Dermatology. **Lecture:2**
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Connective Tissue Disease

Introduction

*AICTDs are a group of polygenic clinical disorders often having heterogeneous and overlapping clinical features.
*The cardinal feature of these conditions is inflammation in the connective tissues which leads to dermal atrophy or sclerosis, to arthritis, and sometimes to abnormalities in other organs.

Aetiology

*Multifactorial and involves:

1. Genetic.
2. Immunological (especially autoantibody production).
3. Environmental factors.

Classification of connective tissue disease:

Localized disease	Intermediate type	Aggressive multisystem disease
Discoid lupus erythematosus	Subacute lupus erythematosus	Systemic lupus erythematosus
	Juvenile dermatomyositis	Adult dermatomyositis
Localized scleroderma	Diffuse scleroderma	
Morphoea	CREST syndrome	Systemic sclerosis

Lupus erythematosus

*Is a spectrum, ranging from the purely cutaneous type (discoid LE), patterns associated with some internal problems (subacute cutaneous LE), to a severe multi system disease (systemic lupus erythematosus).
* Characterized by loss of tolerance to nuclear self antigens, then subsequent development of pathogenic autoantibodies which damage the skin and other organs.

Systemic lupus erythematosus

* Autoantibody to:
1. Double-stranded DNA
2. Sm antigens.
3. Phospholipid
* Acute onset.
* Women more than men (8 : 1).
* The classic rash of acute SLE is an erythema of the cheeks and nose in the rough shape of a butterfly with facial swelling.
* Blisters occur rarely, and when they do they signify very active systemic disease.
* Some develop widespread discoid or annular papulosquamous plaques very like those of discoid LE.
* **20%** of patients, have no skin disease at any stage.
* Other dermatological features include periungual telangiectasia, erythema over the digits, hair fall (frontal margin) and photosensitivity.
* With peak onset in the second and third decades.
* Environmental factors that associate with flares of lupus:
1. sunlight and artificial ultraviolet (UV) light.
2. Pregnancy.
3. Infection.
4. increase oxidative stress and subsequent apoptosis

Course

* Skin transient, continuous or recurrent.
* Internal involvement can be fatal.
* Three quarters of patients survive for 15 years.
* Renal involvement suggests a poorer prognosis.

Complications

1. skin disease may cause scarring or hyperpigmentation.
2. Damage to other organs and the side effects of treatment, especially systemic steroids.

Differential diagnosis

* SLE is a great imitator.
* Malar rash: sunburn, polymorphic light eruption and rosacea,..
* The hair fall: telogen effluvium.

Revised american rheumatism association criteria for SLE

SLE is diagnosed by presence of **4out of these 11 criteria**

Features	Characteristics
Malar rash.	Fixed erythema, flat or raised, sparing the nasolabial folds
Discoid rash.	Erythematous plaques with adherent keratotic scales, scarring and follicular plugging
Photosensitivity	Rash as a result of unusual reaction to sunlight
Oral ulcers	Oral or nasopharyngeal ulceration, which may be painless
Arthritis	Non-erosive, two or more peripheral joints.
Serositis	Pleuritis or Pericarditis
Renal disorder	Persistent proteinuria > 0.5 g/day or Cellular casts
Neurological disorder	Seizures or psychosis.
Haematological disorder	Haemolytic anaemia or Leucopenia (< 4 ××10^9/l), or Lymphopenia(< 1 ××10^9/l), or Thrombocytopenia(< 100 ××10^9/l)
Immunological disorde	Anti-DNA or anti-Sm or antiphospholipid antibodies.
Antinuclear antibody (ANA)	Abnormal titre of ANA by immunofluorescence

Investigation

Test	Usual findings
Skin biopsy	Degeneration of basal cells, epidermal thinning, inflammation around appendages
Skin immunofluorescence	Fibrillar or granular deposits of IgG, IgM, IgA and/or C3 alone in basement membrane zone
Haematology	Anaemia, raised ESR, thrombocytopenia, decreased white cell count
Immunology	Antinuclear antibody (higher titres typical of SLE rather than cutaneous LE), antibodies to double-stranded DNA, false positive tests for syphilis, low total complement level, lupus anticoagulant factor, ENA screen, sm antibody
Urine analysis	Proteinuria or haematuria, often with casts if kidneys involved
Tests for function of other organs	As indicated by history, but always test kidney and liver function

Treatment

1. Systemic steroids: prednisolone to achieve control.
2.Immunosuppressive agents: methotrexate, azathioprine, cyclophosphamide and other.
3. Antimalarial drugs.
4. Sunscreen and appropriate clothing should reduce UV-induced flares.
5. Long-term and regular follow up is necessary and the disease should be managed in conjunction with a rheumatologist.

Subacute cutaneous lupus erythematosus

* Autoantibody to:
1. SS-A(Ro)
2. SS-B(La)
* less severe than acute SLE.
* ST only the skin is affected but about half of patients also have marked systemic disease.
* Autoantibody binding to SSA(Ro) are enhanced by oestradiol, so increased prevalence of subacute cutaneous LE in women.
* Drugs induced subacute cutaneous LE, is widespread than in the idiopathic disease.
* Photosensitivity.
* Skin rash: psoriasiform plaques or annular symmetrical lying on the forehead, nose, cheeks, chest, hands and sun-exposed surfaces of the arms and forearms.

Course

* prolonged.
* skin lesions are slow to clear but, with little or no scarring.

Complication

SSA(Ro) cross the placenta lead to children liable to neonatal LE with *transient annular skin* lesions and *permanent heart block.*

Differential diagnosis

* Psoriasis or widespread discoid LE.
* Annular lesions: tinea corporis or figurate erythemas.

Investigations

As those with acute SLE.

Treatment

1. Antimalarials: hydroxychloroquine.
2. Moderate potency topical corticosteroid creams.
3. oral retinoids.
4. Systemic steroids if there are signs of internal disease.

Discoid lupus erythematosus

* Most common form of LE.
* May have one or two plaques only, or many in several areas.
* Cause is unknown but UVR is a factor.
* Plaques show erythema, scaling, follicular plugging (like a nutmeg grater), scarring and atrophy, telangiectasia, hypopigmentation and a peripheral zone of hyperpigmentation.
*The scale penetrates into the orifices of the hair follicle. Peeling the scale reveals an undersurface that has the appearance of a carpet penetrated by several carpet tacks; it is called carpet tack scale.
* They are well demarcated and lie mostly on sun-exposed skin of the scalp, face and ears.

Course

* 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.
* Hypopigmentation is common in dark-skinned people.
* Discoid LE rarely progresses to SLE.

Differential diagnosis

* Psoriasis.

Investigations

1. A skin biopsy.
2. Direct immunofluorescence shows deposits of IgG, IgM, IgA and C3 at the basement membrane zone.
3. Antinuclear antibodies.

Treatment

1. Potent or very potent topical corticosteroids applied twice daily then weaker preparations used for maintenance.
2. Topical calcineurin inhibitor: tacrolimus.
3. Topical retinoids: tretinoin or tazarotene.
4. Sun avoidance and screens.
5. Oral antimalarials: Stubborn and widespread, (eyes should be tested before and at intervals during treatment).
6. Acitretin.

Dermatomyositis

* Subset of polymyositis with distinctive skin changes.
* There are adult and juvenile types.
* The cause is unknown but an autoimmune mechanism seems likely.
* When starting after the age of 40, signal an internal malignancy.
* Autoantibody to:
1. Jo-1
2. Mi 2

Presentation

* Faint lilac discoloration around their eyes **heliotrope sign**, associated with malar erythema and oedema.
* Poikiloderma, **shawl sign**(pigmentary variation, epidermal atrophy and telangiectasia) of the neck and presternal area.
* Lilac slightly atrophic scaly papules over the knuckles of their fingers, **Gottron's papules**.
* Streaks of erythema over the extensor tendons of the hand, periungual telangiectasia and ragged cuticles.
*Periungual erythema and telangiectasia.
***Scaly red scalp**, erythematous to violaceous, scaly, atrophic scalp lesions may be initially diagnosed as psoriasis, seborrheic dermatitis, or lupus erythematosus.
* The skin signs appear at the same time as the muscle symptoms or months or even years earlier.
* Many, but not all, patients have weakness of proximal muscles so climbing stairs, getting up from chairs and combing the hair become difficult.
* In juvenile dermatomyositis subcutaneous calcification is common.

Course

* Children: self-limiting.
*Adults: prolonged and progressive, Raynaud's phenomenon, arthralgia, dysphagia and calcinosis may follow.
* Jo-1 antibodies in plasma indicates high risk for myositis, arthritis and interstitial lung disease.
* Mi2 antibody indicates a good prognosis.

Complications

1. Myositis lead to permanent weakness, immobility, inflammation, contractures or cutaneous calcinosis.
2. Some die from progessive and severe myopathy.

Differential diagnosis

mixed connective tissue disease, SLE, Toxoplasmosis may cause a dermatomyositis like syndrome.

Investigations

1. search for an underlying malignancy as up to **25%** of adults over the age of 40 have internal ca, in women, ovaries are a favourite hiding place, but breast, gastrointestinal tract and other also common.
2. Muscle enzyme: aldolase and creatinine kinase are often elevated.
3. EMG detects muscle abnormalities.
4. Biopsy of an affected muscle shows inflammation and destruction.
5. MRI detect involved muscles.
6. ESR and antibody test as ANA, jo-1, mi-2.

Treatment

1. Systemic steroids high doses (prednisolone 60 mg/day) for an average adult,a maintenance regimen may be needed for several years thus concomitant osteoporosis prevention with calcium, vitamin D and bisphosphonates will be required.
2. Immunosuppressive agents, azathioprine or methotrexate, maintenance treatment is adjusted according to clinical response and creatinine kinase level.
3. Intravenous gammaglobulin infusions or cyclophosphamide.
4. Avoidance of sunlight will prevent UV-induced flares of skin disease.

- **Muscle disease usually responds much better than skin disease.**

Systemic sclerosis(scleroderma)

*Scleroderma is a disease characterized by sclerosis of the skin and visceral organs, vasculopathy (Raynaud's phenomenon), and the presence of autoantibodies.
* 2 subtypes: diffuse cutaneous (dcSSc) and localized cutaneous systemic sclerosis (lcSSc).

Localized cutaneous systemic sclerosis

* Autoantibody to: Centromere.
*Called CREST syndrome standing for **calcinosis, raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia**.
* Skin disease is confined to extremities and face, and onset is slow.
* Sclerodactyly: fingers become immobile, hard and shiny.
* Calcinosis: abnormal calcium deposition occurs over pressure points.
* Telangiectasia: periungual on the fingers and flat, mat-like or rectangular on the face.
* Other vascular features include pulmonary artery hypertension, digital ulceration and renal crises.
* Prognosis is good.

Diffuse cutaneous systemic sclerosis

* Autoantibody to: Scl-70.
*Skin involvement is more widespread than in lcSSc and as the disease progresses, sclerosis spreads to the face, scalp, and trunk.
*Sclerotic skin can become hypo or hyperpigmented and itchy early in the disease.
* Raynaud's phenomenon (95%).
* Diffuse darkening (hyperpigmentation).
* Pinched nose.
* Mask-like face.
* Decreased oral aperture.
* Square mat telangiectasias.
* Thin lips.
* Prominent periungual capillaries.
* Nail abnormalities (pterygium).
* Calcinosis cutis
* Painful digital ulcers.
* Git: dysphagia, oesophagitis, constipation, diarrhoea and malabsorption.
* lung: Interstitial lung disease, dyspnoe.
* Heart: fibrosis of the heart, pulmonary hypertension, congestive failure.
*kidneys involved late, but this has a grave prognosis from malignant hypertension.

Complications

1. Involvement of internal organs.
2. Ulcers of the fingertips and calcinosis are distressing.
3. Hard skin immobilizes the joints and leads to contractures.

Differential diagnosis

Chilblains and erythromelalgia, morphoea, porphyria cutanea tarda, mixed connective tissue disease.

Investigations

1. Clinically.
2. Fluorescent antinuclear antibody
3. Evaluation of the heart, kidney, lungs, joints and muscles.
4. Xrays of the hands.
5. Muscle enzymes and immunoglobulin levels.
6. Blood count, ESR and test for the scleroderma-associated antibody Scl-70.

Treatment

*Unsatisfactory.

1. The calcium channel blocker: nifedipine.
2. Sildenafil help Raynaud's phenomenon.
3. Systemic steroids, methotrexate, mycophenolatemofetil, salicylates and antimalarials are used, but are not of proven value.
4. D-penicillamine has many adverse effects, especially on renal function.
5.Physiotherapy is helpful.
6. photopheresis is experimental.
7. UVA-1(340–400nm)phototherapy
8.Antagonists to endothelin receptors: bosentan reduce risks from pulmonary hypertension.

Morphoea

* localized form of sclerosis with pale indurated plaques on the skin but **no internal sclerosis.**
*Appears as a bound-down skin thickening with minor skin color change, progresses to involve large areas of skin, and does not improve with time.
*Begin as circumscribed areas of purplish induration, after weeks or months, the major portion of the central region of discoloration becomes thickened, firm, hairless, and ivory-colored.
*The violaceous or lilac-colored active inflammatory border is a highly characteristic feature of morphea.
* Fibrosis slowly clears leaving slight depression and hyperpigmentation.
* In pansclerotic morphoea, contractures can cause marked disability.
* En Coup de Sabre is a rare type may lead to arrest of growth of the underlying bones causing, facial hemiatrophy.
* Linear type may cause shortening of a limb.
* Localised morphea may be divided into 5 subtypes:
1. Plaque.
2. Guttate.
3. Linear.
4. En Coup de Sabre
5. Deep.

Treatments

1. Phototherapy with UVA or long wavelength UVA (UVA-1).
2. Topical calcipotriol (calcipotriene),
3. Topical tacrolimus.
4. Systemic methotrexate, with or without corticosteroids, have all shown some efficacy in clinical studies.

Panniculitis

*Panniculitis is an inflammation of the subcutaneous fat.

Causes of panniculitis.

-Infections, including cellulitis.
-Traumatic.
-Foreign bodies.
-Erythema nodosum.
-Erythema nodosum leprosum (leprosy).
-Nodular vasculitis.
-Polyarteritis nodosa.
-Associated with pancreatitis.
-Associated with SLE (lupus profundus).
-Panniculitis-like subcutaneous T-cell lymphoma.
-Morphoea profunda (deep morphoea).
-Cold-induced.
-Gout.
-Factitial (e.g. from injection of milk).

Presentation

*Tender ill-defined red nodules and indurated plaques on the lower legs, thighs and buttocks.

Treatment

*Depends upon the cause.
-Rest,
-Elevation of affected extremities and local heat often help symptoms.
-NSAIDs may also help in the absence of specific therapy.