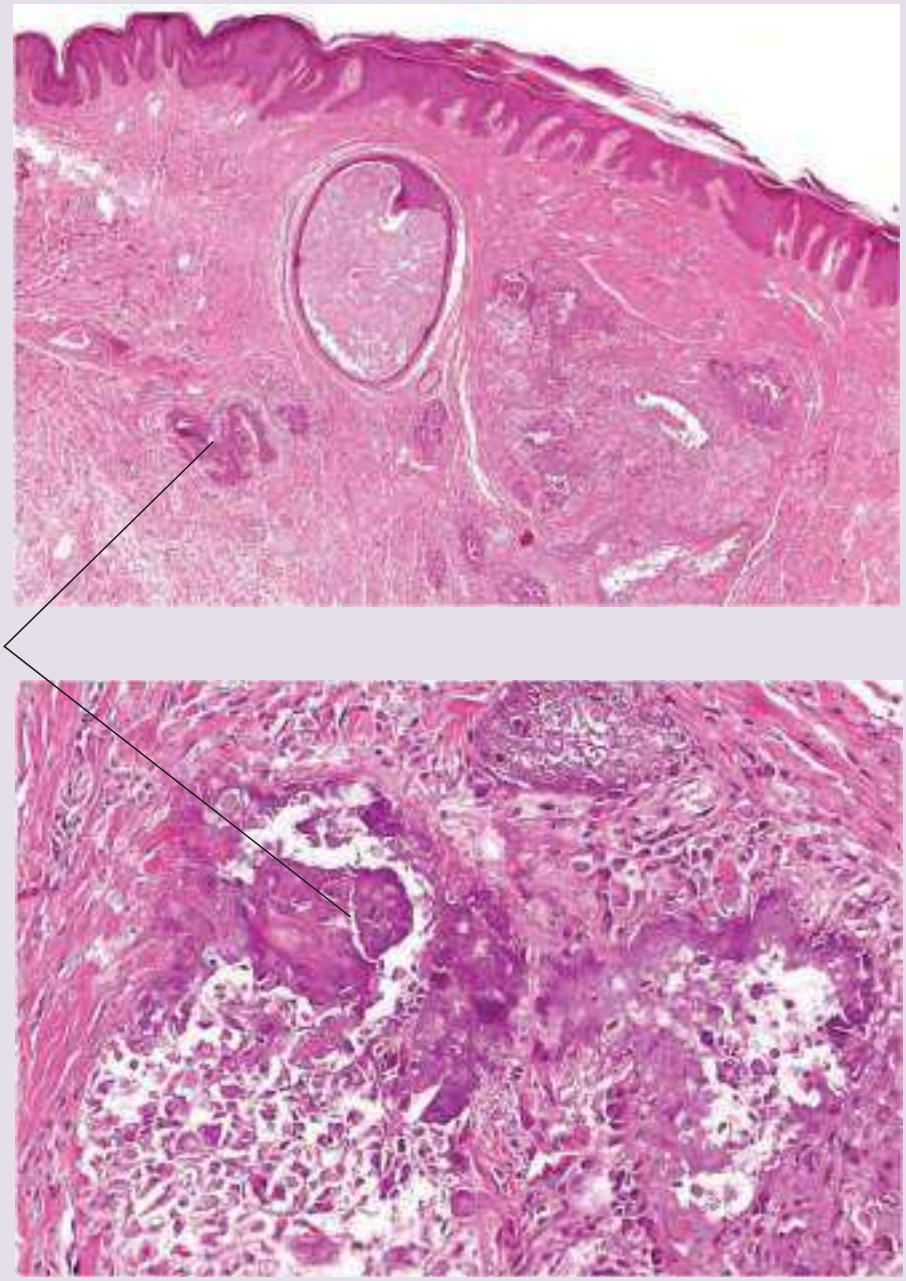


Calcinosis on the tip of the thumb

CI: Various types of cutaneous calcification have to be differentiated: metastatic, dystrophic and tumoral calcinosis, depending on the underlying disorder and pathogenesis. Firm papules or subcutaneous plaques are found, often with discharge of chalky material.



Calcinosis cutis



Hi: Crumbly, basophilic (H&E) masses in the dermis and/or subcutis, transepidermal elimination may be found, histiocytic and granulomatous foreign body reactions.

VARIANTS (depending on underlying disorder)

Dystrophic

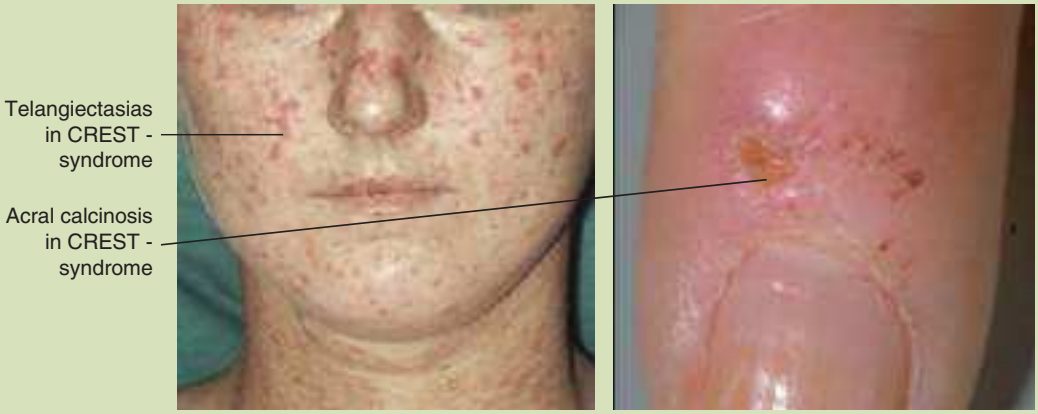
Metastatic, D-hypervitaminosis, hyperparathyreoidism

Metabolic

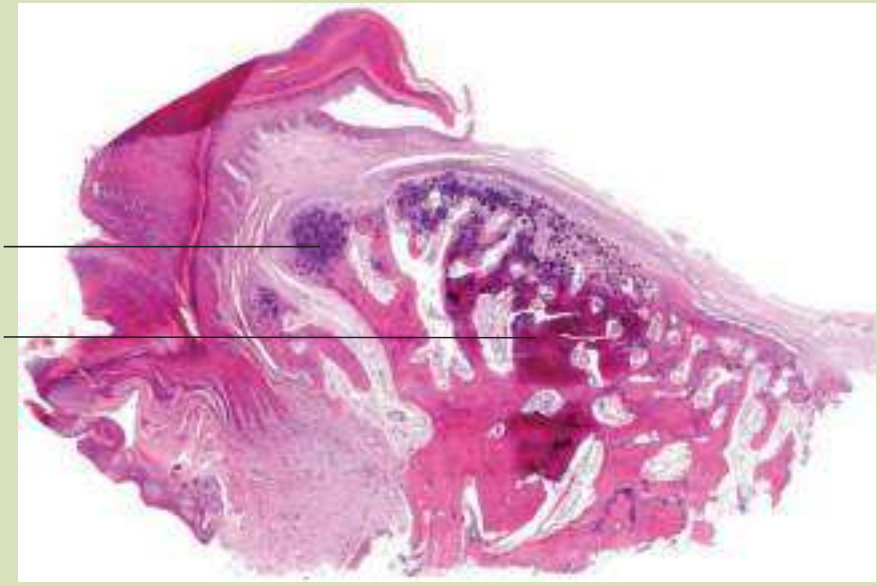
Tumoral

Idiopathic

DIFFERENTIAL DIAGNOSIS: CREST-syndrome

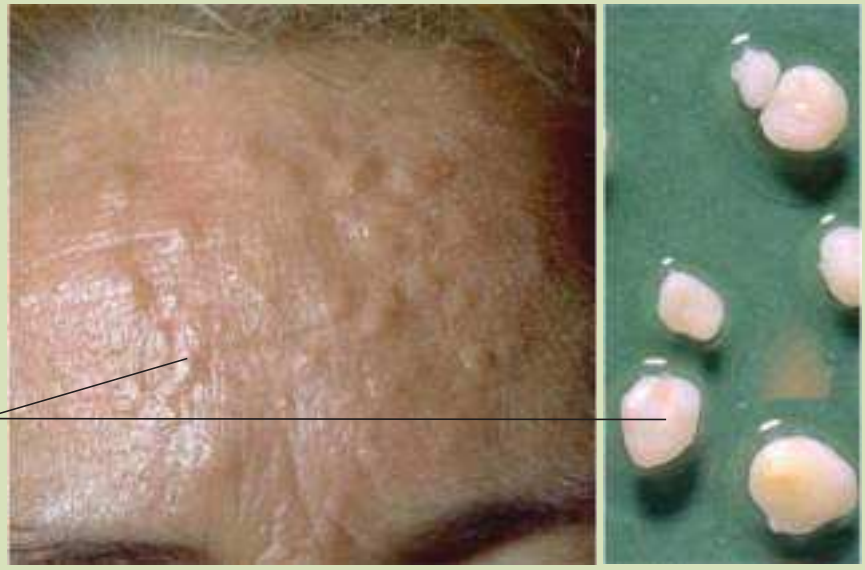


CI: Calcinosis, Raynaud syndrome, Esophageal involvement, systemic scleroderma, telangiectasias.

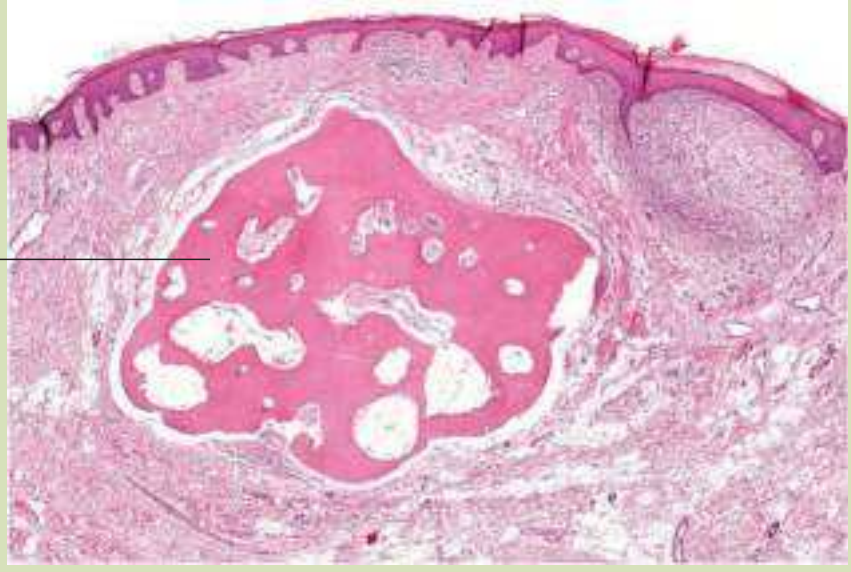


Hi: Deposits of calcium in the upper dermis, transepidermal elimination, mixed cellular, occasionally granulomatous inflammatory infiltrate.

DIFFERENTIAL DIAGNOSIS: Osteoma cutis, primary



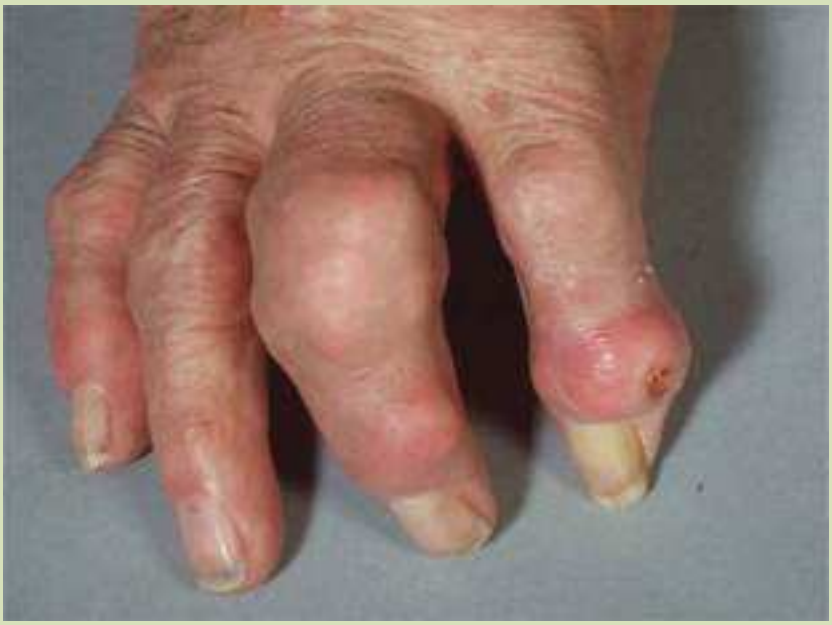
Cl: Hard subcutaneous nodules.



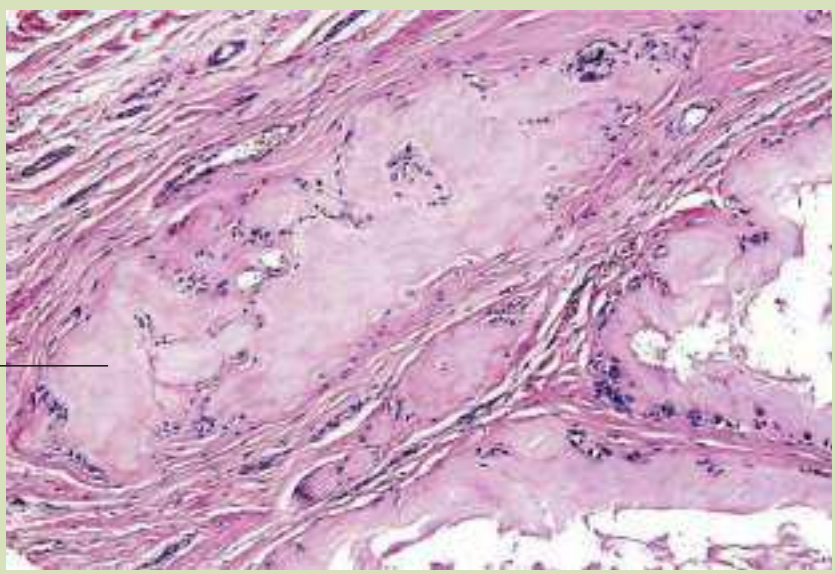
Hi: In the deep dermis or subcutis, lamellar ossification from condensed collagen, eosinophilic bone with formation of lacunae, osteoblasts embedded, inclusion of connective tissue with blood vessels (Haversian channels), osteoclasts and multinucleated giant cells in the periphery, hematopoiesis may be present.

Variant: *Albright's hereditary osteodystrophy: Ossification of condensed collagen (lamellar ossification); subungual exostosis: enchondral ossification with formation of mature trabecular bone.*

DIFFERENTIAL DIAGNOSIS: Tophus (gout)

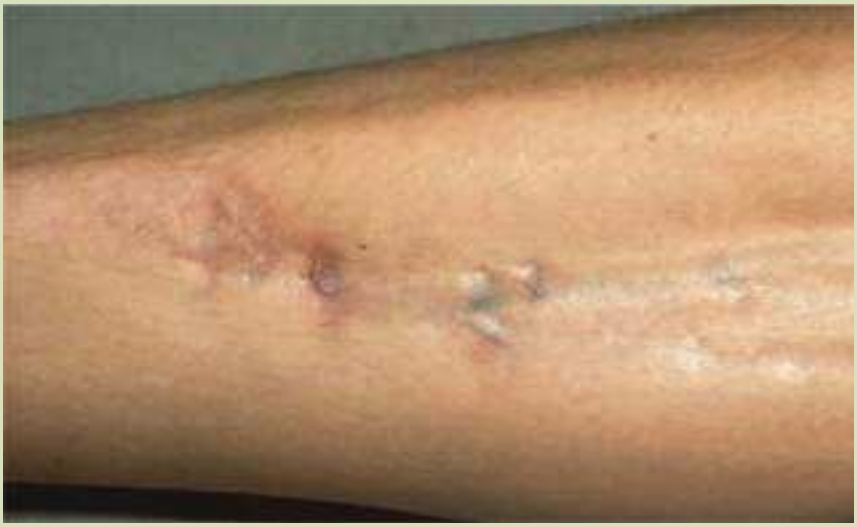


Cl: Accumulation of uric acid crystals in the subcutaneous tissue, presenting as nodules at digital joints, elbows and other sites, due to abnormal purine metabolism.

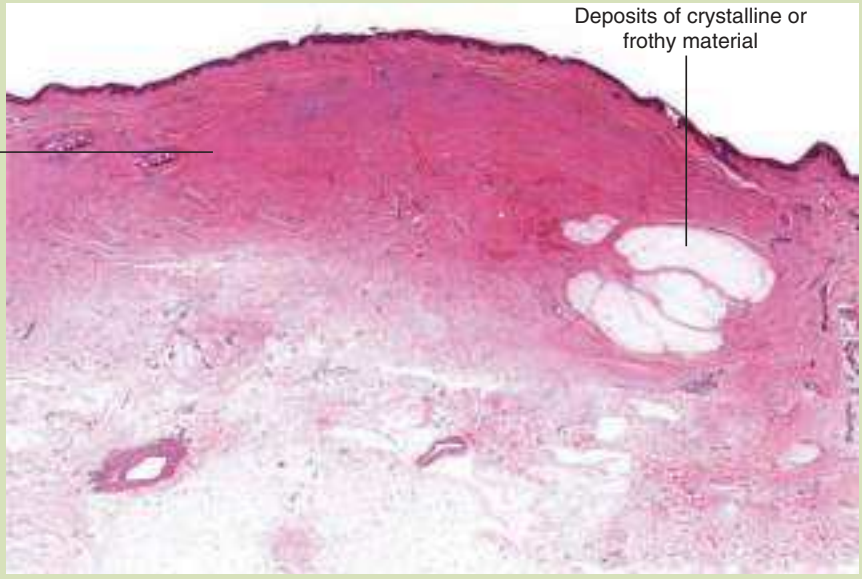


Hi: Amorphous eosinophilic or greyish material in the dermis (crystals of sodium urate), needle like clefts, surrounded by palisading granuloma with foreign body giant cells. Fixation with formalin leaves empty spaces, whereas densely packed brown crystal needles with multicolor birefringence are seen when fixation with alcohol is used.

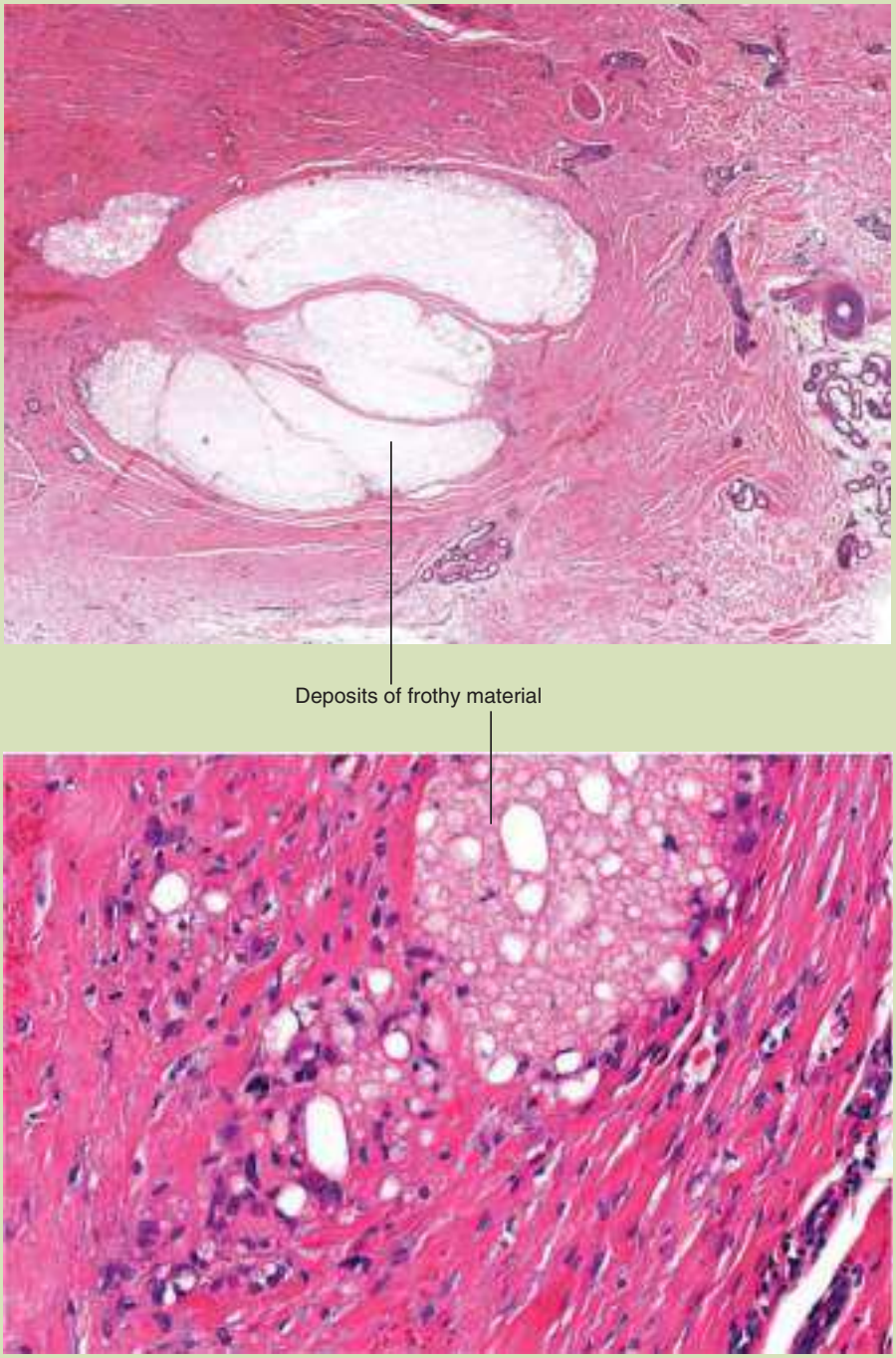
DIFFERENTIAL DIAGNOSIS: Steroid deposits



CI: Variable clinical presentation, often atrophy of the overlying epidermis and dermis.



Steroid deposits



Hi: Frothy amorphous material between collagen bundles.

Other Diagnosis

Subcutaneous fat necrosis of newborn *(adiponecrosis subcutanea neonatorum): exclusive subcutaneous localization, stellate clefting from triglyceride crystals, occasional calcification, spontaneous regression*

Sclerema adiposum neonatorum *(lethal)*

Rheumatoid nodule *(see* Chapter 4, Granulomatous infiltrates, with necrosis, page 193*): Eosinophilic necrobiotic areas surrounded by palisading histiocytic infiltrate.*

Nevus of Nanta*: Unna-type nevus with cutaneous ossification.*

Calciphylaxis (*see* Chapter 5, Vasculopathic changes, page 261)

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CHAPTER 8
Adnexae

CHAPTER MENU

Atlas of Dermatopathology: Practical Differential Diagnosis by Clinicopathologic Pattern, First Edition.
Edited by Günter Burg MD, Werner Kempf MD, and Heinz Kutzner MD. Co-Editors: Josef Feit MD, and Laszlo Karai MD.

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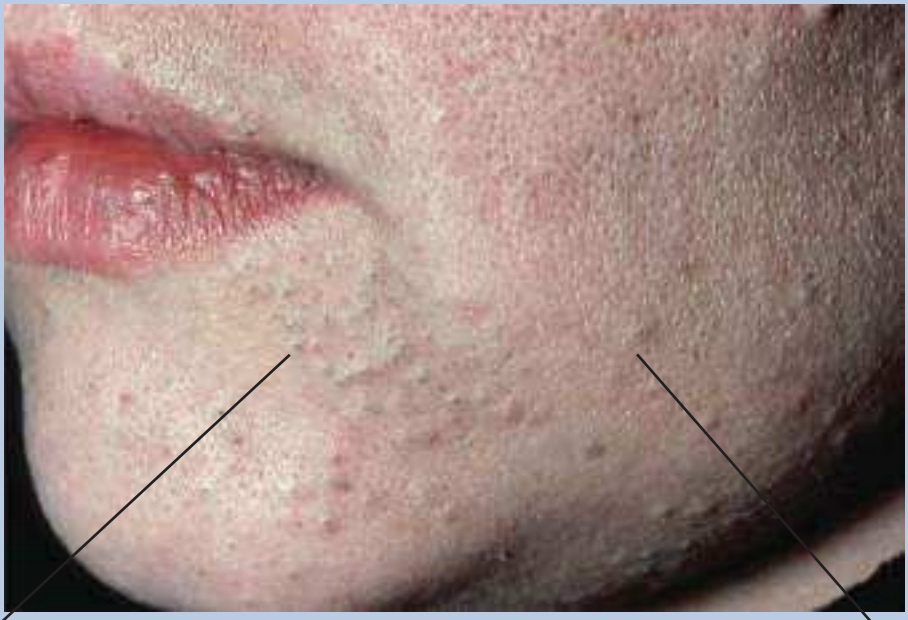
PROTOTYPE: Acne vulgaris

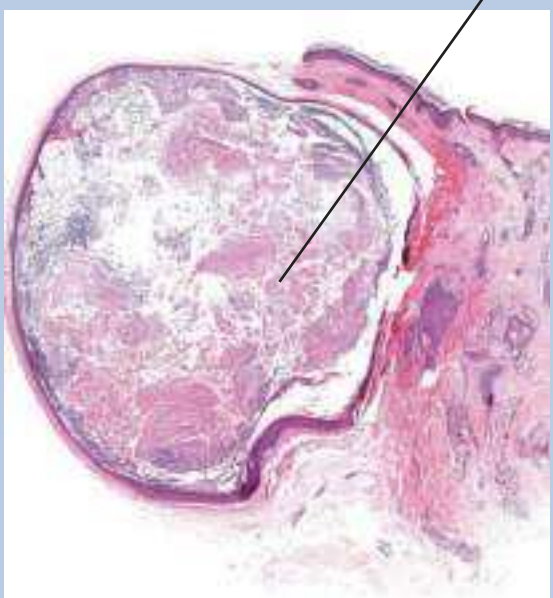
Cl: Preferentially in younger age, in contrast to rosacea. During puberty very common disorder of variable form (see variants) and various degree.

Hi: The pilosebaceous unit is involved. Compact hyperkeratosis in the follicular infundibulum and cystic dilatation. Perifollicular mostly granulocytic inflammation and abscess formation of various degree depending on the form of acne. Scar formation in acne conglobata.

VARIANT: Acne comedonica, Acne cystica



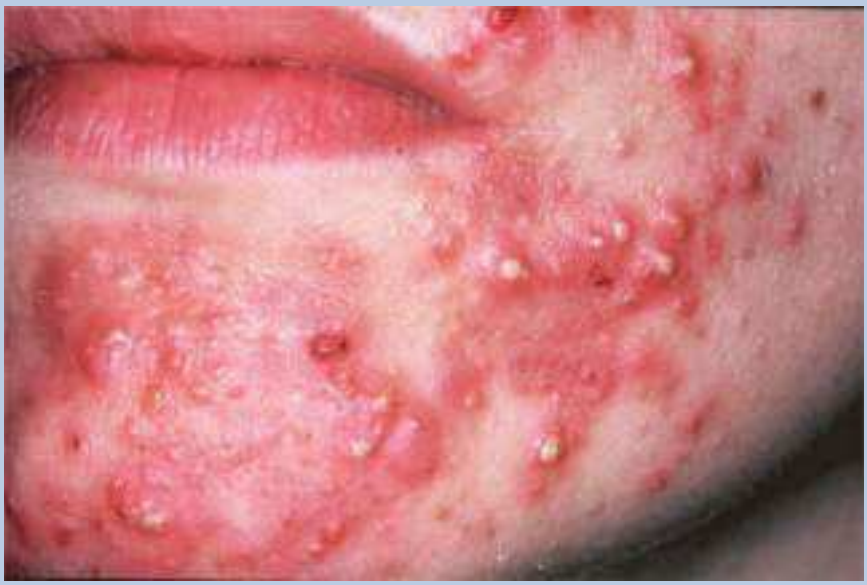
Cl: Closed (whiteheads) comedos developing into open (blackheads) comedos.



Hi: Dilated acroinfundibulum, filled with horn material, sebum, bacteria and debris (left). "Pseudocystic" structures derived from the infundibulum, filled with corneocytes, sebum, bacteria and debris (right).

VARIANT: Acne pustulosa

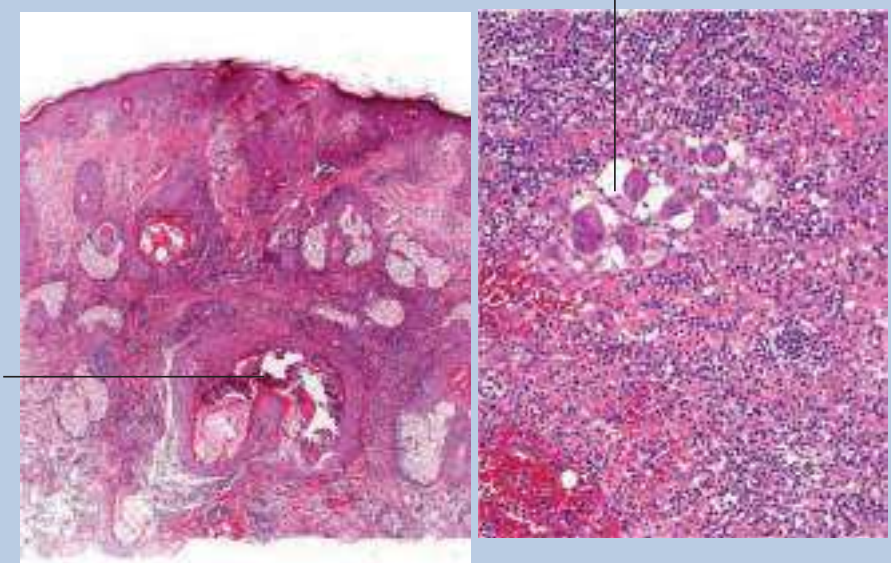
Inflammation and pustules



Cl: Pustules.

Inflammatory infiltrate with foreign body giant cells

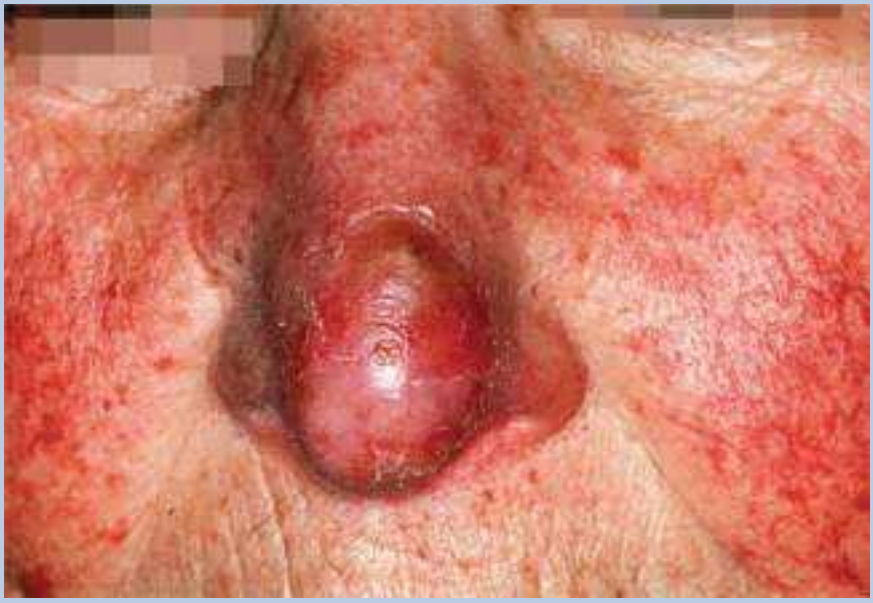
Destruction of follicular structures



Hi: Mixed cellular, inflammatory infiltrate, due to foreign body and immunologic reactions.

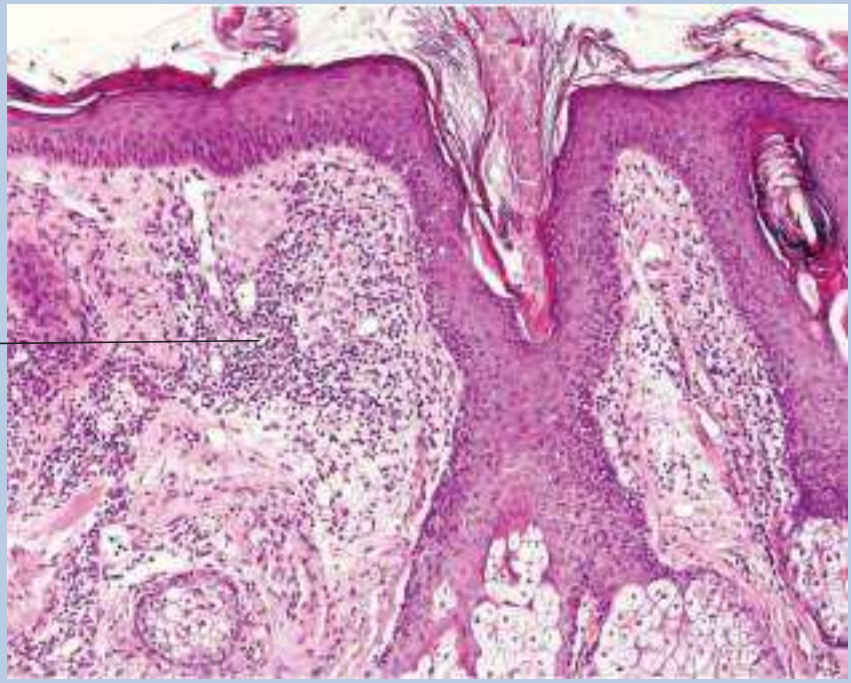
Acne conglobata: *Severe form of acne.*
Acne fulminans: *Rare, severe, inflammatory, hemorrhagic and ulcerating variant of acne, involving predominantly chest and back.*
Acne inversa (“hidradenitis suppurativa”).

PROTOTYPE: Rosacea



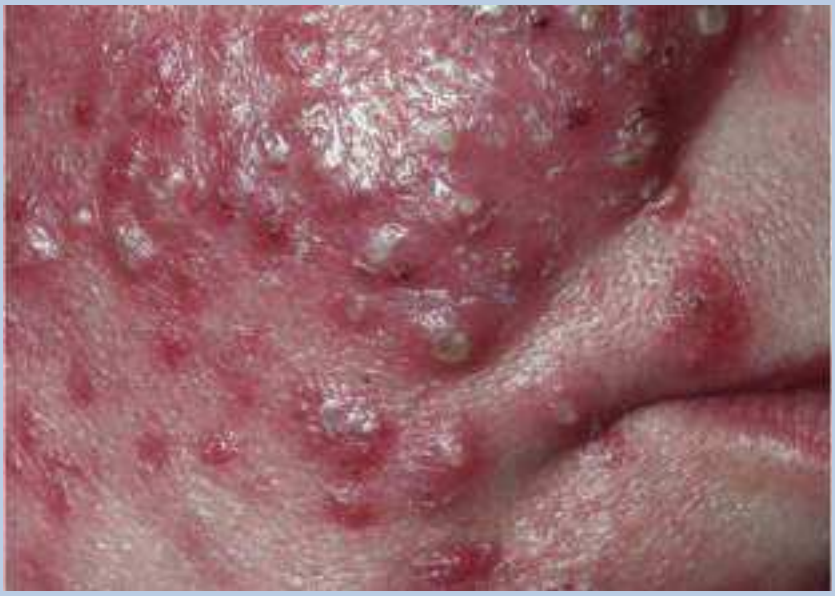
CI: Central face and cheeks, preferentially women: erythema, telangiectasias, papules and pustules.

Rosacea

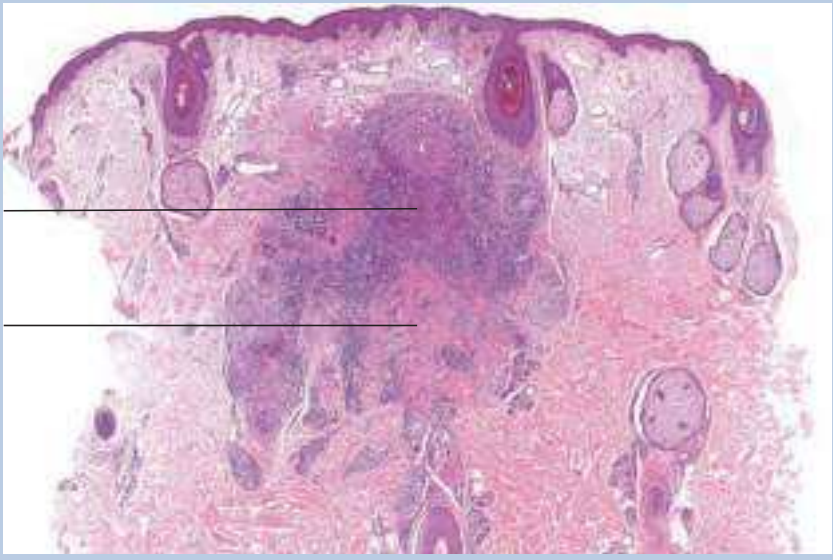


Hi: Dilatation of small vessels / telangiectasias. Perivascular and perifollicular lymphoid infiltrate, dermal edema, occasionally neutrophils and plasma cells, sebaceous hyperplasia.

VARIANT: Rosacea fulminans (Synonym: Pyoderma faciale)

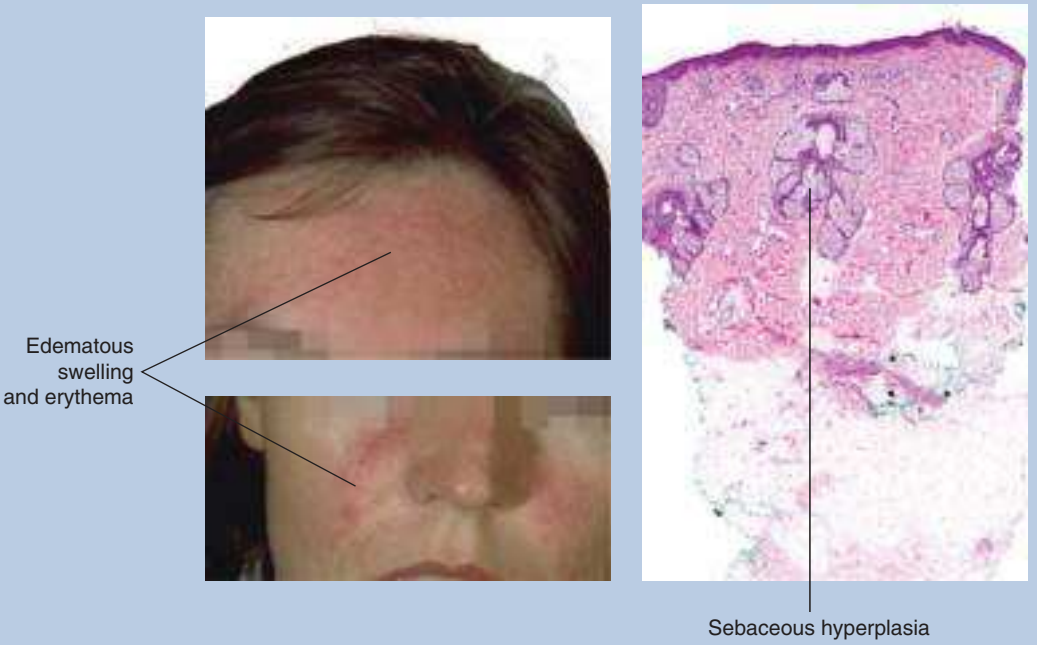


Cl: Sudden development of erythema, plaques and pustular nodules without any signs of acne.

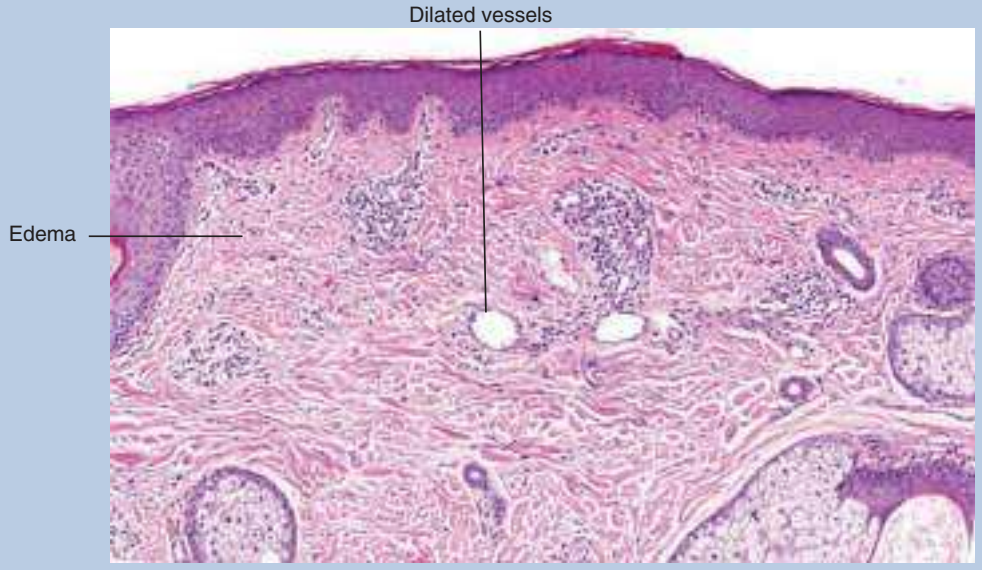


Hi: Dense perivascular and perifollicular infiltrate, mostly eosinophils and neutrophils, occasionally plasma cells, infiltrate covering the whole dermis, septal and lobular panniculitis without leukocytoklasia.

VARIANT: Rosacea, persistent edema (Morbihan)

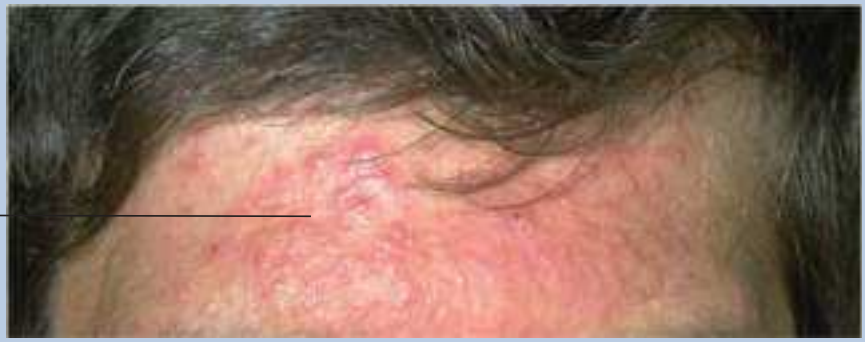


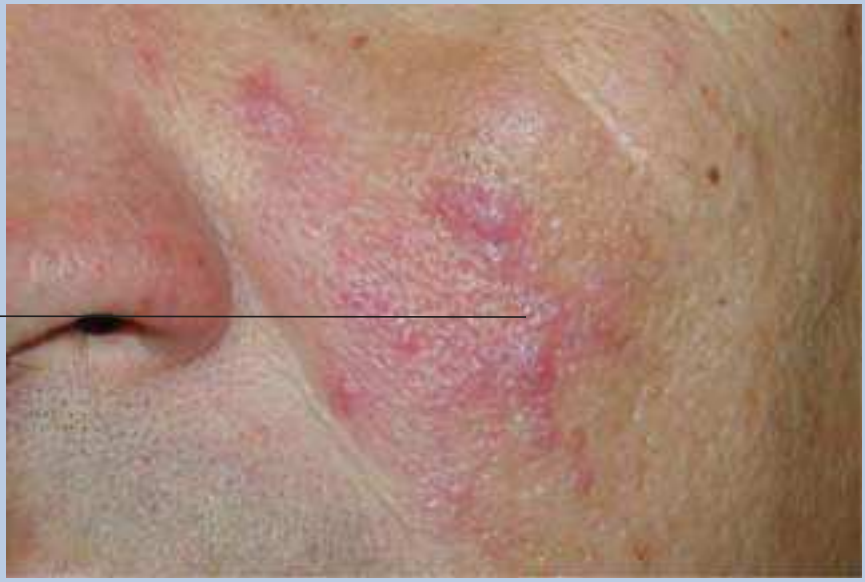
Cl: Edematous swelling and erythema of the forehead and cheeks.



Hi: Overlapping features with rosacea, interstitial edema, telangiectasias, subtle perifollicular lymphohistiocytic infiltrate. Many dilated lymphatic vessels.

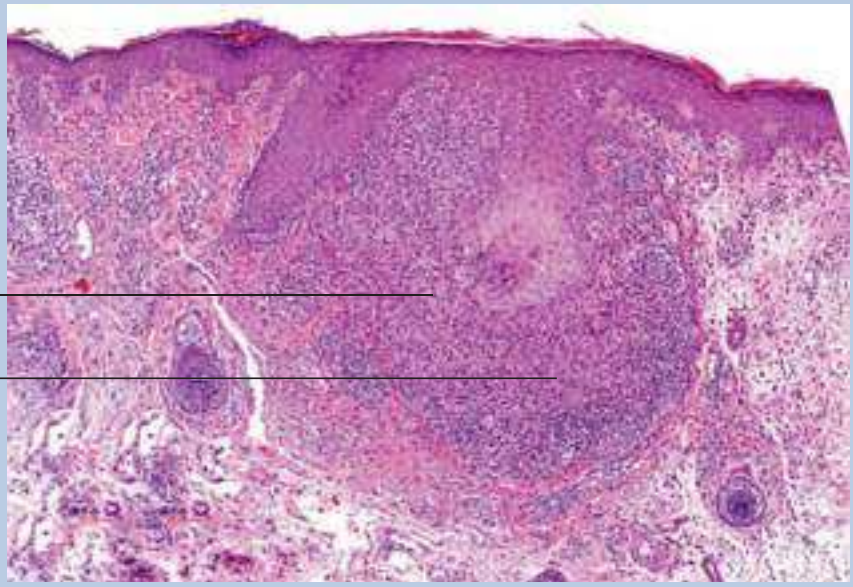
VARIANT: Granulomatous rosacea

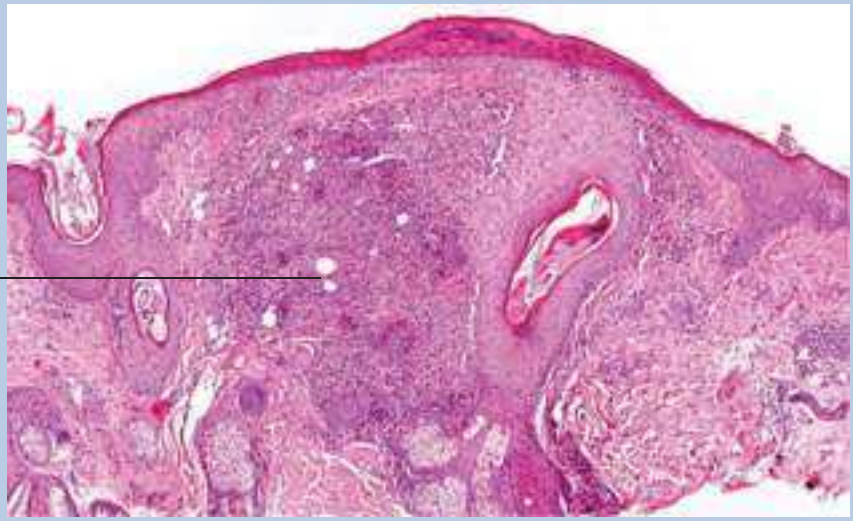




CI: Erythematous and slightly brownish plaques, papules or pustules in a centrofacial distribution involving the forehead, nose and cheeks.

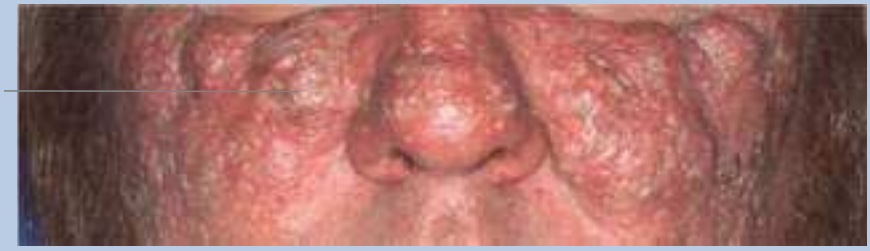
Granulomatous rosacea



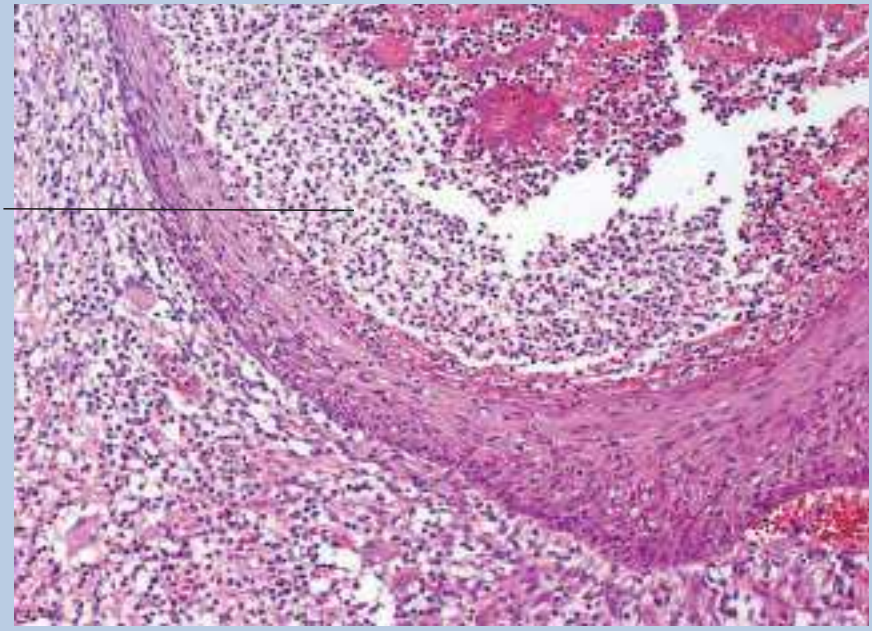


Hi: Folliculocentric granulomatous dermal infiltrate with epithelioid cells and multinucleated giant cells of the Langhans-type, telangiectasias in the upper dermis, lymphocytes, neutrophils and plasma cells, sebaceous hyperplasia.

VARIANT: Rosacea conglobata

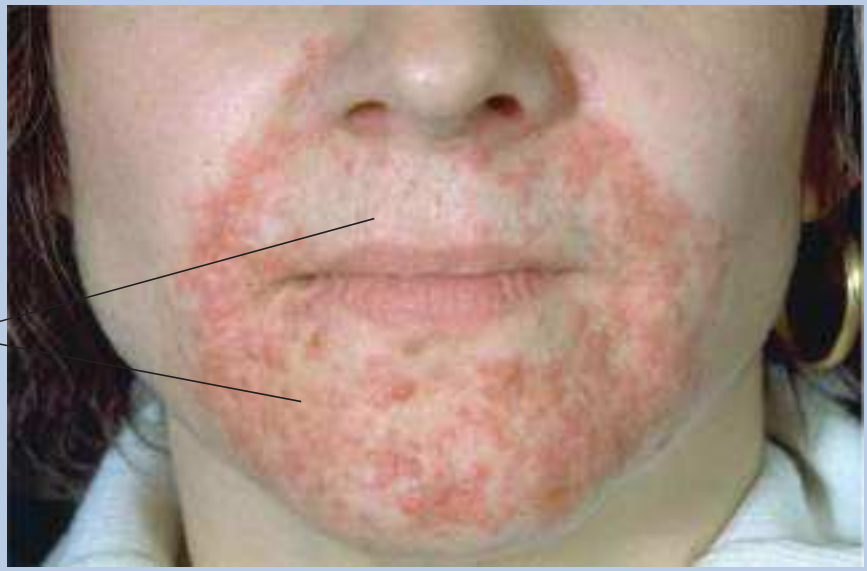


Cl: Severe form of rosacea, showing nodular abscess formation.

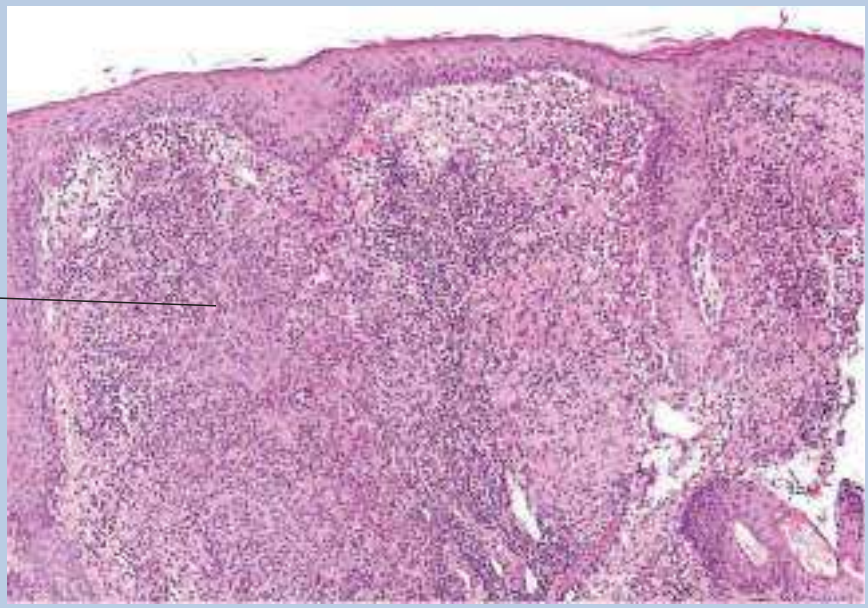


Hi: Extensive granulocytic infiltrate with massive damage of follicular structures and caseation necrosis.

PROTOTYPE: Perioral dermatitis

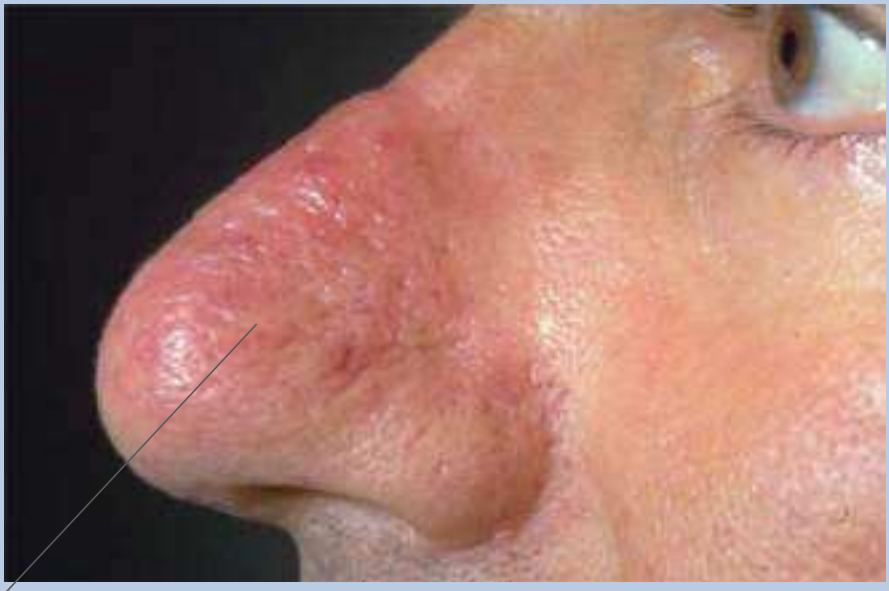


Cl: Younger patients with female preponderance, few or no telangiectasias.



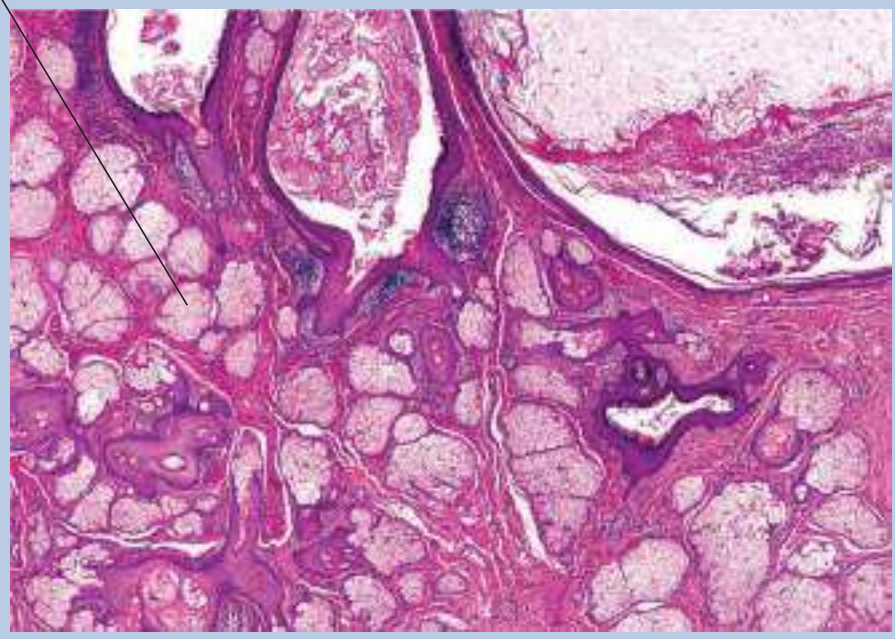
Hi: Lymphohistiocytic infiltrate, involving the hair follicle, granulomatous features may be present.

PROTOTYPE: Rhinophyma



Cl: Disfiguring enlargement of the nose, oily skin, telangiectasias and prominent pores.

Sebaceous hyperplasia



Hi: Extensive hyperplasia of sebaceous structures, telangiectasias, fibrosis.

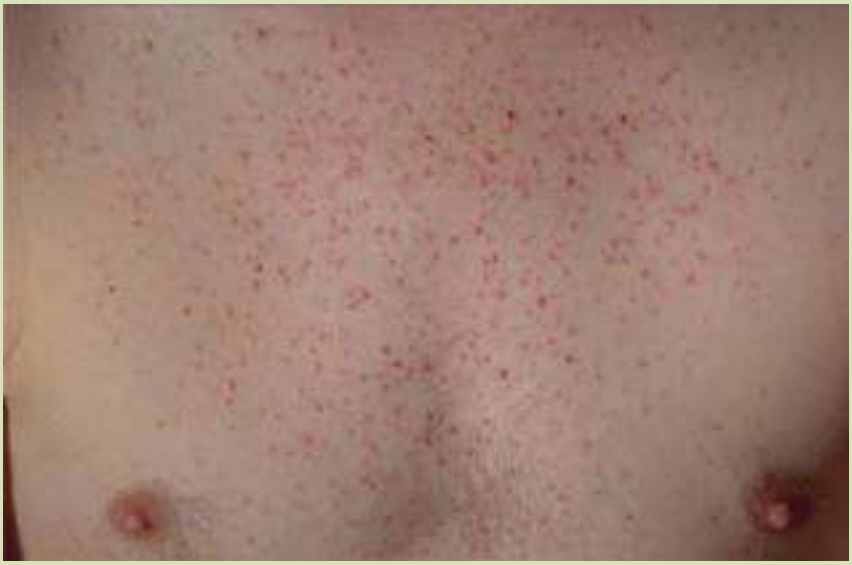
DIFFERENTIAL DIAGNOSIS: Demodex folliculitis

Cl: Rosacea-like changes with papules and pustules, preferentially on the cheeks.

Hi: Demodex mites within the inflamed hair follicles with their heads towards the follicular opening; foreign-body reaction may be present.

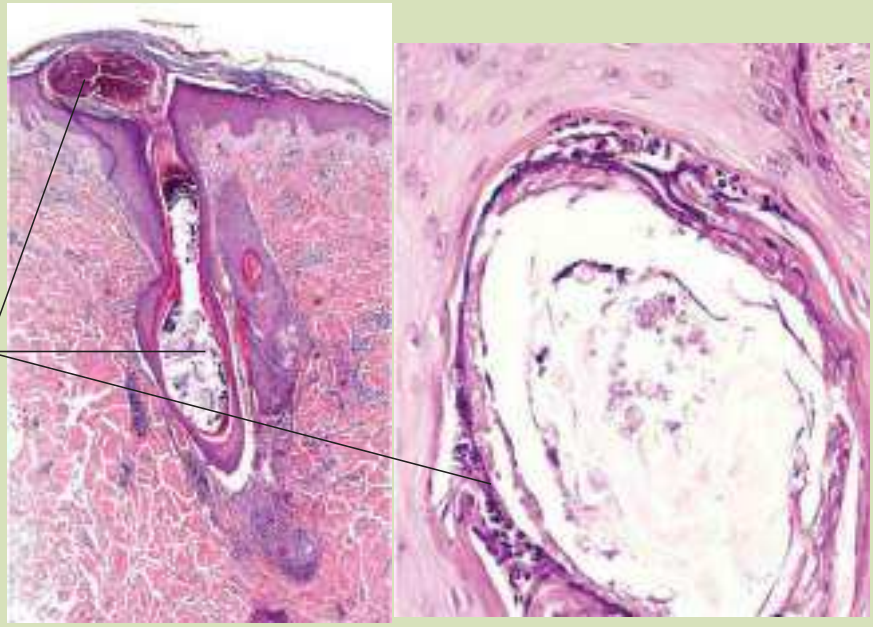
DIFFERENTIAL DIAGNOSIS: *Pityrosporum* folliculitis

Tiny papules and pustules, follicle-bound



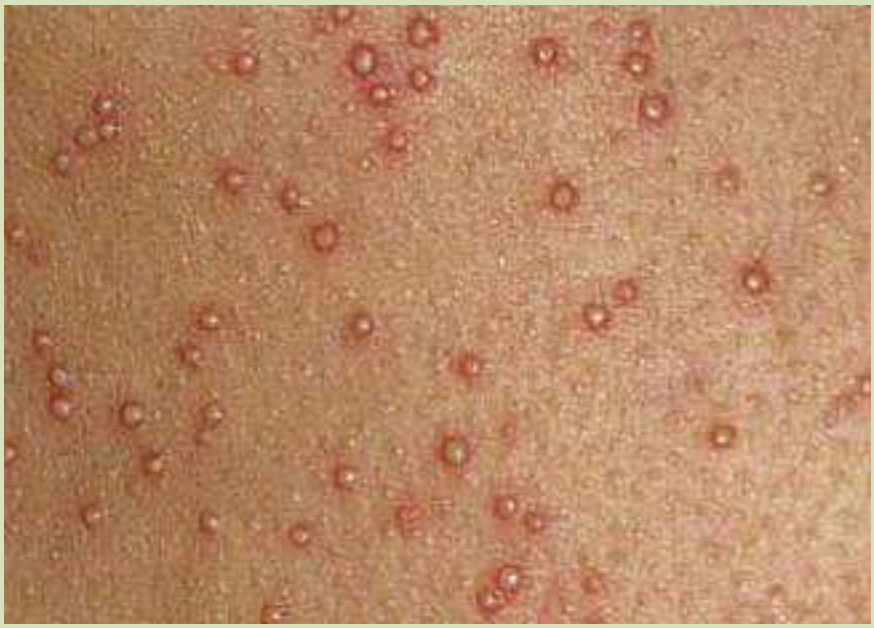
Cl: Acneiform reaction, preferentially involving the face, chest or back. Pruritus.

Detritus, hyperkeratotic material, mixed cellular infiltrate and spores in the follicles

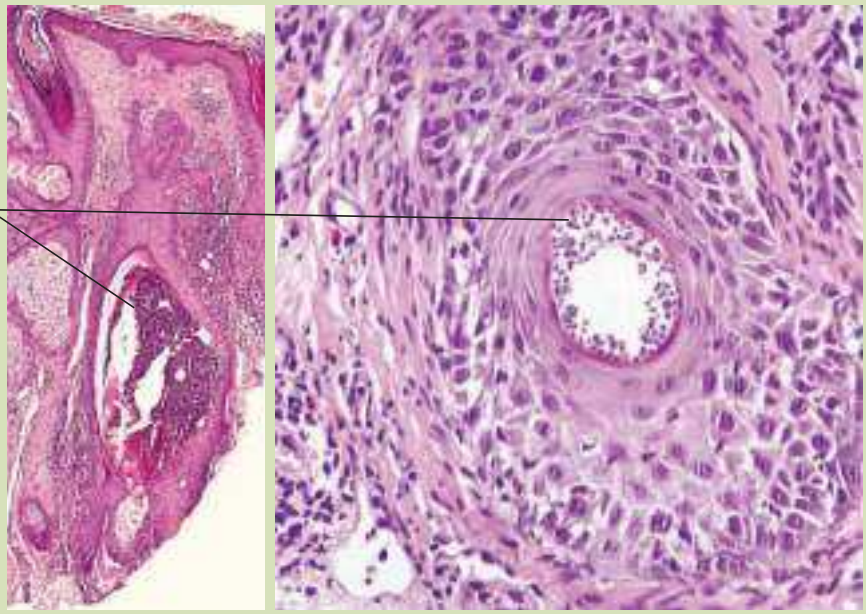


Hi: Detection of spores within the inflamed hair follicles.

DIFFERENTIAL DIAGNOSIS: Bacterial folliculitis

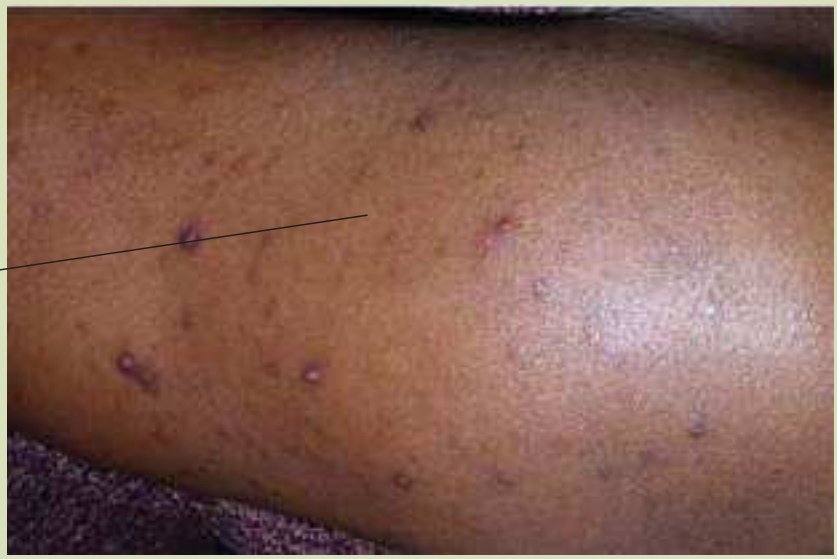


Cl: Acneiform reaction.

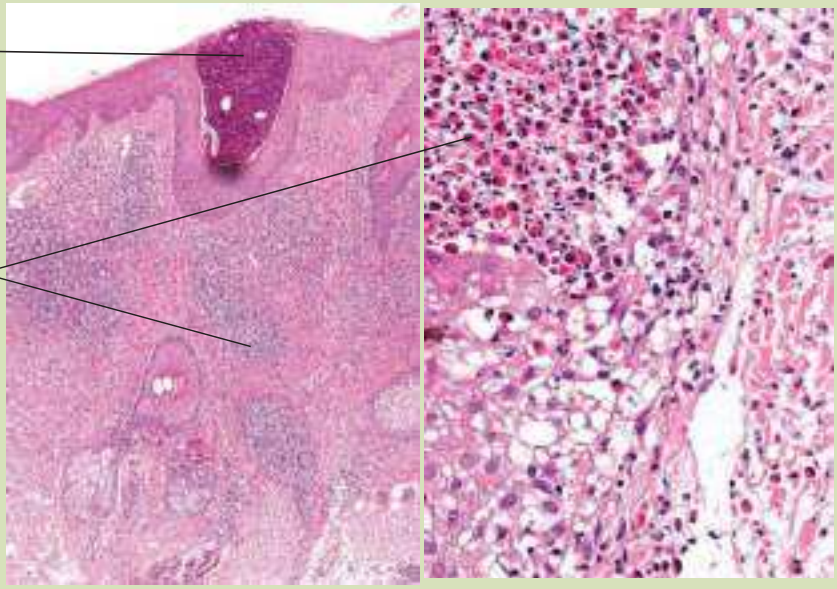


Hi: Detection of Gram positive or negative bacteria within the inflamed hair follicles, in the absence of demodex mites and *pityrosporum* spores.

DIFFERENTIAL DIAGNOSIS: Eosinophilic folliculitis and papular eruption of HIV



Cl: Disseminated papules and pustules.



Hi: Inflamed hair follicles with admixture of eosinophils; serological findings.

Trichophytia: *Detection of hyphae in the inflamed hair follicle (PAS or Grocott stain).*

Eosinophilic folliculitis Ofuji: *Perifollicular lymphohistiocytic infiltrate with admixture of numerous eosinophils and accumulation of eosinophils in the ostia and infundibula of the inflamed hair follicles.*

Lupus miliaris disseminatus faciei: *Dermal granulomas with central necrosis and neutrophils (see* Chapter 4, Granulomatous infiltrates, with necrosis, page 184).

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Perrigouard, C., B. Peltre, *et al.* (2013). "A histological and immunohistological study of vascular and inflammatory changes in rosacea." *Ann Dermatol Venereol* **140**(1): 21–9.

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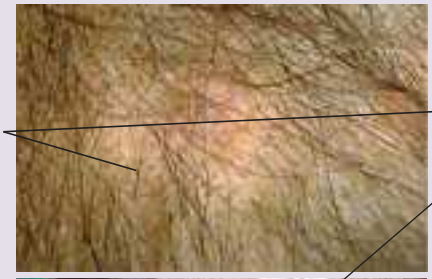
PROTOTYPE: Trichotillomania

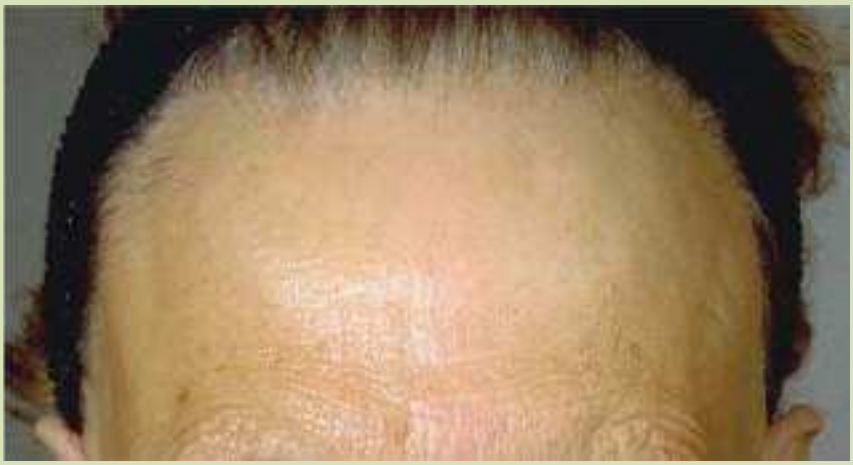


Cl: Solitary, rarely multiple, circumscribed areas of incomplete hair loss with short hairs of varying length; only those hairs reaching at least 3 mm in length can be removed. The hair shafts often show distal splits and fringes. Broken-off hairs may appear as dark dots.

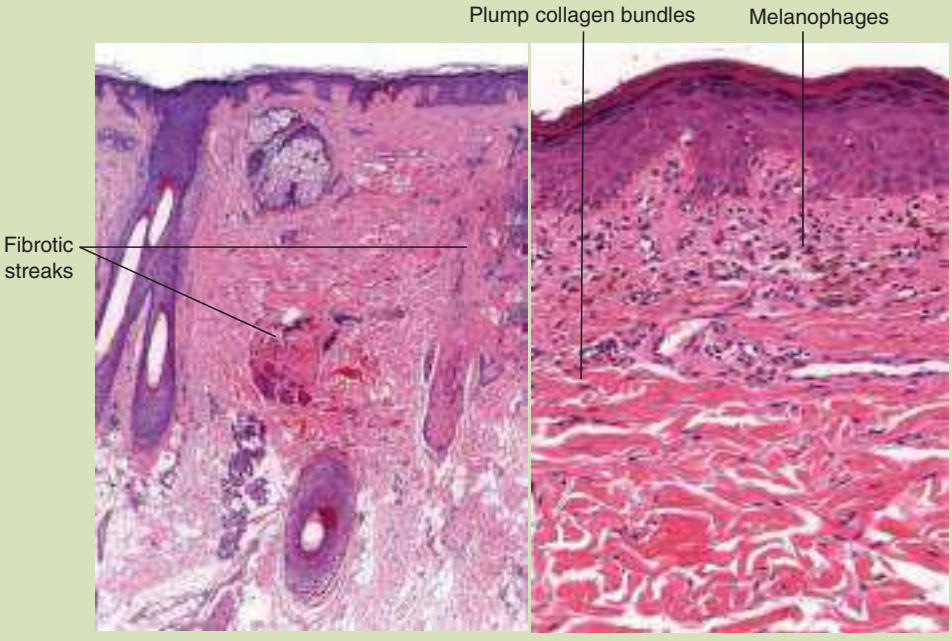
Hi: Normal epidermis, normal follicle counts, normal ratio of terminal to vellus hair, dilated, empty infundibuli, increased ratio of catagen and telogen hairs, clefts around the follicular epithelium, perifollicular erythrocytes and hemorrhage, no inflammatory infiltrate, trichomalacia may occur.

Variant: *Traction and pressure alopecia*

DIFFERENTIAL DIAGNOSIS: Frontal fibrosing alopecia



Cl: Frontal baldness.



Hi: Loss of hair follicles due to scarring process, variant of lichen planopilaris.

Comment

Frontal fibrosing alopecia is considered to be late stage lichen (ruber) planopilaris.

Alopecia areata (*see* Perifollicular inflammation, no fibrosis, page 342**).**

Androgenetic alopecia (*see* Perifollicular inflammation, no fibrosis, page 348): *Decreased ratio of vellus to terminal hairs, perifollicular lymphoid infiltrate often present, no trichomalacia.*

Diffuse telogen effluvium.

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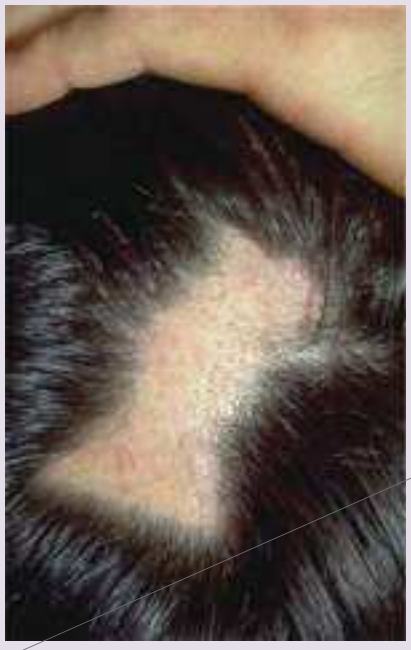
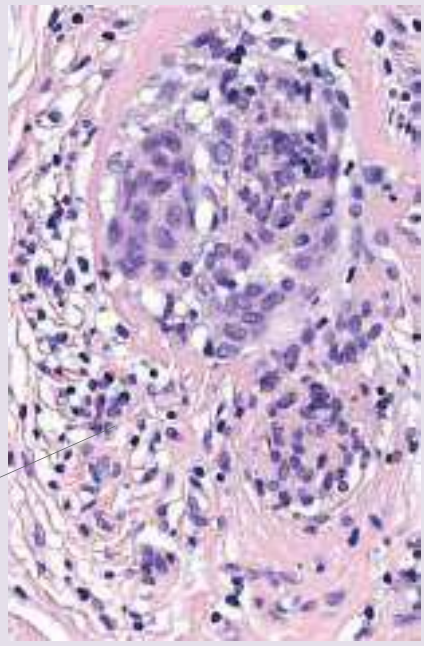
Davis-Daneshfar, A. and R. M. Trueb (1995). "[Tonsural trichotillomania]." *Hautarzt* **46**(11): 804–7.

Stefanato, C. M. (2010). "Histopathology of alopecia: a clinicopathological approach to diagnosis." *Histopathology* **56**(1): 24–38.

PROTOTYPE: Alopecia areata

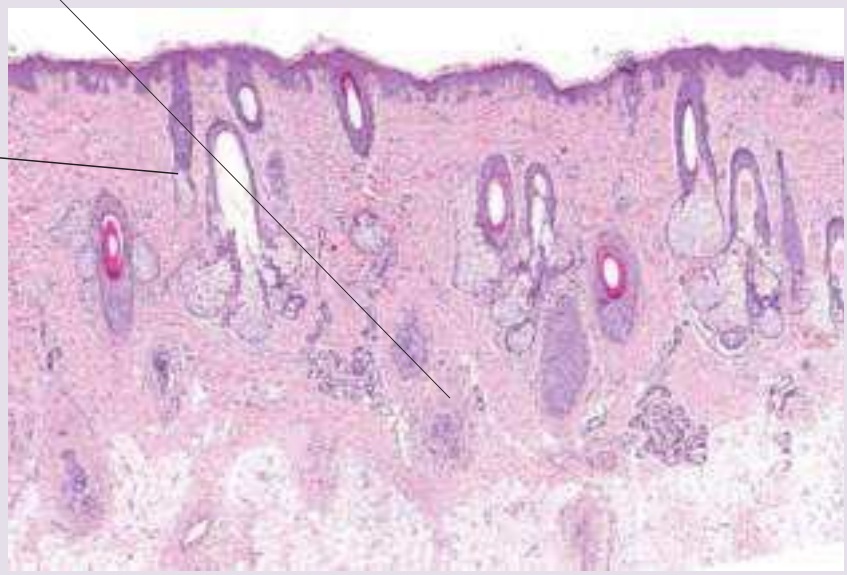




Follicles preserved

Peribulbar and intrabulbar lymphocytic infiltrate

Cl: Focal, multiple or diffuse non-inflamed, non-scarring process; can progress to loss of all scalp hairs (alopecia totalis) or all scalp and body hairs (alopecia universalis), sometimes associated nail changes (pitted nails).



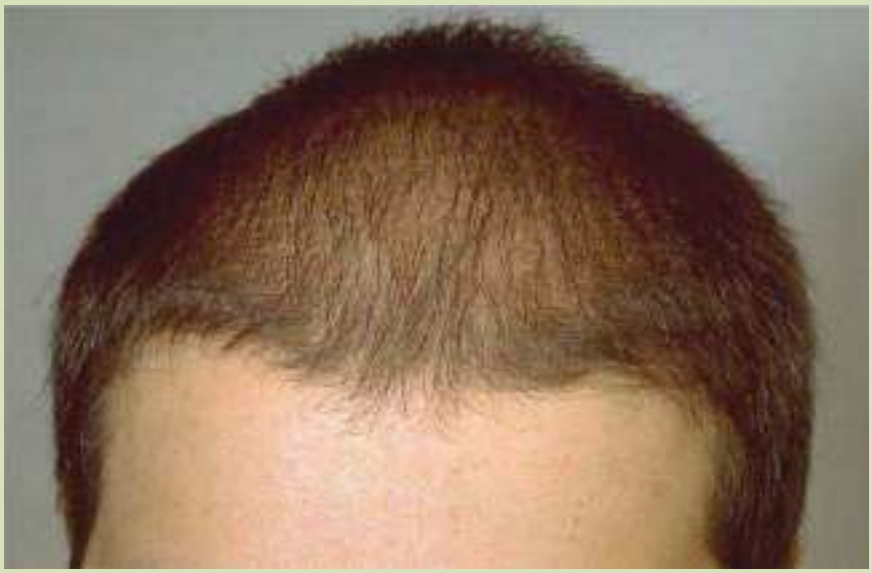
Telogen and catagen hair follicles

Hi: Peribulbar and intrabulbar lymphocytic infiltrate, decreased number of terminal anagen hairs, increased number of terminal catagen and telogen hairs, occasionally eosinophils, edema of hair matrix, pigment incontinence of hair bulbs, angiofibrotic strands.

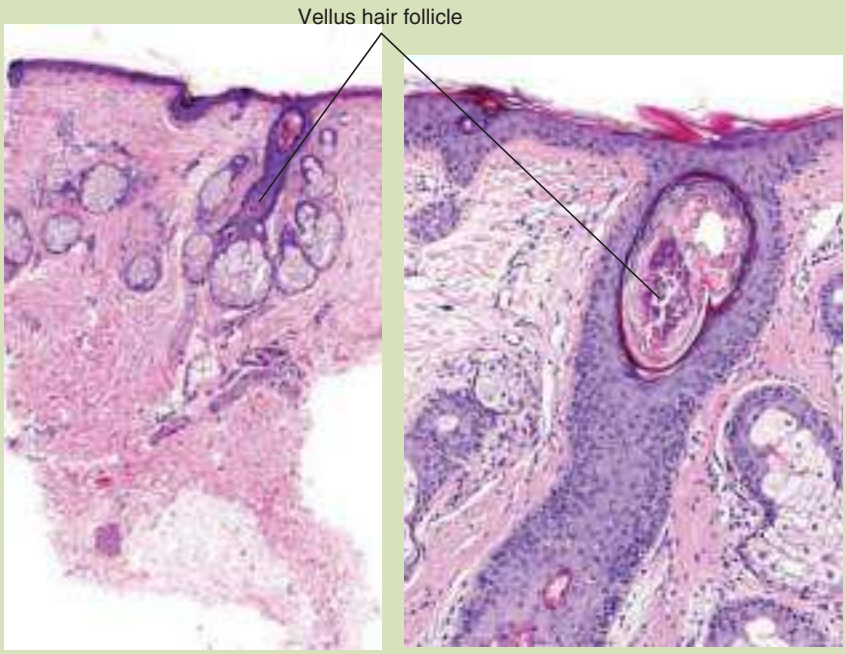
VARIANT

Late stage: *No or little perivascular or peribulbar infiltrates, increased number of miniaturized vellus hairs.*

DIFFERENTIAL DIAGNOSIS: Androgenetic alopecia



Cl: Diffuse hair loss, usually starting in the frontoparietal area; male or female pattern.



Hi: Relative increase in telogen follicles, no scaring, no or very subtle perifollicular inflammation.

Other Diagnosis

Frontal fibrosing alopecia (*see* No inflammation, no fibrosis, page 344).

Alopecia syphilitica *(areolaris).*

References

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Muller, C. S. and L. El Shabrawi-Caelen (2011). "'Follicular Swiss cheese' pattern – another histopathologic clue to alopecia areata." *J Cutan Pathol* **38**(2): 185–9.

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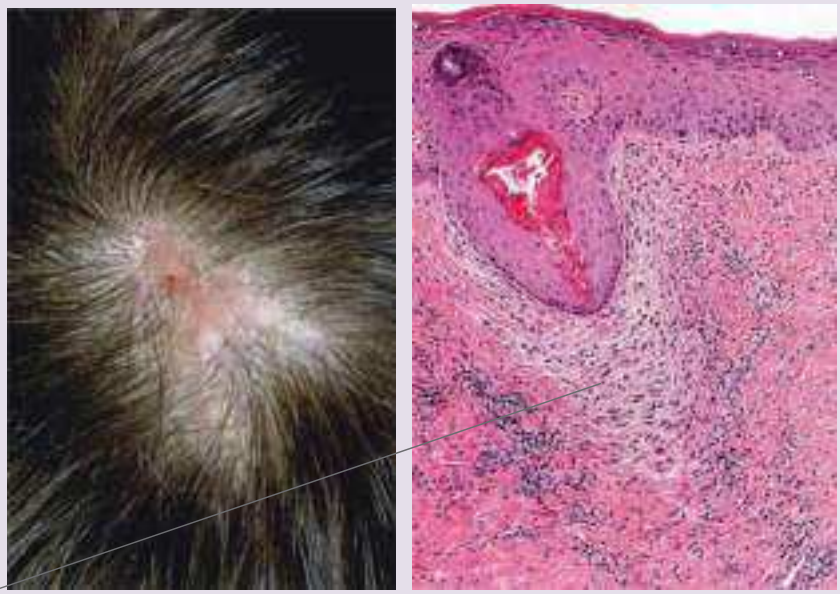
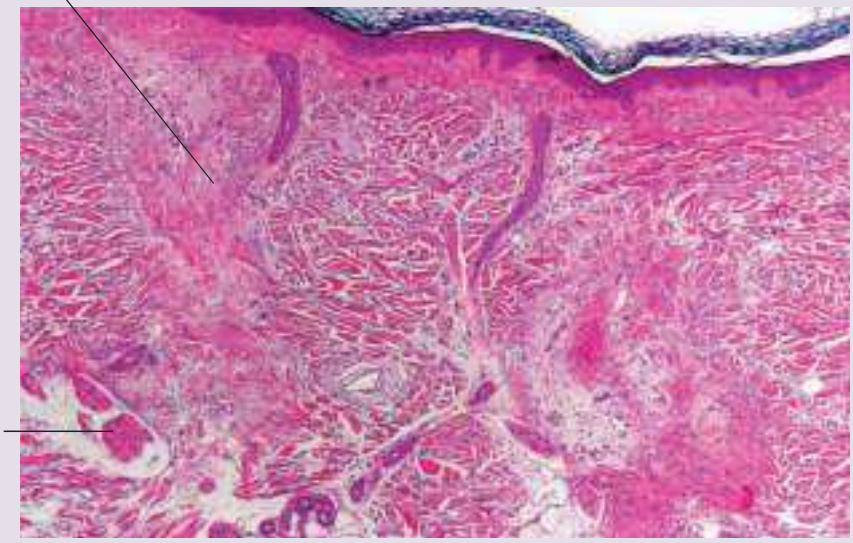
PROTOTYPE: Scarring alopecia, late stage (pseudopelade Brocq)



Cl: Like in alopecia areata, in "pseudo alopecia areata" there are small areas of alopecia without any scaring or significant inflammation. Some if not all cases possibly are late stages of either lupus erythematosus or lichen planus of the scalp.



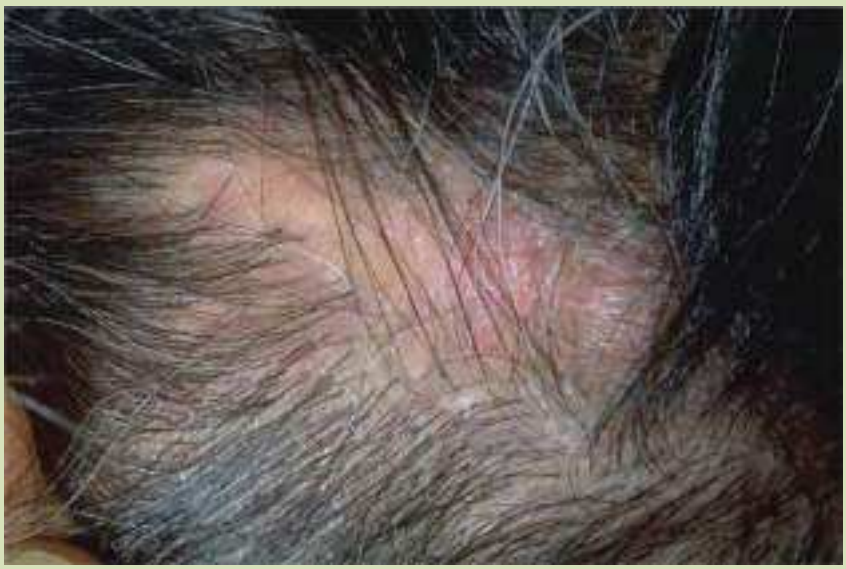
Hi: Follicular epithelial atrophy, concentric lamellar fibroplasias, foreign-body inflammation, selective loss of hair follicles and sebaceous glands, subtle perifollicular lymphohistiocytic infiltrate, epidermis normal or atrophic; fibrotic streaks.

VARIANTS

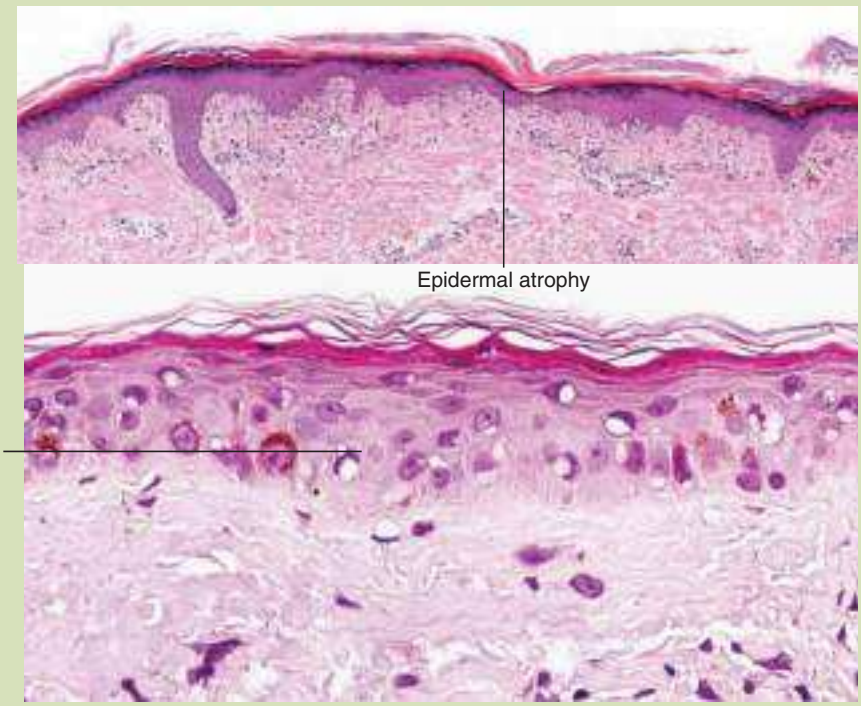
Early stage lichen ruber planopilaris: *Lichenoid interface dermatitis, decreased number of follicles, no mucin deposits, perifollicular lymphocytic infiltrates, perifollicular fibroplasia.*

Frontal fibrosing alopecia (*see* No inflammation, no fibrosis, page 344) is considered a variant of lichen (ruber) planopilaris.

DIFFERENTIAL DIAGNOSIS: Discoid lupus erythematosus, end stage



Cl: Scarring alopecia without follicles.



Hi: Atrophy, loss of follicular structures, fibrosis.

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Note: Page numbers in *italics* refer to Figures.

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