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Cold Hemolysis as the Initial Presentation of B-Cell Acute Lymphoblastic Leukemia: A Case Report

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ABSTRACT

Objectives

Cold hemolysis is a rare but potentially life-threatening condition that may occur as an early manifestation of hematologic malignancies. Prompt recognition is crucial, especially in patients presenting with severe anemia and neurological symptoms, as delayed diagnosis may worsen outcomes.

Methods

A 39-year-old Lebanese woman was admitted to the emergency department in critical condition with severe generalized weakness, fatigue, marked loss of strength, and anosmia. Laboratory evaluation showed leukocytosis with lymphocytosis and monocytosis, elevated lactate dehydrogenase, and increased indirect bilirubin. Coagulation studies revealed mild hyperfibrinogenemia and hypoprothrombinemia. Abdominal ultrasonography demonstrated no organomegaly or lymphadenopathy but identified a 70-mm hemorrhagic cyst of the right ovary. Peripheral blood smear showed critical pancytopenia with a left shift toward blast cells (~10%). Bone marrow aspiration with cytological and flow cytometric analysis in October 2024 confirmed precursor B-cell acute lymphoblastic leukemia (B-ALL). Hemoglobin was critically low (1.88 g/dL). A bedside temperature-dependent test confirmed cold hemolysis.

Results

The patient was transferred to the intensive care unit and received warmed intravenous fluids and blood component transfusions, resulting in stabilization. She was then transferred to the Onco-Hematology Department. Due to the life-threatening presentation, protocol-based chemotherapy with Hyper-CVAD Part A and B was initiated. She required eight hospitalizations. Hematologic remission was achieved, and at discharge her condition was stable with improved blood counts (hemoglobin 9.96 g/dL). Outpatient therapy was recommended.

Conclusion

Cold hemolysis may represent a rare but severe initial manifestation of precursor B-cell acute lymphoblastic leukemia. Early recognition and prompt intensive management are essential for patient survival and improved prognosis.

Keywords:

Cold hemolysis; Acute lymphoblastic leukemia; B-cell acute lymphoblastic leukemia; Severe anemia; Intensive care unit; Hyper-CVAD chemotherapy; Blood transfusion.

Introduction

Cold hemolysis is a rare but potentially life-threatening immunohematologic condition caused by the lysis of red blood cells upon exposure to low temperatures. It is most commonly associated with cold agglutinin disease, infectious processes, or lymphoproliferative disorders; however, its occurrence during the initial stages of acute hematologic malignancies has rarely been reported. [1,2]

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by uncontrolled proliferation of lymphoid progenitor cells in the bone marrow. It often presents with anemia, thrombocytopenia, and an increased risk of infectious complications. Although hemolytic anemia may accompany lymphoproliferative disorders, cold hemolysis as the initial clinical manifestation of ALL is extremely rare. [3,4]

The clinical significance of cold hemolysis lies in its rapid progression, severe anemia, and potential neurological complications, which may necessitate intensive care management. Timely diagnosis and temperature-adapted blood component therapy are essential for patient survival and for the safe initiation of disease-specific treatment. [1,2,5]

The present case describes a 39-year-old woman admitted to the emergency department in severe clinical condition, presenting with generalized weakness, decreased strength, and neurological dysfunction. Initial clinical and laboratory findings indicated severe anemia. Timely diagnostic

evaluation, including peripheral blood examination and bone marrow studies, confirmed precursor B-cell acute lymphoblastic leukemia. Appropriate blood transfusion therapy followed by protocol-based chemotherapy resulted in clinical stabilization. Hematologic remission was achieved through stepwise treatment, underscoring the critical importance of early diagnosis and rapid, coordinated management in the successful treatment of such severe clinical presentations. [3,6]

Case Description

The patient was brought to the Emergency Department by the Emergency Medical Service. According to the emergency team, on the morning of admission the patient gradually developed pronounced pallor of the skin, accompanied by adynamia and generalized weakness. The intensity of symptoms progressively increased, prompting hospitalization. A detailed medical history could not be obtained due to the language barrier and the severity of the patient's general condition.

Upon arrival, the patient was admitted to the Emergency Department and placed under continuous cardiac monitoring. Initial vital signs were as follows: heart rate (HR) 88 beats/min, blood pressure (BP) 90/60 mmHg, body temperature 36.3°C, respiratory rate (RR) 21 breaths/min, and oxygen saturation (SpO_2) 92%. Neurological examination revealed spontaneous eye opening with round and equal pupils. Intermittent clinical signs of encephalopathy were observed; however, no pathological reflexes were elicited.

Cardiac examination demonstrated regular rhythm with clear heart sounds. Pulmonary auscultation revealed vesicular breath sounds bilaterally with symmetric air entry. The tongue was dry and non-tender, and swallowing was intact. Abdominal examination showed a soft, non-tender abdomen, with audible bowel sounds on auscultation; the liver and spleen were not palpably enlarged.

A nasogastric tube was inserted, and gastric lavage was performed. Peripheral venous access was established, and blood samples were collected for laboratory analysis. An electrocardiogram demonstrated sinus rhythm without acute ischemic changes. Digital rectal examination revealed no evidence of melena. Intravenous infusion therapy was initiated, and the patient remained under close monitoring and observation.

Analysis of arterial blood gases and electrolytes indicated metabolic acidosis.In order to correct homeostasis, sodium bicarbonate infusion was started. Coagulation tests revealed hyperfibrinogenemia and hypoprothrombinemia. (The results of the coagulation screening tests are shown in Table 2).

Statistical Analysis

No statistical analysis was performed in this single patient case report. Descriptive data presentation was carried out without the use of statistical software..

Results

On admission, laboratory investigations revealed critical anemia and cytopenia (Complete blood count results are summarized in Table 1).

Table 1.

Test	Value	Units	Reference Range
WBC	13.60	10^9/L	4.49- 12.69
RBC	0.86	10^12/L	3.92 – 5.08
HGB	1.88	g/dl	11.90 – 14.60
HCT	5.70	%	36.60 – 44.00
MCV	66.80	fl	82.90 – 98.00
MCH	21.90	pg	27.00 – 32.30
MCHC	33.00	g/dl	31.80 – 34.70
SD	48.20	fl	38.20 – 49.20
CV	31.00	%	12.10 – 14.30
PLT	101.10	10^9/L	173.00 – 390.00
PCT	0.12	10^-2 L/L	0.18 – 0.39
MPV	11.59	fl	9.10 – 11.90
PDW	15.20	fl	9.90 – 15.40
P-LCR	25.10	%	17.50 – 42.30
NEUT	43.46	%	42.90 – 74.30
NEUT	5.91	10^9/L	2.10 – 8.89
LYMPH	31.94	%	18.30 – 45.70
LYMPH	4.34	10^9/L	1.26 – 3.35
MONO	20.88	%	4.20 – 11.80

MONO	2.84	10^9/L	0.25 – 0.84
EO	2.78	%	0.20 – 5.30
EO	0.38	10^9/L	0.01 – 0.40
BASO	0.94	%	0.10 – 1.00
BASO	0.13	10^9/L	0.01 – 0.07
IG	–	%	≤ 0.60
IG	–	10^9/L	≤ 0.06

Table 1: Laboratory findings from the complete blood count

WBC – White Blood Cell Count, RBC – Red Blood Cell Count, HGB – Hemoglobin, HCT – Hematocrit, MCV – Mean Corpuscular Volume, MCH – Mean Corpuscular Hemoglobin, MCHC – Mean Corpuscular Hemoglobin Concentration, SD – Red Cell Distribution Width – Standard Deviation (RDW-SD), CV – Red Cell Distribution Width – Coefficient of Variation (RDW-CV), PLT – Platelet Count, PCT – Plateletcrit, MPV – Mean Platelet Volume, PDW – Platelet Distribution Width, P-LCR – Platelet Large Cell Ratio, NEUT – Neutrophils, NEUT – Neutrophils, LYMPH – Lymphocytes, LYMPH – Lymphocytes, MONO – Monocytes, MONO – Monocytes, EO – Eosinophils, EO – Eosinophils, BASO – Basophils, BASO – Basophils, IG – Immature Granulocytes, IG – Immature Granulocytes.

Analysis of arterial blood gases and electrolytes indicated metabolic acidosis.In order to correct homeostasis, sodium bicarbonate infusion was started. Coagulation tests revealed hyperfibrinogenemia and hypoprothrombinemia. (The results of the coagulation screening tests are shown in Table 2).

Table 2.

Parameter	Value	Unit	Reference Range
PT	18.40	sec	9.10 – 12.10
PT %	48.21	%	70.00 – 140.00
INR	1.61	–	0.90 – 1.20
APTT	27.80	sec	24.30 – 36.90
TT	15.60	sec	13.00 – 21.00
Fibrinogen	4.08	g/L	2.00 – 4.00

Table 2: Coagulation Hemostasis Laboratory Findings
PT – Prothrombin Time, PT % – Prothrombin Time Percentage, INR – International Normalized Ratio, APTT – Activated Partial Thromboplastin Time, TT – Thrombin Time, Fibrinogen – Fibrinogen.

Marked elevation of lactate dehydrogenase (LDH ↑ 1291.00 U/L), together with increased direct bilirubin levels (D.BIL ↑ 13.70 μmol/L), supported the suspicion of an active hemolytic process.

To confirm cold hemolysis, a bedside diagnostic test was performed. A small amount of freshly collected venous blood was applied to two sterile test tubes: one pre-cooled and the other maintained in a warm environment. Immediate and rapid hemolysis was observed upon contact with the cold test tube, whereas no hemolysis occurred in the warm tube. These findings were consistent with the diagnostic criteria for cold hemolysis.

Warmed 0.9% sodium chloride infusion was initiated immediately, resulting in partial improvement of the patient's neurological status. Following consultation with a hematologist, transfusion of ABO- and Rh-compatible packed red blood cells and fresh frozen plasma was performed in combination with low-molecular-weight heparin. Metabolic acidosis was corrected. Follow-up laboratory analysis revealed leukopenia (WBC 1.80×10^9/L), while erythrocyte and hemoglobin levels showed partial improvement (RBC 2.26×10^{12}/L, HGB 5.80 g/dL).

Abdominal and pleural ultrasonography revealed no significant pathological findings. Gynecological ultrasound demonstrated a 70-mm hemorrhagic cyst of the right ovary with reduced vascularization, without evidence of active bleeding.

The patient's general condition remained severe, prompting transfer to the general intensive care unit for continued treatment. In the ICU, the patient was conscious and responsive, although she intermittently answered questions inappropriately. Breathing was spontaneous, with oxygen saturation reaching 98% on supplemental oxygen. Hemodynamic parameters remained stable. Intensive treatment, continuous monitoring, and correction of metabolic disturbances were continued.

Subsequently, blast cells were detected on peripheral blood smear, raising suspicion of acute leukemia. On the recommendation of a hematologist, bone marrow aspiration was planned. At this stage, the patient's condition was assessed as severe but stable, without signs of clinical deterioration, and she was transferred to the oncology and hematology unit for further diagnostic evaluation and treatment.

Treatment was continued in the hematology department. To accurately verify the diagnosis, cytological examination of the peripheral blood smear was performed, revealing critical pancytopenia and a left shift of the leukocyte differential toward blast cells (~10%). Cytological analysis of the bone marrow aspirate demonstrated severe hypocellularity (Figure 1), with blast cells accounting for 8.5% and lymphocytes for 38% (The laboratory findings of bone marrow cytology are summarized in Table 3).

Table 3.

Cellular Elements	%				
	Before Chemo	Relapse	Remission	Final	Reference range
Blast cells	8.5%%	8.0%	1.0%	1.5%	0.5-1.5%
Myeloblast	-	-	-	-	0.5-1%
Neutrophil promyelocyte	-	2.0%	2.0%	2.5%	0.75-1.5%
Neutrophil myelocyte	0.75%	10.0%	15.0%	8.0%	8.5-13%
Neutrophil Metamyelocyte	33.0%	11.0%	14.0 %	10.0 %	11-14.5%
Sticky Neutrophil Segmental	5.0 %	13.0%	12.0%	13.0%	13-16%
Neutrophil Eosinophil Promyelocyte	27.25%	4.25%	14.25%	17.15%	17-27%
Eosinophil promyelocyte	-	-	-	-	-
Eosinophil Myelocyte	0.5%	-	1.0%	-	1.0%
Eosinophil metamyelocyte	1.0 %	-	-	-	0.25-0.5%
Eosinophil. Sticky Eosinophil	-	-	-	-	0.5-1.0%
Segment Nucleated Basophil.	0.5%	0.5%	1.0%	0.5%	1-2%
Segment Nucleated	1.25%	-	-	-	0-0.25%
Lymphoblast	-	-	-	-	-
Prolymphocyte	-	-	-	-	-
Lymphocyte	38.0%	12.0%	15.0%	11.0%	9-14.5%
Monocyte	14.5%	4.5%	2.0%	5.5%	0.5-2%
White blood mitosis	-	0.25%	0.25%	-	0.25%
Reticular cell	-	-	-	-	0-0.25%
Plasm cell	-	-	-	-	0-0.5%
Macrophage	-	-	-	-	0-0.25%
Basophil megaloblastic	-	-	-	-	-
polychromatophilic	-	-	-	-	-
Oxyphilic	-	-	-	-	-
proerythroblast	-	-	-	-	0-0.5%

Basophil macroblast	1.5%	2.0%	2.0%	1.5%	1.5-2%
Polychromatophilic	-	-	-	-	2-4%
Oxyphilic	3.75 %	-	-	-	0.5-2.75%
Basophil normoblast	1.5%	4.0%	3.5%	1.5%	1-1.5%
Polychromatophilic	0.75%	24.0%	15.0%	0.75%	1.5-4.5%
Oxyphilic	-	4.0%	4.0%	-	0.5-1%
Red blood cell mitosis polychromatophilic	-	0.5%	-	-	0-0.25%
Red blood cell mitosis oxyphilic	-	-	-	-	0-0.25%
megakaryocyte	-	-	-	-	0-0.25%
Osteoblast	-	-	-	-	-
Osteoclast	-	-	-	-	-
Comment	Severe hypocellularity	The bone marrow shows cellularity	Normocellular	Normocellular	-

Table 3: Comparison of Bone Marrow Cytological Findings at Diagnosis and After Completion of Treatment

Figure 1.

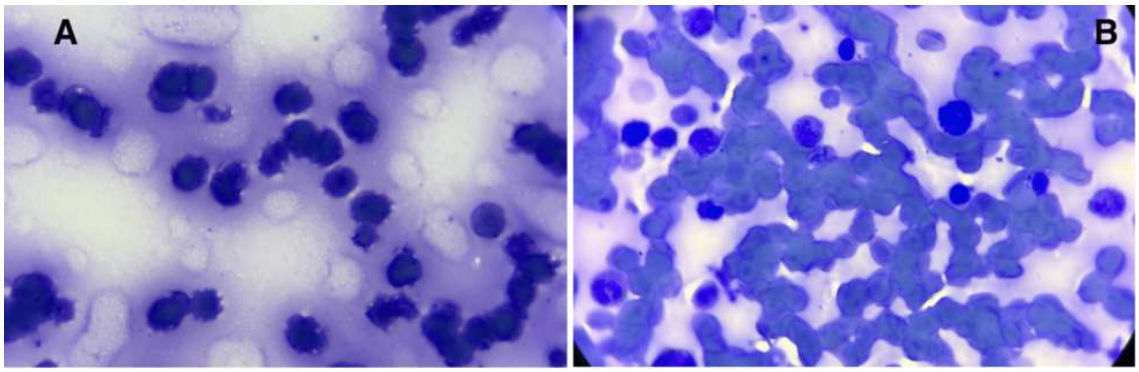

Figure 1: Comparative analysis of bone marrow cytology before chemotherapy and after completion of treatment.
Giemsa–Romanowsky–stained bone marrow smears. The image A, obtained prior to the initiation of chemotherapy, demonstrates severe hypocellularity. The image B shows a representative microscopic cytological view of the bone marrow after completion of treatment, revealing marked restoration with abundant cellular elements

Flow cytometric analysis was performed on bone marrow material using appropriate monoclonal antibodies on a flow cytometer. The study revealed an atypical cell population comprising approximately 48% of cells, characterized by moderate CD45 expression. A significant proportion of the analyzed cells consisted of CD19-positive B-lymphoblasts. Transient surface expression of CD66c (21%), CD20 (32%), and CD10 (48%) was observed on the blasts, along with strong expression of CD34 (95%) and CD38 (100%). Intracellular staining demonstrated cytoplasmic expression of CD79a in 69% of cells, while CyCD3, CyCD22, CyIgM, and myeloperoxidase (MPO) were not detected in the majority of cells. This immunophenotypic profile was consistent with the Common ALL subtype of precursor B-cell acute lymphoblastic leukemia.

Additional molecular genetic testing was performed to evaluate chromosomal aberrations associated with acute leukemias. The analysis did not confirm the presence of an RNA transcript of the chimeric gene characteristic of the t(9;22)(q34;q11) chromosomal aberration in the examined material.

The patient continued to receive blood transfusions based on biological compatibility testing and appropriate premedication, while maintaining stable hemodynamic parameters. Considering the patient's age, degree of malignancy, and the results of clinical and laboratory investigations, inpatient chemotherapy was initiated on life-threatening indications in an urgent-delayed setting. Treatment was administered according to the following protocol: cyclophosphamide 200 mg; methotrexate (MTX) 15 mg, intrathecal; doxorubicin 50 mg; vincristine 2 mg; cytarabine 100 mg; filgrastim 48 MU; and mesna 400 mg.

Follow-up laboratory evaluation revealed profound leukopenia, with persistent anemia: white blood cell count (WBC) 1.87 × 10^9/L, hemoglobin (HGB) 8.19 g/dL, and hematocrit (HCT) 24.10%. Coagulation parameters showed improvement.

Taking into account the patient's somatic status, the extent of chemotherapy administered, and laboratory findings, continued inpatient treatment according to the international cytopenia protocol was deemed appropriate. Concurrent intrathecal chemotherapy was maintained.

In total, the patient underwent four courses of intrathecal chemotherapy. Several chemotherapy-related complications were observed during treatment. Following intrathecal therapy, the patient experienced common chemotherapy-related symptoms, including adynamia, generalized weakness, dizziness, fever, and bone pain. These symptoms were transient and managed with symptomatic therapy.

Cerebrospinal fluid samples obtained prior to each intrathecal chemotherapy session were sent for laboratory analysis. The patient remained under continuous observation, with regular monitoring of laboratory parameters and vital signs.

Over a six-month period from the initiation of treatment, the patient received protocol-based chemotherapy along with supportive symptomatic therapy. Despite periodic chemotherapy-related complications, the patient's overall clinical condition gradually and significantly improved. At present, the patient reports no complaints.

Based on the clinical outcome, the patient was provided with appropriate prescriptions and recommendations to continue treatment on an outpatient basis under the supervision of an onco-hematologist.

Prognosis: Long-term outcomes are difficult to assess due to the patient's underlying disease and comorbidities. At present, hematologic remission has been achieved, and no additional complications are observed.

Discussion

The presented clinical case describes cold hemolysis as a rare and life-threatening initial manifestation of B-cell acute lymphoblastic leukemia. Although hemolytic anemia is commonly described in lymphoproliferative disorders, cold hemolysis as the first clinical manifestation of acute leukemia is exceedingly rare and has been reported only in isolated cases. [1,2]

Cold hemolysis is an immune-mediated process associated with activation of cold agglutinins and intravascular destruction of erythrocytes through complement activation. This mechanism is most frequently observed in chronic lymphoproliferative disorders, infectious diseases, or primary cold agglutinin disease, whereas its occurrence at the initial stage of acute leukemia is rarely reported. In the present case, immune dysregulation associated with early leukemia development likely contributed to the formation of pathological cold agglutinins and rapid hemolysis. [1,2,7]

Clinically, the patient presented in a severe general condition with critical anemia and neurological symptoms related to profound anemia and metabolic acidosis. These features complicated the diagnostic process at the initial stage and required rapid clinical decision-making. In this context, bedside diagnostic testing proved particularly valuable, allowing timely recognition of cold hemolysis and initiation of appropriate thermoadapted infusion and transfusion therapy. [1,2,8]

Without prompt therapeutic intervention, cold hemolysis may progress rapidly and result in fatal outcomes, especially in patients with severe underlying hematologic disease. In this case, close

interdisciplinary collaboration between emergency medicine, intensive care, and hematology teams played a decisive role in patient survival. [1,2,5,9]

After confirmation of leukemia, the patient underwent protocol-based chemotherapy according to the Hyper-CVAD regimen. Despite treatment-related complications, hematologic remission was achieved. This outcome demonstrates that even in cases with an extremely severe initial presentation, favorable results may be obtained through timely diagnosis and an appropriately selected therapeutic strategy. [6,10,11]

This clinical case underscores the importance of considering acute hematologic malignancy in patients presenting with severe anemia and signs of hemolysis, even when the initial clinical presentation is atypical. Early recognition and appropriate management of cold hemolysis are essential for improving patient prognosis and enabling safe and effective treatment of the underlying malignancy. [5,6,12,13]

Conclusions

This clinical case illustrates the complexity and multifactorial nature of the initial presentation of acute hematological disease. The patient was admitted in a critical condition with severe anemia, metabolic disturbances, and neurological symptoms, necessitating rapid and coordinated management. Early recognition of cold hemolysis through clinical reasoning and a simple bedside diagnostic test was essential, allowing prompt initiation of temperature-adapted infusion and transfusion therapy and stabilization of the patient's condition. Subsequent laboratory and diagnostic investigations led to the timely diagnosis of acute leukemia.

The patient's management required intensive care, repeated hospitalizations, and disease-specific onco-hematological treatment. Despite complications related to chemotherapy and intrathecal therapy, hematological remission was achieved with continuous monitoring and supportive care. This case underscores the importance of considering underlying hematological malignancy in patients presenting with severe anemia and hemolysis, particularly when the clinical picture is atypical. Early diagnosis, interdisciplinary collaboration, and an appropriate therapeutic strategy are critical factors in achieving favorable clinical outcomes.

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