American Journal of Medical Case Reports, 2023, Vol. 11, No. 2, 16-18
Available online at http://pubs.sciepub.com/ajmcr/11/2/2
Published by Science and Education Publishing
DOI:10.12691/ajmcr-11-2-2

A Rare Case of Vitamin B12 Deficiency as a Cause of Acquired Hemolytic Anemia

Andrew Sagalov[1,*], Sujitha Ketineni[2], Mohammad Hussain[2], Ruchika Goel[2]

[1]Department of Internal Medicine, SIU School of Medicine, Springfield, IL, USA
[2]Division of Hematology/Oncology, Simmons Cancer Institute, SIU School of Medicine, Springfield, IL
*Corresponding author: andrewsagalov@gmail.com

Received December 14, 2022; Revised January 22, 2023; Accepted February 02, 2023

Abstract An elderly woman was brought to the emergency department following a one-week history of progressively worsening epigastric pain and generalized weakness. Her symptoms began approximately two years before admission; however, she did not seek medical attention as her symptoms were mild. Vital signs were stable on presentation, while her pain persisted following administration of morphine. A computed tomography scan of her abdomen did not identify any acute pathology. Laboratory evaluation revealed megaloblastic anemia, a critically low vitamin B12 count, and evidence of hemolytic anemia (HA). She was treated with cyanocobalamin injections and her abdominal pain resolved. This case demonstrates a rare instance of acquired HA as a complication of vitamin B12 deficiency. Furthermore, our manuscript emphasizes clinicians should recognize megaloblastic anemias are not always macrocytic and to conduct a thorough medical history when evaluating an anemia.

Keywords: *Vitamin B12, hemolytic anemia, pernicious anemia, Homocysteine*

Cite This Article: Andrew Sagalov, Sujitha Ketineni, Mohammad Hussain, and Ruchika Goel, "A Rare Case of Vitamin B12 Deficiency as a Cause of Acquired Hemolytic Anemia." *American Journal of Medical Case Reports*, vol. 11, no. 2 (2023): 16-18. doi: 10.12691/ajmcr-11-2-2.

1. Introduction

Vitamin B12, or cobalamin, is a water-soluble vitamin primarily found in animal products such as red meat and dairy. When vitamin B12 is absorbed in the small intestine, it functions as a cofactor for enzymes involved in DNA synthesis reactions [1]. Vitamin B12 deficiency has a prevalence of 60% in the United States and Britain [2]. Patients with B12 deficiency may develop worsening lethargy, mucocutaneous ulcers, and paresthesia. In severe cases, the lateral corticospinal tracts may be affected and cause vibratory and proprioception deficits. This neurological complication of B12 deficiency is known as subacute combined degeneration and may be irreversible without aggressive vitamin repletion. Vitamin B12 deficiency is often seen in patients who are on a strict vegetarian diet, using metformin, or with antibodies to intrinsic factor. Intrinsic factor is a protein that facilitates the absorption of vitamin B12 in the gut. In rare cases, the effects of B12 deficiency can extend to the bone marrow and cause ineffective intramedullary hematopoiesis, which leads to bone marrow suppression.

Hemolytic anemia is the premature destruction of erythrocytes stemming from an insult to the blood vessel itself or to an extravascular source [3]. The incidence of autoimmune HA is approximately 2 cases per 100,000 people [4]. Affected patients may present with a spectrum of symptoms ranging from jaundice, hematuria, dyspnea, and tachycardia. A complete blood count and comprehensive metabolic panel will diagnose hemolysis by demonstrating a normocytic anemia and increased unconjugated hyperbilirubinemia. A Coombs test should be performed to determine if antibodies are present on the surface of red blood cells. A positive test would need to be investigated further with immunoglobulin levels to differentiate a warm versus cold HA. Warm HAs have a broad differential and include systemic lupus erythematosus, rheumatoid arthritis, infection, pregnancy, and blood disorders such as leukemia. Cold HAs have a narrower etiology and may include lupus, infection, or an aggressive lymphoma. In contrast, a negative Coombs test should prompt an investigation of medication history, malignancy, or hereditary causes.

2. Clinical Presentation

A sixty-nine-year-old female with obesity presented to the hospital with a 1-week history of worsening epigastric pain and generalized weakness. The pain was described as sharp, constant, non-radiating, and not associated with oral intake. She stated it was severe enough to curb her appetite, but denied any significant weight loss prior to admission. She denied excessive alcohol use and reported a balanced diet with adequate meat consumption. Furthermore, she denied a history of trauma to her abdomen. Her past medical history was significant for hypertension, gastroesophageal reflux disease (GERD),

and obstructive sleep apnea. Surgical history was significant for cholecystectomy and hysterectomy, but both procedures long preceded her symptoms. Vital signs were stable and the physical exam was unremarkable except for epigastric tenderness on deep palpation. On auscultation, bowel sounds were normoactive. Additionally, Murphy's and Rovsings' signs were negative, and there was no evidence of abdominal guarding nor rigidity.

A computed tomography abdomen and pelvis scan without contrast was unremarkable. Laboratory evaluation revealed a hemoglobin (6.1 g/dL); (baseline 12.0 g/dL), and MCV (126 fl); (baseline 85 fl). Peripheral blood smear review revealed macrocytic red cells with minimal anisocytosis and negative for schistocytes. Follow-up studies demonstrated low haptoglobin (<30 mg/dL), corrected reticulocyte count (0.182%), and elevated lactate dehydrogenase (2,229 IU/L). The Coombs test was negative. These findings were consistent with a non-immune mediated HA. Further analysis showed critically low vitamin B12 (<50 pg/mL) and elevated homocysteine (15.3 µmol/L). Antibodies to intrinsic factor were positive, consistent with pernicious anemia.

The patient was transfused with one unit of packed red blood cells and received one intramuscular cyanocobalamin injection while inpatient. Over the course of her hospitalization, her hematological indices improved following administration of vitamin B12. She was discharged to home in stable condition after a four-day hospitalization. The treatment resulted in complete resolution of her abdominal symptoms. She will continue to get weekly intramuscular B12 injections. A follow-up LDH of 193 one month after discharge was down from a peak of 2,229. Her MCV (82 fl) and vitamin B12 level (1,087 pg/mL) significantly improved after treatment. She continues to follow-up outpatient with hematology-oncology.

3. Discussion

Differential diagnoses for abdominal pain in the setting of an elevated MCV include a broad spectrum of disorders ranging from occult disease to systemic symptoms requiring urgent intervention. The degree to which MCV is elevated helps to differentiate megaloblastic from macrocytic anemia. This threshold is important to consider because the inhibition of DNA synthesis during erythrocyte production primarily occurs when the anemia is megaloblastic in origin.

An MCV greater than 115 is specific to megaloblastic causes, primarily seen in folate and B12 deficiency. The liver serves as a vitamin B12 reservoir, which explains why symptoms take more than one year to develop because of the body's adequate stores of vitamin B12. Folate can be stored in the body for up to four months, but can be quickly depleted with excessive alcohol use. If duration of symptoms is equivocal, a homocysteine and methylmalonic acid (MMA) level offer the clearest distinction between the two vitamin deficiencies. Folate deficiency presents with an elevated homocysteine level, while MMA level is normal. Vitamin B12 deficiency manifests with both an elevated homocysteine and MMA level [5]. Infection with Diphyllobothrium latum, a parasite primarily found in Scandinavia and Japan, can also cause megaloblastic anemia; however, a thorough travel and dietary history will usually eliminate this tapeworm from the differential [6].

Macrocytic and non-megaloblastic anemia in conjunction with abdominal pain is a common presentation of alcoholic liver disease. A patient with confirmed alcohol use disorder will have evidence of hepatic steatosis on ultrasound, elevated transaminases, and a serum bilirubin less than 3 mg/dL [7]. This is a diagnosis of exclusion once other potential causes of liver disease have been ruled out, usually with imaging or biopsy. If the patient presents with abdominal symptoms associated with unintentional weight loss, clinicians would be wise to rule out gastric cancer secondary to untreated pernicious anemia. A literature review revealed an association between pernicious anemia and the development of non-cardia gastric adenocarcinoma and gastric carcinoid tumors [8].

Treatment of B12 deficiency can be administered in multiple forms including oral tablets, sublingual lozenges, and intramuscular injections. In patients with severe B12 deficiency, the British Society for Hematology recommends injections three times per week for up to two weeks in patients without neurological deficits [9]. Patients with deficits require injections every other day for up to three weeks or sooner if there is no resolution of symptoms [9]. A majority of patients can use oral or sublingual B12 if aggressive repletion is not required to address their deficiency. Definitive cut-off points to delineate clinical deficiency states have not been established and treatment is often guided by symptomatology.

Hemolytic anemia often presents as a normocytic anemia and prompts an evaluation for toxins, medication use, hereditary causes, and recent infection. However, vitamin B12 deficiency is often overlooked because MCV may be normocytic. Furthermore, vitamin B12 deficiency rarely (1%) presents as hemolytic anemia [10]. When our patient initially presented on several occasions with intermittent abdominal pain and generalized weakness as an outpatient to her primary care physician, her blood counts were normocytic; therefore, testing for B12 deficiency was not pursued. The low reticulocyte count and high MCV indicated inadequate bone marrow response to the degree of anemia. We suspect ineffective intramedullary hematopoiesis secondary to hyperhomocysteinemia from vitamin B12 deficiency caused her anemia. In vitro studies have demonstrated that the accumulation of homocysteine due to B12 deficiency increases hemolysis [11]. In severe cases, patients may present with symptomatic pancytopenias that can be challenging to diagnose [12]. Clinicians should be vigilant for reversible causes such as B12 deficiency when laboratory results don't fall in the range normally seen in the literature.

4. Conclusion

Hemolytic anemia in the setting of vitamin B12 deficiency is a rare phenomenon that can be easily missed since patients often presents without symptoms. It is critical to properly evaluate anemia in hospitalized patients, especially in the setting of negative imaging

findings and unremarkable physical examinations. While B12 deficiency commonly presents in the macrocytic or even megaloblastic range, atypical presentations that deviate from established literature findings can create a complex diagnostic scenario and force medical practitioners to widen their differentials. To avoid overlooking B12 deficiency, it is prudent to keep an open mind and have a broad differential when evaluating the causes of anemia.

References

[1] Shipton MJ, Thachil J. *Vitamin B12 deficiency - A 21st century perspective*. Clin Med [Internet]. 2015 [cited 2022 Aug 15]; 15(2): 145-50.

[2] Andrès E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, et al. *Vitamin B12 (cobalamin) deficiency in elderly patients*. CMAJ [Internet]. 2004.

[3] Phillips J, Henderson AC. *Hemolytic anemia: Evaluation and differential diagnosis.* Am Fam Physician [Internet]. 2018.

[4] Michalak, S.S., Olewicz-Gawlik, A., Rupa-Matysek, J. *et al.* Autoimmune hemolytic anemia: current knowledge and perspectives. *Immun Ageing*. 17, 38 (2020).

[5] Aslinia F, Mazza JJ, Yale SH. *Megaloblastic anemia and other causes of macrocytosis.* Clin Med Res [Internet]. 2006.

[6] Sharma K, Wijarnpreecha K, Merrell N. *Diphyllobothrium latum Mimicking Subacute Appendicitis*. Gastroenterology Res [Internet]. 2018.

[7] Singal A, Bataller R, Ahn J, Et al. *ACG Clinical Guideline: Alcoholic Liver Disease.* American Journal of Gastroenterology. 2018 Feb; 113(2): 175-94.

[8] Murphy G, Dawsey SM, Engels EA, et al. Cancer Risk After Pernicious Anemia in the US Elderly Population. *Clin Gastroenterol Hepatol*. 2015; 13(13): 2282-9.e94.

[9] Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. *American Family Physician*. 2017; 96(6): 384-389.

[10] S; HAHDR. *Vitamin B12 deficiency* [Internet]. BMJ (Clinical research ed.). U.S. National Library of Medicine; 2014.

[11] Acharya U, Gau JT, Horvath W, *et al*. *Hemolysis and hyperhomocysteinemia caused by cobalamin deficiency: three case reports and review of the literature*. *J Hematol Oncol*. 2008; 1: 26. Published 2008 Dec 18.

[12] Sasi S, Yassin MA. *A Rare Case of Acquired Hemolytic Anemia and Pancytopenia Secondary to Pernicious Anemia*. *Case Rep Oncol*. 2020; 13(2): 783-788. Published 2020 Jul 2.