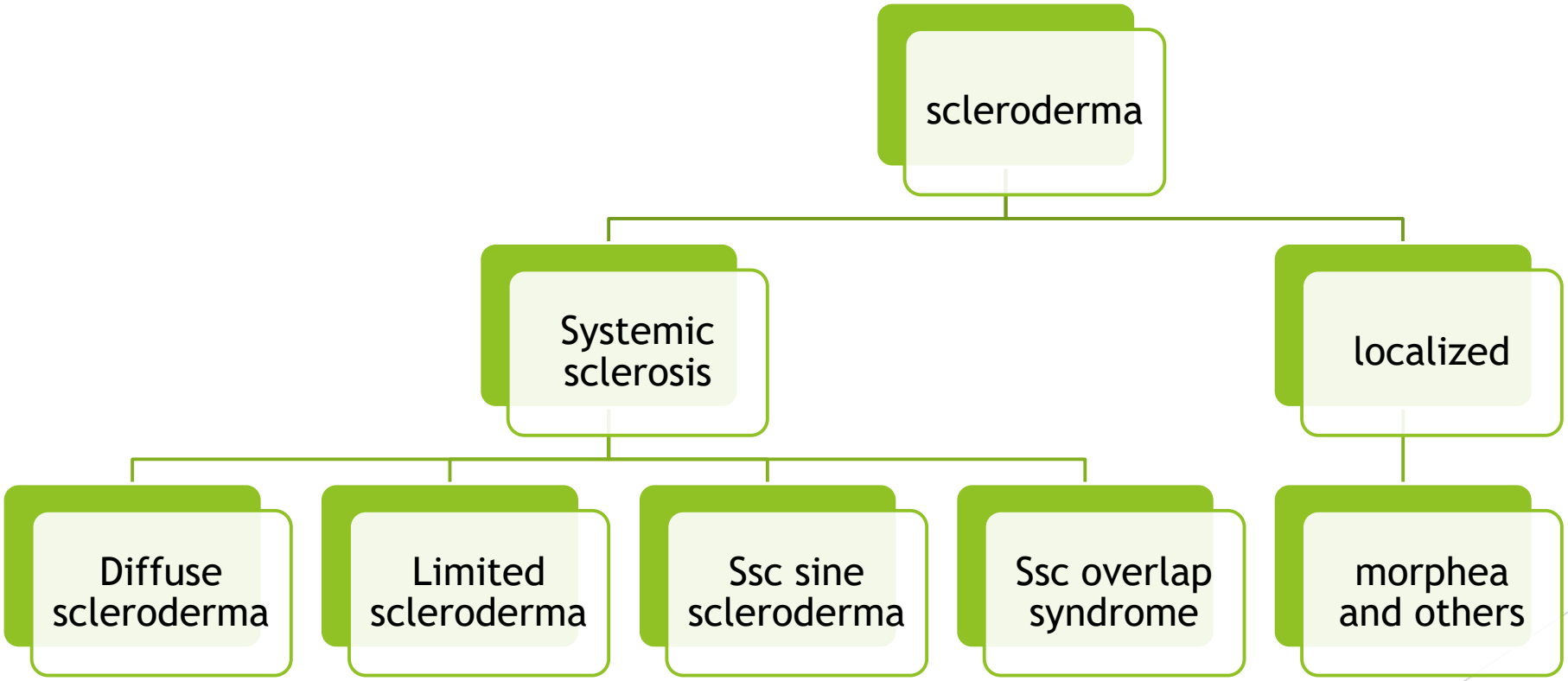
Scleroderma

Ola hijjawi

objective

- Definition and types
- Epidemiology
- Pathogenesis
- Clinical manifestation
- Evaluation
- Treatment
- Prognosis

- Scleroderma
- Chronic multisystem disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs
- It describe the presence of hard skin
- Heterogenous disease with wide spectrum organ involvement, disease progression, severity and outcome


scleroderma
Systemic sclerosis
localized
Diffuse scleroderma
Limited scleroderma
Ssc sine scleroderma
Ssc overlap syndrome
morphea and others

- Classification depend on

- Extent of skin involvement
- Accompanying pattern of internal organ involvement
- Presence of overlap feature with other connective tissue disease

Systemic sclerosis subtypes

Limited cutaneous systemic sclerosis

- Raynaud phenomenon for years, occasionally decades
- Skin involvement limited to hands, face, feet, and forearms (acral distribution)
- Nailfold capillary pattern typical of systemic sclerosis (predominantly nailfold capillary loops with capillary dropout)
- A significant (10 to 15%) late incidence of pulmonary hypertension, with or without skin calcification, gastrointestinal disease, telangiectasias (CREST syndrome), or interstitial lung disease
- Renal disease rarely occurs
- Anticentromere antibody (ACA) in 50 to 60%, but other patterns also occurring in 5 to 10% (especially anti-PM/Scl and anti-Scl-70)

Diffuse cutaneous systemic sclerosis

- Raynaud phenomenon followed, within 1 year, by puffy or hidebound skin changes
- Truncal and acral skin involvement; tendon friction rubs
- Nailfold capillary pattern typical of systemic sclerosis with dilatation (early), dilatation and dropout (active), and tortuosity with dropout (late)
- Early and significant incidence of kidney, interstitial lung, diffuse gastrointestinal, and myocardial disease
- Anti-Scl-70 (30%) and anti-RNA polymerase I, II, or III (12 to 15%) antibodies

Systemic sclerosis sine scleroderma

- Presentation with pulmonary fibrosis or kidney, cardiac, or gastrointestinal disease
- No skin involvement
- Raynaud phenomenon may be present
- Antinuclear antibodies may be present (anti-Scl-70, ACA, or anti-RNA polymerase I, II, or III)

Overlap syndromes

- Features of systemic sclerosis that coexist with those of another autoimmune rheumatic disease, such as systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, vasculitis, or Sjögren's disease

CREST syndrome: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome, also called limited scleroderma or limited cutaneous form of

Epidemiology

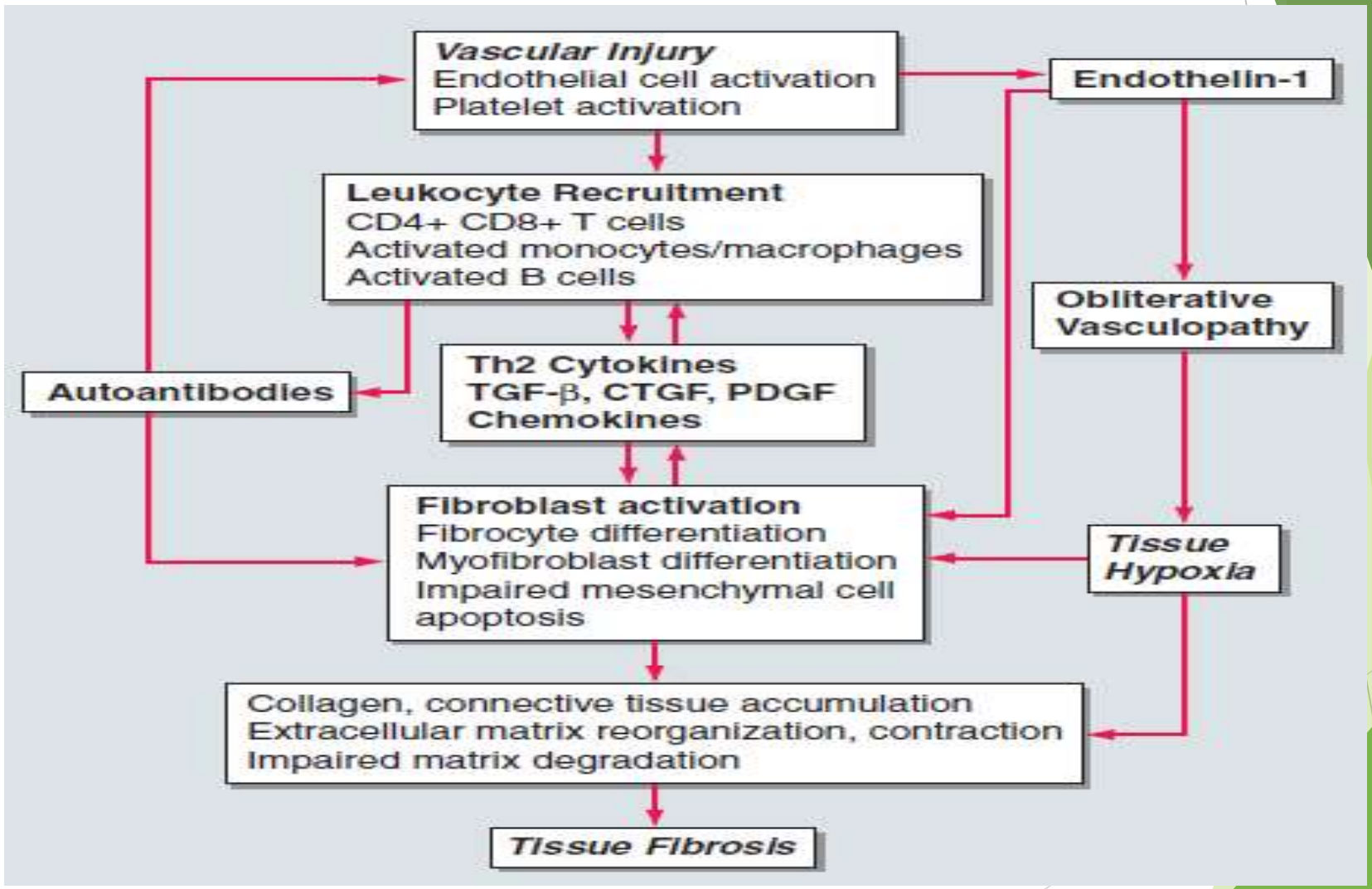
- Incidence and prevalence varies widely across studies
- The overall incidence rate range globally from 8 to 56 new cases per million person per year
- Prevelence rates fall between 38 and 341 cases per million persons
- Female:male ratio 3:1- 8:1

- Female have more limited disease, younger age of onset and more vascular
- Male have more diffuse disease, lung , cardiac and renal involvement
- The interval from first onset of Raynaud's to diagnosis of scleroderma tend to be longer in women than men
- African American tend to have earlier disease onset and more sever disease, and more risk of pulmonary fibrosis and scleroderma renal crises

pathogenesis

- The pathogenesis of systemic sclerosis is complex and remains incompletely understood.

- ✓ Immune activation,
- ✓ vascular damage
- ✓ excessive synthesis of extracellular matrix with deposition of increased amounts of structurally normal collagen

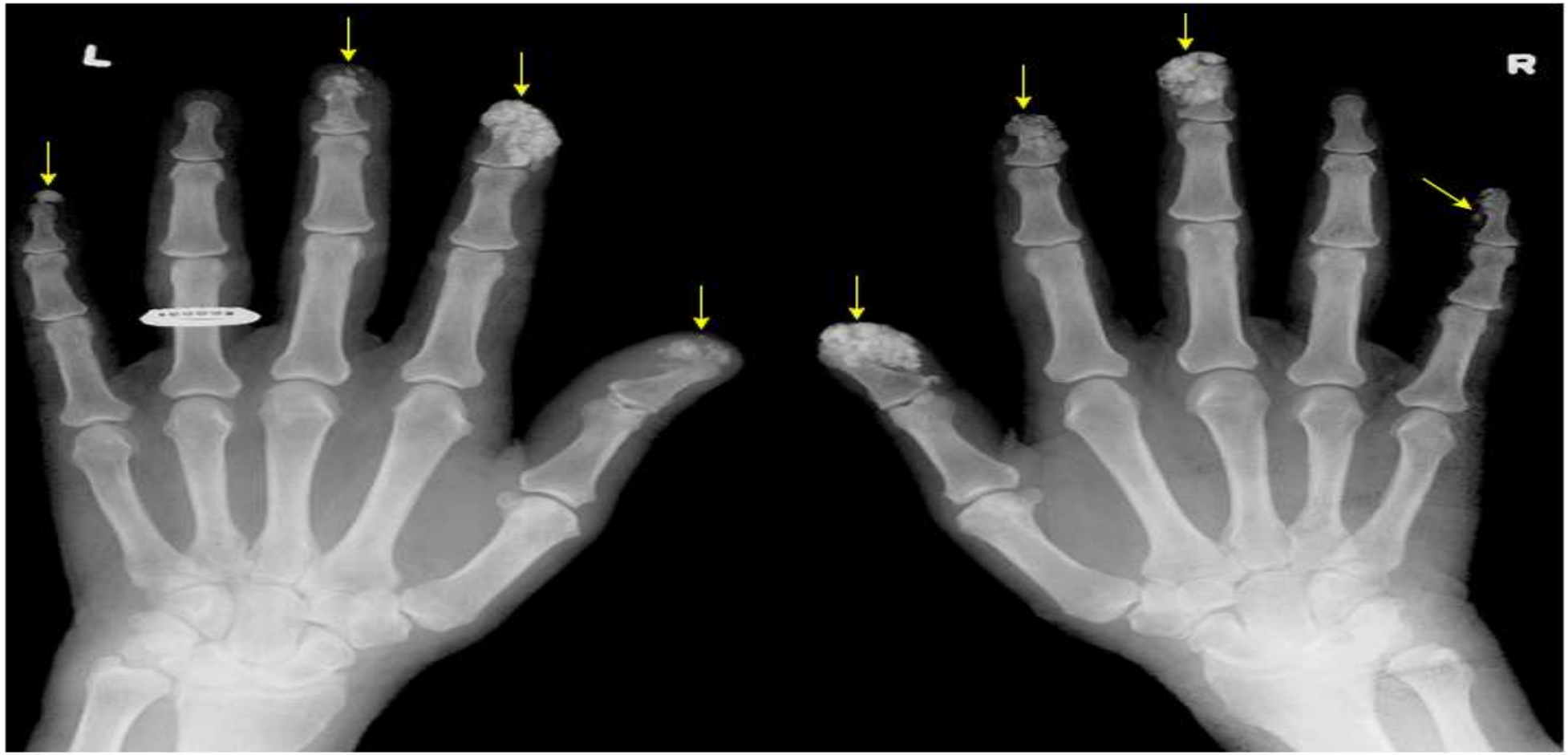

Vascular Injury
Endothelial cell activation
Platelet activation
Endothelin-1
Leukocyte Recruitment
CD4+ CD8+ T cells
Activated monocytes/macrophages
Activated B cells
Obliterative Vasculopathy
Th2 Cytokines
TGF-β, CTGF, PDGF
Chemokines
Autoantibodies
Fibroblast activation
Fibrocyte differentiation
Myofibroblast differentiation
Impaired mesenchymal cell apoptosis
Tissue Hypoxia
Collagen, connective tissue accumulation
Extracellular matrix reorganization, contraction
Impaired matrix degradation
Tissue Fibrosis

Clinical manifestation

- **Cutaneous manifestations**
- Skin involvement is a nearly universal feature of SSc and is characterized by variable extent and severity of skin thickening and hardening.
- The fingers, hands, and face are generally the earliest areas of the body involved
- (peaked nose, Microstomia, telegenctasia)
- Edematous swelling and erythema may precede skin induration

- Pruritus in the early stages
- Edema in the early stages
- Skin hyperpigmentation or depigmentation ("salt and pepper")
- Loss of appendicular hair
- Dry skin (shiny, no wrinkels)
- Tight skin (flexion contracture)
- Capillary changes at the nail beds
- Lipoatrophy
- Ulcerations over the distal interphalangeal joints (DIP) and proximal interphalangeal joints (PIP) related to repetitive microtrauma over tightened skin
- Digital tip ulcers and/or pitting at the fingertips
- Telangiectasia
- Calcinosis cutis

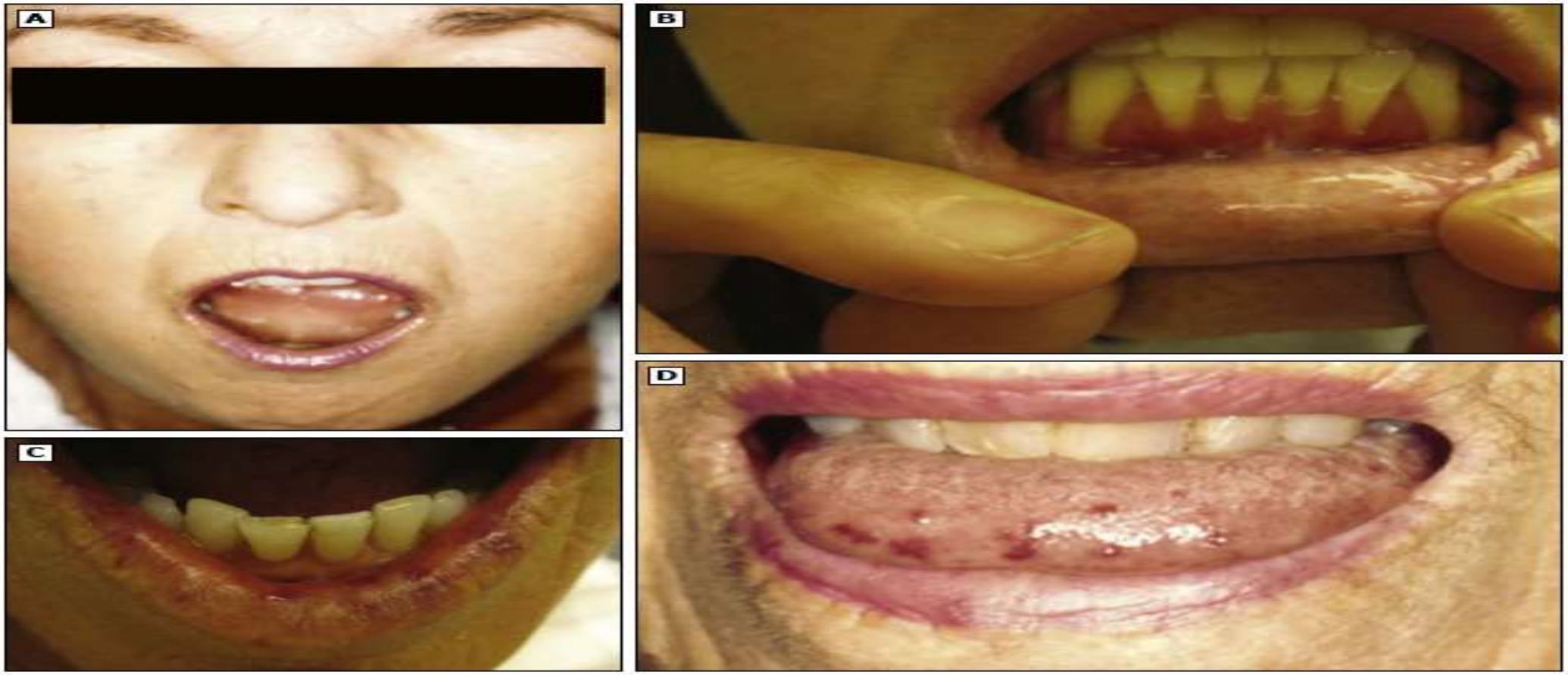
Calcinosis cutis in scleroderma on radiograph



A-P view of the hands in a patient with scleroderma shows extensive calcification involving the soft tissues of the distal phalanges of both hands.

A-P: anteroposterior.

Oral manifestations of systemic sclerosis

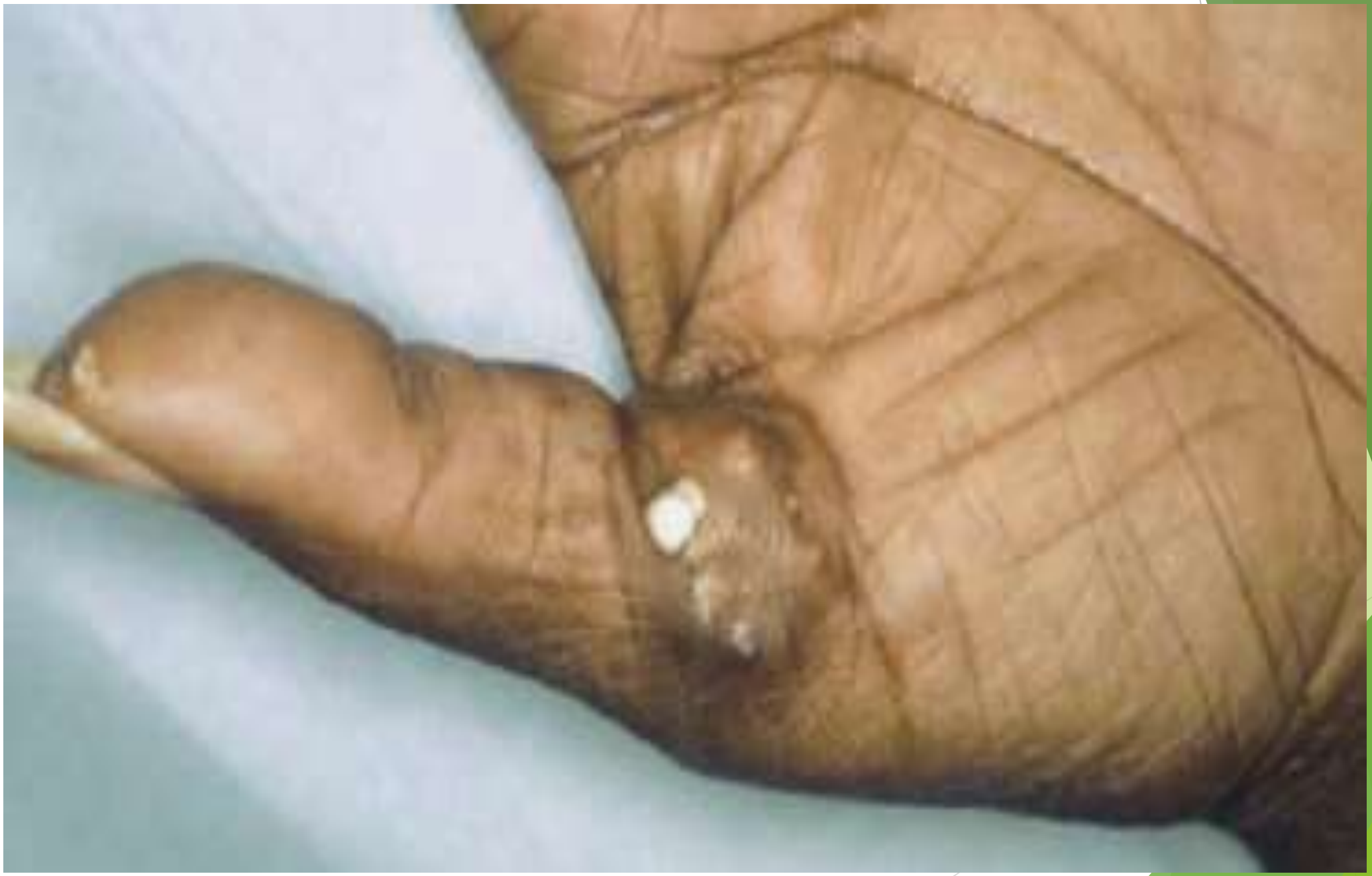


Oral manifestations.

(A) Perioral skin tightening with decreased oral aperture, furrowing around the lips, and dry mucous membranes.

(B) Periodontal disease with regression of gum and loosening of teeth.

(C, D) Telangiectasias on lips and tongue.



- **Digital vasculopathy**
- RP is virtually always present in patients with SSc and can predate other disease symptoms by years, particularly in limited SSc.
- RP is classically viewed as reversible vasospasm due to functional changes in the digital arteries of the hands and feet. However, over time, many patients with SSc develop progressive structural changes in the small blood vessels, with permanently impaired flow.
- In such patients, episodes of RP may be prolonged, lasting 30 minutes or even longer, and can result in
  - ischemic pain,
  - digital ulceration
  - trophic changes
  - and in extreme cases, refractory or progressive ischemia and infarction.
- The early occurrence of digital ulcerations is more commonly seen in patients with diffuse disease and in patients who are positive for anti-topoisomerase I (anti-Scl-70) .

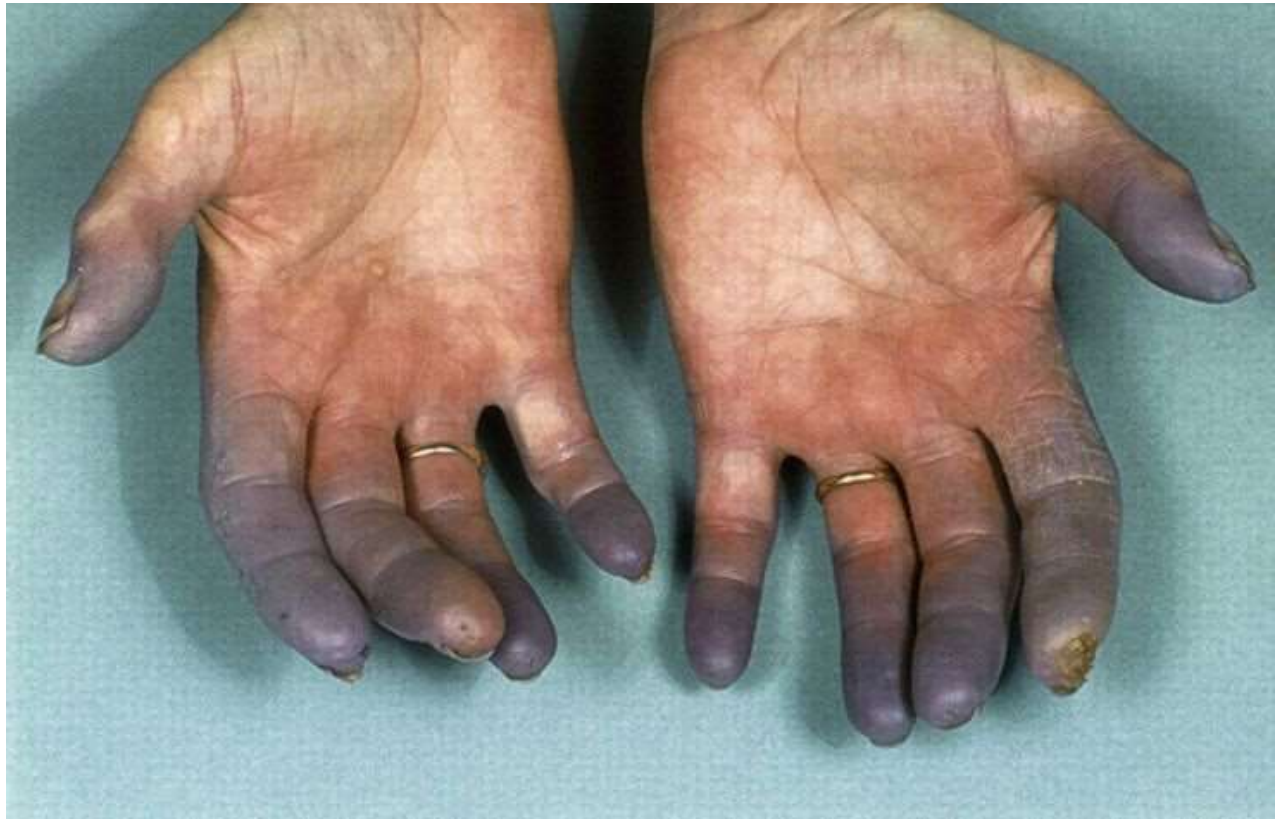
- **Raynaud phenomenon**
- Raynaud phenomenon (RP) is an exaggerated vascular response to cold temperature or emotional stress.
- The phenomenon is manifested clinically by sharply demarcated color changes of the skin of the digits (ie, fingers, toes).
- The underlying problem is thought to be abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses.
- RP is more common among young females, younger age groups, and related family members of patients with RP.

- **Secondary RP**

- autoimmune rheumatic diseases such as systemic sclerosis (SSc; scleroderma), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, and dermatomyositis/polymyositis.
- Various drugs or toxins can also precipitate or exacerbate RP such as amphetamines and chemotherapeutic agents (especially cisplatin and bleomycine)
- Hematologic abnormalities associated with RP include cryoglobulinemia, cold agglutinin disease, paraproteinemia, POEMS (**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein, **S**kin changes) syndrome, and cryofibrinogenemia.
- Occupational and environmental causes of RP include vascular trauma (eg, injury to the distal ulnar artery in hypothenar hammer syndrome)
- the use of tools that vibrate,
- Frostbite
- carpal tunnel syndrome
- Hypothyroidism may predispose to RP, and improvement of cold-induced vasospasm may occur with thyroid hormone replacement.

Raynaud's Phenomenon

	Primary	**Secondary**
Sex	Female	Male and Female
Age of Onset	Menarche	Mid 20's or later
Finger Edema	No	Frequent
Periungual erythema	Rare	Frequent
Arthritis	No	Frequent
Nail fold capillaroscopy	Normal	Dilated tortuous capillaries
Autoantibodies	Absent	Present



- **Musculoskeletal manifestations**
- Joint pain, immobility, and contractures of both small and large joints develop as the result of fibrosis around tendons and other periarticular structures.
- Inflammatory myositis
- Arthritis is most commonly polyarticular, but oligoarticular and monoarticular patterns can also be observed
- Erosive polyarticular symmetrical arthritis of the small joints, particularly the metacarpophalangeal joints and wrists (rare)
- The distal interphalangeal joints are generally not affected.
- The pattern of articular involvement in the hands is similar to that in rheumatoid arthritis
- The presence of tendon friction rubs in patients with SSc is a marker for aggressive disease and increased risk of internal organ involvement including renal crisis

- **Radiographs of the hands may reveal**
- calcifications in the skin (calcinosis cutis) and other soft tissues,
- resorption of the distal phalangeal tufts (acro-osteolysis).
- Articular erosions,
- joint space narrowing, and demineralization are less common radiographic findings

- **Kidney involvement**
- Life-threatening renal involvement called SRC (Scleroderma renal crises)develops in up to 10 percent of patients and is far more frequent in patients with dcSSc than lcSSc.
- SRC almost invariably occurs in the early stages of SSc.
- ✓ Abrupt onset of marked or malignant hypertension (although some patients remain normotensive)
- ✓ Acute onset of oliguric renal failure
- ✓ Urinalysis that reveals only mild proteinuria with few cells or casts
- ✓ Microangiopathic hemolytic anemia and thrombocytopenia
- Glomerulonephritis is uncommon

- **Pulmonary involvement**
- Leading cause of Death

Some degree of pulmonary involvement is present in more than 80 percent of patients with SSc.

The two principal clinical manifestations are

- ILD (interstitial lung disease)
- pulmonary vascular disease, leading to pulmonary arterial hypertension (PAH)

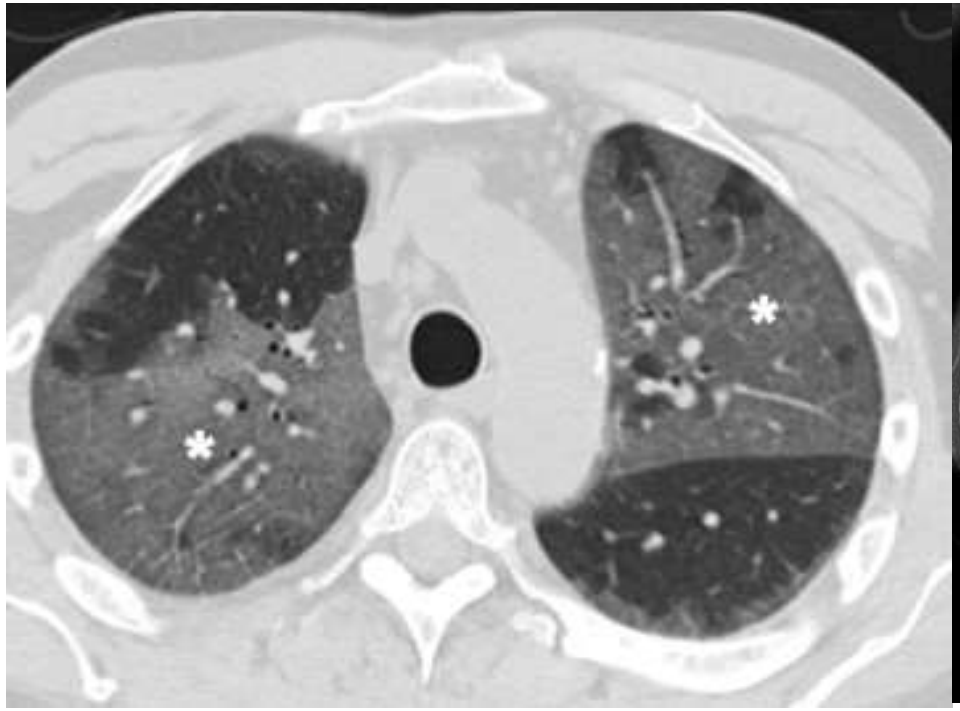
The most common symptoms of pulmonary involvement in SSc are

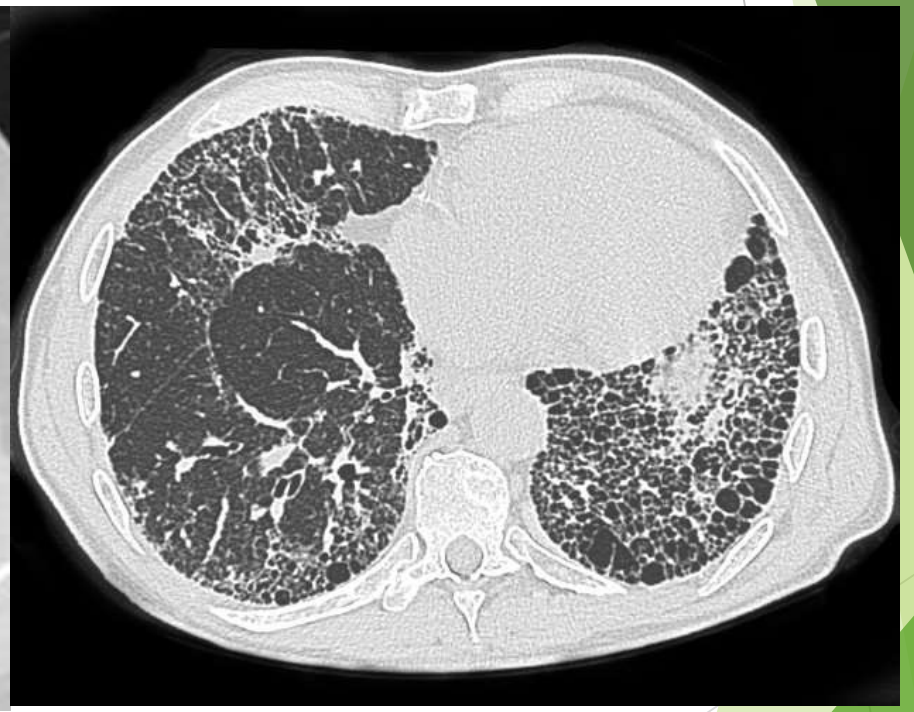
- breathlessness on exertion (which may progress to dyspnea at rest)
- nonproductive cough.
- Chest pain is infrequent and hemoptysis is rare

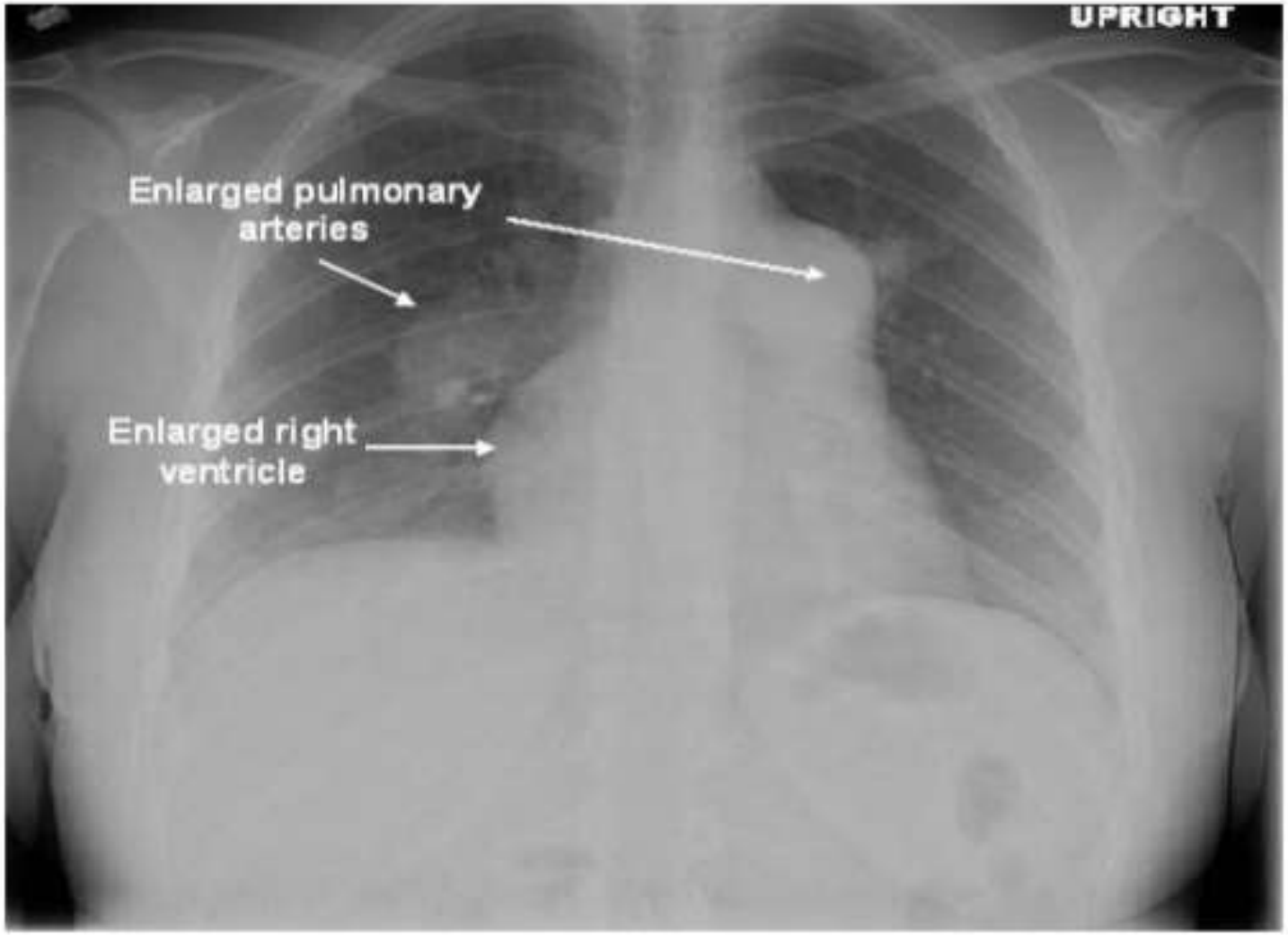
- **Pulmonary HTN**
- occurs in 10 to 40 percent of patients with SSc.
- It is common in patients with longstanding limited cutaneous disease without associated ILD.
- It can also happen secondary to ILD, particularly in those with diffuse SSc.
- Dyspnea with exertion and diminished exercise tolerance are the most common initial symptoms, but are commonly absent until the disease is fairly advanced.
- PAH is typically progressive and, if severe, can lead to cor pulmonale and right-sided heart failure. Thrombosis of the pulmonary vessels is a common late-stage complication and is a frequent cause of death

- **Pulmonry HTN** is defined as
- mean pulomonry arterial pressure > 20mmhg as determined by right side heart catheterization
- **Risk Factor**
- Late age of disease onset
- Sever Raynads phenomena
- Positive centromere or RNP
- Limited cutaneous disese

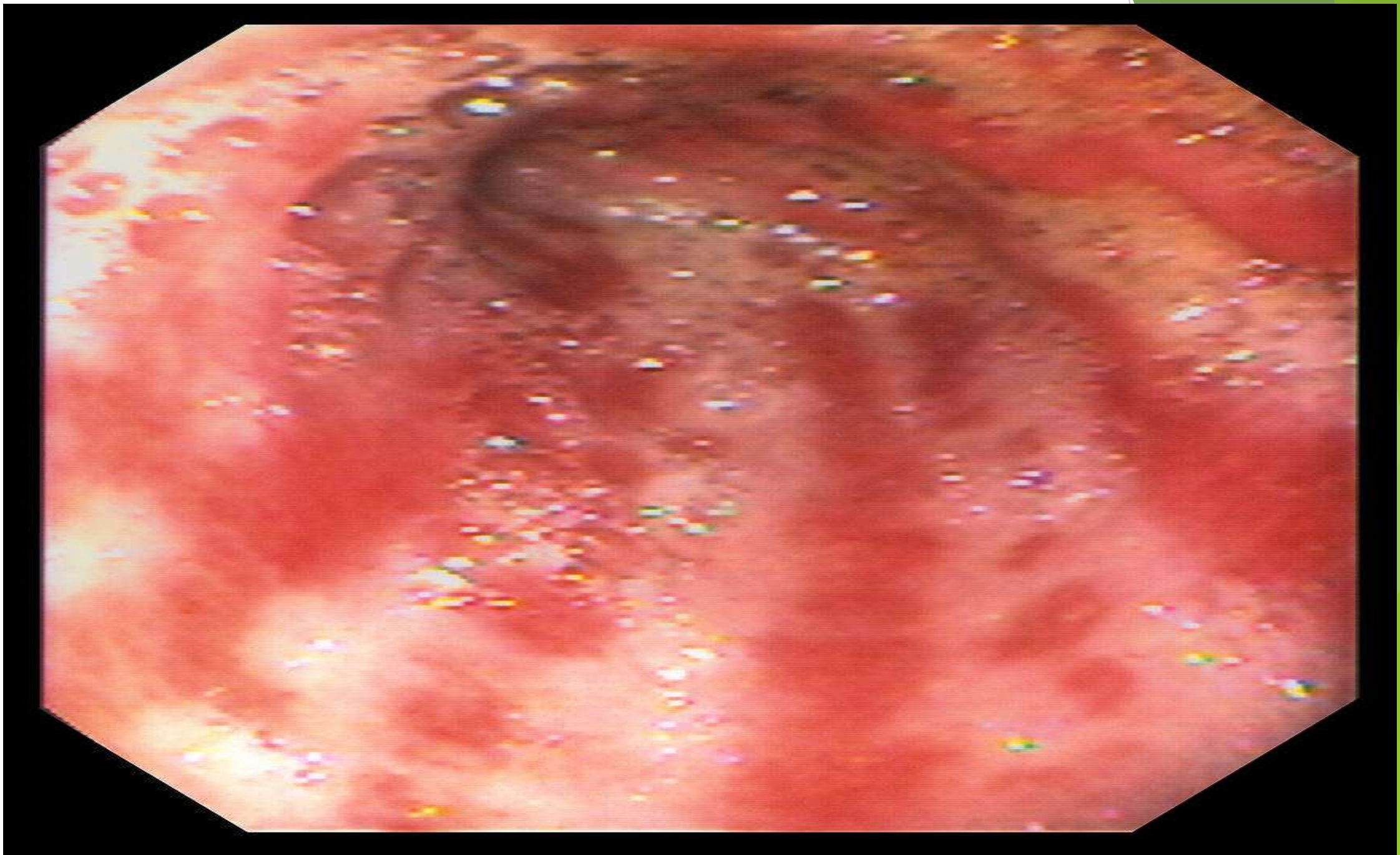
- **Interstial lung disease(ILD)**
- Cause restrictive lung disease
- Decrease in forced vital capacity and DLCO
- More common in diffuse SSc
- More common in positive SCL 70
- More common in Male and African American






UPRIGHT
Enlarged pulmonary arteries
Enlarged right ventricle

- **Gastrointestinal involvement**
- Nearly 90 percent of patients have evidence of gastrointestinal involvement
- Nearly half of these patients may have no symptoms.
- Although the esophagus is the most frequently affected part of the gastrointestinal tract, any part of the gastrointestinal tract may be involved.
- Esophagus- dysphagia and choking, , hoarseness, cough after swallowing,GERD
- Stomach- heart burn ,early satiety, Vascular ectasia (angiodysplasia) in the antrum of the stomach ("watermelon stomach")
- Bowel- bloating, alternating constipation and diarrhea, episodic pseudo-obstruction and bacterial small bowel overgrowth with malabsorption, and fecal incontinence



- **Cardiac involvement**
- Cardiac involvement is frequent in SSc but can be entirely asymptomatic.
- All anatomic domains of the heart can be affected in patients with SSc, including the myocardium, pericardium, and conduction system
- Cardiac complications of SSc can be primary, but can also occur secondary to PAH, ILD, or scleroderma renal crisis (SRC).

- **Neuromuscular involvement**
- Muscle atrophy (sarcopenia), muscle weakness, and myopathy
- Other neurologic abnormalities are less common include central, peripheral, and autonomic neuropathies
- **Genitourinary involvement**
- SSc in men is very commonly associated with erectile dysfunction, which can be an early and even initial manifestation of disease
- Women with SSc may also have sexual dysfunction. This is related to decreased vaginal lubrication or constriction of the vaginal introitus.

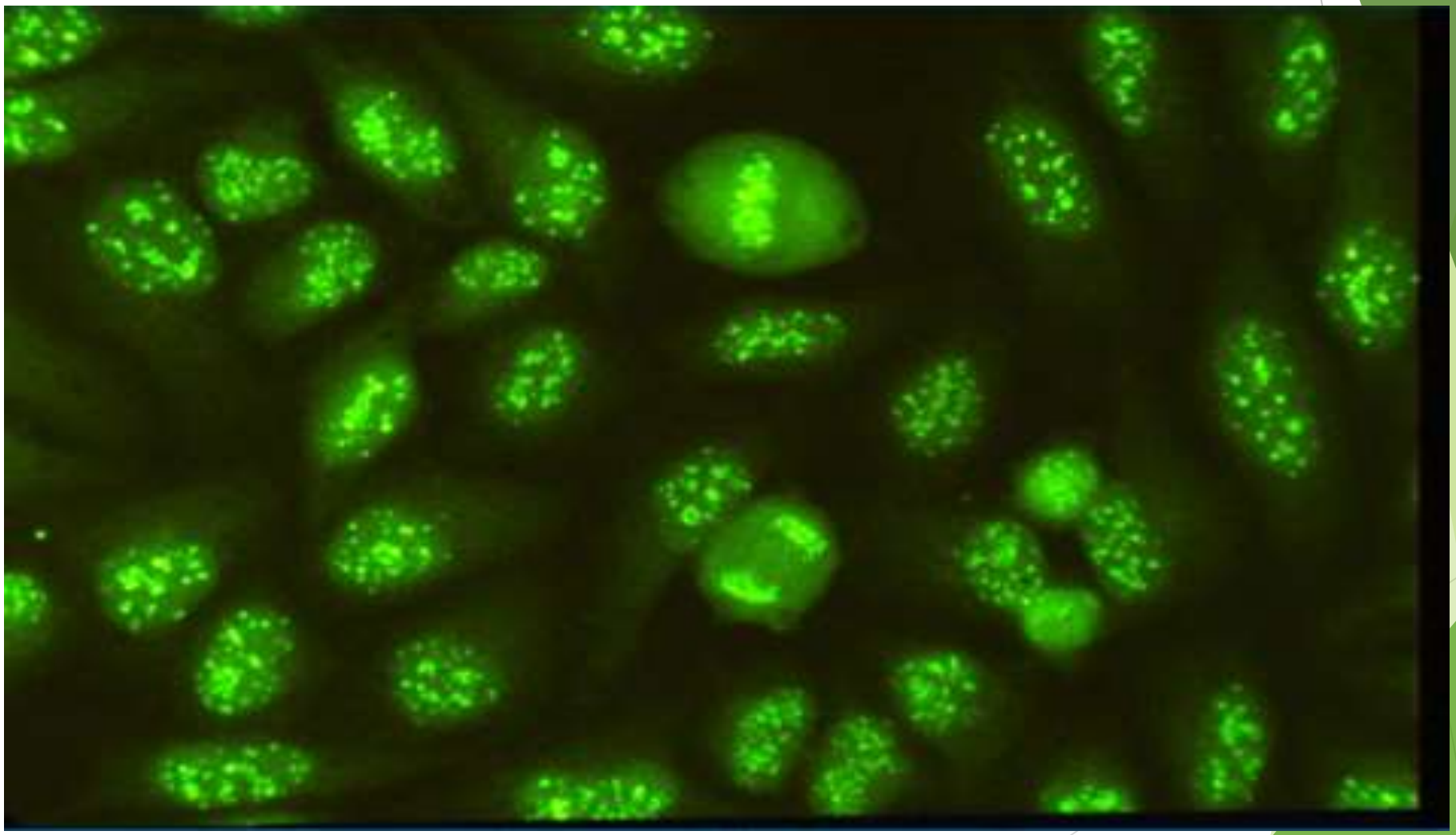
Investigation

Lab test

- Complete blood count and differential, which may reveal anemia due to malabsorption, iron deficiency, or gastrointestinal blood loss
- Serum creatinine level, which may indicate renal dysfunction
- Creatine kinase (CK), which may be elevated in patients with myopathy or myositis
- Urinalysis with urine sediment, which may reveal proteinuria and/or cellular casts

- Antinuclear antibody (ANA)
- ANA test is positive in approximately 95 percent of patients with SSc
- Anti-topoisomerase I (anti-Scl-70) generally associated with diffuse cutaneous SSc (dcSSc) and a higher risk of severe interstitial lung disease (ILD)
- Anticentromere antibody (ACA). The presence of ACA is usually associated with limited cutaneous SSc (lcSSc)
- Anti-RNA polymerase III antibody. Antibodies to RNA polymerase III are found in patients with dcSSc and are generally associated with rapidly progressive skin involvement as well as an increased risk for scleroderma renal crisis (SRC)
- Antibodies to Th/To, are seen in 5 percent of patients with SSc, and present with a nucleolar pattern of immunofluorescence, associated with limited skin disease, a greater frequency of ILD, and substantially increased risk of developing pulmonary arterial hypertension (PAH).

- The anti-topoisomerase I (anti-Scl-70), ACA, and anti-RNA polymerase III tests are highly specific (>99.5 percent in some studies) for SSc but are only moderately sensitive (20 to 50 percent)



Other investigation

- Pulmonary function testing (PFT)

This should be done to assess for the presence or absence of a restrictive ventilatory defect or a decrease in the single breath diffusion capacity for carbon monoxide (DLCO).

- Radiographic imaging of the lung

High-resolution computed tomography (HRCT) of the chest is preferred over a chest radiograph in SSc due to the greater sensitivity of the HRCT

- Doppler echocardiography

This is recommended for initial screening for PAH

Treatment

- **General principles**

- ✓ patients with systemic sclerosis are treated with organ-based symptomatic therapy.
- ✓ patients with diffuse skin involvement and/or severe inflammatory organ involvement are usually treated with systemic immunosuppressive therapy.
- ✓ We avoid glucocorticoids whenever possible due to their association with scleroderma renal crisis; if necessary, we treat with short courses of low-dose glucocorticoids

Organ based treatment

- Methotrexate (MTX) or Mycophenelate mofetil (MMF), Rituximab for diffuse skin disease
- MTX for patients who also have myositis
- NSAID, HCQ,MTX for Arthritis
- MMF, Rituximab for patients with interstitial lung disease.

reserve cyclophosphamide for progressive skin involvement in patients who are refractory to other treatment

Visceral involvement

- Many forms of visceral involvement, including scleroderma renal crisis, gastrointestinal dysmotility, heart failure, and pulmonary hypertension, are not managed with immunosuppression.

- Interstitial lung disease, myocarditis, and pericarditis require immunosuppressive therapies

Raynads phenomena treatment

Nonpharmacologic measures

To help prevent attacks or reduce their severity.

- ✓ avoiding cold exposure,
- ✓ avoiding vasoconstricting drugs
- ✓ smoking cessation
- ✓ Management of emotional stress

Initial pharmacologic therapy

- ✓ long-acting dihydropyridine calcium channel blockers (CCBs)
- ✓ alternative options include

  phosphodiesterase type 5 (PDE5) inhibitors

  topical nitrates

- **Monitoring**

✓ Annual echocardiogram and electrocardiogram for all patients.

✓ Monitor blood pressure twice weekly

✓ Annual pulmonary function tests for at least five years following diagnosis to monitor for interstitial lung disease;

✓ Patients with known interstitial lung disease may require more frequent testing.

✓ Changes in symptoms or pulmonary function tests should be followed by high-resolution CT

✓ Check blood pressure daily in patients with

- Early-stage diffuse cutaneous disease
- Rapidly progressive cutaneous involvement with tendon friction rubs
- Autoantibodies to RNA polymerase III

- An increase in systolic blood pressure of 15 mmHg or diastolic blood pressure of 10 mmHg should trigger an immediate evaluation for scleroderma renal crisis

- **Prognosis**

- ✓ There is a substantial increase in the risk of death in patients with SSc.
- ✓ Most deaths among patients with SSc are related to pulmonary fibrosis, pulmonary arterial hypertension, or cardiac causes
- ✓ Other significant causes of death include kidney disease, malignancy, gastrointestinal, and infectious causes

QUESTIONS??