Sarcoidosis

Goals

- Gain familiarity with the definition and epidemiology of sarcoidosis
- Review the proposed pathogenesis of sarcoidosis
- Recognize histologic findings of sarcoidosis
- Understand the cutaneous manifestations of sarcoidosis

Goals

- Understand systemic manifestations, clinical syndromes of sarcoidosis, and associated diseases
- Learn an approach to the diagnostic work-up of sarcoidosis
- Learn treatments of cutaneous disease and prognosis of cutaneous and systemic sarcoidosis

Definition

- Derived from Greek:
  - *sarco* = “flesh”
  - *eidos* = “like”
  - *osis* = “condition”

Definition

- A multisystem disorder of unknown etiology
- Often presents with bilateral hilar LAD, pulmonary infiltrates, ocular and skin lesions

Definition

- An inflammatory, Th1 response to an undefined antigen
- Recruitment of activated T-cells and macrophages results in the formation of non-caseating, epithelioid granulomas

Epidemiology

- Worldwide occurrence affecting all races, ages and both genders
- Bimodal peaks: ages 25-35 years and 45-65 years in women. Most cases under age 40.
- Slightly higher rate of disease in women

Epidemiology

- Accurate data difficult to collect due to lack of sensitive and specific diagnostic tests

- Estimated annual incidence rate in the US of 35.5/100,000 for African Americans and 10.9/100,000 for whites

Epidemiology

- Swedes, Danes, (?Irish) and US African Americans have the highest rates in the world

- Overall, African American women between the ages of 30-39 years have the highest annual incidence at 107/100,000

Pathogenesis

- Etiology unknown, but 4 proposed theories exist regarding pathogenesis:
  - Immunologic
  - Genetic
  - Infectious
  - Environmental

Immunologic Pathogenesis

- Th1 response to poorly degradable antigenic stimulus
- Increased INF-gamma & IL-2
- IL-2 acts as a local growth factor for T-lymphocytes

Immunologic Pathogenesis

- Oligoclonal pattern w/ over-expression of α- and β- variable chain regions of the TCR

- T-cell activation:

  B7:CD28/CTLA-4 costimulatory pathway

Immunologic Pathogenesis

- T-cells attract macrophages
- Sarcoid alveolar macrophages release TNF-α, IL-12, IL-15 and growth factors

Immunologic Pathogenesis

- Macrophages produce metalloelastase
- Elastin degradation = increased macrophage migration

Immunologic Pathogenesis

- Result is an exaggerated, antigen-driven immune response resulting in granuloma formation
- Accumulation of activated T-cells (CD_4) – especially in central granulomas

Immunologic Pathogenesis

- Non-specific polyclonal B-cell Ig production activated by local T-cells = hypergammaglobulinemia

- Shift to Th2 (IL-4, IL-5, IL-6, IL-9, and IL-10) in hyalanized granulomas may cause fibrosis (lungs)

Genetic Factors

- Race appears to be a risk factor
- Clustering of cases in families

Genetics

- Increased acute phase reactant genes: ORM1 & HP1

- Association w/ HLA-B27, Europe: A1, B8, DR3 (good outcome), B22, B13, B35 (latter two=early onset)

Infectious Pathogenesis

- No proof of an infectious etiologic agent
- Seasonal clustering in winter and early spring (?viral)

Infectious Pathogenesis

- 1987 case-control study of residents of the Isle of Man (GB) :
  - 40% of patients diagnosed w/ sarcoidosis reported contact w/ pt w/ disease

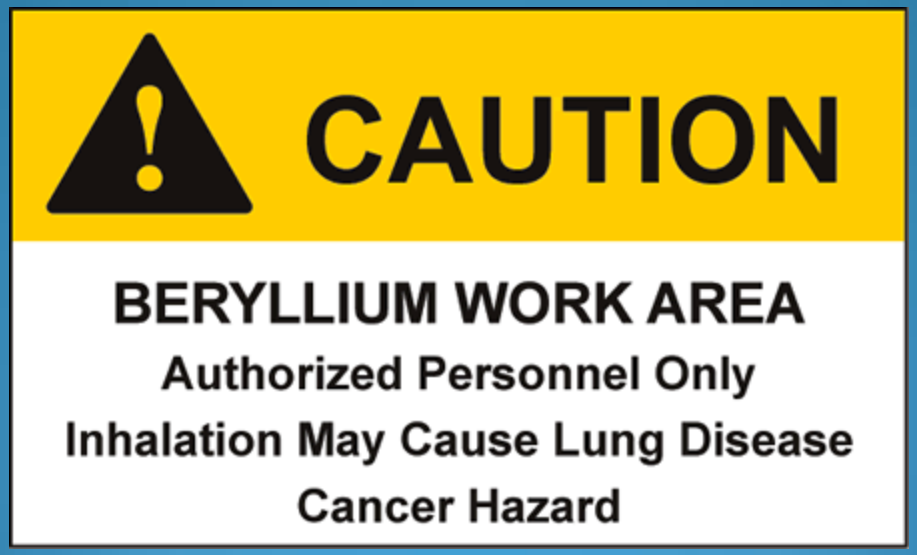
    vs.
  - 1-2 % of controls without sarcoidosis reported contact w/ pt. with disease

Infectious Pathogenesis

- PCR for detection of mycobacteria inconclusive
- Evidence against link to AFB: BCG vaccine, steroid use, anti-AFB tx failures

Environment

- 1940's: women in flourescent light industry in Salem, MA = "Salem Sarcoid" felt due to beryllium exp.

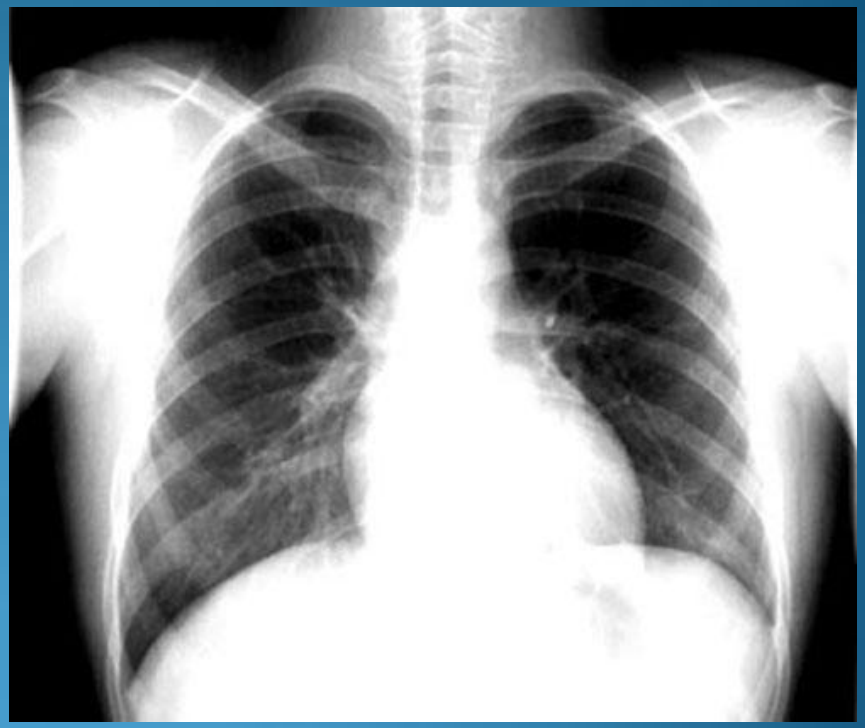


Environment

- Other inorganic antigen exposure possibly: clay, talc, pine pollen and oxalosis

Environment

- Isle of Man study: increased incidence in nurses (? increased CXR's = increased dx).



Environment

- 3/57 firefighters who apprenticed together dx'd w/ sarcoidosis

Environment

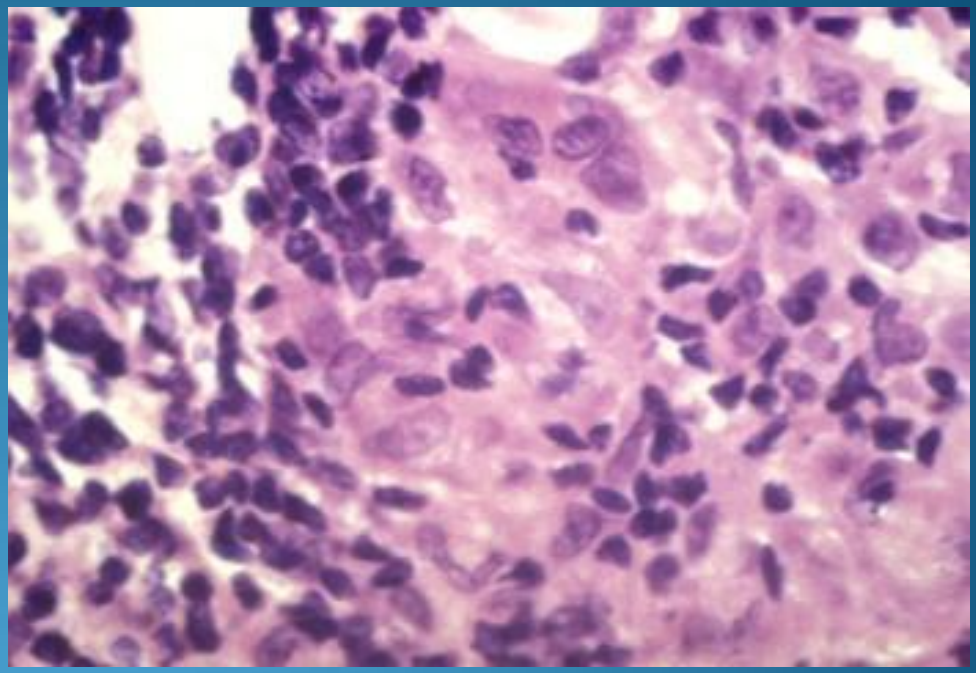
- Increased in US Navy personnel with aircraft carrier exposure (? CXR's).

Environment

- More common in nonsmokers
- Clustering of cases in spring months

Histology of Sarcoidosis

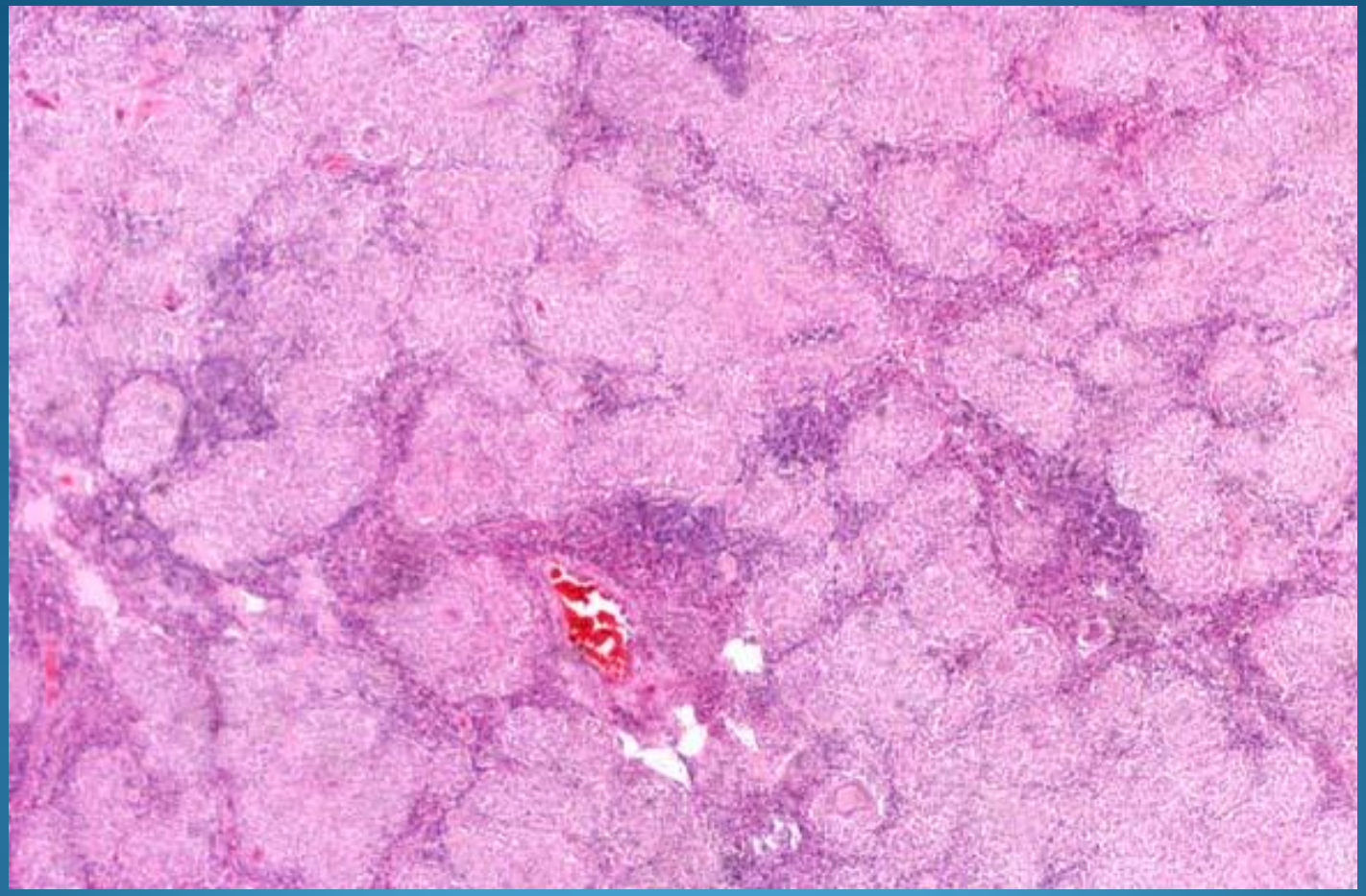
- Well-demarcated islands of epithelioid cells with occasional giant cell formation and no necrosis.

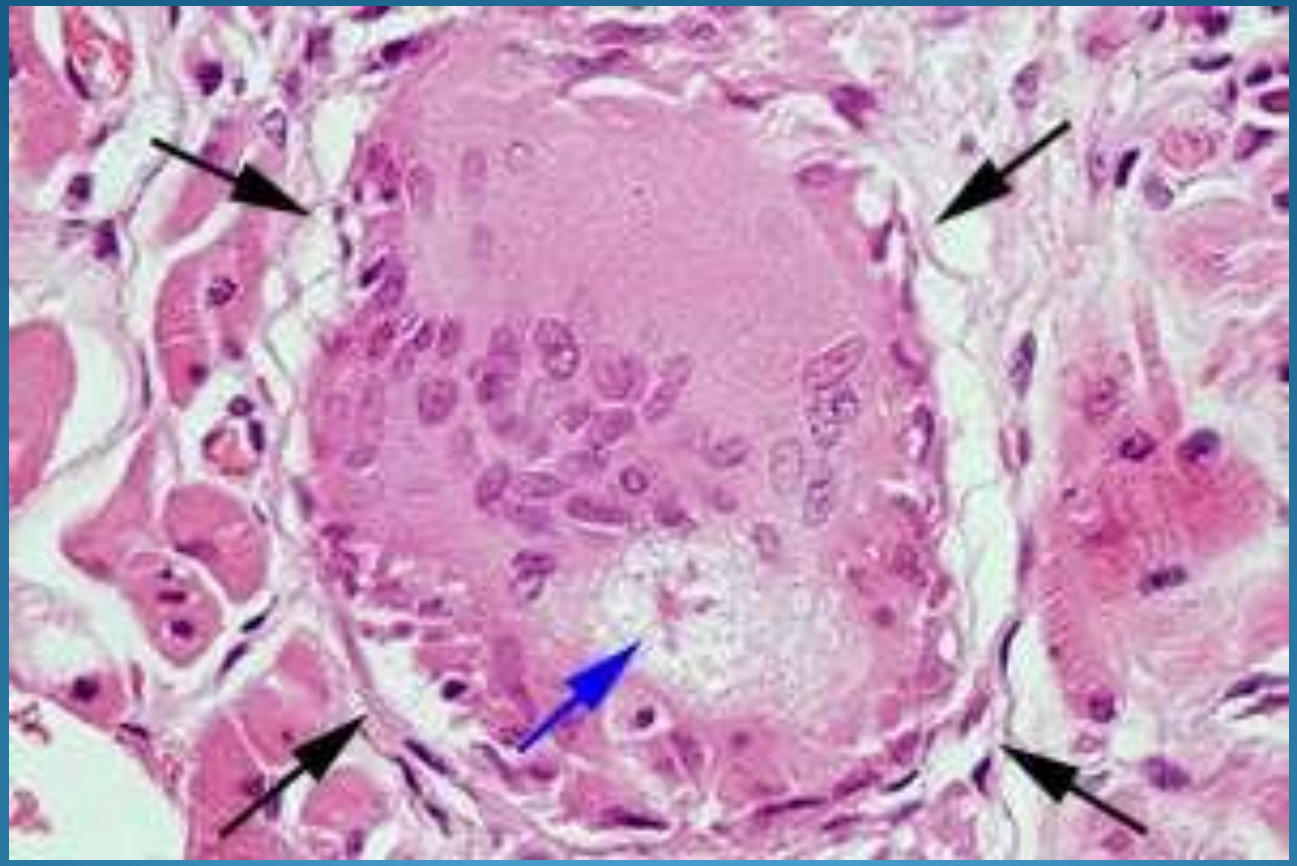


Histology

- Sparse, lymphocytic infiltrate around non-caseating epithelioid granulomas in the dermis ("naked" granulomas)

- Asteroid bodies and Schaumann (conchoidal) bodies may be seen in MNGC's but are non-specific (can be seen in TB)





Asteroid body

Cutaneous Manifestations

- >25 % of sarcoidosis cases involve the skin – lesions often multiple & symmetric
- No prognostic significance (except EN = good)
- Possible increased incidence of HSM & LAD with skin lesions

Cutaneous Manifestations: Specific (contain granulomas)

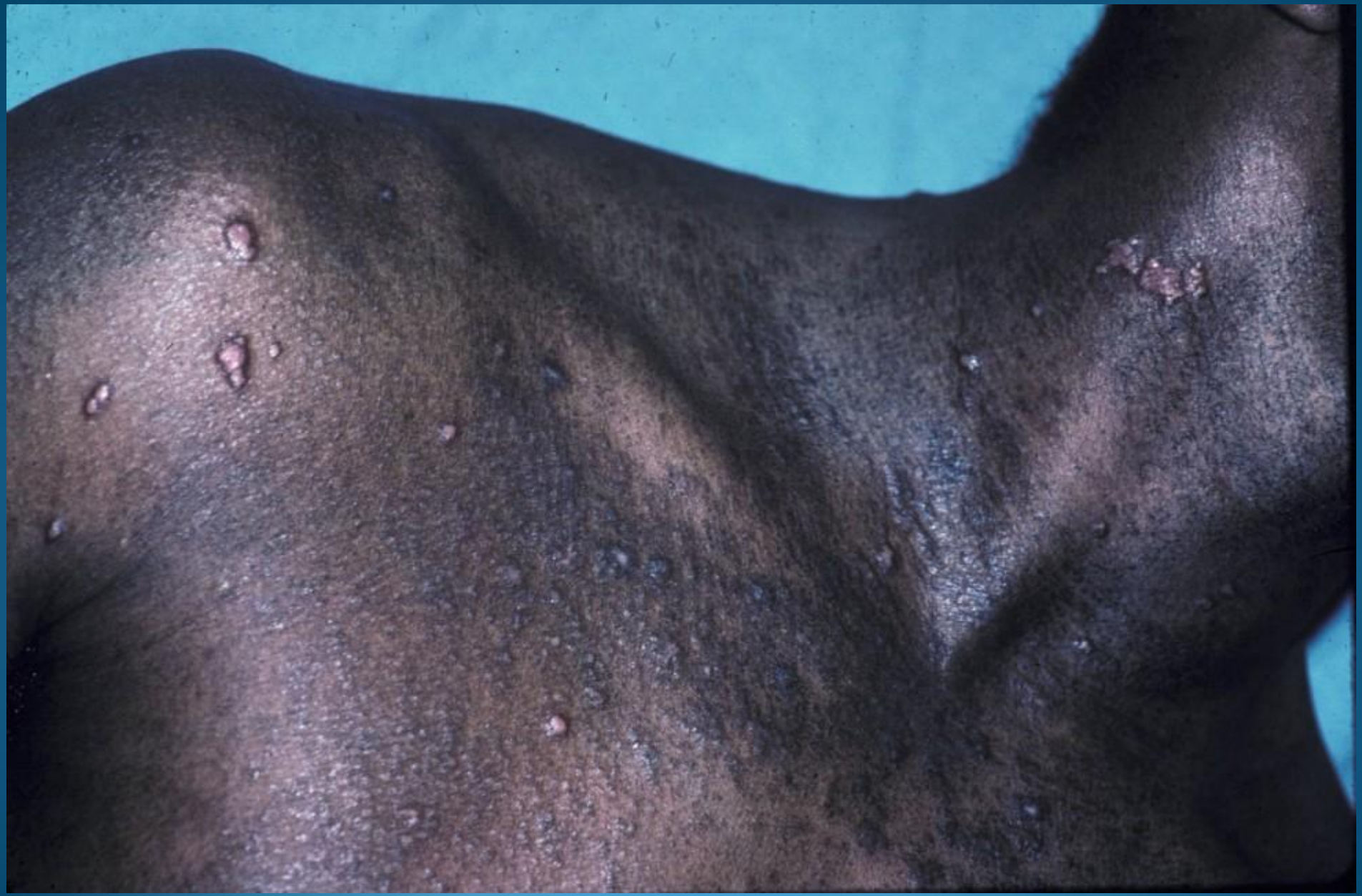
Lesions often asymptomatic and include:

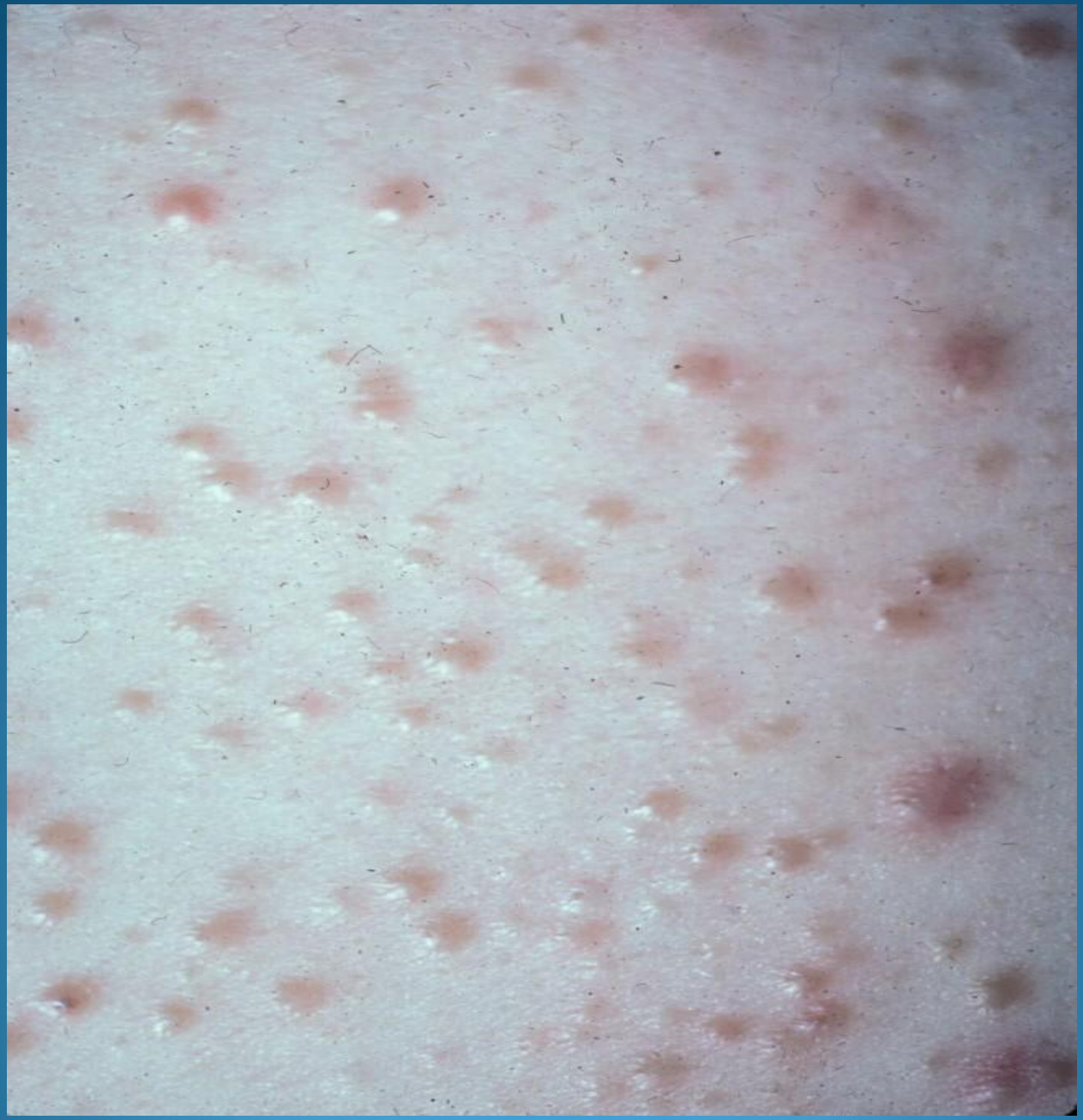
- papules, nodules, plaques
- subcutaneous nodules
- infiltrative scars
- acquired ichthyosis
- lupus pernio *(NB: rule out lung disease/ upper respiratory tract involvement / uveitis/ bone cysts)*

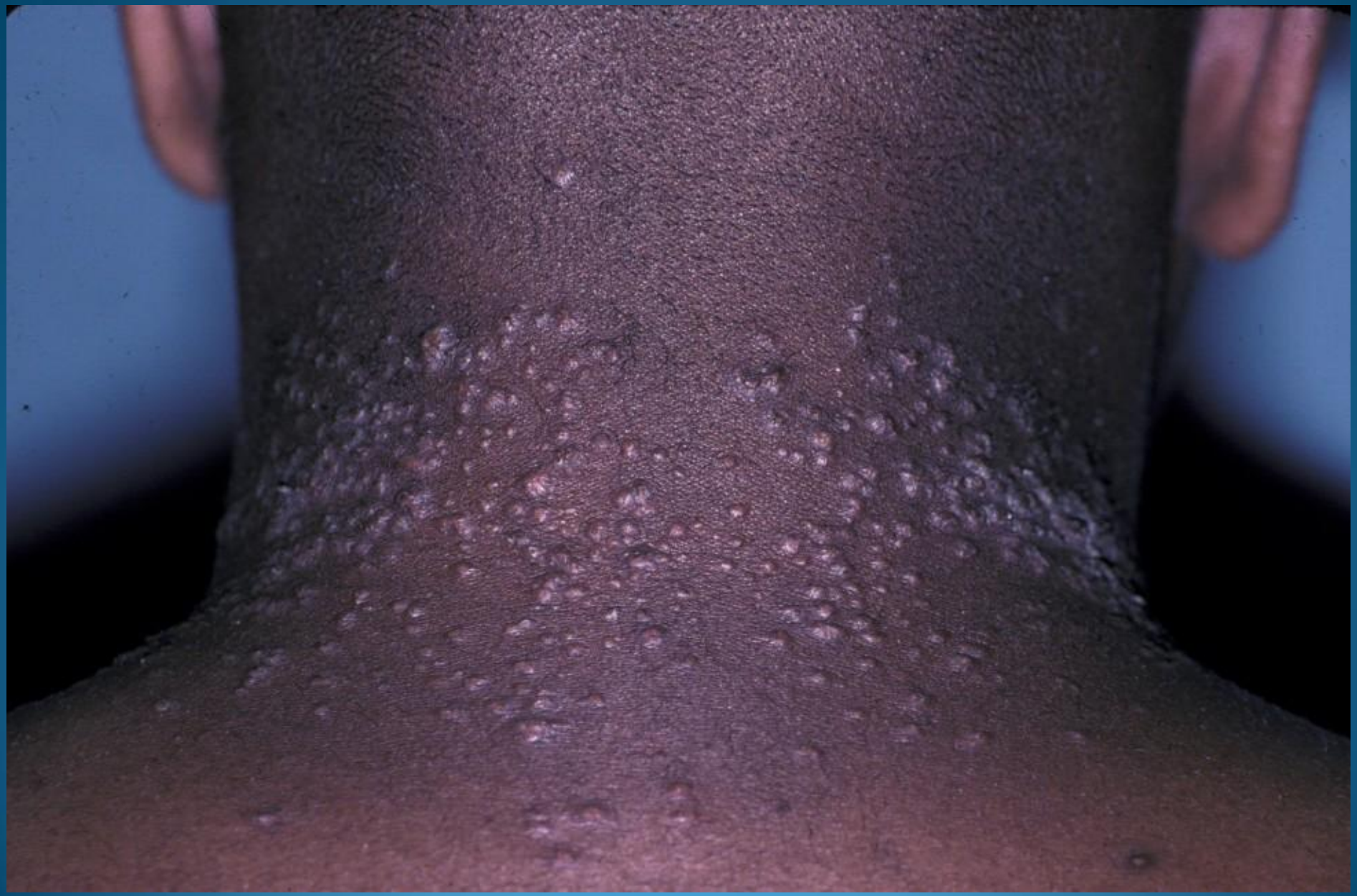
Cutaneous Manifestations

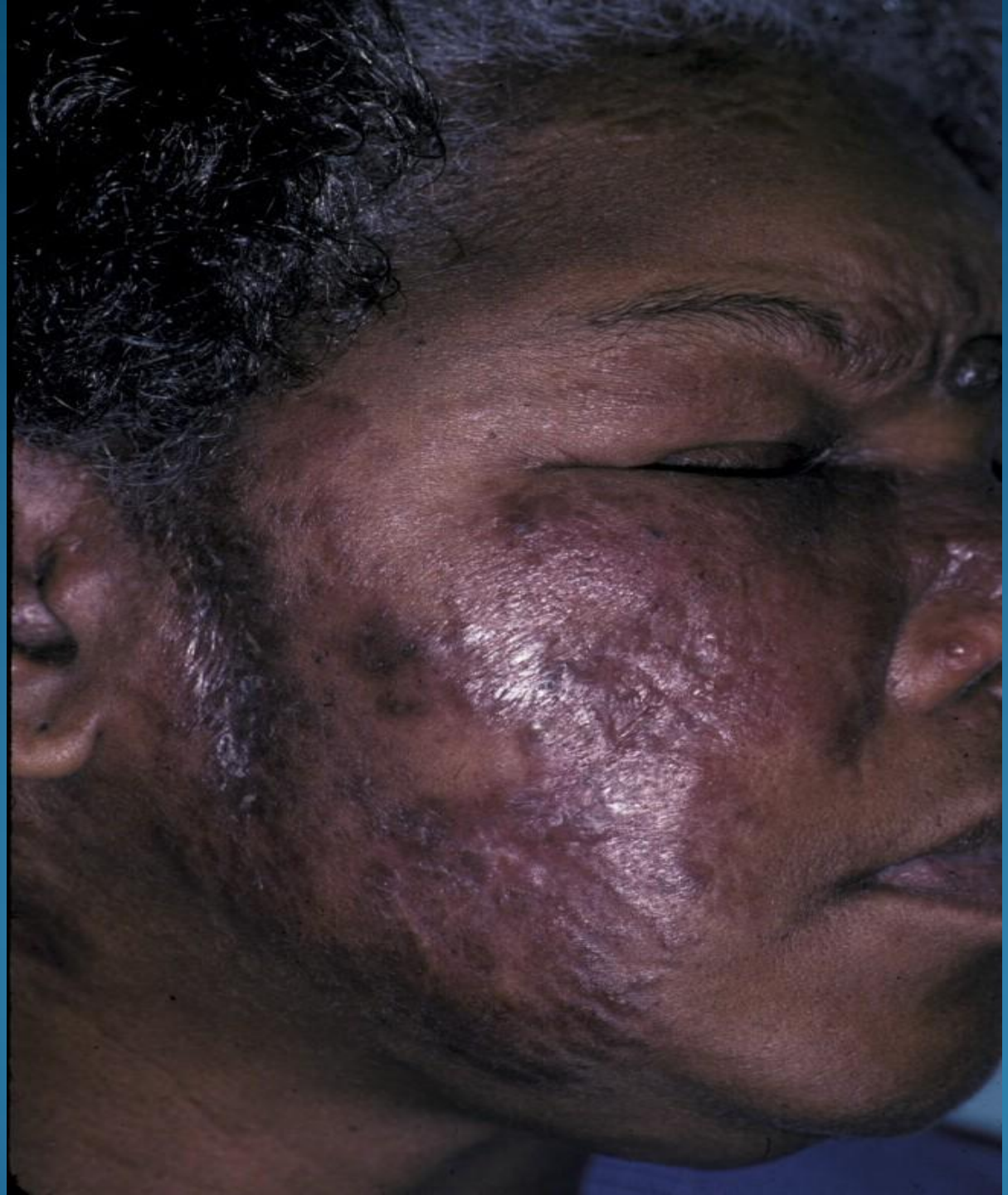
- Lesions (continued):
  - alopecia
  - psoriasiform
  - verrucous lesions
  - ulcerations
  - hypopigmentation
  - atypical presentations (eg lichenoid, folliculitis, penile, vulvar, palmar erythema, annular elastolytic, erythrodermic…)

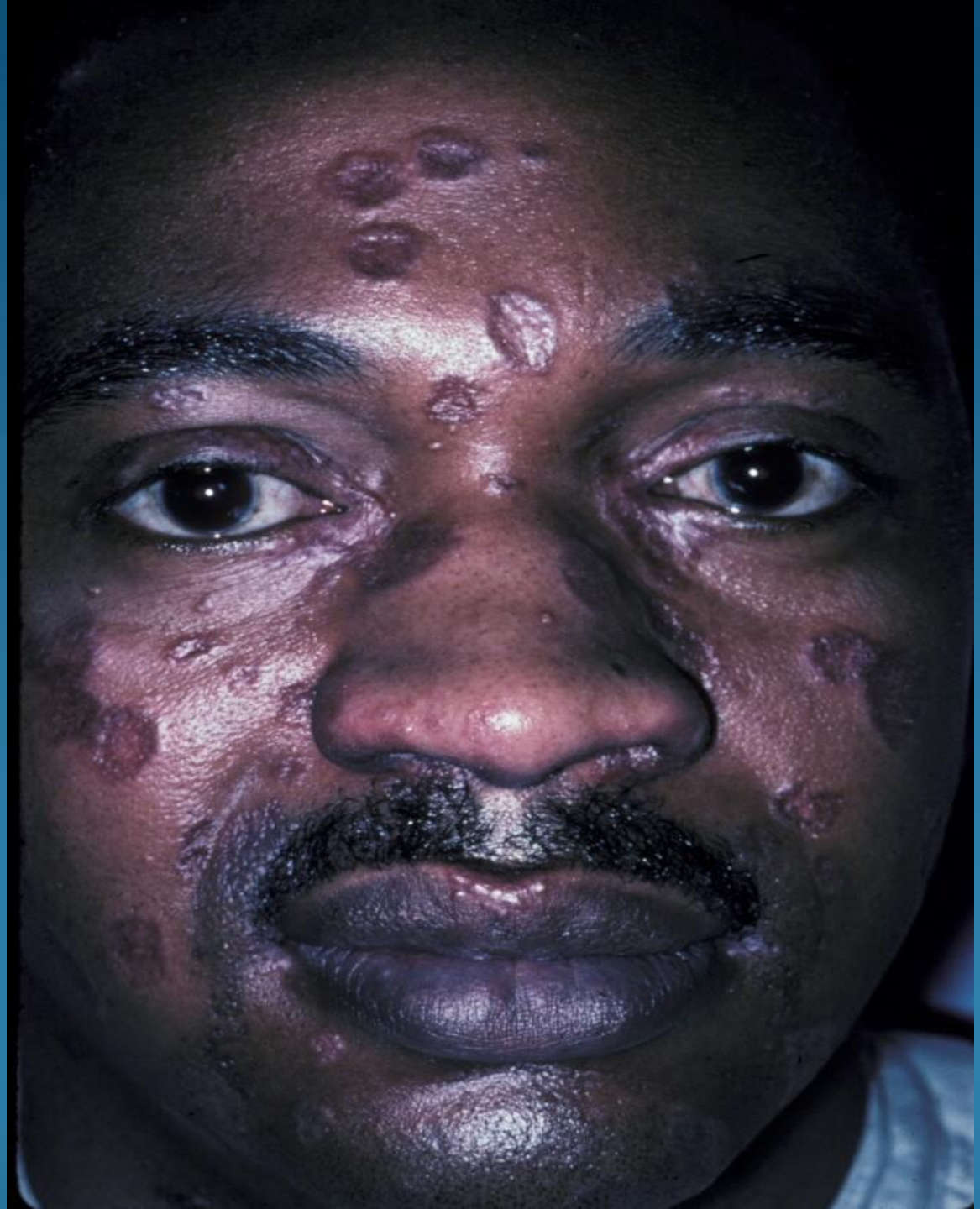
Diascopy = "apple-jelly" color

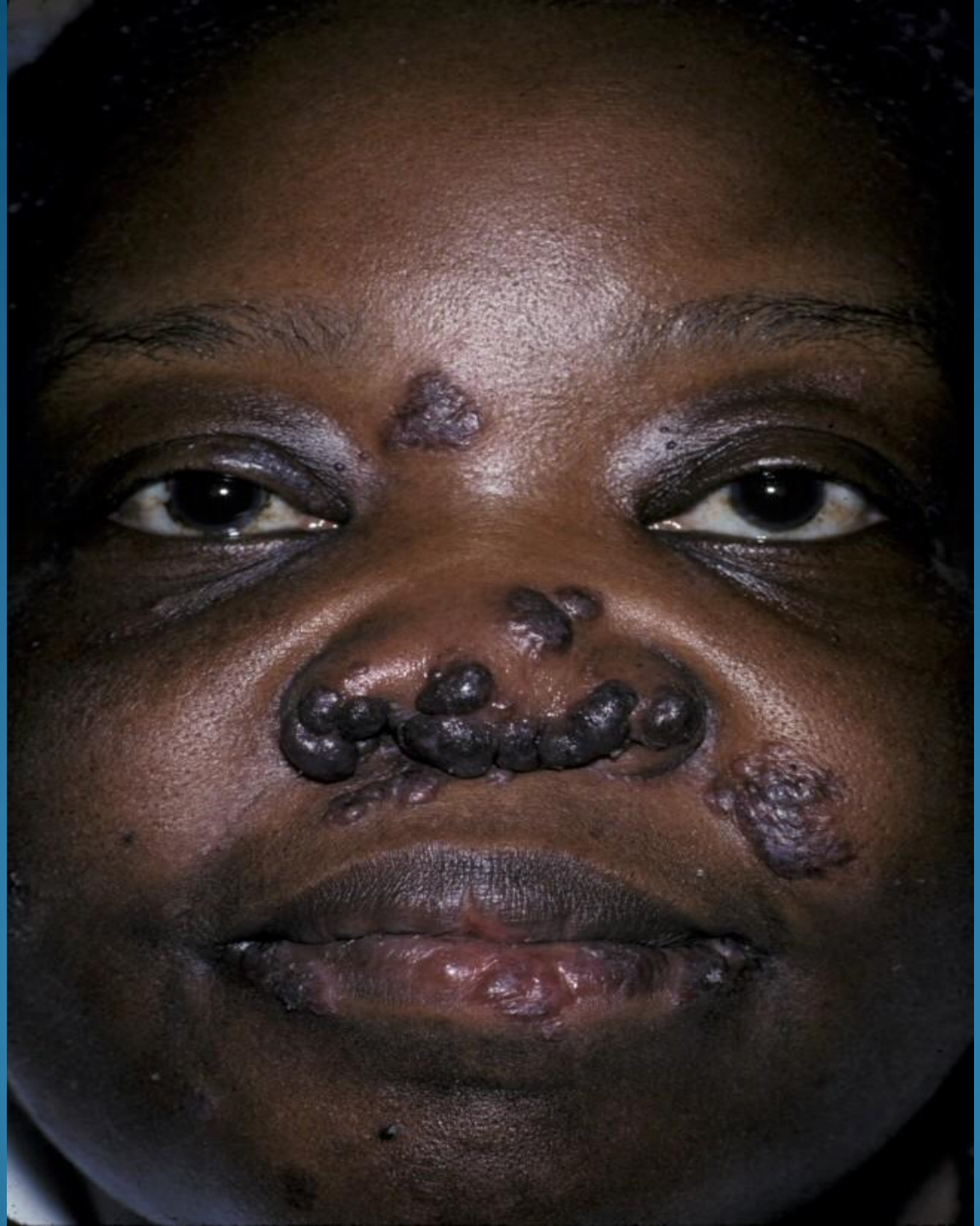


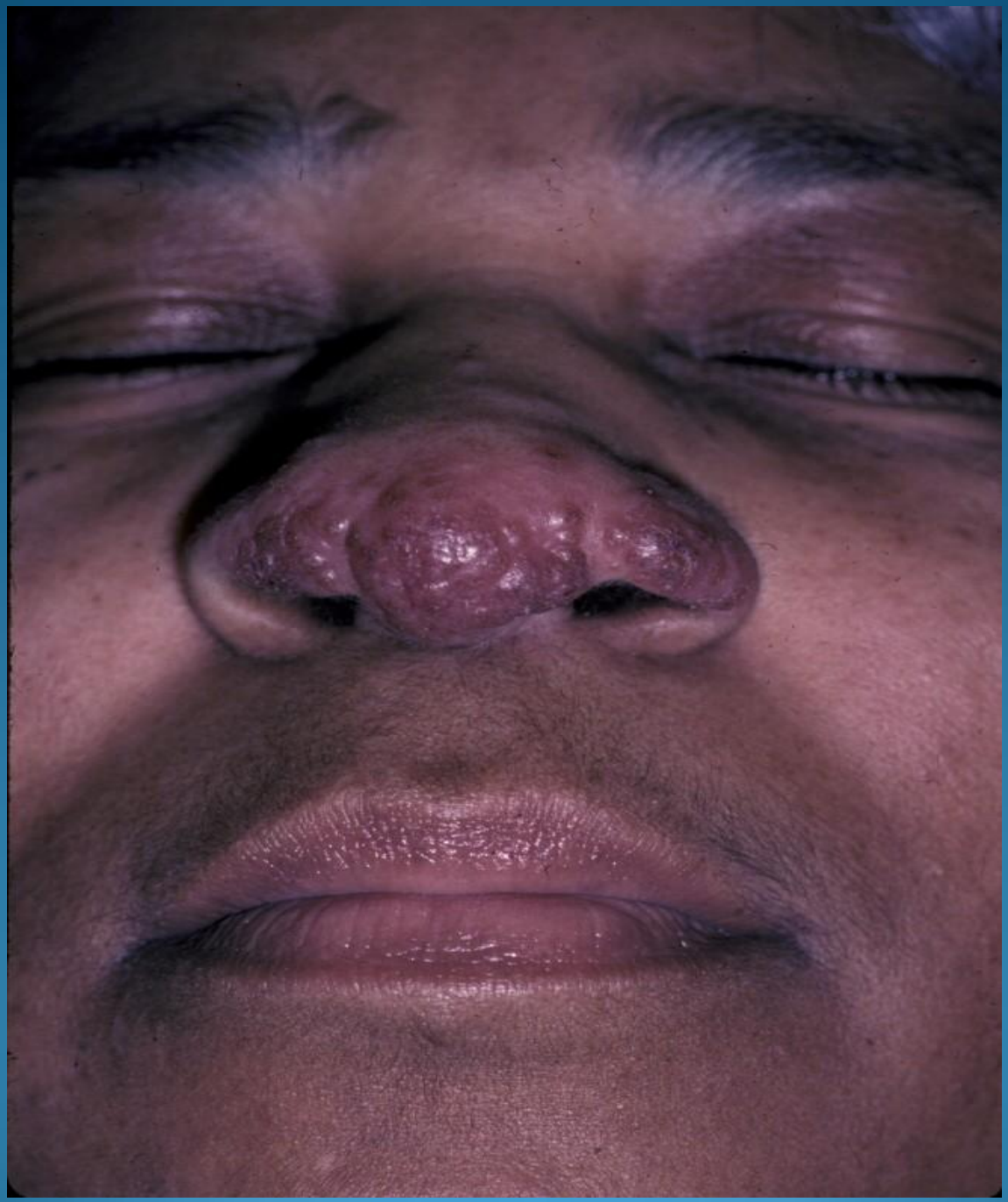


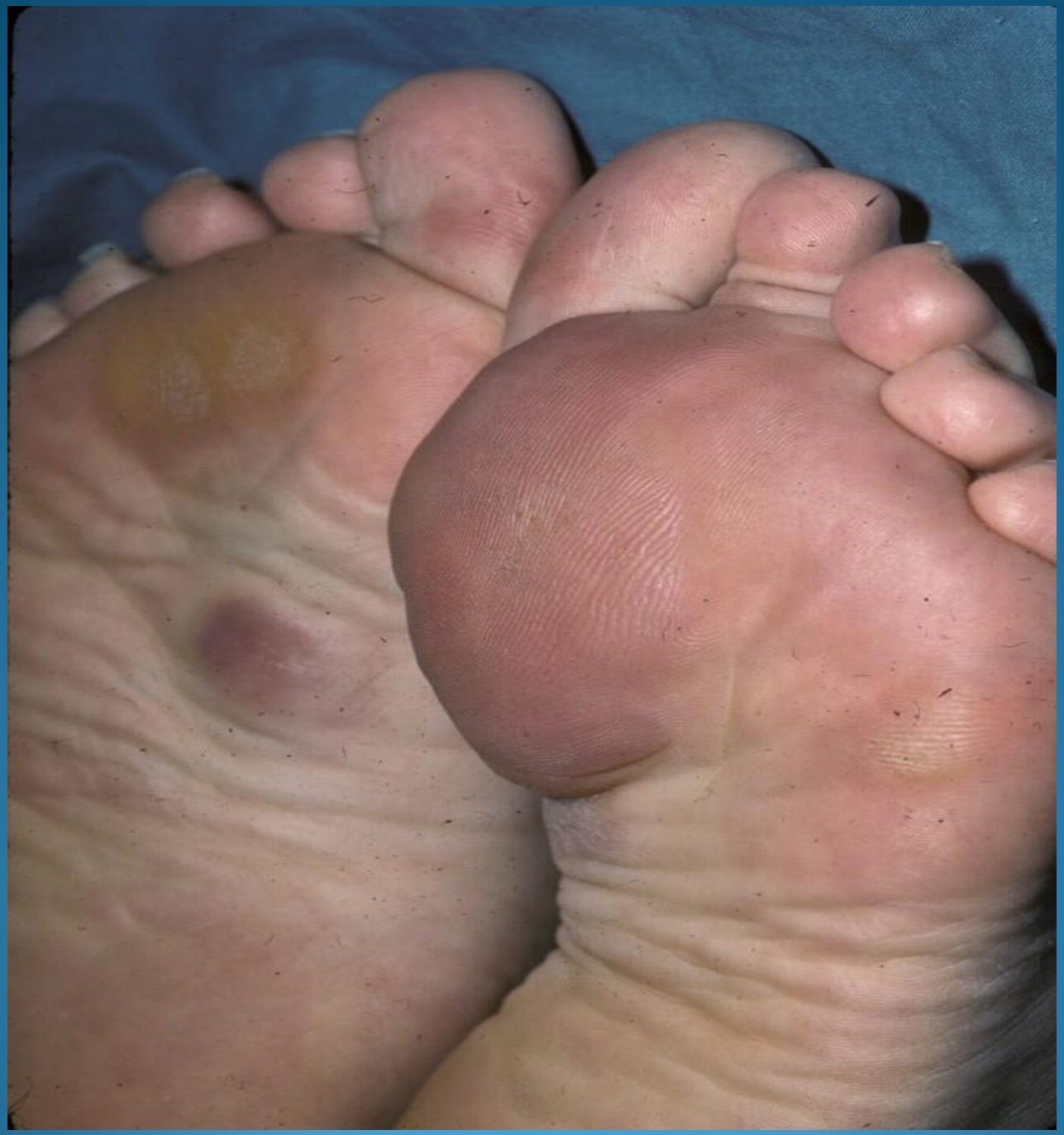


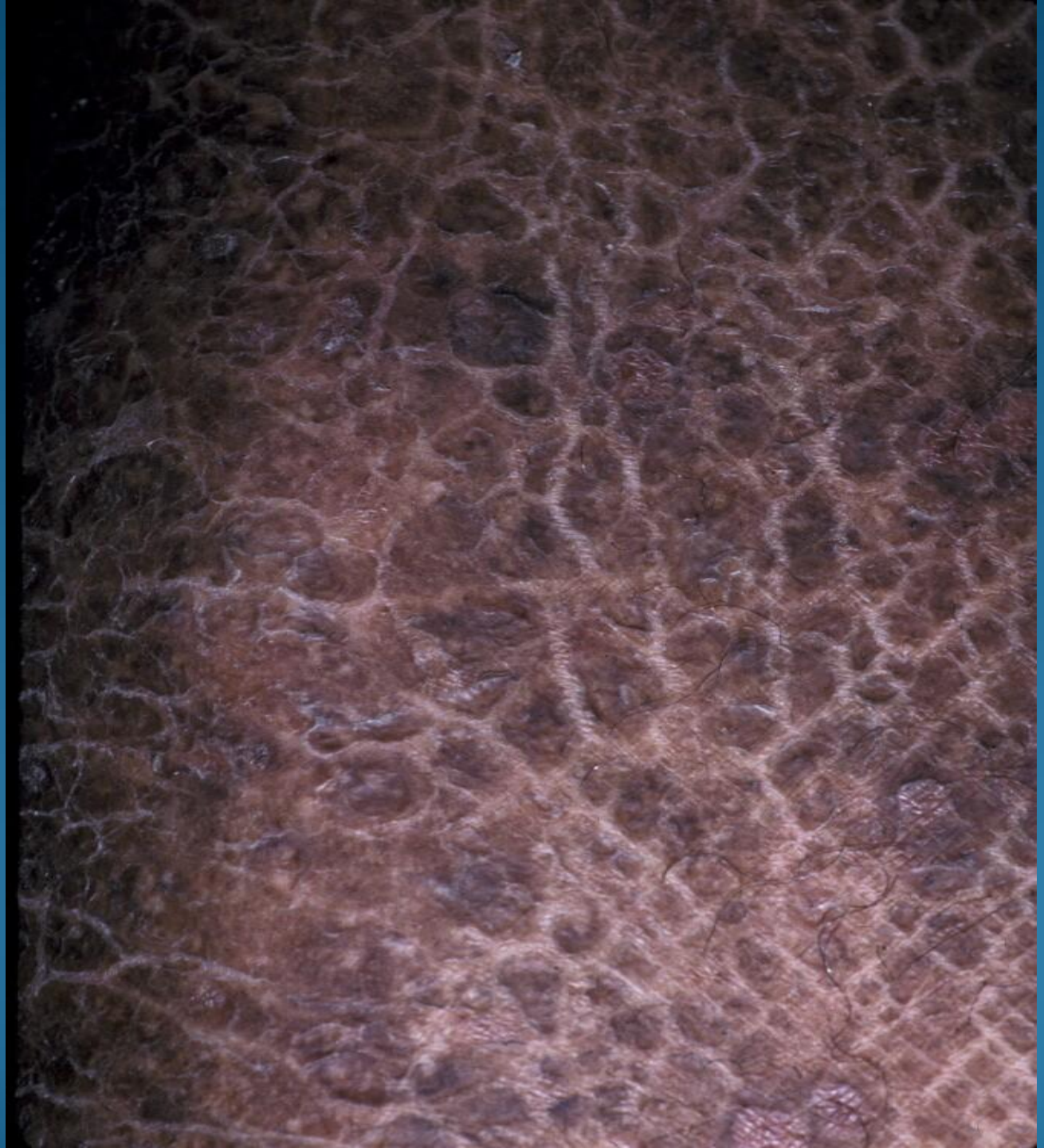


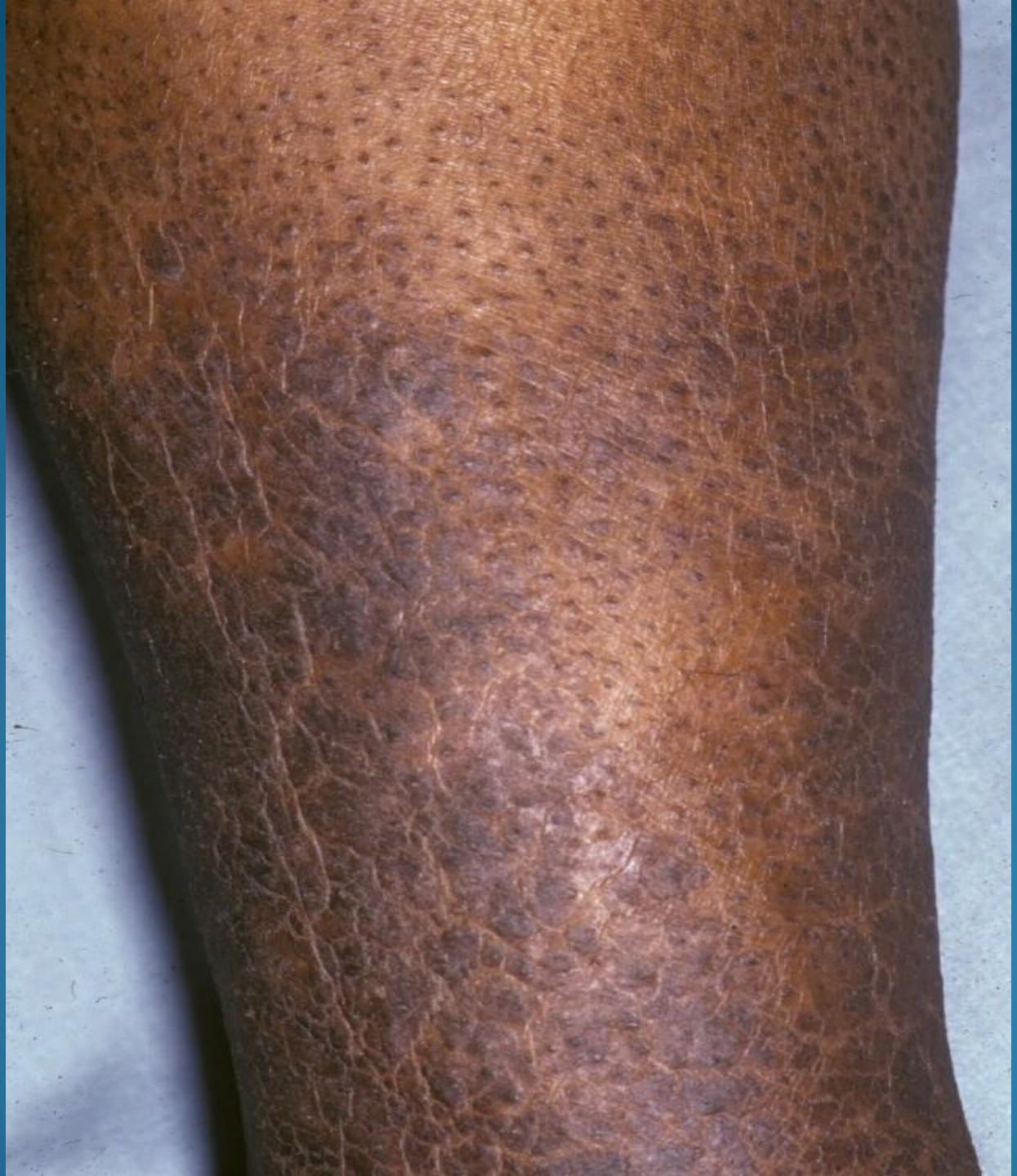


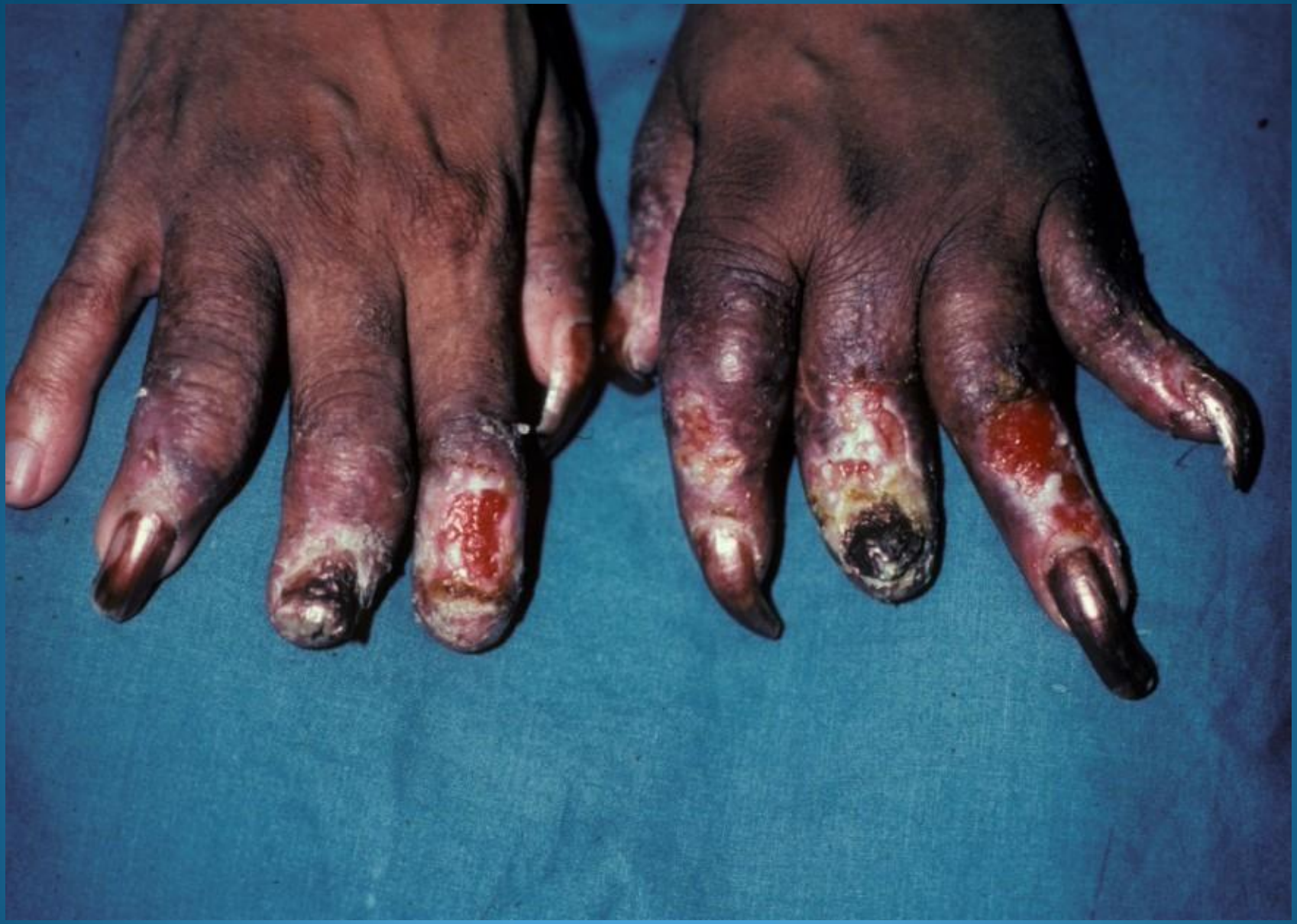


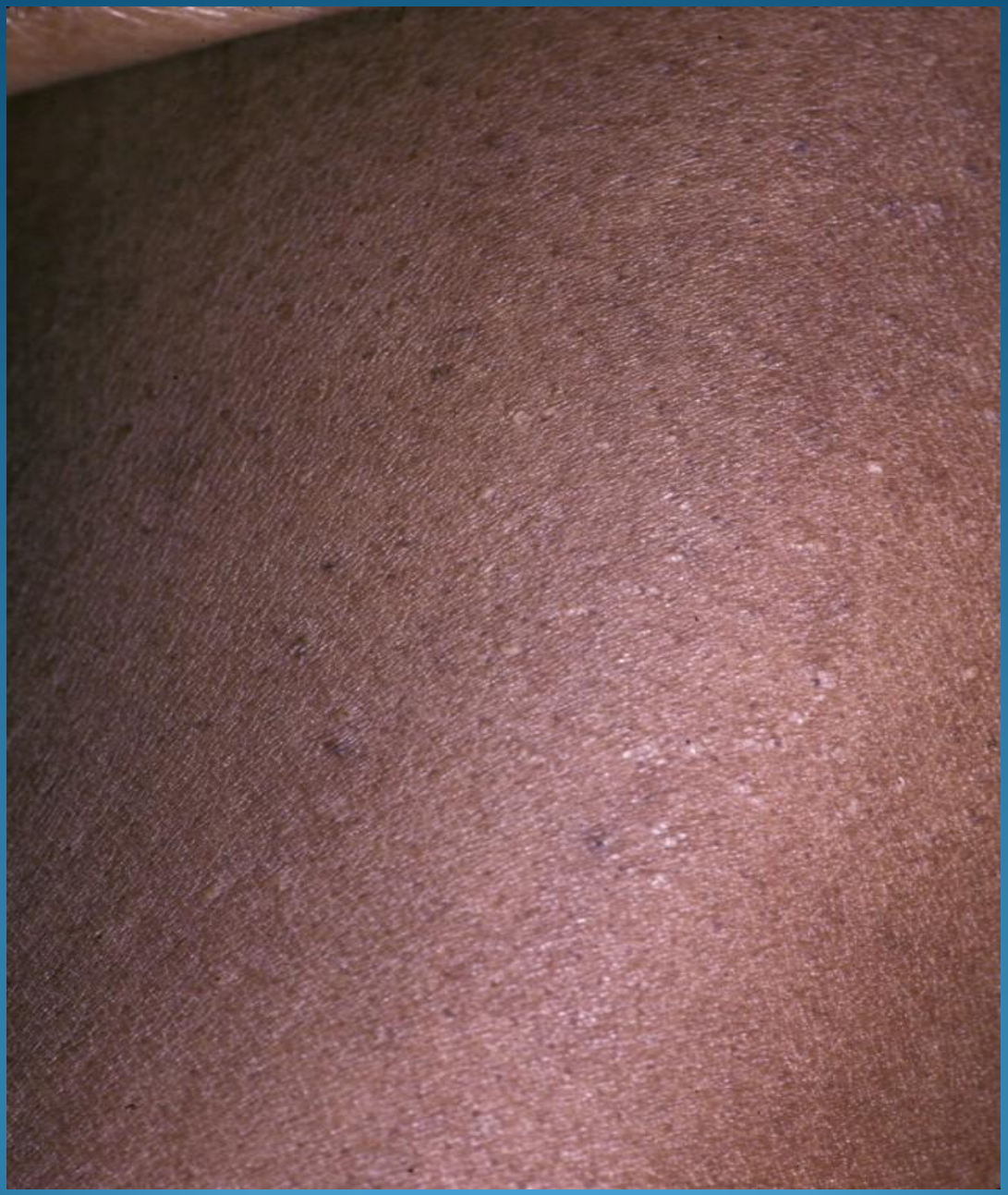


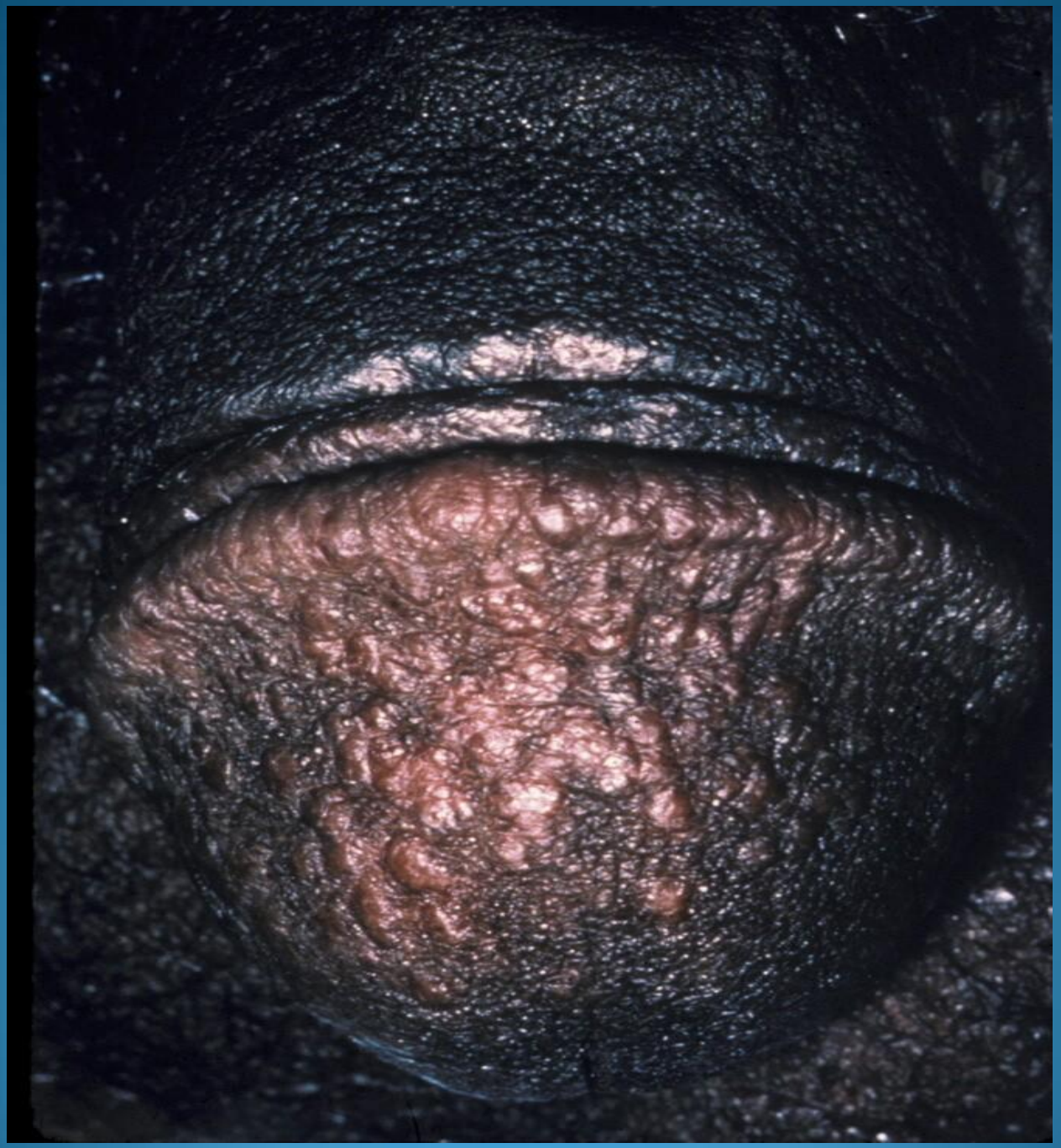








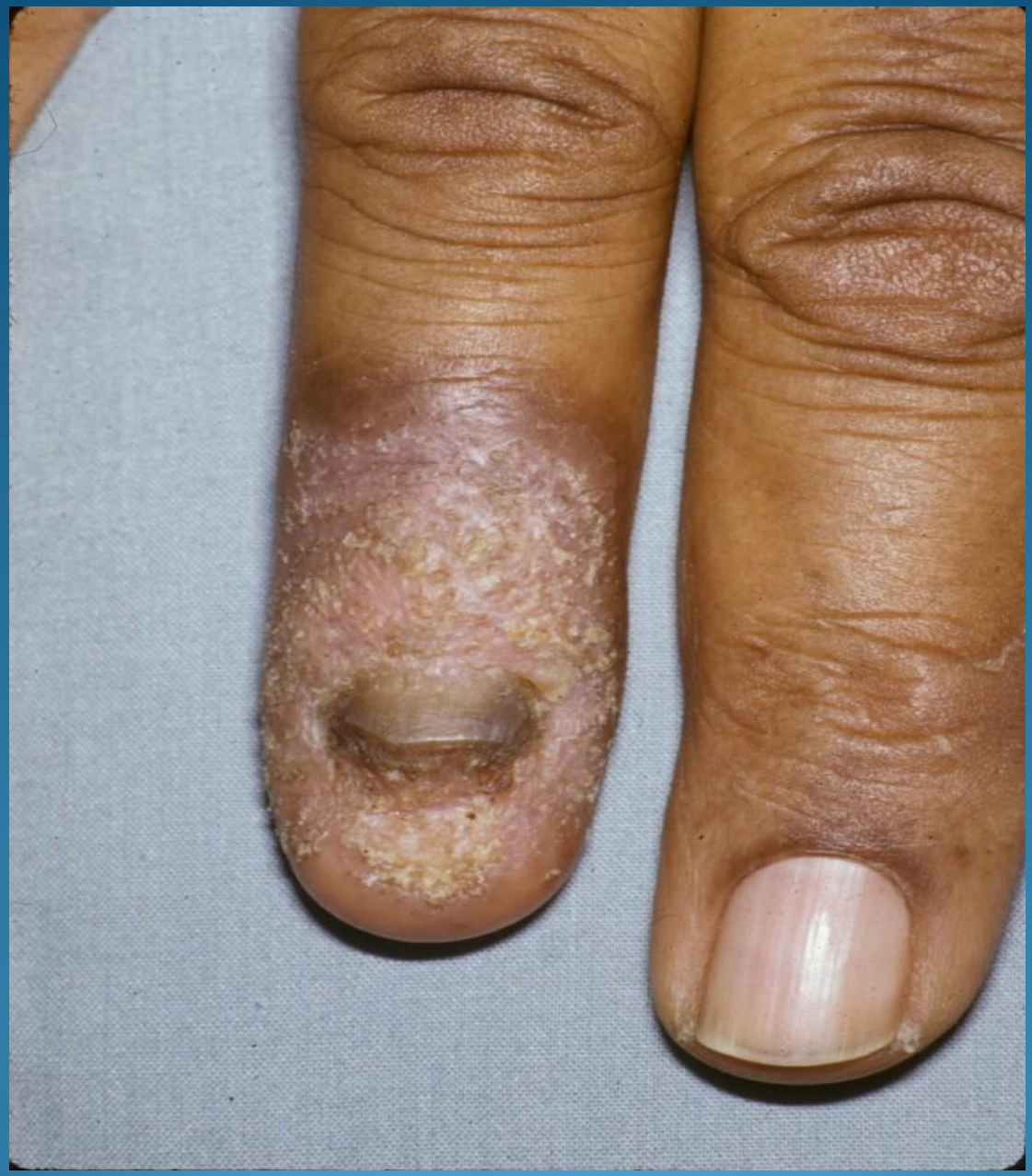


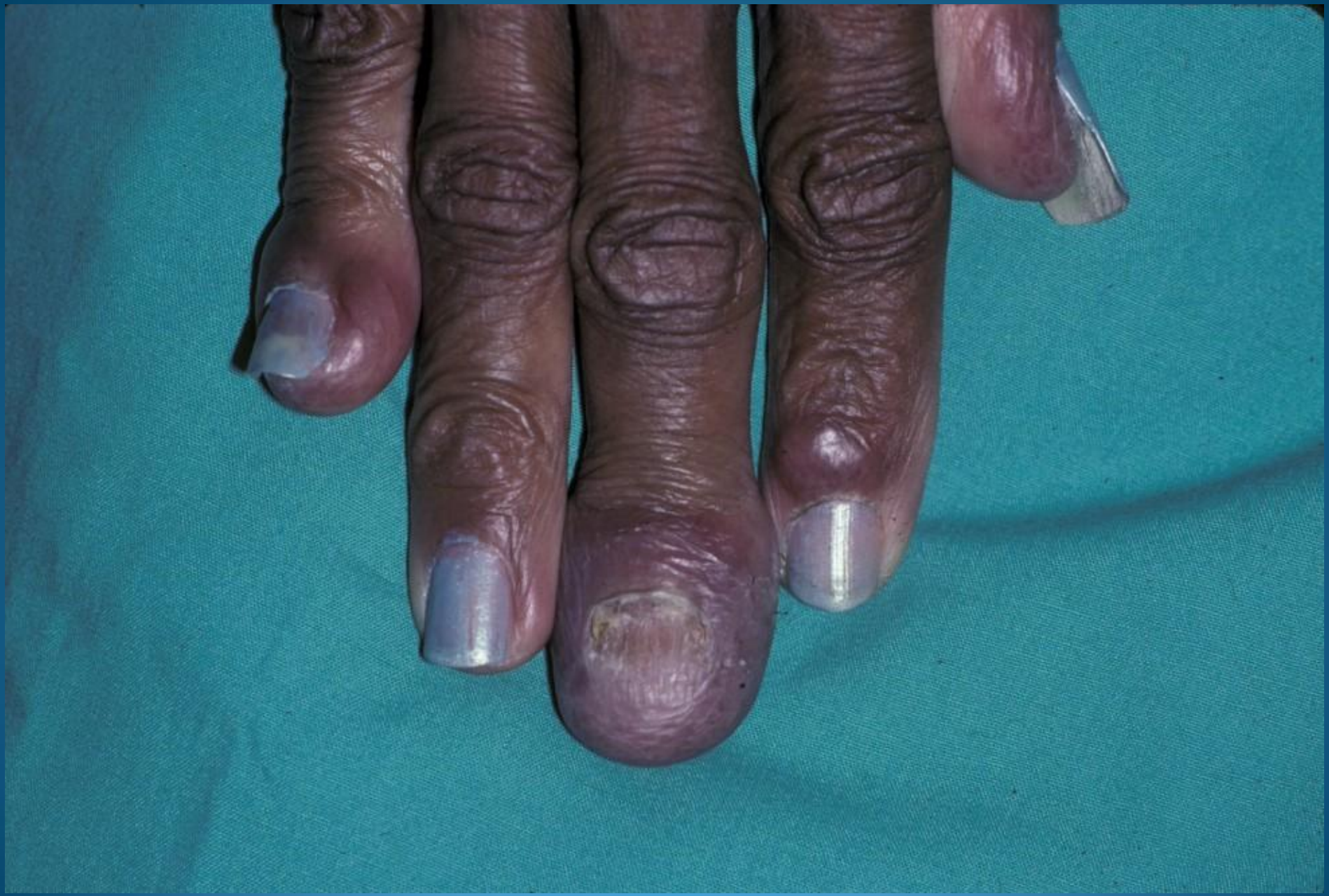


Cutaneous Manifestations: Non-specific (no granulomas)

- Erythema Nodosum commonly seen in European, Puerto Rican and Mexican patients. Rare in Japanese and African Americans.

- Nail changes = clubbing, subungual hyperkeratosis and onycholysis





Systemic Manifestations

- *Constitutional symptoms*:
  - fever
  - fatigue
  - malaise
  - weight loss
- Included in differential diagnosis of *fever of unknown origin*

Systemic Manifestations

- *Pulmonary*: cough, dyspnea, chest pain, irreversible fibrosis
- *Intrathoracic and peripheral lymphadenopathy*: asymptomatic
- *Liver and spleen* (50-80%): obstructive jaundice, elevated Alk Phos, HSM. Splenomegaly = poor outcome

Systemic Manifestations

- *Musculoskeletal* (up to 39%): weakness, pain, tenderness, bone cysts, osteolytic lesions, myopathy, arthralgias, arthritis, tenosynovitis

- Solid organ, bone marrow (leukopenia) & upper respiratory tract infiltration

Systemic Manifestations

- *Renal*: interstitial nephritis, nephrolithiasis, obstruction, risk of CRI
- *Endocrine*= hypercalcemia (17%), diabetes insipidus (pituitary), thyroid
- *Gastrointestinal* (rare): gastric ulcer or mass, pancreatitis, duodenal obstruction

Systemic Manifestations

- *Ocular* (30-50%): anterior uveitis, blurred vision, photophobia, tearing, iritis, scleral plaques, conjunctival nodules
- *Cardiac* (10-20%): arrhythmias, complete heart block, cardiomyopathy & CHF, pericarditis
- *CNS* (5-10%): CN palsy (esp. VII), meningitis, hearing loss, seizures, psychiatric, stroke, etc.

Clinical Syndromes

Lofgren's Syndrome

In Irish, Scandanavian & Puerto Rican patients:

- Acute sarcoidosis
- Erythema Nodosum
- Migratory polyarthritis
- Fever
- Iritis

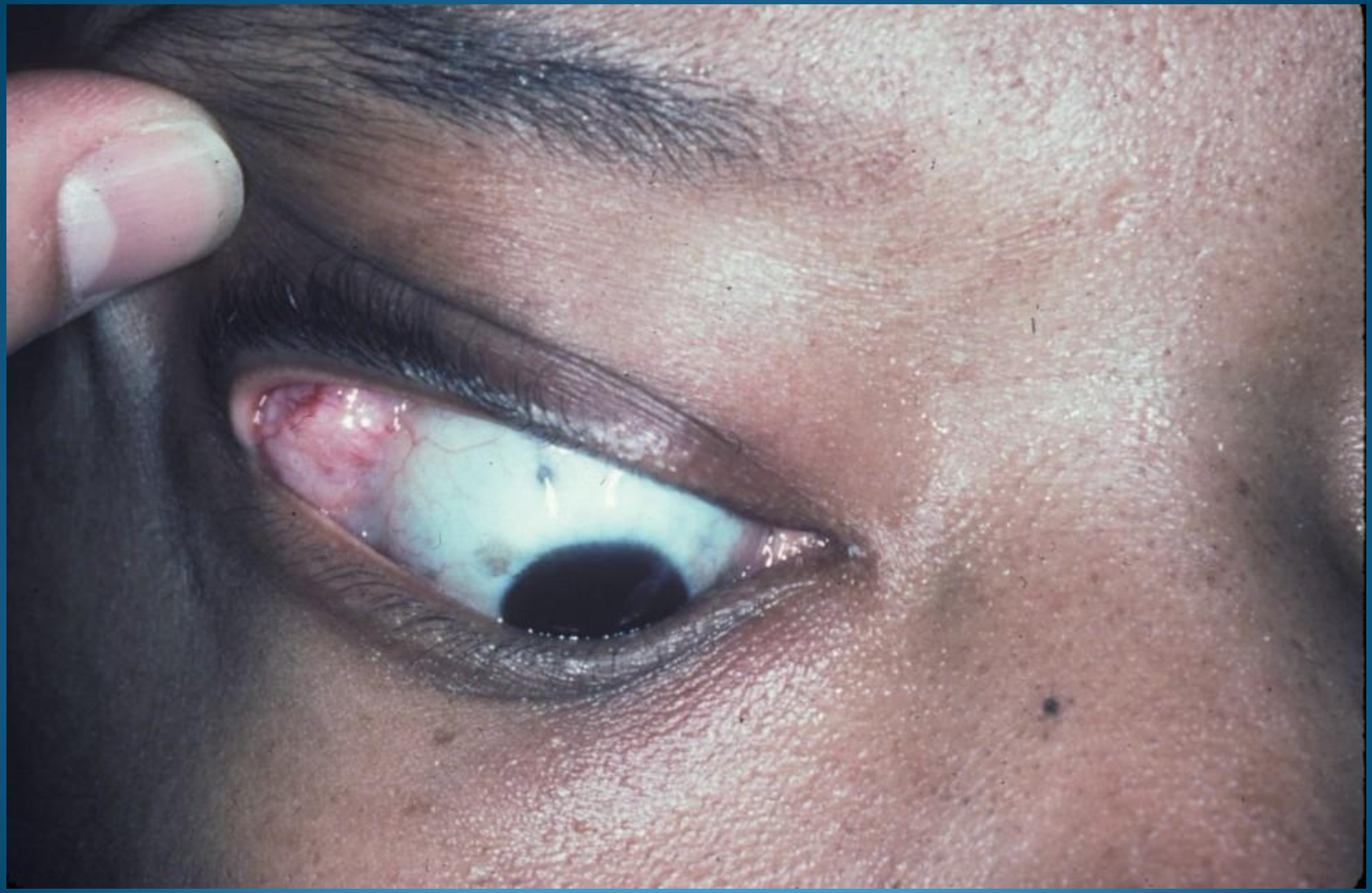
Darier-Roussy

Subcutaneous nodules of the trunk and extremities

Mikulicz's Syndrome

Bilateral sarcoidosis of the following glands:

- parotid
- submandibular
- sublingual
- lacrimal



Heerfordt-Waldenstrom

Combination of:

- fever
- parotid enlargement
- anterior uveitis
- facial nerve palsy

Complications: lethargy, hyperalesia, papilledema, meningism, & other CNS sxs…

Childhood Sarcoidosis

- ages 9-15 years
- fever, weight loss, fatigue
- lymph node, skin, joint and eye involvement
  - *classic triad*: arthritis, skin lesions and uveitis
  - rule out Blau syndrome (familial & no pulmonary sxs)

Treatment of choice: glucocorticoids

Sarcoidosis Associations

- Automimmune
  - Systemic sclerosis
  - SLE
  - Dermatomyositis
  - Sjogren's
  - Hemolytic anemia
  - Type 1 DM
  - Vitiligo
  - Thyroiditis
  - & many others….
- Neoplastic
  - Testicular
  - Lymphoma
  - Lung
  - Bladder
  - Melanoma
  - Kaposi's Sarcoma
  - Carcinoid
  - Other lymphoprolif. disorders…

Sarcoidosis Associations

- Medications
  - Chemotherapy (?antigen release)
  - Interferons alpha & beta
- Immune Restoration (HIV)
- Sweet's Syndrome

Diagnostic Work-up

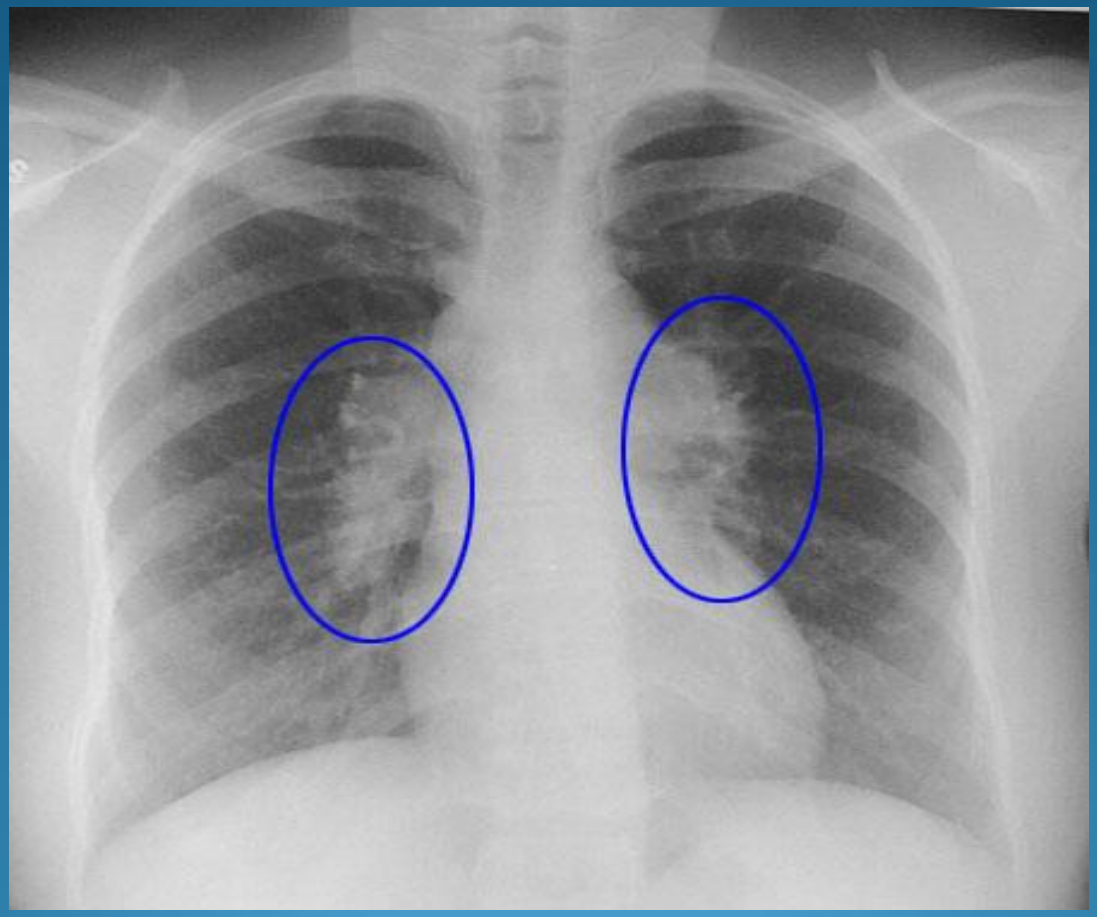
- A diagnosis of exclusion
- Complete H&P and ROS including environmental exposures
- Labs: ACE, Calcium and ESR may be elevated (ACE non-specific w/ 10% FP and 40% FN rates). Check liver and renal fxn and CBC.

Diagnostic Work-up

- History plus non-caseating granulomas in at least one organ system:
- Skin biopsy
- PFT's/ CXR / Bronchoscopy & BAL
- ^{67}Gallium scans (panda or lambda)
- Kviem-Siltzbach test (historical)

Diagnostic Work-up

- Staging:
  - 0 Normal
  - 1 Bilateral hilar lymphadenopathy
  - 2 Bilateral hilar lymphadenopathy & infiltrates
  - 3 Infiltrates without lymphadenopathy
  - 4 Fibrotic changes



Differential Diagnosis

- Foreign body granuloma
- Lymphoma
- Wegener's granulomatosis
- Churg-Strauss
- *M. tuberculosis* & atypical mycobacterium
- *Treponema*
- *Borrelia burgdoferi*
- *Toxoplasmosis*
- *Leishmaniasis*
- *Histoplasmosis*
- *Coccidioidomycosis*
- Brucellosis
- Chlamydia
- Tularemia
- Berylliosis
- Tattoo reaction
- Necrobiosis lipoidica
- Granuloma annulare
- Granulomatous rosacea
- Metastatic Crohn's
- Deep fungal infection
- Cheilitis granulomatosis
- Leprosy

Treatment: Systemic

- First line: Glucocorticoids
- Chronic:
  - Antimalarials
  - Methotrexate
  - Azathioprine
  - Chlorambucil
  - Cyclophosphamide
  - Cyclosporine
  - Minocycline/ Doxycycline*
  - Infliximab*

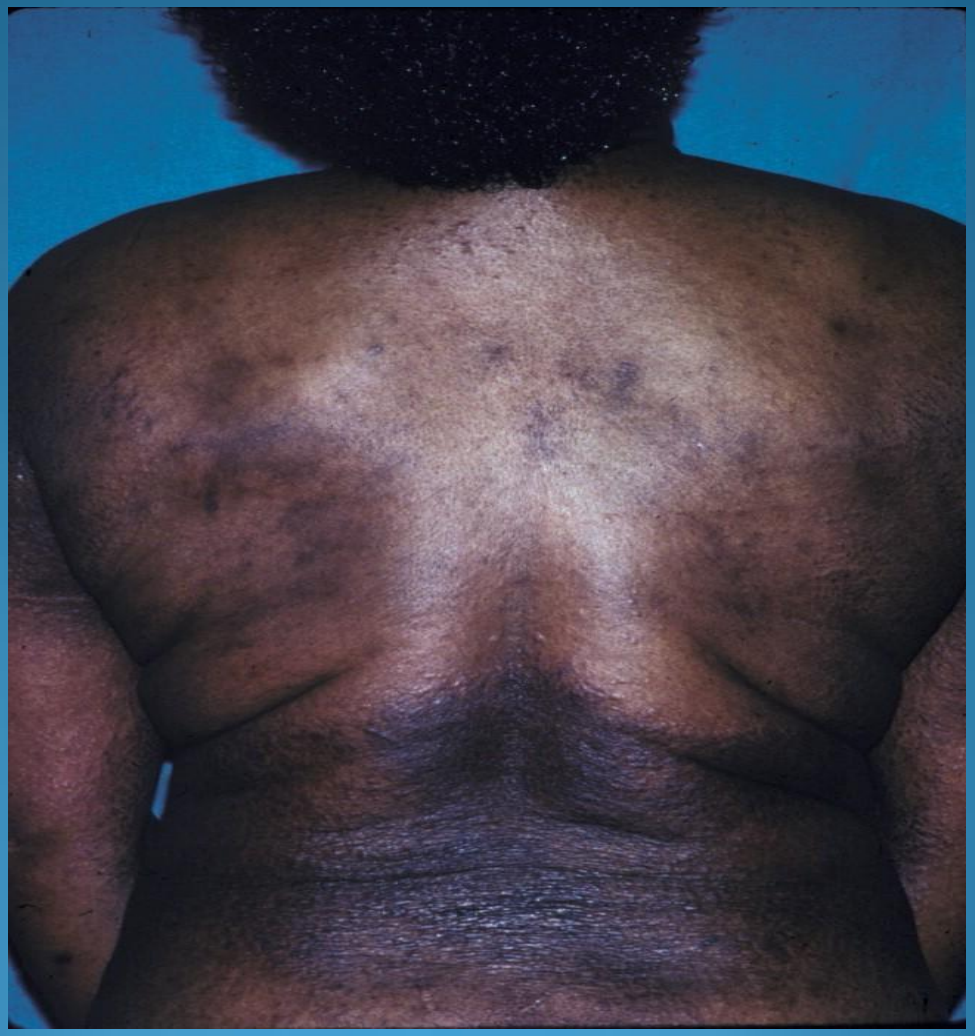
Treatment: Cutaneous

- TOPICAL:
  - superpotent topical corticosteroids
  - Hydrocolloid occlusive dressing
  - Intralesional triamcinolone
  - 5% hydrocortisone powder in ointment w/ phonophoresis
  - Intralesional chloroquine
  - C02 or pulsed dye laser
  - Dermabrasion
  - Excision

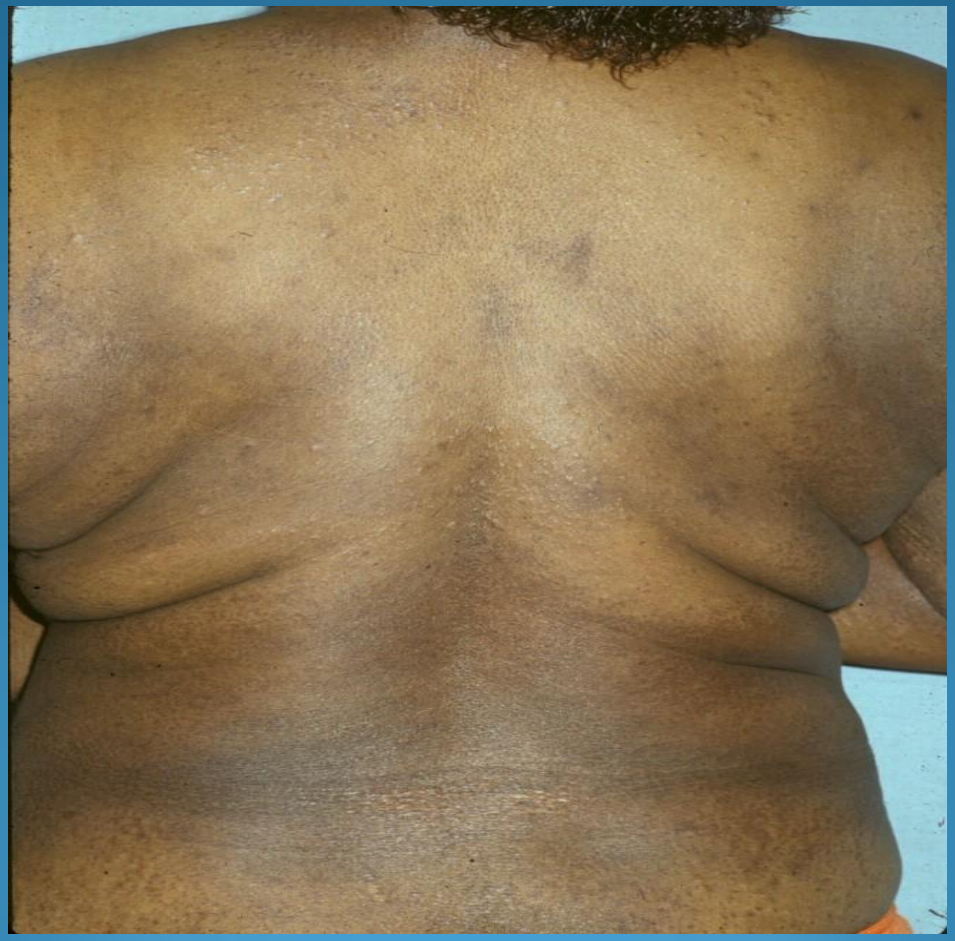
Treatment: Cutaneous

- ORAL:
  - Prednisone
  - Hydroxychloroquine
  - Chloroquine
  - MTX
  - Allopurinol
  - Thalidomide
  - Isotretinoin
  - PUVA
  - Melatonin
  - Tranilast (outside US) (anti-allergy)
  - Prospidine (outside US) (anti-tumor)

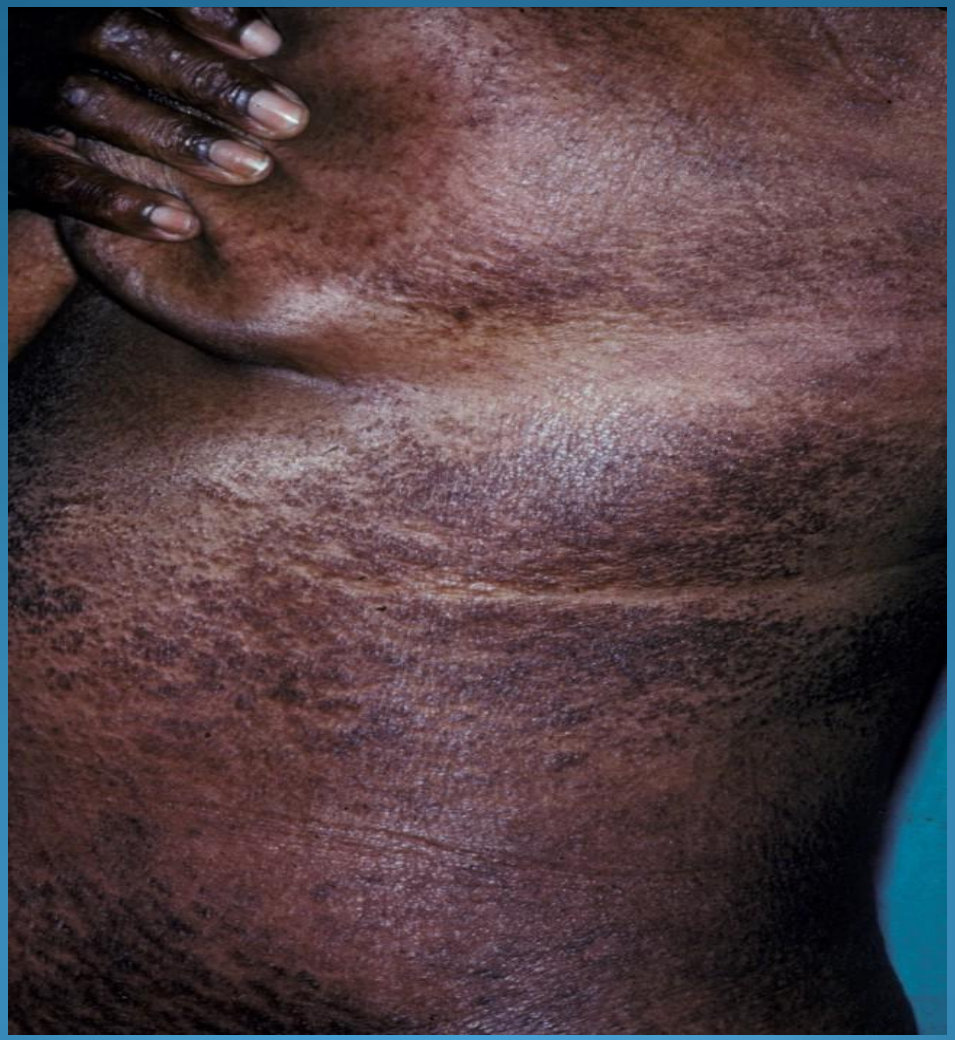
Pre-Plaquenil



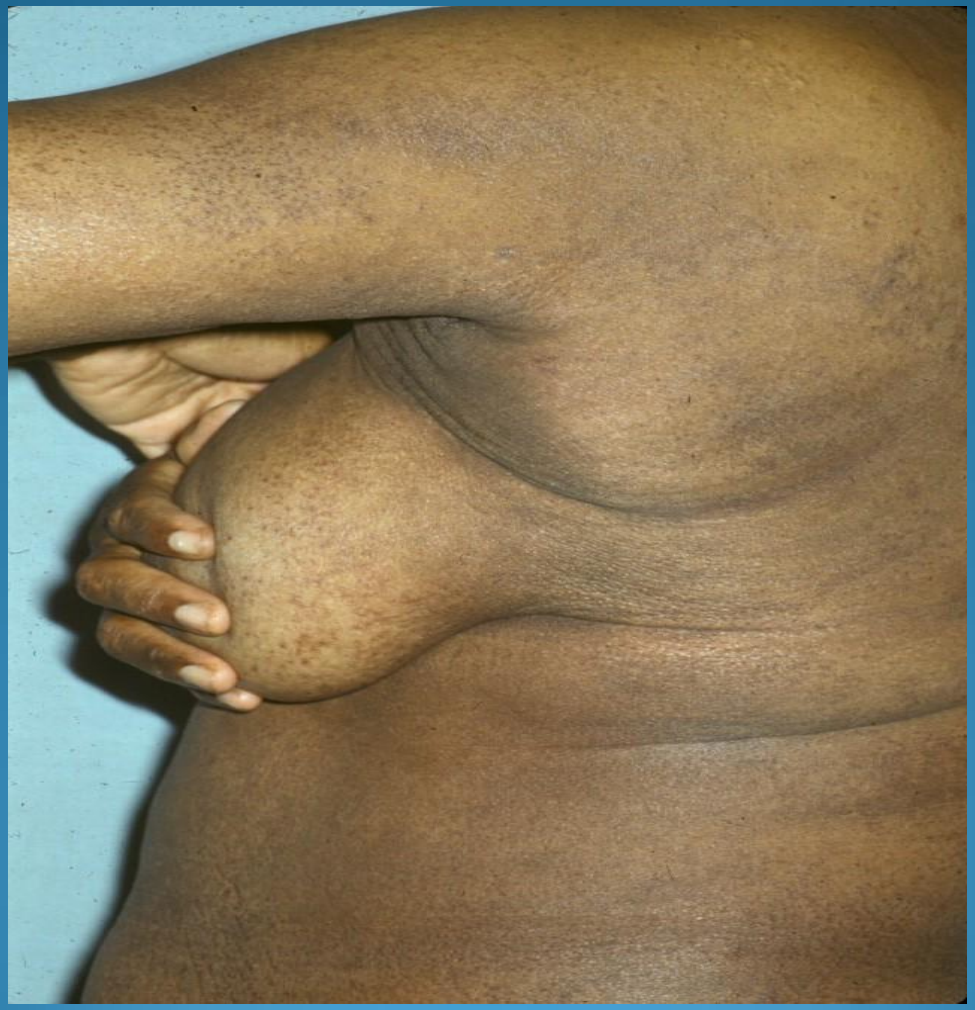
3 mos Post-Plaquenil



Pre-Plaquenil



3 mos Post-Plaquenil



Prognosis

- Up to 60% have spontaneous resolution (>80% with EN)
- Another 10-20% resolve with po steroids
- Chronic and progressive in 10-20%
- Only 1-5 % will die of disease

Prognosis

- Higher mortality rates for African Americans and females
- Highest mortality in those with cardiac or CNS disease (up to 10%)
- Lung disease and heart failure = most common causes of death