CASE REPORT

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Imatinib-resistance without BCR/ABL Point Mutation in Chronic Myeloid Leukemia

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ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative bone marrow neoplasm that occurs because of a fusion gene called *BCR-ABL1*. Imatinib - the inhibitor of this fusion geneis the target therapy in CML. But unfortunately, resistance against imatinib occurs in some patients. In September 2019 47-year-old male was diagnosed with CML-chronic phase and intermediate risk group. Imatinib has been prescribed as a first-line treatment. The patient did not achieve a major molecular response (MMR). Next-generation sequencing using a 54 myeloid-targeted gene panel was negative for *ABL1 L248V, G250E, Y253H, E255K, F311L, T315I, F317L, F311I, M351T*, and other point mutations. After Nilotinib patient achieved MMR within two years. Imatinib resistance is impediment during treating CML. In the future, new molecules for BCR-ABL inhibitors, combination therapy, and molecules entering the blood-brain barrier may improve the outcomes of therapy and prevent imatinib resistance in CML.

Keywords: Imatinib-resistance, CML, ABL1 domain mutations

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative bone marrow disease. It presents granulocyte proliferation and a potential rise in the blast count of the bone marrow. This neoplasm occurs because of BCR-ABL fusion. Imatinib, the BCR-ABL tyrosine kinase inhibitor, has been successfully used as a first-line treatment for CML during the last 25 years. Unfortunately, imatinib resistance has been described and has been the main topic in CML research. BCR-ABL domain mutations are the main cause of resistance and are detected in the majority of cases [1]. In addition to these mutations, many other factors play a key role in imatinib resistance, such as the biology of malignant cells, genetic background, gene amplifications, and pharmacologic aspects. In this case report, we described a patient who was resistant to imatinib without any imatinib-resistant mutations.

CASE PRESENTATION

A 47-year-old male with complaints of sore throat and rapid weight loss was diagnosed with CML-chronic phase and intermediate risk group in September 2019. Imatinib has been prescribed as a first-line treatment.

At the onset of the disease, blood smear showed leukocytosis (269.18×10^9/L), anemia (9.5 g/dL), and normal platelet count (389×10^9/L). Ultrasound screening revealed splenomegaly + 7 ms. The bone marrow aspirate smears showed 2% blasts, 15% erythroid cells, 23% immature granulocytes, 39% mature granulocytes, 11% mature lymphocytes, 4% immature eosinophils, 3% basophils, 3% mature eosinophils. Trephine biopsy showed hypercellular marrow with sheets of immature cells, elevated megakaryocytes, and reticulin grade I.

Interphase fluorescence *in situ* hybridization showed *BCR-ABL1* translocation in 100% of the cells. The reverse transcription-polymerase chain reaction (RT- PCR) for the *BCR-ABL1* fusion transcript p210 was detected at 56.322% international scale (IS).

In February 2021, he presented with persistent thrombocytopenia and anemia. RT- PCR for the *BCR-ABL1* fusion transcript p210 was detected at 16.359% IS. At the end of the first year, the patient did not achieve a major molecular response (MMR), although next-generation sequencing using a 54 myeloid-targeted gene panel was negative for *ABL1 L248V, G250E, Y253H, E255K, F311L, T315I, F317L, F311I, M351T*, and other point mutations (Figure 1). Nilotinib is prescribed as a second-line treatment. Within a month, he achieved significant clinical and hematological improvement. At the end of the second year, the patient achieved MMR.

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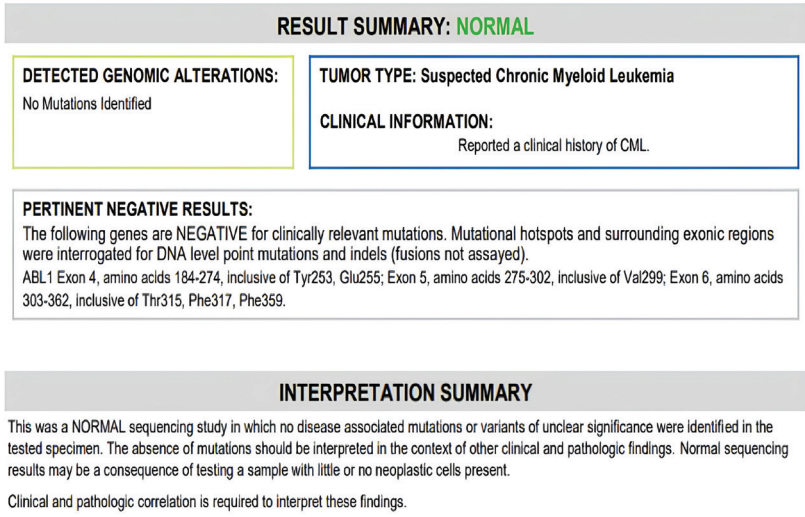

RESULT SUMMARY: NORMAL

DETECTED GENOMIC ALTERATIONS:
No Mutations Identified

TUMOR TYPE: Suspected Chronic Myeloid Leukemia

CLINICAL INFORMATION:
Reported a clinical history of CML.

PERTINENT NEGATIVE RESULTS:
The following genes are NEGATIVE for clinically relevant mutations. Mutational hotspots and surrounding exonic regions were interrogated for DNA level point mutations and indels (fusions not assayed).
ABL1 Exon 4, amino acids 184-274, inclusive of Tyr253, Glu255; Exon 5, amino acids 275-302, inclusive of Val299; Exon 6, amino acids 303-362, inclusive of Thr315, Phe317, Phe359.

INTERPRETATION SUMMARY

This was a NORMAL sequencing study in which no disease associated mutations or variants of unclear significance were identified in the tested specimen. The absence of mutations should be interpreted in the context of other clinical and pathologic findings. Normal sequencing results may be a consequence of testing a sample with little or no neoplastic cells present.

Clinical and pathologic correlation is required to interpret these findings.

Figure 1. The result of the next-generation sequencing using a 54 myeloid-targeted gene panel of the patient
CML: Chronic myeloid leukemia

DISCUSSION

Many patients with chronic phase CML [2] and accelerated phase [3] achieve major cytogenetic and molecular responses with imatinib. However, many patients develop resistance against imatinib, which is often associated with point mutations in BCR-ABL [4]. The prognosis is not favorable for such patients. In addition to molecular resistance against imatinib, other mechanisms such as intrinsic resistance of CML stem cells [5,6], bioavailability of imatinib [7], clonal progression, BCR-ABL-independent signaling pathway involvement, and poor accumulation of imatinib in the central nervous [8,9] have also been described.

Imatinib resistance is a crucial issue in CML treatment. In the future, new, more successful BCR-ABL inhibitors, combination therapy, and molecules that enter the blood-brain barrier may improve the outcomes of CML therapy. This approach can also prevent imatinib resistance in the early phase of CML.

Ethics

Informed Consent: Patient freely and voluntarily gave consent and signed a Informed Consent Form.

Financial Disclosure: The author declared that this study received no financial support.

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