Section: Internal Medicine

Case Series

THE HEMATOLOGICAL HEADS OF CEREBRUS – A CASE SERIES ON ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignant proliferation of immature lymphoid precursors with variable and often nonspecific clinical presentations. We report three diagnostically challenging cases of ALL in young patients, including two cases of T-cell ALL and one case of B-cell ALL, initially presenting with infectious, rheumatologic, and immunologic differentials. Presentations included fever, severe cytopenias, musculoskeletal pain, metabolic derangements, and features mimicking sepsis, pyelonephritis, and primary immunodeficiency. One T-ALL case demonstrated features suggestive of spontaneous tumor lysis syndrome prior to diagnosis. Diagnosis was confirmed through bone marrow examination with immunophenotyping, demonstrating TdT-positive lymphoblasts with lineage-specific markers. All patients were managed with standard induction chemotherapy and supportive care, with clinical improvement. These cases highlight the protean manifestations of ALL in adolescents and young adults and emphasize the importance of maintaining a high index of suspicion in patients presenting with unexplained cytopenias, systemic inflammatory features, or atypical multisystem involvement.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a neoplasm composed of immature B- or T-lymphoid precursor cells, commonly referred to as lymphoblasts.[1] It is the most common malignancy in children, with the majority of cases occurring before 15 years of age.[1] The disease demonstrates a male predominance and a relatively higher incidence among Hispanic/Latino populations.[1,2] B-ALL commonly peaks between 2–5 years of age, whereas T-ALL more frequently presents during adolescence, corresponding to maximal thymic activity.[1]

Symptoms usually result from marrow replacement and extramedullary infiltration by leukemic blasts, leading to suppression of normal hematopoiesis1. Patients commonly present with fever, fatigue, bleeding manifestations, recurrent infections, lymphadenopathy, hepatomegaly, and splenomegaly.[1] Although bone and joint pain are recognized manifestations of ALL, isolated or predominant musculoskeletal symptoms are uncommon and may initially mimic rheumatologic or orthopedic disorders.[3,4]

Misdiagnosis or delayed diagnosis of ALL may occur particularly in older adolescents and young adults because of its nonspecific presentation.[2,4] Cases presenting as pyrexia of unknown origin may occasionally harbor underlying hematologic malignancy.[5] Spontaneous tumor lysis syndrome (STLS), a rare oncologic emergency caused by rapid tumor cell breakdown in the absence of chemotherapy, has also been described in acute leukemias including ALL.[6,7]

The present report discusses three diagnostically challenging cases of ALL, including two cases of T-

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ALL in a 13-year-old male and a 22-year-old female respectively, and one case of B-ALL in a 19-year-old male.

CASE PRESENTATION

Case 1: A 19-year-old male presented with complaints of fever and joint pain for two weeks. The fever was high-grade, intermittent, and associated with chills and rigors. The joint pain initially involved the both knee joints and subsequently progressed to involve the wrists and elbows. He also reported jaw pain for two weeks and a history of black-colored stools for one day.

On presentation, the patient's vitals were stable. The patient was thin-built with pallor noted on examination. Abdominal examination revealed hepatomegaly, with the liver palpable 2 cm below the right costal margin. Musculoskeletal examination demonstrated tenderness in the bilateral knee, shoulder, wrist, and elbow joints. Other systemic examinations were insignificant. Relevant laboratory parameters are summarized in [Table 1].

Table 1: Routine investigatory findings

Parameters	Value	Reference Range/Impression
White Blood Cell Count (103/µL)	11.7	4 - 11 × 103/µL
Red Blood Cell Count (106/µL)	2.82	4.5 - 5.5 × 106/µL
Hemoglobin (g/dL)	6.6	13 - 17 g/dL
Haematocrit (%)	20.2	40 - 50 %
MCV (fL)	71	80 - 100 fL
MCHC (g/dL)	27	32 - 36 g/dL
Platelet Count (103/µL)	13	165 - 415 × 103/µL
Serum LDH (IU/L)	12,209	140 - 280 IU/L
Serum uric acid (mg/dL)	8.2	3.5 - 7.2 mg/dL
Bone marrow blast cells (%)	90	<5%

MCV - Mean Corpuscular Volume, MCHC - Mean Corpuscular Hemoglobin Concentration.

Serological testing for viral markers and fever profile investigations were negative. An ultrasound of the abdomen confirmed hepatomegaly. Peripheral smear examination revealed microcytic hypochromic anemia with 17% atypical cells and associated thrombocytopenia. Bone marrow aspiration showed features suggestive acute leukemia, with approximately 90% blast cells. Bone marrow biopsy with immunohistochemistry demonstrated grade 1 marrow fibrosis with TdT (terminal deoxynucleotidyl transferase) positivity in 90% of blasts, membranous CD10 positivity in 90% of blasts, moderate-intensity nuclear c-MYC positivity in 20% of blasts and Ki-67 positivity in more than 90% of cells.

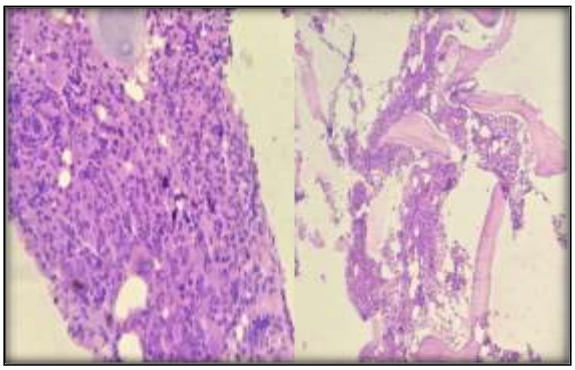

Figure 1: Figure shows the presence of hypercellular bone marrow biopsy, with an increased number of lymphoblastic cells having high N/C ratio and hyperchromatic nucleus. Fibrosis was also detected on special staining with TdT.

Based on the immunophenotypic profile and bone marrow findings, a diagnosis of B-cell acute lymphoblastic leukemia was established, following which the patient was initiated on appropriate chemotherapy and supportive management.

Case 2: A 13-year-old male child was brought with chief complaints of intermittent fever for approximately 20 days and lethargy for 10 days. While first attending a nearby hospital, he was found to have an extremely low hemoglobin count, for which transfusion for packed red blood cells was done.

He was brought to the Institute of Child Health, Egmore after referral from the first hospital, with further complaints of vomiting and loose stools for three days. He had no history of orthopnea or paroxysmal nocturnal dyspnea. Routine investigations including complete blood count and renal function tests, which revealed a picture of leukocytosis, severe anemia and acute kidney injury. An arterial blood gas investigation combined with the breathlessness seen indicated that he was undergoing severe metabolic acidosis, for which oxygen therapy was given.

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Table 2: Complete Blood Count Findings

Parameters	Value	Reference Range/Impression
White Blood Cell Count (103/µL)	32.5	4 - 11 × 103/µL
Red Blood Cell Count (106/µL))	4.31	4.5 - 5.5 × 106/µL
Hemoglobin (g/dL)	8.8	13 - 17 g/dL
Haematocrit %	27.5	40 - 50 %
MCV (fL)	63.8	80 - 100 fL
MCH (pg)	32.0	27 - 33 pg
MCHC (g/dL)	32.0	32 - 35 g/dL
Platelet Count (103/µL)	636	165 - 415 × 103/µL
Lymphocytes (%)	63.7	20 - 40 %

MCV - Mean Corpuscular Volume, MCH - Mean Corpuscular Hemoglobin, MCHC - Mean Corpuscular Hemoglobin Concentration.

Additional tests involved a CT brain which was suggestive of hypodensities seen in the left parietal and right occipital lobes. EEG studies indicated epileptiform activity and the child had one episode of seizures while being admitted. Reactive lymphocytosis was considered due to the multiple lymph node enlargements observed in the pelvic especially scrotal region. This was further supported by splenomegaly which was clinically elicited.

The hematological findings above were indicative of some systemic immunologic cause for the lymphocytosis given that microbiological testing revealed no antigens or antibodies for dengue, smear was negative for malaria and the serum did not reveal any antigens supportive of tropical infections.

In order to suspect an immunological etiology for the above condition, a flow cytometry analysis was performed. The investigation revealed an extremely elevated IgE antibody (count being 2005), with normal IgG and IgM levels. Low CD3, CD4 and CD 5 counts were also observed, prompting further investigations from this angle. Based on family history of similar illnesses a genetic test was advised for the TNFRSF13B gene mutation. The results did indicate a mutation in the gene based on which he was diagnosed with primary immunodeficiency disorder.

On the 10th day after admission, however, a large parotid and submandibular swelling was noticed over the right side of the boy's face. The investigations done for the same included a peripheral smear repeat which showed normocytic normochromic anemia and a USG neck with indicated an enlarged right parotid gland and lymph nodes bilaterally at levels 1a, 1b, 2 and 3 and in the left nodes alone at level 4 and 5.

In light of the above clinical and hematologic picture, there was the possibility of the patient exhibiting symptoms of spontaneous tumor lysis syndrome. In order to search and confirm this differential with an underlying hematologic malignancy, a bone marrow biopsy was performed. This revealed the presence of trilineage hematopoiesis with a significant lymphoblastic predominance, based on which the patient was diagnosed with T cell acute lymphoblastic leukemia. The patient was appropriately managed, recovered and was discharged subsequently.

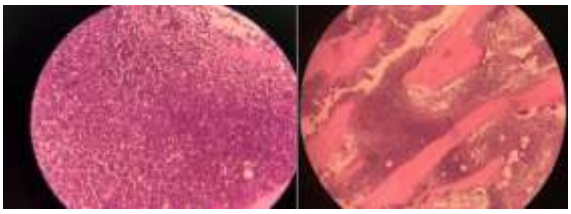

Figure 2: Figure shows high power and low power views of the bone marrow in this patient. Section shows adequate hypercellular marrow composed of sheets of blue round cells with scant cytoplasm. Trilineage hematopoiesis not made out.

Case 3: A 22-year-old nulligravida presented to the outpatient department with complaints of joint pain for one month, bleeding per vaginum for one week and fever for five days. The fever was described as high grade, intermittent in nature and associated with chills and rigors. The joint pain, described as a diffuse aching pain, involved the knees and shoulders on both sides. The patient also reported excessive menstrual bleeding along with passage of dark-coloured stools. No history of gum bleeding, epistaxis or hematuria was elicited. Family history was significant for malignancy, with the patient's mother having succumbed to an unspecified cancer and her brother being diagnosed with osteosarcoma of the tibia.

On presentation, her blood pressure was elevated at 180/90 mmHg, while the remaining vital parameters were within normal limits. On general physical examination, the patient was conscious, oriented and afebrile, with pallor being noted. Systemic examination was otherwise unremarkable.

Routine laboratory investigations revealed severe anemia, leukocytosis with lymphocytic predominance and severe thrombocytopenia (Table 3). Urinalysis demonstrated albuminuria, hinting a possible renal involvement. Contrast-enhanced computed tomography of the abdomen revealed bilateral pyelonephritis and cystitis with hepatosplenomegaly. Based on the initial clinical presentation and laboratory findings, an initial provisional diagnosis of acute febrile illness with thrombocytopenia and bleeding manifestations was considered. However, the presence of bicytopenia with lymphocytic predominance raised suspicion for an underlying hematological malignancy, prompting further evaluation.

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Table 3: Routine investigatory findings

Parameters	Value	Reference Range/Impression
White Blood Cell Count (103/µL)	23.1	4 - 11 × 103/µL
Red Blood Cell Count (106/µL)	2.43	4.5 - 5.5 × 106/µL
Hemoglobin (g/dL)	5.3	13 - 17 g/dL
Haematocrit (%)	18.9	40 - 50 %
MCV (fL)	72	80 - 100 fL
MCH (pg)	22	27 - 33 pg
MCHC (g/dL)	29	32 - 36 g/dL
Platelet Count (103/µL)	10.1	165 - 415 × 103/µL
Serum LDH (IU/L)	19,012	140 - 280 IU/L
Lymphocytes (%)	81	20 - 40 %

MCV - Mean Corpuscular Volume, MCH - Mean Corpuscular Hemoglobin, MCHC - Mean Corpuscular Hemoglobin Concentration

The patient was initially managed with supportive therapy, including transfusion of 2 units of packed red blood cells and 4 units of platelet concentrates, intravenous fluid resuscitation, empirical broad-spectrum antibiotics, antiemetics and proton pump inhibitors, along with close monitoring of vital parameters and bleeding manifestations.

Serological testing for HIV, hepatitis B, CMV, HSV and EBV were negative. On the eighth day of admission, bone marrow biopsy with immunohistochemical analysis was performed, which demonstrated TdT positivity in more than 90% of blasts, CD3 positivity in approximately 30% of blasts and CD20 positivity in fewer than 10% of cells. Correlating the histopathological, immunohistochemical and clinical findings, a diagnosis of T-cell acute lymphoblastic leukemia with concurrent bilateral pyelonephritis and cystitis was established.

The patient was subsequently managed with induction chemotherapy including an anthracycline-based regimen, along with supportive management comprising allopurinol and tranexamic acid. The patient showed symptomatic improvement during the hospital course and was advised regular hematological follow-up.

DISCUSSION

Acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy characterized by clonal proliferation of immature lymphoid precursors within the bone marrow, peripheral blood, and extramedullary tissues.[1] Although ALL is primarily a childhood malignancy, atypical manifestations in adolescents and young adults frequently delay diagnosis.[2] The present series highlights three diagnostically challenging presentations of ALL, including a young adult with B-ALL presenting predominantly with severe musculoskeletal symptoms, and adolescent patients with T-ALL initially evaluated as pyrexia of unknown origin and possible infectious or inflammatory disorders. These cases underscore the protean manifestations of ALL and emphasize the importance of maintaining a high index of suspicion in patients with unexplained constitutional, musculoskeletal, or systemic inflammatory features.

The first case demonstrates the presentation of B-ALL in a 19-year-old male whose predominant symptoms were fever and severe migratory joint and bone pain. Bone pain is a recognized symptom in ALL, particularly in pediatric populations, but presentation with predominant musculoskeletal manifestations remains uncommon and often leads to rheumatologic or orthopedic misdiagnosis.[3,4] Leukemic infiltration of the periosteum and expansion of marrow cavities are believed to contribute to skeletal pain.[3] Kushwaha et al. described a patient presenting with fever, skeletal pain, hypercalcemia, and multiple osteolytic lesions who was ultimately diagnosed with B-ALL despite an initially nonspecific peripheral smear.[8] Similarly, Granacher et al. reported precursor B-ALL in an adult presenting with hypercalcemia and diffuse osteolytic lesions in the absence of peripheral blasts, initially raising suspicion for metastatic malignancy.[9] These reports parallel the present case in demonstrating that ALL may initially masquerade as a musculoskeletal or metabolic disorder, thereby delaying hematologic evaluation.

The second case illustrates the diagnostic complexity of T-ALL presenting with prolonged fever, severe anemia, metabolic derangements, lymphadenopathy, and suspected immunodeficiency. T-ALL commonly presents during adolescence and frequently demonstrates aggressive clinical behavior with mediastinal involvement and high leukocyte burden.[1] However, persistent fever and abnormalities in T-cell markers initially prompted evaluation for infectious and immunologic etiologies in the present patient. So far only four previous cases with a similar presentation have been described previously.

Another remarkable aspect of this case was the later development of parotid and submandibular swelling with extensive cervical lymphadenopathy and eventual lymphoblastic predominance on bone marrow biopsy. The occurrence of acute kidney injury, severe metabolic acidosis, and systemic deterioration suggested possible spontaneous tumor lysis syndrome (STLS), a rare but life-threatening complication occurring in the absence of cytotoxic therapy.[6,7] STLS has been increasingly recognized in highly proliferative hematologic malignancies, including T-cell neoplasms, and is thought to result

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from rapid spontaneous tumor cell turnover leading to metabolic derangements. Contemporary literature, including recent reviews, highlights that STLS may present with features resembling severe sepsis or systemic inflammatory response syndrome, often preceding the diagnosis of an underlying malignancy.[7] Roque et al. similarly emphasized that spontaneous tumor lysis in T-cell malignancies can be an initial manifestation and requires high clinical suspicion for early recognition.[7]

The third case represents an unusual presentation of T-cell Acute Lymphoblastic Leukemia (T-ALL), in which the initial clinical picture closely resembled an acute infectious illness with thrombocytopenia. Fever, melena, arthralgia, and radiological findings suggestive of bilateral pyelonephritis and cystitis initially masked the underlying hematological malignancy. Similar atypical presentations have been described in literature. Tamura et al. reported an adult patient with T-ALL presenting with bilateral nephromegaly secondary to leukemic renal infiltration.[10] Vijayasekharan et al. similarly described pediatric T-ALL presenting with massive bilateral nephromegaly and renal involvement.[11] In contrast to these reports, the present patient did not demonstrate overt renal failure but instead had urinary tract involvement mimicking infective pathology with albuminuria, suggesting that leukemic infiltration or immune dysregulation may manifest with subtler renal findings.

The prominent arthralgia observed in this case also parallels previously reported leukemia cases initially mistaken for rheumatologic disease. Compared with previously published reports, the coexistence of severe thrombocytopenic bleeding, markedly elevated LDH, and urinary tract involvement makes the present case particularly unusual. Another notable aspect of the case was the significant family history of malignancy, including osteosarcoma in a sibling. Although no genetic evaluation was performed, the occurrence of multiple early-onset malignancies within the family may warrant further evaluation for an underlying hereditary cancer predisposition. Collectively, these cases emphasize the importance of considering acute leukemia in young patients presenting with unexplained cytopenias, elevated LDH, and atypical inflammatory or infectious manifestations.

CONCLUSION

These cases highlight the highly variable and often misleading clinical presentation of acute lymphoblastic leukemia (ALL) in adolescents and young adults. Presentations mimicking infectious, rheumatologic, metabolic, and immunologic disorders can delay diagnosis, particularly when musculoskeletal pain, fever, and organ-specific findings dominate the initial clinical picture. Markedly abnormal hematological parameters, especially cytopenias with elevated LDH, should prompt early consideration of hematologic malignancy even in atypical settings.

A high index of suspicion, combined with timely bone marrow examination and immunophenotyping, is essential for early diagnosis and initiation of therapy. Recognition of uncommon presentations such as spontaneous tumor lysis syndrome, renal involvement, and immunologic masqueraders can improve diagnostic accuracy and outcomes in ALL.

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