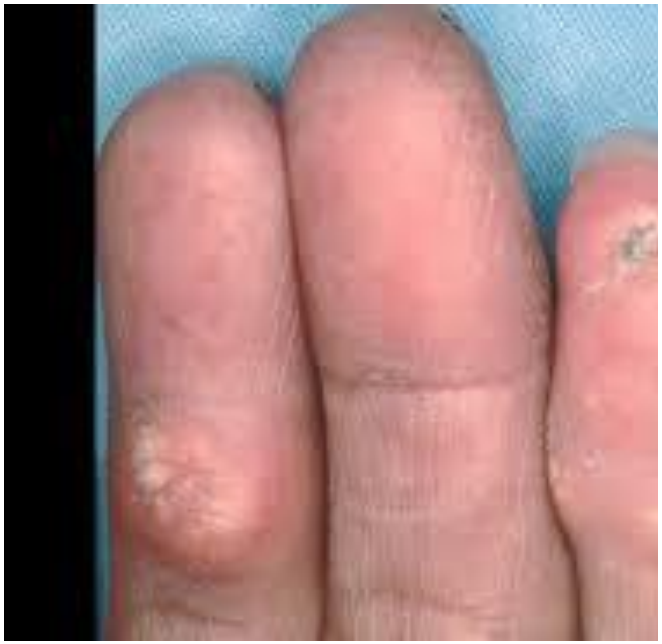
Case based discussion systemic sclerosis

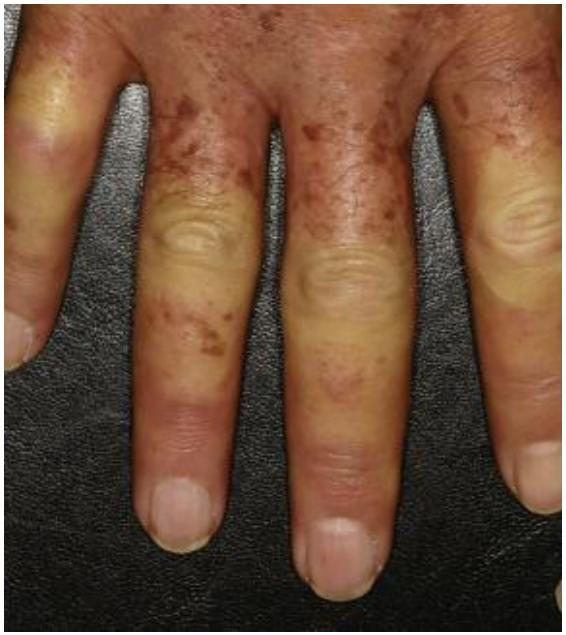
Case 1

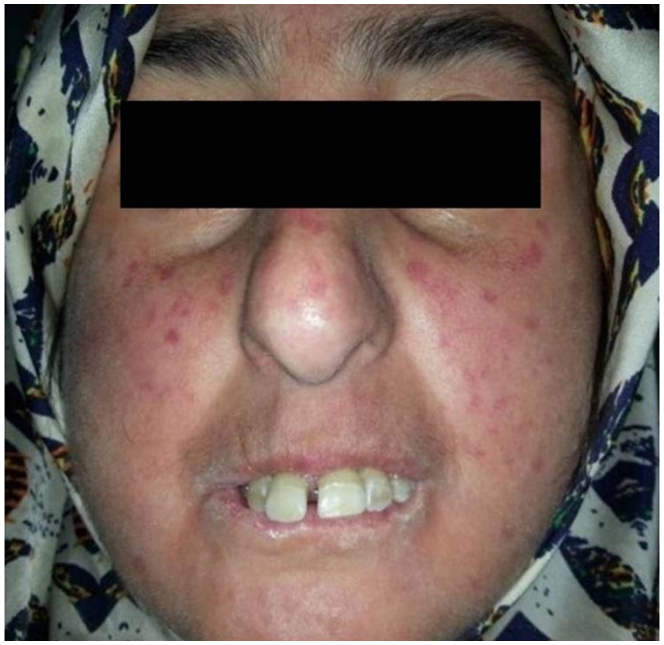
- A 45-year-old female presents to her primary care provider with pain and swelling in her hands or the past 5 years.

- She has been noticing that when her hands are exposed to the cold, they become pale and painful. When this occurs, the feeling may last for as long as 20 minutes before resolution, and following this, a painful warm sensation occurs. Symptoms have been worsening over the past winter.

- Upon further questioning, the patient reports GERD which occurs almost daily. She also reports numbness and tingling of her hands and small lumps on the pulps of her fingers.







? cutaneous features

- 1- What is the most likely diagnosis?
- 2- What additional history you may request?
- 3- What investigations you want to order?

Case 1

- Progressive exertional dyspnea
- CBC: mild anemia
- ANA: + 1:1280 CENTROMERE
- CXR. PFT, DLCO
- ECHO

Scleroderma or systemic sclerosis

- An autoimmune connective tissue disease characterized by excessive collagen build-up around the capillaries and affected tissues, such as the skin, lungs, heart, esophagus and kidneys
- Scleroderma means "hard skin"

- The disease is chronic, and the cause is still unknown
- The prevalence is relatively low with 50-300 cases per 1 million population and an incidence of 2.3-22.8 cases per 1 million population per year
- Risk to women is higher than men with a 3:1 ratio, the majority of which are 30-50 years-old

SUBSETS OF SYSTEMIC SCLEROSIS (SSc): LIMITED CUTANEOUS SSc VERSUS DIFFUSE CUTANEOUS SSc

FEATURES	LIMITED CUTANEOUS SSc	DIFFUSE CUTANEOUS SSc
Skin involvement	Limited to fingers, distal to elbows, face; slow progression	Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Precedes skin involvement; associated with critical ischemia	Onset contemporaneous with skin involvement
Pulmonary fibrosis	May occur, moderate	Frequent, early and severe
Pulmonary arterial hypertension	Frequent, late, may be isolated	May occur, associated with pulmonary fibrosis
Scleroderma renal crisis	Very rare	Occurs in 15%; early
Calcinosis cutis	Frequent, prominent	May occur, mild
Characteristic autoantibodies	Anticentromere	Antitopoisomerase I (Scl-70)

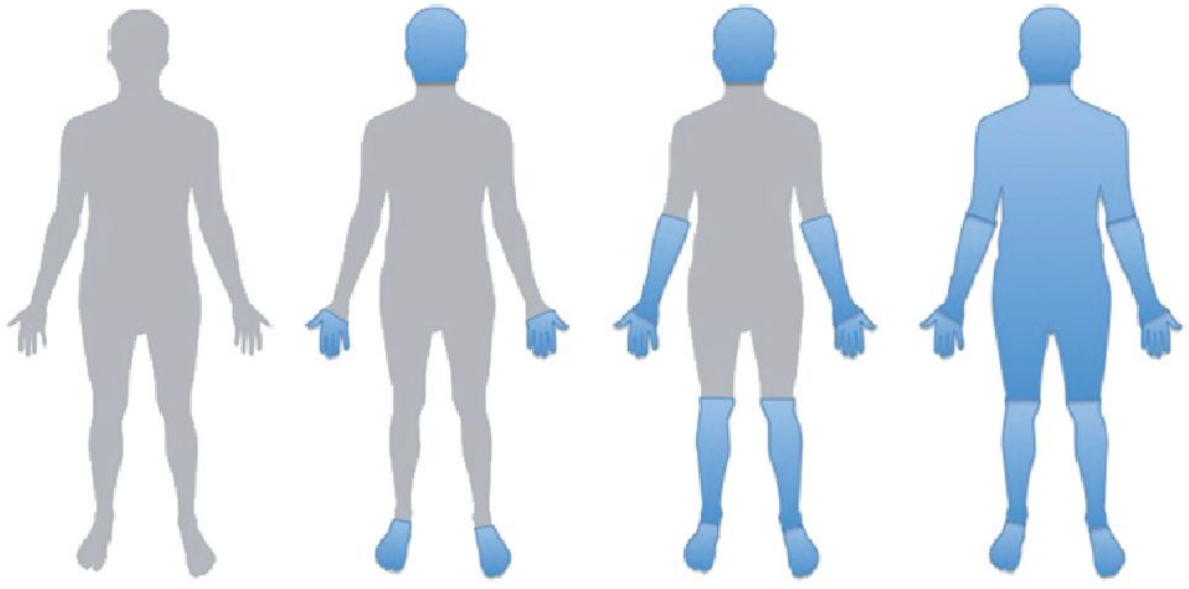


Figure 84-1 Classification of scleroderma and clinical subsets. Most experts classify scleroderma into two major groups: limited and diffuse. Limited includes patients with no skin changes (early scleroderma or systemic sclerosis "sine" scleroderma), and type I (fibrosis limited to the digits) or type II (fibrosis up to the elbows and the knees). Diffuse or type III have more proximal limb or truncal involvement (the face is excluded). SSc, Systemic sclerosis.

SSc

- Anti-centromere antibodies (in limited cutaneous disease). Specific, but not sensitive
- Anti-topoisomerase (anti-Scl-70) antibodies (in diffuse cutaneous disease, with an association with pulmonary fibrosis). Specific, but not sensitive

Table 19.1 The spectrum of scleroderma and scleroderma-like disorders

Localized scleroderma	Dermal inflammation and fibrosis No visceral disease, few vascular symptoms
Plaque morphoea	Fewer than four localized areas of involvement
Generalized morphoea	More than four areas or widespread lesions
Linear scleroderma	Skin sclerosis follows dermatomal Distribution; commonest form of childhood-onset scleroderma
En coup de sabre	Scalp and facial linear lesion often with underlying bone changes
Systemic sclerosis	
Diffuse cutaneous systemic sclerosis	Skin involvement proximal to elbows or knees, short history of Raynaud's phenomenon; associated with anti-scl70 or anti-RNA polymerase antibodies
Limited cutaneous systemic sclerosis	Skin tightening affects extremities only, long history of Raynaud's phenomenon, associated with anti-centromere autoantibodies
Overlap syndromes	Clinical features of systemic sclerosis associated with those of another autoimmune rheumatic disease (SLE, myositis, arthritis)
Systemic sclerosis *sine* scleroderma	Serological, vascular and visceral features of SSc without detectable skin sclerosis
Isolated Raynaud's phenomenon	
Primary	Common, onset in adolescence, female predominance, normal nailfold capillaroscopy and negative autoantibody profile
Secondary	Raynaud's with abnormal nailfold capillaries and/or positive autoantibody testing

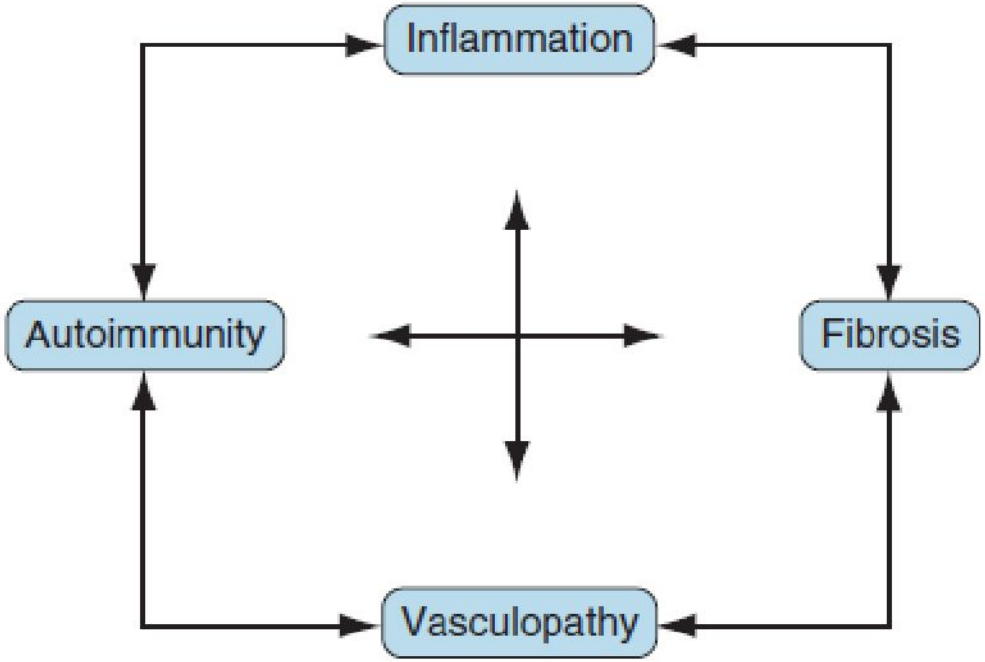


Figure 83-1 The pathophysiologic quartet underlying systemic sclerosis. Patients with systemic sclerosis display evidence of inflammation, autoimmunity, vasculopathy, and fibrosis. Autoimmunity and vasculopathy generally precede the onset and contribute to the progression of fibrosis. Vascular obliteration and interstitial fibrosis perpetuate and further exacerbate chronic autoimmunity and inflammation. *(Courtesy Kathleen Kelley.)*

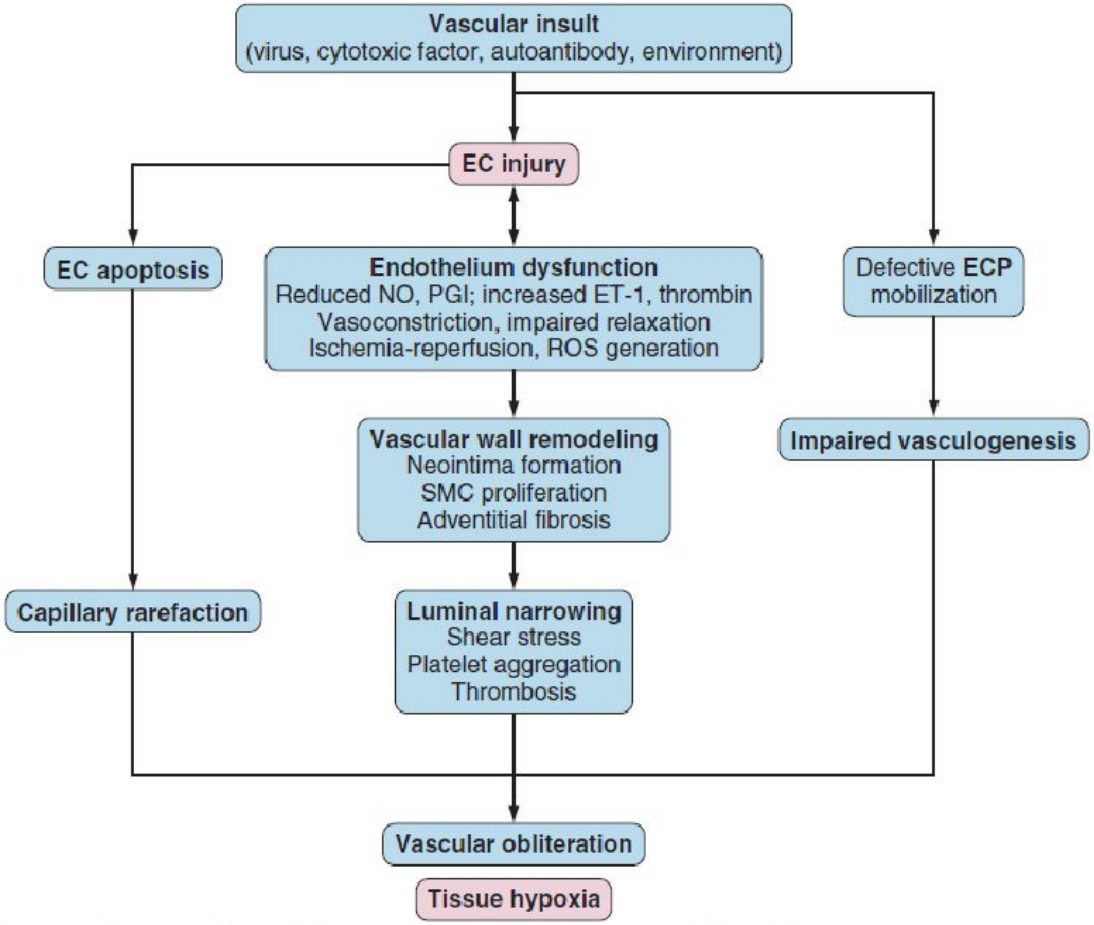


Figure 83-8 Pathogenesis of vasculopathy. An initial vascular insult results in endothelial cell (EC) injury and activation, with reversible functional changes, increased expression of adhesion molecules, and enhanced leukocyte diapedesis resulting in perivascular inflammation. Damaged endothelium promotes platelet aggregation and thrombin release and shows impaired production of vasodilators such as nitric oxide (NO), increased production of vasoconstrictors such as endothelin-1 (ET-1), and release of reactive oxygen species (ROS). Consequent vasoconstriction and defective vasodilation aggravate vascular damage, leading to irreversible and progressive vascular wall remodeling, luminal occlusion, platelet aggregation, in situ thrombosis, and tissue hypoxia. Loss of blood vessels may be further compounded by insufficient vasculogenesis. ECP, Endothelial cell progenitor; PGI, prostaglandin I; SMC, smooth muscle cell.

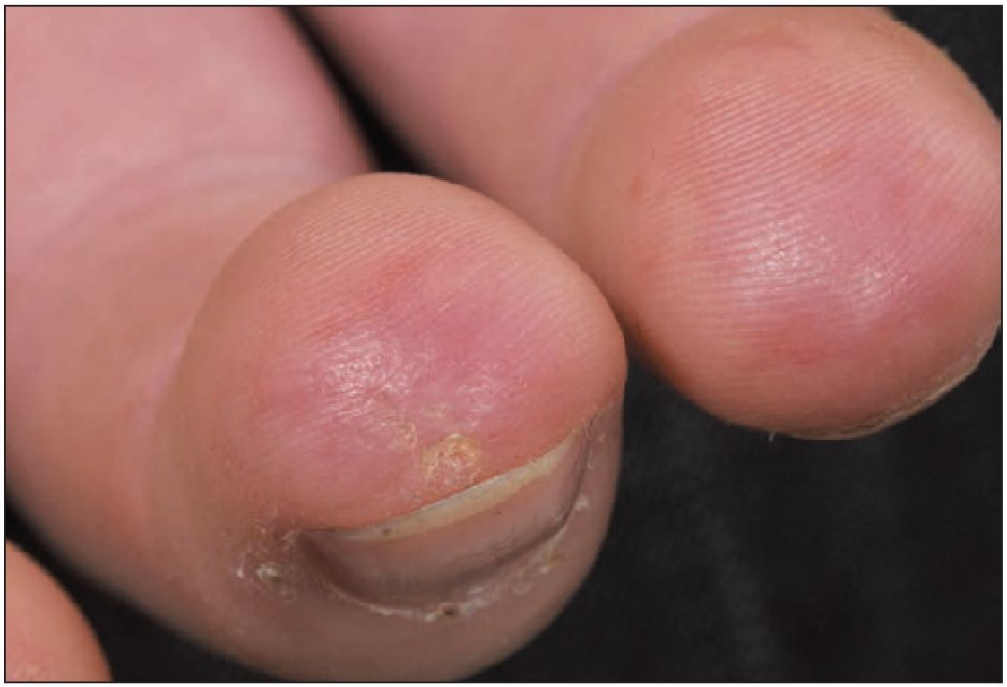
TABLE 83-2 Environmental Agents and Drugs Implicated in Scleroderma-like Syndromes

Chemicals
Silica
Heavy metals
Mercury
Organic chemicals
Vinyl chloride
Benzene
Toluene
Trichloroethylene
Drugs
Bleomycin
Pentazocine
Taxol
Cocaine
Dietary Supplement/Appetite Suppressants
L-tryptophan (contamination)
Mazindol
Fenfluramine
Diethylpropion

Case 2

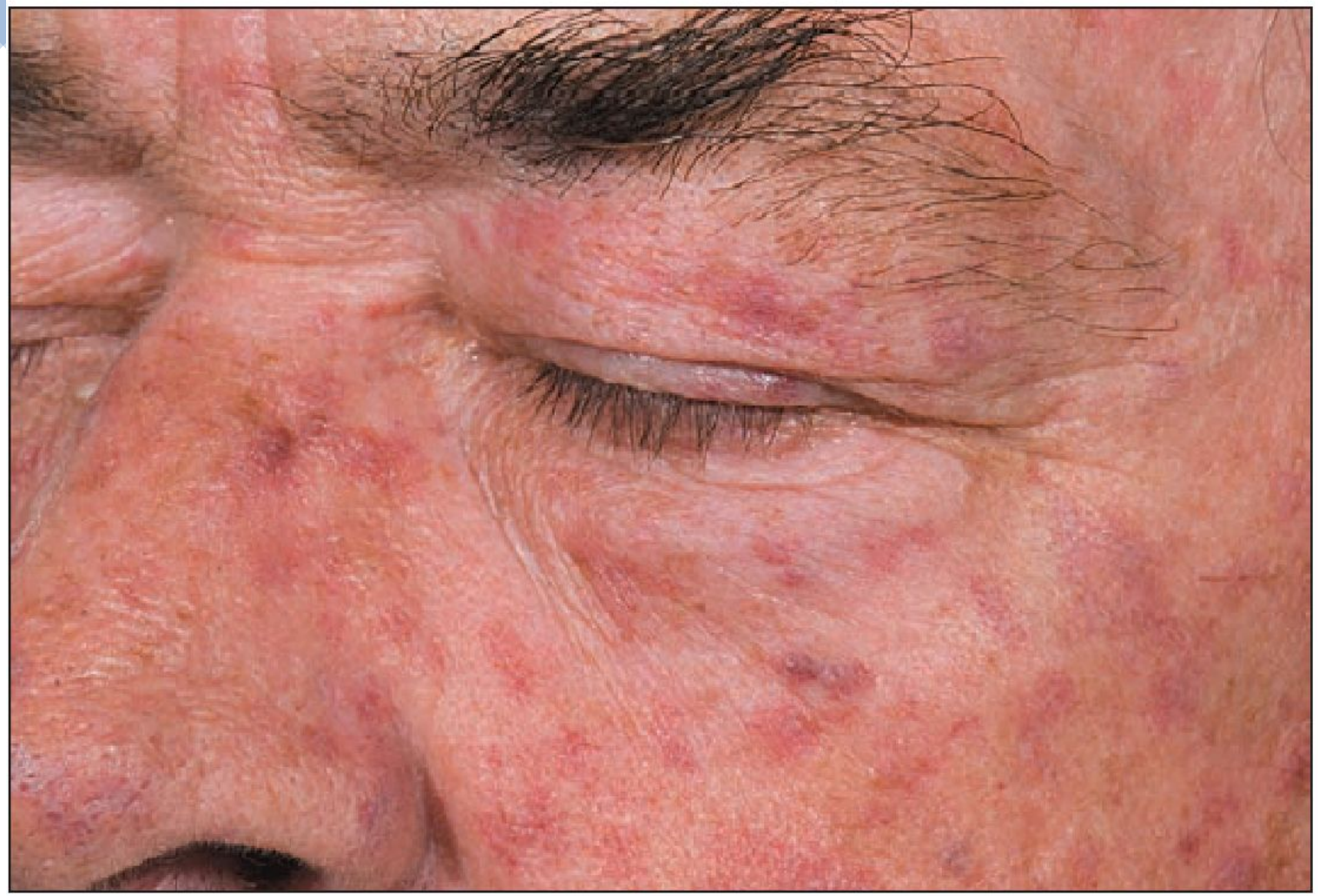
- 35-year-old female presents with a 2-year history of Raynaud's phenomenon.
- She reports gastroesophageal reflux for a similar duration of time. She also has noted that her skin is diffusely pruritic for the past year.
- Physical examination reveals a P 90 BP 160/90.
- HEENT is remarkable for furrowing around the mouth and decreased oral aperture.
- Cardiac exam is normal. Pulmonary exam is normal.
- Skin reveals sclerodactyly with digital pitting scars. There is mild diffuse skin tightening including the proximal upper and lower extremities, abdomen and chest.

- Investigations
- •ANA 1:1280; homogenous pattern.
- Anti topoisomerase 1 positive
- •Radiographs: calcifications in the soft tissues . Interstitial infiltrate on cxr
- •PFTs : low FEV1
- •Echocardiogram: normal



1.13 Digital pitting (demonstrated in the finger on the left side of the image) in a patient with SSc.

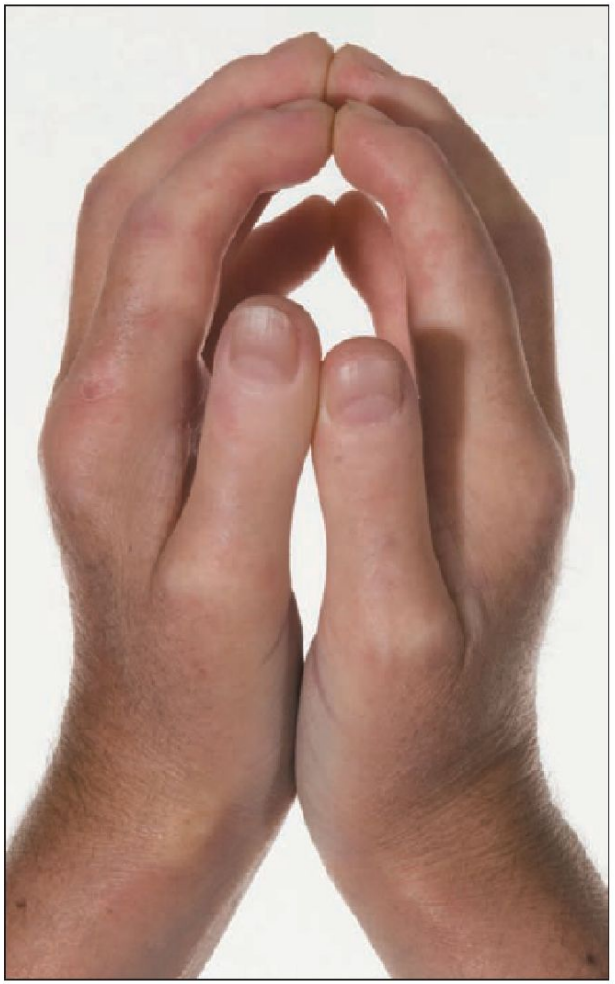
Digital pitting



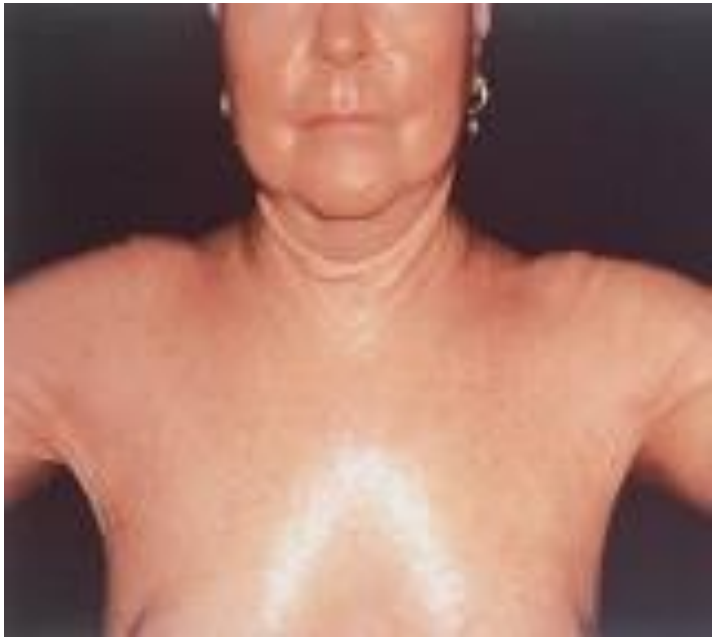
1.14 Telangiectases in a patient with SSc.

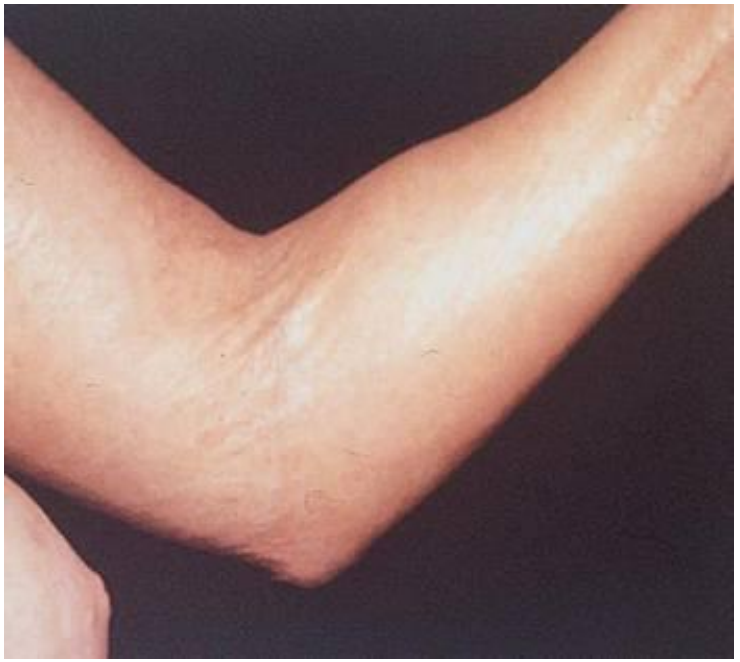
Box 19.1 **Points to consider when looking for underlying cause of Raynaud's phenomenon**

- Occupation—working outdoors, fishing industry, using vibrating tools, exposure to chemicals such as vinyl chloride
- Examination of peripheral and central vascular system for proximal vascular occlusion
- Drugs—such as β-blockers, oral contraceptives, bleomycin, migraine therapy
- Symptoms of other autoimmune rheumatic disorders:
  - Arthralgia or arthritis
  - Cerebral symptoms
  - Mouth ulcers
  - Alopecia
  - Photosensitivity
  - Muscle weakness
  - Skin rashes
  - Dry eyes or mouth
  - Respiratory or cardiac problems



1.8 Sclerodactyly. The skin is thickened, giving rise to flexion contractures of the fingers.





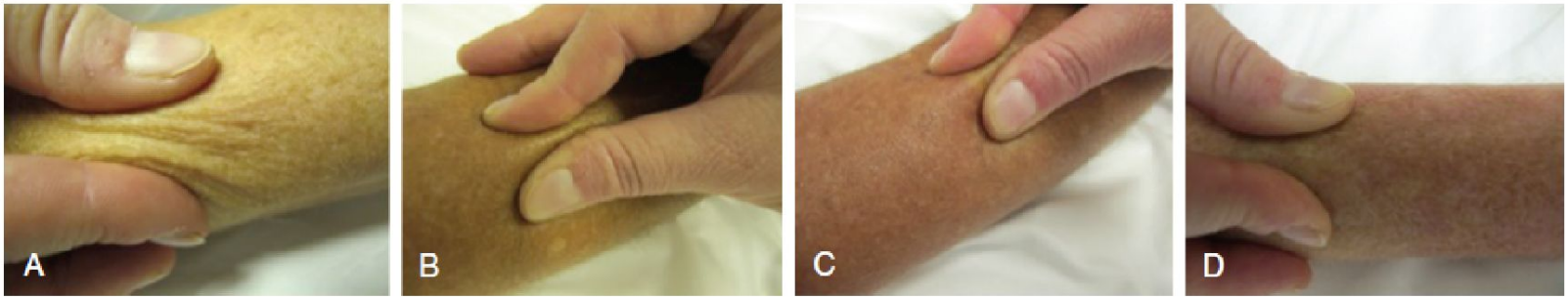


Figure 84-8 Method used to semi-quantify skin thickness in scleroderma. The modified Rodnan skin score is obtained by clinical palpation of 17 different body areas (fingers, hands, forearms, upper arms, chest, abdomen, thighs, lower legs, and feet) and subjective averaging of the thickness of each specific site: **A,** 0 = normal; **B,** 1 = mild; **C,** 2 = moderate; and **D,** 3 = severe. The maximum score is 51.

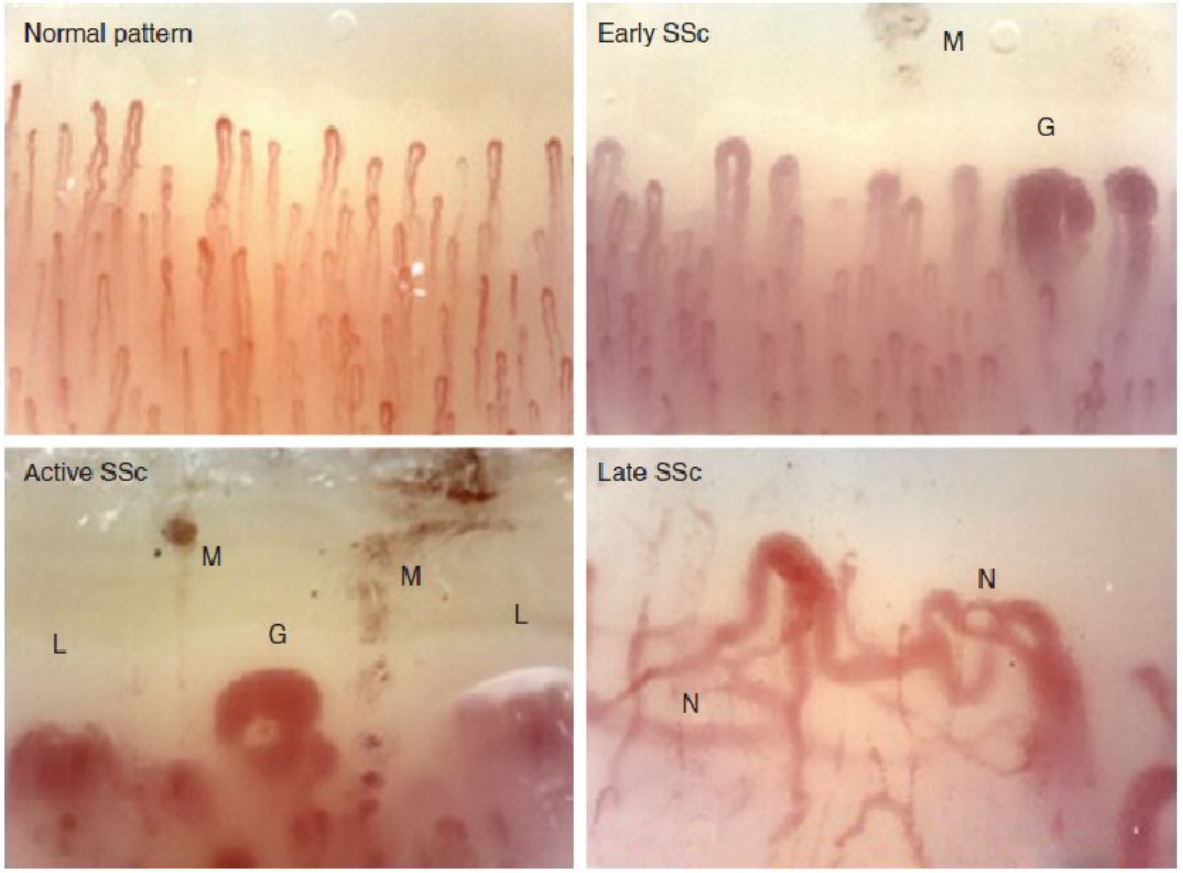


Figure 84-4 Patterns of nail-fold capillary abnormalities assessed by video capillaroscopy in patients with scleroderma. *Top right,* "Early pattern" shows the presence of few enlarged/giant capillaries, few capillary hemorrhages, and no evident loss or distortion of capillaries. *Bottom left,* "Active pattern" presents with frequent dilated capillary loops, frequent microhemorrhages, moderate loss of capillaries, and mild disorganization of the capillary architecture. *Bottom right,* "Late pattern" is characterized by severe loss of capillaries with avascular areas, ramified/bushy capillaries (neovascularization), and disorganization of the normal capillary architecture. G, Giant capillaries; L, loss of capillaries; M, microhemorrhages; N, neoangiogenesis; SSc, systemic sclerosis. *(Courtesy Professor Maurizio Cutolo.)*

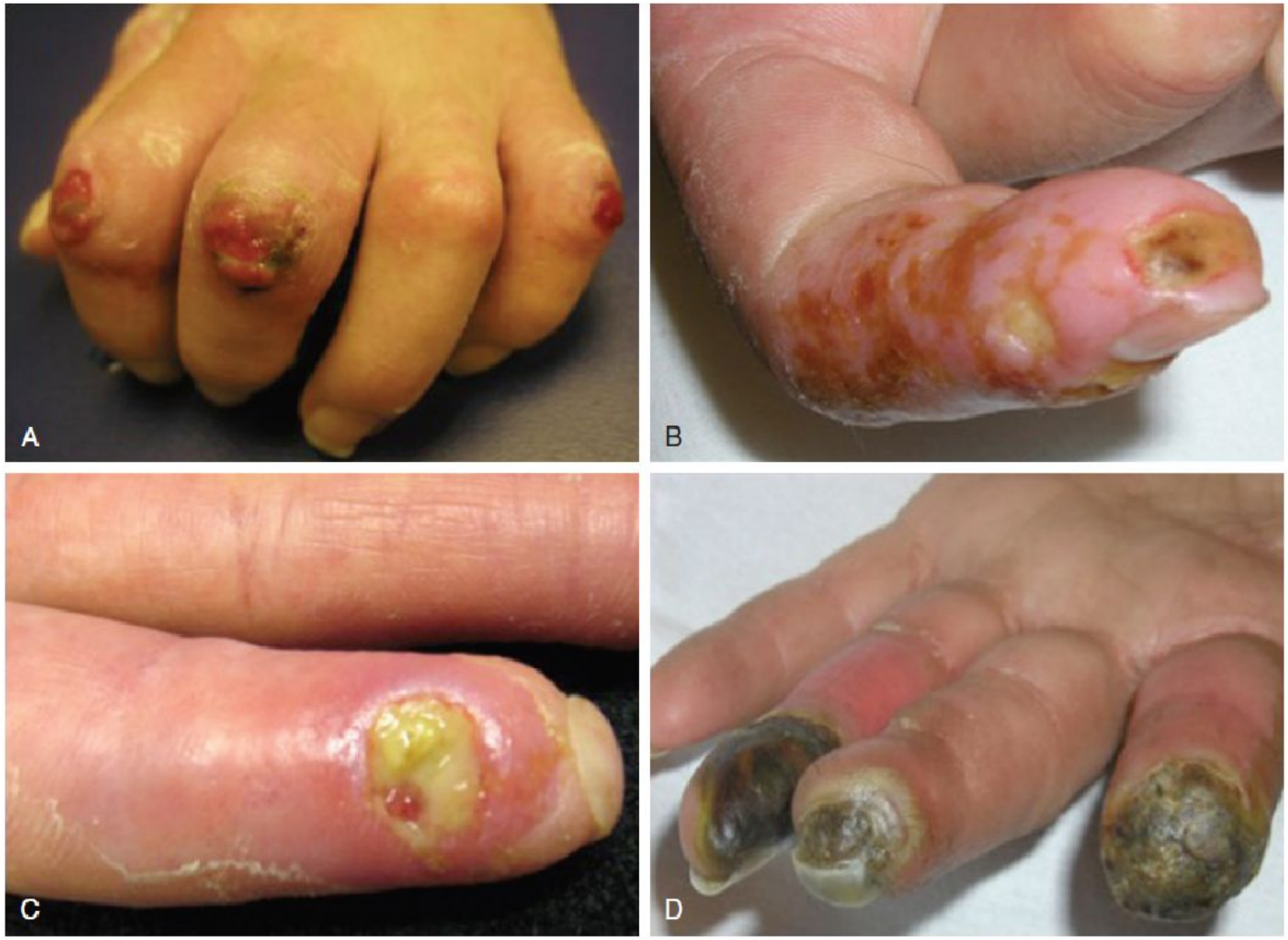


Figure 84-5 Scleroderma and Raynaud's phenomenon can be associated with digital ulcerations and severe digital ischemia. **A**, Traumatic ulcers over the proximal interphalangeal joints. **B** and **C**, Ischemic digital ulcerations as a result of small arterial disease. **D**, Digital gangrene as a result of macrovascular disease.

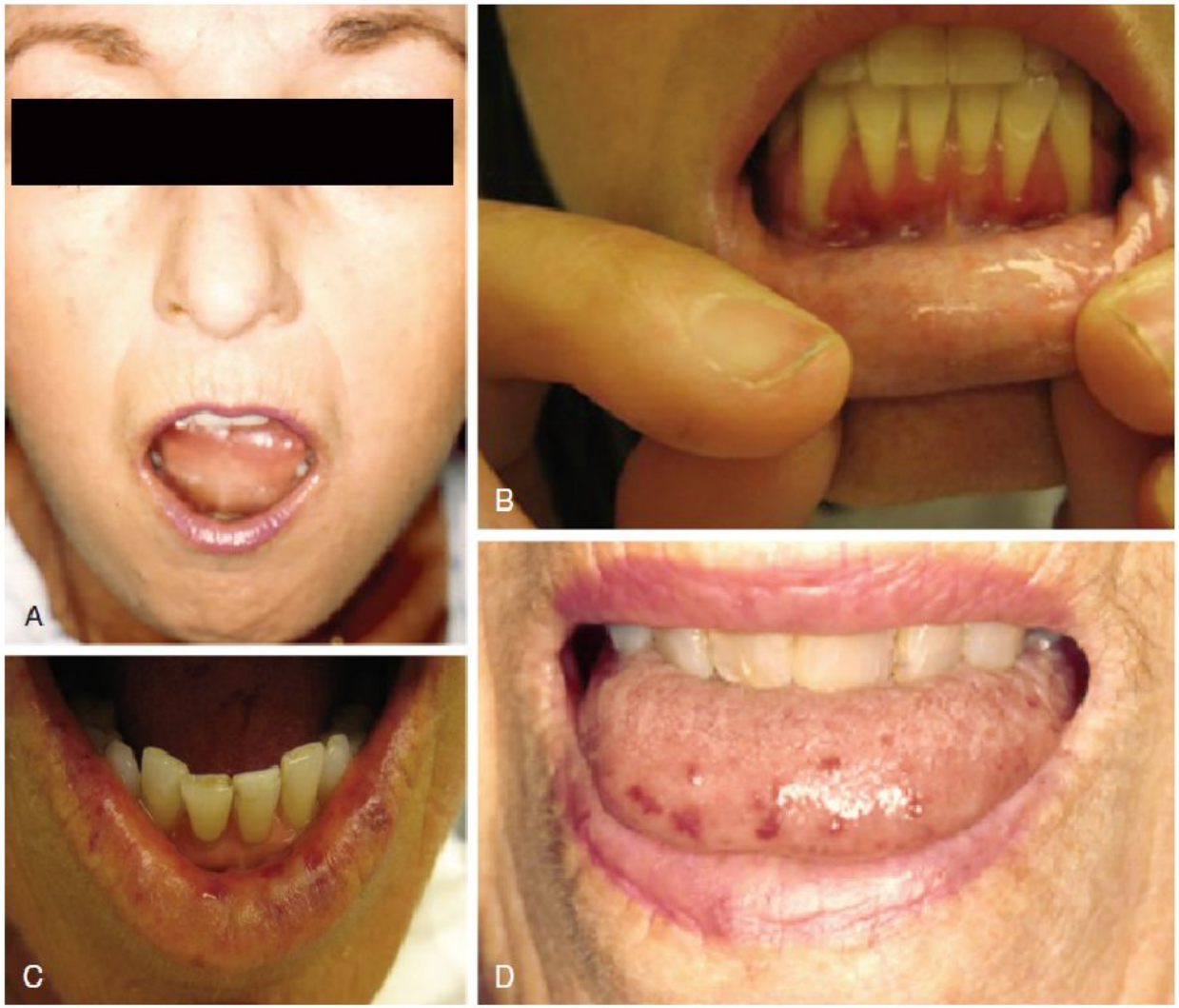
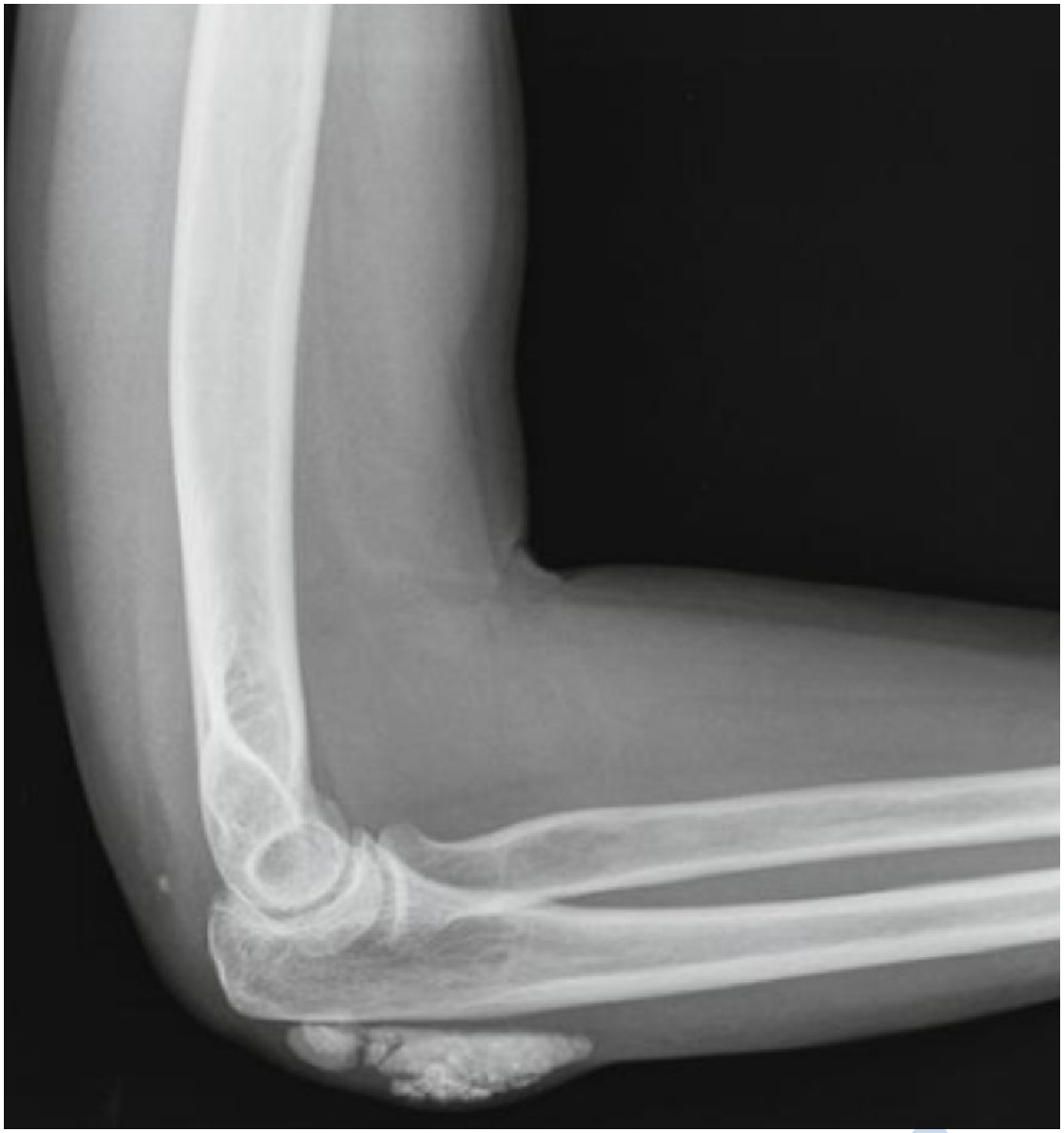
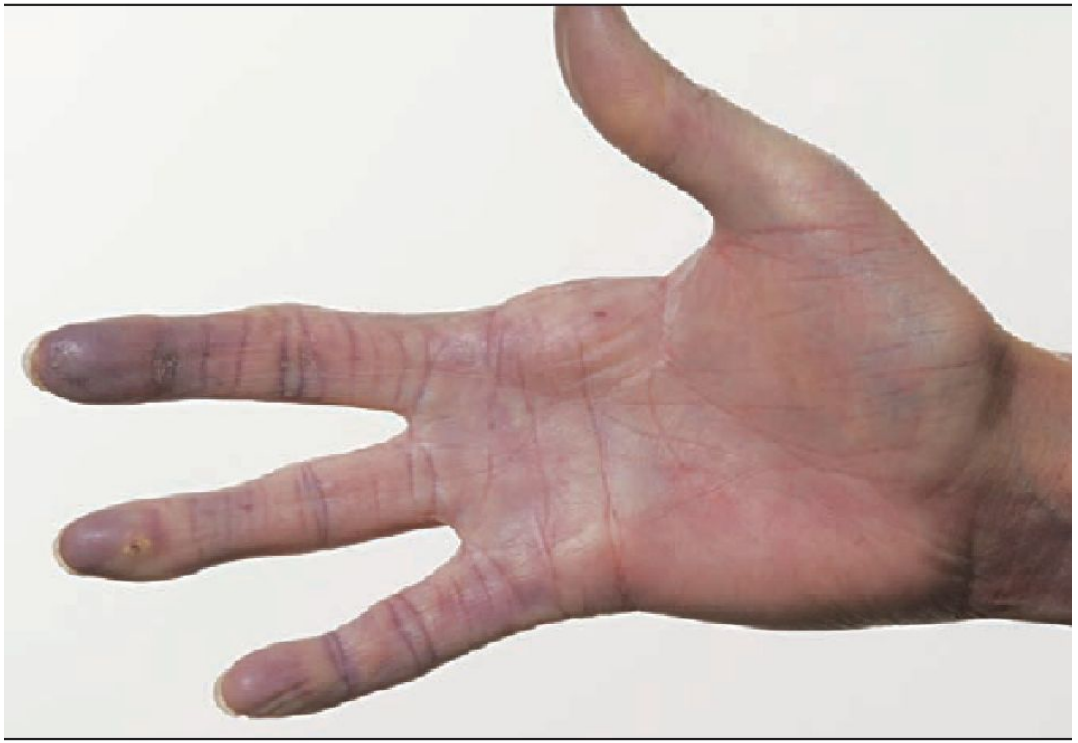


Figure 84-10 Oral manifestations. **A**, Perioral skin tightening with decreased oral aperture, furrowing around the lips, and dry membranes. **B**, Periodontal disease with regression of gum and loosening of teeth. **C** and **D**, Telangiectasias on the lips and tongue.





1.16 Several clinical features of SSc: cyanosis of the middle and ring finger, digital pitting of the middle finger, a calcinotic nodule of the pulp of the ring finger, telangiectases, and amputation of the index finger (this was due to severe digital ischaemia).

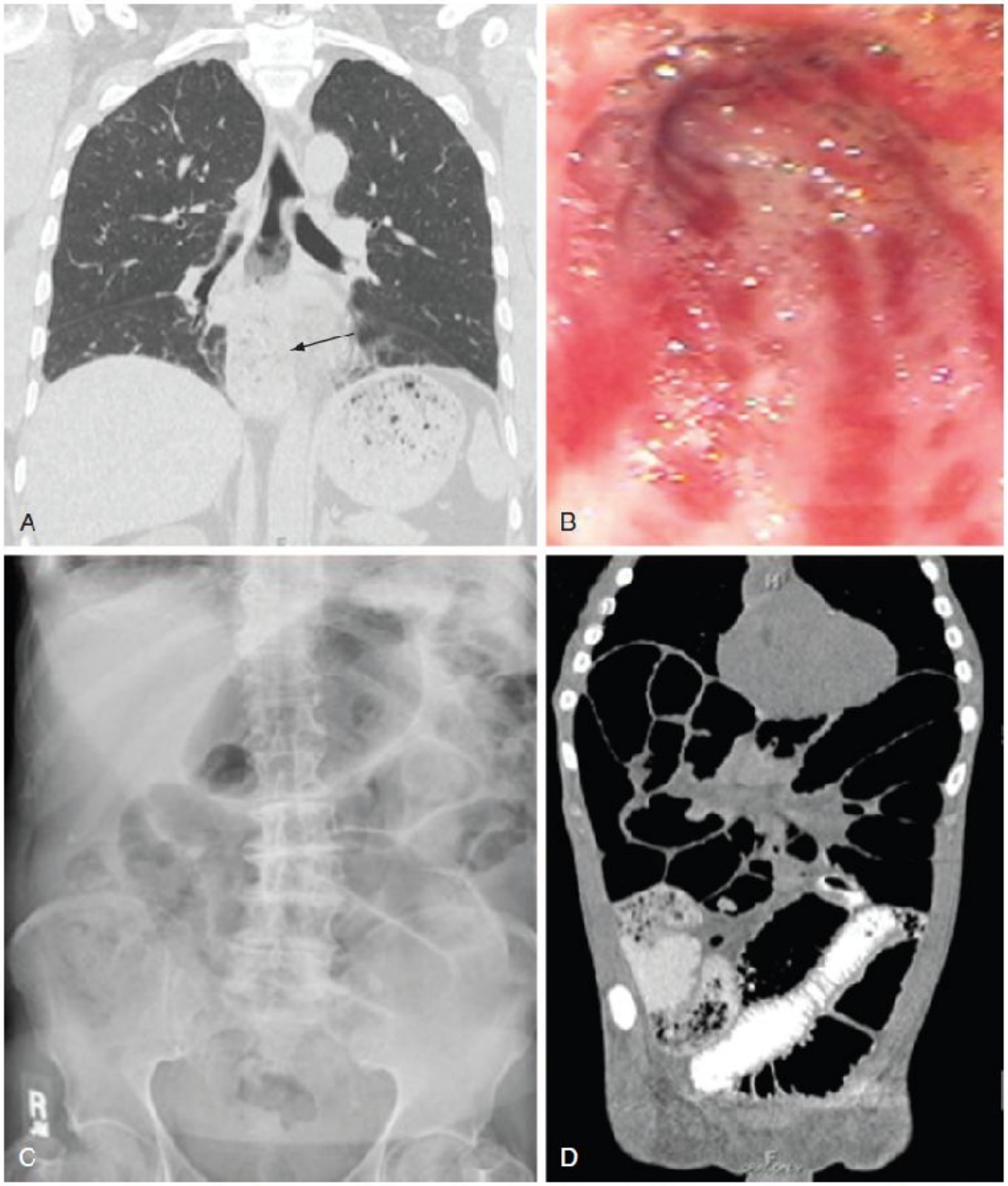
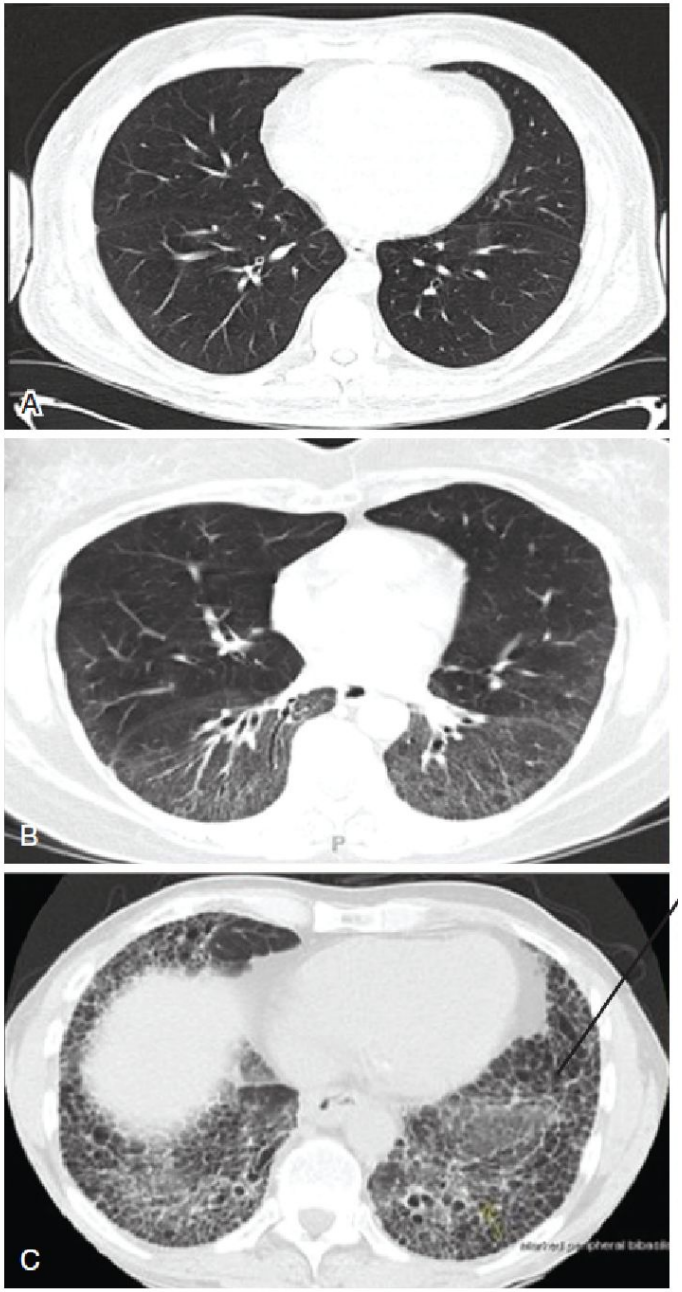


Figure 84-11 Gastrointestinal manifestations in scleroderma. **A,** Chest computed tomography (CT) (sagittal view) showing severe esophageal dysmotility with dilation and *(arrow)* retention of gastric content. **B,** Upper endoscopy: gastric antral vascular ectasias presenting as "watermelon" stomach. **C** and **D,** Plain abdominal radiograph and abdominal CT: small intestinal dysmotility with pseudo-obstruction, pneumatosis cystoides intestinalis.


A
B
P
C

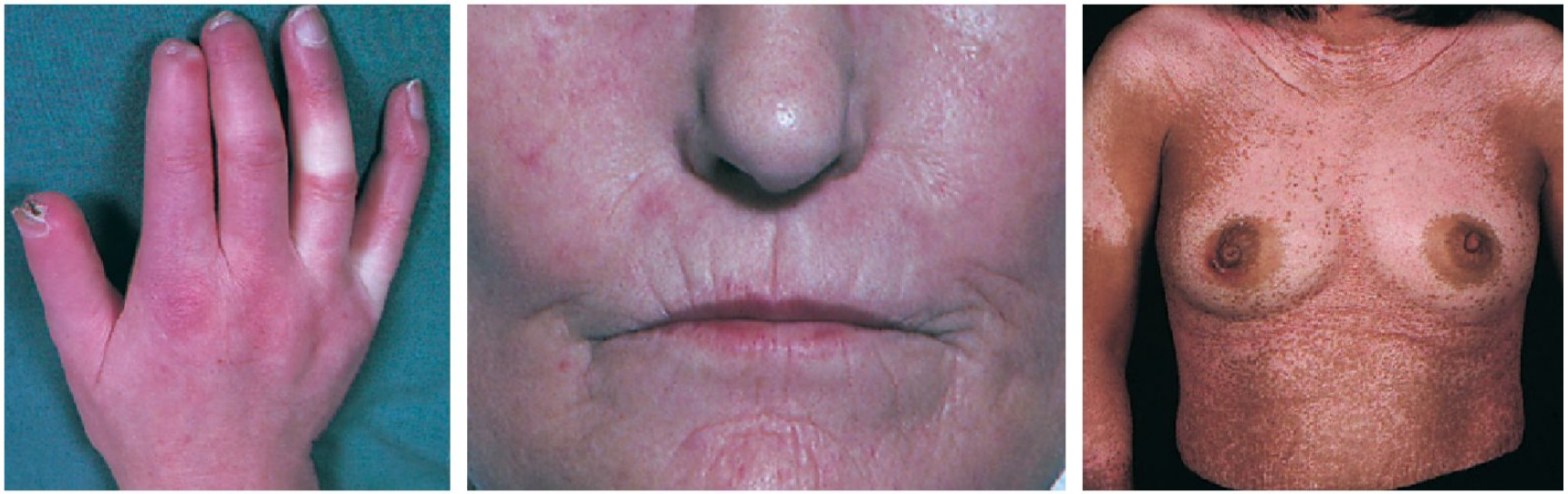


Figure 19.2 Characteristic features of limited cutaneous scleroderma. (a) Puffy fingers, tight skin, Raynaud's phenomenon, loss of distal digits and ulceration of tips of digits. (b) Microstomia and telangiectasia. (c) Hypopigmentation caused by diffuse cutaneous scleroderma.

Box 19.2 **Characteristic findings and suggested treatment for limited cutaneous scleroderma**

Early stage (≤5 years after onset)

- Constitutional symptoms—fatigue common
- Skin thickening—no or minimal progression
- Organs affected—Raynaud's phenomenon, ulcers of digital tips, oesophageal symptoms
- Treatment—vascular treatment (oral or intravenous) with or without digital sympathectomy, removal of calcinosis, treat oesophageal problems

Late stage (>10 years after onset)

- Constitutional symptoms—fatigue common and aggravated by effects of vasculopathy and gut disease
- Skin thickening—stable or slow progression
- Organs affected—Raynaud's phenomenon, ulcers of digital tips, calcinosis, oesophageal stricture, small bowel malabsorption, pulmonary arterial hypertension, lung fibrosis
- Treatment—vascular treatment (oral or intravenous) with or without digital sympathectomy, removal of calcinosis, treat oesophageal and midgut problems

Box 19.3 **Characteristic findings and suggested treatment for diffuse cutaneous scleroderma**

Early stage (≤5 years after onset)

- Constitutional symptoms—fatigue, weight loss, pruritis
- Skin thickening—rapid progression with peak involvement by 2 years typical
- Organs affected—risk of renal, cardiac, pulmonary fibrosis, gastrointestinal, articular and muscular damage
- Treatment—vascular therapy, physiotherapy and occupational therapy as appropriate; immunosuppression for lung fibrosis and severe or progressive skin involvement; low-dose corticosteroids

Late stage (>5 years after onset)

- Constitutional symptoms—generally diminished
- Skin thickening—stable or regression
- Organs affected—musculoskeletal deformities, progression of existing visceral diseases but reduced risk of new complications
- Treatment—treat complications, gradual withdrawal of immunosuppression

Table 19.2 Autoimmune serology in SSc

Antibody	Prevalence	Comments
ACA	60% lcSSc	Associated with typical CREST
Scl-70	40% dcSSc, 15% lcSSc	Predictive of interstitial lung involvement, especially in lSSc
RNApol	20% SSc	Anti-RNApol I or III associated with diffuse subset and renal disease
U1-RNP	10% SSc	Associated with overlap features
U3-RNP	5% SSc	Poor outcome and isolated PHT in dcSSc
PM-Scl	3% SSc	Myositis overlap
Th/To	5% SSc	Lung fibrosis in lcSSc
anti-M2	5–10% SSc	Especially in lcSSc with PBC

TABLE 84-2 American College of Rheumatology/European League against Rheumatism Classification Criteria for the Classification of Systemic Sclerosis

Item	Sub-item(s)	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	—	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers Sclerodactyly of the fingers (distal to the MCPs but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	—	2
Abnormal nailfold capillaries	—	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	—	3
SSc-related autoantibodies *(maximum score is 3)*	ACA Scl-70 RNA Pol	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.

ACA, Anticentromere; MCPs, metacarpophalangeal joints; RNA Pol, anti-RNA polymerase III; Scl-70, antitopoisomerase 1; SSc, systemic sclerosis.

Modified from van den Hoogen F, Khanna D, Fransen J, et al: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 65:2737–2747, 2013.

Box 19.4 **Principles of management of systemic sclerosis**

- Accurate diagnosis
- Appropriate subsetting
- Staging disease within subset
- Vascular and immunosuppressive therapy according to stage and subset
- Risk stratification for major organ-based complications based upon serological, genetic and clinical features
- Screening and early intervention when complications develop
- Organ-based therapy: gastrointestinal, respiratory, cardiac, renal

- THE END