CONNECTIVE TISSUE DISEASES

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Learning Objectives

An overview of systemic lupus erythematosus (SLE), the major example of human systemic autoimmune disease, and the most frequent connective tissue disorder. You will also be taught about other connective tissue diseases but only need to be aware of the key features of these conditions.

Students will be able to:

• describe the pathogenesis and clinical features of SLE

• understand the importance of autoantibody measurement in the assessment of connective tissue disease and list the important antibodies associated with (1) SLE, (2) scleroderma, (3) Sjogren's syndrome and (4) polymyositis

• briefly list the key features of Sjogren's syndrome, scleroderma and polymyositis *(NB detailed knowledge of these conditions is not required)*

• understand what is meant by the term 'overlap syndrome' in the setting of connective tissue disease

A spectrum of autoimmune connective diseases

Rheumatoid arthritis

Sjögren's syndrome

Systemic lupus erythematosus

Dermatomyositis

Polymyositis

Systemic sclerosis

Connective Tissue Diseases

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Systemic sclerosis
- Sjögrens syndrome
- Polymyositis
- Dermatomyositis

Overlap Syndromes

- Mixed Connective Tissue Disease (U1nRNP syndrome)
- Anti-synthetase syndrome
- Myositis/scleroderma (PM-Scl)

DIAGNOSIS

Anti-nuclear antibodies

Autoimmune rheumatic disease

• Systemic lupus erythematosus	95-100%
• Scleroderma	60-80%
• Mixed connective tissue disease	100%
• Polymyositis/dermatomyositis	61%
• Rheumatoid arthritis	52%
• Sjögren's syndrome	40-70%
• Drug-induced lupus	100%

Non-rheumatic autoimmune diseases

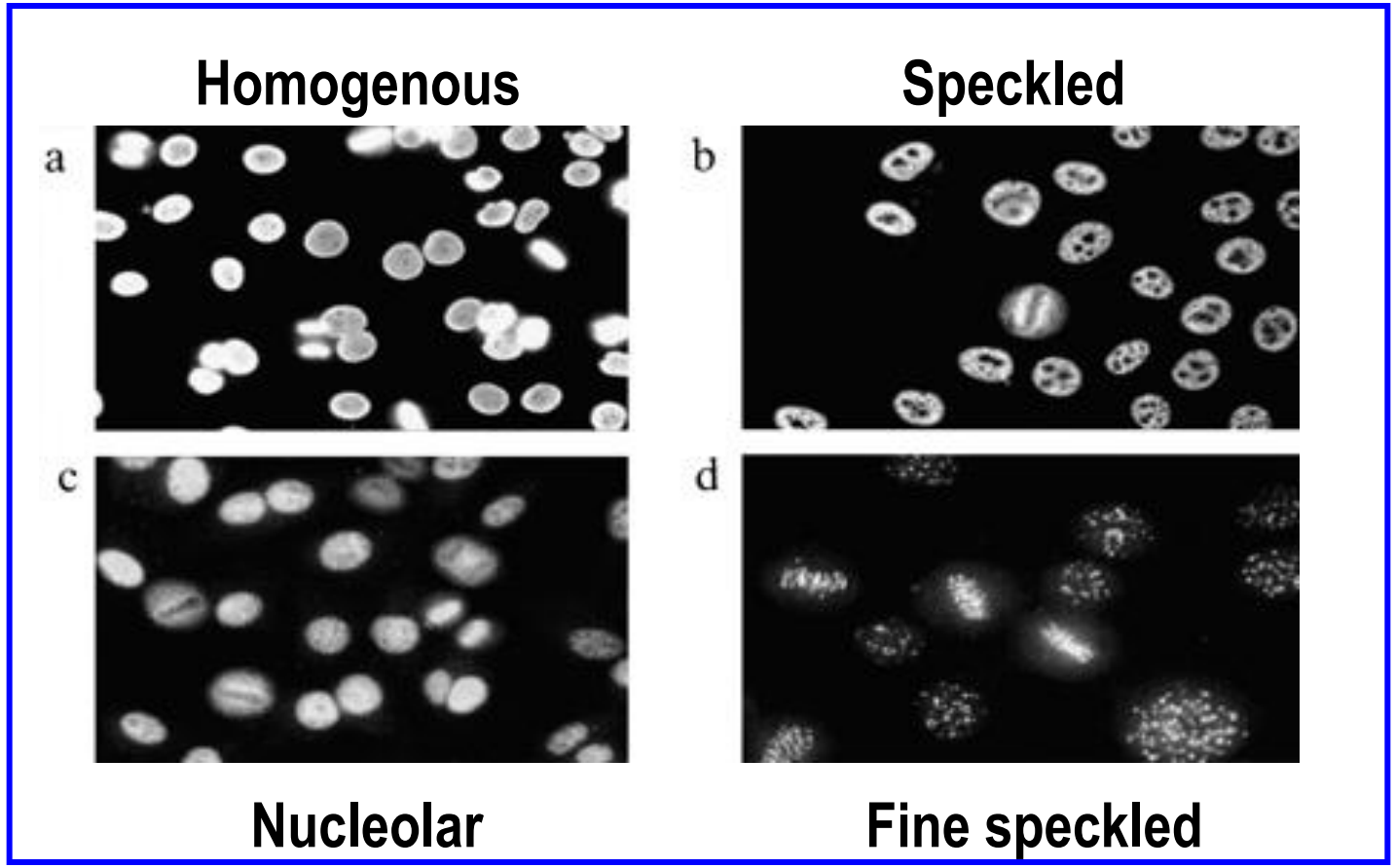
• Hashimoto's thyroiditis	45%
• Graves' disease	50%
• Autoimmune hepatitis	100%
• Primary pulmonary A hypertension	40%

Anti-nuclear antibodies

ANA relatively non-specific, pattern important
Measured by immunofluorescence

SLE

Systemic sclerosis



SLE
Overlap syndromes

Sjogrens

Autoantibodies and connective tissue diseases

Antibody	Clinical interpretation
ANA	Autoimmune diseases, chronic infection drugs and ageing
dsDNA	SLE
Phospholipid (cardiolipin)	Recurrent abortion & thrombosis SLE, RA, MCTD, Scleroderma
Histones	Drug-induced lupus

Autoantibodies and extractable nuclear antigens

Ro (SS-A)	Primary Sjögren`s, SLE, fetal congenital heart block
LA (SS-B)	As with anti-Ro
Sm	SLE
U1RNP	MCTD; occasionally SLE
Jo-1	Myositis and interstitial lung disease
Scl-70 (topoisomerase-1)	Diffuse systemic sclerosis
Centromere	Limited systemic sclerosis with pulmonary hypertension

Systemic Lupus Erythematosus

Chronic autoimmune disease

- M : F 1:9 Presentation 15 - 40 yrs
- Increased incidence among Afro-Caribbean, Asian, Chinese
- Prevalence varies: 4 - 280/100,000

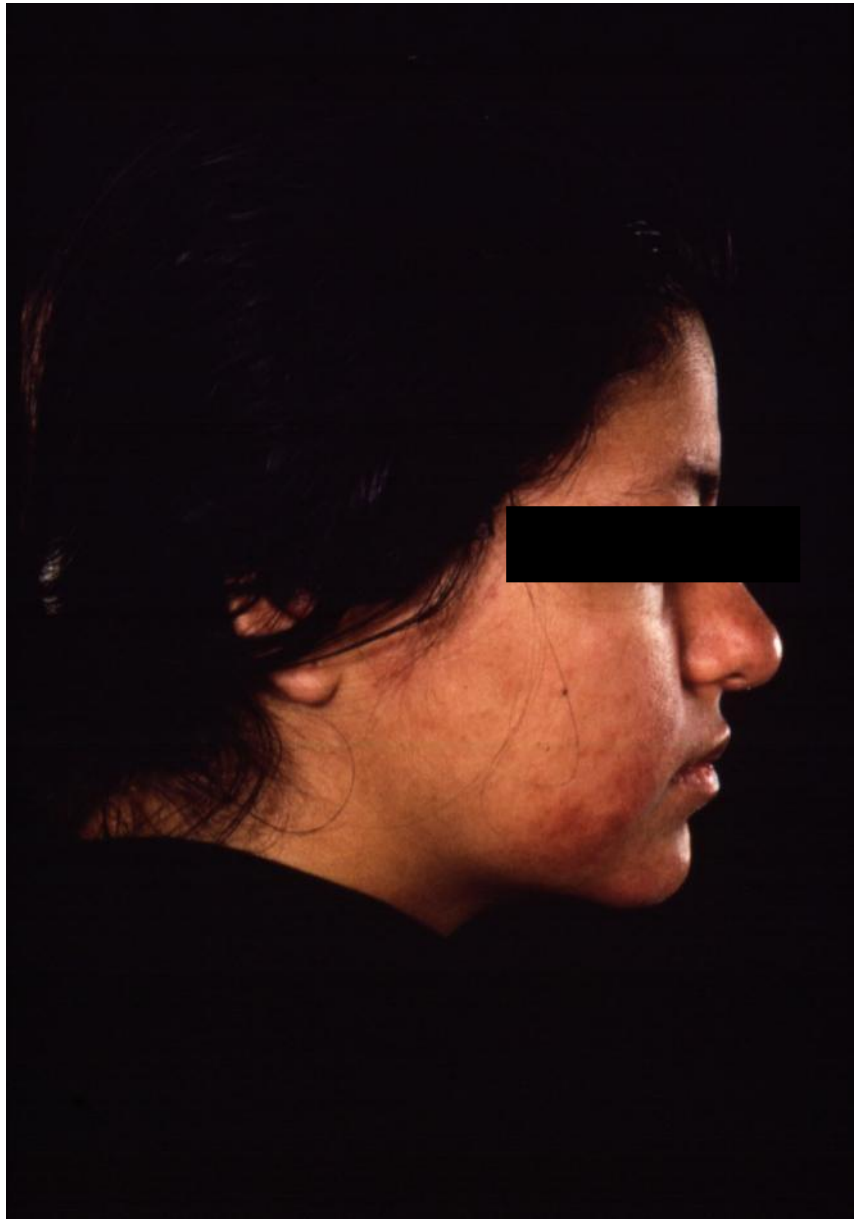
- Principally affects joints and skin
- Lungs, kidneys, haematology, central nervous system, heart

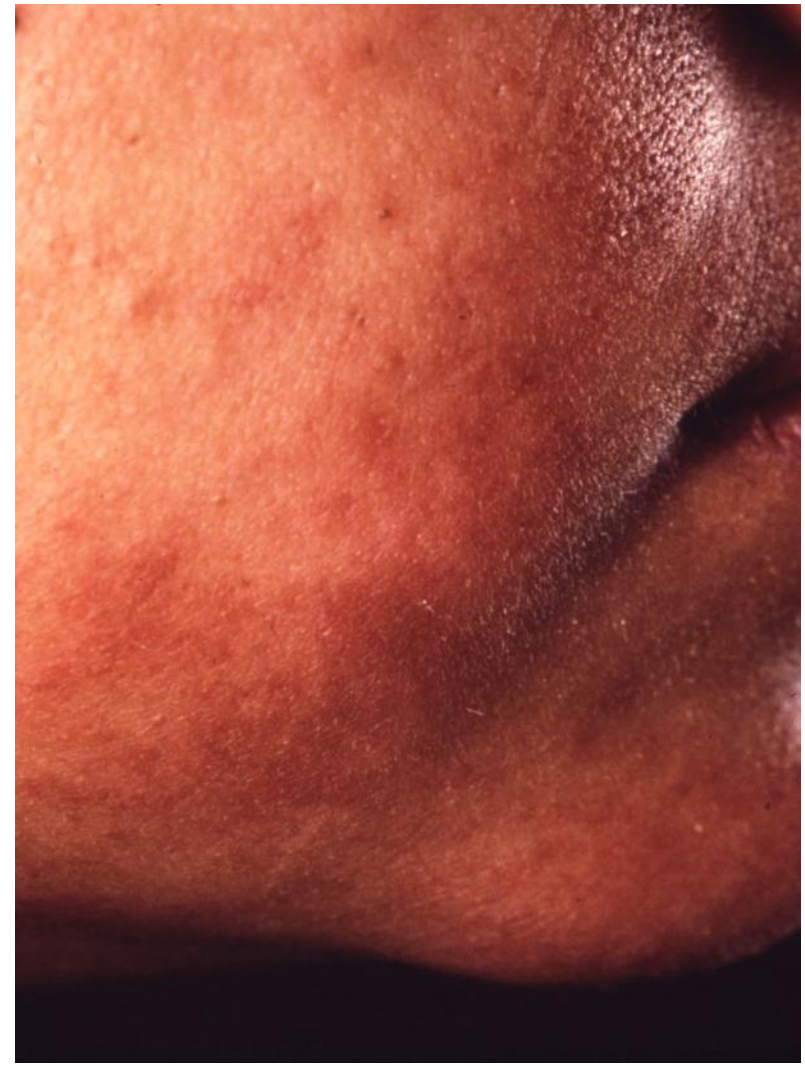
Genetic associations

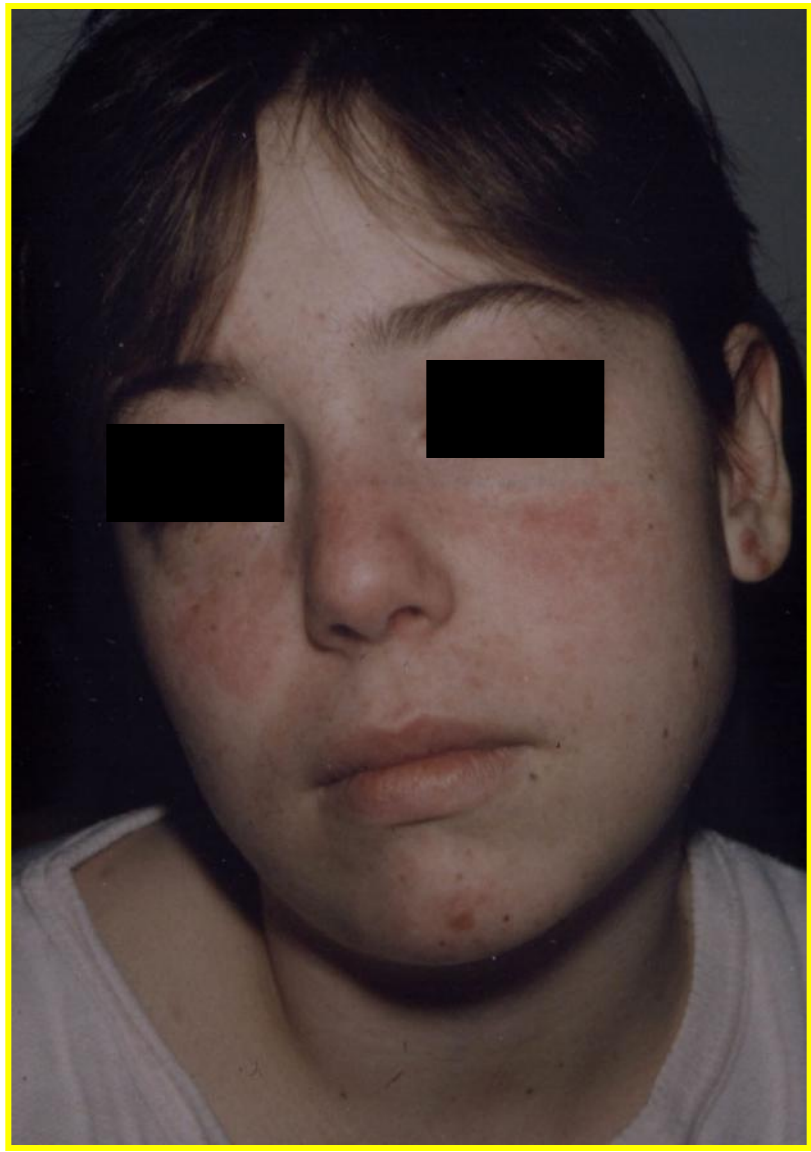
- Multiple genes implicated
- Complement deficiency e.g. C1q and C3
- Fc receptors, IRF5, CTLA4, MHC class II HLA genes

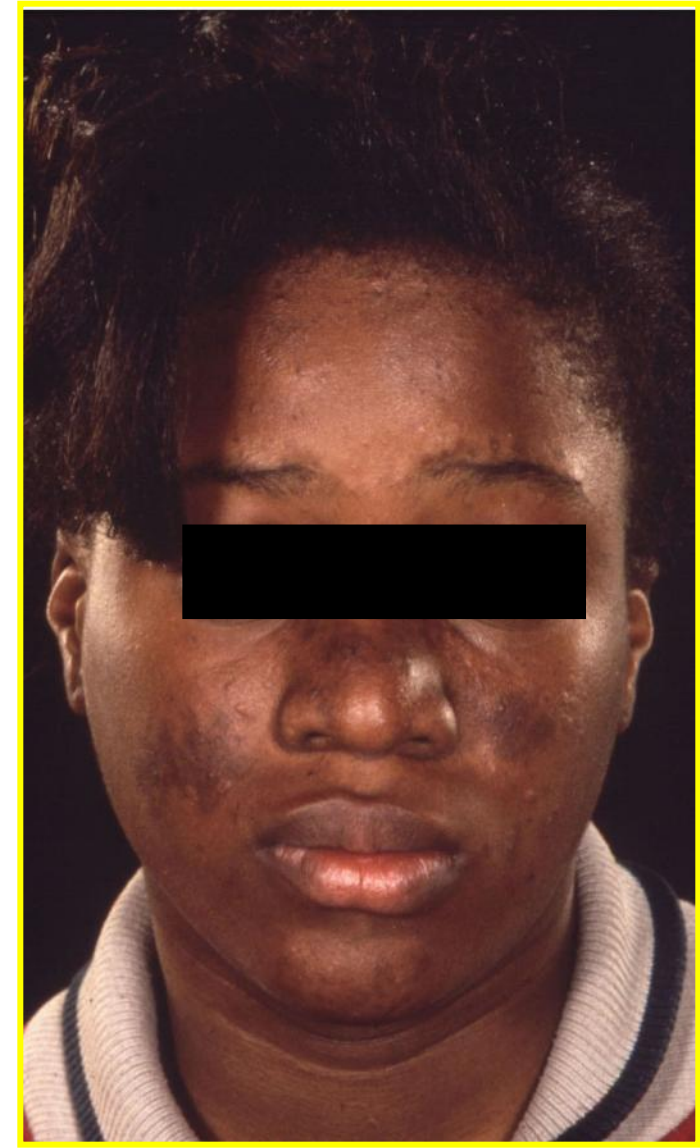
Clinical Features of SLE

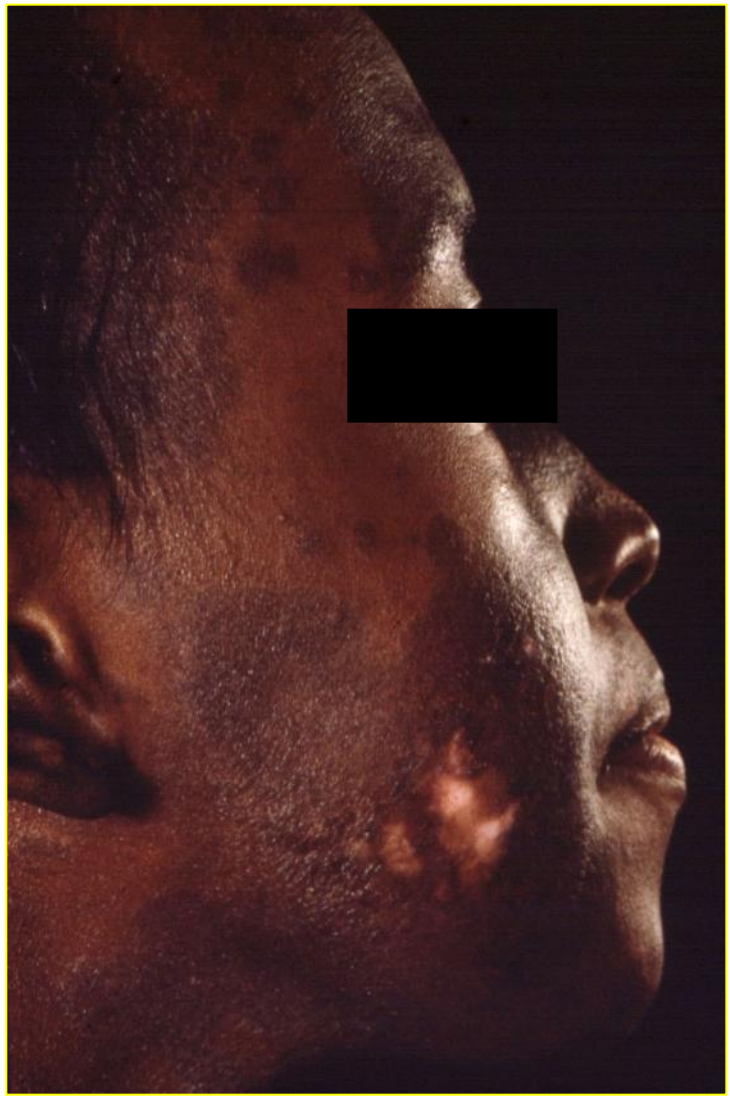
•Constitutional	Fever, fatigue, myalgias, arthralgias
•Mucocutaneous	Oral ulcers, butterfly rash, discoid lesions, aloplecia, vasculitis
•Renal	Glomerulonephritis
•Neuropsychiatric	CNS vasculitis, peripheral neuropathy
•Respiratory	Pleurisy with effusion, pneumonitis
•Cardiac	Pericarditis, myocarditis, endocarditis coronary vasculitis, thrombosis

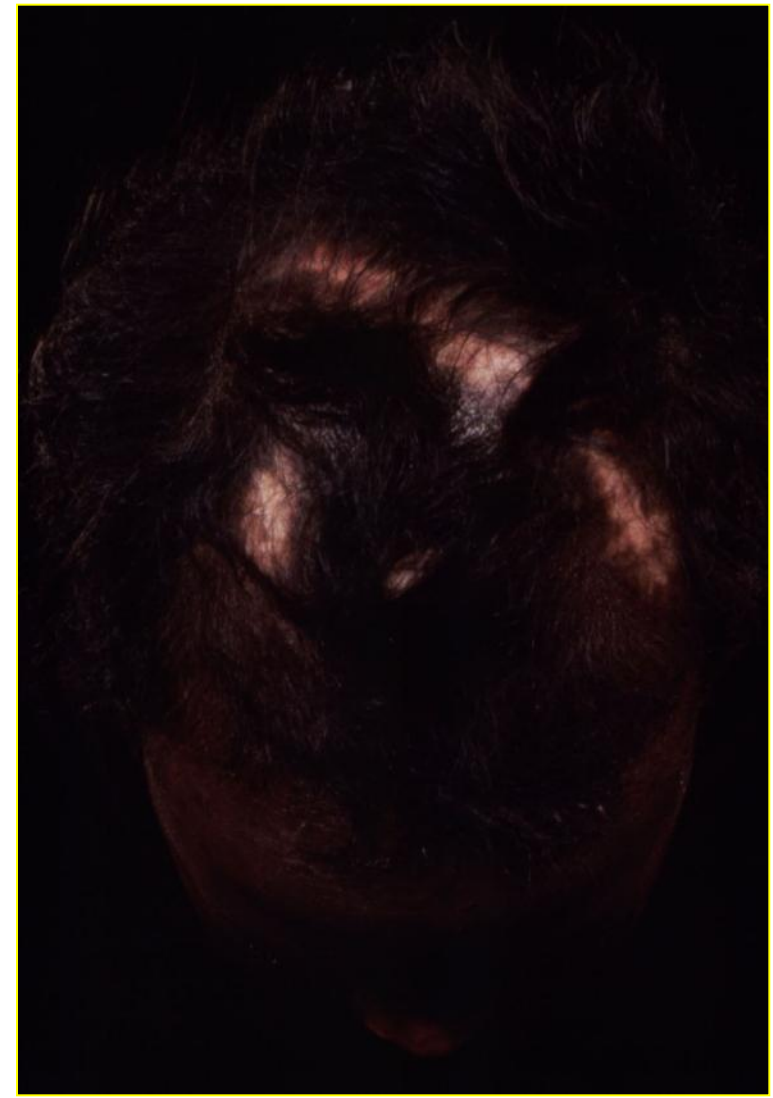




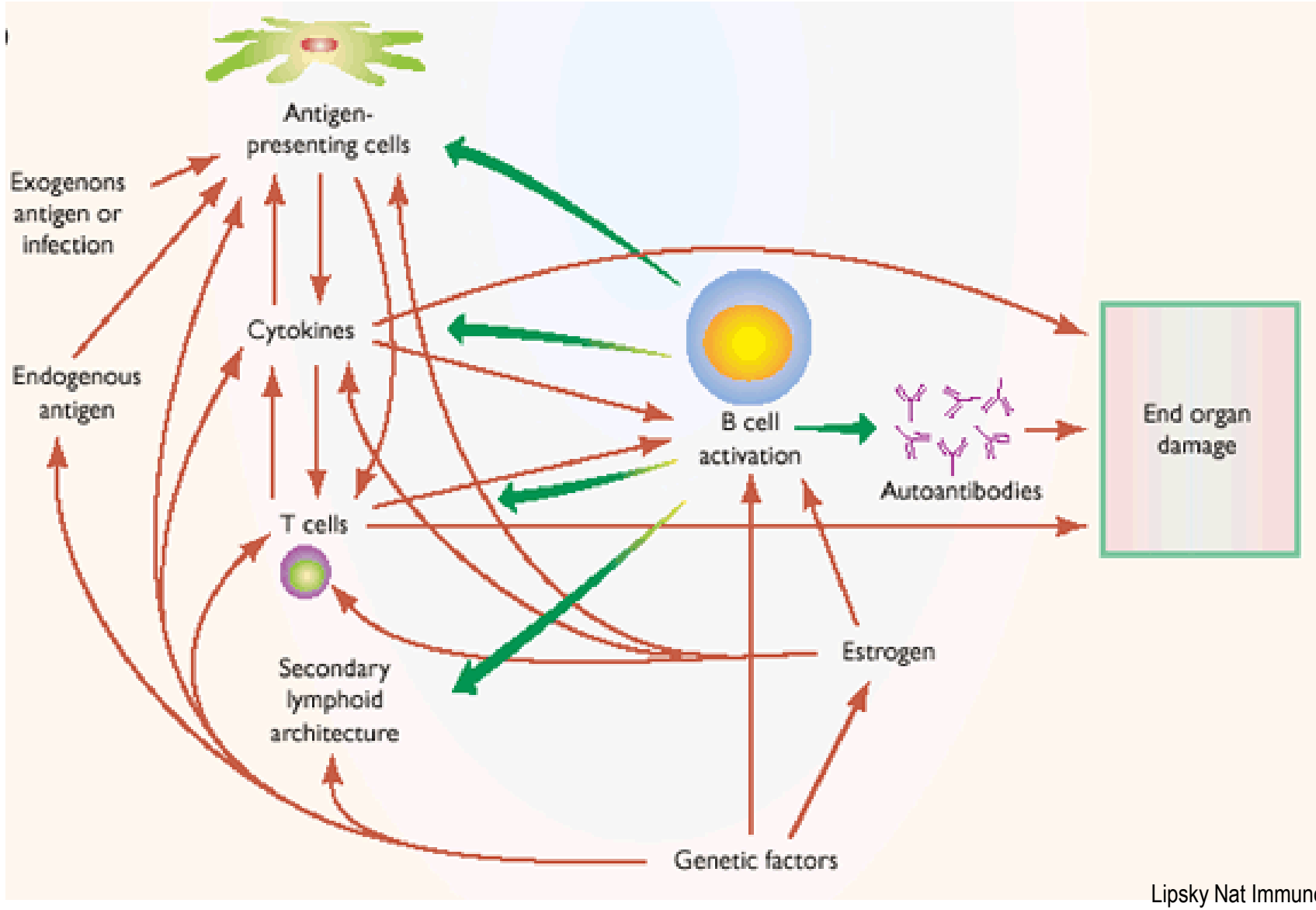








Pathogenesis of SLE – B cell hyperactivity



Lipsky Nat Immunol 2001 vol 2 p764

Pathophysiology: autoantibody formation

Abnormal clearance of apoptotic cell material

↓

Dendritic cell uptake of autoantigens and activation of B cells

↓

B cell Ig class switching and affinity maturation

↓

IgG autoantibodies

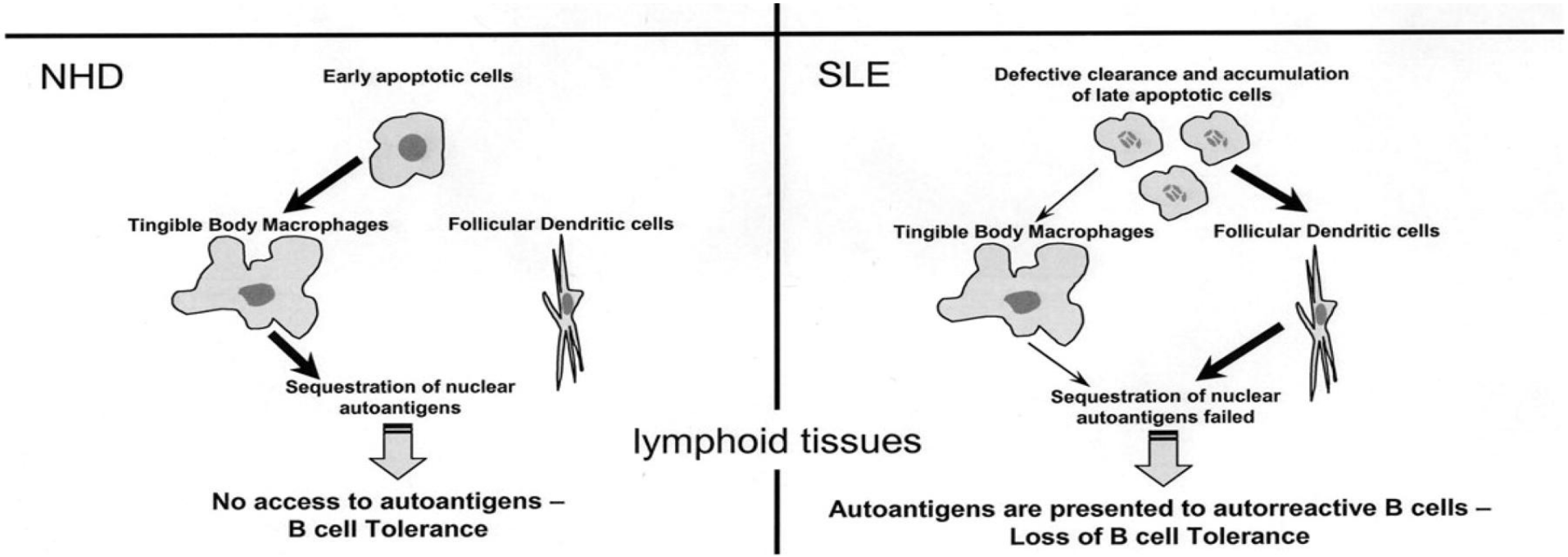
↓

Immune complexes

↓

Complement activation
Cytokine generation

The fate of apoptotic cells in SLE



SLE: diagnostic tests

Antinuclear antibody positive - what next?

Anti-dsDNA and Sm

- More specific but less sensitive

Anti-Ro and/or La

- Common in subacute cutaneous LE
- Neonatal lupus syndrome & Sjögren's

Complement

- Increased consumption: ↓C3, C4

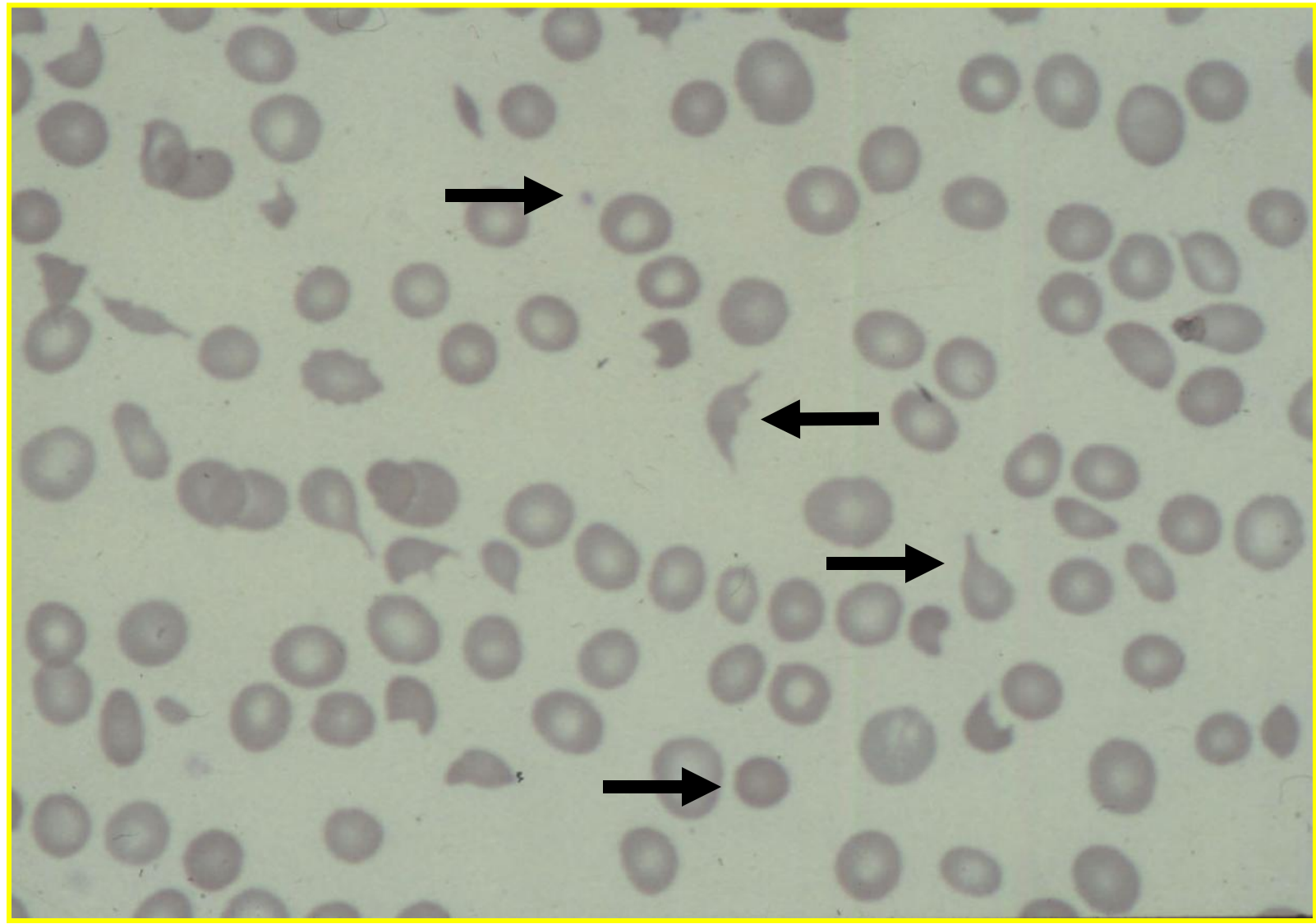
SLE: assessing disease severity

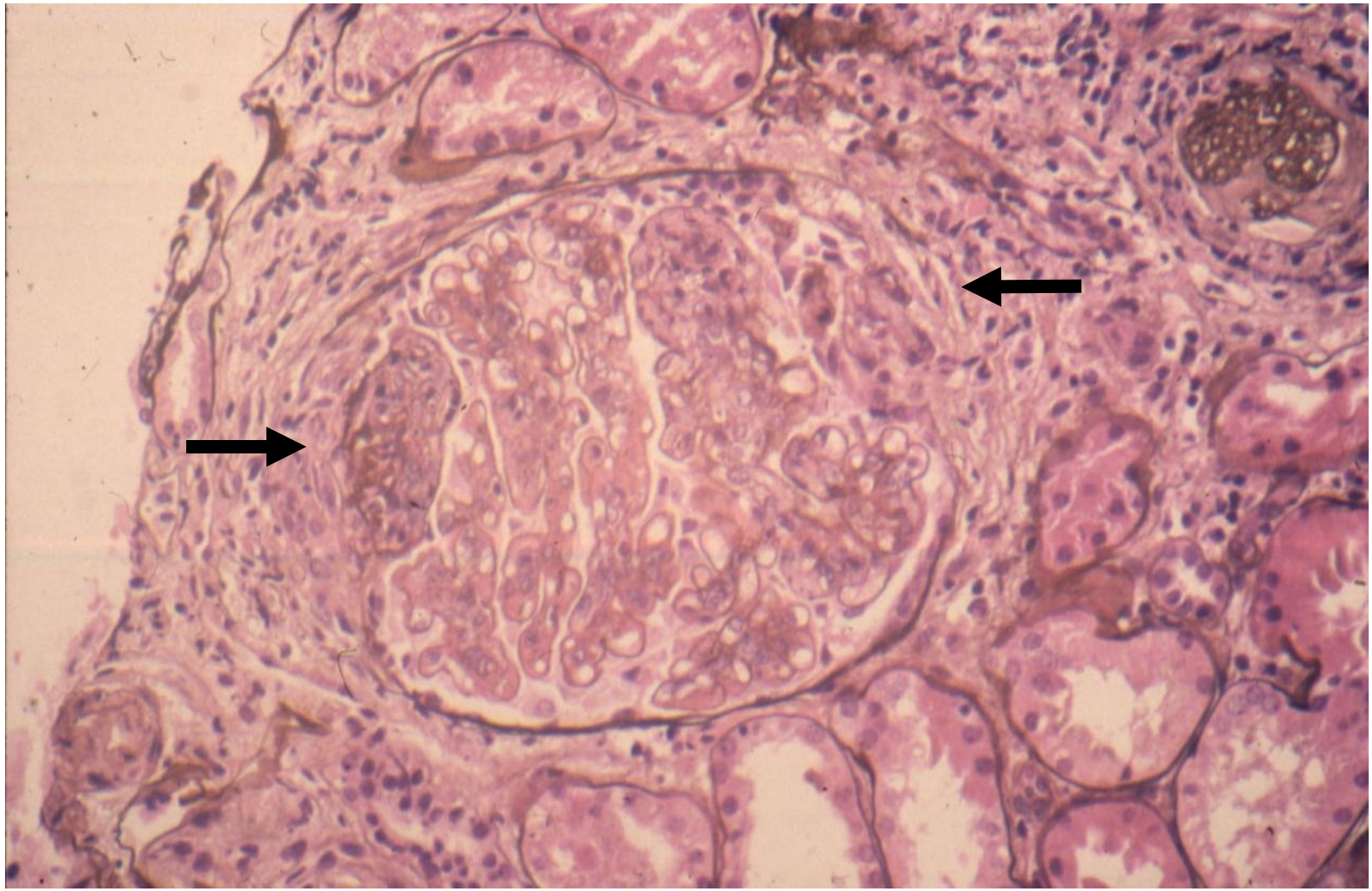
Haematology

- Lymphopaenia, normochromic anaemia
- Leukopaenia, autoimmune haemolytic anaemia, thrombocytopaenia

Renal

- Proteinuria, haematuria
- Active urinary sediment





Systemic Sclerosis

Limited:

- Calcinosis
- Raynaud's phenomenon
- Oesophageal dysmotility
- Sclerodactyly
- Telangectasia

- Pulmonary hypertension

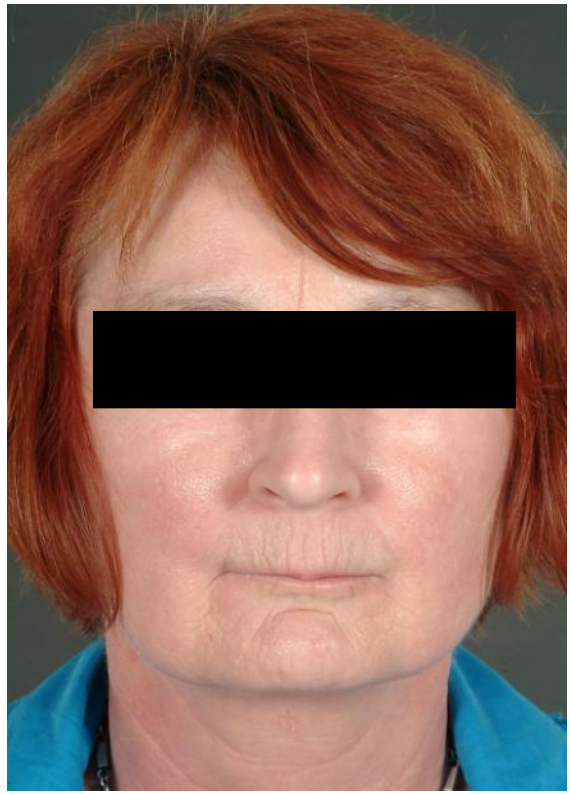
- Anti-centromere Abs

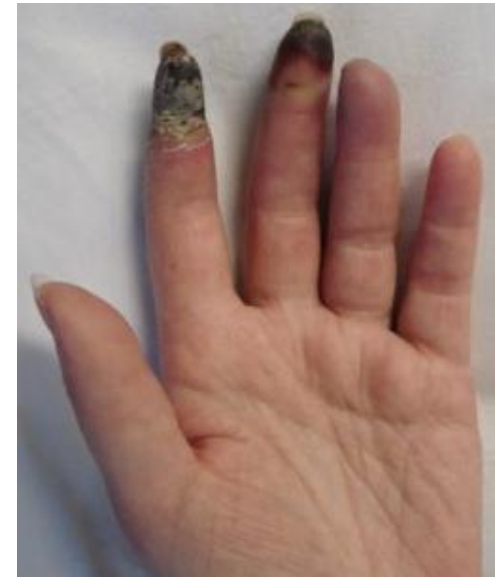
Diffuse:

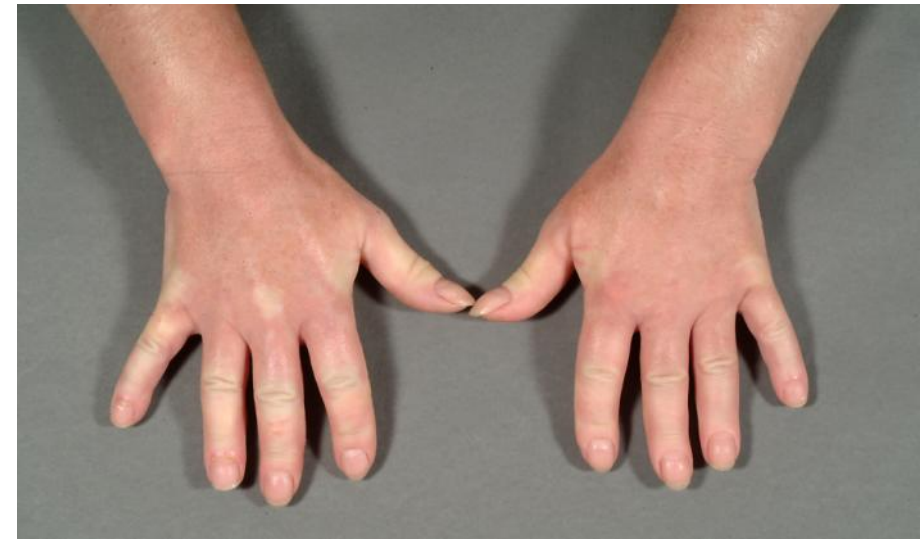
- Scleroderma
- Raynaud's phenomenon
- Oesophageal dysmotility
- Pulmonary fibrosis
- Renovascular hypertension

- Anti-Scl 70 antibodies

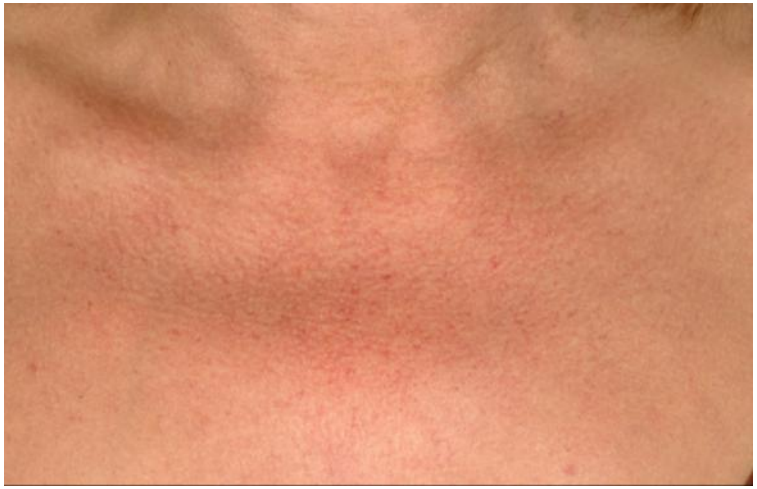
Limited cutaneous systemic sclerosis

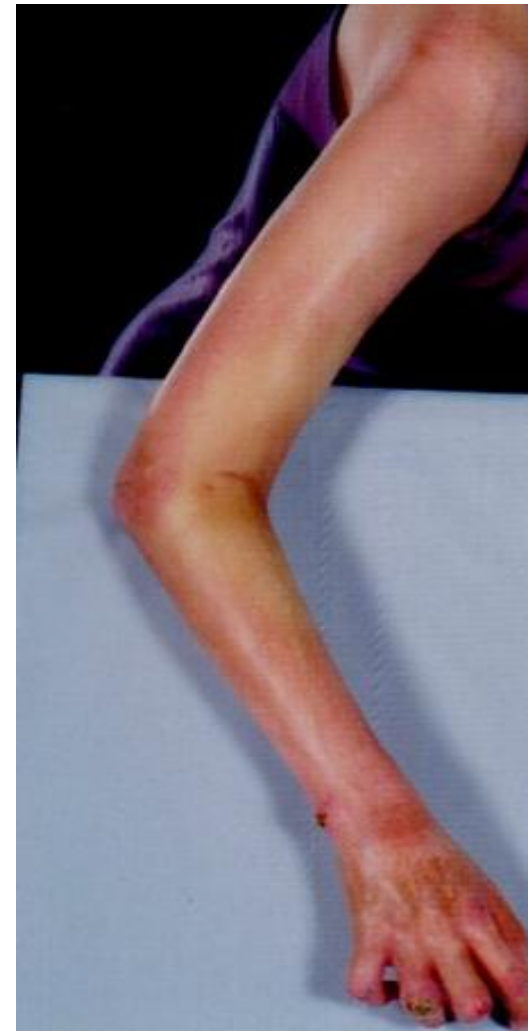


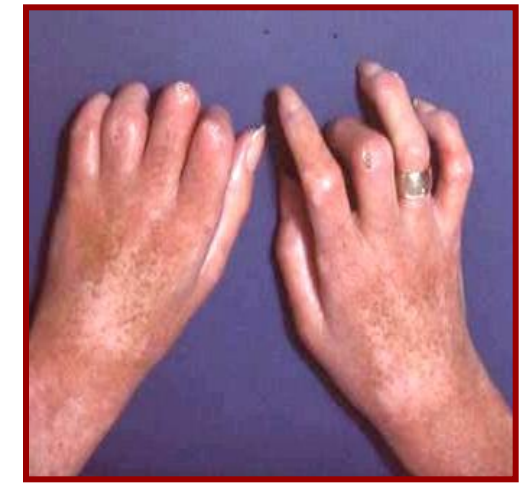




Diffuse cutaneous systemic sclerosis







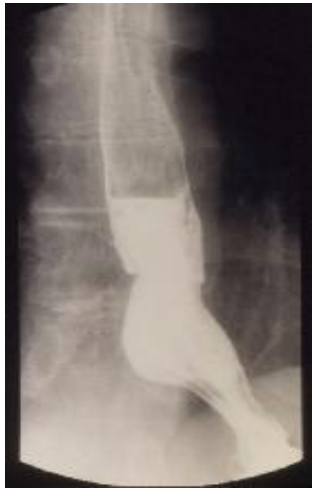
Systemic Sclerosis

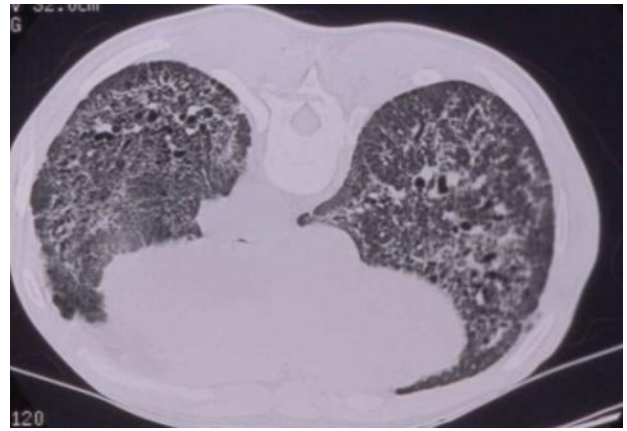
Characterised by thickening & fibrosis of skin

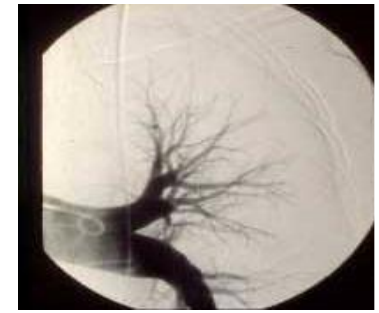
- 4-12/million per year, F:M = 4:1, start at any age

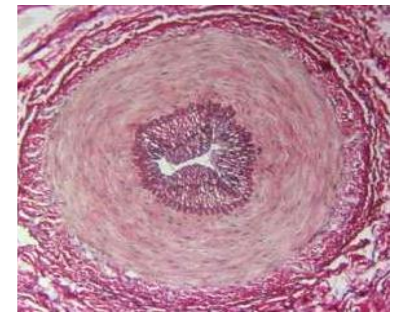
Clinical features

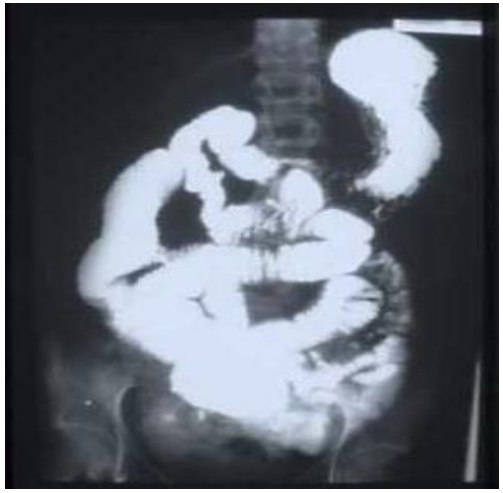
- **Raynaud's phenomenon** – up to 100% during disease
- **Scleroderma -** early oedematous phase, later indurated, tight and shiny
- **Musculoskeletal** - arthralgia or arthritis (30%), myositis, flexion deformities in fingers
- **Pulmonary -** interstitial fibrosis, pulmonary hypertension
- **Renal -** malignant hypertension, "onion skin" vascular occlusion
- **GI -** impaired motility, reflux, malabsorption, bacterial overgrowth



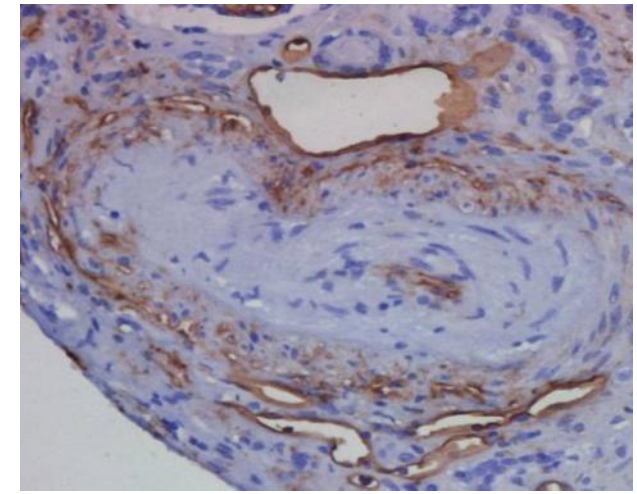


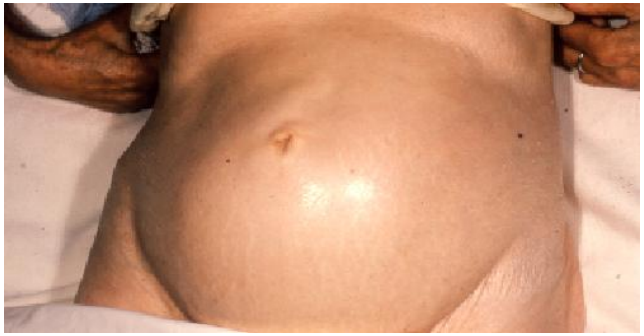


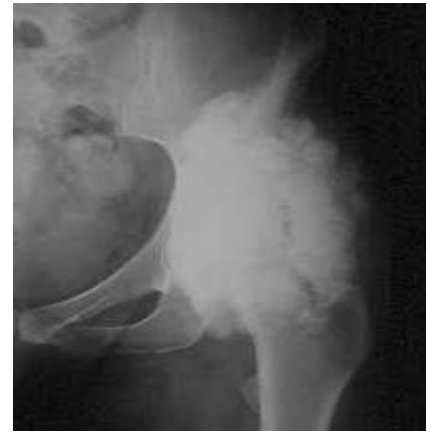




Internal organ complications of systemic sclerosis



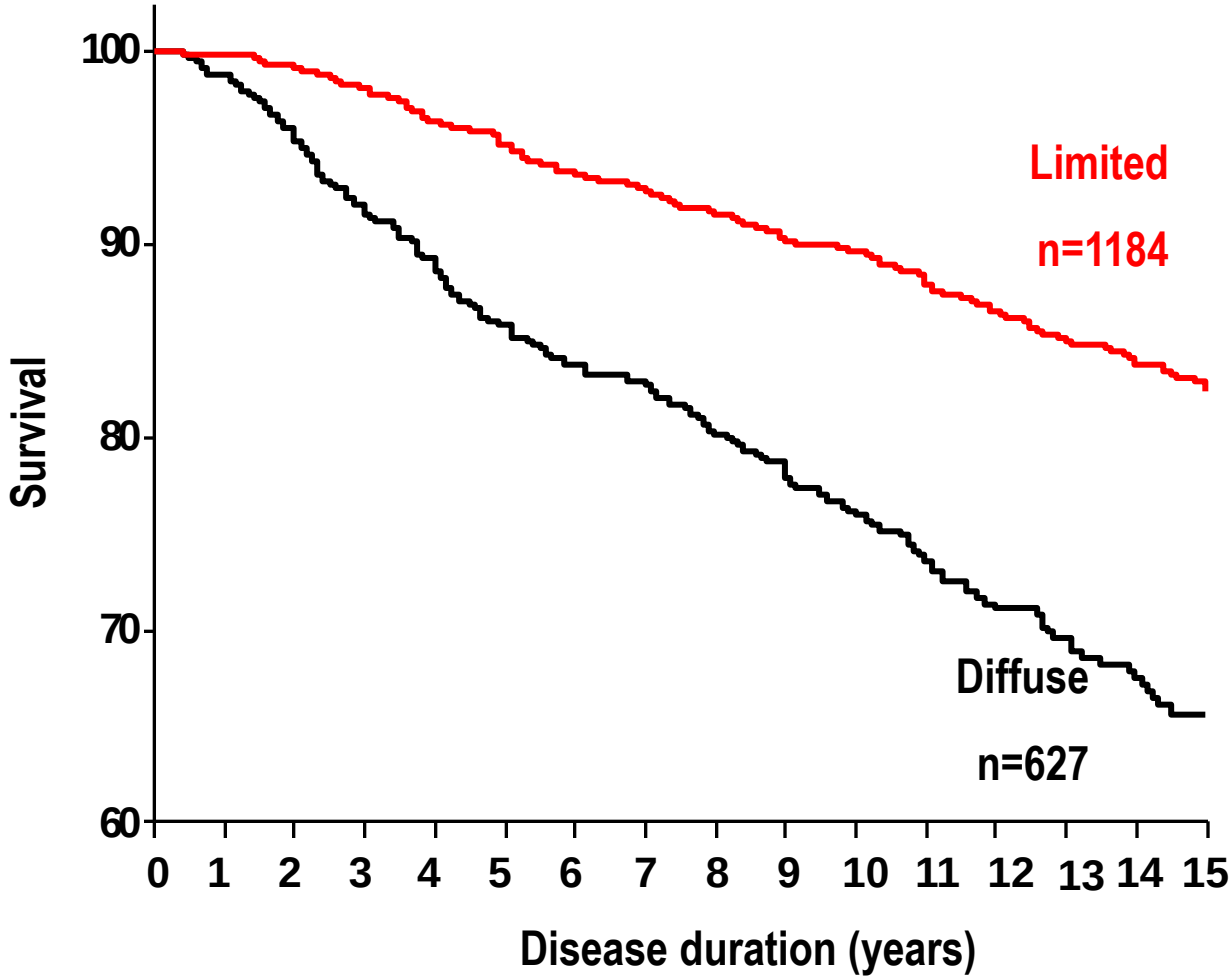


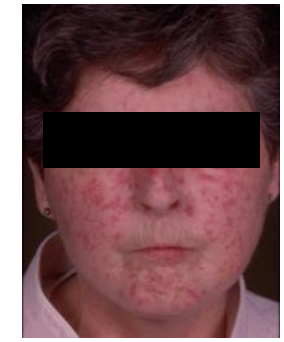


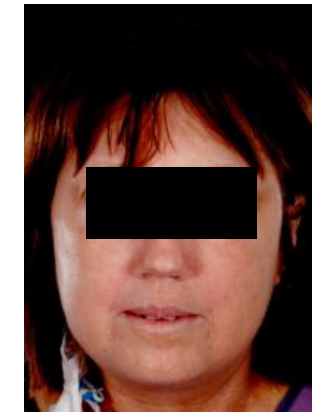
Systemic sclerosis: diagnostic tests

- **Elevated acute phase response: ESR, CRP**
- **Autoantibodies:**
  - Rheumatoid factor (30%)
  - ANA (90%) homogenous, speckled or nucleolar
  - Anti-centromere 50-90% of limited SSc
  - Anti-Scl-70 in 20-40% of diffuse SSc

Comparative survival of limited and diffuse cutaneous SSc subsets







[RFH SSc cohort data, 2007]

Sjögren's syndrome

1. **Primary Sjögren's Syndrome**
    - lymphocytic infiltrate of exocrine glands
    - Sicca symptoms: dry eyes and dry mouth

2. **Secondary Sjögren's Syndrome**
    - Sicca syndrome + RA or connective tissue disease
    - seen in approx. 30% of RA patients

Sjögren's syndrome: case history

Mrs K.B. Aged 37

History goes back many years.

Gritty or sandy feeling in eyes.

Dry mouth - difficult with some foods.

Swelling of the parotid glands.

Fatigue.

Joint pains.

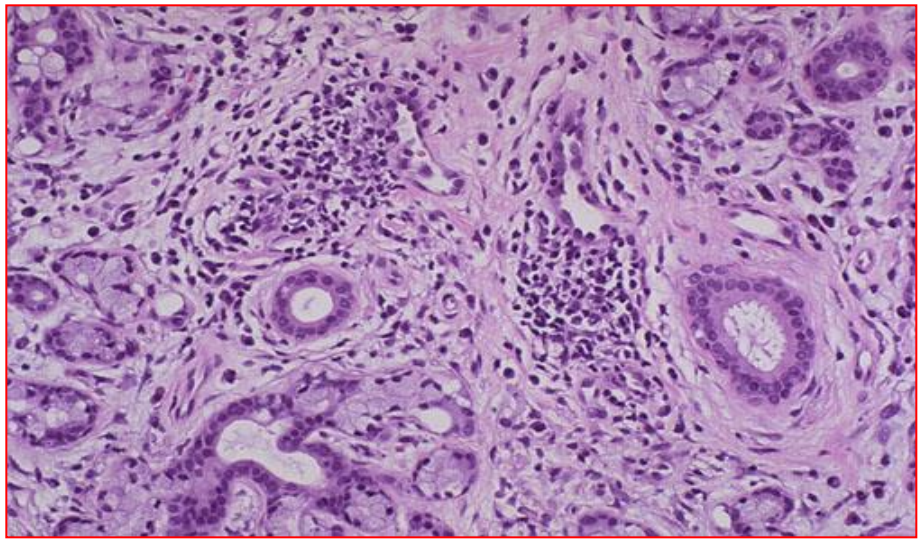
Sjögren's syndrome: case history

Examination

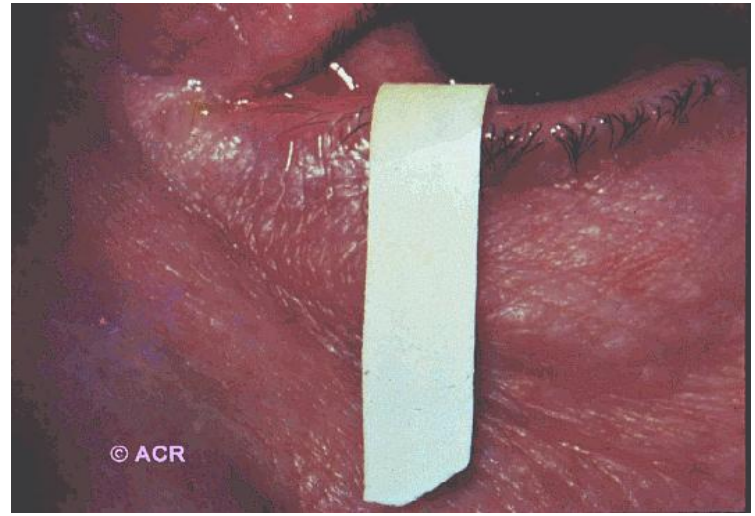
- Inspection of mouth – dental caries
- Palpation of parotids.
- Measurement of tear flow: Schirmer's test
- Measurement of salivary flow + gland biopsy
- Slit lamp exam with Rose Bengal dye

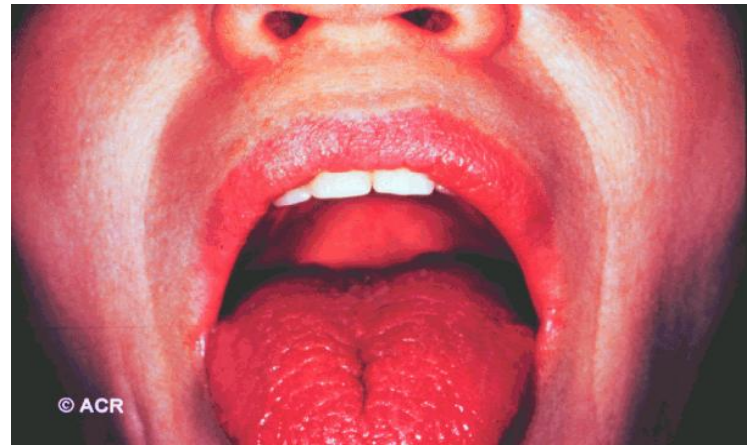
Sjögren's syndrome

Salivary gland biopsy



Sicca complex





Sjögren's syndrome – clinical features

- Dryness from exocrine gland destruction
  - Schirmer's test, Rose Bengal staining
  - eyes, mouth, vagina, oesophagus
  - respiratory - hoarseness, infections

- Arthralgia or arthritis (60-70%)

- Lymphadenopathy (20%), glandular swelling

- Raynaud's (40%), pancreatitis, vasculitic purpura (5%)

- Renal tubular acidosis (10%), neuropathies (2%), central nervous system involvement, interstitial lung disease

Sjögren's syndrome case history: diagnosis

- ESR 85 mm/1st hr, CRP 52 mg/L.
- Total Ig levels raised.
- Rheumatoid factor 1/640.
- ANA +++ (speckled).
- Anti-Ro (SSA) and -La (SSB) ribonucleoproteins autoantibodies

Polymyositis and Dermatomyositis

Idiopathic inflammatory disorders of skeletal muscle

- when assoc with cutaneous lesions = dermatomyositis
- 80% five year survival

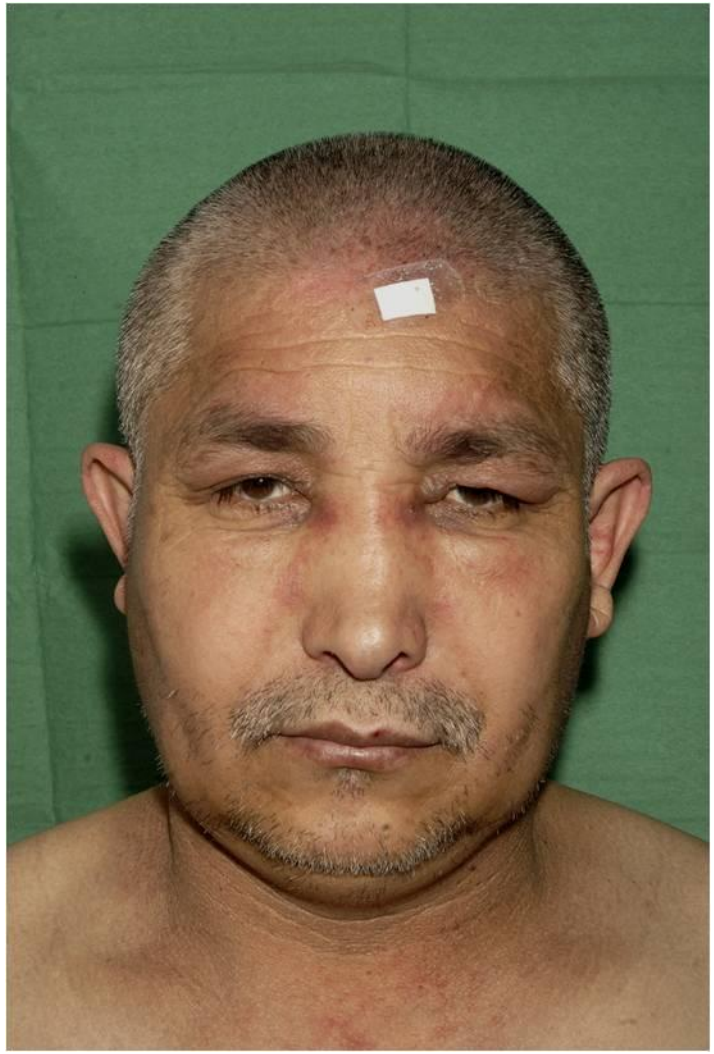
Malignancy

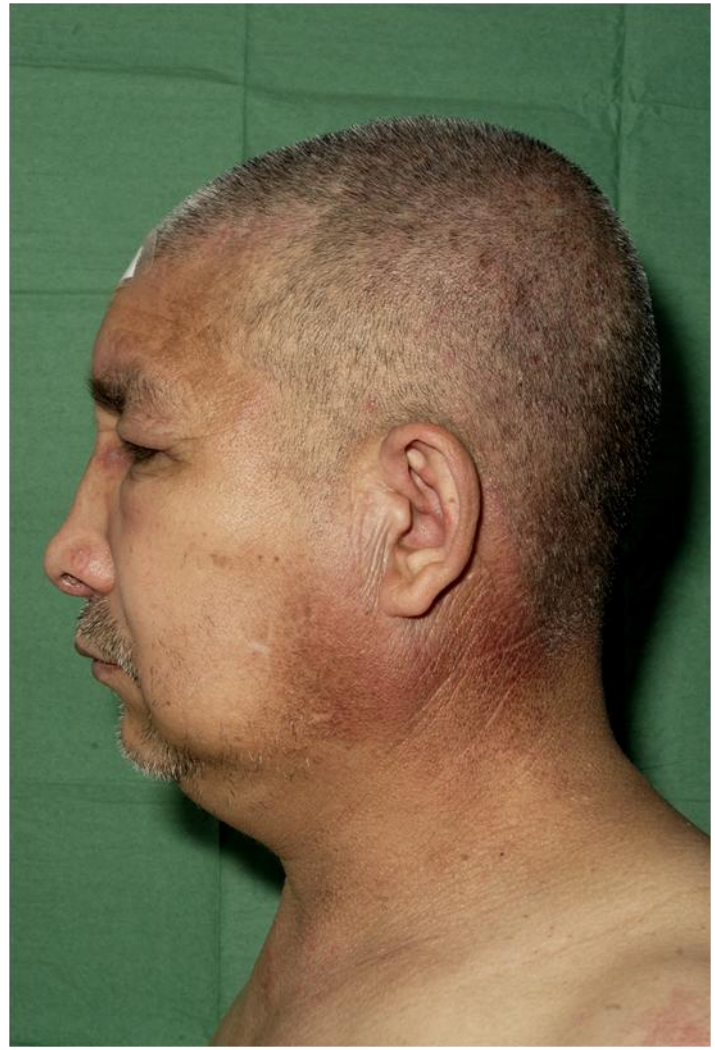
- overall 10% of PM/DM patients have malignancy
- no association in children or young/middle aged adults

PM/ DM: clinical features

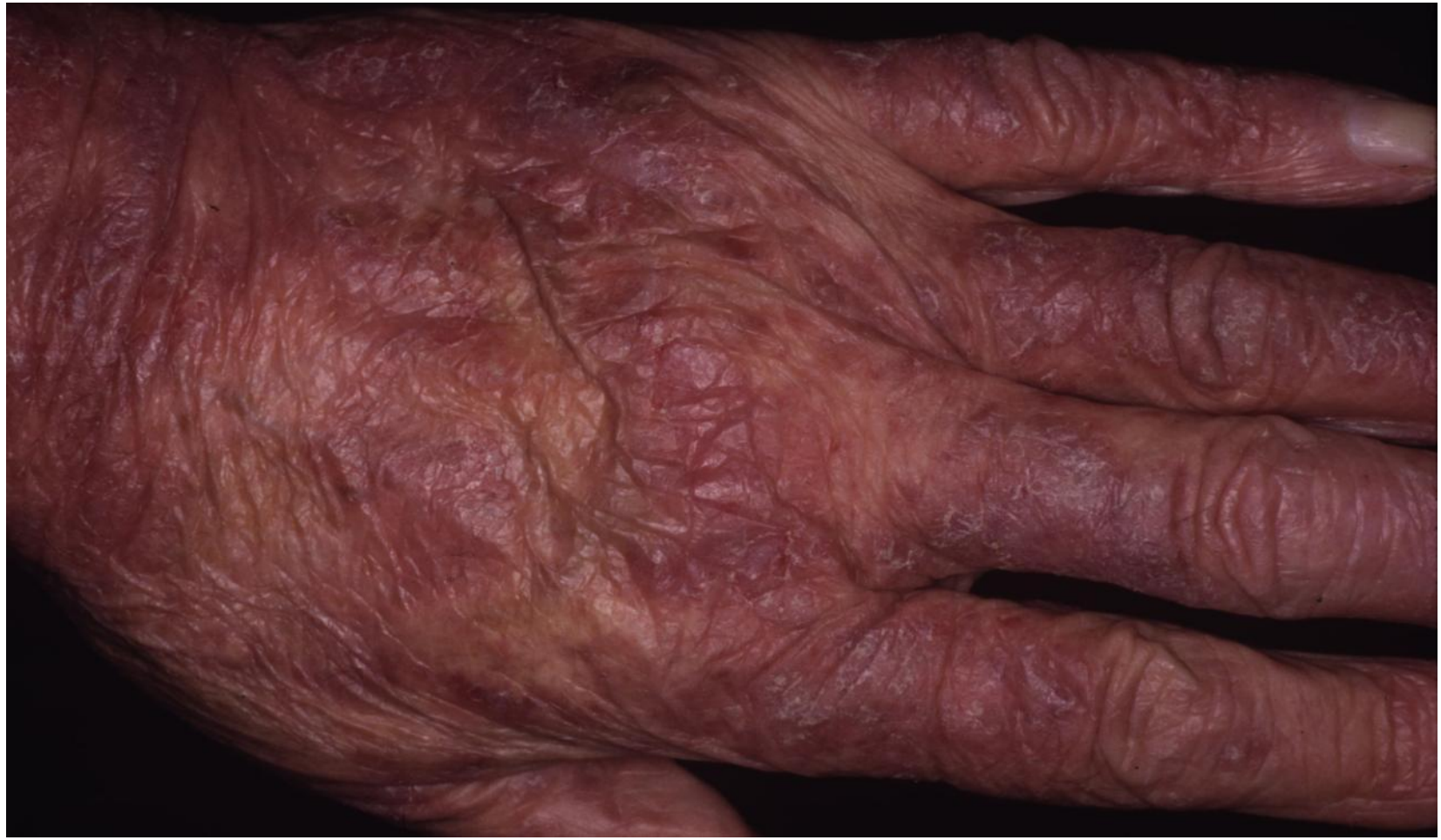
- Painless proximal muscle weakness in limb girdles & neck
- Ocular and facial weakness very unusual
- NB. Respiratory and pharyngeal muscle involvement
- **Heliotrope rash -** eyelids, malar region, forehead, nasolabial folds
- **Gottron's papules:** erythematous, raised over IP regions hands
- **Others:** periungal erythema, s/c calcification in juvenile DM

Periorbital oedema and heliotrope rash





Gottron's papules



DM/PM: diagnosis

- **Elevated muscle enzymes:** Creatine kinase (CK), AST, LDH
- **Electromyogram (EMG):** fibrillation, polyphasic action potentials
- **Muscle biopsy:** muscle necrosis, regeneration, CD8+ve T cell infiltrate
- **Autoantibodies:** up to 90% ANA+ve
  anti-Ro in 10%

Myositis specific antibodies: Anti-aminoacyl t-RNA synthetases (Jo-1 in 20%)
Anti Mi-2, anti PM/Scl, anti-SRP

EMG and MRI images

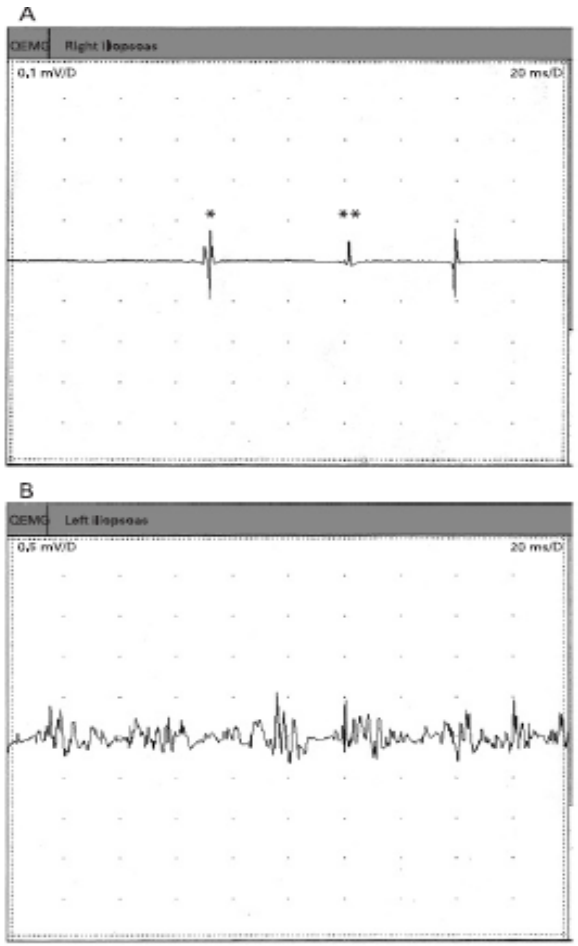
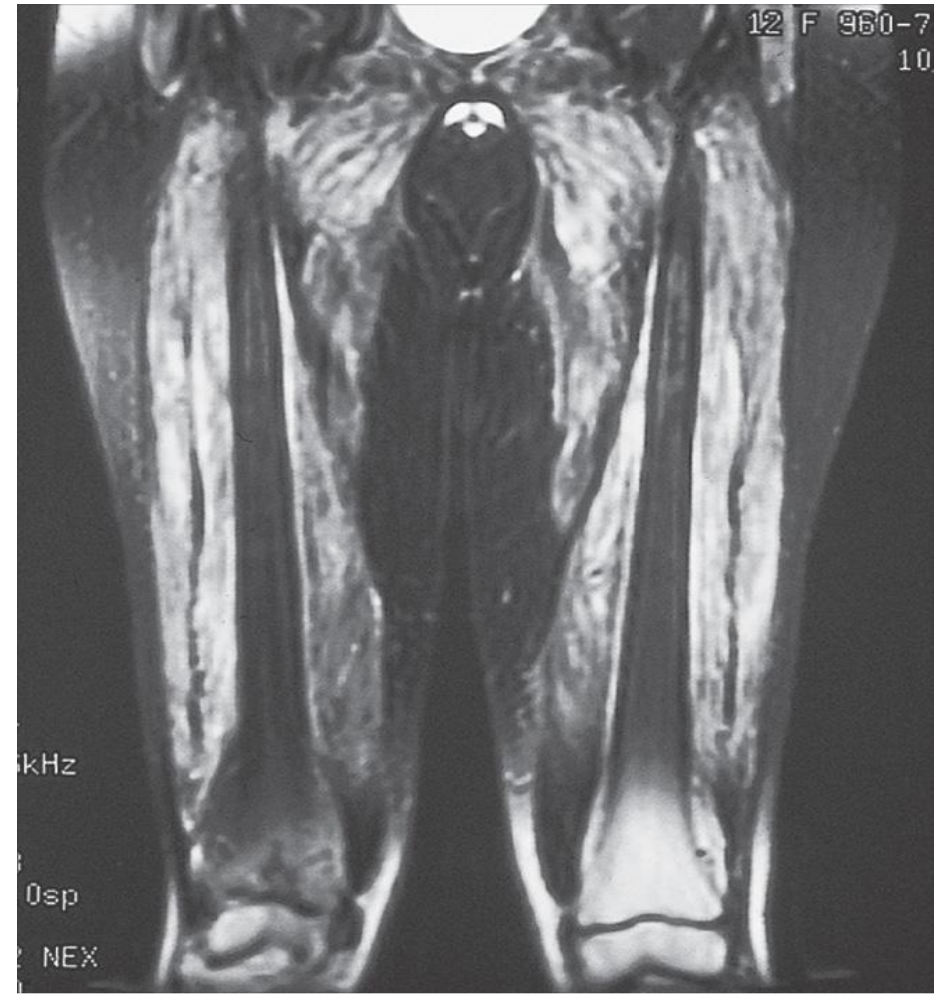
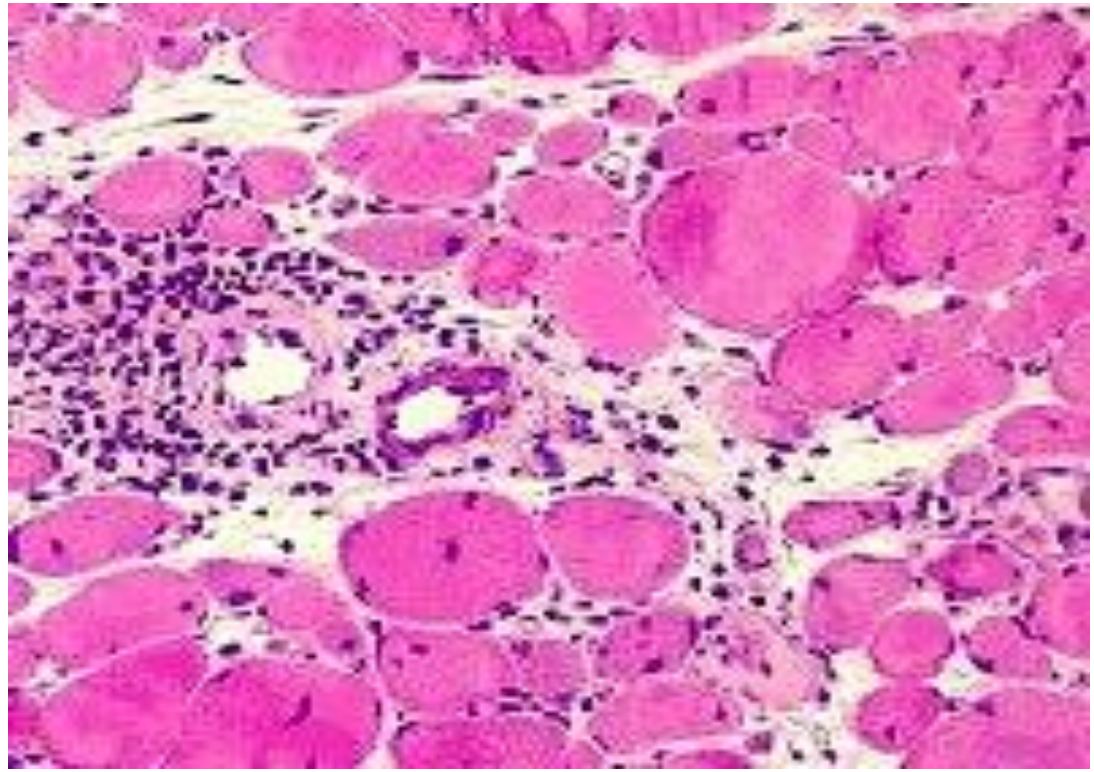


Figure 1 (A) Needle examination of the muscles at rest showed increased electrical activity after needle insertion, and there was spontaneous activity with frequent fibrillations (*) and positive sharp waves (**), which should not be present normally in healthy muscles and reflect muscle membrane instability. (B) During voluntary contraction, there was an increased number of abnormally small complex polyphasic motor units of short duration with clear myopathic features. These findings are consistent with a severe active myopathy.



Myositis: muscle biopsy



Overlap Syndromes

- **Two or more diseases occurring together each with their own specific autoantibody (promiscuous diseases)**

- **Two or more diseases occurring together with a common antibody (promiscuous antibody)**

(Venables, 2008)

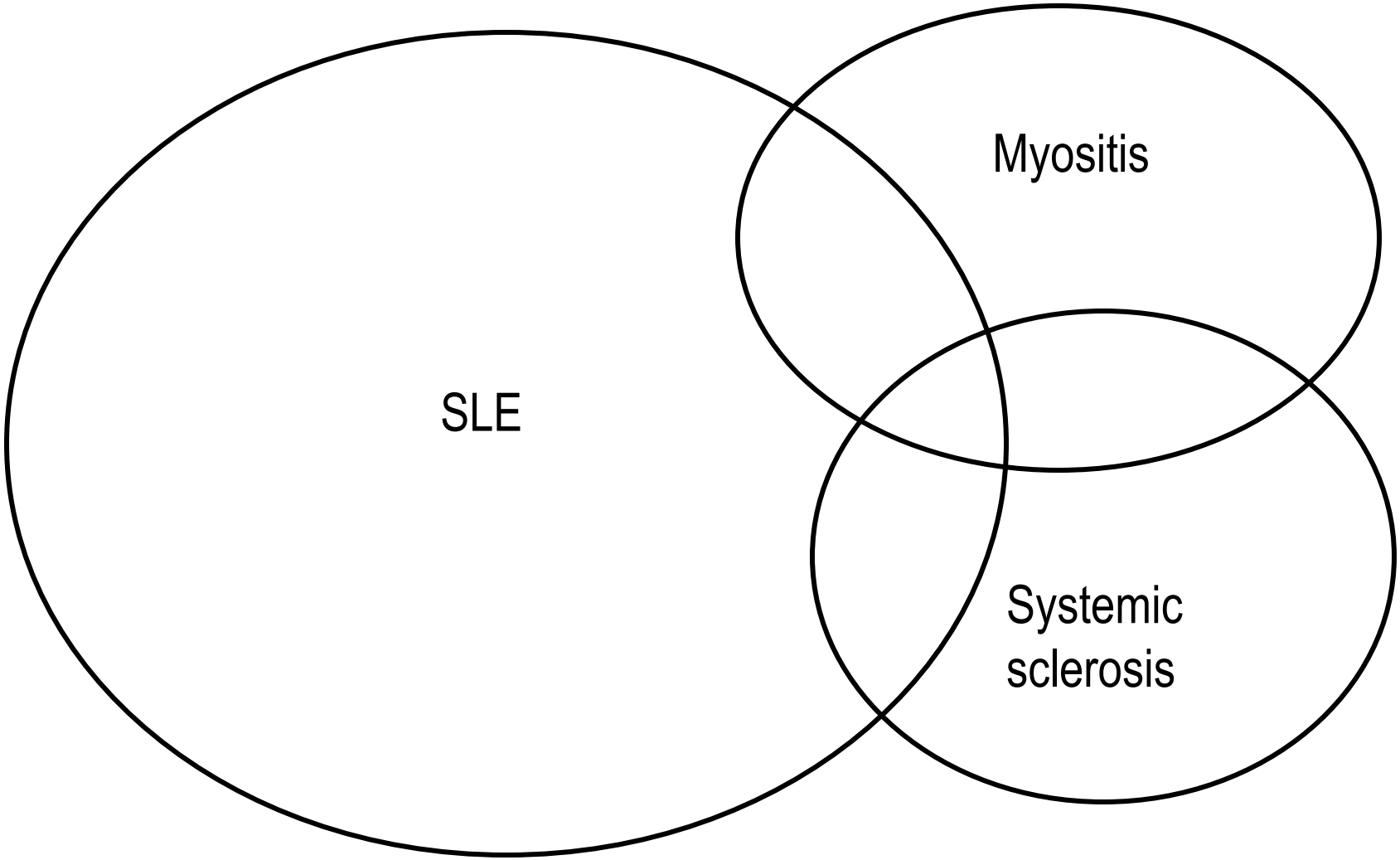
Overlap Syndromes

1. **Mixed connective tissue disease** (U1nRNP syndrome)
2. **Anti-synthetase syndrome** (eg. Anti-Jo1 disease**)**
3. **Polymyositis/scleroderma overlap**

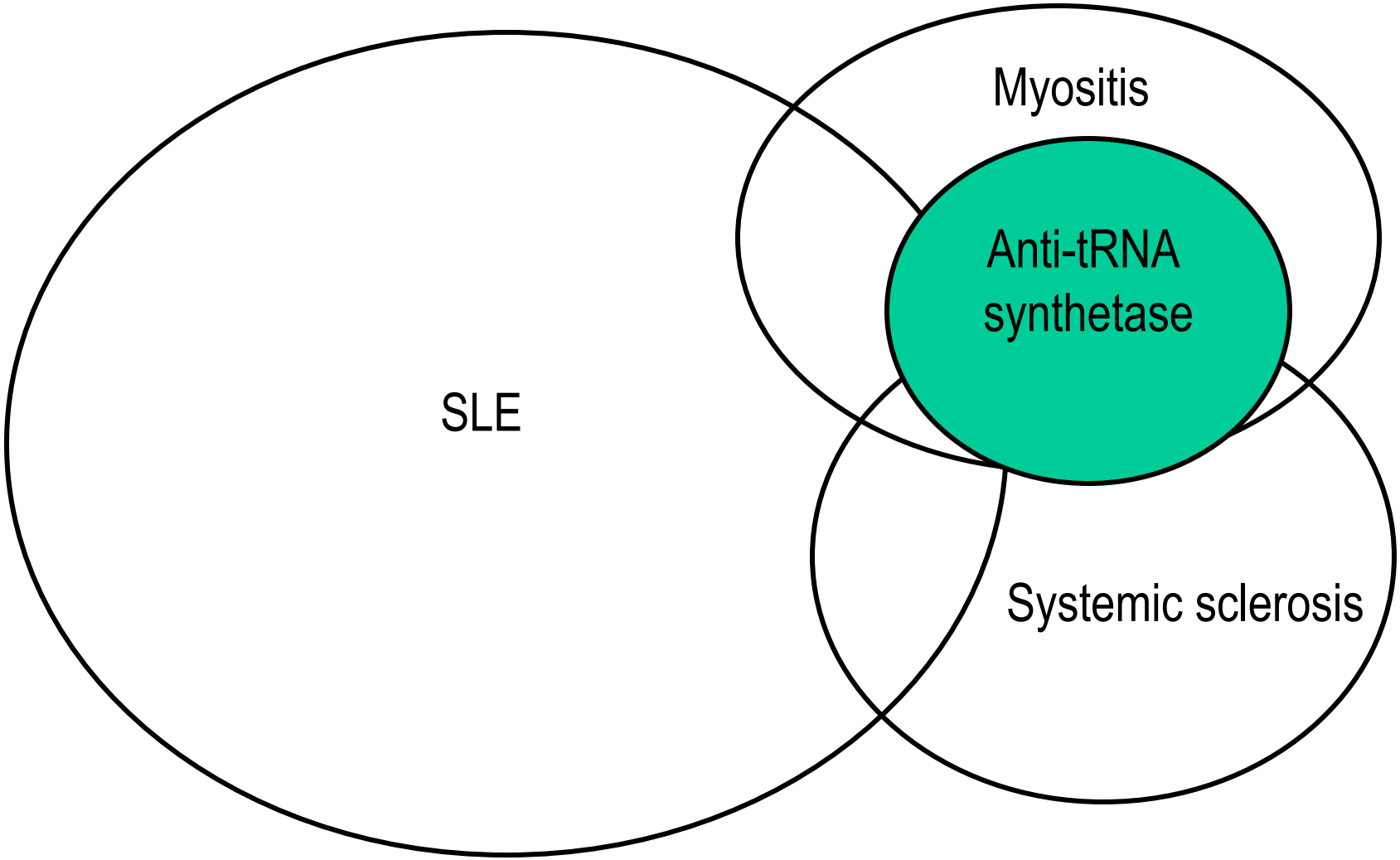
Part of a spectrum of disease:

- MCTD - tends towards SLE
- PM-Scl - tends towards cutaneous systemic sclerosis
- Anti-Jo-1 - tends towards systemic sclerosis + lung disease

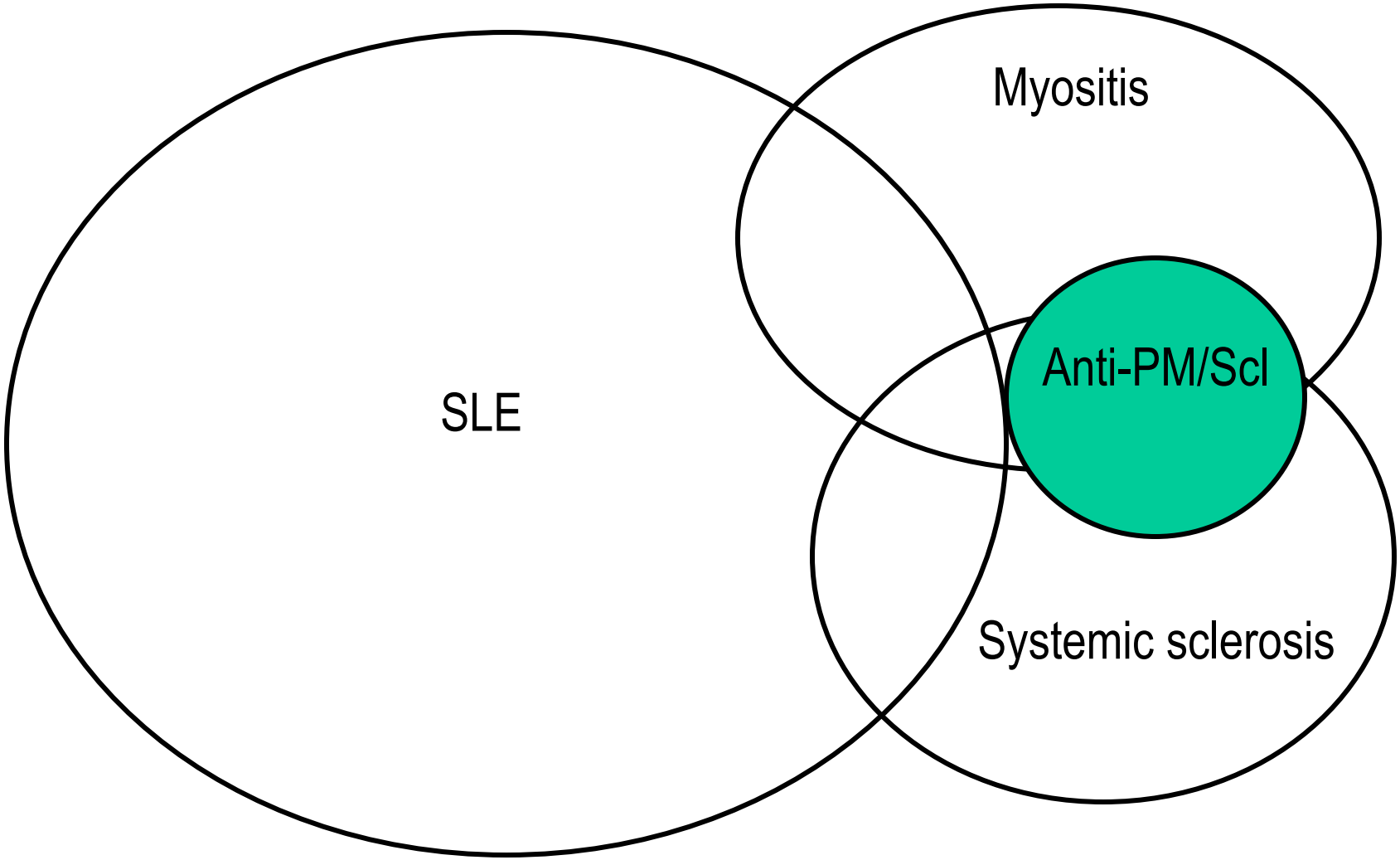
SLE / myositis / systemic sclerosis overlaps



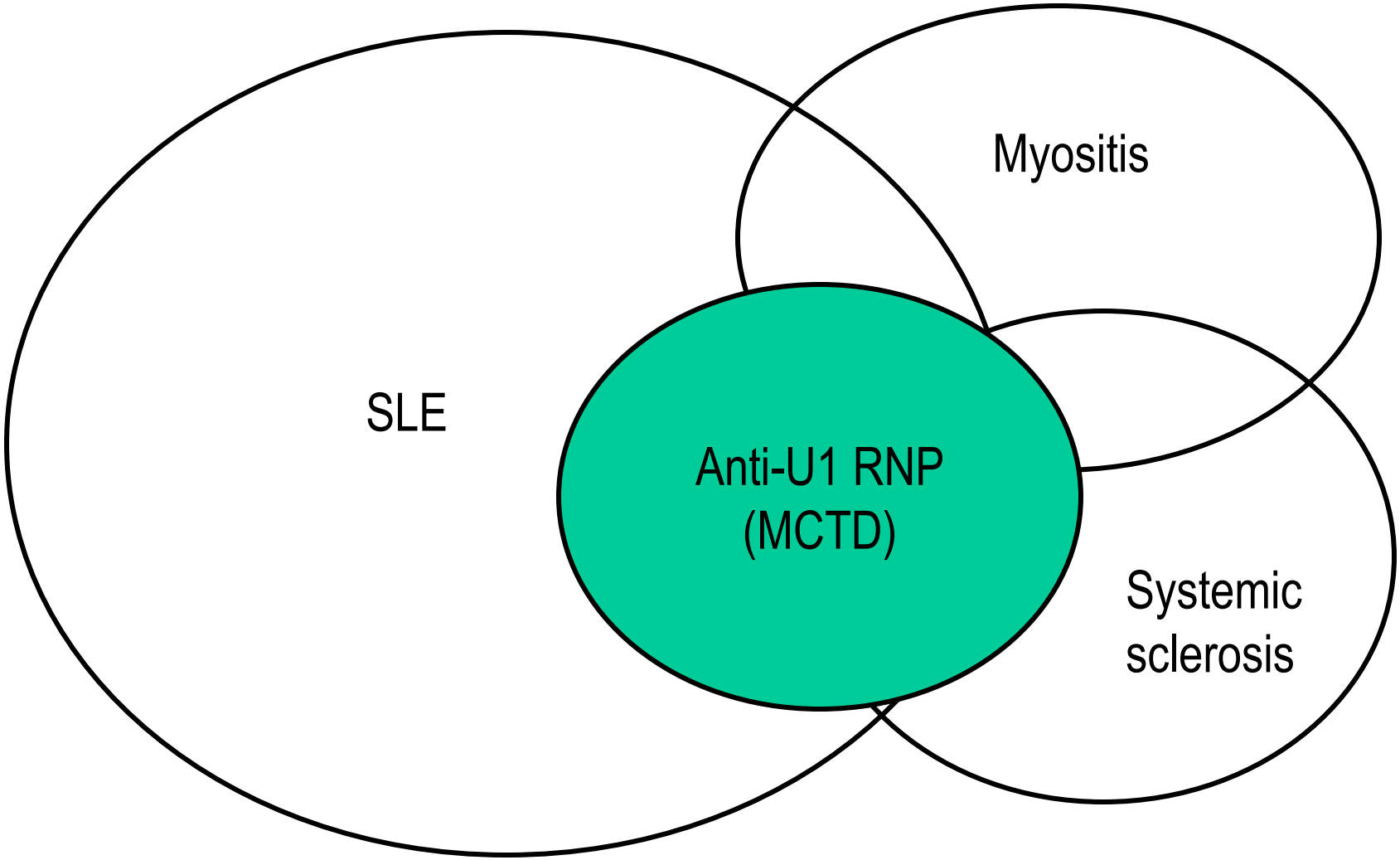
SLE / myositis / systemic sclerosis overlaps



SLE / myositis / systemic sclerosis overlaps

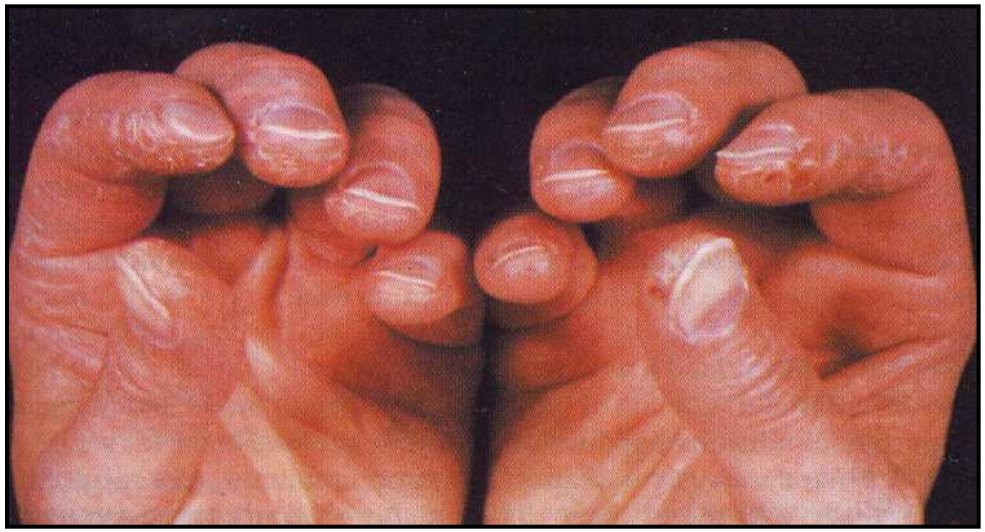


The most famous SLE / myositis / systemic sclerosis overlap

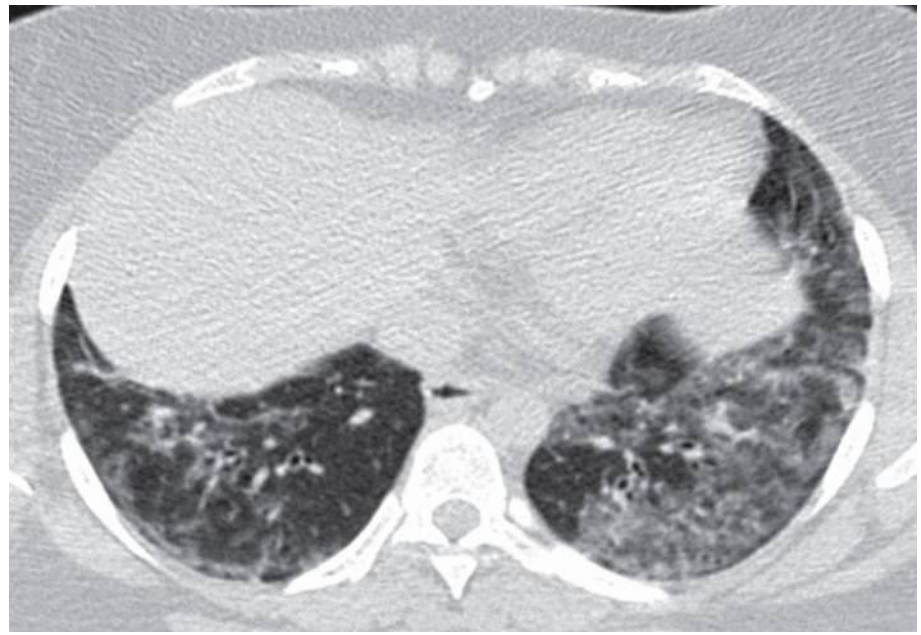


Overlap syndromes: similar spectrum of symptoms

- myositis
- interstitial lung disease
- arthritis
- Raynaud's and dactylitis



Characterisitic skin changes
'Mechanic's hands'



Interstitial lung disease

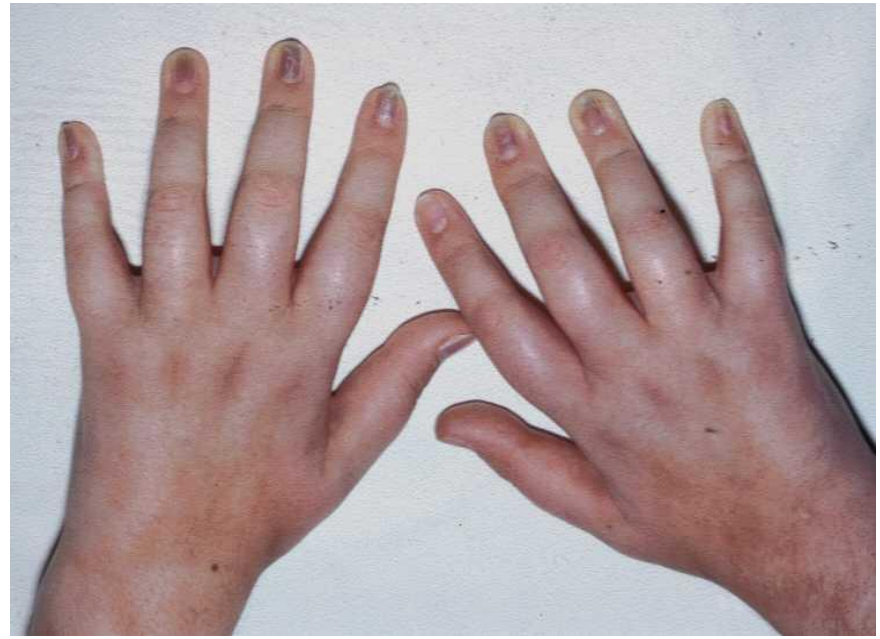
Significance of tRNA synthetase & PM/Scl Abs

- Both are markers for polymyositis
- Diseases are clinically similar and to MCTD
- Neither are screening tests
- Prognosis of PM/Scl better than tRNA synthetase
- Pulmonary fibrosis common in both

Clinical features of patients with antibodies to U1RNP

	% involvement
• Arthritis/ arthralgia	95
• Raynauds	85
• Oesophageal involvement	67
• Impaired lung diffusion	67
• Swollen hands	66
• Myositis	63
• Scleroderma	33
• Serositis	27
• Renal disease	10
• Cerebral involvement	10

Clinical features of MCTD



- Sausage fingers
- Myositis
  - Often a presenting feature
  - Responds well to steroids.
  - Rarely a chronic, long term problem
- Pulmonary fibrosis
  - Mortality less than other overlaps
- Pulmonary hypertension
  - May occur more frequently in patients with APL + anti-RNP
  - May respond to immunosuppression
- Scleroderma
  - May be limited or diffuse. CREST syndrome common

Connective tissue disease: treatment of mild disease

A. Paracetamol +/- NSAID

- Monitor renal function

B. Hydroxychloroquine

- arthropathy
- cutaneous manifestations
- mild disease activity

C. Topical corticosteroids

Connective tissue diseases: treatment of moderate disease

Indication:

- failure of hydroxychloroquine/NSAID
- internal organ involvement

Corticosteroids

- high initial dose to suppress disease activity (0.5-1.5mg/kg/day)
- iv methylprednisolone 3 x 0.5-1g per 24h
- initial oral dose for 4 weeks
- reduce slowly over 2-3 mths to 10 mg/d
- reduce slowly at 1mg per month

Connective tissue diseases: treatment of severe disease

Azathioprine

- moderate to severe disease 2.5 mg/kg/day
- effective steroid-sparing agent
- 20% neutropenia (3/1000 severe BM suppression)
- regular FBC & biochemistry monitoring

Cyclophosphamide

- severe organ involvement, iv pulsed or oral Rx
- eg. nephritis - 6 x 1 monthly iv pulses
- BM suppression, infertility, cystitis (acrolein)

SLE: novel treatment of severe disease

Mycophenolate mofetil (MMF)

- Reversible inhibitor of inosine monophosphate dehydrogenase
- Rate-limiting enzyme in *de novo* purine synthesis
- Lymphocytes – dependent upon *de novo* purine synthesis

Rituximab

- Anti-CD20 mAb therapy
- Leads to depletion of B cells
- Effective in lupus nephritis

Summary

CTD = multisystem autoimmune diseases

- Rare diseases; female preponderance
- Wide range of severity: from mild joint pain to fulminant, life threatening internal organ involvement
- Clinical features depend on organs affected

Treatment

- Symptomatic
- Immune-modulating
- Immunosuppressive