CLINICAL VIGNETTE

The Low Alkaline Phosphatase: When to Suspect More

Arielle Sommer, MD and Wendy Ho, MD, MPH

Case Presentation

A 50-year-old female presented for an annual wellness examination. Her past medical history includes Grave's disease, iron deficiency, gall bladder disease status post cholecystectomy. She has no history of bone disease, fractures, dental disease, or liver disease and10-point ROS was negative. On physical exam, she had mildly elevated blood pressure but was otherwise without significant findings. Routine laboratory testing revealed a mildly elevated platelet count at 478 x10E3/uL, with otherwise normal RBC indices, normal ferritin of 156 ng/mL, and normal percent iron saturation of 35%. Her alkaline phosphatase (ALP) level was low at 15 U/L (normal 37 - 113 U/L) with normal aspartate aminotransferase (AST), alanine transaminase (ALT), and total bilirubin levels.

On chart review, her alkaline phosphatase had ranged from 13-25 U/L over the past 15 years, though secondary causes had never been ruled out. Additional laboratory studies were sent to evaluate for thyroid disease, zinc deficiency and pernicious anemia, though she had no symptoms of any of these conditions. The results showed a normal TSH and zinc level but a high Parietal Cell Antibody Titer of >=1:1280 with a negative Intrinsic Factor Blocking Antibody, and normal vitamin B12 level of 291 pg/mL (normal range 254-1060 pg/mL). A methylmalonic acid level resulted at 0.46 umol/L (normal range, 0.00 – 0.40 umol/L), indicating subclinical vitamin B12 deficiency suspected to be due to pernicious anemia. The patient was started on intramuscular vitamin B12 supplementation and referred to gastroenterology for further evaluation. Given antiparietal cell antibodies are non-specific and can be seen in gastritis and other autoimmune diseases, the role of gastroenterology was to confirm a diagnosis of pernicious anemia by endoscopic evaluation and biopsy, and to rule out autoimmune metaplastic atrophic gastritis (AMAG) if pernicious anemia was found to be present.

Endoscopic evaluation found a normal esophagus, a 2cm erythematous polyp in the distal stomach antrum, normally distensible stomach wall, small hiatal hernia, and a normal duodenum. Gastric mapping biopsies revealed reactive antral gastropathy as well as mild to moderate chronic inactive gastritis superimposed on reactive antral gastropathy and severe oxyntic atrophy (atrophic gastritis) without intestinal metaplasia or Heliobacter pylori infection. Biopsy of the large gastric polyp showed inflammation. The diagnosis of chronic atrophic gastritis and pernicious anemia was confirmed. She was referred to interventional endoscopy for endoscopic mucosal resection of the polyp, which showed hyperplastic polyp with focal intestinal metaplasia. After several doses of weekly vitamin B12 injections, the patient was transitioned to once daily cyanocobalamin 1000mg tablets with excellent response and normalization of methylmalonic acid levels to 0.12 umol/L.

Discussion

Alkaline phosphatases are a group of isoenzymes present on cell membranes that catalyze the hydrolysis of organic phosphate esters in the extracellular space. They are found in many body tissues, but the vast majority of serum alkaline phosphatase is released from liver and bone.[1] All alkaline phosphatases require zinc and magnesium as co-factors.[1] High serum alkaline phosphatases are a commonly encountered in a number of conditions. On the contrary, a low serum alkaline phosphatase is a less commonly encountered and discussed clinical entity with a more limited differential. The clinical context can be key to narrowing the differential. In an adult or child with skeletal and dental abnormalities or atypical complicated fractures, a rare inborn error of metabolism, hypophosphatasia can be considered.[2] In a patient with acute liver failure and hemolysis, a low alkaline phosphatase can indicate Wilson disease.[2] Zinc is a cofactor of alkaline phosphatase, which gets displaced by the excess copper in Wilson's disease, resulting in low levels.[1] However, in patients without obvious historical or physical findings, low values can also indicate hypothyroidism, pernicious anemia, or zinc deficiency.

The literature does not have definitive explanations for the associations of low alkaline phosphatase levels with hypothyroidism, pernicious anemia, and zinc deficiency, though several mechanisms are proposed. In zinc deficiency, alkaline phosphatase synthesis may be limited given the metalloenzyme requires two zinc ions in its active center.[3,4] In *hyper*thyroidism, alkaline phosphatase levels can be *elevated* due to thyroid hormone activation of osteoblast-like cells in rat models.[5] In contrast, overt hypothyroidism is known to reduce osteoclastic bone resorption and osteoblastic activity,[6] leading to lower alkaline phosphatase from lack of thyroid hormone activation of osteoblasts. A similar mechanism is suggested in pernicious anemia, with diminished activity of osteoblasts and reduced production of alkaline phosphatase. There may also be a reduced production of alkaline phosphatase in the liver and intestines.[7] Importantly, recovery of alkaline phosphatase levels

is seen after treatment with vitamin B12, so the association may be at least in part related to vitamin B12.[7]

Pernicious anemia is a common cause of vitamin B12 deficiency. It is a late-stage manifestation of autoimmune chronic atrophic gastritis, which is defined by the loss of gastric glands in the presence of chronic inflammation.[8] This causes decreased production of hydrochloric acid, pepsin, and intrinsic factor, which in turn prevents the formation of vitamin B12-intrinsic factor complexes. When dietary vitamin B12 is ingested, the stomach's hydrochloric acid and enzymes separate the vitamin B12 from attached proteins. Then the vitamin B12 attaches to intrinsic factor, glycoprotein produced by parietal cells (also known as oxyntic cells) located at the gastric body and fundus. The vitamin B12-intrinsic factor complex travels to and is absorbed in the terminal ileum. When vitamin B12 is not attached to intrinsic factor, it cannot be absorbed by the human body, leading to vitamin B12 deficiency. In pernicious anemia, anti-intrinsic factor antibodies both prevent vitamin B12 from binding to intrinsic factor (type 1 intrinsic factor antibodies) and binding to vitamin B12/intrinsic factor complexes (type 2 intrinsic factor antibodies), preventing intestinal absorption of vitamin B12.[9]

Chronic atrophic gastritis can also be associated with iron deficiency, due to decreased gastric acid production. Our patient had a history of iron deficiency presumed due to her chronic heavy menstrual bleeding, though at the time of diagnosis her iron levels had normalized with oral supplementation and cessation of menses.

In current medical practice, pernicious anemia is typically diagnosed through blood lab testing and/or the presence of autoimmune atrophic gastritis on gastric biopsy since the Schilling test is no longer in use. Screening for pernicious anemia includes testing for autoantibodies to intrinsic factor. The specificity of antibodies to intrinsic factor is high and if present, is considered diagnostic of pernicious anemia.[10] However, the sensitivity of this test is low with only about 70% of patients with pernicious anemia having antibodies to intrinsic factor.[11] One can also test for anti-parietal cell antibodies, but their presence is nonspecific. While most (85-90%) patients with pernicious anemia have anti-parietal cell antibodies, many patients without pernicious anemia also carry them.[12] Therefore, the British Committee for Standards in Hematology does not recommend testing for anti-parietal cell antibodies.[13]

The 30% of patients who do not have anti-intrinsic factor antibodies, can be diagnosed due to concomitant low vitamin B12 levels and/or high levels of methylmalonic acid. Elevation is seen only in vitamin B12 deficiency with presence of autoimmune atrophic gastritis, suggested by gastric body-predominant atrophy with antral sparing that distinguishes it from Helicobacter pylori associated atrophic gastritis.[8]

Beyond the risk of vitamin B12 deficiency with complications, pernicious anemia and atrophic gastritis are also associated with increased risk of gastrointestinal cancer, including neuroendocrine tumors. Decreased stomach acid causes high gastrin levels and subsequent cellular metaplasia which can lead to neuroendocrine tumor development. In addition, decreased stomach acid is conducive to bacterial colonization and the production of toxic byproducts which also increases the risk for malignancy. Upper endoscopy should be considered if pernicious anemia is suspected or diagnosed.[8] Patients diagnosed with chronic atrophic gastritis are generally recommended to undergo surveillance endoscopies once every three years, though the optimal surveillance interval is unclear and should be considered based on individual assessment including family history of gastric cancer, endoscopic extent of chronic atrophic gastritis. The goal of endoscopy is to screen for stomach malignancy.

In conclusion, our patient with asymptomatic low alkaline phosphatase level found on routine health screening, led to the diagnoses of pernicious anemia. This calls attention to the differential of low alkaline phosphatase values, a less common and less discussed clinical entity, as well as the evaluation of a patient with suspected pernicious anemia.

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