Scleroderma mimics - clinical features and management

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Scleroderma is often used as a synonym for systemic sclerosis but is perhaps better seen as a collective term covering a range of autoimmune inflammatory conditions in which skin thickening or sclerosis is a hallmark feature. Consensus has emerged that includes localised and systemic forms of scleroderma in a classification that is highlighted in **Figure 1.** This is sometimes termed the scleroderma spectrum and provides a very useful operational framework for management of the conditions. The term morphoea has recently been applied more consistently to the localised forms of scleroderma and this helps to avoid confusion with patients and clinical staff. There are several other conditions which may be pathogenetically or clinically related to scleroderma that represent diagnostic mimics, and these "pseudo-sclerodermas" are the main focus of this chapter. Establishing the underlying cause and correct diagnosis in a patient with diffuse skin thickening is important because disease impact, prognosis and management vary widely between systemic sclerosis, morphoea and the scleroderma mimics.

Practical approach

When skin thickening or tightness is observed this should prompt further clinical and laboratory assessment and the tools available generally permit a reliable differentiation between scleroderma and each of the scleroderma mimics.

First, should be determination of whether the patient has scleroderma, in other words whether they have either systemic sclerosis or morphoea. Morphoea can generally be diagnosed clinically and is characterised by hallmark lesions that typically evolve over time from an erythematous, oedematous and bruise-like appearance, to shiny, whitish yellow, thickened sclerotic skin and later hyperpigmentation and atrophy. There are several different patterns of disease . These include limited plaque, linear, generalised, and mixed and pansclerotic forms. These forms may coexist and have different implications in different age groups. In all forms, the depth of involvement is variable from superficial dermis down to fascia, muscle and bone (1, 2). Deep involvement is commoner in linear and pansclerotic forms(3). Extracutaneous manifestations are now well recognised, occurring in approximately 25% of patients, particularly in linear, generalised and pansclerotic forms. They include arthritis, neurological manifestations (including epilepsy, headaches and neuropathy) ,ocular abnormalities (e.g. uveitis, keratitis and episcleritis), Raynaud's phenomenon and gastroesophageal reflux (4, 5).

Limited plaque and linear forms of morphoea can generally be diagnosed clinically based on morphology and distribution. The term generalised morphoea has historically been used in a variety of contexts, but is best defined as the occurrence of morphoea plaques at more than two of seven

anatomical locations (head, front of trunk, back of trunk, limbs). Plaques may coalesce to cover large areas of the trunk and limbs, but are not circumferential. They rarely involve deeper structures and may be described as disseminated superficial plaque disease. This subtype of morphoea may occur in an isomorphic distribution- at sites of low grade chronic trauma from clothing such as the groins waistband and inframammary areas, or as widespread often symmetrically distributed small plaques. This pattern is usually easily distinguished from SSc on clinical grounds. Typical appearances of established morphoea plaques are shown in Figure 2.

The most difficult differential diagnosis is between systemic sclerosis and pansclerotic morphoea, which is defined by circumferential skin involvement of the majority of body surface areas with sparing of the fingers, toes and nipples.It is a rare form of morphoea accounting for 3.6% of 360 patients in one cohort (3). The key features that differentiate these conditions are summarised in Figure 3. Thus, SSc will likely have Raynaud's phenomenon, oesophageal dysmotility and involvement of the distal extremities, especially the fingers with sclerodactyly and skin thickening. There will be associated laboratory investigations that are supportive including ANA testing that generally demonstrates one of the hallmark SSc reactivities. In addition, there are likely to be typical nailfold capillaroscopic abnormalities(6). In this way cases of SSc will usually fulfil the 2013 ACR EULAR classification criteria, noting that up to 10% of cases that are confidently diagnosed as SSc may only partially fulfil them due to the focus on specificity rather than sensitivity (7, 8). In pansclerotic morphoea , rapid progression of widespread circumferential thickening and tightening of the skin of the trunk and limbs occurs. It typically begins on the trunk and then spreads on to the limbs, frequently involving the neck and occasionally the face. Deep involvement, including fasciitis is common, but not invariably present. Onset on the limbs with puckering and a peau d'orange appearance to the skin and guttering over veins may occur and together with the frequent presence of raised inflammatory markers and blood eosinophilia during the active early inflammatory stages, may make it indistinguishable from eosinophilic fasciitis(9, 10). The typical facial features of SSc including nasal changes, perioral furrowing and matt-like telangiectases are not seen. Sclerodactyly is absent and the fingers and toes are typically spared. Occasional secondary changes are seen in the digits when sclerosis of the forearm and wrist tissues causes obstruction to venous and lymphatic outflow and results in chronic distal oedema and subsequent fibrosis. Raynaud's phenomenon may be present but capillaroscopy abnormalities are not seen in morphoea. Positive ANA is documented in 30-50% of cases but is unlikely to be a hallmark SSc reactivity relevant to the classification criteria, allowing distinction from SSc. The typical appearance of pansclerotic morphoea is shown in Figure 4.

Scleroderma-mimic or morphoea spectrum:

Eosinophilic fasciitis

Eosinophilic fasciitis (EF) is an autoimmune, inflammatory condition, first described by Shulman in 1974(11, 12). There is a significant overlap between this condition and adult pansclerotic morphoea and there is debate as to whether they are separate conditions or part of a spectrum of disease with inflammation and sclerosis occurring at different levels in the skin and subcutaneous tissues, and frequently coexisting. The presence of typical morphoea in plaque or circumferential form in 20-40% of cases of EF, and the development of skin sclerosis overlying areas of fasciitis support this. As in morphoea strenuous exercise, trauma and infection are well-recognised triggers.

It is characterised by the sudden onset of rapidly progressive oedema, erythema and then deep sclerosis of the fascia resulting in puckering of the overlying tissues and a peau d'orange appearance to the skin. Loss of subcutaneous and perivenous fat tissue gives a classical groove or gutter sign overlying veins in the forearms. It typically involves the distal limbs first, but may also involve the trunk. The hands, feet and face are not involved. Weight loss, myalgia, arthralgia, malaise occur early and may precede the onset of fascial inflammation. Pain, limitation of movement, tendon and joint contractures may develop causing a significant negative impact on quality of life. As in pansclerotic morphoea, carpal tunnel syndrome, oesophageal dysmotility and restrictive lung impairment are occasionally seen due to compression from skin and fascial sclerosis. In contrast to SSc, no internal organ involvement per se occurs. An eosinophilia, hypergammaglobulinaemia and raised inflammatory markers (ESR,CRP) are commonly seen early in the disease course, but may be transient. An eosinophilic infiltrate in the panniculus and deep fascia may be present in the early stage of disease but is not invariable. Full-thickness biopsy containing muscle and fascia is considered the gold standard for diagnosis and reveals sclerosis of the mid-deep dermis, the fibrous septa of the subcutis and deep fascia and may extend into underlying muscle. Histological differentiation from deep morphoea is challenging. Magnetic resonance imaging (MRI) is increasingly being used to assess for the presence of fascial inflammation.

Systemic corticosteroids have been the mainstay of treatment, but increasing evidence suggests that treatment with corticosteroids alone produces partial or inadequate responses and addition of an immunosuppressant such as methotrexate or mycophenolate is required. If treated early and aggressively, complete remission can be achieved over 3-5 years (13)

Scleroderma mimics

A number of scleroderma-like conditions (Table 1) can mimic systemic sclerosis and differentiating between these conditions can be challenging, especially in the early, rapidly progressive stages of the disease. They range from autoimmune& inflammatory, to deposition disorders, metabolic and

genetic diseases, conditions triggered by toxicity of drugs or chemicals, and paraneoplastic phenomena. The distribution and depth of involvement, presence of extracutaneous manifestations, blood test results and histopathologic features are important pointers to the correct diagnosis.

Inflammatory and auto-immune

Sclerodermoid graft-versus-host-disease

Sclerotic skin lesions are a rare but well recognised complication of chronic graft-versus-host-disease (GVHD) occurring after allogenic bone marrow, stem cell and occasionally solid organ transplantation (14, 15). It is preceded by acute GVHD in 80% of cases. The skin gradually becomes dry, itchy thickened and tight in a localised or disseminated fashion. Bullae, lichen sclerosis like changes and atrophy may occur. The clinical appearances can resemble plaque (limited or disseminated) or pansclerotic morphoea with or without fasciitis. Deep fascial involvement leads to skin puckering, peau d'orange change, a positive "groove sign", contractures and limitation of movement across joints. A positive "prayer sign" due to limitation of wrist and finger flexibility may occur. Histopathology reveals thickened collagen with loss of periadnexal fat, which may extend into the subcutis and fascia and be indistinguishable from scleroderma. Lichenoid interface changes with vacuolar degeneration or superficial changes similar to lichen sclerosus may also be seen. Histopathological and clinical distinction from SSc, pansclerotic morphoea and fasciitis may be thus difficult. Nailfold capillary changes and calcinosis may be present, but raynauds and SSc specific ANA are usually absent. A previous history of transplantation, characteristic associated oral and genital mucosal, hair and lichen planus-like nail changes, enteritis and hepatitis allow distinction from morphoea and SSc (14, 15). Typical appearance is shown in Figure 5.

Fibro mucinous conditions (Scleredema, Scleromyxoedema)

The aetiopathogenesis of the primary dermal mucinoses is unknown, although cytokines such as tumour necrosis factor α and β, interleukin 1, interleukin 6 and transforming growth factor β and/or polyclonal and monoclonal immunoglobulins and other unidentified factors in the serum of affected patients may induce up-regulation of glycosaminoglycan synthesis.

Scleredema

Scleredema is a rare condition, which occurs in all ages, over 50% under 20 years of age, and in all ethnic backgrounds. Diagnosis is made based on clinical presentation, diagnostic biopsy and the presence or absence of recognoised associations such as recent infection, paraproteinaemia or diabetes.

There is progressive extension of non-pitting oedema, with or without erythema and a peau d'orange appearance. The skin may have a doughy consistency in the early stages which evolves into a firm to woody skin induration, frequently with indistinct margins. It usually occurs symmetrically across the neck, upper chest and back, sometimes extending on to the face. More rarely a generalised form is described, but the hands and feet are spared. There are no waxy skin papules and ANA is negative helping to distinguish scleredema from scleromyxoedema and SSc (see Figure 6).

Several distinct subtypes are described. Type 1, post infectious, occurs most often after a streptococcal or viral URTI and represents up to 55% of cases. It is commonest in children and has a better prognosis with a majority resolving spontaneously over 6 months to 2 years. Type 2 represents up to 25% of cases and is associated with a paraprotein, most commonly a monoclonal gammopathy, but myeloma and amyloidosis can occur. The onset of skin changes may predate the development of the paraprotein and patients with no indentified association at diagnosis should undergo periodic monitoring for paraproteinaemia and malignancy. Types 1 & 2 are commoner in females. Type 3 is associated with diabetes and represents up to 20% of cases. This type is usually seen in male patients (10:1 M:F)with longstanding, poorly controlled insulin dependent diabetes. Scleredema has been diagnosed in 2.5-14% of diabetics. Idiopathic and cases occurring in association with a variety of autoimmune disorders, internal malignancies, exposure to organic solvents and HIV are reported.

Histology typically shows a markedly expanded dermis, 3-4 times normal, with hap-hazardly arranged thickened collagen bundles separated by clefts which typically but not necessarily contain mucin. The process may extend into the subcutis replacing fat. In contrast to SSc, adnexal structures are typically preserved, although in some cases eccrine glands may be lost. In contrast to scleromyxoedema, the dermis is relatively acellular with no increase in fibroblast numbers or proliferation and no inflammatory cell infiltrate. Mucin may also accumulate in skeletal and cardiac muscle. Extracutaneous complications can occur in all subtypes and include serositis, dysarthria, dysphagia, myositis, parotitis, hepatosplenomegaly and ocular and cardiac abnormalities.

A majority of type 2 and 3 patients have slowly progressive courses resistant to therapy (16). Treatment of underlying lymphoproliferative disorder, malignancy and diabetes may have some impact on disease severity. Benefit has been doc umented with UVA1 and PUVA phototherapy , bortezomib, immunosuppression (methotrexate, corticosteroids, ciclosporin,) IvIg, electron beam radiotherapy and extracorporeal photopheresis (17).

Scleromyxoedema

Scleromyxedema is a rare disorder of unknown aetiology that is an important potential mimic of other sclerosing skin diseases (18). Synonyms include generalised and sclerodermoid lichen myxedematosus and Arndt-Gottron disease. Some 150 cases have been described in the English literature, although it is a well-recognised condition and is probably under-reported. It affects the sexes equally and the average age of onset is 59 years. It is a primary cutaneous mucinosis. The diagnosis is based on 4 criteria: the presence of a generalised papular and sclerodermoid eruption, histological features of cutaneous mucin deposition, fibroblast proliferation and fibrosis, a monoclonal gammopathy and no evidence of thyroid disease.

It typically affects the face, post auricular areas, neck, extensor forearms and backs of the hands and less commonly the trunk and legs. The skin may be oedematous and erythematous in the acute stages and pruritus is common. It is characterised by the progressive development of multiple, firm, 1-3mm dome shaped or flat-topped, white to skin coloured, waxy, infiltrative papules, frequently on a background of confluent skin induration and thickening. Papules may be arranged linearly or give a cobblestone appearance. A deep furrowed appearance can develop leading to leonine facies and the "Shar-Pei sign" on the trunk (see Figure 7). The "doughnut sign" may be seen when the skin around the proximal interphalangeal joints is thickened, leaving a central depression over the joint. Sclerodactyly and reduced oral aperture may occur. Progressive thickening and hardening of the skin can cause contractures and limit function. Axillary, pubic and eyebrow hair may be thinned. Raynaud's phenomenon is usually absent and telangiectases and calcinosis do not occur.

The histopathological hallmark is diffuse mucin deposition, mainly hyaluronic acid, in the upper and mid reticular dermis, increased collagen and a proliferation of irregularly arranged, stellate and bipolar fibroblasts. The deep dermis and subcutis are not involved. Later stages show less mucin and increased fibrosis. Mucin deposition has been found in large pulmonary vessels, in the kidney, adrenals, cardiac and coronary vessels, eyelids and cornea. The role of mucin in the development of systemic manifestations of disease is still unknown.

Extracutaneous manifestations are common. Over 80% of cases have a serum paraprotein, usually IgG λ. Its role in pathogenesis is uncertain and the level does not parallel disease activity. Progression to multiple myeloma occurs in less than 10% of cases. Gastrointestinal (mainly oesophageal dismotility), and neurological manifestations are common. The latter occur in 30% of cases and include epilepsy, aphasia, motor impairment, carpal tunnel syndrome, peripheral neuropathy, depression, memory loss, dementia and psychosis. A very rare complication, which may prove fatal, is the "dermato-neuro syndrome" a severe encephalopathic illness preceded by flu-like symptoms and resulting in coma. Exertional dyspnoea, restrictive or obstructive lung disease, upper

airway involvement and more rarely pulmonary hypertension can occur. Proximal muscle weakness, inflammatory myopathy, inflammatory polyarthritis and other haematologic disorders are documented.

It tends to run a progressive course with a poor outcome and in many cases leads to potentially life-threatening complications. The most important manifestations relate to dysphagia, aspiration, and difficulties with facial movement, eating, nutrition and eyelid closure.

Whilst multiple treatments have been proposed in small case series and single reports, the rarity of the condition has prevented randomised controlled studies. There is most evidence for the use of high dose intravenous immunoglobulin (2g/kg every 4-6 weeks) which is currently recommended first-line therapy (17, 19, 20) . When this is unavailable or contraindicated Thalidomide (50-400mg/day) or lenalidomide (25mg daily for 3 weeks per month) with or without systemic corticosteroids is recommended second line therapy. Other treatment options include autologous or allogeneic stem cell transplantation (21) and bortezomib plus dexamethasone (17, 22)

Environmental & drug induced

The scleroderma like conditions that are associated with environmental chemical and drug exposure (Table 1) are interesting in that they appear to overlap significantly with systemic sclerosis and morphoea, have been attributed to increased collagen production by activated fibroblasts and may thus give clues about triggers and disease mechanisms. For example, in the 1980s, ingestion of aniline denatured rapeseed oil in Spain, led to an outbreak of “toxic oil syndrome”, a condition characterised by widespread skin sclerosis which was preceded by fever, oedema, myalgia, pruritus and eosinophilia. The eosinophilia-myalgia syndrome, due to ingestion of high levels of L-tryptophan in food-supplements, was described soon afterwards and presented similarly. Occupational exposure to vinyl chloride, organic solvents and silica dust has been associated with an SSc-like illness which includes Raynaud’s , respiratory symptoms, loss of finger-tip pulps and acro-osteolysis as well as widespread skin sclerosis in individuals with particular HLA subtypes. Similarly, an acute syndrome of skin sclerosis, muscle weakness, arthralgia, impotence, lung and oesophageal involvement has been linked to epoxy resin exposure. Multiple medications have been linked to the development of skin sclerosis and are listed in table X

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) may be considered both an environmental/drug induced disease and a sclero-mucinous condition. It is a systemic fibrosing condition first described in 1997, which occurs in patients with renal impairment following the use of gadolinium based contrast agents

(GBCA)in magnetic resonance imaging(23, 24). The type, especially linear non-ionic forms, the dose (>0.3mmol/kg) and overall amount of gadolinium exposure, and degree of renal impairment (CKD5>CKD3) are important risk factors. Possible cofactors include the presence of a metabolic acidosis and abnormal phosphate levels ,since both increase the likelihood of gadolinium dissociation from its chelate and deposition in the tissues.

The diagnosis of NSF is based on the presence of characteristic clinical features in the setting of chronic kidney disease, and substantiated by skin histology on a deep biopsy extending at least into subcutaneous fat(23, 25). The early signs are erythema and oedema, frequently in association with burning or itch, in a symmetrical distribution on the distal limbs and extremities. Subsequently, erythematous to brawny thickened plaques, papules and nodules develop, producing a peau d'orange, cobblestone or woody indurated appearance. The lower limbs are favored, the trunk may be involved but in contrast with scleredema, scleromyxoedema and scleroderma, the face is spared. The skin over sites of arterio-venous fistulas may be more severely involved. Rarely, diffuse involvement of the limbs, more closely resembling scleroderma is seen. The cutaneous changes generally evolve over weeks, but in 5% a fulminant course is described. Joint contractures and reduced mobility occur in 60%. The typical appearance on the lower legs is shown in Figure 8. Fibrotic damage to internal organs including the heart, lungs, liver, esophagus, skeletal muscle, dura, kidneys and rete testes has been documented in <5% of cases. Raynaud's phenomenon, arthritis, fatigue and paraproteinaemia are typically absent and ANA negative(26).

Typical histopathological features are a marked increase in dermal spindle shaped and dendritic CD34 & procollagen dual positive fibrocytes in the early stages. Increased numbers of haphazardly arranged thick and thin collagen bundles are seen throughout the dermis, surrounded by clefts. Elastic fibres are generally preserved. Tram tracking of CD34+ cell processes around a central elastic fibre is a key feature. A variable increase in dermal mucin is seen. The process involves the entire dermis and extends deep, causing a widening of the septae of the subcutaneous fat, and sometimes extending into muscle.

The course of disease is difficult to predict. Available data suggests that it improves in 22%, stabilises in 25% and progresses in the remainder. Deaths directly attributable to NSF are rare, although the condition may have contributed to death through reduced mobility, thrombotic complications and malnutrition.

Treatment is largely unsatisfactory and prevention has been key (27, 28). Improvement in renal function and renal transplantation have been associated with improvement or resolution of disease up to 40% of cases. Multiple therapeutic options have been reported anecdotally. Some promising

responses were obtained with prolonged extracorporeal photopheresis, ultraviolet UVA1 phototherapy, intravenous sodium thiosulphate, rapamycin and use of imatinib. Thankfully, the introduction of screening for renal impairment, avoidance of gadolinium use in acute renal failure and a switch to exclusive use of cyclic ionic forms of gadolinium for all magnetic resonance contrast imaging has proved effective in prevention. To our knowledge, no new cases have been described since 2012.

Syndromes presenting with localised or widespread skin sclerosis and symptoms similar to SSc have been described following exposure to a variety of environmental toxins and drugs (table) and attributed to increased collagen production by activated fibroblasts. In the 1980s ingestion of aniline denatured rapeseed oil in Spain led to an outbreak of a condition characterised by widespread skin sclerosis which was preceded by fever, oedema, myalgia, pruritus and eosinophilia. The eosinophilia-myalgia syndrome, due to ingestion of high levels of L-tryptophan in food-supplements presented in a similar fashion. Occupational exposure to vinyl chloride, organic solvents and silica dust has been associated with an SSc-like illness which includes Raynaud's , respiratory symptoms, loss of finger-tip pulps and acro-osteolysis as well as widespread skin sclerosis in individuals with particular HLA subtypes. Similarly, an acute syndrome of skin sclerosis, muscle weakness, arthralgia, impotence, and lung and oesophageal involvement has been linked to epoxy resin exposure. Multiple drugs have been linked to the development of skin sclerosis and are listed in table X

Metabolic diseases:

Diabetic cheiroarthropathy

Waxy skin thickening and joint stiffness particularly affecting the backs of the wrists, hands and fingers may occur in longstanding type 1 and type 2 diabetes. It leads to reduced wrist and finger extension and a positive "prayer sign". It has been linked to the accumulation of advanced glycation end products and cross-linking of collagen, and is a marker for other microvascular diabetic complications such as nephropathy and opthalmopathy. Multiple treatment modalities have been employed with limited success in small case series. Improved diabetic control may aid in reversal of some of the changes. A positive prayer sign may be seen in patients with pansclerotic morphoea , SSc, scleromyxoedema and nephrogenic systemic fibrosis, but the absence of other features of these conditions and the presence of diabetes aid in diagnosis.

Myxoedema

Localized (pretibial) myxoedema is associated with autoimmune thyroid disease, most often in female patients with longstanding Graves' disease. High levels of TSH and TSH receptor antibodies

are thought to stimulate mucin production by fibroblasts. In contrast to scleroderma, histopathology reveals a thickened epidermis with overlying hyperkeratosis and follicular plugging. Dermal collagen bundles are separated by large amounts of mucin. Increased perivascular lymphocytes, mast cells and fibroblasts are present. Typically there is bilateral thickening and induration of the skin over the shins and feet with a peau d'orange appearance. Plaques, nodules or a cobblestone appearance are described. The toes, thighs, upper extremities and face can be involved and there may be overlying hyperhidrosis or hypertrichosis. Abnormal thyroid function, the presence of a goitre exophthalmos or thyroid acropachy are distinguishing features. More widespread skin thickening with mucin deposition can be associated with generalised myxoedema in the context of hypothyroidism.

Porphyria cutanea tarda *(PCT)*

PCT is an adult onset cutaneous porphyria, which typically presents with blisters, milia and scarring at sun exposed sites such as the hands and face. Hypertrichosis especially in the preauricular skin may be seen. In up to 20% of cases, morphoea-like shiny, waxy, indurated, yellowish plaques may develop, most usually on the head, neck and upper trunk at sun exposed sites. Occasionally these can be more confluent over the whole trunk and then resemble generalised or pansclerotic morphoea. Liver function and levels of uroporphyrinogen decarboxylase are abnormal and it has been suggested that raised levels of uroporphyrin I drive the collagen synthesis. Iron and ferritin levels may be increased. The urine is darker or reddish coloured. Skin histology may be indistinguishable from true morphoea. If blisters are present, these are typically subepidermal with associated "festooning" of the dermal papillae into the blister cavity. DPAS positive staining occurs in vessel walls and at the dermoepidermal junction. ANA is negative, nailfold capillaries are normal and raynaud's phenomenon absent. Effective treatment is possible with venesection and hydroxychloroquine.

Amyloidosis

Cutaneous involvement in the systemic amyloidoses is characterized by petechiae, haemorrhages, ecchymosis and pruritus. A periorbital and intertriginous bruise-like change is common. Confluent white to yellowish, waxy, partially haemorrhagic papules or nodules can be found that predominantly occur on the face, eyelids and scalp. If the dermis is extensively infiltrated by amyloid, scleroderma-like skin changes, especially of the fingers may occur. Such changes may occur in association with hereditary and non-hereditary amyloidosis and can be associated with underlying inflammatory or neoplastic diseases. Identification of the type of amyloid and associated manifestations will aid in diagnosis.

Paraneoplastic scleroderma mimics

The possibility of there being an underlying neoplasm driving skin sclerosis should always be considered in patients with an atypical presentation. This includes rapid onset and progression of skin sclerosis, new onset of raynaud's phenomenon with sclerodactyly but normal nailfold capillaries and absence of gastroesophageal symptoms and of SSc specific ANA. Thus, haematological, solid organ and neuroendocrine malignancies have all been associated with the development of skin sclerosis and may manifest before or after the skin changes develop. The sclerosis may be widespread or localised and is usually indistinguishable histopathologically from scleroderma. Fevers, malaise and weight loss may be a feature, but raynaud's and oesophageal involvement are rare. Nailfold capillary changes and SSc specific autoantibodies are absent. Patients generally fail to respond to standard therapies and the condition may remit once the malignancy has been successfully treated.

POEMS syndrome develops in the context of a monoclonal plasma cell disorder (virtually always of the λ light-chain type). It is an extremely rare multisystem disorder in which polyneuropathy,organomegaly, endocrinopathy, monoclonal gammopathy or M proteins; and skin abnormalities occur. Other common features include oedema, ascites, pleural effusion, osteosclerotic bone lesions, Castleman disease and thrombocytosis. Skin thickening can occur in up to 50% of cases. The presence of hand and foot involvement, sclerodactyly, facial telangiectases, Raynaud's phenomenon and hyperpigmentation can make it difficult to distinguish from systemic sclerosis. Raised levels of VEGF have been reportedly linked to the skin thickening. On examination, lymphadenopathy and hepatosplenomegaly, sensorimotor peripheral neuropathy, haemangiomas and hypertrichosis are more suggestive of POEMS. Typical SSc associated ANA and nailfold capillary changes are absent.

Genodermatoses mimicking scleroderma

A number of genetic diseases are associated with skin thickening (Table 1). Emphasising the link between collagen, elastic fibre and keratin abnormalities and dispigmentation.
These mainly present in childhood and early adulthood, which can sometimes aid in differentiation and the skin changes tend to be more often focal than generalised.

In the progeria syndromes, including Werner and scleroatrophic huriez syndrome, skin thickening tends to be confined to the face and/or extremities/ distal limbs and this may aid in differentiation from SSC & morphoea. In Werner's syndrome the skin is prematurely aged with nasal beaking and wrinkling, early greying or hair loss, bilateral cataracts, calcinosis, and high pitched voice. The skin is stiff but thinned distally and lower limb ulceration is common. On biopsy, epidermal atrophy, dermal fibrosis and loss of appendages is associated with focal hyperkeratosis and basal hypermelanosis.

There is no inflammation. In Huriez syndrome scleroatrophy of the hands and feet, hypoplastic nails and palmoplantar keratoderma occur and patients are at increased risk of developing squamous cell carcinoma.

The stiff skin syndrome is the most striking genetic mimic of scleroderma. This is an autosomal dominant condition due to a mutation in fibrillin 1. This is the same genetic locus responsible for Marfan syndrome. It encodes the microfibrillar protein fibrillin-1 and the distinct clinical phenotypes associated with mutations likely reflect the multifunctional nature of this protein and the contrasting effect of loss of function or gain of function mutations. Stiff skin syndrome is associated with generalised thickening of the skin that present in early infancy and later is associated with contractural changes in tendons and later with connective tissue nodules. Interestingly, other occasional findings include lipodystrophy and muscle weakness.

The mechanism underlying these diseases likely reflects altered activity of availability of TGFbeta family members and reflect the complex interactions between fibrillin and integrin and latent TGFbeta. In some cases, a mutation in the fibrillin gene has not been found and other related genetic mechanisms or genes are likely to be involved.

Conclusion

The mimics of scleroderma are important because they represent important clinical problems and on occasion are a manifestation of a more complex multisystem medical condition. Whilst some are similar to scleroderma and might share pathogenic and aetiological features others are phenocopies or conditions that may resemble certain features. In general, systemic sclerosis and morphoea can be reliably diagnosed with available investigations and good clinical examination. Distinguishing between some of the scleroderma mimics can be a challenge and benefits for a multidisciplinary approach.

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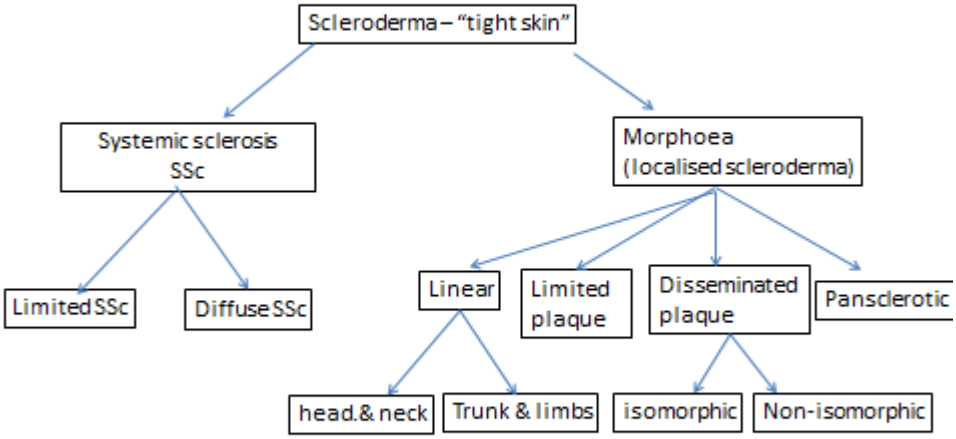
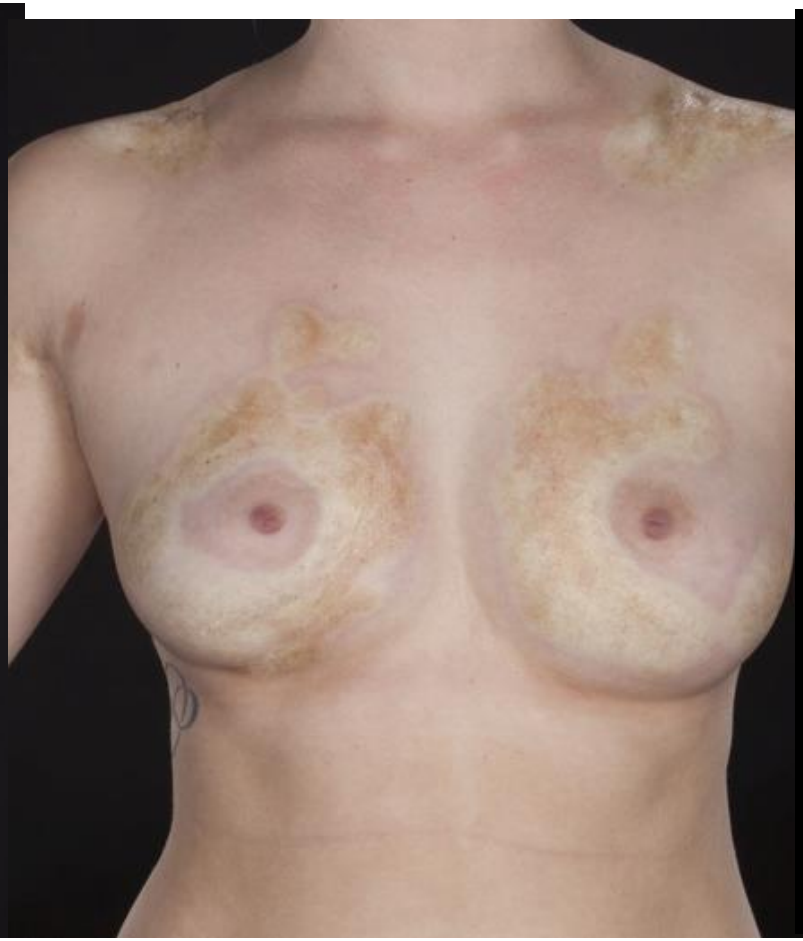
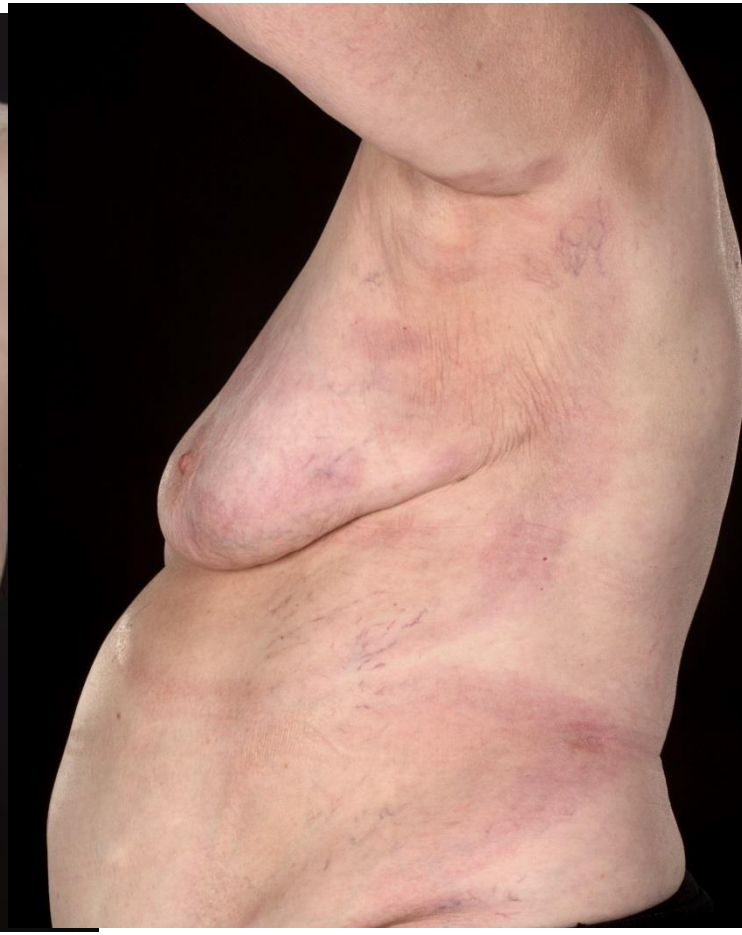
Figure 1 Overview of classification of scleroderma and morphoea



Linear morphoea



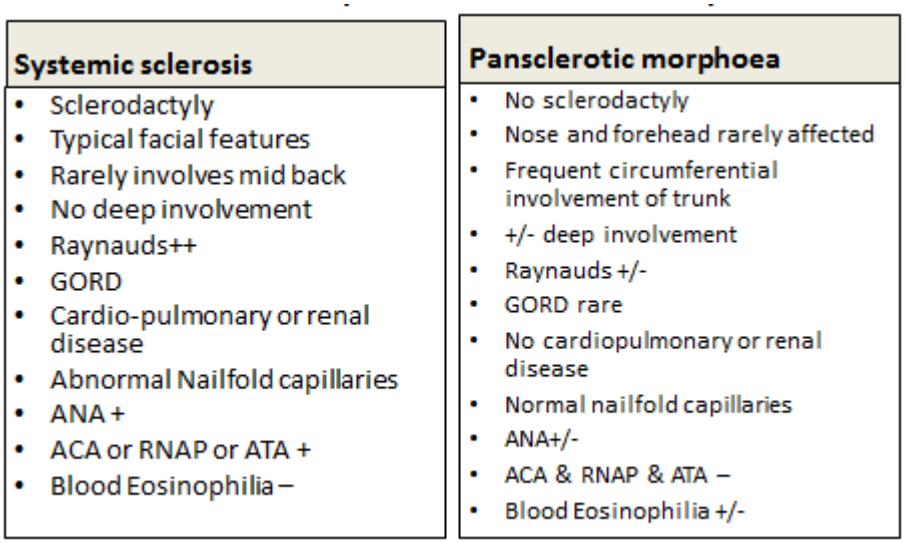
Disseminated plaque morphoea non-isomorphic



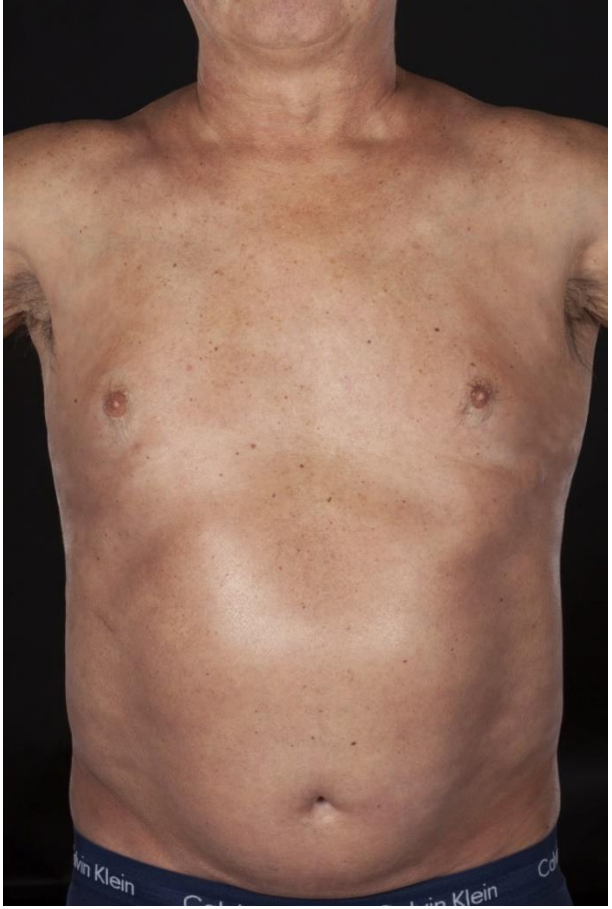
Disseminated plaque morphoea isomorphic

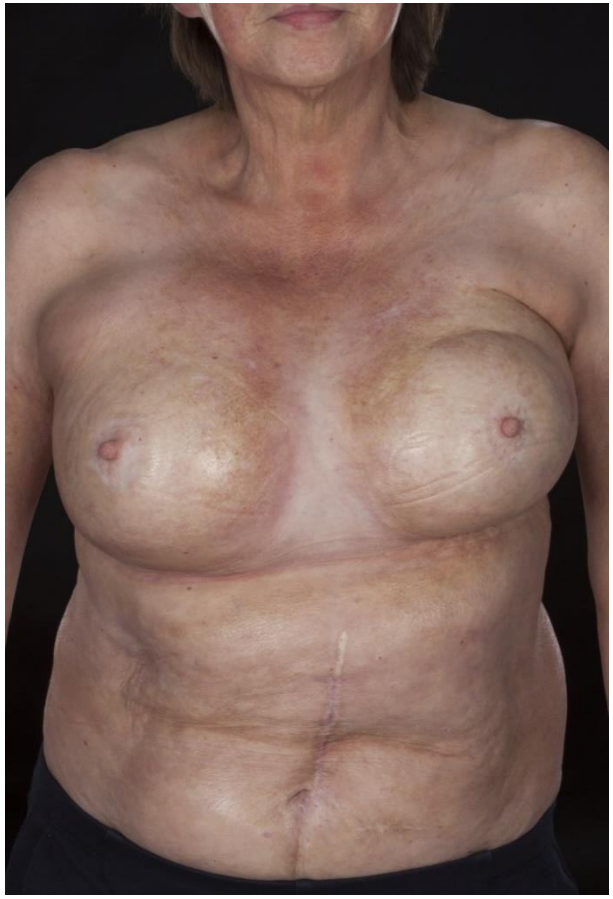
Figure 2 Morphoea

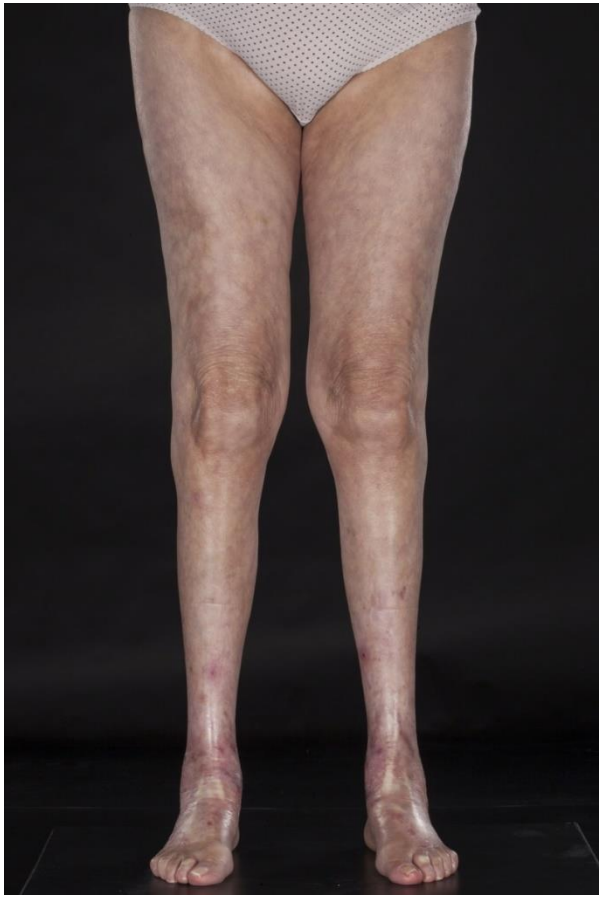
Figure 3 Key features differentiating systemic sclerosis from pansclerotic morphoea



Systemic sclerosis	Pansclerotic morphoea
• Sclerodactyly	• No sclerodactyly
• Typical facial features	• Nose and forehead rarely affected
• Rarely involves mid back	• Frequent circumferential involvement of trunk
• No deep involvement	• +/- deep involvement
• Raynauds++	• Raynauds +/-
• GORD	• GORD rare
• Cardio-pulmonary or renal disease	• No cardiopulmonary or renal disease
• Abnormal Nailfold capillaries	• Normal nailfold capillaries
• ANA +	• ANA+/-
• ACA or RNAP or ATA +	• ACA & RNAP & ATA –
• Blood Eosinophilia –	• Blood Eosinophilia +/-







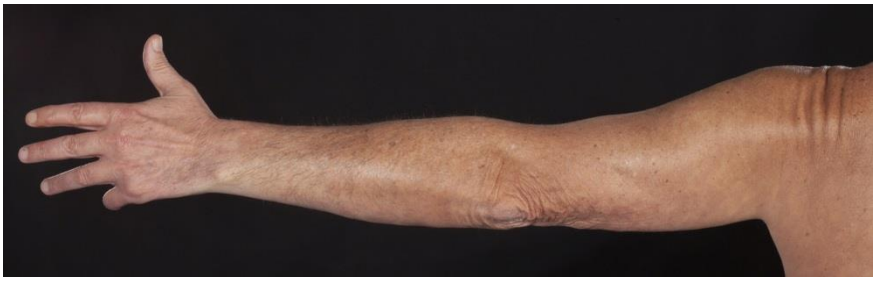
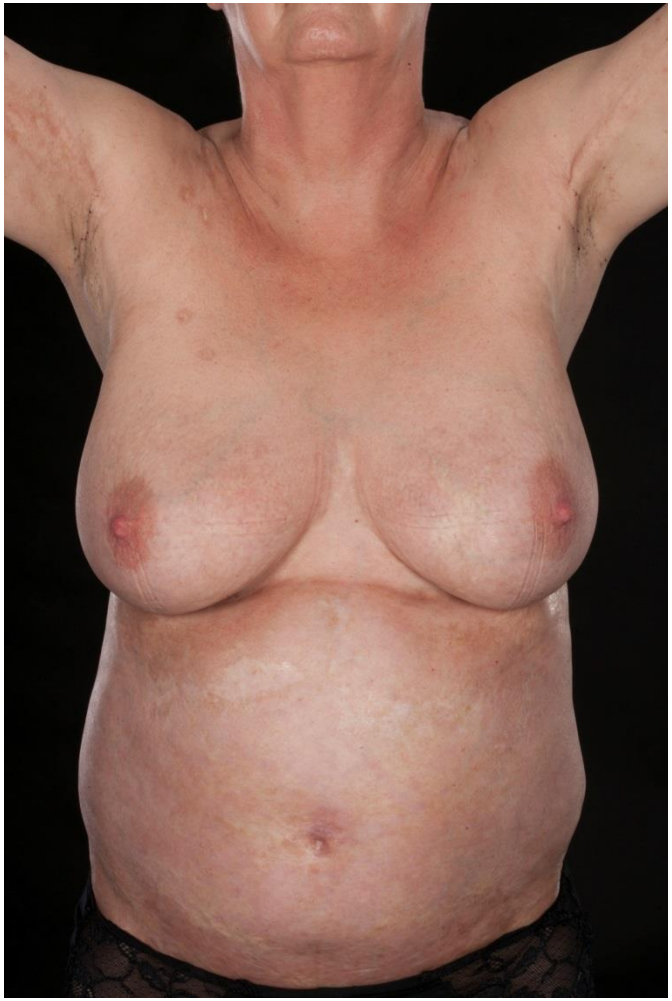


Figure 4. Pansclerotic morphoea: circumferential, trunk and four limbs spearing the periareolar skin

Figure 5 Sclerodermoid chronic graft versus host disease



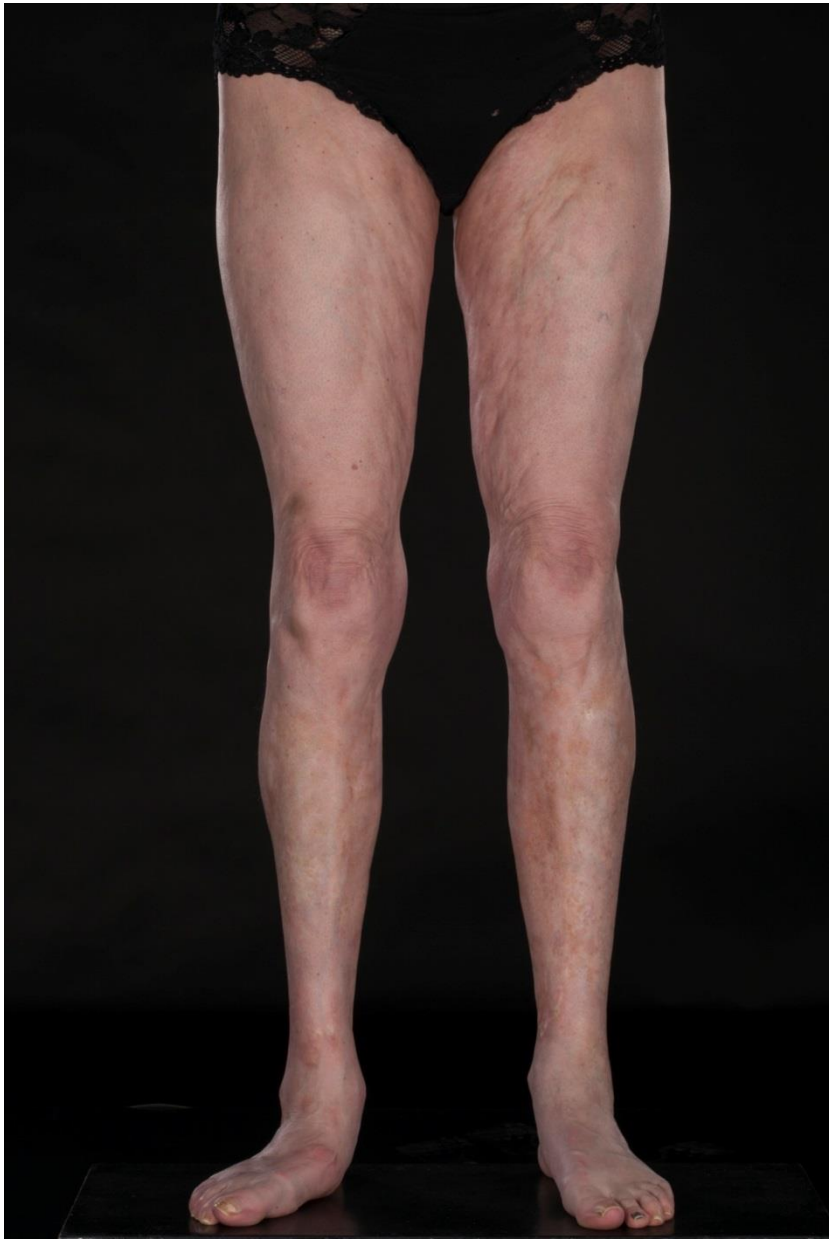
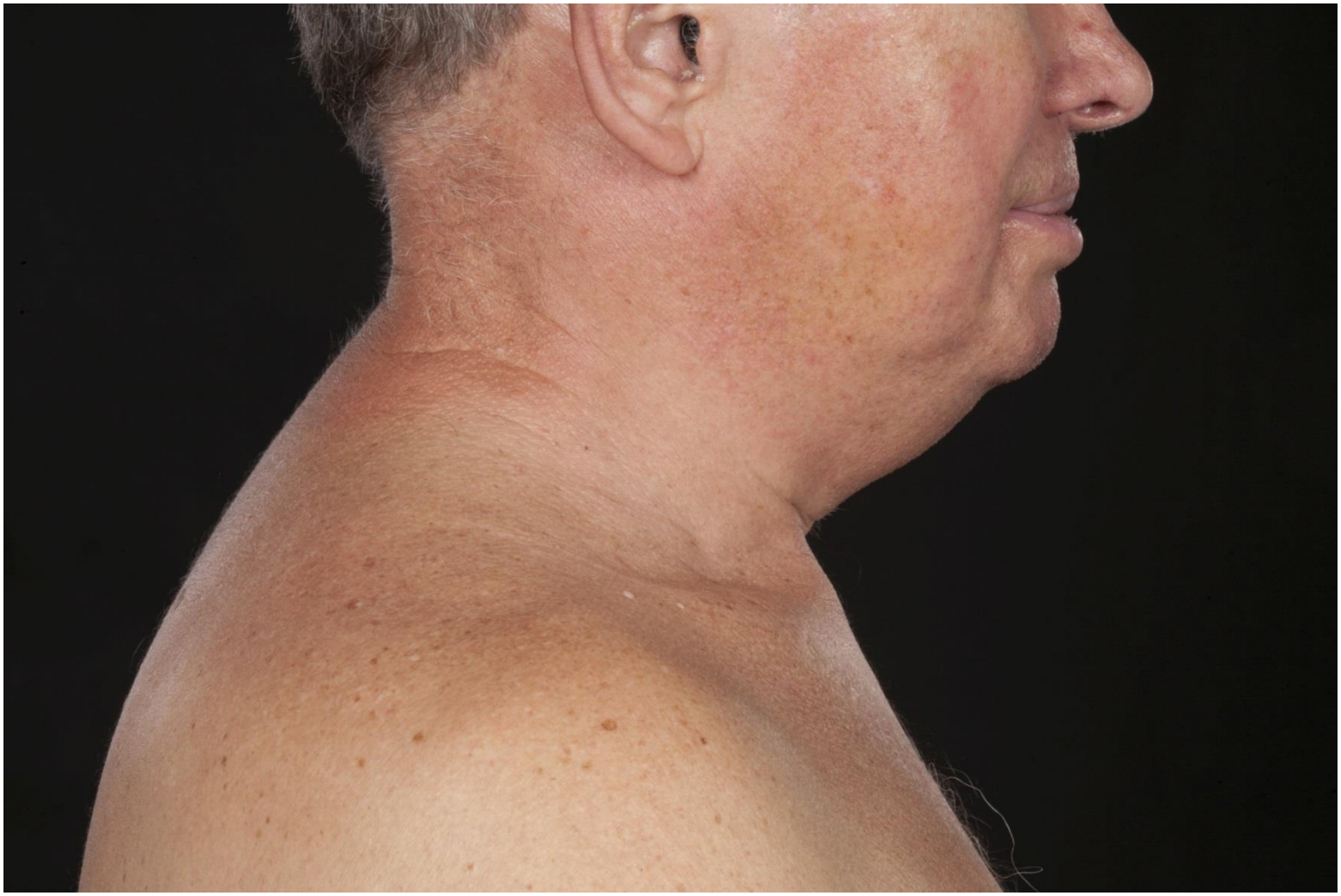
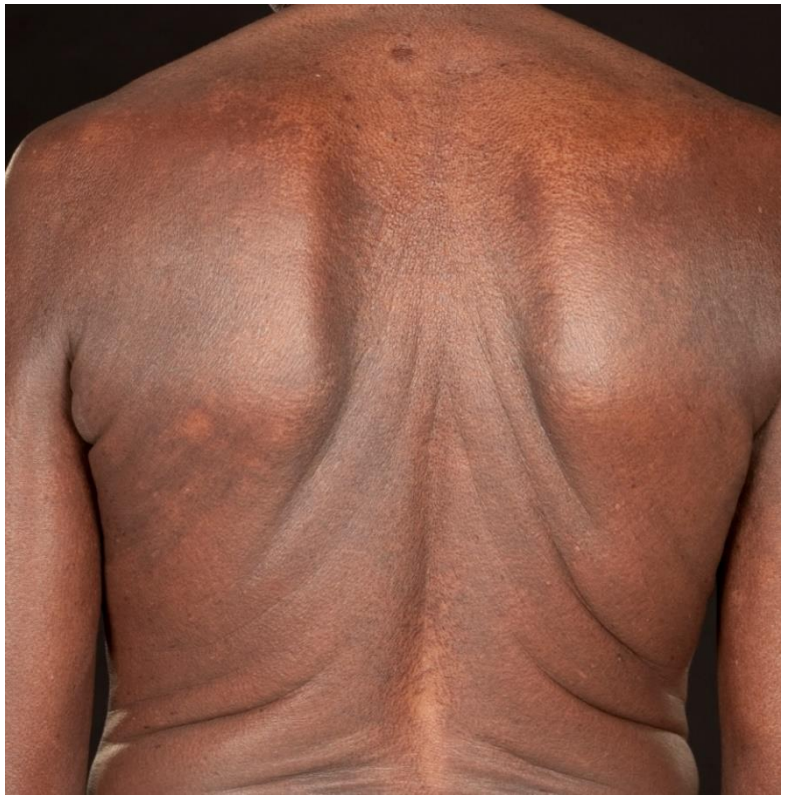
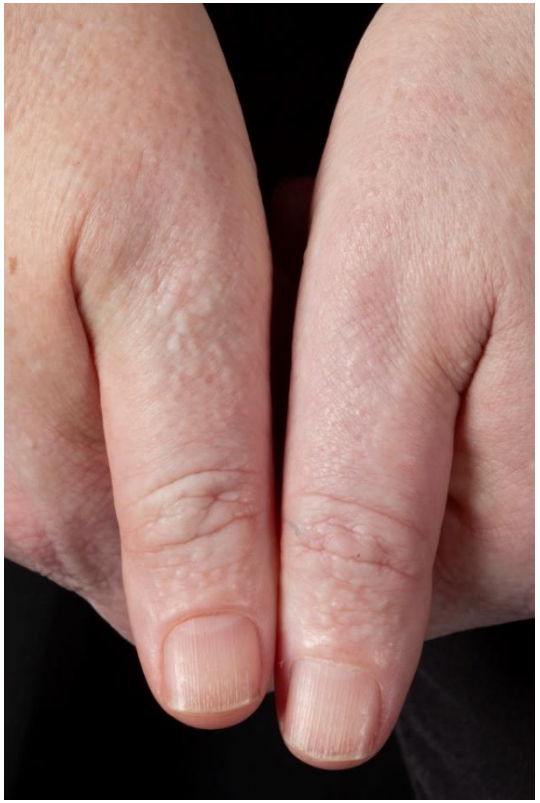


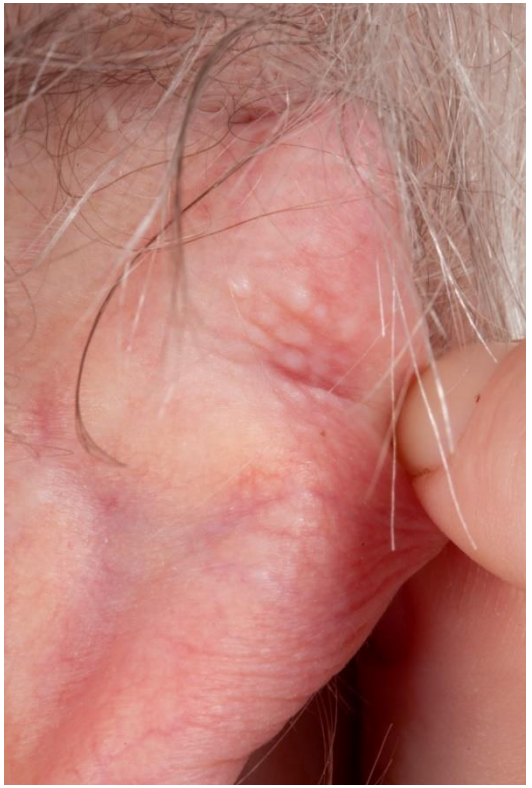
Figure 6 Scleroedema



Woody induration across the upper back , chest and neck in scleroedema







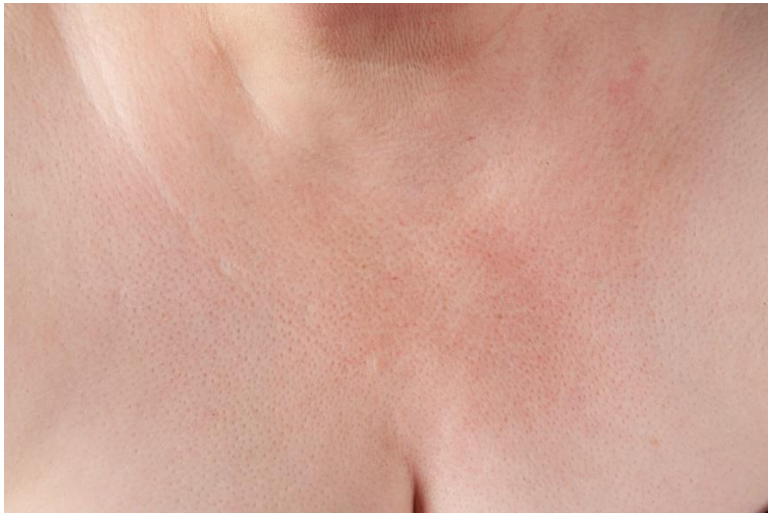


Figure 7. Scleromyxoedema.

Waxy dome shaped papules and Shar pei sign on the back are characteristic

Figure 8. Nephrogenic systemic fibrosis showing brawny indurated plaques