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Anemia
A Case Based Approach

Objectives

- Understanding classification and causes of anemia.

- Understanding how to analyze and interpret iron studies and hemograms.

- Participants will be able to recognize the key physical examination and history taking points in evaluating anemia.

- Participants will be able to apply this knowledge in patient care in sample GI cases.

Case 1

- A 43 year old Caucasian male presents to you as a referral from a primary care physician for possible chronic GI blood loss. On Routine laboratory testing, he was found to have a hemoglobin of 8.5 gm/dl. His MCV was 60.
- He is otherwise asymptomatic and has no other past medical history and is not on any medications
- He has no allergies.

Case 1

- Labs:
  - WBC: 4.5
  - HB: 8.5
    - MCV:60
  - Platelets: 300,000
  - Other labs completely normal (CMP, TSH)

Case 1

- What are the possible causes of his anemia?
- How would you classify this anemia?
- What additional questions are prudent to ask in history taking?
- What are laboratory normal values?

Laboratory Normal Values

Hemoglobin (Hg, Hgb)		
Normal Value:		
	Male:	13.2-16.2 gm/dL
	Female:	12.0-15.2 gm/dL

Mean Cell Hemoglobin Concentration (MCHC)	
Normal Value:	31-35 gm/dl

RBC Mean Cell Volume (MCV)		
Normal Value:		
	Male:	82-100 fL
	Female:	78-100 fL

Laboratory Normal Ranges

Hematocrit (Hct)		
Normal Value:		
	Male:	40-52%
	Female:	37-46%
	Child:	31-43%

Platelet Count (Plt)	
Normal Value:	140-450x10^3/l

White Blood Cell Count (WBC)	
Normal Value:	4.1-10.9x10^3
	•Polymorphonuclear (PMN): 35-80%
	•Immature Polys (Bands): 0-10%
	•Lymphocytes (Lymp): 20-50%
	•Monocytes (Mono): 2-12%
	•Eosinophils (Eos): 0-7%
	•Basophils (Bas): 0-2%

Laboratory Normal Ranges

Ferritin	
Normal Value:	
Male:	18-250 ng/ml
Female:	12-160 ng/ml

Total Iron-Binding Capacity (TIBC)	
Normal Value:	262-474 ng/dl

Total Serum Iron (TSI)	
Normal Value:	
Male:	76-198 ng/dl
Female:	26-170 ng/dl

RBC Lifecycle

Events Occurring in the Red Bone Marrow

Developing RBCs absorb amino acids and Fe²⁺ from the bloodstream and synthesize new Hb molecules.

Cells destined to become RBCs first differentiate into **proerythroblasts**.

Proerythroblasts then differentiate into various stages of cells called **erythroblasts**, which actively synthesize hemoglobin. Erythroblasts are named according to total size, amount of hemoglobin present, and size and appearance of the nucleus.

After roughly four days of differentiation, the erythroblast, now called a normoblast, sheds its nucleus and becomes a **reticulocyte** (re-TIK-ū-lō-sit), which contains 80 percent of the Hb of a mature RBC.

After two days in the bone marrow, reticulocytes enter the bloodstream. After 24 hours in circulation, the reticulocytes complete their maturation and become indistinguishable from other mature RBCs.

Start

RBC formation

Ejection of nucleus

Events in the life cycle of RBCs

Events Occurring in Macrophages

Macrophages in liver, spleen, and bone marrow

Fe²⁺

Fe²⁺ transported in circulation by transferrin

Amino acids

Heme

Biliverdin

Bilirubin

90%

10%

Average life span of RBC is 120 days

Old and damaged RBCs

In the bloodstream, the rupture of RBCs is called **hemolysis**.

New RBCs released into circulation

Bilirubin bound to albumin in bloodstream

Hemoglobin that is not phagocytized breaks down, and the alpha and beta chains are eliminated in urine. When abnormally large numbers of RBCs break down in the bloodstream, urine may turn red or brown. This condition is called **hemoglobinuria**.

Liver

Bilirubin

Events Occurring in the Liver

Excreted in bile

Absorbed into the circulation

Events Occurring in the Kidney

Hb

Urobilins

Bilirubin

Urobilins, stercobilins

Events Occurring in the Large Intestine

Eliminated in feces

Eliminated in urine

Classification of Anemia

- Kinetic Classification
  - Decreased production
  - Increased destruction
  - Blood loss
    - Acute
    - Chronic
- Morphologic Classification
  - Macrocytic
  - Microcytic
  - Normocytic

Decreased Production

- Anemia will eventually result if the rate of RBC production is less than that of destruction.
- Causes of decreased production:
  - Iron, B12, Folate deficiency (dietary lack, malabsorption – seen in pernicious anemia and sprue, chronic blood loss (iron deficiency).
  - Bone marrow disorders (aplastic anemia)
  - Bone marrow suppression (drugs and chemo)
  - Low levels of trophic hormones that stimulate RBC production (EPO in chronic renal failure), hypothyroidism, hypogonadism.

Decreased Production

- Anemia of Chronic Disease:
  - This is associated with chronic disease and inflammation, associated with infectious, inflammatory, or malignant disorders and is characterized by reduced availability of iron secondary to decreased absorption from the GI tract and decreased release from macrophages, a relative reduction in EPO levels and a mild reduction in RBC lifespan.

Increased RBC destruction

- A RBC life span below 100 days is defined as hemolysis.
- Hemolytic anemia ensues when the bone marrow is unable to keep up with the need to replace more than 5 percent of the RBC mass per day (corresponding to RBC survival of about 20 days).

Increased RBC destruction

- Causes:
  - Inherited Hemolytic anemia (sickle cell, thalassemia major, hereditary spherocytosis)
  - Acquired hemolytic anemia (coombs' positive autoimmune hemolytic anemia, TTP – HUS, malaria)

Blood Loss

- Causes:
  - Overt bleeding
    - Melena, hematochezia
  - Occult bleeding
    - Slowly bleeding gastric ulcer , or gastrointestinal malignancy
  - Induced bleeding
    - Repeated diagnostic testing and hemodialysis
      - *hemodilution during IVF infusion can also cause a drop in HB

Morphologic Approach

- The causes of anemia can also be classified according to the measurement of the RBC size as seen on the blood smear and as reported by automatic cell counter indices.
- The normal RBC has a volume of 80-100 femoliters (MCV) and a diameter of a lymphocyte (7-8 microns)

Morphologic Approach

- RBCs larger than the nucleus of a small lymphocyte on a peripheral blood smear are considered large or "macrocytic", while those smaller are considered "microcytic"

Peripheral Smear

A
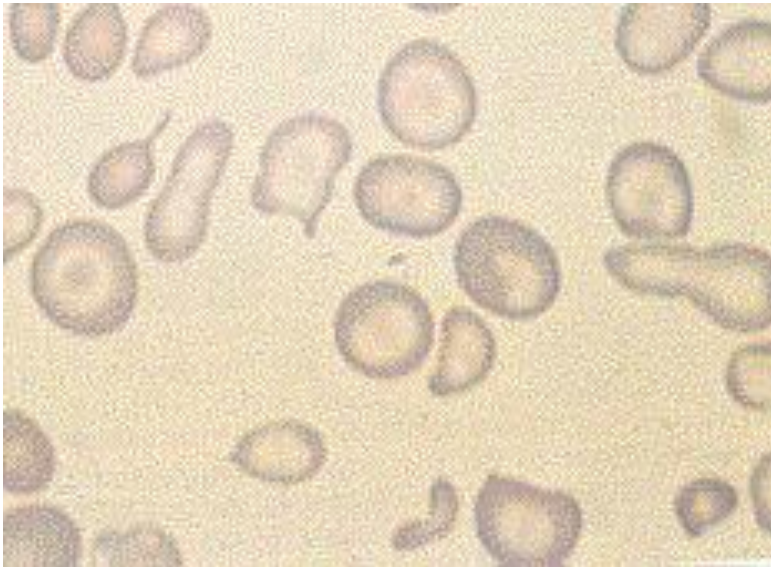
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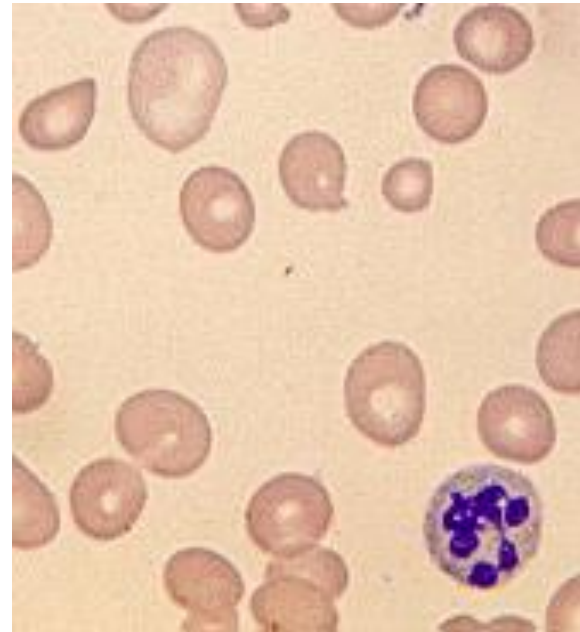
A. Microcytic Anemia

B. Peripheral smear showing ovalocytes, macrocytes, and a hypersegmented polymorphonuclear leukocyte.

Macrocytic Anemias

- Macrocytic anemias are characterized by an MCV above 100 fL (femoliters).
- Causes:
  - An increased MCV is a normal characteristic of reticulocytes, any condition causing marked reticulocytosis will be associated with an increased MCV.
  - Acute blood loss can also cause macrocytosis
  - Abnormal nucleic acid metabolism of erythroid precursors (folate or B12 deficiency), drugs interfering with nucleic acid synthesis such as (zidovudine and hydroxyurea)

Causes: Macrocytic anemia

- Abnormal RBC maturation (ex: myelodysplastic syndrome, acute leukemia)
- Other common causes include:
  - ETOH abuse
  - Liver disease
  - Hypothyroidism

Microcytic Anemia

- Microcytic anemias are characterized by the presence of "small RBCs" (ie. MCV below 80 fl).
- This is usually accompanied by a decreased hemoglobin content within the RBC with parallel reductions in MCV and MCH producing a hypochromic (low MCH), as well as a microcytic (low MCV) appearance on blood smear.
  - MCV (mean corpuscular volume)
  - MCH (mean corpuscular hemoglobin)

Peripheral Smear: Microcytic Anemia

Hypochromic/Microcytic Anemia
Iron Deficiency
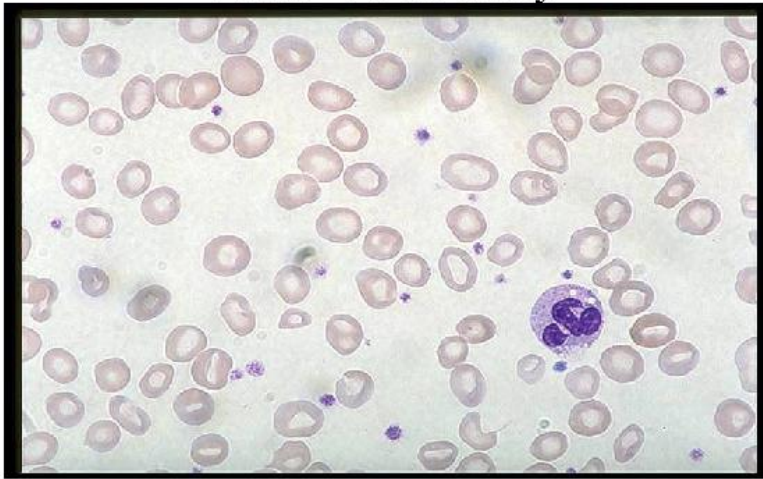
Normal Blood Smear
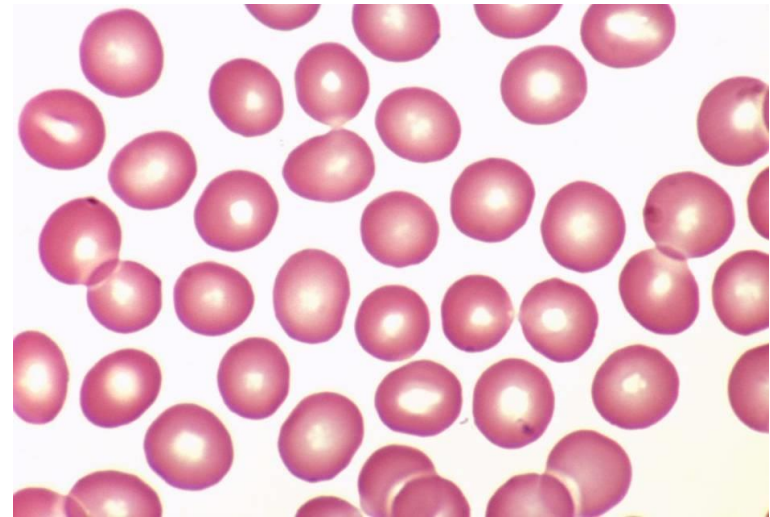
Microcytic Anemia: Causes

- Reduced iron availability
  - Iron deficiency (occult blood loss, heavy menses)* anemia of chronic disease, copper deficiency
- Reduced heme synthesis
  - Lead poisoning, congenital or acquired sideroblastic anemia.
- Reduced globin production
  - Thalassemic states, other hemoglobinopathies.
- Rare disorders due to defects in iron absorption, transport, utilization, and recycling.

Most Common Causes of Microcytic Anemia

- Iron Deficiency Anemia
  - Low serum ferritin, an increased total iron binding capacity (TIBC), and low serum iron concentration.
- Alpha or beta thalassemia minor
  - Usually occurs in patients that are heterozygotes for the alpha or beta forms of this syndrome.
  - Family history is usually negative
  - Peripheral smear shows, hypochromia, microcytosis, target cells, tear-drop forms, and basophilic stippling.
  - Diagnosed by hemoglobin electrophoresis
- Anemia of chronic disease
  - Low serum iron, low TIBC, normal to increased serum ferritin concentration

Back to our patient

- A 43 year old Caucasian male presents to you as a referral from a primary care physician for possible chronic GI blood loss. On Routine laboratory testing, he was found to have a hemoglobin of 8.5 gm/dl. His MCV was 60. Previous HB once year go was 14 gm/dl with a MCV of 87.
- He is otherwise asymptomatic and has no other past medical history and is not on any medications
- He has no allergies.

Evaluation of the Patient

- Initial approach:
  - Is the patient bleeding (GI or non GI related)?
  - Is there evidence for increased RBC destruction?
  - Is the bone marrow suppressed?
  - Is the patient iron deficient?
    - If so, why?
  - Is the patient deficient in folic acid or vitamin B12?

Evaluation of the patient

- History:
  - Is there any history of symptoms or conditions that may lead to an anemic state (melena in a patient on aspirin, heavy menses).
  - Is the anemia of recent onset, subacute, or lifelong. (Recent anemia is likely secondary to an acquired disorder, lifelong may be secondary to a benign condition)
  - Where is the patients country of origin (mediterranean, middle east, subsaharan africa, --ie. Thalassemias)
- Physical Examination:
  - Pallor?
  - Jaundice?
- Laboratory Evaluation:

Labs

- Labs:
  - WBC: 4.5
  - HB: 8.5
    - MCV:60
  - Platelets: 300,000
  - Other labs completely normal (CMP, TSH)
  - Ferritin: 15 ng/dl
  - TIBC: 600 ng/dl
  - Iron: 10 ng/dl

Diagnosis

- Iron Deficiency Anemia of Unexplained Origin
  - Evaluation would include ruling out chronic GI blood loss, malabsorption, hypothyroidism.
    - Peptic ulcer disease, celiac disease (malabsorption), Colon Cancer
      - Evalauation would include an Upper GI endoscopy, Colonoscopy, and if these are non revealing then a small bowel pill camera.
    - If all above negative then consider hemoglobinopathies (thalassemias, etc)

GI Evaluation of Anemias

- After an adequate history and physical examination and laboratory analysis to rule out other (non-GI related) causes of anemia, examination usually begins with an endoscopic evaluation of the GI tract.

Pathology Encountered on Upper Endoscopy that can cause anemia
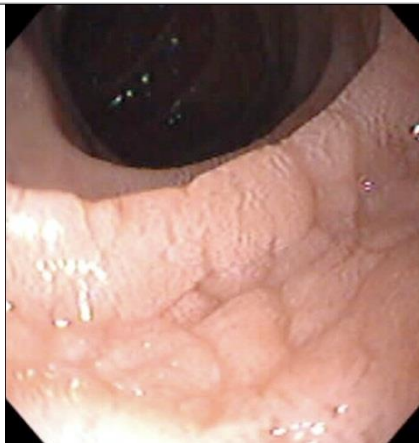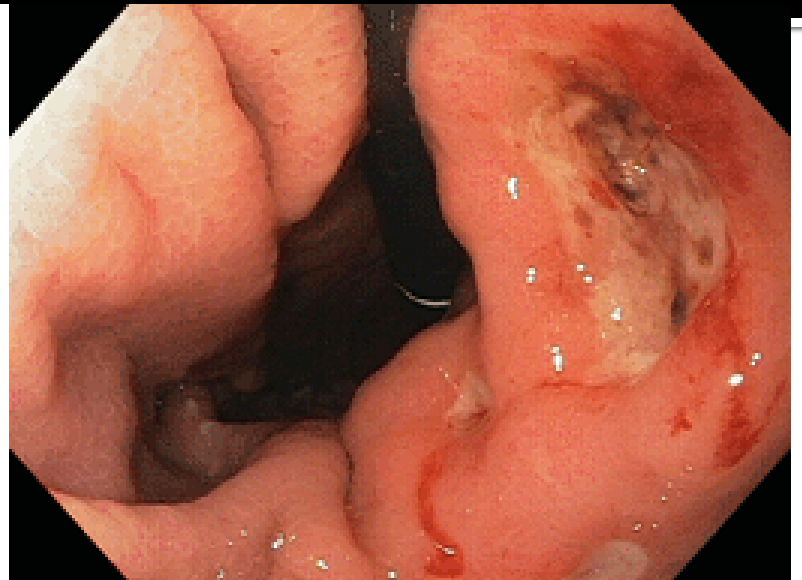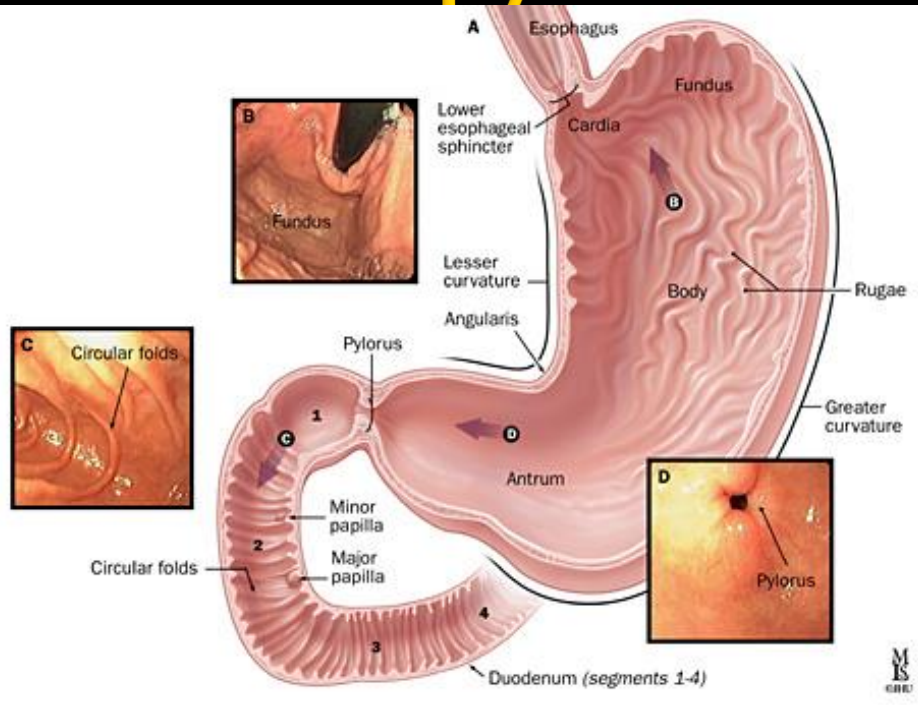
Anemia due to Peptic Ulcer Disease

- Peptic Ulcers
  - Gastric and Duodenal Ulcers
  - Most common cause of PUD is NSAIDS and H.pylori
  - In case of gastric ulcers, repeat endoscopy in 8 weeks to ensure that ulcer is healed (i.e. not malignant)

If ulcer has high risk stigmata of bleeding – then patient may need to be monitored in the hospital prior to discharge.
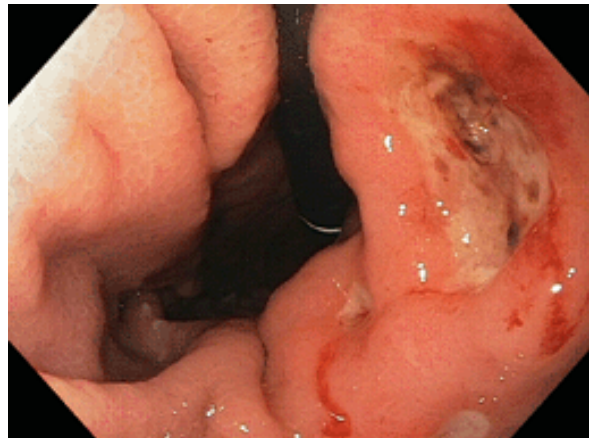
Celiac Disease as a cause of anemia

- In cases where celiac disease is causing anemia – prompt diagnosis and therapy (avoidance of gluten) can reverse the inflammatory cascade in the duodenal mucosa.
- Thereby – absorption again returns to normal and iron deficiency anemia will resolve.

Anemia due to chronic bleeding from AVM's (Arteriovenous Malformations)
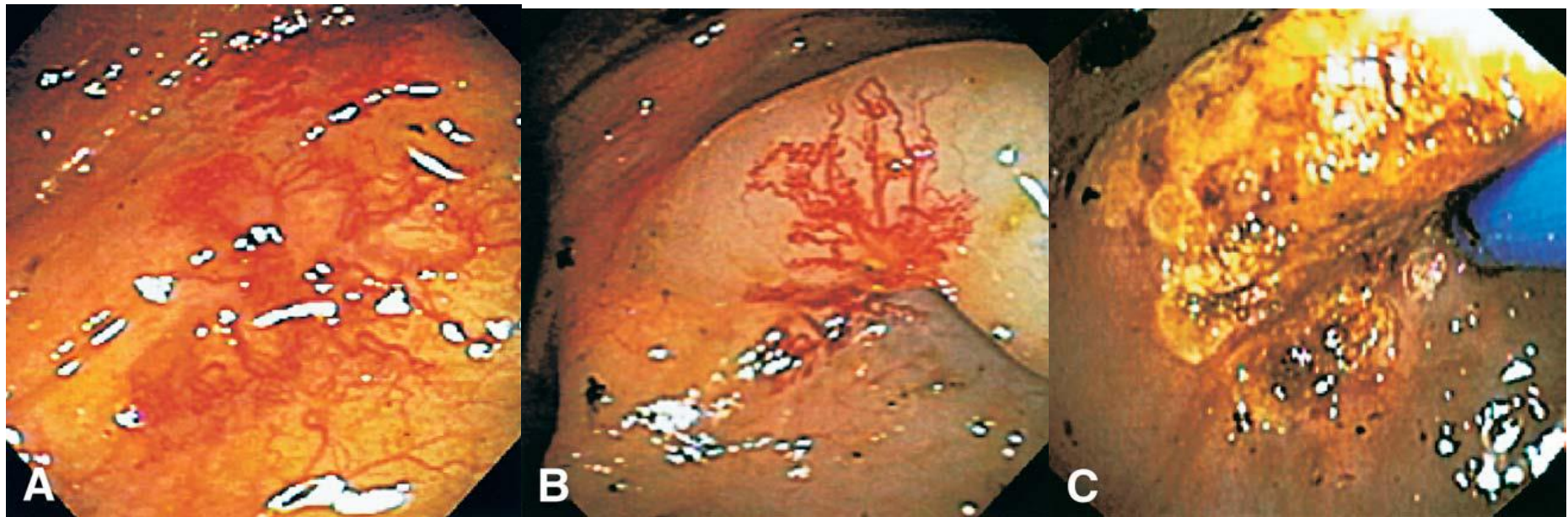
Treatment is usually with APC

A. This sequence of photographs shows a 1-cm AVM in the cecal base.

B. In the second photograph, a submucosal injection of 1:10,000 epinephrine has been performed.

C. The third photograph shows a satisfactory appearance following APC therapy.

Gastric Antral Vascular Ectasia

- The condition is associated with dilated small blood vessels in the antrum, or the last part of the stomach.
- Also called watermelon stomach.
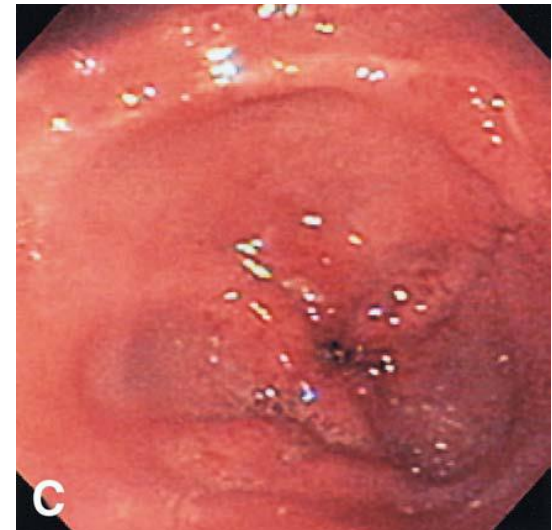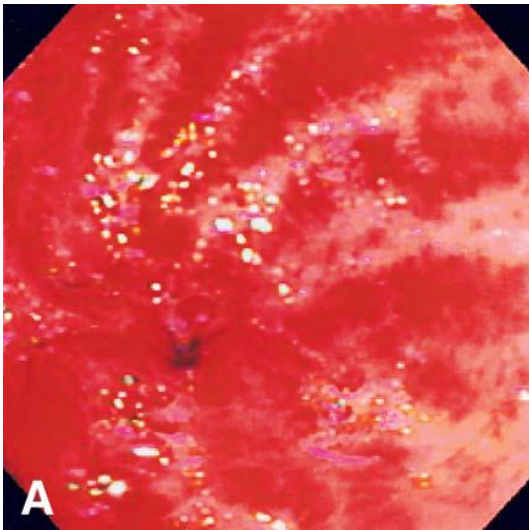
A. The sequence of photographs shows the vascular ectatic lesions that are typical of GAVE.
B. The second photograph is taken after the initial application of the APC.
C. The third photograph is taken in follow-up after three sessions of therapy.

Portal Hypertensive Gastropathy

- Patients will have a history of portal hypertension (i.e. liver cirrhosis or etoh abuse)
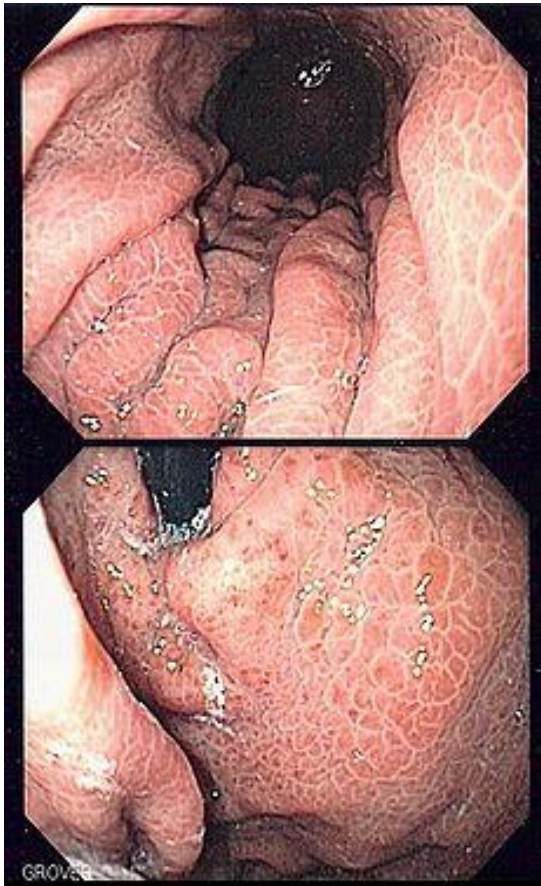
- Mosaic pattern of the stomach
- Classified as mild or severe
- Treatment is aimed at reducing portal pressures (nonselective betal blockade/TIPS)
- There is presence of ectatic blood vessels that are dilated secondary to Portal HTN that bleed.
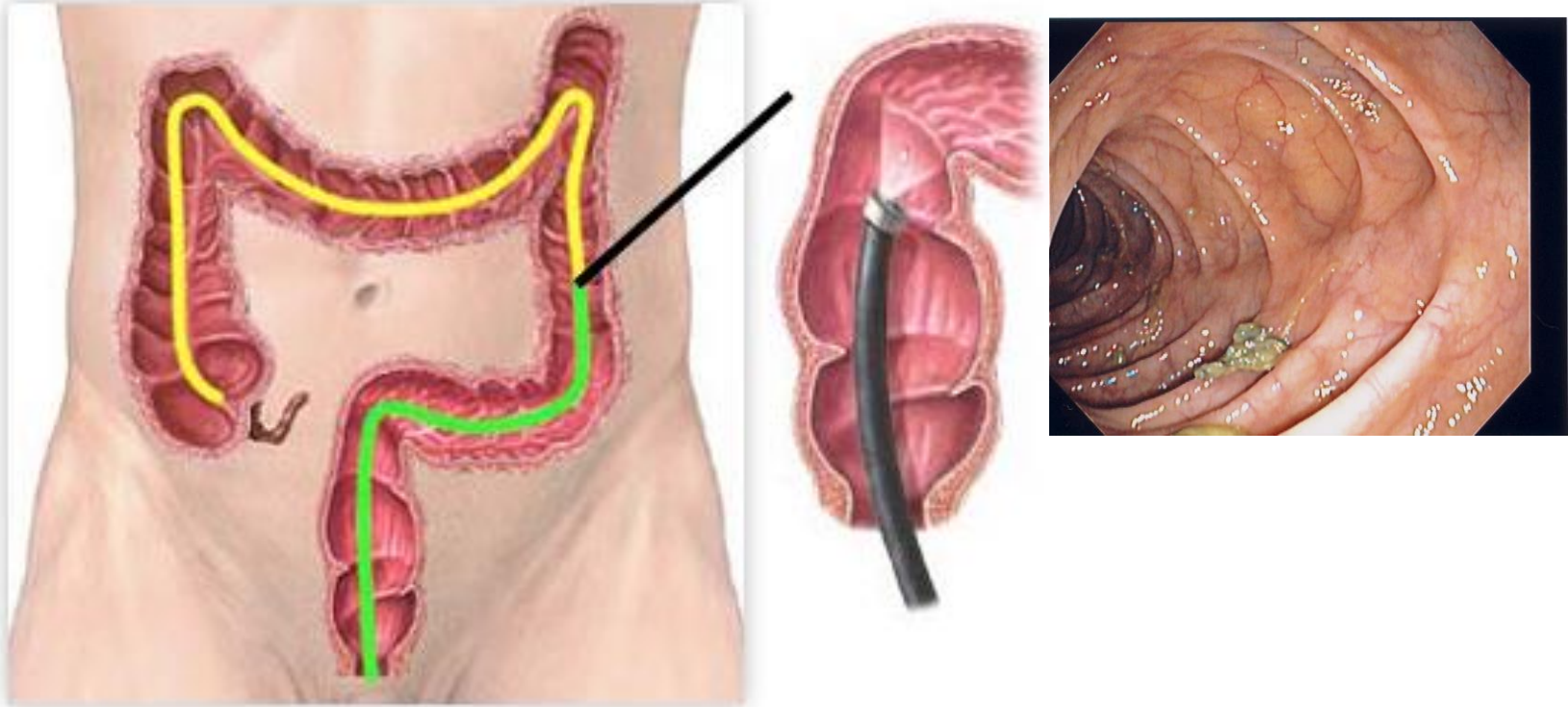
Slow Variceal Bleeding
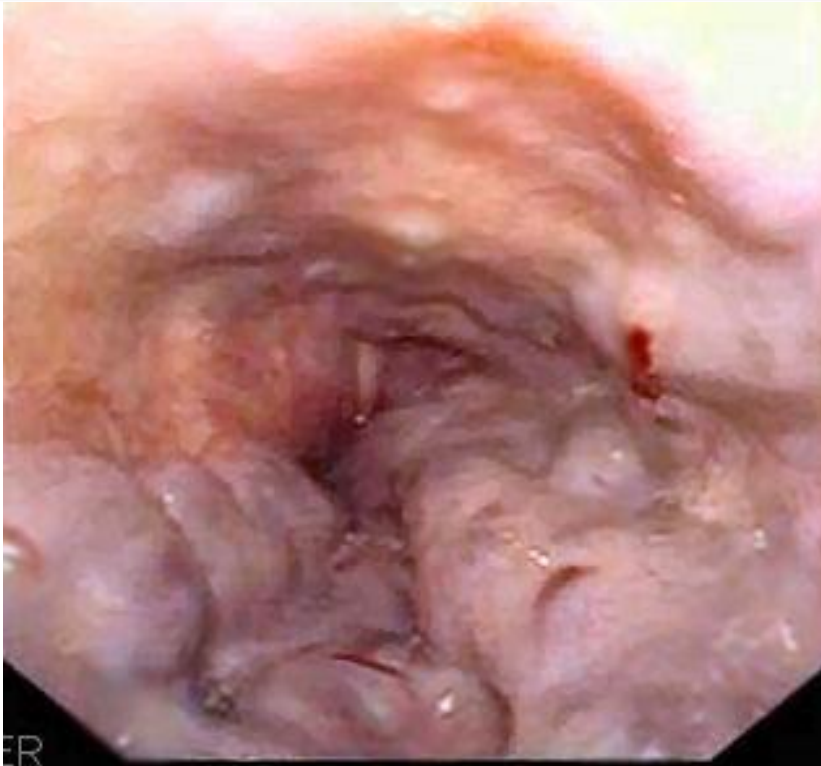
Slow bleeding from esophageal or gastric varices can also be a cause of anemia.

Treatment is aimed at reducing portal pressures.

In case of espohageal varices – endoscopic variceal band ligation can also be employed.

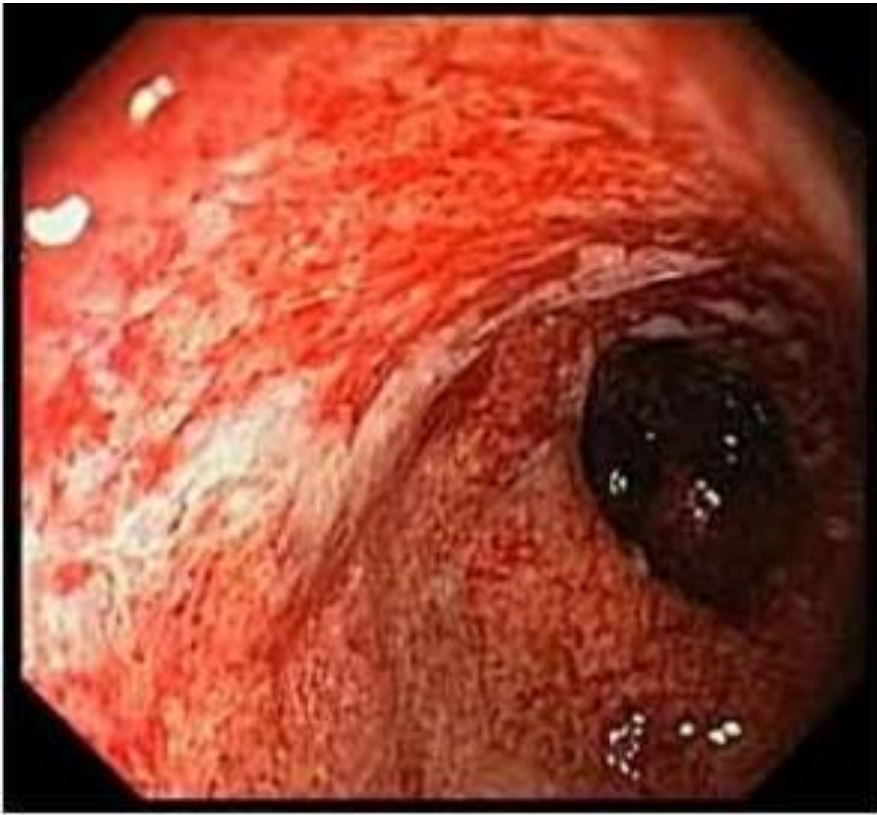# Pathology encountered in Colonoscopy during the evaluation of anemias

AVM, ULCERS, IBD, COLORECTAL CANCER

Colorectal Cancer

- Treatment is stage dependent

- 3rd most common cause of cancer death in the united states

Inflammatory Bowel Disease

IBD, either Crohns disease or Ulcerative Colitis can cause slow and occult bleeding leading to iron deficiency anemia.

Other Pathology also encountered

- As in upper endoscopies, one can also encounter AVM's (arteriovenous malformations) and colonic ulcers that may cause slow bleeding leading to iron deficiency anemia.

Causes of Obscure Small Bowel Blood Loss Causing Anemia

- AVMs
- Small instestinal Malignancies

These can be evaluated via wireless small bowel pill camera and if a lesion of interest is seen, then this can be further pursued via deep enteroscopy.

Wireless Capsule Small Bowel Pill Cam
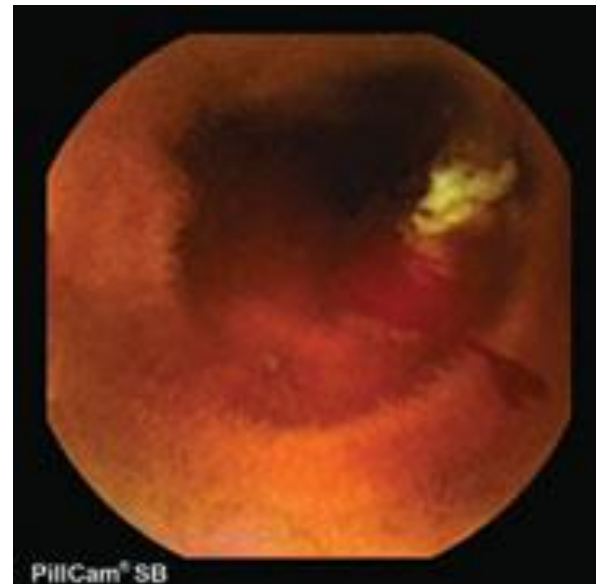
Case 2

- A 75 year old man presents with anemia (HB 7gm/dl).
- His MCV is 80
- All of his other laboratory indices are normal.
- When you are performing a History and Physical, he complains of multiple bright red stools for the last 3 days.
- He is otherwise hemodynamically stable

What is the most likely cause of his anemia?

A. Slow bleeding from Peptic Ulcer disease
B. Slow Bleeding from Esophageal Varices
C. Diverticular bleeding
D. Anemia of chronic disease

Key Points in Presentation

- **Hemodynamically stable**
- **Bleeding is bright red**

  - Therefore his anemia is likely secondary to acute blood loss anemia from bleeding from a lower gastrointestinal source.
    - Diverticular, Hemorrhoids, Colitis,
  - Brisk upper GI bleeding can also give you bright red bleeding (but patient usually will be hemodynamically unstable)
    - Upper GI bleeding will usually present with Melena (dark stools)

Diverticular Bleeding
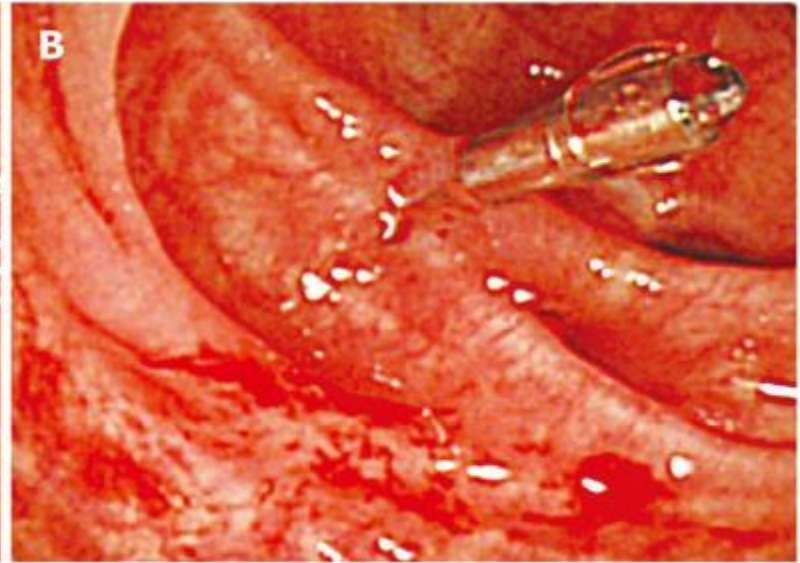
Anemia from upper GI bleeding: Melena

Causes of acute blood loss anemia from upper gastrointerstinal causes include.

- Peptic Ulcer Disease
- Gastric and Esophageal Varices
- AVMs
- Deulifoy lesions
- GAVE (severe)
- Severe portal hypertensive gastropathy

Case 3

- A 23 year old native american female presents to the hospital with one day of being yellow. She was in her usual state of health until last week when she started to get weak. She complains of a flu like syndrome that started approximately a week ago. She recently started tetracycline for some acne that her PCP prescribed.
- She has no other PMH
- She has no other FH
- She takes no medications
- She has no allergies

Case 3

- On Physical Examination, she appears icteric, and has splenomegaly. She also appears weak. Otherwise physical examination is negative.
- Labs:
  - WBC: 4,500
  - HB: 6.0gm/dl (MCV 110)
  - Platelets: 300,000
  - Total Bilirubin 7 gm/dl
  - Direct Bilirubin 0.5 g/dl
  - AST/ALT: 100 U/L,110 U/L
    - Normal AST: 5-35 U/L, Normal ALT: 7-56 U/L
  - Alkaline Phosphatase: 110
    - Normal Alk Phos38-126 U/L

Case 3

- Labs Continued:
  - Vitamin B12: 440 pg/ml (normal 200 - 800 pg/mL)
  - Folate: 5 mcg/L (normal >4 mcg/L)
  - Iron: 102 ng/dl (normal 26-170 ng/dl)
  - Ferritin: 100 ng/dl (normal 12-160 ng/dl)
  - TIBC: 301 ng/ml (normal 262-474 ng/dl)

What is the most likely Diagnosis?

- A. Iron Deficiecy Anemia
- B. Anemia of Chronic Disease
- C. Acute Gastrointestinal blood loss
- D. Acute Hemolysis

Acute Hemolysis

- Red blood cells when lysed release hemoglobin that gets broken down and releases bilirubin.
- This bilirubin travels to the liver where it becomes conjugated to form direct bilirubin.
- In acute hemolysis the liver becomes overwhelmed and majority of bilirubin is indirect.
- Patients will present with anemia and jaundice.
- AST/ALT will be elevated as they are also released from blood cells during hemolysis

Testing for Hemolysis

- Elevated LDH in presence of a reduced haptoglobin is 90 percent specific for diagnosing hemolysis
- Conversely, the combination of a normal LDH and a serum haptoglobin greater than 25 mg/dl is 92 percent sensitive for ruling out hemolysis

Reticulocyte count

- The reticulocytes is the final precursor of a red blood cell in the bone marrow before it is released into the blood stream.
- In any cause of acute anemia (i.e. acute blood loss, acute hemolysis of any cause) the bone marrow will eject more reticulocytes into the blood stream and therefore the reticulocyte count will increase
  - (The marrow will try to produce more blood cells to compensate for the loss).
    - **Normal reticulocyte count in adults 0.5%-1.5%**

Reticulocyte count

- Reticulocyte count may also increase after treatment of other types of anemia (i.e. pernicious anemia and Iron deficiency anemia) where the bone marrow starts actually producing blood cells.
- The MCV may also be elevated in acute blood loss/acute hemolyis anemia.

Back to Case 3

- Causes of hemolysis include:
  - Viral infections
  - Drugs
  - Autoimmune causes

  Treatment is focused on the cause (i.e. steroids in autoimmune, withdrawal of offending agent in case of drugs)
- In this case, anemia is likely not being caused by a gastrointestinal source.
- Therefore – treatment should focus on other causes.

Case 4

- A 54 year old man presents with anemia. You are asked to evaluate for any gastrointestinal source. He has not had any GI bleeding in the past. He has had a colonoscopy 3 years ago that was completely normal.

Case 4

- His labs are as follows:
- WBC: 1000/l (4.1-10.9 thousand/l)
- HGB: 5.0 gm/dl (normal 12-16 gm/dl)
- Platelets: 50,000/L (150,000-450,00/l)

What should be the next step in his evaluation

A. Upper endoscopy
B. Small bowel capsule endoscopy
C. Repeat Colonoscopy
D. Bone Marrow biopsy

Pancytopenia

- This gentleman presents with Pancytopenia
- He likely does not have a gastrointestinal cause of bleeding.
- The presence of severe pancytopenia narrows the differential diagnosis to disorders such as
  - Aplastic anemia
  - Folate or cobalamine deficiency
  - Hematologic malignancy
    - Acute myeloid leukemia

Case 5

- A 67 year old female who has diabetes mellitus since the age of 16, ESRD dependent upon hemodialysis is referred to you for the evaluation of longstanding anemia for the last 5 years. She has had an upper endoscopy, colonoscopy, small bowel capsule endoscopy. approximately 3 years ago that were all normal.
- Clinically she has no bleeding.

Case 5

- WBC: 4.500/L
- HGB: 7.0gm/DL
- Platelets: 300,000/L
- MCV: 90 (82-100 fl (M) 78-100 fl (F))
- Iron: 10 ng/dl (76-198 ng/dl (M) 26-170 ng/dl (F))
- TIBC: 5 ng/dl (262-474 ng/dl)
- Iron Saturation: 270 ng/ml (normal 262-474 ng/ml)
- Ferritin: 700 (18-160 ng/ml (women), 18-270 ng/ml(men))

Case 5 continued

- What is the most likely cause of her anemia?
  - A. Gastric Ulcer
  - B. Duodenal AVMs
  - C. Diverticular Bleeding
  - D. Anemia of Chronic Disease

Anemia of Chronic Disease

- Anemia of chronic disease, also referred to as anemia of inflammatory response, or ACD, is a form of anemia seen in chronic illness, e.g. from chronic infection, chronic immune activation, or malignancy.
- New discoveries suggest that the syndrome is likely largely the result of the body's production of hepcidin, a master regulator of human iron metabolism.
- ACD is the most common anemia found in hospitalized patients.
- The ideal treatment for anemia of chronic disease is to treat the chronic disease successfully, but this is rarely completely possible with current medical treatment.
- No further endoscopy is needed in this patient.

Summary: Diagnosis and Treatment of Anemia

- Initial approach should be to perform a complete history and physical examination along with a review of the results of a complete blood count with peripheral smear.
- Pending the evaluation of this, the anemia can be classified into its specific type.
- For those anemias that may occur secondary to gastrointestinal losses – endoscopic evaluation will be necessary.

Questions