Approach to Anemia

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Outline

- Definition of anemia
- Signs and symptoms related to anemia
- Classification of anemia
- Diagnostic approach

Anemia

- Anemia is the most common problem in consultative hematology
- Anemia is not a diagnosis itself
- Work-up for the cause of anemia can lead to a diagnosis of the underlying disease

Definition of Anemia

- A reduction in absolute number of circulating red blood cells as represented by RBC count, hemoglobin concentration, and hematocrit
- WHO criteria for anemia

	Men	Women
Hb (g/dL)	<13	<12
Hct (%)	<39	<36
RBC $x10^{12}$	<4.5	< 4

World Health Organization; 1968.

Signs and Symptoms Related to Anemia

Depend on the degree of anemia and rate at which it has evolved

- Decreased oxygen delivery to tissues
  - Exertional dyspnea, dyspnea at rest, fatigue, lethargy, confusion and life-threatening complications such as congestive failure, angina, arrhythmia, and/or myocardial infarction.
- Hypovolemia (acute bleeding)
  - Postural dizziness, lethargy, syncope, hypotension, shock, and death.

Causes of Anemia: Kinetic Approach

Decreased RBC production (Hyporegenerative anemia)	Increased RBC destruction	Blood loss
Nutritional deficiency: iron, B12, folate	Hemolysis **Inherited** - Membrane defects: HS, HE, SEO - Enzymopathy: G-6-PD deficiency, pyruvate kinase deficiency - Thalassemias **Acquired** - Immune: AIHA, alloimmune hemolysis - Non-immune: PNH, drugs, chemical, infection, MAHA, mechanical hemolysis	Obvious bleeding
Bone marrow disorders: aplastic anemia, PRCA, MDS, tumor infiltration)		Occult bleeding
Bone marrow suppression: drugs, chemotherapy, radiation, alcohol, toxin)		Induced bleeding
Low levels of hormones: EPO (CKD), thyroid hormone (hypothyroidism), and androgens (hypogonadism)		
Anemia of chronic disease/inflammation		

Clinical approach to anemia. In: Hematology in Clinical Practice, Hillman RS, Ault KA (Eds), McGraw-Hill, New York 2001. p.29.

Causes of anemia: Morphologic Approach

Microcytic anemia (MCV< 80 fL)	Normocytic anemia (MCV 80-100 fL)	Macrocytic anemia (MCV > 100 fL)
Iron deficiency anemia	Acute blood loss	Megaloblastic anemia (vitamin B12 deficiency , folate deficiency, drugs)
Thalassemias	Hemolytic anemia: HS. G-6PD deficiency, PNH	Non-megaloblastic anemia (alcohol, liver disease, hypothyroidism)
Anemia of chronic disease/ inflammation	-Anemia of chronic disease/ inflammation -Anemia of CKD	Other bone marrow disorders: MDS
Sideroblastic anemia (congenital, lead poisoning, alcohol, drugs)	Hypersplenism	Reticulocytosis (eg. hemolytic anemia)
Copper deficiency, zinc poisoning	Bone marrow suppression/invasion: AA, PRCA, acute leukemia, MDS, myelophthisis	

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Approach to Anemia: Onset Approach

Acute (< 2 weeks)

- **Acute bleeding**
- **Acute hemolysis**
  - Hereditary: G-6PD def.
    Hb H dz.
    HS
  - Acquired: Infection
    AIHA
    TTP/HUS
    Chemical or
    Physical agents

Subacute to chronic

- **Hyporegenerative anemia**
  - ACD
  - IDA
  - Bone marrow failure
  - Marrow infiltration: acute leukemia, etc.
- **Hemolytic anemia**
  - Thalassemia disease, membrane defect
  - PNH

Diagnostic Approach

- History taking and physical examination
- Laboratory investigation

History Taking: Initial Evaluation

- Acute vs subacute to chronic onset?
- Any bleeding?
- Evidence of hemolysis, urine color? If so, acute or chronic
- Is the patient iron deficient? If so, why?
- Has the patient systemic/chronic/inflammatory disease?
- Is the bone marrow affected (other cytopenia, myelophthisis)
- Is the patient taking medication, alcohol?
- Is the patient deficient in folate or vitamin B12? If so, why?
- Family history, and history of transfusion

Physical Examination

- Vital signs: tachycardia, hypotension, fever
- Pallor
- Jaundice
- Lymphadenopathy, hepatosplenomegaly, and bone tenderness
- Petechiae, ecchymoses, and other signs of bleeding disorder
- Signs of organ or multisystem involvement (e.g. heart failure, CNS)
- Signs of nutritional deficiency

Laboratory Investigation: Initial Tests

- **Complete blood count**

  -- > Limitation:

  - Increased plasma volume: pregnancy, heart failure
  - Decreased plasma volume: dehydration, burn

  --> Discrepancy: Hb H disease, cold type AIHA
- **Reticulocyte count**
- **Peripheral blood smear**

Complete blood count

- Red cell parameters
- Absolute reticulocyte count
- WBC count and differential
- Platelet count

Comparison to previous CBC

Red cell parameters

- **Direct measurement**
  - Erythrocyte concentration (RBC) — $x10^6/L$
  - Mean corpuscular volume (MCV) — fL
  - Hemoglobin — g/dL
- **Indirect measurement**
  - Hematocrit (Hct) = RBC x MCV/10 — %
  - Mean corpuscular hemoglobin (MCH) = Hb x 10/RBC — pg
  - Mean corpuscular hemoglobin conc. (MCHC) = Hb/Hct x 100 — g/dL
  - Red cell distribution width (RDW) — %

Williams' Hematology, 5th ed, Beutler E, Lichtman MA, Coller BS, et al. (Eds), McGraw-Hill, New York 1995. p.L3.

CBC: normal value

- MCV 80-100 fL
- MCH >27 pg
- MCHC 32-36 g/dL
- WBC 3.8-10.6 $x10^9$/L men

  3.6-11.0 $x10^9$/L woman
- Platelet 150-440 $x10^6$/L
- RDW 11.5-14.5%

Williams' Hematology, 5th ed, Beutler E, Lichtman MA, Coller BS, et al. (Eds), McGraw-Hill, New York 1995. p.L3.

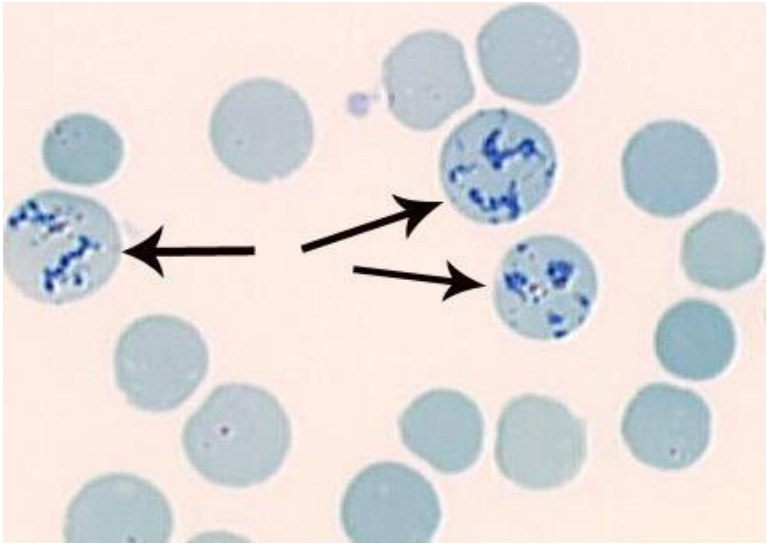
Reticulocyte count

- Non-nucleated RBC with polyribosome RNA as stained by supravital stain
- Polychromasia underestimate reticulocytes
- **Corrected reticulocyte %**

  = % reticulocyte x $\frac{\text{patient's Hct}}{45}$

- **Absolute reticulocyte count**

  = % reticulocyte x RBC



- 25,000-75,000/µL normal
- > 100,000 regenerative anemia
- < 50,000 hypoproliferative anemia
- 50,000-100,000 combined etiologies

Erslev AJ. Reticulocyte enumeration. In: Williams' Hematology, 5th ed, Beutler E, Lichtman MA, Coller BS, et al. (Eds), McGraw-Hill, New York 1995. p.L28.

Reticulocyte index

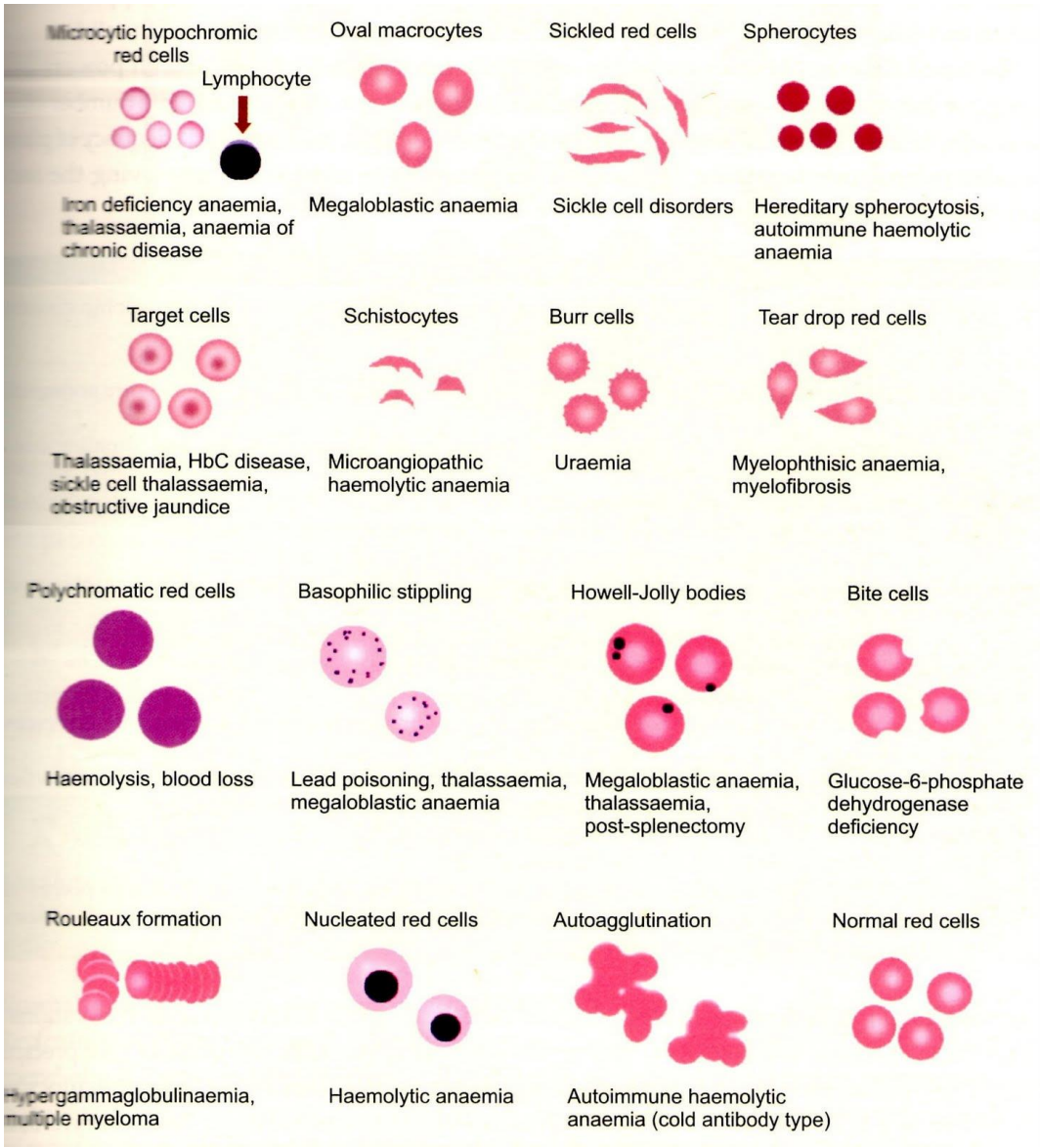
- Reticulocyte index = %corrected RetiC/maturation time

Maturation time (days) :	Hct ≥ 40% = 1
	Hct 30-40% = 1.5
	Hct 20-30% = 2
	Hct < 20% =2.5

- The reticulocyte index (RI) for healthy individual
  - 1.0-2.0%
- RI < 1% with anemia
  - Decreased production of reticulocytes
- RI >2% with anemia
  - Loss of RBC e.g. destruction, bleeding

Erslev AJ. Reticulocyte enumeration. In: Williams' Hematology, 5th ed, Beutler E, Lichtman MA, Coller BS, et al. (Eds), McGraw-Hill, New York 1995. p.L28.

Peripheral blood smear



Case 1

หญิงอายุ 30 ปี เหนื่อยง่าย 3 เดือน มีคนทักว่าซีด

PE: moderately pale, no jaundice, others: normal

WBC	7.3 (3.6 - 10.4) *1000/ul	Hemoglobin	7.5 (13.1 - 16.9) g/dl
Hematocrit	23.5 (39.4 - 50.8) %	Neutrophil	65 (35.6 - 70.5) %
Lymphocyte	30 (21.1 - 50.4) %	Monocyte	2 (2.3 - 11.1) %
Eosinophil	2 (1 - 11.8) %	Basophil	1 (.8 - 1.6) %
MCV	57.8 (76.1 - 99.3) fl	MCH	18.5 (25.2 - 33.2) pg
MCHC	32 (31.6 - 34.8) g/dl	RDW	23.1 (10.8 - 14) %
Platelet count	453 (156 - 393) *1000/ul	MPV	6.6 (6.5 - 9.5) fl
RBC	4.08 (4.36 - 5.9) *1000000/ul	Microcytosis	1 (-) -

Iron deficiency anemia (IDA)

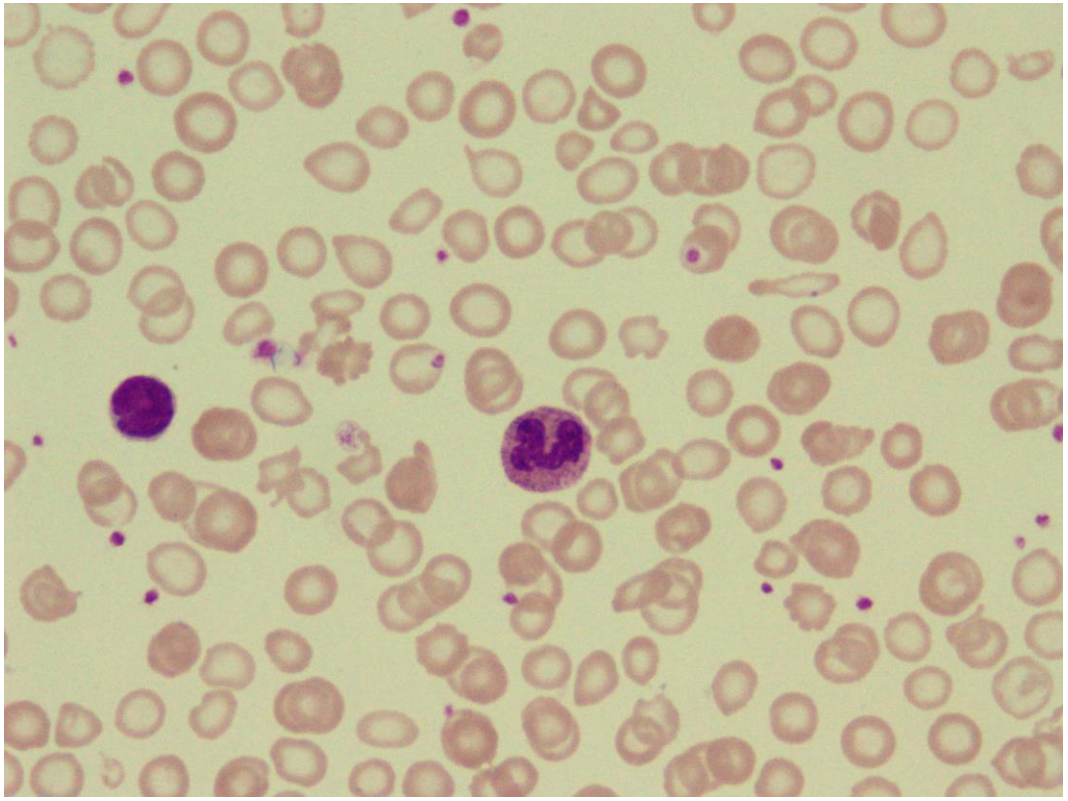
- Iron is a key substrate for heme production
- Causes
  - Low intake :
  - Chronic blood loss***
- Symptoms and signs
  - Anemic symptoms, cold hand and feet, fatigue, dizziness, dyspnea, pica, spoon nail (koilonychia), murmur, pale glossitis, and heart failure

IDA: lab

- CBC
  - Hct ↓, Hb ↓
  - MCV ↓ (when Hb < 10 g/dL), MCH ↓, MCHC ↓
  - RDW↑ (early sign)
- Reticulocyte count ↓
- Iron profile
  - Serum Iron ↓ (<60 µg/dL)
  - TIBC ↑(> 400 µg/dL)
  - Ferritin ↓ *** (< 30 ng/mL)
- Bone marrow study (gold standard but more invasive): no iron stain

Transferrin saturation (Tsat) = SI/TIBC x 100

IDA : PBS



- Hypochromic microcytic RBC
- Poikilocytosis and anisocytosis
- Pencil cell
- Rare or no polychrome

Case 2

ชายอายุ 33 ปี ซีดอ่อนเพลียมานาน เคยได้รับเลือดตอนเด็กปีละ 1-2 ครั้ง

PE: moderate pallor, mild jaundice, spleen 4 cm below LCM

CBC(30101)(7.1.1.1)

WBC	4.7 (3.6 - 10.4) *1000/ul	Hemoglobin	8.2 (13.1 - 16.9) g/dl
Hematocrit	23.7 (39.4 - 50.8) %	Neutrophil	62 (35 - 70) %
Lymphocyte	31 (20 - 50) %	Monocyte	1 (3 - 10) %
Eosinophil	3 (2 - 10) %	Basophil	2 (0 - 2) %
MCV	58.5 (76.1 - 99.3) fl	MCH	20.2 (25.2 - 33.2) pg
MCHC	34.5 (31.6 - 34.8) g/dl	Platelet	155 (140 - 450) *1000/ul
MPV	7.3 (6.5 - 9.5) fl	RBC	4.05 (4.36 - 5.9) *1000000/ul
		RDW	23 (10.8-14) %

Case 2

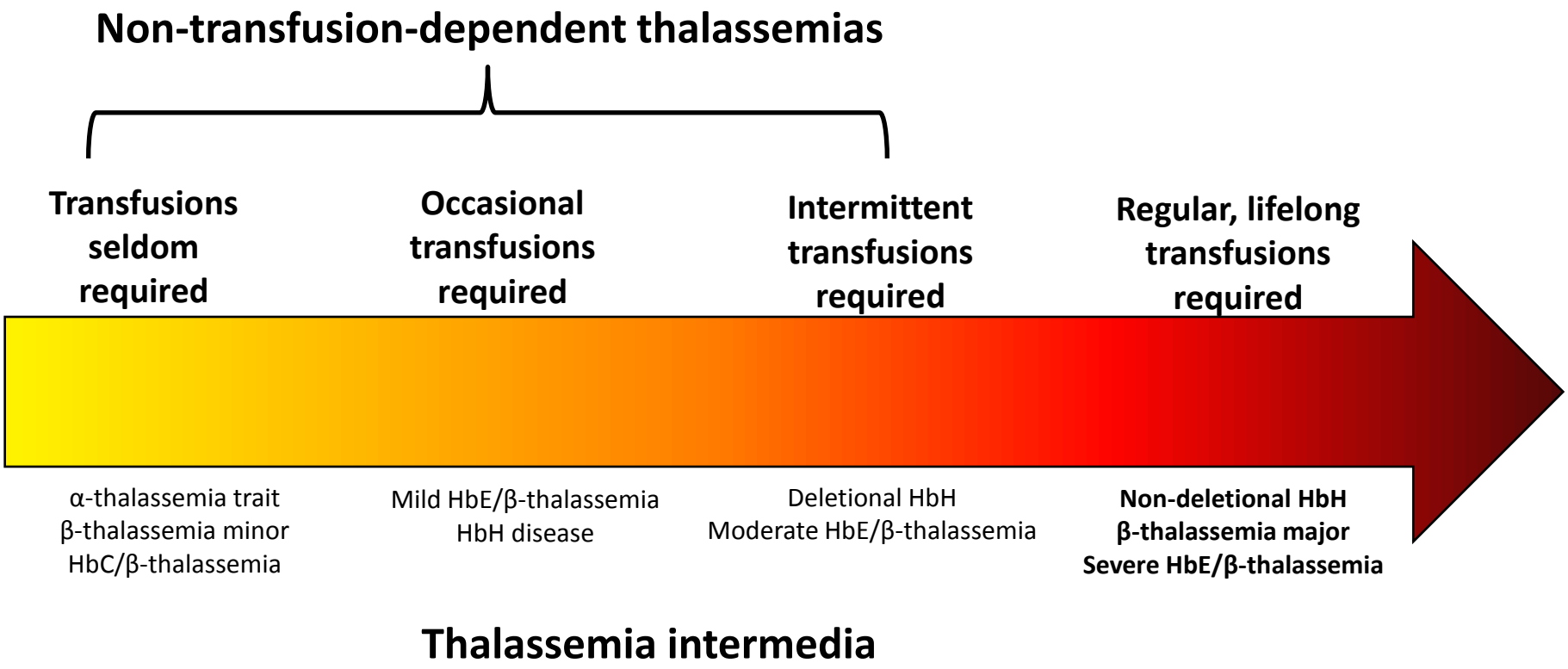
- **Hb typing:** HbE 62.3%

  HbF 30.3%

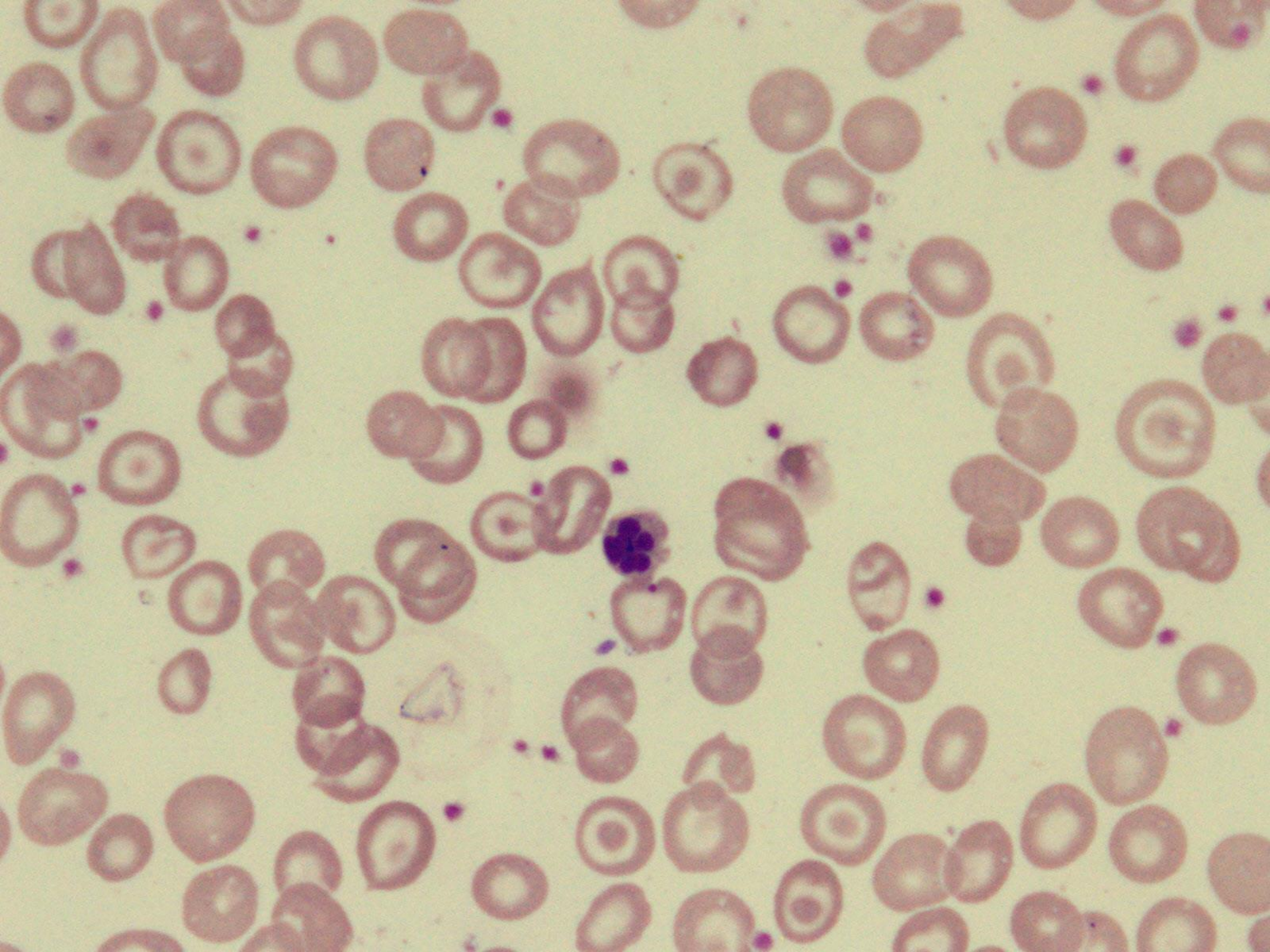
- **Diagnosis:**

  β thalassemia/HbE disease

Thalassemia and hemoglobinopathies



[1]Muncie HL & Campbell JS. *Am Fam Physician* 2009;80:339–344; [2]Galanello & Origa. *Orphanet Journal of Rare Diseases* 2010, 5:11; [3]Harteveld & Higgs. *Orphanet Journal of Rare Diseases* 2010, 5:13; [4]Cohen AR *et al. Hematology Am Soc Hematol Educ Program* 2004;14–34

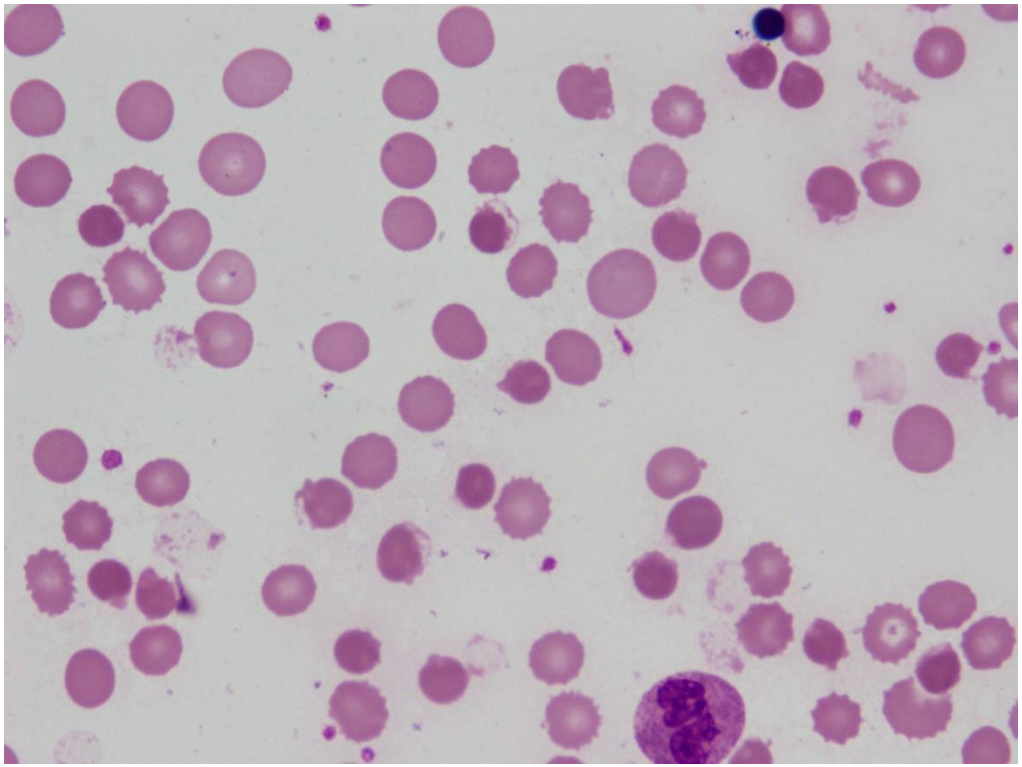


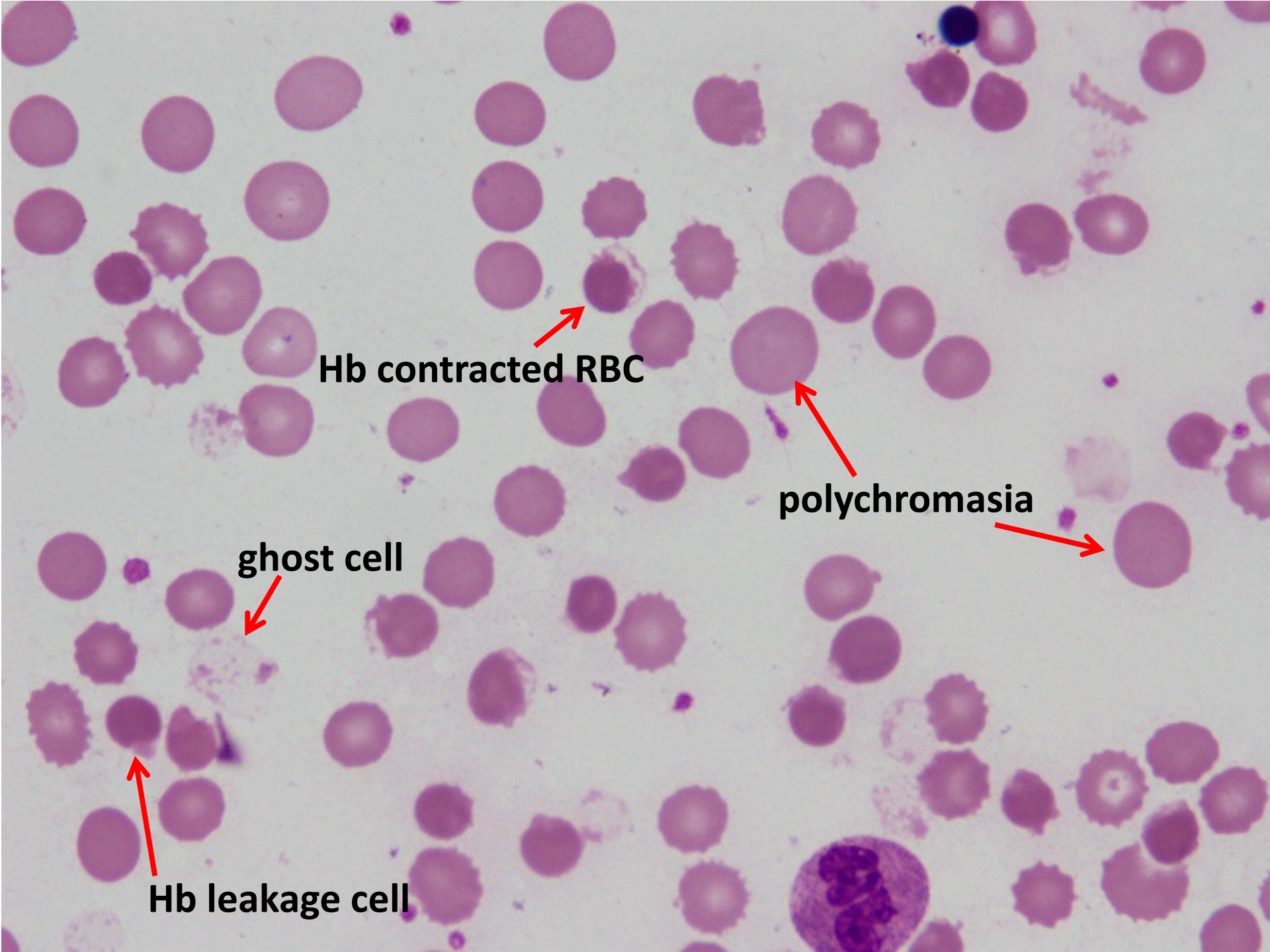
Case 3

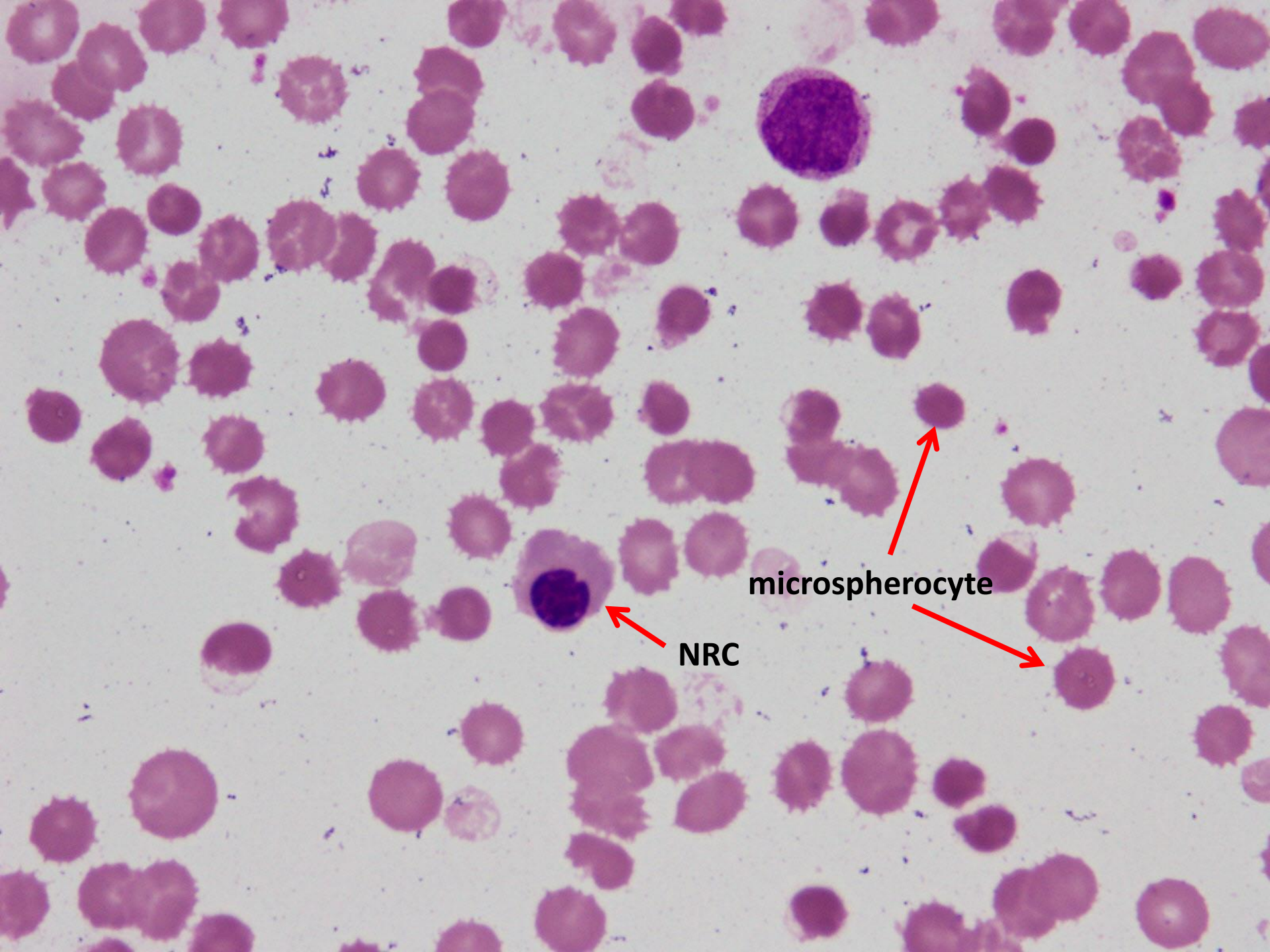
ชายอายุ 20 ปี ไข้ 3 วัน เหนื่อยมากขึ้น

PE: moderately pale, mild jaundice, no organomegaly

CBC: Hb 7 g/dL, Hct 21%, MCV 92 fL, RDW 18%, WBC $15x10^9$/L, PMN 40%, L 50%, atypical lymph 3%, mono 7%, NRC 3/100 WBC, platelet $280x10^9$/L




Hb contracted RBC
polychromasia
ghost cell
Hb leakage cell


microspherocyte
NRC

G-6PD deficiency

- X-linked recessive --> common in males
- Anemia after precipitating factors (infection , drugs)

  - Antimalarials (primaquine)
  - Sulfonamides (sulfamethoxazole, dapsone)
  - Antibiotics (cotrimoxazole, quinolones)

- Dark urine from hemoglobinuria
- Serious complications: renal insufficiency, hyperkalemia

Case 4

A 64-year-old man with underlying T2DM, HT, CKD (creatinine 2.0 mg/dL)

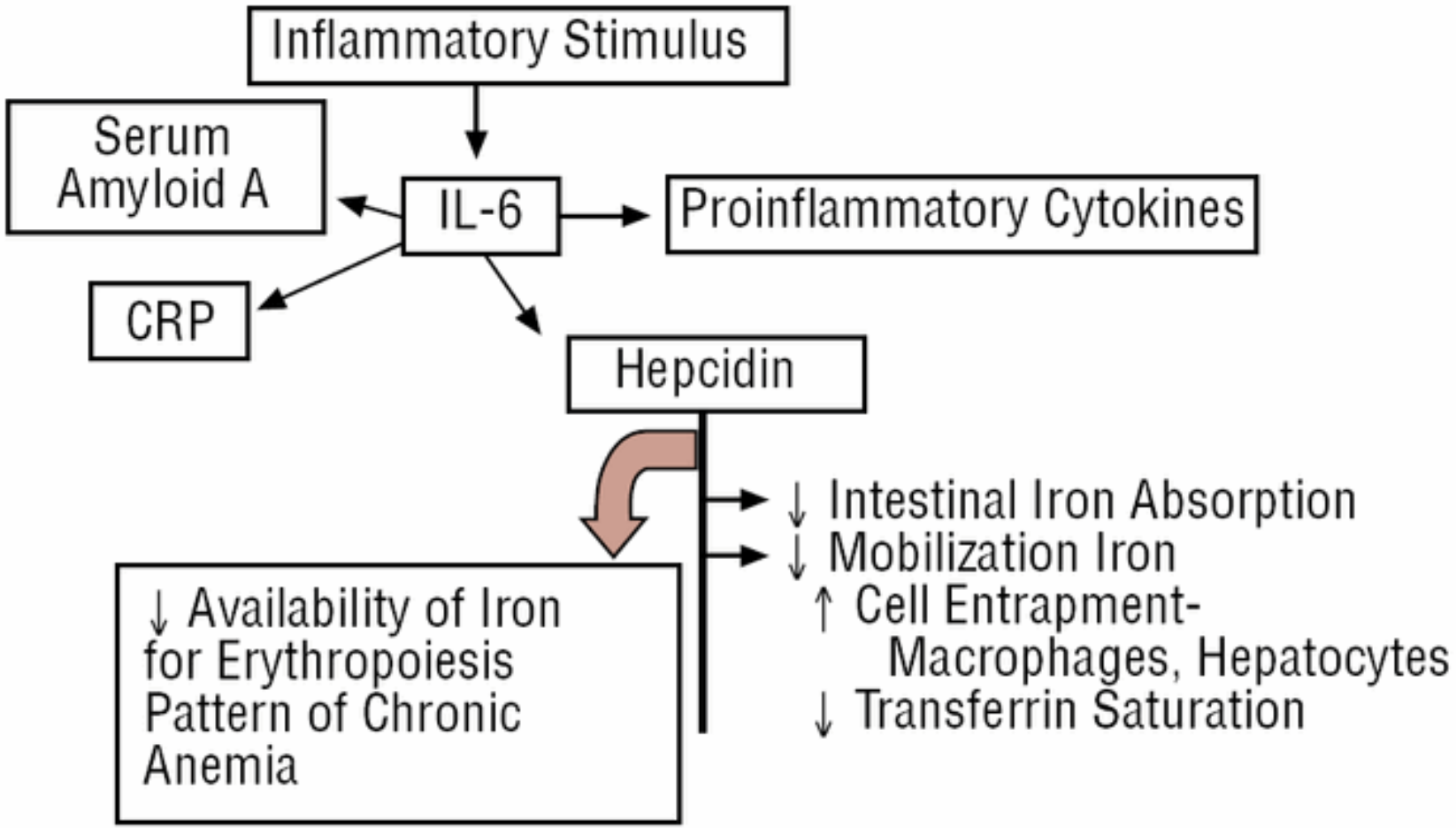
- Hb 9 g/dL, Hct 27.3%
- WBC 5.6 $x10^9$ /L, PMN 76%, L 20%, Mono 2%, Eo 2%, Baso 0%
- Platelet 230 $x10^9$ /L
- MCV 85 fL, MCH 26.6 pg, MCHC 33.4 g/dL, RDW 14.2%

Anemia of chronic disease; ACD (Anemia of inflammation; AI)

- Mild to moderate anemia (Hb 7-12 g/dL) associated with chronic infections, inflammation and malignancies.
- Inadequate erythrocyte production in the presence of low transferrin but preserved or even increased iron macrophage stores in marrow.
- Diagnosis by recognition of the underlying disease and exclusion of other associated cause of anemia

N Engl J Med 2005; 352:1011-1023.

Anemia of chronic disease; ACD (Anemia of inflammation; AI)



N Engl J Med 2005; 352:1011-1023.

Serum levels that differentiate anemia of chronic disease from iron deficiency anemia

Variable	Anemia of Chronic Disease	Iron-Deficiency Anemia	Both Conditions†
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
Soluble transferrin receptor	Normal	Increased	Normal to increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)	High (>2)
Cytokine levels	Increased	Normal	Increased

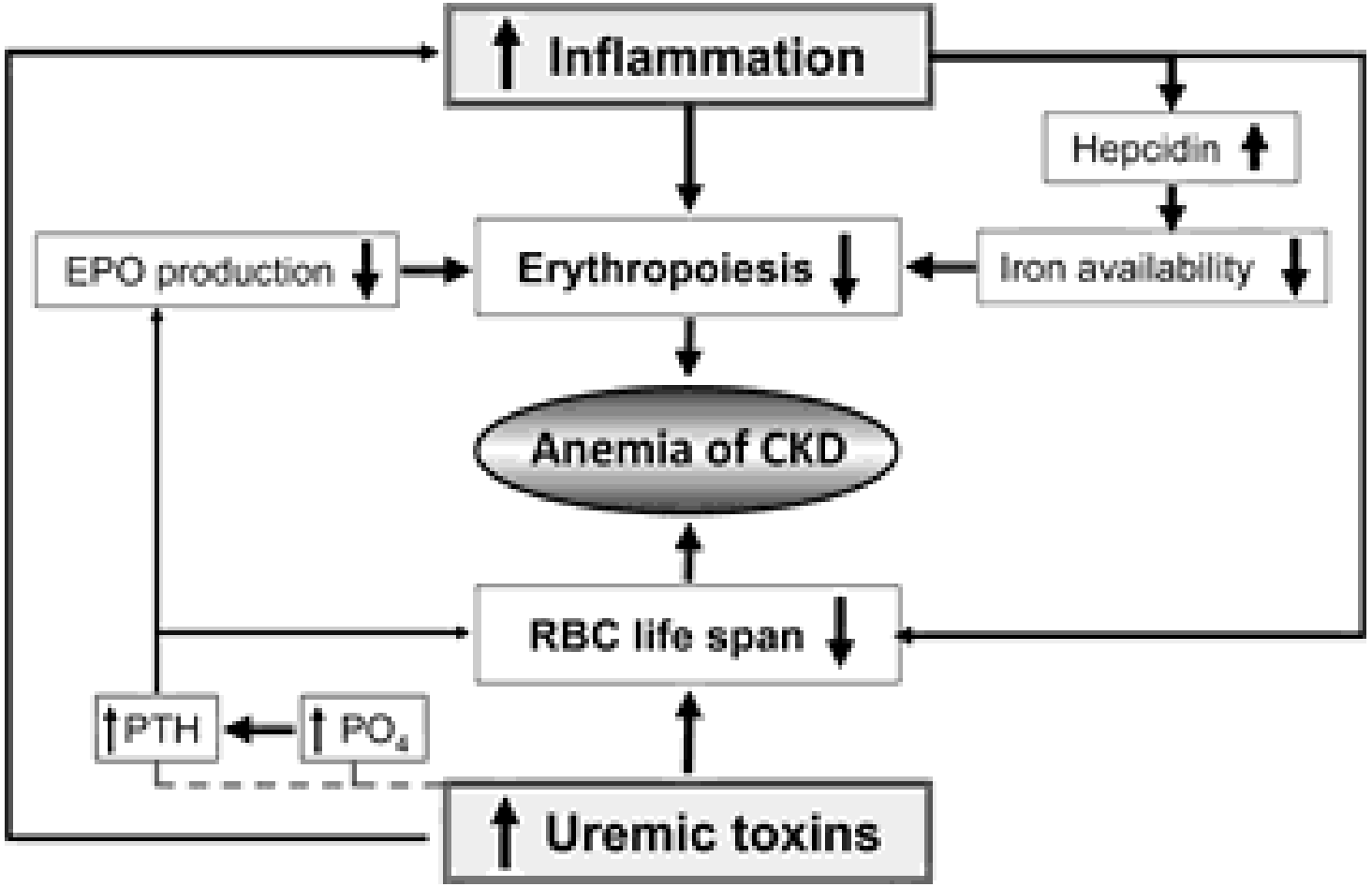
N Engl J Med 2005; 352:1011-1023.

Anemia of chronic kidney disease

- Normocytic, normochromic anemia
- Occurs as early as stage 3 CKD (eGFR < 60 ml/min/1.73m^2), almost universal by stage 4
- Primary cause: insufficient production of EPO
- Associated with adverse consequences
  → Decreased tissue oxygen delivery and utilization
  → Increased cardiac output
  → Ventricular dilatation, ventricular hypertrophy
- Clinical manifestations: angina, heart failure, decreased cognition and mental acuity, impaired host defense against infection

Blood Rev 2002;16:87-96.

Anemia of chronic kidney disease



Blood Rev 2002;16:87-96.

Cause of anemia in CKD

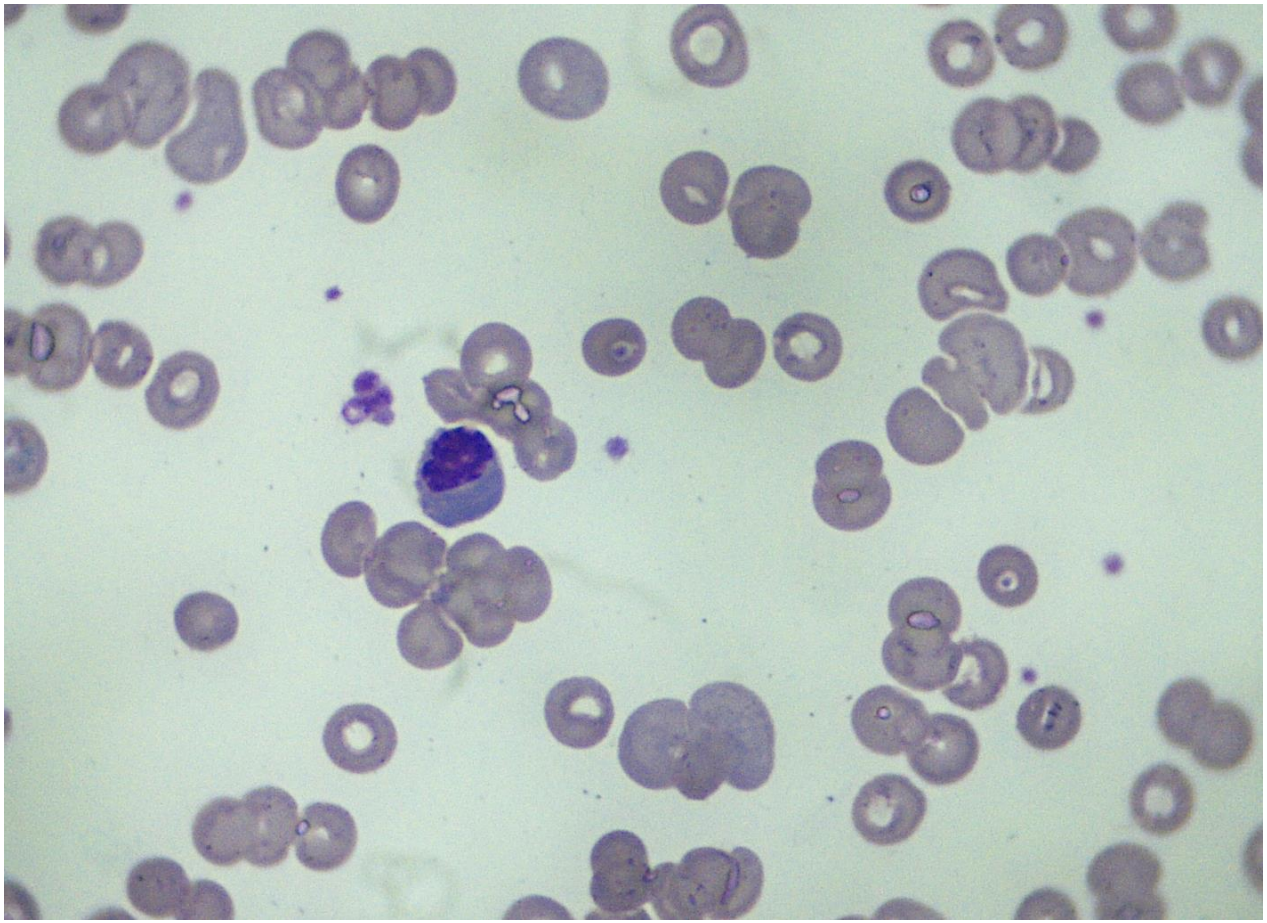
- Relative deficiency of erythropoietin
- Diminished RBC survival
- Bleeding diathesis
- Iron deficiency
- Hyperparathyroidism/bone marrow fibrosis
- Chronic inflammation
- Folate or vitamin B12 deficiency
- Hemoglobinopathy
- Comorbid conditions: hypo/hyperthyroidism, pregnancy, HIV, autoimmune disease, immunosuppressive drugs

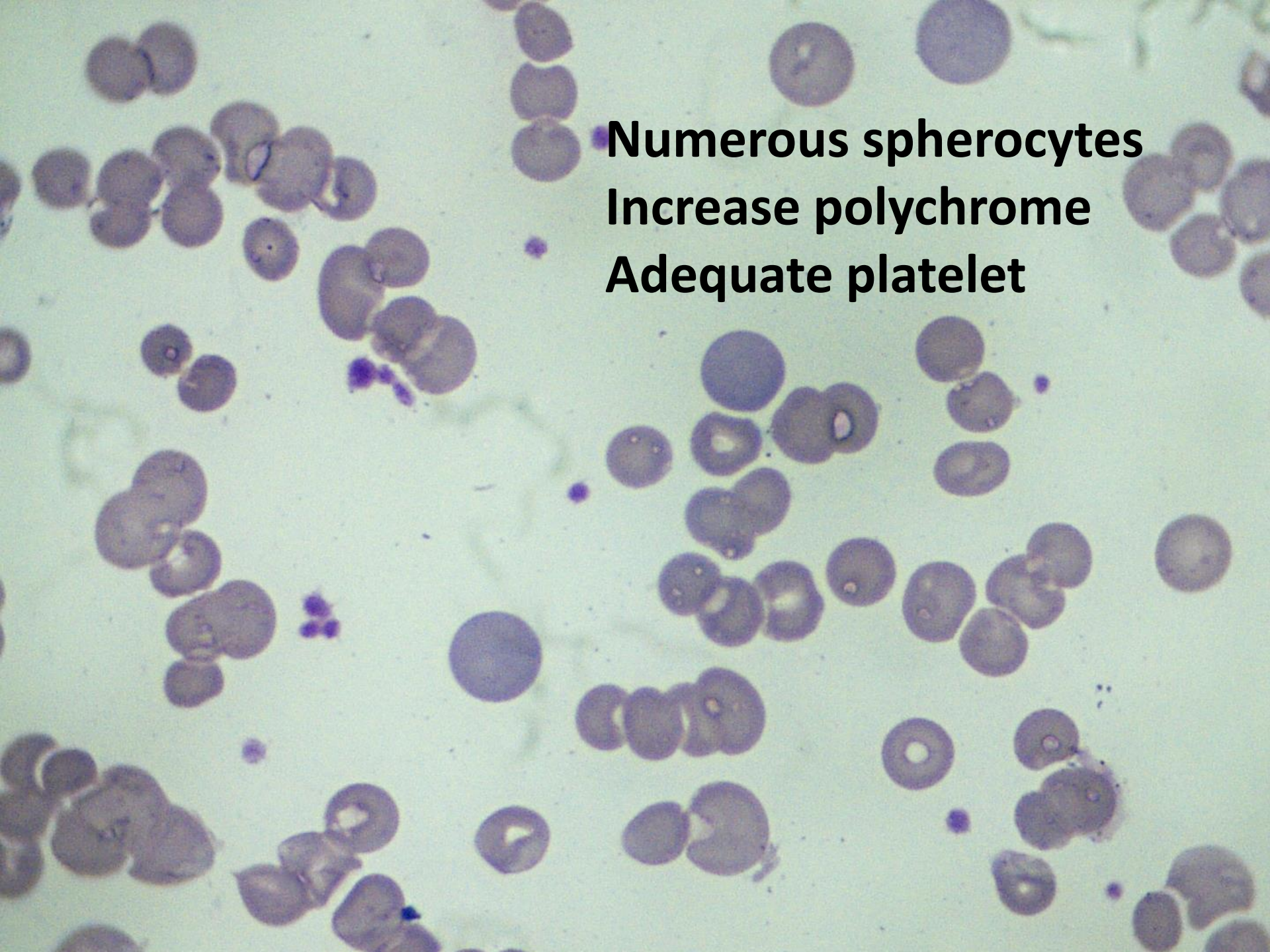
Blood Rev 2002;16:87-96.

Case 5

หญิงอายุ 46 ปี เหนื่อยง่าย 2 สัปดาห์

CBC: Hb 6.2 g/dL, Hct 16%, WBC 19x10^9/L, PMN 76% band 5%, myelocyte 3%, L 16%, platelet 560x10^9/L, MCV 120 fL, RDW 22%




Numerous spherocytes
Increase polychrome
Adequate platelet

Causes of autoimmune hemolytic anemia

- **Warm-autoantibody type**: autoantibody maximally active at body temperature (37°C), usually IgG
  1. Primary of idiopathic warm AIHA
  2. Secondary warm AIHA
     - Lymphoproliferative disorders (NHL, HL, CLL)
     - Connective tissue diseases, particularly SLE
     - Nonlymphoid neoplasms (e.g. ovarian tumors)
     - Chronic inflammatory disease (e.g. ulcerative colitis)
     - Drugs (e.g. α-methyldopa)

- **Cold-antibody type**: autoantibody optimally active at temperature < 37°C, usually IgM
  1. Idiopathic (primary) chronic cold agglutinin disease (CAD)
  2. Secondary cold agglutinin hemolytic anemia
     - Postinfectious (e.g. mycoplasma pneumoniae or infectious mononucleosis)
     - Malignant B cell lymphoproliferative disorder
     - Paroxysmal cold hemoglobinuria (rare)

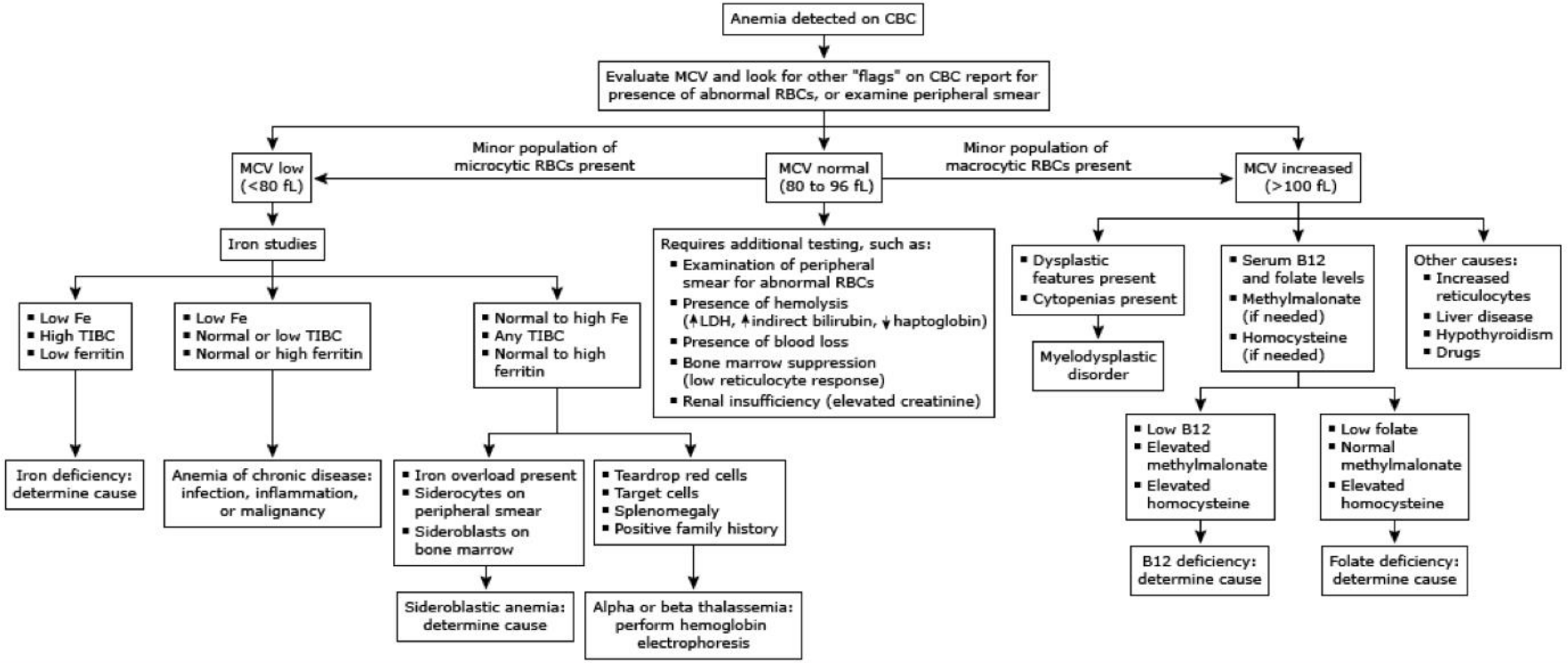
Laboratory Investigation: Confirmatory Tests

Disease	Special characteristic	Lab
G6PD deficiency	X-link recessive (male predominance), acute onset, precipitate(drugs, infection),dark urine, no hepatosplenomegaly PBS : NRC, polychromasia, Hb contracted red cell, Hb leakage cell , bite cell, ghost cell	G6PD enzyme assay
Thalassemias	Thalassemic face and hepatosplenomegaly may be seen. PBS : hypochromic, microcytic, target cell, polychromasia	-Hb typing -Inclusion body (HbH)
Hereditary spherocytosis	Autosomal dominant, pigmented gall stone, mild splenomegaly PBS : numerous spherocyte (normocytic anemia)	Incubated osmotic fragility
AIHA	Acute or subacute, mild splenomegaly PBS : autoagglutination (cold), microspherocyte, polychromasia	Direct Coomb's test (DAT: direct antiglobulin test)

Laboratory Investigation: Confirmatory Tests

Disease	Special characteristic	Lab
PNH	Chronic/Intermittent intravascular hemolyisis, dark urine, thrombosis, jaundice, bone marrow failure PBS : increase polychromasia, may be IDA coexisting, may be pancytopenia	- Urine hemosiderin, - Flow cytometry for CD55, CD59
Iron deficiency anemia	Chronic anemia, spoon nail (koilonychia), pica, history of chronic blood loss PBS: hypochromic microcytic, anisocytosis, pencil cell, reactive thrombocytosis	- Serum ferritin - SI, TIBC, Tsat
Megaloblastic anemia	Chronic anemia, glossitis (beefy tongue), neuropathy or psychotic problem (vit B12 def.) PBS: macrocytic RBC, macroovalocyte, hypersegmented PMN, may be pancytopenia	- Serum cobalamin - Red cell/serum folate
Bone marrow failure/infiltration	Anemia, fever, abnormal bleeding Myelophthisic blood picture	Bone marrow study

Evaluation of anemia in the adult according to the mean corpuscular volume



CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.

Conclusion

- Anemia is not a diagnosis itself
- Initial approach to the diagnosis
  - Perform complete history and physical examination
  - Review of the complete blood count with white blood cell differential, platelet count, reticulocyte count
  - Examination of the peripheral blood smear
- There may be more than one causes of anemia, including blood loss, effects of current medications, etc.