CONNECTIVE TISSUE DISORDERS

Dr.sc.Deny Anđelinović

- The main feature is inflamation in the connective tissues
- The results are dermal atrophy or sclerosis, artrhritis, abnormalities in organs
- Autoimune disorders: antibody against organ systems

LUPUS ERYTHEMATOSUS

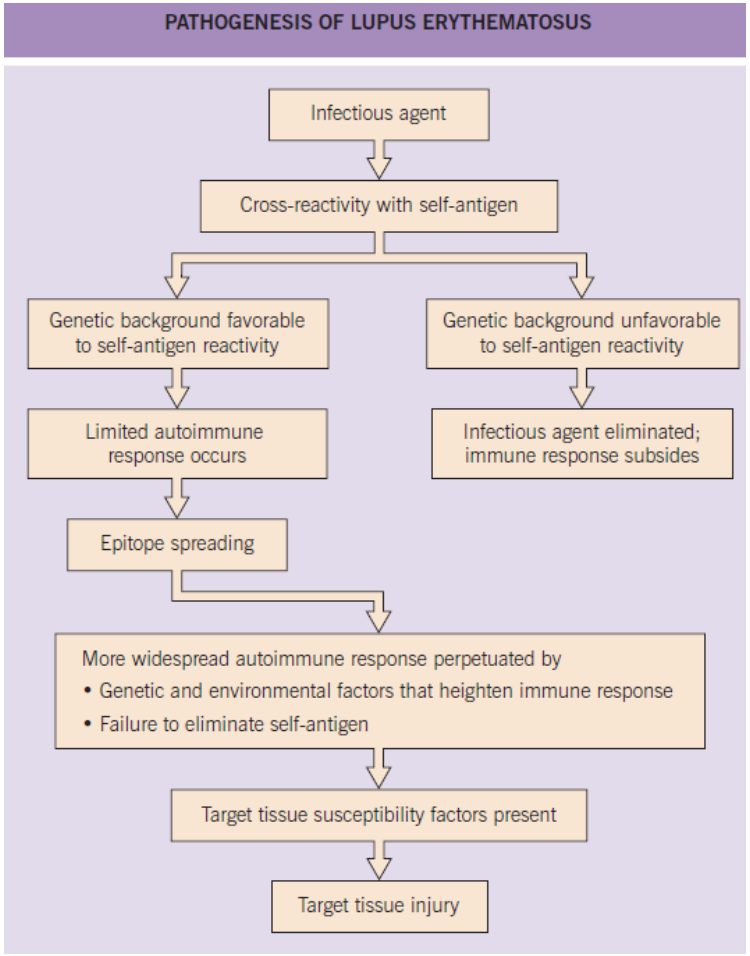
- The therm LE was first use by Cazenave et al to make difference from lupus vulgaris (tbc)
- Common disease with significant mortality and morbidity

- Discoid LE (cutaneous type, chronic skin disorder)
- Subacute cutaneous LE
- Systemic LE

PATHOGENESIS

- Genetic and environmental factors play roll in the initiation and perpetuation of the autoimmune response.
- Genes that affect immunoreactivity are those whose proteins are involved in apoptosis ; the others affect ability to present specific peptides to T cells

- hereditary factors and HLA types (many members in one family) .
- Exposure to sunlight may precipitate the disease (UV lights causes Ro antigen to bind with anti-Ro antibodies on the cell surface)
- Drugs : hydralazine, procainamid, oral contraceptives, minocycline, anticonvulsants


PATHOGENESIS OF LUPUS ERYTHEMATOSUS
Infectious agent
Cross-reactivity with self-antigen
Genetic background favorable to self-antigen reactivity
Genetic background unfavorable to self-antigen reactivity
Limited autoimmune response occurs
Infectious agent eliminated; immune response subsides
Epitope spreading
More widespread autoimmune response perpetuated by
• Genetic and environmental factors that heighten immune response
• Failure to eliminate self-antigen
Target tissue susceptibility factors present
Target tissue injury

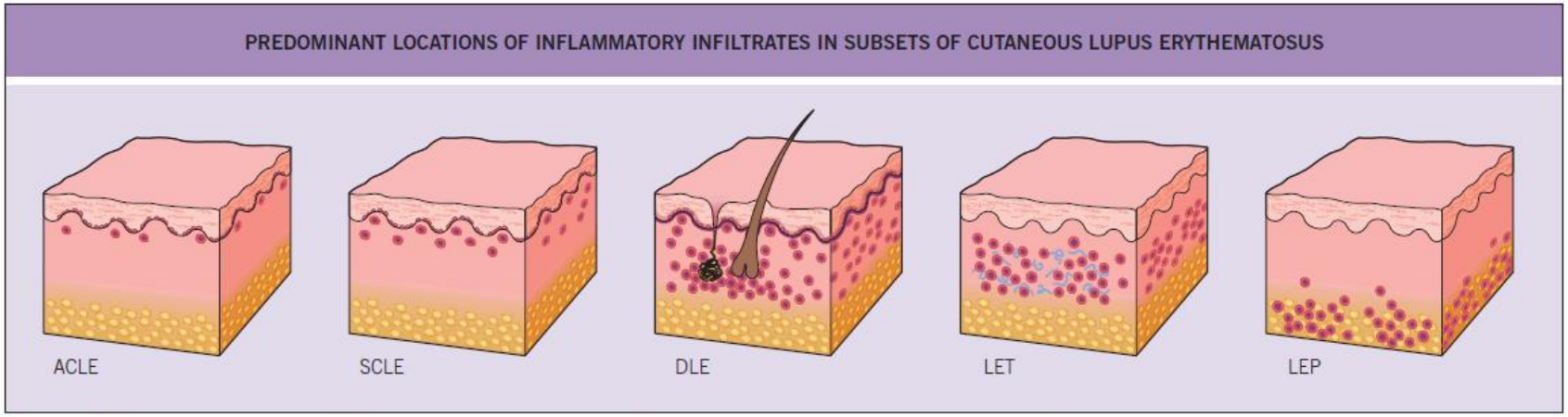


Fig. 42.2 Predominant locations of inflammatory infiltrates in subsets of cutaneous lupus erythematosus. The types of cutaneous lupus erythematosus are: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LET) and lupus panniculitis (LEP); the latter three are forms of chronic cutaneous lupus erythematosus. The primary locations of the infiltrates are as follows: superficial dermis, ACLE and SCLE; superficial plus deep dermis and periadnexal, DLE; superficial and deep dermis, LET; and subcutaneous fat, LEP.

CLINICAL FEATURES of SLE

Butterfly malar rash (transient, follow sun exposure, resolve without scarring)

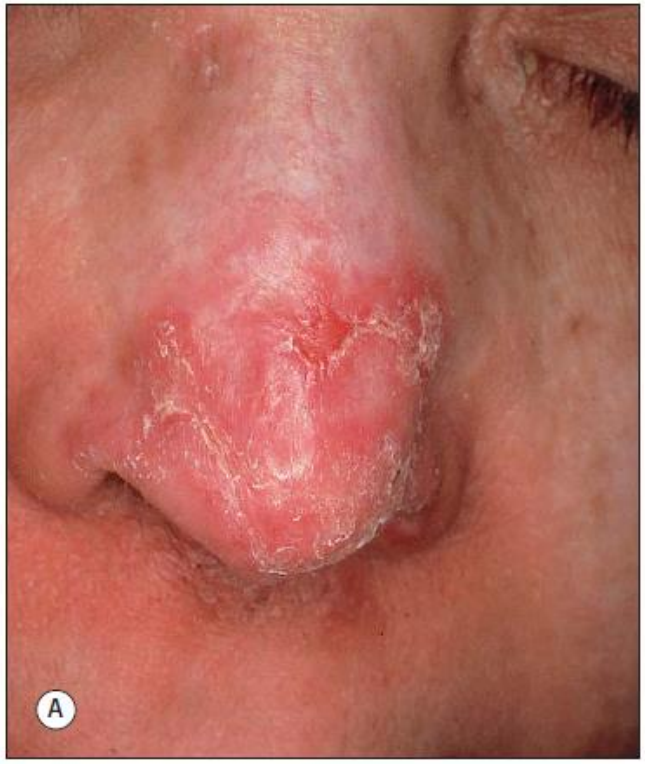
Poikiloderma(hypo-hyperpigmentation, epidermal atrophy)

Acute skin eruptions (like EEM, TEN)

Periungual teleangiectasia, erythema over the digits, hair fall, photosensitivity, annular papulosquamous plaques, mouth ulcers.

CUTANEOUS FINDINGS (NON-SPECIFIC) THAT SUGGEST THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS
Diffuse non-scarring alopecia
Raynaud's phenomenon
Nailfold telangiectasias and erythema
Vasculitis
• Urticarial vasculitis
• Small vessel vasculitis (e.g. palpable purpura)
• Polyarteritis nodosa-like lesions
Cutaneous signs of antiphospholipid syndrome
• Livedo reticularis
• Ulcerations
• Acrocyanosis
• Atrophie blanche-like lesions
• Degos'-like lesions
Livedoid vasculopathy
Palmar erythema
Papular and nodular mucinosis

Table 42.3 Cutaneous findings (non-specific) that suggest the diagnosis of systemic lupus erythematosus. These are in addition to skin signs of other autoimmune connective tissue diseases, which raise the possibility of an overlap syndrome.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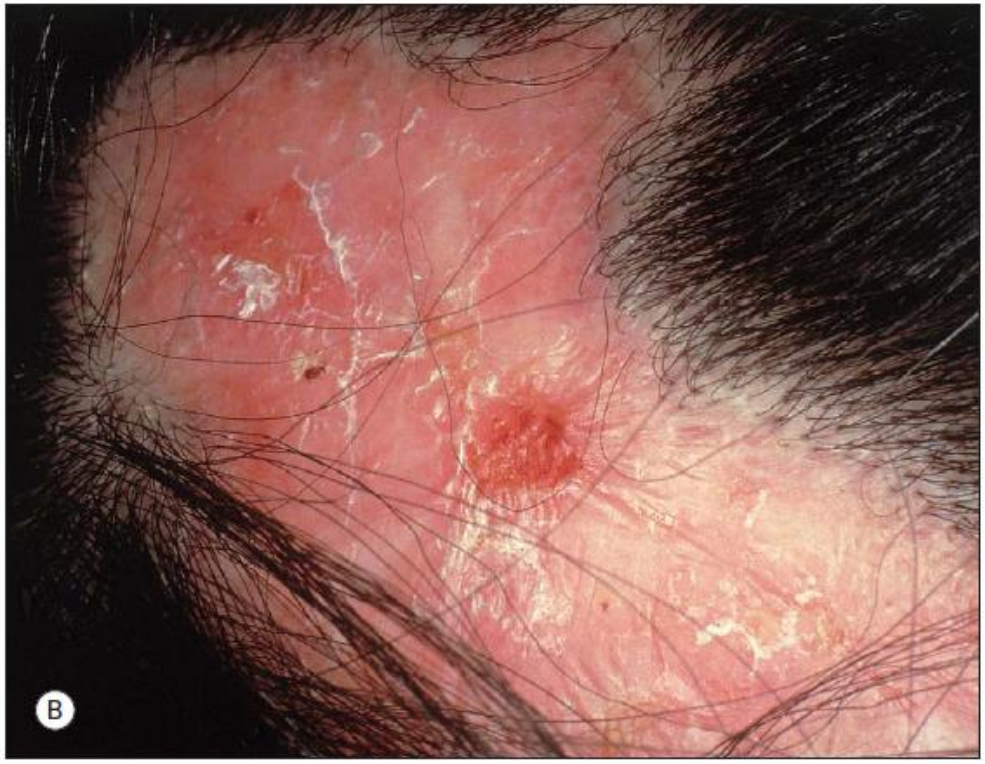
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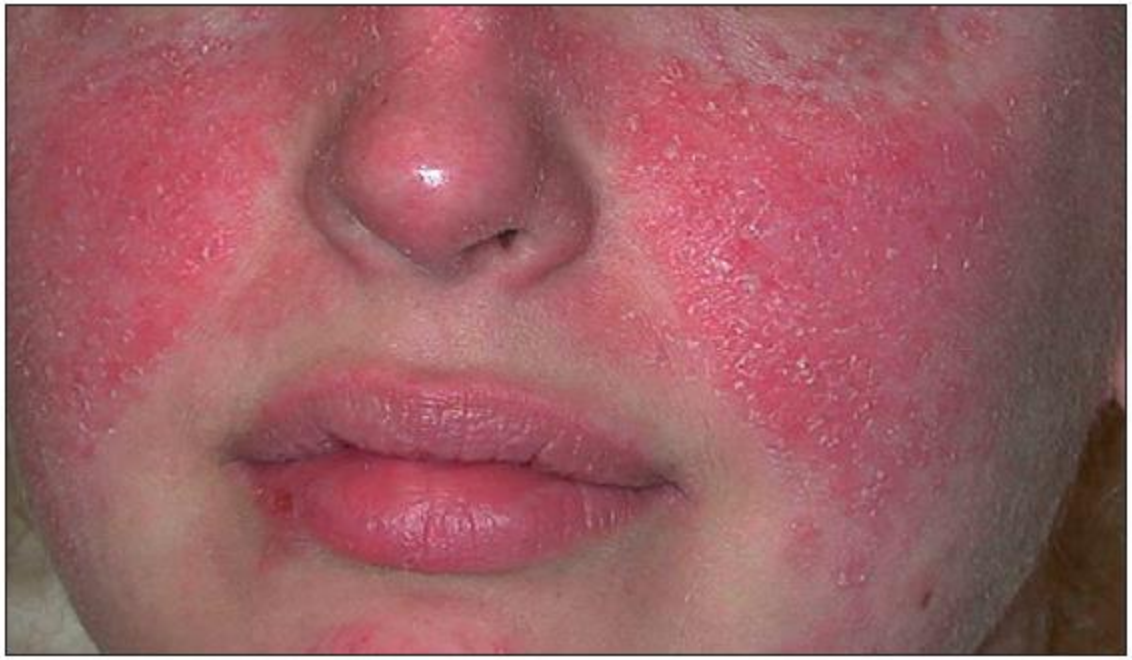
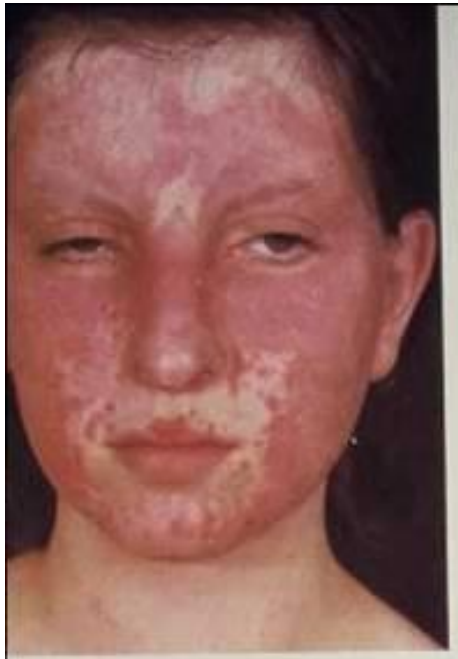
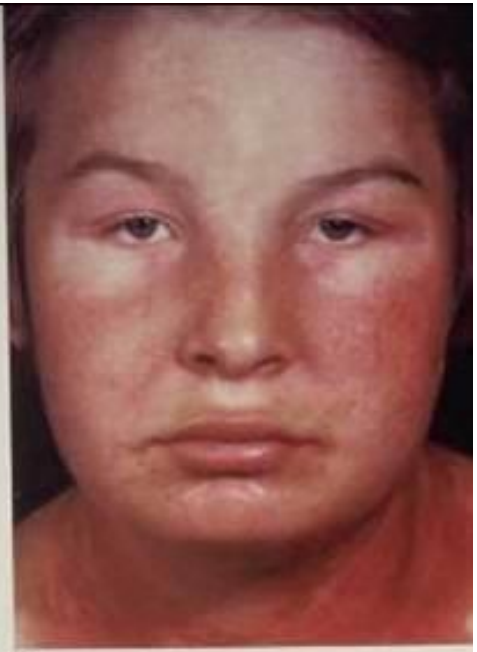
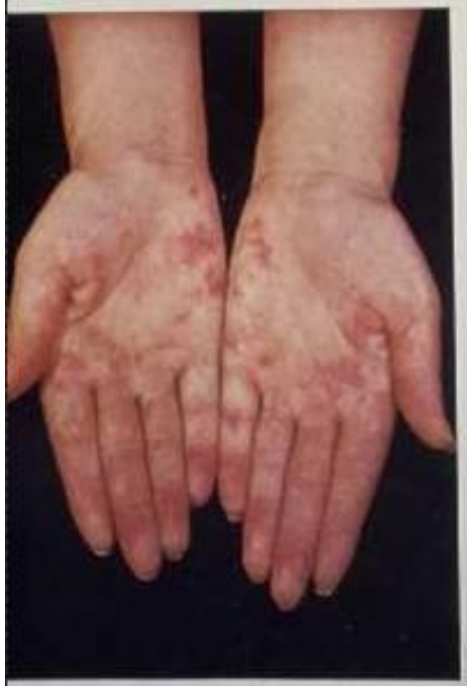


FIg. 42.8 Acute cutaneous lupus erythematosus (ACLE). Characteristic lesions in a butterfly distribution on the face of a young woman.







1
Erythème diffus rose vif à la face, lors de lupus érythémateux épidermo-viscéral.

2
Erythème maculeux, localisé à la paume des mains, lors de lupus érythémateux épidermo-viscéral.

3
Coloration violacée de la peau et congestion du visage, lors de dermatomyosite.

4
Dermatite de contact allergique aiguë.

5
Erysipèle.

6
Erythème médicamenteux photogène.

7
Lupus érythémateux discoïde chronique.

- 20 % of patients have no skin disease at any stage, only organ involvement
- Fever, arthritis, nephritis (anti-DNA ds), pleurisy, pneumonitis, pericarditis, myocarditis, involvement of the CNS.
- Renal involvement suggests a poorer prognosis

CRITERIA FOR THE DIAGNOSIS OD SLE

Malar rash
Discoid plaque
Photosensitivity
Mouth ulcers
Arthritis
Serositis
Renal disorders
Neurological disorders
Hematological disorders
Imunological disorders
Antinuclear antibodies

THE AMERICAN COLLEGE OF RHEUMATOLOGY 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS*	
Criterion	**Definition**
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	a) **Pleuritis** – convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion *OR* b) **Pericarditis** – documented by ECG, rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent **proteinuria** greater than 0.5 g/day or greater than 3+ if quantitation not performed *OR* b) **Cellular casts** – may be red cell, hemoglobin, granular, tubular or mixed
8. Neurologic disorder	a) **Seizures** – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance *OR* b) **Psychosis** – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance
9. Hematologic disorder	a) **Hemolytic anemia** with reticulocytosis *OR* b) **Leukopenia** – less than 4000/mm^3 total WBC on two or more occasions *OR* c) **Lymphopenia** – less than 1500/mm^3 on two or more occasions *OR* d) **Thrombocytopenia** – less than 100 000/mm^3
10. Immunologic disorder	a) **Anti-DNA antibody to native DNA** in abnormal titer *OR* b) **Anti-Sm:** presence of antibody to Sm nuclear antigen *OR* c) Positive finding of **antiphospholipid antibodies** based on: (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; (2) a positive test result for lupus anticoagulant using a standard methods; or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test (FTA-ABS)
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome
**The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.*	

Table 42.5 The American College of Rheumatology 1982 revised criteria for classification of systemic lupus erythematosus[72]. ECG, electrocardiogram; Sm, Smith, WBC, white blood cell.

INVESTIGATIONS

Physical investigation

biopsy of skin lesions

direct immunofluorescence of involved and uninvolved skin (C1q, IgG, IgM, C3 –” lupus band test” at the dermo-epidermal junction)

laboratory tests

specific antibodies (ADNA , ANF, anti Ro, antiLa, SM, LCA)

diagnostic procedures for internal disease (heart, kidney, lung)

- PATHOLOGY often non specific, edema of the upper dermis, lymphohistiocytic infiltrate, fibrinoid deposits in connective tissue, vacuolar degeneration of keratinocytes

TREATMENT

Systemic steroids

Immunosupressive agents : azathioprine, cyclophosphamide

Antimalarial drugs

Sunscreens

Gama globulin iv

Subacute cutaneous lupus erythematosus

Less severe than acute SLE. Half of patients have systemic disease

In some cases SCLE is due to some medications : hydrochlorotiazide , non steroid antiinfl. , terbinafine

Association with anti Ro autoantibodies

CLINICAL FEATURES

Photosensitivity, annular skin lesions, psoriasiform plaque, simetrical . Healing without scarring.

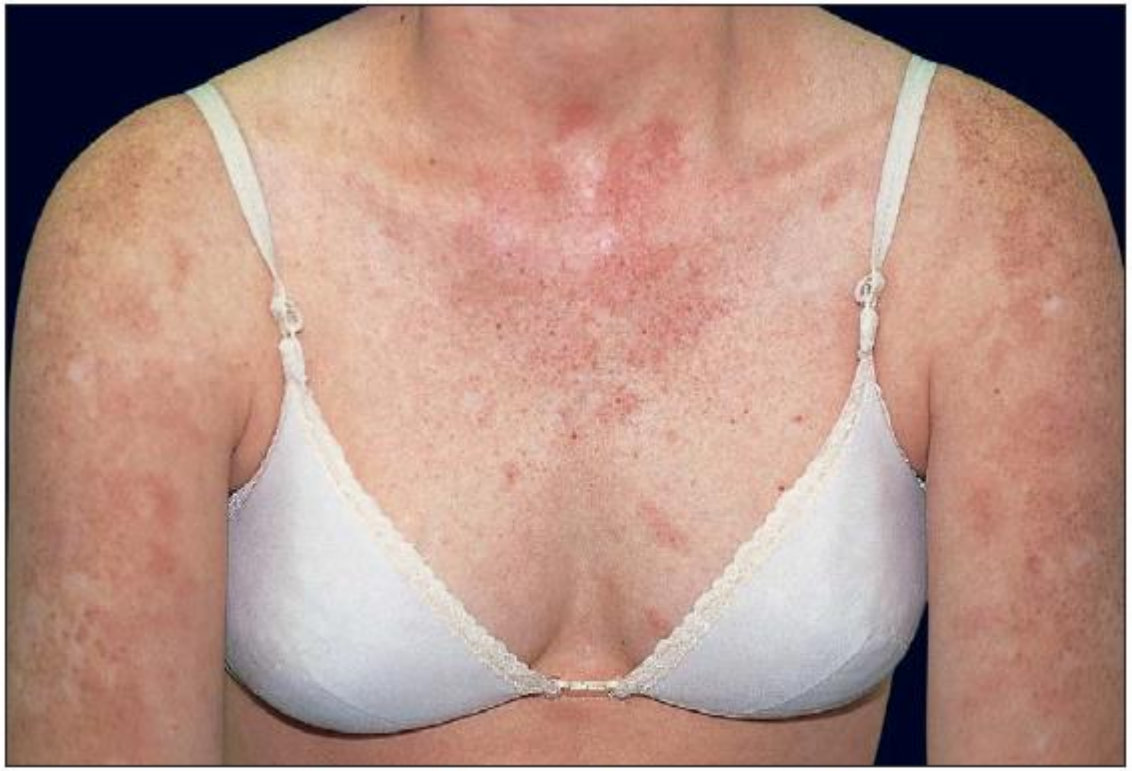


Fig. 42.5 Subacute cutaneous lupus erythematosus (SCLE). There are non-scarring, erythematous, slightly scaly plaques on the upper trunk (V-shaped pattern) and sun-exposed sites of the arms.

Fig. 42.6 Subacute cutaneous lupus erythematosus (SCLE). The lesions on the hands conform to the typical distribution of lupus lesions, sparing the knuckles.

- Systemic disease is not serious
- Anti Ro antibody can cross placenta, children have neonatal LE (transient skin lesions and permanent heart block)

THERAPY

Antimalarials (hydroxychloroquine)

Systemic steroid

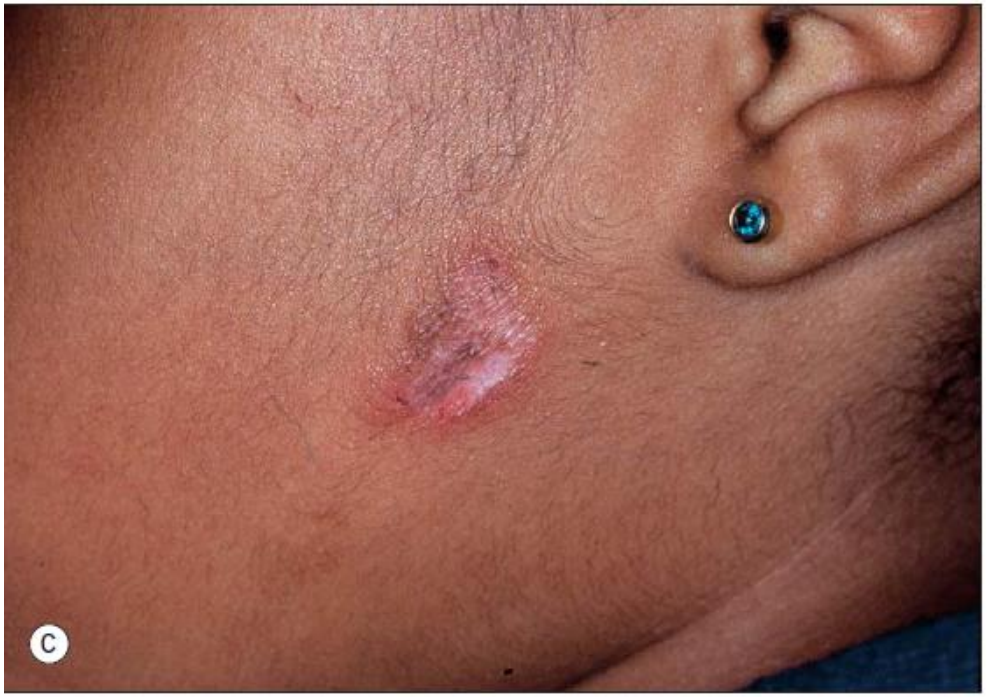
Local steroid therapy

DISCOID LUPUS ERYTHEMATOSUS

- Most common, the most important cause is UVR
- May rarely progress in SLE
- Discoid lesions are most often on sun-exposed skin area
- DLE disseminatus (chest, back or scalp)

CLINICAL FEATURES plaque with erythema, scaling, follicular plugging, atrophy and scaring

- INVESTIGATIONS: 1. skin biopsy
  2. DIF
  3. blood tests (ANA)
  4. screening for SLE and internal diseases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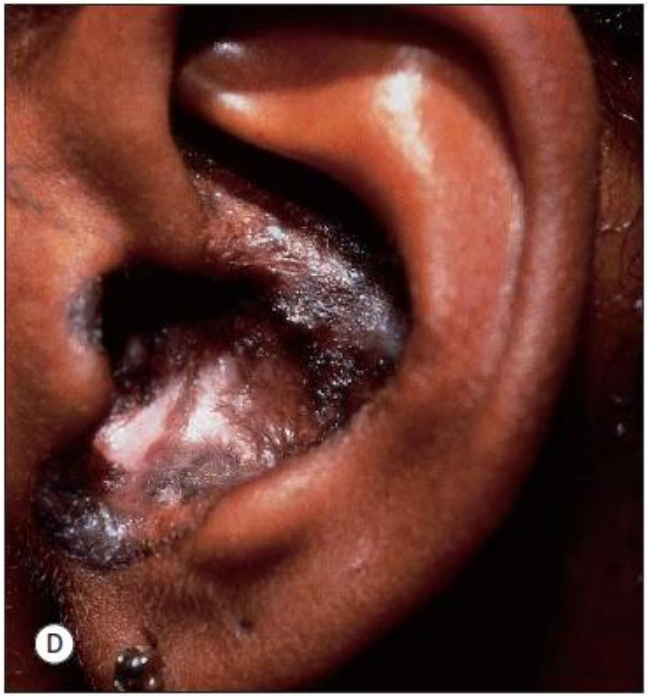
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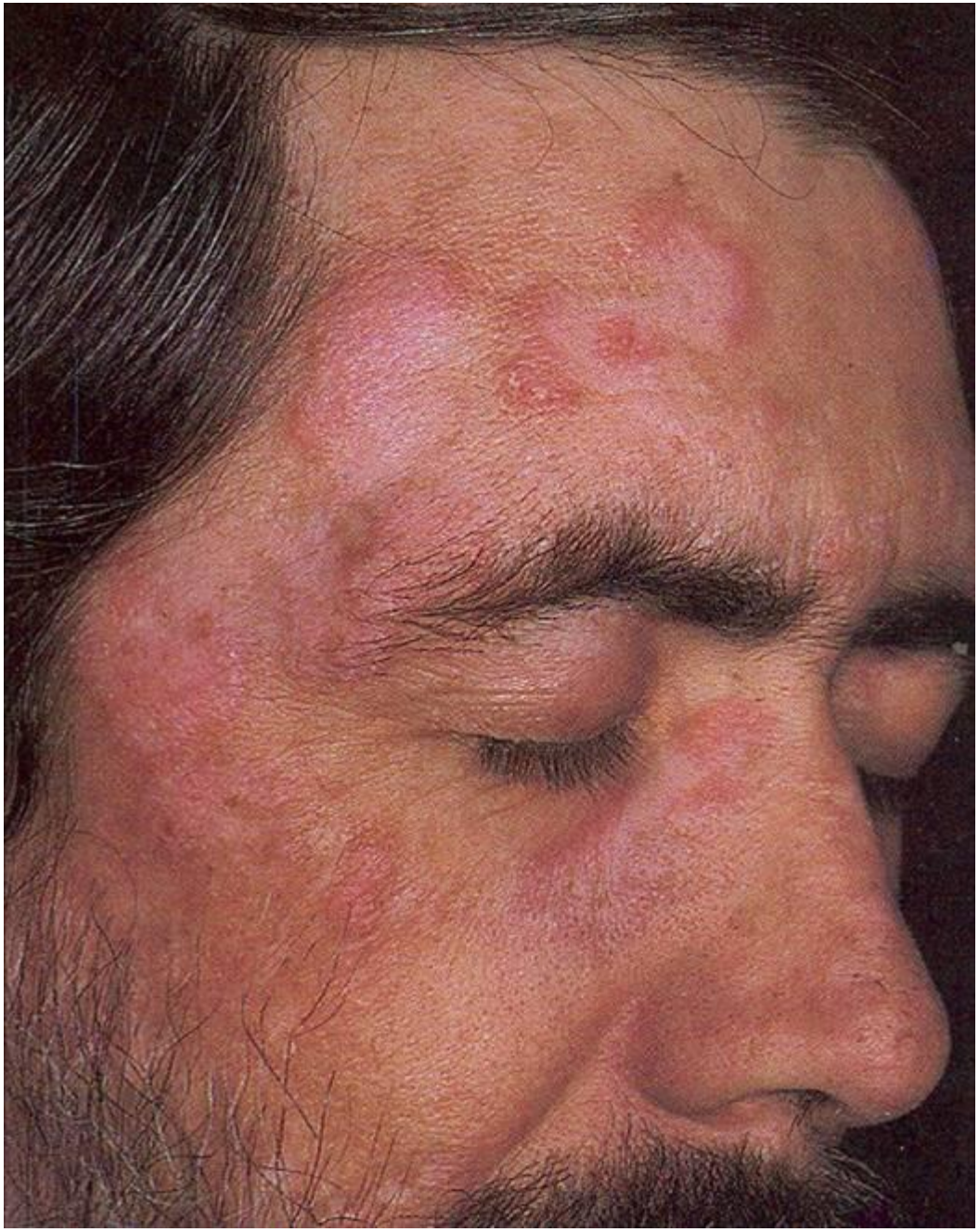

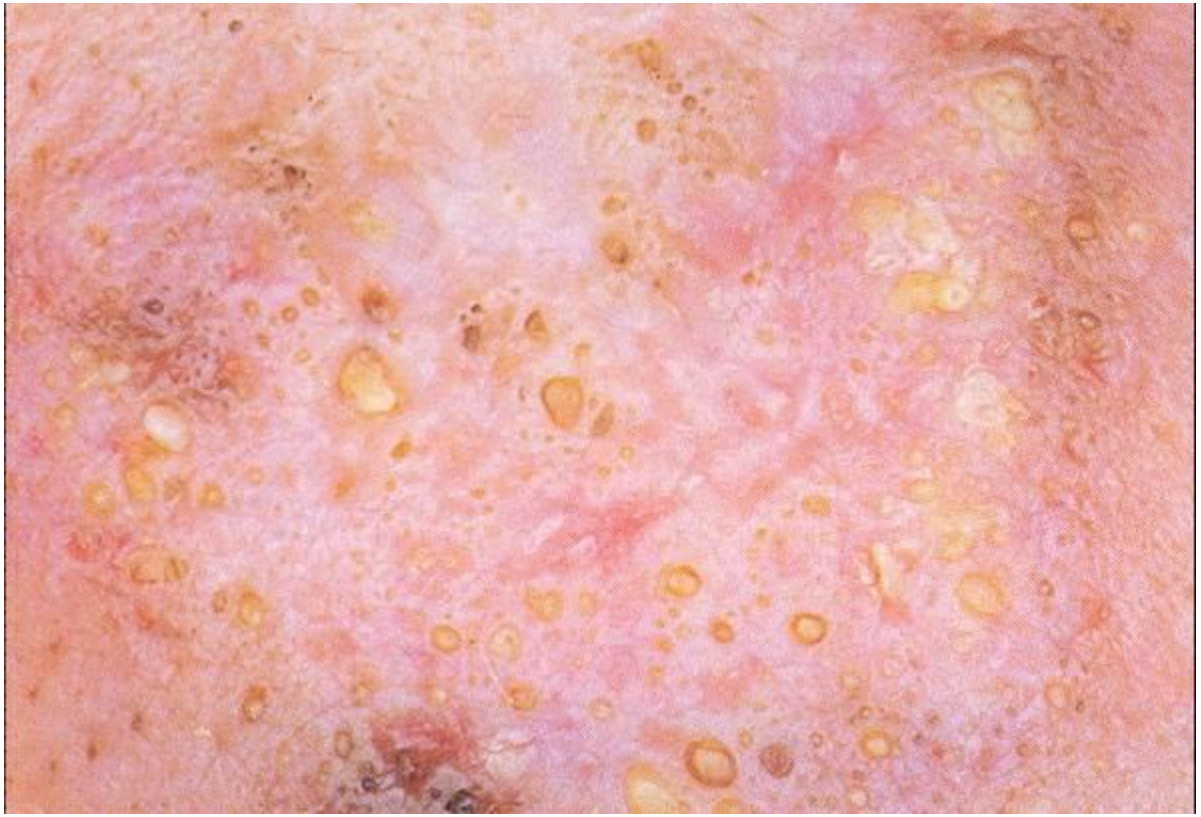

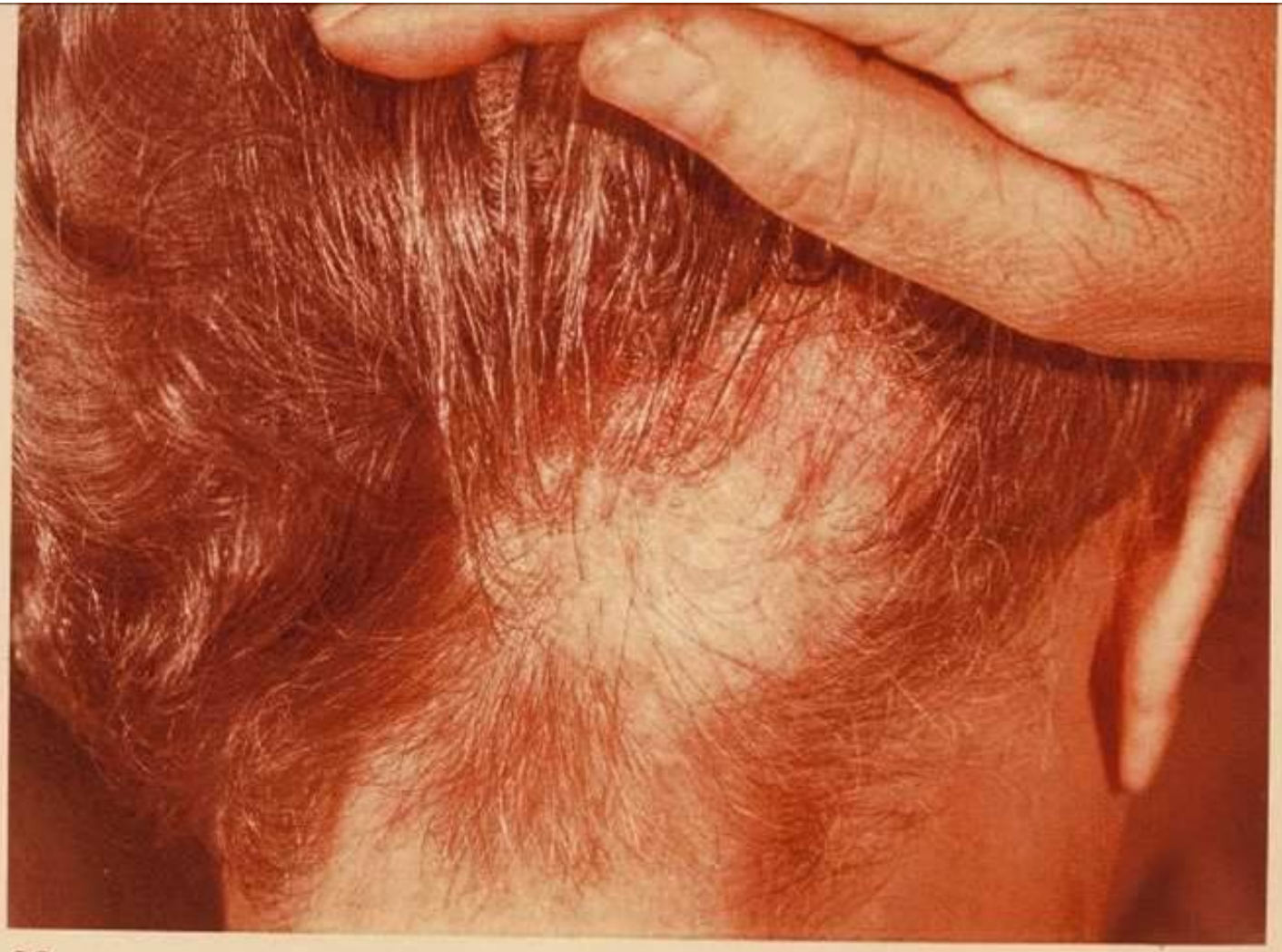

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Chronic lupus erythematosus

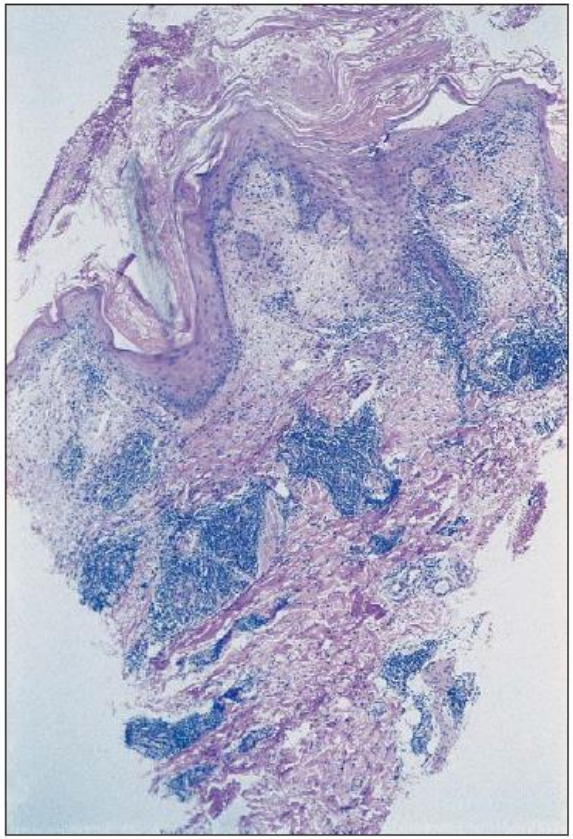


Fig. 42.17 Histology of discoid lesions of lupus erythematosus. In contrast to subacute cutaneous lupus erythematosus, a more intense inflammatory infiltrate, prominent both in the superficial and deep dermis and surrounding adnexal structures, is seen in discoid lesions; marked hyperkeratosis with follicular plugging is also present.

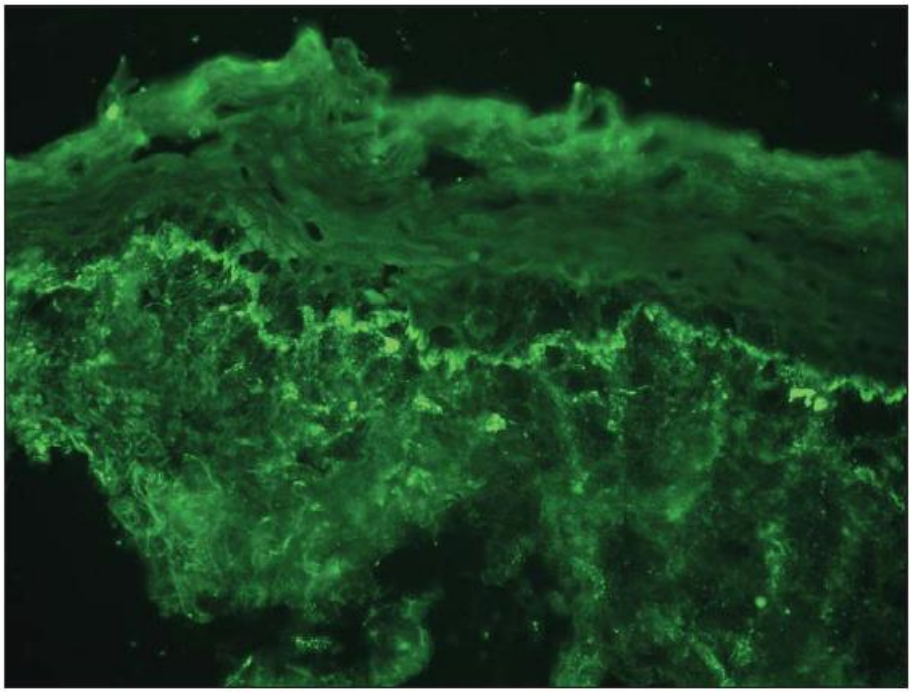


Fig. 42.18 Direct Immunofluorescence of cutaneous lupus. Granular deposits of IgM are present at the dermal–epidermal junction within lesional skin. Antibody deposits at the dermal–epidermal junction are the most characteristic immunohistologic finding in lesions of cutaneous lupus and normal skin of patients with systemic lupus erythematosus. Courtesy of Janet Fairley MD.

OTHER TYPES OF DLE :

TUMID LE (induration and erythema, no scar)
Similar to Jessner's lymphocytic infiltat

LUPUS PANNICULITIS (intense inflammation in the fat leads to induration plaque)

LUPUS PERNIO

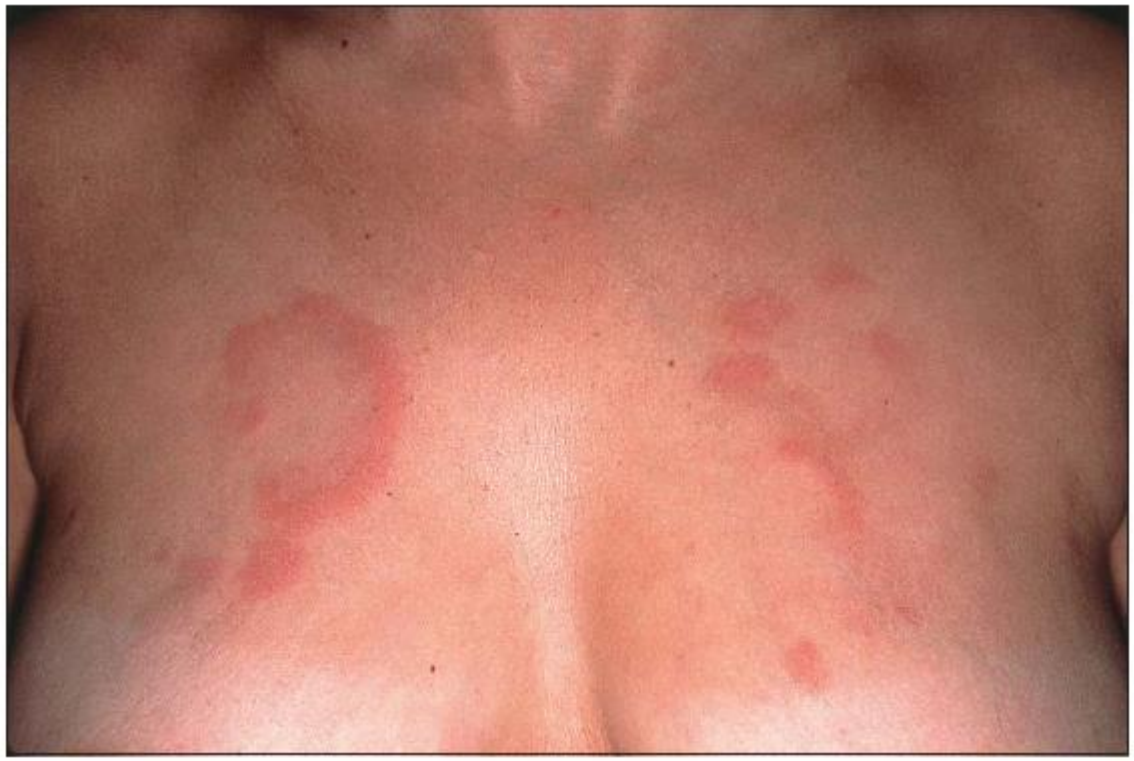


Fig. 42.11 Lupus erythematosus tumidus. Annular plaques on the chest with no epidermal change.

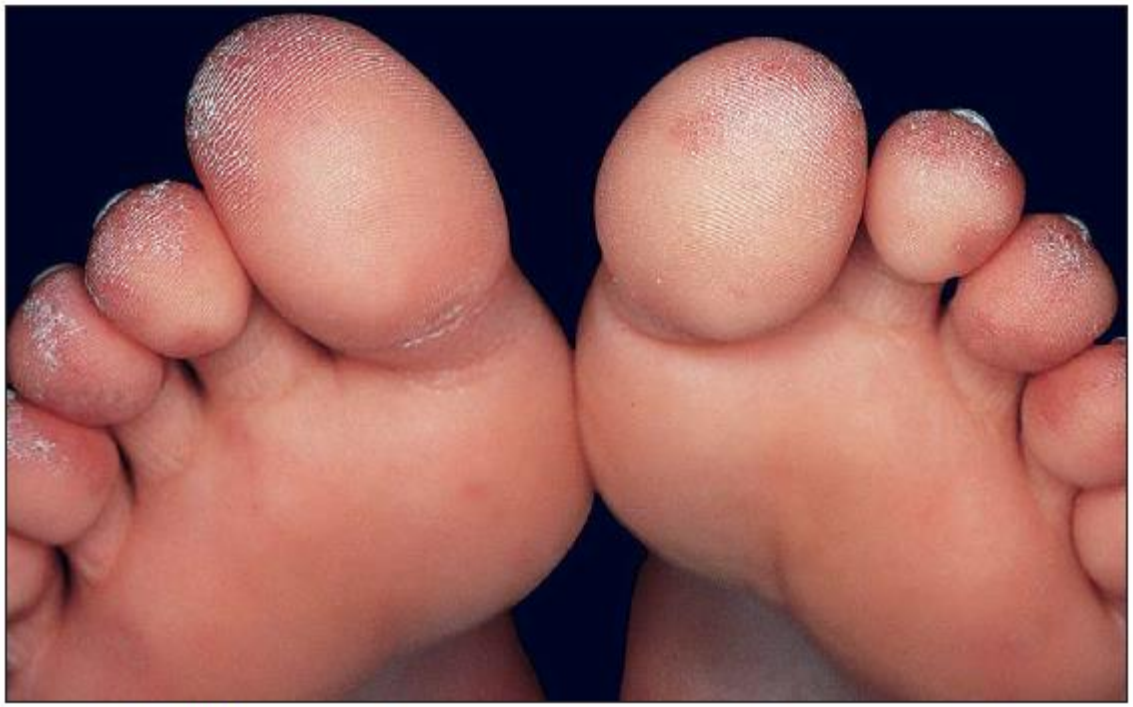


Fig. 42.13 Chilblain lupus (SLE pernio). Violaceous plaques, some with scale, on toes.

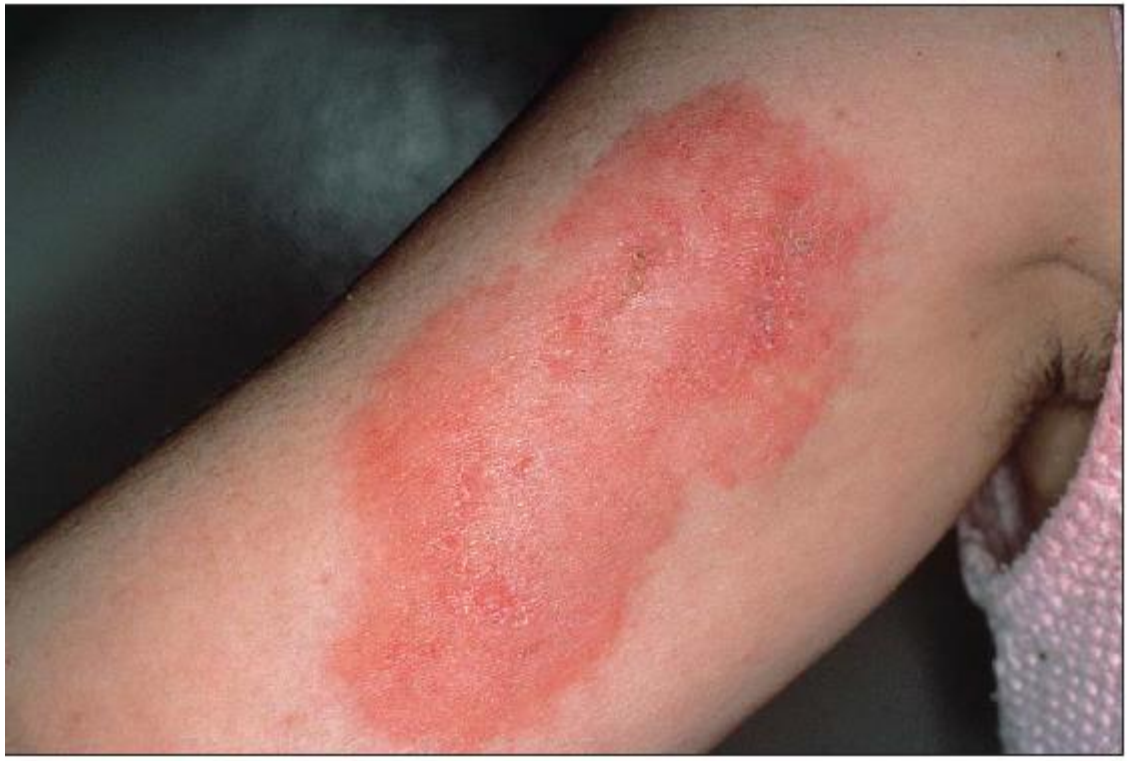


Fig. 42.12 Lupus panniculitis. Erythematous plaque on the upper arm. The lesions may resolve with lipoatrophy.

- TREATMENT
- Systemic antimalarials ; steroids
- localy with steroid cream
- Photoprotective cream, dressing

THERAPY OF CUTANEOUS LUPUS
Local therapy
Sun protection (2) Topical and intralesional corticosteroids (2) Topical calcineurin inhibitors (2) Topical retinoids (3)
Systemic antimalarial therapy*
Hydroxychloroquine (200 mg po qd–bid in adults; up to 6.5 mg/kg ideal body weight/day) (2) Chloroquine (125–250 po qd in adults; up to 3.5–4 mg/kg ideal body weight/day) (2) Quinacrine (100 mg po qd) (2) Combination of hydroxychloroquine or chloroquine and quinacrine (2)
Systemic therapy for antimalarial-resistant cutaneous disease
Retinoids (e.g. acetretin, isotretinoin) (2) Thalidomide (50–100 mg po qd for clearing and, if necessary, 25–50 mg po qd–twice weekly for maintenance) (2) Gold (2) Dapsone (primarily for bullous eruption of SLE) (2) Clofazimine (3) Sulfasalazine (2) Immunosuppressive agents (e.g., azathioprine) (2) Systemic corticosteroids (3) Immune response modifiers (e.g., rituximab, anti-BlyS, CTLA4-Ig, anti-IL-6, anti-IL-10) (3)
**Encourage discontinuation of smoking.*

Table 42.6 Therapy of cutaneous lupus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. BlyS, anti-B-lymphocyte stimulator.

DERMATOMYOSITIS

- Autoimmune disease with systemic inflammatory myopathy and skin changes . It ca be with SLE, RA, Syogren disease, PSS – overlapping syndromes
- Patients have increased risk of malignancy
- Juvenile dermatomyositis have vasculitis and calcinosis

- Disease of autoimmune pathogenesis with symetric inflammatory proximal myopathy and cutaneous eruption
- When started after the age of 40 years may signed an internal malignancy
- Pulmonary disease occurs in 15-30%, cardiac disease, renal disease, GI disease

CLINICAL FEATURES OF 54 PATIENTS IN A DERMATOLOGY-BASED CASE SERIES		
	Adult dermatomyositis	Juvenile dermatomyositis
Number	43	11
Mean age (years)	51.7	7.6
Malignancy	5 (12%)	0
Overlap with other autoimmune connective tissue disease	8 (19%)	1 (10%)
Sex ratio (F:M)	6.2:1	1:1.75

Table 43.1 Clinical features of 54 patients in a dermatology-based case series[1].

PATHOGENESIS : immune mediated process triggered by outside factors (infections, drugs) or malignancy in gennetically predisposed individuals.

Cellular immunity/apoptosis[18–24]

- 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[25]

- 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 – Jo-1 (lung disease); antitranslation – KJ (polymyositis/Raynaud's); and anti-Mi-2 (most specific for dermatomyositis)

Infectious precipitants[26,27]

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

Drug precipitants[28–32]

- D-penicillamine, hydroxyurea, non-steroidal anti-inflammatory drugs, lipid-lowering drugs (statins specifically), phenytoin, lenercept (55 kDa TNF receptor, never FDA approved), alfuzosin (α-agonist for BPH)

Malignancy association (adults)[33,34]

- SKIN SIGNS: lilac discoloration around eyes (heliotrope erythema) of the neck and presternal area; atrophic lilac papule over the knuckles (Gottron s papules), periungual telangiectasiae

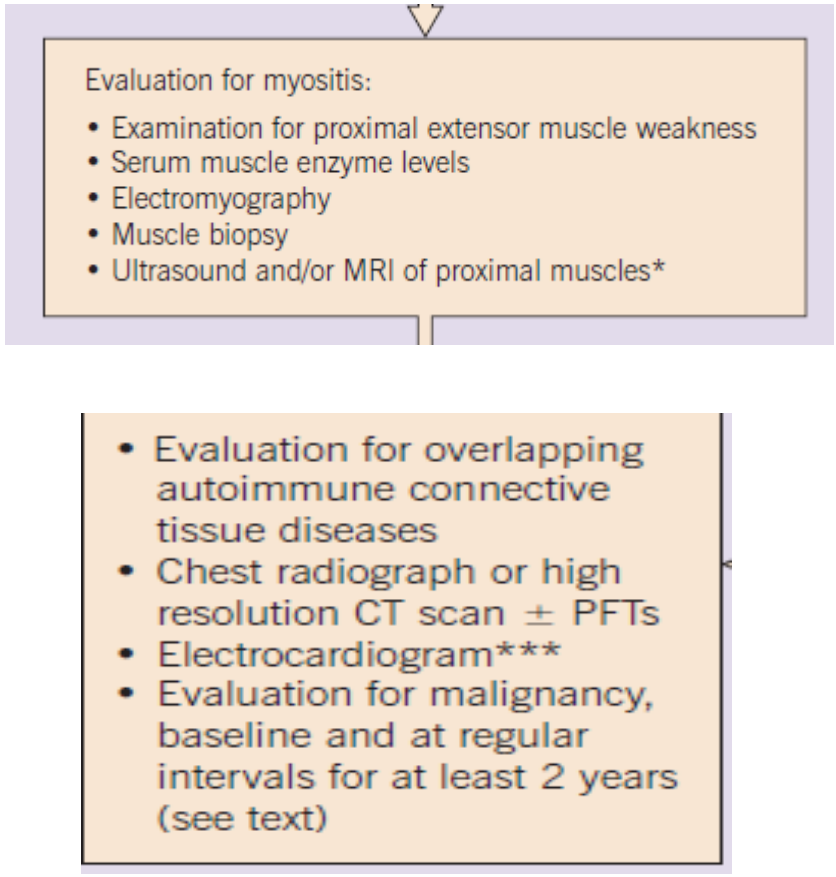
- Weakness of proximal muscles and immobility, patients are often unable to combing the hair, climbing stairs, getting up from chairs

DIFFERENTIAL DIAGNOSIS:

- MCTD, SLE, toxoplasmosis

INVESTIGATIONS:

- muscle enzymes are elevated (aldolase, CPK)
- electromyography (EMG)
- Serum autoantibodies (antinuclear antibodies, JO1, Mi2, nRNP)
- Biopsy of an affected muscle show inflammation and distruction


Evaluation for myositis:
• Examination for proximal extensor muscle weakness
• Serum muscle enzyme levels
• Electromyography
• Muscle biopsy
• Ultrasound and/or MRI of proximal muscles*
• Evaluation for overlapping autoimmune connective tissue diseases
• Chest radiograph or high resolution CT scan ± PFTs
• Electrocardiogram***
• Evaluation for malignancy, baseline and at regular intervals for at least 2 years (see text)

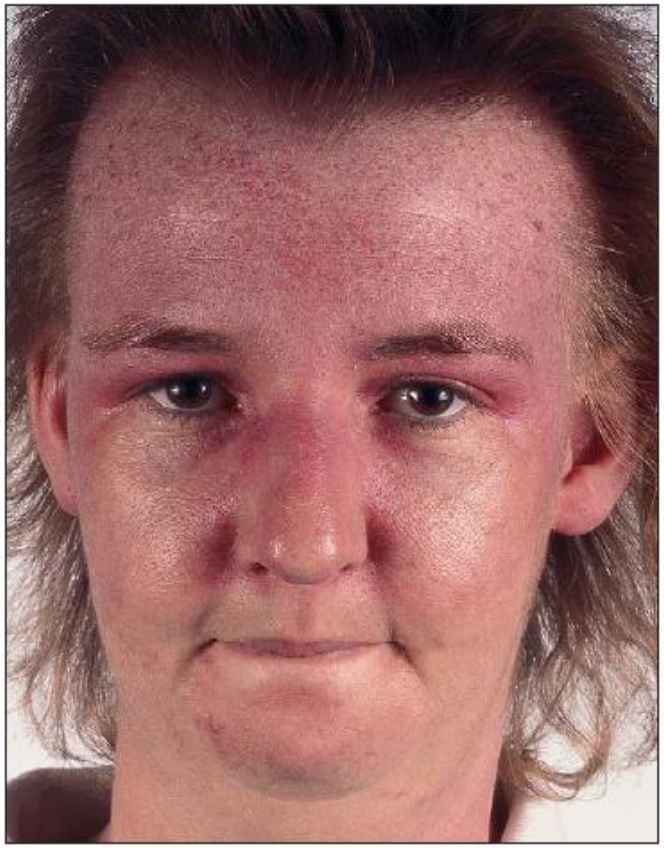


Fig. 43.1 Violaceo
poikiloderma of t
face.

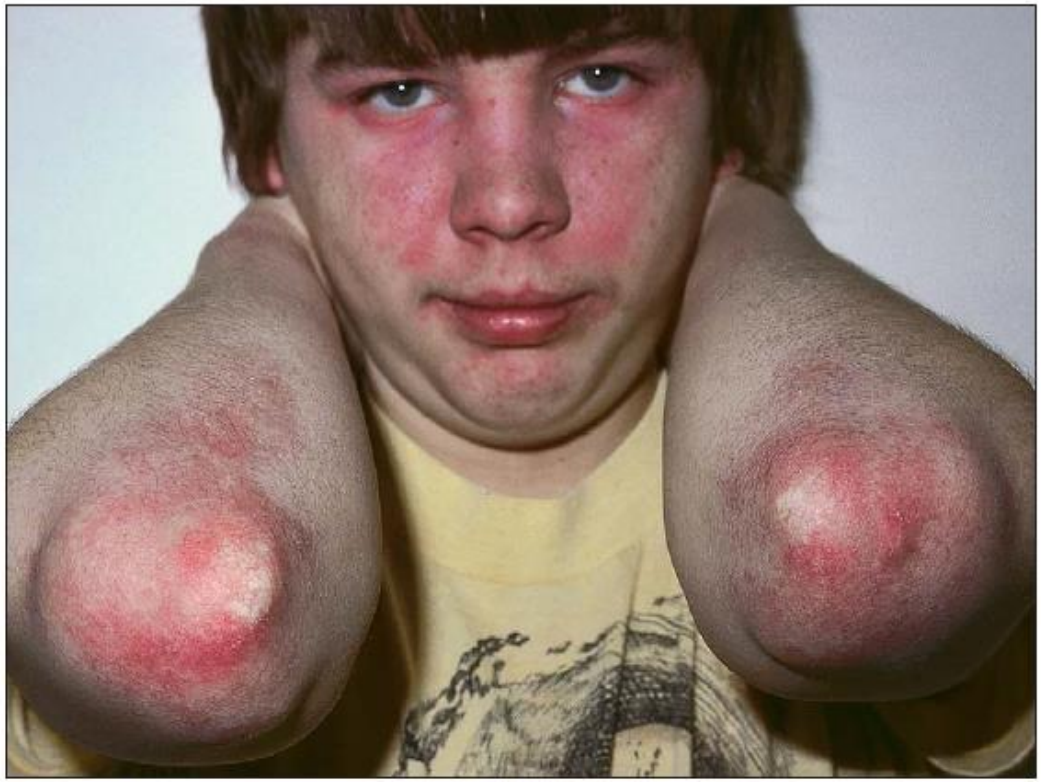


Fig. 43.2 Violaceous poikiloderma of the face, plus thin plaques on the elbows that are sometimes misdiagnosed as psoriasis.

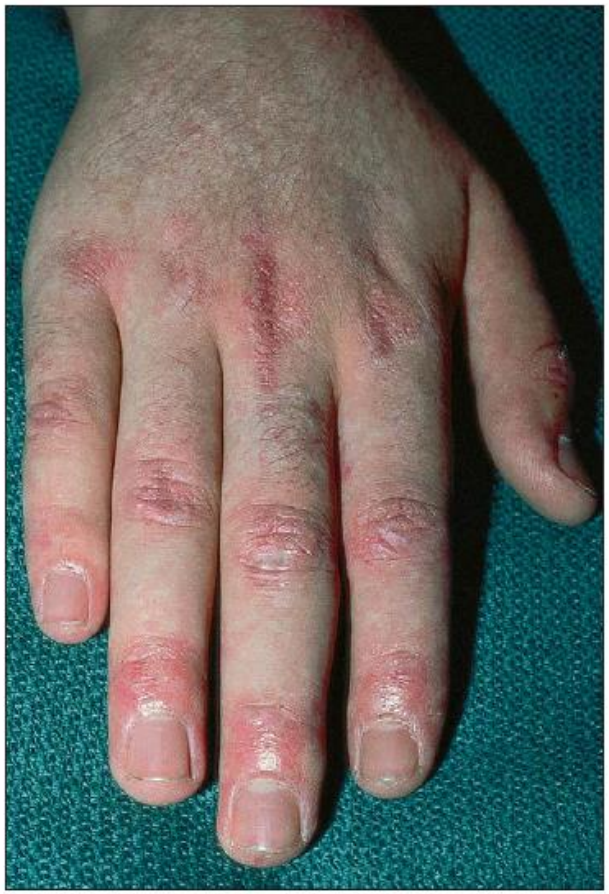


Fig. 43.4 Gottron's sign with violaceous poikiloderma over the knuckles.

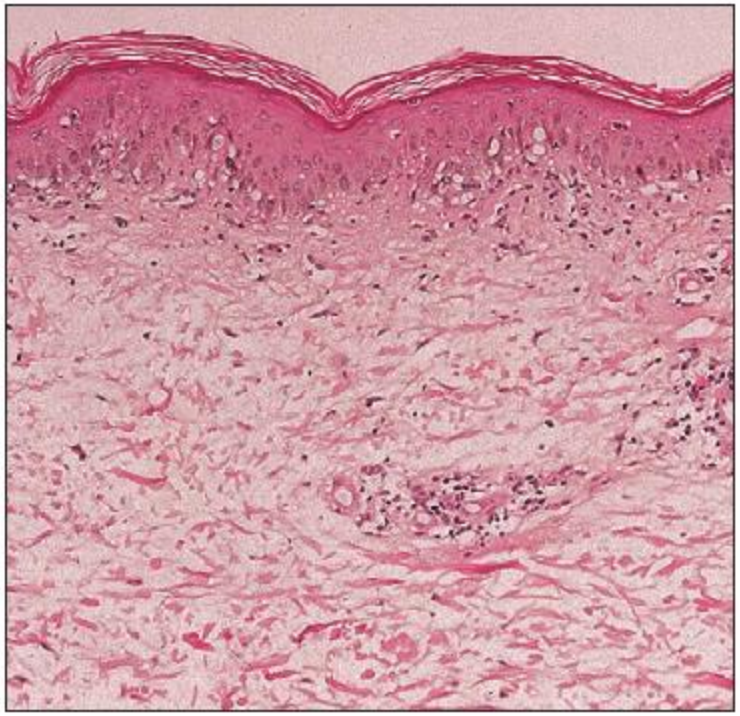


Fig. 43.8
Dermatomyositis. The interface dermatitis can be subtle.

TREATMENT:

- Systemic steroids (60mg)
- Immunosupressive agents (azathioprine, methotrexat) help to reduce high steroide dose

THERAPEUTIC LADDER FOR DERMATOMYOSITIS	
Systemic therapy	
Oral prednisone:	1 mg/kg 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:	15 mg/m^2 weekly (2)
Azathioprine:	2–3 mg/kg/day (3)
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) Cyclosporine (3–5 mg/kg/day) (2) Tacrolimus (0.12 mg/kg/day) (3) Mycophenolate mofetil (1 g bid) (2) Sirolimus (5 mg/day × 2 weeks, 2 mg/day × 2 weeks, then 1 mg/day) (3) Infliximab (5–10 mg/kg q 2 weeks initially) (3) Rituximab (375 mg/m^2/infusion for 4 weekly infusions) (2) Plasmapheresis (3)*
Cutaneous lesions	
Sunscreens (high solar protection factor including protection against UVA) (3) Topical corticosteroids (3) Hydroxychloroquine (200 mg bid; increased frequency of drug eruptions in patients with dermatomyositis) (2) Hydroxychloroquine (200 mg bid) plus quinacrine (100 mg/day) (3) Low-dose weekly methotrexate (5–15 mg weekly) (2) Retinoids (3) Topical tacrolimus (3)	
Others:	Mycophenolate mofetil (3) Dapsone (3) Thalidomide (3)

Table 43.7 Therapeutic ladder for dermatomyositis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. *Double-blind trial showed no benefit.

SCLERODERMA

- Scleroderma is excessive fibrosis in the skin

Systemic:

- Systemic sclerosis
- Limited scleroderma
- GvHD
- Diabetic sclerodactily
- Chronic vibration exposure
- Chemicals (polivinylchloride monomers)

Localized:

- Lichen sclerosus
- Morphoea
- Morphoea profunda
- Fascitis with eosinophilia
- Linear morphoea
- En coup de sabre

- SS is an autoimmune connective tissue disease , affects predominantly women
- Symetric induration of the skin of distal areas (hands, face)
- Started with Raynaud phenomenon

PATHOGENESIS:

- unknown
- A vascular phase often precedes the sclerosis. Hypoxix leads to fibroblast activation and excessive synthesis of stimulatory cytokines (PDGF, TGF- beta1)
- Excessive accumulation of colagen is the result of increase synthesis (TGF- beta1, CTGF)

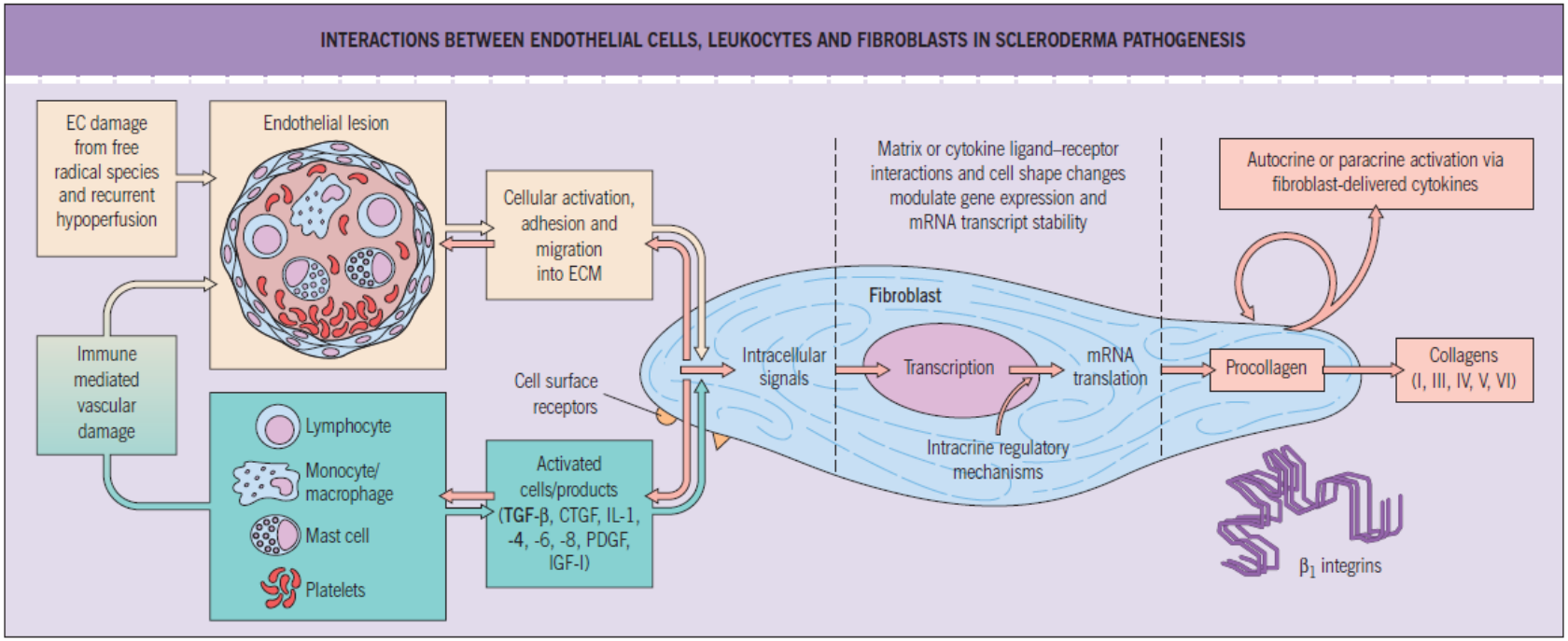


Fig. 44.1 Interactions between endothelial cells, leukocytes and fibroblasts in scleroderma pathogenesis. CTGF, connective tissue growth factor; EC, endothelial cell; ECM, extracellular matrix; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor. Adapted from Hochberg MC, Silman AJ, Smolen JS, et al (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003.

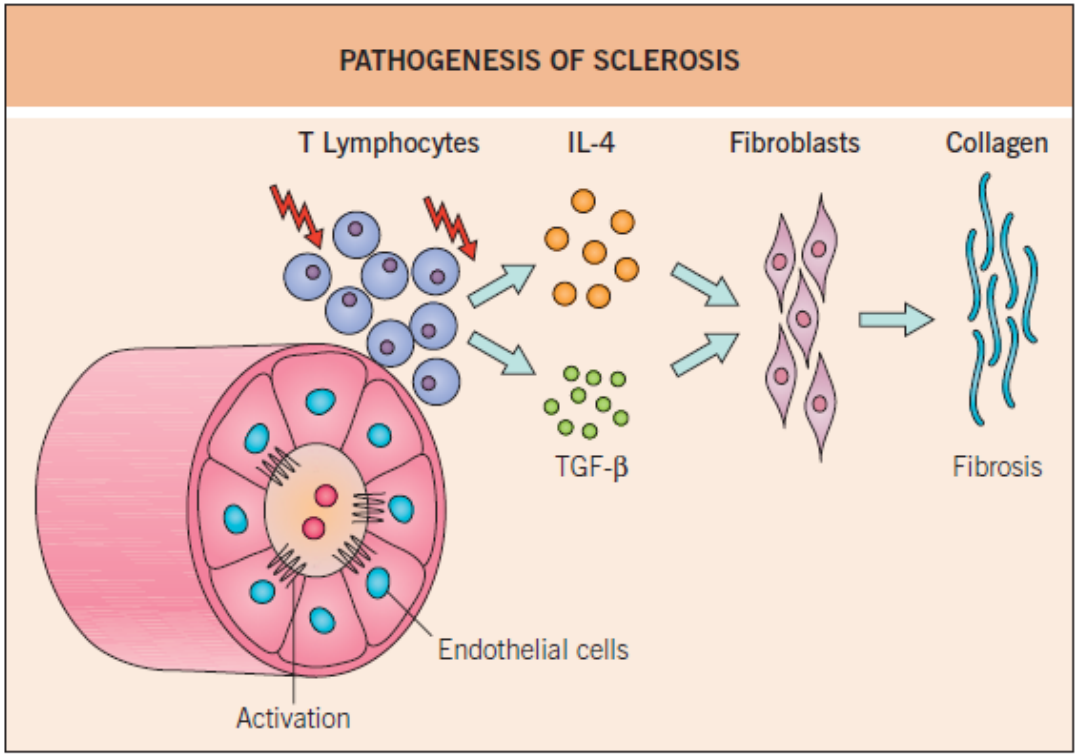


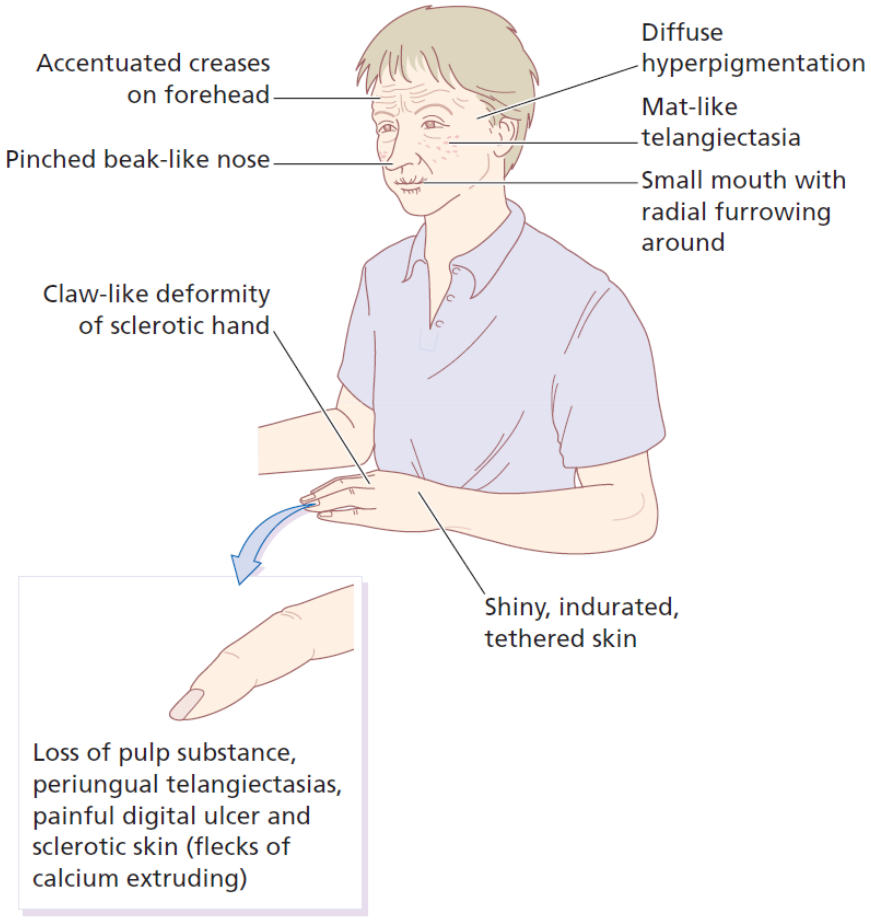
Fig. 96.1 Pathogenesis of sclerosis. Three components are involved during the formation of sclerosis: vascular damage, lymphocyte activation and altered connective tissue production. IL, interleukin; TGF, transforming growth factor.

- An immunological abnormalities are involved in the pathogenesis (autoantibodies)

CLINICAL FEATURES:

- Raynaud s phenomenon
- Hands oedema
- Sclerodactily
- Facial induration
- Esophageal symptoms
- Truncal skin induration- diffuse disease (worse prognosis)

- Teleangiectasiae on face, hands
- Capillary abnormalities in the proximal nail fold
- Calcinosis cutis (CREST syndrome)
- Microstomia (radial furrowing aroun the mouth)
- Cutaneous ulcers
- Edematous phase precedes the development of sclerosis


Accentuated creases on forehead
Diffuse hyperpigmentation
Mat-like telangiectasia
Pinched beak-like nose
Small mouth with radial furrowing around
Claw-like deformity of sclerotic hand
Shiny, indurated, tethered skin
Loss of pulp substance, periungual telangiectasias, painful digital ulcer and sclerotic skin (flecks of calcium extruding)

COMPARISON OF CLINICAL AND LABORATORY FEATURES OF DIFFUSE AND LIMITED SYSTEMIC SCLEROSIS		
	Diffuse SSc (%)	Limited SSc (%)
Raynaud's phenomenon	90	99
Finger swelling	95	90
Tendon friction rubs	70	5
Arthralgia	98	90
Proximal weakness	80	60
Calcinosis	20	40
Mat telangiectasias*	60	90
Esophageal dysmotility	80	90
Small bowel involvement	40	60
Interstitial lung disease	70	35
Pulmonary hypertension	5	25
Cardiomyopathy	15	10
Renal crisis	20	1
Sicca syndrome	15	35
Antinuclear antibodies	90	90
Anticentromere antibody	5–30	50–90
Anti-Scl-70 antibody	20–60	10–15
Cumulative survival (5 years) (10 years)	70 50	90 70
*In addition, nailfold capillary abnormalities are observed in >90% of SSc patients.		

Table 44.2 Comparison of clinical and laboratory features of diffuse and limited systemic sclerosis (SSc). Adapted from Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003.

INTERNAL ORGAN INVOLVEMENT:

- Esophagus: dysphagia, oesophagitis
- Lungs: fibrosis leads to dyspnoea
- Heart: fibrosis to pulmonary hypertension
- kidney

AUTOANTIBODY TESTING:

- ANA is elevated
- Scl70 (antibodies to topoisomerase 1)
- Anti-centromere antibodies

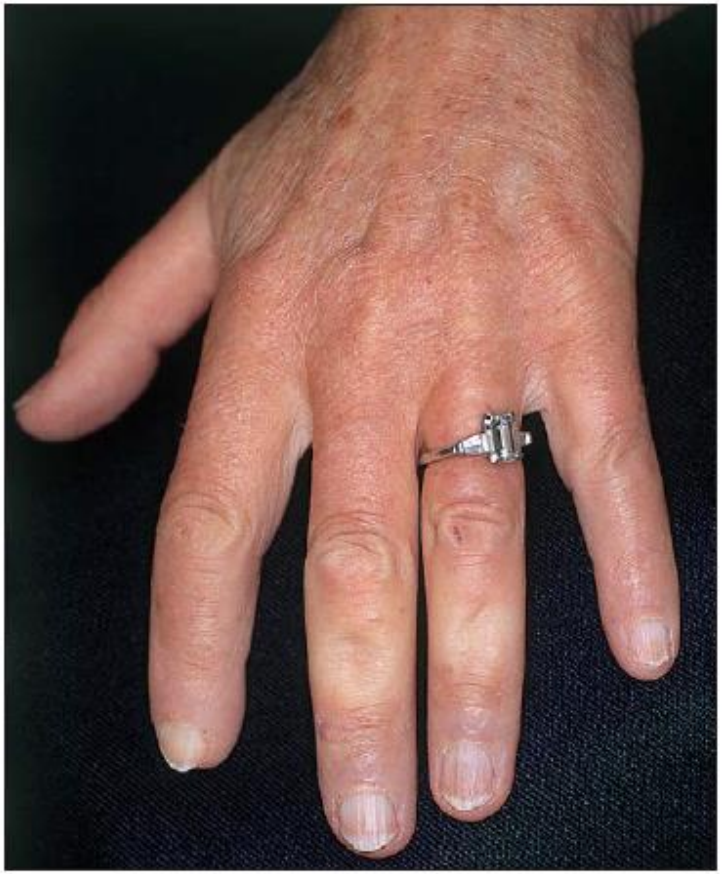
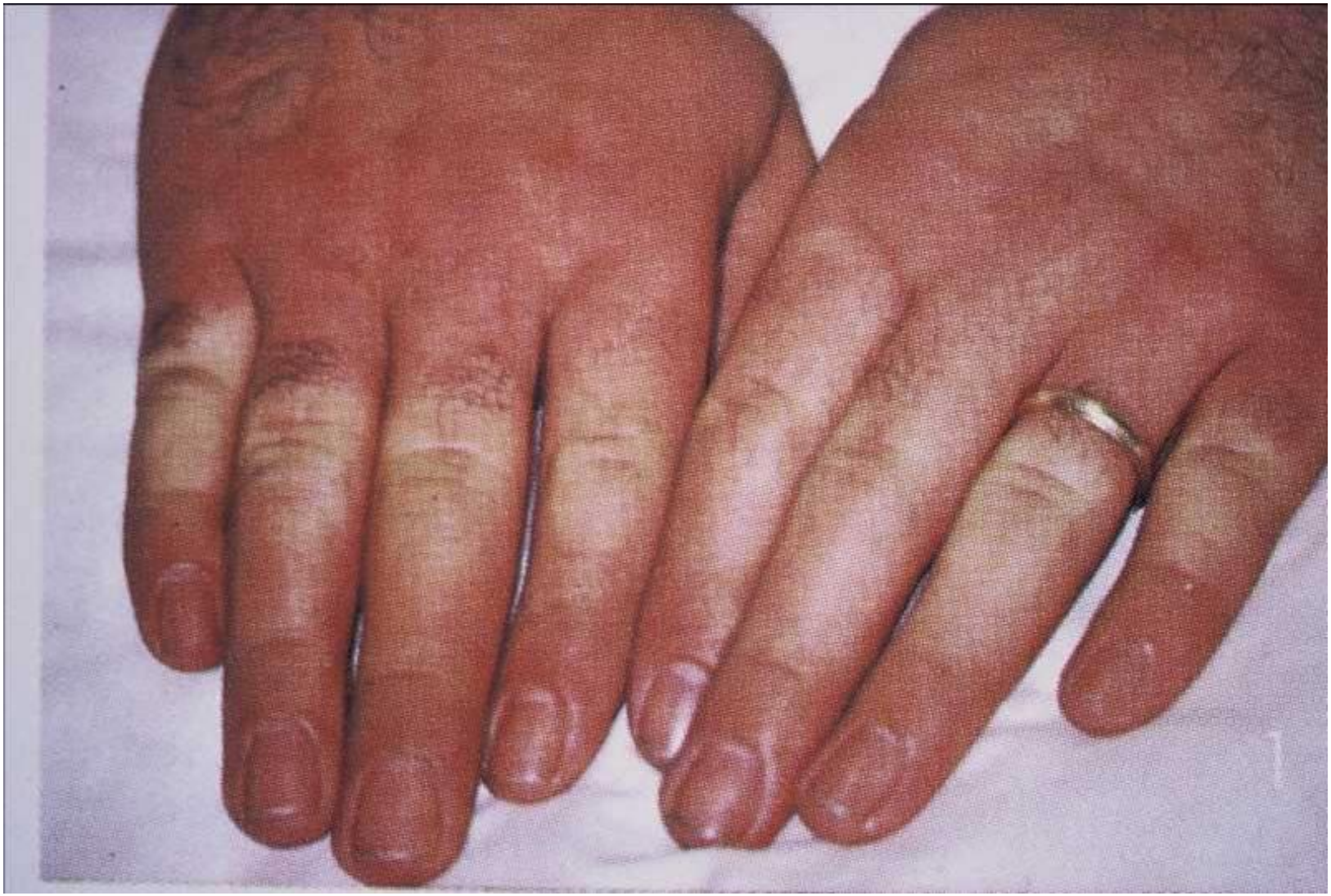
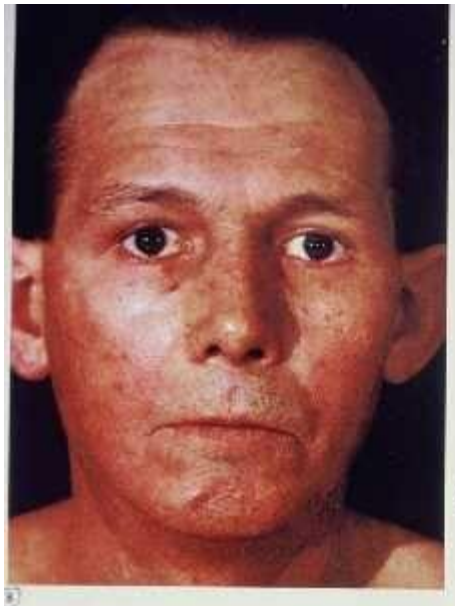
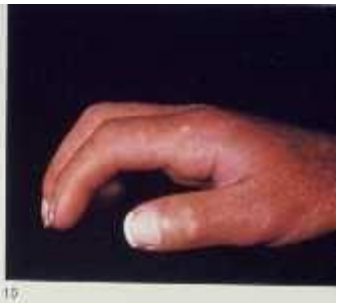


Fig. 44.3 Edematous phase of systemic sclerosis. Note the demonstration of pitting edema on two of the digits. Courtesy of Jean L Bolognia MD.

Pitted scar of the digital pulp in a patient with systemic sclerosis.



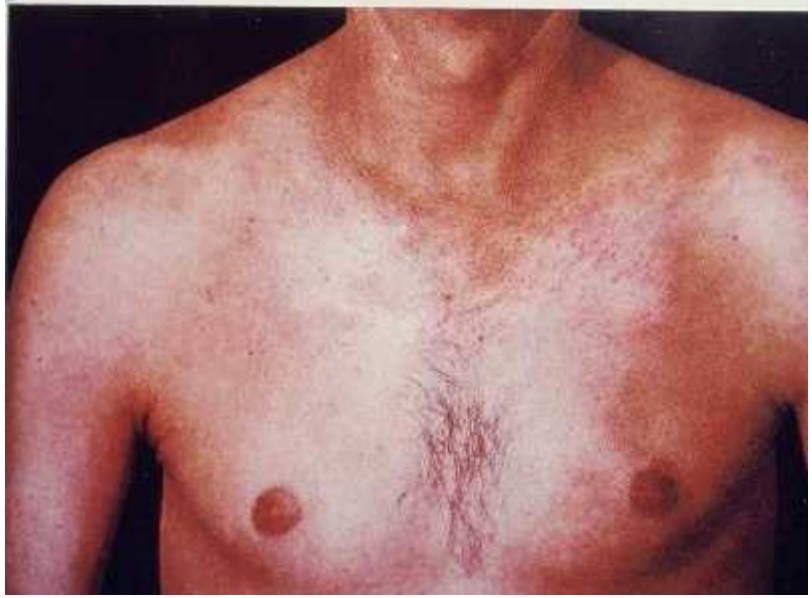




8
Aminie et microstomie lors de sclérodermie progressive.

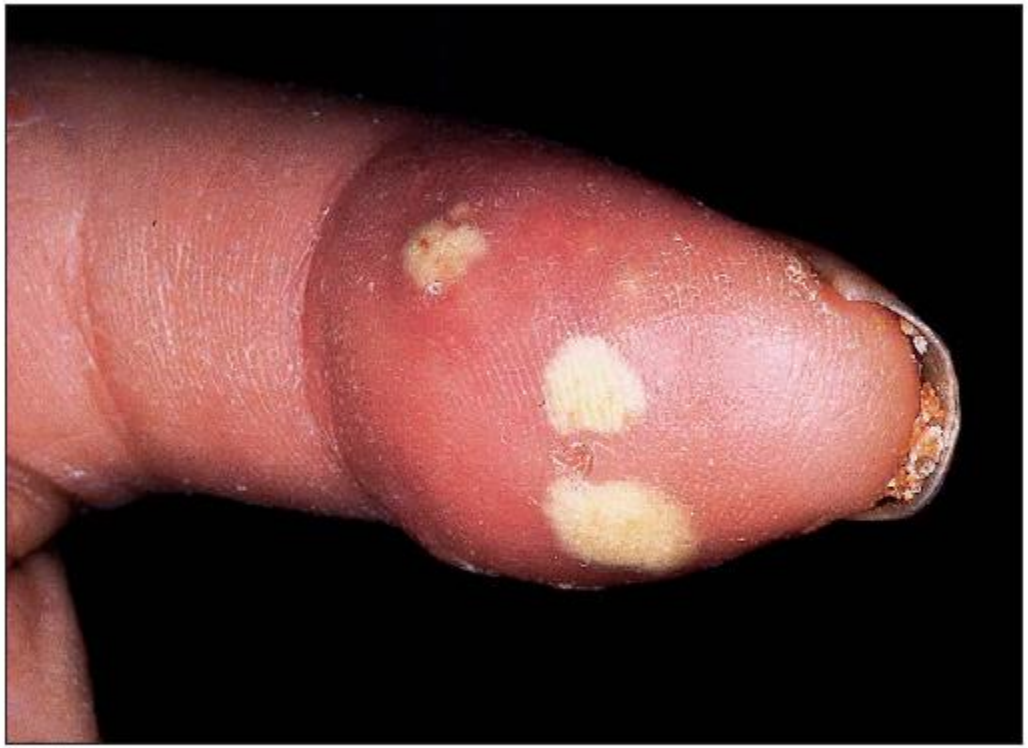
9
Diminution de l'élasticité de la peau au niveau de la cage thoracique lors de sclérodermie progressive.

10
Acrosclérose lors de sclérodermie progressive.



LIMITED SCLERODERMA

CREST Sy (pulmonary fibrosis, anticentromere antibodies)



g. 44.6 Calcinosis cutis of the finger in a patient with systemic sclerosis.

INVESTIGATIONS:

- Skin biopsy: excessive collagen deposition in the dermis and subcutaneous tissue, adnexal structures and eccrine glands are diminished, dense lymphocytic infiltrates in the early phase

EVALUATION OF INTERNAL ORGAN INVOLVEMENT IN PATIENTS WITH SCLERODERMA			
	Symptoms*	**Physical examination**	**Laboratory studies**
Pulmonary	Shortness of breath, dyspnea on exertion	Bibasilar rales	Pulmonary function tests, including diffusion capacity for carbon monoxide, and high-resolution CT scan[†] Bronchoalveolar lavage and lung biopsy[‡]
Cardiac	Palpitations	Friction rubs; increased P_2; signs of right- or left-sided congestive heart failure	Electrocardiogram and echocardiography Right-heart catheterization, if indicated
Renal	Headache, blurry vision	Hypertension	BUN, creatinine, urinalysis
Gastrointestinal	Symptoms of esophageal reflux; dysphagia; postprandial bloating; constipation; diarrhea	Abdominal distention; decrease in bowel sounds	Barium swallow and small bowel follow-through; manometry; endoscopy; if diarrhea, malabsorption work-up

** Patients may be asymptomatic.*
† At baseline and every 6–12 months for a few years.
‡ Optional, depending on results of other studies (e.g. atypical findings suggestive of another diagnosis).

Table 44.5 Evaluation of internal organ involvement in patients with systemic sclerosis. BUN, blood urea nitrogen. Courtesy of Vincent Falanga MD.

TREATMENT:

- Unsatisfactory
- Calcium channel blocker
- Salicylates
- Antimalarials
- Long term penicillin
- D penicillamin
- Photopheresis
- Phototherapy
- Methotrexate
- Cyclosporine
- Interferon alpha and gamma
- Bosentan (antagonists to endothelin receptors)

MORPHOEA

Key features

- Asymmetric sclerotic plaques, usually 2–15 cm in diameter
- Active lesions can have a lilac border, while inactive lesions often become hyperpigmented
- The sclerosus may extend deeply into the fat or underlying structures, causing disability
- There is no associated systemic disease
- Often progresses for several years, then regresses

MORPHOEA

Morphoea is characterised by indurated plaques surrounded with a violaceous halo. Fibrosis slowly clears leaving slight depression or hyperpigmentation

In pansclerotic morphoea contractures can occure

En coup de sabre type on the forehead can lead to facial hemiatrophy

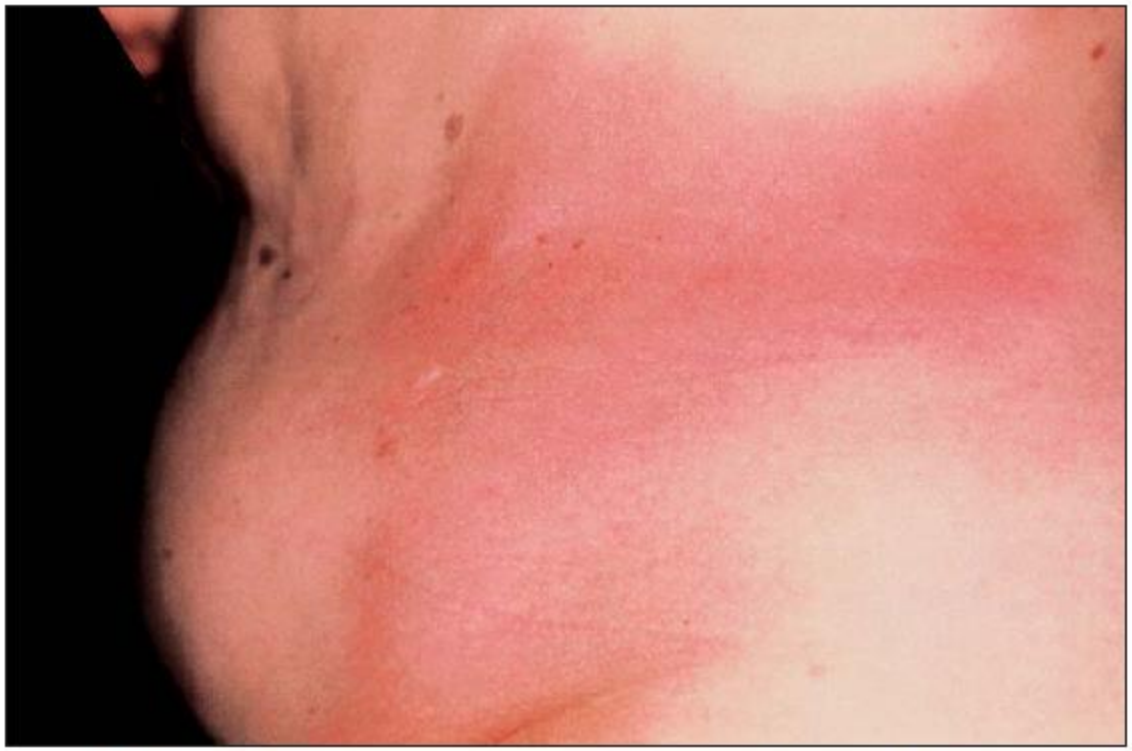


Fig. 96.3 Early inflammatory plaque-type morphea of the trunk. Early stage lesion presenting as an erythematous edematous plaque.

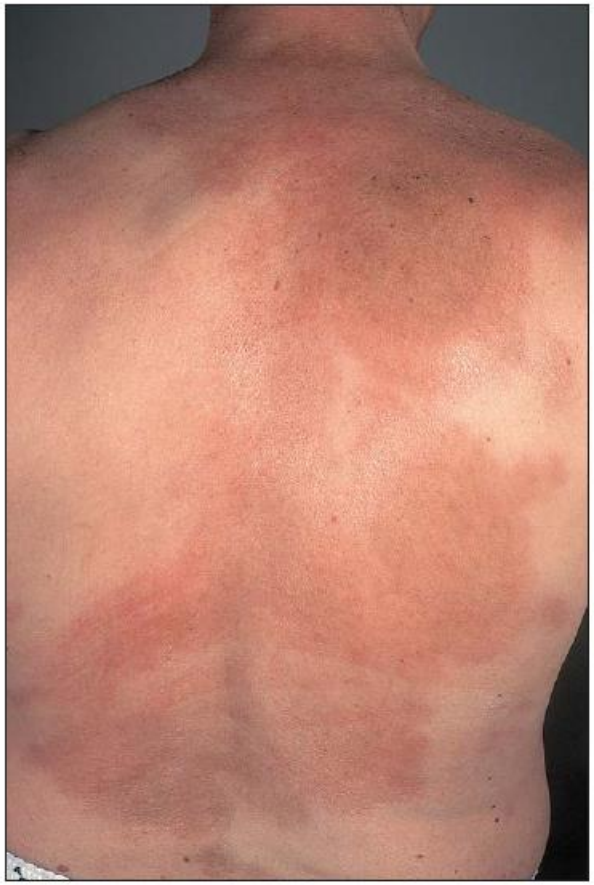


Fig. 96.4 Plaque-type morphea on the back. Multiple hyperpigmente plaques, some of which have a lilac border.

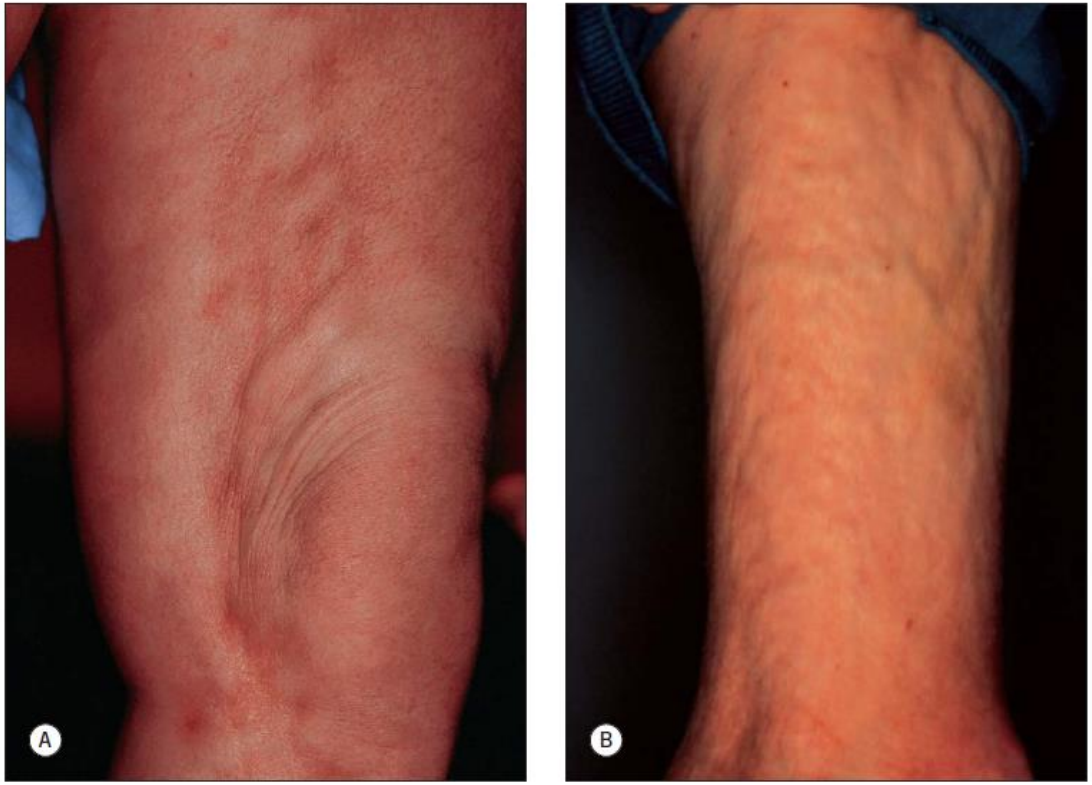


Fig. 96.5 Comparison of deep morphea and eosinophilic fasciitis. A Note the 'pseudo-cellulite' appearance of the involved skin of the thigh in deep morphea. **B** In eosinophilic fasciitis, the level of fibrosis is also deep, resulting in a similar clinical appearance.

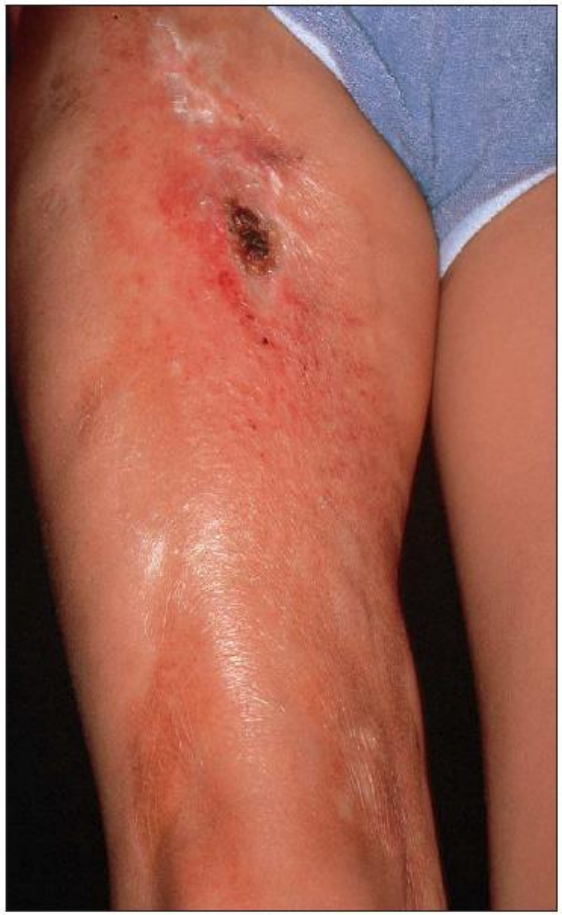


Fig. 96.8 Linear morphea of the leg. The differential diagnosis includes linear melorheostosis which is associated with underlying candlewax-like linear hyperostosis.

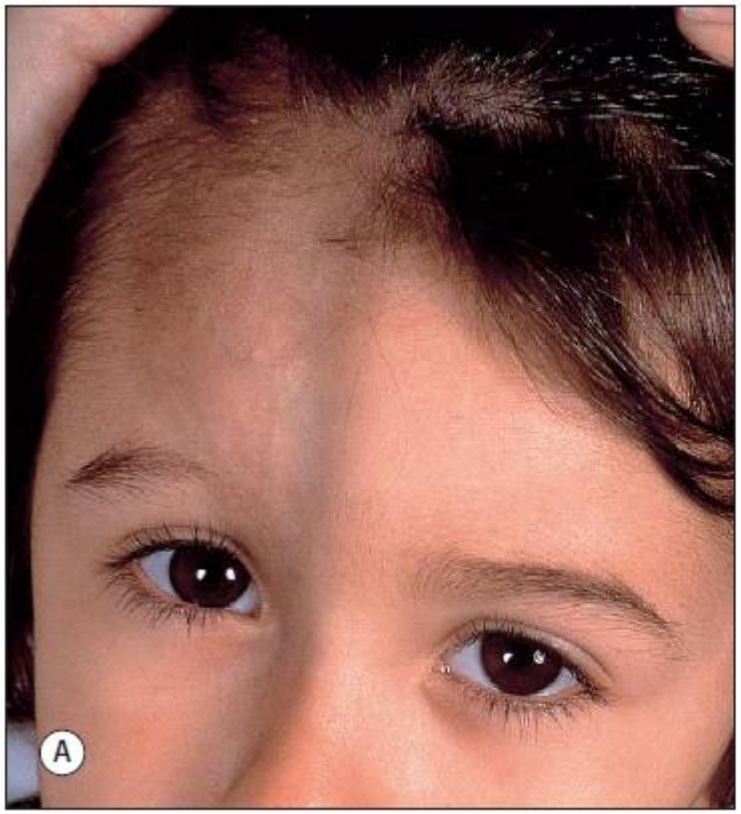


Fig. 96.9 Morphea en coup de sabre. Paramedian depressions (A) are more common than midline involvement (B).

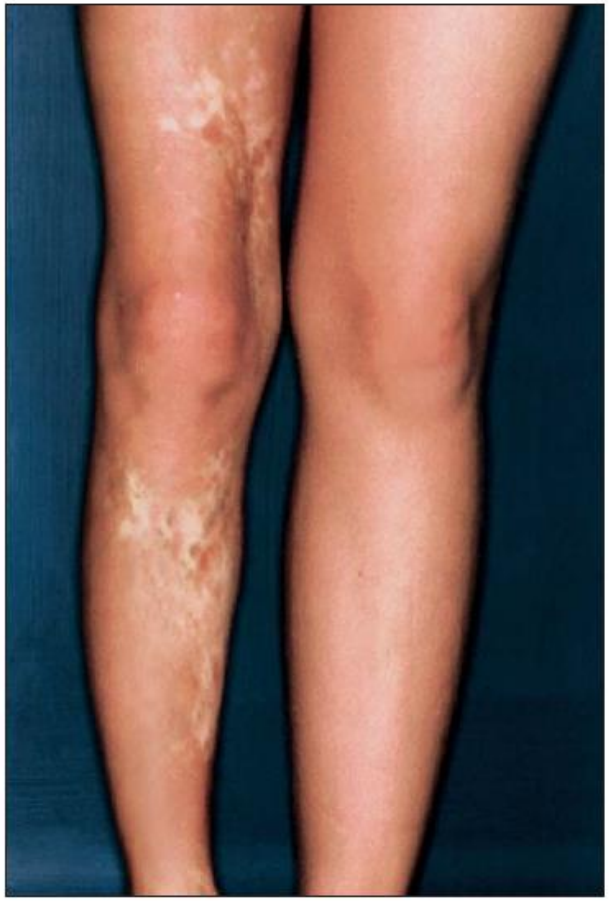
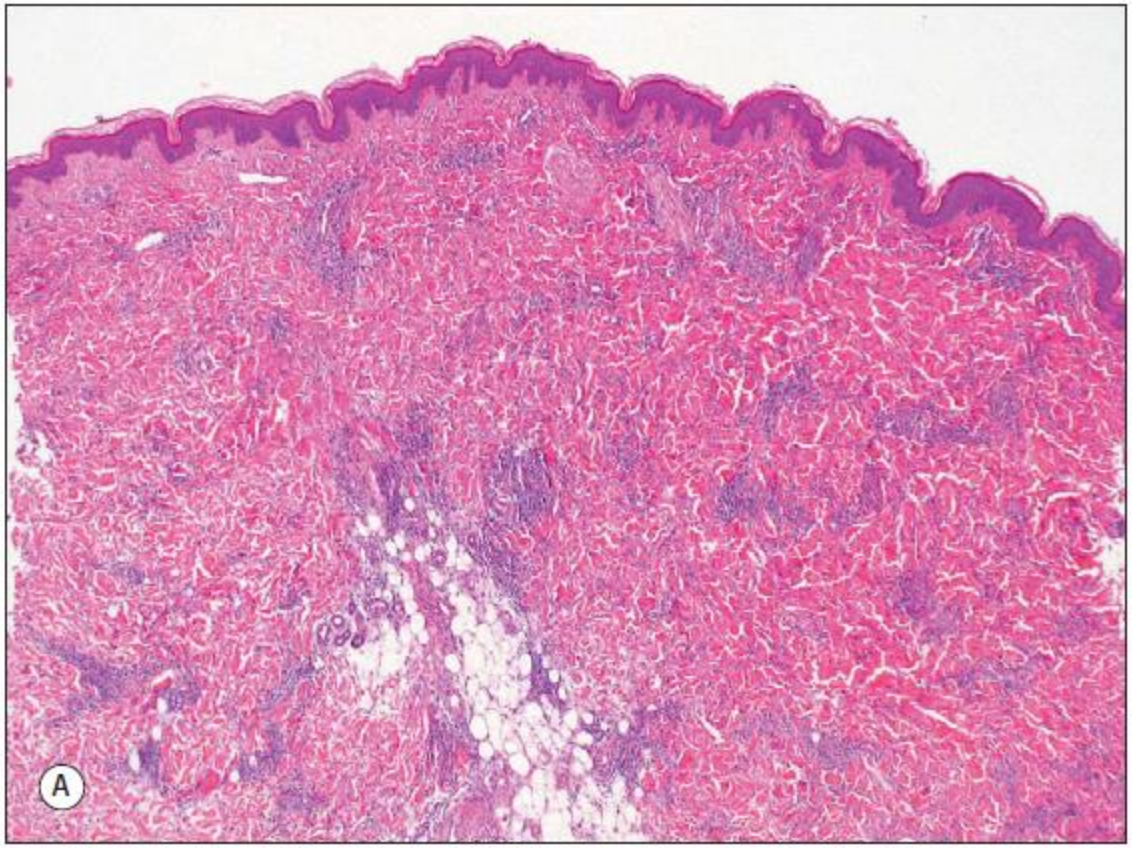


Fig. 96.10 Linear morphea of the leg in a child. Unilateral hypoplasia as a result of untreated linear morphea.


A

Treatment:

- Topical steroids
- Topical calcipotriene
- NSAID
- PUVA
- Hydroxycloroquine

EOSINOPHILIC FASCIITIS

Fascia overlying the muscle is thickened

- Localised areas of the skin are indurated
- The long-term prognosis is good
- Responds to systemic steroids

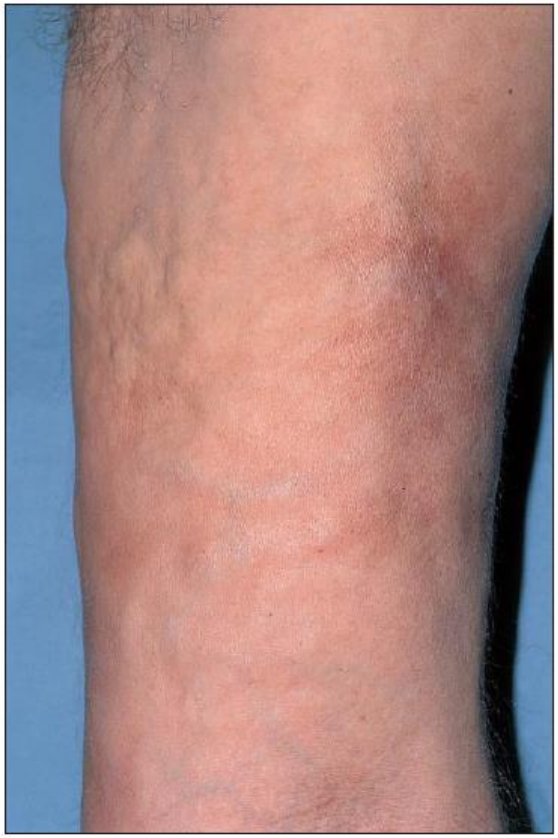


Fig. 44.9 Eosinophilic fasciitis. Induration of the skin with a dimpled or 'pseudo-cellulite' appearance, also referred to as rippling or puckering. Courtesy of Kenneth Greer MD.

LICHEN SCLEROSUS

Patches with sclerotic skin and shiny macules with plugging in the follicular openings

- Localised on the trunk, genital area (vulva, anus, urethral meatus)

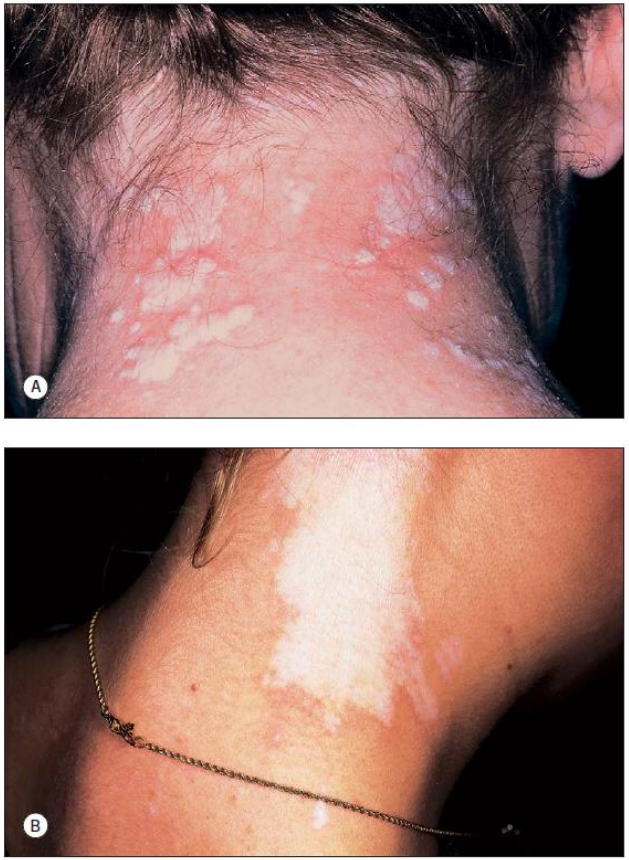


Fig. 96.12 Lichen sclerosus of the neck. Papules and small plaques (A) versus a large coalescent plaque (B).

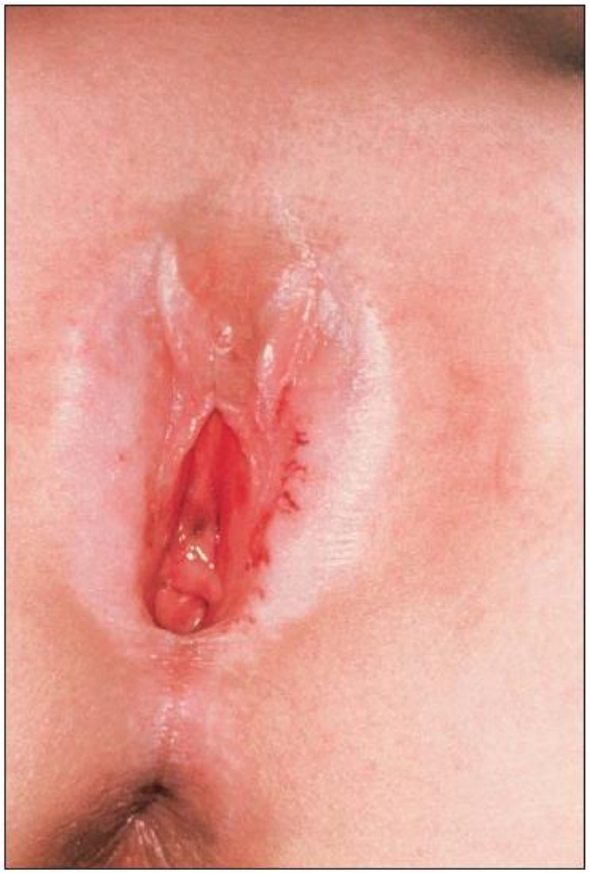


Fig. 96.14 Vulvar lichen sclerosus. Centrally, there is erythema with superficial erosion and purpura. More peripherally, white plaques with a wrinkled surface are seen. Note fissuring of the perineum.

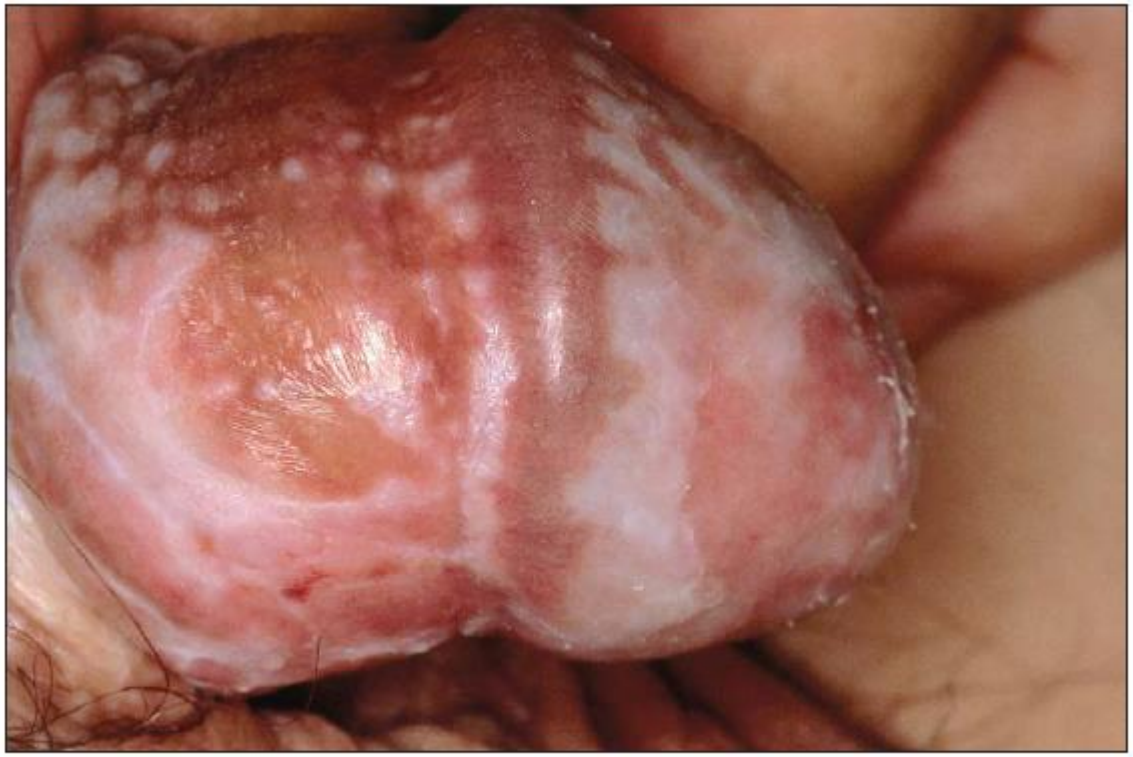


Fig. 96.15 Lichen sclerosus of the penis (balanitis xerotica obliterans). Note the areas of hypopigmentation, erosion and scarring.

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	+ (under occlusion)	3	+	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		–	–

Table 96.2 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.

MIXED CONNECTIVE TISSUE DISEASE

An overlap between SLE and scleroderma or DM

- Women are affected often than men
- Clinical signs: swollen hands and sclerodactily, skin lesions similar to DLE, vasculitis, alopecia, leg ulcers, arthritis, serositis, myositis and Raynaud phenomenon
- The disorder is chronic and turns into SLE or SS

Disease	Autoantibody	Frequency (%)
Systemic lupus erythematosus	Double-stranded DNA	50–70
	Sm antigens (U1, U2, etc.)	15–30
	Phospholipid	10–20
Drug-induced lupus	Nuclear histones	Common
Subacute cutaneous lupus	SS-A(Ro)	50–70
	SS-B(La)	20–30
Dermatomyositis	Jo-1	20–30
	Mi-2	(5–10)
Systemic sclerosis	SCL-70 (topoisomerase 1)	20–30
CREST syndrome	Centromere	20–30
Mixed connective tissue disease	U1-RNP	100
Lichen sclerosis	Extracellular matrix protein 1	Uncertain