Systemic Sclerosis

Definition

A multisystem auto-immune disorder characterized by

1) functional and structural abnormalities of blood vessels

2) fibrosis of the skin and internal organs

(Scleroderma means hard skin)

Epidemiology

1. Prevalence:10-20 / 100000
2. Susceptibility: host factor
   1) age - peak occurrence: fourth-fifth decade
   2) gender - female : male 4:1
   3) genetic background/ 13-14 fold with first relative
   4) Race >more common in black people with worse prognosis.

Classification

1. Systemic sclerosis
   - Diffuse cutaneous systemic sclerosis _30%
   - Limited cutaneous systemic sclerosis Overlap syndromes--- 70%

2. Localized scleroderma
   - Morphoea
   - Linear scleroderma
     - *En coup de sabre*

Classification of systemic sclerosis

1. Diffuse cutaneous systemic sclerosis

   1) Diffuse Skin thickening

   2) Tendency to rapid progression of skin change

   3) Rapid onset of disease following Raynaud's phenomenon

   4) Early appearance of visceral involvement

   5) Poor prognosis (5 year survival about 70%)

Classification of systemic sclerosis

2. Limited cutaneous systemic sclerosis
   1) symmetric restricted fibrosis
      - affecting the distal extremities and face/neck
   2) prolonged delay in appearance of distinctive internal manifestation
   3) prominence of calcinosis and telangiectasia
   4) good prognosis

* CREST syndrome
  - calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia

Classification of systemic sclerosis

Overlap syndromes

- Features of systemic sclerosis together with those of at least one other autoimmune rheumatic disease, e.g. SLE, RA, or polymyositis.

Etiology

Environmental factors

1) silica dust
2) organic solvents
3) biogenic amines
4) urea formaldehyde
5) polyvinyl chloride
6) rapeseed oil
7) bleomycin
8) L-tryptophan
9) silicone implant (?)

Genetic predisposition Defective immunoregulation

1) cell mediated immunity CD4/CD8 , (Th1 , 2,17)
2) Cytokines (IL1-2-4-5-6-12-13-17-21-22/TNFa/ INFy)

3) humoral immunity
   – hypergammaglobulinemia
   – autoantibody production

Antibodies :

1-Antinuclear antibody (+) > 95%

2-Anti-centromere: associated with limited form

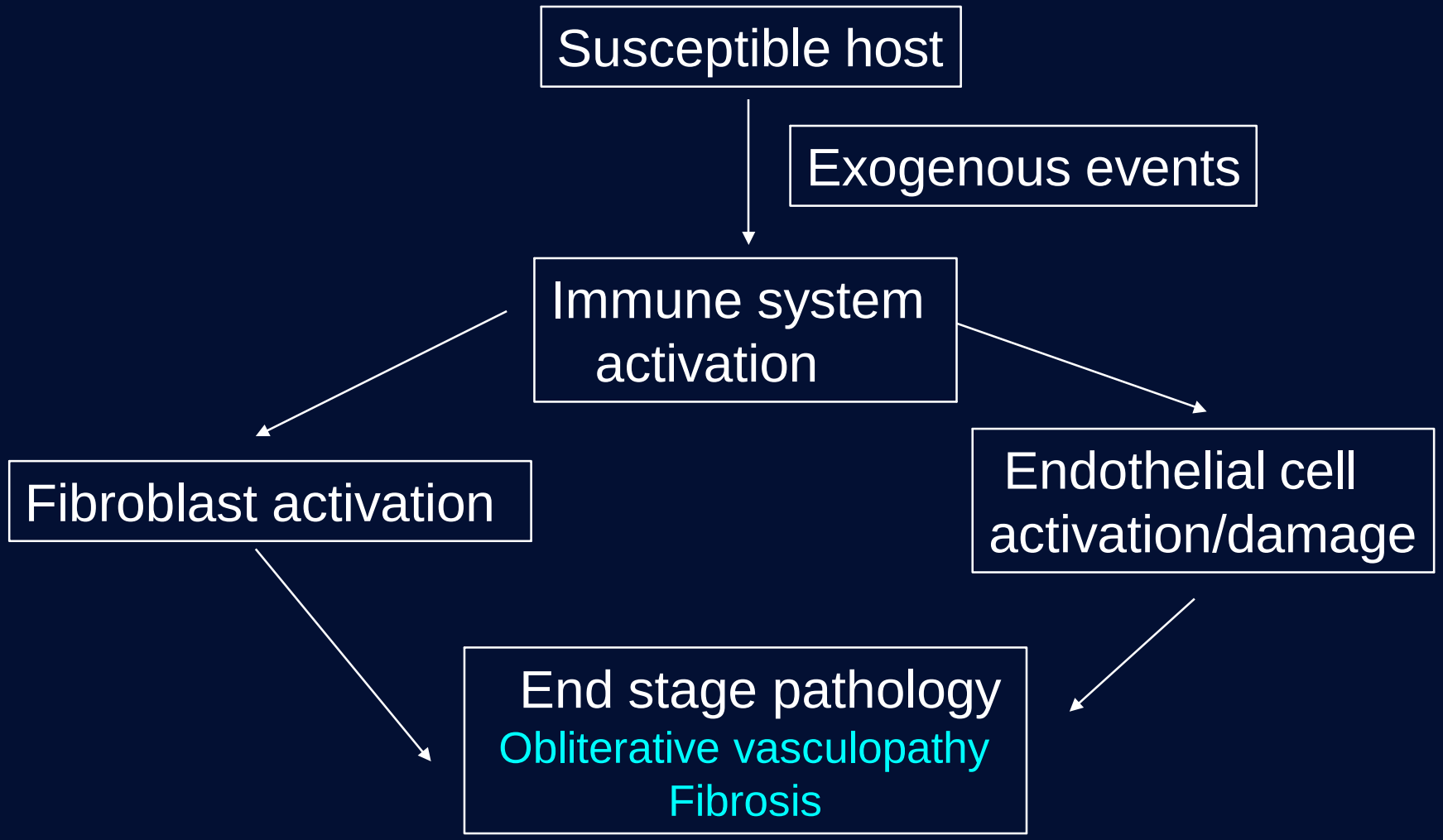
3-Anti topoisomerase : associated with diffuse form / lung fibrosis

4- Anti RNA plymerase:highly specific / risk of renal crises

5-Anti-PmScl- with myositis overlap syndromes

6-Anti fibrillin antibodies : common in africans americans /diffuse form

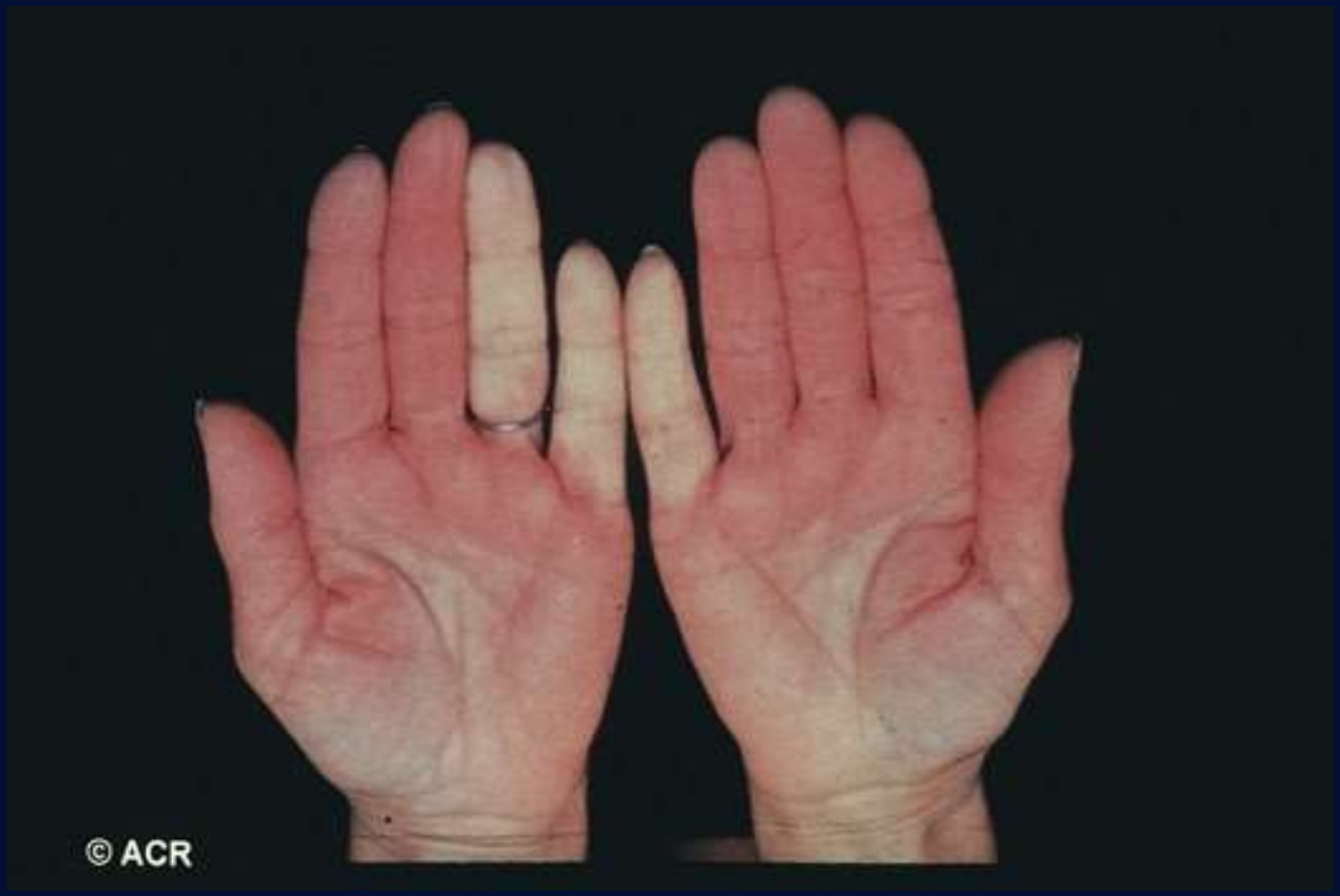
Pathogenesis



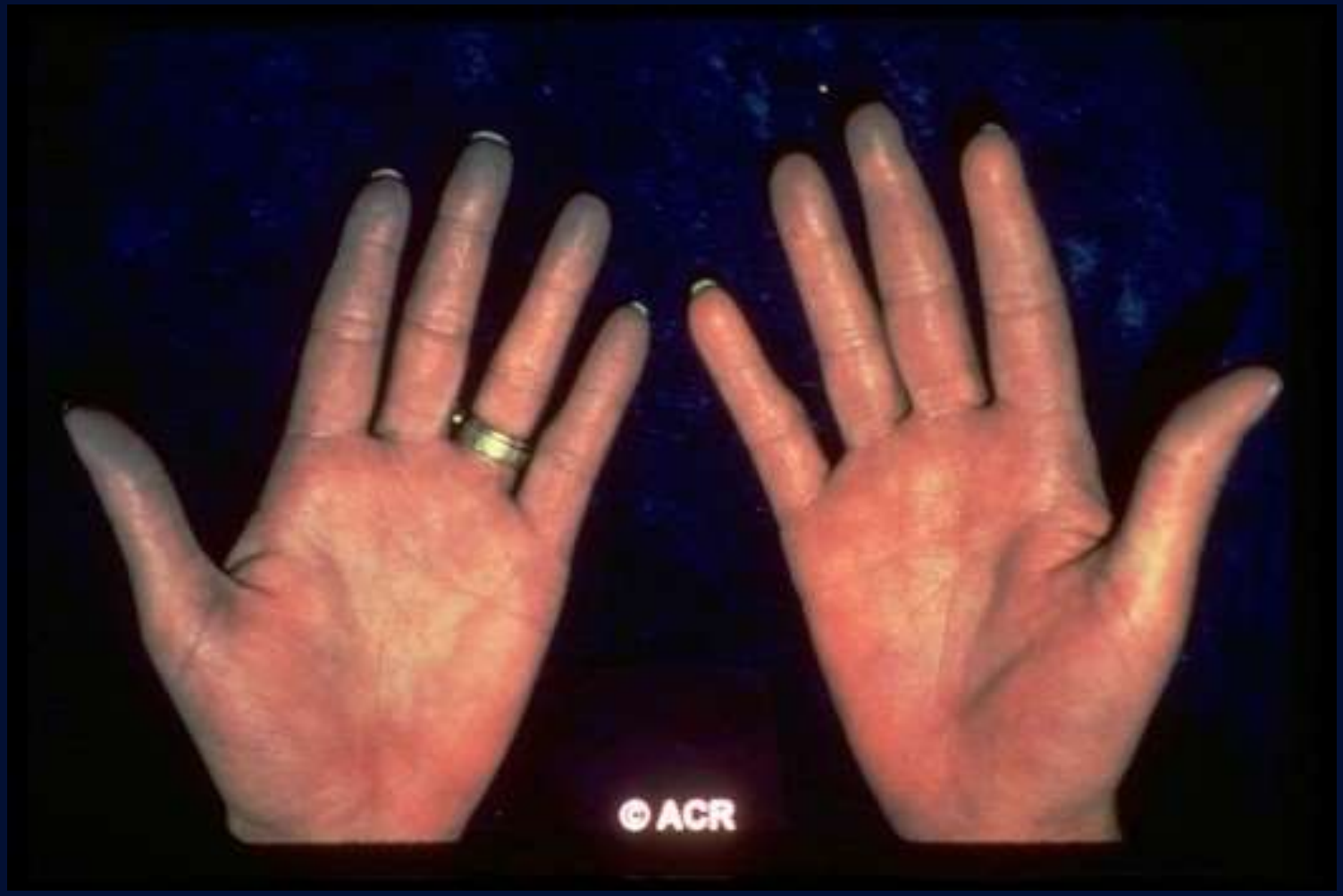
Clinical features

1. Vascular abnormalities
   1) Raynaud's phenomenon
   - cold hands and feet
     with reversible skin color change (white to blue to red)
   - induced by cold temperature or emotional stress
   - initial complaint in 3/4 of patients
   - 90% in patients with skin change
     (prevalence in the general population: 4-15%)
   2) digital ischemic injury

Raynaud's phenomenon

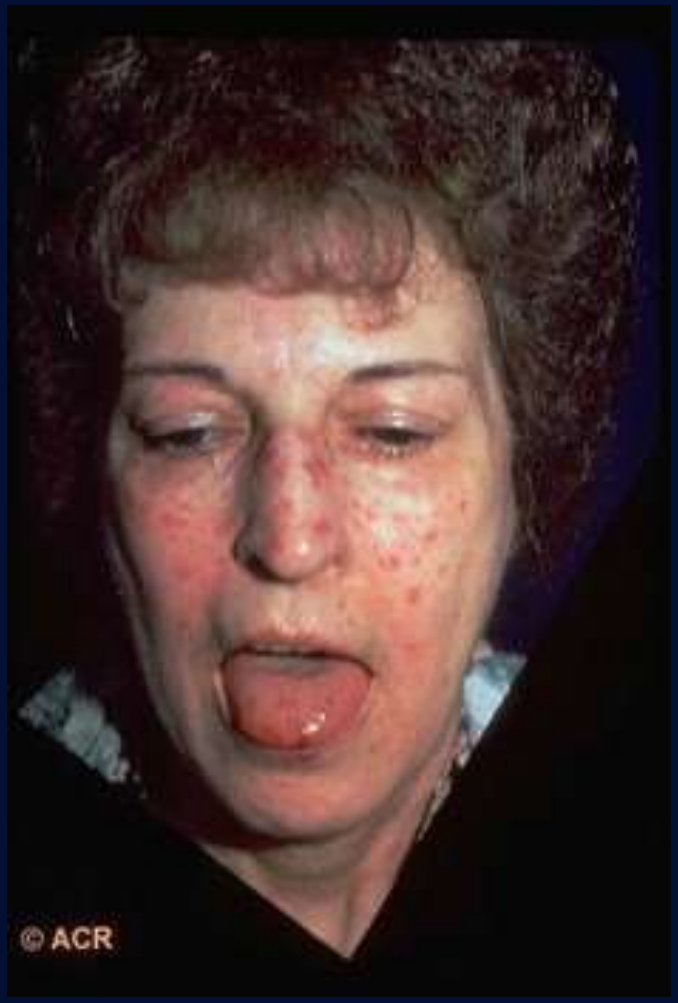


Raynaud's phenomenon



Telangiectasia

- local disruption of angiogenesis
- blanched by pressure



Clinical features

2. Skin involvement (1)

1) stage

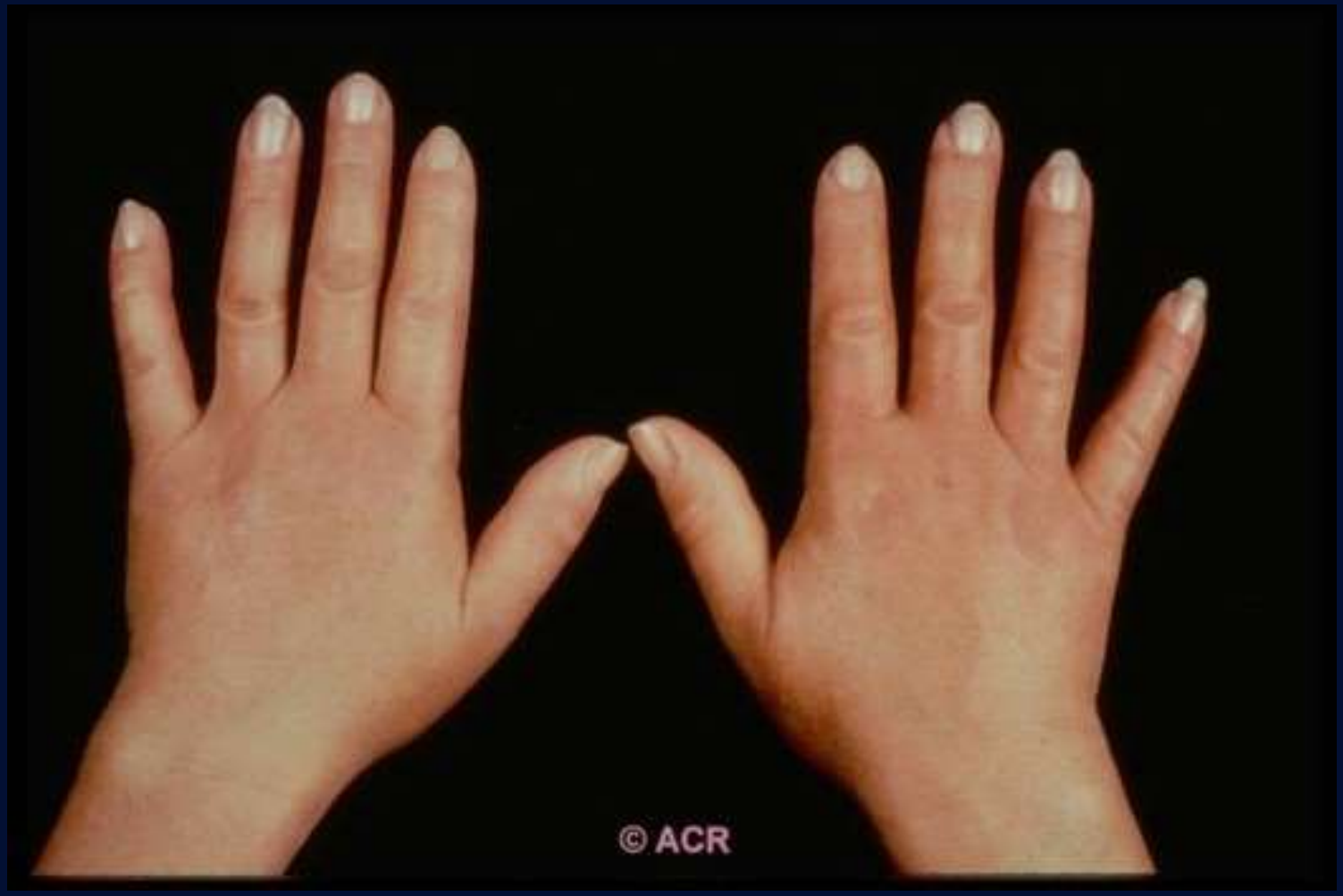
- edematous phase
- indurative phase
- atrophic phase

2) firm, thickened bound to underlying soft tissue

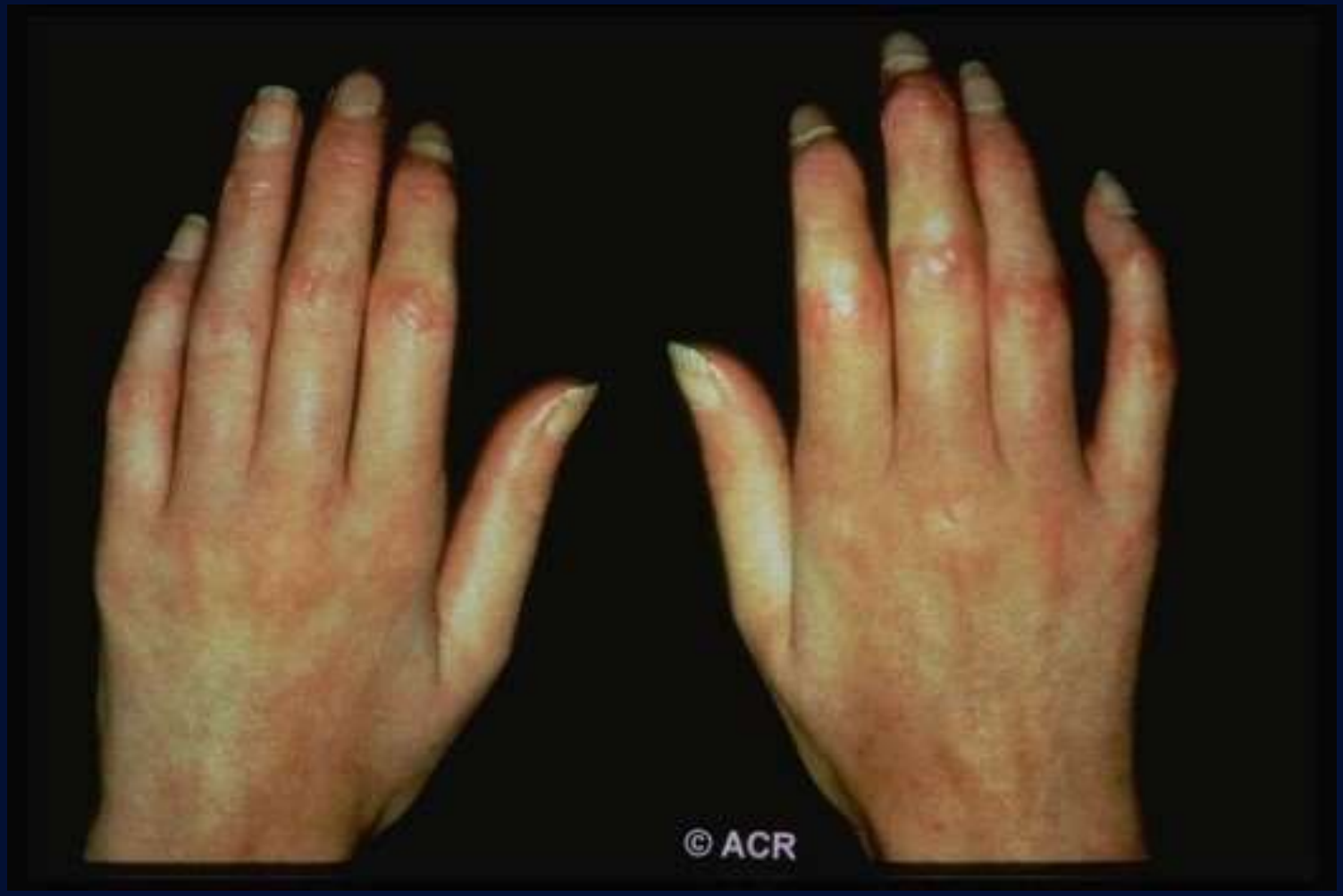
3) decrease in range of motion, loss of facial expression, inability to open mouth fully, contractures

4) ulceration, loss of soft tissue of finger tip, pigmentation, calcific deposit, capillary change

Edematous phase

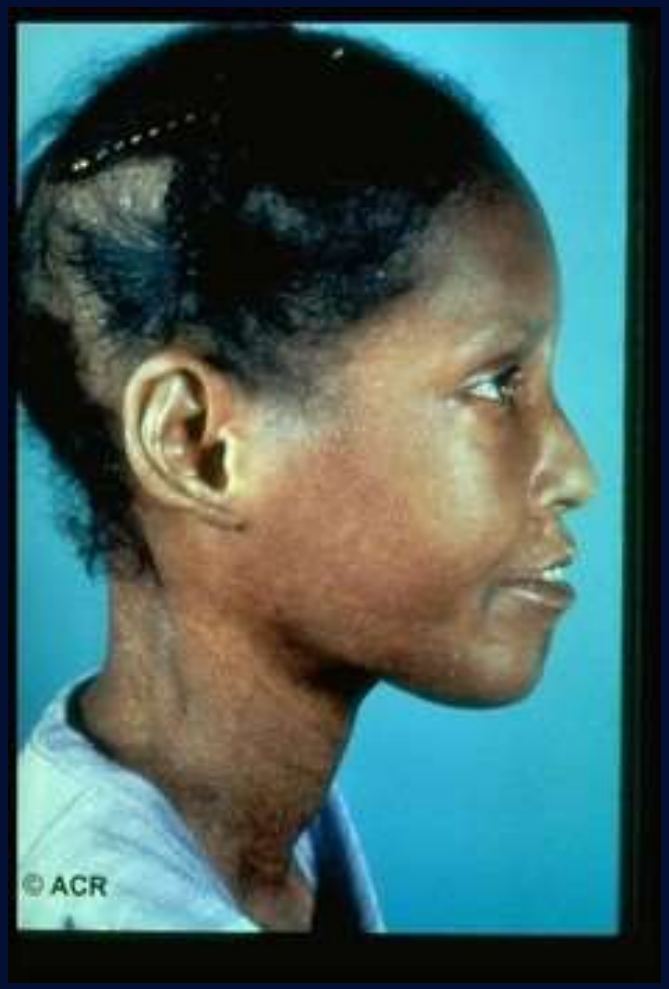


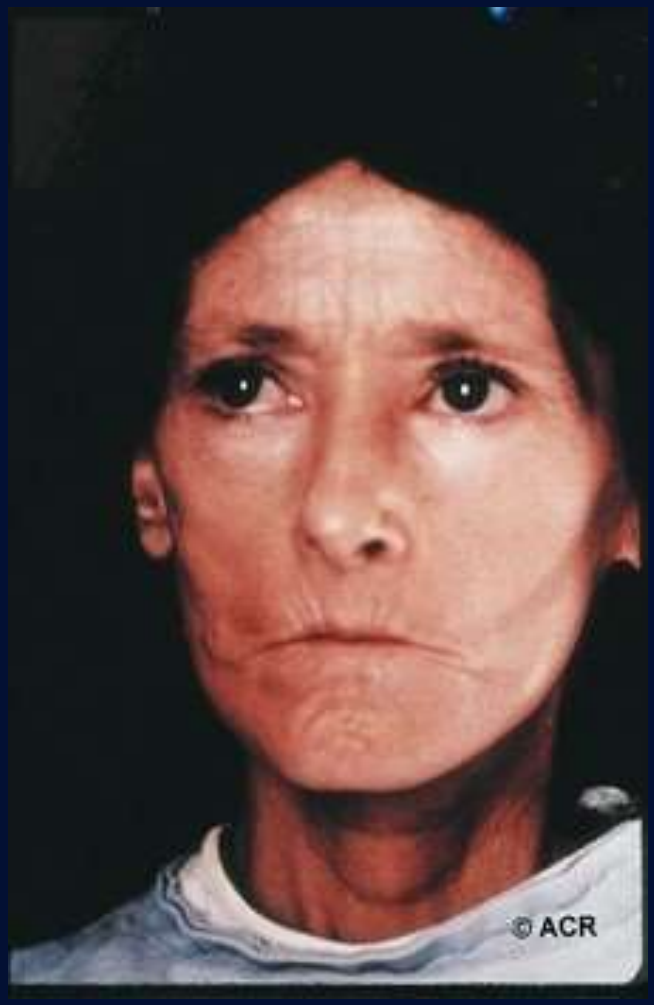
Skin Induration



Acrosclerosis

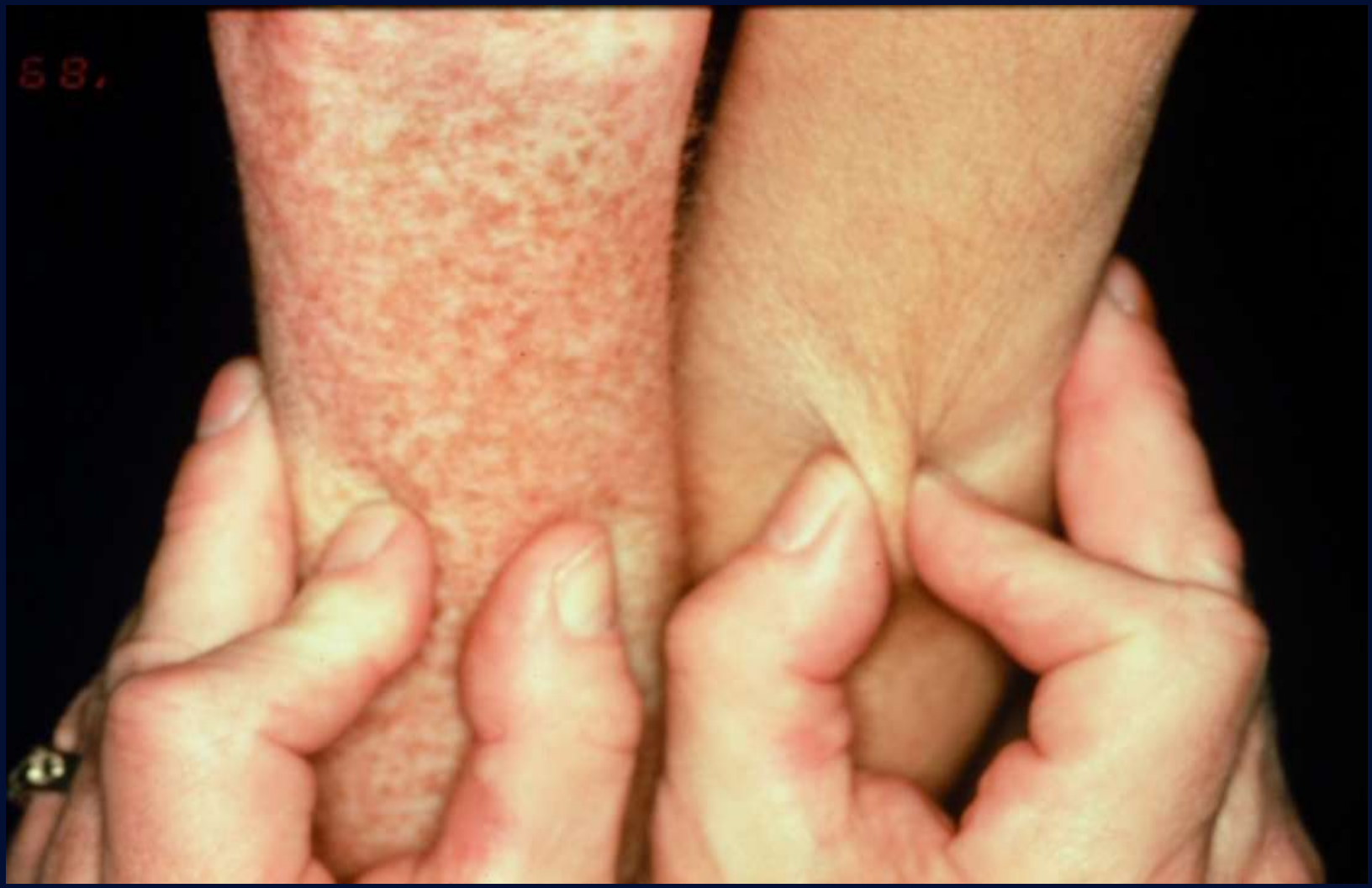
Facial changes





Tight, thin lips with vertical perioral furrows

Thick skin of forearms
(proximal scleroderma)



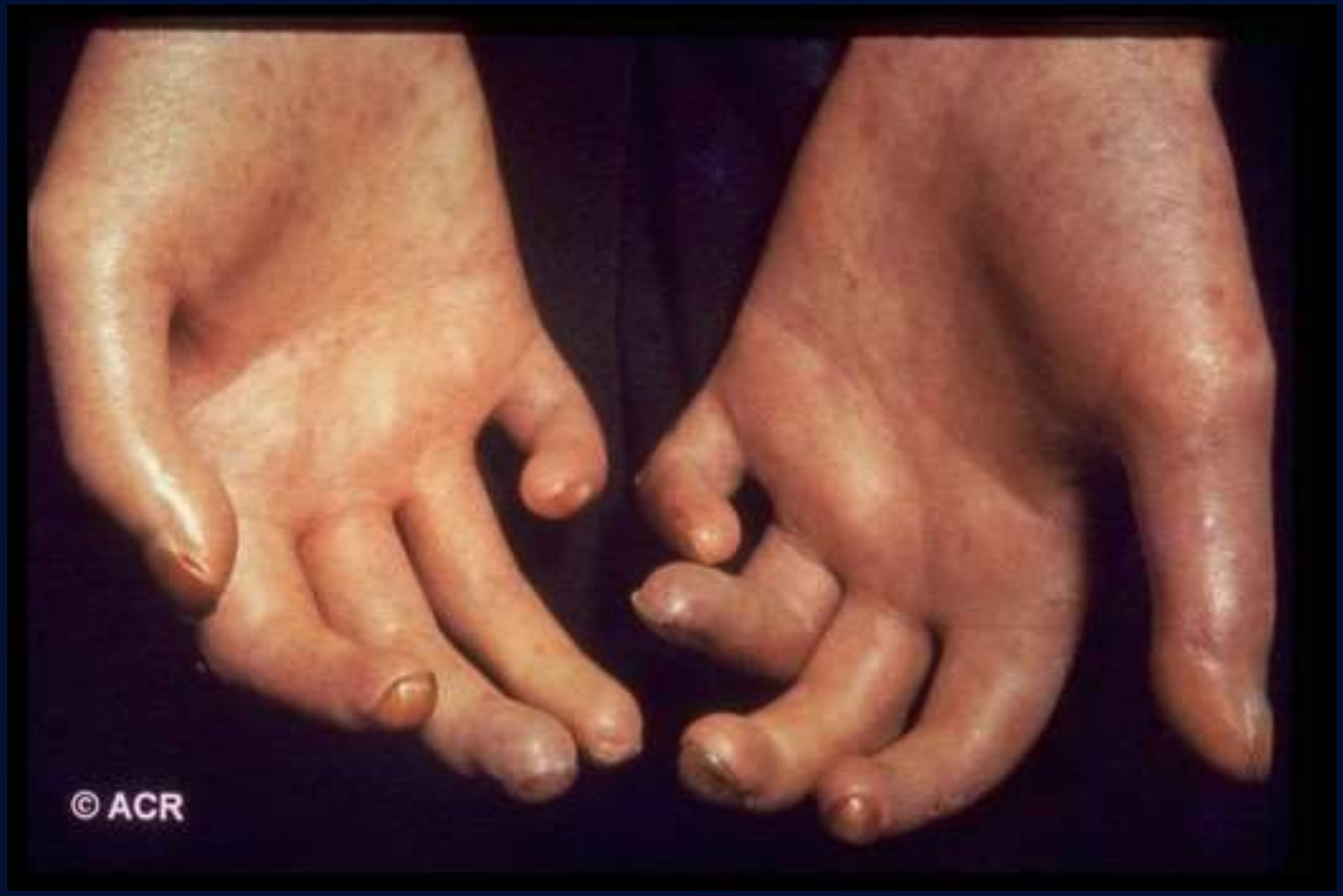
Clinical features

3. Musculoskeletal system

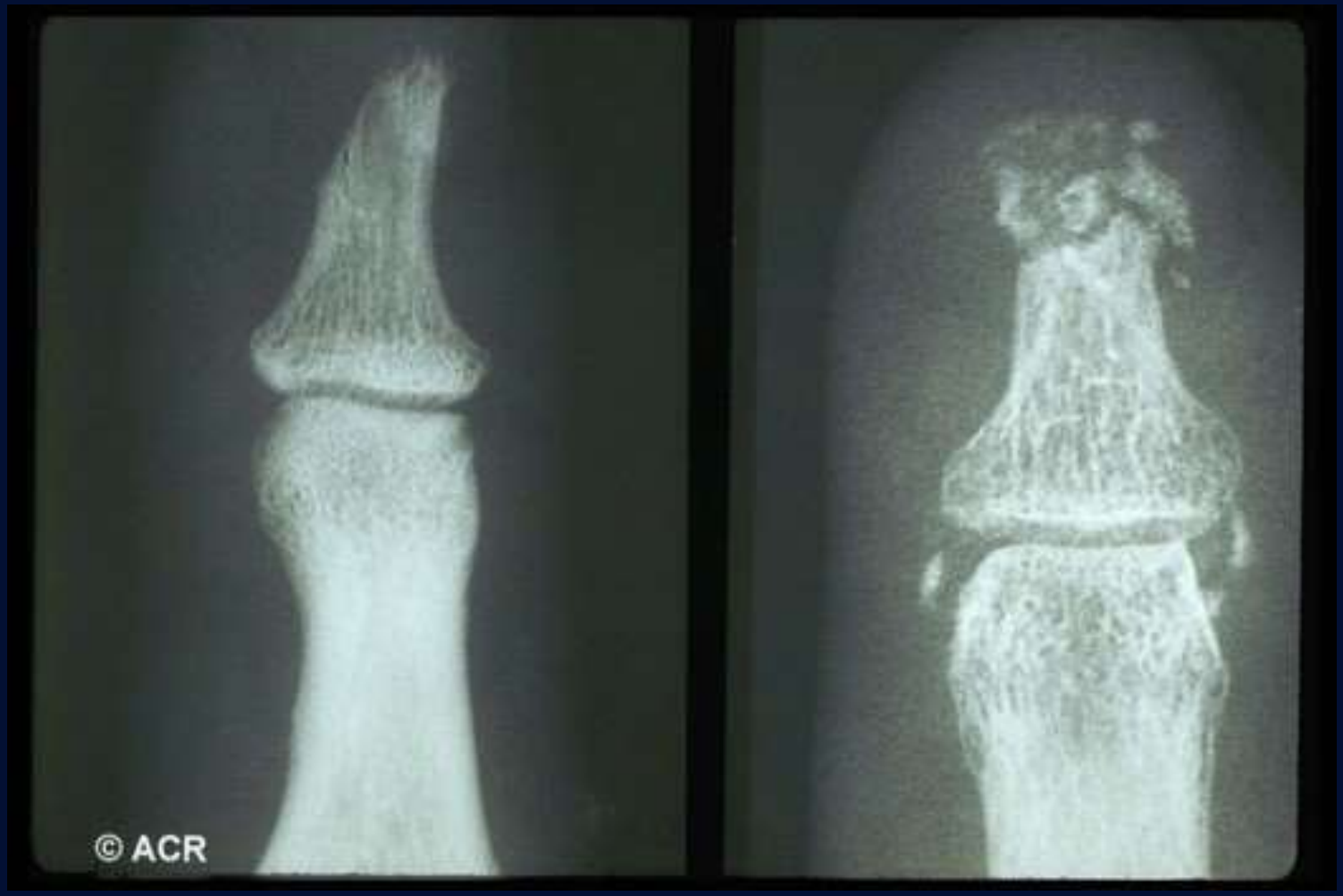
- Polyarthritis and flexion contracture (erosive
- arthropathy uncommon , joints pain due to skin changes

  Muscle weakness and atrophy results from myositis

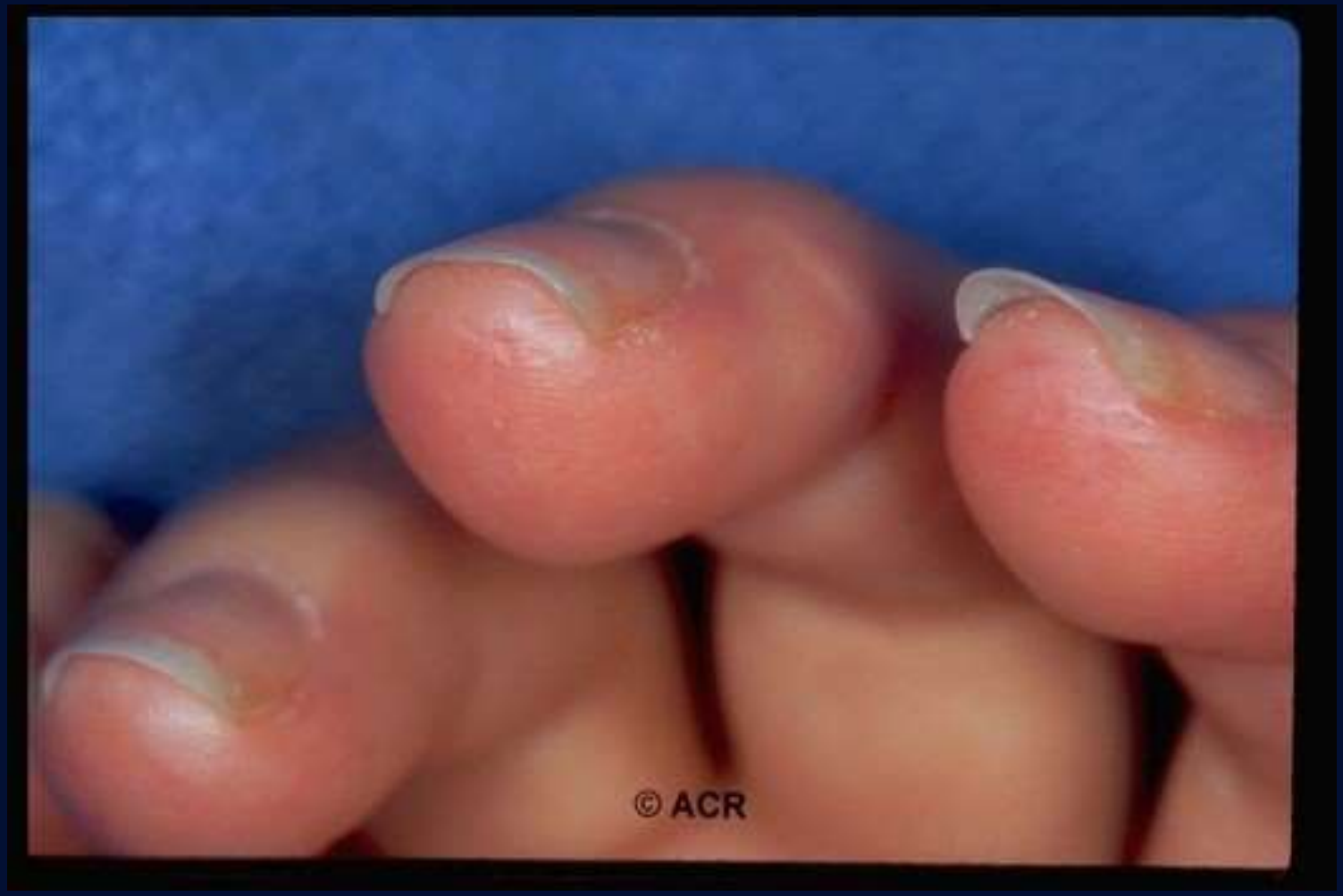
Terminal digit resorption



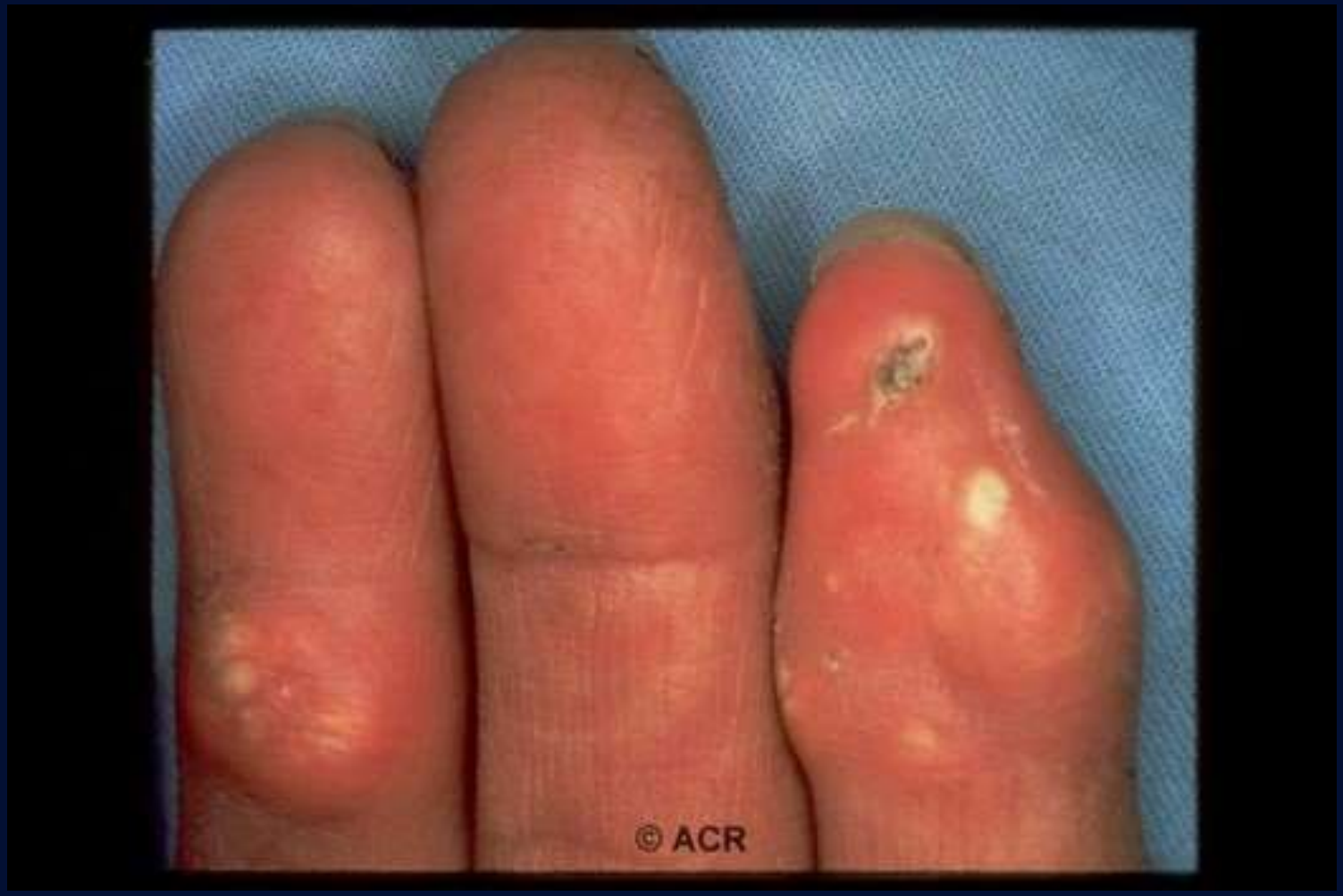
Acrolysis



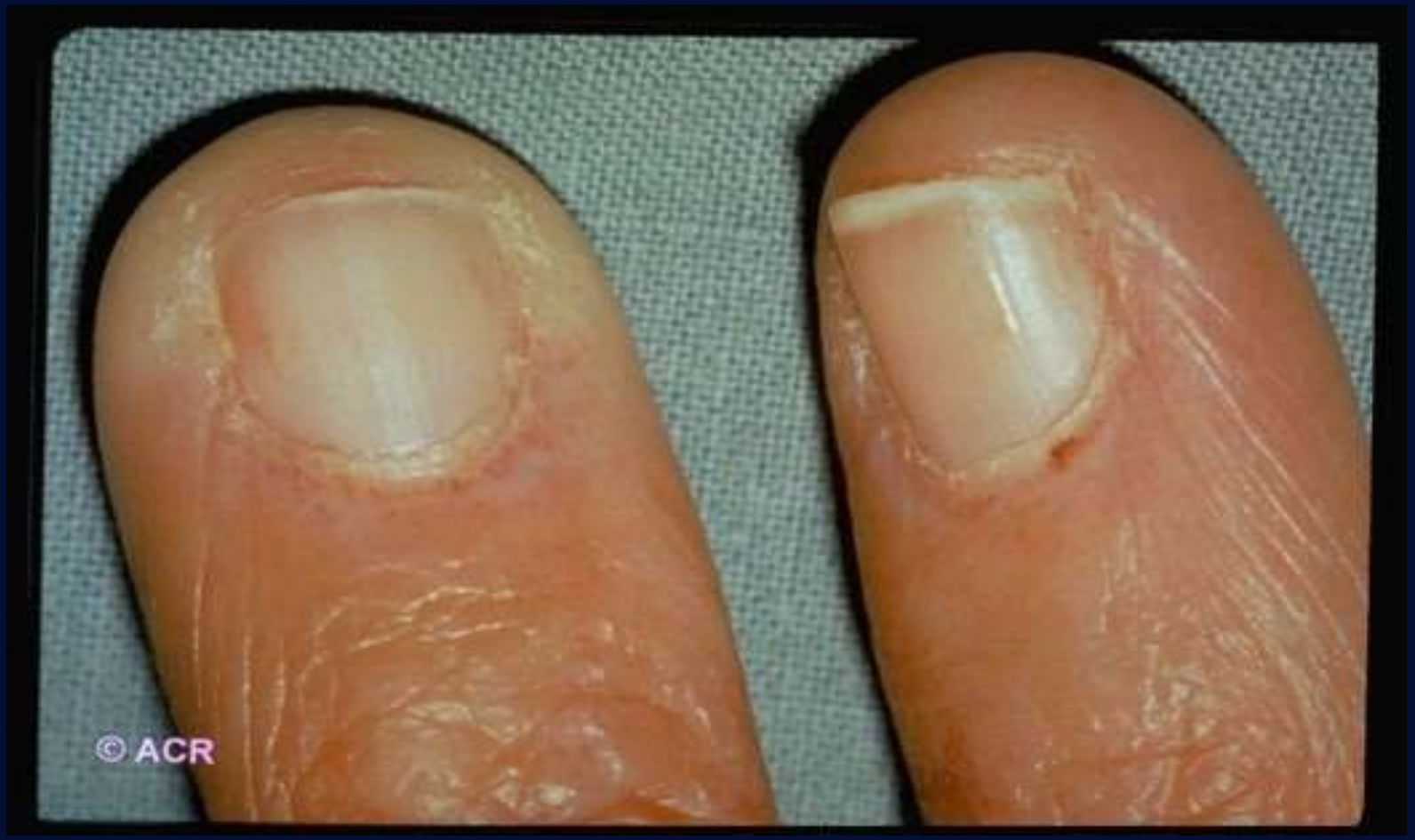
Digital pitting scars



CREST syndrome: calcinosis cutis



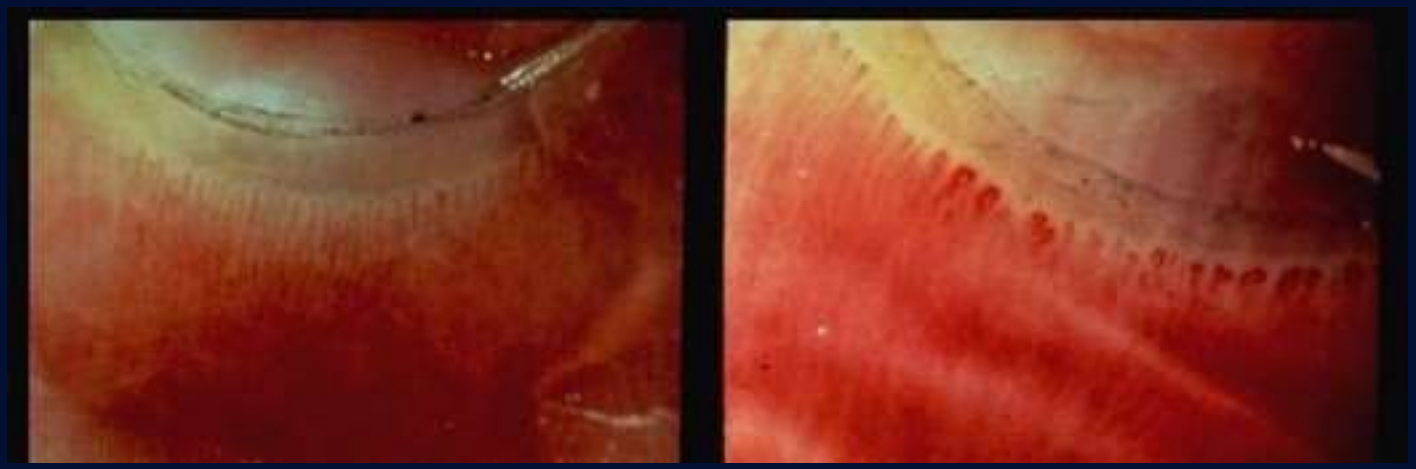
Nailfold capillary abnormalities



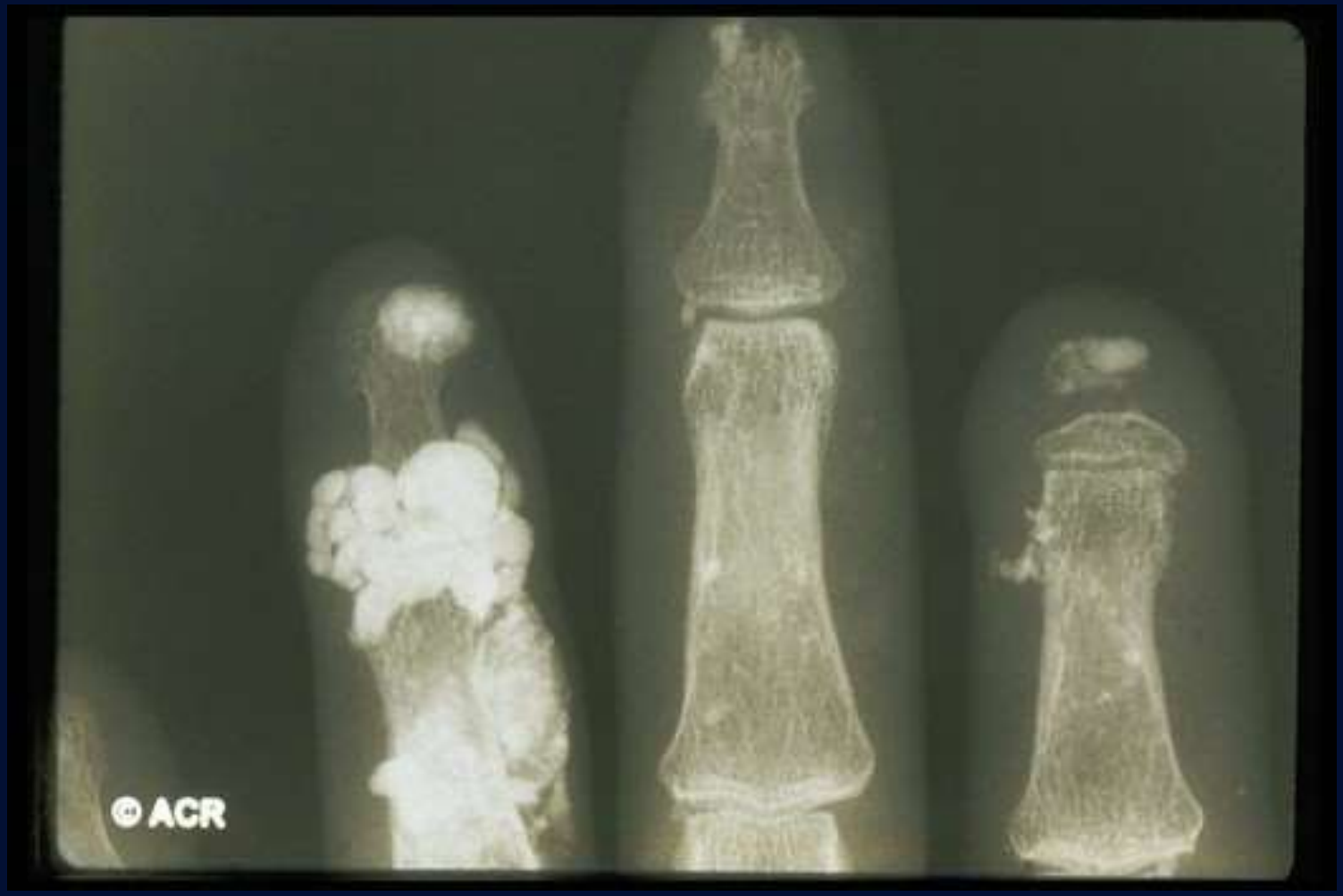
Nailfold capillary abnormalities

Normal

SSc



Calcinosis and acrolysis



Clinical features

4. intestinal involvement

1) esophagus: smooth muscle atrophy and fibrosis leads to heartburn , reflux and erosive esophagitis . Dysphagia /odynophagia may occur due type 2 achalasia (aperistalsis/low pressure LES) .

2) stomach: delayed emptying/ early satiety. Watermelon stomach (ectasia) may cause recurrent UGIB in 20% of the patients.

2) small intestine:Change in bowl pattern with loose frequent floating-foul smelling stool/ abdominal distention . pseudo-obstruction, paralytic ileus, malabsorption, weight loss, cachexia, bacterial overgrowth syndrome

4) large intestine: chronic constipation and fecal impaction / diverticula

Clinical features

5. lungs

1) 2/3 of patients affected

- leading cause of mortality and morbidity in later stage of systemic sclerosis

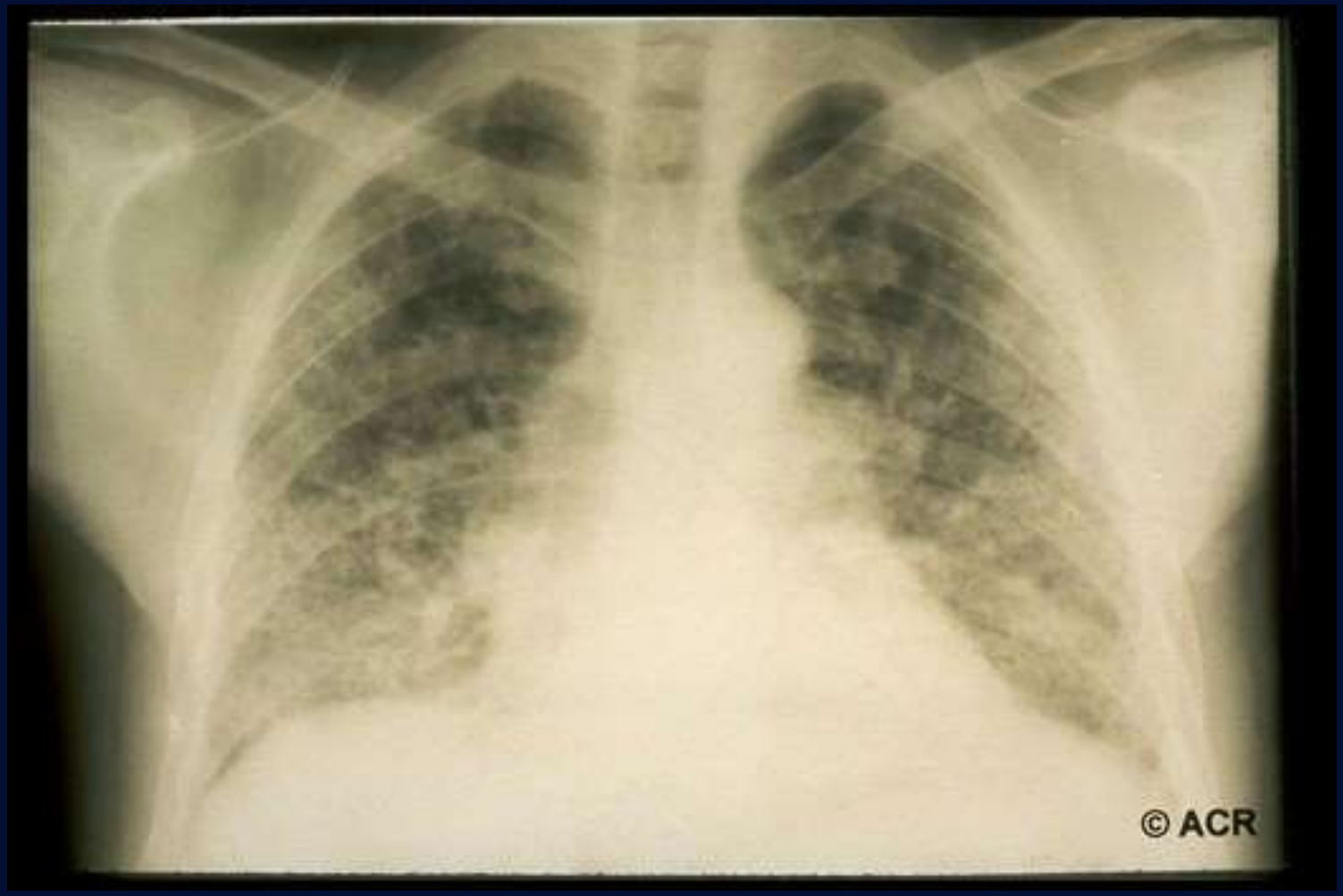
2) pathology

- interstitial fibrosis

-intimal thickening of pulmonary arterioles (pulmonary hypertension)

3) Complains - dry cough, breathlessness

Pulmonary fibrosis



Clinical features

6. heart (10%)

1) pericarditis

2) Diastolic heart failure

3) arrhythmia

4) myocardial fibrosis

Clinical features

7. kidney

1) More associated with diffuse scleroderma in association with rapid progression of skin involvement / Pattern of acute or sub acute HTN crises

2) pathology

- intimal hyperplasia of the interlobular artery
- fibrinoid necrosis of afferent arterioles
- glomerulosclerosis

3) HTN, proteinuria, abnormal sediment, azotemia, microangiopathic hemolytic anemia, renal failure

Clinical features

Exocrine glands

- Xerostomia
- xerophthalmia

Laboratory findings

1. ANA, RF
2. anti-Scl-70 (DNA topoisomerase I) antibody
    1) 20-40% in diffuse scleroderma
    2) 10-15% in limited scleroderma
3. anticentromere antibody: Highly positive with limited form (50-9-%)
4. Anti RNA plymerase:highly specific / risk of renal crises
5. Anti-PmScl- with myositis overlap syndromes
6. Anti fibrillin antibodies : common in africans americans /diffuse form

Other investigations:

1- US joints / MRI
2- Skin biopsy / US 20MHZ/ nailfold capilloroscopy
3-Endoscopy/ colonoscopy/rectal manometry
4-Esophageal scintography
5- chest x ray / CT chest/ PFT/ECHO
6- ECG/ cardiac MRI/ Rt sided cath
7- US kidneys/ urine analysis
8- ESR/CRP

***** Once diagnosis established ECHO/ xr chest should be requested with annual screen if negative

Diagnosis (Old Criteria)

1. major criteria: proximal scleroderma

2. minor criteria:

1) sclerodactyly

2) digital pitting scar or

loss of substance from the finger pads

3) bibasilar pulmonary fibrosis

* one major or 2 or more minor criteria for diagnosis

ACR/EULAR Classification Criteria for Systemic Sclerosis (2013) (Score 9)

Items	Sub-item	Score
1) Proximal scleroderma		9
2) Skin thickening of fingers	puffy fingers	2
	whole finger	4
3) Finger tip lesions	digital tip ulcers	2
	pitting scars	3
4) Telangiectasia		2
5) Abnormal Nailfold capillaries		2
6) Pulmonary Hypertension &/or Interstitial Lung Disease		2
7) Raynaud's Phenomenon		3
8) Scleroderma related antibodies (centromere, Scl-70, RNA polmerase III)		3

Box 121.1 Spectrum of scleroderma and scleroderma-like syndromes

- Systemic sclerosis
- Localized scleroderma (morphoea)
- Eosinophilic fasciitis
- Sclerodermatous genodermatoses (e.g. progeria, acrogeria, Werner's disease)
- Acrodermatitis chronic atrophicans
- Eosinophilia-myalgia syndrome
- Scleredoema adultorum Buschke
- Scleredoema diabeticorum
- Scleromyxeodema
- Sclerodoema amyloidosis
- Nephrogenic systemic fibrosis
- Porphyria cutanea tarda
- Sclerodermatous chronic graft-vs-host disease
- Scleroderma-like lesions in malignancies (paraneoplastic scleroderma)
- Lichen sclerosus et atrophicans

Treatment

A wide spectrum of clinical manifestations and severity

Therefore ,treatment should depend on the system involved

Treatment

Raynaud's phenomenon and ischemia

1) avoid cold exposure

   layers of warm, loose-fitting clothing

2) quit smoking

3) vasodilator therapy

   - calcium channel blocker –nifedipine 10-20 mg TDS/ Amlodipine 10 mg/day
   - -Nitrates / topical GTN
   - -ARBS –losartan 25-50 mg / day
   - -SSRI Luoxetin 20 mg/ day

4) finger / toe necrosis

   - intravenous prostaglandin (PGE_1, PGI_2)/ 0.5-2 ng/kg/min over 6 h on 5 consecutive days
   - amputation

Skin cahnges

-Lymphatic drainage / physiotherapy / phototherapy

--Topical steroids or tacrolimus

-Systemic treatment :
1- short course steroid (not long due to risk of renal crises)
2-Methotrexate
3- Cyclosporin

-Laser therapy for telengectasia or calcinosis cutis
-Local steroid injection / surgery could be used for calcinosis cutis.

Treatment

Gastrointestinal

1) reflux esophagitis and dysphagia
   - elevation of head of bed
   - small frequent meal
   - avoid lying down within 3-4 hours of eating
   - abstaining from caffeine-containing beverages, cigarette smoking
   - H2 blocker, proton-pump inhibitor
2) gastroparesis: promotility agent (metoclopramide)/ domepridone
3) malabsorption syndrome: broad spectrum antibiotics

Treatment

Pulmonary

1) Interstitial fibrosis

- corticosteroid
- cyclophosphamide, azathioprine , mycophenolate

2) pulmonary artery hypertension

- sildenafil
-bosentan , ERA
- Epoprostenol , Prostaglandin analouge

Treatment

Renal

1) renal crisis

- early detection and ACE inhibitor

1 year survival without captopril	15%
1 year survival with captopril	76%

- dialysis

Overlape syndromes

- Features of systemic sclerosis together with those of at least one other autoimmune rheumatic disease, e.g. SLE, RA, or polymyositis
- Scleroderma overlap with rheumatoid arthritis suggest distinct features of diffuse scleroderma with positive Scl-70, pulmonary fibrosis, and later seropositive erosive rheumatoid arthritis.

- **Raynaud's phenomenon is often the first clinical feature of SSc overlaps and must be distinguished from primary cold Raynaud's (i.e., cold-induced vasospasm).**
- **The finding of thickened and dilated capillaries on nail-fold microscopy and pathologic autoantibodies (e.g., Scl-70, anticentromere, PM/Scl, U1-RNP) are important clues about the development of an overlap syndrome.**

- In many cases, these overlaps occur in patients who do not have prominent skin involvement (sine scleroderma) or with the limited form of the disease—CREST.

- The limited form of scleroderma has well documented overlap with primary biliary cirrhosis often referred as Reynold’s syndrome.

Prognosis

1. quite variable and difficult to predict
2. cumulative survival

	diffuse	limited
5 yr	70%	90%
10 yr	50%	70%

3. major cause of death
   1) renal involvement
   2) cardiac involvement
   3) pulmonary involvement

Thank you