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Case Report

Infantile T-cell Acute Lymphoblastic Leukaemia: A Case Report

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Abstract

Introduction: Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children, with a male predominance. Paediatric ALL is usually of B-cell lineage; T-cell leukaemia is uncommon and extremely rare under 1 year of age. Mixed-lineage leukaemia gene rearrangement is the best-known hallmark of infantile leukaemia and is a poor prognostic indicator. While multiagent high-dose chemotherapy remains the first line of treatment for paediatric T-cell lineage ALL (T-ALL), there are numerous side effects of these regimens, and most patients undergo relapse. Due to the rarity of the disease, treatment protocols for infantile T-ALL have not been established to date. **Clinical Description:** We present a case of a 7-month-old Pakistani male that presented with fever and cough and was subsequently diagnosed with T-cell ALL. T-ALL was diagnosed on flow cytometry. Due to poor prognosis, the patient was assigned palliative care. **Practical Implications:** Management of infantile leukaemia has yet to be studied in-depth. With a lack of clear treatment guidelines, the approach toward these patients remains challenging. Further research and clinical trials in this area of study are paramount to improving clinical outcomes for these young patients.

Key words: Acute lymphoblastic leukaemia, leukaemia, neoplasms, paediatric oncology, T-cell leukaemia, T-cell lineage acute lymphoblastic leukaemia

Introduction

Acute lymphoblastic leukaemia (ALL) is the most commonly presenting paediatric malignancy. Despite improvement in treatment strategies and cure rates in recent years, it remains a pertinent cause of morbidity and mortality.[1] ALL is more commonly diagnosed as B-cell lineage ALL (B-ALL) in infants. However, T-cell lineage ALL (T-ALL) is an exceedingly rare presentation under 1 year of age. Childhood and infantile T-ALL are distinctly different on a genetic and molecular level.[1] Multiagent high-dose chemotherapy is the first line of treatment for paediatric T-ALL, and children respond reasonably well, but not without long-term side effects.[2] However, due to the paucity of literature on infantile T-ALL, targeted therapies and treatment protocols have not yet been developed for this tumour entity.

Here, we present a case of a male infant with T-ALL and discuss the challenges in diagnosis and lack of clear treatment options. Written informed consent was obtained from the patient's father to publish this case report and all accompanying images.

Case Presentation

A 7-month-old Pakistani male presented to the paediatric emergency of a welfare hospital with fever and cough. The patient was lethargic, irritable and unwell for over 3 weeks. The patient had no significant birth history, previous hospitalisations or past illnesses. Family history reported by the parents was not positive for any malignancies or known genetic conditions. On examination, bilateral crepitations were noted in the chest. Regional lymph nodes were not palpable, the abdominal examination was unremarkable and no ecchymosis or petechiae were observed.

Diagnosis and management

The patient was admitted for investigations and symptomatic management. Complete blood count showed mild anaemia and leucocytosis with a white blood cell (WBC) count of 183.7 × 10^9/l. Atypical lymphoid cells with coarse nuclear chromatin were observed on a peripheral smear [Figures 1 and 2]. Derangements were noted in certain baseline investigations (C-reactive protein 21.60 mg/L, gamma-glutamyltransferase 712 U/L and alkaline phosphatase 840 U/L), with most other parameters falling within normal ranges. Chest X-ray showed bilateral parahilar vascular haze, raising suspicion of a pulmonary source of infection. A mediastinal mass was not seen. The patient was started on antibiotics and supportive management with close monitoring for clinical improvement. With suspicion of leukaemia, flow cytometry [Figure 3] was performed, which confirmed the diagnosis of T-ALL.

On day 5, after the initial presentation, the patient was started on prednisone with regular checks on blood investigation. The WBC count showed a decreasing trend at 21.6 × 10^9/l with 68% lymphocytes. Fluorescence *in situ* hybridisation was also conducted, which exhibited that mixed-lineage leukaemia (MLL) gene was not rearranged. Therefore, the disease was classified as the central nervous system 1 and prophase 7.

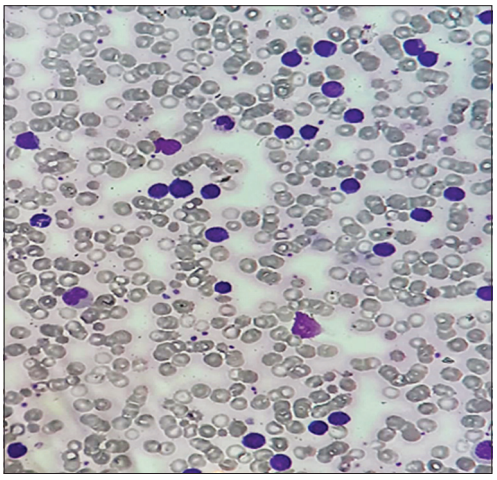


Figure 1: Atypical lymphoid cells with coarse nuclear chromatin on peripheral smear

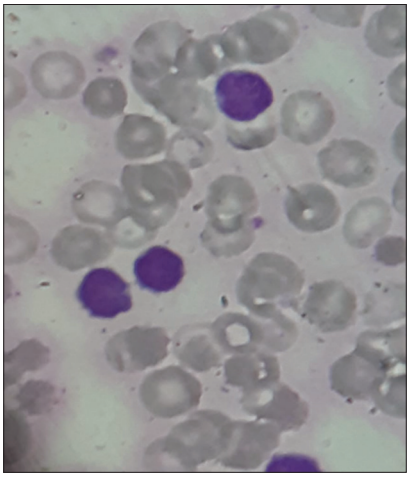
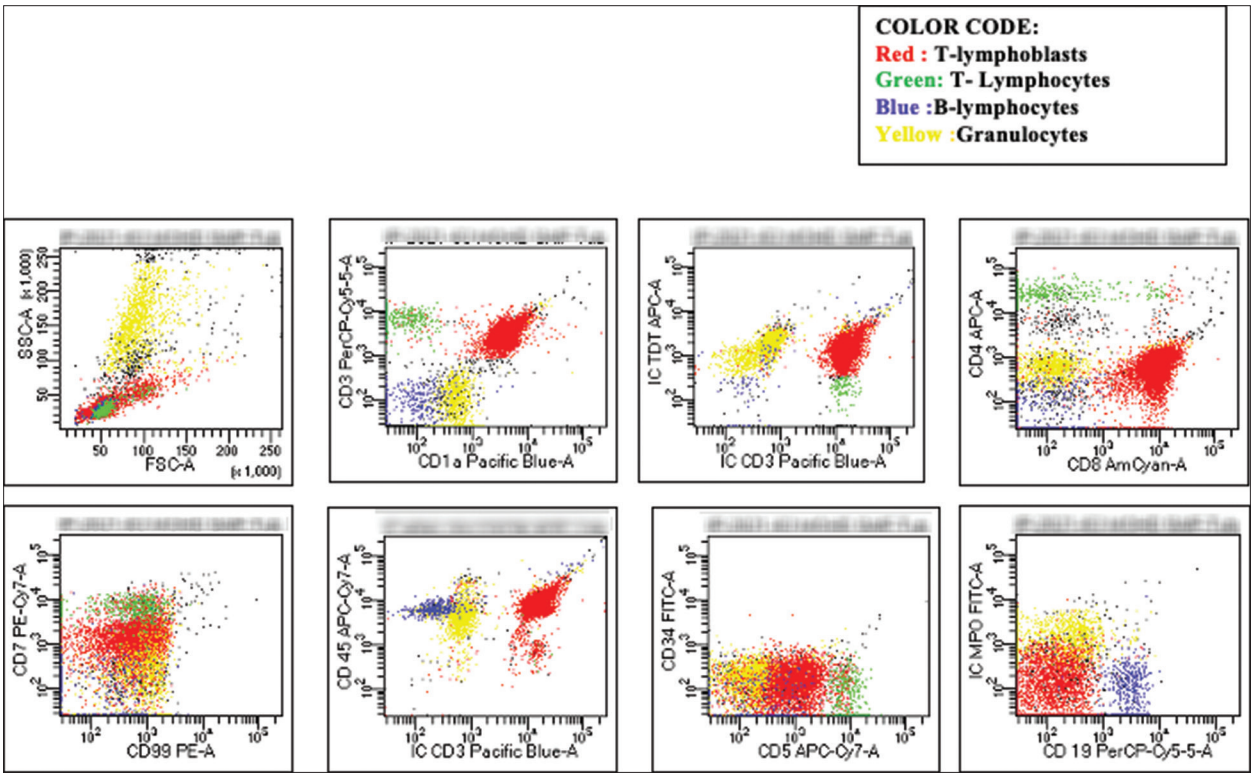


Figure 2: Atypical lymphoid cells with coarse nuclear chromatin were observed on peripheral smear

A multidisciplinary team meeting concluded that the intensive chemotherapy regimen required for the treatment of this infant would not be favourable considering the poor prognosis of the disease. The patient's family was counselled, and with their consent, the patient was shifted to palliative care. Five weeks after the initial presentation, the



Figures 3: Flow cytometry showing 74.7% small- to medium-sized lymphoblasts (forward light scatter properties) exhibiting following phenotype; TdT (-), CD34(-), CD99(-), CD117(-), CD45(+), CD3 (+), surface CD3(+), CD4(-), CD8(+), CD5(Dim+), CD1a (+), CD7(+), intracytoplasmic myeloperoxidase (-), CD13 (-), CD34 (-), CD45 (+), CD19 (-), CD20 (-) and CD10 (-)

patient presented with fever and a generalised rash diagnosed as measles, making a complete recovery after treatment. The most recent investigations showed the patient's WBC count at 14.2 × 10^9/l with regular monitoring in the palliation clinic every 2 weeks.

Discussion

T-ALL accounts for approximately 15% of childhood ALL cases.[2] Even with multiagent chemotherapy treatment, 15% of paediatric T-ALL cases undergo relapse and present an overall dismal prognosis.[2] Adverse prognostic factors for ALL in children include age <1 year or ≥10 years, male gender, WBC count ≥50,000/mm^3 and African, Hispanic and native American ethnicities.[3] A higher expression of the USP7 allele in Africans has been identified as a novel risk locus.[4] Similarly, myeloid leukaemia factor 1 (MLF1) gene deletion has been identified as a plausible marker for infantile TLL,[5] whereas deletion of the SCL/TAL1 interrupting locus (STIL)-T-cell acute leukaemia (TAL1) (STIL-TAL1) fusion gene has been seen in paediatric T-ALL.[6] The presence of a phosphatase and tensin homolog (PTEN) gene deletion has previously been discovered at birth in an infant with T-ALL, suggesting an *in utero* origination of this disease.[5]

However, rearrangements involving the MLL gene (also known as KMT2A) at chromosome band 11q23 are the best-known hallmark of infantile leukaemia.[7] Infants with wild-type MLL genes such as our patient have been observed to present after the age of 6 months with more favourable WBC counts and more mature immunophenotypes, as well as a good response to 7-day prednisone monotherapy.[8] Among

infants with wild-type MLL ALL, low levels of MEIS1 expression have been proven to have a superior clinical outcome with a 5-year disease-free survival (DFS) of 87.5 compared to a high MEIS1 expression DFS of 50.0 and 5-year overall survival (OS) of 100.0 and 71.4 for low and high MEIS1 expression, respectively.[8] Thus, the significant influence of MEIS1 expression on survival rates highlights that this category of infant ALL is highly aggressive leukaemia.[8]

For unclear reasons, increasing age within infants with ALL is associated with a better clinical outcome.[8] However, infantile ALL has an overall lower survival rate than ALL in older children and adolescents.[9] The Interfant-06 treatment protocol study established a correlation between younger age at diagnosis and an inferior outcome, with a 6-year event-free survival (EFS) of 25.1% for patients aged 0–3 years.[10] Furthermore, T-ALL is known to have a skewed gender distribution with 3 times greater prevalence in males than females, most likely due to ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX) being an X-linked tumour suppressor gene.[11]

The main prognostic measure in T-ALL is a minimal residual disease (MRD), and treatment is usually directed by end-of-consolidation MRD response.[12] Glucocorticoids are the cornerstone for T-ALL treatment but are known to paradoxically induce steroid resistance by upregulation of the expression of IL-7 receptors.[13] Decreased expression of the wild-type MLL gene has also been proven to contribute to glucocorticoid resistance in ALL.[14]

The Interfant protocols are the most widely studied treatment regimens for infantile ALL. After treatment with the Interfant protocols, the 4-year EFS for infantile T-ALL was 45.7%, and the 6-year OS of infant ALL with germline KMT2A was 87%.[10] However, these are intensive regimens comprising multiple phases of treatment and are associated with complications including infections, mucositis and liver and neurotoxicity.[15] Compared to Berlin-Frankfurt-Münster (BFM)-based childhood ALL protocols, the Interfant protocols have shown comparable treatment-related mortality with no improvement in survival and a high rate of deaths in complete remission.[16] Hence, there is a dire need for improved therapeutic strategies targeting treatment-related toxicity to improve mortality and reduce relapse rates.[16]

Two methotrexate (MTX) intensification regimens: High-dose MTX (HDMTX) with leucovorin rescue and Capizzi-style escalating intravenous MTX without leucovorin rescue, plus pegaspargase Capizzi-style, and intravenous MTX (C-MTX) were studied in the Children's Oncology Group (COG) AALL0434 trial.[17] More recently, a 4-drug induction regimen with dexamethasone and an anthracycline, plus augmented BFM-like consolidation containing cyclophosphamide, has been recommended for children with T-cell ALL.[18] Nelarabine and vincristine are the first-line treatment options for relapsed T-ALL[19] but are associated with significant, fatal toxicities.[20,21]

The treatment outcomes for paediatric ALL in Pakistan are subpar because developing countries face a unique set of challenges such as limited access to specialised oncology care units, unavailability of supportive care, nutritional deficiencies, financial constraints and lack of parental education.[22,23] Consequently, patients are more likely to present late with more severe disease or abandon treatment and are more susceptible to infectious complications.[23] One-week prednisolone prophase in a cohort of Pakistani children with ALL was useful in stabilising and reducing disease burden.[24] Compared to 14% of induction deaths when direct multiagent chemotherapy was administered, prednisolone prophase was associated with a decreased death rate of 9%.[24] Therefore, considering the poor prognosis of infantile T-ALL and considering the factors above, a palliative treatment strategy is usually adopted in Pakistan. Despite being a rare presentation, further research and clinical trials must be done to treat and manage infantile T-ALL to

establish a clearer clinical approach toward these young patients and improve clinical outcomes.

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Authors' Contributions

Conceived and designed the analysis: NB. Collected the data: NB. Contributed data or analysis tools: SM, SS. Performed the analysis: Not applicable. Wrote the paper: NB, SM, SS.