Autoimmune and Connective Tissue Disorders

A group of heterogeneous illnesses that have in common the development of immunity to particles of self-DNA, with skin-only disease at one end of the spectrum and severe visceral involvement at the other.

**LUPUS ERYTHEMATOSUS**

Lupus erythematosus (LE) range from the purely cutaneous type (discoid LE), through patterns associated with some internal problems (disseminated discoid LE and subacute cutaneous LE), to a severe multisystem disease (systemic lupus erythematosus, SLE).

**DLE** (purely cutaneous) → **SCLE** (some internal problems) → **SLE** (severe multisystem disease)

**Causes of SLE**

1. Genetic factor
   
   Familial aggregation of SLE and +ve FH in 5-13% of lupus patients e.g. complement deficiency and certain HLA types. all these increase susceptibility.

2. Environmental factors
   
   1. UV light, especially UVB, flares SLE in most patients
   2. Drug-induced lupus. Drug-induce lupus may resemble SLE both clinically and serologically. Eg; hydralazine, procainamide, beta-blockers, isoniazid, penicillamine.
   4. Infection. There has been continuing interest in the possibility that infectious agents might initiate or flare

3. Sex hormones
   
   Female : Male = 9:1
   
   The sex difference is most prominent during the female reproductive years. It is likely due to the effect of sex hormones on the immune system. High levels of estrogen and progesterone promote humoral autoreactivity.

4. Abnormal immune system
   
   1. Hyperactivity in B and T lymphocyte,
   2. Autoantibodies to DNA, RNA, and a host of other cell nucleus antigens
   3. Circulating immune complexes
   4. Defective regulatory mechanism.
Overview of the pathogenesis of SLE

Presentation
Typically, but not always, the onset is acute.

SLE is an uncommon disorder,
Women > men (in a ratio of about 9 : 1).
The most common initial complaints are:

**Fever, fatigue and weight loss**

The **classic rash** of acute SLE is an erythema of the cheeks and nose in the rough shape of a butterfly, with facial swelling. Occasionally, a few blisters may be seen.

**Some patients** develop widespread discoid papulosquamous plaques very like those of discoid LE.

About **20% of patients**, have no skin disease at any stage.

**Other dermatological features** include: peri-ungual telangiectasia, erythema over the digits, hair fall (especially at the frontal margin of the scalp), and photosensitivity.

**Ulcers** may occur on the palate, tongue or buccal mucosa.

**Raynaud’s phenomenon** is commonly found in lupus. It lack specificity. (a triphasic reaction of distal digits to cold or emotion, in which the skin colour changes from white to blue to red)

**Investigations**

Conduct a full physical examination, looking for internal disease.

**Biopsy of skin lesions** is worthwhile because the histopathology and immunopathology are distinctive.

**H/P**; There is usually some thinning of the epidermis, liquefaction degeneration of epidermal basal cells, and a mild perivascular mononuclear cell infiltrate.

**DIF**; is helpful: IgG, IgM, IgA and C3 are found individually or together in a band-like pattern at BMZ of involved skin and often uninvolved skin as well, whereas with DLE only in involved skin.

**Antibody screening**

- ANA is positive in up to 100%
- Double stranded DNA positive in 50–70%
- Ro (SSA) and La(SSR) may be positive (e.g. 20%) if ANA negative
- Cardiolipin is positive in subsets with recurrent abortions, thrombosis and livido reticularis
  - A) positive LE cells or B) raised anti-native DNA antibody binding or C) anti-Sm antibody or D) false positive serological test for syphilis.
- Histone is positive in drug induced cases

**Course**

The skin changes may be transient, continuous or recurrent; they correlate well with the activity of the systemic disease.

Internal involvement can be fatal, but the overall prognosis now is for about three-quarters of patients to survive for 15 years. Renal involvement suggests a poorer prognosis.
Differential diagnosis

SLE is a great imitator.
- Its **malar** rash can be confused with sunburn, polymorphic light eruption and rosacea.
- The **discoid lesions** are distinctive, but are also seen in DLE and in SCLE.
  Occasionally, they look like psoriasis or lichen planus.
- The **hair fall** suggests telogen effluvium.
- Plaques on the scalp may cause a scarring alopecia.

**SLE should be suspected when a characteristic rash is combined with fever, malaise and internal disease.**

Criteria for diagnosing lupus

The diagnosis of lupus is a clinical one made by observing symptoms.
Lab tests provide only a part of the picture.

The American College of Rheumatology has designated 11 criteria for diagnosis.

To receive the diagnosis of lupus, a person must have 4 or more of these criteria:

**Criteria of the ARA for the classification of SLE**
1. Serositis:
2. Oral ulcers
3. Arthritis:
4. Photosensitivity:
6. Renal disorder
7. Immunologic disorder
8. Antinuclear antibody Positive
9. Neurological disorder:
10. Malar rash
11. Discoid rash

(person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval or observation.

**Treatment**

*Local Therapy*

Sun protection
- topical steroids.
- topical calcineurin inhibitors
Intralesional Steroid

Systemic Therapy
Antimalarial

Systemic steroids.

Immunosuppressive agents e.g; Azathioprine (Imuran). Mycophenolate mofetil (MMF)

Biologic therapies
anti-TNF medications (etanercept, adalimumab, infliximab) in the treatment of recalcitrant CLE, particularly SCLE

SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS  SCLE

This is less severe than acute SLE, but is also often associated with some systemic disease

Skin lesions of SCLE are annular or psoriasiform

Patients with SCLE may have some of the criteria of SLE as defined by the ARA, including photosensitivity, arthralgias, serositis, renal disease, and serologic abnormalities.

50% of patients with SCLE have SLE.

Practically all have anti-Ro (SS-A) and most have anti-La (SS-B) antibodies.

The serious organ involvement of SLE is uncommon.

The clinical skin lesions are the distinctive feature of SCLE.

Course

the course is prolonged as in SLE. The skin lesions are slow to clear but, in contrast to DLE, do so with little or no scarring.

Complications

Systemic disease is frequent, but not usually serious.

Children born to mothers who have, or have had, this condition are liable to neonatal LE with transient annular skin lesions and permanent heart block.

Differential diagnosis

The morphology is characteristic, but lesions can be mistaken for psoriasis or widespread DLE.

Annular lesions may resemble tinea corporis or figurate erythemas.

Investigations

Patients with SCLE should be evaluated in the same way as those with acute SLE, although deposits of immunoglobulins in the skin and antinuclear antibodies in serum are present less often (80%).

Many have antibodies to the cytoplasmic antigen Ro (SS-A) in 60%.

Treatment

SCLE does better with antimalarials, such as hydroxychloroquine, than acute SLE.

Oral retinoids are also effective in some cases.

Systemic steroids may be needed too.
DISCOID LUPUS ERYTHEMATOSUS:

The most common form of LE
lie mostly on sun-exposed skin of the face, scalp and ears.

Presentation

One or two plaques only, or many in several areas

Plaques show erythema, scaling, follicular plugging (like a nutmeg grater).
They are well demarcated.

Scarring and atrophy, telangiectasia, hypopigmentation and a peripheral zone of hyperpigmentation.

Course

- The disease may spread relentlessly, but in about half of the cases the disease goes into remission over the course of several years.
- Scarring is common and hair may be lost permanently if there is scarring in the scalp.
- Whiteness remains after the inflammation has cleared, and hypopigmentation is common in dark skinned people.
- Discoid LE rarely progresses to SLE.

Investigations

- Most patients with DLE remain well.

However, screening for SLE and internal disease is still needed.

- A skin biopsy is most helpful if taken from an untreated plaque where appendages are still present.

- DIF shows deposits of IgG, IgA, IgM and C3 at the BMZ.

Biopsies for DIF are best taken from older untreated plaques.

Blood tests are usually normal occasionally ANA +ve in 35%.

Differential diagnosis

Psoriasis is hard to differentiate from DLE when its plaques first arise but has larger thicker scales, and later it is usually symmetrical and affects sites different from those of discoid LE.

DLE is more common on the face and ears, and in sun-exposed areas, whereas psoriasis favors the elbows, knees, scalp and sacrum.

DLE is far more prone than psoriasis to scar and cause hair loss.

Histopathology of DLE:

- Liquefaction degeneration of the basal cell layer
- Hyalinization, Edema & Fibrinoid change below epidermis.
- A patchy dermal lymphocytic infiltrate around the appendages

Treatment

- Sun avoidance and screens are important
potent or very potent topical corticosteroids.
It is justifiable to use them on the face, as the risk of scarring is worse than that of atrophy.

**Intralesional injections of triamcinolone** (2.5 or 10 mg/mL)
If discoid LE does not respond.

**Oral antimalarials**
For stubborn and widespread lesions such as hydroxychloroquine, but rarely these cause irreversible eye damage.
The eyes should therefore be tested before and at intervals during treatment.

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**DERMATOMYOSITIS**

Dermatomyositis is a subset of polymyositis with distinctive skin changes

Had a Characteristic Erythematous & Edematous changes in
the Skin + Muscle Weakness & Inflammation

There are adult and juvenile types

When starting after the age of 40, dermatomyositis may signal an internal malignancy.

-The cause is unknown but an autoimmune mechanism seems likely. Autoantibodies to striated muscle are found.

**Presentation**

1. **Skin signs** are characteristic.
   Face;
   Typical patients have a faint lilac discoloration around their eyes (sometimes called 'heliotrope' because of the color of the flower).
   Malar erythema and edema
   Sometimes, less striking erythema of the neck and presternal area.
   Hand;
   Gottron’s papules in most patients (lilac slightly atrophic papules over the knuckles of their fingers)
   Streaks of erythema over the extensor tendons of the hand, peri-ungual telangiectasia

2. **Weakness** of proximal muscles in many patients, but not all. Including; climbing stairs, getting up from chairs and combing the hair become difficult.

The skin signs usually appear at the same time as the muscle symptoms but, occasionally, appear months or even years earlier.

Sometimes, the skin signs appear in isolation.

Raynaud’s phenomenon, arthralgia, dysphagia and calcinosis may follow.

The rash may become scaly and, rarely, itchy; eventually that on the light-exposed areas and overlying involved muscles develops poikiloderma.

**Investigations**

Muscle enzymes levels such as aldolase and creatinine phosphokinase (CPK) are often elevated.
Muscle imaging: MRI is the method of choice for diagnostic imaging of muscle abnormalities in patients with myositis.

Electromyography (EMG) detects muscle abnormalities
Muscle biopsy shows inflammation and destruction.

The ESR is elevated in about ½ of patients
Elevated anti-nuclear antibody (ANA) levels in 40%-80%

Adult dermatomyositis or polymyositis requires a search for an underlying malignancy.

**Course**

In **children** the disorder is often self-limiting.
In **adults** it may be prolonged and progressive.
Features of mixed connective disease may develop.
The presence of **calcinosis** suggests a good prognosis.

**Complications**

Myositis may lead to **permanent weakness** and immobility, and inflammation to contractures or **cutaneous calcinosis**.
Some die from progressive and severe myopathy.

**Differential diagnosis**

Other connective tissue disorders may look similar, particularly mixed connective tissue disease and SLE.
(In LE, the finger lesions favor the skin between the knuckles whereas in dermatomyositis the knuckles are preferred.)

**Treatment**

**Local Therapy**

1. Sun protection
2. Topical steroids
3. Daily use of a medicated shampoo.
4. Topical antipruritic agents
5. Effective moisturization regimens

**Systemic Therapy**

1. Antimalarial
2. Systemic steroids
3. Methotrexate, Cyclosporine and cyclophosphamide
4. Anti-TNF-α therapy and other Biologic therapies

**MORPHOEA**

Morphoea is a localized form of scleroderma
pale indurated plaques on the skin but no internal sclerosis.

Many plaques are surrounded by a violaceous halo.

Little is known about the **cause**, except that Lyme borreliosis may be associated with the disease in Europe but not in the Americas.
Types: 3 clinical type:
Circumscribed,
Linear &
Frontoparietal: (en coup de saber) with or without hemiatrophy of
the face. (rare type).
Prognosis is usually good, and the fibrosis slowly clears leaving slight depression and
hyperpigmentation.
Treatments work slowly, if at all, and include topical steroids, calcipotriene, psoralen with
ultraviolet A (PUVA),

SYSTEMIC SCLEROSIS: (SYSTEMIC SCLERODERMA):
In this disorder the skin becomes hard as connective tissues thicken
Face & Hands (most frequently) but the change may extend proximally to involve the
forearms & upper arms,
Face: facial appearance: is characteristic:
- The forehead is smooth & shiny
- The forehead lines are expressless.
- The nose becomes small & pinched.
- The mouth opening is constricted & radial furrows appear.
- Small, mat – like telangiectases are frequently found on the face, occur in 75% of patients.
Hands & forearms
forearm’s skin will be thinner than normal.
Atrophy occurs 1st in the pulps of the fingers & small painful ulcers are formed, heal with
scars,
the nails are curving over the atrophic phalanges.
Paronychia is common
Pigmentation occurs in a bout 50% of the patients.
Leg ulcers occur in 40% of the patients
Loss of pulp substance,
periungual telangiectasias,
painful digital ulcer and sclerotic skin
(flecks of calcium extruding)
Presentation
Most patients suffer from Raynaud’s phenomenon and sclerodactyly.
Their fingers become immobile, hard and shiny.
Some become hyperpigmented and itchy early in their disease.
Peri-ungual telangiectasia is common.
Investigations
The diagnosis is made clinically because histological abnormalities are seldom present until
the physical signs are well established.
Laboratory tests should include:
fluorescent ANA test
Barium studies are best avoided as obstruction may follow poor evacuation. Other contrast media are available.
X-rays of the hands
Muscle enzymes measurement
antibody Scl-70 Test
immunoglobulin levels,
blood count and ESR
The evaluation of the heart, kidney, lungs, joints and muscles associated scleroderma.

**Course**
As the disease progresses, sclerosis spreads to the face, scalp and trunk.
Most have abnormalities of the gut including dysphagia, oesophagitis, constipation, diarrhoea and malabsorption.
Fibrosis of the lungs leads to dyspnoea.
Fibrosis of the heart to congestive failure.
The kidneys are involved late, but this has a grave prognosis from malignant hypertension.

**Differential diagnosis**
The differential diagnosis includes chilblains and erythromelalgia.
The sclerosis should be distinguished from that of widespread morphoea,
porphyria cutanea tarda,
mixed CT disease,
eosinophilic fasciitis,
diabetic sclerodactyly and
an acute arthritis with swollen fingers.
Rarely the disease is mimicked by progeria, scleromyxoedema, amyloidosis or carcinoid syndrome.
Changes like those of progressive systemic sclerosis affect workers exposed to polyvinyl chloride monomers or to severe chronic vibration, and are also seen in chronic graft-vs.-host reactions after bone marrow transplants.

**Treatment**
This is unsatisfactory.
The calcium channel blocker nifedipine may help Raynaud’s phenomenon.
Systemic steroids, salicylates, antimalarials and longterm penicillin are used, but are not of proven value.
d-penicillamine has many side-effects, especially on renal function.
Physiotherapy is helpful;
photopheresis is experimental.
Recently, there have been promising reports of the efficacy of ultraviolet A-1 (340–400 nm) phototherapy for affected skin in systemic sclerosis.

Complications
Most complications are caused by the involvement of organs other than the skin, but ulcers of the fingertips and calcinosis are distressing.

Hard skin immobilizes the joints and leads to contractures

CREST SYNDROME
This is a variant of systemic sclerosis
Relatively good prognosis

Fluorescent ANA test (indirect IF): nuclear centromeres
The mnemonic stands for Calcinosis, Raynaud’s phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia.
Telangiectasia is peri-ungual on the fingers and flat, matlike or rectangular on the face.
Many patients with this syndrome develop a diffuse progressive systemic sclerosis after months or years.

LICHEN SCLEROSUS
Many think that this condition is related to morphea, with which it may coexist. However, its patches are non-indurated white shiny macules, sometimes with obvious plugging in the follicular openings.

Women are affected far more often than men and, although any area of skin can be involved, the classical ivory coloured lesions often surround the vulva and anus.

Intractable itching is common in these areas and the development of vulval carcinoma is a risk. In men the condition may cause stenosis of the urethral meatus, and adhesions between the foreskin and glans of the penis.

MIXED CONNECTIVE TISSUE DISEASE
This is an overlap between SLE and either scleroderma or polymyositis.

Presentation
As in LE, women are affected more often than men.

Many develop swollen hands and sclerodactyly, and skin lesions like those of cutaneous LE may also be present.

Alopecia is mild and the hair fall mimics telogen effluvium.

Peri-ungual telangiectasia and pigmentary disturbances are common.

About 25% of patients have a small vessel vasculitis with palpable purpura, leg ulcers and painful dermal nodules on the hands or elbows. Many show Raynaud’s phenomenon, arthritis, serositis and myositis. Headaches, weakness, fatigue, lymph node enlargement or hoarseness occur in about one in three patients; renal and central nervous system disease are less common.
Course
The disorder is chronic, and usually turns into either SLE or systemic sclerosis.

Differential diagnosis
The disorder can be confused with SLE, dermatomyositis, polymyositis, systemic sclerosis and other sclerosing processes such as porphyria cutanea tarda.

Investigations
Antinuclear antibody is usually raised.
Anti-double-stranded DNA is usually, but not always, negative.
Anti-RNP Ab is almost always raised.
DIF: of involved and uninvolved skin shows IgG within the epidermal nuclei, also in a speckled pattern.
Only one-third of patients have subepidermal immunoglobulin deposits in involved skin.
CXR is used to assess for infiltrates, effusion or cardiomegaly.
ECG is used to exclude myocardial infarction.
Echocardiogram may be required to rule out effusion.
Most have hypergammaglobulinaemia,
odesophageal dysmotility,
abnormal pulmonary function tests and
Positive rheumatoid factor.
Hypocomplementaemia,
CBC: leucopenia, anaemia, high ESR
cryoglobulinaemia and
falsepositive biological tests for syphilis occur in a few patients.

Treatment
Treatment depends upon which organs are involved, but systemic steroids are usually needed, in the same dosage as for SLE. Immunosuppressive agents reduce the dosage of systemic steroids, and NSAIDs help with arthralgia, myalgia and swelling of the hands.

OTHER CONNECTIVE TISSUE DISEASES

Rheumatoid arthritis
Most patients with rheumatoid arthritis have no skin disease, but some have tiny fingertip infarcts, purpura, ulcers, palmar or peri-ungual erythema, or pyoderma gangrenosum.
The most common skin manifestations are marble-like nodules near joints.
These are always associated with the presence of rheumatoid factor. Some patients with rheumatoid arthritis have a vasculitis of larger blood vessels with deep ‘punched out’ ulcers on the legs.

Relapsing polychondritis
This process can affect any cartilage as the disorder is apparently caused by autoimmunity to collagen.
The ears are the usual target. The overlying skin becomes red, swollen and tender.
The cartilage in joints, the nose and the tracheo-bronchial tree may be involved, so that patients develop floppy ears, a saddle nose, hoarseness, stridor and respiratory insufficiency.
Aortic aneurysms are also seen.
Treatment is with systemic steroids and NSAIDs. Tracheostomy may be necessary.

[See the slideshow for the other images.]