University of Michigan Health System

International Academy of Pathology
October, 2018
Dead sea, Jordan

University of Michigan Health System

Case 7

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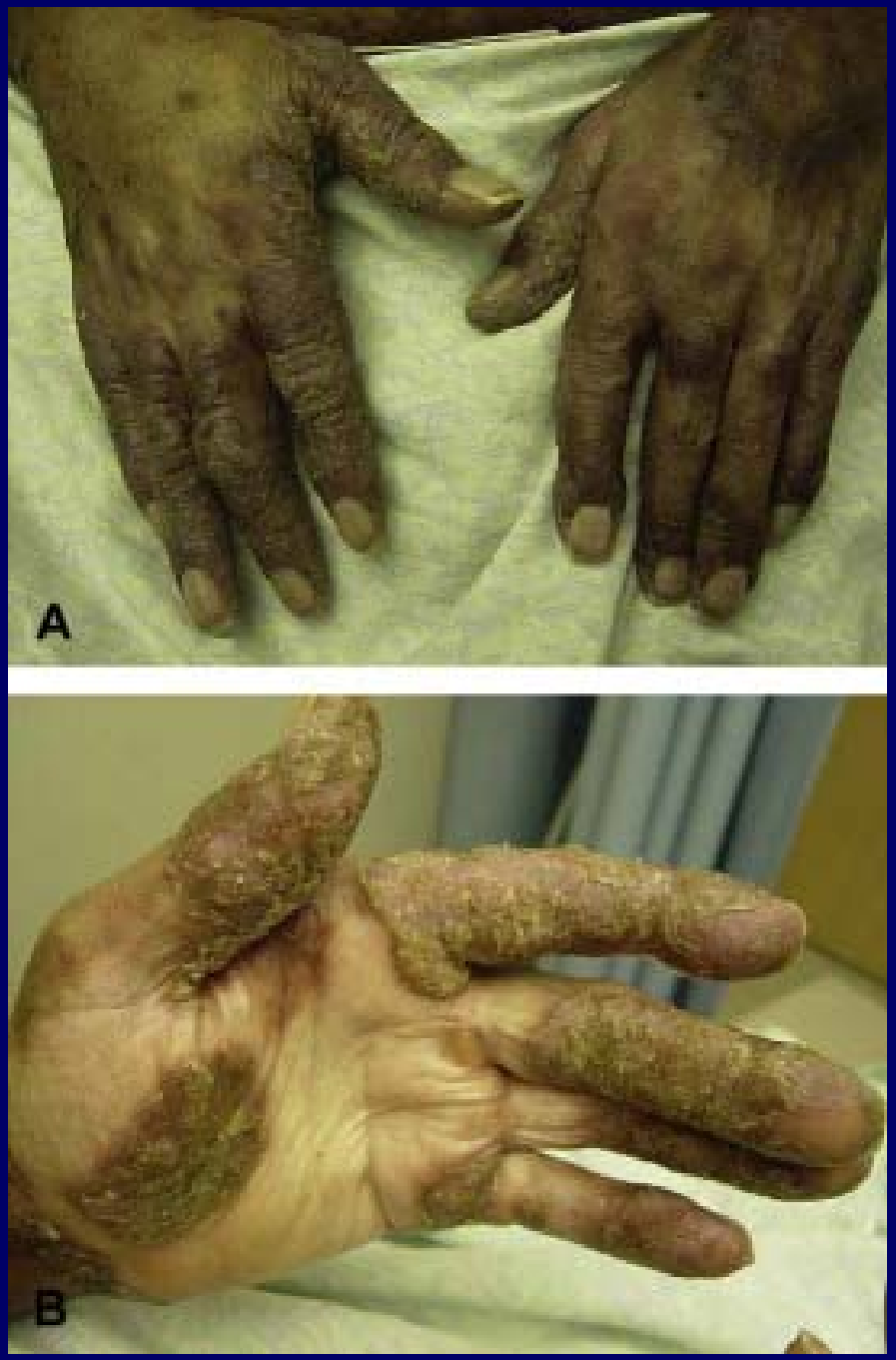
USA

Clinical history

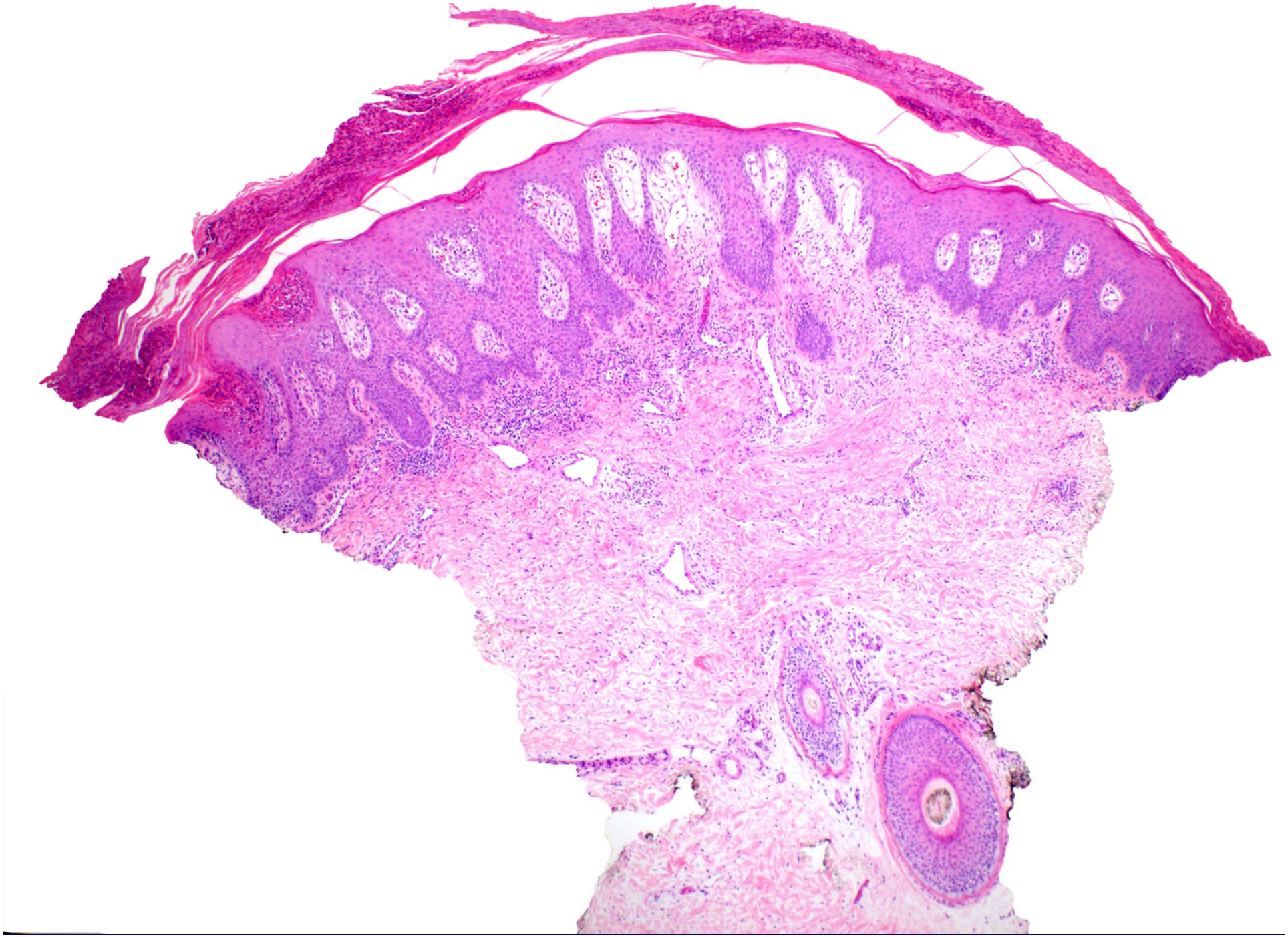
- 46-year-old African American, presents for management of severe psoriasis
- Refractory to treatment over last 2 years
- Diagnosed based on clinical and histopathologic evaluation
- History of hepatitis C

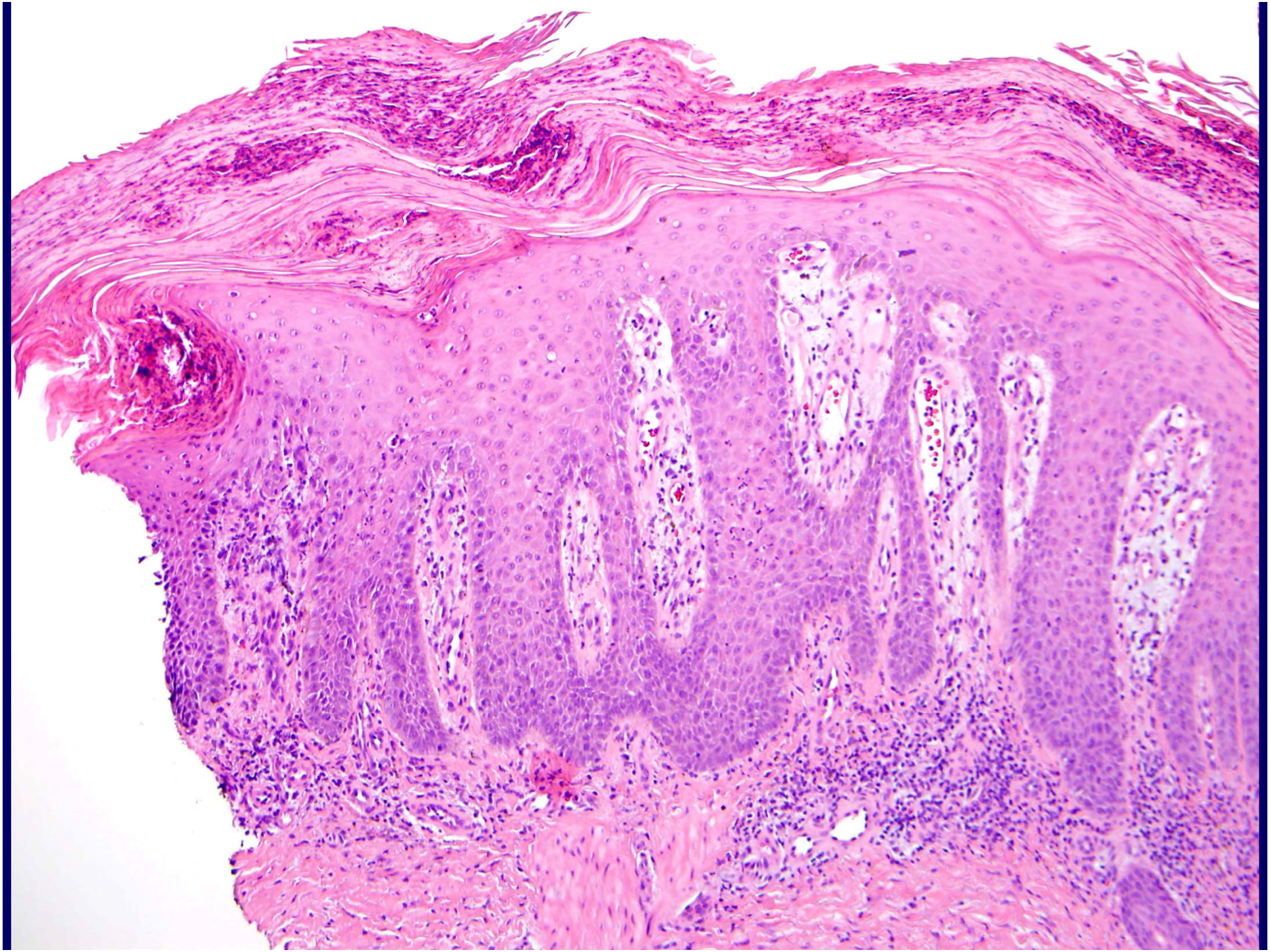
Clinical examination

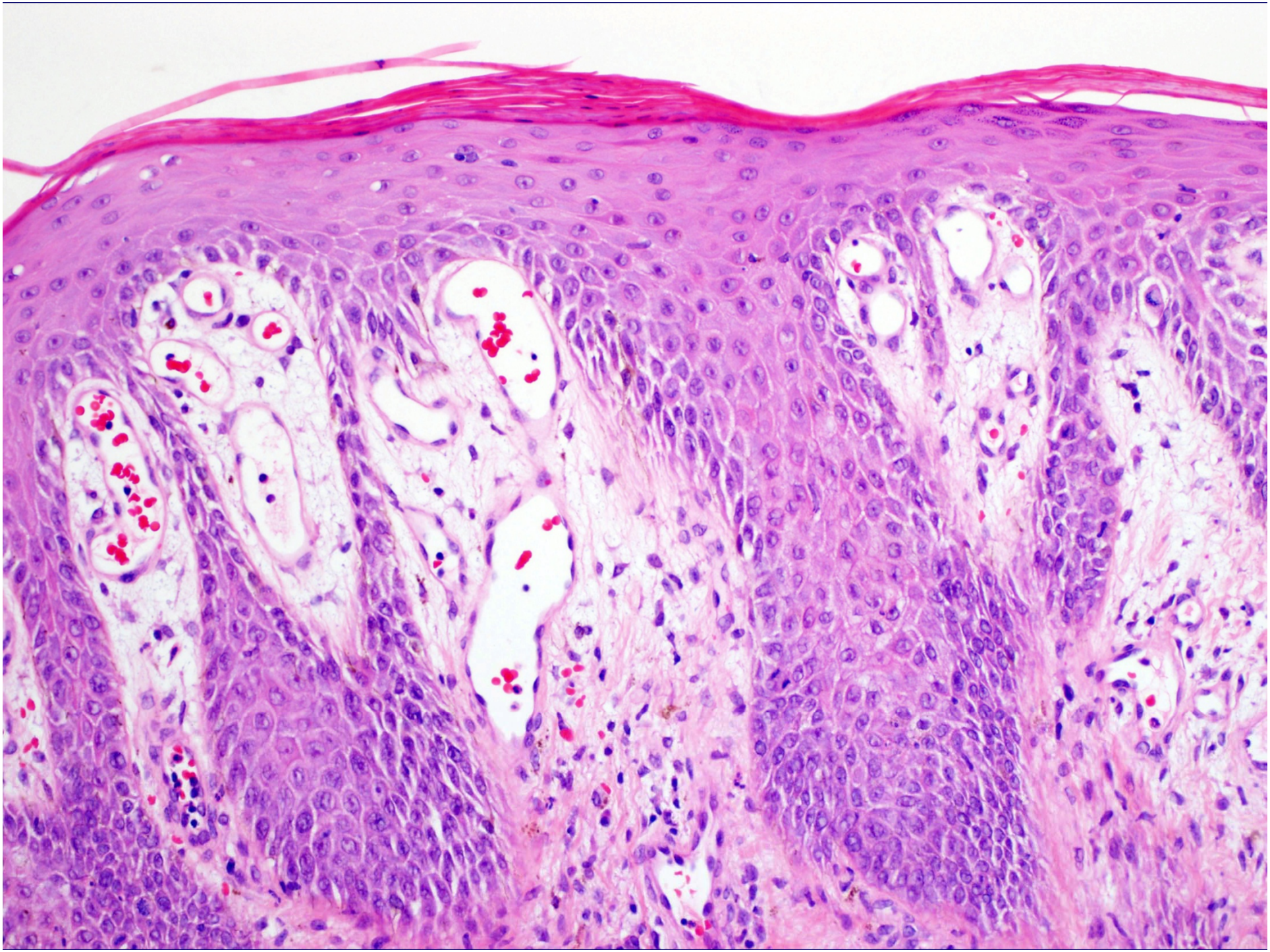
- Hyperkeratotic, crusted, erythematous plaques:
  - Hands, forearms, lower legs, elbows and knees
  - Plantar feet
- Nail pitting



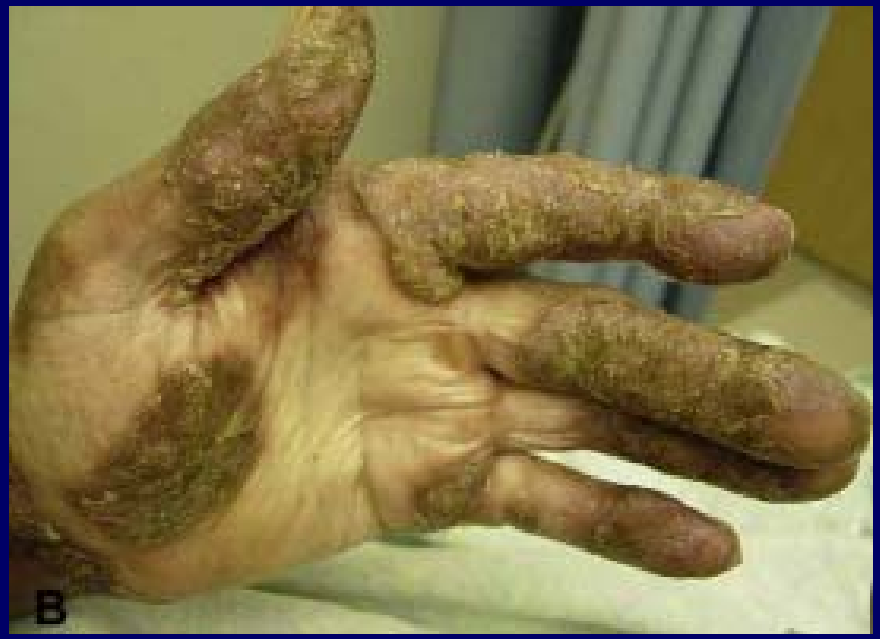
Bentley, Andea et al, J Am Acad Dermatol, 2009; 60 (3): 504-7

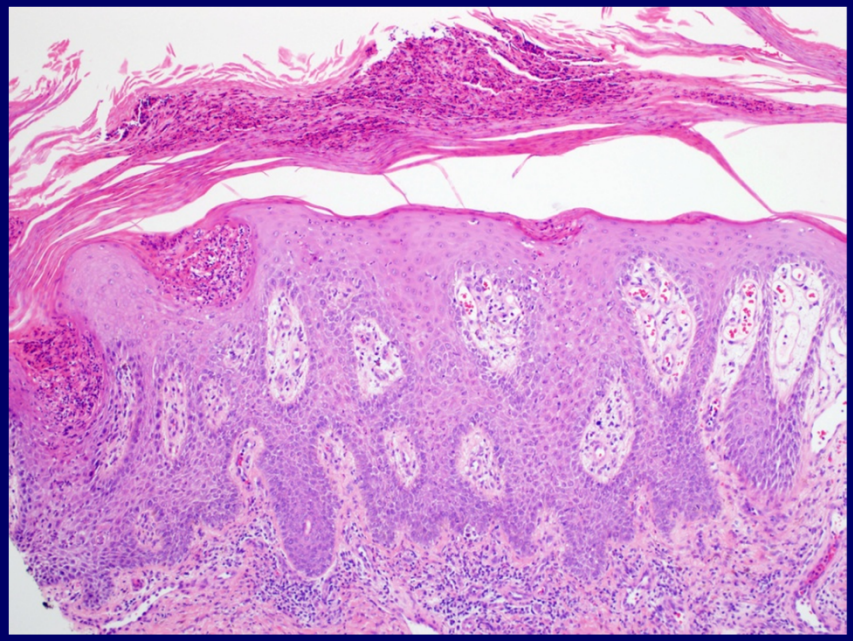




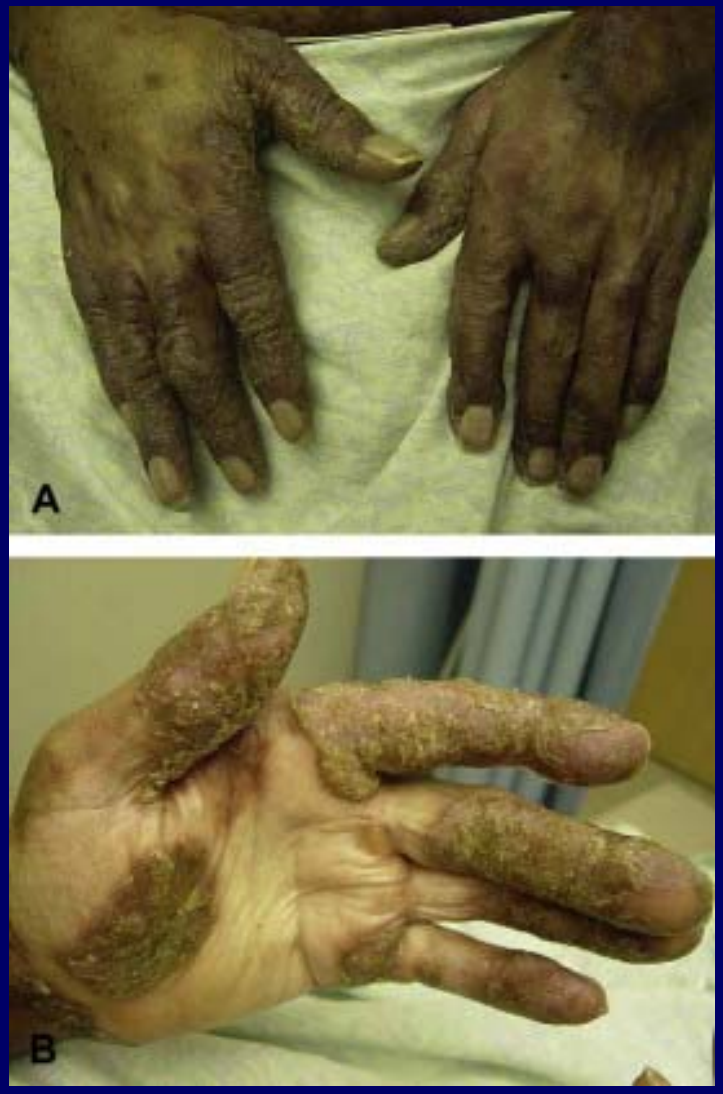


Psoriasis refractory to therapy?



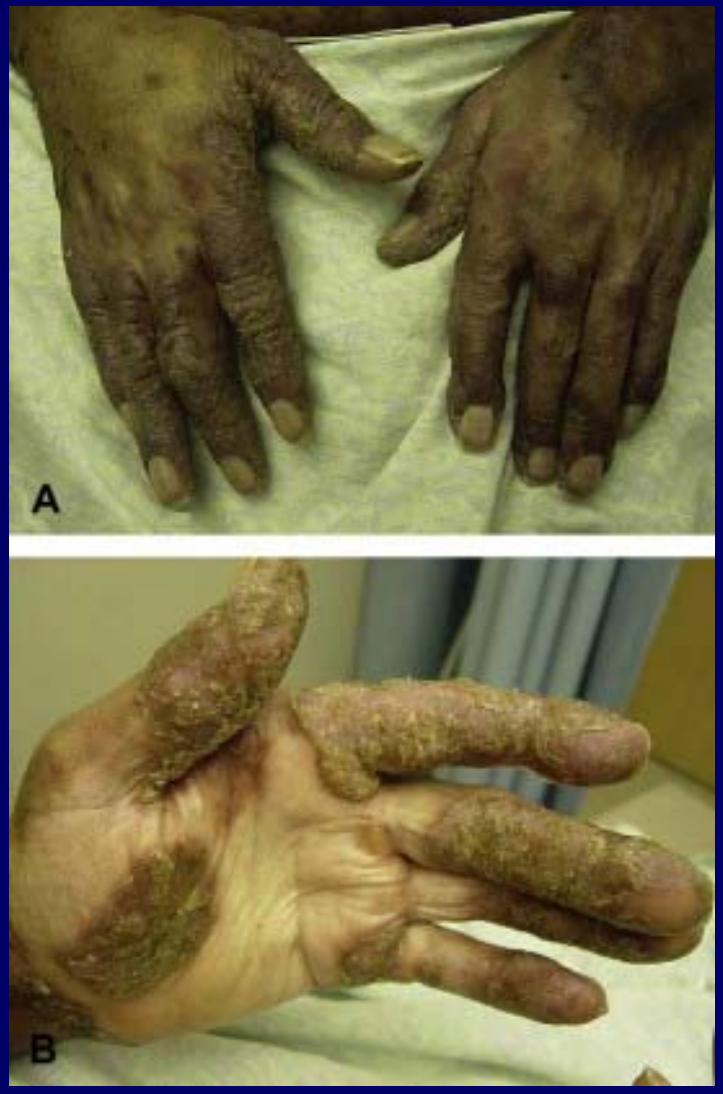


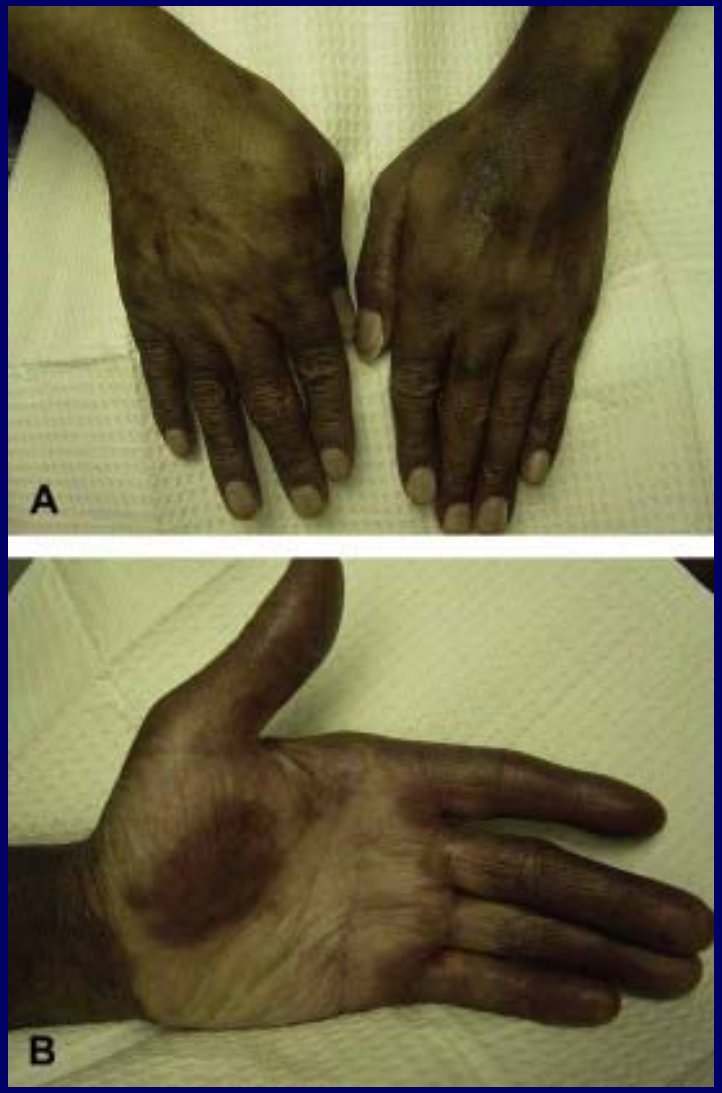
Initiation of Zn chloride 220 mg BID



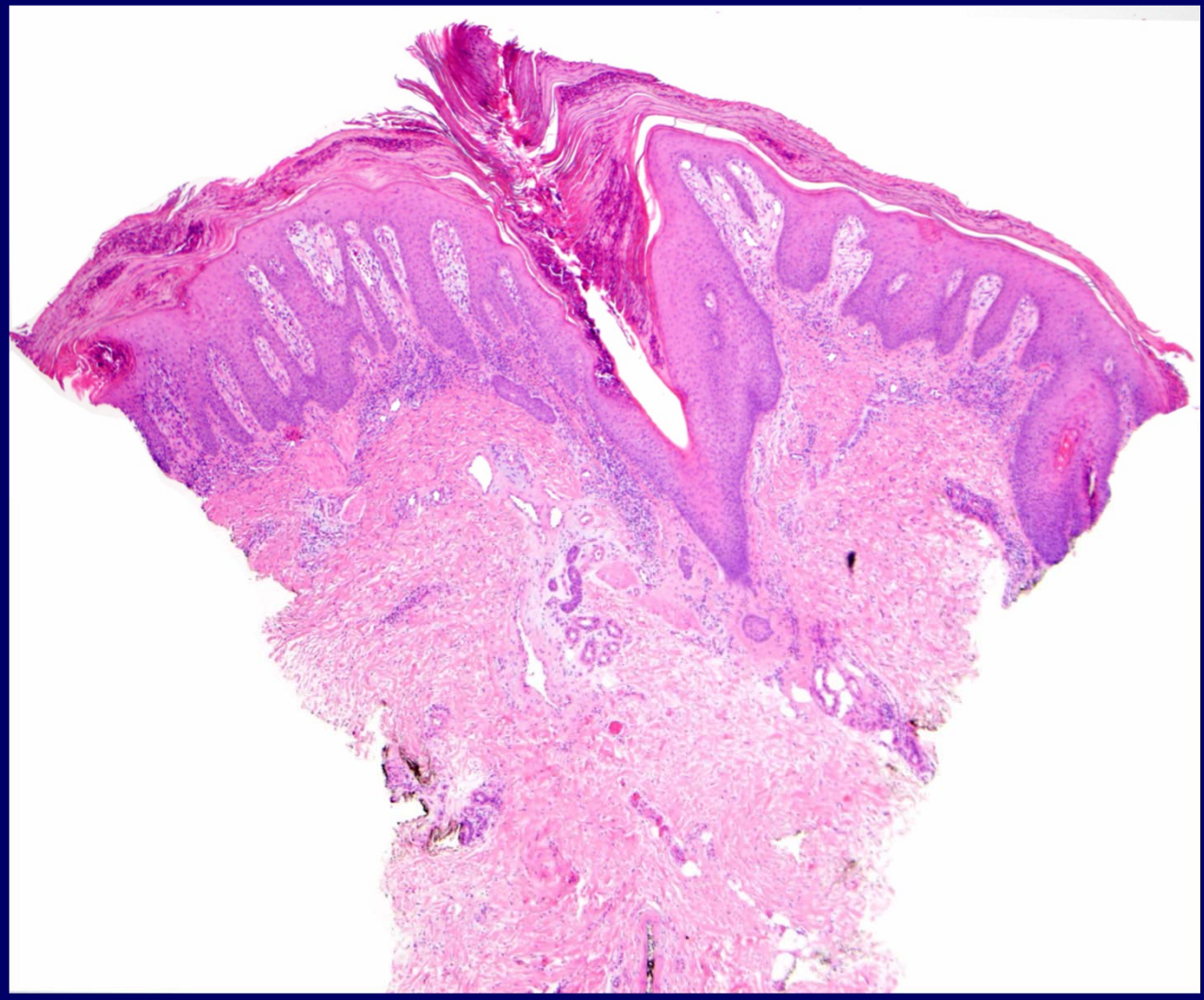
Initiation of Zn chloride 220 mg BID

Follow-up at 3 weeks





Necrolytic acral erythema



Necrolytic acral erythema

- Part of the group of necrolytic erythemas:
  - Acrodermatitis enteropathica (defects in zinc transport protein)
  - Glucagonoma syndrome (Necrolytic migratory erythema)
  - Necrolytic acral erythema
  - Hartnup disease
  - Aminoacidopathies (propionic and methylmalonic acidemia)
  - Selenium deficiency
  - Biotin deficiency
  - Glutamine synthetase deficiency (GS)

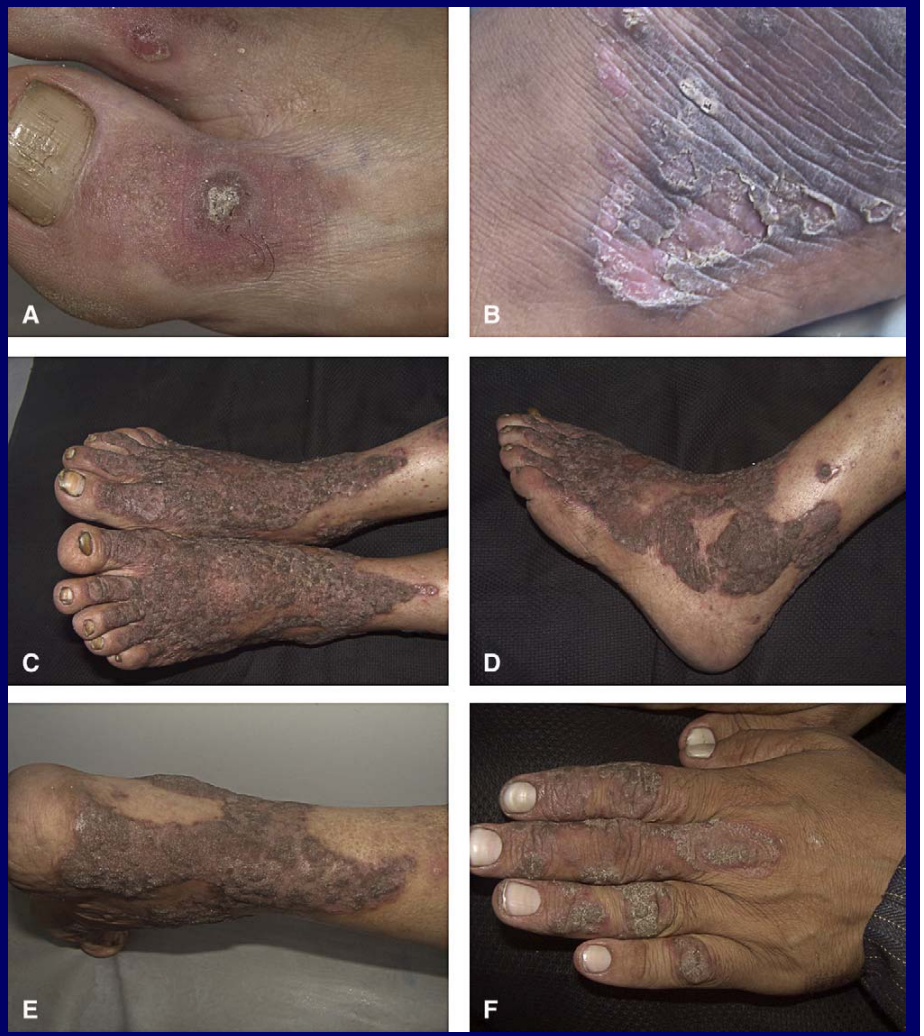
Necrolytic acral erythema

- First described by el Darouti et al. in 1996 with a series of 7 Egyptian patients
- ~70-80 cases reported
- Exclusively in patients with hepatitis C and pathognomonic for this infection
- Majority of cases in Africa (Egyptian) or African-American patients
- Zn levels usually normal

El Darouti, el Ela. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. Int J Dermatol 1996; 35:252-6
Tabibian et al. Necrolytic acral erythema as a cutaneous marker of hepatitis C: Report of two cases and review. Dig Dis Sci. 2012; 55:2735-43

Clinical presentation

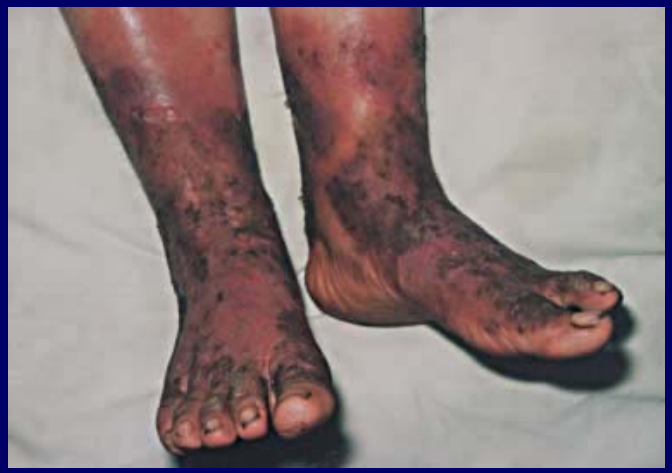
- Acral sites: Feet>Hands
- Dorsal aspects of feet and hands
- Palms, soles, nails rarely involved
- Non-acral involvement: trunk, upper extremities
- Peri-orificial areas and oral mucosa usually spared

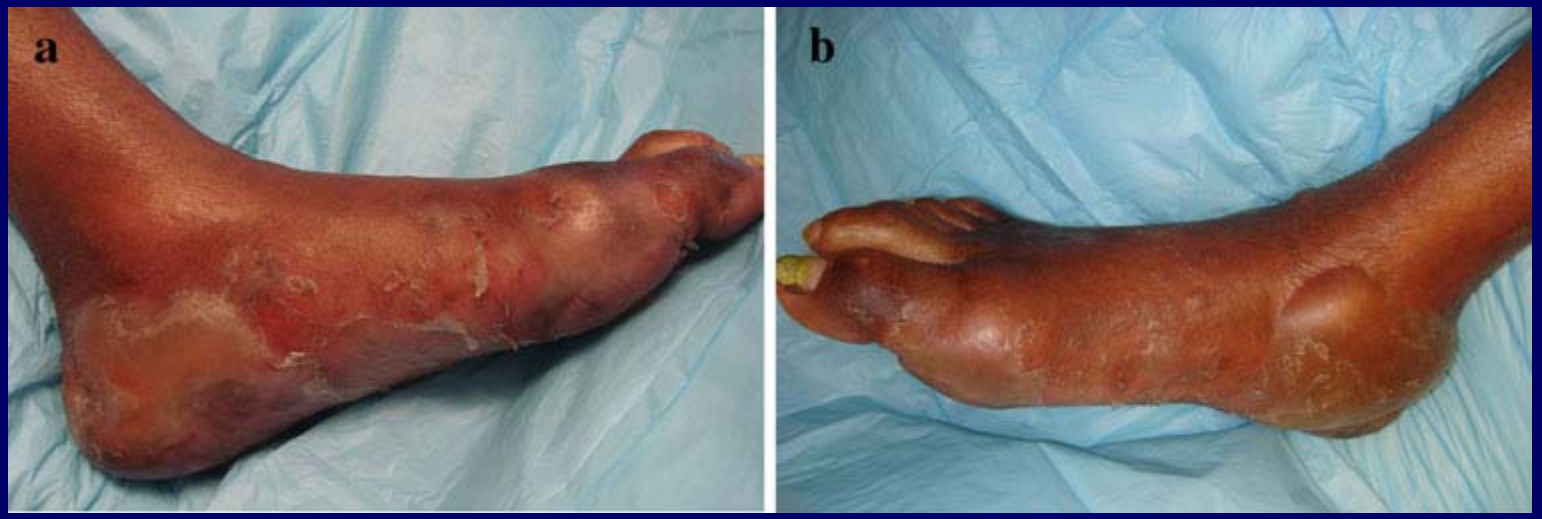


El Darouti, el Ela. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. Int J Dermatol 1996; 35:252-6
Abdallah et al. Necrolytic acral erythema: A cutaneous sig of hepatitis C virus infection. J Am Acad Dermatol 2005; 53:247-51

Early lesion

- Acute lesions: erythema with vesicles and bullae





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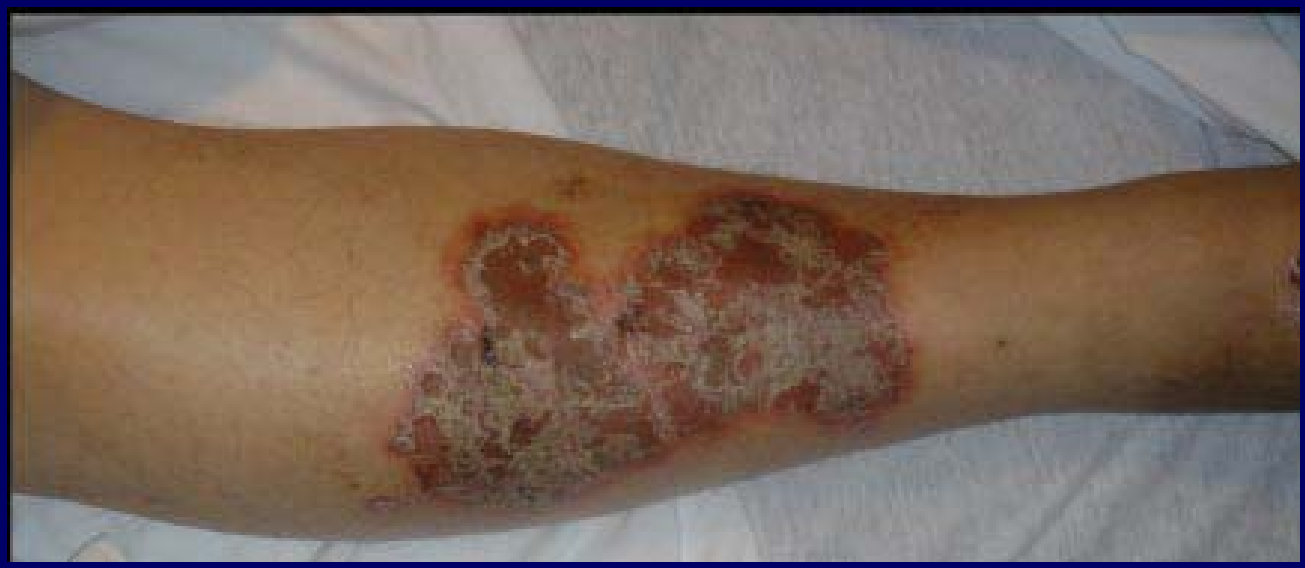
Tabibian et al. Necrolytic acral erythema as a cutaneous marker of hepatitis C: Report of two cases and review. Dig Dis Sci. 2012; 55:2735-43

Clinical presentation

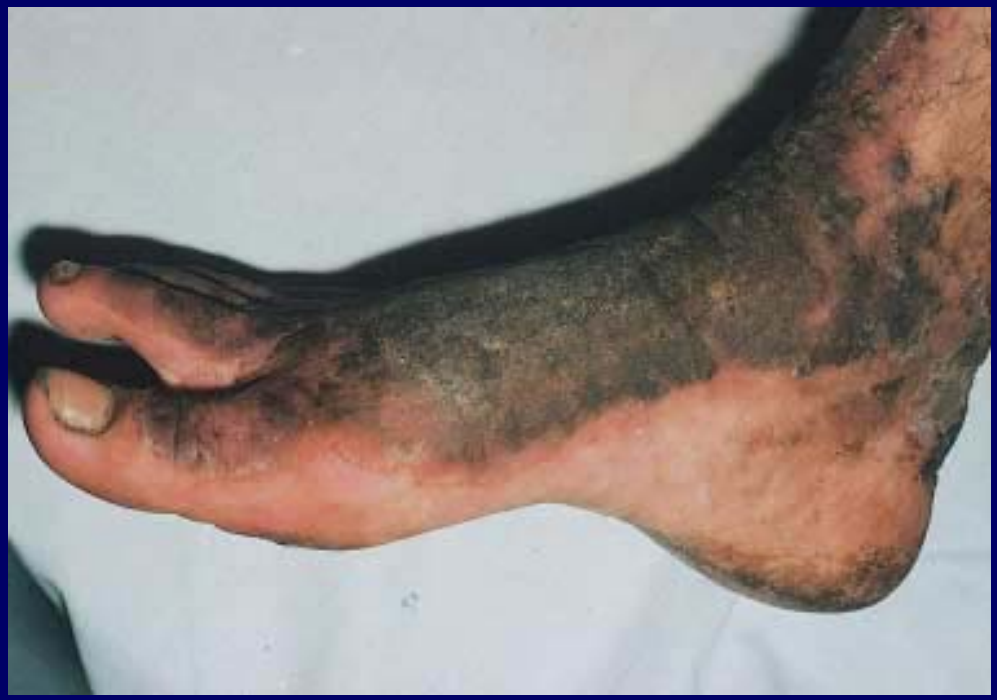
- Dark red rim



Geria AN et al. Necrolytic acral erythema: A review of the literature. Cutis; 2009; 83:309-14

Late lesion

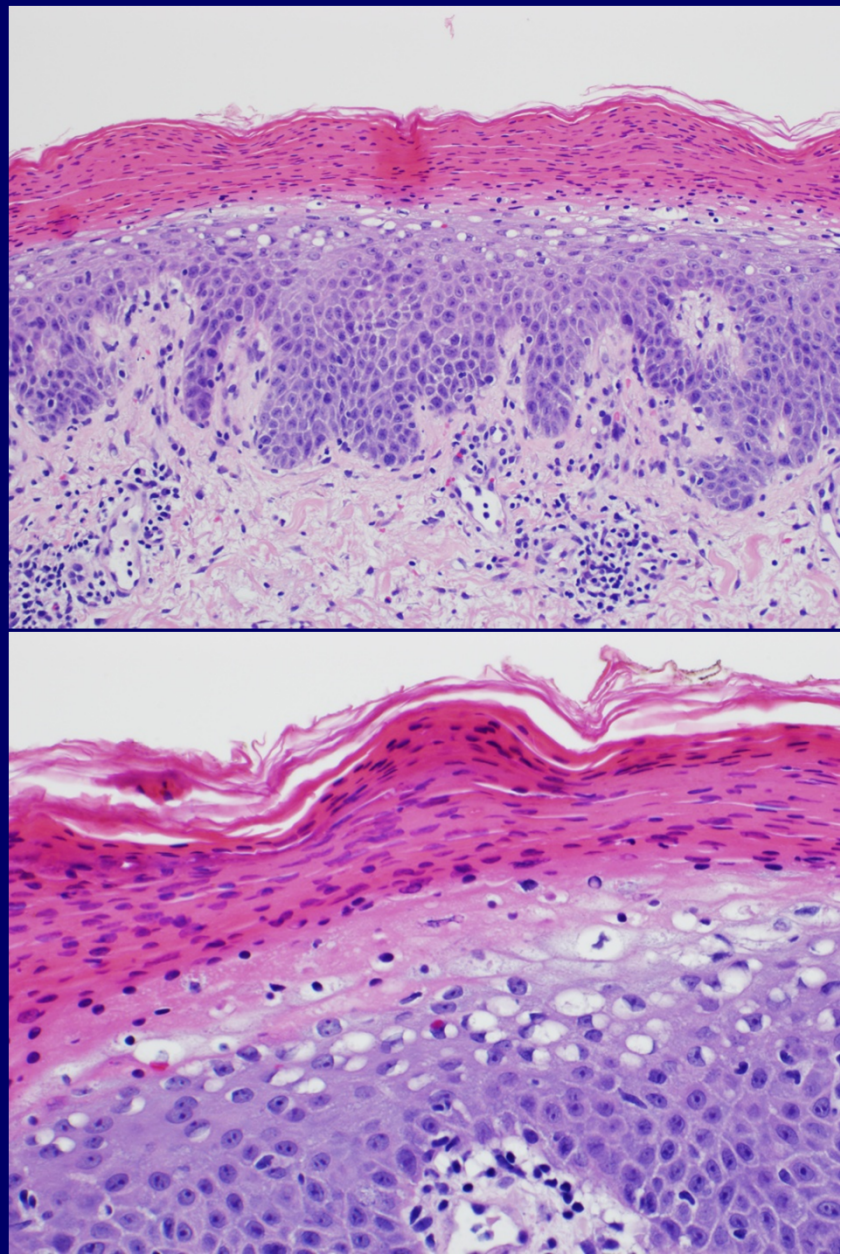
- Plaques with thick scale, erosions and crusting.



Nofal AA et al. Necrolytic acral erythema: a variant of necrolytic migratory erythema or a distinct entity? Int J of Dermatol 2005; 44:916-21

Histology -initial

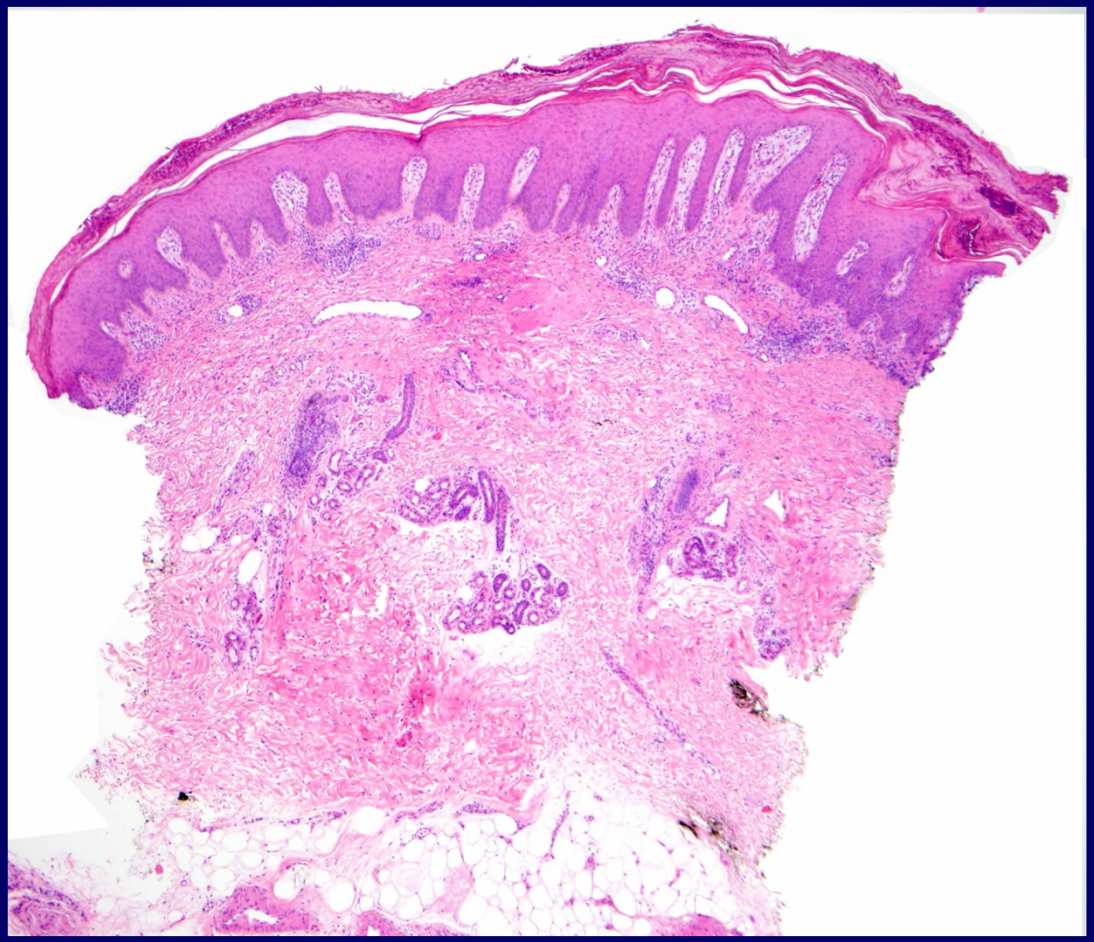
- Parakeratosis
- Pale keratinocytes
- Cytoplasmic vacuolization
- Epidermal necrosis.



El Darouti, el Ela. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. Int J Dermatol 1996; 35:252-6

Histopathology -late

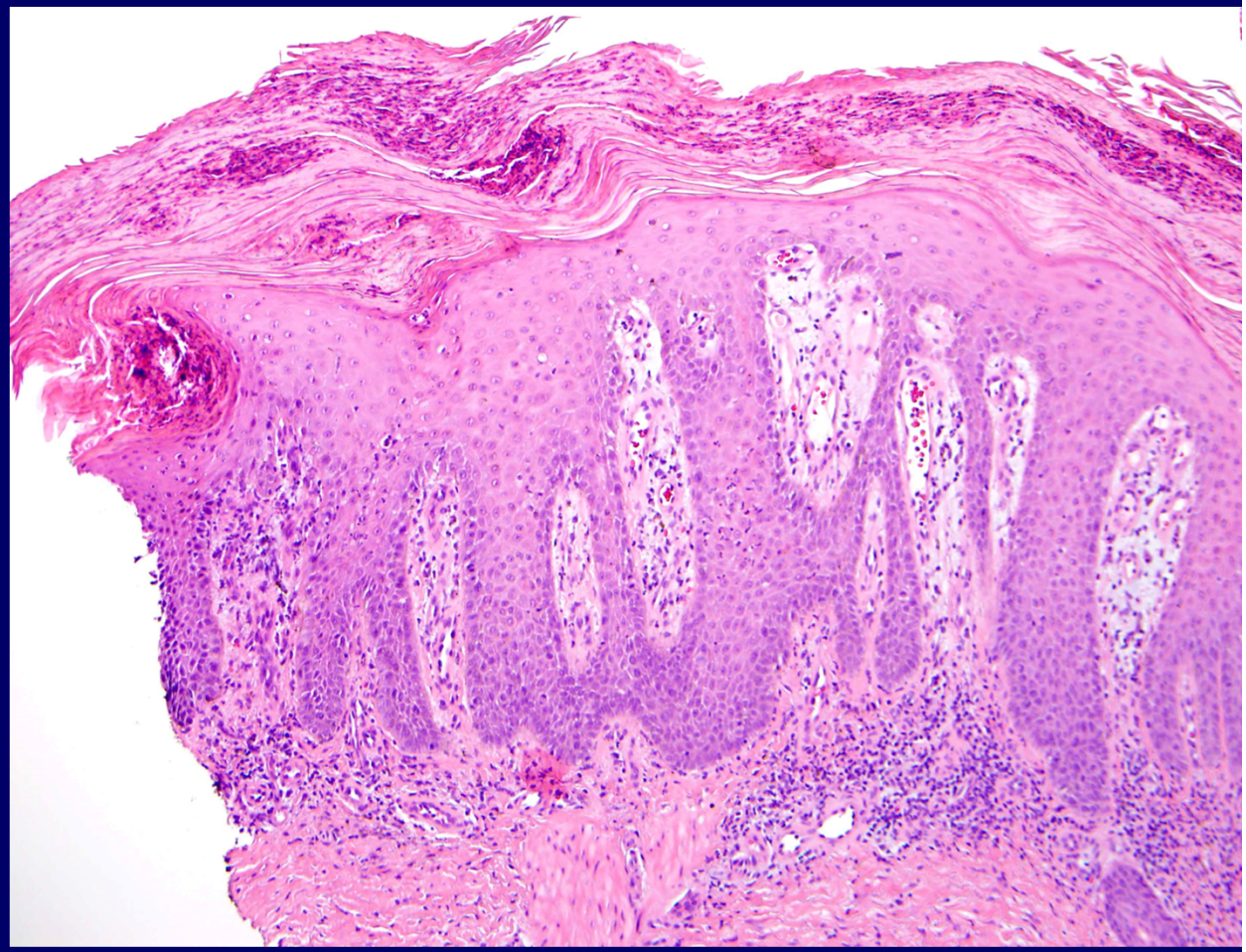
- Psoriasiform hyperplasia



El Darouti, el Ela. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. Int J Dermatol 1996; 35:252-6

Histopathology -late

- Parakeratosis
- Neutrophils in the epidermis
- Apoptotic cells
- No pallor



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Pathogenesis of cutaneous lesions

- Not clear but probably multifactorial
- Hepatocellular dysfunction
- Hyperglucagonemia
- Hypoaminoacidemia
- Hypoalbuminemia
- Zinc deficiency: occult even with normal serum levels
- Diabetes

Treatment

- Zn
  - Response usually within several weeks
- Treatment of underlying Hep C
  - Leads to durable remission
  - Skin results even when treatment is not effective for the hepatitis

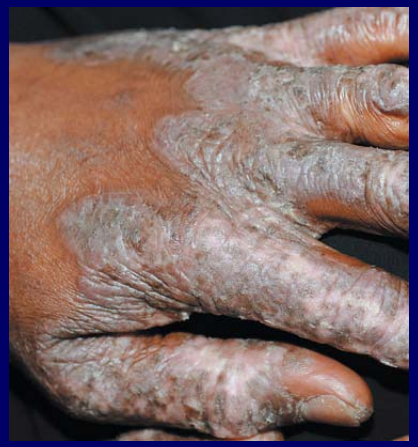
Differential diagnosis

Psoriasis

- Similar clinical and pathologic presentation
- Does not respond to Zn and has no association to Hep C
- Potential for confusion:
  - Nofal et al: 2 of 5 patients dx initially as psoriasis
  - Fielder et al: 1 patient initially dx as psoriasis on clinical and histo exam
  - Kapoor et al: 1 patient dx as psoriasis for 8 years clinical and histo exam, response to Zn therapy

Nofal AA et al. Necrolytic acral erythema: a variant of necrolytic migratory erythema or a distinct entity? Int J of Dermatol 2005; 44:916-21
Fielder LM et al. Necrolytic acral erythema: Case report and review of the literature
Kapoor R et al. Necrolytic acral erythema. N Engl J Med. 2011; 364: 1475-6

NAE/ Psoriasis

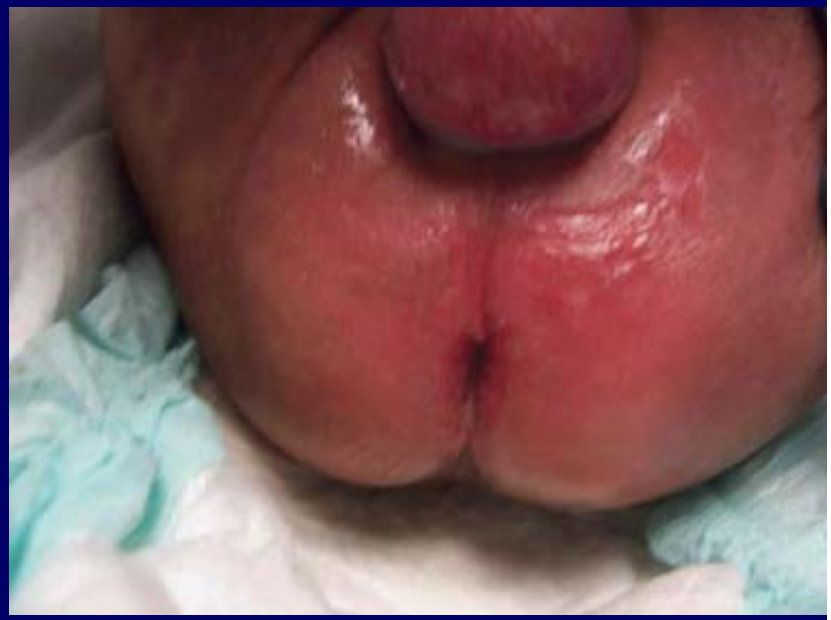


Zn therapy

Kapoor R et al. Necrolytic acral erythema. N Engl J Med. 2011; 364: 1475-6

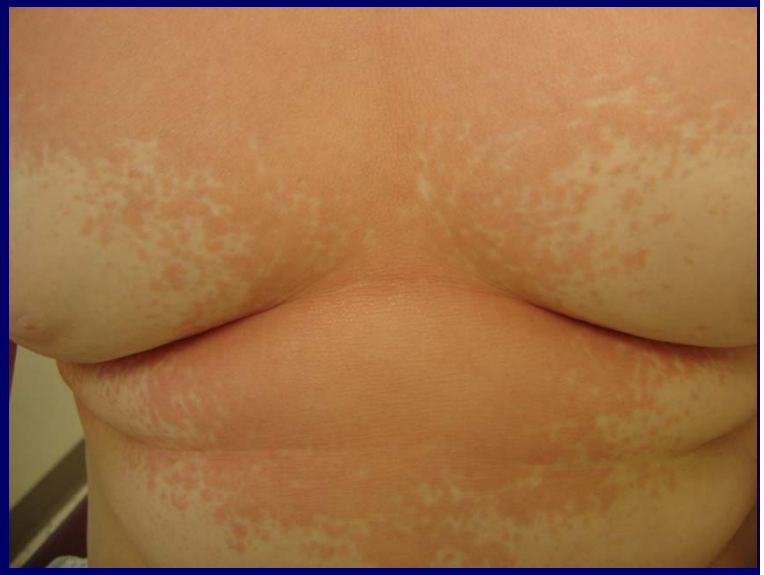
Acrodermatitis enteropathica

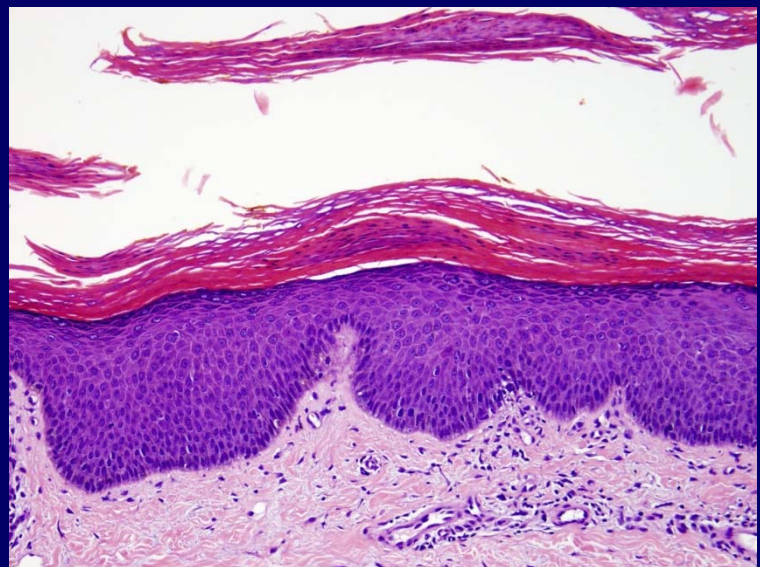
- Similar histology with NAE
- Caused by a defect in zinc transport protein ZIP4.
- No association with Hep C
- Presents in infancy
- Periorificial distribution
- Low Zn levels



Pityriasis Rubra Pilaris

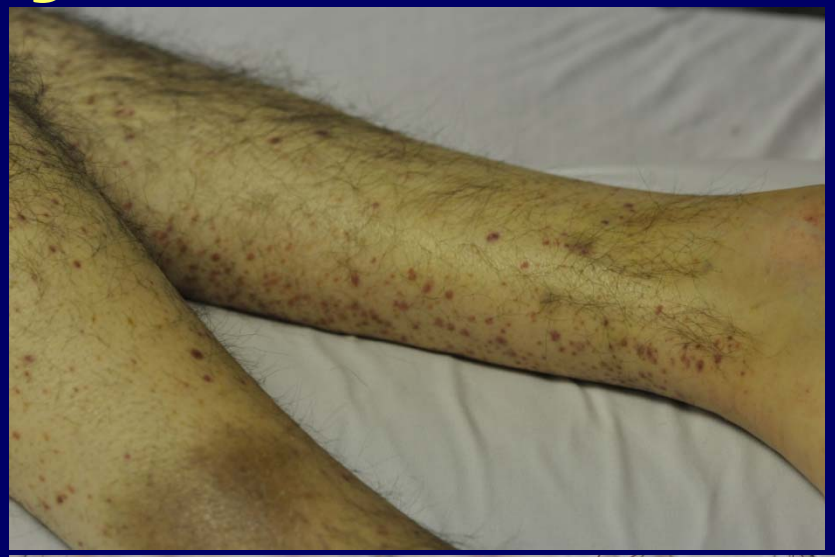
- No association with Hep C
- Small follicular papules with a central plug
- Perifollicular erythema
- Islands of sparing

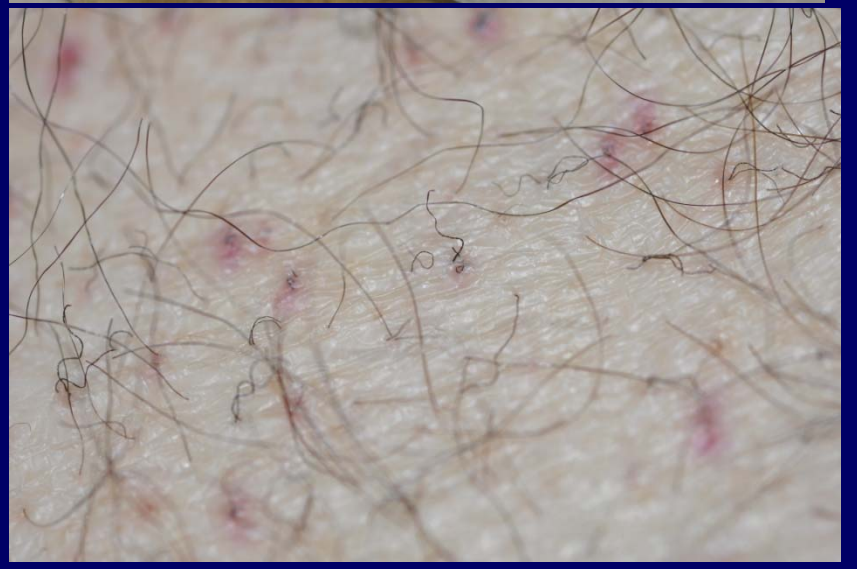




Scurvy

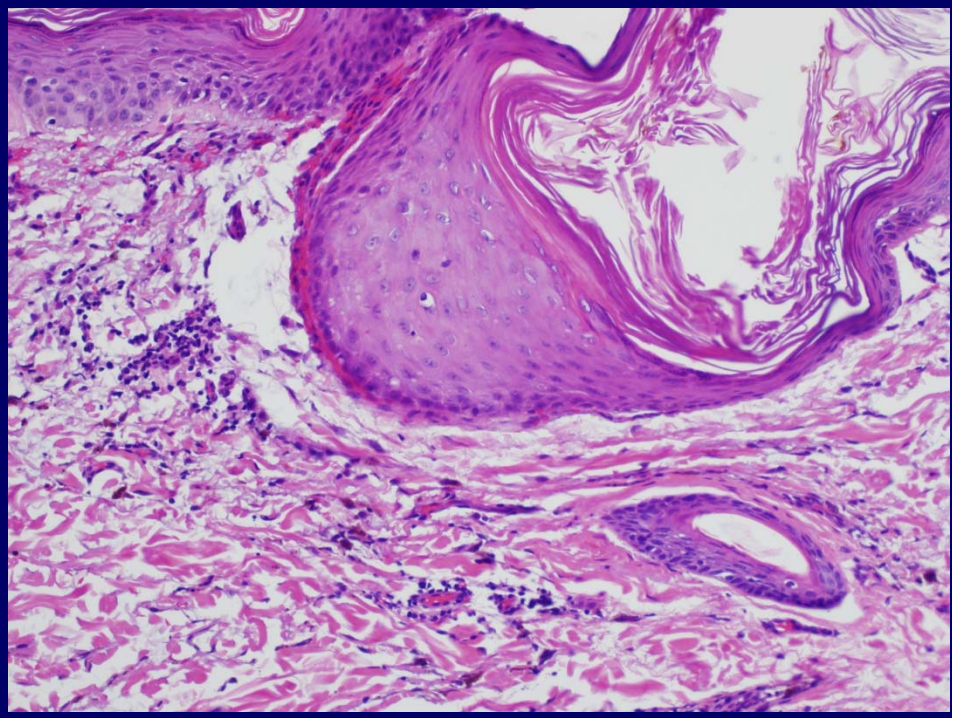
- Vitamin C deficiency
- Perifollicular hemorrhage
- Subungual hemorrhages
- Bleeding gums
- Follicular hyperkeratosis with corkscrew hairs





Scurvy

- Follicular dilatation
- Keratin plugging
- Perifollicular hemorrhages
- Chronic inflammation
- Hemosiderin deposition



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Case 8

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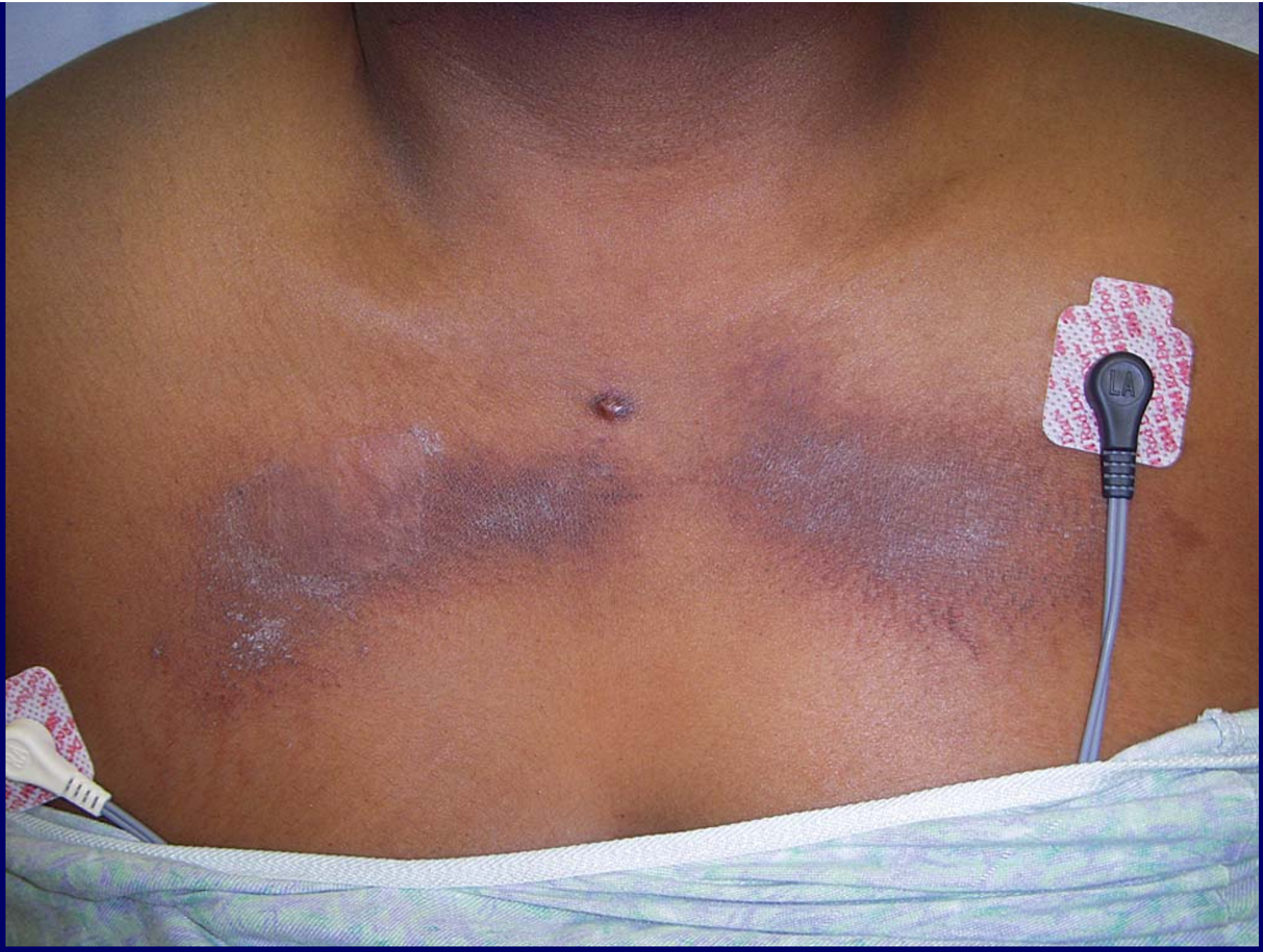
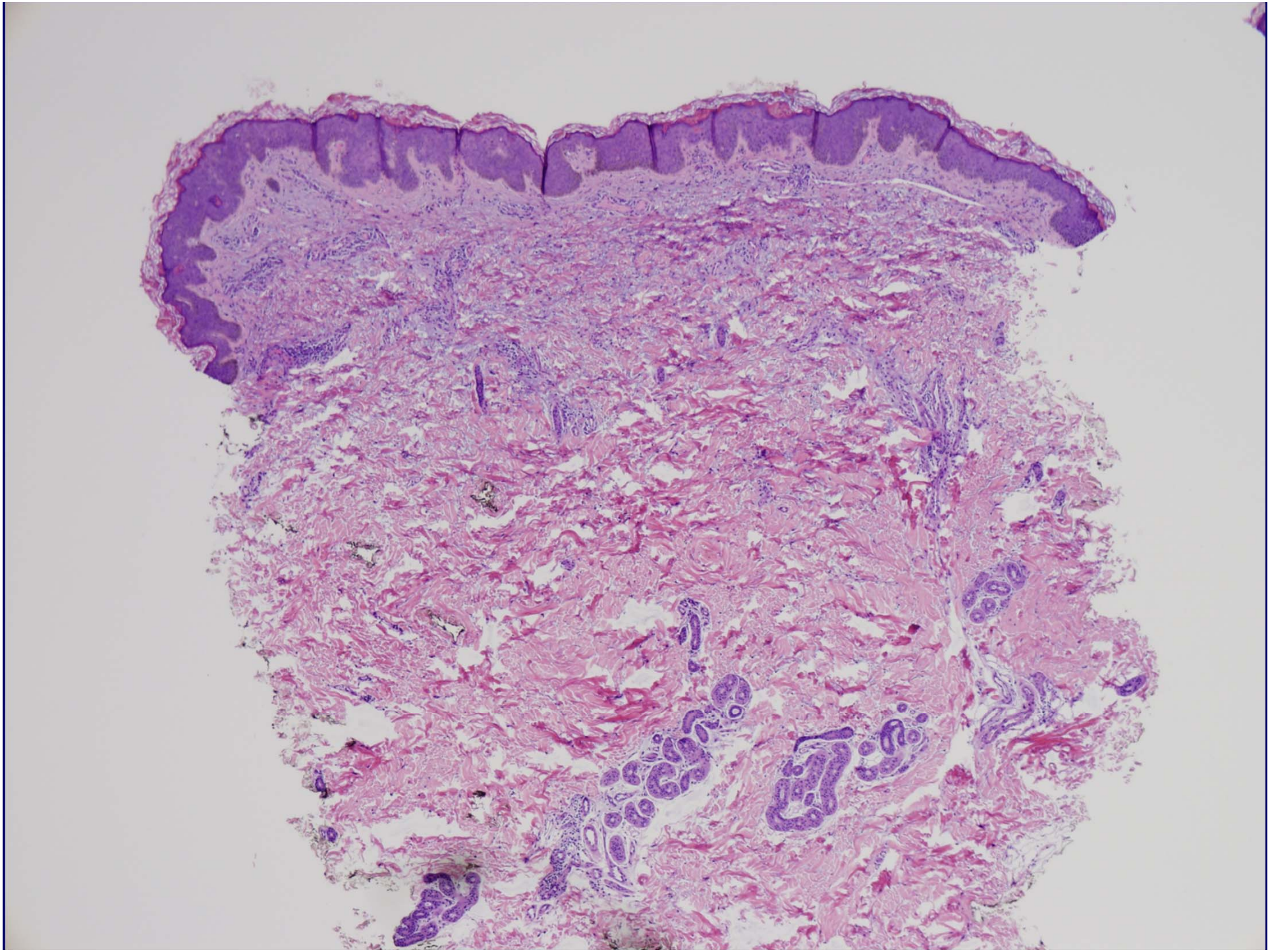
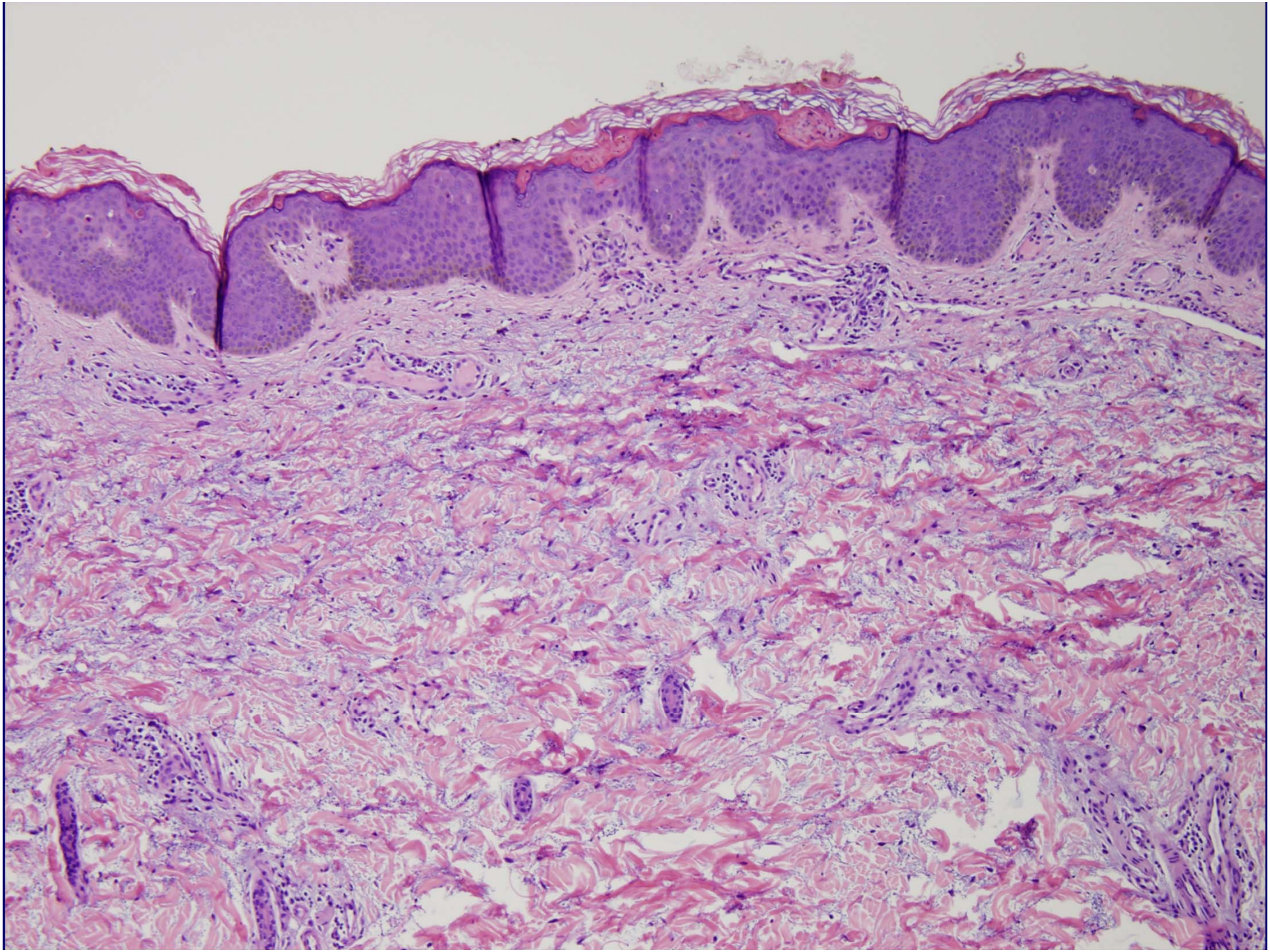
Clinical history

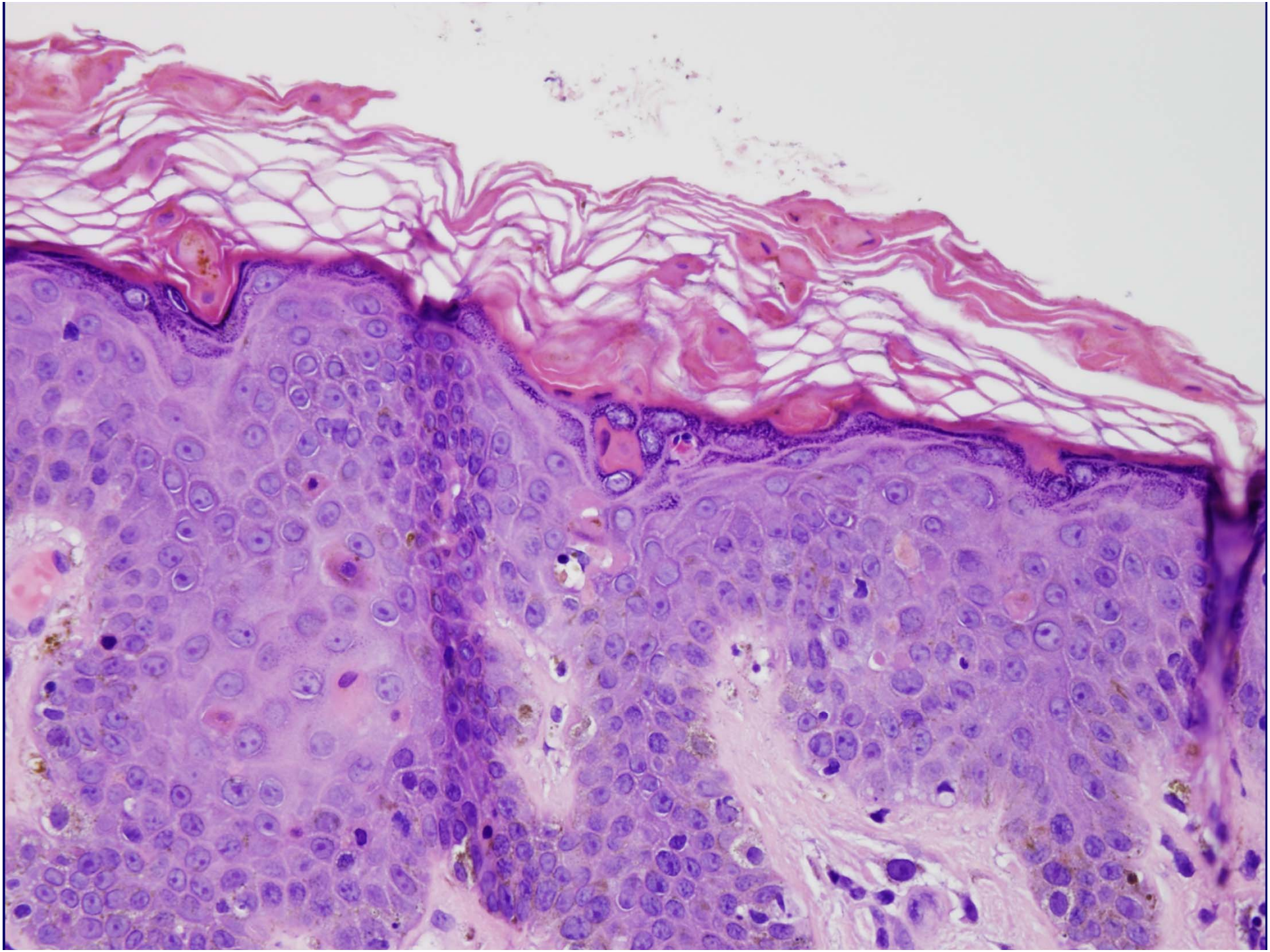
- 26-year-old woman
- Fever, leukocytosis, arthralgias
- Skin rash consisting of pruritic, hyperpigmented papules and plaques with a distinct linear and rippled morphology
- Negative:
  - ANA
  - anti-cyclic citrullinated protein
  - RF
- Elevated: ferritin

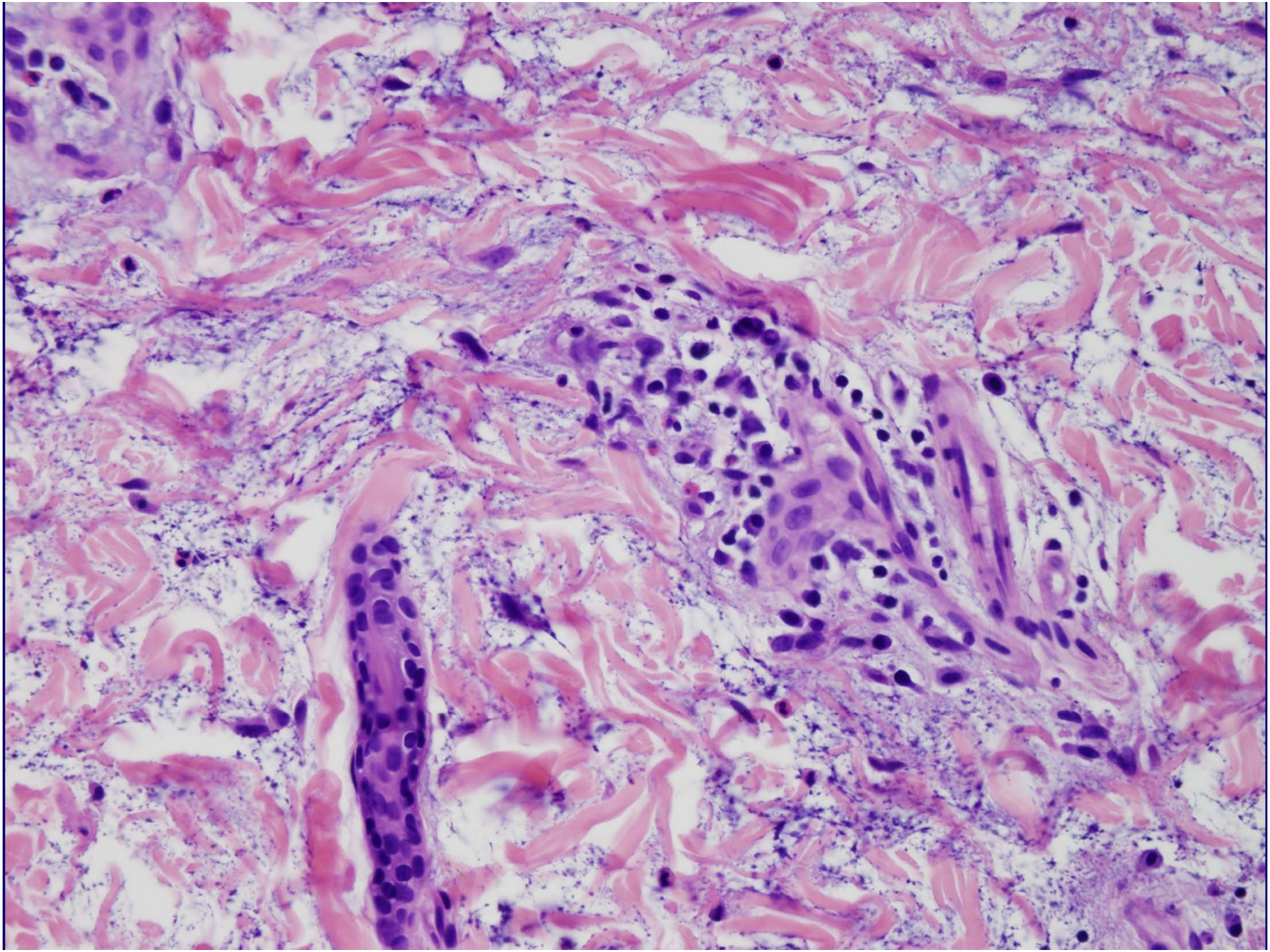


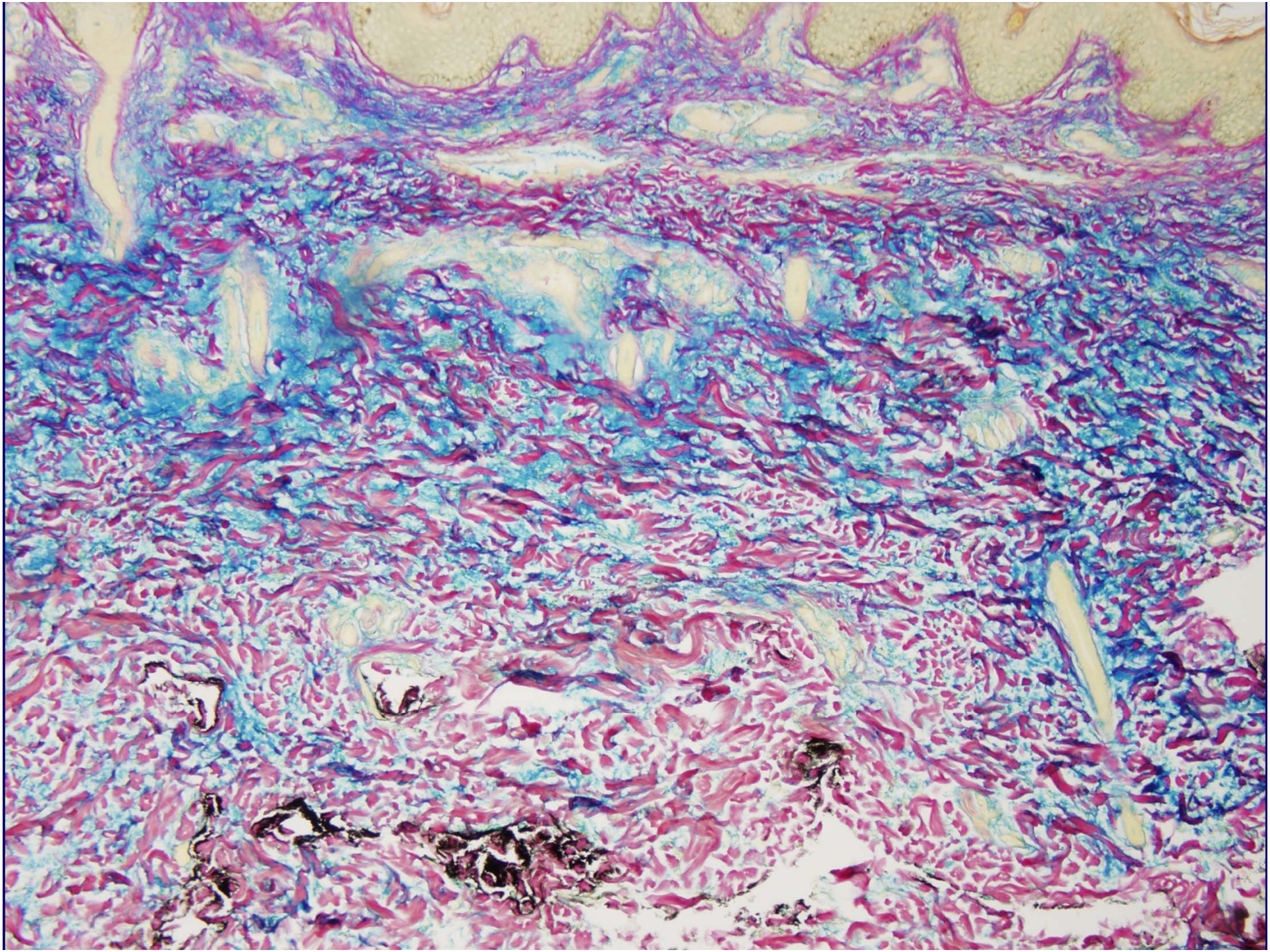
Woods MT, Andea AA. *Am J Dermatopathol*. 2011, 33:736-9



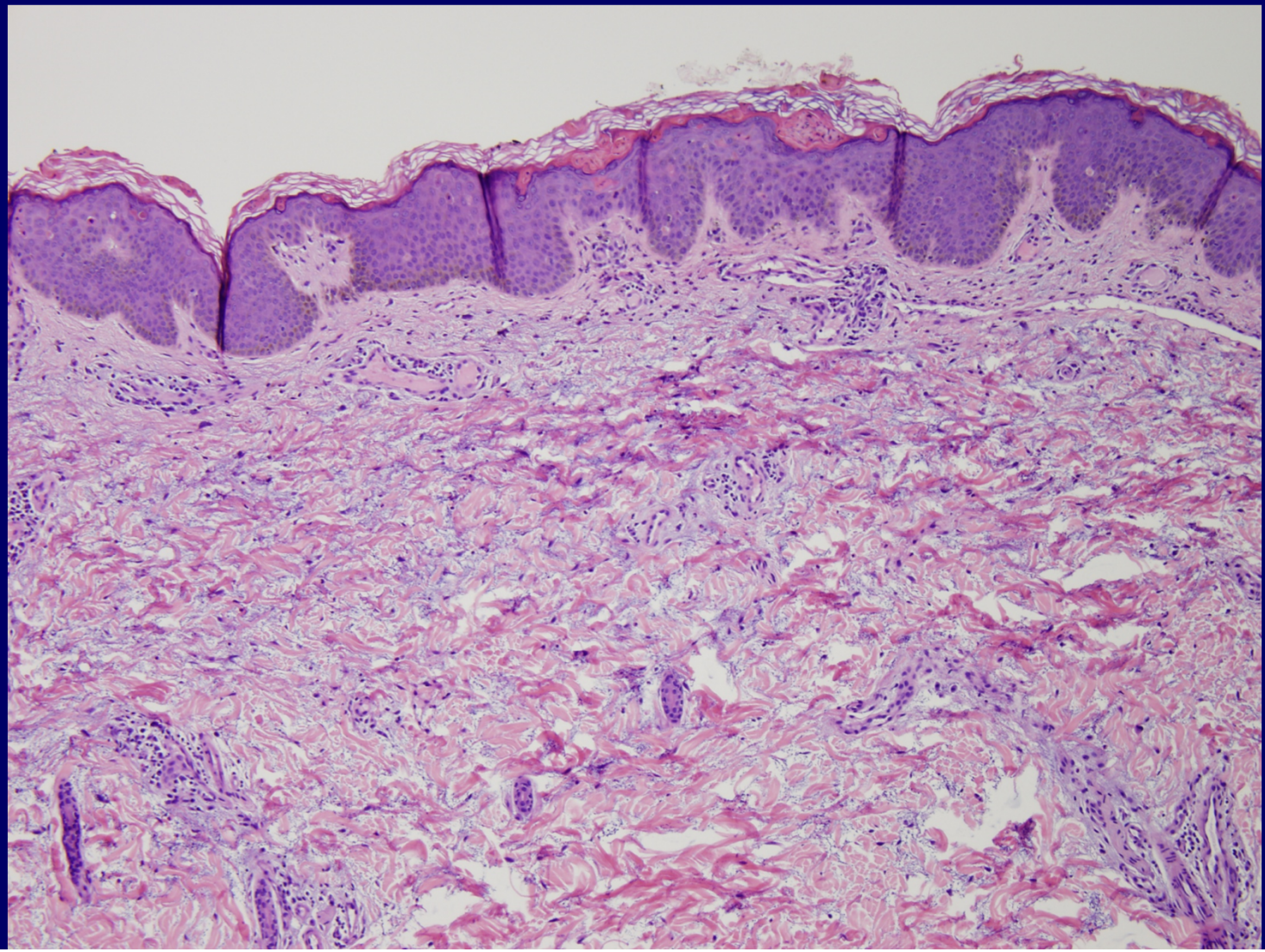








Adult onset Still disease



Adult onset Still disease

- Still disease: Systemic-onset juvenile idiopathic arthritis
- Systemic inflammatory disorder
- Unknown etiology
- High fever
- Polyarthralgia
- Lymphadenopathy
- Rash

Adult onset Still disease

Yamaguchi criteria

Major	Minor
• High fever >39C – Arthralgia – Rash – Leukocytosis	• Sore throat – Lymphadenopathy/ Splenomegaly – Liver dysfunction – Negative RF and ANA

•DX: At least 5 criteria including 2 major

Adult onset Still disease

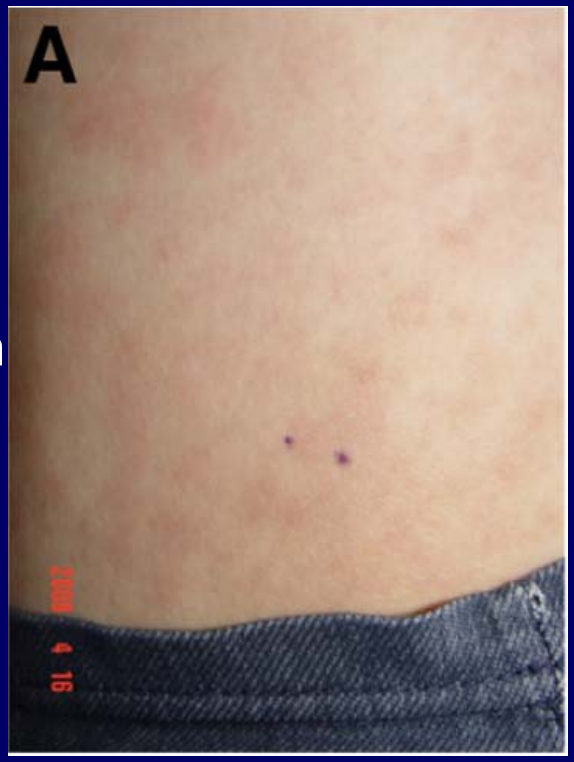
- Additional features:
  - Elevated ferritin: marker of disease activity
  - Elevated IL-6, IL-18
  - Occasionally reactive hemophagocytic syndrome
- Exclusion of infections, other rheumatologic diseases or malignancy
- Delayed dx is common

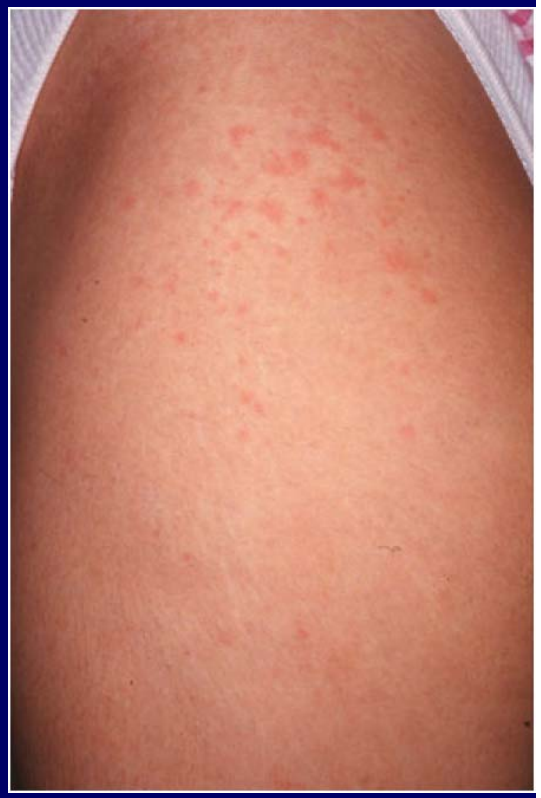
Skin rash

- Two groups
  - Typical: evanescent “salmon-pink”, major dx criterion
  - Atypical: pruritic persistent eruption

Evanescent rash

- ~85% of patients
- Salmon-pink, macular, or maculopapular
- Appears and disappears in parallel with the fever episodes
- Extremities and trunk

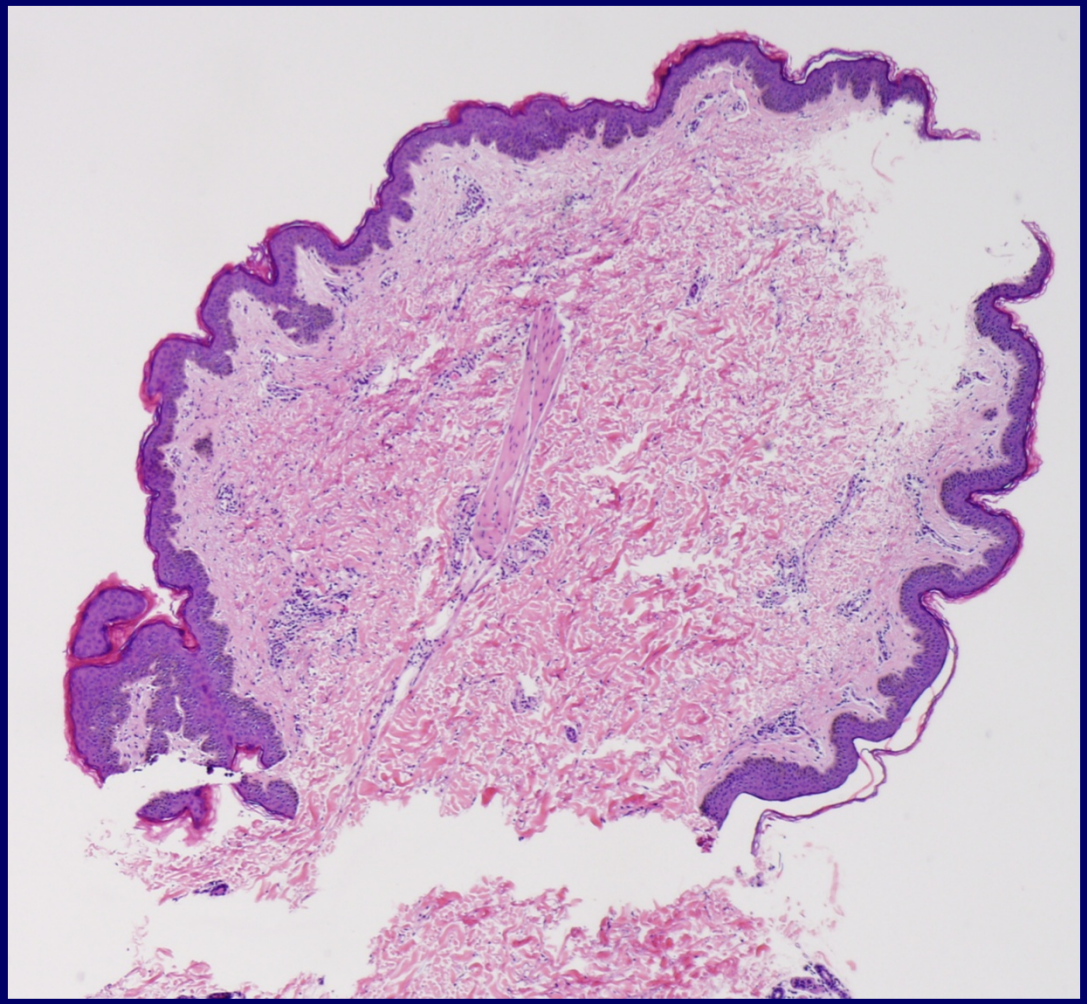




Yamamoto T. Cutaneous manifestations associated with adult-onset Still disease. *Rheumatol Int*. 2012, 32:2233-7
Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

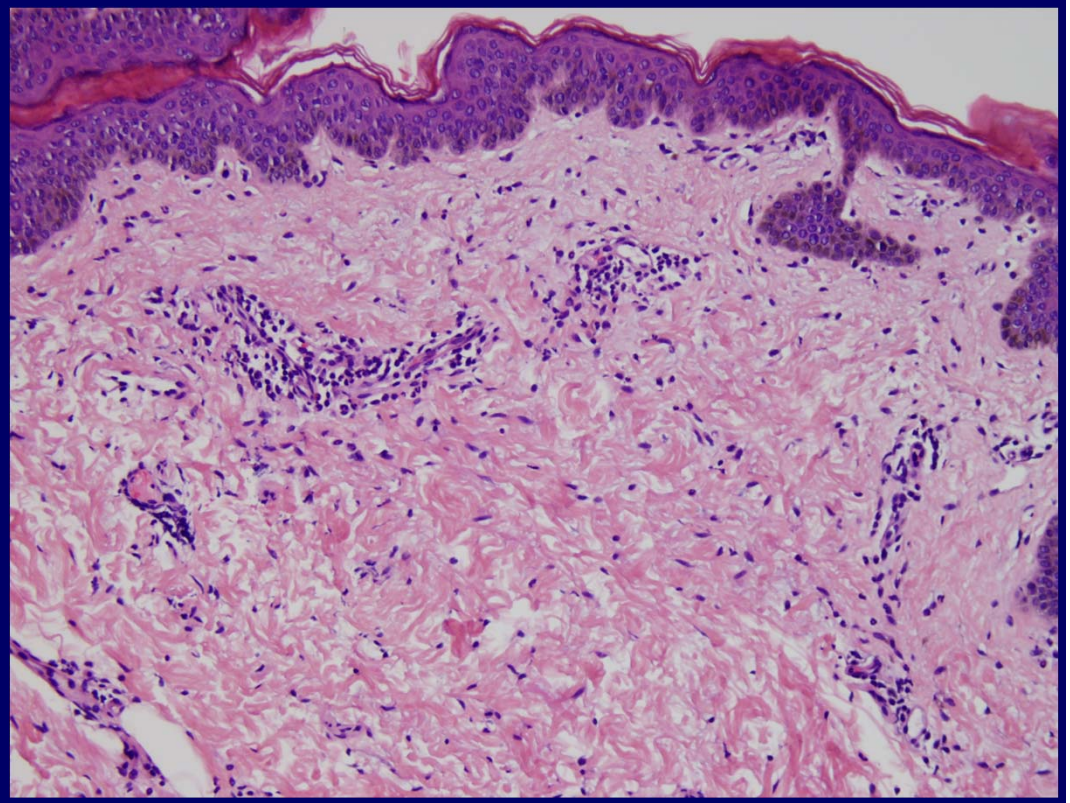
Evanescent rash

- Mild superficial perivascular dermatitis



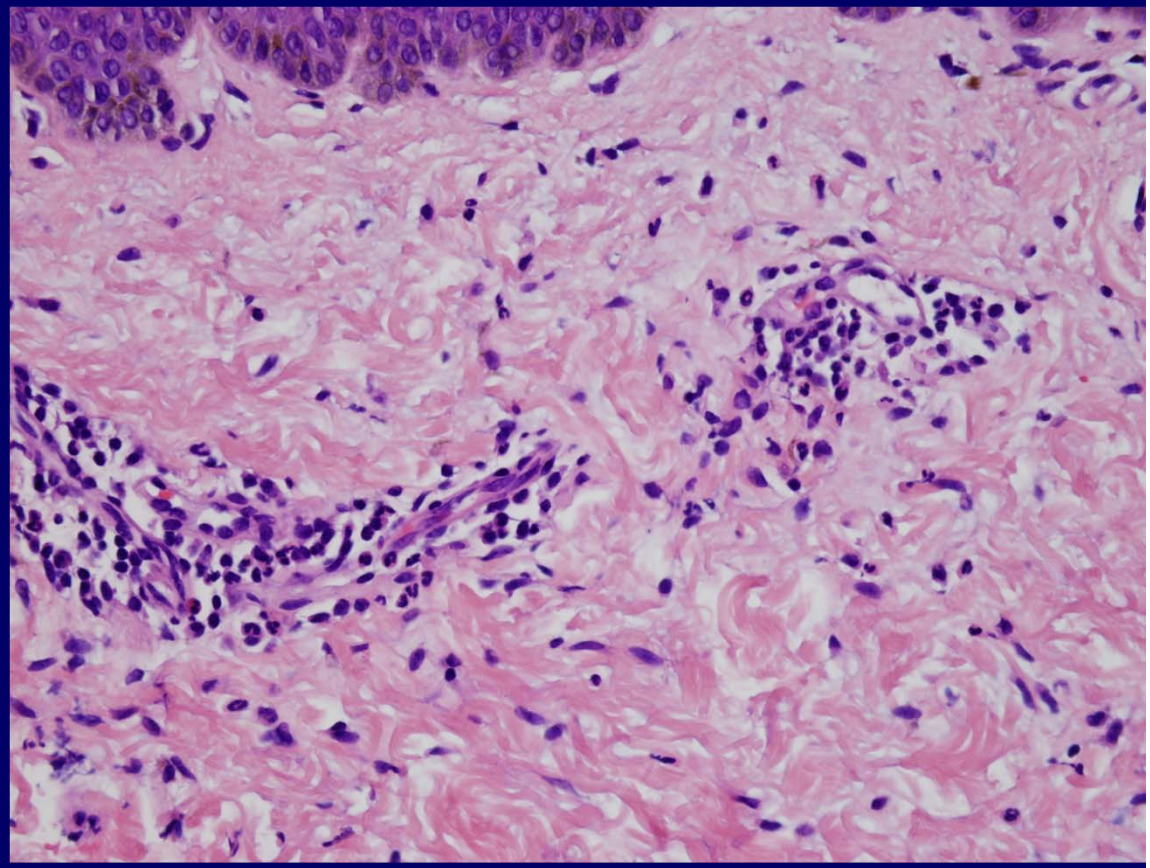
Evanescent rash

- Mild superficial perivascular dermatitis
- Uninvolved epidermis



Evanescent rash

- Lymphocytes, occasional neutrophils



Pruritic Persistent Eruption

- Atypical rash has received little attention
- ~65 cases reported so far

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Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

Pruritic Persistent Eruption

- Usually present at disease onset
- Pruritic persistent papules or plaques
- Trunk, neck, face, extensor extremities
- Few morphologies

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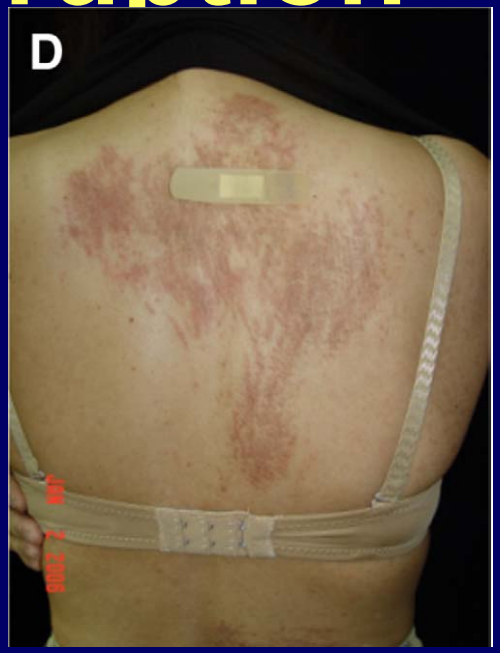
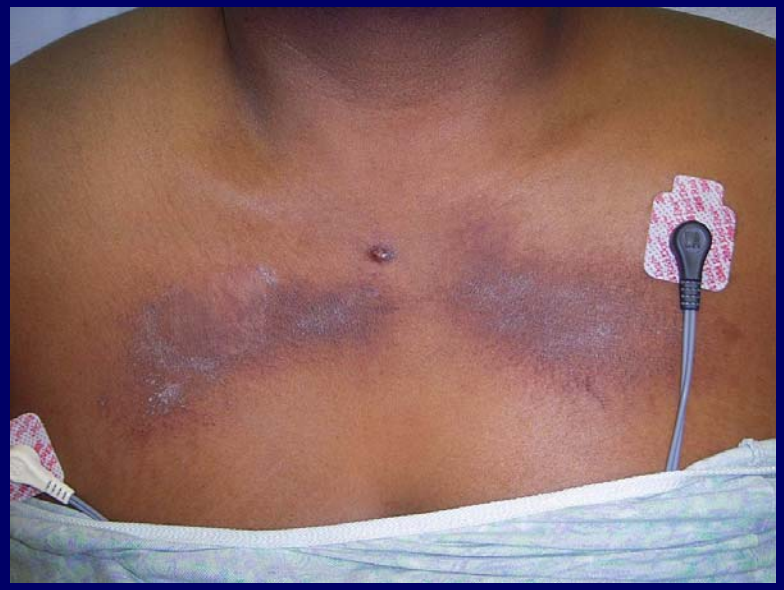
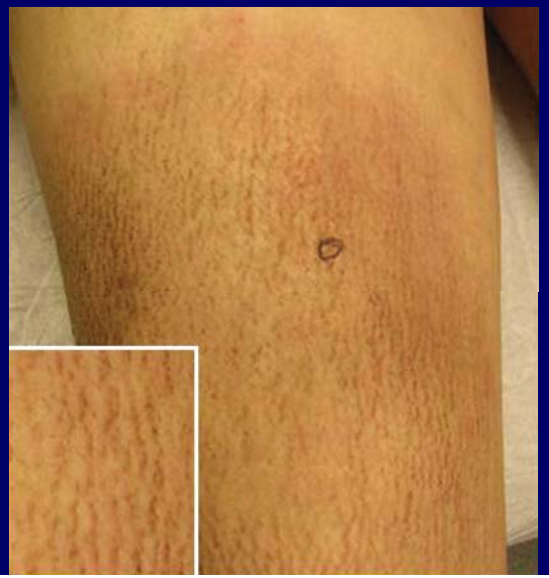
Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

Pruritic Persistent Eruption

- Plaques with hyperpigmented papules with linear/ rippled configuration







Wolgamot G et al. Unique histopathologic findings in a patient with adult-onset Still disease. *Am J Dermatopathol*. 2007, 29:194-6
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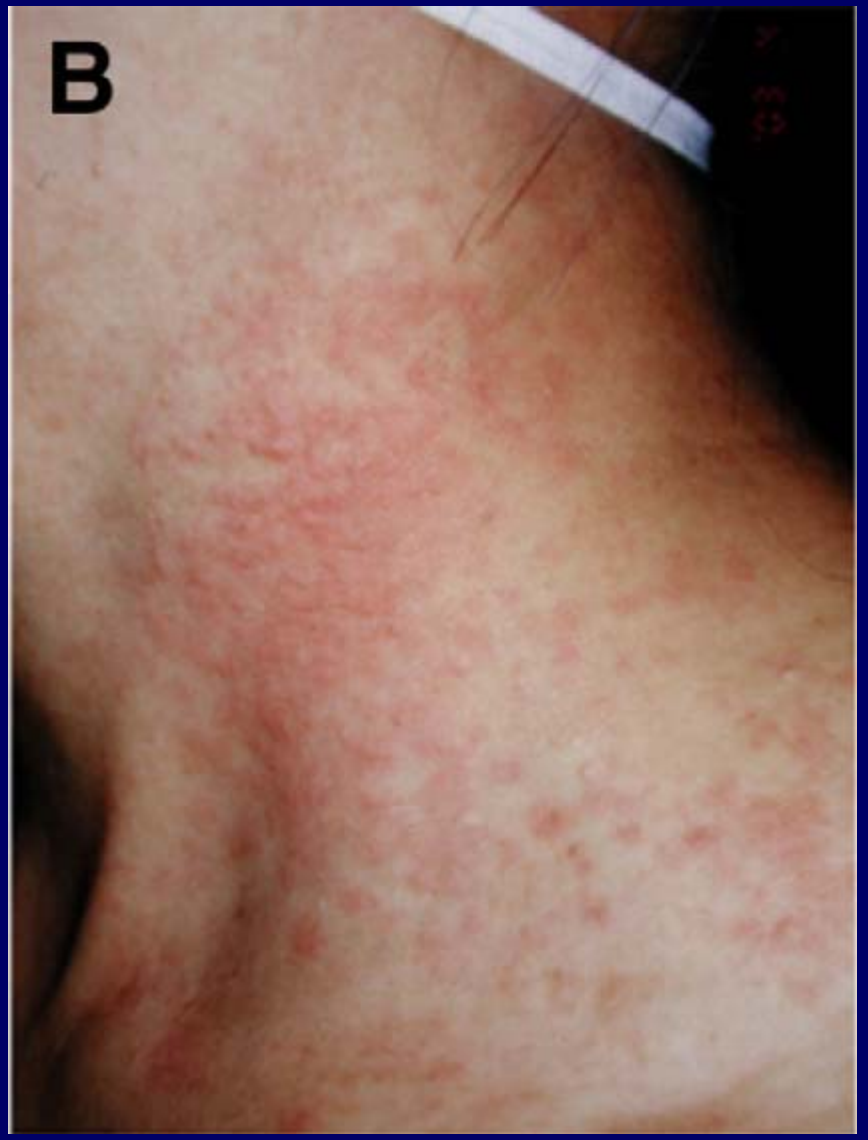
Pruritic Persistent Eruption

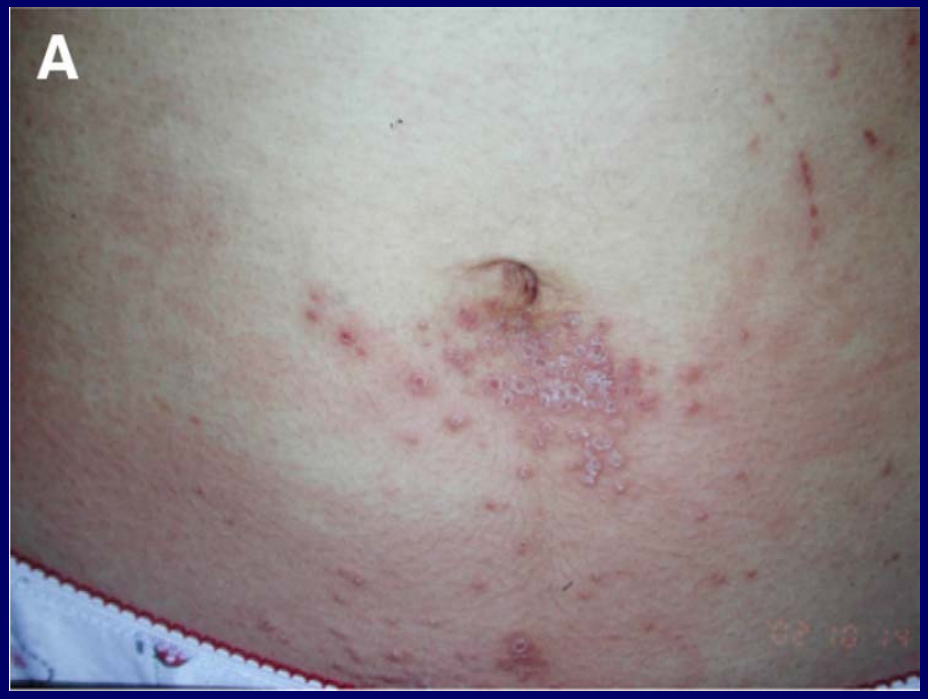
- Urticarial papules

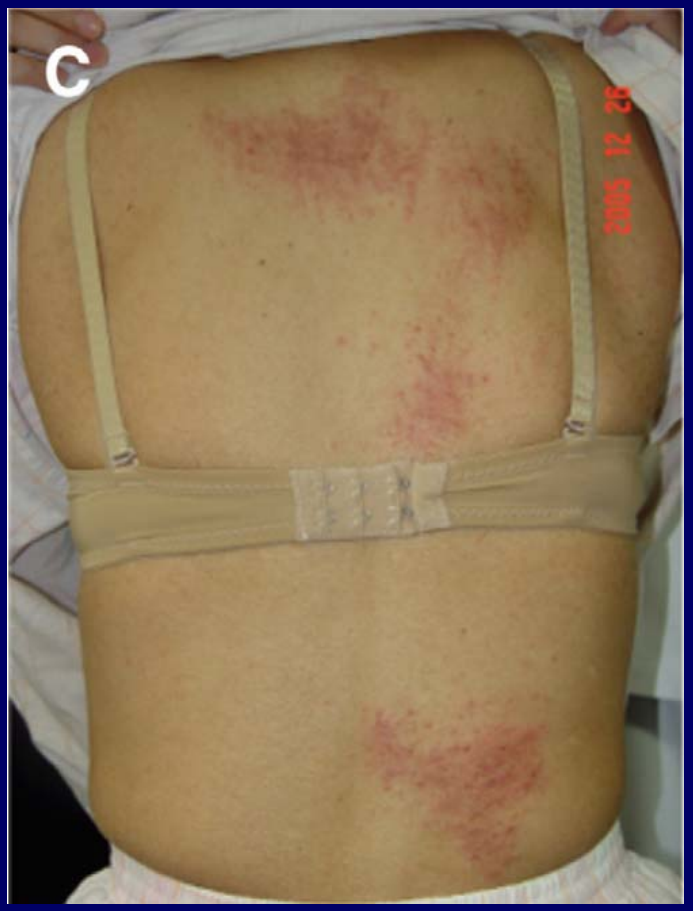


Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

Pruritic Persistent Eruption

- Lichenoid papules

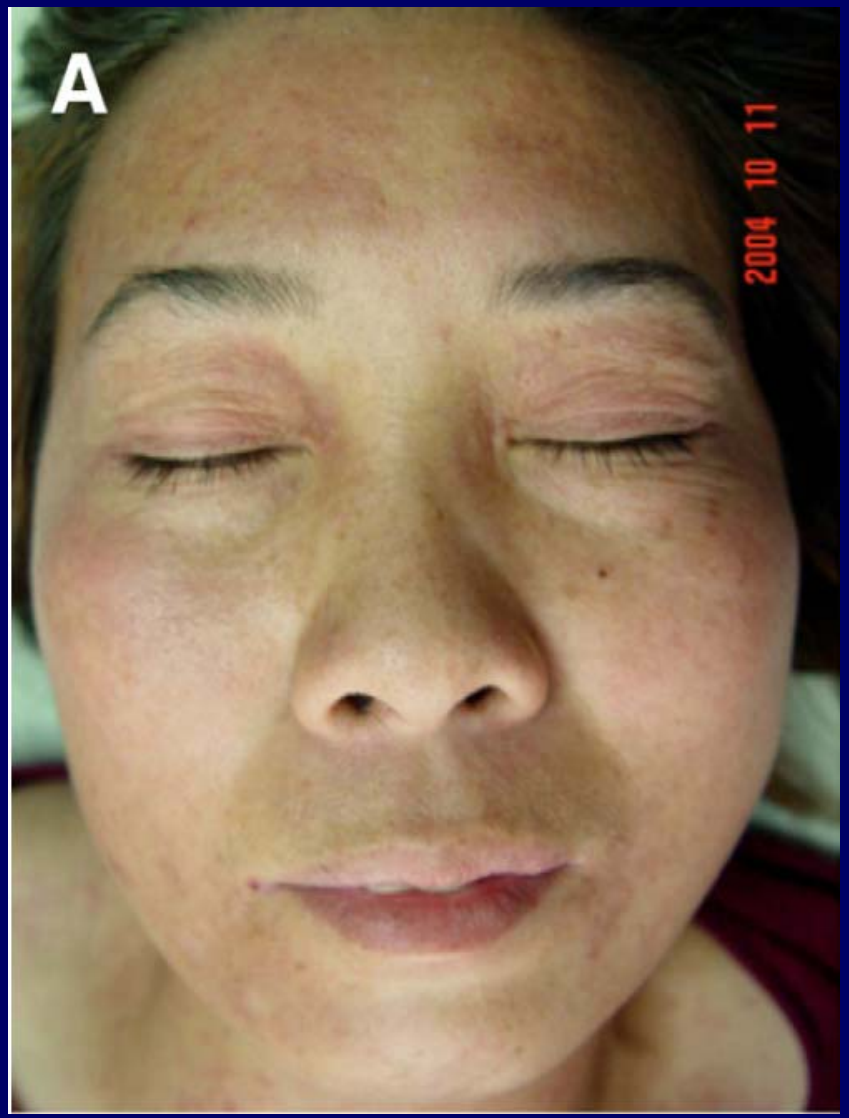




Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

Pruritic Persistent Eruption

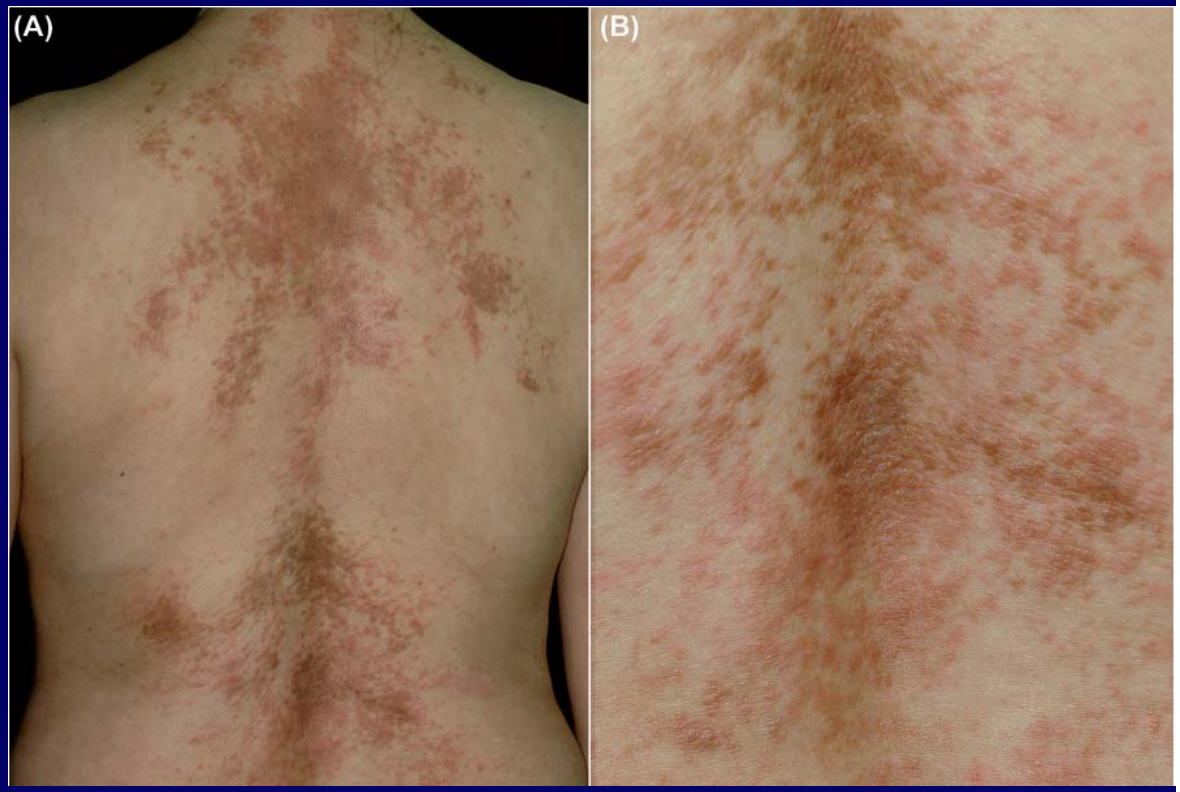
- Dermatomyositis-like



Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

Pruritic Persistent Eruption

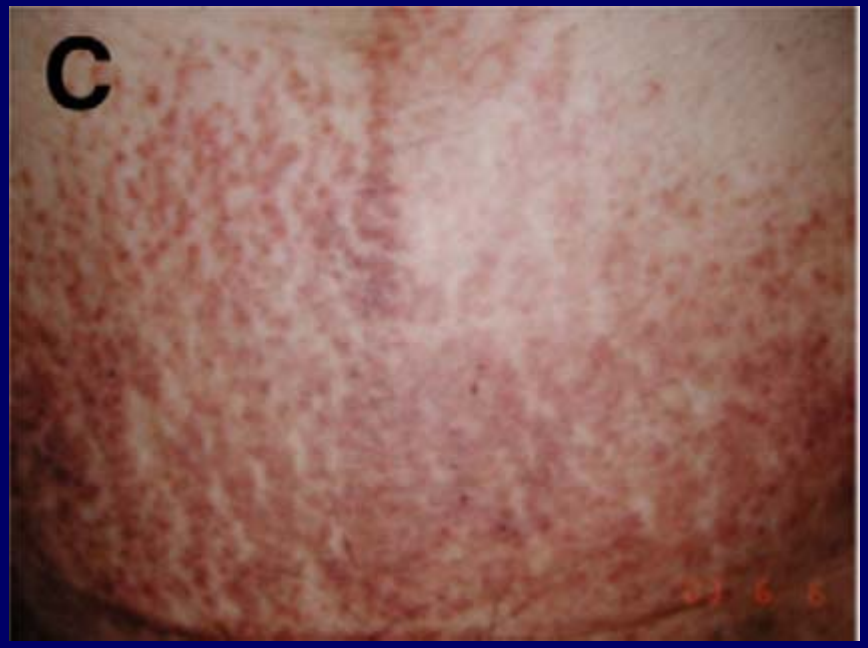
- Prurigo pigmentosa-like eruption in AOSD



Cho and Liao. *Acta Derm Venereol*. 2013, Epub ahead of print
Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

Pruritic Persistent Eruption

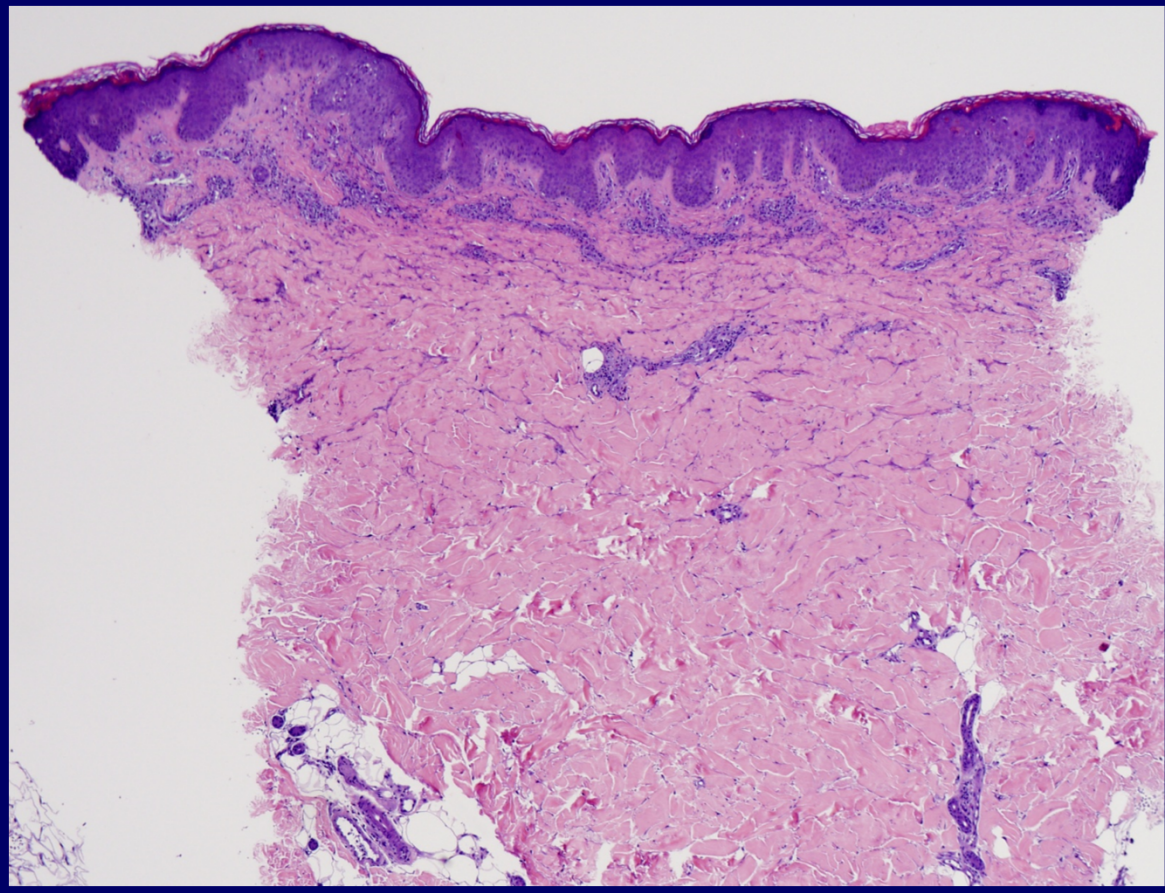
- Lichen amiloidosis-like



Lee JYY. Evanescent and persistent pruritic eruptions of adult onset Still disease: a clinical and pathologic study of 36 patients. *Semin Arthritis Rheum*. 2012, 42:317-26.

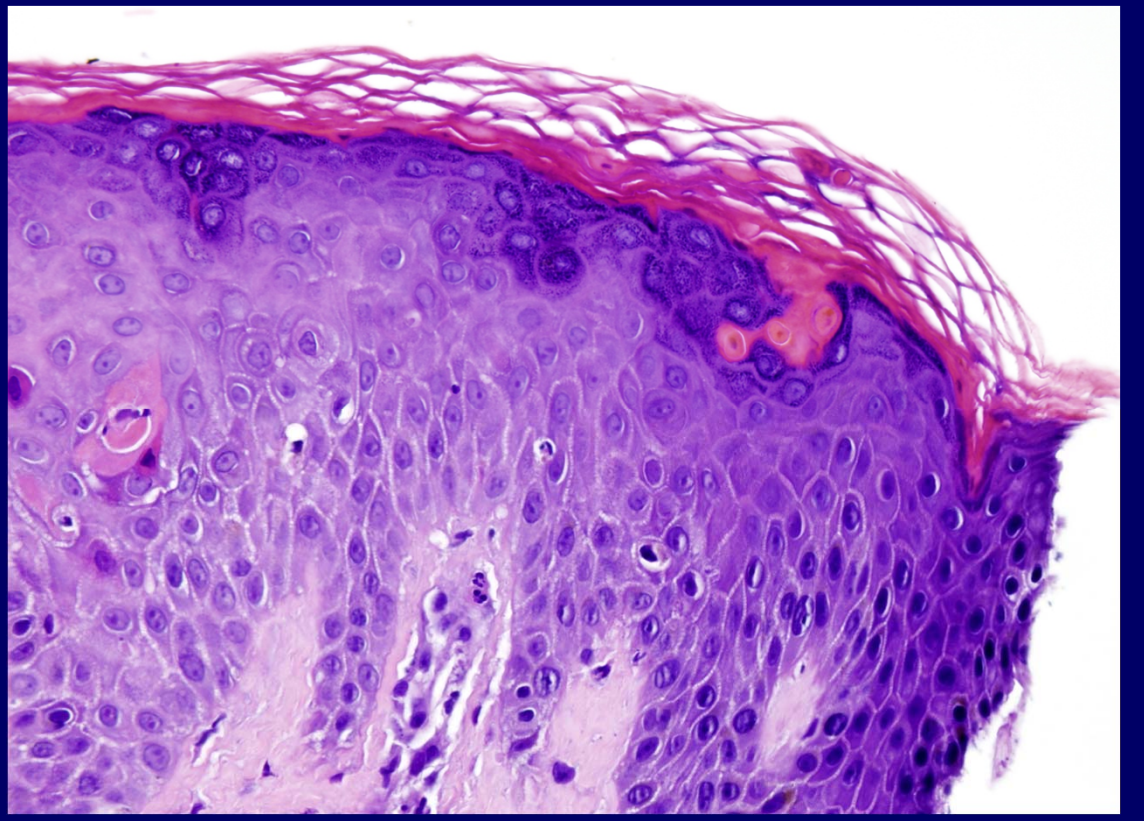
Persistent papulosquamous rash

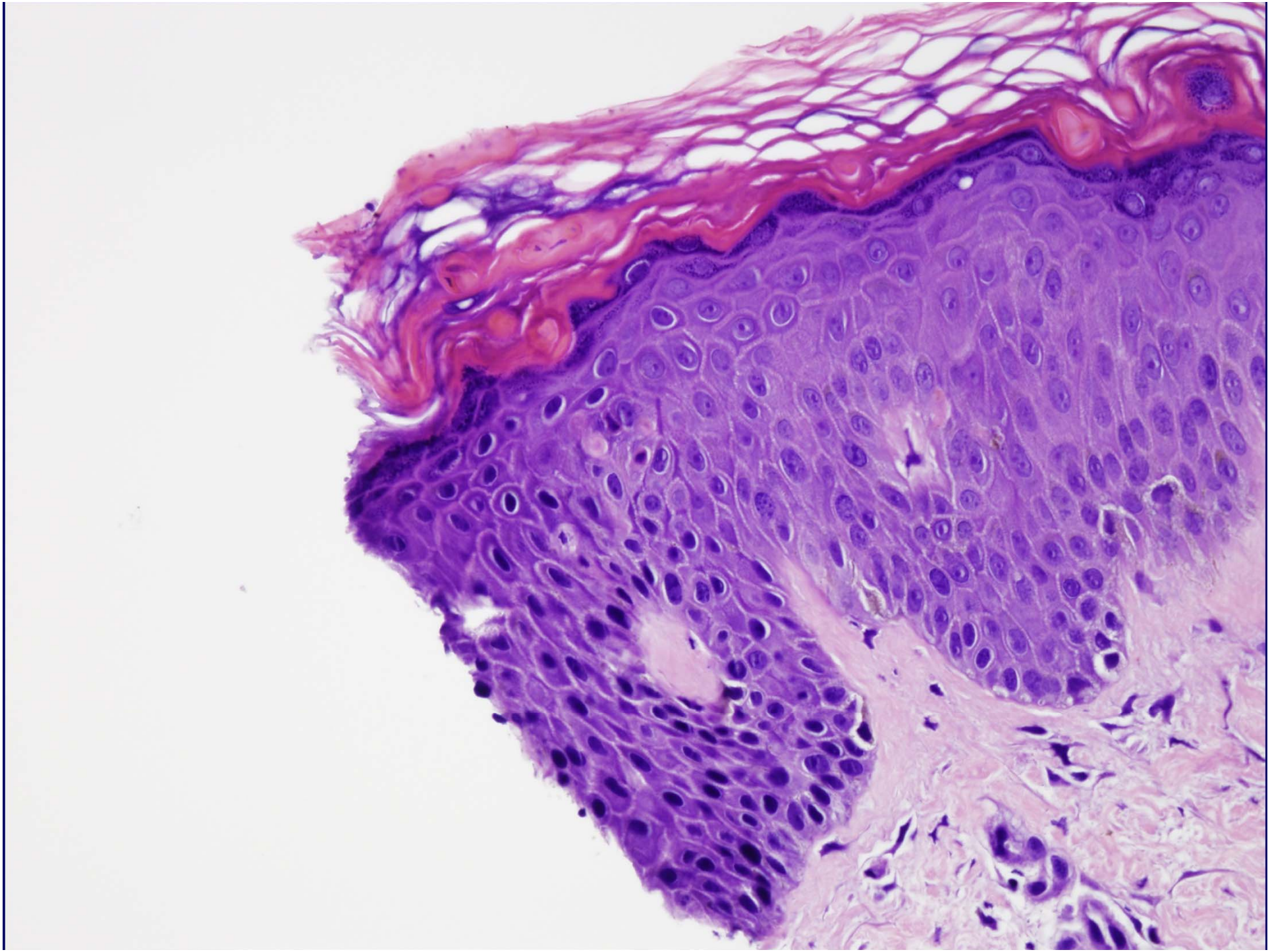
- Superficial perivascular dermatitis

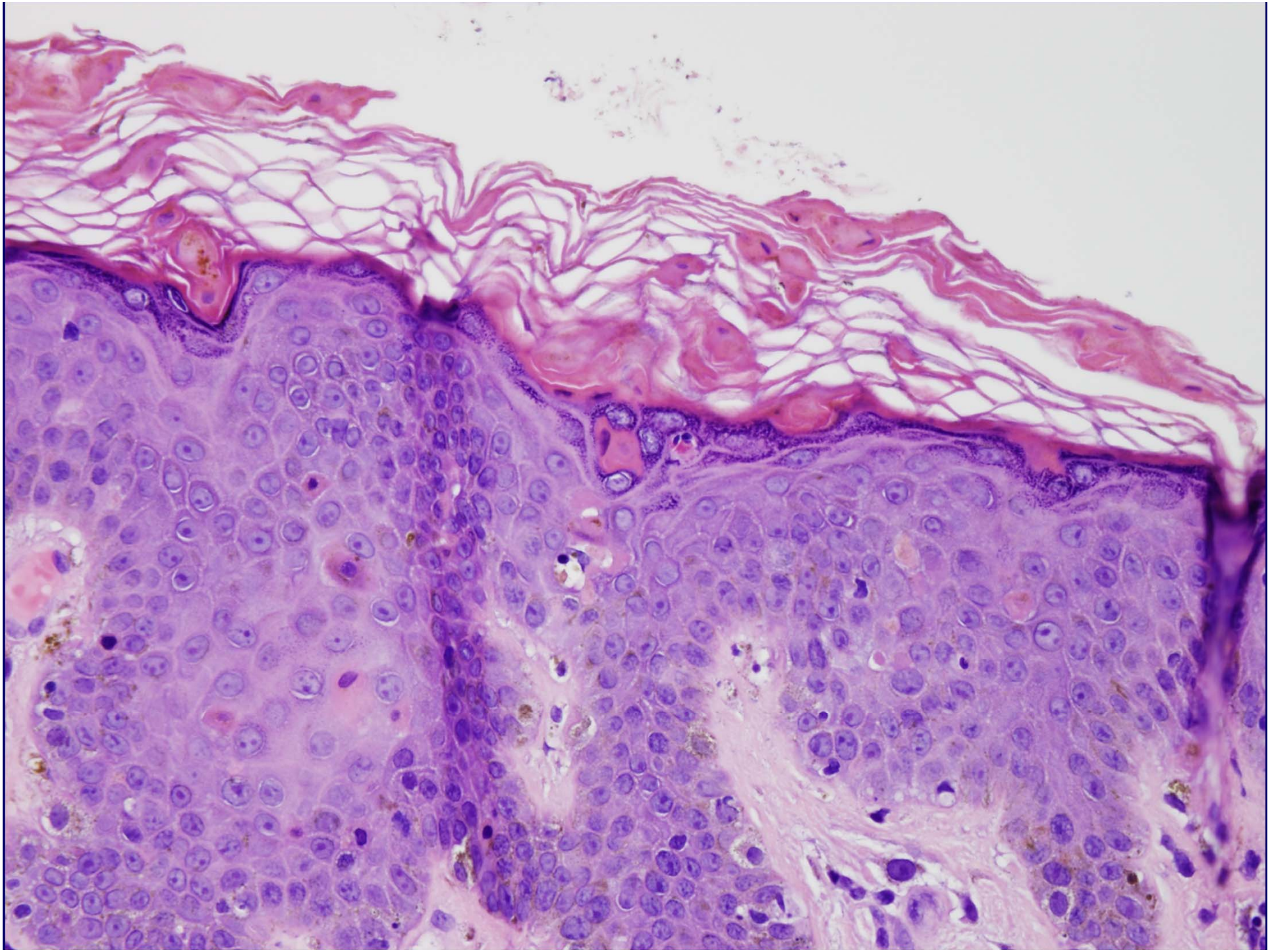


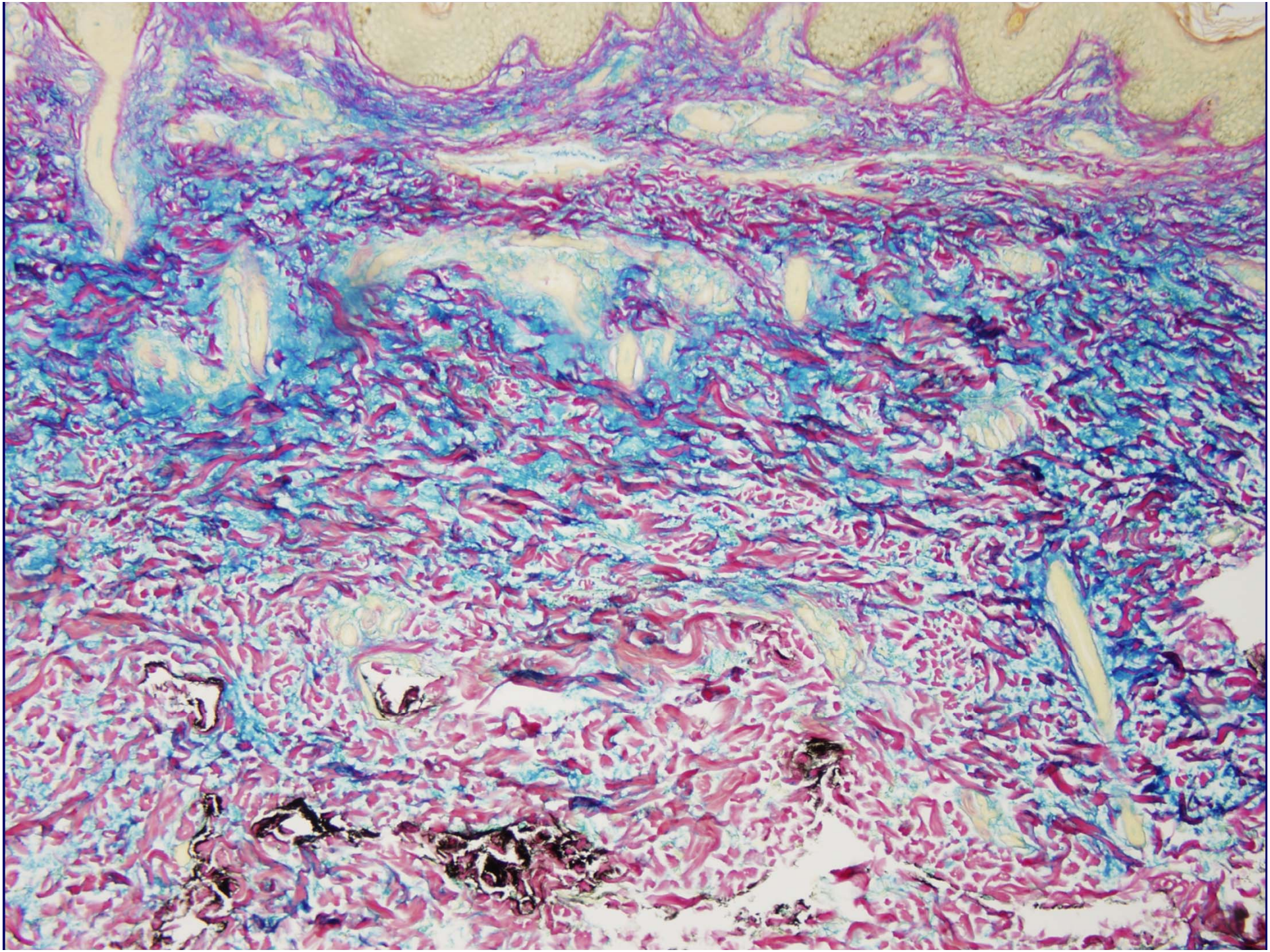
Persistent papulosquamous rash

- Dyskeratotic keratinocytes, in the upper layers of the epidermis
- No significant spongiosis or vacuolar-interface changes



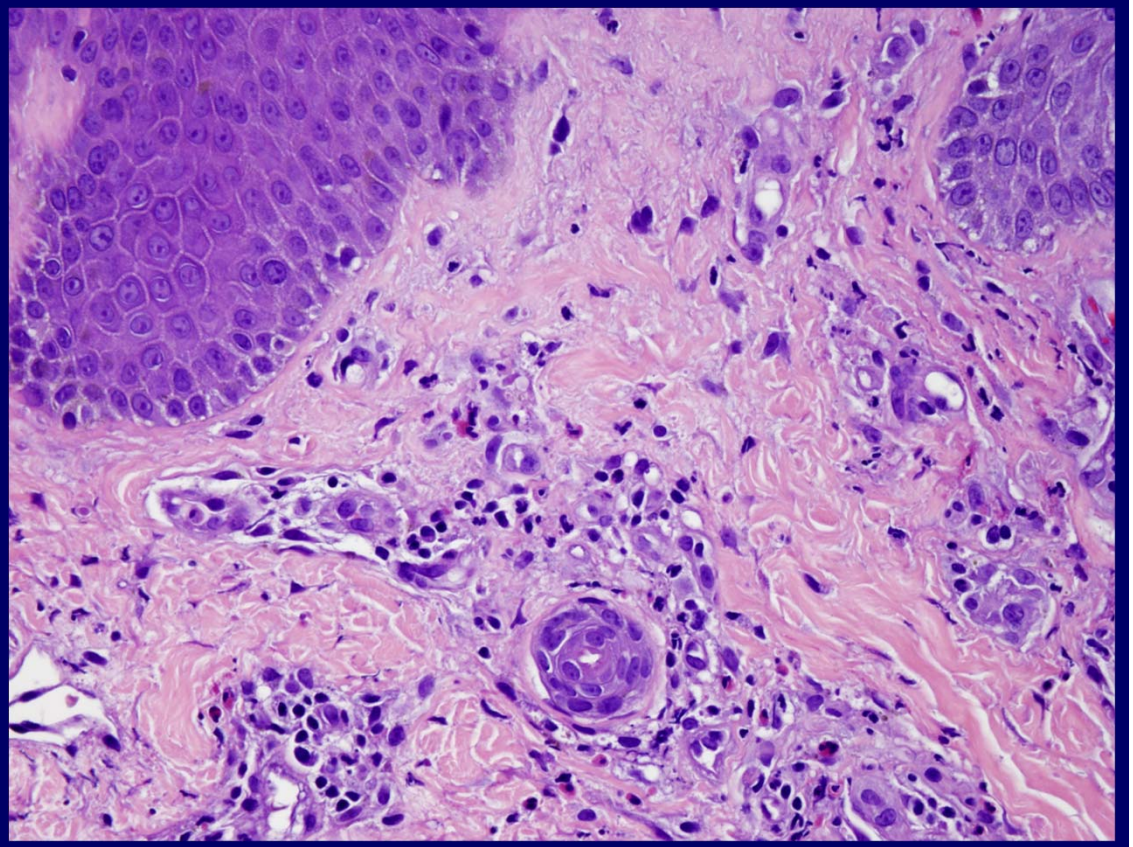






Persistent papulosquamous rash

- Superficial perivascular infiltrate
  - Lymphocytes
  - Few neutrophils
  - Variable eosinophils



Persistent papulosquamous rash

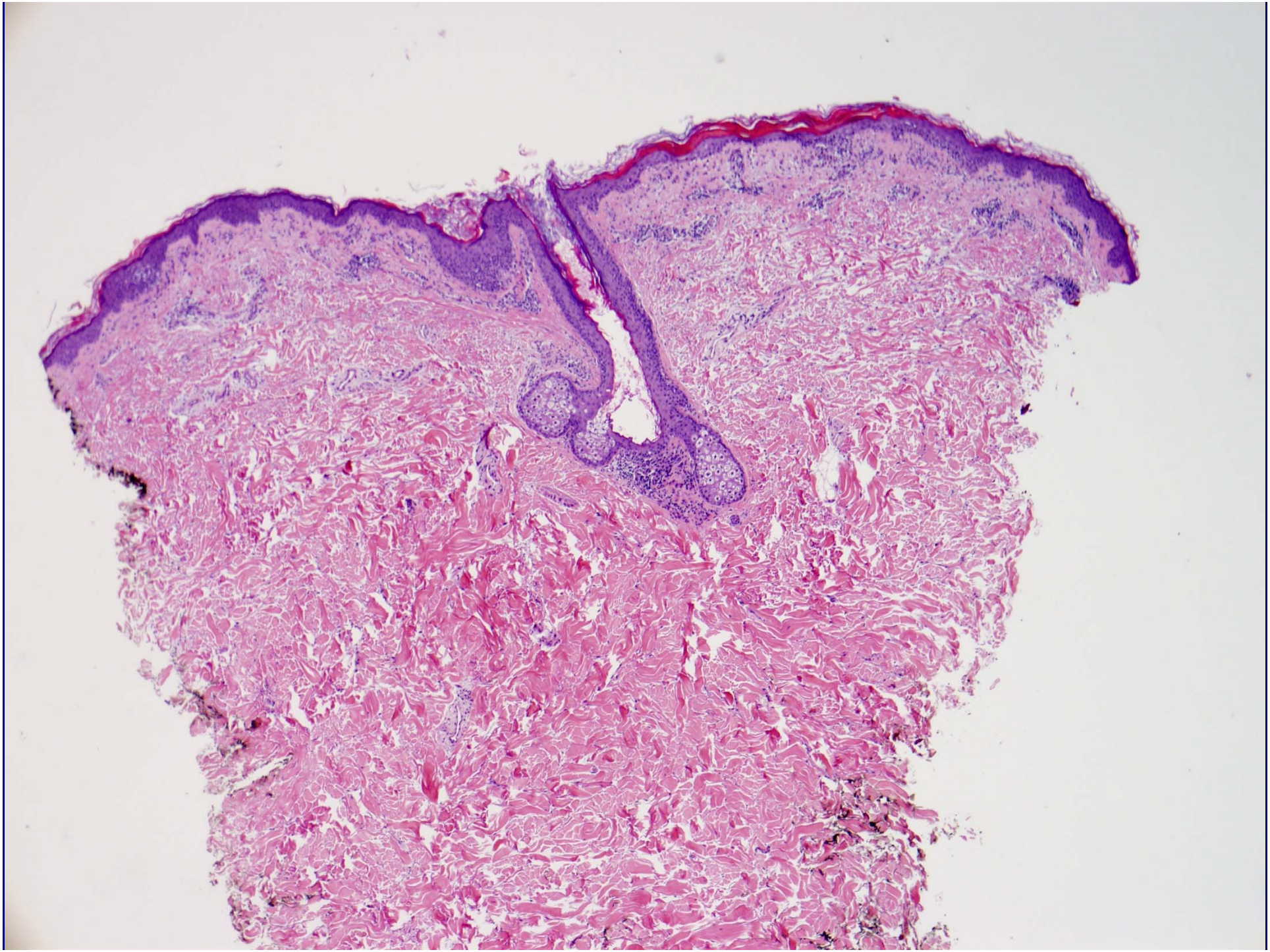
- Atypical AOSD rash often confused with dermographism or drug eruption in early reports
- Awareness of this particular and distinctive histology may facilitate the diagnosis

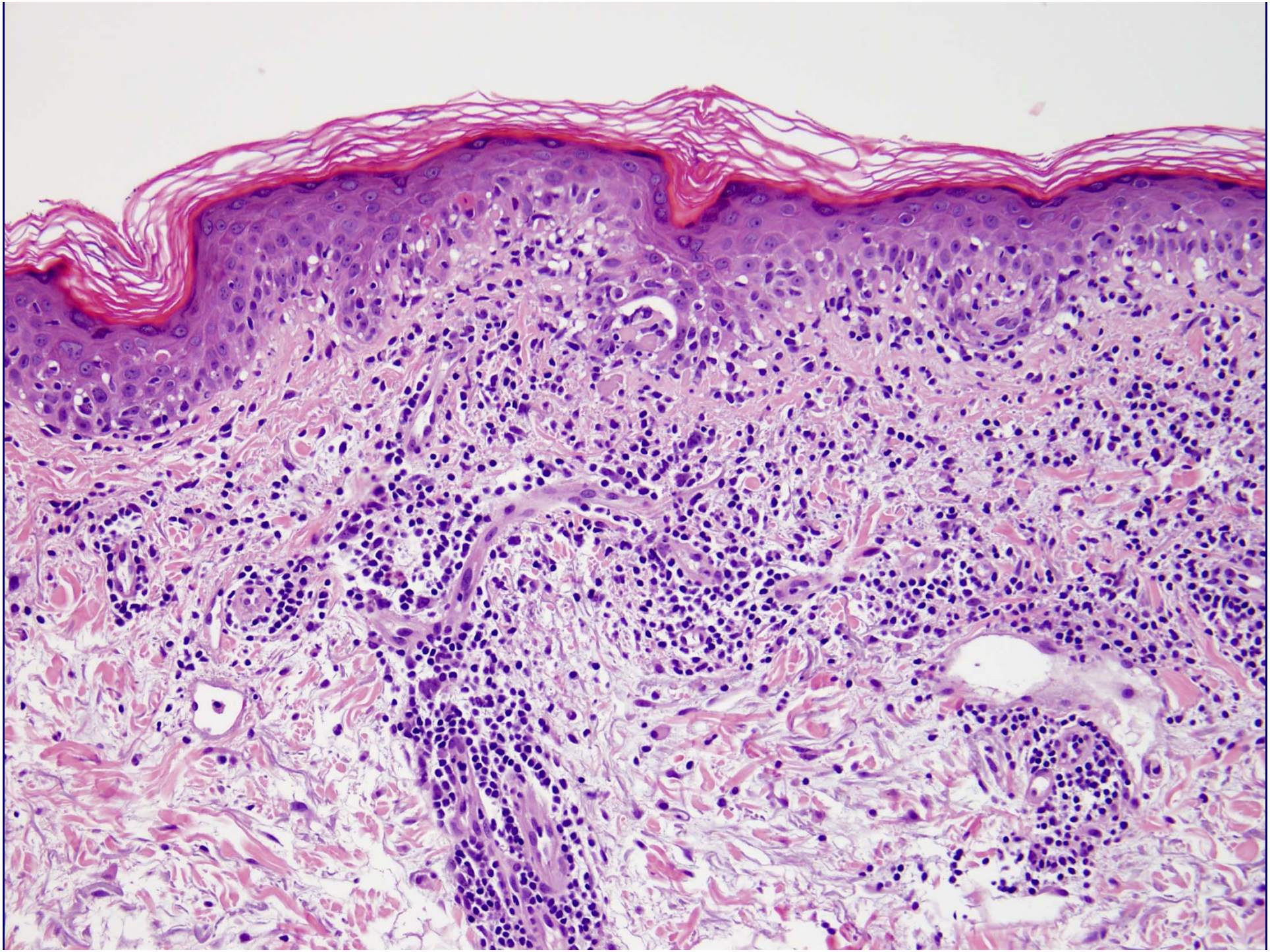
Differential diagnosis

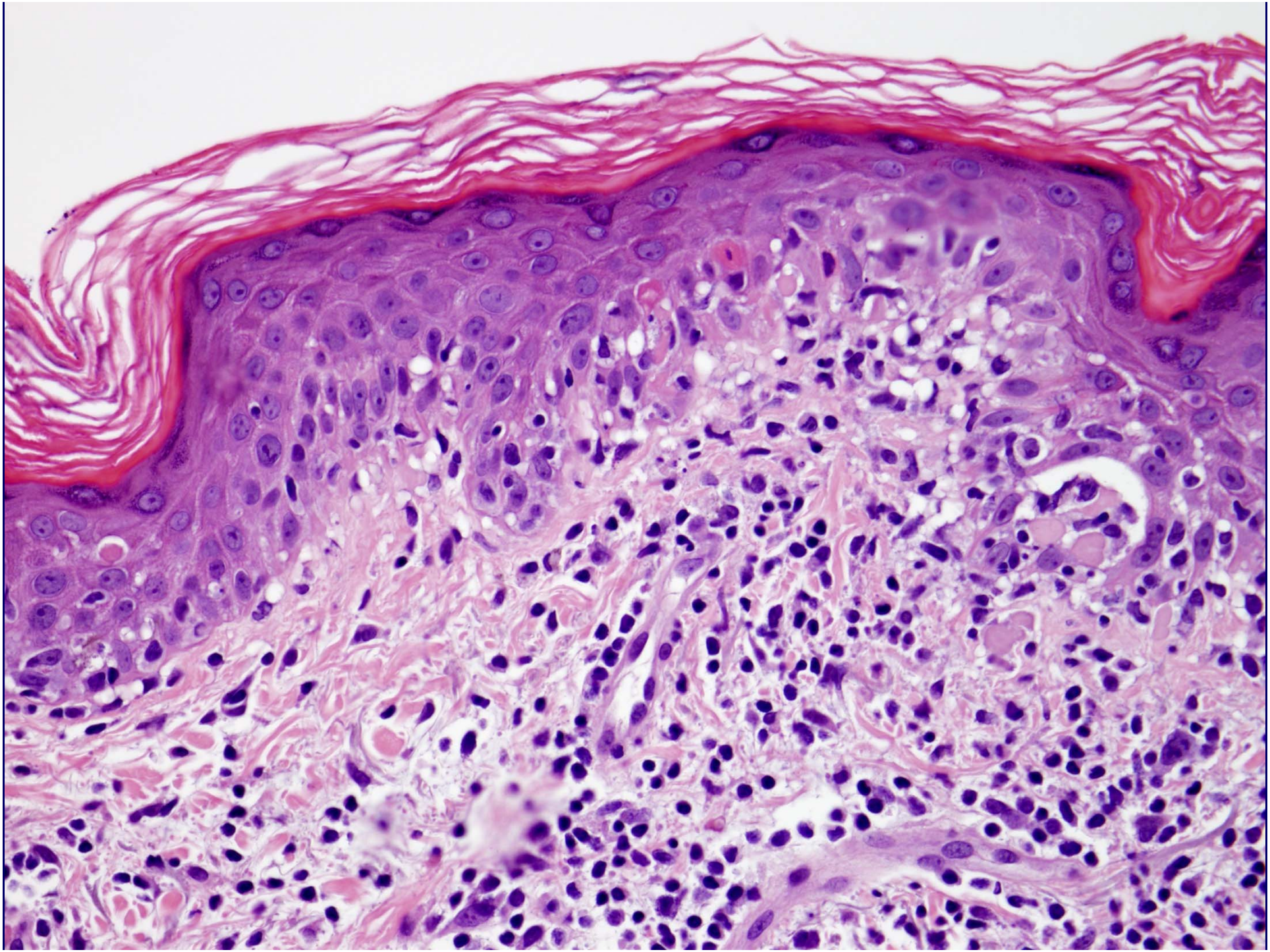
Subacute cutaneous lupus erythematosus

- Annular or papulosquamous lesions
- Photosensitive areas: face, neck, upper trunk, extensor surface of arms
- Non-scarring lesions
- May be associated with drug ingestion

- Positive ANA





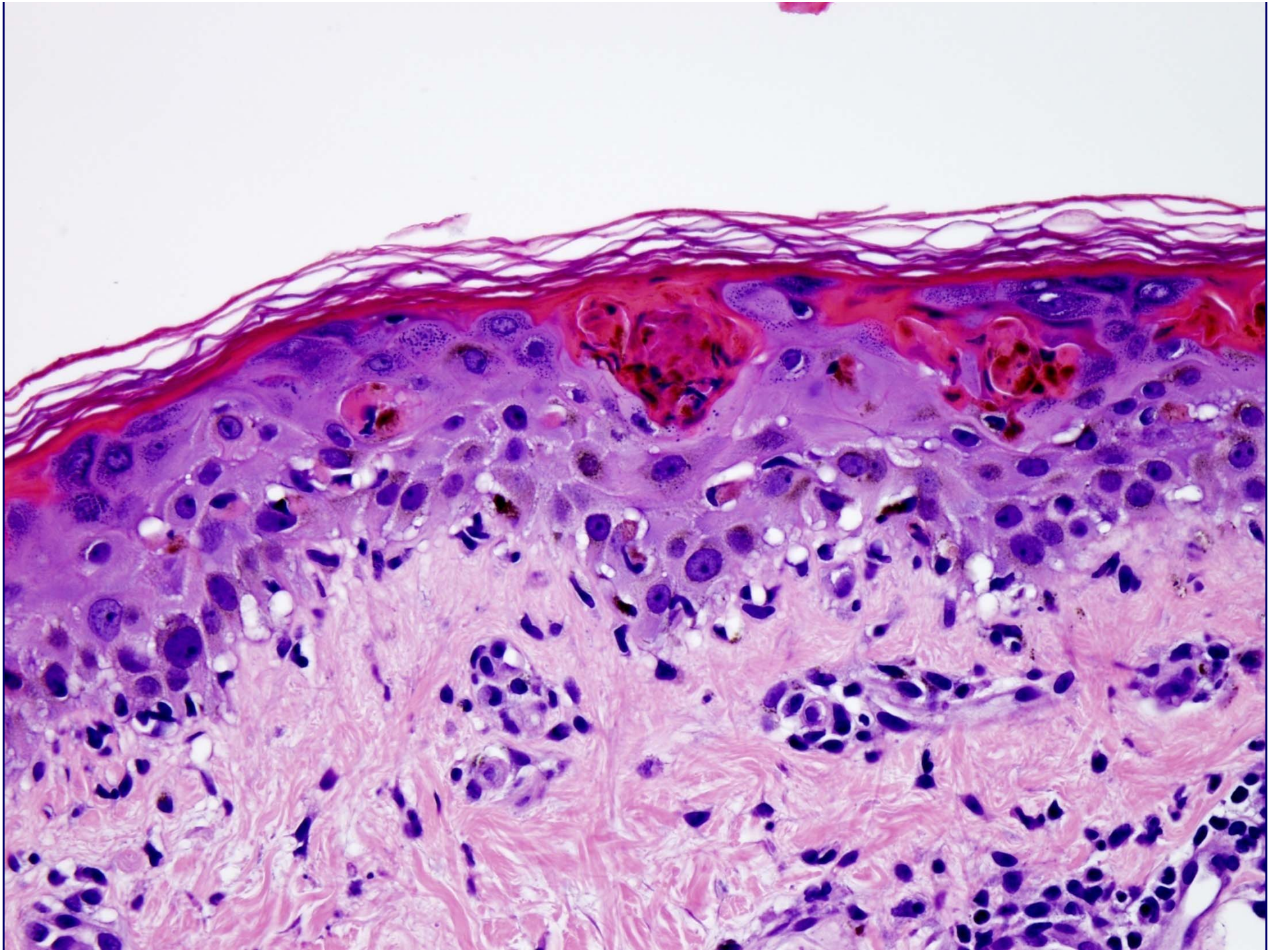


Rheumatoid arthritis

- Similar histology to the evanescent rash of AOSD
- Lacks dyskeratosis
- Positive RF and anti-cyclic citrullinated protein

Erythema multiforme

- Pleomorphic eruption
- Targetoid lesions

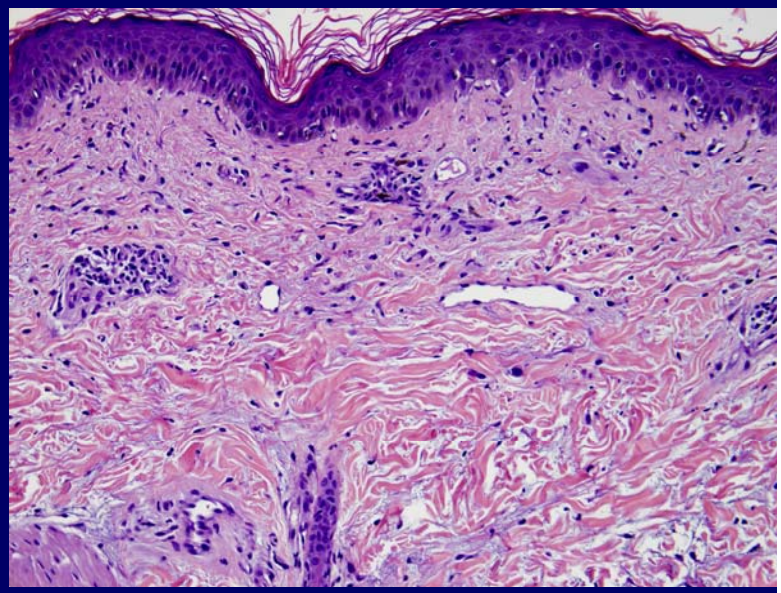


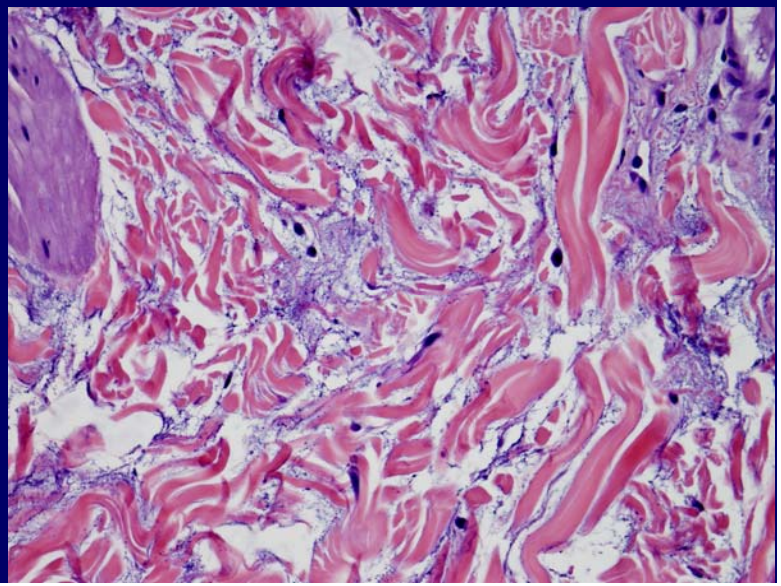
Dermatomyositis

- Polymyositis
- Skin involvement
- 10-20% with underlying malignancy

Dermatomyositis

- Mild vacuolar-interface dermatitis
- Rare apoptotic cells
- Sparse dermal infiltrate, often superficial
- Abundant dermal mucin





Thank you