

Scleroderma-like Fibrosing Disorders

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Scleroderma (systemic sclerosis or SSc) is a relatively rare connective tissue disorder characterized by skin fibrosis, obliterative vasculopathy, and distinct autoimmune abnormalities. The word scleroderma derives from Greek (skleros = hard and derma = skin), highlighting the most apparent feature of this disease, which is excessive cutaneous collagen deposition and fibrosis. Many other clinical conditions present with substantial skin fibrosis and may be confused with SSc, sometimes leading to a wrong diagnosis. As summarized in **Box 1**, the list of SSc-like disorders is extensive, including other immune-mediated diseases (eosinophilic fasciitis, graft-versus-host disease), deposition disorders (scleromyxedema, scleredema, nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy, systemic amyloidosis), toxic exposures including occupational and iatrogenic (aniline-denaturated rapeseed oil, L-tryptophan, polyvinyl chloride, bleomycin, carbidopa) and genetic syndromes (progeroid disorders, stiff skin syndrome). In most cases, even when the etiology is known or suspected, the precise pathogenetic mechanisms leading to skin and tissue fibrosis remain elusive. Importantly, an attentive and meticulous clinical assessment may allow one to distinguish these conditions from SSc and from each other. The distribution and the quality of skin involvement, the presence of Raynaud's or nailfold capillary microscopy, and the association with particular concurrent diseases or specific laboratory parameters can be of substantial help in refining the diagnosis. In most cases, a deep, full-thickness skin-to-muscle biopsy is necessary to confirm the clinical suspicion. Effective therapies are available for some of these conditions. For this reason, a prompt

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Box 1. Spectrum of scleroderma-like fibrosing skin disorders

Immune-mediated/inflammatory

Eosinophilic fasciitis
 Graft-versus-host disease
 Lichen sclerosus et atrophicus
 POEMS syndrome
 Overlap (SLE, dermatomyositis)

Metabolic

Phenylketonuria
 Porphyrria cutanea tarda
 Hypothyroidism (myxedema)

Deposition

Scleromyxedema
 Systemic amyloidosis
 Nephrogenic systemic fibrosis (or nephrogenic fibrosing dermopathy)
 Scleredema adutorum
 Lipodermatosclerosis

Occupational

Polyvinyl chloride
 Organic solvents
 Silica
 Epoxy resins

Genetic

Progeroid disorders (progeria, acrogeria, Werner's syndrome)
 Stiff skin syndrome (or congenital fascial dystrophy)

Toxic or iatrogenic

Bleomycin
 Pentazocine
 Carbidopa
 Eosinophilia–myalgia syndrome (L-tryptophan)
 Toxic oil syndrome (aniline denaturated rapeseed oil)
 Postradiation fibrosis

Abbreviations: SLE, systemic lupus erythematosus; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

diagnosis is important to spare patients from ineffective treatments and inadequate management.

Some SSc-like diseases are obsolete and mostly of historical interest (ie, toxic oil syndrome, L-tryptophan eosinophilia-myalgia syndrome); others

are extremely rare (ie, genetic disorders). For this article, the authors reviewed the most common diseases mimicking SSc, such as nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis, eosinophilic fasciitis, scleromyxedema, and scleredema. General practitioners often detect the onset and initial progression of these conditions. A prompt referral to specialized centers is extremely important to refine or confirm the diagnosis and to initiate the appropriate treatment.

Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy)

Nephrogenic fibrosing dermopathy (NFD) or nephrogenic systemic fibrosis (NSF) was unknown before 1997 when the first few cases were observed in California and subsequently reported in 2000 [1]. These patients were presenting with a rapid confluent fibrotic skin induration associated with lumpy–nodular plaques, pigmentary changes, and flexion contractures of the extremities. The lesions were characterized histologically by fibroblast proliferation, thickened collagen bundles, and mucin deposition, similar to those observed in scleromyxedema. The common denominator for these patients was a history of renal failure and hemodialysis treatment. Their renal disease was secondary to multiple etiologies, and in some cases previous (failing) renal transplantation was present. Despite the initial geographical clustering, patients with similar presentation have been reported worldwide without any ethnic background predilection. Both genders are affected equally (female to male ratio 1:1), with a broad age range (8 to 87 years), including several pediatric cases [2]. In the United States, a NSF registry has been established, with more than 200 cases collected to date [3]. It is likely, however, that the real incidence is much higher and that many existing cases have not been diagnosed or reported.

The disorder initially was called nephrogenic fibrosing dermopathy, indicating the association with renal disease and the apparent involvement of the skin [4]. Subsequent evidence, however, indicated that the fibrosing process was present within muscles, myocardium, lungs, kidneys, and testes [5]. Thus, the term nephrogenic systemic fibrosis now is preferred to recognize the potential systemic nature of this disorder.

Renal disease is invariably present in NSF, but neither the underlying cause nor its duration seems to be relevant. In general, at the time of diagnosis, 90% of patients have been already on hemo- or peritoneal dialysis for a variable period, following acute or chronic renal failure. No other specific clinical conditions have been temporally associated with NSF, with the exception, in different case series, of previous renal transplantation (often malfunctioning), hypercoagulable states, thromboembolic manifestations and vascular surgery or procedures [3]. Some authors have speculated about the almost concurrent emergence of NSF with new dialysis components (eg, dialysate fluids or membranes) or treatments for patients who have renal failure (eg, erythropoietin and angiotensin-converting enzyme [ACE]

inhibitors), without convincing correlation [6,7]. It also was also noted, however, that gadolinium-enhanced MRI or magnetic resonance angiography (MRA) started to be employed commonly in the clinical setting and in particular in renal patients during the early-mid 1990s right before NSF identification. Over the past 2 years, evidence for an association between use of gadolinium and subsequent development of NSF has been growing.

Etiopathogenesis

A strong association between exposure to gadolinium-containing contrast agents and the development of NSF in patients who have renal failure (hemodialysis or glomerular filtration rate [GFR] less than 15 mL/min) initially was reported by two retrospective European studies in 2006, and subsequently confirmed by other authors [8–10]. Recently, deposits of gadolinium and other metals have been shown within NSF skin lesions, strengthening the relevance of the epidemiological observations [11]. Gadolinium (Gd) normally is complexed into chelates (eg, Gadodiamide or Gd-DTPA-BMA or Omniscan), which are soluble and thus suitable for clinical use. In patients who have renal failure Gd half-life is increased substantially (from 1.3 hours up to 120 hours), and Gd-chelate complexes tend to be displaced by excess of certain metal ions such as iron, copper, or zinc (transmetallation) [12]. This dissociation may be enhanced further by a persistent underlying metabolic acidosis. Free Gd ions are less soluble and have a propensity to precipitate into different tissues through direct interaction with cation-binding sites on cellular membranes and extracellular matrix (ECM), or through microembolization in aggregate form [13]. This would explain the presence of Gd deposits in the skin and soft tissues of patients who have had prior exposure to this contrast material. A direct pathogenetic role of Gd in NSF has yet to be proven. Nevertheless, in December 2006, the US Food and Drug Administration issued a public health advisory recommending avoidance of Gd-based contrast agents in patients who have moderate to end-stage kidney disease [14].

The typical histology of NSF skin lesions is characterized by thickened disorganized collagen bundles separated by large clefts and surrounded by dominant fibroblast-like epithelioid or stellate cells (spindle cells), with positive staining for procollagen-I and CD34+ and abundant mucin deposition (Fig. 1A). Inflammatory infiltrates are usually absent, but dendritic and multinucleated giant cells are sometimes present. The infiltrative process usually extends into subcutaneous structures such as adipose interlobular septa, fascial planes (fasciitis), and even deeper into muscle layers, where fibrosis and atrophy can be detected (Fig. 1B). Interestingly, CD34 is a specific marker for adult hematopoietic stem cells, suggesting that these spindle fibroblast-like cells (called fibrocytes) may be circulating and derive from the bone marrow [15]. The mechanisms of fibrocyte recruitment into affected tissues are unknown and may result from active (chemotaxis) or passive

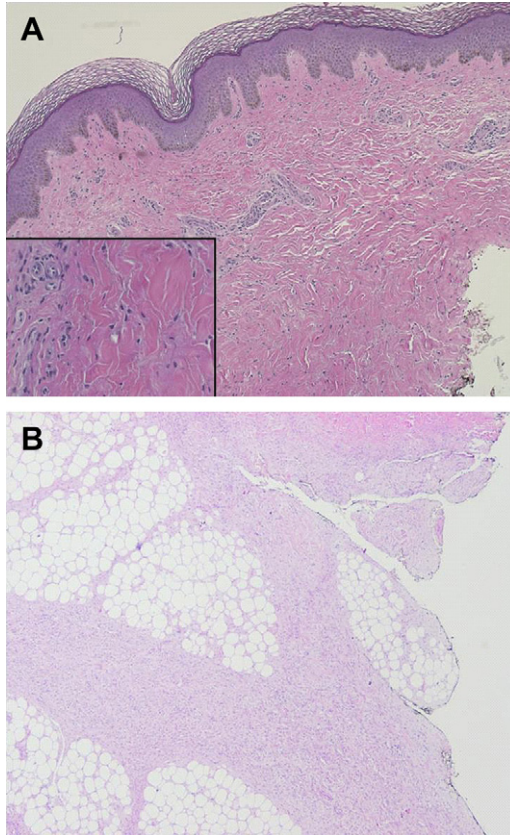


Fig. 1. Nephrogenic systemic fibrosis. (A) Dense dermal fibrosis is present under a normal epidermis. Disorganized collagen bundles are separated by large clefts and surrounded by numerous fibroblast-like (spindle) cells. Minimal perivascular inflammatory infiltrate is present. (B) The infiltrative process is deep, extending into subcutaneous adipose interlobular septa.

transmigration. The association with high doses of erythropoietin use in patients with NSF has been reported [7]. Despite the fact that this hormone has the ability to mobilize hematopoietic progenitors from the bone marrow, including mesenchymal precursors, and contribute to fibrin-induced wound healing, its role in the pathogenesis of NSF has yet to be elucidated [16].

Clinical features

The cutaneous lesions of NSF usually develop over a short period of time (days to weeks), and subsequently assume a chronic, unremitting course. The distribution often is symmetrical, commonly involving the lower extremities up to the knees and the upper extremities up to the elbows. More proximal spread and extension to the trunk is possible. The face

usually is spared. The skin is characterized by a lumpy–nodular thickening with a tendency to form indurated irregular plaques. During early stages, these areas may appear slightly edematous with peau d'orange and erythematous surface features, and can be confounded easily with cellulitis, lymphangitis, or chronic (lymph) edema, not unusual in nephropathic patients. Over time, the skin tends to become bowed-down, with a cobblestone appearance and brawny hyperpigmentation. Objectively, the affected areas and subcutaneous tissues are extremely hard, woody, and can be slightly warm to the touch. The joints underlying NSF lesions usually are involved by a deep fibrotic process, causing severe flexion contractures (particularly hands, wrists, ankles and knees) with substantial loss of range of motion and significant disability. Even ambulation can become compromised severely, and patients can be confined to a wheelchair.

The symptoms in NSF are usually dramatic. The skin and the joints involved by the tight fibrotic process are extremely tender. Pruritus and a burning sensation are very common over affected areas. Nerve conduction studies seem to confirm the presence of a true peripheral neuropathy, further complicating the management of the underlying pain syndrome, which is usually very difficult to control.

Even if no specific diagnostic test is available, the detection in the right clinical context (renal failure) of the characteristic skin changes with unremarkable laboratory findings is adequate to prompt a reasonable suspicion for NSF. In most cases, the distinctive histopathology is confirmatory. Imaging, and in particular MRI (without contrast), can be very helpful to define the extension of the deep fibrosing process and the presence of calcifications. An increased T1 signal is often present within the muscles underlying affected surfaces suggesting presence atrophy and fat degeneration. In addition, fat suppression protocols (eg, fat-suppressed fast T2 weighted sequences) can reveal presence of fascial and muscular edema, particularly during early phases of the disease.

Different from SSc, in NSF serological markers for autoimmunity are absent, and nailfold capillary microscopy examination is normal (Table 1). The body distribution can be similar to SSc (ie, hands can be fully involved), but the face usually is spared. The cobblestone appearance and brawny hyperpigmentation tend to differ from typical SSc skin lesions. Raynaud's phenomenon is usually not present.

Treatment and prognosis

No effective treatment is available for patients who have NSF. In some cases, the normalization of kidney function has been associated with arrest of disease progression and partial reversal of skin lesions, but this is not the rule. Numerous publications have been suggesting favorable therapeutic strategies [17]. These were most exclusively anecdotal reports or very small patient series, however. The reported responses were invariably modest and

Table 1
Differentiating features between scleroderma and scleroderma-like fibrosing disorders

		Scleromyxedema	Scleredema	Eosinophilic fasciitis	Nephrogenic systemic fibrosis
Skin findings					
Quality	Indurated, thick	Papular, waxy	Indurated, doughy	Woody induration	Cobblestone, nodular, indurated plaques
Distribution	Fingers, hands, extremities, face, chest; back spared	Face, neck, extremities, fingers	Neck, back, face	Extremities, trunk Hands and feet spared	Extremities, trunk, hand, feet; face spared
Systemic disease					
Raynaud's phenomenon	Almost universal	Not common	No	Unusual	Unusual
Nailfold capillaries	Universally abnormal	Normal	Normal	Normal	Normal
Antinuclear antibody	Positive 95% to 100%	Uncommon	Negative	Uncommon	Negative
Neurologic disease	Rare	Seizures, dementia, coma	None	Carpal tunnel syndrome	Peripheral neuropathy
Histological changes					
Mucin on biopsy	No	Yes	Yes	No	Yes
Fibrosis	Dermal, epidermal	Dermal	Dermal	Dermal, hypodermal	Dermal, epidermal
Fibrocytes	No (possible)	Yes	No	No	Yes
Inflammation	Perivascular	Perivascular	No	Yes, with/without eosinophils	No
Clinical associations		Monoclonal gammopathy	Infection, monoclonal gammopathy, diabetes	Morphea, immune-mediated cytopenias, hematologic and solid malignancies	Acute or chronic renal failure, renal transplant, exposure to gadolinium-based contrast agents

incomplete. Often, important details about concurrent changes of the underlying kidney function were missing. Most importantly, the results obtained have not been replicated consistently by different centers.

Immunosuppression (ie, cyclophosphamide, thalidomide, mycophenolate mofetil) does not seem to introduce any substantial advantage, even during early stages, when the lesions tend to evolve more rapidly. Interestingly, patients with renal transplantation experience development or progression of NSF despite being on potent antirejection immunosuppressive medications (ie, prednisone, cyclosporine, tacrolimus, or rapamycin). Topical preparations, including corticosteroids creams, are of limited help.

Extracorporeal photopheresis (ECP) has been reported as effective by different groups, but usually requires long periods (months) of administration and achieves mild results [18,19]. Plasmapheresis, intravenous immunoglobulins (IVIG) and ultraviolet (UV-A1) phototherapy also have been proposed [20–22]. In the authors' experience, these treatment strategies have been overall disappointing. A recent report indicates that intravenous sodium thiosulfate is beneficial [23]. This is of interest, because dystrophic dermal calcifications similar to those seen in calciphylaxis are observed in NSF patients.

Aggressive physical therapy remains the most important recommendation and plays a fundamental role in preventing progression of flexion contractures, muscular atrophy, and overall disability. Pain management is extremely challenging, often requiring a combination of agents targeting musculoskeletal and neuropathic pain. Narcotics are often used at high doses, but their efficacy is never satisfactory and decreases over time. Newer drugs with direct antifibrotic effects are being considered in NSF treatment. Substantial skin improvement has been reported with the use of imatinib mesylate [24].

Eosinophilic fasciitis

In 1974, Shulman reported two patients presenting with scleroderma-like skin changes and painful induration of subcutaneous tissues involving the extremities associated with hypergammaglobulinemia, striking peripheral eosinophilia, and histological evidence of diffuse fasciitis [25]. This syndrome was later named eosinophilic fasciitis (EF) by Rodnan and colleagues [26]. Other names used to designate this clinical entity are Shulman's syndrome or diffuse fasciitis with eosinophilia. Since the very first description, there have been more than 250 cases reported in literature; however the true incidence remains unknown. The only substantial case series (52 patients) was from the Mayo Clinic (Rochester, Minn.), published in 1988 [27]. EF tends to be more frequent in males (2:1 ratio), affecting adults in their second to sixth decade of life. More than 30 pediatric cases have been reported, with clinical characteristics similar to those of the adult occurrence, except with higher prevalence in females [28]. EF is largely more prevalent in Caucasians, but sporadically it has been observed in

Asian, African, and African American patients. Epidemics of two clinical entities similar to EF and resulting from the ingestion of toxic contaminants such as aniline-denaturated rapeseed oil and L-tryptophan have been identified in the past [29,30]. Specifically, the toxic oil syndrome (Spain, 1981) and the eosinophilia–myalgia syndrome (United States, 1989) were characterized by eosinophilia, skin fibrosis, and pathologic evidence of fasciitis. Different from EF, these cases presented a more acute course, with fever, severe multisystem involvement, and a high mortality rate. No new cases have been reported over the past decade, and these conditions are now mostly of historical significance.

Etiopathogenesis

The fibrotic changes of EF develop rapidly in the context of an exaggerated immune response and proinflammatory environment. Peripheral blood and tissue eosinophilia, hypergammaglobulinemia, and elevated inflammatory markers are dominant features and correlate with disease activity and response to treatment [27].

The classic histopathologic changes in EF are dermal–hypodermic sclerosis associated with fibrotic thickening of the subcutaneous adipose lobular septa, superficial fascia, and perimysium. The epidermis usually is spared. The adjacent muscles can present mild inflammation without evidence of necrosis. The fibroblastic proliferation is associated with an inflammatory infiltrate, characterized predominantly by macrophages and CD8+ T cells exhibiting an activated cytotoxic phenotype [31]. Eosinophils can be enriched within affected tissues, but they may not be present when biopsies are obtained after institution of corticosteroid therapy. Elevated serum levels of type 2 cytokines such as interleukin (IL)-5 and other profibrotic molecules (transforming growth factor beta [TGF- β]) have been reported in patients who have active disease [32,33]. IL-5 plays an important role in the chemotaxis, activation, and regulation of eosinophil effector function [34]. Tissue-infiltrating eosinophils can generate important local fibrogenic stimuli by increasing their expression of TGF- β and by releasing toxic cationic proteins upon degranulation. In vitro studies have shown the ability of eosinophils to stimulate matrix production in dermal fibroblasts [35]. An activated phenotype, along with increased collagen expression, has been shown in fascial fibroblasts isolated from EF lesions [36].

Different potential triggers have been considered for EF. An antecedent history of vigorous exercise or trauma is present in about 50% of the cases [27]. A positive serology for *Borrelia burgdorferi* has been reported, and spirochetal organisms have been identified in some EF lesions [37,38]. These findings, however, have not been reproduced consistently [39]. Toxic exposures other than aniline-denaturated rapeseed oil and L-tryptophan have not been proven. The association between EF and other autoimmune manifestations such as immune-mediated cytopenias and localized scleroderma

has been observed. Morphea in particular often is reported in conjunction with EF [40,41]. Commonly, it presents in the generalized form or with discrete areas of deeper fibrosis sparing the superficial skin layers (morphea profunda). EF and morphea can have an asynchronous clinical course. In up to 10% to 15% of patients who have EF, underlying hematological disorders or malignancies have been found [27]. A causal relationship between EF and these potential triggers or associated conditions remains unclear and, to date, unproven.

Clinical features

The classic onset of EF is usually acute with rapid and symmetric spreading of skin changes over the extremities within a short period of time (days to weeks), in particular over forearms and calves. Less frequently, the disease process can be confined exclusively to the legs or the arms, or affect an individual limb. The trunk and the neck also can be involved. The hands and face generally are spared, except for some isolated reports [27]. During the early inflammatory phase, the skin is edematous, with dimpling and a peau d'orange appearance. This is followed by a progressive induration of subcutaneous tissues, which can acquire a marble-like consistency. Tethering of the dermis to the fascial and muscular layers causes skin puckering and venous furrowing (Fig. 2A). These are very typical in EF and particularly visible over the medial aspect of arms and thighs. Importantly, the more superficial layers of the skin are not affected by the fibrotic process, and wrinkling of the epidermis still can be elicited by gentle pinching. Hair loss is common in affected areas.

Deeper involvement and fibrosis of periarticular structures can prompt severe flexion contractures and disturbances secondary to peripheral nerve compression, such as carpal tunnel syndrome. Raynaud's phenomenon can be present, but the nailfold capillary microscopy examination is normal. True joint inflammation has been reported, presenting as a symmetric polyarthritis of the small joints (hands) or as oligo-monoarthritis (knees) [27]. Constitutional symptoms such as profound fatigue and weight loss can be observed in patients who have aggressive disease presentation. EF usually does not manifest with visceral involvement. Extensive trunk fibrosis or neck/laryngeal scarring, however, can be associated with significant breathing or swallowing difficulties.

Peripheral eosinophilia is commonly present in up to 80% of cases but is not a prerequisite for diagnosis. Other relevant laboratory findings include polyclonal hypergammaglobulinemia, increased inflammatory markers (ie, erythrocyte sedimentation rate and C-reactive protein), and, occasionally, elevated muscular enzymes (aldolase and creatine phosphokinase), suggesting the presence of underlying muscular involvement. Antinuclear antibodies are rarely positive, and SSc-specific autoantibodies are usually absent. Presence of cytopenias, isolated or in combination, always warrants

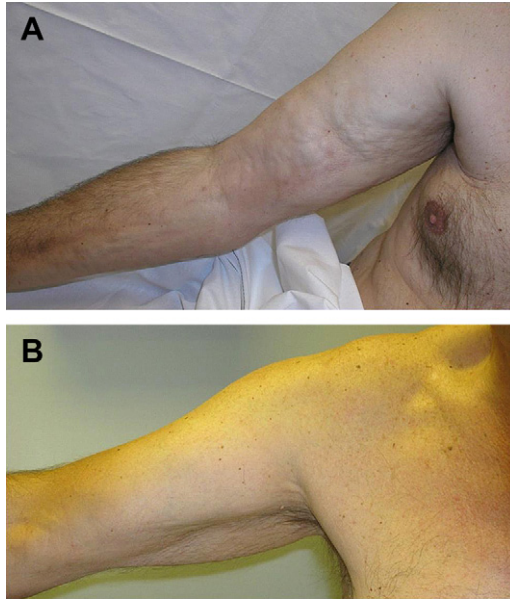


Fig. 2. Eosinophilic fasciitis. (A) Patient presenting bilateral involvement of upper extremities with typical woody induration of the skin and puckering. (B) The same patient after 12 months of corticosteroid treatment.

further investigation, because they may be secondary to underlying hematological disorders, including immune-mediated anemia or thrombocytopenia, pure red cell aplasia, aplastic anemia, myelodysplastic syndromes, and lymphoproliferative processes (T or B cell lymphoma, multiple myeloma) [42–46]. To obtain a definitive diagnosis, an incisional full-thickness biopsy should be pursued. MRI can be very useful to confirm the diagnosis of EF, to monitor the response to therapy or to evaluate patients when disease relapse is suspected [47]. Appropriate MRI image sequences (ie, fluid-sensitive) can show in great detail the presence of fascial thickening and edema, and the involvement of muscular structures.

Compared with SSc, the epidermis in EF is spared by the fibrotic process. Raynaud's phenomenon and visceral involvement are uncommon (see Table 1). Nailfold capillary microscopy is normal. Autoimmune serology is negative. Corticosteroids are rapidly effective.

Treatment and prognosis

There is substantial agreement among published cases or case series that corticosteroids are the first-line treatment for EF and usually effective in more than 70% of patients (Fig. 2B) [27,48]. Other therapies, including nonsteroidal anti-inflammatory drugs, antihistamines (cimetidine), D-penicillamine or antimalarials (hydroxychloroquine) have been reported,

but their efficacy has not been confirmed [27]. Spontaneous resolution also has been observed in some cases.

The ultimate goal in treating EF patients is a complete resolution of the fibrotic manifestations, and this is predicated on an early initiation of the treatment followed by slow tapering. Prednisone (or equivalent corticosteroid) is usually initiated at doses ranging from 0.5 to 1 mg/kg daily. This is maintained until the clinical response is evident, in general within few weeks. Subsequent tapering is slow, particularly with doses below 20 mg daily, and it may take up to 12 to 18 months to achieve a satisfactory or full response. In patients who have aggressive presentation such as extensive body surface involvement, significant weight loss, or when trunk or neck are affected, the authors usually start corticosteroids at the highest doses, often in combination with a second immunosuppressive drug such as methotrexate or mycophenolate mofetil. This strategy allows faster control of the disease and, in the long run, avoidance of excessive cumulative steroid load. A second agent is also useful to achieve further benefit in refractory (unusual) or relapsing cases. In a recent review of 88 published EF cases, clinical variables associated with poor outcome (defined as refractory disease or residual skin fibrosis despite prolonged treatment) were young (pediatric) age of onset, presence of morphea lesions, and trunk involvement [40]. Importantly, the absence of a response should prompt further investigation to rule out presence of an underlying malignancy. Physical therapy plays an important role throughout the disease course to limit the long-term consequences of flexion contractures and disability. Overall, the prognosis of EF is good. Even if prolonged treatment is necessary, most patients usually achieve full disease remission and cure.

Scleromyxedema

Scleromyxedema (papular mucinosis) is a condition of mucinous deposition in the skin associated with a presence of a monoclonal gammopathy characterized by a flesh-colored, papular skin eruption. The exact prevalence of scleromyxedema is unknown, as no formal epidemiologic studies have been performed. It is thought to be quite rare, however, with approximately 150 cases described in the English medical literature. Even this number is difficult to interpret, given that the terminology for this condition has varied with time, and many cases may have been misclassified. For example, early cases of nephrogenic systemic fibrosis may have been misdiagnosed as scleromyxedema before the condition was defined. New terminology proposed by Rongioletti and Rebora [49] in 2001 defined lichen myxedematosus as a broader term under which both scleromyxedema (diffuse, systemic form) and papular mucinosis (focal form) fall. The largest series of scleromyxedema cases to date was published from the Mayo clinic in 1995, where 26 patients evaluated at their institution from 1966 to 1990 were reviewed [50]. This series found that the average age of onset was 55 years, and there

was a roughly equal distribution by gender. In the author's center, where 12 patients have been evaluated, the authors found that the average age of onset is 51 plus or minus 12 years (range 35 to 74 years) and the female-to-male ratio is 3:1. This illness has not been reported in children.

Etiopathogenesis

Histological findings reveal three key features: extensive interstitial mucin deposition throughout the dermis with thickened collagen bundles and wide intercollagenous spaces, an increased number of fibroblast-like cells (fibrocytes), and an enhanced inflammatory infiltrate [51]. The etiology of scleromyxedema is unknown. In almost every reported case, there has been demonstration of a monoclonal protein in the peripheral blood. In one scleromyxedema patient who had absent circulating paraprotein, evidence of a monoclonal protein was found in the affected skin lesions [52]. Not surprisingly, given the striking association with circulating paraproteins, several groups have investigated the possible direct pathogenic role these proteins may play. Ferrarini and colleagues [53] demonstrated stimulation of fibroblast cells by serum from one scleromyxedema patient. Another study found that serum from scleromyxedema patients can stimulate in vitro fibroblast proliferation [54]. These results, however, could not be replicated using purified immunoglobulin from the patient's sera. These conflicting data would perhaps suggest that the measurable paraprotein does not have a direct role in the pathogenesis of scleromyxedema through direct tissue fibroblast stimulation. A study of five patients who underwent peripheral blood stem cell transplant (PBSCT) showed that only two patients had an eradication of their monoclonal protein and that there was no relationship between clinical improvement and monoclonal band disappearance [55]. Additionally, as the authors and others have observed, the level of paraprotein does not decrease even after effective treatment, and there seems to be no dose-dependant relationship between paraprotein quantity and clinical effects. Ferrarini [53] suggested an intrinsic abnormality of the scleromyxedema fibroblasts, because they were exhibiting an increased glycosaminoglycan (GAG) synthesis at baseline compared with controls, but this was not increased with addition of serum. Taken together, these data suggest that in scleromyxedema there may be an intrinsic fibroblast defect or possibly other (unknown) circulating factors that can activate fibroblasts in the pathogenesis of this disease.

Clinical features

The cutaneous findings in scleromyxedema are fairly uniform in appearance and location among different patients. The skin is indurated and papular in quality with a cobblestone feel, and its involvement occurs in a characteristic distribution, with the glabellum, posterior auricular area, and neck being affected most commonly (Fig. 3). Other areas include the



Fig. 3. Scleromyxedema. Patient with classic papular-waxy skin eruption of the face.

back and extremities, and distribution may be similar to scleroderma. One important difference, however, is that the middle portion of the back, commonly affected in scleromyxedema, almost never is involved in scleroderma patients. Sclerodactyly can be present, although papular in quality. In addition to skin findings, patients may have organ involvement that seems to mimic the pattern of scleroderma. Raynaud's phenomenon, esophageal dysmotility, and myopathy have been reported [50]. Less common but potentially life-threatening complications may involve the neurological system in the form of encephalopathy, seizures, coma, and psychosis [56–60]. Additionally, pulmonary hypertension also has been described in patients who have scleromyxedema. The texture of the skin and the histological findings (deep incisional biopsy) remain the most important features distinguishing these two conditions (see Table 1).

Treatment and prognosis

The natural history of this disease has not been defined well, but fatal cases have been reported, most commonly because of neurologic complications [50,59,61]. Various therapies have been employed to treat the symptoms of scleromyxedema with variable success. Historically, melphalan therapy has been the treatment of choice for this condition with multiple reports of benefit, but significant toxicity appears frequent [62–65]. Case reports cite variable improvement with other immunosuppressants including cyclophosphamide and cyclosporine [66–69]. There are multiple cases describing some benefit using thalidomide, although there remains a legitimate concern for the development of disabling peripheral neuropathy

[69–73]. More recent data note benefit of autologous stem cell transplantation in recalcitrant cases [55,74–76].

Multiple groups have reported clinical improvement in scleromyxedema patients following therapy with IVIG [56,61,77–80]. The first case report by Lister and colleagues [77] summarized two patients who were treated with 2 g/kg of IVIG monthly, with responses noted within two to three treatments and maintained by repeated infusions spaced at 10-week intervals. IVIG also has shown benefit in those patients who have complicated neurologic manifestations such as dementia [56]. None of the case reports document any significant long-lasting adverse effects following IVIG therapy. Although long-term follow-up (greater than 3 years) is lacking, these published cases suggest that IVIG is not only an effective treatment for scleromyxedema but safe also. In the authors' center, nine patients have been treated with IVIG, and success has been universal, although the authors also noted that maintenance therapy is necessary.

Scleredema

Scleredema also is associated with deposition of collagen and mucin in the dermis and seems to occur in the setting of three conditions: poorly controlled diabetes, monoclonal gammopathies, and after certain infections, particularly streptococcal pharyngitis. This condition causes scleroderma-like skin changes but in a distribution that is quite different than scleroderma.

Scleredema is a rare condition. Although the exact prevalence is unknown, there are approximately 175 cases in the English medical literature from 1966 to present. The nomenclature is variable, with scleredema adultorum and scleredema of Buschke often being used interchangeably to reflect presence of scleredema of any cause. Scleredema diabeticorum refers to scleredema related to diabetes only. The initial description by Buschke was a postinfectious case, and some authors limit the eponym to this subset. There are also some references subtyping scleredema into three categories according to the three clearly defined disease associations: type 1 in those patients where a preceding febrile illness is identified type 2 including those patients who have an identified circulating paraprotein, and type 3 in patients who have diabetes. There is no clear gender difference, and the disease has been reported in the United States, Europe, Asia, Africa, and Australia. Despite the name adultorum, there are many cases of postinfectious scleredema described in children [81].

It has been estimated that as many as 2.5% to 14% of diabetics have scleredema in some cross-sectional studies, so it is thought that this subset may be under-reported [82–84]. Diabetic patients can be either type 1 or type 2, but commonly tend to be poorly controlled, insulin-requiring and have evidence of diabetic complications such as microangiopathy and retinopathy. In one review of seven cases of diabetes-associated scleredema, the ratio of males to females was 4:3. The mean age at onset was 54 years;

the mean duration of diabetes was 13 years, and there was a high frequency of diabetic complications [85].

Etiopathogenesis

Most literature reports find this disease to be associated with febrile illness, monoclonal gammopathies, or diabetes. Some cases, however, do not fit into one of these three diagnostic categories, and other atypical causal relationships have been considered such as mechanical stress and use of certain medications (infliximab) [86,87]. In patients with type 2 disease, multiple types of monoclonal gammopathies have been described, including multiple myeloma (IgG and IgA), monoclonal gammopathy of undetermined significance, Waldenstrom's macroglobulinemia, and generalized hypergammaglobulinemia [88–90]. Poor diabetic control and presence of microvascular complications (retinopathy, neuropathy) seem to be key risk factors among diabetic patients.

The pathology of scleredema is notable for marked thickening of the upper and lower dermis and mucin deposition between thickened collagen bundles. There are no clear histopathological differences between the different subtypes of scleredema. In diabetes, it is thought that the abnormal metabolic state in the tissues leads to fibroblast activation and increased collagen synthesis. Like in scleromyxedema, the monoclonal proteins found in some patients who have type 2 scleredema do not have a clear pathogenic role. Multiple infectious agents have been associated with type 1 disease, including *Streptococcus*, influenza, varicella, measles, and mumps. Other series only describe preceding febrile illness by history. No one has determined any clear direct relationship between these pathogens and the development of scleredema, but no thorough investigation has been conducted.

Clinical features

Scleredema causes a non-pitting, doughy or woody induration of the skin that typically involves the neck, back, interscapular region, face, and chest (Fig. 4). In one case series from China of 12 patients, 75% had neck involvement; 42% had back involvement, and 17% had shoulder involvement [91]. In this series, 83% of patients were diabetic; none had previous infection, and none had an identified paraprotein. Typically, the extremities, and in particular the distal portion are spared, but some cases of widespread involvement have been reported. In contrast with scleroderma, the mid-back commonly is involved, while the hands and fingers are not (see Table 1). Some cases have demonstrated marked involvement of the face causing ocular muscle palsy, diminished oral aperture, and periorbital edema [92,93]. Systemic involvement has been reported only infrequently, but some case reports highlight involvement of the tongue, pharynx, and upper esophagus [93,94]. Others have reported cardiac dysfunction with myocarditis [95,96].



Fig. 4. Scleredema. Patient with diabetes mellitus type 2 and skin induration of the neck and upper back.

Treatment and prognosis

The natural progression of scleredema depends on the underlying associated condition. Patients with infection-related disease are noted to have a rapid onset of symptoms days to months after the infection, with a course that typically resolves in several months to 2 years. Patients who have type 2 disease tend to have a very insidious onset with gradual progression of symptoms over many years. Also in diabetes-associated scleredema, the onset is typically slow, but some improvement may occur as control of diabetes is established [97].

Because most cases of type 1, infection-associated scleredema resolve spontaneously, there is little information regarding treatment. Some recommend the use of penicillin in cases where recent streptococcal infection is demonstrated. In diabetic patients, there are data suggesting that improvement of glycemic control can impact the course of scleredema and reverse skin changes, but this is not a universal phenomenon [98]. Various immunosuppressants such as corticosteroids and methotrexate have been tried without clear benefit [98,99]. Ultraviolet light therapy, in several forms, has been reported to be beneficial, including UVA-1 treatment, PUVA therapy (bath, cream, oral) and photophoresis [100–105]. Several authors also reported some benefit with various types of radiation therapy [106–108].

Summary

There are many conditions that can mimic the appearance of scleroderma. This article highlighted four scleroderma-like conditions that are often detected in the primary care setting and referred to rheumatologists for further evaluation. Rheumatologists must be able to promptly recognize

these distinct entities to provide valuable prognostic information and treatment options for affected patients.

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