NOTES
MACROCYTIC ANEMIA

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Bone marrow produces larger than normal erythrocytes AKA red blood cells (RBCs)

CAUSES

- *Multifactorial:* nutritional deficits, genetics, substance exposure (e.g. certain drugs, alcohol)

SIGNS & SYMPTOMS

- Fatigue, dyspnea, weight loss, pallor, impaired concentration/memory, diarrhea, onychoschizia (brittle nails)

DIAGNOSIS

LAB RESULTS

- Complete blood count
- Peripheral blood smear analysis
- Blood chemistry
- Iron studies
- Genetic testing

TREATMENT

- Address underlying causes

MEGALOBLASTIC ANEMIA

osms.it/megaloblastic-anemia

PATHOLOGY & CAUSES

- Macrocytic, normochromic anemia characterized by formation of large RBCs

CAUSES

Cobalamin and/or folate deficiency

- Impaired DNA synthesis during erythropoiesis → uncoordinated maturation of cytoplasm and nuclei in erythroblasts (nuclear-cytoplasmic asynchrony) → abnormally large RBCs (macrocytosis) + defective cells with fragile membranes → RBCs die prematurely → anemia

B_{12} deficiency

- Insufficient diet (e.g. vegan diet without B_{12} supplements, alcoholism, systemic/mental illness, food insecurity)
- Malabsorption
  - Lack of intrinsic factor → pernicious anemia
  - *Surgical:* gastrectomy, bariatric surgery → lack of absorptive surface → pernicious anemia
  - Pancreatic insufficiency → impaired binding of B_{12} to intrinsic factor → pernicious anemia
  - *Medications that interfere with absorption:* e.g. biguanides, H_2 receptor blockers, proton-pump inhibitors, neomycin

- Fish tapeworm (*Diphyllobothrium latum*) → competes with host for B_{12}

Folate deficiency

- Insufficient diet
- Adequate diet but increased requirements (e.g. pregnancy, lactation, chronic hemolysis, exfoliative skin disease)
- Malabsorption (e.g. celiac disease, inflammatory bowel disease, gastric surgery)
- Metabolic interference from medications (e.g. methotrexate, phenytoin, trimethoprim)
- Alcoholism

Less common causes of macrocytosis

- Thiamine-responsive megaloblastic anemia syndrome, congenital anemias (Fanconi anemia, Diamond–Blackfan anemia), myelodysplastic syndromes, pure RBC aplasia, lipid abnormalities (e.g. liver disease), thyroid disease, copper deficiency
- Impaired DNA synthesis also causes formation of giant metamyelocytes → neutrophils with hypersegmented nuclei

SIGNS & SYMPTOMS

- From decreased number of functional RBCs in circulation → decreased RBC oxygen-carrying capacity → tissue hypoxia
  - Fatigue
  - Activity intolerance
  - Pallor
  - *Compensatory mechanisms:* increased heart rate, bounding pulse
- From increased rate of hemolysis, destruction of defective cells
  - *Jaundice*: hemolysis → increased serum bilirubin
  - *Splenomegaly:* increased reticuloendothelial activity secondary to extravascular hemolysis
- *From neuronal demyelination (if B_{12} decreased):* numbness, tingling, weakness, possible neuropsychiatric symptomatology

DIAGNOSIS

LAB RESULTS

- Peripheral blood cell analysis
  - Increased mean corpuscular volume (MCV)
  - Increased mean corpuscular hemoglobin (MCH)
  - Normal mean corpuscular hemoglobin concentration (MCHC)
  - Hypersegmented neutrophils
  - Anisocytosis (different sizes of RBCs)
  - Poikilocytosis (abnormally-shaped RBCs)
  - Macroovalocytes (large oval-shaped cells)
- Decreased RBC count secondary to increased hemolytic destruction of defective erythrocytes
- Decreased reticulocyte count → formation impaired in anemias caused by defective DNA synthesis
- Mild leukopenia and/or thrombocytopenia caused by defective DNA synthesis
- Decreased serum hemoglobin and hematocrit related to decreased number of circulating RBCs
- Markers of hemolysis
  - Increased lactate dehydrogenase (LDH)
  - Increased serum unconjugated bilirubin
  - Decreased haptoglobin
- Decreased serum B_{12} and/or folate levels
- Increased homocysteine or methylmalonic acid are also evidence of B_{12} deficiency

TREATMENT

MEDICATIONS

- *Supplementation:* increased dietary vitamin B_{12} and/or folate when indicated
  - Parenteral vitamin B_{12} if pernicious anemia
  - Dietary vitamin B_{12} found in animal products
  - Folate found in both plant, animal products, esp. dark green leafy vegetables

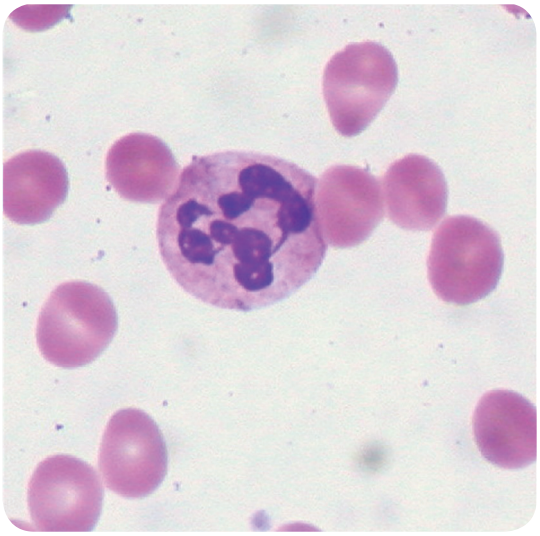

Figure 50.1 A hyperlobated neutrophile in a peripheral blood smear; a characteristic feature of megaloblastic anemia.

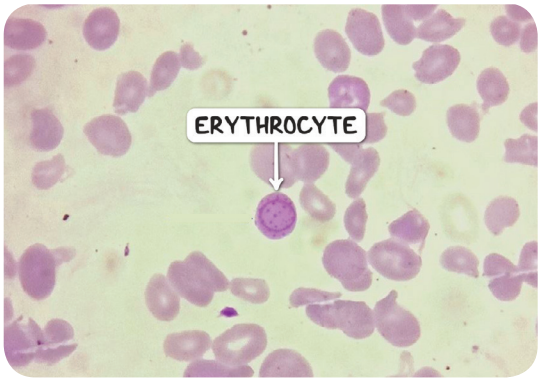

Figure 50.2 An erythrocyte displaying a Cabot ring and basophilic stippling. These features represent disordered erythropoiesis and are seen in many conditions, including megaloblastic anemias.

SIDEROBLASTIC ANEMIA

osms.it/sideroblastic-anemia

PATHOLOGY & CAUSES

- Anemias caused by altered mitochondrial function and defects in heme synthesis within erythroid cells

TYPES

Congenital forms

- Involve inheritance patterns affecting nuclear/mitochondrial genes encoding for erythrocyte synthesis—X-linked/autosomal recessive/mitochondrial inheritance patterns
  - *Syndromic:* presents with clinical manifestations of anemia along with effects on other organ systems (e.g. exocrine pancreatic insufficiency, sensorineural deafness, hepatic/renal failure, myopathy)
  - *Non-syndromic:* main features associated with anemia, iron overload

Acquired forms

- *Clonal:* myelodysplastic syndromes/myeloproliferative neoplasms alter erythrocytes, granulocytes, platelets
- *Reversible (metabolic):* caused by exposure to a substance (e.g. excessive alcohol/drugs such as isoniazid, chloramphenicol; copper deficiency/zinc overload)

Both congenital & acquired

- Impaired erythropoiesis, hemoglobin synthesis → reduced iron in RBCs + defective RBCs undergo apoptosis within bone marrow + fewer functional RBCs in circulation → anemia
- *Circulating RBC morphology:* microcytic/dimorphic (normocytic-to-macrocytic)

COMPLICATIONS

- Systemic effects of heme synthesis defects include impaired utilization of iron → accumulation in mitochondria → systemic iron overload → complications from hemochromatosis (e.g. diabetes, cardiac

pathology)
    - Repeated blood transfusions add to iron overload
- Anemia-induced acceleration of erythropoiesis → erythroid hyperplasia of bone marrow
- Increased risk of infection
- Acute leukemia develops in some cases
- Infection possibly fatal

SIGNS & SYMPTOMS

- Presentation variable depending on cause
- Clinical manifestations of decreased oxygen-carrying capacity of RBCs and hypoxia (e.g. fatigue, dyspnea, palpitations, pallor; mild jaundice if hemolysis significant)
- Erythropoietic hemochromatosis will manifest as varying degrees of iron overload (e.g. hepatosplenomegaly, cardiac arrhythmias, heart failure)

DIAGNOSIS

LAB RESULTS

Bone marrow aspirate smear

- Presence of sideroblasts confirms diagnosis
    - Prussian blue stain reveals iron ring around nucleus

RBC indices

- Low MCH
- MCV may be low/normal/high
    - Acquired sideroblastic anemias often produce macrocytic erythrocytes
    - Hereditary sideroblastic anemias produce microcytic erythrocytes

Blood smear analysis

- Anisocytosis
- Poikilocytosis
- Micro/macrocytosis
- Hypochromic erythrocytes
- Iron-containing inclusions (Pappenheimer bodies) may be present

Complete blood count

- Decreased serum hemoglobin
- Decreased RBC count
- Decreased/low reticulocyte count—related to ineffective erythropoiesis

Iron studies

- Hemochromatosis

Genetic testing

TREATMENT

- If sideroblastic anemia acquired, cause is reversible with treatment

MEDICATIONS

- *X-linked sideroblastic anemia:* vitamin B_6 (pyridoxine)

SURGERY

- Reduce organ damage secondary to iron overload
    - *Mild anemia:* therapeutic phlebotomy

OTHER INTERVENTIONS

- Reduce organ damage secondary to iron overload
    - *Mild anemia:* therapeutic phlebotomy
    - Chelation therapy (e.g. deferoxamine)

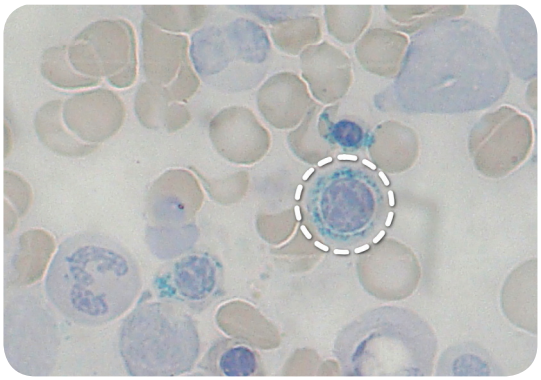

Figure 50.3 An erythrocyte displaying a Cabot ring and basophilic stippling. These features represent disordered erythropoiesis and are seen in many conditions, including megaloblastic anemias.