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Core Topic: Anemia

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Core Topic: Anemia

Marisyl de la Cruz

August 27, 2020
Agenda

• 1st hour
  • Diagnosis and evaluation
  • Approach to anemia
    • Hypoproliferative
    • Hyperproliferative
  • Management of common anemias

• 2nd hour
  • Cases
  • Q & A
Objectives

- Become familiar with signs and symptoms of anemia
- Use laboratory findings to differentiate anemias
- Review pathophysiology of anemia and recognize anemia as a symptom of other conditions
- Understand management of common anemias seen in primary care
Anemia - Definition

- Decrease in the number of circulating red blood cells
- Most common hematologic disorder by far
- Almost always a secondary disorder
- Critical to know how to evaluate and determine cause
Anemia - Causes

- Blood loss
- Decreased production of red blood cells
  - Marrow failure
- Increased destruction of red blood cells
  - Hemolysis
Diagnosis and Evaluation
Evaluation of the Patient

- History and Exam
- CBC with indices (MCV)
- Reticulocyte count
- WBC, diff, platelets
- Blood smear
WBC and diff

- Low total WBC
  - Aplastic anemia
  - Bone marrow suppression or replacement
  - Hypersplenism
  - Cobalamin deficiency

- High total WBC
  - Presence of infection
  - Inflammation
  - Hematologic malignancy
Peripheral Blood Smear

- Look for size and shape of RBC’s - esp for variability in sizes & shapes

- Is there polychromasia present? (Often implies reticulocytosis)

- Are there platelet and WBC abnormalities?
Neutrophil Segmentation

>5 percent of PMNs with five+ lobes and/or the presence of one or more PMNs with six+ lobes

If found with macro-ovalocytic red cells:

- Disorders of vitamin B12 and folate
- Drugs interfering with nucleic acid synthesis (hydroxyurea)
Anemia Workup

**RETICULOCYTE COUNT**

- If elevated, look for causes of increased destruction or bleeding
- If normal or decreased, look for causes of marrow failure
Reticulocyte Count - Absolute Value

- \( = \text{Retic} \% \times \text{RBC Count} \)
  - \(\text{eg} \ 0.01 \times 5,000,000 = 50,000\)
- Normal up to 120,000/\(\mu l\)
- More accurate way to assess body’s response to anemia
Approach to Anemia
ANEMIA

Low Reticulocyte Index
   (Hypoproliferative)

   Microcytic (MCV<80)
   Normocytic (MCV 80–95)

   Macrocytic (MCV>95)

High Reticulocyte Index
   (Hyperproliferative)

   Hemolytic Anemias
   Blood loss
Approach to Anemia

Hypoproliferative Anemias

- Microcytic
  MCV <80
  - Iron deficiency
  - Thalassemias
  - Sideroblastic anemia
  - Lead poisoning

- Normocytic
  MCV 80-100
  - Anemia of chronic disease
  - Early iron deficiency
  - Hypothyroidism
  - Aplastic Anemia

- Macrocytic
  MCV >95
  - Vitamin B12 deficiency
  - Folate deficiency
  - Liver disease/EtOH
  - Hypothyroidism
  - Myelodysplasia
Anemia - Normocytic (MCV 80-100)

- Most commonly caused by anemia of chronic disease (ACD)
  - Impaired absorption of iron from GI tract and iron trapping in macrophages
  - Prevents utilization of iron by the body
  - Because ACD results in iron-deficient erythropoiesis, various labs similar to those seen in iron deficiency
Anemia of Chronic Disease - Pathophysiology
## Normocytic Anemia (MCV 80-100 fl)

<table>
<thead>
<tr>
<th>Type of anemia</th>
<th>Blood film</th>
<th>Ferritin</th>
<th>Fe</th>
<th>TIBC</th>
<th>Marrow Fe stores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic disease*</td>
<td>Normochromic, normocytic</td>
<td>NI or ↑</td>
<td>↓</td>
<td>↓</td>
<td>NI or ↑, clumped</td>
</tr>
<tr>
<td>Early Fe deficiency</td>
<td>Mild anisocytosis, hypochromia</td>
<td>NI or ↓</td>
<td>↓</td>
<td>↑</td>
<td>absent</td>
</tr>
</tbody>
</table>

*including anemia due to renal disease and AIDS
Causes of Anemia of Chronic Disease

- Anemia of chronic renal disease
- Cardiorenal anemia syndrome
- Cancer-associated anemia
- Acquired anemia in hospitalized patients
- Early iron deficiency often causes normocytic anemia as well
ANEMIA OF CHRONIC DISEASE - Causes

- Thyroid disease
- Collagen Vascular Disease
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Polymyositis
- Polyarteritis Nodosa

- Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Crohn’s Disease

- Chronic Infectious Diseases
  - Osteomyelitis
  - Tuberculosis

- Familial Mediterranean Fever
Approach to Anemia

Hypoproliferative Anemias

- Microcytic MCV <80
  - Iron deficiency
  - Thalassemias
  - Sideroblastic anemia
  - Lead poisoning

- Normocytic MCV 80-100
  - Anemia of chronic disease
  - Early iron deficiency
  - Hypothyroidism
  - Aplastic Anemia
  - Acute blood loss

- Macrocytic MCV >95
  - Vitamin B12 deficiency
  - Folate deficiency
  - Hypothyroidism
  - Myelodysplasia
  - Liver disease/EtOH
ANEMIA - Microcytic (MCV < 80)

- Iron Deficiency - High RDW
- Thalassemia minor - Normal RDW
- Rare
  - Sideroblastic anemia
  - Metal poisoning (esp lead, aluminum)
  - Occasional hemoglobinopathies
  - Thalassemia major
Iron Deficiency Anemia - Ferritin

- Obtain a serum ferritin level in patients with MCV < 95

- Reflects iron stores - most accurate test to diagnose iron deficiency anemia (usually <50)

- An acute phase reactant - can be elevated in chronic inflammation or infection
Iron Deficiency Anemia

Stage 1: 
↓ Iron Stores
• Depleted bone marrow stores
• ↓ Ferritin

Stage 2: 
↓ Circulating Iron
• ↑ TIBC
• ↓ Serum Fe

Stage 3: 
Iron-deficient erythropoiesis
• Anemia 1st
• Microcytic anemia later
Thalassemias - low MCV

Ferritin normal to high, serum iron normal/increased, normal TIBC, transferrin saturation normal/increased

Hemoglobin Electrophoresis

- Normal hemoglobin A2 level
  - Sideroblastic anemia
  - Alpha-thalassemia trait

- Increased hemoglobin A2 level
  - Beta-thalassemia trait

- Diagnose other hemoglobinopathy
Approach to Anemia

Hypoproliferative Anemias

- Microcytic MCV <80
  - Iron deficiency
  - Thalassemias
  - Sideroblastic anemia
  - Lead poisoning

- Normocytic MCV 80-100
  - Anemia of chronic disease
  - Early iron deficiency
  - Hypothyroidism
  - Aplastic Anemia
  - Acute blood loss

- Macrocytic MCV >95
  - Vitamin B12 deficiency
  - Folate deficiency
  - Hypothyroidism
  - Myelodysplasia
  - Liver disease/EtOH
Anemia - Macrocytic (MCV > 100)

- If MCV > 110 fl, almost always folate or cobalamin deficiency
- If MCV 100-110 fl, must look for other causes of macrocytosis
Macrocytosis (MCV > 100 fl)

- Abnormal nucleic acid metabolism of erythroid precursors
  - Drugs (cytotoxics, immunosuppressants, anticonvulsants)
  - B₁₂/folate deficiency
- Abnormal RBC maturation
  - Myelodysplastic syndrome
  - Leukemias
  - Marrow infiltration (malignancy, fibrosis)
- Alcohol
- Liver disease
- Hypothyroidism
- Less common
  - Aplasia
  - ‘Artifactual’
  - Cold agglutinins
  - Hyperglycemia
  - Hyperleukocytosis
Macrocytosis of Alcoholism

• 25-96% of alcoholics
• MCV elevation usually slight (100-110 fl)
• Minimal or no anemia
• Macrocytes round (not oval)
• Neutrophil hypersegmentation absent
• Folate stores normal
Megaloblastic Hematopoiesis

- Marrow failure due to disrupted DNA synthesis & ineffective hematopoiesis

- Neutrophil hypersegmentation & macroovalocytes in blood

- Anemia (and often leukopenia & thrombocytopenia)

- Almost always due to cobalamin or folate deficiency
Evolving Cobalamin Deficiency

- Usual sequence:
  - Serum Cobalamin falls
  - Serum methylmalonic acid & homocysteine rise
  - MCV rises within the normal range, with hypersegmentation of neutrophils
  - MCV rises above normal
  - Anemia and/or neuropathy
  - Symptoms
<table>
<thead>
<tr>
<th>Table 2. Clinical Manifestations of Vitamin B₁₂ Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
<tr>
<td>Vitiligo</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Glossitis</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
</tr>
<tr>
<td>Anemia (macrocytic, megaloblastic)</td>
</tr>
<tr>
<td>Leukopenia</td>
</tr>
<tr>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Thrombocytosis</td>
</tr>
<tr>
<td><strong>Neuropsychiatric</strong></td>
</tr>
<tr>
<td>Areflexia</td>
</tr>
<tr>
<td>Cognitive impairment (including dementia-like symptoms and acute psychosis)</td>
</tr>
<tr>
<td>Gait abnormalities</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Loss of proprioception and vibratory sense</td>
</tr>
<tr>
<td>Olfactory impairment</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
</tbody>
</table>
ANEMIA

Low Reticulocyte Index

(Hypoproliferative)

Microcytic (MCV<80)

Normocytic (MCV 80–95)

High Reticulocyte Index

(Hyperproliferative)

Macrocytic (MCV>95)

Hemolytic Anemias

Blood loss
Hemolytic Anemia

- High reticulocyte count - hyperproliferative
- Anemia of increased destruction
  - Normocytic, normochromic anemia
  - Shortened RBC survival
  - Reticulocytosis - Response to increased RBC destruction
Tests Used to Diagnose Hemolysis

- Reticulocyte count (combined with serial Hb)
- Haptoglobin
- Unconjugated bilirubin
- Serum LDH
- UA
<table>
<thead>
<tr>
<th>Test</th>
<th>Finding in hemolysis</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haptoglobin</td>
<td>Decreased</td>
<td>Binds free hemoglobin</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Elevated</td>
<td>Released from lysis of red blood cells</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
<td>Abnormal red blood cells</td>
<td>Based on cause of anemia</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Increased</td>
<td>Marrow response to anemia</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Increased</td>
<td>Increased hemoglobin breakdown</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Urobilinogen, positive for blood</td>
<td>Free hemoglobin and its metabolites</td>
</tr>
</tbody>
</table>
Blood morphology in hemolytic anemias

<table>
<thead>
<tr>
<th>Sickle cells</th>
<th>Sickle cell anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb crystals</td>
<td>Hb CC disease</td>
</tr>
<tr>
<td>Fragments, helmets</td>
<td>Microangiopathic hemolysis</td>
</tr>
<tr>
<td>Microspherocytes</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td></td>
<td>Immune hemolysis</td>
</tr>
<tr>
<td>Elliptocytes</td>
<td>Hereditary elliptocytosis</td>
</tr>
</tbody>
</table>

*Note: hemolysis is not excluded by a normal blood smear*
Microangiopathic Hemolytic Anemia

- Fragmented RBC’s
- Schistocytes (black arrows)
- Helmet cells (red arrows)
- Causes:
  - TTP
  - HUS
  - DIC
  - Prosthetic Heart Valve
  - HELLP syndrome in pregnancy
Tests to define the cause of hemolysis

- Hemoglobin electrophoresis
- Hemoglobin A₂ (beta-thalassemia trait)
- RBC enzymes (G6PD)
- Direct & indirect antiglobulin tests (immune)
- Cold agglutinins
- Osmotic fragility (spherocytosis)
- Acid hemolysis test (PNH)
- Clotting profile (DIC)
Management of Anemias
Management

• Anemia of Chronic Disease
  • Treatment of underlying disorder
  • Iron supplementation reserved for those who have concomitant iron deficiency
  • RBC transfusions reserved for life, threatening symptomatic anemia
Management of Iron Deficiency Anemia

Iron deficiency anemia diagnosed

Premenopausal women

Abnormal uterine bleeding?

No

Treat with iron

If no response, initiate evaluation for occult GI blood loss

Yes

Initiate workup for bleeding

Upper endoscopy and colonoscopy; consider celiac serology

No evidence of GI source

Observe

Treat with iron (Table 3)

Response

Observe

Repeat upper endoscopy and colonoscopy

Evidence of GI source

Treat underlying cause

No response

Evidence of GI source

Treat underlying cause

No evidence of GI source

Capsule endoscopy

Normal

Consider repeat capsule endoscopy

Abnormal

Treat underlying cause; push enteroscopy
Management - Iron Deficiency Anemia

- PO Iron
  - Treatment dose typically 120 – 150 mg of elemental iron per day
    - 325 mg ferrous sulfate tablet (65 mg of elemental iron)
  - GI effects: epigastric discomfort, nausea, diarrhea, and constipation
    - Ferrous fumarate (43%) > ferrous gluconate (31%) > ferrous sulfate (30%)
  - Strategies to improve tolerability
    - Change interval to every other day
    - Take with food or milk although can reduce absorption
    - Switch to formulation with lower amount of elemental iron
    - Switch from tablet to a liquid
Management - Iron Deficiency Anemia

- IV iron
  - Most common indications:
    - GI effects
    - Worsening symptoms of inflammatory bowel disease
    - Unresolved bleeding
    - Renal failure–induced anemia treated with erythropoietin
    - Insufficient absorption in patients with celiac disease
  - Dose depends on whether the goal is to treat anemia or to fully replace iron stores
### Table 3. Iron Therapy: Formulations and Dosing

<table>
<thead>
<tr>
<th>Form</th>
<th>Formulation</th>
<th>Elemental iron (mg)</th>
<th>Adult dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous</strong></td>
<td></td>
<td></td>
<td>Based on weight and amount of desired change in hemoglobin*</td>
</tr>
<tr>
<td>Sodium ferric gluconate (Ferrlecit)</td>
<td>Solution for injection</td>
<td>12.5 mg per mL</td>
<td></td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Solution for injection</td>
<td>50 mg per mL</td>
<td></td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>Solution for injection</td>
<td>20 mg per mL</td>
<td></td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>Solution for injection</td>
<td>30 mg per mL</td>
<td></td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>324-mg tablet</td>
<td>106 mg</td>
<td>One tablet twice per day</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300-mg tablet</td>
<td>38 mg</td>
<td>One to three tablets two or three times per day</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325-mg tablet</td>
<td>65 mg</td>
<td>One tablet three times per day</td>
</tr>
</tbody>
</table>

*—Elemental iron (mg) = 50 × (0.442 [desired hemoglobin level in g per L – observed hemoglobin level in g per L] × lean body weight + 0.26 × lean body weight).²

Information from references 2 and 16.

Short et al. AFP 2013 Jan 15;87(2):98-104
Management - Iron Deficiency Anemia

- Hgb rises slowly, usually ~ 1-2 weeks after treatment
  - Will increase approximately 2 g/dL over the next three weeks
- Hgb deficit should be halved by approximately one month
- Hgb level should return to normal by 6-8 weeks
Management - Vitamin B12 deficiency

• Parenteral therapy or oral therapy (1000 mcg)

• Replacement usually daily for first week, weekly for first month, then monthly for life

• If vitamin B12 deficiency coexists with folate deficiency, vitamin B12 should be replaced first to prevent subacute combined degeneration of the spinal cord
Management - Folate Deficiency

• Treat with folic acid PO 5 mg daily x 4 months

• Continued treatment depends on underlying disease

• Lifelong therapy may be needed in chronic inherited anemias, myelofibrosis, renal dialysis
Summary

• Anemia is a symptom of an underlying disease

• Looking at the CBC (MCV, MCH, and RDW) and reticulocyte count provides clues to diagnosis
  • If reticulocyte count elevated, look for causes of increased destruction or bleeding
  • If retic count normal or decreased, look for causes of marrow failure

• Correction of the underlying disorder often results in resolution of the anemia
Questions?