A Visual Guide to Scleroderma and Approach to Treatment

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This book is dedicated to our patients in the hope that it will result in early recognition, prompt therapy, and better outcomes.

Preface

Although clinical manifestations of scleroderma make it a very "visual" disease, the low prevalence (estimated to be approximately 1 in 4,000 US adults) means that many physicians, rheumatologists included, may fail to recognize the disease particularly in its early stages. In addition, scleroderma varies widely in severity so that the sometimes subtle findings of mild disease may be missed.

In addition, there is often confusion between localized scleroderma (morphea) which does not involve internal organs and systemic sclerosis (including limited and diffuse disease) which does. The similar terminology only serves to compound this confusion.

This book is intended to be an easily accessible tool for residents, fellows, and practicing physicians to recognize and accurately categorize scleroderma in its diverse forms and multiple clinical manifestations. Chapter 4 on nailfold capillaroscopy is particularly relevant, since this technique is now included in the 2013 ACR/EULAR classification criteria for systemic sclerosis.

Several chapters also include therapeutic approaches. Although a detailed discussion of treatment is beyond the scope of this book, our goal is to increase knowledge of available treatment options.

Houston, TX — Maureen D. Mayes

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Chapter 1
Brief Overview of Scleroderma: Localized Scleroderma and Systemic Sclerosis (SSc)

Maureen D. Mayes

Abstract Scleroderma is characterized by and gets its name from the (almost) universal feature of skin thickening. Skin manifestations of scleroderma can be dramatic and impressive. However, because it is a relatively uncommon disease, these manifestations can be overlooked or misinterpreted by physicians and patients alike. The purpose of this book is to provide clinicians, physicians in training, and other medical professionals with a practical guide to the identification of the most common features of this condition.

Keywords Scleroderma • Localized scleroderma • Circumscribed scleroderma • Morphea • Systemic sclerosis

Introduction

Scleroderma is characterized by and gets its name from the (almost) universal feature of skin thickening. Skin manifestations of scleroderma can be dramatic and impressive. However, because it is a relatively uncommon disease, these manifestations can be overlooked or misinterpreted by physicians and patients alike. The purpose of this book is to provide clinicians, physicians in training, and other medical professionals with a practical guide to the identification of the most common features of this condition.

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Table 1.1 Distinguishing features of localized versus systemic scleroderma

Feature	Localized/ circumscribed scleroderma (morphea)	Systemic sclerosis (SSc)
Raynaud's phenomenon	Absent	Present in 95 % of cases
Ischemic digital lesions	Absent	Present in 40 %
Skin involvement	Skin thickening in a patchy or linear distribution	Symmetric hand involvement
	Subcutaneous atrophy	Proximal involvement may also occur, but always in addition to distal skin thickening
	Usually assymetric	Usually symmetric
Antinuclear antibody (ANA)	Positive in 30–50 %	Positive in 85–90 %
SSc-specific antibodies (anticentromere, anti topoisomerase or Scl-70, and anti-RNA-polymerase III)	Negative	Positive in 65 % of cases
Gastro esophageal reflux disease (GERD)	Frequency similar to the general population	Present in 85 %
Interstitial lung disease (ILD)	Absent	Present in 30–40 %

Types of Scleroderma

To the internist and rheumatologist, the term "scleroderma" is equivalent to systemic sclerosis but to our dermatology colleagues it is recognized in both a localized and a systemic form. Localized or circumscribed scleroderma (morphea) only affects the skin and subcutaneous tissues [1], whereas the systemic disease (systemic sclerosis, SSc in both its limited cutaneous and diffuse cutaneous forms) involves internal organs as well as skin and subcutaneous structures [2]. The nomenclature can be confusing because the term "localized scleroderma" is frequently confused with the limited cutaneous form of the systemic disease (limited cutaneous SSc or lcSSc).

Table 1.1 summarizes the major distinguishing characteristics between morphea of localized/circumscribed scleroderma and systemic sclerosis. Since morphea or localized disease is not associated with Raynaud's phenomenon and does not involve internal organs, it does not shorten lifespan. There are several subtypes of morphea which are outlined and illustrated in Chap. 2.

The systemic form of the disease (SSc) is divided clinically into two major subtypes consisting of limited cutaneous (lcSSc) and diffuse cutaneous disease (dcSSc). This distinction is based solely on the extent of skin involvement since both forms can involve, and usually do involve, internal organs to some extent. The reason to make this distinction is that the extent, severity, and rate of progression of

internal organ disease tend to parallel that of skin involvement with the diffuse cutaneous form having a more severe course than limited cutaneous SSc.

The aim of this book is not classification of SSc (the 1980 criteria for the classification of SSc [3] are currently under revision [4]) but recognition of typical features that will aid the clinician in the identification of scleroderma complications. The photos, radiographs, and figures are representative of this disease, but cannot cover the entire spectrum due to the heterogeneity of disease manifestations.

This volume opens with examples of localized disease and ends with a discussion of pseudo-scleroderma conditions. It is a compilation of years of experience from noted experts in this field. Therefore, the purpose of this book is to serve as a teaching tool for clinicians, trainees, and other medical professionals to result in better recognition, more accurate diagnosis, earlier intervention, and improved patient care.

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Chapter 2
Localized Scleroderma

Carolyn A. Bangert, Andrew Kim, and Heidi Jacobe

Abstract Morphea (localized scleroderma) is an autoimmune disease characterized by sclerosis of the skin and, in some cases, subcutaneous tissue. It occurs in children and adults. It is distinct from systemic sclerosis, but may nevertheless be associated with significant functional and cosmetic impairment. Morphea has several distinct subtypes, including circumscribed, linear, and generalized, all of which can occur in superficial and deep forms. The linear subtype is more common in children, and the circumscribed is more common in adults. Evaluation is aimed at confirming the diagnosis and clinical subtype, assessing the stage of activity, and determining the potential for/or the presence of morbidity. Therapy includes topical, phototherapy, or systemic treatments and is aimed at halting progression, preventing morbidity, and speeding remission.

Keywords Morphea • Localized scleroderma • Linear scleroderma • Hemifacial atrophy • Parry–Romberg syndrome

Introduction

Morphea (localized scleroderma) is an autoimmune disease of the skin characterized by sclerosis of the dermis, subcutaneous fat, and in some cases, fascia and deeper tissues. Although commonly confused with systemic sclerosis (SSc, scleroderma) due to identical histologic features, it is distinct from SSc in the absence of acrosclerosis, SSc antibodies, and different end-organ involvement. Morphea has

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been associated with permanent functional and cosmetic impairment, particularly in its deeper and linear and generalized forms.

Morphea affects both children and adults, with the linear subtype predominating in children, and the generalized and circumscribed predominating in adults. The pathogenesis is poorly understood, with most studies extrapolating causality from SSc. The upregulation of vascular adhesion molecules (ICAM-1 and VCAM-1) and vascular damage triggers a Th2 response that results in the upregulation of TGF-β, which induces the overproduction of collagen and other extracellular matrix components leading to the clinical and histologic changes of sclerosis.

Morphea has several subtypes, each with a distinct distribution and depth of involvement. Although classification schemes vary, it is generally subdivided into circumscribed (plaque), linear (including morphea en coup de sabre and hemifacial atrophy, or Parry–Romberg syndrome), and generalized (including pansclerotic), and mixed (Table 2.1). Each subtype may be superficial or deep. Morphea characteristically occurs in three stages: inflammatory, sclerotic, and atrophic. The inflammatory, or active, phase is characterized by progression of lesions in size, depth, and number and is usually associated with clinical evidence of inflammation in the skin lesions (Figs. 2.1, 2.2, and 2.3). The sclerotic phase is characterized by stable sclerosis with varied amounts of pigmentary alteration. Of note, lesions at this point do not enlarge (Figs. 2.4 and 2.5). The atrophic phase is characterized by permanent changes that are variable in severity depending on the extent and subtype of disease (Figs. 2.6, 2.7, 2.8, and 2.9). Patients may have a more limited course or a chronic course, with several episodes of relapses and remissions occurring over many years [1]. In some cases, previously inactive morphea may reactivate many years after initial presentation. In some cases morphea may be associated with systemic findings of arthritis, ocular changes, and neurologic manifestations, but lacks the systemic involvement seen in SSc [2].

Evaluation and therapy of morphea is first aimed at confirming the diagnosis (Table 2.1). Diagnosis is made based on clinical findings and corroborating evidence of inflammation [3], sclerosis on histology, and imaging if clinically indicated [4, 5]. Antinuclear and other antibodies may be present but are not generally helpful in confirming the diagnosis. Once the diagnosis is confirmed, appropriate evaluation includes ascertainment of subtype (Table 2.2, Figs. 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, and 2.19), activity of lesions, extent of involvement, associated findings, and presence or potential for cosmetic or functional disfigurement (Fig. 2.16).

Treatment varies depending on the extent and depth of disease, disease activity, and potential for morbidity (Fig. 2.20). Although randomized controlled trials are few, topical therapy is generally used for more limited superficial disease, phototherapy for more extensive superficial disease (Fig. 2.21), and systemic immunosuppressive therapy for deeper or more extensive disease and disease with a greater potential for morbidity. Therapy is most effective in the inflammatory phase and has no role in improving the atrophic phase. Therapeutic goals include arresting activity and halting progression, speeding remission, and preventing long-term morbidity. The optimal duration of therapy is unknown. For systemic therapy,

Table 2.1 Differential diagnosis of morphea

Most likely
1. Scleroderma (systemic sclerosis)
2. Lipodermatosclerosis
3. Eosinophilic fasciitis
4. Trauma-induced fat necrosis (intramuscular injections)
5. Nephrogenic systemic fibrosis
6. Chronic graft-versus-host disease
Consider
1. Lichen sclerosus
2. Pretibial myxedema
3. Connective tissue nevi
4. Morpheaform basal cell carcinoma
5. Chemical-mediated sclerosing skin conditions (chemotheraphy with bleomycin or toxanes, toxic oil syndrome, rapeseed oil, etc.)
6. Lyme disease (acrodermatitis atrophicans)
7. Phenylketonuria
8. Scleromyxedema, scleroderma chronica, pretibial myxedema
9. POEMS syndrome
Always rule out
1. Carcinoma of the breast metastatic to skin (carcinoma en cuirase)
2. Porphyria cutanea tarda

POEMS polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes
Adapted from Jacobe H, Saxton-Daniels S: Morphea. Chapter 64. In: Fitzpatrick's Dermatology in General Medicine, 8e. Edited by Goldsmith, et al. New York: McGraw-Hill; 2012:692-701. With permission from McGraw-Hill Global Education Holdings, LLC

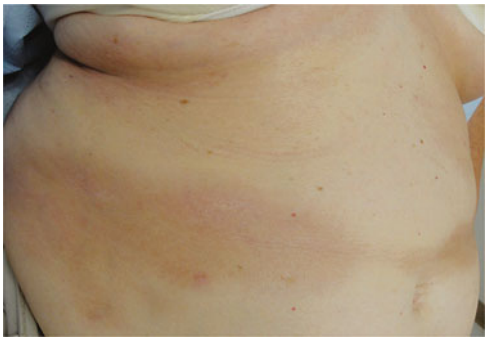

Fig. 2.1 This patient has plaques with central sclerosis (*central brown yellow* areas) surrounded by peripheral erythema on the abdomen and inframammary folds. This is characteristic of active lesions. With successful treatment, erythema quickly resolves and is replaced by post-inflammatory hyperpigmentation. Central sclerosis is more persistent, gradually softening over several months

limited data consisting of expert consensus and one observational study indicates longer duration of methotrexate (MTX) at about 2 years or so seems to decrease risk of reactivation in short-term [6, 7]. In the author's experience, once disease activity

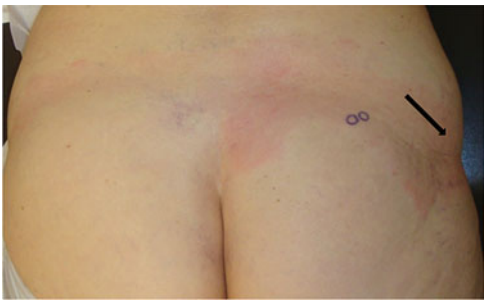

Fig. 2.2 Inflammatory linear morphea with involvement of the subcutaneous tissue evidenced by loss of the normal contour of the hip (*black arrow*). This is an indication for systemic treatment as treatments directed from the outside would not penetrate into the area of pathology (oral methotrexate and prednisone were prescribed). Although treatment halted progression and produced skin softening, loss of subcutaneous tissue persists

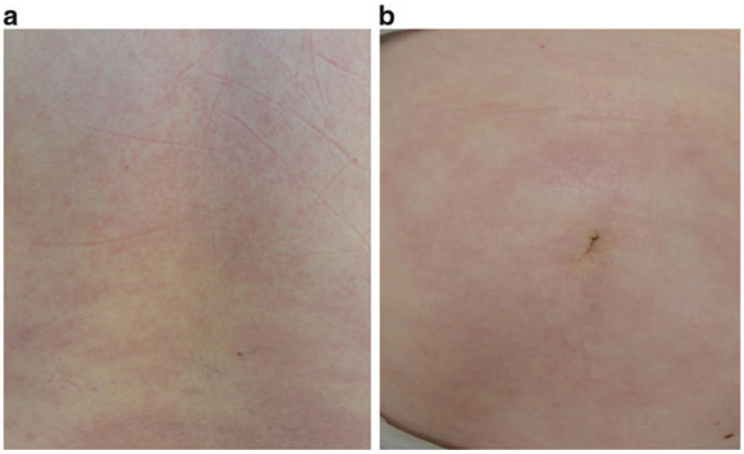

Fig. 2.3 Early inflammatory morphea is characterized by minimal induration and poorly circumscribed, reticulated erythematous plaques. Aggressive treatment at this stage produces near complete resolution of the lesions, especially phototherapy such as UVA1

has been halted for 6 months and improvement in sclerosis has halted, MTX may be slowly tapered by 2.5 mg every 1–2 months. The prognosis is variable and depends on disease subtype, extent of disease, and interindividual variability.

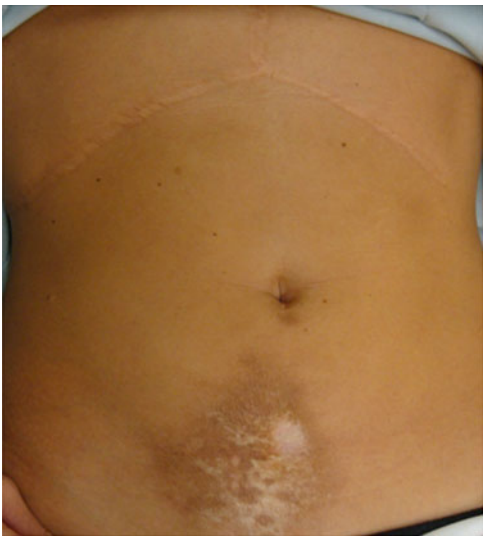

Fig. 2.4 Hyper- and hypopigmentation on the abdomen in a patient with circumscribed morphea. If there is a sclerotic component, the patient may respond modestly to topical or intralesional therapy, but this form of morphea is largely unaltered by therapeutic intervention

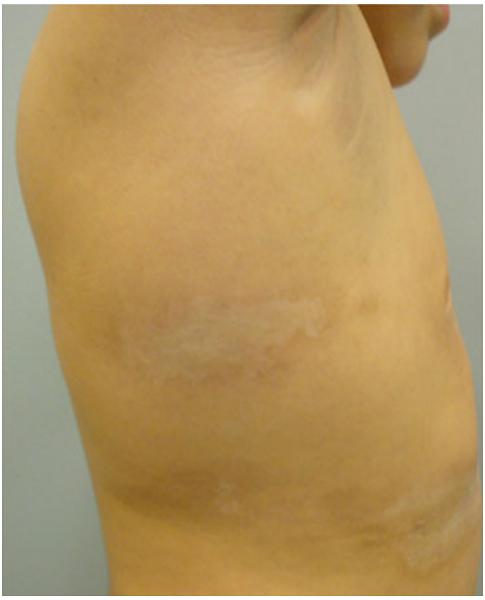

Fig. 2.5 Child with multiple linear lesions of the trunk. These lesions are transitioning from the active to sclerotic phase with central sclerosis and a mixture of peripheral hyperpigmentation and erythema. This lesion is amenable to treatment with either phototherapy or methotrexate. In the experience of the authors, systemic glucocorticoids may be unnecessary in these lesions if they are slowly progressive

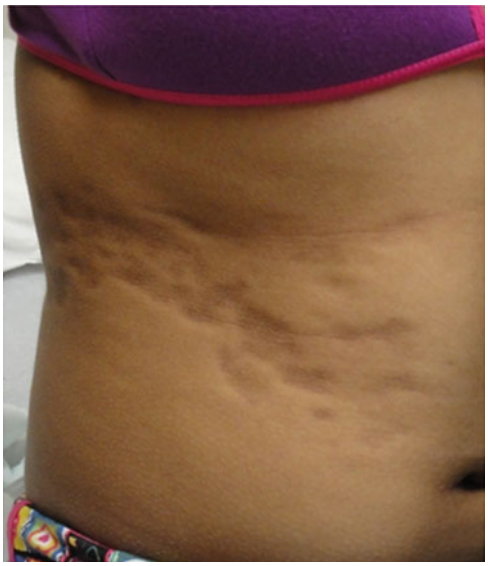

Fig. 2.6 Atrophic phase linear morphea of the abdomen with hyperpigmentation and dermal atrophy with associated cliff drop. This is in contrast to subcutaneous atrophy in which the normal body contour is altered. The sclerosis and hyperpigmentation may improve with time, but therapy medical is not indicated

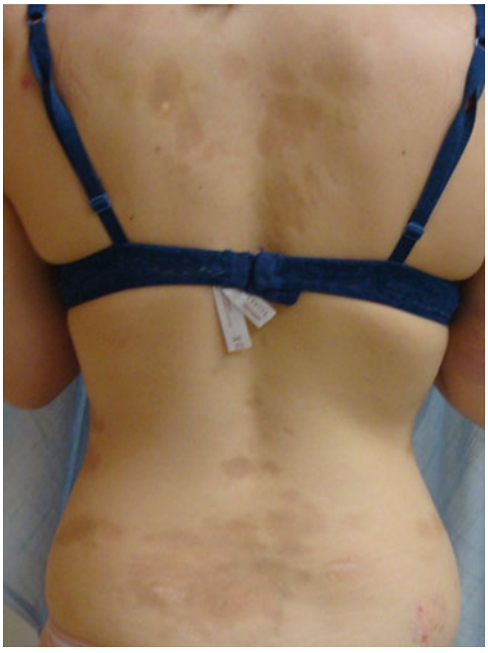

Fig. 2.7 Hyperpigmentation in a patient with atrophic (dermal atrophy) stage morphea. The lesions are soft to palpation. This phase of morphea does not respond to medical treatment, although the dyspigmentation may gradually improve with time

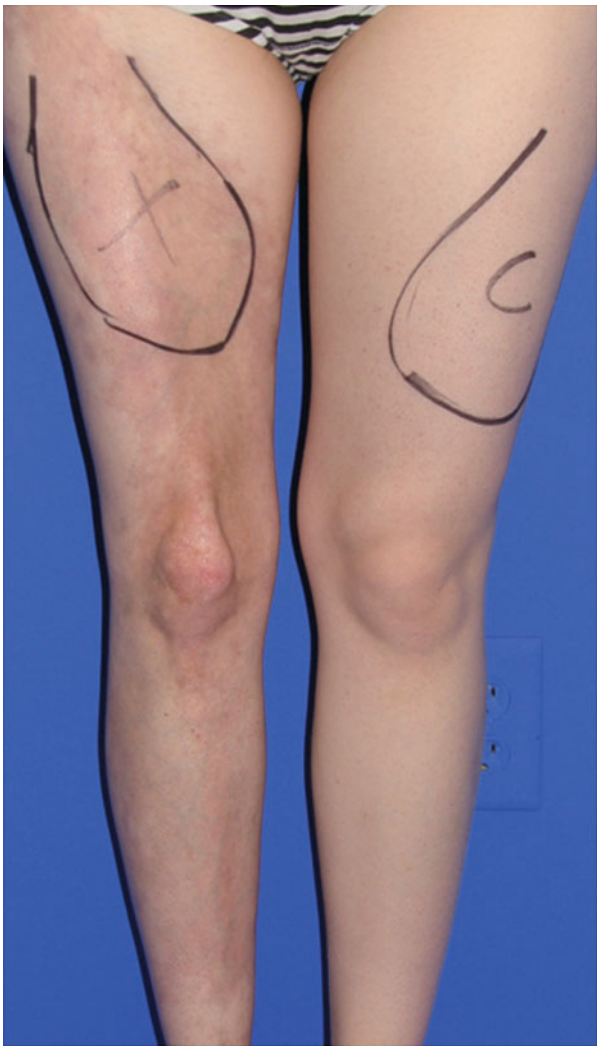

Fig. 2.8 Atrophic phase-deep linear morphea on the leg of a child with appreciable limb length and limb girth discrepancy. There is atrophy of the subcutaneous tissue with loss of the patellar fat pad, but sclerosis has resolved. Unfortunately, these lesions are inactive and are not expected to improve with immunosuppressives. When the disease of this type is active, aggressive therapy with a 3-month course of pulsed or oral steroids and maintenance with methotrexate is indicated to prevent morbidity. Physical therapy is also recommended to maintain the range of motion in joints

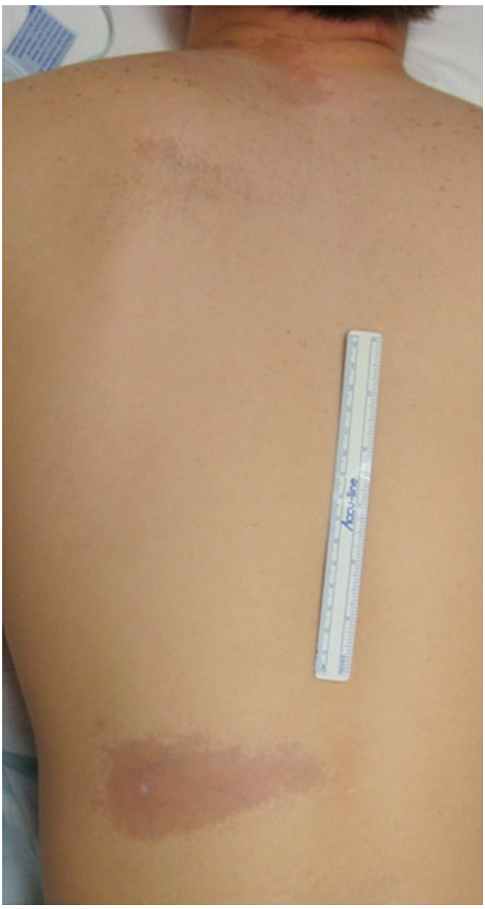

Fig. 2.9 Linear morphea of the upper back and shoulder in an adult patient with dyspigmentation, hair loss, and dermal atrophy with increased vascular prominence of the posterior shoulder consistent with damage but no evidence of disease activity. Linear morphea most frequently involves the extremities and head. Involvement of the trunk and one or both limbs on the ipsilateral side is not uncommon, but concomitant head involvement is rare. Linear lesions on the trunk may be confused with circumscribed morphea, but the abrupt discontinuation of the lesion at the midline is a diagnostic clue. Treatment of active linear morphea depends on the depth of disease, but generally involves systemic immunosuppressive therapy

Table 2.2 Proposed classification of morphea subtypes

Morphea subtype	Modifiers	Clinical
Circumscribed (Fig. 2.10)	Superficial (Fig. 2.10a)	Single or multiple oval/round lesions limited to epidermis and dermis
	Deep (Fig. 2.10b)	Single or multiple oval/round lesions involving subcutaneous tissue, fascia, or muscle
Linear (Figs. 2.14, 2.15, and 2.16)	Trunk/limbs	Linear lesions involving possible primary site of involvement in subcutaneous tissue with or without involvement of epidermis, dermis, muscle, or bone
Figures 2.11, 2.12, and 2.13	Head	En coup de sabre, progressive facial hemiatrophy, linear lesions of the face (may involve underlying bone)
Generalized		
1. Coalescent plaque	Figure 2.17	≥4 plaques in at least 2 of 7 anatomic sites (head–neck, right/left upper extremity, right/left lower extremity, anterior/posterior trunk); Isomorphic pattern: coalescent plaques inframammary fold, waistline, lower abdomen, proximal thighs; symmetric pattern: symmetric plaques circumferential around breasts, umbilicus, arms, and legs
2. Pansclerotic	Figure 2.19	Circumferential involvement of majority of body surface area (sparing fingertips and toes), affecting skin, subcutaneous tissue, muscle, or bone; no internal organ involvement
Mixed		Combination of any above subtype: ex: linear-circumscribed

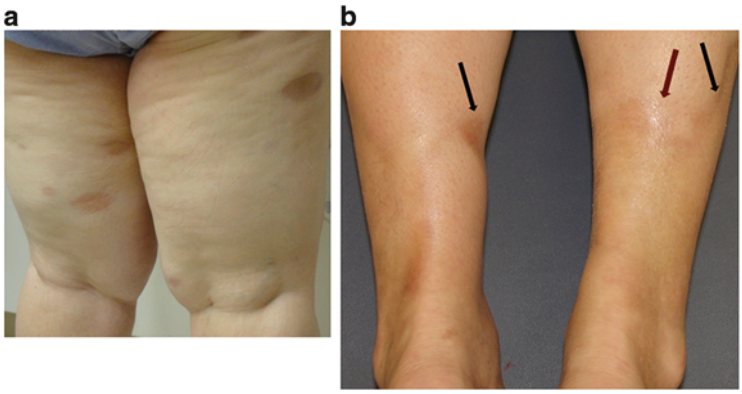

Fig. 2.10 (**a**) Circumscribed morphea with oval plaques bilateral thighs. Lesions are in varied stages of evolution including hyperpigmented inactive plaques (L thigh) and active erythematous plaques (R thigh). Presence of active and inactive lesions is relatively common. In this case the active lesions may be treated with a topical preparation such as fluocinonide 0.05 % ointment or calcipotriene ointment. If the lesions continue to multiply, therapy aimed at suppressing progression such as phototherapy is indicated. (**b**) Circumscribed morphea with subcutaneous involvement indicated by abnormal contour of bilateral lower extremities (*black arrows*). These lesions display both activity (*red arrow*) manifested by peripheral erythema and induration and pigmentary alteration and atrophy (dermal and subcutaneous). This patient responded well to oral methotrexate

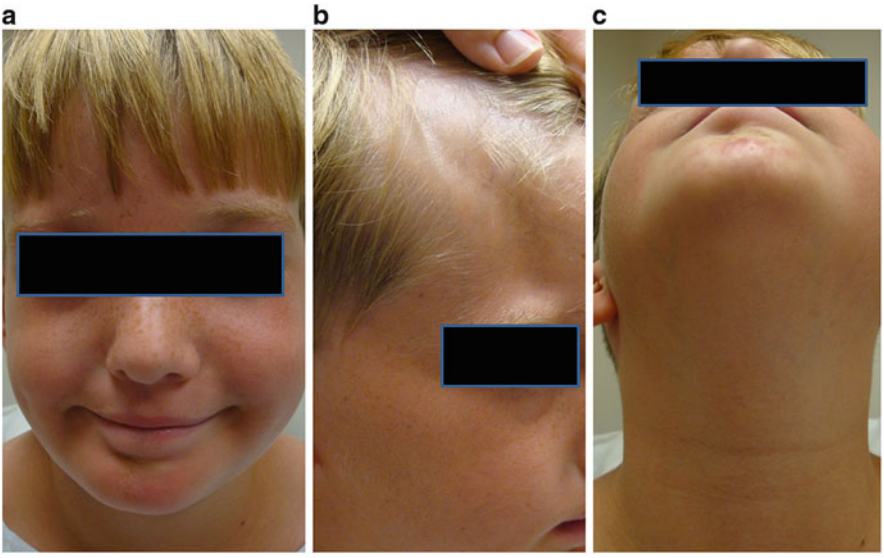

Fig. 2.11 Linear morphea of the head and neck in a child with hemifacial atrophy involving the right chin and cheek (**a**, **c**) and en coup de sabre of the right lateral forehead (**b**). En coup de sabre and hemifacial atrophy are variants of linear morphea of the head and neck that may occur separately but frequently coexist. Complications include ocular and neurologic changes. A history of headaches, seizures, or eye changes should be solicited and evaluation by ophthalmology and neurology initiated if present. En coup de sabre generally involves the paramedian or lateral forehead, scalp, and other regions of the upper face, while hemifacial atrophy most commonly involves skin and deeper tissues (including muscle and bone) of the lower face. A clinically apparent inflammatory phase is rare, making assessment of disease activity challenging. Systemic therapy is usually employed for treatment of active disease

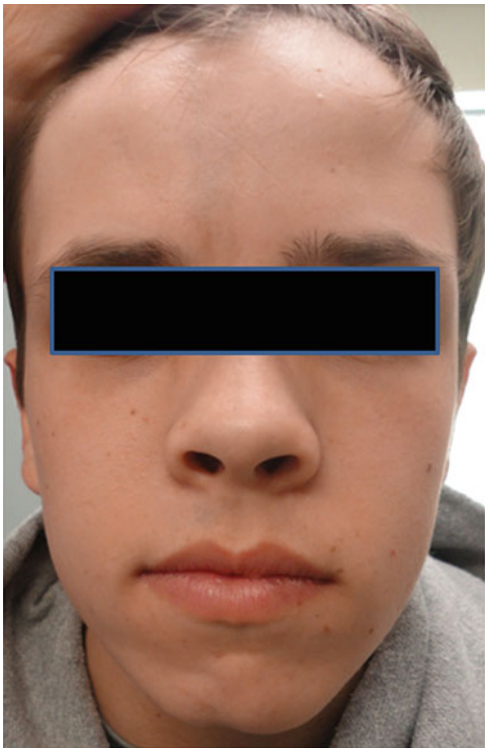

Fig. 2.12 Linear morphea of the forehead, nose, and chin (en coup de sabre) in a child. Ascertaining clinical activity is difficult, and is primarily done by history and serial photography. Systemic immunosuppressive therapy is used to arrest disease progression, but significant improvement in the sclerosis and atrophy is unlikely

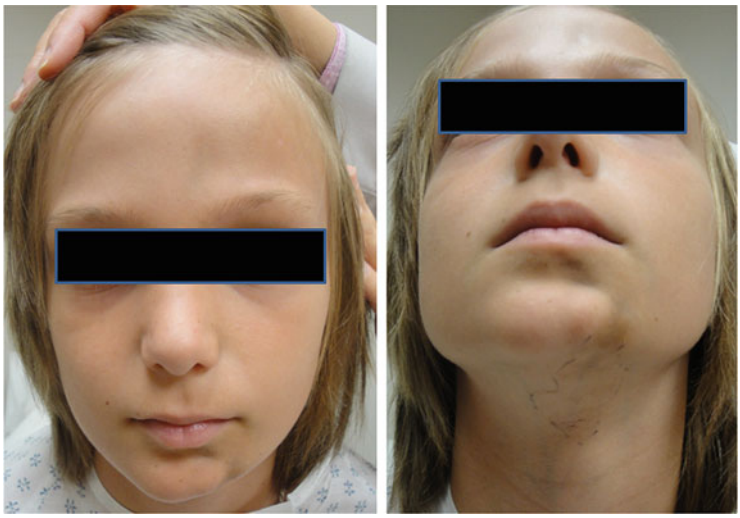

Fig. 2.13 Child with linear morphea (en coup de sabre) involving the left forehead, upper lip, chin, and neck. Lesions are inactive.

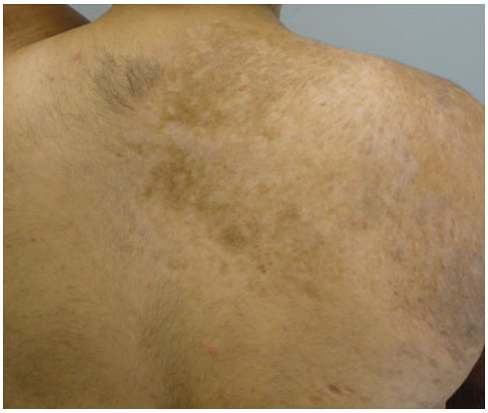

Fig. 2.14 Linear morphea of the upper back and shoulder in an adult patient with dyspigmentation, hair loss, and dermal atrophy with increased vascular prominence of the posterior shoulder consistent with damage but no evidence of disease activity. Linear morphea most frequently involves the extremities and head. Involvement of the trunk and one or both limbs on the ipsilateral side is not uncommon, but concomitant head involvement is rare. Linear lesions on the trunk may be confused with circumscribed morphea, but the abrupt discontinuation of the lesion at the midline is a diagnostic clue. Treatment of active linear morphea depends on the depth of disease, but generally involves systemic immunosuppressive therapy

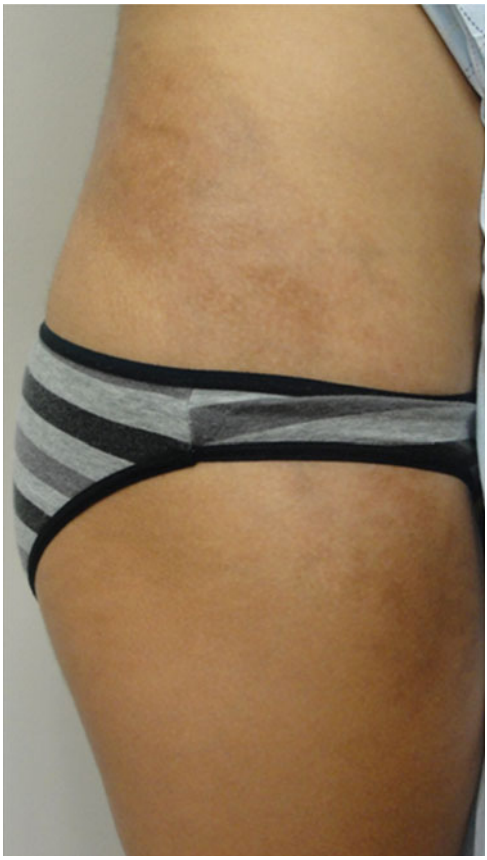

Fig. 2.15 Hyperpigmentation in linear morphea of the abdomen and thigh. Her disease is inactive and requires only clinical monitoring

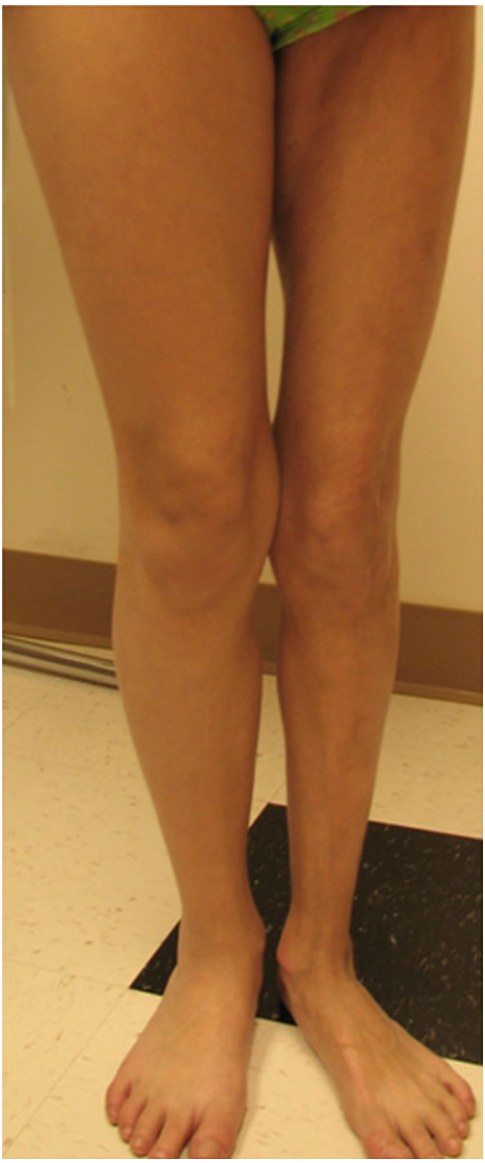

Fig. 2.16 Child with linear morphea of the left lower extremity. In this case, there is severe damage with limb length discrepancy and subcutaneous and muscular atrophy. The skin has softened. This lesion will not improve with immunosuppressives. Rather, treatment is aimed at minimizing damage via physical therapy

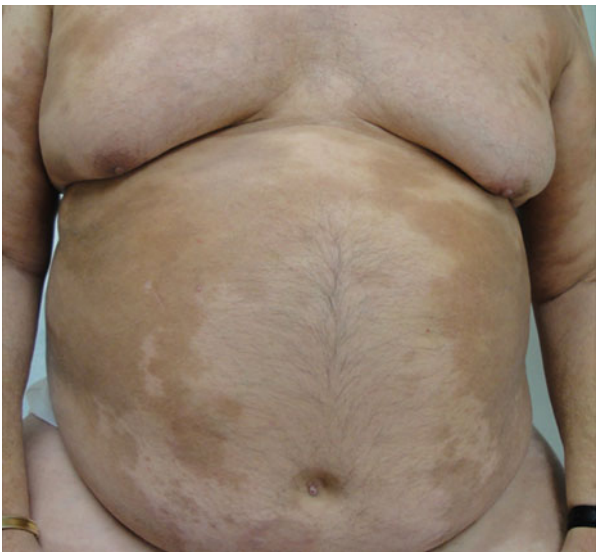

Fig. 2.17 Generalized morphea with typical coalescent plaques distributed over trunk and extremities. This patient's lesions are inactive due to aggressive treatment with prednisone tapered over 4 months and methotrexate weekly for 2 years which produced remission and lesion softening. Note that residual hyperpigmentation remains

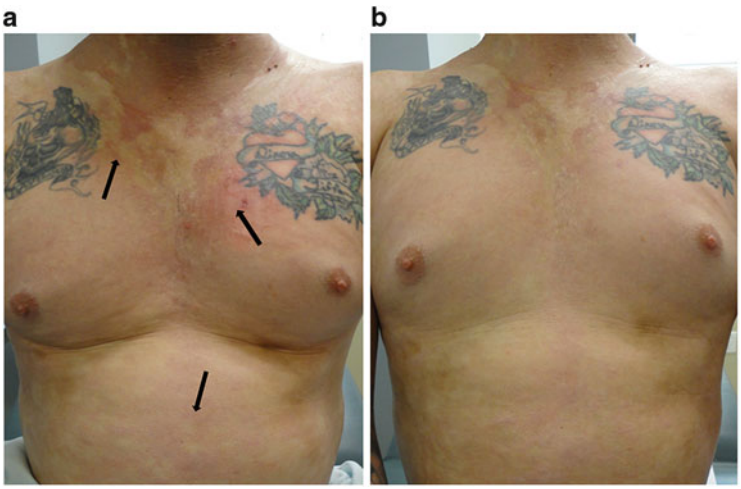

Fig. 2.18 Patient with active pansclerotic morphea (note erythema indicated by *arrows*) (**a**). This patient was treated with oral prednisone and methotrexate with resolution of activity and eventual softening and hyperpigmentation (**b**)

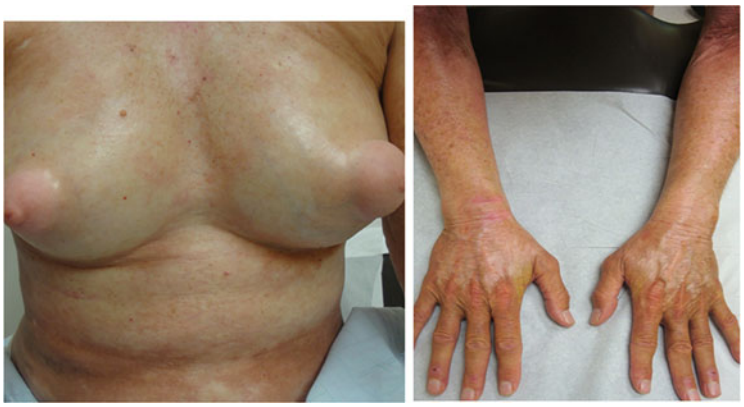

Fig. 2.19 Pansclerotic morphea with characteristic contiguous sheets of sclerosis beginning on trunk spreading to total body involvement sparing the face, areolae, fingers, and toes. This underscores the difference between pansclerotic morphea and systemic sclerosis, which begins with acrosclerosis. This patient developed a restrictive pulmonary defect due to circumferential sclerosis of the chest, skin ulcerations, and contractures. Despite treatment with prednisone, methotrexate, UVA1 phototherapy, antithymocyte globulin, cyclosporin, and mycophenolate mofetil, she succumbed due to complications of her morphea. Pansclerotic morphea warrants early aggressive treatment with immunosuppressives due to its poor prognosis

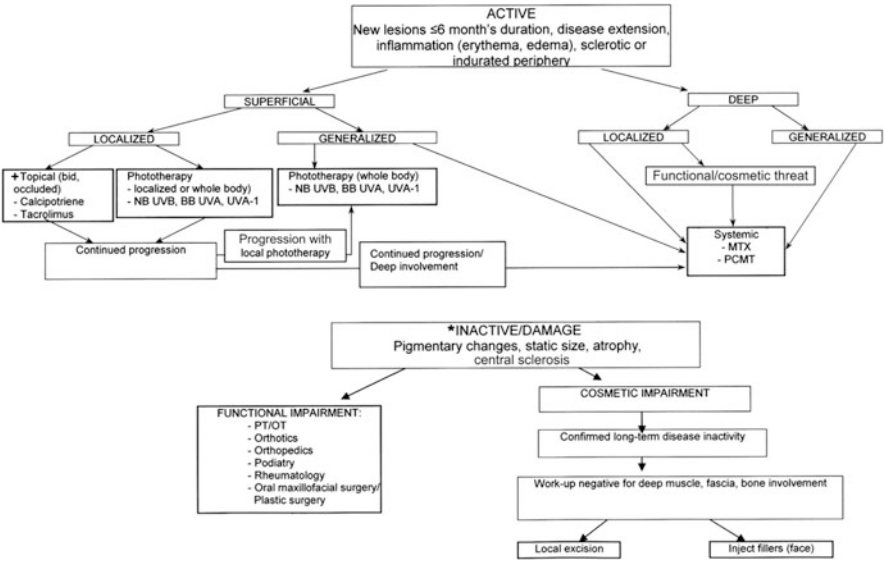

Fig. 2.20 Therapeutic algorithm for morphea based on existing evidence [Adapted from Jacobe H, Saxton-Daniels S: Morphea. Chapter 64. In: Fitzpatrick's Dermatology in General Medicine, 8e. Edited by Goldsmith, et al. New York: McGraw-Hill; 2012:692-701. With permission from McGraw-Hill Global Education Holdings, LLC]

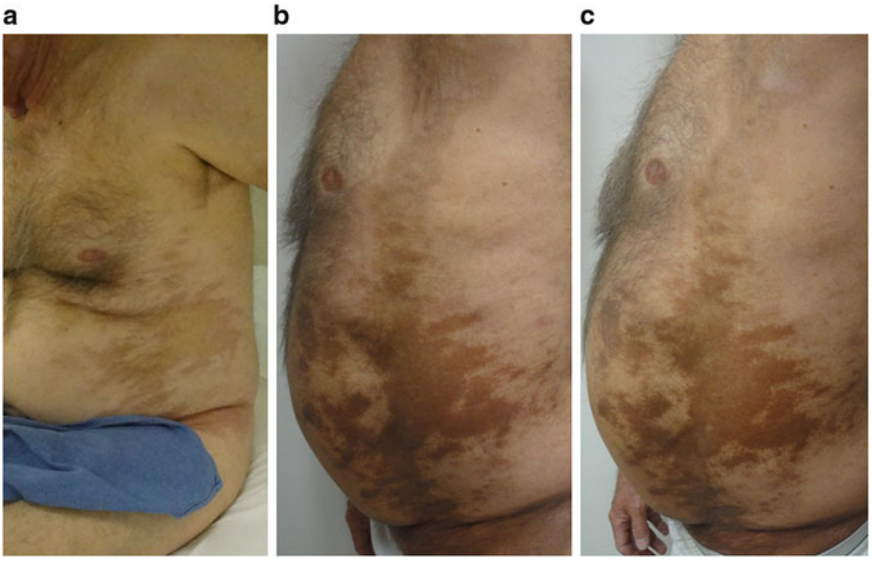

Fig. 2.21 Patient with generalized morphea before (**a**) during (**b**), and after UVA1 (**c**) phototherapy. UVA1 phototherapy produces profound hyperpigmentation of lesions

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Chapter 3
Skin Manifestations and Musculoskeletal Disease in SSc

Janet Pope and Maureen D. Mayes

Abstract Clinically, systemic sclerosis is dominated by two features: small vessel vasculopathy and organ fibrosis. These two pathological features are responsible for the clinical manifestations of Raynaud's phenomenon, digital ulcers, renal crisis, pulmonary arterial hypertension, skin thickening, interstitial lung disease, cardiac complications, and other organ involvement. In spite of this commonality, there is a great deal of heterogeneity in disease expression in scleroderma with some individuals having mild involvement and others with severe and progressive disease.

This chapter will focus on the more visually apparent complications of SSc including Raynaud's phenomenon, telangiectasias, pigment changes, skin thickening, contractures, arthritis, and periarthritis.

Keywords Raynaud's phenomenon • Telangiectasias • Pigment changes • Modified Rodnan skin score • Tendon friction rubs • Tenosynovitis

Introduction

The clinical presentation of SSc is characterized by features that result from the small vessel vasculopathy and fibrosis which usually starts as dermal fibrosis in the fingers and hands and then may extend to include more proximal areas of the extremities, face, and trunk.

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M.D. Mayes (ed.), *A Visual Guide to Scleroderma and Approach to Treatment*,
DOI 10.1007/978-1-4939-0980-3_3,

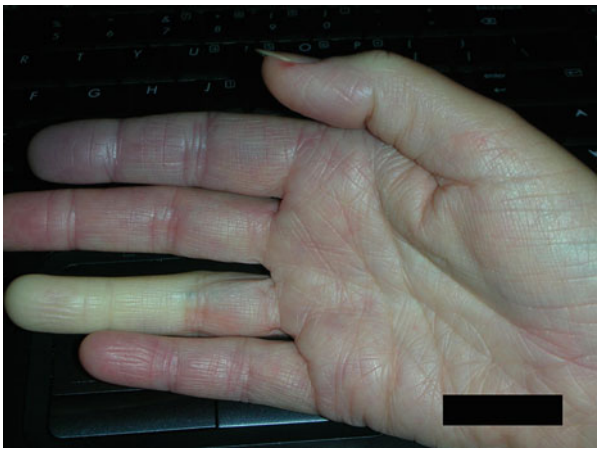

Fig. 3.1 Raynaud's phenomenon in both the phase of pallor (fourth digit) and cyanosis (second digit) in a patient with long-standing limited cutaneous SSc with mild sclerodactyly which is not evident in this view

For most, but not all, SSc cases, the earliest clinical feature is Raynaud's phenomenon characterized by color changes of the fingers (cyanosis and pallor on cold exposure (Fig. 3.1), which can be followed by rubor on rewarming). Primary Raynaud's phenomenon (without associated autoimmune disease) is common in the general population with estimates of 5–15 % of the US adults [1] and represents a spasm of small blood vessels which return to normal caliber once the cold challenge ends. When associated with SSc, however, Raynaud's phenomenon is accompanied by structural changes in small blood vessels that result in permanently narrowed lumen and decreased capacity to dilate [2]. This chronic ischemia leads to digital pitting scars, loss of fingerpad substance, and painful digital ulcers (discussed in detail in Chap. 5).

Visualizing nailfold capillaries provides a "window" into this small vessel vasculopathy and can best be evaluated by nailfold capillaroscopy techniques as discussed and illustrated in Chap. 4. Dilated capillaries typical of SSc can sometimes be appreciated by the naked eye or with minimal magnification as see in Fig. 3.2. Identification of these changes can be helpful in distinguishing primary from secondary Raynaud's phenomenon early in SSc.

Telangiectasias

Another frequent feature of SSc is the development of telangiectasias which typically occur on the hands and face including lips and oral mucosa [3]. Interestingly, these telangiectasias seldom occur on the legs. They can be "pinpoint" or "mat-like" in nature. Figures 3.3 and 3.4 show several of the dot-like telangiectasias of the palm and fingers of patients with limited cutaneous disease. This can be a subtle finding at first but, when present, it is helpful in the diagnosis of SSc since

Fig. 3.2 Dilated nailfold capillaries in a patient with early SSc

these telangiectasias do not occur in primary Raynaud's disease. Telangiectasias can also occur on the lips (Fig. 3.5) and on the oral mucosa.

As time goes on, telangiectasias can become larger (mat-like) and more numerous as illustrated in Figs. 3.6, 3.7, and 3.8.

Telangiectasias of the face can be treated with laser therapy but usually require multiple sessions and there is a tendency for these lesions to recur.

Ischemic Changes

In addition to finger ulcers that are discussed in Chap. 5, there are additional chronic ischemic changes that are typical of SSc. Figure 3.9 shows the time course over 6 months of digital infarcts in a patient with long-standing SSc. The area of infarction was fairly superficial and the lesions healed with conservative treatment although there was digital pulp loss.

Figure 3.10 shows the loss of fingerpad substance with subsequent tapering of the fingers due to chronic ischemia. This patient also has the typical telangiectasias and calcinosis of SSc.

Although the fingers are the most common site for ischemic digital ulcers, skin breakdown and ulcer formation can occur in other sites as well. Figure 3.11 shows an ulcer over the third MCP joint of a patient with early onset diffuse SSc. Figure 3.12 shows a small but painful ulcer of the ear in a patient with diffuse SSc.

Figure 3.13 shows a painful and chronic elbow ulcer in a patient with diffuse SSc. Treatment of these ischemic changes include protection against repeated injury, vasodilators, and wound care to prevent secondary infections.

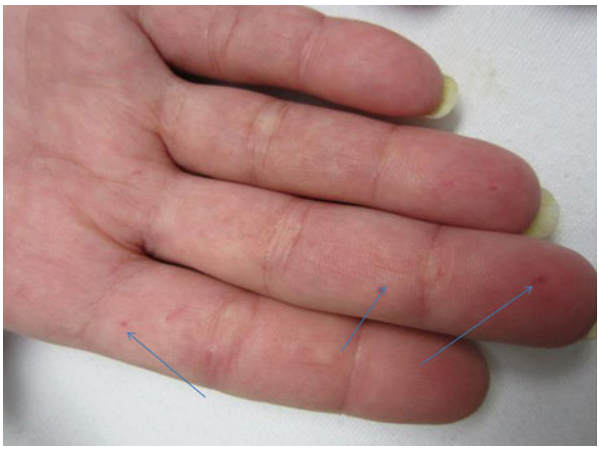

Fig. 3.3 Dot-like telangiectasias of the palmar surface of a patient with limited cutaneous SSc

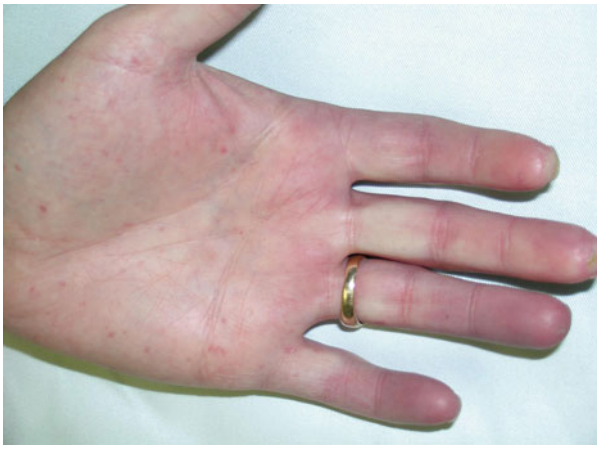

Fig. 3.4 Multiple telangiectasias of the palm

Pigment Changes

Diffuse hyperpigmentation can occur in scleroderma, usually in the early phase of diffuse cutaneous disease, and can precede skin thickening. Patchy "salt-and-pepper" hypopigmentation (Figs. 3.14 and 3.15) can also be seen most commonly affecting hands, arms, and anterior chest. Although troubling to the patient, the pigment changes have no clinical consequence and, over time, the skin can return to a more normal shade but this process can take several years.

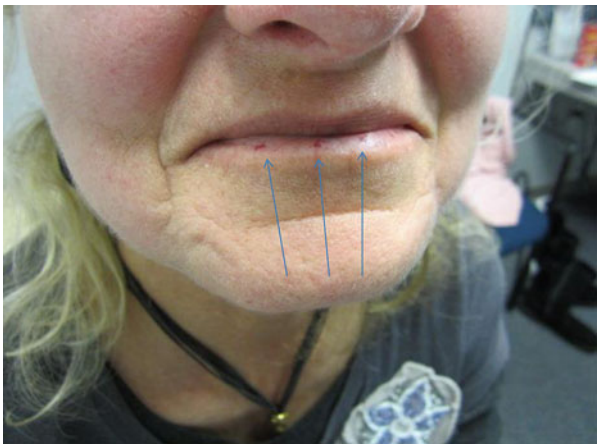

Fig. 3.5 Telangiectasias of the lips

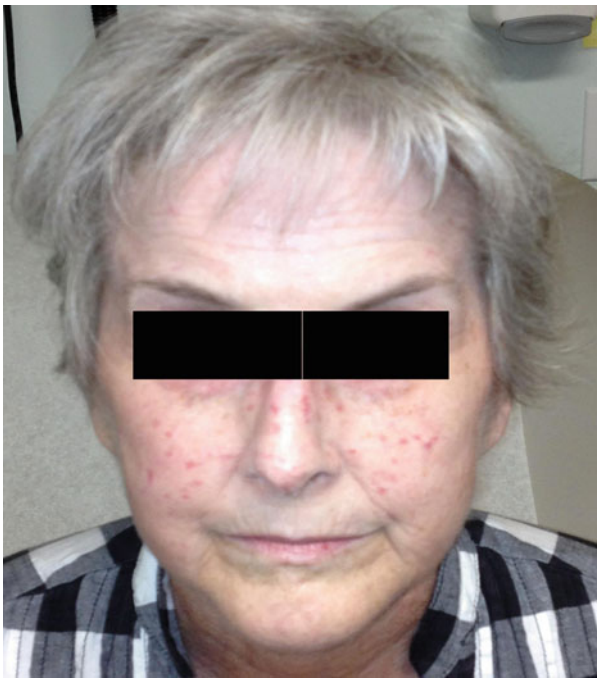

Fig. 3.6 Prominent telangiectasias over the nose and cheeks, as well as the lower lip, in a patient with long-standing (25 years from onset) limited SSc. The telangiectasias (by definition) blanche with pressure and then refill when pressure is released

Skin Thickening

Clinically, SSc is divided into limited cutaneous and diffuse cutaneous disease based solely on the distribution of skin involvement with limited disease defined as skin thickening of the distal extremities below the elbows and knees and diffuse disease defined as skin thickening that extends to the proximal extremities and/or

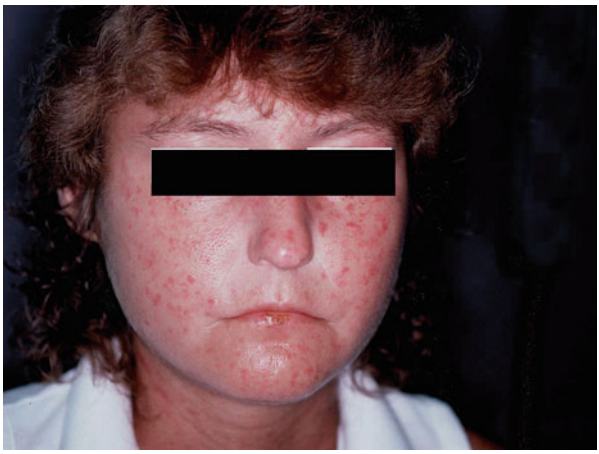

Fig. 3.7 Telangiectasias of the face and neck in a patient with diffuse SSc

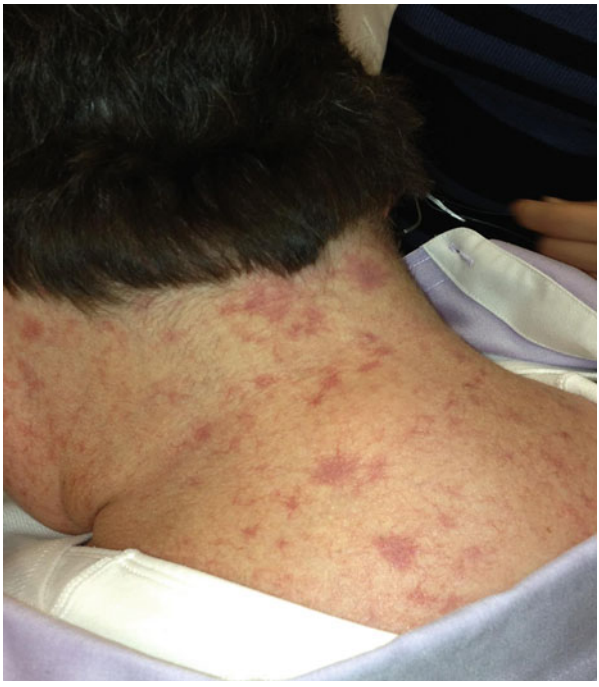

Fig. 3.8 Prominent telangiectasias of the neck and upper back, in a patient with long-standing (20 years) limited SSc

the trunk [4]. Another classification system [5] proposes 3 subtypes with Type 1 being sclerodactyly alone (skin thickening confined to the fingers), Type II being cutaneous sclerosis of the extremities plus the fingers, and Type III being truncal skin sclerosis as well as extremity and hand involvement. In both approaches, it is clear that those with more extensive skin involvement tend to have more severe internal organ disease.

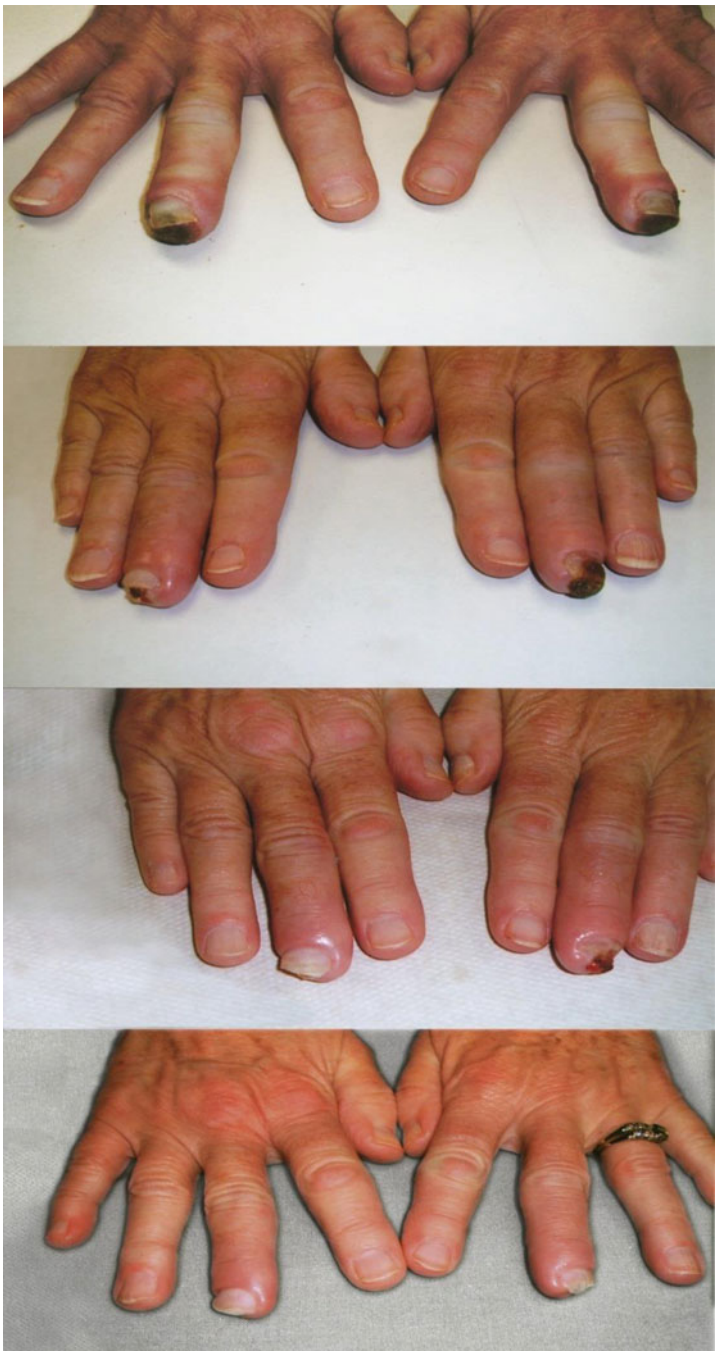

Fig. 3.9 Time course of healing of digital tip Infarcts over 6 months from the top photo taken within 3 weeks of onset to the bottom photo 6 months later. There is loss of fingertip tissue but surgical intervention was not required

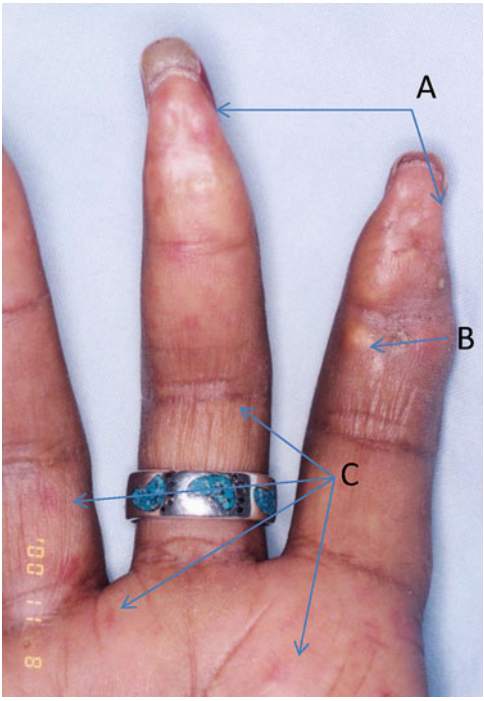

Fig. 3.10 (*A*) Loss of fingerpad substance due to chronic Ischemia and recurrent ulcers. (*B*) Subcutaneous calcinosis. (*C*) Telangiectasias of the palm and palmar surface of digits

Although the hallmark of SSc is thickened skin, it is difficult to effectively demonstrate this in a two-dimensional photo. Figure 3.16 shows the trunk of a man with early (10 months from onset) diffuse SSc. Figure 3.17 shows the hand of the same patient as in Fig. 3.16 demonstrating the loss of skin wrinkles and flexion contractures of the fingers that developed in this short span of time.

The degree and extent of skin thickening can be measured and traced over time using the modified Rodnan skin score (mRSS) [6] which grades skin thickness as moderate, mild, or severe in 17 body areas. Uninvolved is scored as 0, mild thickening as 1, moderate thickening as 2, and severe thickening as 3. Table 3.1 shows a typical scoring sheet for this system. For example, a case with severe skin thickening (score = 3) at all body areas would have the maximum score of 51. With experienced examiners, the mRSS is reliable and reproducible and has intra-investigator reliability that is comparable to joint scores in rheumatoid arthritis [7]. It has proven utility in clinical trials but can also be useful in clinical practice to determine progression, stability, or regression of SSc skin involvement.

The usual course of skin thickening in SSc is characterized by initial phase of hand swelling, followed by skin thickening that progresses over months to 2–3 years, then stabilizes, and then can improve on its own even in the absence of effective treatment [8]. However, flexion contractures of the joints, particularly the hands, tend not to improve even as the skin softens in other areas. In addition,

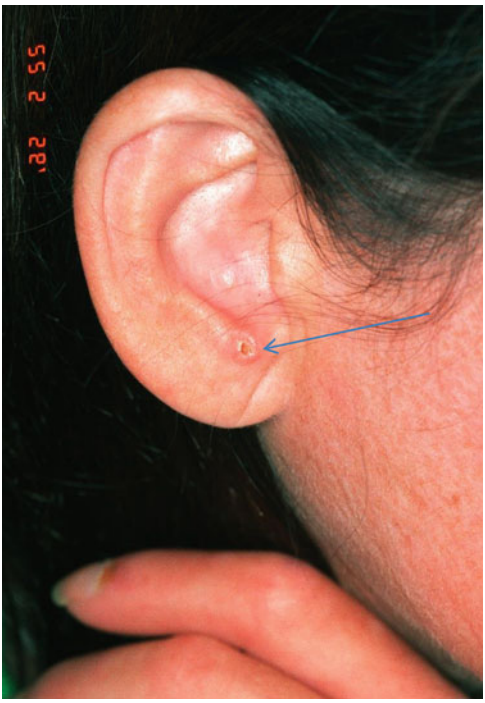

Fig. 3.11 Ulcer over the anti-tragus in a patient with diffuse SSc. These lesions are quite tender and are likely due to a combination of pressure during sleep and poor blood supply. Management is primarily directed to relieving pressure with bandage cushioning or changing sleep position

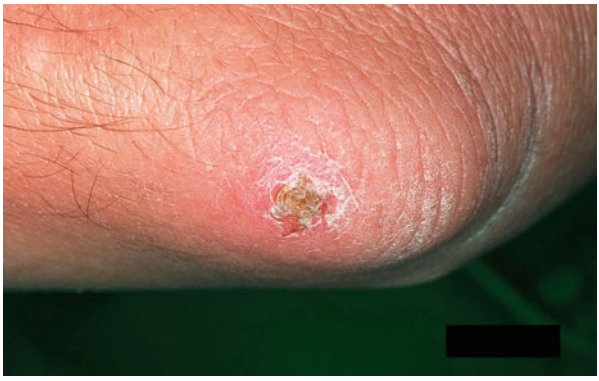

Fig. 3.12 Painful chronic elbow ulcer in a patient with diffuse cutaneous SSc

internal organ involvement particularly interstitial lung disease and gastrointestinal dysmotility can progress even when the skin scores are improving.

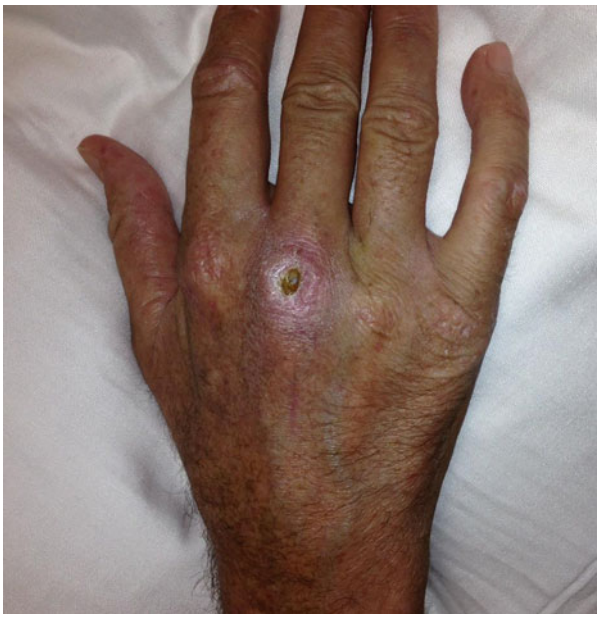

Fig. 3.13 Ulcer over the third MCP in a man with early onset (2 years) diffuse SSc

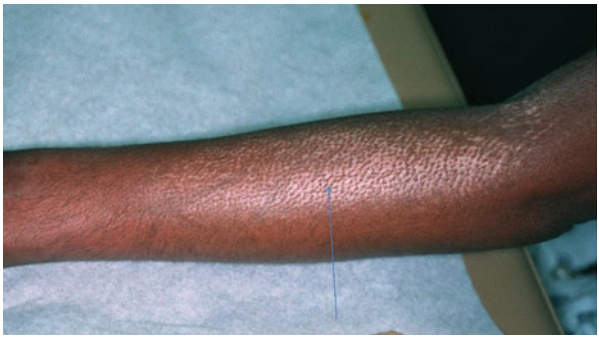

Fig. 3.14 Typical SSc-related hypopigmentation with salt-and-pepper appearance created by maintenance of pigment around hair follicles and loss of pigment between

Flexion Contractures

Flexion contractures of the hands result in significant functional disability in SSc and typically occur in the first 5 years of disease. Figures 3.18 and 3.19 show severe flexion contractures with the fingers flexed almost completely into the palms. Not all SSc patients develop contractures even after years of disease and some develop mild or moderate contractures as noted in Fig. 3.20.

While contractures of the fingers are the most common in SSc, some severe diffuse patients will also develop elbow and knee contractures and may also have decreased range of motion of shoulders, hips, and knees all due to skin fibrosis with tethering to underlying structures.

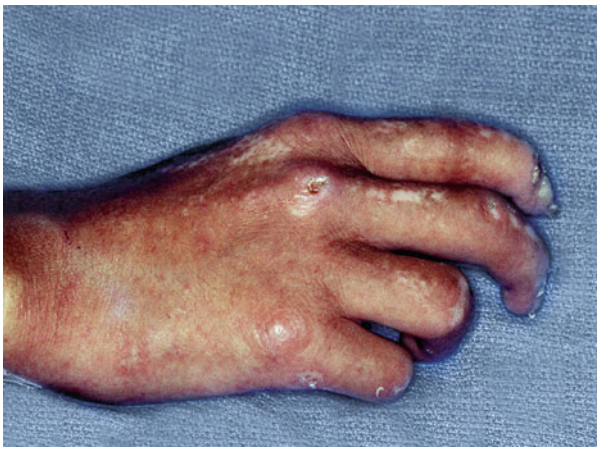

Fig. 3.15 Spotty hypopigmented areas, flexion contractures, and ulcer over the third MCP joint in a patient with diffuse SSc

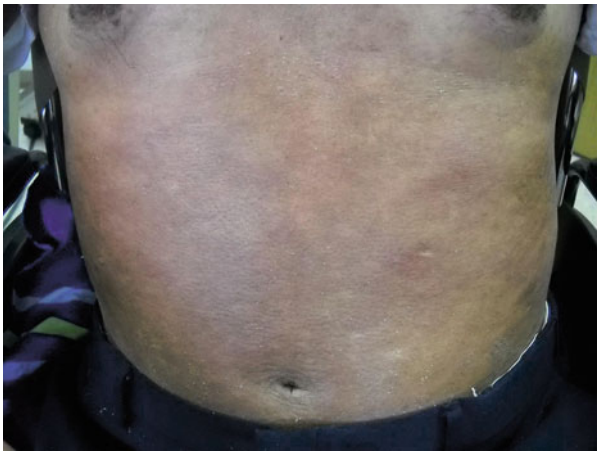

Fig. 3.16 Thickened skin of the trunk in a 68-year-old man with early (10 months from onset) diffuse SSc

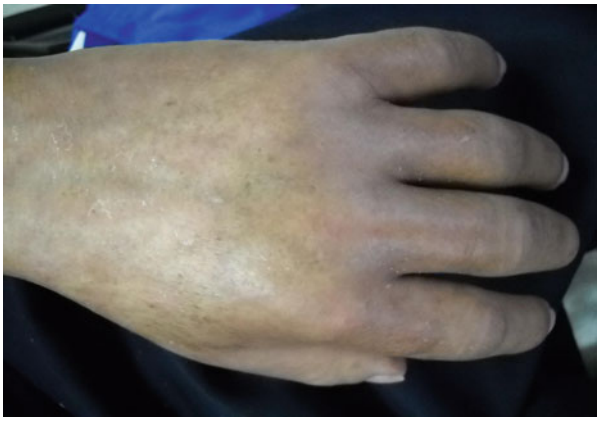

Fig. 3.17 Thickened skin of the dorsum of the hand (as well as of the fingers) in the same patient as above. Note the loss of skin wrinkles and lack of prominence of the extensor tendons

Table 3.1 Typical score sheet for assessment of skin thickening by the modified Rodnan skin scoring system

	Right	Left
Fingers	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__
Dorsum hands	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__
Forearms	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__
Upper arms	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__
Face	0__ 1__ 2__ 3__	
Chest	0__ 1__ 2__ 3__	
Abdomen	0__ 1__ 2__ 3__	
Thighs	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__
Legs	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__
Feet	0__ 1__ 2__ 3__	0__ 1__ 2__ 3__

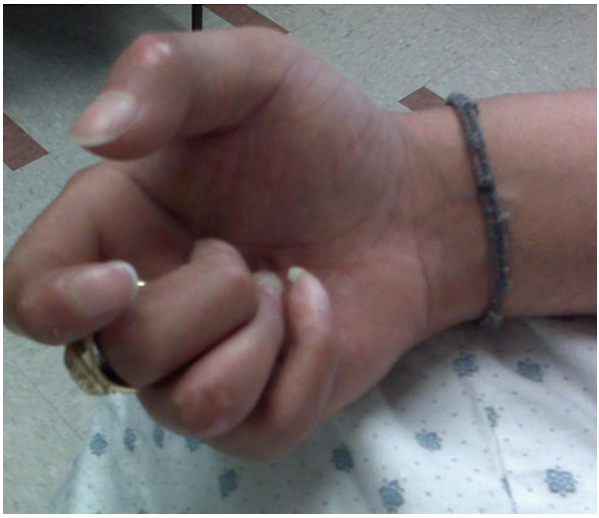

Fig. 3.18 Severe flexion contractures of the hands in an SSc patient with long-standing diffuse SSc. This is his maximal finger extension

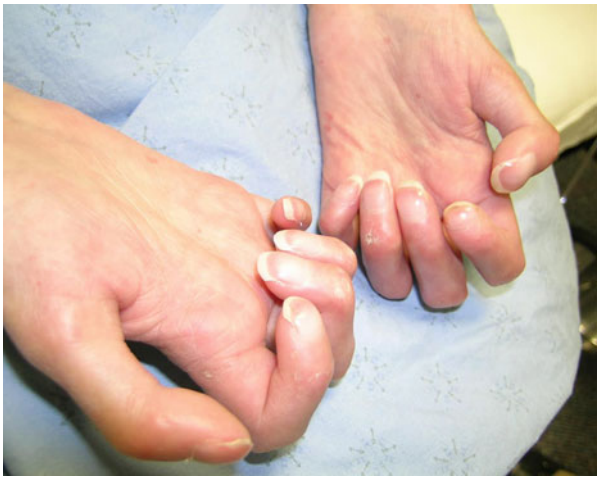

Fig. 3.19 Maximum extension of the fingers in this long-standing SSc patient. Note also that there is shortening of the tip of the left index finger tip (shortened nail of this finger)

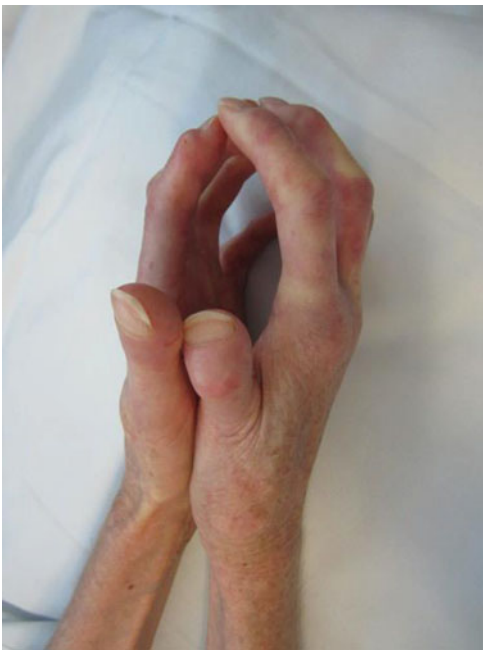

Fig. 3.20 Moderate flexion contractures in a patient with long-standing SSc

Treatment of the contractures is a difficult clinical challenge. Physical therapy and occupational therapy are essential to improve or maintain the range of motion [9].

Synovitis, Tenosynovitis, and Tendon Friction Rubs

Frequently the onset of SSc is heralded by a diffuse, persistent, and non-pitting swelling of the hands. Typically patients may report that they had to have their rings resized. The swelling may be accompanied by an uncomfortable dull aching sensation and it may be hard to identify underlying tenosynovitis or synovitis in the setting of this diffuse swelling.

The use of diagnostic ultrasound techniques has resulted in a new appreciation of synovial inflammation, as well as tenosynovitis in SSc. In the setting of diffuse hand swelling, ultrasound may provide guidance for treatment as it can reliably distinguish soft tissue swelling from true synovitis or tenosynovitis [10].

Palpable (and sometimes audible) tendon friction rubs occur primarily in early diffuse disease. They commonly occur at the wrist and ankles but can occur in multiple other areas as well. Treatment with anti-inflammatory medication may be needed if the friction rubs are painful.

Treatment of inflammation in SSc—synovitis, tenosynovitis, and tendon friction rubs—is problematic as these conditions are most common in early diffuse disease

at a time when it is best to avoid corticosteroids in doses of >10 mg a day due to the concern that higher doses may trigger SRC. If they are used—smallest dose for shortest period with careful home monitoring of BP. MTX may be helpful but clinical trials are mixed and the role of biologic therapy is unclear (for review, see [11]).

Conclusion

The recognition of SSc complications as depicted here can guide the clinician to the correct diagnosis and provide a guide to appropriate management.

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Chapter 4
Nailfold Capillaroscopy

Michael Hughes and Ariane L. Herrick

Abstract Microvascular abnormalities are a key feature of systemic sclerosis and typically occur early in the disease course. Nailfold capillaroscopy is a noninvasive clinically useful tool that can provide valuable information for the diagnosis and prognosis of primary Raynaud's disease and the scleroderma spectrum of autoimmune disorders. This chapter presents the diverse range of capillaroscopic abnormalities found in patients with SSc-spectrum disorders, and exemplifies the role of capillaroscopy in diagnosis and assessment.

Keywords Raynaud's phenomenon • Systemic sclerosis • Nailfold capillaroscopy • Videomicroscopy • Dermatoscope • Thermography

Introduction

Microvascular abnormalities are believed to be critical in the pathogenesis of systemic sclerosis (SSc), and occur early on in the disease course. These abnormalities can be visualized using the noninvasive technique of capillaroscopy, which may be considered a "window" into the microcirculation. Nailfold capillaroscopic abnormalities in SSc-spectrum disorders have been well described, the main abnormalities being dilated loops, areas of avascularity, hemorrhage, and distortion of the capillary architecture.

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Thus capillaroscopy is an invaluable investigation for the clinician to distinguish between primary and secondary Raynaud's phenomenon: normal capillaries are reassuring, whereas abnormal capillaries are suggestive of an underlying SSc-spectrum disorder. This is a critical distinction as both the management and prognosis of these patient groups is different.

Capillaroscopy can be performed using different techniques. Although most of the original work on capillaroscopy was performed using a widefield technique (magnification in the order of $\times 14$), advances in technology mean that more recently high magnification videocapillaroscopy (magnification in the order of $\times 200$) is being increasingly used. For clinicians without access to either of these methods, the nailfold capillaries can also be examined (albeit in less detail) using a dermatoscope or ophthalmoscope. This chapter will present the reader with a visually diverse range of capillaroscopic abnormalities found in patients with SSc-spectrum disorder, and exemplify the role of capillaroscopy in diagnosis and assessment. Images included were acquired using different methods: widefield capillaroscopy, videocapillaroscopy, and dermatoscopy. Clinical images (e.g., photographs and radiographs) and related investigations (e.g., thermograms) are also presented as appropriate to enrich the clinical scenarios.

Case 1

Scenario: A 17-year-old female with Raynaud's phenomenon and previous digital ulceration requiring several hospitalization for intravenous Iloprost (a prostacyclin vasodilator). She had a positive antinuclear antibody (ANA) of 1:1,000, no sclerodactyly and no proximal muscle weakness. Periungual erythema and visibly enlarged nailfold capillaries with hemorrhage were visible to the naked eye (Fig. 4.1).

Nailfold capillaroscopy (widefield technique) was abnormal with enlarged capillaries and multiple hemorrhages (Fig. 4.2), consistent with the diagnosis of SSc [1]. These appearances have been described as an "early" pattern ("early" = a small number of "giant" capillaries and hemorrhages, but no obvious loss of capillaries and relatively well-preserved capillary architecture [2]). The nailfold capillaroscopy appearances played a key role (in combination with her previous digital ulceration and positive ANA) in making the diagnosis of an SSc-spectrum disorder.

Case 2

Scenario: A 21-year-old female with an SSc-spectrum disorder (scleroderma, Raynaud's phenomenon, pulmonary interstitial fibrosis, anti-PM-Scl antibody, and elevated plasma creatinine kinase).

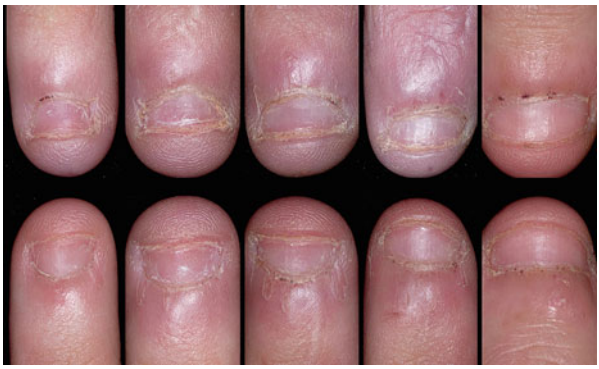

Fig. 4.1 Unmagnified view showing periungual erythema and visibly enlarged nailfold capillaries with hemorrhage [Copyright Salford Royal NHS Foundation Trust]

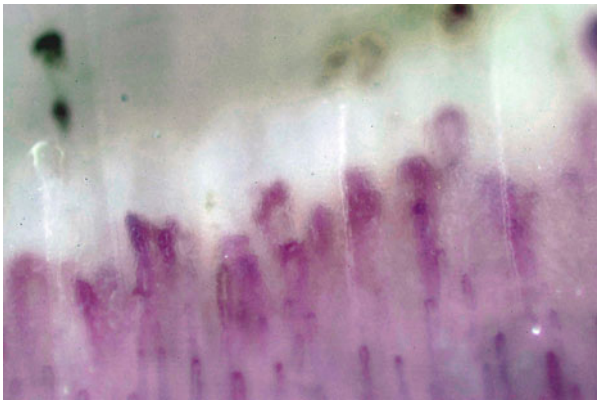

Fig. 4.2 Abnormal nailfold capillaries using the widefield technique with enlarged capillaries and multiple hemorrhages. This is an early pattern with a small number of giant capillaries and hemorrhages but no obvious loss of capillaries and relatively well-preserved capillary architecture [Copyright Salford Royal NHS Foundation Trust]

Nailfold capillaroscopy (widefield technique) (Fig. 4.3) was abnormal with areas of angiogenesis (also described as "bushy," "ramified," "arborized" capillaries). These appearances are characteristic of patients with a myositic component to their disease [3]. Gottron's papules (erythematous, raised papules over the metacarpal and interphalangeal joints) were seen on physical examination in keeping with an overlap with dermatomyositis (Fig. 4.4).

Case 3

Scenario: A 59-year-old female with limited cutaneous SSc (anti-centromere antibody) positive.

Videocapillaroscopy (×300 magnification) was abnormal with enlarged and giant capillaries (capillaries which are homogenously enlarged, with a diameter of greater than 50 μm) and areas of hemorrhage (Fig. 4.5). Videocapillaroscopy allows observers to measure capillary density and dimensions. An association

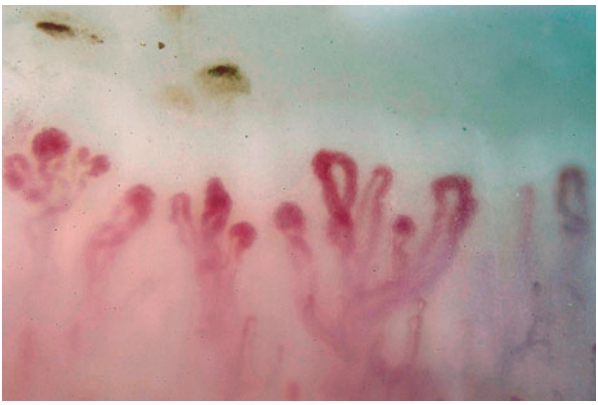

Fig. 4.3 Abnormal nailfold capillaries using the widefield technique demonstrating areas of angiogenesis (also described as "bushy," "ramified," "arborized" capillaries) which are characteristic of patients with a myositic component to their disease [Copyright Salford Royal NHS Foundation Trust]

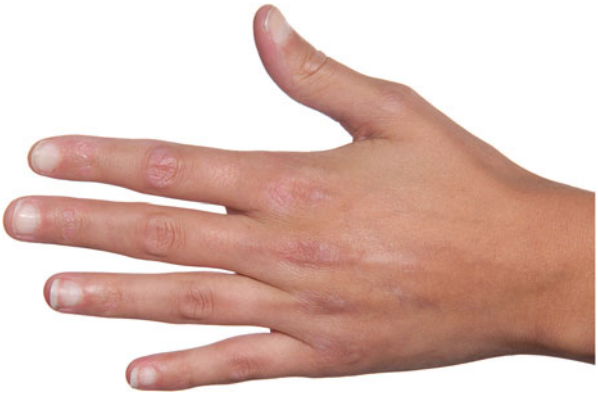

Fig. 4.4 Photograph of the hand of patient in Fig. 4.3 showing Gottron's papules: erythematous, raised papules over the metacarpal and interphalangeal joints [Copyright Salford Royal NHS Foundation Trust]

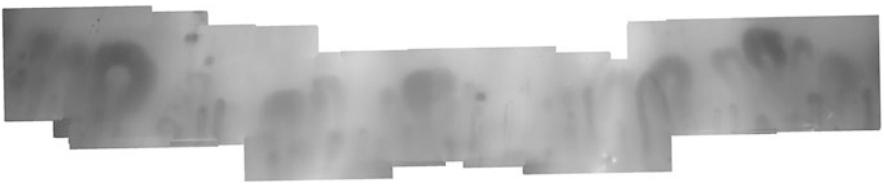

Fig. 4.5 Abnormal nailfold capillaries by videocapillaroscopy (×300 magnification) with enlarged and giant capillaries (capillaries which are homogenously enlarged, with a diameter of greater than 50 μm) and areas of hemorrhage [Copyright Salford Royal NHS Foundation Trust]

Fig. 4.6 Abnormal nailfold capillaries by widefield microscopy showing giant capillaries, areas of hemorrhage, and areas of avascularity [Copyright Salford Royal NHS Foundation Trust]

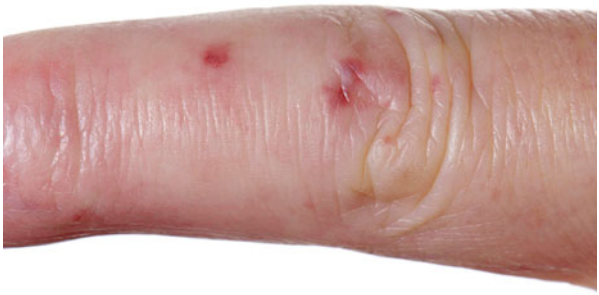

Fig. 4.7 The same patient as in Fig. 4.6 with finger and hand telangiectasias [Copyright Salford Royal NHS Foundation Trust]

between anti-centromere antibody positivity and the degree of capillary abnormality has been reported [4].

Case 4

Scenario: A 69-year-old female with limited cutaneous SSc (anti-centromere antibody positive) and a history of digital gangrene.

Nailfold capillaroscopy (widefield microscopy) (Fig. 4.6) showed giant capillaries, areas of hemorrhage, and areas of avascularity. She had widespread telangiectasias, including some on her fingers (Fig. 4.7), which are a very visible manifestation of the vasculopathy demonstrated on capillaroscopy. The degree of capillaroscopic abnormality has been associated with the severity of digital ischemia and telangiectasias, as well as with anti-centromere antibody [4], as well exemplified in this scenario.

Fig. 4.8 Abnormal capillaries with enlarged and giant capillary loops and areas of avascularity [Copyright Salford Royal NHS Foundation Trust]

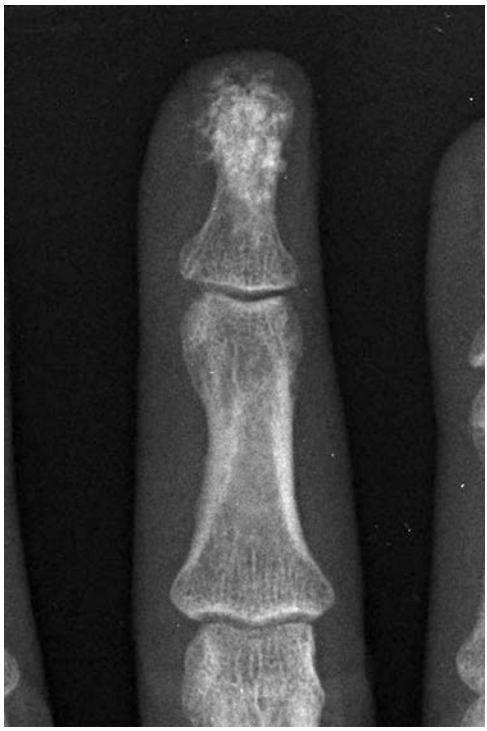

Fig. 4.9 Radiograph of the hand of the subject in Fig. 4.8 showing soft tissue calcinosis most obviously at the tip of the middle finger [Copyright Salford Royal NHS Foundation Trust]

Case 5

Scenario: A 65-year-old female with limited cutaneous SSc.

Capillaroscopy (Fig. 4.8) was abnormal with enlarged and giant capillary loops and areas of avascularity. Radiograph (Fig. 4.9) of the hands showed areas of

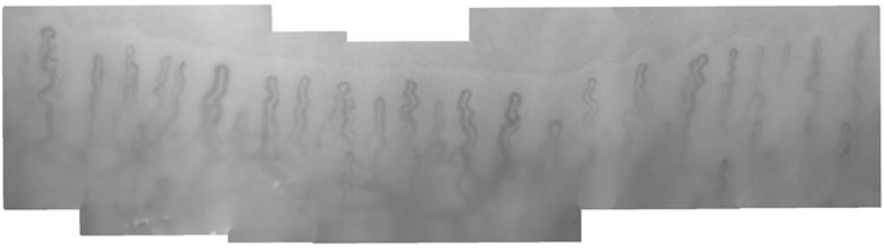

Fig. 4.10 Normal nailfold capillaries with regular "hair-pin" loops as seen by videocapillaroscopy (×300 magnification) [Copyright Salford Royal NHS Foundation Trust]

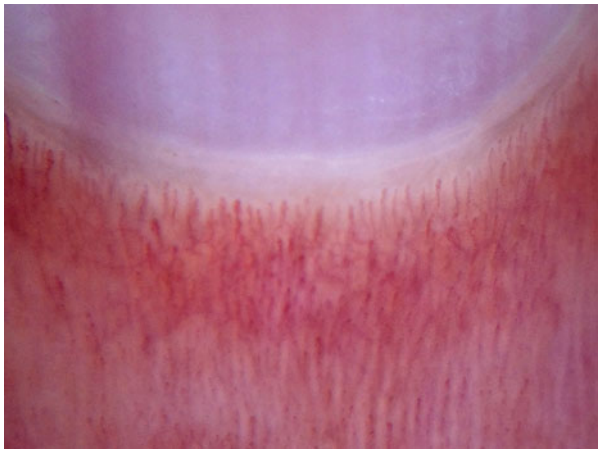

Fig. 4.11 Normal nailfold capillaries as demonstrated by dermoscopy (×10 magnification) [Copyright Salford Royal NHS Foundation Trust]

calcinosis (soft tissue calcification), most obviously at the tips of both middle fingers. An association between calcinosis and nailfold capillaroscopic changes has been reported [5], although this warrants further investigation.

Case 6

Scenario: A 35-year-old female with long-standing Raynaud's phenomenon, being assessed for an underlying SSc-spectrum disorder. Her ANA was negative.

Nailfold capillaries were normal, with regular "hair-pin" loops, as demonstrated by both videocapillaroscopy (×300 magnification) (Fig. 4.10) and dermoscopy (×10 magnification) [6, 7] (Fig. 4.11). The combination of the negative ANA and the normal nailfold capillaroscopy made an SSc-spectrum disorder highly unlikely [8, 9]: she was therefore reassured, given lifestyle advice and offered oral vasodilator treatment.

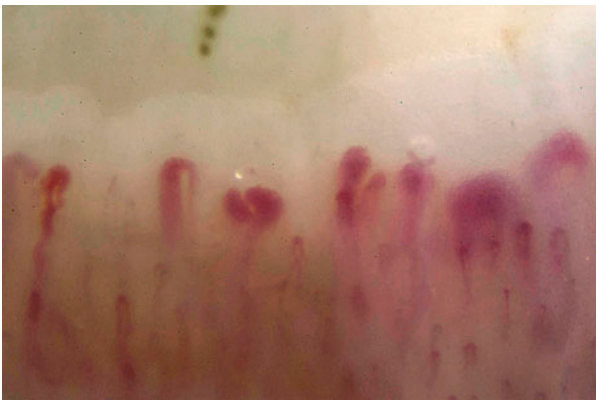

Fig. 4.12 Abnormal nailfold capillaries by widefield technique with dilated loops, areas of avascularity and some hemorrhages considered to represent an active phase of disease [Copyright Salford Royal NHS Foundation Trust]

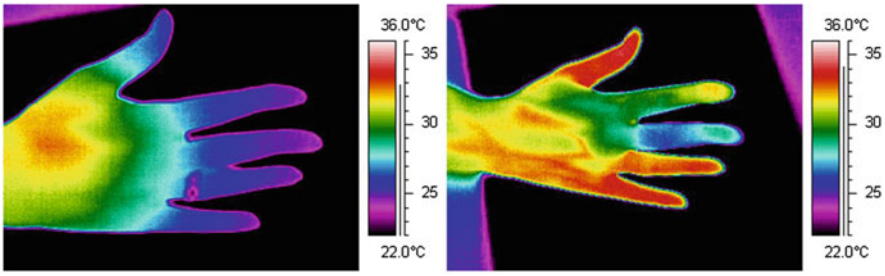

Fig. 4.13 Abnormal thermography of the hand in Fig. 4.12. The left image shows the fingers at 23 °C, the right image at 30 °C with persistence of the temperature gradient (>1 °C, fingertip cooler than dorsum) along the right middle finger. This persisting temperature gradient is consistent with the underlying structural vascular abnormality of SSc [Copyright Salford Royal NHS Foundation Trust]

Case 7

Scenario: A 46-year-old female with limited cutaneous SSc (Raynaud's phenomenon and positive anti-centromere antibody).

Nailfold capillaroscopy (widefield technique) (Fig. 4.12) was abnormal with dilated loops, areas of avascularity and some hemorrhages. These appearances have been described as "active" ("active" = frequent giant capillaries and hemorrhages, some capillary loss, and some distortion of the capillary architecture) [2]. Thermography (which measures surface temperature) was abnormal (Fig. 4.13—left image shows the fingers at 23 °C, the right image at 30 °C). In contrast to the previous patient, even at a room temperature of 30 °C there was a persisting temperature gradient (>1 °C, fingertip cooler than dorsum) along the right middle finger. This

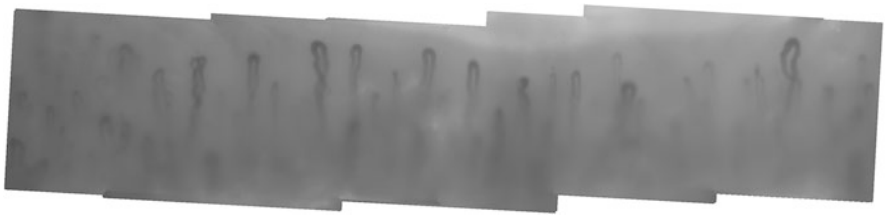

Fig. 4.14 Normal nailfold capillaries by videocapillaroscopy (×300 magnification) [Copyright Salford Royal NHS Foundation Trust]

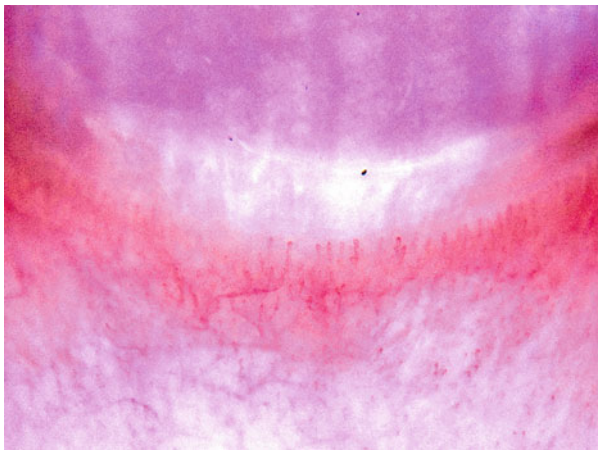

Fig. 4.15 Normal capillaries by dermoscopy (×10 magnification) [Copyright Salford Royal NHS Foundation Trust]

persisting temperature gradient (fingertip cooler) even at 30 °C is consistent with the underlying structural vascular abnormality of SSc [10].

Case 8

Scenario: A 31-year-old female with primary Raynaud's phenomenon (ANA negative).

Videocapillaroscopy (magnification ×300) (Fig. 4.14) and dermoscopy (magnification ×10) (Fig. 4.15) were normal which, combined with the negative ANA, were consistent with a diagnosis of primary Raynaud's phenomenon. Thermography (Fig. 4.16—left image shows the fingers at 23 °C, the right image at 30 °C), which measures surface temperature, was also consistent with primary Raynaud's phenomenon, showing complete reversal of the vasospastic response at 30 °C [10].

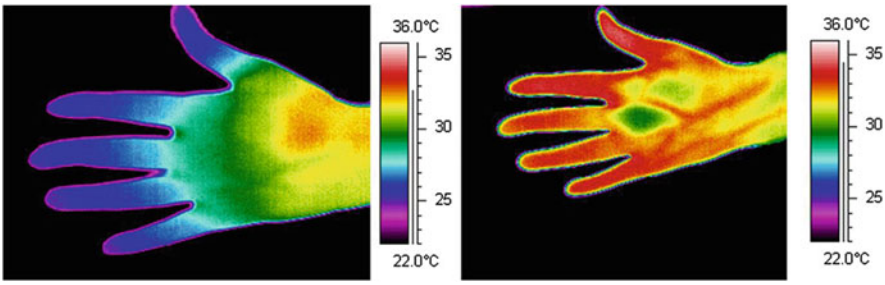

Fig. 4.16 The left image shows thermography of the fingers at 23 °C and the right image at 30 °C demonstrating complete reversal of the vasospastic response [Copyright Salford Royal NHS Foundation Trust]

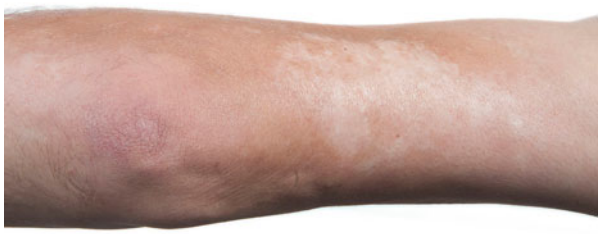

Fig. 4.17 Photograph of the upper limb demonstrating morphea [Copyright Salford Royal NHS Foundation Trust]

Case 9

Scenario: A 40-year-old male with a long history of Raynaud's phenomenon (ANA negative) and morphea of the upper limb (Fig. 4.17). The concern was that there might be underlying SSc.

Capillaroscopy (Fig. 4.18) was normal (widefield technique). This made the diagnosis of SSc unlikely, and the patient was reassured that his scleroderma was localized.

Case 10

Scenario: A 79-year-old female with limited cutaneous SSc (anti-centromere antibody-positive).

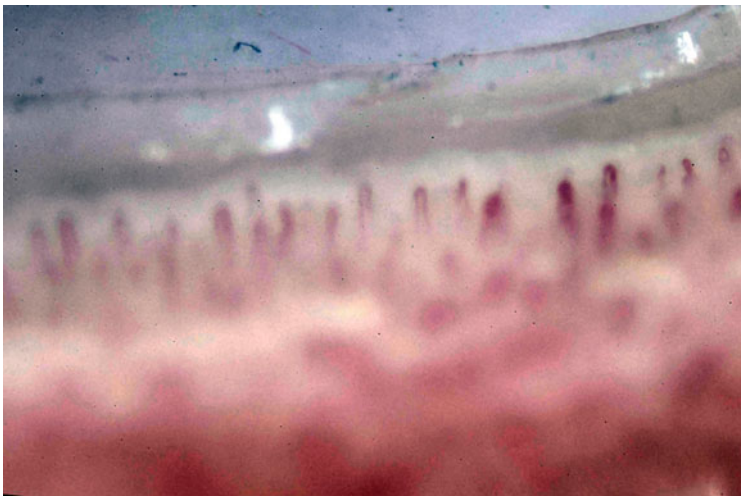

Fig. 4.18 Normal nailfold capillaroscopy using a widefield technique in the patient in Fig. 4.17 [Copyright Salford Royal NHS Foundation Trust]

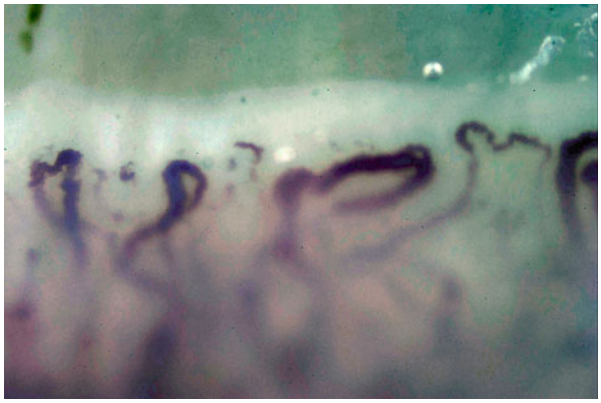

Fig. 4.19 Grossly abnormal capillaries utilizing the widefield technique with major disorganization of the capillary architecture and reduced capillary density, consistent with the "late" pattern of abnormality ("late" = giant capillaries and hemorrhages almost absent [although admittedly there were some hemorrhages in this case], severe capillary loss/avascularity, ramified/bushy capillaries, and distortion of the normal capillary architecture) [Copyright Salford Royal NHS Foundation Trust]

Capillaroscopy (widefield technique) (Fig. 4.19) was grossly abnormal with a major disorganization of the capillary architecture and reduced capillary density, consistent with the "late" pattern of abnormality ("late" = giant capillaries and hemorrhages almost absent [although admittedly there were some hemorrhages in this case], severe capillary loss/avascularity, ramified/bushy capillaries, and distortion of the normal capillary architecture) [2].

Fig. 4.20 Abnormal capillaries by videocapillaroscopy (×300 magnification) with areas of avascularity, some distortion of the normal capillary architecture and one angiogenic ("bushy") capillary [Copyright Salford Royal NHS Foundation Trust]

Fig. 4.21 Photograph of the hand from the subject in Fig. 4.20 showing flexion deformities of the fingers and healing ulcers resulting in impairment in hand function [Copyright Salford Royal NHS Foundation Trust]

Case 11

Scenario: A 39-year-old female with diffuse cutaneous SSc and severe digital vasculopathy with recurrent digital ulceration (ANA of 1:1,000 with a positive anti Scl-70 antibody).

Videocapillaroscopy (×300 magnification) (Fig. 4.20) was abnormal with areas of avascularity, some distortion of the normal capillary architecture and one angiogenic ("bushy") capillary. On physical examination, there were flexion deformities of the fingers and healing ulcers resulting in impairment in hand function (Fig. 4.21). The severity of nailfold capillary abnormality may be a predictor of digital ulceration [11, 12].

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Chapter 5
Ischemic Digital Ulcers

Fredrick M. Wigley

Abstract Systemic sclerosis (scleroderma) is unique among the rheumatic diseases because a widespread obliterative vasculopathy exists involving the peripheral arteries and microcirculation. Various forms of digital ulceration and tissue breakdown are recognized. This chapter illustrates these different lesions by presenting representative examples of each type.

Keywords Raynaud's phenomenon • Digital ulcers • Tissue ischemia • Vasculopathy • Amputation • Macrovascular disease • Fissure

Introduction

Systemic sclerosis (scleroderma) is unique among the rheumatic diseases because a widespread obliterative vasculopathy exists involving the peripheral arteries and microcirculation [1, 2]. Vascular changes involving capillaries, arterioles, and small arteries are well documented. Macrovascular disease in larger peripheral arteries is also common [3]. Pathological specimens from digital vessels demonstrate striking intimal thickening with marked luminal narrowing and evidence of thrombi, while the smooth muscle of the media is usually normal. The involved vessels normally are important in both tissue nutrition and body thermoregulation. Raynaud's phenomenon is often the initial clinical manifestation of this peripheral vascular disease (Figs. 5.1 and 5.2). The abnormal response to cold and stress is caused by the abnormalities in the regulation of regional blood flow in the skin and digits.

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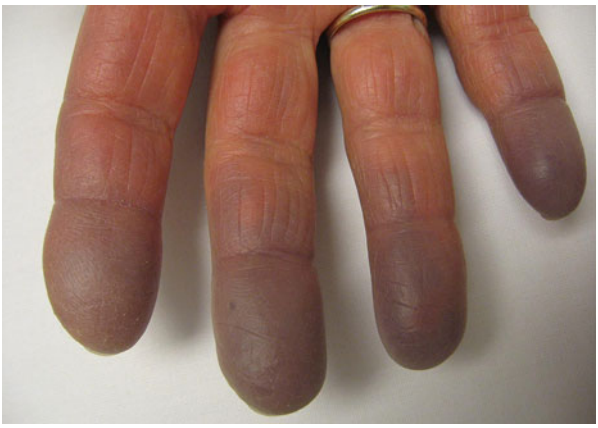

Fig. 5.1 The Cyanotic phase of Raynaud's phenomenon due to vasospasm and reduced blood flow in the cutaneous arterioles and capillaries of the fingers

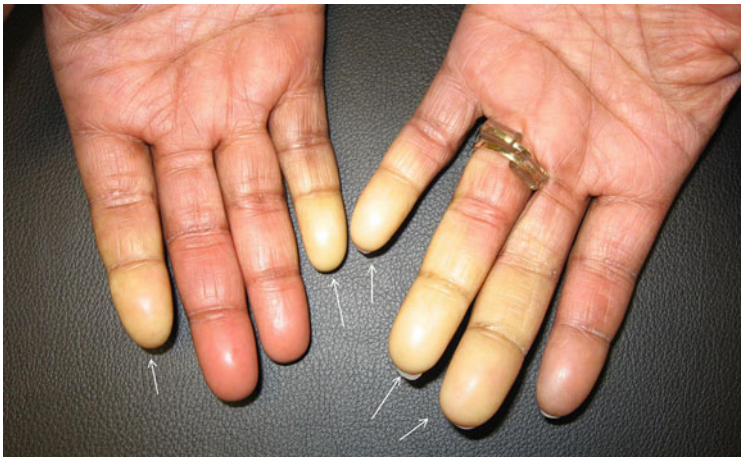

Fig. 5.2 The Pallor phase of Raynaud's phenomenon due to reversible vascular closure of digital arteries and cutaneous arterioles in involved fingers (see *arrows*)

Scleroderma is also associated with fibrotic skin, especially of the fingers. Fibrotic skin changes in association with the peripheral vascular disease lead to skin hypoxia, critical ischemia, and eventual tissue injury. Digital ulcers are reported in about 25–50 % of patients with scleroderma [4]. Prolonged critical ischemia can cause deep tissue injury and digital loss. Digital amputation secondary to occlusion of digital arteries occurs in a subset of (about 11 %) patients, usually with limited skin disease with the presence of anti-centromere antibody [5].

Various forms of digital ulceration and tissue breakdown are recognized (Figs. 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17,

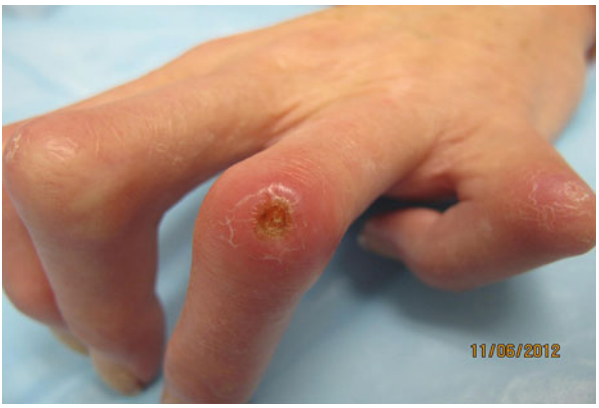

Fig. 5.3 Cutaneous ulcer at the site of a contracture of a proximal interphalangeal (PIP) joint in a patient with diffuse cutaneous scleroderma. These lesions occur due to trauma at the site of a joint contracture due to overlying fibrotic and avascular skin and soft tissue. In late stages of scleroderma, the skin is fragile due to secondary thinning and atrophy of subcutaneous tissue

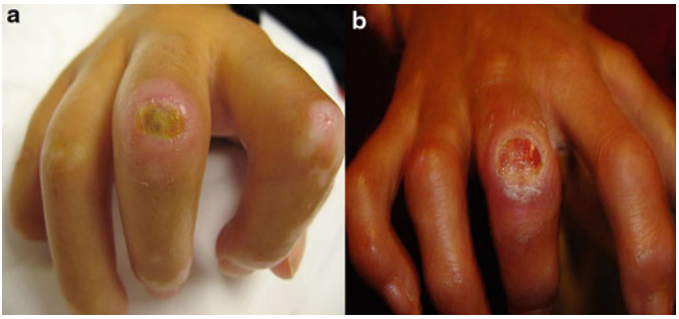

Fig. 5.4 Cutaneous ulcer at site of a contracture of the proximal interphalangeal (PIP) joint in patients with late diffuse cutaneous scleroderma. Lesion (**a**) is superficial with dry crusted exudate and no signs of secondary infection. Lesion (**b**) is deep and there is associated healthy granulation tissue in it, the ulcer bed

5.18, 5.19, 5.20, 5.21, 5.22, 5.23, 5.24, 5.25, and 5.26). These include distal digital ischemic ulcers secondary to digital artery and skin arteriole disease; breakdown of islands of skin on the digits due to microvascular occlusion in fibrotic skin; skin fissures due to drying of skin surface; ulcerations at the site of joint contractures where fragile skin is easily traumatized; deep tissue injury leading to gangrene; and loss of digits due to macrovascular occlusion of major peripheral arteries in the arm, palm, or fingers. Similar events occur in the lower extremities. This chapter illustrates these different lesions by presenting representative examples of each type of lesion.

Treatment of these lesions includes vasodilators, protection from repeated trauma, and attention to good wound care [6–8].

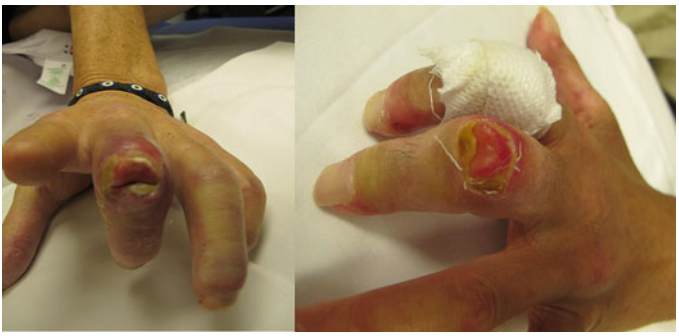

Fig. 5.5 Deep ulcerations at proximal interphalangeal (PIP) joint of a patient with late diffuse cutaneous scleroderma. Note that the joint capsule is exposed due to the large wound in the overlying avascular skin. Skin grafting or amputation is needed in such cases

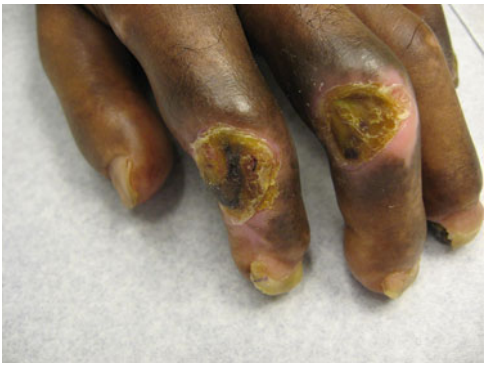

Fig. 5.6 Ulcerations on the proximal interphalangeal (PIP) joint of the fingers of a patient with diffuse scleroderma. Note the crusted exudate without signs of secondary infection. These wounds are caused by injury to areas of fibrotic and avascular skin in joint contracture area subject to trauma

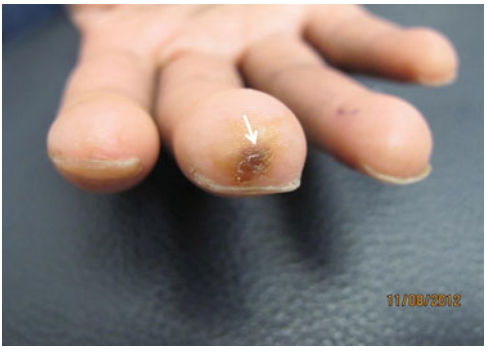

Fig. 5.7 Distal ischemic area of finger of patient with scleroderma. This lesion will likely develop into a shallow ulcer due to small vascular disease in the finger and skin arterioles

Fig. 5.8 Digital ulcer due to vascular compromise and tissue ischemia. This lesion is present in a patient with limited scleroderma. Note the deep ulcer has no signs of infection and is located on the distal finger typical of an ischemic ulcer due to closure of digital arteries and cutaneous arterioles

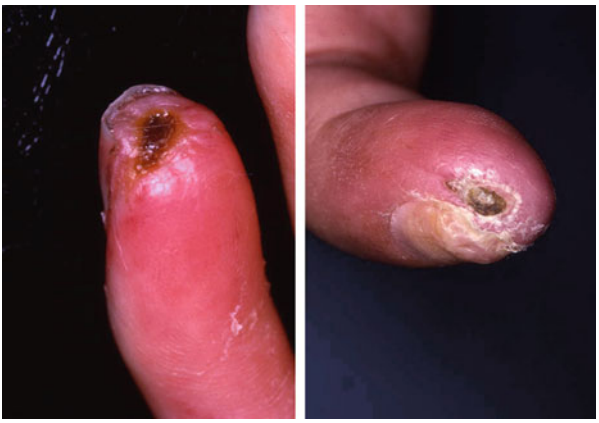

Fig. 5.9 Examples of relative small vascular disease secondary to scleroderma causing ischemic digital ulcers. These lesions will improve over several weeks and may be prevented with vasoactive drugs

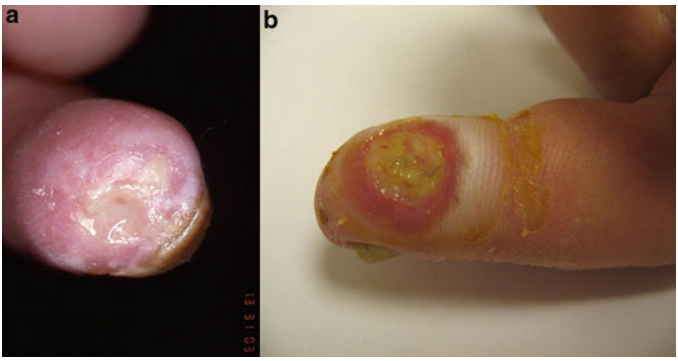

Fig. 5.10 Digital ulcers in a patient with limited scleroderma due to vascular compromise and tissue ischemia. Lesion (**a**) is deep with modest exudate, while lesion (**b**) has surrounding erythema suggesting expanding area of ischemia and/or superimposed infection. The location on the distal palmer finger is typical of an ischemic ulcer due to closure of digital arteries and cutaneous arterioles

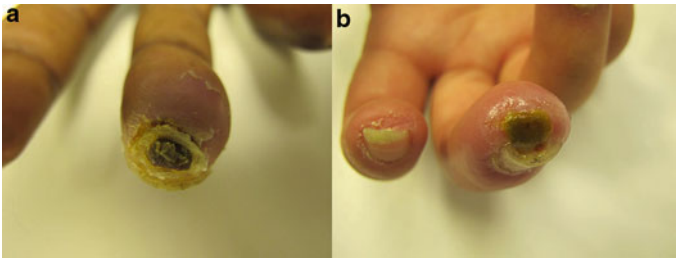

Fig. 5.11 Digital ischemic ulcers on distal fingers of patients with scleroderma. Note both ulcer lesions (**a**) and (**b**) are covered with cap-crusted dried exudate. There are no signs of infection

Fig. 5.12 A patient with limited scleroderma presents with digital lesion typical of superficial infarction of distal finger. Note the areas of dry gangrene without signs of secondary infection. Ulceration of the tissue found under this dry blackened tissue. These lesions are secondary to digital artery disease with vascular occlusion

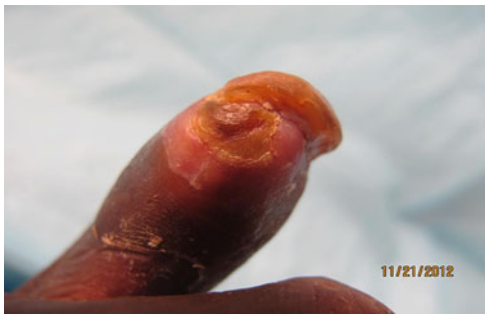

Fig. 5.13 Healing ischemic digital ulcer on distal thumb in a patient with scleroderma. Raynaud's phenomenon and/or digital ulcers on the thumb are a manifestation of an underlying secondary vascular disease. The thumb is often spared in patients with primary Raynaud's phenomenon

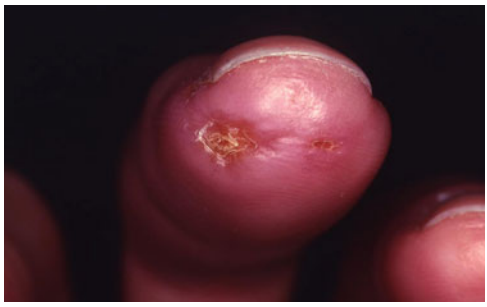

Fig. 5.14 This is an example of a digital pit typical of a healed ischemic event seen in patients with scleroderma. These events are secondary to small vessel disease in the digital and cutaneous circulation

Fig. 5.15 Healed distal ulcer in a patient with scleroderma. Superficial lesions often leave painless crusted dry material at site of lesion with small pitting of skin

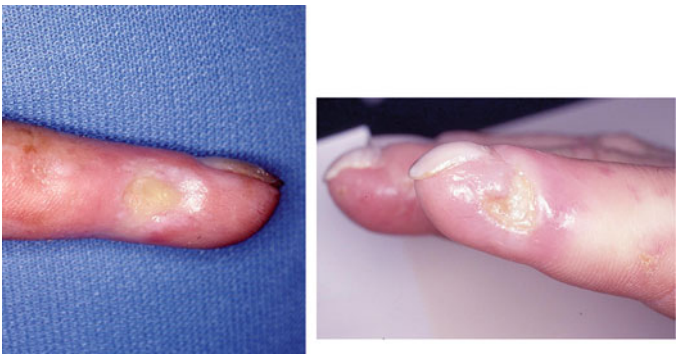

Fig. 5.16 Note the shallow ulcer on the lateral finger of these patients with scleroderma. These lesions represent small vessel disease in the skin of the distal finger. Often these lesions expand along the shaft of the finger following areas of fibrotic and avascular skin

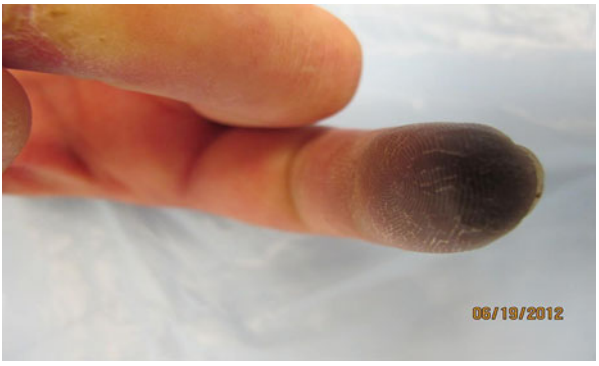

Fig. 5.17 Patient with acute distal finger ischemia due to digital artery vasospasm and impending occlusion. This type of presentation is seen prior to deep tissue infarction that will occur if blood flow to the finger is not improved

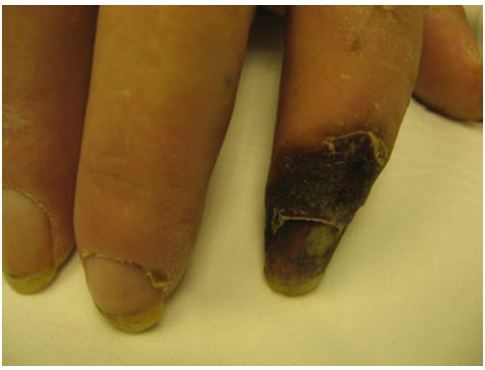

Fig. 5.18 Major digital artery occlusion has lead to distal infarction of finger in a patient with limited scleroderma. Note the sharp demarcation defining level of tissue perfusion. Patients with anti-centromere antibodies are at increased risk for these larger vessel occlusions and subsequent digital amputation

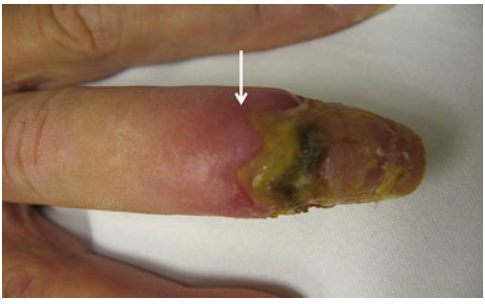

Fig. 5.19 Patient with limited scleroderma with digital artery occlusion leading to infarction of distal finger. Note area (see *arrow*) of hyperemia representing Ischemic area with vasodilated small cutaneous vessels attempting to limit further tissue injury

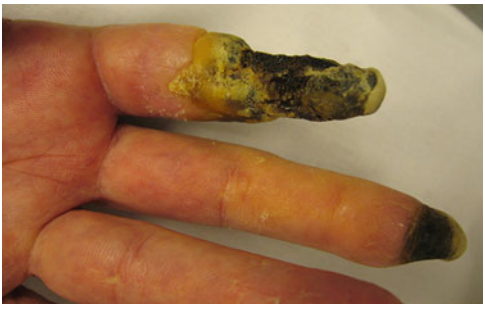

Fig. 5.20 Major artery disease in a patient with limited scleroderma leading to deep tissue infarctions. This type of event leads to amputation of the distal finger. Patients with anti-centromere antibody are at increased risk for these larger vessel events

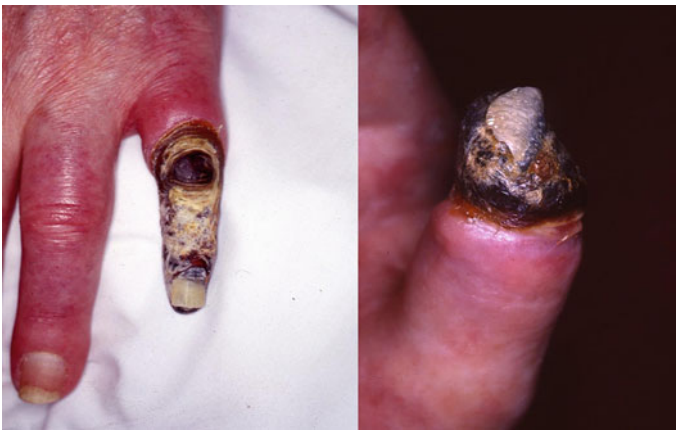

Fig. 5.21 Two examples of larger digital artery occlusion leading to deep tissue injury and dry gangrene. These lesions are completed and amputation beyond the area of the demarcation will result

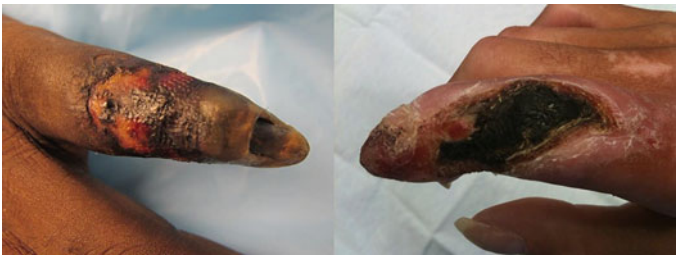

Fig. 5.22 Deep and superficial digital tissue infarctions in patients with scleroderma. This type of presentation is secondary larger digital artery disease coupled with compromise in the cutaneous arterioles

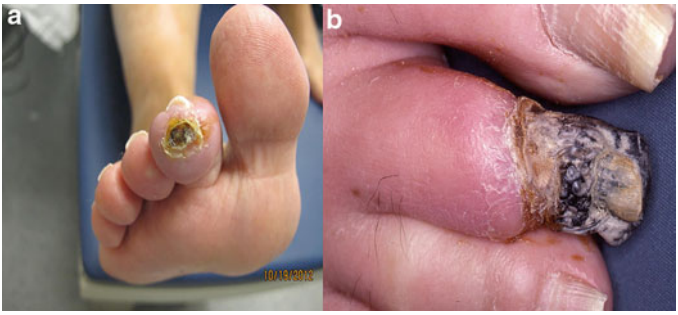

Fig. 5.23 Digital lesions of the toes in patients with scleroderma. Note lesion (**a**) is a small vessel-occlusive event typical of an ischemic ulcer on distal toe. Lesion (**b**) is due to larger digital artery disease and is often associated with macrovascular disease in the distal limb. In both cases Doppler ultrasound was used to rule out any correctable proximal larger vessel lesion

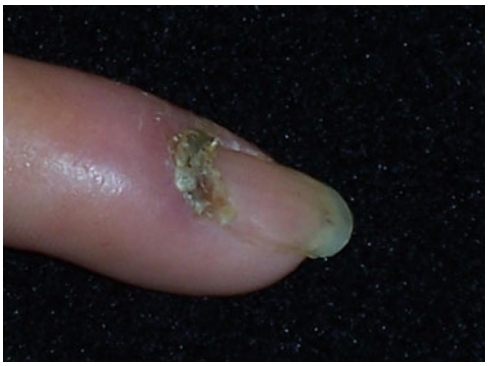

Fig. 5.24 Paronychia lesion due to small vessel disease in the nailfold. This is seen in this patient with diffuse scleroderma and is often associated with soft tissue infection

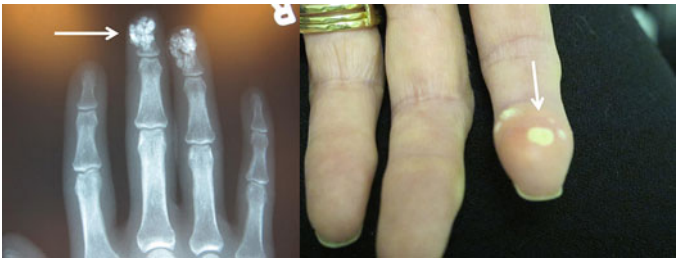

Fig. 5.25 Areas of subcutaneous calcinosis in distal fingers of patients with scleroderma mimicking digital ischemic ulcer. The X-ray (*left*) demonstrates a cluster of calcium hydroxyapatite in the subcutaneous tissue. The clinical picture (*right*) shows the hard white lumps of calcium under the skin. These lesions can spontaneously drain, cause local Inflammation, or they can ulcerate and get secondarily infected. Surgical removal can be done if problematic

Fig. 5.26 Fingers of patient with limited scleroderma with painful fissure (see *arrow*). Note the areas of cyanosis consistent with compromised blood flow due to ongoing vasospasm of cutaneous arterioles. Fissures are often mistaken for Ischemic ulcers but most commonly occur due to dry fibrotic skin

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Chapter 6
Lung Involvement in Systemic Sclerosis

John T. Huggins, James G. Ravenel, and Richard M. Silver

Abstract Thoracic manifestations of systemic sclerosis (SSc) are common, occurring in some form in nearly all patients in both limited and diffuse SSc subsets. Most SSc-related mortality is now attributed to end-stage lung disease. All patients with SSc should be screened for the development of ILD and pulmonary hypertension at the time of diagnosis and periodically thereafter. Early diagnosis and appropriate therapy (immunosuppression for ILD and specific vasodilator therapy for pulmonary hypertension) show promise for improved prognosis.

Keywords Interstitial lung disease • Usual interstitial pneumonia • Nonspecific interstitial pneumonia • Pericardial effusion • Esophagus • Cardiomyopathy • Pulmonary veno-occlusive disease • Pulmonary function test • Forced vital capacity • Diffusing capacity for carbon monoxide

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Introduction

Thoracic manifestations of systemic sclerosis (SSc) are common, occurring in some form in nearly all patients. It is important to note that pulmonary complications may occur in SSc patients who might be classified as diffuse cutaneous SSc, limited cutaneous SSc or even in SSc patients without overt skin involvement (SSc *sine* scleroderma). The lungs, including the parenchyma and vascular supply, the heart, and the esophagus are often affected by the fibrosis and vasculopathy that characterizes SSc. Most SSc-related mortality is now attributed to end-stage lung disease, either pulmonary fibrosis and/or pulmonary arterial hypertension. At autopsy or by high resolution chest computed tomography, approximately 90 % of SSc patients will have evidence of interstitial lung disease (ILD). Survival in these patients has been inversely correlated to the degree of restrictive ventilatory defect on pulmonary function testing (PFT). For patients with minimal to no restriction, the 10-year survival was 87 %, compared to a survival rate of 75 % and 58 % in patients with moderate and severe restriction, respectively. All patients with SSc should be screened for the development of ILD and pulmonary hypertension at the time of diagnosis and periodically thereafter. PFT is an essential, noninvasive means to detect the presence of SSc-related pulmonary complications. For SSc-related ILD, nonspecific interstitial pneumonitis followed by usual interstitial pneumonitis is the most common histopathologic finding. Esophageal involvement often leads to the development of a poorly contracting esophagus, which in turn may predispose the patient to chronic aspiration. The lack of coordinated peristalsis results in symptoms of dysphagia, phagodynia, peptic esophagitis, cough, Barrett metaplasia, and to frank fibrotic strictures. Cardiac manifestations of SSc include pericarditis with or without pericardial effusion, myocarditis, myocardial fibrosis, coronary artery disease, and arrhythmias. Symptoms of cardiac involvement include nonspecific chest pain, palpitations, dyspnea, and orthopnea.

Case 1 (Fig. 6.1)

Forty-eight-year-old woman with a long history of limited cutaneous SSc, Raynaud's phenomenon, and telangiectasias presented with the insidious onset of progressive dyspnea on exertion. Mediastinal windows on chest CT at the level of the pulmonary outflow tract is shown. Pulmonary artery (red arrow) is dilated with a diameter larger than the corresponding ascending aorta (blue arrow) (see Fig. 6.1a). This meets CT criteria for the possibility of underlying pulmonary arterial hypertension, which was ultimately confirmed by right heart catheterization. Figure 6.1b, c is the corresponding lung windows. In Fig. 6.1b, note the basilar changes present on the supine image as compared to prone image in Fig. 6.1c. Most of the changes seen on the supine image in the right lower lobe (red arrow) cleared with prone positioning (blue arrow). Lung atelectasis often occurs in basilar regions on supine

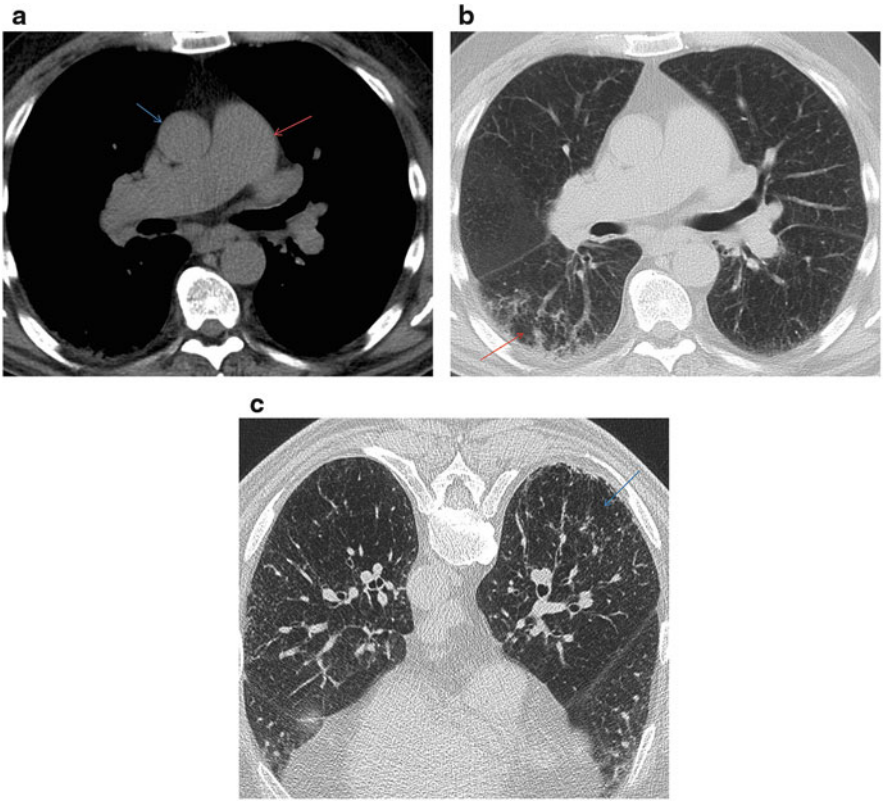

Fig. 6.1 (continued)

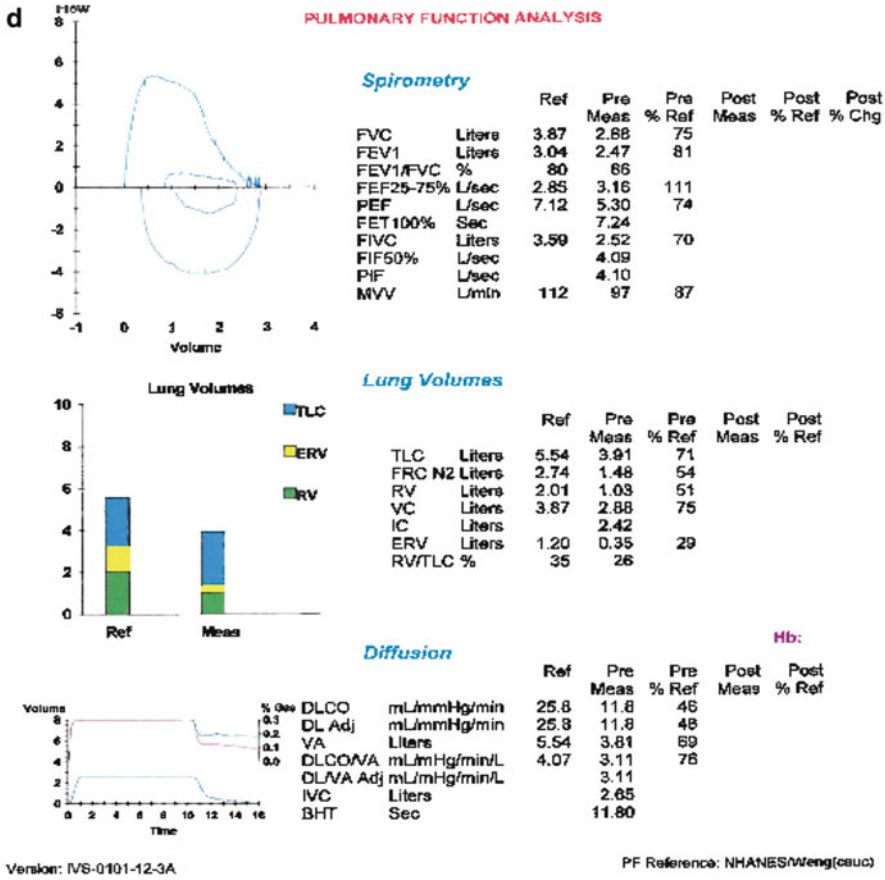

Fig. 6.1 (**a**) A mediastinal window on chest CT at the level of the pulmonary outflow tract is shown. Pulmonary artery (*red arrow*) is dilated with a diameter larger than the corresponding ascending aorta (*blue arrow*). (**b**, **c**) High resolution chest CT taken in a supine position. Please note the basilar changes present on the supine image would suggest the presence of interstitial lung disease. However, with prone positioning (**c**), most of the changes seen on the supine image (**b**) in the right lower lobe (*red arrow*) cleared. This was due to lung atelectasis often occurs in basilar regions on supine. (**d**) Complete pulmonary function data is shown. Spirometry is suggestive of mild restriction with a reduction of FVC and increased FEV1/FVC ratio calculated at 0.86. Lung volumes confirm mild restriction with a TLC of 71 % predicted. Diffusing capacity for carbon monoxide is substantially reduced at 46 % of predicted

chest CT scans and may be misinterpreted as findings of ILD; however, when the radiographic changes clear with prone imaging, they are due to gravitational effects with associated lung atelectasis and not due to ILD. High resolution chest CT (HRCT) is the modality of choice for the evaluation of a patient with a clinical suspicion of ILD and requires both thin collimation (1 mm slice thickness) and a detail or lung reconstruction algorithm. Modern HRCT protocols incorporate a whole lung volumetric acquisition. Important adjuncts include expiratory images to assess for air trapping and prone images to clear any gravitational changes from the lung bases. These adjuncts are usually performed at three levels (e.g., aortic arch, tracheal carina, and top of diaphragms) as a survey rather than separate whole lung acquisitions. Figure 6.1d shows the PFT for this case. The flow-volume loop is consistent with restriction. Spirometry is suggestive of a restrictive defect with the noted finding of a forced expiratory volume 1 second (FEV1)/forced vital capacity (FVC) ratio >0.7 and a FVC % predicted <80 % of predicted.

Case 2 (Fig. 6.2)

Thirty-eight year old man with limited cutaneous SSc who presents with progressive dyspnea on exertion. Mediastinal windows on chest CT show a dilated pulmonary artery (red arrow), which is larger than the corresponding aorta (red arrow) (see Fig. 6.2a). At the level of the heart, marked right atrial enlargement is seen (blue arrow) and the right ventricle is larger than the left ventricle (see Fig. 6.2b). An RV/LV ratio of greater than 1 at the level of the atrioventricular valves is highly suggestive of right ventricular pressure overload. Lung windows show diffuse ground glass nodules present throughout the lung (see Fig. 6.2c). These nodules are located in the centrilobular region of the lung. Such centrilobular nodules are seen in up to 25 % of patients with pulmonary arterial hypertension. Another pattern seen on chest CT in patients with PAH is termed mosaic perfusion. Mosaic perfusion represents a subset of mosaic attenuation characterized by differing lung attenuation on CT. The three major pathologic causes of this pattern are pulmonary vascular, small airways, and primary parenchymal disease. These entities can be differentiated on CT by correlating inspiratory with expiratory images and evaluating the pulmonary vasculature. The mosaic pattern can be explained by a nonuniform distribution of disease. In pulmonary vascular disease, hypoperfused lung appears lower in attenuation than adjacent normal or hyperperfused lung. Similarly, in small airways disease, regional variations in the presence of air trapping lead to a patchwork of low-attenuation lung that is interposed with normally ventilated higher-attenuation lung. The differences in attenuation are accentuated on expiratory imaging. Conversely, in parenchymal disease, the higher-attenuation lung is abnormal, and stands in contrast with adjacent normal lower-attenuation lung to produce a patchwork mosaic pattern. In this case vessels are normally distributed and similar in size throughout normal and abnormal lung. The relative difference in lung density does not change at expiratory imaging.

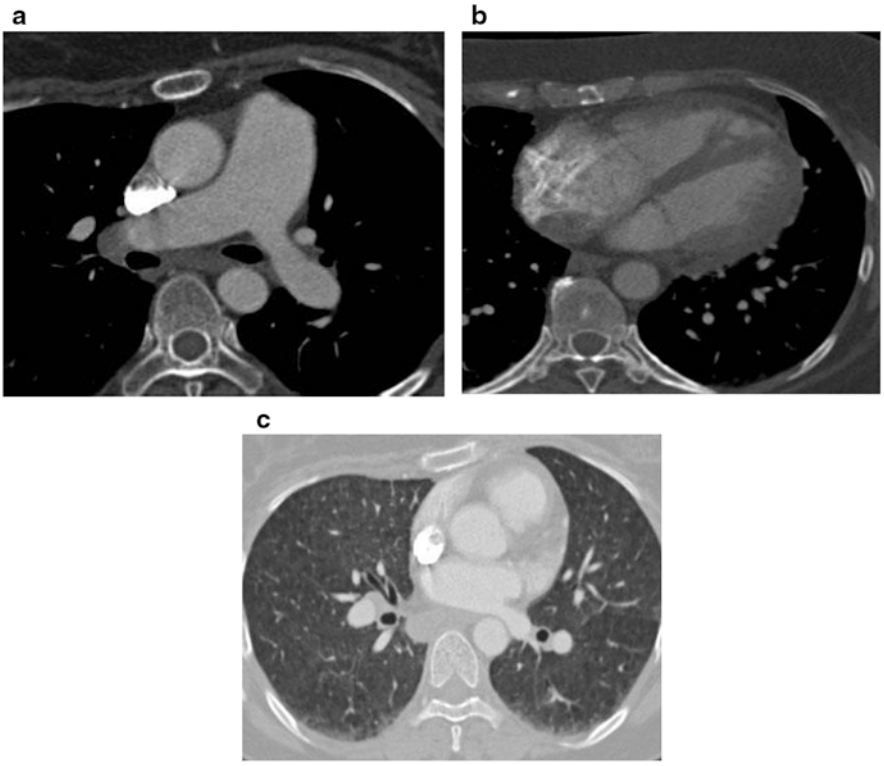

Fig. 6.2 (**a**) Mediastinal windows on chest CT show a dilated pulmonary artery (*red arrow*), which is larger than the corresponding aorta. (**b**) At the level of the heart, marked right atrial enlargement is seen (*blue arrow*) and the right ventricle is larger than the left ventricle. An RV/LV ratio of greater than 1 at the level of the atrioventricular valves is highly suggestive of right ventricular pressure overload. (**c**) Lung windows on chest CT show diffuse ground glass nodules present throughout the lung. These nodules are located in the centrilobular region of the lung

The histopathological correlation of centrilobular nodules in PAH is unknown; however, some have suggested that the presence of cholesterol granulomas may explain the development of these radiographic findings. The development of cholesterol granulomas in the setting of PAH may be due to recurrent alveolar hemorrhage and the breakdown of surfactant proteins. However, the presence of pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemagiomatosis may present with similar findings of centrilobular nodules and evidence of pulmonary arterial hypertension. Although the development of PVOD occurs with some frequency in SSc, it is not known if all cases of scleroderma-related PAH cases with the radiographic finding of centrilobular nodules are related to the presence of underlying PVOD. Response to PAH-specific therapies and prognosis of PAH in the presence of the centrilobular nodules appear to be worse.

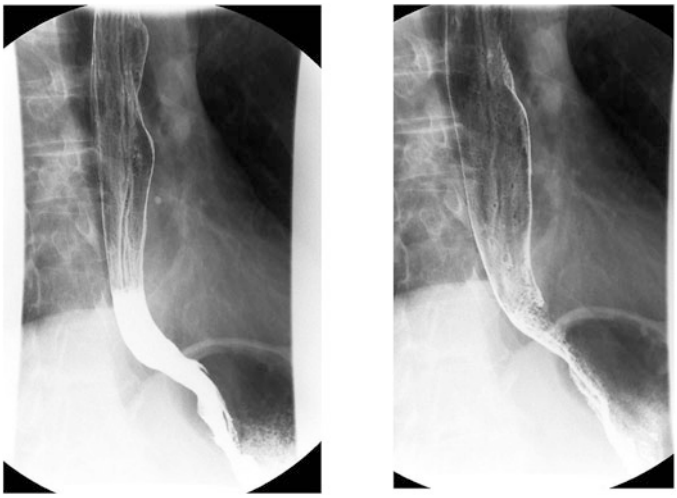

Fig. 6.3 (**a**) The barium swallow shows a patulous esophagus with poor peristalsis. (**b**) Gastrointestinal involvement is the third most commonly affected organ system in scleroderma

Case 3 (Fig. 6.3)

Thirty-eight-year-old woman with diffuse cutaneous SSc who is referred for a barium swallow for the evaluation of severe dyspepsia and heartburn. The barium swallow shows a patulous esophagus with poor peristalsis. Gastrointestinal involvement is the third most commonly affected organ system, with Raynaud's phenomenon and skin involvement being more common in scleroderma. The GI tract may be involved in 40–45 % of patients with esophageal involvement in up to 80 % of patients. The muscularis portion of the esophagus becomes progressively replaced with collagen. The net result is the development of a poorly contracting esophagus which dilates. The lack of coordinated peristalsis results in dysphagia, peptic esophagitis, cough, Barrett metaplasia, and sometimes frank fibrotic strictures. In some cases, GERD-related symptoms may be silent despite significant esophageal pathology.

Case 4 (Fig. 6.4)

Forty-year-old man with diffuse cutaneous SSc who presents with cough and progressive shortness of breath. Mediastinal windows on chest CT show a circumferential pericardial effusion (red arrow) (see Fig. 6.4a). Lung window shows evidence of mild ILD. Note the presence of intralobular septal thickening (see Fig. 6.4b). Pericardial disease is present in up to 50 % of SSc patients at autopsy. It is usually clinically silent and benign, and typically does not evolve to pericardial tamponade or pericardial restriction. However, the development of cardiac

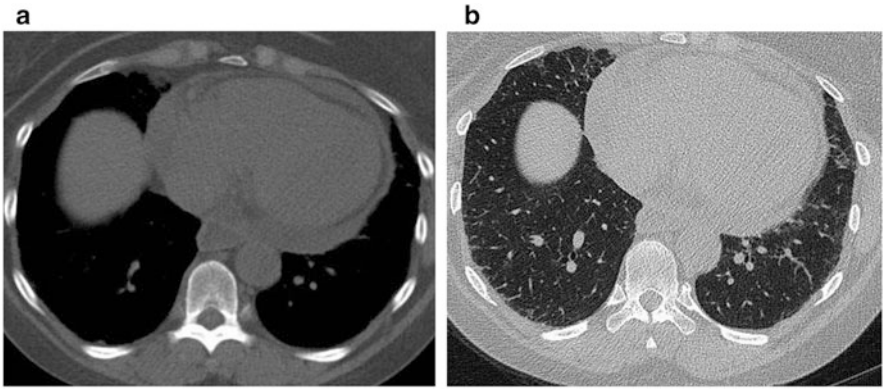

Fig. 6.4 (**a**) A mediastinal window on chest CT shows a circumferential pericardial effusion (*red arrow*). (**b**) Lung window on chest CT shows evidence of mild ILD. Note the presence of intralobular septal thickening

tamponade has been described in SSc patients presenting with large pericardial effusions. Pericardial effusions are frequently observed in PAH and could be the radiographic manifestation for the development of PAH in scleroderma. The development of systemic venous hypertension affects the development of pericardial effusions while the development of pulmonary venous hypertension will cause the development of pleural effusions. Attempts to drain large pericardial effusions in the setting of significant PAH have been associated with an increase in hemodynamic compromise and death.

Case 5 (Fig. 6.5)

Thirty-eight-year-old man with history of Raynaud's phenomenon and sclerodactyly who presents with a nonproductive cough and progressive shortness of breath. ANA was positive at 1:1,280 with a nucleolar pattern, and anti-Scl 70 antibodies were also present. PFTs are shown in Fig. 6.5a. Flow/volume loop shows restriction. On spirometry, FEV1/FVC ratio is normal at 0.84 with a reduced FVC 1.44 L (44 % predicted). This spirometric pattern is consistent with a severe restrictive defect. Lung volumes confirmed moderately severe restriction with a total lung capacity of 2.30 L (50 % predicted). Diffusing capacity for carbon monoxide was severely reduced at 37 % of predicted. HRCT of the chest is shown in Fig. 6.5b. Subpleural reticulations with minimal ground glass opacities are noted in the left lower lobe (white arrow). In the right lower lobe, traction bronchiectasis is noted (purple arrow). This HRCT of the chest is consistent with the fibrotic phase of nonspecific interstitial pneumonia (NSIP). In contrast, a different SSc patient is shown having a usual interstitial pneumonia (UIP) pattern. HRCT of the chest shows extensive honeycombing in the lower lobes (blue arrow)

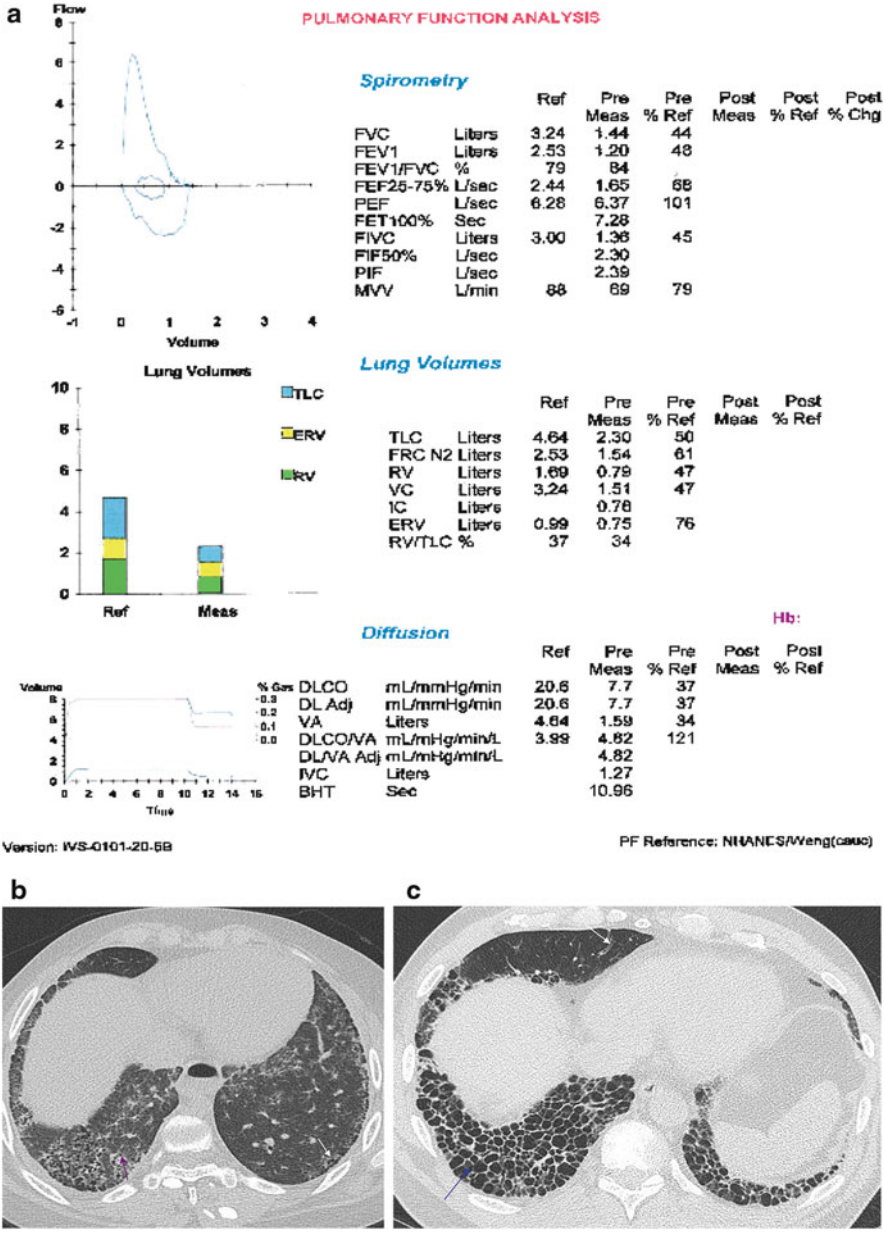

Fig. 6.5 (**a**) Pulmonary function tests are shown. The flow/volume loop shows restriction. On spirometry, FEV1/FVC ratio is normal at 0.84 with a reduced FVC 1.44 L (44 % predicted). This spirometric pattern is consistent with a severe restrictive defect. Lung volumes confirmed moderately severe restriction with a total lung capacity of 2.30 L (50 % predicted). Diffusing capacity for carbon monoxide was severely reduced at 37 % of predicted. (**b**) HRCT of the chest shows subpleural reticulations with minimal ground glass opacities noted in the left lower lobe (*white*

and traction bronchiectasis (white arrow) (see Fig. 6.5c). The presence of traction bronchiectasis and honeycombing are radiographic clues to the presence of pulmonary fibrosis.

Evidence of parenchymal pulmonary lung disease is found in over 80 % of patients with SSc, and is second only to esophageal involvement as a visceral complication in scleroderma. Pulmonary involvement is the leading cause of death in SSc. The most common SSc-related ILD patterns are nonspecific interstitial pneumonitis (NSIP) followed by UIP. Certain SSc-related autoantibodies have been associated with the development of SSc-associated ILD, including anti-topoisomerase 1 (also known as anti-Scl-70), anti-U3 ribonucleoprotein (RNP), anti-U11/U12 RNP, anti-Th/To, and antihistone antibodies. HRCT findings of NSIP pattern include ground glass opacities in a peripheral distribution with a basilar predilection (cellular form of NSIP). While ground glass opacities have been thought to represent an "active" form of disease, it is recognized that many cases will not resolve on radiographic follow-up. The presumption in these cases is that the ground glass represents fibrosis at the level of the intralobular septa and alveolar wall rather than an inflammatory exudate. This is particularly true when ground glass opacities are seen in the same area as traction bronchiectasis and/or honeycomb lung. The subpleural area may be uninvolved. As the disease progresses, there is volume loss with increased reticulations and traction bronchiectasis (fibrotic form of NSIP). The honeycomb pattern is rarely seen in NSIP, but is often noted in the UIP form. The UIP pattern shows bibasilar reticular pattern associated with traction bronchiectasis and fine honeycomb pattern, which can coalesce into larger cystic airspaces as the UIP pattern progresses. In a rare pattern, centrilobular fibrosis can be seen on HRCT. In this pattern, consolidative opacities and ground glass opacities form along the central airway. Recurrent aspiration seems to be a significant contributor to this pattern.

Cyclophosphamide therapy in SSc-ILD patients with dyspnea, evidence of restriction, and ground glass opacities on HRCT has been associated with modest improvement in FVC (% predicted) [1] as well as with improvement in quantitative lung fibrosis by HRCT scan [2].

Fig. 6.5 (continued) arrow). In the right lower lobe, traction bronchiectasis is noted (*purple arrow*). This HRCT of the chest is consistent with the fibrotic phase of nonspecific interstitial pneumonia (NSIP). (**c**) In contrast, a different SSc patient is shown having a usual interstitial pneumonia (UIP) pattern. HRCT of the chest shows extensive honeycombing in the lower lobes (*blue arrow*) and traction bronchiectasis (*white arrow*)

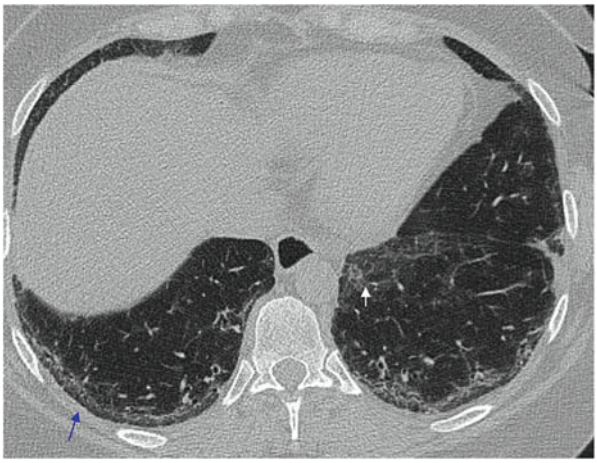

Fig. 6.6 HRCT of the chest is shown. Subpleural bands with increased reticulations are noted (*purple arrow*). Mild ground glass opacities are noted in the LLL (*white arrow*)

Case 6 (Fig. 6.6)

Twenty-five-year old man with known history of diffuse cutaneous SSc presents with progressive dyspnea on exertion. PFTs were notable for moderate restriction and a reduced diffusing capacity for carbon monoxide. HRCT of the chest is shown. Subpleural bands with increased reticulations are noted (purple arrow). Mild ground glass opacities are noted in the LLL (white arrow). This patient was treated with low-dose prednisone therapy and 12 months of cyclophosphamide with improvement in dyspnea and FVC.

Case 7 (Fig. 6.7)

Thirty-two-year-old woman with a known history of SSc *sine* scleroderma (a term reserved for patients having only internal organ involvement without skin sclerosis) presented with a history of palpitations, weight gain, and lower extremity edema. On physical examination, jugular venous pressure was increased and Kussmaul sign was present. Cardiac MRI was performed and shown in Fig. 6.7a–c. In Fig. 6.7a, there is relative enlargement of the right atrium and right ventricle. Infiltrative disease/myocardial fibrosis is best detected on a delayed phase MRI following gadolinium administration. As opposed to ischemic changes which are typically subendocardial, the delayed enhancement in infiltrative disease is seen in the mid myocardial wall and is usually patchy in distribution. Figure 6.7b, c shows two different displays of the delayed enhancement sequences. Note the patchy high signal in the intraventricular septum (arrows).

Cardiac manifestations occurring in scleroderma include pericarditis with or without pericardial effusion, myocarditis, myocardial fibrosis, coronary artery

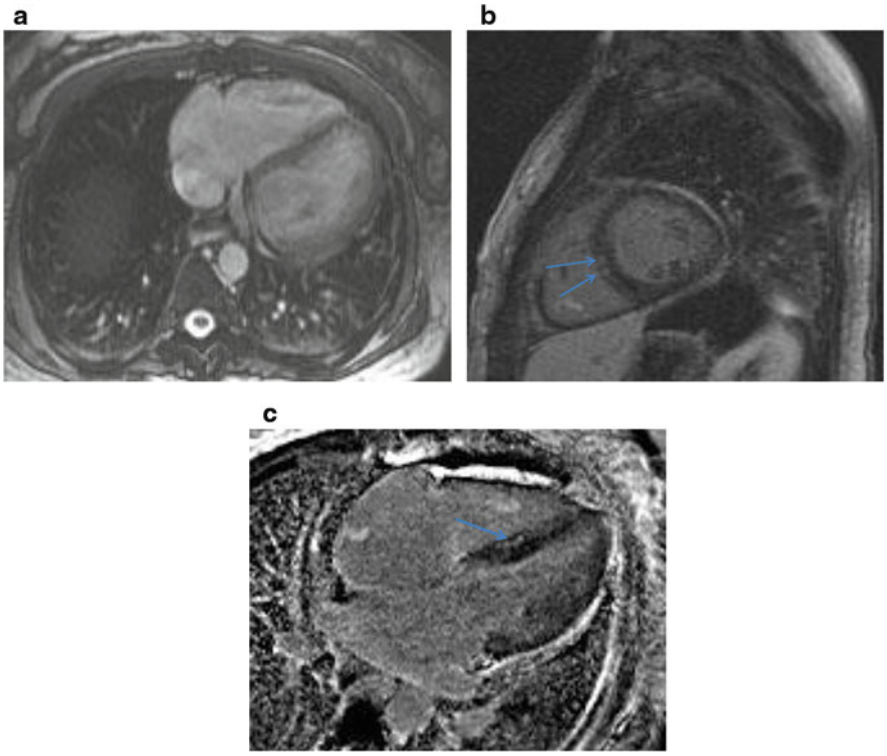

Fig. 6.7 (**a**) Cardiac MRI shows enlargement of the *right atrium* and *right ventricle*. Infiltrative disease/myocardial fibrosis is best detected on a delayed phase MRI following gadolinium administration. As opposed to ischemic changes which are typically sub-endocardial, the delayed enhancement in infiltrative disease is seen in the mid-myocardial wall and is usually patchy in distribution. (**b**, **c**) Cardiac MRI shows two different displays of the delayed enhancement sequences. Please note the high signal in the intra-ventricular septum (*arrows*)

disease, and arrhythmias. Symptoms due to cardiac involvement are nonspecific and include nonspecific chest pain, palpitations, dyspnea, and orthopnea. However, the development of Kussmaul sign is highly suggestive of a constrictive/restrictive cardiomyopathy. Infiltrative processes leading to the development of myocardial fibrosis in the setting of SSc may result in the development of a dilated or restrictive cardiomyopathy. Myocardial fibrosis may be seen in up to 90 % of SSc cases at autopsy. Heart failure associated with left ventricular dysfunction may improve with systemic steroid therapy; however, most cases of SSc-related restrictive cardiomyopathies appear to be recalcitrant to medical therapy.

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Chapter 7
Gastrointestinal Involvement in Systemic Sclerosis

Dinesh Khanna, Jason Baker, Philip J. Clements, and Christopher P. Denton

Abstract Involvement of the gastrointestinal tract (GIT) occurs in approximately 90 % of patients with systemic sclerosis (SSc) and has a major impact on quality of life. This visual guide provides images of SSc-associated GIT involvement to aid the clinician in the recognition, diagnosis, and treatment of these complications.

Keywords Systemic sclerosis • Scleroderma • Gastrointestinal involvement • Dysmotility • Gastric antral vascular ectasia • GAVE • Watermelon stomach • Pseudo-obstruction • Pneumatosis intestinalis • Barium study

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Introduction

Involvement of the gastrointestinal tract (GIT) occurs in approximately 90 % of patients with systemic sclerosis (SSc) and has a major impact on quality of life [1]. Every part of the GIT can be involved in SSc, including the mouth (xerostomia), esophagus (dysmotility, acid reflux), stomach (vascular ectasia, gastroparesis), intestines (vascular lesions, hypomotility, bacterial overgrowth, pseudo-obstruction), and anorectal system (fecal incontinence). This visual guide provides images of SSc-associated GIT involvement to aid the clinician in the recognition and treatment of these complications.

Esophagus

Gastroesophageal Reflux Disease (GERD)

Although heartburn is the most common symptom of GERD, other symptoms can occur including odynophagia, mouth ulcers, substernal chest pain, chronic laryngitis, chronic nocturnal cough, and asthma [2].

Figure 7.1 is a barium swallow study that shows dilatation of the esophagus (left hand panel) related to loss of smooth muscle with subsequent impaired peristalsis and distention. The right hand panel of Fig. 7.1 shows an esophageal stricture caused by chronic acid reflux resulting in scar formation and retraction. Figure 7.2 is a high resolution computerized tomographic (HRCT) image of the thorax that shows an air fluid level in the esophagus in an SSc patient who also has interstitial lung disease (ILD).

Esophageal manometry assesses the motor function of the esophagus both quantitatively and qualitatively and is used to clinically diagnose esophageal motor function [3]. The addition of the impedance measurement tracks the actual position of the bolus within the esophagus. Figure 7.3 illustrates a normal swallow with a depiction of the impedance related to the bolus. The red color indicates pressures greater than 100 mmHg while yellow to blue indicates pressures ranging from 0 to 40 mmHg. There is normal upper esophageal sphincter resting pressure and coordinated muscle relaxation as indicated by a pressure comparable to esophageal resting pressure. As the bolus enters the esophagus, the upper and lower esophageal sphincters relax initiating the starting point of esophageal peristalsis. The contractions of the stratified muscle fibers in the upper esophageal body propel the bolus through the transition zone into the lower esophageal body. The contractions of the smooth muscle fibers within the lower esophageal body produce the pressure needed to propagate the bolus through the relaxed lower esophageal sphincter into the stomach.

Scleroderma has been associated with smooth muscle atrophy of the distal portion of the esophagus [4] with preservation of striated muscle in the upper

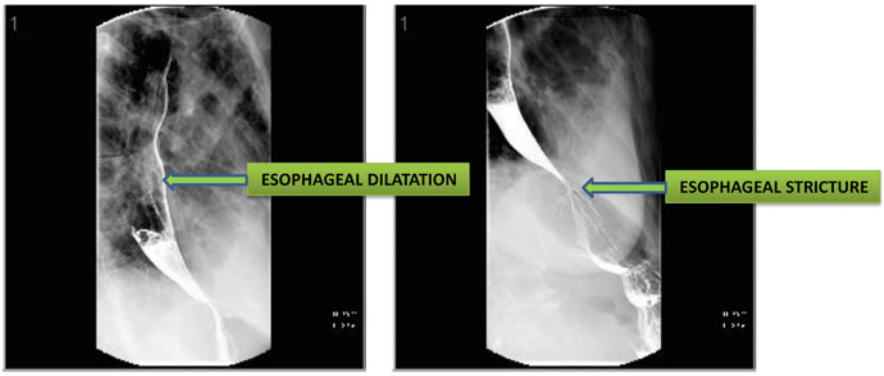

Fig. 7.1 Barium swallow showing esophageal dilatation (*left*) and stricture formation (*right*)

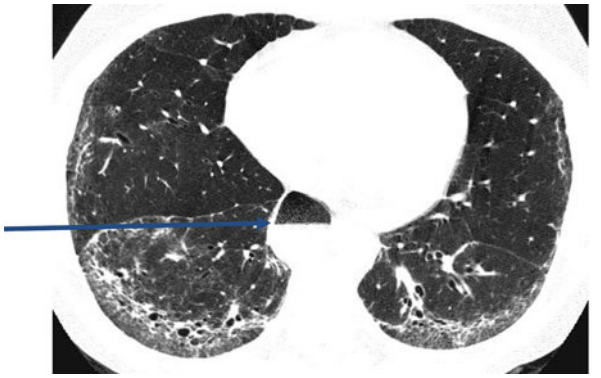

Fig. 7.2 Chest HRCT showing dilated esophagus with an air fluid level in an SSc patient who also has ILD (arrow denotes air fluid level)

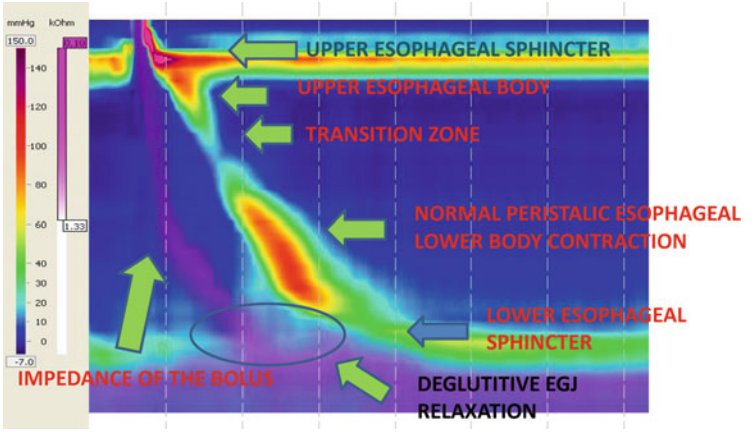

Fig. 7.3 High resolution manometry with impedance: normal; normal UES resting pressure and coordinated relaxation; normal peristaltic pattern; complete bolus clearance; *LES* normal resting pressure and coordinated relaxation

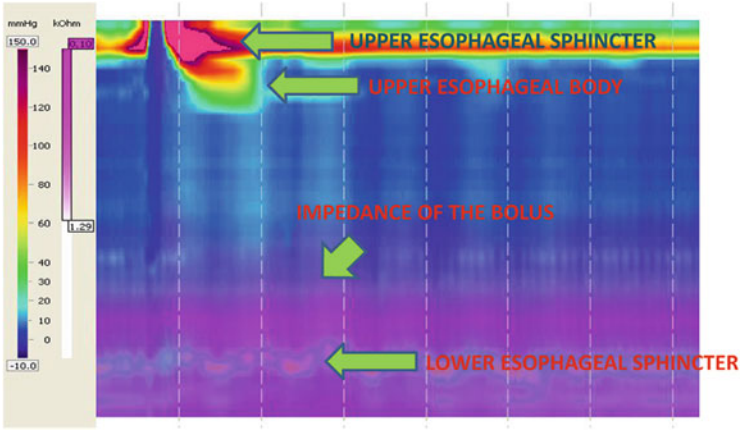

Fig. 7.4 High resolution manometry with impedance: scleroderma patient; *UES* normal pressures; failed peristalsis; failed clearance of bolus; *LES* low sphincter pressure

esophagus. Figure 7.4 illustrates these abnormalities in a manometry study of a scleroderma patient. Following normal relaxation of the upper esophageal sphincter and a contraction representing peristalsis within the upper esophagus body, the lower esophageal body depicts minimal to nonexistence lower esophageal body peristalsis. Furthermore, the lower esophageal sphincter elicits marginal relaxation.

The bolus is retained in the esophagus rather than emptying into the stomach through the LES.

Esophageal manometry in scleroderma typically shows either low amplitude of contractions in the distal esophagus or total loss of contractions (esophageal aperistalsis as illustrated in Fig. 7.4) with diminished lower esophageal pressure [5].

Treatment of GERD consists of anti-reflux measures and proton-pump inhibitors (PPIs) to control symptoms and to prevent complications of peptic esophagitis. While medications such as PPIs can control esophageal acid exposure, they do not eliminate non-acid reflux which is frequently associated with non-heartburn symptoms such as nocturnal cough, bronchospasm, etc., as listed above. Anti-reflux measures include elevation of the head of the bed, not eating within 2–3 h of bedtime, avoidance of carbonated beverages and acid-stimulating foods, etc. If symptoms continue despite behavior changes (anti-reflux precautions) and maximum doses of PPIs, pro-kinetics may be useful [6].

Stomach

Gastroparesis and GAVE

Gastroparesis can also occur in SSc [6, 7] and such delayed gastric emptying can worsen reflux. For gastroparesis, patients should be advised to eat frequent small meals and avoid lactose-containing products (e.g., milk). Again, prokinetic therapy may be effective in increasing GI motility.

Gastric antral vascular ectasia (GAVE or watermelon stomach) is an endoscopic finding defined as dilated submucosal blood vessels in the antrum that radiate from the pylorus like the stripes of a watermelon. Figure 7.5 is an image taken on upper gastrointestinal endoscopy that shows the dilated blood vessels in the typical striped "watermelon" pattern.

For GAVE, which typically presents with iron deficiency anemia due to occult blood loss, endoscopic therapy using lasers or electro-coagulation techniques or other ablation approaches is usually needed. Most patients require more than one session but long-term outcomes are generally good.

Small Bowel

Intestinal dysmotility has been reported in 40–88 % of patients with SSc. Figure 7.6 shows a barium study of the small bowel demonstrating the multiple thin folds of the bowel wall with a wire-spring appearance. This figure also shows the delayed transit time as barium collects throughout the small bowel. The dysmotility can lead to bacterial overgrowth syndrome, intestinal pseudo-obstruction, and pneumatosis intestinalis (also known as pneumatosis cystoides intestinalis) with gas in the bowel wall on X-ray [8].

Bacterial Overgrowth Syndrome

Small intestinal bacterial overgrowth (SIBO) syndrome is caused by stasis of the intestinal contents, resulting in proximal migration and colonization of bacteria from the colon into the small bowel. These bacteria break down bile acids which then can no longer solubilize fats for absorption leading to excess gas production, steatorrhea, and weight loss. Symptoms include bloating and malabsorptive diarrhea associated with weight loss in spite of, or out of proportion to, dietary intake. Episodes of diarrhea typically last several days and can be followed by periods of constipation in a cyclic fashion. What differentiates SIBO from irritable bowel syndrome is the more prolonged periods of diarrhea and the associated weight loss in SSc which is not usually seen with irritable bowel patients.

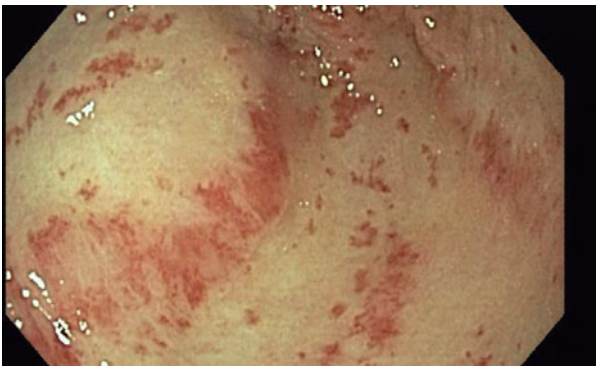

Fig. 7.5 Gastric antral vascular ectasia

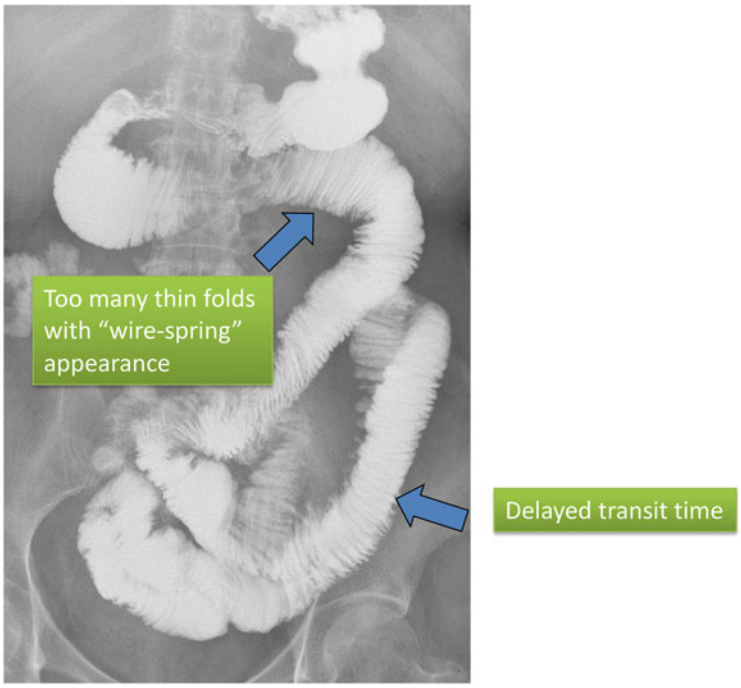

Fig. 7.6 Scleroderma involvement of the bowel on barium study

For characteristic cases, diagnosis can be made on clinical grounds and empiric antibiotic treatment may be initiated with symptom improvement/resolution being considered confirmatory. When the diagnosis is not clear-cut, studies such as a hydrogen/methane breath test can be done. In this procedure, the patient breathes into a balloon at baseline and expired air is analyzed for hydrogen and/or methane. A sugary liquid (glucose or lactulose) is then given and expired air collected at

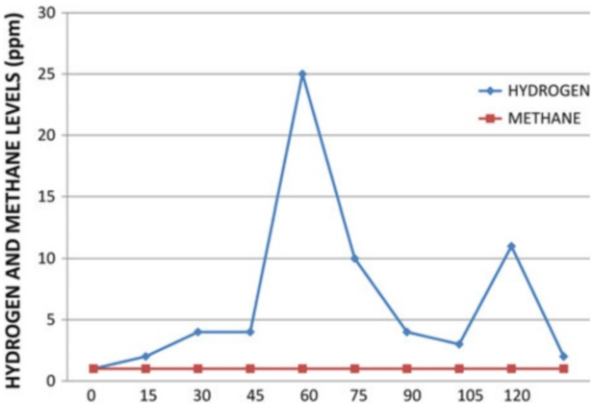

Fig. 7.7 Hydrogen Breath Test for SIBO: positive

frequent intervals over the next 2–3 h. The test is considered positive if there is an early increase (over baseline) in hydrogen or methane as the small bowel bacteria break down the sugar.

Figure 7.7 shows a positive hydrogen breath test in an SSc patient with hydrogen producing bacterial overgrowth in the small bowel. Baseline levels of hydrogen and methane in expired air are typically in the 1–5 ppm range (time zero on the *x*-axis). A peak of hydrogen production is shown at 60 min (25 ppm on the *y*-axis) corresponding to bacterial breakdown of the sugar solution in the small bowel, followed by a smaller peak of expired hydrogen at 120 min as the sugar reaches the large bowel. In this example, the bacteria do not produce methane so the expired methane concentration remains low.

Treatment approaches for SIBO include broad-spectrum antibiotics for 2–4 weeks to assess the improvement in symptoms, especially of bloating and diarrhea [9]. Some patients may require cyclic antibiotics at varying frequencies. Rotating different antibiotics is often done to prevent bacterial resistance. It is also recommended that patients receive standard doses of a multivitamin along with calcium and vitamin D supplements [4]. Additional nutritional support should be guided by laboratory tests. In severe cases total parenteral nutrition may be required.

Probiotics have been proposed as an approach to therapy but controlled studies regarding efficacy are lacking [9].

Intestinal Pseudo-obstruction

Intestinal pseudo-obstruction can also be seen in SSc patients and presents with typical symptoms of abdominal pain, distention, nausea, vomiting, and inability to pass flatulence [1]. Patients usually require hospital admission and radiographs to rule out mechanical obstruction. Figure 7.8 is an abdominal X-ray that shows such a patient with dilatation of both small and large bowel. The initial treatment includes bowel rest, intravenous fluids, and correction of electrolyte imbalances. In addition,

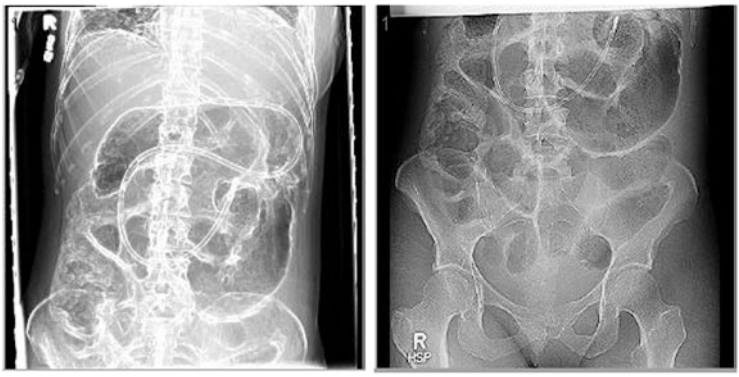

Fig. 7.8 Small and large bowel dilatation in an SSc patient with pseudo-obstruction

prokinetic therapy and broad-spectrum antibiotics may be added to decrease the bacterial load in the small intestine.

Pneumatosis Cystoides Intestinalis/Pneumatosis Intestinalis

Pneumatosis intestinalis, or air in the bowel wall, has been reported in SSc [7]. It is sometimes an incidental finding noted on X-ray. In an asymptomatic patient there is no need for therapy. Occasionally the air-filled cysts can rupture leading to benign pneumoperitoneum. However, in patients with pseudo-obstruction and dilated bowel, free air in the peritoneal cavity can be a sign of bowel rupture and needs to be managed as such. Figure 7.9 is a plain abdominal X-ray of a 35-year-old man with diffuse scleroderma and recurrent pseudo-obstruction and malnutrition dilated gas- and fluid-filled bowel loops are present. Gas shadow (arrows) within the bowel wall of small intestinal loops is typical of pneumatosis intestinalis. Figure 7.10 is an abdominal CT scan of the same patient as in Fig. 7.9. Arrows indicate sites of gas within the wall of small bowel loops that are fluid-filled. In addition, there are multiple loops of dilated small bowel and rather featureless thickening of intestinal wall consistent with scleroderma involvement.

Colon and Anorectal Disorders

Colonic involvement is seen in 20–50 % of patients with SSc and usually presents as constipation. Colonic contractions are typically reduced or absent in patients with SSc, resulting in prolonged colonic transit and symptoms of constipation.

For treatment of constipation, stimulant and osmotic laxatives are preferred as these laxatives exert their effects primarily via alteration of electrolyte transport by

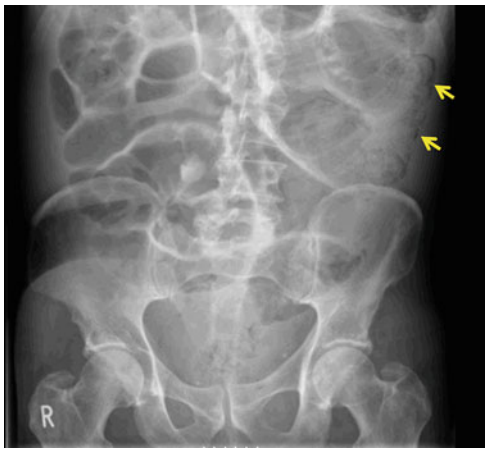

Fig. 7.9 Small and large bowel dilatation in an SSc patient with pseudo-obstruction and with pneumatosis intestinalis on the left flank (*arrows*)

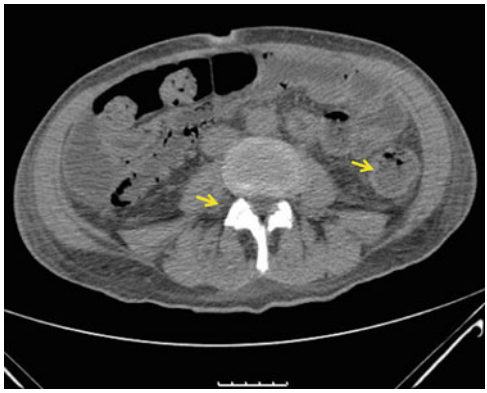

Fig. 7.10 Abdominal CT of the patient shown in Fig. 7.7 with pneumatosis of bowel loops (*arrows*)

the intestinal mucosa and by increasing intestinal motor activity. Patients may require laxatives every 2–3 days to maintain a healthy bowel regimen. For patients with this form of slow-transit constipation, the usual approaches to constipation are not recommended, that is, a high-fiber diet and bulk-forming laxatives can actually make the constipation worse.

Anorectal involvement is also common in patients with SSc although frequently underreported. Symptoms include chronic diarrhea, fecal incontinence, and rectal prolapse.

For anorectal involvement, biofeedback therapy has been used [10]. Sacral nerve stimulation has also been successful in some people with fecal incontinence [11].

Patient-Reported Outcome Measures

The UCLA Scleroderma Clinical Trial Consortium GIT 2.0 [UCLA SCTC 2.0] [12] includes 34 items and 7 multi-item scales (reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning) resulting in a total GIT score to assess health-related quality of life (HRQOL) and GI tract symptom severity in SSc. The GIT 2.0 typically takes 6–8 min to complete and can be found at http://uclascleroderma.researchcore.org/. Serial use of this questionnaire can provide important information to the clinician and to the patient to evaluate improvement, or lack thereof, and to guide management.

Conclusion

Gastrointestinal involvement is common in SSc and not only can interfere with function and social interaction but severe GI involvement is associated with considerable morbidity.

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Chapter 8
Calcinosis Cutis in Systemic Sclerosis

Gloria A. Salazar and Maureen D. Mayes

Abstract Calcinosis cutis is defined as deposition of insoluble calcium salts in the skin and subcutaneous tissues. It can occur in multiple disorders but it is commonly seen in systemic sclerosis (SSc) especially in the limited type. It is frequently a late finding, but can develop at any point during the disease process and the severity varies from single small lesions typically in the hands to generalized calcinosis also known as calcinosis universalis. The pathogenesis is not well understood but theories include calcium and phosphate microenvironment imbalance, inflammatory causes, and chronic/recurrent ischemia. Calcinosis cutis is a common cause of morbidity in SSc patients and currently there is no treatment consensus although multiple therapies have been attempted with varying degrees of success.

Keywords Calcinosis • Scleroderma • Systemic sclerosis

Introduction

Calcinosis cutis is characterized by the deposition of insoluble calcium salts in the skin and subcutaneous tissues [1]. Calcinosis is known to occur in a variety of disorders one of which is systemic sclerosis (SSc) particularly the limited cutaneous subtype previously known as CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias). It has been

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reported that 25–40 % of patients with limited SSc develop calcinosis during the course of the disease [2, 3]. Although this complication typically develops 10 years or more after disease onset, it has also been reported to precede the diagnosis of SSc [2]. Calcinosis cutis can occur in diffuse cutaneous disease as well as in the limited form but is less frequent. In addition to the skin, areas that can be affected include the subcutaneous fat, muscle, and tendons [1].

Calcinosis is often painful, especially when lesions are over pressure points or when they ulcerate, and this leads to considerable distress and functional impairment. The severity of calcinosis cutis ranges from a single small nodule (typically in the hands) to multiple nodules to diffuse/continuous areas or "sheets" of subcutaneous calcium. Areas that are most commonly affected include the hands particularly the volar aspect of the fingertips (Figs. 8.1, 8.2, 8.3, and 8.4), forearms (Fig. 8.5), elbows (Fig. 8.6), and knees (Fig. 8.7). Less common areas are paraspinal regions with a predilection for the cervical spine [4–6]. Although SSc-related calcinosis causes considerable morbidity, it does not appear to overall survival [7].

Plain X-rays of the affected area are usually adequate to visualize the calcific lesions if the diagnosis is not clear on clinical examination [8, 9]. However, the X-ray frequently reveals more extensive calcinosis than what is clinically apparent (Fig. 8.4). This is an important feature as this finding would influence any attempt to surgically remove the deposits. For the most part, a surgical approach to finger lesions is discouraged due to the extensive involvement and the ischemic nature of the tissue which leads to impaired wound healing. Surgical intervention to remove individual lesions, particularly those involving paraspinal tissue needs to be considered on a case-by-case basis.

A distinct clinical subset of calcinosis in scleroderma comprises individuals with an overlap of scleroderma and inflammatory myositis that develop diffuse, extensive, and confluent areas of calcinosis (calcinosis universalis) in a pattern also seen in juvenile dermatomyositis (Figs. 8.8, 8.9, 8.10, 8.11, 8.12, and 8.13). Calcinosis universalis is characterized by "sheets" of calcium developing in the skin and subcutaneous structures with a predilection for the buttocks, abdomen, hips, and lower extremities more than upper extremities. When the dense deposits overlie joints, they impair joint mobility particularly of the low back, hips, and knees and can make sitting or even lying painful. Scleroderma patients with this pattern frequently have antibodies to PmScl or U1 RNP but may not have overt myositis, that is, they may not have weakness or elevations in muscle enzymes.

Calcinotic lesions can ulcerate and extrude a chalky milk-like substance that is composed of calcium salts (typically consists of hydroxyapatite and amorphous calcium phosphate) as shown in Figs. 8.4, 8.5, 8.7, 8.8, and 8.9 and may become secondarily infected [10].

Little is known about the pathogenesis of this condition. Serum calcium and phosphate levels are uniformly normal. Calcinosis is hypothesized to result from local tissue damage due to repetitive low-level trauma, hypovascularity resulting in chronic hypoxia, and an imbalance between inhibitors of ectopic calcification such as matrix gammacarboxyglutamic acid protein (MGP) and fetuin-A and promoters of calcification such as osteonectin [11–13].

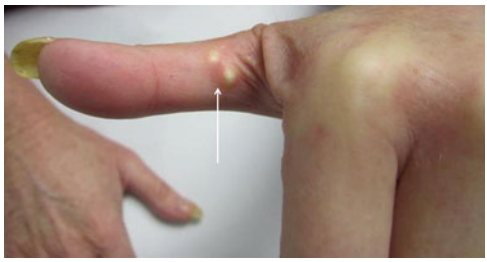

Fig. 8.1 Two small superficial calcinotic nodules in the thumb as shown by the *arrow*

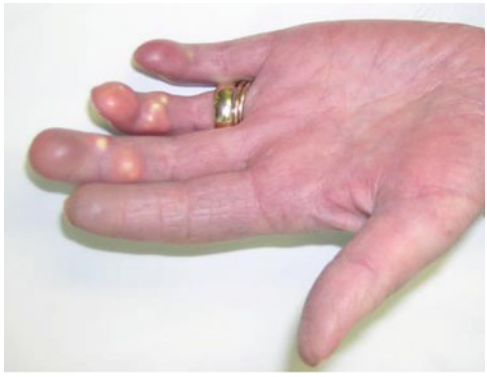

Fig. 8.2 Multiple areas of calcinosis affecting the third to fifth digits of this patient with systemic sclerosis. In this case the calcinosis is located in the flexor aspect of the digits. When this happens, the lesions can affect the mechanics of the adjacent joints and tendons. When they are this superficial, the deposits are prone to ulceration

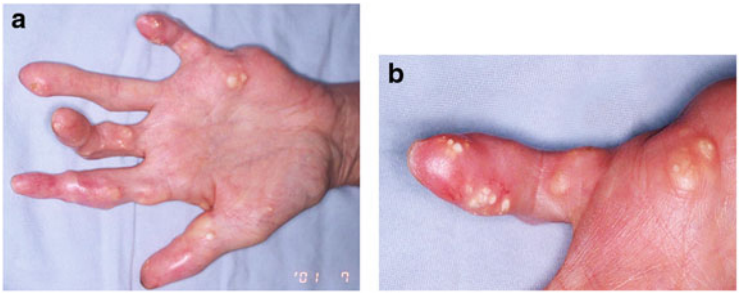

Fig. 8.3 (**a**) Multiple areas of calcinosis of the left hand in a patient with long-standing limited SSc. (**b**) Close-up of the calcinosis of the fifth digit and palm of the patient above. These areas periodically erupt to the surface and drain

Many pharmacological agents have been suggested for treatment of calcinosis but, due to lack of evidence beyond case studies and case series, none has been accepted as a standard therapy (for review, see [14]). The list of reportedly effective therapies is long and includes calcium channel blockers (particularly diltiazem), intravenous immunoglobulin, bisphosphonates, low-dose warfarin, colchicine, CO_2 laser therapy, aluminum hydroxide, minocycline, salicylates, extracorporeal shock wave lithotripsy, probenecid and ceftriaxone [14], and more recently infliximab [15] and rituximab [16]. However, one must interpret these reports cautiously in

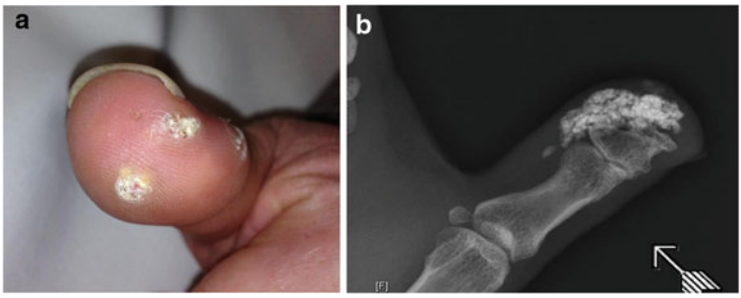

Fig. 8.4 (**a**) Photo of thumb showing calcium deposits that are extruding to the surface. (**b**) X-ray of the same thumb demonstrating that the calcium deposits are distributed throughout the thumb pad and are more extensive than the clinical appearance would indicate

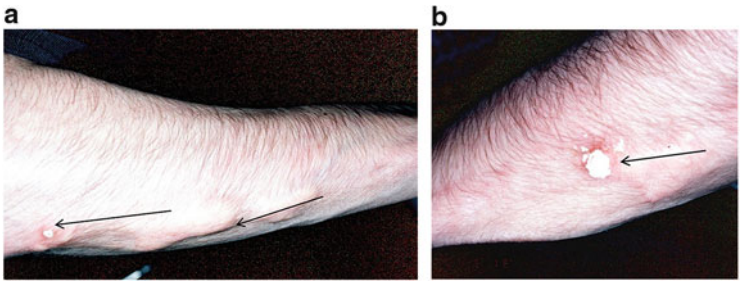

Fig. 8.5 (**a**) Forearm of patient with multiple areas of calcinosis. (**b**) Close-up of area of forearm calcinosis above showing extrusion of calcinotic material that was hard and adherent to the underlying tissue

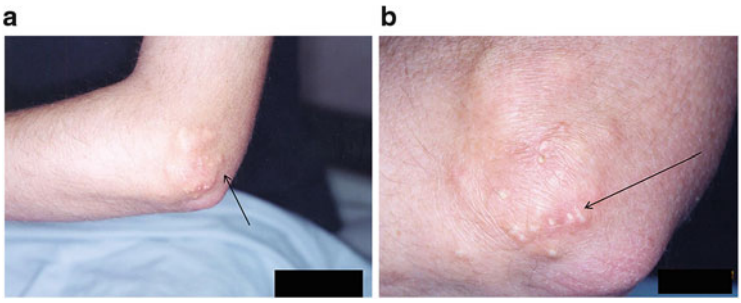

Fig. 8.6 (**a**) Elbow calcinosis in a patient with diffuse SSc. (**b**) Close-up of the elbow calcinosis showing multiple discrete nodules

light of the fact that some cases of SSc-related calcinosis spontaneously improve and there is a publication bias in favor of positive rather than negative reports. It should be noted that the cases presented here in the accompanying figures have been tried on many of these therapies without improvement.

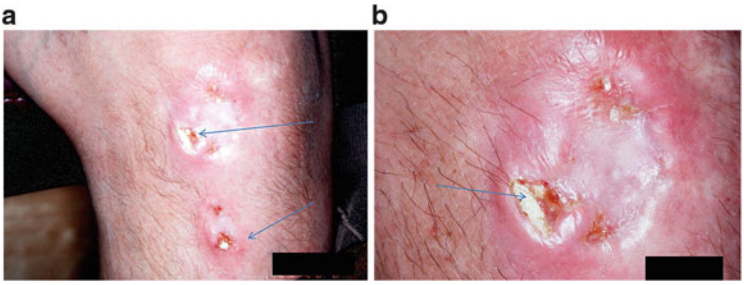

Fig. 8.7 (**a**) Calcinosis of the knee in a patient with long-standing diffuse SSc. These areas periodically erupt to the surface and drain. (**b**) Close-up of the knee showing an exposed calcium deposit that was hard and adherent to the underlying tissue

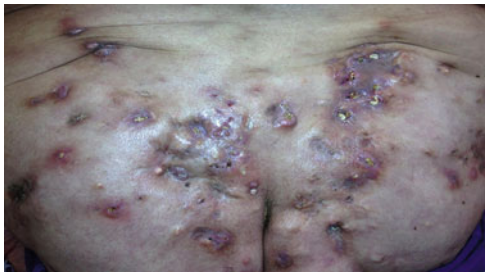

Fig. 8.8 Buttock area of a patient with overlap of scleroderma and myositis with severe calcinosis and multiple areas of eruption. The underlying tissue has a diffuse, confluent "rock-hard" texture

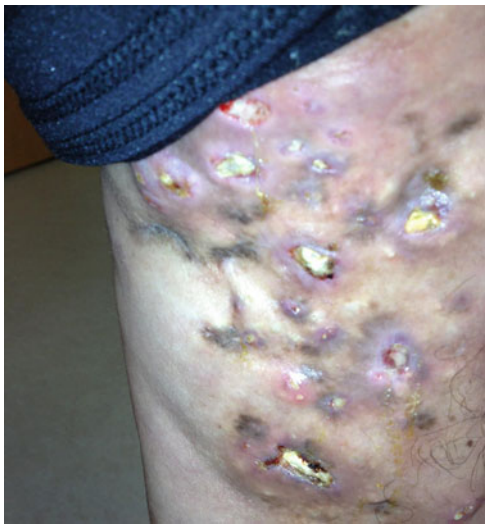

Fig. 8.9 Left side of abdomen of patient in Fig. 8.8 above demonstrating the circumferential nature of the calcinosis

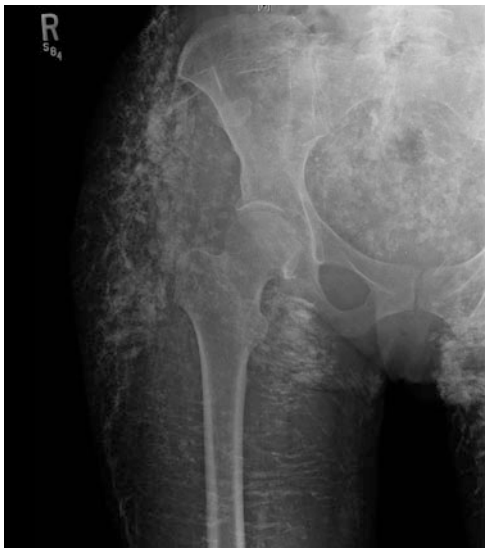

Fig. 8.10 X-ray of patient in Figs. 8.8 and 8.9 above demonstrating extensive sheet-like calcification

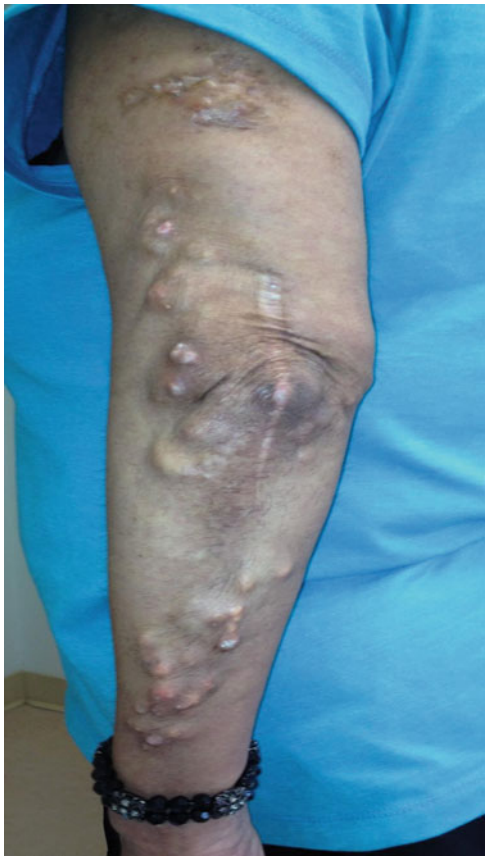

Fig. 8.11 Left arm of patient above showing multiple areas of calcinosis. The scar over the elbow indicates an area of surgical removal of calcinosis

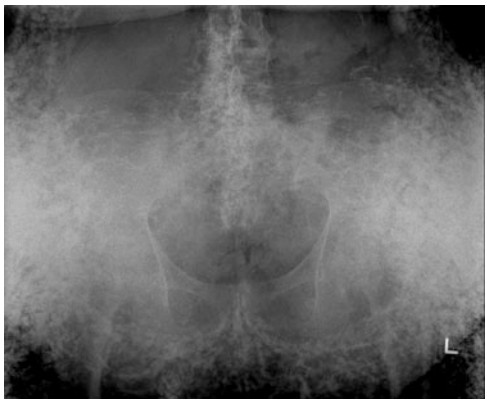

Fig. 8.12 Diffuse calcinosis in the buttock region of a patient with long-standing scleroderma without clinical myositis

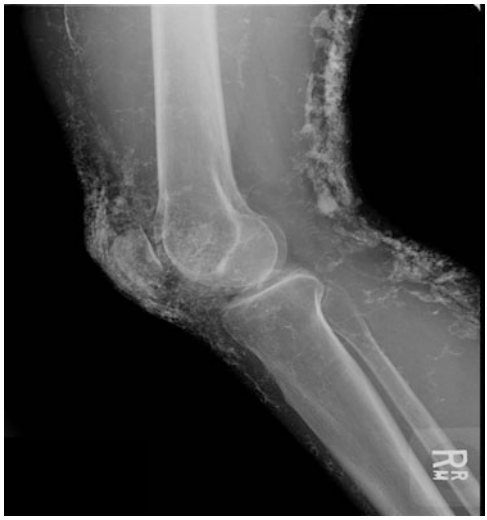

Fig. 8.13 X-ray of right knee of patient with PmScl antibody-positive scleroderma/myositis overlap of 10 years duration. There was severely limited range of motion of both knees due to overlying calcinosis

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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.

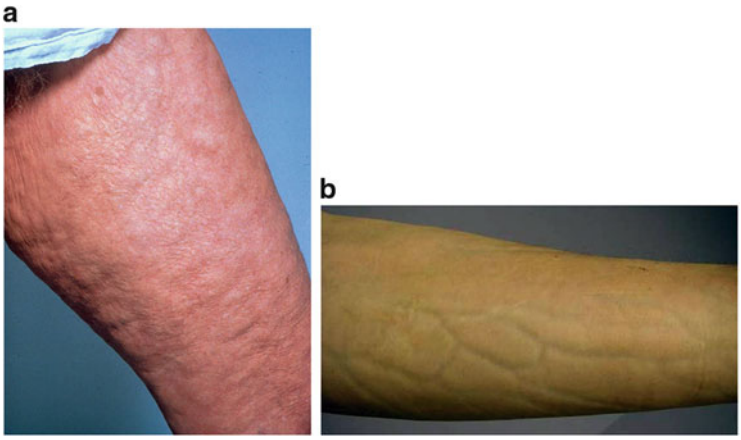

Fig. 9.1 (**a**) Peau d'orange appearance of the thigh showing the characteristic skin puckering of Eosinophilic Fasciitis (**b**) Groove sign of venous furrowing in Eosinophilic Fasciitis in which indentations or inward bowing of the skin are seen along the course of superficial veins [Reprinted from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

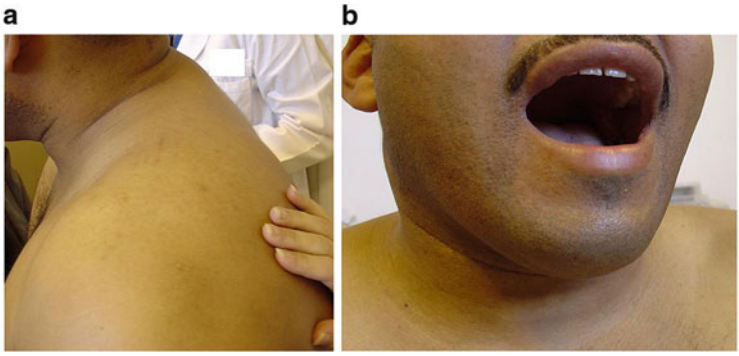

Fig. 9.2 (**a**) Scleredema patient showing classic upper back involvement (**b**) Scleredema facial involvement causing inability to open the mouth fully in this patient

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

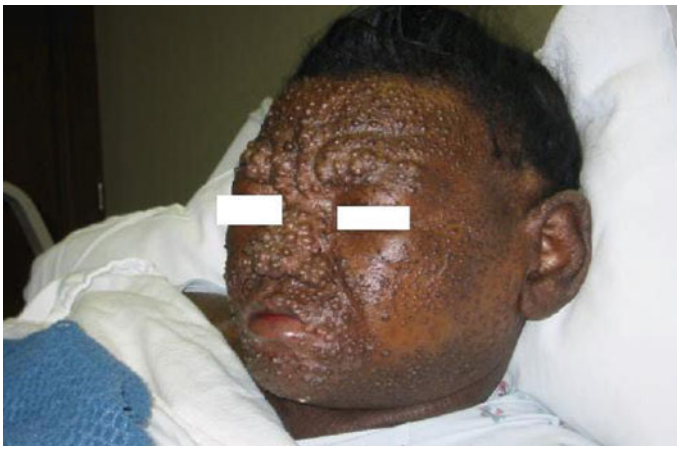

Fig. 9.3 Patient with scleromyxedema with typical papules and thickened skin folds most notably of the forehead. She had an IgG lambda paraprotein

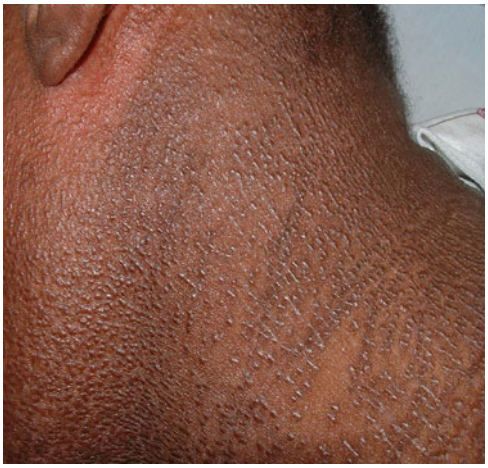

Fig. 9.4 Close up of the neck of the patient in Fig. 9.3 showing numerous discrete papules

[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,

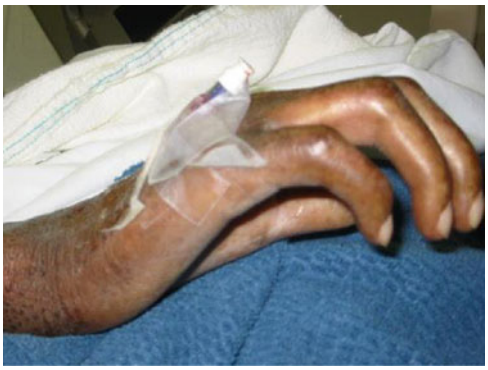

Fig. 9.5 The hand of the patient in Figs. 9.3 and 9.4 above with very SSc-like skin thickening and flexion contractures of the fingers. However, the presence of mucinous papules on the dorsum of the hands and forearms is distinct from the skin changes of true SSc

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].

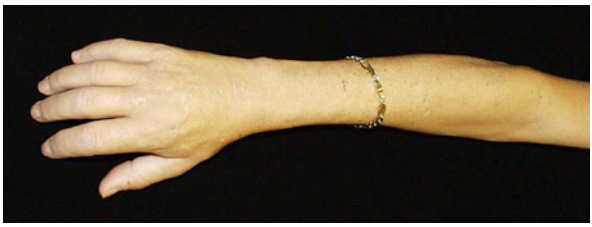

Fig. 9.6 Arm of a patient with nephrogenic systemic fibrosis showing skin changes from the elbow to the level of the metacarpal phalangeal joints (MCPs) but sparing the fingers [Reprinted from Kay J. What Causes Nephrogenic Systemic Fibrosis?: Imaging studies and kidney problems may trigger this gadolinium-induced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

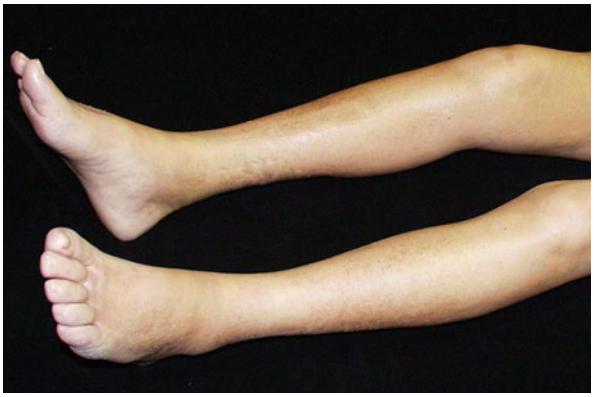

Fig. 9.7 Legs of a patient with Nephrogenic Systemic Fibrosis showing thickened and indurated skin of the legs with flexion contractures of the knees [Reprinted from Kay J. What Causes Nephrogenic Systemic Fibrosis?: Imaging studies and kidney problems may trigger this gadolinium-induced fibrosing syndrome. 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.

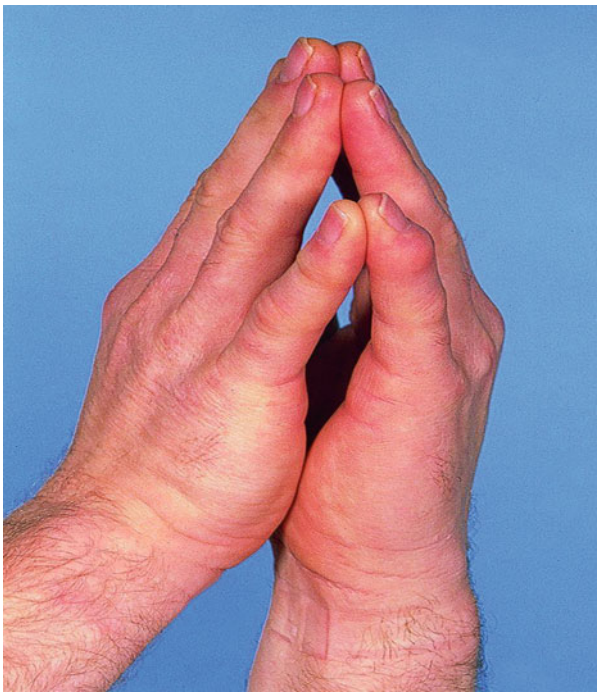

Fig. 9.8 "Prayer sign" of patient with diabetic cheiroarthropathy with inability to fully appose the fingers. The lack of Raynaud's phenomenon, normal nailfold capillaries and negative ANA, in the presence of diabetes, help to distinguish this from SSc

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.

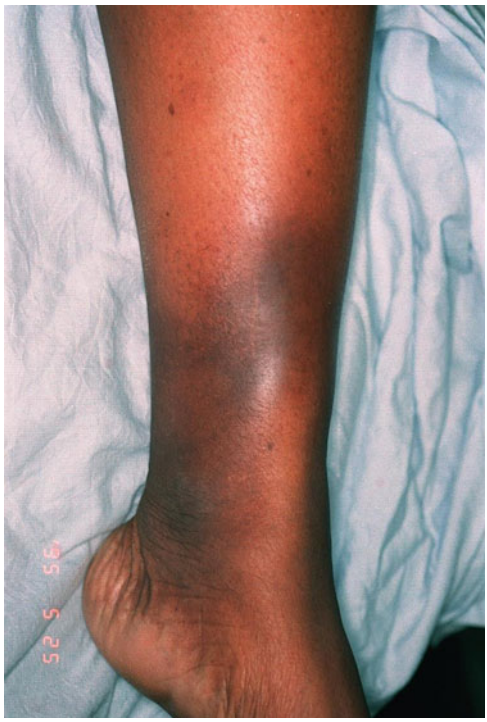

Fig. 9.9 Early changes of lipodermatosclerosis with hyperpigmentation and skin thickening

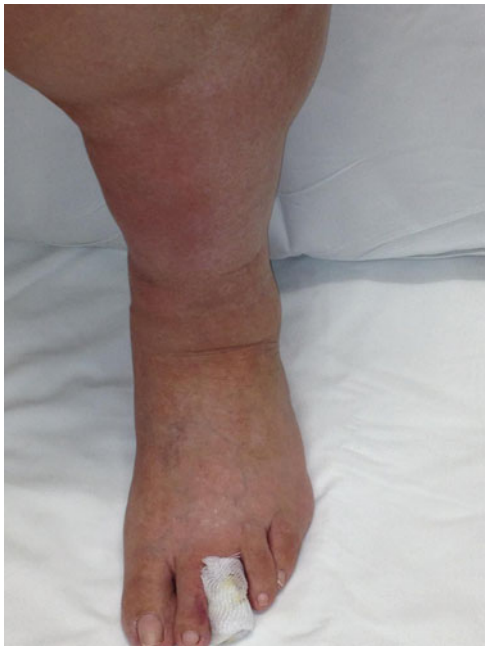

Fig. 9.10 Later changes of lipodermatosclerosis in another patient showing the "hourglass" appearance with thickened skin

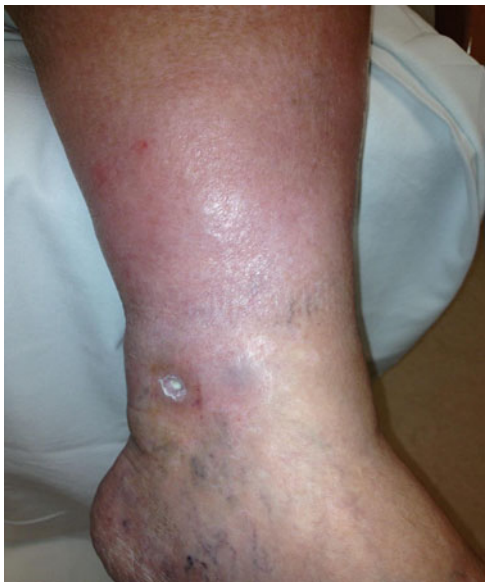

Fig. 9.11 Ulcer near the medial malleolus of the patient in Fig. 9.10

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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