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Case Report

T-ALL with TEL/AML1 Translocation, Aberrant Expression of CD19 and 33: Case Report and Literature Review

Abstract

We herewith introduce a 9-year-old boy presenting with leukocytosis, anemia and high lymphoblast count who had a pale complexion as well as weight loss. His cytogenetic analysis revealed aberrant chromosomal rearrangements in different clonal populations harboring 46XY karyotype with t (12; 21) (p12; q22), which was confirmed by DNA sequencing. Flowcytometry assay detected aberrant B lymphocyte and myeloid CD markers such as CD19 (22.0%) and CD33 (20.5%), respectively. To our knowledge, this is the first case of a patient initially diagnosed as TEL/AML1 transcript positive T-ALL expressing CD19 and CD33 markers. The present article also highlights the need for molecular gene rearrangement studies to determine the precise lineage of ambiguous ALL clones.

Abbreviations

M: Male; CD: Cluster of Differentiation; TDT: Terminal Deoxynucleotidyl Transferase; MPO: Myeloperoxidase; IgM: Immunoglobulin M; HLA: Human Leukocyte Antigen

Introduction

T-Acute lymphoblastic leukemia (T-ALL) is one of the most important hematologic malignancies occurring due to clonal proliferation of T lymphocytes in approximately 15-25% of ALL patients [1]. In comparison with B-ALL patients, those suffering from T-ALL are at risk of increased leukocyte count (WBC>20×10^9/L), organomegaly, enlarged mediastinal mass and central nervous system (CNS) involvement [2]. Immunophenotype studies have enabled the differentiation between T- and B-cells. Cluster of differentiation (CD) molecules 79a and CD22 as well as cCD3 and TCR are specific for B-cells and T-cells, respectively. Myeloid markers such as CD13, CD33 and myeloperoxidase (MPO) may be observed in different ALL types, and MPO expression can be a marker of ambiguous lineage leukemia, for example in T or B ALL with aberrant expression of myeloid lineage markers [3].

Several chromosomal abnormalities may be detected in this type of leukemia, including t (1; 19) (q23; p13), t (11; 19) (q23; p13.3), t(4; 11) (q21; q23), t(9; 22) (q34; q11), hyper- and hypo-diploidy as well as t(12; 21) (p12; q22) [4]. t-(12; 21) (p12; q22) is caused by fusion of part of Translocation-Ets-Leukemia (TEL) (12p12) gene within acute myeloid leukemia 1 (AML1) (21q22) gene. This translocation has been reported to be highly frequent in 1-12 year old children but it is rarely observed in childhood AML and adult ALL [2,5].

Immunophenotype study of this translocation revealed the presence of CD10, CD19 and CD22, precursor B-cell phenotype as well as other markers of this cell line such as HLA-DR, CD10, CD13, CD19, CD24, CD33, CD34, CD40, CD45 and CDw65 but the absence of CD9, CD20 and CD86 [6-8]. In general, t(12; 21) (p12; q22) is observed in common ALL, pre-B-ALL (BCP-ALL) and rarely in pro-B-ALL, and is raised as the most common gene rearrangement in childhood BCP-ALL [9,10]. In the study of Ma et al, one of the patients had T-ALL, which has been the only report of t(12; 21) translocation in T-ALL [11].

The presence of t(12; 21) translocation usually involves a favorable prognosis and response to treatment since the majority of TEL/AML1 positive patients show non-invasive clinical symptoms, non-hyperdiploid DNA content and younger than 10 years of age [12-14]. Favorable prognosis resulting from this fusion can be demonstrated with its low incidence in recurrent cases (8.9% and 10%) in addition to

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high percentage of event-free survival (EFS) (approximately 89-100%) [13,15,16]. Detection of TEL/AML1 gene fusion is considered an important marker for prognosis of response to treatment. In this study, we have investigated a patient with diagnosis of T-ALL having t(12;21) (p12; q22) translocation, which has not been reported except for one case.

Case Presentation

A 9-year-old boy with a pale complexion and weight loss (BMI<20.5 upon admission) for several weeks was referred to Shafa Hospital in Ahwaz. Peripheral blood (PB) sample was taken and bone marrow (BM) aspiration was done for further investigation. Initial ultrasound of patient's abdomen showed normal liver size but a spleen size of 159 mm, which was larger than normal. Complete blood count (CBC) showed leukocytosis and anemia (WBC: 172.3 $\times 10^9$/L, Hemoglobin (Hb): 7.3 g/dL, Red blood cell (RBC): 2.68 $\times 10^{12}$/L) but other hematologic and biochemical tests were normal. Wright-Giemsa staining of BM smear indicated a high count of lymphoblasts (Figure 1). EDTA-anticoagulated BM sample was investigated to determine the involved cell line and specific expression of CD markers. The results indicated the expression of markers such as CD7 (94.0%), CD19 (22.0%), CD33 (20.5%), cCD3 (95.6%), TdT (29.4%), MPO (17.2%), CD38 (99.4%), CD2 (83.8%), CD5 (68%), CD19 (22%), CD34 (37.5%) and cCD79a (15.2%). The BM sample showed t(12:21), and the presence of TEL/AML1 fusion was confirmed by molecular methods and sequencing. After purification RNA and cDNA production, the two steps of nested-polymerase chain reaction (Nested-PCR) were performed and the primer sequences are listed in Table.1. Then, PCR products were electrophoresed on acrylamide gel. Amplification of TEL/AML1 transcript was used as the positive and negative control. PCR product of TEL/AML1 transcript was sequenced using ABI PRISM 3730 DNA Analyzer (Applied Biosystems, Foster City, CA) (Figure 2).

The patient received Vincristine (VCR), L-Asparaginase (L-ASP), Prednisolone and Daunorubicin as induction and was discharged with improved health status. For complete remission he received Prednisolone, 6-Mercaptopurin, Vincristine and Methotrexate.

Discussion

Translocation (12; 21) (p12; q22) is one of the most important genetic lesions occurring in ALL. This fusion is caused by integration of two critical genes involved both in hematopoiesis and leukemogenesis. Cytogenetic and molecular studies such as fluorescent in situ hybridization (FISH) and real-time PCR (RT-PCR) have enabled the detection of this translocation and its subsequent fusion [13,15]. After detection of this translocation by Shurtleff et al., TEL/AML1 fusion was introduced as an ''excellent prognosis'' marker, although 5-year event free survival in patients harboring this fusion was not significantly different from other patients who were negative for it [6]. In general, the presence of this

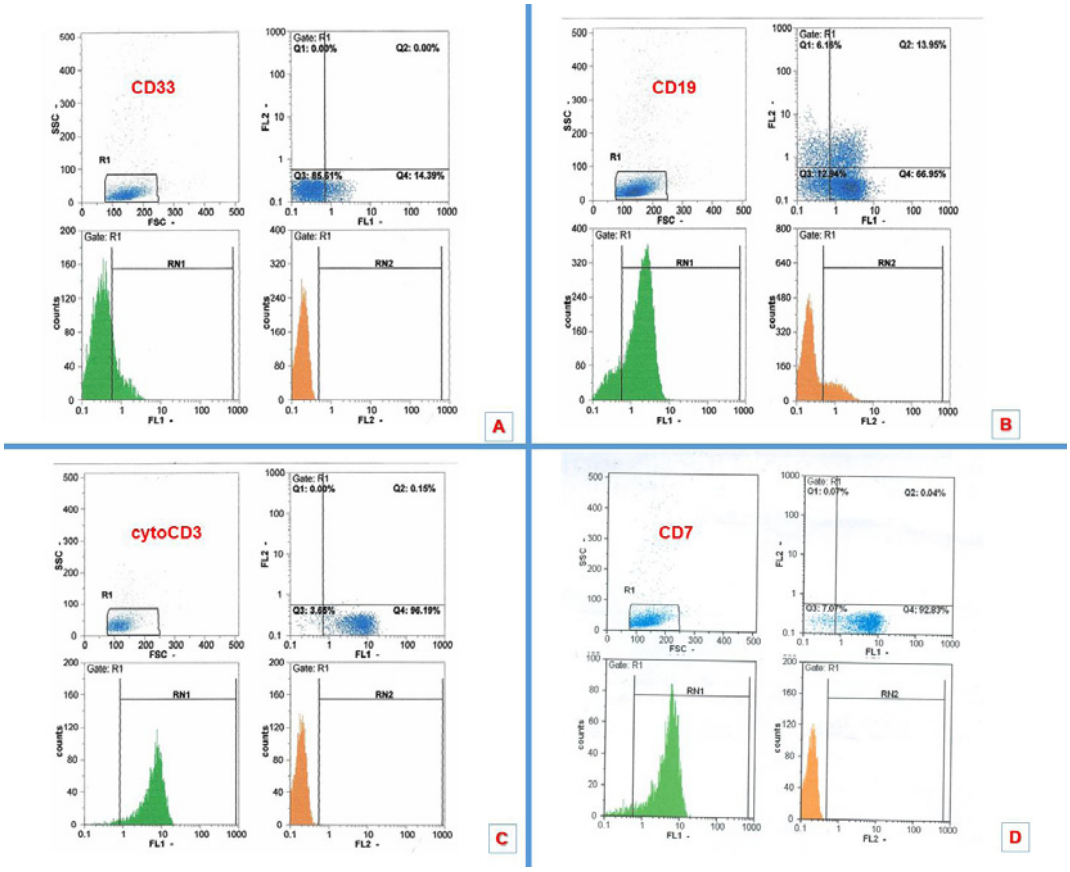

Figure 1: Graph of flowcytometry analysis. Flowcytometry demonstrating aberrant expression of CD33 and CD19 (plot A and B) and positive expression of cytoCD3 and CD7 for confirmation of T-ALL (plot C and D) in this case. **FL**: Fluorochrome.

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translocation places the patients in a separate group with low risk for recurrence and better response to treatment. According to different studies, it is believed that the presence of TEL/AML1 fusion is indicative of B-ALL. In addition, presence of this fusion is associated with lower leukocyte count and lower age (1-10 years), which are considered as favorable prognostic factors [17].

Table 1: Primers for nested PCR analysis of TEL/AML1 fusion gene

Primers	Sequences(5'....3')
F	TGCACCCTCTGATGGTGAAC
R	AACGCCTCGCTCATCAAGC
Nested-F	AAGCCCATCAACCTCTCAGAGG
Nested-R	CGCACCAGGAGAACATGGCT

The product PCR size of TEL/AML1 is 181bp. Abbreviations: **F**: forward, **R**: reverse.

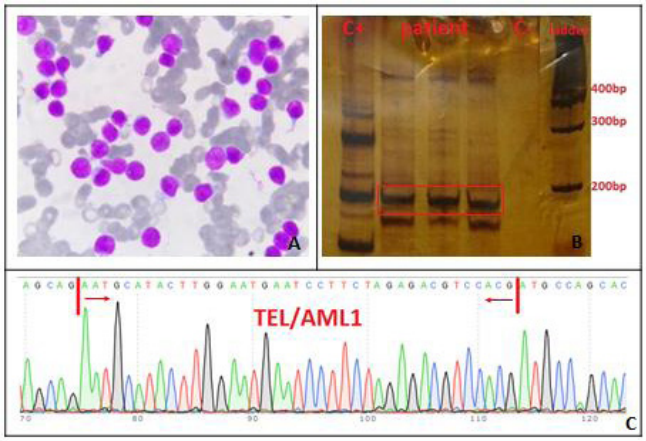

Figure 1: Bone marrow smear, gene expression, immunophenotypic features of T-ALL with t(12:21) fusion.(A) Bone marrow smear from the patient under study, increase in lymphoblasts and absence of rosette form can be seen, (B) Molecular analysis of TEL/AML1 indicates the presence of fusion on acrylamide gel with nearby positive and negative controls (positive fusion of patient's TEL/AML1 is in red box), (C) In this Figure, the TEL/AML1 sequence is observed (between two red lines), which confirms the detection of fusion. **C**: control sample.

Study of immunophenotype is an important biological parameter in patient's survival and prediction of response to treatment. Aberrant phenotype occurs with the development of lymphoid and myeloid markers in myoblasts or lymphoblasts, and has an overall frequency of 80% in both ALL and AML [18]. Specific T-lymphoid markers include CD1a, CD3, CD4, CD5, CD7 and CD8 but B-lymphoid antigens are CD10, CD19, CD22, and cytoplasmic CD79a. MPO, CD13 and CD33 are also common myeloid markers. CD34, HLA-DR, and TdT are used to investigate the precursor cells (Table 2). The world health organization defines Pre-T ALL as a malignancy often occurring in TdT-positive males, which is sometimes associated with the expression of CD10, CD79a and cCD3 markers. Myeloid markers (CD13 and CD33) are "often present" but CD117 is rarely observed [19]. In the study of Suggs et al, the expression of CD13 and CD33 was reported in 24% of pre-T ALL cases, who were male patients aged 13-25 years [20]. The study of Yao et al, dealt with a patient suffering from T-cell lymphoma with aberrant expression of CD79a and CD20. The patient had both B- and T-cell markers and was deceased six months after initial diagnosis due to poor prognosis. This study also showed that the presence of a marker is not specific to a certain disease type and a panel of antibodies should be used for further investigation [21], (Table 2). In the study of Forestier et al., 1140 children aged 1-15 years were diagnosed with B-ALL from 1992 to 2004, from which 288 cases were positive for t(12;21) [8]. However, in the study of MA et al., who simultaneously investigated different ALL types like common, pre-B, early B- and T- for presence of t(12;21), only one case of T-ALL (7.5%) expressed this fusion [11].

In this study, the patient showed t(12;21) despite the presence of T-cell immunophenotype. The favorable prognosis of other ALL types harboring this translocation was also reported in this patient and we observed a good response to treatment in him until under follow up. As a result, the presence of t(12;21) may be observed in various ALL subgroups, which rules out its specificity for B-cells. Aberrant expression of B-cell and myeloid lineage markers in T-ALL complicates

Table 2: Co-expression of markers in previous studies on T-ALL.

Aberrant markers	Age	Gender	Positive markers	Negative markers	Clinical Features	References
B-cell lineage markers	29	M	CD2, CD3, CD27, TCR alpha-beta, CD52, CD38, CD45, CD26, bright CD19	CD4, CD5, CD7, CD8, CD10, CD30 and CD56.	enlarged left cervical lymph node lymphadenopathy pruritus and drenching night sweats bilateral cervical, axillary and bilateral inguinal	(22)
	75	M	CD3, CD19, CD20, and CD79a	CD4, CD8, CD10, CD30, CD34, CD56, CD68, TDT, MPO, PAX-5, and surface immunoglobulin	Enlarged left lymph nodes Without fatigue, dyspnea, fever, or night sweats symptoms Hyper metabolic foci involving the left axilla, bilateral internal jugular areas, mediastinum, right hilum, bilateral lungs, and spleen.	(23)
TEL/AML1:t(12; 21)	-----	-----	TDT, cCD3, CD99 (O13)	CD1a	----------	(11)
This case	9	M	HLA-DP/DQ/DR , MPO, TdT, CD2, CD3, cCD3 CD5, CD7, CD8, CD10, CD19, CD20, cCD22 CD33, CD34, CD38,Cyto CD79a	CD1a, CD4, CD13, IgM, CD3/ HLA-DR	Paleness, weight loss, Splenomegaly	-----

Abbreviation: M: Male, CD: Cluster of Differentiation, TDT: Terminal Deoxynucleotidyl Transferase, MPO: Myeloperoxidase, IgM: Immunoglobulin M, HLA: Human Leukocyte Antigen.

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the diagnosis. Despite the fact that such cases rarely occur, they can significantly complicate leukemia diagnosis and survey of this group of patients requires an antibody panel for immunophenotypic markers.

Highlights

- CD19 and CD33can be expressed in T-ALL.
- Aberrant expression of t (12; 21), the specific B-ALL translocation, can occurinT-ALL.
- Investigation of aberrant gene rearrangement can be useful fordetermining the precise lineage of ambiguous ALL clones.

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Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences and with the 1964 Helsinki declaration.

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