Hematology

5/11

Megaloblastic Anemia

432 ***Hematology*** *Team*

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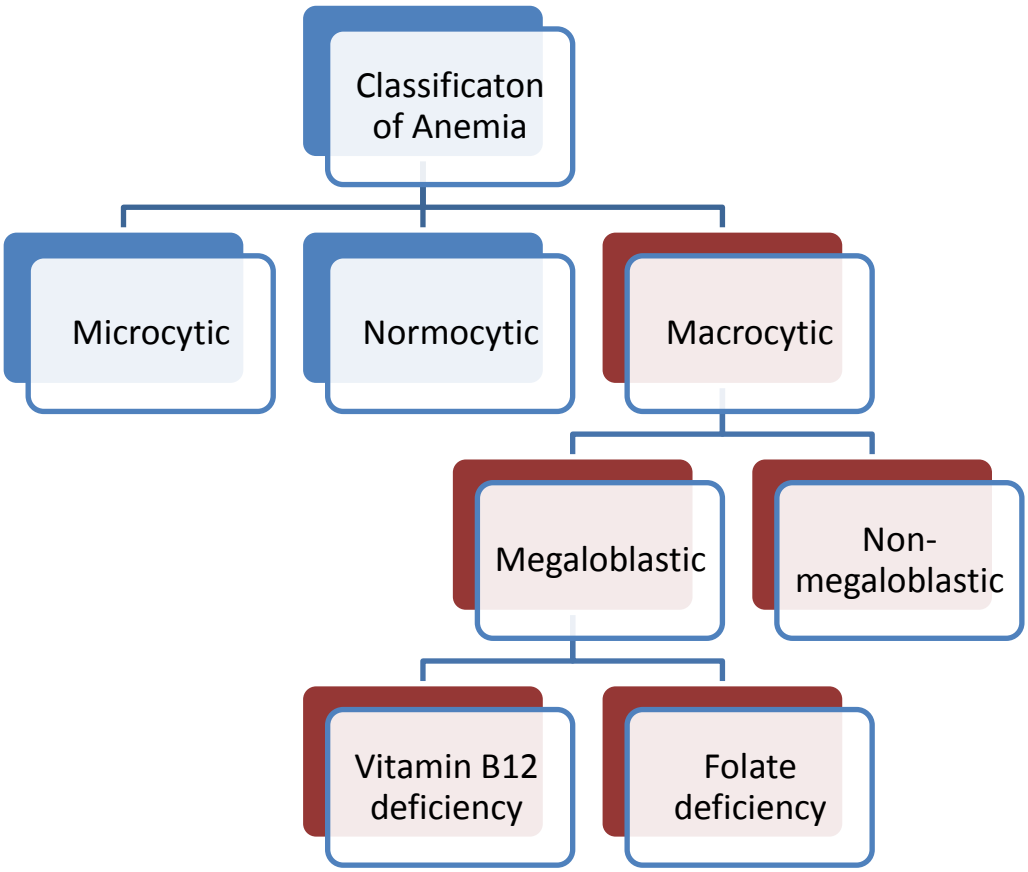
Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Megaloblastic Anemia

Mind Map:



Introduction

Normal RBCs values;

Adults

Indices	Male	Female
Hemoglobin (g/dL)	13.5-17.5	11.5-15.5
Hematocrit (PCV) (%)	40-52	36-48
Red Cell Count ($\times 10^{12}$)	4.5-6.5	3.9-5.6
Mean Cell Volume (MCV) (FL)size of the cell	80-95	
Mean Cell Hemoglobin (MCH) (pg)	27-34	
Mean cell haemoglobin concentration g/dL)	30 – 35	
Reticulocyte count ($x10^9$/L)	25 – 125	

Children

Hemoglobin (g/dL)	
Newborn	15.0 –21.0g/dL
3 months	9.5 – 12.5g/dL
1 year to puberty	11.0 – 13.5g/dL

Anemia:

Anemia	Microcytic, Hypochromic Anemia Due to hemoglobin disorder (e.g. thalassemia and iron def. anemia)	Normocytic, Normochromic Anemia Due to a problem in RBC count (e.g. sickle cell anemia and aplastic anemia)
Causes	1- Iron deficiency. 2- Thalassemia. 3- Lead poisoning. 4- Sideroblastic anemia (some cases). 5- Anemia of chronic disease (some cases).	1- Many hemolytic anemias. 2- Anemia of chronic disease (some cases). 3- After acute blood loss. 4- Renal disease. 5- Mixed deficiencies. 6- Bone marrow failure, e.g. post-chemotherapy, infiltration by carcinoma, etc.
RBCs values	1- MCV < 80 fL (**Low**) 2- MCH <27pg (**Low**)	1- MCV 80 – 95 fL (**normal**) 2- MCH>26pg **(high)** not important

Megaloblastic Anemia

Macrocytic anemia:

Characterized by large size erythrocyte (MCV >95) Due to DNA disorder (e.g. Megaloblastic anemia).

Divided into:

- Non-Megaloblastic (non-megaloid, Macrocytosis).
- Megaloblastic anemia (megaloid) **enlarged erythroid precursor.**

Non-Megaloblastic (Non-megaloid, Macrocytosis)

Enlarged RBCs in the peripheral blood with **normal** erythrocyte production from the bone marrow.

Causes:

	Macrocytic anemia (Macrocytosis)	Macrocytosis with Normoblasts (erythroid precursure is normal)
Most important	**1- Alcohol** *(most common)* **2- Liver disease** *(especially alcoholic)* **3- Reticulocytosis** (increase in haemolysis or haemorrhage) RBCs in the stage before maturation, gives wrong reading. **4- Hypothyroidism.** **5- Myelodysplasia MDS** including acquired Sideroblasticanaemia. **6- Pregnancy.** **7- Newborn.**	1- Normal neonates (Physiological) 2- Chronic alcoholism* 3- Myelodysplastic syndromes* 4- Chronic liver disease* 5- Hypothyroidism 6- Normal pregnancy 7- Therapy with anticonvulsant drugs* **Dr. FATMA said that these are the only causes she wants us to know**
Less important	1. Myeloma and macroglobulinaemia. 2. Leucoerythroblastic anaemia. 3. Myeloproliferative disease. 4. Aplastic anaemia or red cell aplasia. 5. Chronic respiratory failure.	1. Haemolyticanaemia. 2. Chronic lung disease (with hypoxia). 3. Hypoplastic and aplastic anaemia. 4. Myeloma. ***Some patients show B_{12}- and folate-independent megaloblastic erythropoiesis.***

REMEMBER:

1. Non-megaloblastic anemia (Macrocytosis): abnormality is in the peripheral blood, not in the bone marrow.
2. Macrocytosis with Normoblasts can be normal in neonates.

Megaloblastic anemia

It's a group of anemias that results from the abnormal synthesis of DNA during erythropoiesis in the bone marrow. (Asynchronous DNA synthesis: maturation of the RBCs nucleus being delayed relatively to that of the cytoplasm).

Most important features of megaloblastic anemia are:

- Macrocytes (large cells).
- Hypersegmented neutrophils.

Hypersegmented neutrophils **(classical in vitamin B12 deficiency)**: mainly found in megaloblastic anemia but could appear in non-megaloblastic in cases of:

1- Renal failure
2- Congenital (familial) abnormality
3- Iron deficiency

NOTE:

- Abnormal DNA synthesis will inhibit the division of the cells, which will make the cell bigger.
- Pernicious anemia is associated with deficiency of vit B12 or folic acid.

Causes of megaloblastic anemia:

1- Cobalamin (vitamin B12) deficiency **or abnormalities of cobalamin metabolism most common.**
2- Folate deficiency **or abnormalities of folate metabolism 2nd most common.**
3- **Therapy** with **antifolate** drugs (e.g. methotrexate)
4- Independent of either cobalamin or folate deficiency and refractory to:
   a) Some cases of acute myeloid **leukemia,** myelodysplasia. (Poor absorption of folate and cobalamin).
   b) Oroticaciduria (responds to uridine)
   c) Therapy with drugs interfering with synthesis of DNA (e.g. cytosine arabinoside, **hydroxyurea**, 6-mercaptopurine, azidothymidine (AZT)
   d) Thiamine responsived.

Other causes : (Not Important)

5- Suggested but poorly documented causes of megaloblastic anaemia not due to cobalamin or folate deficiency or metabolic abnormality:
   a) Vitamin E deficiency.
   b) Lesch-Nyhan syndrome (responds to adenine).
6- Abnormalities of nucleic acid synthesis
   a- Drug therapy:
      - Antipurines (mercaptopurine, azathioprine)
      - Antipyrimidines (fluorouracil, zydovudine (AZT))
      - Others (hydrozyurea)
   b- Oroticaciduria (abnormality in DNA synthesis).
7- Uncertain aetiology.
8- Myelodysplastic syndromes, * erythroleukaemia.
9- Some congenital dyserythropoietic anaemias.

**** Some patients show normoblastic erythropoiesis** (these causes are not characteristic).*

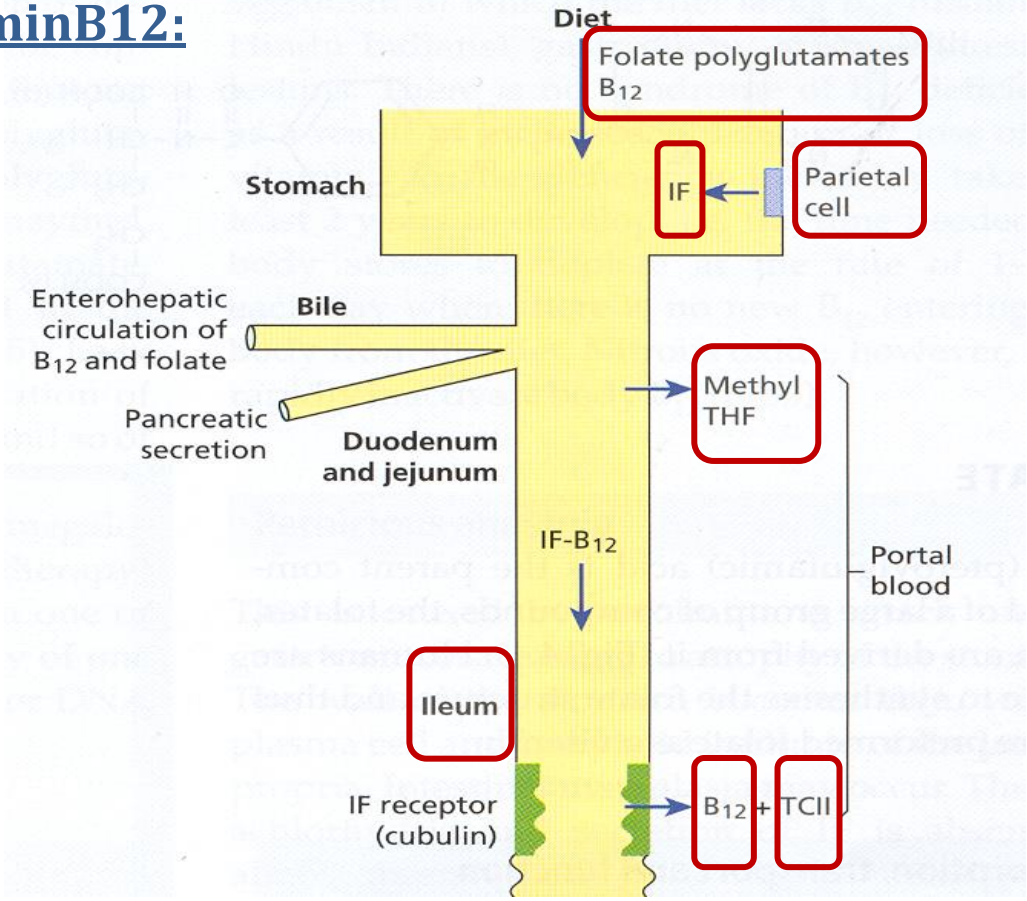
REMEMBER:

1. Megaloblastic anemia due to inhibition of DNA synthesis and affect RBCs in the bone marrow.
2. **Most common** causes of megaloblastic anemia **B12 deficiency** then **folic acid deficiency.**

Vit B12 & folate nutrition and absorption:

	Vitamin B12	Folate
Dietary source	Only food of animal origin, **red meat, especially liver**	Most foods, especially **liver, green vegetable and yeast**; destroyed by cooking.
Average daily intake	7 - 30 µg	200-250 µg
Minimum daily requirement	1-3 µg	100-200 µg
Body stores*	3-5 mg, mainly in the liver	8-20 mg, mainly in the liver
Time to develop deficiency in the absence of intake or absorption*	**Anemia in 2-10 years**	**Macrocytosis in 5 months.**
Requirements for absorption	**Intrinsic factor** secreted by gastric parietal cells	Conversion of polyglutamates to monoglutamates by intestinal folate conjugase
Site of absorption	**Terminal ileum**	**Duodenum and jejunum**

VitaminB12:



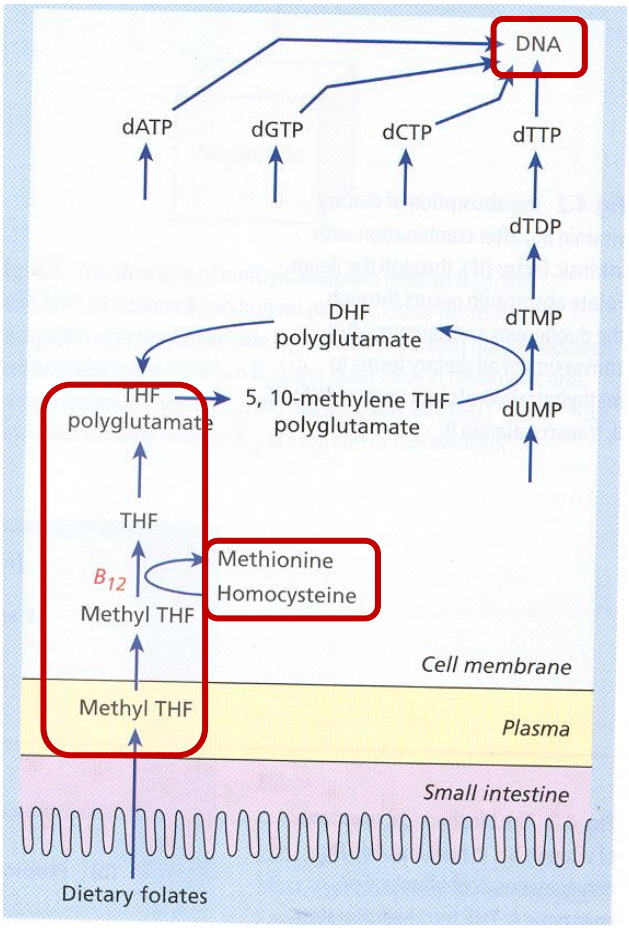
Causes of vitamin B12 deficiency:

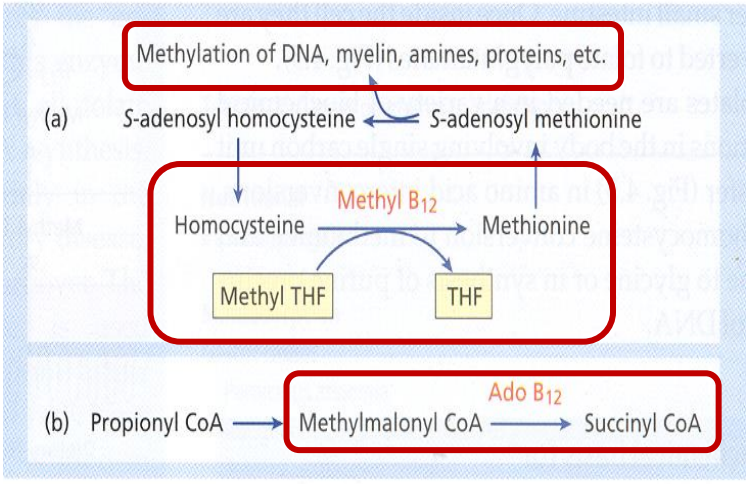
1- Inadequate intake.
2- Veganism, lactovegetarianism (some cases).
3- Inadequate secretion of intrinsic factor.
4- Pernicious anemia.
5- Total or partial gastrectomy.
6- Congenital intrinsic factor deficiency (rare).
7- Inadequate release of B_{12} from food.
8- Partial gastrectomy (common, bypass surgery), vagotomy, gastritis, acid-suppressing drugs, alcohol abuse.
9- Diversion of dietary B_{12}.
10- Abnormal intestinal bacterial flora multiplejejunal diverticula, small intestinal strictures, stagnant intestinal loops.
11- Diphyllobothrium latum (fish tapeworm).
12- Malabsorption (one of the main causes).
13- Crohn's disease, ileal resection, chronic tropical sprue, congenital selective B_{12}malabsorption with proteinuria (Imerslund-Grasbeck syndrome).

NOTE: Ingestion of food containing vitamin B12→Parietal cell in stomach secrete intrinsic factor → bend to B12 in terminal ileum →get absorbed by **TC2(transcobalamin 2)** in the terminal ileum. **Anything will interfere with this process will cause vitamin B12 deficiency.**

Folate:

Dietary Folate must be converted to **mythel THF** (tetrahydrofolate) to get absorbed in the small intestine. Then with the help of **B12** and **homocysteine**, mythel THF will be converted to **THF**. If any one of the three: mythel THF, homocysteine or vit B12 is absent **the reaction won't happen.**





NOTE: 1- **Homocysteine** level will be **high** in case of vitamin B12 deficiency.

2- Vitamin B12 deficiency will also cause indirect folic acid deficiency.

Causes of folate deficiency:

1. **Inadequate dietary intake.**
2. **Malabsorption: (**Coeliac disease, jejunal resection, tropical sprue**)**
3. **Increased requirement: (Pregnancy**, premature infants, chronic haemolytic anemia, myelofibrosis, various malignant diseases)
4. **Increased loss: (**Long-term dialysis, congestive heart failure, acute liver disease**)**
5. **Complex mechanism:** (Anticonvulsant therapy, * ethanol abuse*)**

* Only some cases with macrocytosis are folate deficient.

Clinical Features of Megaloblastic anemia

1. Weakness, anorexia, weight loss, diarrhea or constipation, tiredness, shortness of breath, angina of effort, heart failure. (due to low Hemoglobin).
2. **Mild jaundice** (hemolytic anemia), glossitis (with enlargement and redness of the tong) (beefy tongue), stomatitis, **angular cheilosis**. (Fissures around the lips).
3. Purpura, melanin pigmentations.
4. **Infections.**
5. **Neuropathy due to vit B_{12} and folate deficiency:**
   It's mostly due to vitamin B_{12} deficiency.
   Progressive neuropathy affecting:
   - The peripheral sensory nerves.
   - Posterior and lateral columns of the spinal cord (subacute combined degeneration of the cord).
   - Optic atrophy.
   - Psychiatric symptoms. (e.g hallucination).
   - The neuropathy is likely due to accumulation of S-adenosyl homocysteine and reduced level of S-adenosyl methionine in nervous tissue resulting in defective **methylation of myelin** and other substrates.
6. **Neural tube defect (NTD):**
   - (**Anencephaly, spina bifida or encephalocoele**) in the fetus due to **folate** or **Vitamin B_{12} deficiency in the mother**. This result in build-up of homocysteine **and S-adenosylhomocysteine** in the fetus, which impair methylation of various proteins and lipids.
   - Genetic a mutation **in the parents** in **5,10 methylene tetrahydrofolatereductase (absence of this enzyme)→low** serum **red cell** and **folate** and **high** serum **homocysteine** and fetus with NTD.
   - Cleft palate and hair lip.

*NTD happens due to deficiency more than Genetic

REMEMBER: Neuropathy and hypersegmented neutrophils are classical to Vitamin B12 deficiency.

Hematological findings in Megaloblastic Anemia:

Peripheral Blood:

- **Macrocytic anaemia**, oval macrocytes, anisocytosis, poikilocytosis high MCV.
- Dimorphic anemia when it is associated with iron deficiency or with thalassaemia trait.
- Hypersegmented neutrophils.
- **Leucopenia** and **thrombocytopenia**

Bone Marrow:

- Hypercellular marrow with M:E ratio in normal or reduced.
- Accumulation of **primitive cells** due to selective death of more mature cells.
- Megaloblast (large erythroblast which has a nucleus of open, fine, lacy chromatin).
- **Dissociation between the nuclear and cytoplasmic development in the erythroblasts**.
- Mitosis and dying cells are more frequent than normal.
- Giant and abnormally shaped, metamyelocytes, polypoid megakaryocytes. (most important finding).
- Increased stainable iron in the macrophage and in the erythroblasts.

Other laboratory abnormalities (Not Important)

- Chromosomal abnormalities
- Ineffective haemopoiesis. (Intramedullary cell death by apoptosis) associated with increased serum indirect bilirubin.
- ↑ urobillinogen and faecalstercobillinogen.
- ↑ LDH ↑ serum iron ↑ blood carbon monoxide.
- ↑ Serum lysozyme.
- ↓ Reduced haptoglobins.

Treatment:

Even if the diagnosis is confirmed we must test for vit B_{12} and folic acid levels.

Large amount of hydroxocabalamin → neural defect in pregnant ladies.

Important

Treatment of Megaloblastic anemia

	Vitamin B_{12} deficiency	Folate deficiency
Compound	Hydroxocobalamin	Folic acid
Route	Intramuscular	Oral
Dose	1000 µg	5 mg
Initial dose	6x1000 µg over 2-3 weeks	Daily for 4 months
Maintenance	1000 µg every 3 months	Depends on underlying disease; life-long therapy may be needed in (1)chronic inherited haemolytic anaemia, (2)yelofibrosis, (3) renal dialysis
Prophylactic	(1)Total gastrectomy (2)Ileal resection	(1)Pregnancy, (2)severe haemolytic anaemias, (3)dialysis, (4)prematurity

Summary (from Essential Hematology)

1. Macrocytic anemia show an increased size of circulating red cells (MCV>98fl).
2. Causes include vitamin B12 (B12, Cobalamin) or folate deficiency, alcohol, liver diseases, hypothyroidism, myelodysplasia, paraprotenemia, cytotoxic drugs, aplastic anemia, pregnancy and the neonatal period.
3. B12 or folate deficiency cause megaloblastic anemia, in which the bone marrow erythroblasts have a typical abnormal appearance.
4. B12 deficiency is usually caused by B12 malabsorption brought about pernicious anemia in which there is autoimmune gastritis, resulting in sever deficiency of intrinsic factor, a glycoprotein made in the stomach which facilitate B12 absorption by the ilium.
5. Other gastrointestinal diseases as well as vegan diet may cause B12 deficiency.
6. Folate deficiency may be caused by a poor diet, malabsorption (e.g. glutin-induced enteropathy) or excess cell turnover (e.g. pregnancy, heamolytic anemias, malignancy).
7. Treatment of B12 deficiency is usually with injections with hydroxycobalamin and of folate deficiency with oral folic (pteroyglutamic) acid.

Questions

1/ A 43-year-old woman complains of constant tiredness, light-headedness, and occasional palpitations and shortness of breath while ascending the stairs. Physical examination shows pallor of the oral mucosa and glossitis. Neurologic examina tion reveals paresthesias, numbness, decreased vibration sensation, and loss of deep tendon reflexes. The results of laboratory studies include hemoglobin of 7.2 g/dL, WBC of 4,500/mL, platelets of 140,000/mL, serum vitamin B12 of 40 pg/mL (normal >200 pg/mL),. Examination of peripheral blood shows macrocytic anemia, with poikilocytosis of RBCs and hypersegmented neutrophils. Bone marrow examination in this patient will reveal which of the following pathologic findings?

(A) Absent stainable bone marrow iron
(B) Atypical megakaryocytes with fibrosis
(C) Hypercellularity with megaloblastic erythroid maturation
(D) Hypocellularity with absence of erythroid precursors

2/ which of the following mechanisms of disease best describes the pathogenesis of anemia in the patient described in Question 1?

(A) Bone marrow fibrosis
(B) Defective heme synthesis
(C) Immune destruction of circulating erythrocytes
(D) Impaired DNA synthesis

3/ A patient with a history of chronic alcoholism presents with a macrocytic anemia and thrombocytopenia. Blood smear examination demonstrates numerous oval macrocytes and hypersegmented neutrophils. Which of the following is the most likely diagnosis?

(A) Anemia of chronic disease
(B) Folic acid deficiency
(C) G6PDdeficiency
(D) Iron deficiency anemia

Answers:

- 1- C
- 2- D
- 3- B

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com