Autoimmune Hemolytic Anemia After Relapse of Chronic Myeloid Leukemia: A Case Report

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ABSTRACT: Autoimmune hemolytic anemia is one of the differential diagnoses for anemia in patients with lymphoproliferative neoplasia, such as chronic lymphocytic leukemia, who experience sudden drop in hemoglobin.1 The association between autoimmune hemolytic anemia and chronic myeloid leukemia on the contrary is unusual. Here we present a patient with a background of chronic myeloid leukemia treated previously with Tyrosine Kinase Inhibitors, then developed autoimmune hemolysis simultaneously with chronic myeloid leukemia relapse. Hemolysis was treated with steroids with good response.

KEYWORDS: chronic myeloid leukemia (CML), autoimmune hemolytic anemia (AIHA)

Background
Autoimmune hemolytic anemia (AIHA) is one of the differential diagnoses for anemia in patients with lymphoproliferative neoplasia, such as chronic lymphocytic leukemia, who experience sudden drop in hemoglobin.1 The association between AIHA and chronic myeloid leukemia (CML) on the contrary is unusual. Here we present a patient with a background of CML treated previously with Tyrosine Kinase Inhibitors (TKI), then developed autoimmune hemolysis simultaneously with CML relapse.

Objective
To draw physician attention to an unusual cause of anemia in CML.

Case Report
A 51-year-old Egyptian gentleman was diagnosed with CML in 2007. He was commenced on imatinib but failed to achieve major molecular response (MMR) 4.5 log reduction at 1 year as per European Leukemia Net recommendation, so he was switched to nilotinib. He achieved and maintained MMR 4.5 log reduction for around 6 years after starting nilotinib, so his primary hematologist decided for treatment-free remission trial in 2013. He presented to our hospital in March 2019 with 2-week history of left upper quadrant abdominal pain associated with anorexia and easy fatigability. Physical examination was positive for pallor and hepatosplenomegaly and it did not reveal any source of bleeding. Lab tests on presentation showed: white blood cells (WBCs) of 90.2 with neutrophilia, eosinophilia, and basophilia. Hemoglobin (Hb) was 6.6 g/dL, with mean corpuscular volume (MCV) of 62, and platelets of 497. Renal and liver function tests were within normal limits and uric acid was 745 μmol/L. Anemia work up was impressive of positive direct antoglobulin test (DAT) but with slightly elevated lactate dehydrogenase (LDH) and normal reticulocyte count. Viral serology was negative for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HIV. Peripheral smear was suggestive of CML with 1% blasts besides hypochromic microcytic anemia. Cytogenetic and fluorescence in situ hybridization (FISH) studies on a bone marrow biopsy confirmed CML relapse in chronic phase in addition to the presence of erythroid hyperplasia. The patient was started on hydroxyurea 500 mg twice daily with allopurinol 300 mg twice daily and discharged after uneventful transfusion of 2 units of matched packed red blood cells (RBCs). However, his Hb increased only to 7 g/dL. His anemia was initially attributed to CML relapse. Two weeks later, he presented with tiredness and Hb of 5.8 g/dL. Another 2 units of compatible packed RBCs were transfused and his Hb improved to 7.7 g/dL. Repeated anemia work up showed picture of hemolysis with elevated reticulocyte count, LDH, and positive DAT. Diagnosis of AIHA was made and the patient was discharged on prednisolone 80 mg daily. Chronic myeloid leukemia treatment was restarted 1 week later with nilotinib 400 mg twice daily. Follow up after 6 weeks from steroid therapy showed improvement of Hb level to 9 g/dL (Figure 1). The patient currently is doing well and being followed regularly in hematology clinic. He achieved complete hematologic remission and the milestone of molecular response at 3 months from restarting nilotinib therapy.

Discussion
Anemia in chronic myeloid leukemia is multifactorial. It can be central due to inadequate erythropoiesis in the bone marrow or peripheral as a result of splenomegaly and subsequent RBCs...
destruction or a combination of both mechanisms.\textsuperscript{2} Autoimmune hemolysis as a peripheral cause of anemia in CML is rare. Our patient was diagnosed with recurrence of CML and was found to have low Hb that did not increase to the expected level after blood transfusion. The etiology of anemia in his situation is believed to be peripheral in origin as the bone marrow biopsy showed proliferation of RBCs precursors. Splenomegaly as a peripheral cause might have contributed to his anemia but the presence of autoantibodies, evident by positive DAT, and the improvement of Hb level after steroid therapy make hypersplenism a less likely cause of his severe anemia. We do not think that autoimmunity was a consequence to the delivered packed RBCs as DAT was positive prior to blood transfusion and the units were compatible with the patient’s blood. The previous exposure to TKI might be a culprit especially for imatinib as few case reports described autoimmune hemolysis after receiving imatinib as CML treatment. The first case of imatinib associated AIHA was reported in 2003 by Novaretti et al.\textsuperscript{3} Their patient was a middle-aged man whose CML was managed with imatinib for around 10 months before developing autoimmune hemolysis. Like our case, he improved with steroid therapy which was given along with imatinib. However, CML in our patient was treated initially with imatinib and then with nilotinib as a second line therapy for around 6 years. Due to the remote use of nilotinib, it is difficult to claim that it was responsible for hemolysis especially that it had been stopped for several years before hemolysis event. Similar to our patient, concomitant diagnosis of CML relapse at the time of AIHA diagnosis was reported in 6 out of 9 CML cases by Cwynarski et al.\textsuperscript{4} In contrast to our case, Their CML had been treated with allogeneic bone marrow transplantation and AIHA was managed with second line therapy such as splenectomy or intravenous immunoglobulin (IVIG) in addition to steroids. The mechanism of hemolysis in those cases was believed to be linked to an immune reconstitution after transplantation. As a conclusion, AIHA is a rare cause of anemia in CML, it should be kept in mind during the evaluation of anemia especially after CML relapse.

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Author Contributions
Both authors contributed equally.

Patient Consent
Written informed consent was taken from the patient during his hospital stay.

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