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CASE REPORT

Pseudo-thrombotic Microangiopathy – An Unusual Presentation of Cobalamin Deficiency

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Abstract

Vitamin B12 is a water-soluble vitamin cofactor for many enzymatic reactions in the body. It plays a vital role in the normal maturation of red blood cells and in producing proteins needed for normal neurological function. The most common presentations of vitamin B12 deficiency are hematological abnormalities and neurological manifestations. Pseudo-thrombotic microangiopathy, a syndrome of hemolysis and thrombocytopenia, may mimic the presentation of thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, an uncommon presentation of vitamin B12 deficiency. We present the case of a 58-year-old male with no significant past medical history who presented with severe macrocytic anemia and thrombocytopenia with laboratory findings suggestive of hemolytic anemia. He was found to have vitamin B12 deficiency with positive serological markers suggesting pernicious anemia is the underlying cause. Our case demonstrates that vitamin B12 deficiency should be considered in cases of suspected thrombotic microangiopathy, especially in the setting of significantly elevated lactate dehydrogenase levels and low reticulocyte count to avoid the initiation of unnecessary and expensive treatment modalities such as plasmapheresis.

Keywords: Vitamin B12 deficiency, Hemolysis, Hemolytic anemia, Thrombotic microangiopathy, Pseudo-thrombotic microangiopathy

1. Introduction

Vitamin B12 is a water-soluble vitamin that plays an essential role in the production of red blood cells and deoxyribonucleic acid (DNA), and is essential for proper neurologic function. It is found in many foods, including meats, fish, and dairy products.[2] The prevalence of vitamin B12 deficiency in the United States varies by age, occurring in approximately 6% of patients under 60 years old and about 20% in patients over 60 years old.[1] In the adult population, deficiency of B12 is commonly the result of decreased absorption in the gastrointestinal tract, which may be due to pernicious anemia, gastric bypass procedures, surgical procedures of the small intestine, inflammatory bowel diseases, and the prolonged use of certain medications such as proton pump inhibitors and metformin1,3. Decreased dietary intake of vitamin B12 can also result in deficiency, and people who maintain a vegan diet have the highest risk. When vitamin B12 deficiency does occur, it most commonly presents as megaloblastic anemia and neurologic dysfunction.[3] In a small percentage of patients, vitamin B12 deficiency may present with hemolytic anemia and thrombocytopenia, similar to thrombotic microangiopathy (TMA).[4] Here we present the case of a 58-year-old male with severe anemia, thrombocytopenia, and laboratory findings in keeping with hemolysis, noted to have low vitamin B12 levels.

2. Case presentation

This is a case of a 58-year-old African-American male with no known past medical history who presented to the ED with a complaint of worsening fatigue and lethargy for three weeks. He was in his usual state of health until five months prior when he got into a motor vehicle accident, causing him to develop impaired mobility and subsequent lower

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extremity weakness and numbness of the toes bilaterally. He also endorsed shortness of breath on exertion and significantly poor appetite, along with an unintentional weight loss of 10–15 pounds in the past few weeks. His diet mainly consisted of low-nutritional products, including carbonated sodas and takeout. He denied any evidence of bleeding, including hematemesis, melena, or hematochezia. Also denied any previous history of blood transfusions or a family history of anemia (including thalassemia or sickle cell disease) or bleeding disorders. The patient did not consume any over-the-counter medications or herbal supplements and denied smoking or alcohol consumption.

On presentation, he had a blood pressure of 110/77 mmHg, heart rate of 130 bpm, respiratory rate of 18 breaths per minute, temperature of 100.3 F, and oxygen saturation of 97% on room air. A physical exam was pertinent for conjunctival pallor and mild scleral icterus, but no abdominal tenderness, hepatosplenomegaly, or lymphadenopathy was appreciated. At presentation, his labs were significant for remarkable macrocytic anemia, thrombocytopenia, and indirect hyperbilirubinemia, with values as shown in the table below (Table 1).

A fecal occult test was negative. Testing for human immunodeficiency virus, hepatitis B and C were negative. A peripheral smear noted very few schistocytes and hypersegmented neutrophils (Fig. 1).

He received 2 units of packed red blood cells on the first day of his admission while the remainder of the laboratory workup was pending. An abdominal ultrasound was significant for a mildly elongated spleen with a length of 13.7 cm without a focal splenic lesion identified.

Table 1. Laboratory tests on admission.

Laboratory test on admission	Result	Normal Range
Hemoglobin (g/dl)	5.6	14–18
Red blood cell (10^6/microliter)	1.46	4.70–6.10
Mean corpuscular volume (fl)	104.8	80.0–100.0
Platelets (1000/UL)	95	130–400
White blood cells (1000/UL)	6.1	4.5–11.0
Prothrombin time (sec)	15.9	12–15.1
International normalized ratio	1.36	0.85–1.14
Partial thromboplastin time (sec)	30.4	25.4–36.7
Chemistry		
Sodium (mmol/L)	133.0	136–145
Potassium (mmol/L)	4.3	3.5–5.1
Chloride (mmol/L)	99	98–107
Serum bicarbonate (mmol/L)	26	20–31
Blood urea nitrogen (mg/dl)	30	9–23
Creatinine (mg/dl)	0.85	0.70–1.30
Calcium (mg/dl)	9.5	8.7–10.4
Aspartate aminotransferase (Units/L)	48	8–34
Alanine aminotransferase (Units/L)	172	10–49
Alkaline phosphatase (Units/L)	63	46–116
Total bilirubin (mg/dl)	4.4	0.3–1.2
Direct bilirubin (mg/dl)	1.0	0.1–0.3

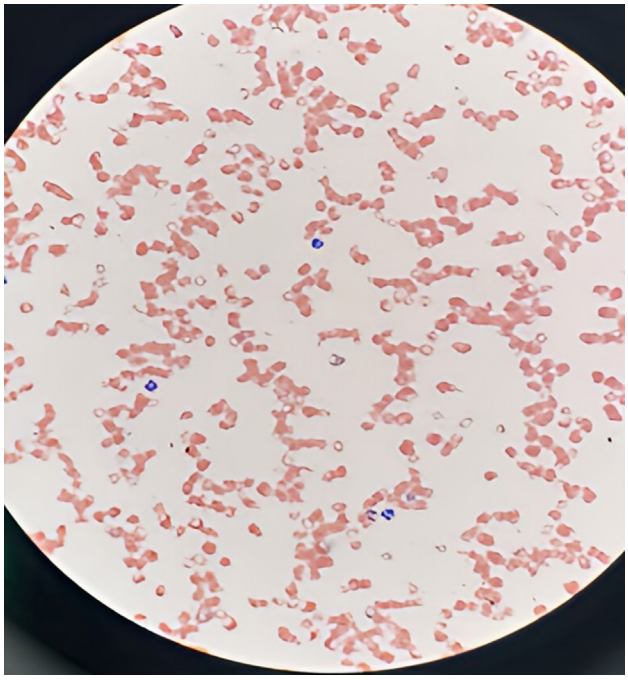

Fig. 1. Peripheral blood smear showing hypersegmented neutrophils and very few schistocytes.

Further work-up for anemia revealed a lactate dehydrogenase (LDH) level of >4500 unit/L and haptoglobin level of <8 mg/dl, indicating intravascular hemolysis and a reticulocyte count of 1% and reticulocyte index of 0.8% indicating significant hypoproliferation (Table 2). The direct Coombs test was negative, ruling out autoimmune hemolytic anemia. Labs to evaluate for nutritional status were notable for significantly elevated ferritin, normal iron level, normal folate level, normal copper level, low Vitamin B12 level of 188 pg/mL, and elevated homocysteine level (Table 2). Serum protein electrophoresis showed a normal pattern without monoclonal proteins.

Anti-parietal cell antibody was positive with a titer of 1:640 (normal range <1:20), and the intrinsic factor antibody was positive. Based on these laboratory findings, the likely cause of this patient's hemolysis was attributed to vitamin B12 deficiency secondary to Pernicious anemia. Glucocorticoid therapy or plasma exchange was therefore not indicated. He was treated with daily vitamin B12 intramuscular injections of 1000 mcg and folic acid supplementation was added due to ongoing hemolysis. He initially had a fall in platelet count attributed to dilution due to the administration of intravenous fluids. Over the

Table 2. Results of hematological workup.

Laboratory test on admission	Result	Normal Range
Reticulocyte (%)	1.0	0.5–2.7
Absolute Reticulocyte count (10^6/microliter)	0.014 (L)	0.016–0.095
Haptoglobin (mg/dl)	<8 (L)	43–212
Lactate dehydrogenase (Unit/L)	>4500	120–246
Fibrinogen (mg/dl)	147	244–550
D-dimer (ug/ml)	84.452	0.000–0.500
Ferritin (ng/ml)	1276	38–380
Serum Iron (mcg/dl)	167	50–180
Transferrin iron binding capacity	Result not calculated because one or more required values exceed analytic limits	250–425
Transferrin saturation (%)	Result not calculated because one or more required values exceed analytic limits	20–48
Vitamin B 12 (pg/ml)	188	200–1100
Folate level (ng/ml)	7.6	Low <3.4 Borderline: 3.4–5.4 Normal: >5.4
Homocysteine (umol/L)	42.7	<11.4
Copper level (mcg/dL)	117	70–175

subsequent five days, his reticulocyte count showed a good response to B12 supplementation, and his hemoglobin remained stable. He noted some improvement in the numbness and weakness of the lower extremities. He was discharged with a prescription for home physical therapy, to continue vitamin B12 supplementation with 1000 mcg of oral B12 daily and to follow up with hematology.

On his follow-up visit two weeks later, his repeat complete blood count showed a hemoglobin of 10.7 g/dl, mean corpuscular volume of 93 fl, white blood cell count of 4100/UL, lactate dehydrogenase of 336 Unit/L, and a vitamin B12 level of 554 mg/dl.

3. Discussion

Vitamin B12 deficiency in patients >60 years old is relatively common, with a prevalence of at least 20% in this population. Most patients with vitamin B12 deficiency can present insidiously with anemia or neurological symptoms, including paresthesia, memory impairment, loss of coordination, and difficulty ambulating.[5] It may also be asymptomatic with noted hematological abnormalities on laboratory investigations, including macrocytic megaloblastic anemia, leukopenia, and thrombocytopenia. Hemolysis is an uncommon complication of vitamin B12 deficiency which occurs in about 1.5–2.5% of patients with severe B12 deficiency.[4,6]

The pathophysiology of hemolysis associated with B12 deficiency is unclear. It is considered secondary to intramedullary and extramedullary mechanisms.[7] Intramedullary hemolysis occurs when the RBCs are destroyed in the bone marrow before reaching the peripheral circulation. Vitamin B12 is a cofactor for many reactions in the body, including the biochemical mechanisms essential for the production of DNA and the formation and maturation of normal RBC precursors. In the absence of B12, DNA synthesis in the RBC precursors is impaired, and the RBC precursors with the defective DNA often undergo apoptosis - a process known as ineffective erythropoiesis.[8] A reduction in the production of normal RBC precursor cells, therefore, means a decrease in the production of normal RBCs and anemia. Additionally, the RBCs that are produced in the setting of vitamin B12 deficiency often have fragile membranes which are easily destroyed as they travel through the bone marrow channels prior to their release into circulation.[9] These two pathologic mechanisms are the primary causes of intramedullary hemolysis in B12 deficiency.

Extramedullary hemolysis in B12 deficiency refers to the destruction of fragile RBCs as they pass through the capillary membrane. Elevated homocysteine level is thought to be a major contributor to extramedullary hemolysis in B12 deficiency.[10] Vitamin B12 functions as a cofactor for the enzyme methionine synthase, which is responsible for the conversion of homocysteine to the essential amino acid methionine. When B12 is deficient, the conversion of homocysteine to methionine is reduced, resulting in an accumulation of homocysteine. Elevated homocysteine level is thought to result in oxidative stress, possibly in the form of oxygen free radicals that damage the fragile RBC membranes.[6,11] Additionally, elevated levels of homocysteine have been associated with endothelial dysfunction, which may contribute to extramedullary hemolysis.[11]

In cases where B12 deficiency results in hemolysis and thrombocytopenia, it may be mistaken for a

thrombotic microangiopathy (TMA) such as thrombocytopenic thrombotic purpura and hemolytic uremic syndrome. This clinical syndrome of thrombocytopenia and hemolysis associated with B12 deficiency is often called pseudo-TMA.[4,7,12] Similarly, to true TMA, hemolysis can occur within the vasculature (extramedullary hemolysis) and can result in the fragmented RBCs (schistocytes) on the peripheral smear. However, unlike true TMA, thrombocytopenia is not the result of platelet consumption in the formation of microthrombi but rather from decreased platelet production in the bone marrow.[9]

Recognizing pseudo-TMA is crucial in preventing unnecessary investigations and treatments. If unrecognized, patients with pseudo-TMA may undergo further workup for hemolytic anemia, including a bone marrow biopsy or the initiation of unnecessary treatments such as plasmapheresis, the primary therapy for true-TMAs such as thrombocytopenic thrombotic purpura. In cases of severe B12 deficiency, bone marrow biopsy samples may have similar histopathological findings to myelodysplastic syndrome, another potential cause of ineffective erythropoiesis. These findings may lead to the pursuit of other expensive investigations.[13]

Laboratory investigations are crucial to differentiating the pseudo-TMA of B12 deficiency from true TMA. Patients with TMA often have markedly elevated LDH levels, usually out of proportion to the observed hemolysis and normal to mildly elevated levels of unconjugated bilirubin, as was observed in our case with our patient having an LDH level of >4500.[14] The intramedullary hemolysis of the nucleated abnormal RBCs precursors is thought to lead to a more significant elevation of the LDH when compared to the extramedullary hemolysis of the mature RBCs, which are non-nucleated.[15] Other laboratory indicators of pseudo-TMA include high mean corpuscular volume, low reticulocyte count, and a low reticulocyte index (<2), which were all observed in our case.[9,14,16]

Further laboratory investigations done in our cases demonstrated positive anti-parietal cell antibodies as well as positive antibodies to intrinsic factors, pointing towards a diagnosis of pernicious anemia as the likely cause of our patient's vitamin B12 deficiency.

Splenomegaly was observed on abdominal imaging in our case. Splenomegaly has been reported as an infrequent clinical feature of pernicious anemia in the literature, with a few cases reporting massive splenomegaly. Splenic enlargement in pernicious anemia is postulated to be due to the occlusion of the splenic red bulb by macrocytes in some cases.[17]

4. Conclusion

Hematological abnormalities are common manifestations of vitamin B12 deficiency; however, hemolysis and pseudo-TMA are uncommon. B12 deficiency should be suspected in patients with evidence of hemolysis and thrombocytopenia when there is a significant elevation of the LDH coupled with evidence of hypoproliferation such as a low reticulocyte count and a low reticulocyte proliferation index.

Disclaimer

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Conflict of interest

The authors have no financial and/or personal conflicts of interest to declare.

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