Vitamin B12 Malabsorption and Pseudo-Thrombotic Microangiopathy in an Adolescent.

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Abstract

Thrombotic microangiopathies (TMAs) are a group of rare disorders that can be considered life threatening. The hallmark of this disease is a microangiopathic hemolytic anemia with an associated thrombocytopenia which could be congenital or acquired. Acquired vitamin B12 deficiency is overlooked in developed countries but can mimic a TMA. We report the case of 17-year-old male with malabsorption of vitamin B12 with development of pseudo-TMA. When faced with a clinical presentation of a TMA in a child or an adolescent patient, physicians must be aware of the possibility of vitamin B12 deficiency especially in patients at risk for malabsorption.

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Introduction

Thrombotic microangiopathies (TMAs) are a group of rare disorders that are characterized by microangiopathic hemolytic anemia and thrombocytopenia with thrombosis of the microvasculature. This is often associated with organ dysfunction and encompass congenital and acquired etiologies[1]. Distinguishing between these disorders is important, as many TMAs are life-threatening.

Acquired B12 deficiency is overlooked because of its rarity in developed countries[2]. Hematologic manifestations of B12 deficiency can include pancytopenia because of ineffective hematopoiesis. Defective red blood cells (RBCs) undergo phagocytosis in the marrow and as a result mimic an intravascular hemolytic process.

We describe the case of a 17- year-old male who had a history of intestinal resection and celiac disease which lead to a pseudo – TMA through malabsorption of vitamin B12.

Case Description

A 17-year-old male with history of intestinal resection secondary to gastroschisis at birth was referred to the emergency room for shortness of breath, fatigue, and lightheadedness for a week. His history was significant for celiac disease, iron and B12 deficiency with symptomatic anemia in the past, requiring transfusions. It

had been at least a year since he had taken his last supplements and he had not adhered to a gluten-free diet. He denied constitutional symptoms, fevers, bleeding, or recurrent illnesses. His physical examination was significant for weight below the third percentile, pallor, mildly icteric sclerae and hepatosplenomegaly. He was alert and oriented with no noticeable neurological deficits.

His complete blood count (CBC) was significant for pancytopenia with a WBC: 2.42 x 10ˆ3/uL, Hb: 5.9 g/dL, MCV: 95.4 fL, Plt: 111 x 10ˆ3/uL and a reticulocytopenia of 0.6%. Review of his peripheral smear was significant for anisocytosis, microcytosis, poikilocytosis and schistocytes. Routine chemistries were suggestive of hemolysis with an elevated LDH of >50 000 U/L, an unconjugated hyperbilirubinemia of 3.7 mg/dL and an undetectable haptoglobin. His synthetic liver function was unremarkable with normal coagulation studies despite a notable transaminitis. A liver ultrasound showed diffuse echogenicity with likely fatty infiltration but no evidence of portal hypertension. He had a negative direct coombs, iron studies were unremarkable and a B12 <109 pg/mL. His renal function was also unremarkable. He was transfused two units of packed red blood cells, which allowed for stabilization of his hemoglobin and he was started on oral iron and B12 supplementation.

The differential included a pancytopenia secondary to B12 deficiency with a superimposed hemolytic process as well as concern for a malignant bone marrow infiltrative process given his pancytopenia and hepatomegaly. Paroxysmal nocturnal hemogobinuria testing was negative. A bone marrow biopsy and aspirate displayed no changes consistent with myelodysplasia or malignancy. There was evidence of erythroid hyperplasia and megaloblastic maturation along with hypersegmented neutrophils consistent with his B12 deficiency as shown in Fig. 1. His liver biopsy showed non-alcoholic steatohepatitis attributed to his uncontrolled celiac disease and the decision was made to convert his oral B12 to an intramuscular formulation.

Repeat B12 and LDH were 525 pg/mL and 503 U/L respectively showing resolution of his symptoms. Despite not being included in the initial differential, a hemolytic anemia in the presence of a progressive thrombocytopenia warrants the consideration of a TMA. However, given the resolution of his symptoms with B12 supplementation the diagnosis of pseudo-TMA secondary to B12 deficiency was made.

Discussion

B12 deficiency is the leading cause of megaloblastic anemia and in developed countries is often overlooked. It is more common in the elderly but the estimated prevalence is around 6% in people younger than 60 years in the United Kingdom and United States [2]. Causes of severe of B12 deficiency generally involve disruption of some aspect of the physiologic pathway for B12 absorption comprising intrinsic factor and the cubam receptor in the terminal ileum [3]. In the reported case, there are several factors that could have contributed to B12 deficiency, his history of intestinal resection and his uncontrolled celiac disease. Despite not being frequently reported, B12 deficiency in patients with celiac disease has a prevalence of between 8% and 41% [4, 5].

Hematologic manifestations consist of all blood elements being affected by this ineffective megaloblastic hematopoiesis. Initially, the cell content and size of RBC usually precede the onset of anemia. Nuclear hypersegmentation of neutrophils is another common early manifestation. Neutropenia and thrombocytopenia can infrequently follow as late features with a resulting pancytopenia that can ultimately become severe enough to mimic a severe aplastic anemia.

Hematopoietic precursor cells produced in the bone marrow are defective in B12 deficiency. As a result, they undergo cell death in the marrow and are phagocytosed before they can exit into the blood as reticulocytes. This intramedullary hemolysis manifests itself with increased markers of cell turnover such as LDH and markers of increased hemoglobin breakdown such as indirect hyperbilirubinemia and decreased or absent haptoglobin. As a means of compensating, erythropoietin levels rise and the bone marrow becomes more hypercellular (as shown in Fig. 1), however the reticulocyte count fails to rise [6].

In our case, his pancytopenia and reticulocytopenia were evident and consistent with a megaloblastic picture. However, his LDH seemed to be elevated out of proportion to the degree of hemolysis he experienced. When

compared to patients with thrombotic thrombocytopenic purpura (TTP), Noël et al showed that patients who had pseudo-TMA had significantly higher LDH levels, platelet counts and lower reticulocyte counts in the adult population [7]. Hyperhomocysteinemia has also been implicated (not checked in our patient) in increasing the risk of hemolysis in vitamin B12 in vitro in addition to causing endothelial damage leading to intravascular hemolysis and RBC fragmentation [8]. This combination of intramedullary and intravascular hemolysis could potentially account for the degree of LDH elevation seen in this case.

There have been three other cases of reported pediatric pseudo- TMA secondary to B12 in the literature [9-12]. These cases all occurred because of decreased intake and our case highlights the need to follow patients with malabsorptive syndromes. Because many of the cases were initially thought to have thrombotic thrombocytopenic purpura (TTP), they received plasma exchange with gradual improvement of their symptoms. This improvement is thought to be due to B12 contained in the infused plasma during the exchange[13].

The PLASMIC score has served as prediction tool for severe ADAMTS13 deficiency[14] but has not been evaluated in differentiating TTP from a pseudo-TMA. While it is well recognized as a helpful adjunct in the adult population, few studies have looked at its utility in children and adolescents. Linder et al showed retrospectively that the PLASMIC score was able to accurately identify pediatric patients at highest risk for severe ADAMTS13 deficiency with a sensitivity of 100% and a specificity of 78.1% [15]. In evaluating the PLASMIC scores of pediatric cases in the literature; 75% of the patients with B12 induced pseudo-TMA would have been placed in a low risk category (TABLE 1). This may prove to be a helpful adjunct to physicians when faced with this clinical presentation.

The treating team deduced that his initial pancytopenia had been secondary to his B12 deficiency given his history. This case posed a diagnostic challenge and highlights to pediatric hematologists this unusual presentation of B12 induced TMA and that it should be considered in the differential with a patient presenting with a TMA syndrome.

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Figure Legend

Table 1: WBC: white blood cell count, Hb: hemoglobin, MCV: mean corpuscular volume, Plt: platelet count,

ANC: Absolute Neutrophil Count, Retic: reticulocyte count, LDH: lactate dehydrogenase.

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