

Case Report

Early T Cell Precursor Acute Lymphoblastic Leukaemia with t(1;12;13) (p22;p11.2;q14) in a 7-Month Old Girl

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Abstract

We describe a case of an infant diagnosed with Early T cell Precursor Acute Lymphoblastic Leukaemia (ETP-ALL). This leukaemia is a high risk subgroup of T-Acute Lymphoblastic Leukaemia/Lymphoma. In this subtype, T cell differentiation is characteristically arrested very early at the thymic progenitors cells. This type of leukaemia has distinct immature immunophenotype (CD1a-, CD8-, CD5+ dim and positivity for at least one marker of stem cell or myeloid lineage) and have been demonstrated to have several recurrent mutations that involve RAS signaling mediators, gene coding cytokines, epigenetic controllers and haematopoietic transcriptional regulators. ETP-ALL is associated with poor prognosis and a poor response to chemotherapy which is reflected in our patient as she showed partial response to induction chemotherapy. The case highlights a case of ETP-ALL in an infant with complex karyotype.

Keywords: ETP- Acute lymphoblastic leukaemia; Immunophenotyping; Infant leukaemia

Introduction

T-Acute Lymphoblastic Leukaemia/Lymphoma make up about 15% of childhood Acute Lymphoblastic Leukaemia/Lymphoma (ALL) and 25% of adult ALL. In the recent WHO classification of haematological malignancies, a new separate subgroup has been classified within the T-ALL category, the Early T cell Precursor Acute Lymphoblastic Leukaemia [1]. This is a rare subgroup, characterised by very early arrest in T cell precursors differentiation. In normal T cell ontology, the early thymocytes, which originates in the bone marrow and subsequently migrate to the thymus for further differentiation, have a subset of normal early T cell precursors (ETP) in which they retain multilineage differentiation potential. ETP-ALL reflects the neoplastic counterpart of the ETPs [2]. ETP-ALL has unique immunophenotyping characteristics in which they express CD7 and may express cytoplasmic CD3 but are negative for T-lineage cell surface antigen (CD 1a, CD8 and CD5 dim) and they express one or more myeloid and haematopoietic stem cell markers such as CD13, CD33, CD34 and CD117 [1].

Case Presentation

This is a 7-month-old baby girl who was born prematurely at 28

weeks gestation. Her corrected gestational age is 4 months old. She had a stormy neonatal period, and spent 60 days in Neonatal Intensive Care Unit (NICU). She presented again to the hospital at 7 months old with a one week history of fever and intermittent cough. On further questioning, she has been unwell for the past six weeks, with recurrent fever and poor weight gain. Her parents also noticed multiple bruising on her trunks and limbs. Clinical examination showed a pale and lethargic child with some petechiae and ecchymoses on her abdomen. She had splenomegaly measuring 6cm and hepatomegaly measuring 5 cm. There were multiple palpable lymph nodes on the occipital, bilateral mandibular, bilateral cervical, bilateral axillary and bilateral inguinal regions. They were firm and well defined nodes with sizes ranging from 1cm to 2 cm. There was also a scalp swelling (*leukaemia cutis*) at the vertex measuring 5 cm × 5 cm. The swelling was firm and not fluctuant. Other examinations were unremarkable. Full blood count revealed leucocytosis (Total white count: $25 \times 10^9/L$), severe anaemia (Haemoglobin level: 3.9 g/dL) and thrombocytopenia (Platelet count: $27 \times 10^9/L$). Examination of the peripheral blood film showed 55% blast cells. The cells were small to moderate in size, with scanty cytoplasm, and clumped chromatin pattern. The nucleoli were inconspicuous. There were also many smudge cells (Figure 1). Unfortunately, the bone marrow aspirate from bilateral tibias was severely haemodiluted with no fragments present. Trephine biopsy was also unsatisfactory. Immunophenotyping (IPT) was performed on peripheral blood by standard flow cytometry methods using FACSDIVA flow cytometer with eight colour reagent panels. CD45 gating strategy was applied. There were about 50% leukaemic blasts that were gated at dim to moderate CD45 and low side scatter (Figure 2). These cells expressed T cell markers CD7, CD2, and dim CD5. They also express NG2 and HLA-DR with heterogenous expression of CD33, CD38, CD123 and CD117. The blasts were negative for MPO and other B-lymphoid marker. Based on WHO 2016 classification, this would be suggestive of early T cell precursor lymphoblastic leukaemia. Her karyotype showed 46 XX (62.5%) and

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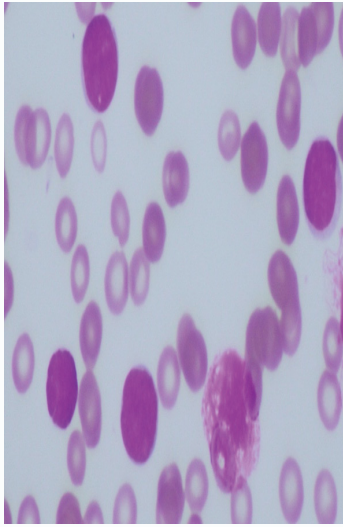


Figure 1: Peripheral blood film showing 55% blast cells. The cells were small to moderate in size, with scanty cytoplasm, and clumped chromatin pattern. The nucleoli were inconspicuous. There were also many smudge cells.

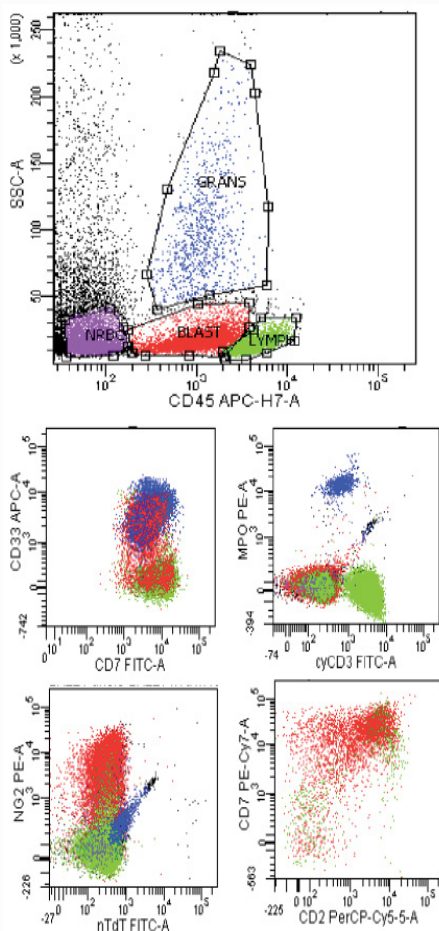


Figure 2: Immunophenotyping of bone marrow at diagnosis showed 50% blast population (red dots). The blast population express these immunophenotypes: CD3⁺, CD1a⁺, CD4⁺, CD8⁺, CD5^{dim} and CD7⁺, CD2⁺, NG2⁺, heterogeneous CD33 and HLA-DR⁺. Colour of populations: purple = nucleated red blood cells/debris green = lymphocytes, blue = granulocytes using CD45 gating strategy.

46 XX, t(1;12;13) (p22;p11.2;q14) (37.5%) complex karyotype with an apparently balanced three way translocation. This patient was started on Interfant-06 protocol. During the induction phase, she developed paralytic ileus in which chemotherapy was withheld for 4 weeks. At the end of the induction phase, clinically, the child showed partial response to the therapy, with resolution of the leukaemia cutis, and reduction of the size of splenomegaly and hepatomegaly. Peripheral blood film examination revealed pancytopenia with leucoerythroblastic picture and occasional suspicious cells. The marrow aspirate showed a hypercellular marrow with 29% blast cells. Immunophenotyping showed similar markers at presentation. She is currently undergoing reinduction phase.

Discussion

Early T-Cell Precursors (ETPs) are a subset of thymocytes that have recently immigrated from the bone marrow to the thymus³ and they have multilineage differentiation potential. Apart from their T-lymphoid potential, they also carry a natural killer, dendritic, and myeloid cell potential (multipotency) [4]. ETPs that have oncogenically transformed made up a proportion of T-ALL cases and hence might respond poorly to lymphoid-cell-directed chemotherapy [3]. This is termed as Early T cell precursor -ALL. It was initially described in a study by the St. Jude Children's Research Hospital in 2009 as a distinct subtype of paediatric T-ALL, and is generally associated with poor prognosis [4]. In children, ETP-ALL is associated with older age and a lower presenting WBC count. Early T-cell Precursor Lymphoblastic Leukaemia (ETP-ALL). is a type of T-ALL characterized by early arrest in T-cell differentiation and associated with poor prognosis and response poorly to intensive chemotherapy. ETP-ALL has distinct immunophenotyping characteristics. Firstly, they lack Cd1a and CD8. Secondly, they show weak CD5 expression (<75% of neoplastic clone). Thirdly, they also express one or more myeloid or stem cell associated markers such as CD117, CD34, HLA-DR, CD13, CD33, Cd11b or CD65 [4]. A scoring system has been proposed based on 11 commonly available markers; CD5, CD8, CD13, CD33, CD34, HLA-DR, CD2, smCD3, CD4, CD10 and CD56. When applied, the specificity of the scoring system 100% and the sensitivity is 94% [5]. When this scoring system is applied to the phenotype of our patient, it was consistent with ETP-ALL. The immunophenotype of the lymphoblasts in our patient was CD3⁺, CD1a⁺, CD4⁺, CD8⁺, CD5^{dim} and CD7⁺, CD2⁺, NG2⁺ and HLA-DR⁺ and these fits for pro-T-ALL phenotype. However, in view of the expression of myeloid and stem cell markers such as CD33, CD38, CD123 and CD117 and negative for TdT, these findings showed a similar profile to normal or stem cell like thymocyte T-cell precursors, leading to its name, ETP-ALL. Complex karyotype is defined as ≥ 3 or ≥ 5 chromosome aberrations, which is rare findings among ALL. In our patient, she harbored a complex cytogenetic abnormalities involving three chromosomes 1, 12 and 13. In the (1;12;13) translocation, the 12p segment has been translocated onto 1p, the 1p segment onto chromosome 13, and the long arm segment of chromosome 13 onto chromosome 12 at 12p11. t(1;12;13) (p22;p11.2;q14). Genes located on 12p11-p13 region may play a role in oncogenesis. One of the most common genes located at 12p is *ETV6*, also known as *TEL*, encodes as transcription factor and it is strictly required for maintaining the function of Hematopoietic Stem Cells (HSCs) in the bone marrow [6]. Meanwhile the q14 region of chromosome 13 contains a coding region, the *RB1* locus, for the *RB* gene. This gene, which has been demonstrated to code for a nuclear phosphoprotein, is believed to act as a tumor suppressor gene. The clinical characteristics of ETP-ALL mirrors T-ALL in terms

of haemoglobin level, gender and involvement of the nervous system. It has been shown that ETP-ALL has generally lower total white cell count, with lower frequency of mediastinal mass and typically affect higher age group (>10 years old) when compared with classical T-ALL. ETP-ALL has no characteristic cytogenetic profile however ETP-ALL had more 13q- and DNA copy abnormalities than seen in classical T-ALL [2]. In terms of treatment and prognosis, ETP-ALL has significant association with higher rate of relapse and also induction failure. Patients with ETP-ALL has reduced overall survival rate (19%) compared with classical T-ALL (84%). They also have higher risk of relapse with a 10-year event free survival of only 22% as compared with classical T-ALL (69%) [2].

Conclusion

The diagnosis of this patient was made by a typical features shown by flow cytometry. It is important to identify this entity, as it response poorly to chemotherapy. To our knowledge, this is the first reported case ETP-ALL in an infant with complex karyotype.

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