A case of vitamin B12 deficiency with some unusual features

Teresa Melo[1], Liliana Ribeiro dos Santos[1,2*], Patrícia Martins[1], Ana Paula Vilas[1]

European Journal of Medical Case Reports
Volume 5(1):01–03
https://doi.org/10.24911/ejmcr/173-1560272435

ABSTRACT

Background: Vitamin B12 (VB12) deficiency is a pleomorphic disease with a wide range of manifestations. Its major cause is pernicious anemia, an autoantibody-mediated disease that results in low levels of intrinsic factor.

Case Presentation: We present a case report of a middle-aged man with severe megaloblastic anemia due to VB12 deficiency in relation to an unsuspected Crohn's disease with exclusive ileum involvement. He also had some unusual neurological manifestations of this vitamin's deficiency, such as hypersudoresis. Unlike most cases, the anemia was not hypoproliferative and hemolysis existed.

Conclusion: This case reports some unusual aspects of VB12 deficiency and reminds us that ileum disease should be considered in patients with a negative autoimmune profile.

Keywords: Crohn's disease, vitamin B12 deficiency, case report, weight loss, night sweats, anemia.

Received: 18 November 2019 **Accepted:** 24 September 2020 **Type of Article:** CASE REPORT **Specialty:** Internal Medicine

Correspondence to: Liliana Ribeiro Santos
*Centro Hospitalar e Universitario Lisboa Norte, Lisboa, Portugal; Divion of Medicine, University College of London, London, United Kingdom.
Email: santos.lilianaribeiro@gmail.com
Full list of author information is available at the end of the article.

Background

Vitamin B12 (VB12) deficiency is a pleomorphic disease with a wide range of manifestations. Its major cause is pernicious anemia, an autoantibody-mediated disease that results in low levels of intrinsic factor [1,2]. Vitamin B12 (VB12) is only found in food of animal origin. It is absorbed in the terminal ileum and for its absorption, the glycoprotein intrinsic factor (IF) is needed [3]. Megaloblastic anemia due to VB12 deficiency is mainly caused by IF deficit. This glycoprotein is produced by the gastric parietal cells and its serum levels will decrease if these gastric cells are destroyed by antibodies anti-parietal cells or if it is destroyed by antibodies anti-IF [2].

Case Presentation

A 50-year-old man presented with 9 kg weight loss (12% of total weight) over the last 5 months and selective anorexia for proteins, night sweats, pallor, exertion fatigue, and tinnitus during the last month. He was otherwise healthy apart from chronic constipation and hemorrhoidal disease. He had no history of diabetes, mechanical valve replacement, or family history of hematologic or GI disorders. He did not take medications (namely metformin or antiacids/proton pump inhibitors). He did not smoke or drink alcohol and he denied restriction on food intake. On medical evaluation, severe anemia was diagnosed (hemoglobin 5.8 gr/dl, hematocrit 17.8%, mean corpuscular volume 133 fL); the other blood cell lines were normal (leukocytes 4,490/mm3 and platelets 152,000/mm3). He was admitted to the hospital. The physical examination was unremarkable, except for a low body mass index (18.8 kg/m2). The liver was palpable and less than 1 cm from the right lower costal margin in the midclavicular line. Spleen and lymph nodes were not palpable. Further investigation confirmed a megaloblastic anemia due to VB12 deficiency (<100 pg/ml; RV = 210-910). The anemia, however, was not hypoproliferative [reticulocyte count of 12.5%, reticulocyte index (RI) of 2.12]. A peripheral blood smear showed schistocytes. Haptoglobin level was undetectable and lactate dehydrogenase of 807 U/l was RV 100-250; the serum bilirubin was of 0.85 mg/dl; Coombs test was negative; the urinalysis was positive for bilirubin and urobilinogen. The hematological features were suggestive of hemolytic anemia. Pernicious anemia was considered as the most probable cause of VB12 deficiency. On the upper digestive endoscopy, the fundus mucosa appeared atrophic (Figure 1). The histopathological aspects were of nonatrophic chronic gastritis. *Helicobacter* pylori was not identified and the microbiological study was negative. Antibodies against the IF and gastric parietal cells were negative. The hypothesis of ileum pathology was

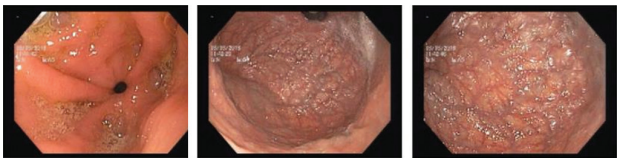

Figure 1. *Atrophic fundus mucosa on the upper digestive endoscopy.*

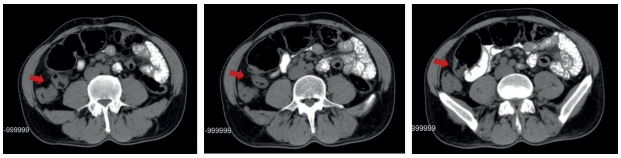

Figure 2. *Abdominal CT scan showing regular and extensive circumferential parietal thickening of the last ileum loop.*

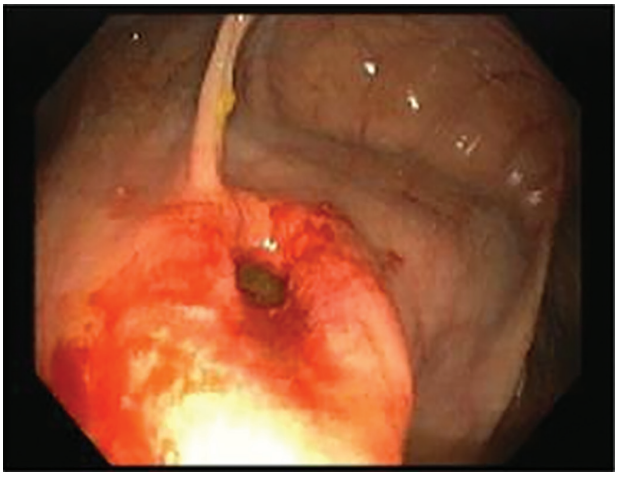

Figure 3. *Colonoscopy with oedema, hyperaemia and ulcerations of the ileocecal valve, which was impossible to pass through.*

considered [lymphoproliferative disorder *vs.* inflammatory bowel disease (IBD)]. An abdominal computed tomography scan showed regular and extensive circumferential parietal thickening of the last ileum loop (Figure 2); no lymph node or spleen enlargement were noticed. The colonoscopy showed edema, hyperemia, and ulcerations of the ileocecal valve, which was impossible to pass through; ulcerations of the ileum were visible; and the colonic mucosa was normal (Figure 3). Ileum biopsies were compatible with IBD, suggesting Crohn's disease (CD): there was edema of the lamina propria, transmural inflammation with lymphoid aggregates, and focal ulceration of the epithelium surface and crypts; no granulomas were seen. Fecal calprotectin (FCP) was of 10 times the cut-off level (556 µg/g). After the diagnosis of VB12 deficiency, intramuscular daily VB12 supplementation was started. Complete clinical and laboratory remission followed. After CD was diagnosed, VB12 was switched to oral [1,4] and sulfasalazine (3 g/day) was started. The clinical remission was sustained but microcytic anemia appeared (hemoglobin 10.8 gr/dl, MCV 78 fL) with documentation of iron deficiency (serum iron 22.5 µg/dl = RV 33-193; total iron-binding capacity 402 ug/dl = RV 250-450; transferrin saturation 6% = RV 26-42; ferritin 11ug/l = RV 30-400). Budesonide (9 mg) was added and 1 year later he had no symptoms and he recovered the weight lost. Follow-up analysis showed normalization of HB (14.7 g/DL), MCV, RBC, and reticulocyte counts, which are important indices to assess therapeutic diagnosis and response in patients with VB12 deficiency. VB12 level was 639 pg/ml (NR 195-770) and FCP decreased to100 µg/g. A magnetic resonance enterography was carried out and only on the last 15 cm of the ileon a slight thickness of the wall without involvement of ileocecal valvule was seen.

Discussion

Pernicious anemia is the most common cause of megaloblastic anemia due to VB12 deficiency [1]. This vitamin deficiency results from low levels of IF, either due to immune IF destruction by autoantibodies or by low gastric production, mainly due to parietal gastric cells destruction by autoantibodies but also as a result of gastrectomy. In a minority of cases, the low VB12 levels result from ileum malabsorption. This was the case of our patient, in whom the megaloblastic anemia was due to VB12 deficiency in relation to CD disease with distal ileum involvement [3]. Although anemia is frequent in CD, it usually relates to iron deficiency and exceptionally to VB12 deficiency [5]. In the latter, extensive involvement of the ileum exists and even so, some authors question whether it causes enough malabsorption to result in a clinical disease. In the presented case, instead of the anemia being ferropenic (as expected in CD) or hypoproliferative (as expected in VB12 deficiency), it was hemolytic. In hemolytic anemias, the RI usually is higher than 3. Our patients had an RI of 2.12, which probably results from the association of hemolytic anemia with ineffective erythropoiesis caused by the VB12 deficiency. Concerning hemolysis, some authors suggest that the VB12 deficiency results in hyperhomocysteinemia [1,5], which in turn can cause microangiopathy and hemolytic anemia in this setting [6]. The plasma homocysteine levels of our patient were not measured. Our patient had a significant weight loss. However, anorexia is a common manifestation of megaloblastic anemia due to VB12 deficiency, but it is unlikely to solely explain the magnitude of weight loss in the patients with ileal disease. Typically, these patients need to undergo ileal resection to restore back to health [7]. Our patient recovered totally with only vitamin levels correction (even before he began to be treated with IBD). The patient also complained of night sweats. Although hypersudoresis has been reported in isolate cases of VB12 deficiency; however, its incidence is not known. It is probably a dysautonomic manifestation of the VB12 deficiency. The most common neurological manifestations of this deficiency, however, are abnormal

proprioception or unsteady gait, which our patient did not have [2]. In a large retrospective register-based study by Lossos et al. [8], neurological involvement is reported in 3% of cases of IBDs. The night sweats also disappeared with the VB12 deficiency correction, establishing a definitive correlation between these two elements.

Conclusion

Standard workup with serological testing, imaging, and endoscopic evaluation is crucial to establish the diagnosis of patients with suspected CD. However, lack of classic GI symptomatology or nonspecific symptoms may result in diagnostic delay, complications, and worse prognosis. (1) This case emphasizes the importance of increased index of suspicion of ileum disease in patients with VB12 deficiency even in the absence of gastrointestinal symptoms. (2) Although rare, peripherical neuropathy due to VB 12 deficiency can be one of the first manifestations of IBDs. (3) Despite anemia in VB12 deficiency is usually hypoproliferative due to ineffective erythropoiesis, in rare cases it may be hemolytic.

What is new?

Most cases of megaloblastic anemia due to VB12 deficiency result from IF deficiency. When pernicious anemia has been ruled out, ileum disease should be considered, even in asymptomatic patients. Although anemia in VB12 deficiency is usually hypoproliferative due to ineffective erythropoiesis, in rare cases it may be hemolytic. Therefore, IBD should be considered in asymptomatic patients who present severe megaloblastic anemia without criteria of pernicious anemia

Funding

None.

Conflicting interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication

Written consent was obtained from all the participants/subjects/patients.

Ethical Approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Teresa Melo[1], Liliana Ribeiro dos Santos[1,2], Patrícia Martins[1], Ana Paula Vilas[1]

1. Centro Hospitalar e Universitario Lisboa Norte, Lisboa, Portugal
2. Division of Medicine, University College of London, London, United Kingdom

References

1. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res. 2006;4(3):236–41. https://doi.org/10.3121/cmr.4.3.236
2. Bizzaro N, Antico A. Diagnosis and classification of pernicious anemia. Autoimmun Rev. 2014;13(4–5):565–8. https://doi.org/10.1016/j.autrev.2014.01.042
3. Oberley MJ, Yang DT. Laboratory testing for cobalamin deficiency in megaloblastic anemia. Am J Hematol. 2013;88(6):522–6. https://doi.org/10.1002/ajh.23421
4. Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2005;20(3):CD004655. https://doi.org/10.1002/14651858.CD004655.pub2
5. Bermejo F, Algaba A, Guerra I, Chaparro M, De-La-Poza G, Valer P, et al. Should we monitor vitamin B12 and folate levels in Crohn's disease patients? Scand J Gastroenterol. 2013;48(11):1272–7. https://doi.org/10.3109/00365521.2013.836752
6. Jagadish Kumar K, Chowdary D, Shetty AU, Anitha C. Microangiopathic hemolytic anemia - a rare presentation of vitamin B12 deficiency. Indian J Pediatr. 2018;85(4):322–4. https://doi.org/10.1007/s12098-017-2491-1
7. Elseherif Y, Alexakis C, Mendall M. Determinants of weight loss prior to diagnosis n inflammatory bowel disease: a retrospective observational study. Gastroenterol Res Pract. 2014;2014:762191. https://doi.org/10.1155/2014/762191
8. Lossos A, River Y, Eliakim A. Neurologic aspects of inflammatory bowel disease. Neurology. 1995;45:416–21. https://doi.org/10.1212/WNL.45.3.416

Summary of the case

1	**Patient (gender, age)**	50-year-old man
2	**Final diagnosis**	CD and VB12 deficiency
3	**Symptoms**	Weight loss, fatigue, night sweats, pallor
4	**Medications**	Intramuscular VB12 supplementation and sulfasalazine
5	**Clinical procedure**	VB12 deficiency: intramuscular VB12 supplementation. Complete clinical and laboratory remission followed. After CD was diagnosed, VB12 was switched to oral and sulfasalazine was started.
6	**Specialty**	Internal medicine