# Vitamin B12 deficiency presenting as pancytopenia and retinopathy in a young boy—Helicobacter pylori, a novel causative agent

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## CASE REPORT

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## ABSTRACT

Deficiency of vitamin B12 (cobalamin) is a well-known cause of megaloblastic anaemia. It is a reversible cause of bone marrow failure and demyelinating nervous system disorder, hence early detection and prompt treatment of vitamin B12 deficiency is essential. After diagnosing vitamin B12 deficiency, tracking down its root cause is important in individualising the treatment approach. Helicobacter pylori-related (H. pylori) B12 deficiency presenting as pancytopenia in pediatric age groups has been reported. However, vitamin B12 deficiency presenting as retinopathy in paediatric age groups has been rarely reported in the medical literature. We herein present the case of an adolescent male with pancytopenia and retinopathy, secondary to vitamin B12 deficiency-associated H. pylori infection.

**Key Words**
Pancytopenia, retinopathy, Helicobacter pylori, vitamin B12 deficiency

## What this report adds:

**1. What is known about this subject?**

Vitamin B12 deficiency should be kept in mind when any child presents with pancytopenia. After diagnostic confirmation of vitamin B12 deficiency, it is prudent to investigate further to find the underlying aetiology for the deficiency.

**2. What is the key finding of this report?**

Helicobacter pylori is a novel causative agent for vitamin B12 deficiency presenting as pancytopenia.

**3. What are the implications for future practice?**

Anaemic retinopathy may occur in children with severe anaemia, but prompt treatment of the underlying aetiology for anaemia completely resolves the retinopathy.

## Background

Megaloblastic anaemia can occur due to impaired DNA synthesis resulting from deficiencies of vitamin B12 (cobalamin) and folate. Vitamin B12 is produced by microorganisms and is detected in trace amounts mostly in foods of animal origin. Humans cannot synthesise vitamin B12. Early detection and prompt treatment of vitamin B12 deficiency is essential, since it is a reversible cause of bone marrow failure and demyelinating nervous system disease.[1] Signs and symptoms arising out of vitamin B12 deficiency are varied and non-specific. Vitamin B12 deficiency-associated pancytopenia has been reported in children and adults.[2,3,4,5] After diagnosing vitamin B12 deficiency, tracking down the root cause of the deficiency is important in individualising the treatment approach.

In developing countries, Helicobacter pylori (H. pylori) is the most common cause of gastric infection. In most individuals it is usually asymptomatic, but it is known to cause gastritis, gastric and duodenal ulcers, gastric adenocarcinoma, and MALT (mucosa-associated lymphoid tissue) lymphomas.[6] H. pylori-related B12 deficiency presenting as pancytopenia in paediatric age groups is reported in a few case studies.[2,7,8] However, vitamin B12

deficiency presenting as retinopathy in paediatric age groups has been rarely reported in the medical literature. We report a case of an adolescent male, who presented with pancytopenia and retinopathy, secondary to vitamin B12 deficiency, in whom the H. pylori was implicated to be the causative agent.

## Case details

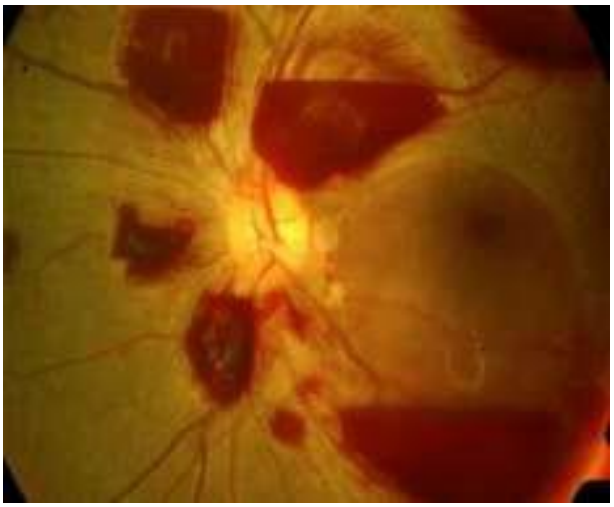
A 17-year-old adolescent male who was the first child of non-consanguineous parents, presented to our outpatient department with easy fatigability, weight loss, and poor appetite for two months duration. He also complained of low-grade intermittent fever associated with yellowish discoloration of the eyes and occasional blurring of vision for the past 10 days. A community physician noticed severe pallor and the patient was referred to our institute for further management. He was a developmentally normal adolescent who ate a mixed diet. His past medical history was non-contributory. He had an uneventful birth history and there were no similar events among his family members.

On examination, he had pallor, icterus without significant lymphadenopathy, hyperpigmentation of the oral cavity, and dorsum of the hands and feet. His visual acuity was 6/36 and 6/24 on the right and left eye, respectively. Fundus examination revealed features suggestive of anaemic retinopathy (Figures 1 and 2) in concordance with his severe pallor. His vital parameters and anthropometric measurements were appropriate for his age.

**Figure 1: Fundus examination (right eye)**

*Right-eye fundoscopic view: clear media and healthy disc with multiple splinter haemorrhages, more around the disc and a few white-centered haemorrhages. Extensive subhyaloid haemorrhages overlying the macula extending more than 10DD with a characteristic fluid level*

**Figure 2: Fundus examination (left eye)**



*Left-eye fundoscopic view: clear media and healthy disc with multiple splinter and blot-shaped haemorrhages, with a few white-centered haemorrhages in all four quadrants, more around the disc. Subhyaloid haemorrhages overlying the macula and superior quadrant with a characteristic fluid level*

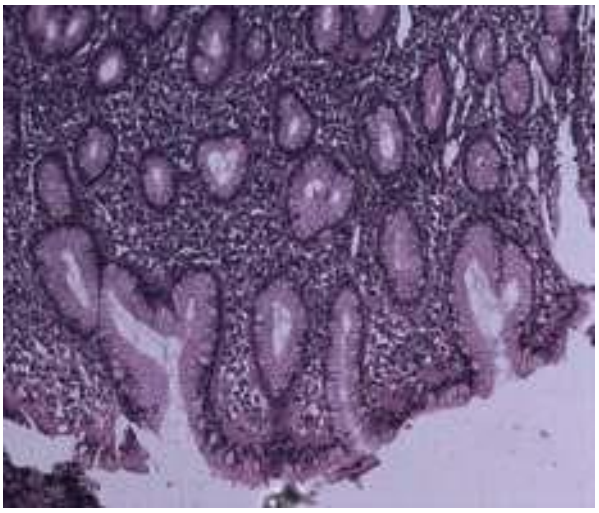
The jugular venous pulse was normal. Cardiovascular system examination showed normal heart sounds with a grade 2/6 ejection systolic murmur in the pulmonary area (haemic murmur). Abdominal examination revealed hepatomegaly with liver 2cm below the right costal margin and splenomegaly with spleen 3cm below the left costal margin. Other systems were normal. Blood investigations revealed pancytopenia with low haemoglobin (4.1gm/dL;normal 11.5-15.5gm/dL), reduced total leucocyte count of 2,100cells/$mm^3$ (4,500–13,500cells/$mm^3$) and thrombocytopenia (80,000/$mm^3$;normal 1.5–4.5 lakhs/$mm^3$). He had an elevated mean corpuscular volume (105.5 fL;normal 77–95fL), with normal mean corpuscular haemoglobin (27.3 pg/cell;normal 25–33pg/cell); a mean corpuscular haemoglobin concentration (32g/dL;normal 31–37g/dL); and his peripheral smear examination showed cytological variation with microcytic hypochromic to macrocytic normochromic picture, anisopoikilocytosis and schistocytes with leucopenia and thrombocytopenia. Liver function tests revealed normal aspartate and alanine aminotransferases with total bilirubin of 59.8µmol/l (3–22µmol/l) and direct bilirubin of 9µmol/l (0–5µmol/l). An infection work-up was done and was negative for malaria, dengue, scrub typhus, enteric fever, leptospirosis, and viral hepatitis. Blood cultures were sterile. He did not have any temperature spikes documented after admission to the hospital. With further work-up for haemolytic anaemia, reticulocyte count was 1.2 per cent, serum ferritin 621 ng/dl, LDH 5712 IU, and direct Coombs test was negative. Vitamin B12 and folate levels were <60pg/dl (208–963 pg/ml) and 3.78 ng/ml (2.7–

17.0ng/mL), respectively. The bone marrow revealed erythroid hyperplasia with megaloblastic maturation with suppressed megakaryocytes and leucopoiesis. Serum homocysteine levels were elevated (30 micromoles/litre) and qualitative urine analysis for methylmalonic acid was positive.

Due to logistic issues, we were unable to measure serum methylmalonic acid. With the above clinical picture, a diagnosis of vitamin B12 deficiency was made. We investigated further to find its cause. The dietary intake of B12 was fairly normal for his age. Anti-parietal cell antibodies and anti-intrinsic factor antibodies were negative. An upper gastrointestinal endoscopy showed erythematous gastropathy and gastric biopsy revealed Helicobacter pylori-induced chronic gastritis (Figures 3 and 4).

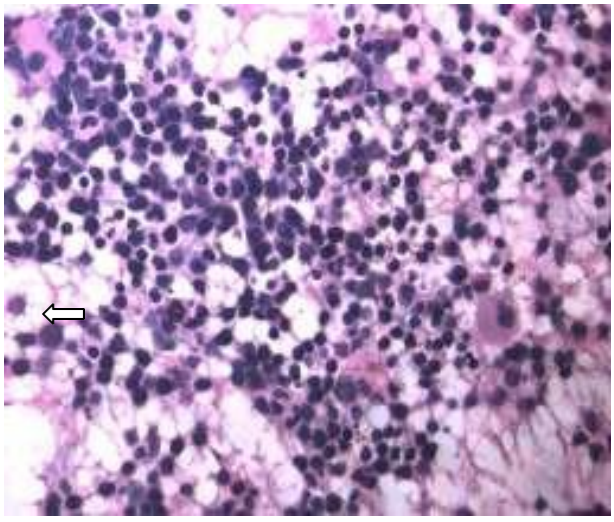
Due to the severity of anaemia we could not exactly prove a temporal relationship by treating only the H. pylori infection; rather, we concomitantly began treating for H. pylori and vitamin B12 deficiency. The adolescent male was started on injections of vitamin B12 1,000 mcg weekly for four weeks, then monthly for three months, and finally once every three months for six months. He was given pantoprazole 40mg, amoxycillin 750mg, and clarithromycin 500mg once a day for four weeks. After two weeks of treatment with the above regimen, haemoglobin level increased to 7 mg/dl, total leucocyte counts 4,040 cell/Cu mm and platelets to 1.05lakhs/cu mm. He improved both symptomatically and clinically. He was discharged and was advised to attend for regular follow-up. After two months of treatment, he became asymptomatic with normal haemoglobin 12 gm/dl, total leucocyte counts 6,700 cells blood counts/cu mm and platelets 2 lakhs/cu mm. Liver function test, vitamin B12 levels, urine methylmalonic acid, and homocysteine levels were within the normal range. Fundus examination revealed no abnormalities. Now, he is on regular follow-up on an outpatient basis.

**Figure 3: Antral biopsy high-power view**



*Architectural disarray of glands with no activity with bifidding of glands*

**Figure 4: Antral biopsy high-power view**



*Slender, comma-shaped Helicobacter pylori seen; architectural disarray of glands with no activity*

## Discussion

Methionine synthase and L-methylmalonyl coenzyme A mutase require vitamin B12 (cobalamin) as cofactor for their enzymatic activity. Methionine synthase catalyses the conversion of homocysteine to methionine, with methylcobalamin as cofactor for its enzymatic activity. Adenosylcobalamin is a cofactor in the synthesis of succinyl CoA from methyl malonyl CoA, catalysed by the enzyme L-methyl malonyl CoA mutase.[1] Thus vitamin B12 deficiency is characterised by elevations of serum homocysteine and methyl malonic acid. The interaction between vitamin B12 and folate is responsible for the megaloblastic anaemia seen in both vitamin deficiencies. Asynchrony between the maturation of cytoplasm and nuclei leads to macrocytosis, immature nuclei, and hypersegmentation in granulocytes in the peripheral

blood. In megaloblastic cells, there is delayed maturation of nuclei with normal cytoplasmic development. The bone marrow becomes hypercellular and dysplastic mimicking acute leukaemia. The ineffective erythropoiesis results in intramedullary haemolysis and release of lactate dehydrogenase, features that are consistent with haemolytic anaemia.[1] Hyperhomocysteinemia seen in vitamin B12 deficiency can also lead to haemolysis; however, the mechanism of haemolysis associated with vitamin B12 deficiency is not fully understood.[9] The patient demonstrated ongoing haemolysis as evidenced by icterus and hepatosplenomegaly, with elevated LDH, bilirubin, and homocystine, as well as the presence of schistocytes in the peripheral blood smear. Leukaemia was excluded by bone marrow aspiration.

In vitamin B12 deficiency, anaemic retinopathy occurs due to the common pathology of capillary disruption and subsequent haemostatic fibrin plug formation. In addition, direct anoxia causes endothelial dysfunction.[10] Furthermore, platelets play a crucial role in vascular integrity by maintaining haemostasis. Hence, retinal lesions are often seen in anaemic patients with concomitant thrombocytopenia.[11] Our patient had low platelet counts (88,000/cu.mm$^3$). This correlation may validate the pathophysiologic hypothesis of vascular instability in anaemia by disruption of the balance between endothelial dysfunction and its reparative mechanisms. Vascular instability causes extrusion of blood from the disrupted site and its subsequent diffusion along and above the nerve fibre layer of the retina.

Megaloblastic anaemia due to vitamin B12 deficiency is rare in childhood. Inadequate dietary intake of vitamin B12, impairment of gastric secretion, lack of intrinsic factor secretion by the stomach, impaired intestinal absorption of intrinsic factor (IF)-cobalamin complex, and the absence of vitamin B12 transport proteins (transcobalamin II) are the common causes of vitamin B12 deficiency.[8]

Laboratory investigations for vitamin B12 deficiency comprise: 1) Tests to detect vitamin B12 deficiency, which consists of serum vitamin B12 assay, serum methyl malonic acid, and serum homocysteine levels. 2) Tests to determine the cause of deficiency, which includes anti-intrinsic factor and anti-parietal cell antibodies for pernicious anaemia, fasting serum gastrin, and pepsinogen levels for atrophic body gastritis, and endoscopy to confirm gastritis. 3) The test for malabsorption of vitamin B12 by the Schilling test is no longer available and is replaced by a serum holotranscoblamin level after oral vitamin B12 loading, but this is still in the developmental stages and evidence of clinical utility of this test is currently lacking.[1] Our patient's vitamin B12 deficiency was detected by low serum vitamin B12 with high methylmalonic acid and homocysteine levels. To determine the cause for the deficiency we did anti-parietal cell and anti-intrinsic factor antibodies, which were negative for pernicious anaemia. The patient reported here was consuming a mixed diet, which ruled out dietary cobalamin deficiency, and congenital if deficiency cannot be considered because of his age. We proceeded with endoscopy to rule out gastritis. Endoscopic findings were suggestive of H. pylori-induced chronic gastritis as evidenced by the gastric biopsy. As other aetiologies of vitamin B12 deficiency were excluded, we construed that H. pylori could be the novel causative agent of vitamin B12 deficiency associated pancytopenia in the index child.

The mechanisms of vitamin B12 malabsorption caused by H. pylori infection are unclear. However, the following are possibilities: 1) Decreased acid secretion in H. pylori-triggered gastritis may lead to disintegration of cobalamin from food binders and its subsequent transfer to haptocorrin in the stomach. 2) A secretory dysfunction of the intrinsic factor. 3) Diminished secretion of ascorbic acid from the gastric mucosa and increased gastric pH .[12]

Carmel et al.'s study found that patients with food-cobalamin malabsorption and low levels of serum cobalamin had a higher seroprevalence of Helicobacter pylori (H. pylori) infection. The association between H. pylori infection and food cobalamin malabsorption suggests that gastritis induced by H. pylori infection predisposes to a more severe form of food-cobalamin malabsorption[13]. In Kaptan et al.'s study, upper gastrointestinal endoscopy confirmed H. pylori infection in 77 (56 per cent) of 138 patients with cobalamin deficiency. It has also been shown that H. pylori is a causative agent in the development of adult cobalamin deficiency, and eradication of H. pylori infection alone may correct cobalamin levels. It may be contemplated that association of cobalamin deficiency and H. pylori infection is coincidental, but reinstatement of anaemia and the cobalamin-deficient state in a significant group of patients via eradication therapy is strongly suggestive of this gram-negative rod's role in the pathogenesis.[6] Hershko et al.'s study also suggests that pernicious anaemia possibly starts many years before the establishment of clinical cobalamin deficiency, by an autoimmune process likely triggered by H. pylori. In these patients, eradication of microorganisms impede the development of pernicious anaemia and also the need for lifelong cyanocobalamin replacement therapy.[14] In order to ascertain the association of H. pylori infection with cobalamin deficiency, we have to eradicate the patient's

H. pylori infection before vitamin B12 treatment. Owing to the very low haemoglobin level in our patient, we treated both conditions concurrently.

There are many recommended schedules for intramuscular injections of vitamin B12 (called cyanocobalamin in the United States and hydroxocobalamin in Europe). Patients with severe abnormalities should receive injections of 1,000µg at least several times per week for one to two weeks, then weekly until clear improvement is shown, followed by monthly injections.[1] In our centre, we follow weekly intramuscular injection of vitamin B12 1,000mcg for four weeks, then monthly for three months, and once every three months for six months. Our patient was treated with the above regimen and responded well. Currently, high-dose oral vitamin B12 (1,000–2,000mcg) therapy is becoming popular. Many studies have shown high-dose vitamin B12 therapy taken daily is effective as intramuscular monthly injections in correcting blood and neurologic abnormalities.[15,16]

In developing countries, H. pylori causes gastric infection among adolescents; in cases of vitamin B12 deficiency, associated pancytopenia, H. pylori infection must be kept in mind as a causative agent. Through this case report, we would like to emphasise the fact that for pancytopenia secondary to vitamin B12 deficiency, identifying the underlying aetiology along with targeted therapy plays a pivotal role in treatment of this condition rather than mere supplementation of the deficient vitamin. To the best of our knowledge, this is the first case report describing vitamin B12 deficiency-associated anaemic retinopathy in paediatric age groups.

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## PEER REVIEW

Not commissioned. Externally peer reviewed.

## CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

## PATIENT CONSENT

The authors, Anitha P, Sasitharan R, Thambarasi T, Krithika P, Mohan M, Venkataraman P, James S, Vinoth PN declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.