

# Differential diagnosis of scleroderma and pseudoscleroderma

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- anti-centromere antibodies
- pseudoscleroderma

## Introduction

The definitive diagnosis of a disease depends on knowledge of its cause [1]. The etiology of scleroderma and other collagen-vascular disorders is largely unknown at present, and the diagnosis is based on clinical, laboratory and histologic criteria defined by experts. Systemic scleroderma (SSc), in contrast to morphea (circumscribed scleroderma) is a systemic disorder whose leading symptom is sclerosis of the skin [2]. Besides classical SSc in its diffuse and limited forms, several unusual clinical manifestations exist [3]. Further, a variety of other diseases presents with sclerosis of the skin (pseudosclerodermas). Differential diagnosis is complicated by the fact that several pseudosclerodermas can imitate scleroderma beyond the symptom of sclerosis of the skin, and that, in rare cases, visceral scleroderma can occur without sclerosis of the skin [4]. The heterogeneity of various forms of SSc as well as the multitude of scleroderma-like diseases routinely confounds diagnosis. Even though sclerodermas and pseudosclerodermas are relatively rare, the correct diagnosis is important

## Summary

The different forms of scleroderma and the pseudosclerodermas, which clinically partially imitate scleroderma, are rare. Due to the large variety and variability of the clinical course, particularly at the onset of disease, diagnosis may be difficult. For differential diagnosis, the presence of Raynaud phenomenon, antinuclear antibodies and the distribution of sclerosis play essential roles. Besides discussing the diseases that should be considered in the differential diagnosis, we present an algorithm which should facilitate the diagnosis and allow one to promptly initiate appropriate treatment.

to prevent false treatment strategies. The following article depicts how differential diagnosis of the symptom sclerosis of the skin can be made rationally.

## Systemic scleroderma

Sclerodermas in a strict sense include SSc and circumscribed scleroderma. SSc is a multiorgan disease with a progressive, potentially fatal course [5]. While the cause is unknown, microvascular changes, disturbed immunomodulation and an overproduction and deposition of collagen play central roles. SSc is relatively rare with a reported incidence of 2 to 20 per million population [6]. In addition to the connective tissue of the skin, internal organs and blood vessels are involved to a variable degree. In 1980, the American College of Rheumatology defined criteria for diagnosing SSc [7]. The major criterion was proximal diffuse sclerosis and minor criteria were sclerodactyly, rat bite necrosis and loss of finger pads as well as bilateral basal pulmonary fibrosis.

The most important internationally employed classification differentiates two disease forms, diffuse cutaneous SSc

(dSSc) and limited cutaneous SSc (lSSc) [2]. In 2001, the classification was modified in regard to diagnostically difficult early or limited forms of SSc [8]. The highly characteristic CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal involvement, sclerodactyly and telangiectasia) is now included as a subtype of lSSc. More than 60 % of patients present with the findings of lSSc. Classically, these patients have long-standing Raynaud phenomenon together with swelling of the fingers and a mild, slowly progressing disease course. Organ involvement occurs later and more rarely. Nevertheless, in about 15 % of cases pulmonary hypertension constitutes a serious complication. Patients with dSSc have a significantly more rapid disease course. Characteristic features are Raynaud phenomenon, arthritides and acral sclerosis with rapid centripetal progression, as well as a high incidence of renal, cardiac and pulmonary complications [3].

The key symptom of SSc, sclerosis of the skin, appears in different stages during the course of the disease. At first, edema is frequent, followed by sclerosis of connective

tissue. Finally, a general atrophy develops. The distribution of sclerosis is important not only for diagnosis, but also for classifying into the subtypes and estimating the severity of SSc. In differential diagnosis the distinction must be made between involvement of fingers distal to the metacarpophalangeal joints typical for SSc and proximal involvement. In addition to distribution of sclerosis, Raynaud phenomenon and capillaroscopy as well as determination of antinuclear antibodies are the main parameters for diagnosing SSc.

### Raynaud phenomenon (RP)

The phenomenon described by Maurice Raynaud in 1862 and named after him plays a central role in diagnosing SSc, especially difficult early forms [9]. It is characterized by reversible vasospasm of acral arteries and arterioles and the resulting typical color changes in the form of white ischemia, blue cyanosis and red hyperemia (Figure 1) [10]. Beyond history, further objective modalities to diagnose RP are available: standardized questionnaire, color charts, a cold stimulus, re-warming of skin after a defined cold challenge or instrumental measurement of cold-induced capillary spasm [8]. RP is a frequent complaint, especially in patients with a rheumatic disorder [10].

Primary RP is differentiated from secondary RP. Primary RP usually presents in adolescence as recurrent episodes provoked by stress and cold with mild symptoms. Complications such as necrosis or ulceration due to hypoxia do not occur in this form, which affects about 3 % of the population. Involvement is symmetrical. Secondary RP occurring in collagen-vascular disorders usually display asymmetric signs and symptoms and is often accompanied by ulcers or necrosis as well as an elevat-

ed sed rate. Capillaroscopy has been employed for decades as an objective examination method in RP. Typical pathological findings are avascular fields and megacapillaries [11].

### Antinuclear antibodies (ANA)

Following clinical evaluation of the patient for differential diagnosis, autoantibody testing should be performed. ANA are autoantibodies directed against nuclear antigens that can further be differentiated according to targeted structure. Many target antigens were in the past named ENA (extractable nuclear antigens), a term that should no longer be used. The detection of autoantibodies and the determination of their specificity play a major role. ANA occur in about 90 % of patients with scleroderma [12]. The most important ANA in systemic scleroderma are anti-Scl-70 antibodies and anti-centromere antibodies (ACA) [13, 14]. Anti-Scl-70 antibodies are found in up to 70 % of patients with dSSc and possess a specificity of nearly 100 % [15]. ACA, on the other hand, are associated with ISSc, especially CREST syndrome, but can also appear in other rheumatic diseases. Also anti-RNA polymerase antibodies should be mentioned because of their association with dSSc, frequent occurrence of organ involvement and a poor prognosis. It is interesting to note that the appearance of autoantibodies in many collagen-vascular diseases can precede the onset of illness by years [13, 16]. ANA can be found usually in low titers, even in healthy people [17]. In the event of positive titers, a further differentiation should be undertaken, as disease-specific autoantibodies have a high predictive value for developing a systemic autoimmune disease in the future. When ANA titers are not elevated and no RP exists, SSc is highly unlikely.

### Systemic sclerosis sine scleroderma

The first report of visceral sclerosis without cutaneous sclerosis dates back to 1954 and was termed progressive systemic sclerosis without scleroderma in 1962 [18, 19]. Newer literature classifies SSc sine scleroderma into the group of SSc. Poormoghim et al. observed 555 consecutive patients with SSc without diffuse skin involvement [4]. In 507 cases, ISSc was diagnosed. In 48 patients typical organ manifestations of SSc were found without skin sclerosis. Of these, 98 % had RP and 93 % a positive ANA titer. These rates do not differ significantly from those of ISSc patients. Differences were found in pulmonary involvement. Dyspnea on exertion or pulmonary hypertension occurred in 65 %. In the ISSc group only 37 % had dyspnea on exertion and 13 % pulmonary hypertension. For the diagnosis of SSc sine sclerosis, a positive ANA titer and RP should be present. Further, the patient should display typical organ manifestations and other collagen-vascular diseases should be excluded.

### Overlap syndrome

About 10 % of patients with systemic scleroderma have clinical features of overlap syndrome, in which clinical and serological characteristics of individual rheumatic diseases overlap. The most common disease in this group is mixed connective tissue disease described by Sharp in 1972 [20]. Here, too, RP and elevated ANA are frequently found, with differentiation often yielding anti-U1RNP antibodies [1]. Skin manifestations are swelling of the hands and sclerodactyly. Spread proximal to the wrists is rare. Further common problems are arthritis, esophageal involvement, pulmonary diffusion disturbances, myositis and serositis. Rarely, renal or cerebral disorders occur.

### Circumscribed scleroderma

Circumscribed scleroderma is a disease limited to the skin, and here to certain areas, of unknown cause [21]. The incidence is relatively low with 3/100,000 and a female predominance exists. In contrast to SSc, children and adolescents are affected more often. Various classifications of circumscribed scleroderma exist. Usually, five entities are differentiated: linear circumscribed scleroderma, plaque-type morphea, bullous morphea,



**Figure 1:** Raynaud phenomenon. Vasospastic, ischemic attack in two patients with systemic sclerosis. Typical asymmetric distribution and ulceration of fingertips (arrows).

generalized morphea and deep morphea [22]. In these diseases usually no RP, ANA or organ involvement are found. Clinically characteristics of morphea are one or more circumscribed oval plaques. At the border of the plaque presenting in the inflammatory phase one finds a typical “lilac ring”. In the course of the disease a central sclerosis develops which ends in a hypo- or hyperpigmented atrophy. The lesions tend to be asymmetric and are usually located on the trunk, less so on the extremities. Classically, the fingers are spared. Manifestation on the lower extremities occurs more often in the linear form. Atrophy and sclerosis can extend to subcutaneous tissue and involve subcutaneous fat and rarely fascias and muscles. Contractures can be the clinical result. Bones can be involved resulting in melorheostosis. Children can develop differences in length of the legs. A rare form is pansclerotic scleroderma involving the entire skin with exception of fingers (Figure 2). Therapeutic options include high-dose intravenous penicillin therapy, steroids, UVA-1 and psoralen-UVA phototherapy as well as methotrexate [23, 24]. There is no reduction of life expectancy [21]. A special form, scleroderma en coup de sabre, is a unilateral, linear involvement of the head and face. It can be associated with intracerebral inflammation, epilepsy, uveitis and other neurologic abnormalities [25]. Difficulties can occur in the differential diagnosis of scleroderma en coup de sabre and progressive hemofacial atrophy (Parry-Romberg syndrome) [26]. The latter is a developmental disorder manifesting in the first two decades of life.

### Eosinophilic fasciitis

Eosinophilic fasciitis, which some authors believe to be an acute form of morphea, presents with relative acute, symmetric swelling and induration of the extremities (Figure 3) [27]. The onset of the disease is appeared to be associated with preceding trauma or severe exertion. A characteristic finding is the negative vein sign, so termed because the vein is not prominent but appears as a sunken line. Laboratory tests show peripheral eosinophilia, hypergammaglobulinemia and elevated sed rate [28]. In the acute stage histology is characteristic with eosinophilic and mononuclear infiltrates along the fascia.



**Figure 2:** Morphea in pansclerotic distribution.

In the further course, features become uncharacteristic and show fibrotic changes around the fascia. The peripheral eosinophilia can usually no longer be determined. For diagnosis a sufficiently deep biopsy including the fascia must be performed. In contrast to SSc, the fingers, feet and the face are almost always spared. An involvement of internal organs is rare, but associations with myopathy, neuropathy, carpal tunnel syndrome, hematological disturbances and autoimmune thyroiditis have been reported [29]. While RP or a pathologic capillaroscopy are absent, low-titer ANA can occur. Therapeutic options include systemic glucocorticoids, maybe in combination with UVA-1 phototherapy. Classically, eosinophilic fasciitis



**Figure 3:** Eosinophilic fasciitis. Characteristic woody induration. The veins are not prominent, but rather sunken into the skin.

responds quickly and well to treatment [29]. In resistant cases, cyclosporine and methotrexate have been used successfully [28, 30].

### Pseudosclerodermas

The list of diseases that can imitate scleroderma not only with regards to typical skin lesions is given in Table 1. Some of the most important diseases are discussed in differential diagnostic terms in the following.

### Sclerodermiform genodermatoses

A group of genodermatoses, also known as premature aging syndromes, such as progeria, acrogeria or Werner disease,

**Table 1:** Differential diagnosis of sclerodermiform diseases. Presentation of diseases that can, at least in part, imitate sclerodermas.

- Circumscribed scleroderma
- Eosinophilic fasciitis
- Sclerodermiform genodermatoses (e.g. progeria, Werner disease)
- Acrodermatitis chronica atrophicans
- Scleroderma-like syndromes induced by environmental factors (e.g. eosinophilia-myalgia syndrome)
- Scleredema adutorum Buschke
- Scleredema diabeticorum
- Scleromyxedema
- Nephrogenic fibrosing dermatopathy
- Porphyria cutanea tarda
- Graft-versus-host disease
- Scleroderma-like lesions in malignancies

can present with features similar to scleroderma [26]. Premature aging syndromes often result from mutations in nuclear proteins needed to maintain genome integrity [31]. Progeria is a rare genodermatosis manifesting in the first years of life and having a greatly shortened life expectancy [32]. Clinical features include high-degree growth retardation, an unproportionally large head, alopecia, skeletal deformities, wrinkled skin and significant signs of premature aging. The skin on the extremities and fingers can display features similar to scleroderma. Acrogeria is a localized premature aging syndrome which shows no other abnormalities besides atrophy of skin and subcutaneous tissue. Werner disease is a rare autosomal recessive disease featuring premature aging, typical stature and thin distal extremities as well as deformities and ulcers of feet and legs. Endocrinologic disturbances, among others, can occur. The skin can present with scleroderma-like changes such as atrophy, induration and distal sclerosis, especially of legs and feet.

#### Acrodermatitis chronica atrophicans

Acrodermatitis chronica atrophicans is a late stage of *Borrelia* infection [33]. Clinically, in the early inflammatory stage, one often finds a unilateral, darkly livid, edematous swelling usually of a lower extremity, which after months transforms into the atrophic stage with cigarette paper-like skin. Forearms and lower legs are often affected [34]. Differentiating morphea and acrodermatitis chronica atrophicans can be difficult both clinically and histologically. Histologically, one finds in addition to fibrosis perivascular infiltrates including plasma cells in both diseases.

#### Scleroderma-like syndromes induced by environmental factors

Several exogenous factors can induce scleroderma-like diseases. The list includes silica dust, solvents such as aromatic hydrocarbons, vitamin K and drugs such as bleomycin or penicillamine [26, 35]. Further, x-rays have been suspected as triggers. In the USA in 1989 a previously unknown disease was observed: eosinophilia-myalgia syndrome (EMS) [36]. It was notable that affected patients had taken L-tryptophan. First, a contamination of the L-tryptophan raw product was etiologi-



**Figure 4:** Scleredema. Typical induration of neck and shoulders.

cally suspected. The exact cause could never be determined. Symptoms of the disease include myalgia, exanthemas, respiratory symptoms, paresthesias, swelling and muscular weakness. Discontinuation led to dramatic improvement of most symptoms in over 70 % of patients. Sclerodermiform changes usually persisted.

#### Scleredema adultorum Buschke

A disease rarely misdiagnosed as SSc is scleredema, where mucin is deposited in dermal connective tissue [37]. In its acute form, the disease is known as scleredema adultorum Buschke. It is a primary mucinosis of unknown etiology characterized by rapidly developing induration of the nape of the neck, shoulders and upper limbs and which can become chronic in individual cases (Figure 4). The fingers are always spared in the acute form and internal organ involvement is very rare. Often, an association with diabetes mellitus is observed [38]. Febrile infections, acute diseases of the upper respiratory tract as well as HIV infections are discussed as triggers. The disease usually runs a self-limited course and heals within two years. Bath PUVA and UVA-1 phototherapy are therapeutically effective.

#### Scleredema diabeticorum

In addition to scleredema adultorum Buschke, scleredema diabeticorum is also associated with diabetes mellitus and is characterized by scleroderma-like lesions on fingers and hands and a thick, waxy skin [26]. Secondly, joint con-



**Figure 5:** Nephrogenic fibrosing dermopathy. Scleroderma-like fibrosis in a patient who underwent kidney transplantation.

tractures can develop. Improvement of the metabolic situation can lead to stabilization and, in some cases, to improvement.

#### Scleromyxedema

Scleroderma must be differentiated from the very rare scleromyxedema. In the latter, firm, smooth papules develop on limbs, trunk and face, and internal organs are frequently involved [37, 39]. RP does not exist. Deposits of mucin in the papillary dermis are found. Characteristically, monoclonal IgG (lambda) and a multiple myeloma are present [40]. Prognosis is defined by internal organ involvement including severe involvement of the central nervous system and is poor overall. Treatment is difficult. Effective treatment with plasmapheresis and cyclophosphamide has been reported [41]. High-dose intravenous immunoglobulins have successfully been used in single cases [40]. Some patients have achieved lasting remission following autologous stem cell transplantation [42].

#### Nephrogenic fibrosing dermopathy

In 1997 a disease was first described that has in the meantime been termed nephrogenic fibrosing dermopathy (synonym: scleromyxedema-like illness of renal disorder) [43]. More than 100 cases have since been reported in the literature. This patient collective consists primarily of patients with kidney trans-

plants or renal insufficiency. Papules form and then coalesce into plaques. The disease is accompanied by thickening and induration of the skin and strong pruritus (Figure 5). Contractures occur as a complication. The face is spared, but often a pinguecula is observed. Histology is an important diagnostic criterion. In contrast to scleroderma, a cell-rich fibrosis with CD34-positive fibroblasts permeating the dermis and the connective tissue septa is present. Therapeutic options are limited. An improvement in the course of time has been observed in some cases.

**Porphyria cutanea tarda**

Porphyria cutanea tarda is a disease caused by a deficient activity of hepatic uroporphyrinogen decarboxylase which appears in two forms, a familial form inherited in an autosomal dominant manner and a sporadic form [49]. Clinical manifestations are usually associated with liver damage, provoked by alcohol, estrogens, viral hepatitis, iron overload or hexachlorobenzene. Photoactive porphyrins accumulate in

the skin and can be activated by light. In addition to increased fragility, blistering, erosions, milia and scars, in about 10 % of patients sclerodermiform skin changes appear. In advanced sclerosing cases, differentiation from morphea might only be possible by demonstrating porphyrins in urine.

**Graft-versus-host disease**

Chronic graft-versus-host disease is a multisystemic disease, occurring in up to 25 to 50 % of patients, depending on protocol, receiving allogenic bone marrow transplantation [45]. The chronic form, in which 90 % have skin involvement, is characterized by lichenoid and sclerodermoid skin lesions. These can be localized, disseminated or generalized. Histology reveals dermal sclerosis, vacuolar degeneration of basal keratinocytes and single-cell necrosis in the epidermis with peripheral aggregates of lymphocytes.

**Scleroderma-like lesions in malignancies**

Kikuchi et al. recently reported on five patients with pseudoscleroderma associated with various malignancies [46]. In contrast to SSc, the distribution of skin

lesions was quite variable and the mean duration of disease significantly shorter.

**Diagnostic criteria when scleroderma is suspected**

Due to the complex differential diagnostic possibilities, a standardized approach to the patient presenting with sclerosis of the skin is needed. We recommend an approach as shown in Figure 6 for unclear cases. History and clinical examination should clarify distribution of fibrosis and the presence of RP, perhaps including cold provocation testing. Capillaroscopy of the nail folds and testing for ANA should follow. If neither ANA nor Raynaud phenomenon is present, SSc is highly unlikely. Laboratory tests should include blood count with differential blood count, Borrelia serology and a search for paraproteins. Diabetes mellitus should be excluded. Finally, porphyrin diagnostics may be done. As a next step, biopsy optimally including the fascia, especially when eosinophilic fasciitis is suspected, may yield further information. In doubtful cases and in cases with systemic sclero-

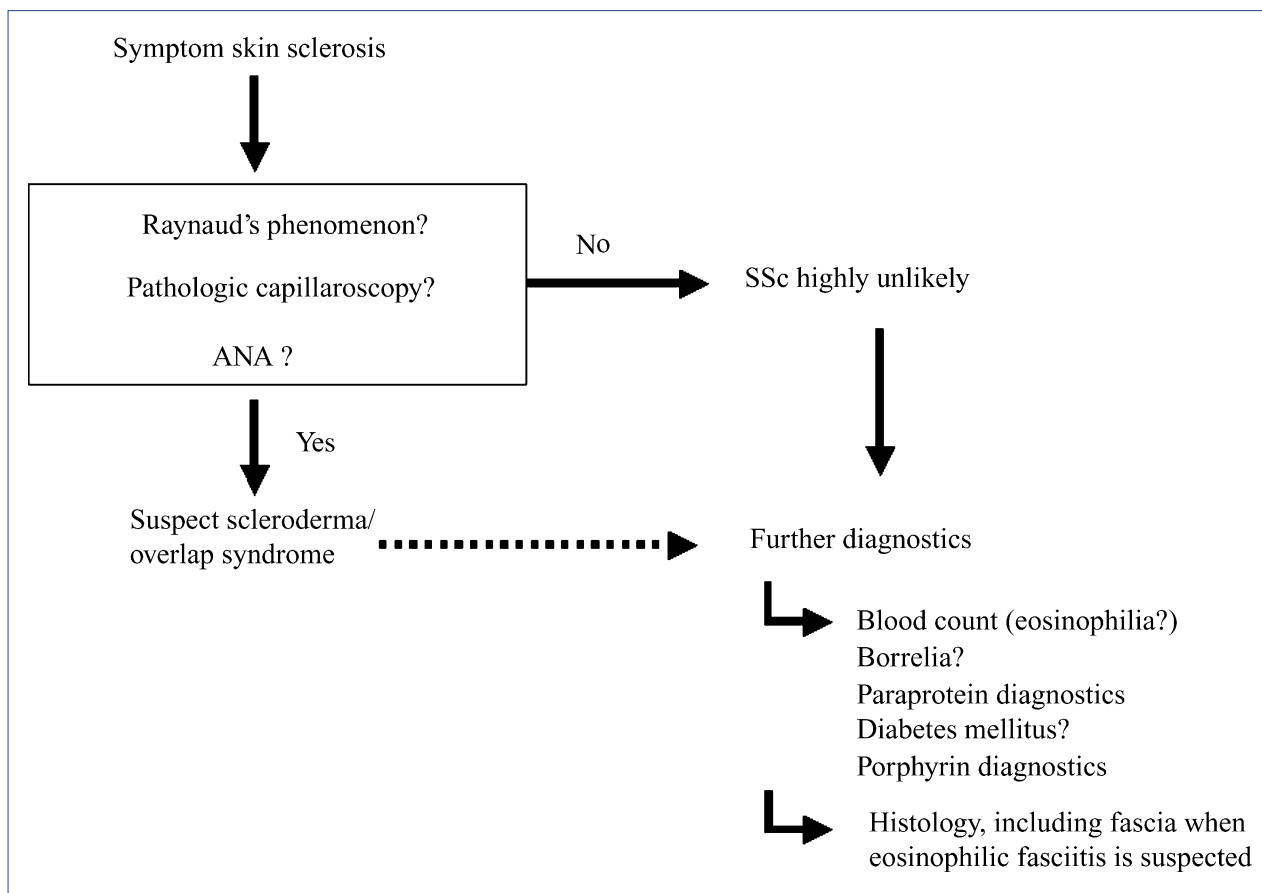


Figure 6: Strategies for differential diagnosis. Algorithm of the differential diagnostic approach to patients presenting with sclerodermoid features.

derma, presentation of the patient in a clinic with special interest in these diseases in the German Network for Systemic Scleroderma can be considered ([www.sklerodermie.info](http://www.sklerodermie.info)). <<<

#### Conflict of interest

None.

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