Diffuse connective tissue diseases

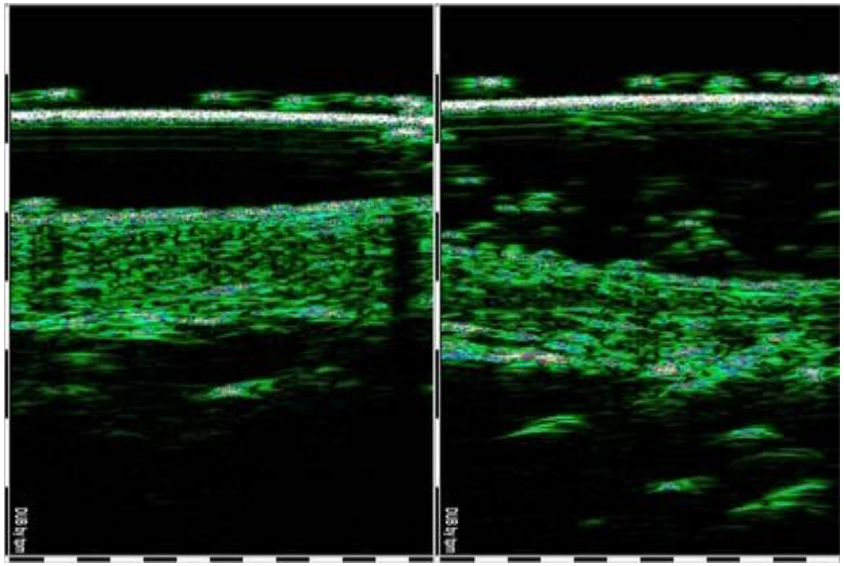
Membres

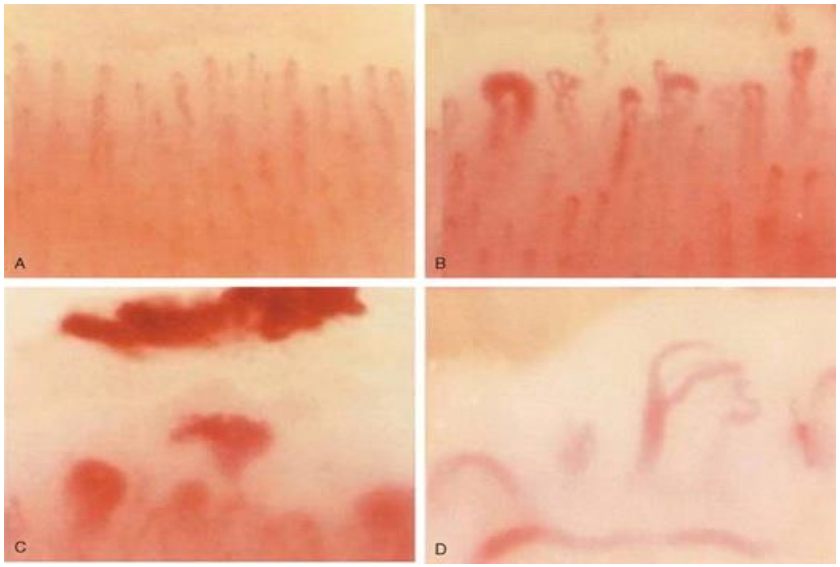
- Rheumatoid arthritis
- Systemic lupus eritematous
- Systemic sclerosis
- Idiopathic inflammatory myopathies
- Mixed connective tissue disease
- Sjogren sindrom

Systemic sclerosis

Definition

- **Systemic sclerosis** (SSc) is a heterogeneous and rare, multisystem connective tissue disease, based on autoimmunological processes, vascular endothelial cell damage and an extensive activation of fibroblasts, causing a massive production and accumulation of extracellular matrix proteins and collagen.





Epidemiology

- Incidence is about 19 cases per million per year
- Peak occurrence in ages 35–65
- Greater in females: 7–12:1
- Rare in children and men under 30

Etiology

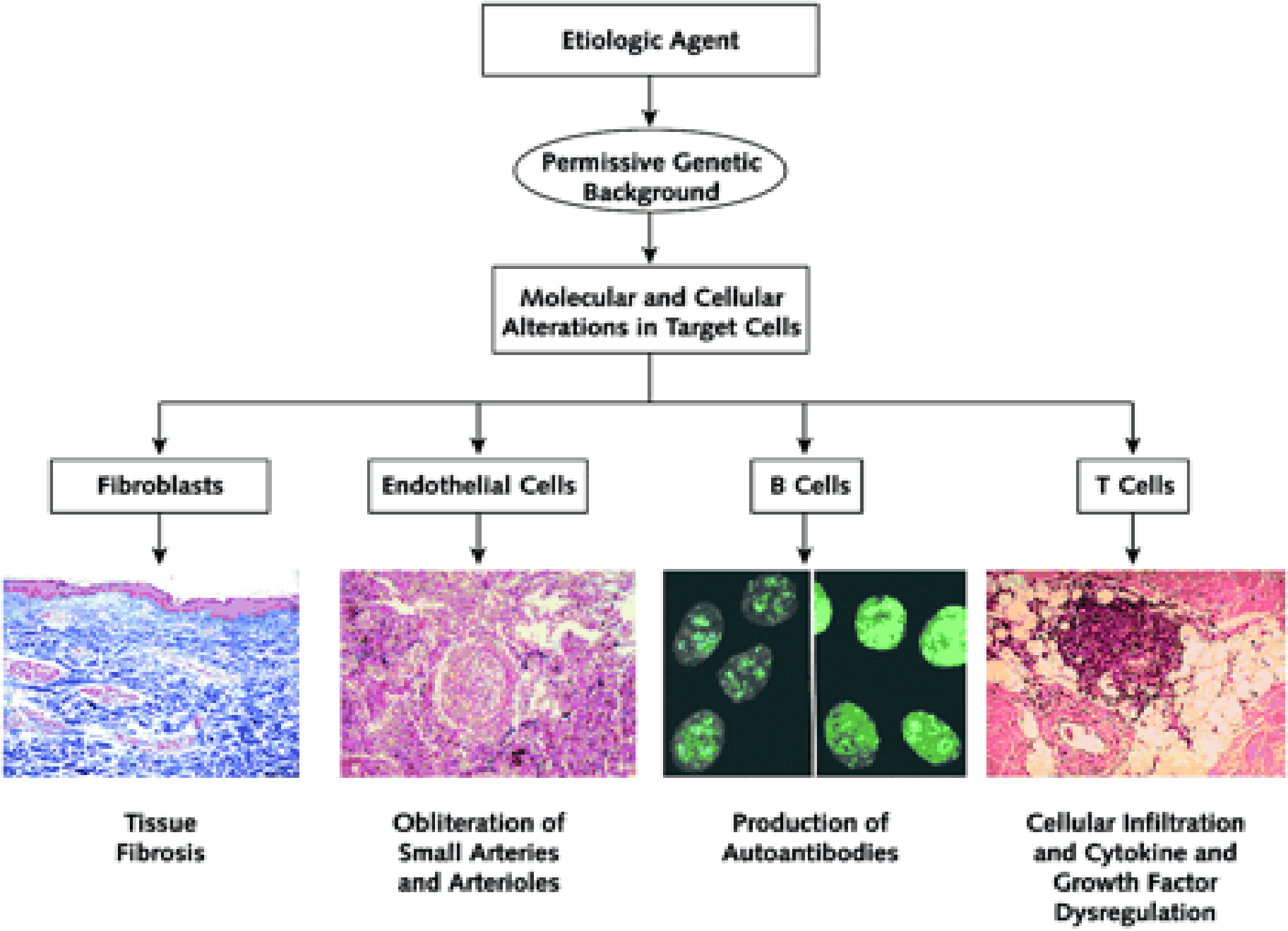
Systemic sclerosis is a condition that is of unknown cause.

Genetic susceptibility

Exposure to infections

Environmental exposure - Scleroderma is found to be more common in:

- Gold and coal miners
- Exposure to polyvinyl chloride
- Exposure to certain hydrocarbons such as benzene, toluene and trichloroethylene
- Exposure to drugs such as pentazocine and bleomycin.


Etiologic Agent
Permissive Genetic Background
Molecular and Cellular Alterations in Target Cells
Fibroblasts
Endothelial Cells
B Cells
T Cells
Tissue Fibrosis
Obliteration of Small Arteries and Arterioles
Production of Autoantibodies
Cellular Infiltration and Cytokine and Growth Factor Dysregulation

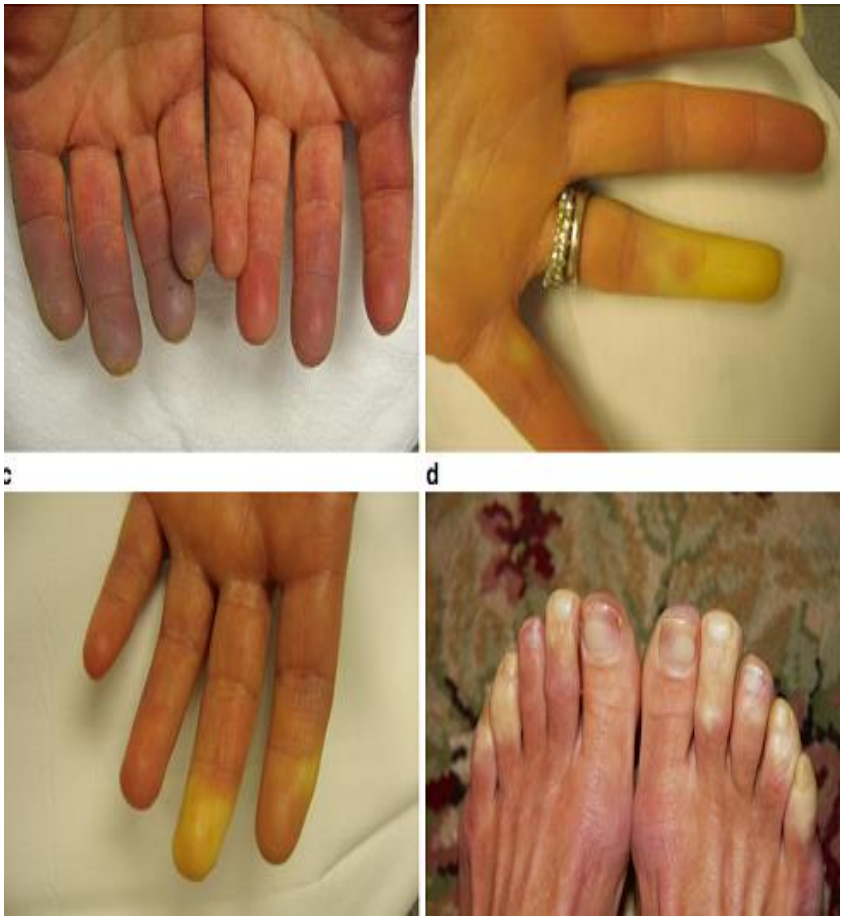
Clinical features

Raynaud phenomenon

is usually the first symptom of systemic sclerosis.

Patients experience episodes of vasospasm.

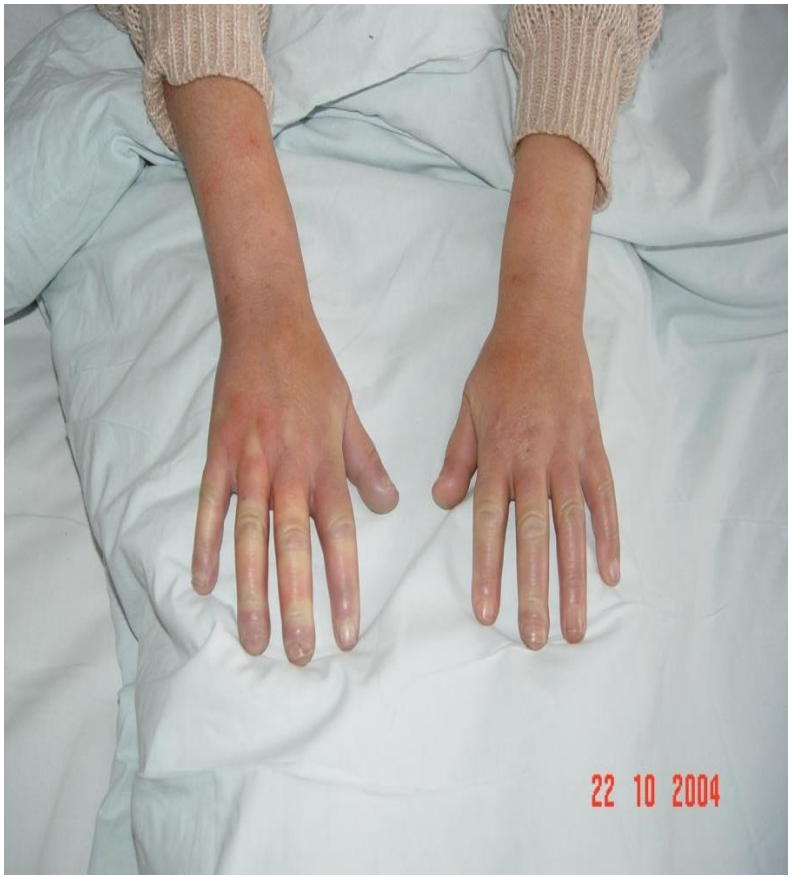
As less blood is reaching these extremities the skin changes colour to white and the fingers and toes may feel cold and numb. As they warm up, they go blue and then red before returning to normal again.

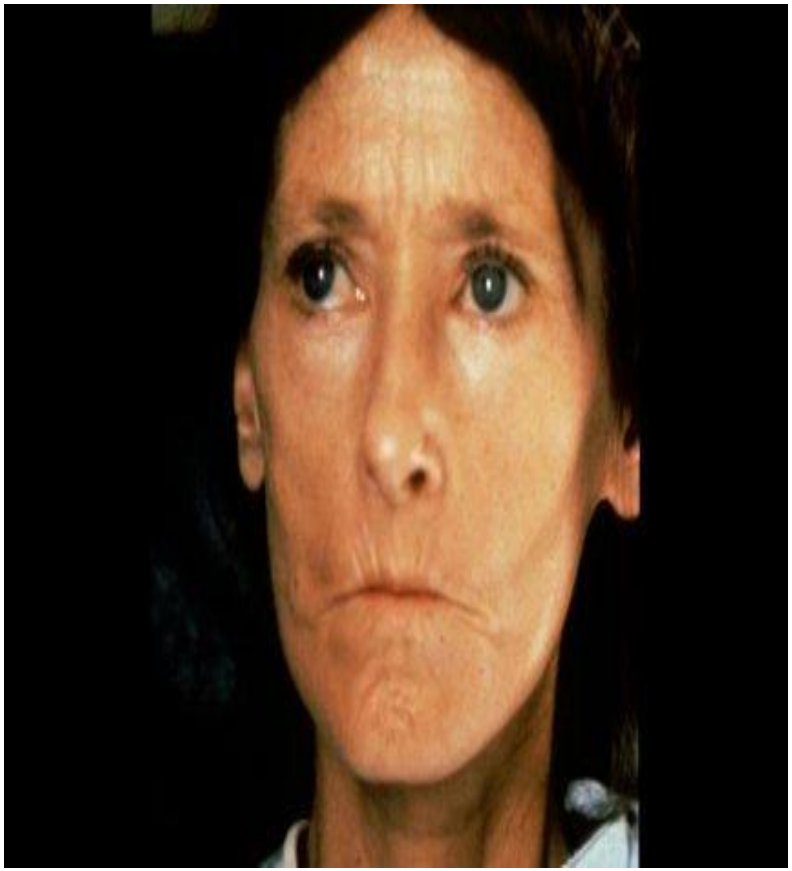


Other skin changes include:

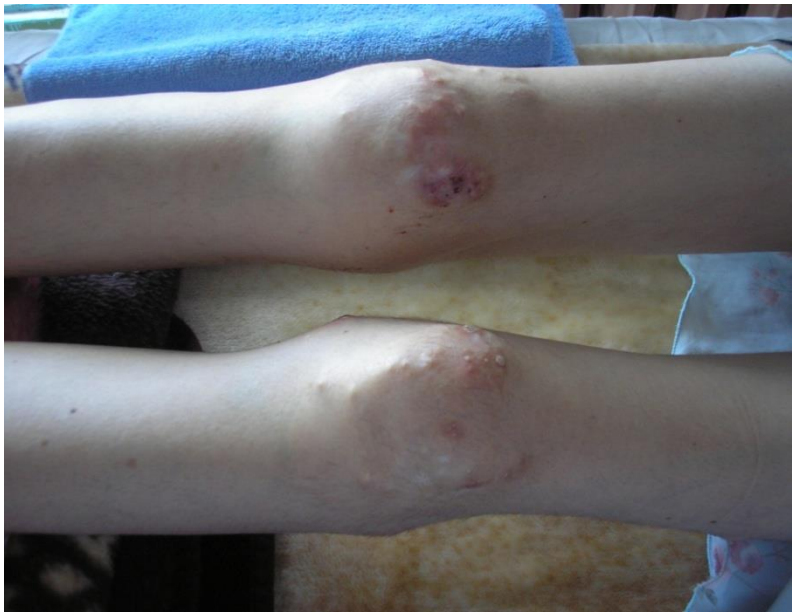
- Itchy skin
- *Thickening* of the skin of the fingers, then atrophy (thinned) and sclerosis (scarring). The tight skin may affect most parts of the body, including the face, resulting in loss of expression and difficulty opening the mouth properly.
- Fragile nails become smaller with ragged cuticles
- Taut, shiny skin that may have dark or pale patches (*hyper- or hypopigmentation*).
- Visibly dilated blood vessels (*telangiectases*) appear on the fingers, palms, face, lips, tongue and chest.

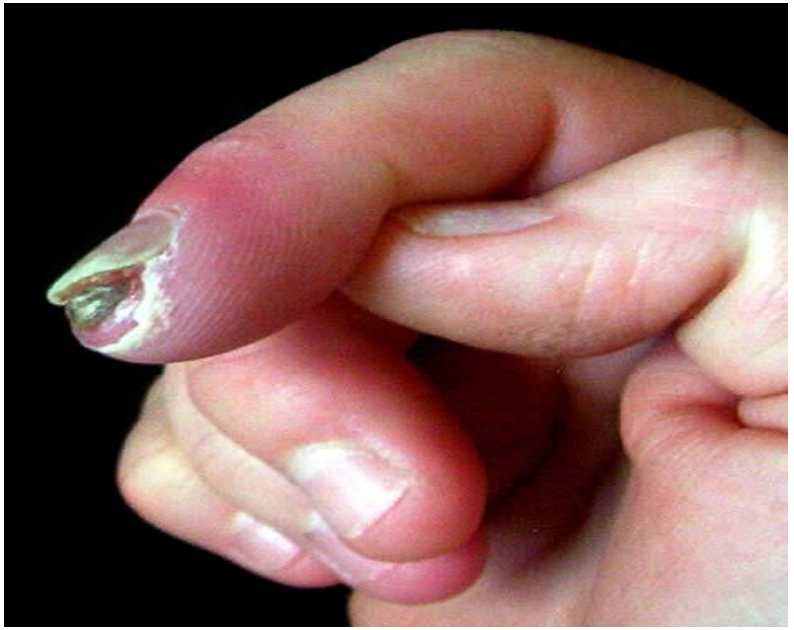
Skin changes in SS





- Calcinosis (calcium deposits) develops in the skin, particularly the fingers, hands and other bony areas. These can breakdown and discharge chalky material.
- Ulcers may follow minor injuries over the joints, or on the tips of fingers and toes where the circulation is poor.
- Ulceration can lead to dry gangrene and eventual loss of the tips of the fingers (like frost bite).
- Ulcers may also arise over calcinosis and on the lower legs.





Classification

The differing patterns of skin involvement include:

- ***Limited cutaneous systemic sclerosis,CREST syndrome***: usually have their skin sclerosis confined to their hands. Less commonly the skin of the face and neck become involved. In the **CREST syndrome** the following changes occur: Calcinosis, Raynaud's Phenomenon, Oesophageal Dysfunction, Sclerodactyly, Telangietasia (CREST is an acronym for these changes).
- ***Diffuse cutaneous systemic sclerosis***: skin lesions on the chest, abdomen, upper arms or shoulders is characteristic. Patients with this form of systemic sclerosis are more likely to experience internal organ disease than those with the limited cutaneous form.
- ***Systemic sclerosis sine scleroderma***: patients with this form of the disease do not all have skin manifestations.

Organs involvement

Problems that may occur include:

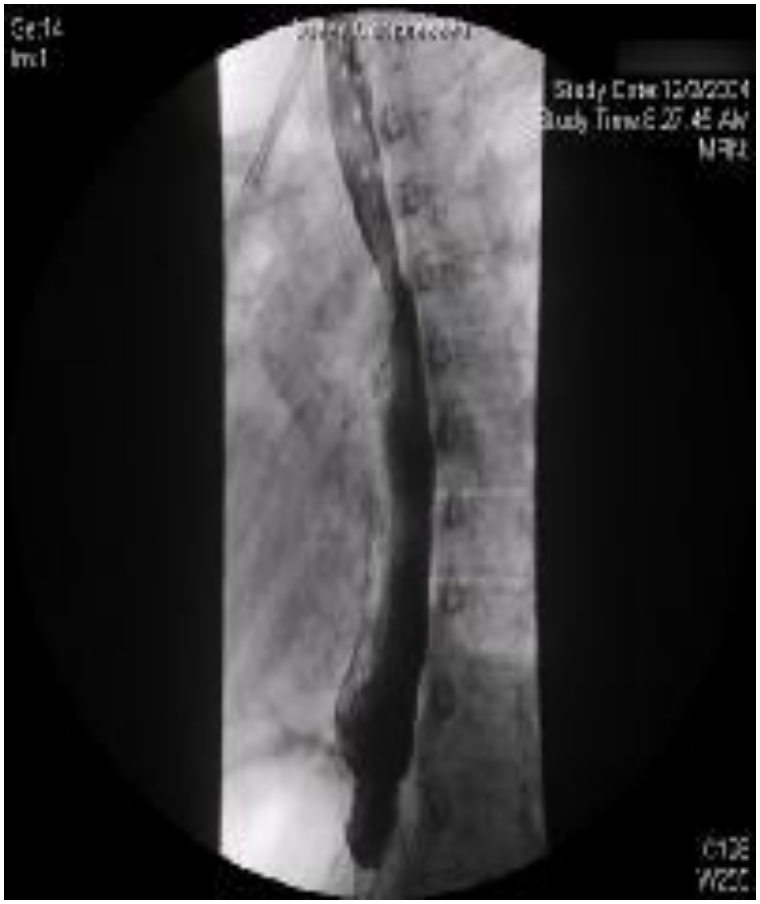
- Friction rubs over the joints and tendons, particularly the knees
- Eye changes with tightness of lids, reduced tear secretion, retinopathy
- Joint pain, muscle pain and weakness and limited movement resulting in contractures
- The digestive tract may be affected throughout its length. Oesophageal reflux is common causing difficulty in swallowing solid and liquid food. This can lead to nausea, vomiting, weight loss, stomach cramps, diarrhoea, constipation and bleeding
- Lung and heart involvement may manifest as shortness of breath, high blood pressure, chest pain, pleurisy, pneumothorax, pericarditis arrhythmias, general heart enlargement and heart failure
- Progressive kidney disease (SRC) resulting in proteinuria, high blood pressure and eventually renal failure.

Diagnosis

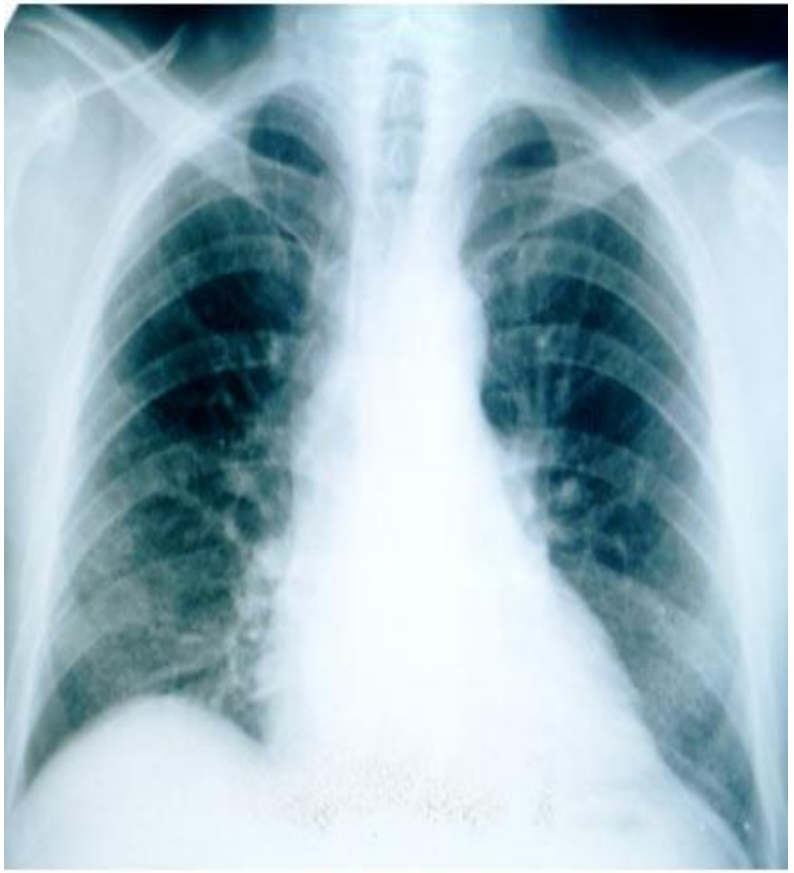
- The diagnosis is generally made from the patient's history and the findings on examination of the skin and other organs.
- A skin biopsy is not usually necessary but characteristically shows excessive ground substance and odd-looking endothelial cells in the dermis and later deposits of collagen. The epidermis is usually atrophic.
- Up to 90% have elevated **antinuclear antibodies** (ANA)
- Thyroid antibodies may occur and result in an under-active thyroid gland
- **Anticentromere antibodies** are characteristic of CREST syndrome and may be present in Raynaud phenomenon before systemic sclerosis appears.
- **Scl-70** (antitopoisomerase) is unique to systemic sclerosis and is more likely to be associated with severe systemic sclerosis involving the lungs. Many other less specific antibodies have been reported to be associated with different patterns of disease.
- Anaemia, raised sedimentation rate (ESR) and increased gamma globulins (hypergammaglobulinaemia) and varying immune abnormalities are quite common especially positive rheumatoid factors.

X-ray findings

Oesophageal hipomotility

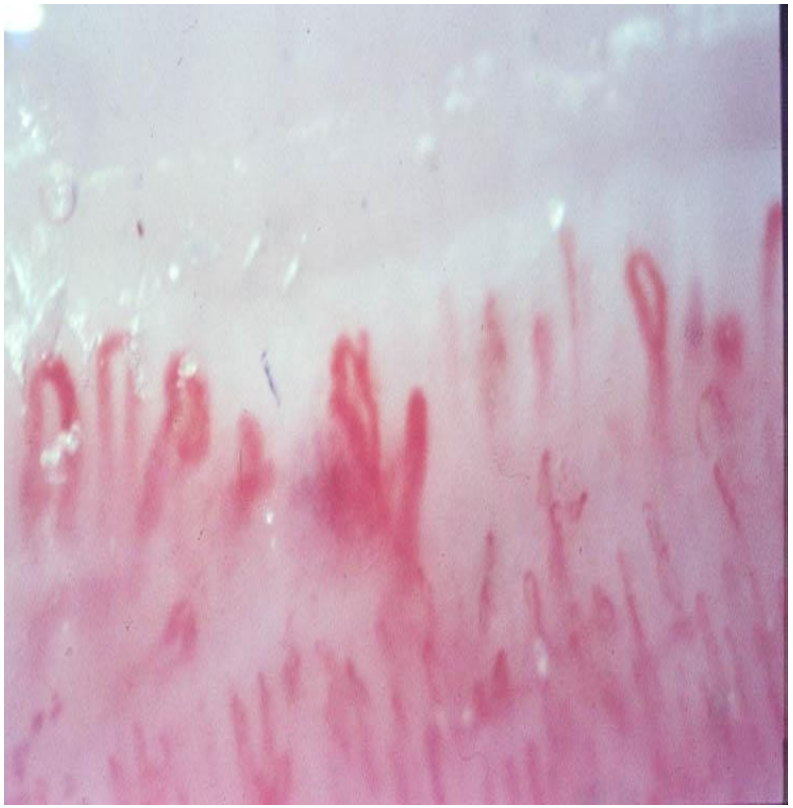


Bibasilal pneumofibrosis

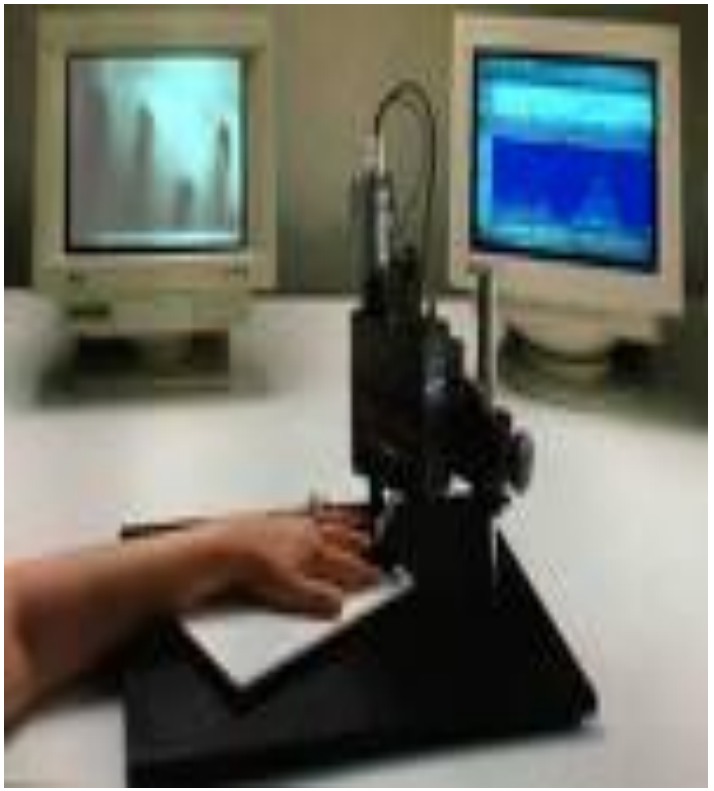


Capilaroscopy

Early SS



Capilaroscop



Diagnostic criteria

The American College of Rheumatology classification criteria (1980) for scleroderma include either **thickened (sclerodermatous) skin changes proximal to the metacarpophalangeal joints** or at least two of the following:

1. Sclerodactyly.
2. Digital pitting (loss of tissue on the finger pads due to ischemia).
3. Bibasilar pulmonary fibrosis.

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2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)*

Item	Sub-items(s)	Weight/score †
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3

* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category.
Patients with a total score of ≥ 9 are classified as having definite scleroderma.

Sensitivity 91% Specificity 92%

Van den Hoogen et al. 2013 Classification Criteria for Systemic Sclerosis. Arthritis and Rheumatism. Vol. 65, No. 11, November 2013, pp 2737–2747

Treatment

General Principles

- No single drug has been found to treat all of the manifestations of scleroderma, so no effective disease-specific therapy exists.
- Management, therefore, is based on the symptoms and disease manifestations of each individual patient and is often *organ-specific.*
- Routine screening and early intervention for internal organ manifestations may significantly reduce morbidity and mortality.

Treatment

Immunomodulatory agents

- Cyclophosphamide - in SSc-associated pulmonary fibrosis
- Methotrexate -significant improvement in skin score
- Mycophenolate - favorable outcomes in skin, lung, and survival rate
- Rituximab } for severe cases
- Immunoablation }
- Anti–tumor necrosis factor agents - variable effect on skin, good effect on joints

Treatment

Vascular therapies for Raynaud phenomenon

- Nondrug - hand warmers, protective clothing
- Pharmacologic for Raynaud phenomenon - Calcium channel blockers (nifedipine, amlodipine, diltiazem); Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Selective serotonin reuptake inhibitor - Fluoxetine
- Treatment for ulcer healing -Phosphodiesterase inhibitors (Sildenafil, tadalafil); Parenteral vasodilators (Iloprost, prostaglandin E1), Endothelin receptor antagonists (Bosentan); Statins; Local management of ulcers (wound-healing techniques, topical antibiotics, soaking, occlusion, débridement, systemic antibiotics)

Idiopathic inflammatory myopathies

Definion

- The idiopathic inflammatory myopathies (IIM) are rare and heterogenous autoimmune diseases, characterized by inflammation of skeletal muscle and other organ systems.

Epidemiology

- Annual incidence rates for IIM vary from 2.18 to 8.7 ×1 mln.
- The female to male incidence rate ratio in PM/DM varies between 1.5 and 2.4.
- A higher incidence of PM/DM has been observed in black compared to white patients.

Etiology and classification

- The etiopathology of IIM remains unknown, but genetic and environmental factors probably interact to produce disease.
- Adult-onset IIM can be broadly classified into ***polymyositis*** (PM), ***dermatomyositis*** (DM), and ***inclusion body myositis*** (IBM).

Environmental risk factors

Infectious agents

- Acute myopathies can ensue due to infection, with or without evidence of active muscle infection.
- Infectious agents such as cocksackie, cytomegalovirus, and toxoplasma and have been implicated in IIM, but studies have been largely unsuccessful in identifying evidence for specific infectious agents.

Non-infectious agents

- A number of drugs, foods, dietary supplements, and vaccinations have also been associated with the onset of myositis

Genetic risk factors

- The strongest associations arise from the MHC region, as seen in other autoimmune diseases.
- *HLA-DRB1* and *HLA-DQA1* are confirmed risk factors for IIM.

Patogenesis

- The mechanisms that cause impaired muscle performance are likely to be a combination of cell-mediated muscle fiber necrosis, indirect effects of inflammatory cells by secretion of molecules that affect muscle fiber contractility, and an acquired metabolic myopathy secondary to loss of capillaries and local inflammation.

- Different molecular mechanisms may predominate in various variants and phases of disease.

Clinical features

- Symmetric **proximal muscle weakness** evolving over weeks to months is the presenting symptom in most patients.
- Typical complaints include difficulty rising from a low chair, walking up steps, and washing one's hair.
- In more severe cases, weakness of the neck flexors, pharyngeal weakness, and diaphragmatic weakness can cause head drop, dysphagia, and respiratory compromise, respectively.

Clinical features

- On physical examination, weakness of the proximal arm muscles, especially the deltoids, but often including the biceps and triceps, is expected.
- Hip flexors are the most commonly affected leg muscles, but the hamstrings and quadriceps are also frequently weak.
- As a general rule in the autoimmune myopathies, distal weakness should only occur in the presence of severe proximal muscle weakness.

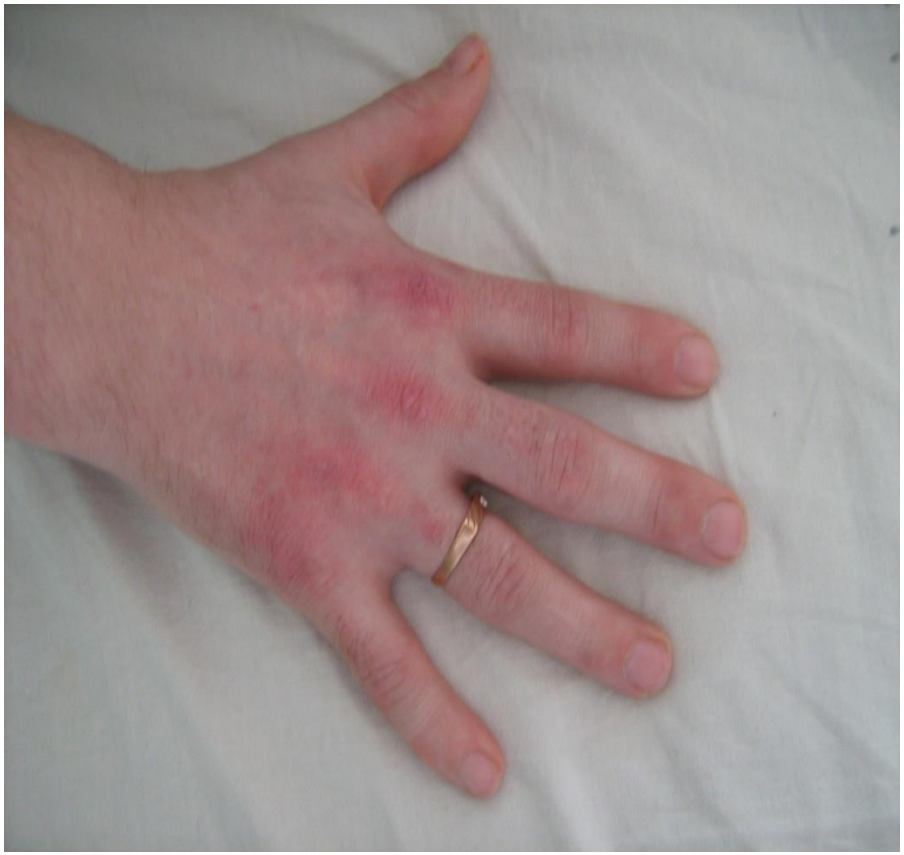
Clinical features

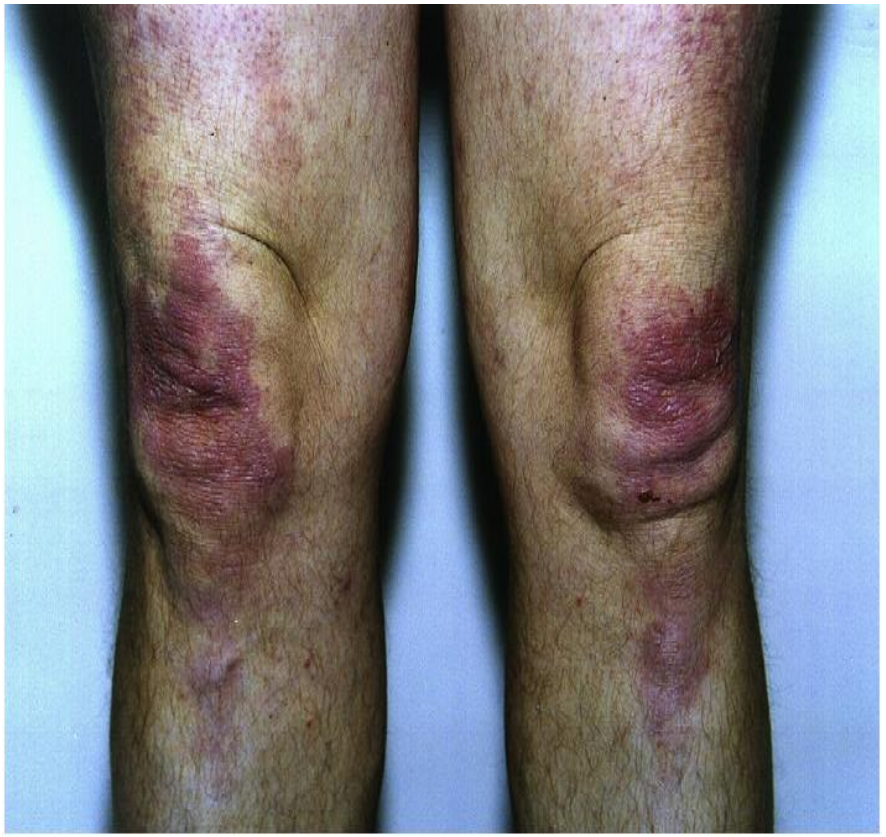
- In addition to muscle weakness, arthralgias or frank arthritis, myalgias, severe fatigue, Raynaud phenomenon may be present.
- Dyspnea may reflect *diaphragmatic weakness* or, especially in patients with the antisynthetase syndrome, *interstitial lung disease*.
- The latter is often associated with a persistent dry cough, crackles on chest auscultation, and decreased oxygen saturation with exercise.

Clinical features

- Patients with dermatomyositis may present with cutaneous manifestations either before or after the development of muscle symptoms.
- **Gottron papules** are raised violaceous lesions at the extensor surfaces of the metacarpophalangeal, proximal interphalangeal, and the distal interphalangeal joints.
- The **Gottron sign** is an erythematous rash involving these sites that can also be found at the extensor surfaces of the elbows and knees.

GOTTRON PAPULES AND SIGN



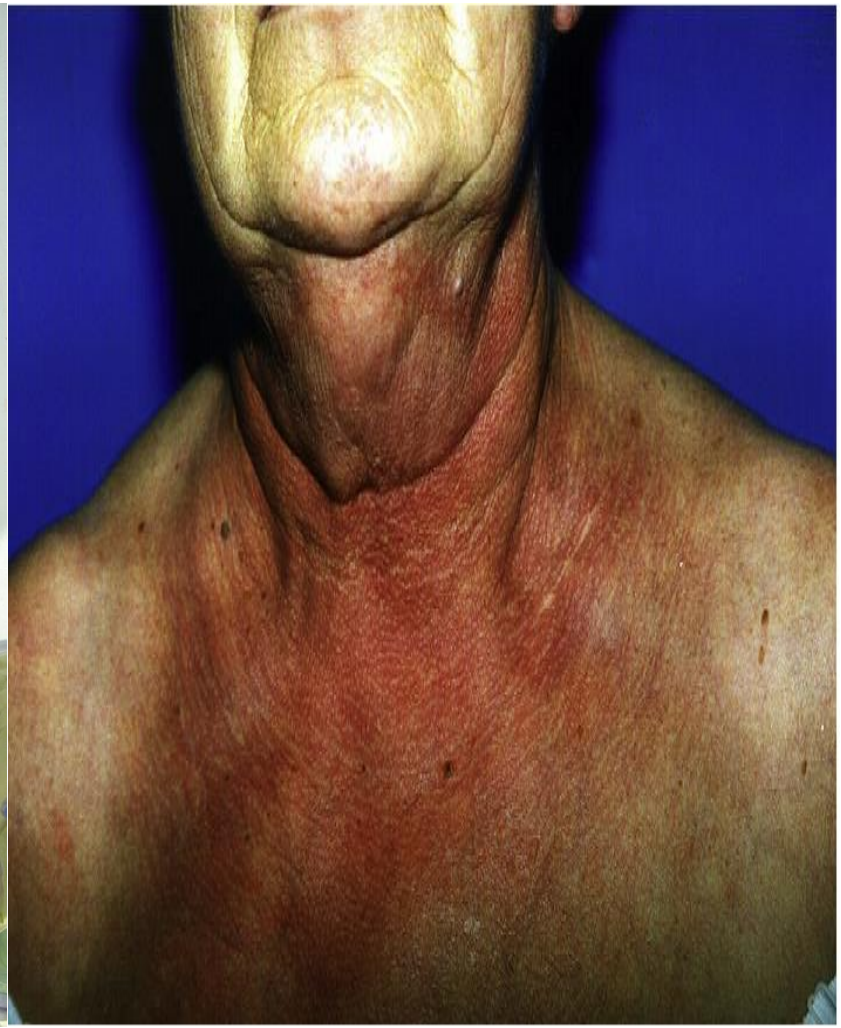


Clinical features

- The heliotrope rash is an often red or purplish discoloration of the eyelids; in blacks, this may appear hyperpigmented.
- Although both the heliotrope and Gottron rashes are pathognomonic for dermatomyositis, other less specific rashes may occur.
- These include an erythematous or poikilodermatous rash across the posterior neck and shoulders (the shawl sign) and a similar rash on the anterior neck and chest (the V-sign).
- In some patients, dermatomyositis-associated rashes are *sun-sensitive (fotosensitivity)*.

Heliotrope rash of the eyelids

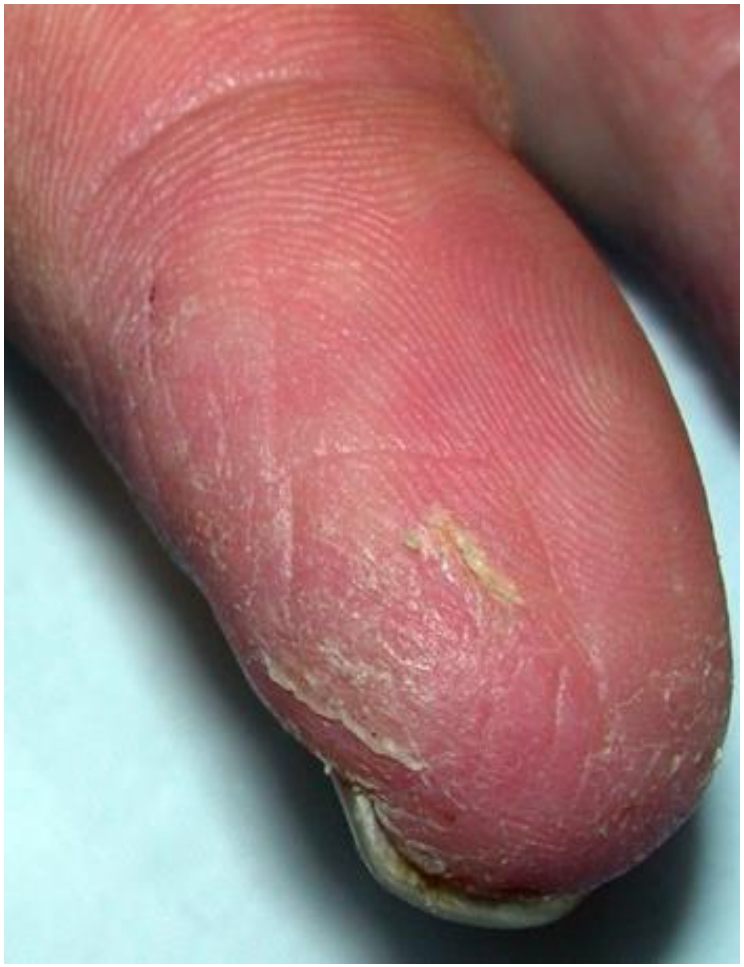
V-sign

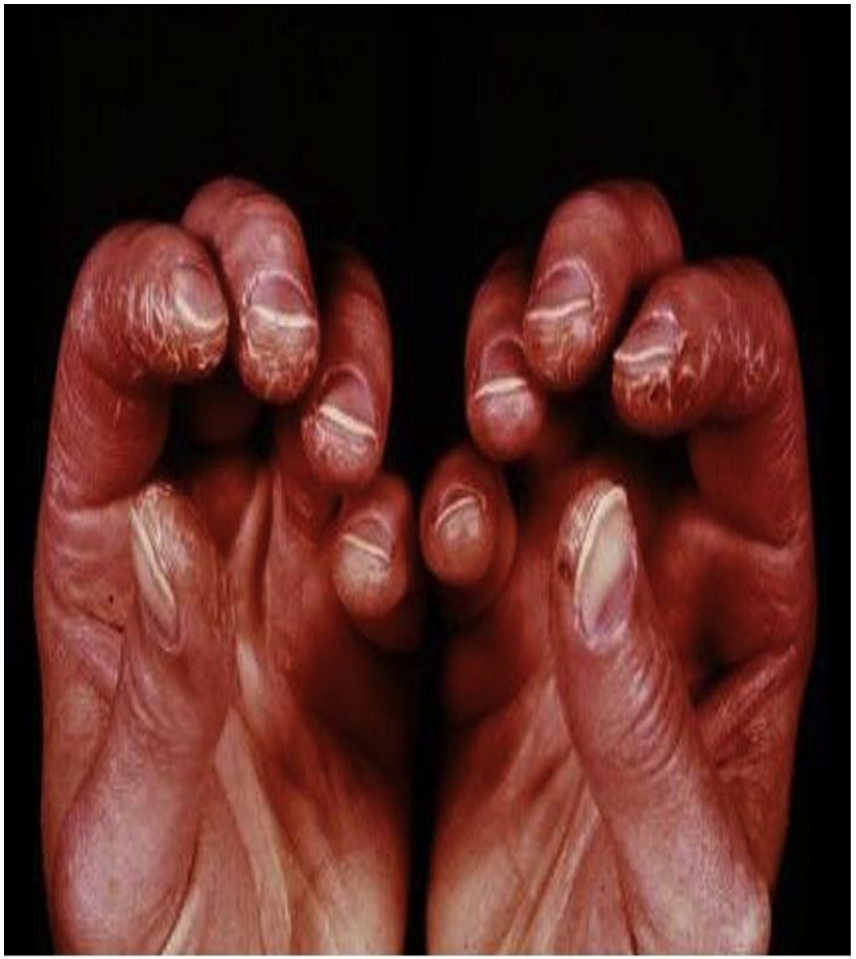


Clinical features

- In some patients, particularly those with the antisynthetase syndrome, hyperkeratotic skin thickening, often with painful cracking, on the radial surfaces of the fingers (mechanic's hands) or toes (mechanic's feet) may develop.
- In addition, periungual telangiectasias and nailfold capillary changes may develop.

Mechanic’s hands





Diagnostic tests

- Creatine kinase (CK), aldolase, AST, ALT, and lactate dehydrogenase, are released from damaged muscle and elevated levels are often, but not always, found in patients with autoimmune myopathy.
- As in other systemic autoimmune diseases, there is a strong association of autoantibodies against specific autoantigens with distinct clinical phenotypes.

Diagnostic tests

- **Anti-Jo-1** (Histidyl t-RNA synthetase) - PM or DM with ILD
- **Anti-Mi-2** (DNA helicase) - Dermatomyositis with rash > muscle symptoms, treatment responsive
- **Anti-SRP** (Signal recognition particle) - Severe, acute, resistant necrotizing myopathy

Diagnostic tests

Muscle biopsy

- Muscle biopsies can positively identify non-inflammatory myopathies, and differentiate between IIM subtypes.
- The major histopathologic findings of myositis consist of focal inflammation with T cells, macrophages, and dendritic cells, often together with injury, death, and repair of muscle cells.

Diagnostic tests

Neurophysiology

- Classical (EMG) findings in IIM consist of: (1) early recruitment of low amplitude, short duration and polyphasic motor unit action potentials; (2) spontaneous fibrillations, positive sharp waves, and increased insertional activity; and (3) high-frequency complex repetitive discharges, which all correlate inversely with muscle strength in IIM patients.
- These changes are not specific for IIM and may also be seen in dystrophies and metabolic myopathy.
- EMG has approximately 90% sensitivity for picking up inflammatory myopathy but this partly depends on the skill of the neurophysiologist.

Diagnostic tests

Other investigations

- If dysphagia is present, patients should be appropriately investigated with speech and language therapy assessment, barium swallow, and/or videofluoroscopy as appropriate.

Diagnosis of interstitial lung disease

- PFTs may help detect subclinical ILD, and are useful for monitoring progression of disease or therapeutic response.
- ILD is suggested by a normal/raised FEV 1/FVC ratio, FVC or total lung capacity less than 80% predicted, and/or a decrease in diff using capacity for carbon monoxide (DL CO).
- Patients with respiratory muscle weakness may also present with a restrictive pattern and decreased DL CO .
- A decreased DL CO may also be seen in pulmonary hypertension.
- A number of biomarkers may be useful in the assessment of IIM-ILD.
- Chest radiographs are also useful for screening and detection of ILD complications, e.g. pneumothoraces.
- High-resolution CT (HRCT) is sensitive and can also distinguish between fibrotic disease and active inflammation. Irregular linear opacities with areas of consolidation and ground-glass attenuation suggest active infl ammation. Honeycombing is suggestive of endstage lung disease with established fi brosis.

Diagnostic criterias based on Bohan and Peter system

- 1. Proximal muscle weakness
- 2. Positive muscle biopsy
- 3. Elevated enzyme levels in the serum (CK, GOT, GPT, LDH, Aldolase)
- 4. Myopathic pattern on the electromyogram (EMG)
- 5. Characteristic skin rashes in DM

We consider‘definite DM’ the presence of three of diagnostic criteria (DC) 1, 2, 3 and 4þskin rashes;

‘probable DM’ when the patient has two of DCs 1, 2, 3, 4þskin rashes; and‘possible DM’ one of DCsþskin rashes.‘Definitive PM’means four of DCs 1, 2, 3, 4;‘probable PM’if three of DCs 1, 2, 3, 4; and

‘potential PM’ if two of DCs 1, 2, 3, 4 are present

Management and treatment of myositis

- Initial treatment of choice in inflammatory myositis is with corticosteroids.
- The typical initial dose is 0.75–1 mg/kg (e.g. 60–80 mg prednisolone) per day for 3–4 weeks, and after normalization of CK and clinical parameters, dose reduction by 20–25% every 3–4 weeks until the lowest dose to control the disease is reached.
- Treatment with intravenous methylprednisolone 1 g daily for 3 days may be necessary in aggressive disease.

Management and treatment of myositis

- Other treatments may be initiated for further control of disease and as steroid-sparing agents, e.g. methotrexate, azathioprine, ciclosporin, tacrolimus, cyclophosphamide, and mycophenolate mofetil.
- Intravenous immunoglobulin use has also been studied; a study in refractory DM showed improvement of muscle strength after 3 months.
- Plasma exchange has shown limited results in the treatment of myositis.

Management and treatment of myositis

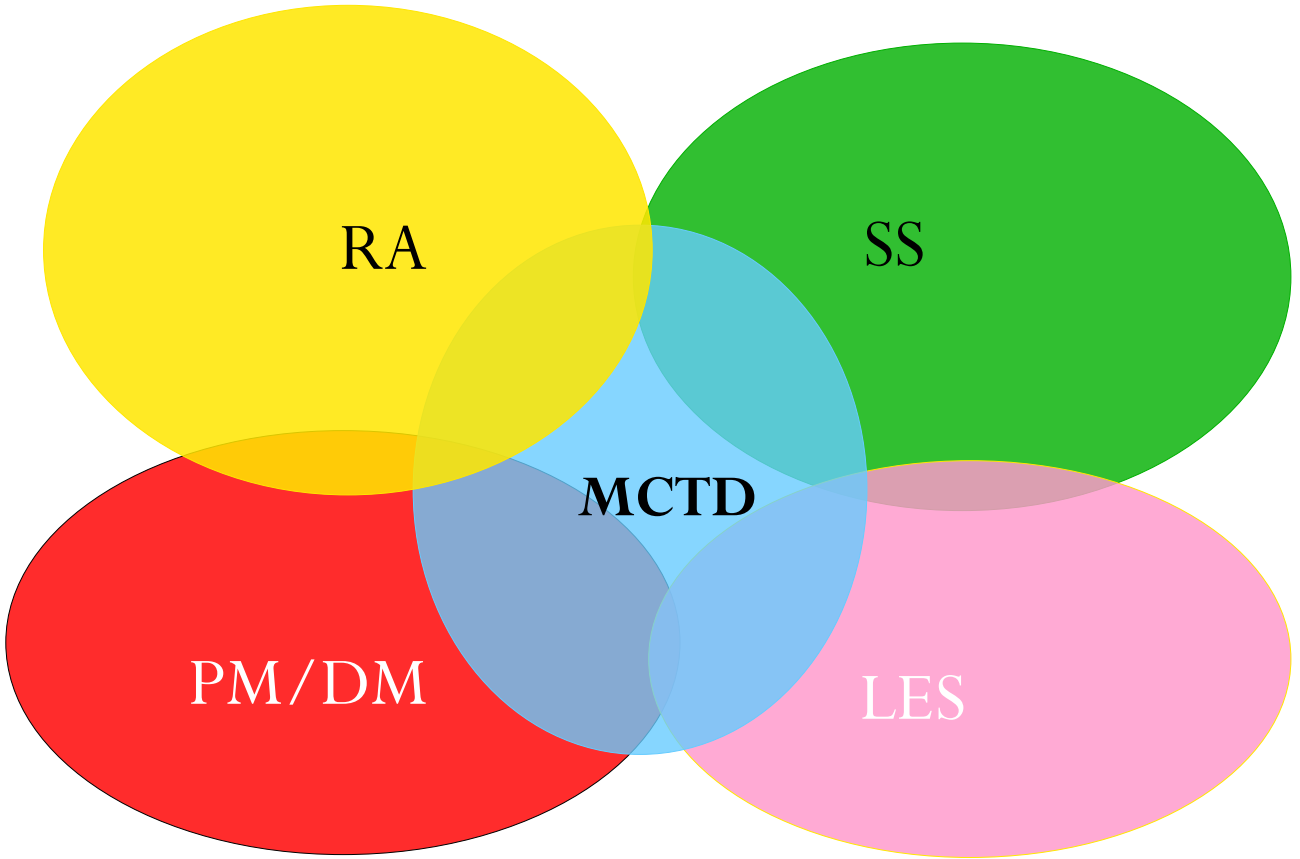
- Anti- TNFα therapy is not recommended in IIM, where only variable improvements have been noted in serum muscle enzyme levels and muscle strength.
- The largest randomized placebo-controlled trial in IIM to date investigated **rituximab** with crossover at 8 weeks. No significant difference in improvement was noted between the two arms at 12 months, but 83% of patients achieved the definition of improvements and a significant glucocorticoid-sparing effect was noted.
- **Exercise and rehabilitation programmes** are safe and of benefit in stable treated myositis patients, improving function, aerobic fitness, and muscle strength.
- The issues of muscle weakness, loss of joint motion, and fatigue in myositis should be addressed in physiotherapy-led programmes.

Mixed connective tissue disease

Mixed connective tissue disease

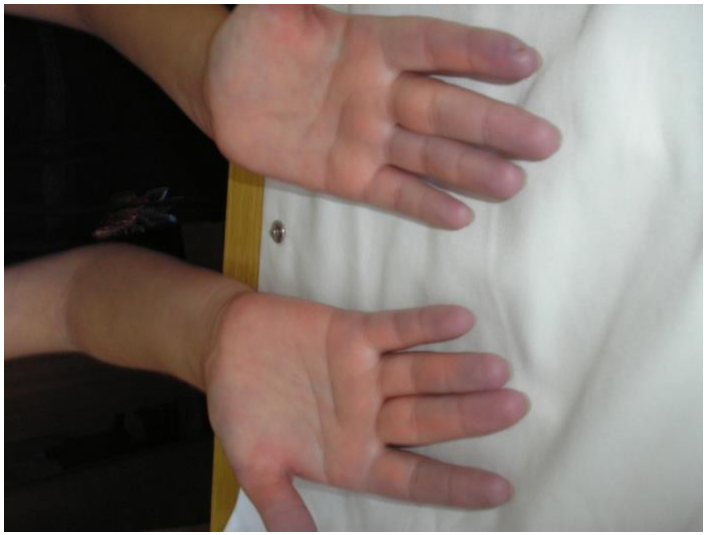
- Mixed connective tissue disease (MCTD) was first described in 1972 as an entity with mixed features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM) and rheumatoid arthritis (RA) together with the presence of high-titre **anti-U1small nuclear (sn) anti-ribonucleoprotein (anti-RNP) antibodies**

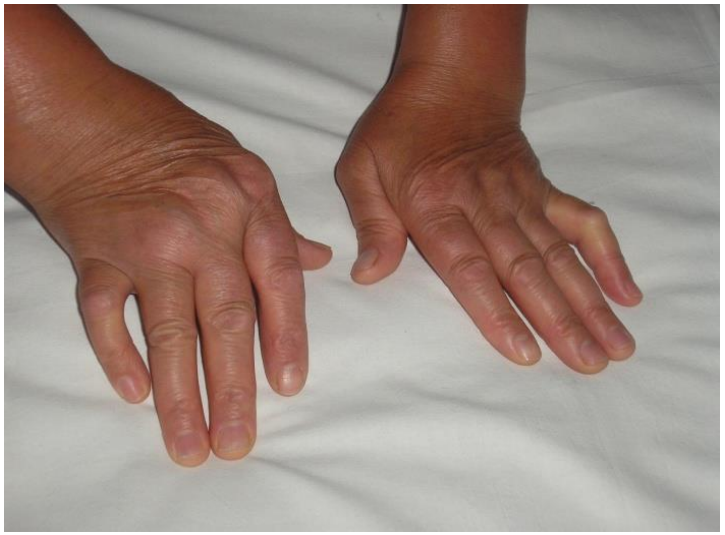
Mixed connective tissue disease

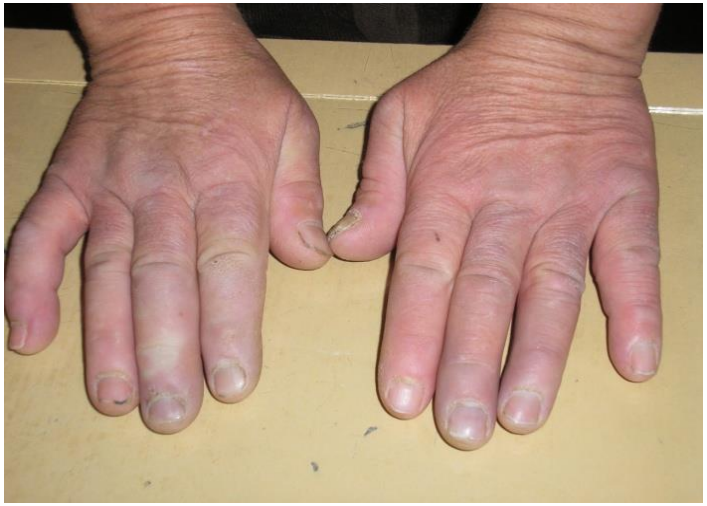


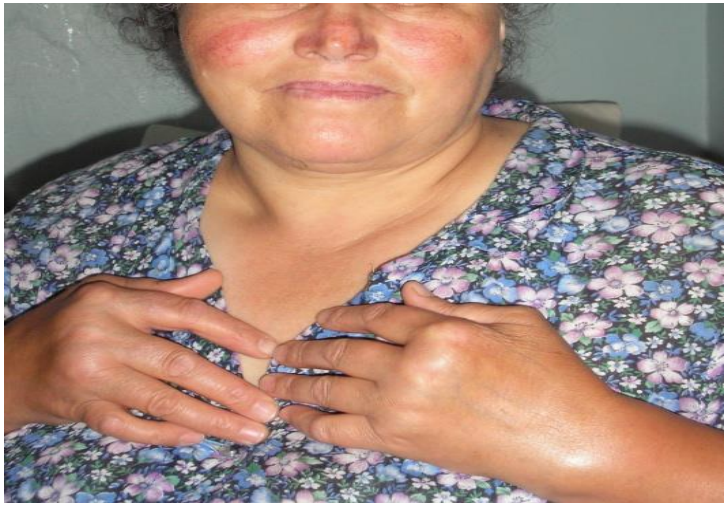
Overview of clinical manifestations

- MCTD may begin with any clinical manifestations of SLE, SSc, PM or RA, at disease onset or during clinical course.
- The most common clinical features are polyarthritis, RP, sclerodactyly, swollen hands, muscle disorders and oesophageal dysmotility.
- Severe renal disease is rare and the presence of anti-U1-RNP antibodies may be **protective** against the development of **diffuse proliferative glomerulonephritis**
- Alopecia, malar rash, lymphadenopathy are less common, but can be present.
- Unspecific constitutional symptoms such as fever, fatigue, arthralgias or myalgias are also common









Haematological manifestations

- Leucopenia, anaemia of chronic disease, broad-based hypergammaglobulinemia and positive Coomb's test without haemolysis are the most frequent reported haematological features.
- Other less common haematological features include thrombocytopenia, thrombotic thrombocytopenic purpura (TTP) and red cell aplasia.
- Although they are not specific of MCTD, anaemia and leucopenia tend to correlate with disease activity and usually improve with therapies employed to treat other organ manifestations.

Autoantibodies in MCTD

- The **anti-U1-RNP** antibodies are the hallmark of the disease.
- Patients with high titres without any criteria of MCTD or other defined CTD, usually evolve into MCTD over 2 years.
- Otherwise, anti-U1-RNP antibodies are not the only antibodies found in the sera of patients with MCTD. Anti-Ro/SS-A, antisingle-stranded DNA, anti-Sm and anti-double-stranded DNA antibodieshave also been detected, nevertheless, they are not specific of MCTD.
- Antiphospholipid antibodies have been reported in patients with MCTD.
- Anticardiolipin antibodies (aCL) are present in approximately 15% of patients; however, they are less prevalent than in patients with SLE. aCL have been associated with PAH in patients with MCTD, but not with thrombotic events or other manifestations of the antiphospholipid syndrome.

Criteria proposed to diagnose mixed connective tissue disease, Kahn (1991)

Serological criteria

- Presence of high titer anti-RNP corresponding to speckled

ANA at titer1:2000

Clinical criteria

- Raynauds phenomenon
- synovitis
- myositis
- swollen fingers

Requirements for diagnosis

- Serological criteria
- plus Raynaud's phenomenon and at least two of the three following signs (synovitis, myositis and swollen fingers)

Overview of treatment

- Patients diagnosed of MCTD were initially described as having a good prognosis, being extremely responsive to corticosteroid therapy.
- However, subsequent long-term studies have revealed that not all patients have a benign clinical course and that not all clinical manifestations are responsive to steroids.
- Some patients may have mild self-limited disease, whereas others may develop severe major organ involvement with life-threatening manifestations.

Overview of treatment

- In any case, therapy should be individualised for each patient to address the specific organs involved and the severity of underlying disease activity.
- Inflammatory manifestations such as fever, serositis, myositis, arthritis and skin rash usually respond to steroid treatment, whereas clinical sclerodermatous manifestations such as sclerodactyly, moderate oesophagueal disease, RP, sclerodermatous bowel disease and pulmonary interstitial disease more often require cytotoxic immunosuppressive treatment.
- In general, **corticosteroids** (prednisone and methylprednisolone) and **cytotoxic agents**, most often cyclophosphamide, are the most frequently employed immunosuppressants.
- Antimalarials (hydroxychloroquine), methotrexate and different types of vasodilators have also been used with varying degrees of success.

Sjogren syndrome

Definition

- **Sjogren syndrome** (SjS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands.

Epidimiology

- The incidence of SjS has been calculated as 4 cases per 100,000.
- SjS primarily affects white perimenopausal women, with a female:male ratio ranging from 14-24:1

Classification

1. Primary SjS

2. Secondary SjS

- Systemic autoimmune diseases
- Systemic lupus erythematosus
- Systemic sclerosis
- Rheumatoid arthritis
- Still disease
- Sarcoidosis
- Inflammatory myopathies
- Organ-specific autoimmune diseases
- Primary biliary cirrhosis
- Autoimmune thyroiditis
- Multiple sclerosis
- Diabetes mellitus
- Chronic viral infections
- Chronic HCV infection (Mediterranean countries)
- HTLV-1 I infection (Asian countries)
- HIV infection

3. Mimicked SjS

- Other diseases infiltrating exocrine glands
- Granulomatous diseases (sarcoidosis and tuberculosis)
- Amyloidosis
- Neoplasias (lymphoma)
- IgG4-related disease
- Type V hyperlipidemia
- Graft-versus-host disease
- Eosinophilia-myalgia syndrome
- Radiation injury
- Medication-related dryness

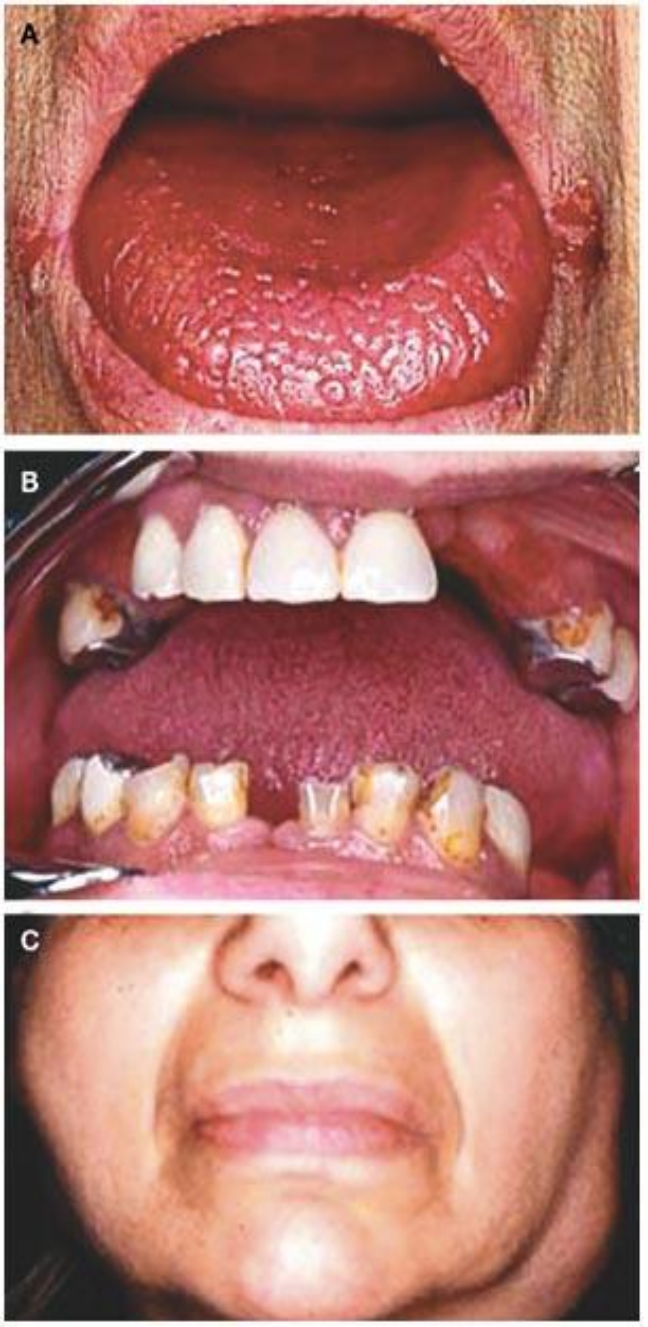
Clinical Findings

Sicca features

- **Xerostomia**, the subjective feeling of oral dryness, is the key feature in the diagnosis of primary SjS, occurring in more than 95% of patients.
- Other oral symptoms may include soreness, adherence of food to the mucosa, and dysphagia.
- Reduced salivary volume interferes with basic functions such as speaking or eating.
- Various oral signs may be observed in SjS patients. In the early stages, the mouth may appear moist, but as the disease progresses, the usual pooling of saliva in the floor of the mouth disappears.

Clinical Findings

- Typically, the surface of the tongue becomes red and lobulated, with partial or complete depapillation (A).
- The lack of salivary antimicrobial functions may accelerate local infection, tooth decay, and periodontal disease (B).
- Chronic or episodic swelling of the major salivary glands (parotid and submandibular glands) is reported in 10–20% of patients and may commence unilaterally, but often becomes bilateral (C).

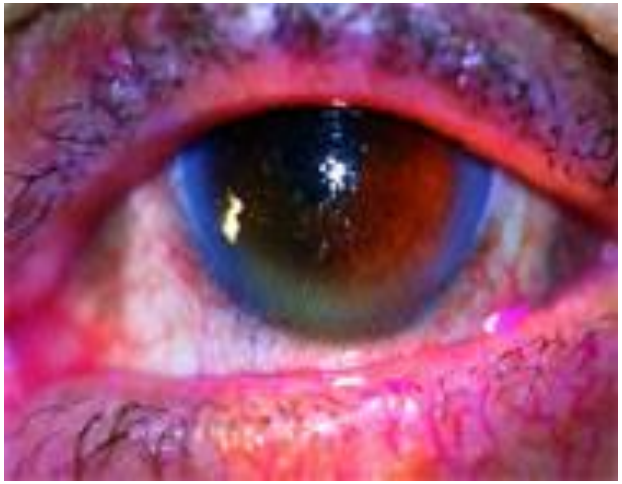


Clinical Findings

- The subjective feeling of ocular dryness is associated with sensations of itching, grittiness, and dryness, although the eyes have a normal appearance.
- Other ocular complaints include photosensitivity, erythema, eye fatigue, or decreased visual acuity.
- Environmental irritants such as smoke, wind, air conditioning, and low humidity may exacerbate ocular symptoms.
- Diminished tear secretion may lead to chronic irritation and destruction of corneal and bulbar conjunctival epithelium (**keratoconjunctivitis sicca**).

Clinical Findings

- In severe cases, slit-lamp examination may reveal filamentary keratitis, marked by mucus filaments that adhere to damaged areas of the corneal surface.
- Tears also have inherent antimicrobial activity and SjS patients are more susceptible to ocular infections such as blepharitis, bacterial keratitis, and conjunctivitis.
- Severe ocular complications may include corneal ulceration, vascularization, and opacification.

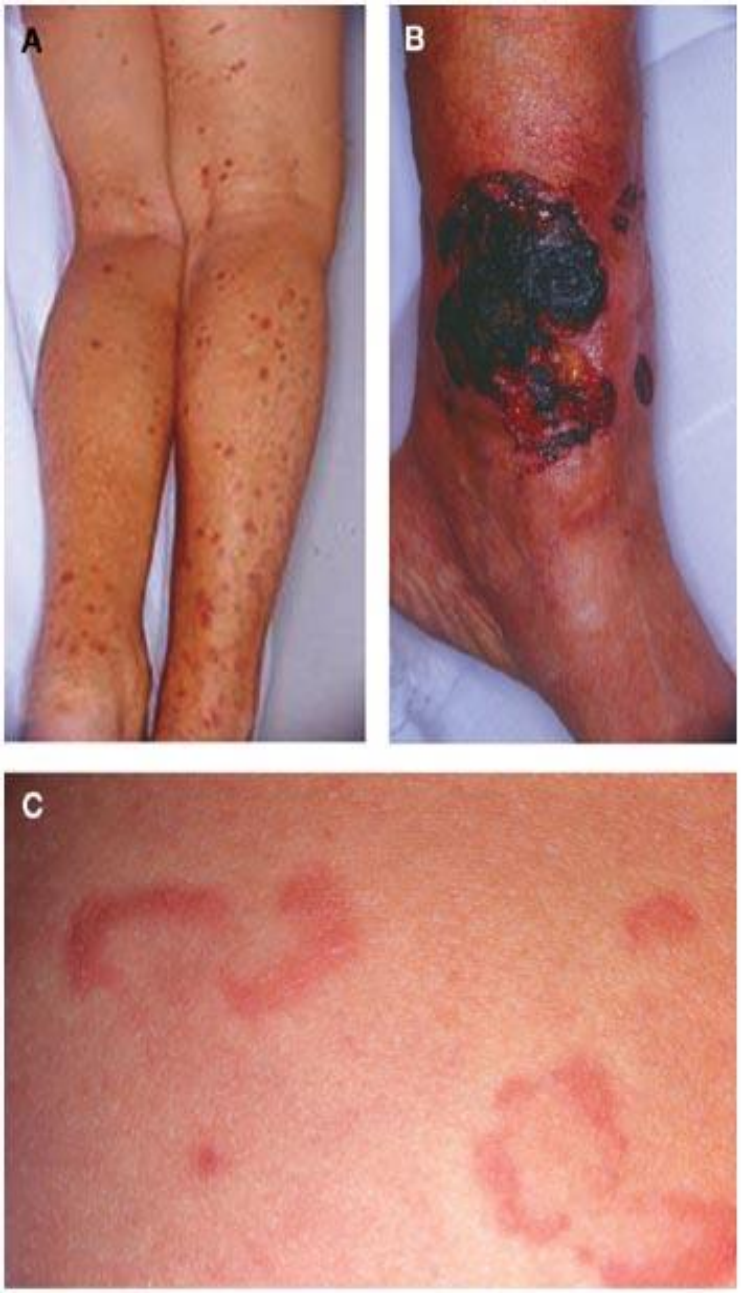


Clinical Findings

- Reduction or absence of respiratory tract glandular secretions can lead to *dryness of the nose, throat, and trachea* resulting in persistent hoarseness and chronic, nonproductive cough.
- Likewise, involvement of the exocrine glands of the skin leads to *cutaneous dryness*.
- In female patients with SjS, *dryness of the vagina and vulva* may result in dyspareunia and pruritus, affecting their quality of life.

Organ Manifestations

- **Skin** - Cutaneous dryness, palpable purpura, Ro-associated polycyclic lesions, urticarial lesions, ulcers
- **Joints** - Arthralgias, nonerosive symmetric arthritis
- **Lungs** - Obstructive chronic pneumopathy, bronchiectasis, interstitial pneumopathy
- **Cardiovascular** - Raynaud phenomenon, pericarditis, autonomic disturbances
- **Liver** - Associated hepatitis C virus infection, primary biliary cirrhosis, type 1 autoimmune hepatitis



Organ Manifestations

- **Nephro-urologic** - Renal tubular acidosis, glomerulonephritis, interstitial cystitis, recurrent renal colic
- **Peripheral nerve** - Mixed polyneuropathy, pure sensitive neuronopathy, mononeuritis multiplex, small-fiber neuropathy
- **Central nervous system** - White matter lesions, cranial nerve involvement (V, VIII, and VII), myelopathy
- **Thyroid** - Autoimmune thyroiditis
- **General symptoms -** Low-grade fever, generalized pain, myalgias, fatigue, weakness, fibromyalgia, polyadenopathies

Diagnostic tests

- **Complete blood cell count**
- Normochromic, normocytic anemia. Isolated cases of hemolytic anemia
- Mild leukopenia (3–4×10 9 /L); lymphopenia, neutropenia
- Mild thrombocytopenia (80–150 × 10 9 /L)
- **Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)**
- Elevated ESR (>50 mm/h) in 20–30% of cases, especially in patients with hypergammaglobulinemia
- Normal values of CRP

Diagnostic tests

- **Serum protein**
- Hypergammaglobulinemia
- Monoclonal band
- **Liver function tests**
- Raised transaminases (associated with hepatitis C virus or autoimmune hepatitis)
- Raised alkaline phosphatase and/or bilirubin (associated with primary biliary cirrhosis)
- **Electrolytes and urinalysis**
- Proteinuria (glomerulonephritis)
- Hyposthenuria, low plasma bicarbonate, and low blood pH (renal tubular acidosis)

Diagnostic tests

- **Antinuclear antibody test**
- Positive in more than 80%
- **Rheumatoid factor**
- Positive in 40–50% of patients, often leading to diagnostic confusion with rheumatoid arthritis
- **Anti-extractable nuclear antigens antibodies** - Positive anti-Ro/SS-A (30–70%) and anti-La/SS-B (25–40%)
- **Complement** (C3, C4, and CH50)
- Complement levels are decreased in 10–20% of patients
- **Cryoglobulins**
- Present in 10–20% of patients
- **Other autoantibodies**
- Antimitochondrial antibodies (associated with primary biliary cirrhosis)
- Antithyroid antibodies (associated with thyroiditis)
- Anti-dsDNA (associated with systemic lupus erythematosus)
- Anticentromere (associated with a limited form of systemic sclerosis)

Special Tests

Salivary gland biopsy

- Minor salivary gland biopsy remains a highly specific test for the diagnosis of SjS.
- Focal lymphocytic sialadenitis, defined as multiple, dense aggregates of 50 or more lymphocytes in perivascular or periductal areas in the majority of sampled glands, is the characteristic histopathologic feature of SjS.
- The key requirements for a correct histologic evaluation are an adequate number of informative lobules (at least four) and the determination of an average focus score (a focus is a cluster of at least 50 lymphocytes).

Special Tests

Assessment of oral involvement

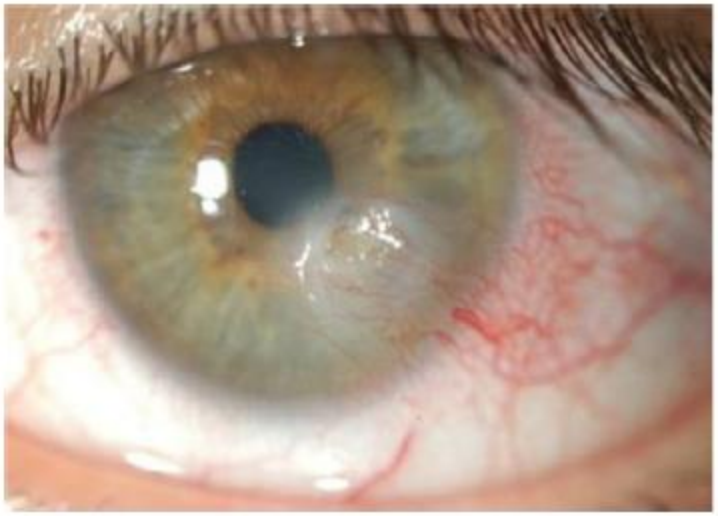
Several methods to assess oral involvement have been proposed, such as measurement of the salivary flow rate, sialochemistry, sialography, or scintigraphy.

- Ultrasonography is a noninvasive method that may provide useful information about the etiology of parotid enlargements.

Special Tests

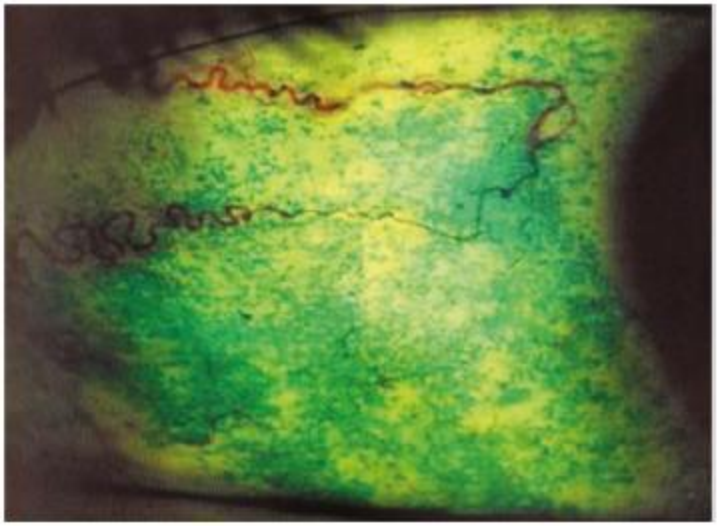
Assessment of ocular involvement

- The main ocular tests are the Schirmer test and rose bengal or lisamine green staining.
- The Schirmer test for the eye quantitatively measures tear formation via placement of filter paper in the lower conjunctival sac.
- The test result is positive when less than 5 mm of paper is wetted after 5 minutes.
- Rose bengal (or lissamine green) scoring involves the placement of 25 mL of rose bengal solution in the inferior fornix of each eye and having the patient blink twice. Slit-lamp examination detects destroyed conjunctival epithelium due to desiccation.



Roze Bengal

Lissamine green



2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's Syndrome

- Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm2 – scor 3
- Anti-SSA/Ro positive – scor 3
- Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye –scor 1
- Schirmer's test ≤5 mm/5 minutes in at least 1 eye – scor 1
- Unstimulated whole saliva flow rate ≤ 0.1 ml/minute – scor 1.

The classification of primary Sjogren's syndrome applies to any individual who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a ***score of more than 4*** *when the weights from the 5 criteria items are summed.*

Treatment

- Treatment of sicca manifestations is mainly symptomatic and is typically intended to limit the damage resulting from chronic involvement.
- Moisture replacement products can be effective for patients with mild or moderate symptoms.
- Frequent use of preservative-free tear substitutes are recommended, while ocular lubricating ointments are usually reserved for nocturnal use.

Treatment

- Saliva replacement products and sugar-free chewing gums may be effective for mild to moderate dry mouth.
- Alcohol and smoking should be avoided and thorough oral hygiene is essential.
- For patients with residual salivary gland function, oral **pilocarpine** and **cevimeline** are the treatment of choice.
- The doses that best balance efficacy and adverse effects are 5 mg every 6 hours for pilocarpine and 30 mg every 8 hours for cevimeline.
- In patients with contraindications or intolerance to muscarinic agonists, **N-acetylcysteine** may be an alternative.

Treatment

- As a rule, the management of extraglandular features should be organ-specific, with **glucocorticoids** and **immunosuppressive agents** limited to potentially severe scenarios.
- **Nonsteroidal anti-inflammatory drugs** usually provide relief from the minor musculoskeletal symptoms of SjS, as well as from painful parotid swelling.
- **Hydroxychloroquine** may be used in patients with fatigue, arthralgias, and myalgias.
- For patients with moderate extraglandular involvement (mainly arthritis, extensive cutaneous purpura, and non-severe peripheral neuropathy), 0.5 mg/kg/d of prednisone may suffice.

Treatment

- For patients with internal organ involvement (pulmonary alveolitis, glomerulonephritis, or severe neurologic features), a combination of prednisone and immunosuppressive agents (cyclophosphamide, azathioprine, or mycophenolate mofetil) is suggested.
- With regard to **biologic agents**, evidence from controlled trials suggests the lack of efficacy of tumor necrosis factor inhibitors in primary SjS.
- B-cell targeted agents seem to be the most promising future therapy. **Rituximab** has shown improvement in some extraglandular features (vasculitis, neuropathy, glomerulonephritis, and arthritis).