Autoimmune hemolytic anemia associated with Tyrosine-kinase inhibitors: a case study

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Abstract

This is a case of autoimmune hemolytic anemia (AIHA) associated with tyrosine-kinase inhibitors (TKIs) in a patient with CML (chronic myeloid leukemia) in major molecular response (MMR). The patient was first started on treatment with imatinib in June 2019 during which he had a normal hemoglobin, without any evidence of hemolysis. Within a few months of initiating the treatment, the patient had progressively worsening dyspnea and fatigue while remaining in MMR. Subsequent laboratory investigations showed anemia with hemoglobin (Hb) of 8.9 g/dL, reticulocyte count of 435.5 x 10^9 /L, and a positive direct antiglobulin test (DAT). The patient was then initiated on treatment with other TKIs such as dasatinib and bosutinib, all requiring discontinuation due to hemolytic anemia. Discontinuation of TKI with associated monitoring of BCR-ABL via polymerase chain reaction led to a gradual improvement of the patient's Hb to 13.2 mg/dl and stability of other hematologic indices. Due to the relapse of CML, the patient was ultimately started on Asciminib after which his hemolyis remained compensated without evidence for subsequent hemolysis. Our case demonstrates that patients under treatment with multiple generations of tyrosine kinase inhibitors (TKIs) can develop autoimmune hemolytic anemia. Management includes steroids, rituximab and may also require discontinuation of TKI.

Case presentation

A 73-year-old male was diagnosed with CML in chronic phase with positive Philadelphia chromosome and BCR-ABL (Breakpoint cluster gene protein – Abelson proto-oncogene) p210 fusion in June 2019. His initial laboratory findings showed a hemoglobin (Hb) level of 13.8 g/dL, WBC count of 81.2 x 10^9/L, and platelet count of 264 x 10^9/L. He was initiated on imatinib mesylate 400 mg once daily, achieving complete hematologic response within one month with normalization of his WBC count, and major molecular response by April 2020, which is defined as 0.1 % or less of BCR-ABL transcript level in peripheral blood.[1]

In January 2021, the patient developed exertional dyspnea and chest pain. Labs showed new macrocytic anemia with a Hb level of 8.9 g/dl, mean corpuscular volume of 115.3 fL, and hematocrit of 26.7%, with these findings occurring despite the patient remaining in MMR. Anemia workup revealed normal values for thyroid stimulating hormone, free T4, vitamin B12, folic acid, and methylmalonic acid. Bone marrow aspirate revealed erythroid hyperplasia without overt dysplastic features and no morphological evidence of residual CML. The patient's direct antiglobulin test was positive for IgG and negative for C3. Additional labs showed an elevated bilirubin at 2.7 mg/dL, lactate dehydrogenase at 672 U/L, reticulocyte count 435.5 x 10^9 /L, and haptoglobin <3 mg/dL(reference range 50 to 220 mg/dL, consistent with AIHA. The patient was started on prednisone 60 mg once daily with an 11-to-12-week taper following which his Hb improved with a peak of 13.3 g/dL. Despite the response to prednisone, he was not able to tolerate the drug due to side effects including severe fatigue and insomnia, leading to tapering of prednisone and concurrent initiation of rituximab in June 2021. Following four weekly doses of rituximab, his Hb level was remeasured and found to be 9.3 g/dL.

The AIHA was thought to be secondary to imatinib therapy, and the drug was discontinued in August 2021, after which Hb gradually improved. Evaluation after 4 months revealed a Hb level of 13.2 g/dL, and other blood indices were stable. However, in December 2021 molecular testing by PCR showed relapsing and hence he was started on dasatinib 50 mg once daily[2] after which the patient achieved MMR again in May 2022. However, due to the development of adverse effects including relapse of hemolytic anemia with associated shortness of breath and severe generalized fatigue, dasatinib dose was reduced and it was eventually discontinued in December 2022. From December 2022 – Dec 2023 the patient was treated with modalities including prednisone, IVIG and rituximab for hemolytic anemia. A complete rheumatology work up was also done which was negative. In November 2023, the hemoglobin had improved closer to 14, however a bone marrow biopsy revealed positive cytogenetics for Philadelphia chromosome in 3 metaphases and BCR–ABL1 p210 was also positive at 14.9717%, following which the patient was started on Bosutinib 100 mg daily starting dose, later discontinued in July 2024 due to evidence for hemolysis again, and due to intolerable side effects. In January 2025, BCR-ABL p210 was positive at 19.6% requiring the initiation of Asciminib 80mg daily. As of April 2025, the patient's labs revealed compensated hemolysis with reduced haptoglobin < 3, and elevated indirect bilirubin and reticulocyte count. The patient continued to be in MMR with BCR-ABL transcripts at 0.02%.

Figure 1



Discussion

Imatinib, which is a first line tyrosine kinase inhibitor is generally well-tolerated and is the standard treatment in CML patients[1]. The most common non-hematological adverse effects of imatinib mesylate include fluid retention, rash, and related events, nausea, vomiting, diarrhea, and musculoskeletal pain. Hematological side effects include cytopenias, particularly anemia, thrombocytopenia, and neutropenia.[3] In patients who do not respond to first line TKIs, second- and third-generation TKIs such as ponatinib and asciminib are used. In cases where patients fail multiple TKI therapies or present with advanced-phase CML, allogeneic hematopoietic stem cell transplantation may be considered. This option is typically reserved for patients with resistance to at least two TKIs or those in accelerated or blast phases of CML[4,5,6.] Novaretti et al. (2003) reported the first case of immune-mediated hemolytic anemia associated with imatinib mesylate[3]. Hamamyh et al. (2020), discussed 54 cases of AIHA in CML, among these, 4 cases included imatinib as a part of the CML therapy[7]. Isomura et. Al, 2023 discussed a case of Alectinib induced hemolytic anemia as part of lung adenocarcinoma[8]. The treatment of AIHA for patients discussed in the case reports included steroids with the continuation of CML treatment with imatinib[9,10.11]. For the four patients described in the review article for whom tyrosine kinase inhibitors were used as a part of treatment, management of AIHA included steroids of varying doses and duration, rituximab, bortezomib, mycophenolate mofetil, plasmapheresis, and splenectomy[3,7,12]. In the U.S. Food and Drug Administration (FDA) access data for imatinib,[12] they recommend managing cytopenias with dose reduction or dose interruption and rarely require treatment discontinuation. That being said, these recommendations are not necessarily applicable for patients with an autoimmune etiology responsible for their associated cytopenias as seen in the patient described in this report.

Conclusion

This a rare case of AIHA in a CML patient under treatment with TKIs including imatinib, dasatinib, bosutinib which were eventually discontinued to treat the AIHA. Initial management strategies, with steroids and subsequently with rituximab, were not successful. A gradual improvement in hemoglobin was noted whenever the tyrosine kinase inhibitor was held. Unfortunately, our patient experienced a relapse in his CML and is currently under treatment with a third-generation tyrosine kinase inhibitor (Asciminib). As depicted in this case, TKI - induced AIHA should be considered in a patient being treated with first, second or third generation tyrosine kinase inhibitors for CML if they develop an otherwise unexplained anemia.

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