Systemic lupus erythematosus (SLE)

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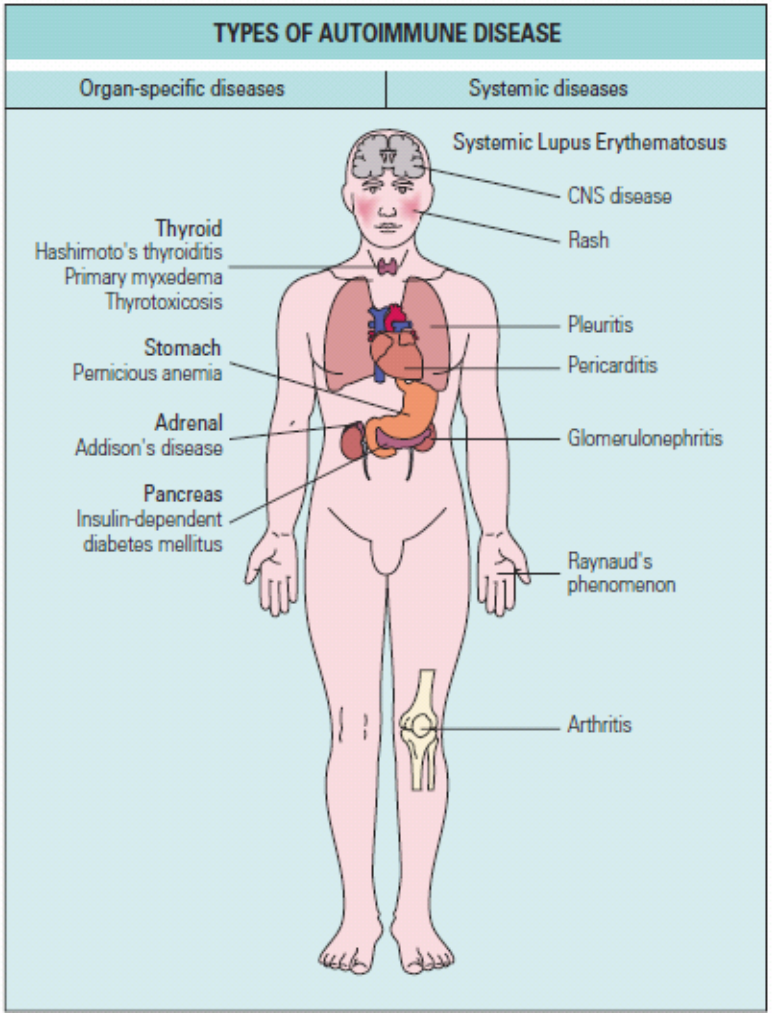
Introduction

- SLE is a chronic inflammatory disease most commonly affecting young women.
- SLE is characterized by hyperreactivity of B cells and overproduction of organ nonspecific autoantibodies.
- The cause or causes of SLE remains unknown, with several environmental factors as important potential triggers for those with underlying genetic influences.
- Typically the course of the disease is a series of remissions and exacerbations.
- With good management, the ten years survival may be over 90%.



Clinical picture

- **Variable**
- **Systemic features** - fever, loss of weight, fatigue (50-100%)
- **Organ involvement** – different extension and severity

Skin involement

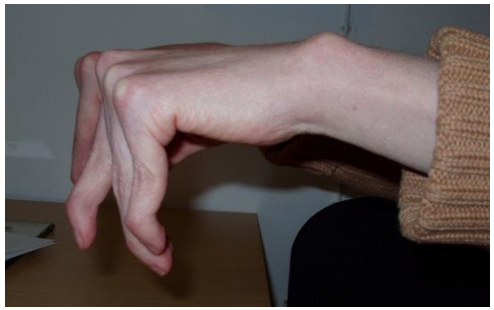
- **LE-specific skin lesions**
  - **Acute cutaneous LE** - malar "butterfly" rash, generalized erythema
  - **Subacute** – annular, papulosquamous (psoriasiform)
  - **Chronic** – „classic" discoid LE , localized discoid, generalized discoid, hypertrophic (verrucous) discoid LE, lupus profundus, mucosal LE

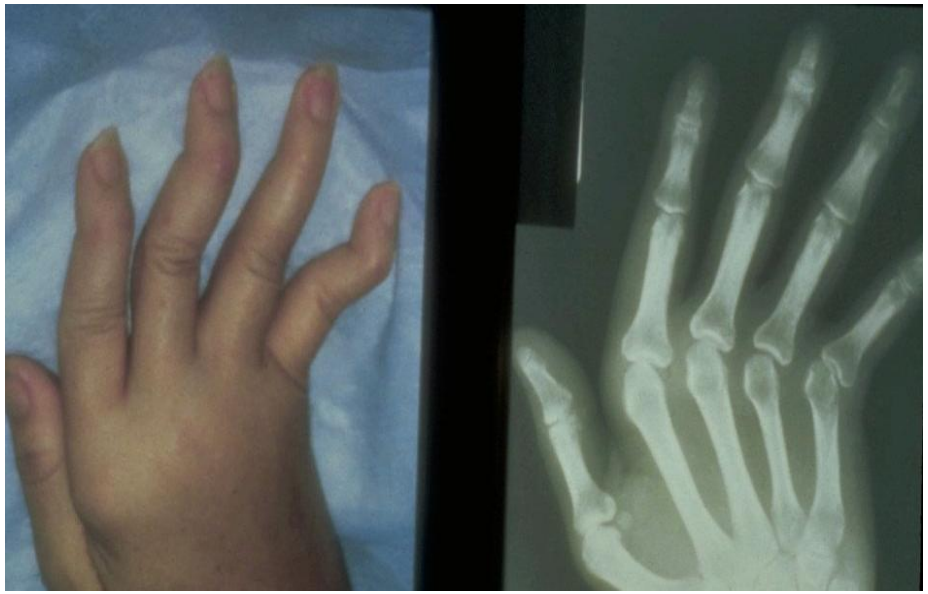
- **LE-non-specific lesions**
  - **Cutaneous vascular disease** – vasculitis (leukocytoclastic, palpable purpura), urticarial vasculitis, periarteritis nodosa–like
  - **Vasculopathy** - atrophy blanche, periungual telangiectasia, livedo reticularis, thrombophlebitis, Raynaud phenomenon, erythromelalgia
  - **Alopecia (non-scarring)** – "lupus hair", alopecia areata
  - **LE-non-specific bullous lesions**- epidermolysis bullosa–like bullous LE, dermatitis herpetiformis–like bullous LE
  - **Urticaria**

Joint involvement

- **non-erosive arthritis**
  - no destructions on X-ray
  - **Jaccoud's arthropathy -** in 10% to 35% of SLE patients.
    - It is a deforming non erosive arthropathy characterised by ulnar deviation of the second to 5th fingers with MCP subluxation.

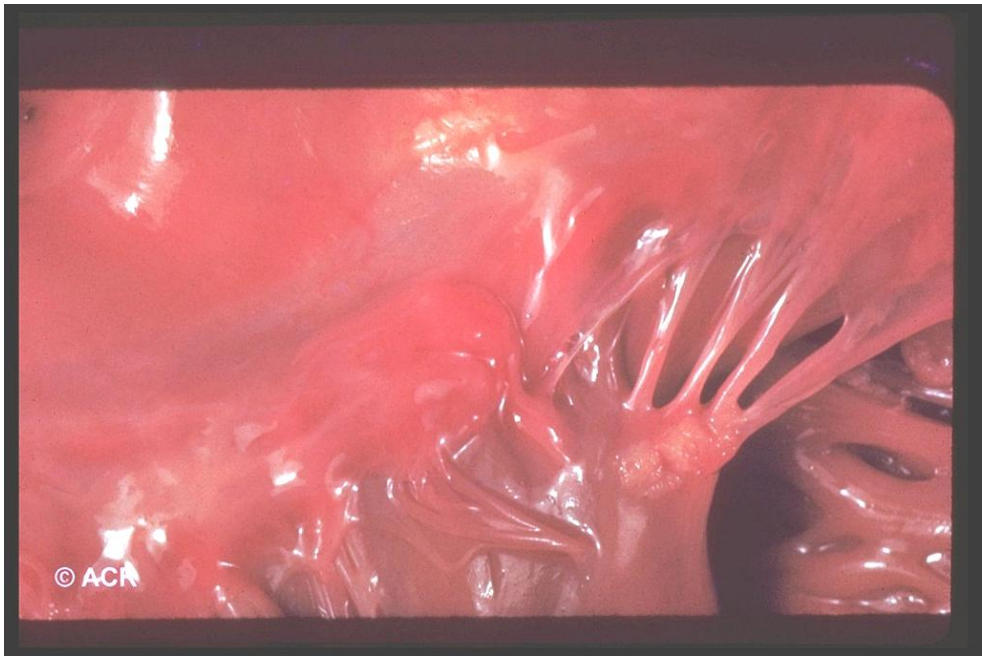
- monoarthritis
- oligoarthritis
- polyarthritis

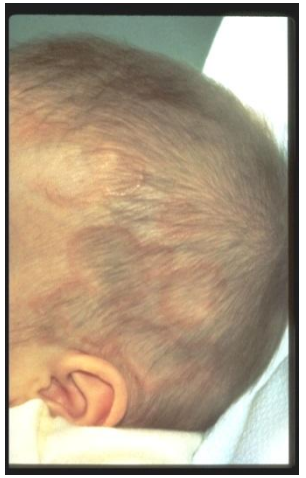




Heart involement

- Pericarditis
- Myocarditis
- Libmann-Sacks endocarditis
- Coronary artery disease
- Conduction disturbances
- Congenital heart block
  - Neonatal Lupus

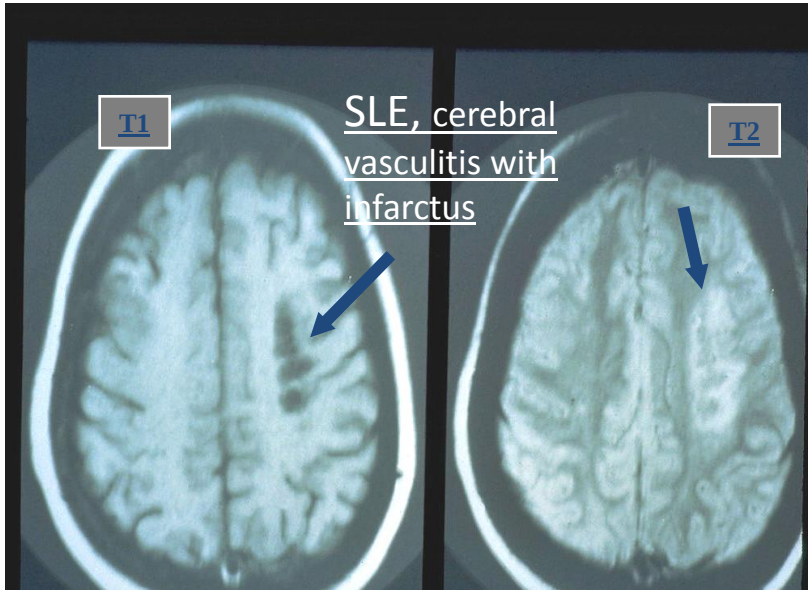




CNS involement

- **Central** - aseptic meningitis, cerebrovascular accident, demyelinating syndrome, headache, movement disorder, seizure disorder, myelopathy, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis.

- **Periferal** - Guillain-Barre syndrome, autonomic disorder, mononeuropathy, single/multiplex, myasthenia gravis, cranial neuropathy, plexopathy, polyneuropathy.



Lung involvement

Acute

- **lupus pneumonitis** - fever, dyspnea, cough, pleuritic chest pain, and, occasionally, hemoptysis. Chest radiography and CT scan show unilateral or bilateral alveolar infiltrates with ground-glass opacification.
- **diffuse alveolar hemorrhage-** is a very serious condition in SLE, mortality from 50% to 90%.
  -dyspnea, cough, fever, infiltrates and a dramatic fall in hemoglobin. Hemoptysis is present in only 50% of the cases.

  -vasculitis with pulmonary capillaritis and a distinctive small-vessel vasculitis/microangiitis of the arterioles and small muscular pulmonary arteries.

Chronic

- **pleural involvement** 30% to 60% of patients with SLE. Pleural effusions may occur and are usually small but can occasionally be massive, frequently bilateral.
- **diffuse interstitial pneumonitis** (progressive dyspnea, restrictive ventilatory disturbance).
- **pulmonary hypertension,** 0.5% to 14% of SLE patients, can occur in lupus patients due to either the disease process or complications such as pulmonary embolism, valvular heart disease, and interstitial lung disease.

Renal involement

- **One of the most serious manifestations**
- From silent lupus nephritis, to nephrotic syndrome and decreasing glomerular filtration rate with rapid progression to end-stage renal disease (ESRD).
- The features most commonly seen in lupus nephritis are **proteinuria, presence of urinary casts, hematuria, pyuria, a rising serum creatinine value, and hypertension.**
- Renal biopsy is essential

- Minimal mesangial LN- class I
- Mesangial proliferative LN- class II
- **Focal proliferative LN - class III**
- **Diffuse LN- class IV**
- Membranous LN- class V
- Advanced sclerosis LN- class VI

Gastrointestinal involement

- Any area of the gastrointestinal tract may be involved by SLE or its complications:
  - esophageal disease
  - mesenteric vasculitis
  - inflammatory bowel disease
  - pancreatitis
  - liver disease
  - peritonitis
- About 50% of patients may experience anorexia, nausea, and vomiting without clear evidence of involvement of the gastrointestinal tract.

Haematological changes

- **Anemia**
  - 50% percent of patients with SLE have anemia
  - anemia of chronic disease
  - iron-deficiency anemia
  - autoimmune hemolytic anemia
- **Leucopenia**
  - lymphocytopenia is usually associated with antibodies to lymphocytes and is associated with active SLE.
- **Thrombocytopenia**
  - antiplatelet antibodies are a frequent finding in SLE
- **Abnormalities in coagulation**
  - Antiphospholipid antibodies
    - Lupus anticoagulans
    - Anticardiolipin antibodies

Laboratory findings

- **Nonspecific changes in inflammation**
  - increased ESR
  - CRP – usually normal, or low/medium increas
- **Organ involvement**
  - proteinuria, hematuria
  - increase in ALT, AST, usually without increase in ALP
- **Immunology**

  - autoantibodies
  - low C3,C4, CH50
  - hypergamaglobulinemia
  - increase in immune complexes

Autoantibodies

- **ANA autoantibodies (95% pacients)**
- Some autoantibodies have a high diagnostic specificity for systemic lupus erythematosus (SLE), particularly anti-Sm, anti-dsDNA, anti-ribosome P, and PCNA.
- The levels of some autoantibodies parallel disease activity.
- Certain autoantibodies are associated with clinical subsets of disease.
- Some autoantibodies may directly or indirectly cause cell or tissue injury.

- **dsDNA** –highly specific for SLE with renal (40-90% pacients)
- **Sm**- highly specific for SLE with renal disease
- **Ribosomal P0, P1, P2**- highly specific for SLE, increased risk of neuropsychiatric disease
- **RNA Helicase A** – marker for early lupus
- **Anti-histone antibodies –** drug induced lupus

ACR/SLICC criteria for SLE

Table 2

ACR CRITERIA FOR DIAGNOSIS OF SLE

Condition	Description
Malar rash	A "butterfly rash" of flat or raised fixed erythema tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging associated with scarring
Photosensitivity	A reaction to sunlight causing rash that may last for several weeks after brief sun exposure
Oral ulcers	Often painless oral or nasopharyngeal ulceration
Arthritis	Nonerosive arthritis tenderness, swelling, or effusion involving 2 or more peripheral joints
Serositis	Pleuritis (chest pain on inspiration) or pericarditis; note that premature coronary artery disease is associated with inflammatory conditions like SLE
Renal disorder	Persistent proteinuria
Neurologic disorder	Seizures or psychosis in the absence of offending drugs or known metabolic derangements
Hematologic disorder	Leucopenia (often an early sign), hemolytic anemia, lymphopenia, thrombocytopenia in the absence of offending drugs
Immunologic disorder	Positive LE cell preparation, anti-DNA, anti-Sm, or false positive serologic test for syphilis
Antinuclear antibody	An abnormal titer of antinuclear antibody at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

ACR= American College of Rheumatology; LE = lupus erythematosus; SLE = systemic lupus erythematosus.
Adapted from references 3, 4, and 7.

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria	Immunologic Criteria
1. Acute Cutaneous Lupus*	1. ANA
2. Chronic Cutaneous Lupus*	2. Anti-DNA
3. Oral or nasal ulcers *	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab *
5. Arthritis *	5. Low complement (C3, C4, CH50)
6. Serositis *	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal *	
8. Neurologic *	
9. Hemolytic anemia	
10. Leukopenia *	
11. Thrombocytopenia (<100,000/mm^3)	

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

Therapy

- **The management of patients with systemic lupus erythematosus (SLE) is decided on an individual basis, guided by the degree and severity of specific symptoms and organ system involvement.**

- **Non-steroidal anti-inflammatory drugs (NSAIDs)** are an important first-line therapy for the treatment of constitutional signs, musculoskeletal symptoms, and mild serositis.
- **Antimalarial agents** are frequently effective for chronic constitutional signs and cutaneous and musculoskeletal manifestations, with an excellent therapeutic benefit-to-toxicity profile.
- Most clinical manifestations of SLE respond well to **corticosteroids**, with a wide dose range depending on the organ systems involved and the degree of severity.
- **Immunosuppressive agents** are useful in patients with life- or organ-threatening manifestations, as well as for steroid sparing in patients who are either steroid dependent or steroid refractory.
  - **Azathioprin**- The usual dose of azathioprine is 1 to 2 mg/kg/day. In most controlled trials in lupus, azathioprine has been initially combined with corticosteroids.
  - **Methotrexate**- arthritis
  - **Mykophenolate mofetil-** nephritis
  - **Cylophosphamide**- in combination with corticosteroids in lupus nephritis, CNS involvement
  - **Cyklosporine A** -lupus nephritis
- **Belimumab-** is a human monoclonal antibody that inhibits B-cell activiting factor (BAFF), also known as B-lymphocyte stimulator (BLyS).
- **Rituximab** - is a chimeric murine-human monoclonal antibody that binds specifically to the CD20 antigen.

Inflammatory muscle disease

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Inflammatory muscle disease

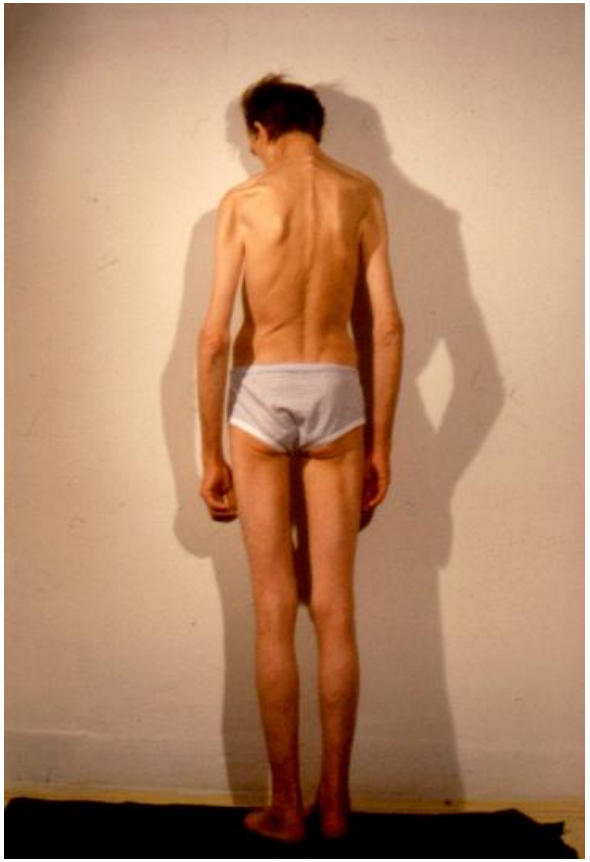
- **Chronic inflammation of striated muscle** (myositis) with characteristic cutaneous features (rash of dermatomyositis) and a variety of systemic complications.
- Cellular and humoral immunologic features include serum **autoantibodies** that are associated with clinical syndromes.
- Usually there is **painless, symmetrical proximal muscle weakness** with or without rash.
- Serum **muscle enzymes are increased**, most notably the creatine kinase.
- An **abnormal electromyogram** shows myopathy, and a muscle biopsy demonstrates inflammatory infiltrates.
- **Involvement of other organ systems** includes the lung, heart, gastrointestinal tract, and joints.

Types of inflammatory muscle disease

- Polymyositis
- Dermatomyositis
- Juvenile dermatomyositis
- Inclusion body myositis
- Myositis asociated with other connective tissue disease
- Myositis asociated with malignancy

Clinical picture

Syndrome	Est. frequency
1. Painless proximal weakness (over 3-6 mo)	**55%**
2. Acute or subacute proximal pain and weakness (over weeks to 2 mo)	**30%**
3. Insidious proximal and distal weakness	10%
4. Proximal myalgia alone	5%
5. Dermatomyosity rash alone, extremity edema	<1%



Dermatologic manifestation

- **DM has a characteristic skin rash** that may precede, develop simultaneously with, or follow muscle symptoms.
- **Gottron papules** and the **heliotrope rash.**
  - Gottron papules are **scaly, erythematous papules and plaques** located over bony prominences, particularly the metacarpophalangeal and proximal and distal interphalangeal joints of the hands.
- **Gottron sign** is a **macular erythema** that occurs in the same distribution and over other extensor areas such as the elbows, knees, and ankles.
- Cutaneous photosensitivity with **facial erythema**, or **a "V sign"** over the anterior chest may also be seen in DM.

Lung involvement

1. Non-pulmonary etiology

-Respiratory muscle weakness

-Cardiac involvement

2. Pulmonary etiology

- Interstitial lung disease

-Non-specific interstitial pneumonitis (NSIP)

-Usual interstitial pneumonitis (UIP)

-Diffuse alveolar damage (DAD)

-Organizing pneumonias (cryptogenic organizing pneumonia—COP)

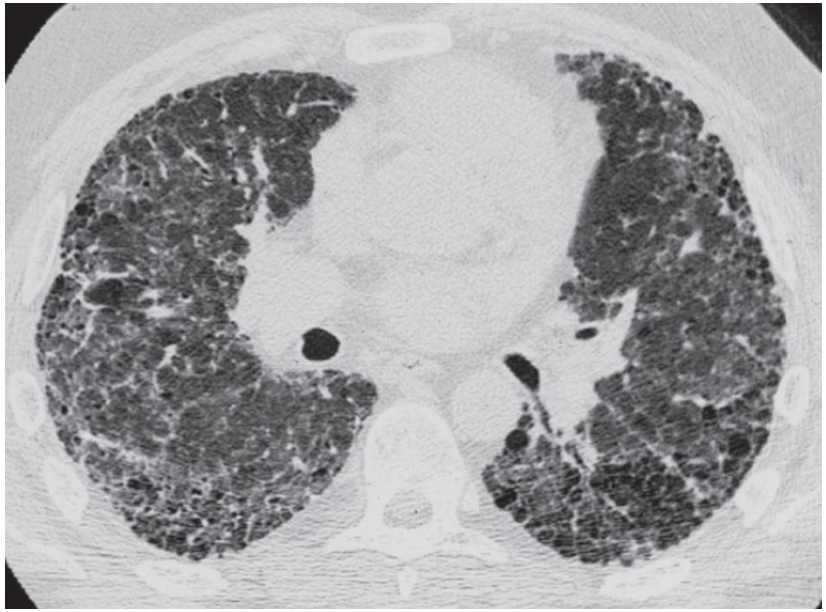
-Pulmonary hypertension

-Alveolar hemorrhage

-Pneumomediastinum

-Infection (with or without aspiration)

-Drug induced (e.g., methotrexate)



Other organ involvement

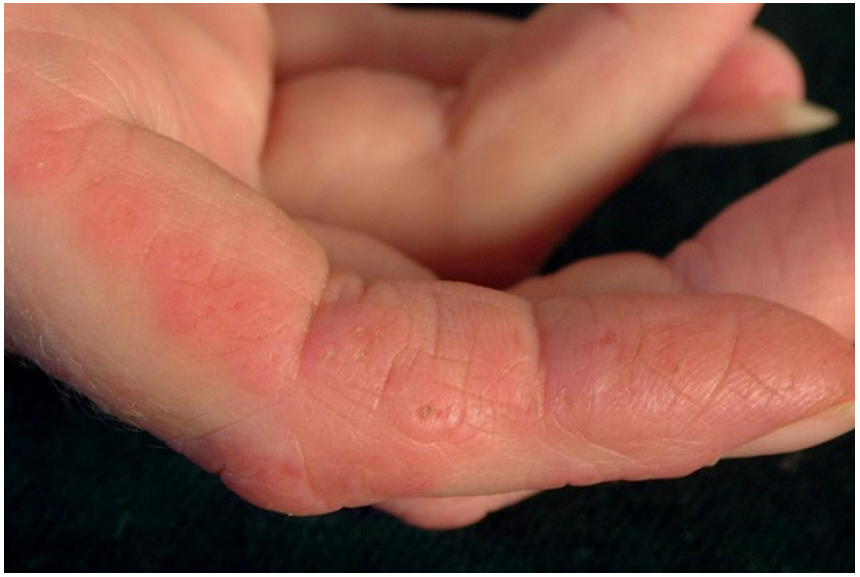
- **Joint -** polyarthralgias or polyarthritis (nonerosive)

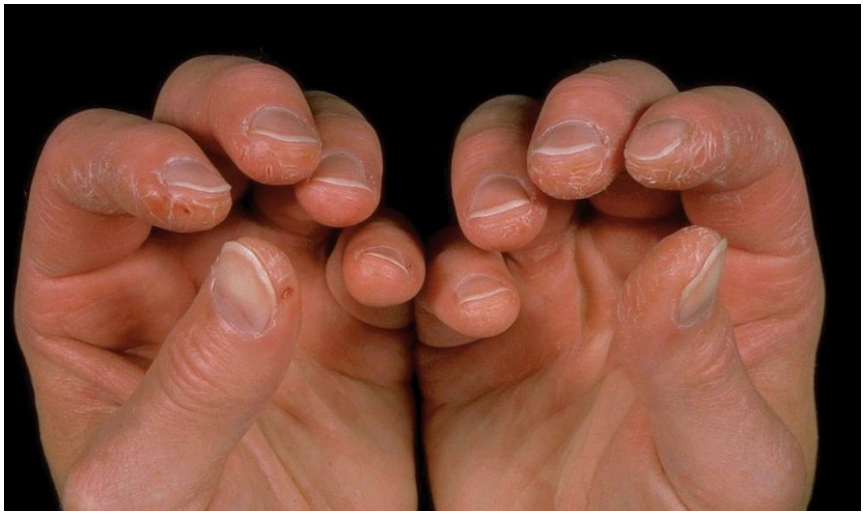
- **GIT** - the pharyngeal musculature is striated and thus can become inflamed and weak like striated muscle in other locations.
  - **dysphonia** and oropharyngeal **swallowing** dysfunction (upper dysphagia) can develop with difficulty in the initiation of deglutition or nasal regurgitation of liquids
  - **aspiration** of oral contents leads to chemical pneumonitis, sometimes complicated by secondary bacterial infection.

- **Heart -** subclinical heart involvement is common in PM-DM. The most common finding is a rhythm disturbance, presumably from inflammatory or fibrotic alteration of the conducting system, and complete atrioventricular block has been reported.

Antisynthetase syndrome

- Myositis
- Interstitial lung disease
- Arthritis
- Raynaud‘s phenomenon
- Fever
- Mechanic‘s hands
- Antisynthetase antibodies (anti-Jo-1)





Laboratory

Serum muscle enzymes

- CK, aldolase, aspartate (AST) and alanine aminotransferases (ALT), and lactate dehydrogenase.
- The finding of increased serum transaminases in a patient with fatigue and muscle weakness often leads to an erroneous diagnosis of hepatitis and an unnecessary liver biopsy.
- During a flare of disease, the serum CK will usually increase weeks before overt muscle weakness develops.
- Serum myoglobin can be a useful marker of muscle damage, is elevated at least as frequently as the serum CK, and is cleared by the kidney.

Clasification criteria

BOHAN AND PETER CRITERIA FOR THE DIAGNOSIS OF POLYMYOSITIS AND DERMATOMYOSITIS

Individual criteria

1 . Symmetric proximal muscle weakness

2. Muscle biopsy evidence of myositis

3. Increase in serum skeletal muscle enzymes

4. Characteristic electromyographic pattern

5. Typical rash of dermatomyositis

Diagnostic criteria

Polymyositis:

Definite: all of 1-4

Probable: any 3 of 1-4

Possible: any 2 of 1-4

Dermatomyositis:

Definite: 5 plus any 3 of 1-4

Probable: 5 plus any 2 of 1-4

Possible: 5 plus any 1 of 1-4

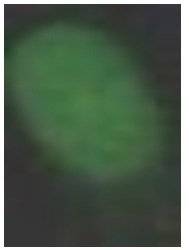
Modified from Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975;292:344-347,403-407.

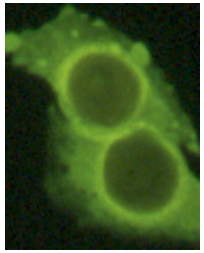
Autoantibodies

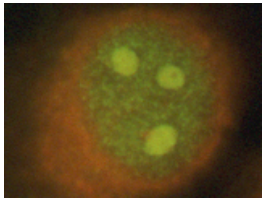
Antibodies	Nature of target antigens	Frequency (%)	Clinical significance
Myositis-specific autoantibodies			
Anti-ARS			Antisynthetase syndrome (myositis, ILD, polyarthritis, mechanic's hand, Raynaud's phenomenon and fever)
– Anti-Jo-1	Histidyl-tRNA synthetase	15–20	
– Anti-PL-7	Threonyl-tRNA synthetase	5–10	
– Anti-PL-12	Alanyl-tRNA synthetase	<5	
– Anti-EJ	Glycyl-tRNA synthetase	5–10	
– Anti-OJ	Isoleucyl-tRNA synthetase	<5	
– Anti-KS	Asparaginyl-tRNA synthetase	<5	
– Anti-Zo	Phenylalanyl-tRNA synthetase	<1	
– Anti-YRS	Tyrosyl-tRNA synthetase	<1	
Anti-SRP	Signal recognition particle	5–10	Necrotizing myopathy
Anti-Mi-2	218/240 kDa helicase family proteins, components of nucleosome remodeling deacetylase	5–10	DM
Anti-CADM-140	Interferon induced with helicase C domain protein 1	20~35 in DM (50~70 in C-ADM)	Specific in C-ADM
Anti-p155(/140)	Transcriptional intermediary factor 1-γ	15–20 in DM	DM, especially in malignancy-associated DM
Anti-NXP2 (anti-MJ)	NXP2	<5	Juvenile DM (calcinosis and muscle contractures)
Anti-SAE	SAE	<1	DM
Anti-200/100	Unknown 200/100 kDa proteins	7 (42 in necrotizing myopathy)	Necrotizing myopathy
Myositis-associated autoantibodies			
Anti-U1RNP	U1 small nuclear RNP	10	MCTD, overlap syndrome
Anti-Ro/SSA	52 kDa and 60 kDa protein	13–37 (anti-Ro52) 4 (anti-Ro60)	Associated with anti-ARS
Anti-Ku	70/80 kDa DNA-PK regulatory subunit	20–30	PM–SSc overlap in Japanese
Anti-PM-Scl	Nucleolar protein complex of 11–16 proteins	8–10	PM–SSc overlap in Caucasian

ARS: Aminoacyl-tRNA synthetases; C-ADM: Clinically amyopathic dermatomyositis; DM: Dermatomyositis; ILD: Interstitial lung disease; MCTD: Mixed connective tissue disease; PM: Polymyositis; RNP: Ribonucleoprotein; SAE: Small ubiquitin-like modifier activating enzyme; SSc: Systemic sclerosis.

Medscape







Therapy

1. Glucocorticoids
2. Immunosuppressive drugs
3. Combination of drugs
4. Physical therapy

Therapy

- **Corticosteroids** - Daily oral corticosteroids are the primary initial therapy used to treat myositis. A common practice is to begin with prednisone at 1 to 2 mg/kg/day.
  - In cases of severe myositis, and those with significant active pulmonary, cardiac, or gastrointestinal disease or other poor prognostic features, intravenous methylprednisolone, 1 g/day for 3 consecutive
- **Methotrexate -**the first choice for corticosteroid-sparingtherapy in patients with an inflammatory myopathy.
- **Azathioprine-** is considered to be as effective as methotrexate in managing corticosteroid-resistant myositis patients, yet the time to response may be longer than that seen in methotrexate.
- **Mycophenolate -** small case series suggest that some corticosteroid-resistant PM/DM patients respond to mycophenolate mofetil.
- **Cyclophosphamide -** appears to be less effective and more toxic for myositis than methotrexate or azathioprine, but it may be useful in cases with vasculitis and interstitial lung disease.
- **Intravenous gammaglobulin** uncontrolled and controlled studies suggest the effectiveness of intravenous gammaglobulin (IVIG) in adults and children with DM and PM.
- **Cyklosporin** - small case series suggest that some corticosteroid-resistant adult and juvenile patients may benefit from cyclosporine therapy.
- **Rituximab -** is a chimeric murine-human monoclonal antibody that binds specifically to the CD20 antigen.