

CLINICAL VIGNETTE

Vitamin B12 Anemia: A Case-Based Review

Robert Nisenbaum, MD

Clinical Case

A 56-year-old man seen in routine follow-up for DM Type 2 and HTN. He is feeling generally well and without new or acute complaints, but reports some long-standing fatigue and a tingling in his feet bilaterally, which has been attributed to diabetes. DM history also included GERD, hyperlipidemia, osteoarthritis, and BPH.

Medications included low-dose aspirin, atorvastatin 80 mg, finasteride 5 mg, lisinopril 40 mg, meloxicam 15 mg as needed, metformin 1000 mg twice daily, omeprazole 40 mg once daily and terazosin 5 mg.

Exam was essentially normal, except for some decreased sensation to monofilament testing in bilateral feet, in a stocking-glove distribution.

Labs drawn prior to his appointment were notable for a HgB of 11.7, Platelet count is 248, WBC of 3.55. RBC indices included an MCV of 102.1, MCH 35, MCHC 34.3, and RDW 17.6. Automated differential included an elevation in neutrophils, variant forms of lymphocytes, nucleated RBC's and giant thrombocytes. HgB A1C was noted to be 6.3, creatinine was 1.03, ALT 26 and T. Bilirubin 0.57. Electrolytes were all normal.

After review of his pre visit laboratory studies, the patient was referred for additional labs. These included a normal ferritin and other iron studies, B12 level of 104, folate of 16.0. Methylmalonic acid (MMA) was 4673 and homocysteine (HcY) 95.4. To investigate the patient's B12 deficiency, intrinsic factor blocking antibody was sent and noted to be positive. He was diagnosed with pernicious anemia and started on B12 supplementation.

The patient was started on 1000 mcg of cyanocobalamin po daily and 1000 mcg IM weekly. He was kept on this dosage interval for 4 months (with serial labs) until his MMA and HcY levels normalized, although, at this point, his hemoglobin remained less than 13 and his B12 level was only 201. Based on the normalization of his MMA and HcY, his cyanocobalamin injections were spaced out to monthly and he was maintained on 1000 mcg po daily as well. On this regimen his labs remained adequate. Four months later, he reported a renewed sense of energy and the tingling in his feet had decreased dramatically.

Discussion

This is an interesting case of symptomatic vitamin B12 deficiency in a patient with two risk factors for developing such deficiency, namely long-term use of PPIs and metformin. Indeed amongst long-term users of metformin, 10-30% will have some level of B12 deficiency, albeit typically less severe than this case. The mechanism of B12 deficiency in metformin users is thought to be related to calcium-dependant ileal membrane antagonism, which is effectively reversed when giving metformin with supplemental calcium.¹

Multiple studies have also shown the association between mild vitamin B12 deficiency and chronic PPI use, including a large case-control study comparing approximately 26,000 patients with B12 deficiency to 184,000 patients without deficiency. In this study, chronic acid suppression via PPI or H2 blockade was associated with B12 deficiency, with an odds ratio of 1.65 and 1.25 respectively. The presumptive mechanism is related to the need for gastric acidity to cleave vitamin B12 from ingested proteins prior to absorption.²

Despite this patient's long-term use of both omeprazole and metformin, the presence of intrinsic factor blocking antibodies reveal the primary etiology of his B12 deficiency to be pernicious anemia. Pernicious anemia is an autoimmune gastritis in which there is an autoimmune response directed against the gastric H/K –ATPase causing achlorhydria.³

Various treatment protocols for B12 deficiency have been advised, though for pernicious anemia, repletion is generally intramuscular and maintenance either IM or oral.³ Despite the lack of intrinsic factor in pernicious anemia, oral supplementation at high doses (at least 1000 mcg) daily has been shown to be effective though passive diffusion across the intestinal membrane, though the supporting evidence of this approach has been described by the Cochrane Collaboration as being of low-quality. Furthermore, the evidence supporting the safety of using oral vitamin B12 (versus parenteral) was described as being very low-quality and further trials with better randomization and blinding procedures was suggested.⁴

Whether by IM or oral repletion, correction of the underlying manifestations of pernicious anemia take weeks to months to resolve, with the megaloblastic anemic responding in 6 to 8 weeks, but the neurologic manifestations needing longer to fully resolve.³

In addition to its hematologic and neurologic effects, pernicious anemia due to type A atrophic gastritis is reported to have a 1-3% incidence of gastric adenocarcinoma. However, a large population-based cohort study found the incidence of gastric cancer in patients with pernicious anemia to be similar to the background US population. Despite this, some studies have suggested the highest risk of malignancy to be in the first year of the diagnosis of pernicious anemia. As such, the American Society of Gastrointestinal Endoscopy recommends a surveillance endoscopy soon after at the diagnosis of pernicious anemia is made and if upper gastrointestinal symptoms develop.⁵

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Submitted March 30, 2019