Chapter 11
Scleroderma Mimics

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Keywords Eosinophilia-myalgia syndrome • Fibrosis • Morphea • Nephrogenic fibrosing dermopathy • Raynaud • Scleredema • Scleromyxedema

Scleroderma is an uncommon condition, but has features that are commonly encountered in a general population such as Raynaud's phenomenon and gastroesophageal reflux. Therefore having an appropriate level of suspicion for the diagnosis will help facilitate getting them to the appropriate specialist. However, there are other patients who present with features considered to be typical of scleroderma, such as Raynaud's and skin thickening, who may have a syndrome mimicking scleroderma. So familiarity with these mimickers is critical for rheumatologists of other physicians who evaluate patients with scleroderma. Raynaud's phenomenon and digital ischemia can be associated with multiple different etiologies, rheumatic and non-rheumatic and should be considered even in scleroderma patients with atypical findings (i.e., isolated toe ischemia). Skin thickening may have differential of conditions ranging from minor skin irritations (i.e., lichenification from scratching) to a number of systemic diseases that require expertise evaluation (scleroderma, scleromyxedema). This chapter will focus on the differential diagnosis of these two common presentations, Raynaud's phenomenon and skin thickening.

Differential Diagnosis of Raynaud's Phenomenon

When a patient presents with Raynaud's phenomenon or ischemic digital lesions, one needs to consider the broad differential of potential etiologies that includes other rheumatic diseases, structural vessel abnormalities, embolic phenomena, or circulating factors that may be cold precipitating.

Approximately 4–15% of the general population have symptoms characteristic of Raynaud's phenomenon [1–4]. In the majority of cases, Raynaud's phenomenon is not associated with either structural vascular changes or ischemic tissue damage (primary Raynaud's phenomenon). Primary Raynaud's typically begins in the teenage years and is more common in women (female:male ratio approximately 4:1). In primary Raynaud's phenomenon, the patients are otherwise healthy, the episodes are symmetric in the fingers and/or toes, and they do not lead to tissue damage (digital pits, ulceration, or gangrene). Examination of these patients is unremarkable (including nailfold capillary examination), and laboratory data, including antinuclear antibody and ESR, should be normal. The goal for the evaluating physician is to determine whether the presence of Raynaud's phenomenon is an uncomplicated primary process or the first symptom of a secondary illness such a connective tissue disease or related to other causes such as medications or structural vessel disease (Table 11.1). There are several key points in the history and physical examination that should help clarify things. Patients with primary Raynaud's should have symmetric attacks that occur without any evidence of tissue damage such as digital pitting, ulceration, or gangrene. In addition, they should have structurally normal blood vessels as assessed by nailfold capillary microscopy. Large prospective studies have demonstrated that abnormal nailfold capillaries or scleroderma-specific autoantibodies are associated with a significant risk of future development of definite scleroderma and may be appropriately classified as

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Table 11.1 Differential diagnosis of Raynaud's phenomenon

Small artery disease	Systemic lupus erythematosus
	Dermatomyositis
	Antiphospholipid antibody syndrome
	Small vessel vasculitis
	Cryoglobulinemia
	Cryofibrinogenemia
	Cold agglutinin disease
	Polycythemia
	Thromboangiitis obliterans
Structural vasculopathy	Thoracic outlet syndrome
	Carpal tunnel syndrome
	Atherosclerosis
Abnormal vasomotion	Primary Raynaud's phenomenon
	Acrocyanosis
	Pheochromocytoma
Medications/toxins	Sympathomimetics
	Polyvinyl chloride
	Nicotine
	Cocaine

early scleroderma when both are present [5]. Alternatively, those patients with Raynaud's alone and normal nailfold capillaries and negative serologies (including ANA) will only rarely progress to definite scleroderma [5]. Raynaud's phenomenon also frequently occurs in other connective tissue diseases, particularly systemic lupus erythematosus (20%, including infrequent cases of digital gangrene) [6], dermatomyositis (as high as 65% in some subsets) [7], and mixed connective tissue disease (85%, often with scleroderma-like nailfold capillary patterns) so a careful review of associated symptoms and appropriate serologic evaluation is warranted for patients exhibiting features of these diseases.

Other potential causes of Raynaud's phenomenon include mechanical obstruction (thoracic outlet syndrome), neurovascular (carpal tunnel syndrome), and circulating factors which are either cold precipitating (cold agglutinins) or circulating proteins that may cause small vessel occlusion (antiphospholipid antibodies, paraproteinemias). Some medications as well may cause Raynaud-like phenomenon, particularly sympathomimetics by inducing vasospasm and certain chemotherapeutic agents or toxins which may induce direct vascular injury (bleomycin, polyvinyl chloride, nicotine) [8, 9]. Other forms of vascular damage may also lead to clinical syndromes including digital ischemia that may mimic Raynaud's phenomenon (cutaneous polyarteritis nodosa, thromboangiitis obliterans, cryoglobulinemic vasculitis).

Differential Diagnosis of Skin Thickening

Scleroderma-like disorders often show substantial clinical overlap with scleroderma, but the diagnostic evaluation, risk for internal organ complications, and treatment options are often quite different. Misdiagnosis or a delay in diagnosis is common and can impede access to potentially effective therapy or avoid potentially toxic therapies that are not needed. Several key clinical features early in presentation help distinguish these diseases and can prompt expedient screening for internal organ complications and facilitate treatment and appropriate referral to a specialty center.

Several diseases can present with thickening of the skin and mimic diffuse scleroderma [5]. Such diseases include scleromyxedema, nephrogenic fibrosing dermopathy (NFD), eosinophilic fasciitis (EF), scleredema, toxic exposures (eosinophilia-myalgia syndrome and toxic oil syndrome), and pansclerotic morphea. These syndromes can be differentiated from scleroderma by the pattern of distribution of skin changes, texture and quality of the skin, and the presence and type of associated systemic manifestations, including Raynaud's phenomenon (Table 11.2). These disorders have very diverse etiologies and often an unclear pathogenic mechanism. Distinct clinical characteristics, skin histology, and systemic and laboratory associations distinguish these conditions from scleroderma and from each other. A prompt diagnosis is important to spare the patients from ineffective treatments and unnecessary diagnostic evaluations and allow for accurate determination of prognosis.

There is a long list of disorders which may mimic scleroderma by having cutaneous fibrosis and includes other immune-mediated diseases (eosinophilic fasciitis, graft-vs-host disease), deposition disorders (scleromyxedema, scleredema, nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy, systemic amyloidosis), toxic exposures including occupational

Table 11.2 Differentiating features of scleroderma-like disorders and scleroderma

Disorder	Distribution of tight skin	Quality of skin	Systemic features/associated conditions	Laboratory abnormalities	Raynaud's phenomenon/nail-fold capillaries
Eosinophilia-myalgia syndrome	Upper and lower extremities; sparing hands and feet	Woody induration deeper than superficial dermis	Severe myalgias, muscle cramping, myoclonus, polyneuropathy	Peripheral eosinophilia	None
Eosinophilic fasciitis	Extremities and trunk; hands and feet spared	Woody induration deeper than superficial dermis	Can overlap with plaque morphea, hematologic conditions, preceding intense exercise or trauma	Peripheral eosinophilia	Uncommon/normal
Nephrogenic fibrosing dermopathy	Extremities and trunk; face spared	Nodular, indurated plaques with brawny hyperpigmentation	Marked flexion contractures, renal failure and/or insufficiency; exposure to gadolinium	Renal failure/insufficiency (may be transient)	Rare/normal
Pansclerotic morphea	Extremities, face, feet; hands spared	Thick induration similar to that of diffuse scleroderma	Contractures; no systemic features of scleroderma	None	Uncommon/normal
Scleredema	Neck, back, proximal arms, face	Doughy induration	Discomfort in areas of involvement Poorly controlled diabetes Recent streptococcal infection Monoclonal gammopathy	Hyperglycemia MGUS	None
Scleroderma	Hands and face common; diffuse subset involves proximal extremities and trunk; mid-back spared	Thick, smooth, shiny induration	Gastroesophageal reflux, dysphagia, interstitial lung disease, pulmonary hypertension	Positive antinuclear antibody, scleroderma specific autoantibodies	Universal/common
Scleromyxedema	Scleroderma distribution with prominent findings around glabella, ears and posterior neck	Cobblestone induration with 2–3-mm waxy papules	Dysphagia; musculoskeletal pain, neurologic involvement (seizures, coma)	Monoclonal gammopathy	Uncommon/normal
Toxic oil syndrome	Extremities with sparing of hands and feet	Urticaria-like progressing to doughy edema to scleroderma-like fibrosis	Pulmonary infiltrates, pleural effusions, myalgias, severe pruritis, fever, peripheral neuropathy	Peripheral eosinophilia, elevated triglycerides, hypercholesterolemia, thrombocytopenia	None

and iatrogenic (aniline-denatured rapeseed oil, L-tryptophan, polyvinyl chloride, bleomycin, carbidopa), and genetic syndromes (progeroid disorders, stiff skin syndrome). A carefully performed clinical history and physical examination may distinguish these conditions from scleroderma 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 some cases, a full-thickness biopsy is helpful to confirm the clinical suspicion. Effective therapies are available for some of these conditions, whereas others are more refractory. For this reason, a prompt diagnosis is important to guide treatment decisions wisely. We will discuss some of the conditions most often confused with scleroderma either by the nature of the skin involvement or the presence of systemic features which may also mimic scleroderma. We will not include some other conditions that resemble scleroderma, but where the diagnosis is clear based on other clinical features, such as graft-versus-host disease (in those post transplant) or genetic conditions (occurring in the very young with other complications).

Eosinophilia-Myalgia Syndrome and Toxic Oil Syndrome

Some scleroderma-like diseases are mostly of historical interest (i.e., toxic oil syndrome, eosinophilia-myalgia syndrome) but provide a paradigm from which to understand toxin-induced fibrosing syndromes, which are likely to happen again at some point in the future. Some toxins produce a disease that is indistinguishable from idiopathic systemic sclerosis. The most notable example of this is the exposure to aerosolized silica dust, most common in coal and gold miners [10]. However, other clusters of a scleroderma-like diseases occurred in outbreaks that were linked to a specific toxic exposure. The two classic examples of this type of event are the epidemic of eosinophilia-myalgia syndrome associated with contaminated L-tryptophan supplements and toxic oil syndrome from tainted rapeseed oil in Spain in 1981. Eosinophilia-myalgia syndrome (EMS) was identified in 1989 and definitively linked to the exposure to L-tryptophan in 1990. The source was noted be a single impurity by a single manufacturer [11]. The syndrome consists of peripheral eosinophilia with prominent myalgias with induration of the upper and lower extremities. The distribution of skin involvement is distinct from scleroderma in that it spares the hands and feet typically. The induration of skin is deeper with a "woody" quality, more similar to eosinophilic fasciitis (see description below), and characteristically involves muscles and peripheral nerves and may have life-threatening complications including cardiac involvement [12]. Muscular involvement is distinct in that it consists of prominent myalgia with muscle cramping and myoclonus. Peripheral nerve involvement is also common including an axonal sensorimotor polyneuropathy.

Toxic oil syndrome (TOS) was another acute epidemic which occurred in Spain in 1981 related to an adulterated rapeseed oil which had been denatured with aniline. The acute syndrome was manifested by interstitial pulmonary infiltrates and pleural effusions, myalgias, and peripheral eosinophilia. Associated features included skin itching and rash, peripheral sensory neuropathy, dysphagia, and pulmonary hypertension. Rarer manifestations included thrombocytopenia, vascular thromboembolism, and hepatic cholestasis. Later manifestations included a scleroderma-like skin disease progression of interstitial fibrosis and pulmonary hypertension, and the pulmonary manifestations led to the increase in mortality in these patients (standardized mortality ratio of about 500 in 1981 and 100 in 1982) [12, 13]. When the skin was involved, it seemed to have a clear progression from a more toxic-allergic presentation with distinct urticarial lesions to edema to fibrosis [14].

While we are unlikely to see new patients with these syndromes, there will likely be other similar outbreaks in the future related to yet to be defined toxins, so having an appropriate level of awareness of these prior experiences is important.

Nephrogenic Systemic Fibrosis

A more recent exposure-associated scleroderma mimicker is nephrogenic fibrosing dermopathy (NFD) or nephrogenic systemic fibrosis (NSF) which was first reported in 2000 [15]. A new entity was initially described among patients receiving renal dialysis consisting of a rapid development of fibrotic skin induration with associated nodular plaques, hyperpigmentation of the skin, and marked flexion contractures of the extremities. Unlike TOS and EMS, nephrogenic fibrosing dermopathy has been reported in a wide geographic area with no gender or age predilection and not caused by a single source exposure. In 2006–2007, it became clear that the condition was related to exposure to gadolinium-based contrast agents (GBCA) in patients with varying types and degrees of renal failure. In the United States, a NSF registry has been established with more than 375 collected to date (http://www.icnsfr.org). However, it is likely that the prevalence is much higher, with many cases not included in the registry, but new cases are uncommon given the widespread development of guidelines for the use of GBCA in patients with renal insufficiency (http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm).

The skin lesions of NSF usually develop subacutely over weeks typically only weeks after gadolinium exposure and subsequently assume a chronic, progressive course with rapid development of joint contractures. The distribution is often symmetrical, commonly involving the extremities up to the knees and elbows. The hands and the trunk may be involved, but typically spares the face. The texture of the skin is different than scleroderma in that the skin has a lumpy-nodular thickening with a tendency to form indurated irregular plaques with reticular discoloration varying from violaceous to brawny hyperpigmentation. A deeper subcutaneous fibrotic process can lead to severe flexion contractures (particularly hands, wrists, ankles, and knees) which may cause significant disability. 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. In addition to the differing clinical features, NSF may be distinguished from scleroderma by the absence of Raynaud's and scleroderma-specific antibodies, and nailfold capillary microscopy examination is normal.

Scleredema

Scleredema is a condition 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. It has been estimated that as many as 2.5–14% of diabetics have scleredema in some cross-sectional studies, so it is thought that this subset may be underreported [16]. Diabetic patients with scleredema are commonly poorly controlled, insulin requiring and have evidence of diabetic complications such as microangiopathy and retinopathy. The pathology of scleredema is notable for marked thickening of the upper and lower dermis and mucin deposition between thickened collagen bundles. Scleredema causes a non-pitting, doughy induration of the skin that typically involves the neck, back, inter-scapular region, face, and chest (Fig. 11.1). Typically the distal extremities are spared, and in contrast with scleroderma, the mid-back is commonly involved. There may be prominent involvement of the face causing ocular muscle palsy, diminished oral aperture, and periorbital edema. Systemic involvement has been only infrequently reported, but some case

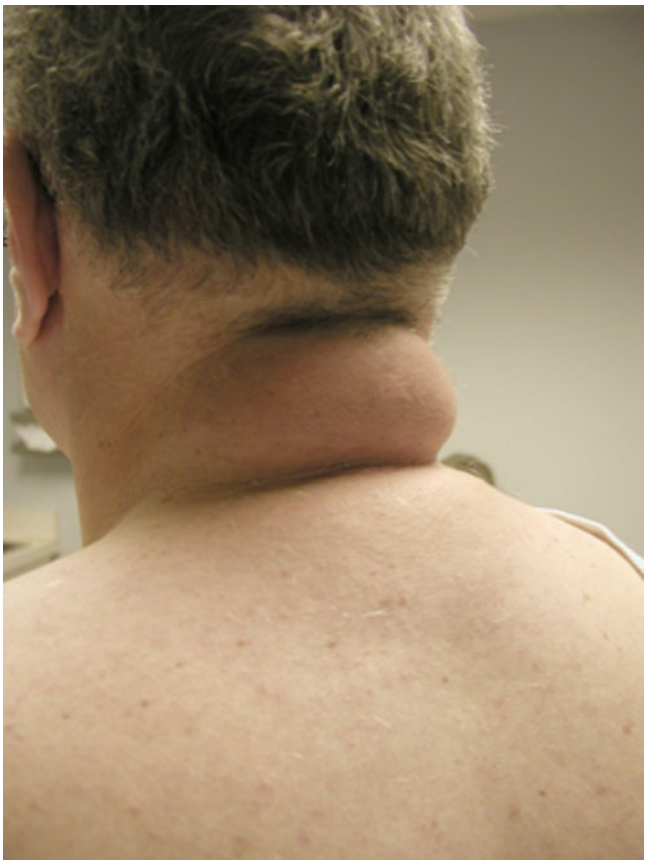

Fig. 11.1 Posterior neck in a patient with monoclonal gammopathy-associated scleredema

reports highlight involvement of the tongue, pharynx, and upper esophagus leading to dysphagia as a potentially reported systemic symptom [17]. 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 with diabetic and monoclonal gammopathy-associated scleredema have a very insidious onset with gradual progression of symptoms over many years.

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 average age of onset is around 50–55 years with a roughly equal gender distribution, and this illness has not been reported in children. Diagnosis requires the presence of a characteristic skin involvement, diagnostic biopsy (extensive interstitial mucin, thickened collagen bundles, and increased number of spindled fibroblast-like cells), and the presence of a monoclonal protein (typically IgG either kappa or lambda). The skin in scleromyxedema is indurated and papular in quality with a cobblestone feel, and its involvement occurs in a characteristic distribution with the glabella, posterior auricular area and neck being most commonly affected (Fig. 11.2). Other areas include the back and extremities and may be similar in distribution to scleroderma. Similar to scleredema, the midportion of the back is commonly affected in scleromyxedema, and is almost never involved in scleroderma patients. Sclerodactyly can be present, and appear identical to scleroderma, although is 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 [18, 19]. Less common but potentially life-threatening complications may involve the neurological system in the form of encephalopathy, seizures, coma, and psychosis [20, 21]. The natural history of this disease has not been well defined, but fatal cases have been reported, most commonly due to neurologic complications [22].

Eosinophilic Fasciitis

Eosinophilic fasciitis was first described in 1974 by Schulman who reported two patients with scleroderma-like skin changes, painful induration of subcutaneous tissues with marked peripheral eosinophilia, and histological evidence of diffuse fasciitis [23]. EF has a slight male predominance and has been reported more in Caucasians than other groups with reported cases occurring across the age spectrum. Peripheral blood and tissue eosinophilia, hypergammaglobulinemia, and elevated inflammatory markers are dominant features early in the disease course, and overall spontaneous remission is common [24]. 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 is usually spared. Eosinophils can be enriched

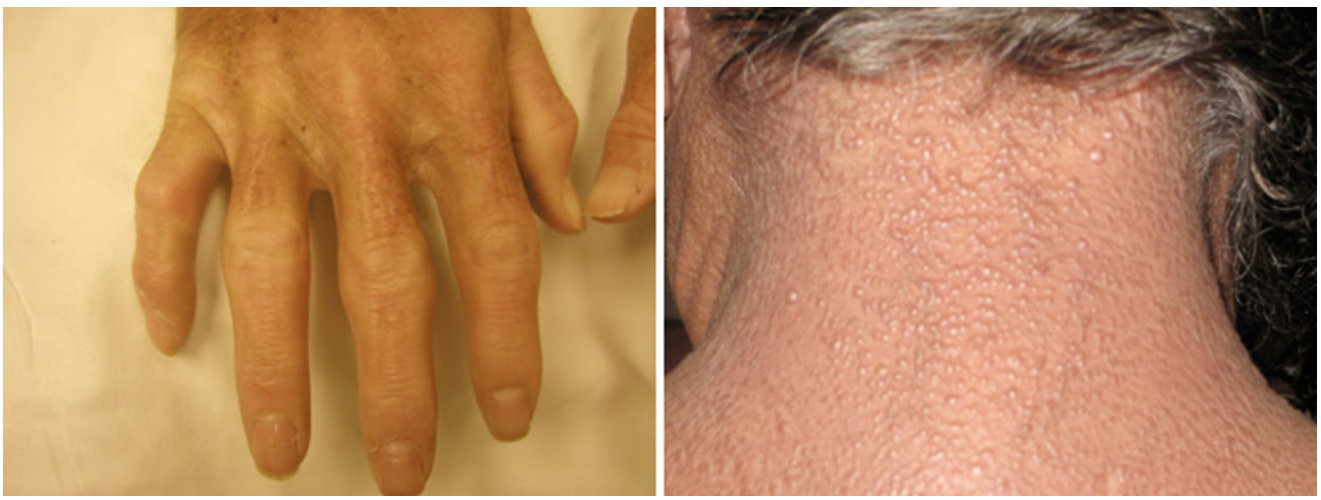

Fig. 11.2 The posterior neck and hand in two patients with scleromyxedema

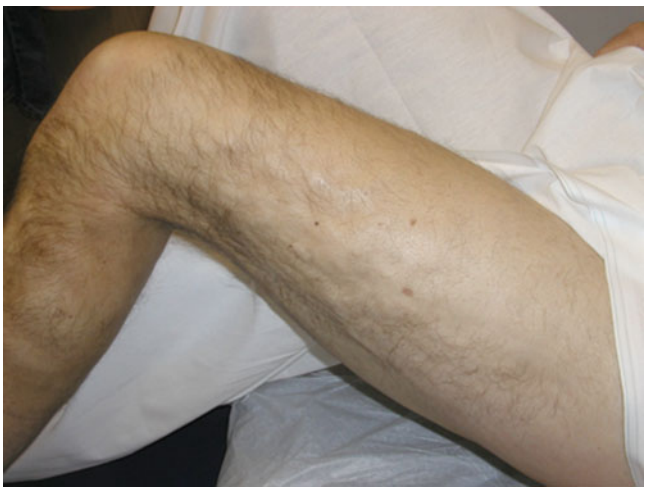

Fig. 11.3 The leg of a patient with eosinophilic fasciitis with puckering and "peau d'Orange" appearance

within affected tissues, but they may not be present when biopsies are obtained after institution of corticosteroid therapy. Given the similar appearance of EF to the toxin-associated epidemic syndromes (TOS and EMS), exposure histories have been examined for EF. The only clear historical association has been with an antecedent history of vigorous exercise or trauma which is found in about half of the described cases [24]. There are reported associations between EF and immune-mediated cytopenias and localized scleroderma (morphea profunda) [24]. The onset and distribution of EF is very similar to NSF which is usually subacute symmetric thickening predominantly over the distal extremities within a short period of time (typically weeks). There may be involvement of the trunk or neck but typically spares the hands and face. Early on, the skin is edematous with a "peau d'Orange" appearance (Fig. 11.3). This is followed by a progressive "woody" induration of subcutaneous tissues leading to skin puckering and the "venous groove sign." Importantly, the superficial dermis is spared allowing an examiner to be able to pinch the skin, which may be a helpful distinguishing feature from scleroderma and other scleroderma-like disorders. Deeper involvement and fibrosis of periarticular structures can prompt severe flexion contractures as well as 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, and systemic features are absent except in cases where the extensive fibrosis around the chest or neck may lead to chest wall restriction or dysphagia. Common laboratory features include peripheral eosinophilia, hypergammaglobulinemia, and elevated inflammatory markers, but have low specificity to this condition compared with scleroderma and other scleroderma-like disorders. Monoclonal gammopathies and autoantibodies are typically absent however. The standard treatment for EF is corticosteroids, which is often intentionally avoided in scleroderma, making this diagnostic distinction particularly important. In addition, the natural history is typically of remission with excellent prognosis.

Localized Scleroderma

Most forms of localized scleroderma are more prevalent in children and quite distinct in appearance from systemic disease. These include isolate patches of morphea and linear (*en coup de sabre*) variants of localized scleroderma. However, some forms, such as generalized morphea and pansclerotic morphea, may be difficult to distinguish from diffuse cutaneous systemic sclerosis and require special mention. Generalized morphea refers to multiple patches of scleroderma skin involvement that evolves in discrete lesions. The lesions are typically circular with a violaceous or erythematosus border (when active) with a white, fibrotic center. Some patients with have extensive involvement of the skin which typically involves the trunk (back > chest) and may linearly extend down one or more extremities (linear morphea), but characteristically spares the fingers in these cases. Pansclerotic morphea typically spreads homogeneously over large areas of skin typically involving the whole trunk and proximal extremities with sparing of hand, fingers and distal forearms; however, the feet are often deeply involved (Fig. 11.4). Histological examination reveals fibrosis that extends through all layers of the dermis and subcutaneous tissues and may extend deeper into muscles and around tendons. Occasionally patients with morphea have antinuclear antibodies, but typically do not have Raynaud's phenomenon or abnormal nailfold capillaries. The distribution of skin involvement is differentiated from diffuse cutaneous systemic sclerosis the typical sparing of the fingers and hands and the plaque-like distribution of skin lesions. This condition may or may not involve the back, so the lack of back involvement may not be helpful to distinguish the two conditions as it is with scleredema, scleromyxedema, and generalized morphea.

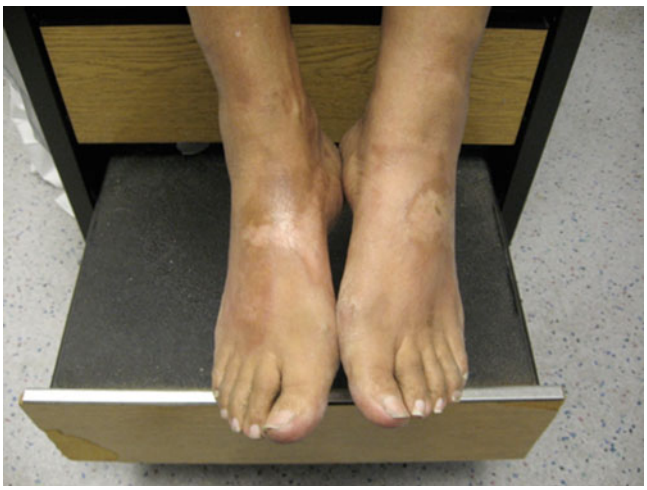

Fig. 11.4 The feet of a patient with pansclerotic morphea. The fingers were normal in this patient, and the feet are characterized by hyperpigmented morphea plaques that coalesce and resemble diffuse scleroderma

Table 11.3 Screening algorithms and treatment options for scleroderma and related disorders

	Screening test in all patients	Treatment options
Scleroderma	Pulmonary function tests	Immunosuppression
	Echocardiogram	Vasodilators for Raynaud
	Ambulatory blood pressure monitoring	Acid suppression for GERD
		Vasodilators for pulmonary hypertension
Nephrogenic systemic fibrosis	None	Intravenous immunoglobulin
		Tyrosine kinase inhibitors
		Physical therapy
Eosinophilic fasciitis	Complete blood counts	Prednisone
Scleromyxedema	Serum protein electrophoresis with immunofixation	Intravenous immunoglobulin
		Thalidomide
Scleredema	Serum protein electrophoresis with immunofixation	UV light-based therapy
		Strict diabetes control
	Fasting blood glucose; hemoglobin A1C	Low grade radiotherapy
Pansclerotic morphea	ANA and scleroderma-specific antibodies	Immunosuppression
		UV light-based therapy

Treatment Differences

Therapeutic strategies to treat these scleroderma-like conditions are widely variable and typically based on very little objective data. These conditions are rare, but need to be included in the differential when evaluating a patient with suspected scleroderma, so internal organ disease screening may be performed, appropriate treatments may be suggested, and a more clear prognosis may be given. The therapeutic choices for someone with a "skin-only" disease may be markedly different than ones with potential for severe systemic involvement (scleroderma, scleromyxedema). Some conditions, such as infection-associated scleredema, eosinophilic fasciitis, and plaque morphea, may be self-limited conditions that require short term or even no treatment, whereas others may require prolonged courses of immunosuppression and chronic management of complications (scleroderma, NFS). Table 11.3 includes common therapies and internal organ complication screening strategies for each of the conditions discussed in this chapter.

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