

Acute Undifferentiated Leukemia Presented With Mediastinal Sarcoma

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Abstract

Acute undifferentiated leukemia (AUL) is a rare, aggressive type of acute leukemia associated with poor prognosis, in which the blasts lack lineage commitment to either the myeloid or lymphoid lineages. It is classified according to the World Health Organization (WHO) classification under the category of acute leukemias of ambiguous lineage (ALAL). Here we present a case of a 20-year-old man, who was referred to Military Cancer Center in February 2025, as a case of mediastinal myeloid sarcoma, which was diagnosed by biopsy of the mass. Bone marrow examination was performed in our center and showed infiltration by blasts, flow cytometry of bone marrow aspirate specimen revealed that blasts do not express lineage-specific markers with expression of primitive markers, so the diagnosis of AUL was established. For precise diagnosis of AUL, a comprehensive and broad panel of immunomarkers should be run to rule out any lineage commitment for the clone. Review of literature revealed only one previously published similar case.

Keywords: Acute undifferentiated leukemia; Sarcoma; Flow cytometry

Introduction

Acute undifferentiated leukemia (AUL) is a rare type of acute leukemia that is characterized by the lack of expression of lineage-specific markers that distinguish myeloid, B- or T-lymphoid lineages with expression of primitive stem cell markers such as CD34, CD38, and human leukocyte antigen-DR isotype (HLA-DR), and usually positive for CD45 and CD7 [1, 2]. The lineage-specific marker for myeloid lineage is my-

eloperoxidase (MPO); for the B-lymphoid lineage, they are CD19, CD22 and CD79a; and for T-lymphoid lineage, it is cytoplasmic CD3 [3]. Genetic data on AUL are limited because of rarity of cases [4]. No characteristic cytogenetic abnormalities could be assigned to AUL, but the limited available data suggest that expression of genes associated with poor prognosis are often expressed, such as *BAALC*, *ERG*, and *MNI*; and to date, no reports have documented cases showing genetic mutations usually seen in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), including *FLT3*, *WT*, *MLL*, or *BCR-ABL* [1]. Some studies showed cases with deletion 5, trisomy 8, trisomy 13 and trisomy 12 [5, 6]. These cases do not have well-established treatment protocol and harbor high risk of relapses with a median overall survival (OS) time of only 9 months, far lower than ALL and AML [7].

Myeloid sarcoma (MS) is extramedullary mass of myeloblasts that can occur in isolation (*de novo*) or with AML and myeloid neoplasms [8]. It can occur at any age and any site, but the most involved sites are skin, lymph nodes, soft tissue, and bone [9]. Fine needle aspiration (FNA) is usually inadequate for diagnosis of MS, and tissue biopsy is the preferred method [10]. Genetic aberrations in MS include monosomy 7, trisomy 8, MLL, NPM1, FTL3, inv(16), monosomy 16, loss of 16q, 5q, or 20q [1]. The treatment depends on the disease presentation, whether it is an initial diagnosis or relapse, as well as the age of the patient and performance status. Treatment options include chemotherapy, radiation, surgery and allogeneic stem cell transplantation [11]. The prognosis in cases of MS at diagnosis of AML is poor, while isolated MS shows better outcomes [9, 12].

Case Report

A 20-year-old man with a history of congenital hypothyroidism and cryptorchidism presented to Al Mafraq Governmental Hospital with shortness of breath (SOB). A chest X-ray revealed right sided pleural effusion, and the patient was referred to King Abdulla University Hospital in Irbid in January 2025 for further investigations, where they placed pigtail catheter and drained exudative fluid. Echocardiogram was performed and revealed pericardial effusion, then serial echo revealed progression of pericardial effusion. Computed tomography (CT) scan was requested and showed multiple posterior mediastinal lymph nodes with pleural and pericardial ef-

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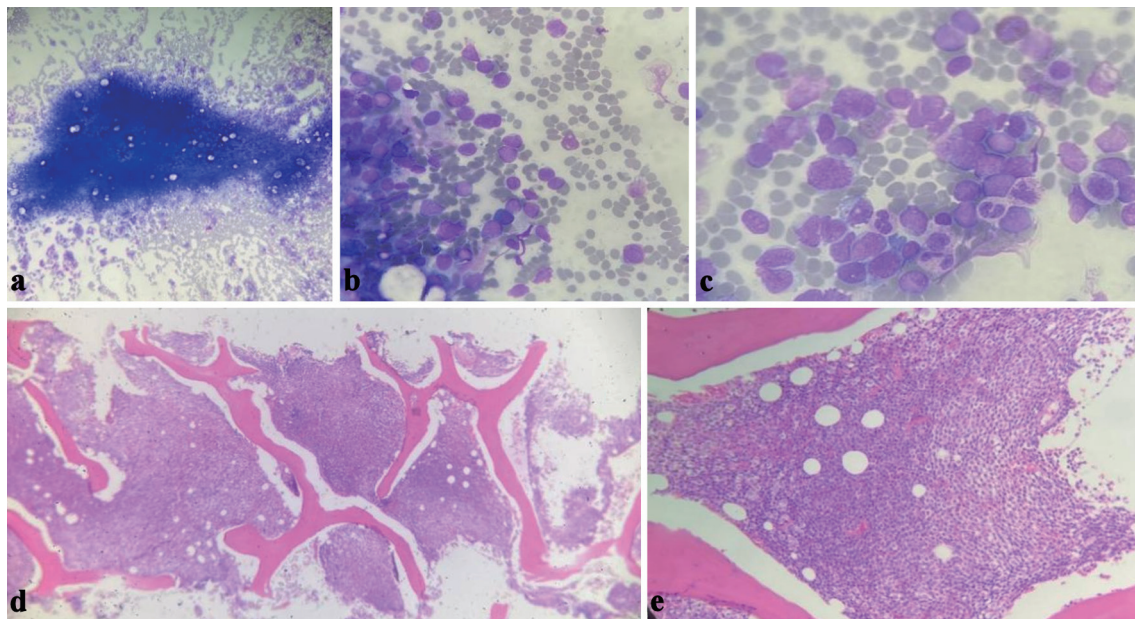


Figure 1. Bone marrow aspirate (a, b, c) showing the blasts infiltrating the bone marrow, the morphology is more toward myeloid leukemia. Bone marrow biopsy (d, e) showing diffuse total infiltration by blasts.

fusion. Pericardiocentesis and pleurocentesis were performed for symptoms relief, and the collected fluids were sent to the laboratory for investigations. Cytology showed 90% mononuclear blastoid cells, and flow cytometry revealed positive cells for CD34, CD33, and human leukocyte antigen-DR isotype (HLA-DR), and negative for CD2, CD3, CD10, CD19, CD20, CD13, CD14, CD64, MPO and terminal deoxynucleotidyl transferase (TdT).

MS was suspected according to immunophenotype of the cells, so tru-cut biopsy for mediastinal lymph nodes was done and showed infiltration by atypical mononuclear cells with high nuclear/cytoplasmic (N/C) ratio. Immunohistochemical stains revealed tumor cells positive for CD34 and negative for all lineage-specific markers. So, the diagnosis of MS was confirmed. Positron emission tomography (PET) scan was done to determine the extent of the disease and showed increased bone marrow activity in addition to the bulky mediastinal mass.

The patient was referred to Military Cancer Center in February. Complete blood count showed leukocytosis (white blood cell (WBC) count = $15 \times 10^6/\text{mL}$) with normal hemoglobin (Hb) and platelets count, liver and kidney functions were normal, international normalized ratio (INR) was 1.53, and lactate dehydrogenase (LDH) level was 229 U/L. Bone marrow examination was performed and showed infiltration by blasts constituting around 60% of bone marrow cells (Fig. 1). A wide comprehensive flow cytometry panel was run and showed positivity for CD34, CD38, HLA-DR, CD33, and CD7 and negative for all other myeloid and lymphoid markers including MPO, CD117, CD13, CD11b, CD14, CD16, CD35, CD36, CD64, CD300e (IREM-2), CD5, CD1a, and CD10 (Fig. 2). So, the diagnosis of AUL was reported (Table 1). Cytogenetic tests showed monosomy 16 in 65% of metaphases. Cardiology consultation was requested before starting

chemotherapy. Pericardiocentesis was recommended by the cardiologist, and 400 mL of serous fluid was drained. After that the patient complained about abdominal pain, so surgical consultation was sent. The abdominal CT scan with contrast was done, which revealed splenic infarction.

Treatment was initiated with the 3 + 7 regimen, consisting of induction with cytarabine and idarubicin, followed by consolidation with high-dose cytarabine (HiDAC) regimen. Allogenic stem cell transplantation was scheduled.

Follow up-bone marrow aspirate was performed 4 weeks post induction chemotherapy and showed complete remission. The patient developed blurring of vision and headache during treatment protocol. A cerebrospinal fluid (CSF) test for blasts was performed and showed negative results, and brain CT scan and magnetic resonance imaging (MRI) were suggestive of fungal sinusitis. Ophthalmologic and ear, nose and throat (ENT) consultations were performed, and the patient was started on antifungal treatment and high-dose steroid.

The patient continued consolidation until the donor for allogenic transplant was found; but unfortunately, the patient went to Al-Mafraq Governmental Hospital in May complaining of SOB and vomiting. His WBC count was $0.3 \times 10^6/\text{mL}$, Hb was 6.8 g/dL and platelets count $2 \times 10^6/\text{mL}$. He was admitted to the hospital, and few hours later he developed loss of consciousness. Urgent brain CT scan was performed and revealed brain hemorrhage with edema and brain stem herniation; the patient died on the same day.

Discussion

In the 2016 update of the World Health Organization (WHO) classification of myeloid neoplasms, AUL is considered a sub-

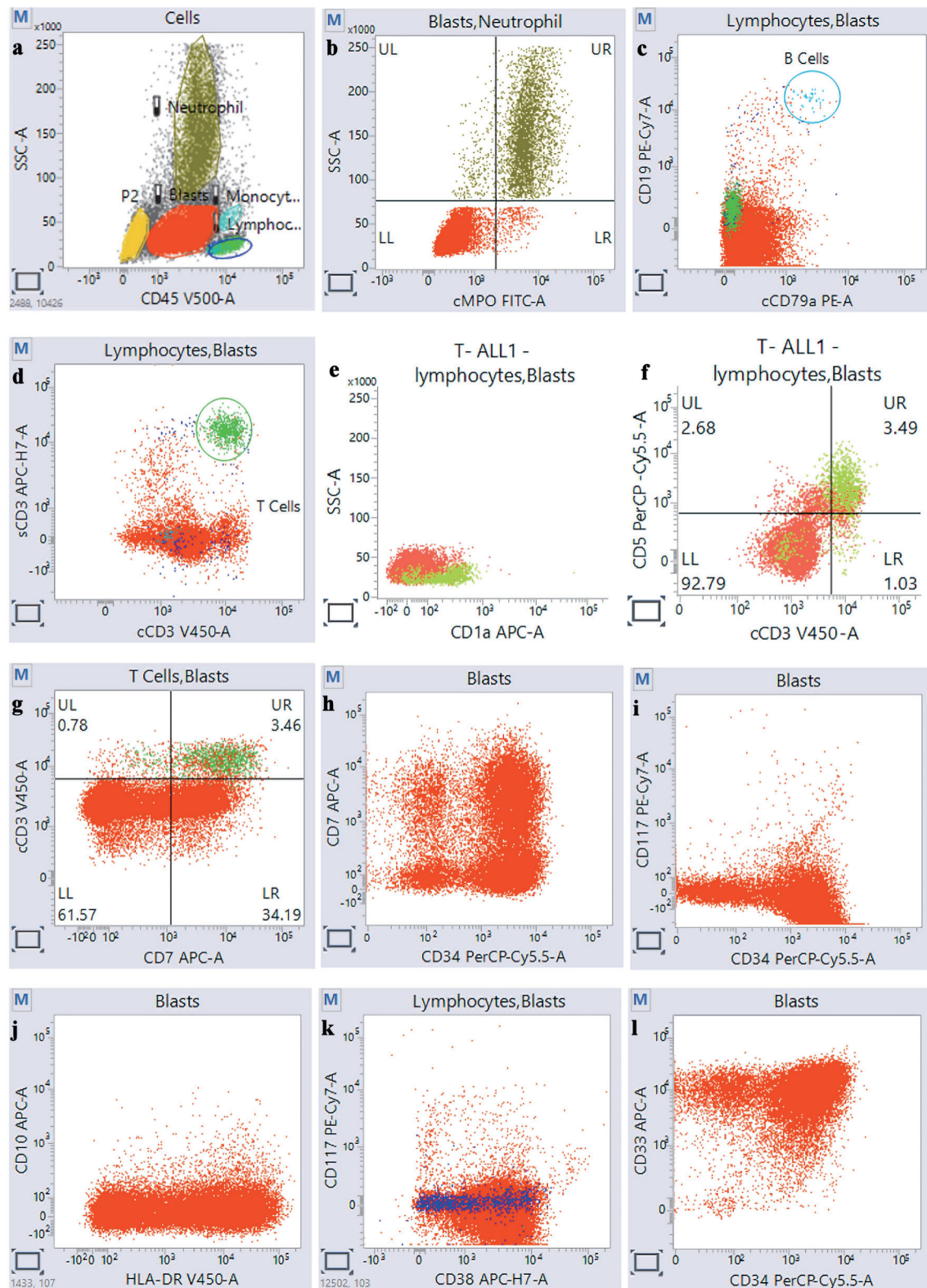


Figure 2. Flow cytometry of acute undifferentiated leukemia case showing blast population (red) positive for CD45 (a), negative for lineage-specific antigen (b, c, d), negative for T-cell markers (e, f), positive for CD7 (g, h), positive for primitive markers, which are CD34, HLA-DR, and CD38, and negative for CD117 (i, j, k), positive for only one myeloid marker CD33 (l), and negative for all other markers (m, n, o, p, q, r, s, t). HLA-DR: human leukocyte antigen-DR isotype.

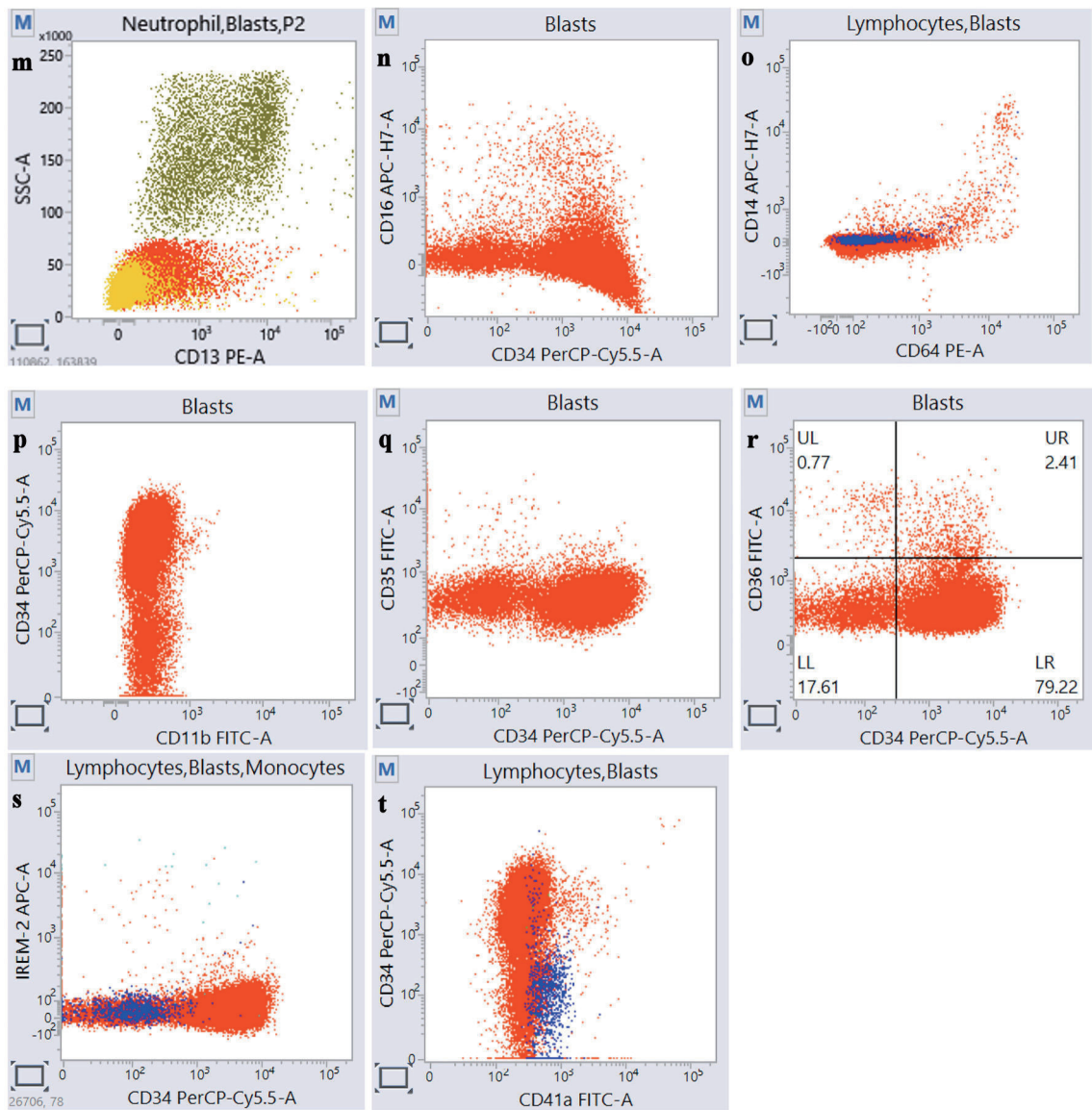


Figure 2. (continued) Flow cytometry of acute undifferentiated leukemia case showing blast population (red) positive for CD45 (a), negative for lineage-specific antigen (b, c, d), negative for T-cell markers (e, f), positive for CD7 (g, h), positive for primitive markers, which are CD34, HLA-DR, and CD38, and negative for CD117 (i, j, k), positive for only one myeloid marker CD33 (l), and negative for all other markers (m, n, o, p, q, r, s, t). HLA-DR: human leukocyte antigen-DR isotype.

Table 1. Timeline of the Case

Time point	Event	Description
Day 0	Patient presented with SOB	CXR showed right pleural effusion
Day 5	Pleurocentesis	Exudative fluid
Day 8	Echocardiogram	Pericardial effusion
Day 15	Chest CT scan	Posterior mediastinal mass
Day 18	Mediastinal mass biopsy	Myeloid sarcoma
Day 19	PET scan	Bulky hypermetabolic mediastinal mass with bone marrow hyperactivity
Day 28	Bone marrow aspirate	AUL

SOB: shortness of breath; CXR: chest X-ray; CT: computed tomography; PET: positron emission tomography; AUL: acute undifferentiated leukemia.

category of acute leukemias of ambiguous lineage (ALAL). This rare subtype of acute leukemia lacks evidence of either lymphoid or myeloid lineage or displays evidence of more than one lineage [1]. AUL lacks the main lineage-specific immunophenotypic markers, including MPO, cCD3, CD19, CD22 and CD79a, and mostly expresses only one lineage marker, such as CD13, CD33, and CD7, in addition to stem cell markers, which represent the immature characteristic of the clone, including CD34, CD38, HLA-DR and TdT [13].

AUL is extremely rare with an incidence rate of approximately 1.34 persons/million, and it is more frequent in older age. With the advancement of diagnostic technology, the incidence has significantly decreased [14]. Compared to other subtypes of acute leukemias, AUL is often associated with worse prognosis [15].

Diagnosis of AUL mainly depends on bone marrow and flow cytometry to investigate the leukemic cells and classify the type of leukemia. Before classifying acute leukemia as undifferentiated, it is essential to perform a comprehensive immunophenotyping panel to exclude any lineage commitment [1]. Weinberg et al compared AUL with minimally differentiated AML-M0, which can be easily confused with AUL, and reported no difference in terms of age, blood count, bone marrow findings, OS, relapse-survival, and rates of complete remission [16]. In terms of immunophenotyping, AML-M0 lacks the specific myeloid marker (MPO) and expresses at least two myeloid-associated markers, while AUL expresses single, relatively nonspecific myeloid-associated marker, along with the primitive stem cell markers. ALAL, not otherwise specified, can also be confused with AUL, in which expression of more than one membrane antigen of certain lineage is expressed [1, 17]. Similar to our case, Luo et al reported a case of a patient diagnosed with AUL and MS. In their case, the blasts expressed low CD45, CD34, CD33, and CD7 but not CD2, CD10, CD5, CD4, CD8 and CD117 [17]. In our case the cells expressed the same markers but with higher CD45 expression. Cytogenetic abnormalities in AUL are not well recognized because of rarity of cases, but the reported cases showed -5q, +8, +13, Ph+, 11q23 and i(17) [15-19]. The only cytogenetic abnormality that could be detected in our patient was monosomy 16, which can occur in MS.

MS is also known as extramedullary AML and chloroma. The incidence varies among different studies ranging from 2.5% to 30% of all AML cases. MS can present as isolated disease, as a presentation of AML, or as a disease progression in myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), and MDS/MPN [9]. When MS precedes the hematological malignancy, it can be confused with lymphoma, and as MS rarely occurs in mediastinum, this causes more confusion and raises the suspicion of lymphoma. Paul et al [20] and Akkaya et al [21] have reported two cases of young patients, who presented with mediastinal sarcoma and were misdiagnosed as lymphomas and later found to be MS. This error can be contributed to rarity of these cases, so careful morphological examination and well-directed immunohistochemical stains for myeloid lineage markers will exclude the diagnosis of lymphoma [20, 21].

The mechanism of MS development is not clear, but the

presence of homing signal that allows the blast cells to re-localize to secondary sites is considered the main explanation of this migration. MS is usually positive for myeloid and monocytic antigens such as CD33, CD68 and immature markers such as CD34 and CD117. CD99, TdT and CD56 can be detected. Lineage-specific markers for T cells and B cells should be negative to exclude the possibility of lymphoma [22].

MS is common in AML-M0, AML-M4 and AML-M5. MS in AUL is very rarely seen as only one case was reported in literature, where immunohistochemical stains of mass biopsy and flow cytometry of bone marrow specimen confirmed the same tumor cells in both sites [17]. In our patient, the positive immunohistochemical stains of mediastinal lymph node biopsy was consistent with the findings from flow cytometry of the blasts in the bone marrow.

This case report highlights the possibility of rare subtypes of acute leukemia with rare presentation and unusual site of involvement to raise the index of suspicion and keep in mind such cases.

Conclusions

For precise diagnosis of AUL, a comprehensive and broad panel of immunomarkers should be run to rule out any lineage commitment for the clone.

Acknowledgments

None to declare.

Financial Disclosure

The authors have nothing to disclose.

Conflict of Interest

None to declare.

Informed Consent

Ethical approval was obtained from the Royal Medical Services Ethical Committee. The patient provided informed consent for publication of this case report; submission does not include images that may identify the person.

Author Contributions

Dr. Hala Alsoukhni: bone marrow aspirate interpretation, literature review, and manuscript writing. Dr. Dima AL-Dabbas: data collection. Dr. Mohammad Masalha: flow cytometry analysis. Dr. Omar Shkaibi: bone marrow biopsy interpretation.

Dr. Walla'a Aljbouir: radiology interpretation. Dr. Mohammad Obaidat: treatment and follow-up. All the authors have read and approved the manuscript.

Data Availability

The datasets analyzed during the current study are available from the corresponding author.

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