Chronic myeloid leukemia with the e13a3 atypical fusion gene: A case report

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Abstract. The present report aims to improve our systematic understanding of the clinicopathological characteristics of chronic myeloid leukemia (CML) associated with the e13a3 transcript and to offer insights into potential treatment options for this rare subtype of CML. This case presents a 39-year-old male patient of Chinese descent diagnosed with CML featuring an atypical fusion gene identified by the e13a3 transcript. The patient was treated with second-generation tyrosine kinase inhibitor. An analysis of BCR-ABL1 using reverse transcription PCR following 6 months of treatment revealed a negative BCR-ABL1 fusion, indicating deep molecular remission. After 2 years of treatment, the patient developed skin sclerosis. Overall, to prevent missed diagnoses and misdiagnoses, it is recommended that a comprehensive clinical evaluation be performed, and the underlying etiology be proactively identified.

Introduction

Chronic myeloid leukemia (CML) is classified as a tumor-related disease characterized by clonal expansion of hematopoietic stem cells from the bone marrow. The global incidence is 1-2 cases per 100,000 adults, representing 15% of newly diagnosed leukemia cases in adults (1). Notably, ~50% of patients with CML lack typical symptoms in the early stage and are often incidentally discovered through routine physical examinations or blood tests. Bone marrow biopsy is the gold standard for confirming hyperplasia of bone marrow cells and abnormal maturation of the myeloid cell line. Molecular diagnosis relies on the detection of the BCR-ABL1 fusion gene, which can be identified through the translocation of chromosomes t(9;22)(q34;q11) using fluorescence *in situ* hybridization (FISH) or quantitative PCR (2).

It is noteworthy that 5-10% of cases negative for the Philadelphia (Ph) chromosome require further verification of BCR-ABL1 mutations through next-generation sequencing (3). Over 95% of CML cases are linked to the Ph chromosome, whereas ~5% display variant Ph chromosomes characterized by complex translocations (4). These chromosomal rearrangements lead to the fusion of the 3' end of the ABL1 gene on chromosome 9 with the 5' end of the BCR gene on chromosome 22, resulting in the BCR-ABL1 fusion gene (5). For numerous years, traditional karyotyping has served as the primary diagnostic approach for identifying t(9;22)(q34;q11.2); however, this method possesses significant limitations, potentially leading to the oversight of BCR-ABL1 rearrangements in ~5% of patients with CML. Over 95% of CML cases exhibit BCR-ABL1 e13a2 or e14a2 fusion transcripts at the time of diagnosis. Approximately 1% of patients possess a breakpoint between exons 1 and 2 of the BCR gene, resulting in the production of the e1a2 transcript (6).

The prognosis of CML has significantly improved with the application of tyrosine kinase inhibitors (TKIs), with the 5-year survival rate increasing from 50 to >90% (7). However, ~9% of patients may progress to blast crisis or accelerated phase, leading to a sharp reduction in survival. Regular assessment of hematological, cytogenetic and molecular indicators is necessary to monitor treatment response (8). Therefore, individualized treatment and lifelong monitoring are crucial for optimizing the management of CML.

The current report presents a case of a patient with CML who tested negative for both reverse transcription (RT)-PCR and cytogenetic analysis during the initial diagnostic phase. Subsequent FISH revealed a concealed insertion of the ABL1 gene into the BCR gene on chromosome 22. The e13a3 BCR-ABL1 fusion transcript was subsequently validated via DNA sequencing employing alternative primer sets. The patient received a diagnosis of CML with the e13a3 atypical fusion gene and underwent treatment with nilotinib.

Case report

In September 2021, a 39-year-old male patient was referred to the Department of Hematology, (Shandong Provincial Hospital Affiliated to Shandong First Medical University,

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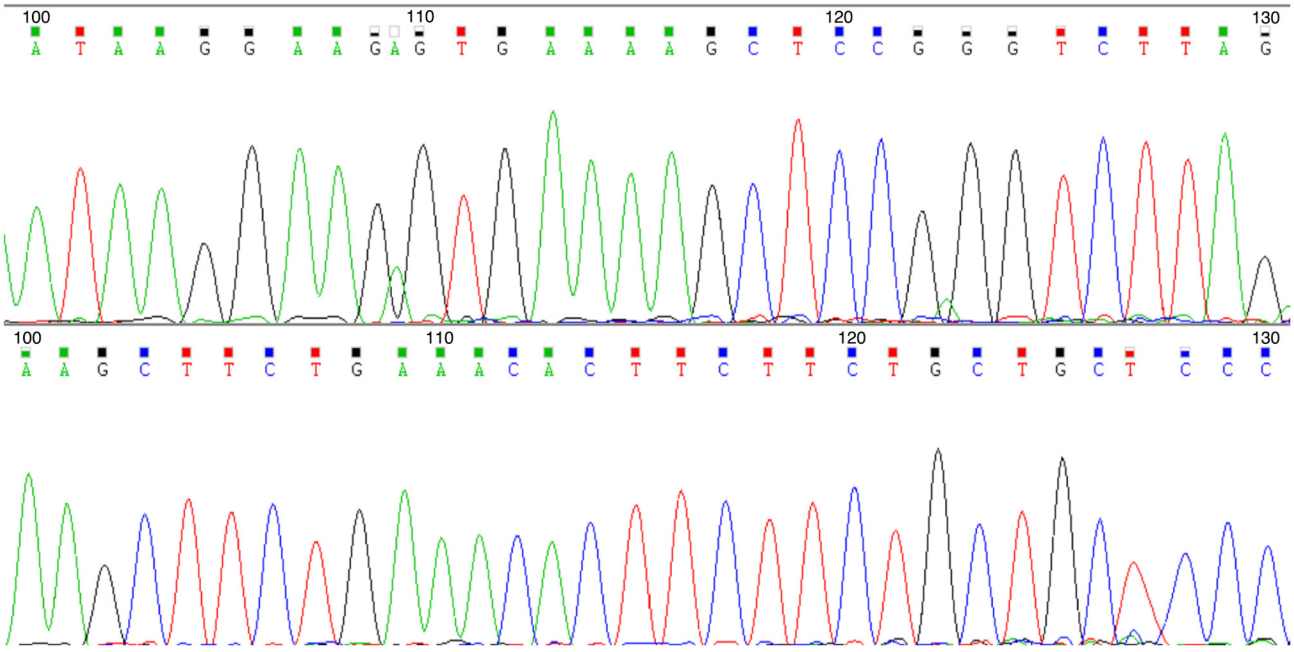

Figure 1. Electropherogram of Sanger sequencing for the BCR-ABL1 fusion gene. The chromatogram displays the nucleotide peaks corresponding to A (green), T (red), G (black) and C (blue). The sequence readout is shown above the peaks, with numbering indicating the position along the BCR-ABL1 transcript. A, adenine; T, thymine; G, guanine; C, cytosine.

Jinan, China) after abnormal blood parameters were identified during a routine health examination. The patient had exhibited splenomegaly for 3 years. A CT scan of the abdomen conducted upon admission verified the existence of splenomegaly. Laboratory analyses indicated a white blood cell count of 95.94x10^9/l (reference range,3.5-9.5x10^9/l), a hemoglobin concentration of 97 g/l (reference range, 130-175 g/l) and a platelet count of 929x10^9/l (reference range, 125-350x10^9/l). The absolute neutrophil count was 73.49x10^9/l (reference range, 1.8-6.3x10^9/l). Analysis of the peripheral blood smear revealed notable leukocytosis, comprising ~1% blasts (reference range,0-1%), 1% promyelocytes (reference range, 1.0-2.2%), 23% myelocytes and metamyelocytes (reference range, 4.5-8.5%), and 16% basophils (reference range, 0-0.5%). Platelets were often observed in a scattered arrangement. The analysis of the bone marrow smear indicated active hematopoietic proliferation, exhibiting a granulocyte-to-erythrocyte ratio of 11.19:1.00. Granulopoiesis was markedly heightened, characterized by an augmented ratio of neutrophilic myelocytes and metamyelocytes. Prominent nucleoli were identified in 74% of cells, a significant number of which displayed excessive granulation. The levels of eosinophils and basophils were elevated. The neutrophil alkaline phosphatase (NAP) score was 8 (The NAP activity test employs the Fast Blue B staining method. Under an oil immersion microscope, 100 mature neutrophils are observed, and cytoplasmic granules are scored from 0 to 4 based on staining intensity and density: 0 points, no granules; 1 point, <25% of cytoplasm lightly stained; 2 points, 25-50% moderately stained; 3 points, 50-75% deeply stained; 4 points: >75% densely and deeply stained; the individual scores are summed to yield a total score ranging from 0 to 400. The normal reference range is 30-130 points), indicating a significant likelihood of CML. Flow cytometry of the bone marrow demonstrated an increased percentage of granulocytes at early, intermediate, and late maturation stages. Myelocytes comprised 83.0% of nucleated cells and exhibited expression levels of CD33, CD64, CD13 and CD15, alongside partial expression of CD10, CD11b and CD16, indicative of the chronic phase of CML.

Molecular analysis (9) for the BCR-ABL1 fusion gene (p190/p210/p230) yielded negative results, as did tests for JAK2 V617F, CALR exon 9 and MPL exon 10 mutations. Subsequent analysis of atypical BCR-ABL1 fusion transcripts revealed a positive result for the e13a3 fusion variant. Chromosomal karyotype analysis verified the existence of t(9;22)(q34; q11.2). Following these findings, the patient received a diagnosis of chronic-phase CML (e13a3 type) (Fig. 1). To elucidate the characteristics of the fusion gene, RT-PCR was used to amplify the BCR/ABL e13a3 sequence. The amplified product was subjected to Sanger sequencing to confirm the precise breakpoint of the e13a3 fusion transcript. RNA was extracted from cells using the Lab-Aid 896 Blood Total RNA Kit (Xiamen Zeesan Biotech Co., Ltd.). RT was performed using the LF Enzyme 03 Reverse Transcription Kit (Xiamen Zeesan Biotech Co., Ltd.) under the following thermal conditions: 37˚C for 15 min (cDNA synthesis) and 85˚C for 5 sec (reverse transcriptase inactivation). The BCR:ABL1 fusion gene was amplified using the following five primers: ABL-3 reverse, CCATTGTGATTATAGCCTAAGACCCGGAG; BCR-1 forward, CTCCAGCGAGGAGGACTTCTCCT; BCR-6 forward, CCTGAGAGCCAGAAGCAACAAAGATGCC; BCR-12 forward, AGAACATCCGGGAGCAGCAGAAGAA; and BCR-19 forward, ACTGAAGGCAGCCTTCGACGTC.

The reaction was performed with the following thermal profile: Initial denaturation at 95˚C for 3 min, followed by 39 cycles of denaturation at 95˚C for 10 sec, annealing at 63˚C for 20 sec and extension at 72˚C for 30 sec, with a final extension at 72˚C for 5 min. The reaction was terminated by holding

at 4˚C. Amplified products were analyzed using agarose gel electrophoresis. The reaction system consisted of 1 μl each of forward and reverse primers, 3 μl of cDNA template, 10 μl of PCR Mix, and ddH2O to make up the total volume to 20 μl. After purification of the amplified products, sequencing reactions were performed using the BigDye Terminator v3.1 sequencing kit (Thermo Fisher Scientific, Inc.), and sequence analysis was ultimately completed with the 3130xl Genetic Analyzer (Thermo Fisher Scientific, Inc.). Treatment commenced with nilotinib at a dosage of 300 mg administered twice daily. After 6 months of consistent therapy, the atypical BCR-ABL1 fusion gene became undetectable, and the patient proceeded with regular monthly follow-up. At 2 years post-therapy initiation, the patient exhibited skin induration in the limbs, diagnosed as cutaneous amyloidosis, attributed to a drug-related adverse effect of nilotinib. The treatment with the TKI was sustained as the patient could endure the condition. The patient remains in profound molecular remission as of the last check-up inn June 2024.

Discussion

The BCR-ABL1 fusion gene serves as a critical molecular marker in CML, with the e13a2 (b2a2) and e14a2 (b3a2) transcripts representing >95% of all instances. Nonetheless, infrequent BCR-ABL1 transcripts, specifically e13a3 (b2a3) and e14a3 (b3a3), are observed in a minor fraction of patients, with an occurrence rate of 0.1-0.3% (10,11). In a substantial cohort study involving 2,331 patients with CML, only 4 cases (0.1%) exhibited e13a3 or e14a3 transcripts (12). Despite infrequency of occurrence, recent evidence indicates that the e13a3 transcript may impart distinct clinical and molecular attributes. The e13a3 transcript is produced by the direct fusion of exon e13 (b2) of the BCR gene with exon a3 of the ABL1 gene, resulting in the exclusion of exon a2 of ABL1 (13). This exon encodes the SH3 domain, which is essential for the negative regulation of BCR-ABL1 kinase activity, suggesting that the e13a3 transcript may modify BCR-ABL1-mediated signaling pathways (14). The absence of the SH3 domain may impact downstream signaling, including the STAT5 pathway, thereby affecting the proliferative characteristics of leukemic cells (15). However, the specific biological implications of this structural modification require additional examination.

In terms of clinical manifestations, patients possessing the e13a3 transcript may display unique characteristics. An increased basophil count at initial presentation has been documented in certain cases (16). Moreover, these patients typically exhibit a positive response to TKI, frequently attaining molecular responses more swiftly, with some achieving deep molecular remission (DMR) (17). In a study of 33 patients with CML with uncommon BCR-ABL1 transcripts, all 4 e13a3 cases attained a minimum 1-log reduction in BCR-ABL1 transcripts within 3 months, and 50% achieved undetectable transcript levels within 2 years (18).

At present, RT-PCR is the established molecular method for identifying prevalent CML-associated transcripts, chiefly e13a2 and e14a2. Nonetheless, the lack of the ABL1 a2 exon in e13a3 may result in conventional RT-PCR assays failing to detect this variant, thereby producing false-negative outcomes (12). A report indicated that a patient with CML initially tested negative for BCR-ABL1 via RT-PCR. However, FISH later identified BCR-ABL1 gene rearrangement, which was subsequently corroborated by Sanger sequencing that confirmed the presence of the e13a3 transcript (13). This highlights the inadequacy of depending exclusively on RT-PCR in these instances. FISH is an essential adjunctive diagnostic method for identifying BCR-ABL1 rearrangements in cases of negative RT-PCR results (16), whereas Sanger sequencing can accurately delineate the atypical transcript (17). Therefore, when CML is clinically suspected but RT-PCR results are negative, the incorporation of FISH and Sanger sequencing is advised to reduce the risk of misdiagnosis or overlooked diagnosis. In recent years, next-generation sequencing (NGS) has emerged as an alternative to traditional PCR, providing the ability to detect rare transcripts such as e13a3 and facilitating dynamic monitoring of molecular responses (18). Therefore, for patients possessing the e13a3 transcript, refining RT-PCR primer design to focus on the a3 exon, alongside FISH, Sanger sequencing and NGS, can significantly improve diagnostic sensitivity and specificity.

While data on e13a3 patients is scarce, current studies indicate that this transcript may affect TKI response, molecular remission rates and treatment-free remission (TFR) outcomes following TKI cessation (19). The specific BCR-ABL1 transcript variant influences the rate and magnitude of molecular responses elicited by TKIs. Patients with the e13a2 transcript demonstrate a protracted molecular remission and diminished optimal response rates at 12 months during imatinib therapy in contrast to those with e14a2 (11). The e13a3 transcript, which omits the ABL1 a2 exon, may similarly undermine the structural integrity of the BCR-ABL1 protein and its interaction with TKIs, potentially resulting in a protracted molecular remission compared to e13a2 or e14a2 instances. Second-generation TKIs (2G TKIs), such as nilotinib and dasatinib, typically elicit more profound and rapid molecular responses compared to imatinib. Patients with the e14a2 transcript attain molecular remission more swiftly under 2G TKI therapy compared with those with the e13a2 variant (19). Despite the limited clinical data on e13a3, its structural similarity to e13a2 implies that patients with e13a3 may exhibit inadequate responses to imatinib, rendering 2G TKIs a more suitable treatment option. The transcript type affects both the initial response to TKI and the long-term disease-free survival (DFS) and overall survival (OS). Patients with the e14a2 transcript exhibit elevated rates of attaining stable DMR and sustaining TFR following TKI cessation in comparison to those with e13a2 (11). The long-term prognostic implications of e13a3 remain ambiguous. However, its molecular characteristics and response patterns indicate that DFS and OS may resemble those of e13a2 patients, potentially exhibiting slower molecular remission and reduced TFR maintenance, while not significantly impacting OS (20).

Adverse events linked to TKI therapy are essential factors influencing long-term outcomes. Nilotinib is associated with an increased occurrence of cutaneous adverse reactions, including keratosis pilaris, which, while generally mild, may impact treatment adherence (20). In addition, certain patients may necessitate dose modifications or therapeutic transitions owing to TKI-associated toxicities, which could indirectly affect molecular remission and prognosis.

In CML, 1-2% of patients with CML possess atypical BCR-ABL1 transcripts, such as e13a3, e14a3, e1a2 and e19a2 (21). These uncommon transcripts influence diagnostic accuracy, treatment response, precision in minimal residual disease monitoring, and long-term prognosis (22). Standardized quantitative PCR assays predominantly focus on e13a2 and e14a2, which diminishes detection sensitivity for rare transcripts, potentially leading to an underestimation of relapse risk (23). A current therapeutic objective in CML management is to enable TFR after the successful cessation of TKI treatment. The viability of TFR in patients with atypical transcripts remains predominantly uncertain. Research indicates that e14a2 patients are more likely to sustain TFR than e13a2 patients; however, information regarding e13a3 cases is limited (11). Generally, patients with e14a2 typically show more pronounced DMR, resulting in elevated TFR success rates, while individuals with e13a2 or atypical transcripts generally experience suboptimal TFR maintenance (24). Considering the structural attributes of the e13a3 BCR-ABL1 fusion protein, there may be a diminished likelihood of maintaining TFR following the cessation of treatment (19). Patients contemplating TFR should undergo a meticulous evaluation of molecular response kinetics. Significantly, 2G TKIs may enhance the durability of treatment-free remission in comparison to imatinib. Nilotinib is associated with an increased probability of maintaining treatment-free remission after cessation, likely attributable to its capacity to elicit more rapid and significant molecular responses (19). Patients attaining Molecular Response (MR)4.5 (25) or more profound responses through prolonged nilotinib or dasatinib treatment may demonstrate improved TFR outcomes. Nonetheless, patients exhibiting atypical transcripts such as e1a2 have shown elevated rates of treatment discontinuation failure, indicating that TFR strategies may be inappropriate for this subgroup (26). In e13a3 patients, the early achievement of MR4 (BCR-ABL1/ABL1 $\leq$0.01%) or more profound responses may improve TFR success. However, additional research is required to validate this hypothesis. Future research should concentrate on clarifying remission patterns, determining optimal TKI regimens, and developing discontinuation strategies for e13a3 patients to refine treatment protocols, enhance quality of life and improve disease management (24).

The diagnosis and management of the present study's rare patient with e13a3 BCR-ABL1 CML highlights the complexities and strategic considerations involved in treating atypical transcript cases. The patient's diagnosis was initially overlooked by routine RT-PCR and was subsequently validated through Sanger sequencing. To enhance molecular diagnostics, RT-PCR protocols must be refined to identify atypical transcripts such as e13a3 and integrated with FISH and NGS to improve diagnostic sensitivity and specificity. The present patient attained complete cytogenetic remission within 6 months on a 2G TKI (nilotinib), indicating that e13a3 patients may exhibit favorable early responses to TKIs. The emergence of drug-related adverse events, such as skin sclerosis, underscores the necessity for rigorous safety monitoring during TKI therapy in patients with atypical BCR-ABL1 transcripts. Consequently, management must prioritize disease remission and proactive surveillance of treatment-related toxicities, facilitating personalized therapeutic modifications to enhance adherence and tolerance.

The transition of treatment objectives for CML from prolonged medication use to TFR renders the prognosis for achieving TFR in patients with atypical BCR-ABL1 transcripts markedly uncertain. This case illustrates that patients with e13a3 transcripts can attain rapid DMR during TKI therapy, indicating the viability of pursuing TFR with rigorous molecular surveillance. However, it is essential to underscore that the results of this single-case study possess inherent limitations regarding generalization. The emergence of drug-related adverse reactions, such as skin hardening, in this patient highlights the potential intricacies of safety profiles during prolonged TKI administration in atypical transcript carriers.

The present report offers clinical insights into TKI efficacy in e13a3 CML, yet the molecular mechanisms influencing signaling dynamics have not been fully elucidated. Structural analyses reveal that the e13a3 transcript truncates the SH3 domain of ABL1, which typically suppresses kinase activity via allosteric interactions with the SH1 domain (27). The lack of SH3 disrupts the SH3-SH2 complex, destabilizing the kinase's inactive conformation. The absence of SH3 residues critical for its inhibitory role (such as Tyr-89 and Tyr-134) leads to persistent kinase activation (12). This structural modification also hinders the binding of allosteric inhibitors such as asciminib to the myristoyl pocket, thereby facilitating resistance. Conversely, ATP-competitive TKIs retain efficacy as their interaction with the active kinase conformation remains unaltered (28). Kinase assays and molecular dynamics simulations elucidate that SH3 truncation affects the spatial configuration of the ATP-binding cleft and modifies the allosteric signaling network (26), accounting for the varied TKI resistance profiles in BCR-ABL1 leukemogenesis.

The present single-case report lacks the statistical power to establish definitive clinical correlations, and the observed outcomes may not represent the wider population of patients with atypical transcripts. Consequently, clinical management should implement a dual-faceted strategy: Pursuing molecular responses via personalized TKI regimens while remaining alert to the onset of treatment-related toxicities, thereby facilitating prompt dose adjustments or therapeutic shifts to enhance adherence and efficacy. In summary, the long-term management of patients with e13a3 BCR-ABL1 CML requires the incorporation of accurate molecular diagnostics, customized therapeutic approaches and vigilant monitoring for adverse events. Future multicenter collaborative studies and systematic reviews that consolidate data from analogous rare cases are essential to substantiate these preliminary findings and to formulate evidence-based clinical guidelines. Until such data are accessible, clinicians should regard the current findings as hypothesis-generating and exercise prudence when extrapolating these results to other instances involving atypical transcripts.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XZ and NS confirm the authenticity of all the raw data. XZ designed the study. ML performed the acquisition, analysis and interpretation of data. NS performed the analysis and interpretation of data, and contributed to manuscript drafting and critical revisions of the intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication, authorizing the use of their imaging, pathological and clinical data for publication.

Competing interests

The authors declare that they have no competing interests.

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