Consultations In Medical Dermatology

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Conflict of Interest

Advisory Boards/Honoraria

Amgen

Leo Pharmaceuticals

Quote from an anonymous patient:

“What I am told on the first visit is patient education – on the second an excuse.”

Possibilities for a patient who presents with a complex medical dermatosis and systemic signs and symptoms:

1. Clinicopathologic diagnosis of dermatosis integrates all findings eg. Sarcoidosis – skin, eye, lungs, etc
2. Clinicopathologic diagnosis reveals a reactive dermatosis – communication with internist or pediatrician will outline underlying medical conditions eg. Vasculitis
3. No direct relationship – eg. Scabies/Fibromyalgia

Patients wishes to know from the internet whether they need x or y therapy for their presumptive diagnosis. Instead it is important to not let the patient “drive” for their own benefit.

Step 1. – Clinicopathologic diagnosis- Caution influence of therapy on biopsy and clinical appearance

Step 2. – Assess the extent (internal manifestations of disease)

Step 3. – Assess for etiology

Step 4. - Therapeutic ladder

Lichen Planus

Key Features

- Idiopathic, inflammatory disease of the skin, hair, nails and mucous membranes, seen most commonly in middle-aged adults
- Flat-topped violaceous papules and plaques favoring the wrists, forearms, genitalia, distal lower extremities and presacral area
- Clinical variants include annular, bullous, hypertrophic, inverse, linear, ulcerative, vulvovaginal-gingival, drug-induced and lichen planopilaris
- Some lichenoid drug eruptions have a photodistribution, while others are clinically and histologically indistinguishable from idiopathic lichen planus

Lichen Planus

Key Features (Cont.)

- The most commonly incriminated drugs include angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, antimalarials, quinidine and gold
- Histologically there is a dense, band-like lymphocytic infiltrate and keratinocyte apoptosis with destruction of the epidermal basal cell layer
- In this T-cell-mediated autoimmune disorder, basal keratinocytes express altered self-antigens on their surface

MAJOR LICHENOID DERMATOSES AND POSSIBLE ASSOCIATED TARGET ANTIGENS	
Lichenoid dermatoses	**Possible target antigens**
Lichen planus	V, D, C, T
Lichenoid drug eruption	D
Erythema dyschromicum perstans	V, D
Graft-versus-host disease (see Ch. 52)	Allo, V
Keratosis lichenoides chronica	
Pityriasis lichenoides* (see Ch. 9)	V
Lichen nitidus	V
Lichen striatus	V
Fixed drug eruption (see Ch. 21)	D
Erythema multiforme (see Ch. 20)	V, D, C
Lupus erythematosus (see Ch. 41)	V, Auto, D
Dermatomyositis (see Ch. 42)	V, Auto, T, D
Paraneoplastic pemphigus (see Ch. 29)	T
Mycosis fungoides (CTCL) (see Ch. 120)	T, V
Lichenoid pigmented purpura (see Ch. 22)	D, V
Secondary syphilis (see Ch. 82)	
*Acute and chronic.	

Table 11.1 Major lichenoid dermatoses and possible associated target antigens. The variation in clinical presentations may reflect the differences in the effector mechanisms by which epidermal cells are damaged and/or target antigens. The shaded entities are discussed in this chapter. Allo, alloantigens; Auto, autoantigens; C, contact allergens; D, drug antigens; T, tumor antigens; V, viral antigens.

DRUGS IMPLICATED IN LICHENOID DRUG ERUPTIONS

ANTIMICROBIALS

- Ethambutol
- Griseofulvin
- Isoniazid
- Ketoconazole
- Pyrimethamine
- Streptomycin
- Sulfamethoxazole
- Tetracyclines

ANTIHYPERTENSIVES

- **Captopril**
- **Enalapril**
- **Labetalol**
- **Methyldopa**
- **Propranolol**
- Diazoxide *
- Doxazosin
- Prazosin

ANTIMALARIALS

- **Chloroquine**
- **Hydroxychloroquine**
- **Quinacrine**

ANTIDEPRESSANTS, ANTIANXIETY DRUGS, ANTIPSYCHOTICS AND ANTICONVULSANTS

- Amitriptyline
- Carbamazepine
- Chlorpromazine
- Imipramine
- Levomepromazine
- Lorazepam
- Methopromazine
- Phenytoin

TNF-α INHIBITORS

- Adalimumab
- **Etanercept**
- **Infliximab**
- Lenercept

DIURETICS

- **Chlorothiazide**
- **Hydrochlorothiazide**
- Furosemide
- Spironolactone

HYPOGLYCEMIC AGENTS

- Chlorpropamide
- Glyburide
- Tolazamide
- Tolbutamide

METALS

- **Gold salts**‡
- Arsenic
- Bismuth
- Mercury
- Palladium

NSAIDS

- Acetylsalicylic acid
- Benoxaprofen
- Diflunisal
- Fenclofenac
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Naproxen
- Sulindac

MISCELLANEOUS DRUGS

- Allopurinol
- Amiphenazole
- Anakinra
- Cinnarizine
- Cyanamide
- Dapsone
- Gemfibrozil
- Hydroxyurea
- Imatinib
- Interferon-α
- Iodides
- Isotretinoin
- Levamisole
- Lithium
- Mercapto-propionylglycine
- Mesalamine
- Methycran
- Nifedipine
- Omeprazole
- Orlistat
- **Penicillamine**
- Propylthiouracil
- Procainamide
- Pyrithioxin
- Simvastatin
- Quinine
- **Quinidine**
- Rituximab
- Sildenafil
- Sulfasalazine
- Trihexyphenidyl

*Also used to treat hypoglycemia.
‡Including in alcoholic beverages.

Table 11.2 Drugs implicated in lichenoid drug eruptions. More commonly associated drugs are in **bold**. NSAIDs, nonsteroidal anti-inflammatory drugs.

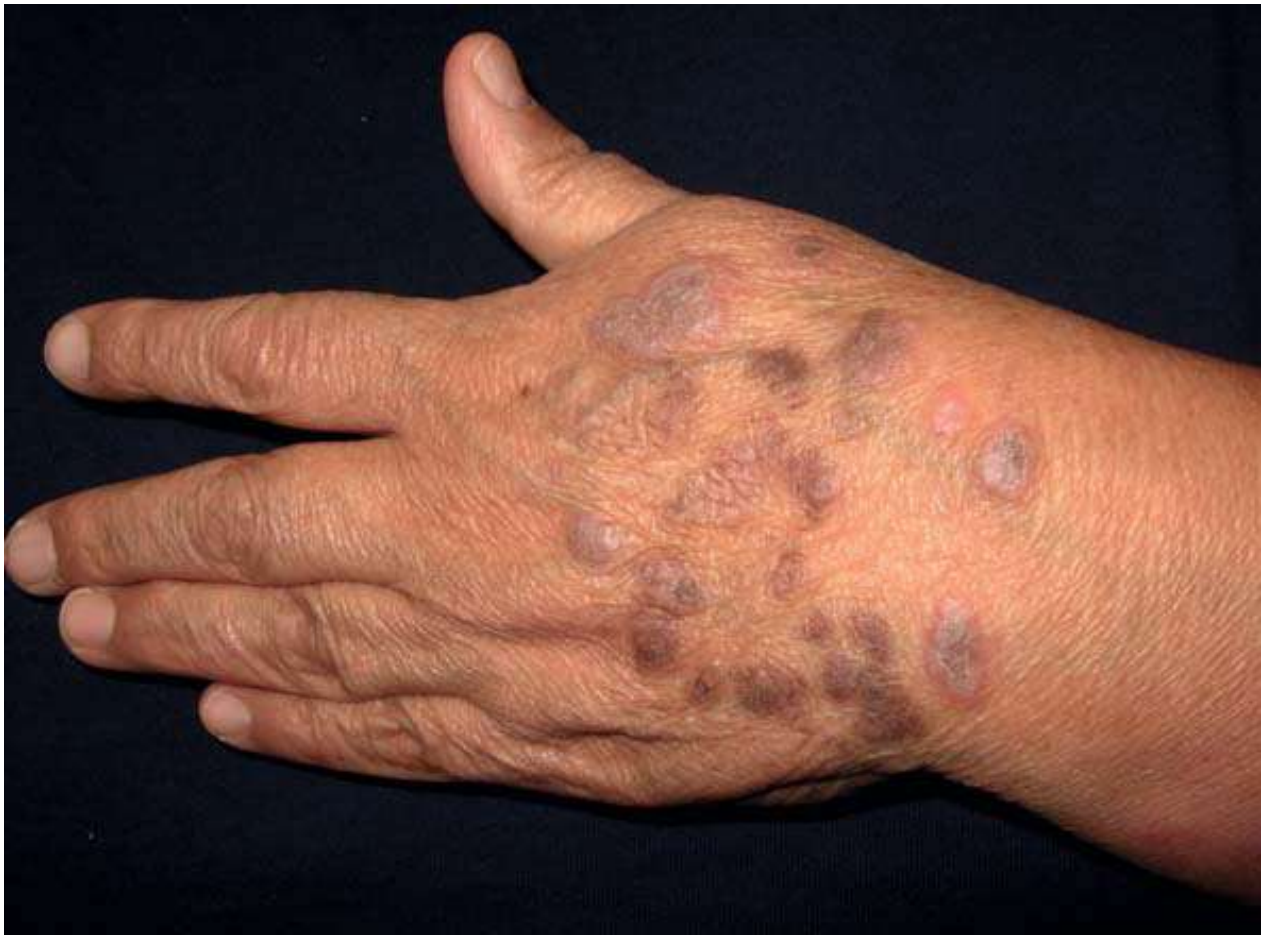


Fig. 11.5 Lichen planus on the dorsal surface of the hand. Wickham's striae can be easily identified in the upper lesion. Note the flat-topped nature of the lesions and the post-inflammatory hyperpigmentation. *Courtesy, Frank Samarin, MD*

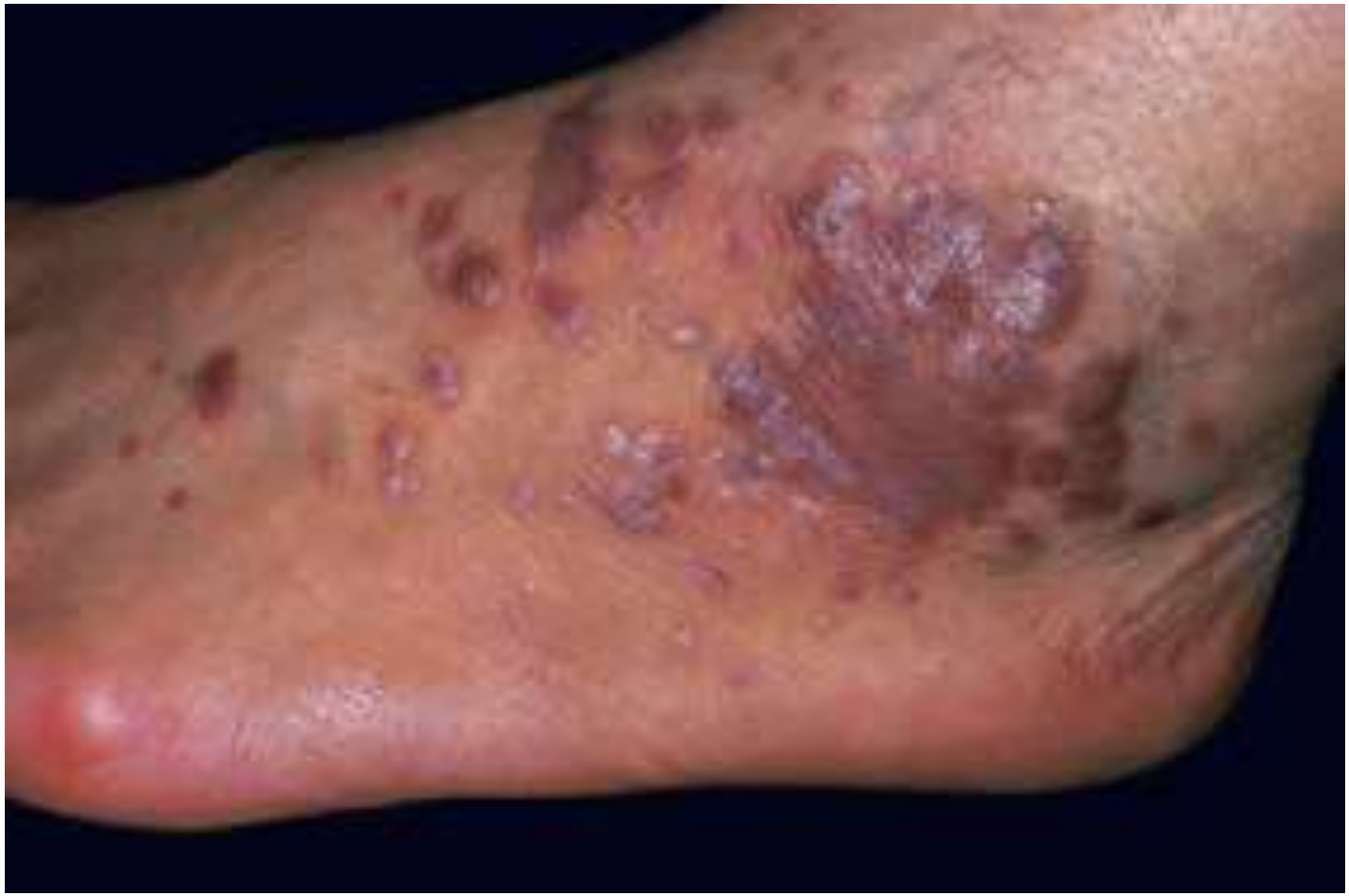


Fig. 11.6 Lichen planus. Violaceous papules and plaques with white scale and Wickham's striae.

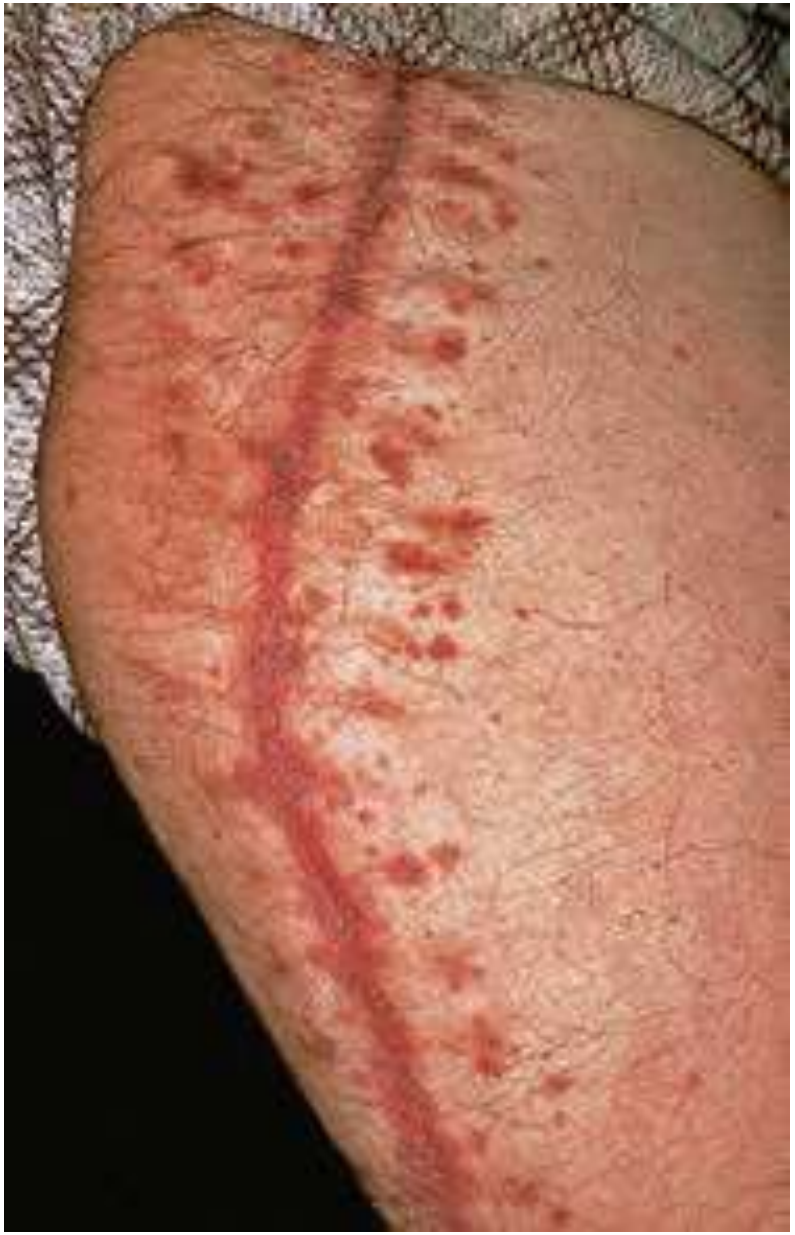


Fig. 11.7 Koebnerization of lichen planus into the site of the excision of the saphenous vein. Lesions also appeared where Steri-Strips™ had been applied.

Fig. 11.8 (A)

Fig. 11.8 Annular lichen planus of the glans penis (A) and the trunk (B). On the penis, the lesions have led to a figurate outline with central hyperpigmentation.
A, Courtesy, Frank Samarin, MD

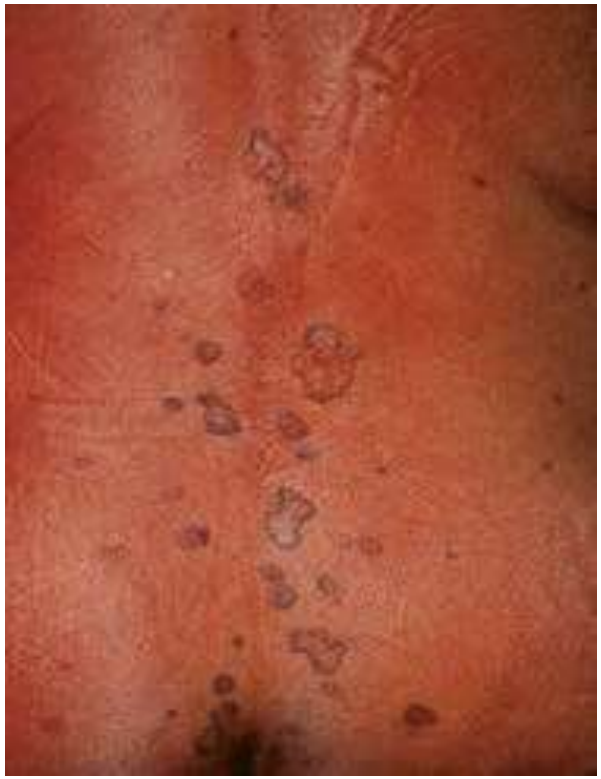


Fig. 11.8 (B)

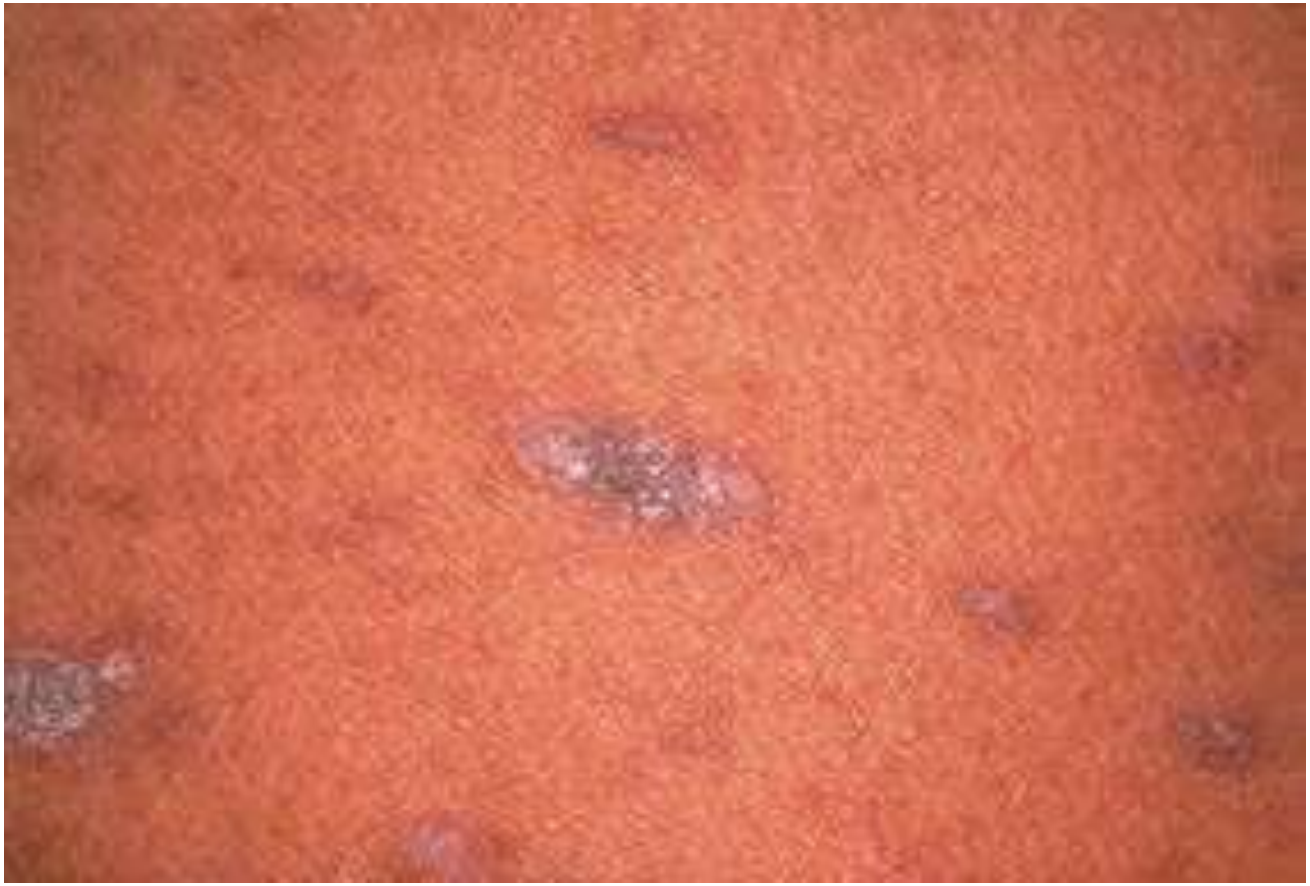


Fig. 11.9 Exanthematous lichen planus. Papulosquamous lesions on the back.

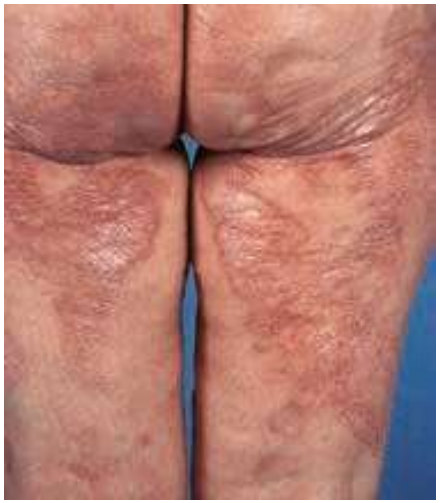


Fig. 11.10 (A)

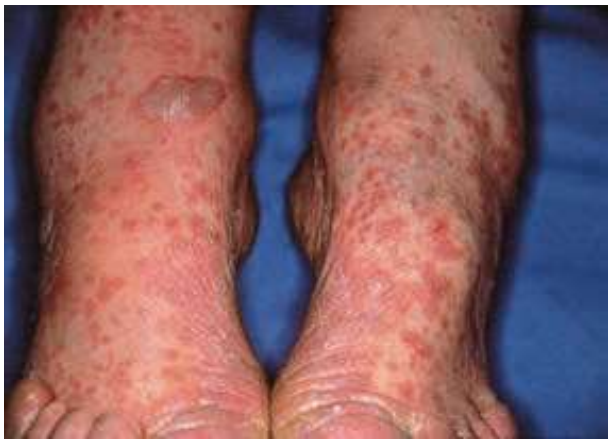


Fig. 11.10 (C)

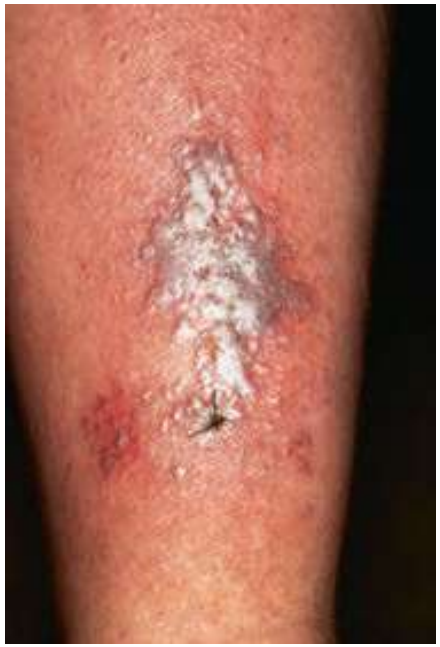


Fig. 11.10 (B)

Fig. 11.10 Unusual variants of lichen planus. **(A)** Atrophic lichen planus of the lower extremeties. **(B)** Bullous lichen planus on the shin. **(C)** Lichen planus pemphigoides in a patient with anti-basement membrane zone autoantibodies.

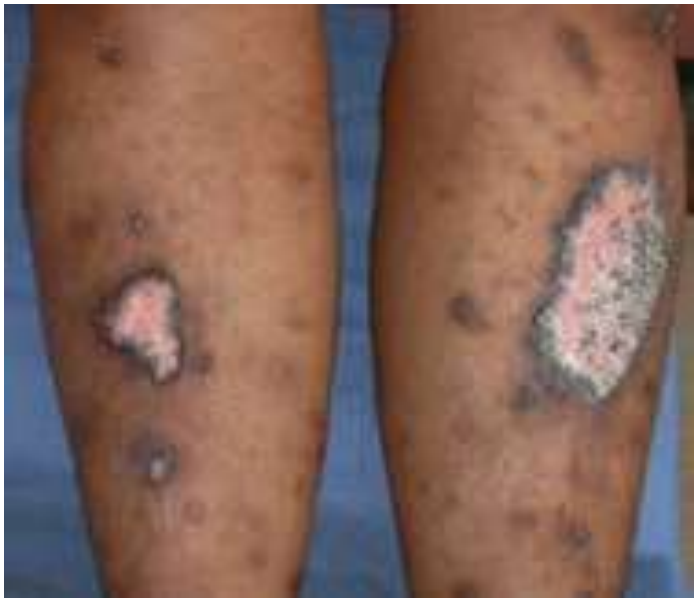


Fig. 11.11 (A)

Fig. 11.11 (B)

Fig. 11.11 Hypertrophic lichen planus. (A) on the shins, very thick descrete plaques with dyspigmentation are admixed with smaller linear plaques and areas of postinflammatory hyperpigmentation. **(B)** On the dorsal digits, thin violaceous plaques in addition to thick keratotic plaques that favor the knuckles.

B, Courtesy, Joyce Rico, MD

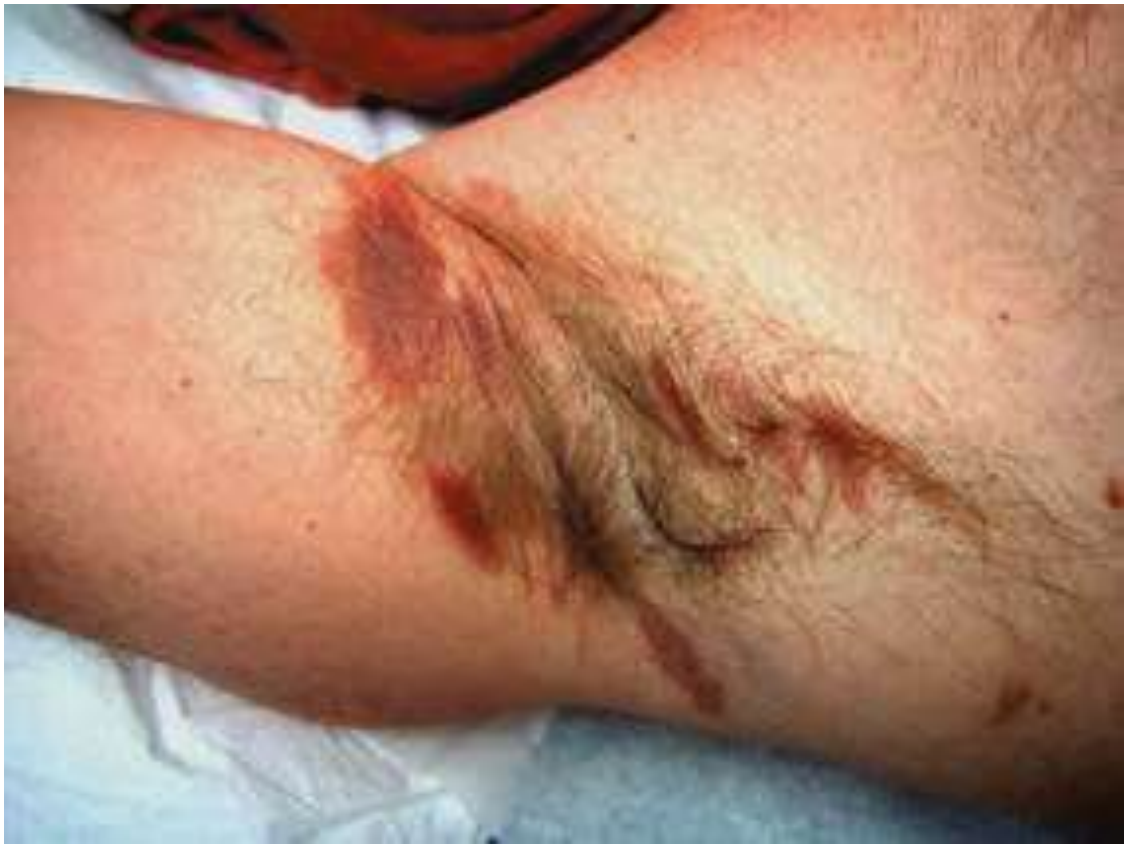


Fig. 11.12 Inverse lichen planus. Oval thin violaceous plaques in the axilla. Postinflammatory hyperpigmentation is also present. *Courtesy, Jeffrey P. Callen, MD*

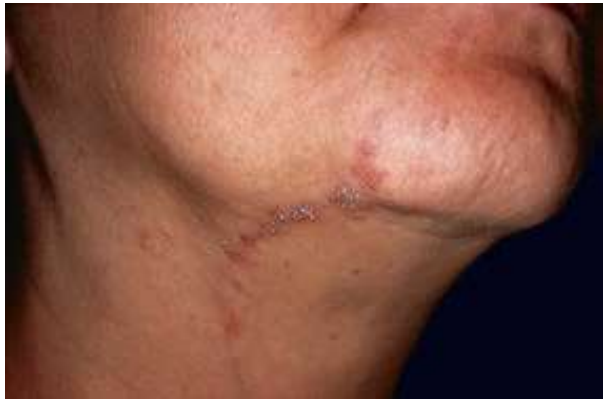


Fig. 11.13 (A)

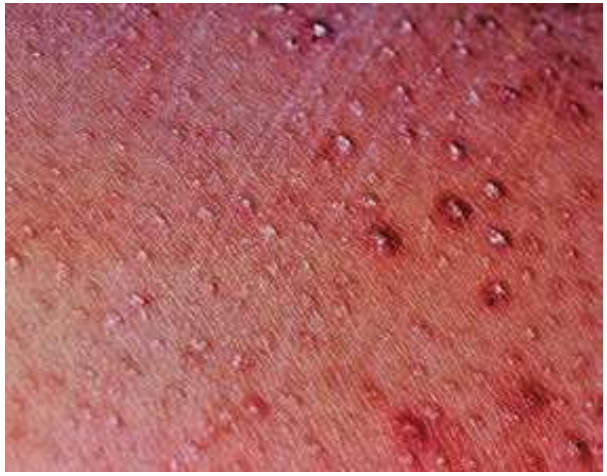


Fig. 11.13 (B)

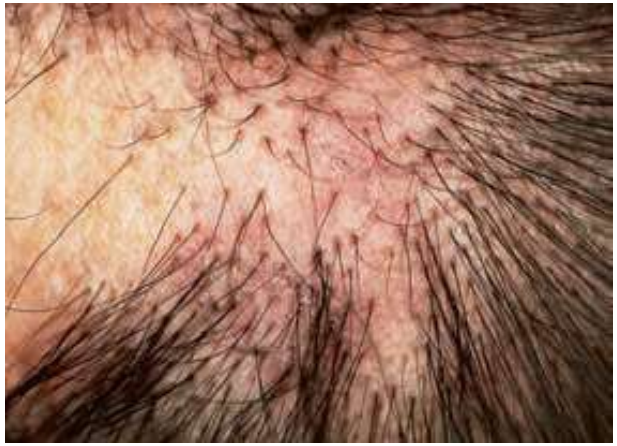


Fig. 11.13 (C)

Fig. 11.13 Lichen planopilaris. (A) Keratotic spines surrounded by a violaceous rim in a linear variant and **(B)** scattered on the trunk. **(C)** Cicatricial alopecia with “end-stage” changes centrally, but perifollicular inflammation at the margins.

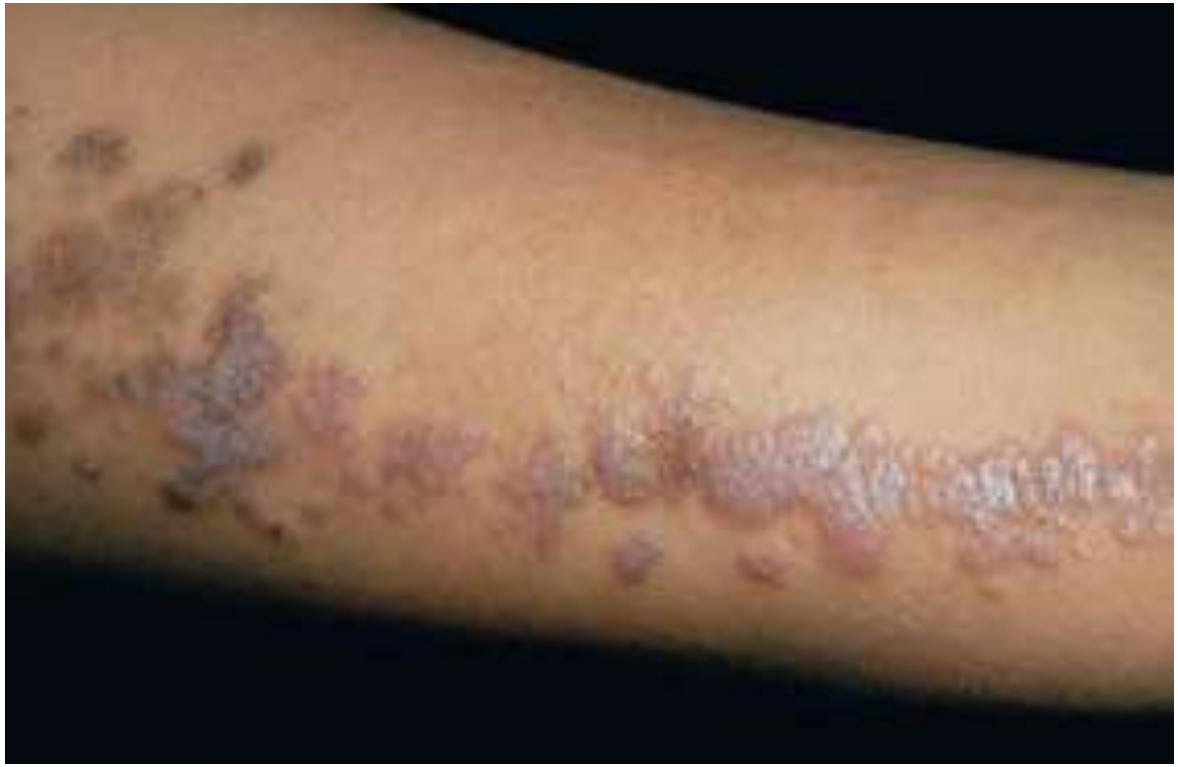


Fig. 11.14 Linear lichen planus. Coalescence of violaceous lesions with Wickham's striae along the lines of Blaschko on an extremity. Note the postinflammatory hyperpigmentation proximally. *Courtesy, Joyce Rico, MD*

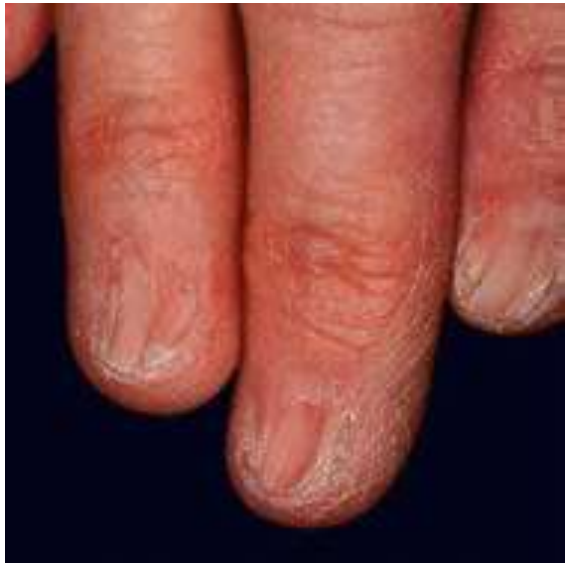


Fig. 11.15 (A)

Fig. 11.15 (B)

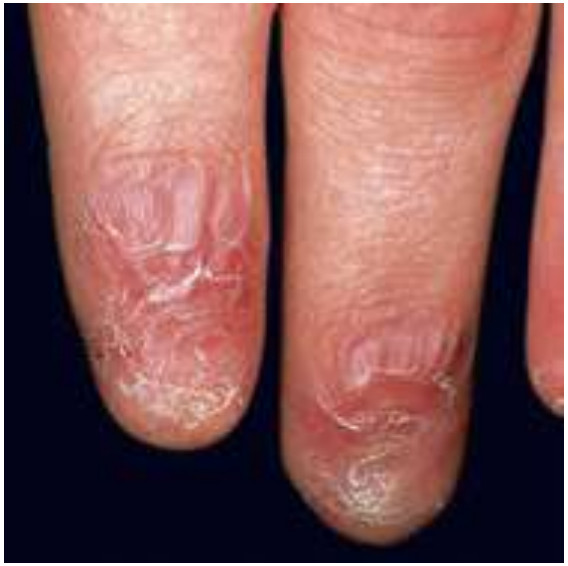


Fig. 11.15 (C)

Fig. 11.15 Nail lichen planus. (A) Thinning of the nail plate with lateral loss. **(B)** Longitudinal fissuring of shortened nail plates. **(C)** Violaceous discoloration of the periungual area with pterygium formation.

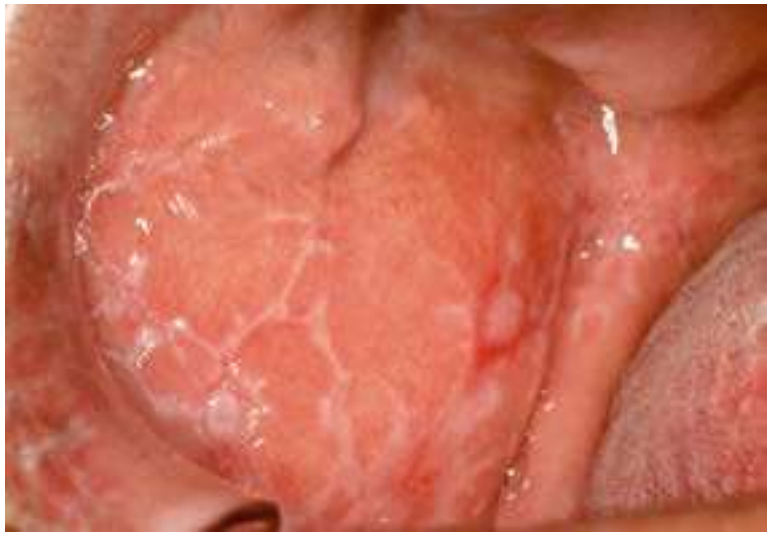


Fig. 11.16 (A)

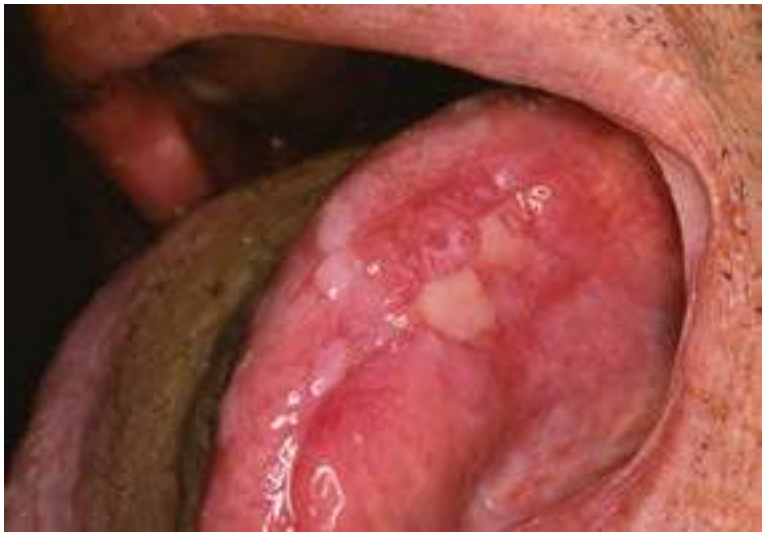


Fig. 11.16 (B)

Fig. 11.16 Oral lichen planus. (A) White lacy pattern and an erosion on the buccal mucosa, the most common location for the reticular from. Note the ring configuration with short radiating spines. **(B)** Erosions on the lateral aspect of the tongue in addition to lacy white plaques and scarring.
B, Courtesy, Louis A. Fragola, Jr, MD

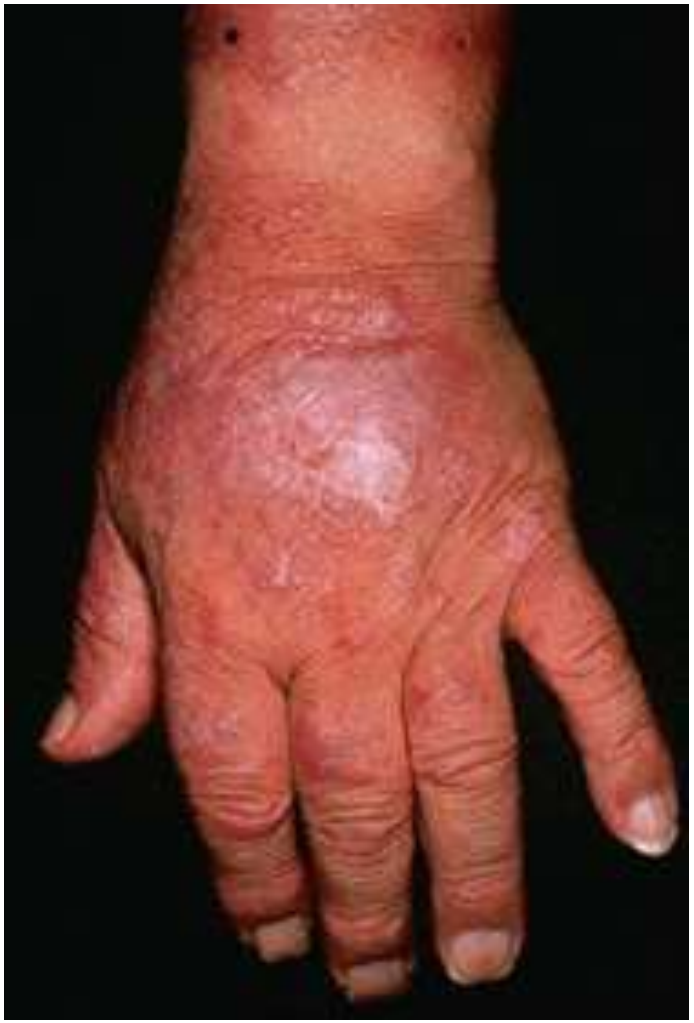


Fig. 11.17 Lichenoid drug eruption. Photodistributed lichenoid eruption due to hydrochlorothiazide (note sparing under watchband).

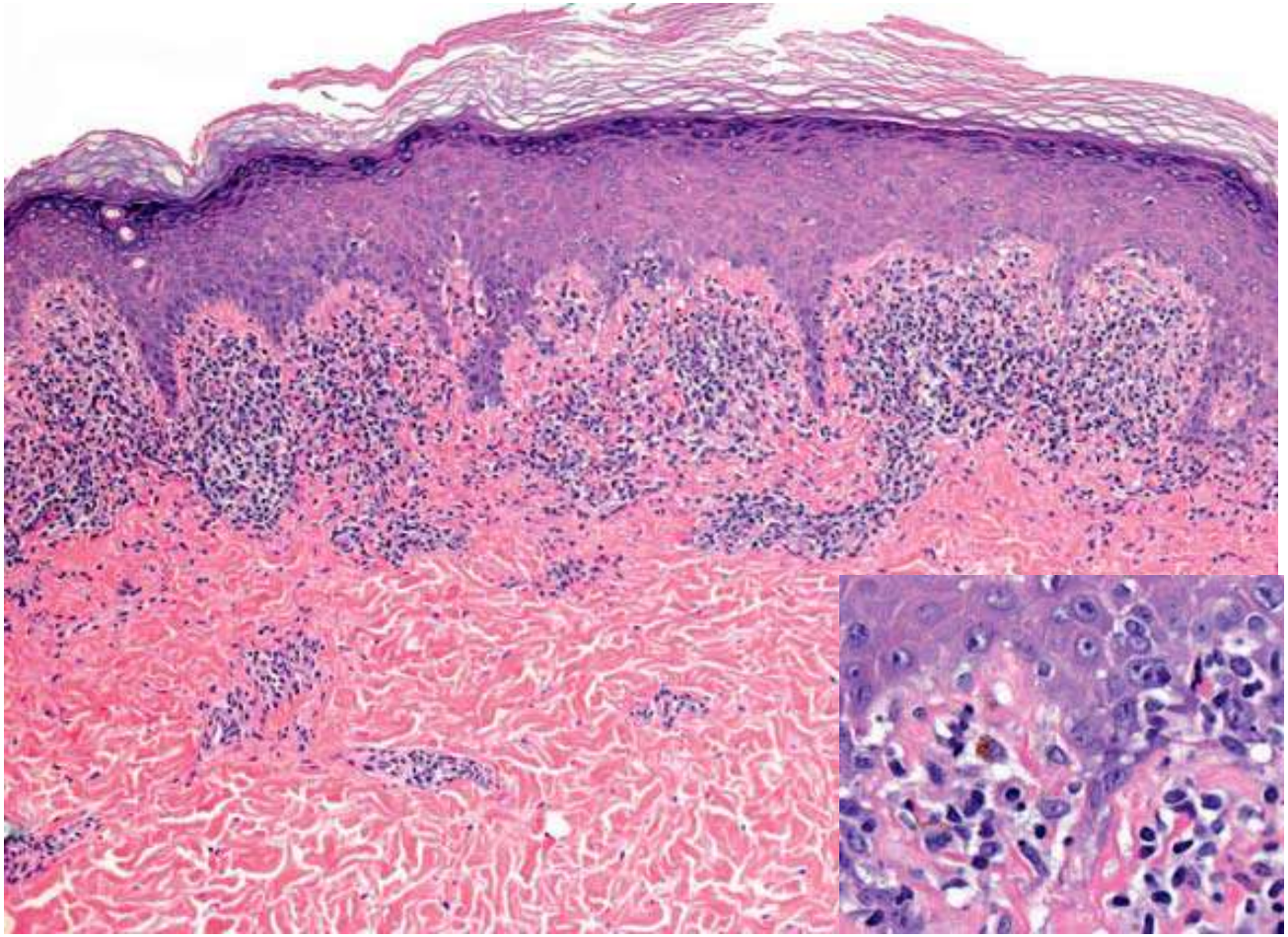


Fig. 11.18 Histopathologic features of lichen planus. Hyperkeratosis, focal increase in the granular layer, sawtoothing of the epidermis with keratinization of the basal layer, and a lichenoid infiltrate. Apoptosis of keratinocytes and melanophages are also present (insert). *Courtesy, Lorenzo Cerroni, MD*

THERAPEUTIC LADDER FOR LICHEN PLANUS
Topical corticosteroids (2)
Superpotent topical corticosteroids (oral LP (1); cutaneous LP (2))
Topical calcineurin inhibitors (e.g. pimecrolimus and tacrolimus in oral LP (1); tacrolimus in vulvar (2) and other forms (3) of LP)
Intralesional corticosteroids (2)
Intramuscular triamcinolone acetonide [0.5–1 mg/kg/month × 3–6 months] (3)
Narrowband UVB (2)
Oral metronidazole *[500 mg po bid] (2)
Antimalarials *(2)
Systemic retinoids* (1 for etretinate; 3 for alitretinoin)
Griseofulvin *(2)
PUVA (2)
UVA1 (2)
308-nm excimer laser for oral LP (2)
Systemic corticosteroids† (1)
Low-dose weekly methotrexate (2)
Mycophenolate mofetil (2)
Thalidomide (2)
Cyclosporine (3)
Sulfasalazine *(1 for cutaneous LP)
Extracorporeal photochemotherapy (2)
Targeted immunomodulators (TNF-α inhibitors, alefacept, basiliximab) (3)
*Implicated in lichenoid drug eruptions. †Often a first-line therapy for severe, acute cutaneous LP.

Table 11.5 Therapeutic ladder for lichen planus. Systemic treatments are usually reserved for more severe disease. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

TIPs for Oral Lichen Planus

- Water pick
- Manage Candida acutely with fluconazole and chronically with daily clotrimazole troche
- CREST whitening (dilute peroixde)
- 1mg tacrolimus capsule – open & dissolve in ½ liter water swish and spit for 2 minutes (Ortonne)
- Topical and/or intralesional corticosteroids
- Oral methotrexate or mycophenolate if needed
- Biopsy as indicated for exclusion of SCC

Torti DC, Jorizzo JL. Arch Dermatol 2007;143:511-515

Bullous Pemphigoid

Key Features

- Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease; it predominantly affects the elderly
- It is usually a chronic disease, with spontaneous exacerbations and remissions, which maybe accompanied by significant morbidity
- BP is associated with tissue-bound and circulating autoantibodies directed against BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e), components of junctional adhesion complexes called hemidesmosomes that promote dermal-epidermal cohesion

Bullous Pemphigoid

Key Features (Cont.)

- The spectrum of clinical presentations is extremely broad. Characteristically, BP is an intensely pruritic eruption with widespread blister formation. In early stages, or in atypical variants of the disease, only excoriated, eczematous or urticarial lesions (either localized or generalized) are present
- Diagnosis relies on immunopathologic examiniations, particularly direct and indirect immunofluorescence microscopy as well as anti-BP180/BP230 ELISAs

MAJOR AUTOANTIGENS OF SUBEPIDERMAL AUTOIMMUNE-MEDIATED BLISTERING DISEASES

Disease	Target antigen(s)	Mol. wt. (kDa)	Morphologic structures
Bullous pemphigoid (BP)	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e	230	Hemidesmosomal plaque
Gestational pemphigoid	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e	230	Hemidesmosomal plaque
Mucous membrane (cicatricial) pemphigoid	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e[†]	230	Hemidesmosomal plaque
	Laminin 5 (332; $\alpha_3\beta_3\gamma_2$; epiligrin)	165, 140, 105	Anchoring filaments
	Laminin 6 (311; $\alpha_3\beta_1\gamma_1$)[‡]	165, 220, 200	Anchoring filaments/extracellular matrix
	Integrin β_4 subunit[§]	200	Hemidesmosomal plaque/anchoring filaments
Linear IgA bullous dermatosis (LABD)	LAD antigen[¶]	97/120	Anchoring filaments
	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e[†]	230	Hemidesmosomal plaque
	Type VII collagen[†]	290/145	Anchoring fibrils
Epidermolysis bullosa acquisita	Type VII collagen[†]	290/145	Anchoring fibrils
Anti-p200 pemphigoid	Laminin gamma-1 chain	200 kDa	Extracellular matrix
Bullous systemic lupus erythematosus	Type VII collagen[†]	290/145	Anchoring fibrils

[†]Detectable in a subset of patients
[‡]Binding to laminin 6 (331) depends on the presence of cross-reactive autoantibodies directed against the α-chain of laminin 5 (332).
[§]Reactivity with the cytoplasmic domain of the β4 subunit of the α6β4 integrin described in a subset of patients with ocular cicatricial pemphigoid.
[¶]It constitutes the most characteristic serologic marker for LABD. The 120 kDa LAD antigen corresponds to the cleaved, shed extracellular domain of BP180/BPAG2. The 97 kDa protein results from its further proteolytic degradation.

Table 30.1 Major autoantigens of subepidermal autoimmune-mediated blistering diseases. Not an exhaustive list. In the course of these diseases, it is possible to detect autoantibodies directed against additional antigens, the significance of which remains to be established. In certain cases, a so-called "intermolecular epitope spreading" phenomenon is thought to occur.

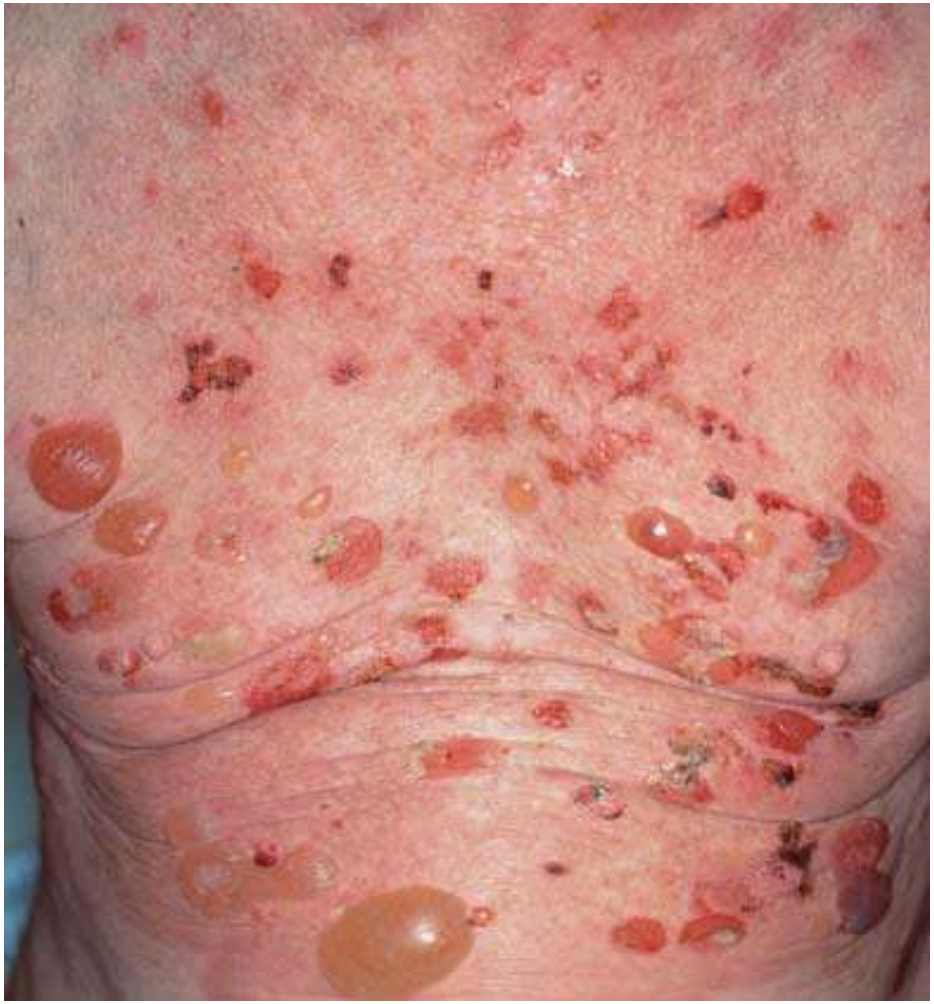


Fig. 30.2 Bullous pemphigoid – bullous presentation. Classic presentation with multiple tense bullae arising on normal and erythematous skin. Several of the bullae have ruptured, leaving circular erosions.

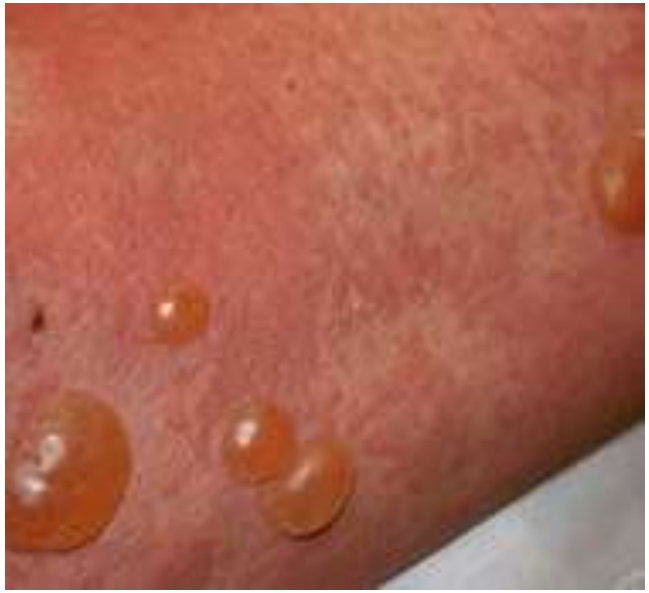


Fig. 30.3 (A)

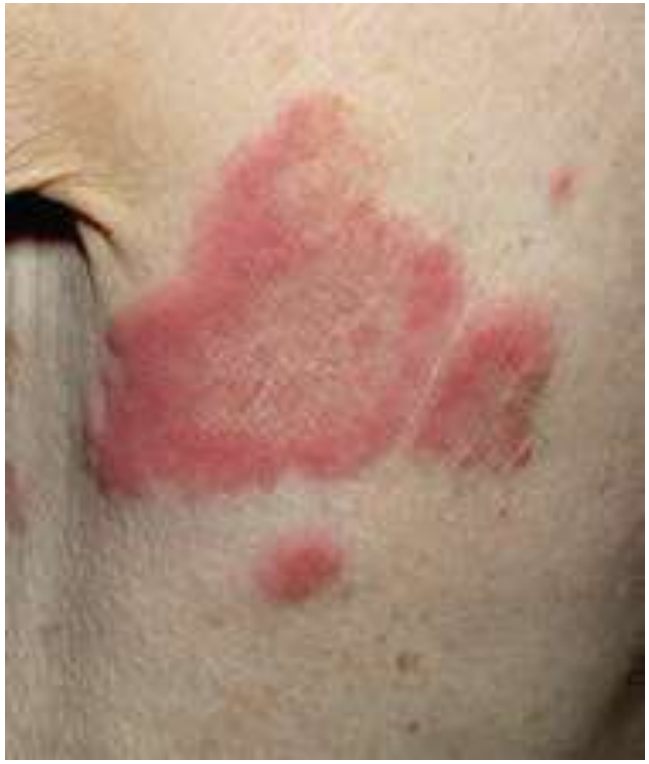


Fig. 30.3 (B)

Fig. 30.3 Bullous pemphigoid – urticarial (and bullous) presentation. (A) Pink urticarial papules and plaques as well as tense bullae containing serous fluid. **(B)** Firm annular urticarial plaques.

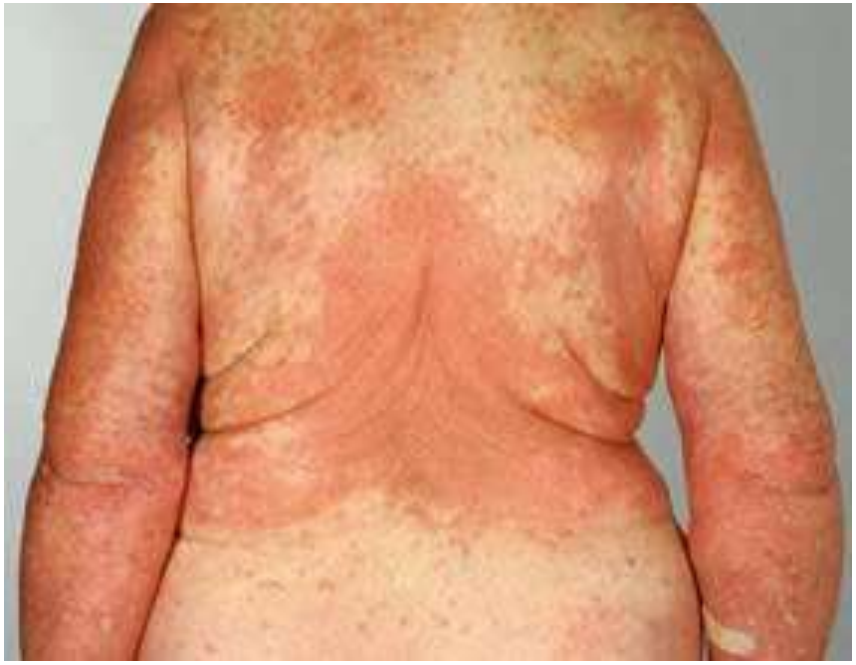


Fig. 30.4 (A)

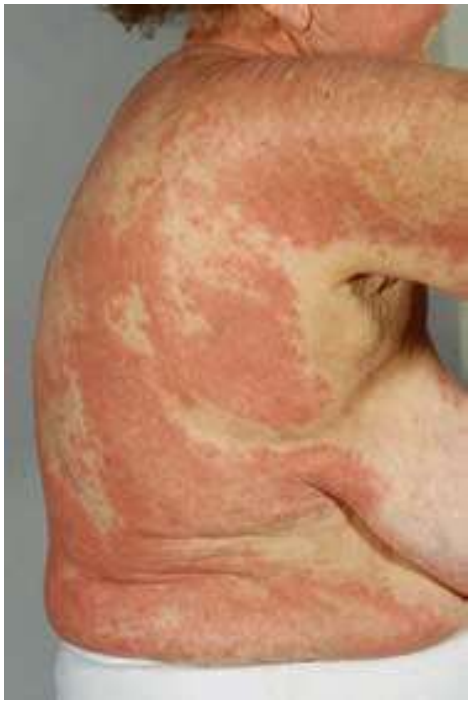


Fig. 30.4 (B)

Fig. 30.4 Bullous pemphigoid – eczematous presentation. (A), (B) Large pink eczematous plaques on the trunk and upper extremities.

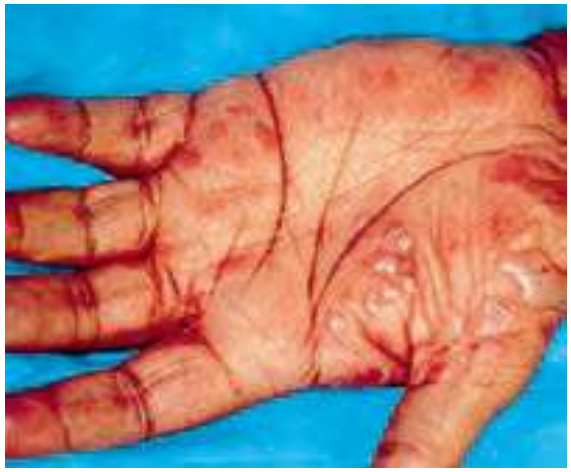


Fig. 30.5 (A)

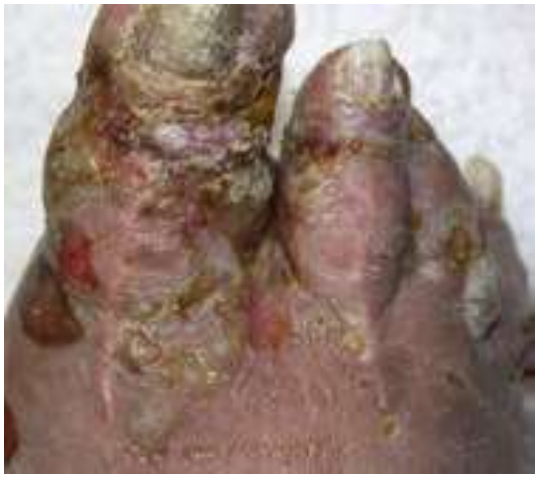


Fig. 30.5 (B)

Fig. 30.5 (C)

Fig. 30.5 (D)

Fig. 30.5 Bullous pemphigoid – unusual clinical variants. Grouped vesicles and bullae on the palms **(A)** and toes **(B)** that can resemble pompholyx (dyshidrosiform pemphigoid). **(C)** Vegetating plaque in the inguinal crease (pemphigoid vegetans). **(D)** Toxic epidermal necrolysis-like lesions with large erosions.

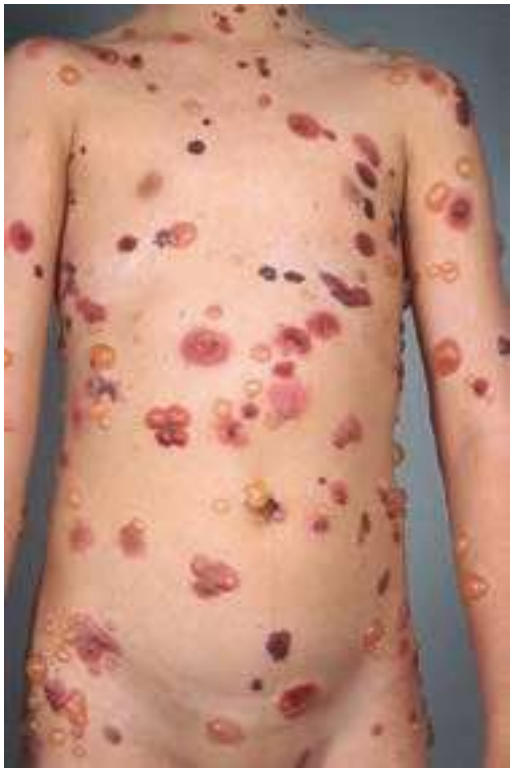


Fig 30.6 (A)

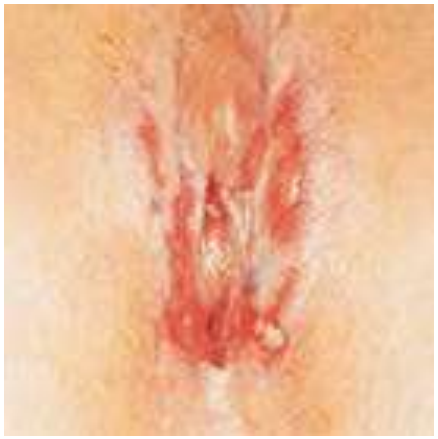


Fig. 30.6 (B)

Fig. 30.6 Childhood bullous pemphigoid. (A) Generalized tense bullae and crusted erosions. **(B)** Localized vulvar involvement (vulvar childhood pemphigoid).

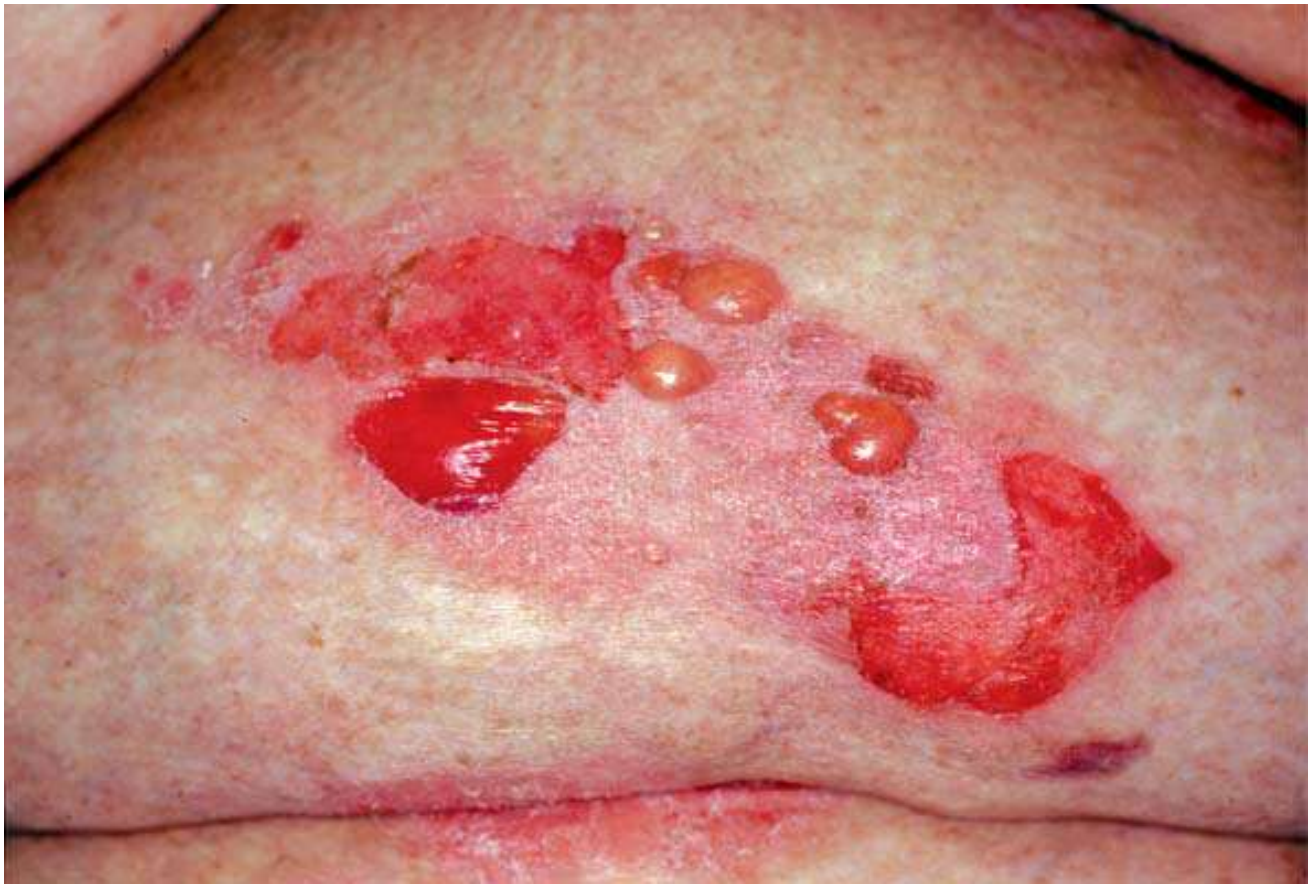


Fig. 30.7 Bullous pemphigoid localized to a psoriatic plaque. No obvious trigger was detected, as the patient was not receiving phototherapy. *Courtesy, Jean L. Bolognia, MD*

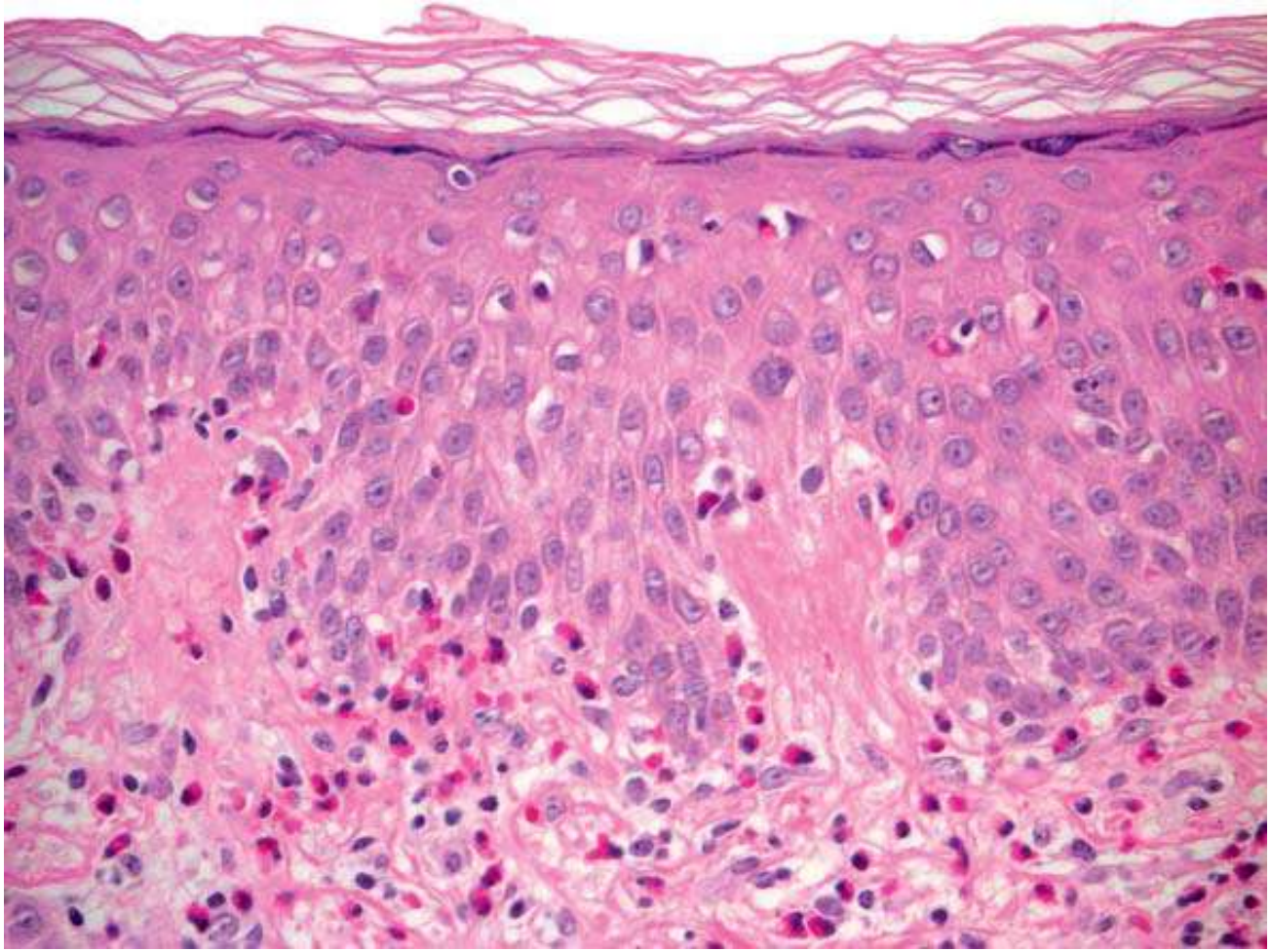


Fig. 30.8 Urticarial phase of bullous pemphigoid – histologic features. Eosinophils are present within the dermis as well as the epidermis (eosinophilic spongiosis). Some of the eosinophils have lined up at the dermal-epidermal junction, a typical finding in the urticarial stage of BP. *Courtesy, Lorenzo Cerroni, MD*

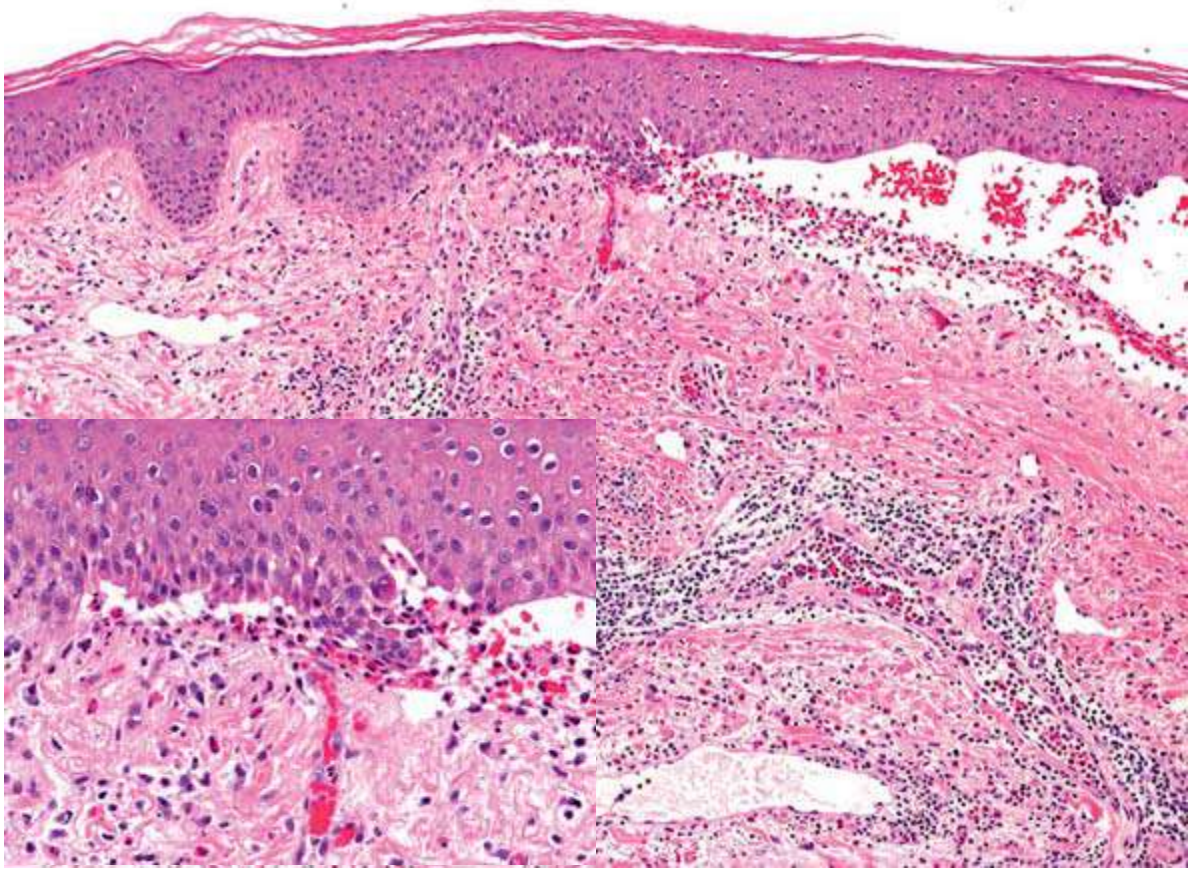


Fig. 30.9 Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see insert). *Courtesy Lorenzo Cerroni, MD*

SURVEY OF CONTROLLED TRIALS FOR THE TREATMENT OF PATIENTS WITH BULLOUS PEMPHIGOID						
Authors (year)	Design	Intervention		Number of patients	Response	Remarks
Roujeau et al.[34] (1984)	Randomized multicenter	Group 1: Group 2:	Prednisolone (0.3 mg/kg/day) Prednisolone + 8 plasma exchanges	41	Total and daily corticosteroid doses needed for disease control lower in group 2	Low prednisolone dose
Morel & Guillaume[35] (1984)	Randomized multicenter	Group 1: Group 2:	Prednisone (0.75 mg/kg/day) Prednisone (1.25 mg/kg/day)	42	At day 51, remission in group 1 (33%) and group 2 (55%) not significantly different	Trend for a better response in group 2
Guillot et al.[36] (1986)	Non-randomized retrospective	Group 1: Group 2:	Prednisolone alone Prednisolone plus long-term plasma exchange	21	At month 6, relapse rate and total corticosteroid doses lower in group 2	Risk of severe side effects in group 2
Dreno et al.[37] (1993)	Randomized multicenter	Group 1: Group 2:	Methylprednisolone (1– 1.5mg/kg/day) Prednisolone (1– 1.5mg/kg/day)	57	At day 10, no difference in response except for better decline of pruritus in group 1	Analysis of early response only
Guillaume et al.[38] (1993)	Randomized multicenter	Group 1: Group 2: Group 3:	Prednisolone (1 mg/kg/day) alone Prednisolone and azathioprine (100–150 mg/day) Prednisolone and 4 plasma exchanges	98	At month 6, no significant difference in remission rate between group 1 (42%), group 2 (39%) and group 3 (29%)	More complications in group 2. No adjustment of doses of azathioprine based on TPMT levels
Fivenson et al.[39] (1994)	Randomized single center	Group 1: Group 2:	Nicotinamide (1.5 g/day) plus tetracycline (2 g/day) Prednisone (40– 80mg/day)	18	At month 1, no difference in response, but fewer side effects in group 1	Low number of studied patients. High drop-out rate
Joly et al.[40] (2002)	Randomized multicenter	Group 1: Group 2:	Topical clobetasol propionate Prednisone 0.5– 1mg/kg/day	341	At week 3, control rates better in group 1	At year 1, topical therapy is associated with a significantly reduced mortality and complication rate
Beissert et al.[41] (2007)	Randomized multicenter prospective	Group 1 Group 2	Methylprednisolone (0.5 mg/kg) with azathioprine (2 mg/kg) Methylprednisolone (0.5 mg/kg) with mycophenolate mofetil (2 g daily)	38 35	Disease control similar in the two groups	In group 1, higher incidence and severity of liver toxicity. Trend for faster disease control and less total cumulative doses of steroids in group 1. No adjustment of doses of azathioprine based on TPMT levels
Joly et al.[42] (2009)	Randomized multicenter prospective	Group 1 Group 2	Topical clobetasol propionate *standard* regimen for 12 months (40 g daily as starting dose) Topical clobetasol propionate, *mild* regimen for 6 months (10– 30g daily as starting dose)	153 159	Time to achieve disease control of BP similar in both groups. At 1 year, trend for higher relapse rate in patients with moderate BP treated with mild regimen	In moderate BP treated with mild regimen, decrease in the risk of death/side effects. Lower cumulative dose of clobetasol in mild regimen

Table 30.3 Survey of controlled trials for the treatment of patients with bullous pemphigoid. TPMT, thiopurine methyltransferase.

Tips for Bullous Pemphigoid

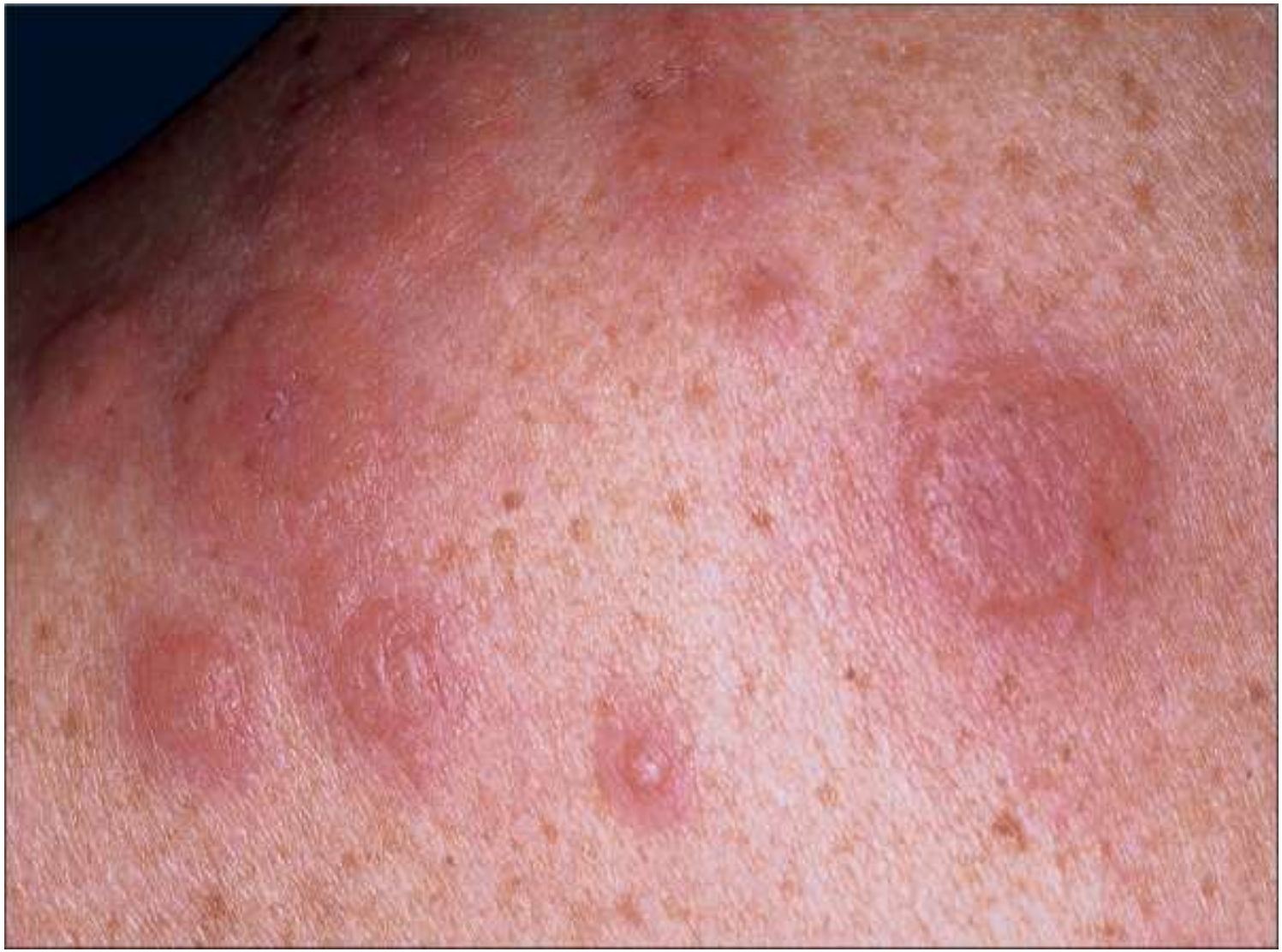
1. Antibacterial body washes/Bleach baths
2. Topical triamcinolone 0.1% cream 3:1 in Silvadene cream
3. Weekly methotrexate corrected for age/creatinine
4. Lower dose prednisone
5. 2 year program

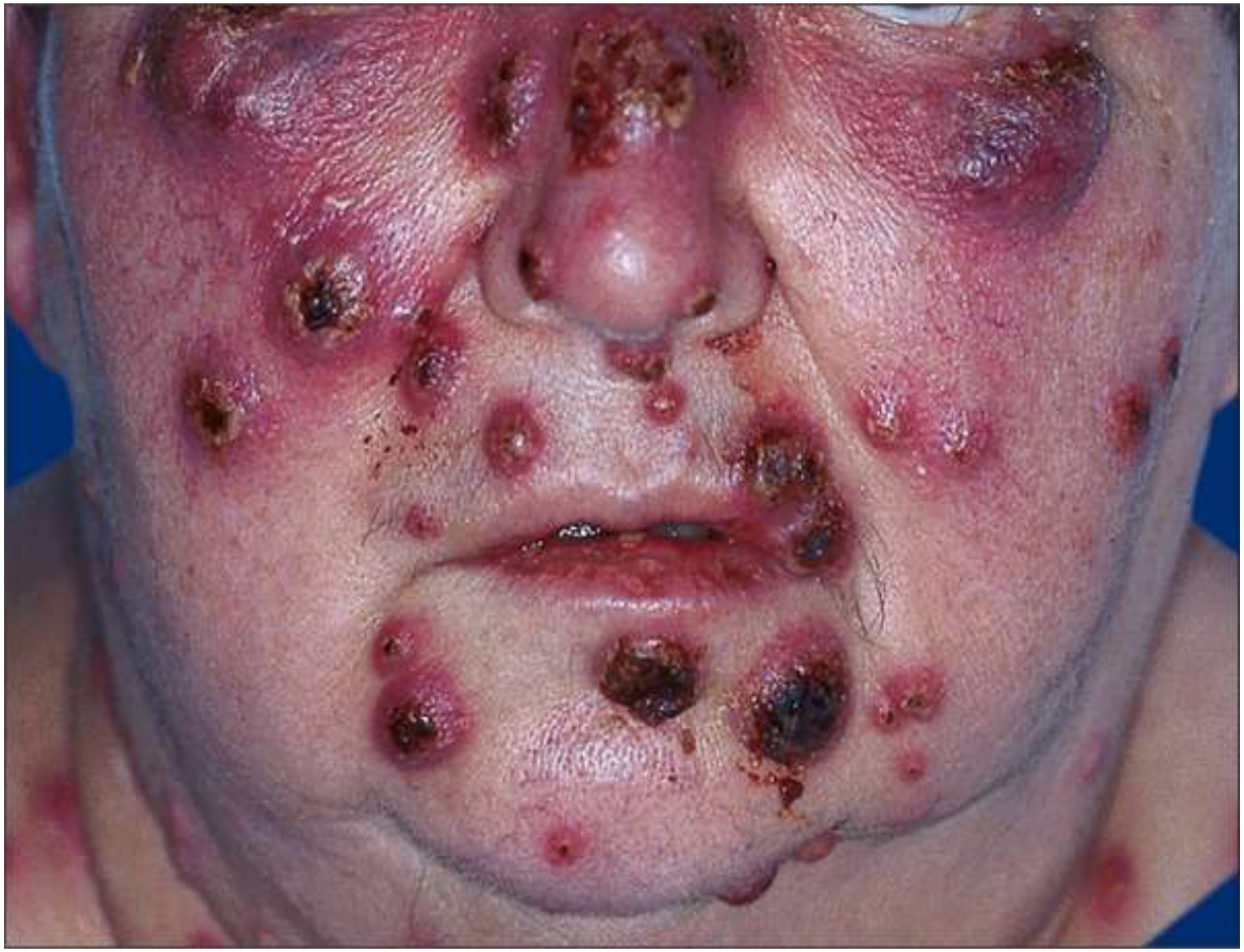
Kwantra SG, Jorizzo JL. J Dermatol Treat 2013;24:327-331.

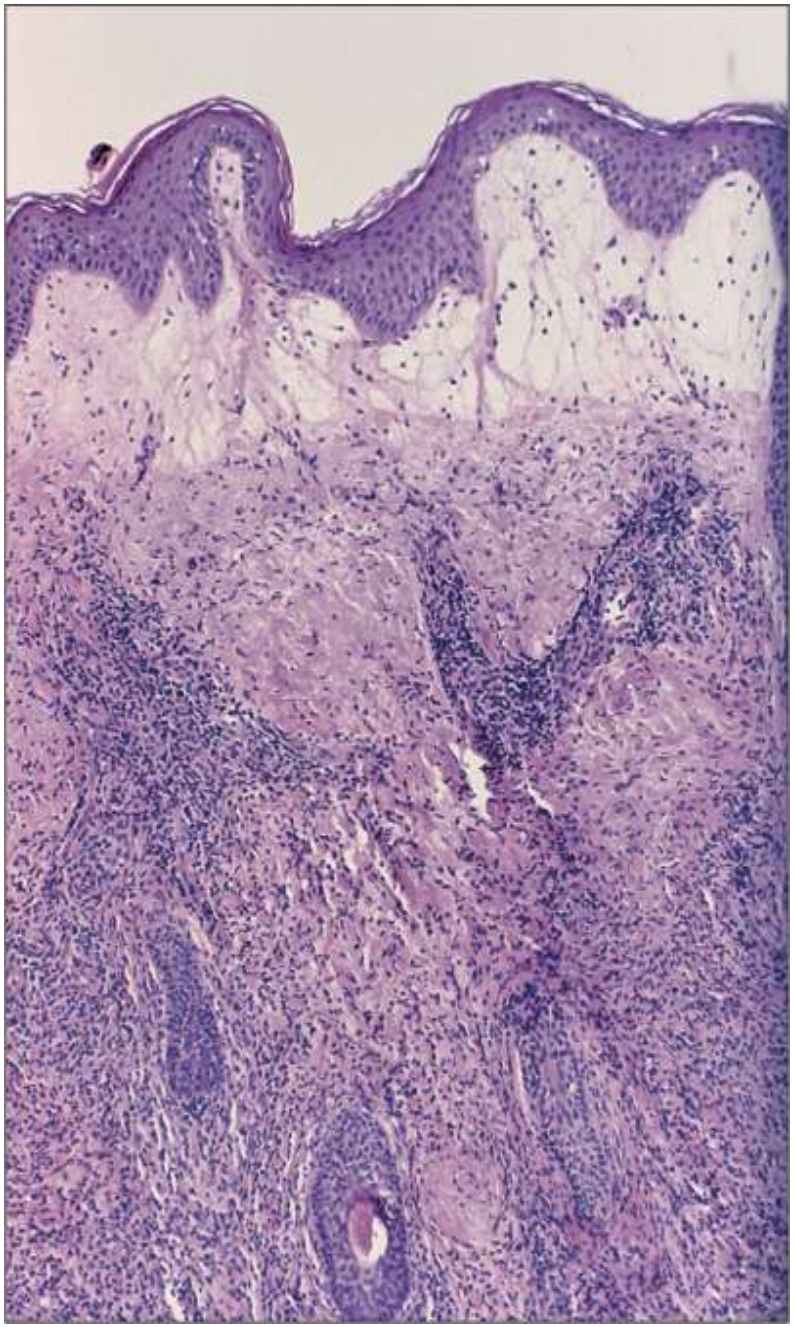
Sweet's Syndrome

Key features

- **Constitutional signs and symptoms such as fever and malaise**
- **Clinically, erythematous plaques are seen; occasionally they are bullous**
- **Histologically, dense perivascular neutrophilic infiltrate, edema and, infrequently, bullae; leukocytoclasia with minimal to no evidence of vasculitis**
- **Associated conditions include infections, malignancies (especially acute myelogenous leukemia), inflammatory bowel disease, autoimmune disorders, drugs and pregnancy**







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Sweet's Syndrome Related Articles 2014 alone

1. Clinicopathologic Expansion: SQ variant (not new); Hands (not new) Hystiocytoid

   Full blown histopathologic LCCV (not new) Insect bite overlap on histopathology
2. Internal Involvement (Sterile neutrophilic lesions) Neuro Sweet's, Upper respiratory tract, Lung)

   Eye – optic nerve, keratitis
3. Etiology

   Many more drugs

   More cancers

   More infections (Sporotrichosis, leprosy, schistosomiasis

   More autoimmune diseases – SLE, throiditis

Behcet’s Disease

Behcet's Disease

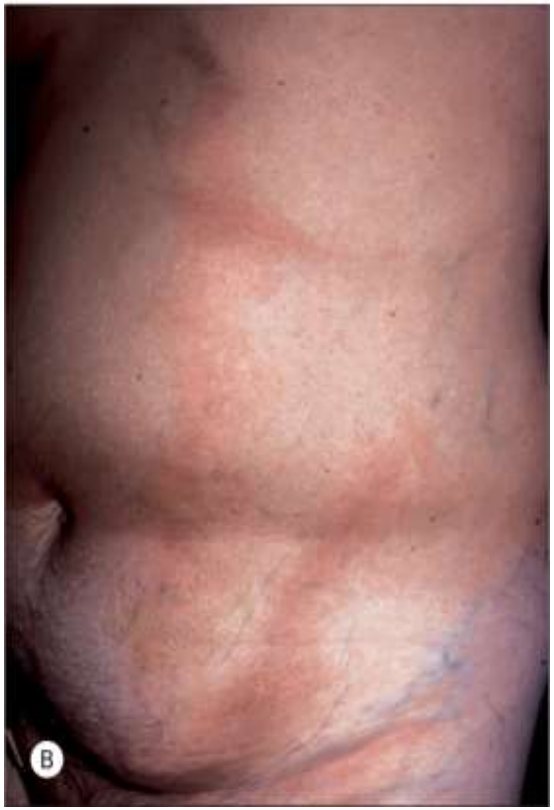
Key Features

- A multisystem, polysymptomatic disease
- Diagnosis is based on International Study Group criteria of recurrent oral ulceration, recurrent genital ulceration, ocular abnormalities (eg. uveitis, retinal vasculitis) and cutaneous lesions
- Cutaneous findings range from sterile papulopustules and palpable purpura to erythema nodosum-like lesions
- Histologically, a neutrophilic angiocentric inflitrate with leukocytoclastic (early) or lymphocytic (late) vasculitis is the characteristic finding


A


B


A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Important Issues Regarding Behcet's Disease

1. Do not overdiagnose complex aphthosis

   Reference: Letisinger JA, McCarty MA, Jorizzo JL. Complex Aphthosis…. J Am Acad Dermatol 2005;52:500-8.
2. Exclude HLA-B27 – associated sacroileitis spectrum disease and/or inflammatory bowel disease
3. Use a therapeutic ladder mucosal/ocular and other major systemic are at polar ends.

Bowel-Associated Dermatosis-Arthritis Syndrome

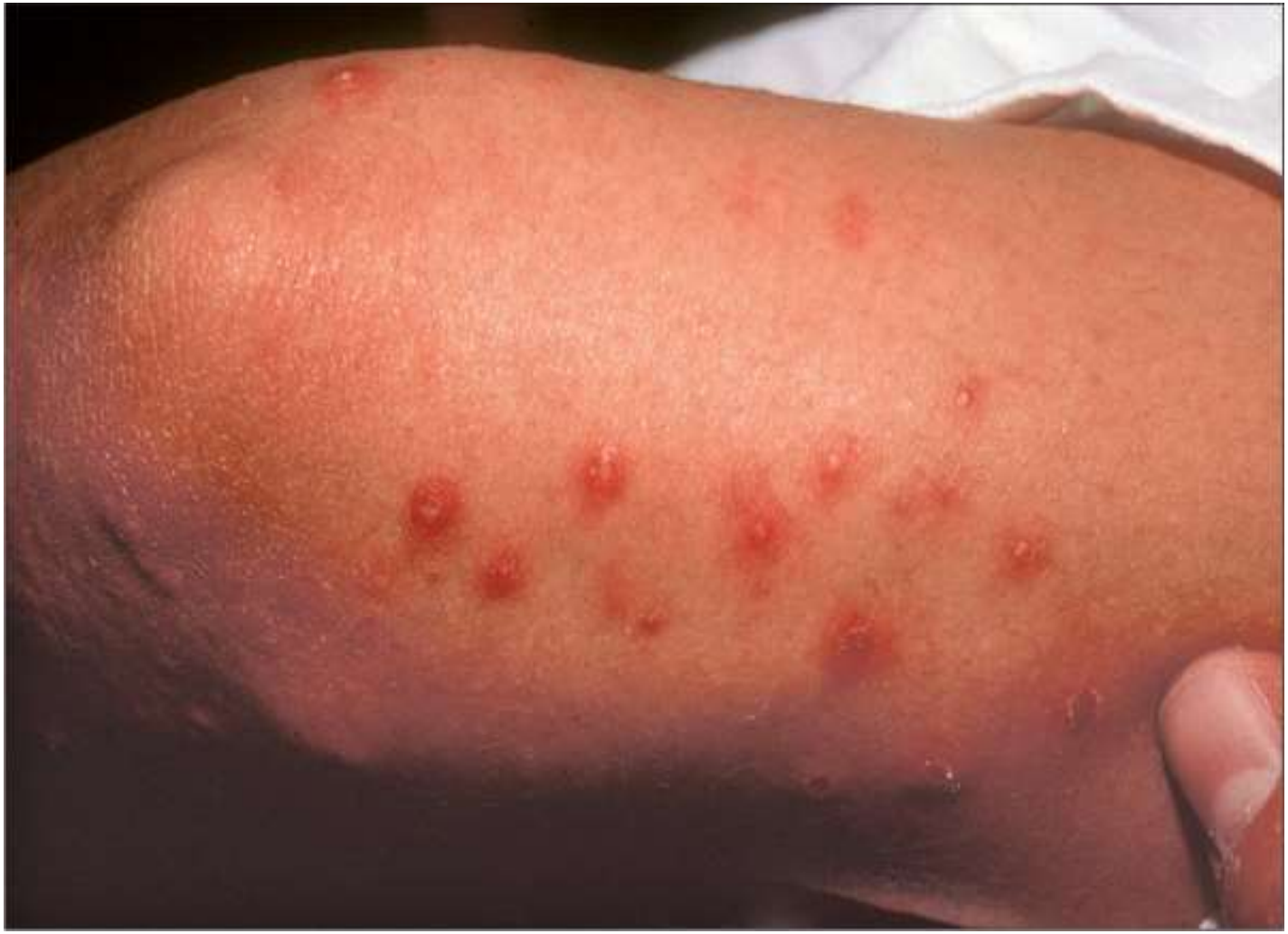
Key Features

- Constitution signs and symptoms are serum sickness-like
- Cutaneous lesions include erythematous and purpuric papules and vesicles as well as nodular panniculitis
- Associated polyarthritis and tenosynovitis
- Histopathology includes dermal nodular perivascular neutrophilic infiltrate with edema and lobular neutrophilic and septal panniculitis

  Reference: Jorizzo JL et al. Arch Intern Med 1983;143:457-61

Clinical points regarding Bowel-Associated Dermatosis-Arthritis Syndrome

- Bowel surgery suggests blind loops – evaluate carefully with gastroenterologist
- Inflammatory bowel diseases are important causes of this syndrome.
- While dermatologic therapeutic ladder is useful – management of underlying disease is the focus.



Pyoderma Gangrenosum

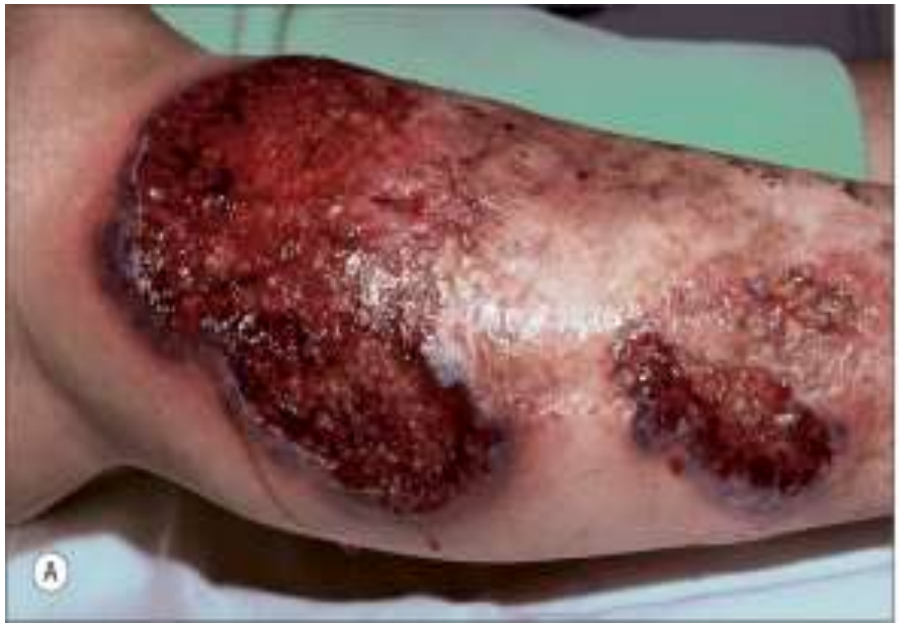
Key Features

- Four major clinical forms: ulcerative, bullous, pustular, and superficial granulomatous
- Initial lesion is often a pustule on an erythematous base or an erythematous nodule
- Characteristic lesion is an ulcer with a necrotic undermined border; the base may be purulent or vegetative

Pyoderma Gangrenosum

Key Features (Continued)

- Histologically, early lesions are difficult to distinguish from Behcet's lesions
- Associated with inflammatory bowel disease, arthritis, monoclonal gammopathy and other hematologic disorders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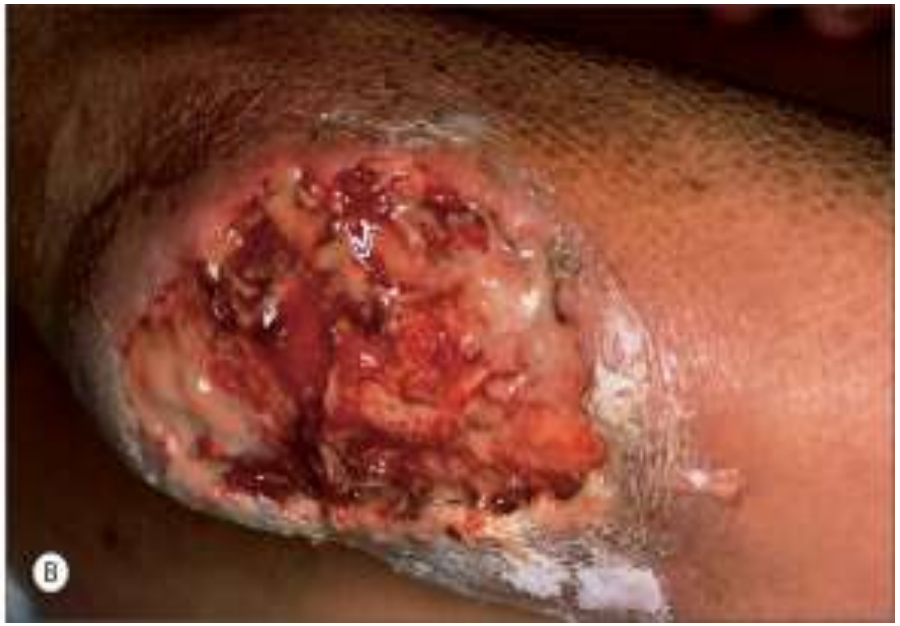
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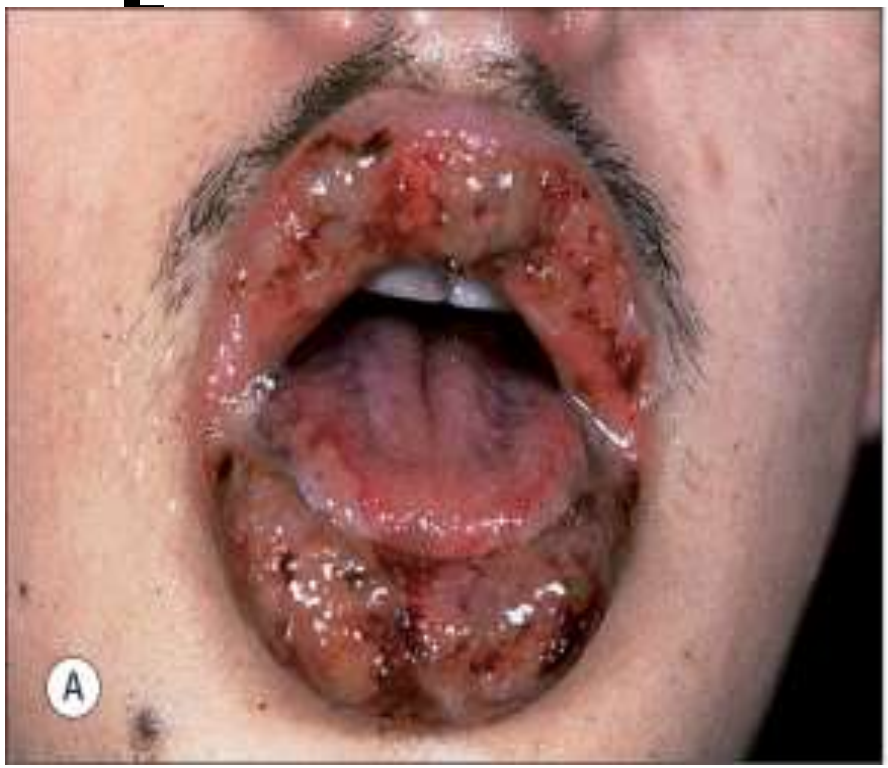
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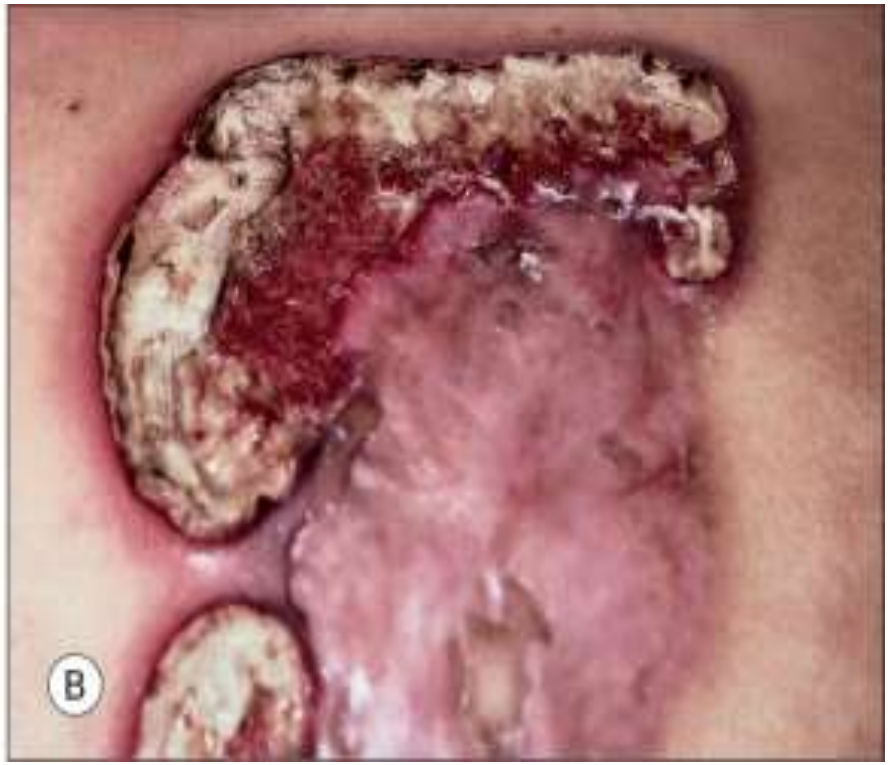
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Clinical Points regarding Pyoderma Gangrenosum

- Most referred patients have large ulcers; but no inflammation – “Gulliver’s sign” (a pterygium)
- Literature is similar to Sweet’s regarding expansion of systemic manifestations and etiology
- Re-exclude mimics (diagnosis of exclusion but also contaminants on culture)
- Especially: Wegener’s, histoplasmosis, atypical AFB, Sporotrichosis, factitial disease

Neutrophilic Vascular Reactions: Update 2015
Patient Evaluation: Overview

- Confirm clinical diagnosis histopathologically
- Assess extent of disease (less critical then vasculitis)
- Attempt to establish etiology
- Therapeutic ladder

Neutrophilic Vascular Reactions: Update 2015

Etiology

Work with a colleague, generally in internal medicine, to perform sequential evaluations that include history and physical examination not just laboratory tests.

Categories include:

Drugs:(be careful: association does not prove causation!)

Infections: Viral, bacterial, Deep fungal, AFB, other

Disease with immune complexes: Autoimmune connective tissue diseases, other autoimmune, inflammatory bowel disease, autoimmune liver disease, Behcet's disease, malignancy especially myelodysplastic diseases. (Curth's postulates)

Neutrophilic Vascular Reactions: Update 2015
Therapeutic Ladder:
Non-ulcerative Cutaneous Lesions

- No Therapy
- Topical therapies
- (access to site of pathology)
- Gradient Support Hose
- Antibiotics
- Pentoxifylline
- Colchicine
- Dapsone/Sulfapyridine
- Combination Colchicine/Dapsone

Neutrophilic Vascular Reactions: Update 2015 Therapeutic Ladder: Ulcerative Cutaneous Lesions or Minimal Systemic Disease

- Various topical (from corticosteroids to dapsone to metronidazole to imiquimod)
- Weekly Pulse Methotrexate
- Prednisone with slow taper
- Thalidomide

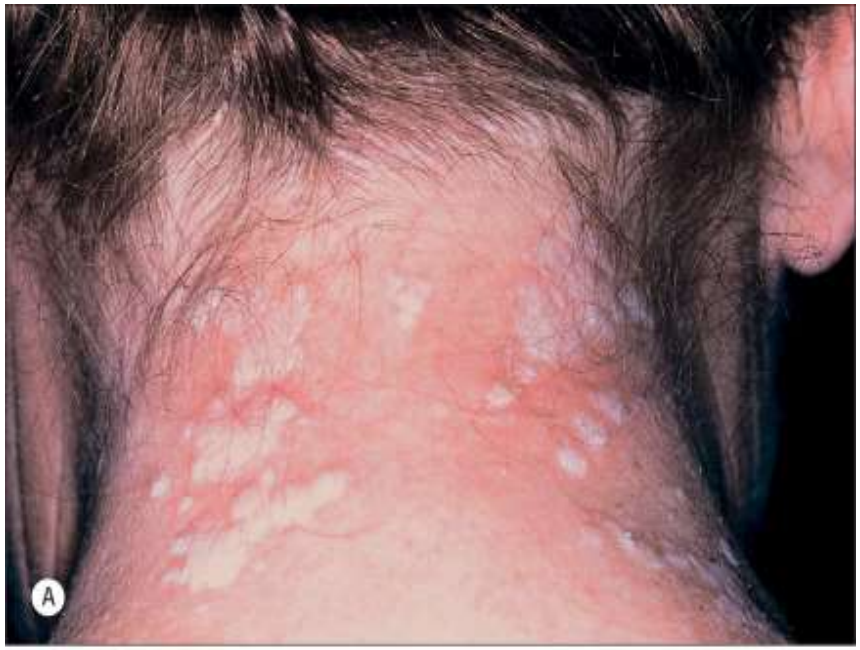
Neutrophilic Vascular Reactions Update: 2015 Therapeutic Ladder - More Severe Diseases

- Prednisone alone or in combination (1 or 2 depending on subset)
- Pulse Prednisone
- Azathioprine
- Cyclophosphamide; pulse or daily (1-for larger vessel vasculitis)
- Mycophenolate mofetil
- Chlorambucil
- Cyclosporine
- TNF alpha inhibitors
- Leflunomide
- Rituximab (2-Mostly SLE patients with vasculitis)
- Gevokizumab (anti Il-1beta)
- Countless treatments aimed at underlying diseases

Lichen Sclerosus

Key Features

- Sclerotic white plaques with epidermal atrophy and, in extramucosal sites, follicular plugging
- Most commonly affects female or male genitalia, less often non-genital skin
- May cause scarring of the vaginal introitus or phimosis
- Severe pruritus may occur
- No systemic manifestations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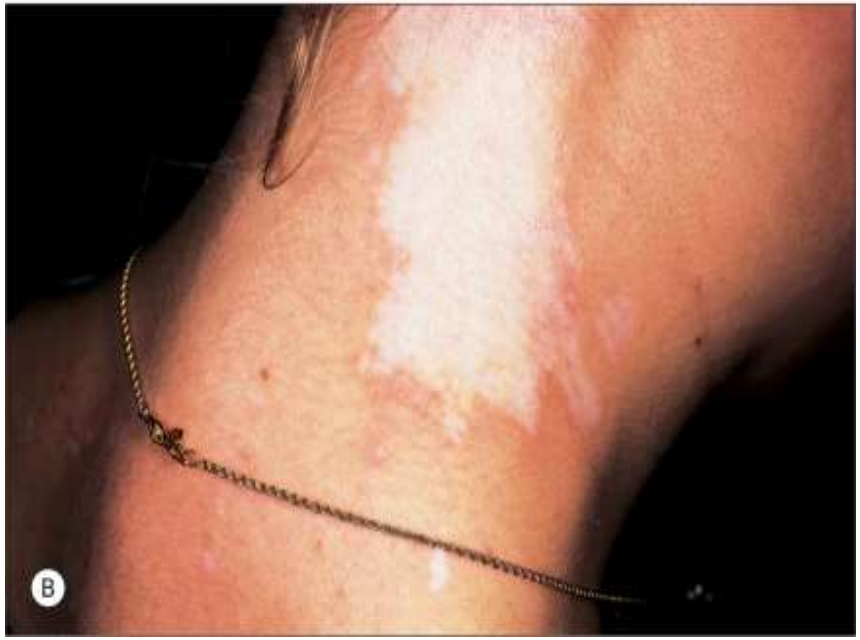
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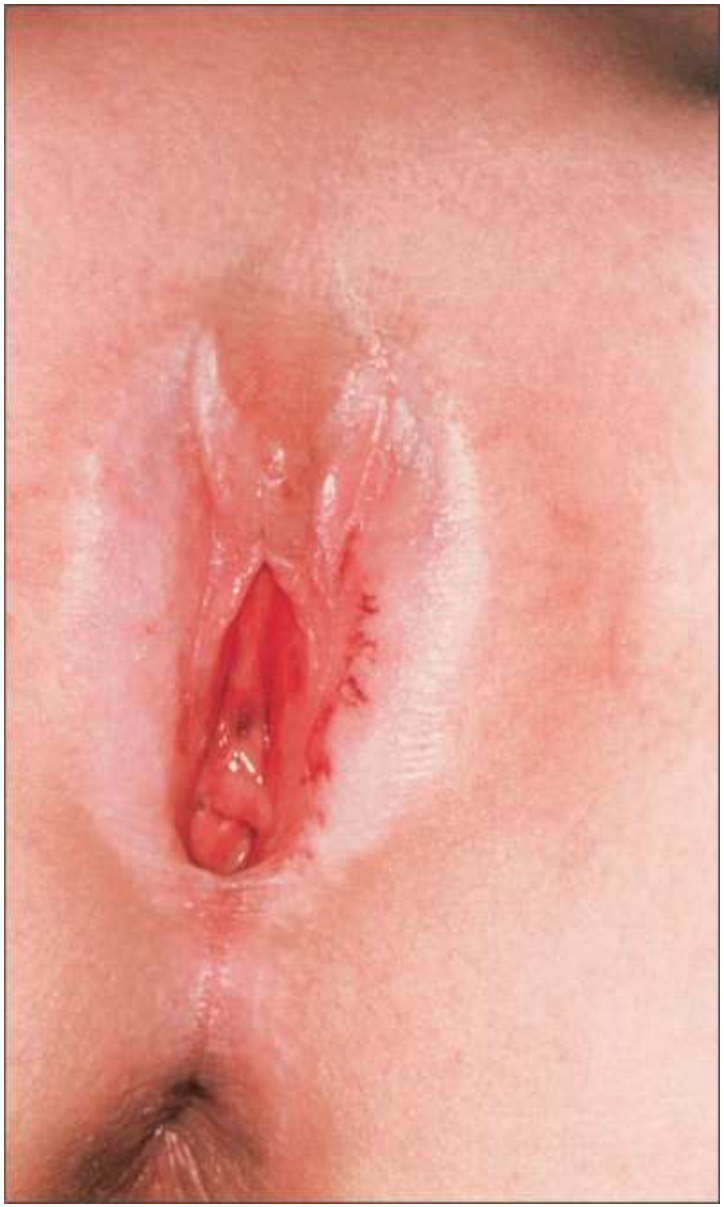
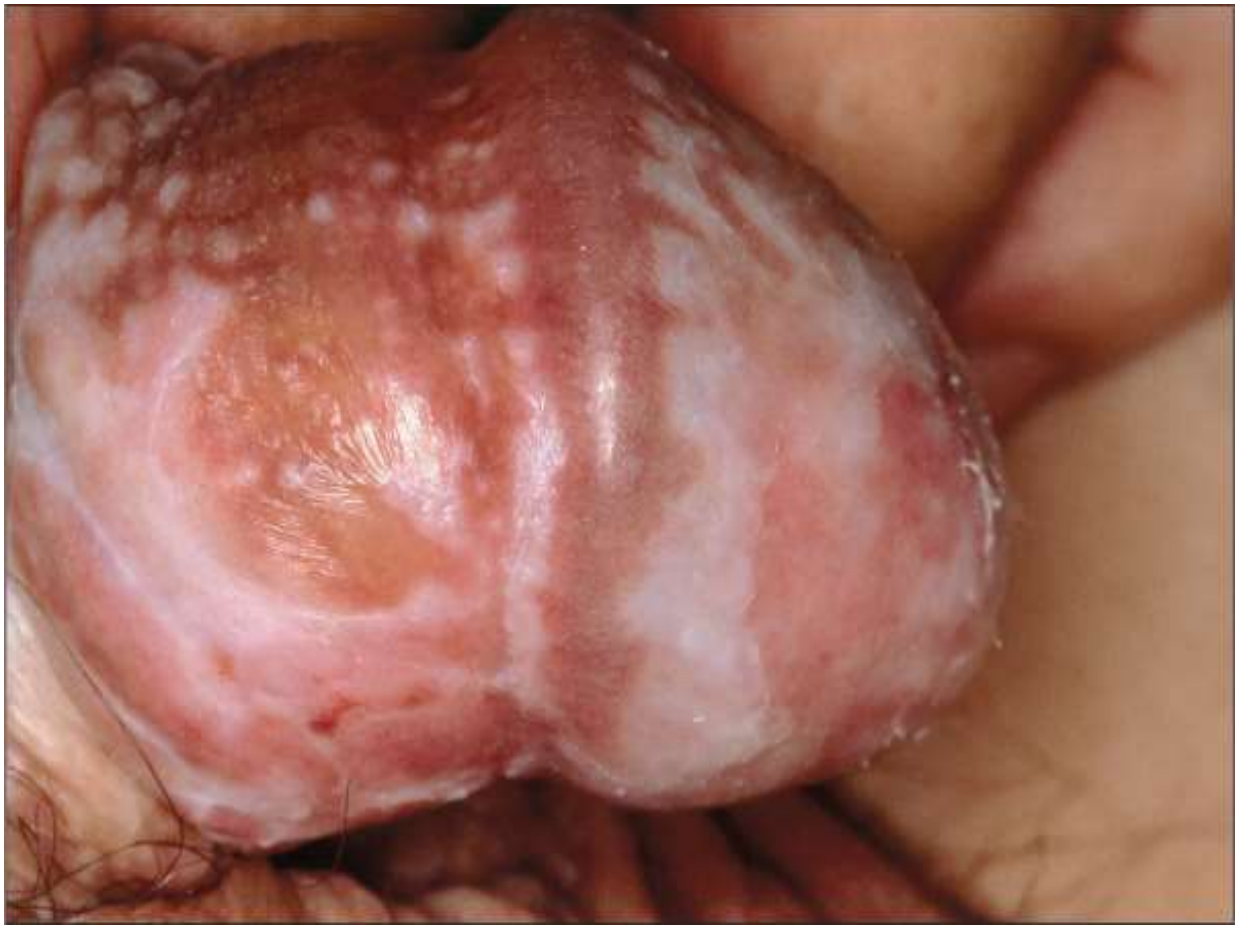
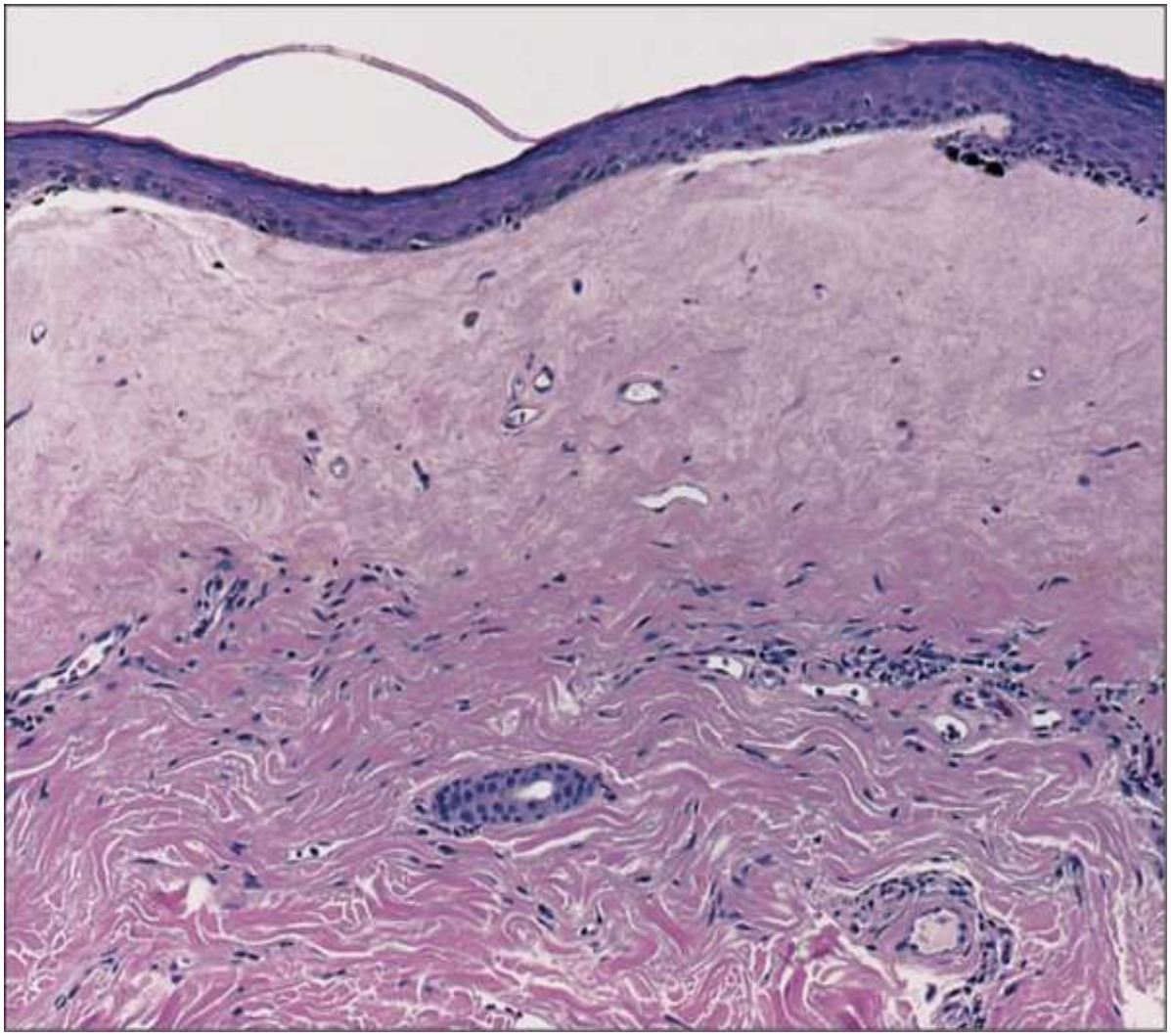






TREATMENT OF MORPHEA AND LICHEN SCLEROSUS					
	Treatment modalities	Morphea		Lichen sclerosus	
		Efficacy	Level of evidence	Efficacy	Level of evidence
Local	Topical corticosteroids	+	3	+++ (ultrapotent)	1
	Intralesional corticosteroids	+	3	++	2
	Topical calcineurin inhibitors	+ (early lesions)	2	++	2
	Vitamin A analogues	+	3	+	2
	Vitamin D analogues	+	3	+	3
	Testosterone	No experience		0	1
	Progesterone	No experience		0	1
	Intralesional interferon-γ	0	1	No experience	
Systemic	Penicillin	++ (approx. 5% of patients)	3	No experience	
	Hydroxy-/chloroquine	No experience		+	3
	Corticosteroids	+	3	+	3
	Vitamin A analogues*	+	3	++	1
	Vitamin D analogues	0	1	+	3
	Cyclosporine	0	3	No experience	
	Penicillamine	++	3	No experience	
	Methotrexate	++	2	No experience	
Phototherapy	Oral photochemotherapy	++	3	+	3
	Bath photochemotherapy	+++	2	++	3
	Cream photochemotherapy	++	3	+	3
	UVA1	+++	2	++	2
	Photodynamic therapy	+	3	++	3
	Extracorporeal photopheresis	+	3	No experience	
Others	CO_2 laser	No experience		++	3
	Surgery	Selected patients		Selected patients	
	Physical therapy	Important		–	–

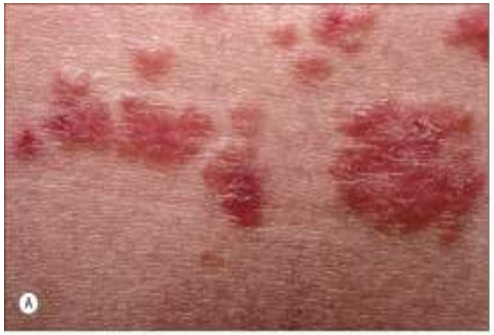
*e.g. acetretin.

Table 44.2 Treatment of morphea and lichen sclerosus. +++, Highly effective; ++, effective; +, moderately effective; 0, low efficacy or ineffective. 1, prospective controlled trial; 2, retrospective study or large case series; 3, small case series or individual case reports.

Sarcoidosis

Key Features

- A systemic granulomatous disorder of unknown origin that most commonly involves the lungs
- Cutaneous manifestations of sarcoidosis are seen in up to one-third of patients, and they may be the first clinical sign of the disease
- Red-brown to violaceous papules and plaques appear most often on the face, lips, neck, upper back and extremities
- Variants of sarcoidosis include subcutaneous, lupus pernio and ulcerative
- Erythema nodosum is a non-specific inflammatory skin finding associated with acute, transient sarcoidosis
- Histologically, sarcoidosis is characterized by non-caseating epitheloid granulomas, usually without surrounding lymphocytic inflammation (i.e. ‘naked’ granulomas)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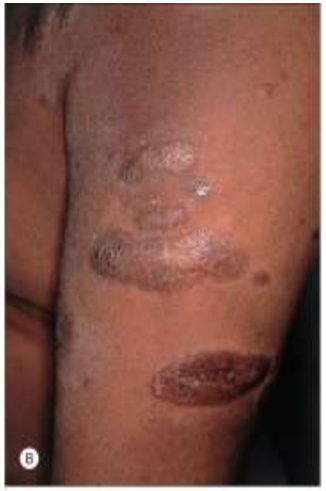
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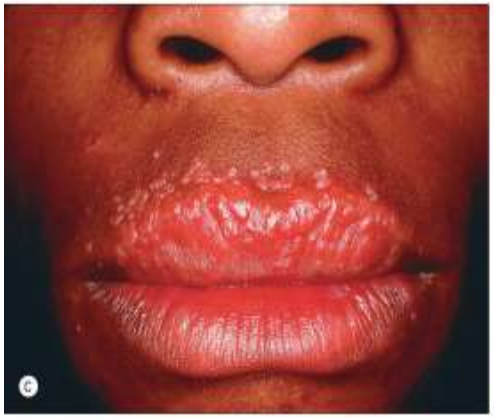
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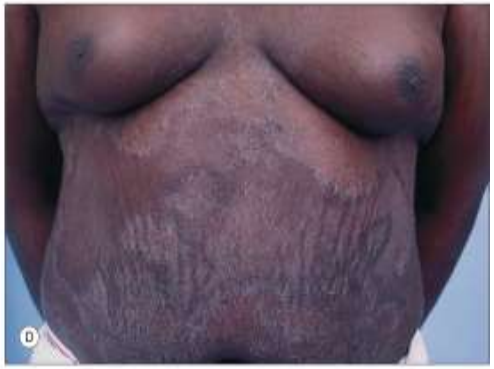
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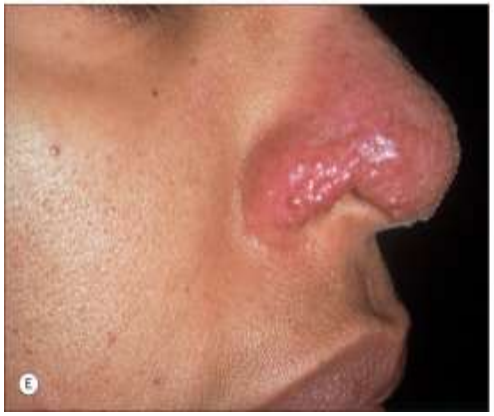
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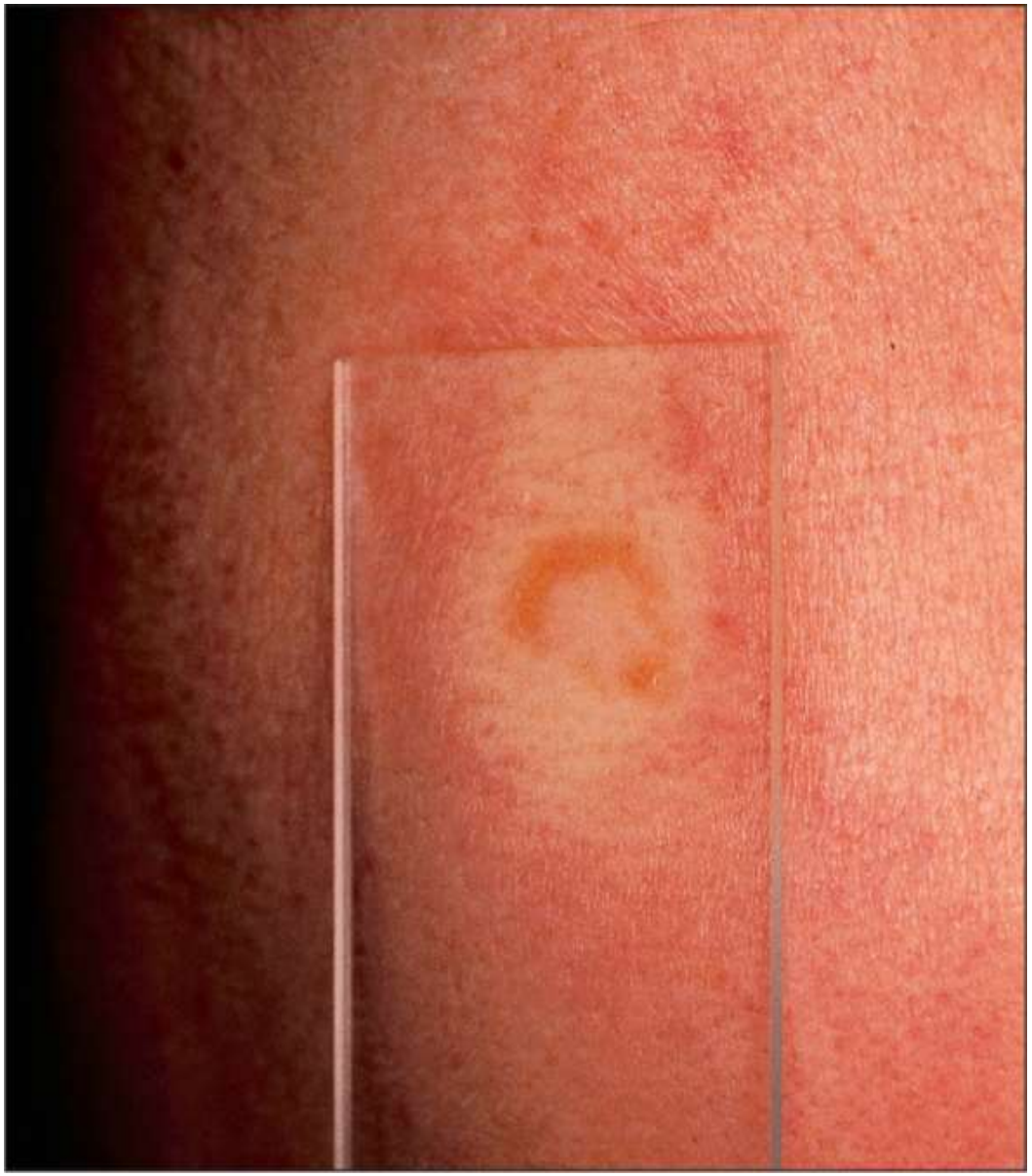

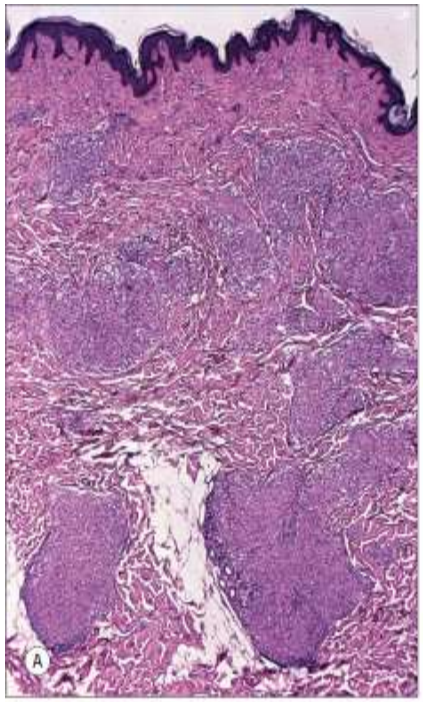
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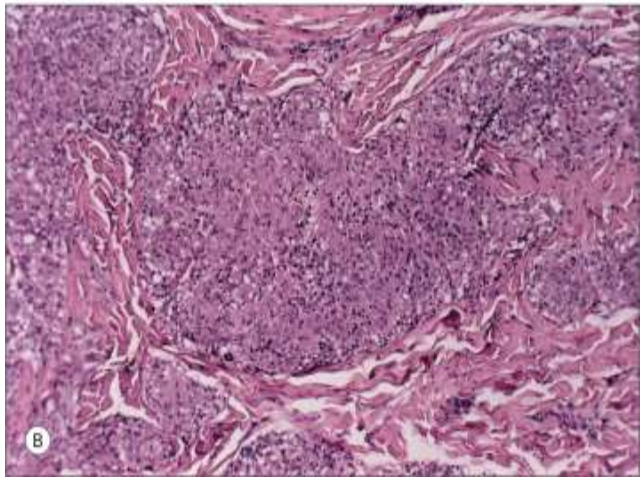
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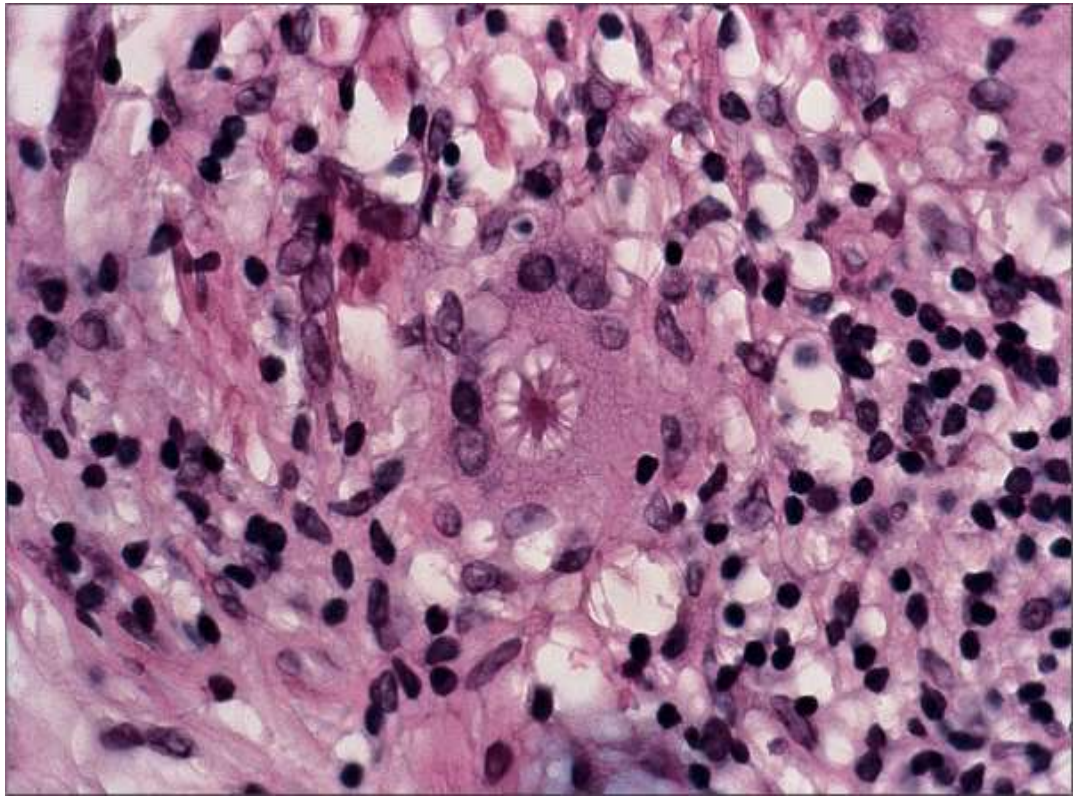


Sarcoidosis: Systemic Features

- SURT
- Intrathoracic
- Ocular
- Lymph Nodes
- Musculoskeletal
- Neurosarcoidosis
- Hepaticsarcoidosis
- Cardiac
- Endocrine metabolic

HISTOLOGIC FEATURES OF THE MAJOR GRANULOMATOUS DERMATITIDES								
	Sarcoidosis	**Granuloma annulare**	**Necrobiosis lipoidica**	**AEGCG**	**Cutaneous Crohn's disease**	**Rheumatoid nodule***	**Interstitial granulomatous dermatitis***	**Palisading neutrophilic and granulomatous dermatitis***
Typical location	Superficial and deep dermis†	Superficial and mid dermis†	Entire dermis, subcutis	Superficial and mid dermis	Superficial and deep dermis	Deep dermis, subcutis	Mid and deep dermis	Entire dermis
Granuloma pattern	Tubercle with few peripheral lymphocytes ("naked")	Palisading or interstitial	Diffuse palisading and interstitial; horizontal "tiers"	Palisading, irregular	Tubercle with surrounding lymphocytes	Palisading	Palisading in small "rosettes"	Palisading; prominent neutrophils and leukocytoclasia
Necrobiosis (altered collagen)	No	Yes ("blue")	Yes ("red")	No	No	Yes ("red")	Yes ("blue")	Yes ("blue")
Giant cells	Yes	Variable	Yes	Yes	Yes	Yes	Variable	Variable
Elastolysis	No	Variable	Variable	Yes	No	No	Variable	Variable
Elastophagocytosis	No	No	No	Yes	No	No	No	No
Asteroid bodies	Yes	Variable	Variable	Yes	No	No	Variable	Variable
Mucin	No	Yes	Minimal	No	No	Variable	Minimal	Variable
Extracellular lipid	No	Variable	Yes	No	No	Variable	No	No
Vascular changes	No	Variable	Yes	No	No	Yes	No	Yes

*See Chapter 45.
†Subcutaneous variant can also occur

Table 93.2 Histologic features of the major granulomatous dermatitides. Interstitial granulomatous dermatitis and palisading neutrophilic and granulomatous dermatitis are often considered two ends of a spectrum. Tan-shaded area is not covered in this chapter. AEGCG, annular elastolytic giant cell granuloma.

TREATMENT OF CUTANEOUS SARCOIDOSIS

Topical, intralesional or systemic corticosteroids (2)
Topical calcineurin inhibitors (3)
Minocycline (2)
Systemic hydroxychloroquine or chloroquine (2)
Intralesional chloroquine (3)
Allopurinol (3)
Isotretinoin (3)
Methotrexate (2)
PUVA (psoralen plus UVA) (3)
Thalidomide (2)
TNF-α inhibitors (adalimumab, infliximab, etanercept)* (3)
Leflunomide (2)
Mycophenolate mofetil (3)
Surgical excision (3)
Pulsed dye or CO_2 laser (3)
Photodynamic therapy (3)

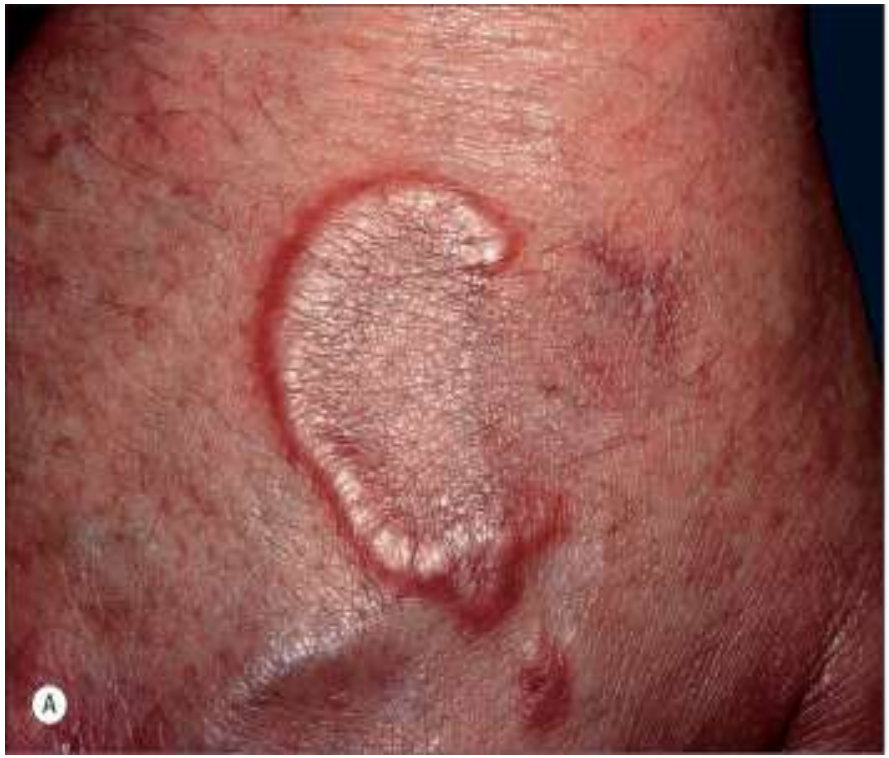
*Can trigger sarcoidosis.

Table 93.3 Treatment of cutaneous sarcoidosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. TNF, tumor necrosis factor.

Granuloma Annulare

Key Features

- Small grouped papules assuming an annular configuration often in a symmetrical and acral distribution
- Seen primarily in children and young adults
- Clinical variants include localized, generalized, micropapular, nodular, perforating, patch and subcutaneous forms
- Reports of an association with diabetes mellitus are controversial
- Histopathologic specimens show infiltrative or palisading granulomatous dermatitis with focal degeneration of collagen and elastin and deposition of mucin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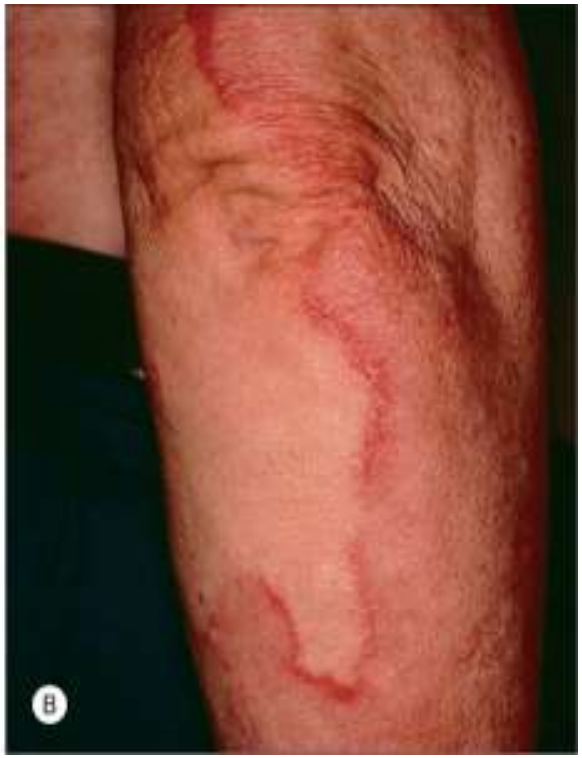
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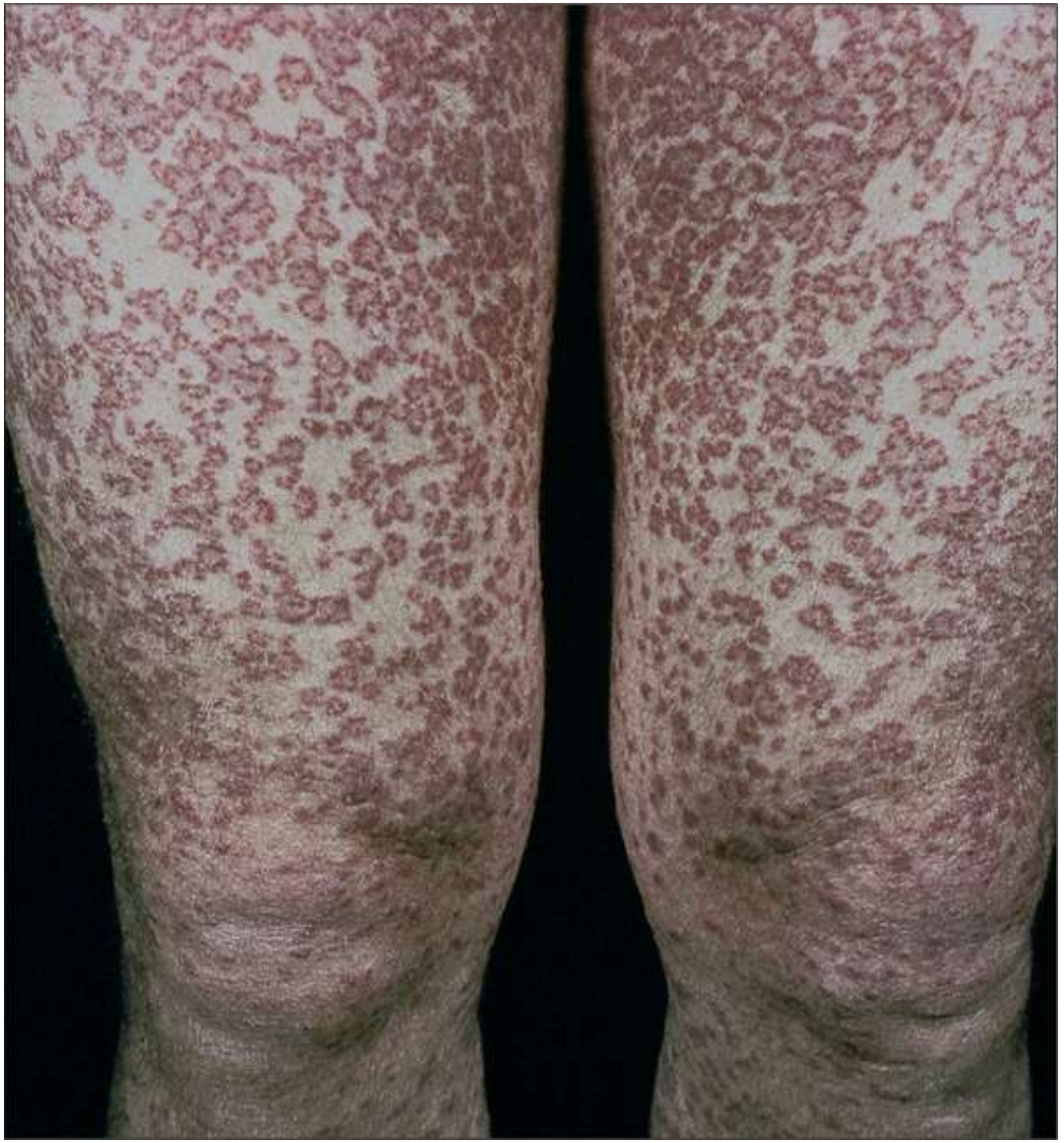

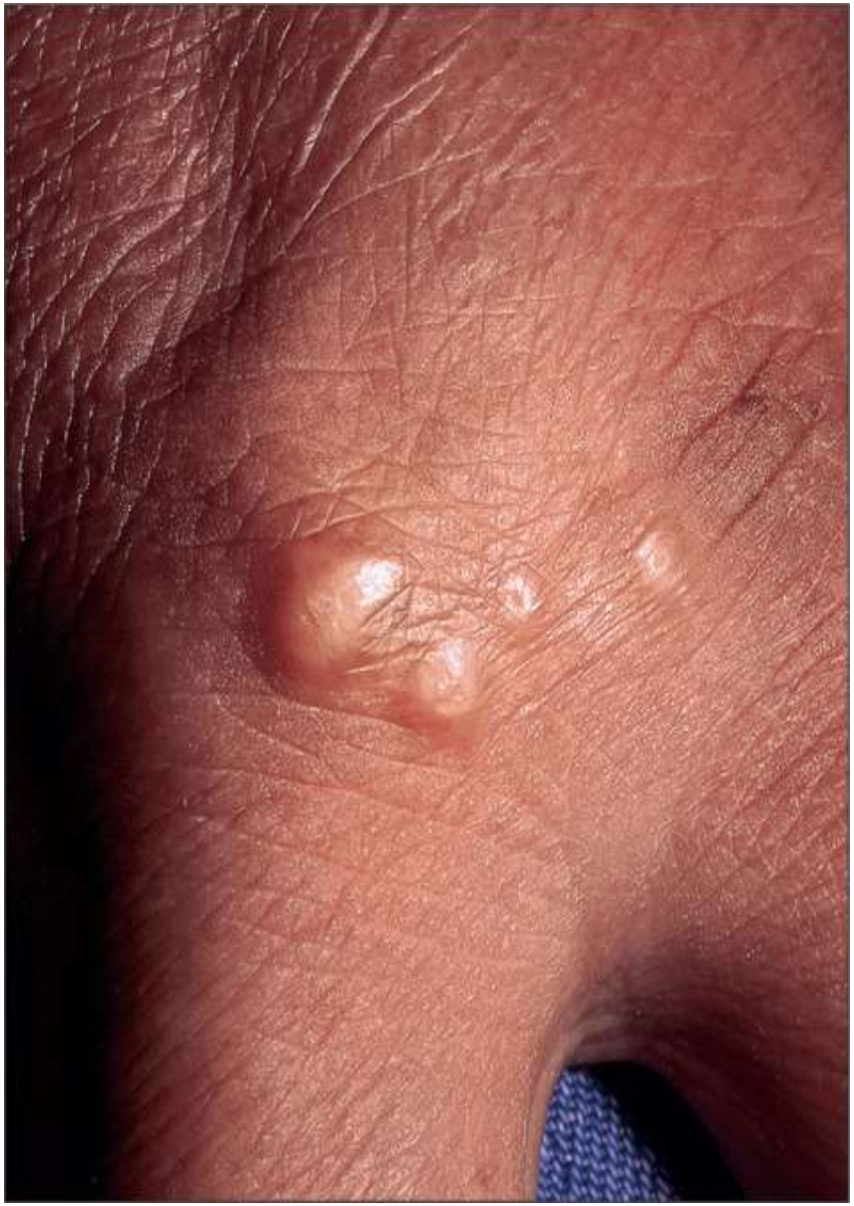

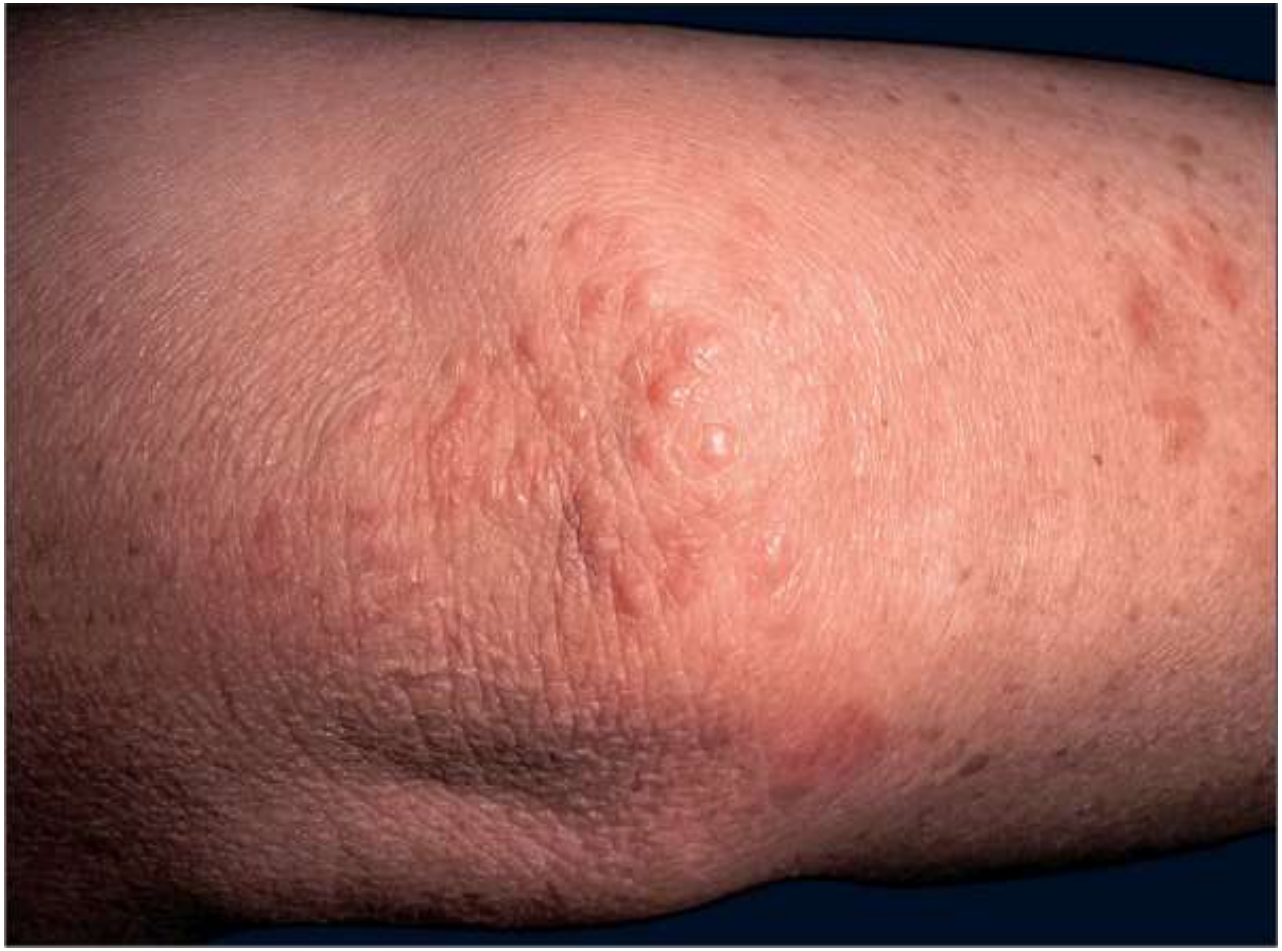

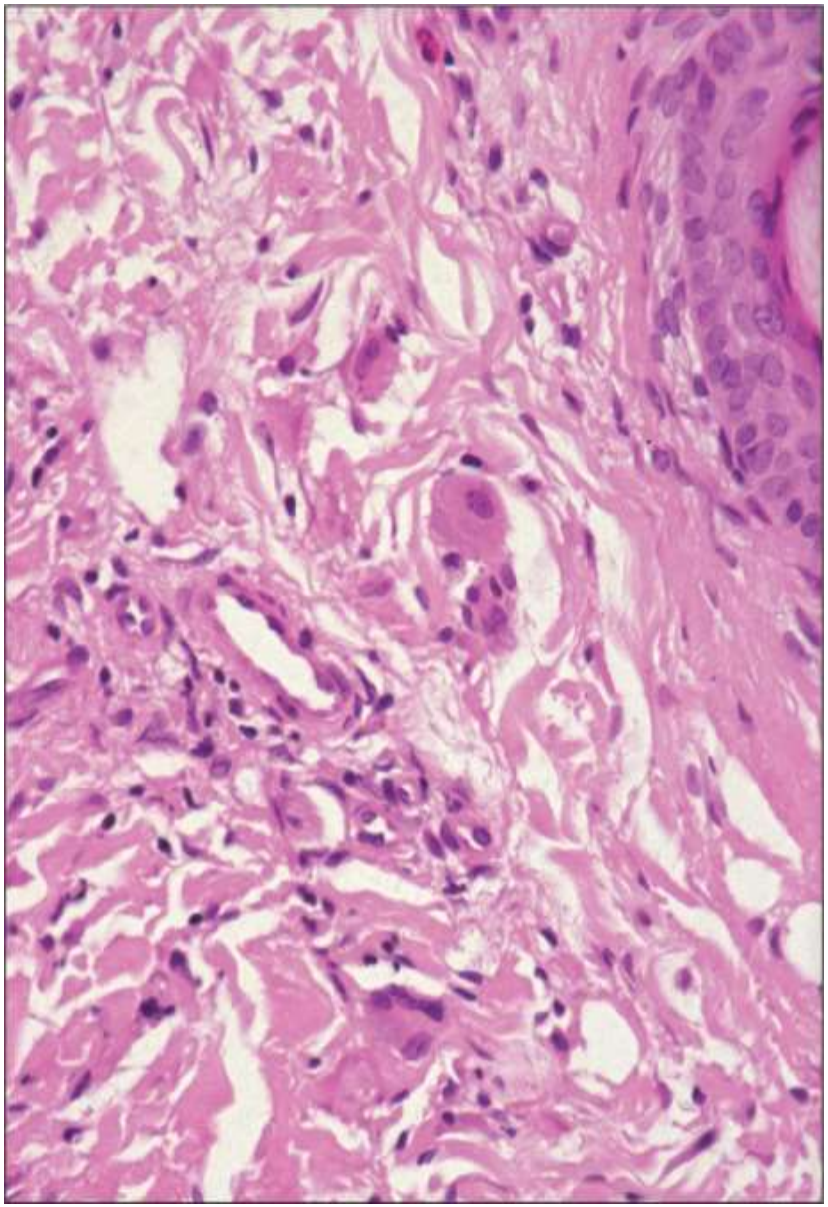

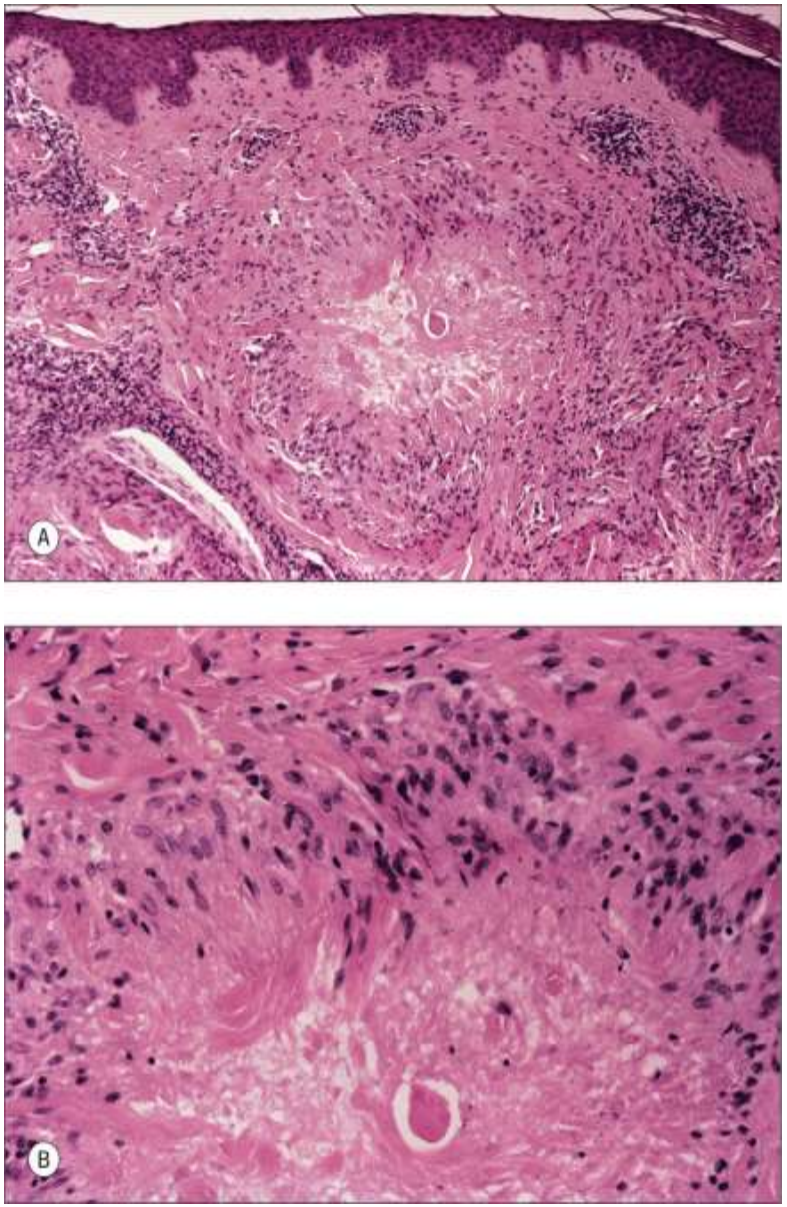
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B

TREATMENT OF GRANULOMA ANNULARE

Topical corticosteroids (3)
Intralesional corticosteroids (2)
Topical calcineurin inhibitors (3)
Topical imiquimod (3)
Cryosurgery (2)
Hydroxychloroquine or chloroquine (2)
Niacinamide (nicotinamide) (3)
Minocycline + ofloxacin + rifampin* (3)
Pentoxifylline (3)
Intralesional interferon (3)
5-lipoxygenase inhibitor (zileuton) plus vitamin E† (3)
Dapsone (3)
Isotretinoin (3)
PUVA (psoralen plus UVA) or UVA1 (2)
Cyclosporine (3)
TNF-α inhibitors (adalimumab, infliximab) (3)
Methotrexate (3)
Fumaric acid esters (3)
Chlorambucil (3)
Photodynamic therapy with topical 5-aminolevulinic acid (3)
CO_2 laser (3)
Surgical excision (3)

*Administered monthly: minocycline (100 mg), ofloxacin (400 mg) and rifampin (600 mg) × 3 months
†Doses of 2400 mg po daily (zileuton) and 400 IU po daily (vitamin E).

Table 93.4 Treatment of granuloma annulare. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Treatment of Granuloma Annulare (Cont.)

- Narrowband UVB (2)
- UVA-1 (2)
- Triple antibiotic (3)

Lupus Erythematosus Update: 2015 Introduction

- Dermatologists are uniquely qualified to understand clinicopathologic aspects of lupus erythematosus especially from the mucocutaneous vantage point.
- Avoid Lupus/Skin/Antimalarials rut
- Match the therapy to the presumed pathogenesis of lesions

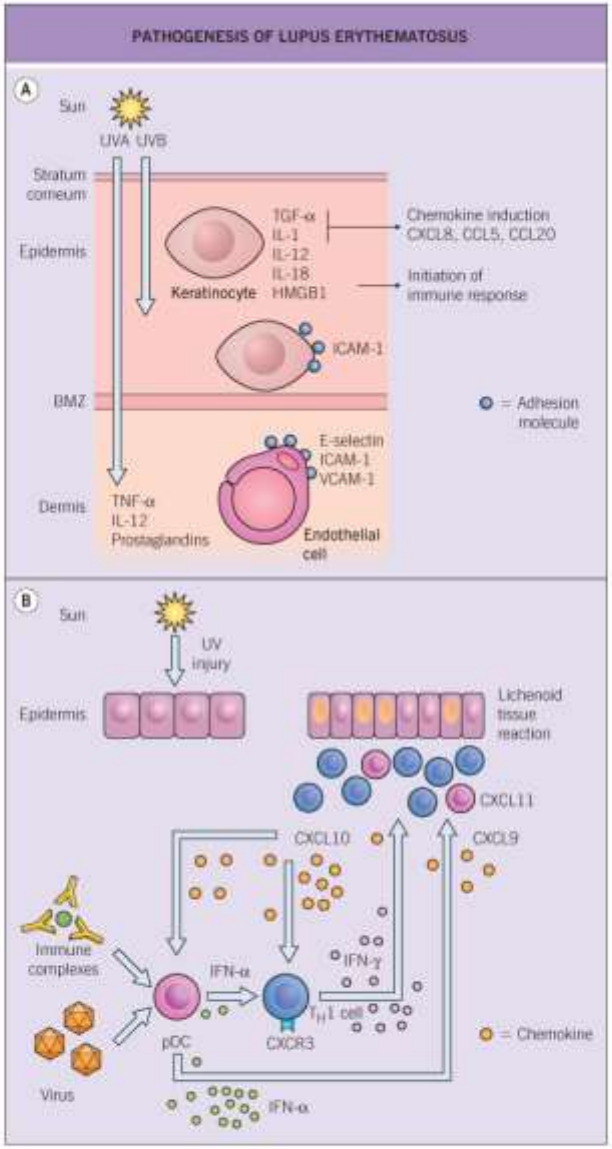


Fig. 41.1 Pathogenesis of lupus erythematosus. A In photosensitive cutaneous LE, ultraviolet radiation (UVA and UVB) triggers cytokine and chemokine production, initiating an immune response. **B** A lichenoid tissue reaction is the endpoint of a complex cascade that includes activation of dendritic cells, release of interferon (IFN), production of chemokines, and activation of T cells. BMZ, basement membrane zone; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) receptor; HMGB1, high-mobility group box 1; IL, interleukin; ICAM, intercellular adhesion molecule; pDC, plasmacytoid dendritic cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Adapted from Dutz JP et al., In: Wallace DJ, Hahn BH (eds). Dubois' Lupus Erythematosus, 7th edn. Philadelphia: Lippincott, Williams & Wilkins, 2005, and Meller S, Gilliet M, Homey B. Chemokines in the pathogenesis of lichenoid tissue reactions. J Invest Dermatol. 2009;129:315–19.

Lupus Erythematosus: Approach

- Evaluate dermatologic lesions based on clinicopathologic features
- Work with a colleague in Pediatrics or Internal Medicine to evaluate relevant internal involvement
- Classify patient appropriately as to subset
- Construct a therapeutic ladder

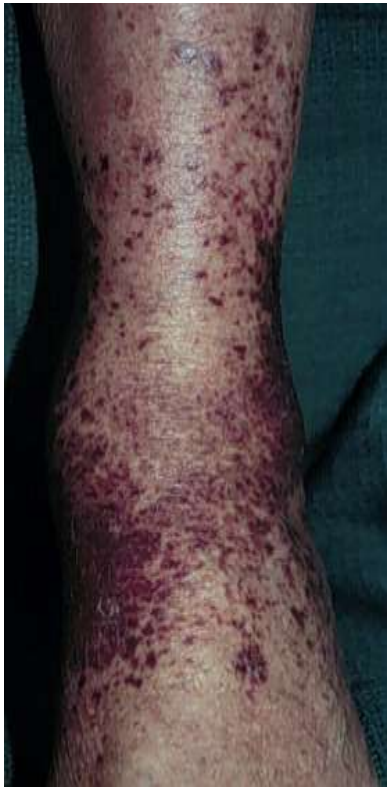
Lupus Erythematosus Update: 2015 Therapeutic Classification

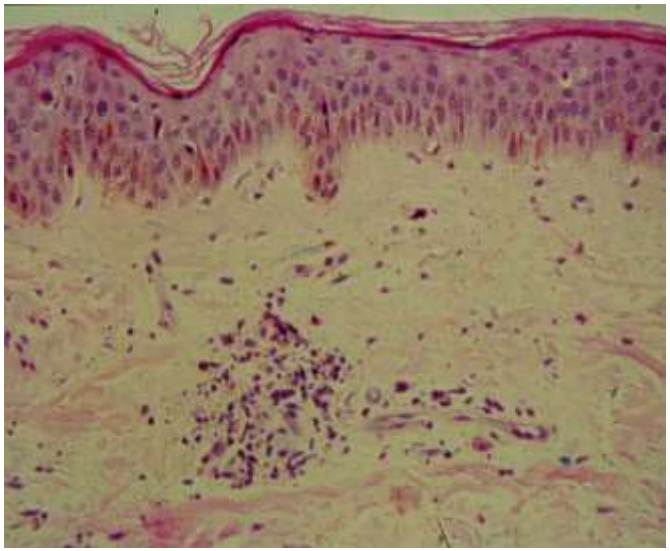
- Vascular reactions in SLE
- Lesions characterized by a lymphocytic infiltrate at the DE junction
  - Discoid lesions (CCLE or SLE)
  - Subacute lesions (SCLE)
  - Poikiloderma (SLE)
- Special lesions
  - Lupus panniculitis
  - Vesiculobullous lesions
  - Tumid lesions

Lupus Erythematosus Update: 2015 Vascular Reactions

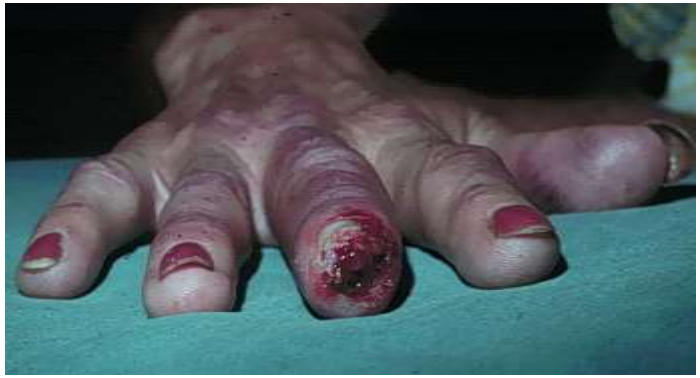
- Probably immune complex-mediated (CIC)
  - Cutaneous small vessel vasculitis
  - Larger vessel vasculitis
  - Other forms
    - Urticarial vasculitis
    - Other serum sickness-like lesions
- Uncertain mechanism
  - Erythemas
  - Erythema multiforme-like lesions
  - Livedo reticularis
  - Other vascular reactions

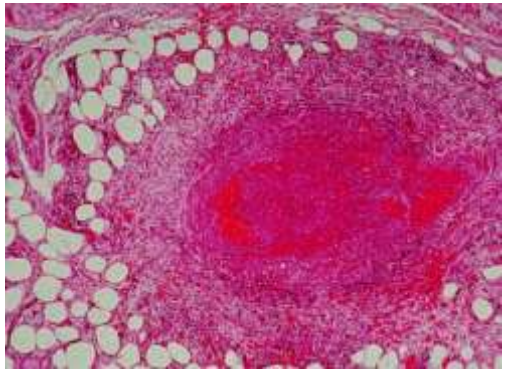
Lupus Erythematosus
Cutaneous Small Vessel Vasculitis

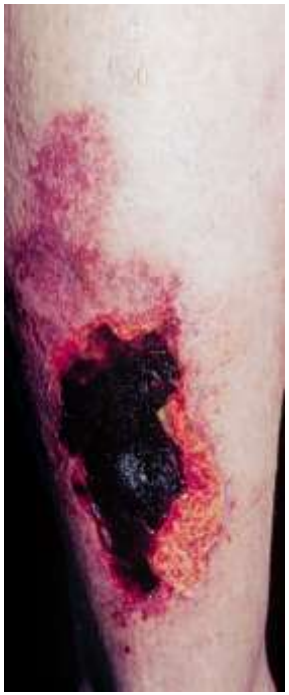




Lupus Erythematosus
Larger Vessel Vasculitis



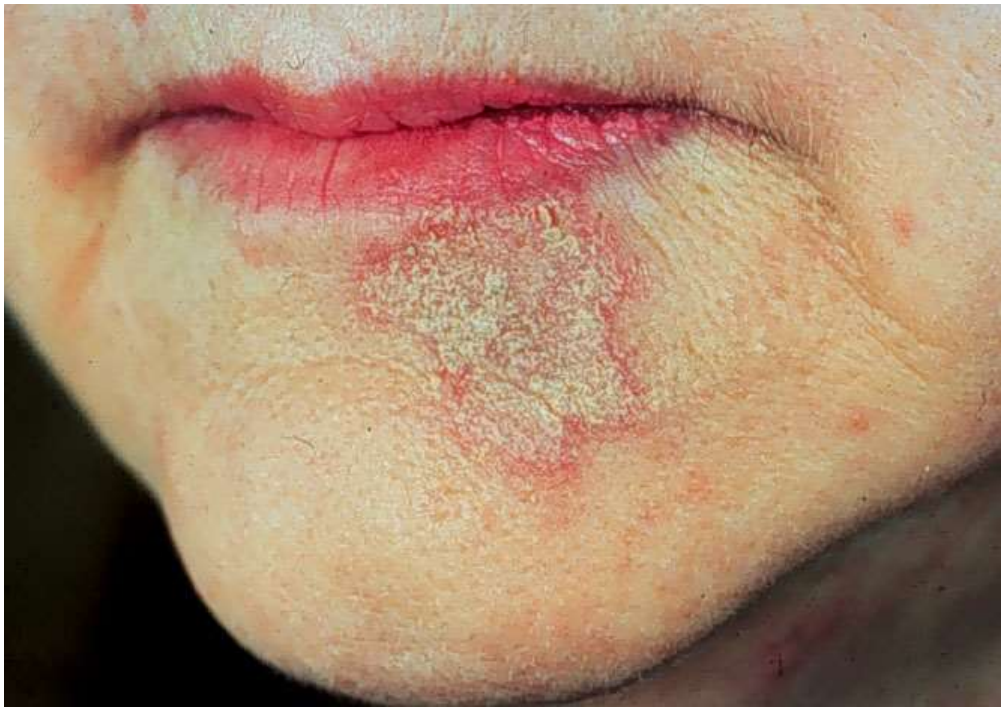




Lupus Erythematosus Update: 2015 Interface Lesions

- Discoid lesions (scarring)
  - CCLE
  - SLE
- Subacute cutaneous lesions (nonscarring)
  - Annular-polycyclic
  - Psoriasiform
- Poikiloderma - SLE

Lupus Erythematosus
Spectrum of Interface Lesions: Discoid Lesion



Lupus Erythematosus Update: 2015
CCLE vs. SLE

- Biopsy confirmation
- Complete cutaneous examination to exclude:
  - Nailfold telangiectasias
  - Vasculitic lesions
  - Poikiloderma
  - SCLE annular lesions

Lupus Erythematosus Update: 2015 CCLE vs. SLE

- Complete history and physical examination aimed at ARA criteria for SLE
- Screening laboratory tests aimed at ARA criteria to include at least:
  - ANA profile
  - Urinalysis
  - Complete blood count and platelets
  - SMAC
- Role of direct immunofluorescence

Autoantibodies And Their Clinical Associations 2015

Anti-dsDNA	Glomerulonephritis
	Vasculitis
Anti-Sm	Glomerulonephritis
	CNS involvement
Anti-Ro	Cutaneous manifestations
	Thrombocytopenia
	Sjogren’s syndrome
	Congenital heart block
	Neonatal lupus syndrome
	Antinuclear antibody-negative lupus

Autoantibodies And Their Clinical Associations 2015 continued...

Anti-La	Sjogren's syndrome
	Cutaneous manifestations
	Congenital heart block
	Decreased frequency of renal and CNS disease
Anti-RNP	Myositis
	Raynaud's phenomenon
	Mixed connective tissue disease
Antiribosomal P	Depression
	Psychosis

Autoantibodies And Their Clinical Associations 2015 continued...

Antiphospholipid	Recurrent spontaneous abortions Arterial and venous thrombosis Thrombocytopenia

Lupus Erythematosus: Current ACR Criteria (Undergoing Revision)

- **Malar rash**
- **Discoid lupus**
- **Photosensitivity**
- **Oral ulcers**
- **Arthritis**
- **Proteinuria>0.5g/day or cellular casts**
- **Seizures or psychosis**

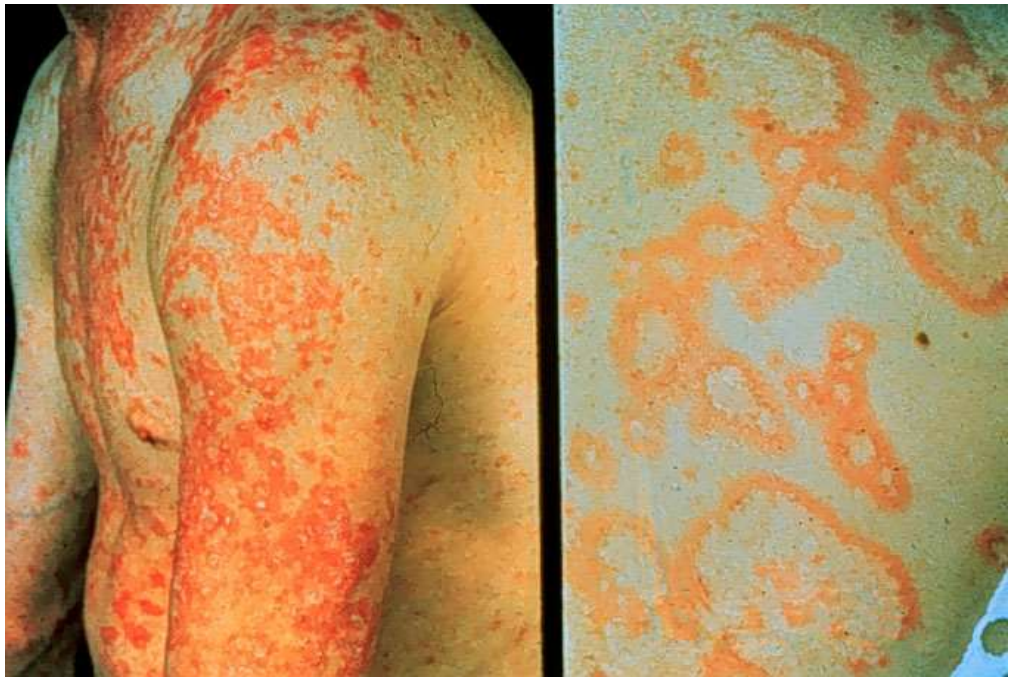
} CCLE vs SLE issues

- Pleuritis or pericarditis
- Hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia
- Antibody to DNA or Sm antigen
- Positive FANA

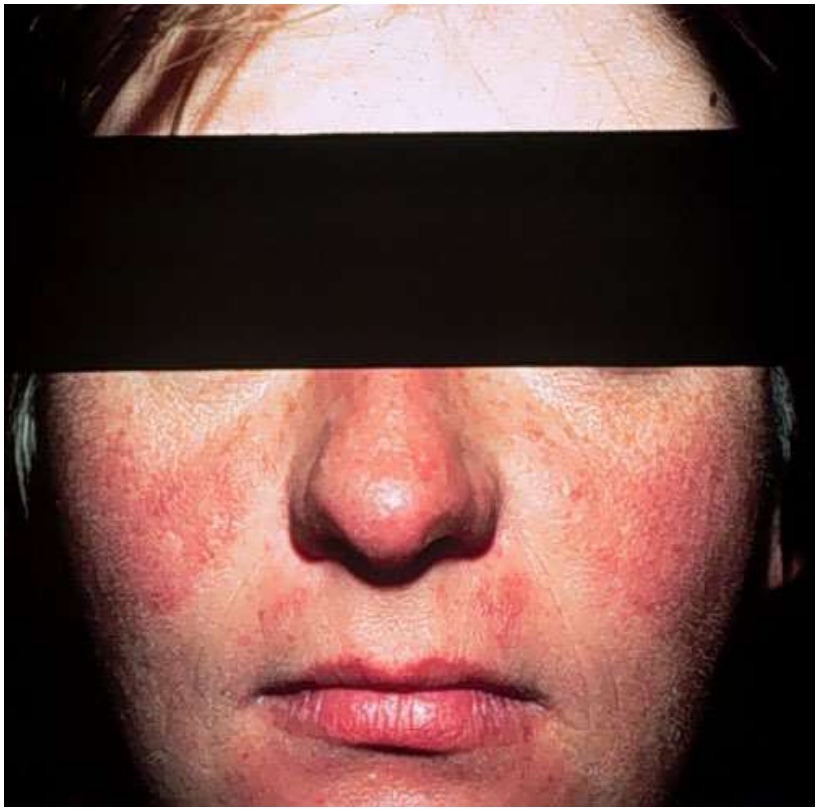
Refer to: Arthr Rheum 2012;64:2677-2686
For Systemic Lupus; International Collaborating Clinics Classification Criteria

Lupus Erythematosus

Spectrum of Interface Lesions: Subacute Lesions



Lupus Erythematosus
Spectrum of Interface Lesions: Poikiloderma



Drug Induced LE (Often SCLE)

- Thiazide diuretics
- NSAIDS (remember Aleve/naproxen)
- Calcium channel blockers
- Antifungals – terbinafine, griseofulvin
- Beta blockers
- ACE inhibitors – eg. Captopril
- TNF alpha inhibitors
- Misc – ranitidine, taxofere, cinnarizine, stations, procainamide, penicillamine, phenytoin, interferons alpha & beta

Lupus Erythematosus Update: 2015
Interface Lesions: Therapeutic Ladder

- Mild and/or localized disease
  - Sunscreens (High SPF with UVA protection) (2)
  - Topical corticosteroids (2)
  - Superpotent topical corticosteroids (2)
  - Intralesional corticosteroids (2)
  - Topical immunomodulators
    - eg. Tacrolimus +/- Keratolytics (2)
  - Hydroxychloroquine 200mg bid (1)
  - Above plus Quinacrine 100mg qd (2)

Lupus Erythematosus: Update 2015

Therapeutic Ladder

Extensive/Persistent Cutaneous Disease

- Oral Retinoids (2)
- Dapsone/Sulfapyridine (2)
- Chlofazimine (3)
- Methotrexate (3)
- Thalidomide (2)
- Auranofin (3)
- Azathioprine (2)
- Mycophenolate

Lupus Erythematosus: Update 2015 Therapeutic Ladder Systemic Disease

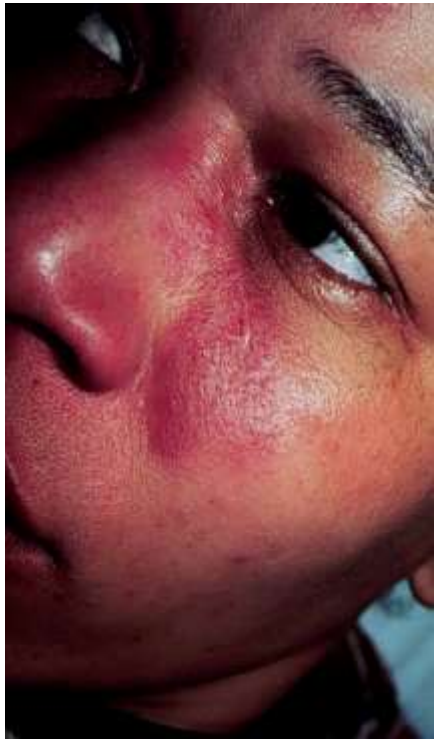
- Prednisone (1)
- Azathioprine (1)
- Mycophenolate (1)
- Leflunomide (2)
- Cyclophosphamide (1)
- IVIG (2)
- Cyclosporine (1)
- Rituximab (2)
- Belimumab (Anti B-LyS) (1)
- Tofacitinib (JAK inhibitor)

Lupus Erythematosus: Update 2015
Therapeutic Ladder
Systemic Disease Experimental Therapies

- Mesenchymal stem cells
- Nanoparticle-based drug delivery
- Sirukumab (anti-Il-6)
- Tocilizumab (anti-Il-6 receptor)
- Eculizumab (anti-C5)
- Many others strategies

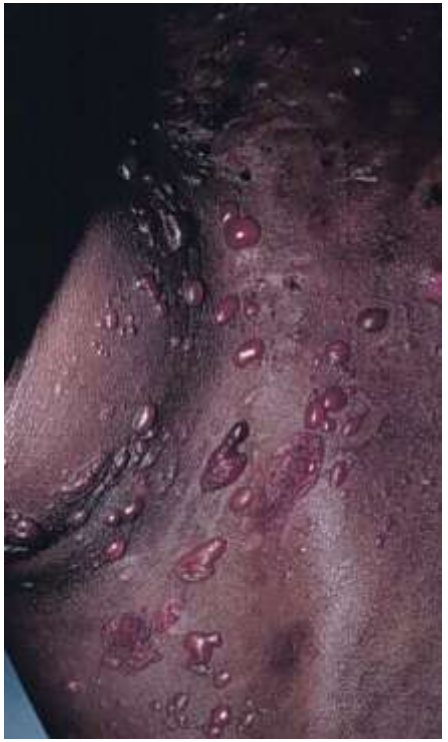
Lupus Erythematosus Update: 2015
Special Lesions: Therapeutic Ladder

- Lupus Panniculitis
  - Antimalarials (2)
  - Other



Lupus Erythematosus Update: 2015
Special Lesions: Therapeutic Ladder

- Vesiculobullous Lesions (EBA relationship)
  - Dapsone (2)
  - Azathioprine (3)
  - Mycophenolate mofetil (3)



Dermatomyositis: 2015
Why is this important for dermatologists?

- Serious, treatable, multisystem disease
- Prognosis and therapy different from lupus erythematosus
- Malignancy association in adults
- Diagnosis is commonly (maybe even usually) missed

Dermatomyositis: 2015

Reasons we dermatologists might miss the diagnosis

- Miss poikiloderma - diagnose as psoriasis - risk of phototherapy
- Note poikiloderma but miss photodistribution and nail fold changes - diagnose as cutaneous T-cell lymphoma
- Note poikiloderma and photodistribution - diagnose as lupus erythematosus - ANA and skin biopsy specimen may seem to support the misdiagnosis

Dermatomyositis Update: 2015 - Diagnosis Bohan and Peters, 1975

- Clinical signs and symptoms of proximal extensor muscle weakness
- Elevations of muscle enzymes (e.g. CPK, Aldolase)
- EMG changes of myositis
- Typical muscle histologic changes (infiltrate, necrosis, fibrosis, phagocytosis, regeneration)
- Typical cutaneous eruption

New criteria are evolving

Role of MRI debated

Juvenile Dermatomyositis: 2015

- 8-22% of all DM/PM
- Higher incidence of vasculitis
- Early studies: 1/3 died, 1/3 crippled, 1/3 remission
- Recent studies: Low mortality (vasculitis with GI hemorrhage)
- Calcinosis cutis more common

Dermatomyositis: 2015
Malignancy Association

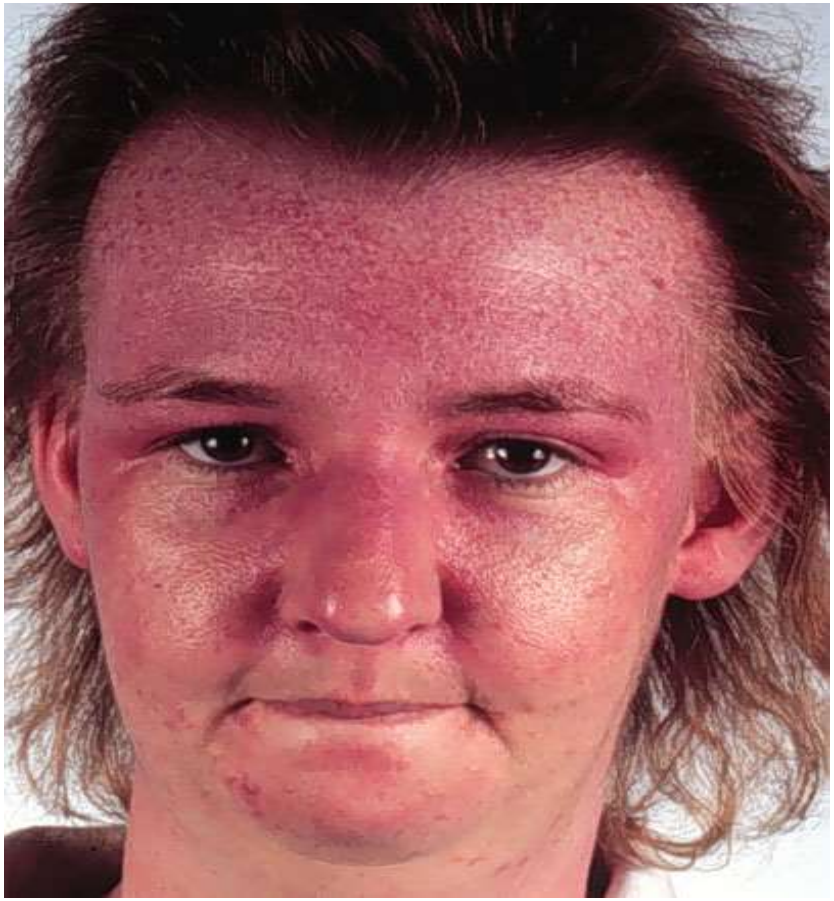
- No increase in incidence of neoplasia in children
- 5-11 fold increase in neoplasia in adults

  (PM: 2-3%; DM: 15-20%)
- Particularly lung, ovary, breast, stomach
- Usually DM antedates tumor by 1-2 years
- Drop off in malignancy after two years - Large Danish study
- “Directed” evaluation – repeated at intervals

Dermatomyositis: 2015
Clinical Features - Cutaneous

- **Heliotope sign**
- **Photodistributed poikiloderma-violaceous**
- Poikiloderma over extensor surfaces-violaceous
- Gottron's sign
- Cuticular dystrophy
- Nail fold telangiectasia
- Calcinosis cutis (complication: especially childhood)

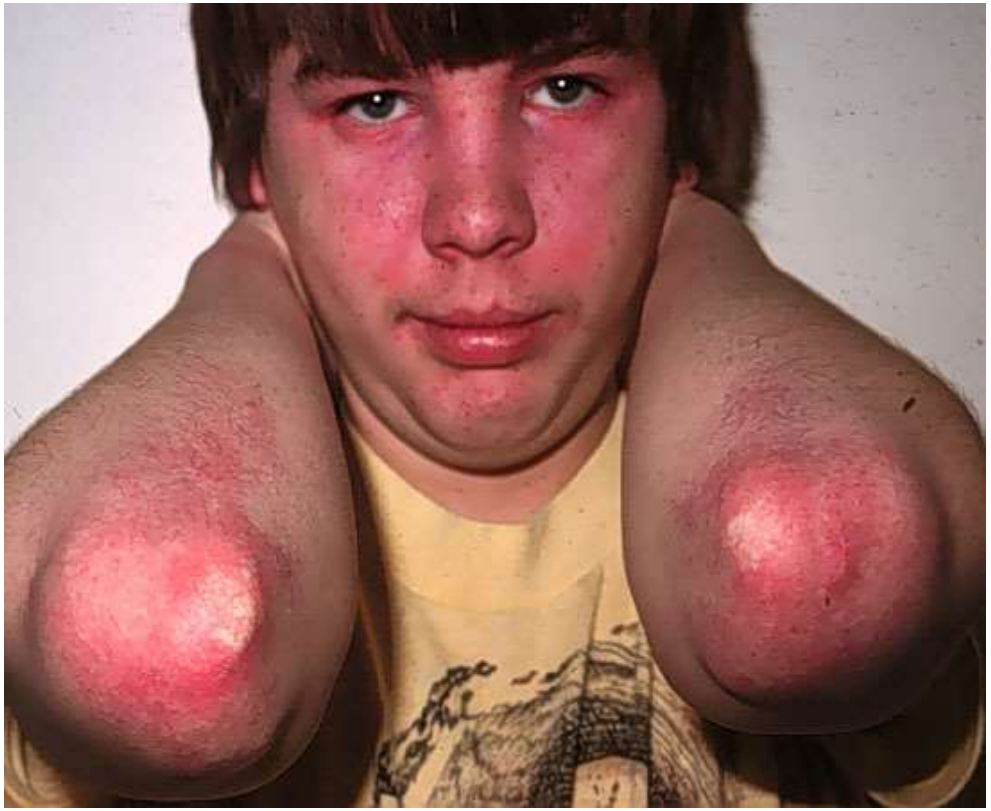
Dermatomyositis: 2015
Clinical Features - Cutaneous



Dermatomyositis: 2015 Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous
Gottron's sign
Cuticular dystrophy
Nail fold telangiectasia
Calcinosis cutis (complication: especially childhood)

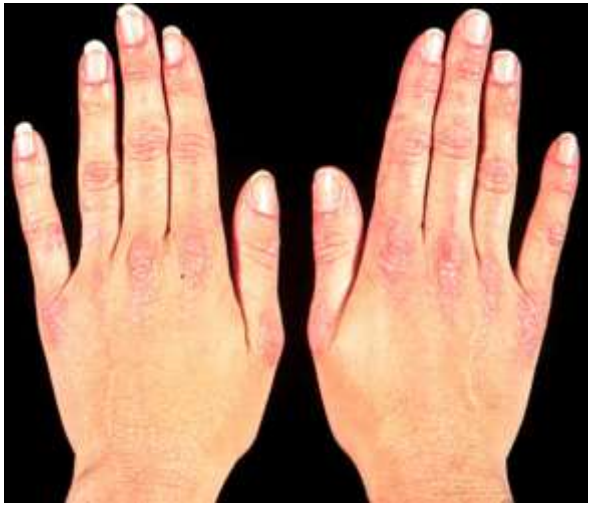
Dermatomyositis: 2015
Clinical Features - Cutaneous

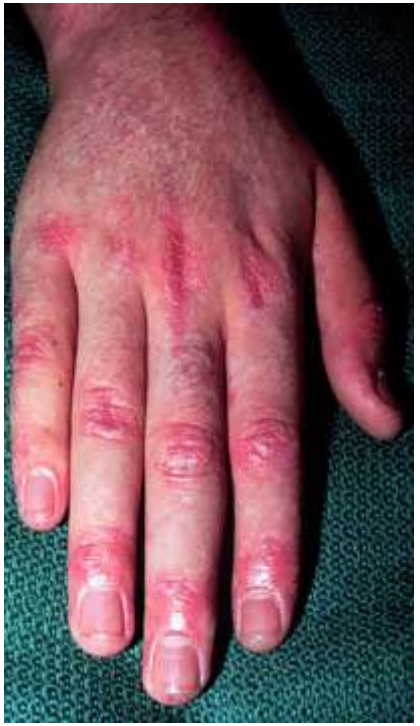


Dermatomyositis: 2015
Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous
Gottron's sign
Cuticular dystrophy
Nail fold telangiectasia
Calcinosis cutis
(complication: especially childhood)

Dermatomyositis: 2015
Clinical Features - Cutaneous





Dermatomyositis: 2015 Clinical Features - Cutaneous

Heliotope sign
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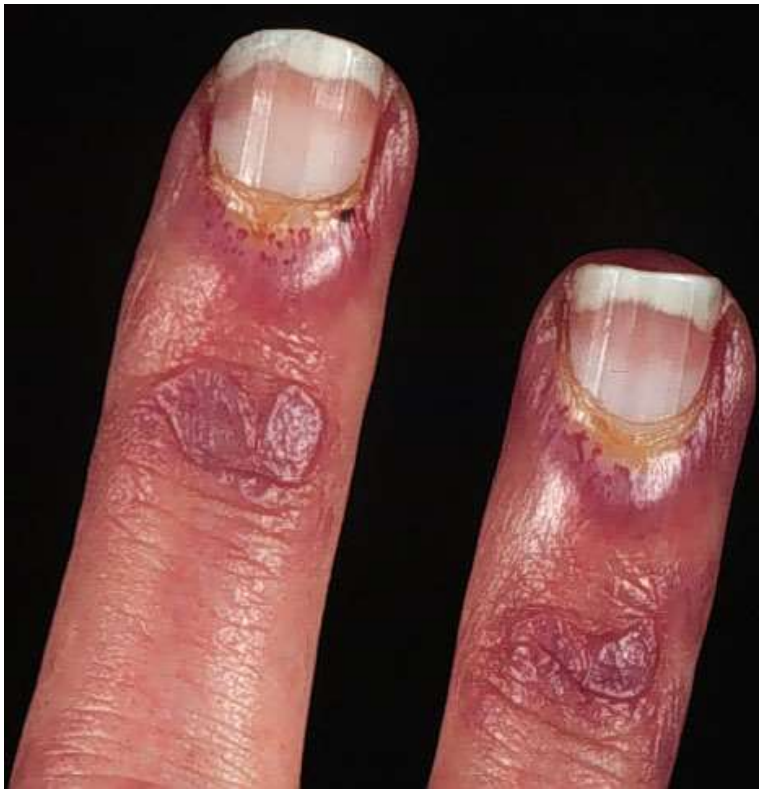
Dermatomyositis: 2015
Clinical Features - Cutaneous



Dermatomyositis: 2015 Clinical Features - Cutaneous

Heliotope sign
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Gottron's sign
Cuticular dystrophy
Nail fold telangiectasia
Calcinosis cutis (complication: especially childhood)

Dermatomyositis: 2015
Clinical Features - Cutaneous

Dermatomyositis: 2015 Selected Systemic Aspects

- Articular disease - if erosive, implies overlap
- Dysphagia - proximal is related to myositis true distal esophageal disease suggests overlap
- Lung disease - 15-30% diffuse interstitial fibrosis (Jo-1 antibody)

REVISED CLASSIFICATION SYSTEM FOR THE IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES
Dermatomyositis
Adult-onset
Classic DM
Classic DM with malignancy
Classic DM as part of an overlapping connective tissue disorder
Clinically amyopathic DM*
Amyopathic DM
Hypomyopathic DM
Juvenile-onset
Classic DM
Clinically amyopathic DM
Amyopathic DM
Hypomyopathic DM
Polymyositis
Isolated polymyositis
Polymyositis as part of an overlapping connective tissue disorder
Polymyositis associated with internal malignancy (?)†
Inclusion body myositis

*Both adult-onset and juvenile-onset amyopathic DM and hypomyopathic DM can be further subcategorized as "provisional" and "confirmed" when patients have biopsy-confirmed hallmark cutaneous manifestations of DM without muscle weakness and with normal muscle enzymes for ≥6 months (provisional) or 24 months (confirmed).

†Although more recent population-based studies have clearly confirmed that adult-onset classic DM is associated with a significant risk for internal malignancy, these same studies have questioned whether such a relationship exists for polymyositis.

Table 42.1 Revised classification system for the idiopathic inflammatory dermatomyopathies. This classification scheme recognizes, with equal weighting, the cutaneous and muscle manifestations of this group of disorders.

Dermatomyositis 2015 Pathogenesis

GENETICS[13-15]

- Monozygotic twins affected
- Associated human leukocyte antigens (HLA)
  - HLA-DR3 and B8 (juvenile dermatomyositis)
  - HLA-DR52 (patients with anti-Jo1 antibodies)
  - HLA DR7 and -DRw53 (patients with anti-Mi-2 antibodies)
  - HLA B14 and -B40 (adults with dermatomyositis overlap)
  - HLA – DRB1*15021 (Japanese with juvenile dermatomyositis)
- TNF-α 308A allele polymorphism

Dermatomyositis 2015 Pathogenesis (Cont)

CELLULAR IMMUNITY/APOPTOSIS[16-22]

- Histopathologic findings in skin and muscle ($CD8^+$ lymphocytes)
- Lymphocyte-mediated experimental myositis in mice
- Increased Ki-67 and p53 expression in keratinocytes after UVB irradiation
- Increased CD40 expression on muscle cells
- Decreased circulating CD54 (ICAM-1)-positive lymphocytes
- Fas ligand on T cells and Fas receptor on muscle cells
- MHC Class I overexpressed in affected muscle tissues
- Elevated expression of COX-1, COX-2, and 5-LOX mRNA in affected muscle tissues

Dermatomyositis 2015
Pathogenesis (Cont.)

HUMORAL IMMUNITY[23]

- Association with autoimmune diseases (Hashimoto's thyroiditis, Graves' disease, myasthenia gravis, type I diabetes mellitus, primary biliary cirrhosis, dermatitis herpetiformis, vitiligo, and other autoimmune connective tissue diseases)
- Myositis-specific antibodies versus antibodies against aminoacyl-tRNA synthestases, non-synthetases, cytoplasmic antigens, and nuclear antigens. Examples include: antisynthetase, anti-Jo-1 (lung disease), and anti-Mi-2 (most specific for dermatomyositis)

Dermatomyositis 2015
Pathogenesis (Cont.)

INFECTIOUS PRECIPITANTS[24,25]

- Seasonal variation
- Picornavirus substrate for aminoacyl-tRNA synthetases
- *Escherichia coli*, muscle protein and capsid protein of a picornavirus that induces mouse myositis all have some homology of amino acid sequences with Jo-1
- Echovirus infection in patients with hypogammaglobulinemia
- Coxsackievirus-9 myositis

Dermatomyositis 2015
Pathogenesis (Cont.)

DRUG AND VACCINE PRECIPITANTS[26-31]

- Hydroxyurea, D-penicillamine, TNF-α inhibitors, nonsteroidal anti-inflammatory drugs, lipid-lowering drugs (statins >gemfibrozil), cyclophosphamide, BCG vaccine; single case reports of phenytoin, alfuzosin (α-agonist for BPH), omeprazole, ipecac (repeated exposures), interferon-α-2b, tegafur, etoposide, articaine, sulfacetamide sodium opthalmic drops

MALIGNANCY ASSOCIATION (ADULTS)[32,33]

Dermatomyositis: 2015
Laboratory Aspects

- Sedimentation rate only elevated in 50%
- Elevated: CPK, Aldolase, urine creatine, serum myoglobin, rarely urine myoglobin, other serum enzymes
- Positive ANA (90+%), anti-Jo-1 (25%), anti-Mi-1 and anti-Mi-2
- Negative anti-DNA

SERUM AUTOANTIBODIES IN ADULT AND JUVENILE DERMATOMYOSITIS				
Autoantibodies	**Target antigen function**	**Clinical phenotype**	**Autoantibody frequency, %**	
			Adult DM	**Juvenile DM**
Anti-aminoacyl-tRNA synthetases (e.g. anti-Jo-1 [histidyl], anti-PL-7 [threonyl]; see Ch. 40)	Intracytoplasmic protein synthesis	Antisynthetase syndrome (myositis, mechanic's hands, Gottron's papules, arthritis, fever, Raynaud's phenomenon, high frequency of interstitial lung disease)	up to 20%	1–3
Anti-SRP	Protein translocation	Acute-onset necrotizing myopathy (severe weakness, high CK); may be refractory to treatment	5	<1
Anti-Mi-2	Helicase – transcription	Adult DM and juvenile DM (hallmark is cutaneous disease, milder muscle disease with good response to treatment)	15	<10
Anti-p155/140	See Ch. 40	Cancer-associated myositis in adult DM; severe cutaneous disease in adult DM and juvenile DM	80 (amyo); 20–30 (classic)	~25
Anti-p140	Likely NXP-2 – nuclear transcription, RNA metabolism	Juvenile DM with calcinosis	NA	~25
Anti-SAE	Post-translational modification	Adult DM; may present with clinically amyopathic DM	NA	NA
Anti-CADM-140 (MDA5)	Innate immunity	Clinically amyopathic DM; rapidly progressive interstitial lung disease	10– 15	NA

Table 42.4 Serum autoantibodies in adult and juvenile dermatomyositis (DM). The autoantigen CADM-140 was subsequently found to be identical to two previously identified gene products, interferon induced with helicase C domain protein 1 (IFIH1) and melanoma differentiation-associated gene 5 (MDA5). CADM, cancer-associated dermatomyositis; CK, creatine kinase; NA, not applicable; NXP-2, nuclear matrix protein NXP2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle. *Adapted from ref. 35.*

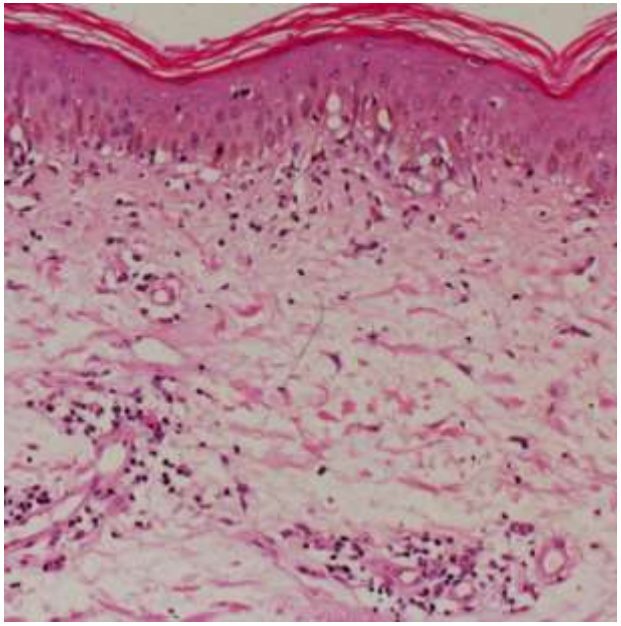
Dermatomyositis: 2015
Muscle Biopsy

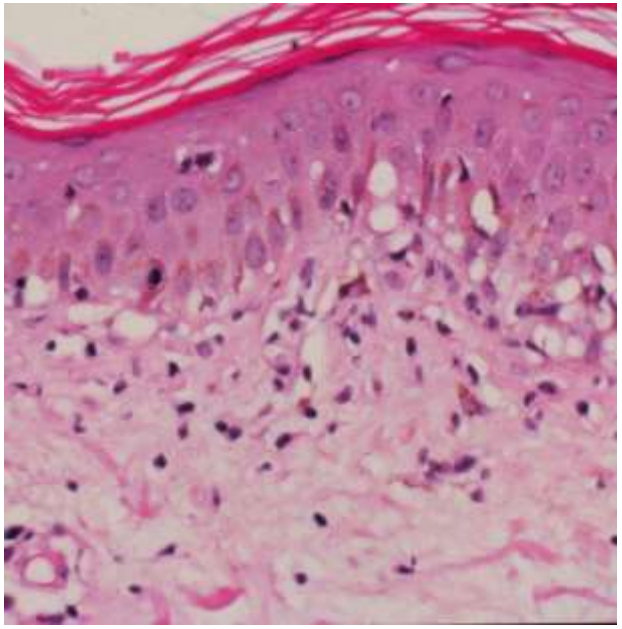
- Can provide evidence supporting diagnosis
- Can definitively exclude certain other conditions in the differential
- Incisional vs needle biopsy
- Quadriceps, triceps

Dermatomyositis: 2015
Histopathologic Aspects

- Skin: Epidermal atrophy, interface change, vascular dilatation, occasional mucin deposition
- Muscle: Mixed/primarily lymphocytic infiltrate, necrosis of muscle fibers, fibrosis, phagocytosis, regeneration

Dermatomyositis: 2015 Histopathologic Aspects





Dermatomyositis: 2015
Electromyography

- Abnormal in about 90% of active cases
- Characteristic triad
- May support diagnosis and help exclude other conditions

Dermatomyositis: 2015 Prognosis

- Precorticosteroid era: 50-60% mortality
- Newcastle series: Childhood mortality 5%, Overall mortality 28% (6 years)
- Johns Hopkins survey: Similar to Newcastle overall mortality 27% (8 years)
- Variable morbidity data in childhood PM/DM from 1/3 with severe impairment versus mean of no objective impairment
- Our data on 20 children after 2-20 years

Dermatomyositis: 2015

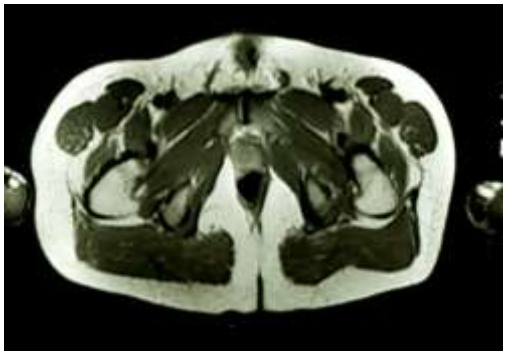
Classic clinicopathologic disease in patients with normal muscle enzymes

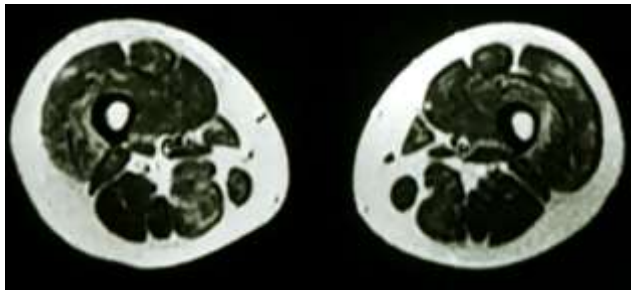
- Group 1: Cutaneous changes only: 5 patients (1-10 years)
- Group 2: Cutaneous changes only at baseline with subsequent evolution of myositis: 2 patients (1/2-2 1/2 years)
- Group 3: Cutaneous changes with normal muscle enzymes but invasive tests revealed myositis: 4 patients (4 positive EMG, 2 positive biopsy)

Stonecipher MR, Jorizzo JL, White WL et al. J Am Acad Dermatol 1993;28:951-956.

Dermatomyositis: 2015

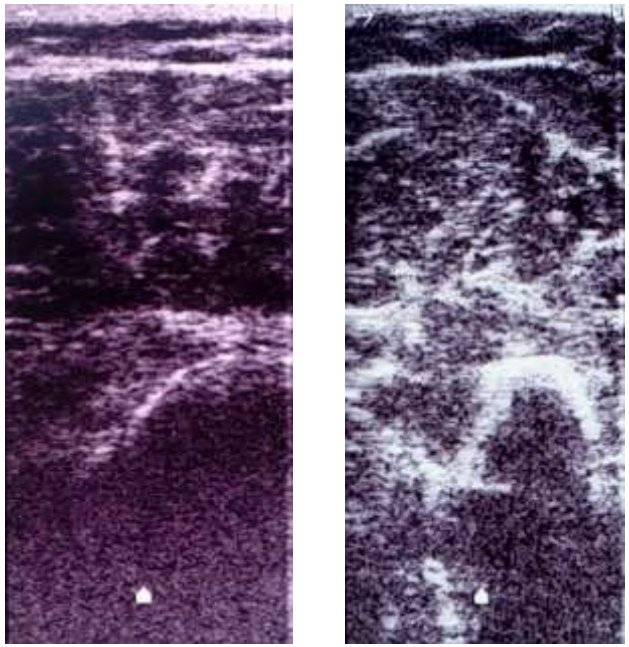
Magnetic Resonance Imaging





Dermatomyositis: 2015

Ultrasound



Dermatomyositis Update: 2015 Therapeutic Ladder

- Systemic Corticosteroids (2)
  - Prednisone 1mg/kg/day taper to 1/2 over 6 months
  - Then attempt to reach qod dosing
  - Usually required for 2 years
  - Pulse and split dose options
- Methotrexate low dose weekly pulse (2)
- Azathioprine 2-3 mg/kg/day(3)
- IVIG(1)

Key

(1) - Double blind studies

(2) - Clinical series

(3) - Anecdotes

Therapeutic Ladder for Dermatomyositis
SYSTEMIC THERAPY

Oral prednisone:	1 mg/kg/day tapered to 50% over 6 months and to zero over 2-3 years (1) Option to use pulse, split-dose, or alternate-day (2)
Methotrexate:	5-20 mg weekly (2)
Azathioprine:	2-3 mg/kg/day (1)
Others:	High-dose IvIg (2 g/kg/month) (1) Pulse cyclophosphamide (0.5-1.0 g/m^2 monthly) (2) Chlorambucil (4 mg/day) (2) Cyclospporine (3-5 mg/kg/day) (2) Tacrolimus (0.12 mg/kg/day (3) Mycophenolate mofetil (1 g twice daily) (2) Sirolimus (5 mg/day x 2 weeks, 2 mg/day x 2 weeks, then 1 mg/day) (3) Infliximab (5-10 mg/kg every 2 weeks initially) (3) Etanercept (3)† Rituximab (375 mg/m^2/infusion for 4 weekly infusions) (2) Fludarabine (3) Hematopoietic stem cell transplantation (3) Plasmapheresis (3)†

†Double-blind trial showed no benefit.

Therapeutic Ladder for Dermatomyositis
CUTANEOUS LESIONS

Sunscreens (high sun protection factor including protection against UVA) (3)
Topical corticosteroids (3)
Topical tacrolimus (3)
Hydroxychloroquine (200 mg twice daily; increased frequency of drug eruptions in patients with dermatomyositis) (2)
Hydroxychloroquine (200 mg twice daily) plus quinacrine (100 mg/day) (3)
Low-dose weekly methotrexate (5-15 mg weekly) (2)
Mycophenolate mofetil (3)
High-dose IVIg (2 g/kg/month) (1)
Retinoids (3)
Dapsone (3)
Thalidomide (3)
Leflunomide (3)
Antiestrogens (e.g. Tamoxifen, anastrazole) (3)
TNF-α inhibitors (e.g. Infliximab, etanercept) (3)*
Rituximab (3)
Tacrolimus (3)

*Reported cause of drug-induced dermatomyositis.

Scleroderma Update: 2015

- Greek: “Hard skin”
- Rare autoimmune disease
- Idiopathic
- High morbidity
- Variable mortality
- Spectrum of disease: Morphea, limited disease (CREST), diffuse disease (PSS)

Scleroderma Update: 2015 ACR Diagnostic Criteria

- Major criterion
  - Proximal scleroderma

    Indurated, hard skin. Often the skin is shiny with loss of cutaneous surface markings. Loss of elasticity occurs. Hyper- and hypopigmentation are common.
- Minor criteria
  - Sclerodactyly
  - Digital pitted scars or loss of substance of the finger pad
  - Bibasilar pulmonary fibrosis

  Diagnosis is 97% certain with one major, or two minor or more criteria present. There are no specific diagnostic criteria for localized cutaneous scleroderma, scleroderma variants, overlap syndromes, and environmentally induced scleroderma at this time.

Scleroderma: Update: 2015 Classification

Local Forms

- Linear scleroderma
- Generalized morphea
- Morphea (plaque, guttate, or subcutaneous)

Systemic Sclerosis

- Limited (no truncal involvement)
- Diffuse (widespread skin involvement)

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

MUCINOSES

- Scleredema — Induration of the upper back, neck and face; occasional internal involvement (see Ch. 46)
- Scleromyxedema — Waxy papules (often in a linear array): diffuse induration favoring the face, upper trunk, arms and thighs; monoclonal gammopathy; neurologic, gastrointestinal and pulmonary involvement (see Ch. 46)

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

IMMUNOLOGIC

Chronic GVHD*	Morpheaform plaques favoring the trunk, which may become generalized; eosinophilic fasciitis (see Ch. 52)
Eosinnophilic faciitis	Symmetric induration with a “pseudo-cellulite” appearance on the extremities (sparing hands and feet) (see text)
Generalized morphea*	Expansion and coalescence of morphea plaques to involve a large portion of the trunk and extremities (see Ch. 44)
Fibroblastic rheumatism	Sclerodactyly; fibrotic nodules on the hands

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

PARANEOPLASTIC

POEMS syndrome	Sclerotic skin on the extremities (see Ch. 114)
Amyloidosis (primary systemic)†	Diffuse induration favoring the face, distal extremities and trunk (see Ch. 47)
Carcinoid syndrome	Sclerotic skin on the legs (see Table 53.3)

NEOPLASTIC

Carcinoma *en cuirasse**	Sclerodermoid encasement of the chest by metastic carcinoma (usually breast cancer)

METABOLIC

Diabetic cheiroarthropathy	Thickened skin and limited mobility of the hands (see Table 53.4)
Porphyria cutanea tarda*	Morpheaform plaques in sun-exposed areas (see Chs 44 & 49)

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

NEUROLOGIC

- Reflex sympathetic dystrophy*
- Spinal cord injury

Painful, cold, swollen extremity eventually develops cutaneous sclerosis (see Ch. 6)

Sclerotic skin in affected areas

TOXIN-MEDIATED

- Nephrogenic systemic fibrosis*
- Eosinophilia-myalgia syndrome
- Toxic oil syndrome*

Associated with exposure to gadolinium-based contrast agents (US, 1997-present; now worldwide) (see text)

Associated with L-tryptophan ingestion (US, 1989) (see text)

Associated with toxic oil ingestion (Spain, 1981) (see text)

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

DRUG-OR-CHEMICAL-INDUCED (SEE TEXT)

Bleomycin*	Acrosclerosis, Raynaud's phenomenon; pulmonary fibrosis (more common, usually no concurrent skin lesions)
Taxanes	Edema followed by sclerosis of the lower extremities; acrosclerosis
Vinyl chloride chlorinated hydrocarbons*	Acrosclerosis, acral fibrotic papulonodules, Raynaud's phenonmenon, acro-osteolysis; pulmonary fibrosis

VENOUS INSUFFICIENCY

Lipodermatosclerosis*	Woody induration and hemosiderin pigmentation on the lower legs; may also involve the pannus (see Ch. 100)

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

GENETIC DISORDERS

Restrictive dermopathy§	Tight, thin skin over the entire body; joint contractures; *LMNA* or *ZMPSTE24* mutations
Hutchinson-Gilford progeria	Sclerotic skin on the lower trunk, buttocks and thighs; *LMNA* mutations (see Ch. 63)
Werner syndrome	Tight, sclerotic skin on the distal extrememities; *RECQL2* mutations (see Ch. 63)
Stiff skin syndrome	Fibrosis of the skin/fascia of the buttocks and thighs with hip contractures (see text)
Phenylketonuria	Sclerotic skin on the thighs and buttocks with hip contractures (see Ch. 63)
Winchester syndrome*	Diffuse, symmetric, leathery skin thickening; fibrotic plaques or bands; *MMP2* mutations (see Table 70.2)
Ataxia-telangiectasia	Tight, sclerotic facial skin (see Ch. 60)

Differential Diagnosis of Sclerodermoid Conditions Clinical Features

GENETIC DISORDERS (CONT.)

▪ Huriez syndrome	Sclerodactyly; atrophic skin on dorsal surfaces on hands and feet; palmoplantar keratoderma (see Ch. 58)
▪ H syndrome	Hypertrichosis in association with areas of hyperpigmentation and induration (primarily lower trunk and lower extremities), sensorineural hearing loss, short height, heart anomalies, hepatosplenomegaly, scrotal masses, hypergonadotripic hypoganadism, antibody-negative insulin-dependent diabetes mellitus, facial telangiectasias; mutations in *SLC29A3* which encodes nucleoside transporter hENT3

Can overlap with morpheaform disorders, which are listed in Table 44.1
†Primary cutaneous amyloidosis can also occur in patients with systemic sclerosis and Generalized morphea.
§Sclerodermoid changes are typically present at birth.

Scleroderma Update: 2015
Differential Diagnosis: Sclerodermoid Conditions

- Genetic (PKU, Progeria, Werner's, Rothmund-Thompson)
- Environmental (Vibration, Polyvinyl chloride, Silica, aeromatic hydrocarbons, Spanish oil, L-tryptophan, Silicone)
- Metabolic (PCT, Amyloidosis, Diabetes)
- Immunologic (GVH, Scleromyxedema)
- Drugs (Bleomycin, INH, others)
- Malignancy (Carcinoid, melanoma, other, paraneoplastic)
- Post infections (Scleredema, Acrodermatitis chronica atrophicans, Partial lipodystrophy)
- Neurological (Limb immobilization, Spinal injury)
- Radiation (Breast CA, Chernobyl nuclear accident)
- Renal disease (nephrogenic systemic fibrosis)

Scleroderma: Update 2015
Morphea Overview

- Cutaneous form of scleroderma
- No recognized internal organ involvement
- Rarely coexists with connective tissue vascular diseases
- Thought not to progress to PSS
- Debate exists in children

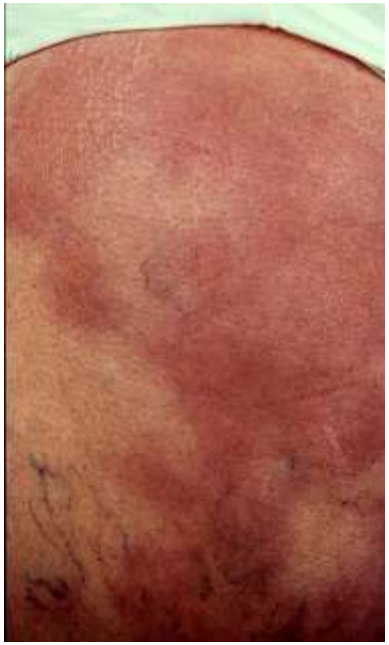
Scleroderma: Update 2015
Morphea Overview (Cont.)

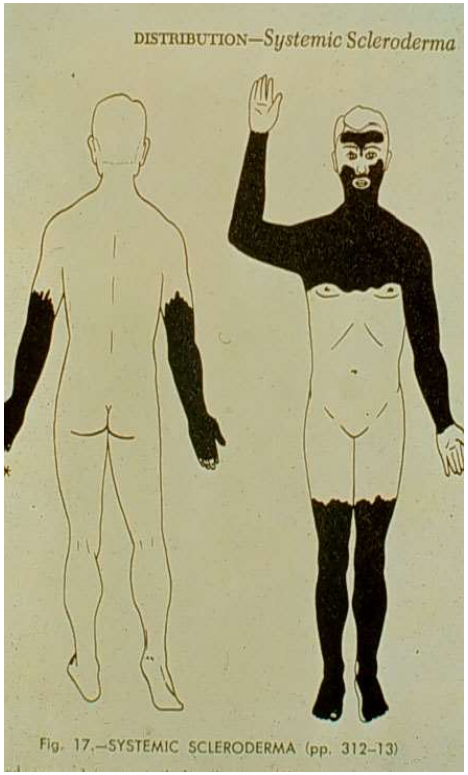
- Not fatal, but produces considerable morbidity including contractures and skin textural change and disfigurement
- ANA and/or ssDNA maybe positive, blood eosinophilia and elevated IgG may relate to prognosis

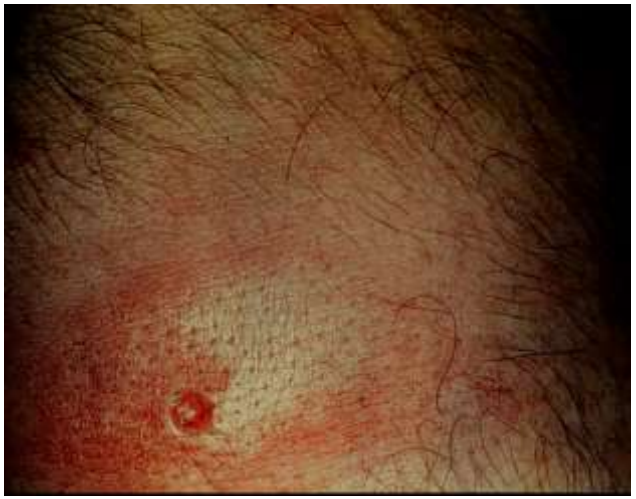
Scleroderma Update: 2015 Morphea Overview (Cont.)

- No treatment has become widely accepted as effective
- Physical therapy is crucial to prevent contractures
- In the absence of good double blind prospective placebo controlled trials much of the remaining points in the discussion will be anecdotal

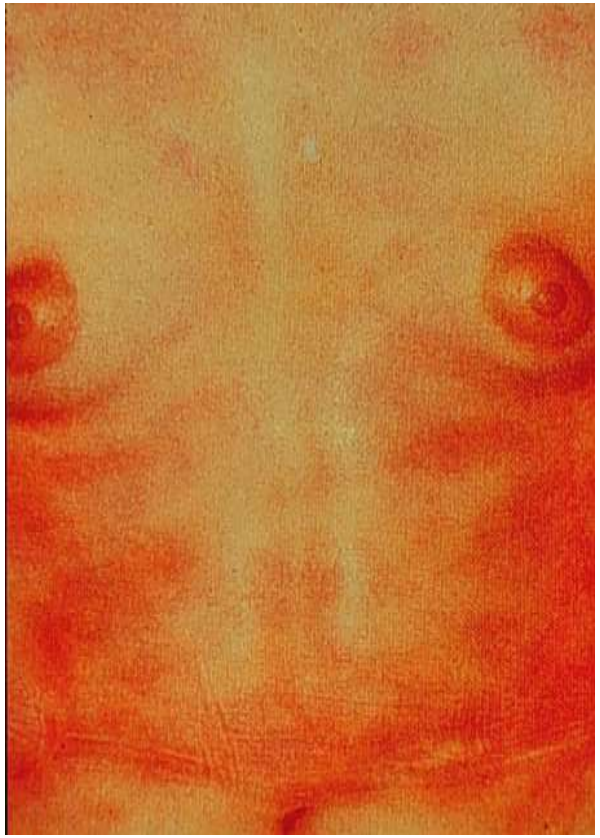
Morphea - Clinical Forms
Plaque Type Morphea



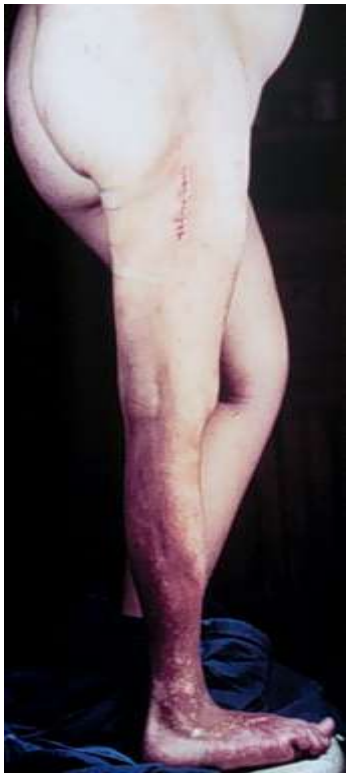


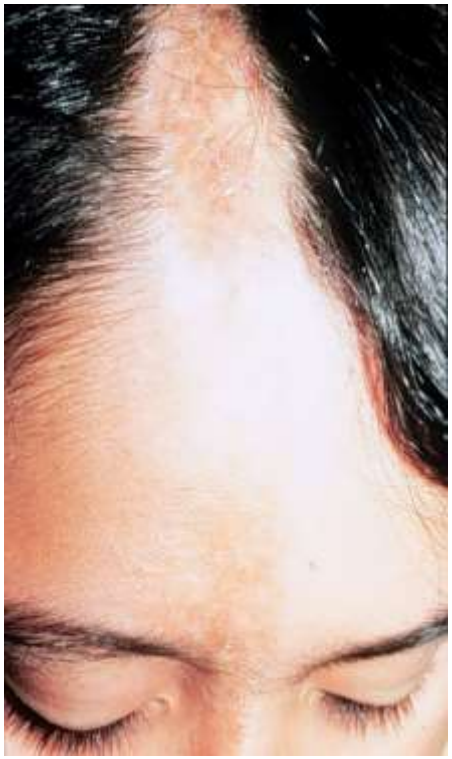


Diffuse Type Morphea



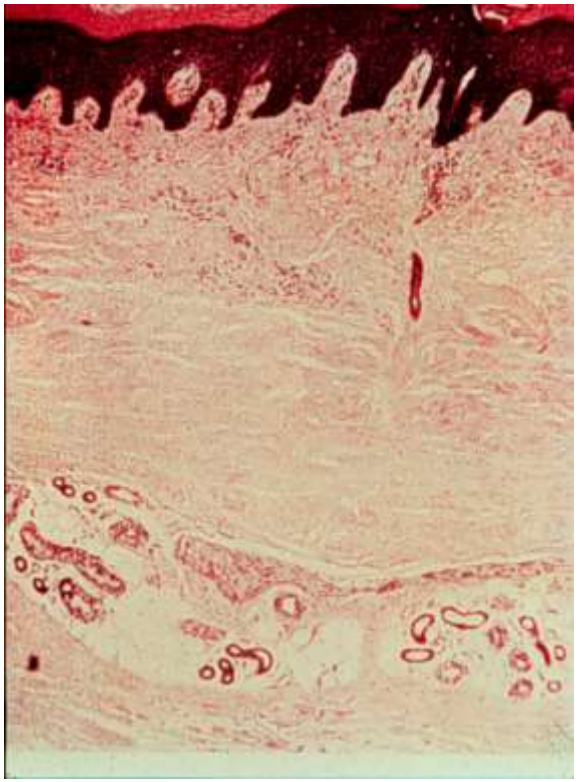
Linear and En Coupe de Sabre Type Morphea





Scleroderma Update: 2015

Histopathologic Features



Localized Scleroderma: 2015 Topical Treatment - General

- Emollients (3)
- Topical corticosteroids (3)
- Superpotent topical corticosteroids (2)
- Topical calcipotriene plus occlusion (2)
- Topical imiquimod (3)
- Topical tacrolimus plus keratocytic (3)
- Intralesional corticosteroids (3)
- Physical therapy (3)
- PUVA and other phototherapy including UVA-1 (2)
- Methotrexate (2)
- Prednisone taper/methotrexate (2)
- Other

Scleroderma Update: 2015

Systemic Scleroderma Clinical Features

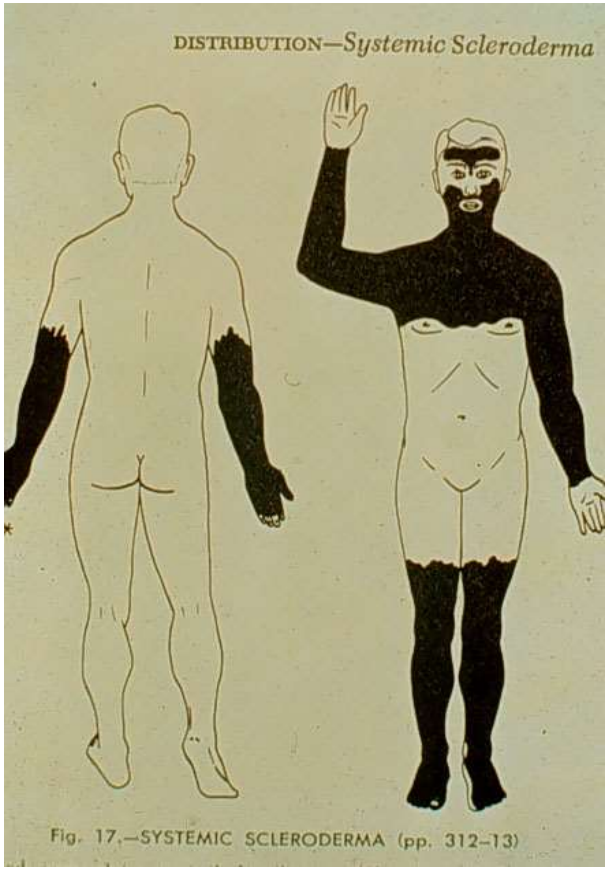
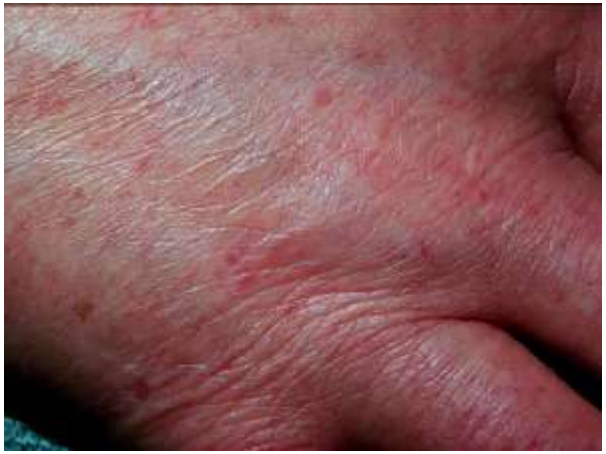
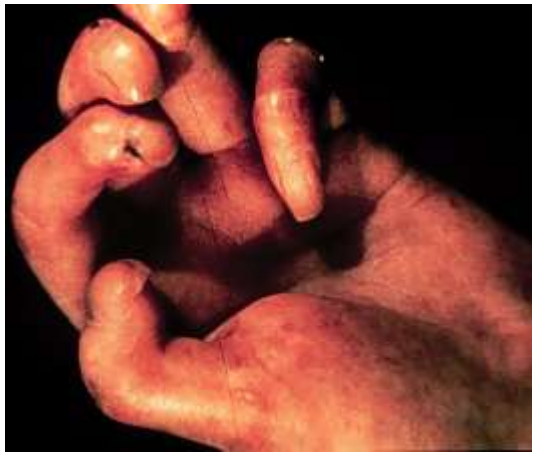


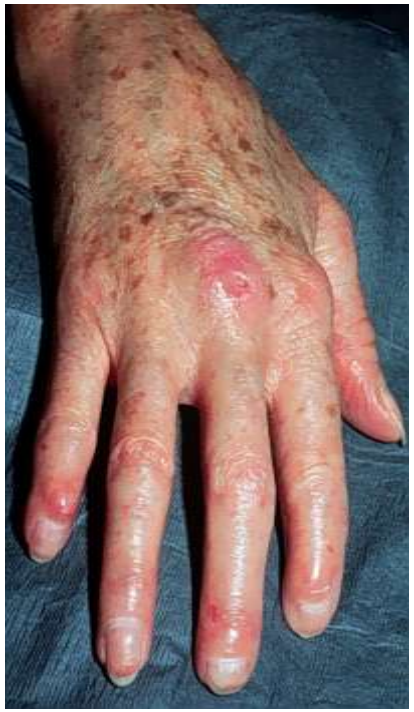
Fig. 17.—SYSTEMIC SCLERODERMA (pp. 312–13)

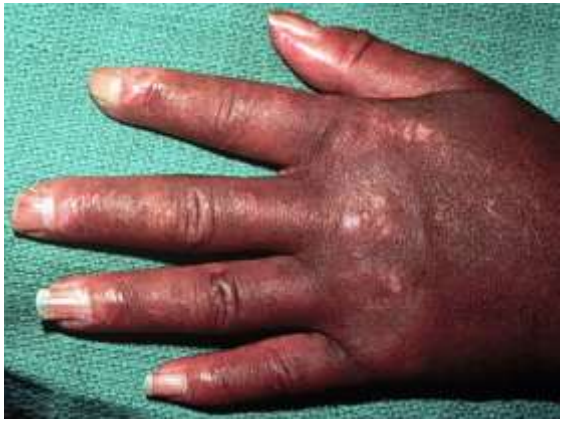
Scleroderma Update: 2015
Systemic Scleroderma Clinical Features

Scleroderma Update: 2015
Systemic Scleroderma Clinical Features









Scleroderma Update: 2015 Systemic Features

- Raynaud's phenomenon
- Pulmonary hypertension, fibrosis
- GI: Esophagus, small intestine (malabsorbtion, bacterial overgrowth)
- Cardiac: Pericarditis, myocarditis, conduction abnormalities
- Renal: Severe arterial hypertension
- Arthralgias and myalgias

Scleroderma Update: 2015 Pathogenesis

- Unknown
- Viral etiology theories
- Borrelia theories for morphea
- Environmental theories
- Immunologic/vascular theories
- Microchimerism (Fetal CD3+ cells in maternal circulation with GVH-like response)

Scleroderma Update: 2015
Pathogenesis (Cont.)

- Genetic factors - unclear
- Microvascular targets - capillary damage, adhesion molecules, perivascular infiltrates
- Immune dysfunction - T cell subsets, cytokines, autoantigens to topoisomerase I, centromeric proteins and RNA polymerases
- Connective tissue fibrosis - TGF-beta, CTGF and collagen receptors (alpha 1 beta 1, alpha 2 beta 2)

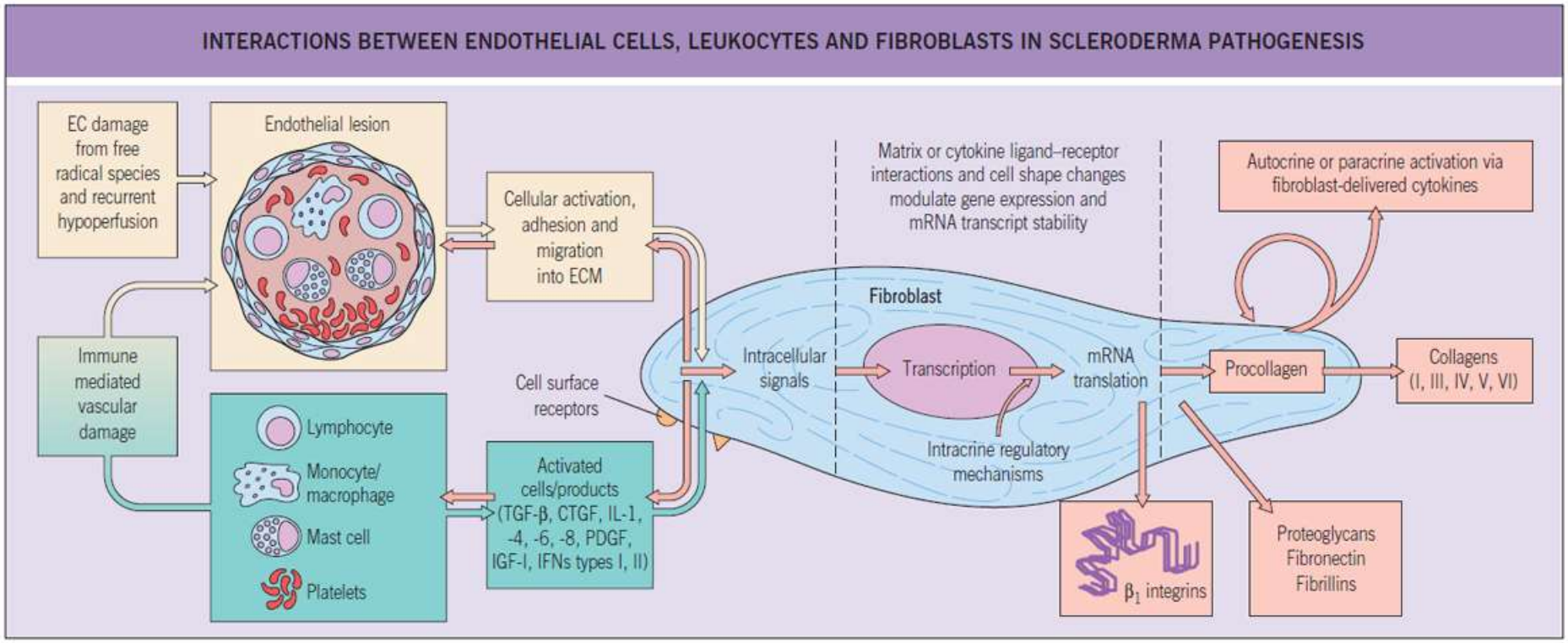


Fig. 43.1 Interactions between endothelial cells, leukocytes and fibroblasts in scleroderma pathogenesis. CTGF, connective tissue growth factor; EC, endothelial cell; ECM, extracellular matrix; IFN, interferon; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor. Genetic susceptibility loci that may increase the risk of developing scleroderma include a region on chromosome 15q (which contains the fibrillin-1 gene) as well as polymorphisms in *STAT4* and the promotor for CTGF.

Adapted from Hochberg MC, Silman AJ, Smolen JS, et al (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003.

MAJOR CLINICAL AND LABORATORY MANIFESTATIONS OF SYSTEMIC SCLEROSIS AND OTHER SELECTED CONDITIONS CHARACTERIZED BY CUTANEOUS INDURATION						
	Systemic sclerosis	**Morphea**	**Eosinophilic fasciitis**	**Scleredema**	**Scleromyxedema**	**NSF**
Major clinical variants	• Limited • Diffuse	• Plaque-type morphea • Linear morphea • Generalized morphea		• Post-infectious (type I) • Monoclonal gammopathy-associated (type II) • Diabetes mellitus-associated (type III)		
Raynaud's phenomenon	++	–	–	–	–	–
Symmetric induration	++*	–	++*	++	++	+
Sclerodactyly	++	–	–	–	–	–
Facial involvement	+	– plaque-type and generalized + linear (en coup de sabre)	–	± types I and II – type III	+	–
Systemic involvement	++	–	+	–	++	+
Antinuclear antibodies	++	± generalized and linear – plaque-type	–	–	–	–
Anticentromere antibodies	+ limited	–	–	–	–	–
Anti-topoisomerase I (Scl-70) antibodies	+ diffuse	–	–	–	–	–
Monoclonal gammopathy	–	–		+ type II	++	–
Spontaneous remission	–	++ plaque-type + generalized ± linear	++	++ type I ± types II and III	–	±†

*May be preceded by edematous phase.
†With improved renal function.

Table 43.1 Major clinical and laboratory manifestations of systemic sclerosis and other selected conditions characterized by cutaneous induration. NSF, nephrogenic systemic fibrosis; ++, almost always; +, common; ±, sometimes; –, rare or unusual.

Courtesy, Vincent Falanga, MD.

Scleroderma Update: 2015
Therapy - General

- Therapy for specific features
  (Raynaud's, esophageal reflex, hypertension)
- Therapies used for Raynaud's phenomenon
  - Avoid cold, stop smoking, biofeedback
  - Calcium channel blockers - (e.g. Nifedipine extended release etc.)
  - Nitroglycerin ointment 2% - (1/4-1 inch q6h)
  - Hydralazine 40-50mg/day
  - ACE inhibitors (e.g. Captopril 25-150mg tid; Prevent renal crisis)
  - Botulinum toxin type A
  - Angiotensin-receptor blocker (losartan 50mg/day)
  - Prostaglandins (egilopros, epoprostenolol)
  - Iloprost (prostacyclin analog IV pulse)
  - Pentoxifylline 400mg tid
  - Sildenaphil (phosphodiesterase inhibitor)
  - Endothelin inhibitor (Bosentan)
  - Tyrosine kinase inhibitor (imatinib)

EVALUATION AND TREATMENT OF INTERNAL ORGAN INVOLVEMENT IN PATIENTS WITH SYSTEMIC SCLEROSIS			
	Symptoms/signs*	**Studies**	**Treatment**
Pulmonary: • Interstitial lung disease • Pulmonary artery hypertension	Shortness of breath, dyspnea on exertion, dry cough Tachypnea, bibasilar rales, signs of right-sided CHF (e.g. peripheral edema, hepatomegaly, dilated neck veins)	• Interstitial lung disease: Pulmonary function tests, including DLCO† High-resolution CT† • Pulmonary artery hypertension: Echocardiogram Right heart catheterization	• Interstitial lung disease: immunosuppression, primarily cyclophosphamide or mycophenolate mofetil • Pulmonary artery hypertension: vasodilators including endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), prostacyclin analogues (iloprost [inhaled], epoprostenol [IV], trepostinil [sc]), and PDE5 inhibitors (sildenafil, tadalafil)
Cardiac	Shortness of breath, dyspnea on exertion, palpitations Signs of right- or left-sided CHF (e.g. tachypnea, rales, peripheral edema [see above])	Electrocardiogram Right heart catheterization	Diuretics, ACE inhibitors, β-blockers (unless contraindicated), angiotensin II receptor blockers, aldosterone antagonists May need to consider withdrawal of calcium channel blockers
Renal, including scleroderma renal crisis‡	Headache, blurry vision Hypertension	Blood pressure BUN, creatinine, urinalysis	Blood pressure control, in particular the use of ACE inhibitors
Gastrointestinal	Dyspepsia, dysphagia, postprandial bloating, constipation, diarrhea Signs of malnutrition	Upper gastrointestinal series (barium swallow) with small bowel follow-through Manometry Endoscopy Malabsorption evaluation	Proton-pump inhibitors for gastroesophageal reflux Domperidone or metoclopramide to improve motility and bloating

*Patients may be asymptomatic.
†At baseline and every 6–12 months for first five years after initial diagnosis, then yearly.
‡Suspected if, compared to baseline, the systolic pressure is elevated >20 mmHg or the diastolic pressure is elevated >10 mmHg.

Table 43.5 Evaluation and treatment of internal organ involvement in patients with systemic sclerosis.
ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; CHF, congestive heart failure; CT, computerized tomography; DLCO, diffusion capacity of carbon monoxide; IV, intravenous; PDE5, phosphodiesterase type 5; sc, subcutaneous.

Scleroderma: Update 2015
Therapy Possible Systemic Agents

- Minocycline
- Hydroxychloroquine
- Quinacrine
- Colchicine
- Phenytoin
- D-Penicillamine
- Aminobenzoate potassium (Potaba)
- PUVA and other phototherapy
- Gamma or alpha interferon
- Relaxin
- Bosentan (oral endothelin receptor antagonist)

Scleroderma: Update 2015 Therapy Possible Systemic Agents (Continued)

- Prednisone
- Methotrexate
- Azathioprine
- Mycophenolate mofetil
- Cyclophosphamide
- Chlorambucil
- Cyclosporine
- Imatinib (Gleevec – Dual transforming growth factor beta and platelet derived growth factor inhibitor)
- Extracorporeal photophoresis
- Stem cell transplantation

Scleroderma Update: 2015
Possible Systemic Agents (Cont.)

- Thalidomide derivatives
- TNF alpha inhibitors
- Rituximab
- IVIG
- Other
- Biological therapies directed at these targets:
  - TGF-beta
  - Connective tissue growth factor
  - IL-4, IL-13, MCP-1
  - Endothelin