Microcytic and Macrocytic Anemia

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Objectives

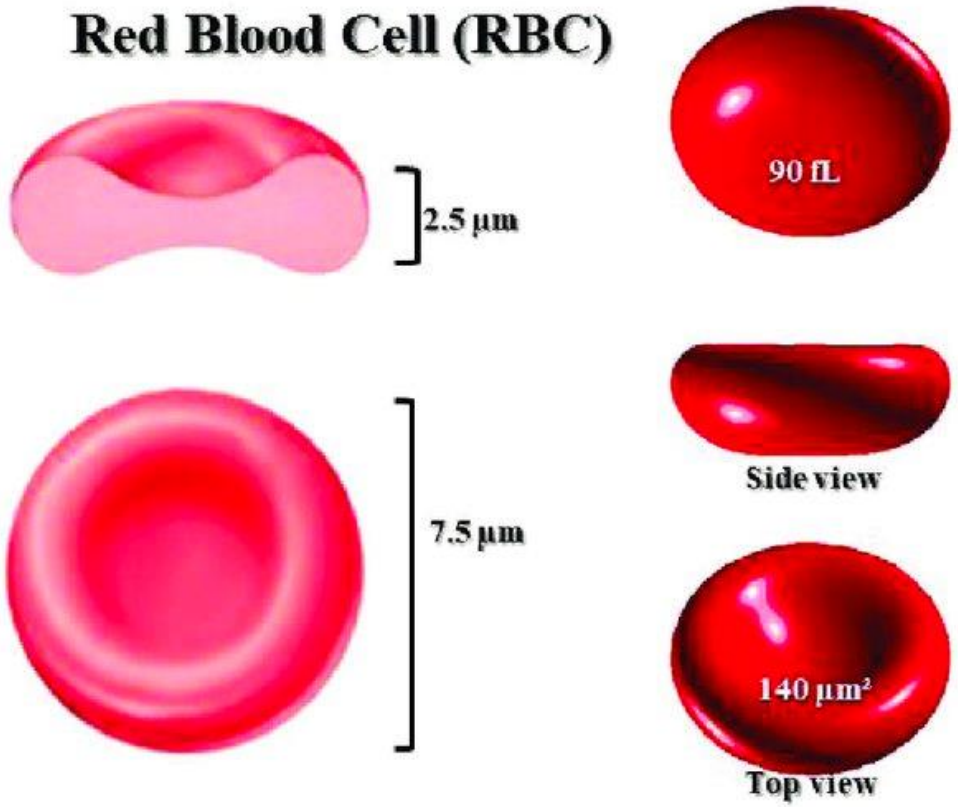
- To review etiologies of microcytosis/macrocytosis with and without anemia and the diagnostic evaluation of each

- To address management of most common causes of microcytic and macrocytic anemia

Structure and function of RBC

Microcytosis MCV < 80 fL
Macrocytosis MCV >100 fL

- Biconcave
- High surface area to volume
- No organelles
- Made up of hemoglobin and a plasma membrane
- Highly deformable
- Transports oxygen via heme groups
- Life span 120 days



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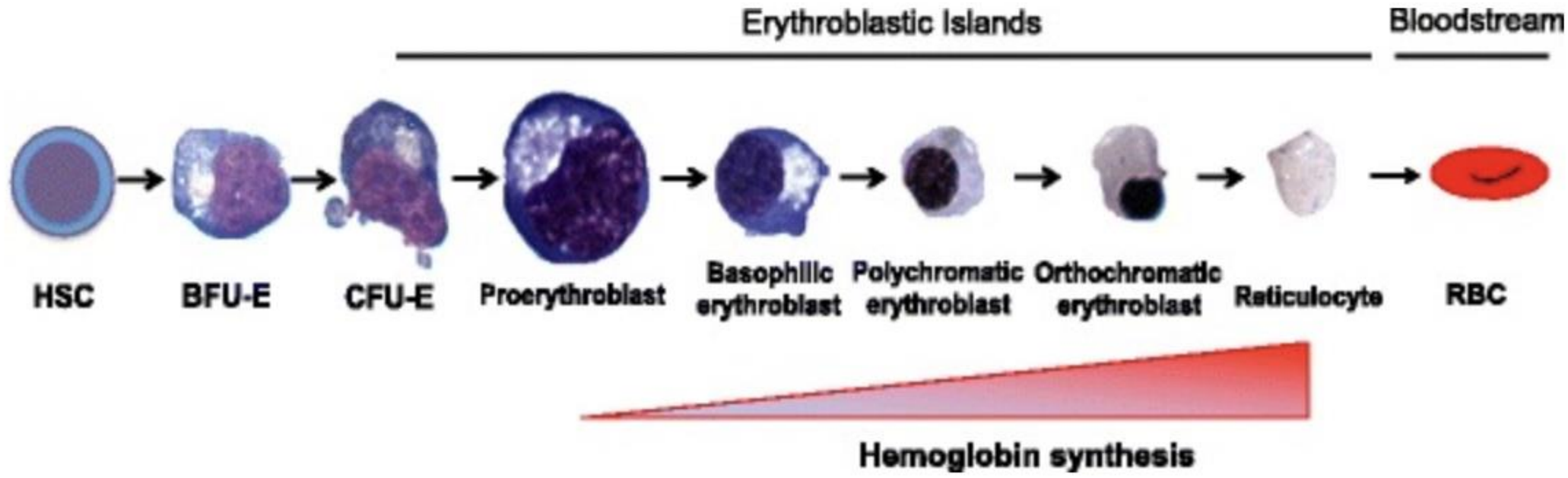
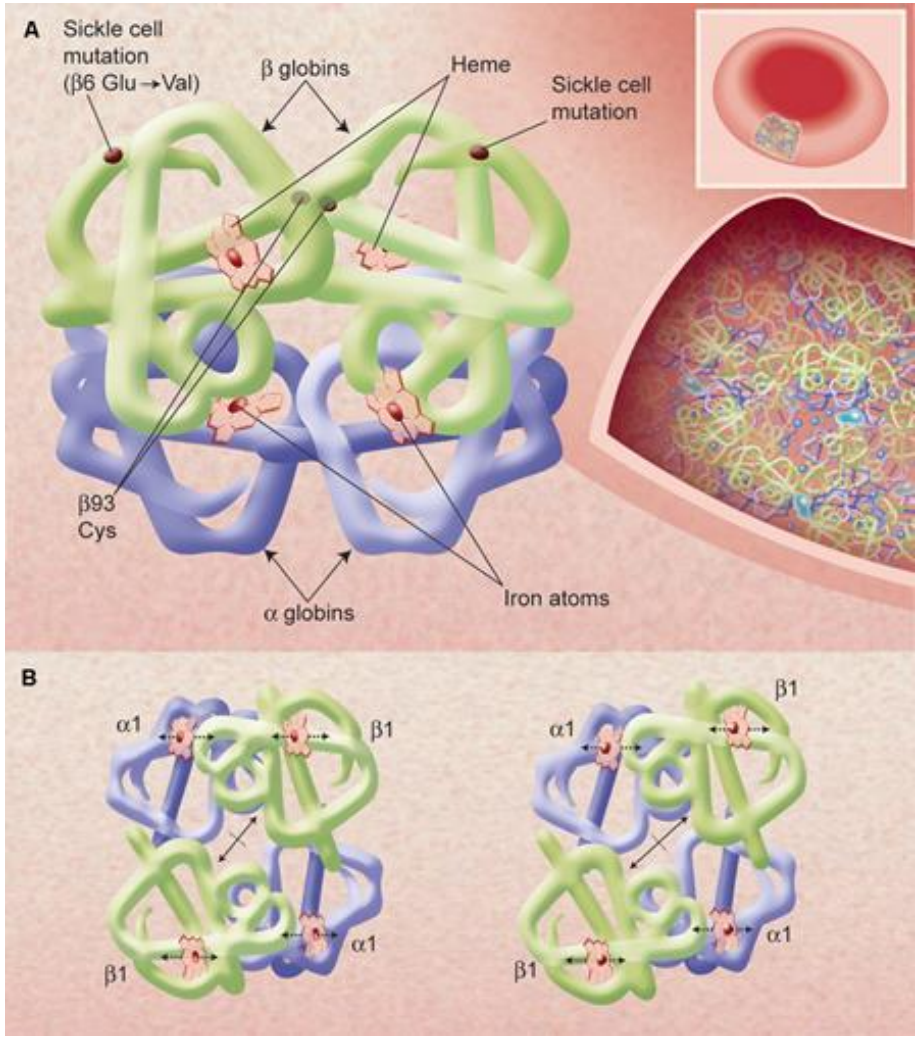
Erythropoesis



Zivot et al. Molecular Medicine (2018) 24:11
https://doi.org/10.1186/s10020-018-0011-z

Hemoglobin molecule



Alan N. Schechter, Hemoglobin research and the origins of molecular medicine,
Blood (2008) 112 (10): 3927–3938.

Interpreting the RBC indices

- **Hgb –** Measured hemoglobin concentration in whole blood
- **HCT -** % of RBCs in blood volume
- **MCV =** Mean volume of one RBC = (HCT X 10)/RBC count per Liter **-90 fL is average**
- **Mean corpuscular hemoglobin (MCH)-** Mean hemoglobin concentration in 1 RBC (Hemoglobin concentration/Total number of RBCs)
- **Mean corpuscular hemoglobin concentration (MCHC) -** Mean hemoglobin concentration in RBCs (Hemoglobin concentration/proportion of RBC) = Hb /HCT x 100
- **RDW** - Measure of anisocytosis (**variability in RBC size**) i.e. standard deviation of MCV = (Standard deviation of red cell volume X 100)/Mean cell volume – normal 11-15%

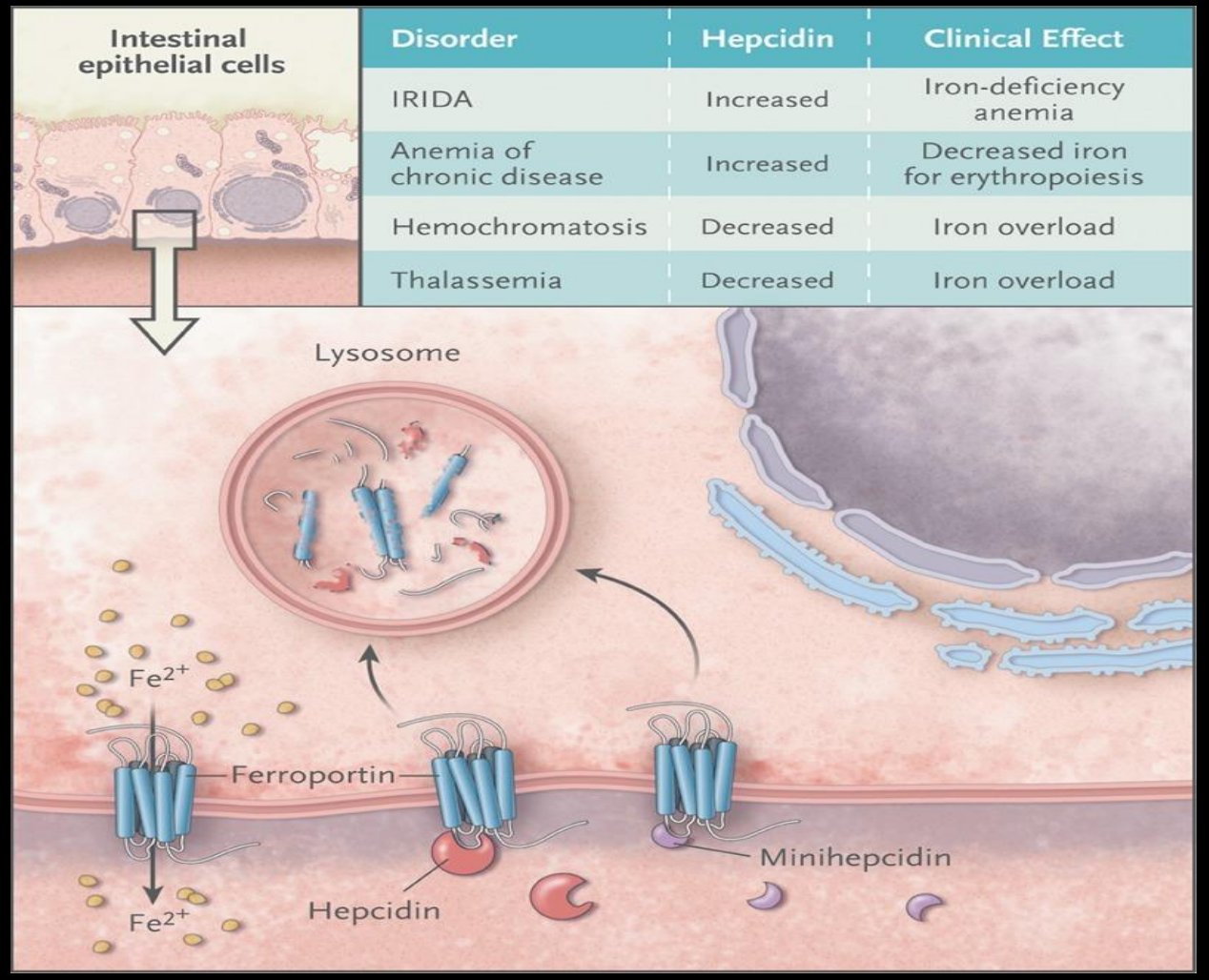
Normal values CBC at BIDMC

COMPLETE BLOOD COUNT		
White Blood Cells	4.0 - 10.0	K/uL
Red Blood Cells	3.9 - 5.2 (female) 4.6 - 6.1 (male)	m/uL
Hemoglobin	11.2 - 15.7 (female) 13.7 - 17.5 (male)	g/dL
Hematocrit	34 – 45 (female) 40-51 (male)	%
MCV	82 - 98	fL
MCH	26 - 32	pg
MCHC	32 - 37	g/dL
RDW	10.5 - 15.5	%
RDW-SD	35.1 - 46.3	fL

What makes a RBC microcytic?

- Decreased hemoglobin content – often associated with decreased MCH
- In iron deficiency it is because of decreased iron availability. The maturing red cell divided before it reached the hemoglobin concentration normally required to arrest mitosis
- In thalassemia it is due to decreased globin availability
- Occurs in ACD/AI as there is decreased iron availability for erythropoiesis as iron staying in bone marrow macrophages due to increased hepcidin

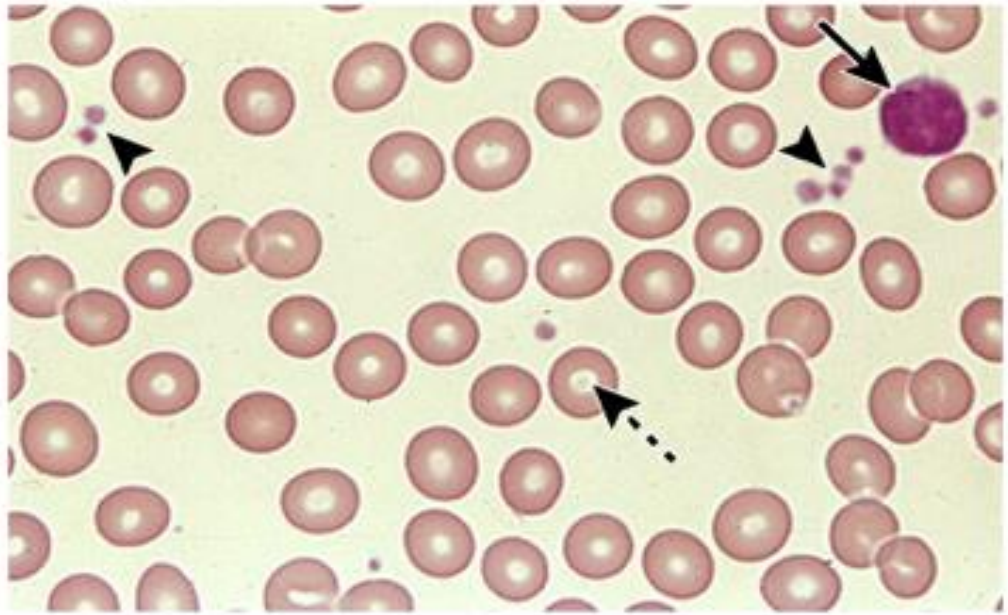
Hepcidin–Ferroportin Axis.



Andrews NC. N Engl J Med 2012;366:376-377.

The NEW ENGLAND JOURNAL of MEDICINE

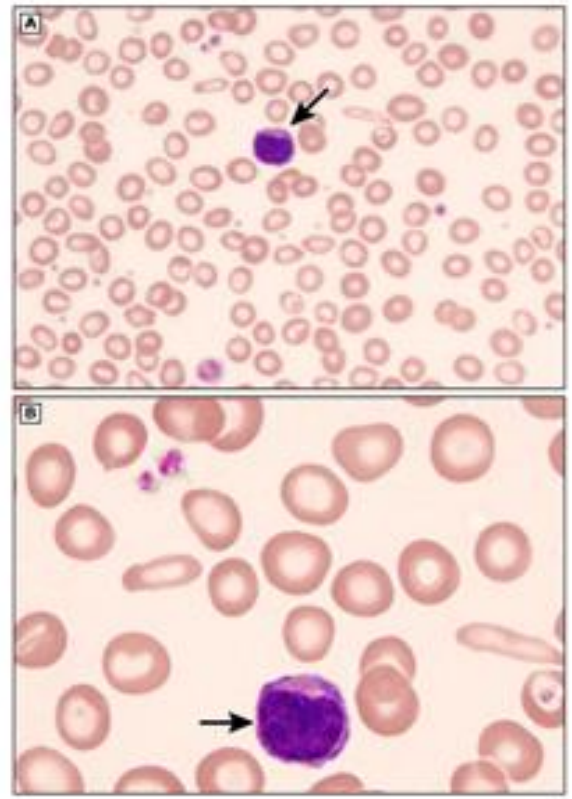
Normal peripheral blood smear



High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Peripheral blood smear in iron deficiency anemia showing microcytic, hypochromic red blood cells

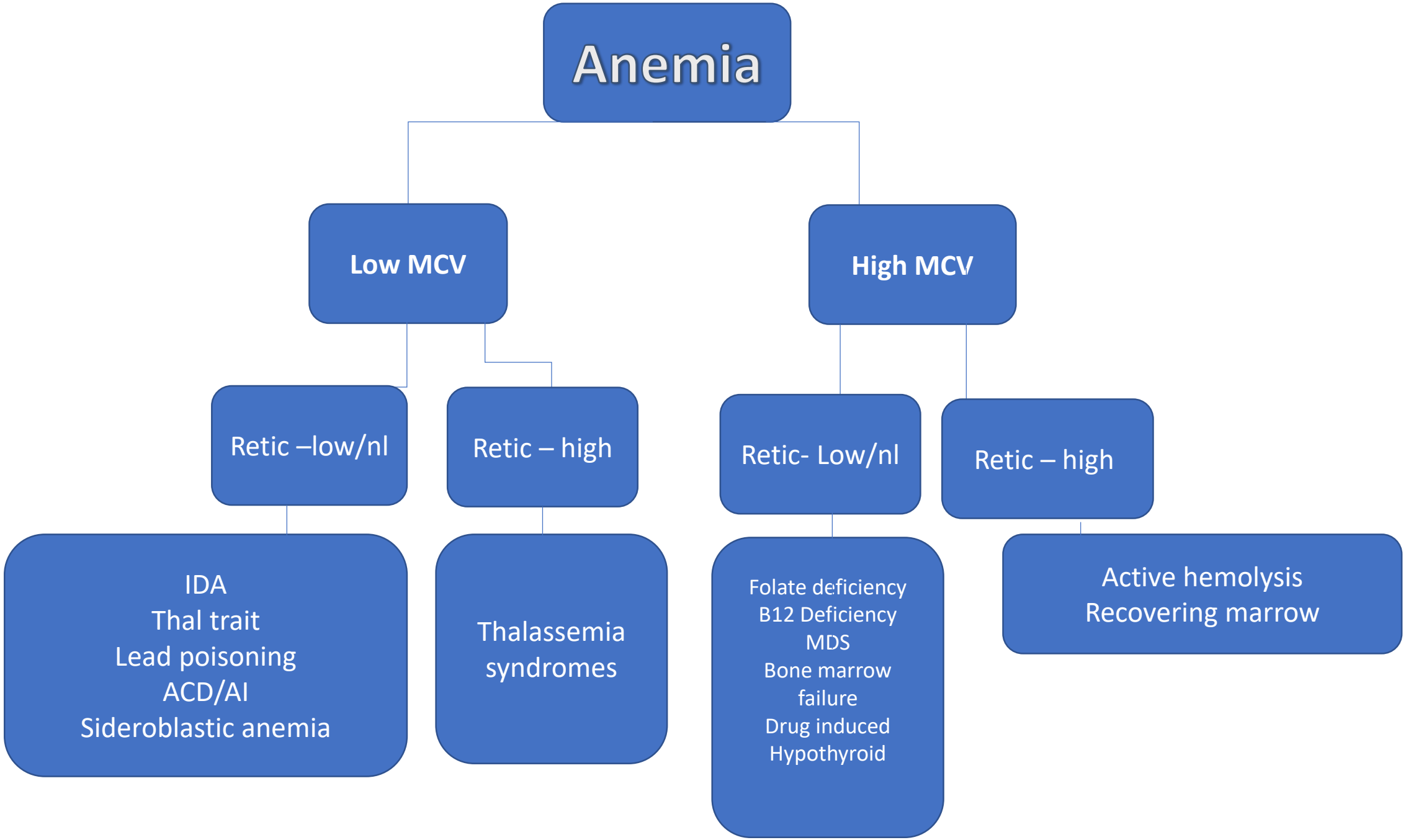


The same peripheral blood smear from a patient with iron deficiency is shown at two different magnifications. Small (microcytic) red blood cells are shown, many of which have a thin rim of pink hemoglobin (hypochromia). Occasional "pencil"-shaped cells are also present. A small lymphocyte is shown for size comparison (arrow). Normal red blood cells are similar in size to the nucleus of a small lymphocyte (arrow), and central pallor in normal red blood cells should equal approximately one-third of the cell diameter.

Kindly supplied by Dr. Garman Pihan, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Etiologies of microcytosis and microcytic anemia

- **Iron deficiency**
- **Thalassemia syndromes**
- Anemia of chronic disease (more commonly normocytic)
- Other thalassemic hemoglobinopathies
- Lead poisoning (or other toxins causing sideroblastic anemias)
- Sideroblastic anemia (hereditary)
- Copper deficiency (sometimes)
- Zinc toxicity
- Rare – MDS with acquired thalassemia, iron refractory iron deficiency anemia, divalent transporter mutations, atransferritinemia


Anemia
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IDA
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Sideroblastic anemia
Thalassemia syndromes
Folate deficiency
B12 Deficiency
MDS
Bone marrow failure
Drug induced
Hypothyroid
Active hemolysis
Recovering marrow

Further evaluation of microcytosis/microcytic anemia

- Iron studies
- If not iron deficient – hemoglobin electrophoresis
- LFTs, LDH, retic, peripheral smear
- In some cases, renal function and erythropoetin level, lead level

Case 1

Patient is a 38 yo premenopausal woman G3P3 seen for routine visit with her PCP who notes increasing fatigue. She feels that at the end of the day she is exhausted and is finding it difficult to get going in the morning. She eats a regular diet. Periods last 7 days and she described them as heavy for 4 days requiring change of her pad every 2 hours. Her labs are as follows:

WBC 7.0, HgB 10.9, HCT 37, MCV 79, MCH 24 (26-32), MCHC 30 (32-37), RDW 15.4 (10.5-15.5), PLTs 456 (nl 150-400)

Retic 1.3, Iron 18 (30-160), TIBC 470 (26-470), Ferritin 12 (13-150)

Iron deficiency anemia

- Microcytic anemia, reactive thrombocytosis
- Low iron saturation, high normal TIBC, low ferritin
- Peripheral smear with microcytic, hypochromic red cells
- Gold standard for diagnosis of iron deficiency is bone marrow biopsy (but we almost never do it)
- We can make iron deficiency better with iron repletion, but the question is always why is the patient iron deficient – most common is blood loss (menorrhagia, GI blood loss, decreased absorption/dietary (celiac disease, chronic PPI use etc)

Iron deficiency anemia

- In this patient there is a clear cause – menstruation and multiple pregnancies

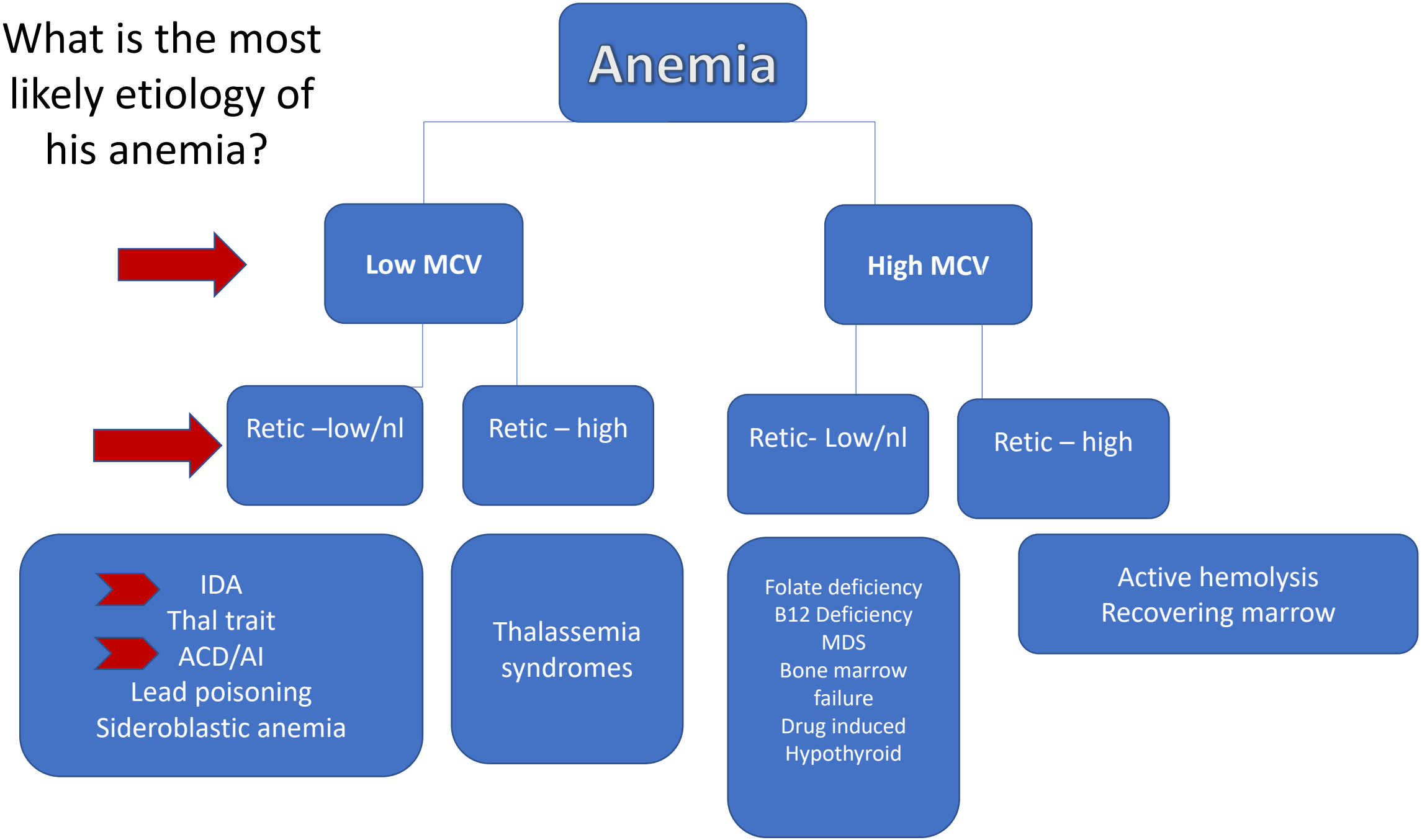
- Low threshold to assess for GI blood loss, celiac disease in patients with no clear cause

Case 2

73 yo gentleman with diabetes, CKD (baseline creatinine 1.4), HTN noted to have a new anemia with hemoglobin 11.5 (down from 12.5 last year), HCT 35. Denies BRBPR, melena. Last colonoscopy 6 years ago was normal. Renal function has been stable with creatinine 1.3-1.4 over the past 3 years.

Additional labs: WBC 5.6, Hgb **11.2** (13.7-17.5), HCT **34.6** (40-51), MCV **80** (82-98 fL), RDW 15 (10.5-15.5 %)PLTS 160, Iron **30** (45-160), TIBC 335 (260-470), ferritin 60 (30-400), B12 520, retic 1.0 (0.4-2.0). Peripheral smear with mildly microcytic, normocytic red cells. Erythropoetin level 19 (nl 2.6-18.5 mIU/mL)

What is the most likely etiology of his anemia?



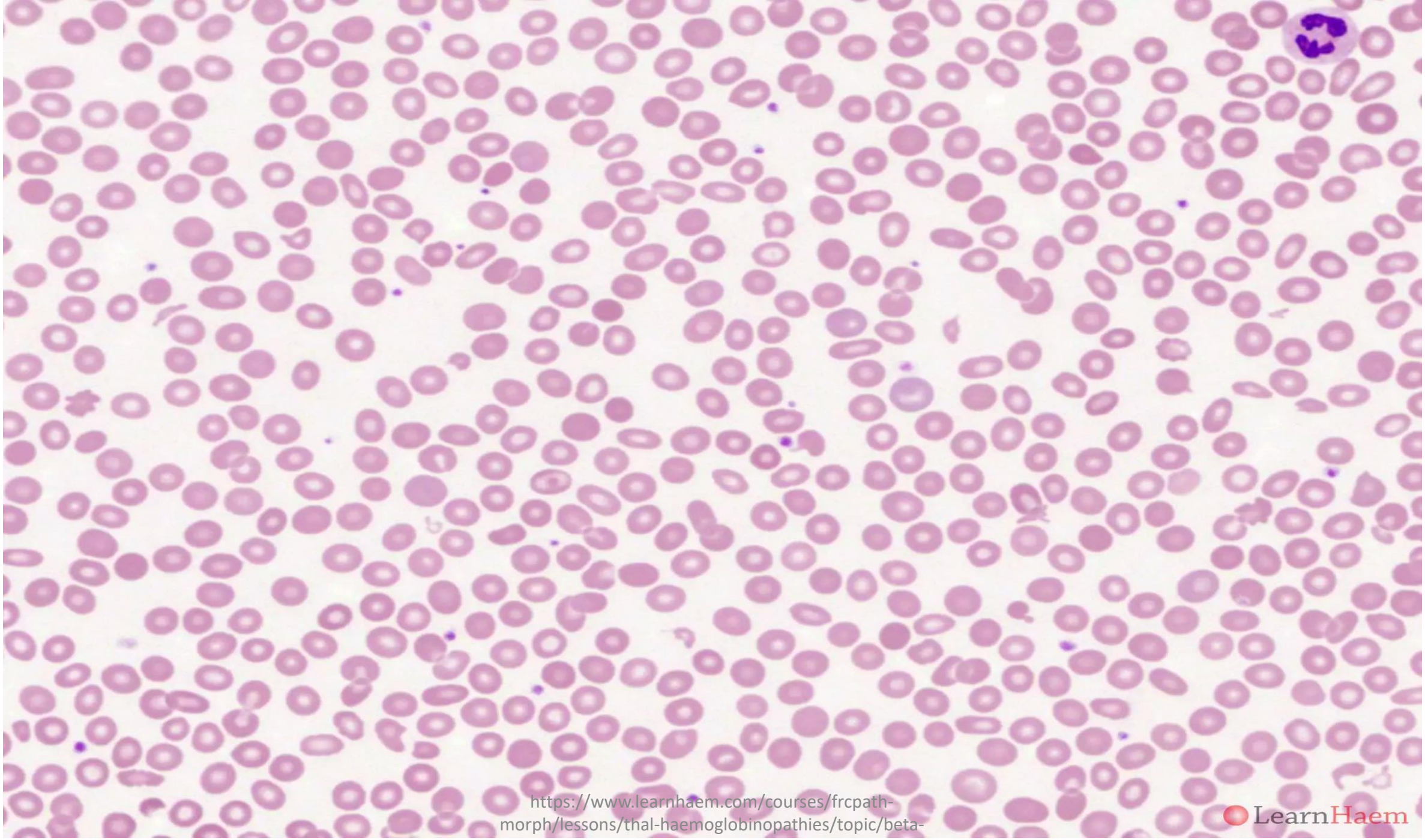
Most likely a mixed picture – IDA and ACD

- Likely anemia of CKD with a very mild anemia starting last year. Epo level is high normal, but inappropriately low for degree of anemia
- MCV is low/normal, serum iron low, TIBC normal, ferritin normal (but on lower end of normal and **< 100**), Iron saturation (serum iron/TIBC) is low and is **< 20%**
- Patient with anemia of chronic kidney disease have increased hepcidin levels which leads to decreased iron availability for erythropoesis (functional iron deficiency) as well as decreased iron absorption (absolute iron deficiency)

Case 3

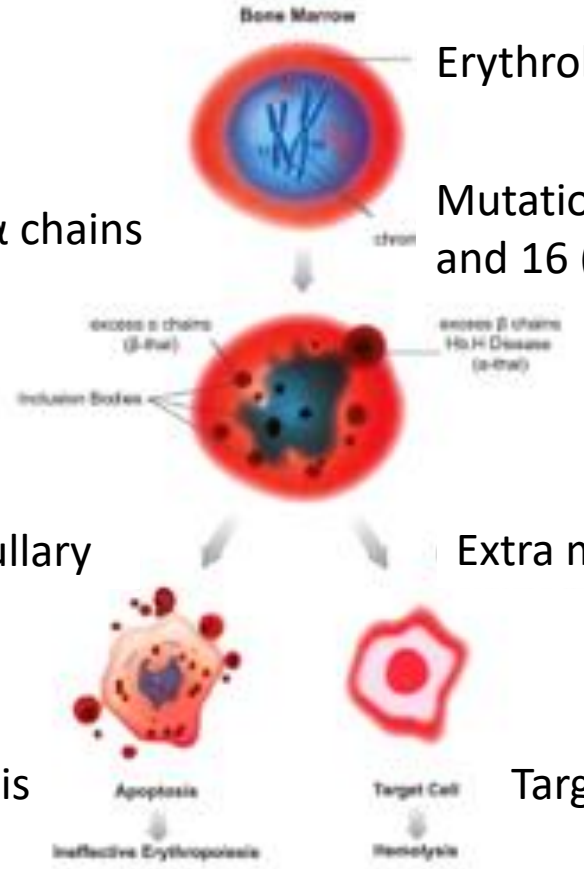
55 yo Italian gentleman with h/o GERD which he controls with diet was seen for routine visit by a new PCP. His baseline HCT is **37**, Hgb **10.9**, RBC **6.2**, **MCV 69**, MCH **20** (26-32), RDW 15 (10.5-15.5), PLTS 232, nl differential.

Iron 50, TIBC 325, Ferritin 250 (nl 30-400), retic 1.9. Peripheral blood smear was performed



https://www.learnhaem.com/courses/frcpath-morph/lessons/thal-haemoglobinopathies/topic/beta-thalassaemia-trait/

How I treat thalassemia



Erythroblast

Mutations and deletions Ch 11 (β –thal) and 16 (α thal)

Excess α chains (β-thal)

Excess βchains Hb H disease (α thal)

Intra medullary

Extra medullary

Apoptosis

Target cell

Ineffective erythropoesis

Hemolysis

Eliezer A. Rachmilewitz,Patricia J. Giardina, How I treat thalassemia, Blood, 2011, Figure 1

Blood (2011) 118 (13): 3479–3488.

Hemoglobin Electrophoresis

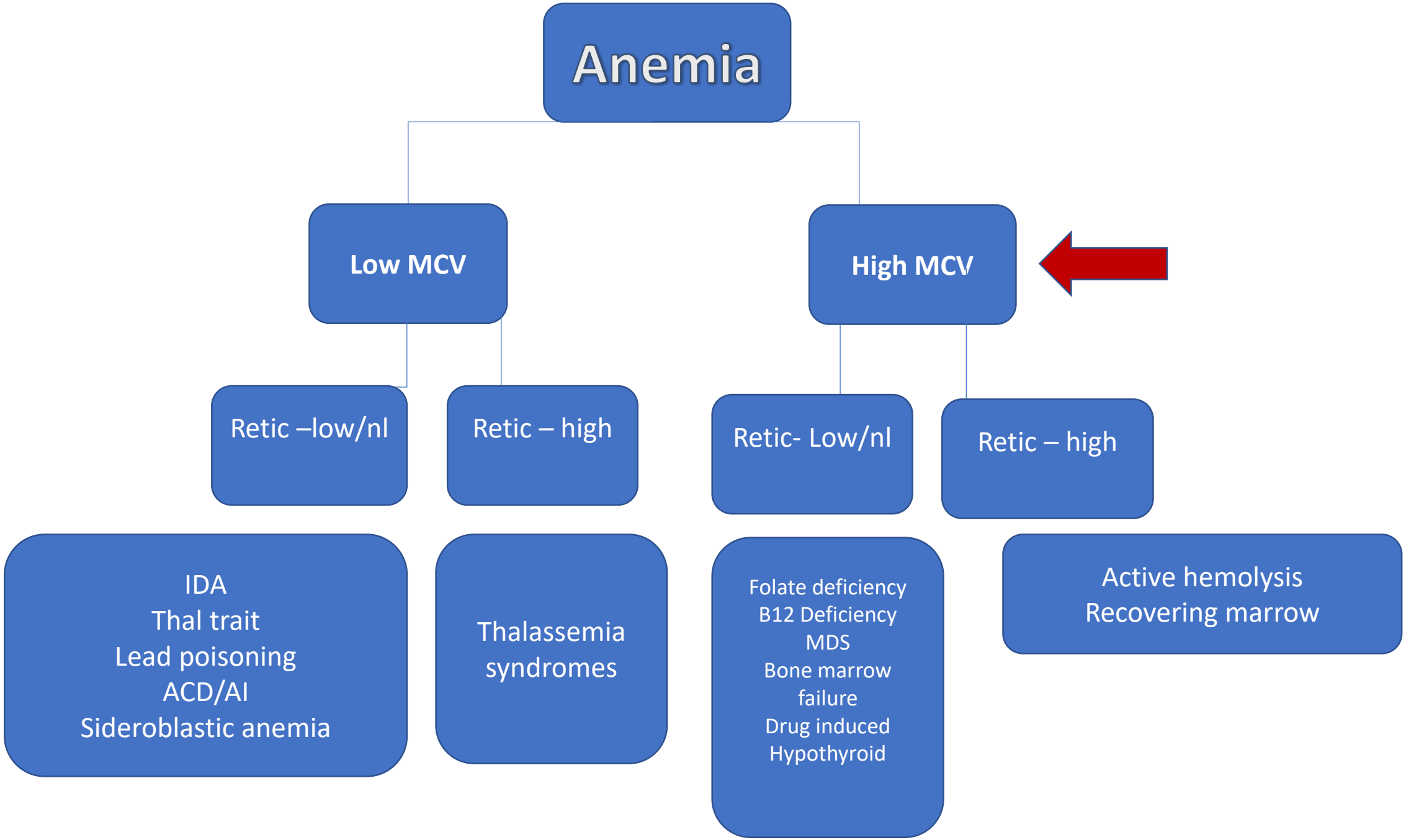
Most consistent with Thalassemia trait

- Elevated Hgb A2

Hemoglobin A	95	96.8 - 97.8	%	E	
	Hb A2 may be falsely decreased in the presence of iron deficiency				
Hemoglobin S	0	0 - 0	%	E	
Hemoglobin C	0	0 - 0	%	E	
Hemoglobin A2	5	2.2 - 3.2	%	E	
Hemoglobin F	0	0 - 2.0	%	E	

Thalassemia trait

- Thalassemias are a quantitative defect of hemoglobin synthesis.
- In beta-thalassemia minor, the red cell number is often elevated, reduced MCV, MCH, and the red cell distribution width (RDW) will typically be mildly elevated.
- The normal to mildly elevated RDW can help differentiate thalassemias from other microcytic hypochromic anemias, such as iron deficiency anemia where the RDW is typically higher.
- Do **NOT** give these patient iron unless they have true iron deficiency or blood loss anemia as they can become iron overloaded from ineffective hematopoiesis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Recovering marrow

Macrocytosis

- MCV > 100 (BIDMC upper end of normal 98 fL)
- Can categorize as follows:
  1. Larger cells because of increased number of young red cells in the peripheral blood (reticulocytes).
  2. Problems with DNA synthesis resulting in megaloblastic anemia
  3. Multifactorial or other mechanisms (ETOH, liver disease, MDS, hypothyroid etc.)

What causes megaloblastic anemia?

- Nucleic acid metabolism is impaired leading to compromised cell division and nuclear-cytoplasmic dyssynchrony
- Common causes include B12 and folate deficiency as well as copper deficiency
- Medications (allopurinol, chemotherapies (Hydrea), ART for HIV, antibiotics which interfere with folate absorption, PPIs which decrease B12 absorption)

Evaluation of macrocytosis

- CBC diff with peripheral smear, reticulocyte count, LFTs, LDH, vitamin B12, folate, TSH, medication history, ETOH history, dietary history (?vegan)

- If other cytopenias, would pursue additional evaluation by a hematologist upfront especially if any immature WBC forms or severe cytopenias

Macrocytosis without anemia

- Common causes are B12 or folate deficiency, pregnancy, ETOH, and if mild may be normal range for an individual

- While macrocytosis without anemia can be a sign of early MDS, if this is the only finding, there is no proven utility in bone marrow biopsy with FISH/cytogenetics and mutational analysis.

J. Rauw et al. Leukemia Research, Volume 35, Issue 10, October 2011, Pages 1335-1338

Macrocytosis without anemia

- In one series of bone marrow examinations of mostly older adults, a score including unexplained macrocytosis, abnormal RDW, and elevated lactate dehydrogenase (LDH) identified 114 of 313 (36 percent) as having MDS. Many of these having no diagnoses after bone marrow biopsy.

J. Rauw et al. Leukemia Research, Volume 35, Issue 10, October 2011, Pages 1335-1338

Most common etiologies of macrocytic anemia

1. ETOH (mechanism unknown) – 1 bottle of wine per day, mild elevation in MCV, resolves if abstain from ETOH for 2-4 months
2. Vitamin b12 deficiency
3. Folate deficiency
4. Hemolysis

Causes of B12 deficiency

- **Gastric abnormalities -** autoantibodies intrinsic factor or parietal cells, Gastrectomy/bariatric surgery, gastritis, autoimmune metaplastic atrophic gastritis
- **Small bowel malabsorption** -celiac disease, ileal resection or bypass, IBD, bacterial overgrowth, Blind loop, malabsorption syndromes, fish tapeworm
- **Pancreatic insufficiency**
- **Strict vegan diet**
- **Medications impairing absorption** (metformin, PPI, H2 blockers, neomycin)

Causes folate deficiency

- **Nutritional deficiency** – poor PO intake, elderly in nursing homes, substance abuser, alcohol abuse
- **Malabsorption** – celiac, IBD, short gut, infiltrative bowel disease
- **Medications/drugs** – MTX, ethanol, trimethoprim, phenytoin
- **Increased folate requirements** – pregnancy and nursing, chronic hemolysis, exfoliative dermatitis

Case 4

68 yo woman with h/o HTN, hyperlipidemia presented to her PCP with increasing fatigue, tingling in her feet, unsteady gait and feeling overall weak. She has had about a 5 pound weight loss over the past 3 months. Denies ETOH use. Initial laboratory studies revealed the following:

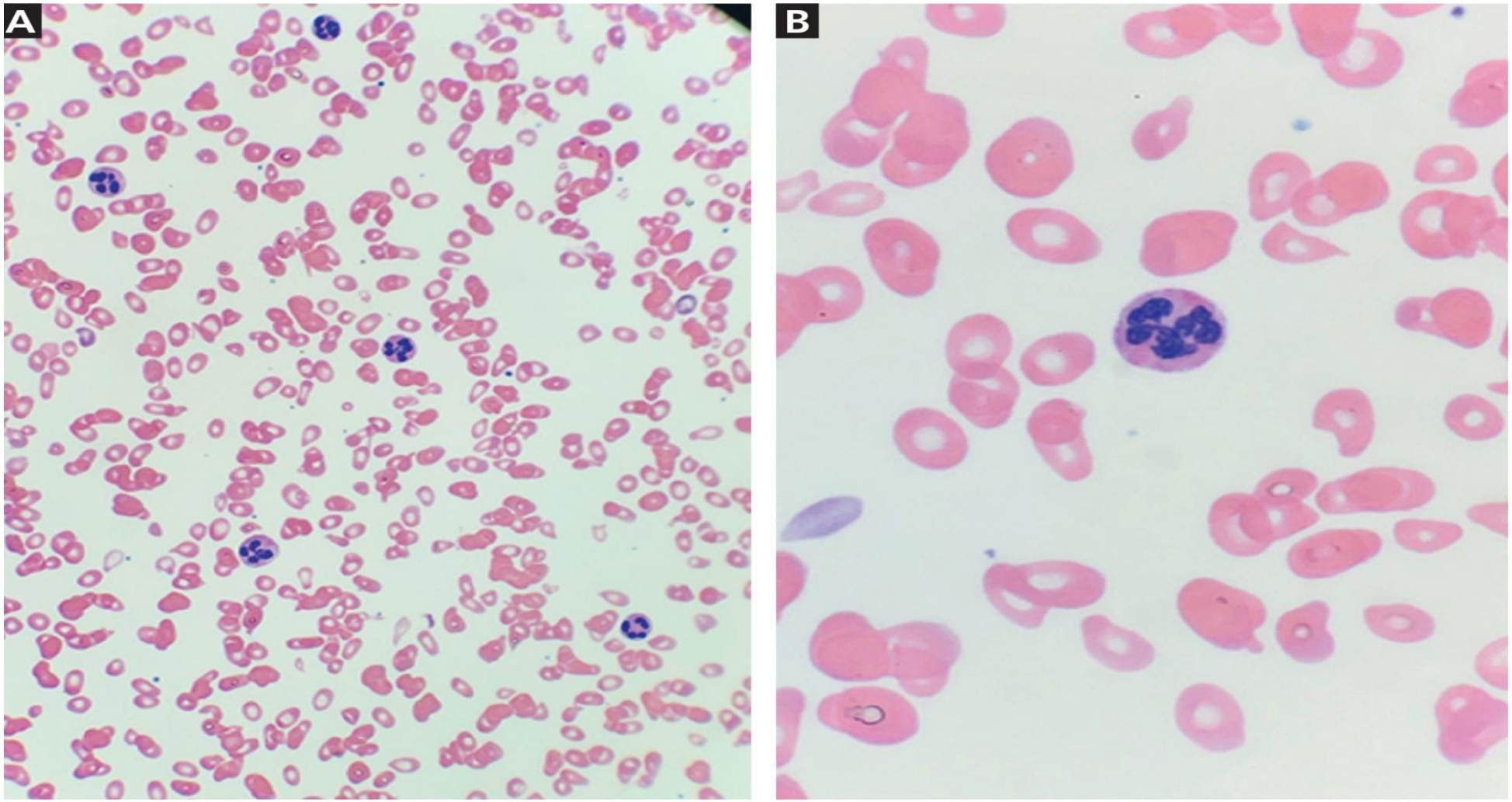
WBC 2.0, Hgb 7.2, HCT 21, MCV 126 MCHC 37 RDW 15, platelets 78,000. Iron studies normal. Retic 1.8% Renal function and electrolytes normal. **ALT 50, AST 60**, alk phos 60, direct bili 0.3**, total bilirubin 2.8**, **LDH 1230**

Case 4 continued

- Patient was sent to the ED given her cytopenias and a hematology consult was obtained

- Additional laboratory tests were requested including B12, folate, peripheral smear, haptoglobin, PT, PTT

Peripheral blood smears show hypersegmented neutrophils consistent with megaloblastic anemia.



Nellowe Candelario, and Catherine Klein CCJM 2022;89:8-9

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Then the rest of labs came back….

- Folate 18
- Haptoglobin <10
- Vitamin B12 – 87
- Additionally, intrinsic factor antibody returned positive

Diagnosis: Pernicious Anemia

- Decreased B12 absorption due anti intrinsic factor antibodies leading to severe deficiency.
- This leads to impaired DNA synthesis in hematopoetic presursors
- Pancytopenia and hemolysis then result from ineffective hematopoesis

Treatment

- Vitamin B12 1000 mcg IM daily x 1 week and then weekly x 4 and then monthly
- This patient had improvement in cytopenias and increase in reticulocyte count, decrease LDH in a periods of days and within 2 weeks has significant improvement in cytopenias although neuropathy persisted

Take home points

- The most common causes of microcytosis are iron deficiency, thalassemia and anemia of chronic disease
- Iron studies, RBC indices, retic count and peripheral smear are helpful in distinguishing the etiology of microcytic anemia
- The most common causes of macrocytosis are ETOH, B12/folate deficiency, hemolysis
- Hematology consultation should be pursued for macrocytosis with cytopenias or early WBC forms as this can suggest a primary bone marrow process such as MDS, leukemia or marrow failure

Question 1

Which of the following is true regarding iron deficiency anemia?

A. Patients with iron deficiency have high hepcidin levels
B. Early iron deficiency is characterized by low TIBC and low transferrin saturation
C. TIBC is high, ferritin is low, iron saturation is low, retic count is high
D. TIBC is high, ferritin is low, iron saturation is low, retic count is low

Answer

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Question 2

Each of the following are common causes of macrocytosis EXCEPT:

A. Hemolysis
B. Vitamin B12 deficiency
C. Folate deficiency
D. Lead poisoning
E. ETOH use

Answer

Each of the following are common causes of macrocytosis EXCEPT:

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Questions?