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(CASE REPORT)

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Atypical morphological appearance of acute lymphoblastic leukemia confirmed by immunophenotyping

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Abstract

Despite significant advances in diagnostic techniques for acute leukemia, namely immunophenotyping and molecular biology, morphology remains the first essential examination for detecting leukemia and determining whether it is myeloblastic or lymphoblastic in order total discordance with immunophenotyping data. The aim of this study is to report a case of pre-B ALL with a morphological appearance of blasts with "Cup-like" nuclear invagination most often observed in FLT3, NPM, and CEBPA-type AML. We report the case of a 36-year-old man presenting with a tumor and hemorrhagic syndrome with hyperleukocytosis. The blood smear showed blasts with cup-like nuclear invagination, an appearance classically associated with acute myeloblastic leukemia (AML) with FLT3, NPM1, or CEBPA mutations. However, bone marrow immunophenotyping revealed pre-B acute lymphoblastic leukemia (ALL), confirmed by the expression of CD19, CD10, CD34, and TdT, and the absence of myeloperoxidase.This discrepancy between morphology and immunophenotyping illustrates the importance of not limiting oneself to cytological data. Despite appropriate management, the clinical course was rapidly unfavorable, with early death before specific treatment could be initiated.This case highlights the need to systematically combine morphology, immunophenotyping, and molecular analyses in order to obtain an accurate diagnosis, avoid morphological traps, and guide the therapeutic strategy in acute leukemias.

Keywords: Acute lymphoblastic leukemia; Immunophenotyping; Morphology; Diagnostic discordance; Cup-like blasts

1. Introduction

The diagnosis of acute leukemia is now based on a combination of several complementary approaches: morphology, immunophenotyping, and molecular biology. Blood smears and myelograms remain the first-line tests, allowing rapid determination of whether the proliferation is myeloblastic or lymphoblastic [1]. However, morphological analysis alone can be misleading, as certain cytological features can mimic another hematopoietic lineage. In this context, immunophenotyping plays an essential role in confirming the diagnosis, specifying the subtype, and guiding the therapeutic strategy [2].

Acute leukemias are serious malignant blood disorders characterized by clonal proliferation of immature blasts in the bone marrow and peripheral blood. They account for approximately 3% of adult cancers, with an estimated annual incidence of between 4 and 5 cases per 100,000 inhabitants [3,4]. Acute lymphoblastic leukemia is much more common in children, whereas in adults it accounts for only about 20% of acute leukemias, with a generally less favorable prognosis [5,6]. The diagnosis is based on a combination of clinical and biological evidence, including blood smears, myelograms, cytology, immunophenotyping, and molecular biology [7,9].

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We report here the case of a young adult with pre-B acute lymphoblastic leukemia, whose morphological appearance of the cup-like blasts initially suggested acute myeloblastic leukemia. This discrepancy illustrates the importance of immunophenotyping in confirming the diagnosis and accurately classifying acute leukemias.

2. Case presentation

A 36-year-old man with no significant medical history and a moderate smoking habit consulted for axillary lymphadenopathy that had appeared 15 days earlier and quickly become diffuse. He presented with petechial purpura on his lower limbs, a febrile abscess on his right index finger, night sweats, anorexia, and unquantified weight loss.

Clinical examination revealed a fever of 38.2°C, bilateral cervical lymphadenopathy, petechial purpura of the lower limbs, gingival hyperalgesia without oral hemorrhagic syndrome, and no hepatosplenomegaly, testicular infiltration, or neurological deficit.

Initial tests showed normocytic normochromic aregenerative anemia with hemoglobin at 7.6 g/dL, severe thrombocytopenia at 6,000/mm^3, and hyperleukocytosis at 77,960/mm^3 with 82% blasts in the blood smear (Figure 1). The blasts were small to large in size, with fine chromatin, nucleoli, nuclei sometimes showing deep indentations, a high nucleocytoplasmic ratio (9/10), basophilic cytoplasm without granulations, and occasional cup-like depressions. MPO staining was negative (Figure 2). Uric acid was elevated at 80.3 mg/L, with no renal failure; the glomerular filtration rate (GFR) was estimated at 99 ml/min (Table 1).

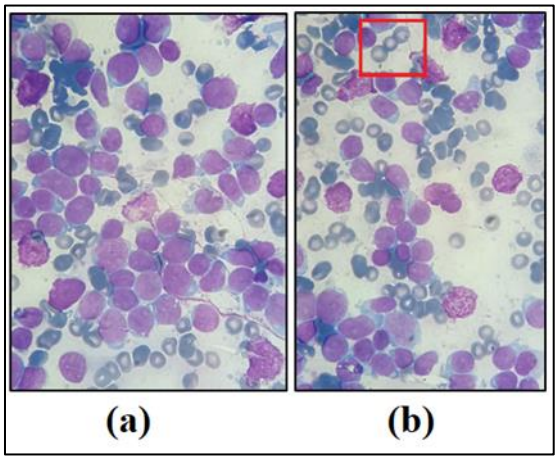

Figure 1 1a Blood smear on day 1 showing hyperleukocytosis with circulating blasts (MGG staining, G×1000). **Figure 1b.** Same blood smear showing a blast with cup-like nuclear depression, a cytological feature commonly described in certain AML cases with FLT3, NPM1, or CEBPA mutations (MGG staining, G×1000)

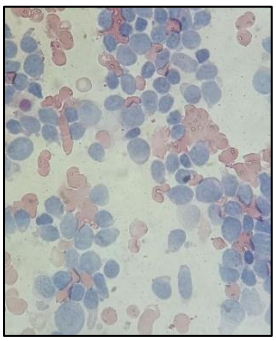

Figure 2 Myeloperoxidase (MPO) cytochemical staining performed on day 1: absence of specific cytoplasmic staining, confirming the negativity of circulating blasts (MPO staining, G×1000)

Urgent treatment was initiated with parenteral hyperhydration, allopurinol at 10mg/kg, prednisone at 60mg for 7 days, and an antiseptic mouthwash. Further investigation is initiated: myelogram, immunophenotyping, karyotype (search for Philadelphia chromosome and additional abnormalities), brain CT scan, transthoracic echocardiography, and serology. Over the following days, the patient presented with mild bulimia, persistent sweating, ankle edema, and eye redness, with partial improvement of the purpura. Biologically, worsening anemia (Hb at 5.9 g/dL), persistent thrombocytopenia, and a significant decrease in leukocytosis (38,600/mm^3) were noted. The brain CT scan showed no abnormalities.

Medullary immunophenotyping reveals 94% of blasts expressing CD19, CD79a, CD10, HLA-DR, TdT, and CD34 markers, with negative MPO, consistent with pre-B acute lymphoblastic leukemia. The myelogram reveals rich, amegakaryocytic marrow, confirming medullary invasion by 98% of blasts with a morphology similar to that observed on the blood smear, with a high percentage of blasts with irregular contours and a mirror-like appearance (Figure 3).

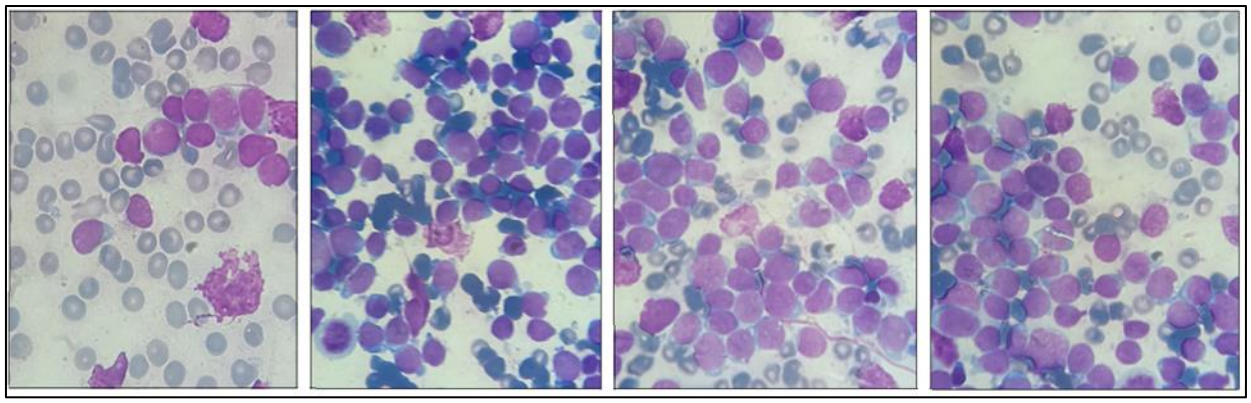

Figure 3 Myelogram on day 5 showing rich marrow invaded by blasts

The chest X-ray showed no abnormalities, and the echocardiogram revealed preserved systolic function with an LVEF of 56%. Liver function tests were normal. Renal function, initially preserved, subsequently showed a moderate elevation in creatinine (5.62 mg/L), reflecting a transient alteration related to lysis syndrome. In addition, hyperferritinemia (935 ng/mL), elevated LDH (432 IU/L), and CRP at 31.2 mg/L were noted, consistent with an active inflammatory process and lysis syndrome. Early treatment of lysis syndrome was initiated with parenteral hyperhydration and allopurinol, combined with red blood cell and platelet transfusions. On the eighth day of corticosteroid therapy, a follow-up blood smear revealed the persistence of circulating blasts, indicating corticosteroid resistance. At the same time, a cytogenetic study including testing for BCR-ABL translocation was requested in order to refine the classification of the leukemia and guide the therapeutic strategy. Treatment was directed towards a GRALL protocol pending the BCR-ABL result. If the result had been positive, a GRAAPH protocol would have been chosen. The GRALL protocol is based on a combination of vincristine, prednisone, anthracycline, and L-asparaginase, followed by consolidation phases (cytarabine, methotrexate, cyclophosphamide, mercaptopurine) and maintenance (methotrexate + mercaptopurine). The GRAAPH protocol, intended for Ph1-positive ALL, combines GRALL-type chemotherapy with a tyrosine kinase inhibitor (imatinib, dasatinib, or nilotinib). Unfortunately, the patient died before the results were obtained due to the rapid progression of his leukemia.

Table 1 Summary of biological parameters

Biological parameters	**J1**	**J4**	**J6**	**J7**
Hb (g/dL)	7,6	5,9	8	7,7
MCV (fL)	90	92,8	89	90
MCH (pg)	31	32,6	31,6	32,1
Platelets (/mm^3)	6 000	7 000	2 000	3 000
Leukocytes (/mm^3)	77 960	38 600	15 710	17 820
PNN (/mm^3)	2 339	2 250	1 180	2 690
Lymphocytes (/mm^3)	10 135	14 070	9 780	11 500

CRP (mg/L)	17	—	31,2	—
Uric acid (mg/L)	80,3	80,3	21,7	—
Calcium (mg/L)	81	81	82,4	—
Phosphorus (mg/L)	50,2	50,2	48,2	—
Creatinine (mg/L)	9,9	—	—	5,62
Urea (g/L)	0,31	—	—	0,46
Sodium (mmol/L)	—	—	132	—
Ferritin (ng/mL)	—	—	935	—
LDH (IU/L)	—	—	432	—
PT (%)	—	—	—	59
INR	—	—	—	1,34

Hb = Hemoglobin; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; PNN = Polymorphonuclear neutrophils; CRP = C-reactive protein; LDH = Lactate dehydrogenase; PT = Prothrombin time; INR = International Normalized Ratio.

3. Discussion

According to recent data from GLOBOCAN 2020, more than 474,000 new cases of leukemia were diagnosed worldwide, with an increasing burden observed in middle-income countries, particularly in North Africa and Asia [9]. The gradual increase in incidence could be linked to improved access to diagnostic tools, but also to the impact of environmental factors [10,11]. Our observation illustrates the clinical severity and rapid progression of type B acute lymphoblastic leukemia in young adults. Despite rapid initial treatment, the fulminant course highlights the crucial importance of early diagnosis and appropriate therapeutic stratification. Since its first version in 2002, the WHO classification has been based on a range of arguments incorporating clinical, morphological, immunophenotyping, and molecular analyses. Morphology remains of fundamental importance, but it can sometimes be a source of diagnostic error. In practice, morphological observation remains an essential step in the initial diagnosis. Through blood smears and myelograms, it allows for rapid orientation toward a myeloid or lymphoid lineage and guides additional tests [12]. However, certain atypical presentations, such as the cup-like appearance of our blasts, remind us that morphology must always be interpreted in conjunction with immunophenotyping and molecular biology [13]. In our case, the presence of blasts with cup-like nuclear depression suggested acute myeloblastic leukemia. This morphological profile is well described in the literature, particularly in association with FLT3 and NPM1 mutations in AML [14,16]. However, immunophenotyping allowed the diagnosis to be corrected in favor of pre-B ALL. Several studies have highlighted this problem of morphology-immunophenotyping discordance. In some series, cases initially classified as AML on cytology were found to be ALL or ambiguous leukemias after immunophenotyping [17]. Other studies confirm that, although morphology and cytochemistry remain important, they may lack specificity in certain atypical forms [18,19]. This highlights the need for an integrated approach, systematically combining morphology, immunophenotyping, and molecular biology.

In our observation, immunophenotyping played a central role thanks to the identification of specific markers (CD19, CD10, CD34, TdT), confirming the lymphoblastic lineage and guiding therapeutic management. Several studies confirm its diagnostic and prognostic value. Gémes et al. [20] showed that multiparametric phenotyping can identify treatment-resistant subpopulations, improving the accuracy of therapeutic strategies. Béné et al. also emphasize its fundamental role in lineage assignment and the detection of aberrant profiles, particularly in atypical forms [21,22]. Basso et al. [23] have highlighted the value of multiple staining in distinguishing normal cells from pathological cells, even in nonspecific presentations. More recently, Suratman [24] and Rahmawati [25] recommend its systematic integration from the initial evaluation onwards, due to its speed, sensitivity, and growing role in the development of CD19-targeted immunotherapies.

This case, although typical in terms of immunophenotype, illustrates the serious consequences of delays in performing cytogenetic testing and initiating specific treatment. It reinforces the idea that morphology, although essential, can be misleading and that only an integrated approach, combining blood smears, myelograms, immunophenotyping, and molecular analyses, can ensure a reliable diagnosis, guide therapeutic strategy, and anticipate the follow-up of residual disease.

4. Conclusion

Immunophenotyping is a major diagnostic tool in acute leukemia, enabling the identification of the lineage and guiding therapeutic management. Nevertheless, morphology and molecular biology remain indispensable complementary tools. This case illustrates the limitations of morphological analysis alone and demonstrates that only an integrated approach, combining blood smears, myelograms, immunophenotyping, and cytogenetic/molecular analyses, can provide a reliable diagnosis and appropriate therapeutic stratification.

Compliance with ethical standards

Disclosure of conflict of interest

Disclosure of conflict of interest There is no conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study by signing the Free and Informed Consent Form

References

[1] Ally F, Chen X. Acute myeloid leukemia: diagnosis and evaluation by flow cytometry. Cancers. 2024;16(22):3855.

[2] Basharat M, Khan SA, Ahmed D. Immunophenotypic characterisation of morphologically diagnosed cases of acute myeloid leukaemia (AML). Pak J Med Sci. 2019;35(2):470–475.

[3] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660

[4] Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 2017;7(6):e577. doi:10.1038/bcj.2017.53

[5] Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet. 2013;381(9881):1943–1955. doi:10.1016/S0140-6736(12)62187-4

[6] Campana D. Role of minimal residual disease monitoring in adult and pediatric acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009;23(5):1083–1098. doi:10.1016/j.hoc.2009.07.004

[7] Béné MC, Castoldi G, Knapp W, et al. Proposals for the immunological classification of acute leukemias. Leukemia. 1995;9(10):1783–1786.

[8] Sallan SE. Acute lymphoblastic leukemia in adults and children. Semin Oncol. 1990;17(3 Suppl 4):1–5.

[9] International Agency for Research on Cancer. Cancer Today (GLOBOCAN 2020). Available from: https://gco.iarc.fr/today

[10] Miranda-Filho A, Piñeros M, Ferlay J, et al. Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol. 2018;5(1):e14–e24. doi:10.1016/S2352-3026(17)30232-6

[11] Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect. 2007;115(1):138–145. doi:10.1289/ehp.9023

[12] Sekar, M. D., Raj, M., & Manivannan, P. (2023). Role of morphology in the diagnosis of acute leukemias: Systematic review. Indian Journal of Medical and Paediatric Oncology, 44(05), 464-473.

[13] Juskevicius, R., Thompson, M. A., Shaver, A., & Head, D. (2020). Clinical presentation, diagnosis, and classification of acute myeloid leukemia. In Acute Leukemias (pp. 11-55). Cham: Springer International Publishing.

[14] Chen, W., Konoplev, S., Medeiros, L. J., Koeppen, H., Leventaki, V., Vadhan-Raj, S., ... & Bueso-Ramos, C. E. (2009). Cuplike nuclei (prominent nuclear invaginations) in acute myeloid leukemia are highly associated with FLT3 internal tandem duplication and NPM1 mutation. Cancer, 115(23), 5481-5489.

[15] Chen, W., Rassidakis, G. Z., Li, J., Routbort, M., Jones, D., Kantarjian, H., ... & Bueso-Ramos, C. E. (2006). High frequency of NPM1 gene mutations in acute myeloid leukemia with prominent nuclear invaginations ("cuplike" nuclei). Blood, 108(5), 1783-1784.

[16] Kussick, S. J., Stirewalt, D. L., Yi, H. S., Sheets, K. M., Pogosova-Agadjanyan, E., Braswell, S., ... & Wood, B. L. (2004). A distinctive nuclear morphology in acute myeloid leukemia is strongly associated with loss of HLA-DR expression and FLT3 internal tandem duplication. Leukemia, 18(10), 1591-1598.

[17] Salem, A. K., Al-hag, A. Y., & Aljaber, N. (2020). Correlation of cyto-morphology with flow cytometric immunophenotyping in acute leukemia's: A Comparative study. Hematol Blood Disord 2020; 3 (2): 1-4 Hematol Blood Disord 2020 Volume 3 Issue 3, 39, 17.

[18] Kresno, S. B., Haryanto, S. H., Kosasih, A. S., Muthalib, A., & Atmakusumah, D. (2004). Immunophenotyping in leukemia and its diagnostic significance. Medical Journal of Indonesia, 13(3), 195-202.

[19] Venugopalan, R. K., Singh, N., Anthony, M. L., Kunnumbrath, A., Gupta, A. K., Nath, U. K., ... & Chandra, H. (2023). Leukemia-associated aberrant immunophenotype: A flow cytometry-based experience of 110 cases from a tertiary care center in Northern India. Journal of Cancer Research and Therapeutics, 19(5), 1335-1339.

[20] Gémes N, Sági JC, Kiss Á, et al. Multiplex immunophenotyping of human acute myeloid leukemia patients revealed single-cell heterogeneity with special attention on therapy sensitive and therapy resistant subpopulations. Front Immunol. 2025.

[21] Béné MC, et al. Impact of immunophenotyping on management of acute leukemias. Haematologica. 1999;84(9):818–827.

[22] Hamed, E. O. and El-Deen, A. F. (2018). Flow cytometric diagnosis of acute leukemia and aberrant antigen: sohag university experience. Open Journal of Blood Diseases, 08(02), 37-48.

[23] Basso G, et al. New methodologic approaches for immunophenotyping acute leukemias. Haematologica. 2001;86(6):609–613.

[24] Suratman R, et al. The Role of Immunophenotyping in the Diagnosis of Acute Leukemia. Bioscientia Medicina. 2023.

[25] Rahmawati E, et al. Immunophenotyping in Acute Leukemia. Int J Health Sci Res. 2025.