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Life-threatening Pseudo-thrombotic Microangiopathy Caused by Severe Vitamin B12 Deficiency

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Abstract Vitamin B12 deficiency is a common cause of macrocytic anemia. Life-threatening hematologic complications including immune and non-immune hemolytic anemia are present in about 10% of the cases. Pseudo-thrombotic microangiopathy is an extremely rare presentation found in around 2.5% of patients with vitamin B12 deficiency. We present a case of a 70-year-old male patient who presented with progressive fatigue and syncope. He was found to severe macrocytic anemia with hemoglobin of 4.1 g/dL. Further workup showed very low serum vitamin B12 level at 22 pg/mL (normal 180-914), methylmalonic acid of 93.23 umol/L (normal 0-0.4) and homocysteine of 93 umol/L (normal 4-12). Anti-parietal cell and intrinsic factor blocking antibodies were positive. He was noted as well to have thrombocytopenia, low haptoglobin, increased lactate dehydrogenase and increased serum creatinine. Peripheral blood smear showed schistocytes, hyper-segmented neutrophils, and marked dimorphic anemia. His presentation was concerning for thrombotic thrombocytopenic purpura; however, PLASMIC score was intermediate. He was monitored in the intensive care unit. He received supportive treatment with intravenous hydration and packed red blood cells transfusion. He was started on daily intramuscular cyanocobalamin supplements. Significant improvement in his symptoms with near normalization of complete blood count after one month of treatment was noted. His condition improved without the need for plasmapheresis.

Keywords: *hemolysis, Vitamin B12, anemia, autoimmunity*

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1. Introduction

Vitamin B12 deficiency is a common cause of macrocytic anemia [1]. Up to 10% of patients can present with life-threatening hematologic complications, including pancytopenia, hemolytic anemia and pseudo-thrombotic microangiopathy (pseudo-TMA) [2]. Pseudo-TMA is exceedingly rare, found in around 2.5% of patients with vitamin B12 deficiency [2]. The clinical features of thrombocytopenia and microangiopathic hemolytic anemia are shared with other primary TMA syndromes, including thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), drug-induced TMA, and complement-mediated TMA. Pseudo-TMA is a life-threatening condition. It lacks the response to conventional therapy like plasmapheresis in TTP. Therefore, there is a need for prompt recognition and evaluation of pseudo-TMA. We present a case of pseudo-TMA in a patient with severe vitamin B12 deficiency secondary to pernicious anemia.

2. Case Report

A 70-year-old male with a past medical history of insulin-dependent type 2 diabetes mellitus, essential hypertension and WHO grade 3 obesity presented with progressive fatigue for the last three months. Two days prior to presentation, he complained of lightheadedness and two episodes of syncope and fall when he used the toilet. He also complained of exertional dyspnea, reduced appetite and decreased memory. Symptoms were severe enough to make him bedbound. He denied chest pain, palpitations or easy bruising or bleeding, including hematemesis, melena or hematochezia. He reported taking non-steroidal anti-inflammatory drugs and aspirin for pain related to arthritis, but otherwise was not taking anticoagulation or herbal supplements. Physical examination was unremarkable except for tachycardia and conjunctival pallor. Lab workup showed a hemoglobin of 4.1 g/dL, mean corpuscular volume (MCV) of 124.2 fL, platelet count 51×10^3/uL, and white blood cell count 5.8×10^3/uL.

Coagulation profile showed International Normalized Ratio 1.23 (normal 0.91-1.16) and partial prothrombin time 28.2 seconds (normal 25-35). Basic metabolic workup showed Blood Urea Nitrogen 68 mg/dL (normal 7-25) and serum creatinine 1.56 mg/dL (normal 0.70-1.30). Reticulocyte count was 2.43% (normal 0.5-1.8), with an absolute reticulocyte count of 0.7 cells/mm^3 and an absolute reticulocyte index (ARI) of 0.26 (Table 1).

Table 1. Patients' complete blood count on initial presentation, discharge and one month after treatment

Parameter (normal reference)	On admission	On discharge	One month after discharge
WBC (4-10.6×10^3/uL)	5.80	4.39	7.92
RBC (4.2-5.7×10^6/uL)	0.91	2.51	3.46
Hemoglobin (13.0-17.0×g/dL)	4.1	8.6	11.1
Hematocrit (39-50%)	11.3	26.6	33.8
Platelets (13.0-17.0×10^3/uL)	51	133	195
MCV (82.0-98.0 fL)	124.2	106	97.7
MCHC (32-35 g/dL)	36.3	32.3	32.8
ARC (2.5-10 /mm3)	0.7	6.4	3.6
ARI (0.5%-2.5%)	0.26	4.27	2.41

Abbreviations: WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCHC, Mean corpuscular hemoglobin concentration; ARC, absolute reticulocyte count; ARI, absolute reticulocyte index.

Further workup revealed vitamin B12 level of 22 pg/mL (normal 180-914), methylmalonic acid of 93.23 umol/L (normal 0-0.4) and homocysteine of 93 umol/L (normal 4-12). Further anemia workup showed serum folate of 16.50 ng/mL (normal 6.6-1,000), serum iron of 265 mcg/dL (normal 50-212), ferritin of 802 ng/mL (normal 24-336), and TIBC <320 mcg/dL (normal 250-450). Hemolytic anemia workup showed haptoglobin <6 mg/dL (normal 26-164), lactate dehydrogenase (LDH) 2,437 units/L (normal 140-271) and negative direct antiglobulin test. Peripheral blood smear was obtained and revealed few schistocytes and nucleated red blood cells, frequent hyper-segmented neutrophils, thrombocytopenia, and marked anemia with dimorphic red blood cell morphology. Serology testing was positive for anti-parietal cell antibody and intrinsic factor blocking antibody. Testing for COVID-19 in the setting of coronavirus pandemic via nasopharyngeal swab was negative.

Due to the evidence of hemolysis in addition to an elevated serum creatinine, there was initial concern for TMA syndromes like TTP. PLASMIC-TTP score was 5 with intermediate risk of TTP. Although, ADAMTS13 was sent, he did not undergo plasmapheresis. Eventually, his ADAMTS13 came back normal.

The patient was monitored in the intensive care unit due to severe anemia. He was managed with intravenous hydration and transfused a total of six units of packed red blood cells (RBCs). Given the patient's laboratory and clinical features, a diagnosis of Coombs-negative hemolytic anemia with thrombocytopenia secondary to severe vitamin B12 deficiency was made. The patient was then started on intramuscular cyanocobalamin 1000 mcg daily during his hospital stay. The vitamin B12 deficiency was deemed to be secondary to underlying pernicious anemia. Although, his creatinine was elevated at admission, it quickly improved with hydration and packed RBCs transfusion.

Prior to discharge, his symptoms improved in addition to hemoglobin and platelet count, 8.4 g/dL and 133,000/uL respectively. Serum homocysteine levels also normalized. One week later, symptoms of fatigue, appetite loss and presyncope/lightheadedness resolved. His hematologic parameters continued to improve, along with resolution of hemolysis indices. He continued to receive monthly intramuscular cyanocobalamin injections at the Hematology clinic. A month after his discharge, the patient was noted to have near-normalization of his complete blood count, along with resolution of previously experienced symptoms (Table 1).

3. Discussion

TMA syndromes are characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ injury due to vascular micro-thrombosis [3]. The classic presentation of vitamin B12 deficiency is megaloblastic anemia with or without neurologic symptoms [4]. Immune or non-immune mediated hemolysis has been reported in some cases. The hemolysis can mimic primary TMA and is sometimes called "pseudo-TMA". Pseudo-TMA is a rare manifestation and has been reported in only 2.5% of vitamin B12 deficiency [2]. It is usually not responsive to conventional plasmapheresis and it can be managed simply by vitamin B12 supplementation [5].

The exact mechanism of hemolysis in vitamin B12 deficiency is not completely understood [6]. Vitamin B12 is crucial for deoxyribonucleic acid synthesis and hematopoietic cell division [7]. It regulates two major enzymatic reactions; the first is methylmalonic acid conversion to succinyl-coA and the second is homocysteine conversion to methionine [8]. Without adequate vitamin B12 stores, hematopoietic precursors are unable to mature and cellular arrest occurs leading to intramedullary cell death and eventually, hemolysis of immature red blood cells [9]. In vitro studies suggest a vital role for the elevated homocysteine level seen in megaloblastic anemia in triggering hemolysis [10]. In the literature, two young siblings presented with renal thrombotic microangiopathy secondary to hereditary disorder of cobalamin mechanism. After treatment with hydroxy-cobalamin and folic acid, homocysteine level was reduced significantly and hemolysis completely resolved. This suggests a possible association between hyper-homocysteinemia and hemolysis [11].

In our case, we present a patient with severe vitamin B12 deficiency due to autoimmune pernicious anemia

who presented with hypo-proliferative macrocytic anemia and thrombocytopenia. On initial presentation, he was noted to have mild acute kidney injury. The clinical picture was concerning for possible TTP. PLASMIC-TTP score for our patient was intermediate, 5 points. The PLASMIC-TTP score is used to quantify the likelihood of TTP [12]. It is recommended with an intermediate score to keep close observation and to consider plasmapheresis if no other cause is identified [13]. Given our patient's hypo-proliferative macrocytic anemia, severely low serum vitamin B12 and serum creatinine improvement with fluids and transfusion, the clinical presentation was solely due to vitamin B12 deficiency. Therefore, treatment with intramuscular cyanocobalamin 1000 mcg daily was initiated. Patient's condition significantly improved in the aftermath of this intervention.

It is very crucial to differentiate between TMA and pseudo-TMA syndrome to avoid unnecessary plasmapheresis, which has a mortality rate of 2.3% and a major complications rate of 24% [14]. The differentiation can be challenging due to overlapping clinical characteristics, but there are some helpful ways described in the literature. The most helpful parameter in the differentiation may be the reticulocyte count [15]. Patients with pseudo-TMA had an average reticulocyte count of 3% compared to 18 % in TTP patients [9]. The use of ARI is more accurate; as it considers hematocrit and reticulocyte life span [16]. If ARI is less than 2, it is considered inappropriately low and indicates a hypo-proliferative anemia. Moreover, the MCV can be helpful distinguishing between TTP and pseudo-TMA. Both vitamin B12 deficient and TTP patients can present with an elevated MCV. In the setting of hemolytic anemia, elevated MCV can be due to the high reticulocyte count. However, macrocytosis with MCV greater than 115 fL is almost always associated with megaloblastic anemia like vitamin B12 deficiency. In our case, the elevated MCV and low absolute reticulocyte index is more consistent with megaloblastic anemia due to vitamin B12 deficiency rather than TTP. However, 3 cases of pseudo-TMA due to vitamin B12 deficiency have been reported in the literature with normal MCV [5,17,18]. In addition, patients with TTP are likely to have LDH levels less than 2500 IU/L, while higher levels do favor vitamin B12 deficiency [15,18].

4. Conclusion

Severe vitamin B12 deficiency can present with clinical picture mimicking TMA syndromes, sometimes called "pseudo-TMA". Pseudo-TMA is characterized with non-immune hemolytic anemia, thrombocytopenia and schistocytes with inappropriately low reticulocyte count. Pseudo-TMA can be treated by vitamin B12 supplementation, thereby avoiding unnecessary plasmapheresis. We recommend screening for vitamin B12 deficiency in patients with hypo-proliferative macrocytic anemia, thrombocytopenia and schistocytes especially if there is no evidence of end organ damage.

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