Pure red cell aplasia due to azathioprine therapy for Crohn’s disease

Nagesh Kamath, C. Ganesh Pai, Thylbert Deltombe

ABSTRACT
Various mechanisms contribute to anemia in inflammatory bowel diseases (IBD), drug-related causes being less frequent. The hematological and other adverse events of azathioprine (AZA) therapy are well documented, but drug-associated pure red cell aplasia (PRCA) is an uncommon event. We hereby describe two cases of AZA-associated PRCA in patients with Crohn’s disease. The diagnosis was supported by pathological reports, and prompt hematological recovery was seen with discontinuation of the offending drug. This report highlights the need to consider this rare entity in IBD patients in appropriate settings and for adopting adequate precautionary measures.

KEY WORDS: Anemia, azathioprine, Crohn’s disease, pure red cell aplasia

Introduction

Anemia, a common problem in patients with inflammatory bowel diseases (IBD), is reported in 6–74% of patients.[1] The important causes include overt blood loss by itself or by causing iron deficiency, seen more often in ulcerative colitis, and Vitamin B12 deficiency due to ileal involvement seen typically in Crohn’s disease (CD). Anemia can also be secondary to the underlying chronic disease or extensive bowel resection or rarely due to aplastic anemia and myelodysplastic syndrome.[2]

Azathioprine (AZA) and 6 mercaptopurine are immunosuppressant, thiopurine analogs effective in maintaining steroid-free remission in IBD. Leukopenia occurs in 5–25% of patients on the drug, of which 3% have a severe decrease in white blood cells (WBCs).[3] Pure red cell aplasia (PRCA) is a rare adverse event characterized by normocytic, normochromic anemia associated with reticulocytopenia, normal granulocyte and platelet (PLT) counts, and isolated erythroblastopenia in the bone marrow.[4] We report two cases of PRCA in patients with CD while on AZA therapy who recovered promptly on discontinuing the drug.

Case Reports

Case 1
A 14-year-old girl with ileocolonic CD presented with progressive fatigue, headache, fever, sore throat, and vomiting over 3 weeks. She had been maintaining well during regular follow-up with periodic laboratory checks on AZA 75 mg/day over the previous 6 months. There was no overt bleeding from the gut or from other sites. Physical examination was remarkable only for severe pallor.

The hemoglobin (Hb) was 2.5 g/dl, hematocrit (HCT) 7.3%, WBC count 6800/µl and PLT count 243.0 × 10^3/µl. The serum liver, renal, and iron profile were normal. The blood smear revealed a sparse distribution of normocytic, normochromic red blood cells (RBCs) showing mild anisopoikilocytosis and poikilocytosis. No other abnormalities were seen in the RBCs. The WBCs were normal in number and distribution. The absolute reticulocyte count was normal 0.1087 × 10^6/µl (0.02–0.11), but the reticulocyte index of 0.3% indicated suppressed erythropoiesis. Bone marrow aspirate showed suppression of

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the erythroid series with normoblastic maturation, relatively increased leukopoiesis with normal maturation, a myeloid to the erythroid ratio of 4:1, and normal megakaryocytes. Abnormal cells were not seen, and the iron store was normal.

The patient received two units of packed RBC, and AZA was replaced with oral mesalamine 400 mg 3 times a day. Her anemia resolved over the next few weeks, and she has been symptom-free over the following 22 months.

**Case 2**

A 39-year-old male was diagnosed with isolated small bowel CD when he presented with a sub-acute intestinal obstruction that necessitated the resection of 100 cm of jejunum bearing 5 strictures. The histopathology revealing fissuring ulcers, transmural inflammation, and granulomas suggestive of CD. Postoperatively, he was initiated on oral AZA the dose of which was gradually stepped up to 125 mg/day. Before initiation of AZA, his Hb was 11.9 g/dl, HCT 37.2%, WBC count 12,100/µl, and PLT count 340.0 × 10^3/µl. Five months later, while on regular follow-up with periodic laboratory checks, he complained of increasing fatigability over 1 week. He had no symptoms to suggest active bowel disease or intestinal blood loss.

His Hb was 6.8 g/dl, WBC count 3700/µl and PLT count 180.0 × 10^3/µl. Hb was absent in urine. Serum lactate dehydrogenase, serum renal and liver profiles were normal. The blood smear revealed sparsely distributed normocytic, normochromic RBCs, showing aniso-polikilocytosis and polychromasia and the WBCs were normal in the distribution of cell types. Coombs’s tests were negative. The absolute reticulocyte count was 0.0144 × 10^9/µl (0.02–0.11), and the reticulocyte index was 0.1% indicating suppressed erythropoiesis. Bone marrow examination was not done. AZA was discontinued, and his Hb and HCT normalized over the next few weeks in the absence of any RBC transfusions. He has been maintaining remission on parenteral and later oral methotrexate following a subsequent relapse.

The causality assessment in the two cases was found to be probable as per Naranjo probability scale (+7), and the World Health Organization Uppsala Monitoring Center causality category and the severity assessed as severe for the first case and moderate in the second case.[5]

**Discussion**

The report highlights two patients without any prior hematological abnormalities maintaining remission on AZA, rapidly developing symptoms of anemia from PRCA, which resolved on discontinuation of the drug. Myelosuppression with thiopurines frequently occurs during the first 8 weeks after drug initiation but has been reported up to 11 years, occurring either suddenly or gradually over several months. AZA-associated red cell aplasia is a rare variant of this which was first reported in two patients in 1975.[9] So far, more than 20 cases have been reported in the literature. This drug is commonly prescribed in renal transplant patients, systemic sclerosis, autoimmune hepatitis, systemic lupus erythematosus with lupus nephritis, and rheumatoid arthritis.

The mechanisms involved in the development of PRCA secondary to TP are unknown. This untoward event could develop due to the excessive inhibition of DNA synthesis or direct cellular toxicity within the erythroid precursors brought about by the drug metabolite 6 thioguanine (6TGN).[5] Higher levels of this metabolite have been associated with bone marrow aplasia, but the correlation between 6TGN levels and this latter adverse event is at best modest. There may be other as yet unknown metabolites that are responsible for PRCA. Transient aplastic crisis can be seen with parvovirus B19 infection.[9] Bone marrow aspirates in such cases show giant proerythroblasts, large eosinophilic nuclear inclusion bodies, and cytoplasmic vacuolization that were absent in our patient. Blood smear or the bone marrow aspirate did not show any malignant cells. Hence, hematologic malignancy was ruled out in our patients. Furthermore, blood counts improved after discontinuation of the drug.

PRCA encompasses a variety of inherited and acquired disorders characterized by an isolated failure of red cell production with preservation of proliferation of the other lineages. The drugs associated with PRCA include phenytoin, AZA, chloramphenicol, procainamide, and isoniazid. It should be suspected in patients with normochromic normocytic anemia with reticulocytopenia in the right clinical setting, the bone marrow appearance characteristically showing a markedly raised myeloid: Erythroid ratio.

Treatment of PRCA is aimed at restoring erythrocyte production by addressing the cause, if any and maintaining Hb at an adequate level with red cell transfusions and if necessary, erythropoietin.[9]

**Conclusion**

The above cases highlight the need to consider PRCA, a rare adverse effect of thiopurines, as a cause of anemia in patients with IBD on these drugs. Early recognition and intervention can avoid serious and possibly fatal outcome.

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**Conflicts of Interest**

There are no conflicts of interest.

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