CASE TWO

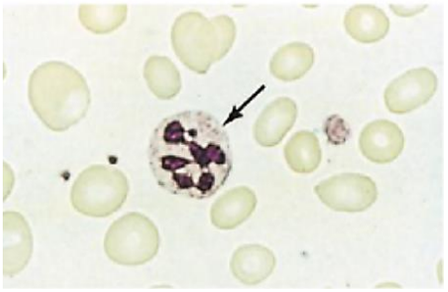
Short case number: 3_30_2
Category: Immune and haemopoietic systems
Discipline: Medicine
Setting: General Practice
Topic: Anaemia_macrocytic

Case

Maude McArthur, a 75 year old widow from the nearby retirement village presents complaining of a sore tongue. It has become quite difficult to eat lately and she is really only having tea and toast. You observe that Maude's tongue is quite inflamed as well as the corners of her mouth.
You are concerned about Maude's diet and think she may have a nutritional problem.

Questions

1. What are the key features of the history and examination in your assessment of Maude and why?



2. What clinical findings would suggest a vitamin B_{12} and/or folate deficiency?
3. Explain the role of Vitamin B_{12} and folate in red cell metabolism.
4. Preliminary investigations reveal that Maude has a macrocytic anaemia. With a blood film similar to the one pictured. Explain how B_{12} and folate results in macrocytic red blood cells.
5. Further investigations reveal that Maude has a B_{12} deficiency which is not really explained by her diet, as her diet has only recently changed. You are concerned that Maude may have pernicious anaemia. In revising the absorption and transport of B_{12}, explain pernicious anaemia and how it results in B_{12}deficiency.
6. Outline the investigations used in the diagnosis and assessment of pernicious anaemia.

Note. From Kumar & Clark's Clinical Medicine (8th ed.) p.399, by P. Kumar and M.L. Clark, 2012, Edinburgh: Saunders Elsevier.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.
- Clinical Examination. A systematic guide to physical diagnosis. Talley and O'Connor

ANSWERS

Question 1

What are the key features of the history and examination in your assessment of Maude and why?

You suspect a nutritional deficiency in B12 and folate, so on history and examination you would need to enquire about

- Nutritional intake (in particular green leafy vegetables)
- Dentition
- Home Situation /cooking arrangements
- ETOH intake
- Risk factors for pernicious anaemia (other autoimmune conditions, 1st degree relative with PA or autoimmune conditions)

Folate is present in most foods, notably green vegetables, liver and nuts, but it may be destroyed by cooking. In patients with grossly deficient diets folate deficiency is relatively common because stores are meagre, being sufficient for only 3-4 months.

Examination:

A full haematological examination should be completed. In particular look for signs of severe anaemia, including pallor, tachycardia, wide pulse pressure, systolic ejection murmurs due to a compensatory rise in cardiac output, and cardiac failure if myocardial reserve is reduced.

The legs should also be examined for evidence of the neurological abnormalities caused by vitamin B12 deficiency: peripherally neuropathy, and subacute combined degeneration of the spinal cord. B12 deficiency can also result in optic atrophy, and mental changes.

Question 2

What clinical findings would suggest a vitamin B_{12} and/or folate deficiency?

Clinical signs of folate and B12 deficiency

Skin

- angular cheilosis - sore mouth
- glossitis - beefy red tongue
- pigmentation, alopecia

Gut

- epithelial abnormalities - anorexia, weight loss
- stomach + small bowel - altered bowel habit, malabsorption

CNS

- mental abnormalities – dementia
- peripheral neuropathy, subacute combined degeneration of the cord - paraesthesia, numbness, difficulty in walking, weakness

Eyes

- retrobulbar neuritis - poor vision
- optic atrophy – blindness

Question 3

Explain the role of Vitamin B_{12} and folate in red cell metabolism.

Vitamin B12 and folate are important for DNA synthesis in red cell metabolism.

The human body needs folate and vitamin B 12 to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in biological reactions involving folate. It is especially important during periods of rapid cell division and growth.

Question 4
Preliminary investigations reveal that Maude has a macrocytic anaemia. With a blood film similar to the one pictured. Explain how B_{12} and folate results in macrocytic red blood cells.

B12 and folic acid are coenzymes in the DNA synthetic pathway. A deficiency of these vitamins or impairment in their utilization results in deranged or inadequate synthesis of DNA. The synthesis of RNA and protein is unaffected, however, so there is cytoplasmic enlargement not matched by DNA synthesis, which appears to delay or block mitotic division. Thus there appears to be asynchronism between the cytoplasmic maturation and nuclear maturation.

Question 5
Further investigations reveal that Maude has a B_{12} deficiency which is not really explained by her diet, as her diet has only recently changed. You are concerned that Maude may have pernicious anaemia. In revising the absorption and transport of B_{12}, explain pernicious anaemia and how it results in B_{12}deficiency.

Vitamin B12, or cyanocobalamin, is a group of cobalt-containing water-soluble vitamins. They are coenzymes necessary for red blood cell production - folate polyglutamate is the major red cell form of folate. Vitamin B12 is derived primarily from food of animal origin, including dairy products. Absorption of B12 from the gastrointestinal tract is dependent on acid and intrinsic factor secreted by the gastric mucosa. The recommended daily average intake in the adult is 3-5 micrograms. A normal liver stores about 3 mg which is sufficient for several years.

Pernicious anaemia (PA) is a disease of the stomach that is characterised by megaloblastic anaemia due to vitamin B12 deficiency, itself, secondary to intrinsic factor deficiency and gastric atrophy. It usually has an autoimmune basis

PA primarily affects the elderly - most patients are over 60 years of age; less than 10% of cases are under 40 years of age; it is rare in children. Women are affected more often than men, in a ratio of 3:2.

Auto-antibodies to gastric parietal cells are present in 90% of cases but are not pathognomonic as they may occur:

- in other disorders, for example, Addison's disease; iron deficiency anaemia
- in normal relatives of those with PA
- in 16% of randomly selected women over 60 years

Auto-antibodies to intrinsic factor are more specific. They are found in the serum in 55% of cases and in gastric juice in 80%. They are of two types:

- blocking antibody - directed towards the combining site for vitamin B12 on IF
- binding antibody - reacts with an antigenic determinant on IF distinct from the B12 combining site; the reaction may be with free IF or with IF-B12 complex in the terminal ileum to inhibit absorption.

Question 6
Outline the investigations used in the diagnosis and assessment of pernicious anaemia.

Anti – intrinsic factor antibodies are widely available for testing of PA. They have a sensitivity of 50 – 60 % and a specificity approaching 100% for the diagnosis. Antiparietal cell antibodies are more sensitive but less specific.

Gastric biopsy may demonstrate chronic atrophic gastritis, and due to the increased risk of gastric malignancy, referral to a gastroenterologist for gastric monitoring is usually indicated.

The Schilling test is the classic test for inadequate B12 absorption and consists of two parts. The first part remains available in a number of laboratories; the second part is no longer performed because of the unavailability of intrinsic factor. The test is rarely of additional clinical utility.