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REVIEW ARTICLE

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# Systemic sclerosis and scleroderma-like syndromes

## ABSTRACT

Systemic sclerosis (SSc) is a rare disease which belongs to the group of systemic connective tissue diseases characterised by thickening and fibrosis of the skin and internal organs with their failure. Diseases with similar clinical manifestations are referred to as the so-called scleroderma-like syndromes. It is a diverse group with varying aetiology, diagnosis and management. The differential diagnosis should take into account, among other things, contact with chemicals, the presence of Raynaud's phenomenon, capillaroscopic changes, comorbidities and abnormalities in laboratory tests. Scleroderma-like syndromes are particularly supported by the absence of Raynaud's phenomenon and antinuclear antibodies and the normal appearance of capillaries. Performing a skin biopsy can lead closer to an appropriate diagnosis.

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**KEY WORDS: systemic sclerosis; scleroderma-like syndromes; Raynaud's phenomenon; eosinophilic fasciitis; scleroedema; scleromyxoedema; nephrogenic systemic fibrosis; diabetic cheiroarthropathy; lipodermatosclerosis; toxic oil syndrome; tryptophan-induced eosinophilia-myalgia syndrome; epidemic dropsy; Werner syndrome**

## SYSTEMIC SCLEROSIS (SSC)

Systemic sclerosis (SSc) is an autoimmune disease representing systemic connective tissue diseases. It is characterised by thickening and fibrosis of the skin and internal organs, leading to their failure. This results in damage to the microcirculation, changes in morphology and excessive connective tissue accumulation. It is characterised by an almost 100 per cent prevalence of antinuclear antibodies and a group of subtype-specific antibodies: anti-topoisomerase I (anti-Scl-70) and anti-centromere antibodies (ACAs). Its course depends on the clinical presentation and can sometimes take a dramatic form [1–4].

There are two main clinical forms of SSc: limited SSc (lSSc, or acrosclerosis) and diffuse SSc (dSSc). The division was created based on the degree of skin involvement, as both types involve internal organs at some stage [1–5].

The former, lSSc, the clinical form of which used to be called CREST syndrome, is characterised by limited skin lesions that do not extend beyond the elbow and knee line. It develops slowly, taking a chronic course. The first noticeable symptom is usually Raynaud's phenomenon, which involves episodic blanching with subsequent bruising and reddening of the fingers, toes or auricles. It occurs in 90% of patients and may precede the onset of the disease by up to several years [1–3, 5]. Characteristic ACAs are typically present and detected in approximately 70–80% of patients with lSSc. However, anti-Scl-70 antibodies, typical of dSSc, are absent [1, 2]. The main symptoms form the acronym CREST (Tab. 1) [6].

Skin lesions most commonly affect the face, fingers, forearms and lower legs [1, 2, 7]. Moreover, lSSc involves the oesophagus more frequently than dSSc [5]. The sec-

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**Table 1.** Main symptoms of CREST syndrome

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|---|
| **C** — calcinosis (calcification in soft tissues) |
| **R** — Raynaud's phenomenon |
| **E** — esophageal dysmotility (esophageal dysfunction) |
| **S** — sclerodactyly (hardening of the skin of the fingers) |
| **T** — telangiectasias (clusters of dilated small vessels) |

ond most frequently involved organ is the lung, which manifests as interstitial lung disease (ILD). Cardiac involvement is less common than in dSSc, while severe pulmonary arterial hypertension (PAH) and primary cholangitis develop more frequently [1, 2, 4]. PAH usually develops after many years of disease. Ischaemic digital ulcers are also more common. Trigeminal neuralgia is typical [5]. The prevalence of symptoms in lSSc is shown in Figure 1 [5].

Capillaroscopy shows numerous dilated capillaries (megacapillaries) without areas of avascularisation. The thickening of the skin remains at a similar level for many years. No correlation has been shown between skin involvement and the degree of internal organ involvement [5, 7]. It should be noted that organ involvement occurs much more slowly than the progression of skin lesions. The early period of the disease is defined as the first five years. If no marked improvement is observed after this period, the disease progresses to the late stage, in which internal organ involvement is observed [5].

The dSSc subtype used to be called progressive SSc. It is a more severe and violent form than lSSc. Internal organ involvement, especially of the lungs and heart, is more frequent and rapid. It is characterised by extensive, symmetrical skin lesions that involve the face and proximal parts of the extremities, sometimes sparing the fingers [1–4].

The typical development of the disease may be preceded by fatigue, pruritus, arthralgia or arthritis with swelling of the fingers and toes [5]. The sclerosis progresses dynamically, peaking three to six years after the onset of the disease. It may go into remission after a few years, leaving the skin thinner and softer. The extent of sclerosis correlates with the involvement of internal organs, which occurs almost simultaneously with skin sclerosis. The lungs are most commonly involved, leading to ILD in approximately 35% of patients [8]. Less commonly, the disease involves the gastrointestinal tract, heart or kidneys [1–3].

Joint contractures are often present. Raynaud's phenomenon may present simultaneously with sclerotisation or after skin sclerosis. Anti-Scl-70 antibodies are detected in 30% of patients and precede the onset of Raynaud's phenomenon, while ACAs are absent in this form. Capillaroscopy shows numerous dilated capillaries (megacapillaries) and areas of avascularisation [1, 2, 5].

It is accepted that the prognosis and subsequent course of the disease are determined by the early period, which covers the first three years. During this period, skin and organ lesions develop rapidly. This is also the time of highest mortality [1, 2, 5]. For this reason, it is crucial to make the diagnosis as soon as possible and institute appropriate treatment. In the later stages of the disease, the involvement of further organs is less frequent, and the progression of existing lesions is slower [3, 5].

The primary complications of SSc include scleroderma renal crisis (SRC), ILD and cardiac complications [1–5]. SRC is characterised by rapidly increasing hypertension accompanied by acute renal failure. It affects between 5% and 20% of patients with dSSc, with 80% of cases presenting within four years

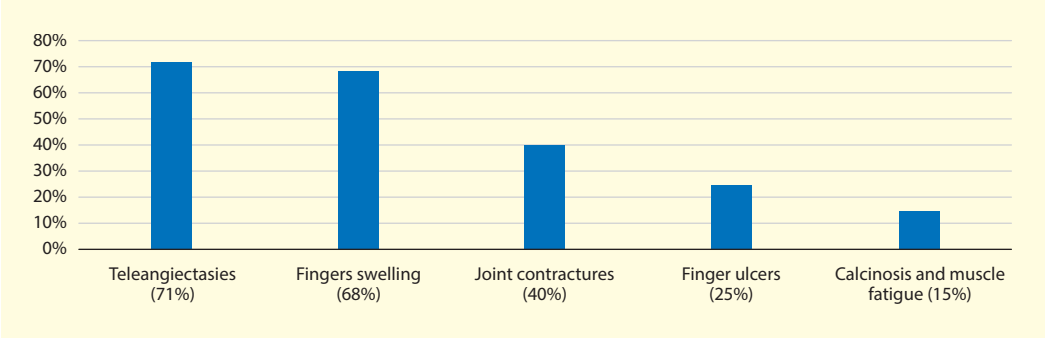


**Figure 1.** Prevalence of limited systemic sclerosis (lSSc)

of the disease onset [1–3]. The widespread use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as treatment has significantly reduced the mortality of this syndrome, which is slowly losing ground as a cause of increased mortality in SSc.

Regular blood pressure measurements and serum creatinine determinations every two to four weeks in patients with SSc allow early diagnosis and the introduction of appropriate treatment. An increase in blood pressure above 140/90 mm Hg or at least a twofold increase in blood creatinine or proteinuria indicates the need for a full-dose ACEI. The aim should be to reduce systolic blood pressure by 10–20 mm Hg over 24 hours [1–3, 5, 7].

If BP is not stabilising, other hypotensive drugs, such as calcium channel blockers (CCBs), are added to the treatment.

In cases of escalating renal failure, dialysis is used. In half of the patients, renal function improves sufficiently after 6–24 months of dialysis to discontinue further renal replacement therapy. Transplantation can be considered two years after the onset of SRC [1–3]. Due to the increase in mortality, efforts should be made to eliminate risk factors for SRC development, especially in the early stages of dSSc. These include glucocorticosteroids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs), cyclosporine A (CsA), urinary tract infections, and severe dehydration [1, 2, 5]. It is important to note that SRC can also develop in lSSc; however, depending on the sources, it is two to as much as ten times less common than in dSSc [2, 5].

Skin lesions in SSc are characterised by a typical course. Initially, there is an oedematous stage in which the skin reddens, and the backs of the hands, fingers, forearms, legs, feet and face swell. The swelling, usually painless, is most noticeable in the morning. It may be accompanied by persistent itching and hypo- or hyperpigmentation. The oedematous stage can last many months and progress smoothly to the sclerosis stage [1, 2, 9]. This stage is characterised by progressive fibrosis and increased tightness of increasingly thick skin. The skin during this period becomes shiny, pigmented and tightly adheres to the subcutaneous tissue. Fibrosis usually begins in the sacral region.

Facial involvement results in microstomia due to subcutaneous fibrosis in the mouth area and reduced range of motion of the temporomandibular joint. Transverse wrinkles around the mouth called smoker's lines develop. The lips become thinner and thinner, and the redness of the lips disappears. Atrophic changes also affect the mucous membranes of the mouth and the nose, and the nose's features sharpen [4, 7]. There is a smoothing of the wrinkles on the dorsal surface of the fingers. The skin folds over the joints enlarge, and the epidermis becomes increasingly thinner. Hair loss presents due to the destruction of the hair follicles. Damage to the sweat and sebaceous glands leads to reduced sweating [9].

In the later stages of the disease, patients often develop areas of vitiligo, which leads to depigmentation with concomitant perifollicular pigment retention, resulting in a ‚salt-and-pepper' skin appearance [7, 9, 10].

After a few years, the sclerotic stage is superseded by the atrophic one. The thickened, fibrotic skin softens over time and returns to its initial thickness, but the fusion with the adipose tissue beneath it permanently prevents it from being folded [3, 9]. It is not uncommon for pigmentary changes to become permanent. In addition, clusters of telangiectasias manifest most commonly on the face and less frequently on the neck and shoulders, hands or lips. There is damage to fingertip skin, small digital pitting scars and ulcers, once called rat bite ulcers.

Calcinosis is a painful complication. It usually presents on the extended parts of the limbs as subcutaneous thickenings, which sometimes progress to fistulas with the discharge of whitish fluid and the subsequent development of hard-to-heal ulcers [7]. Calcium deposits often limit joint mobility. Severe calcinosis is referred to as Thibierge-Weissenbach syndrome [1, 2].

Other rarer forms of SSc include:

— SSc sine scleroderma — with typical internal organ symptoms and vascular lesions with associated antibodies present, without classic skin lesions;
— overlap syndrome of SSc and another systemic connective tissue disease — most often involves presentation of features of rheumatoid arthritis (RA), dermatomyositis, systemic lupus erythematosus (SLE), or mixed connective tissue disease;
— high risk for SSc, or so-called "early scleroderma", which progresses to full-blown SSc (mainly lSSc) in 65–80% of individuals within five years. Raynaud's phenomenon,

finger swelling, specific antinuclear antibodies (ANAs, ACAs, anti-Scl-70) and typical capillaroscopy changes are present. However, classic skin and organ lesions are absent [1, 2].

SSc is a relatively rare disease. According to the latest data, the incidence ranges from 7.2 to 33.9 cases per 100,000 people in Europe. Women are affected two to three times more often than men, with the peak incidence at the age of 30–50 [1–3, 8].

Its aetiopathogenesis is not well understood. The interplay between genetic and environmental factors has been shown to have a significant role in its development. The characteristic fibrosis results from an abnormal immune response and an infiltration of CD4+ cells, which result in inflammation of the skin and vessels, leading to excessive production of collagen and other substances by fibroblasts in the dermis and subcutaneous tissue. Skin fibrosis increases the thickness of the dermis and destroys hair follicles, as well as sweat and sebaceous glands. Damage to blood vessels develops through the proliferation of the tunica intima and tunica media and damage to the endothelium, resulting in vasoconstriction. Due to the different nature of vascular damage, this process is sometimes called vasculopathy [3, 4, 11].

Laboratory tests reveal SSc-specific ANAs (90%), especially ACAs (in lSSc in 70–80%, associated with PAH), anti-Scl-70 (in dSSc in 30%, associated with digital ulcers, ILD and skin fibrosis) and anti-RNA-polymerase III antibodies [according to the available literature, they are associated with SRC, ILD, gastrointestinal damage in the form of gastric antral vascular ectasia (GAVE) and increase the risk of cancer — chiefly breast cancer] [1, 2, 5, 7, 9, 12–14].

In addition, anti-Th/To antibodies (more often with coexisting ILD, PH), anti-PM/Scl antibodies (about 3%, in myositis, ILD), anti-fibrillarin antibodies (8–10%, associated with cardiac and pulmonary involvement), and anti-U1-snRNP antibodies (joint involvement) are also found [1, 2, 7, 13].

Additionally, there may be slight anaemia, a slight elevation of the ESR (a marked increase suggests complications), an increase in immunoglobulin G (IgG) and M (IgM), the presence of rheumatoid factor (RF) in 20-30% of patients, increased levels of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) (in cases of cardiac involvement) [1, 2].

X-rays (radiographs) of the hands may show osteolysis of the distal phalanges (pencil-in-cup deformity, complete resorption of the distal phalanx), subluxations in the interphalangeal joints and calcifications. Contrast studies of the gastrointestinal tract, however, show impaired oesophageal peristalsis of the oesophagus (wide tube shape), small intestine (]alternating strictures and dilatations) and large intestine (diverticulosis).

Upper gastrointestinal endoscopy can reveal features of gastro-oesophageal reflux, telangiectasias and GAVE [1, 2].

Capillaroscopy may reveal megacapillaries and avascular areas. Histopathological examination in the early stages of the disease produces a high rate of false-negative results due to the non-specific clinical picture; therefore, histopathological examination is not used to diagnose the disease.

Skin biopsy and histopathological examination may be useful to differentiate it from other diseases with skin fibrosis [1, 2]. The histological picture shows diffuse sclerosis of the middle and lower dermis. The epidermis is usually not involved. There is an accumulation of dense collagen in the dermis and a loss of epithelial appendage structures. A superficial and deep perivascular lymphocytic inflammatory infiltrate is observed. At the dermal-subcutaneous junction, there is also plasma cell infiltration [11]. The papillary layer of the dermis is usually spared. Later, skin atrophy, flattening of the rete ridges, and involvement of the microcirculatory vessels with their obliteration and fibrosis occur [10].

Due to the risk of developing serious complications, the diagnosis of SSc should be expanded to include assessment of the degree of involvement of/damage to internal organs by ECG, cardiac ultrasound, spirometry, diffusing capacity of the lungs for carbon monoxide (DLCO), post-exercise pulse oximetry, chest X-ray, high-resolution computer tomography (HRCT) or, in doubtful cases, also magnetic resonance imaging (MRI) and bronchoalveolar lavage (BAL) [1, 2, 7].

Regular skin thickness and lesion severity measurements using the modified Rodnan Skin Score (mRSS) assess disease progression and severity. A total skin score (TSS) is calculated, which correlates with the involvement of internal organs [1–3, 5].

**Table 2.** Classification criteria for systemic sclerosis (SSc) according to American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013

| **Classification criteria of SSc according to ACR/EULAR 2013** | |
|---|---|
| **Criteria** | **Score** |
| Skin thickening of the fingers of both hands and extending proximal to the MCP | 9<br>*sufficient criterion* |
| Thickening of the skin of the fingers:<br>• puffy fingers<br>• sclerodactyly | <br>4<br>2<br>*only the highest score is included in the scoring* |
| Fingertip lesions:<br>• scars on the fingertips (known as pitting scars)<br>• fingertip ulcers | <br>3<br>2<br>*only the highest score is included in the scoring* |
| Telangiectasias | 2 |
| Capillary abnormalities of the nailfold typical of scleroderma | 2 |
| Pulmonary arterial hypertension and/or interstitial lung disease | 2 |
| Raynaud's phenomenon | 3 |
| Antibodies specific for SSc (ACA, anti-Scl 70, against RNA polymerase III) | 3 |

MCP — metacarpophalangeal joints; ACA — anti-centromere antibody; anti-Scl-70 — antibody against topoisomerase

The disease classification is based on the 2013 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria (Tab. 2). A diagnosis is made with a score of ≥ 9. However, it is important to note that these criteria do not apply in patients with features of scleroderma-like disease and in cases of skin sclerosis that spares the fingers [1–3, 7].

When treating patients with SSc, it is vital to remember that GCs are ineffective, unlike in the case of many connective tissue diseases and scleroderma-like syndromes. Furthermore, they increase the risk of SCR and cause the progression of skin lesions. For this reason, NSAIDs, beta blockers and CsA should also be avoided in these patients [1, 2].

There is no causal treatment; so-called 'organ-specific' therapy is used. It is a treatment targeted at the clinical presentation, disease stage and complications. Autologous haematopoietic stem cell transplantation (auto-HSCT) is the most effective treatment, used in severe cases with rapidly progressive organ lesions refractory to immunosuppressive therapy [1, 2].

In the early stages of dSSc in patients with rapidly progressive skin lesions, methotrexate (MTX) at a dose of 10–15 mg/week, mycophenolate mofetil (MMF) or cyclophosphamide (CTX) may be considered. Rituximab (RTX; anti-CD20 antibody) is used to reduce the progression of skin lesions [1, 2].

Physiotherapy, kinesitherapy and occupational therapy should be used to improve or maintain mobility in all patients. Appropriate psychotherapy for patients is also essential.

For Raynaud's phenomenon and ulceration and necrosis of the phalanges, first-line treatment includes prolonged-release dihydropyridine CCBs. If these are ineffective, phosphodiesterase type 5 inhibitors (PDE5Is) such as sildenafil, vardenafil, avanafil and tadalafil are used. Fluoxetine is the third-line treatment. In the event of resistance to treatment, iloprost, a synthetic prostacyclin analogue (PCA), or bosentan, which is categorised as a non-selective endothelin receptor antagonist (ERA) type A and B [1, 2], may be applied.

Organ-specific therapy for ILD, according to recent recommendations, includes first-line treatment with MMF orally (PO, *per os*) at a dose of 500–3000 mg/d. As a second-line treatment, CTX by intravenous infusion (IV) at a dose of 600 mg/m$^2$ every 30 days for six months may be considered. If there is improvement, the interval between doses is lengthened, or other immunosuppressive drugs are administered. An alternative to intravenous use is the oral administration of CTX ≤ 2 mg/kg/d for 12 months. Extreme caution should be exercised when using GCs concomitantly, and doses higher than 10 mg/d of prednisone should not be used. Oral nintedanib [inhibitor of fibroblast growth factor

receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR] and subcutaneous tocilizumab (interleukin-6 receptor inhibitor) slow the progression of interstitial lesions but have little effect on the development of skin lesions [1, 2].

RTX is increasingly being applied for ILD in the course of SSc. The results of randomised trials using RTX are promising. Recent literature shows RTX has shown similar efficacy in treating ILD as CTX, improving increased forced vital capacity (FVC) and DLCO while causing fewer adverse reactions [15, 16].

Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) is the second most common form of PAH [17]. The main cause of CTD-PAH is SSc [18-20]. Precapillary PAH presents in 5–19% of patients with SSc [18, 19].

PAH in SSc most often develops due to concomitant ILD or PAH [18–22]. When the myocardium is involved, pulmonary hypertension due to left heart disease (PH-LHD) is differentiated [21, 23]. Depending on the cause of precapillary PAH in SSc, there are different prognoses — patients with extensive ILD and significant deterioration of haemodynamic parameters have a particularly unfavourable prognosis [21]. CTD-PAH is found four times more frequently in women than in men. It is usually diagnosed in patients over 50 [17–21, 24–30].

PAH treatment includes:

— ERAs: ambrisentan, bosentan, macitentan;
— PDE5Is: sildenafil, tadalafil;
— prostacyclins and PCAs: epoprostenol, iloprost, treprostinil;
— riociguat [soluble guanylate cyclase (sGC) stimulator] — acts on the receptor for nitric oxide [31].

The general treatment algorithm for pulmonary arterial hypertension associated with SSc (PAH-SSc) essentially follows the treatment regimen for all types of CTD-PAH. In the presence of cardiovascular and respiratory comorbidities (such as obesity, hypertension, diabetes mellitus, coronary artery disease, mild interstitial lung disease, among others), initial treatment is started with a PDE5I or ERA monotherapy [32].

In the absence of comorbidities, patients are divided into three risk groups for estimated one-year mortality. In the low- and moderate-risk groups, initial treatment includes combination therapy with ERA and PDE5 inhibitors. In the high-risk group, an additional PCA, such as epoprostenol or treprostinil, is included in the initial therapy [32].

After initial treatment, patients are sorted into four risk groups. In low-risk patients, initial treatment is continued. In intermediate low-risk, a prostacyclin receptor agonist (PRA) can be included, or a PDE5I can be replaced with sGC [32].

For intermediate high- and high-risk cases, it is recommended that a PCA be added to therapy and that eligibility for lung transplantation be considered [32]. It should be emphasised that connective tissue disease, including SSc, is not an absolute contraindication to lung transplantation [33].

It should be noted that PAH-SSc is also characterised by several specific features regarding therapy. In contrast to most PAH-CTD cases, GCS and CTX are not recommended in patients with PAH-SSc [34]. Although randomised clinical trials have shown a beneficial effect of epoprostenol compared with placebo, the effect on survival is weaker than in patients with idiopathic pulmonary arterial hypertension (IPAH) treated with a continuous infusion of the drug [34–38].

In patients with SSc, therapy should take into account the frequent co-occurrence of ILD and heart failure with preserved ejection fraction (HFpEF), as well as other vascular injuries, including but not limited to digital ulcers [21, 29, 39].

For joint pain, paracetamol or tramadol should be used, and NSAIDs should be avoided. Polyarthritis is treated symptomatically with tramadol.

In case of progression of joint lesions, MTX or alternatively low-dose GCs are used. In myositis, oral azathioprine (AZA) at 50–100 mg/d, MTX or prednisone (< 20 mg/d) is administered. In more severe cases, intravenous methylprednisolone is used at 500–1000 mg/d with 3 or 4 infusions every 1–2 days [1, 2].

Gastroenterological disorders are treated symptomatically. Proton pump inhibitors (PPIs) are used for gastro-oesophageal reflux disease (GORD), prokinetic drugs are administered for motility disorders and periodic antibiotics are given for small intestinal bacterial overgrowth (SIBO).

In calcinosis cutis, intravenous immunoglobulin (IVIG) or RTX can be tried. Surgical treatment is abandoned due to frequent recurrences.

Cardiac complications are treated depending on the comorbid symptoms. In the case of arrhythmias or conduction disorders, implantation of a cardioverter defibrillator is considered even in the early stages of the disease. Heart failure is treated symptomatically, and in the case of myocarditis, if GCs are ineffective, CTX is administered [1, 2].

Due to the lack of causal treatment, the prognosis depends on the extent of the organ lesions. The 10-year survival rate is 65–73% [8]. More than half of deaths are associated with ILD, PAH and cardiovascular complications. Pulmonary, cardiac or renal involvement significantly worsens the prognosis [1–3].

## SCLERODERMA-LIKE SYNDROMES

SSc mimics include a large group of conditions. They share skin sclerosis with SSc, while the extent and distribution of sclerosis and the degree of involvement of other organs can vary. In addition to the skin, subcutaneous tissue and sometimes even soft tissues or bone are often involved [12].

The aetiology is varied and often not completely understood. Excessive local accumulation of collagen and other extracellular matrix components is usually responsible for sclerosis. Due to the differences in the treatment and the different prognosis, these entities should be differentiated from SSc. Adequate history taking, covering contact with chemicals, the absence or presence of Raynaud's phenomenon, the presence of capillaroscopy changes and other concurrent conditions is essential. In addition, the diagnosis is mainly based on a detailed physical examination and laboratory diagnostics.

Scleroderma-like syndromes are particularly supported by the absence of Raynaud's phenomenon and antinuclear antibodies and the normal appearance of capillaries. In case of doubt, a skin biopsy may be helpful [12].

Some of the best-known scleroderma-like syndromes are:

— eosinophilic fasciitis (EF);
— scleroedema;
— scleromyxoedema;
— nephrogenic systemic fibrosis (NSF);
— diabetic cheiroarthropathy (limited joint mobility, LJM);
— lipodermatosclerosis (LDS);
— toxic oil syndrome (TOS);
— eosinophilia-myalgia syndrome associated with tryptophan (EMS);
— epidemic dropsy (ED);
— Werner syndrome (WS);
— Hutchinson-Gilford syndrome;
— stiff-person syndrome;
— phenylketonuria,
— porphyria cutanea tarda;
— exposure to bleomycin, vinyl chloride;
— scleroderma-like syndrome in primary biliary cirrhosis.

## EOSINOPHILIC FASCIITIS (EF)

EF is also known as diffuse fasciitis with eosinophilia or Shulman's syndrome. It is a connective tissue disease that mimics SSc. It manifests as erythema, oedema and fibrosis with subsequent sclerosis of the skin, fascia and subcutaneous tissue [40].

The disease predominantly affects the upper and lower limbs (70–83% of patients). It may be limited to the lower limbs only (12–25% of patients) or the upper limbs (5–6% of patients). The lesions are almost always symmetrical [40]. Trunk involvement is relatively rare. Typically, EF does not involve the feet, hands or face [12].

It starts suddenly, usually with the onset of painful bilateral swelling of the limbs. The swollen skin is reddened and uneven and has a ‚peau d'orange' appearance. The sclerosis is often so severe that it is described as woody [12]. As the skin hardens, pigmentation is affected, resulting in the ‚groove sign' — furrows caused by the retraction of the subcutaneous tissue along the superficial veins, visible when the affected limb is elevated. This sign typically occurs on the palmar surface of the forearm but can present on any limb and helps differentiate EF from SSc [12, 40].

Further fibrosis leads to the development of joint contractures and nerve compression syndromes [40]. Range of motion restriction is caused by inflammatory involvement of the fascia crossing or adjacent to the joints, typically in the wrists and ankles. Contractures may occur in the fingers, especially in the dorsiflexion of the wrist joint. However, this is due to tension in the fascia and tendons of the hand rather than the thickening of the skin of the fingers. This remains normal in EF, which is one of the differentiating features from SSc. For this reason, patients with EF usually do not show restriction of finger extension with palmar flexion of the wrist joint [12].

Other systemic changes often co-occur. Muscle pain, atrophy, and consequent

weakness may occur; however, this is not the predominant symptom differentiating EF from myopathy [12].

Its aetiopathogenesis is not fully known. It has been suggested that the onset of EF may result from trauma or prolonged exposure to cold. Chemical agents such as trichloroethylene or L-tryptophan may also be associated with disease manifestation. However, scleroderma-like syndromes induced in this way are usually considered separate disease entities, distinct from EF [40].

Because it is a rare disease, only a few hundred cases have been reported. Available data show that EF is mostly found in Caucasians. It is most commonly diagnosed at the age of 47–57, with women being affected 1.3–2.1 times more often than men [40].

Laboratory tests reveal peripheral blood eosinophilia (58–85% of patients) and hypergammaglobulinaemia (35–45% of patients) [40]. In addition, elevated inflammatory markers and increased aldolase activity are observed. Eosinophilia is usually transient and occurs at the onset of the disease, making diagnosis difficult. In addition, it rapidly resolves following steroid therapy, which is often started before laboratory tests. Markers of inflammation are also not always present and are transient [12].

*En bloc* full-thickness biopsy is the gold standard for diagnosis. Histopathological examination demonstrates significant thickening of the fascia and inflammatory infiltrates with variously abundant eosinophils within the fascia. However, there are significant limitations to the usefulness of biopsy in diagnosis. A full-thickness biopsy is necessary because EF often does not involve the dermis and epidermis, so a skin-to-muscle sample must be taken. The degree of inflammation and the number of eosinophils can fluctuate, especially if steroid treatment has been started previously [12].

MRI is also used in diagnosis, especially in acute cases. It can reveal the thickening of the fascia in T1WI, T2WI, and STIR images and enhancement of the fascia after administration of a gadolinium contrast agent [12].

The diagnosis is based on the patient's history, clinical picture, laboratory tests and MRI findings. The diagnostic criteria by Pinal-Fernandez et al. are presented in Table 3 [41].

The primary consideration in the differential diagnosis should be SSc. It can be differentiated from SSc by the absence of Raynaud's phenomenon, digital ulcers, ischaemic digital ulcer scarring, involvement of the skin of the fingers, and the different nature of the skin lesions (peau d'orange, groove sign). EF is suggested by peripheral blood eosinophilia and fascial lesions on full-thickness biopsy. In addition, EF usually responds well to GCs, which differentiates it from SSc. There is also a lack of serum antibodies, which are typical of SSc (e.g. anti-Scl-70, ACAs) [40]. Other diseases that need to be differentiated from EF are other scleroderma-like syndromes or Lyme disease. The treatment of EF is not based on the results of randomised trials; it relies only on case series descriptions and retrospective

**Table 3**. Eosinophilic fasciitis (EF) diagnostic criteria published in 2014 by Pinal-Fernandez et al. [41]

| EF diagnostic criteria |
|---|
| **Major criteria:** |
| 1. Symmetrical or asymmetrical, diffuse (e.g., involving the limbs, trunk, abdomen) or limited only to the limbs swelling, hardening and thickening of the skin and subcutaneous tissue |
| 2. Presence of thickened fascia with accumulation of lymphocytes, macrophages with or acidophilic granulocytes on histopathological examination of skin and fascia |
| **Minor criteria:** |
| 1. Peripheral blood eosinophilia > $0.5 \times 10^9$/L |
| 2. Hypegammaglobulinemia > 1.5 g/L |
| 3. Muscle weakness and/or increased serum aldolase activity |
| 4. Groove sign and/or peau d'orange |
| 5. On MRI in T2-weighted images presence of hyperintense signal from fascicles |
| **Exclusion criteria:** |
| Diagnosis of SSc |
| The criteria of diagnosis are met if two major criteria or one major and two minor criteria are present. Meeting an exclusion criterion excludes the diagnosis of EF |

MRI — magnetic resonance imaging; SSc — systemic sclerosis

analyses [40]. Its aetiopathogenesis is unknown, so no causal treatment currently exists. GCs in moderate to high doses are accepted as first-line treatment [12].

EF studies recommend MTX, especially for patients with concomitant localised scleroderma, and MMF. These drugs are usually used as second-line treatment when steroid therapy is insufficient or as agents that help reduce the dose of GCs in long-term therapy [40].

Other drugs include hydroxychloroquine, CsA, AZA, CTX, infliximab, RTX, and phototherapy is also employed. In most cases, the response to treatment is partial or complete [12].

EF's course runs for months or even years. In most patients, the sclerosis regresses. The normalisation of aldolase activity and the improvement in range of motion and fascial status are gradual.

It has been suggested that haematological disorders and myelodysplastic syndromes may co-occur with EF, although the exact incidence is unknown due to the disease's rarity [12]. Isolated reports suggest that lymphocytic leukaemia, myelomonocytic leukaemia and aplastic anaemia have been diagnosed in about 10% of EF patients. However, EF is not considered a typical paraneoplastic rheumatic syndrome [40].

It is also worth noting that EF most commonly co-occurs with the plaque form of localised scleroderma. These diseases coexist 1.4–3 times more frequently than in the general population. In these patients, a worse response to GC treatment is observed [40].

## SCLEROEDEMA

Scleroedema is sometimes also referred to as Buschke disease or scleroedema of Buschke [42]. It is a rare mucinosis with unknown aetiology. It is characterised by symmetrical induration of the neck, lateral neck, upper back, shoulder girdle and upper limbs. The skin of the face may also be involved. This leads to issues with fully opening the mouth, making it difficult to chew and swallow food. The hands and feet are free of lesions, so there is no sclerodactyly. Raynaud's phenomenon is also not observed, as there is no microcirculatory dysfunction [12].

Sclerosis in the joint area causes restrictions in mobility. The induration of the skin may be preceded by erythema or a ring-like rash. The swollen skin is hard and may be itchy and, less commonly, painful [12]. The patient's complexion is sallow, and the affected skin may sometimes turn orange or reddish [42].

Some unusual symptoms of Buschke disease include asymptomatic bilateral sudden swelling of the eyelids with periorbital oedema. Sometimes internal organs are involved — most commonly the tongue and heart — but the disease can also affect the lungs, skeletal muscles, oesophagus, parotid glands, liver, spleen, pleura and eyes. It results in motor limitations, dysphagia, Sjögren's syndrome, and pleural, pericardial or peritoneal effusion [43].

The classic division includes three types:

— type 1 manifests in patients after a viral or bacterial infection with fever, usually involving the upper respiratory tract. It is an acute and rapidly developing form, resolving spontaneously within a few weeks to 2 years [44]. It usually affects children and adolescents [12, 43];

— type 2 is associated with monoclonal gammopathy, mainly IgG, in monoclonal gammopathy of undetermined significance (MGUS) less commonly in symptomatic myeloma. It has a slow and chronic course. It is usually self-limiting, and the lesions regress following chemotherapy [42–44];

— type 3 is also called scleroedema diabeticorum [45]. It occurs in approximately 20% of patients with scleroedema [43]. It is usually associated with poorly controlled, long-standing insulin-dependent diabetes mellitus with multiple microangiopathic complications. It is characterised by a slow, progressive course. In contrast to the previous two types, it is much more frequent in young men [44]. The average duration of diabetes leading to the development of Buschke disease is 13 years [12]. It has been suggested that 2.4–14% of diabetic patients may develop scleroedema [12, 43].

Its aetiopathogenesis remains unknown. It is probably related to irreversible collagen glycosylation, altered collagenase activity and the accumulation of collagen and mucin in the dermis. Increased production of type 1 collagen and glycosaminoglycans by reticular dermis fibroblasts and increased deposition of mucopolysaccharides in the interfibrillar spaces of the dermis are found [43].

A skin biopsy is not required to confirm the diagnosis, although it helps exclude other conditions. Histopathological examination reveals marked thickening of the collagen bundles, separated by extensive clear spaces filled with mucin. In addition, mild mononuclear

inflammatory infiltrates surrounding the capillaries are detected. The subcutaneous fat layer presents infiltrates with enlarged collagen fibres. In contrast, no changes are found in the epidermis or dermal appendages [11, 43].

The diagnosis is based on the patient's history and clinical and histological features. Screening for paraproteins is recommended. Other laboratory and immunological tests are not required to make the diagnosis.

Ultrasound can be used to measure the thickness of the skin, which helps assess the activity and severity of the disease [43]. The differential diagnosis should primarily include SSc and scleromyxoedema.

Currently, no effective treatments are known. Suggested treatment regimens have a limited therapeutic effect. For type 3, optimal diabetes control is the most relevant management. Type 1 is usually self-limiting and does not require treatment [44].

Phototherapy is considered first-line treatment [43, 44]. In cases unresponsive to treatment or severe forms, IVIG is recommended [43]. Some suggested treatments include GCs, immunosuppressants, penicillamine, electron beam therapy, and high-dose intravenous penicillin. Physiotherapy is recommended for motor limitation [12, 43, 44].

The prognosis primarily depends on the type of Buschke disease. Type 1 usually has a benign, self-limiting course and resolves spontaneously, usually between 6 and 24 months. Types 2 and 3 progress slowly and can involve internal organs and contribute to the development of life-threatening complications [43].

Monoclonal gammopathy occurs on average in about 25% of adult patients with scleroedema. It is usually of the IgG kappa type (in contrast to scleromyxoedema, where IgG lambda antibodies are usually present), which may be associated with or precede multiple myeloma [12].

## SCLEROMYXOEDEMA

Scleromyxoedema is also known as papular mucinosis. It is a rare cutaneous mucinosis. It is progressive and is associated with monoclonal gammopathies such as Waldenström macroglobulinaemia or multiple myeloma [46].

Scleromyxoedema is characterised by a generalised lichenoid papular eruption and skin induration. The lesions appear suddenly on the face (especially the forehead), neck, nape, trunk, distal parts of the forearms and dorsal surfaces of the hands. The skin of the hands is not affected by the eruption. Sometimes, fingers may be involved, leading to sclerodactyly with associated contractures [12].

The distinctive thick and hard skin is associated with the deposition of mucin in its layers. This causes enlargement of the skin folds, making the skin look like an elephant's [47]. A face with thickened features, also known as a leonine facies, takes on a mask-like appearance due to impaired facial expression [12]. Hairy scalp involvement may also occur. Papular lesions are often accompanied by persistent pruritus. Occasionally, loose skin (cutis laxa, Shar-Pei sign) is observed due to elasticity loss. This produces loose folds [47].

In addition to skin lesions, systemic disorders may present in 60–90% of patients. Skin lesions usually precede the onset of general symptoms. The disease may involve the cardiovascular system (myocardial infarction, hypertension, atherosclerosis), gastrointestinal system (oesophageal motility disorder), musculoskeletal system (myositis, dermatomyositis, polyarthritis, migratory arthritis, carpal tunnel syndrome), lungs (pulmonary hypertension), kidneys (renal failure) or nervous system [47].

The most common symptoms are dysphagia (46%), exertional dyspnoea (27%), proximal myopathy (10–50%) and muscle weakness. Neurological symptoms occur in 10–15% of cases and include encephalopathy, peripheral neuropathy, coma and dermatoneuro syndrome. It is a potentially fatal complication. Initially, there are flu-like symptoms followed by fever, convulsions and then coma, often ending in death [47, 48].

Such haematopoietic diseases as leukaemias, malignant granuloma and, in about 10% of cases, multiple myeloma may occur. Scleromyxoedema also causes ophthalmic complications, which occur in 24% of patients (corneal deposits, eyelid skin thinning, eyelid oedema, lagophthalmos, ectropion, mucinous papules) and psychiatric complications such as psychosis and depression [46, 47]. Systemic symptoms correlate with a more severe course and increased mortality [47, 48].

Scleromyxoedema's pathogenesis remains unknown. A clear causal relationship between paraproteinaemia and disease symptoms has not been established [47, 48].

Scleromyxoedema usually presents between the ages of 30 and 50, equally affecting women and men [47].

**Table 4.** New modified classification of variants of lichen myxoma (LM) according to Rongioletti and Reborah [49]

| New modified classification of variants of LM |
|---|
| **Generalized papular variant (scleromyxedema)** |
| **Localized variant**<br>Discrete lumpy LM<br>Peripheral chronic papular mucinosis<br>Self-limiting papular mucinosis<br>Papular juvenile mucinosis<br>LM nodular |
| **Atypical forms** |

Lichen myxoedematosus can be divided according to the new classification proposed by Rongioletti and Rebora (Tab. 4) [49].

The histopathological picture shows abundant mucin deposits between collagen bundles in the dermis, excessive proliferation of fibroblasts and increased numbers of mast cells. In contrast, the epidermis is atrophic. A reduction in the number and fragmentation of elastin fibres is also observed [11].

In 80–100% of patients, paraproteinaemia is diagnosed — most often monoclonal IgG lambda, less frequently kappa. It is present already at the onset of the disease [47, 48]. In the absence of this, it is recommended that patients be closely monitored over the coming years.

Scleromyxoedema should be differentiated primarily from scleroedema and SSc, especially when diffuse skin lesions or Raynaud's phenomenon are present.

The diagnosis requires the finding of four features:

— lichenoid papular eruption with typical localisation;
— skin biopsy confirming features of scleromyxoedema (mucin deposition, spindle fibroblast proliferation and excessive collagen synthesis);
— monoclonal gammopathy in the peripheral blood;
— absence of thyroid dysfunction [47, 48].

Scleromyxoedema treatment presents many difficulties, as it does not resolve spontaneously and is usually refractory to treatment. High IVIG doses are used as first-line treatment. In addition, studies are attempting to use extracorporeal photopheresis, melphalan (a bifunctional alkylating compound), prednisone, retinoids, plasmapheresis, dermabrasion, total skin electron beam therapy, CTX, CsA or MTX.

The combination of IVIG with thalidomide in refractory and relapsed cases is particularly emphasised. European guidelines recommend a combination of IVIG and systemic GCs for dermatoneuro syndrome [48]. The classic treatment regimen is shown in Table 5 [48].

Scleromyxoedema is a chronic and potentially fatal disease. An unfavourable prognosis is associated with an increased risk of infection, cardiovascular disease and nervous system diseases [47, 48].

## NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Nephrogenic systemic fibrosis (NSF) is a relatively new disease entity that occurs only in patients with renal failure, usually in its end stage, who are mostly exposed to gadolinium contrast agents [12, 50–52].

It is a rapidly progressive condition that involves systemic fibrosis. The skin manifestations involve the distal segments of the limbs — mainly the forearms and lower legs, less frequently the trunk, while sparing the face and fingers. The involved skin becomes hard,

**Table 5.** Treatment regimen for scleromyxedema

| **First line** |
|---|
| High-dose intravenous immunoglobulin (IVIG) |
| **Second line** |
| Thalidomide |
| Systemic steroid |
| **Third line** |
| Bortezomib (selective reversible inhibitor of the 26S proteasome) |
| Auto-HCT |
| Melphalan |

auto-HCT — autologous hematopoietic cell transplantation

‚woody', symmetrically thickened and painful [12]. The induration is accompanied by erythematous or pigmented confluent plaques or fibrotic papules [50–52].

NSF is not only limited to the skin of the body; subcutaneous tissue, fascia, striated muscles, and internal organs such as the heart and lungs can be involved, leading to dangerous complications and even death [50, 51].

The first symptoms are slight thickening and induration, swelling, increased skin tone with discolouration, paraesthesia and persistent pruritus. Over time, the swelling subsides, and the skin becomes hard and thickened, looking like a cobblestone or a peau d'orange. Dark patches and papules appear [50].

In the late stage, the skin becomes atrophic and hairless. The disease gradually involves the skeletal muscles and internal organs. Joint pain and stiffness, muscle weakness with reduced mobility, joint contractures, and yellowing of the sclera may also occur [50, 52]. However, Raynaud's phenomenon is not observed. Concomitant hypercoagulability is found in 10% of patients, and fractures resulting from long immobilisation increase the risk of death [50, 51].

The disease is rare. NSF is most commonly diagnosed in stages 4 and 5 of chronic kidney disease (CKD) [51, 52]. Approximately 90% of patients are receiving renal replacement therapy at the time of diagnosis [51]. Findings indicate that NSF can occur in patients with renal failure regardless of its aetiology and treatment modality — haemodialysis, peritoneal dialysis, renal transplantation [12].

Its aetiopathogenesis remains unclear. It has been suggested that increased levels of transforming growth factor beta (TGF-$\beta$) and circulating CD34+/procollagen I+ fibroblasts stimulate collagen production and lead to skin thickening. NSF risk factors include renal replacement therapy, erythropoietin and iron preparations, hyperphosphataemia, immunosuppression, inflammation, oxidative stress and liver disease [50, 51].

There is a close causal relationship between gadolinium exposure over a period of two weeks to 18 months and the development of NSF [12]. Gadodiamide is entirely excreted by the kidneys. The half-life of this compound in a healthy person averages 1.3 h, while it increases to 34.3 h in patients with stage 5 CKD [50, 51]. Gadodiamide is 97% removed from the body after the third haemodialysis. In the case of peritoneal dialysis, 2/3 of the administered dose is excreted after 20 days [51].

Prolonged exposure to gadolinium chelates leads to ion dissociation and deposits in internal organs. The average risk of developing NSF in patients with advanced CKD after exposure to gadolinium is 2.5–5%. This risk increases with subsequent exposures and the administration of higher doses [51].

A significant decrease in the incidence of NSF has been reported after guidelines limiting the use of gadolinium-based contrast agents in patients with renal failure were implemented [50, 52]. However, it is worth noting that the available literature reports cases of NSF in patients who have never received gadolinium-based contrast agents [50].

A biopsy of the affected skin is the diagnostic gold standard. Histological examination in the early stage shows a slight proliferation of CD34+ fibroblasts and an irregular distribution of collagen bundles and elastin fibres.

In a more advanced stage, collagen bundles and fibrous subcutaneous septa thicken, fissure-like spaces develop, and mucin deposits in the skin. Dendritic cells accumulate, and elastin fibres proliferate [11, 51].

Striated muscles develop atrophy of muscle fibres, fibrosis of the perimysium and endomysium, and calcium deposits. Changes in the myocardium correspond to those in the striated muscles, with additional pericardial fibrosis and calcification of the walls of large vessels.

The lungs show weak interstitial fibrosis, thickening of the adventitia of small and medium-sized pulmonary arteries, and pleural and diaphragmatic fibrosis. Fibrosis of the urinary tract and dura mater has also been noted [51].

Laboratory findings are non-specific. Elevated inflammatory parameters, hypoalbuminaemia, sometimes antiphospholipid antibodies or pseudo-hypocalcaemia (a result of gadolinium chelates) are observed [50].

The diagnosis is made based on the overall clinical picture and histological examination. The histological and clinical picture resembles scleromyxoedema but is differentiated from it by less mucus, no inflammatory cell infiltration in the affected skin, and a different localisation of the lesions that spares the face [11].

The differential diagnosis should furthermore include SSc, EF, TOS, LDS, porphyria, pretibial myxoedema present in Graves' disease, chronic graft-versus-host disease (cGVHD) and paraneoplastic syndromes.

**Table 6.** Recommendations to reduce the risk of developing nephrogenic systemic fibrosis (NSF) based on 2007 European Medicine Agency (EMA) and Food and Drug Administration (FDA) recommendations

| Recommendations to reduce the risk of developing NSF after exposure to gadolinium |
|---|
| 1. Do not use gadolinium-containing contrast agents included in nonionic and ionic linear-structure compounds (gadodiamide, gadersetamide, gadopentate) in patients with glomerular filtration rate < 30 mL/min per 1.73 $m^2$ p.c. In patients with glomerular filtration rates of 30–59 mL/min per 1.73 $m^2$ p.c., the need for the listed contrast agents should be considered depending on the clinical situation. Polycyclic preparations are preferred. |
| 2. Multiple doses of the product should be avoided. It is recommended to observe at least a week interval between tests. |
| 3. Before performing an MRI scan, check creatinine levels and calculate creatinine clearance in patients with a history of kidney disease, diabetes, and those over 65 years of age. |
| 4. In hemodialysis patients, dialysis is recommended after an examination during which a contrast agent was used. In contrast, there is no evidence to support initiating hemodialysis to prevent or treat NSF in patients who are not on hemodialysis. |
| 5. Patients in stage 4, 5 chronic kidney disease after MRI should be observed for 4–6 months after exposure. |

Based on the recommendations of the UK Commission on Human Medicines, the European Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use — 2007 and the recommendations of the FDA — 2007, updated in 2010. MRI — magnetic resonance imaging; NSF — nephrogenic systemic fibrosis

The treatment of NSF is mainly symptomatic. Therapy aims to improve renal function, thereby reducing symptoms and sometimes resulting in complete remission. In addition, analgesics are combined with appropriate physiotherapy to reduce painful contractures. Currently, there is no effective causal treatment [50, 51].

Attempts are being made to use GCs, pentoxifylline, CTX, CsA, thalidomide, interferon $\alpha$ (INF-$\alpha$), plasmapheresis, intracorporeal photopheresis, UV therapy, photodynamic therapy, ACEI, sodium thiosulphate, immunoglobulins and imatinib (Bcr-Abl tyrosine-kinase inhibitor) with varying therapeutic effects. There are no controlled clinical trials that objectively assess the efficacy of the above approaches [12, 50, 51].

Renal transplantation shows the most promise. For this reason, an NSF diagnosis is an indication that a patient should be referred for priority renal transplantation [50, 51].

NSF is a devastating condition that takes a fulminant course in 5% of cases. Spontaneous remissions have been observed, especially when renal function improves [51]. There is no doubt that NSF significantly shortens the mean survival time of CKD patients. Left untreated, it rapidly leads to death [50, 51].

In the absence of effective therapeutic approaches, early diagnosis of risk factors for CKD should be performed first and foremost, and the disease development should be prevented by avoiding the exposure of CKD patients to gadolinium contrast agents [50, 51].

The recommendations developed in 2007 and updated in 2010 aim to reduce the development of NSF (Tab. 6) [51, 53–55].

## DIABETIC CHEIROARTHROPATHY (LIMITED JOINT MOBILITY, LJM)

Diabetic cheiroarthropathy is sometimes referred to as stiff hand syndrome, diabetic hand syndrome, or syndrome of limited joint mobility (LJM). It leads to painless restriction of mobility in the hand joints, the development of permanent flexion contractures and symmetrical thickening and hardening of the skin of the fingers and dorsal side of the hands [56].

The thickening of the skin can sometimes involve the arms, leading to flexion contractures in the elbow joints [12]. When the shoulder joint is involved, it is referred to as shoulder-hand syndrome [56]. The patient's skin has a shiny and waxy appearance, making this condition similar to SSc [57].

LJM develops slowly. It usually develops on the elbow and spreads radially. Initial symptoms include decreased mobility of the metacarpophalangeal and proximal interphalangeal joints of the proximal and distal fingers [56]. However, these symptoms are often underestimated by patients and attributed to ageing. As the disease progresses, hand stiffness, swelling with thickening and increased skin tone, weakness and sensory disturbances may occur [56, 58].

In its more advanced stage, the disease prevents full extension of the metacarpophalangeal joints, resulting in the characteristic 'prayer' sign. It involves the inability to bring the metacarpals fully together when both hands are placed parallel as if for prayer [12, 56–59].

The second typical symptom is the so-called ‚tabletop' sign. When the hand

with extended fingers is placed on a flat surface, the metacarpals and fingers are unable to touch it [56, 58]. Another test specific to this entity is a positive ‚fold sign'. It involves failed attempts to grasp the skin fold on the dorsal side of the middle phalanx of the hand without using excessive force and causing pain [58].

Its incidence due to the underdevelopment of precise criteria is estimated to be 8–50% [56, 58]. LJM is more common in insulin-dependent diabetes mellitus, although it can also be observed in long-term type 2 diabetes. It correlates strongly with duration and severity of diabetes [12, 56, 58, 59].

Studies have shown a correlation between LJM with coexisting albuminuria and diabetic angiopathy [58]. In addition, patients with LJM are more likely to be diagnosed with diabetic retinopathy and neuropathy [56, 58]. The most severe limitation of hand joint mobility is observed in patients with diabetes diagnosed before puberty. An increase in glycated haemoglobin ($HbA_{1c}$) and disease duration are independent risk factors [58].

Its exact aetiopathogenesis remains unknown. The formation of advanced glycation end-products, collagen cross-linking, disruption of skin vasculature and arteriovenous fistulas due to prolonged uncontrolled hyperglycaemia are thought to play a key role in the development of the disease [56, 58].

Histopathological examination reveals fibrosis associated with thickening of collagen bundles resulting from abnormal glycation of collagen cross-links and abnormal degradation of collagen [12]. Ultrasound and MRI can also be helpful in making the diagnosis [56]. The thickness of the finger flexor tendon sheaths is assessed in both examinations. If thickness is greater than 1 mm, LJM should be suspected [60].

Due to the appearance of the skin and the presence of contractures, the disease should be differentiated from SSc. A detailed history, the absence of Raynaud's phenomenon, a normal capillaroscopy picture and a negative ANA test result guide the correct diagnosis [12]. In younger patients, LJM should also be differentiated from juvenile idiopathic arthritis (JIA).

Treatment can be challenging. Its foundation is proper glycaemic control and well-targeted rehabilitation with physiotherapy interventions. This allows for an increased range of motion and improved muscle strength. NSAIDs and topical GCs are used to manage severe pain. In severe cases, the tendons can be surgically relieved of the resulting adhesions. In smokers, addiction treatment is recommended [56, 58, 59].

LJM can lead to severe disability associated with impaired mobility and hand deformity. Advanced disease may prevent the patient from pursuing insulin therapy independently. Concomitant coeliac disease makes diabetes treatment more difficult and promotes poorer glycaemic control, thus leading to more complications [56]. Early diagnosis of diabetic cheiroarthropathy allows screening for microvascular complications.

## LIPODERMATOSCLEROSIS (LDS)

Lipodermatosclerosis is also referred to as sclerosing panniculitis and hypodermitis sclerodermaformis. It is a chronic disease involving sclerosis and discolouration of the skin of the lower limbs. It presents as inflammation of the subcutaneous tissue, a form of necrosis of the fat layer beneath the epidermis. It is associated with chronic venous or, less commonly, arterial insufficiency [61–63]. In addition to stasis, autoimmune diseases, peripheral vascular disease and infections may predispose to this condition [11].

LDS can be divided into acute (symptoms last < 1 month), subacute (1 month to 1 year) and chronic (> 1 year). The subacute form presents with a wide variety of symptoms, exhibiting features of both acute and chronic LDS. The chronic form is the most common and diagnosed [64].

LDS leads to the formation of tender, sclerotic plaques. Subcutaneous fibrosis and induration affect the skin of the lower legs. The first symptom is usually pain [65].

In advanced LDS, a noticeable constriction above the ankles develops due to fat necrosis and chronic ulceration. The proximal part of the lower limb, in turn, becomes swollen. This results in an ‚inverted champagne bottle' or ‚hourglass' appearance [12]. The affected skin may take on a brownish-red colouration. This is due to the deposition of haemosiderin [64, 65].

As a result of venous insufficiency, patients with LDS present with chronic, painful and difficult-to-heal venous ulcers, atrophie blanche, varicose veins and stasis dermatitis [66]. In addition, deterioration of wound healing is noted in patients due to chronic inflammation and fibrosis [64].

Sometimes, LDS can present as acute inflammation, which manifests as a painful, reddened, itchy and indurated area of increased skin warmth. It usually affects the distal third of the lower limb. It is differentiated from cellulitis by the lack of response to antibiotic therapy [12, 64].

Occasionally, a stasis-arthritis syndrome develops, which is an exacerbated LDS. It involves the fascia of the ankle joint and the tissues around the Achilles tendon, which can result in permanent joint stiffness [66].

It is a common condition. It generally affects middle-aged and older individuals. It occurs more frequently in women. The diagnosis is usually made in patients over 40, although in some cases, symptoms do not present until the age of 75 [64].

Its exact aetiopathogenesis remains unknown. A number of factors have been suggested to contribute to the development of the disease, including tissue hypoxia, protein escape into interstitial tissue and leukocyte activation. Risk factors also include venous insufficiency, venous hypertension, obesity, prolonged immobilisation, ageing, history of deep vein thrombosis, family history of venous insufficiency and smoking [61, 64, 65].

Patients with LDS are found to have significantly reduced oxygen content in the skin and a reduced number of capillaries. The development of venous hypertension is influenced by faulty venous valves, reduced venous return and impaired muscle pumps in the lower limbs [62].

Increased pressure in the venous circulation causes fibrinogen and other inflammatory mediators to diffuse from the capillaries into the dermis and subcutaneous tissue. This can interfere with tissue oxygen exchange, resulting in chronic cellular hypoxia. Venous hypertension also leads to an increase in the number of leukocytes. Their relocation outside the vascular lumen causes them to become activated and release pro-inflammatory factors. Chronic inflammation develops, predisposing to collagen accumulation and fibrosis of the subcutaneous tissue [61, 62, 64].

Excessive stress on the venous system and inflammation increase capillary permeability, leading to oedema. Furthermore, it has been suggested that there is a link between abnormalities in fibrinolysis and protein C and S deficiency and the development of LDS [64].

Diagnosis is based on the patient's history and clinical presentation. Biopsy is often abandoned because of impaired wound healing [12, 63, 64]. Histopathological examination shows septal and lobular panniculitis, pseudo-cysts in the adipose lobules, necrosis of adipocytes, sclerosis and lobular lymphocytic infiltration, macrophage accumulations forming lipogranuloma and iron deposition [11, 63].

Venous Doppler ultrasound and air plethysmography can reveal venous insufficiency at a stage without overt signs of stasis [64].

The differential diagnosis should include cellulitis, erythema nodosum, morphoea, vasculitis, panniculitis, and necrobiosis lipoidica.

Treatment consists primarily of treating venous insufficiency. Primary therapy is based on the use of compression stockings or socks and elevation of the lower limbs. Patients should be activated as soon as possible and, if obese, encouraged to reduce weight. Smokers should be persuaded to quit [12, 61].

In more advanced forms, stanozolol (an anabolic steroid) is used. It has been shown to reduce skin thickness and help with pain management. The beneficial effect of topical therapy with GCs in relieving symptoms has been demonstrated for acute LDS. Systemic treatment with oral steroids is recommended for chronic or acute LDS unresponsive to primary treatment. Specifically, danazol (a synthetic 17$\alpha$-ethynyltestosterone derivative) and oxandrolone (an anabolic steroid) are recommended. Subcutaneous triamcinolone (a synthetic GC) can reduce inflammation and thus lessen symptoms [64, 65].

The anti-inflammatory and anti-angiogenic effects of doxycycline and minocycline have also been used [67, 68]. In ulcers, effective wound treatment and prevention of infection are essential. Pentoxifylline and hydroxychloroquine may also be helpful in the treatment of ulcers [69]. Endovenous ablation, sclerotherapy or classic surgery should be used to treat varicose veins [64, 70].

In case of concomitant stasis dermatitis, emollients and topical steroids are used. Studies report that ultrasound therapy can be effective in relieving persistent symptoms such as erythema, pain and induration [64]. It has been established that UVA1 phototherapy may also benefit patients [71].

Other therapies include capsaicin cream, diosmin, hydroxyethylrutoside (a mixture of rutosides representing flavone glycosides) and aescin (a saponin found in chestnut seeds), which can relieve pain and reduce swelling; however, they do not stop the progression of the disease [64].

Venous insufficiency is a progressive disease. Applied treatment can alleviate symptoms and slow the progression of the disease, but associated conditions, such as LDS, for example, usually recur, and patients have them for the rest of their lives.

## TOXIC OIL SYNDROME (TOS)

The features of TOS overlap with EF, SSc and morphoea. TOS can affect all organs as well as the vasculature. The main symptom is fibrosis of the vascular lumen, skin, peripheral nerves and intestines [72–74].

The course of TOS can be divided into three phases:

— acute phase — lasts approximately 2 months. The first symptoms are arthralgia and arthritis, myositis, severe non-cardiogenic pulmonary oedema, peripheral oedema, and eosinophilia combined with rash [72, 73];
— intermediate phase — lasts 2 to 3 months. During this phase, patients present with dysphagia, significant weight loss, severe muscle pain with spasms, skin oedema, peripheral neuropathy, paraesthesia, PAH, Raynaud's phenomenon, Sjögren's syndrome, and large vessel thromboembolism [72, 73];
— chronic phase — the swollen skin hardens, and neurological symptoms increase, manifesting as paresis and paralysis. Liver, pancreas and intestinal symptoms caused by fibrosis of these organs are also present. Carpal tunnel syndrome and livedo reticularis also manifest. In addition, there is right ventricular hypertrophy [72, 73].

TOS was described in 1987 in Spain in people consuming rapeseed oil contaminated with aniline. Consumption of contaminated oil caused musculoskeletal and systemic symptoms in 20,000 victims of the epidemic. Statistically, women under 40 were more frequently and more severely affected than men [72].

Diagnosis is based on symptoms and clinical data. There are no specific abnormalities in laboratory tests. Initially, chronic interstitial infiltration and lymphocytic vasculitis are found in histopathology. In a later phase, a biopsy reveals fibrosis and occlusive arteriopathy [73].

The differential diagnosis of the first phase should include ILD (pulmonary symptoms predominate in the early phase). IPAH, SSc, inflammatory polyneuropathy, and EMS should be considered for the chronic phase.

There is no causal treatment, and symptomatic treatment is used depending on the reported complaints. Pulmonary oedema is recommended to be treated in intensive care units. PAH is treated with vasodilators and, in severe cases, with lung and heart transplantation. Steroid therapy may produce beneficial effects in some patients [72].

According to currently available data, the prognosis was highly variable. More than 300 people died in the first few years. One-third of patients developed chronic TOS [72]. Possible complications included myalgia, cramps, weakness and an increased risk of cardiovascular disease [72–74].

## EOSINOPHILIA-MYALGIA SYNDROME ASSOCIATED WITH TRYPTOPHAN (EMS)

EMS is a rare disorder associated with excessive intake of L-tryptophan in dietary supplements. The risk of developing EMS rises with increasing L-tryptophan intake and age [75].

EMS is characterised by eosinophilia combined with very severe myalgia. The disease onset is sudden [76, 77]. The acute phase lasts 3–6 months and is characterised by pain, muscle spasms and dyspnoea [76–78]. Extremely severe myalgia leads to disability, making it difficult to walk and perform basic activities. Leg, arm and back muscles are most commonly affected. Muscle stiffness may occur. Sometimes, cough, fatigue, fever, joint pain combined with joint swelling, and paraesthesia in the hands and feet are additionally present [75–77].

In the early phase of the disease, there is a short-lived itchy maculopapular or urticarial rash that resolves spontaneously, sometimes leaving discolouration [77]. The chronic phase mainly affects the skin. The lower limbs are most commonly affected, slightly less frequently the arms, trunk and face. EMS usually spares the fingers and toes [76, 77].

About half of the patients develop swelling, which hardens over time. The skin becomes tight and thickened, resembling skin affected by SSc. The peau d'orange appearance is reminiscent of EF [76, 77]. Some patients develop severe alopecia [77, 78].

Neurological symptoms such as numbness, hypersensitivity, progressive muscle weakness, urinary disturbances, mood or behavioural changes and cognitive deficits are

sometimes present. Depression or sleep disorders may develop. Arrhythmias, myocarditis and gastroenterological disorders are relatively rare. Myalgia relapses and remits. Fatigue, muscle cramps and dyspnoea are also present [75, 77, 79]. Dry mouth may occur [79].

The cases identified to date are related to the 1989 EMS epidemic in the United States. It was caused by the ingestion of contaminated L-tryptophan supplements. The exact contaminant is still unknown. It is estimated that between 5,000 and 10,000 people contracted EMS. Women were more commonly affected. In addition to the United States, cases of EMS have also been reported in Germany, Canada and the United Kingdom [77].

In addition to eosinophilia, laboratory tests showed normal or slightly elevated aldolase levels, abnormal liver tests, erythrocyte sedimentation rate (ESR) within the normal range and negative ANA [75–78].

The clinical manifestations and histopathological picture resemble EF. No specific lesions are detected on skin biopsy in the early stages of the disease. Due to the lack of specific tests and the rarity of the syndrome, EMS must be differentiated from conditions such as fibromyalgia, chronic fatigue syndrome, SLE, arthritis and fasciitis, SSc and EF.

Although symptoms do not resolve spontaneously with tryptophan withdrawal, products containing tryptophan should be discontinued as soon as possible. GCs are administered. Depending on the symptoms, muscle relaxants, analgesics and diuretics are also used. Exercise should be limited in the acute phase, while in the chronic one, it is suggested to maintain the highest tolerated physical activity. Occasionally, hospitalisation may be necessary [77–79].

The prognosis in most cases is good. Most patients make a full recovery. Of the 1,500 cases recorded in the Centers for Disease Control and Prevention (CDC) databases, there have been 37 deaths that can be linked to EMS [75, 77].

## EPIDEMIC DROPSY (ED)

ED is a rare condition caused by poisoning with contaminated mustard oil. The alkaloids in *Argemone mexicana* oil cause generalised dilatation of capillaries, increase their permeability and predispose to endothelial proliferation. The disease may resemble connective tissue diseases due to the number of systems involved [10, 80].

ED has a subacute onset and begins with gastrointestinal symptoms followed by erythema and hyperpigmentation. Cutaneous manifestations also include erythematous, painful swelling presenting symmetrically in the lower limbs. The skin hardens and telangiectasias develop. The clinical and histopathological picture closely resembles that of SSc [80].

Swelling outside the lower limbs may involve the scrotum and abdominal wall or present as anasarca in some patients [10]. Other symptoms include fever, myalgia and arthralgia, headache and hair loss. Respiratory symptoms may include cough and orthopnoea. Congestive heart failure, PAH, pneumonia, pericardial effusion and renal involvement are also observed [10, 80].

The later stage includes ocular involvement, which manifests as visual deterioration, retinal haemorrhage, vasculitis and glaucoma [10, 80, 81].

In laboratory tests, moderate to severe normocytic normochromic anaemia is observed. Pancytopenia is present in 54% of patients. Proteinuria with albumin loss, hypoproteinaemia, and mild to moderate renal azotaemia are common [10, 80, 81].

Histopathological changes can be found in any organ. In the liver, cytolysis and degeneration of the nucleus are observed; in the kidney, haemorrhages in the glomeruli and interstitium and swelling of tubular epithelial cells are present. In the stomach and duodenum, erosions and congestion of the mucosa are present. The lungs, on the other hand, show thickening of the alveolar septa and congestion. In the heart, degenerative changes can be observed with significant involvement of the coronary arteries. Adipose tissue shows increased vascularisation with marked vasodilatation in all skin layers [10, 80].

Microthromboses are found in many vessels. A rare mononuclear infiltrate is observed. Vascular nodules, or sarcoids, form on the skin due to the formation of vascular excrescences [10].

When the skin is involved, ED should be differentiated primarily from SSc and other scleroderma-like syndromes such as TOS.

ED occurs mainly in the Indian subcontinent. Mustard oil is commonly used there for cooking, and *Argemone mexicana* seeds resemble mustard seeds. Intentional or accidental contamination of mustard oil with *A. mexicana* seed oil results in an epidemic [10, 80].

Argemone oil adulteration is detected by the nitric acid test, ferric chloride test, copper acetate test or blotting paper chromatography. The differential diagnosis should include nephrotic syndrome, severe hypothyroidism, hypoproteinaemic conditions, beriberi or filariasis [10, 80].

To date, several outbreaks of the disease have been reported worldwide. The most serious outbreak to date occurred in 1998 in New Delhi. At that time, 2,552 cases were reported, including 65 deaths [80]. In June 2021, six cases and two deaths were reported in the village of Gundari, India [82].

Its exact aetiopathogenesis is not well understood. Alkaloids cause generalised dilatation of capillaries and increase their permeability. Protein-rich plasma components penetrate the extravascular space. This leads to the development of hypovolaemia and a decrease in plasma osmotic pressure. Declining renal blood flow activates the renin-angiotensin-aldosterone system, leading to sodium and water retention. A state of relative hypovolaemia is created, which provides a constant stimulus for the kidneys to conserve salt and water. The oedema manisfests as anasarca [10, 80].

Extensive oedema may subsequently enlarge as a result of right heart failure. A high resistance to diuretics and a gradual resolution over many months are typical of ED. The hardness of the oedematous lesions indicates a high protein content in the oedematous fluid. Transudation from the pulmonary capillaries in the alveolar interstitial tissues leads to pulmonary oedema of non-cardiac origin, with symptoms of mild hypoxia, respiratory alkalosis, and restrictive ventilatory abnormalities [10, 80].

PAH leads to increased right ventricular systolic pressure and right ventricular dilatation and, over time, to right ventricular failure. Congestive hepatomegaly is observed. Anaemia has a multifactorial basis and results from gastrointestinal bleeding, bone marrow suppression, and shortened red blood cell lifespan [10, 80].

Treatment begins by removing the contaminant. Symptomatic treatment is used. Patients are advised to adopt a sparing lifestyle, leg elevation and a protein-rich diet. Calcium preparations, B vitamins, vitamin C and E are used. GCs and antihistamines can be tried, but the available studies do not demonstrate their efficacy.

Congestive heart failure and respiratory symptoms should be treated. Diuretics and digoxin are commonly used. In cases of pneumonia, antibiotic therapy is used. Renal failure often requires dialysis. Concomitant glaucoma is treated either pharmacologically or surgically [80].

The most serious complications include acute cardiac decompensation, leading to the development of congestive heart failure, and glaucoma, which, if untreated, causes blindness. The mortality rate is approximately 5% and is usually due to heart failure, renal failure, pneumonia or respiratory failure [80].

Due to sparse evidence, the effects of long-term exposure to argemone oil are unknown. In 25% of patients, swelling persists for more than two months, while in 10%, it lasts more than five months. Skin hyperpigmentation and excessive hair loss last four to five months after exposure. Most patients recover in three months [80].

## WERNER SYNDROME (WS)

WS is a rare autosomal recessive disorder from a group of premature ageing syndromes. WS is sometimes referred to as adult progeria [83]. It is differentiated from Hutchinson-Gilford progeria syndrome by the later onset of the first symptoms, which present on average at the age of 26 [84].

Patients with WS do not present with any abnormality until puberty. The first — and often overlooked — symptom is the lack of a growth spurt at puberty, which results in low height in 95% of patients [85, 86]. The classic symptoms start manifesting in the second or third decade of life. Early symptoms include greying and hair loss (100% of patients), bilateral cataracts before 30 (99%), hoarseness before 20 and skin lesions (96%) [85, 86]. It is worth noting that WS almost always presents with posterior subcapsular cataracts rather than nuclear cataracts, which are typical in elderly patients [85, 87].

The beaked nose and sunken cheeks give the face a characteristic ‚bird-like' appearance. Wrinkles and age spots on the face are observed relatively early. Poor facial expression is also noticeable. Abnormal fat distribution results in a distorted body silhouette, with slender limbs and a thickened torso. Flat feet and bone and joint deformities are sometimes present [83–88].

The skin lesions present in WS are scleroderma-like foci. Sclerosis and thinning of the skin with atrophy of the subcutane-

ous tissue are present. Focal hyperkeratosis is observed within the bony prominences of the hands, feet, and knees [83, 85–88]. Concomitant pigmentation disorders usually involve the feet and lower legs. In addition, muscle atrophy and contractures in the elbow and hip joints are observed. A typical symptom is poikiloderma, i.e. a combination of telangiectasia, reticulate hyperpigmentation and foci of hypopigmentation [85, 86, 88].

Difficult-to-heal ankle ulcers, which resemble those found in SSc, are typical and present in approximately two-thirds of patients with WS [84]. They should arouse particular diagnostic vigilance in patients of young age. They most likely arise from a combination of mechanical damage to the thinned skin, increased atherosclerosis and uncontrolled diabetes. In about half of patients, non-healing ulcers cause serious complications, including lower limb amputations, and predispose to skin cancer [84, 85, 87, 88].

Due to impaired calcium metabolism, soft tissue calcifications and osteoporotic changes develop [84–88]. In contrast to classic osteoporosis in WS, the lesions most often affect the long bones of the lower limbs and spare the spine [85–87].

Patients often present with endocrine disorders such as hypogonadism, gynaecomastia, menstrual disorders, premature cessation of ovarian function, infertility or impotence [86, 87].

WS predisposes to type 2 diabetes and atherosclerosis, resulting in a higher risk of ischaemic heart disease [83–88]. However, other features of natural ageing, such as senile dementia and Alzheimer's disease, are not observed [85-87]. Hypertension is usually absent.

Neurological symptoms are rare and include sensory disturbances, myopathy and muscle fatigue. Due to atherosclerosis, strokes and transient ischaemic attacks may occur [86, 87].

There is also an increased risk of 2 to 60 times of developing cancers, mainly from mesenchymal tissues. These are often rare and multiple cancers [85]. According to the available literature, the incidence of cancer in WS is 5.6–25% [88]. Most commonly, there is an increased risk of follicular thyroid carcinoma, melanoma (acral, subungual, mucosal), meningiomas, soft tissue sarcomas, osteosarcoma, leukaemias, myelodysplasia [84–86, 88].

A mutation in the gene encoding the WRN protein on chromosome 8p12-p11.2 is considered in the aetiopathogenesis. It represents DNA helicases, is involved in DNA damage repair, telomere structure maintenance, genome stabilisation, and shows exonuclease activity. Lack of this protein results in abnormalities in DNA replication, transcription and repair [83, 85–87].

Both sexes are affected equally [88]. The incidence is estimated to be approximately 1:100,000–1:200,000 individuals. The syndrome is more common in the Japanese and Sardinian populations, where its incidence due to founder mutations ranges from 1:20,000 to 1:50,000 people [83, 89]. It is the most common representative of the premature ageing syndromes [87].

The diagnosis of WS is based primarily on typical clinical symptoms. The diagnosis is certain if four main symptoms (cataracts, skin lesions, premature greying or thinning of hair, short stature) and two additional symptoms (voice change, osteoporosis) are present after puberty [83, 86]. Genetic testing is performed to confirm the diagnosis.

Laboratory findings are not very specific. Hyperglycaemia and hyperlipidaemia are often present. Elevated urinary hyaluronic acid is sometimes observed [85–87].

X-ray findings include osteoporotic changes, soft tissue calcifications and degenerative changes. In addition, the diagnosis can be expanded to include ECG, cardiac ultrasound and electromyography (EMG) [86–89].

The differential diagnosis should include, but not be limited to, SSc; atypical WS, Hutchinson-Gilford progeria syndrome, mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL); mandibuloacral dysplasia (MAD); and Rothmund-Thomson syndrome (RTS).

There is no causal treatment. Individually tailored symptomatic treatment is used. Comorbidities, including diabetes and dyslipidaemia, should be treated to reduce the risk of cardiovascular complications. Patients should be encouraged to modify their lifestyle — reducing weight, physical activity, and quitting smoking.

Patients with WS should receive multidisciplinary medical care to prolong and improve their quality of life. Special cancer vigilance should be maintained. Regular ophthalmological follow-up is recommended. It is necessary to treat skin lesions and avoid skin damage [83, 86, 87].

Preliminary studies have shown that experimental treatment using epigenetic ther-

apy can be effective in patients with a nonsense mutation involving a premature stop codon in the WNR gene. The efficacy of such treatment has been confirmed in patients with Duchenne muscular dystrophy in a mutation with the same mechanism. Ataluren (which allows ribosomes to translate the complete mRNA molecule) and aminoglycosides were used to restore the production of a functional full-length WNR gene transcript [90].

Due to its hereditary nature, the patient and their immediate family should be referred to a genetic counselling service. In addition, the patient and their relatives should be provided with appropriate psychological therapy.

The prognosis is unfavourable. Mean survival ranges from 40 to 60 years [84–87, 89, 90]. The most common causes of death are malignancies and complications of generalised atherosclerosis [85, 86, 89, 90]. Atherosclerosis is responsible for about 50% of deaths, mainly through myocardial infarction, heart failure and stroke [88].

## CONCLUSIONS

Scleroderma-like syndromes include a diverse group of diseases in which skin induration and fibrosis occur at some stage. They show different aetiology, size and pattern of fibrosis and a predisposition to affect different organs. A proper diagnosis is made on the basis of the clinical picture typical of the disease entity, the patient's history focused on comorbidities and contact with chemical substances, and imaging and laboratory tests. In some cases, an additional skin biopsy is indicated. Treatment and prognosis vary depending on the diagnosis.

Table 7 shows the characteristics of the different scleroderma-like syndromes and those that differentiate them from SSc.


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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

**Table 7.** Characteristics of scleroderma-like syndromes

| Team name | Features | Distinguishing features from SSc |
|---|---|---|
| Eosinophilic fasciitis | Symmetrically occupies limbs, does not occupy feet, hands and face<br>Skin with a woody texture has the appearance of "orange peel", pigmentation disorders, causing the "groove sign"<br>Contractures in dorsal flexion at the wrist joint<br>Hematological disorders and myelodysplastic syndromes<br>Usually, remission nature of skin lesions<br>Responds well to glucocorticosteroids | Absence of Raynaud's phenomenon, ischemic ulcers of the fingers, scarring from ulcers, unaltered skin of the fingers<br>Peau d'orange, groove sign<br>Peripheral blood eosinophilia and hypergammaglobulinemia<br>On biopsy, significant thickening of the fascia, inflammatory infiltrates with numerous eosinophils<br>Absence of antinuclear antibodies<br>Absence of interstitial lung disease, cardiovascular and nephrological complications |
| Scleroderma edema | Symmetrical sclerosis of the neck, lateral part of the neck, face, upper back, shoulder girdle, upper limbs<br>Microstomy<br>The first symptom may be an erythema or a ring-shaped rash<br>Orange or red coloration of the skin<br>Possible systemic complications<br>Type 1 associated with infection, type 2 with IgG kappa monoclonal gammopathy, type 3 with uncontrolled diabetes | No sclerodactyly, no Raynaud's phenomenon<br>Skin biopsy shows accumulation of collagen and mucin in the dermis<br>Absence of antinuclear antibodies<br>MGUS or multiple myeloma may coexist |

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**Table 7.** Characteristics of scleroderma-like syndromes

| Team name | Features | Distinguishing features from SSc |
|---|---|---|
| Lichen mucinous sclerosis | It occupies the face, hairy scalp, neck, nape, trunk, further parts of forearms, dorsal surfaces of hands<br>"Elephant skin", "lion face", shar-pei symptom<br>Sclerodactyly with contractures, mask-like facial expression<br>Systemic disorders, dermato-neuro syndrome, leukemias, malignant granuloma, multiple myeloma | Generalized papular lichenoid rash with induration<br>Unaltered hand skin<br>Occurs with comparable frequency in both sexes<br>In skin biopsy, mucin deposition, fibroblast proliferation and excessive collagen synthesis<br>Absence of antinuclear antibodies<br>IgG lambda monoclonal gammopathy — Waldenstrom's macroglobulinemia or multiple myeloma |
| Nephrogenic systemic fibrosis | End-stage renal failure, exposure to gadolinium contrast agent<br>„Woody", symmetrically thickened, painful skin, lesions occupy forearms and lower legs<br>Image of „cobblestones", "orange peel"<br>Over time, atrophic, hairless skin<br>Systemic changes | Saves face and fingers<br>Erythematous, discolored plaques or fibrotic papules<br>Absence of Raynaud's phenomenon<br>Hypercoagulability, fractures<br>In skin biopsy, thickening of collagen bundles, fissure-like spaces, accumulation of mucin, dendritic cells, increase in elastin fibers, no inflammatory cell infiltration<br>Absence of antinuclear antibodies |
| Diabetic cheiroarthropathy | Presence of diabetes with complications<br>Glossy, waxy skin<br>Painless restriction of mobility in the joints of the hands, permanent contractures, symmetrical thickening and hardening of the skin of the fingers and the dorsal side of the hands<br>"Prayer" sign, "Table top" sign, "symptom of the fold" | Absence of Raynaud's phenomenon, normal picture on capillaroscopy, negative ANA test result<br>Shoulder–hand syndrome<br>Occupation mainly of the hands<br>No interstitial lung disease<br>History of diabetes |
| Lipodermatosclerosis | Hardening and brown-red discoloration of the skin of the lower extremities with plaques<br>The first symptom is pain<br>Inflammation of subcutaneous tissue with no response to antibiotic therapy<br>Image of "inverted champagne bottle", "hourglass"<br>Compression therapy is the main method of treatment | History of chronic venous insufficiency, difficult-to-heal venous ulcers, white atrophy, varicose veins, varicose eczema<br>Stasis-arthritis syndrome<br>In venous Doppler ultrasonography and air plethysmography features of stasis<br>In skin biopsy, inflammation of subcutaneous tissue, pseudocysts in fatty stroma, necrosis of adipocytes, sclerosis and lymphocytic infiltration, lipogranuloma, iron accumulation<br>Absence of Raynaud's phenomenon, normal picture on capillaroscopy, negative ANA test result |
| Toxic oil syndrome | Fibrosis of the lumen of vessels, skin, peripheral nerves and intestines<br>Systemic symptoms, pulmonary edema, pulmonary hypertension<br>Raynaud's phenomenon<br>Nature of the epidemic | History of consuming aniline-contaminated canola oil<br>Negative ANA test result<br>On biopsy, chronic interstitial infiltration and lymphocytic vasculitis, fibrosis as well as infiltrative arteriopathy |
| Tryptophan-induced eosinophilia-myalgia syndrome | Precedes a brief itchy maculopapular or urticarial rash with hyperpigmentation<br>Hardening swelling occupies the lower limbs, arms, torso and face<br>Saves fingers and toes<br>Image of „orange peel"<br>Increased baldness | History of L-tryptophan intake in dietary supplements<br>Eosinophilia combined with very severe muscle pain<br>No interstitial lung disease, cardiac complications<br>Negative antinuclear antibodies |

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**Table 7.** Characteristics of scleroderma-like syndromes

| Team name | Features | Distinguishing features from SSc |
|---|---|---|
| Epidemic drops | Initially, gastrointestinal symptoms, erythema and discoloration<br>Erythematous, painful, hardening swelling occupying symmetrically the lower limbs, scrotum, abdominal wall, may take the form of "anasarca"<br>Telangiectasias, "sarcoids"<br>Cardiovascular, pulmonary, nephrological complications<br>High resistance to diuretics | History of poisoning with contaminated mustard oil<br>Pancytopenia, proteinuria with albumin loss, hypoproteinemia, mild to moderate renal azotemia<br>Negative antinuclear antibodies |
| Werner syndrome | Graying and hair loss, bilateral cataracts before age 30, hoarseness<br>„Birdlike" appearance, poor facial expressions<br>Muscle atrophy and contractures<br>Within the bony prominences, foci of hyperkeratosis<br>Poikiloderma, pigmentation disorders on the feet and lower legs<br>Soft tissue calcifications and osteoporotic changes | Occurs in the 2–3rd decade of life<br>Lack of growth spurt during puberty<br>Hard-to-heal sores around the ankles<br>Features of osteoporosis from a young age<br>Increased risk of developing cancers mainly from mesenchymal tissues<br>Both sexes are equally affected |

IgG — immunoglobulin G; ANA — antinuclear antibody

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