CASE REPORT

Rapid Progression From Chronic Phase to Blast Crisis: Prognostic Implications of Bone Marrow Fibrosis in Chronic Myeloid Leukemia

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ABSTRACT

Chronic myeloid leukaemia (CML) demonstrates variable responses to tyrosine kinase inhibitors (TKI). The prognostic impact of bone marrow fibrosis (BMF), particularly at diagnosis, remains under-recognised, especially in adolescent patients. We report a case of a 14-year-old male diagnosed with chronic-phase CML who progressed rapidly to blast crisis within 12 months. Despite treatment with imatinib followed by nilotinib, the patient failed to achieve a complete cytogenetic response due to severe cytopenia and frequent dose interruptions. Retrospective analysis of the initial bone marrow biopsy revealed grade 3 fibrosis. The disease remained refractory despite high-dose induction chemotherapy. This case highlights the potential prognostic relevance of BMF in adolescent CML and supports the integration of reticulin staining into the diagnostic workup to guide timely intervention.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm (MPN) characterised by the BCR-ABL1 fusion gene resulting from the t(9:22) translocation. Tyrosine kinase inhibitor (TKI) has revolutionised the treatment landscape and prognosis of CML. Increasing evidence suggests that the presence of bone marrow fibrosis (BMF) at diagnosis may be associated with inferior treatment outcomes, including delayed molecular responses, suboptimal TKI efficacy, and reduced likelihood of achieving treatment-free remission.[1,2] Adolescents with CML typically exhibit a more indolent course, making early blast crisis an unusual and alarming progression. The role of BMF in paediatric or adolescent CML is rarely reported, and its prognostic relevance remains unclear in this population. We present a case of adolescent CML that progressed rapidly from chronic phase to blast crisis, highlighting the potential prognostic significance of BMF detected at diagnosis.

CASE REPORT

Initial Presentation and Diagnosis

A 14-year-old male presented with a three-month history of fatigue, poor appetite, early satiety, and significant weight loss. Physical examination revealed pallor and massive splenomegaly, palpable 15cm below the left costal margin. There was no hepatomegaly or lymphadenopathy. Initial laboratory results showed severe normochromic normocytic anaemia (haemoglobin 6.7g/dL), marked leucocytosis (white cell count 330 x 10^9/L), and thrombocytosis (platelet count 456 x 10^9/L). A peripheral blood smear showed teardrop cells, marked leucocytosis with granulocytic precursors at all stages, and 5% blasts.

The initial bone marrow aspirate was haemodiluted with no excess blasts, while the trephine biopsy showed hypercellularity with increased megakaryocytes. Reticulin staining was not performed initially due to a reagent

shortage. BCR-ABL1 rearrangement was confirmed via molecular analysis. The patient was diagnosed with chronic-phase CML, with a Sokal Index of 1.2 (intermediate risk).

Treatment Course and Challenges

Imatinib was initiated shortly after diagnosis. However, at 6 months post-diagnosis, the patient failed to achieve a complete cytogenetic response (CCyR), with persistent BCR-ABL1 positivity in 77% of cells by fluorescence in situ hybridization (FISH). Treatment was frequently interrupted and dose-adjusted due to recurrent grade 4 cytopenia. Next-generation sequencing detected no BCR-ABL1 kinase domain mutations, including T315I. Due to poor tolerability, imatinib was discontinued and replaced with nilotinib at 6 months post-diagnosis. However, similar hematologic toxicity limited dose escalation. Despite ongoing treatment, serial peripheral blood smears and bone marrow assessments confirmed persistent chronic-phase CML. Quantitative BCR-ABL1 polymerase chain reaction was not performed, as serial FISH analyses remained consistently positive.

Retrospective reticulin staining of the diagnostic trephine biopsy later confirmed grade 3 fibrosis (Figure 1). Given the high-grade fibrosis and TKI intolerance, the patient was referred for allogeneic stem cell transplantation (allo-SCT). A matched sibling donor was identified.

Progression to Blast Crisis

At approximately 12 months from initial presentation, the patient progressed to blast crisis. Bone marrow aspiration resulted in a 'dry tap', while trephine biopsy revealed diffuse infiltration by blasts (Figure 2). Immunohistochemistry demonstrated blast positivity for CD34 [Figure 3(a)], CD117 [Figure 3(b)], MPO [Figure 3 (c)], and CD61 [Figure 3(d)]. Reticulin staining confirmed persistent grade 3 fibrosis [Figure 3(e)]. Peripheral blood flow cytometry showed 45% blasts expressing CD45 dim, CD117, HLA-DR, CD34, and CD13, consistent with acute myeloid leukaemia (AML).

Induction chemotherapy was initiated per local paediatric AML protocol, comprising mitoxantrone (12 mg/m^2 daily for four days) and cytarabine (100 mg/m^2 twice daily for ten days), along with nilotinib (200 mg every other day) and prophylactic intrathecal chemotherapy. The course was complicated by a grade 5 infection, indicating poor tolerance to intensive chemotherapy. As of the time of this report, the disease remains refractory. Salvage chemotherapy is ongoing, and allo-SCT with the matched sibling donor is planned, although the timing remains uncertain.

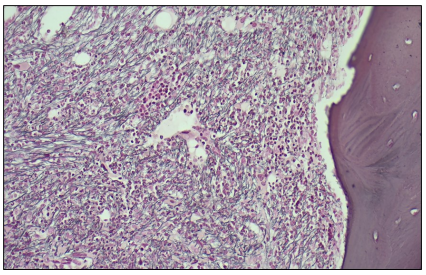

Figure 1: Retrospective reticulin stain of the diagnostic trephine biopsy showing grade 3 marrow fibrosis (400x magnification).

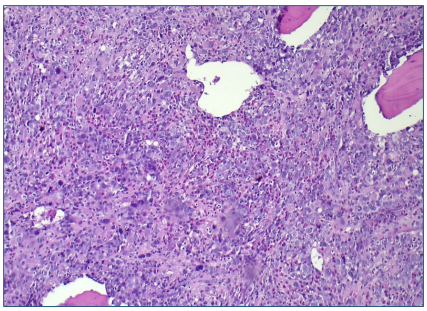

Figure 2: Trephine biopsy at blast crisis showing diffuse infiltration by blasts (Hematoxylin and Eosin stain 400x magnification).

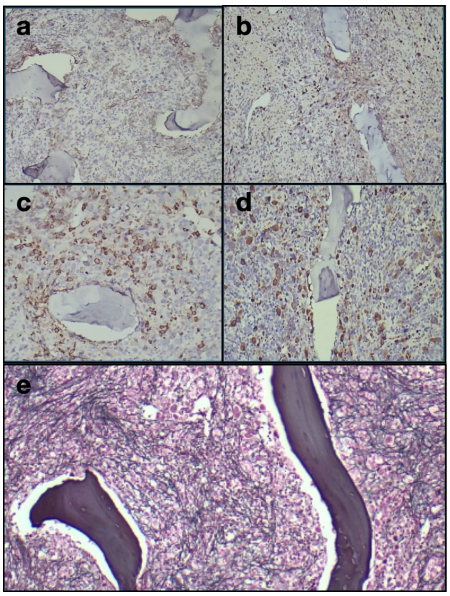

Figure 3: Immunohistochemical and reticulin staining of the trephine biopsy at blast crisis. (a) CD34-positive blasts; (b) CD117-positive blasts; (c) MPO-positive blasts; (d) CD61 highlighting megakaryocytes; (e) Reticulin stain showing grade 3 fibrosis (400x magnification for all panels).

DISCUSSION

This case raises the question of whether early identification of BMF should influence upfront TKI selection or transplant referral timing, particularly in younger patients. BMF in CML is commonly observed at diagnosis, with studies reporting grade 2-3 fibrosis in up to one-third of patients.[3] Its presence has been associated with delayed molecular responses, suboptimal TKI outcomes, and reduced likelihood of achieving treatment-free remission.[1,2,4] While it is more extensively described in adult populations, its occurrence and significance in adolescents with CML are not well established due to limited data.

The pathogenesis of BMF in CML is believed to be driven by clonal proliferation of megakaryocytes and monocytes that secrete fibrogenic cytokines such as platelet-derived growth factor and transforming growth factor-beta, leading to fibroblast activation and reticulin deposition.[5] In contrast, in other MPNs such as primary myelofibrosis, BMF is often driven by JAK2, CALR, or MPL mutations that activate the JAK-STAT signalling pathway, resulting in excessive cytokine production and marrow stromal remodelling.[6] Since JAK2 mutations are typically absent in BCR-ABL1 positive CML, the fibrotic process in CML likely arises from alternative, BCR-ABL1 -driven mechanisms.

TKI therapy has demonstrated the potential to reverse BMF, potentially mitigating its adverse prognostic effects in the TKI era.[5] Imatinib has been shown to significantly reduce fibrosis grade in many CML patients, although higher-grade fibrosis may require a longer duration to achieve optimal response.[5] However, long-term imatinib exposure has also been reported to induce new or progressive marrow fibrosis in some patients, with resolution observed after switching to second-generation TKIs.[7] Although BMF does not necessarily prevent therapeutic response, it remains associated with delayed cytogenetic and molecular responses.[1]

The rate of CCyR appears similar regardless of fibrosis severity; however, patients with moderate to severe fibrosis tend to show poorer early responses and suboptimal outcomes when treated with first-generation TKIs such as imatinib.[4] These findings suggest that significant fibrosis at diagnosis may support the early use of second-generation TKIs, though further evidence is warranted.

Currently, BMF alone does not constitute an indication for allo-SCT in CML. However, in patients with persistent high-grade fibrosis, intolerance to multiple TKIs, or progression risk, allo-SCT remains a viable and often necessary option.[8,9] In our patient, the combination of high-grade fibrosis and TKI intolerance led to early consideration of allo-SCT. Unfortunately, delays in workup due to social factors resulted in disease progression to blast crisis.

Based on this case and emerging evidence, we recommend that all newly diagnosed CML patients, especially those with atypical features or cytopenia, undergo reticulin staining as part of their baseline marrow workup. Identifying high-grade fibrosis early may help guide the intensity of monitoring, TKI selection, and timely referral for transplant consideration.

CONCLUSION

This case highlights the potential prognostic relevance of BMF in CML, particularly in adolescent patients. High-grade fibrosis at diagnosis may be associated with poor tolerance to TKI, delayed or suboptimal treatment response, and an increased risk of rapid disease progression. Although BMF may be reversible with TKI therapy, its presence warrants close molecular monitoring and should prompt timely consideration of alternative strategies, including early referral for allo-SCT. Given the potential for BMF to predict poor response and rapid disease progression in CML, incorporating reticulin staining into routine diagnostic protocols may improve risk stratification and treatment planning, particularly in adolescents.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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