Doctor.021

no. 3

HLS PATHOLOGY

Writer: *Yasmeen AL-shabatat & Layan Lafi*

Corrector: *Yasmeen AL-shabatat & Layan Lafi*

Doctor: *Dr. Tareq AL Adily*

Note!

what is written in the slides

Doctor' s words

writer's words

ANEMIA OF DECREASED PRODUCTION

- It is anemia of low production from the bone marrow and it is classified into three main categories / General causes:

1. Nutritional deficiency most common
2. Anemia of Chronic inflammation
3. Bone marrow failure

Let's start with MICROCYTIC ANEMIA

IRON DEFICIENCY ANEMIA (IDA)

Important especially in clinical practice

- Most common type of anemia
- Affects 10% of people in developed countries and 25-50% of people in developing countries, so it is more common in low resources countries
- Iron storage pool /stored in 2 forms:

1. iron is stored in **ferritin which is** (small water soluble molecule)
2. iron is stored in **hemosiderin** (insoluble) presents in bone marrow, liver and spleen

Both (ferritin and hemosiderin) forming 15-20% of total iron and the bulk remaining percentage presents in the Hb.

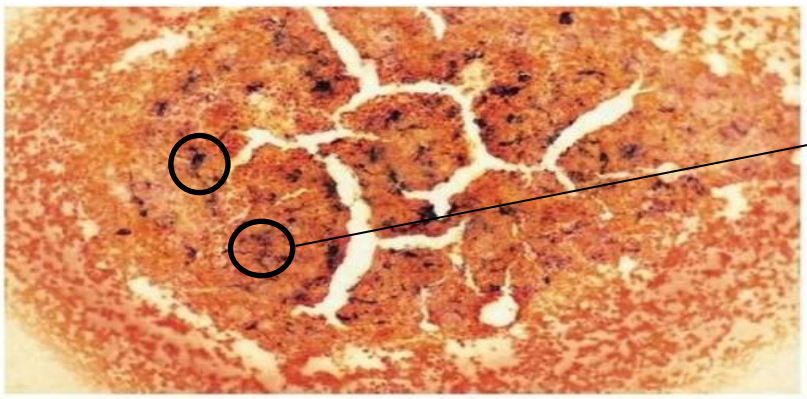
- Hemosiderin consists of large iron particles, granular in shape, intracellular (mainly in the macrophages in the BM), visible by light microscope
- Serum ferritin is derived from stored ferritin.
  NOTE: Hemosiderin itself reflects the amount of stored iron.
- Serum iron is transported by transferrin, **normally** only one third of transferrin is saturated by iron

INDICATORS OF IRON STATUS

- Bone marrow aspirate (best one ، accurate) by insert a needle in the bone marrow shows: earliest changes in the iron amount in BM, invasive procedure, Perl's Prussian blue stain a special iron stain appears in form of blue granular particles (**↓ in IDA**)
- Serum ferritin level (↓ in IDA) * reflects hemosiderin in BM (low hemosiderin, low serum ferritin level) the problem in the ferritin that is an acute phase protein increases in the inflammatory conditions that masks iron deficiency.
- Serum iron level (↓ in IDA) reflects transferrin and the transferrin saturation becomes lower than 1/3 which is abnormal
- Total iron binding capacity [TIBC] This is the opposite test of transferrin saturation, It is done by adding iron to the blood sample then if it takes a lot of ironthis indicates the deficiency of iron (**↑ in IDA**)
- Reticulocyte hemoglobin content (CHr): MHC in the RBCs (↓ in IDA)
- Mean reticulocyte volume (MRV): MCV in RBCs (↓ in IDA)

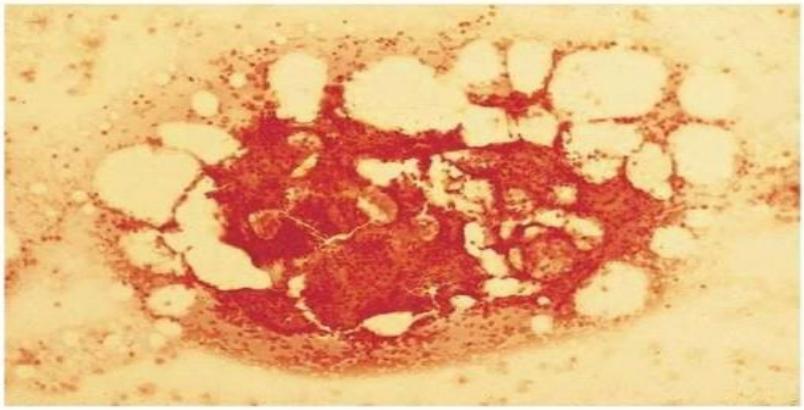
* Affected by inflammation (increased)

- Bone marrow examination of hemosiderin. it is stained with Perl's stain



- It has normal stores of iron in granular hemosiderin

Aspirate of normal
marrow (BM): bluish-black
(haemosiderin) in macropha
fragment. Perls' stain ×40.



- She\ he has iron deficiency because we don't see any blue part

Aspirate of normal
a fragment with no stainable
Perls' stain ×40.

IRON HEMEOSTASIS

- Normal loss of body iron: shedding skin and mucosal epithelium (no excretion) because it is difficult to excrete iron from our body
- Dietary iron is either hem (red meat) well absorbed or non-hem (inorganic, vegetarian) difficult to be absorbed which needs vit c
- 20% of hem and 1% of non-hem iron are absorbed in duodenum

- Hepcidin: hormone (hep: secreted from liver), normally inhibits iron absorption (degrade ferroportin on enterocytes in the small bowel)

Regulation of hepcidin:

- Hepcidin hormone is **positively** regulated by **HFE protein** on Cell membrane of hepatocytes, which is activated when serum **iron level rises**
- Hepcidin hormone is also **positively** regulated by **IL-6**, which increases in inflammation
- Hepcidin is **negatively** regulated to decrease or stop its secretion by **erythroferrone**, a hormone secreted by erythroblasts in bone marrow
- **We can see low hepcidin in 3 diseases:**

Low hepcidin:

1. **In iron deficiency**.

Very low hepcidin:

2. **thalassemia major** (high erythroferrone due to large number of erythroblast)
3. **primary hemochromatosis** (defective HFE)

CAUSES OF IRON DEFICIENCY

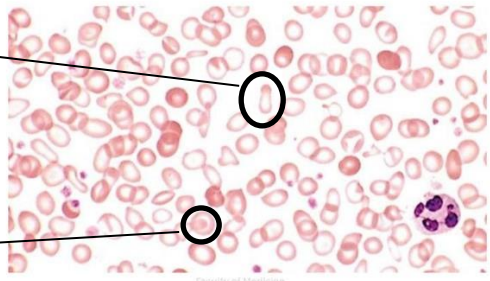
- Chronic blood loss because iron is difficult to be controlled by the body, there is a high tendency to loss it with Hb
- Dietary: vegetarians, infants (low iron in the Breast milk), teenagers (fast food, menstrual cycle in females,,,,)
- Decreased absorption due to some diseases: like **gastrectomy, hypochlorhydria** (low stomach acid (HCL)that is important to ferrous conversion and absorption of iron), **intestinal diseases** like Inflammatory bowel disease and Celiac disease that lead to inflammation so iron level will decrease, and **elderly** due to physiological atrophy of the stomach which decreases iron absorption
- Increased demands: growing children, pregnancy, myeloproliferative neoplasms (White blood cells take up more iron than red blood cells)
- Hypotransferritinemia: decreased synthesis of transferrtin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in urine (nephrotic syndrome)
- Enzyme deficiency, a congenital disease, is rare but should be considered when the deficiency develops very early in life and it is difficult to treat

MORPHOLOGY

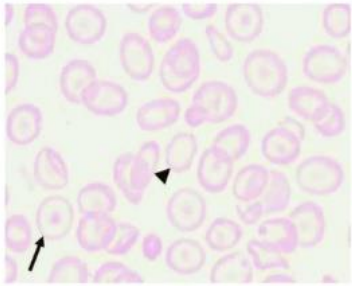
- RBCs appear small and empty (hypochromic microcytic). When there is not enough hemoglobin due to iron deficiency, red blood cells become smaller and dull in color
- Different and abnormal shapes of RBCs appear (poikelocytosis) because Iron is important for the integrity of the cell membrane of RBCs, so they will have abnormal shapes
- Target cells: RBCs with a red dot in the middle appear in iron deficiency anemia , thalassemia and sickle cell anemia
- Low reticulocytes (Erythropoietin is high, but **ineffective** **the BM can not produce RBCs due to** Iron deficiency)
- **Thrombocytosis** is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid)

poikelocytosis Small and elongated

Target cell has red dot in the middle

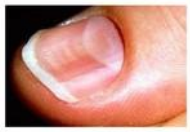


IDA: note the hypochromia and poikelocytosis



IDA: note the target cells (arrow)

SYMPTOMS



- IDA is a chronic anemia (never comes quickly)
- General symptoms of anemia (Hypotension, dizziness, fatigue)
- Pica (special symptom, when patients have strong desire to eat abnormal things) مثل التراب والثلج
- Glossitis, stomatitis
- Spooning of fingernails (koilonychia)
- Restless leg syndrome (an irresistible urge to move the legs as aneurological condition)
- Hair loss
- Blue sclera
- Weakened immunity
- Cognitive impairment lately and in severe cases

ANEMIA OF CHRONIC INFLAMMATION

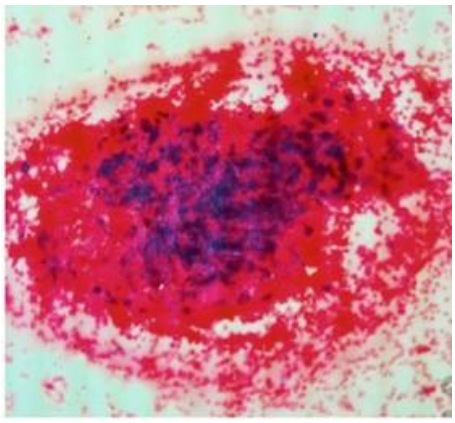
- Also called anemia of chronic disease
- Seen in chronic infections, cancer, chronic immune diseases

  - There are chronic non-inflammatory diseases such as Alzheimer's disease and Parkinson's disease, those patients do not suffer from anemia, so it appears in chronic inflammatory diseases

- Common in hospitalized patients
- High IL-6→high hepcidin →blocks iron transfer from macrophages to RBC precursors in bone marrow (degrade ferroportin on macrophages this keeps the iron inside macrophages in the BM in form of hemosiderin). Also suppress erythropoietin secretion from kidneys. (It is an exception like anemia of renal disease)

  NOTE¡ Hepcidin is the normal antagonist for erythropoietin.

LABORATORY FINDINGS



- Similar to IDA: serum iron is low
- RBCs: normal morphology, then hypochromic microcytic
- Reticulocytes ↓ due to low erythropoietin
- In contrast:
- Bone marrow iron stores ↑In certain theory: The benefit of this is that iron is stored in macrophages in the BM, preventing the iron from reaching harmful bacteria as a form of protection for the body
- Serum ferritin↑ one of the acute phase reactants

Let's start with MACROCYTIC ANEMIA!

MEGALOPLASTIC ANEMIA

- Caused by deficiency in vitamin B12 or folate
- Both are required for synthesis of thymidine (nucleic acid in DNA),thus DNA replication is impaired and the cell dies by apoptosis
- Abnormalities occur in all rapidly dividing cells, but **hematopoietic cells** (erythroid cells) are most severely affected
- Maturation of RBC progenitors is deranged due to abnormalities in the nucleus of these cells, **many** undergo apoptosis inside bone marrow so (ineffective erythropoiesis, mild hemolysis which is a side process, not the main one, as in hemolytic anemia, so it isn't classified as a hemolytic anemia.)
- **Some of** Viable nucleated RBCs take a **longer time** to mature (Not all of them will undergo apoptosis), resulting in typical morphology as large cells due to the accumulation of more cytoplasm than normal over time because the cytoplasm doesn't need thymidine , so it continues growing (megaloblastoid ; mega: large , blastoid : immature nucleus)

FOLATE (B9) DEFICIENCY

- Normally, minimal amount of folate is stored in human body
- Folate is vastly present in food (green leaves), but it is destroyed by cooking
- Causes of deficiency:

1. Decreased dietary intake
2. Increased demands (pregnancy(first supplement and REMEMBER¡ GIVE VITAMIN **B9** FOR THE **9 MONTHS** OF PREGNANCY) , chronic hemolytic anemia : high turnover , cells die and a lot of erythroblasts that proliferate so they need more folate , as a result they can develop a second anemia which is folate deficiency)
3. Intestinal diseases
4. Beans, legume, alcohol, phenytoin (it is anti-epileptic drug that inhibits the absorption of folic acid)
5. Methotrexate (chemotherapy agent): inhibits folate metabolism and cellular usage

VITAMIN B12

- Mainly present in animal products (you can found it in eggs, meat, and milk,,)
- Resistant to cooking
- Synthesized by bacteria in bowel
- Enormous stores in the liver. B12 takes 5 to 20 years to be completely depleted from its stores (a lot of time for the disease to develop and a lot of time for treatment)
- Dietary deficiency occurs most commonly in vegetarians
- More commonly: deficiency results from defective absorption

PERNICIOUS ANEMIA

(important cause of B12 deficiency)

- Autoimmune gastritis
- Autoreactive T-lymphocytes, causing injury to parietal cells (normally secrete HCL and intrinsic factors so both of them will decrease)
- Activates B-lymphocytes and plasma cells to synthesize and secrete auto antibodies that further damage parietal cells, and blocks binding of vitamin B12 to intrinsic factors and may be iron deficiency anemia occurs due to decrease in HCl.

OTHER CAUSES OF VITAMIN B12 DEFICIENCY

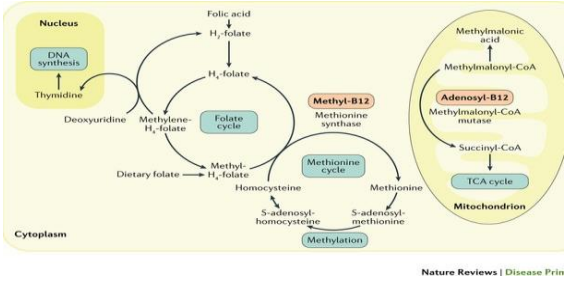
- Gastrectomy . As mentioned above, this leads to a decrease in intrinsic factors that are important for B12 absorption.

REMEMBER THE INTRINSIC FACTORS ARE IMPORTANT FOR B12 ABSORPTION . AND HCL FOR NON-HEME IRON ABSORPTION .

- Small bowel diseases (malabsorption)
- Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
- **Metformin that is used by diabetic patients** (inhibits absorption)

OTHER FUNCTONS OF VITAMIN B12

- Recycling of tetrahydrofolate to produce folate
- Synthesis of **myelinsheath**
- Synthesis of neurotransmitters (dopamine, serotonin)



Not required, just to make it clear to you

- Metabolism of homocysteine (toxic to neurons)
- Degree of neuronal damage does not correlate with the degree of anemia

MORPHOLOGY OF MEGALOPLASTIC ANEMIA

Big and elongated with high MCV> 110fL and it is hyperchromatic

Neutrophils: hypersegmetation of the nucleus more than 4 segments (appears as earliest Feature)
Dr.Treq said more than 4 segments and then he said more than 5 segments. SOOOO ☺

Macroovalocyte: characteristic of megaloblastic anemia

SYMPTOMS

- Chronic, general symptoms of anemia
- Glossitis (beefy tongue)
- Mild jaundice (Due to mild hemolysis and the excretion of bilirubin from the cells)
- In severe cases: pancytopenia (platelets and neutrophils production fails)

In vitamin B12 deficiency:

- Posterior and lateral columns degeneration of spinal cord which mainly leads to sensory problems (paresthesia, loss of proprioception)
- Peripheral neuropathy sensory , motor whatever
- Neuropsychotic symptoms

APLASTIC ANEMIA (AA)

a: non, plasia: production, so it is total bone marrow failure

Damage to multipotent stem cell in bone marrow

- Bone marrow becomes depleted of hematopoietic cells
- Peripheral blood pancytopenia (pan: all) even platelets and neutrophils become very low
- Low reticulocytes
- Affects all age groups, but it is more common in the young
- Patients develop life-threatening infections, bleeding and symptoms of anemia

PATHOGENESIS

- Extrinsic factor

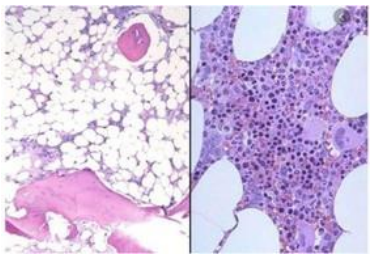
- Antigen cross reactivity with stem cells (drug, virus, environmental factor)
- Activated T-lymphocytes destroys stem cells
- Evidence: immunosuppressive drug restores bone marrow in 70% of cases
- Most cases are idiopathic
- Associated factors: **chloramphenicol** **(antibiotic, with Limited use)** , gold injections to treat Rheumatism, NSAID, pregnancy, some hepatitis viruses

- Intrinsic factor (problem within stem cells)

- 10% of aplastic anemia patients have inherited defects in telomerase (stability of chromosomes)
- that is why Stem cells die early by apoptosis
- These genetically altered stem cells might express abnormal antigen?? This causes Attracting T- cells

LAPORATORY FINDINGS

- Peripheral blood: pancytopenia, anemia is **normochromic** or **macrocytic**
- Bone marrow: decreased hematopoietic cells and predominance of fat



SPECIAL TYPES OF BONE MARROW FAILUR

- **Fanconi anemia: rare,** inherited form of AA, defect in DNA repair proteins, patients develop AA and transform to acute leukemia in early life
- **Pure red cell aplasia**: only erythroid cells are absent in bone marrow, canbe ***congenital*** (Diamond-Blackfan anemia) or ***acquired*** affected people with (autoimmune diseases, or infection with Parvovirus B19 infection *disrupts the immature cell and this causes the disappearance of the red blood cell*)

MYELOPHTHISIC ANEMIA

resembles aplastic anemia, patients come with pancytopenia but the mechanism differs. In myelophthisic anemia the bone marrow fully infiltrated and destroyed by either cancer or infectious process

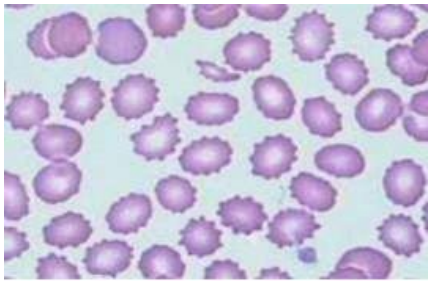
- Myelo: bone marrow, phthesia: **Infiltration of bone marrow** causing physical damage to hematopoietic cells
- **Cancer: *most commonly*** in bone marrow tumors like **acute leukemia**, **advanced lymphoma and myeloma**, metastatic cancer like breast cancer, colon cancer which are solid cancers that makes metastasis and then destruction to the bone marrow
- **Granulomatous dissease (inflammatory cells + physical mass in the tissue): TB**

▪Storage diseases inborn errors of metabolism, so the tissues in the body store either lipid, glycogen or sphingomyelin: most commonly is Gaucher

▪ Immature granulocytic and erythroid precursors commonly appear in peripheral blood making pancytopenia, that is what makes it different from AA.

ANEMIA OF RENAL DISEASE

▪ Mainly results from decreased erythropoietin production from kidneys

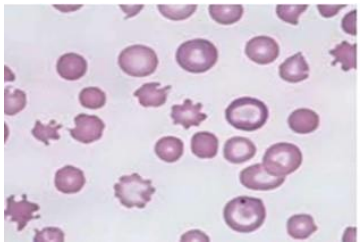


▪ Does not correlate well with kidney function (serum creatinine). Mild renal injury may cause severe anemia and vice versa

▪ Decreased RBC production (low retic count)

▪ Patients with uremia (means urine in the blood) develop abnormal platelets function leads to anemia of chronic disease (bleeding), **echinocytes** means spiked cell membrane, and the SECOND NAME IS (***Burr cells***) appear

ANEMIA OF LIVER DISEASE



▪ Multiple factors causing anemia (multifactorial)

▪ Decreased synthesis of clotting factors (bleeding)

▪ Especially Bleeding from varices becomes anemia of chronic blood loss

▪ Decreased synthesis of transferrin thus develops iron deficiency

▪ Acanthocyte (spur cell) appears with longer spikes

ANEMIA OF HYPOTHYROIDISM

- Thyroid hormones stimulate erythropoiesis
- Also stimulates erythropoietin production
- Anemia is most commonly normocytic, but can be marcocytic

because maturation takes longer time due to decreased thyroid hormones

MYELODYSPLASTIC SYNDROME

Acquired neoplastic disease of bone marrow

- Primarily disease of old age
- Mutations in BM stem cell, results in prolonged survival and defective maturation same principle of **megaloplastic anemia** thatis take long time to mature abnormally
- Mature blood cells do not exist bone marrow like in the normal way so the bone marrow fill with the erythroid cells
- Patients commonly develop neutropenia and thrombocytopenia as well
- Anemia is refractory to treatment that means it is resistant to treatment because the problem in mutations of DNA can't be corrected
- RBCs are macrocytes

PAST PAPERS

1) Which of the following are NOT characteristic of iron deficiency anemia?

A) Absent Perl's staining pattern

B) Low reticulocyte hemoglobin content

C) Can be caused by liver disease

D) Low total iron binding capacity

E) Low mean cell volume

ANS: D

2) Which of the following best describes a person with acute GIT hemorrhage?

A) Fluid is shifted from intravascular space to interstitial fluid

B) Iron deficiency might occur, causing complications

C) Erythropoietin is immediately secreted after hemorrhage has occurred

D) Erythrocytes may appear as hypochromic microcytic

ANS: B

3) A patient showed up to the hospital with hair loss, spooned fingernails, and tendency to eat dirt. Which of the following do you expect to see when examining a histological section of the patient's blood?

A) Microcytic hypochromic erythrocytes with reticulocytosis and thrombocytopenia

B) Ovalocytes with central pallor and low reticulocyte count

C) Lightly stained erythrocytes that have central & peripheral acidophilia with an area of pallor in between

D) Hypochromic microcytic anemia with anisopoikelocytosis that is densely stained with Perl's Prussian blue stain.

ANS: C

4) Which of the following is NOT characteristic of megaloblastic anemia?

A) Severely high bilirubin level

B) Chronic course of disease

C) Macroovalocytes

D) Loss of proprioception

E) Can be caused by strict vegan diet

ANS: A

5) The best test to use for differential diagnosis between iron deficiency anemia and anemia of chronic inflammation is:

A) Serum iron level

B) Mean cell volume

C) Bone marrow iron stores

D) Reticulocyte count

ANS: C

6) Pernicious anemia is described as:

A) Macrocytic anemia

B) Autoimmune gastritis

C) Intrinsic factor deficiency

D) Vitamin B12 deficiency

E) All the answers are correct

ANS: E

7) A 30-year-old woman complains of recent easy fatigability, bruising, and recurrent throat infections. Physical examination reveals numerous petechiae over her body and mouth. Abnormal laboratory findings include hemoglobin of 6 g/dL, WBC of 1,500/mL, and platelets of 20,000/mL. The bone marrow is hypocellular and displays increased fat. What is the appropriate diagnosis?

A) Aplastic anemia

B) Iron-deficiency anemia

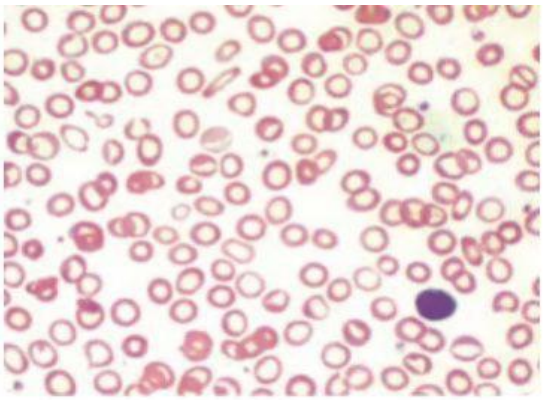
C) Megaloblastic anemia

D) Myelofibrosis with myeloid metaplasia

E) Pure red cell aplasia

ANS: A

8) A 20-year-old thin fashion model complains that she cannot concentrate and is always tired. She has heavy menstrual bleeding every month but is otherwise healthy. The peripheral blood smear is shown in the image. Which of the following laboratory findings would be expected in this patient?



A) Hyperbilirubinemia
B) Increased serum ferritin
C) Low plasma iron saturation
D) Positive direct Coombs test
E) Vitamin B12 deficiency

ANS: C

V3

Any correction is in yellow