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ENDGAMES

CASE REVIEW

A link between asthenia, pallor, and jaundice

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A 45 year old white man presented to the emergency department with progressively worsening weakness and chest discomfort on moderate intensity physical activity over the past two months. He also reported paleness and "yellowish eyes" in the past month. He had a history of anxiety, treated with alprazolam as needed.

At presentation, his vital signs were normal. On physical examination he had mild generalised pallor, scleral icterus, and tender non-painful hepatomegaly.

He was admitted to the internal medicine ward for further evaluation.

Laboratory studies showed haemoglobin 70 g/L (reference range 13-17), mean corpuscular volume 111.5 fL (83-101), haematocrit 19.4% (40-50%), leucocyte count 3.3×10^9/L (4-10), platelet count 151×10^9/L (150-450), reticulocyte production index 0.52 (>2), lactate dehydrogenase 1460 U/L (125-220), total bilirubin 35.92 µmol/L (5.13-20.52), direct bilirubin 11.97 µmol/L (1.71-8.55), haptoglobin <0.07 g/L (0.30-2), vitamin B_{12} 57.55 pmol/L (156-672), ferritin 177 ng/mL (50-250), and folic acid 26.74 nmol/L (>12.24). The peripheral blood smear showed macrocytosis and hypersegmented neutrophils.

Antibodies against parietal cells were positive; Coombs test and anti-intrinsic factor antibodies were negative.

Upper gastrointestinal endoscopy showed atrophic gastritis of the body and fundus. Staining for *Helicobacter pylori* was negative (fig 1). Biopsy confirmed the presence of type A atrophic gastritis with moderate intestinal metaplasia.

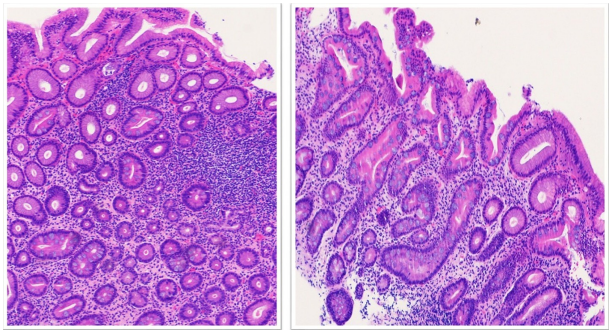

Fig 1 Gastric body fragments showing glandular atrophy plus moderate intestinal metaplasia and a moderate mononuclear infiltrate of the lamina propria (haematoxylin and eosin stain, original magnification ×100)

Questions

1.What is the most likely diagnosis?

2.What strategy can primary care practitioners take to reach the diagnosis?

3.What are the differential diagnoses?

4.How is this condition managed?

5.How is this condition followed up?

Answers

1.

What is the most likely diagnosis?

Short answer

Pernicious anaemia with intramedullary haemolysis as a result of ineffective erythropoiesis.

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Discussion

Pernicious anaemia is a macrocytic anaemia caused by vitamin B_{12} (cobalamin) deficiency, as a consequence of an intrinsic factor deficit. The deficiency in intrinsic factor is caused by an autoimmune disease that targets gastric parietal cells and leads to gastric atrophy of the body and fundus (type A chronic atrophic gastritis). Intrinsic factor aids the absorption of vitamin B_{12} in the terminal ileum, so its deficiency results in low levels of vitamin B_{12} and in pernicious anaemia.[1 2]

The prevalence of pernicious anaemia ranges from 50 to 4000 cases per 100 000 people.[3] The mean age of diagnosis is 50-60 years.[2] Its presentation is highly variable, ranging from asymptomatic disease in the early stages to symptoms of anaemia, such as dyspnoea on exertion, palpitations, and asthenia. It sometimes presents with neurological manifestations, from peripheral neuropathy (commonly paraesthesia and numbness) to signs and symptoms of spinal cord injury (loss of vibration and position sense with sensory ataxia and limb weakness). Cerebral manifestations such as delusions, hallucinations, and paranoid schizophrenic ideation ("megaloblastic madness") can also be present.[3 4]

Haemolysis can also occur as a result of DNA synthesis and nuclear maturation defects, which lead to ineffective erythropoiesis and intramedullary haemolysis,[3] and autoimmune thyroid disease occurs in 18-40% of patients.

Even though pernicious anaemia is considered a benign disease, patients are prone to the development of intestinal-type gastric adenocarcinoma and gastric carcinoid type I. The incidence rate of gastric cancer is 0.27% per person years—a seven times higher relative risk than in the general population.[5] The main reasons for this increased risk are the presence of hypochlorhydria or achlorhydria, which leads to hypergastrinaemia (risk factor for enterochromaffin-like cell hyperplasia and gastric carcinoids) and overgrowth of carcinogenic nitrosamine producing bacteria, which also contributes to the development of gastric cancer.[5 6]

2. What strategy can primary care practitioners take to reach the diagnosis?

Short answer

Request tests for hypoproliferative macrocytic anaemia and serum cobalamin levels.[2-8] Request endoscopic examination with histological analysis.[6 8]

Discussion

There are no defined criteria for the diagnosis of pernicious anaemia because it can present with a variety of laboratory, endoscopic, and histological findings (box 1). However, it is accepted that the demonstration of megaloblastic anaemia, macro-ovalocytes, and hypersegmented neutrophils in the blood smear; low serum vitamin B_{12} levels; atrophic gastritis (body or fundus); and the presence of antibodies to gastric parietal cells or intrinsic factor are sufficient to make the diagnosis.[2]

Diagnosis is based on the presence of macrocytic anaemia with a low reticulocyte production index, reduced serum cobalamin levels, and the presence of atrophic body gastritis and intrinsic factor deficiency.[8]

Importantly, the measurement of serum cobalamin can be misleading, especially for values around the lower limit of normal.[3] In this case, the diagnosis should be confirmed by determining plasma methylmalonic acid and total homocysteine, which are increased in the presence of a cobalamin deficit.

Holotranscobalamin (transcobalamin bound to cobalamin), also referred to as active vitamin B_{12}, is considered an early marker of vitamin B_{12} deficiency, with some studies reporting a higher specificity and sensibility than for total vitamin B_{12}.

A holotranscobalamin value of <35-40 pmol/L is consistent with vitamin B_{12} deficiency,[8] although there is no consensus on the optimal cut-off values. The British Society for Haematology suggests using cut-off values that are based on manufacturers' reference ranges or determined by the laboratory performing the test.[9]

Holotranscobalamin can be used instead of total vitamin B_{12} in certain populations, such as pregnant women, because unlike total serum cobalamin it does not show a physiological reduction during pregnancy.[9]

Although holotranscobalamin performs better than total vitamin B_{12}, a confirmatory test (methylmalonic acid or homocysteine) is still needed when results are indeterminate.[9-12]

Once vitamin B_{12} deficiency has been confirmed the cause needs to be determined. Pernicious anaemia is caused by an immune mediated destruction of the gastric parietal cells, which results in achlorhydria with hypergastrinaemia and low levels of intrinsic factor secretion. Thus, the presence of endoscopic signs of chronic atrophic type A gastritis and its histological corroboration are usually considered sufficient to confirm the diagnosis.[6 7]

Serological positivity to intrinsic factor or parietal cell autoantibodies (or both) supports a diagnosis of pernicious anaemia. Intrinsic factor antibodies have a sensitivity and specificity of 37% and 100%, respectively (enzyme linked immunosorbent assay; ELISA), whereas parietal cell antibodies have a sensitivity and specificity of 81.5% and 90.3%, respectively.[2] Although parietal cell antibodies have the higher sensitivity, they can be absent in the later stages of the disease because of a reduction in the number of target (parietal) cells.[6]

A proposed general approach to the diagnosis of pernicious anaemia is shown in fig 2.

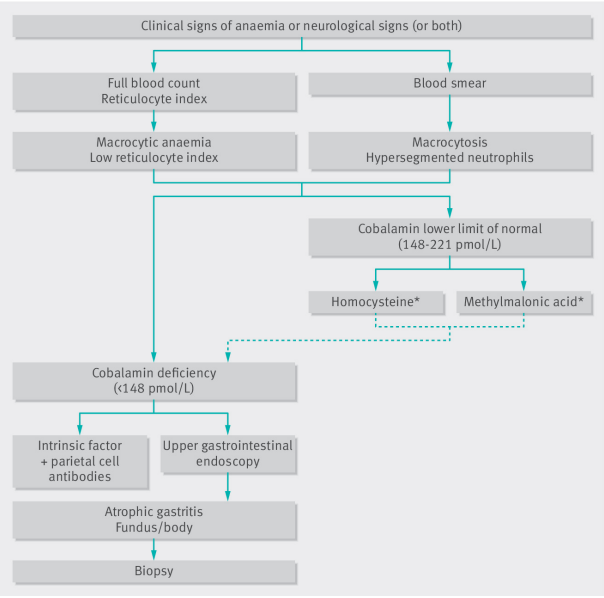

Fig 2 Diagnostic approach to pernicious anaemia. *High levels suggest cobalamin deficiency

Iron studies should also be considered in the initial assessment of pernicious anaemia because iron absorption can be impaired when gastric pH is raised.[13]

Box 1: Common abnormalities related to pernicious anaemia

Complete blood count

- Macrocytosis
- Anaemia
- Leucopenia
- Thrombocytopenia
- Pancytopenia

Peripheral blood smear

- Macrocytosis
- Hypersegmented polymorphonuclear leucocytes

Biochemistry

- High lactate dehydrogenase
- High indirect bilirubin
- Low haptoglobin

Specific tests

- Normal or low vitamin B_{12}
- High homocysteine
- High methylmalonic acid
- Low iron stores
- Hypergastrinaemia
- Achlorhydria

Serology tests

- Positivity for serum antibodies to gastric parietal cells, or
- Positivity for serum antibodies against intrinsic factor

Endoscopic findings

- Type A chronic atrophic (autoimmune) gastritis

Histological findings

- Mononuclear cellular infiltrates of the submucosa—the lamina propria between the gastric glands
- Intestinal metaplasia

3.

What are the differential diagnoses?

Short answer

Other causes of vitamin B_{12} deficiency, macrocytic anaemia, and intravascular haemolysis.

Discussion

The differential diagnoses of pernicious anaemia are the same as those of macrocytic anaemia. They include folate deficiency, myelodysplasia, alcoholic liver disease, hypothyroidism, drugs that block folate metabolism (eg methotrexate), and other causes of vitamin B_{12} deficiency (eg partial or total gastrectomy, fish tapeworm infection, Crohn's disease, ileal resection, and a vegan diet).[4-15] Box 2 lists the common causes of macrocytosis.[9-18]

4.

How is this condition managed?

Short answer

With lifelong cyanocobalamin or hydroxocobalamin supplementation.[2]

Discussion

Pernicious anaemia is treated with cyanocobalamin or hydroxocobalamin. The route, dosage, and schedule of administration vary widely between healthcare institutions and doctors. Box 3 summarises some of the accepted treatment regimens.[2-22]

Lifelong vitamin B_{12} supplementation is warranted. Effective treatment corrects blood counts in 8-12 weeks and improves neurological signs and symptoms within three months if given soon after onset.[21 22]

This condition can be managed by GPs in the community, but referral to specialists should be considered in certain scenarios (box 4).

Supportive therapy with iron and folic acid should be started in patients with severe anaemia to enhance haematopoiesis.[6]

If iron deficiency is present, supplementation should be started promptly. Oral iron formulations are considered first line therapy, with intravenous iron replacement being indicated for patients who do not respond to oral treatment.[23]

Folic acid supplementation can worsen or precipitate neurological manifestations of vitamin B_{12} deficiency. We therefore suggest starting folic acid after at least one dose of vitamin B_{12} and only when folate levels are low or at the lower limit of normal. We also suggest assessing folic acid levels as a part of the initial evaluation and seven days (reticulocytosis peak) after the start of vitamin B_{12} supplementation. Treatment with folic acid should be maintained until anaemia resolves.

5.

How should this condition be followed up?

Short answer

Annual clinical review, full blood count, thyroid stimulating hormone and free thyroxine assays, serum cobalamin and ferritin analysis, and regular endoscopy for gastric cancer are advised.

Box 2: Common causes of macrocytosis

Low vitamin B_{12}

- Low dietary intake and a vegan diet
- Total or subtotal gastrectomy
- Pernicious anaemia
- Fish tapeworm (*Diphyllobothrium latum*)
- Bacterial overgrowth of the small intestine
- Terminal ileal diseases
- Drugs:
  - Proton pump inhibitors
  - Metformin
- Genetic defects:
  - Intrinsic factor deficiency
  - Imerslund-Gräsbeck syndrome
  - Transcobalamin deficiency
  - Impaired synthesis of adenosylcobalamin
  - Dysfunction of methylcobalamin synthesis
  - Methylmalonic acidaemia

Folate deficiency

- Low dietary intake
- Subtotal gastrectomy
- Coeliac disease and tropical sprue
- Achlorhydria
- Bacterial overgrowth of the small intestine
- Increased consumption:
  - Pregnancy
  - Chronic haemolytic anaemias
  - Malignant diseases
- Drugs:
  - Methotrexate
  - Anticonvulsants (eg phenytoin)
  - Trimethoprim
  - Sulfasalazine
- Genetic defects
  - Methylenetetrahydrofolate reductase deficiency
  - Glutamate formiminotransferase-cyclodeaminase deficiency
  - Dihydrofolate reductase deficiency

Drugs

- Chemotherapeutic agents
- Antiretrovirals
- Anticonvulsants
- Anti-inflammatory drugs
- Nitrous oxide

Other

- Chronic liver disease
- Chronic alcohol misuse
- Reticulocytosis
- Hypothyroidism
- Myelodysplastic syndromes
- Acute leukaemia
- Aplastic anaemia

GPs can arrange this, with referral to a specialist if associated diseases (autoimmune disease or gastric cancer) are present or if treatment response is inadequate.

Discussion

Primary care physicians play a crucial role because pernicious anaemia requires lifelong surveillance to ensure the administration of adequate quantities of cobalamin, to prevent the onset of iron deficiency, and to arrange regular endoscopic surveillance for gastric cancer. Furthermore, regular evaluation for autoimmune thyroid disease is warranted.[2 13]

The optimal screening strategy for long term complications has not been agreed. Some authors suggest yearly clinical review and laboratory testing (complete blood count, serum cobalamin and ferritin measurement) plus:

Box 3: Accepted treatment strategies for pernicious anaemia

1000 µg of intramuscular cyanocobalamin given daily for 7-10 days, weekly for four weeks, and then monthly for life[2]

Patients without neurological symptoms[9]

1000 µg of intramuscular hydroxocobalamin given three times a week for two weeks, then 1000 µg once every three months for life

Patients with neurological symptoms[9]

1000 µg of intramuscular hydroxocobalamin every two days until no further improvement, followed by 1000 µg once every two months for life

1000-2000 µg of oral cyanocobalamin daily*† for life[19]

*Should not be used in patients with symptoms caused by anaemia (haemoglobin <80 g/L), those with neurological manifestations, or those in hospital.

†Not widely used (except in Sweden and Canada) because most studies supporting this approach show some design or methodological limitations, and vitamin B_{12} has an unreliable absorption rate.[19 20]

Box 4: Indications at presentation for referral to specialised care

- Consultation with a haematologist or neurologist is recommended if the diagnosis is unclear (eg pancytopenia or neurological manifestations)
- Refer to a gastroenterologist if the patient also had iron or folic acid deficiency (or both) to rule out other conditions that can cause malabsorption (eg coeliac disease) and investigate the need for intravenous iron treatment
- Consider admission to the emergency department for all patients with severe symptoms of anaemia

- Five year follow-up with endoscopy of the upper gastrointestinal tract in patients with enterochromaffin-like cells hyperplasia, or
- Three year follow-up with endoscopy of the upper gastrointestinal tract in patients with pernicious anaemia who are under 60 years, or
- Four year follow-up every four years after diagnosis of pernicious anaemia.[2]

Follow-up endoscopies can be arranged by GPs. If extensive metaplastic atrophy, gastric epithelial dysplasia, adenomas, or dysplasia in hyperplastic polyps is found at endoscopic examination, patients should be referred to gastroenterology for further evaluation.[24]

Patients with certain clinical and laboratory findings during follow-up should be referred to specialised care (box 5).

Patient outcome

Blood transfusion relieved this patient's symptoms. Vitamin B_{12} levels were restored with daily 1000 µg of cyanocobalamin, administered intramuscularly for seven days, then weekly for four weeks, and monthly thereafter. Supportive treatment with 357 mg of iron(III)-hydroxide polymaltose complex and 5 mg of folic acid, orally once a day, was also started.

After the first week of treatment, his reticulocyte production index rose to >2. This confirmed a good treatment response and he was discharged. At follow-up with an internal medicine specialist six weeks later there was an overall improvement, with haemoglobin of 101 g/L, mean corpuscular volume 102 fL, ferritin 251 ng/mL, and cobalamin 2000 pg/mL.

During the first year of follow-up he will be evaluated by internal medicine and will then be followed up by his GP. Clinical evaluation, a full blood count, ferritin, and vitamin B_{12} assessment are warranted, as repeat endoscopy of the upper gastrointestinal tract in the next three years.

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Patient consent obtained.

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Box 5: Referral for specialist evaluation during follow-up and increased risks associated with pernicious anaemia

- Changes in symptoms or laboratory findings suggestive of haematological, upper airway, or digestive system cancers should prompt referral to specialised care
- The risk of haematological, tonsillar, hypopharyngeal, gastric, small intestine, and oesophageal cancers is increased in elderly people with pernicious anaemia[25]
- Referral to an internal medicine specialist and other specialists (eg endocrinologist) should be considered if concomitant autoimmune diseases are suspected
- Associations between pernicious anaemia and autoimmune thyroid disease, type 1 diabetes, and Addison's disease have been described[13 24]

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