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Case Reports

A Rare Case of Hemolysis Secondary to Severe Vitamin B12 Deficiency

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Abstract

An 80 year old female with a past medical history of hypertension, hyperlipidemia, hypothyroidism, and chronic back pain presented to the hospital with fatigue and was found to have a severe macrocytic anemia. Blood work showed pancytopenia and positive markers of hemolysis. Additional work up was consistent with severe vitamin B12 deficiency and pernicious anemia. Her blood counts improved with blood transfusions and vitamin B12 repletion. We discuss the proposed pathophysiology of this rare case of pernicious anemia presenting with hemolysis.

BACKGROUND

Vitamin B12 is a water-soluble vitamin obtained in the diet from animal products. It is absorbed in the terminal ileum by intrinsic factor which is produced by parietal cells. B12 is a cofactor for the enzymes involved in the DNA synthesis. B12 deficiency can cause hematologic pathologies such as macrocytic anemia, and accounts for 18-20% of cases of clinical macrocytosis. The etiologies of B12 deficiency include autoimmune, also known as pernicious anemia, malabsorption, dietary insufficiency, or toxin exposure.[1]

CASE PRESENTATION

An 80-year-old female with a past medical history of hypertension, hyperlipidemia, hypothyroidism, and chronic back pain presented to the hospital due to fatigue. On review of systems, she reported unquantified weight loss as well as decreased appetite. She denied having any fever, chills, temperature intolerance, lymphadenopathy, dizziness, syncope, abdominal pain, hematuria, hematochezia, or melena. Her vitals were notable for tachycardia, and on physical exam she appeared pale with conjunctival pallor. She had no lymphadenopathy, petechiae or signs of clinical bleeding, and stool occult blood was negative.

Initial labs revealed a white blood cell count of 1.3 x 10^9/L, absolute neutrophil count of 0.1 x 10^9/L, hemoglobin of 5.2 g/dL, hematocrit of 15.3%, mean corpuscular volume of 110 fL, platelet count of 71 x 10^9/L, a reticulocyte percentage of 1%, and hematologic morphology notable for 1+ tear drop cells (**Table 1**). Initial imaging included chest x-ray and CT of the abdomen and pelvis, both of which were unremarkable, notably without lymphadenopathy, hepatosplenomegaly, or masses. The patient was transfused 3 units of packed red blood cells.

Further work-up revealed a significantly elevated D-dimer of 1851 ng/mL, reduced fibrinogen of 146 mg/dL, and a normal prothrombin time, partial thromboplastin time, and internal normalized ratio. Additionally, laboratory results showed evidence of hemolysis with a haptoglobin less than 8 mg/dL and lactate dehydrogenase elevated at 3562 IU/L (**Table 2**). Notably, her serum vitamin B12 was below the detectable level. Iron studies showed elevated iron and ferritin with low transferrin and total iron binding capacity. The hematology team was consulted for further evaluation, who noted that severe vitamin B12 deficiency can cause hemolysis and proposed a plan to replete her vitamin B12 and evaluate for pernicious anemia with anti-parietal cell antibodies and intrinsic factor blocking antibodies.

The patient was seen by nutrition services and evaluated for food insecurity and insufficient dietary intake, both of which were non-contributory. After a three-day course of intramuscular vitamin B12 repletion, the patient's fatigue improved and her hemoglobin levels stabilized at 9.7 g/dL. Infectious workup was unrevealing. Folate and copper were within normal limits. Intrinsic factor blocking antibodies returned positive, indicating pernicious anemia in this patient. The patient was arranged for outpatient hematology follow-up with weekly intramuscular vitamin B12 infusions and close blood count monitoring with a plan to obtain a bone marrow biopsy if her blood counts did not improve.

DISCUSSION

In this patient, we observed a case of severe vitamin B12 deficiency consistent with pernicious anemia. Pernicious anemia is an autoimmune disease in which antibodies are produced against intrinsic factor, which absorbs B12, or its source, parietal cells.[2] Gastric parietal cells produce in-

Table 1. Laboratory Values on Presentation

Parameter	Results	Normal Values
White Blood Cell Count	1.3 x 10^9/L	4.2-10 x 10^9/L
Red Blood Cell Count	1.38 x 10^{12}/L	3.8-5.1 x 10^{12}/L
Hemoglobin	5.2 g/dL	11.2 - 14.9 g/dL
Hematocrit	15.3%	35-48%
Mean Corpuscular Volume	110.9 fL	85.2 - 100.2 fL
Platelets	71 x 10^9/L	168 - 382 x 10^9/L
Absolute Neutrophil Count	0.1 x 10^9/L	1.9 - 6.7 x 10^9/L
Reticulocyte Percentage	1.0%	0.9 - 2.7 %
Reticulocyte Index	0.15%	0.5% to 2.5%
Red Blood Cell Morphology	1+ Tear Drop Cells	Normal
Thyroid Stimulating Hormone	13.022 µU/mL	0.330 - 4.120 µU/mL
Free T4	0.90 nG/dL	0.70 - 1.40 nG/dL

Table 2. Comprehensive Workup

Parameter	Results	Normal Values
D-dimer	1851 ng/mL	0 - 300 ng/mL
Fibrinogen	146 mg/dL	150 - 480 mg/dL
Prothrombin Time	12.6 sec	10.0 - 13.0 sec
Partial Thromboplastin Time	27.0 sec	24.0 - 37.0 sec
Internal Normalized Ratio	1.0	0.8 - 1.2
Lactate Dehydrogenase	3562 IU/L	119 - 265 IU/L
Haptoglobin	<8 mg/dL	63 - 273 mg/dL
Bilirubin	0.6 mg/dL	0.2 - 1.3 mg/dL
Methylmalonic Acid	38.60 umol/L	0.00 - 0.40 umol/L
Vitamin B12	<148 pg/mL	227 - 1,053 pg/mL
Iron	197 mcg/dL	37 - 170 mcg/dL
Ferritin	418 ng/mL	5 - 204 ng/mL
Transferrin	169 mg/dL	178 - 367 mg/dL
Total Iron Binding Capacity	248 mcg/dL	250 - 450 mcg/dL
Copper	93 mcg/dL	85 - 185 mcg/dL
Folate	560 ng/mL	> 366 ng/mL
Hepatitis Panel	Non Reactive	Non Reactive
Parvovirus	Equivocal	Negative
Human Immunodeficiency Virus Antibody/Antigen Combination	Non Reactive	Non Reactive
Anti-Parietal Cell Antibodies	1:40	<1:20
Intrinsic Factor Blocking Antibodies	Positive	Negative

trinsic factor which binds to B12 in the stomach and allows for its absorption in the terminal ileum. Etiology and associations of pernicious anemia include conditions that interfere with this absorption such as autoimmune atrophic gastritis, chronic atrophic gastritis, autoimmune thyroid disease, type I diabetes mellitus, and vitiligo.[3] H. pylori infection is another possible etiology due to the cross-reactivity of anti-H. pylori antibodies with the H+/K+/ATPase proton pump on parietal cells.[3] Pernicious anemia can present with symptoms of shortness of breath, pallor, or fatigue, just as with other causes of anemia. Pernicious anemia can also affect the lateral and posterior columns of the spinal cord, with the potential of causing subacute combined degeneration, which manifests with symmetrical paresthesia, loss of vibratory or positional sense, and changes in mood or cognition.[4]

The mechanism of degeneration involves the role of B12 as a cofactor for methylmalonyl-CoA mutase in odd-chain fatty acid metabolism. Without B12, methylmalonyl-CoA cannot be converted to succinyl-CoA, resulting in an accumulation of methylmalonic acid (MMA) and its precursor propionyl-CoA.[5] Propionyl-CoA then replaces Acetyl-CoA in the neuronal membrane, resulting in demyelination, which leads to subacute combined degeneration of the spinal cord.[5] This degeneration can affect the spinal cerebellar tracts, lateral

corticospinal tracts, and dorsal columns with clinical manifestations of peripheral neuropathies and cognitive changes.[6] Other manifestations can include gait ataxia and optic neuropathy.[6]

Our patient displayed anemic symptoms of pallor and fatigue, though lacked neurologic sequelae despite having an undetectable level of vitamin B12. Our patient did, however, demonstrate an uncommon finding of hemolysis. Hemolysis secondary to pernicious anemia, or B12 deficiency, is a rare complication that has been reported in a few case studies.[7] There are several proposed mechanisms by which B12 deficiency causes hemolysis. One mechanism relates to the necessity of B12 to synthesize deoxyribonucleic acid (DNA); without adequate levels of vitamin B12, DNA replication becomes impaired, thereby leading to impaired hematopoiesis.[4] B12 is a necessary cofactor for the enzyme methionine synthase (MS) in DNA synthesis.[8] MS is involved in the conversion of homocysteine to methionine which demethylates N5-methyl-tetrahydrogolate to produce THF which is a cofactor in both purine and pyrimidine synthesis.[8] Without adequate DNA synthesis, nuclear maturation slows relative to cytoplasmic maturation, leading to dyssynchrony in the bone marrow that produces the megaloblastic changes seen with B12 deficiency.[9] These changes can be seen on peripheral smear, including hypersegmented neutrophils and macroovalocyte red blood cells.[9] Ultimately, the implications of B12 deficiency on hematopoiesis can result in anemia with or without other cytopenias.

An additional mechanism for cytopenic findings in B12 deficiency is the arrest in the development of hematopoietic cells caused by decreased hematopoiesis. The hematopoietic arrest is thought to cause intramedullary cell death, resulting in a hemolytic profile of increased lactate dehydrogenase and decreased haptoglobin.[4] Another proposed mechanism is that B12 deficiency can lead to oxidative stress through the buildup of homocysteine.[4] This oxidative stress can also lead to hemolysis.

In our patient who presented with severe pancytopenia, the likely etiology included both hypoproliferation and hemolysis. Her very low reticulocyte index pointed towards a lack of production of red blood cells. Her elevated lactate dehydrogenase, d-dimer, and low haptoglobin all pointed towards the destruction of cells. Overall, this case demonstrates the diverse hematologic pathologies caused by vitamin B12 deficiency. This patient's pancytopenia secondary to pernicious anemia was treated with red blood cell transfusion and vitamin B12 repletion, with appropriate response and count recovery. After three weeks of treatment, the patient's absolute neutrophil count rose to 4.7 x 10^9/L, hematocrit rose to 36.0%, and platelets rose to 397 x 10^9/L.

The standard of treatment for pernicious anemia includes early and aggressive vitamin B12 repletion. Typical repletion regimens include up to a week of weekly intramuscular injections of 1000 mcg of vitamin B12, followed by weekly injections for around four weeks, followed by lifelong monthly injections or high-dose oral supplementation.[4] Typically, hypoproliferation due to pernicious anemia resolves with adequate vitamin B12 repletion in approximately four to six weeks. Secondary neurological symptoms, which this patient did not have, can take months to improve and may often be permanent.

Author Contributions

All Authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the ICJME criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures/Conflicts of Interest

The authors declare they have no conflicts of interest

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