ANEMIA

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Choosing Wisely recommendations related to anemia

- Don’t transfuse RBC for iron deficiency without hemodynamic instability
  - Cheaper and safer alternatives exist rather than transfusion in some settings
  - Pre op patients with iron deficiency and patients with chronic iron def. without hemodynamic instability can be treated with iron supplementation
- Don’t perform repetitive CBC and chemistry testing in the face of clinical and lab stability.
  - Repeat phlebotomy is highly associated with changes in hemoglobin level in patients and can contribute to clinically significant anemia
  - Significant cost savings can result for the hospital with eliminating unnecessary daily phlebotomy in stable patients
- Don’t transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g hemoglobin) in a stable non-cardiac patient
  - Avoid routine practice of ordering 2 units of RBC, if 1 unit will be sufficient to reach 7 to 8 g in stable non-cardiac patient

Initial questions to consider in anemic patient (adult)

- Is the patient bleeding now or in the past?
- Is the patient iron deficient? If so, why?
- Is the patient deficient in B12 or folate? If so, why?
- Is there evidence for increased RBC destruction (hemolysis)
- Is the bone marrow suppressed/replaced? If so, why?

Acute and chronic etiology of anemia in adult

- Evaluate acuity/chronicity
  - Acute
    - Blood loss, GI or GYN sites
    - Trauma
    - Hemolysis
    - Acute neoplasm/acute leukemia
  - Chronic disease picture/ persistent anemia
    - Chronic renal disease/elevated creatinine, liver disease
    - Chronic nutritional deficiency (iron, B12, folate)
    - Chronic neoplasm involving blood (chronic leukemia, MDS)

Pathology consult (peripheral smear review)

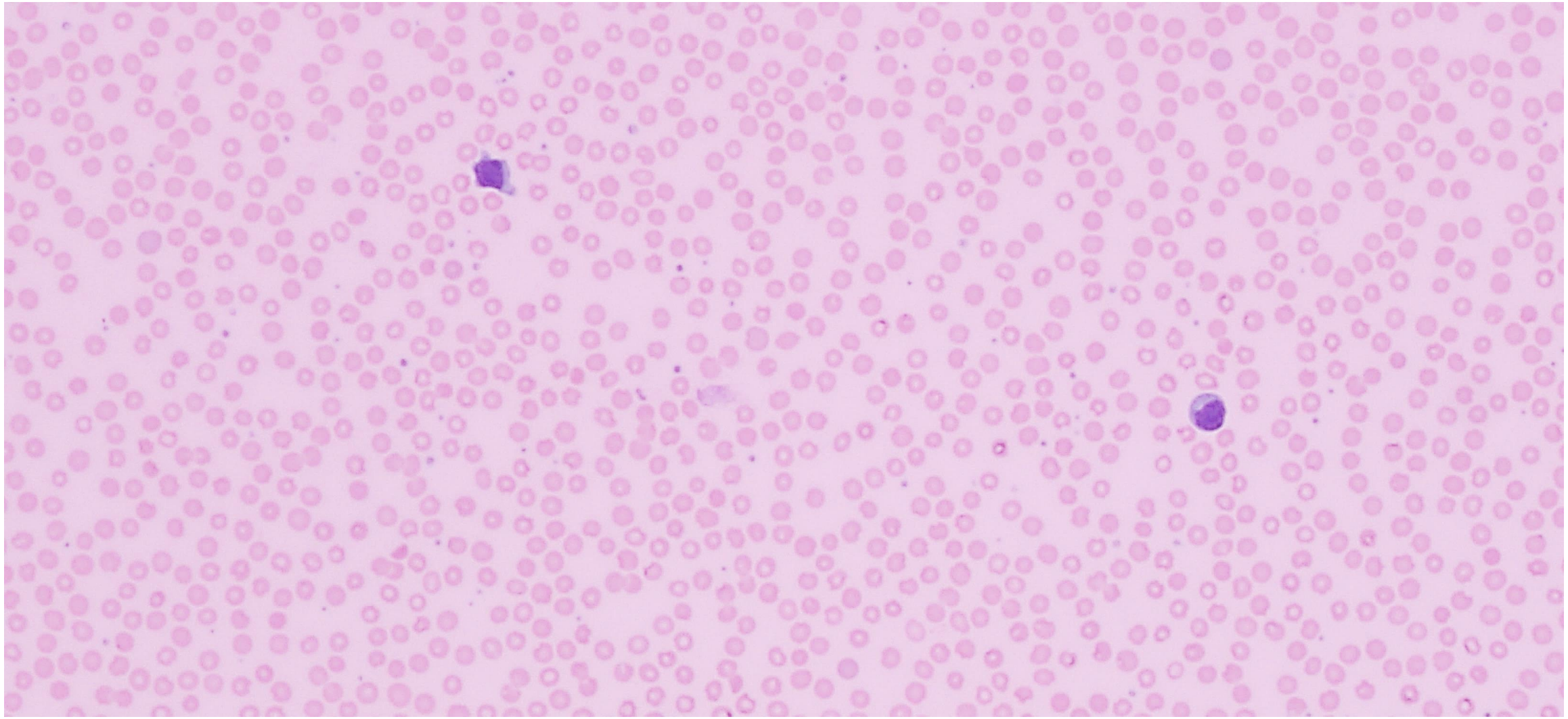
- Important in the initial evaluation of the anemic patient
- Streamlines further lab work up according to findings of blood smear, with suggestions for studies most likely to be diagnostic
- Summarizes CBC trends and available pertinent testing (lab, imaging)
- Provides DDx of most likely etiology of anemia
- Addresses major DDx which may not be evident by numbers on CBC
  - Schistocytes, prominent reticulocytes, nucleated RBC, sickle RBCs
  - Neoplasms, ex. Acute and chronic Leukemia, MDS

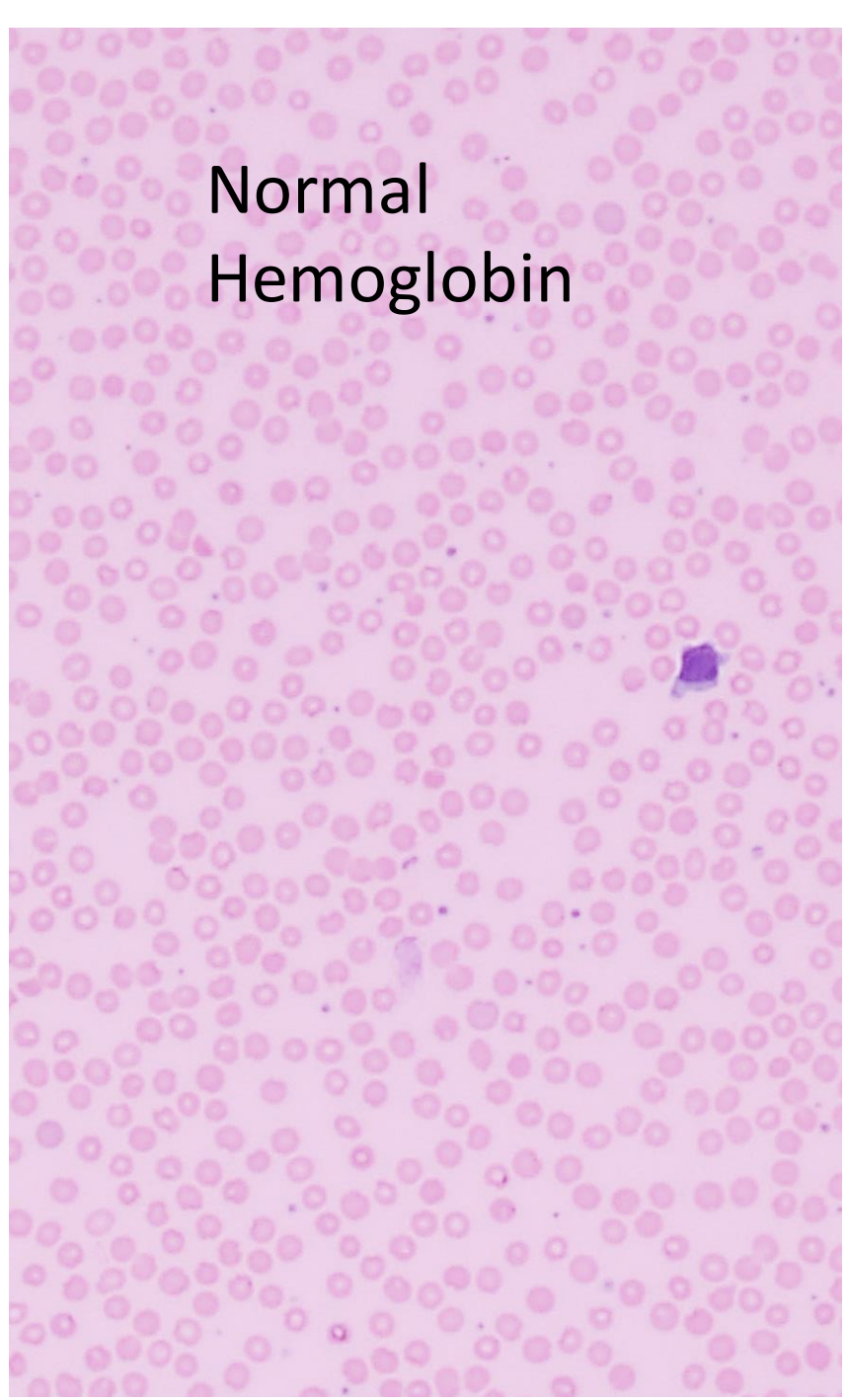
Special considerations in elderly patient

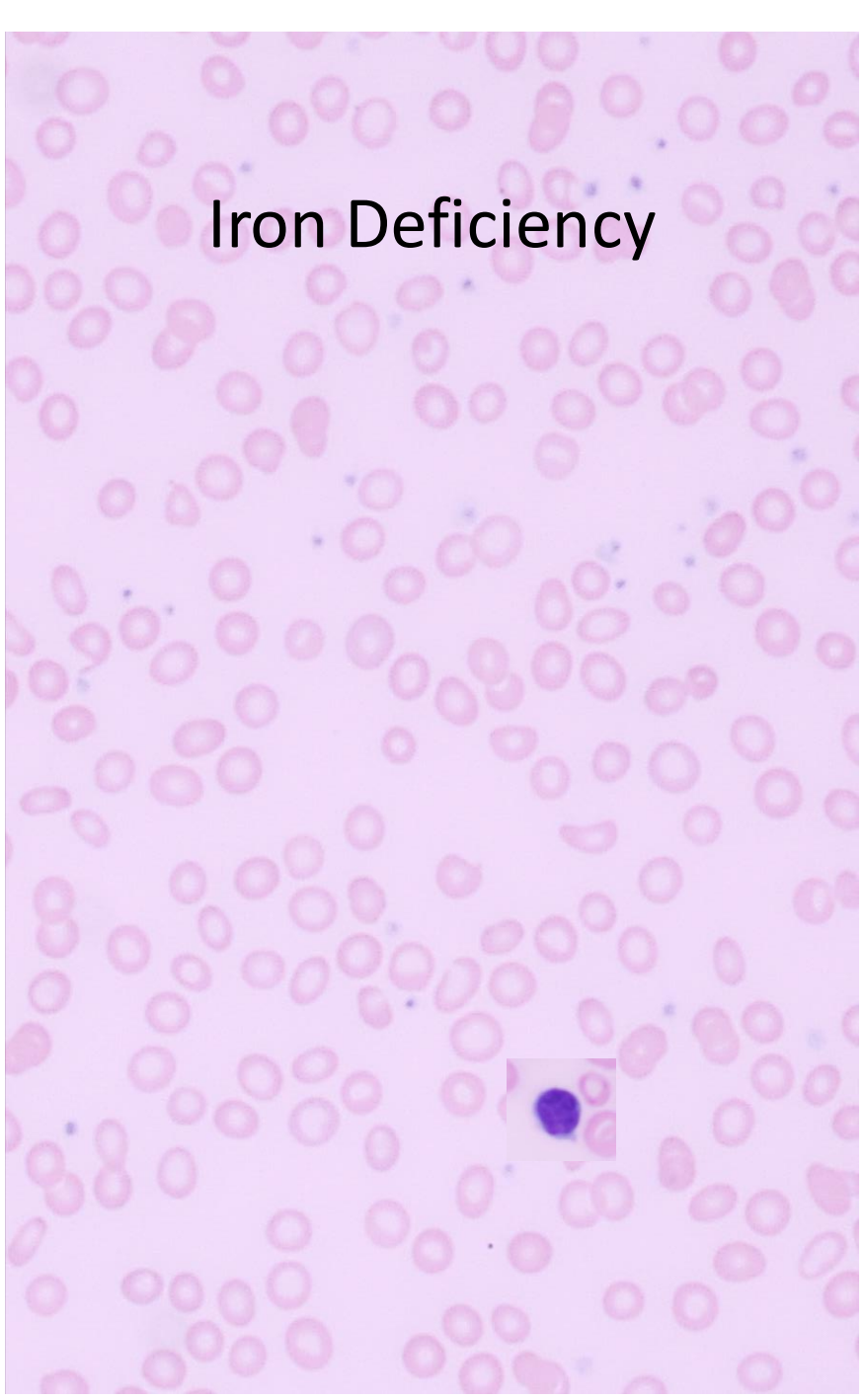
- More likely to be multifactorial
- Etiology of anemia often not evident by looking at CBC indices
  - Example, combined iron deficiency and B12 deficiency may be normocytic
- Requires correlation of clinical picture with lab studies and blood smear
- More likely to show component of chronic disease
  - 1/3 of anemia in elderly has component of anemia of chronic disease
  - Due to chronic renal disease and/or other associated inflammatory conditions
- More likely to show evidence of neoplasm

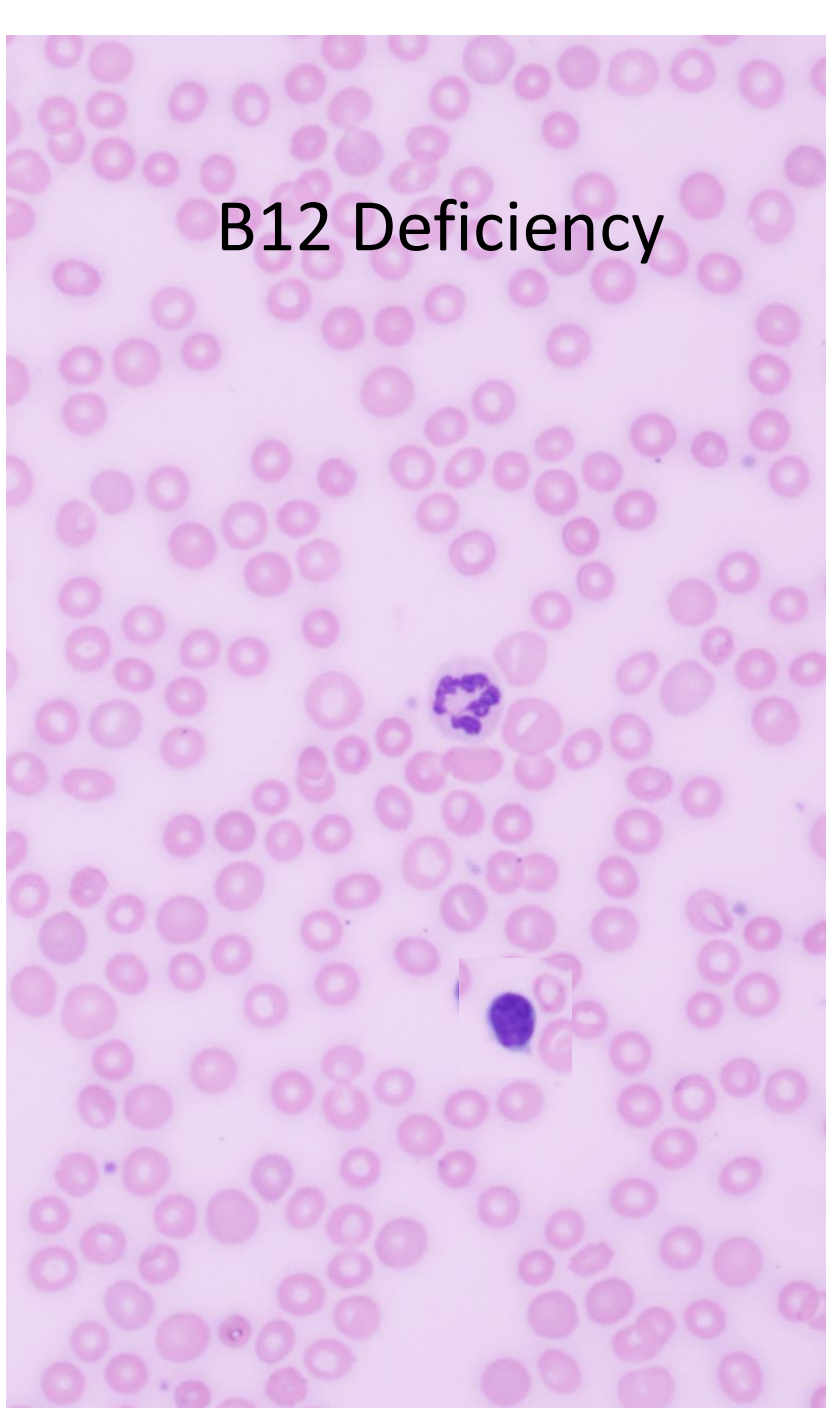
Blood smear negative for anemia

Hemoglobin 12.0 to 16.0
MCV 80 to 100
RDW 11.5 to 14.5



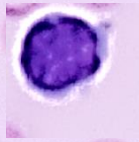

Normal
Hemoglobin


Iron Deficiency


B12 Deficiency

1. Case one: CBC data

- WBC 8
- Hemoglobin 7.5 (12-16)
- Hematocrit 22 (36-46)
- MCV 65 (80-100)
- RDW 20 (11.5-14.5)
- Platelet 450 (140-440)



What tests are most likely abnormal?

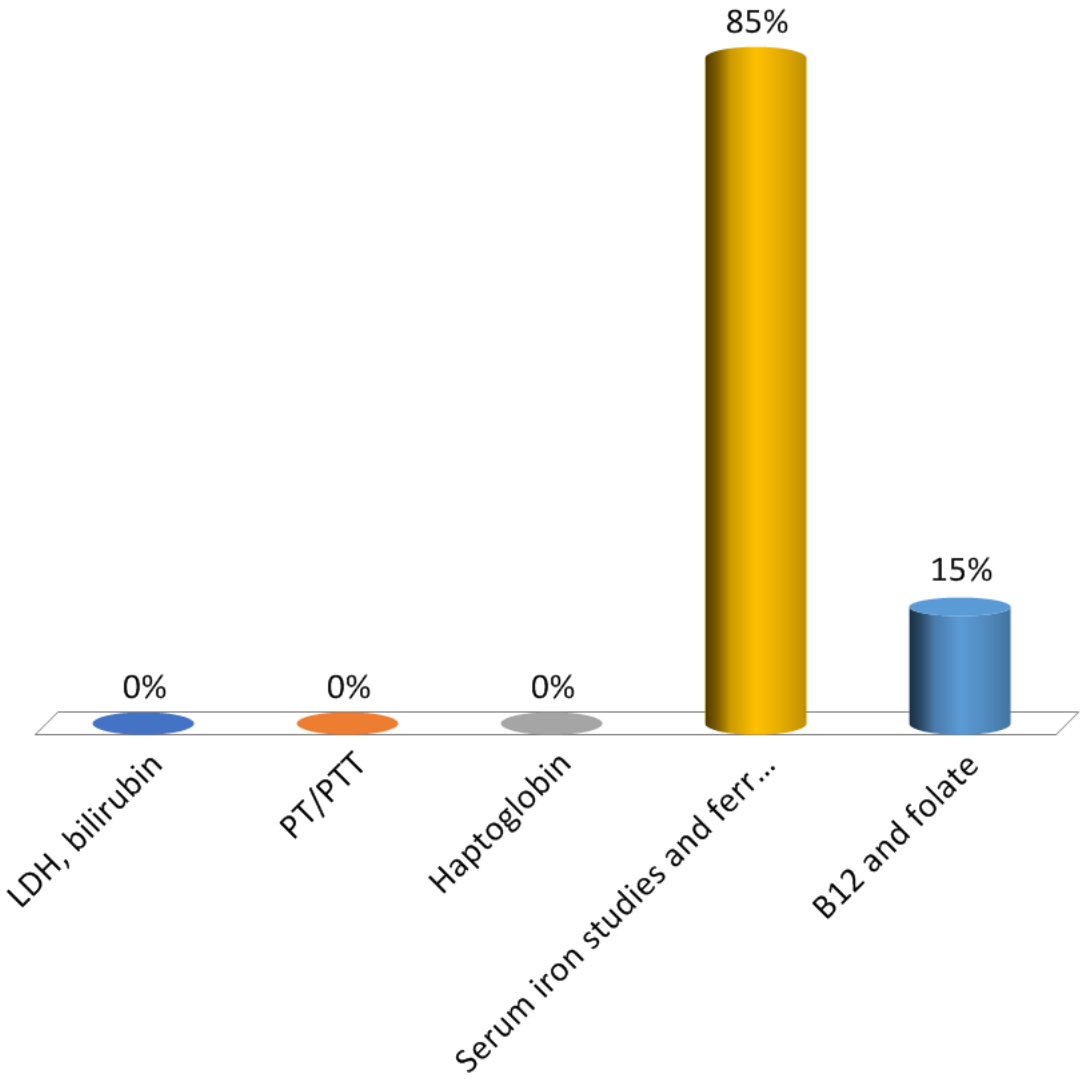
A. LDH, bilirubin

B. PT/PTT

C. Haptoglobin

D. Serum iron studies and ferritin

E. B12 and folate

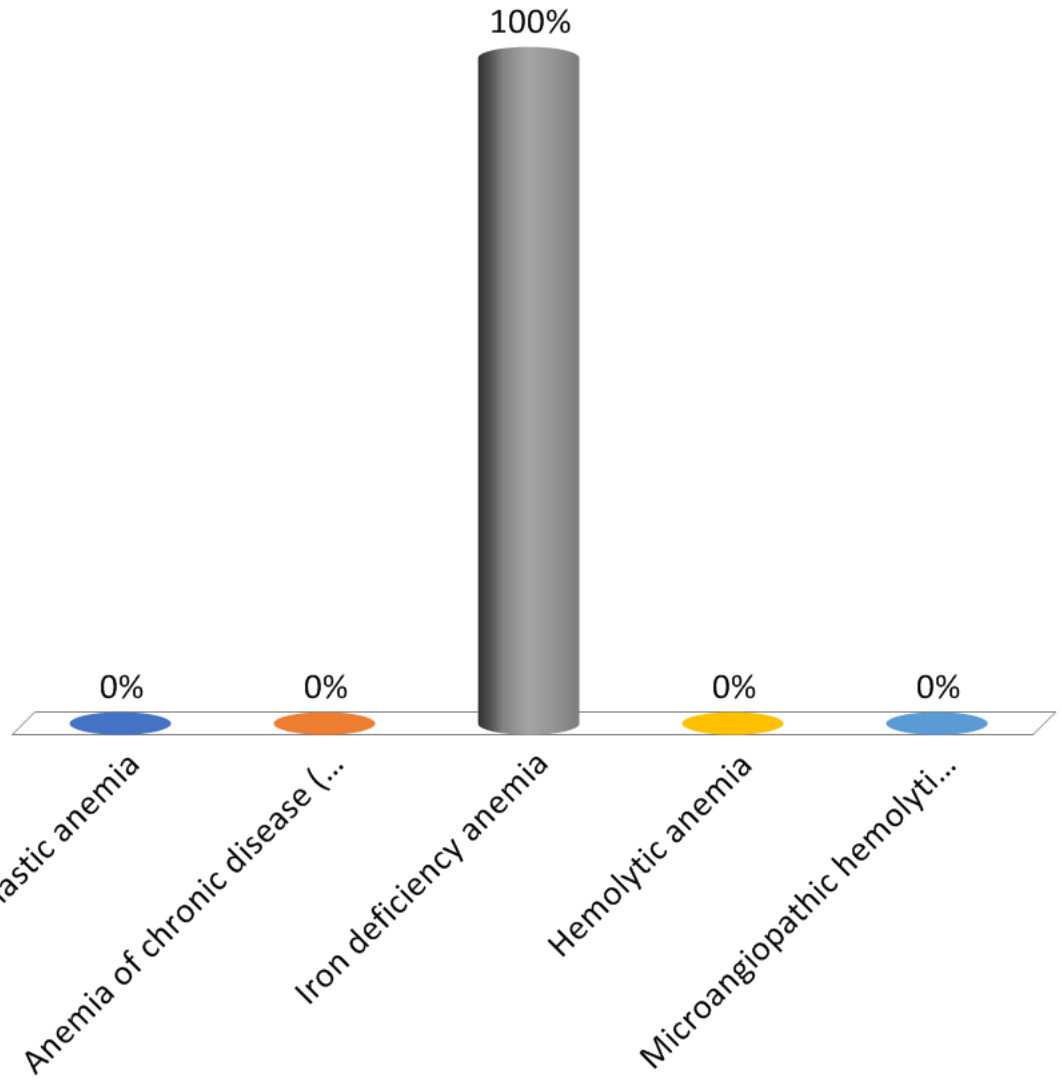


Test results:

- Haptoglobin normal
- LDH normal
- PT/PTT normal
- Serum ferritin 3.3 (11-306)
- Serum iron 11 (28-170)
- TIBC 522 (250-450)
- Transferrin saturation 2.1% (20-50%)
- Creatinine normal
- B12 317 (>300)
- Folate 7.3 (>5.9)

Diagnosis?

A. Megaloblastic anemia
B. Anemia of chronic disease (anemia of inflammation)
C. Iron deficiency anemia
D. Hemolytic anemia
E. Microangiopathic hemolytic anemia



Laboratory findings during the development of iron deficiency

	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Severe iron deficiency with severe anemia
Hemoglobin	Normal range*	Normal range*	**9 to 12 g/dL (90 to 120 g/L)**	**6 to 7 g/dL (60 to 70 g/L)**
Red blood cell size and appearance	Normal	Normal	**Normal or slight hypochromia (slight decrease in MCHC)**	**Microcytosis (decrease in MCV) and hypochromia (decrease in MCHC)**
Serum ferritin	40 to 200 ng/mL (40 to 200 mcg/L; 89.9 to 449 picoM/L)	**<40 ng/mL¶ (<40 mcg/L; <89.9 picoM/L)**	**<20 ng/mL (<20 mcg/L; <45 picoM/L)**	**<10 ng/mL (<10 mcg/L; <22.5 picoM/L)**
Serum iron	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	**<60 mcg/dL (<10.7 microM/L)**	**<40 mcg/dL (<7.1 microM/L**
Total iron-binding capacity (TIBC; transferrin)	300 to 360 mcg/dL (53.7 to 64.4 microM/L)	300 to 390 mcg/dL (53.7 to 69.8 microM/L)	**350 to 400 mcg/dL (62.6 to 71.6 microM/L)**	**>410 mcg/dL (>73.4 microM/L)**
Transferrin saturation (serum iron/TIBC)	20 to 50%	20%	**<15%**	**<10%**
Bone marrow iron stain	Adequate iron present	**Iron absent**	**Iron absent**	**Iron absent**

You suspect Iron deficiency in a 37 year old female with low normal hemoglobin, and iron studies show:

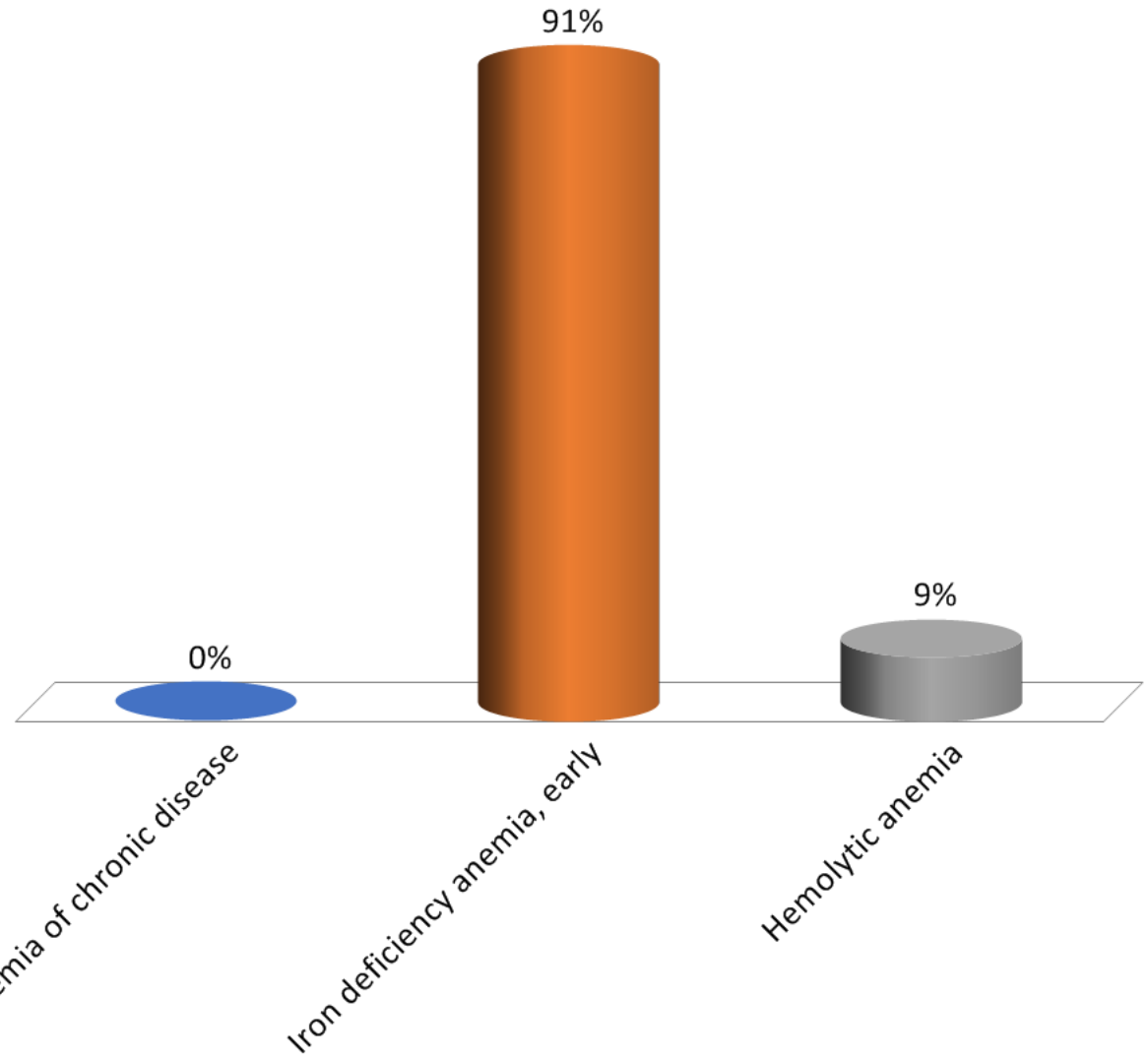
- Serum iron normal
- TIBC mildly elevated to 455
- Transferrin saturation normal

What is Diagnosis?

A. Anemia of chronic disease

B. Iron deficiency anemia, early

C. Hemolytic anemia

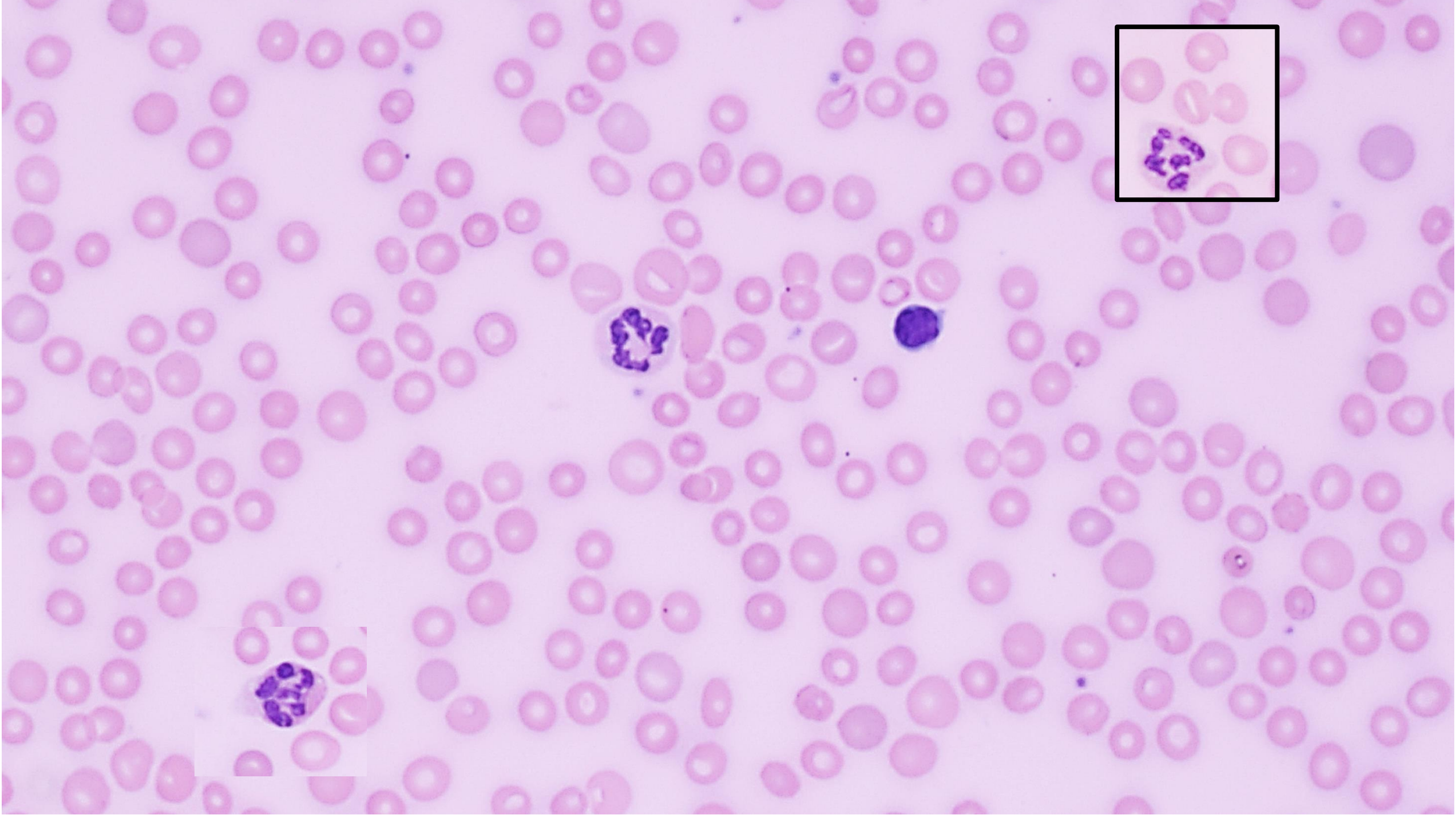


TIBC

- Elevated TIBC is a sensitive indicator of low marrow storage iron, and therefore may be the first sign of early iron deficiency
- It is thought to represent the body's attempt to mobilize iron stores from the bone marrow in an iron deficient state, in order to maintain erythropoiesis
- Elevated TIBC may occur prior to development of anemia, with normal serum iron
- Other conditions with elevated TIBC: pregnancy, oral contraceptive

2. Case two: CBC data

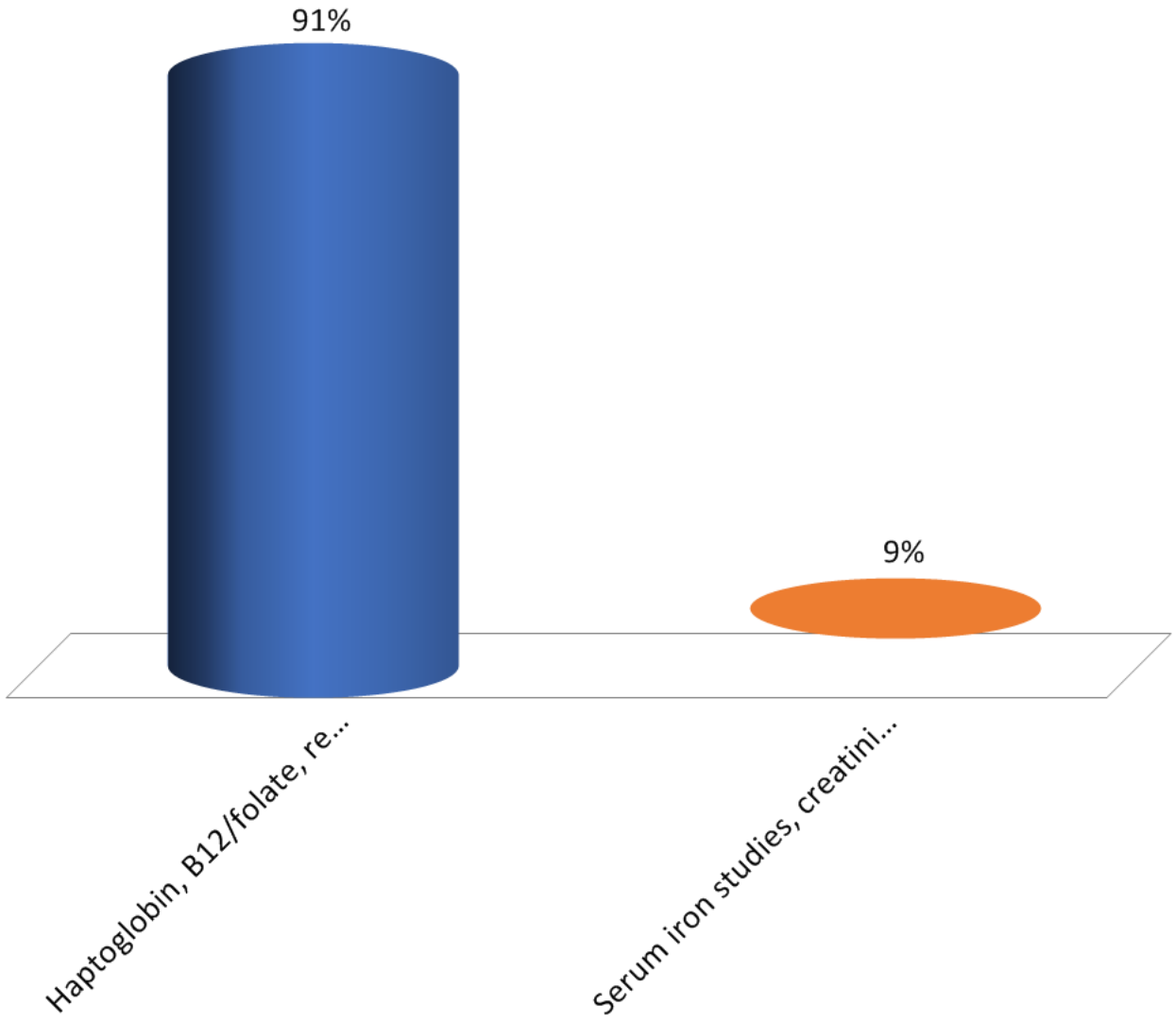
- WBC 5.0
- Hemoglobin 8.1
- Hematocrit 24.4
- MCV 101.4
- RDW 24.9
- Platelets 70



What is most likely to be abnormal in a macrocytic anemia?

A. Haptoglobin, B12/folate, reticulocyte index

B. Serum iron studies, creatinine, erythropoietin



Macrocytic RBC ddx

- Megaloblastic anemia (B12 and or folate deficiency)
- Hemolysis, due to reticulocytosis and nucleated RBCs
- Myelodysplasia
- Macrocytic RBC may occur with or without anemia in significant alcohol use, in hypothyroidism, and with certain medications (chemotherapy or HAART therapy in HIV patients)
- Spurious macrocytosis (cold agglutinins due to RBC doublets in subclinical hemolysis, hyperglycemia due to osmotic dysequilibrium)

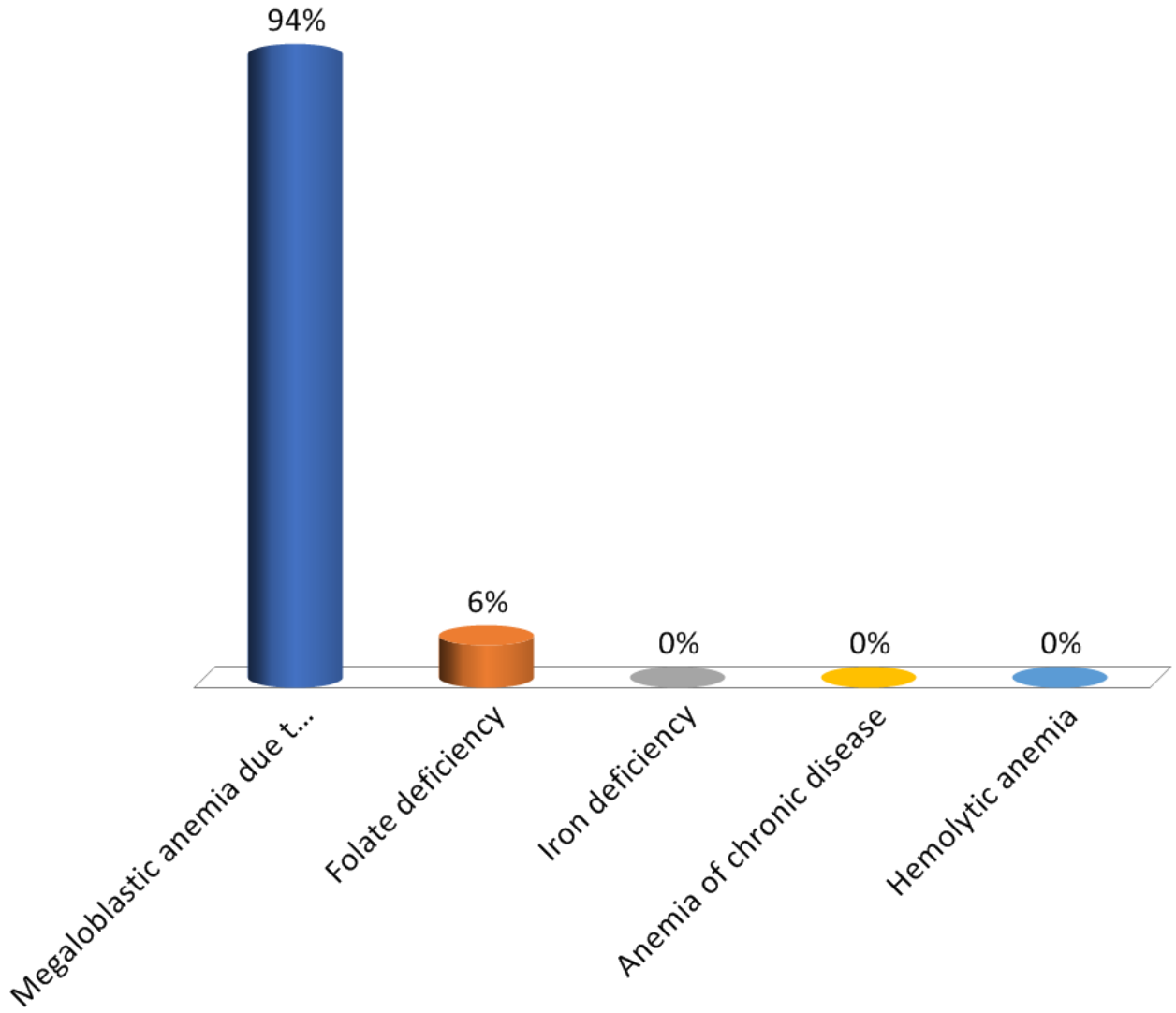
- Iron deficiency or anemia of chronic disease microcytic or normocytic

Lab results of this case:

- B12 150 (normal >200)
- Folate 10 (normal >5.9)
- Serum iron studies normal
- Creatinine normal
- Haptoglobin, LDH, bilirubin normal

Diagnosis?

A. Megaloblastic anemia due to B12 deficiency
B. Folate deficiency
C. Iron deficiency
D. Anemia of chronic disease
E. Hemolytic anemia



B12 /folate deficiency

- Causes isolated anemia, or multilineage cytopenias
- B12 deficiency – years to develop, often strict vegans, or autoimmune atrophic gastritis with impaired absorption of B12, celiac disease, IBD, bariatric surgery
- Folate deficiency – weeks to months to develop, alcohol abuse or poor diet
- Typically macrocytic, may be normocytic especially if combined with other factors (iron deficiency or chronic disease)
- RBC count is low, RDW is high, hypersegmented neutrophils seen
- Can present subtly, with low normal B12/folate levels

Borderline or low normal B12 level

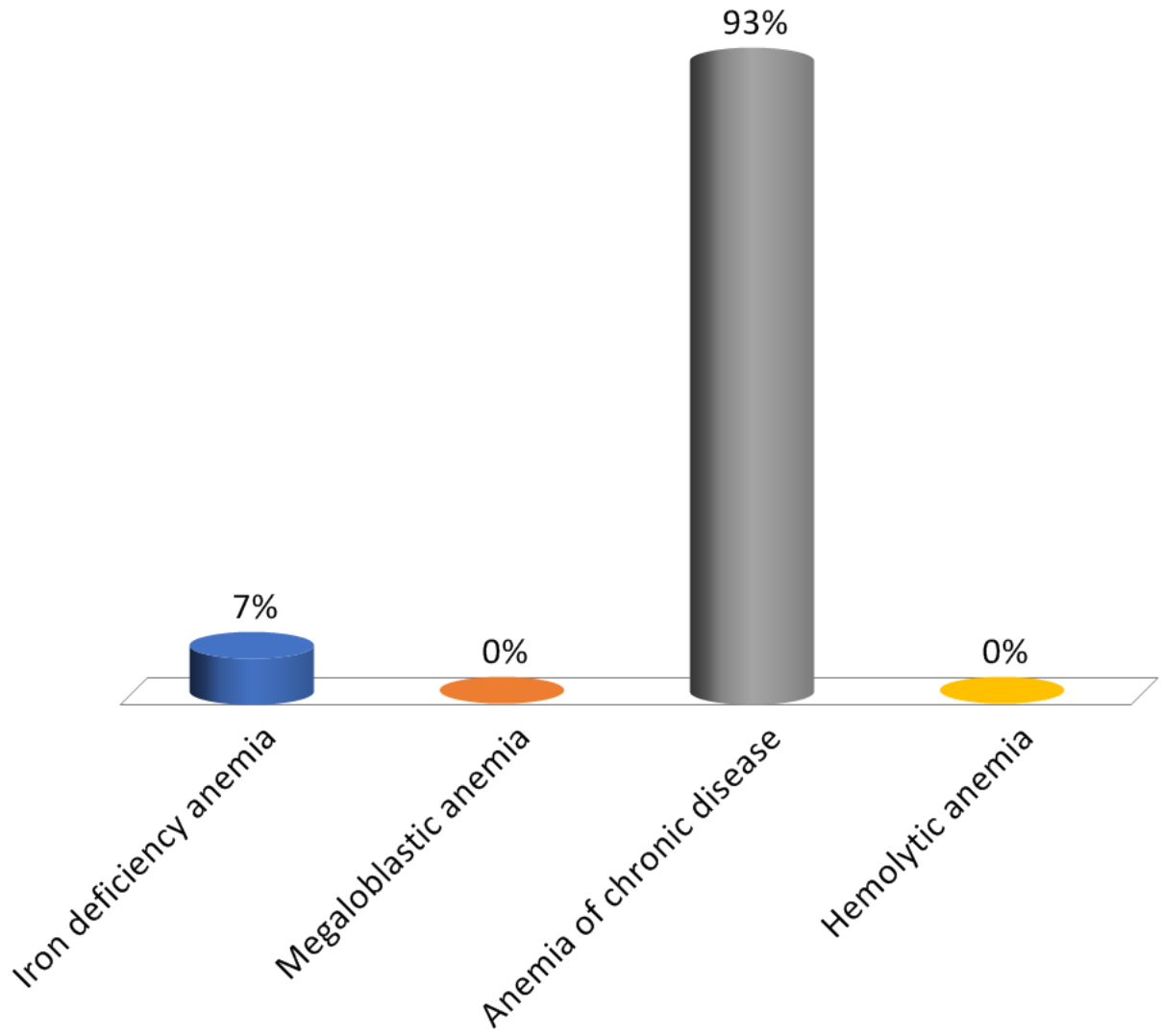
- Methyl malonic acid (MMA) and homocysteine (HC) recommended
- MMA and HC elevated –
  - deficiency of B12 present, folate deficiency not excluded
- MMA normal, HC elevated –
  - consistent with folate deficiency, not B12 deficiency
- MMA and HC normal –
  - no evidence B12 or folate deficiency

3. Case three: CBC data

- WBC 5.5
- Hemoglobin 10.5 (mild anemia)
- Hematocrit 32
- MCV 92 (normocytic)
- RDW 13 (normal)
- Platelet 143

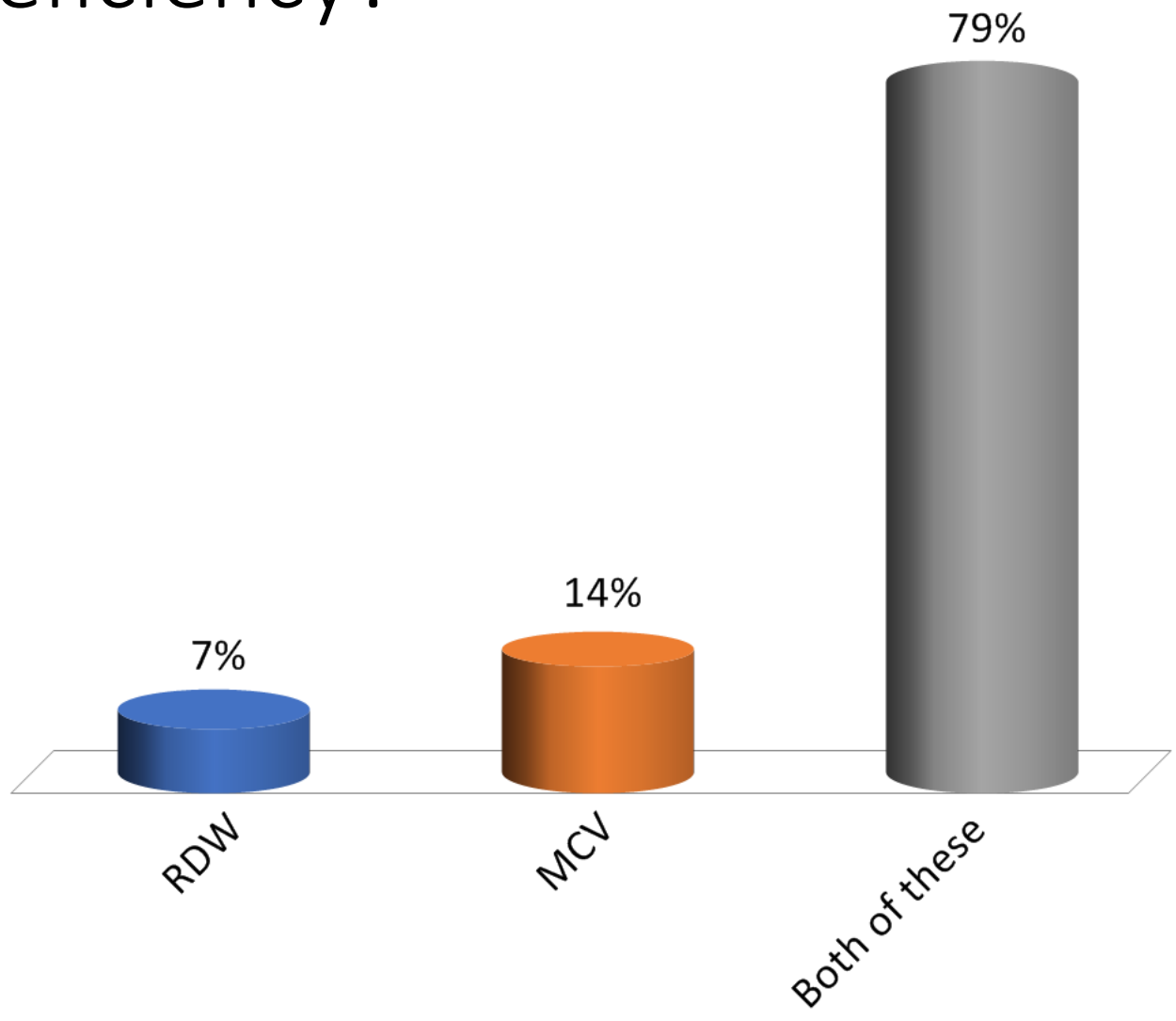
What is most likely diagnosis?

A. Iron deficiency anemia
B. Megaloblastic anemia
C. Anemia of chronic disease
D. Hemolytic anemia



What parameter(s) in the CBC is typically normal in anemia of chronic disease and abnormal in both iron deficiency and B12 deficiency?

A. RDW
B. MCV
C. Both of these

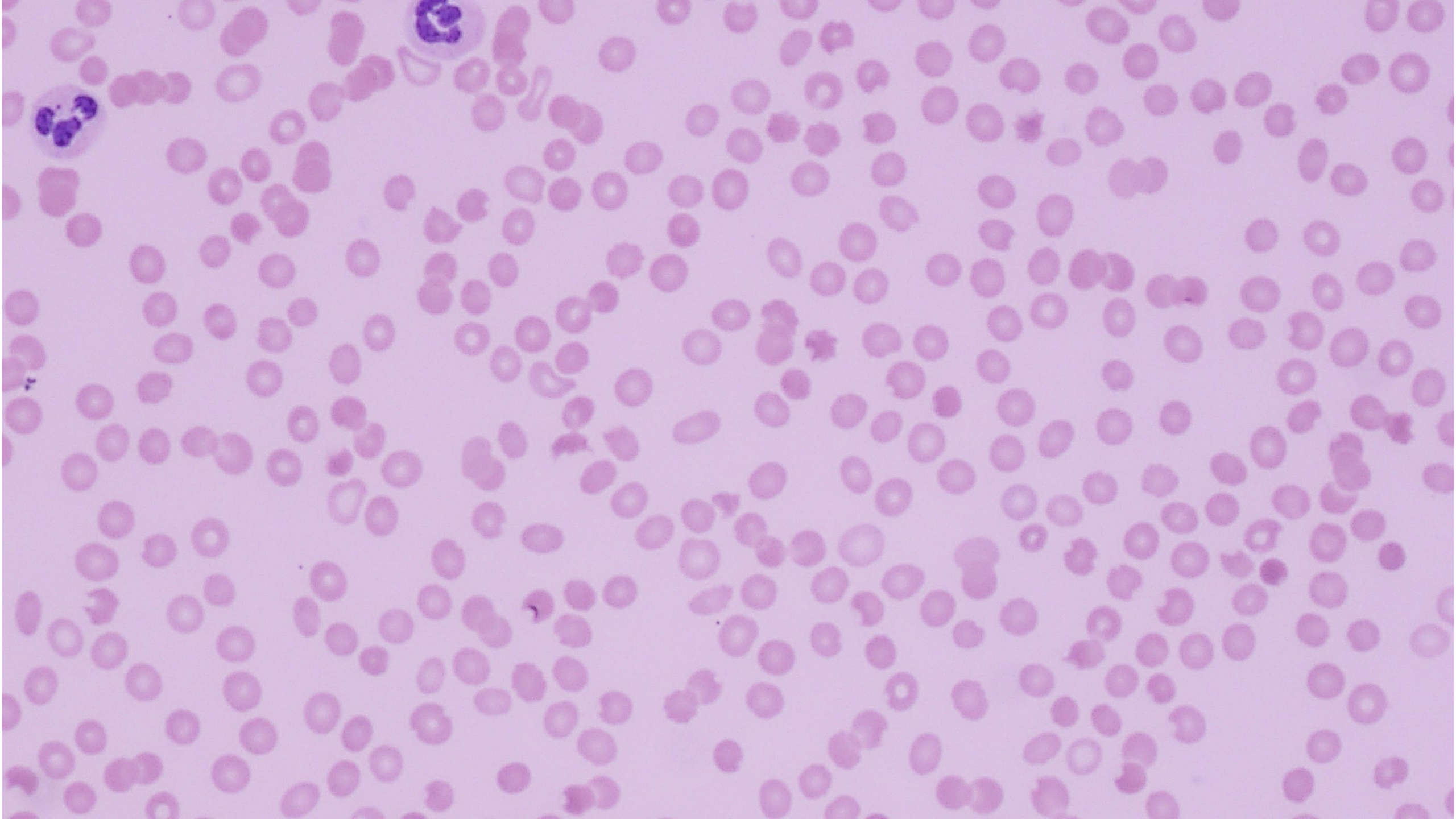


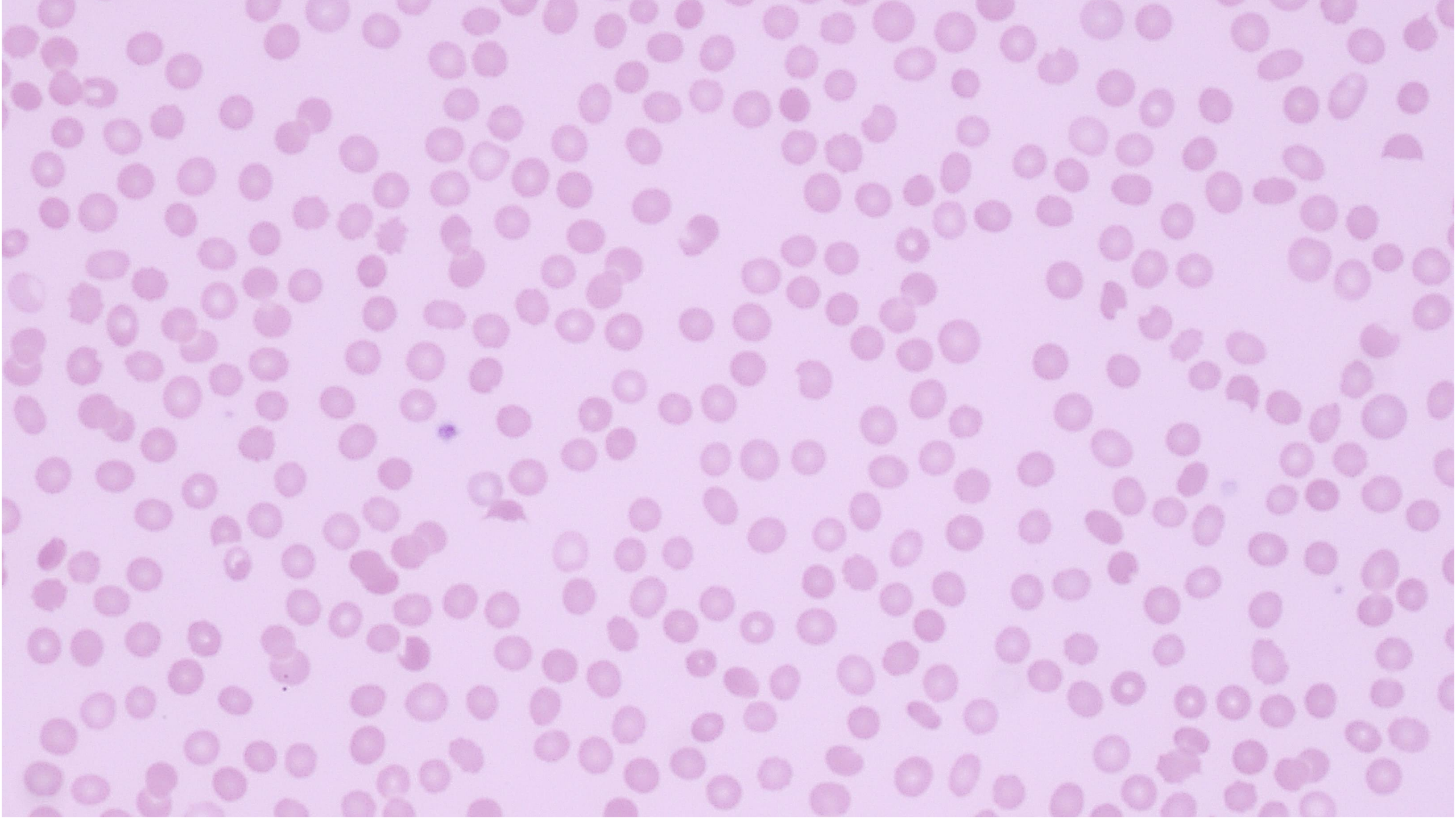
Anemia of chronic disease (ACD)

- Reduced RBC production by bone marrow
- Component of reduced RBC survival
- Relative decrease in erythropoietin production in response to anemia
- Associated with large number of conditions
- ACD degree of anemia usually mild
- 20% ACD may be severe, with lowered trans. sat 10% in the range of iron deficiency, and may be combined with iron deficiency
- Blood smear hypochromia and reticulocytosis can be helpful to suggest superimposed iron deficiency

4. Case four: CBC data

- WBC normal
- Hemoglobin 10.6
- MCV 90.8
- RDW 13.5
- Platelets 45,000



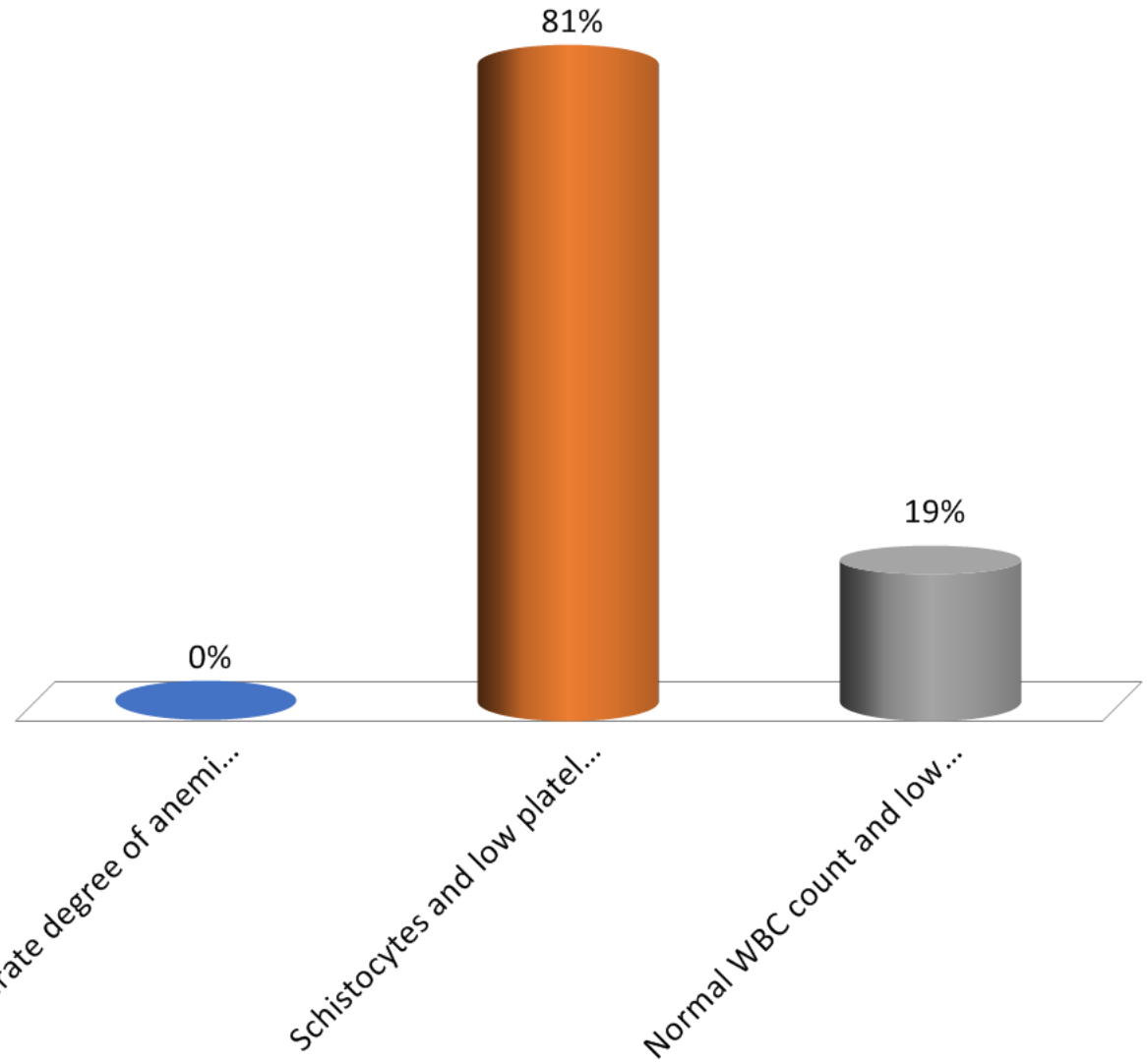


What are the 2 most important clues from CBC and smear for the diagnosis?

A. Moderate degree of anemia and normal MCV

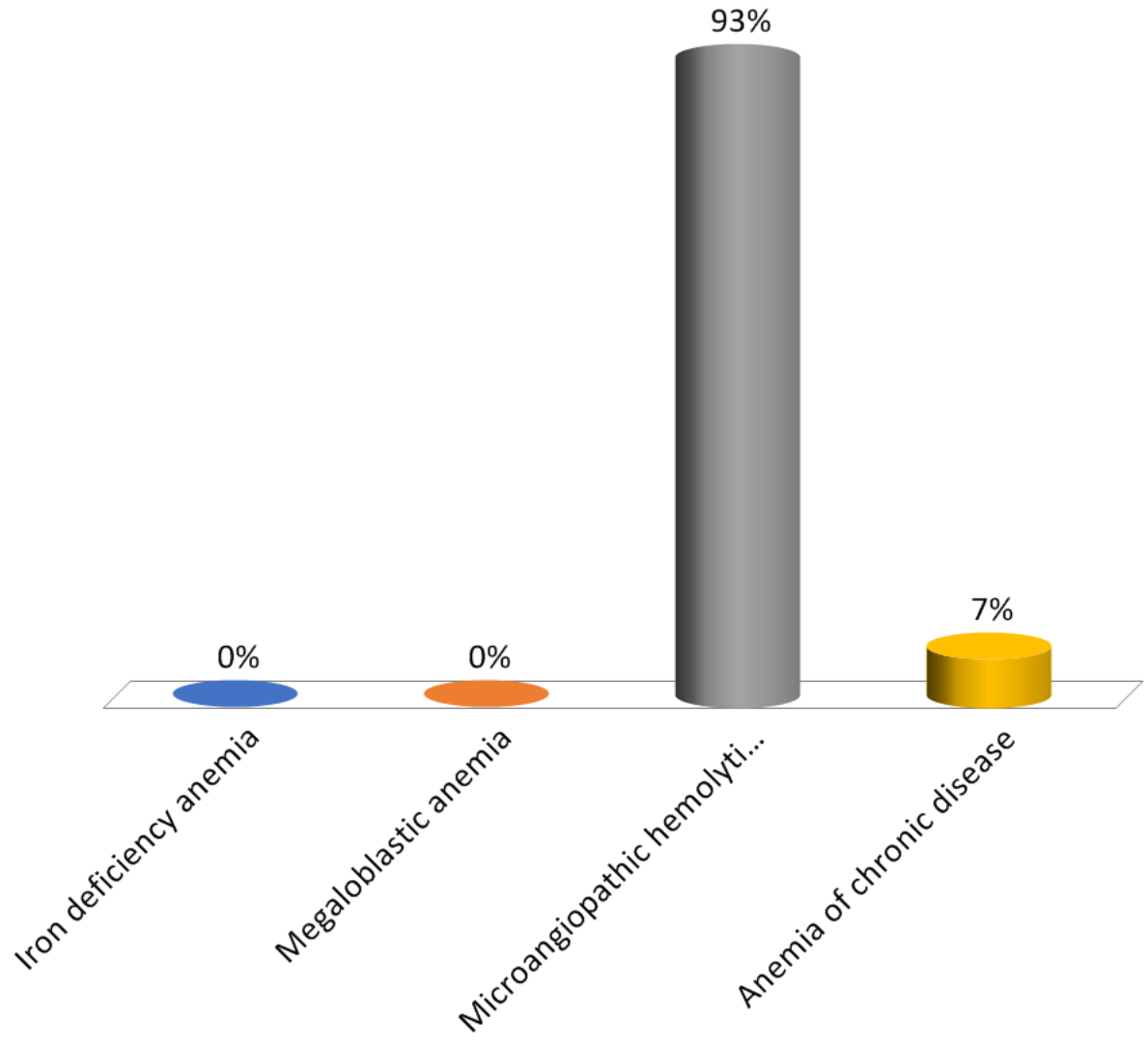
B. Schistocytes and low platelets

C. Normal WBC count and low platelets



Most likely diagnosis?

A. Iron deficiency anemia
B. Megaloblastic anemia
C. Microangiopathic hemolytic anemia
D. Anemia of chronic disease



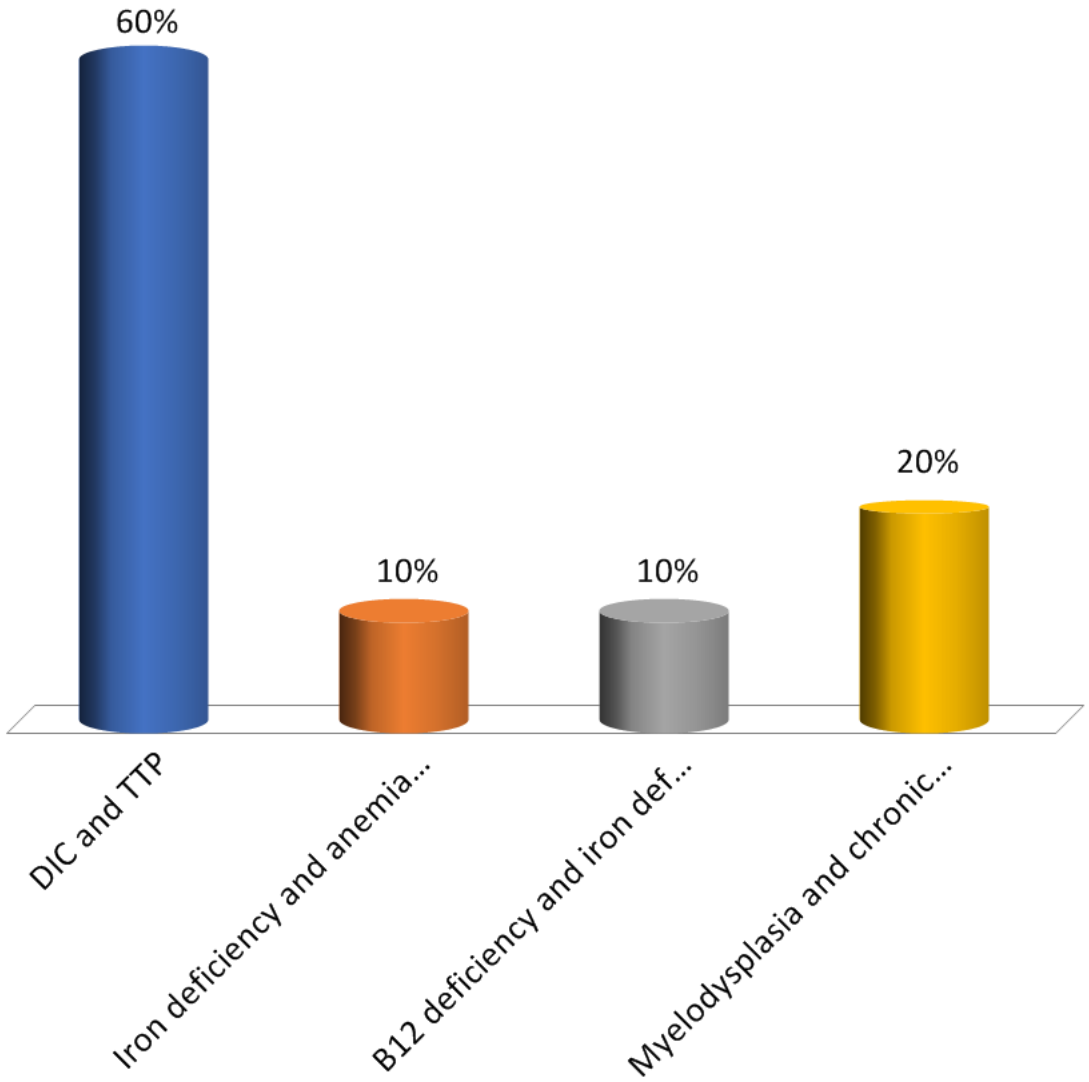
Microangiopathic Hemolytic Anemia (MAHA)/ and Thrombotic microangiopathy (TMA)

- Descriptive term for non-immune hemolytic anemia resulting from intravascular RBC fragmentation that produces schistocytes, and typically has low platelets
  - Schistocyte – fragmented RBC, often with jagged irregular shape, lacking central pallor

- Can be broadly divided into 2 groups:
  - Primary thrombotic microangiopathies (TMA)
    - TTP Thrombotic Thrombocytopenic Purpura (hereditary or acquired)
    - HUS Hemolytic Uremic Syndrome, Shiga toxin mediated
    - Drug induced TMA
    - Complement mediated TMA (hereditary or acquired)
    - Rare hereditary disorders of vitamin B12 metabolism or factors in hemostasis
  - Systemic disorders resulting in MAHA and thrombocytopenia
    - DIC
    - Severe hypertension
    - Pregnancy associated syndromes (severe pre-eclampsia/HELLP syndrome)
    - Systemic malignancy or infection
    - Autoimmune disorders such as Lupus
    - Complications of stem cell or solid organ transplantation

Which of these pairs present as MAHA?

A. DIC and TTP
B. Iron deficiency and anemia of chronic disease
C. B12 deficiency and iron deficiency
D. Myelodysplasia and chronic disease

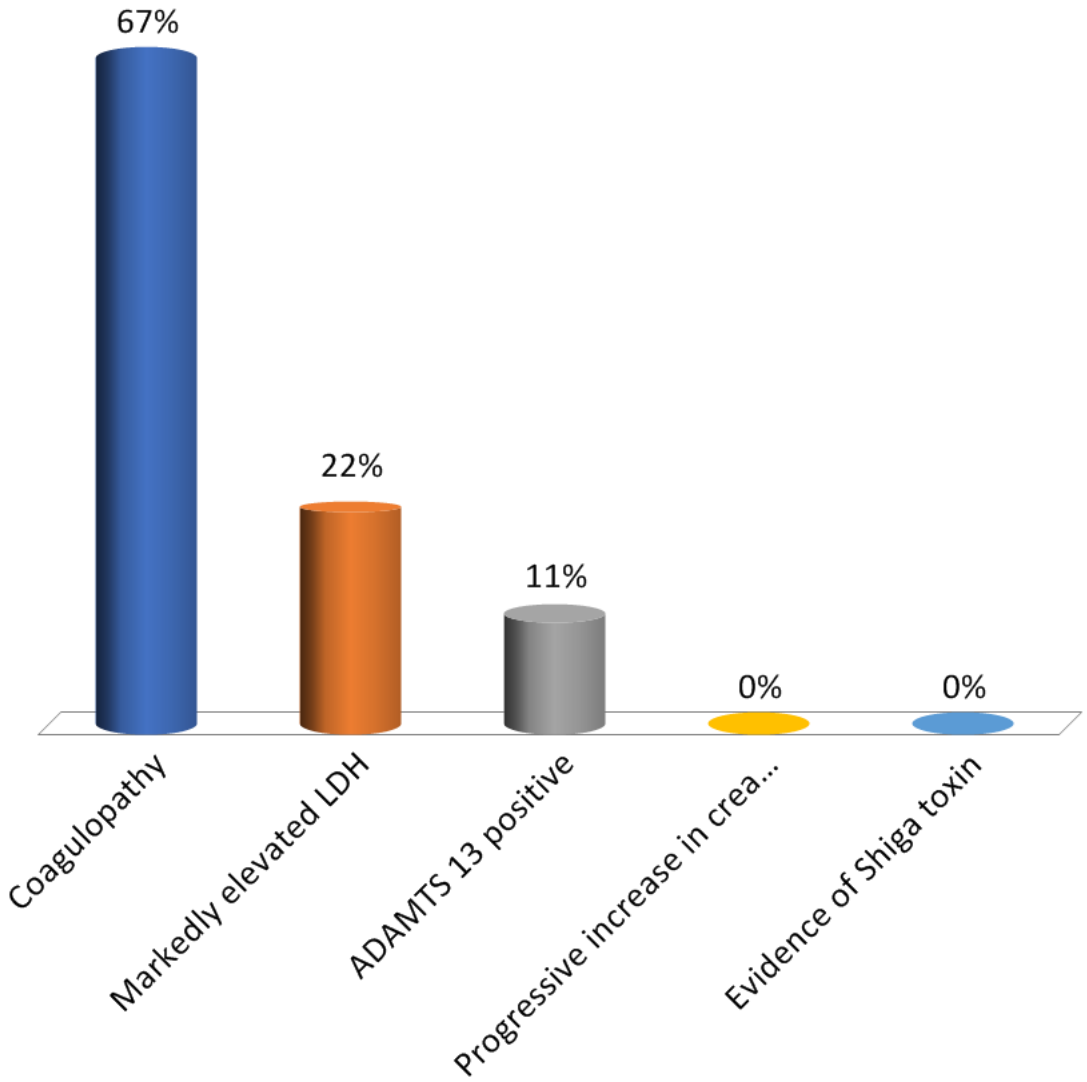


Most important labs to distinguish DIC from TTP/HUS

- LDH – usually extremely high in TTP/HUS, reflecting both hemolysis and tissue damage due to systemic ischemia
- PT/PTT – prolonged in DIC due to activation of coagulation, not in TTP
- Fibrinogen – low in DIC due to activation of coalgulation, not in TTP
- Creatinine – Renal insufficiency common in TTP, however may be mild whereas in HUS and atypical forms of HUS, acute renal failure more common

Which of the following is present in DIC, but not in TTP/HUS?

A. Coagulopathy
B. Markedly elevated LDH
C. ADAMTS 13 positive
D. Progressive increase in creatinine and mental status changes
E. Evidence of Shiga toxin



DIC versus TTP

- DIC will have coagulopathy
  - Elevated PT/PTT
  - Low fibrinogen
  - Associated conditions typically triggering DIC (infection, drug)
- TTP/HUS typically normal fibrinogen, normal PT/PTT
- Other bullet points in this question are features of TTP or HUS

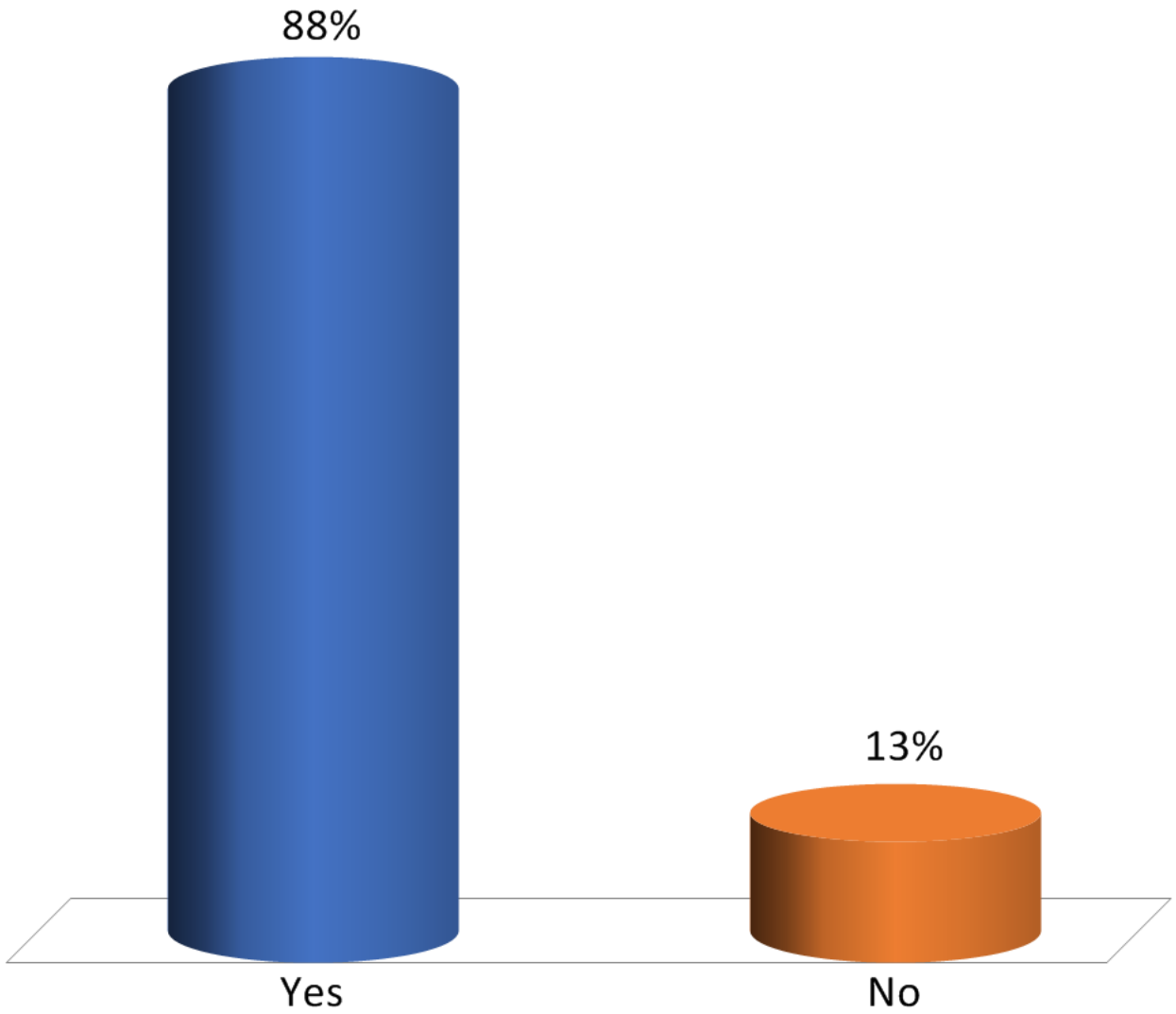
Here are labs found on our patient with blood smear showing schistocytes:

- Marked elevation LDH 1000
- Normal fibrinogen
- Normal PT/PTT
- Low haptoglobin
- Elevated Creatinine

Is the likely diagnosis TTP/HUS?

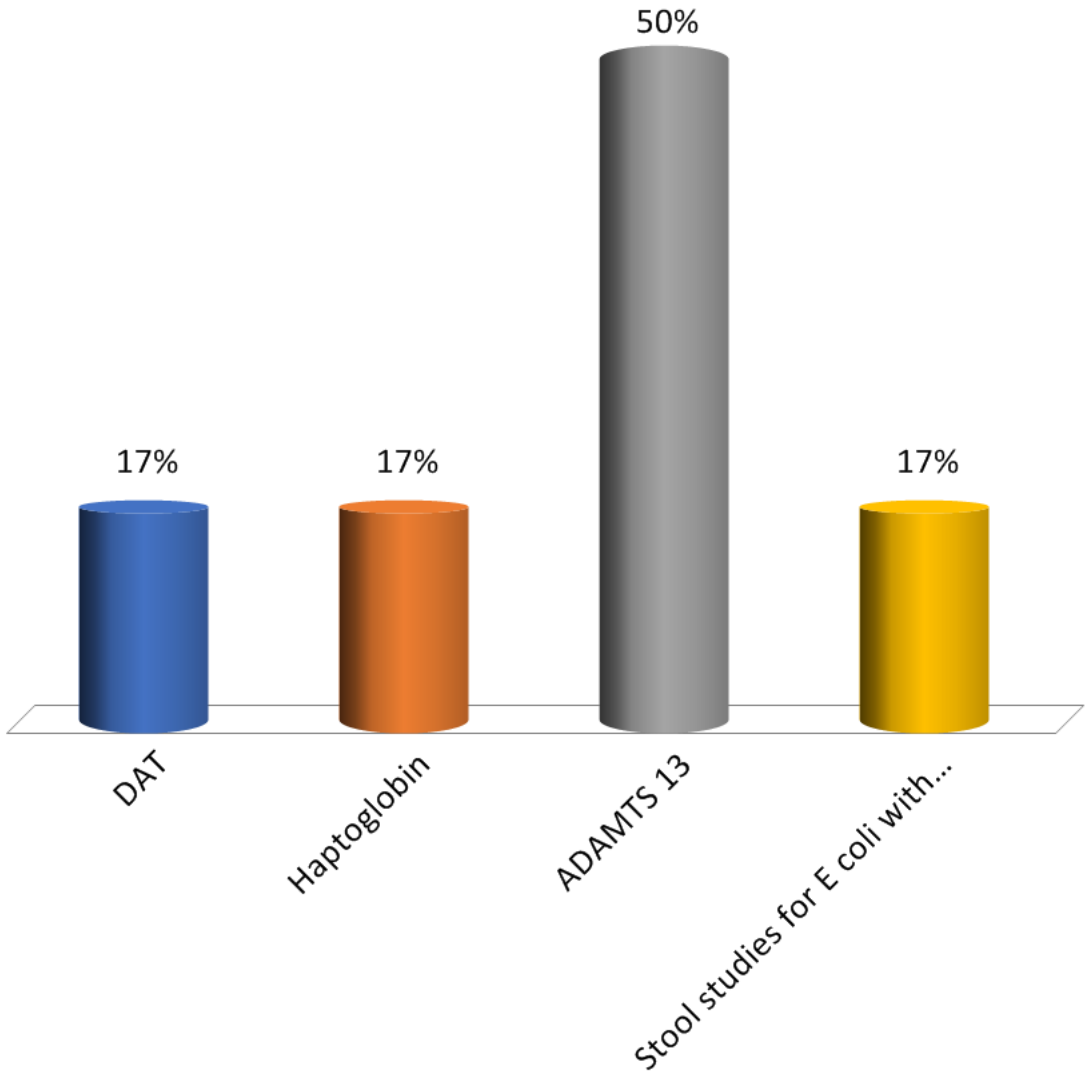
A. Yes

B. No



What is next lab study needed to confirm the diagnosis?

A. DAT
B. Haptoglobin
C. ADAMTS 13
D. Stool studies for E coli with immunoassay for Shiga toxin

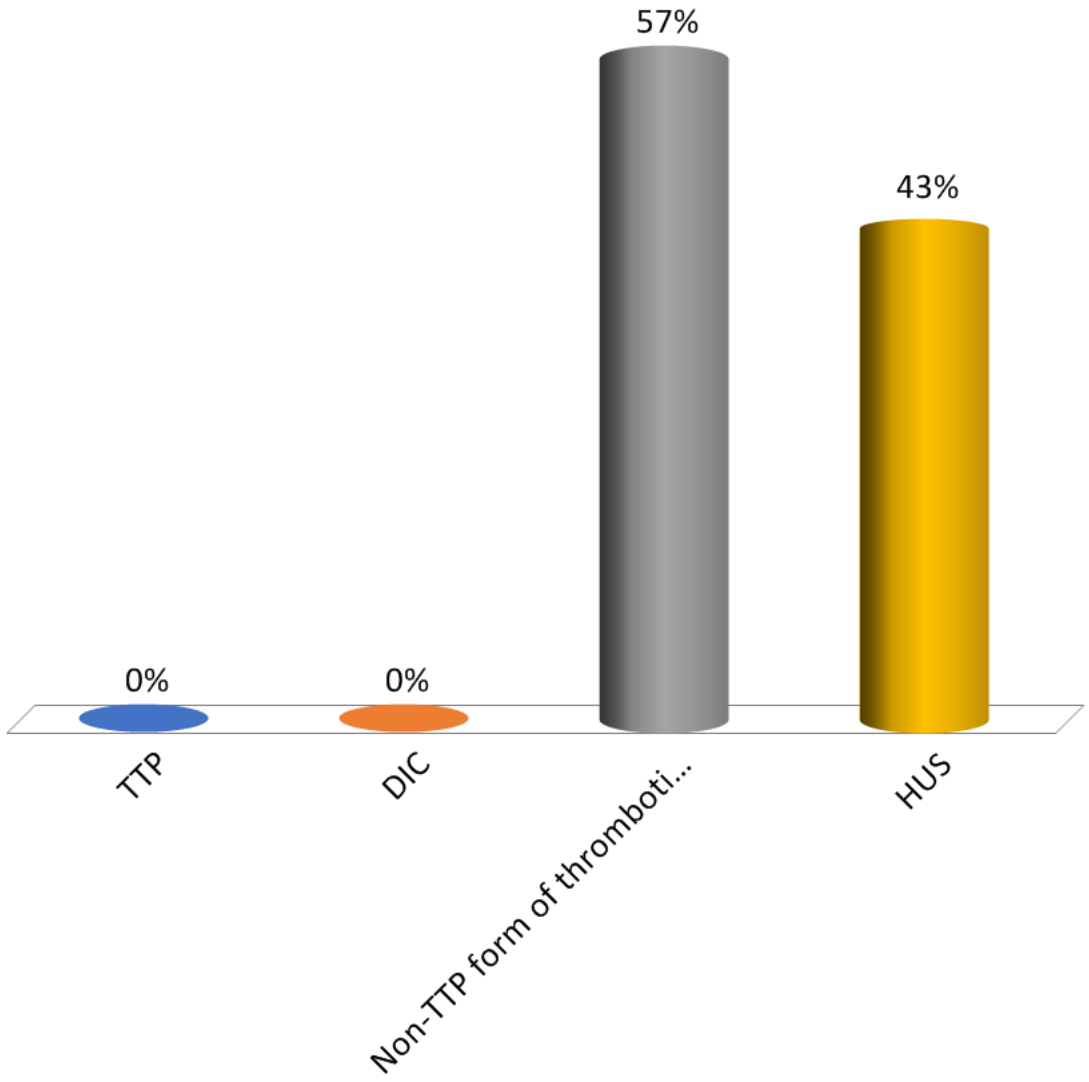


Patient case:

- Adult male patient
- Moderate anemia, low platelets which decreased (by 1/2) in 3 days
- Elevated LDH to 1000
- Creatinine increase from normal to 3.5 in 3 days
- Low haptoglobin
- Normal PT/PTT and fibrinogen
- Schistocytes on blood smear
- Likely TTP, testing for ADAMTS13 sent out
- Patient transferred to outside institution for plasma exchange

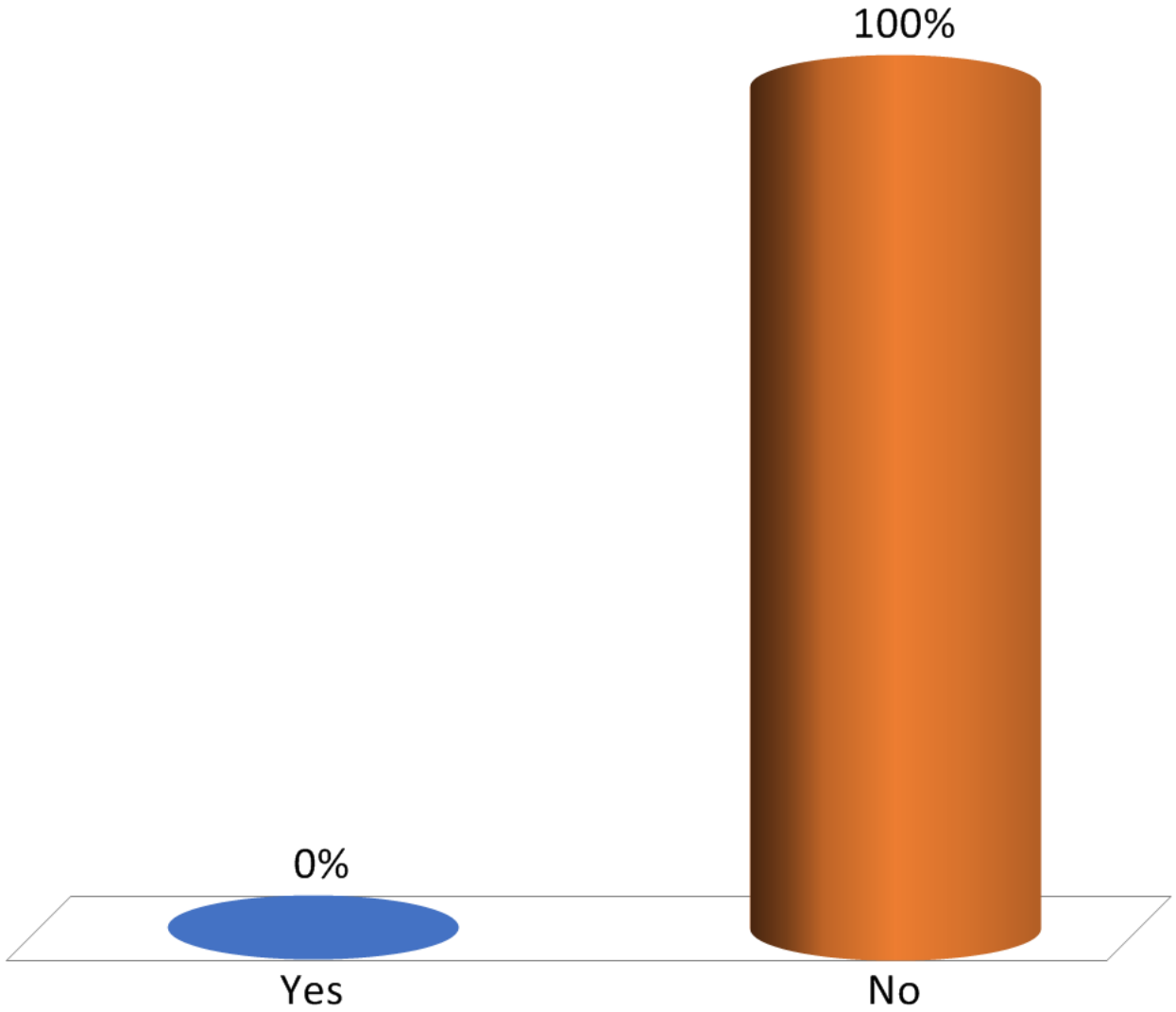
ADAMTS 13 testing comes back (-). What is now the likely diagnosis?

A. TTP
B. DIC
C. Non-TTP form of thrombotic microangiopathy
D. HUS



Will plasma exchange hurt patient in non-TTP form of thrombotic microangiopathy?

A. Yes
B. No

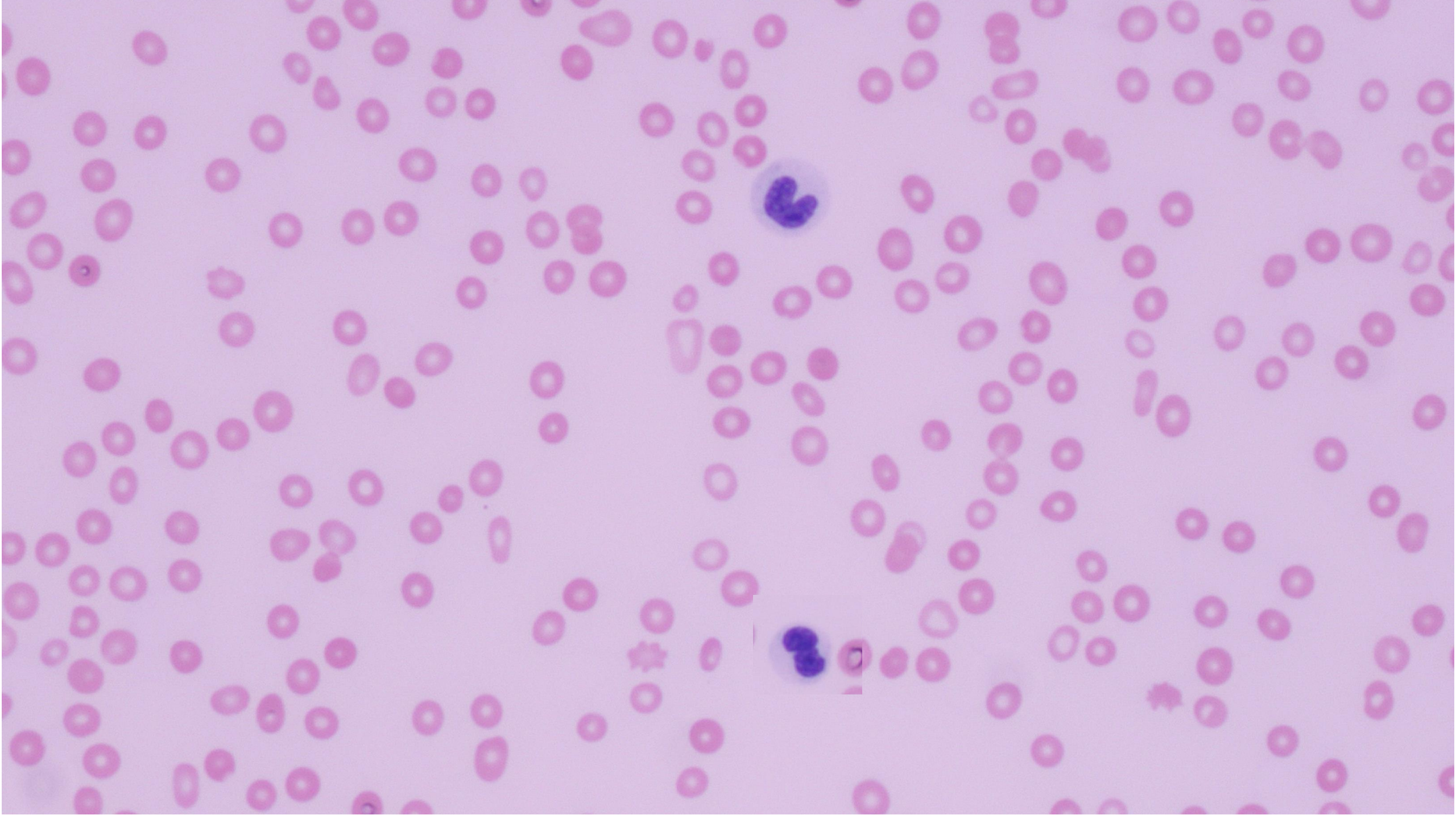


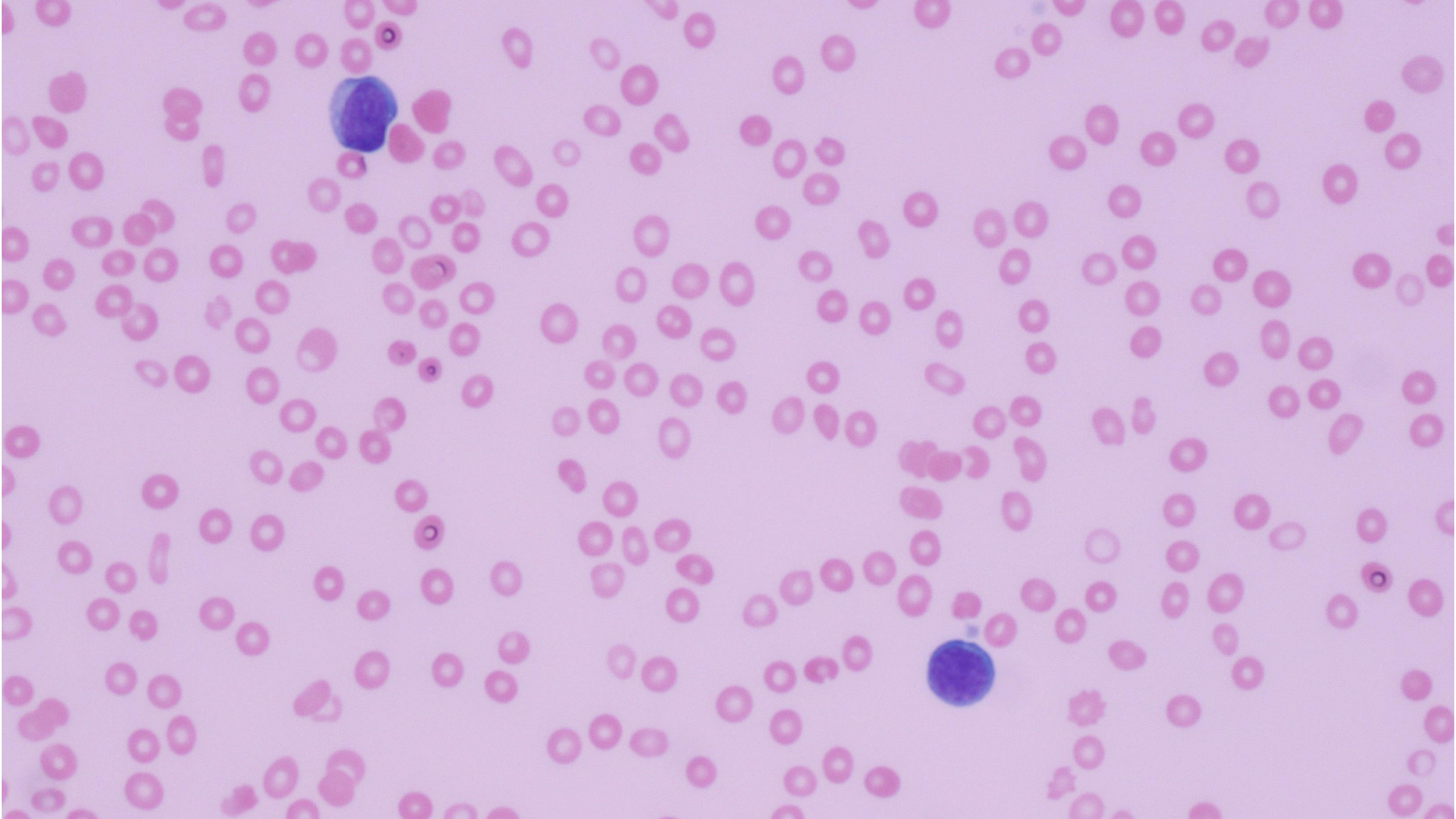
Feature	Pre-Eclampsia		Eclampsia	TTP	HUS		DIC	ITP
	Mild Typical	Severe, HELLP			Typical	Atypical		
High Risk Patients	Pregnancy or recently delivered patients			Adults	Children	Adults	Sepsis	Young female
MAHA	No	ALWAYS	No	ALWAYS	ALWAYS	ALWAYS	Yes	No
Low Platelets	Yes	ALWAYS	Yes	ALWAYS	Yes	Yes	Yes	ALWAYS
Liver inflam	Yes	ALWAYS	Yes	No	No	No	No	No
Coagulation activation	No	No	No	No	No	No	ALWAYS	No
Neurologic symptoms	Yes	Yes	ALWAYS	ALWAYS	Yes	Yes	No	No
Renal dysfunction	ALWAYS	Yes	ALWAYS	Yes	ALWAYS	ALWAYS	No	No
Hypertension	ALWAYS	Yes	ALWAYS	No	No	No	No	No

5. Case five: CBC data

- Pancytopenia

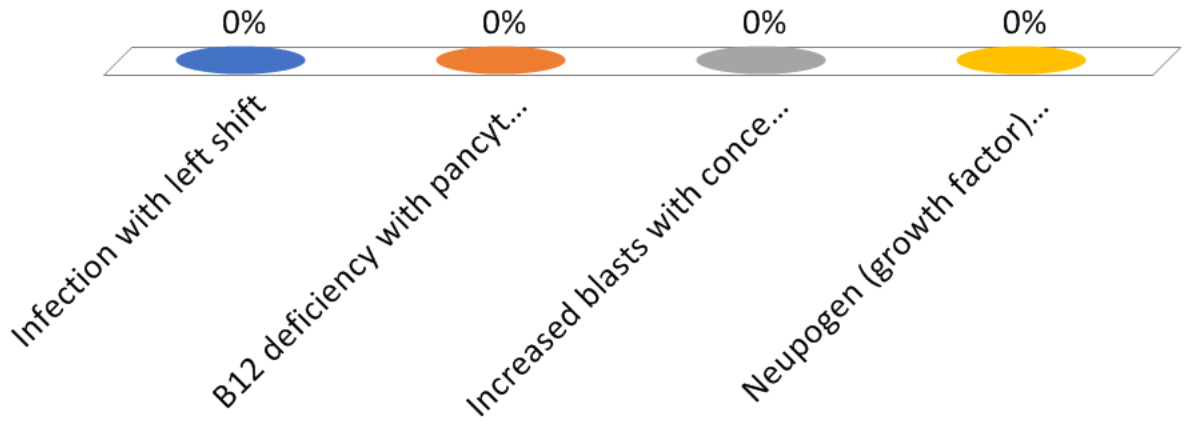
- WBC 4.1 (normal 4.5 - 11)
- Neutrophils 1.2 (normal 1.8 - 7)
- Hemoglobin 6.2 (13.5 -17.5)
- Platelet count 15 (140-440)





Based upon CBC and smear review, what is likely diagnosis?

A. Infection with left shift
B. B12 deficiency with pancytopenia
C. Increased blasts with concern for acute leukemia
D. Neupogen (growth factor) administration



Differential diagnosis of pancytopenia with few blasts in blood

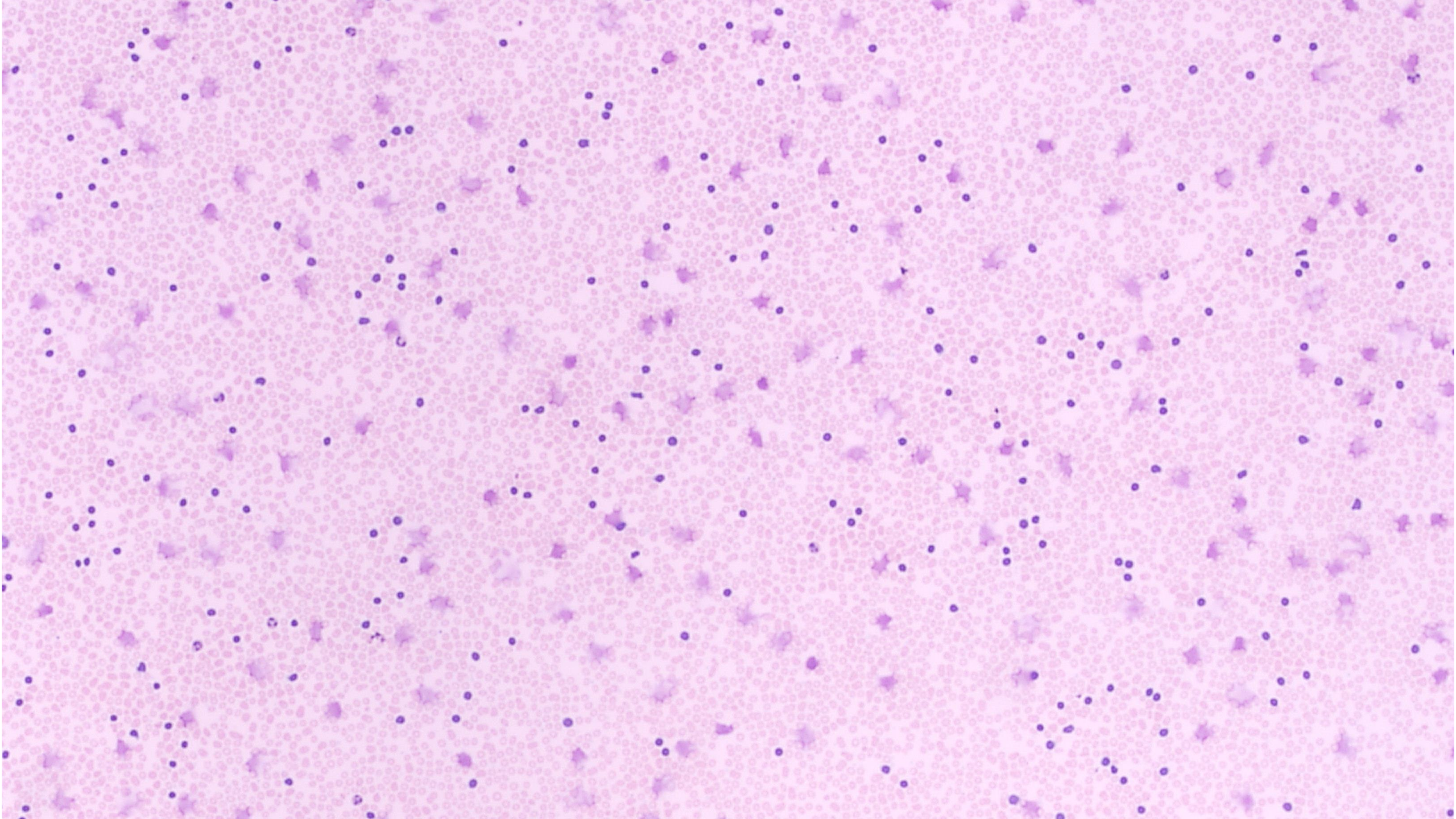
- High grade MDS
- Early acute leukemia

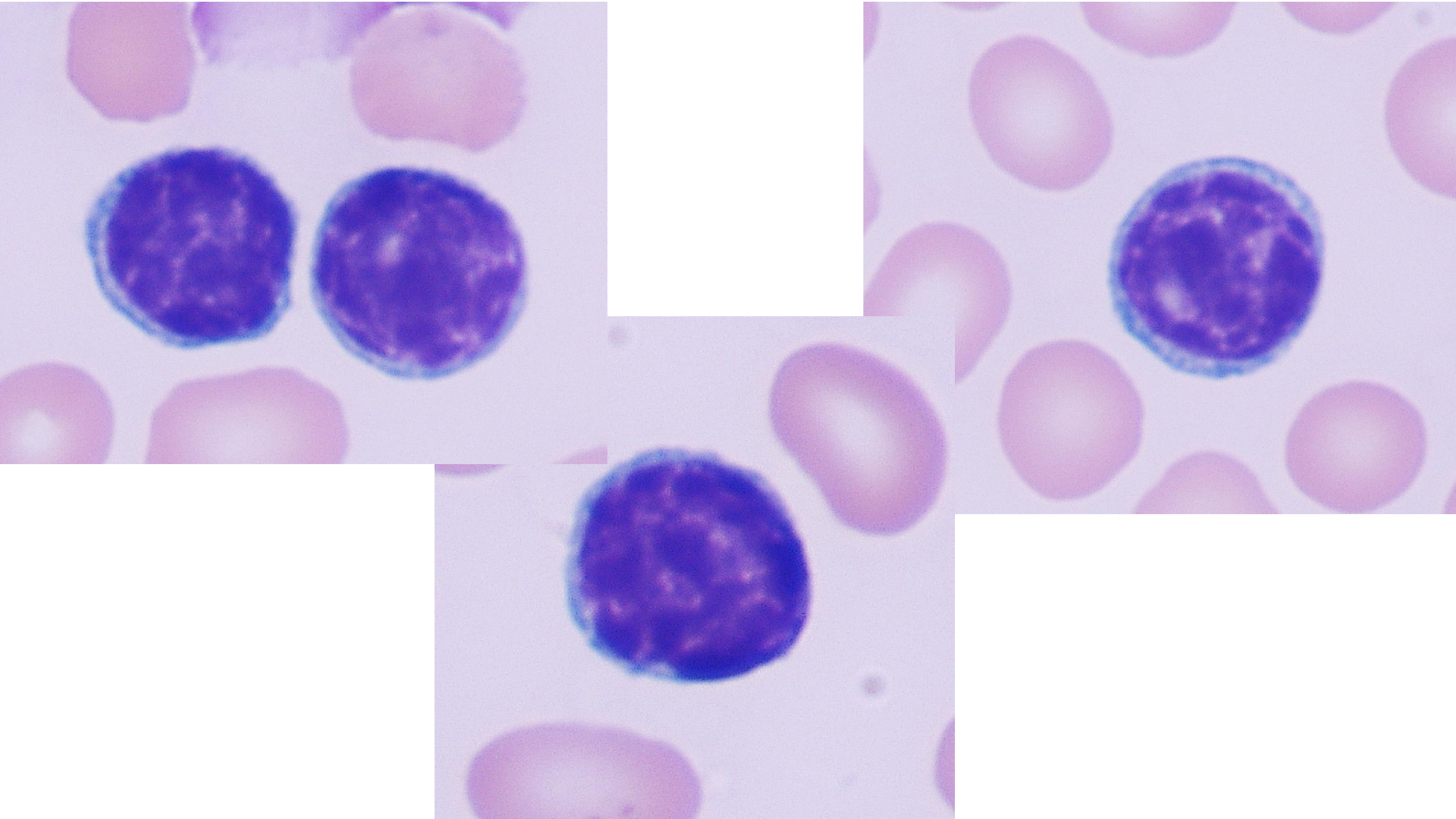
Early cells in peripheral blood with cytopenias

- Acute leukemias will have anemia and thrombocytopenia, and typically significant neutropenia, with “leukemic hiatus”
- Leukemic hiatus:
  - Disruption in the normal continuity of granulocytic maturation, early to mature
  - May have some mature neutrophils present with blasts, however do not see the orderly progression from blast, to promyelocyte, to myelocyte, etc. as would be present with marked infection or with growth factor therapy (Neupogen)
- The overall WBC count varies, can be high or low, depending upon how early the patient presents in course of disease
- Some cases show background evidence myelodysplasia (MDS), like in this case
- Even rare blasts in peripheral blood, with cytopenias, and dysplasia indicates at least high grade MDS, bone marrow evaluation needed to rule out evolving acute leukemia

6. Case six: CBC data in 65 year old male

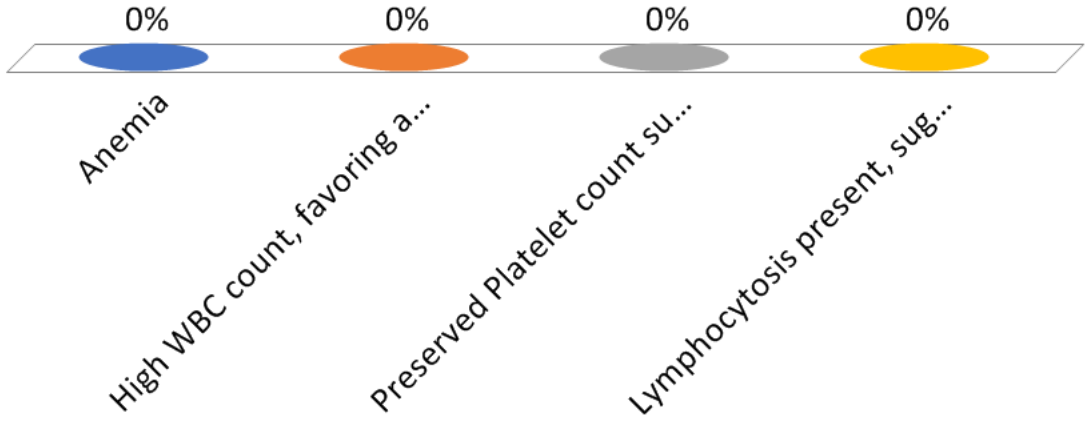
- WBC 123 (normal 4.5-11)
- Lymphocytes absolute number 115 (normal 1.5-3)
- Hemoglobin 10.0 (normal 12-16)
- Platelets 154





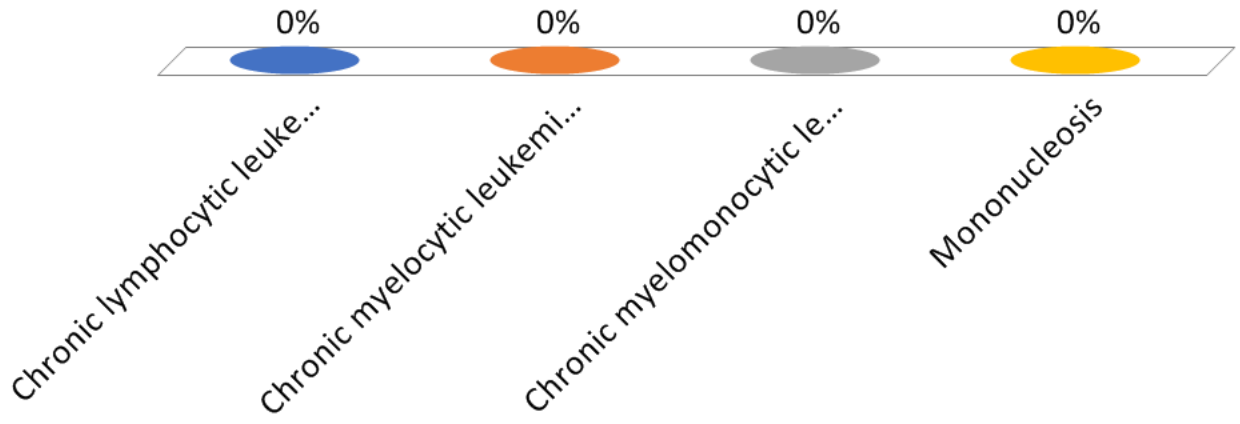
You suspect a leukemia, what is big clue as to the acute or chronic nature?

A. Anemia
B. High WBC count, favoring acute process
C. Preserved Platelet count suggests chronic leukemia
D. Lymphocytosis present, suggesting acute leukemia



What is diagnosis?

A. Chronic lymphocytic leukemia (CLL)
B. Chronic myelocytic leukemia (CML)
C. Chronic myelomonocytic leukemia (CMML)
D. Mononucleosis



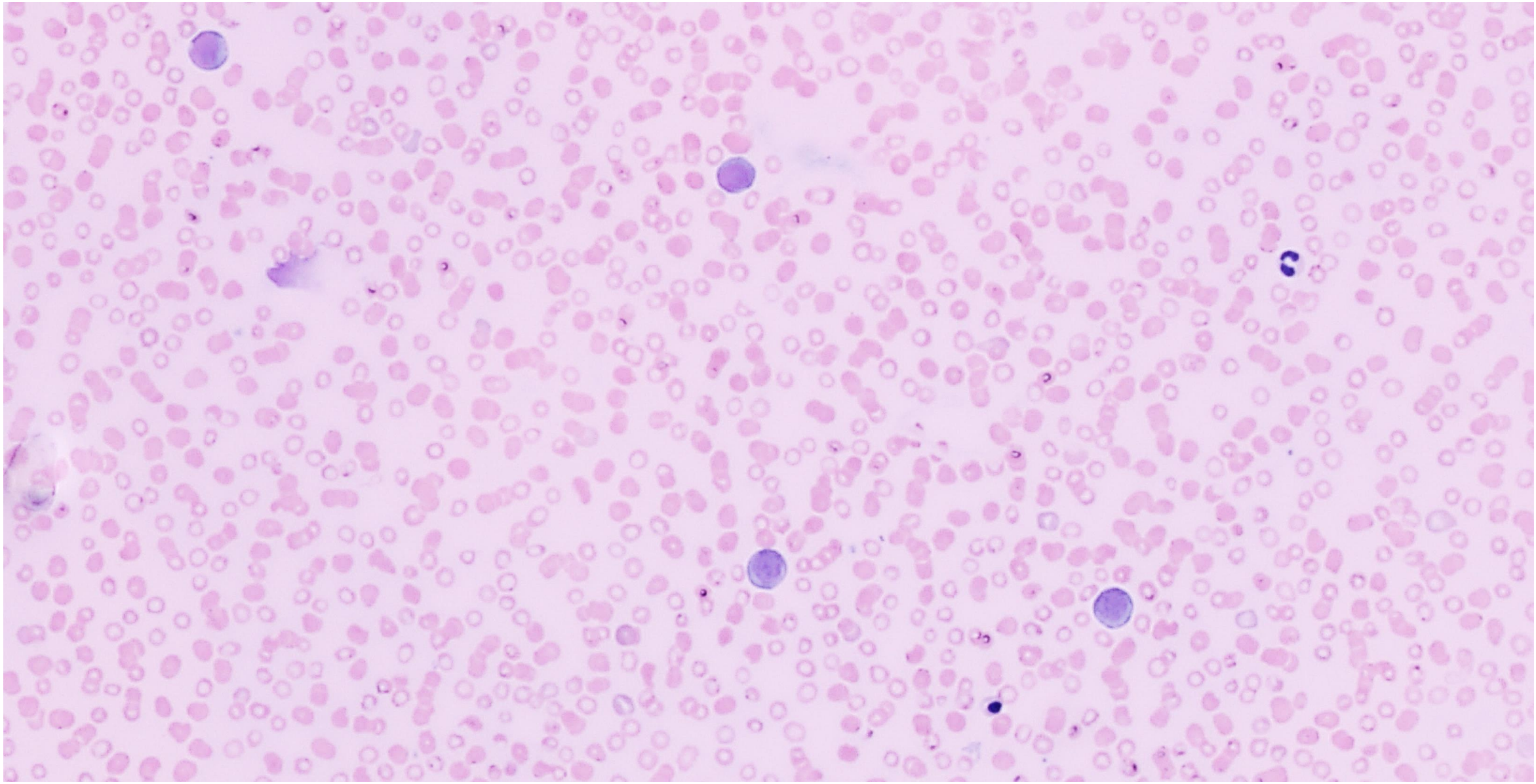
CLL – Chronic lymphocytic leukemia

- Blood smear very helpful in this aspect
- Examination of lymphoid cells can help point to diagnosis of CLL
- Clumped (block like or turtle back or soccer ball) chromatin pattern
- Infectious mononucleosis is common in younger age patient with enlarged viral appearing lymphocytes

Acute versus chronic leukemia

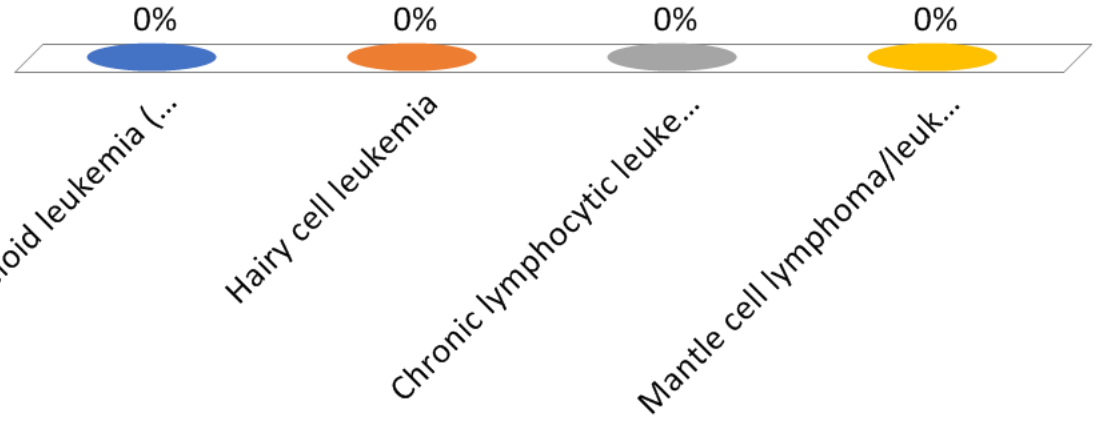
- Acute leukemia will have thrombocytopenia together with anemia
- While chronic leukemia can have thrombocytopenia, a normal platelet count will usually exclude acute leukemia
- Usually acute leukemia will have reported blasts (not always)
- Chronic leukemias may have thrombocytopenia, but could even have normal hemoglobin and normal platelet count, as seen in CLL

Acute leukemia



What is one type of chronic leukemia which mimics acute leukemia due to cytopenias including thrombocytopenia?

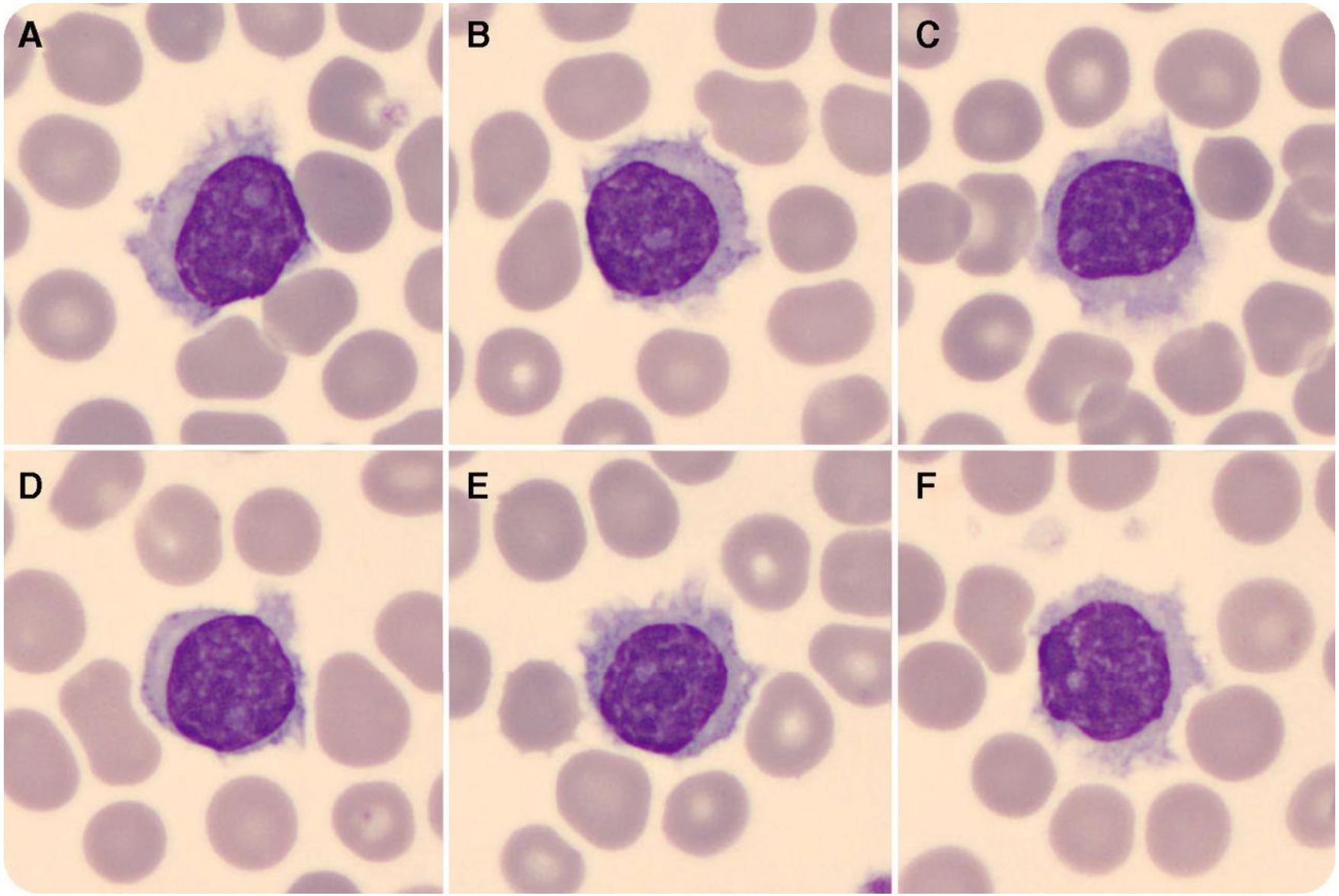
A. Chronic myeloid leukemia (CML)
B. Hairy cell leukemia
C. Chronic lymphocytic leukemia (CLL)
D. Mantle cell lymphoma/leukemia



Classic presentation of Hairy Cell Leukemia

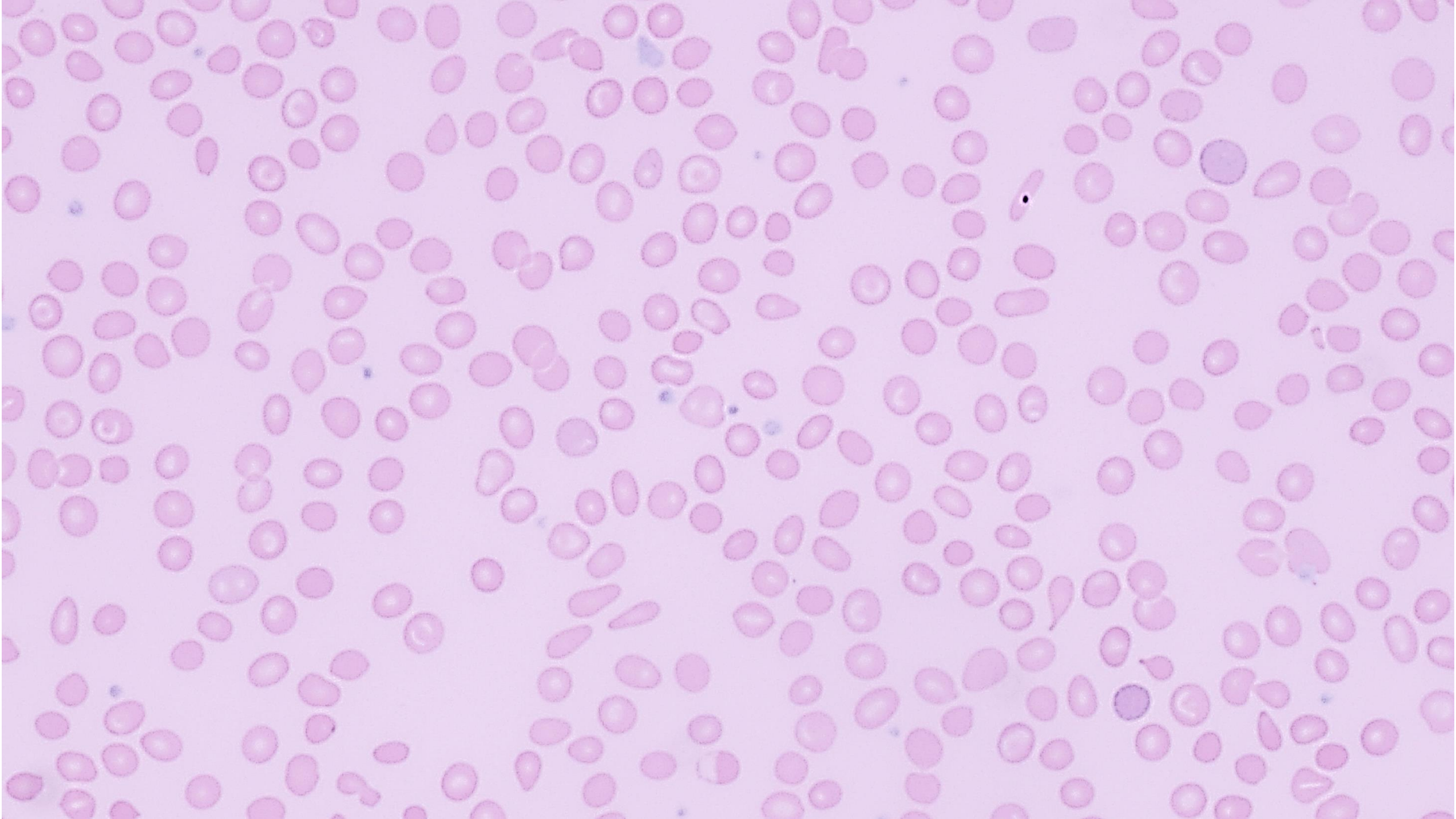
- Pancytopenia
- Enlarged spleen
- May or may not have lymphocytosis
- Need peripheral smear review to assist with diagnosis

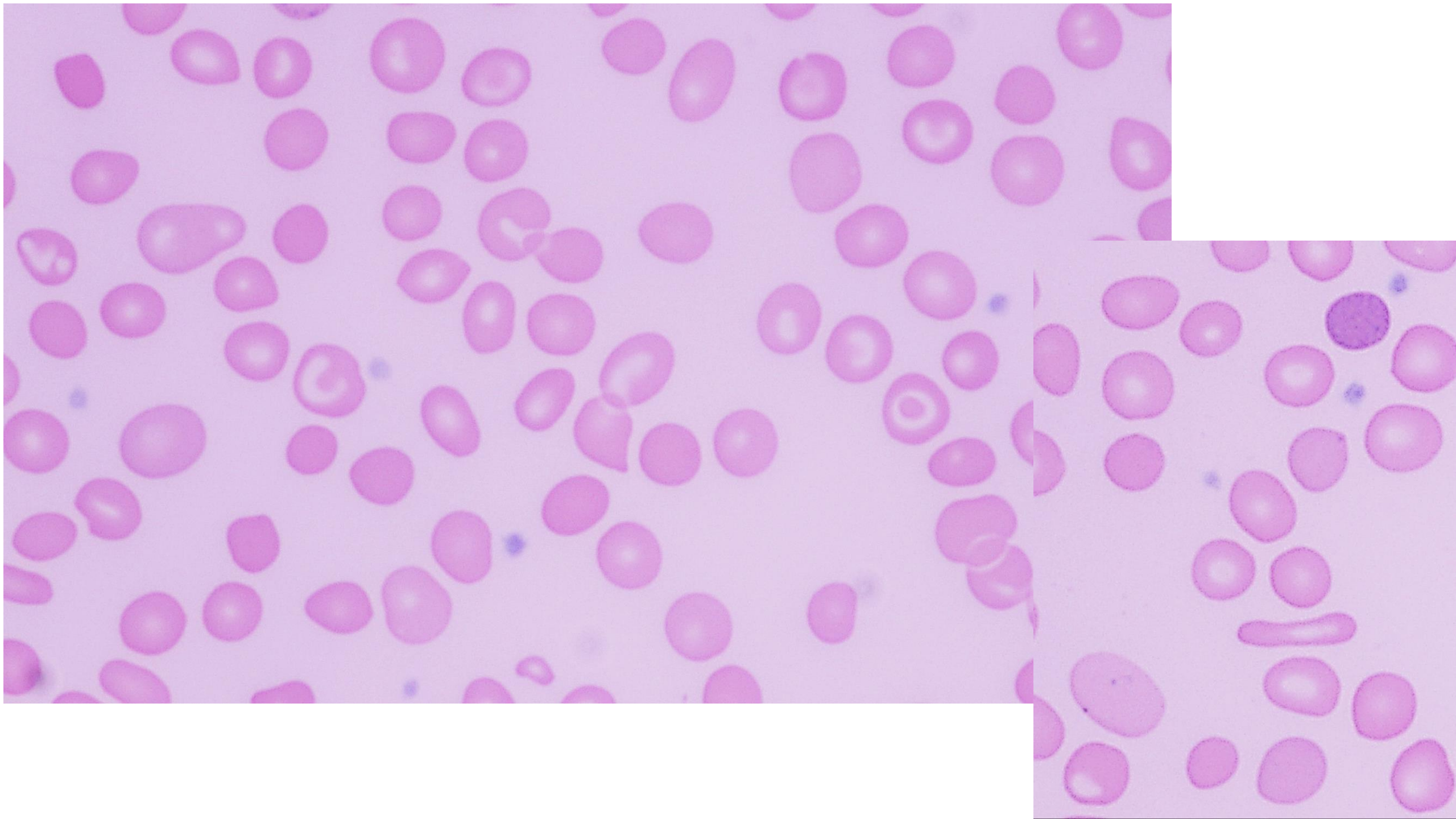
Hairy Cell Leukemia



7. Case seven: CBC data

- WBC normal
- RBC normal at 5.13
- Hemoglobin 10.2 (12-16)
- MCV 61.3 (80-100)





Q: Frequent target cells, marked microcytosis, normal/high RBC count and basophilic stippling are features of ?

- Sickle cell anemia
- Thalassemia trait
- Iron deficiency anemia
- B12 deficiency

Q: Which follow up test helps to confirm?

- Hemoglobin A2 level
- Serum iron studies
- B12 level

Thalassemia trait

- Beta thal trait will have elevated Hemoglobin A2
- Alpha thal trait will not, and so will need further gene sequencing if hemoglobin A2 is in the normal range