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# Case Reports

# Uncommon Presentation of Pernicious Anemia, Hypothyroidism, and Pericardial Effusion

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## ABSTRACT

Introduction: Pernicious anemia is not commonly investigated as an etiology for Vitamin B12 deficiency. However, it is associated with other autoimmune disorders and may be linked with H. pylori infections as well as an increased risk of gastric cancers.

Case Presentation: The patient was a 42 year old male patient who presented with hemoglobin of 4.5, MCV of 133.3, and pancytopenia. His symptoms at admission were dyspnea and peripheral neuropathy. His past medical history was significant for hypothyroidism and plaque psoriasis. The patient was found to have low serum vitamin B 12 with positive parietal cell antibodies. Echocardiogram revealed a stable pericardial effusion. He was administered one unit of packed red blood cells, parenteral cobalamin, and oral levothyroxine. He clinically improved with conservative management.

Conclusion: This case highlights the constellation of signs, symptoms, laboratory findings, and imaging that can be seen with pernicious anemia, and it also discusses management. It is important for the patient to undergo proper workup of the autoimmune conditions associated with pernicious anemia when appropriate.

## INTRODUCTION

Pernicious anemia (PA) is an autoimmune disorder in which antibodies against intrinsic factor and parietal cells leads to decreased absorption of Vitamin B12 and causes gastric mucosa atrophy. It is estimated that pernicious anemia is under-diagnosed, with prevalence ranging from 0.1% to 1.9%. It is most common in those of Scandinavian descent, with increased incidence in women and adults older than 60. Vitamin B12 is needed for myelin synthesis and erythropoiesis. Consequently, patients present with fatigue, dyspnea and pallor, all signs of anemia. Glossitis, although a classic sign, is not commonly seen. Patients can present with gastrointestinal symptoms and can also have neurological findings ranging from peripheral sensory deficits to motor deficits indicating subacute combined degeneration. Patients with pernicious anemia can have other autoimmune disorders, especially endocrine pathologies. In addition, these patients are at a 2-3 fold higher risk for developing carcinoid tumors and epithelial gastric cancers. In this case report, we describe a patient with pernicious anemia, hypothyroidism, and pericardial effusion.

## CASE REPORT

Our patient was a 42 year old Caucasian man who presented to the emergency room with dyspnea upon exertion. He reported chronic shortness of breath and chest tightness which had recently worsened. During review of systems, the patient also reported prolonged bleeding after cuts. He denied a history of ecchymoses, hemarthrosis, or mucosal bleeding. He also denied a family history of hematologic disorders. He reported a craving for ice and fruit. He denied hemoptysis and blood in stool, and he had never undergone endoscopy or colonoscopy in the past. The patient also reported chronic tingling in his upper and lower extremities. His past medical history was significant for hypothyroidism, asthma, and plaque psoriasis. The patient was uninsured,

and he had been noncompliant with all of his medications due to a lack of financial resources. The social history was positive for multiple stays in prison. He reported drinking two alcoholic beverages per week and smoking half a pack per day.

The physical exam was significant for pallor and a systolic heart murmur which was louder with the patient leaning forward. Due to significant dyspnea and an elevated D-dimer, the patient underwent a Chest CT Pulmonary Embolism protocol which revealed a moderate pericardial effusion measuring 2.1 cm in thickness. A bedside trans-thoracic echocardiogram was normal with an ejection fraction of 65% and no hemodynamic compromise. Cardiac enzymes were also within normal limits. Laboratory tests in the emergency room revealed a hemoglobin of 4.5 with MCV of 133.3. Platelet count was 67,000 and WBC count was 3.1. FOBT was negative. Due to concern for severe anemia with pancytopenia and a significant pericardial effusion, the patient was admitted for management and further workup. Further laboratory tests were obtained. The patient's LDH was >2500 and haptoglobin was <40. At this point, our differential diagnoses were myelodysplastic syndrome, autoimmune hemolytic anemia, and iron, folate, or Vitamin B12 deficiency.

A peripheral smear was obtained, and it revealed hypersegmented neutrophils, macrocytes, and basophilic stippling. While macrocytes can be present with hypothyroidism, and hypersegmented neutrophils can also occur with iron deficiency anemia, the constellation of these findings along with basophilic stippling raised concern for B12 or folate deficiency. Moreover, the lack of schistocytes on the smear and a negative Coombs test ruled down hemolytic anemia. Although the patient's ESR was elevated at 79, it could have secondary to plaque psoriasis, and ESR is unreliable as an inflammatory marker when hemoglobin is less than 9. His Vitamin B12 and folate levels returned, and the patient was found to be vitamin B12 deficient with high levels of homocysteine (204). Serum folate and RBC folate were both normal. Serum iron and ferritin were both elevated with normal TIBC. At first glance, this would seem to rule down iron deficiency anemia. However, B12 deficiency is actually associated with elevated iron levels and could be hiding an underlying iron deficiency. Thus it was decided to repeat iron studies at a later date. CMP was significant for slightly elevated total bilirubin (1.3) and aspartate aminotransferase (54), which also fit with vitamin B12 deficiency.

The patient had adequate bone marrow compensation with 4.34% reticulocytes. A myelodysplastic syndrome thus seemed unlikely. The patient was transfused one unit of PRBC the night of admission. The next morning, the patient reported improved energy and was able to ambulate with significantly decreased dyspnea. Due to the his history of hypothyroidism, TSH and T4 were obtained, and TSH returned at 12.86 with T4 at 0.75. He was subsequently administered subcutaneous vitamin B12 1000 mcg and oral levothyroxine. At this time, antithyroid antibodies were not obtained in order to contain costs as the patient lacked health insurance. Moreover, it would not have changed management, which would still only be administration of levothyroxine.

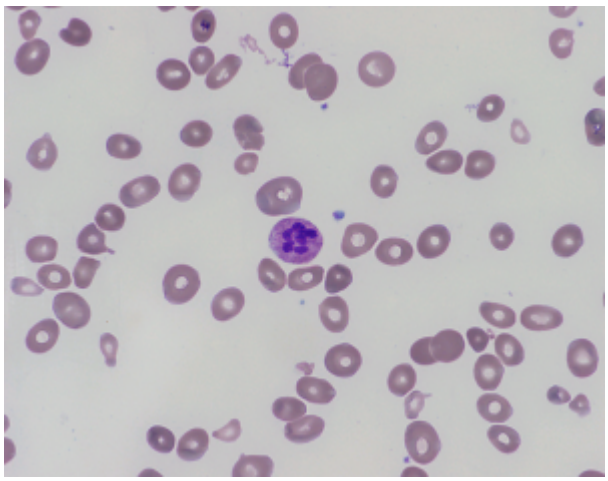
The various etiologies for B12 deficiencies were investigated. A nutritional deficiency seemed unlikely as the patient reported a well balanced diet which included meat. In addition, he was not a heavy drinker. Malabsorption was also on the differential, although the patient did not report a history of gastrointestinal symptoms. Since the patient had an existing autoimmune disorder (psoriasis), it seemed reasonable to obtain a celiac panel, which returned with positive deamidated gliadin peptide IgG antibody with normal levels of deamidated gliadin peptide IgA antibody, celiac total serum IgA, and tissue transglutam (TTG). Due to normal levels of IgA, celiac disease was unlikely to be the etiology for his B12 deficiency and resulting anemia. During the patient's hospital stay, the patient also underwent workup for pernicious anemia. He was also found to have positive parietal cell antibodies (93.8) with negative intrinsic factor blocking antibodies, and this was sufficient to diagnose him with pernicious anemia.

Cardiology was consulted for the pericardial effusion, and the patient did not require any acute intervention due to the stable nature of the effusion. The patient was discharged with 1000 mcg B12 subcutaneously daily for 14 days, followed by weekly administration for one month, and then lifelong monthly injections. The patient was instructed to follow up with a primary care provider for monitoring of his anemia as well as testing for H. pylori. He was also asked to see gastroenterology for endoscopy with biopsy. At his most recent clinic visit one month later, his hemoglobin was 10.5 with an MCV of 96.5, with normal WBC and platelet counts.

## DISCUSSION

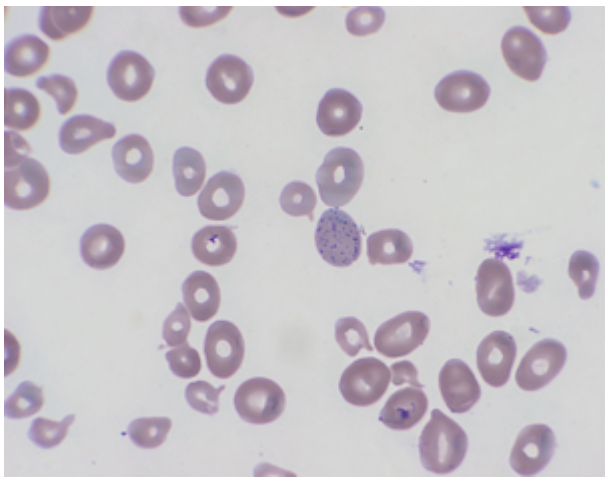
This patient with significant macrocytic anemia presented very typically with dyspnea, marked pallor, and peripheral neuropathy. His hemoglobin of 4.5 initially caused alarm, but he was clinically stable despite such severe anemia. Patients with vitamin B12 deficiency are able to adapt to low hemoglobin due to the chronicity of the condition, and elderly patients with B12 deficiency have been known to tolerate hemoglobin as low as 5 (Carmel, 2008). The patient only received one packed red blood cell transfusion in order to prevent a fluid overload state. In this case, blood transfusion could have also worsened the patient's pericardial effusion.

This patient's peripheral smear had classic, but nonspecific findings for vitamin B12 deficiency, with hypersegmented neutrophils, basophilic stippling, and macrocytes. Macrocytic anemia is the first and most common finding with B12 deficiency (Carmel, 2008). When it is secondary to alcoholism, MCV is lower than 115, while megaloblastic anemia can lead to MCV as high as 150. Pancytopenia can also occur, as was seen with this patient (Bizzaro & Antico, 2014). In addition to this classic findings, the patient also demonstrated increased lactate dehydrogenase and iron, which indicate intramedullary erythroblastolysis, In addition, he had mildly increased total bilirubin and aspartate aminotransferase, as would be expected with B12 deficiency (Hvas & Nexo, 2006).



Peripheral smear showing a hypersegmented neutrophil along with dacrocytes and macro-ovalocytes

Figure 1: Peripheral smear showing a hypersegmented neutrophil along with dacrocytes and macro-ovalocytes



Peripheral smear showing basophilic stippling

Figure 2: Peripheral smear showing basophilic stippling

Often, patients are empirically treated with B12, folate, and iron without further workup. However, in a patient with no obvious signs of nutritional deficiency, pernicious anemia could be the cause. It is generally diagnosed with the findings of megaloblastic anemia, decreased serum vitamin B12, low hemoglobin (<13 for men, <12 for women), autoantibodies to parietal cells and/or intrinsic factor (IF), and atrophic gastric mucosa (Bizzaro & Antico, 2014). The Schilling test is no longer commonly performed for diagnosis. The patient's IF antibodies were negative. While IF antibodies have high specificity (>95%), they have low sensitivity (50-70%), which could explain the patient's negative results. The patient did have positive parietal cell antibodies, which have higher sensitivity (90-92%) but are not as specific (Hvas & Nexo, 2006). The patient was thus appropriately diagnosed with pernicious anemia, with the treatment being regular parenteral cobalamin.

Pernicious anemia is associated with a significantly higher risk of carcinoid tumors and intestinal-type gastric cancer, particularly in the first year following diagnosis. Thus, it is an essential differential to investigate. When found, the American Society for Gastrointestinal Endoscopy recommends a onetime endoscopy after diagnosis to identify precancerous lesions (Hirota et al., 2006). Unfortunately, few patients with pernicious anemia undergo endoscopies for biopsies of the gastric mucosa (Bizzaro & Antico, 2014). Gastroenterology outpatient service was asked to see this patient in their clinic at a future appointment. Atrophic gastritis and pernicious anemia have also been linked to H. pylori, with the prevailing theory being that molecular mimicry between H. pylori organisms and epithelial antigens leads to the formation of autoantibodies and an autoimmune reaction (Neumann, Coss, Rugge, & Genta, 2013). Due to this association, it is hoped that the patient will undergo workup for H. pylori in outpatient clinic, as its diagnosis and subsequent treatment could prevent morbidity and mortality.

Pernicious anemia is also associated with other autoimmune disorders. This patient already had plaque psoriasis, an autoimmune condition, and his hypothyroidism could have been secondary to Hashimoto's thyroiditis, although it was not confirmed. 30% of patients with hypothyroidism can have serum anti-parietal cell antibodies (Klein & Levey, 1984). In turn, anti-thyroid antibodies may be present in 50% of patients with PA (Bizzaro & Antico, 2014). If the patient had been found to have Hashimoto's, he could have been considered for a diagnosis of polyglandular autoimmune syndrome, which involves constellations of co-occurring endocrine disorders. Polyglandular autoimmune syndrome Type IIIB specifically comprises of hypothyroidism and pernicious anemia. Patients with pernicious anemia also have a higher risk of Diabetes Mellitus, but the patient's HgA1c was 5.7% with normal levels of random serum glucose.

In addition to anemia, the patient also presented with a pericardial effusion, for which the cause is not clear. Pericardial effusion can present in 30-80% of patients with myxedema (Kabadi & Kumar, 1990). However, the patient had a TSH of only 12.86, which indicates mild hypothyroidism and an unlikely cause of the effusion. Autoimmune disorders in general can lead to pericardial effusions, and the patient had a diagnosis of psoriasis. There have also been a few reports of patients with severe megaloblastic anemia who presented with pericardial effusions (Lawson & Parker, 1976). Fortunately, the patient's pericardial effusion was stable and did not require any intervention.

This case demonstrates a clinical picture of a patient with severe macrocytic anemia and explores the differentials for Vitamin B12 deficiency. It illustrates the various autoimmune conditions that can be present with pernicious anemia. This case also highlights the importance of investigating for H. pylori and screening with endoscopy for malignancy in a patient diagnosed with pernicious anemia. Due to the patient's lack of financial resources and health insurance, various laboratory investigations could not be undertaken. This patient is being followed in outpatient clinic by a primary care provider, hematology-oncology and gastroenterology. It is expected that the patient's MCV will be normal in about 8 weeks. The patient's peripheral neuropathy will improve by 3 months (Carmel, 2008). Iron studies will be repeated in clinic as B12 deficiency could be masking underlying iron deficiency, which could also develop secondary to atrophic gastritis (Carmel, 2008). With close follow-up, the patient's vitamin B12 deficiency, hypothyroidism, and pericardial effusion can be properly monitored and managed.

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