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Chronic myeloid leukemia with involvement of membranous labyrinth

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ABSTRACT

This case report explains an extraordinary presentation of chronic myeloid leukemia (CML) in a 39-year-old male with a T315I mutation, presenting with acute bilateral hearing loss and imbalance secondary to myeloid blast crisis. Neurological involvement was confirmed through MRI brain and cerebrospinal fluid analysis. Initial treatment with ponatinib and FLAG (fludarabine, cytarabine, G-CSF) regimen showed promise, but complications necessitated discontinuation. The patient's complex clinical trajectory, marked by complications and intolerance to tyrosine kinase inhibitors, highlights the intricate nature of CML blast crisis with T315I mutation management. Recognizing atypical presentations and early mutation analysis are pivotal for tailored treatment strategies.

1. Introduction

Chronic myeloid leukemia (CML) is characterized by abnormal production and dysregulated proliferation of granulocytes, primarily neutrophils, driven by the fusion oncoprotein BCR-ABL1, also known as the Philadelphia chromosome (Ph+). While often discovered incidentally through routine blood work, CML can manifest with symptoms related to anemia or splenomegaly. Organ dysfunction, particularly in the kidney, lung, heart, and brain, may occur due to leukostasis. A handful of cases of neurological involvement in CML have been described in the literature so far [3]. CML is classified into chronic, accelerated, or blast phases based on various laboratory parameters, guiding treatment decisions. However, further research revealed that approximately 33 % of CML patients treated with imatinib failed to achieve a complete cytogenetic response (CCyR), while others either developed resistance to imatinib or could not tolerate it due to its adverse effects. Among TKI resistance mutations, T315I has the poorest prognosis and is resistant to first and second-generation TKI but does respond to more potent third generation TKI including ponatinib and asciminib [4,5].

Here, we report a 39-year-old male with T315I mutated CML presenting with acute hearing loss and imbalance, progressing to blast crisis despite an initial promising response to FLAG and ponatinib.

2. Case description

A 39-year-old male was referred to Mayo Clinic Florida in June 2021 with a diagnosis of CML in the accelerated phase. He was treated with nilotinib at an outside facility. A repeat bone marrow biopsy performed at Mayo Clinic on the initial presentation showed no morphologic or immunophenotypic evidence of acute leukemia. Cytogenetic and molecular studies confirmed the presence of Ph+. Laboratory evaluation revealed hemoglobin 8.1 g/dl (low), platelets 36 × 10 [9]/L (low), white blood cells 3.2 × 10 [9]/L (low), absolute neutrophil count 4.01 × 10 [9]/L (normal), absolute basophils count 0.19 × 10 [9]/L (high). Based on the MD Anderson Criteria, [6] the patient was determined to have CML AP (accelerated phase), and it was decided to continue him on nilotinib. The patient was referred to a primary hematologist for further care. Due to subsequent cytopenia, the dose of nilotinib was initially reduced, followed by discontinuation in September 2021.

Five days after the discontinuation of nilotinib, the patient presented to our emergency department with acute bilateral hearing loss, tinnitus, and imbalance. Physical examination was unremarkable except for complete hearing loss. T1-weighted contrast-enhanced magnetic resonance imaging (MRI) of the brain showed abnormal enhancement of the cochlea and vestibule bilaterally (Panel A, arrows), leptomeningeal enhancement on the surface of the cerebellar folia (Panel A, arrowheads), enhancement of the left trigeminal nerve (Panel B, arrow) and cranial nerve (CN) VII and VIII involvement. Blood counts were normal

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except for thrombocytopenia. A repeat bone marrow biopsy was negative for blast transformation (<5 % blasts) but was hypercellular with 100 % cellularity, trilineage hematopoiesis, and marked fibrosis, consistent with CML and secondary myelofibrosis. The polymerase chain reaction (PCR) results showed an increase in BCR-ABL1 p210 from 27.3 % to 33.5 % and an ABL1 kinase mutation analysis revealed a T315I mutation. CSF analysis revealed 402 nucleated cells, 0 % neutrophils, 30 % lymphocytes, 70 % other cells, 65 protein (elevated), 55 glucose, and increased myeloid blasts.

He was administered prophylactic intrathecal chemotherapy (IT) with cytarabine and hydrocortisone with a plan to initiate systemic therapy for CML with the myeloid blast phase. He presented to the Emergency Department four days later, with severe headache and vomiting. Computed tomography (CT) scan of the brain was suggestive of early hydrocephalus. Subsequently, he was admitted and given palliative radiation therapy; 400 cGy x 5 fractions. Later he was initiated on systemic chemotherapy with the FLAG regimen along with ponatinib. Repeat MRI showed resolution of the abnormal enhancement (Panels C and D), although hearing loss persisted. The patient continued IT chemotherapy and ponatinib. While the plan was to continue consolidation therapy and perform allogeneic stem cell transplantation, the treatment course was complicated by prolonged transfusion refractory thrombocytopenia, deconditioning, and invasive fungal pneumonia. Later, he contracted COVID-19 and passed away because of its complications. The sequence of clinical events with pertinent labs is highlighted in Fig. 2.

3. Discussion

This case features a 39-year-old male with CML blast crisis, exhibiting neurological symptoms including hearing loss, tinnitus, and imbalance. The rare T315I mutation was identified, marking the first reported instance of isolated bilateral hearing loss due to membranous labyrinth involvement in the T315I mutated CML blast crisis.

According to the MDACC (MD Anderson Cancer Center) criteria, the CML AP is based on the presence of any of the following: 15–29 % blast cells in the blood or bone marrow, $\geq$ 20 % basophils in the blood, platelet count < 100,000/micro-L unrelated to therapy and the presence of additional clonal cytogenetic abnormalities in Ph+ cells [7]. Blast phase is defined by the presence of >30 % blasts in the blood or bone marrow or the presence of CNS or extramedullary disease [6]. Upon presentation, our patient did not have any signs of extramedullary involvement and his workup did not reveal any evidence of blast phase CML, owing to which his disease was classified as CML AP and he was continued on nilotinib. When appropriately treated with TKIs, many patients respond with either complete cytogenetic response (CCR) or a major molecular remission (MMR). In our case, however, the patient was unable to tolerate nilotinib and hence, it had to be discontinued.

The patient's subsequent presentation with acute onset hearing loss and imbalance was suggestive of CNS involvement from CML. This was later confirmed by the MRI findings of vestibulocochlear and leptomeningeal enhancement (Fig. 1). CSF analysis also revealed the presence of increased myeloid blasts, confirming the diagnosis of CML BP (blast phase). In the era of potent TKIs, CNS blast crisis is rare. Moreover, the presence of blast infiltration in the CNS is particularly unfavorable as many drugs, including imatinib, do not have significant activity in the CNS [1]. Similar cases of isolated CNS blast crisis have been reported in patients who never obtained a CCR or lost their previous response at the time of the isolated blast crisis.

The relation between leukemia and deafness was first described by Vidal in 1856 [8]. Otological involvement is seen in approximately 15–40 % of patients with CML, and the associated deafness may present as unilateral, bilateral, or initial unilateral evolving into bilateral sensorineural hearing loss [2,3]. It can be the presenting symptom of CML in some cases and a complication of preexisting CML in other cases. The etiology of neurotological manifestations of CML is complex and thought to be multifactorial. The proposed mechanisms include leukemic infiltration, leukostasis/hyperviscosity, middle or inner ear hemorrhage, and infections [2,3,9]. Since our patient had normal cell counts, leukostasis was ruled out. There was no evidence of any middle or inner ear hemorrhage. Based upon his evaluation, there was no evidence of any active infection. His CSF and MRI findings were indicative of these manifestations being a result of CNS blast crisis, pointing towards leukemic infiltration as the possible mechanism. The ideal treatment approach in isolated CNS blast crisis is not clearly defined as comparative trials are lacking due to the rarity of this condition. In the cases described in the literature, those suggested to be secondary to leukostasis treated with leukapheresis whereas most of the others treated with intrathecal chemotherapy with or without cerebrospinal irradiation. Since our patient had normal blood cell counts, we decided not to undertake leukapheresis. Instead, we decided to treat him with a systemic chemotherapy regimen having better penetrance to CNS with intrathecal chemotherapy, but due to his deteriorating condition and development of hydrocephalus, we had to delay systemic treatment and

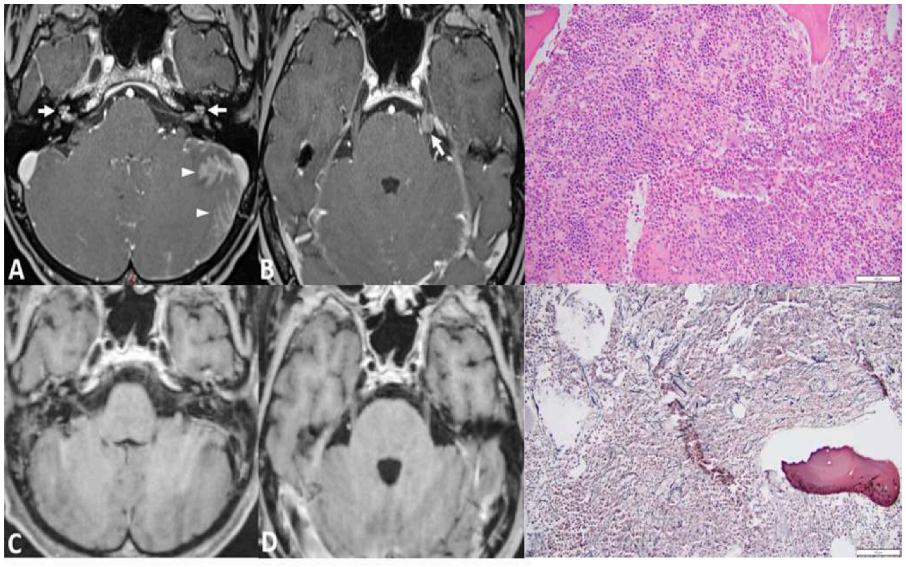

Fig. 1. Pathology and MRI findings of vestibulocochlear and leptomeningeal enhancement.

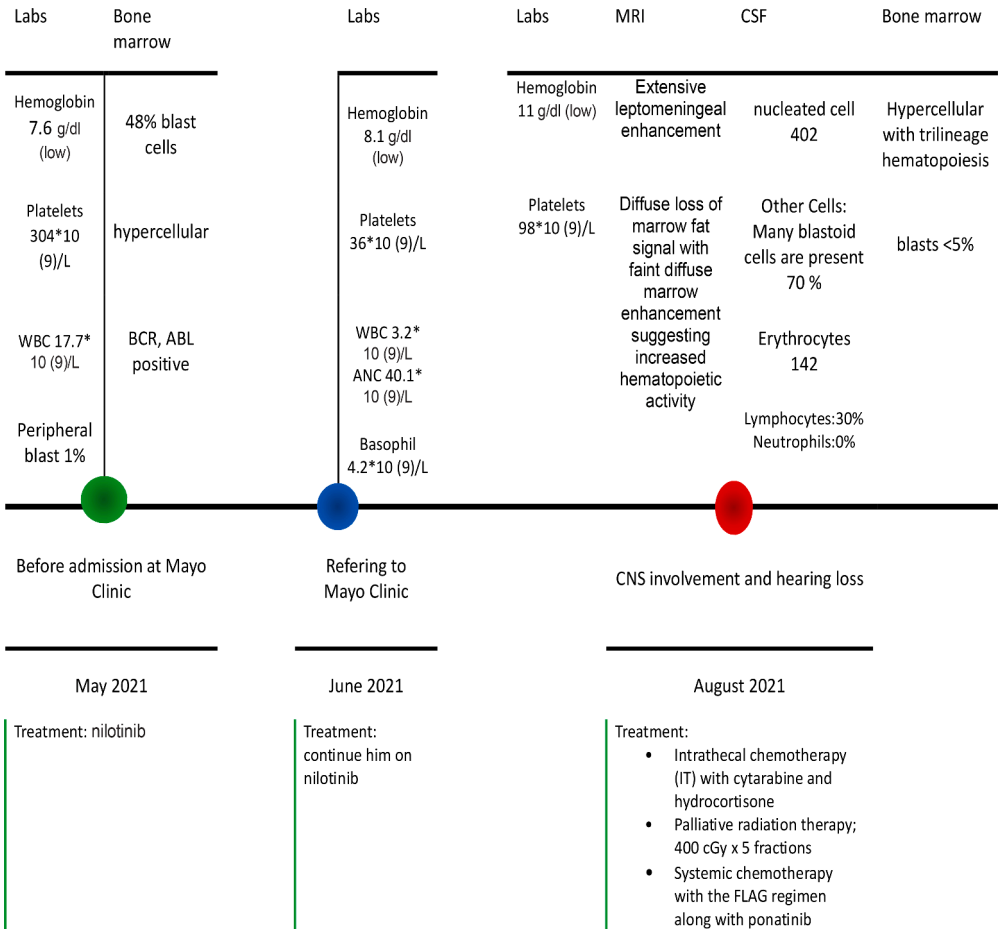

Fig. 2. The sequence of clinical events with pertinent labs is highlighted.

proceeded with localized radiation therapy.

Mutation analysis plays an important role in determining the prognosis of CML and selecting an appropriate TKI. Numerous mutations have been discovered, including, but not limited to, T315I, M351T, Y253H, H396R, F359V, V299L [8]. Out of these, T315I mutated CML is known to have the poorest prognosis and confers resistance to almost all TKIs except the third generation TKI, ponatinib, and the allosteric inhibitor of the BCR-ABL1 tyrosine kinase, asciminib [4]. Since our patient was later found to have the T315I mutation, ponatinib was incorporated into his treatment regimen.

This case posed challenges due to the unusual presentation of the CML blast crisis with hearing loss and imbalance. Isolated CNS involvement in bilateral membranous labyrinth, without excessive blasts or organ infiltration, added complexity. Rapid disease progression, T315I mutation, and TKI intolerance compounded management complexity.

4. Conclusion

Physicians treating CML patients should consider blast crisis with unexplained extramedullary symptoms. Atypical presentations may obscure diagnosis, underscoring the importance of phase identification. Early mutation analysis guides tailored TKI therapy due to mutation-specific drug resistance.

Informed consent

"Not applicable."

CRediT authorship contribution statement

Mobachir El Kettani: Writing – original draft, Writing – review & editing. **Kashish Shah:** Writing – original draft, Writing – review & editing. **Hareem Farooq:** Writing – original draft. **Ke Li:** Writing – original draft. **Talha Badar:** Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Talha Badar reports article publishing charges were provided by the Mayo Clinic in Florida. Talha Badar reports a relationship with Takeda that includes: consulting or advisory. Talha Badar reports a relationship with Pfizer that includes: consulting or advisory. Talha Badar reports a relationship with MorphoSys that includes: consulting or advisory. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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