# Systemic sclerosis in adults. Part I: Clinical features and pathogenesis

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**ABBREVIATIONS**

| | |
|---|---|
| ACA | Anti-centromere antibodies |
| ACR | American college of rheumatology |
| ANA | Anti-nuclear antibodies |
| CD | Cluster of differentiation |
| CT | Cutaneous telangiectasia(s) |
| CTD | Connective tissue disease |
| dcSSc | Diffuse cutaneous SSc |
| DU | Digital ulcer(s) |
| eIF2B | Eukaryotic translation initiation factor 2B |
| ENA | Extractable nuclear antigen |
| ET-1 | Endothelin 1 |
| EULAR | European league against rheumatism |
| EUSTAR | The European Scleroderma Trials and Research |
| FVC | Forced vital capacity |
| GAVE | Gastric antral vascular ectasia |
| GI | Gastrointestinal |
| GORD | Gastroesophageal reflux disease |
| HLA | Human leukocyte antigen |
| HRCT | High-resolution computed tomography |
| IFI16 | Interferon Gamma Inducible Protein 16 |
| IGF1 | Insulin-like growth factor 1 |
| IL-X | Interleukin-X |
| ILD | Interstitial lung disease |
| IRF5 | Interferon Regulatory Factor 5 |
| lcSSC | Limited cutaneous systemic sclerosis |
| MCPJ | Metacarpophalangeal joint(s) |
| MCTD | Mixed connective tissue disease |
| MDT | Multidisciplinary team |
| mRSS | modified Rodnan skin score |
| NOS | Nitric oxide synthase |
| NVC | nailfold vidoecapillaroscopy |
| PAH | Pulmonary arterial hypertension |
| PDGF | Platelet-derived growth factor |
| PF | Puffy fingers |
| PIPJ | Proximal interphalangeal joint |
| PM | Polymyositis |
| RNAP3 | RNA-Polymerase III |
| RP | Raynaud’s phenomenon |
| Scl-70/TopoI | Topoisomerase-I |
| SLE | Systemic Lupus erythematosus |
| SRC | Scleroderma renal crisis |
| SSc | Systemic sclerosis |
| STAT4 | Signal transducer and activator of transcription 4 |
| TGF-β | Transforming growth factor beta |
| Th2 | T Helper cell 2 |
| U1-RNP | U1 small nuclear ribonucleoprotein |
| U3-RNP/Fibrillarin | U3 small nuclear ribonucleoprotein |
| VEDOSS | Very early diagnosis of systemic sclerosis |

## ABSTRACT

Systemic sclerosis (SSc, also referred to as systemic scleroderma or scleroderma) is a rare, complex immune-mediated connective tissue disease characterised by progressive skin fibrosis and other clinically heterogenous features. The etiopathogenesis of SSc involves vasculopathy and immune system dysregulation occurring on a permissive genetic and epigenetic background, ultimately leading to fibrosis. Recent developments in our understanding of disease specific autoantibodies and bioinformatic analyses has led to reconsideration of the purely clinical classification of diffuse and limited cutaneous SSc subgroups. Autoantibody profiles are predictive of skin and internal organ involvement and disease course. Early diagnosis of SSc, with commencement of disease modifying treatment, has the potential to improve patient outcomes. Many early presenting clinical manifestations, and signs of disease progression and activity in SSc are cutaneous, meaning Dermatologists can and should play a key role in the diagnosis and management of this significant condition. The first article in this continuing medical education (CME) series discusses epidemiology, clinical characteristics and pathogenesis of SSc in adults, with an emphasis on skin manifestations, the important role of Dermatologists in recognising these, and their correlation with systemic features and disease course.


## EPIDEMIOLOGY

**Key points:**

- SSc has an estimated incidence between 0.6-5.6 per 100,000 adults per year, with a high female predominance.
- SSc has the highest mortality of any rheumatic disease, however, the survival rate has improved with earlier detection and management of internal organ involvement.

The annual incidence of SSc is estimated between 0.6 -5.6 per 100,000 adults and prevalence between 7.2 - 44.3 per 100,000 adults.[4–8] A female predominance is reported worldwide, with women affected between 3.8 to 15 times more frequently than men.[4] The mean age at diagnosis ranges between 33.5-59.8 years.[4] Paediatric (juvenile) SSc represents less than 5% of all patients with SSc, and whilst it shares an abundance of clinical similarities with adult onset SSc, it will not be the focus of discussion in this CME article.[9]

SSc has the highest mortality of any connective tissue disease,[10] however, survival has improved, with an estimated cumulative five-year survival of 84% in dcSSc and 93-96% in lcSSc.[2,11,12,13] The most important causes of disease-related mortality are cardiac, respiratory (interstitial lung disease (ILD), pulmonary artery hypertension (PAH)) and renal (SSc-renal crisis (SRC)).[1–3,12,14] Non SSc-related causes of death include infection, malignancy and atherosclerosis.[1–3,14] Predictors of poor prognosis include male sex, older age, dcSSc subtype, presence of lung, renal or cardiac manifestations, digital ulcers and joint involvement.[1,11,14–16]

## DIAGNOSIS AND CLASSIFICATION

### Key points

- SSc is clinically classified as lcSSc and dcSSc, each with a distinct distribution of skin involvement, systemic manifestations and prognosis.
- Immunoserological autoantibody profiles are also used to aid diagnosis, classification and predict disease course.
- Early diagnosis of SSc can improve patient outcomes and Dermatologists can play a pivotal role in recognising early cutaneous features.
- It is important Dermatologists have an approach to diagnosis of SSc, and differentiating it from ‘scleroderma-like’ conditions.

The diagnosis of SSc is based on clinical findings, autoantibody profiles and additional specific investigations. SSc classification criteria have evolved significantly over time to guide assessment and diagnosis. Table I summaries the latest (2013) classification criteria released by The American College of Rheumatology (ACR) in conjunction with the European League Against Rheumatism (EULAR).[17] The criteria consider a broad spectrum of clinical features, together with vascular, serological and imaging findings. Variable weightings are placed on certain features according to clinical significance, such that patients with a score ≥9 are considered to have a definite diagnosis of SSc[17] (Table I).

These latest criteria improved sensitivity for the diagnosis of early SSc, which is vital to early initiation of disease modifying and outcome-altering treatment.[17] Despite this, diagnosis and treatment initiation is still frequently delayed by many years following onset of Raynaud's phenomenon (RP) and non-RP symptoms.[18] It is essential to recognise individuals with early symptoms and identify those who are likely to progress rapidly, in order to implement management, prevent complications and improve outcomes. The 'very early diagnosis of systemic sclerosis' (VEDOSS) project has identified RP, puffy fingers and positive anti-nuclear antibodies (ANA) as markers of early disease that predict progression to definite established SSc.[19,20] The diagnosis is confirmed by the presence of SSc-associated autoantibodies and/or abnormal nailfold capillaries. Patients with a combination of puffy fingers and disease specific autoantibodies have a predicted 94% probability of satisfying disease classification criteria within five years.[19,20] Capturing patients in this very early phase is seen as a window of opportunity for changing and improving longer term patient outcomes and is therefore extremely important for Dermatologists to recognise.

Given that many early manifestations of SSc are cutaneous, patients often seek dermatological services for initial assessment. Thus Dermatologists need to play a crucial role in recognising early SSc, assessing risk for disease progression and/or signs of systemic disease. Upon recognition of suspicious features, Dermatologists should investigate, treat and refer for appropriate ongoing multidisciplinary team (MDT) involvement. The potential pivotal role of Dermatologists in making the diagnosis, instituting MDT treatment and minimising morbidity in SSc should not be underestimated, and thus our collective improved and continued education and involvement in disease management is vital.

**Disease subgroups: limited cutaneous (lcSSc) versus diffuse cutaneous (dcSSc)**

Two distinct clinical subsets of SSc have been identified based on the distribution of skin involvement; lcSSc and dcSSc.[21] Skin thickening in lcSSc is limited to the distal limbs and face and does not extend proximal to the elbows, knees or involve the trunk. Meanwhile, dcSSc has skin thickening of distal as well as proximal extremities, face and trunk. Disease subtyping has important prognostic implications, as each has a distinct and largely predictable pattern of internal organ involvement. Some features overlap between the two subsets and both subtypes may co-exist with other connective tissue diseases such as systemic lupus erythematosus (SLE) or polymyositis (PM) in overlap connective tissue diseases (CTDs). This binary clinical disease classification has been used for many years and whilst it does have clinical utility, it is overly simplistic when used in isolation, and additional serological markers also need to be considered.

**Autoimmune serology and associations with clinical features and disease course**

Autoantibody profiles assist with diagnosis, classification and prognostication of SSc, and aid in excluding scleroderma-like conditions (scleroderma-mimics or pseudosclerodermas),

which by definition are SSc-specific autoantibody negative. Approximately 95% of SSc patients are ANA positive.[22–24] SSc-specific autoantibodies, including anti-centromere antibodies (ACA), anti-topoisomerase I/Scl-70 antibodies and anti-RNA polymerase (RNAP) I-III antibodies are associated with specific clinical features (Table II), and are therefore extremely important to consider in SSc management. SSc-overlap syndromes may have other autoantibodies such as anti-PM/Scl antibodies (myositis) and anti-U1-RNP (myositis and/or SLE). These autoantibodies should always be tested for in a clinical setting of suspected SSc diagnosis. Notably, double SSc-specific autoantibody positivity is extremely rare.[13] Some more recently identified, uncommon SSc-specific antibodies are being evaluated in the research setting including anti-eIF2B, anti-RuvBL1/2, anti-BICD2 and anti-IFI16 antibodies.[25]

Overall, skin-ANA classification of SSc (lcSSc vs dcSSc, and SSc-specific autoantibody profile) has validated data-driven utility in clinical practice. Nihtyanova, *et al.* recently reported the combination of autoantibodies and skin involvement predicts survival, timing, risk and incidence of systemic complications.[13] Five autoantibodies (ACA, anti-Scl-70, anti-RNAP, anti-U3-RNP, 'other') and two skin subsets (lcSSc, dcSSc) were identified and each group assessed for survival and organ complications (Table III). ACA positive patients had the best survival overall, however, they accrued significant complications over the disease course. Patients with dcSSc and either Scl-70 positive or 'other' antibody profiles (including ANA+ENA− and ANA−) had worst survival overall. Patients who were anti-RNAP3 positive also did poorly.

**Emerging classification approaches**

Work by a number of groups is in progress to refine and improve current SSc classification approaches even further. These are based on our ever increasing need to better stratify this complex multi-organ disease according to likelihood of various clinical manifestations, short and long term prognosis, as well as the prospect of future individualised targeted treatment approaches. Whilst not yet ready for clinical application, these approaches begin to examine the current skin-ANA classification further, to consider a spectrum of more detailed patient subgrouping.[26] In addition, molecular level (proteomic (protein) and transcriptomic (RNA, gene expression)) classification from skin and blood samples is also emerging as a promising means of predicting treatment responses.[27,28] These emerging refined and molecular level classification approaches need further work, but will likely one day enable targeted and personalised therapeutic decision making in SSc.

**Differential diagnosis and diagnostic considerations**

When considering a diagnosis of SSc, it is important to have a clinical approach to distinguishing key differential diagnoses. Other causes of thickening of the skin include morphea (localised scleroderma) and scleroderma-like conditions (also referred to as scleroderma-mimics or pseudosclerodermas) (Figure 1).

Importantly, terminology in this area can be confusing. The term ‘scleroderma’, literally meaning ‘thick skin’, should be used as an umbrella term to encompass both morphea (localised scleroderma) and systemic sclerosis (systemic scleroderma). Referring to either specific diagnosis, as ‘scleroderma’ is confusing, misleading and can result in significant patient anxiety; especially in the setting of a diagnosis of morphea.

Morphea (also known as localised scleroderma), refers to sclerotic skin disease limited to the skin and underlying connective tissues (such as subcutaneous tissue, fascia, muscle and bone). Although many classification systems exist, morphea is most widely categorised according to anatomical distribution of skin fibrosis, as; limited, linear, generalised and mixed pattern. Severe forms of generalised morphea can sometimes be confused with SSc and it is important for Dermatologists to have a clear understanding of the distinguishing features (Table IV). Nailfold capillary abnormalities and sclerodactyly are not features of morphea, even severe pansclerotic generalised morphoea subtypes spare the digits (and areolae). Morphea never has associated fibrosis of any internal organs nor the presence of SSc-specific autoantibodies.[29] Severer forms of morphea, including linear and generalised subtypes, may have extracutaneous manifestations, such as arthralgias, myalgias and gastroeosophageal reflux, thought to be due to the systemic autoimmune inflammatory nature of the disease, but never due to internal organ fibrosis. Although rare, SSc and morphea can co-exist. Keloidal or localised plaque morphoea are most frequently seen in this setting.

Scleroderma-like diagnoses are broad and include scleromyxoedema, sclerodema adultorum, nephrogenic systemic fibrosis and sclerodermatous graft versus host disease (Figure 1). Relevant features on clinical history, examination, autoimmune serology and histology are needed to work through these differential diagnoses and systematically exclude or confirm SSc. Simply, the presence of RP, SSc-specific autoantibodies and nailfold capillary abnormalities definitively distinguish SSc from these conditions.

In the clinical setting of a favoured or confirmed diagnosis of SSc, SSc-overlap syndromes, potential external triggers and malignancy should also be considered.

As previously mentioned, SSc can co-exist with other connective tissue diseases (CTD), in a scleroderma overlap syndrome, or overlap CTD. Clinically, features of SSc and another CTD are present, often with autoantibodies of both. Autoantibodies against U1-RNP tend to characterise an overlap CTD, and Pm-Scl antibodies are specific to SSc occurring with myositis/dermatomyositis.

Environmental and occupational exposures, such as epoxy resins, vinyl chlorides and silica have been implicated in the pathogenesis of SSc, and a thorough history to elucidate the potential presence of these may be necessary (Figure 1).

Notably, there is an overall increased risk of malignancy in SSc, particularly lung, haematological, liver, bladder and breast.[30–33] Patients who have negative autoimmune serology and, even more so, those who are RNAP3 antibody positive, have an increased risk of malignancy.[8,31,33] Patients with anti-RNAP3 antibodies have the highest risk of synchronously diagnosed malignancy, usually between 6 months before and 12 months after SSc onset.[33] Clinicians must be alert to paraneoplastic SSc and should investigate or refer accordingly.

## Section II: Proposed pathogenic mechanisms

### Key points

- SSc pathogenesis is complex, multifaceted and incompletely elucidated.
- SSc pathogenesis involves early vasculopathy, innate and adaptive immune system dysfunction and ultimately abnormal connective tissue formation.
- An interplay between underlying predisposing genetic variation and epigenetic changes likely interact with secondary environmental triggering factors to influence disease susceptibility and onset.
- The specific role of autoantibodies in disease pathogenesis is unclear.

The complex, multifactorial aetiopathogenesis of SSc remains incompletely understood. A combination of early vascular abnormalities, immune system dysregulation and dysfunctional connective tissue turnover, involving profibrotic signalling, are key to disease development (Figure 2).[18,34]

### Genetic predisposition

Family history of SSc in affected individuals is rare and concordance rates for SSc in monozygotic twins is low (4.7%).[35] Nonetheless, studies have demonstrated a genetic predisposition to disease development and identified numerous genes associates with SSc.[36] These include HLA class II genes, with different alleles associated with the major autoantibody types and varying between ethnic groups (Table II). Genes encoding transcription factors involved in interferon signalling (e.g. IRF5)[37], other inflammatory cytokines, signalling molecules (e.g. STAT4, CD247)[38], genes influencing vascular function (e.g. eNOS)[39] and extracellular matrix components (e.g. fibrillin-1)[40] have also been implicated.[36,41,42]

## Environmental Triggers

The postulated triggers for the early changes in SSc include infection, toxins, immune-mediated cytotoxicity, oxidative stress, toxins, anti-endothelial antibodies and ischaemia-reperfusion injury.[18,34,43] Environmental and occupational exposures, specifically silica, solvents, pesticides and epoxy resins have been implicated as potential causative factors.[44] Consequently, SSc is recognised as an occupational disease in persons with recurrent silica dust exposure e.g. in stonemasons.

These environmental factors are thought to trigger disease processes in genetically susceptible individuals through epigenetic modifications, including DNA methylation, histone acetylation and microRNA expression.[36] Better characterisation of these epigenetic changes may lead to new therapeutic approaches and better understanding of SSc pathogenesis in the future.[18,36]

## Vasculopathy

The aforementioned triggers induce vasculopathy through various mechanisms. Platelet activation and upregulation of adhesion molecules leads to luminal occlusion which adds to ischaemia and production of reactive oxygen species.[43] In response to injury, endothelial cells may undergo apoptosis, endothelial-mesenchymal transition or activation to secrete pro-fibrotic and pro-inflammatory mediators.[34,43] Furthermore, there is an imbalance between vascular tone mediators promoting vasoconstriction (e.g. endothelin), inflammation (e.g. superoxide anions) and vasodilation (e.g. nitric oxide).[18,43,44] All these factors contribute to defective vasculogenesis and impaired vessel repair.[34,43,45]

**Immune dysregulation**

Innate and adaptive immune system abnormalities contribute significantly to SSc pathogenesis. Skin-infiltrating T cells are predominantly of the T-helper 2 (Th2) subtype with a corresponding increase in Th2 cytokines (e.g. IL-4, IL-13, IL-5), which have been associated with fibrosis in animal studies.[34] The SSc-specific autoantibodies mentioned above are important for the diagnosis of the disease subsets, however their role in disease pathogenesis is unclear.. More recently however, other circulating autoantibodies have been described, which may activate receptors of the innate (e.g. toll like receptors) and adaptive (e.g. Fc-Receptors) immune system as well as induce fibroblast activation[34,43] The cell-cell and cell-matrix interactions between immune cells, endothelial cells and fibroblasts stimulate production and release of cytokines and growth factors. Type 1 interferon and interferon-inducible genes have been strongly implicated in SSc pathogeneses.[46,47] Other strong contributors include TGF-β which drives fibrosis pathways as well as PDGF, ET-1 and IGF1.[34,43] For a detailed overview of the postulated molecular aetiopathogenesis of SSc please see reference 43 (Varga, *et al.,* 2017).

The association between malignancy and anti-RNAP3 antibodies further emphasises the role of immunological abnormalities in SSc.[18,32,33,48] Tumours may produce somatic mutations, which induce antibody formation against the mutated protein e.g. mutated RNA polymerase III inducing anti-RNAP3 antibodies and thus leading to a systemic autoimmune response.[49]

Ultimately, vasculopathy, coupled with immune dysregulation, promotes excessive deposition of extracellular matrix proteins, mainly collagen, leading to the characteristic inflammation and tissue fibrosis seen in SSc.[18,34]

## Section III: Clinical presentation

SSc is clinically heterogeneous. Patients may present with skin, vascular, internal organ-based and/or constitutional symptoms. Skin abnormalities occur early in the disease course and thus Dermatologists play a crucial role in recognition of these manifestations and escalation of care.

### CUTANEOUS MANIFESTATIONS

**Key points**

- Inflammation of the fingers, causing early oedema (puffy fingers) with subsequent progressive skin fibrosis and atrophy (sclerodactyly), is pathognomonic of SSc.
- Orofacial fibrosis results in reduced oral aperture, amima, xerostomia and sicca syndrome, with consequences for dental health.
- Rapidly progressive, diffuse skin fibrosis is a predictor of early internal organ involvement.

### Skin Fibrosis

**General**

Skin thickening is the uniting feature of all SSc and pseudoscleroderma disorders. In SSc, this is due to fibrosis and as discussed above, the extent of skin fibrosis determines whether the disease is considered diffuse or limited, with prognostic implications. Skin thickness (induration) in lcSSc tends to develop slowly and shows little variability over time whereas it tends to increase rapidly in early dcSSc, peak around 12-18 months and decrease in late disease.[18] The rate and extent of induration varies greatly between patients. Three dcSSc phases have been described: (i) oedematous phase lasting 6-12 months, (ii) fibrotic/indurative phase lasting at least 1-4 years, and (iii) an atrophic phase that continues indefinitely.[50] These

phases may overlap and although uncommon, patients may have recurrence or ‘flare’ of progressive skin involvement in later disease.[50] Importantly, this may be a marker of concurrent internal organ progression. Autoantibodies influence the fibrotic process, with anti-RNAP3 positive patients having a more rapidly progressing diffuse fibrosis than other autoantibody groups.[51,52] Rapid skin thickness progression is an independent predictor of early mortality and development of scleroderma renal crisis (SRC).[51,52]

**Sclerodactyly**

Sclerodactyly refers to the tightening and thickening of skin over the fingers or toes distal to the metacarpo-/metatarso-phalangeal joints but proximal to the proximal interphalangeal joints.[17] It is usually symmetrical and in the early inflammatory stage of the disease, fingers often have a puffy, oedematous appearance (“puffy fingers”).[53] This is reversible, however, over time the skin thickness (fibrosis) progresses and dermal atrophy occurs, leading to spindle-shaped fingers surrounded by contracted skin (Figure 3a). The resulting fixed-flexion deformity at the proximal interphalangeal joints greatly impairs activities of daily living. The diagnostic sensitivity and specificity of sclerodactyly is recognised as part of the ACR/EULAR 2013 classification criteria (refer to Table I; 4 of required 9 points). Furthermore, sclerodactyly was present in almost 20% of patients considered to have very early onset SSc and thus may serve as a key initial clinical feature to prompt further work-up.[19]

**Orofacial fibrosis**

Fibrosis of the skin around the mouth can lead to radial perioral furrowing, microstomia (oral aperture less than 4.5cm), microcheilia, impaired speech and mastication (Figure 3b).[54] Up to 80% of patients are affected and there is a significant psychosocial impact.[55] Tightening of

the skin on the face can cause a pointed, beaked nose, impaired eye opening and decreased facial expression (amima).[56] Sclerosis of eccrine glands causes xerostomia and reduced tear secretion with resulting sicca syndrome.[54,56] Additionally, xerostomia coupled with reduced mouth opening impedes proper oral care and can result in damage to teeth and gums, as well as weight loss due to reduced food intake.[57] Sclerosis of the lingual frenulum is rare but can impair speech and swallowing.[54]

### Skin overlying joints

Fibrosis of the skin overlying joints and the associated tendons leads to friction rubs, contractures and joint deformities. Patients can experience arthralgia, myalgia and muscle weakness. Consequent reduced mobility can have significant functional impact.[58] Thirty-50% of patients develop fixed deformities.[58,59]

## CUTANEOUS VASCULOPATHIC CHANGES

### Key points

- Nailfold capillaroscopy is important in the diagnosis of SSc. Examination can be undertaken using a dermatoscope, enabling rapid detection of capillary abnormalities.
- RP occurs in the majority of SSc patients, months to years prior to onset of other non-RP features. Association with puffy fingers and nailfold capillary changes are red flags to the early diagnosis of SSc.
- Digital ulcers (DU) classically refer to ischaemic fingertip ulcers, but may also occur secondary to trauma or calcinosis. DU cause significant pain and functional impairment.
- Cutaneous telangiectases occur on the face, chest and palms, are often of cosmetic concern, and are a marker of systemic microvascular disease.

**Nailfold capillary changes**

Nailfold capillary morphology and structure can be visualised non-invasively using high or low magnification. Whilst high resolution nailfold vidoecapillaroscopy (NVC) with 200-fold magnification is the gold standard for nailfold capillary assessment, it is not readily available in most clinical settings. Low resolution (x10) visualisation using a dermatoscope has comparable sensitivity to NVC and allows clinicians to routinely assess nailfold capillaries.[60]

Normally, nailfold capillaries are arranged in orderly "hairpin" rows (Figure 4a). In SSc, classic abnormalities are enlarged capillaries, capillary loss ("dropout") and microhaemorrhages (Figure 4b-d).[61,62] A disturbance in the normal arrangement of these hairpin capillaries is present in ~74% of SSc patients and serves as a marker of systemic microcirculation changes.[63,64] Early disease features include few giant capillaries and microhaemorrhages, in active disease, these increase in number, capillaries become more disorganised and dropout occurs.[62] In late stages, severe capillary loss leads to avascular areas and due to aberrant neovascularisation, and overt disorganisation of capillary architecture ensues.[62,65]

In recognition of the diagnostic significance and insight into disease activity provided by nailfold capillary abnormalities, this feature is one of the 2013 EULAR/ACR classification criteria and VEDOSS confirmatory criteria.[17,19] Nailfold capillaroscopy may be a future outcome measure for clinical trials of SSc-associated vasculopathy.[66]

A rapid algorithm for assessment of nailfold capillary pattern suitable for individuals of variable capillaroscopy experience has also been developed to facilitate clinicians and can be read in detail in reference 67 (Smith, *et al. 2019).*[67]

**Raynaud's Phenomenon (RP)**

The majority (>90%) of SSc patients experience RP.[17] Time from onset of RP to development of non-RP symptoms often varies according to SSc subtype; being shorter in dcSSc (months) than lcSSc (years).[21] RP typically affects the fingers and less commonly the toes, ears, lips and nipples.[62,68] The aberrant digital perfusion is characterised by a triphasic colour change: initial pallor (vasospasm), followed by blue/purple cyanosis (deoxygenation of sequestered blood) and then erythema (post-ischaemic hyperaemia).[68] Not all colour changes may occur but at least two changes are usually required to make the diagnosis. This process is often coupled with numbness, tingling, pain and impaired function.[69] Triggers include cold temperatures or strong emotions/stress, however, unlike primary RP, symptoms are often present throughout most of the year.[70]

Identifying patients with possible secondary RP requires careful assessment for co-existing features. Concurrent puffy fingers, oesophageal dysfunction and/or positive ANA are suggestive of very early SSc.[19] Detection of specific autoantibodies and aberrant nailfold capillaroscopy are independent predictors of progression from RP to SSc.[71] Other red flags include sclerodactyly, DU, digital pitting scars, telangiectasia and onset after 40 years of age.[62,68] There are numerous other causes of secondary RP including extra- or intravascular compression or occlusion (e.g. atherosclerosis, vasculitis), drug-induced (e.g. beta-blockers), other connective tissue diseases such as SLE, or simply autoimmune RP (RP in the presence of positive ANA, but no definitive CTD diagnosis).[68] In contrast to primary RP, patients with secondary RP are at risk of developing persistent tissue ischaemia and tissue loss.[72] For a detailed recent review of RP classification and assessment, see reference 68 (Pauling, *et al.*, 2019).

**Ischaemic digital ulcers (DU)**

Approximately 50% of SSc patients experience DU, which typically first occur early in the disease course (majority within the first 5 years).[59,72–74] The term 'digital ulcer' usually refers to ulcers of the distal fingers and toes which are ischaemic in origin due to microvascular pathology and RP (Figure 5a). The key differential diagnoses are ulcers occurring over areas of calcinosis or related to trauma, which typically occur over extensor surfaces of the small joints of the hands which are under increased skin tension due to sclerodactyly.

Ischaemic DU are painful, have a large impact on function as well as overall health related quality-of-life.[75–77] They are one of the key contributors to impaired functional capacity as perceived by patients.[58] In a group of patients meeting VEDOSS criteria, ischaemic DU were observed in those with pulmonary and/or gastrointestinal involvement and not in those without evidence of internal organ involvement.[78] A recent EUSTAR survey found that classification of ischeamic DU into episodic, recurrent and chronic, as opposed to recurrent and not recurrent, more accurately reflects the clinical course.[77,79] Digital ulcers can be complicated by secondary infections (particularly with *Staphylococcus aureus*), which may progress to osteomyelitis and require amputation.[80,81]

**Cutaneous telangiectases**

These superficial dilated cutaneous blood vessels are typically found on the face, chest and palms in over half of SSc patients.[64] (Figure 6) They are a marker of microvascular abnormalities; the presence of profuse and pseudotumoural cutaneous telangiectasia (CT) are associated with DU, late NVC pattern and PAH.[82] Rapid progression of CT may serve as a

marker of progression of internal vascular abnormalities. Numerous palmar telangiectases are seen more commonly in patients with RNAP3 antibodies.

CT are also of cosmetic concern and patients may report anxiety due to their appearance. Patients presenting with RP and concurrent telangiectasia should have further investigation for underlying SSc.

## CALCINOSIS

### Key points

- Calcinosis typically occurs at finger tips and over extensor surfaces.
- Calcinosis may be asymptomatic or cause pain and ulceration depending on size and location.

Calcinosis is the intradermal or subcutaneous deposition of insoluble calcified material (mostly calcium hydroxyapatite) and occurs in 20-40% of SSc patients.[64,83–86] Calcinosis is most commonly found over the finger tips and extensor surfaces of extremities (elbows, knees, shoulders) (Figure 7)[85,87] The aetiopathogenesis is poorly understood. A combination of chronic vasculopathy with corresponding ischaemia, repetitive trauma and localised structural damage is postulated to contribute.[85] An association with HLA-DRB1*04 and polymorphisms in genes involved in extracellular matrix protein deposition or systemic calcification inhibitors (e.g. Fetuin A) have also been implicated.[88–90] Calcinosis is more common in patients who are ACA positive, have a history of surgical debridement, osteoporosis and longer disease duration.[83,87] The size and location of the deposits determine the associated morbidity, such that patients may be asymptomatic or experience significant pain from local pressure, ulceration through skin, superimposed infections and joint contractures.

## PRURITUS

Approximately 40% of SSc patients experience pruritus, typically in the early, inflammatory phase of the disease.[91,92] This may be due to inflammatory irritation of nerves and/or fibrotic nerve ending entrapment. Pruritus is independently associated with greater skin fibrosis (higher mRSS scores), gastrointestinal involvement, as well as reduced mental and physical functioin.[91–93] This symptom and its pathogenesis remain poorly defined in SSc.

## SYSTEMIC MANIFESTATIONS

- The lungs, heart, kidneys and gastrointestinal tract can all be involved in SSc
- Certain antibody profiles and risk factors predispose patients to more severe or rapid internal organ involvement
- Screening for organ involvement at baseline and throughout disease is important

The majority of morbidity and mortality in SSc results from internal organ manifestations including ILD, PAH, SRC, gastrointestinal abnormalities and cardiac dysfunction (Table V). Autoantibody profile influences the time course and severity of organ involvement (Table II). Screening for internal organ complications should be done at diagnosis and according to symptoms and risk factors (Table V). Regular follow up to identify complications is essential. It is important Dermatologists are aware of the need for multidisciplinary care, regular organ monitoring, and the progressive irreversible nature of organ involvement in SSc. Put simply, regular pulmonary and cardiac monitoring, investigation of kidney and GI functions and the early institution or escalation of appropriate treatments saves lives, so all clinicians involved in the care of patients with SSc must be aware and vigilant. Importantly, progression of skin disease is an indicator of systemic disease progression, and should be managed accordingly.

Monitoring of skin disease in SSc will be discussed in Part II of this CME series.

## Conclusion

Systemic sclerosis is a complex multi-system connective tissue disease characterised by progressive skin fibrosis and other cutaneous and systemic clinical features. Ongoing work in finessing disease classification systems has shown us that autoantibody profiles are predictive of skin and internal organ involvement and disease course and should be routinely used in clinical practice. Early diagnosis of SSc, with commencement of disease modifying treatment, has the potential to improve outcomes. Many early manifestations, and signs of disease progression and activity in SSc are dermatological, meaning Dermatologists can and should play a key role in the diagnosis and management.

The second article in this CME series will discuss monitoring of skin disease and SSc treatment.

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**FIGURES**

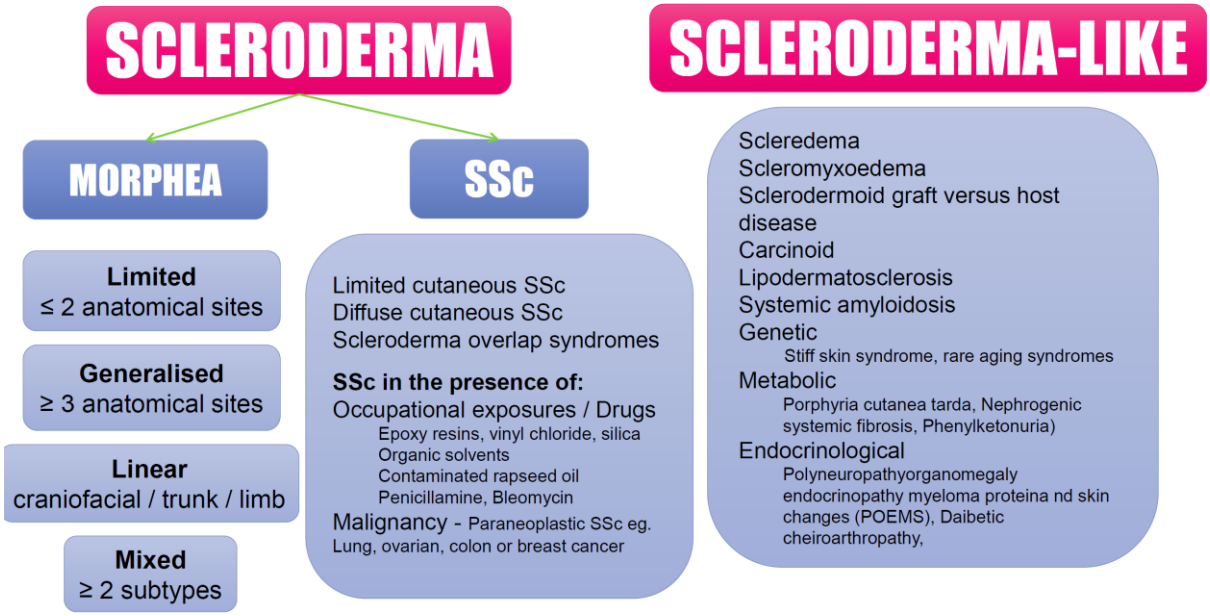



**Figure 1:** Differential diagnoses to consider in a patient with suspected scleroderma[17,94–97]

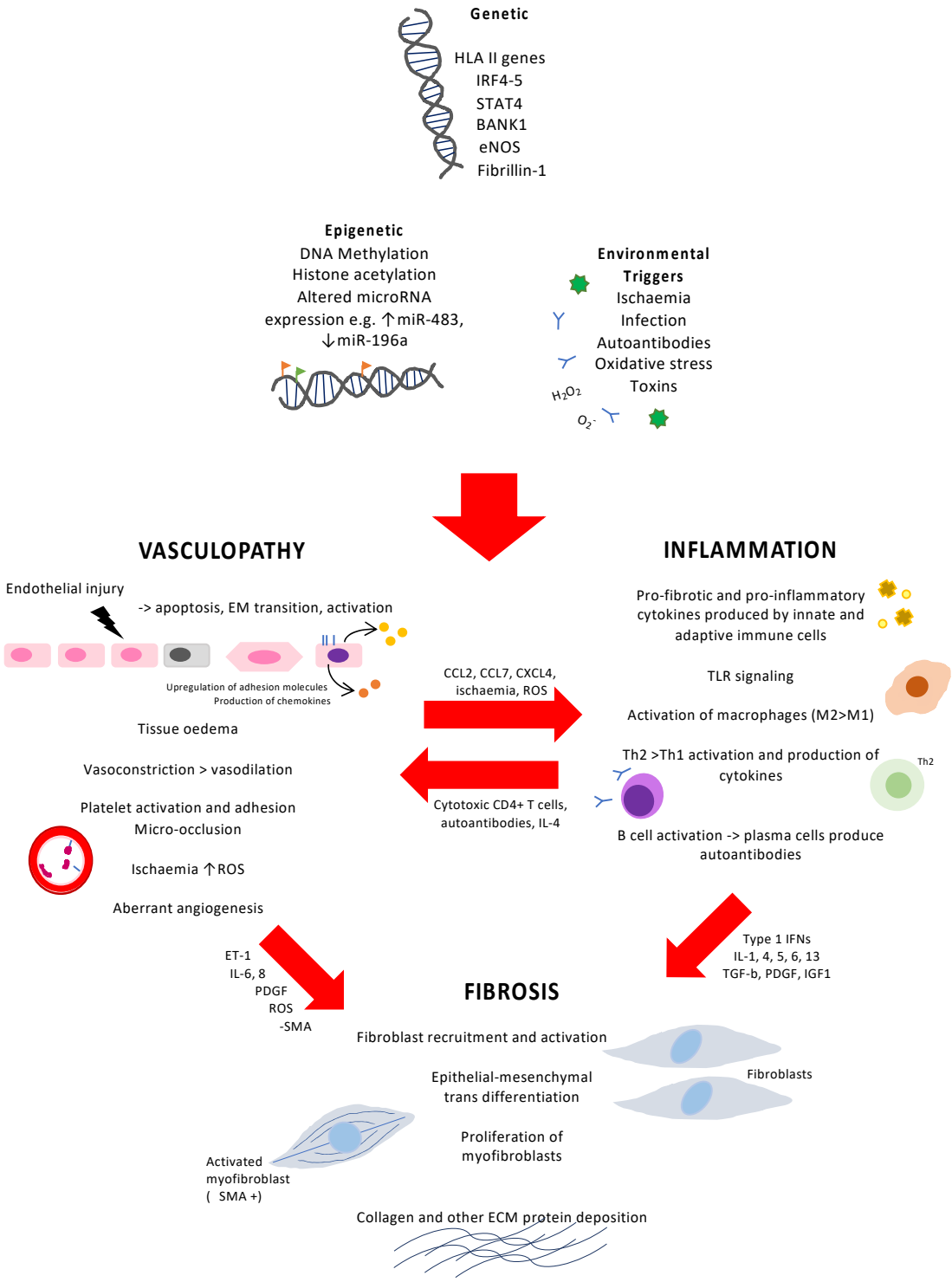
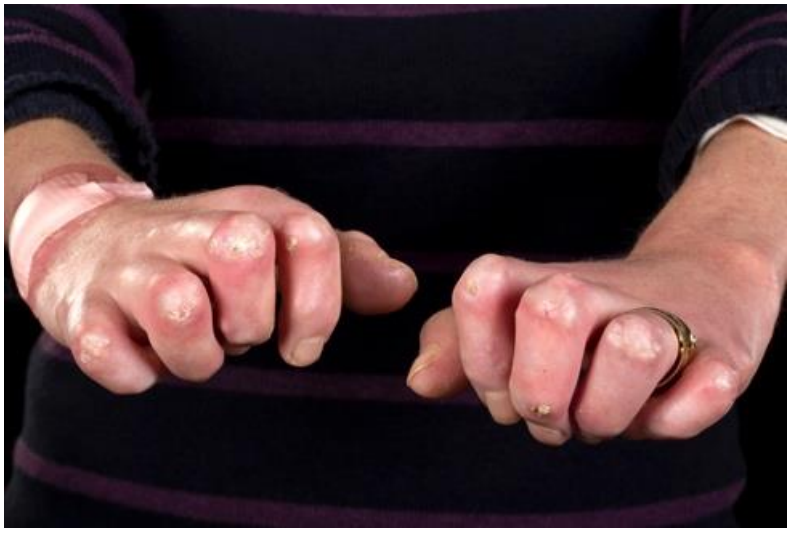
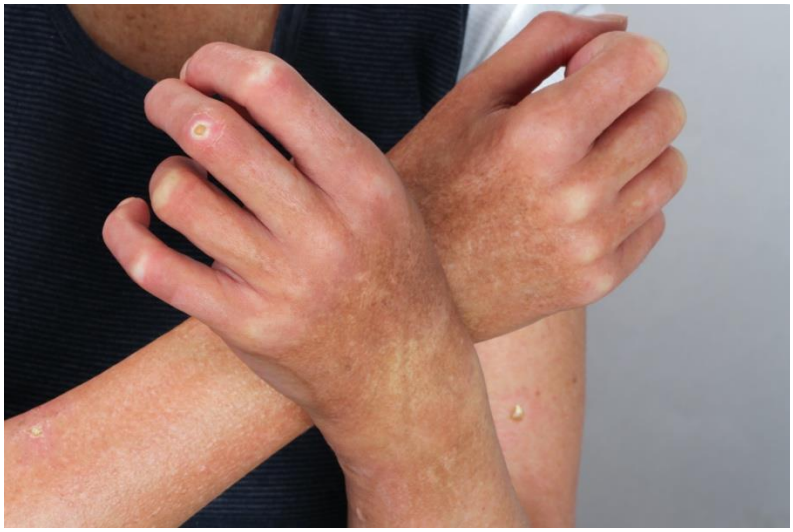

Genetic
HLA II genes
IRF4-5
STAT4
BANK1
eNOS
Fibrillin-1
Epigenetic
DNA Methylation
Histone acetylation
Altered microRNA
expression e.g. ↑miR-483,
↓miR-196a
Environmental
Triggers
Ischaemia
Infection
Autoantibodies
Oxidative stress
Toxins
VASCULOPATHY
INFLAMMATION
Endothelial injury
-> apoptosis, EM transition, activation
Upregulation of adhesion molecules
Production of chemokines
Tissue oedema
Vasoconstriction > vasodilation
Platelet activation and adhesion
Micro-occlusion
Ischaemia ↑ROS
Aberrant angiogenesis
CCL2, CCL7, CXCL4,
ischaemia, ROS
Cytotoxic CD4+ T cells,
autoantibodies, IL-4
Pro-fibrotic and pro-inflammatory
cytokines produced by innate and
adaptive immune cells
TLR signaling
Activation of macrophages (M2>M1)
Th2 >Th1 activation and production of
cytokines
Th2
B cell activation -> plasma cells produce
autoantibodies
ET-1
IL-6, 8
PDGF
ROS
-SMA
Type 1 IFNs
IL-1, 4, 5, 6, 13
TGF-b, PDGF, IGF1
FIBROSIS
Fibroblast recruitment and activation
Fibroblasts
Epithelial-mesenchymal
trans differentiation
Proliferation of
myofibroblasts
Activated
myofibroblast
( SMA +)
Collagen and other ECM protein deposition

**Figure 2:** Overview of systemic sclerosis (SSc) pathogenesis. SSc etiopathogenesis remains incompletely understood, however, likely starts with a permissive genetic background, epigenetic alterations and environmental triggers inciting disease. Resulting abnormalities in and interplay between vascular, immunologic and fibrotic pathways drive disease progression and manifestations.

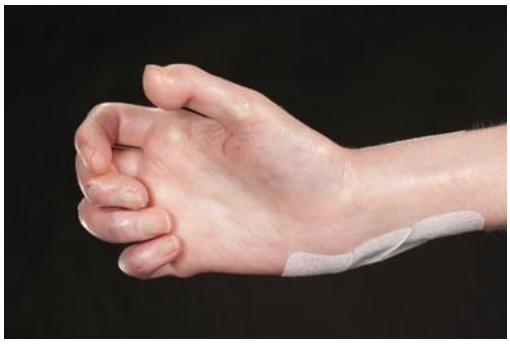
**a)**



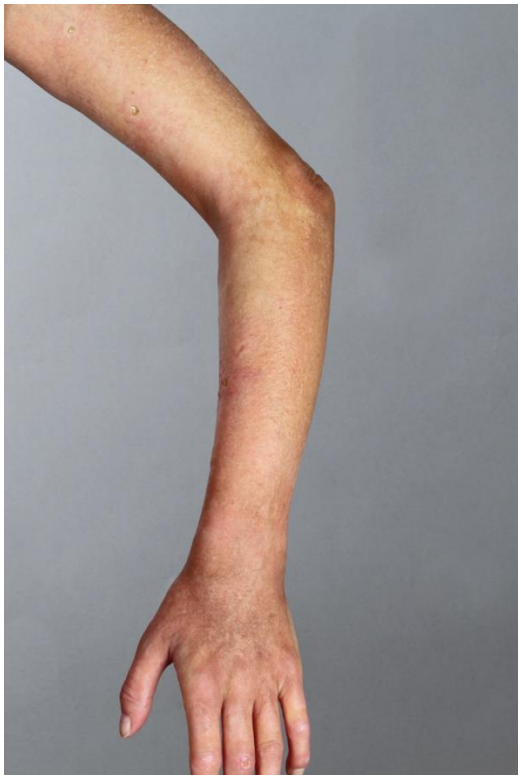
**b)**



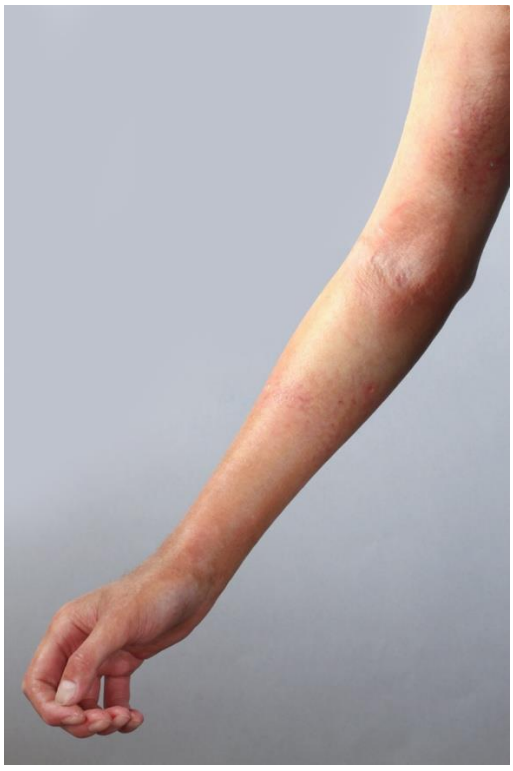
**c)**



**d)**



**e)**



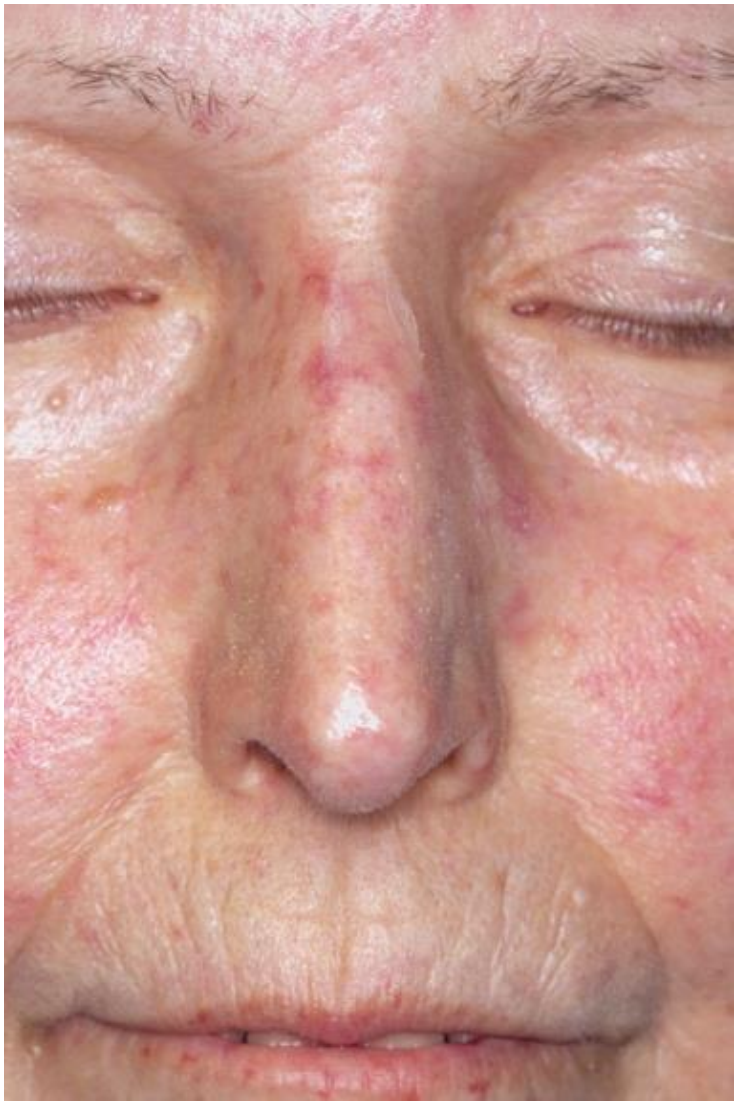
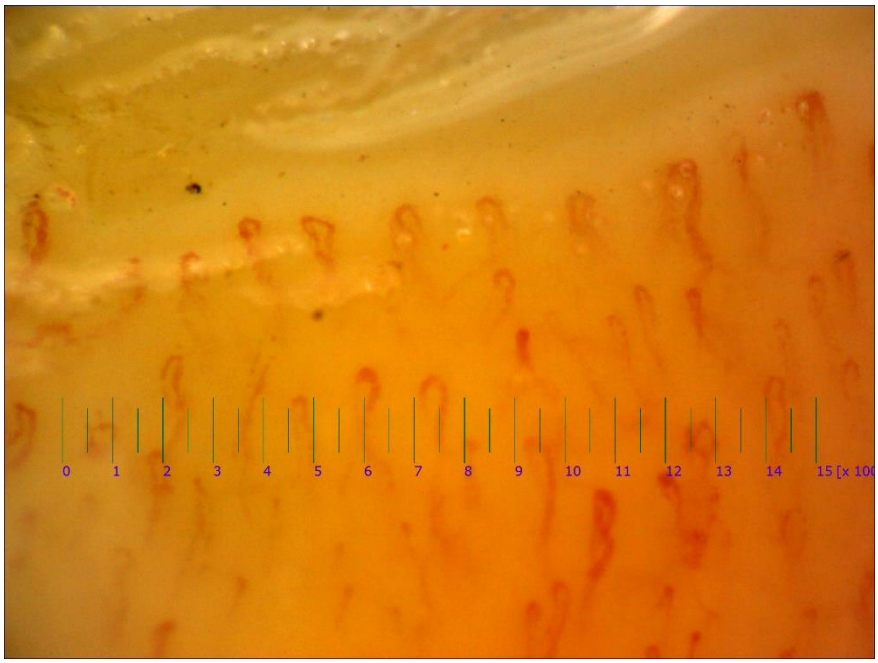
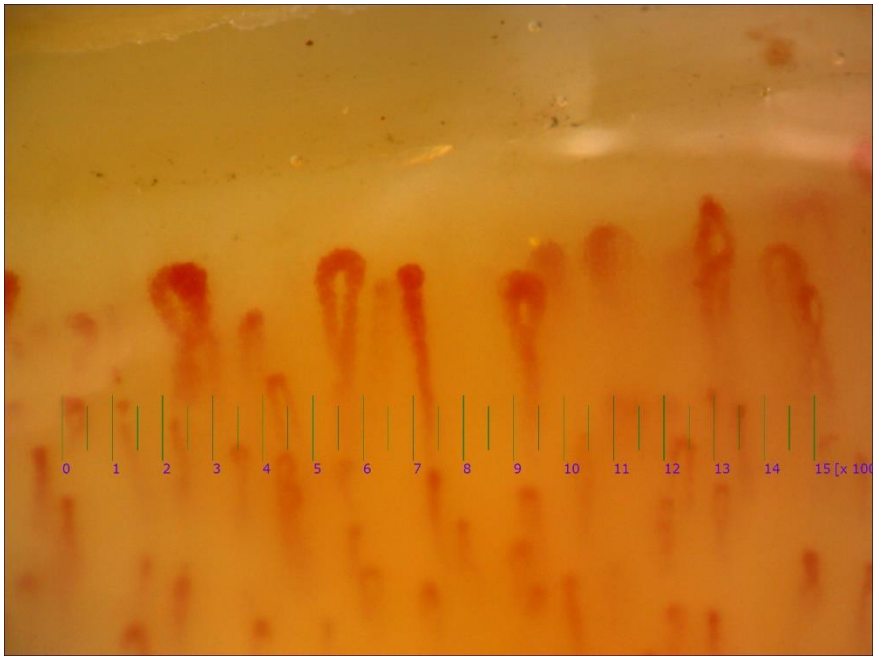
f) 

**Figure 3:** Skin fibrosis in SSc. (a) - (c) Sclerodactyly with symmetrical skin tightening over the fingers and small joints of the hands with resulting fixed-flexion deformity at the PIPJ. Note also the involvement of the wrists plus the presence of ulcers and calcinosis over the PIPJs; (d) and (e) fibrosis of the skin over the forearms; (f) fibrosis of the skin around the mouth with radial perioral furrowing, microstomia and microcheilia. Note also the facial telangiectasia.

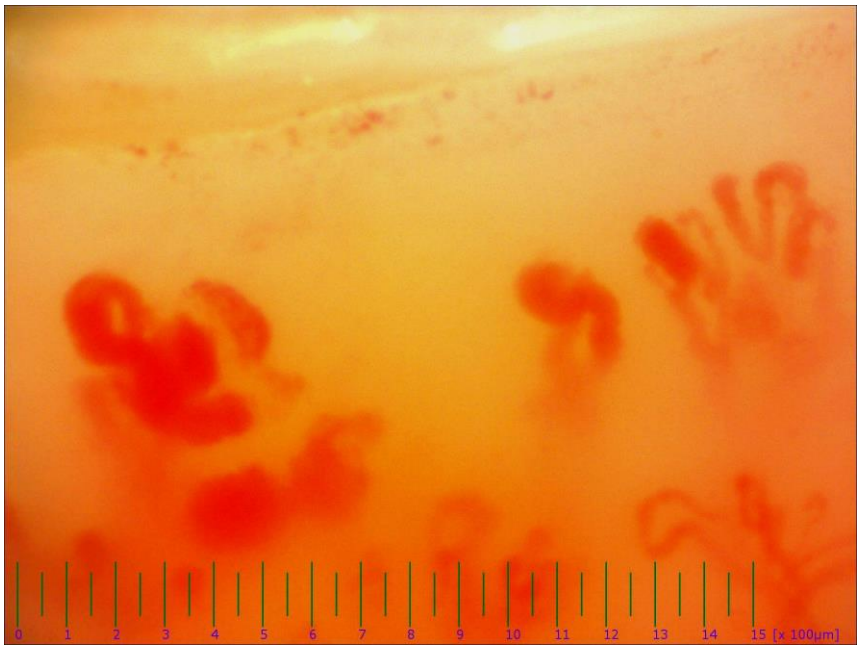
**a)**


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 [x 100

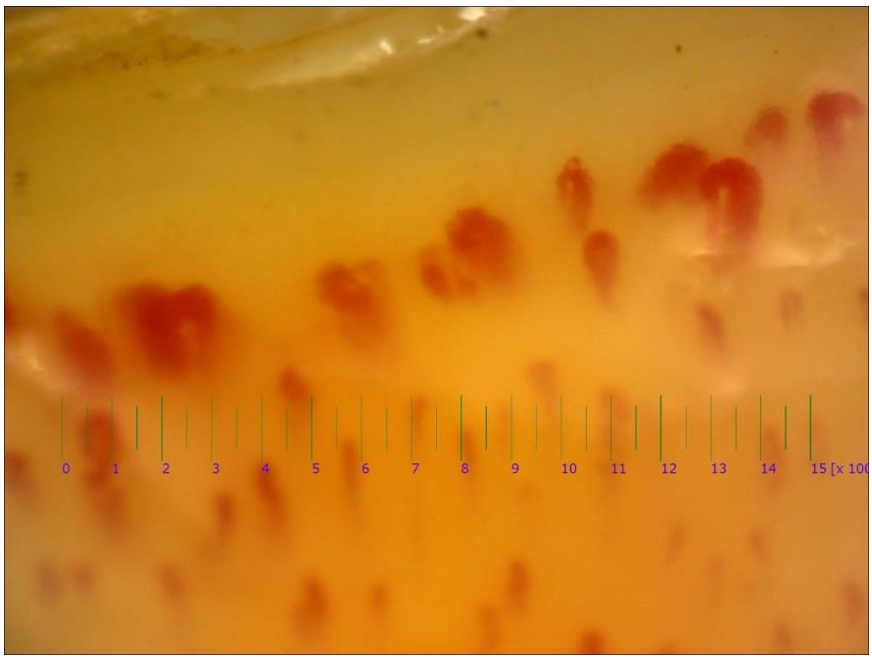
**b)**


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 [x 100

**c)**


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 [x 100µm]

**(d)**


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 [x 100

**(e)**

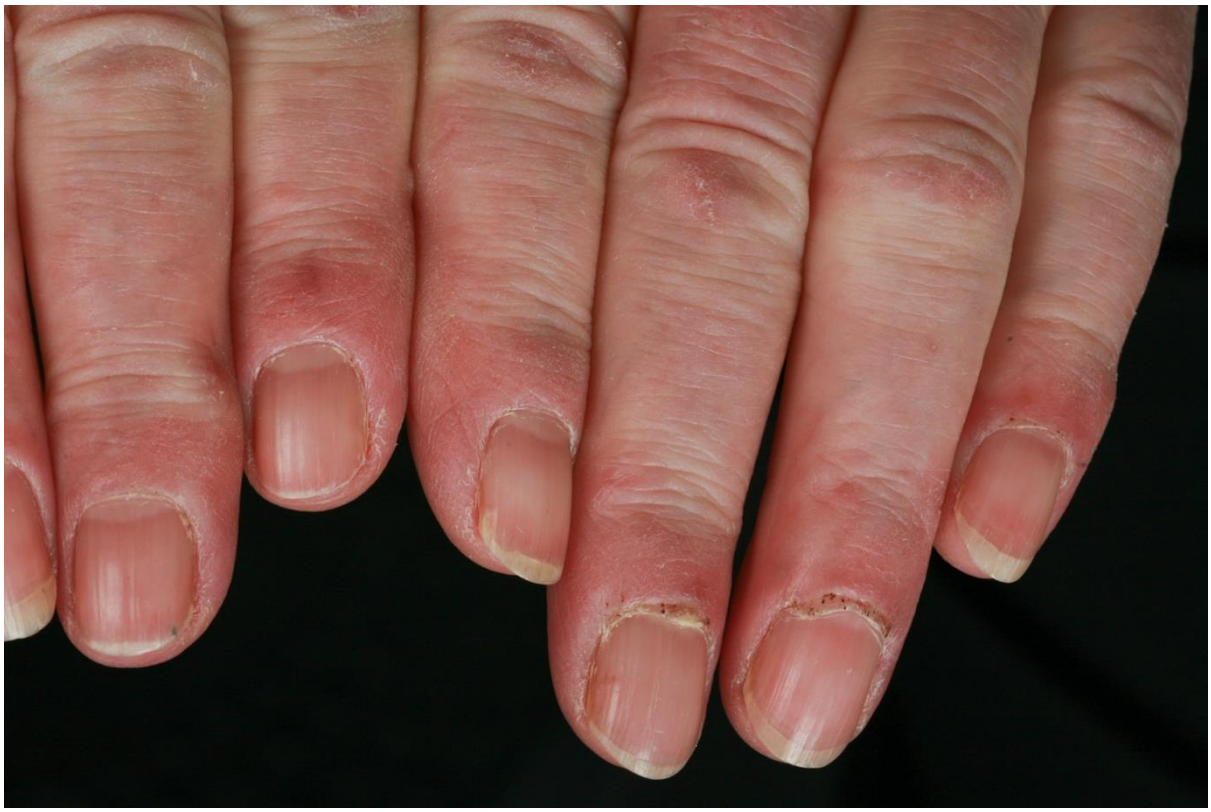


**Figure 4:** Nailfold capillaroscopy changes throughout SSc. (a) Normal, orderly hairpin capillary architecture; (b) dilated capillaries with preserved density seen in early SSc; (c) dilated capillaries with reduced density seen in active SSc; (d) haemorrhages, neoangiogenesis, avascular areas (“drop out”) and giant capillaries seen in late SSc; (e) macroscopic appearance.

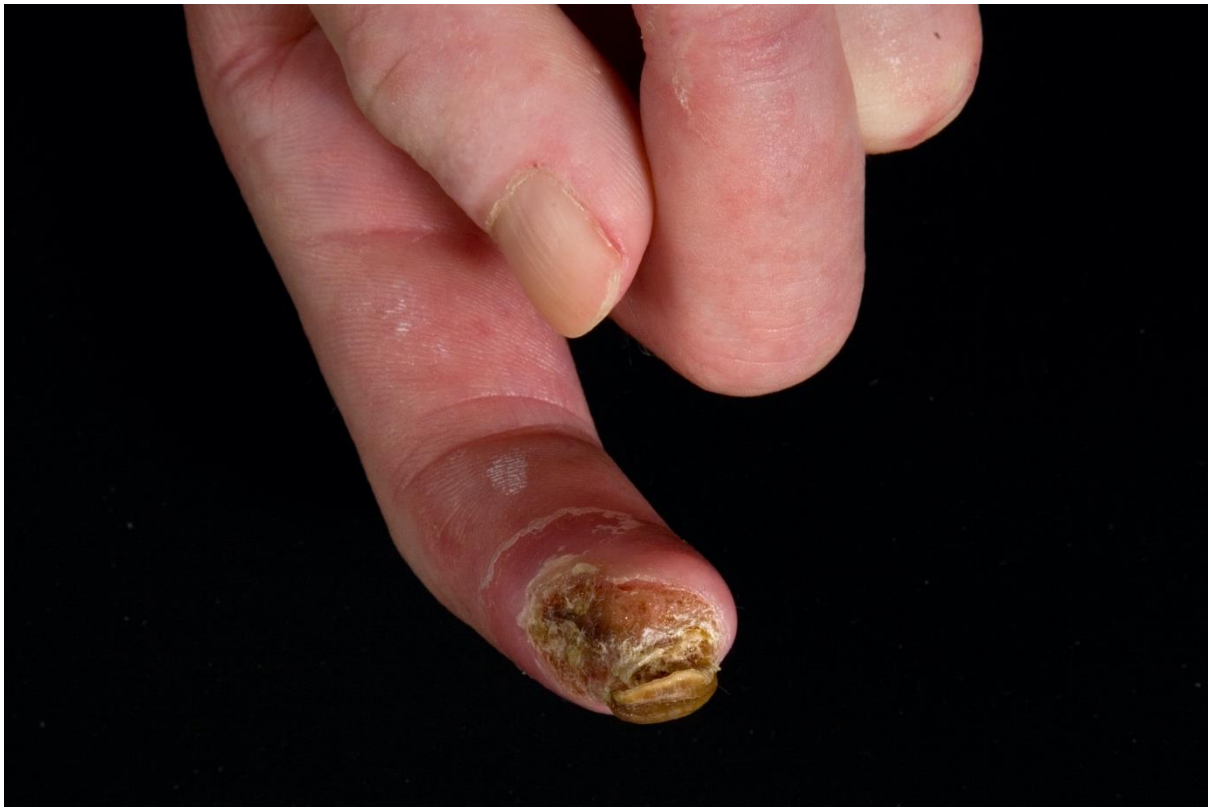


**Figure 5:** Ischaemic digital ulcers in the setting of SSc

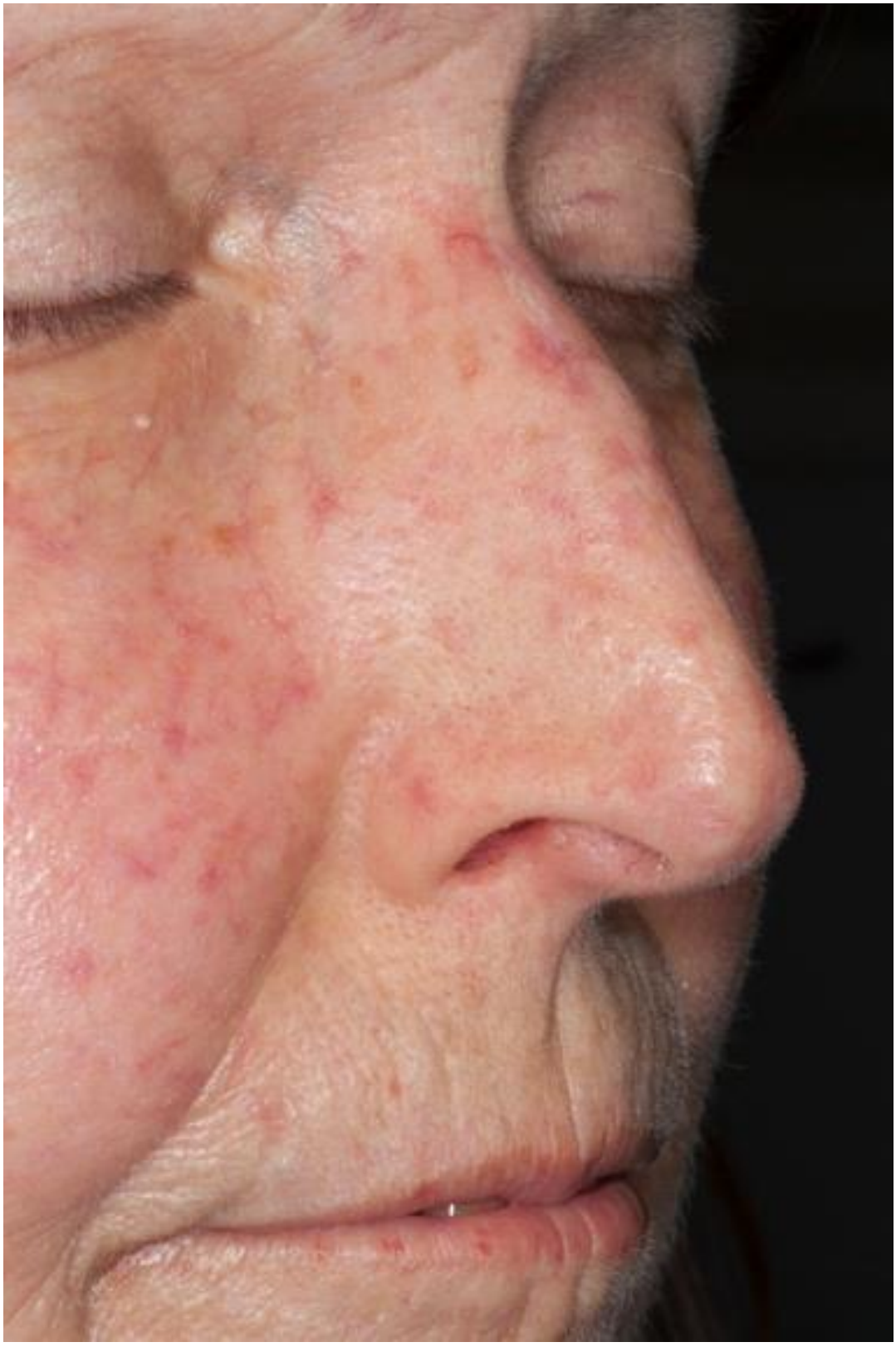
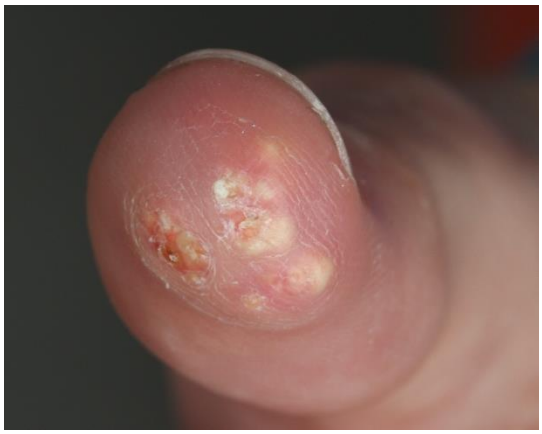
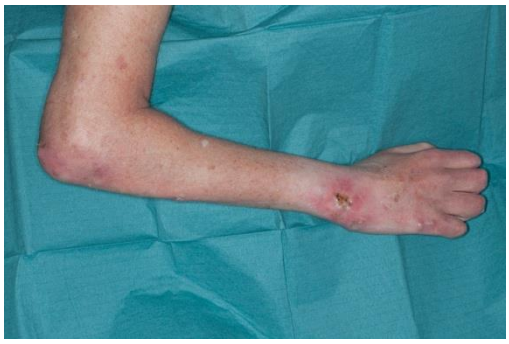


**Figure 6:** Matted cutaneous telangiectasia on the face

(a)



(b)



(c)

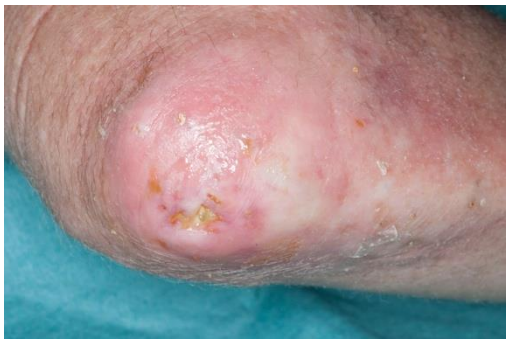


**Figure 7:** Calcinosis in SSc, occurring at finger tips (a) and over extensor surfaces of the wrist (b) and elbows (c) with secondary ucleration

## TABLES

**Table I: Classification criteria for Systemic sclerosis as per the 2013 ACR/EULAR guidelines**[17]

| Main criteria | Additional criteria | Weighting* |
|---|---|---|
| Sclerosis of the hands proximal to the metacarpophalangeal joint (sufficient criterion) | | 9 |
| Sclerosis of the fingers (only count higher score) | Puffy fingers<br>Sclerodactyly (between MCPJ and PIPJ) | 2<br>4 |
| Fingertip lesions (only count higher score) | Digital ulcers<br>Fingertip pitting scars | 2<br>3 |
| Telangiectasia | | 2 |
| Abnormal nailfold capillaries | | 2 |
| Pulmonary involvement (maximum score of 2) | PAH<br>ILD | 2<br>2 |
| Raynaud's phenomenon | | 3 |
| SSc-typical autoantibodies (maximum of 3 points) | Anti-centromere<br>Anti-topoisomerase I<br>Anti-RNA polymerase III | 3<br>3<br>3 |

*The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 are classified as having definite SSc.

**Table II** Systemic sclerosis serological findings and their clinical correlations

| Antibody target | Estimated prevalence[24] | SSc subtype | Key cutaneous features[22–24,98] | Key systemic features[13,22–24,98] | Demographic associations[22–24,98] | HLA associations[99,100] |
|---|---|---|---|---|---|---|
| Centromere (ACA) | 20-25% | Limited | - calcinosis<br>- RP<br>- sclerodactyly<br>- telangiectasia<br>- digital ulcers | - PAH (15-20%)<br>- oesophageal dysmotility and gastrointestinal dysfunction<br>- Low risk of ILD, cardiac and renal disease | Female predominance. Best prognosis - survival ~96% at 5 years, 65% at 20 years) | DRB1*01<br>DRB1*04<br>DQB1*0501<br>DQA1*04:01<br>DRB1*07:01 (Europeans) |
| Topoisomerase-I (Scl-70) | 20-30% (geographical variation) | Diffuse or limited | - digital ulcers<br>- joint contractures<br>- tendon friction rubs | - High risk for ILD (early)<br>- PAH<br>- SRC<br>- cardiac disease<br>- myopathy | More prevalent in Europeans. Poor prognosis (in combination with dcSSc). Survival 91% at 5 years, 46.5% at 20 years. | DPB1*13:01<br>DPB1*09:01 (Japanese)<br>DRB1*11:04 (European)<br>DQB1/A1 (African-Americans) |
| PM/Scl | 2-4% | Overlap Polymyositis/limited SSc | - calcinosis | - myositis<br>- ILD (50% by 15 years)<br>- PAH (~36% by 15 years)<br>- Cardiac<br>- Renal | Younger age at onset. Good prognosis. Low risk of death initially (98% survival at 5 years) but increased in second decade of disease (59% survival at 20 years) | DR3<br>DRB1*0301–5 |
| To/Th | <5% | Limited | - calcinosis | - ILD (45%)<br>- PAH (25%) | Higher mortality due to pulmonary complications | - |
| RNA polymerase III (RNAP3) | 1-22% | Diffuse (rapidly progressive) | - joint contractures<br>- tendon friction rubs | - myositis<br>- SRC (early)<br>- less cardiac disease<br>- GAVE<br>- Moderate risk for ILD<br>- PAH (later) | Some have onset of diffuse sclerosis prior to RP. Survival 88% at 5 years, 47% at 20 years | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | - increased risk of malignancy within 3 years of diagnosis[32,33] | | |
| U1-RNP | 5-10% | Limited, overlap syndromes (MCTD) | - joint contractures | - myositis<br>- PAH<br>- pulmonary fibrosis | More prevalent in African-Americans and Asians. Younger age at onset | - |
| U3-RNP/Fibrillarin | 4-10% | Diffuse | - digital ulcers<br>- calcinosis<br>- hypo/per-pigmentation<br>- joint contractures<br>- tendon friction rubs | Early severe organ involvement:<br>- PAH (highest risk)<br>- ILD<br>- SRC<br>- cardiac<br>- small bowel dysmotility<br>- myopathy | More frequent in African Americans. Associated with younger age at onset.<br>Poor prognosis. Survival 85% 5 years, 60% at 20 years. | HLA-DRB1*08:04 (African-American)<br><br>HLA-DQB1*06:09 |

**Table III** The seven skin and antibody clusters identified by Nihtyanova, *et al.* to predict complications and survival in SSc. Adapted from Nihtyanova, *et al*.[13]

| **Classification subgroup** | | **Prevalence** | **Systemic manifestations** | **Relative Prognosis** |
|---|---|---|---|---|
| **Skin** | **Antibody** | | | |
| lcSSc | ACA | 28.2% | Lowest incidence ILD and SRC | Best |
| lcSSc | Anti-Scl-70 | 10.4% | Highest incidence ILD, lowest incidence PAH | Second best |
| dcSSc | Anti-Scl-70 | 11.3% | Second highest incidence of cardiac SSc and ILD | Worst |
| Any | Anti-RNAP | 11.1% | Lowest incidence cardiac SSc, highest incidence SRC | |
| Any | Anti-U3 RNP | 4.2% | Highest incidence PAH, highest incidence cardiac SSc | |
| lcSSc | Other | 22.3% | Low overall risk of SRC and cardiac SSc | |
| dcSSc | Other | 12.5% | Higher rates of ILD, cardiac SSc and SRC | Second worst |

**Table IV** Some of the key distinguishing features to assist with differentiating SSc from severe morphea subtypes

| | **SCLERODERMA** | |
|---|---|---|
| | **SSc** | **Morphea** |
| **Clinical skin thickening** | Yes | Yes |
| **Raynaud's phenomenon** | Yes | Possible in severe subtypes*, but uncommon |
| **Puffy fingers / Sclerodactyly** | Yes – pathognomonic | No |
| **Nail fold capillary changes** | Yes | No |
| **ANA** | Yes (95%) | Possible in severe subtypes*, approximately 30% |
| **SSc-specific autoantibodies** | Yes – pathognomonic | No |
| **Internal organ fibrosis** | Yes | No |

*Linear and generalised subtypes

**Table V** Overview of systemic manifestations in systemic sclerosis

| **Organ system affected**[18,101] | **Complications** | **Prevalence** | **Clinical features** | **Risk factors** | **Screening and monitoring** [18,102] |
|---|---|---|---|---|---|
| Respiratory[4,13,64,103,104] | Interstitial lung disease (ILD) | 30 – 52.3% (usually within 5 years from diagnosis) | Dyspnoea, decreased exercise tolerance, chronic cough, basal lung crackles on auscultation | dcSSc, anti-topoisomerase antibodies, male sex | Pulmonary function tests (FVC and diffusion capacity) at baseline and every 4-6 months during first 3 years. Consider HRCT |
| | Pulmonary arterial hypertension (PAH) | 5-12% | Asymptomatic (early), later: dyspnoea, decreased exercise tolerance, chronic cough | Older age, late disease onset, digital ulcers, numerous pseudotumoral telangiectasia | Use DETECT algorithm[105]* Doppler echocardiography, pulmonary function tests (FVC and diffusion capacity) annually, right heart catheterisation may be needed to confirm diagnosis. |
| Cardiac[106–110] | Heart failure | 7-32% | Shortness of breath, decreased exercise tolerance, chest pain, palpitations, syncope, fatigue, dizziness, peripheral oedema | Anti-topoisomerase antibodies, older age | Annual doppler echocardiogram, electrocardiogram, troponin or BNP, cardiac MRI if high risk |
| | Pericardial effusion | | | | |
| | Valve sclerosis (rare) | | | | |
| | Arrhythmias and conduction defects | | | | |
| Renal[111–114] | Scleroderma Renal crisis (SRC) | 2-15% (usually within 5 years from diagnosis) | Hypertension, pulmonary and peripheral oedema, electrolyte disturbances, elevated creatinine, uraemia, metabolic acidosis, proteinuria | Male sex, anti-RNAP3 antibodies, dcSSc, older age, systemic corticosteroid use (>15mg prednisolone/day) | Measure creatinine clearance, urea, electrolytes and urinalysis at baseline and at least annually. For patients with risk factors: measure |

| | | | | | |
|---|---|---|---|---|---|
| | Renal vasculopathy | ~20% | Asymptomatic or isolated proteinuria, increased creatinine and/or hypertension. | dcSSc.<br>May or may not progress to SRC | blood pressure three times weekly |
| Gastrointestinal[55,115] | Impaired oesophageal mobility | 64-90% | Dysphagia, odynophagia, heartburn, regurgitation, chronic cough (microaspiration), hoarseness, oesophageal dilatation | Older age, dcSSc, anti-centromere antibodies, anti-topoisomerase-I antibodies (except GAVE), anti-RNAP3 (GAVE) | Symptom based investigations e.g. barium swallow, gastric-emptying study, breath test, oesophageal manometry, endoscopy |
| | Gastroesophageal reflux disease (GORD) | | Dyspepsia, Barret's oesophagus, strictures, reflux oesophagitis | | |
| | Intestinal and gastric dysmotility | | Malabsorption, bloating, early satiety, Small intestinal bacterial overgrowth syndrome, nausea, vomiting, pain, diarrhoea/constipation, faecal incontinence (sphincter dysfunction), weight loss | | |
| | Gastric antral vascular ectasia (GAVE) | 5.7-22.3% | GI bleeding, iron deficiency anaemia | | Gastroscopy ("Watermelon stomach") |
| Urogenital[101,116,117] | Male sexual dysfunction | >80% | Erectile dysfunction, penile deformities, penile rigidity. | Psychological stress, cardiovascular risk factors including older age, smoking, hypercholesterolaemia, arterial hypertension. | International Index of Erectile Function (IIEF-5) questionnaire |
| | Female sexual dysfunction | >50% | Discomfort, dyspareunia, impaired sexual activity and enjoyment | Longer disease duration, depressive symptoms, relationship distress | Female Sexual Function Index 300 (FSFI), Female Sexual Function in SSc 306 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | (FSFS) questionnaire, Female Sexual Distress Scale (FSDS) |
| Malignancy[30–32] | Lung, haematological, liver, bladder, breast, non-melanoma skin cancer | 4-10.8%<br><br>1.75x Relative Risk | Organ specific symptoms, constitutional symptoms (fatigue, weight loss, night sweats, lethargy) | Male sex, anti-RNAP3 antibodies, long term immunosuppression | Symptom directed organ specific investigation. Stratify risk based on antibody profile. |

*The DETECT algorithm is a screening tool for pulmonary artery hypertension that uses pulmonary function tests (FVC and DLCO), serum urate, ECG, serum NTproBNP and other features to provide a predictive score and guide further investigation. A right heart catheter may be indicated

**CME QUESTIONS**

A 28 year old female attends your clinic with a 10 month history of new and progressing skin changes. Physical examination reveals indurated sclerosis of the skin on her forearms and bilateral chest, symmetrical skin tightening over the proximal fingers and scattered telangiectasia on her face. Nailfold capillaroscopy show microhaemorrhages with periungal erythema. She reports symptoms of Raynaud's phenomenon and muscle weakness but denies reflux and arthralgia. She has positive antinuclear antibody serology (1:1280) and positive anti-U1-RNP antibodies. Her full blood count, creatinine and liver function are normal.

What is the most likely diagnosis?

a) Pansclerotic morphea
b) Generalised morphea
c) A scleroderma overlap syndrome
d) Systemic lupus erythematosus
e) Diffuse cutaneous systemic sclerosis

A patient with newly identified VEDOSS (Raynaud's phenomenon, puffy fingers, ANA+, ACA+) asks you about risk of progression and comorbidities associated with her condition. You advise her of the following:

a) Her condition is likely to improve spontaneously over time, she will not experience any systemic effects nor require treatment
b) She is likely to satisfy formal systemic sclerosis diagnostic criteria within 5 years (with likely limited cutaneous SSc), she will need to be managed by a multi-disciplinary team and have screening for systemic manifestations
c) She will develop pulmonary fibrosis, renal disease and/or cardiac complications early due to her high risk antibody profile
d) Her children will suffer from the same disease and she should have genetic counselling
e) She has a very high risk of being diagnosed with a malignancy in the next three years

Which of the following factors puts a patient with systemic sclerosis most at risk of developing scleroderma renal crisis:

a) Use of prednisolone at 20mg/day
b) Rapid skin progression with anti-RNAP3 antibodies
c) Female sex
d) Combination of A and B
e) Combination of A and C

Which of the following is true regarding the pathogenesis of Systemic Sclerosis:

a) Specific SSc-autoantibodies have been shown to be directly involved in disease pathogenesis
b) Type 1 IFN and TGF-β do not play a significant role in disease pathogenesis
c) Skin-infiltrating T cells are predominantly of the T-helper 1subtype
d) Vasculopathy is characterised by upregulated inflammatory mediators with a loss of vascular tone due to excess nitric oxide and insufficient vasoconstriction
e) Immune and vascular dysfunction ultimately lead to aberrant fibroblast activation, proliferation and extracellular matrix deposition

Which of the following is not associated with the anti-RNAP3 antibodies in Systemic sclerosis:

a) Rapid progression of skin manifestations
b) Increased risk of concurrent malignancy
c) Overlap with other connective tissue disorders
d) Numerous palmar telangiectasia
e) Increased risk of early scleroderma renal crisis