Case study

An Atypical Presentation of Vitamin B12 Deficiency with Hemolytic Anemia

Abstract

Vitamin B12 deficiency is a common nutritional deficiency in both developed and developing countries. This water-soluble vitamin is synthesized by bacteria and archaea and plays a major role in DNA synthesis and effective hematopoiesis. Most common etiologies of B12 deficiency include pernicious anemia and dietary deficiency. Hematological manifestations including anemia, leukopenia, thrombocytopenia, and macrocytosis can commonly be seen with vitamin B12 deficiency. Vitamin B12 deficiency is a rare cause of hemolytic anemia with approximately 1.5% of cases. Hemolysis with vitamin B12 deficiency remains a rare entity that has not been well described in the literature. Here we present a case of a 49-year-old male presenting with presyncope and fatigue who was found to have hemolytic anemia secondary to severe vitamin B12 deficiency with clinical improvement after vitamin supplementation therapy and provide a brief review of literature.

Introduction

Vitamin B12 is a water-soluble vitamin that is synthesized by bacteria and archaea and plays a major role in DNA synthesis and effective hematopoiesis. Vitamin B12 deficiency is a common disorder with the potentiality of severe complications. The most common etiologies include pernicious anemia and dietary deficiency. It has been estimated that 10% of patients with vitamin

B12 deficiency will experience life threatening hematological complications, such as severe anemia, pancytopenia, or hemolysis. Given the advances in modern assays, early detection of vitamin B12 deficiency has led to less frequent complications. Hemolysis with vitamin B12 deficiency remains a rare entity that has not been well described in the literature. Thus, maintaining high suspicion is recommended to diagnose and provide appropriate therapeutic intervention.

Case Presentations

A 49-year-old Caucasian male with a past medical history of gastroesophageal reflux, chronic NSAID use and diabetes mellitus type 2 presented to the emergency department (ED) with a chief complaint of 4 weeks of progressively worsening episodes of presyncope, fatigue, and shortness of breath on exertion. He stated that he had several episodes of blurry vision, particularly upon standing and occasionally occurring at rest as well. He reported associated symptoms including poor concentration, decreased sensation in his feet, and a feeling of unsteadiness when walking. The patient had not been seeing a primary care physician due to lack of health insurance. However, he was last seen in April 2019 for epigastric pain. At that time, acute coronary syndrome was ruled out and the patient was diagnosed with gastroesophageal reflux and diabetes mellitus type 2, both of which had been managed with diet. He had taken ibuprofen up to several times per day in recent weeks for knee and back pain and headaches; he did not take any other medications or supplements. He also reported that his bowel movements had "slowed down" and he noticed a few episodes of dark stools.

His vital signs on presentation were notable for a blood pressure of 118/74 mmHg, heart rate 80 beats/minute, oxygen saturation of 98% on ambient air, and respiratory rate of 12 breaths/minute.

On physical examination, the patient appeared fatigued; he was alert and oriented to person, place, time, and situation. His sclerae were anicteric but pale. Auscultation of the heart showed regular rate and rhythm with no murmurs, and auscultation of the lungs showed no added sounds. Examination of the abdomen revealed normoactive bowel sounds with no tenderness, guarding or organomegaly. On neurological examination, he was found to have diminished triceps, patellar and achilles reflexes bilaterally, and decreased sensation to light touch in the bilateral feet. Initial laboratory workup showed basic metabolic panel results within normal limits. Complete blood count was remarkable for white blood cell count of 3 k/ul (4.5-11 k/ul), and severe macrocytic anemia with hemoglobin 6.1 gm/dl (13.2-17.5 gm/dl) and mean corpuscular volume (MCV) 124.5 fl (80-100 fl), as well as moderate schistocytes and ovalocytes. Liver function tests showed total bilirubin 1.8 mg/dl, with indirect bilirubin elevated at 1.4 mg/dl. AST and ALT were elevated at 59 U/L and 43 U/L respectively. Haptoglobin was found to be less than 10 mg/dl (30-200 mg/dl), and lactate dehydrogenase (LDH) was 3036 U/L, consistent with hemolysis. B12 was found to be severely deficient at less than 150 pg/ml (200-900 pg/ml), and folate level was normal 18.4 nmol/L. Otherwise, iron studies, magnesium, and phosphate were within normal limits.

In the ED he was given one unit of packed red blood cells, and then admitted to the floor. Hematology was consulted for further investigation. Initial diagnosis included severe anemia secondary to vitamin B12 deficiency and hemolysis of unknown etiology. The patient continued to have hemolysis for 48 hours after admission with no clear cause. Differential diagnoses at the time were autoimmune hemolytic anemia (AIHA), pernicious anemia, and Paroxysmal nocturnal hemoglobinuria. Direct Coombs' test to investigate autoimmune hemolysis was negative. An empirical treatment with steroids was unsuccessful with minimal response and was stopped for

lack of supportive findings of autoimmune hemolytic anemia. Viral panels of hepatitis and HIV were nonreactive. Flow cytometry did not show evidence of Paroxysmal nocturnal hemoglobinuria. Anti-intrinsic factors and parietal antibodies were ordered to investigate for pernicious anemia and were negative. Ultimately, a provisional diagnosis of hemolytic anemia secondary to vitamin B12 deficiency was made. The patient was treated with intramuscular 1000 mg injections of vitamin B12 over the course of 72 hours, after which his labs started to improve significantly; his hemoglobin trended up to 9.9 gm/dl, and hemolysis markers including LDH and haptoglobin improved. It was concluded that the most likely reason for the patient's hemolysis was severe vitamin B12 deficiency. Fortunately, the patient's presenting symptoms of weakness and peripheral neuropathy had also improved significantly at the time of discharge.

Discussion

Vitamin B12 deficiency can present with various hematological and neurological symptoms, depending on its severity. The association of hemolysis with vitamin B12 deficiency has been a recognized phenomenon [8,9]. However, upon literature review, reports of hemolytic anemia caused by vitamin B12 deficiency are quite rare [4,8-11], particularly when due to nutritional causes alone [4]. We report a rare case of vitamin B12 deficiency-induced hemolytic anemia with no concurrence of pernicious anemia. The etiology of his B12 deficiency was unclear, and it is presumed to be nutritional. This patient had hemolysis given elevated LDH and undetectable haptoglobin levels that responded to treatment with B12 supplementation.

Vitamin B12 deficiency is usually a laboratory diagnosis [5].* Findings of macrocytic anemia, evidenced by an MCV higher than 115 fl, should prompt evaluation for B12 deficiency [1,6].

Evaluations usually begin with testing vitamin B12 levels where levels below <200 pg/ml are diagnostic and levels below <100 pg/ml considered very low [1,6]. Other findings include the presence of hypersegmented neutrophils on blood smear.

In a study published in 2006, Andres et al. studied 201 patients with vitamin B12 deficiency and reported hematological findings observed with these patients [7]. The results showed various presentations where 10% of the patients had life threatening hematological manifestations, including symptomatic pancytopenia (5%), thrombotic microangiopathy (2.5%), and hemolytic anemia (1.5%) [7]. Of these patients, a considerable proportion had invasive and comprehensive diagnostic investigations to rule out other causes. These patients were occasionally misdiagnosed and mistreated with aggressive therapies such as steroids, immunoglobulins, and plasmapheresis [7]. It is probable that a number of these patients with findings indicative of peripheral blood hemolysis were the ones with the highest homocysteine levels.

Vitamin B12 plays an essential role as a required cofactor in DNA/RNA synthesis [4, 5]. It helps in regenerating tetrahydrofolate and converting homocysteine to methionine. This shows why levels of homocysteine and methylmalonic acid are elevated in B12 deficiency [4]. The mechanism behind RBC destruction is not well-understood. Initial studies suggest an intramedullary mechanism rather than an intravascular one [5, 7]. One possible mechanism for intravascular and intramedullary hemolysis described in literature was elevated homocysteine levels. It has been demonstrated in vitro that elevated homocysteine levels increase the risk of hemolysis [5].

The recommended treatment includes high dose vitamin B12 replacement (either orally or intramuscularly). This has been found to be effective at improving anemia and decreasing MCV [4]. Appropriate laboratory evaluation, including methylmalonic acid levels and homocysteine levels, should be done prior to initiating replacement therapy. It may take 1-2 months of replacement therapy for improvement in blood counts and a period of 6 months for improvement in neurological symptoms [11]. Clinicians may also monitor levels of Methylmalonic acid to assess the effectiveness of therapy [4].

In conclusion, B12 deficiency should be considered in the differential diagnosis of hemolytic anemia, in addition to its more common manifestation of macrocytic anemia. Appropriate recognition of this treatable disorder will allow for timely initiation of B12 supplementation and clinical improvement for the patient. Further research is highly recommended to understand the underlying mechanism behind this phenomenon.

Conclusion

Vitamin B12 deficiency is a common diagnosis with various clinical presentations. Hemolysis due to vitamin B12 deficiency is a rare presentation that necessitates high clinical suspicion for effective timely treatment. Pernicious anemia and nutritional deficiency are the most common causes of vitamin B12 deficiency.** Appropriate laboratory evaluation, including assessing vitamin B12 levels and methylmalonic acid levels and homocysteine levels, should be done prior to initiating replacement therapy.*** The mechanism behind RBC destruction is not well-understood, but may be due to intramedullary hemolysis related to abnormal and fragile red blood cells. Effective replacement high dose therapy should be initiated as it has been shown to be effective in improving both symptoms and blood counts.

References

1. Allen LH. How common is vitamin B-12 deficiency? Am J Clin Nutr. 2009;89(2):693S-6S.
2. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr. 2004;24(1):299–326.
3. Castellanos-Sinco HB, Ramos-Peñafiel CO, Santoyo-Sánchez A, Collazo-Jaloma J, Martínez-Murillo C, Montaño-Figueroa E, et al. Megaloblastic anaemia: Folic acid and vitamin B12 metabolism. Rev médica Hosp Gen Méx. 2015;78(3):135–43.
4. Cheema A, Bramson J, Bajwa R et al. Hemolytic anemia an unusual presentation of vitamin B12 deficiency. J Hematol Thrombo Dis. 2018;6:1.
5. Hoffman R. Hematology: Basic Principles and Practice. New York, NY: Churchill Livingstone; 2005.
6. Lin J-S, Shen M-C, Cheng W-C, Tsay W, Wang Y-C, Lin B-B, et al. Age, sex and vitamin status affect plasma level of homocysteine, but hyperhomocysteinaemia is possibly not an important risk factor for venous thrombophilia in Taiwanese Chinese: Hyperhomocysteinaemia and Venous Thrombophilia. Br J Haematol. 2002;117(1):159–63.
7. Andres E, Affenberger S, Zimmer J, Vinzio S, Grosu D, Pistol G, et al. Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency. Clin Lab Haematol. 2006;28(1):50–6.

8. Acharya U, Gau J-T, Horvath W, Ventura P, Hsueh C-T, Carlsen W. Hemolysis and hyperhomocysteinemia caused by cobalamin deficiency: three case reports and review of the literature. J Hematol Oncol. 2008;1(1):26.
9. Sasi S, Yassin MA. A rare case of acquired hemolytic anemia and pancytopenia secondary to pernicious anemia. Case Rep Oncol. 2020;13(2):783–8.
10. Noël N, Maigné G, Tertian G, Anguel N, Monnet X, Michot J-M, et al. Hemolysis and schistocytosis in the emergency department: consider pseudothrombotic microangiopathy related to vitamin B12 deficiency. QJM. 2013;106(11):1017–22.
11. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. Blood. 1998;92(4):1191–8.

*Indeed, but given the frequency of vitamin B12 deficiency, especially in the elderly, especially mild or subtle deficiencies, any clinical picture of psychocognitive impairment should be suspected, even mild, as it could still be remedied with treatment. In fact, between 10 and 20% of the population over 60-65 years of age may be deficient in this vitamin. In case of doubtful borderline vitamin B12 levels, determination of elevated methylmalonic acid helps diagnosis.

**Autoimmune gastritis (badly called pernicious anemia) is one of the most frequent causes of vitamin B12 deficiency and it is considered that 1.9 to 4% of the population over 60 years of age may have a non-deficient picture, diagnosed or treated by this mechanism.

Food-bound vitamin B12 malabsorption is generally due to atrophic gastritis with a prevalence of up to 30% in the Caucasian population over 60 years of age and is associated with Helicobacter pylori infection.

***An added risk in vitamin B12 deficiency in general is receiving folates in patients with B12 deficiency, thus avoiding the appearance of hematological alterations but not neuropsychiatric ones and possibly precipitating the latter, being necessary to know the B12 levels prior to the administration of folate in any person with a possible risk of this deficiency.

Bibliographic reference to add:

Aguirre Errasti Ciriaco. Reflexiones acerca del diagnostico de la carencia de vitamina B12. Medicina Clínica 2001. 116; (12) : 457-8.