

## Case Report

# TdT Negativity and ETP Phenotype in Young Patients with Acute T- Lymphoid Leukemia: A Case Report

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## Introduction

Acute Lymphoblastic Leukemia (ALL) is a hematopoietic malignancy, which is caused by uncontrolled proliferation of immature B/T lymphoid cells. In the United States of America (USA), the incidence of ALL at all ages is 1.38/100,000 people per year, with an estimated 5930 new cases and 1500 deaths due to ALL [1,2]. ALL is more common in childhood than in adults. It constitutes 75-80 % of childhood acute leukemias [3]. The average age of diagnosis is 15 years old and 55.4% of the patients are under 20 years old [4,5].

According to the immunophenotype classification, ALL originates from B cells (B-ALL) and T cells (T-ALL); 85% and 15% respectively [6,7]. Among ALL, T-ALL is detected in adults at a higher rate compared to childhood, but this rate decreases as the age progresses [8]. The World Health Organization (WHO) defines T-ALL as Terminal Deoxynucleotidyl Transferase (TdT) as well as lymphoblasts where the markers CD1a, CD2, CD3, CD4, CD5, CD7 and CD8 are positive. Cytoplasmic CD3 (cCD3) and CD7 are also often positive. T-ALL can be divided into pro-T, pre-T, cortical T and medullary T according to the stages of intra-thymic differentiation [9,10]. In addition, early T cell precursor (ETP) immunophenotype has been identified according to surface markers (lack of CD1a and CD8 expression, negative or weak CD5 expression, and one or more myeloid or stem cell marker expression) [11]. Although it was reported that TdT is negative in 5-12 % of cases, TdT is usually positive at T-ALL [12-16].

TdT is an intranuclear DNA polymerase that catalyzes the addition of deoxynucleotides to oligonucleotides. TdT is highly expressed in lymphoid precursors where it plays a pivotal role in T-cell receptor and immunoglobulin heavy chain gene rearrangement. Indeed, almost all cortical thymocytes and a small subset of bone marrow B-cells express TdT in their nuclei. TdT is an important marker in distinguishing ALL from reactive conditions or mature lymphoid neoplasms [17].

## Abstract

TdT is generally positive in patients with T-Acute Lymphoblastic Leukemia/Lymphoma (T-ALL/LBL) and can often become negative after chemotherapy. TdT negativity at the time of diagnosis is not a common condition and is evaluated in favor of a poor prognosis. Due to its infrequent occurrence, there are not enough clinical studies, and there are often publications on the basis of case and case series. While its incidence increases in young people and children, the possibility of accompanying Early T Precursor (ETP) phenotype also increases. The presence of the ETP phenotype has negative repercussions on prognosis. Here, we will describe the diagnosis and treatment process of a young adult patient with TdT negative T-ALL accompanied by the ETP phenotype.

Herein, we reported the diagnosis process and the management of a patient who has TdT negative T-ALL with ETP immunophenotype.

## Case Presentation

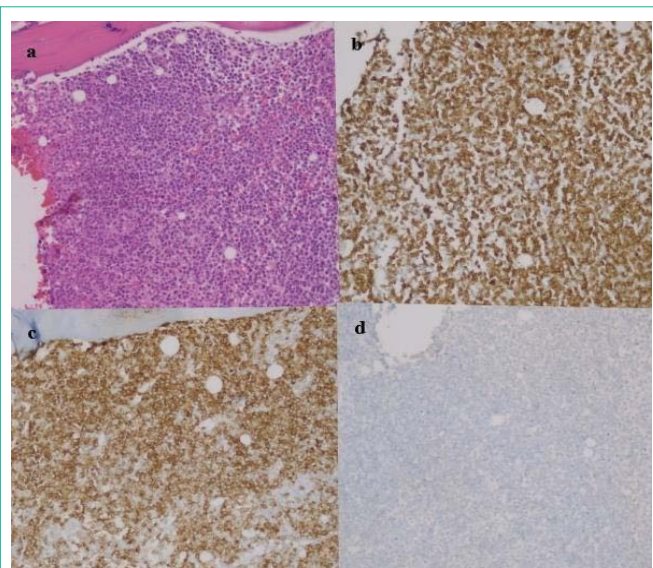
A 20-year-old female patient with no known additional diseases applied to our health facility due to painless swelling behind the right ear. There was no weight loss, fever, or night sweats in the system questionnaire. On her physical examination, bilateral posterior auricular, submandibular, jugular, supraclavicular, left axillary, bilateral inguinal lymphadenopathy and hepatosplenomegaly were detected. In laboratory examination, hemoglobin 12 g/L, leukocyte count  $8.92 \times 10^3/\mu\text{L}$ , neutrophil count  $1.11 \times 10^3/\mu\text{L}$ , lymphocyte count  $6.81 \times 10^3/\mu\text{L}$ , platelet count  $137 \times 10^3/\mu\text{L}$ , erythrocyte sedimentation rate 44 mm/hour, C-Reactive Protein (CRP) 20.26 mg/L (0-5 mg/L), Lactate Dehydrogenase (LDH) 513 U/L (135-225). Her renal function, liver function, and electrolytes were normal on biochemical laboratory evaluation.

On peripheral blood smear 40% blasts were seen and bone marrow aspiration and biopsy were performed. Bone marrow biopsy showed 90% narrow basophilic cytoplasm blast population. Immuno-histochemical examinations revealed extensive and strong positive with CD3 and CD10, mostly positive with CD34 and negative staining with TdT. It is shown in Figure 1.

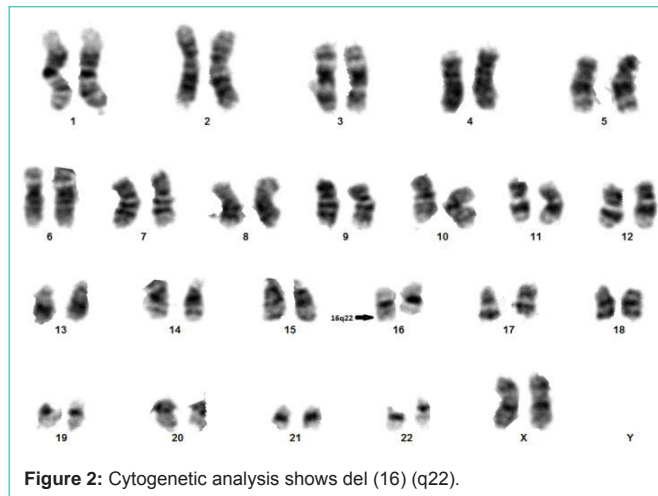
In bone marrow aspiration flow cytometric examination CD1a (-), cTdT (-), CD4 (-), CD8 (-), CD19 (-), MPO (-), CD2 (+), CD3 (+), CD5 (+), CD7 (+), CD10 (+), HLA-DR (+), CD13 (+), CD33 (+) were detected. The patient was diagnosed as TdT negative T-ALL with ETP immunophenotype.

In the cytological examination of Cerebrospinal Fluid (CSF) sampling and in radiodiagnostic intervention there were no findings in favor of primary disease involvement. In karyotype analysis, isolated del (16) (q22) was detected. It is shown in Figure 2.

As an induction regimen, Augmented Hyper-CVAD treatment



**Figure 1:** Histology of bone marrow biopsy. (A) hematoxylin eosin staining, 90% narrow basophilic cytoplasm blast population. (B) and (C) Immunohistochemical examinations revealed extensive and strong positive with CD3 and CD10. (D) Tumour cells were negative for TdT stain.



**Figure 2:** Cytogenetic analysis shows del (16) (q22).

was given. The chemotherapy schedule explained in Table 1.

After the second cycle, she went into remission and no CSF findings were found in favor of central involvement. Allogeneic Stem Cell Transplant (ASCT) was planned and she was a candidate for matched-unrelated donor transplantation. However, the patient died as a result of carbapenem resistant Klebsiella Pneumonia septicemia in the middle of fourth course of Augmented Hyper-CVAD therapy.

### Discussion

TdT expression is a major immunophenotypic marker used to distinguish ALL cases from acute myeloid leukemia (AML). It is also useful in distinguishing B cell lymphoblastic lymphoma (TdT positive) and Burkitt lymphoma (TdT negative). Almost all of ALL cases express TdT [17]. First, in 1999, Faber et al. reported three cases with TdT negative T-ALL [18].

According to the prospective study of UKALL XII / ECOG 2993 in T-ALL; having a leukocyte count >100x10<sup>9</sup> /L, complex karyotype (≥5 chromosomal anomaly), central nervous system involvement

were accepted as risk factors for poor prognosis [8]. In a study by Zhou et al. TdT negativity was accepted as an independent risk factor for poor prognosis in T-ALL patients [16]. ETP-positive ALL was seen in 15% of pediatric cases and was accepted in a very high-risk group [11]. TdT negative cases are more likely to accompany the ETP immunophenotype compared to TdT positive cases [16].

More than 50% of T-ALL patients have NOTCH1 mutation and 10-15 % have FBXW7 mutation. The presence of these mutations is considered among the risk factors for poor prognosis [19-21]. However, isolated del (16) (q22) was detected in the karyotype analysis in our case. Isolated del (16q) in studies and case series; Refractory Anaemia with Excess Blasts (RAEB) has been reported in patients with chronic myelomonocytic leukemia and AML, but its prognostic significance has not been established [22-25].

Among T-ALL, there are many first-line treatment options such as Augmented Berlin-Frankfurt-Munster (BFM), Hyper-CVAD, PEG-asparaginase, Augmented Hyper-CVAD, methotrexate-containing combinations, hyper-CVAD and nelarabine combination [26].

Patients with TdT-negative T-ALL have a higher rate of disease progression and experience shorter overall survival. TdT-negative T-ALL is associated with a higher percentage of ETP-ALL than non-ETP-ALL (42.9% vs 12.0%). Both ETP-ALL and TdT-negative ALL are poor independent prognostic factors and are highly correlated [27].

**Table 1:** Augmented HYPER-CVAD protocol schedule.

Hyper-CVAD (courses 1, 3, 5, and 7) alternated with high-dose methotrexate/ara-C (courses 2, 4, 6, and 8) administered on day 21; Hyper-CVAD = Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone + Pegaspargase.	
Cyclophosphamide	300 mg/m <sup>2</sup> by IV over 3 hours every 12 hours for 6 doses days 1, 2, 3 of
Vincristine	2 mg by IV weekly for 3: Days 1, 8, 15
Doxorubicin	50 mg/m <sup>2</sup> by IV over 24 hours
Dexamethasone	80 mg by IV daily days 1-4 and 15-18
G-CSF	10 mcg/kg/day by IV or subcutaneously within 72 ± 48 hours
Methotrexate	200 mg/ m <sup>2</sup> by IV over 2 hours followed by 800 mg/m <sup>2</sup> over 22 hours on day 1
Ara-C	3 gm/m <sup>2</sup> by IV every 12 hours for 4 doses on days 2 and 3
Pegaspargase	2000 units/m <sup>2</sup> by IV on day 5 of even courses
This regimen includes CNS prophylaxis with systemic therapy(methotrexate and ARA-C)	

Inv (16) causes a fusion transcript by rearrangement of the CBFβ gene located at 16q22 and the MYH11 gene located at 16p13.1. The product of the CBFβ-MYH11 gene fusion blocks embryonic hematopoiesis at the stem-progenitor cell level and impairs neutrophilic differentiation [28]. The E-cadherin gene (E-cad) on chromosome 16q22.1 encodes a protein product important in the maintenance of the epithelial phenotype mediated by a Ca<sup>++</sup>-dependent, homotypic cell-cell adhesion. The gene has been termed a “metastasis suppressor” gene, because the E-cadherin protein can suppress tumor cell invasion and metastasis [29]. There are many studies on the association of 16q22 deletions with myeloid neoplasms and carcinomas [30]. Its relation to lymphoid neoplasms is not clear.

We considered it appropriate to give Augmented Hyper-CVAD protocol because our patient was in the Young Adult and Adolescent (AYA) ALL group and we predicted poor prognosis.

## Conclusion

Our patient also had both TdT negative and ETP immunophenotype. Therefore, we predicted that it would have a poor prognosis. Based on the literature data, we thought that stem cell transplantation was the most appropriate option after the first remission in these patients due to its poor prognosis. Since it is not seen frequently and there are not enough cases in the literature, the available data is limited and more cases are needed. Prognosis may improve with increasing treatment options over time.

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