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Case Report

Spontaneous Remission in a Patient with Chronic Myeloid Leukemia: A Case Report

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Chronic myeloid leukemia · Spontaneous remission · Philadelphia chromosome · Tyrosine kinase inhibitors

Abstract
Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm in which granulocytic cells are the main proliferative component. At diagnosis, more than 90% of CML cases have the characteristic Philadelphia chromosome, containing the *BCR::ABL1* fusion gene. The natural history of untreated CML is an initial indolent chronic phase which will be followed by an accelerated phase, blast phase, or both. Tyrosine kinase inhibitors (TKIs) have dramatically altered the natural history of CML. TKI discontinuation with the goal of treatment-free remission is currently part of current management recommendations. However, spontaneous remission without receiving any treatment is extraordinarily rare in CML patients. Herein, we report a 56-year-old male who presented with leukocytosis and was diagnosed as a case of CML in the chronic phase; however, treatment with TKIs was not initiated due to spontaneous hematological as well as molecular remission.

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell neoplasm characterized by the presence of the Philadelphia (Ph) chromosome, which usually results from a balanced translocation between chromosomes 9 and 22. This genetic rearrangement generates a *BCR::*

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ABL1 gene fusion, which codes the active tyrosine kinase. CML accounts for approximately 15% of leukemia cases in adults. CML prevalence is steadily increasing due to the dramatic effect of tyrosine kinase inhibitors (TKIs) on survival [1–3]. TKIs have dramatically altered the natural history of CML. The broad use of TKIs has improved overall survival to the point where the life expectancy of CML patients is nearly equal to that of the general population [4, 5].

TKI discontinuation with the goal of treatment-free remission is currently part of current management recommendations [6]. However, CML spontaneous remission without taking any cytotoxic therapy is rarely described in the literature [7–9]. Herein, we report a 56-year-old male who was referred to the hematology clinic due to leukocytosis and was diagnosed as a case of CML in the chronic phase; however, treatment with TKIs was not initiated due to spontaneous hematological and molecular remission. 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/10.1159/000533660).

Case Report

A 56-year-old male patient with a past medical history of diabetes mellitus was well controlled on metformin. He was referred to the hematology clinic for evaluation after the result of a routine complete blood count (CBC) which showed leukocytosis. He denied any symptoms and stated that the abnormal results were incidental. There was no history of fever, weight loss, night sweats, or recurrent infections. There was no history of recent blood transfusion or vaccination. Also, there was no reported family history of hematological malignancy. He is an ex-smoker and has no alcohol consumption. On physical examination, he has stable vital signs with no palpable lymph nodes or organomegaly. Blood tests, including CBCs, were completely normal 6 months before this presentation. Abdomen ultrasound was normal, apart from a small right renal cyst.

Laboratory investigation showed the following: hemoglobin of 11.1 g/dL (13.5–17.5 g/dL), leucocytes of 26.8 × 10^9/L (4–10 × 10^9/L) with absolute neutrophil count of 16.3 × 10^9/L (2–7 × 10^9/L), lymphocyte count of 4.3 × 10^9/L (1–3 × 10^9/L), basophil counts of 1.6 × 10^9/L (0.02–0.1 × 10^9/L), and platelet counts of 165 × 10^9/L (150–400 × 10^9/L). LDH was elevated at 477 U/L. Liver and kidney functions were normal. Peripheral smear revealed neutrophilic leukocytosis with the shift to the left and basophilia, a picture suggestive of CML. Bone marrow aspirate and biopsy were consistent with CML in the chronic phase. Sokal's score was 0.8 which corresponds to intermediate risk.

Fluorescence in situ hybridization analysis revealed *BCR::ABL1* rearrangement, *t*(9;22) in 86% of cells analyzed. Chromosomal analysis showed abnormal karyotype; 46,XY,*t*(9;22)(q34;q11.2)[31]/46,XY[4] (Fig. 1, 2).

The molecular analysis tested positive for an e14a2 *BCR::ABL1* gene fusion by single-step RT-PCR. Quantitative RT-PCR indicates a *BCR::ABL1* to *ABL1* ratio of 0.7117 with 65,043 copies of *BCR::ABL1* and 91,393 copies of *ABL1* in this blood, equivalent to a percentage ratio of 78% on the international scale (IS).

Two weeks after the initial laboratories, follow-up CBC showed WBCs dropped from 26.8 to 18, and 2 weeks after that, it dropped to 5.3 and basophilia has resolved; serial follow-up results are demonstrated in Figure 3. Molecular follow-up showed improvement of a *BCR::ABL1* to *ABL1* percentage ratio from 78% (IS) at diagnosis to 3% and 0.06% at 3- and 5-month follow-up, respectively (Fig. 4). At 6-month follow-up, he tested negative for a *BCR::ABL1* gene fusion by RTqPCR at a sensitivity of 0.00001. Given the hematological and molecular spontaneous remission, TKI was not started.

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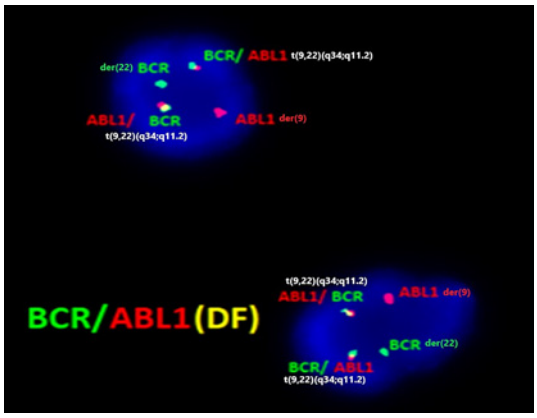

Fig. 1. Interphase fluorescence in situ hybridization (iFISH) shows reciprocal translocation involving the BCR and ABL1 gene regions which results in the Philadelphia (Ph) chromosome.

The patient was referred to the hematology clinic for evaluation of leukocytosis, but a confirmed diagnosis of CML had not yet been made. Outpatient diagnostic tests, including a bone marrow examination, were performed. As the white blood cell counts were not significantly elevated, a cytoreductive agent was not initiated. During the follow-up appointment after 2 weeks, a repeated CBC revealed an improvement in the patient's counts. Consequently, a TKI was not started, and the decision was made to continue observation.

Discussion

CML is a myeloproliferative neoplasm in which granulocytic cells are the main proliferative component. Most patients with CML are diagnosed incidentally in the chronic phase. The disease is classically staged into chronic phase (most patients at presentation), accelerated phase, and blast phase. The natural history of untreated CML is an initial indolent chronic phase which will be followed by an accelerated phase, blast phase, or both [10–12]. Identifying high-risk CML patients is crucial for choosing the right TKI. To select the best TKI for CML treatment, evidence, patient characteristics, and physician experience must be considered. Key areas of study in CML include gene expression, leukemic stem cells, genomics, genetic polymorphisms, resistance genes, and *BCR::ABL1* kinase domain mutations. Moving forward, the treatment of CML will primarily concentrate on molecular interventions to specifically target CML-leukemic stem cells. The objective is to attain a sustained absence of detectable BCR-ABL1 transcripts and maintain long-term remission following discontinuation of TKI therapy [13]. However, spontaneous CML resolution without treatment has rarely been reported.

Spontaneous resolution of leukemia, although rare and poorly understood, has been observed in various situations such as severe infection, blood product transfusion, immune-mediated processes, and termination of pregnancy [13, 14]. It is believed that an immune-mediated process involving the excessive production of inflammatory cytokines stimulates the activity of natural killer cells, T lymphocytes, and macrophages, potentially exerting an antileukemia effect. Additionally, nonirradiated allogeneic blood product transfusion has been associated with spontaneous remission in leukemias, possibly due to the presence of antileukemic lymphocytes [15]. In the context of CML, potential factors contributing to spontaneous resolution include the immune response, activation of natural killer cells, genetic alterations within leukemic cells, and spontaneous apoptosis. The immune system's strong response against leukemic cells, enhanced cytotoxic activity of natural killer cells, and genetic changes affecting cell signaling pathways, apoptosis induction, or suppression of leukemic cell

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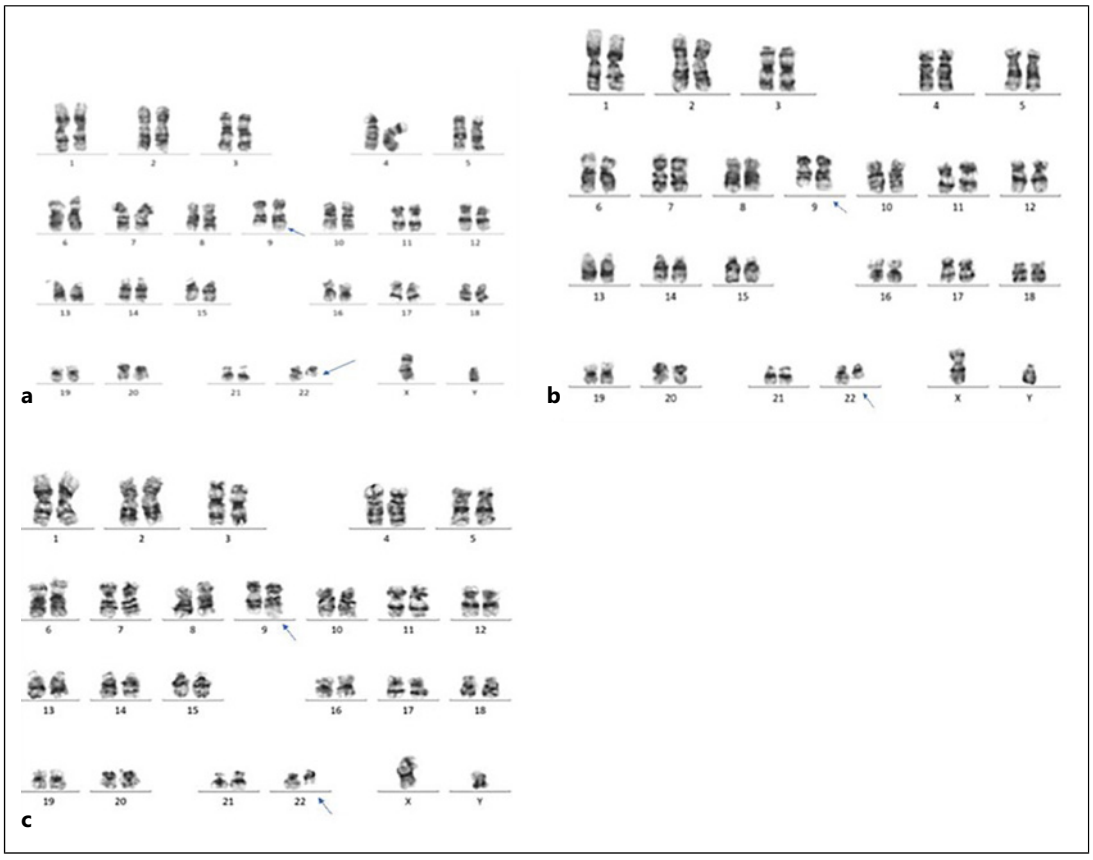

Fig. 2. a–c Cytogenetic analysis performed by G-banding revealed the presence of the classical *t*(9;22)(q34;q11), ABL, and BCR genes, which are the hallmark of the *t*(9;22) translocation in the diagnosis of CML patients.

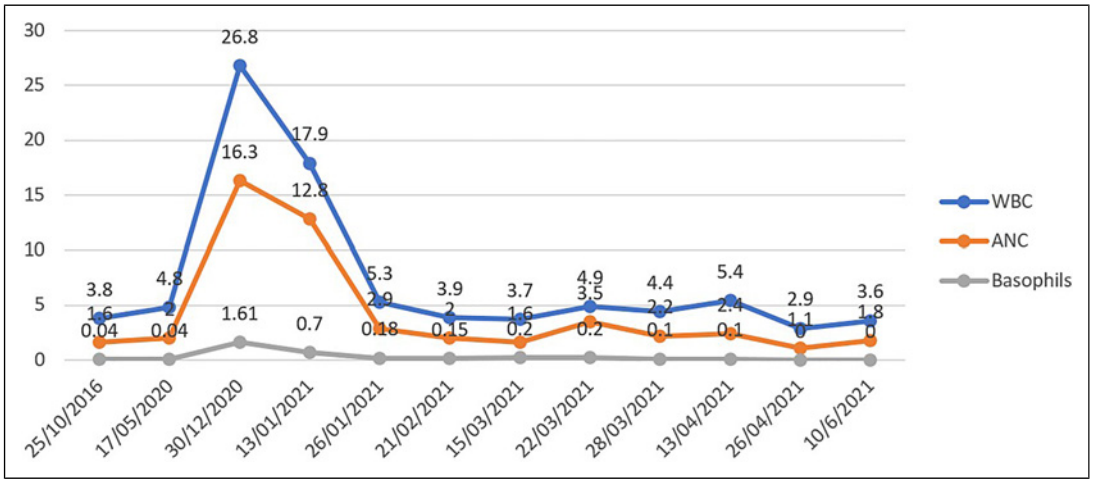

Fig. 3. CBC trends before and after diagnosis of CML.

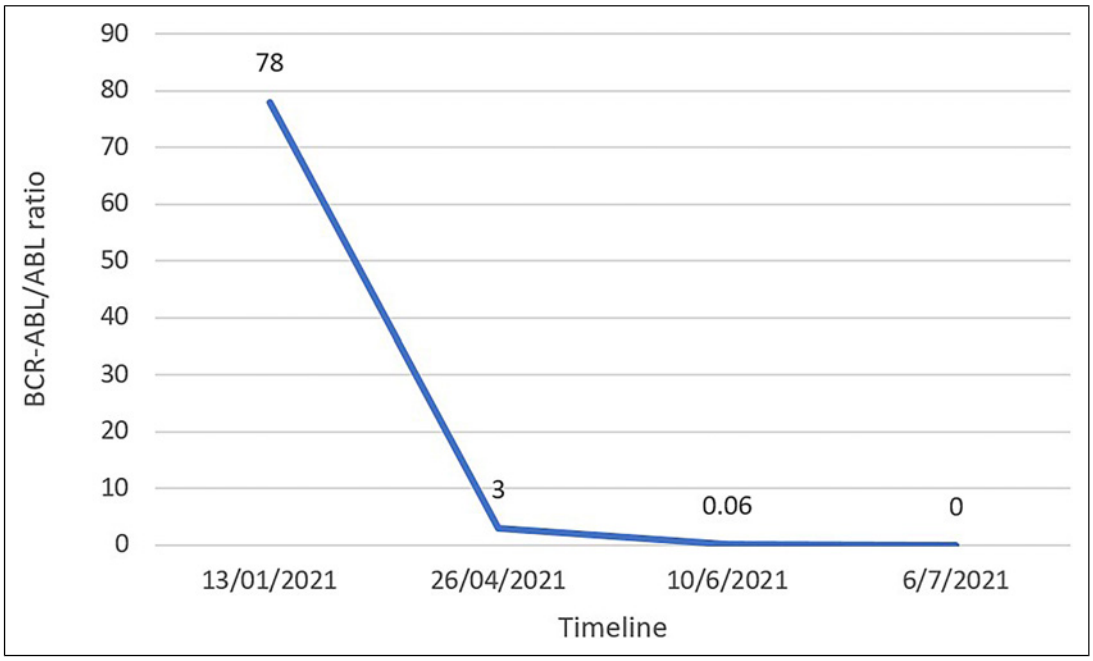

Fig. 4. *BCR::ABL1/ABL* ratio trends after diagnosis of CML.

growth may all contribute to resolving CML [16]. However, further research is needed to fully comprehend the mechanisms underlying spontaneous resolution of CML and leukemia in general.

Smadja et al. [9] reported the first case of Ph-positive CML with spontaneous hematological and chromosomal regression in a 27-year-old gentleman who tested positive for Ph chromosome in 100% of cells at diagnosis and then regressed to 37% after 8 years of follow-up without receiving any kind of cytotoxic therapy. Provan et al. [8] reported the first case of spontaneous complete remission of CML without receiving any treatment in a 71-year-old male patient who has spontaneous blood counts recovery, hepatosplenomegaly regression, and complete loss of Ph chromosome and restoration of normal karyotype which was confirmed by Southern blot analysis over 4 years of follow-up. Similarly, Musashi et al. [7] reported the second case of spontaneous complete remission in a CML patient who remained in remission over 11 years of follow-up by reverse-transcription PCR. The striking feature of the last two cases is the disappearance of Ph-positive cells from the marrow without any treatment.

In our case, the patient was incidentally found to have a leukocytosis with a *BCR::ABL1* to *ABL1* ratio of 78% detected by quantitative RT-PCR, but before starting TKI, the patient was noted to have spontaneous hematological and molecular regression which continued till complete molecular remission in 6 months and thereafter. To our knowledge, this is the third reported case of spontaneous complete resolution of CML in the literature overall and the first described case in the era of quantifications of *BCR::ABL1* by real-time quantitative PCR. The mechanism of spontaneous remission in our case, as in other reported cases, is unknown, and it remains one of the unanswered questions and the unmet needs in CML which requires further investigations [17].

In conclusion, the presence of spontaneous resolution in CML is a notable phenomenon that warrants attention. When encountered, a cautious approach is recommended. Particularly for individuals with low counts, close monitoring of clinical and laboratory parameters is crucial to confirm the stability of the remission. Regular follow-up visits and repeated testing over a few months should be conducted to ensure the sustained resolution. If the

patient remains stable, the frequency of visits can be gradually reduced. However, vigilant observation is necessary for any signs of disease progression, prompting timely treatment initiation if needed. Further research is required to fully understand and characterize this phenomenon.

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Statement of Ethics

The case was approved by Hamad Medical Corporation Medical Research center (MRC-04–22-589), and the patient signed a written informed consent to publish their case (including publication of images). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Author Contributions

Conception and design of the study and approval of the version of the manuscript to be published: Dr. A. Alshurafa and Dr. M. Yasin. Acquisition of data: Dr. A. Alshurafa, Dr. Ekeibed, Muna Al Zeyara, and Dr. Zafar Nawaz. Drafting the manuscript: Dr. A. Alshurafa, Dr. Ekeibed, Dr. Akiki, and Muna Al Zeyara. Revising the manuscript for intellectual content: Dr. A. Alshurafa, Dr. Akiki, Dr. M. Yasin, and Dr. Zafar Nawaz.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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