CLINICAL VIGNETTE

Pernicious Anemia: A Rare and Overlooked Disorder in the Outpatient Setting

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Case Presentation

A 76-year-old male presented to urgent care complaining of a tingling sensation in his feet, face, and on the top of his head; a burning sensation in his mouth and tongue; arm weakness; fatigue; and decreased appetite. He had experienced these symptoms over the past several months but recalls similar symptoms about five years prior. At that time, he was told that he had a vitamin B12 deficiency and was subsequently given oral vitamin B12 supplementation for several months. He noted improvement in symptoms and normalization of vitamin B12 levels. Five years later, the symptoms resumed, and his daughter resumed giving him oral vitamin B12 supplementation. After three months of daily oral supplementation, however, the patient's symptoms did not improve, prompting his daughter to bring him into urgent care.

The patient reported numbness and tingling in his feet and face and occasionally in his hands, similar to his prior symptoms. He also described a burning sensation in his mouth. His daughter denied changes in her father's mental status, mood, or neurological status. His diet included coffee and cookies or pastries for breakfast; and beans, bread, and occasional chicken for lunch and dinner. Past medical history was significant for coronary artery disease, hypertension, gastroesophageal reflux disease (GERD) and an *H. pylori* infection that was apparently difficult to treat. His past surgical history was significant for an abdominal aortic aneurysm status post repair with a stent in 2009 but no other abdominal surgeries. He denied any recent travel, diarrhea, or unexplained weight loss. He denied any family history of autoimmune conditions or gastric cancer. He was not taking any medications that would cause vitamin B12 deficiency, such as metformin, although he was taking omeprazole periodically for the past month for his GERD symptoms.

Our initial hypothesis was vitamin B12 deficiency due to his restrictive diet. He was therefore counseled on nutrition and switched to 3000 mcg sublingual vitamin B12 for improved absorption. At his 2-month follow up appointment, his symptoms and vitamin B12 levels did not improve despite adhering to the new vitamin B12 prescription and increasing protein in his diet. His hemoglobin, MCV, and RDW were all within normal limits as shown in Table 1, which were consistent with his previous labs. Follow up labs were sent, including methylmalonic acid, homocysteine, folate, vitamin B12, intrinsic factor blocking antibody assay, and *H. pylori* stool antigen. The results are shown in Table 1, but most notable is the positive intrinsic factor blocking antibody.

Table 1: Relevant Laboratory Findings for a Patient with Chronic Vitamin B12 Deficiency

	Value	**Reference Range**
Hemoglobin	14.5	13.5-17.1
Hematocrit	42.0	38.5-52.0
MCV	94.4	79.3-98.6
RDW CV	12.3	11.1-15.5%
Vitamin B12	<150	254 - 1,060
Folate	15.7	8.1 - 30.4
Homocysteine	25	<15
Methylmalonic acid	0.55	0.00 - 0.40
Intrinsic factor blocking antibody	Positive	Negative
Stool *H. pylori* antigen	Negative	Negative

He was diagnosed with pernicious anemia and was started on 1000 mcg of intramuscular (IM) vitamin B12 (cyanocobalamin) every other day for the first week, then weekly for 4 weeks thereafter. After six injections, his symptoms resolved, and his repeat vitamin B12 level was within normal limits. He was subsequently referred to gastroenterology for further evaluation, and esophagogastroduodenoscopy (EGD) was scheduled, and he was continued on monthly IM injections of vitamin B12 in the interim.

Discussion

Diagnosing pernicious anemia can be challenging given its complexity and breadth of clinical presentation.[1] Its diagnosis in the outpatient setting can be especially challenging since the etiology of vitamin B12 deficiency is vast and pernicious anemia, while often considered, is not usually the leading differential diagnosis. More commonly considered are gastric abnormalities (e.g., gastritis, gastrectomy, etc.), small bowel disease (e.g., ileal resection, inflammatory bowel disease [IBD], Celiac disease, etc.), pancreatic insufficiency, bacterial intestinal overgrowth due to antibiotics, vegetarian or low animal protein diet, or certain medications (e.g., chronic use of protein pump inhibitors [PPI], neomycin, metformin, or histamine 2 receptor antagonists). However, pernicious anemia, as its name suggests, can have deleterious effects if left untreated, leading to severe and possibly irreversible neurological symptoms, including death. Once diagnosed, it requires

indefinite - likely lifetime - treatment with parenteral vitamin B12 supplementation.[1]

Pernicious anemia is a rare disorder that causes a deficiency in dietary vitamin B12 due to a reduction of intrinsic factor, a protein that binds to dietary vitamin B12 and promotes its transport to and absorption in the terminal ileum. This leads to a megaloblastic anemia. Symptoms are often nonspecific, as seen with anemia in general, but can also include glossitis and neuropsychiatric manifestations as the disease progresses. It can affect all ages, but it is generally known as a disease of the elderly given that it predominantly affects those over 60 years old.[2]

Pernicious anemia is considered an autoimmune disorder due to the presence of gastric autoantibodies directed against intrinsic factor and parietal cells. This prevents the formation of the vitamin B12-intrinsic factor complex, which in turn dramatically decreases vitamin B12 absorption. Since the pathophysiology of pernicious anemia typically involves the autoimmune destruction of oxyntic gastric mucosa, it is often considered a synonym for autoimmune gastritis,[3] although it is technically the end stage of the clinical spectrum of autoimmune gastritis. Furthermore, patients with pernicious anemia also have a higher incidence of concomitant autoimmune disorders, including vitiligo, diabetes mellitus type 1, and autoimmune thyroid disease, just to name a few.[4]

Clinical studies suggest an implication of long-standing H. pylori infection in the pathogenesis of pernicious anemia, but its role in the pathophysiology is still poorly understood.[5] Our current understanding is that H. pylori causes gastritis and gastric atrophy by stimulating an autoimmune process against the gastric parietal cells and proton pump α, β subunits via molecular mimicry. It also triggers antibody production against intrinsic factor in genetically susceptible individuals. There are multiple case reports that highlight H. pylori as the causative agent of vitamin B12 deficiency and posits that anti-H. pylori treatment can potentially reverse the underlying pathogenesis and could, in theory, correct vitamin B12 deficiency over time.[6]

Diagnosis of pernicious anemia is challenging for several reasons: the Schilling test (to determine vitamin B12 absorption from the gut) is now obsolete, and an approved B12 absorption test doesn't exist. There are currently multiple diagnostic algorithms and criteria. However, in clinical practice, diagnosis is generally achieved with vitamin B12 deficiency coupled with a positive Intrinsic Factor antibody test.[7] Once diagnosed, patients should undergo endoscopy with biopsies of the gastric mucosa to confirm atrophic gastritis for risk stratification and to rule out gastric neoplasia, including neuroendocrine tumors.[8]

While our understanding of pernicious anemia has advanced significantly, it is still a neglected disorder and is often underdiagnosed. Given its rarity along with its vague and insidious presentation, it comes as no surprise that this disorder is easily overlooked, especially in the outpatient setting. Additionally, given recent evidence suggesting a positive correlation between long standing H. pylori infection and pernicious anemia, we argue that a pernicious anemia workup be considered in patients with a history of untreated and/or longstanding H. pylori infections undergoing a vitamin B12 deficiency workup. Outpatient providers, especially primary care physicians, play an important role in diagnosing pernicious anemia. While one might think that ordering an intrinsic factor antibody test has low utility in a patient with vitamin B12 deficiency, our continued understanding of pernicious anemia's epidemiology, nuanced clinical manifestations, and associated conditions could very well mean the difference between improved quality of life and debilitating sequelae.

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