

Case Report

Warm Autoimmune Hemolytic Anemia as First Presentation of Chronic Myeloid Leukemia: A Case Report

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Keywords

Case report · Warm autoimmune hemolytic anemia · Chronic myeloid leukemia · Philadelphia chromosome

Abstract

Introduction: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the Philadelphia chromosome and uncontrolled granulocyte production. While autoimmune hemolytic anemia (AIHA) is commonly associated with lymphoproliferative disorders such as chronic lymphocytic leukemia, its occurrence in CML is rare, with only a few documented cases. Here, we report a case of concurrent chronic-phase CML and AIHA.

Case Presentation: We present a 34-year-old female diagnosed with warm AIHA as the first presentation of CML. Diagnostic workup, including peripheral smear, revealed hemolysis with elevated lactate dehydrogenase and a positive direct antiglobulin test (DAT), along with a positive Philadelphia chromosome, confirming CML. Steroid therapy successfully managed the AIHA, leading to normalization of hemoglobin levels and subsequent tapering and discontinuation of steroids. **Conclusion:** While AIHA is a rare cause of anemia in CML, it should be considered during anemia evaluation, particularly in cases of CML relapse.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that accounts for approximately 15–20 percent of adult leukemias [1, 2]. The hallmark of the disease is the uncontrolled production of granulocytes, resulting from a reciprocal translocation between chromosomes 9 and 22. This translocation produces an abnormal chromosome, the Philadelphia (Ph) chromosome, which leads to the formation of the BCR-ABL1 oncogene. This oncogene exhibits high tyrosine kinase activity, which promotes excessive cell division [3]. The 2022 WHO classification for CML emphasizes the chronic phase as the primary focus, omitting the accelerated phase as a distinct category. The classification now highlights the importance of identifying high-risk features associated with progression and resistance during the chronic phase, rather than categorizing an intermediate accelerated phase. The blast phase remains a critical aspect of disease progression but is not part of the new classification focus [4]. The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment landscape for CML, transforming it from a once-fatal disease into a manageable chronic condition. TKIs, such as imatinib, dasatinib, and nilotinib, specifically target the BCR-ABL1 oncoprotein, effectively controlling disease progression and significantly improving patient survival rates [5–9].

Autoimmune hemolytic anemia (AIHA) is caused by autoantibody-induced hemolysis. AIHA is usually idiopathic; however, it may be associated with infection, lymphoproliferative disorders, autoimmune diseases, and several medications [10]. The clinical presentation of AIHA includes anemia with elevated reticulocyte counts and positive direct antiglobulin (Coombs) test. Destruction of red blood cells (RBCs) can be intravascular in cold agglutinin AIHA mediated by IgM, and extravascular in warm AIHA mediated mainly by IgG with the latter being associated with lymphoproliferative disorders namely chronic lymphocytic leukemia [11, 12].

The association between AIHA and chronic lymphocytic leukemia has been established but it is extremely unusual to be linked with CML. Looking in the medical literature a few case reports and series have been published linking both entities. Herein, we present a patient who was diagnosed with chronic phase CML and AIHA. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000542341>).

Case Presentation

A 34-year-old Moroccan female with a past medical history of hypertension was referred from a private clinic after presenting with leukocytosis, fatigue, and abdominal pain. Initial blood tests revealed a hemoglobin (Hb) level of 7.3 g/dL with a mean corpuscular volume of 94 fL, a white blood cell (WBC) count of $183.6 \times 10^3/\mu\text{L}$ with neutrophilia, eosinophilia, and basophilia, and a platelet count of $369 \times 10^3/\mu\text{L}$.

A peripheral smear showed marked leukocytosis with left-shifted neutrophils, basophilia, eosinophilia, monocytosis, and approximately 1% blasts. Renal and liver function tests, as well as the coagulation profile, were within normal limits, and the uric acid level was elevated at 518 $\mu\text{mol/L}$.

An anemia workup showed normal ferritin and iron profiles, with evidence of AIHA supported by a positive direct antiglobulin test (DAT) and significantly elevated lactate dehydrogenase (LDH) levels of 1,024 U/L, low haptoglobin, and a high reticulocyte count (Table 1). Further Coombs' testing revealed IgG negativity, C3D positivity, and a positive eluate. The peripheral smear displayed features of both CML and AIHA (as shown in Fig. 1, 2).

Table 1. Relevant laboratory investigations

	Initial laboratories	After 6 weeks	Normal
WBC, $\times 10^3/\mu\text{L}$	183	5.4	4–10
Hb, g/dL	7.3	11.2	12–15
Platelets, $\times 10^3/\mu\text{L}$	369	370	150–410
LDH, U/L	1,024	646	135–214
Bilirubin T, $\mu\text{mol/L}$	19	6	0–21
Reticulocyte count, $\times 10^3/\mu\text{L}$	209	95	50–100
Haptoglobin, mg/dL	10	40	30–200

WBC, white blood cell; Hb, hemoglobin; LDH, lactate dehydrogenase; Bilirubin T, total bilirubin.

An abdominal ultrasound demonstrated splenomegaly with a spleen size of 21 cm (normal: up to 12 cm).

Cytogenetic analysis using FISH on peripheral blood confirmed the presence of a BCR/ABL1 rearrangement in 96% of analyzed nuclei. Karyotyping of the bone marrow aspiration revealed an abnormal clone involving a translocation between chromosomes 9 and 22 at cytogenetic bands q34 and q11.2, respectively, producing the Philadelphia chromosome. BCR-ABL transcript analysis showed a BCR::ABL1 to ABL1 percentage ratio of 73% (International Scale, IS), consistent with the FISH findings. The morphological features of the bone marrow aspirate and biopsy supported the diagnosis of chronic-phase CML (as shown in Fig. 3). The Sokal Index was calculated to be 1.2, placing the patient at intermediate risk, while the EUTOS score categorized her as low risk.

These findings suggested a diagnosis of CML with concurrent AIHA. The patient was started on hydroxyurea 1,000 mg twice daily, prednisolone 60 mg daily, and allopurinol 300 mg daily. She also received two units of matched packed RBCs.

After 2 weeks, there was no significant change in the WBC count, which remained around $200 \times 10^3/\mu\text{L}$, despite increasing the hydroxyurea dosage to 1,000 mg three times daily. The patient's Hb level was low, necessitating a blood transfusion. We anticipated that starting TKI therapy might further decrease Hb levels, so we delayed its initiation for 2 weeks until the hemolysis stabilized. The treatment was switched to imatinib, and 1 week after initiation, there was a marked improvement, with the WBC count decreasing to $46 \times 10^3/\mu\text{L}$.

Repeated anemia workup continued to show evidence of hemolysis with an elevated reticulocyte count, LDH, and a positive DAT, confirming the diagnosis of AIHA. The patient was maintained on prednisolone 60 mg daily.

After 6 weeks of steroid therapy, her Hb levels improved to 11.2 g/dL, allowing for tapering and eventual discontinuation of the steroids. The patient is currently doing well and is being followed regularly in the hematology clinic.

Discussion

AIHA is caused by autoantibodies that target self-RBCs, leading to their destruction. Warm AIHA results in accelerated red cell destruction due to the presence of warm agglutinins, which are almost always IgG antibodies. These antibodies bind to antigens on erythrocytes at 37°C, making warm AIHA the most common type of this condition. It contrasts with alloimmune hemolysis, where the individual produces antibodies against foreign RBC antigens [13]. Most accelerated red-cell clearance occurs through the spleen and liver

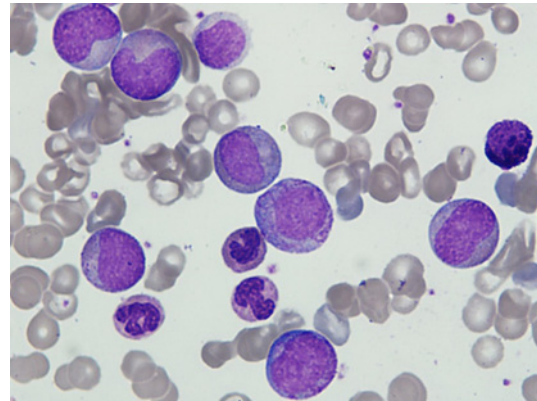


Fig. 1. Peripheral blood smear (Wight's stain) shows neutrophilic leukocytosis with marked left shift, and basophilia, magnification $\times 100$.

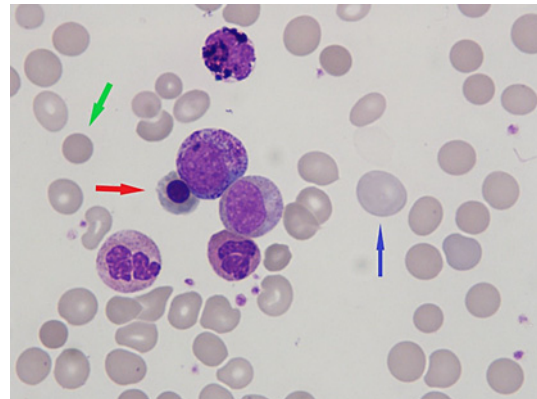


Fig. 2. Peripheral blood smear (Wight's stain) shows leucoerythroblastic picture, and morphologic features of hemolysis. Blue arrow: polychromatophilic RBC. Green arrow: spherocyte. Red arrow: nucleated RBC, magnification $\times 100$.

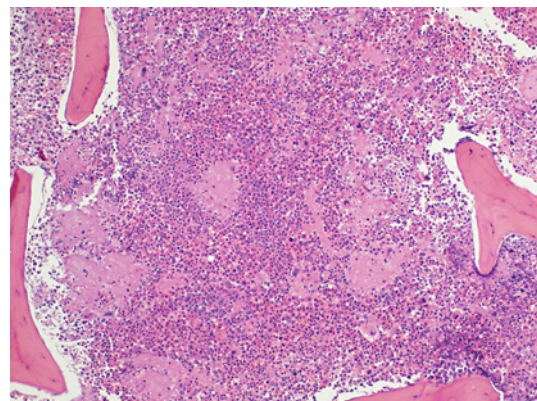


Fig. 3. Bone marrow biopsy (hematoxylin and eosin stain) shows markedly hypercellular bone marrow with granulocytic hyperplasia and areas of necrosis, magnification $\times 10$.

(extracellular hemolysis). IgG-coated red cells are recognized by splenic macrophages, which carry Fc γ receptors for the IgG heavy chain. This leads either to the phagocytosis of the red cells or, more commonly, to the removal of a portion of the red-cell membrane, resulting in microspherocytes, which can be visualized on a peripheral blood smear [14]. IgG subtypes may also activate complement, leading to the formation of the membrane attack complex (C5b-9) on the surface of red cells, resulting in intravascular hemolysis. This intravascular hemolysis manifests as hemoglobinuria and markedly elevated LDH levels [15].

Approximately 50% of cases of warm AIHA are primary and idiopathic; the remaining cases are secondary to other disorders, including myeloproliferative disorders such as CML, medication use, autoimmune diseases, infections, and other conditions [16, 17]. The occurrence of AIHA in patients with CML is extremely rare. The infrequent occurrence and variable onset of AIHA in these patients make it difficult to assert that CML, per se, is the main culprit. In terms of possible underlying etiology, patients can be classified into two categories: the transplant group and the non-transplant group. Hemolysis following hematopoietic cell stem transplantation is a rare but well-known complication that can be categorized as either alloimmune or autoimmune. The etiology of AIHA in the hematopoietic cell stem transplantation group is thought to be related to donor cell immune reconstitution [18], concomitant viral infection, or relapse of CML [19]. In the non-transplant group, the cause of AIHA is believed to be linked to drugs used specifically for CML treatment, although the exact mechanisms behind this association remain poorly understood. However, when AIHA does occur in this context, it almost always develops after the diagnosis of CML during the chronic phase [14]. Additionally, anemia in VML may originate centrally from insufficient erythropoiesis in the bone marrow or peripherally due to splenomegaly, leading to the destruction of RBCs. In many cases, both mechanisms contribute to this condition [20].

Our patient was diagnosed with CML and was found to have low Hb levels that did not improve as expected after a blood transfusion. The etiology of the anemia in this case is thought to be peripheral in origin, as the bone marrow biopsy showed proliferation of RBC precursors. The presence of autoantibodies, indicated by a positive DAT, and the improvement in Hb levels following steroid therapy suggest that AIHA is the most likely cause of her anemia. The patient had not received any treatment or blood transfusion at the time of the initial anemia workup, which was supported by the positive DAT. Therefore, medication-induced AIHA, specifically from imatinib, is considered an unlikely cause [21, 22].

The temporal relationship between AIHA and CML remains an area of clinical uncertainty. While our case suggests a potential link between AIHA and CML, it is crucial to consider the possibility of pre-existing autoimmune antibodies or the coincidental occurrence of these two conditions. Distinguishing between a causal relationship and a coincidental co-occurrence is inherently challenging due to the complex nature of autoimmune and hematological disorders.

Conclusion

In conclusion, although AIHA is a rare cause of anemia in CML, it should be considered during the evaluation of anemia, especially in cases of CML relapse. Clinicians should be mindful that, despite its uncommon occurrence, AIHA must be included in the differential diagnosis for patients presenting with an unexplained drop in Hb levels.

Statement of Ethics

This case report was approved by the Hamad Medical Corporation's Medical Research Center (MRC-04-24-585). Written informed consent was obtained from the patient for publication of the details of his medical case and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.A., A.Y.E., and M.A.Y.: conceptualization and literature review. A.T.: data collection, interpretation, and manuscript writing. A.S.: provision of pathological images and interpretation. A.A.: supervision, manuscript review, and editing. All authors reviewed and approved the final version of the manuscript. Both A.A. and A.T. have equal distribution.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participant but are available from the corresponding author (A.A.) upon request.

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