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Case Report Open Access

Hemolytic Anemia an Unusual Presentation of Vitamin B12 Deficiency

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Abstract

Vitamin B12, or cobalamin, is a water soluble vitamin which is synthesized by bacteria and archaea. Vitamin B12 is absorbed in the terminal ileum after binding intrinsic factor, a glycoprotein produced by the parietal cells in the stomach. The most common cause of B12 deficiency worldwide is pernicious anemia. Pernicious anemia is a deficiency of vitamin B12 due to lack of intrinsic factor. Usually, this is secondary to production of autoantibodies directed against the intrinsic factor of gastric parietal cells, leading to atrophic gastritis. Common findings in Vitamin B12 deficiency include anemia, leukopenia, and thrombocytopenia, macrocytosis, and hypersegmented neutrophils. Vitamin B12 deficiency is a rare cause of hemolytic anemia (approximately 1.5% of cases). Here, we present a case of a 59-year-old male found to have hemolytic anemia secondary to marked vitamin B12 deficiency and improved after vitamin supplementation and provide a brief review of literature.

Keywords: Vitamin B12; Cobalamin; Hemolytic anemia; Hemolysis; Vitamin deficiency

Introduction

Hemolytic anemia secondary to vitamin B12 deficiency is a rare presentation. As suggested by the name pernicious anemia, vitamin B12 deficiency has the potential for severe complications, with approximately 10% of patients experiencing life threatening hematological manifestations such as pancytopenia, pseudo-microangiopathy, severe anemia, or hemolysis [1]. Fortunately, with modern assays allowing for early detection, such manifestations have become less frequent. However, hemolytic anemia due to vitamin B12 deficiency is uncommon, and not well described. Therefore, high clinical suspicion is needed to promote timely diagnosis and therapeutic intervention.

Case

A 59-year-old male with no reported past medical history presents with complaints of progressive weakness, lethargy, dysthymic mood, bilateral feet tingling, and an estimated 30 pounds weight loss over the course of the last year. Additionally, the patient reports that during the course of the last year he had been having an increasingly difficult time performing daily workplace responsibilities due to progressive generalized weakness. He also complained of lightheadedness and nausea after prolonged standing which improved with rest. The patient visited his primary care physician for progressive symptoms and found to be severely anemic. He was then referred to the hospital for further evaluation and possible blood transfusion. In the emergency department (ED), his vital signs were temperature of 97.8 degrees Fahrenheit, respiratory rate of 14 breaths/minute, heart rate of 94 beat/minute, blood pressure of 168/68 mmHg, and pulse oximetry of 98% on ambient air. The physical examination showed mucosal and conjunctival pallor, no scleral icterus, no palpable lymph nodes, non-distended abdomen, normal bowel sound with no organomegaly, unremarkable cardio and lung examination, and decreased pin prick and vibratory sensation on bilateral lower extremities. Initial laboratory studies revealed white blood cell count (WBC) of 3.1 k/ul (4.5-11 k/ul) with an absolute neutrophil count (ANC) 1.6 × 10^3/ul, hemoglobin (Hgb) 5.0 gm/dl (13.2-17.5 gm/dl), hematocrit (Hct) 14.4% (40-53%), platelets 137 k/ul (140-450 k/ul), and a mean corpuscular volume (MCV) 130.9 fl (80-100 fl). Liver function tests showed alkaline phosphate 139 U/L, aspartate aminotransferase 156 U/L (reference range 5-34 U/L), alanine aminotransferase 96 U/L (10-40 U/L), and total bilirubin of 4 mg/dl. Both a liver ultrasound and an abdominal computerized tomography (CT) scan were unremarkable. Additional laboratory investigation revealed very low vitamin B12 level of 52 pg/ml (200-900 pg/ml), markedly elevated lactate dehydrogenase (LDH)>2700 U/L, undetectable haptoglobin <6 mg/dl (30-200 mg/dl), methylmalonic acid level of 56.36 umol/l (0-40 umol/l), normal homocysteine level, normal iron profile, a decreased vitamin B12 binding capacity <400 pg/ml (reference range 800-1200 pg/ml), and negative indirect and direct combs test. Other autoimmune and infectious causes of hemolysis were excluded by extended worked up.

The patient was transfused 2 units of packed red blood cells in the ED and 1000 mcg intramuscular vitamin B12 daily was initiated, with the hemoglobin responding appropriately. On hospital day two, the patient underwent an esophagogastroduodenoscopy which showed no evidence of upper gastrointestinal source of bleeding or autoimmune erosive gastritis. Given the patients' laboratory and clinical features a diagnosis of hemolytic anemia secondary to severe vitamin B12 deficiency was made. He was continued on vitamin B12 injections, and monitored in the hospital for an additional 24 hours. The patient's initial symptoms of lethargy, weakness, dysthymia, and bilateral sensory loss of his feet improved significantly, and his hemoglobin was stable at 10.3 gm/dl at the time of discharge.

Discussion

In a review of literature, we found that case reports of Vitamin B12 deficiency causing hemolytic anemia are quite rare. Furthermore,

descriptions of a nutritional vitamin B12 deficiency, without evidence of pernicious anemia, causing hemolysis are even scarcer. Vitamin B12 deficiency, depending on the severity and duration of disease, can present with multiple hematological and neurological findings [2]. The patient in this case presented with symptoms, and laboratory findings of long standing severe vitamin B12 deficiency, as well as laboratory findings consistent with a hemolytic anemia.

Initial laboratory findings suggestive of vitamin B12 deficiency includes the presence of macrocytic anemia, with an MCV>115 fl being suggestive of folate or B12 deficiency, rather than other causes of macrocytic anemia such as hypothyroidism or myelodysplasia [3,4]. The first test in evaluation of vitamin B12 deficiency is generally a serum vitamin B12 level, with levels <200 pg/ml considered suggestive of deficiency and levels <100 pg/ml considered very low [3,4]. Such low levels, however, are not that commonly observed, and serum assays have a high rate of false positive or false negative results (up to 50%) [1]. Due to the relative insensitivity of direct vitamin B12 measurements, clinicians are advised not to rely upon laboratory cut-offs, and should proceed with other laboratory investigations, such as homocysteine or methylmalonic acid levels, when vitamin B12 deficiency is suspected [2].

Vitamin B12 is an essential cofactor required for biochemical pathways involved in DNA/RNA synthesis and fatty acid metabolism [4]. The role of vitamin B12 in DNA/RNA synthesis is in the regeneration of tetrahydrofolate and conversion of homocysteine to methionine [4]. As these two processes are joined, such that deficiencies in either vitamin B12 or folate will result in ineffective hematopoiesis and measurable accumulation of homocysteine in the serum [4,5]. Vitamin B12 is also essential in the formation of succinyl CoA, which is an important intermediate enzyme in the tricarboxylic acid cycle that is involved in fatty acid metabolism [4]. In the absence of vitamin B12, the chemical pathway is rerouted to excessive production of methylmalonic acid which allows for its detection in the serum [4]. Detection of elevated levels of homocysteine and methylmalonic acid in the serum is therefore useful in making the diagnosis of vitamin B12 deficiency, with elevated methylmalonic acid being more specific for B12 deficiency [1]. Generally, levels of both homocysteine and methylmalonic acid are elevated in the setting of clinical manifestations of vitamin B12 deficiency and these levels rapidly correct with initiation of treatment [1]. Therefore, it is recommended to check these serum levels when there is reasonable suspicion of vitamin B12 deficiency prior to initiating replacement therapy.

High dose oral vitamin B12 replacement has been found to be effective in both patients with a nutritional vitamin deficiency and pernicious anemia, with reductions in MCV and improvements in hematocrit [6]. Effective replacement therapy should be anticipated to demonstrate improvement in blood counts within 1-2 months with subsequent improvement of neurological symptoms within a period of 6 months [7]. Methylmalonic acid levels may also be monitored to evaluate effectiveness of therapy.

Intramedullary destruction of red blood cells in the setting of vitamin B12 deficiency is a well-recognized, but not well understood phenomenon [8]. Additionally, elevated homocysteine levels have been described in literature as a possible etiology for both intravascular and intramedullary hemolysis with the role of homocysteine in increasing the risk of hemolysis in vitamin B12 and folate deficiency being demonstrated in vitro [8]. While the mechanism of hemolysis in this setting is not well understood, one proposed mechanism is related to the pro-oxidant attributes of homocysteine leading to endothelial damage and subsequent microangiopathy [9,10]. In the case presented here, however, we found normal homocysteine levels with clear evidence of hemolysis. This may suggest an alternative mechanism for this rare entity. Given the low incidence of hemolysis due to vitamin B12 deficiency, early suspicion and diagnosis in the appropriate clinical setting is suggested. Further investigation is warranted to better understand the pathophysiology associated with vitamin B12 deficiency associated hemolysis.

Conclusion

Hemolysis due to vitamin B12 deficiency is a rare presentation requiring high clinical suspicion to allow for early diagnosis and treatment. Pernicious anemia, due to autoantibodies to intrinsic factor in parietal cells, is the most common cause of vitamin B12 deficiency. Appropriate laboratory evaluation, including methylmalonic acid levels and homocysteine levels, should be done prior to initiating replacement therapy. The common thought of possible for vitamin B12 deficiency causing hemolysis is due to toxic effects of high homocysteine levels. Although, as previously stated, the homocysteine level in our case was normal prior to therapy initiation. This indicates that there is a different or multiple possible mechanisms of hemolysis. Intramedullary hemolysis resulting in ineffective erythropoiesis due to abnormal and fragile red blood cells is a possible etiology that needs to be further studied to confirm.

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