MACROCYTIC ANEMIA

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- Macrocytic anemia is simply means anemia with MCV >100.
- These can be divided into megaloblastic and non-megaloblastic types depending on the marrow findings.

MEGALOBLASTIC ANEMIA

- Megaloblastic anemia is characterized by the presence in the bone marrow erythroblasts with delayed nuclear maturation because of defective DNA synthesis (megaloblasts).
- Megaloblasts are large and have large immature nuclei.

Causes of megaloblastic anemia

- Vitamin B12 deficiency or abnormal B12 metabolism
- Folic acid deficiency or abnormal folate metabolism
- Other defects of DNA synthesis, such congenital enzyme deficiency in DNA synthesis (e.g. orotic aciduria), or resulting from therapy of drugs interfering with DNA synthesis (e.g. hydroxycarbamide {hydroxyurea}, azathioprine, zidovudine-AZT.

Haematological findings

- Anemia maybe present with MCV >96fl unless there is a co-existing cause of microcytosis when there maybe a dimorphic picture with normal/ low average MCV.
- Peripheral blood firm shows oval macrocytes with hypersegmented polymorphs with 6 or more lobes in the nucleus.
- If severe there maybe leucopenia and thrombocytosis.

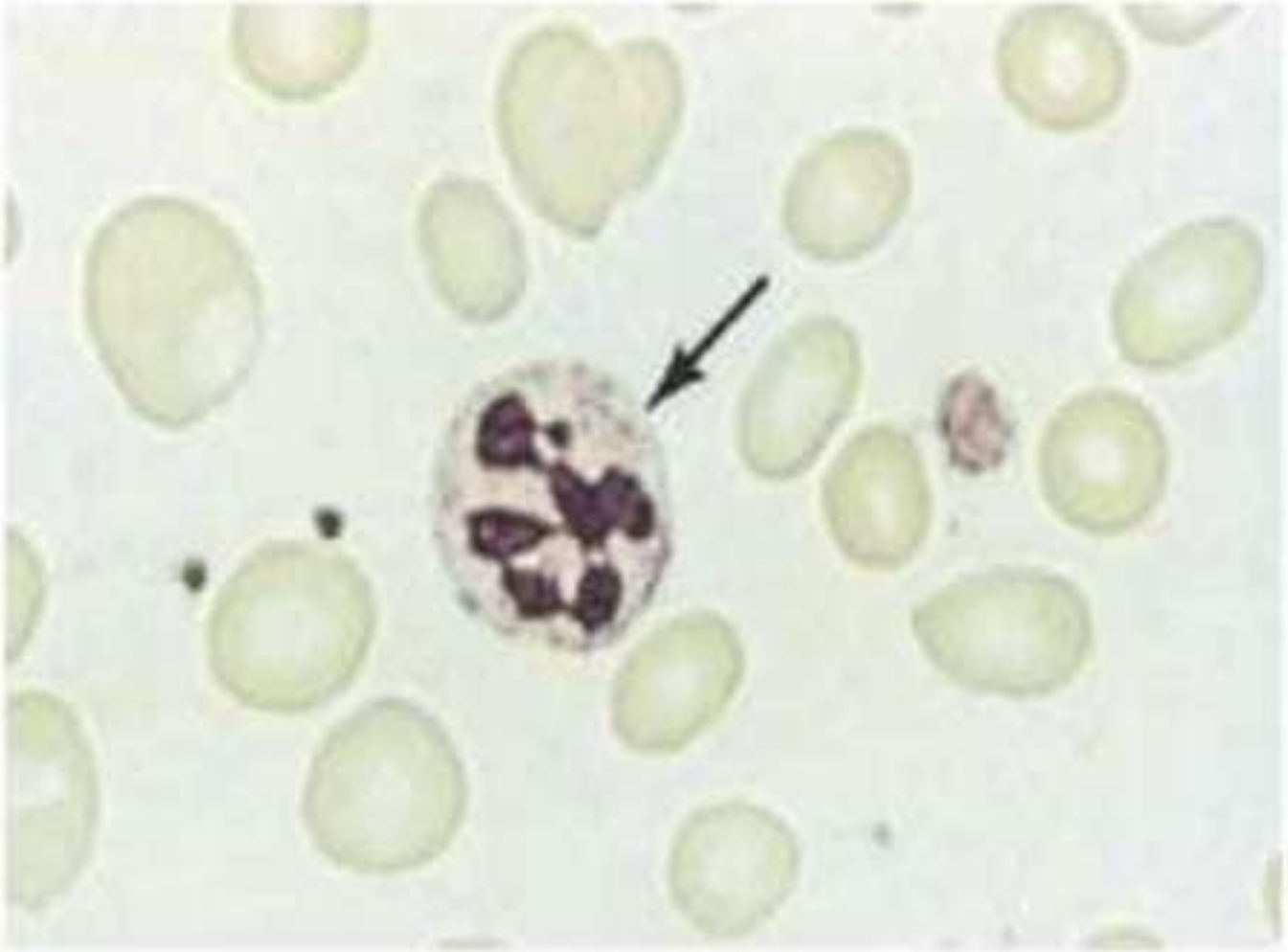

Figure 8.11 Macrocytes and a hypersegmented neutrophil (arrowed) on a peripheral blood film.

- Folate and B12 are necessary for the synthesis of DNA precursors.
- Lack of folate or B12 impairs the synthesis of DNA precursors which in turn causes:-
- Megaloblastic anemia.
- Hypersegmented neutrophils.
- Megaloblastic changes in rapidly dividing epithelial cells (e.g. intestine)

Biochemical basis

- The key biochemical problem common to both vitamin B12 and folate deficiency is a block in DNA synthesis owing to an inability to methylate deoxyuridine monophoshate to deoxythimidine monophoshate, which is then used to build DNA. The methly group is supplied by the folate coenzyme, methylene tetrahydrofolate.

Folate Deficiency

- Folate is obtain from green vegetables such as spinach, broccoli and offal such as liver and kidney and some fruits is absorbed in the jejunum. Folate deficiency usually develops within months because of the body stores are minimal.
- Cooking causes a loss of about 60-90% of the folate. The minimal daily requirement is about 100µg

Causes of folate deficiency

- Poor intake
- Poor intake due to anorexia:- GI disease e.g. partial gastrectomy, celiac disease & Crohn's disease.
- Antifolate drugs:- phenytoin, primidone, methotrexate, pymethamine, and trimethoprim.
- Pregnancy, lactation
- Hemolysis
- Cancer

Clinical picture and lab. findings

- Sign and symptoms of anemia
- Glossitis
- Macrocytic RBCs and hypersegmented neutrophils
- ↓ serum folate
- ↑serum homocysteine
- Normal methylmalonic acid

Treatment of folate deficiency

- Folate deficiency can be treated by giving 5mg of folic acid daily.
- Treatment should be given for about 4 months to replace body stores.
- Treating the underlying cause i.e. celiac disease.
- Prophylactic folic acid (400µg daily) is recommended for all women planning a pregnancy to reduced neural tube defects.

B12 Deficiency

- Dietary vitamin B12 is complexed to animals derived proteins. Unlike folate B12 deficiency takes years to develop due to large hepatic stores of B12, about 2-3mg and the daily losses are small (1-2µg).

Causes of vitamin B12 deficiency

- The most common cause of vitamin B12 deficiency is *pernicious anemia*
- Other causes include:-
- Low dietary intake as in vegans
- Gastrectomy
- Congenital deficiency of intrinsic factor
- Ileac disease or resection i.e. Crohn's disease
- Bacterial overgrowth
- Tropical sprue
- Fish tape worm (diphyllothrium latum)
- Pancreatic insufficiency

Pernicious Anemia

- Pernicious anemia (PA) is an autoimmune disorder characterized by destruction of parietal cells (body of the stomach) which lead to intrinsic factor deficiency and vitamin B12 malabsorption.

- Pernicious anemia is more common in the elderly >60years with female sex affected more often than males.
- There is an association with other autoimmune disease particularly Thyroid disease, Addison's disease, and Vitiligo.
- There is an increase risk of gastric carcinoma with PA (1-3%) than in the normal population.

Clinical Features

- Symptoms of anemia
- Lemon yellow color
- Red sore tongue (Glossitis)
- Angular stomatitis
- Neurological features are those of polyneuropathy involving the peripheral nerves, posterior and lateral columns of the spinal cord (subacute combine degeneration of the cord).


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- Symmetrical paraesthesiae in the fingers and toes
- Loss of vibration sense and proprioception
- Progressive weakness and ataxia
- Paraplegia may result
- Dementia
- Psychiatric problems
- Hallucinations
- Optic atrophy

Investigation

- Complete blood count
- Blood smear
- Serum bilirubin
- LDH may raise due to Hemolysis
- ↓Serum vitamin B12
- ↑serum homocysteine
- ↑serum methylmalonic acid

- Anti gastric parietal cell antibodies in 90% (low specificity)
- Anti intrinsic factor antibodies in 50% (specific for pernicious anemia)
- Schilling test

Treatment of B12

- Hydroxocobalamin 100µg IM to a total of 5-6mg over the course of 3 weeks, 1000µg is necessary every 3 months for the of the patient life.
- Oral B12 2mg/ day.
- Sublingual nuggets of B12 (2x100µg daily)

Other Causes of Macrocytic Anemia

- Alcohol
- Liver disease
- Drugs (e.g. 5 FU)
- Reticulocytosis
- Hypothyroidism
- Some haemalogical disorders i.e. aplastic anemia, sideroblastic anemia and pure red cell aplasia.
- Cold agglutinin due to autoagglutination of RBCs.

Case

- A 76 year old man comes to the office because he is having numbness and tingling of his hands and feet, he also has a little memory problem and he is a long time alcoholic.
- Lab findings:-
- HCT 30
- MCV 110

- What is the most likely diagnosis?
- A. folate deficiency
- B. vitamin B12 deficiency
- C. alcohol
- D. degeneration of the cord

- What is the next step of your management?
- A. Schilling test
- B. smear
- C. replace B12
- D. replace folic acid

GRACIAS