CLINICAL VIGNETTE

Severe Vitamin B_{12} Deficiency and Pancytopenia

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A 59-year-old male presented with 2 months of progressively worsening fatigue, poor oral intake, nausea, vomiting, dizziness, and unintentional weight loss of 20-lbs. He had recently been diagnosed with severe anemia (hemoglobin 6.1 grams/dL) 2 weeks prior and was transfused 2 units of red blood cells at another hospital. He denied any hematemesis, hematochezia, melena, hematuria, or prior history of anemia. He had no other known medical problems and was taking no medications and not using any recreational drugs or alcohol.

Vital signs and physical examination on presentation were all within normal limits. Initial lab findings were significant for pancytopenia with a hemoglobin of 5.6 grams/dL, mean corpuscular volume of 93.7 fL, white blood cell count of 3200 cells/mm3 (absolute neutrophil count of 1700 cells/mm3), and platelets of 77000 cells/mm3. He was transfused red blood cells with an appropriate response in his hemoglobin. Unfortunately, iron studies were not obtained prior to transfusion. Further evaluation of his pancytopenia included an international normalized ratio and prothrombin time that were within normal limits. However, he had a low haptoglobin (<15 milligrams/dL), elevated bilirubin (1.5 milligrams/dL), and elevated lactate dehydrogenase (>2900 Units/L) which were concerning for a hemolytic process. In addition, his calculated reticulocyte index was 0.55 which was consistent with a hypoproliferative process.

During his hospitalization, the patient had a CT abdomen pelvis and right upper quadrant ultrasound performed due to his nausea, vomiting, and weight loss. Imaging studies were only remarkable for borderline hepatomegaly with hepatic steatosis. When his vitamin B_{12} level returned severely low (<146 picograms/mL) a diagnosis of pancytopenia and intramedullary hemolysis secondary to vitamin B_{12} deficiency was made as folate level was within normal limits). He was initially started on intramuscular vitamin B_{12} injections due to concerns about impaired oral absorption since he presented with gastrointestinal complaints. Eventually a diagnosis of pernicious anemia was confirmed after both his intrinsic factor and parietal cell antibodies returned positive. After nearly a week of intramuscular vitamin B_{12} injections, his reticulocyte index significantly increased to 8.68. An esophagogastroduodenoscopy was scheduled as an outpatient for further evaluation of his pernicious anemia.

Discussion

Severe vitamin B_{12} deficiency can cause extensive hematologic changes, at times mimicking features of microangiopathic hemolytic anemia, myelodysplastic syndrome, or acute leukemia.[1–4] Low B_{12} or folate leads to impaired DNA synthesis,[5] thus affecting all hematopoietic cell lines. Despite the association between pancytopenia and B_{12} deficiency, only about 2.5% of patients with B_{12} deficiency have symptomatic pancytopenia.[1] Severe B_{12} deficiency more classically presents as megaloblastic anemia due to delayed maturation of the nucleus relative to cytoplasm of precursor RBCs. This nuclear-cytoplasmic asynchrony leads to hypersegmentation of granulocytes and intramedullary hemolysis due to ineffective erythropoiesis.[5,6] Severe B_{12} deficiency can also lead to increased hypercellular, dysplastic bone marrow,[7,8] which may result in thrombocytopenia as well as neutropenia due to intramedullary destruction of myeloid cells.[9]

More typical manifestations of B_{12} deficiency include neurological symptoms such as general weakness, unsteady gait, poor proprioception, and vibratory sensory changes.[5] Deficiency of B_{12}, a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-coenzyme A mutase, leads to accumulation of methylmalonyl CoA which inhibits fatty acid synthesis and impairs myelin synthesis. The resulting "subacute combined degeneration" involves demyelination in the dorsal and lateral columns of the spinal cord, cranial and peripheral nerves, and cortical white matter.[5] Neurological manifestations associated with B_{12} deficiency are helpful diagnostically but may not always occur. In some cases, the severity of megaloblastic anemia was found to be inversely correlated with the degree of neurologic dysfunction.[10] Other less common conditions associated with B_{12} deficiency include atrophic glossitis, malabsorption, and thrombosis.[5,11]

The most common cause of severe vitamin B_{12} deficiency is pernicious anemia which results from autoimmune gastritis destruction of gastric parietal cells.[12] Without parietal cells, there is no production of intrinsic factor to bind ingested B_{12}. A positive test for anti-intrinsic factor or anti-parietal cell antibodies confirms the diagnosis of pernicious anemia with 100% specificity. However, there is a high possibility of false negative results given its sensitivity of only 50%.[5] Conditions causing severe malabsorption including ileal resection, gastric bypass surgery, gastrectomy, inflammatory bowel disease, and celiac disease can also lead to B_{12} deficiency.[5] To diagnose

malabsorption as the primary cause, B_{12} levels would need to remain low after consumption of sufficient amounts of B_{12}.[5] In addition, some drugs are known to cause B_{12} deficiency, including metformin and proton pump inhibitors.[5] Because B_{12} is found only in animal products, a vegan diet or diet low in meat and dairy products can also lead to B_{12} deficiency.

Treatment of vitamin B_{12} deficiency involves parenteral or oral replacement. Most adults with B_{12} deficiency present asymptomatically and can take weekly oral vitamin repletion for a few weeks.[13] Adults with severe B_{12} deficiency including symptomatic anemia or neurologic findings are treated more urgently with 1000 micrograms via intramuscular injection at least several times per week for 1-2 weeks, then weekly until clear improvement is shown.[5,13] In rare cases of severe anemia with hemodynamic instability, blood transfusion may be considered.[5] There is usually rapid hematologic response to parenteral treatment—increase in reticulocyte count in 1 week and resolution of megaloblastic anemia in 6-8 weeks.[5] Although neurologic symptoms may worsen transiently during treatment, these symptoms typically subside over weeks to months.[14] In addition to lifelong treatment of vitamin B_{12} deficiency for individuals with pernicious anemia,[15] such individuals may also require additional gastrointestinal evaluations. Pernicious anemia is associated with increased gastrointestinal malignancies and carcinoid tumors for which endoscopic evaluation may be appropriate.[16]

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