Pernicious Anemia Presenting With Pseudo Thrombotic Microangiopathy and Falsely Elevated B 12 Levels

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Abstract

Pseudo thrombotic microangiopathy is a distinct clinical entity that is seen in patients with B12 deficiency. We describe a patient who presented with microangiopathic hemolytic anemia, thrombocytopenia, altered mentation and renal insufficiency. Thrombotic thrombocytopenic purpura was a major concern; however the peripheral blood smear showed hypersegmented neutrophils and the altered mental status as well as renal dysfunction improved with red cell transfusions. It was concluded that her clinical picture was more consistent with ineffective erythropoiesis, which can mimic thrombotic thrombocytopenic purpura (TTP). She was ultimately diagnosed with pernicious anemia based on positive intrinsic factor antibody, elevated methylmalonic acid, and homocysteine levels. Her B12 levels were falsely elevated which confounded the diagnosis. Distinguishing between these two conditions is imperative to avoid unwarranted plasmapheresis.

Keywords: B12 deficiency; Pernicious anemia; Pseudo thrombotic microangiopathy; False elevated B12 levels; TTP

Introduction

Pernicious anemia (PA) is a leading cause of vitamin B12 deficiency worldwide, being more common in patients of African and European descent [1]. Cyanocobalamin deficiency rarely leads to severe hematologic manifestations including pancytopenia, severe anemia (hemoglobin < 6 g/dL) and hemolysis [2]. It is also associated with ineffective erythropoiesis which can lead to pseudo-thrombotic microangiopathy (Pseudo TMA), a distinct clinical entity that can mimic thrombotic thrombocytopenic purpura (TTP) [3]. Here, we describe a patient of PA with elevated B 12 levels, who presented with the features of TTP including altered mental status (AMS), hemolytic anemia,

thrombocytopenia and renal dysfunction. Plasma exchange was held, and she was treated only with intramuscular B12 injections and supportive care.

Case Report

A 58-year-old African American woman with history of stroke, deep vein thrombosis, abnormal uterine bleeding (AUB) and B12 deficiency presented to our institution with 2 weeks of progressive fatigue, dyspnea on exertion, non-productive cough, dizziness and palpitations. Her family members also noted AMS 1 day prior to presentation. She reported noncompliance with medications and denied recent AUB, fevers, diarrhea or bleeding from any site. Physical exam was significant for tachypnea, conjunctival pallor and dry oral mucosa. Patient was sleepy but arousable and had residual right sided weakness from previous stroke. Rectal exam was notable for hemorrhoids with a negative stool guaiac test.

Initial laboratory investigations revealed hemoglobin of 1.8 (11.7 - 14.9 g/dL), platelets 63 (161 - 369 × 10^3/μL), white cell count of 7.2 (4.4 - 10.6 × 10^3/μL), reticulocyte production index (RPI) of 0.22%, mean corpuscular volume (MCV) 100.9 (81.8 - 96.9 fL), total bilirubin of 3.4 (0.2 - 1.2 mg/dL), direct bilirubin of 1.2 (0.0 - 0.2 mg/dL), lactate dehydrogenase (LDH) of 3,372 (85 - 210 U/L), blood urea nitrogen (BUN) of 36 (8 - 20 mg/dL), and creatinine of 1.0 (0.6 - 1.4 mg/dL). Baseline creatinine was 0.5 mg/dL. A venous blood gas showed pH of 7.1 and significantly elevated lactate at 21 (0.5 - 1.60 mmol/L). Whole-body computed tomography (CT) scan did not reveal any acute cardiopulmonary process, internal bleeding, or lymphadenopathy. Peripheral blood smear (PBS) demonstrated anisocytosis, poikilocytosis, hypochromasia, target cells, schistocytes and hypersegmented neutrophils with as many as six to eight segments.

TTP was a major concern initially, however plasma exchange was held in the light of very low hemoglobin, prior history of B12 deficiency and presence of hypersegmented neutrophils on PBS. Packed red cells (PRBCs) transfusion led to an appropriate rise in hemoglobin, and improvement in her mental status. Additional tests including direct Coombs test (DCT), ADAMTS 13 level, B12, folate, methylmalonic acid (MMA), homocysteine, and anti-intrinsic factor antibody (IFA) were sent, and intramuscular cyanocobalamin daily was initiated. However, B12 levels were found to be elevated at 985.2 pg/mL (180 - 914 pg/mL) and folate levels were within normal limits.

The unexpectedly elevated B12 level was against our initial diagnosis. A bone marrow biopsy was considered but deferred until MMA and homocysteine levels were back as her clinical status and laboratory parameters including blood counts and metabolic profile continued to improve with PRBC transfusion. It took about 2 days before the patient began to show evidence of reticulocytosis. Results eventually revealed that both MMA and homocysteine were elevated at 112,000 (87 - 318 nmol/L) and 54.5 (< 10.4 μmol/L) respectively. IFA was positive. DCT was found to be negative. The ADAMTS 13 level was 66% (reference value: 68-163%).

Subsequently, the patient was diagnosed with severe B12 deficiency, inducing ineffective erythropoiesis leading to an elevated bilirubin, LDH, thrombocytopenia, anemia and schistocytes. Once reticulocytosis and continued clinical improvement were observed, the patient was discharged and was advised to follow in hematology clinic and continue lifelong B12 injections.

Discussion

TTP is characterized by the classical pentad of microangiopathic hemolytic anemia, thrombocytopenia, fever, AMS, and renal failure [4]. Acquired TTP was a major consideration in our patient in light of AMS, anemia, thrombocytopenia, and renal dysfunction. She also had features suggestive of hemolysis including increased indirect bilirubin, LDH, and schistocytes on PBS. However, the patient had a prior history of B12 deficiency, known to cause ineffective erythropoiesis, which can mimic TTP.

Vitamin B12 plays a central role in cell maturation. Decreased levels cause intramedullary destruction of blood cells (ineffective erythropoiesis) which in turn, leads to hemolysis, formation of schistocytes and pancytopenia [5]. In fact, ineffective erythropoiesis presenting as a pseudo TMA has been described. Noel et al noted unique distinctions including a higher LDH level and a lower reticulocyte count in patients with pseudo TMA as compared to those with TTP [3]. Our patient had a similar profile with high LDH and low RPI. Additionally, her PBS showed hypersegmented neutrophils with six to eight segments, which has a sensitivity and specificity of 90% and 97% respectively for diagnosis of B12 deficiency [6].

To alleviate the metabolic and clinical derangements secondary to hypoxia from the extremely low hemoglobin, PRBCs were transfused. B12 levels were drawn after one unit of PRBC transfusion and were found to be elevated. This was especially puzzling as previous studies performed to detect alterations in laboratory parameters indicative of anemia, before and after blood transfusion have demonstrated that nearly all nutritional deficiency anemias can be diagnosed post transfusion except for folate deficiency, and that cobalamin levels are unaffected by PRBC transfusion [5, 7]. However, no patients with such a profound anemia (hemoglobin: 1.8 g/dL) were included in these studies. Thus, the data from the PBS and the resolution of the renal failure and AMS with transfusions along with the poor reticulocyte index helped define the diagnosis.

PA is a major cause of B12 deficiency, especially in people over 60 years of age [8]. It occurs either due to loss of gastric parietal cells, as seen in atrophic body gastritis leading to impaired intrinsic factor (IF) secretion or secondary to the presence of autoantibodies against IF, which prevents B12-IF complex formation and hence disrupts its absorption [9]. B12 assays lack sensitivity and can be falsely normal in certain conditions including liver disease, myeloproliferative disorders, and end-stage renal disease [10]. In addition, the presence of inhibitor antibodies as seen in PA, often mask B12 deficiency by binding to reagent IF used in these tests [11]. Consequently, diagnosis can be easily missed in patients with apparently normal levels.

To overcome this issue, routine measurement of MMA and homocysteine has been suggested in individuals with high suspicion of cobalamin deficiency, despite the initial higher cost. While B12 levels tend to fall late in the course of disease and measure both chemically active and inert forms, MMA represents only active cobalamin levels and is better for assessment of depleted functional B12 stores [12]. These two tests played a key role in unequivocally diagnosing cyanocobalamin deficiency in this case.

Pseudo TMA secondary to ineffective erythropoiesis is seen more often with PA as compared to other causes of B12 deficiency like malabsorption or dietary insufficiency [3]. The identical presentations of pseudo TMA and TTP coupled with falsely normal B12 levels commonly seen in PA pose a serious diagnostic challenge and treatment dilemma. A recent systematic review reported that 14/41 patients with B12 deficiency received plasmapheresis even though it was not clinically indicated, with two patients developing plasma reactions and catheter-related complications [13]. In a study by the Canadian Apheresis Study Group to assess the adverse events during therapeutic plasma exchanges (TPE), it was seen that they occurred in 612 (12%) of the 5,235 procedures. 28 severe complications including one cardiac and two respiratory arrests also occurred [14]. Thus, distinguishing between these two clinical entities is of utmost importance to prevent improper resource utilization, inappropriate treatment, and untoward complications.

This case illustrates that B12 deficiency should be a consideration in patients with suspected TTP. Additionally, in instances of high clinical suspicion, MMA and homocysteine levels can be used to unequivocally diagnose B12 deficiency despite normal cyanocobalamin levels.

Conflict of Interest

The authors have no conflict of interest in relation to this work.

Informed Consent

Informed consent was obtained.

Author Contribution

VK , EQ, JS and IV contributed to conceptualization. VK and EQ wrote the original draft. IV, JS and PR helped with editing. VK and PR contributed to final revision.

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