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CASE REPORT

Bactrim Induced Hemolysis and Thrombocytopenia in a Patient with Pernicious Anemia

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Abstract

This case report presents a 87-year-old female who had a history of pernicious anemia and was given Bactrim, which suppressed folic acid and caused a more profound anemia, thrombocytopenia and hemolysis. **(International Journal of Biomedicine. 2017;7(4):327-329.)**

Key Words: pernicious anemia • thrombocytopenia • hemolysis • Bactrim • cyanocobalamin • folic acid

Abbreviations

AML, acute myelogenous leukemia; **CBC**, complete blood count; **DHFR**, dihydrofolate reductase; **Hb**, hemoglobin; **Hct**, hematocrit; **IF**, intrinsic factor; **INR**, international normalized ratio; **LDH**, lactate dehydrogenase; **LFTs**, liver function tests; **MCV**, mean corpuscular volume; **MDS**, myelodysplastic syndrome; **PMH**, past medical history; **Plt**, platelets; **PABA**, para-aminobenzoic acid; **PT**, prothrombin time; **PTT**, partial thromboplastin time; **RBC**, red blood cells; **TIBC**, total iron-binding capacity; **TMP-SMX**, trimethoprim–sulfamethoxazole; **TSH**, thyroid stimulating hormone; **UTI**, urinary tract infection; **WBC**, white blood cells.

Introduction

Vitamin B_{12} deficiency anemia is common in the US with a prevalence of 5%-10% among subjects older than 60 years of age.[1] Pernicious anemia is a common cause of B_{12} deficiency with a prevalence of 0.1% in the general population and 1.9% among patients over 60 years old.[1] Causes of pernicious anemia can be diet, inadequate absorption (chronic atrophic gastritis in 90% of cases and autoimmune production of autoantibodies against IF), gastrectomy, gastritis, infection, intestinal disorder, medication toxic effect, and sometimes heredity.[2] Clinical presentation can vary and may require extensive diagnostic workup Sulfonamides can interfere with the folic acid-tetrahydrofolate synthesis pathway, which is important for purine, DNA and amino acid synthesis.[3] Drug interactions should also be considered.[3] Elderly patients are at higher risk of B_{12} deficiency anemia and treatment with sulfonamides should be given cautiously, and followed up with routine lab work including CBC and monitoring of liver and kidney function tests.[3]

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Case Report

Our patient is an 87-year-old female with PMH of untreated pernicious anemia for more than one year, cholelithiasis, dementia, and UTI (treated with Bactrim). She was admitted to the hospital due to an episode of syncope. According to the patient's family, she was mostly bedridden, had nausea for several months, poor *per os* intake, weight loss, generalized weakness and deteriorating functional status for the past several months. Family members reported that she had no overt bleeding. On admission, the patient's vitals were within the normal range with the exception of tachycardia. The physical exam illustrated a cachectic, malnourished appearance, loss of orientation, with inappropriate responses to questions and minimal communication to her family members. Laboratory results showed Hb–4.3g/dL, Hct–12.7%, RBC–1.35×10^{12}/L,

MCV–94 (80.4–95.9), and Plt of 142×10^9/L. Subsequently, the patient developed thrombocytopenia after transfusion of 3 units of pRBC. Her platelet level dropped to 8×10^9/L and WBC dropped to 3.7×10^9/L. After one unit of donor platelet transfusion, the patient had an anemia and hemolysis workup. Results supported the diagnosis for pernicious anemia with hemolysis: low level of B_{12}–88 pg/mL and folate–3.8 ng/mL, and IF antibodies. There was no evidence of iron deficiency as she had a high level of ferritin–1861 ng/mL, iron–192 ug/dL, with low levels of TIBC, haptoglobin–<20 mg/dL, while her direct anti-globulin profile was negative. TSH was in normal limits, fibrinogen level–176 mg/dL, and INR–1.29. PT was slightly elevated and PTT was in normal limits. Renal and hepatic tests were normal, except for elevated total bilirubin–2.3 mg/dL, direct bilirubin–1.4 mg/dL, and LDH–272 U/L, which revealed hemolysis. A peripheral smear did not show platelet clumping, nor schistocytes, which ruled out thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. Patient had good response to platelet transfusion ×1 and to intramuscular cyanocobalamin 1000 mcg supplementation daily for 7 days. At discharge, patient's Hgb improved to 8.8 g/dL, Hct to 25.3%, WBC to 4.3×10^9/L, and Plt to 136×10^9/L. It was recommended to continue to inject cyanocobalamin intramuscularly once a week for 4 weeks, then once a month for the rest of her life and continue folate 5 mg daily by mouth. One month later on a clinic follow-up, the patient's blood profile showed: Hb–10.2 g/dL, RBC–3.39×10^{12}/L, WBC–15.4×10^9/L, and Plt–215×10^9/L.

Discussion

The risk of vitamin B_{12} deficiency and pernicious anemia increases with age while the prevalence of vitamin B_{12} deficiency is 5%-10% after 60 years of age.[1,4] Clinical presentation can vary and may require extensive diagnostic intervention. Both deficiencies of vitamin B_{12} and folate can lead to megaloblastic anemia; however, vitamin B_{12} deficiency will additionally lead to neurological damage,[2] and it may take years for symptoms of vitamin B_{12} deficiency to develop due to large body storage, while symptoms of folate deficiency will develop in 4-5 months if dietary intake of folate is diminished. Hematological presentation of Vitamin B_{12} deficiency presents with macroovalocytic anemia with elevated level of iron, indirect bilirubin, LDH, low level of haptoglobin due to ineffective erythropoiesis and failed maturation, which leads to an increase in the destruction of red blood cells in bone marrow and periphery.[5,6] Macrocytosis is not specific for vitamin B_{12} or folate deficiency. In severe cases of deficiency, pancytopenia can develop.[5] Patients with vitamin B_{12} deficiency have elevated both methylmalonic acid and homocysteine whereas patients with folic acid deficiency have only homocysteine elevated.[7]

Our patient had a 1-year history of untreated pernicious anemia. Due to a prior UTI, the patient received Bactrim treatment, which aggravated her condition due to additional folate suppression as its side effect. Bactrim interferes with the tetrahydrofolate synthesis pathway as it is a structural analog of PABA.[3,8,9,2] Sulfonamides compete with PABA to bind to dihydropteroate synthase and inhibit conversion of PABA and dihydropteroate diphosphate to dihydrofolic acid, or dihydrofolate.[1,2,3,8,9,7] Inhibiting the production of dihydrofolate intermediates interferes with the normal bacterial synthesis of folic acid.[1,2,3,8,9,7] Trimethoprim serves as a competitive DHFR inhibitor; it also inhibits the de novo synthesis of tetrahydrofolate, the biologically active form of folate. Folic acid is an essential product for DNA and amino acid synthesis in bacterial growth.[6] Trimethoprim is a weak DHFR inhibitor, and in high doses, it has been implicated in megaloblastic pancytopenia.[2,8,9] Co-administration of folinic acid can prevent or reduce the antifolate activity of TMP-SMX without affecting its antimicrobial activity.[3,10] Bactrim is metabolized by the liver (10-20%) and the rest is excreted by the kidneys. Dosing adjustments should be made for patients with any kidney impairment.[3,10] A main contraindication of trimethoprim use is megaloblastic anemia due to folate deficiency; because our patient had a history of pernicious anemia, this fact should have been taken into consideration.

S. Yeruva et al. reported that hemolysis was observed in 1.5% of vitamin B_{12} deficiency cases.[11] Hemolysis with thrombocytopenia can develop secondary to ineffective erythropoiesis from B_{12} deficiency anemia plus a recent use of Bactrim, which in turn inhibits erythropoiesis. Ineffective erythropoiesis can lead to pancytopenia, but the morphological bone marrow picture may mimic that of MDS.[12] For this reason, bone marrow aspiration/biopsy before a therapeutic trial with vitamin B_{12} is not indicated.[12] Severe vitamin B_{12} deficiency, if accompanied by folic acid deficiency, can present with transient chromosomal abnormalities.[13]

M. Wollan et al. described a pediatric patient who, due to combined deficiency of the folic acid and vitamin B_{12}, developed nonrandom del(7q), a clonal abnormality usually associated with MDS or secondary AML.[14] Treatment with both folic acid and vitamin B_{12} corrected the clinical as well as the marrow morphologic and cytogenetic.[14] Dr. Kim in his study presented 12 patients with pancytopenia that were misdiagnosed as MDS and were successfully treated with vitamin B_{12}.[15] Our patient recovered after the blood transfusion and vitamin B_{12} IV replacement. If her anemia did not resolve, the patient would require a bone marrow biopsy and malignancy workup.

Conclusion

Elderly patients are at a higher risk of B_{12} deficiency anemia, and treatment with sulfonamides should be given with accuracy and careful planning. Furthermore, each patient should be followed up with routine lab tests, such as CBC, LFTs, and kidney function monitoring. Our patient had a history of pernicious anemia and was given Bactrim, which suppressed folic acid and caused a more profound anemia, thrombocytopenia and hemolysis.

Competing interests

The authors declare that they have no competing interests.

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