Concomitant T315I and E459K mutations in chronic myeloid leukemia: A case report

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Abstract. The present report aims to improve the understanding of the clinicopathological features of chronic myeloid leukemia (CML) harboring concomitant T315I and E459K mutations. CML with the T315I mutation alone and in combination with other mutations has demonstrated sensitivity to olverembatinib, a third-generation tyrosine kinase inhibitor, providing valuable insights into potential treatment strategies for this rare mutational profile. In the present study, a 57-year-old woman with a 7-year history of CML relapsed 1 year after stopping imatinib treatment. The patient presented with right arm pain and bone lesions confirmed by imaging. Laboratory tests and bone marrow analysis confirmed CML in the chronic phase, and the patient initially responded well to dasatinib. After 5 months, severe pancytopenia developed. Next-generation sequencing (NGS) revealed concomitant T315I and E459K mutations in the breakpoint cluster region-Abelson tyrosine kinase 1 tyrosine kinase domain, as well as an ASXL transcriptional regulator 1 mutation, indicating progression to the blast phase. Treatment was switched to olverembatinib, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) was recommended. Overall, patients with multiple mutations in CML tend to have a worse prognosis due to treatment resistance and disease progression. NGS is crucial for detecting low-frequency mutations and allo-HSCT also serves a key role in treating high-risk cases.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm driven by the Philadelphia chromosome, resulting from a reciprocal translocation between chromosomes 9 and 22, and forming the breakpoint cluster region (BCR)-Abelson tyrosine kinase 1 (ABL1) fusion gene (1). This fusion gene encodes constitutively active tyrosine kinases, making it a key therapeutic target for inhibitors such as imatinib, which is used as frontline therapy. However, mutations in the BCR-ABL1 tyrosine kinase domain (TKD) cause imatinib resistance in the majority of patients with CML and remain a notable challenge (2,3). The global incidence of CML is 1-2 cases per 100,000 adults, representing 15% of newly diagnosed leukemia cases in adults (4). 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 or quantitative PCR (qPCR) (5). Identifying novel or concomitant mutations that contribute to resistance is critical for optimizing therapeutic strategies and improving patient outcomes. The threonine-to-isoleucine substitution at position 315 (T315I) is responsible for ~20% of clinical resistance cases in imatinib-naïve patients with CML (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).The glutamic acid-to-lysine substitution at position 459 (E459K) has been described in a limited number of CML cases (9,10), and its role in disease progression and resistance to TKIs remains poorly understood. The present report describes a patient with CML harboring both T315I and E459K mutations.

Case report

In June 2024, a 57-year-old woman presented to the Department of Orthopedic Oncology with a history of right upper arm pain and restricted mobility of the right shoulder joint lasting >4 months. The patient had a 7-year history of CML and had achieved complete molecular remission after 6 years of regular imatinib therapy. However, the patient had discontinued treatment and follow-up 1 year prior to the current admission. Upon admission, laboratory examination revealed a white blood cell count of $44.70x10^9$/l, a hemoglobin level of 105 g/l and a platelet count of $1,195x10^9$/l (Table I). Bone marrow aspiration confirmed CML in the chronic phase, with BCR-ABL1 p210 positivity and no detectable TKD mutations.

Imaging studies indicated malignancy in the right humerus, with computed tomography revealing bone destruction in the upper to mid humerus and localized lytic lesions in the scapula. Magnetic resonance imaging (MRI) demonstrated proximal humerus cortical disruption, heterogeneous signal intensities and surrounding soft-tissue masses with mixed high and low fat-suppressed T2-weighted imaging signals, consistent with a malignant process (Fig. 1A and B). The patient was started on dasatinib (100 mg once daily), with recommendations for regular blood count monitoring and surgical intervention after disease control. After 1 month of treatment, the patient achieved complete hematological remission, with notable improvement in arm pain. However, a biopsy was not performed during this period.

The patient continued dasatinib therapy but presented to the hospital again in November 2024, with fatigue and petechiae on the lower limbs. Laboratory evaluations revealed severe pancytopenia, with a hemoglobin level of 60 g/l, a white blood cell count of $1.55x10^9$/l and a platelet count of $11.00x10^9$/l (Table II).

Dasatinib was discontinued, and the patient subsequently received a transfusion of 2 units of leukocyte-depleted red blood cells and 1 therapeutic dose of platelets. Cytological examination of the bone marrow smear demonstrated notable hypoplasia and dilution (Fig. 2). Smears were stained with Wright-Giemsa stain for 15-20 min at room temperature (18-25˚C), followed by rinsing and air-drying. Morphological analysis was performed under an Olympus BX53 optical microscope equipped with 100X oil immersion objectives, with digital image acquisition and cell quantification conducted using Motic DS Assistant v2.0 software (Motic China Group Co., Ltd.), revealing a granulocyte-to-erythroid ratio of 6.57:1. Both granulocytic and erythroid lineages exhibited pronounced hypoplasia. Erythroid precursors were primarily at intermediate and late maturation stages, while mature erythrocytes displayed marked anisopoikilocytosis, including occasional elliptocytes and tear-drop-shaped cells. Lymphocytes constituted 70.5% of nucleated cells. No megakaryocytes were identified, and only a few scattered platelets were observed.

RNA was extracted from bone marrow or peripheral blood using the nucleic acid extraction reagent from the Lab-Aid 896 Blood Total RNA Kit (Xiamen Zhixuan Biotech Co., Ltd.). The extracted RNA was reverse transcribed to obtain cDNA using the LF Enzyme 03 Reverse Transcription Kit (Xiamen Zhixuan Biotech Co., Ltd.). The reverse transcription temperature protocol was as follows: 37˚C for 15 min (cDNA synthesis), followed by 85˚C for 5 sec (inactivation of reverse transcriptase). The BCR-ABL1 fusion type of the patient was subsequently determined. The first round of amplification in the semi-nested PCR was performed using the corresponding upstream and downstream primers for the fusion type, with cDNA as the template. The amplification conditions were as follows: 95˚C for 5 min; 95˚C for 40 sec, 61˚C for 1 min, 72˚C for 2 min, for 30 cycles; 72˚C for 7 min and hold at 12˚C. The amplification reagent used was from the Phanta Max Super-Fidelity DNA Polymerase Kit (Vazyme Biotech Co., Ltd.). The first-round amplification primers were as follows: Type 210 upstream, ABL1-A 5'-GAAGCTTCTCCCTGACAT CCGT-3' (the ABL1-A primer was located on exon 13 of the BCR gene); type 190 upstream, 190-1F 5'-ACCGCATGTTCC GGGACAAAAG-3' (the 190-1F primer is positioned on exon 1 of the BCR gene); universal downstream, ABL1-R 5'-TCC ACTTCGTCTGAGATACTGGATT-3'.

The second round of amplification in the semi-nested PCR was performed using the first-round amplification product as the template. The amplification conditions were as follows: 95˚C for 5 min; 95˚C for 40 sec, 62˚C for 1 min, 72˚C for 1.5 min, for 30 cycles; 72˚C for 7 min and hold at 12˚C. The amplification reagent used was the Phanta Max Super-Fidelity DNA Polymerase Kit. The second-round amplification primers were as follows: ABL1-C, 5'-GCGCAACAAGCCCACTGT CTATGG-3'; ABL1-R, 5'-TCCACTTCGTCTGAGATACTG GATT-3'.

Bidirectional Sanger sequencing (Fig. 3) was performed using the second-round amplification primers on the second-round products, and the mutations in the sequencing results were analyzed. The sequencing primers were as follows: ABL1-C, 5'-GCGCAACAAGCCCACTGTCTATGG-3'; ABL1-R, 5'-TCCACTTCGTCTGAGATACTGGATT-3'.

Quantitative analysis of BCR-ABL1 transcripts revealed a high disease burden (95.8877%). The high disease burden was calculated based on qPCR (qPCR) analysis (FAM/BHQ1; DAAN GENE BCR-ABL1 Quantitative Detection Kit, DAAN GENE Co., Ltd. of Sun Yat-sen University) of BCR-ABL1 transcript levels normalized to the reference gene ABL1 the relative quantification was performed using the comparative Cq method ($2^{-\Delta\Delta Cq}$ method) (11,12), using the formula: BCR-ABL1%=(BCR-ABL1 transcript copies/ABL1 transcript copies) x100. For the patient, the ratio far exceeded the National Comprehensive Cancer Network (NCCN) guideline threshold (>10% on the International Scale) for high disease burden (13). However, no specific mutations were detected, possibly as the patient had not yet progressed to a stage involving kinase domain mutations or due to the limited sensitivity of Sanger sequencing.

Subsequent next-generation sequencing (NGS) detected mutations in the ASXL transcriptional regulator 1 (ASXL1) gene, along with ABL1 TKD mutations, specifically T315I and E459K (Fig. 4A-C). The variant allele frequencies (VAFs) for the T315I and E459K mutations were 35 and 22%, respectively, while the ASXL1 mutation exhibited a VAF of 18%. These alterations were not detectable using conventional techniques, such as Sanger sequencing and qPCR. The NGS procedure was performed as follows: Genomic DNA was isolated from peripheral blood using the Blood

Table I. Laboratory results in June 2024.

Laboratory results	Value (reference range)
White blood cell count, n x10^9/l	44.7 (4.0-10.0)
Red blood cell count, n x10^{12}/l	3.83 (4.1-5.2)
Hemoglobin, g/l	105 (115-150)
Hematocrit, %	32.60 (36-44)
Platelet count, n x10^9/l	1,195 (150-400)
Lymphocyte absolute count, n x10^9/l	3.17 (1.0-3.0)
Monocyte absolute count, n x10^9/l	1.16 (0.2-1.0)
Neutrophil absolute count, n x10^9/l	28.89 (2.0-7.0)
Aspartate aminotransferase, U/l	13 (10-40)
Alkaline phosphatase, U/l	129 (30-120)
RDW-coefficient of variation, %	16.10 (11.5-14.5)
RDW-standard deviation, fl	51 (39-46)
Mean platelet volume, fl	8.50 (7.5-11.5)
Platelet-large cell ratio, fl	18.10 (13-43)
Glucose, mmol/l	13.27 (3.9-6.1)
Lactate dehydrogenase, U/l	576.10 (125-220)

RDW, red cell distribution width.

Table II. Laboratory results in November 2024.

Laboratory results	Value (reference range)
White blood cell count, n x10^9/l	1.55l (4.0-10.0)
Red blood cell count, n x10^{12}/l	2.02 (4.1-5.2)
Hemoglobin, g/l	60 (115-150)
Hematocrit, %	18.40% (36-44%)
Platelet count, n x10^9/l	11.00 (150-400)
Lymphocyte absolute count, n x10^9/l	0.71 (1.0-3.0)
Monocyte absolute count, n x10^9/l	0.09 (0.2-1.0)
Neutrophil absolute count, n x10^9/l	0.73 (2.0-7.0)
Aspartate aminotransferase, U/l	8 (10-40)
Alkaline phosphatase, U/l	148 (30-120)
RDW-coefficient of variation, %	19.40 (11.5-14.5)
RDW-standard deviation, fl	62.40 (39-46)
Mean platelet volume, fl	7.20 (7.5-11.5)
Platelet-large cell ratio, fl	7.70 (13-43)
Glucose, mmol/l	7.33 (3.9-6.1)
Lactate dehydrogenase, U/l	278.40 (125-220)

RDW, red cell distribution width.

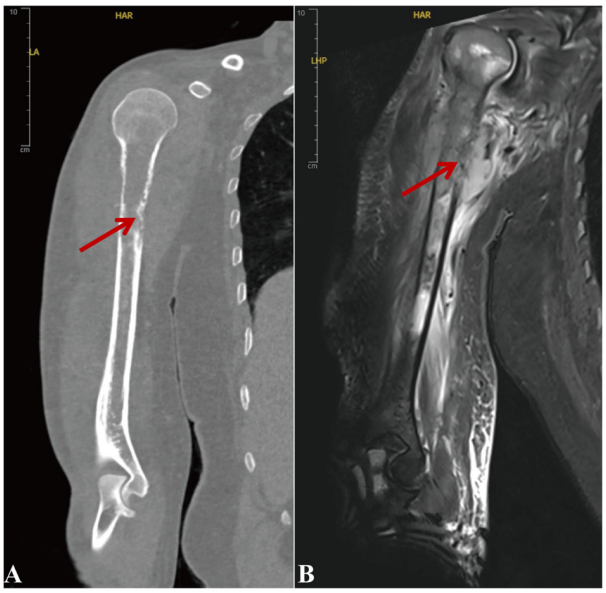

Figure 1. Imaging findings of the right humerus. (A) Computed tomography showing bone destruction in the upper to mid humerus and localized lytic lesions in the scapula. (B) Magnetic resonance imaging revealing cortical disruption, heterogeneous signal intensities and surrounding soft-tissue masses with mixed high and low fat-suppressed T2-weighted imaging signals, consistent with malignancy. The arrows indicate the lytic bone lesion

Genomic DNA Extraction Kit (Tiangen Biotech Co., Ltd.), following the manufacturer's protocol. Purity was assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Inc.), and DNA concentration was measured with a Qubit Fluorometer (Thermo Fisher Scientific). Subsequently, DNA libraries were prepared using the Watchmaker DNA Library Prep Kit with Fragmentation (cat. no. WM-503; Watchmaker Genomics). The constructed libraries underwent quantification by Qubit Fluorometry and quality assessment using a Fragment Analyzer (Hangzhou Houze Biotechnology Co., Ltd.). The libraries were then lyophilized into dry powder using a vacuum centrifugal concentrator (Ningbo Scientz Biotechnology Co., Ltd.). Hybridization capture was performed utilizing panel probes and NadPrep Hybrid Capture Reagents [Nanoda (Nanjing) Biotechnology Co., Ltd.]. After elution, library enrichment was achieved through PCR amplification using a thermal cycler (Thermo Fisher Scientific, Inc.). The enriched libraries underwent a second round of quantification and quality control using the Qubit Fluorometer and Fragment Analyzer, respectively. The final library yield was 766 ng, with an average fragment size of ~480 bp. Quantified by Qubit fluorometry at ~15.32 ng/μl, the final library concentration was determined to be 48.36 nmol/l (48.36 nM). Final sequencing was performed on the Salus Pro platform (Salus BioMed) at a depth of 500x, NGS was performed using 150 bp paired-end sequencing with the following components: Salus Pro Sequencing Reagent Kit (SRM-PE150-250M; includes sequencing reagent cartridge, dilution buffer, denaturation buffer, neutralization buffer and hybridization buffer) and Salus Pro Sequencing Chip (PRM-PE-250M), supplied by Shenzhen Salus Medical Technology Co., Ltd.; and the open-source bioinformatics software bcl2fastq (v2.20.0.422; https://support.illumina.com/downloads/bcl2fastq-conversion-software-v2-20.html),fastp(0.20.1; https://github.com/OpenGene/fastp), BWA (0.7.8-r455; https://github.com/lh3/bwa), sambamba (v0.4.7; https://github.com/biod/sambamba/releases/tag/v0.4.7), VarDict (1.8.2-2; https://github.com/AstraZeneca-NGS/VarDict) and ANNOVAR (20211012; https://annovar.openbioinformatics.org/en/latest/), ensuring high reliability of the results.

Following these findings, the therapeutic regimen was adjusted to olverembatinib (40 mg, administered every other

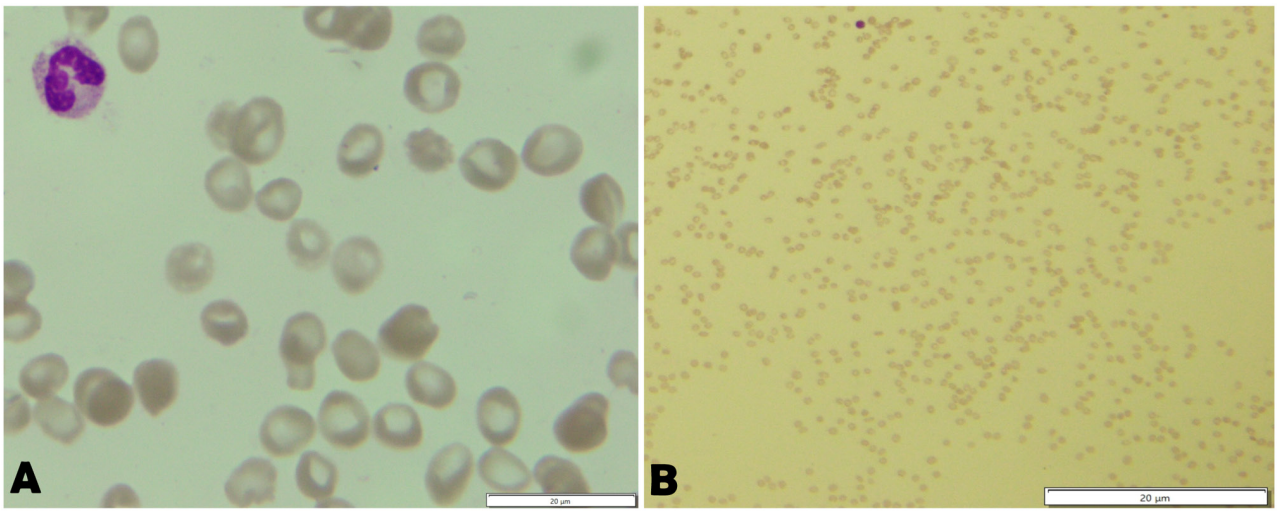

Figure 2. Bone marrow imaging. Severely decreased proliferative bone marrow images, taken using an optical microscope at (A) x100 and (B) x10 magnification. Both granulocytic and erythroid lineages exhibited pronounced hypoplasia. Erythroid precursors were primarily at intermediate and late maturation stages, while mature erythrocytes displayed marked anisopoikilocytosis, including occasional elliptocytes and tear-drop-shaped cells. No megakaryocytes were identified.

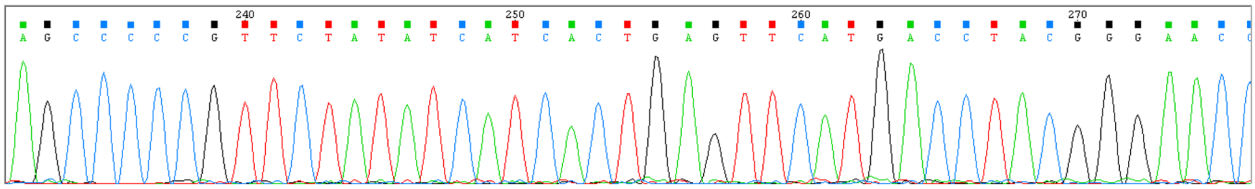

Figure 3. DNA sequencing electropherogram showing the sequence from nucleotide positions 240 to 270. Black G represents the guanine base; red T represents the thymine base; blue C represents the cytosine base; green A represents the adenine base. The sequence of letters at the top represents the corresponding DNA base sequence. The waveform graph below shows the peaks for different bases during the electrophoresis process, with the height of the peaks reflecting the concentration of that base at that position.

day), and allogeneic hematopoietic stem cell transplantation (allo-HSCT) was proposed as the subsequent step in disease management. The use of both dasatinib and olverembatinib adheres to the NCCN International Guidelines for CML (14). The patient had their last check-up in March 2025 and is currently preparing funds for the transplant.

Discussion

The present case underscores the notable clinical challenges in managing CML complicated by the rare coexistence of T315I and E459K mutations, along with an ASXL1 mutation, which is strongly associated with disease progression, TKI resistance and a poor prognosis. The T315I mutation, often referred to as the 'gatekeeper mutation,' involves the substitution of threonine with isoleucine at position 315, leading to the loss of a critical hydrogen bond and causing steric hindrance at the ATP-binding site; it is also among the most prevalent mutations in CML, notably identified in a study of 386 patients who had progressed to the blastic phase (15). The management of this mutation remains a major therapeutic challenge, as it confers resistance to first-line therapy with imatinib and to second-generation TKIs, including dasatinib and nilotinib (16).

The reported prevalence of the T315I mutation varies across studies and populations. For instance, it was observed in 21.6% of non-responders in CML cohorts from India (17) and Pakistan (18), in 11.8% in a Western study (19) and in as high as 43.4% in a study performed by Elsir Khair *et al* (20). In Chinese CML cohorts, the mutation rate of T315I is ~5.3% (21), with markedly higher detection rates among drug-resistant patients (22). These findings highlight the regional and cohort-specific variability in T315I prevalence, emphasizing its critical role as a major resistance mechanism in CML.

Moreover, multiple studies have consistently demonstrated that patients harboring the T315I mutation experience notably worse clinical outcomes compared with those with other mutations or alternative mechanisms of imatinib resistance (23). For example, a study from Pakistan reported that 77.3% (17/22) of T315I-positive patients showed disease progression, with 58% advancing to the blastic phase (18). Additionally, the study noted that patients in the blastic phase were 0.24 times more likely to develop the mutation compared with those in the chronic or accelerated phases. Similarly, a study involving 176 patients with CML demonstrated that individuals with the T315I mutation in the blastic phase had the worst survival outcomes, with a mean survival time of only 4 months compared with 22.4 months for patients in the chronic phase (24).

The E459K mutation in CML, unlike the well-characterized T315I mutation, is rarely reported and remains poorly

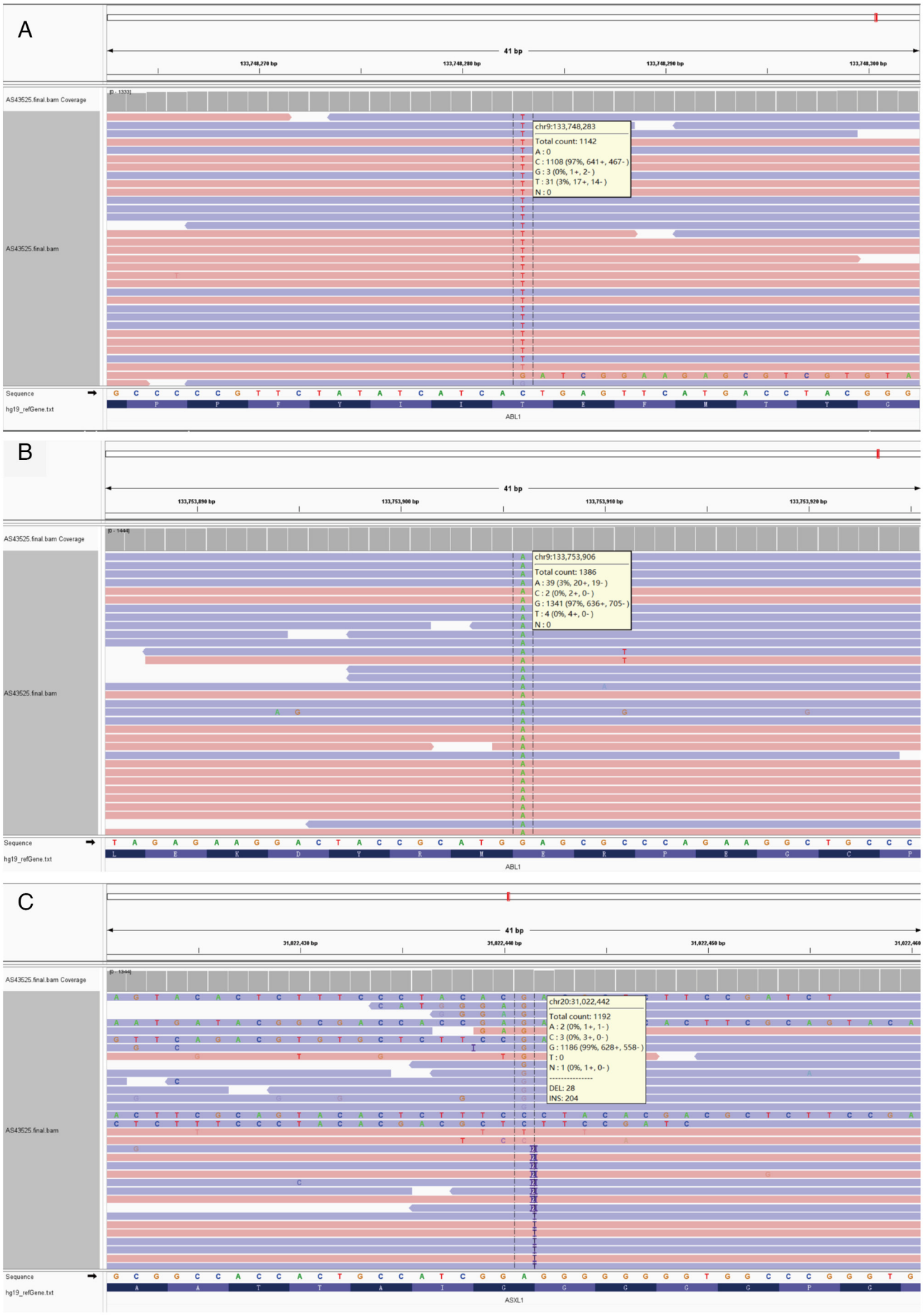

Figure 4. Next-generation sequencing results. (A) T315I mutation in the ABL1 kinase domain. (B) E459K mutation in the ABL1 kinase domain. (C) Mutation in ASXL. ABL1, Abelson tyrosine kinase 1; ASXL, ASXL transcriptional regulator 1 gene.

Table III. Drug sensitivity and resistance profiles for different mutations.

TKI drugs and mutation types	Sensitivity	Response rate	Mechanism	(Refs.)
Ponatinib				
T315I	Sensitive	60.0%	Binds to the inactive conformation of the BCR-ABL1	(30)
E459K	Sensitive	43.0%	Binds to the inactive conformation of the BCR-ABL1	(13)
Asciminib				
T315I	Sensitive	67%	Allosterically binds the myristoyl site of BCR-ABL1	(31)
E459K	Sensitive	Increasing the dose can achieve a complete response	Binds the myristoyl pocket of ABL1	(29)
Olverembatinib				
T315I	Sensitive	85.3%	Targets the ATP binding site of BCR-ABL1 tyrosine kinase	(32)
T315I + E459K	Sensitive	33%	Unreported	(32)

TKI, tyrosine kinase inhibitor; BCR, breakpoint cluster region; ABL1, Abelson tyrosine kinase 1.

understood. Previous studies have associated E459K with resistance to dasatinib following imatinib failure (25,26), a finding further supported by the present case. However, its clinical relevance, role in disease progression and contribution to TKI resistance are still underexplored. Using NGS, both a Malaysian cohort study and research performed in a Chinese population identified the rare E459K mutation in the BCR-ABL1 TKD (9,27).

E459K mutations have been recognized as emerging in response to first-generation TKI therapies, such as imatinib, in patients with CML. Molecular modeling suggests that the E459K substitution within the α-helix near the TKD replaces a negatively charged glutamic acid with a positively charged lysine, thereby disrupting salt bridges and hydrogen bonds with residues such as R460 and E528. This alteration notably impairs imatinib binding, which depends on interaction with the inactive kinase conformation (10). Although bosutinib and nilotinib, which rely less on the inactive state, initially inhibit the E459K mutation effectively, their efficacy diminishes over time as compound mutations (28), such as the coexistence of T315I and E459K, emerge with enhanced transforming potential. The presence of E459K exacerbates T315I-induced conformational changes, increasing steric hindrance at the ATP-binding pocket and further reducing drug affinity, thereby complicating therapeutic strategies (29).

Moreover, during treatment, the E459K mutation often undergoes clonal selection, leading to clonal dominance in some patients, an event closely associated with loss of response and treatment failure (30). In current research on the compound mutations T315I and E459K, the sensitivity rates of ponatinib for T315I and E459K mutations are 60 and 43%, respectively. The relevant mechanisms may be associated with the binding of the drug to the inactive conformation of BCR-ABL1. Asciminib also shows high sensitivity. Olverembatinib, by targeting the ATP-binding site of the BCR-ABL1 tyrosine kinase, has a sensitivity rate as high as 85.3% in patients with T315I mutation. In patients with the compound mutation of T315I and E459K, orelabrutinib is also effective, with a sensitivity rate of 33%, but the specific mechanism has not been elucidated. The relevant studies (14,31-33) are summarized in Table III.

Mutations in the ASXL1 gene predominantly occur in exon 12, typically presenting as frameshift or nonsense mutations (34), and are frequently detected in acute myeloid leukemia. ASXL1 mutations have also been identified and extensively investigated in CML cases (35-38). Furthermore, patients harboring ASXL1 mutations have been reported to have markedly shorter overall survival compared with those without such mutations (39-43).

Preclinical studies have demonstrated that ASXL1 mutations are associated with poor responses to chemotherapy (44). Additionally, these mutations are associated with genomic instability and an increased risk of progression to the blast phase in CML (36). Multivariate analysis revealed that ASXL1 mutation was the sole independent risk factor associated with inferior event-free survival, with a hazard ratio of 4.25 (95% CI, 1.59-11.35) (45). In the present case, ASXL1 mutations were detected using NGS, suggesting disease progression toward the blastic phase.

The BCR-ABL1 TKD mutation status serves a critical role in guiding clinical decision-making for patients with CML exhibiting suboptimal responses to TKIs. The failure to perform conventional cytogenetics may have missed rare additional chromosomal abnormalities in the present case. However, recent advancements in NGS-based technologies have enabled the sensitive detection and quantitative monitoring of BCR-ABL1 TKD mutations. These methods can identify and quantify sequence variations in BCR-ABL1 transcripts at abundances as low as 1%, while also providing insights into the clonal architecture in cases with multiple mutations (46,47). In the present case, NGS revealed the coexistence of T315I and E459K mutations, along with an ASXL1 mutation, which were not detected by conventional methods during earlier evaluations. The application of NGS was crucial in identifying these low-frequency mutations that traditional assays might have missed. However, the clinical

implementation of NGS for BCR-ABL1 TKD mutation testing faces several challenges. High costs, limited accessibility and the lack of standardized guidelines have impeded its widespread adoption. Moreover, although evidence supporting NGS-based BCR-ABL1 mutation testing in treatment-resistant patients with CML is growing, it has not yet been incorporated into formal clinical recommendations.

Although the present imaging findings and clinical course suggest extramedullary leukemic infiltration, definitive pathological confirmation is essential to establish the diagnosis of blast-phase CML with extramedullary disease, which may have influenced the accuracy of diagnosis and subsequent treatment decisions. In the present case, using MRI, a large soft-tissue mass was observed encasing the affected bone, combined with cortical disruption and bone destruction, likely indicating leukemic cell infiltration. The soft tissue encasement of bone is consistent with previous reports of myeloid sarcoma in CML (48). These imaging findings are associated with the patient's persistent arm pain and elevated BCR-ABL1 transcript levels.

The patient's history of CML, the presence of a lesion in the right scapula, the alleviation of pain following TKI therapy and the subsequent detection of an ASXL1 mutation collectively suggest that the right scapular lesion represented an extramedullary manifestation of CML. This extramedullary involvement is considered to be associated with disease progression to the blast phase, specifically acute myeloid transformation, which carries a worse prognosis. This clinical context partially compensates for the absence of a biopsy-confirmed diagnosis.

Nevertheless, the lack of timely pathological confirmation remains a limitation. A biopsy could have clarified the disease stage, guided more aggressive treatment strategies and facilitated earlier initiation of the transplant process. Additionally, if the bone lesion had been pathologically confirmed as CML-related, the timing of initiating olverembatinib treatment might have been altered. The uncertainty surrounding the lesion's nature limited diagnostic clarity, potentially delaying the development of a more personalized and comprehensive treatment plan.

The U.S. Food and Drug Administration (FDA) and NCCN guidelines indicate that patients with the T315I mutation in CML exhibit high resistance to imatinib, dasatinib, nilotinib and bosutinib (49). Therefore, ponatinib is recommended as a treatment option for these patients. According to the NCCN guidelines (V1, 2023), ponatinib demonstrates a 43% efficacy rate in patients with the E459K mutation. Olverembatinib exhibits high specificity for the T315I mutation, with efficacy comparable to ponatinib, but a higher rate of response in patients with the single T315I mutation (33). Among patients treated with olverembatinib, the incidence of grade ≥3 thrombocytopenia is markedly lower compared with that in patients treated with ponatinib and is not notably associated with dose adjustment (50). However, in cases involving compound mutations (T315I + E459K), monotherapy with ponatinib may be insufficient to fully suppress the expansion of resistant clones. The compound mutation is relatively rare, and a previous related study reported two cases of patients with the same compound mutation (33). Patient 1 received 30 mg oral olverembatinib every other day and achieved a major molecular response (MMR) after 3 months. However, the patient voluntarily withdrew from the study at 4 months due to concurrent breast cancer, with no disease progression observed at withdrawal, and remained in MMR. Patient 2 received 50 mg oral olverembatinib every other day and achieved 4.5-log molecular response after 3 months but progressed to blast phase and died at 13 months. Initially, the present case differed from the literature reports, as no specific mutation was detected at the beginning, and when the patient developed resistance to first-generation drugs, treatment was switched to dasatinib. After confirming the occurrence of compound mutations, olverembatinib treatment was immediately initiated, which is in line with the methods recommended in the literature. Furthermore, although the present patient also progressed to the accelerated phase (similar to patient 2), they retained eligibility for transplantation, which is a critical distinction. While prior case reports focused primarily on treatment regimens and outcomes, the present study emphasizes imaging-driven diagnostic insights and a systematic discussion of therapeutic options, offering pivotal guidance for clinical decision-making.

Current literature evidence lacks clear guideline recommendations for patients with the T315I + E459K compound mutation. Some studies have reported that ponatinib or asciminib treatment may be attempted (51,52). Dual targeting with ponatinib and asciminib may overcome compound mutations and achieve improved therapeutic effects by simultaneously inhibiting the ATP and myristoyl-binding sites (53). In CML, overexpression of BCL-2 is closely associated with TKI resistance. APG-2575, a selective BCL-2 inhibitor, restores the apoptotic capacity of tumor cells by targeting the anti-apoptotic protein BCL-2. Preclinical studies demonstrate that APG-2575 enhances $CD8^+$ T cell-mediated antitumor immune responses through activation of the NLRP3 signaling pathway (54). A study on ponatinib-resistant patients with CML revealed that the combination of ponatinib and the BCL-2 inhibitor ABT-263 markedly increased apoptosis sensitivity in primary CML cells (55). Investigations into the efficacy of third-generation TKIs and novel combination therapies and preclinical studies of BCL-2 inhibitors (such as APG-2575) combined with third-generation TKIs warrant exploration in compound-mutated CML.

In terms of drug selection, olverembatinib was specifically chosen in the present study, as its molecular structure was optimized to target the T315I mutation. The drug exhibits a stronger inhibitory effect on CML harboring the T315I mutation compared with other TKIs (33). Olverembatinib, as a third-generation ATP-competitive TKI, has a unique design that achieves broad coverage of BCR-ABL1 mutations. Through the allosteric adaptation of its flexible pyrazolo(3,4-d)pyrimidine scaffold to the ATP-binding pocket, it effectively inhibits a variety of ABL1 TKD mutations, including T315I. In addition to ABL1, it can target the Src family and proto-oncogene c-KIT, and its inhibitory spectrum is notably wider compared with that of traditional TKIs (56). In the present case, the E459K mutation was located at the SH2-TKD interface, which may disrupt the auto-inhibitory conformation, increase the basal kinase activity and induce compensatory activation of Src family kinases to enhance pathogenicity. Asciminib, on the other hand, achieves allosteric inhibition by binding to the myristoyl pocket of ABL1

(non-ATP site) and is effective against both wild-type and T315I-mutant ABL1. However, it lacks the ability to regulate the Src family or other bypass kinases (57).

Furthermore, compared with asciminib, which is also effective against T315I-mutated CML, olverembatinib is the first drug approved in China for treating CML with the T315I mutation and is supported by more robust evidence (56). Moreover, during the present patient's illness, asciminib had not yet been approved in China, so olverembatinib was the best drug choice for the patient. However, FDA approval allows the use of asciminib for the treatment of patients with the T315I mutation. A previous study has also shown that, for patients with the E459K mutation, increasing the dose of asciminib can partially overcome resistance, although the efficacy remains limited (30). The present case not only fills the gap in case reports of dual E459K and T315I mutations in CML but also provides key evidence for the formulation of individualized treatment strategies. The first global case reporting dual E255K and G250E mutations revealed that nilotinib had limited efficacy against E255K + G250E dual mutations (BCR-ABL1/ABL1 did not decrease to <0.5%), indicating that patients with such resistance must prioritize ABL1 TKD mutation screening (58). The first-line choice is a broad-spectrum TKI, and the second-line consideration is a mutation-specific inhibitor (such as asciminib). The present case, after detecting E459K and T315I mutations by NGS, promptly changed the treatment strategy. Since asciminib had not been approved, the medication was adjusted from nilotinib to olverembatinib to ensure the quality of the patient's treatment.

Further research is needed to determine whether asciminib can be considered a superior treatment option for patients with this dual mutation, or whether combining asciminib with ponatinib, olverembatinib or other agents offers a viable therapeutic strategy. Nonetheless, patients harboring compound mutations typically face poor prognoses, and the use of these drugs is often part of a bridging strategy. NCCN guidelines prioritize allo-HSCT for T315I-positive blast-phase CML, given the poor survival rates associated with TKIs alone (14). The patient in the present study is currently awaiting transplantation opportunities.

In conclusion, the present case highlights the notable clinical challenges in managing CML with rare concomitant mutations such as T315I, E459K and ASXL1. The coexistence of T315I and E459K may reflect a compound clone with potential synergistic effects on TKD stability. The coexistence of the mutations T315I and E459K reported in the present study is extremely rare in the database, and no studies have been found that directly compare this compound mutation with individual mutations. Further functional studies are warranted to clarify whether their co-occurrence exacerbates therapeutic challenges or represents distinct sub-clonal evolution pathways. NGS serves a pivotal role in guiding therapeutic decisions and monitoring disease progression. Additionally, timely pathological biopsy is essential to confirm the disease stage, enabling more precise treatment strategies and facilitating early interventions such as transplantation. Future research should focus on elucidating the mechanisms underlying rare compound mutations and developing targeted therapies to improve the prognosis of high-risk patients with CML. It is recommended to perform in-depth studies on the mechanisms that favor the emergence of multiple mutations in the BCR-ABL1 fusion gene, including selective and therapeutic pressures and clonal dynamics. In addition, efforts to expand access to advanced diagnostic tools are required. Moreover, multi-center collaboration is needed to establish standardized NGS-based mutation screening protocols for managing TKI-resistant CML.

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Availability of data and materials

The data generated in the present study may be found in the NCBI SRA database under accession number SRP584754 or at the following URL: https://www.ncbi.nlm.nih.gov/sra/?term=SRP584754.

Authors' contributions

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