Chapter 9
Systemic Sclerosis Mimics

Gloria A. Salazar, Virginia D. Steen, and Maureen D. Mayes

Abstract Scleroderma-like or pseudo-scleroderma disorders are a wide group of diseases with various etiologies that lead to skin fibrosis therefore mimicking systemic sclerosis. Although they all have skin thickening in common, the distribution, pattern, and character of the involvement as well as systemic manifestations vary between them. The importance of recognizing these mimics resides in their different prognoses and treatment options. A complete clinical history, detailed physical exam as well as laboratory studies and skin biopsy can help differentiate them.

Since the list of scleroderma mimics is long, this chapter will focus on a few key disorders (eosinophilic fasciitis, scleredema, scleromyxedema, nephrogenic systemic fibrosis, diabetic cheiroarthropathy, and lipodermatosclerosis). Other rare conditions, such as metabolic diseases (phenylketonuria, porphyria cutanea tarda), exposure to chemical agents such as bleomycin, vinyl chloride, tryptophan and toxic oil syndrome, and genetic diseases such as progeria, Werner's syndrome, and Stiff Man Syndrome, which can also cause skin sclerosis will not be discussed.

The absence of typical SSc features such as Raynaud's phenomenon, antinuclear antibodies, and nailfold capillary changes should raise the index of suspicion for an alternative diagnosis.

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Introduction

Systemic Sclerosis (SSc) is an autoimmune disease whose most characteristic feature is skin thickening. However, there is a wide range of other conditions that can lead to skin fibrosis and therefore mimic SSc. These disorders also known as scleroderma-like or pseudo-scleroderma are all characterized by sclerosis of the dermis, subcutis, and sometimes the underlying soft tissues and bone. They all have in common chronic skin fibrosis with excessive local accumulation of collagen and other extracellular matrix (ECM) components [1, 2]. Because their management and outcomes are quite different to that of SSc it is important to be aware of these mimics.

Although skin thickening is a common feature, the distribution, pattern, and character of skin involvement varies widely between these disorders and sets them apart from each other. Other clues or helpful facts when dealing with these disorders include history of chemical exposures, presence or absence of Raynaud's phenomenon, other underlying diseases or nailfold capillary abnormalities, and laboratory studies [1, 2]. When the diagnosis is in doubt, a skin biopsy can be a helpful confirmatory tool.

The list of scleroderma-like disorders is long but in this chapter we will discuss some of the most notable including eosinophilic fasciitis (EF), scleredema, scleromyxedema, nephrogenic systemic fibrosis (NSF), diabetic cheiroarthropathy, and lipodermatosclerosis (LDS). Localized scleroderma including linear scleroderma and the different types of morphea can also be confused with systemic disease. This is considered in detail in Chap. 2.

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF) is an uncommon scleroderma-like disease characterized by inflammation and sclerosis of the fascia and the subcutaneous tissue of the limbs typically sparing the hands, feet, and face [2].

Initially, patients with EF typically present with edema and induration in the extremities. The induration is often so pronounced that it is described as having a woody texture and a "peau d' orange" (skin of the orange) puckering (Fig. 9.1a) may also be seen. The groove sign, an indentation caused by retraction of the subcutaneous tissues along the tract of superficial veins is seen with elevation of an involved limb (Fig. 9.1b). This sign is often seen on the volar aspect of the forearm but can be seen on any extremity and helps to distinguish EF from SSc.

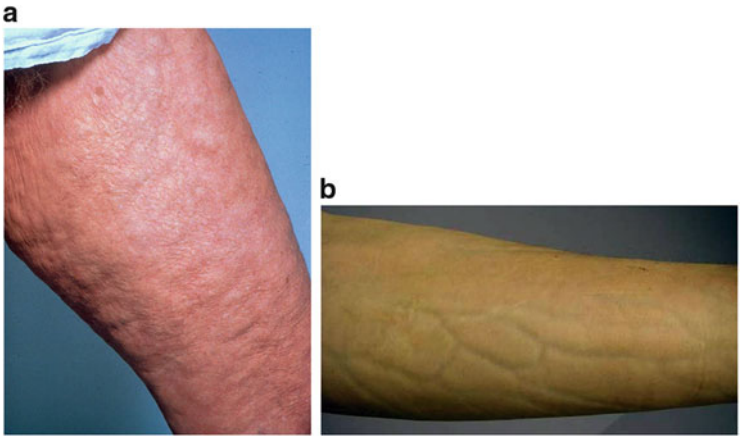

Fig. 9.1 (**a**) Peau d'orange appearance of the thigh showing the characteristic skin puckering of Eosinophilic Fasciitis (**b**) Groove sign of venous furrowing in Eosinophilic Fasciitis in which indentations or inward bowing of the skin are seen along the course of superficial veins [Reprinted from the American College of Rheumatology slide collection © 2013 American College of Rheumatology. Used with permission]

Though patients may have myalgias and muscle atrophy, weakness is not a prominent symptom as it is in inflammatory myositis. Range of motion is often limited by inflammation of the fascia crossing or adjacent to joints particularly in the wrists and ankles. The skin of the fingers remains normal in EF, a clear distinction from SSc. There can be contractures in the fingers which are most evident when the wrist is dorsiflexed, due to tightening of the fascia and tendons in the palm rather than skin thickening of the fingers. These patients will usually have full extension of the fingers when the wrist is palmar-flexed. The diagnosis of EF is aided by laboratory testing, imaging, and histologic examination. Peripheral blood eosinophilia, elevation of inflammatory markers, hypergammaglobulinemia, and an increased aldolase can all be seen on presentation [3]. However, peripheral eosinophilia is often early and transient making the diagnosis challenging. It resolves quickly with the initiation of steroids which are often given as a trial before laboratory work is done. Therefore it is not necessary to make the diagnosis. Inflammatory markers are also not uniformly present and are often transient as well.

In a case series of EF seen at Georgetown University Hospital, aldolase was elevated in nine out of ten patients at presentation; thus, it may be more reliably elevated than the traditionally associated lab values in EF [4], presumably reflecting perimysial inflammation.

Although an en-bloc full thickness biopsy is the diagnostic gold standard, there are considerable limitations in the utility of biopsy for diagnosis. As the dermis and epidermis is typically spared in EF, an en-bloc biopsy from skin to muscle is required. Additionally, the degree of inflammation is variable and eosinophils are also quite variably present in the thickened fascia [5] particularly if corticosteroid treatment has been initiated. Consequently, MRI has become a useful tool for the

diagnosis of EF and in the acute setting may show fascial thickening on T1, T2, and STIR imaging and enhancement of the fascia with gadolinium [6]. Thus, an accurate diagnosis can be made on the basis of clinical presentation, laboratory testing, and MRI findings.

No controlled treatment trials for EF have been reported; however it is generally accepted that moderate to high-dose corticosteroids are the mainstay of treatment and most patients experience a partial to complete response [7]. Normalization of aldolase levels, improvement in range of motion, and normalization of the fascia occur gradually, often requiring a steroid sparing agent. In these patients hydroxychloroquine and methotrexate are considered the agents of choice, but multiple agents have been suggested in case reports or small case series with varied results including phototherapy, cyclosporine, azathioprine, cyclophosphamide, infliximab, and rituximab (for review, see [8]). Of concern is the suggested association of EF with hematologic abnormalities and myelodysplastic syndromes [2] although the frequency of this co-occurrence is unclear.

Scleredema

Scleredema is a fibrotic cutaneous disorder that characteristically presents with symmetrical induration of the posterior and lateral aspects of the neck, upper back, shoulder girdle, and upper extremities (Fig. 9.2a) and mobility of the underlying joints is reduced [1, 9]. The face may also be involved (Fig. 9.2b) leading to reduced oral aperture and difficulty chewing and swallowing. As opposed to SSc, the fingers are typically spared therefore sclerodactyly is absent and Raynaud's phenomenon is not seen.

Scleredema has three subtypes: type 1 which is an acute and rapidly evolving form also known as scleredema of Buschke; type 2 which is associated with paraproteinemias, and type 3 also known as scleredema diabeticorum which is associated with diabetes [9]. Type 1 usually involves pediatric patients (although it has also been described in adults as scleredema adultorum of Buschke) and is often preceded by an acute febrile illness including streptococcal infection, influenza, scarlet fever, measles, and mumps. Type 2 has no preceding febrile or underlying illness but tends to follow a slowly progressive course with an increased risk of developing paraproteinemia including multiple myeloma. Type 3 occurs in diabetic patients with an insidious onset and is most commonly seen in younger patients who are insulin-dependent and have long-standing disease (mean 13 years). It has been reported that 2.4–14 % of diabetics may develop scleredema [10].

The skin of affected patients is described as non-pitting, hard, edematous looking, doughy or woody as shown in Fig. 9.2a, b. Pathologically, scleredema shows a thickened dermis with swollen collagen fibers separated by clear spaces that are filled with an amorphous material identified as hyaluronic acid, and show positive staining with toluidine blue or colloidal iron [9].

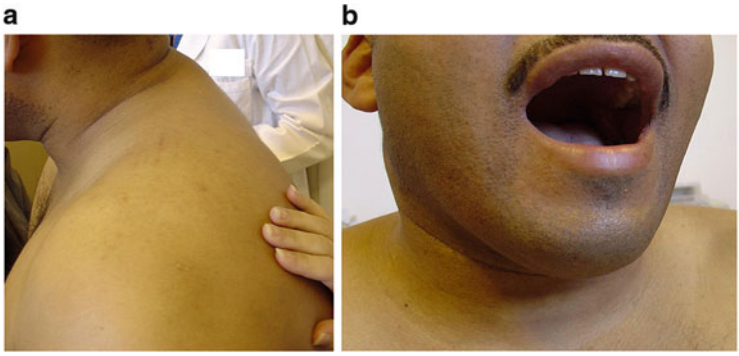

Fig. 9.2 (**a**) Scleredema patient showing classic upper back involvement (**b**) Scleredema facial involvement causing inability to open the mouth fully in this patient

Monoclonal gammopathy may be seen in adults with scleredema (seen in about 25 % of the patients) usually IgG kappa type (as opposed to scleromyxedema which usually has IgG lambda) and may be associated with or precede frank multiple myeloma.

Management for type 2 scleredema includes optimal control of diabetes. Multiple other modalities have been proposed for types 1 and 3 with variously reported therapeutic benefit including phototherapy, corticosteroids, immunosuppressant agents, or intravenous immunoglobulin (IVIg) [9].

Scleromyxedema

Scleromyxedema, also known as papular mucinosis, is characterized by the presence of multiple papules and cutaneous mucin deposition that results in skin induration and enlargement of body folds (Figs. 9.3 and 9.4) [11].

The distribution of affected skin in scleromyxedema includes the face, neck, distal forearms, and dorsum of hands (sparing the palms) and occasionally affects the fingers leading to sclerodactyly (Fig. 9.5). When the lesions are diffuse, scleromyxedema can clinically mimic scleredema or SSc. The widespread mucin deposition in the forehead and glabella causes the appearance of the so-called leonine facies or mask-like facies due to thickened and hardened skin folds.

Histologically the dermis is filled with an amorphous material that pushes apart the collagen fibers. The mucinous material is best identified using colloidal iron, toluidine blue, or Alcian blue stains and increased numbers of fibroblasts are typically seen [2].

Neurologic abnormalities such as severe acute central nervous system syndrome and encephalopathy have been reported in patients with scleromyxedema [12]. The presence of inflammatory myopathy, esophageal dysmotility, and even Raynaud's phenomenon in some patients makes scleromyxedema a definite SSc mimicker

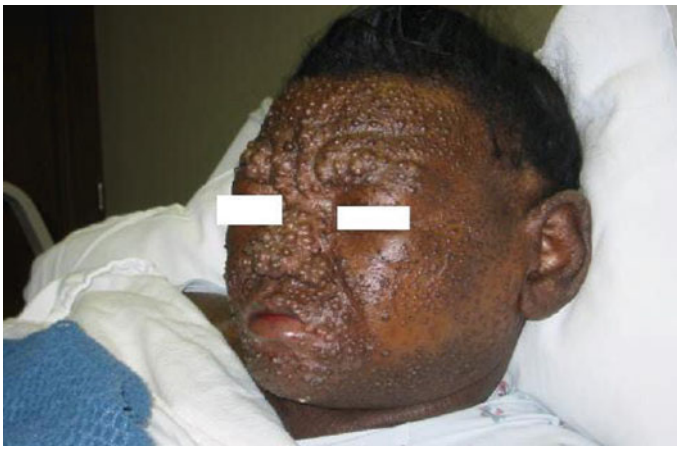

Fig. 9.3 Patient with scleromyxedema with typical papules and thickened skin folds most notably of the forehead. She had an IgG lambda paraprotein

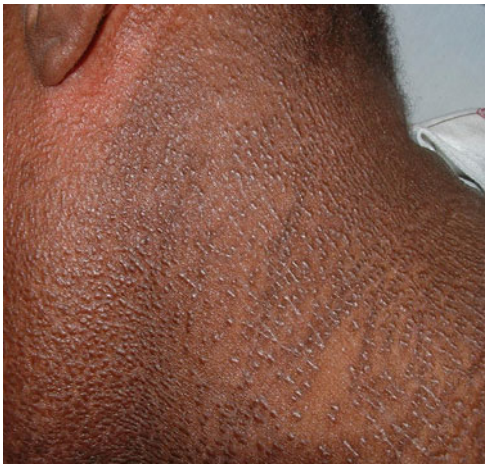

Fig. 9.4 Close up of the neck of the patient in Fig. 9.3 showing numerous discrete papules

[2, 11] However, the papular appearance especially of the face is distinctly different from SSc.

Monoclonal gammopathy frequently an IgG lambda type is commonly detected in the serum and may be associated with multiple myeloma [1, 2].

Scleromyxedema is not self-resolving and tends to be resistant to treatment. Extracorporeal photophoresis, and in some patients with monoclonal gammopathies, melphalan, and prednisone have been used with some success. Reported treatment protocols include IVIG [13], retinoids, PUVA, plasmapheresis,

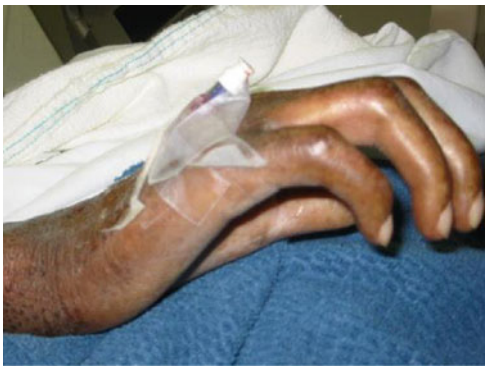

Fig. 9.5 The hand of the patient in Figs. 9.3 and 9.4 above with very SSc-like skin thickening and flexion contractures of the fingers. However, the presence of mucinous papules on the dorsum of the hands and forearms is distinct from the skin changes of true SSc

dermabrasion, total body electron beam irradiation, extracorporeal photopheresis, and other immunosuppressive agents such as cyclophosphamide, cyclosporine, or methotrexate (for review, see [11]).

Nephrogenic Systemic Fibrosis

Nephrogenic fibrosing dermopathy or NSF is a rapidly progressive fibrotic disorder occurring in patients with renal compromise, usually end-stage renal disease, after exposure to gadolinium-containing contrast agents [14, 15].

NSF has been reported in patients with renal failure of any etiology and in various renal replacement regimens including hemodialysis, peritoneal dialysis, or post renal transplantation and happens in close association to gadolinium exposure (ranging from 2 weeks to 18 months). The skin becomes hard, "woody" and thick symmetrically with erythematous or hyperpigmented plaques that coalesce (Figs. 9.6 and 9.7). The classic distribution of NSF includes the limbs (usually distal up to knees and elbows) and the trunk sparing the face. It affects not only the skin but also the subcutaneous tissue, fascia, striated muscles and may affect internal organs such as the heart and lung leading to internal organ damage and progressive, severe contractures of extremities.

There is no proven effective therapy. Several modalities have been reported to be effective including renal transplantation, plasma exchange, and IVIg (for review, see [16]). Recently imatinib has been reported to improve NSF [17]. Controlled clinical trials are lacking and are unlikely to be conducted. After implementation of guidelines restricting the use of gadolinium-based contrast agents in patients with impaired renal function, there has been a sharp reduction in new cases [16].

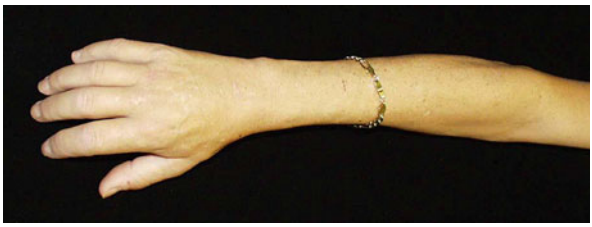

Fig. 9.6 Arm of a patient with nephrogenic systemic fibrosis showing skin changes from the elbow to the level of the metacarpal phalangeal joints (MCPs) but sparing the fingers [Reprinted from Kay J. What Causes Nephrogenic Systemic Fibrosis?: Imaging studies and kidney problems may trigger this gadolinium-induced fibrosing syndrome. The Rheumatologist. September 2007. With permission from John Wiley & Sons, Inc.]

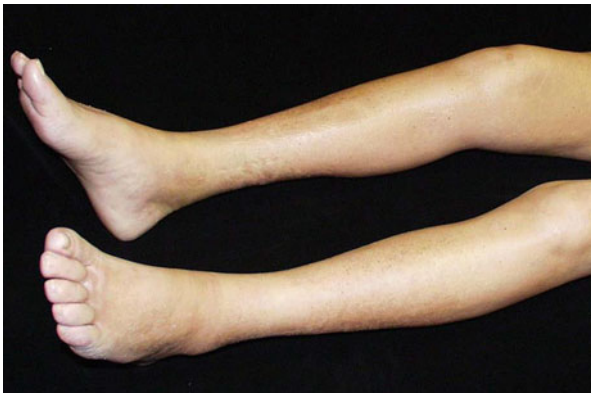

Fig. 9.7 Legs of a patient with Nephrogenic Systemic Fibrosis showing thickened and indurated skin of the legs with flexion contractures of the knees [Reprinted from Kay J. What Causes Nephrogenic Systemic Fibrosis?: Imaging studies and kidney problems may trigger this gadolinium-induced fibrosing syndrome. The Rheumatologist. September 2007. With permission from John Wiley & Sons, Inc.]

Diabetic Cheiroarthropathy

Diabetic cheiroarthropathy, also known as limited joint mobility syndrome, causes symmetric, bilateral thickening and induration of the skin of the fingers and hands with subsequent contractures of finger joints causing what is known as the "prayer" sign (Fig. 9.8) in which the palmar surfaces of the hands cannot be completely apposed [17]. Skin thickening can extend to the arms resulting in flexion contractures at the elbows. It is strongly associated with the duration and severity of diabetes and is most commonly seen in type 1 diabetes but can also be seen with long-standing type II diabetes and, as the number of diabetic patients increases in the general population, this condition can be expected to increase.

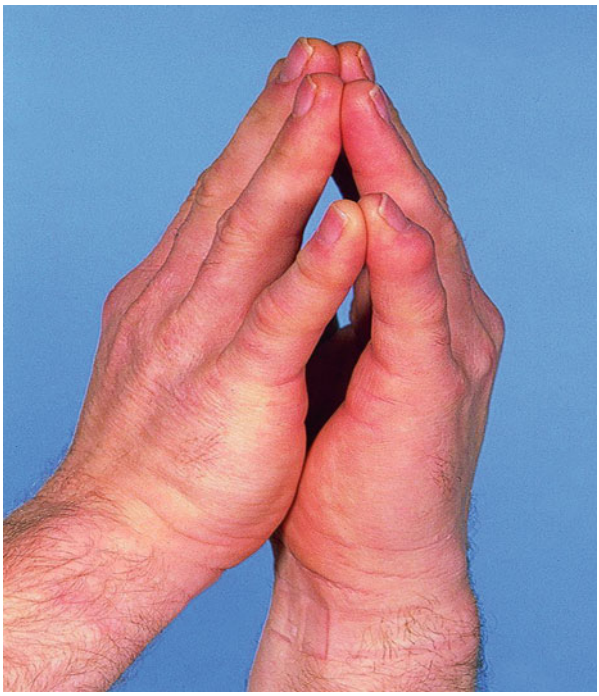

Fig. 9.8 "Prayer sign" of patient with diabetic cheiroarthropathy with inability to fully appose the fingers. The lack of Raynaud's phenomenon, normal nailfold capillaries and negative ANA, in the presence of diabetes, help to distinguish this from SSc

Histology shows dermal fibrosis characterized by thickened collagen bundles believed to be due to increased glycosylation of collagen rather than the overproduction of collagen.

As with other SSc mimics, the lack of Raynaud's phenomenon, normal nailfold capillaries, and negative ANA, in the setting of diabetes, help to distinguish this from true SSc. Treatment consists of "tight" control of the diabetes.

Lipodermatosclerosis

LDS or sclerosing panniculitis is characterized by induration and hyperpigmentation of the lower legs (Fig. 9.9) and is associated with chronic venous insufficiency [18]. It has been described as having an "hourglass" or "inverted champagne bottle" appearance (Fig. 9.10). The major complication is the development of chronic and painful skin ulcers that are slow to heal (Fig. 9.11). Although usually chronic, LDS can occur acutely as painful, warm, erythematous, indurated areas of the lower third of the leg and can be mistaken for cellulitis but is unresponsive to antibiotic therapy.

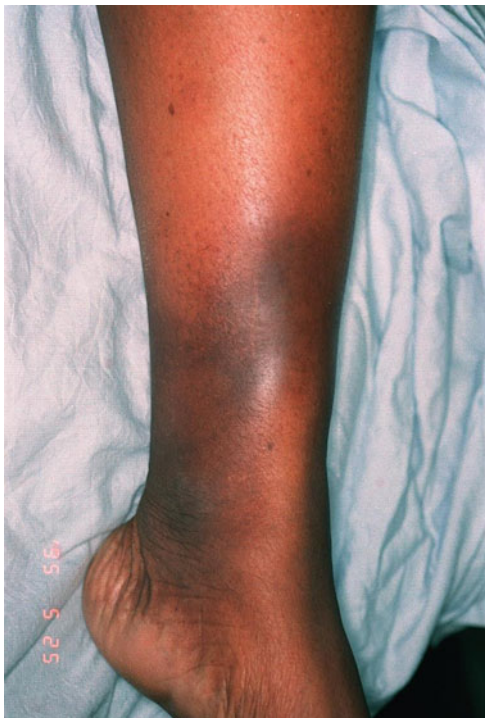

Fig. 9.9 Early changes of lipodermatosclerosis with hyperpigmentation and skin thickening

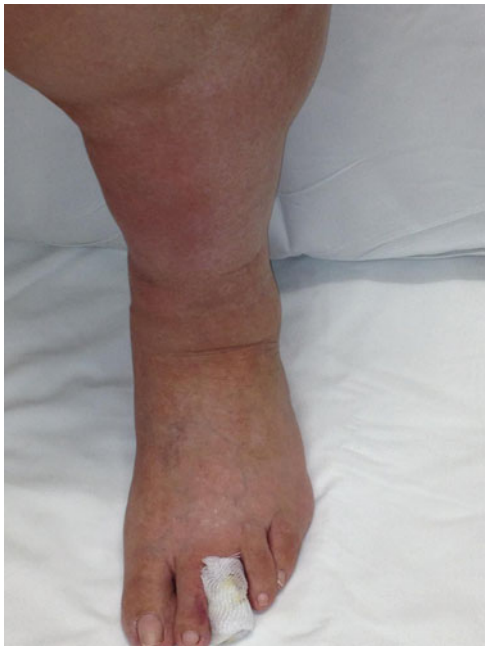

Fig. 9.10 Later changes of lipodermatosclerosis in another patient showing the "hourglass" appearance with thickened skin

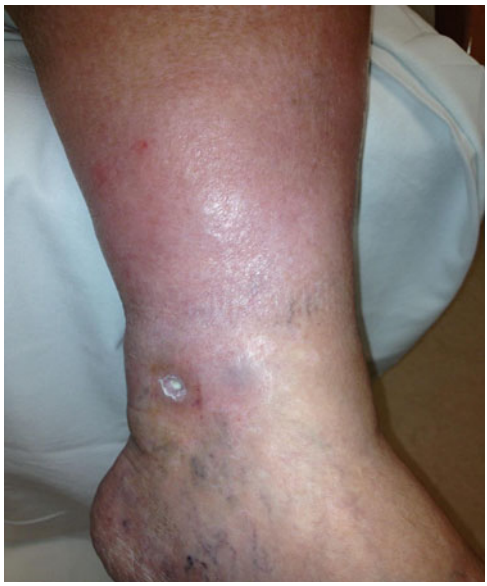

Fig. 9.11 Ulcer near the medial malleolus of the patient in Fig. 9.10

Diagnosis is made primarily on clinical grounds since biopsies in this condition are problematic due to concerns about poor wound healing. When a biopsy is done, the histopathology typically shows a panniculitis [18].

As with most of these rare pseudo-scleroderma conditions, there are no controlled clinical trials to guide LDS treatment, but the mainstay of therapy consists of compression stockings and, if ulcers are present, good wound care. Fibrinolytic agents, especially in the acute stage may be helpful. Pentoxyfylline has also been suggested as adjunctive therapy with or without hydroxychloroquine [19].

Conclusion

Table 9.1 highlights some of the most distinguishing features of the various SSc mimics in terms of the distribution, histology, skin appearance, absence of Raynaud's phenomenon, musculoskeletal complications, systemic symptoms, clinical associations, and laboratory findings.

In conclusion, pseudo-scleroderma disorders include a wide range of diseases that are capable of producing skin fibrosis and that have varied etiologies. They can be distinguished from each other by the pattern, character, and distribution of skin involvement and recognition of associated disease. In the appropriate clinical setting, diagnosis is confirmed by laboratory and imaging studies and, in some cases, skin biopsy. As always, it is important to get the correct diagnosis as prognosis and treatment varies widely.

Table 9.1 Summary of key distinguishing features of SSc mimics

SSc mimics	Eosinophilic fasciitis	Scleredema	Scleromyxedema	Nephrogenic systemic fibrosis	Diabetic cheiropathy	Lipodermatosclerosis
Distribution	Extremities, symmetric *spares fingers, feet, face*	Neck, back, shoulders face, *spares fingers*	Face, neck, back, forearms, hands	Trunk, *symmetric distal limbs*, spares face	Hands, upper extremity	Lower legs
Histology	Dermal and hypodermal *thickened fascia* eosinophilc infiltration in dermal/subcutaneous junction	Dermal, *swollen collagen fibers, clear spaces*, mild mucin, no increase in fibroblasts or inflammation	Dermal, *excessive mucin* deposition	All layers affected (*can include muscle*) thick collagen bundles separated by mucin, numerous "spindle-shaped" *fibroblasts*	Dermal fibrosis with increased collagen	Panniculitis
Skin findings	*Woody induration*, peau d'orange, groove sign	*Indurated, doughy, non-pitting* edematous looking	*Papular eruption, waxy, folds*, leonine, and masked facies	Hyperpigmented coalescent plaques *woody*	Thickened waxy skin, painless, prayer sign	Hyperpigmented, thickened, hour glass appearance
Raynaud's phenomenon	Usually No	No	*Rare*	No	No	No
Musculoskeletal	*Joint contractures*	Reduction of ROM, joint effusions (rare)	Arthralgias, arthritis, myositis	*Joint contractures*, muscle and joint fibrosis	*Joint contractures Reduction of ROM*	*Painful*
Systemic symptoms	Rare if any	Hepatosplenomegaly, dysphagia, ophthalmoplegia, CMP, infiltrations	Esophageal dysmotility. PH, neurological (encephalopathy, seizures, coma, psychosis)	*Heart and lung fibrosis*	*None*	*None*
Clinical associations	Hematologic and solid malignancies, myelodysplasia, immune-mediated cytopenias	Type 1: strep, scarlet fever, influenza, measles, mumps Type 2: *monoclonal gammopathy* (IgG kappa) Type 3: *DM*	*Monoclonal gammopathy* (IgG lambda most common)	*ESRD*, association with *gadolinium* use	*Poorly controlled, long-standing diabetes*	*Venous insufficiency, stasis ulcers*
Laboratory	*Eosinophila*, hypergammaglobulinemia	Type 2: monoclonal gammopathy Type 3: hyperglycemia Hypothyroidism	IgG lambda paraproteinemia	None	Hyperglycemia	None

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