A. Scleroderma

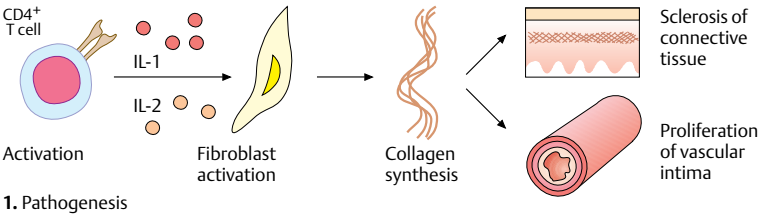
Scleroderma, or progressive systemic sclerosis (PSS), is characterized by fibrosis of the connective tissue with preferential involvement of the skin, vessels, lungs, pleura, myocardium, pericardium, esophagus, and small intestine. The cause of this multisystem disease is unknown.

1. The affected tissues exhibit an abundance of activated $CD4^+$ T cells, which trigger collagen synthesis in fibroblasts by way of IL-1 and IL-2. Increased collagen deposition in the extracellular space leads to sclerosis of the connective tissue. In vessels, the collagen deposits cause endothelial damage and occlusion due to intimal proliferation. This ultimately results in thickening and induration of the skin, dysfunction of the affected internal organs, and infarctions resulting from obliteration of the vessels.
2. Raynaud's syndrome, a circulatory disorder affecting the distal parts of the extremities, is an early symptom of scleroderma. It may precede the other symptoms by several years. In the later course of disease, initially painless edemas form in the hands (sausage-like fingers) and eventually progress to sclerodactyly (Madonna fingers) with acro-osteolysis. "Rat-bite necrosis" of the fingertips may develop due to impaired circulation. The characteristic features of scleroderma patients with facial sclerosis are a small mouth (microstomia) and pointed nose. Telangiectasias of the skin and mucosae are also common. Myocardial fibrosis and bilateral basal pulmonary fibrosis occur in 40% of all patients with scleroderma. There may be elevation of two parameters of inflammation, C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR), in addition to the detection of typical autoantibodies in the patient's serum. The demonstration of anti-centromere antibodies or antibodies against topoisomerase I (anti-Scl-70 antibodies) is a primary immunological feature. Anti-nuclear antibodies of different specificities can also be found, whereas anti-dsDNA and Sm antibodies are absent.
3. CREST syndrome is an older designation of a limited form of scleroderma. The acronym is made up of the first letters of the characteristic symptoms of the syndrome: calcinosis (C), Raynaud's syndrome (R), esophageal motility disturbance (E), sclerodactyly (S), and telangiectasia (T). Anti-centromere antibodies are a typical finding observed in 70% of all patients with CREST syndrome. The condition is often associated with primary biliary cirrhosis (PBC).

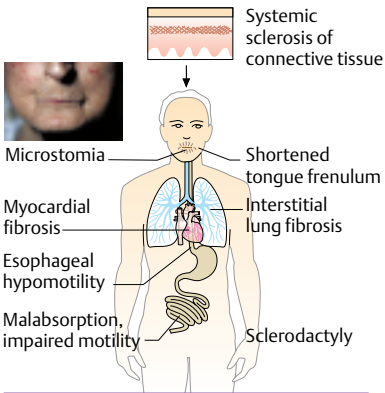
In addition to immunosuppressive therapy with steroids or basic therapeutic preparations, treatment is also symptomatic. Calcium antagonists are used to treat the circulatory disorders associated with Raynaud's syndrome; prostaglandin infusions are used for skin ulcerations. Prostacyclins have proved to be effective for angiopathy.

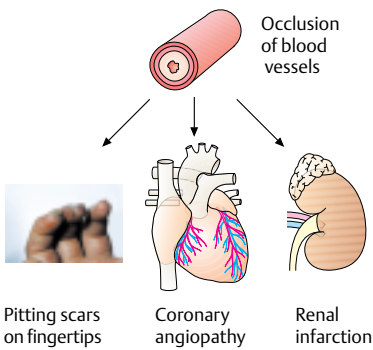
B. Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD), or overlap syndrome, is characterized by the overlapping of symptoms of different connective tissue diseases (SLE, scleroderma, rheumatoid arthritis, polymyositis, dermatomyositis, Sjögren's syndrome). Raynaud's phenomenon is usually the first early symptom of the disease. Other features, in decreasing order of frequency, are sclerodactyly and swelling of the hands, polyarthralgia, pulmonary symptoms, impaired esophageal motility, myositis, and skin manifestations. High titers of autoantibodies against ribonuclease P (U1-RNP) are a typical findings. Anti-nuclear antibodies and rheumatoid factors can also be detected. Autoantibodies against dsDNA, Scl-70, Sm, Ro, La, and PM are infrequently detected. The treatment of MCTD is similar to that of scleroderma or SLE. The actual regimen varies in accordance with the type and severity of the predominant symptoms.



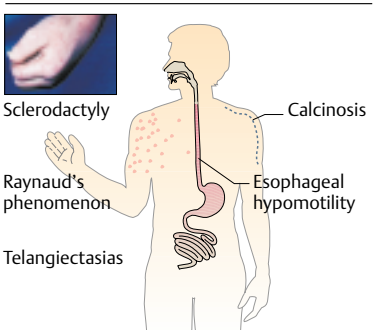
1. Pathogenesis





Auto-Ab → Centromere (CREST)
→ Topoisomerase I
ANA

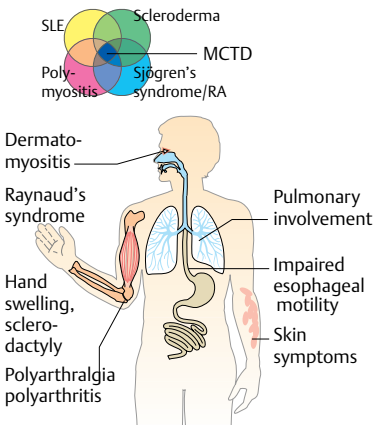
2. Symptoms



Anti-centromere Ab → Association with PBC

3. CREST syndrome

A. Scleroderma



Anti-U1-RNP-Ab → ANA highly positive

B. Mixed connective tissue disease (MCTD)

A. Clinical Features

Distinctions are made between primary and secondary Sjögren's syndrome. The primary form is an autoimmune disease of the exocrine glands with extraglandular systemic involvement, whereas the secondary form is also associated with other autoimmune diseases, such as rheumatoid arthritis (50–60% of cases), connective tissue diseases (SLE, scleroderma, polymyositis), vasculitis (polyarteritis nodosa) and/or primary biliary cirrhosis (50% of cases), Hashimoto's autoimmune thyroiditis, and chronic active hepatitis. Second only to rheumatoid arthritis, Sjögren's syndrome is one of the most common inflammatory rheumatic diseases. Women are affected nine times more often than men. The onset is usually after 40 years of age. Dryness of the eyes (xerophthalmia) and dry mouth (xerostomia) are the most common symptoms of Sjögren's syndrome. Inflammation of the salivary and lacrimal glands followed by lymphocytic infiltration and destruction of the glandular tissue is the underlying basis of these "sicca" symptoms. Polyarthralgia (nonerosive arthritis), myalgia, Raynaud's syndrome, and lymphadenopathy are extraglandular manifestations of Sjögren's syndrome. Complications in the lungs (interstitial pneumonia), kidneys (interstitial nephritis, tubular acidosis), and liver (in PBC) are rare manifestations.

B. Pathogenesis

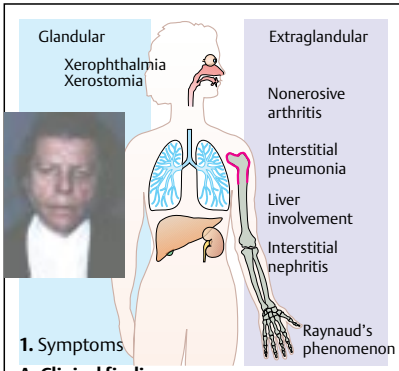
A number of factors play a role in the development of Sjögren's syndrome, which is associated with HLA DR3, DQ1, and DQ2 antigens. The prevalence of Sjögren's syndrome in women suggests that estrogens play at least a supporting role in its pathogenesis. The actual trigger of glandular dysfunction is assumed to be a viral infection. Epithelial cells in the infected gland present viral antigens. This attracts T cells, which infiltrate the glandular tissue and cause a local inflammatory reaction, resulting in damage to the glandular tissue. The T cells activate the glandular epithelium and, most importantly, B cells. This results in excessive, uncontrolled B-cell proliferation, which initially manifests in the peripheral blood as hypergammaglobulinemia in association with the presence of immune complexes. Increases in the ESR and CRP levels can be detected in addition to anti-nuclear antibodies (ANA), rheumatoid factors, and autoantibodies against Ro antigen (SS-A) and La antigen (SS-B). Since these autoantibodies also occur in other autoimmune diseases, their differential diagnostic value is limited. The aggressive polyclonal activation of B cells ultimately progresses to non-Hodgkin's lymphoma in 10–15% of cases.

C. Diagnosis

In addition to these hematological features, certain pathological changes are also of diagnostic importance, for example, *Schirmer's test* of tear secretion (degree of wetting of a strip of paper placed on the lower eyelid), *Saxon's test* of saliva production (the patient must chew on a compress), *sialography*, *salivary gland scintigraphy* for visualization of the ducts (rarefaction and luminal narrowing), and *labial biopsy* for histological diagnosis (e.g., of periductal lymphocytic infiltration). Siccalike syndromes, such as amyloidosis and AIDS, and the effects of certain drugs (e.g., antidepressants) must be considered in the differential diagnosis.

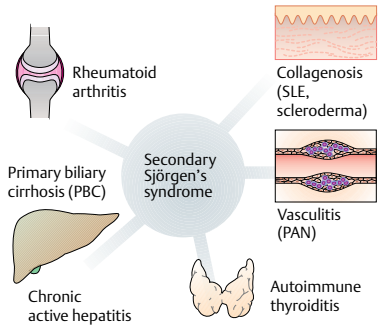
Management

Treatment is initially symptomatic and is limited to the local application of artificial tears (methylcellulose) and artificial salivary fluid. Nonsteroidal anti-inflammatory drugs and cortisone are used to treat mild joint involvement. Severe extraglandular manifestations require the use of azathioprine.

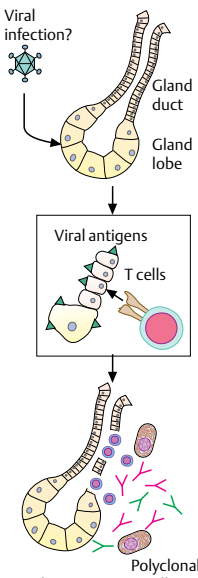


1. Symptoms

A. Clinical findings

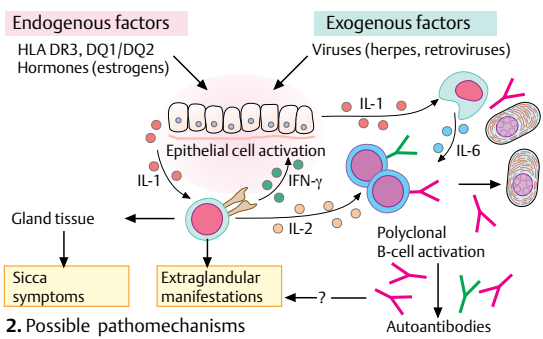


2. Secondary Sjögren's syndrome

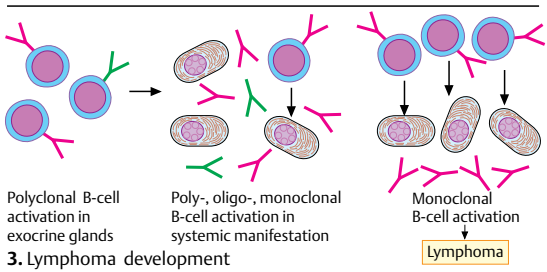


1. Exocrine glands

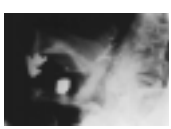
B. Pathogenesis



2. Possible pathomechanisms



3. Lymphoma development



Sialography

Lip biopsy, histology

ANA, rheumatoid factors anti-Ro-, anti-La Ab

C. Diagnosis