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Case Report

ACUTE B-CELL LYMPHOBLASTIC LEUKEMIA IN A 19-YEAR-OLD MALE WITH PYREXIA OF UNKNOWN ORIGIN

TARUGUVANDLA SANDHYA RANI, RAVITEJA NALABOTHULA, SHANMUKHA SAI BOLISETTY, MANNE LAKSHMI NARASIMHA SANDEEP*

Department of General Medicine, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India.
***Corresponding author: Manne Lakshmi Narasimha Sandeep; Email: mannesandeep97@gmail.com**

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ABSTRACT

Pyrexia of unknown origin (PUO) is a clinical challenge defined by a persistent fever exceeding 3 weeks without a discernible etiology, despite preliminary examinations. This case report details a 19-year-old male engineering student who was originally managed for pyrexia and subsequently identified with B-cell acute lymphoblastic leukemia, showing the complex nature of the diagnosis procedure in cases of PUO.

Keywords: Pyrexia of unknown origin, B-cell acute lymphoblastic leukemia, Immunohistochemical markers.

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INTRODUCTION

In 1961, Petersdorf and Beeson first described prexia of unknown origin (PUO) as a disorder in which the body temperature rises beyond 38.3°C on three or more occasions over a minimum of 3 weeks, but no diagnosis is determined after a week of inpatient evaluation [1]. The definition was subsequently revised to incorporate technological advancements that facilitate intricate outpatient assessments, a rising population of immunocompromised individuals, including those with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome, and the emergence of more complex treatment alternatives. Durack and Street's 1991 updated definition categorized instances into four distinct subclasses: Classic fever of unknown origin (FUO), nosocomial FUO, neutropenic FUO, and HIV-related FUO [2]. FUO presents a challenging diagnostic challenge due to over 200 distinct illnesses, encompassing malignant, infectious, rheumatic, inflammatory, and miscellaneous ailments. Malignancies such as lymphoma, renal cell carcinoma, and leukemia commonly appear with protracted fever, considerable weight loss, and early anorexia. Infectious etiologies encompass tuberculosis (TB), brucellosis, Q fever, and viral diseases such as Epstein-Barr virus and cytomegalovirus, commonly linked to fever patterns, chills, and organ involvement. Rheumatic and inflammatory disorders such as systemic lupus erythematosus, giant cell arteritis, and Still's disease may manifest with fever, arthralgia, and lymphadenopathy. Various reasons encompass drug fever, factitious fever, subacute thyroiditis, and inherited fever disorders, including familial Mediterranean fever. A targeted diagnostic strategy depends on patient history, physical examination, and specific laboratory tests to uncover insights and refine potential causes, thereby avoiding excessive and non-informative testing [3]. This case report aims to emphasize the diagnostic intricacies and management difficulties of B-cell acute lymphoblastic leukemia (B-ALL) manifesting with unusual symptoms, including fever and pancytopenia.

CASE REPORT

A 19-year-old male engineering student reported with a 1-month history of high-grade persistent fever along with chills, rigidity, joint aches, and severe weight loss. He had been originally treated with intravenous antibiotics at a local hospital, but the fever lingered despite continued therapy. The patient's physical examination did not disclose any clarified diagnostic signals, and laboratory studies showed pancytopenia. Fever profile, including common viral etiologies, gave no positive results; however, inflammatory markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) (positive) were increased. A peripheral smear showed moderate dimorphic anemia, with mainly microcytic, hypochromic red blood cells. Blood and urine cultures did not yield any growth. His Vitamin B12 levels were within the normal range.

The initial treatment: Despite administration of intravenous antibiotics and antipyretics, the fever persisted, with peaks reaching 104°F. Due to the ongoing fever and the patient's clinical presentation, he was classified as having PUO. Antibiotics were withheld for 1 week to exclude drug-induced fever, yet the fever continued. Joint involvement was also observed. A rheumatology consultation yielded no significant findings, and the antinuclear antibody (ANA) profile was negative. Adult-onset Still's disease was considered but excluded due to the absence of a characteristic rash, negative ferritin levels (<3000), and negative rheumatoid factor and ANA.

Subsequent evaluations: Medical oncology was consulted, and a bone marrow aspiration and biopsy were conducted. The aspiration indicated a particulate marrow with diluted cellular trails, whereas the biopsy demonstrated hypercellular marrow with reactive plasmacytosis, resulting in an unclear diagnosis. Due to the suspicion of malignancy, and considering leukemia improbable given the patient's age and the possibility of steroid masking, a positron emission tomography-computed tomography (PET-CT) scan was conducted. The scan indicated metabolically active periportal and portocaval lymph nodes, along with metabolically active marrow with lytic lesions in the left iliac bone, ribs, and proximal left humerus. A biopsy was not viable due to the lymph nodes' position and their proximity to crucial organs. The difference diagnosis: Considering the clinical presentation and the endemic prevalence of TB in India, TB was identified as a potential etiology. The patient commenced anti-TB therapy following a pulmonology consultation. After 3 weeks of treatment, the fever persisted, and the patient had nausea and vomiting, resulting in the cessation of anti-TB medications.

The patient was referred to the infectious disease section, where further inquiry uncovered a history of intimate interaction with

cattle, heightening suspicion of brucellosis. *Brucella* serology was conducted and yielded a negative result. A palpable axillary lymph node was detected on additional investigation. The general surgery department conducted an excisional biopsy of the axillary lymph node. The microscopic analysis of the lymph node sample demonstrated significant mitotic activity and scattered tumor large cells.

Histopathological findings

Immunohistochemical markers demonstrated positive for CD3 (Fig. 1), CD30 (Fig. 2), CD15 (Fig. 3) and CD20 (Fig. 4), and diffuse terminal deoxynucleotidyl transferase (TdT). These findings indicated the participation of B-cell lineage. The repeat PET-CT of the entire body revealed several metabolically active lymph nodes in the mediastinal, perioesophageal, and bilateral costophrenic areas, as well as in sever.

With the diagnosis of B-ALL, the patient started induction therapy of vincristine, dexamethasone, and daunorubicin. By the 6th day of therapy, the patient's fever abated, and joint pain significantly decreased. A subsequent bone marrow biopsy after the first chemotherapy cycle showed substantial reduction in lymphoblasts, signifying a good initial response. Pancytopenia improved with hemoglobin rising to 11.2 g/dL, white blood cell count increasing to 4500/mm^3, and platelet count increasing to 120,000/mm^3. Liver function tests became normal, and serum ferritin decreased to 400 ng/mL. The patient completed the induction phase of therapy successfully without significant issues. Supportive care included transfusions, hydration, and prophylactic antimicrobials. He was discharged in stable condition and for consolidation therapy per the B-ALL protocol.

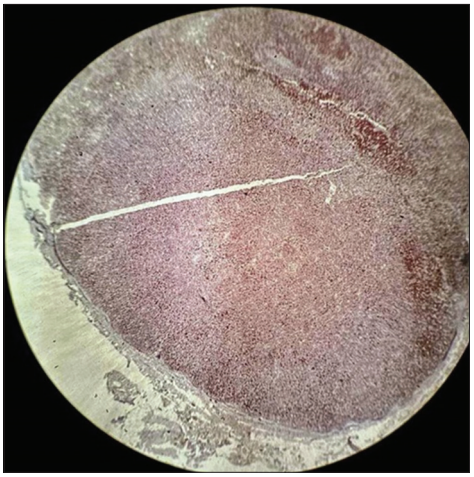

Fig. 1: Histopathological findings in acute B-cell lymphoblastic leukemia showing cluster of differentiation 3 positivity

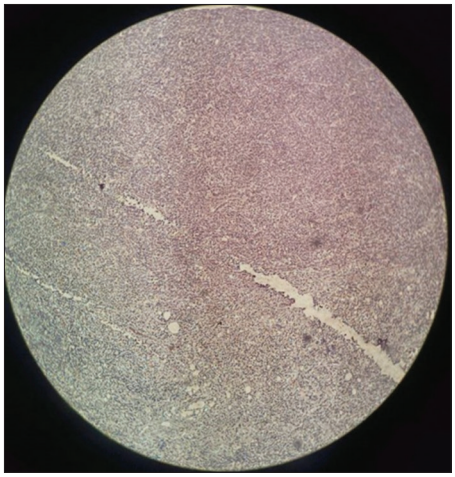

Fig. 2: Cluster of differentiation 30

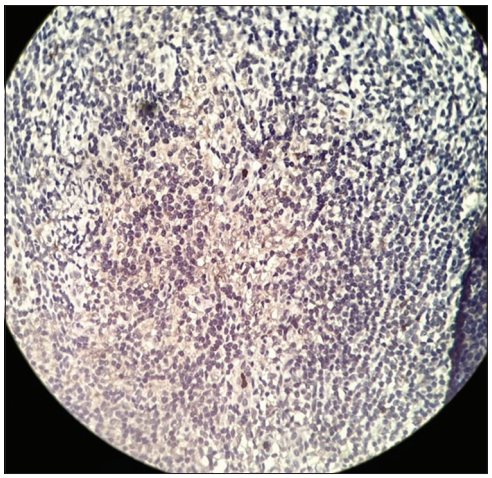

Fig. 3: Cluster of differentiation 15

DISCUSSION

The present case shows the challenges in identifying PUO, particularly when the presentation is nonspecific and the patient initially does not react to treatment. The extended febrile illness and systemic manifestations in this young male obscured the underlying hematological malignancy, which was discovered only after comprehensive evaluation and biopsy. Early use of PET-CT and bone marrow biopsy helped in accurate diagnosis and early initiation of treatment with a favorable clinical outcome.

Pyrexia of uncertain origin necessitates the evaluation of an extensive range of differential diagnoses. This typically includes infectious, autoimmune, inflammatory etiologies, cancers, and various other miscellaneous factors [4]. Investigations must be undertaken to verify or exclude the most probable diagnosis/diagnoses, based on the history and examination results. The investigation needs to progress through a minimum of two phases of baseline assessments, succeeded by more targeted evaluations, after which each anomalous result should be carefully considered; an increase in testing will likely yield a greater number of false leads. Preliminary blanket testing for all potential etiologies is inappropriate. A comprehensive initial assessment comprises a complete blood count with differential, renal electrolyte analysis, liver function tests, CRP, ESR, coagulation profile, creatine kinase measurement, a minimum of two blood cultures (collected before antibiotic administration), and an HIV test. A chest X-ray, abdominal ultrasound, and urine dipstick analysis should also be conducted. Possible second-line assessments encompass microbiological analyses, imaging studies, and biopsies [5,6].

Clinical manifestations facilitating its diagnosis encompass fever, diaphoresis, weight reduction, and left upper quadrant pain. Laboratory evaluations frequently reveal leukocytosis, anemia, raised ESR, and increased lactate dehydrogenase levels. Radiological inspection and pathological evaluation post-biopsy are crucial for the observation of splenomegaly [1].

B-ALL, a rare but severe syndrome, may manifest in young adults with nonspecific symptoms, including fever, weight loss, joint pain, and pancytopenia, potentially resembling other disorders such as infections, autoimmune diseases, or TB. Timely identification and suitable management, encompassing bone marrow biopsy and immunohistochemistry, were essential for achieving an accurate diagnosis [7].

Malignant lymphomas are the predominant neoplastic etiology of FUO. In addition to primary systemic lymphoma, other uncommon

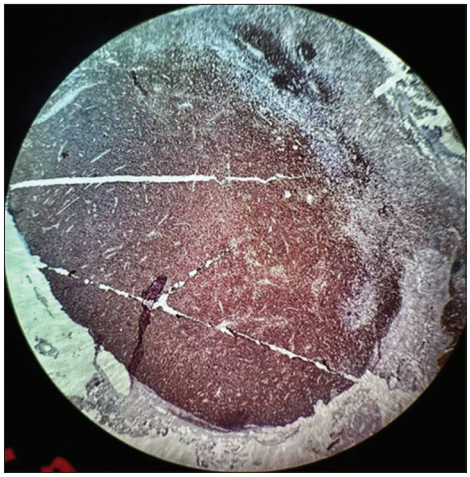

Fig. 4: Cluster of differentiation 20

manifestations of lymphomas presenting as FUO include intravascular lymphoma, primary central nervous system lymphoma, colonic lymphoma, and pituitary lymphoma [8].

Our case demonstrates that TdT and CD20 positivity is present in over 95% of the aberrant cells, hence supporting the diagnosis of CCC B-ALL. The study by Farag *et al*., reveals the diagnosis of CD5 positive diffuse large B-cell lymphoma, which can be further classified as non-germinal center type diffuse large B-cell lymphoma. The liver findings indicated marrow involvement by B-cell non-Hodgkin lymphoma [9]. In the present case, CD3 positivity was also observed which indicates a mixed for T/B-lineage ALL [10].

In a study done by Reddy and Reddy [11] conducted in children with PUO, malignancies constituted the second most prevalent etiology of FUO. The most frequently identified malignancies included CALLA positive B-ALL (57.14%), Hodgkin's lymphoma (14.23%), and Non-Hodgkin's lymphoma (14.2%). Another case report by Onweni *et al*. [12] the FUO was reported as diffuse large B-Cell lymphoma.

In the present case study, *Brucella* serology was performed and resulted in a negative outcome. In contrast, the study by Pathak *et al*. [13] reveals that Brucellosis, a zoonotic infection endemic in Asia, is a significant contributor to pyrexia of unexplained origin (PUO), especially in individuals who have interacted with infected animals. This study examined 282 serum samples from patients with pyrexia of undetermined origin (PUO) and individuals with occupational exposure, detecting brucellosis in up to 6.02% by several serological methods. One isolate of *Brucella abortus* was confirmed using polymerase chain reaction and biochemical testing [10].

CONCLUSION

The patient's clinical presentation, correlated by histological results and laboratory testing, validated the diagnosis and informed suitable care. The continuous monitoring of blood indicators and imaging results was essential in evaluating illness progression and therapy efficacy. The affirmative expression of CD30, CD3, CD20, and CD15 markers further corroborated the diagnosis and facilitated the customization of the therapy strategy. Consistent follow-up with the assessment of hematological markers and imaging is recommended to gauge treatment effectiveness and identify early indications of relapse. Given that this is a case study, we recommend additional research that will elicit interest an interpretation.

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Nil.

CONFLICTS OF INTEREST

Nil.

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