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Early T-cell Precursor Acute Lymphoblastic Leukemia- A Neoplasm with Dual Lineage Phenotype- Case Study of Two Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author S designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AS and JSN managed the analyses of the study. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Early T-cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) is a subtype of T-ALL/LBL which is derived from thymic cells at the early T-cell precursor (ETP) differentiation stage that have the potential to differentiate into multiple lineages, including lymphoid and myeloid. ETP-ALL accounts for 15% of childhood T-ALL and 10-30% of adult T-ALL. It has characteristic immunophenotypic expression of CD7, a lack of CD1a and CD8, weak expression of CD5 (with <75% positive blasts), and positive expression of one or more stem cell or myeloid markers including CD117, HLADR, CD13, CD33, CD11b or CD65. We here in report two cases of ETP-ALL with brief review of literature.

Keywords: ETP-ALL; T-ALL; CD1a; CD8.

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1. INTRODUCTION

T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) is a malignant neoplasm of immature T cell with subtypes that correspond to different T-cell maturation stages [1-4]. These account for 10–15% of childhood and 10-30% of adult ALL cases [5].

Early T-cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) is a subtype of T-ALL/LBL derived from thymic cells at the early T-cell precursor (ETP) differentiation stage that have the potential to differentiate into multiple lineages, including lymphoid and myeloid [6,7]. World Health Organization (WHO) classification of acute leukemia, 2016 update has included ETP-ALL as a new provisional entity which was kept under early-T-ALL/LBL category in 2008 WHO classification [8].

ETP-ALL accounts for 15% of childhood T-ALL and 10-30% of adult T-ALL [6-11].

It was defined by a distinct immunophenotypic expression of CD7, a lack of CD1a and CD8, weak expression of CD5 (with <75% positive blasts), and positive expression of one or more stem cell or myeloid markers including CD117, HLADR, CD13, CD33, CD11b, or CD65 [6].

ETP-ALL/LBL is also characterized by a distinct molecular profile with a lower frequency of NOTCH1 mutations and frequent occurence of FLT3 and DNMT3A mutations [12-14]. Most importantly, it has comparatively worse outcome in children and young adults than other T-ALL/LBL subtypes [6,15].

The purpose of this case study is to highlight the clinical, immunophenotypic and molecular characteristics of ETP-ALL and discuss two cases experienced at our institution.

2. CASE REPORT

We have reported total of 12 cases of T-ALL on flowcytometry from July, 2019 to January, 2021 out of which 2 cases are of Adult ETP-ALL(16%).

Case 1: A 35 year old woman presented to OPD with complaints of generalized lymphadenopathy, fever and weakness for 1 months. There was no significant family or past history. On examination, she had pallor, with multiple small, painless nodes palpable in b/l cervical, axillary and inguinal region. Moderate splenomegaly was also present. Respiratory, cardiovascular and neurological examinations were unremarkable. Complete blood count showed moderate anemia (Hb-6.5 g/dl), high TLC (90,000/ul) and mild thrombocytopenia (Platelet count-75,000//ul). Peripheral blood smear confirmed leucocytosis with approximately 82% blasts (Fig. 1). These blasts were small to medium sized with high N:C ratio, round nucleus with irregular contour, condensed chromatin, inconspicuous to prominent nucleoli and scant agranular basophilic cytoplasm (Fig. 2). A provisional diagnosis of MPO negative acute leukemia was made.

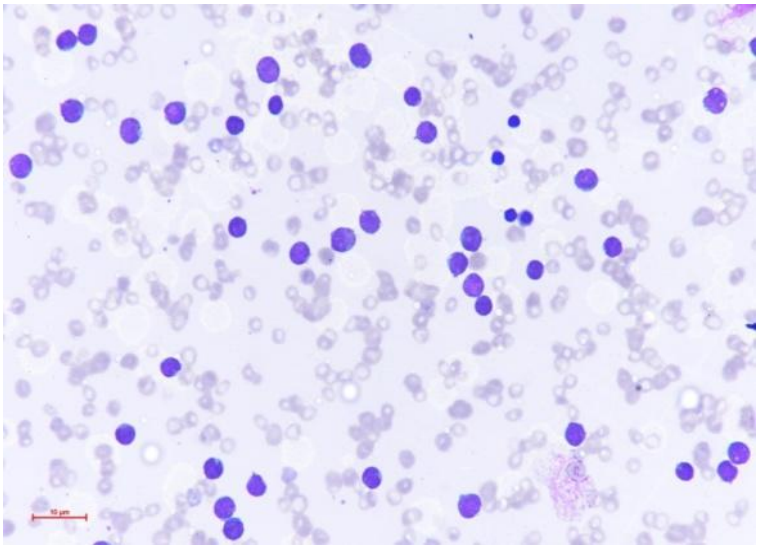


Fig. 1. Leucocytosis with approximately 82% blasts (400x)

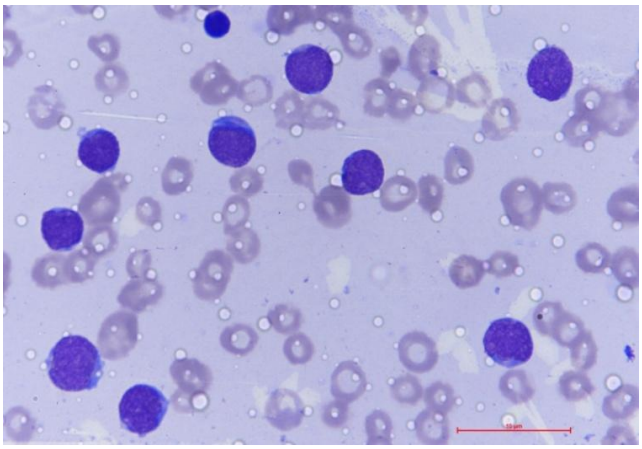
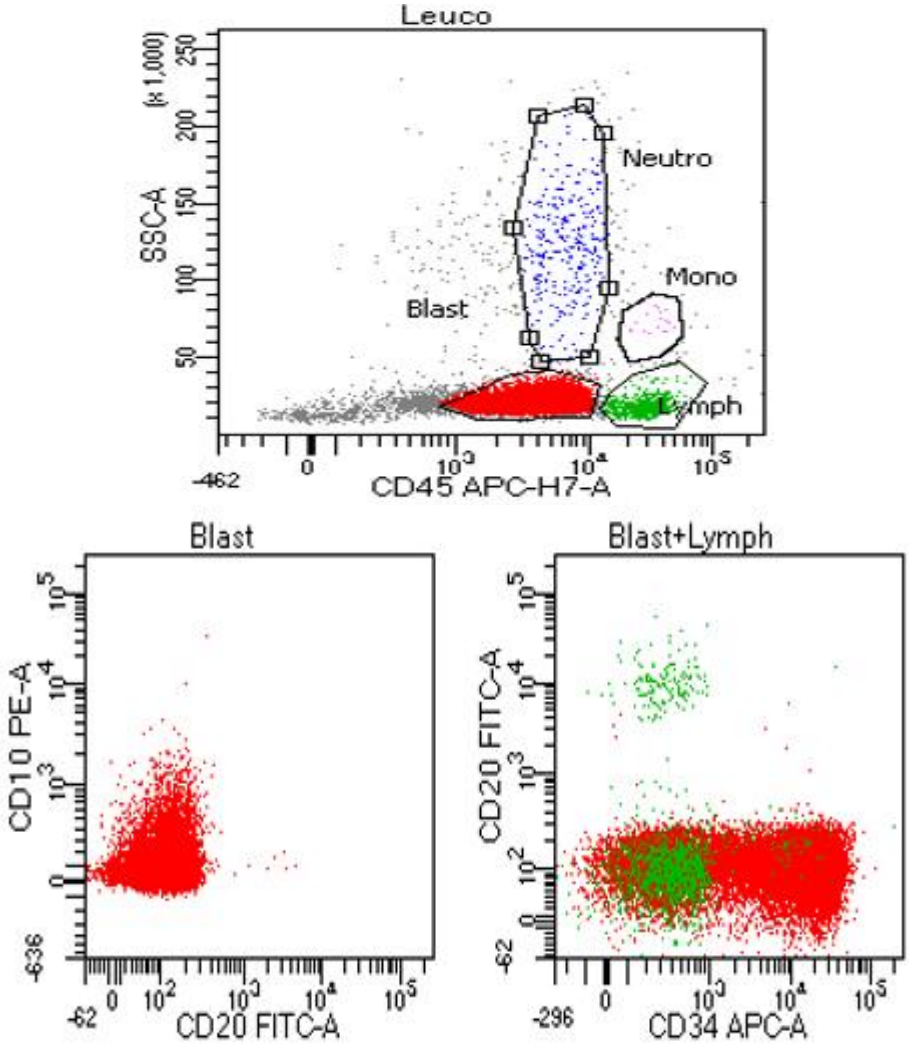


Fig. 2. Small to medium sized blasts with high N:C ratio, round to oval nucleus with irregular nuclear contour, inconspicuous to prominent nucleoli and scanty to moderate agranular basophilc cytoplasm. (1000x)



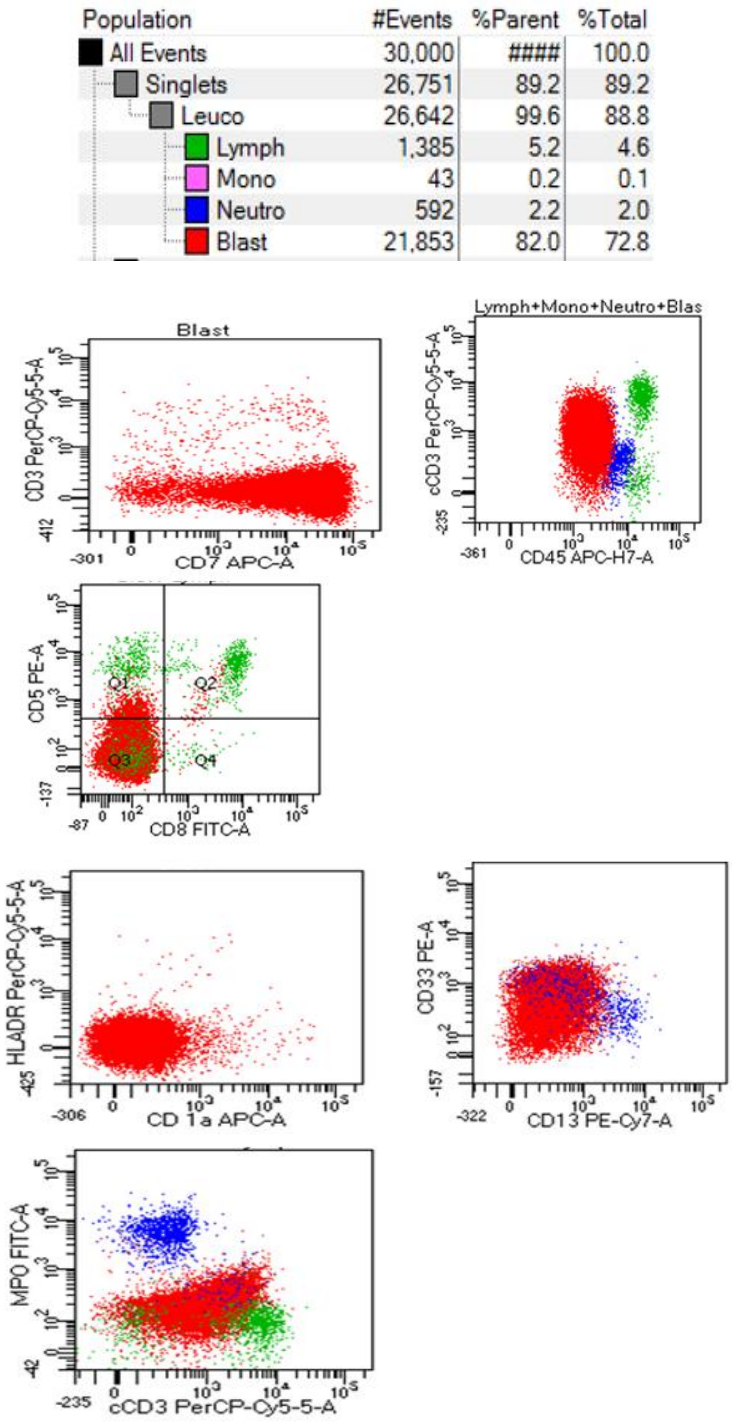


Fig. 3. Scatter plot of flowcytometric analysis of ETP-ALL showing its characteristic immunophenotypic profile

Immunophenotyping of the blasts in the peripheral blood was performed by standard flow cytometry methods, using standardised antibody panels. Immunophenotyping was performed by a FACS Canto II flow cytometer with six-colour reagent panels. It showed 82% cells gated in low

side scatter and moderate CD 45 region which was positive for cytoplasmic CD3, CD7, CD5 (dim and partial), CD34, CD13 & CD33 (dim and partial) and negative for surface CD3, CD1a, CD8, HLA-DR and cyto MPO. Final diagnosis of ETP-ALL was made.

Case 2: A 20 yr old male presented to OPD with complaints of generalized lymphadenopathy and fever for 3 months. There was no significant family history or past history. General examination showed pallor with multiple small, painless palpable nodes in b/l cervical and axillary regions. Respiratory, cardiovascular, abdominal and neurological examination was unremarkable. Initial laboratory investigations revealed pancytopenia with severe anemia (Hb-3 g/dl), Moderate leucopenia (TLC-1100/ul) and moderate thrombocytopenia (Platelet count-50,000/ul). Peripheral blood smear showed 65% atypical cells, confirmed on bone marrow examination which revealed cellular marrow with marked infiltration by blasts. These were small to medium sized with high N:C ratio, round nucleus with irregular contour, condensed to fine granular chromatin, prominent nucleoli and scant to moderate agranular basophilic cytoplasm. Provisional diagnosis of precursor lymphoblastic leukemia was made.

Immunophenotyping of the blasts in the bone marrow sample was performed and it showed 75% cells gated in low side scatter and dim to moderate CD45 region which was positive for cytoplasmic CD3, CD7, CD5 (dim and partial), CD34, CD38, HLA-DR, CD33 (dim and partial) and CD117 (dim and partial) and negative for surface CD3, CD1a, CD8, CD13 and cyto MPO. Final diagnosis of ETP-ALL was given.

3. DISCUSSION

ETP-ALL is a recently described subgroup of T-ALL distinguished by very early arrest in T-cell differentiation, identified by a well defined gene expression signature and immunophenotype [6,9,16].

Normal early T-cell precursors (ETPs) are a subtype of thymocytes, which have migrated from the bone marrow to the thymus, and retain multilineage differentiation potential, indicating that they are derived from hematopoietic stem cells [17-19]. However, recently, a mouse model of T-ALL using a Sleeping-Beauty-based transposon system suggested that ETP-ALL may be derived from more mature T-cells [20]. Thus, the exact cellular origin of ETP-ALL is not clear.

Recently, a study attempted to make diagnosis of ETP-ALL using the expression of CD5 and concluded that CD5- negative T-ALL could be diagnosed as ETP-ALL because CD5 negativity was associated with positive myeloid/stem cell antigens but not CD1a and CD8 expressions [21].

Currently, precise immunophenotyping is the most important tool to make a diagnosis of ETPALL, distinguishing ETP-ALL from classical T-ALL. In our case report both cases were diagnosed by flowcytometric analysis.

Both pediatric and adult ETP-ALL show distinct mutations. Pediatric ETP-ALL has a higher expression of oncogenic transcription factors: LMO1, LMO2, LYL1, and ERG [6,7]. Whole-genome sequencing studies showed that ETP-ALL has a high frequency of activating mutations in the genes involved in cytokine receptor and RAS signaling (e.g., NRAS, KRAS, FLT3, IL-7R, JAK3, LAK1, SH2B3, and BRAF) and inactivating mutations in the genes encoding key transcription factors involved in hematopoietic development (e.g., GATA3, ETV6, RUNX1, IKZF1, and EP300) and involved in epigenetic gene control (e.g., EZH2, EED, SUZ12, SETD2, and EP300 genes) [7]. In adult ETP-ALL patients whole exome sequencing revealed a distinct mutation spectrum from that of pediatric ETP-ALL, particularly in affecting genes involved in epigenetic regulation with higher frequencies of DNMT3A and FAT3 mutations [14]. DNMT3A alterations in lymphoid malignancies are limited to T-lineage disease. In all cases, DNMT3A mutations increase in frequency with age, and are extremely rare in children and adolescents [22].

Collectively, characteristic immunophenotype and distinct genetic profiles distinguish ETP-ALL from classical T-ALL. The characteristic gene profile of ETP-ALL may provide new therapeutic strategies for this leukemia.

Coustan-Smith et al. reported that patients with ETP-ALL showed a poor initial response to standard intensive chemotherapies and unfavorable outcomes [6]. Recent protocols for T-ALL patients include consecutive phases of induction, consolidation, delayed intensification, and maintenance, with drug combinations that commonly include doxorubicin or daunorubicin,

dexamethasone or prednisone, vincristine, asparaginase, cyclophosphamide and cytarabine, together with methotrexate and intrathecal chemotherapy as prophylaxis for CNS infiltration. In past, ETP-ALL has been associated with poor prognosis. but in recent years application of early response-based intensification regimens has greatly improved the outcome of these patients [23].

In the TLLSGL99-15 study, three of four relapsed ETP-ALL patients were successfully treated with allogenic hematopoietic stem cell transplantation (allo-SCT), indicating that allo-SCT could be an effective therapeutic option for ETP-ALL, hence mandating the precise diagnosis [15].

4. CONCLUSION

Diagnosis of ETP-ALL needs combination of cell morphology, cytochemical staining as well as flowcytometric analysis. The main purpose of this report is to make physicians aware of this entity, its controversial prognostic significance and the need for novel treatment strategies.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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