Case Report

Chronic myeloid leukemia presenting with isolated thrombocytosis in a pediatric patient: A case report of molecular relapse and therapeutic challenge

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ABSTRACT

Chronic myeloid leukemia (CML) in children typically presents with symptomatic splenomegaly or constitutional symptoms; isolated thrombocytosis as an initial presentation is uncommon. We report an 8-year-old male with CML in chronic phase presenting as an incidental finding of marked thrombocytosis during investigation for headaches. The patient harbored a BCR-ABL b3a2 fusion transcript confirmed by reverse transcriptase polymerase chain reaction. Initial management with imatinib achieved excellent molecular and hematological responses with BCR-ABL negativity at 9 months. Subsequent therapeutic non-adherence resulted in molecular relapse with BCR-ABL reactivation. A further complication arose when imatinib dose reduction resulted in severe refractory thrombocytosis, prompting the introduction of hydroxyurea for rapid cytoreduction. This case highlights diagnostic challenges in recognizing CML with isolated thrombocytosis, the critical importance of adherence to tyrosine kinase inhibitor (TKI) therapy in pediatric CML, and the need for multidisciplinary management when single-agent TKI therapy proves inadequate.

Key words: BCR-ABL positive, Chronic myeloid leukemia, Imatinib, Molecular monitoring, Pediatric, Thrombocytosis

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) characterized by the balanced translocation t(9; 22)(q34; q11), resulting in the *BCR-ABL1* fusion gene [1]. This oncogenic fusion protein encodes a constitutively active tyrosine kinase that drives uncontrolled myeloid proliferation. In adult populations, CML accounts for approximately 15–20% of all leukemias [1], whereas in pediatric populations, it represents only 2–3% of all childhood leukemias [2]. The incidence in children is approximately 0.6–1.0/million children annually globally [2,3]. At presentation, the vast majority of CML cases are detected in chronic phase (92–95% at diagnosis), characterized by leukocytosis with myelopoiesis, typically accompanied by splenomegaly and constitutional symptoms. However, atypical presentations do occur and should not be overlooked.

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The presentation of CML with isolated or predominant thrombocytosis (>600,000 cells/mm^3) in the absence of marked leukocytosis or significant anemia is exceptionally rare in pediatric cohorts and frequently mimics other primary MPNs, thereby significantly delaying definitive diagnosis [4]. Comprehensive cytogenetic analysis and sensitive molecular detection are essential for accurate diagnosis. High-sensitivity quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) on the international scale (IS), combined with fluorescence *in situ* hybridization (FISH), has become the diagnostic gold standard for BCR-ABL1 detection and monitoring of molecular response during therapy [1]. The introduction of tyrosine kinase inhibitors (TKIs), particularly first-generation (imatinib) and second-generation agents (dasatinib, nilotinib), has dramatically transformed treatment outcomes in CML, with imatinib maintaining first-line status in both adult and pediatric populations [1,5].

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We report this case to highlight the diagnostic challenges of CML presenting with isolated thrombocytosis, to underscore the critical importance of therapeutic adherence in pediatric patients, and to discuss management strategies for complex therapeutic scenarios, including molecular relapse and refractory thrombocytosis.

CASE PRESENTATION

An 8-year-old male child presented with marked thrombocytosis during laboratory investigation for persistent headaches. The patient reported no constitutional symptoms, and his general health status was preserved. Family history revealed paternal polyarthritis and maternal chronic inflammatory bowel disease, but no known hematologic malignancies.

Clinical examination was unremarkable with an absence of palpable splenomegaly or hepatomegaly. No lymphadenopathy or cutaneous manifestations were noted.

Peripheral blood examination revealed hemoglobin 13.2 g/dL (reference range: 11.5–15.5), white blood cell (WBC) count 45,000 cells/mm^3 (reference range: 4,500–13,500), and a platelet count of 892,000 cells/mm^3 (reference range: 150,000–400,000). The differential leukocyte count showed: Neutrophils 58%, lymphocytes 32%, monocytes 8%, and eosinophils 2%. Based on the striking thrombocytosis, an initial diagnostic consideration of essential thrombocythemia (ET) was pursued; however, molecular testing for the JAK2 V617F mutation was negative. Cytogenetic analysis subsequently revealed the t(9; 22) translocation in 98% of metaphases analyzed. Reverse transcriptase polymerase chain reaction (RT-PCR) analysis confirmed the presence of the BCR-ABL fusion transcript type b3a2, confirming the diagnosis of CML in chronic phase. A bone marrow examination showed normocellular marrow with increased myeloid precursors and prominent megakaryopoiesis. Flow cytometry was consistent with chronic-phase myeloproliferative disease.

The patient was initiated on imatinib mesylate at 260 mg/m^2 daily. Response assessment at 9 months of therapy revealed a complete hematological response with hemoglobin 12.8 g/dL, WBC count 8,900 cells/mm^3, and platelet count 187,000 cells/mm^3. BCR-ABL RT-PCR was negative, indicating a major molecular response. Several months following this initial successful response, a period of documented therapeutic non-adherence occurred. Subsequent laboratory evaluation revealed a positive BCR-ABL RT-PCR, confirming molecular relapse. Adherence counseling was reinforced, imatinib therapy was resumed at the full dose, and a repeat RT-PCR within 4–6 weeks confirmed BCR-ABL negativity, indicating recapture of molecular response.

Approximately 1 month following recovery from the molecular relapse, the patient developed a maxillo-sphenoidal infection requiring broad-spectrum antimicrobial therapy. During this infectious episode, the imatinib dose was reduced by 50% due to persistent headaches. Within weeks of this dose reduction, the platelet count increased dramatically to 1,250,000 cells/mm^3, with moderate anemia (hemoglobin 9.5 g/dL). FISH analysis identified *BCR-ABL* fusion gene positivity in 12% of cells, whereas a qualitative RT-PCR performed on the same date yielded negative results. Given the persistence of severe thrombocytosis, hydroxyurea was introduced for rapid cytoreduction following a multidisciplinary consultation. The response to combination therapy at 1 month following the initiation of hydroxyurea was favorable, showing a platelet count of 420,000 cells/mm^3, hemoglobin of 11.2 g/dL, WBC count of 6,800 cells/mm^3, and a negative BCR-ABL RT-PCR. Timeline illustrating the correlation between platelet count evolution and therapeutic interventions is shown in Figure 1.

DISCUSSION

This case presents several instructive clinical points regarding CML presentation, diagnosis, molecular monitoring, and therapeutic management in pediatric populations. The presentation of CML with isolated or predominant thrombocytosis in the absence of marked leukocytosis is unusual, particularly in pediatric patients [4,6]. In the present case, the striking thrombocytosis (892,000/mm^3) in the context of a normal-range hemoglobin and only moderately elevated WBC initially prompted consideration of other primary MPNs. The primary differential diagnosis in a pediatric patient with marked, isolated thrombocytosis includes other MPNs, most notably ET. The distinction between CML with prominent thrombocytosis and ET hinges on molecular confirmation. The presence of the *BCR-ABL* fusion gene definitively establishes a CML diagnosis [1], whereas ET is characterized by driver mutations in *JAK2*, *CALR*, or *MPL* genes [7]. In this patient, negative JAK2

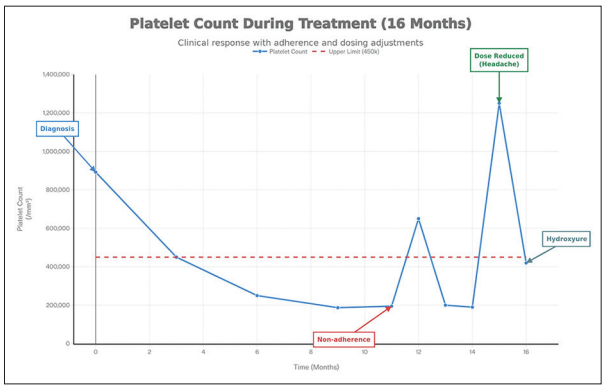

Figure 1: Clinical course and therapeutic response. Timeline illustrating the correlation between platelet count evolution (y-axis) and therapeutic interventions (x-axis). Note the rapid recurrence of thrombocytosis following non-adherence and dose reduction, and the subsequent response to the addition of Hydroxyurea. Dashed line indicates the upper limit of normal platelet count

molecular testing in the face of an atypical presentation necessitated a comprehensive genetic investigation, which eventually led to the critical detection of BCR-ABL and the correct diagnosis. Diagnostic algorithm for pediatric isolated thrombocytosis is shown in Figure 2.

The successful initial response to imatinib, with a major molecular response at 9 months, was followed by a molecular relapse during a documented period of treatment discontinuation. This phenomenon is well-established in TKI-treated CML and underscores the narrow therapeutic window and critical dependence of sustained response upon continuous, adequate drug exposure [1,8]. Modern molecular monitoring using IS quantification allows for the early detection of rising BCR-ABL1 transcript levels, enabling timely intervention [8]. In pediatric populations, sustained adherence to chronic daily oral TKI therapy represents a formidable clinical challenge, with adherence rates ranging from 50% to 80% in published cohorts [8,9]. The reversibility of the molecular relapse on prompt resumption of full-dose therapy in this patient

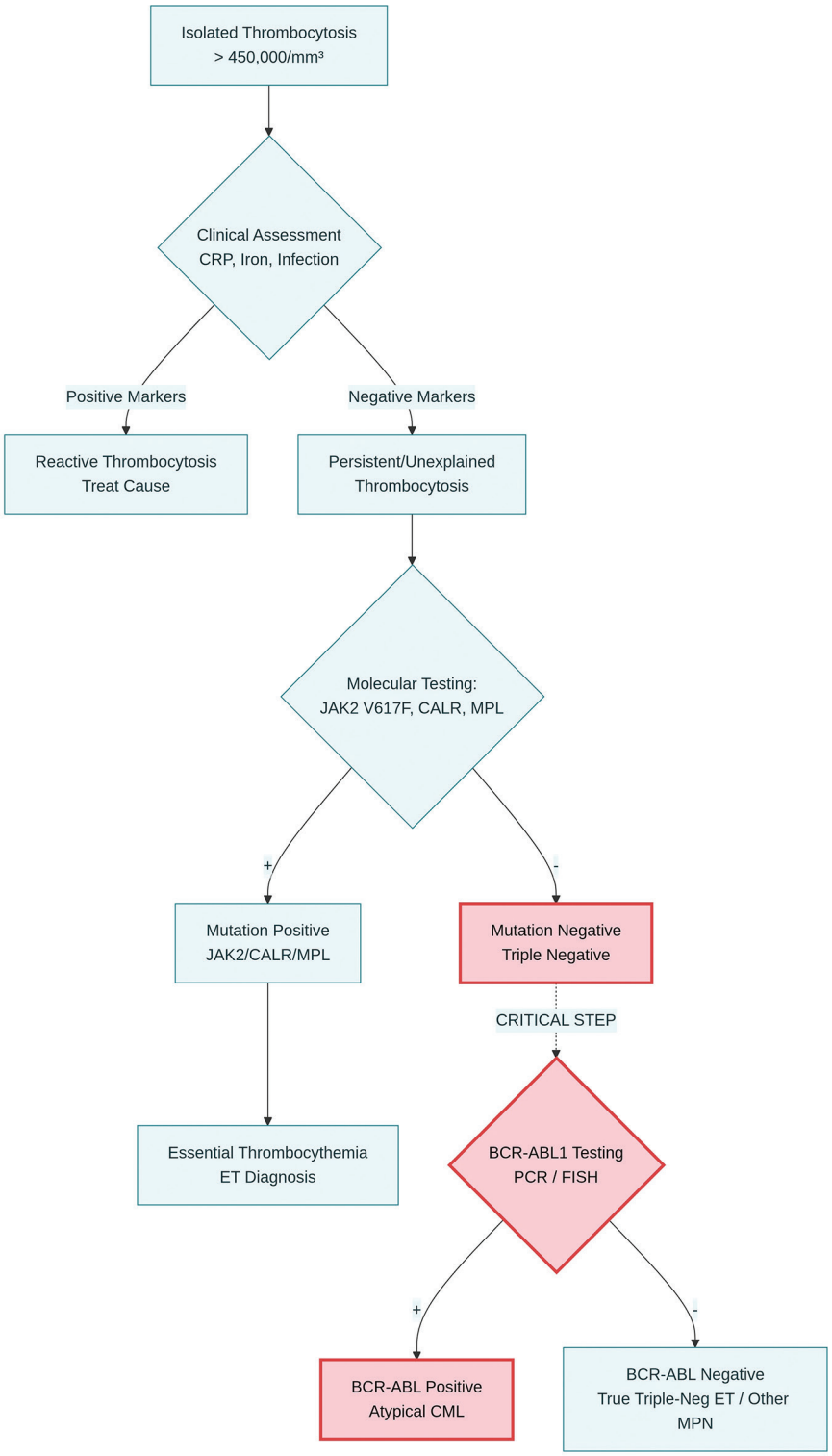

Figure 2: Diagnostic algorithm for pediatric isolated thrombocytosis. Flowchart depicting the critical diagnostic pathway to distinguish essential thrombocythemia from atypical chronic myeloid leukemia (CML). The red path highlights the necessity of BCR-ABL1 testing in patients with "triple-negative" thrombocytosis (JAK2/CALR/MPL negative) to avoid missing a CML diagnosis

demonstrates that resistance emerged from inadequate drug exposure rather than acquired BCR-ABL1 kinase domain mutations. However, cumulative episodes of non-adherence carry a substantial risk for the selection of TKI-resistant clones, potentially necessitating a switch to alternative TKIs [1,8,9].

Furthermore, the reduction in imatinib dosing due to headache-related adverse effects resulted in a rapid loss of disease control, manifesting as severe refractory thrombocytosis. This observation highlights the sensitive dose-response relationship in TKI therapy and suggests that the patient's disease biology is highly sensitive to even moderate variations in drug exposure. Full dosing of imatinib was necessary to maintain optimal suppression of BCR-ABL-driven proliferation [10]. The detection of BCR-ABL positivity by FISH (12% of cells) despite a negative qRT-PCR requires clarification. Possible explanations include variations in laboratory timing, different detection sensitivities between methodologies, sampling artifact, or residual disease at levels above FISH but below RT-PCR sensitivity. Repeat qRT-PCR on the IS was recommended to clarify the actual BCR-ABL burden and guide therapeutic decisions [1]. In situations where single-agent TKI monotherapy proves insufficient for platelet or leukocyte control, hydroxyurea has been employed as an adjunctive therapy. Its rapid cytoreductive effects make it particularly useful in acute settings of thrombocytosis. However, long-term combination therapy with a TKI and hydroxyurea requires careful monitoring for cumulative toxicities [11]. Finally, it is important to recognize that CML in pediatric populations differs from adult disease in several aspects, including its epidemiology (2–3% of childhood leukemias vs. 15–20% of adult leukemias), a typical diagnosis in school-age children (mean age 6–12 years), and the critical importance of structured adherence interventions and family engagement given the lifelong dependence on TKIs [2,8,9]. Intensive long-term molecular monitoring and comprehensive assessment of both disease and chronic TKI toxicities are essential [3].

CONCLUSION

This case illustrates the diagnostic and therapeutic complexities of CML in a pediatric patient presenting with isolated thrombocytosis. The atypical presentation and initial diagnostic confusion with ET underscore the necessity for comprehensive molecular and cytogenetic investigation in patients presenting with primary myeloproliferative features. The importance of adherence support, counseling, and family engagement in long-term pediatric CML management cannot be overstated. The introduction of hydroxyurea for rapid cytoreduction demonstrates the need for multidisciplinary collaboration and therapeutic flexibility when single-agent therapy proves inadequate. Long-term molecular and clinical monitoring and supportive care remain the cornerstone management strategies.

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