Case Report

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Infantile B-cell acute lymphoblastic leukaemia with the highest recorded count of white blood cells in the literature: case report and literature review

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Introduction: Infantile leukaemia is an uncommon haematological cancer that manifests within the first year of life. This malignancy is highly aggressive and possesses distinctive immunophenotypic, cytogenetic, and molecular attributes. It can originate from either myeloid or lymphoid cells. It often exhibits a higher incidence among females.

Case presentation: A 1-month-old male infant, initially seemingly healthy, presented with irritability and feeding difficulties. Born without complications, routine neonatal assessments appeared normal, and physical examination revealed no abnormalities. However, laboratory tests indicated an extremely high white blood cell count, low platelets, and elevated haemoglobin. Further examinations showed a white blood cell count of 1450 × 10^6/l with a blood film revealing significant leukocytosis dominated by blast cells. Abdominal ultrasound confirmed hepatosplenomegaly which was not present during pregnancy. Subsequent bone marrow analysis and flow cytometry established a diagnosis of B-cell acute lymphoblastic leukaemia (B-ALL).

Clinical discussion: It is rare for infantile ALL to manifest within the first month after birth. In most cases, the diagnosis is established before birth. When characteristic signs such as hepatosplenomegaly, leukaemia cutis, or infiltrative involvement of the extramedullary and central nervous systems are present, postnatal diagnoses are relatively straightforward. However, there are instances where children present with non-specific and ambiguous symptoms that resemble other medical conditions.

Conclusion: This case underscores the importance of paediatricians being vigilant and attuned to the subtle indicators that differentiate common illnesses from serious conditions such as infantile ALL.

Keywords: acute lymphoblastic leukaemia, case report, infantile ALL, leukaemia, leukocytosis

Introduction

Infantile leukaemia is a rare and distinct type of leukaemia that rarely presents within the first month of life when compared to other forms of the disease. It constitutes a small portion, roughly 2.5–5%, of all paediatric cases of acute lymphoblastic leukaemia (ALL) and 6–14% of paediatric cases of acute myeloid leukaemia[1]. The age at which it is diagnosed is a crucial factor affecting both its occurrence and the chances of survival[2]. According to available data, infantile leukaemia occurs at a rate of 41 cases per million, which translates to ~160 cases per year. Unfortunately, the 5-year survival rate for infantile leukaemia, standing at around 45%, is notably lower than that observed in older patients with leukaemia[2,3]. The youngest case reported up to now, excluding instances of birth presentation, involved a neonate who was only three weeks old[4].

B-lymphoblastic leukaemia (B-ALL) is prevalent among individuals in this age category and exhibits a distinctive immunophenotype, often lacking CD10 expression. In this subgroup, there is frequent occurrence of central nervous system (CNS) infiltration by leukaemia cells[5]. Approximately 80% of B-ALL cases involve rearrangements of the KMT2A gene (formerly known as MLL), which is associated with a poor prognosis[6]. Despite the advancements in the treatment of childhood acute leukaemia, infantile leukaemia still presents a challenging outlook. Current treatment protocols remain a subject of debate. Additionally, due to the aggressive nature of the disease,

HIGHLIGHTS

- Infantile leukaemia is an uncommon haematological cancer that manifests within the first year of life.
- There are instances where children present with non-specific and ambiguous symptoms that resemble other medical conditions.
- This case underscores the importance of paediatricians being vigilant and attuned to the subtle indicators that differentiate common illnesses from serious conditions such as infantile acute lymphoblastic leukaemia.

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complications related to treatment are common in these vulnerable patients[3].

Infantile B-ALL is a challenging condition known for its resistance and intriguing biological characteristics, which have garnered significant attention. It is advisable to conduct a thorough evaluation involving immunophenotypic, cytogenetic, and molecular analyses to predict the disease's progression and eventual outcome. In this study, we offer insights by presenting an outstanding case of infantile B-ALL, contributing to a better understanding of its clinical presentation, laboratory finding, and diagnostic characteristics. This work has been reported in line with the SCARE criteria[7].

Case presentation

A 1-month-old male infant presented with a history of irritability and poor feeding. There were no significant past medical or surgical issues, and the baby was born via normal vaginal delivery following an uncomplicated pregnancy. Routine neonatal assessments appeared normal, and there were no evident physical abnormalities. Vital signs, including temperature, oxygen saturation, respiratory rate, and heart rate, were all within the expected ranges.

However, laboratory tests showed an unreadable white blood cell (WBC) count, along with low platelet levels and elevated haemoglobin. Due to these abnormalities, the infant was referred to our laboratory (Professional Labs) for further examination. After dilution, the WBC count was determined to be 1450×10^6/l (Table 1). A blood film analysis revealed significant leukocytosis, primarily consisting of blast cells (Fig. 1). An abdominal ultrasound confirmed the presence of hepatosplenomegaly.

Subsequently, the infant underwent a bone marrow aspirate and biopsy, along with flow cytometry which revealed an ~98% of peripheral cells are B-lymphoblasts expressing CD19 (D), cCD79a, CD34 (P), CD38 (D), CD58, CD22 (P), CD81 (D), nTdT (D), and HLA-DR (P), which provided conclusive evidence of B-ALL. The infant was referred for chemotherapy protocol and stem cell transplantation at a tertiary paediatric oncology unit.

Table 1

Laboratory findings of the patient.

Parameter	Result	Normal range
Red blood cell	2.28×10^6/ul	$4.00–5.20 \times 10^6$/ul
Haemoglobin	13.7	10.3–14.9 g/dl
Haematocrit	32.6	30–44
Mean corpuscular volume	143	75–100 g/dl
Mean corpuscular haemoglobin	60.1	25–29 Pg
Mean corpuscular haemoglobin concentration	42.0	32–36 g/dl
Red distribution width	25.0	11.0–16.0%
Leucocytes	1450.00×10^9/l	$4–11 \times 10^9$/l
Platelets	60×10^9/l	$150–400 \times 10^9$/l
Lactate dehydrogenase	2652	160–450 U/l
Uric acid	14.2	2.1–5.6 mg/dl
Calcium	12.1	8–10 mg/dl
Prothrombin time	15	11–14 s
Activated partial thrombin time	39.6	23–35 s

Discussion

ALL is a heterogeneous group of lymphoid neoplasm that results from monoclonal proliferation and malignant transformation of lymphoid B or T progenitor cells in bone marrow, blood and extramedullary sites[8] . The clinical presentation of ALL is non-specific; patients can present with symptoms due to blast infiltration of the bone marrow, lymph nodes and other organs infiltration, also it could present with what is known as the "B symptoms" which include fever, weight loss and night sweat[9]. ALL demonstrates a bimodal age pattern, with the initial peak incidence at around 5 years of age and the second peak at around 50 years of age[10]. Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood. Flow cytometry can be performed to identify the lineage-defining antigens and so determine the ALL subtypes[11].

Leukaemia was the fourth most common cancer in Palestine in 2015 (8.5% of all cancer cases) with incidence rate 7.8 per 100 000 populations[12]. No available data on ALL in Palestine specifically. Updated statistics of incidence and mortality from ALL in the United States in 2019 is estimated as 5930 new cases and 1500 deaths[13].

Infantile leukaemia is characterized by the occurrence of acute leukaemia within the first year of life. In this age group, neuroblastoma and brain tumours are also documented, with all these neoplasms having a similar frequency of occurrence[3]. Among infants with leukaemia, there is a slight prevalence of lymphoid leukaemia over myeloid leukaemia, and of the cases falling into the lymphoid category, roughly 95% are of the B-lineage. A defining genetic feature in infantile leukaemia is the rearrangement of the KMT2A gene, situated on chromosome 11's long arm (11q23). This translocation can involve various partner chromosomes and is a recurring, non-random event in B-ALL. The resulting fusion protein is known to contribute to the development of leukaemia by increasing HOXA9 expression[14]. Another suggested mechanism that supports leukaemia growth is the heightened expression of the tyrosine kinase FLT3[15].

While there is a limited amount of epidemiological data available regarding infantile B-ALL, the majority of published studies indicate a higher incidence of this disease among females. However, our study's findings contradict this trend. Notably, our patient exhibited several adverse clinicopathological factors characteristic of this subtype of B-ALL, including hyperleukocytosis, hepatosplenomegaly at presentation, and a CD10-negative immunophenotype. CNS infiltration is a prevalent clinical feature in this patient group. According to existing research, the pro-B immunophenotype is more frequently observed in infants. In our study, the patient tested negative for CD20. Unlike what is typically reported in the existing literature, our case did not exhibit aberrant expression of myeloid antigens[16].

Early detection plays a pivotal role in securing the most favourable prognosis. According to various clinical studies published to date, key clinical characteristics of infantile ALL often involve hepatosplenomegaly in approximately 80% of patients[17,18], leukaemia cutis present in 60–80% of cases[17–19], extramedullary infiltration, and CNS infiltration, which is evident in over one-third of patients. Notably, leukaemia cutis has served as the initial presenting symptom in around half of the cases[19,20].

Generally, the treatment for infantile B-ALL differs from that of childhood B-ALL. Despite advancements in therapy, the

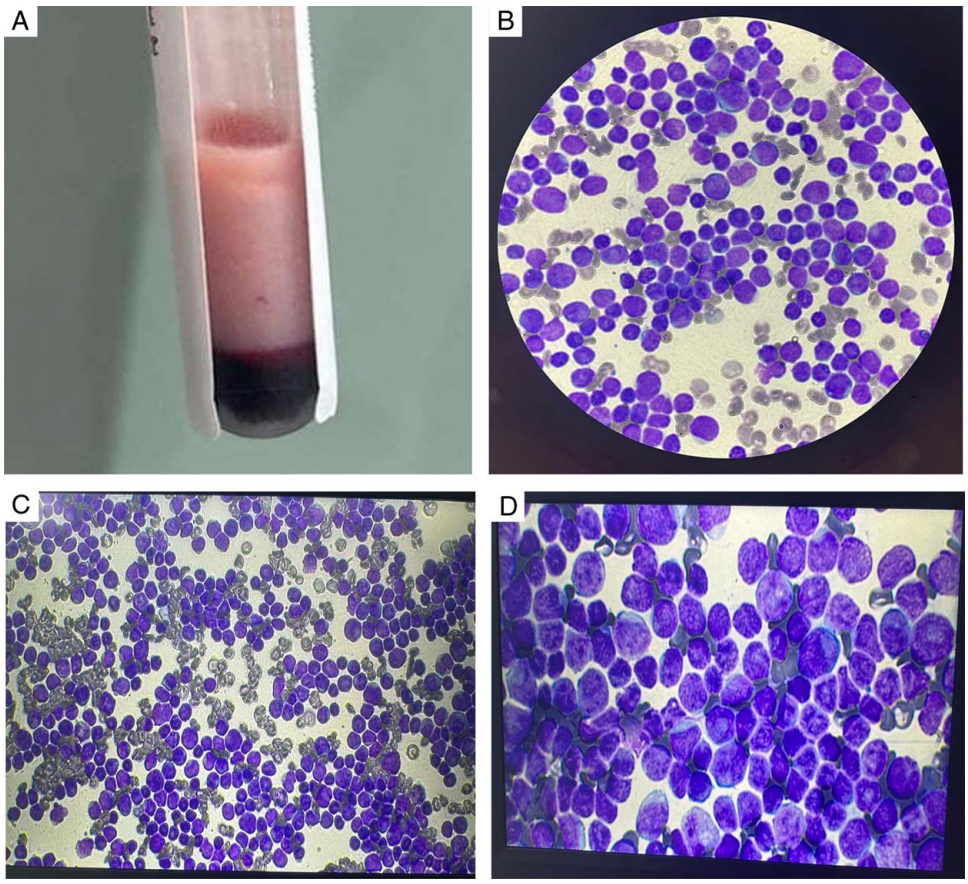

Figure 1. Peripheral blood smear morphology and Buffy coat. (A) Lipemic appearance of plasma with marked increase in buffy coat due to high white blood cells (WBCs) count. (B) Peripheral blood smear at 40× magnification shows marked increase in WBCs count. (C, D) Peripheral blood smear at 100× power shows homogenous population of immature WBCs with medium to large size, fine to coarse chromatin, high N:C ratio, basophilic cytoplasm and inconspicuous nucleoli. The estimated blast count in this sample exceeds 95%. Additionally, the figure depicts macrocytic normochromic red blood cells (RBCs), with a few unspecified Anisopoikelocytosis. There is a moderate increase in polychromasia, but no evidence of rouleaux formation or agglutination. Furthermore, numerous clearly identifiable circulating nucleated RBCs are observed.

mortality rate for infantile leukaemia remains high. Numerous studies have investigated the molecular characteristics and clinical outcomes of this rare condition, suggesting that its causes differ from those of other childhood leukaemias and may involve prenatal factors[21,22].

Three significant groups have conducted clinical trials specifically targeting infant ALL: Interfant (Interfant-06)[23], COG (AALL0631), and JPLSG (MLL-10). These groups have adopted a risk stratification approach based on KMT2A gene rearrangement. The outcomes of Interfant-06, which compared myeloid-type consolidation to a lymphoid protocol, were less promising. COG AALL0631 introduced an FLT3 inhibitor, which demonstrated some improvement in a specific subset of patients, although the overall event-free survival rate remained unchanged. The results from JPSLG were more encouraging, but the challenge of hematopoietic stem cell transplant (HSCT) remains a hurdle for some countries such as low-income ones[24].

Patients undergoing HSCT are particularly susceptible to complications and toxicities. As a result, the provision of HSCT to these patients necessitates a strong multidisciplinary team and standardized support services. Exciting advancements in molecular biology have paved the way for the creation of innovative therapeutic approaches, leading to improved outcomes. In developed nations, treatments targeting CD19 and CD33 are currently in various stages of clinical development. The emergence of these targeted therapies holds great promise, especially for young patients with ALL[24].

While the survival rate for older children with leukaemia in developed countries is approaching 90%, infants with leukaemia face an exceptionally bleak 5-year survival rate of less than or equal to 50%. However, the potential availability of advanced targeted therapies, HSCT, and effective supportive care may offer the opportunity to enhance outcomes for these patients in our specific healthcare settings[24,25]. Relapse is the main reason for treatment failure in childhood ALL. Relapses occur in bone marrow in 50–60% of cases. Other sites of recurrence include CNS in ~20%, isolated testicular relapse in ~5% and a combination of marrow and extramedullary disease in the remainder[26,27].

We performed routine blood investigations to look for an underlying explanation to this presentation. The blood film incidentally revealed a classical pathological picture of infantile ALL with an extremely high WBCs with the highest recorded count of 1450.00 × 10^9/l compared to the previous reported measures and high percentage of blasts.

Conclusion

In summary, infantile B-ALL represents a distinctive disease characterized by age-related clinical, pathological, and genetic features. Despite its limitations, this case report makes a valuable contribution to the limited body of literature on this condition, particularly with a such incredible WBCs count.

Ethical approval

Our institution has exempted this study from ethical review.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Writing the manuscript: O.N.S., M.Y.A., A.A. Imaging description: M.Y.A., O.N.S., M.H., H.O.S., S.S. Reviewing and editing the manuscript: M.Y.A.

Conflicts of interest disclosure

None.

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All authors attest that they meet the current ICMJE criteria for authorship.

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