CLINICAL VIGNETTE

Elevated Serum Vitamin B12: An Underappreciated Marker of Disease

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A 69-year-old male with no significant past medical history presented to the emergency department (ED) with progressive vision loss, polyuria, polydipsia, and confusion. He had not seen a physician in 30 years and reported being in his usual state of health until two-weeks prior to presentation, when he developed progressive visual changes to the point where he could no longer perceive light, as well as onset of mental confusion, prompting his family to bring him for evaluation. In the ED, the patient was oriented only to person and lacked light perception in both eyes. His blood glucose was 812 mg/dL without an anion gap and his CBC showed a mild normocytic anemia of 11.9 g/dL. Computed tomography (CT) of the brain showed bilateral occipital strokes. He was admitted to the medical intensive care unit for management of hyperosmolar hyperglycemic syndrome (HHS) and stroke. After intravenous fluids, his hemoglobin dropped to 9.9 g/dL, prompting further evaluation for anemia. This included ferritin of 797 ng/mL, serum iron of 60 mcg/dL, total iron binding capacity (TIBC) of 241 mcg/dL and 25% saturation. Serum folate was 9.2 ng/mL and vitamin B12 was 2,294 pg/mL (normal range 190-950 pg/mL). Basic metabolic panel and TSH were otherwise unremarkable. Liver function tests were not drawn during his hospitalization.

The patient was discharged with subcutaneous insulin and presented for post-hospital discharge and establishing care. The elevated serum vitamin B12 was noted, and the patient denied any supplements or vitamin consumption. Complete metabolic panel was ordered and revealed aminotransferase elevations in the three to four hundreds. He was referred to gastroenterology where additional labs and liver biopsy established diagnosis of IgG4 disease. In retrospect, his new onset insulin-dependent diabetes was attributed to autoimmune pancreatitis, a feature of IgG4 disease.

Serum vitamin B12 levels are often ordered in the evaluation of many conditions including anemia, neuropathy, and cognitive changes. Usually practitioners are looking for low levels, indicating insufficiency. However, not infrequently, vitamin B12 levels return elevated despite the patient denying use of supplements. While this unexpected elevation is often ignored, further evaluation may reveal underlying disease.

Elevated serum vitamin B12 can be found in several disease states, most notably liver disease, and hematologic disorders, though some have reported an association with solid tumors.[1,2] To understand these disease associations, one must first understand the pathophysiology of vitamin B12 metabolism. Vitamin B12, also known as cobalamin, is a water-soluble vitamin naturally found in many foods. It is required for central nervous system development, including myelin synthesis, red blood cell formation and DNA synthesis.[3] Once ingested, the digestive enzyme, pepsin, and the acidic environment of the stomach separate vitamin B12 from the proteins it is bound to in the food source ingested. As it travels to the duodenum, it binds tightly to intrinsic factor, which facilitates absorption in the distal ileum. In the blood, about 80 to 95% of vitamin B12 is bound to haptocorrin, a protein made predominately by myeloid cells. The sialic acid rich form of haptocorrin made by precursor myeloid cells has a longer half-life than the sialic acid poor haptocorrin made by mature granulocytes, and therefore predominates in the circulation. A small portion of vitamin B12 is also found bound to a transport protein named transcobalamin II, which is produced by hepatocytes, enterocytes, and endothelial cells.

At the tissue level, vitamin B12 is poorly absorbed by passive diffusion. For tissues to uptake vitamin B12, the haptocorrin-bound vitamin B12 must be de-glycosylated and is then absorbed in a non-specific manner in the liver. The uptake of the cobalamin-transcobalamin II protein complex is mediated by receptors mainly found in liver endothelial cells. Once endocytosed, vitamin B12 is released via proteolysis from the protein complex. Finally, vitamin B12 is excreted in bile into the duodenum where over 90% is reabsorbed due to the presence of intrinsic factor. The remainder of unbound cobalamin analogues are excreted in feces but the majority of vitamin B12 excretion occurs via urine given its water-solubility.

With the understanding of vitamin B12 metabolism, one can understand the hematologic conditions leading to increased levels. Due to elevated production of haptocorrin from myeloid precursor cells, chronic myelogenous leukemia leads to elevated B12 levels up to 10 times the upper limit of normal. Elevated vitamin B12 can also be seen in about 30 to 50% of cases of polycythemia vera, particularly the sialic poor forms of haptocorrin, due to the larger number of mature leukocytes in this condition. Other hematologic conditions associated with elevated vitamin B12 levels include: hypereosinophilic syndrome, myelofibrosis, and acute myelogenous leukemia (AML), particularly acute promyelocytic leukemia (APL).

It is also possible to see falsely normal or falsely elevated vitamin B12 levels in pernicious anemia. Pernicious anemia, the most common cause of vitamin B12 deficiency, occurs due to loss of gastric parietal cells from autoimmune destruction of

parietal cells through antibodies directed at their proton pumps. With the loss of parietal cells, no intrinsic factor is present to bind vitamin B12 and facilitate absorption. Intrinsic factor antibody, a different antibody then the proton pump antibody, is present in nearly 70% of cases and its presence is considered diagnostic of the disease. This antibody, when present, can interfere with the vitamin B12 laboratory assay leading to a falsely elevated result. The assay relies on competitive binding vitamin B12 with reagent intrinsic factor so the presence of intrinsic factor blocking antibodies in the sample interferes.[4] This interaction should be taken into consideration particularly when there is high suspicion for vitamin B12 deficiency.

Finally, as the liver is a primary source of vitamin B12 storage and transport, several acute and chronic liver diseases can cause elevated vitamin B12 levels. Acute hepatitis leads to elevated vitamin B12 through the inflammatory destruction of hepatocytes, releasing stored vitamin B12 into the blood. In cirrhosis, dying hepatocytes release stored vitamin B12 while absorption of serum vitamin B12 is diminished due to reduced hepatocyte numbers. Patient with hepatocellular carcinoma see an elevated level of haptocorrin-bound vitamin B12 due to decrease clearance of this complex by the liver, possibly from decrease receptors in malignant tissue and/or changes in vascularity of the tumor and adjacent liver tissue. For this patient, elevated serum vitamin B12 was the indicator of underlying IgG-4 related liver disease and ultimately the correct diagnosis for his new onset diabetes. This case illustrates the importance of elevated vitamin B12 levels as an indicator of liver disease and serves as a reminder that otherwise unexplained elevated vitamin B12 levels should be evaluated at minimum for underlying liver and hematologic diseases.

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