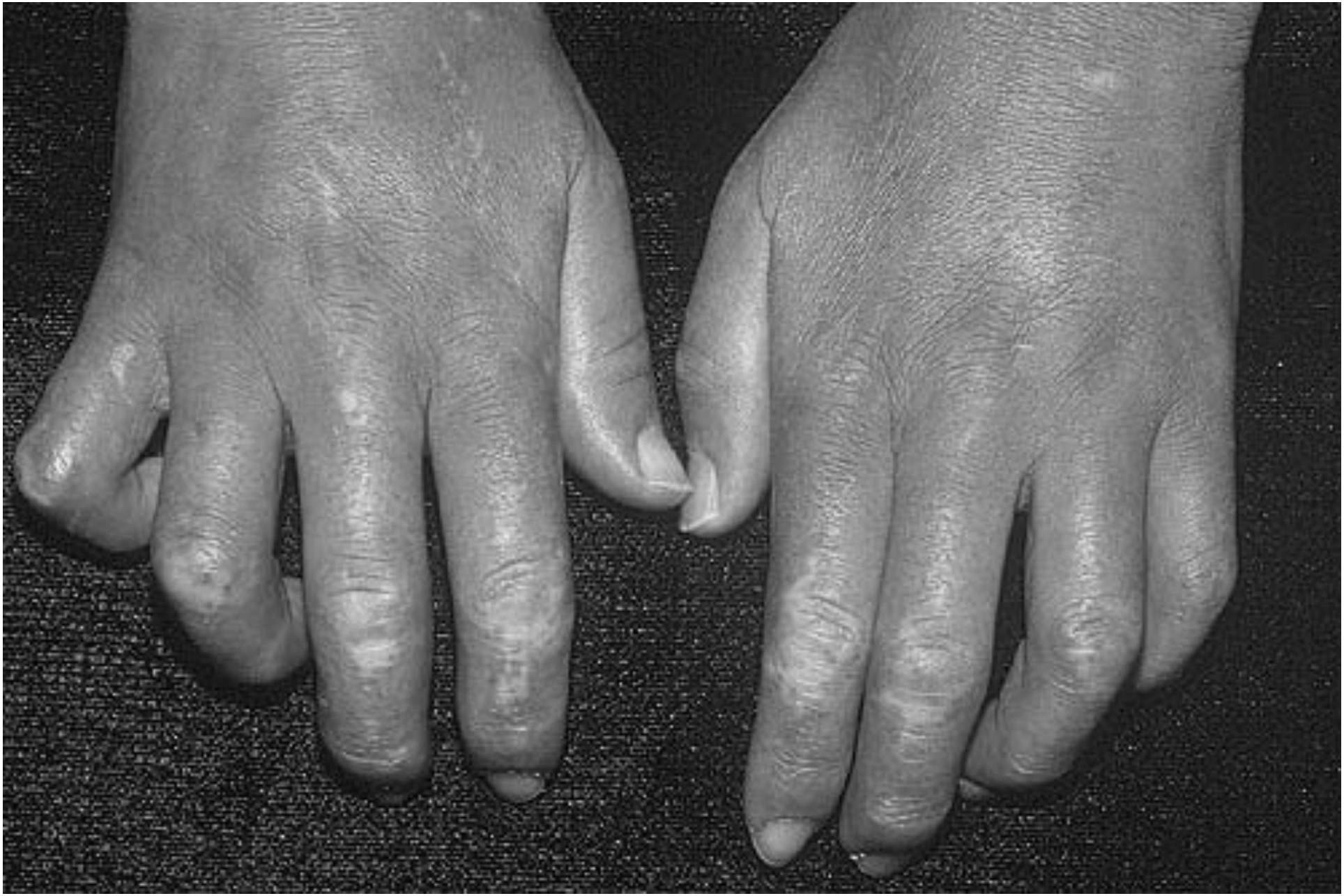


Immune Diseases Kristine Krafts, M.D.

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity

Immunologic Tolerance

- "Tolerance" = unresponsiveness to an antigen
- "Self-tolerance" = unresponsiveness to one's own antigens
- In generating billions of B and T cells, some will react against self antigens!
- There are two ways of muzzling these cells: central tolerance and peripheral tolerance

Immunologic Tolerance

Central tolerance

- Auto-reactive T and B cells deleted during maturation
- Occurs by apoptosis in thymus and bone marrow
- Process not perfect (some get out!)

Peripheral tolerance

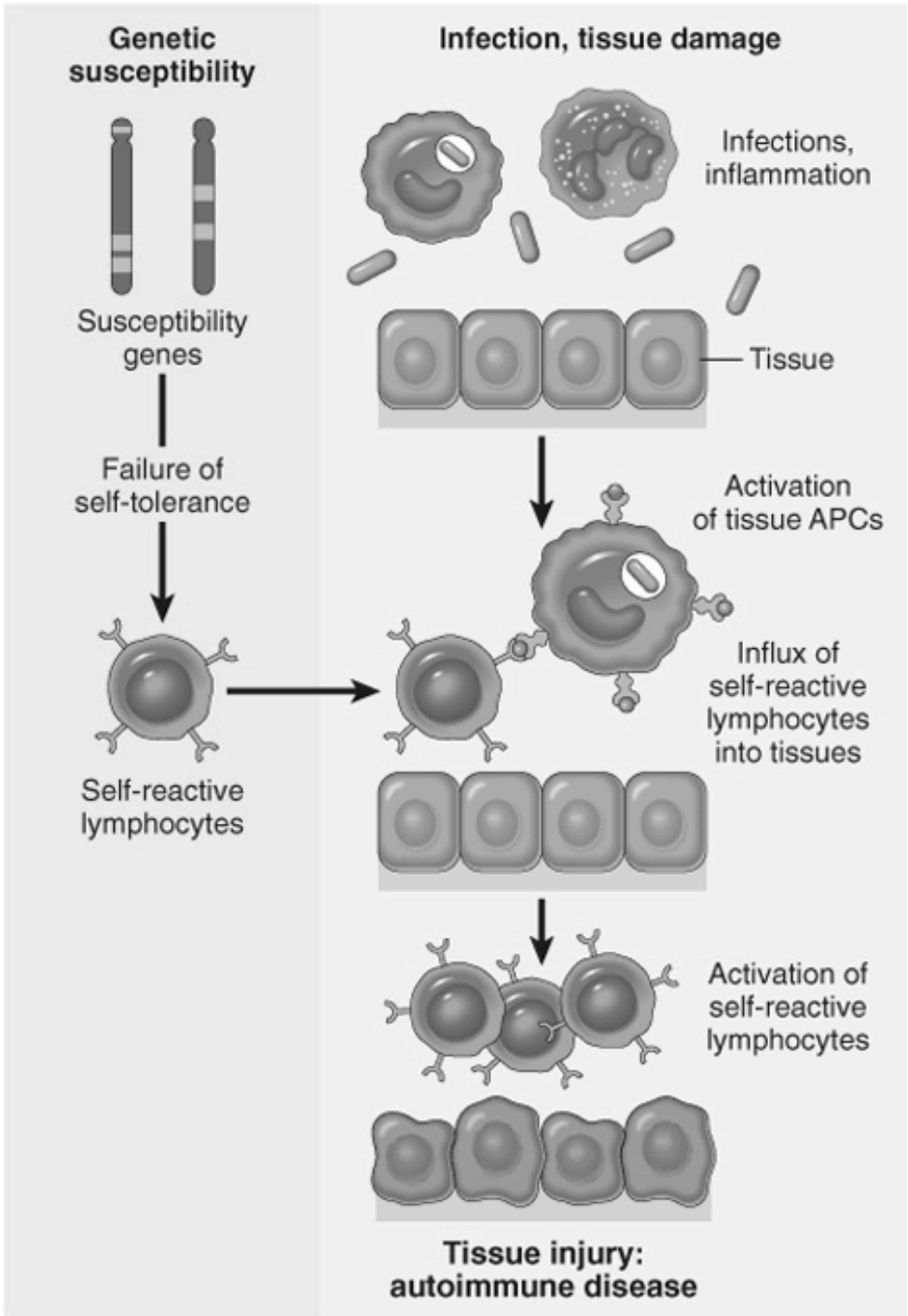
- Auto-reactive cells muzzled in peripheral tissues
- Some become “anergic” (inactive) in periphery
- Some are suppressed by regulatory T cells
- Some undergo apoptosis when activated

Autoimmunity

- "Autoimmunity" = immune reaction against self
- Self-tolerance breaks down, causing disease
- Two main reasons for breakdown:

  Genes
  - HLA-DR4: ↑ risk of rheumatoid arthritis
  - HLA-B27: ↑ risk of ankylosing spondylitis

  Environmental triggers
  - Expose hidden self-antigens
  - Activate APCs
  - Mimic self antigens


Genetic susceptibility
Infection, tissue damage
Susceptibility genes
Failure of self-tolerance
Self-reactive lymphocytes
Infections, inflammation
Tissue
Activation of tissue APCs
Influx of self-reactive lymphocytes into tissues
Activation of self-reactive lymphocytes
Tissue injury: autoimmune disease

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases
  - Lupus

Lupus

Things You Must Know

- Typical patient: young woman with butterfly rash
- Symptoms unpredictable (relapsing/remitting)
- Multisystem (skin, kidneys, joints, heart)
- Antinuclear antibodies

Lupus Etiology

Autoantibodies!

- Antinuclear Ab present in all patients with SLE... but found in other autoimmune diseases too
- Anti-RBC, -lymphocyte, -platelet, or –phospholipid antibodies may be present too

Underlying cause unclear

- Genetic predisposition…
- …plus triggers (UV radiation, drugs)

What's so bad about having these autoantibodies?

They cause tissue injury!

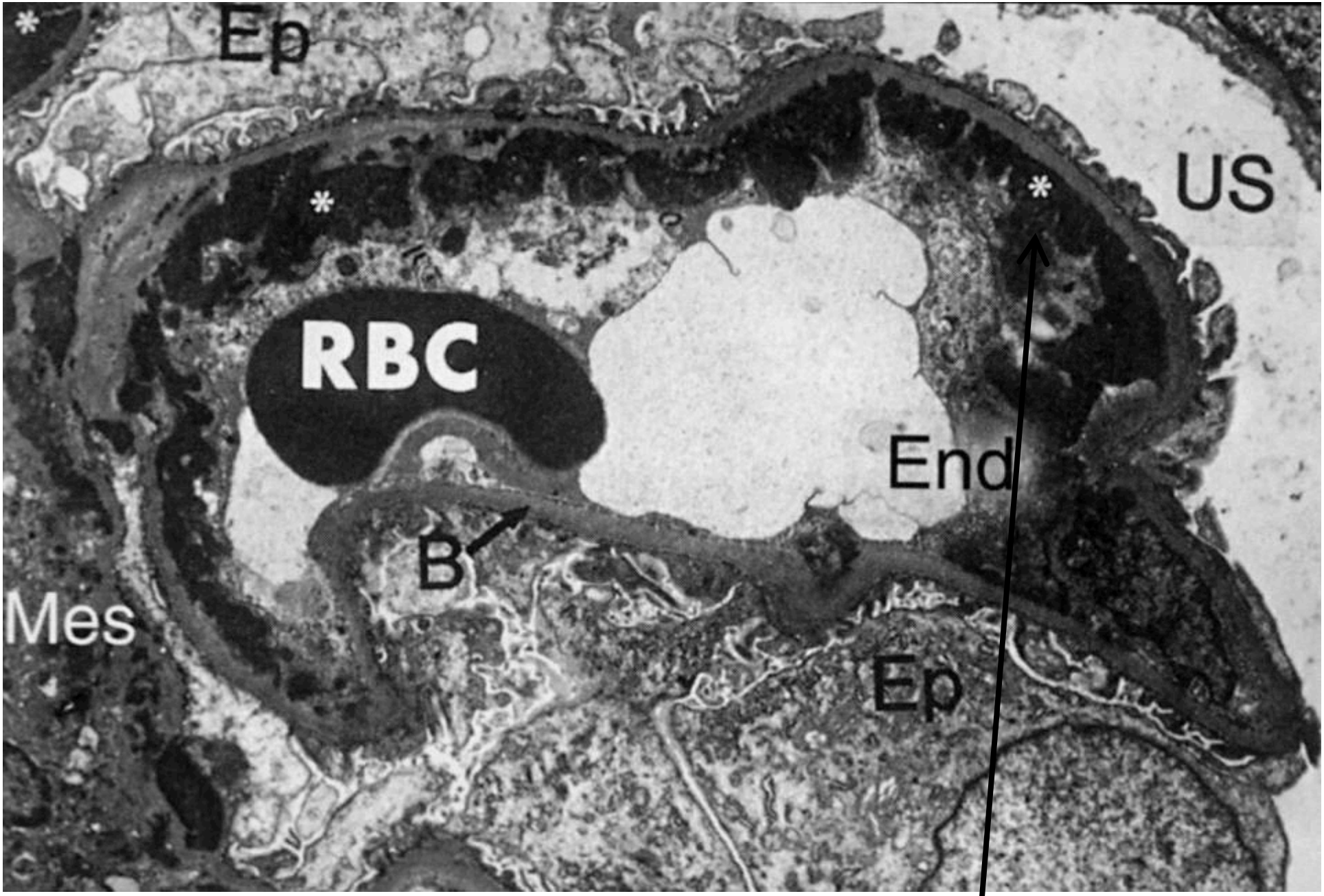
- Form immune complexes
- Cause destruction, phagocytosis of cells

Multisystem effects:

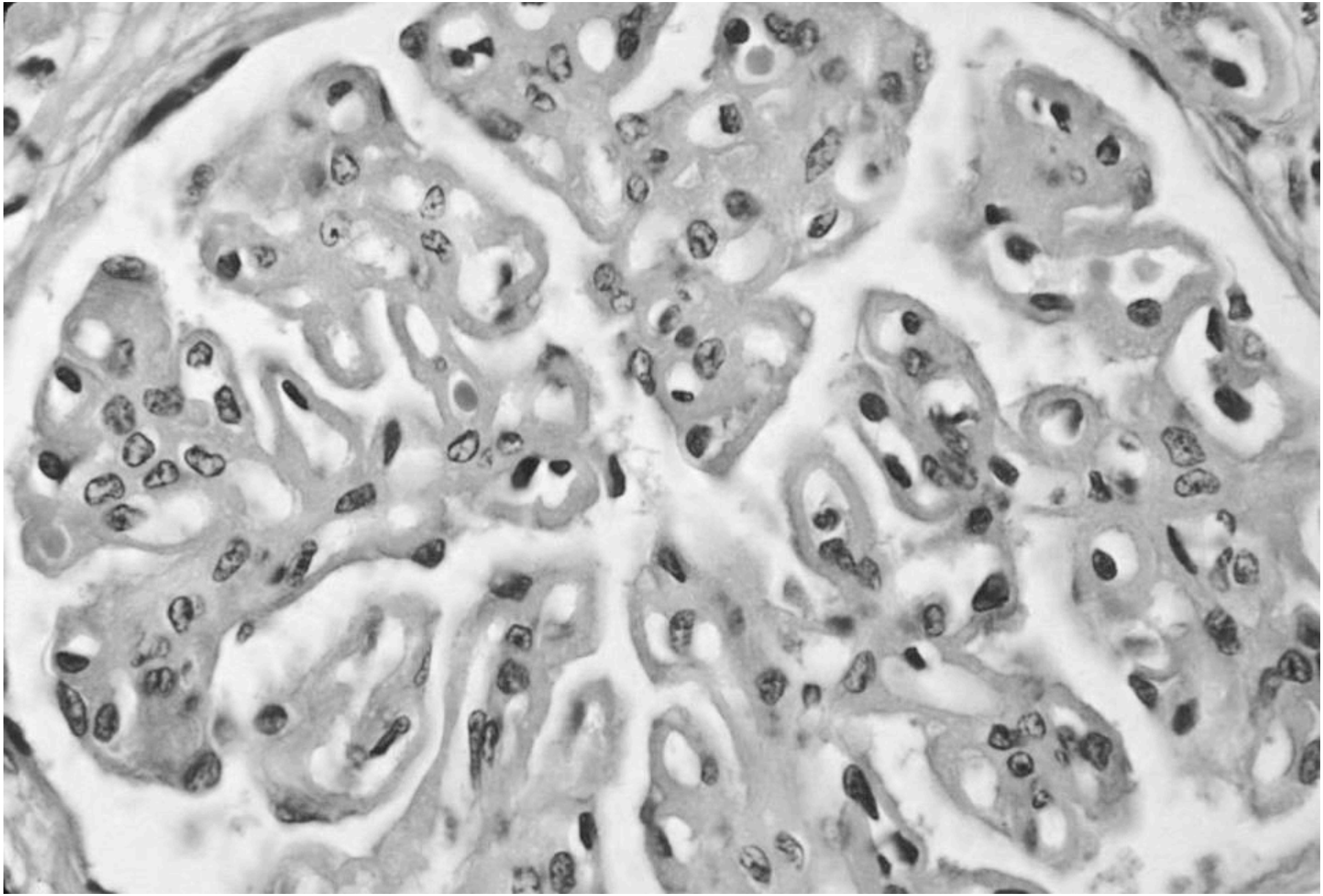
- Kidney (renal failure)
- Skin ("butterfly rash")
- CNS (focal neurologic deficits)
- Joints (arthritis)
- Heart (pericarditis, endocarditis)

Discoid Lupus

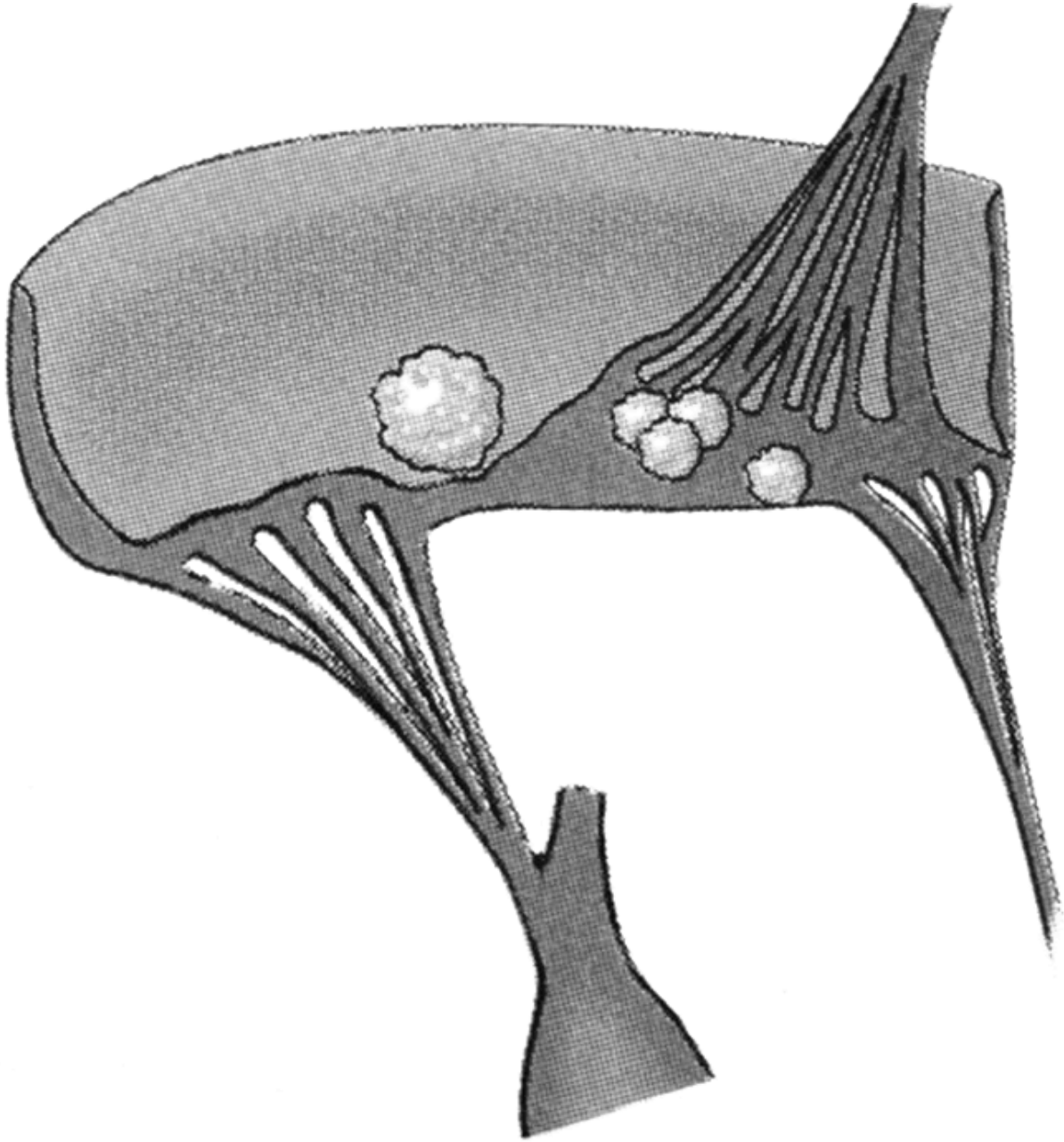
- Skin involvement only
- May evolve into systemic lupus



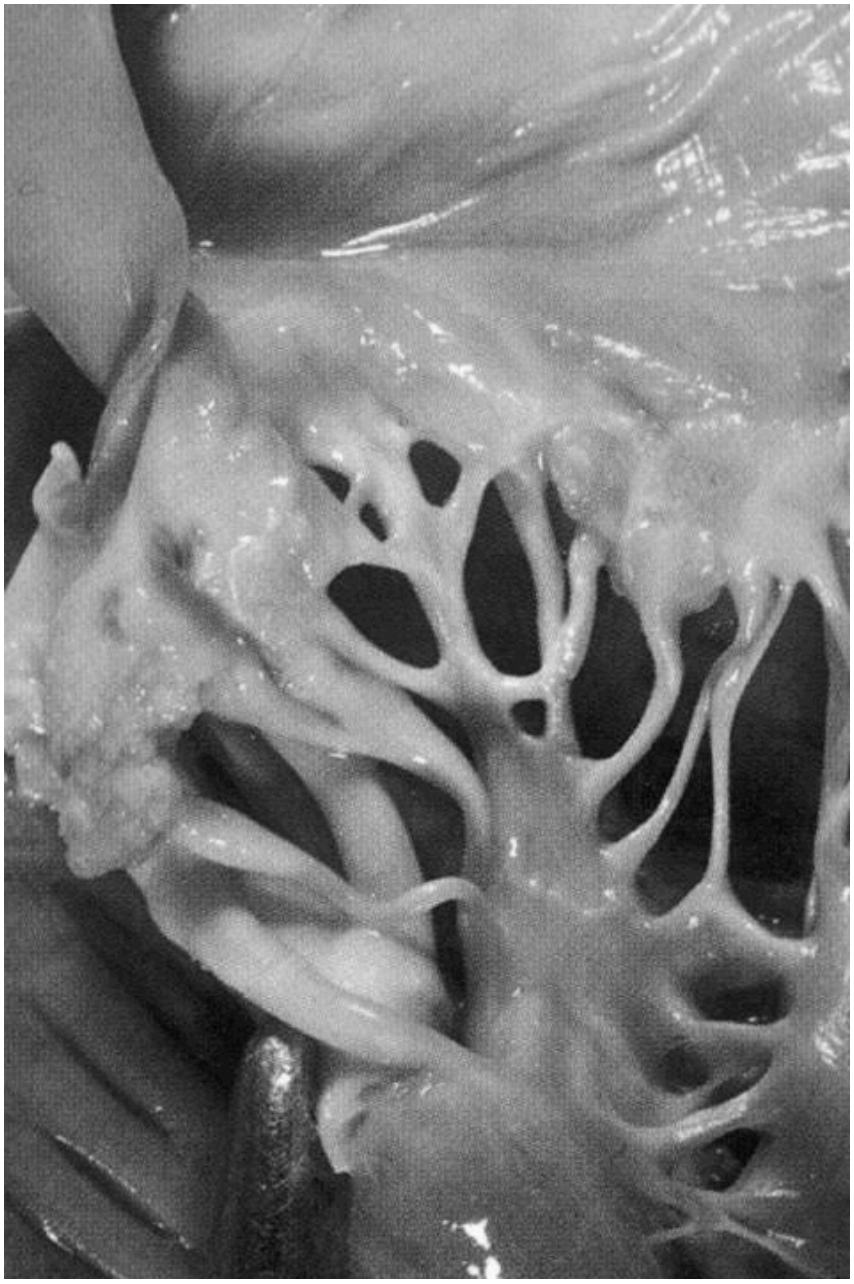
EM of glomerular capillary loop: subendothelial deposits



Glomerulus: “wire loop” appearance



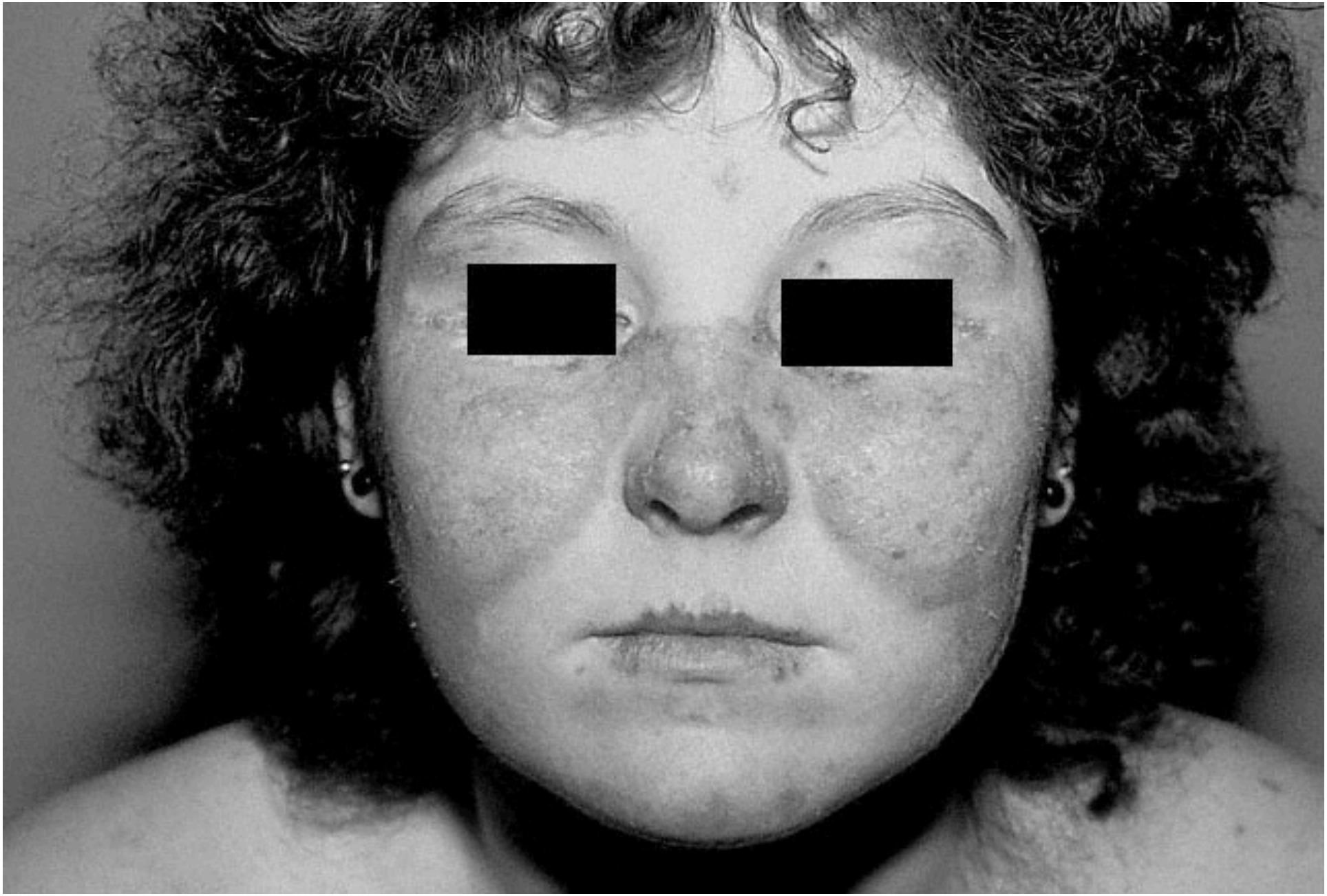
Heart valve: Libman-Sacks lesions



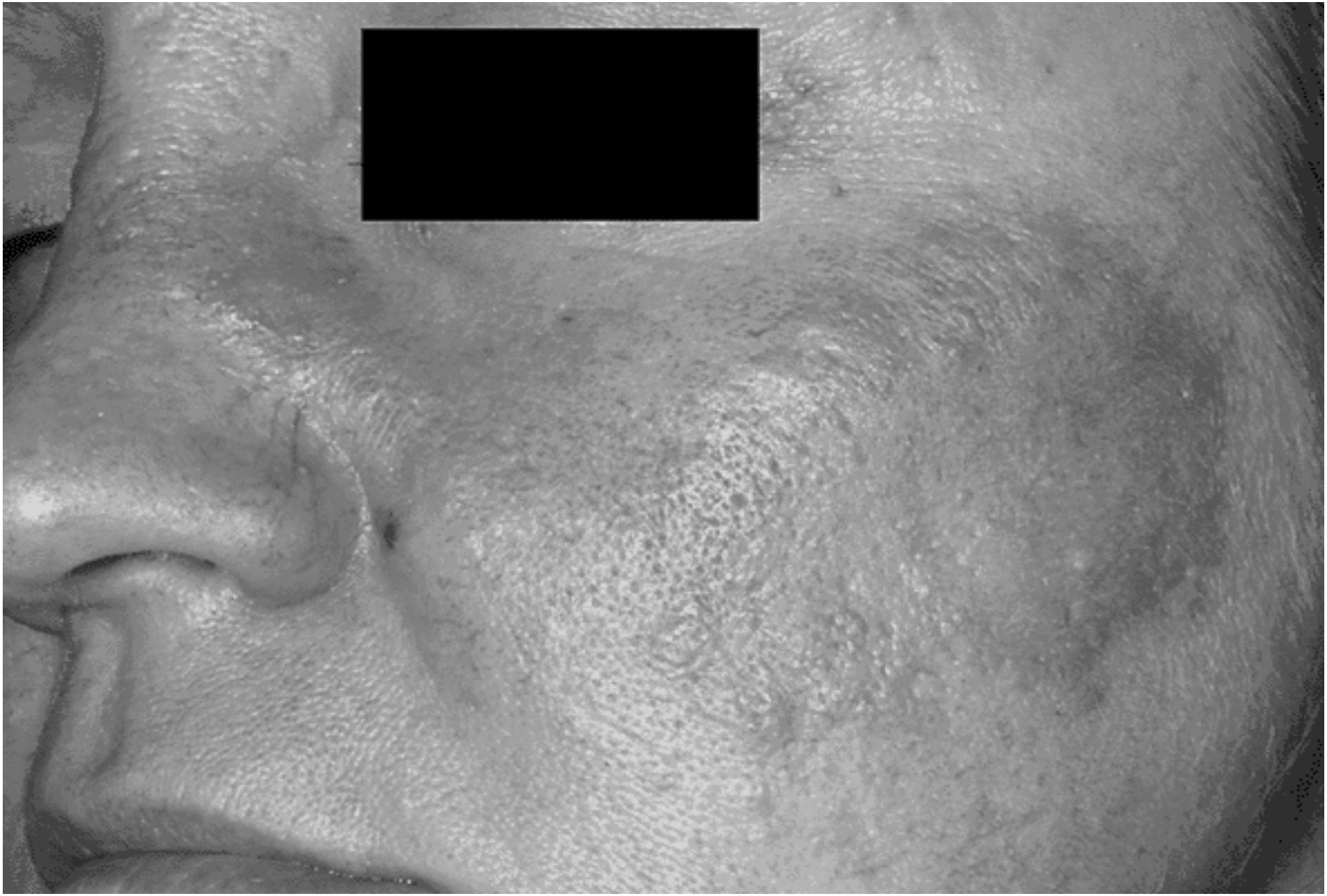
Heart valve: Libman-Sacks lesions

Lupus: Things a Dentist Might See

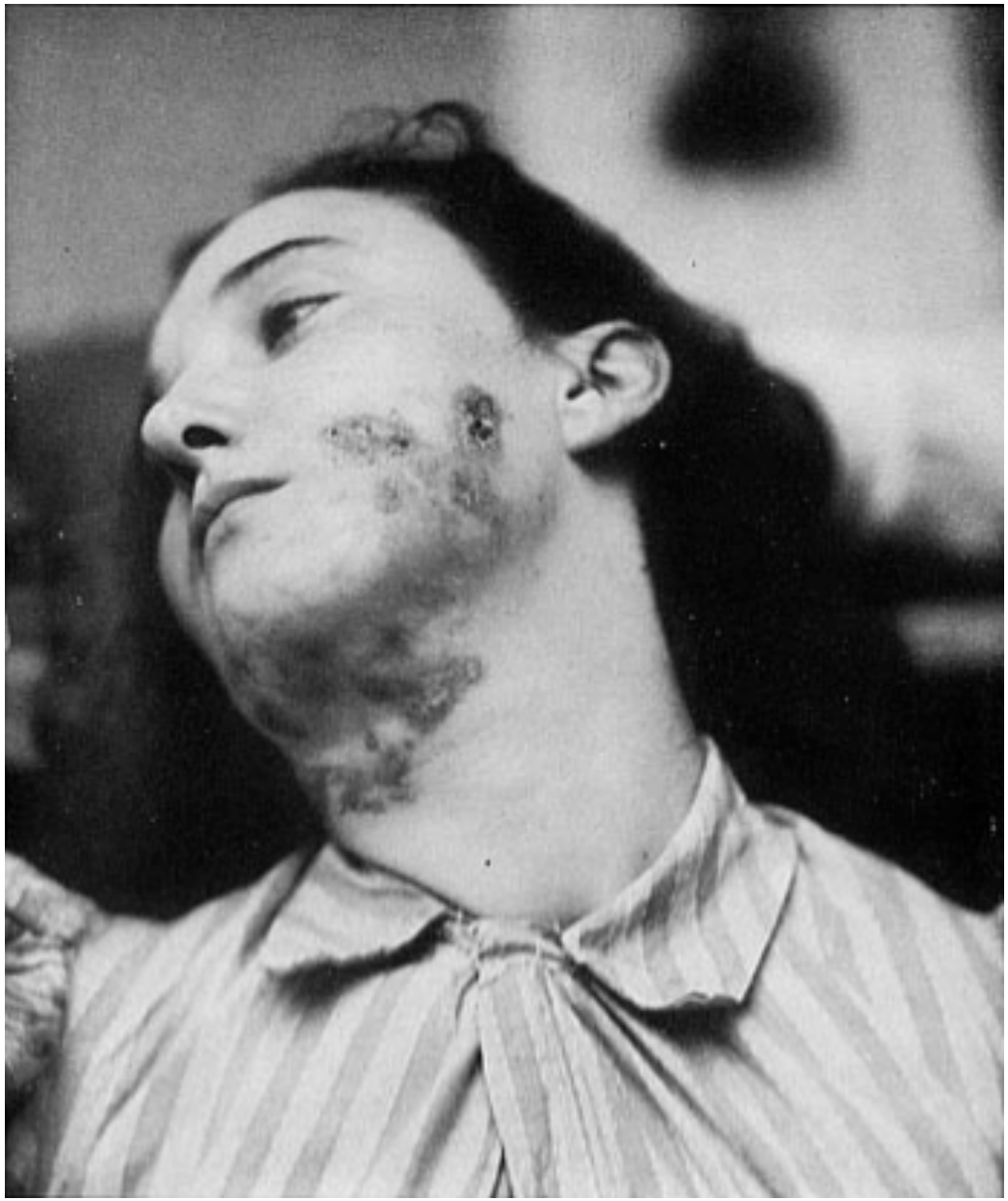
- Young woman with polyarthritis and a butterfly (or other) skin rash
- Fatigue
- Sensitivity to sunlight
- Headaches, seizures, or psychiatric problems
- Pleuritic chest pain
- Unexplained fever
- Oral lesions (rare): nonspecific, red-white, erosive



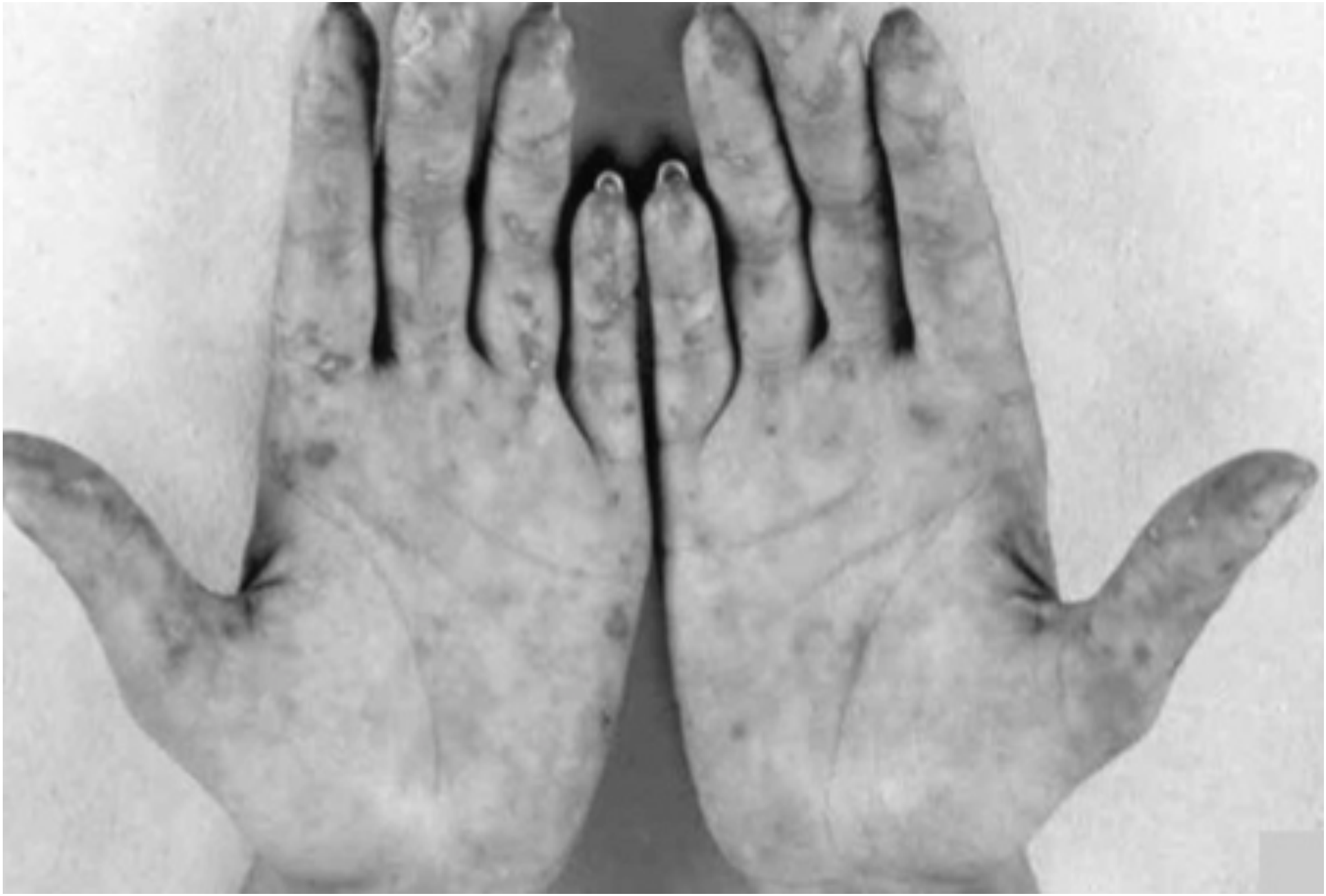
Lupus: butterfly rash



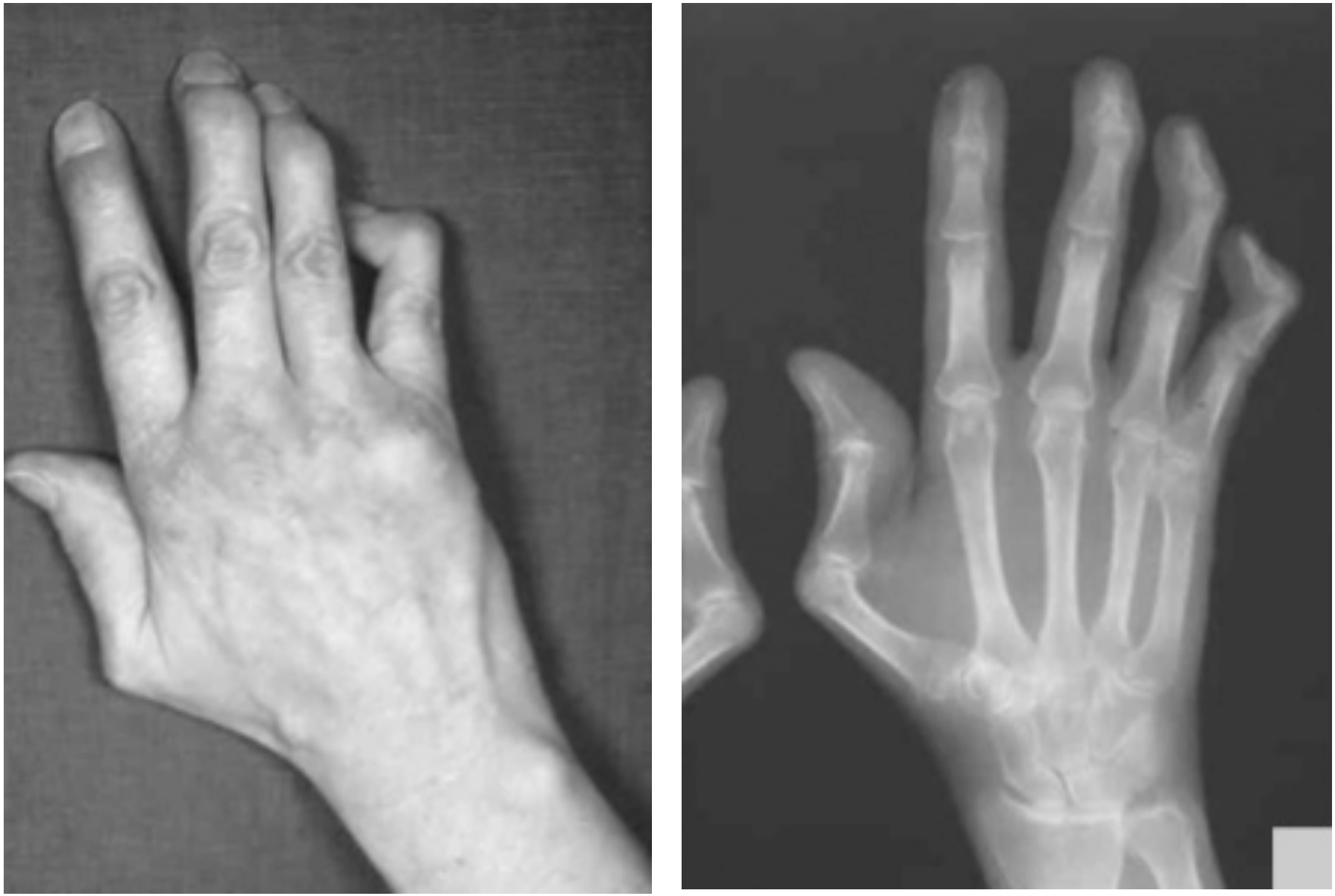
Lupus: butterfly rash



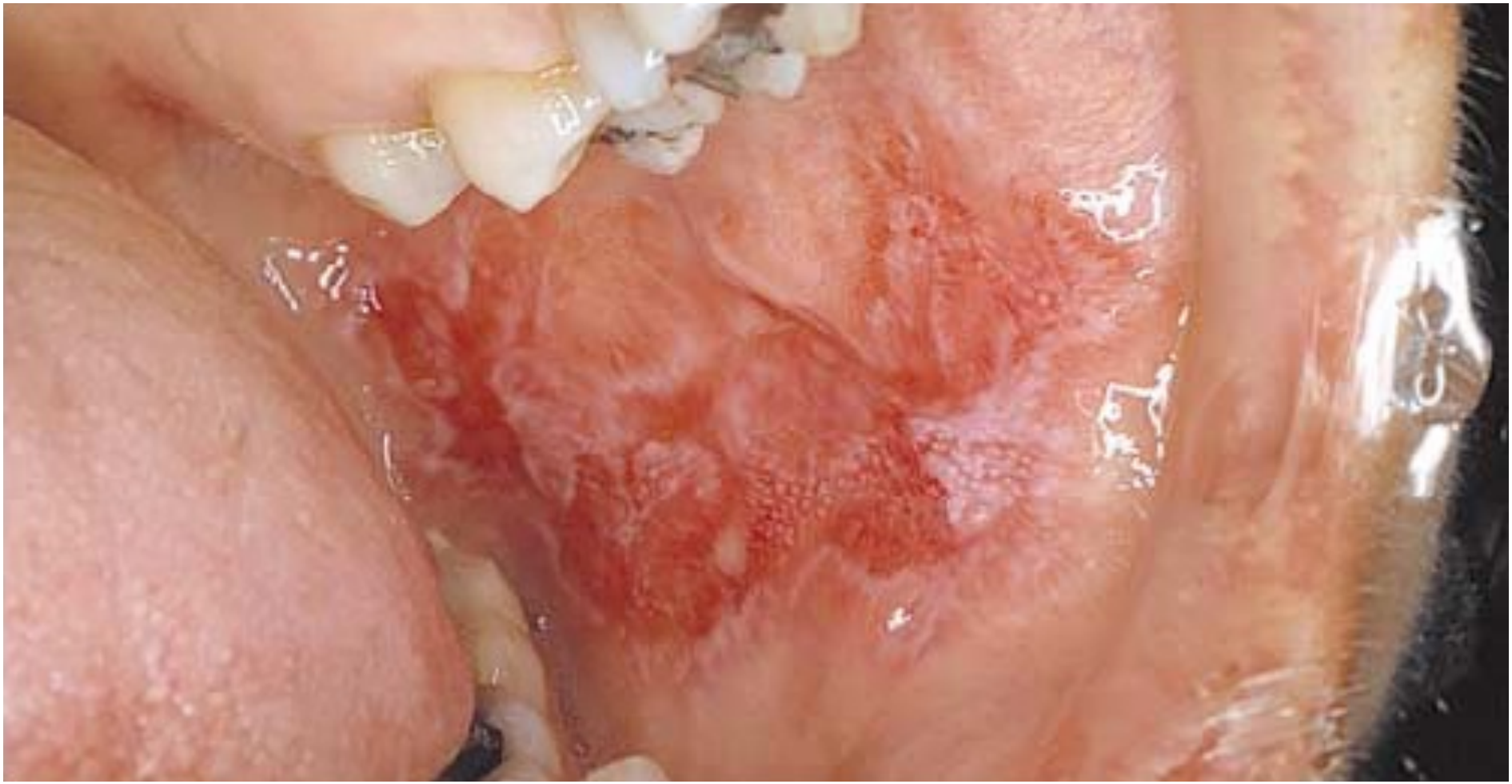
Lupus facial lesions



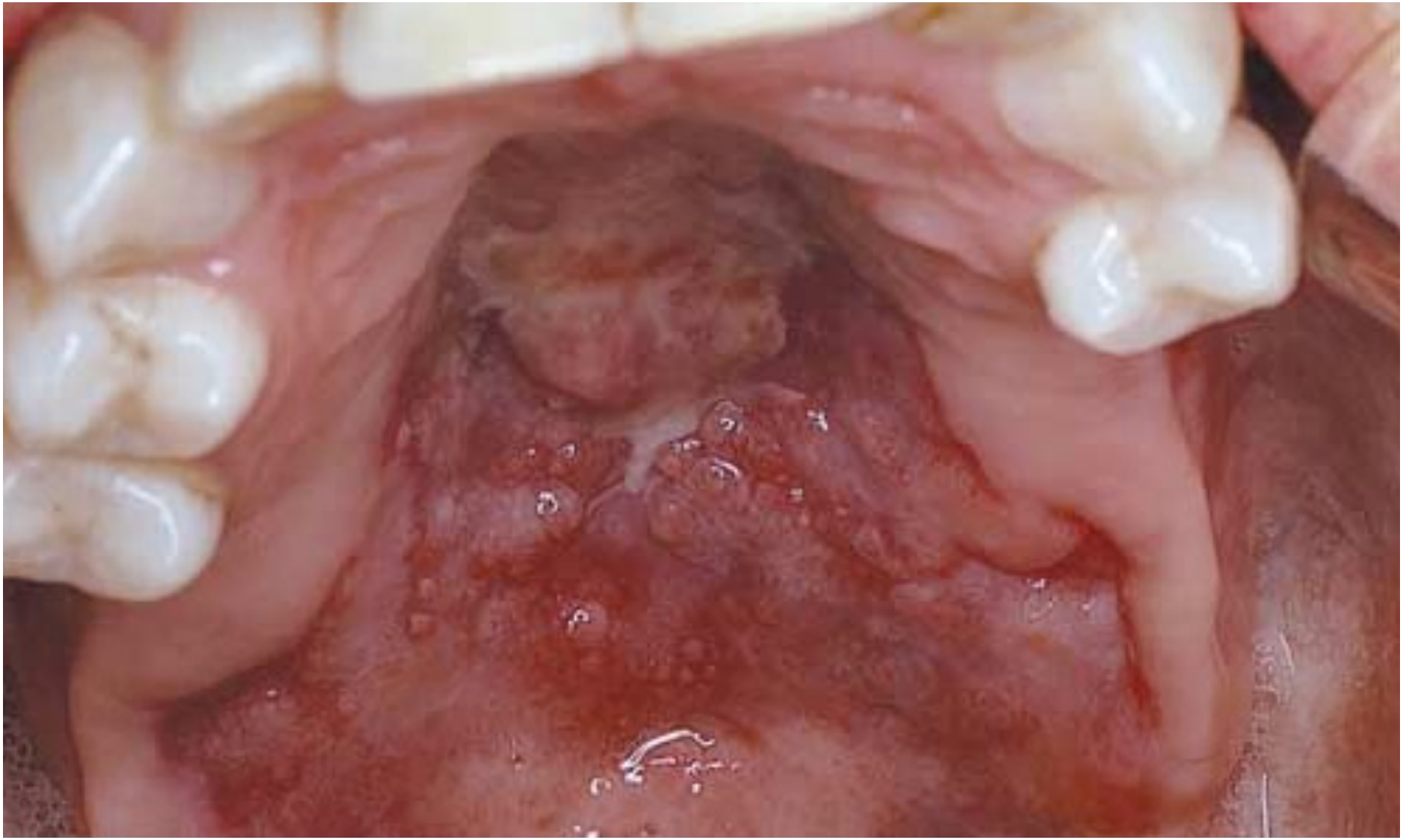
Lupus: vasculitic rash



Lupus: “hitch-hiking thumb”



Lupus mucosal lesions



Lupus palatal lesions

Lupus Prognosis

- Variable! Some have few symptoms, rare patients die within months.
- Most patients: relapses/remissions over many years.
- Acute flare-ups controlled with steroids
- 80% 10-year survival
- Most common cause of death: renal failure

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases
  - Lupus
  - Rheumatoid arthritis

Rheumatoid Arthritis

Things You Must Know

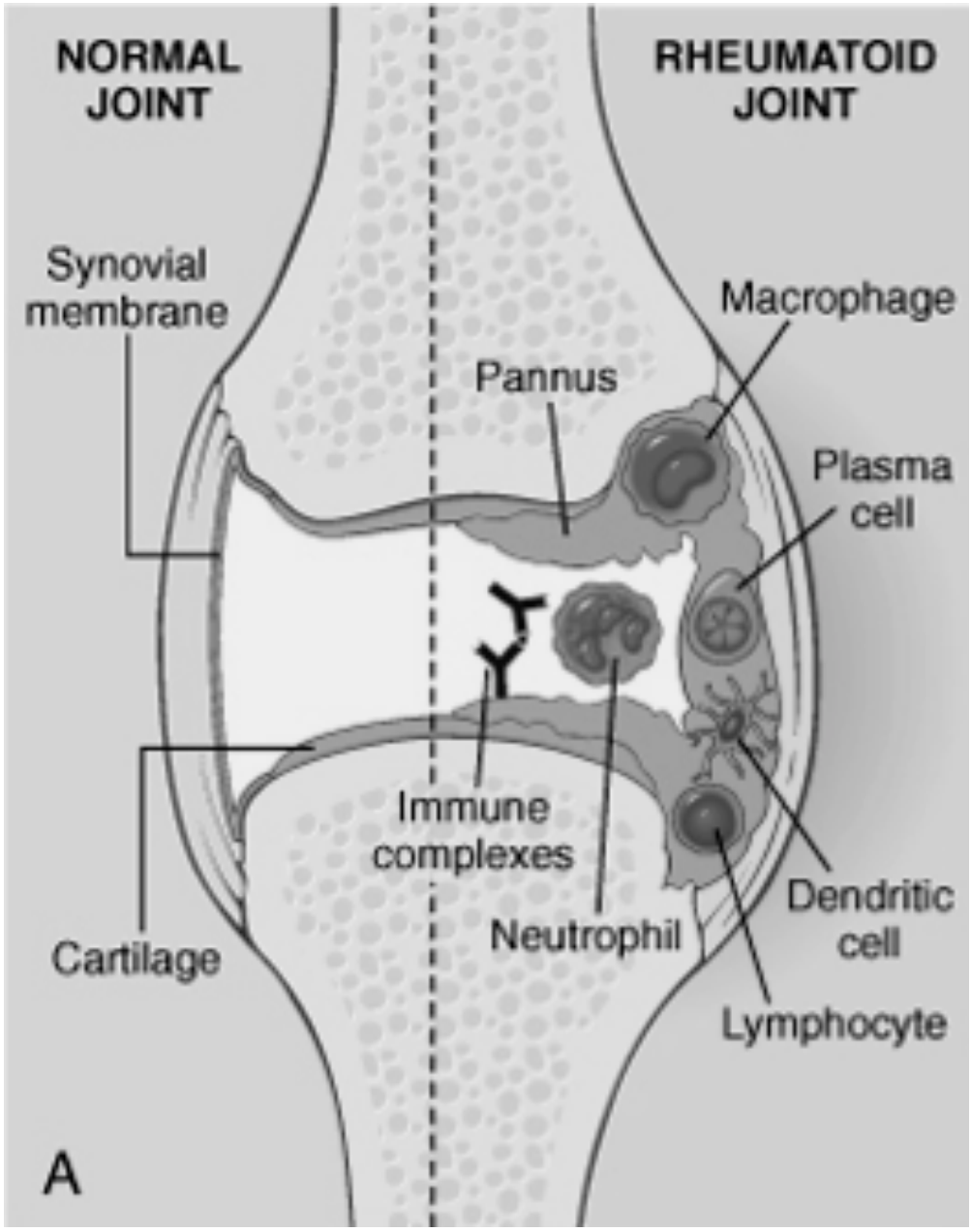
- Symmetric, mostly small-joint arthritis
- Systemic symptoms (skin, heart, vessels, lungs)
- Rheumatoid factor
- Cytokines (especially TNF) cause damage

RA Etiology

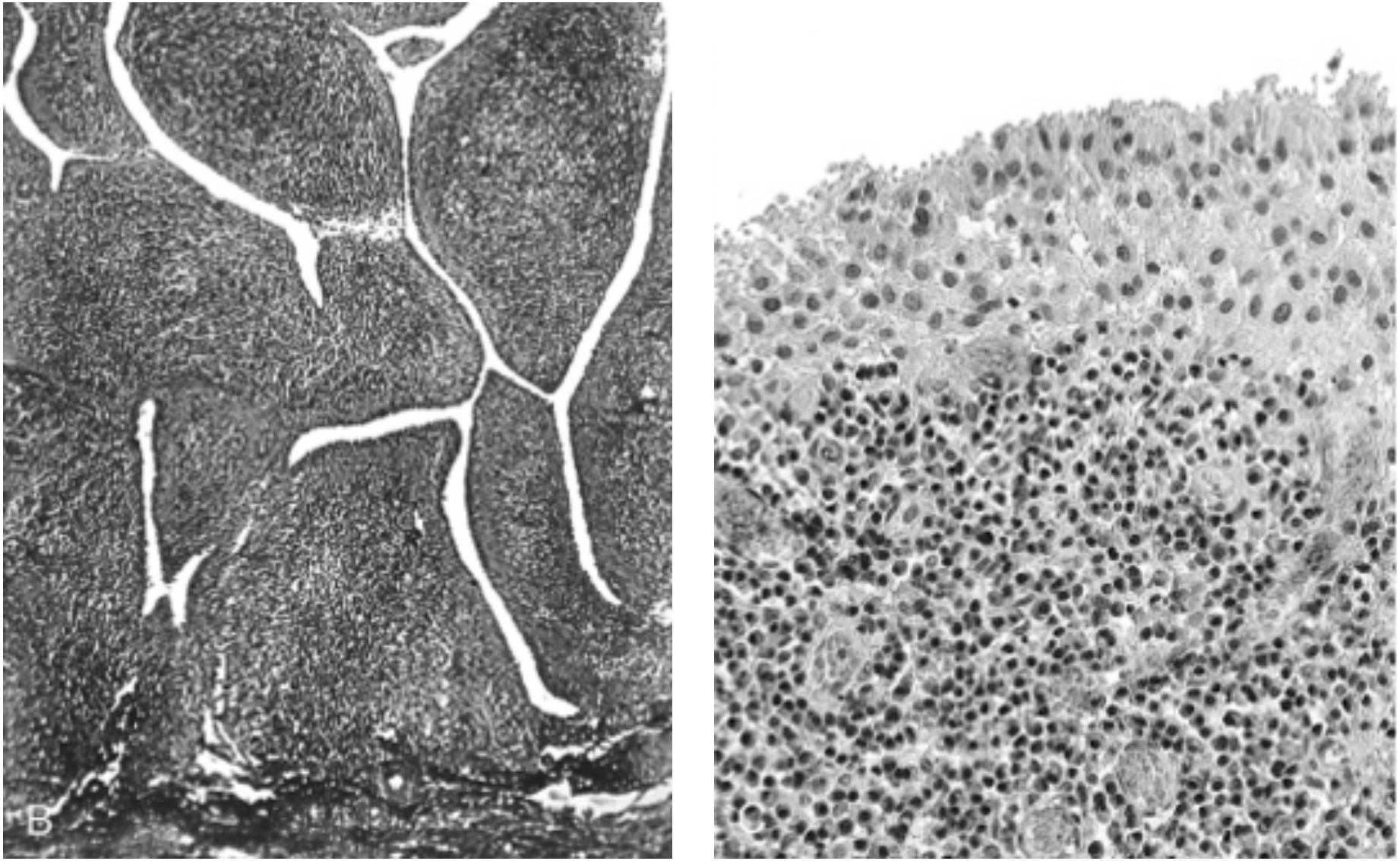
- Genetically predisposed patient
- Something (bug? self-Ag?) activates T cells
- T cells release cytokines:
  - activate macrophages (causing destruction)
  - cause B cells to make antibodies against joint
  - Most important of these cytokines: TNF
- Cytokines cause inflammation and tissue damage

RA Joint Disease

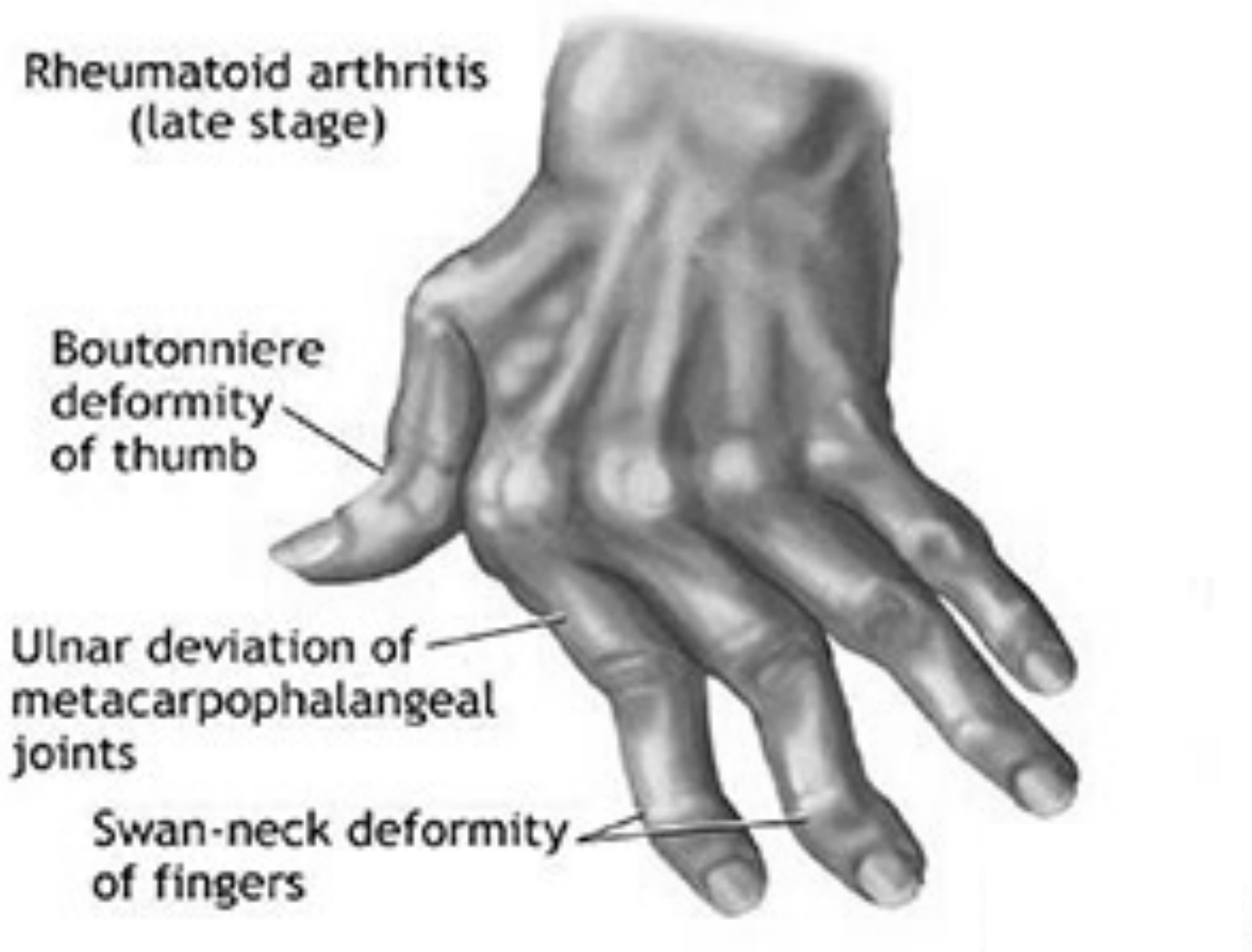
- Mainly small joints (hands), but also knees, elbows, shoulders
- Symmetric; characteristic hand features
- Chronic synovitis with pannus formation:
  - synovial cell proliferation
  - inflammation
  - granulation tissue



Rheumatoid arthritis joint lesion



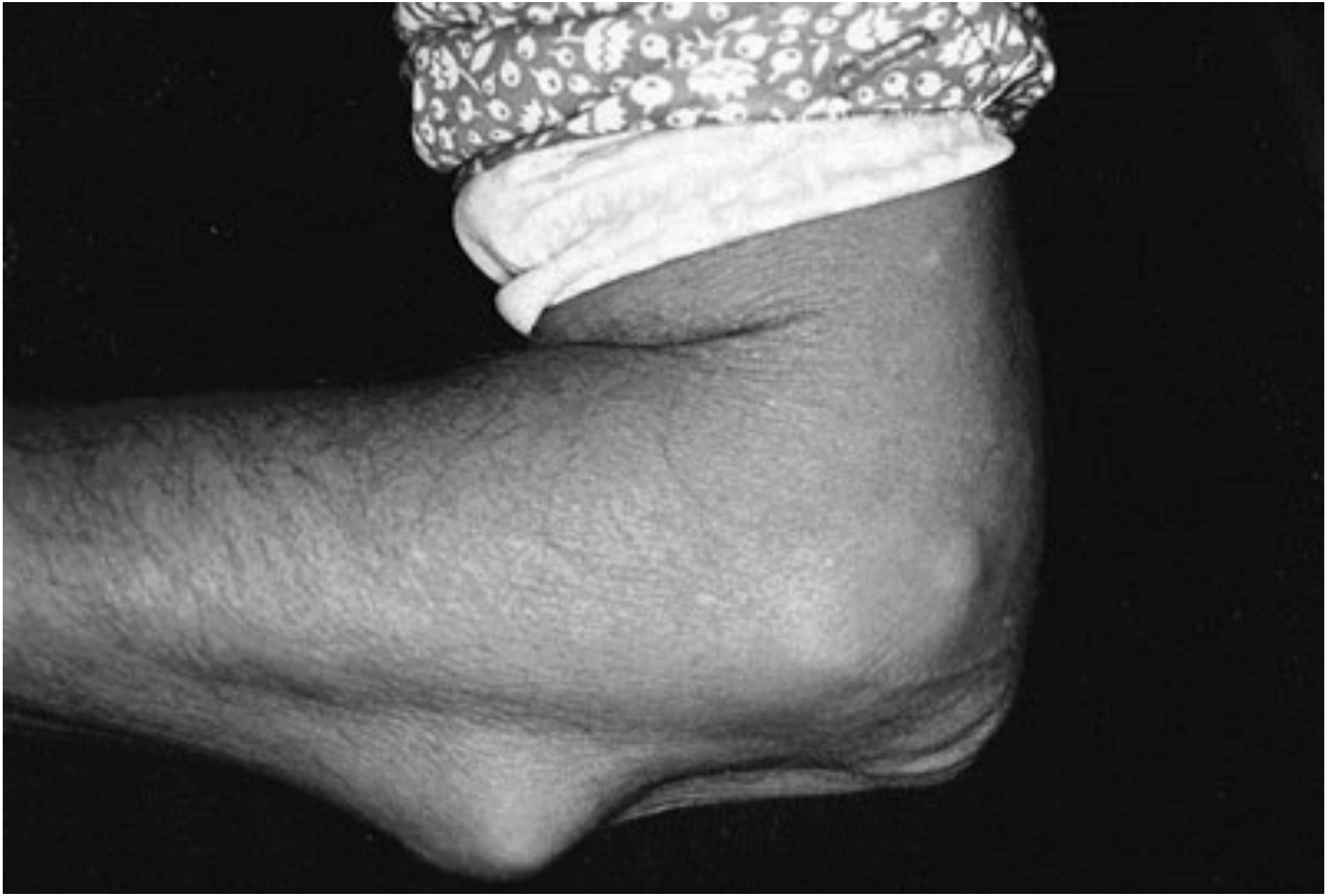
Rheumatoid arthritis: villi (L) and lymphoid aggregates (R)



Rheumatoid arthritis joint deformities

RA Systemic Disease

- Weakness, malaise, fever
- Vasculitis
- Pleuritis, pericarditis
- Lung fibrosis
- Eye changes
- Rheumatoid nodules on forearms



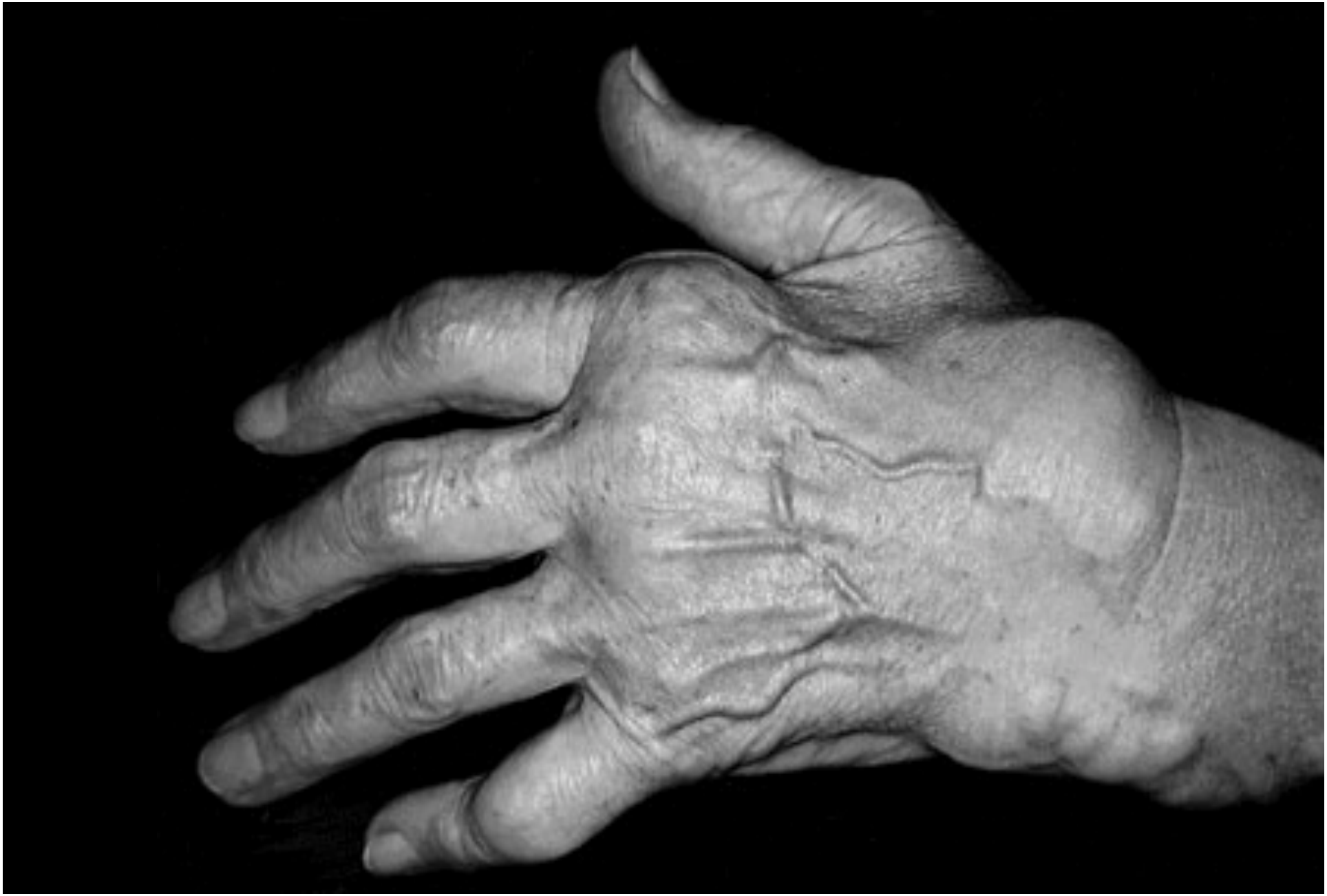
Rheumatoid nodules

Rheumatoid Factor

- Circulating IgM antibody
- Directed against patient's OWN IgG!
- Forms IgM-IgG immune complexes, which deposit in joints and cause badness
- Present in 80% of patients

RA: Things a Dentist Might See

- Female patient with aching, stiff joints, especially in morning
- Symmetric joint swelling
- Fingers: ulnar deviation, swan-neck deformities, boutonniere deformities
- Rheumatoid nodules



Rheumatoid arthritis joint deformities

RA: Prognosis

- Variable!
- A few patients stabilize
- Most patients have chronic course with progressive joint destruction and disability
- Lifespan shortened by 10-15 years
- Treatment: steroids, anti-TNF agents

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases
  - Lupus
  - Rheumatoid arthritis
  - Sjögren syndrome

Sjögren Syndrome

Things You Must Know

- Inflammatory disease of salivary and lacrimal glands
- Dry eyes, dry mouth
- T cells react against some Ag (self? viral?) in gland; gland gets destroyed
- Increased risk of lymphoma

Sjögren Etiology

- CD4+ T cells attack self antigens in glands (why?!)
- Autoantibodies are present, but probably are not the primary cause of tissue injury
  - ANAs
  - RF
  - Anti-SS-A, anti-SS-B
- Viral trigger?
- Genetic predisposition

Sjögren Signs and Symptoms

Salivary and lacrimal glands

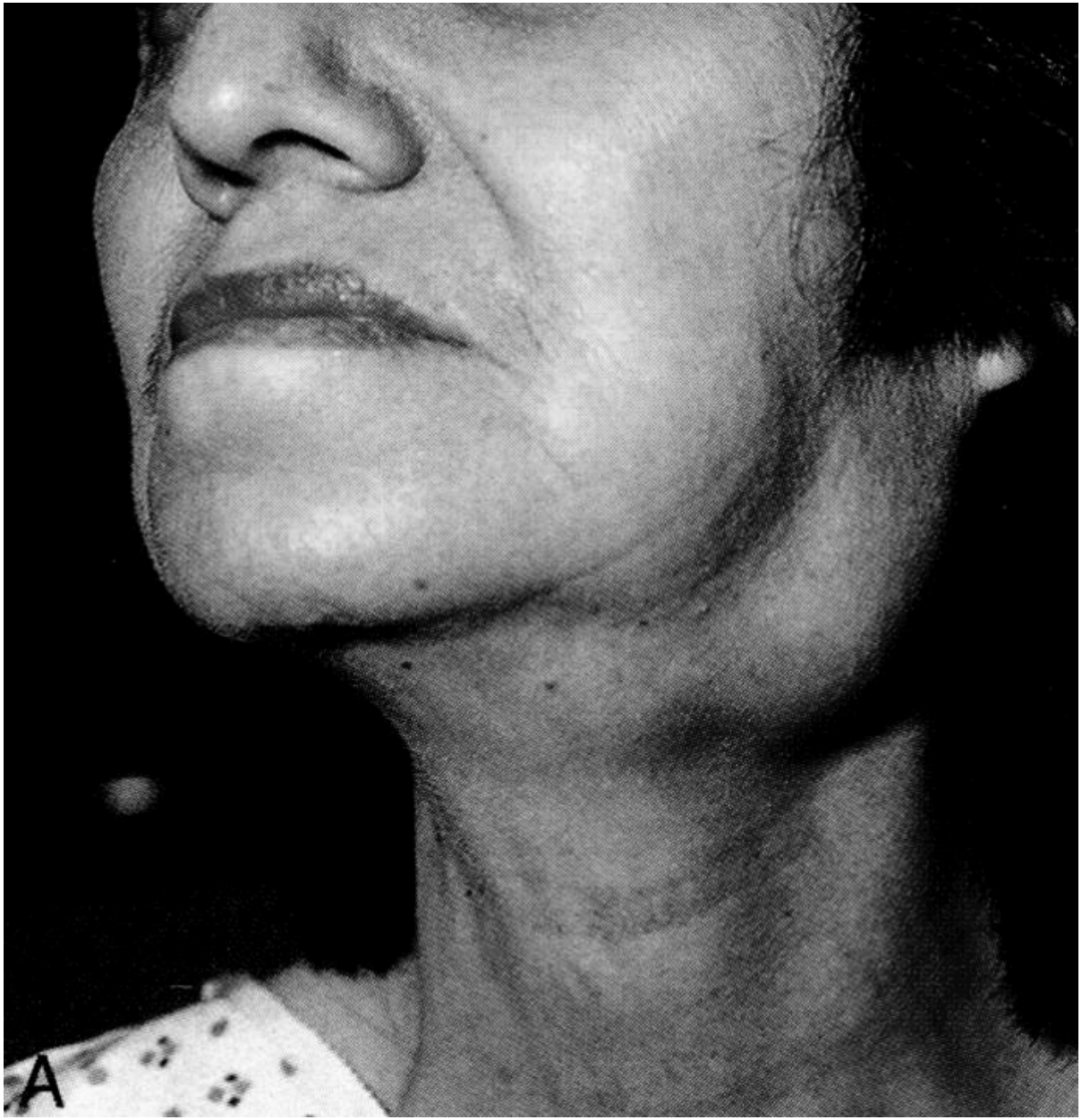
- enlarged
- marked inflammation and gland destruction
- 40x increased risk of lymphoma!

Systemic disease

- fatigue
- arthralgia/myalgia
- Raynaud phenomenon
- vasculitis
- peripheral neuropathy
- often, patient has another autoimmune disease too

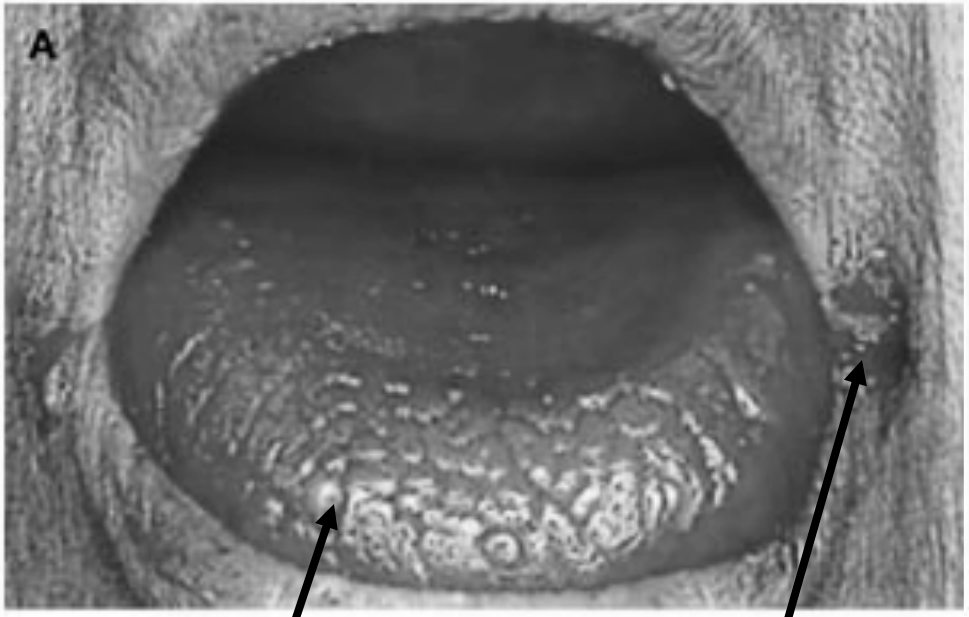
Sjögren: Things a Dentist Might See

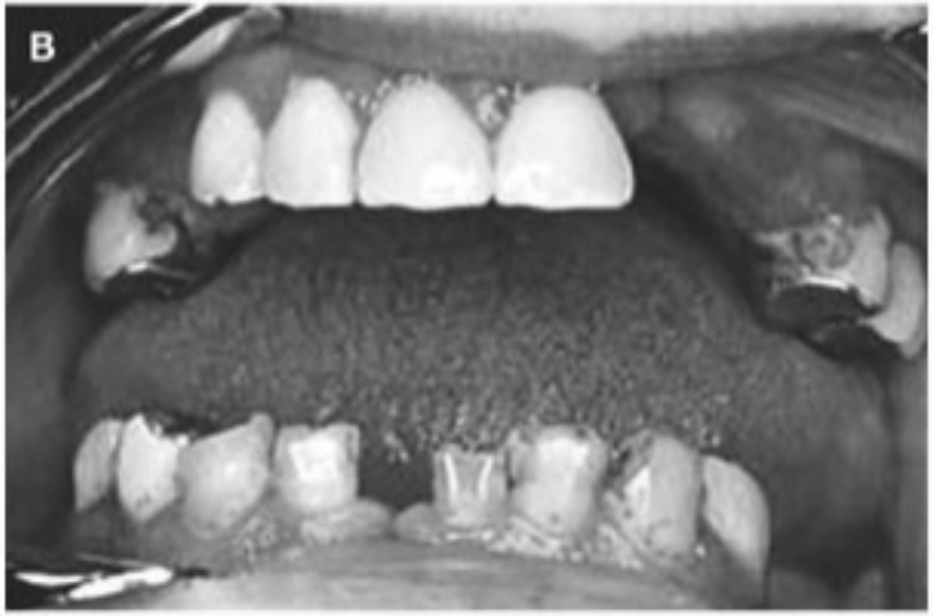
- Female between 35-45
- Enlarged salivary glands
- Raynaud phenomenon
- Keratoconjunctivitis sicca (dry eyes)
- Oral changes:
  - xerostomia (dry mouth)
  - mucosal atrophy
  - candidiasis
  - mucosal ulceration
  - dental caries
  - taste dysfunction



Sjögren syndrome: salivary gland enlargement

Oral changes in Sjögren Syndrome





atrophic papillae, deeply fissured epithelium

angular cheilitis

missing teeth and multiple caries

Sjögren Treatment

- Treatment is mostly supportive and symptom-based
- Oral treatment: adequate hydration, scrupulous dental hygiene, cholinergic agents (stimulate saliva release), frequent dental exams
- Eye treatment: lubricating solutions, surgical procedures
- Systemic symptom treatment: steroids, other immunosuppressive drugs

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases
  - Lupus
  - Rheumatoid arthritis
  - Sjögren syndrome
  - Scleroderma

Scleroderma (Systemic Sclerosis)

Things You Must Know

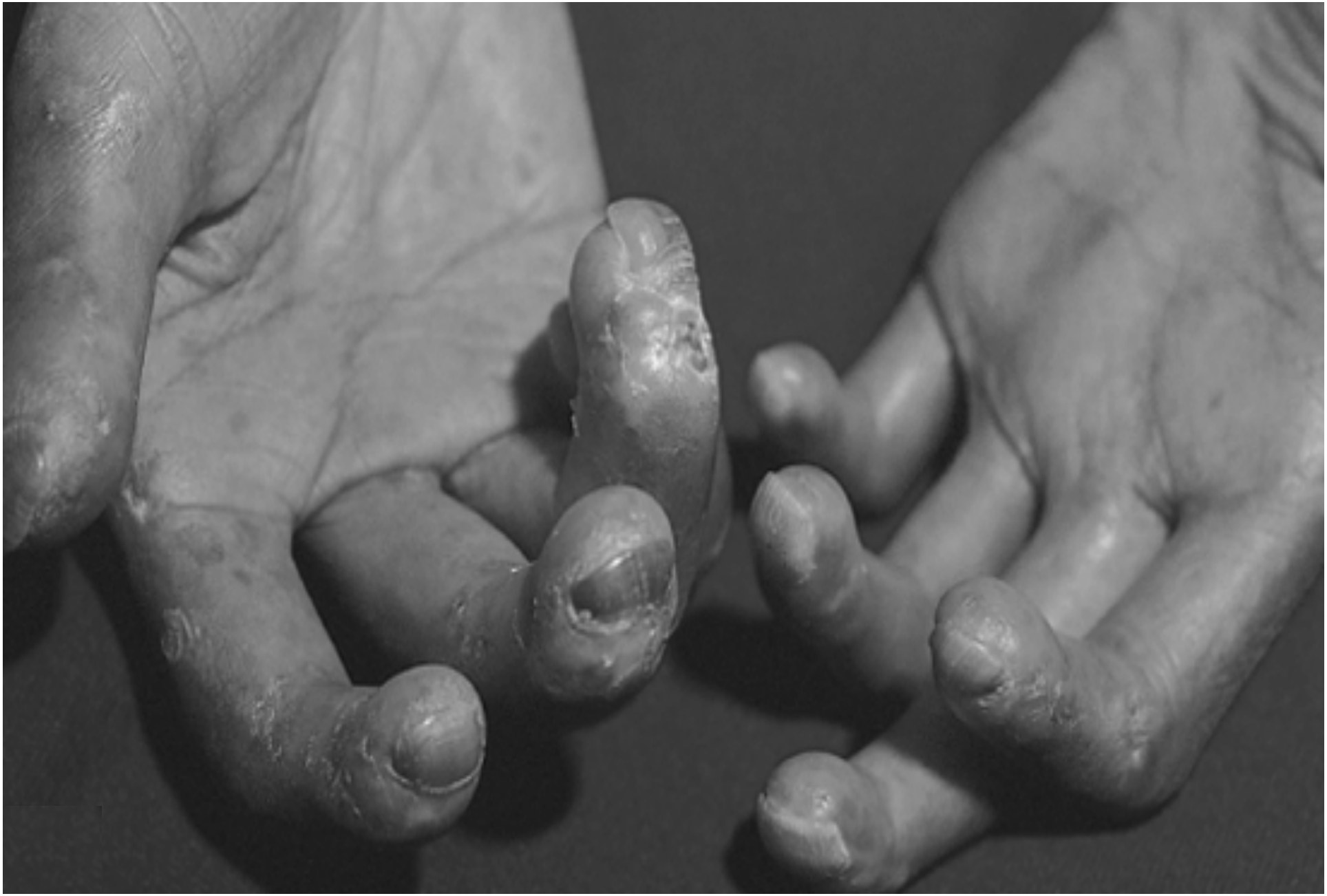
- Excessive fibrosis throughout body: skin, viscera
- Claw hands, mask-like face
- Microvascular disease also present
- Diffuse and limited types

Scleroderma Etiology

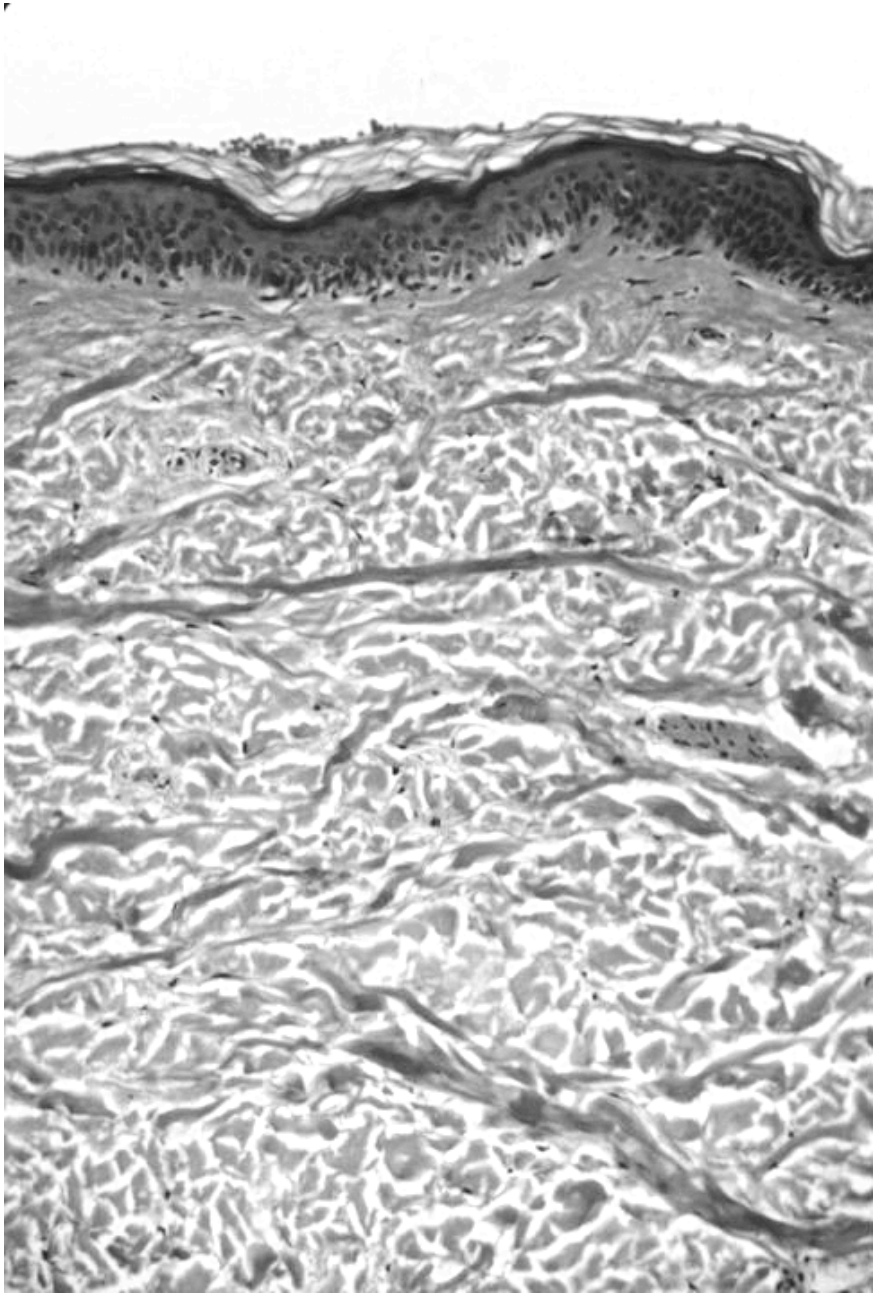
- CD4+ T cells accumulate for some reason
- T cells release cytokines that activate mast cells and macrophages, which release fibrogenic cytokines
- B cell activation also occurs (diagnostic antibody: anti-Scl 70) but doesn't play major role
- The cause of microvascular changes is unknown

Scleroderma Signs and Symptoms

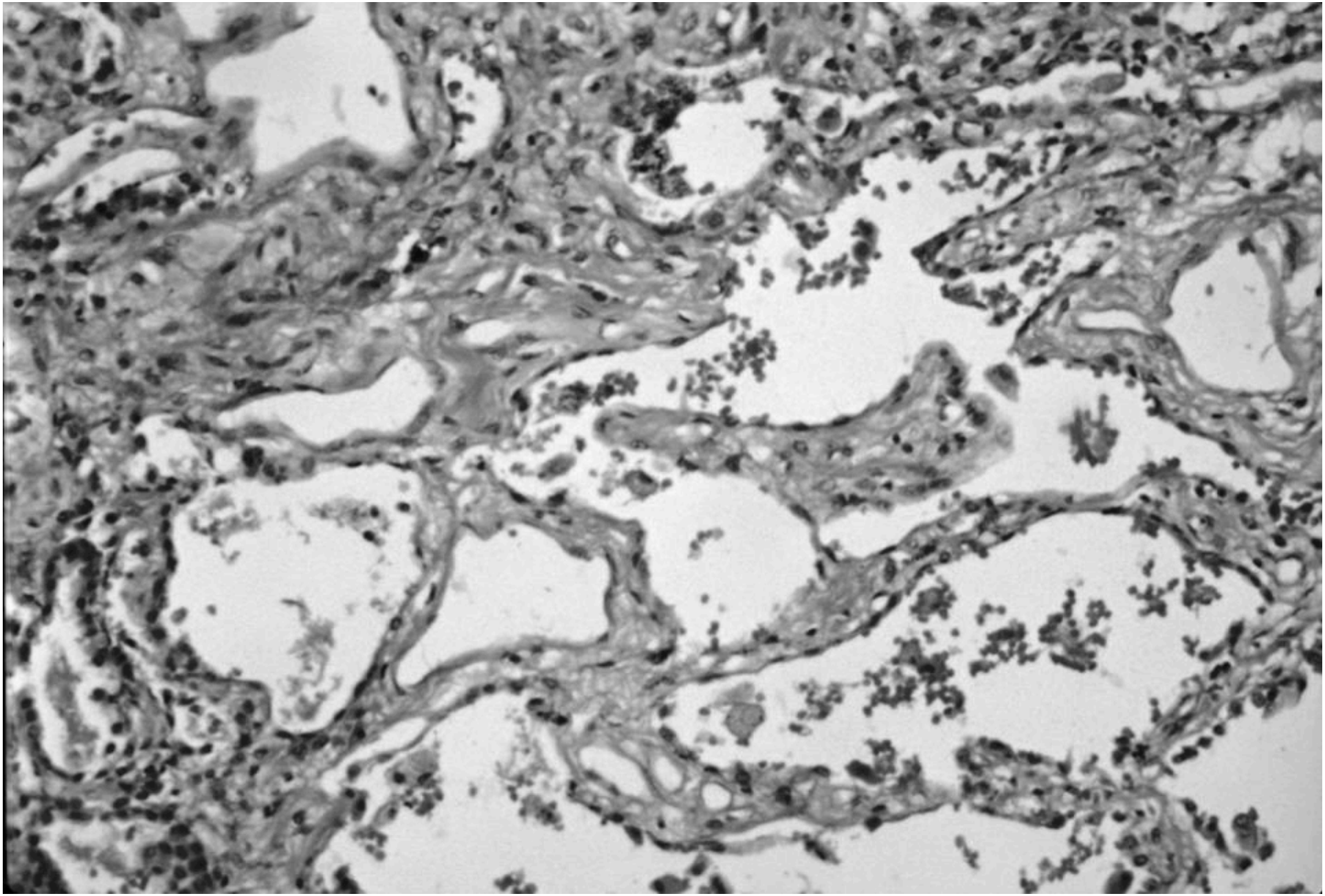
- Skin: diffuse, sclerotic atrophy. Fingers first.
- GI: “rubber-hose” lower esophagus
- Lungs: fibrosis, pulmonary hypertension
- Kidneys: narrowed vessels, hypertension
- Heart: myocardial fibrosis



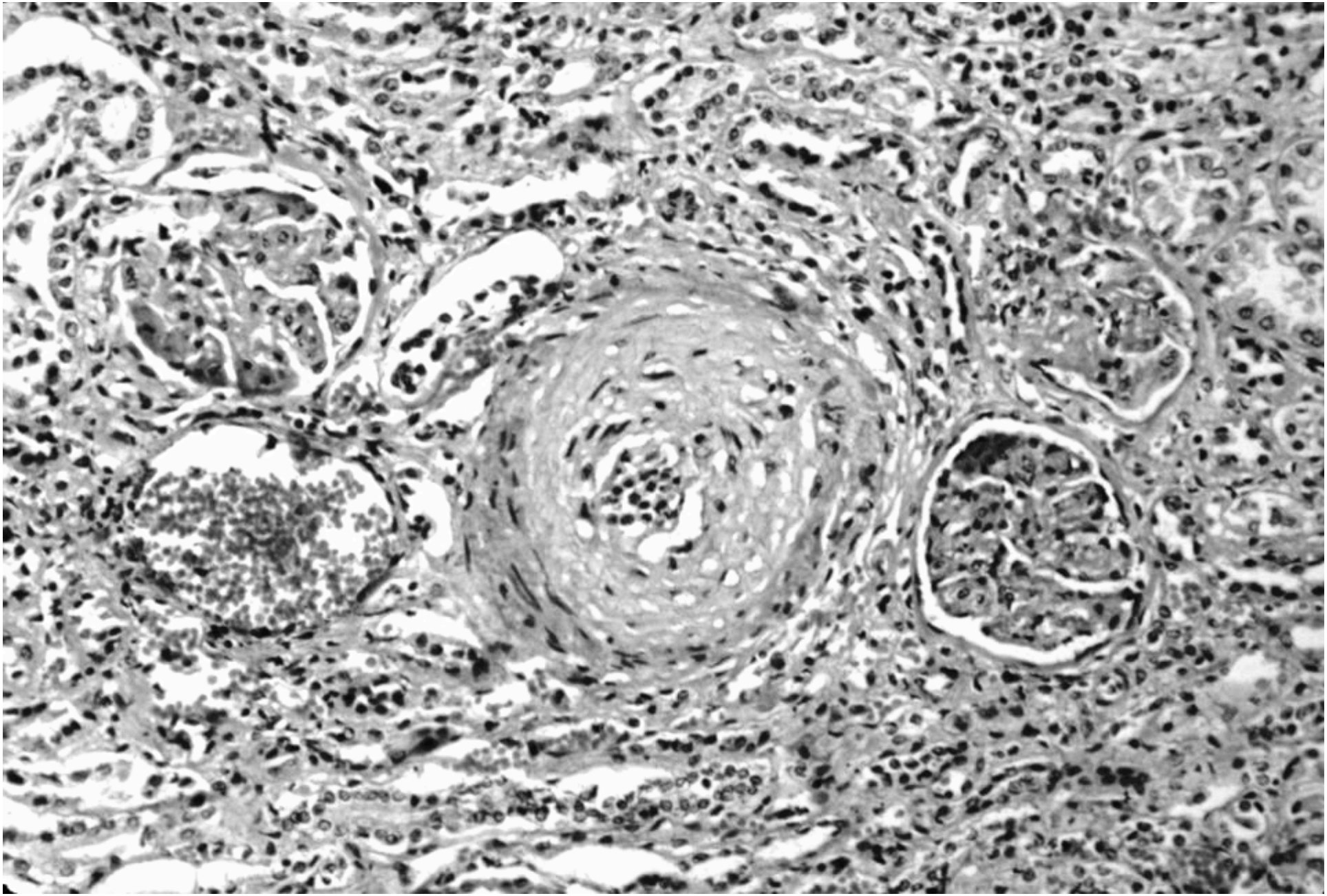
Scleroderma: claw hands



Scleroderma: sclerotic skin



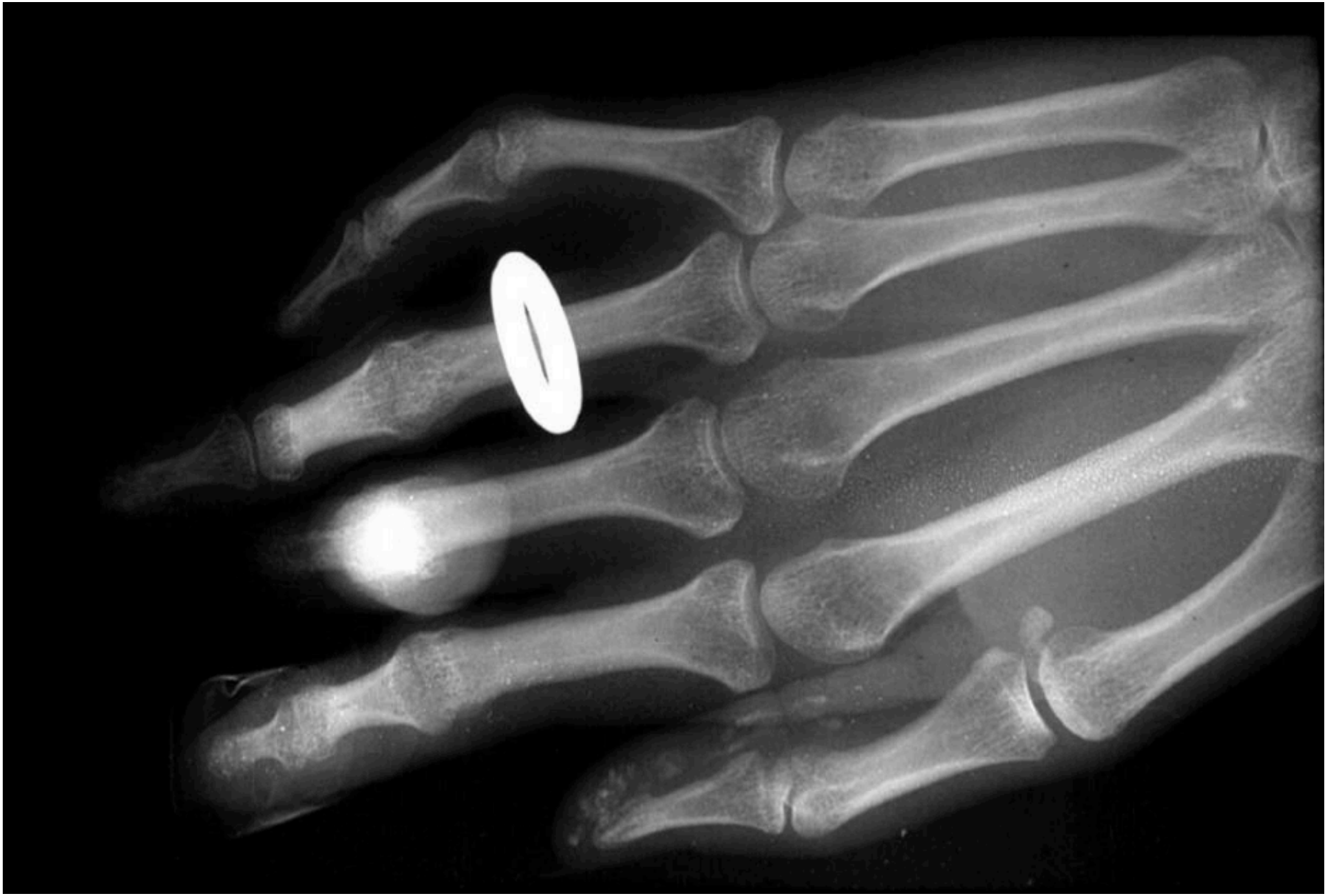
Scleroderma: fibrosis in alveolar walls



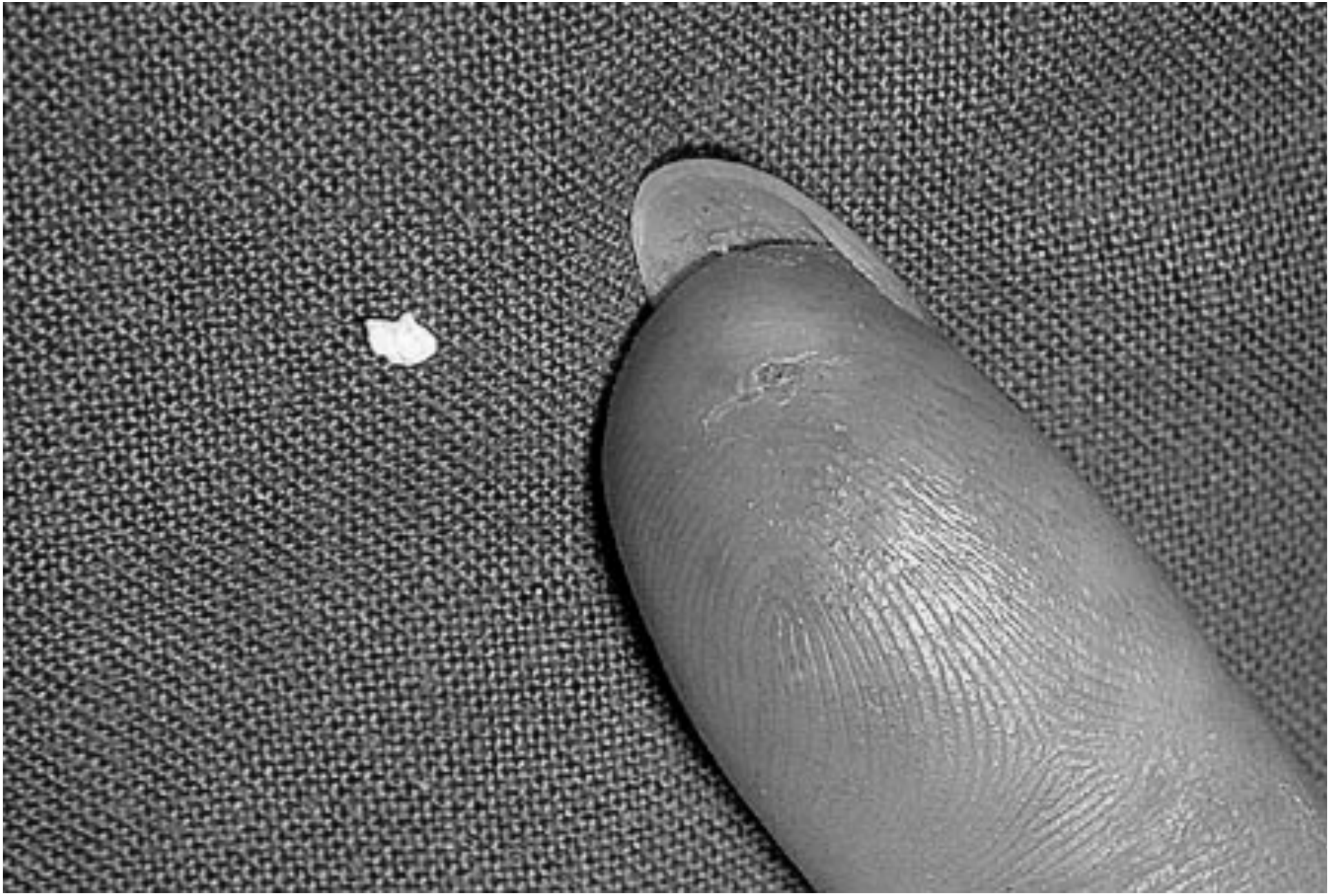
Scleroderma: narrowed renal vessel

Scleroderma: Limited Type

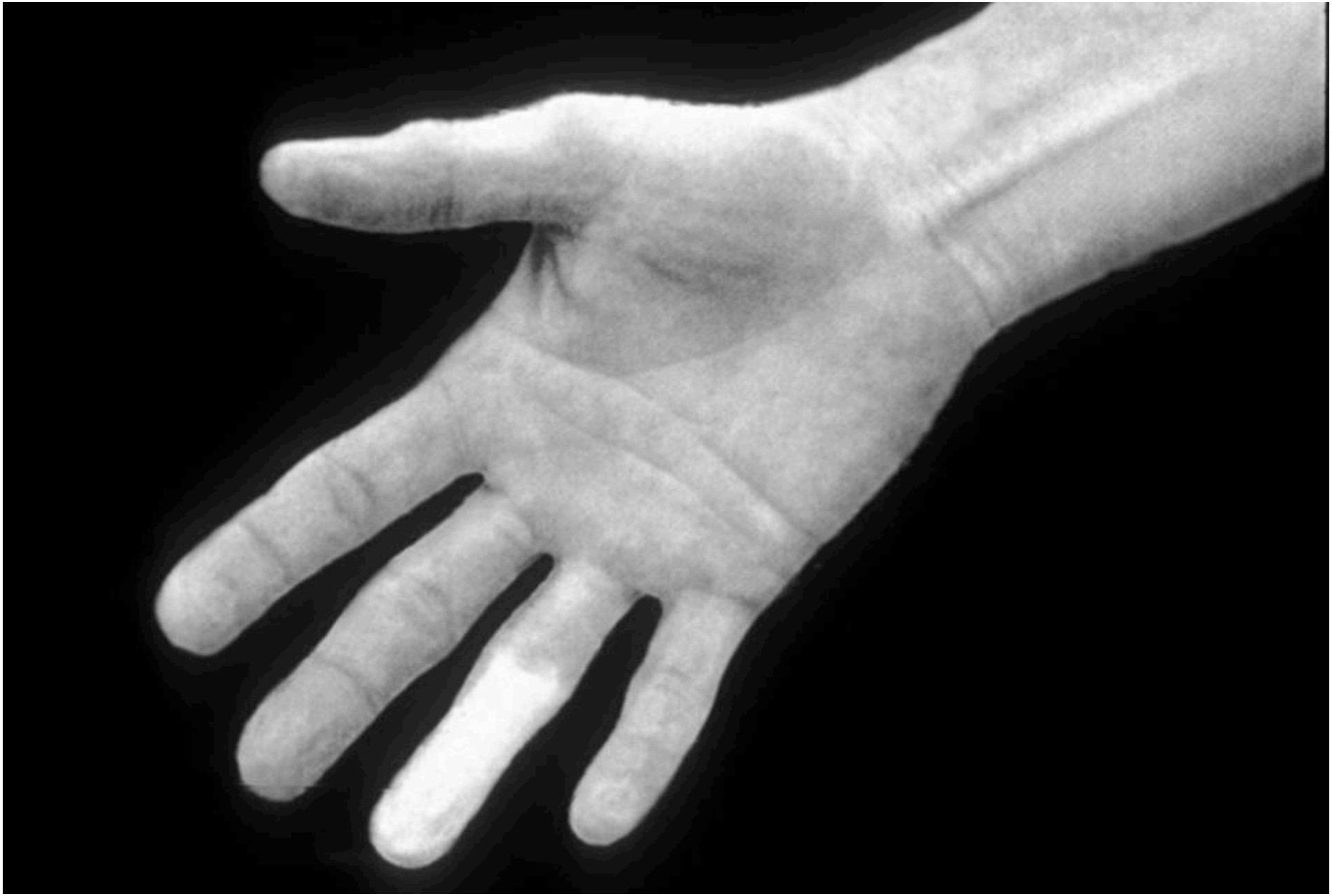
- Mild skin involvement (face, fingers)
- Involvement of viscera occurs later
- Also called CREST syndrome
  - Calcinosis
  - Raynaud phenomenon
  - Esophageal dysmotility
  - Sclerodactyly
  - Telangiectasia
- Benign course



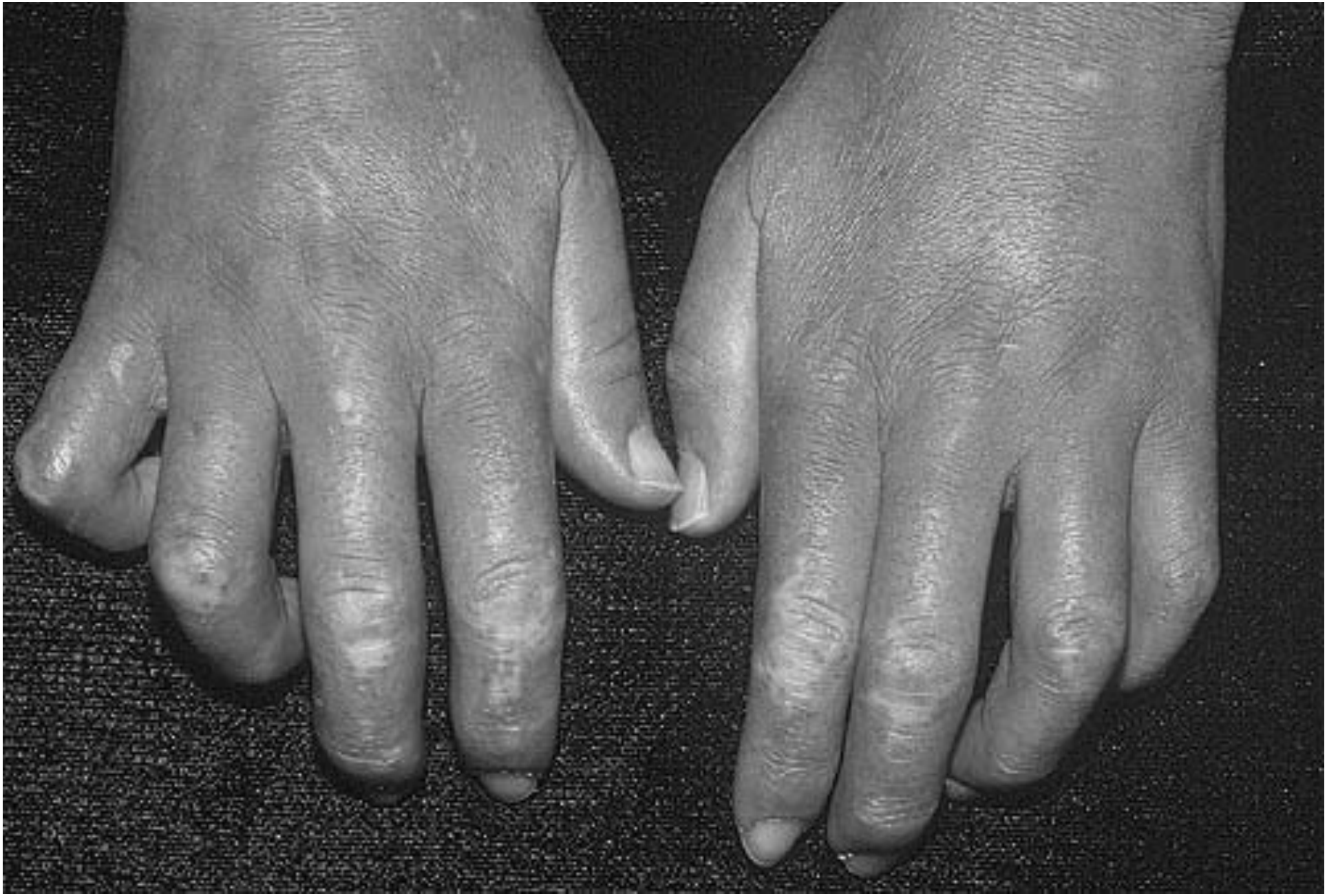
Scleroderma: calcinosis



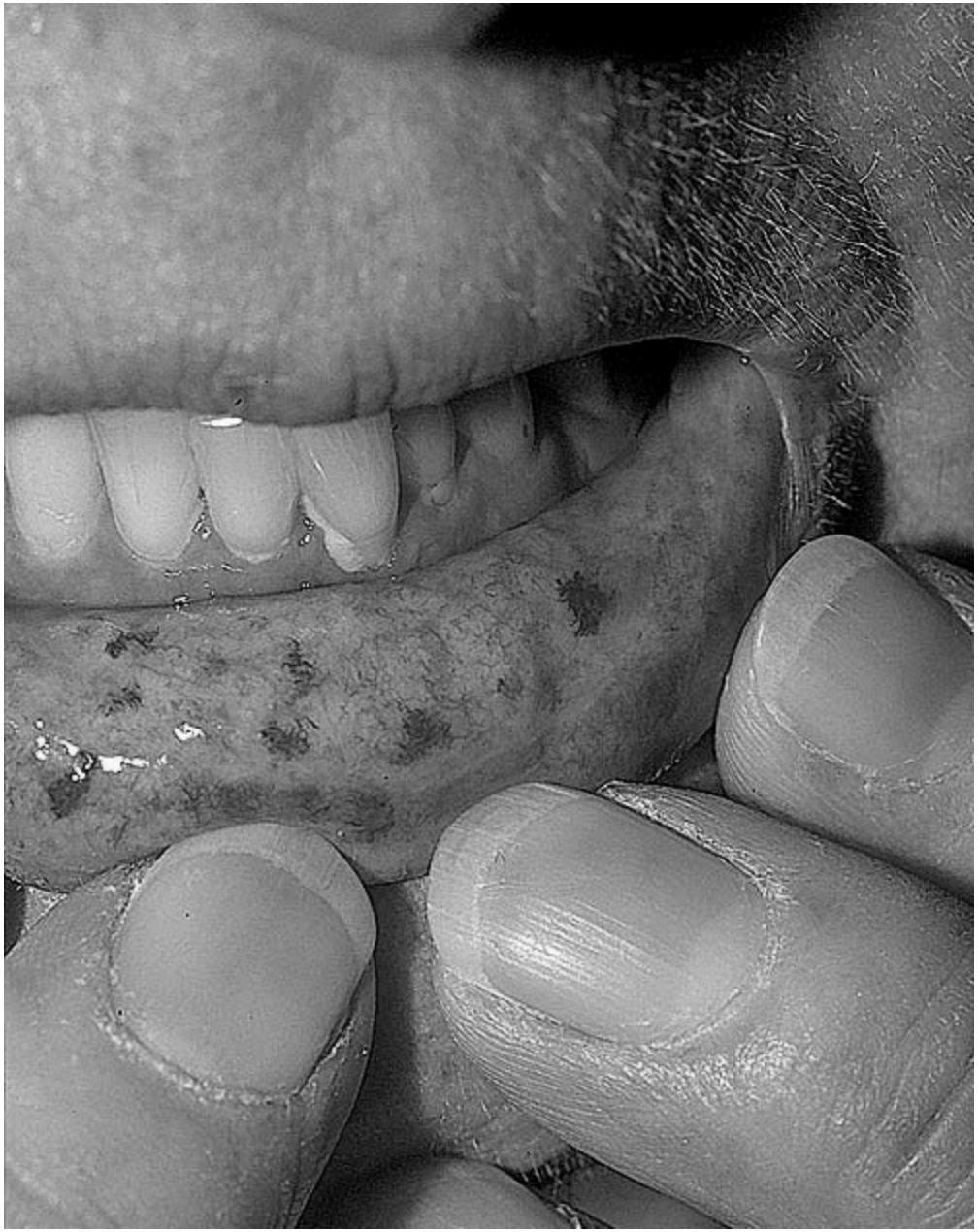
Scleroderma: calcinosis



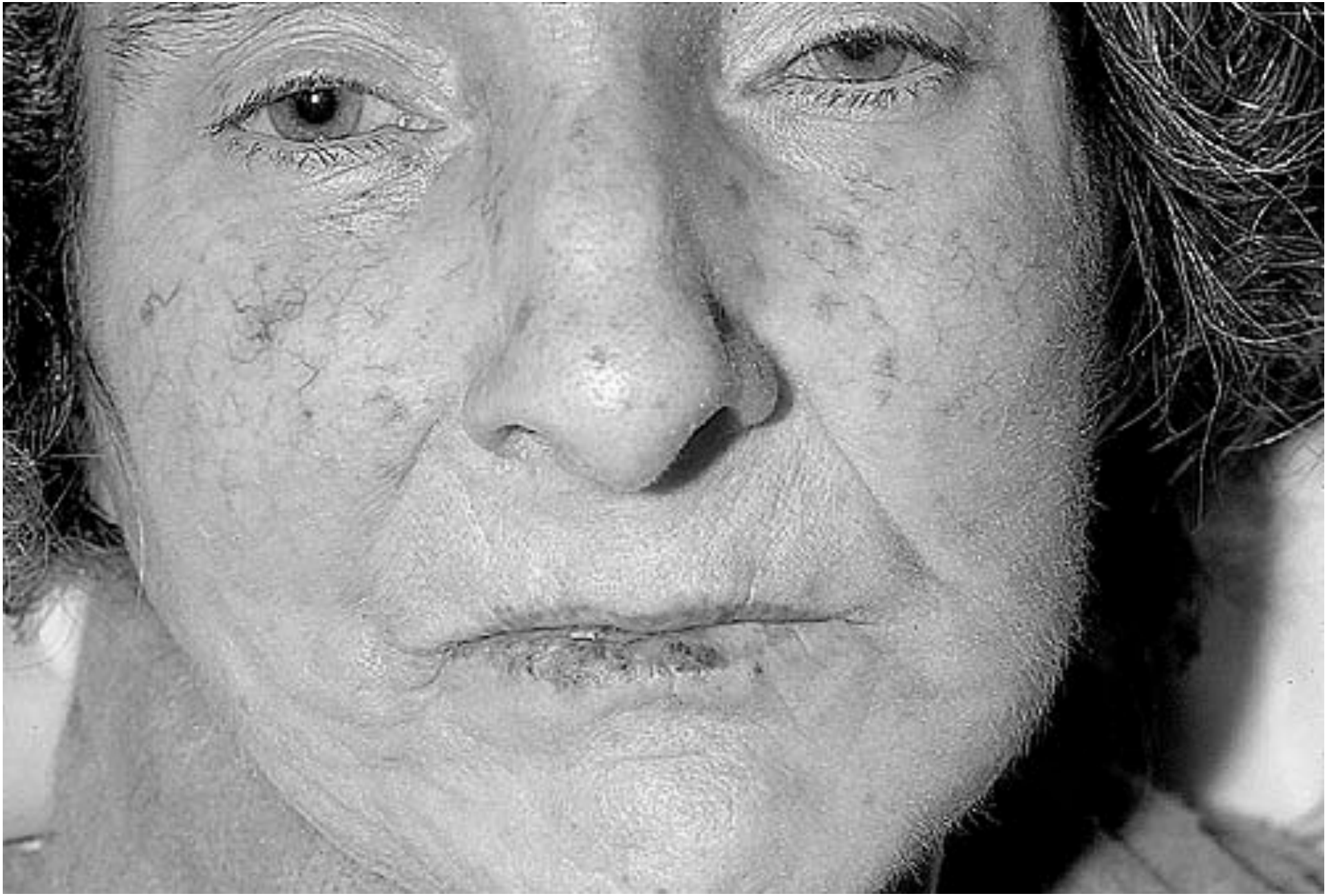
Scleroderma: Raynaud phenomenon



Scleroderma: sclerodactyly



Scleroderma: telangiectasias



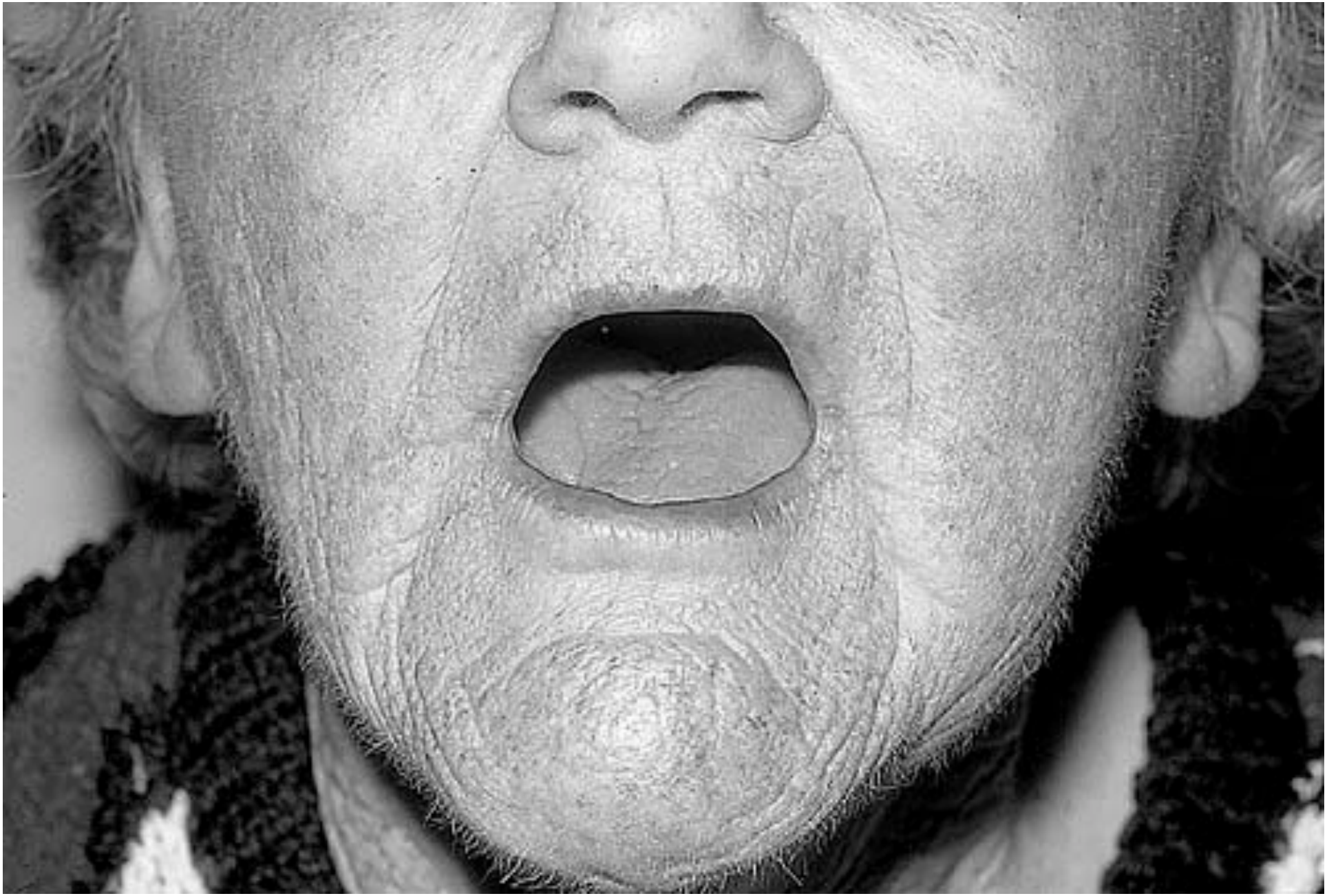
Scleroderma: telangiectasias

Scleroderma: Diffuse Type

- Initial widespread skin involvement
- Early visceral involvement
- Rapid course

Scleroderma: Things a Dentist Might See

- Female between 50-60
- Raynaud phenomenon
- Stiff, clawlike fingers
- Mask-like face
- Difficulty swallowing
- Dyspnea, chronic cough
- Difficulty getting dentures in



Scleroderma: restricted mouth opening

Scleroderma Prognosis

- Steady, slow, downhill course over years
- Limited scleroderma may exist for decades without progressing
- Diffuse scleroderma is more common and has worse prognosis
- Overall 10-year survival = 35-70%

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

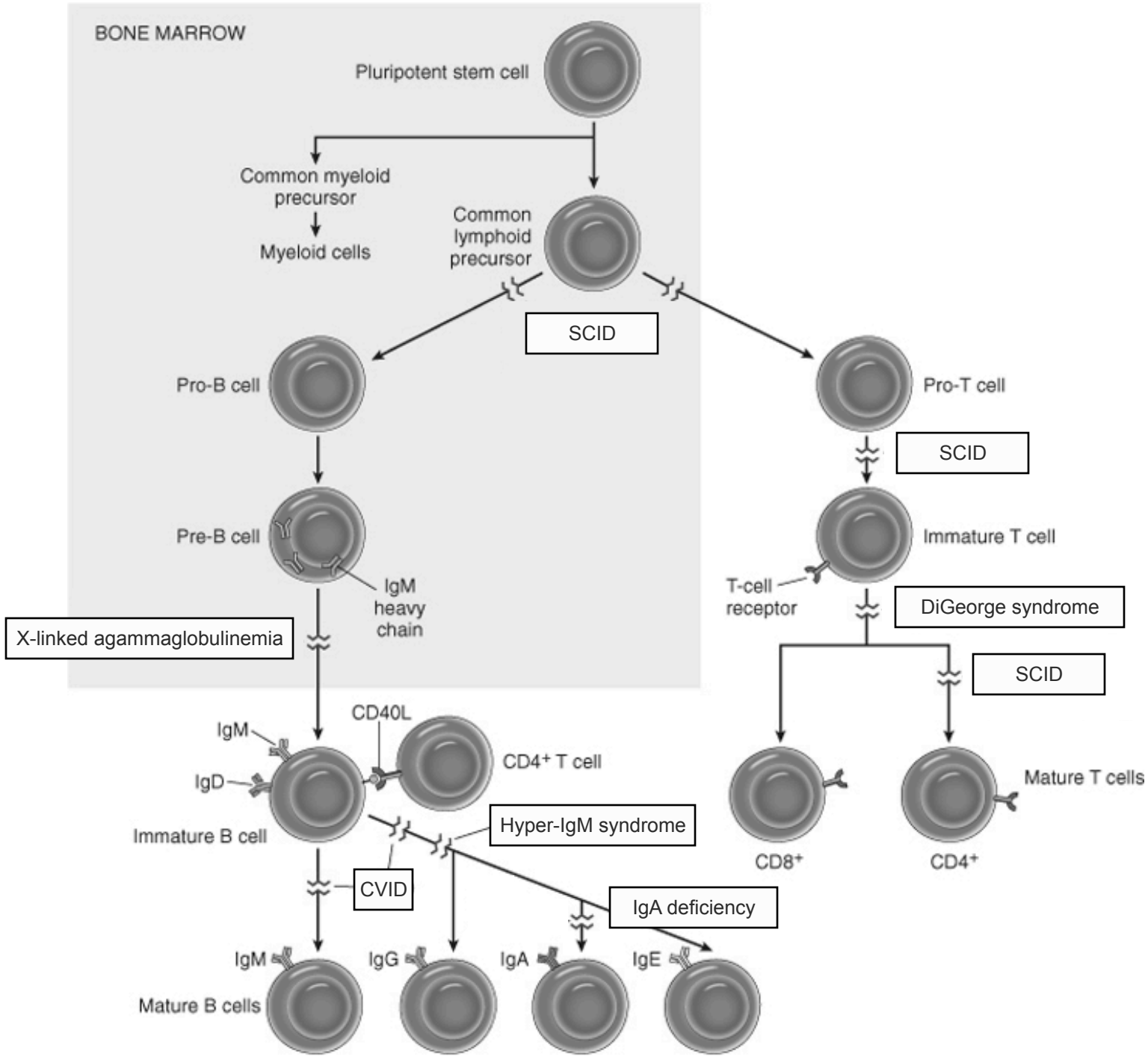
- Basic concepts

Basic Concepts

- Immune deficiencies
  - primary (inherited)
  - secondary (to infection, immunosuppression, etc.)
- Patients more susceptible to infections and cancer
- Type of infection varies:
  - Ig, C' or phagocytic cell defect: bacterial infection
  - T cell defect: viral and fungal infections
- This lecture covers primary immune deficiencies

Primary Immune Deficiencies

- Rare!
- Genetic
- Can affect any part of immune system:
  - Adaptive (humoral or cellular)
  - Innate (C', phagocytes, NK cells)
- Typical patient: infant with recurrent infections
- Primary importance for our class: boards


BONE MARROW
Pluripotent stem cell
Common myeloid precursor
Myeloid cells
Common lymphoid precursor
SCID
Pro-B cell
Pro-T cell
SCID
Pre-B cell
IgM heavy chain
Immature T cell
T-cell receptor
DiGeorge syndrome
X-linked agammaglobulinemia
SCID
IgM
IgD
CD40L
CD4+ T cell
Immature B cell
Hyper-IgM syndrome
CD8+
CD4+
Mature T cells
CVID
IgA deficiency
IgM
IgG
IgA
IgE
Mature B cells

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases
  - X-linked agammaglobulinemia

X-Linked Agammaglobulinemia

- Pre-B cells can't differentiate into B cells
- Patients have no immunoglobulin
- Affects males
- Presents at 6 months of age (maternal Ig gone)
- Recurrent bacterial infections
- Treatment: intravenous pooled human Ig

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases
  - X-linked agammaglobulinemia
  - Common variable immunodeficiency

Common Variable Immunodeficiency

- Group of disorders characterized by defective antibody production
- Affects males and females equally
- Presents in teens or twenties
- Basis of Ig deficiency is variable (hence the name) and often unknown
- Patients more susceptible to infections, but also to autoimmune disorders and lymphoma!

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases
  - X-linked agammaglobulinemia
  - Common variable immunodeficiency
  - Isolated IgA deficiency

Isolated IgA Deficiency

- Most common of all primary immune deficiencies
- Cause is unknown
- Most patients asymptomatic
- Some patients get recurrent sinus/lung infections or diarrhea (IgA is the major Ig in mucosal secretions)
- Possible anaphylaxis following blood transfusion (patients have anti-IgA antibodies, and there is IgA in transfused blood!)
- Increased incidence of autoimmune disease (who knows why)

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases
  - X-linked agammaglobulinemia
  - Common variable immunodeficiency
  - Isolated IgA deficiency
  - Hyper-IgM Syndrome

Hyper-IgM Syndrome

- Patients make normal (or even increased) amounts of IgM
- But can't make IgG, IgA, or IgE!
- X-linked in most cases
- Patients also have a defect in cell-mediated immunity
- Patients have recurrent bacterial infections and infections with intracellular pathogens (Pneumocystis jiroveci)

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases
  - X-linked agammaglobulinemia
  - Common variable immunodeficiency
  - Isolated IgA deficiency
  - Hyper-IgM Syndrome
  - DiGeorge Syndrome

DiGeorge Syndrome

- Developmental malformation affecting 3rd and 4th pharyngeal pouches
- Thymus doesn't develop well
- Patients don't have enough T cells
- Infections: viral, fungal, intracellular pathogens
- Patients may also have parathyroid hypoplasia
- Treatment: thymus transplant!

Immune Diseases Outline

Autoimmune diseases

- Immunologic tolerance and autoimmunity
- Specific diseases

Primary immune deficiencies

- Basic concepts
- Specific diseases
  - X-linked agammaglobulinemia
  - Common variable immunodeficiency
  - Isolated IgA deficiency
  - Hyper-IgM Syndrome
  - DiGeorge Syndrome
  - Severe combined immunodeficiency

Severe Combined Immunodeficiency

- Group of syndromes with both humoral and cell-mediated immune defects
- Patients get all kinds of infections
- Lots of very different genetic defects
- Half of cases are X-linked
- Treatment: bone marrow transplantation

Immune Diseases Outline

Disease	Transmission	Defect	Clinical stuff
XLA	X-linked	No mature B cells; no Ig	Infant with recurrent bacterial infections
CVID			
IgA deficiency			
Hyper-IgM			
DiGeorge			
SCID			