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
<table>
<thead>
<tr>
<th>Lichenoid dermatoses</th>
<th>Possible target antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen planus</td>
<td>V, D, C, T</td>
</tr>
<tr>
<td>Lichenoid drug eruption</td>
<td>D</td>
</tr>
<tr>
<td>Erythema dyschromicum perstans</td>
<td>V, D</td>
</tr>
<tr>
<td>Graft-versus-host disease (see Ch. 52)</td>
<td>Allo, V</td>
</tr>
<tr>
<td>Keratosis lichenoides chronica</td>
<td></td>
</tr>
<tr>
<td>Pityriasis lichenoides* (see Ch. 9)</td>
<td>V</td>
</tr>
<tr>
<td>Lichen nitidus</td>
<td>V</td>
</tr>
<tr>
<td>Lichen striatus</td>
<td>V</td>
</tr>
<tr>
<td>Fixed drug eruption (see Ch. 21)</td>
<td>D</td>
</tr>
<tr>
<td>Erythema multiforme (see Ch. 20)</td>
<td>V, D, C</td>
</tr>
<tr>
<td>Lupus erythematosus (see Ch. 41)</td>
<td>V, Auto, D</td>
</tr>
<tr>
<td>Dermatomyositis (see Ch. 42)</td>
<td>V, Auto, T, D</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus (see Ch. 29)</td>
<td>T</td>
</tr>
<tr>
<td>Mycosis fungoides (CTCL) (see Ch. 120)</td>
<td>T, V</td>
</tr>
<tr>
<td>Lichenoid pigmented purpura (see Ch. 22)</td>
<td>D, V</td>
</tr>
<tr>
<td>Secondary syphilis (see Ch. 82)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drugs Implicated in Lichenoid Drug Eruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIMICROBIALS</strong></td>
</tr>
<tr>
<td>- Ethambutol</td>
</tr>
<tr>
<td>- Griseofulvin</td>
</tr>
<tr>
<td>- Isoniazid</td>
</tr>
<tr>
<td>- Ketoconazole</td>
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<tr>
<td>- Pyrimethamine</td>
</tr>
<tr>
<td>- Steptomycin</td>
</tr>
<tr>
<td>- Sulfamethoxazole</td>
</tr>
<tr>
<td>- Tetracylines</td>
</tr>
<tr>
<td><strong>METALS</strong></td>
</tr>
<tr>
<td>- <strong>Gold salts</strong></td>
</tr>
<tr>
<td>- Arsenic</td>
</tr>
<tr>
<td>- Bismuth</td>
</tr>
<tr>
<td>- Mercury</td>
</tr>
<tr>
<td>- Palladium</td>
</tr>
<tr>
<td><strong>ANTIHYPERTENSIVES</strong></td>
</tr>
<tr>
<td>- Captopril</td>
</tr>
<tr>
<td>- Enalapril</td>
</tr>
<tr>
<td>- Labetalol</td>
</tr>
<tr>
<td>- Methyldopa</td>
</tr>
<tr>
<td>- Propranolol</td>
</tr>
<tr>
<td>- Dilazide *</td>
</tr>
<tr>
<td>- Doxazosin</td>
</tr>
<tr>
<td>- Ruzosin</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
</tr>
<tr>
<td>- Acetylsalicylic acid</td>
</tr>
<tr>
<td>- Ibuprofen</td>
</tr>
<tr>
<td>- Indomethacin</td>
</tr>
<tr>
<td>- Naproxen</td>
</tr>
<tr>
<td>- Sulindac</td>
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<tr>
<td><strong>ANTIMALARIALS</strong></td>
</tr>
<tr>
<td>- Chloroquine</td>
</tr>
<tr>
<td>- Hydroxychloroquine</td>
</tr>
<tr>
<td>- Quinacrine</td>
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<tr>
<td><strong>ANTIDEPRESSANTS, ANTIANXIETY DRUGS, ANTI-Psychotics AND ANTICONVULSANTS</strong></td>
</tr>
<tr>
<td>- Amitriptyline</td>
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<tr>
<td>- Carbamazepine</td>
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<tr>
<td>- Chlorpromazine</td>
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<tr>
<td>- Imipramine</td>
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<tr>
<td>- Levomepromazine</td>
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<tr>
<td>- Lorazepam</td>
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<tr>
<td>- Methpromazine</td>
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<tr>
<td>- Phenothiazin</td>
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<tr>
<td>- Allopurinol</td>
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<tr>
<td>- Amiphenazole</td>
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<tr>
<td>- Anakrin</td>
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<tr>
<td>- Cinnarazine</td>
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<tr>
<td>- Dapsone</td>
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<tr>
<td>- Gemfibrozil</td>
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<tr>
<td>- Hydroxyurea</td>
</tr>
<tr>
<td>- Matinib</td>
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<tr>
<td>- Interferon-α</td>
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<tr>
<td>- Iodides</td>
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<tr>
<td>- Isotretinoin</td>
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<tr>
<td>- Levamisole</td>
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<tr>
<td>- Lithium</td>
</tr>
<tr>
<td>- Mercapto-propionylglycine</td>
</tr>
<tr>
<td>- Mesalamine</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS DRUGS</strong></td>
</tr>
<tr>
<td>- Methycran</td>
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<tr>
<td>- Nefazodone</td>
</tr>
<tr>
<td>- Omeprazole</td>
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<tr>
<td>- Orlistat</td>
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<tr>
<td>- Penicillamine</td>
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<tr>
<td>- Prolithiourea</td>
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<td>- Rofecoxaun</td>
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<tr>
<td>- Pyritinone</td>
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<tr>
<td>- Simvastatin</td>
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<tr>
<td>- Quinine</td>
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<tr>
<td>- Quinidine</td>
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<tr>
<td>- Ruxinab</td>
</tr>
<tr>
<td>- Sildenafil</td>
</tr>
<tr>
<td>- Sulfasalazine</td>
</tr>
<tr>
<td>- Thioxyphenidyl</td>
</tr>
<tr>
<td><strong>DIURETICS</strong></td>
</tr>
<tr>
<td>- Chlorothiazide</td>
</tr>
<tr>
<td>- Hydrochlorothiazide</td>
</tr>
<tr>
<td>- Furosemide</td>
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<tr>
<td>- Spironolactone</td>
</tr>
<tr>
<td><strong>HYPOGLYCEMIC AGENTS</strong></td>
</tr>
<tr>
<td>- Chlorpropamide</td>
</tr>
<tr>
<td>- Glyburide</td>
</tr>
<tr>
<td>- Tolazamide</td>
</tr>
<tr>
<td>- Tolbutamide</td>
</tr>
</tbody>
</table>

*Also used to treat hypoglycemia.

†Including in alcoholic beverages.
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 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. 11.9 Exanthematous lichen planus. Papulosquamous lesions on the back.
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 Hypertrophic lichen planus. (A) on the shins, very thick discrete 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 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 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 Oral lichen planus. (A) White lacy pattern and an erosion on the buccal mucosa, the most common location for the reticular form. 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

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Dosage/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids (2)</td>
<td></td>
</tr>
<tr>
<td>Superpotent topical corticosteroids</td>
<td>(oral LP (1); cutaneous LP (2))</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors</td>
<td>(e.g., pimecrolimus and tacrolimus in oral LP (1); tacrolimus in vulvar (2)</td>
</tr>
<tr>
<td></td>
<td>and other forms (3) of LP)</td>
</tr>
<tr>
<td>Intraleisional corticosteroids (2)</td>
<td></td>
</tr>
<tr>
<td>Intramuscular triamcinolone acetonide</td>
<td>[0.5–1 mg/kg/month × 3–6 months] (3)</td>
</tr>
<tr>
<td>Narrowband UVB (2)</td>
<td></td>
</tr>
<tr>
<td>Oral metronidazole * [500 mg po bid]</td>
<td>(2)</td>
</tr>
<tr>
<td>Antimalarials † (2)</td>
<td></td>
</tr>
<tr>
<td>Systemic retinoids* (1 for etretinate;</td>
<td>3 for alitretinoin)</td>
</tr>
<tr>
<td>Griseofulvin † (2)</td>
<td></td>
</tr>
<tr>
<td>PUVA (2)</td>
<td></td>
</tr>
<tr>
<td>UVA1 (2)</td>
<td></td>
</tr>
<tr>
<td>308-nm excimer laser for oral LP (2)</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids † (1)</td>
<td></td>
</tr>
<tr>
<td>Low-dose weekly methotrexate (2)</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil (2)</td>
<td></td>
</tr>
<tr>
<td>Thalidomide (2)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (3)</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine † (1 for cutaneous LP)</td>
<td></td>
</tr>
<tr>
<td>Extracorporeal photochemotherapy (2)</td>
<td></td>
</tr>
<tr>
<td>Targeted immunomodulators (TNF-α inhibitors, alefacept, basiliximab) (3)</td>
<td></td>
</tr>
</tbody>
</table>

*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 peroxide)
- 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 examinations, particularly direct and indirect immunofluorescence microscopy as well as anti-BP180/BP230 ELISAs.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Target antigen(s)</th>
<th>Mol. wt. (kDa)</th>
<th>Morphologic structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullous pemphigoid (BP)</td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td>Gestational pemphigoid</td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td>Mucous membrane (cicatricial) pemphigoid</td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e+</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td></td>
<td>Laminin 5 (332; α3β1γ2, epiligrin)</td>
<td>165, 140, 105</td>
<td>Anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>Laminin 6 (311; α3β1γ1)†</td>
<td>165, 220, 200</td>
<td>Anchoring filaments/extracellular matrix</td>
</tr>
<tr>
<td></td>
<td>Integrin β4 subunit§</td>
<td>200</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td>Linear IgA bullous dermatosis (LABD)</td>
<td>LAD antigen*</td>
<td>97/120</td>
<td>Anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP180/BPAG2/collagen XVII</td>
<td>180</td>
<td>Hemidesmosomal plaque/anchoring filaments</td>
</tr>
<tr>
<td></td>
<td>BP230/BPAG1e†</td>
<td>230</td>
<td>Hemidesmosomal plaque</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td>Type VII collagen†</td>
<td>290/145</td>
<td>Anchoring fibrils</td>
</tr>
<tr>
<td>Anti-p200 pemphigoid</td>
<td>Laminin gamma-1 chain</td>
<td>200 kDa</td>
<td>Extracellular matrix</td>
</tr>
<tr>
<td>Bullous systemic lupus erythematos</td>
<td>Type VII collagen†</td>
<td>290/145</td>
<td>Anchoring fibrils</td>
</tr>
</tbody>
</table>

* 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 autoantgens 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 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 Bullous pemphigoid – eczematous presentation. (A), (B)
Large pink eczematous plaques on the trunk and upper extremities.
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 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. Bologna, 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
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Design</th>
<th>Intervention</th>
<th>Number of patients</th>
<th>Response</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Roujeau et al.24  (1984) | Randomized multicenter | Group 1: Prednisolone (0.3 mg/kg/day)  
Group 2: Prednisolone + 8 plasma exchanges | 41                 | Total and daily corticosteroid doses needed for disease control lower in group 2 | Low prednisolone dose                                                   |
| Morel & Guillaume25 (1984) | Randomized multicenter | Group 1: Prednisone (0.75 mg/kg/day)  
Group 2: Prednisone (1.25 mg/kg/day) | 42                 | At day 51, remission in group 1 (33%) and group 2 (59%) not significantly different | Trend for a better response in group 2                                  |
| Guillot et al.26  (1986) | Non-randomized retrospective | Group 1: Prednisolone alone  
Group 2: 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.27    (1993) | Randomized multicenter | Group 1: Methylprednisolone (1–1.5 mg/kg/day)  
Group 2: Prednisolone (1–1.5 mg/kg/day) | 57                 | At day 10, no difference in response except for better decline of pruritus in group 1 | Analysis of early response only                                           |
| Guillame et al.28  (1993) | Randomized multicenter | Group 1: Prednisolone (1 mg/kg/day) alone  
Group 2: Prednisolone and azathioprine (100–150 mg/day)  
Group 3: Prednisolone and 4 plasma exchanges | 98                 | At month 6, no significant difference in remission rate between group 1 (42%), group 2 (59%) and group 3 (29%) | More complications in group 2. No adjustment of doses of azathioprine based on TPMT levels |
| Fivenson et al.29  (1994) | Randomized single center | Group 1: Nicotinamide (1.5 g/day) plus tetracycline (2 g/day)  
Group 2: Prednisone (40–80 mg/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.30 (2002) | Randomized multicenter | Group 1: Topical clobetasol propionate  
Group 2: Prednisone 0.5–1 mg/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 |
| Beisert et al.31  (2007) | Randomized multicenter prospective | Group 1: Methylprednisolone (0.5 mg/kg) with azathioprine (2 mg/kg)  
Group 2: Methylprednisolone (0.5 mg/kg) with mycophenolate mofetil (2 g daily) | 38                 | 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.32 (2009) | Randomized multicenter prospective | Group 1: Topical clobetasol propionate standard regimen for 12 months (40 g daily as starting dose)  
Group 2: Topical clobetasol propionate, mild regimen for 6 months (10–30 g daily as starting dose) | 153                | 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

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
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, thyroiditis
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 (e.g., uveitis, retinal vasculitis) and cutaneous lesions
- Cutaneous findings range from sterile papulopustules and palpable purpura to erythema nodosum-like lesions
- Histologically, a neutrophilic angiocentric infiltrate with leukocytoclastic (early) or lymphocytic (late) vasculitis is the characteristic finding
Important Issues Regarding Behcet’s Disease

1. Do not overdiagnose complex aphthosis

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

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
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 than vasculitis)
- Attempt to establish etiology
- Therapeutic ladder
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
<table>
<thead>
<tr>
<th>Treatment modalities</th>
<th>Morphoea</th>
<th>Level of evidence</th>
<th>Lichen sclerosus</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Efficacy</td>
<td></td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>+</td>
<td>3</td>
<td>+++ (ultrapotent)</td>
<td>1</td>
</tr>
<tr>
<td>Intralesional corticosteroids</td>
<td>+</td>
<td>3</td>
<td>++</td>
<td>2</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors</td>
<td>+ (early lesions)</td>
<td>2</td>
<td>++</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin A analogues</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Testosterone</td>
<td>No experience</td>
<td>0</td>
<td>No experience</td>
<td>1</td>
</tr>
<tr>
<td>Progesterone</td>
<td>No experience</td>
<td>0</td>
<td>No experience</td>
<td>1</td>
</tr>
<tr>
<td>Intraleisional interferon-γ</td>
<td>0</td>
<td>1</td>
<td>No experience</td>
<td>1</td>
</tr>
<tr>
<td>Systemic</td>
<td>Efficacy</td>
<td></td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>++ (approx. 5% of patients)</td>
<td>3</td>
<td>No experience</td>
<td>3</td>
</tr>
<tr>
<td>Hydroxy-/chloroquine</td>
<td>No experience</td>
<td></td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin A analogues*</td>
<td>+</td>
<td>3</td>
<td>++</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>0</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>3</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td>Penicillamine</td>
<td>++</td>
<td>3</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
<td>2</td>
<td>No experience</td>
<td></td>
</tr>
<tr>
<td>Phototherapy</td>
<td>Efficacy</td>
<td></td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Oral photochemotherapy</td>
<td>++</td>
<td>3</td>
<td>+</td>
<td>3</td>
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<td>Bath photochemotherapy</td>
<td>++++</td>
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<td>Cream photochemotherapy</td>
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<td>3</td>
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<td>3</td>
</tr>
<tr>
<td>UVA1</td>
<td>++++</td>
<td>2</td>
<td>++</td>
<td>2</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>+</td>
<td>3</td>
<td>++</td>
<td>3</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
<td>+</td>
<td>3</td>
<td>No experience</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>Efficacy</td>
<td></td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>CO₂ laser</td>
<td>No experience</td>
<td></td>
<td>++</td>
<td>3</td>
</tr>
<tr>
<td>Surgery</td>
<td>Selected patients</td>
<td></td>
<td>Selected patients</td>
<td></td>
</tr>
<tr>
<td>Physical therapy</td>
<td>Important</td>
<td></td>
<td>Important</td>
<td></td>
</tr>
</tbody>
</table>

*E.g. acitretin.

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)
Sarcoidosis: Systemic Features

- SURT
- Intrathoracic
- Ocular
- Lymph Nodes

- Musculoskeletal
- Neurosarcoidosis
- Hepatic sarcoidosis
- Cardiac
- Endocrine metabolic
<table>
<thead>
<tr>
<th>HISTOLOGIC FEATURES OF THE MAJOR GRANULOMATOUS DERMATITIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sarcoidosis</strong></td>
</tr>
<tr>
<td>Typical location</td>
</tr>
<tr>
<td>Granuloma pattern</td>
</tr>
<tr>
<td>Necrobiosis (altered collagen)</td>
</tr>
<tr>
<td>Giant cells</td>
</tr>
<tr>
<td>Elastolysis</td>
</tr>
<tr>
<td>Elastophagocytosis</td>
</tr>
<tr>
<td>Asteroid bodies</td>
</tr>
<tr>
<td>Mucin</td>
</tr>
<tr>
<td>Extracellular lipid</td>
</tr>
<tr>
<td>Vascular changes</td>
</tr>
</tbody>
</table>

*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.

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<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical, intralesional or systemic corticosteroids (2)</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors (3)</td>
</tr>
<tr>
<td>Minocycline (2)</td>
</tr>
<tr>
<td>Systemic hydroxychloroquine or chloroquine (2)</td>
</tr>
<tr>
<td>Intraleseional chloroquine (3)</td>
</tr>
<tr>
<td>Allopurinol (3)</td>
</tr>
<tr>
<td>Isotretinoin (3)</td>
</tr>
<tr>
<td>Methotrexate (2)</td>
</tr>
<tr>
<td>PUVA (psoralen plus UVA) (3)</td>
</tr>
<tr>
<td>Thalidomide (2)</td>
</tr>
<tr>
<td>TNF-α inhibitors (adalimumab, infliximab, etanercept)* (3)</td>
</tr>
<tr>
<td>Leflunomide (2)</td>
</tr>
<tr>
<td>Mycophenolate mofetil (3)</td>
</tr>
<tr>
<td>Surgical excision (3)</td>
</tr>
<tr>
<td>Pulsed dye or CO₂ laser (3)</td>
</tr>
<tr>
<td>Photodynamic therapy (3)</td>
</tr>
</tbody>
</table>

*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
**TREATMENT OF GRANULOMA ANNULARE**

- Topical corticosteroids (3)
- Intraleisional corticosteroids (2)
- Topical calcineurin inhibitors (3)
- Topical imiquimod (3)
- Cryosurgery (2)
- Hydroxychloroquine or chloroquine (2)
- Niacinamide (nicotinamide) (3)
- Minocycline + ofloxacin + rifampin* (3)
- Pentoxifylline (3)
- Intraleisional 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)
- CO₂ 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.
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
- Poikilodermma - 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 Erythematous 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
<table>
<thead>
<tr>
<th>Autoantibodies &amp; Clinical Associations 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-dsDNA</strong></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td><strong>Anti-Sm</strong></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>CNS involvement</td>
</tr>
<tr>
<td><strong>Anti-Ro</strong></td>
</tr>
<tr>
<td>Cutaneous manifestations</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
</tr>
<tr>
<td>Congenital heart block</td>
</tr>
<tr>
<td>Neonatal lupus syndrome</td>
</tr>
<tr>
<td>Antinuclear antibody-negative lupus</td>
</tr>
<tr>
<td>Autoantibodies</td>
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<td>---------------</td>
</tr>
<tr>
<td>Anti-La</td>
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<td>Anti-RNP</td>
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<td>Antiribosomal P</td>
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</tr>
</tbody>
</table>
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

- 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
Mild and/or localized disease
- Sunscreens (High SPF with UVA protection) (2)
- Topical corticosteroids (2)
- Superpotent topical corticosteroids (2)
- Intraleisional 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 erythematous
- Malignancy association in adults
- Diagnosis is commonly (maybe even usually) missed
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

[Image of a person with dermatomyositis, showing erythematous patches on the shoulders.]
Dermatomyositis: 2015
Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous

**Gottron’s sign**

Cuticular dystrophy
Nail fold telangiectasia
Calciosis 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
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Clinical Features - Cutaneous

Heliotope sign
Photodistributed poikiloderma-violaceous
Poikiloderma over extensor surfaces-violaceous
Gottron’s sign
Cuticular dystrophy
Nail fold telangiectasia

Calcinosism cutis (complication: especially childhood)
Dermatomyositis: 2015
Clinical Features - Cutaneous

![Image of cutaneous lesions]
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)
<table>
<thead>
<tr>
<th>Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult-onset</td>
</tr>
<tr>
<td>Classic DM</td>
</tr>
<tr>
<td>Classic DM with malignancy</td>
</tr>
<tr>
<td>Classic DM as part of an overlapping connective tissue disorder</td>
</tr>
<tr>
<td>Clinically amyopathic DM*</td>
</tr>
<tr>
<td>Amyopathic DM</td>
</tr>
<tr>
<td>Hypomyopathic DM</td>
</tr>
<tr>
<td>Juvenile-onset</td>
</tr>
<tr>
<td>Classic DM</td>
</tr>
<tr>
<td>Clinically amyopathic DM</td>
</tr>
<tr>
<td>Amyopathic DM</td>
</tr>
<tr>
<td>Hypomyopathic DM</td>
</tr>
<tr>
<td>Polymyositis</td>
</tr>
<tr>
<td>Isolated polymyositis</td>
</tr>
<tr>
<td>Polymyositis as part of an overlapping connective tissue disorder</td>
</tr>
<tr>
<td>Polymyositis associated with internal malignancy (?)†</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
</tr>
</tbody>
</table>

*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**

- 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
CELLULAR IMMUNITY/APOPTOSIS

- 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
HUMORAL IMMUNITY

- 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 synthetases, non-synthetases, cytoplasmic antigens, and nuclear antigens. Examples include: antisynthetase, anti-Jo-1 (lung disease), and anti-Mi-2 (most specific for dermatomyositis)
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
- Coxsackie virus-9 myositis
DRUG AND VACCINE PRECIPITANTS\textsuperscript{26-31}

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

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

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.
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)

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 IV Ig (2 g/kg/month) (1)
   Pulse cyclophosphamide (0.5-1.0 g/m² monthly) (2)
   Chlorambucil (4 mg/day) (2)
   Cyclosporine (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/m²/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)
### IMMUNOLOGIC

- **Chronic GVHD**<sup>*</sup>  
  Morpheaform plaques favoring the trunk, which may become generalized; eosinophilic fasciitis (see Ch. 52)

- **Eosinnophilic fasciitis**  
  Symmetric induration with a “pseudo-cellulite” appearance on the extremities (sparing hands and feet) (see text)

- **Generalized morphea**<sup>*</sup>  
  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 metastatic 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
- Nephrogenic systemic fibrosis*
- Eosinophilia-myalgia syndrome
- Toxic oil syndrome*

Painful, cold, swollen extremity eventually develops cutaneous sclerosis (see Ch. 6)
Sclerotic skin in affected areas

TOXIN-MEDIATED

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 phenomenon, acro-osteolysis; pulmonary fibrosis

**VENOUS INSUFFICIENCY**

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

- **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 extremities; *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, hypergonadotropin hypogonadism, 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, aromatic 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)
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)
- Intralional 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
Scleroderma Update: 2015
Systemic Scleroderma Clinical Features
Scleroderma Update: 2015
Systemic Features

- Raynaud’s phenomenon
- Pulmonary hypertension, fibrosis
- GI: Esophagus, small intestine (malabsorption, 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 promoter for CTGF.

<table>
<thead>
<tr>
<th>Major clinical and laboratory manifestations of systemic sclerosis and other selected conditions characterized by cutaneous induration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic sclerosis</strong></td>
</tr>
<tr>
<td>Major clinical variants</td>
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<td></td>
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<tr>
<td>Raynaud's phenomenon</td>
</tr>
<tr>
<td>Symmetric induration</td>
</tr>
<tr>
<td>Sclerodactyly</td>
</tr>
<tr>
<td>Facial involvement</td>
</tr>
<tr>
<td>Systemic involvement</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
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<tr>
<td>Anticentromere antibodies</td>
</tr>
<tr>
<td>Anti-topoisomerase I (ScI-70) antibodies</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
</tr>
<tr>
<td>Spontaneous remission</td>
</tr>
<tr>
<td>*May be preceded by edematous phase.</td>
</tr>
<tr>
<td>*With improved renal function.</td>
</tr>
</tbody>
</table>

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.*
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 (prostacycllin analog IV pulse)
- Pentoxifylline 400mg tid
- Sildenaphil (phosphodiesterase inhibitor)
- Endothelin inhibitor (Bosentan)
- Tyrosine kinase inhibitor (imatinib)
<table>
<thead>
<tr>
<th>Internal Organ Involvement</th>
<th>Symptoms/signs*</th>
<th>Studies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Interstitial lung disease</td>
<td>Shortness of breath, dyspnea on exertion, dry cough Tachypnea, bibasilar rales, signs of right-sided CHF (e.g. peripheral edema, hepatomegaly, dilated neck veins)</td>
<td>- Interstitial lung disease: Pulmonary function tests, including DLCO ¹ High-resolution CT ¹</td>
<td>- Interstitial lung disease: immunosuppression, primarily cyclophosphamide or mycophenolate mofetil</td>
</tr>
<tr>
<td>- Pulmonary artery hypertension</td>
<td></td>
<td></td>
<td>Pulmonary artery hypertension: vasodilators including endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), prostacyclin analogues (iloprost [inhaled], epoprostenol [IV], treprostinil [sc]), and PDE5 inhibitors (sildenafil, tadalafil)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Shortness of breath, dyspnea on exertion, palpitations Signs of right- or left-sided CHF (e.g. tachypnea, rales, peripheral edema [see above])</td>
<td>Electrocardiogram Right heart catheterization</td>
<td>Diuretics, ACE inhibitors, β-blockers (unless contraindicated), angiotensin II receptor blockers, aldosterone antagonists May need to consider withdrawal of calcium channel blockers</td>
</tr>
<tr>
<td>Renal, including scleroderma renal crisis ²</td>
<td>Headache, blurry vision Hypertension</td>
<td>Blood pressure BUN, creatinine, urinalysis</td>
<td>Blood pressure control, in particular the use of ACE inhibitors</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dyspepsia, dysphagia, postprandial bloating, constipation, diarrhea Signs of malnutrition</td>
<td>Upper gastrointestinal series (barium swallow) with small bowel follow-through Manometry Endoscopy Malabsorption evaluation</td>
<td>Proton-pump inhibitors for gastroesophageal reflux Domperidone or metoclopramide to improve motility and bloating</td>
</tr>
</tbody>
</table>

*Patients may be asymptomatic.
¹At baseline and every 6-12 months for first five years after initial diagnosis, then yearly.
²Suspected 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.
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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)
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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
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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