Block N

By Fatima Haider

KGMC - 5

Never let Monkeys Eat Bananas

Neutrophils

Lymphocytes

Monocytes

Eosinophils

Basophils

Normal ranges

WBC count	4-11	x 10^9/L

Cells	Differential count %	Absolute count (x10^9/L)
Neutrophils	50-70	1.5-6.5
Lymphocyte	20-44	1.2-3.4
Monocytes	2-9	0.1-0.6
Bands	0-6	0-0.7
Eosinophils	0-5	0-0.5
Basophils	0-2	0-0.2

- Drug-induced agranulocytosis (~ 70% of cases) [22][23]
  - Immune-mediated mechanism (type II hypersensitivity reaction): Drugs or drug-protein complexes stimulate the development of antibodies against granulocytes.
  - Drug toxicity mechanism: direct damage to myeloid precursors
    - Antithyroid drugs: propylthiouracil, methimazole, carbimazole, thiamazole
    - Antiinflammatory drugs: sulfasalazine, NSAIDs
    - Antibiotics: trimethoprim-sulfamethoxazole, dapsone
    - Antipsychotic drugs: clozapine
    - Anticonvulsants: carbamazepine, valproate, phenytoin, ethosuximide
    - Cardiovascular drugs: ticlopidine, antiarrhythmics (procainamide, flecainide)
    - Antifungal agents: amphotericin B, flucytosine
    - Other: colchicine, ganciclovir
    - Chemotherapeutic agents
- Drug-independent agranulocytosis (~ 30% of cases) [22]
  - Bone marrow disorders and malignancies : aplastic anemia, leukemia, myelodysplastic syndromes, vitamin B_{12} deficiency, folate deficiency
  - Peripheral granulocyte destruction: hypersplenism, autoimmune diseases

- **Clinical features:** triad of aphthous stomatitis, sore throat (agranulocytic angina), and fever

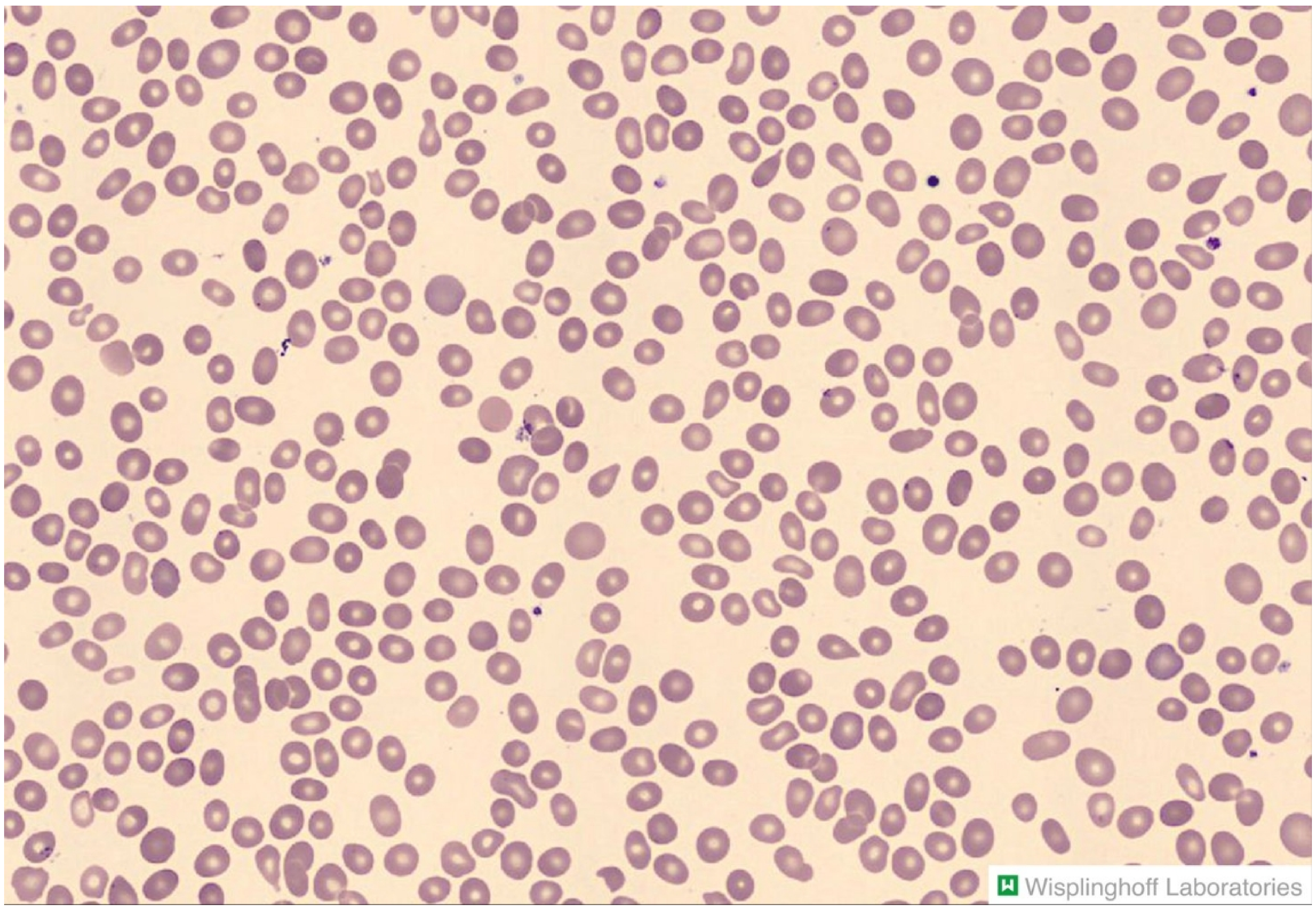
CD4/CD8 ratio

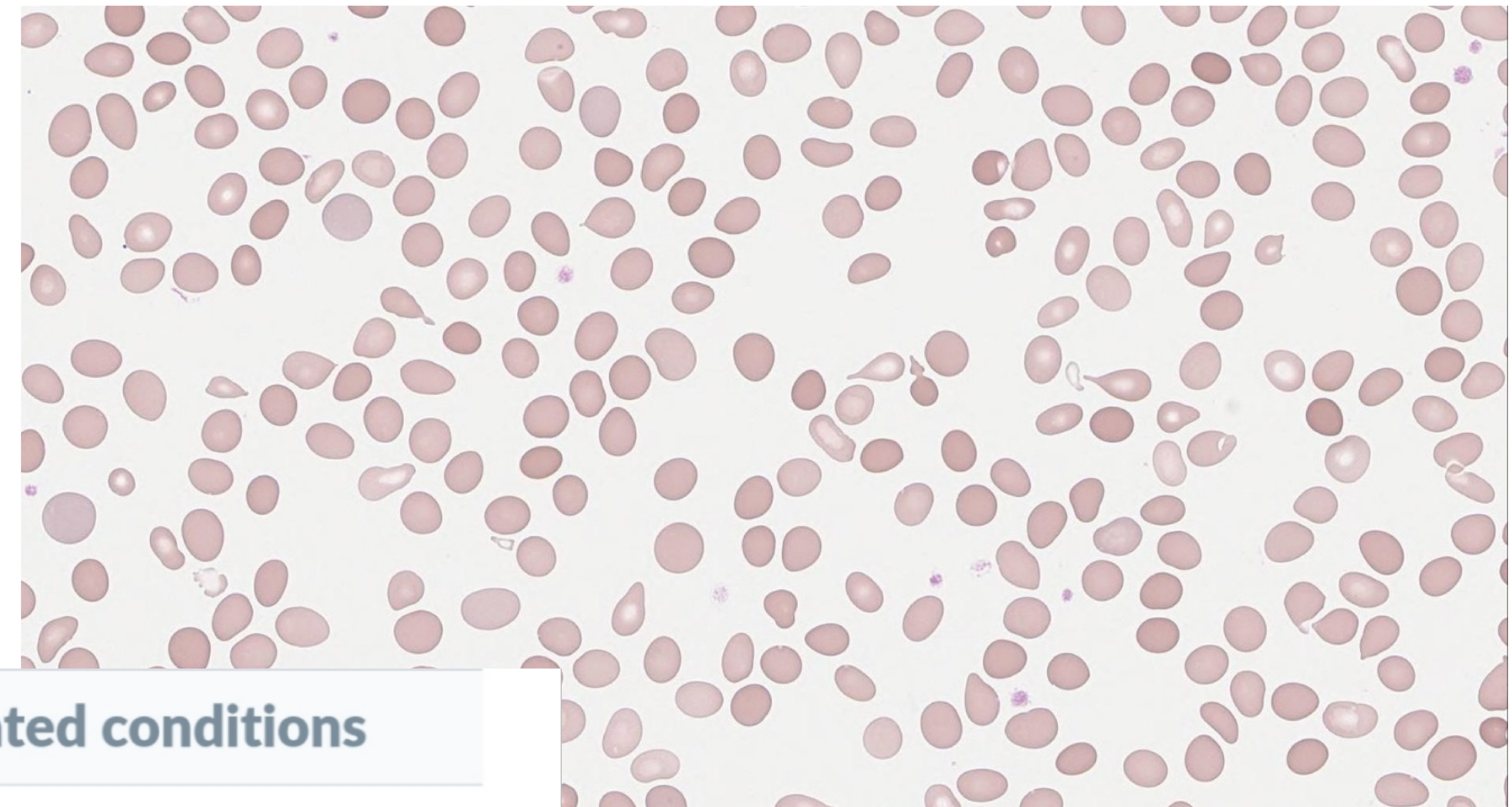
- **Definition**: $CD4^+$ T cell levels divided by $CD8^+$ T cell levels
- **Interpretation**
  - ↑ CD4/CD8 ratio associated with:
    - Sarcoidosis
    - Crohn disease
    - Some vasculitides and collagenases (e.g., granulomatosis with polyangiitis)
  - ↓ CD4/CD8 ratio associated with
    - HIV
    - Extrinsic allergic alveolitis

Dysmorphic RBCs

* Dacryocytes → Teardrop cells
* Sickle Cells
* Schistiocytes → Fragmented RBCs
* Macrocytes / Megalocytes → Large, spherical
* Spherocytes → Small, spherical, no central pallor
* Elliptocytes → oval or elliptical
* Echinocytes (Burr cells)
* Target cells → Bullseye appearance
* Acanthocytes (Spur cells)
* Stomatocytes → Slit-like central pallor
* Degmacytes (bite cells)

Dacryocytes (Teardrop cells)

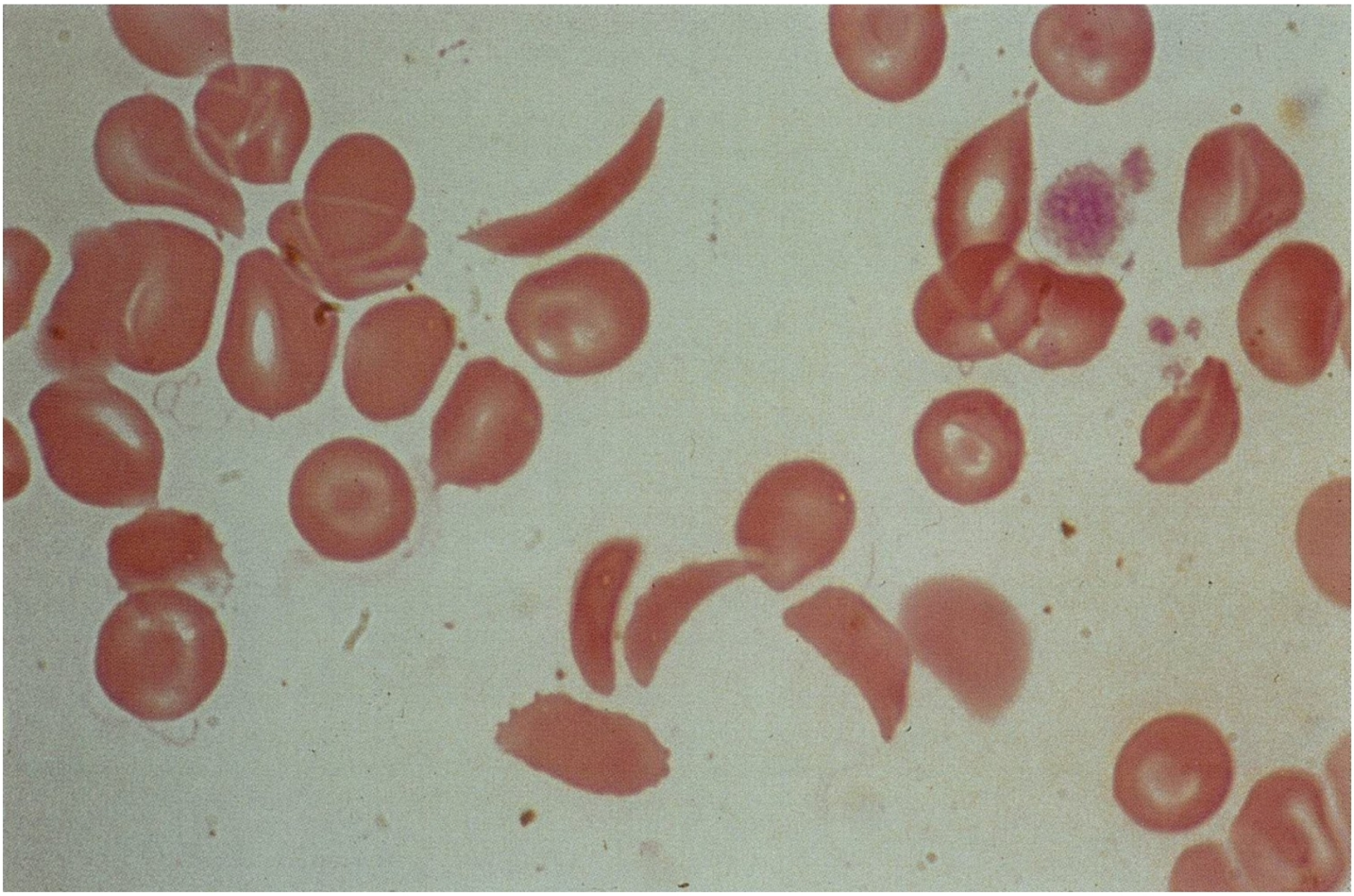




Associated conditions

- Extramedullary hematopoiesis
  - **Conditions associated with** bone marrow **infiltration** (e.g., **myelofibrosis**)
  - Thalassemia
  - Splenomegaly

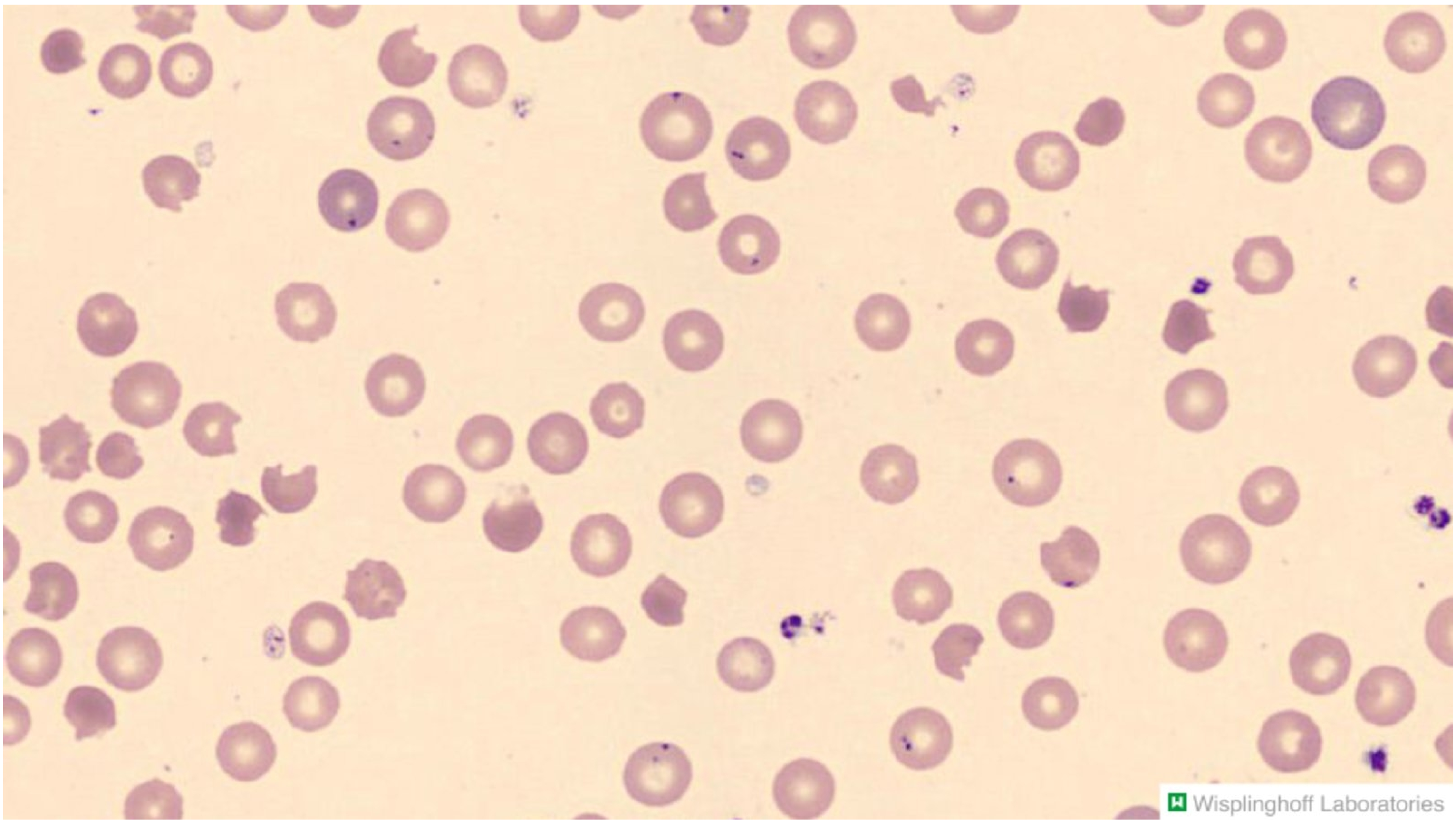
Sickle Cell disease



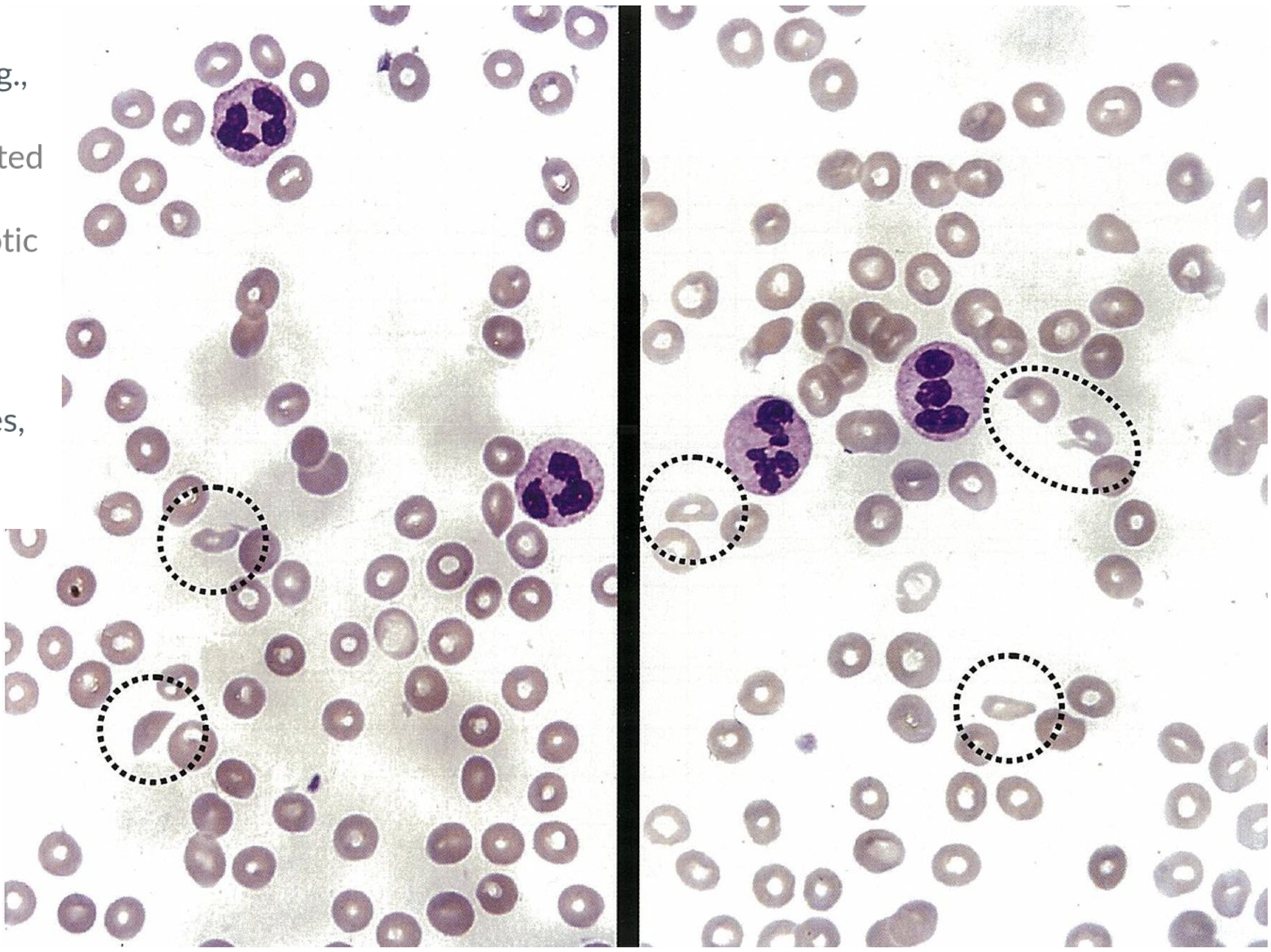
Sickle cell disease with drepanocytes and target cells - Photomicrograph of peripheral blood smear There are crescent to sickle-shaped erythrocytes (green overlay, black circles), which are referred to as drepanocytes or sickle cells. Erythrocytes with a red center and a white contouring ring (T), known as target cells, are visible on the left. Drepanocytes are pathognomonic of sickle cell disease. Target cells can be found in sickle cell disease and other hemoglobinopathies.

- **Sickle cell anemia**
  - Conditions associated with hypoxia (e.g., acidosis , high altitude) contribute to RBC sickling

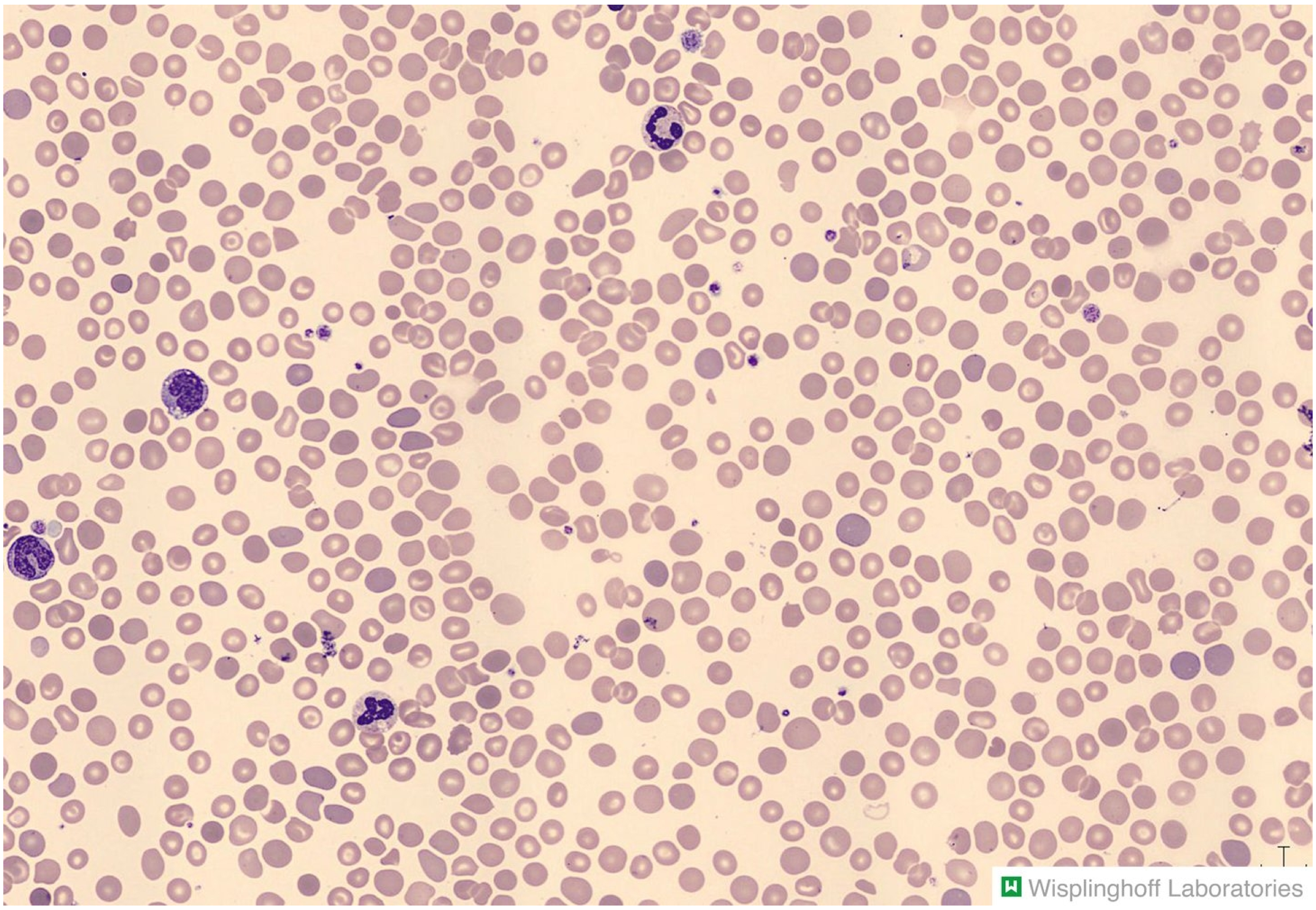
Schistiocytes (Fragmented RBCs)



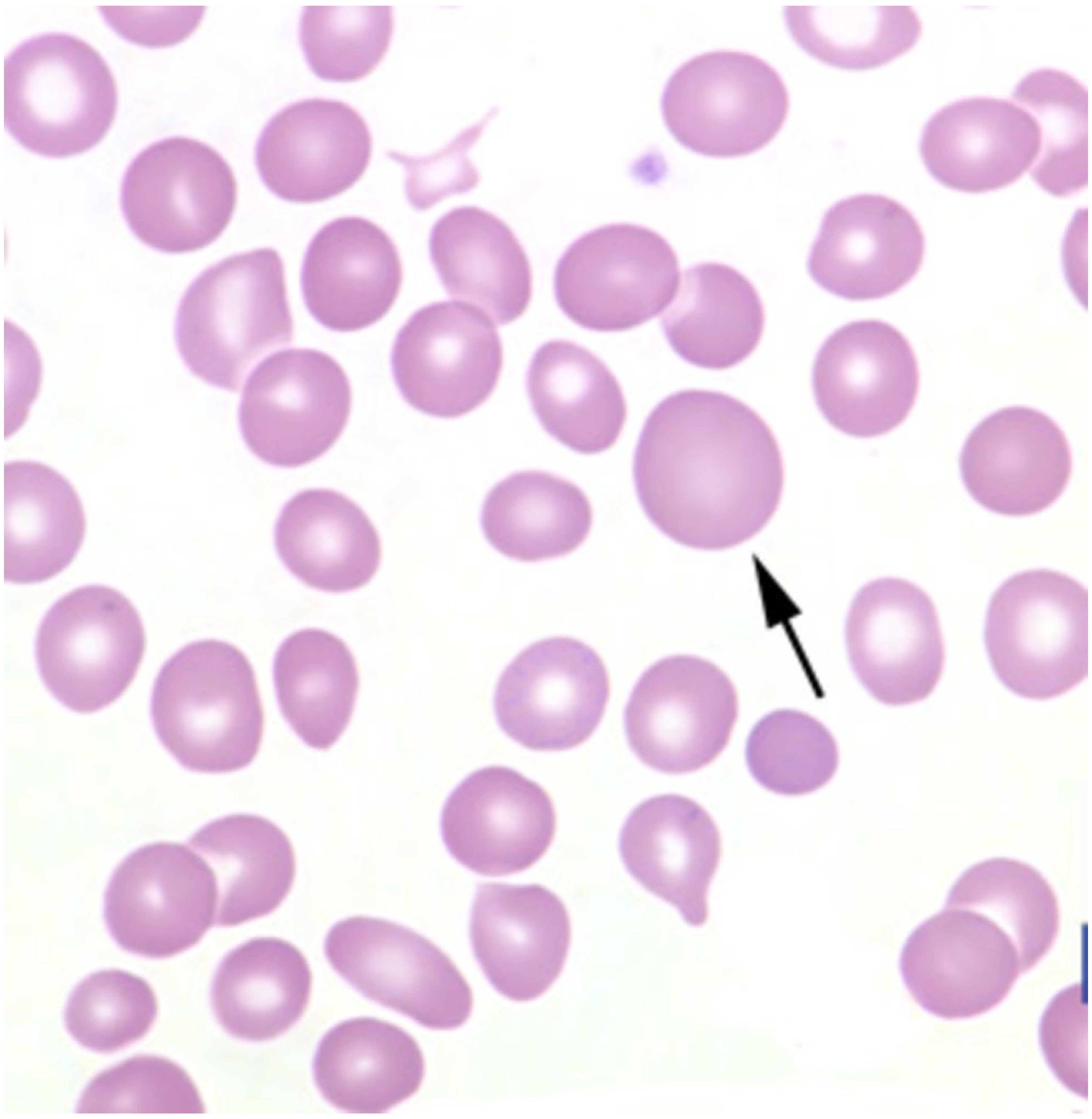
- **Microangiopathic hemolytic anemia** (e.g., hemolytic-**uremic syndrome**, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura)
- **Mechanical damage**: artificial cardiac valves, extracorporeal circulation



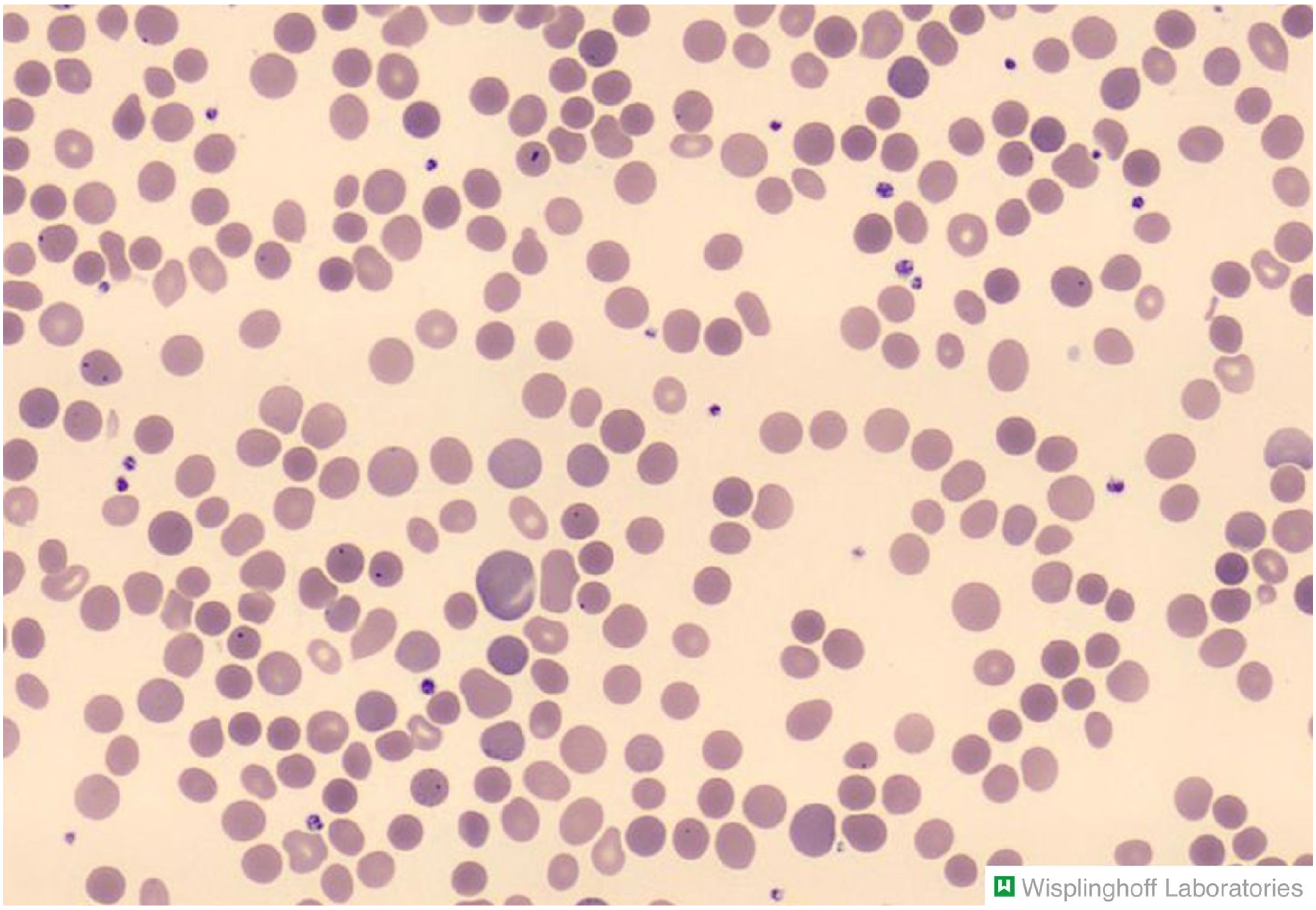
Macrocytes / Megalocytes



- Megaloblastic anemia **(folate deficiency, vitamin B_{12} deficiency)**

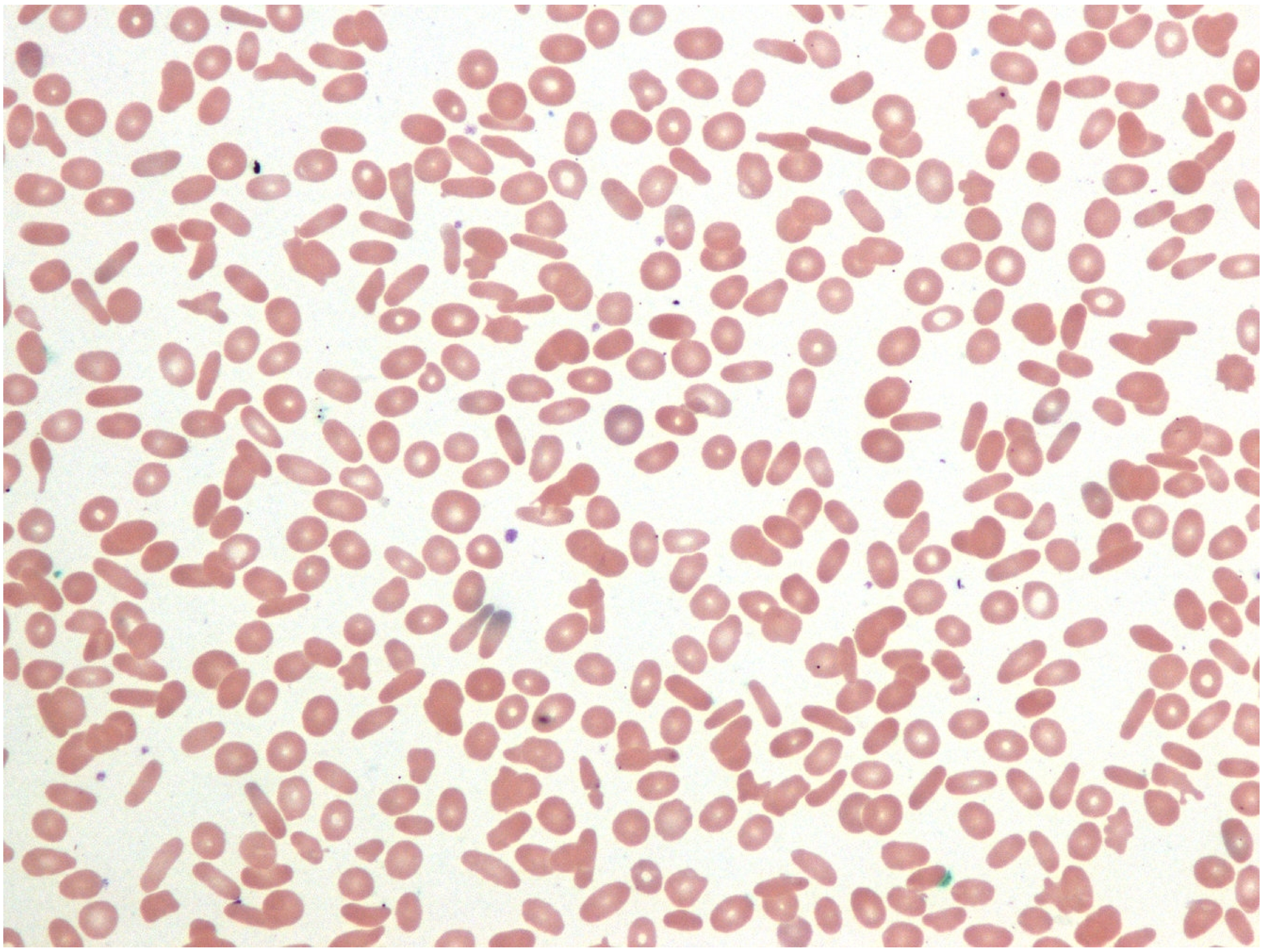


Spherocytosis



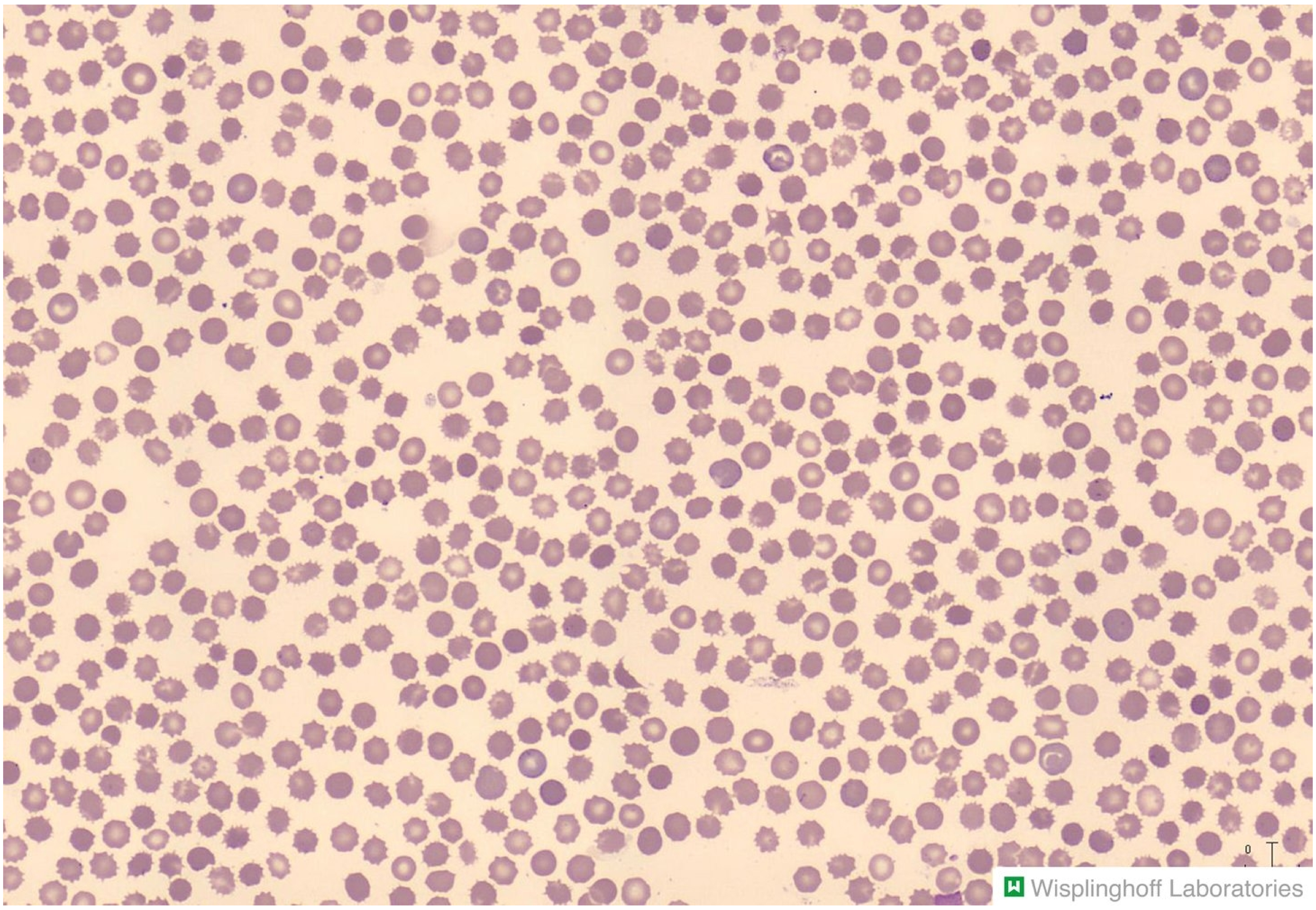
- Hemolytic anemias
    - **Hereditary spherocytosis**
    - **Autoimmune hemolytic anemia**
    - ABO incompatibility in infants
    - Hemolytic transfusion reaction

Hereditary Elliptocytosis



- **Hereditary elliptocytosis**: caused by mutations in genes encoding RBC membrane proteins (e.g., spectrin, protein 4.1); usually asymptomatic
- May also be seen in thalassemia, myelofibrosis, and iron deficiency anemia.

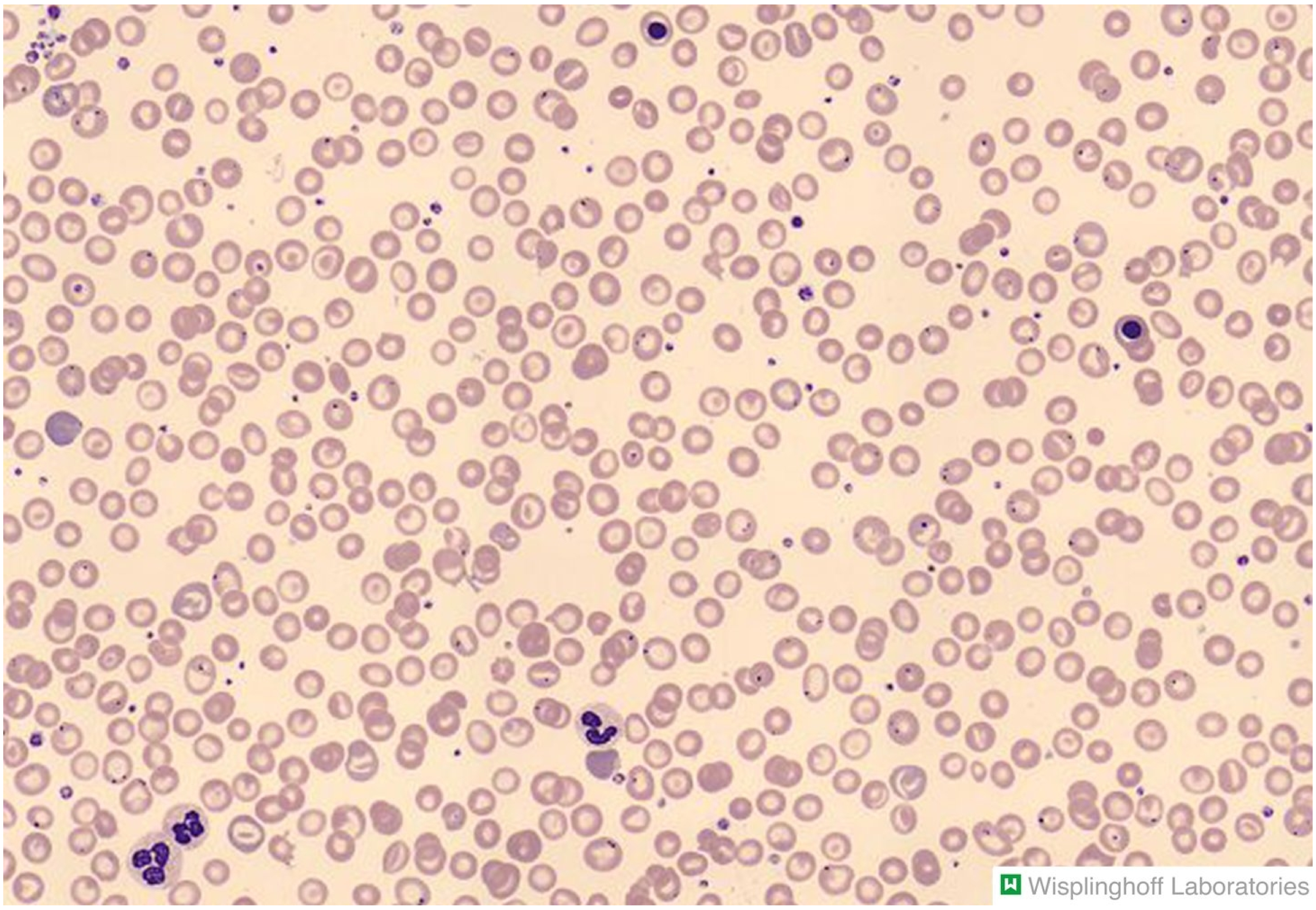
Echinocytes (Burr cells)



• Smooth, rounded, and evenly spaced cytoplasmic projections (smaller than projections of acanthocytes)	• Uremia • Liver disease • Pyruvate kinase deficiency • Oxidative or colloid osmotic stress in already dysmorphic erythrocytes (e.g., spherocytes) • Artifacts

Acanthocytes (spur cells)	• Thorny irregular cytoplasmic projections of varying length and width	• In blood
		  ◦ Hemolytic anemia in hepatic disorders (e.g. alcoholic cirrhosis)
		  ◦ Myelodysplastic syndromes
		  ◦ Following splenectomy
		  ◦ Neurodegenerative disorders
		  ◦ Hereditary abetalipoproteinemia (Bassen-Kornzweig syndrome)
		• In urine
		  ◦ Glomerular damage (e.g., glomerulonephritis)

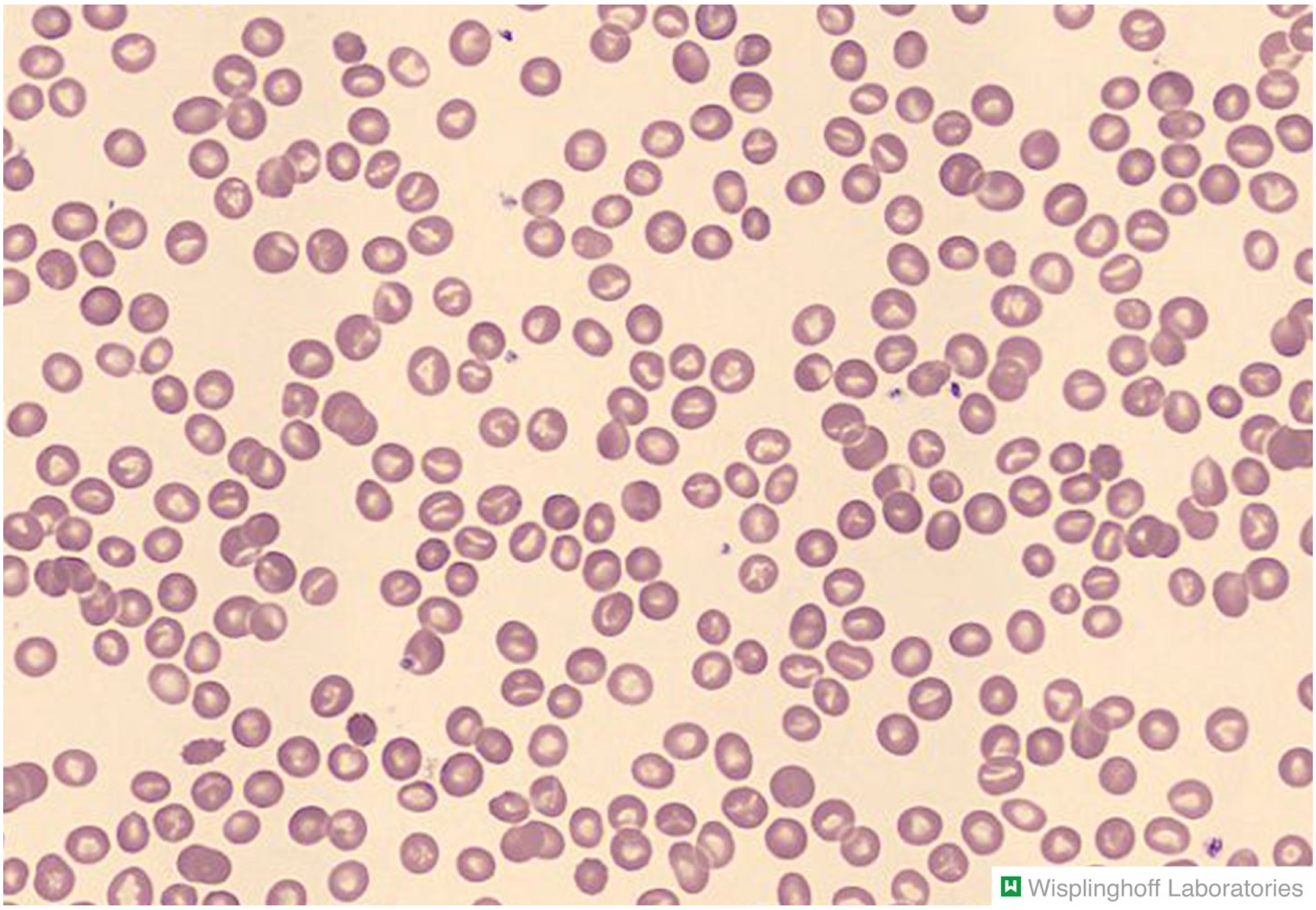
Target Cells



HALT
when u see a TARGET
- Hemoglobinopathies
- Asplenia
- Liver disease
- Thalassemia

- Hemoglobinopathies
  - **Thalassemia**
  - Hemoglobin C and S
- Liver disease
- Asplenia
- LCAT deficiency
- Artifacts

Stomatocytes



- Hepatic disorders
- Hemolytic anemias
- Hereditary stomatocytosis

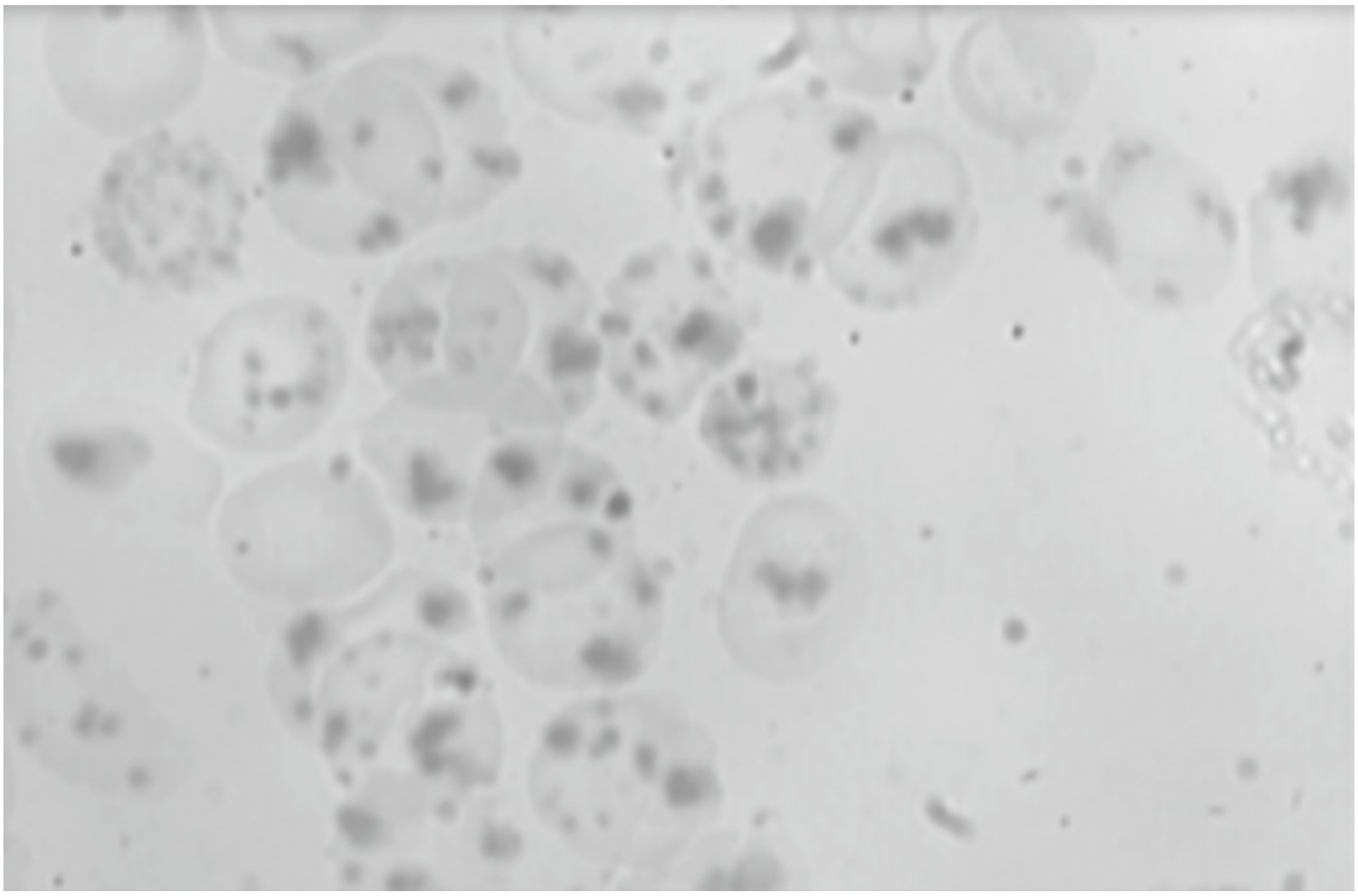
Degmacytes (bite cells)	• Removal of denaturated hemoglobin inclusions (Heinz bodies) by splenic macrophages results in one or more semicircular punches on the cell margin resembling bite marks.	• Glucose-6-phosphate dehydrogenase deficiency

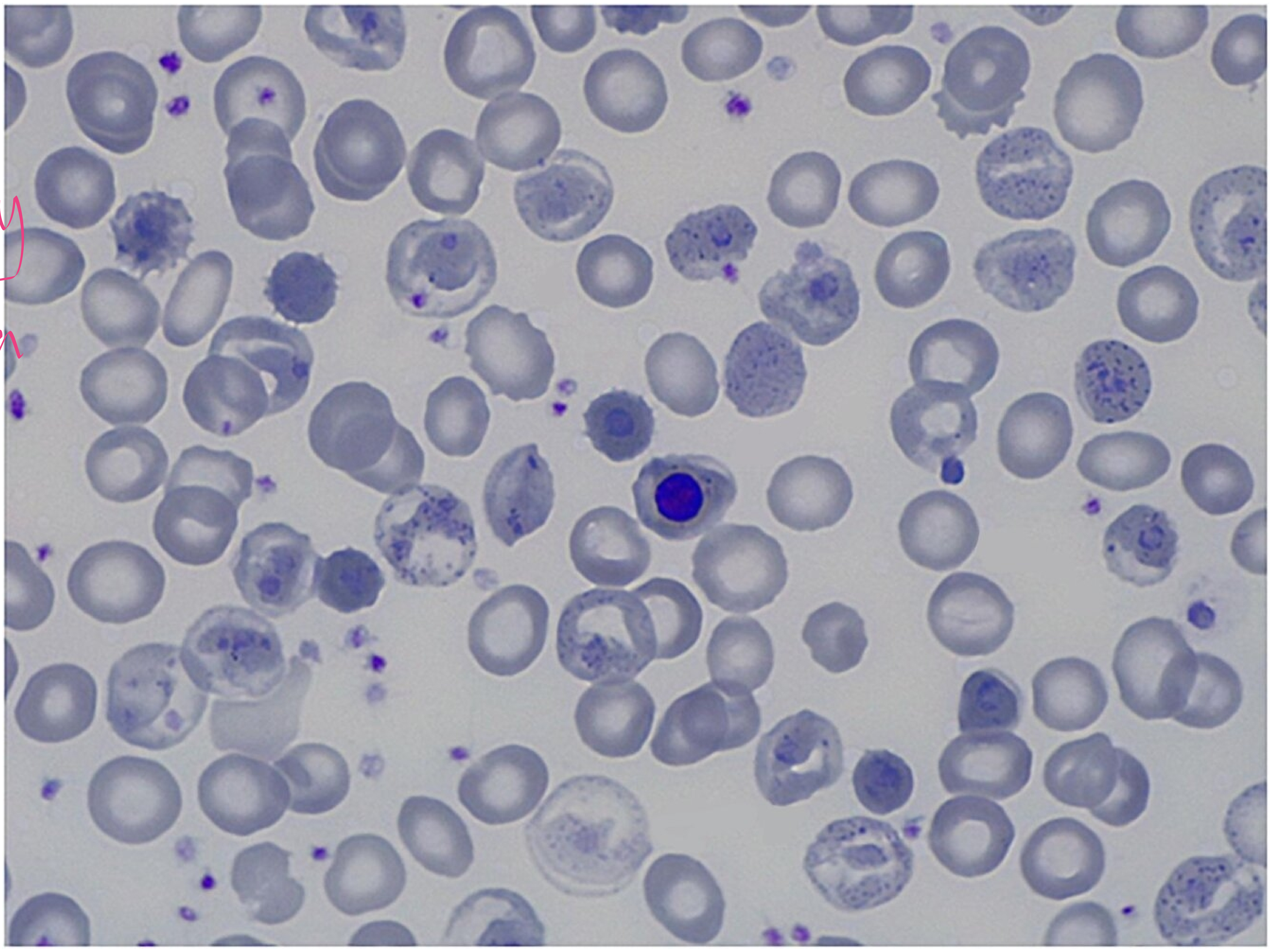
RBCs with inclusion bodies

Overview of erythrocyte inclusion bodies			
	Content	**Appearance**	**Cause**
Heinz bodies	• Denaturated hemoglobin (contains iron)	• Small • Red or pink • Detected by treating RBCs with supravital stains (e.g., methyl violet, crystal violet)	• **Glucose-6-phosphate dehydrogenase (G6PD) deficiency** • Thalassemia
Pappenheimer bodies	• Iron	• Small, blue or purple basophilic granules	• Sideroblastic anemia • Hemolytic anemia • Sickle cell disease
Basophilic stippling	• RNA • Do not contain iron • Ribosomal precipitates	• Small, basophilic granules throughout cytoplasm	• Nonspecific finding that appears in a variety of disorders with impaired cell division • **Lead intoxication** • **Sideroblastic anemia** • **Thalassemia** • Severe anemias of varying etiology

Ringed sideroblasts	• Iron	• Perinuclear ring within mitochondria of erythroblasts: visualized **in bone marrow** with Prussian blue stain	• Sideroblastic anemia
Howell-Jolly bodies	• DNA (nuclear remnants) • Do not contain iron	• A typically small, basophilic spot, located toward the periphery of the cell	• **Asplenia**
Iron granules	• Mitochondria with increased iron content	• Ring-shaped perinuclear inclusions in sideroblasts formed in the bone marrow • Are visualized with Prussian blue stain	• Sideroblastic anemias (e.g., in myelodysplastic syndromes, chronic alcohol use, lead toxicity, etc.)

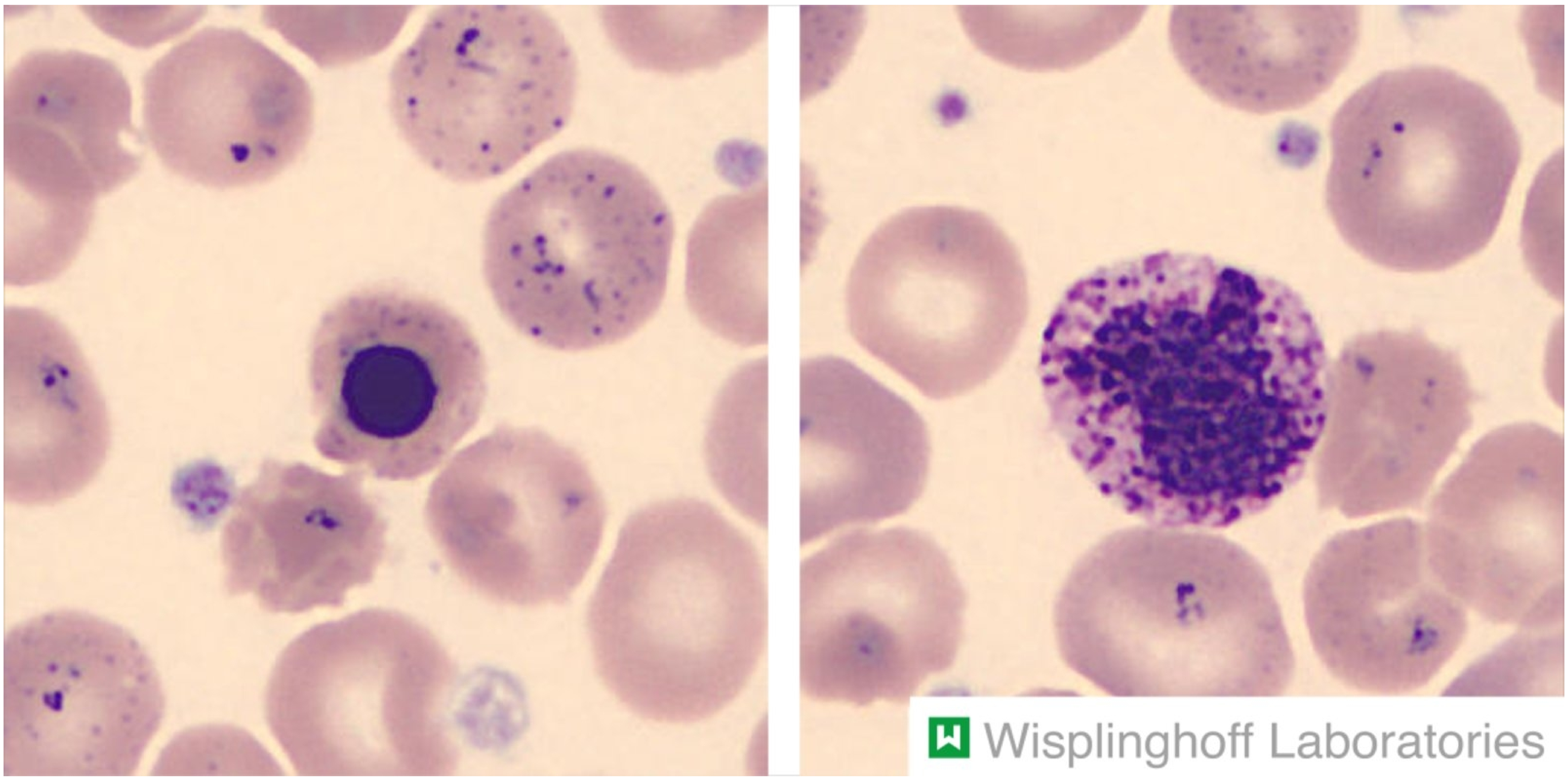
Heinz bodies



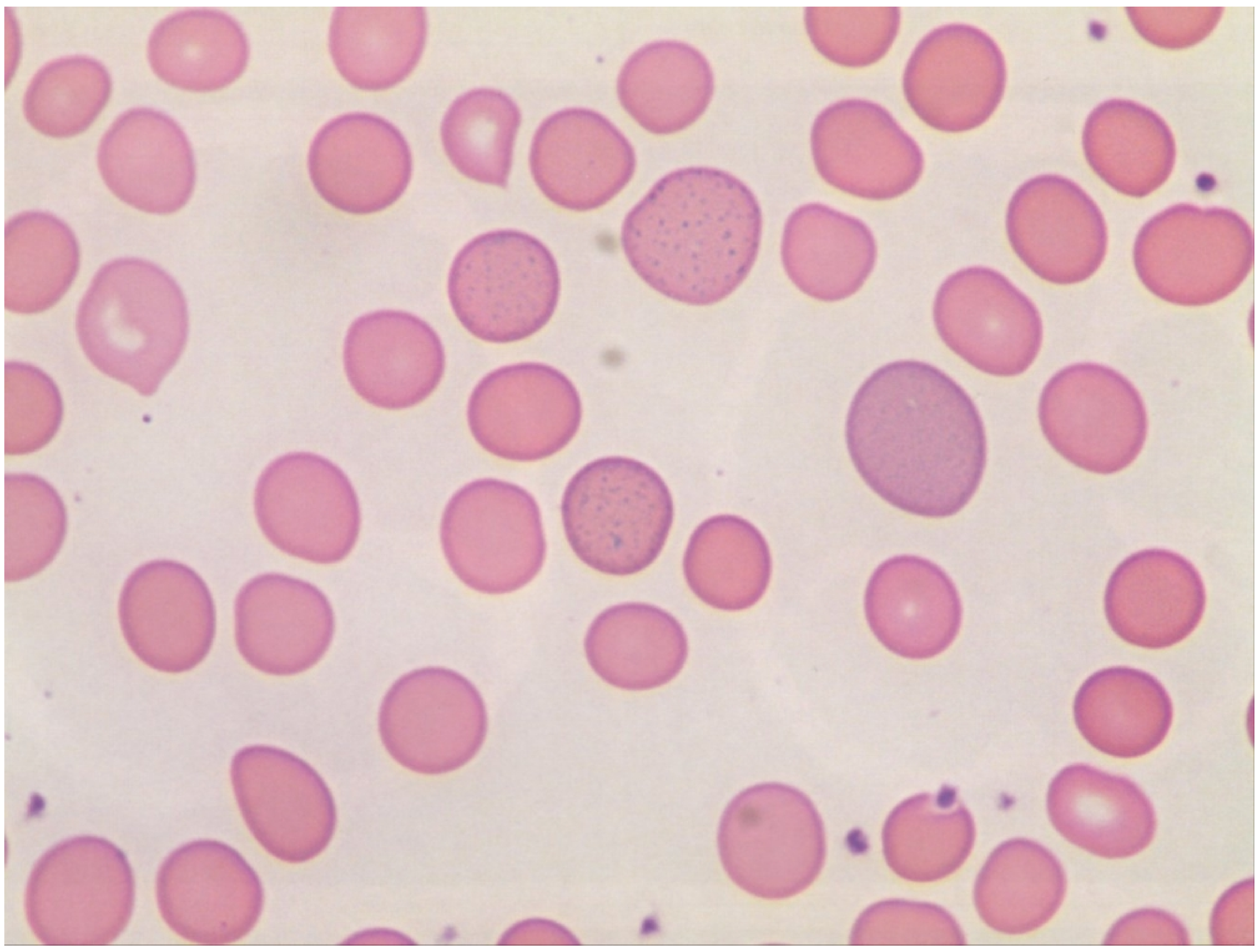


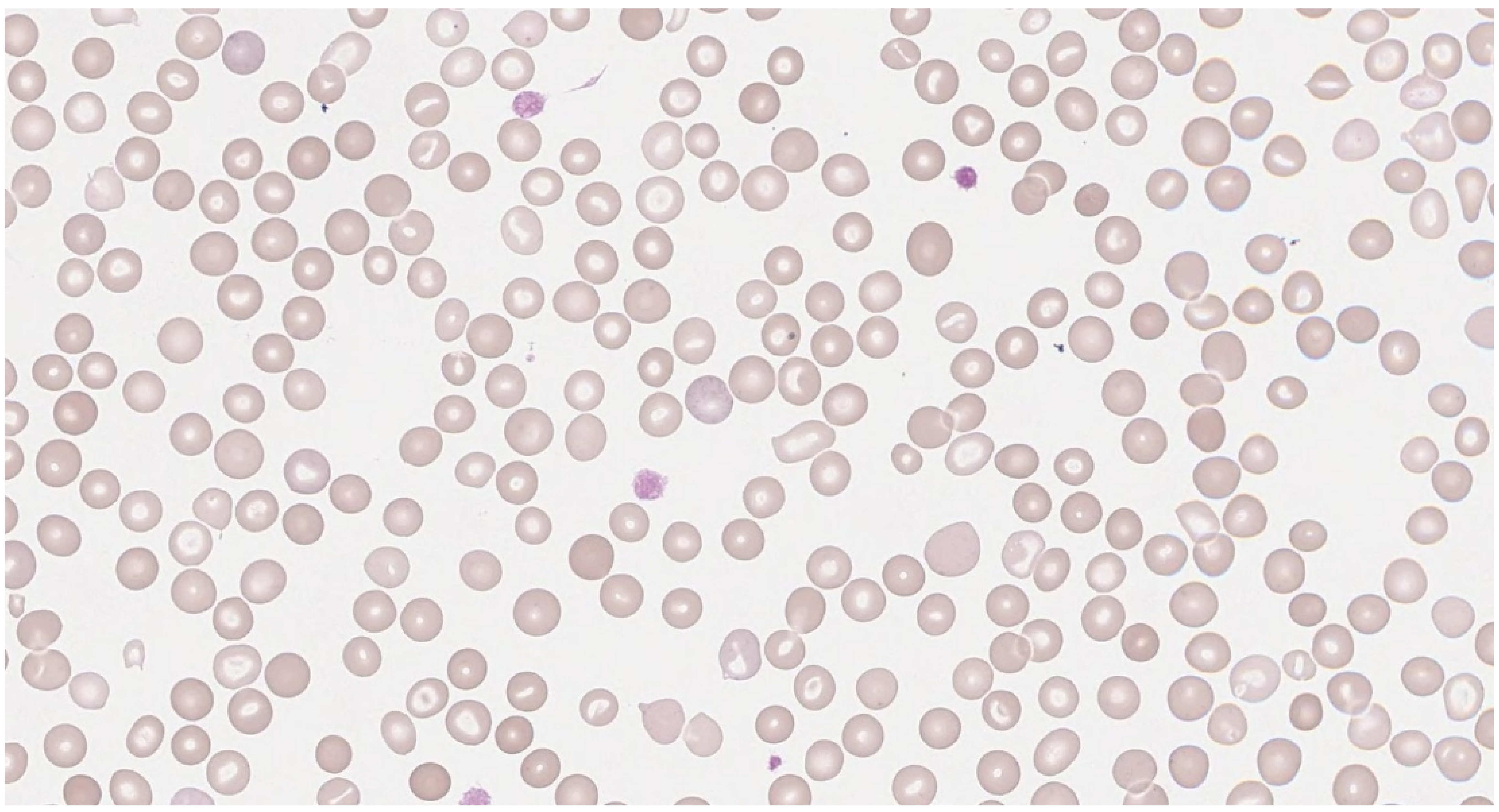
- G6PD deficiency
- Thalassemia

Basophilic Stippling of RBCs

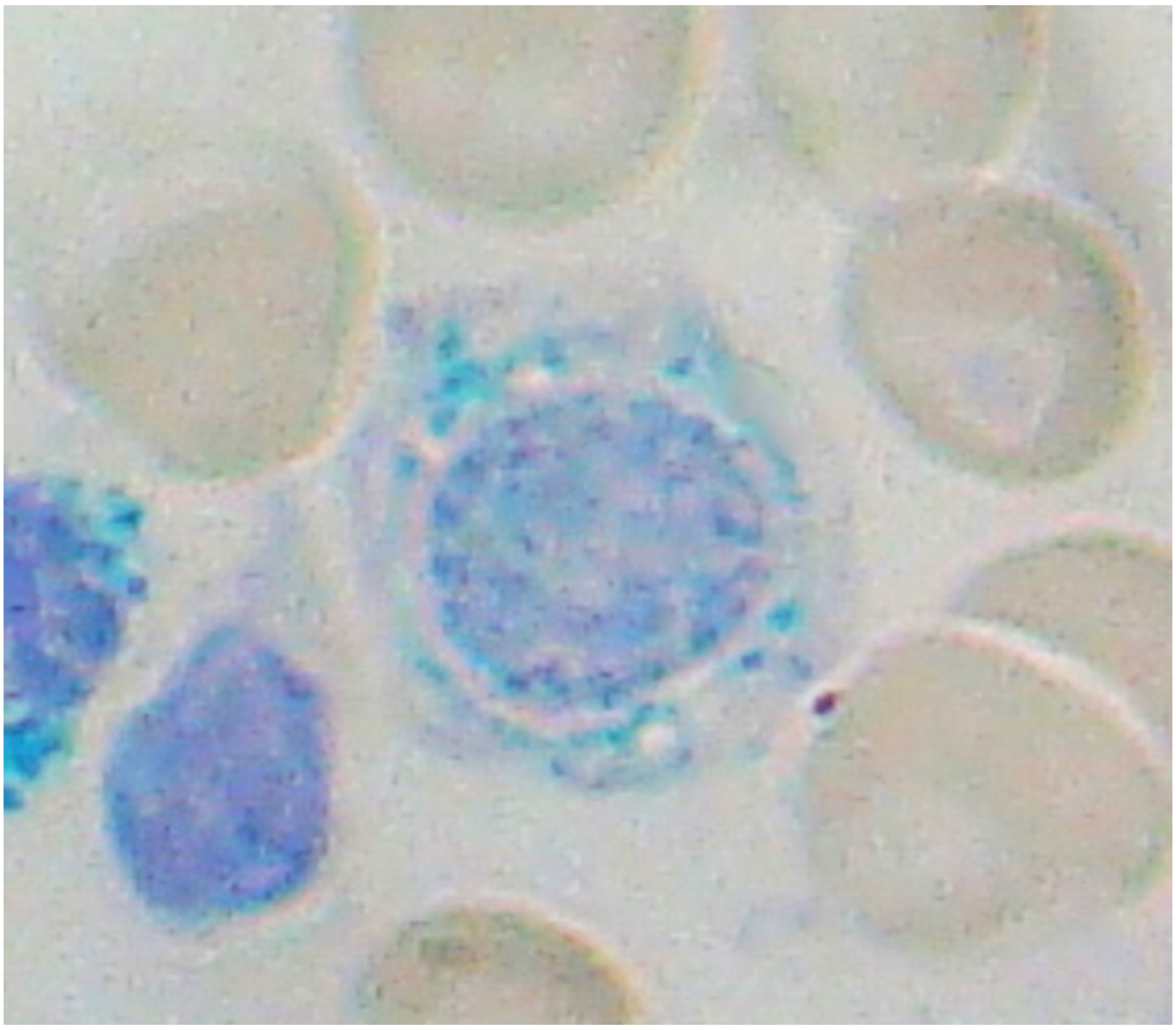


- Nonspecific finding that appears in a variety of disorders with impaired cell division
- **Lead intoxication**
- **Sideroblastic anemia**
- **Thalassemia**
- Severe anemias of varying etiology



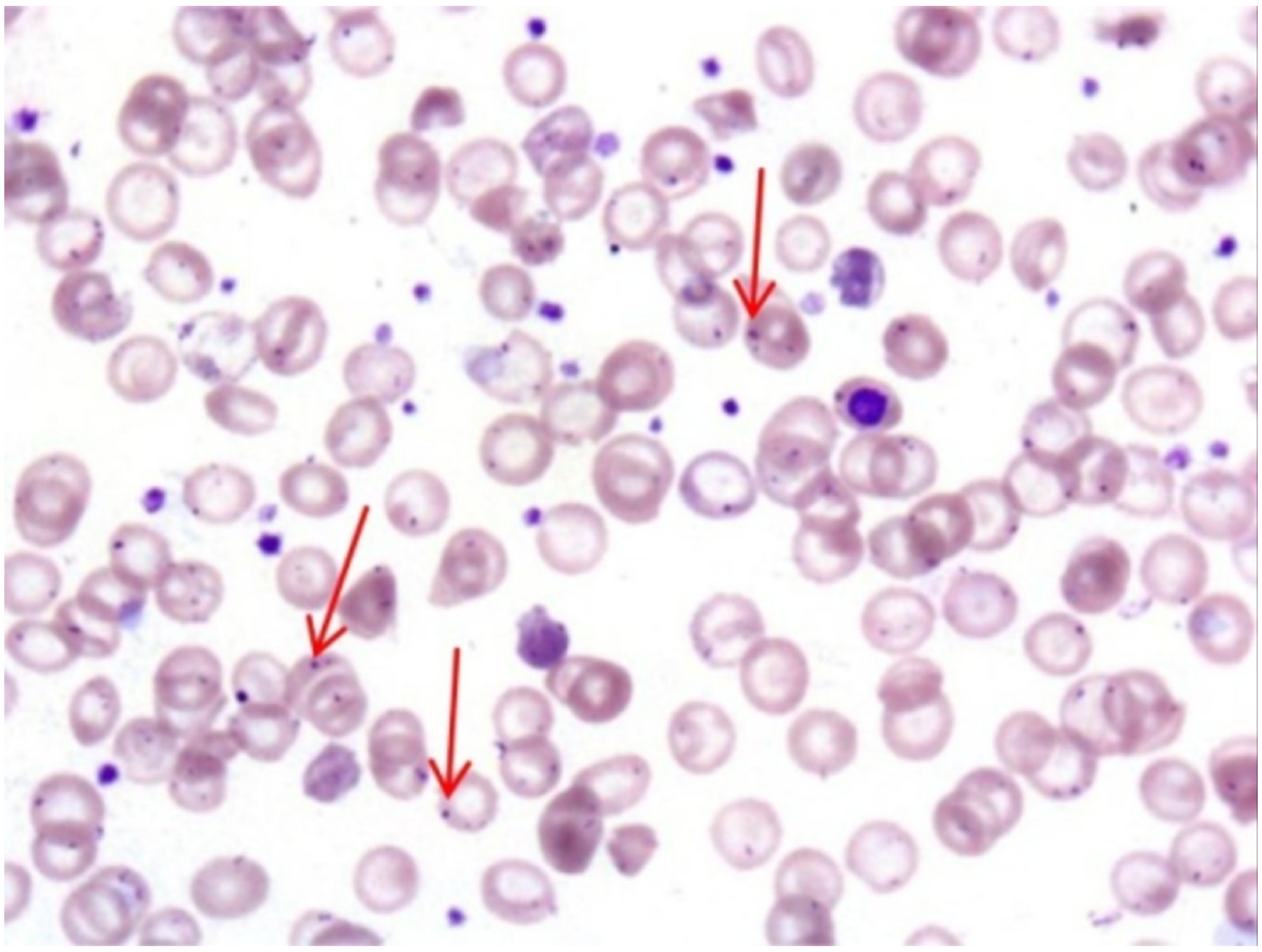


Ringed Sideroblast



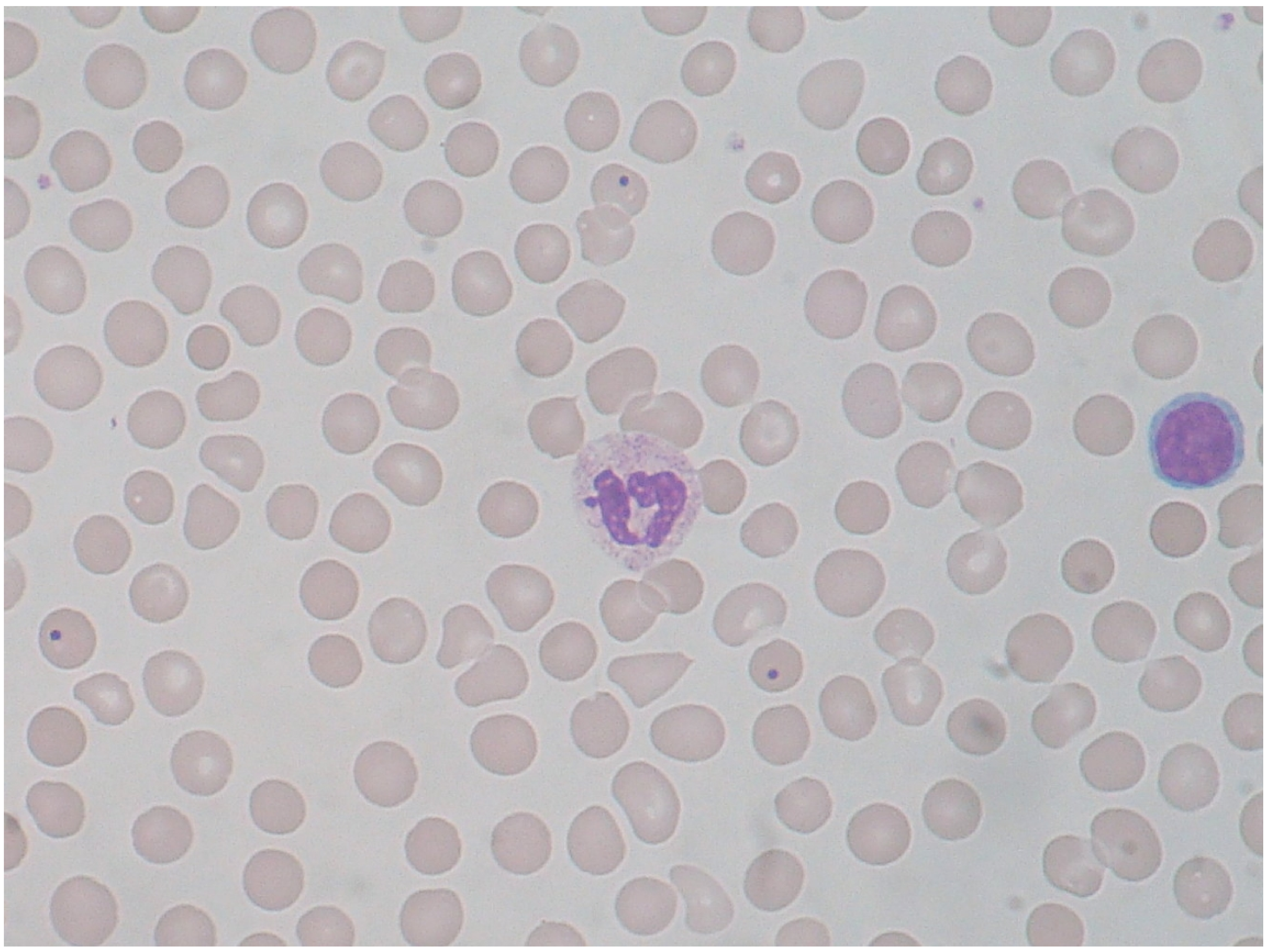
* Content → Iron
* Seen in Sideroblastic anemia

Howel Jolly bodies



Asplenia

• DNA (nuclear remnants) • Do not contain iron	• A typically small, basophilic spot, located toward the periphery of the cell	• **Asplenia**



Sideroblastic anemia is due to ineffective heme synthesis, which may be congenital (X-linked defect in the δ-ALA synthase gene) or acquired (e.g., vitamin B6 deficiency, or lead poisoning leading to sequential inhibition of δ-ALA dehydratase and ferrochelatase).

Methemoglobin has an iron molecule in the oxidized state (Fe^{3+}) rather than the reduced state (Fe^{2+}), which renders it unable to transport oxygen to the tissue.

Hemoglobin variants

Overview of hemoglobin variants

Hemoglobin	Globin chains	Physiologic	Beta thalassemia		Alpha thalassemia				Sickle cells			Hemoglobin C	
			Minor (trait)	Major (Cooley's anemia)	Silent carrier (minima)	Trait (minor)	Hb H disease (intermedia)	Hb Barts disease (major)	Sickle cell trait	Sickle cell disease	Hemoglobin SC disease (HbSC)	HbC carrier	H di
HbA	ααββ	Normal	↓	**Absent**	Normal	↓	↓↓	Absent	↓	**Absent**	Absent	↓	A
HbA_2	ααδδ	Normal	↑	↑↑	Normal	↓	↓↓	Absent	↓	**Absent**	↓	↓	A
HbF	ααγγ	Normal	↑	↑↑	Normal	Normal	↑/Normal	Absent	Normal	↑	Normal	Normal	A
HbH	ββββ	Absent	Absent	Absent	Absent	↑	↑↑	↑↑	Absent	Absent	Absent	Absent	A
Hb Barts	γγγγ	Absent	Absent	Absent	Absent	Absent	↑	↑↑	Absent	Absent	Absent	Absent	A
HbS	ααββ	Absent	Absent	Absent	Absent	Absent	Absent	Absent	↑	↑↑	↑	Absent	A
HbC	ααββ	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	↑	↑	↑

Microcytic anemia

- **Defective heme synthesis**
  - **Iron deficiency anemia** (IDA): the most common
  - Lead poisoning
  - Anemia of chronic disease (late phase)
  - Sideroblastic anemia
- **Defective globin chain**: Thalassemia

The causes of microcytic anemia can be remembered with **IRON LAST**: **IRON** deficiency, **L**ead poisoning, **A**nemia of chronic disease, **S**ideroblastic anemia, **T**halassemia.

Normocytic anemia

Hemolytic anemia

- **Intrinsic defects**
  - **Hemoglobinopathies**
    - Sickle cell anemia
    - HbC disease
  - **Enzyme deficiencies**
    - Pyruvate kinase deficiency
    - G6PD deficiency
  - **Membrane defects**
    - Paroxysmal nocturnal hemoglobinuria
    - Hereditary spherocytosis
- **Extrinsic defects**
  - Autoimmune hemolytic anemia
  - Microangiopathic hemolytic anemia
  - Macroangiopathic hemolytic anemia
  - Infections
  - Mechanical destruction

Nonhemolytic normocytic anemia

- **Blood loss**
- **Aplastic anemia**
- **Anemia of chronic kidney disease**
- Iron deficiency anemia (early phase)
- Anemia of chronic disease (early phase)
- Dilutional anemia of pregnancy [5]

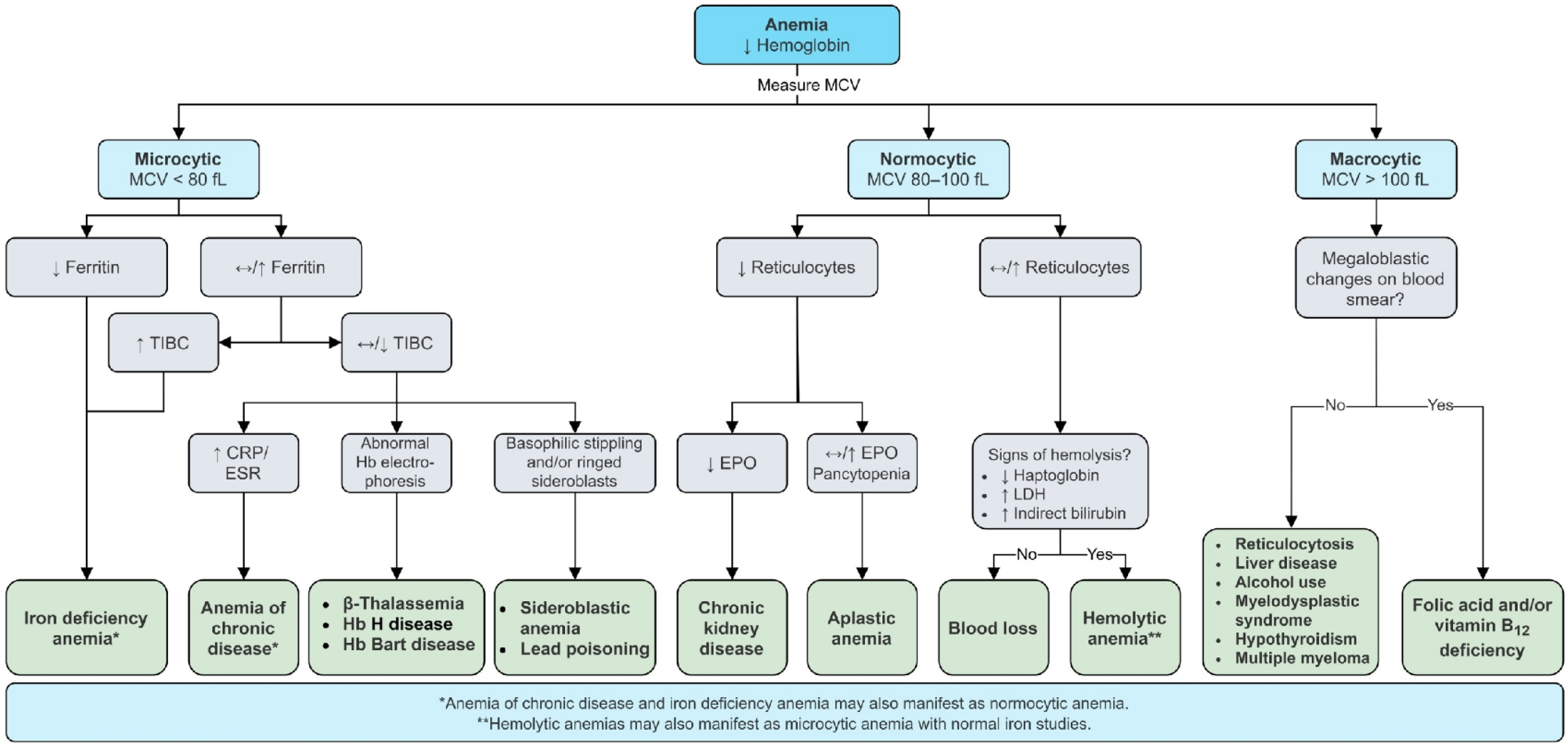
Macrocytic anemia

Megaloblastic anemia

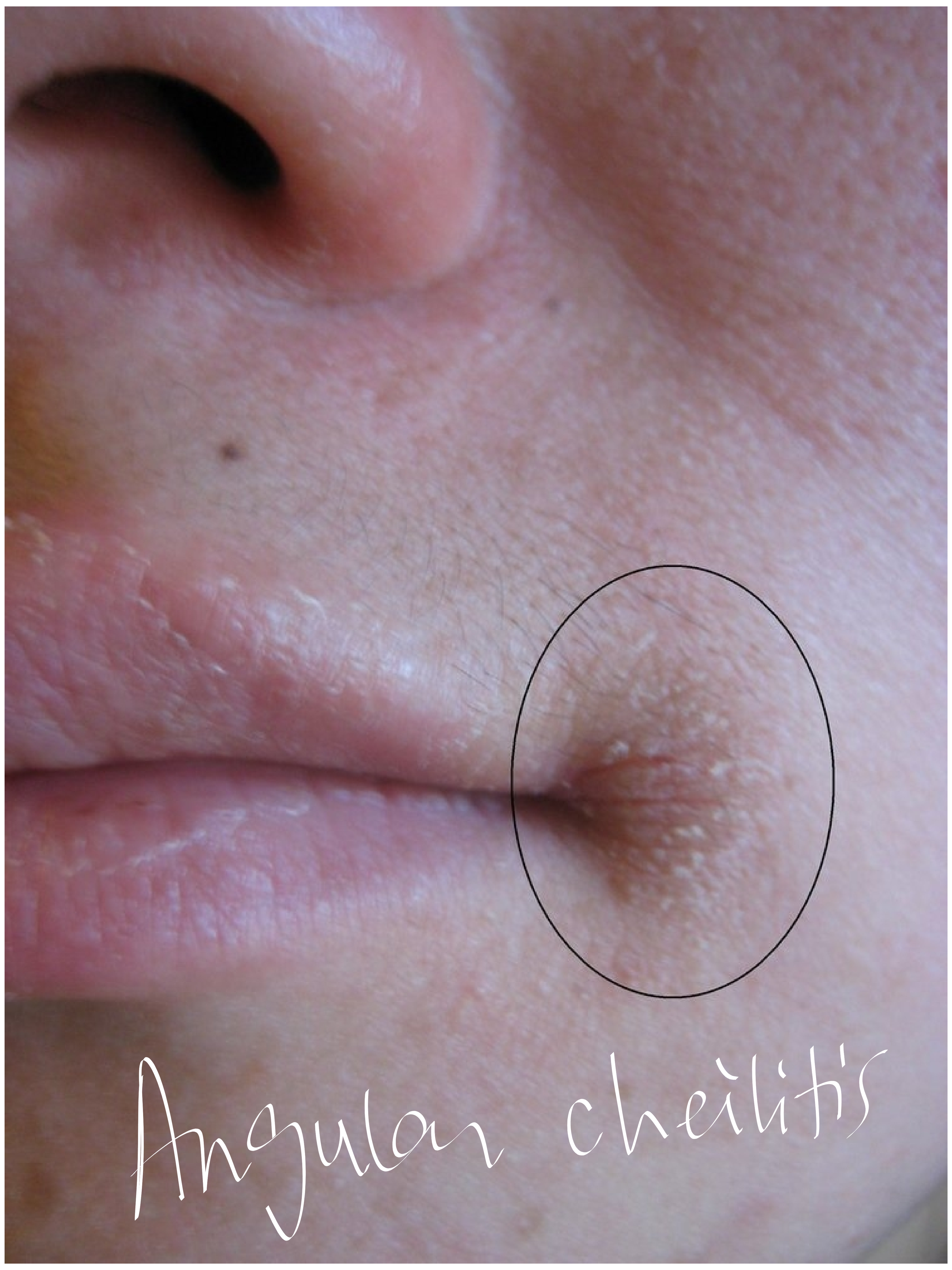
- **Vitamin B_{12} deficiency**
- **Folate deficiency**
- Medications
  - Phenytoin
  - Sulfa drugs
  - Trimethoprim
  - Hydroxyurea
  - MTX
  - 6-mercaptopurine
- Fanconi anemia
- Orotic aciduria

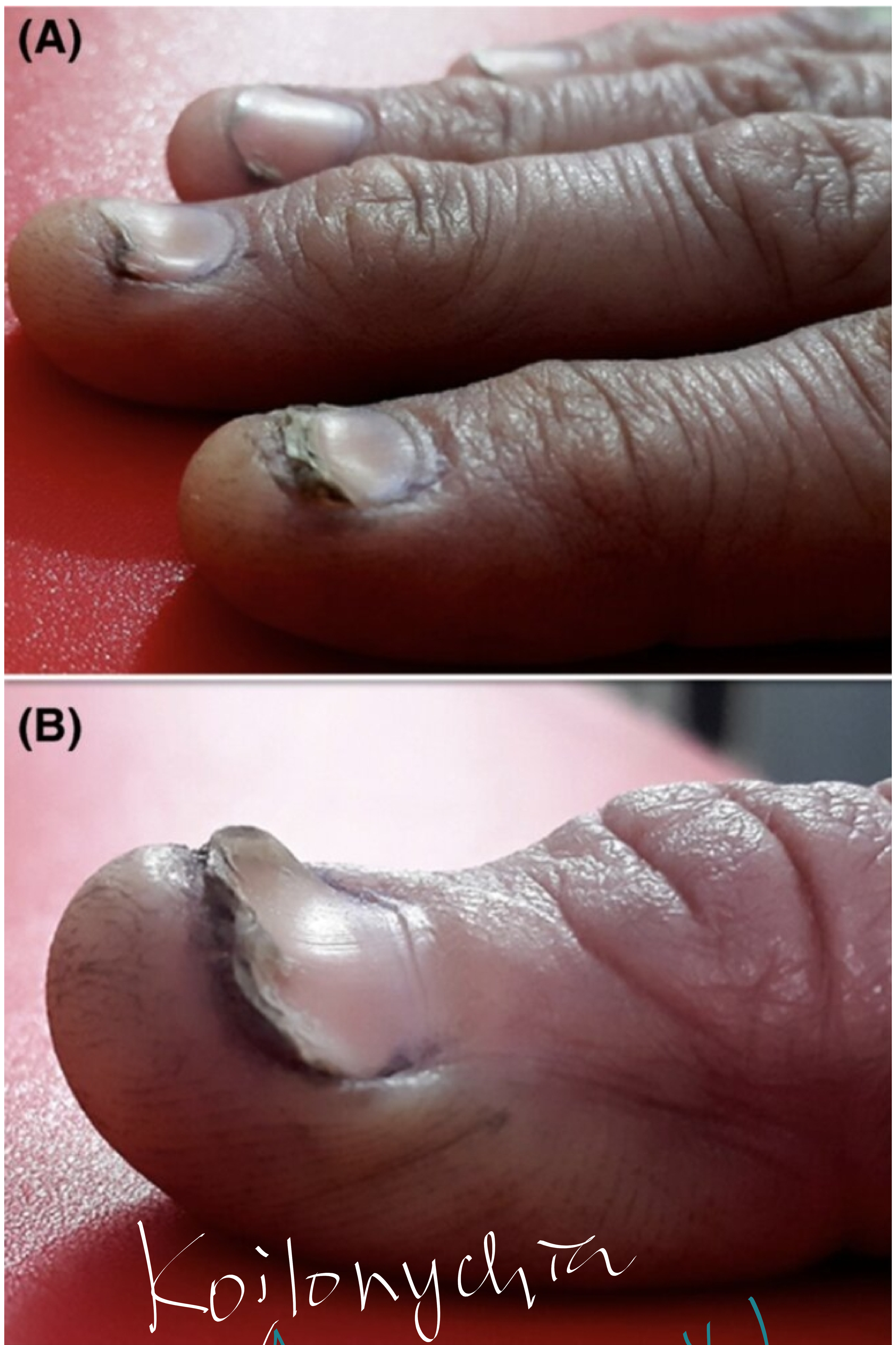
Nonmegaloblastic anemia

- Liver disease
- Alcohol use
- Diamond-Blackfan anemia
- Myelodysplastic syndrome
- Multiple myeloma
- Hypothyroidism

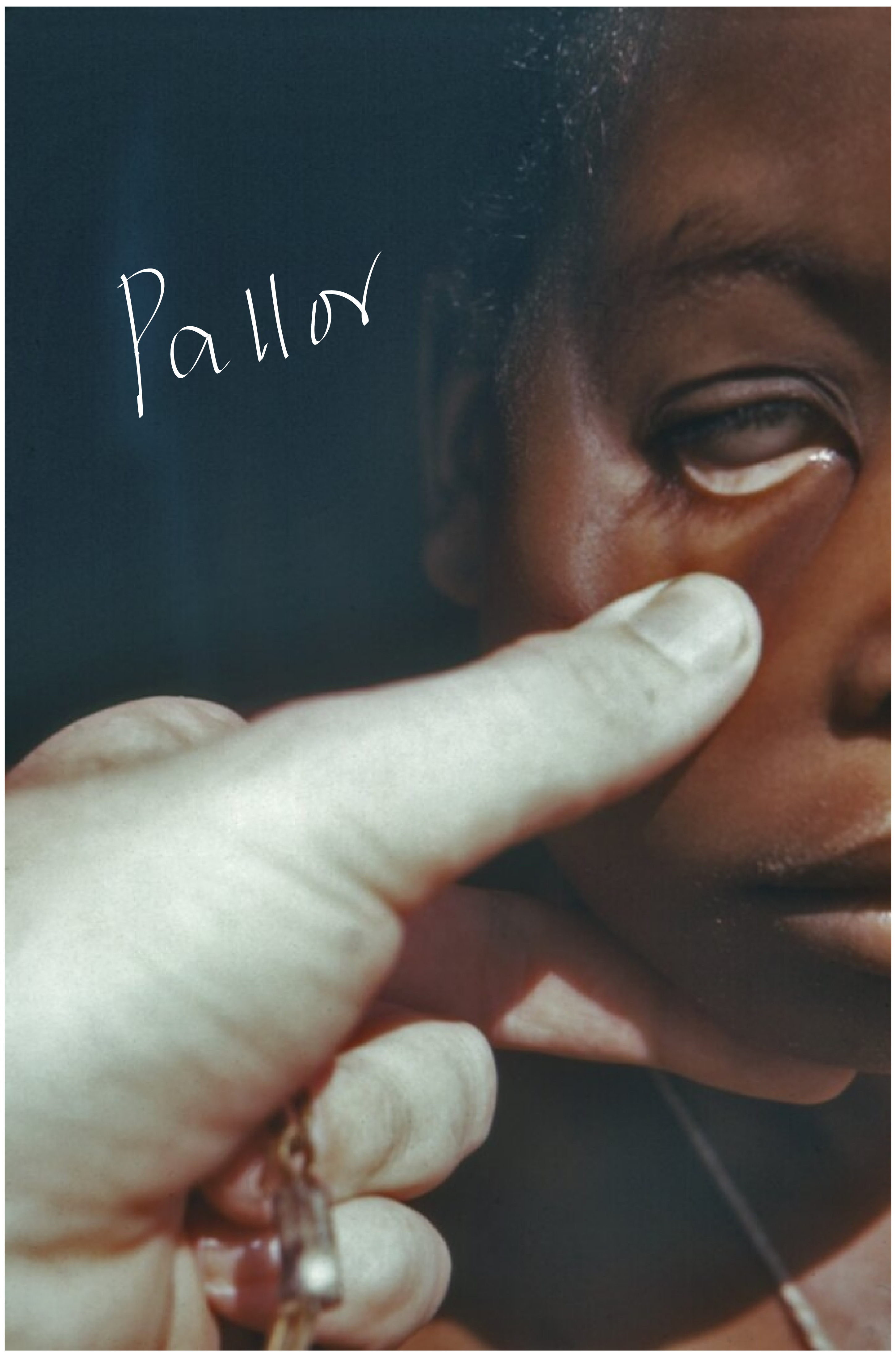

Anemia
↓ Hemoglobin
Measure MCV
Microcytic
MCV < 80 fL
Normocytic
MCV 80–100 fL
Macrocytic
MCV > 100 fL
↓ Ferritin
↔/↑ Ferritin
↑ TIBC
↔/↓ TIBC
↑ CRP/ ESR
Abnormal Hb electro-phoresis
Basophilic stippling and/or ringed sideroblasts
↓ Reticulocytes
↔/↑ Reticulocytes
↓ EPO
↔/↑ EPO Pancytopenia
Signs of hemolysis?
• ↓ Haptoglobin
• ↑ LDH
• ↑ Indirect bilirubin
No
Yes
Megaloblastic changes on blood smear?
No
Yes
Iron deficiency anemia*
Anemia of chronic disease*
• β-Thalassemia
• Hb H disease
• Hb Bart disease
• Sideroblastic anemia
• Lead poisoning
Chronic kidney disease
Aplastic anemia
Blood loss
Hemolytic anemia**
• Reticulocytosis
• Liver disease
• Alcohol use
• Myelodysplastic syndrome
• Hypothyroidism
• Multiple myeloma
Folic acid and/or vitamin B12 deficiency
*Anemia of chronic disease and iron deficiency anemia may also manifest as normocytic anemia.
**Hemolytic anemias may also manifest as microcytic anemia with normal iron studies.

IRON DEFICIENCY ANEMIA





(spoon nails)



Cyanosis

Glucose-6-phosphate dehydrogenase deficiency

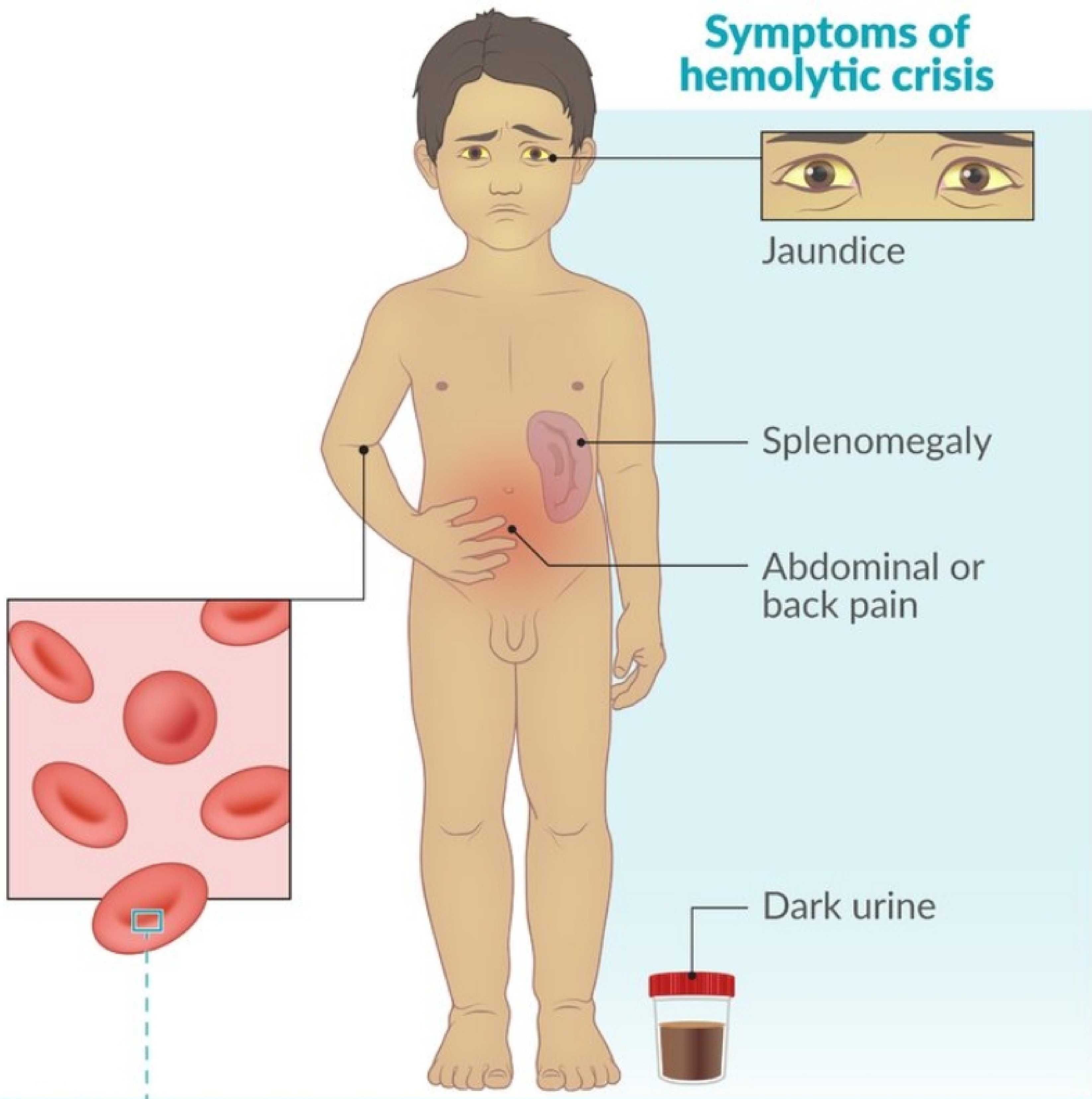
Epidemiology
Most commonly affects male individuals of African, Mediterranean, and Asian descent

Inheritance
X-linked recessive

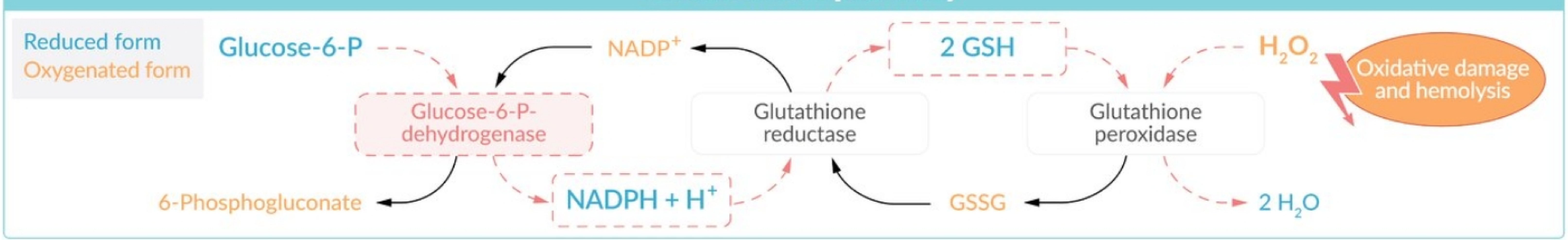
Triggers of hemolytic crisis
- Fava beans
- Infections
- Drugs that cause oxidative stress, e.g., antimalarials, sulfa drugs

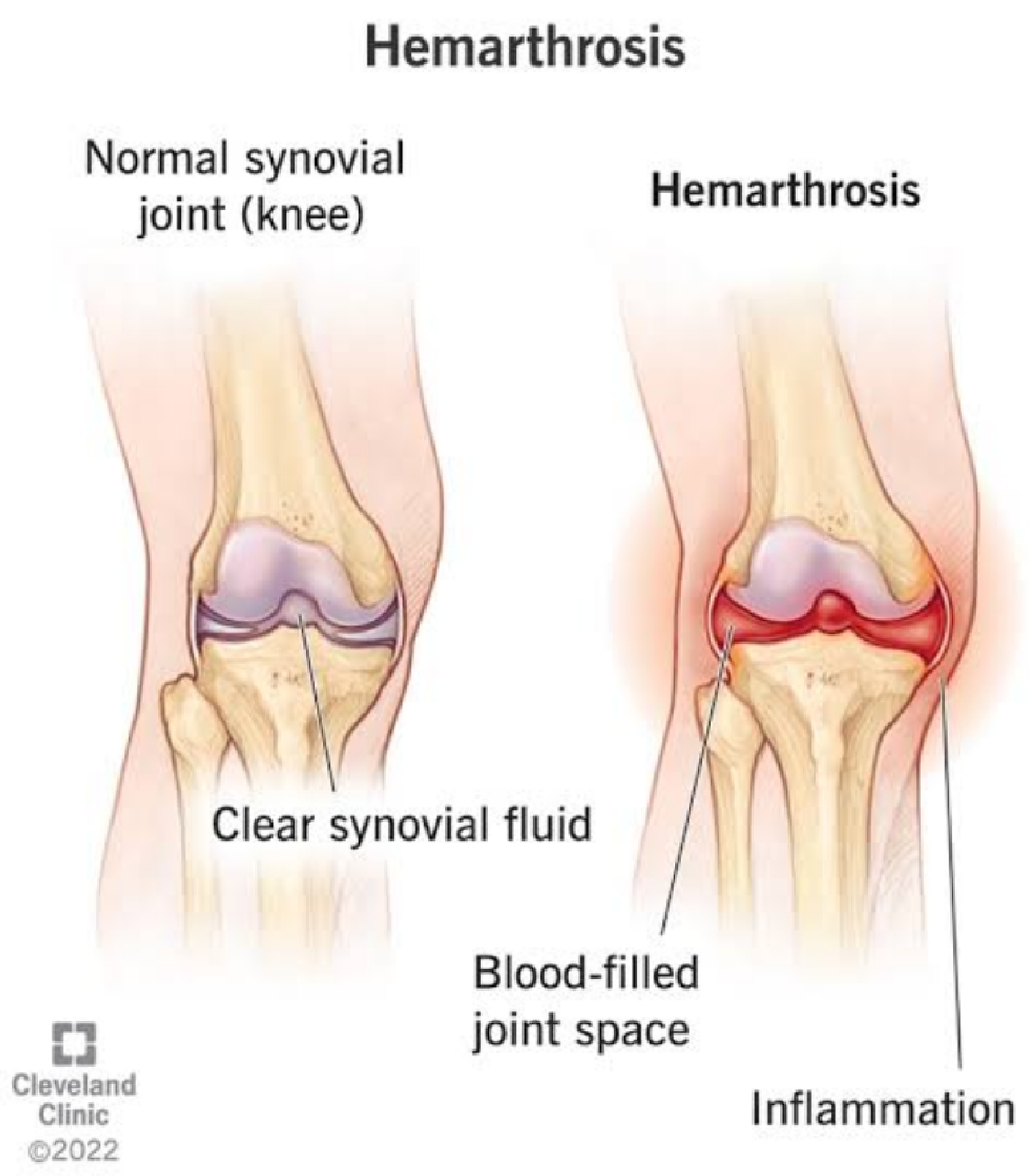
Diagnostics
- Signs of hemolytic anemia (e.g., ↑ reticulocyte count, ↑ unconjugated bilirubin)
- Histology: bite cells, Heinz bodies
- Confirmatory test: quantitative G6PD enzyme analysis

Treatment
Avoidance of triggers



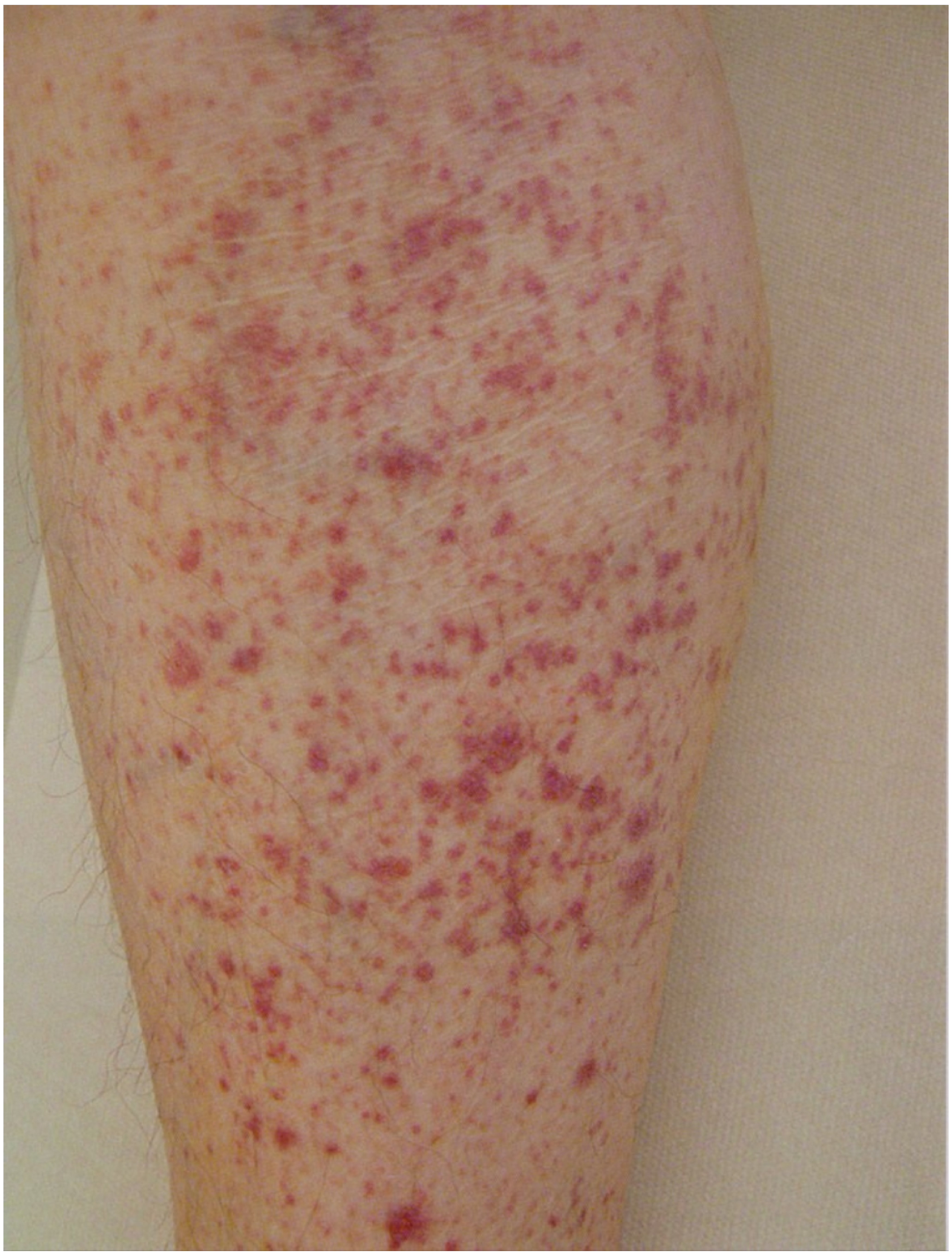
Biochemical pathway





Hemarthrosis in Hemophilia

Activated partial thromboplastin time (aPTT): usually prolonged



Petechial bleeding in
Thrombocytopenia

Impaired secondary hemostasis in lupus erythematosus - Diffuse ecchymoses are visible on the radial aspect of the forearm. The hemorrhage is extensive and diffuse, which indicates an impairment of secondary hemostasis. Specific antibodies that reduce factor VIII activity inhibit secondary hemostasis in individuals with systemic lupus erythematosus.

Interpretation of laboratory findings in bleeding disorders [18][20][28]					
Defective pathway	**Disorders**	**Platelet count**	**PFA or bleeding time**	**PT/INR**	**aPTT**
Disorders of primary hemostasis	**Thrombocytopenia**	• ↓	• ↑	• Normal	• Norr
	Platelet dysfunction (e.g., aspirin therapy. chronic kidney disease)	• Normal	• ↑	• Normal	• Norr
Disorders of secondary hemostasis	**Extrinsic pathway** (e.g., factor VII deficiency)	• Normal	• Normal	• ↑	• Norr
	Intrinsic pathway (e.g., hemophilia, heparin therapy)	• Normal	• Normal	• Normal	• ↑
	Intrinsic and extrinsic pathways (e.g., deficiency of vitamin K-dependent coagulation factors)	• Normal	• Normal	• ↑	• ↑
Disorders of primary AND secondary hemostasis	**Von Willebrand disease**	• Normal	• ↑	• Normal	• Norr [27]
	Disseminated intravascular coagulation (DIC)	• ↓	• ↑	• ↑	• ↑

Variants of von Willebrand disease [2]				
Type		**Description**	**Etiology**	**Mechanism**
Inherited von Willebrand disease [1]	**Type 1** (80–85%)	• VWD caused by mutations in the *vWF* gene	• Autosomal dominant inheritance	• Mild to moderate deficiency of vWF and factor VIII
	Type 2 (15–20%)		• Autosomal dominant inheritance	• Dysfunctional vWF
	Type 3 (~ 3%)		• Autosomal recessive inheritance	• Complete absence of vWF and factor VIII
Acquired von Willebrand disease (aVWD)		• VWF deficiency that occurs secondary to other medical conditions [3]	• Lymphoproliferative and myeloproliferative diseases (e.g., multiple myeloma, monoclonal gammopathies, lymphoma, essential thrombocythemia) • Autoimmune diseases (e.g., SLE) • Cardiovascular defects (e.g., ventricular septal defect, aortic stenosis) • Hypothyroidism • Side effects of certain drugs (e.g., valproic acid)	• Unknown

Impaired platelet production in bone marrow [1]

Bone marrow conditions → ↓ **megakaryocytes** → ↓ thrombopoiesis

- **Bone marrow failure**: aplastic anemia, paroxysmal nocturnal hemoglobinuria
- **Bone marrow suppression**: drugs (e.g., linezolid, daptomycin, valproic acid, valacyclovir), chemotherapy, radiation
- **Congenital thrombocytopenias**: Wiskott-Aldrich syndrome, Alport syndrome, **Bernard-Soulier syndrome**, Fanconi anemia, von Willebrand disease
- Other congenital conditions: Gaucher disease
- **Infection**: **CMV**, **EBV**, hepatitis C virus, HIV, mumps and rubella, **parvovirus B19**, rickettsia, VZV, dengue
- **Malignancy**: leukemia, lymphoma, bone marrow infiltration, myelodysplastic syndrome
- **Nutritional deficiency**: vitamin B12 deficiency and/or folate deficiency (e.g., in chronic alcohol abuse)
- Other: necrotizing enterocolitis

If platelet production is impaired, the number of megakaryocytes on bone marrow biopsy will also be decreased.

Increased platelet turnover in the periphery

- **Immune thrombocytopenia** (ITP) and other autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis)
- **Disseminated intravascular coagulation** (DIC) and sepsis
- **Thrombotic thrombocytopenic purpura** (TTP) and **hemolytic uremic syndrome** (HUS)
- **Drug-induced immune thrombocytopenia** (DITP): Platelet-activating antibodies cause a hypercoagulable state and simultaneous reduction in platelet count.
  - The following drugs are most likely to be associated with DITP: [2][3]
    - Sodium-channel blockers: quinine, class I antiarrhythmics (e.g., quinidine), valproate, carbamazepine
    - Calcium-channel blockers: amlodipine
    - Antibiotics: linezolid, vancomycin, TMP-SMX, penicillin, ceftriaxone, rifampin
    - Antiviral agents: ganciclovir, protease inhibitors (e.g., indinavir), zidovudine
    - Antithrombotic agents: glycoprotein IIb/IIIa inhibitors (e.g., abciximab), heparin
    - Others: oxaliplatin, suramin, ibuprofen, mirtazapine
  - See also **Heparin-induced thrombocytopenia** (HIT)
- Pregnancy: **preeclampsia** and **HELLP syndrome**
- Infection (see above)
- Post-transfusion thrombocytopenia
- **Mechanical damage** due to artificial cardiac valves or extracorporeal circulation (e.g., dialysis)

Increased peripheral turnover also increases numbers of megakaryocytes on bone marrow biopsy!

TTP

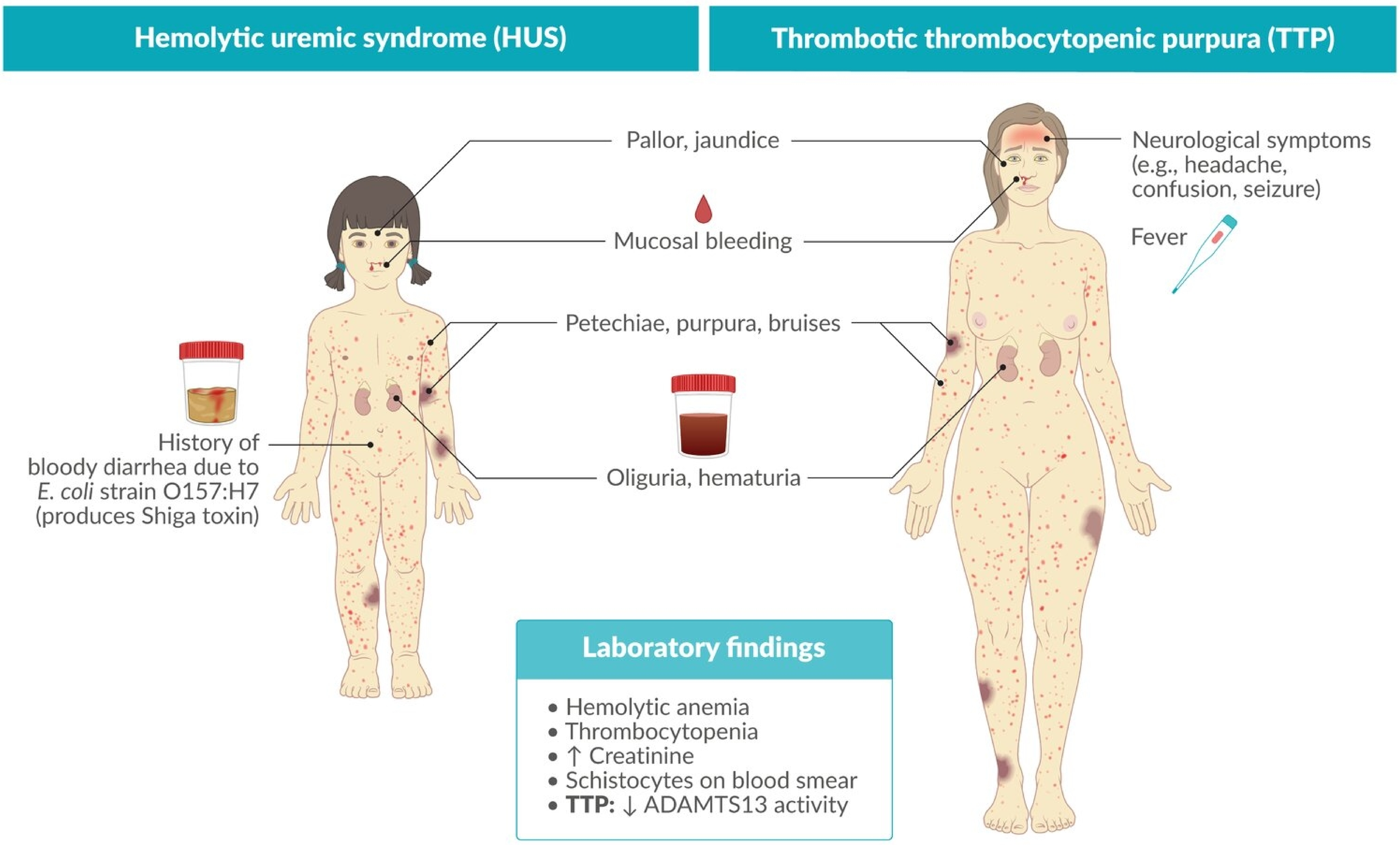
Clinical features

TTP patients are typically previously healthy adults. Microangiopathic hemolytic anemia and thrombocytopenia may be the only presenting signs. However, the classic **pentad** of clinical findings consists of: [2][3][4]

- **Fever**
- **Neurological signs and symptoms**
  - Altered mental status, delirium
  - Seizure, focal defects, stroke
  - Headache, dizziness
- **Low platelet count** (i.e. thrombocytopenia)
  - Petechiae, purpura
  - Mucosal bleeding
  - Prolonged bleeding after minor cuts
- **Microangiopathic hemolytic anemia**
  - Fatigue, dyspnea, and pallor
  - Jaundice
- **Impaired renal function**
  - Hematuria, proteinuria
  - Oliguria, anuria (uncommon)

The typical patient is a previously healthy adult presenting with mental status changes, fever, petechiae, fatigue, and pallor. Laboratory tests will then indicate hemolytic anemia and possibly acute kidney injury (AKI). Impaired kidney function may not be present, and only a minority of patients will present with all five clinical findings.

"**N**asty **F**ever **R**uined **M**y **T**ubes:" **N**eurological symptoms, **F**ever, **R**enal function impairment, **M**icroangiopathic hemolytic anemia, **T**hrombocytopenia are the clinical features of TTP.


Hemolytic uremic syndrome (HUS)
Thrombotic thrombocytopenic purpura (TTP)
Pallor, jaundice
Mucosal bleeding
Petechiae, purpura, bruises
Oliguria, hematuria
History of bloody diarrhea due to E. coli strain O157:H7 (produces Shiga toxin)
Neurological symptoms (e.g., headache, confusion, seizure)
Fever
Laboratory findings
• Hemolytic anemia
• Thrombocytopenia
• ↑ Creatinine
• Schistocytes on blood smear
• TTP: ↓ ADAMTS13 activity

Heparin-induced thrombocytopenia

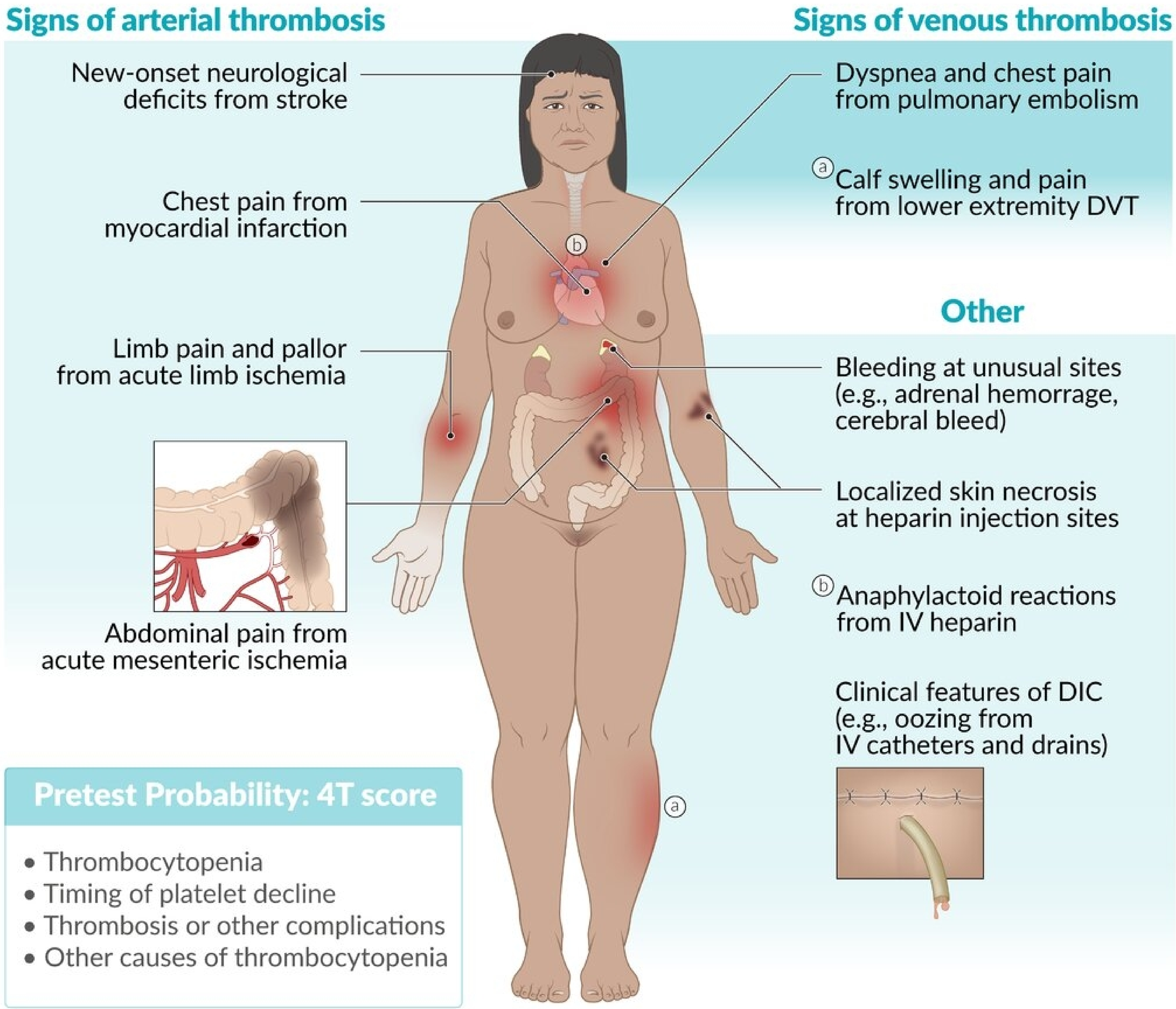
Definition
An antibody-mediated response to heparin leading to thrombocytopenia and an increased risk of thrombosis

Epidemiology
Occurs in 0.1–7% of patients receiving heparin products

Risk factors
- Female sex
- Surgery
- Major trauma
- Use of unfractionated heparin
- Duration of heparin exposure (> 5 days)

Diagnostics
- CBC, peripheral blood smear
- Coagulation studies (PTT, INR, fibrinogen)
- Confirmatory studies (PF4 heparin immunoassay, functional platelet activation assay)

Treatment
- Stop all heparin exposure
- Initiate nonheparin anticoagulation
- Screen for thrombosis



Deep vein thrombosis (DVT) - There is diffuse edema and erythema of the right leg and foot. The diameter of the right calf is visibly greater than that of the left. These features are typical of DVT. Clinical history and investigations (e.g., Doppler ultrasonography, D-dimer levels) help distinguish between DVT and cellulitis, which also manifests with a painful, warm, erythematous, and edematous leg.

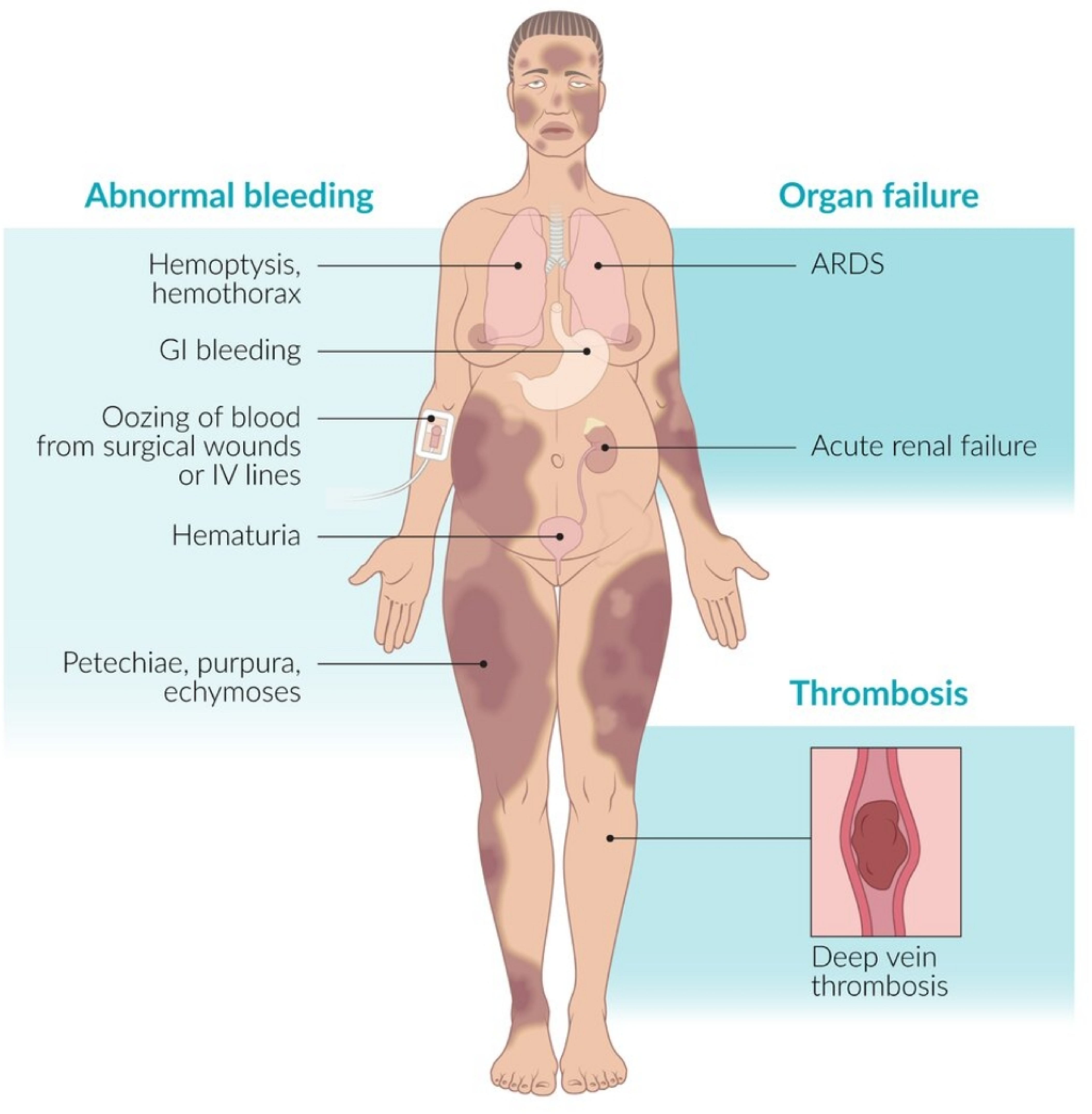
Disseminated intravascular coagulation

Definition
Thrombosis, hemorrhage, and organ dysfunction secondary to platelet consumption and exhaustion of clotting factors

Etiology
Sepsis and other severe infections, trauma, and obstetric complications

Diagnostics
No specific criteria
Clinical findings: abnormal bleeding, organ failure, thrombosis
Laboratory findings: Thrombocytopenia, ↑ D-dimer, ↑ PT and aPTT, ↓ fibrinogen

Management
Stabilize patient as needed.
Start urgent treatment of the underlying cause.
Additional measures may include administration of blood products, anticoagulation, or vitamin K



Differential diagnoses by underlying process

- **Decreased production of platelets and clotting factors**
  - Severe hepatic dysfunction
  - Vitamin K deficiency
  - Bone marrow suppression
  - Hemophilia
- **Increased destruction of platelets and clotting factors** [15]
  - Thrombotic thrombocytopenic purpura
  - Immune thrombocytopenic purpura
  - Heparin-induced thrombocytopenia
  - Acute hemolytic anemia
  - Hemolytic uremic syndrome
- **Increased consumption of platelets and clotting factors**
  - DVT/pulmonary embolism
  - Surgery
  - Infections
- **Increased loss of platelets and clotting factors**
  - Massive blood transfusion causing dilutional coagulopathy
  - Capillary leak syndrome

The differential diagnoses listed here are not exhaustive.

- **Thrombocytosis**
  - Definition: absolute platelet count of > 400,000/mm^3
  - Causes
    - Reactive thrombocytosis : secondary to certain conditions, e.g.:
      - Malignancy (e.g., CML)
      - Splenectomy
      - Chronic inflammation
        - Autoimmune diseases: e.g., rheumatoid arthritis, celiac disease, connective tissue disorders
        - Chronic infections: e.g., tuberculosis, syphilis
      - Anemia: hemolytic anemia, iron deficiency
      - Increased cellular turnover following acute blood loss
      - Pregnancy
      - Following cytostatic therapy
    - Splenectomy
    - Essential thrombocythemia

Pancytopenia

- **Definition**: a decrease in the number of cells of all cell lines (i.e., RBCs, WBCs, and platelets) in the peripheral blood
- **Causes**
  - **Aplastic anemia**
  - Fanconi anemia
  - **Multiple myelomas**
  - **Myelodysplastic syndrome**
  - Acute and chronic leukemia
  - Chemotherapy
  - Autoimmune disease (e.g., SLE)
  - Infections (e.g., CMV, EBV)

Warfarin Induced Skin Necrosis

Presentation: painful purpura, hemorrhagic blisters, and large areas of necrosis; mostly affects subcutaneous adipose tissue

Acute Leukemia

Clinical features are either related to bone marrow failure, infiltration of organs by leukemic cells, or a combination of both.

General features of acute leukemia
• Sudden onset of symptoms and rapid progression (days to weeks) • **Anemia**: fatigue, pallor, weakness • **Thrombocytopenia:** epistaxis, bleeding gums, petechiae, purpura • Immature leukocytes: **frequent infections**, fever • **Hepatosplenomegaly** (caused by leukemic infiltration) [2] • Oncologic emergencies can be the first sign of leukemia, e.g., an elderly patient presenting with priapism or DIC may have **leukostasis** (more common in AML than ALL): See oncologic emergencies for further details.

Clinical features of ALL	Clinical features of AML
• **Fever**, night sweats, unexplained weight loss • **Painless** lymphadenopathy • **Bone pain** (presenting as limping or refusal to bear weight in children) • Airway obstruction (stridor, difficulty breathing) due to mediastinal or **thymic infiltration** (primarily in T-cell ALL) [15][16] • Features of SVC syndrome • **Meningeal leukemia** (or leukemic meningitis) → headache, neck stiffness, visual field changes, or other CNS symptoms (caused by CNS involvement) [1][16] • Testicular enlargement (rare finding)	• **Leukemia cutis** (or myeloid sarcoma): nodular skin lesions with a purple or gray-blue color • Gingival hyperplasia (AML subtype M4 and M5) • Signs of CNS involvement, e.g., headache, visual field changes (uncommon)

Fever and lymphadenopathy are rare in AML, but can be common first signs in ALL!

Fever in a patient with acute leukemia must always be treated as a sign of infection until proven otherwise!

Remember metastasis for ALL by thinking of the following: ALL meta**S**ta**S**ize**S** to the CNS and te**S**te**S**.

Leukemia cutis - Multiple erythematous papules and nodules are seen on the face and neck of this patient as a result of infiltrating malignant neoplastic cells accumulating in the dermis.

	Findings in ALL	Findings in AML
Immunohistochemistry	• MPO negative • Terminal deoxynucleotidyl transferase (TdT) positive • Periodic acid-Schiff (PAS): often positive	• MPO positive • TdT negative • PAS negative

Common agents used in chemotherapy regimens for acute leukemia [18][20][25][32][33]	
ALL	• Alkylating agents: e.g., cyclophosphamide • Anthracyclines: e.g., daunorubicin, doxorubicin • Antimetabolites: e.g., cytarabine, methotrexate, 6-mercaptopurine • Enzyme therapy: e.g., L-asparaginase • Alkaloids: e.g., vincristine • Glucocorticoids: e.g., prednisone, dexamethasone
AML	• Anthracyclines (e.g., idarubicin, high-dose daunorubicin) • Antimetabolites (e.g., **cytarabine**, methotrexate) • Hypomethylating agents (e.g., azacitidine)

APL	• Differentiation agents: to induce the maturation of immature malignant WBCs
	  ○ **ATRA (All-trans retinoic acid)**
	  ○ **Arsenic trioxide**
	• Chemotherapy with anthracyclines (e.g., idarubicin)

In APL, the **t(15;17) translocation** and subsequent formation of the *PML-RARA* fusion gene can inhibit myeloblast differentiation under physiological levels of retinoic acid. **High doses of ATRA (a vitamin A derivative)** may induce myeloblast differentiation and **promote remission.**

Splenic rupture due to splenomegaly

Differential diagnosis between leukemoid reaction and myeloproliferative neoplasms			
Disease	**CBC and peripheral blood smear**	**LAP score**	**Genetics/cause**
Polycythemia vera	• Erythrocytosis • Thrombocytosis • Leukocytosis	• ↑	• *JAK2* mutation in 95% of cases
Primary myelofibrosis	• Progressive pancytopenia • Dacryocytes	• ↑	• *JAK2* mutation in up to 60% of cases
Essential thrombocythemia	• Isolated thrombocytosis	• ↑	• *JAK2* mutation in 50% of cases
Chronic myeloid leukemia	• Extreme leukocytosis • Basophilia • Neutrophils may have the Pseudo-Pelger-Huet anomaly	• ↓	• Philadelphia chromosome
Leukemoid reaction [13]	• Leukocytosis • Fewer granulocytic precursors, basophils, and eosinophils compared to CML • Neutrophils have toxic granulation, toxic vacuolation, and Dohle bodies	• ↑	• No mutation • Typically secondary to infections or drugs (e.g., steroids) • Associated with certain solid tumors (e.g., lung and kidney cancer)

CLL

Clinical features

About half of cases of CLL remain asymptomatic for a long period, resulting in late or incidental diagnosis.

- Weight loss, fever, night sweats, fatigue (B symptoms)
- **Painless lymphadenopathy**
- Hepatomegaly and/or splenomegaly may occur.
- Repeated **infections**
  - Severe bacterial infections (e.g., necrotic erysipelas)
  - Mycosis (candidiasis)
  - Viral infections (herpes zoster)
- Symptoms of **anemia** and **thrombocytopenia**
- **Dermatologic symptoms**
  - Leukemia cutis
  - Chronic pruritus
  - Chronic urticaria

Lymphadenopathy is a typical finding in lymphoid malignancies such as CLL and helps to differentiate CLL from CML, a myeloid malignancy.

Hodgkin Lymphoma

Clinical features

- **Painless lymphadenopathy**
  - First develops in a single group of lymph nodes, typically **cervical**, supraclavicular and/or mediastinal lymph nodes [5][6][7]
  - Spreads contiguously through the lymphatic system; cervical nodes → supraclavicular lymph nodes → axillary nodes → inguinal nodes [8]
- **Splenomegaly or hepatomegaly** [9]
- **B symptoms** [10]
  - **Night sweats**, **weight loss** > 10% in the past 6 months, **fever** > 38°C (100.4°F)
  - Can occur in a variety of diseases (see “Differential diagnosis of B symptoms” below)
  - In the case of confirmed HL, the presence of a single B symptom suffices for a positive diagnosis of B symptoms.
- **Pel-Ebstein fever**: intermittent fever with periods of high temperature for 1–2 weeks, followed by afebrile periods for 1–2 weeks; relatively rare but very specific for HL
- **Alcohol-induced pain**: pain in involved lymph nodes after ingestion of alcohol; relatively rare but highly specific for HL
- **Pruritus**: focal or generalized

Differential diagnoses of B symptoms

- Non-Hodgkin lymphomas, Hodgkin lymphomas
- Other hematopoietic malignancies (e.g., CML, ALL)
- Solid tumors
- Tuberculosis
- HIV

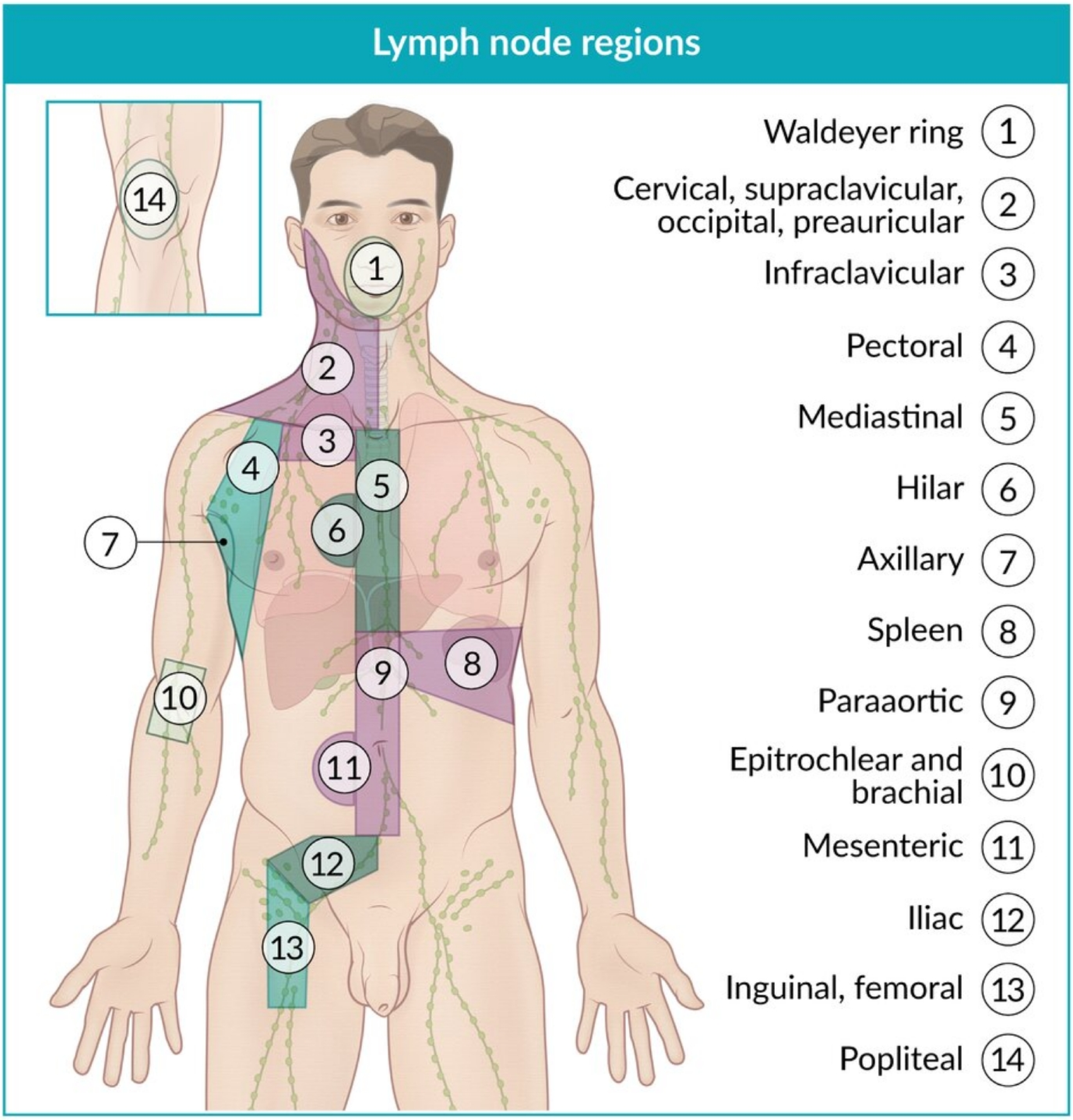
Hodgkin vs. non-Hodgkin lymphoma

Hodgkin lymphoma vs. non-Hodgkin lymphoma		
Feature	**Hodgkin lymphoma**	**Non-Hodgkin lymphoma**
Age distribution	• Bimodal (late adolescence and older adulthood)	• Increases with age (peak > 50 years)
Etiology	• Immunosuppression (e.g., HIV) • EBV infection	• Chromosomal translocation, commonly t(14;18) • Autoimmune diseases (e.g., Hashimoto thyroiditis, rheumatic disease) • Infections (HIV, EBV, HTLV-1)
Lymph node involvement	• Lymph node groups localized above the diaphragm • Contiguous spread • Extranodal involvement rare	• Multiple lymph node groups • Noncontiguous spread • Extranodal involvement common
Histology	• Reed-Sternberg cells	• Majority are neoplastic cells of B-cell lineage
Five-year survival rate	• 80–90%	• ~ 70%

Lugano classification of lymphomas [9]

- The Lugano classification is used for staging of Hodgkin lymphoma and staging of non-Hodgkin lymphomas.

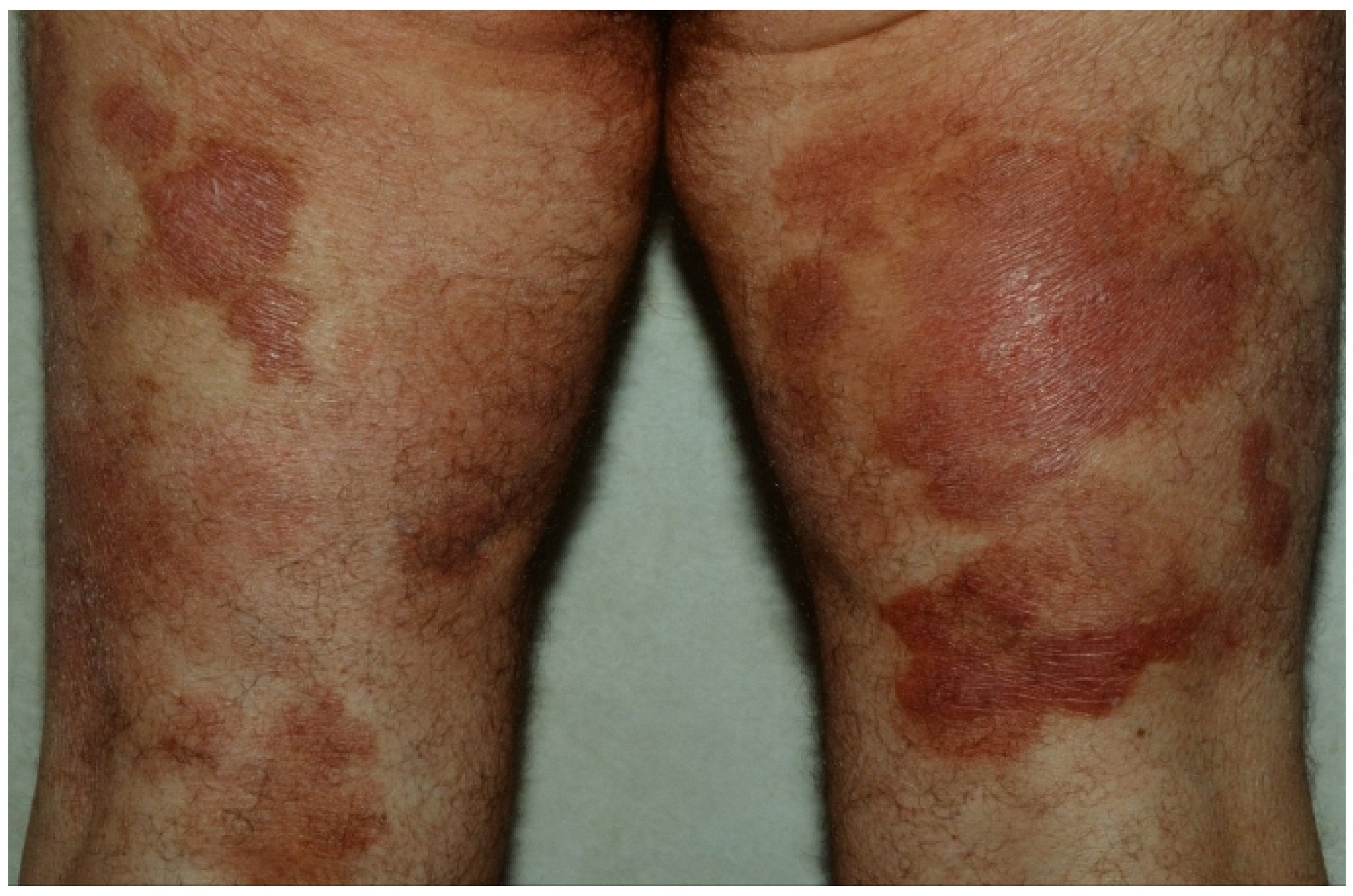
Lugano classification of primarily nodal lymphomas [9]		
Stage		**Features**
Limited-stage lymphoma	**I**	• Isolated involvement of either ◦ 1 lymph node area **(I)** ◦ 1 extranodal focus **(IE)**
	II	• **Confined to one side of the diaphragm** with involvement of any of the following ◦ ≥ 2 lymph node areas **(II)** ◦ ≥ 1 lymph node area with limited contiguous extranodal spread **(IIE)**
II bulky		• Features of either II or IIE that include a large single nodal mass [9]
Advanced-stage lymphoma	**III**	• Involvement of either of the following: ◦ Lymph nodes **on both sides of the diaphragm** ◦ Supradiaphragmatic lymph nodes plus the spleen (**IIIS**)
	IV	• **Disseminated, noncontiguous spread** into extralymphatic organs (e.g., liver, lung, bone marrow)
A and B modifiers are only used for Hodgkin lymphoma stages [9]		
A: absence of B symptoms		
B: B symptoms present		



Lymph node regions
Waldeyer ring 1
Cervical, supraclavicular, occipital, preauricular 2
Infraclavicular 3
Pectoral 4
Mediastinal 5
Hilar 6
Axillary 7
Spleen 8
Paraaortic 9
Epitrochlear and brachial 10
Mesenteric 11
Iliac 12
Inguinal, femoral 13
Popliteal 14

Cutaneous T cell Lymphoma

Mycosis fungoides



- **Treatment for early stage disease** [7]
    - **Topical corticosteroids** (first-line)
    - Topical nitrogen mustard (second-line)
- **Treatment for moderate to late stage disease** [8]
    - Total skin electron beam therapy (TSEBT)
    - Systemic chemotherapy (e.g., bexarotene)
    - Topical corticosteroids may also be used.

- **Multiple myeloma**: a malignant plasma cell dyscrasia characterized by uncontrolled proliferation and the diffuse infiltration of monoclonal plasma cells in the bone marrow

Classification

- **Based on immunoglobulin type** [2]
  - IgG and IgA: typical multiple myeloma; majority of patients
  - Bence Jones myeloma (free light chains excreted in urine): 15–20% of multiple myelomas
  - IgD, IgE, and IgM: very rare subtypes of multiple myelomas

Pathophysiology

- Neoplastic proliferation of **plasma cells**
  - Bone marrow infiltration by malignant plasma cells → suppression of hematopoiesis → leukopenia, thrombocytopenia, anemia
  - Cell proliferation → pro-osteoclastogenic factors (e.g., TNF-α, IL-1, RANK-L) → osteolytic lesions → hypercalcemia
- Overproduction of **monoclonal immunoglobulin** and/or light chains → dysproteinemia (a state of pathologically increased synthesis of immunoglobulins and/or their subunits) → kidney damage (e.g., myeloma cast nephropathy) and/or paraprotein tissue deposition (may cause amyloidosis) [3] [4]
  - Nonfunctioning antibodies → functional antibody deficiency
  - ↑ Serum viscosity → hyperviscosity syndrome

Clinical features

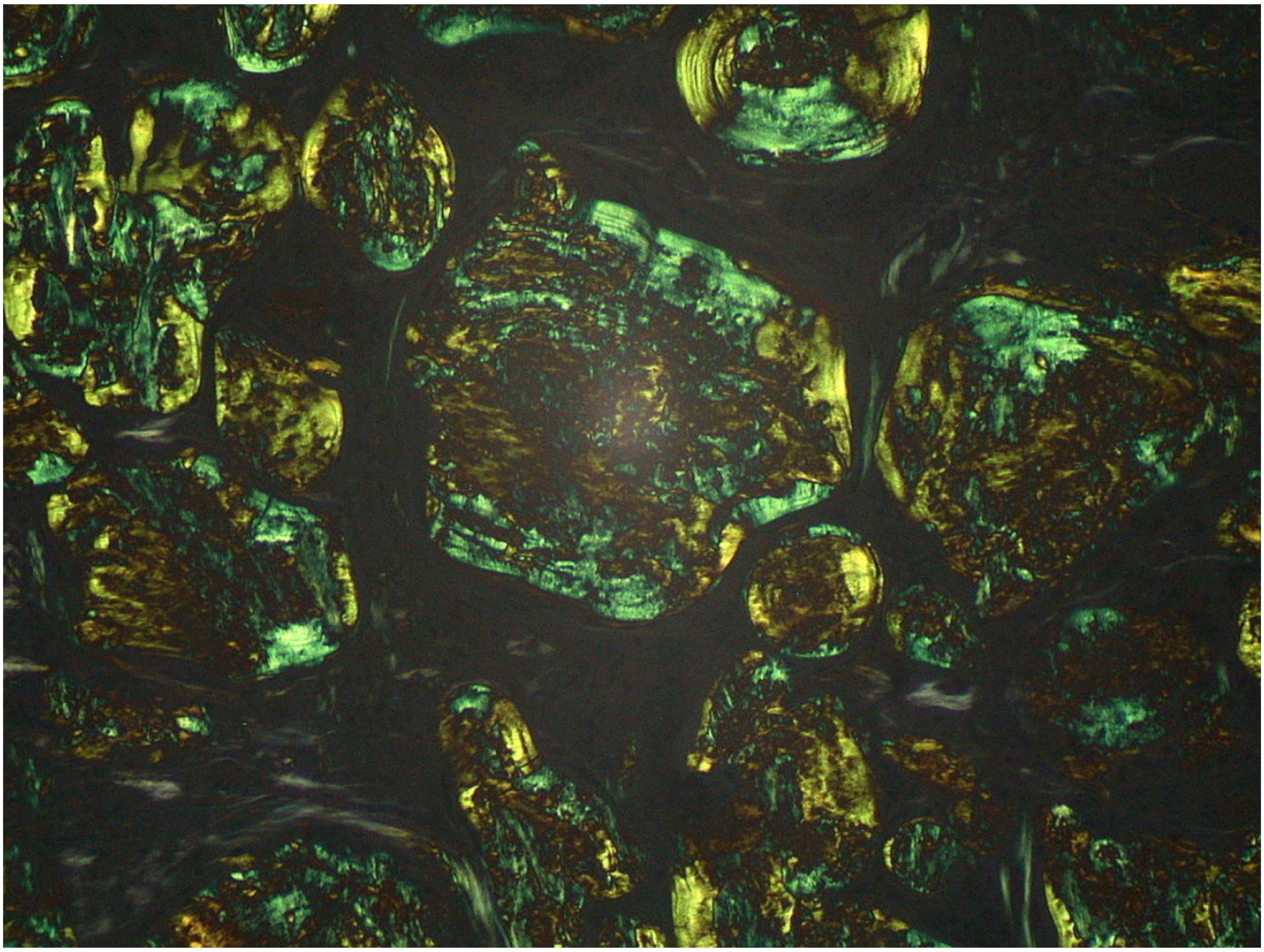
- Often asymptomatic
- Mild fever, night sweats, weakness, and weight loss
- Bone pain, especially **back pain** (most common symptom)
- Symptoms of hypercalcemia
- Spontaneous fractures
- Increased risk of infection
- Increased risk of petechial bleeding
- Foamy urine (caused by Bence Jones proteins in urine)

Multiple Myeloma

Multiple lytic lesions, punched-out holes in the skull seen on X-Ray skull

Osteolytic Lesions
in multiple myeloma

Diagnostic criteria for plasma cell dyscrasias associated with multiple myeloma [8][18][24]	
Plasma cell dyscrasia	**Diagnostic criteria**
Solitary plasmacytoma	• Presence of a solitary mass (bone or soft tissue) with biopsy-confirmed clonal plasma cells • PLUS no or minimal bone marrow involvement (< 10% plasma cells in bone marrow) • PLUS no evidence of additional bone lesions on imaging • PLUS no end-organ damage (i.e., no CRAB criteria)
Monoclonal gammopathy of undetermined significance (MGUS)	• Paraproteins: monoclonal immunoglobulins (IgG or IgA) detectable in serum < 3 g/dL • PLUS < 10% of monoclonal plasma cells in bone marrow • **PLUS no myeloma defining event** (i.e., no CRAB criteria)
Waldenstrom macroglobulinemia [25][26]	• Monoclonal IgM of any concentration detectable on SPEP, UPEP, and/or immunofixation • PLUS bone marrow biopsy findings of infiltration by small lymphocytes with plasmacytoid or plasma cell differentiation



Apple green birefringence under polarized light seen in Amyloidosis.

Congo red stain used

- Gastric MALTomas
  - Present similarly to peptic ulcer disease and gastritis
  - **Abdominal pain**
  - **Melena**, hematemesis, potentially anemia
  - Fatigue, weight loss
- Non-gastric MALTomas
  - Salivary MALToma: **parotid enlargement**
  - Thyroid MALToma: may present with compression symptoms (e.g., dysphagia, hoarseness)

According to the WHO classification, the following disorders are **myeloproliferative neoplasms**:

- **Common (classic)**
  - **Essential thrombocythemia**
  - **Polycythemia vera**
  - **Primary myelofibrosis**
  - **Chronic myeloid leukemia**
- **Less common**
  - Chronic eosinophilic leukemia
  - Chronic neutrophilic leukemia
  - Myeloproliferative neoplasms, unclassifiable

All MPNs can potentially progress to AML. [2]

Sickle Cell Disease

Acute manifestations

- Vaso-occlusive events
  - Dactylitis in **children < 5 years of age** [6]
    - Typically the earliest manifestation of sickle cell disease
    - Most common in children between 6 months and 2 years of age; uncommon in older children and adults
  - Vasoocclusive crises (sickle cell pain crisis) [1][7]
    - Most common acute complication of sickle cell disease
    - Characterized by recurrent episodes of severe throbbing or sharp pain
    - Typically affects the limbs, chest, and back and lasts for ~ 7 days
    - Often associated with other vasoocclusive events (especially dactylitis in children)
  - Acute chest syndrome
  - Priapism
  - Stroke (common in children)
  - Sickle cell hepatopathy
  - Organ infarctions (any organ; particularly the spleen)
  - Avascular necrosis
- **Infection**
  - Pneumonia
  - Meningitis
  - **Osteomyelitis** (most common cause: ***Salmonella* spp.**, *Staphylococcus aureus*)
  - **Sepsis** (most common cause: ***Streptococcus pneumoniae***)
- **Acute hemolytic crisis**
  - **Splenic sequestration**
  - **Aplastic crisis**

- **Peripheral blood smear** findings may include:
  - Crescent-shaped sickled RBCs (drepanocytes or **sickle cells**)
  - Target cells
  - **Howell-Jolly bodies**: occur with splenic dysfunction
  - Reticulocytosis: indicates the presence of hemolysis

Chronic manifestations

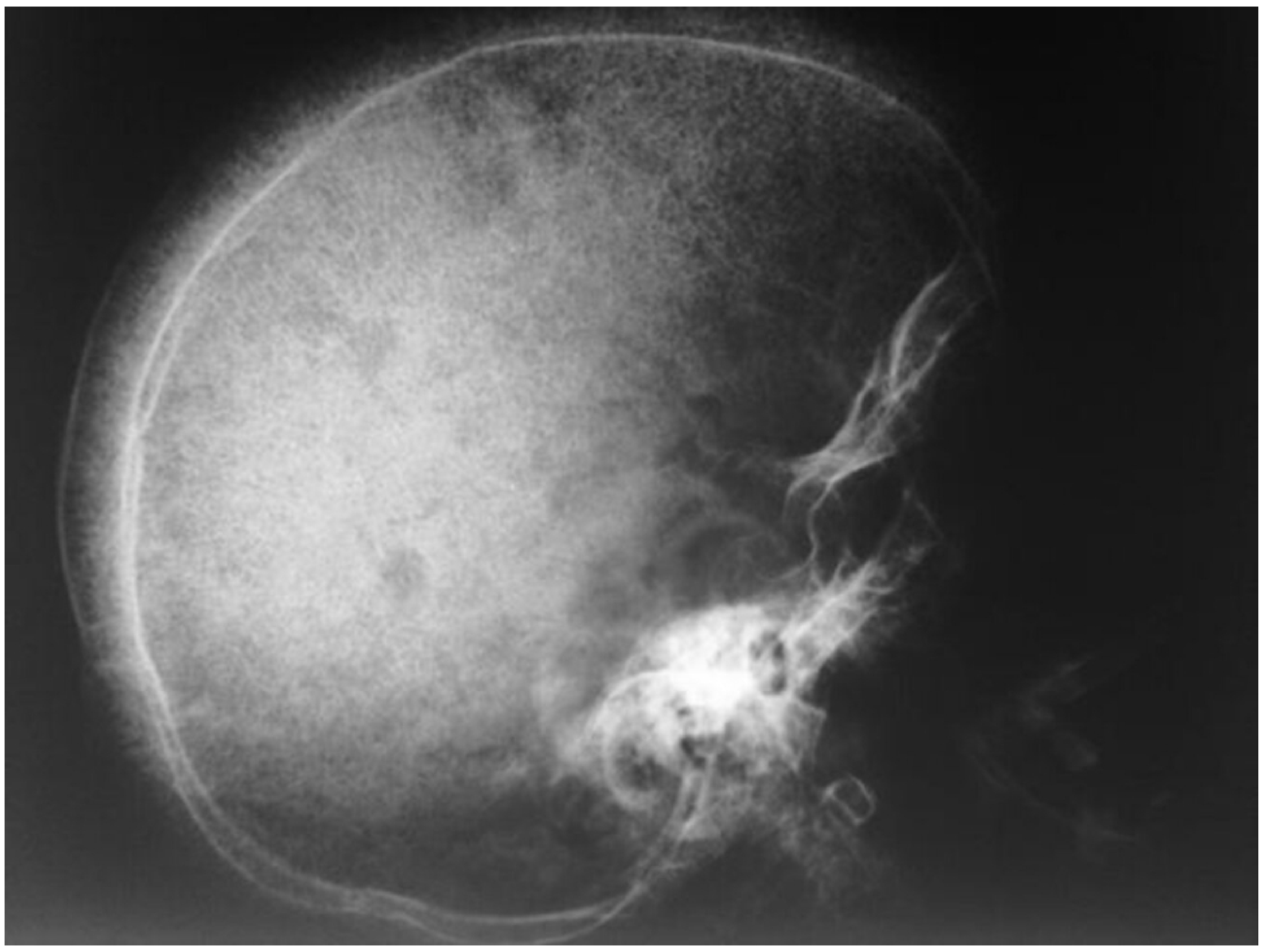
- Chronic hemolytic anemia: fatigue, weakness, pallor; usually well-tolerated
- Chronic pain
- Cholelithiasis (pigmented stones)

Symptoms of other forms of sickle cell syndrome (HbSC disease and HbS/beta-thalassemia) are similar to sickle cell disease but less severe.

Dactylitis in sickle cell disease

Dactylitis - The entire left index finger of this patient with psoriatic arthritis is swollen. This appearance is typical of dactylitis, which can be caused by a variety of conditions, including spondyloarthropathies, infections, and sickle cell disease.

Seen in Thalassemia and sickle cell anemia



Skull x-ray [14]

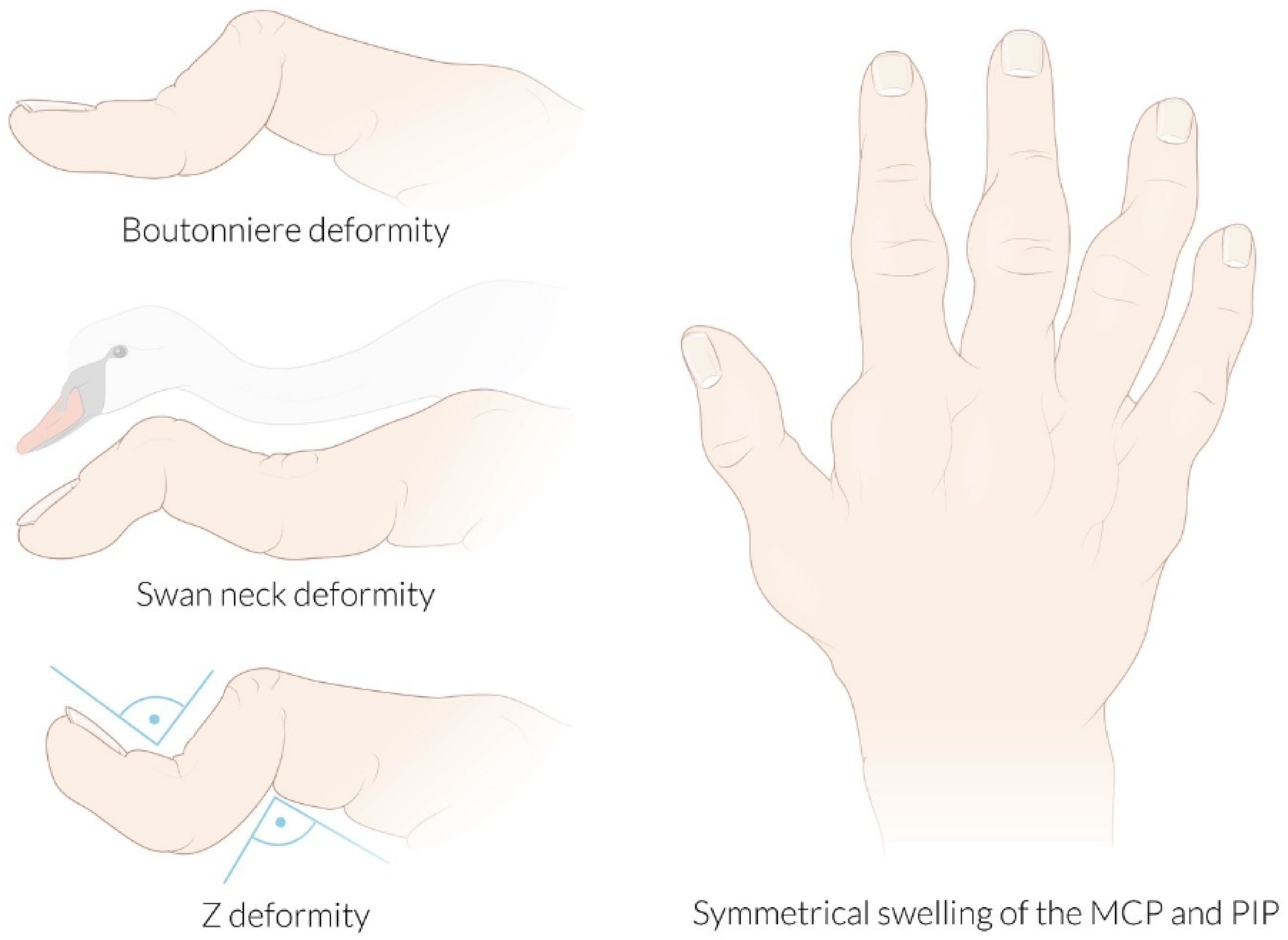
- May show hair-on-end ("crew cut") sign
- Caused by periosteal reaction to erythropoietic bone marrow hyperplasia

Rheumatoid Arthritis

- Rheumatoid hand is characteristic and typically manifests with one or more of the following deformities:
  - Deepening of the interosseous spaces of the dorsum of hand
  - Swan neck deformity: PIP hyperextension and DIP flexion
  - Boutonniere deformity: PIP flexion and DIP hyperextension.
  - Hitchhiker thumb deformity (Z deformity of the thumb): hyperextension of the interphalangeal joint with fixed flexion of the MCP joint [13]
  - Ulnar deviation of the fingers
  - Piano key sign: dorsal subluxation of the ulna

Rheumatoid Nodules

Swan Neck Deformity

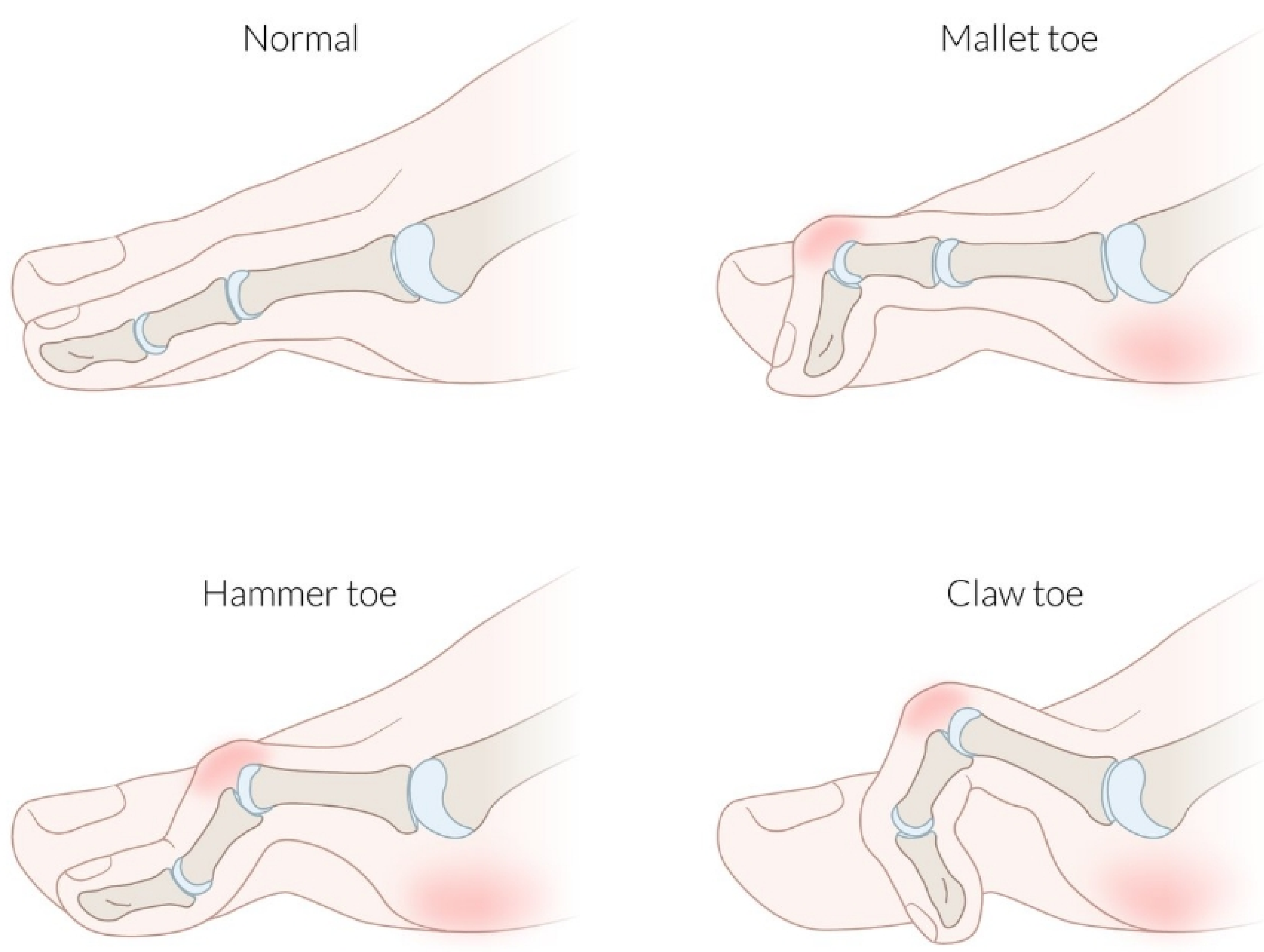


Boutonniere deformity

Rheumatoid Arthritis

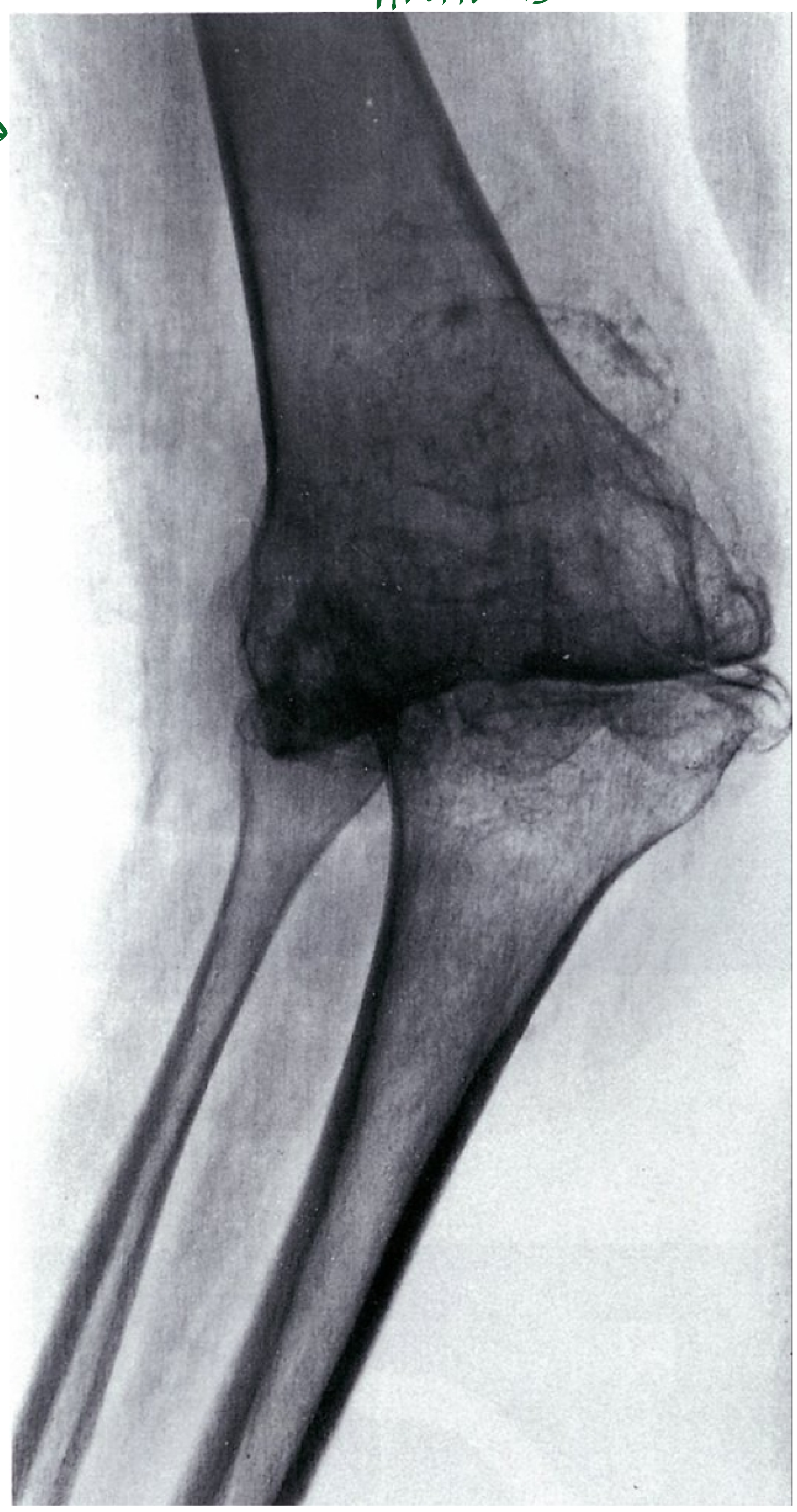
- Hammer toe or claw toe
- **Atlantoaxial subluxation** (see "Rheumatoid arthritis of the cervical spine" below)

- Physical examination: compression test (Gaenslen squeeze test)
  - Painful compression of hands (or feet) at the level of the MCP joint (metatarsophalangeal joint)
  - Painful handshake is an early sign of arthritis



MRI cervical spine showing atlanto axial subluxatio in Rheumatoid Arthritis

X-Ray knee showing knee joint destruction in Rheumatoid Arthritis



Olecranon bursitis

Popliteal (Baker) Cyst

GOUT


Podagra


Podagra


Soft tissue tophi


Gouty tophi


Gouty tophi of hands


Gouty tophi


Mono arthritis in acute gouty arthritis

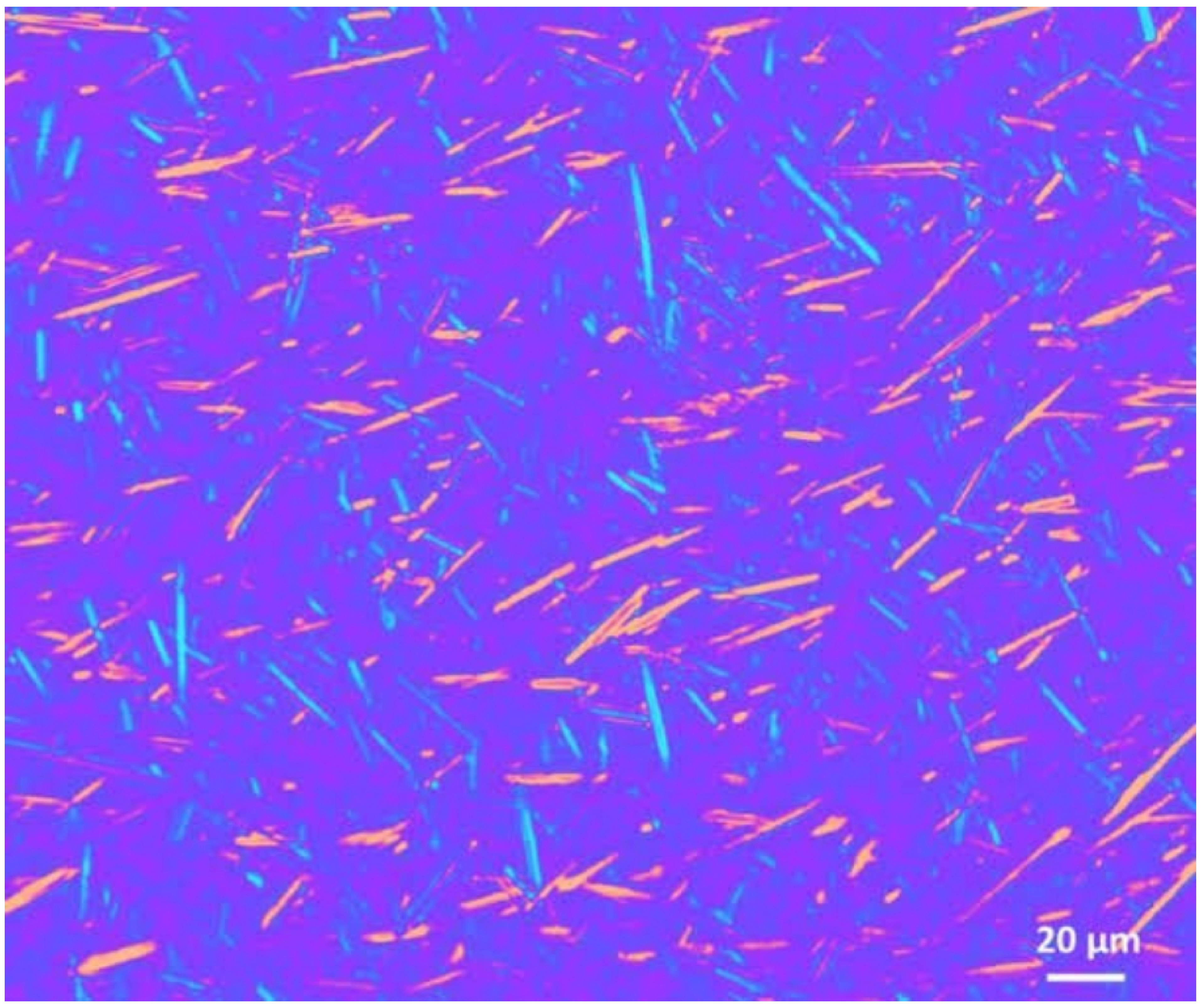

Gouty Tophi

* Deposition of
mono Sodium urate (MSU) crystals

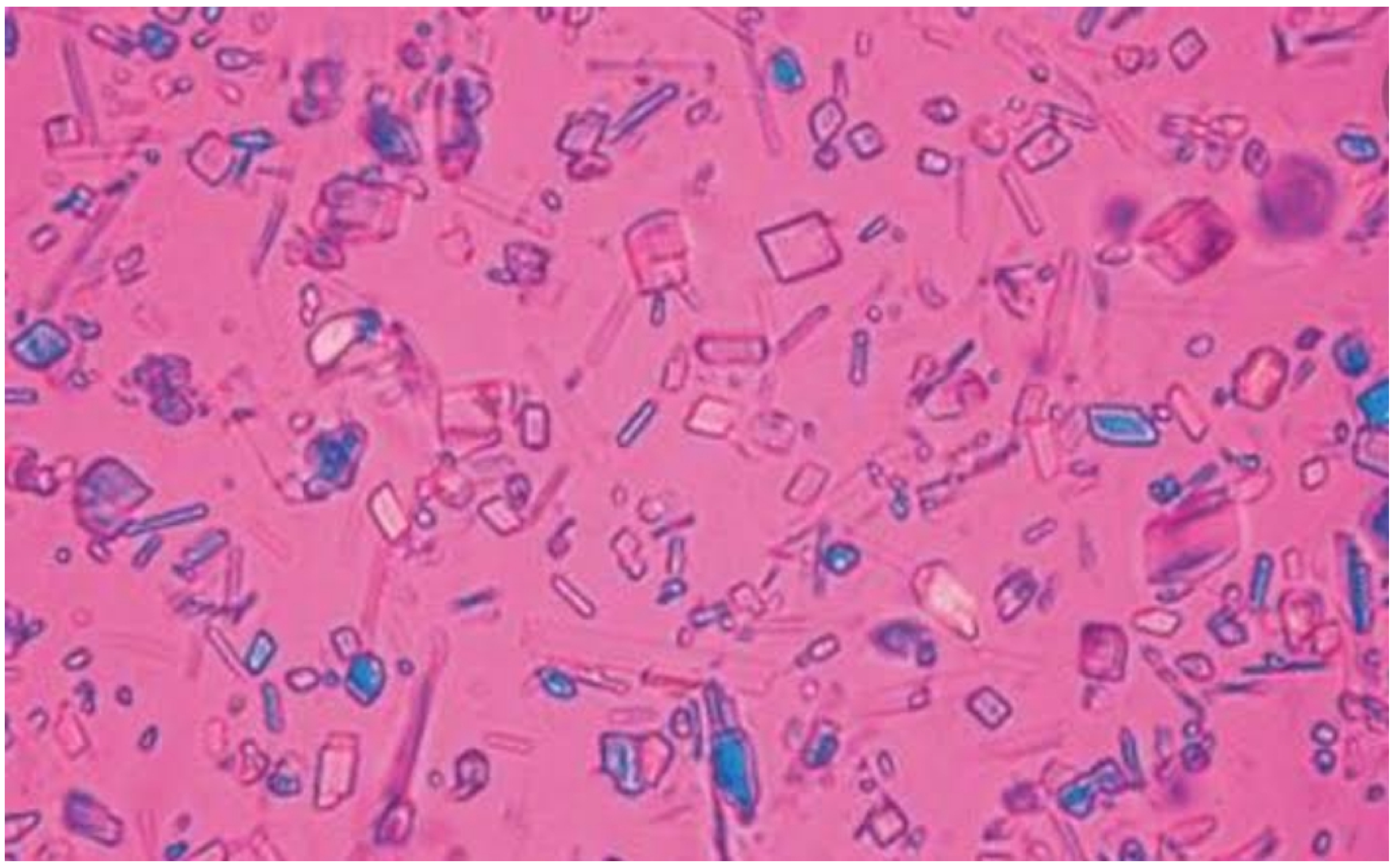
* Joint Aspiration is the
most accurate test

Gouty tophi

Podagra X-Ray foot



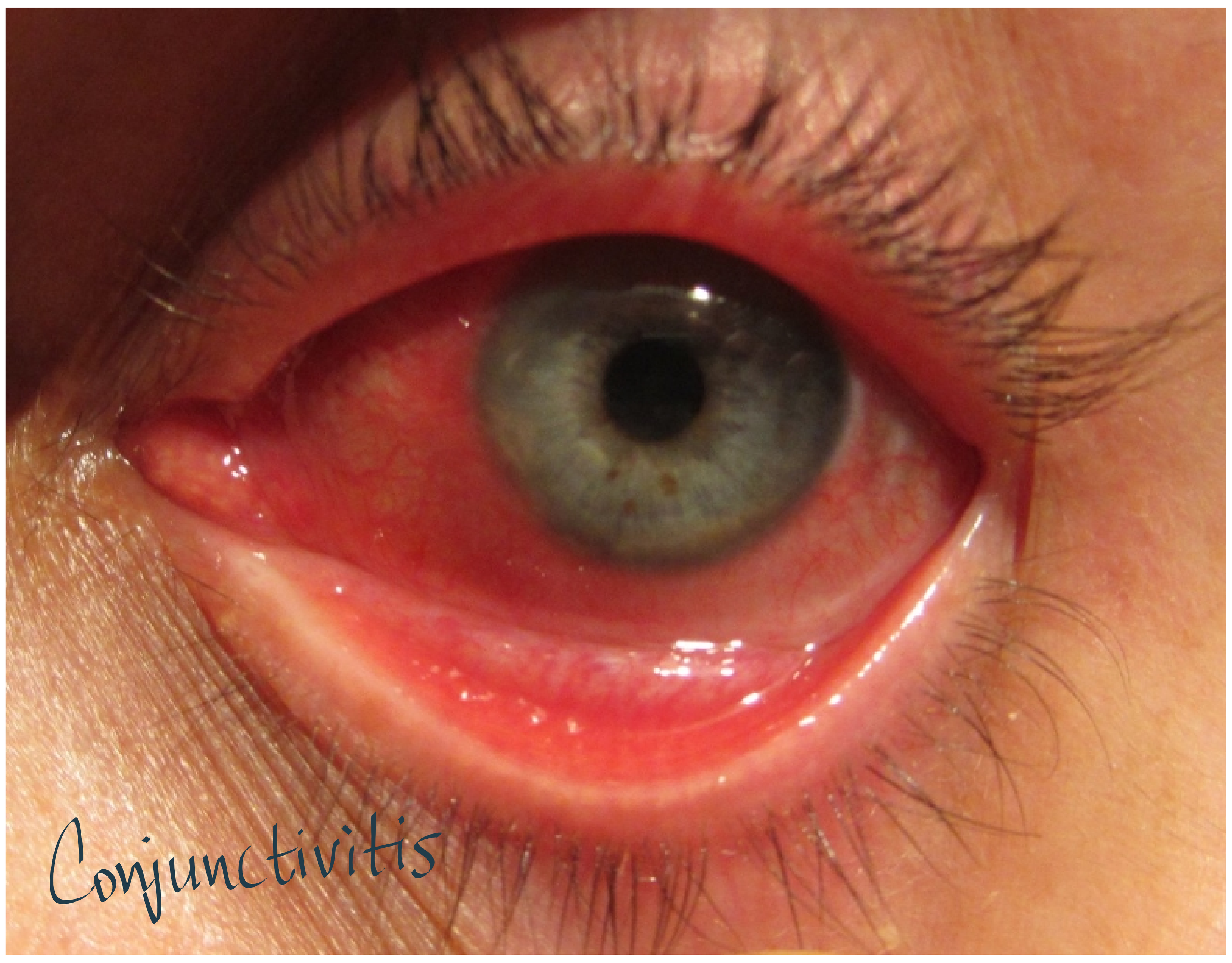
Gout → Negatively birefringment needle-like crystals under polarized light



Pseudogout → Positively birefringent rhomboid shaped crystals under polarized light

Reactive Arthritis

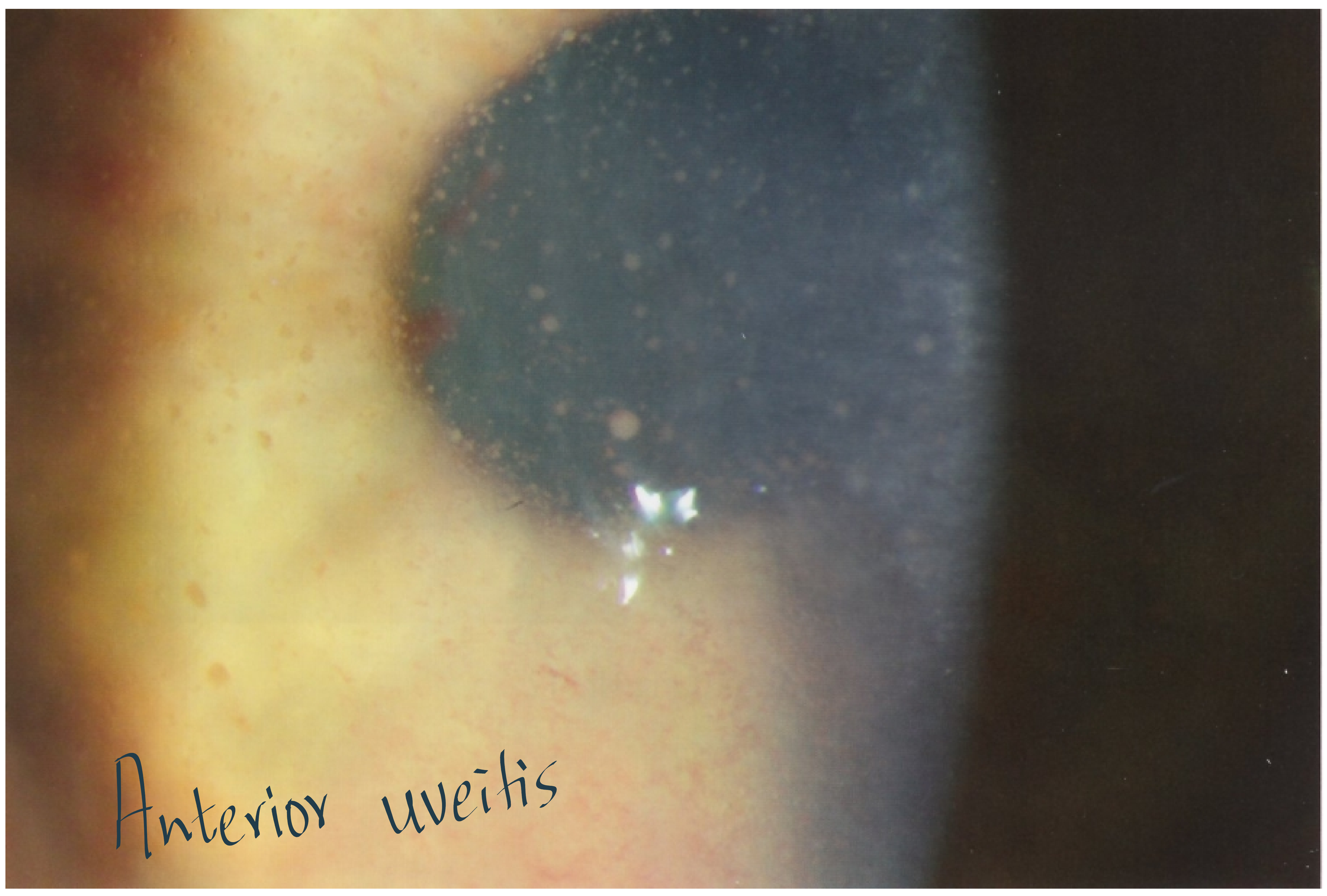
Knee effusion



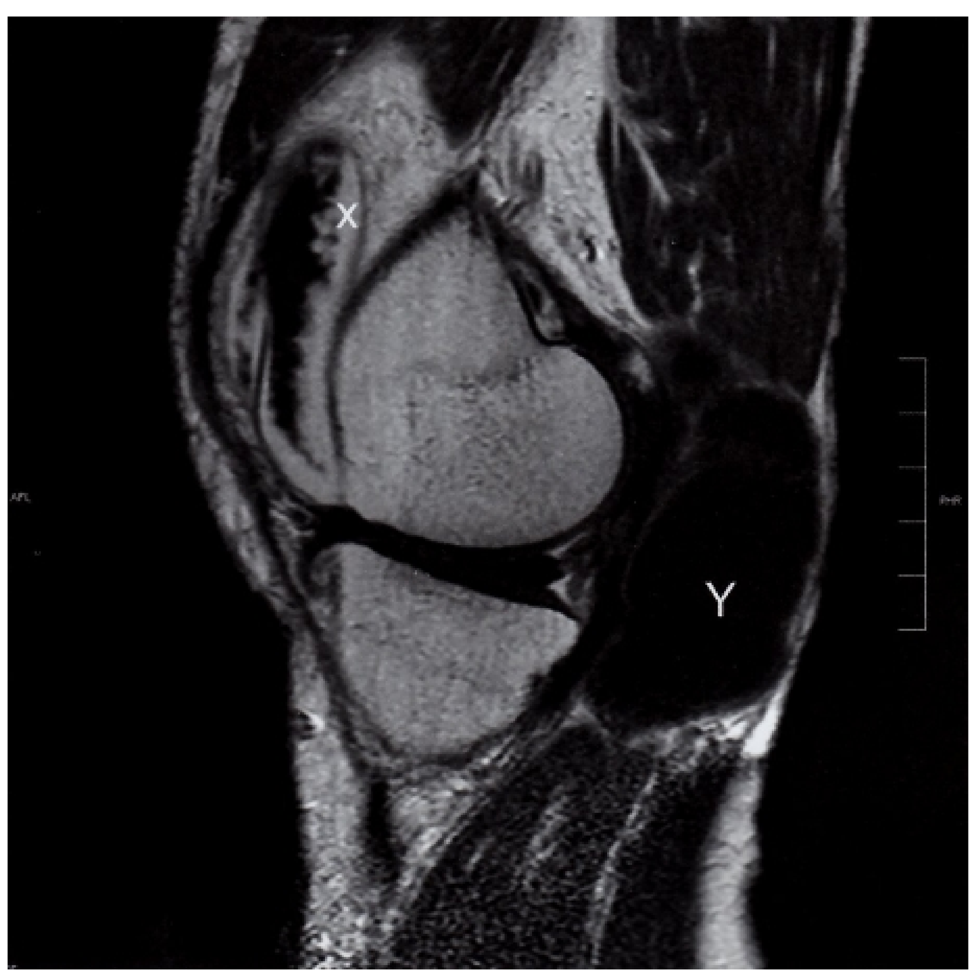
Conjunctivitis

Balanitis circinata

Keratoderma blenorrhagicum

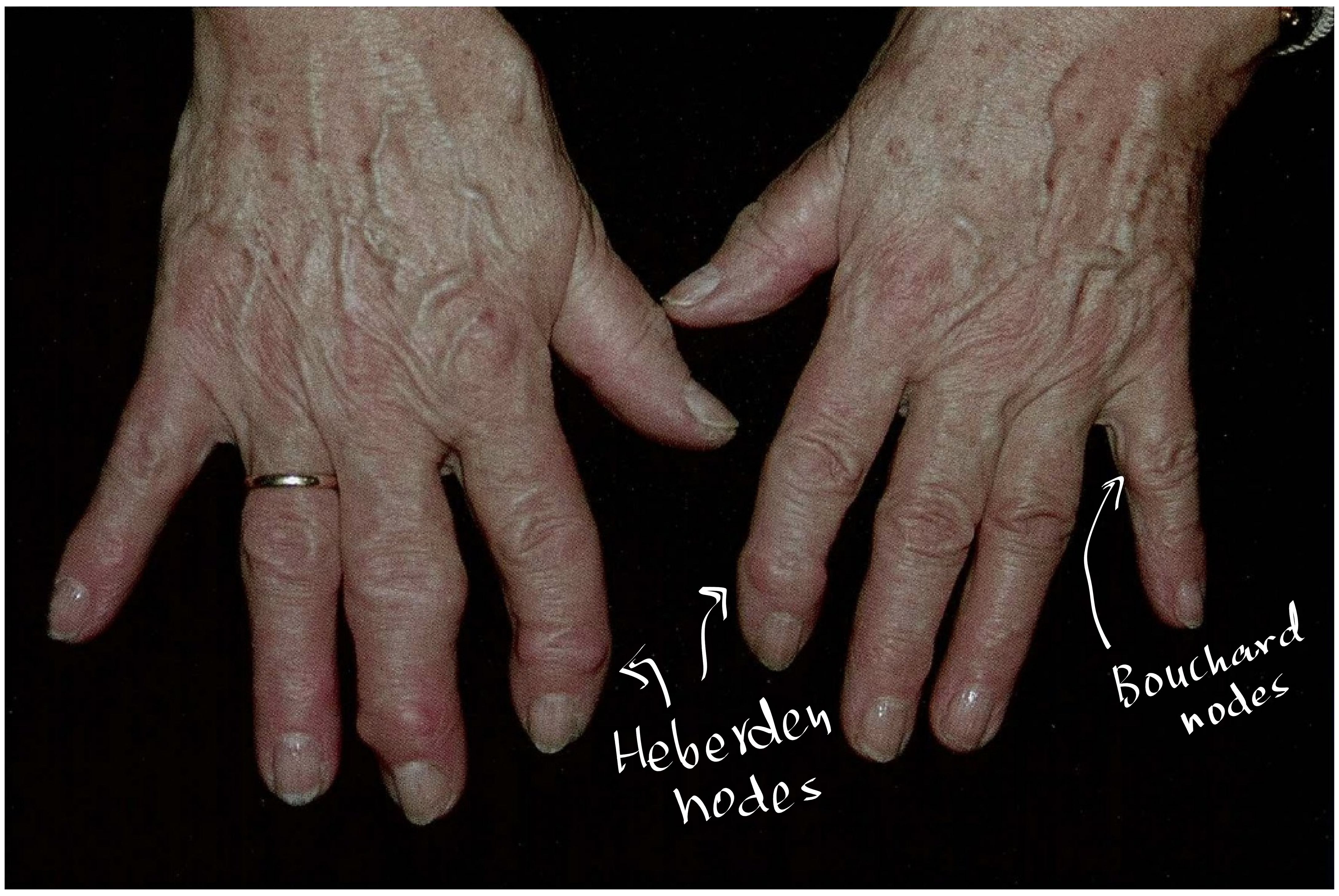


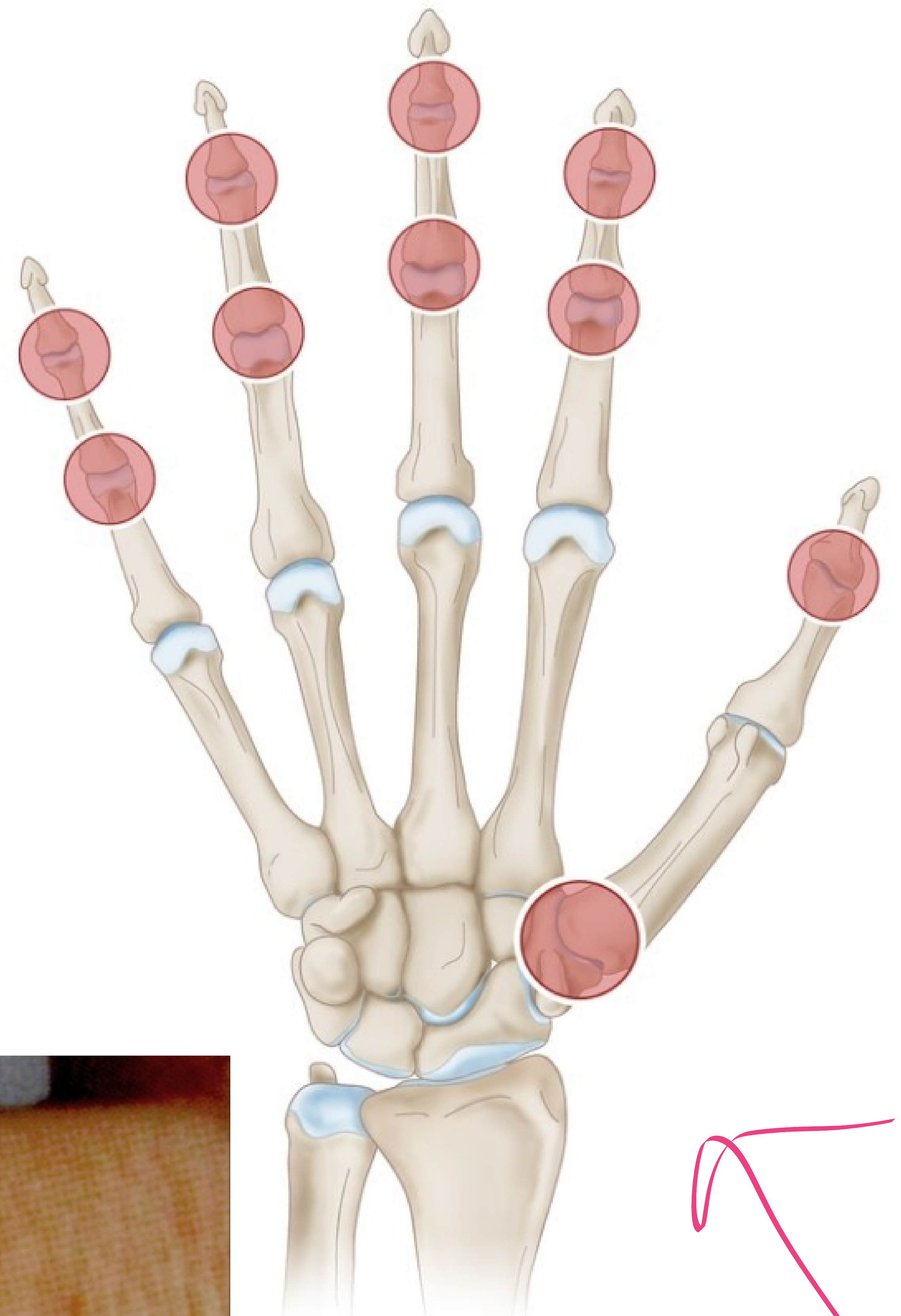
Anterior uveitis

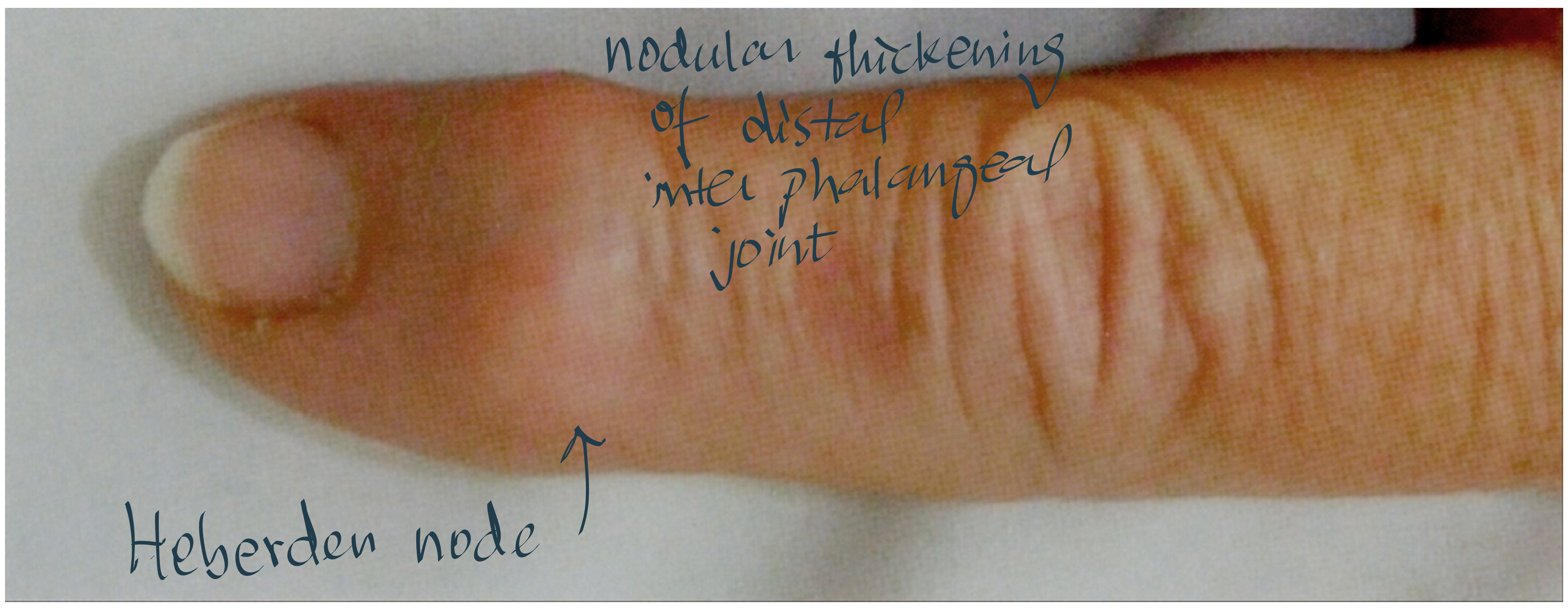


MRI knee showing synovitis of knee joint

OSTEO ARTHRITIS







Distribution pattern of osteoarthritis of the hand - Osteoarthritis of the hand affects especially the distal interphalangeal joints (Heberden nodes), proximal interphalangeal joints (Bouchard nodes), and the first carpometacarpal joint, between the trapezoid and the first metacarpal (Rhizarthrosis).

Sarcoidosis

Etiology
Multisystem disorder with T-cell dysfunction and noncaseating granuloma formation

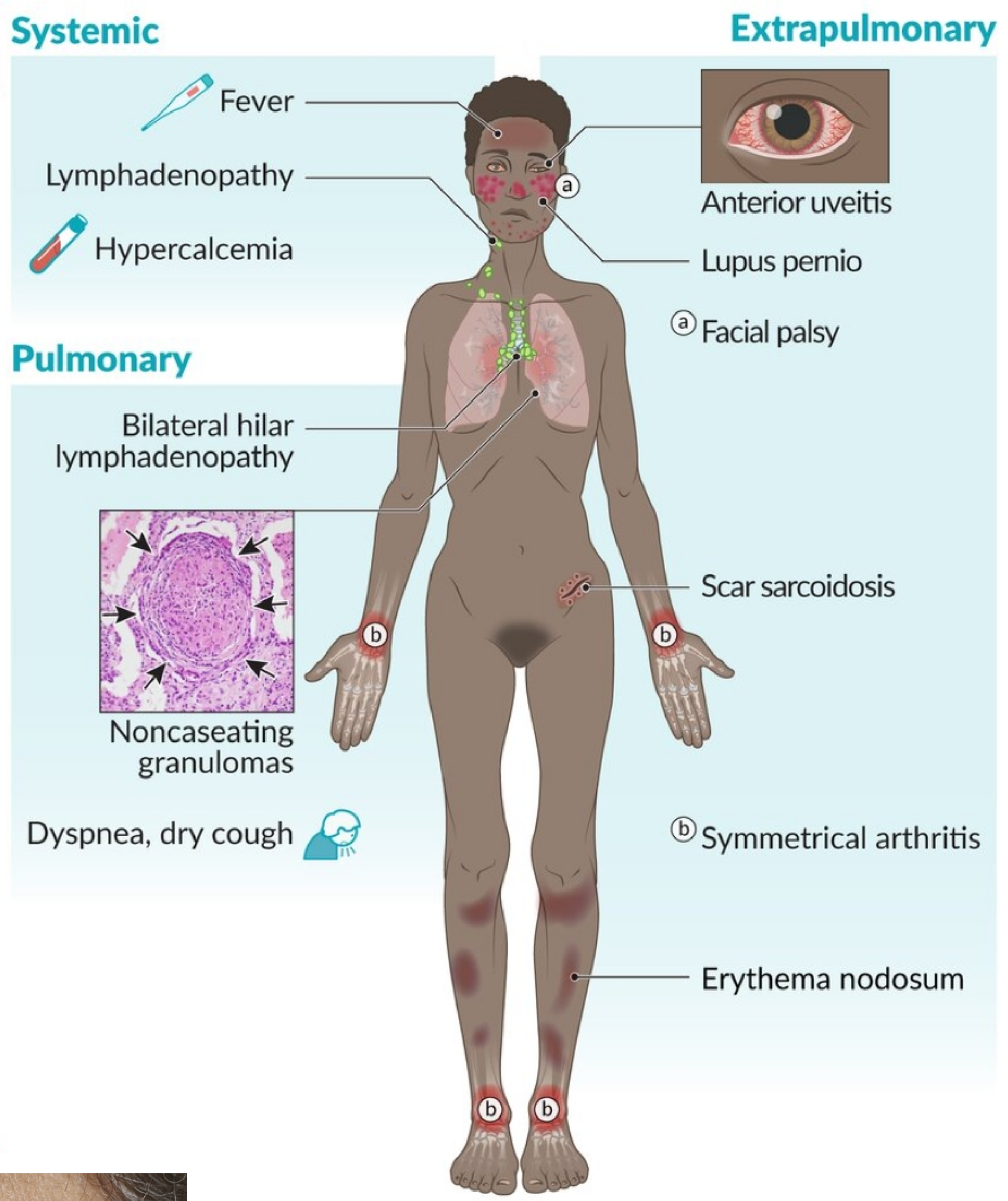
Epidemiology
♀ > ♂; peak age: 30–55 years
Incidence highest in the US among African American women

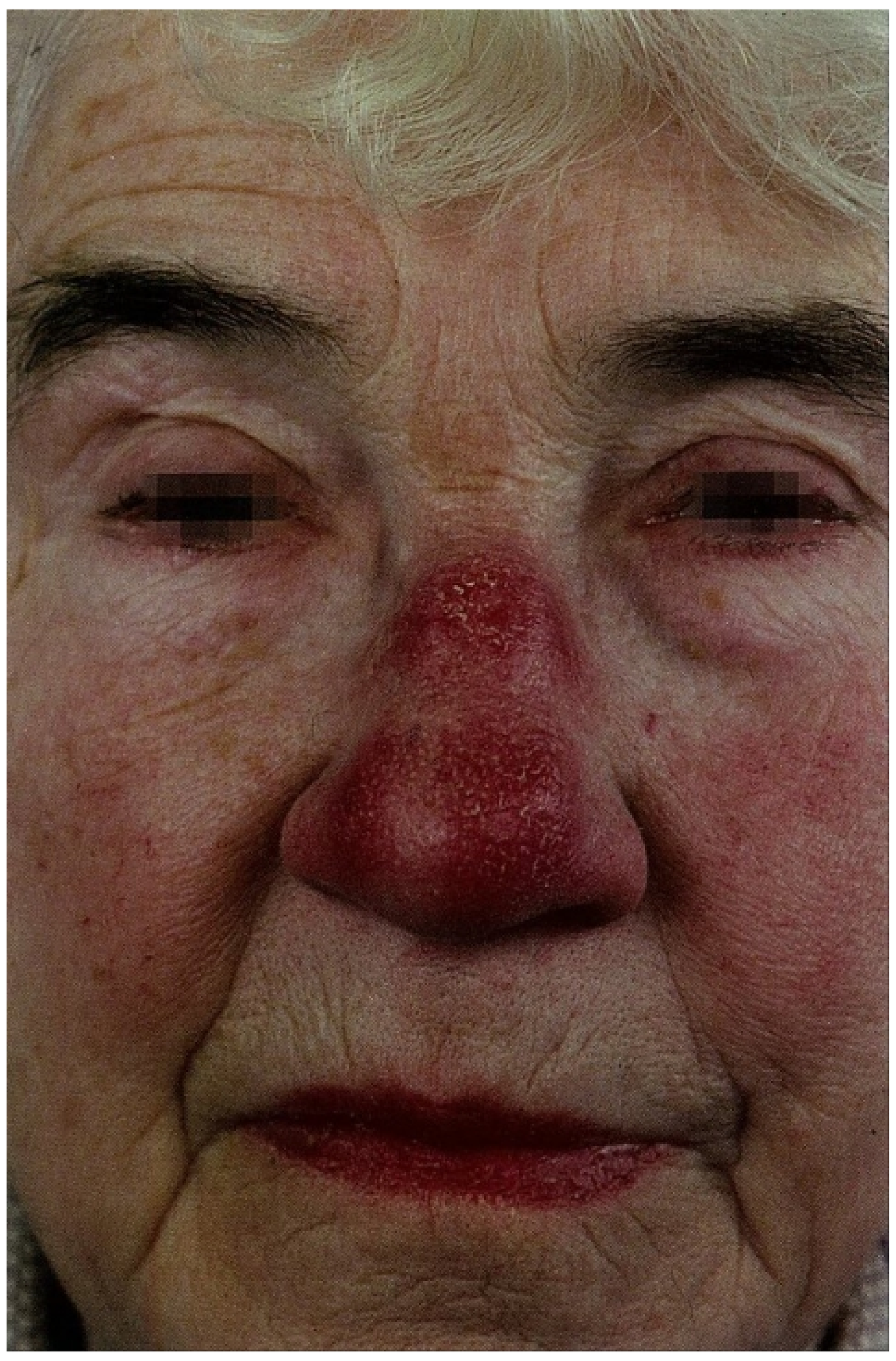
Histopathyoogy (gold standard)
Noncaseating granulomas on biopsy; exclude more common granulomatous diseases

Diagnostic studies
- Chest x-ray: bilateral hilar lymphadenopathy
- Bronchoalveolar lavage: CD4:CD8 ratio > 3.5 supports the diagnosis

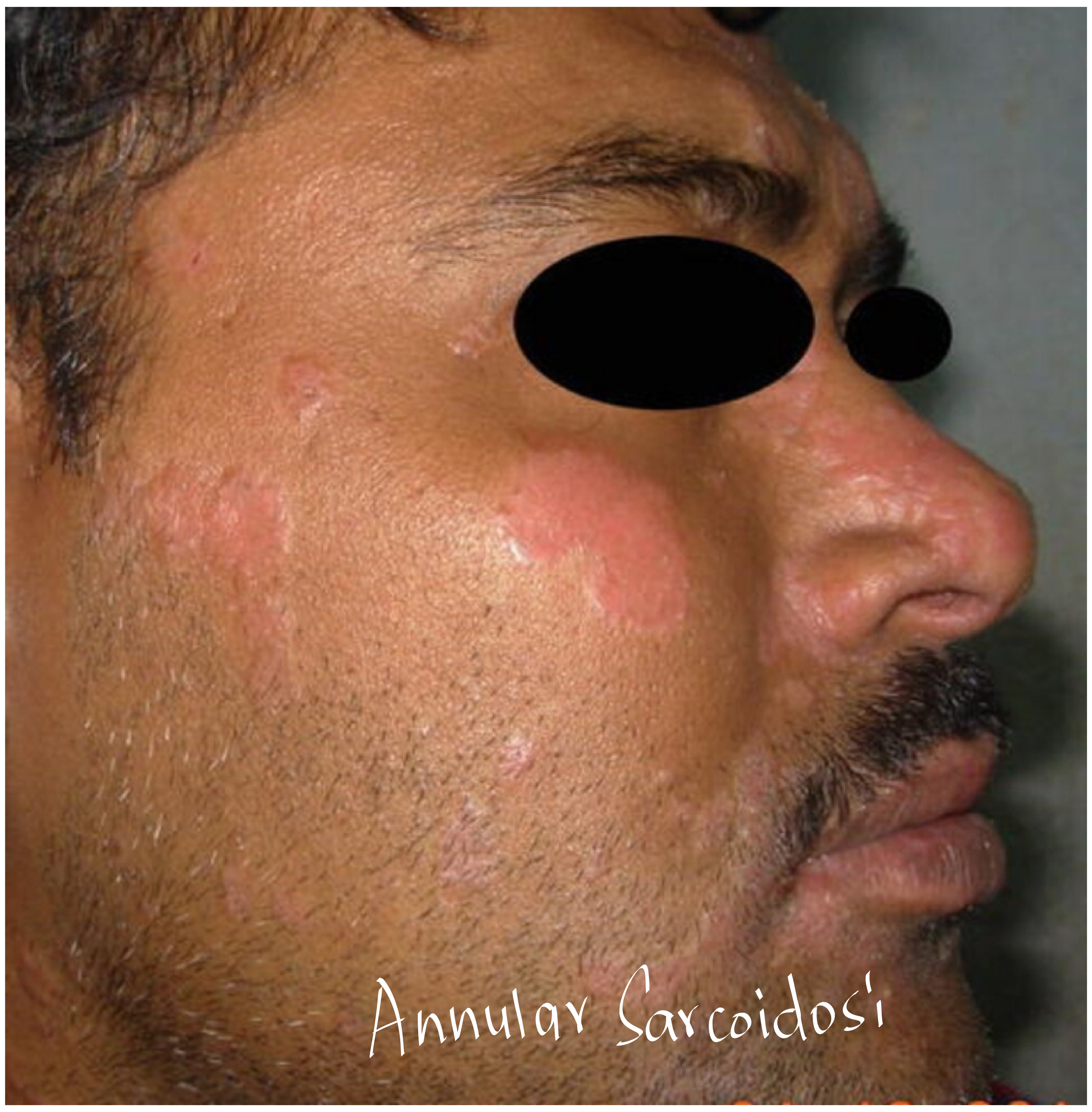
Complications
Bronchiectasis, pulmonary fibrosis, chronic renal failure

Prognosis
Spontaneous remission in 20%–70% of patients





Lupus pernio ← (pathognomonic of sarcoidosis)


Annular Sarcoidosi


Cutaneous
manifestation
of
Sarcoidosis

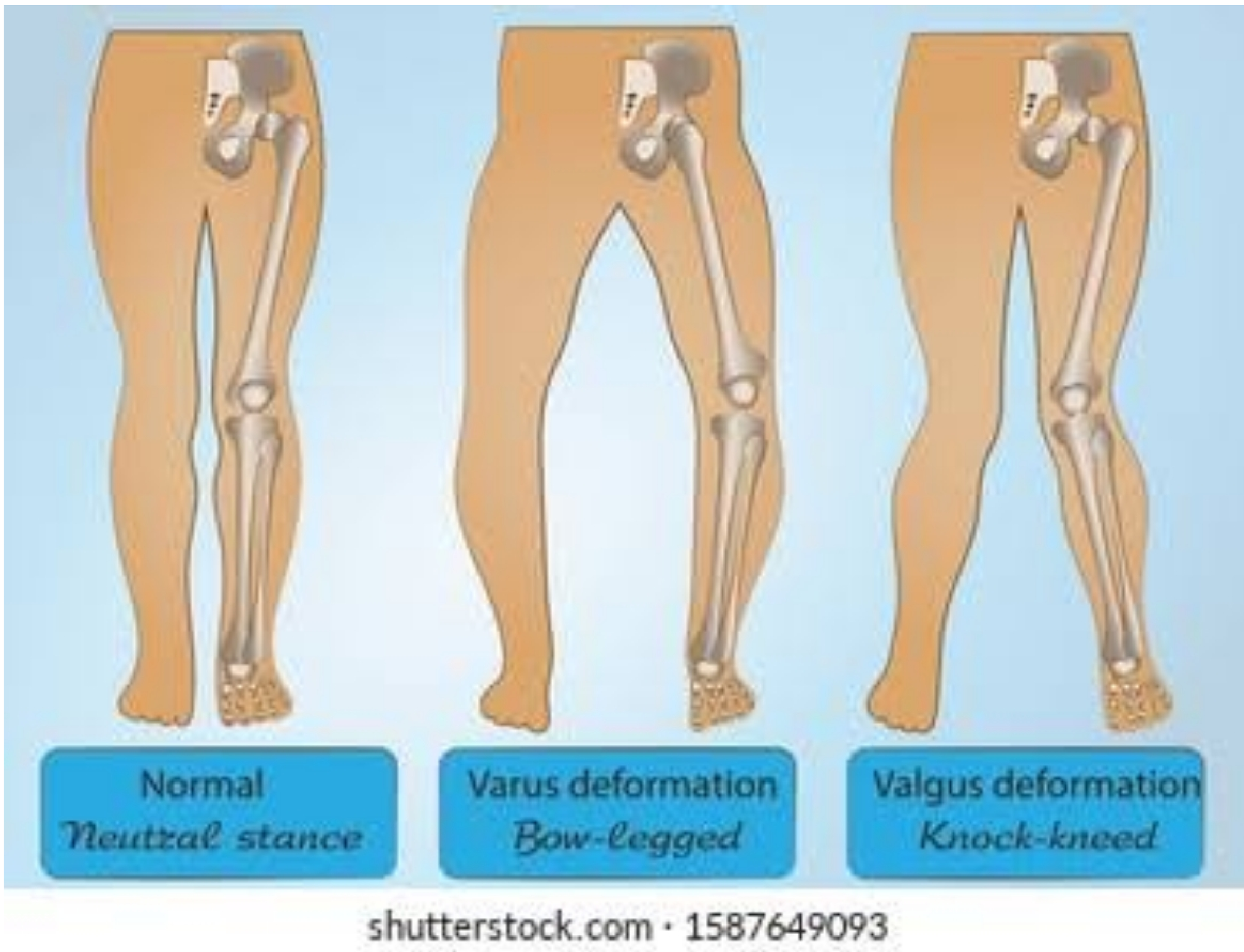

Maculopapular
Sarcoidosis


Scar
Sarcoidosis


Morpheaform
Sarcoidosis


Psoriasiform Sarcoidosis

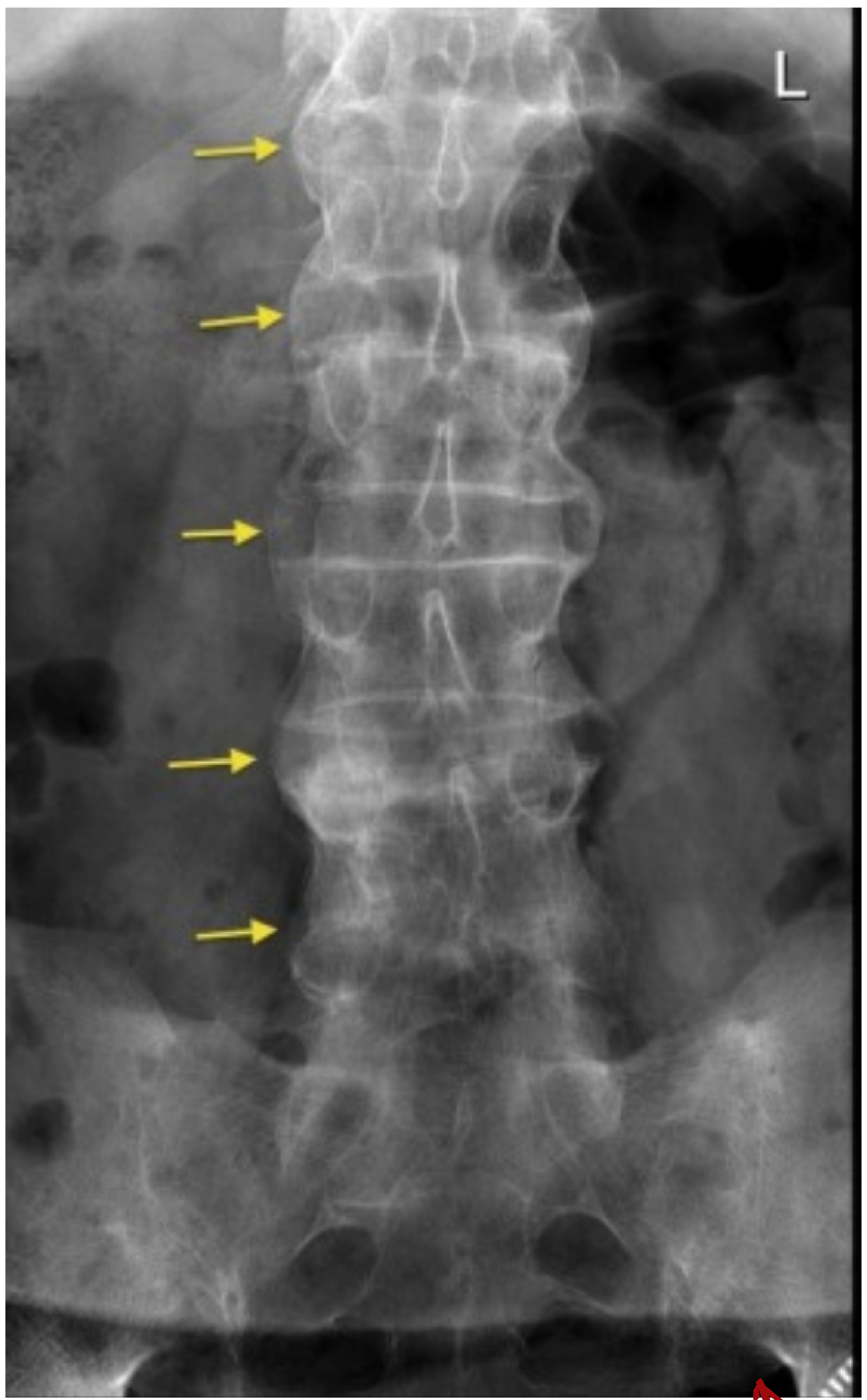

Plaque
Sarcoidosis



Varus Deformity seen in knee osteoarthritis

Valgus Deformity in Rheumatoid arthritis

Ankylosing Spondylitis



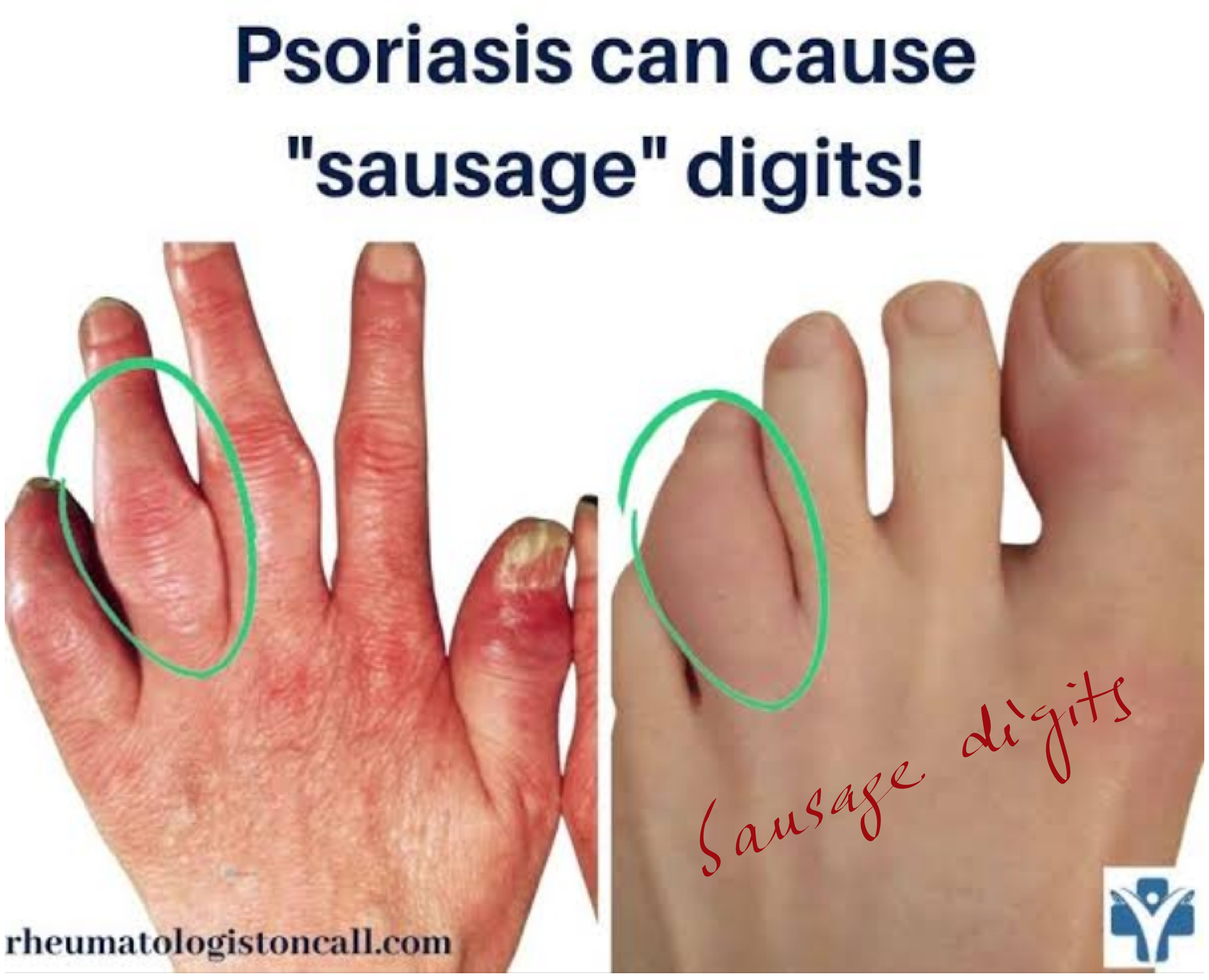
* X-Ray → best initial test
* MRI Spine → most accurate test
* HLA-B27 positive
* ↑ ESR, CRP

Bamboo Spine

↑ X-Ray

Ankylosing spondylitis. There is ossification along the margins of the disk spaces in this patient's lumbar spine (arrows), producing an appearance similar to a stick of bamboo. Note how difficult it is to see the sacro-iliac joints, as they have fused.

PSORIATIC ARTHRITIS



Sausage digits

Pencil-in-cup deformity at DIP seen on X-Ray

Onycholysis

Sausage Digits

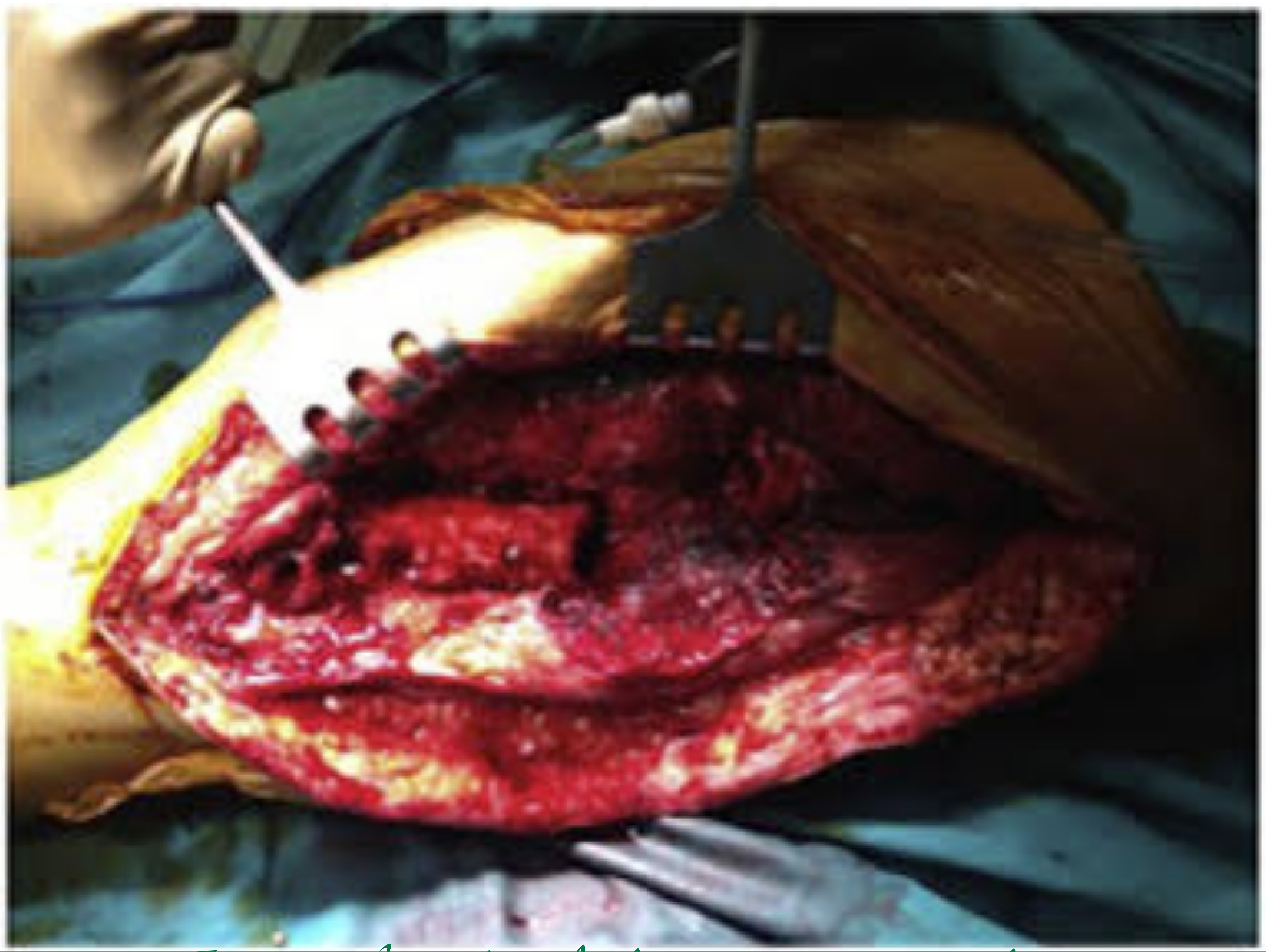
Telescopic fingers seen in Arthritis mutilans

* Methotrexate (DMARDs) is the first treatment of choice

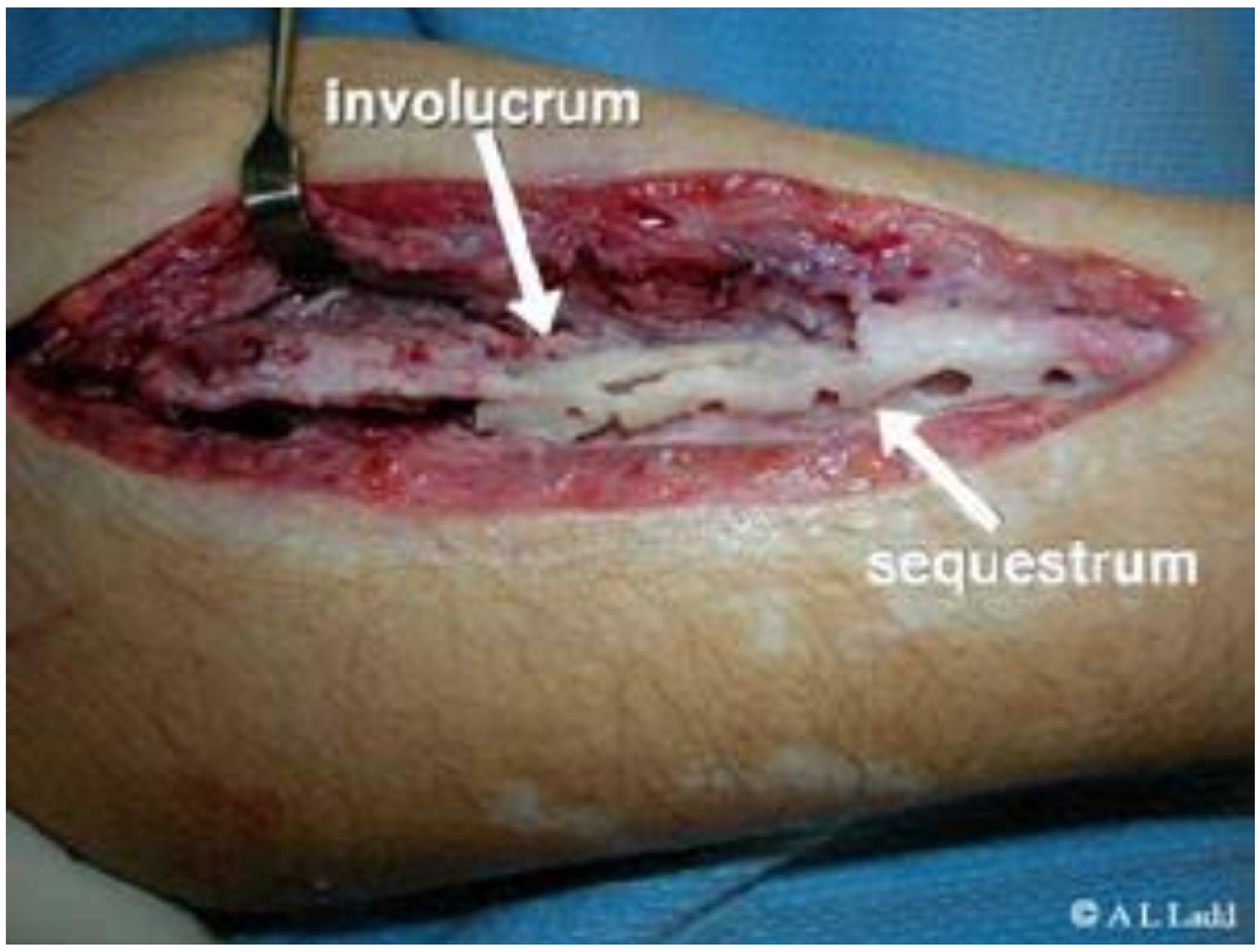
OSTEOMYELITIS

X-Ray → Lytic lesions with surrounding sclerosis

• Biopsy is the most accurate test.

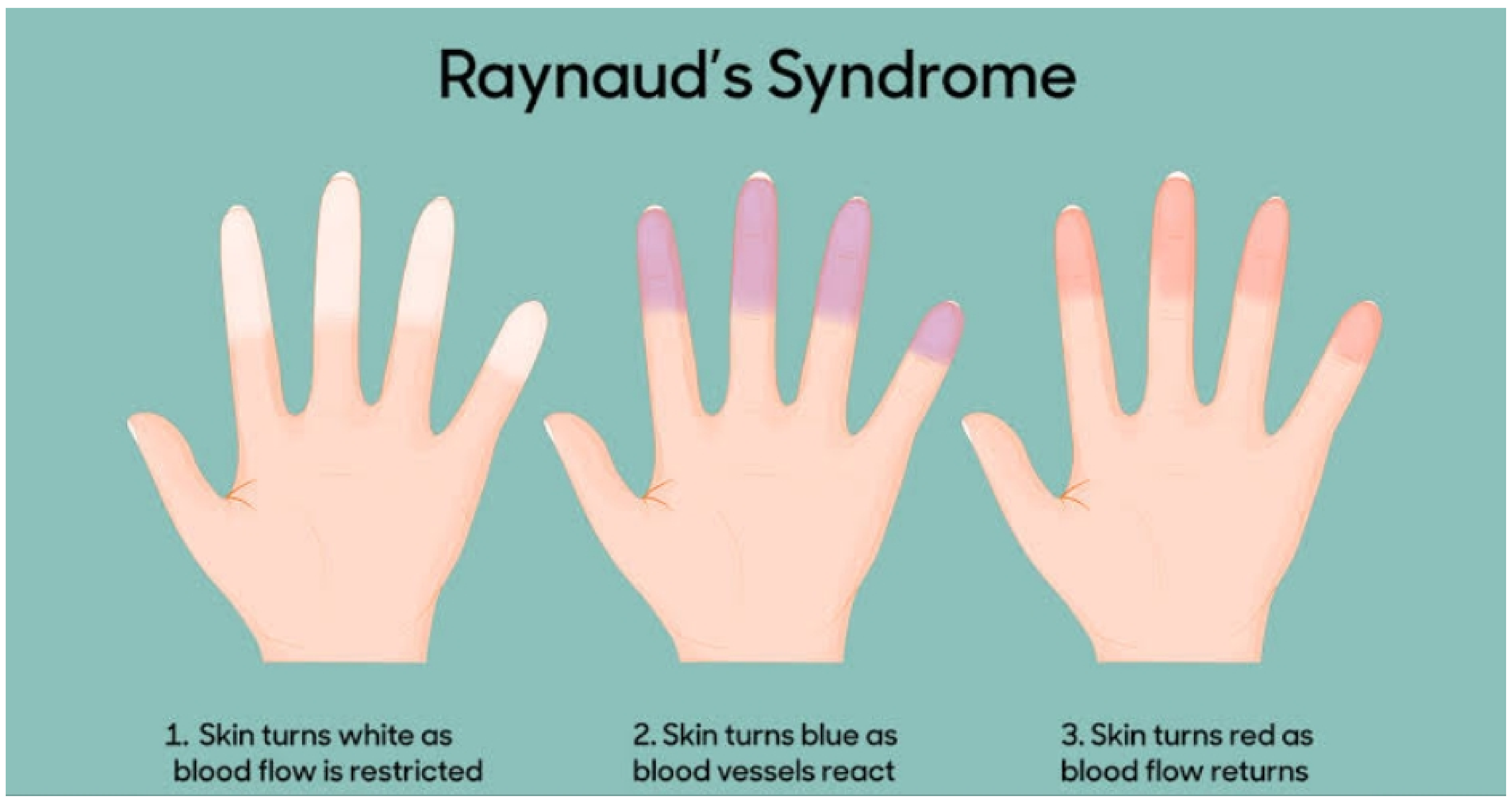


Tx → surgical debridement of necrotic infected bone



* Sequestrum → dead piece of bone
* Involucrum → new bone formation

SLE



Malar Rash

↙ Discoid Rash ↑

* ANA positive
* Anti dsDNA antibody
* Anti-Smith Antibodies

Systemic Sclerosis

Calcinosis cutis

Telengiectasia in CREST Syndrome

Calcinosis cutis on elbow of patient

Telengiectasia in CREST Syndrome

Raynaud phenomenon

Sclerodactyly

Sclerodactyly

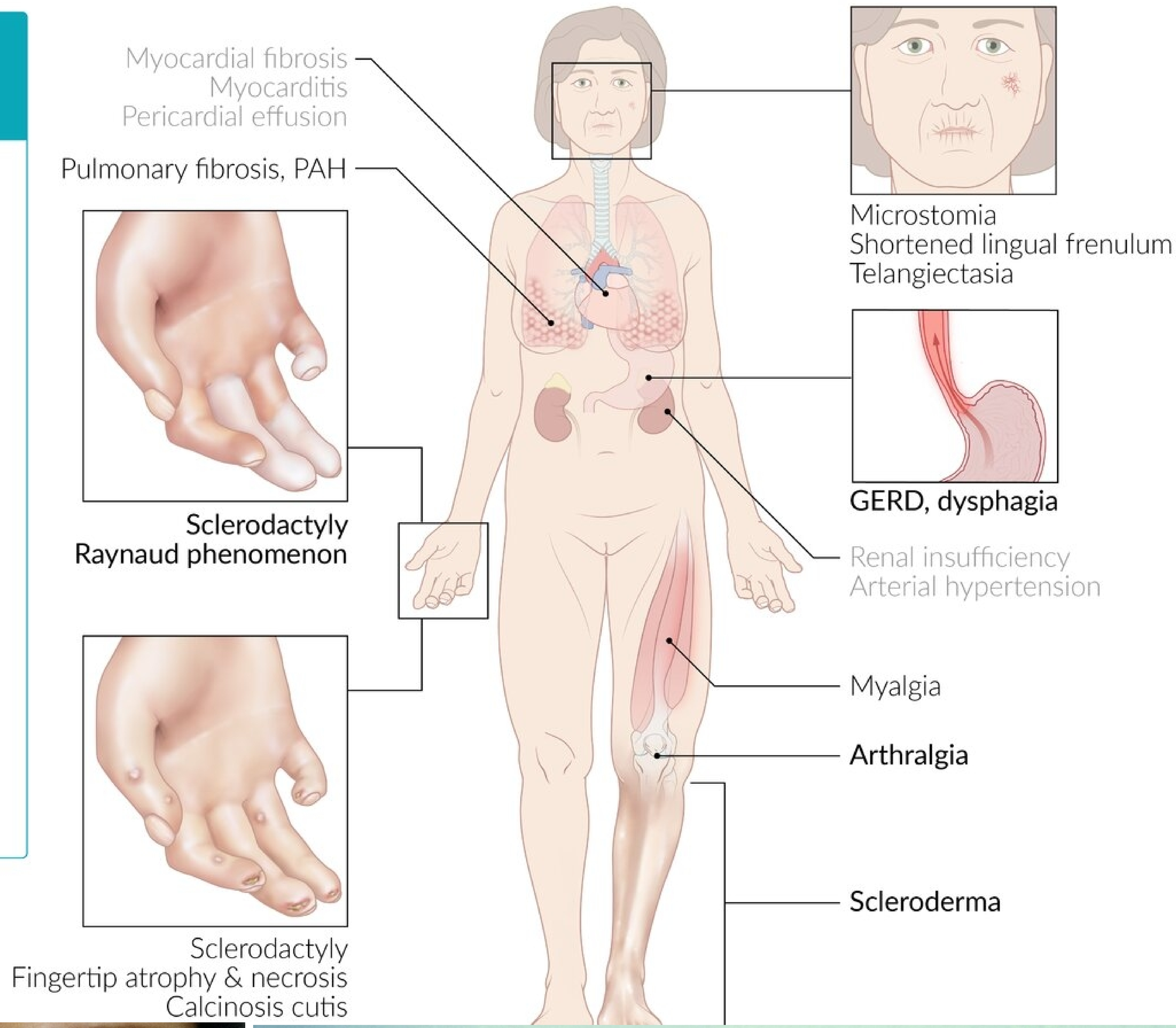
Systemic sclerosis (SSc)

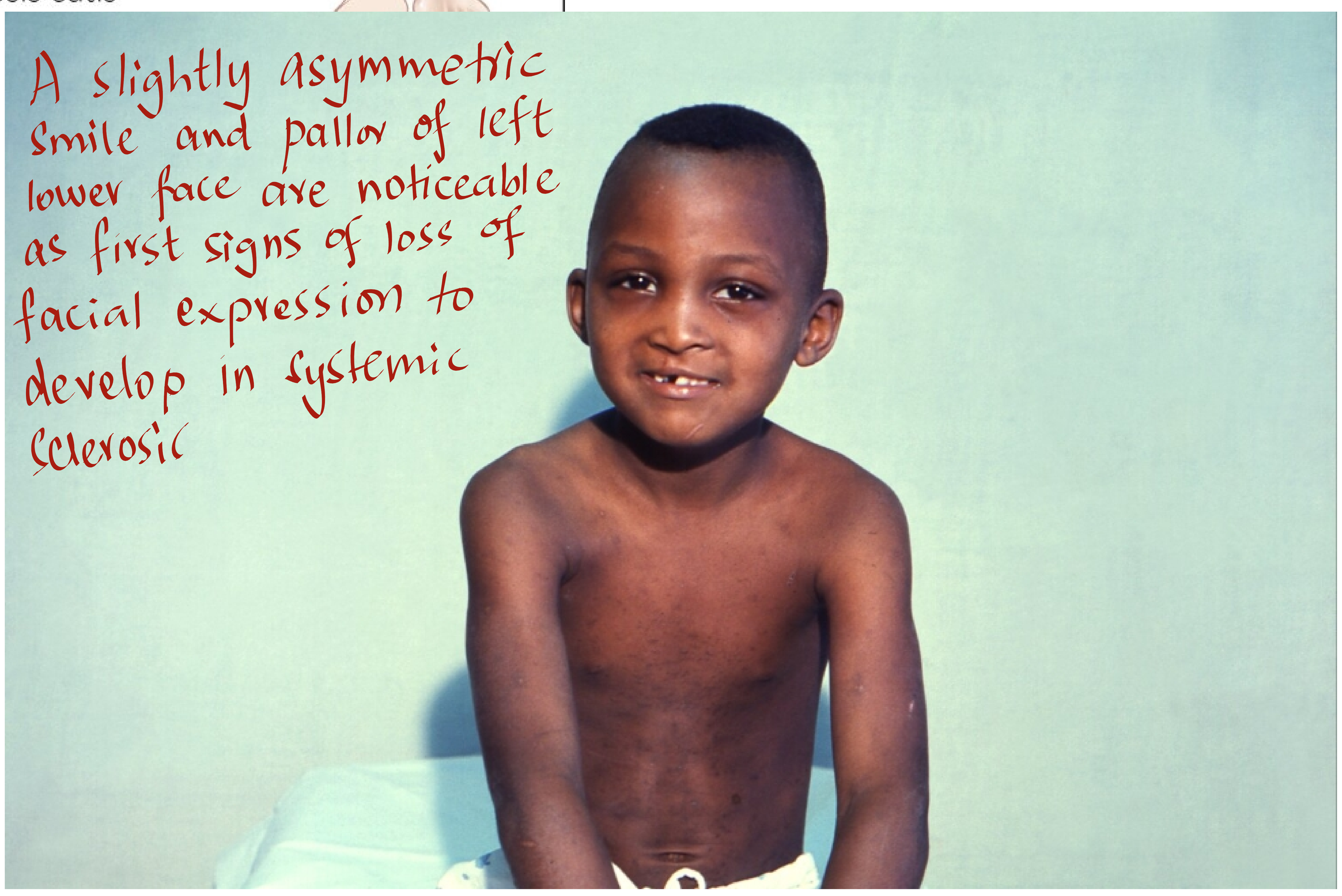
Epidemiology
♀ > ♂
Peak age: 30–50 years

Antibody serology
(usually mutually exclusive)
Antinuclear antibodies (ANA)
Anti-Scl-70 antibodies
Anticentromere antibodies (ACA)

Patterns of cutaneous involvement
Limited SSc (neck, face, and distal limbs, sparing the trunk)
Diffuse SSc (trunk to the elbow)

CREST syndrome
(more common in limited SSc)
C: Calcinosis cutis
R: Raynaud phenomenon
E: Esophageal hypomotility
S: Sclerodactyly
T: Telangiectasias



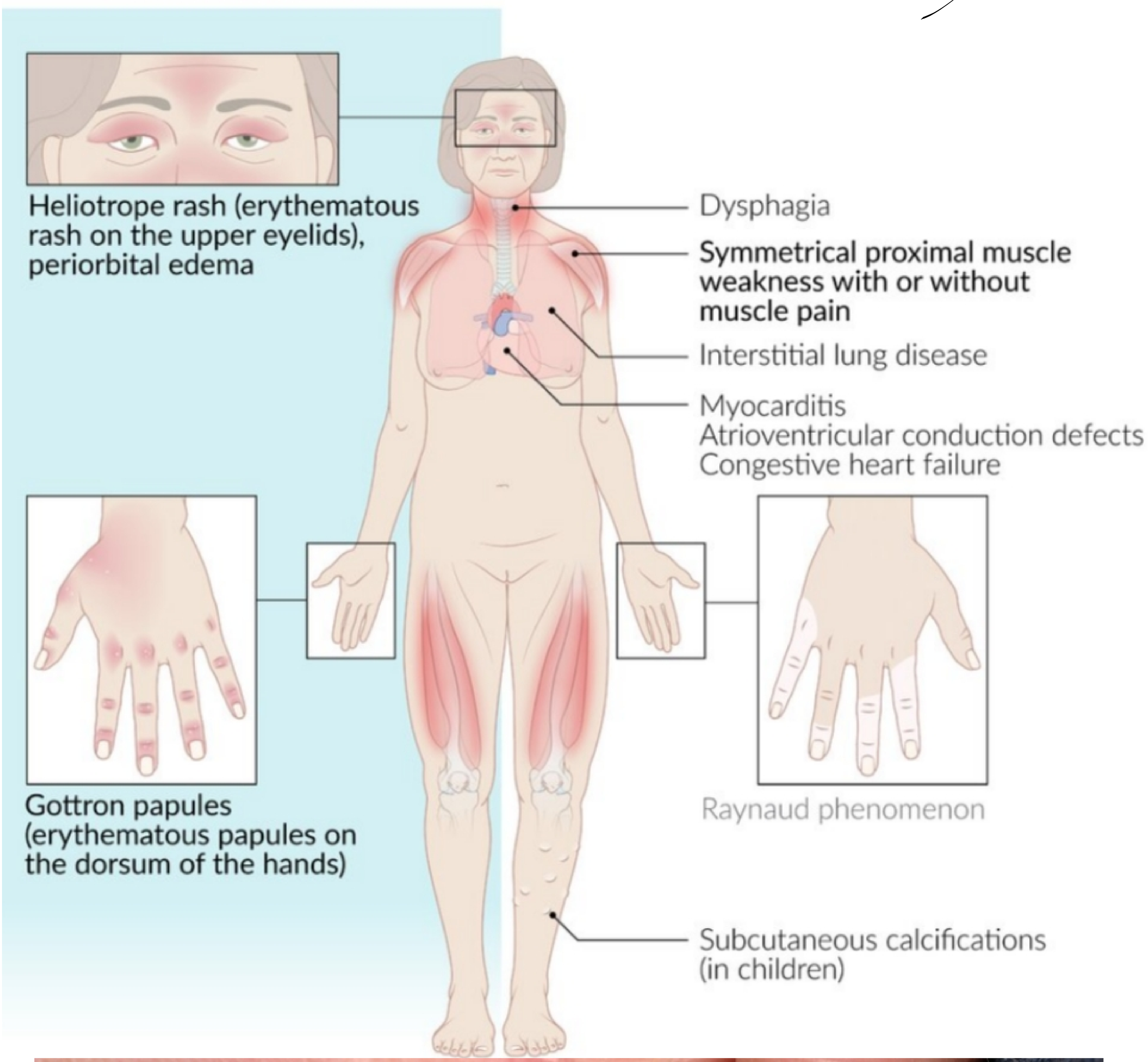


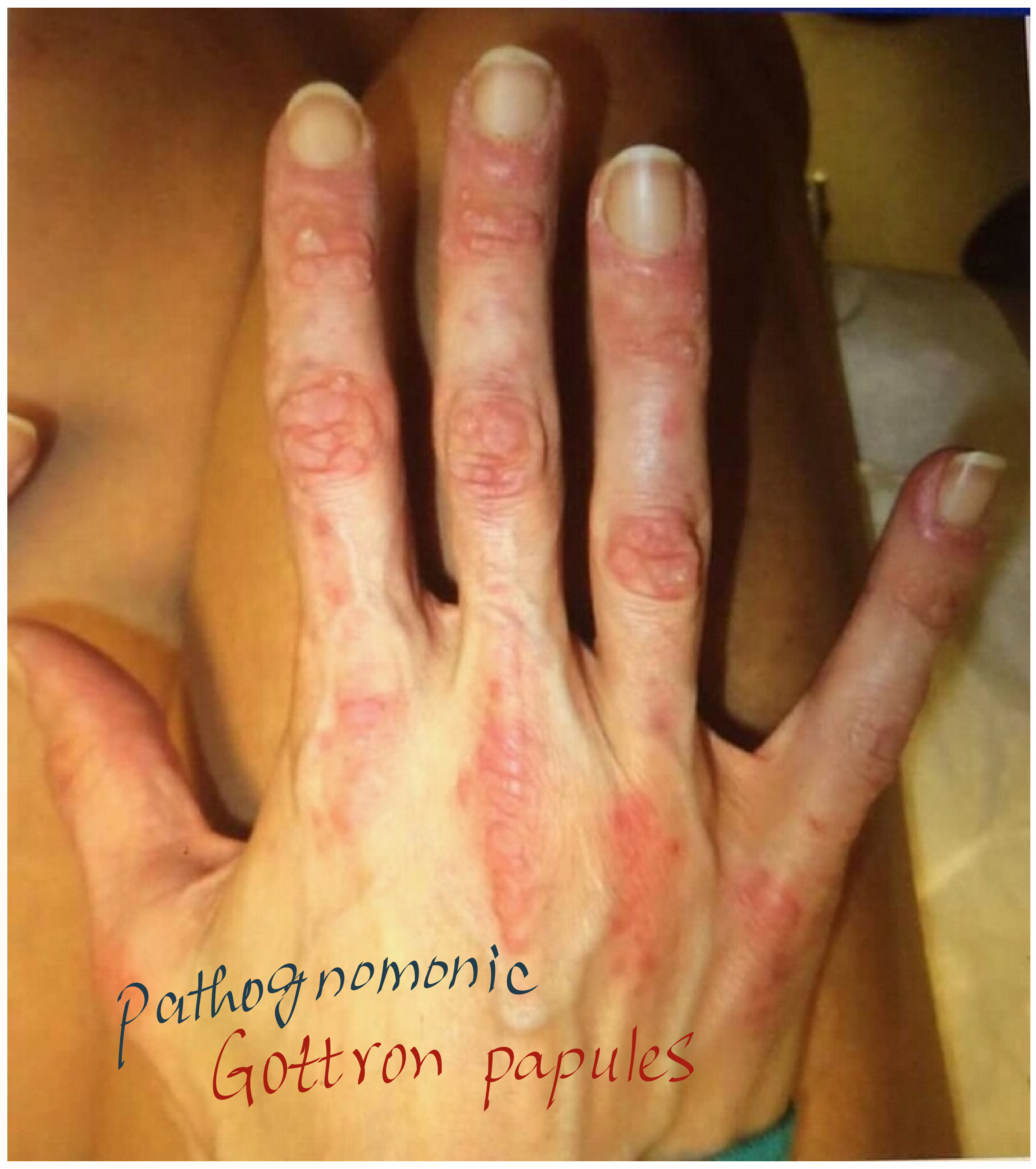
Salt and pepper appearance of Skin

Smooth, firm, shiny skin

Dermatomyositis

Dermatomyositis





Serology
ANA (nonspecific)
Anti-Mi-2 antibodies (specific for DM)

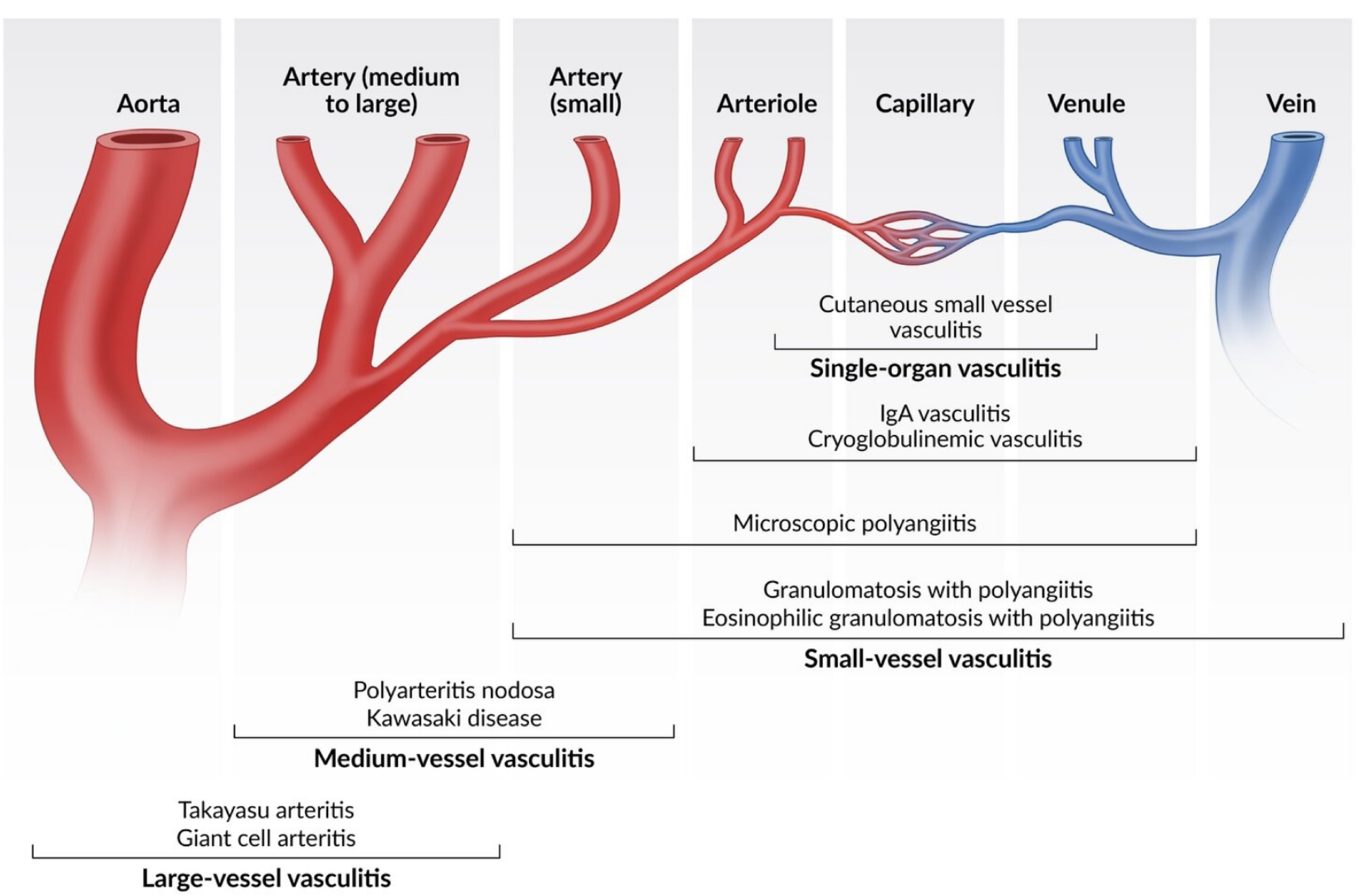
Laboratory findings
↑↑ Serum creatine kinase,
↑ Aldolase, ↑ myoglobin, ↑ LDH,
↑ AST, ↑ ALT

Note
Associated with malignancy (esp. in patients with dermatomyositis)
Polymyositis (DM without skin involvement) is a diagnosis of exclusion in the absence of the characteristic findings of the other inflammatory myopathies

Heliotrope Rash

Gottron papules

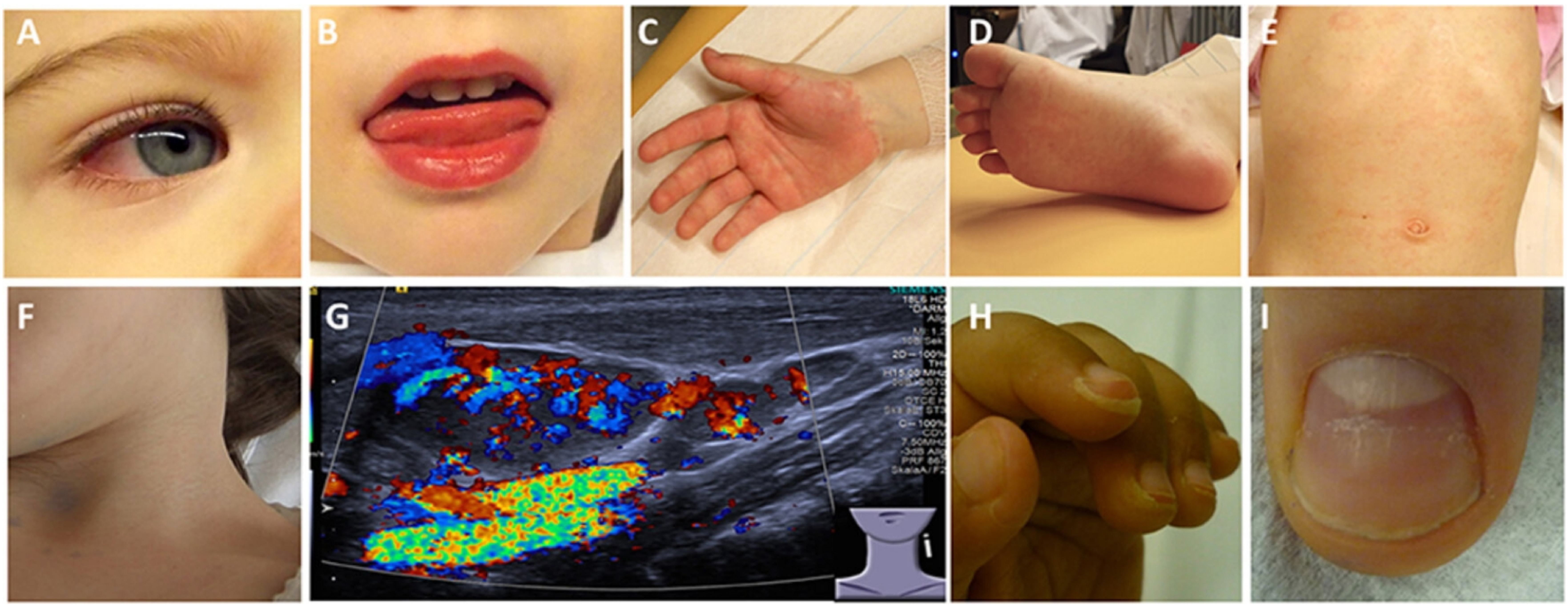
Vasculitides



Giant Cell Arteritis

Kawasaki Disease

Also known as "mucocutaneous lymph node syndrome"



A- Bilateral, non purulent Conjunctivitis

B - Stomatitis with bright red lips

C - Erythema and edema of hands

D - Erythema and edema of feet

E - Truncal Rash

F - Cervical Lymphadenopathy

G - U/s of enlarged cervical Lymph node

H - Desquamation of fingertips

I - Beau lines (Deep grooves in the nails)

IgA Vasculitis

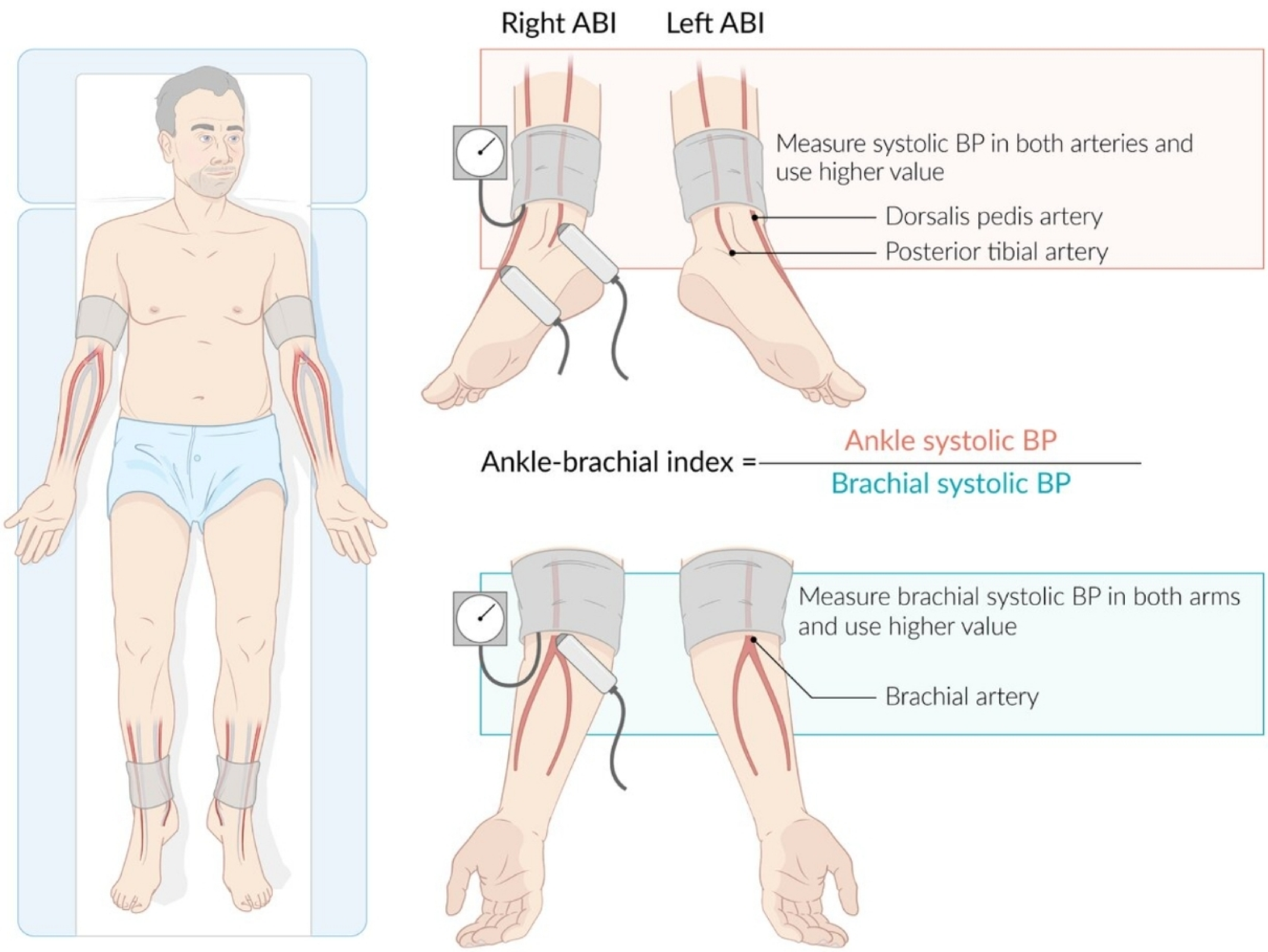
Peripheral Arterial Disease

Intermittent claudication

- Seen in approx. 10–35% of patients
- Pain, cramps, or paresthesia distal to arterial occlusion
  - Femoropopliteal disease (most common): typically causes calf claudication
  - Aortoiliac disease (Leriche syndrome)
    - Level of the aortic bifurcation or bilateral occlusion of the iliac arteries
    - Triad of bilateral buttock, hip, or thigh claudication, erectile dysfunction, and absent/diminished femoral pulses
  - Tibiofibular disease: typically causes foot claudication
- Worsens upon exertion
- Completely relieved by rest or lowering affected limbs
- Reproducible on asking the patient to walk the same distance at which symptoms typically occur

Calculate Ankle Brachial Index (ABI)

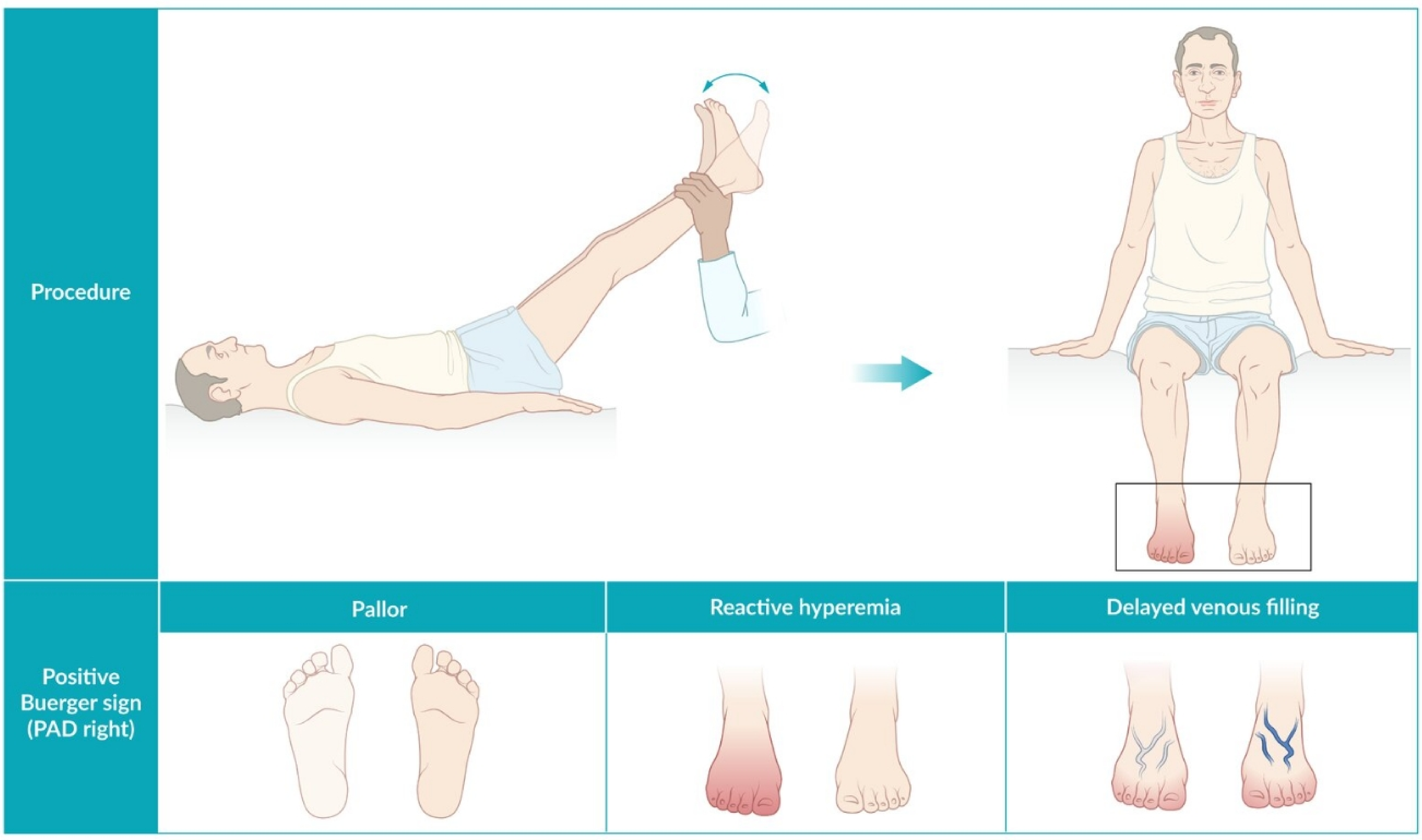
- Calculate the ABI for each leg: Divide the highest ankle pressure by the highest brachial pressure.



Peripheral ARTERIAL Disease (PAD)

Examination findings

- **Trophic changes**
  - ↓ Skin temperature, ↓ perspiration
  - ↓ Hair on legs, ↓ nail growth, brittle nails
  - Atrophied muscles
  - Dry atrophic, shiny skin and/or bluish skin discoloration
  - Livedo reticularis (advanced disease)
  - **Gangrene**, **ulcers**, **necrosis** (end-stage disease): See also "Arterial ulcer."
- **Absent or diminished pulses**: examine distal pulses bilaterally, including
  - Upper extremity: brachial artery, radial artery
  - Lower extremity: femoral artery , popliteal artery , posterior tibial artery , and dorsalis pedis artery
- **Buerger sign** [4][5]
  - With the patient in the supine position, elevate the lower limbs to a 45° angle at the hip.
  - Evaluate for pallor of the feet.
  - Ask the patient to sit up with their legs off of the examination table in the dependent position.
  - Evaluate the time taken for the color to return to the feet and for the veins to become distended.
  - Positive Buerger sign
    - Skin pallor on limb elevation
    - Reactive hyperemia on limb dependency
    - A venous filling time of > 20 seconds may indicate advanced ischemia.
- **Bruit**: over the affected artery may be heard in > 60–70% of cases with PAD



Buerger Disease
(Thrombophlebitis obliterans)

- **Migratory superficial thrombophlebitis** (recurrent): often seen prior to the onset of limb ischemia [3][6]
  - Tender nodules along the course of the affected vein
  - Induration
  - Erythema
- **Raynaud phenomenon**
- **Chronic or acute limb ischemia**: may progress from distal to proximal vessels
  - Intermittent claudication
  - Pain at rest, cool extremities, and/or diminished or absent pulses
  - Ulceration and/or gangrene of fingertips and/or toes (digits may autoamputate)

• Associated with smoking

- **Ankle-brachial index (ABI)**: may be decreased [3]

- **Angiography**
  - Findings
    - Segmental occlusions in the distal vessels of the extremities
    - Corkscrew-shaped collateral vessels around the site of occlusion
    - Normal proximal arteries without evidence of atherosclerosis

Cryoglobulinemia

Clinical features

- Nonspecific systemic symptoms: fatigue, malaise, myalgia, arthralgia [3]
- Cutaneous lesions (nearly 100% of cases): palpable purpura, ulceration, necrosis
- Vasomotor symptoms: Raynaud phenomenon, acrocyanosis
- Polyneuropathy
- Hepatosplenomegaly
- Glomerulonephritis (severe cases or late complication)

The triad of **arthralgia, palpable purpura, and fatigue** is seen in ~ 80% of patients with cryoglobulinemic vasculitis. [3]

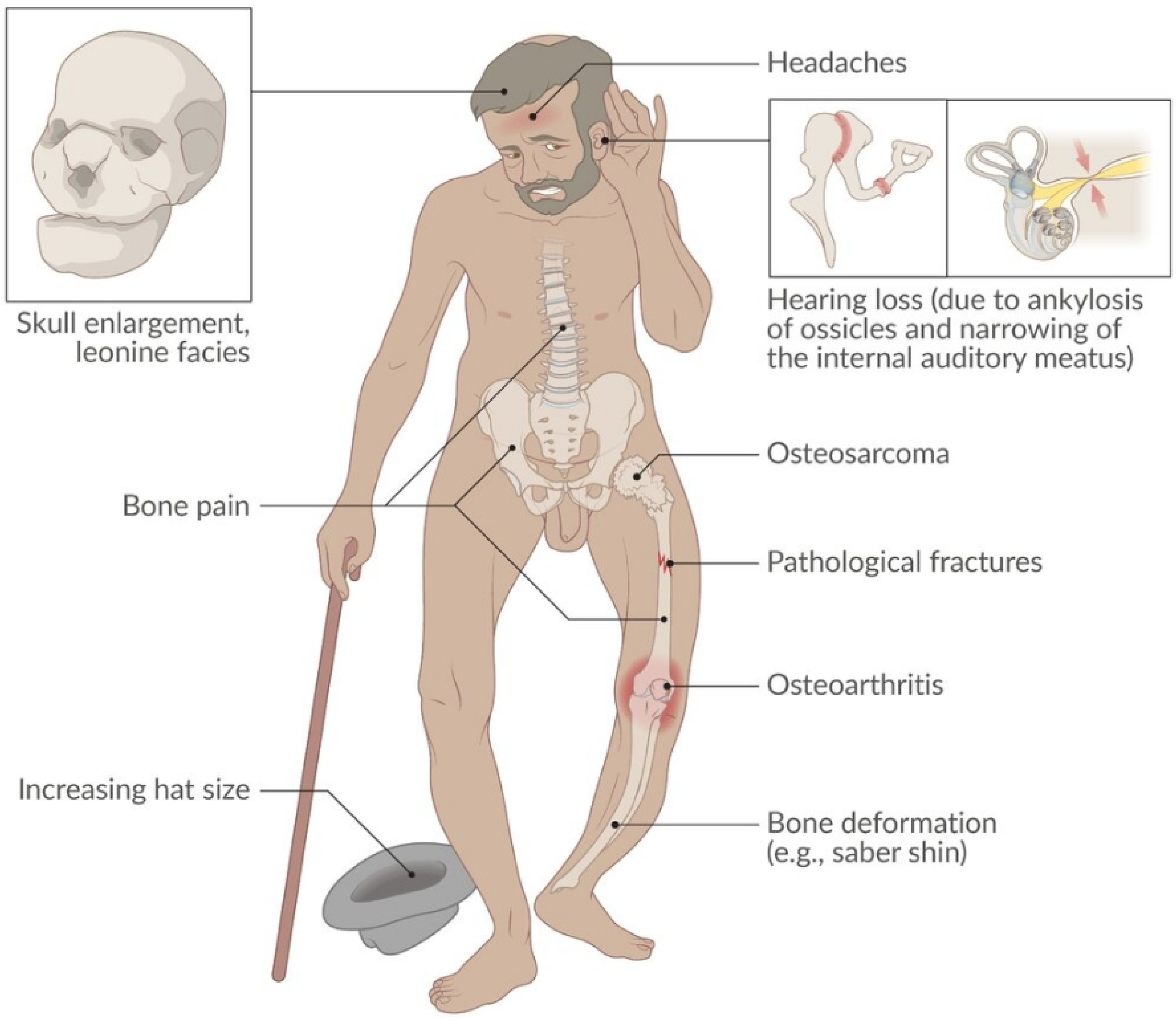
Paget Disease

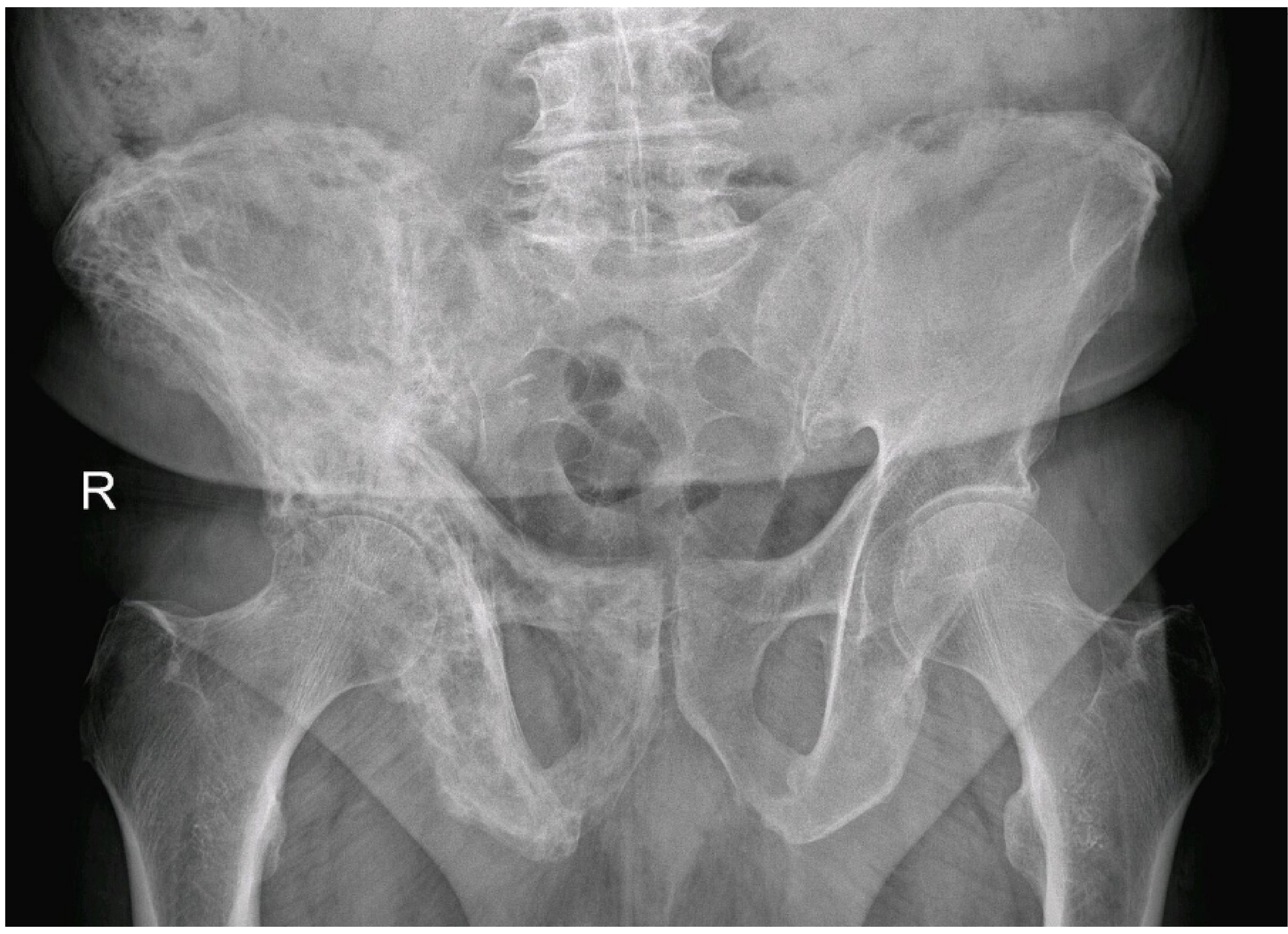
Paget disease of the bone (osteitis deformans)

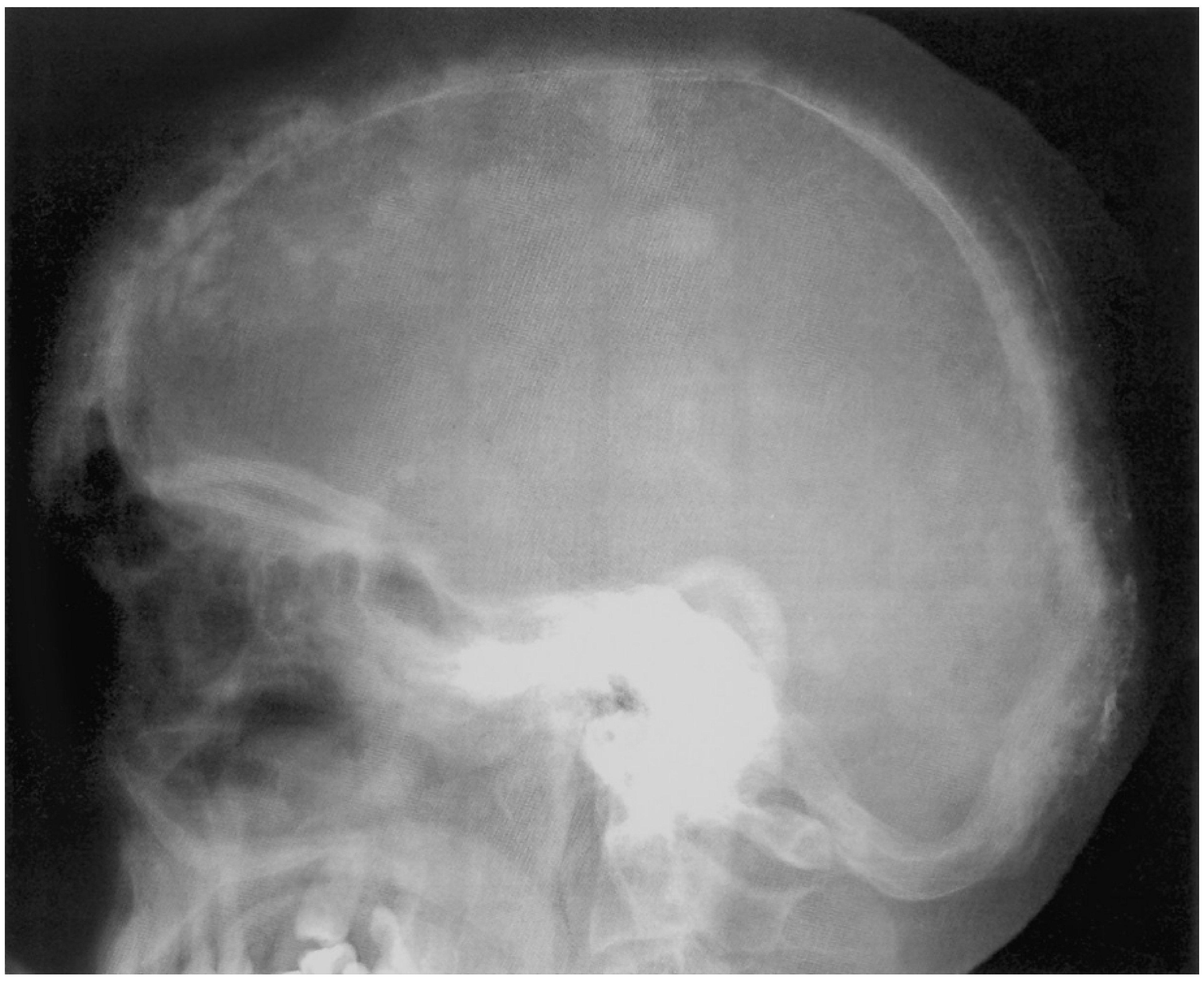
Pathophysiology
Increased bone remodeling (↑ osteoclastic and osteoblastic activity) → replacement of lamellar bone with weak woven bone

Diagnosis
- Isolated elevation of ALP with normal calcium, phosphate, and PTH
- Urinalysis (markers of collagen degradation)
- X-ray (bone deformation with sclerotic and osteolytic lesions)
- Skeletal scintigraphy (bony lesions)

Treatment
- Indicated in active disease (↑ ALP or active foci on skeletal scintigraphy)
- First-line: bisphosphonates







* Bisphosphonates are the mainstay of treatment

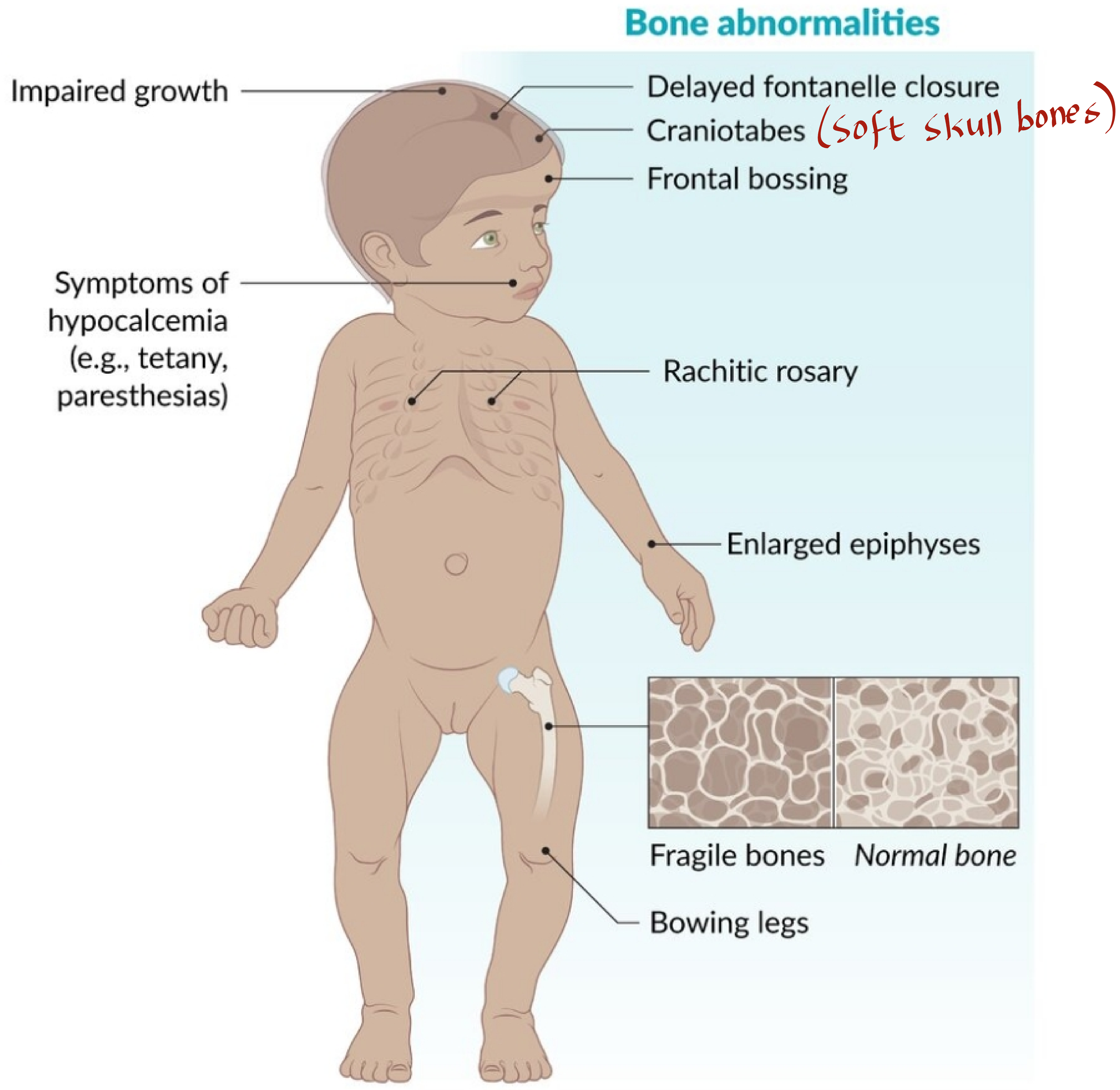
Rickets secondary to vitamin D deficiency

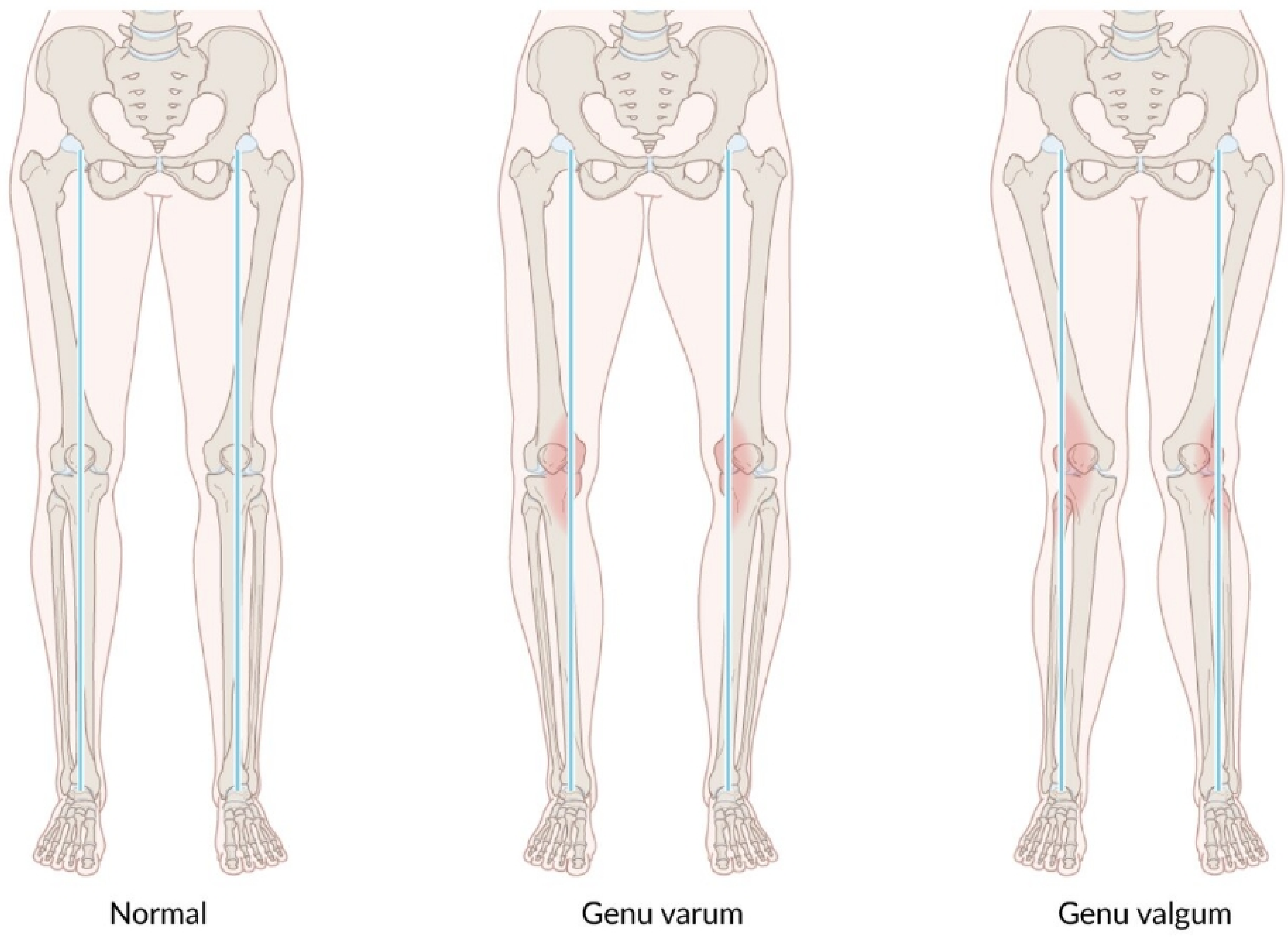
Etiology
- Vitamin D deficiency due to:
  - Insufficient synthesis due to low UV radiation exposure (e.g., northern climates) and/or dark skin
  - Insufficient oral intake (e.g., in infants who are exclusively breastfed)
  - Malabsorption
  - Defective vitamin D metabolism

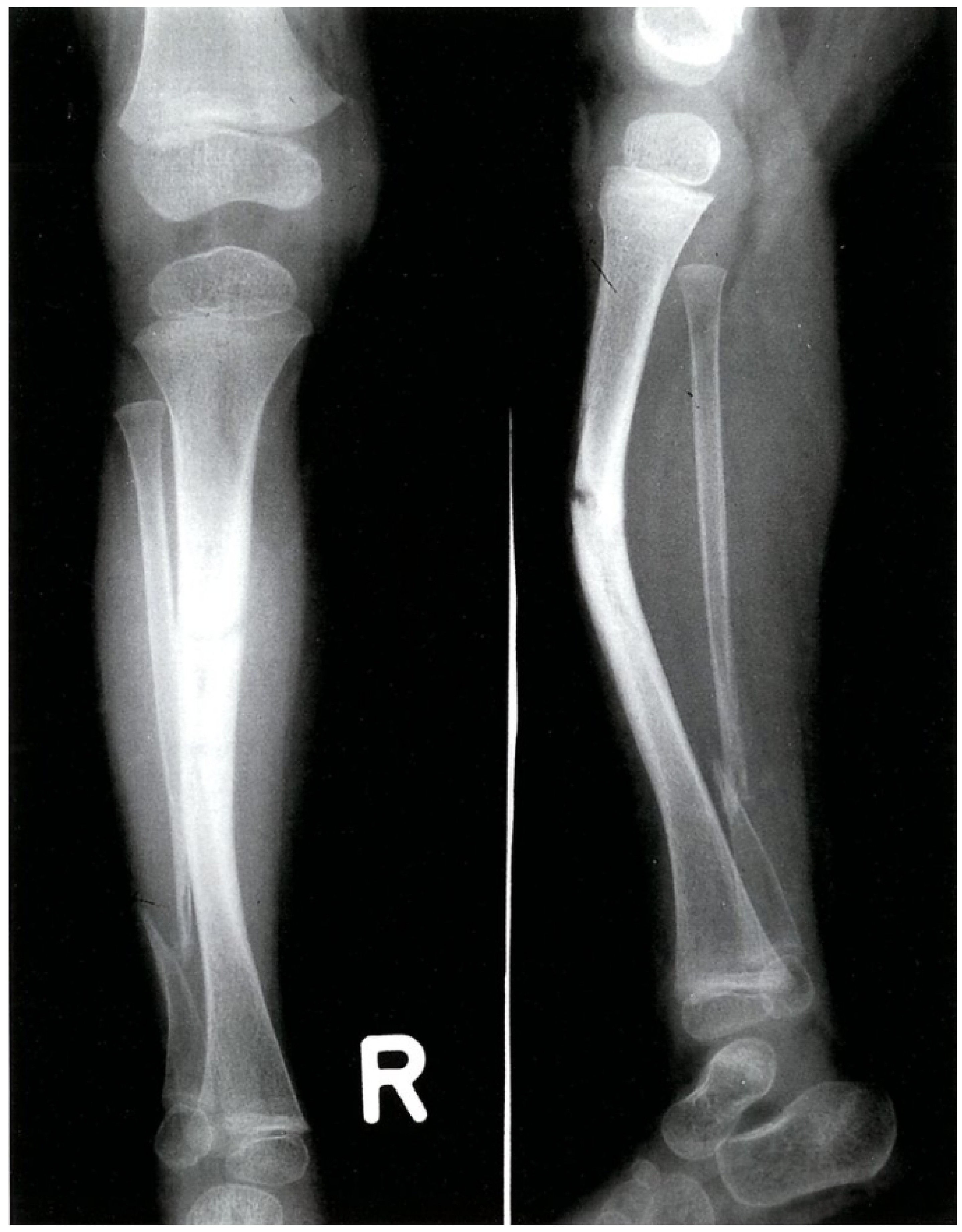
Pathophysiology
Vitamin D deficiency → defective mineralization of osteoid and growth plates

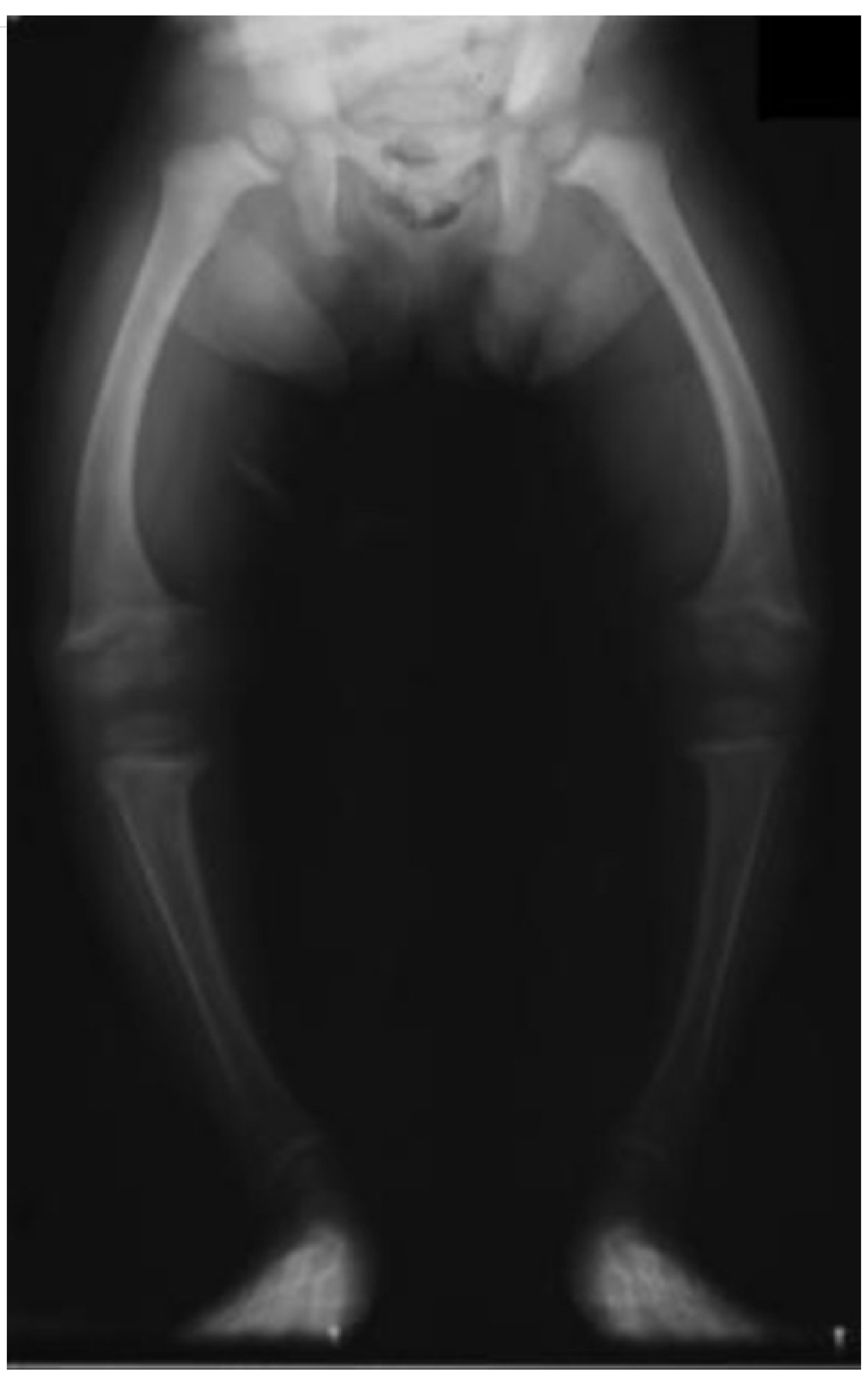
Diagnostics
↓ Vitamin D, ↓ serum Ca^{2+}, ↑ PTH, ↓ PO_4^{3-}, ↑ ALP

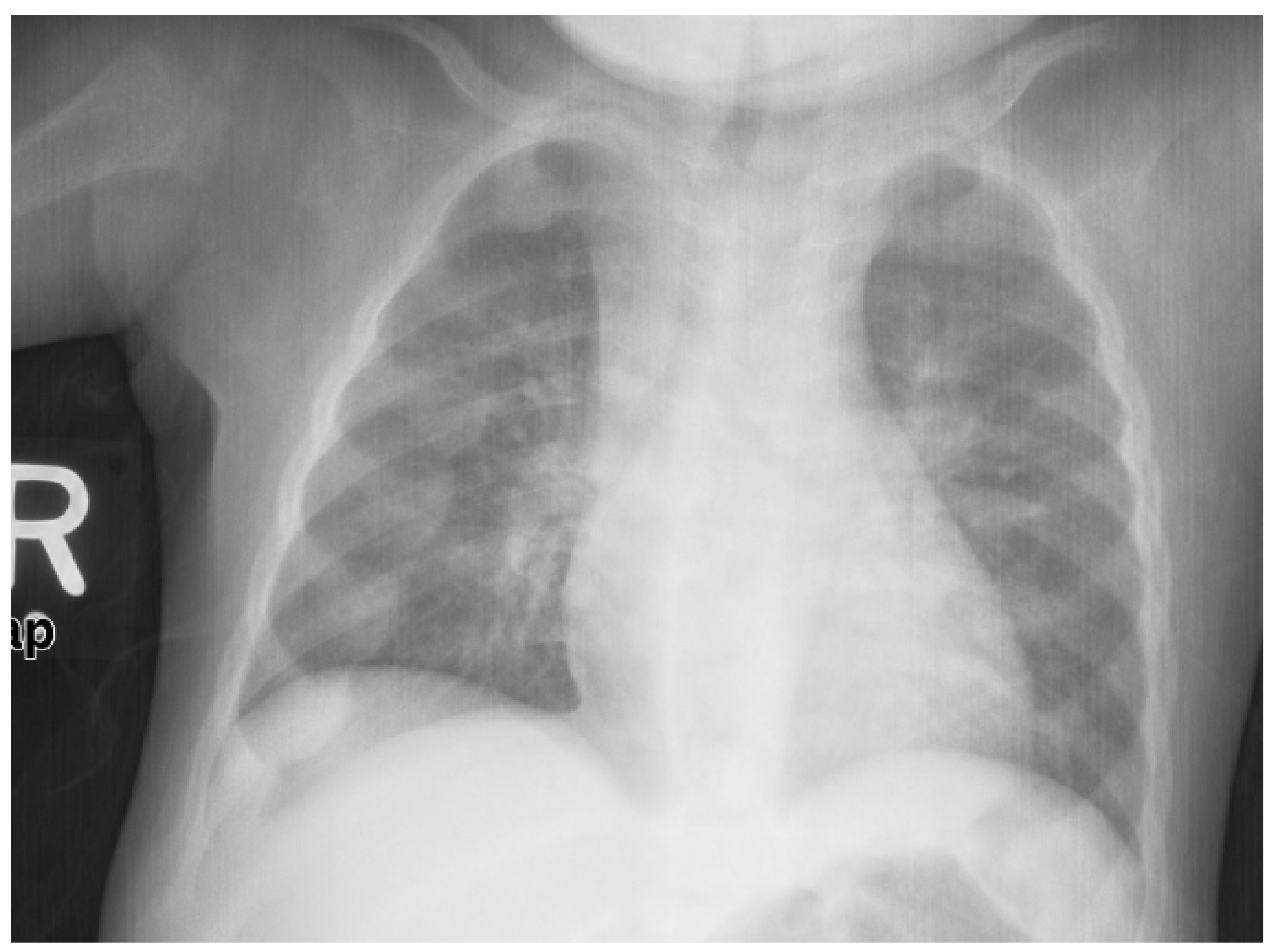
Treatment
- Dietary supplementation (vitamin D, calcium)
- Treatment of underlying cause











Chicken pox
Varicella

Pathogen
Varicella-zoster virus

Course
Widespread vesicular rash with lesions beginning as macules and rapidly becoming papules
Simultaneous occurrence of various rash stages
Remission of exanthem after 8 days

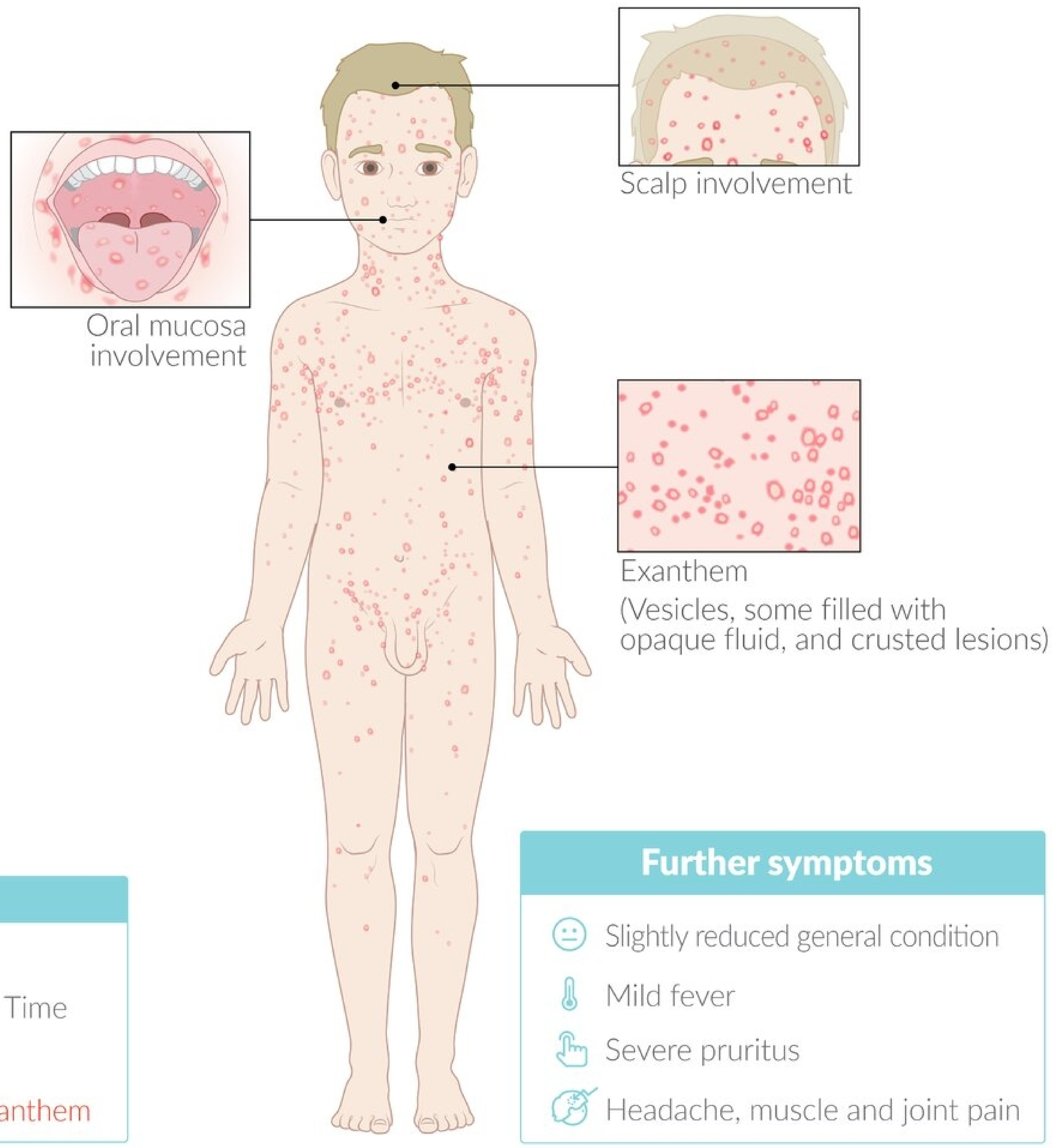
Complications
Bacterial superinfection
Meningitis, acute cerebellar ataxia, encephalitis
Herpes zoster (Shingles) from virus reactivation
Congenital varicella syndrome

Treatment
Symptomatic

Vaccine
Yes

Course of disease

Incubation period: 10—21 days
Contagious period: 2 days | 5 days
Time
Exposure
Onset of exanthem



Further symptoms

- Slightly reduced general condition
- Mild fever
- Severe pruritus
- Headache, muscle and joint pain





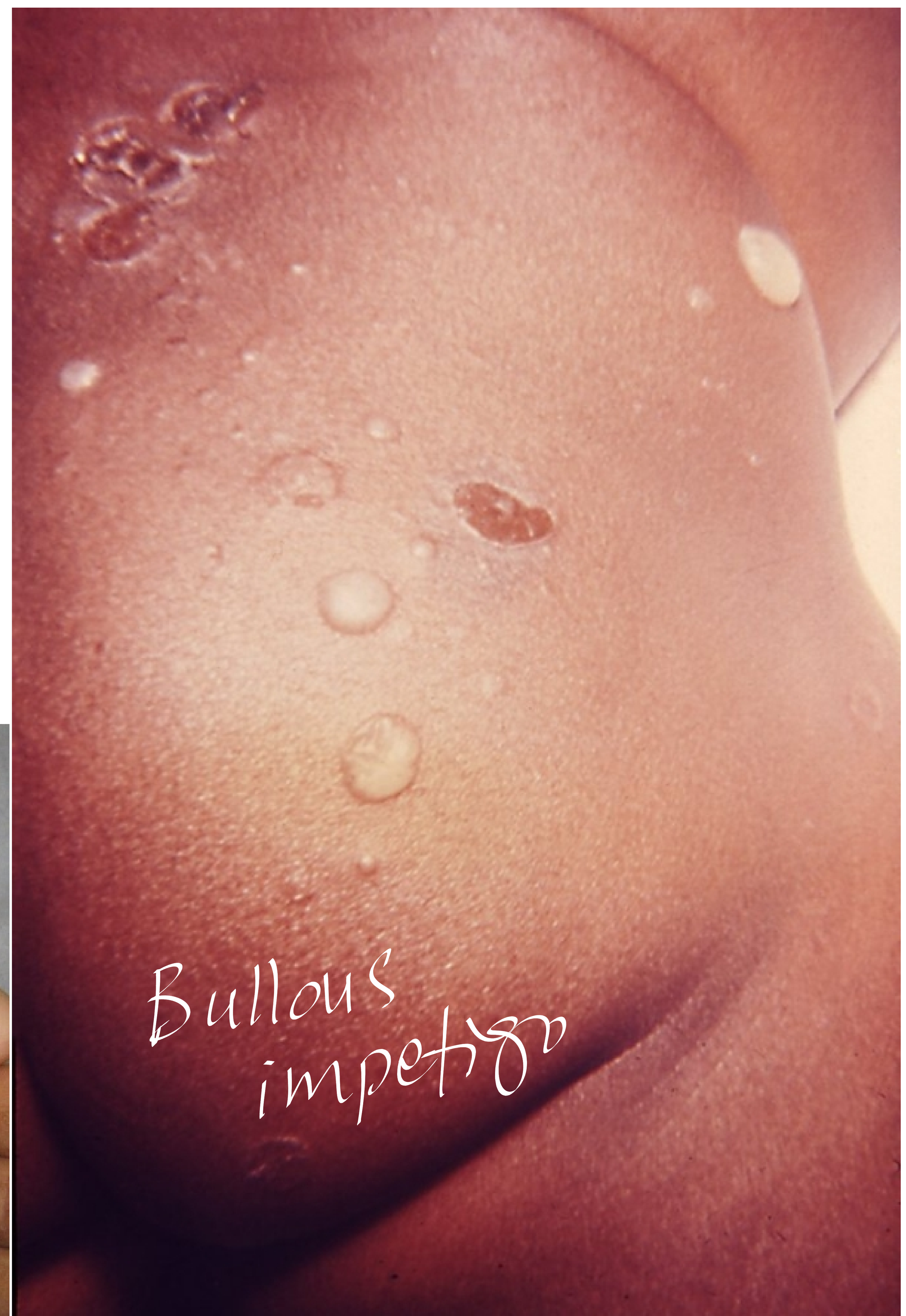
Warts (HPV)

Molluscum Contagiosum

Etiology

- **Pathogen**: a DNA poxvirus (molluscum contagiosum virus)
- **Transmission**:
  - **Direct** skin **contact** (contact sports, sexually transmitted)
  - **Autoinoculation** (scratching or touching lesion, e.g., while shaving)
  - Fomites (e.g., on bath sponges/towels)
- Risk factors: immunosuppression , active atopic dermatitis (in children), hot and humid climates, crowded living conditions [2]

Impetigo



Impetigo - Confluent scabbed erosions and honey-colored crusts are visible in the perioral region. This appearance is typical of impetigo, which, in this patient, developed secondary to preexisting eczema and immunosuppression caused by HIV infection.

Folliculitis

Leprosy

hand deformities

Syphilis

Syphilis

Epidemiology
Sex: Approx. 6:1 (♂:♀)
Incidence of primary and secondary syphilis (US): Approx. 10.8/100,000 (rising)
Peak incidence: 20–29 years

Etiology
Pathogen: Treponema pallidum
Transmission: Sexual; vertical; bloodborne

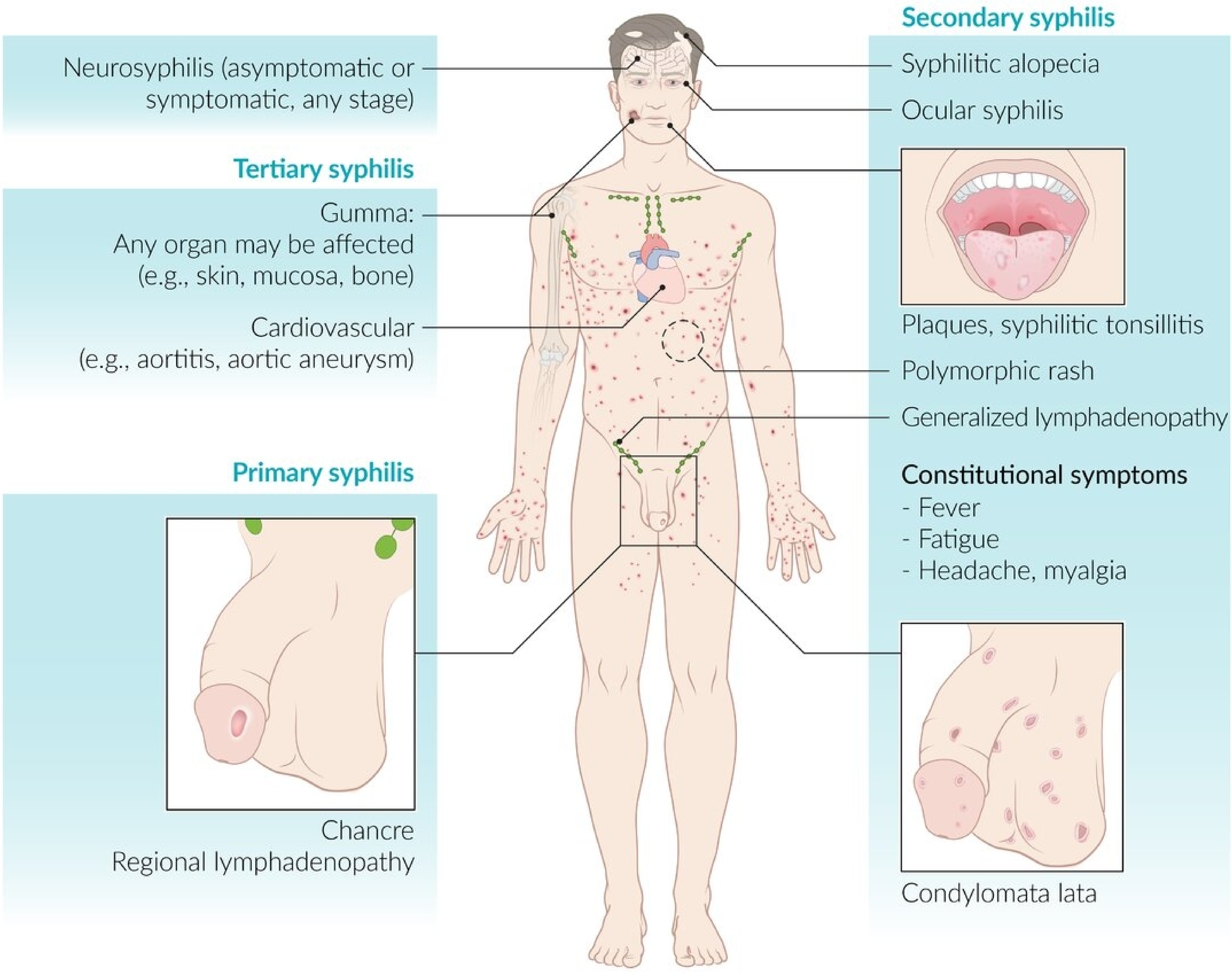
Classification
Early stages: primary and secondary syphilis
Latent syphilis
Late stage: Tertiary syphilis

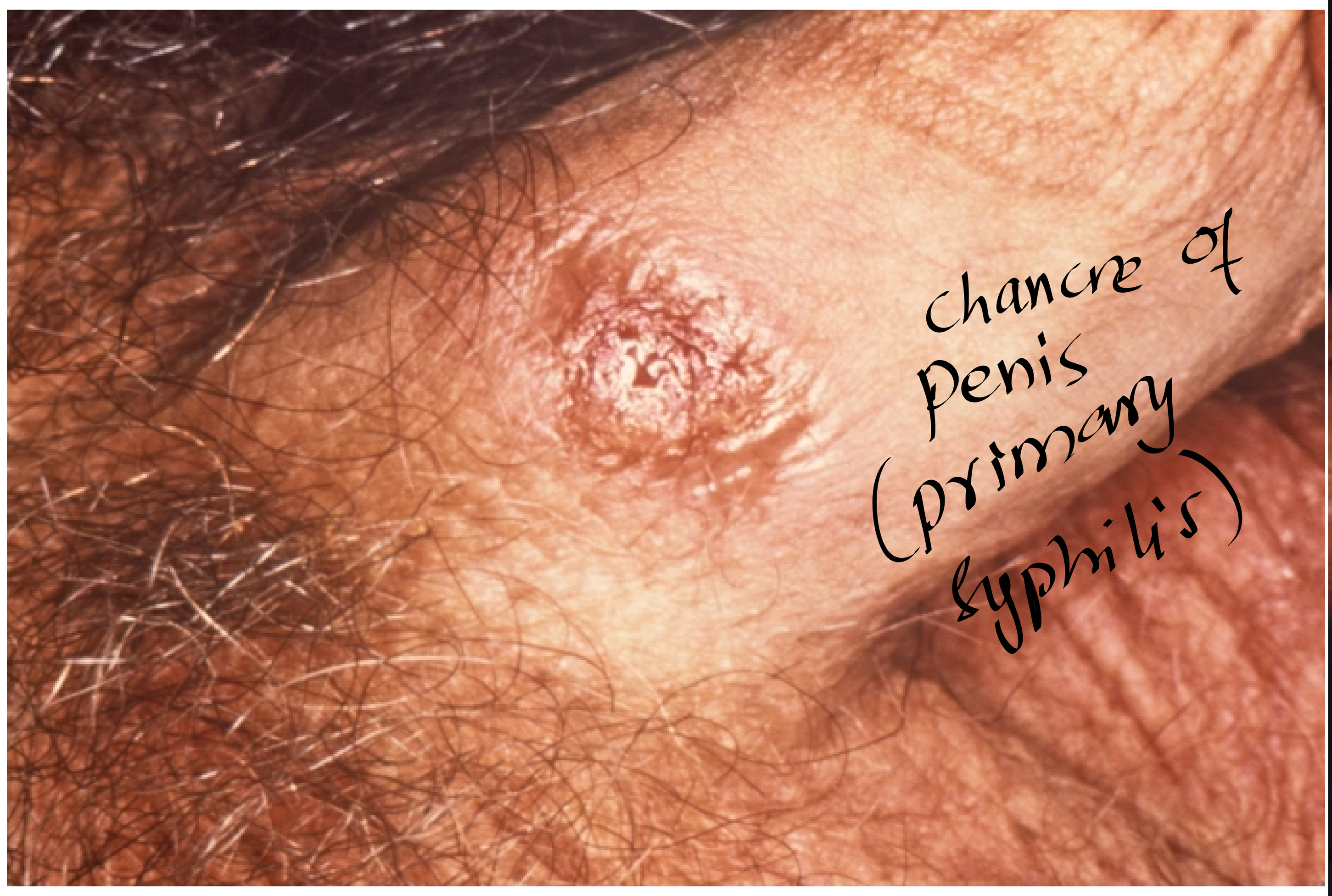
Diagnosis
Direct detection of the pathogen (e.g., PCR, darkfield microscopy)
Serology (e.g., RPR, TPPA, FTA-ABS, VDRL)

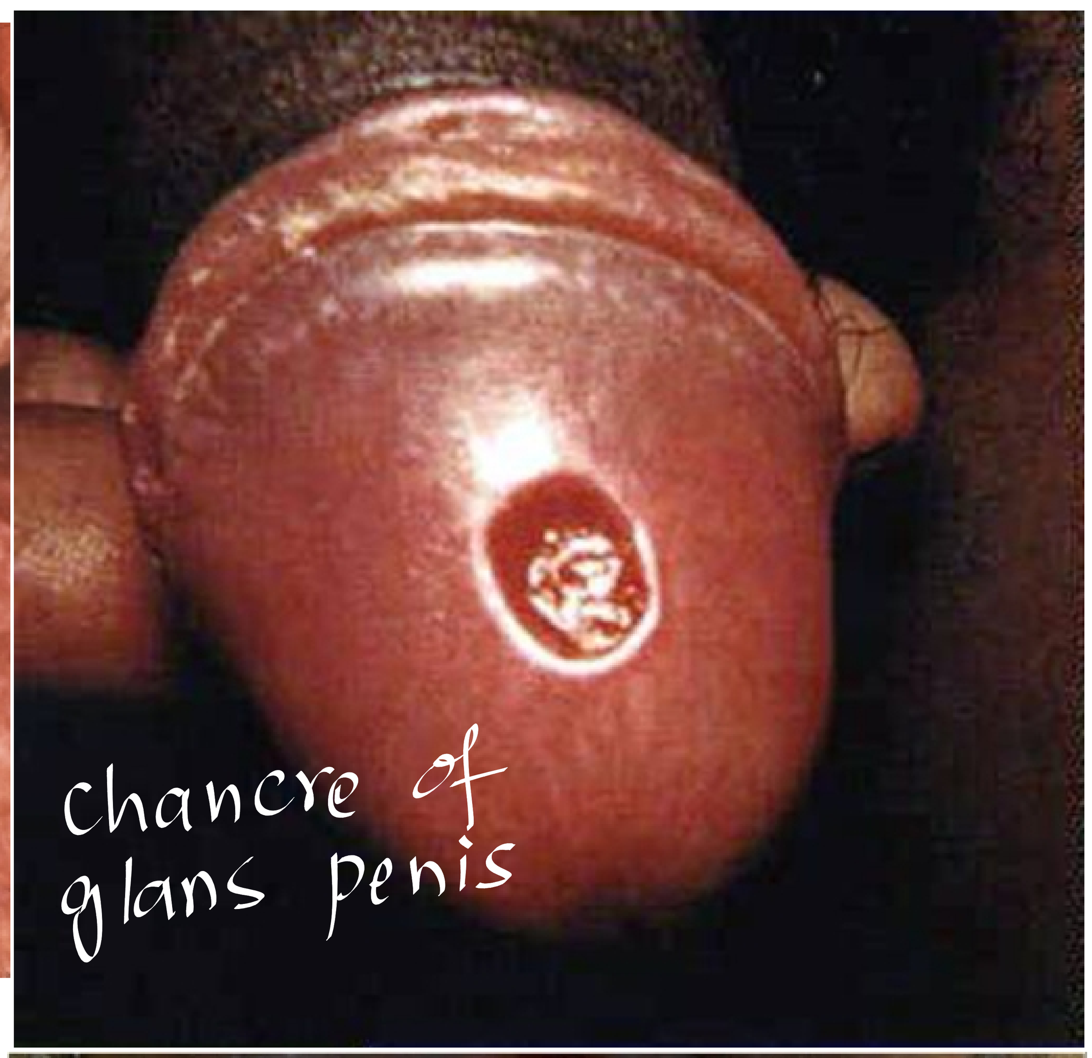
Therapy
First-line therapy: penicillin G

Complications
Vertical transmission (congenital syphilis)
Malignant syphilis (rare; may be seen in immunocompromised individuals)
Treatment complication: Jarisch-Herxheimer reaction

Note
Primary and secondary stages are highly infectious
Coinfection with other sexually transmitted infections is possible (e.g., HIV)
National notifiable condition

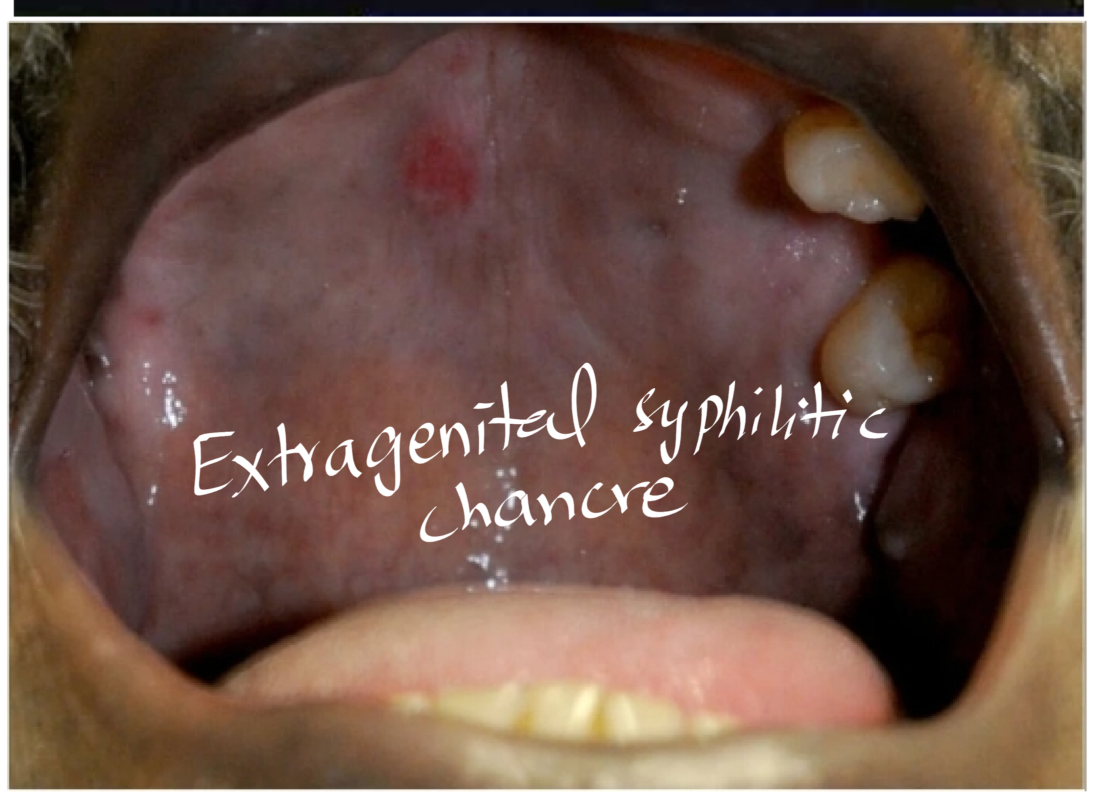



chancre of penis (primary syphilis)


chancre of glans penis


Facial gummas in tertiary syphilis

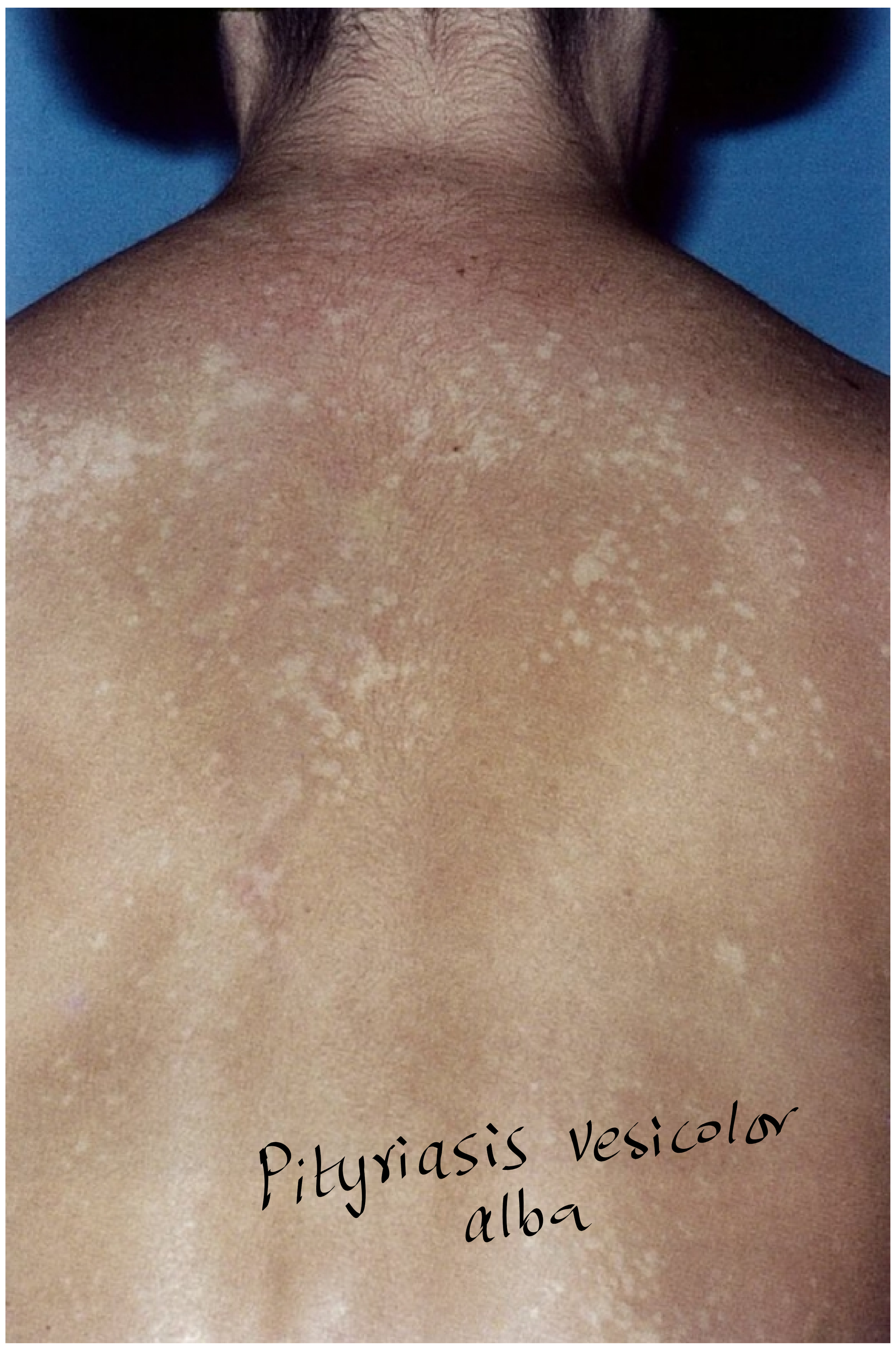

chancre


Extragenital syphilitic chancre


Maculopapular rash in secondary syphilis

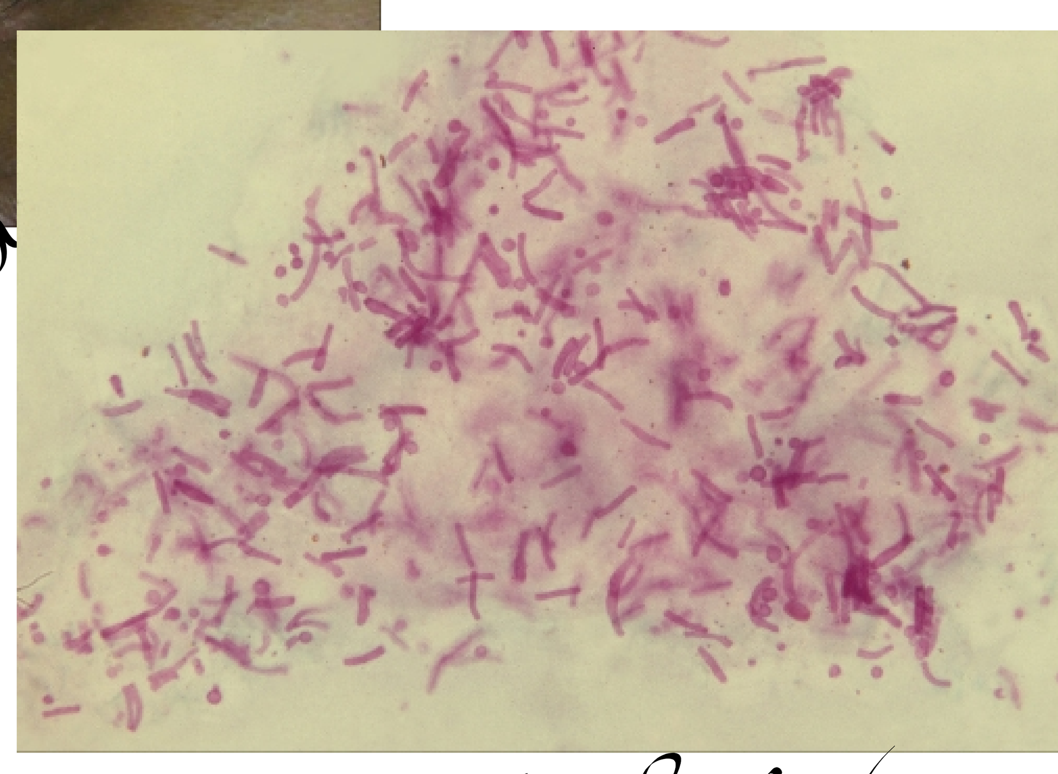

Rash in secondary syphilis

Pityriasis Versicolor
(Tinea Versicolor)



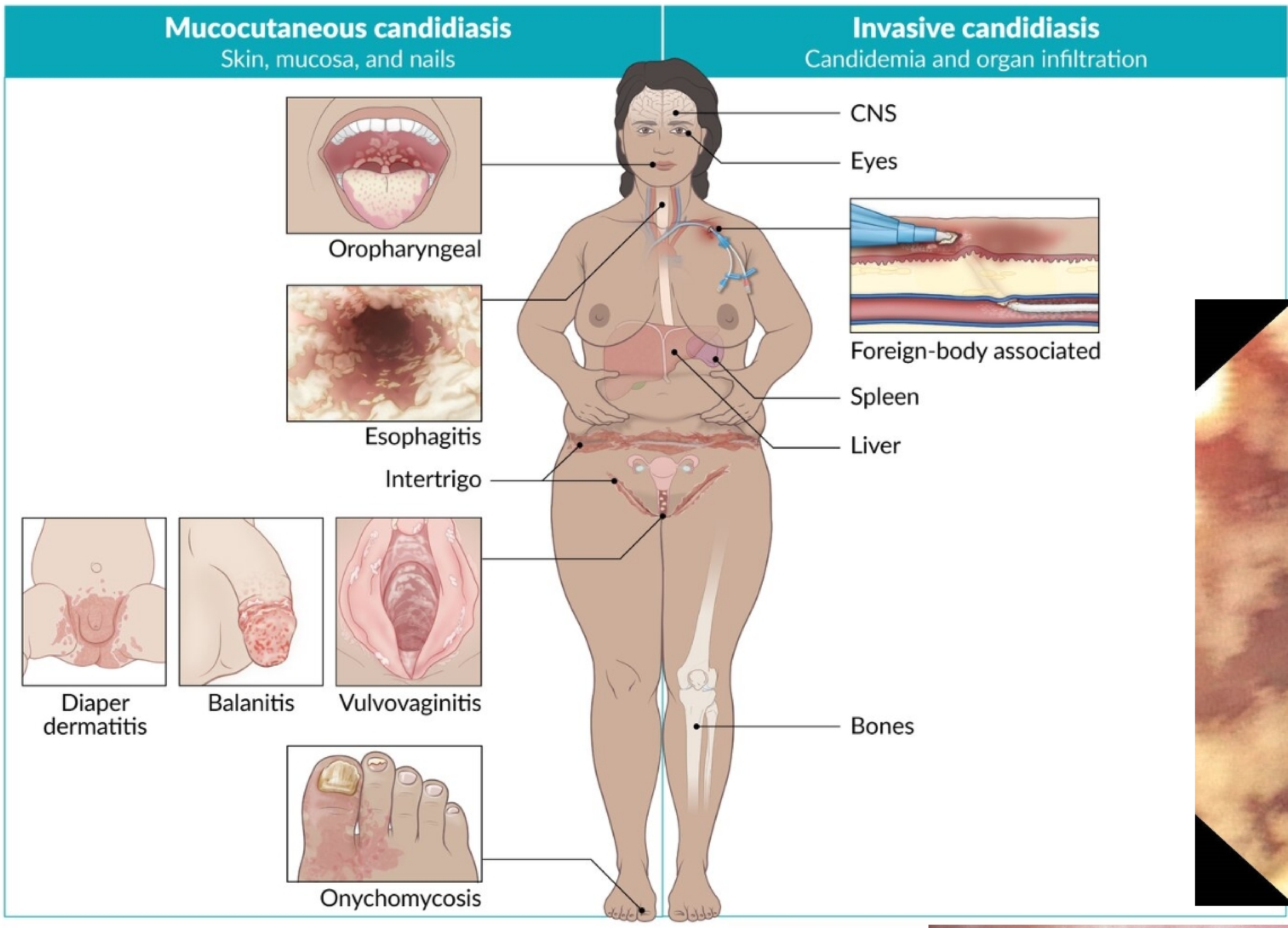
Pityriasis versicolor alba

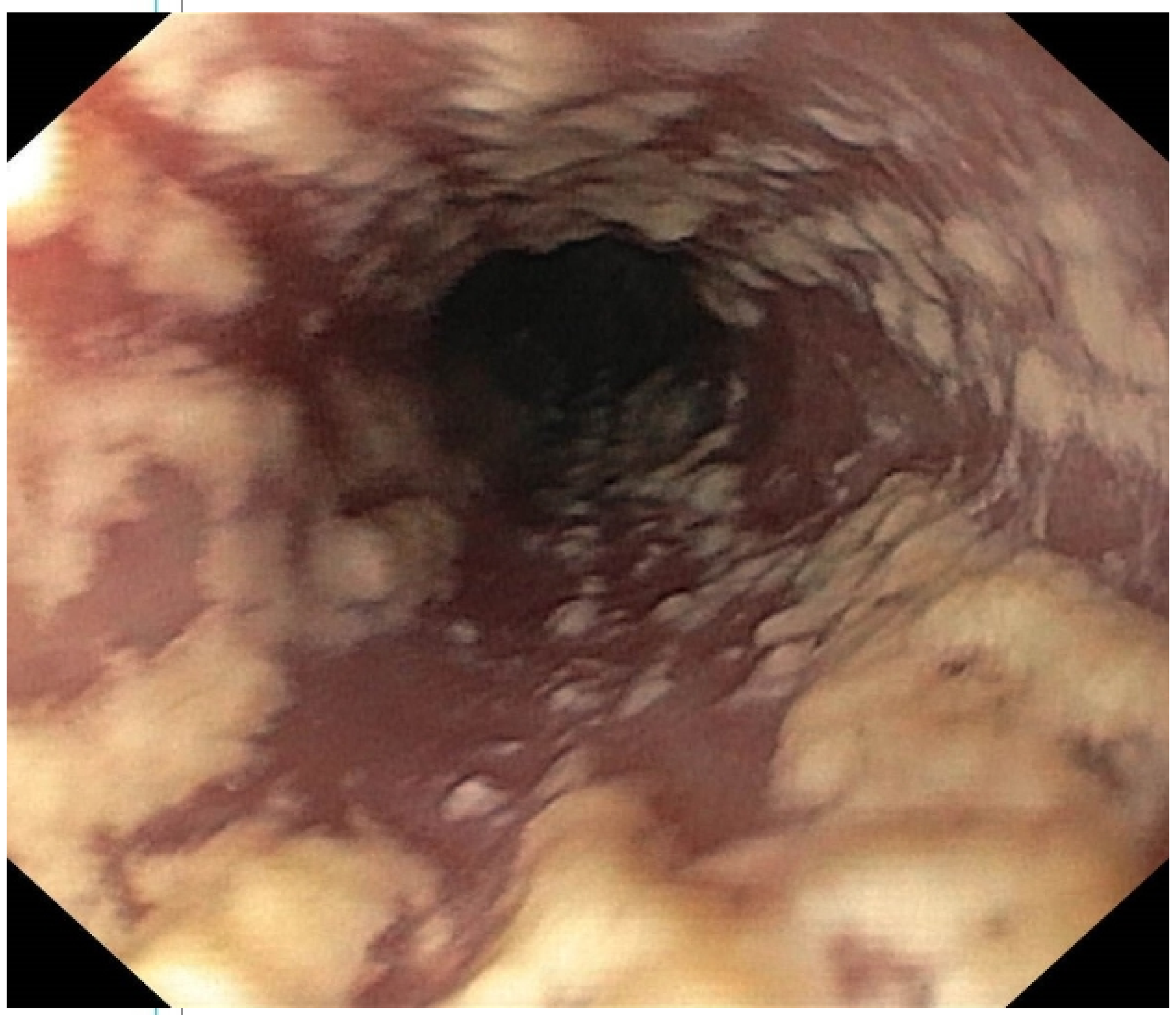
Tinea versicolor alba

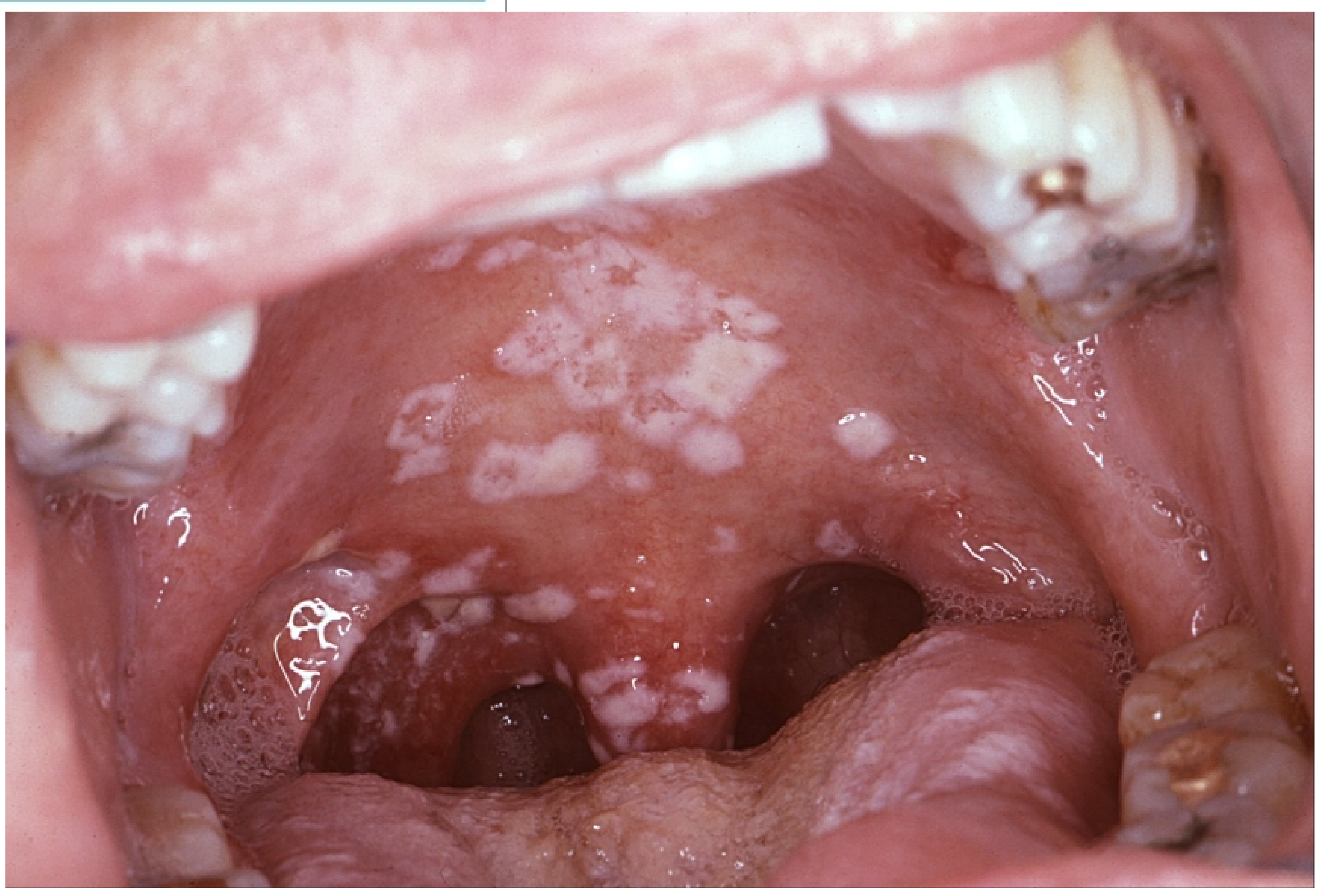


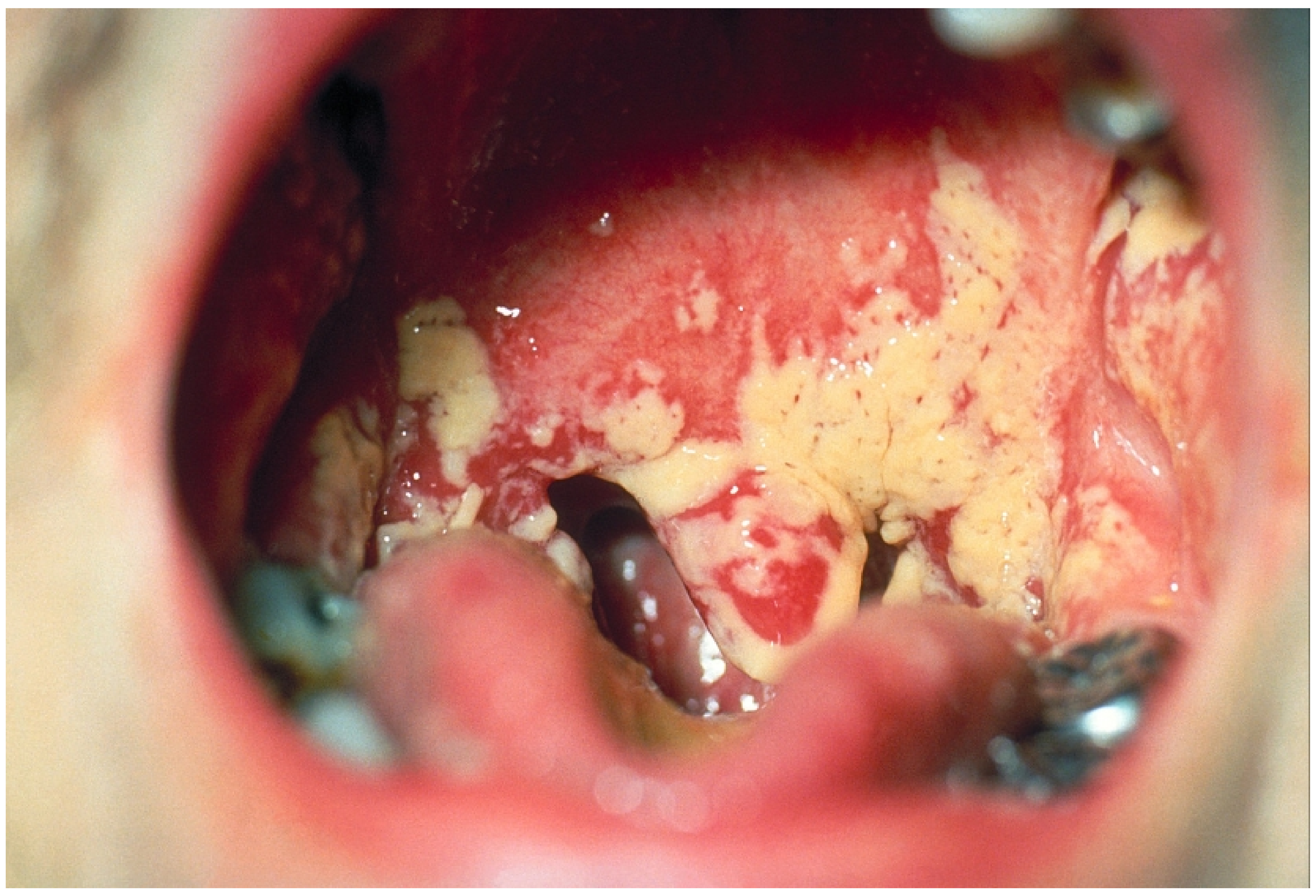
Malassezia furfur

Candidiasis





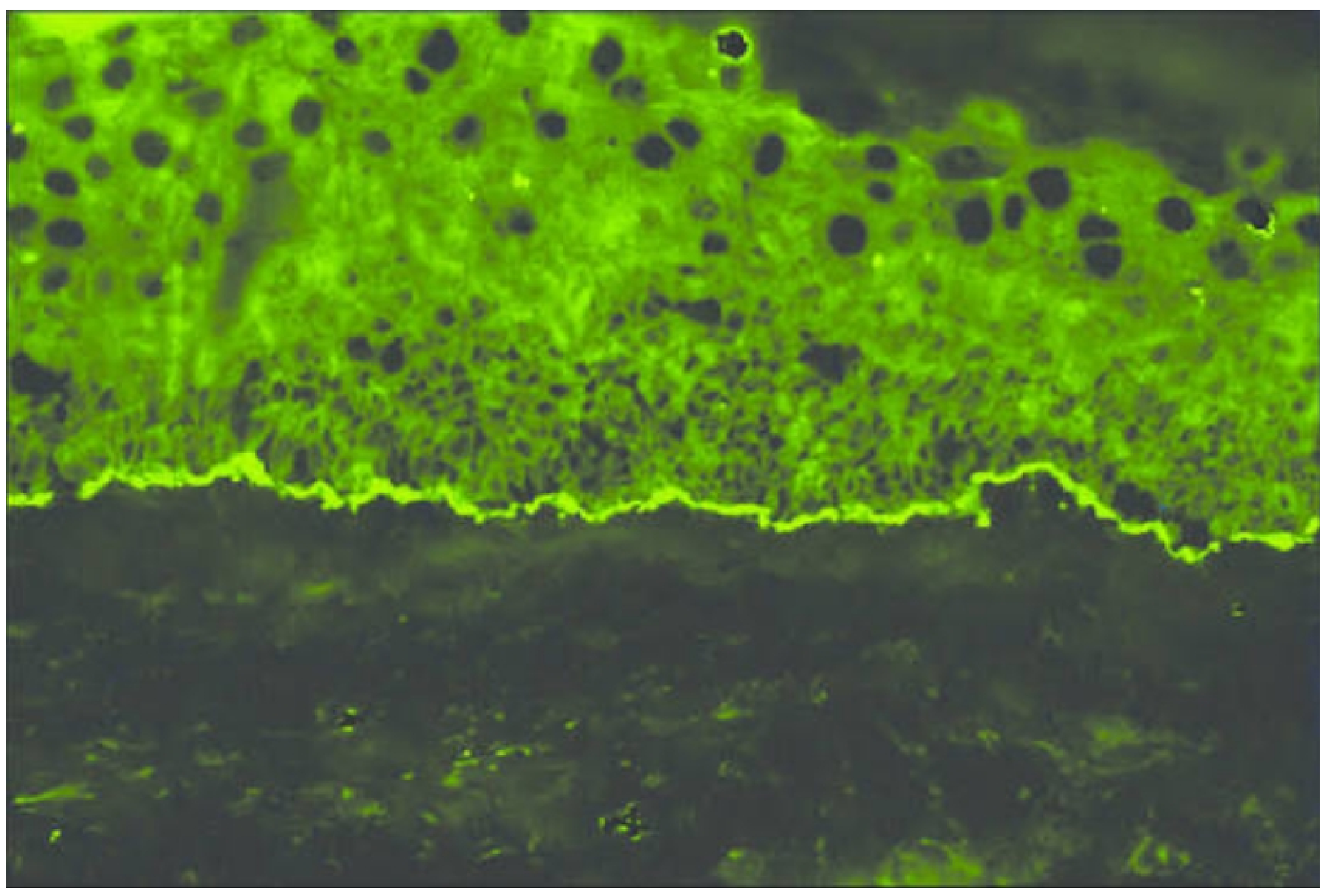




Bullous pemphigoid

* Autoimmune blistering disorder
* Large tense bullae
* Blisters are very itchy
* Blisters are tense and don't rupture easily

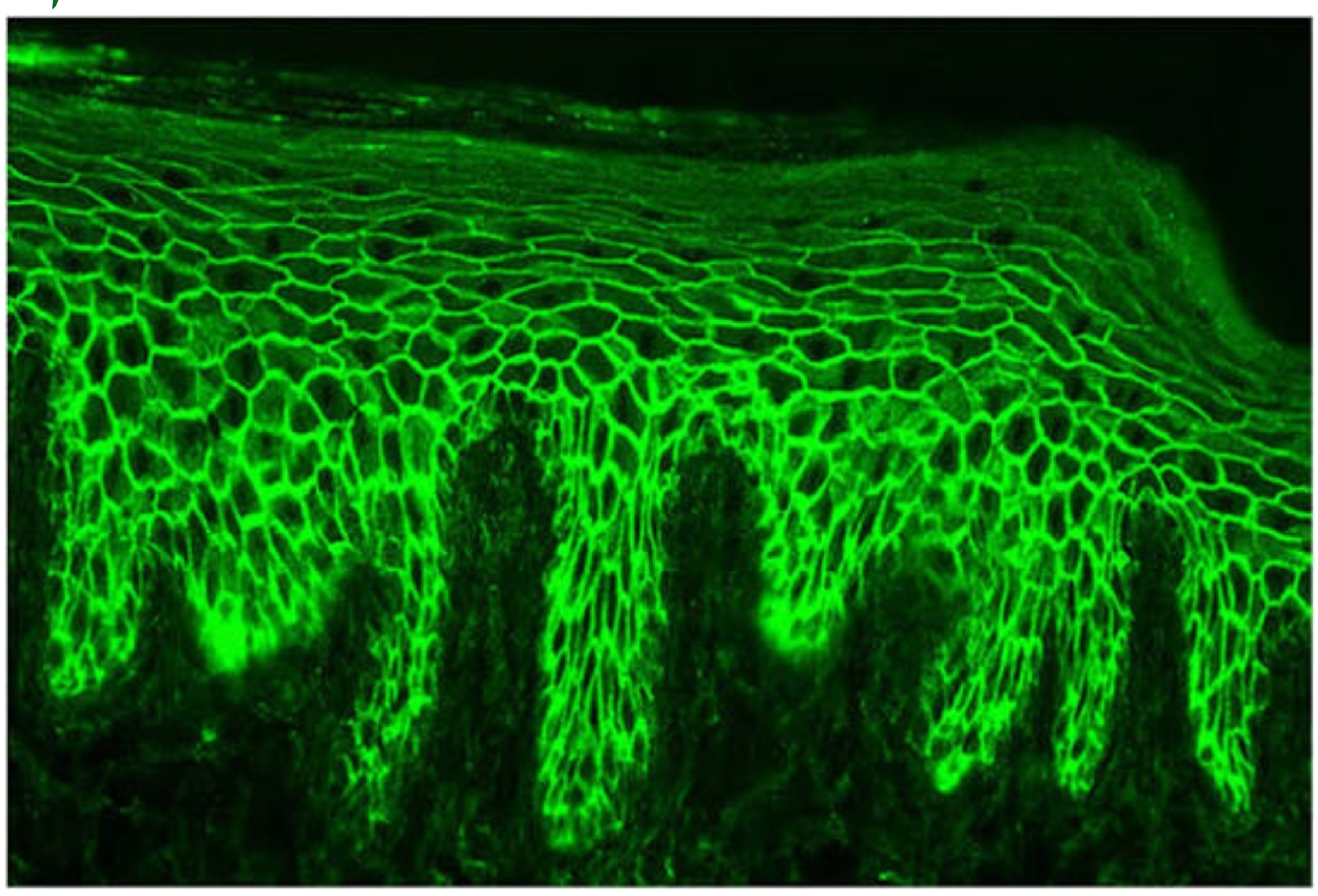
Direct Immunofluorescence → Linear deposition of immunoglobulins along the basement membrane with increased eosinophils in dermis



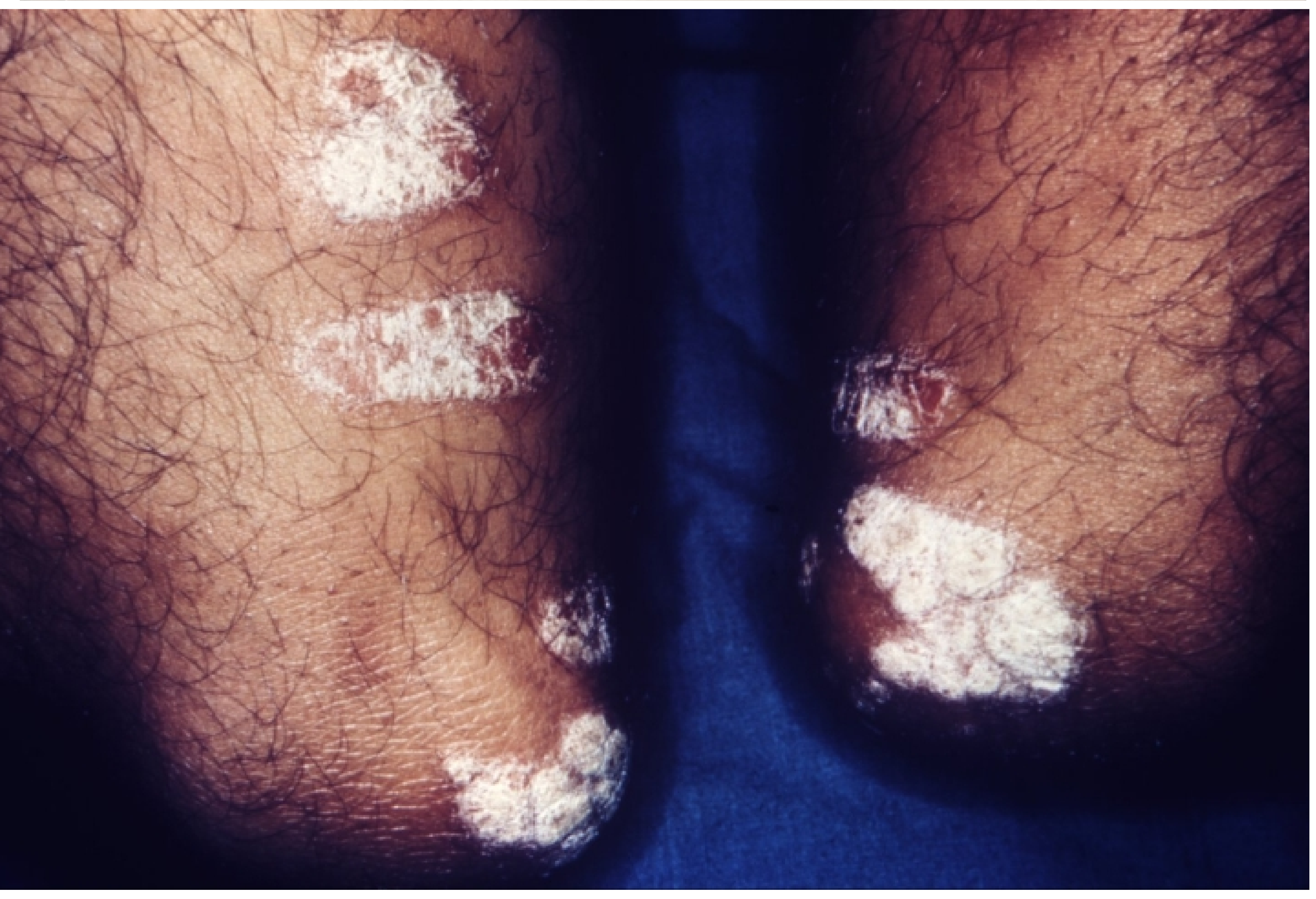
Pemphigus vulgaris

* Auto immune blistering disorder
* Mucosal involvement is common
* Blisters are NOT itchy
* Blisters rapidly denude
* Nikolsky's Sign → separation of superficial skin layers with slight rubbing

Direct IF → Fishnet-like (tombstone) pattern of immunoglobulins surrounding epidermal cells



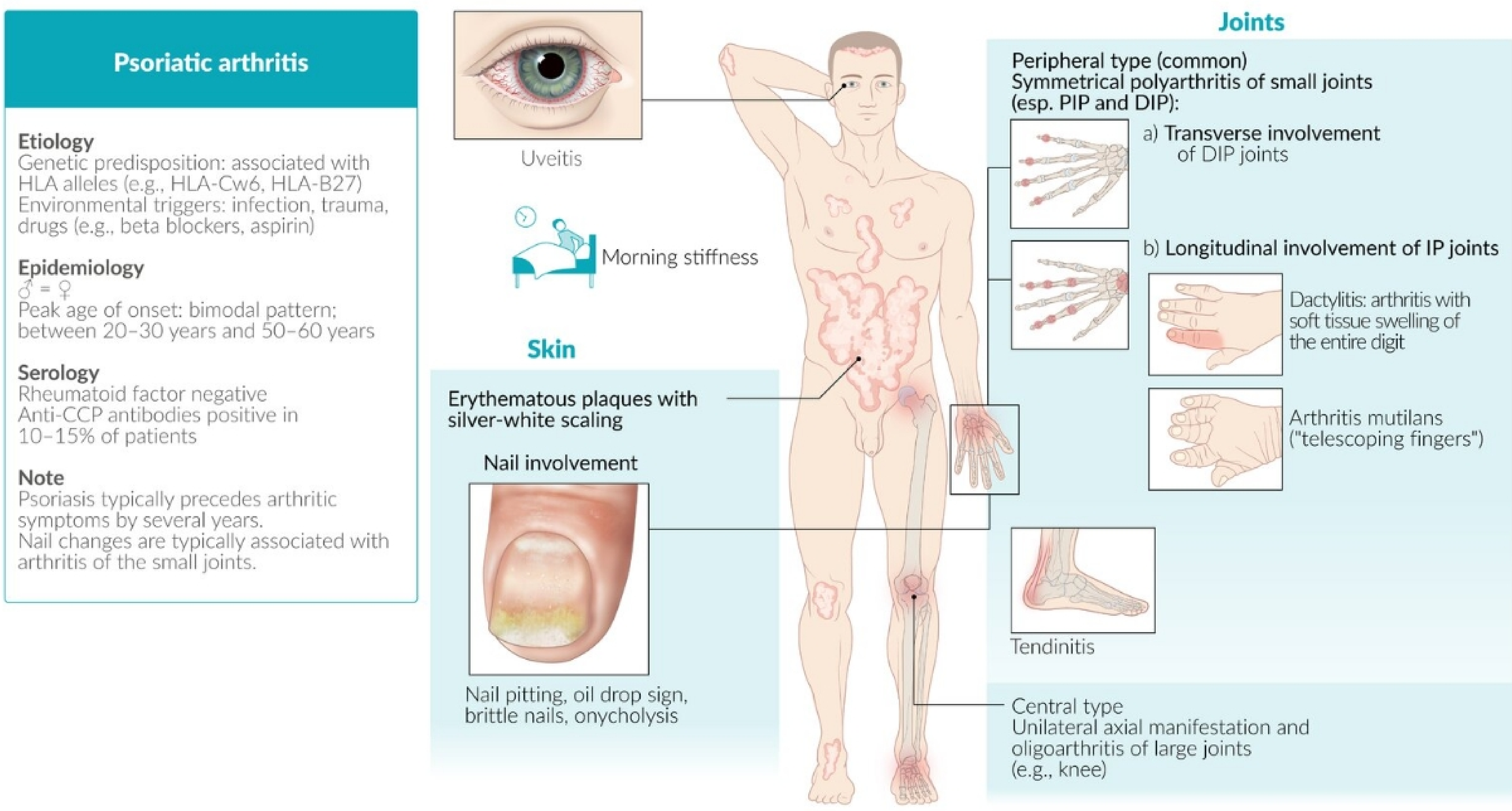
Psoriasis

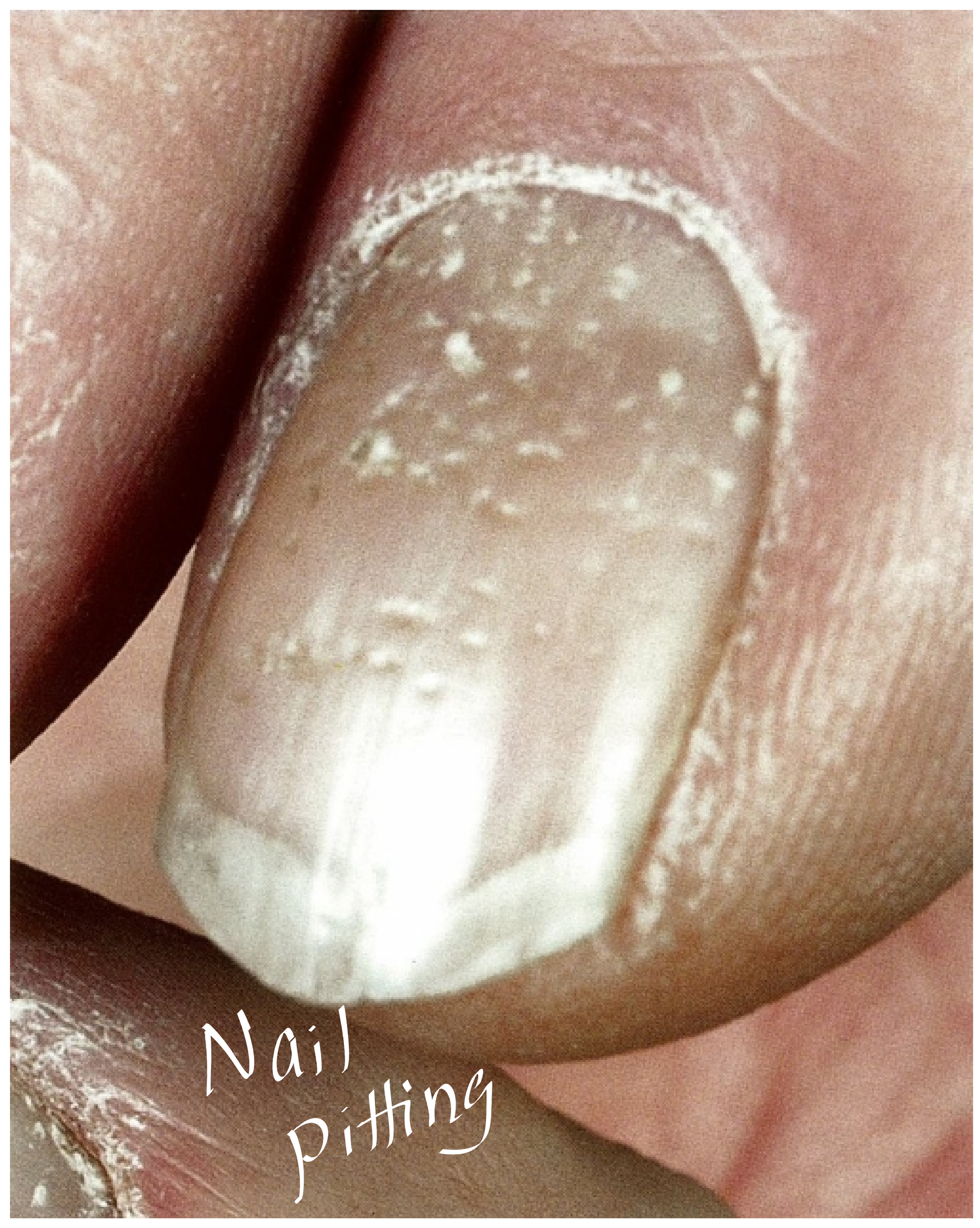


↑ Sterile pustules on erythematous base

* It is a T-cell mediated disease that involves increased keratinocyte proliferation along with inflammation and angiogenesis

PSORIASIS





* Auspitz Sign i.e visible pinpoint bleeding when scale is removed from plaque due to thin epidermis above dermal papilla

* Koebnerization i.e new plaques occur at sites of repeated trauma

Lichen planus





Etiology

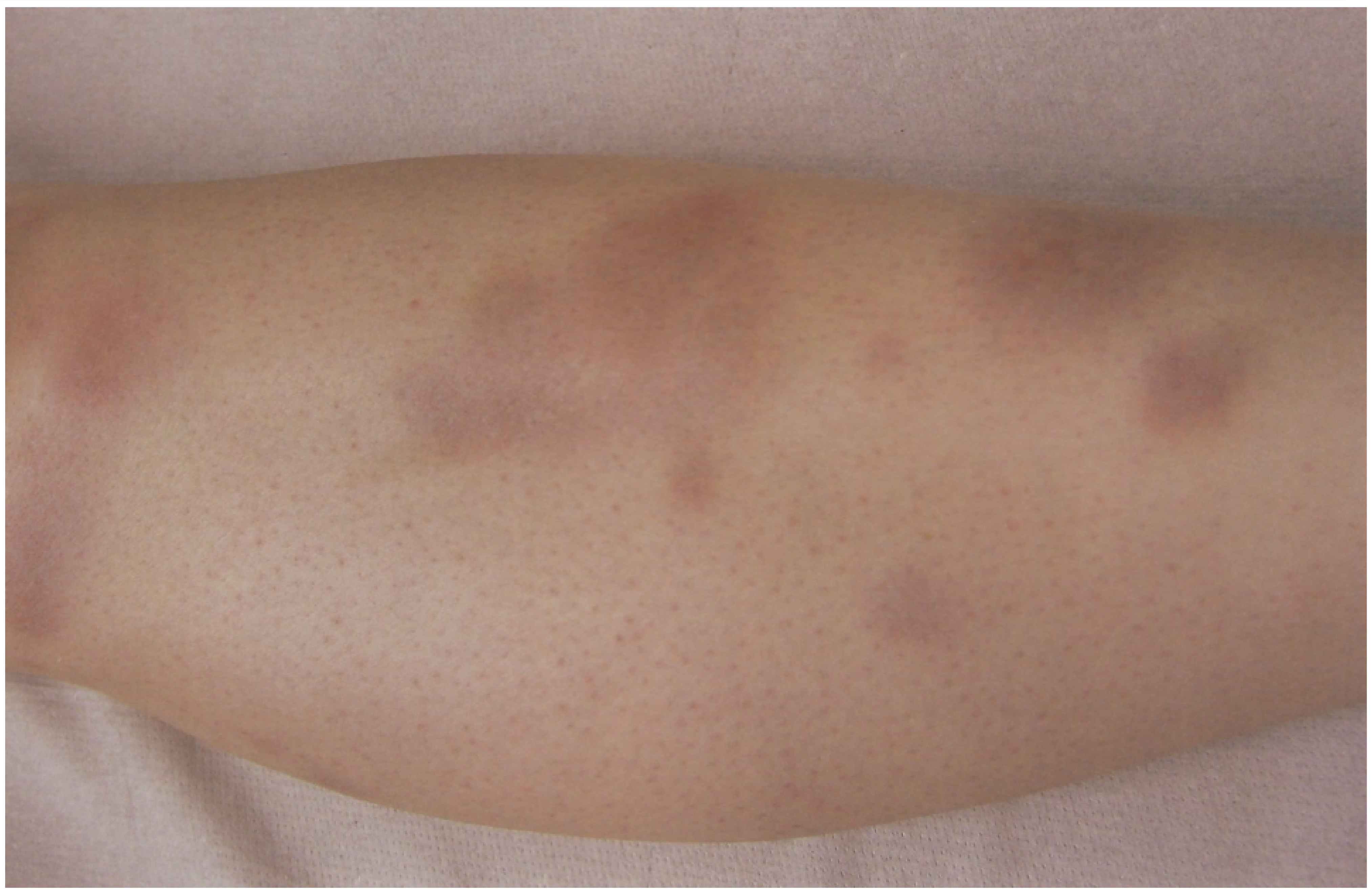
Although the exact etiology of lichen planus is unknown, possible etiologic factors include:

- Altered immune response with T cell activation [5][6]
- Associated with **hepatitis C infections** [7]

Clinical features

Lichen planus can affect the skin, mucosa, scalp, genitalia, and nails, and manifests with varying symptoms depending on the subtype of the disease.

Erythema Nodosum



* painful, erythematous nodules on lower legs and sometimes forearms

Erythema Multiforma







Severe forms of erythema multiforme


Stevens Johnson Syndrome

(epidermal separation of <10% of body surface area)

Toxic epidermal necrolysis

(epidermal separation of >30% of body surface area)


Both show Nikolsky's sign ie separation of superficial skin layer with slight rubbing

Urticaria (Hives)

* characterized by superficial, intense erythema and edema in a localized area

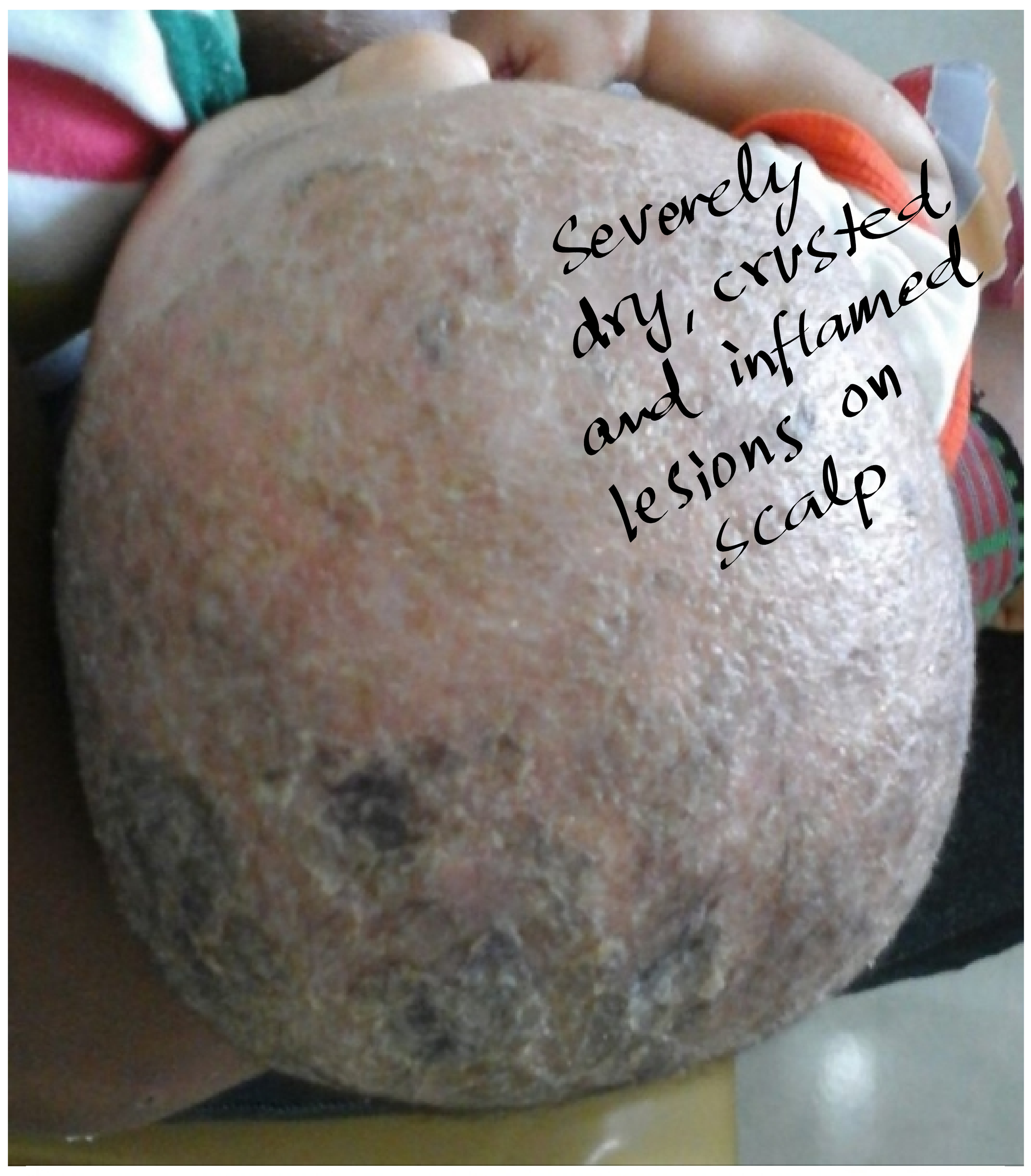
* Tx → Anti histamines

Common Triggers

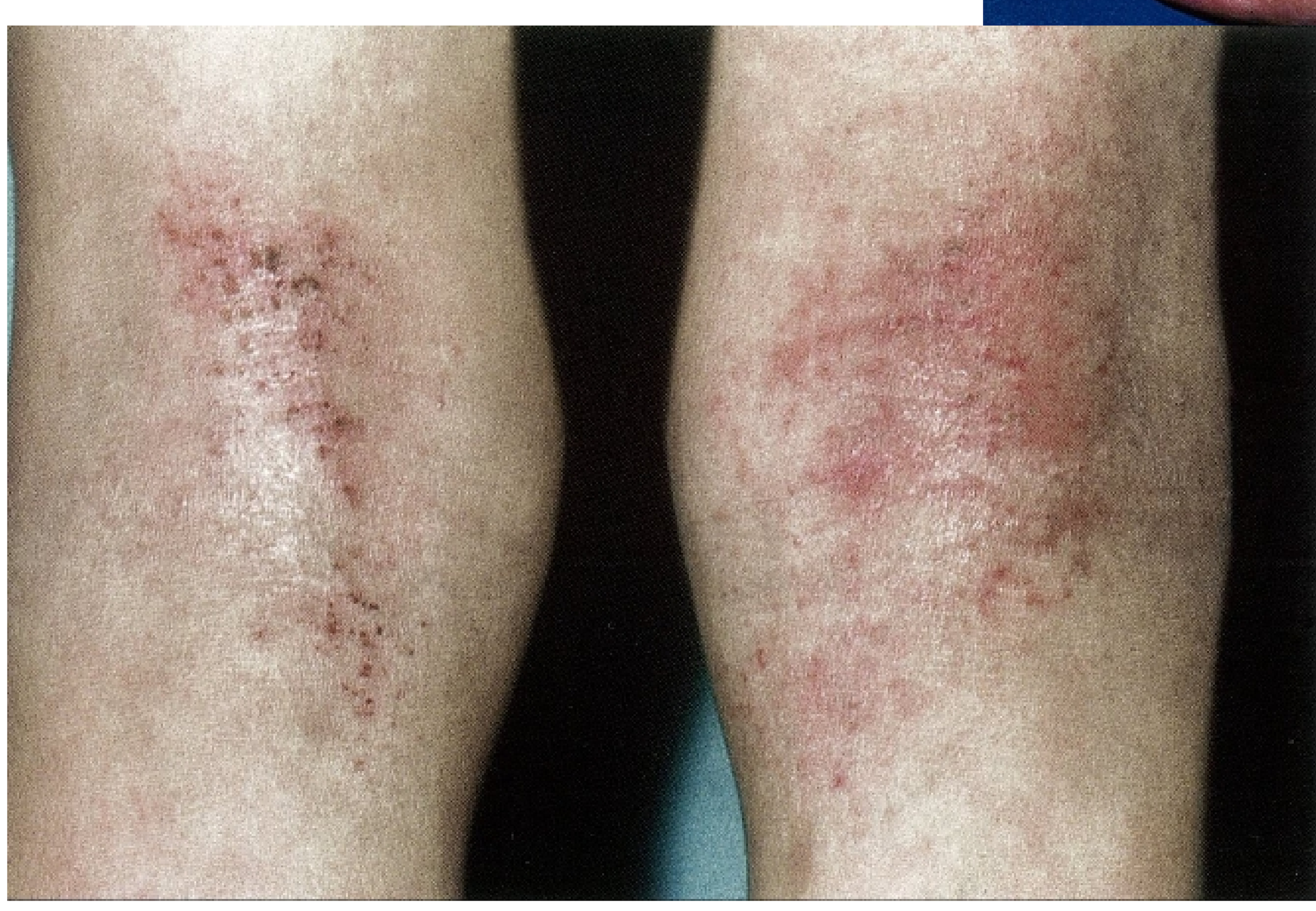
- **Allergens**: Foods, medications, or insect stings often cause hives.
- **Environmental Factors**: Pollen, sunlight, or water exposure can act as triggers.
- **Stress**: Emotional or physical stress may worsen symptoms.

ECZEMA (DERMATITIS)

ATOPIC DERMATITIS



* genotypically complex
familial disease with
strong maternal influence



Seborrheic Dermatitis

- overgrowth of fungus, Malassezia furfur
- predilection for areas with oily skin

Allergic Contact Dermatitis

List of Important Autoantibodies

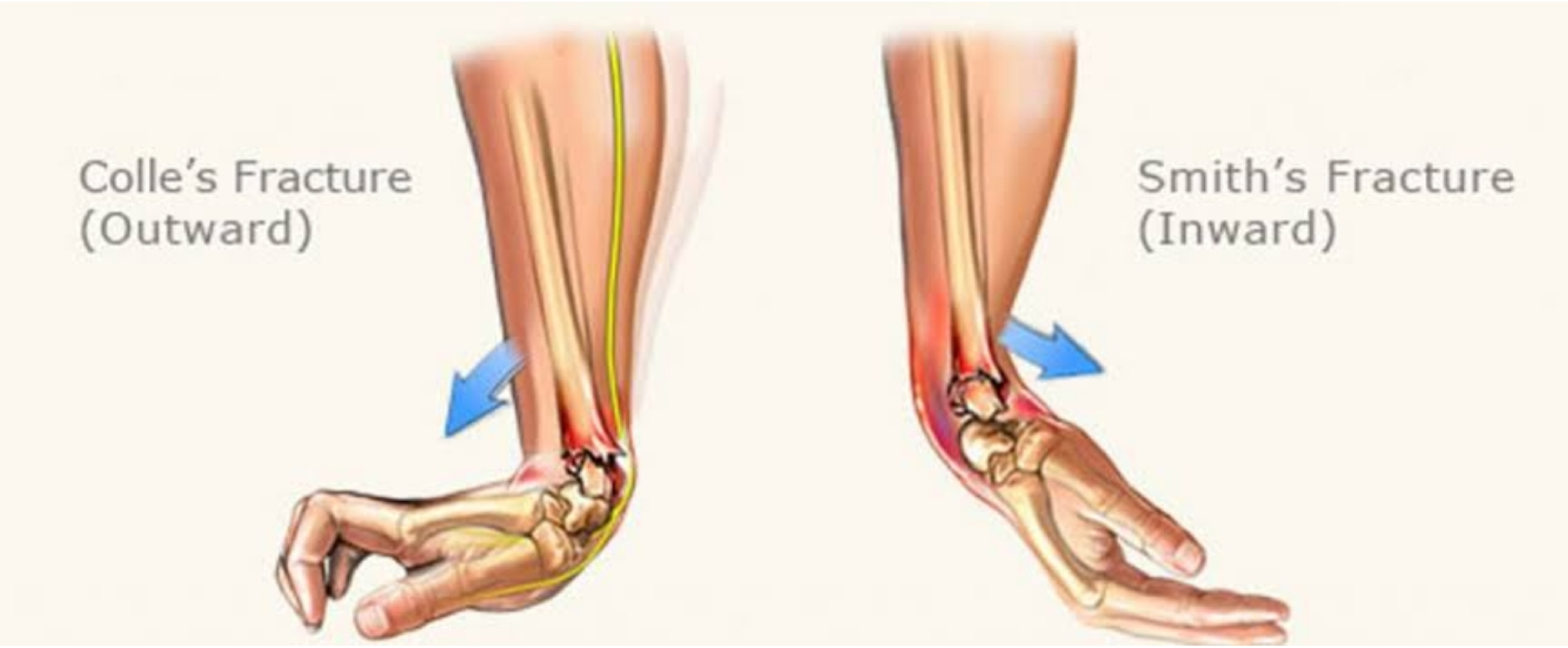
Anti-dsDNA and Anti-smith	SLE (but the initial test is ANA – very sensitive)
Anti-histone	Drug-induced lupus (e.g. Hydralazine)
Anti-scl70	Systemic Sclerosis
Anti-centromere	Limited sclerosis/CREST syndrome
Anti-Jo1	Polymyositis
Anti-Ro, Anti-La	Sjogren's disease
Anti-mitochondrial	Primary biliary cirrhosis
Anti-smooth muscle	Autoimmune hepatitis
pANCA	Churg Strauss (Eosinophilic Granulomatosis with Polyangiitis) / UC / 1ry sclerosing cholangitis.
cANCA	Wegener's Granulomatosis (Granulomatosis with Polyangiitis)
Anti-tissue transglutaminase, Anti-gliadin, Anti-endomysial	Celiac Disease
ANA	RA, SLE (initial), and many other auto-immune diseases.

Scalpel blades for cutting

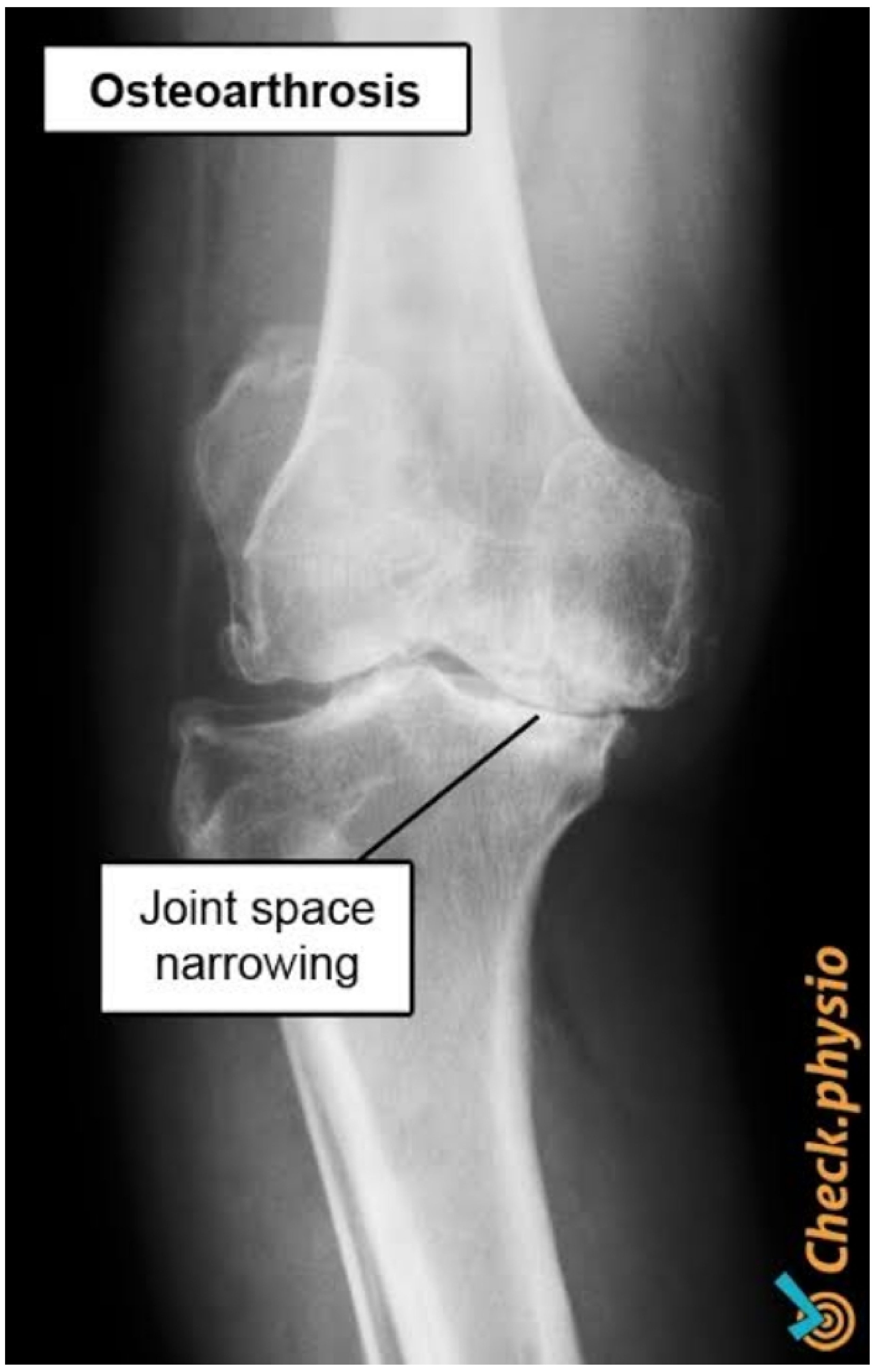
Grasping Instruments

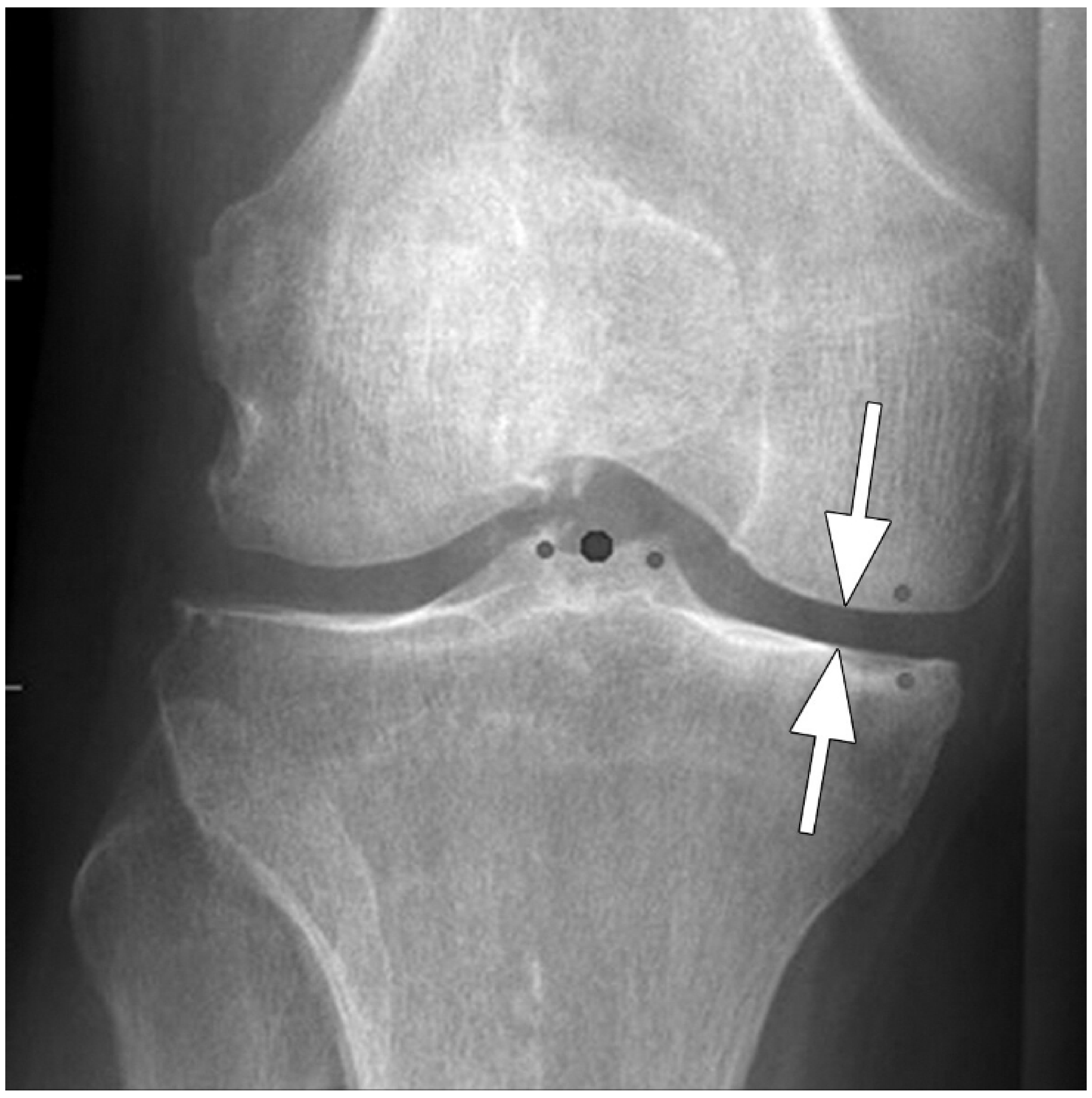
Toothed forceps: Skin (prevents slippage)

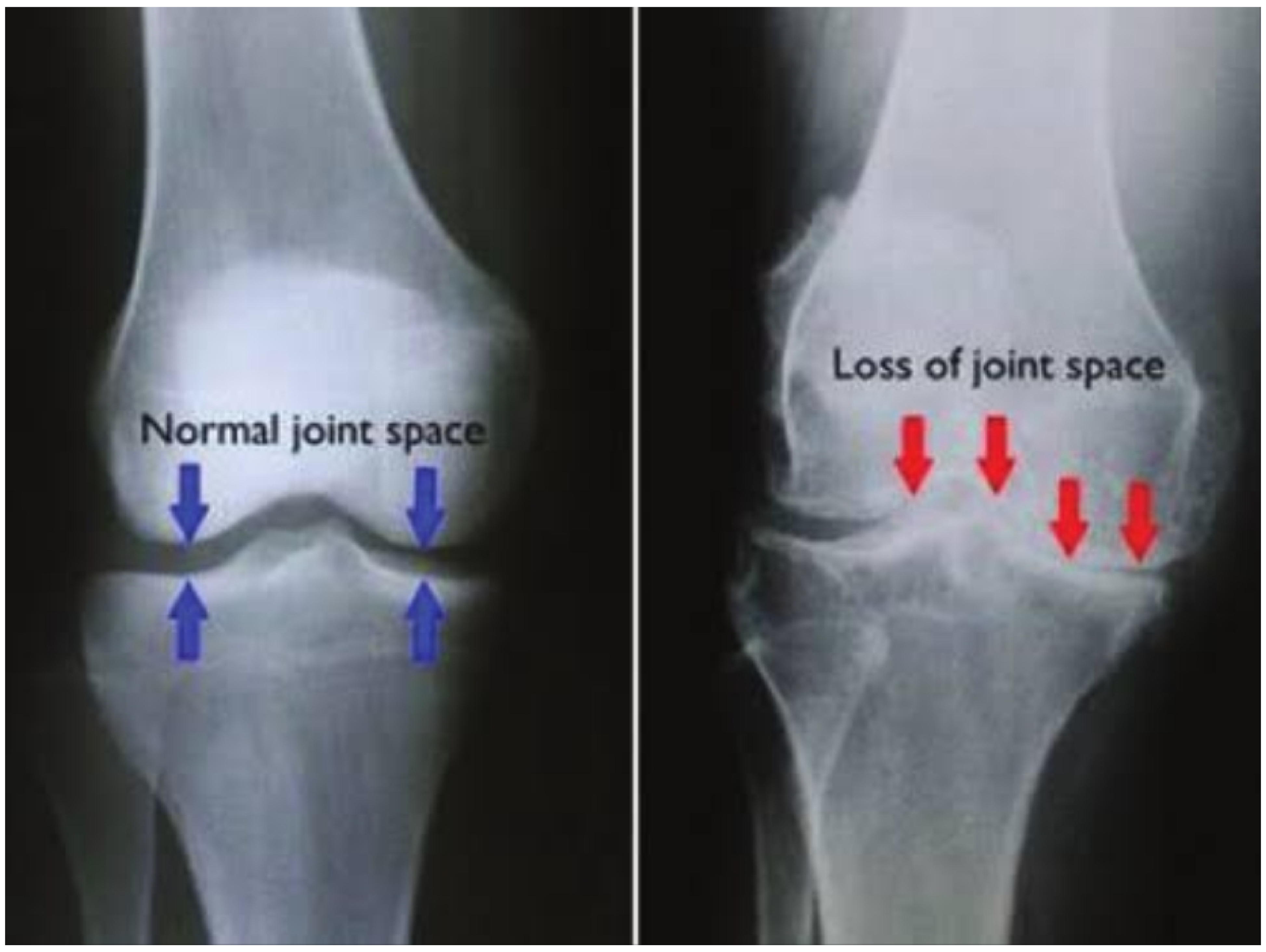
Non-toothed forceps: Viscera, bowel

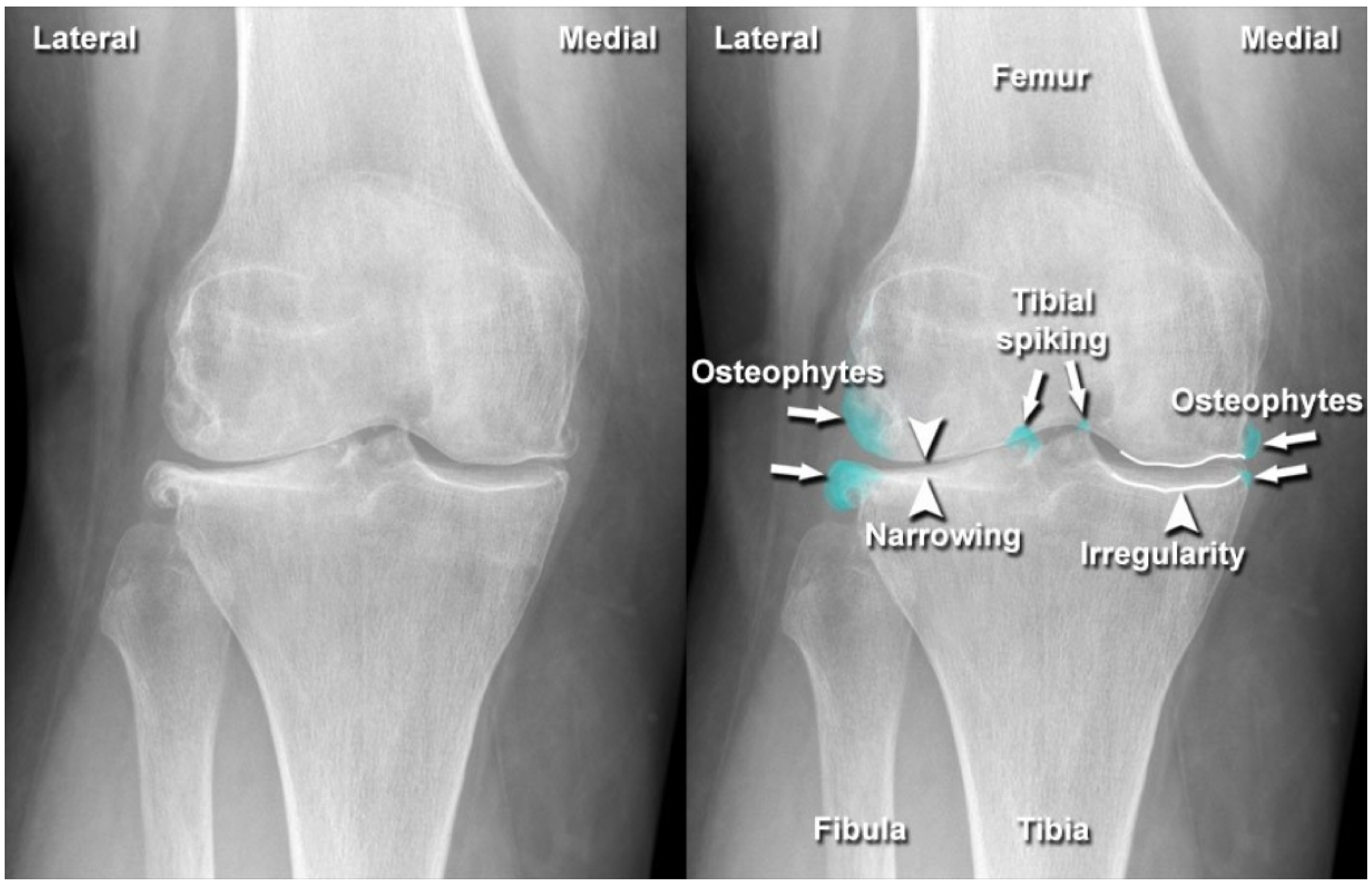

Colle’s Fracture
(Outward)
Smith’s Fracture
(Inward)

Osteoarthritis









Rheumatoid Arthritis

Figure 1

Figure 2