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GUIDELINES

European dermatology forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis

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Abstract

The term 'sclerosing diseases of the skin' comprises specific dermatological entities which have fibrotic changes of the skin in common. These diseases mostly manifest in different clinical subtypes according to cutaneous and extracutaneous involvement and can sometimes be difficult to distinguish from each other. The present guideline focuses on characteristic clinical and histopathological features, diagnostic scores and the serum autoantibodies most useful for differential diagnosis. In addition, current strategies in the first- and advanced-line therapy of sclerosing skin diseases are addressed in detail. Part 2 of this guideline provides clinicians with an overview of the diagnosis and treatment of scleromyxedema, scleredema (of Buschke) and nephrogenic systemic sclerosis (nephrogenic fibrosing dermopathy).
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Scleromyxedema

Epidemiology and pathogenesis

Scleromyxedema, also known as generalized/diffuse and sclerodermoid lichen myxoedematosus or Arndt-Gottron disease, is a rare disease that usually affects adults between the ages of 30 and 80 years with no race or gender predominance. In a multicenter retrospective study of 30 patients with scleromyxedema, the mean age of affected patients was 59 years.[1] This illness has rarely been reported in infants and young children.

The pathogenesis of scleromyxedema is unknown. The main hypothesis is that circulating cytokines such as IL-1, TNF-alpha and TGF-beta, which are known to stimulate glycosaminoglycan synthesis and fibroblast proliferation in the skin, could play a role.[2,3] The condition is usually associated with monoclonal gammopathy. Clinical remission of scleromyxedema following autologous haematopoietic stem cell transplantation (HSCT) suggests that the bone marrow may be a source of circulating cytokines.[4] However, paraprotein levels usually do not correlate with the severity of disease, disease progression or the response to treatment.[1]

Diagnostic procedures

Clinical presentation and physical examination The characteristic skin finding in scleromyxedema are widespread eruption of 2–3 mm, firm, waxy, closely spaced, dome-shaped or flat-topped papules involving the hands, forearms, head, neck, upper trunk and thighs. Papules are often arranged in a strikingly linear array, and the surrounding skin is shiny and indurate (sclerodermoid) in appearance. Rarely, non-tender subcutaneous nodules are present. The glabella is typically involved with deep, longitudinal furrows that produce a characteristic leonine face. Deep furrowing is also typically evident on the trunk or limbs and is called the 'Shar-Pei sign'. Erythema, oedema and a brownish discoloration may be seen in the involved areas; pruritus is common. Eyebrow, axillary and pubic hair may be sparse in patients with scleromyxedema. The mucous membranes are spared. As the condition progresses, erythematous and infiltrated plaques may appear with skin stiffening, sclerodactyly and decreased motility of the mouth and joints. On the proximal interphalangeal joints, a central depression surrounded by an elevated rim (due to skin thickening) can be seen and is referred to as the 'doughnut sign'. Unlike scleroderma, telangiectasias and calcinosis are absent and the Raynaud's phenomenon occurs rarely.[2,3]

The following extracutaneous manifestations may occur:

- Paraproteinemia (typical): Monoclonal gammopathy, usually IgG with a predominance of lambda light chains over kappa light chains,[1,5,6] less frequently IgM-kappa, IgA-kappa or IgA-lambda.[5] Occasionally reported concomitant haematologic or visceral malignancies[1,7–9] were considered to be a consequence of melphalan treatment.[5]
- Central and peripheral nervous systems: Carpal tunnel syndrome, peripheral sensory and motor neuropathy, memory

loss, vertigo, gait problems, stroke, seizures and psychosis.[10,11] The dermato-neuro syndrome is a rare and potentially lethal acute neurologic complication characterized by fever, confusion, dysarthria, lethargy, convulsions and coma.[11,12]
- Musculoskeletal system: Arthralgia or arthritis of the peripheral joints, especially of the hands; proximal or generalized weakness due to inflammatory myopathy and fibromyalgia.[13–15] Spontaneous or interferon alfa-induced rhabdomyolysis is a rare finding.[16,17]
- Cardiovascular system: Congestive heart failure, myocardial ischaemia, heart block and pericardial effusion.[1,18,19]
- Gastrointestinal system: Dysphagia, oesophageal dysmotility.[5]
- Respiratory system: Dyspnoea, obstructive or restrictive pathology,[5,6,20] hoarseness and aspiration due to decreased epiglottis and vocal cord mobility.[21]
- Kidneys: Acute renal failure is a rare event.[22]
- Eyes: Infrequent corneal opacities, ectropion.

In a multicenter retrospective study of 30 patients with scleromyxedema, the most common extracutaneous manifestations were neurologic abnormalities (30%), rheumatologic abnormalities (25%) and cardiac abnormalities (22% of patients).[1]

Histopathology Histological specimens from extracutaneous sites may demonstrate mucin deposition in the subendothelial space and in the interstitium of the kidney, lungs, pancreas, adrenal glands and nerves.[19] Lymph node involvement with infiltration by numerous fibroblasts surrounded by mucin and collagen deposits has been observed.[23] Atypical forms of scleromyxedemalack monoclonal gammopathy or demonstrate an interstitial granulomatous-like pattern on histopathology.

In summary, the diagnosis of scleromyxedema is based upon the recognition of the following clinicopathologic criteria:[24,25]
- Generalized/diffuse papular and sclerodermoid eruption
- Microscopic triad, including mucin deposition (composed primarily of hyaluronic acid in the upper and mid-reticular dermis), fibrosis and irregularly arranged fibroblast proliferation
- Monoclonal gammopathy
- Absence of thyroid disorder.

Differential diagnoses

The major disorders to be considered in the differential diagnosis of scleromyxedema are scleredema, localized scleroderma (LS), systemic sclerosis (SSc), nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy and the localized type of lichen myxoedematosus (including subtypes such as acral persistent papular mucinosis, discrete lichen myxoedematosus, papular mucinosis of infancy and nodular lichen myxoedematosus).[3,26] The consistence of clinical and histopathologic features should be considered to distinguish each of these disorders from scleromyxedema. Waxy papules in linear arrays and with a characteristic distribution that includes the glabella and posterior auricular area, involvement of the middle portion of the back (always spared in scleroderma), facial involvement (spared in NSF), dermal mucin deposition (absent in LS and SSc), fibroblast proliferation (absent in scleredema), sclerosis and systemic involvement (absent in localized lichen myxoedematosus) and concomitant monoclonal gammopathy favour a diagnosis of scleromyxedema.[2,3] Occasionally, patients have overlapping features between scleromyxedema and localized lichen myxoedematosus.[3]

Treatment

Due to the rarity of the disease, no randomized trials have evaluated therapies for scleromyxedema, and data are primarily limited to case reports and case series. No specific treatment appears to be uniformly effective, and the relative efficacies of the treatments that have been utilized remain unclear.

First-line therapy Systemic therapy with intravenous immunoglobulin (IVIg) is the treatment of choice for patients with scleromyxedema. Case reports and case series have documented improvement in the cutaneous and extracutaneous signs and symptoms of scleromyxedema during IVIg therapy, with a generally favourable tolerability profile.[1,27] The mechanism through which IVIg improves scleromyxedema is unclear. Suggested mechanisms underlying the immunomodulatory effects of IVIg include neutralization of circulating autoantibodies by anti-idiotype antibodies, functional blockade and modulation of Fc fragment receptors at the surface of macrophages, and inhibition of fibrosis via modulation of the production of cytokines or cytokine antagonists.[28] IVIg should particularly be considered in patients with either fast deterioration of skin symptoms, the dermato-neuro syndrome or life-threatening involvement of internal organs. The recommended standard dose is 2 g per kg bodyweight per cycle. This dose should be divided into four/five partial doses on four/five days, especially in patients with severe organ involvement, such as kidney or heart involvement in particular, renal involvement, with concomitant diuretics, diabetes, hypertension, obesity or in elderly patients. The interval between cycles should be gradually increased from 4 weeks to maximally 6 weeks (elimination half-life is 21 days). As with the other conditions, the use of IVIg is initially recommended over a period of 6 months. If there is no response to treatment after this time, treatment should be discontinued. As skin involvement is present in nearly all cases and responds very well to treatment with IVIg, it should be used as an indicator of response. Therefore, re-evaluation after three cycles is recommended. In isolated cases, clinical response to central nervous

system or internal organ involvement can be used as an additional indicator of response in scleromyxedema. Long-term therapy can be used in exceptional cases, that is patients with a severe or life-threatening relapse.[1,29–31] Side effects such as skin rash, arthralgia, myalgia, fever, headache, thoracic or abdominal pain, nausea and tachycardia may occur. However, the side effects experienced by patients receiving IVIg for scleromyxedema generally are mild and self-limiting, and vanish after slowing down the infusion rate. Severe adverse events related to IVIg treatment are rare and include anaphylactic shock in patients with IgA deficiency and anti-IgA antibodies, renal insufficiency in at-risk patients, aseptic meningitis, haemolytic anaemia and thrombosis. Myocardial ischaemia and death secondary to suspected myocardial infarction have been reported in scleromyxedema patients with known cardiac risk factors during treatment with IVIg.[32]

Second-line therapies When IVIg treatment is not an option or yields an insufficient response, thalidomide (or lenalidomide) and systemic glucocorticoids are the next-line options for treatment. Thalidomide and systemic glucocorticoids can be given alone or in combination with IVIg.[33–36]

Thalidomide. The mechanism of action of thalidomide in scleromyxedema is unknown. The immunomodulatory effects of thalidomide on proinflammatory and profibrotic cytokines, and its antiangiogenic properties may contribute to the inhibition of fibrosis. Treatment with thalidomide should begin at a dose of 50–100 mg per day and should be slowly increased according to clinical response and tolerance to up to 150–400 mg per day. Once a satisfactory response is achieved, the lowest dose effective for maintaining improvement is used for maintenance therapy. Teratogenicity and irreversible peripheral neuropathy are side effects of thalidomide that can limit its use. Thus, patients should be monitored for the development of peripheral neuropathy during treatment. Other potential adverse effects of thalidomide include drowsiness, constipation, thrombosis and leucopoenia. A few case reports have documented the use for scleromyxedema of lenalidomide, a thalidomide derivative with a more favourable safety profile. Lenalidomide (25 mg per day for 3 weeks per month) appeared beneficial when used in combination with IVIg.[37]

Systemic glucocorticoids. Systemic glucocorticoids have been used for scleromyxedema in conjunction with chemotherapeutic agents or as monotherapy. It is postulated that benefit from systemic glucocorticoids may result from immunosuppressive and anti-fibrotic effects of these agents. Prednisone (0.5–1 mg/kg/day), prednisolone (0.3–0.5 mg/kg/day) and oral high-dose dexamethasone (40 mg once daily for 4 days per week during three consecutive weeks each month) have been associated with improvement in cutaneous manifestations of scleromyxedema in individual patients.[38–40] However, failure of systemic glucocorticoid therapy to improve scleromyxedema has also been reported. In patients in whom systemic glucocorticoid therapy induces remission of scleromyxedema, the accompanying paraproteinemia may or may not improve.

Severe and refractory disease Patients who do not respond to the therapies above may benefit from interventions aimed at treating the associated plasma cell dyscrasia. Examples of the therapeutic options typically reserved for these patients include autologous HSCT and bortezomib together with dexamethasone.[41] Data on the efficacy of these therapies for cutaneous and extracutaneous manifestations of scleromyxedema are limited. In addition, the response to these treatments is variable and relapse may occur. Thus, the risks associated with these therapies must be considered carefully prior to treatment.

Autologous HSCT. Multiple cases of scleromyxedema treated with autologous HSCT have been reported since the initial report of a complete remission in 2001.[4] In a review of 17 reported cases of scleromyxedema treated with autologous HSCT and published between 2001 and 2011, complete remission (resolution of all clinical symptoms, skin abnormality and serum paraprotein) was achieved in 10 patients (59%), and partial remission was achieved in five patients (29%). However, only two of the complete responders remained in remission after follow-up periods that ranged from 14 to >60 months.[42]

Bortezomib plus dexamethasone. In case reports, combination therapy with bortezomib and dexamethasone has been associated with rapid improvement in cutaneous manifestations and constitutional symptoms of scleromyxedema, including a patient who relapsed after autologous HSCT.[41]

Melphalan. Although melphalan was often considered a first-line treatment for scleromyxedema in the past, the potential for drug-related serious adverse events limits the use of this agent. A review of 17 patients who received melphalan for scleromyxedema at a single medical centre (1–4 mg per day or cyclic therapy) found that although 12 patients had improvement of skin disease, improvement was temporary in eight patients and nine patients (53%) died of haematologic malignancy or septic complications that were considered to be related to melphalan therapy.[5] Therefore, melphalan can only be recommended for advanced-line treatment of severe scleromyxedema (Fig. 1).

Treatment of dermato-neuro syndrome The therapeutic approach to patients with dermato-neuro syndrome is not

standardized. Various treatments seemed to yield benefit in case reports. Examples include IVIg[30] systemic glucocorticoids plus plasmapheresis or IVIg, systemic glucocorticoids plus cyclophosphamide and plasmapheresis, melphalan plus IVIg and bortezomib plus dexamethasone.[10–12] The most suitable choice appears to be IVIg associated with systemic glucocorticoids tapered according to the efficacy.

Other therapies and cosmetic interventions Case reports have documented clinical improvement in patients treated with topical betamethasone and topical dimethyl sulphoxide, topical and intralesional glucocorticoid therapy, oral isotretinoin, acitretin, interferon alfa, hydroxychloroquine, cyclosporine A and chemotherapeutic agents, including cyclophosphamide, methotrexate, chlorambucil and 2-chlorodeoxyadenosine. The efficacies of these agents for scleromyxedema remain to be confirmed in prospective trials. UVA-1 or PUVA phototherapy, Grenz ray, total skin electron-beam therapy and extracorporeal photopheresis have also been reported to improve scleromyxedema in case reports. However, these therapies do not have an impact on paraproteinemia and systemic involvement. Facial disfigurement can be treated with dermabrasion plus surgery or carbon dioxide laser with good cosmetic results.

Clinical course and prognosis

Scleromyxedema is a disease with an unpredictable but usually progressive and disabling course in the absence of successful treatment.[3] The disease usually progresses over the course of years and occasionally over the course of several months. Our experience suggests that spontaneous resolution does not occur. However, at least one case of apparent spontaneous resolution has been reported.[43] Systemic consequences of scleromyxedema may result in death.[1] In a case series where follow-up was available for 21 patients with scleromyxedema (mean follow-up time 33.5 months, range 2 months to 11 years), five patients (23.8%) died at the end of follow-up, whereas 12 and 4 patients were alive with and without disease, respectively.[1] In this series, death was caused by extracutaneous complications of scleromyxedema including dermato-neuro syndrome (two patients) and myocardial insufficiency due to endocardial mucin deposition (one patient), or by myeloid leukaemia (one patient) or Hodgkin lymphoma (one patient). Even when therapy is successful, long-term maintenance therapy is usually required as relapse commonly occurs upon discontinuation of treatment. Because of the various cutaneous and extracutaneous manifestations of scleromyxedema, a multidisciplinary team is often needed for the optimal management of patients. Depending on the clinical manifestations, dermatologists, haematologists, cardiologists, pulmonologists, gastroenterologists, hand surgeons and other specialists should be involved.

Recommendations

- The diagnosis of scleromyxedema is based upon recognition of consistent clinical, pathologic and laboratory findings (paraproteins). The presence of the following features is supportive of the diagnosis: generalized/diffuse papular and sclerodermoid eruption, microscopic triad, including mucin deposition, fibrosis and fibroblast proliferation, monoclonal gammopathy and absence of thyroid disorder.
- Patients with scleromyxedema generally require systemic therapy. High-dose IVIg as initial treatment is suggested (evidence grade 2C). Thalidomide (or lenalidomide) and systemic glucocorticoids are alternative treatment options that may also be used alone or in conjunction with IVIg therapy. There is not yet sufficient experience for the use of TNF blockers.
- Long-term maintenance treatment with IVIg is usually required, and close clinical follow-up is necessary. Patients should be reassessed monthly with a full skin examination, review of systems and re-evaluation of the therapeutic regimen. Assessment intervals can be increased to more than 4 weeks when the disease has stabilized.
- Patients who do not respond to IVIg, thalidomide or systemic glucocorticoids may benefit from other therapies. Examples of treatment options for severe and refractory scleromyxedema include autologous HSCT, melphalan and bortezomib plus dexamethasone.
- The risk-benefit ratios of treatment must be carefully considered prior to therapy.
- Recurrence of scleromyxedema is common after withdrawal of an effective therapy.
- Serologic studies, including assessment of the status of the associated monoclonal gammopathy, are not useful for monitoring disease activity.
- Patients should be cautioned that development of neurologic symptoms (e.g. dysarthria) and flu-like illness may be the initial signs of dermato-neuro syndrome. Patients with such symptoms should be admitted to the hospital for close observation and evaluation.

Scleredema

Epidemiology and pathogenesis

Scleredema (of Buschke) is a rare scleromucinous connective tissue disease of unknown aetiology. To our knowledge, there is no racial or ethnic predilection to the disease. Contradictory to Buschke's original description as 'scleredema adultorum', scleredema occurs in individuals of all ages, and more than 50% of

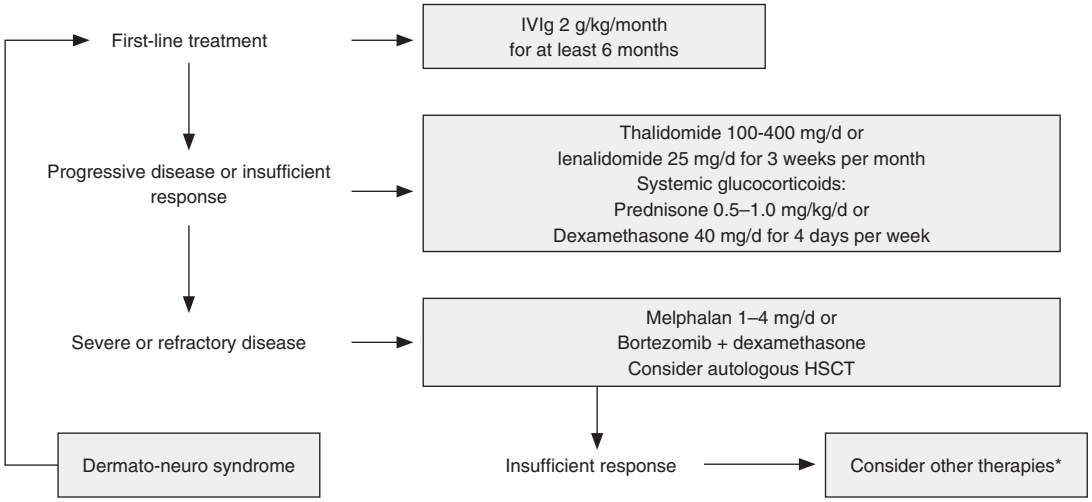

Figure 1 Treatment algorithm for scleromyxedema. *Other therapies include topical betamethasone and topical dimethyl sulphoxide, topical and intralesional glucocorticoid therapy, oral isotretinoin, acitretin, interferon alfa, hydroxychloroquine, cyclosporine and chemotherapeutic agents, including cyclophosphamide, methotrexate, chlorambucil, and 2-chlorodeoxyadenosine, UVA1 or PUVA phototherapy, Grenz ray, and total skin electron-beam therapy. HSCT, hematopoietic stem cell transplantation; IVIg, intravenous immunoglobulin.

patients are aged under 20 years.[44] Its exact prevalence and incidence are unknown. Three types of scleredema can been distinguished according to their association with preceding or underlying conditions: Type 1 (the classic 'Buschke' type, 55% of cases) usually follows a febrile infection (especially streptococcal or viral respiratory tract infection) and affects mainly children.[45–47] Type 2 (25%) is associated with paraproteinemia including monoclonal gammopathy,[48–51] multiple myeloma[52–56] and amyloidosis.[57] Type 3 (20%) was named scleredema diabeticorum by Krakowski and colleagues[58] because of its strict association with diabetes mellitus. Other associated diseases include primary hyperparathyroidism,[59,60] rheumatoid arthritis,[61,62] ankylosing spondylitis,[49] Sjögren's syndrome,[62] dermatomyositis,[63] Waldenström's macroglobulinemia, anaphylactoid purpura, primary biliary cirrhosis[64] and IgA deficiency.[65] Cases of concomitant neoplasms have been reported, such as malignant insulinoma,[66] gall bladder carcinoma,[67] carcinoid tumour[68] and adrenocorticotropic hormone-producing pituitary tumour.[69] In types 1 and 2 scleredema, women are affected almost twice as frequently as men. In contrast, in type 3 scleredema, the male-to-female ratio is considered to be 10:1.[48,70]

The pathogenesis of scleredema remains unknown. The excessive production by fibroblasts of mucin (heavily glycosylated high-molecular weight proteins) and collagens in the reticular dermis[71] may be provoked by diverse stimuli, including infections and inflammatory processes, drugs, toxins, immunoglobulins and cytokines, genetic factors, and hyperinsulinism, or chronic hyperglycaemia in case of type 3 scleredema.[45,72,73] The lack of lymphocytic infiltrates in the lesions excludes a directly T-cell-mediated aetiology.

Diagnostic procedures

Clinical presentation and physical examination The clinical symptoms of scleredema include cutaneous and extracutaneous findings, the latter being present especially in types 2 and 3 scleredema.[45,70,73–81] In the early stages, scleredema manifests as a woody, non-pitting, indurated plaques of the skin of the neck, which later spreads to shoulders and the upper part of the trunk, but spares hands and feet.[73–75] The affected skin wrinkles or takes on a 'peau d'orange' appearance when pinched. This induration may occasionally follow a transient erythematous eruption.[45–47] A durometer or an ultrasonography measurement of skin thickness may be performed in order to evaluate the severity and to monitor the disease.[82]

Clinical score A modified Rodnan scale (as in scleroderma or scleromyxedema) may be used to evaluate the severity of skin involvement and to document its activity.

Patient history Preceding febrile illnesses, symptoms of malignancies or of diabetes/glucose intolerance associated with other endocrinopathies should be carefully considered. Type 2 scleredema may lack associated paraproteinemia at the time of diagnosis. It is thus suggested to distinguish between type 2a and 2b scleredema for cases without and with lymphoproliferative

disorder at the time of diagnosis, respectively. Identification of possible systemic complications requires questions about difficulties in movement, fatigue (muscle or heart involvement), dysphagia (mainly involvement of the upper part of the oesophagus), respiratory problems and neurologic symptoms (e.g. paraesthesia, pain).

Histopathology A skin biopsy is required to confirm the diagnosis and to exclude other sclerosis-like disorders. Direct immunofluorescence is negative and has little, if any, value for differential diagnosis.

The following histopathologic findings are characteristic for scleredema:

- The epidermis is usually not involved.
- The dermis is up to four times thicker than normal due to enlarged collagen bundles in deep reticular dermis with wide, clear, mucin-filled spaces between them. However, the absence of mucopolysaccharide deposits does not exclude the diagnosis.[24,45,83]
- Mucin deposits represent non-sulphated acid mucopolysaccharides, mainly hyaluronic acid (stainable with Alcian blue dye, colloidal iron or toluidine blue).
- The subcutaneous fat is replaced by coarse collagen fibres.[45]
- Skin appendages are usually preserved (unlike in scleroderma). However, some authors have reported the loss of eccrine glands.[24,84]

Laboratory parameters At the time of diagnosis, blood tests mainly aim at identifying a lymphoproliferative disorder in patients without a recent history of infection or diabetes. However, as scleredema is very rare, it is recommended that these tests are performed in all patients. Fasting glucose, HbA1c, leucocyte count (lymphocytes), serum protein electrophoresis, and serum and urine immunofixation must be performed to screen for diabetes and monoclonal gammopathy.[84] If paraproteinemia becomes apparent, additional investigations should be discussed, including cytofluorometry analysis (for the detection of B-cell lymphoproliferation). Other laboratory tests may be needed in

Table 1 Differential diagnoses to scleredema

Differential diagnosis	Distinguishing features
Systemic sclerosis	• Skin thickening typically begins at the fingertips, progressing to involve the hands and feet (spared in scleredema). • Raynaud's phenomenon, abnormal nail fold capillaries, ANA (absent in scleredema). • No mucin deposits.
Scleromyxedema	• Induration of the skin progresses acrally and typically forms characteristic large folds or firm papules (unlike in scleredema). • However, systemic complications, the association with monoclonal gammopathy and mucin deposits are common in both diseases!
Scleromyositis (SSc-myositis overlap syndrome)	• Typical clinical symptoms. • Commonly positive for ANA, especially anti-PM/Scl (absent in scleredema).
Myxoedema	• Clinical and serological thyroid function abnormalities.
Eosinophilic fasciitis	• Induration in areas corresponding to the anatomic localization of the fascia on the trunk and extremities (unlike in scleredema). • Eosinophilia (absent in scleredema). • No mucin deposits*.
Cutaneous amyloidosis	• Characteristic amyloid deposits found in the affected tissues when stained with Congo red dye†.
Lymphedema	• The removal or damage to lymph nodes is common in the medical history. • Affects the extremities, is most strongly expressed acrally (unlike in scleredema). • Keratinocyte hyperproliferation, condensed dermal collagen and mononuclear perivascular infiltrate (unlike in scleredema). • No mucin deposits.
Cardiac or renal edema	• Oedema is usually non-solid, 'pitting' and is likely to occur in acral locations (unlike in scleredema). • Symptoms of heart or renal failure. • Different histopathological features, no mucin deposits.
Radiotherapy-induced skin thickening	• Previous radiotherapy‡. • Lesions are usually limited to the exposed area. • No mucin deposits.
Graft-versus host disease	• History of hematopoietic cell transplantation. • No mucin deposits.

*The biopsy should be sufficiently deep to reach the fascia.
†Amyloidosis, however, may be a consequence of advanced lymphoproliferative disease as the underlying cause of type 2 scleredema.
‡Scleredema after radiation treatment is nevertheless possible.[87]
ANA, antinuclear antibodies.

Table 2 Treatment of scleredema

Treatment	Therapeutic measures
Treatment of the identified cause	
Type 1	Antimicrobial agents, if indicated
Type 2	Therapy of the identified lymphoproliferative disorder in consultation with a haematologist
Type 3	Antidiabetics, insulin (blood glucose self-monitoring)
Treatment of the general condition	Weight loss, if necessary; physiotherapy (to increase the range of motion of involved joints), respiratory rehabilitation[73]
In severe cases or if the cause is unidentified: Specific local or systemic treatment	First-line: medium- to high-dose UVA1 or PUVA*,[84,88–93] Second-line: methotrexate (± glucocorticoids, except for diabetic patients) Advanced-line: Other treatments†

*For more information, please refer to the section about localized scleroderma. If UVA1/PUVA is not available, methotrexate should be given.
†If methotrexate fails or is contraindicated, based on a risk-benefit approach, the following alternative treatments can be proposed: glucocorticoids (systemic or intralesional),[94] cyclosporine,[95–97] prostaglandin E1,[98] intravenous immunoglobulin,[99] high-dose penicillin,[100] factor XIII infusion,[101] cyclophosphamide,[56] narrow-band UVB,[93] radiotherapy,[102] electron-beam radiotherapy[48,103–105] and extracorporeal photopheresis.[106]

differential diagnosis to exclude other conditions, depending on the clinical presentation. ANA testing is negative and may thus facilitate differential diagnosis with SSc.

Imaging High-frequency ultrasonography may be performed to monitor the activity and severity of skin involvement. In cases of systemic involvement, specific diagnostic examinations are required (e.g. pulmonary function tests, ultrasonography of internal organs, including the heart, liver or spleen, oesophageal manometry, radiography or ultrasonography of bones and joints). In cases of monoclonal gammopathy or clinical evidence of enlarged lymph nodes, chest and abdomino-pelvic CT scan, positron emission tomography scan, lumbar and dorsal MRI, and/or myelogram/osteomedullar biopsy are the methods of choice.

In summary, the diagnosis of scleredema is made clinically, with the definitive diagnosis confirmed by histopathology. A typical woody thickening of the skin which spares acral locations (hands and feet are usually not involved), history of a preceding infection, underlying paraproteinemia or diabetes, and accumulation of mucopolysaccharides in the microscopic evaluation are the main diagnosis criteria of scleredema.[24,84–86]

Differential diagnoses

Scleredema may cause diagnostic difficulties, as the differential diagnosis includes various diseases. The characteristic thickness of the dermis and the accumulation of mucopolysaccharides distinguish scleredema from other sclerotic disorders.[45] Table 1 lists the major differential diagnoses and some characteristics usable for distinguishing them from scleredema.

Treatment

The treatment should primarily focus on the underlying condition. If an infection is identified, it may be treated with appropriate anti-infectious agents. If a lymphoproliferative disorder is identified (scleredema type 2), there is a need for discussions with a haematologist. In diabetic patients (scleredema type 3), the control of diabetes is mandatory. If not already prescribed, insulin and blood glucose self-monitoring may be necessary. Overweight patients should be given dietary advice. If the patient has severe scleredema in the absence of an underlying condition, phototherapy or drug treatment of the skin lesions can be proposed (Table 2). Unfortunately, the number of patients reported in the literature who benefited from a specific treatment is very small. It is thus very difficult to give evidence-based medical recommendations. The lack of randomized controlled trials about scleredema creates a difficulty in drawing conclusions about the best treatment regimens, optimum dose and long-term efficacy.[88]

Clinical course and prognosis

The efficacy of treatments for scleredema can be assessed using the mRSS, Health Assessment Questionnaire, the range of motion of involved joints and the Dermatology Life Quality Index. Type 1 scleredema associated with a preceding infection is characterized by a good prognosis and even spontaneous resolution. The active phase lasts 2–8 weeks and is followed by a resolution in a couple of months to 2 years.[107] Scleredema type 1 lesions persisting for 10 years are uncommon.[108]

Unlike type 1, type 2 (which is associated with blood dyscrasia) should be carefully followed up. The prognosis is not good; the lesions are persistent with possible systemic involvement leading to life-threatening complications. In patients with or without identified lymphoproliferation, leucocyte count (lymphocytes), serum protein electrophoresis, and serum and urine immunofixation as well as a thorough physical examination for lymph node enlargement and/or hepato-splenomegaly should be performed annually. If monoclonal gammopathy of unspecified significance is detected, the risk of multiple myeloma or another related malignancy is about 1% per year. Therefore, careful follow-up of patients is required.[109] The treatment of underlying diseases is crucial; however, this may not be satisfactory in some type 2 scleredema cases.

Diabetic scleredema (type 3) has a poor prognosis, with a chronic progressive course and systemic complications. It also requires follow-up of patients with monitoring of the metabolic state (fasting blood glucose, HbA1c, body weight). Sleep apnoea syndrome is common, and specific diagnostic tests are necessary to confirm the disorder. As diabetic scleredema is under-recognized, there is a need for appropriate education.[94]

Recommendations

- The diagnosis of scleredema is made clinically. A histopathologic examination is performed to confirm a definitive diagnosis.
- Scleredema type 1 does not usually require treatment, as it is self-limited and usually resolves in a short period of time.
- In types 2 and 3 scleredema, the treatment of an underlying condition is needed. Better glucose control has been proven to be beneficial in some cases of type 3.
- Patient follow-up in types 2 and 3 scleredema is needed to screen for paraproteinemia and systemic complications.
- No specific therapy of scleredema is available, although numerous methods have been proposed with variable results. The recommended first-line treatment is UV-based management as monotherapy. If this fails, methotrexate is recommended.

Nephrogenic systemic fibrosis

Epidemiology and pathogenesis

Nephrogenic fibrosing dermopathy, a dermatologic form of the generic term nephrogenic systemic fibrosis (NSF), is a relatively new disease entity. NSF was first reported in 2000 and is believed to be seen almost only in patients with moderate-to-severe kidney failure, particularly in patients on dialysis.[110] It was linked to the usage of gadolinium-based contrast agents (GBCAs) for MRI which were adopted in the late 1990s for use in patients with impaired renal function.[111] Depending on the type of GBCA, the incidence rate of NSF may vary. For gadodiamide, it has been estimated to be between 3% and 7% in patients with renal insufficiency.[112] Based on multicenter retrospective reviews[113,114] and alerting reports by the European Medicines Agency and the US Food and Drug Administration,[115,116] important risk factors for NSF have been identified (Table 3). Importantly, the adapted, selective use of GBCAs thereafter led to a significant drop in incidence of NSF.[117,118] NSF has been documented in all age groups, including in children.[119]

It has been proposed that excess GBCA in patients with renal insufficiency undergoing MRI may be deposited in the tissue upon transmetallation. GBCAs include lanthanides which decades ago were reported to induce profibrogenic processes.[122,123] More recently, chelated gadodiamide and gadopentetate forms specifically have been shown to increase the release of profibrotic cytokines and growth factors in macrophages/monocytes in vitro within minutes after receptor-mediated cellular uptake.[124]

Diagnostic procedures

Clinical presentation and physical examination There is no specific test available for the diagnosis of NSF. The initial symptoms include hyperpigmented skin areas and papules, which may coalesce to patches and plaques with a peau d'orange appearance. NSF commonly forms symmetrical lesions, which are predominantly located on the lower legs and develop within the first 2–8 weeks after exposure to a GBCA.[117] Pain and pruritus are frequent symptoms. Systemic involvement such as scleral plaques, muscle fibrosis and induration, flexion contractures, fibrosis of vessel walls of internal organs (lung, kidneys), and calcification of soft tissue has been described. Delayed onset of NSF at up to 10 years after gadolinium uptake has been described.[125]

Clinical score Girardi *et al.*[126,127] proposed a clinicopathologic scoring system that has been tested on the reported cases in an NSF registry. It integrates major and minor clinical criteria, and histopathological characteristics. This scoring system can hardly be further validated in clinical practice because the incidence of NSF appears to diminish. It may, however, be helpful to differentiate between borderline cases of NSF and other sclerosing skin disorders.

Histopathology On routine light microscopy, depending on the disease severity, a deep biopsy may show fibrocyte proliferation ranging from subtle proliferation of dermal fibrocytes in early lesions to florid proliferation. Thick collagen bundles with surrounding clefts are a prominent finding, with a variable increase in dermal mucin and elastin. Immunohistochemical staining shows CD34 positive dermal dendritic cells. Gadolinium may be visualized with special testing but is not diagnostic.[128]

Laboratory parameters Abnormal creatinine and increased urea nitrogen in serum are to be considered in the context of the pre-existing renal insufficiency. Some patients show blood eosinophilia.

Differential diagnoses

Sclerosing skin processes that may occur in patients with impaired renal function, such as scleromyxedema, lipodermatosclerosis, eosinophilic fasciitis or localized and SSc, are the most relevant differential diagnoses for NSF. Unlike in eosinophilic fasciitis, fever, arthritis and malaise are uncommon in NSF.[129] Unlike SSc, Raynaud's phenomenon is typically absent in NSF. Antinuclear antibodies and rheumatoid factors are typically negative, and there is no association with paraproteinemia.

Treatment

Established NSF lesions do not respond to systemic or topical glucocorticoid treatment or to other immunosuppressive drugs. Other approaches such as extracorporeal photopheresis, UVA1 phototherapy, plasmapheresis or imatinib mesylate have been used with inconsistent clinical improvement.[130–137] Based on the published data, no specific therapeutic recommendation can be made. Reconstitution of renal function is considered the best therapeutic approach.[138]

Table 3 Risk factors for nephrogenic systemic fibrosis[113-115,120,121]

General risk factors
• Use of GBCA for MRI in patients with acute or chronic renal insufficiency (GFR <30 mL/min/1.73 m^2)
• Use of higher-than-standard dose of GBCA for MRI
• Current inflammatory or thrombotic episodes in patient
Risk stratification based on GBCA type
High-risk GBCAs:
• Linear non-ionic chelates (gadoversetamide [OptiMARK®], gadiodiamide [Omniscan®])
• Linear ionic chelates (gadopentetic acid [Magnevist®, Gado-MRT-ratiopharm®, Magnegita®, Marktiv®])
Medium-risk GBCAs:
• Linear ionic chelates including gadofosveset trisodium (Vasovist®), gadoxetic acid disodium (Primovist®) and gadobenate dimeglumine (MultiHance®)
Low-risk GBCAs:
• Macrocyclic chelates (gadoteric acid [Dotarem®], gadoteridol [ProHance®], gadobutrol [Gadovist®])

GBCA, gadolinium-based contrast agent; GFR, glomerular filtration rate; MRI, magnetic resonance imaging.

Clinical course and prognosis

The sclerosing process in NSF may proceed within days or weeks. In patients who experience improvement of renal function (e.g. after kidney transplantation), the condition may regress spontaneously.[138,139] Although NSF per se is not lethal, it has a major impact on the patient's quality of life and may cause reduced mobility. Cardiovascular complications are the main cause of death in patients with end-stage renal impairment with or without NSF.[140]

Recommendations

- NSF is an iatrogenic condition observed in patients with end-stage renal failure and is associated with gadolinium exposure. No treatments with proven efficacy based on randomized controlled trials are available.
- The key preventive measure is avoidance of high-risk GBCAs, especially in patients with an estimated glomerular filtration rate of <30 mL/min.
- If in a patient MRI with a GBCA is indispensable, a low-risk gadolinium medium should be the contrast agent of choice (Table 3). The dose of the GBCA should be reduced to the minimum effective dosage for imaging.[115,120]
- Based on the dialysability of GBCAs, it is recommended that at least one full four-hour dialysis session is performed after GBCA-based MRI in patients with renal insufficiency; this should remove 97% of the dose. Three full sessions of dialysis increase the GBCA clearance up to 99.7%.[141]

References

1 Rongioletti F, Merlo G, Cinotti E *et al.* Scleromyxedema: a multicenter study of characteristics, comorbidities, course, and therapy in 30 patients. *J Am Acad Dermatol* 2013; **69**: 66–72.
2 Rongioletti F, Rebora A. Mucinoses. In Bolognia J, Jorizzo JL, Schaffer JV eds. Dermatology, Vol. **1**, 3rd edn. Elsevier, Philadelphia, 2012: 687.
3 Rongioletti F. Lichen myxedematosus (papular mucinosis): new concepts and perspectives for an old disease. *Semin Cutan Med Surg* 2006; **25**: 100–104.
4 Feasel AM, Donato ML, Duvic M. Complete remission of scleromyxedema following autologous stem cell transplantation. *Arch Dermatol* 2001; **137**: 1071–1072.
5 Dinneen AM, Dicken CH. Scleromyxedema. *J Am Acad Dermatol* 1995; **33**: 37–43.
6 Blum M, Wigley FM, Hummers LK. Scleromyxedema: a case series highlighting long-term outcomes of treatment with intravenous immunoglobulin (IVIG). *Medicine* 2008; **87**: 10–20.
7 Chan JC, Trendell-Smith NJ, Yeung CK. Scleromyxedema: a cutaneous paraneoplastic syndrome associated with thymic carcinoma. *J Clin Oncol* 2012; **30**: e27–e29.
8 Alfadley A, Al Hoqail I, Al Eisa A. Scleromyxedema: possible association with seminoma. *J Am Acad Dermatol* 2000; **42**: 875–878.
9 Giménez Garcia R, Garcia SG, Suarez Vilela D, Moro Sanchez MJ. Scleromyxedema associated with non-Hodgkin lymphoma. *Int J Dermatol* 1989; **28**: 670–671.
10 Rongioletti F, Hazini A, Rebora A. Coma associated with scleromyxedema and interferon alfa therapy. Full recovery after steroids and cyclophosphamide combined with plasmapheresis. *Br J Dermatol* 2001; **144**: 1283–1284.
11 Fleming KE, Virmani D, Sutton E *et al.* Scleromyxedema and the dermato-neuro syndrome: case report and review of the literature. *J Cutan Pathol* 2012; **39**: 508–517.
12 Rey JB, Luria RB. Treatment of scleromyxedema and the dermatoneuro syndrome with intravenous immunoglobulin. *J Am Acad Dermatol* 2009; **60**: 1037–1041.
13 Espinosa A, De Miguel E, Morales C, Fonseca E, Gijón-Baños J. Scleromyxedema associated with arthritis and myopathy: a case report. *Clin Exp Rheumatol* 1993; **11**: 545–547.
14 Cokonis Georgakis CD, Falasca G, Georgakis A, Heymann WR. Scleromyxedema. *Clin Dermatol* 2006; **24**: 493–497.
15 Helfrich DJ, Walker ER, Martinez AJ, Medsger TA Jr. Scleromyxedema myopathy: case report and review of the literature. *Arthritis Rheum* 1988; **31**: 1437–1441.
16 Rothe MJ, Rivas R, Gould E, Kerdel FA. Scleromyxedema and severe myositis. *Int J Dermatol* 1989; **28**: 657–660.
17 Ozdag F, Akar A, Eroglu E, Erbil H. Acute rhabdomyolysis during the treatment of scleromyxedema with interferon alfa. *J Dermatolog Treat* 2001; **12**: 167–169.
18 Pomann JJ, Rudner EJ. Scleromyxedema revisited. *Int J Dermatol* 2003; **42**: 31–35.
19 De Simone C, Castriota M, Carbone A, Marini Bettolo P, Pieroni M, Rongioletti F. Cardiomyopathy in scleromyxedema: report of a fatal case. *Eur J Dermatol* 2010; **20**: 852–853.
20 Le Moigne M, Mazereeuw-Hautier J, Bonnetblanc JM *et al.* Clinical characteristics, outcome of scleromyxedema: a retrospective multicentre study. *Ann Dermatol Venereol* 2010; **137**: 782–788.
21 Rapp MF, Guram M, Konrad HR, Mody N, Trapp R. Laryngeal involvement in scleromyxedema: a case report. *Otolaryngol Head Neck Surg* 1991; **104**: 362–365.
22 Lee YH, Sahu J, O'Brien MS, D'Agati VD, Jimenez SA. Scleroderma renal crisis-like acute renal failure associated with mucopolysaccharide accumulation in renal vessels in a patient with scleromyxedema. *J Clin Rheumatol* 2011; **17**: 318–322.

23 Delyon J, Bézier M, Rybojad M *et al.* Specific lymph node involvement in scleromyxedema: a new diagnostic entity for hypermetabolic lymphadenopathy. *Virchows Arch* 2013; **462**: 679–683.
24 Rongioletti F, Rebora A. Cutaneous mucinoses: microscopic criteria for diagnosis. *Am J Dermatopathol* 2001; **23**: 257–267.
25 Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol* 2001; **44**: 273–281.
26 Nashel J, Steen V. Scleroderma mimics. *Curr Rheumatol Rep* 2012; **14**: 39–46.
27 Bidier M, Zschoche C, Gholam P, Enk AH, Hadaschik EN. Scleromyxedema: clinical follow-up after successful treatment with high-dose immunoglobulins reveals different long-term outcomes. *Acta Derm Venereol* 2012; **92**: 408–409.
28 Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science* 2001; **291**: 484–486.
29 Sroa N, Campbell S, Bechtel M. Intravenous immunoglobulin therapy for scleromyxedema: a case report and review of literature. *J Drugs Dermatol* 2010; **9**: 263–265.
30 Gholam P, Hartmann M, Enk A. Arndt-Gottron scleromyxedema: successful therapy with intravenous immunoglobulins. *Br J Dermatol* 2007; **157**: 1058–1060.
31 Körber A, Franckson T, Grabbe S, Dissemond J. Successful therapy of scleromyxedema Arndt-Gottron with low-dose intravenous immunoglobulin. *J Eur Acad Dermatol Venereol* 2007; **21**: 553–554.
32 Binitha MP, Nandakumar G, Thomas D. Suspected cardiac toxicity to intravenous immunoglobulin used for treatment of scleromyxedema. *Indian J Dermatol Venereol Leprol* 2008; **74**: 248–250.
33 Sansbury JC, Cocuroccia B, Jorizzo JL, Gubinelli E, Gisondi P, Girolomoni G. Treatment of recalcitrant scleromyxedema with thalidomide in 3 patients. *J Am Acad Dermatol* 2004; **51**: 126–131.
34 Guarenti I, Sebastiani V, Pinto G, de Souza PR, de Almeida H Jr. Successful treatment of scleromyxedema with oral thalidomide. *Int J Dermatol* 2013; **52**: 631–632.
35 Martins A, Paiva Lopes MJ, Tavares Belo R, Rodrigues JC. Scleromyxedema – thalidomide therapy. *J Eur Acad Dermatol Venereol* 2008; **22**: 622–624.
36 Efthimiou P, Blanco M. Intravenous gammaglobulin and thalidomide may be an effective therapeutic combination in refractory scleromyxedema: case report and discussion of the literature. *Semin Arthritis Rheum* 2008; **38**: 188–194.
37 Brunet-Possenti F, Hermine O, Marinho E, Crickx B, Descamps V. Combination of intravenous immunoglobulins and lenalidomide in the treatment of scleromyxedema. *J Am Acad Dermatol* 2013; **69**: 319–320.
38 Rayson D, Lust JA, Duncan A, Su WP. Scleromyxedema: a complete response to prednisone. *Mayo Clin Proc* 1999; **74**: 481–484.
39 Lin YC, Wang HC, Shen JL. Scleromyxedema: an experience using treatment with systemic corticosteroid and review of the published work. *J Dermatol* 2006; **33**: 207–210.
40 Horn KB, Horn MA, Swan J, Singhal S, Guitart J. A complete and durable clinical response to high-dose dexamethasone in a patient with scleromyxedema. *J Am Acad Dermatol* 2004; **51**: S120–S123.
41 Cañueto J, Labrador J, Román C *et al.* The combination of bortezomib and dexamethasone is an efficient therapy for relapsed/refractory scleromyxedema: a rare disease with new clinical insights. *Eur J Haematol* 2012; **88**: 450–454.
42 Bos R, de Waal EG, Kuiper H, Hazenberg BP, Vellenga E. Thalidomide and dexamethasone followed by autologous stem cell transplantation for scleromyxedema. *Rheumatology* 2011; **50**: 1925–1926.
43 Hardie RA, Hunter JA, Urbaniak S, Habeshaw JA. Spontaneous resolution of lichen myxedematosus. *Br J Dermatol* 1979; **100**: 727–730.
44 Greenberg LM, Geppert C, Worthen HG, Good RA. Scleredema "adultorum" in children. Report of three cases with histochemical study and review of world literature. *Pediatrics* 1963; **32**: 1044–1054.
45 Morais P, Almeida M, Santos P, Azevedo F. Scleredema of Buschke following Mycoplasma pneumoniae respiratory infection. *Int J Dermatol* 2011; **50**: 454–457.
46 Venencie PY. Buschke's scleredema. *Ann Dermatol Venereol* 1987; **114**: 1291–1292.
47 Venencie PY, Powell FC, Su WP, Perry HO. Scleredema: a review of thirty-three cases. *J Am Acad Dermatol* 1984; **11**: 128–134.
48 Angeli-Besson C, Koeppel MC, Jacquet P, Andrac L, Sayag J. Electron-beam therapy in scleredema adultorum with associated monoclonal hypergammaglobulinaemia. *Br J Dermatol* 1994; **130**: 394–397.
49 Chang HK, Kim YC, Kwon BS. Widespread scleredema accompanied with a monoclonal gammopathy in a patient with advanced ankylosing spondylitis. *J Korean Med Sci* 2004; **19**: 481–483.
50 Paz RA, Badra RE, Marti HM, Maxit MJ. Systemic Buschke's scleredema with cardiomyopathy, monoclonal IgG kappa gammopathy and amyloidosis. Case report with autopsy. *Medicina (B Aires)* 1998; **58**(5 Pt 1): 501–503.
51 McFadden N, Ree K, Soyland E, Larsen TE. Scleredema adultorum associated with a monoclonal gammopathy and generalized hyperpigmentation. *Arch Dermatol* 1987; **123**: 629–632.
52 Szturz P, Adam Z, Vasku V *et al.* Complete remission of multiple myeloma associated scleredema after bortezomib-based treatment. *Leuk Lymphoma* 2013; **54**: 1324–1326.
53 Santos-Juanes J, Osuna CG, Iglesias JR, De Quiros JF, del Rio JS. Treatment with chemotherapy of scleredema associated with IgA myeloma. *Int J Dermatol* 2001; **40**: 720–721.
54 Grudeva-Popova J, Dobrev H. Biomechanical measurement of skin distensibility in scleredema of Buschke associated with multiple myeloma. *Clin Exp Dermatol* 2000; **25**: 247–249.
55 Valente L, Velho GC, Farinha F, Bernardo A, Ribeiro P, Massa A. Scleredema, acanthosis nigricans and IgA/Kappa multiple myeloma. *Ann Dermatol Venereol* 1997; **124**: 537–539.
56 Salisbury JA, Shallcross H, Leigh IM. Scleredema of Buschke associated with multiple myeloma. *Clin Exp Dermatol* 1988; **13**: 269–270.
57 Dziadzio M, Anastassiades CP, Hawkins PN *et al.* From scleredema to AL amyloidosis: disease progression or coincidence? Review of the literature *Clin Rheumatol* 2006; **25**: 3–15.
58 Krakowski A, Covo J, Berlin C. Diabetic scleredema. *Dermatologica* 1973; **146**: 193–198.
59 Jacob N, Gleichmann U, Stadler R. Scleredema adultorum in secondary hyperparathyroidism. *Hautarzt* 2002; **53**: 121–125.
60 Berk MA, Lorincz AL. Scleredema adultorum of Buschke and primary hyperparathyroidism. *Int J Dermatol* 1988; **27**: 647–649.
61 Ranganathan P. Infliximab-induced scleredema in a patient with rheumatoid arthritis. *J Clin Rheumatol* 2005; **11**: 319–322.
62 Miyagawa S, Dohi K, Tsuruta S, Shirai T. Scleredema of Buschke associated with rheumatoid arthritis and Sjogren's syndrome. *Br J Dermatol* 1989; **121**: 517–520.
63 Marill FG, Grould P. Scleredema, 1st manifestation of a dermatomyositis. *Bull Soc Fr Dermatol Syphiligr* 1968; **75**: 561–564.
64 Goss F, Krawietz W, Luderschmidt C, Pape GR. Scleredema adultorum Buschke and primary biliary cirrhosis in a 58-year-old patient. *Internist* 1984; **25**: 130–134.
65 Theodoridis A, Capetanakis J. Scleredema of Buschke with IgA deficiency. *Acta Derm Venereol* 1979; **59**: 182–183.
66 Matsunaga J, Hara M, Tagami H. Scleredema of Buschke associated with malignant insulinoma. *Br J Dermatol* 1992; **126**: 527–528.
67 Manchanda Y, Das S, Sharma VK, Srivastava DN. Scleredema associated with carcinoma of the gall bladder. *Br J Dermatol* 2005; **152**: 1373–1374.

68 Yu JI, Park W, Lee KK, Park W. Scleredema adultorum of Buschke associated with a carcinoid tumor. *Int J Dermatol* 2009; **48**: 784–786.
69 Oyama N, Togashi A, Kaneko F, Yamamoto T. Two cases of scleredema with pituitary-adrenocortical neoplasms: an underrecognized skin complication. *J Dermatol* 2012; **39**: 193–195.
70 Beers WH, Ince A, Moore TL. Scleredema adultorum of Buschke: a case report and review of the literature. *Semin Arthritis Rheum* 2006; **35**: 355–359.
71 Rimon D, Lurie M, Storch S *et al.* Cardiomyopathy and multiple myeloma. Complications of scleredema adultorum. *Arch Intern Med* 1988; **148**: 551–553.
72 Schmidt KT, Gattuso P, Messmore H, Shrit MA, Massa M, Welykyj S. Scleredema and smoldering myeloma. *J Am Acad Dermatol* 1992; **26**(2 Pt 2): 319–321.
73 Meguerditchian C, Jacquet P, Beliard S *et al.* Scleredema adultorum of Buschke: an under recognized skin complication of diabetes. *Diabetes Metab* 2006; **32**(5 Pt 1): 481–484.
74 Farrell AM, Branfoot AC, Moss J, Papadaki L, Woodrow DF, Bunker CB. Scleredema diabeticorum of Buschke confined to the thighs. *Br J Dermatol* 1996; **134**: 1113–1115.
75 Boin F, Hummers LK. Scleroderma-like fibrosing disorders. *Rheum Dis Clin North Am* 2008; **34**: 199–220; ix.
76 Mohanasundaram K, Kumarasamy S, Kumar R, Rajendran CP. Scleredema adultorum of Buschke: with unusual manifestations in a young female. *Indian J Dermatol Venereol Leprol* 2012; **78**: 503–505.
77 Ioannidou DI, Krasagakis K, Stefanidou MP, Karampekios S, Panayiotidis J, Tosca AD. Scleredema adultorum of Buschke presenting as periorbital edema: a diagnostic challenge. *J Am Acad Dermatol* 2005; **52**(2 Suppl 1): 41–44.
78 Brenner M, Herzinger T, Berking C, Plewig G, Degitz K. Phototherapy and photochemotherapy of sclerosing skin diseases. *Photodermatol Photoimmunol Photomed* 2005; **21**: 157–165.
79 Wright RA, Bernie H. Scleredema adultorum of Buschke with upper esophageal involvement. *Am J Gastroenterol* 1982; **77**: 9–11.
80 Sansom JE, Sheehan AL, Kennedy CT, Delaney TJ. A fatal case of scleredema of Buschke. *Br J Dermatol* 1994; **130**: 669–670.
81 Ray V, Boisseau-Garsaud AM, Ray P *et al.* Obesity persistent scleredema: study of 49 cases. *Ann Dermatol Venereol* 2002; **129**: 281–285.
82 Cole GW, Handler SJ, Burnett K. The ultrasonic evaluation of skin thickness in scleredema. *J Clin Ultrasound* 1981; **9**: 501–503.
83 Vereecken P, Lutz R, De Dobbeleer G, Heenen M. Nonpitting induration of the back. Scleredema adultorum of Buschke type III. *Arch Dermatol* 1997; **133**: 649, 652.
84 Martin C, Requena L, Manrique K, Manzarbeitia FD, Rovira A. Scleredema diabeticorum in a patient with type 2 diabetes mellitus. *Case Rep Endocrinol* 2011; **2011**: 560273.
85 Cole HG, Winkelmann RK. Acid mucopolysaccharide staining in scleredema. *J Cutan Pathol* 1990; **17**: 211–213.
86 Cole GW, Headley J, Skowsky R. Scleredema diabeticorum: a common and distinct cutaneous manifestation of diabetes mellitus. *Diabetes Care* 1983; **6**: 189–192.
87 Mylona E, Golfinopoulou S, Skarmea A *et al.* Post-radiation scleredema adultorum and diffuse eosinophilic fasciitis in the same patient. *Scand J Rheumatol* 2011; **40**: 240–241.
88 Kroft EB, Berkhof NJ, van de Kerkhof PC, Gerritsen RM, de Jong EM. Ultraviolet A phototherapy for sclerotic skin diseases: a systematic review. *J Am Acad Dermatol* 2008; **59**: 1017–1030.
89 Kokpol C, Rajatanavin N, Rattanakemakorn P. Successful treatment of scleredema diabeticorum by combining local PUVA and colchicine: a case report. *Case Rep Dermatol* 2012; **4**: 265–268.
90 Nakajima K, Iwagaki M, Ikeda M, Kodama H. Two cases of diabetic scleredema that responded to PUVA therapy. *J Dermatol* 2006; **33**: 820–822.
91 Grundmann-Kollmann M, Ochsendorf F, Zollner TM, Spieth K, Kaufmann R, Podda M. Cream PUVA therapy for scleredema adultorum. *Br J Dermatol* 2000; **142**: 1058–1059.
92 Hager CM, Sobhi HA, Hunzelmann N *et al.* Bath-PUVA therapy in three patients with scleredema adultorum. *J Am Acad Dermatol* 1998; **38** (2 Pt 1): 240–242.
93 Yoshimura J, Asano Y, Takahashi T *et al.* A case of scleredema adultorum successfully treated with narrow-band ultraviolet B phototherapy. *Mod Rheumatol* 2016; **26**: 302–306.
94 Rongioletti F, Kaiser F, Cinotti E *et al.* Scleredema. A multicentre study of characteristics, comorbidities, course and therapy in 44 patients. *J Eur Acad Dermatol Venereol* 2015; **29**: 2399–2404.
95 Mattheou-Vakali G, Ioannides D, Thomas T, Lazaridou E, Tsogas P, Minas A. Cyclosporine in scleredema. *J Am Acad Dermatol* 1996; **35**: 990–991.
96 Dogramaci AC, Inan MU, Atik E, Gokce C. Scleredema diabeticorum partially treated with low-dose methotrexate: a report of five cases. *Balkan Med J* 2012; **29**: 218–221.
97 Breuckmann F, Appelhans C, Harati A, Rotterdam S, Altmeyer P, Kreuter A. Failure of low-dose methotrexate in the treatment of scleredema diabeticorum in seven cases. *Dermatology* 2005; **211**: 299–301.
98 Ikeda Y, Suehiro T, Abe T *et al.* Severe diabetic scleredema with extension to the extremities and effective treatment using prostaglandin E1. *Intern Med* 1998; **37**: 861–864.
99 Eastham AB, Femia AN, Velez NF, Smith HP, Vleugels RA. Paraproteinemia-associated scleredema treated successfully with intravenous immunoglobulin. *JAMA Dermatol* 2014; **150**: 788–789.
100 Krasagakis K, Hettmannsperger U, Trautmann C, Tebbe B, Garbe C. Persistent scleredema of Buschke in a diabetic: improvement with high-dose penicillin. *Br J Dermatol* 1996; **134**: 597–598.
101 Venturi C, Zendri E, Santini M, Grignaffini E, Ricci R, De Panfilis G. Scleredema of Buschke: remission with factor XIII treatment. *Int J Tissue React* 2004; **26**: 25–28.
102 Bowen AR, Smith L, Zone JJ. Scleredema adultorum of Buschke treated with radiation. *Arch Dermatol* 2003; **139**: 780–784.
103 Lee MW, Choi JH, Sung KJ, Moon KC, Koh JK. Electron beam therapy in patients with scleredema. *Acta Derm Venereol* 2000; **80**: 307–308.
104 Tamburin LM, Pena JR, Meredith R, Soong VY. Scleredema of Buschke successfully treated with electron beam therapy. *Arch Dermatol* 1998; **134**: 419–422.
105 Pilgrim U, Vogel A, Meves C. Connective tissue fibers in sclero-myxedema and scleredema adultorum. A quantitative electron microscopic study (author's transl). *Dermatologica* 1973; **147**: 46–63.
106 Stables GI, Taylor PC, Highet AS. Scleredema associated with paraproteinaemia treated by extracorporeal photopheresis. *Br J Dermatol* 2000; **142**: 781–783.
107 Parmar RC, Bavdekar SB, Bansal S, Doraiswamy A, Khambadkone S. Scleredema adultorum. *J Postgrad Med* 2000; **46**: 91–93.
108 Pitarch G, Torrijos A, Martinez-Aparicio A, Vilata JJ, Fortea JM. Scleredema of Buschke associated with diabetes mellitus. Study of four cases. *Actas Dermosifiliogr* 2005; **96**: 46–49.
109 Minato H, Nishikori M, Tanioka M, Miyachi Y, Utani A. Scleredema with diffuse pigmentation. *J Eur Acad Dermatol Venereol* 2010; **24**: 100–101.
110 Gathings RM, Reddy R, Santa Cruz D, Brodell RT. Gadolinium-associated plaques: a new, distinctive clinical entity. *JAMA Dermatol* 2015; **151**: 316–319.
111 Prince MR, Arnoldus C, Frisoli JK. Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. *J Magn Reson Imaging* 1996; **6**: 162–166.
112 Thomsen HS, Marckmann P. Extracellular Gd-CA: differences in prevalence of NSF. *Eur J Radiol* 2008; **66**: 180–183.
113 Prince MR, Zhang H, Morris M *et al.* Incidence of nephrogenic systemic fibrosis at two large medical centers. *Radiology* 2008; **248**: 807–816.

114 Wertman R, Altun E, Martin DR *et al.* Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American universities. *Radiology* 2008; **248**: 799–806.

115 European Medicines Agency. Assessment report for Gadolinium-containing contrast agents. 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf (last accessed 09 February 2017).

116 US Food and Drug administration. New warnings required on use of gadolinium-based contrast agents. 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm225286.htm (last accessed 09 February 2017).

117 Thomsen HS, Morcos SK, Almen T *et al.* Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol* 2013; **23**: 307–318.

118 Bennett CL, Qureshi ZP, Sartor AO *et al.* Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease. *Clin Kidney J* 2012; **5**: 82–88.

119 Jan F, Segal JM, Dyer J, LeBoit P, Siegfried E, Frieden IJ. Nephrogenic fibrosing dermopathy: two pediatric cases. *J Pediatr* 2003; **143**: 678–681.

120 Khawaja AZ, Cassidy DB, Al Shakarchi J, McGrogan DG, Inston NG, Jones RG. Revisiting the risks of MRI with Gadolinium based contrast agents – review of literature and guidelines. *Insights Imaging* 2015; **6**: 553–558.

121 Sadowski EA, Bennett LK, Chan MR *et al.* Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; **243**: 148–157.

122 Evans CH, Drouven BJ. The promotion of collagen polymerization by lanthanide and calcium ions. *Biochem J* 1983; **213**: 751–758.

123 Drouven BJ, Evans CH. Collagen fibrillogenesis in the presence of lanthanides. *J Biol Chem* 1986; **261**: 11792–11797.

124 Newton BB, Jimenez SA. Mechanism of NSF: new evidence challenging the prevailing theory. *J Magn Reson Imaging* 2009; **30**: 1277–1283.

125 Larson KN, Gagnon AL, Darling MD, Patterson JW, Cropley TG. Nephrogenic systemic fibrosis manifesting a decade after exposure to gadolinium. *JAMA Dermatol* 2015; **151**: 1117–1120.

126 The International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR). Available at: http://www.icnfdr.org/(last accessed 15 February 2017).

127 Girardi M, Kay J, Elston DM, Leboit PE, Abu-Alfa A, Cowper SE. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol* 2011; **65**: 1095–1106. e7.

128 Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). *Curr Opin Rheumatol* 2006; **18**: 614–617.

129 Cowper SE. Nephrogenic fibrosing dermopathy: the first 6 years. *Curr Opin Rheumatol* 2003; **15**: 785–790.

130 Mathur K, Morris S, Deighan C, Green R, Douglas KW. Extracorporeal photopheresis improves nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: three case reports and review of literature. *J Clin Apher* 2008; **23**: 144–150.

131 Tran KT, Prather HB, Cockerell CJ, Jacobe H. UV-A1 therapy for nephrogenic systemic fibrosis. *Arch Dermatol* 2009; **145**: 1170–1174.

132 Tsagalis G, Psimenou E, Laggouranis A. Combination treatment with plasmapheresis and sirolimus does not seem to benefit nephrogenic systemic fibrosis. *Int J Artif Organs* 2008; **31**: 913–914.

133 Elmholdt TR, Buus NH, Ramsing M, Olesen AB. Antifibrotic effect after low-dose imatinib mesylate treatment in patients with nephrogenic systemic fibrosis: an open-label non-randomized, uncontrolled clinical trial. *J Eur Acad Dermatol Venereol* 2013; **27**: 779–784.

134 Gilliet M, Cozzio A, Burg G, Nestle FO. Successful treatment of three cases of nephrogenic fibrosing dermopathy with extracorporeal photopheresis. *Br J Dermatol* 2005; **152**: 531–536.

135 Lauchli S, Zortea-Caflisch C, Nestle FO, Burg G, Kempf W. Nephrogenic fibrosing dermopathy treated with extracorporeal photopheresis. *Dermatology* 2004; **208**: 278–280.

136 Richmond H, Zwerner J, Kim Y, Fiorentino D. Nephrogenic systemic fibrosis: relationship to gadolinium and response to photopheresis. *Arch Dermatol* 2007; **143**: 1025–1030.

137 Kintossou R, D'Incan M, Chauveau D *et al.* Nephrogenic fibrosing dermopathy treated with extracorporeal photopheresis: role of gadolinium? *Ann Dermatol Venereol* 2007; **134**: 667–671.

138 Cuffy MC, Singh M, Formica R *et al.* Renal transplantation for nephrogenic systemic fibrosis: a case report and review of the literature. *Nephrol Dial Transplant* 2011; **26**: 1099–1101.

139 Leung N, Shaikh A, Cosio FG *et al.* The outcome of patients with nephrogenic systemic fibrosis after successful kidney transplantation. *Am J Transplant* 2010; **10**: 558–562.

140 de Souza Machado Igreja AC, Cowper SE, de Carvalho Mesquita K, Carvalho CostaI M. Nephrogenic systemic fibrosis: concepts and perspectives. *An Bras Dermatol* 2012; **87**: 597–607.

141 Gheuens E, Daelemans R, Mesens S. Dialysability of gadoteric acid in patients with end-stage renal disease undergoing hemodialysis. *Invest Radiol* 2014; **49**: 505–508.

