



Diagnostic Challenges in Acute Leukemia: A Case Report of Inconclusive Bone Marrow with Blasts in Peripheral Smear

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ABSTRACT

Introduction: Acute leukemia is a hematologic malignancy characterized by the proliferation of immature leukocytes that disrupt normal hematopoiesis, leading to cytopenias and systemic symptoms. Diagnosis typically relies on bone marrow evaluation. Peripheral blood findings may be critical when marrow results are inconclusive. **Case:** A 23-year-old male with melena, severe anemia, generalized weakness, and a two-week history of back pain. Physical examination revealed pallor and splenomegaly. Initial laboratory findings showed severe macrocytic anemia, leukocytosis, and thrombocytopenia. A peripheral blood smear revealed 63% blasts with a high nuclear-to-cytoplasmic ratio and prominent nucleoli. Despite these findings, the diagnosis of acute leukemia, bone marrow aspiration was inconclusive. Elevated lactate dehydrogenase indicated a high tumor burden. **Discussion:** Peripheral smear evaluation, supported by cytogenetic and flow cytometry studies, is vital for early diagnosis. Acute leukemia must remain a differential consideration even in the absence of definitive bone marrow findings. **Conclusion:** This case highlights the diagnostic challenge of acute leukemia with inconclusive initial bone marrow findings. Peripheral blood smear detection of circulating blasts was crucial in establishing the diagnosis. Early recognition through integrated diagnostic evaluation remains essential for the timely initiation of treatment.

Keywords: Acute leukemia, blast cells, bone marrow evaluation, case report, peripheral blood smear, thrombocytopenia.

ABSTRAK

Pendahuluan: Leukemia akut adalah keganasan hematologis yang ditandai oleh proliferasi leukosit imatur yang mengganggu hematopoiesis normal, menyebabkan sitopenia dan gejala sistemik. Diagnosis umumnya berdasarkan evaluasi sumsum tulang. Temuan pada darah tepi dapat penting jika hasil sumsum tulang tidak meyakinkan. **Kasus:** Pria berusia 23 tahun dengan keluhan melena, anemia berat, kelemahan umum, dan nyeri punggung sejak dua minggu. Pemeriksaan fisik menunjukkan pucat dan splenomegali. Pemeriksaan laboratorium awal menunjukkan anemia makrositik berat, leukositosis, dan trombositopenia. Apusan darah tepi menunjukkan 63% sel *blast* dengan rasio inti-sitoplasma tinggi dan nukleolus yang menonjol. Meskipun temuan ini mendukung diagnosis leukemia akut, hasil aspirasi sumsum tulang tidak meyakinkan. Kadar *lactate dehydrogenase* yang meningkat mengindikasikan beban tumor yang tinggi. **Pembahasan:** Evaluasi apusan darah tepi didukung oleh pemeriksaan sitogenetik dan *flow cytometry*, sangat penting untuk diagnosis dini. Leukemia akut harus tetap menjadi pertimbangan diagnosis banding, meskipun temuan sumsum tulang belum definitif. **Simpulan:** Kasus ini menyoroti tantangan diagnostik leukemia akut dengan hasil aspirasi sumsum tulang awal yang tidak konklusif. Deteksi blast sirkulasi pada apusan darah tepi berperan penting dalam menegakkan diagnosis. Pengenalan dini melalui evaluasi diagnostik yang terintegrasi tetap esensial untuk memulai terapi secara tepat waktu. **Putu Itta Sandi Lesmana Dewi, Tjokorda Gede Dharmayudha. Tantangan Diagnostik pada Leukemia Akut: Laporan Kasus Hasil Aspirasi Sumsum Tulang yang Inkonklusif dengan Adanya Sel Blast pada Apusan Darah Tepi.**

Keywords: Leukemia akut, sel *blast*, evaluasi sumsum tulang, laporan kasus, apusan darah tepi, trombositopenia.

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INTRODUCTION

Leukemia is a malignant disorder of the hematopoietic system characterized by the

clonal proliferation and accumulation of abnormal, immature leukocytes within the bone marrow, peripheral blood, spleen, and

other organs.¹ These dysfunctional cells disrupt normal hematopoiesis by displacing healthy hematopoietic precursors, resulting

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in cytopenias such as thrombocytopenia, anemia, and neutropenia that predispose patients to bleeding, fatigue, and infections, respectively.²

The development of leukemia can be broadly attributed to three major mechanisms. First, genetic mutations and chromosomal translocations, including alterations in transcription factors and epigenetic regulators, play a key role in driving the malignant transformation of hematopoietic progenitor cells.³ Second, immune dysregulation contributes to leukemogenesis by impairing immune surveillance mechanisms that would otherwise eliminate abnormal clones. Lastly, alterations in the bone marrow microenvironment, including changes in stromal support, cytokine networks, and niche signaling, further promote leukemic cell survival and proliferation.⁴ Understanding these mechanisms is essential not only for treatment but also for timely and accurate diagnosis.

Timely and accurate diagnosis of acute leukemia is critical, as delays can significantly impact prognosis.⁵ Bone marrow aspiration is typically the cornerstone for diagnosis, enabling cytological, immunophenotypic, and molecular evaluation.⁶ However, diagnostic challenges arise when bone marrow aspiration yields inconclusive results, either due to technical limitations such as dry tap, hemodilution, or inadequate sampling, or due to the underlying disease biology.^{7,8} In such cases, peripheral blood smear analysis becomes vital, especially when blasts are identifiable.⁹

CASE

A 23-year-old male presented to the emergency department with melena for the past 10 days, accompanied by generalized weakness and pallor. He also reported dizziness and reduced ability to perform daily activities. He denied any history of similar symptoms, fever, hematochezia, hematemesis, nausea, or vomiting. Notably, the patient had been experiencing lower back pain for the preceding two weeks, for which he had been taking diclofenac sodium 25 mg. No family history of malignancy or chronic illnesses. The patient worked at a cellphone retail store and reported irregular sleep

patterns, typically falling asleep at 4:00 AM and waking at 10:00 AM.

On physical examination, he appeared severely pale, with stable vital signs. Splenomegaly was observed (Schuffner grade 2) without evidence of hepatomegaly. Lumbar palpation over the L3–L4 vertebral region elicited tenderness.

Initial laboratory investigations revealed: severe macrocytic anemia: hemoglobin 2.5 g/dL, MCV 102.6 fL, MCH 32.1 pg, MCHC 31.3 g/dL, leukocytosis: $28.43 \times 10^3/\mu\text{L}$, severe thrombocytopenia: $17 \times 10^3/\mu\text{L}$, elevated C-reactive protein (CRP): 127 mg/L, elevated lactate dehydrogenase (LDH): 504 U/L.

By day five of hospitalization, repeat laboratory tests revealed leukopenia ($1.67 \times 10^3/\mu\text{L}$) and worsening thrombocytopenia ($10 \times 10^3/\mu\text{L}$). The peripheral smear now showed bicytopenia and a blast percentage of 63%, consistent with an evolving acute leukemia.

Bone marrow aspiration from the posterior superior iliac spine was performed but yielded inconclusive results. Abdominal ultrasonography confirmed splenomegaly, and the reticulocyte count remained within normal limits. The persistently elevated LDH indicated ongoing cell turnover and lysis, often associated with a poor prognosis in hematologic malignancies. Due to severe thrombocytopenia and impaired functional status, esophagogastroduodenoscopy (EGD)

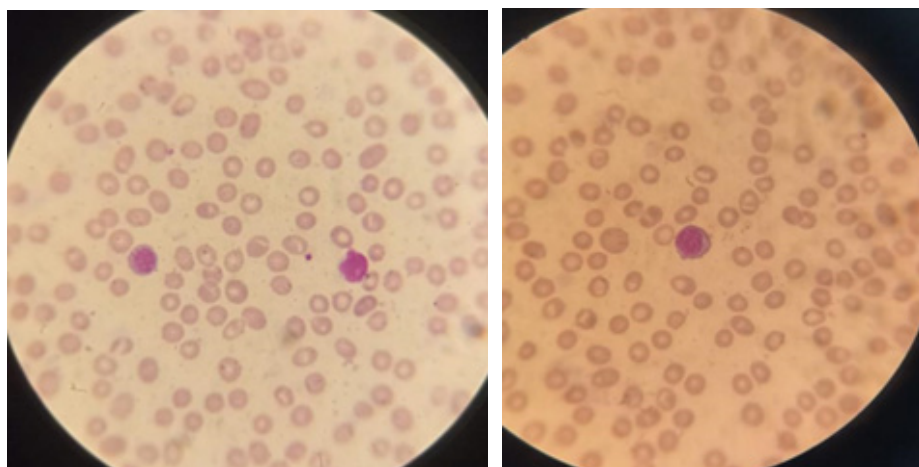
to evaluate the source of gastrointestinal bleeding was not performed.

This patient's working diagnosis was acute leukemia, based on the presence of systemic symptoms, pancytopenia with marked leukocytosis, and 63% circulating blasts on peripheral smear. Although bone marrow aspiration was inconclusive and flow cytometry was not available, the clinical findings, splenomegaly, back pain, elevated LDH, and peripheral blast morphology were strongly suggestive of acute leukemia, most likely acute myeloid leukemia (AML). In this case, the peripheral blood smear proved essential in guiding early diagnosis and clinical decision-making in a limited diagnostic resources setting.

DISCUSSION

This case highlights the diagnostic complexity of acute leukemia, particularly when bone marrow findings are inconclusive. Our patient, a 23-year-old male, presented with melena, profound weakness, and severe anemia, raising concern for gastrointestinal bleeding or hematologic malignancy. Laboratory studies revealed pancytopenia with severe anemia (Hb 2.5 g/dL), thrombocytopenia, and significant leukocytosis. The peripheral blood smear demonstrated blast-like cells, suggestive of acute leukemia, despite an inconclusive bone marrow aspirate.

Acute leukemia is characterized by the clonal proliferation of immature hematopoietic precursors, or blasts, in the bone marrow,



*Photo documentation by Putu Itta Sandi Lesmana Dewi.

Figure. Peripheral blood smear showing blasts in a suspected case of aleukemic leukemia with high nucleus-to-cytoplasm ratio and prominent nucleolus in a suspected case of aleukemic leukemia



peripheral blood, or other tissues. It typically presents with symptoms related to marrow failure anemia, bleeding, and infection, as well as organ infiltration in some cases.¹⁰ The presence of circulating blasts with cytopenias is a red flag for leukemia, warranting immediate diagnostic evaluation.

Since both acute and chronic leukemias typically exhibit widespread infiltration in the bone marrow, bone marrow aspiration (BMA) is commonly performed when acute leukemia is suspected.¹¹ Differentiation between acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) can often be made based on blast characteristics. However, in some cases, morphological examination alone may not be sufficient to distinguish between acute leukemia subtypes. For the most accurate diagnosis, cells obtained through BMA should be further analyzed using flow cytometry to assess their immunophenotype.¹²

In this case, the bone marrow aspirate failed to yield a definitive diagnosis. Inconclusive marrow studies may occur due to a "dry tap" resulting from extensive marrow infiltration or fibrosis, hemodilution, or inadequate sampling.¹³ When the marrow aspirate is non-diagnostic, a core needle biopsy becomes essential. Additionally, peripheral blood flow cytometry can be a useful alternative when blasts are present in circulation, offering immunophenotypic data necessary to classify the leukemia subtype (e.g., AML vs. ALL).^{14,15} The patient's macrocytic indices (MCV 102.6 fL) and elevated LDH could raise suspicion for megaloblastic anemia, which can mimic leukemia in rare cases.¹⁶ However, the leukocytosis, presence of blasts, and profound thrombocytopenia are more consistent with an acute leukemia rather than a nutritional deficiency.

Bashawri, *et al.*, discussed the indications for bone marrow examination and identified the most frequent diagnoses among 1,813 patients, while also evaluating the correlation between bone marrow aspiration (BMA) and bone marrow biopsy (BMB).¹⁷ The findings revealed that the primary indication for the examination was for the diagnosis and management of acute leukemia (22.2%). BMA served as a valuable diagnostic tool in various

conditions, particularly in hematological disorders.¹⁷ In another study by Ali Dogan, *et al.*, acute leukemia, specifically AML and ALL, was the most common diagnosis based on BMA, identified in 99 patients (19.8%), and these results were found to be 100% consistent with BMB findings.¹⁸ A separate retrospective study by Calvet, *et al.*, demonstrated that BMA contributed to the diagnosis and treatment of 40 out of 193 ICU patients (20.7%). BMA results were shown to significantly aid in diagnosing and managing patients both with and without hematologic malignancies at the time of admission.¹⁹

Several case reports have highlighted the diagnostic challenges posed by inconclusive bone marrow aspiration (BMA), particularly in patients with suspected acute leukemia. A case presented by Takeda, *et al.*, involved a 44-year-old man with B-cell precursor acute lymphoblastic leukemia (ALL), in whom initial BMA revealed extensive bone marrow necrosis and was non-diagnostic; the final diagnosis was achieved through peripheral blood flow cytometry.²⁰ Similarly, Bhatia, *et al.*, reported a pediatric case of precursor T-cell ALL where a dry-tap BMA due to marrow necrosis hindered early diagnosis, which was eventually confirmed through immunophenotyping.²¹ Another study by Wu, *et al.*, described asymmetric marrow involvement in post-allogeneic stem cell transplant patients; BMA from one iliac crest failed to detect relapse, emphasizing the importance of bilateral biopsies and imaging.²² These findings underscore the limitations of relying solely on BMA and the necessity of integrating peripheral blood analysis, immunophenotyping, and biopsy, especially in cases with hemodilution, necrosis, or dry taps, to achieve timely and accurate diagnosis.

NSAID use (diclofenac) may have contributed to the melena by causing gastric mucosal injury, but it cannot explain the hematologic abnormalities observed. It is possible that the gastrointestinal bleeding unmasked an underlying hematologic malignancy or that the patient's back pain and splenomegaly were subtle signs of leukemic infiltration that predated the bleeding episode.²³ In resource-limited settings or in cases with inconclusive marrow findings, the peripheral smear

remains a valuable diagnostic tool. Timely recognition and referral for hematologic evaluation are critical to initiate prompt treatment and prevent complications.²⁴

A comparable case was described by Tashiro, *et al.*,²⁵ involving a young adult with systemic symptoms and leukocytosis in whom initial bone marrow aspiration was non-diagnostic due to hemodilution and reduced cellularity. In that instance, the diagnosis of acute leukemia was ultimately established through careful evaluation of peripheral blood smears and flow cytometric analysis, highlighting the critical role of alternative diagnostic modalities when bone marrow examination is inconclusive. The authors emphasized the need to maintain a high index of suspicion and to leverage peripheral blood immunophenotyping and bone marrow biopsy in cases with diagnostically ambiguous presentations. This report parallels the current case and reinforces the importance of integrating peripheral hematologic findings into the diagnostic workflow for suspected acute leukemia, particularly in urgent clinical settings.²⁵

This case illustrates the importance of including acute leukemia in the differential diagnosis of melena. Patients with acute leukemia usually had upper gastrointestinal tract bleeding, and the most common endoscopic findings were related to gastric erosions and duodenal ulcers.²⁶ In our patient, the bleeding was probably predisposed by thrombocytopenia. In patients with hematologic neoplasms, the benefit of endoscopy should be carefully weighed to avoid potential harms, including increased risks of bacteremia and bleeding.²⁷ Thrombocytopenia is a well-established cause of bleeding tendency in hematologic neoplasms. It also demonstrates that unexplained cytopenias may be the first sign of acute leukemia, before circulating blasts can be detected.²⁸ Comprehensive investigations are needed, and cytogenetic findings may offer important diagnostic information.

CONCLUSION

This case illustrates the diagnostic complexity of acute leukemia, particularly if initial bone marrow aspiration yields inconclusive results.



Despite prominent clinical features including gastrointestinal bleeding, cytopenias, and systemic symptoms, diagnosis was initially hindered by the absence of definitive findings from marrow evaluation. The detection of circulating blasts on peripheral blood smear proved instrumental in guiding further diagnostic investigation, ultimately leading to the diagnosis. This clinical scenario aligns with previously documented cases in which

reliance on peripheral smear morphology and subsequent flow cytometric analysis facilitated diagnosis despite nondiagnostic marrow findings. The present case underscores the necessity of a high index of clinical suspicion and a comprehensive diagnostic approach that incorporates hematologic, immunophenotypic, and molecular data to ensure timely recognition and treatment initiation. Early identification

remains critical to improving outcomes in patients with acute leukemia who present with atypical or diagnostically challenging features.

Informed Consent

The patient or a family member has provided written or verbal consent for the publication of the manuscript and all identifiable data.

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