

A Veteran Presenting With Fatigue and Weakness

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Fed Pract. 2024;41(10).
Published online October 15.
doi:10.12788/fp.0516

Case Presentation: A 65-year-old male veteran presented to the Veterans Affairs Boston Healthcare System (VABHS) emergency department with progressive fatigue, dyspnea on exertion, lightheadedness, and falls over the last month. New bilateral lower extremity numbness up to his knees developed in the week prior to admission and prompted him to seek care. Additional history included 2 episodes of transient loss of consciousness resulting in falls and a week of diarrhea, which had resolved. His medical history was notable for hypothyroidism secondary to Hashimoto thyroiditis, seizure disorder, vitiligo, treated hepatitis C virus (HCV) infection, alcohol use disorder in remission, diabetes mellitus, posttraumatic stress disorder, and traumatic brain injury. His medications included levothyroxine and carbamazepine. He previously worked as a barber but recently had stopped due to cognitive impairment. On initial evaluation, the patient's vital signs included a temperature of 36.3 °C, heart rate of 77 beats per minute, blood pressure of 139/83 mm Hg, respiratory rate of 18 breaths per minute, and 99% oxygen saturation while breathing ambient air. Physical examination was notable for a frail-appearing man in no acute distress. His conjunctivae were pale, and cardiac auscultation revealed a normal heart rate and irregularly irregular heart rhythm. A neurologic examination revealed decreased vibratory sensation in both feet, delayed and minimal speech, and a blunted affect. His skin was warm and dry with patchy hypopigmentation across the face and forehead. Laboratory results are shown in the Table. Testing 2 years previously found the patient's hemoglobin to be 11.4 g/dL and serum creatinine to be 1.7 mg/dL. A peripheral blood smear showed anisocytosis, hypochromia, decreased platelets, ovalocytes, elliptocytes, and rare teardrop cells, with no schistocytes present. Chest radiography and computed tomography of the head were unremarkable. An abdominal ultrasound revealed a complex hypoechoic mass with peripheral rim vascularity in the right hepatic lobe measuring 3.9 cm × 3.6 cm × 3.9 cm.

► **Lindsey Ulin, MD, Chief Medical Resident, VABHS and Brigham and Women's Hospital (BWH):** To build the initial differential diagnosis, we are joined today by 3 internal medicine residents who were not involved in the care of this patient. Dr. Hickey, Dr. Ross and Dr. Manivannan, how did you approach this case?

► **Meghan Hickey, MD, Senior Internal Medicine Resident, VABHS and Boston Medical Center (BMC):** The constellation of fatigue, weakness, blunted affect, and delayed, minimal speech suggested central nervous system involvement, which I sought to unify with hemolytic anemia and his liver mass. The first diagnosis I considered was Wilson disease; however, this genetic disorder of copper metabolism often presents with liver failure or cirrhosis in young or middle-aged women, so this presentation

would be atypical. Next, given the hypopigmentation was reported only on sun-exposed areas of the patient's face, I considered possibilities other than vitiligo to avoid diagnostic anchoring. One such alternate diagnosis is porphyria cutanea tarda (PCT), which presents in middle-aged and older adults with a photosensitive dermatitis that can include acute sensory deficits. Manifestations of PCT can be triggered by alcohol consumption, though his alcohol use disorder was thought to be in remission, as well as HCV, for which he previously received treatment. However, anemia is uncommon in PCT, so the patient's low hemoglobin would not be explained by this diagnosis. Lastly, I considered thrombotic thrombocytopenic purpura (TTP) given his anemia, thrombocytopenia, and neurologic symptoms; however, the patient did not have fever or a clear inciting cause, his renal

dysfunction was relatively mild, and the peripheral blood smear revealed no schistocytes, which should be present in TTP.

► **Caroline Ross, MD, and Alan Manivannan, MD; Senior Internal Medicine Residents, VABHS and BMC:**

We noted several salient features in the history and physical examination. First, we sought to explain the bilateral lower extremity numbness and decreased vibratory sensation in the feet leading to falls. We also considered his anemia and thrombocytopenia with signs of hemolysis including elevated lactate dehydrogenase (LDH), low haptoglobin, and elevated total bilirubin; however, with normal coagulation parameters. These results initially raised our concern for a thrombotic microangiopathy (TMA) such as TTP. However, the peripheral smear lacked schistocytes, making this less likely. The combination of his neurologic symptoms and TMA-like laboratory findings but without schistocytes raised our concern for vitamin B₁₂ deficiency. Vitamin B₁₂ deficiency can cause a pseudo-TMA picture with laboratory finding similar to TTP; however, schistocytes are typically absent. We also considered the possibility of hepatocellular carcinoma (HCC) with bone marrow infiltration leading to anemia given the finding of a liver mass on his abdominal ultrasound and low reticulocyte index. However, this would not explain his hemolysis. We also considered chronic disseminated intravascular coagulation in the setting of a malignancy as a contributor, but again, the smear lacked schistocytes and his coagulation parameters were normal. Finally, we considered a primary bone marrow process such as myelodysplastic syndrome due to the bicytopenia with poor bone marrow response and smear with tear drop cells and elliptocytes. However, we felt this was less likely as this would not explain his hemolytic anemia.

► **Dr. Ulin:** To refine the differential diagnosis, we are joined by an expert clinician who was also not involved in the care of this patient to describe his approach to this case. Dr. Orlander, can you walk us through your clinical reasoning?

TABLE Laboratory Results

Test (units)	Results	Reference range
Hemoglobin, g/dL	5.2	14.0-18.0
Hematocrit, %	15.3	40-52
Corpuscular volume, mean, fL	95.6	82-98
White blood cell count, K/uL	4.3	4.0-11.0
Platelet count, K/uL	101	150-440
Reticulocyte count, %	0.8	0.6-2.0
Prothrombin time, sec	12.5	9.8-13.3
International normalized ratio	1.1	2.0-3.5
Partial thromboplastin time, sec	26.5	27.9-37.0
Serum creatinine, mg/dL	1.9	0.5-1.5
Total bilirubin, mg/dL	1.4	0.2-1.2
Serum ferritin, ng/mL	286	20-300
Lactate dehydrogenase, u/L	5,080	125-243
Haptoglobin, mg/dL	< 8	30-200
Thyrotropin, uIU/mL	52.7	0.35-5.00

► **Jay Orlander, MD, MPH: Professor of Medicine, Section of General Internal Medicine, Boston University Chobanian & Avedisian School of Medicine, Associate Chief, Medical Service, VABHS:**

I will first comment on the hepatic mass. The hypoechoic liver mass with peripheral vascularity suggests a growing tumor. The patient has a history of substance use disorder with alcohol and treated HCV. He remains at increased risk for HCC even after prior successful HCV treatment and has 2 of 4 known risk factors for developing HCC—diabetes mellitus and alcohol use—the other 2 being underlying metabolic dysfunction-associated steatotic liver disease (MASLD) and the presence of hepatic fibrosis, which we have not yet assessed. Worsening liver function can lead to cognitive issues and alcohol to peripheral neuropathy, but his story is not consistent with this. For his liver mass, I recommend a nonurgent magnetic resonance image for further evaluation.

Next, let's consider his markedly elevated

thyrotropin (TSH). Cognitive impairment along with lethargy, fatigue, and decreased exercise tolerance can be prominent features in severe hypothyroidism, but this diagnosis would not explain his hematologic findings.¹

I view the principal finding of his laboratory testing as being that his bone marrow is failing to maintain adequate blood elements. He has a markedly low hematocrit along with low platelets and low-normal white blood cell counts. There is an absence of schistocytes on the blood smear, and after correcting his reticulocyte count for his degree of anemia (observed reticulocyte percentage [0.8%] x observed hematocrit [15.3%] / expected hematocrit [40%]), results in a reticulocyte index of 0.12, which is low. This suggests his bone marrow is failing to manufacture red blood cells at an appropriate rate. His haptoglobin is unmeasurable, so there is some free heme circulating. Hence, I infer that hemolysis and ineffective erythropoiesis are both occurring within the bone marrow, which also explains the slight elevation in bilirubin.

Intramedullary hemolysis with a markedly elevated LDH can be seen in severe vitamin B₁₂ deficiency, which has many causes, but one cause in particular warrants consideration in this case: pernicious anemia. Pernicious anemia has an overall prevalence of about 0.1%, but is more common in older adults, and is estimated to be present in 2% to 3% of adults aged > 65 years.² Prevalence is also increased in patients with other autoimmune diseases such as vitiligo and hypothyroidism, which our patient has.³ The pathophysiology of pernicious anemia relates to either autoimmune gastric parietal cell destruction and/or the development of antibodies against intrinsic factor, which is required for absorption of vitamin B₁₂. Early disease may present with macrocytosis and a normal hemoglobin initially, but anemia develops over time if left untreated. When the primary cause of pernicious anemia is gastric parietal cell destruction, there is also an associated lack of stomach acid production (achlorhydria) with resulting poor micronutrient absorption; specifically, vitamin D, vitamin C, and iron. Hence, 30% of patients diagnosed with pernicious anemia have concurrent iron deficiency, which may counteract macrocytosis and result in a normal mean corpuscular volume.⁴ Some medica-

tions are also poorly absorbed in achlorhydric states, such as levothyroxine, and treatment doses need to be increased, which could explain his markedly elevated TSH despite presumed medication adherence.

Vitamin B₁₂ is essential for both the peripheral and central nervous systems. Long-standing severe B₁₂ deficiency can explain all of his neurological and neurocognitive changes. The most common neurologic findings in B₁₂ deficiency are symmetric paresthesias or numbness and gait problems. The sensory neuropathy affects the lower extremities more commonly than the upper. Untreated, patients can develop progressive weakness, ataxia, and orthostatic hypotension with syncope, as well as neuropsychiatric changes including depression or mood impairment, cognitive slowing, forgetfulness, and dementia.

Dr. Ulin: Dr. Orlander, which pieces of objective data are most important in forming your differential diagnosis, and what tests would you obtain next?

Dr. Orlander: The 3 most salient laboratory tests to me are a complete blood count, with all cell lines impacted but the hemoglobin and hematocrit most dramatically impacted, reticulocyte count of 0.8%, which is inappropriately low and hence suggests a hypoproliferative anemia, and the elevated LDH > 5000 IU/L.

Since my suspected diagnosis is pernicious anemia, I would obtain a blood smear looking for hypersegmented neutrophils, > 1 white blood cells with 5 lobes, or 1 with 6 lobes, which should clinch the diagnosis. Methylmalonic acid (MMA) levels are the most sensitive test for B₁₂ deficiency, so I would also obtain that. Finally, I would check a B₁₂ level, since in a patient with pernicious anemia, I would expect the level to be < 200 pg/mL.

>Dr. Ulin: Before we reveal the results of the patient's additional workup, how do you approach interpreting B₁₂ levels?

>Dr. Orlander: Measuring B₁₂ can sometimes be problematic: the normal range is considered 200 to 900 pg/mL, but pa-

tients with measured low-normal levels in the range of 200 to 400 pg/mL can actually be physiologically deficient. There are also several common causes of falsely low and falsely high B₁₂ levels in the absence of B₁₂ deficiency. Hence, for patients with mild symptoms that could be due to B₁₂ deficiency, many clinicians choose to just treat with B₁₂ supplementation, deeming it safer to treat than miss an early diagnosis. B₁₂ is involved in hydrogen transfer to convert MMA into succinyl-CoA and hence true vitamin B₁₂ deficiency causes an increase in MMA.

Decreased production of vitamin B₁₂ binding proteins, like haptocorrin, has been proposed as the mechanism for spurious low values.⁵ Certain conditions or medications can also cause spurious low serum vitamin B₁₂ levels and thus might cause the appearance of vitamin B₁₂ deficiency when the patient is not deficient. Examples include multiple myeloma, HIV infection, pregnancy, oral contraceptives, and phenytoin use. An example of spuriously low vitamin B₁₂ level in pregnancy was demonstrated in a series of 50 pregnant individuals with low vitamin B₁₂ levels (45-199 pg/mL), in whom metabolite testing for MMA and homocysteine showed no correlation with vitamin B₁₂ level.⁶

Further complicating things, some conditions can cause spuriously increased vitamin B₁₂ levels and thus might cause the appearance of normal vitamin B₁₂ levels when the patient is actually deficient.⁷ Examples include occult malignancy, myeloproliferative neoplasms, alcoholic liver disease, kidney disease, and nitrous oxide exposure (the latter of which is unique in that it can also cause true vitamin B₁₂ deficiency, as evidenced by clinical symptoms and high MMA levels).^{8,9}

Lastly, autoantibodies to intrinsic factor in individuals with pernicious anemia may compete with intrinsic factor in the chemiluminescence assay and result in spuriously normal vitamin B₁₂ levels in the presence of true deficiency.¹⁰⁻¹² If the vitamin B₁₂ level is very high (eg, 800 pg/mL), we do not worry about this effect in the absence of clinical features suggesting vitamin B₁₂ deficiency; however, if the vitamin B₁₂ level is borderline or low-normal and/or other clinical features suggest vitamin

Clinical Takeaways

- B₁₂ deficiency can present with typical symptoms of anemia such as fatigue and reduced exercise tolerance, and can also cause neurologic symptoms including paresthesias, weakness, cognitive impairment, and ataxia. Pernicious anemia is a common cause of B₁₂ deficiency, which may present with macrocytosis without anemia initially, but anemia develops over time if untreated. Many patients may present with concurrent iron deficiency, as achlorhydria in pernicious anemia results in poor micronutrient absorption.
- Severe B₁₂ deficiency can cause intramedullary hemolysis. Laboratory studies may reveal elevation in indirect and total bilirubin, low haptoglobin, and elevated lactate dehydrogenase. Hypersegmented neutrophils can be seen on blood smear. As the bone marrow fails to maintain adequate blood elements, a low reticulocyte index may occur.
- Interpretation of B₁₂ testing is difficult as results may be influenced by certain disease states, medications, and the presence of intrinsic factor antibodies. Patients with low-normal levels can also be deficient. If clinical suspicion is high, obtain a methylmalonic acid level, as this is the most sensitive test for B₁₂ deficiency.

B₁₂ deficiency, it is prudent to obtain other testing such as an MMA level.

► **Dr. Ulin:** We are also joined by Dr. Rahul Ganatra, who cared for the patient at the time the diagnosis was made. Dr. Ganatra, can you share the final diagnosis and provide an update on the patient?

► **Rahul Ganatra, MD, MPH, Director of Continuing Medical Education, VABHS:**

The patient's hemoglobin rose to 6.9 g/dL after transfusion of 2 units of packed red blood cells, and his dyspnea on exertion and fatigue improved. Iron studies, serum thiamine, serum folate, ADAMTS13 activity levels, and AM cortisol level were normal. Upon closer examination of the peripheral blood smear, rare hypersegmented neutrophils were noted. Serum B₁₂ level returned below assay (< 146 pg/mL), and serum MMA was 50,800 nmol/L, confirming the diagnosis of severe vitamin B₁₂ deficiency. Antibodies against intrinsic factor were detected, confirming the diagnosis of pernicious anemia. Treatment was initiated with intramuscular cyanocobalamin every other day and was transitioned to weekly dosing at the time of hospital discharge. After excluding

adrenal insufficiency, his levothyroxine dose was increased. Finally, a liver mass biopsy confirmed a concomitant diagnosis of HCC. The patient was discharged home. Five weeks after discharge, his serum B₁₂ level rose to > 1000 pg/mL, and 10 months after discharge, his TSH fell to 0.97 uIU/mL. Several months later, he underwent stereotactic body radiotherapy for the HCC. One year after his initial presentation, he has not resumed work as a barber.

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Ethics and consent

All patients or their surrogate decision makers understand and have signed appropriate patient release forms. This article has received an abbreviated peer review.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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