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CASE REPORT

Chronic Myeloid Leukemia Progression to Acute Mixed-Lineage Leukemia: a Diagnostic Challenge Complicated by Severe Complications

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SUMMARY

Background: **Chronic myeloid leukemia (CML) is a myeloproliferative disorder that can progress to an accelerated or blast phase if left untreated or inadequately managed. Acute transformation of CML, particularly into mixed lineage leukemia, is a rare and challenging complication. This case report describes the clinical course of a 30-year-old male patient with CML progressing to acute mixed lineage leukemia and complicated by gastrointestinal bleeding.**

Methods: **The patient, initially diagnosed with CML in June 2019, was treated with imatinib. However, after discontinuing treatment on his own, the disease progressed to acute myeloid leukemia (AML-M2a) by June 2020, confirmed by bone marrow analysis, flow cytometry, and cytogenetics showing BCR-ABL1 positivity. Despite multiple chemotherapy regimens, including VCLP, VDP with dasatinib, and COP with dasatinib, the patient's condition failed to improve. He developed recurrent gastrointestinal bleeding, which was managed with acid suppression, blood transfusions, and infection control measures.**

Results: **The patient experienced persistent bone marrow failure, characterized by blasts in peripheral blood and bone marrow, as well as refractory gastrointestinal bleeding despite supportive care. During chemotherapy, the patient also developed severe infections and psychiatric symptoms, complicating the treatment course.**

Conclusions: **This case highlights the aggressive progression of CML to acute mixed lineage leukemia and underscores the challenges in managing patients with resistant disease. The patient's gastrointestinal bleeding and recurrent infections further complicated treatment, emphasizing the need for early intervention and close monitoring of high-risk CML patients.**

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KEYWORDS

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INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by the presence of the BCR-ABL1 fusion gene, typically leading to the overproduction of myeloid cells [1]. In the chronic phase, CML is often manageable with tyrosine kinase inhibitors (TKIs) such as imatinib, which target the BCR-ABL1 oncoprotein [2,3]. However, some patients may experience disease progression to an accelerated or

blast phase, which is associated with a significantly worse prognosis [4].

Progression to acute leukemia, particularly acute myeloid leukemia (AML) or mixed lineage leukemia, is a rare but severe complication of CML [5]. This transformation, known as blast crisis, is marked by a rapid increase in immature myeloid or lymphoid blasts in the bone marrow and peripheral blood, making it difficult to control the disease with standard therapies [6,7].

In this report, we present the case of a 30-year-old male with CML who initially responded to imatinib treatment but experienced a rapid transformation to acute mixed lineage leukemia (AML-M2a) following treatment discontinuation. The patient developed complications including gastrointestinal bleeding and infections during chemotherapy, making management of the disease even more challenging. This case highlights the importance of continuous treatment in CML patients, early detection of disease progression, and the need for aggressive management strategies in cases of blast crisis.

CASE REPORT

A 30-year-old male was initially diagnosed with chronic myeloid leukemia (CML) in the chronic phase in June 2019, after presenting with abdominal distention. Following diagnostic work-up, including complete blood counts and bone marrow analysis, he was started on imatinib (400 mg, qd) as targeted therapy. However, after two months of treatment, the patient discontinued imatinib on his own and did not attend follow-up appointments.

In June 2020, the patient presented again with abdominal discomfort. Bone marrow morphology revealed an increase in blast cells (58%) (Figure 1), and flow cytometric analysis indicated the presence of a population of immature cells (54.4% of nucleated cells) expressing CD117, CD33, CD10, CD19, CD34, and MPO, among others. This led to the diagnosis of acute myeloid leukemia (AML-M2a) with mixed lineage features (myeloid and B-lymphoid) as part of CML progression (Figure 2). Cytogenetic analysis revealed a BCR-ABL1 (P210) fusion gene, while next-generation sequencing did not detect mutations in FLT3, KIT, or CEBPA. Karyotyping showed 46,XY,t(9;22)(q34;q11) and -7, confirming the progression to acute mixed lineage leukemia (AML).

The patient was started on chemotherapy, but disease remission was not achieved. In August 2020, after multiple chemotherapy regimens (including VCLP and VDP with dasatinib), the patient developed gastrointestinal bleeding and was diagnosed with non-atrophic gastritis with erosion, along with severe pancytopenia. Despite receiving various antimicrobial treatments (including meropenem, vancomycin, and voriconazole), proton pump inhibitors, and hemostatic agents, his condition worsened, and he exhibited psychiatric symptoms, leading to discontinuation of treatment against medical advice.

In November 2020, the patient was re-admitted with worsening anemia, thrombocytopenia, and fever. Bone marrow examination again showed no remission, and he was started on COP chemotherapy combined with dasatinib. The patient subsequently experienced recurrent febrile episodes and gastrointestinal bleeding, with black tarry stools indicating ongoing blood loss. Supportive care, including blood transfusions and acid suppression, was provided, but the patient and his family ultimately opted for discharge.

DISCUSSION

Here we present the clinical case of a 30-year-old male with chronic myeloid leukemia (CML) who progressed to acute mixed lineage leukemia following discontinuation of imatinib therapy. This case highlights several diagnostic and therapeutic challenges associated with CML blast crisis, especially in patients with mixed lineage leukemia, which carries a significantly worse prognosis than typical CML transformation to myeloid or lymphoid blast crisis [8].

Initially, the patient responded to standard therapy with imatinib, but after discontinuation of treatment, disease progression was rapid, resulting in a high blast count (58%) and mixed lineage features (myeloid and B-lymphoid) upon re-evaluation. The cytogenetic findings, including BCR-ABL1 positivity and the presence of t(9;22) and -7 abnormalities, confirmed the blast phase of CML [4]. The presence of the -7 chromosomal abnormality, known to correlate with poor prognosis, added to the complexity of disease management [9].

One of the key diagnostic challenges in this case was distinguishing the mixed lineage leukemia features from other forms of CML transformation. Mixed lineage leukemia, characterized by the co-expression of markers from both myeloid and lymphoid lineages, is relatively rare and can complicate treatment decisions [10]. In this case, flow cytometry revealed a population of immature cells expressing markers such as CD117, CD33, CD10, and CD19, which helped confirm the diagnosis of acute mixed lineage leukemia. However, mixed lineage cases often pose therapeutic dilemmas, as standard chemotherapeutic regimens may not be equally effective against both lineages [11].

Therapeutically, the patient was treated with multiple chemotherapy regimens, including VCLP, VDP combined with dasatinib, and COP, but the disease remained refractory. The poor response to chemotherapy is not uncommon in cases of CML blast crisis, especially when accompanied by adverse cytogenetic features such as -7 [12]. This highlights the aggressive nature of CML in blast phase and underscores the need for alternative strategies, such as targeted therapies or allogeneic stem cell transplantation [13], which were not pursued in this case due to the patient's deteriorating condition and multiple complications.

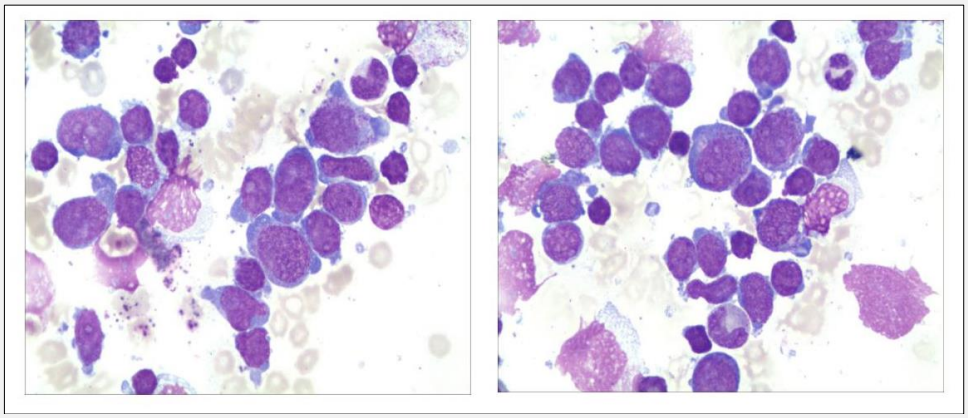

Figure 1. Bone marrow smears showed that blasts accounted for 47.8% of the absolute neutrophil count (ANC).

These cells measured 18 - 25 µm in size, had moderate amounts of cytoplasm, large nuclei, and prominent nucleoli. Lymphoblasts accounted for approximately 20.2%, with cell sizes ranging from 10 - 15 µm, scant cytoplasm, large nuclei, and faintly visible nucleoli.

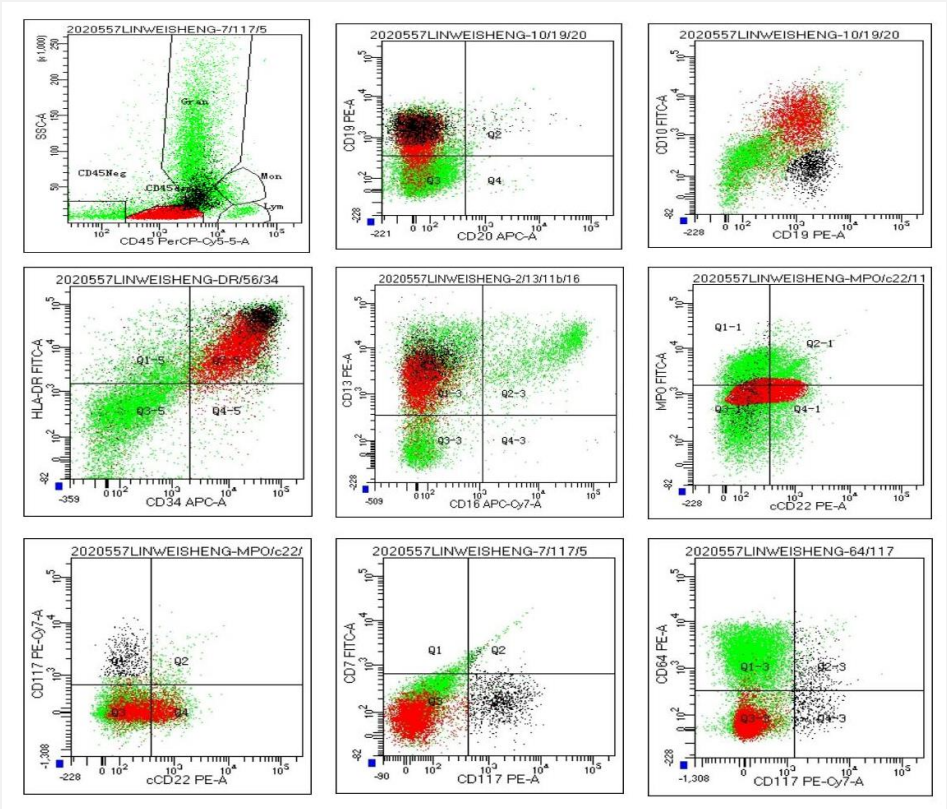

Figure 2. Flow cytometry results show a population of CD34+ pro-B lymphoblasts accounting for approximately 44.7%, and another population of CD34+CD117+ myeloid blasts accounting for about 8.9%.

The patient's clinical course was further complicated by gastrointestinal bleeding, which was confirmed by endoscopy to be caused by non-atrophic gastritis with erosions. Gastrointestinal bleeding in leukemia patients can be multifactorial, often related to thrombocytopenia, chemotherapy toxicity, or infections [14]. In this case, despite aggressive management with proton pump inhibitors, antifungal agents, and supportive care, the bleeding persisted, contributing to the patient's overall decline.

Another notable aspect of this case was the development of psychiatric symptoms, including agitation and treatment refusal. Psychiatric disturbances in leukemia patients, particularly those undergoing intensive therapy, are well-documented and can significantly impact treatment adherence and outcomes [15]. In this patient, the refusal of medication ultimately hindered further therapeutic efforts, limiting options for managing the disease progression.

In summary, this case illustrates the challenges in diagnosing and treating CML in blast crisis, particularly when it involves mixed lineage features. The rapid progression following treatment discontinuation, refractory response to chemotherapy, and multiple complications, including gastrointestinal bleeding and psychiatric symptoms, underscore the complexity of managing such cases. This case also highlights the importance of continuous therapy and regular follow-up in CML patients to prevent disease progression and the need for early and aggressive intervention in blast crisis cases. Despite advancements in TKI therapy, refractory cases such as this one demonstrate the need for ongoing research into novel therapeutic options for high-risk CML patients.

Declaration of Interest:

All authors declare no conflict of interest.

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