

Unraveling enigmatic peripheral blood findings in a rare case of gamma-delta T-cell acute lymphoblastic leukemia

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ABSTRACT

Gamma-delta T-cell acute lymphoblastic leukemia ($\gamma\delta$ T-ALL) is an uncommon and aggressive variant of T-cell leukemia characterized by the proliferation of immature T-cells expressing $\gamma\delta$ T-cell receptors. Here, we present a case of a 16-year-old male with $\gamma\delta$ T-ALL exhibiting complex clinical and peripheral blood findings. Histopathological examination of bone marrow further confirmed the leukemic nature of the condition, with a markedly hypercellular marrow infiltrated by abnormal lymphoid cells showing blast morphology. Immunophenotyping of these $\gamma\delta$ -positive cells provided crucial diagnostic insights, including negativity for CD48, strong positivity for CD99, and positivity for TdT in a subset of cells, leading to the diagnosis of $\gamma\delta$ T-ALL. Notably, cytogenetic analysis identified *MLLT4(ADFN)/MLL(KMT2A)* fusion and a TP53 deletion. The diagnostic process highlighted the challenges in differentiating $\gamma\delta$ T-ALL from other T-cell neoplasms and underscored the importance of extended immunophenotyping for accurate diagnosis.

INTRODUCTION

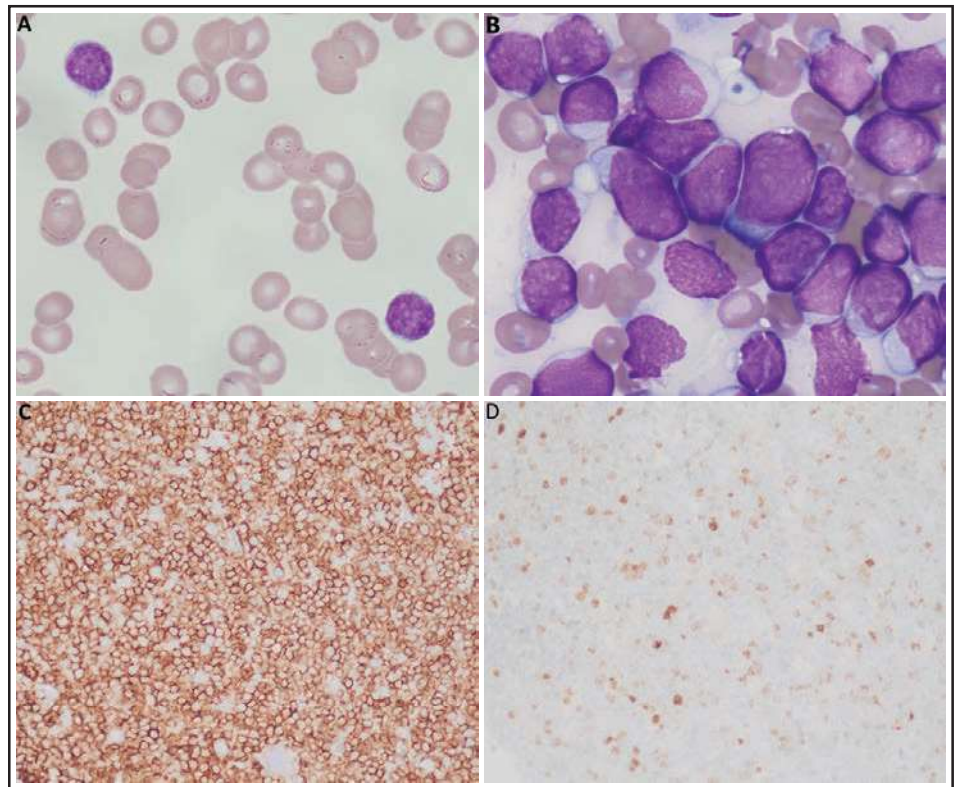
Gamma-delta T-cell acute lymphoblastic leukemia ($\gamma\delta$ T-ALL) represents a distinct variant of lymphoblastic leukemia with unique clinical and biological features.¹ Comprising approximately 10 to 15% of T-ALL cases, $\gamma\delta$ T-ALL is uncommon and associated with a poor prognosis. In a study involving pediatric patients diagnosed with T-ALL, those expressing the $\gamma\delta$ T-cell receptor displayed higher minimal residual disease (MRD) levels during remission induction and experienced lower overall survival rates compared to patients with alpha-beta ($\alpha\beta$) T-ALL.²

CASE REPORT

We report a case of a 16-year-old male who presented with ataxia, fever, fatigue, and evidence of encephalopathy. Physical exam demonstrated no appreciable hepatosplenomegaly, lymphadenopathy, gastrointestinal or skin involvement. Ultrasound revealed mild splenomegaly (18.9 cm in longest dimension). Their past medical history was insignificant with no history of chronic illnesses or previous admission to the hospital.

Their bloodwork showed pancytopenia with a hemoglobin of 83 g/L, thrombocytopenia of $35 \times 10^9/L$, and mild leukocytosis of $12.77 \times 10^9/L$ composed of approximately 90% abnormal lymphoid cells. Evidence of evolving transaminitis and disseminated intravascular coagulation (DIC) was noted, with the latter indicated by abnormalities in coagulation tests and the presence of occasional schistocytes observed by morphologic examination. The abnormal lymphoid population was predominantly comprised of small forms with variably dispersed chromatin and indistinct nucleoli (Figure 1A). Flow cytometric analysis of the peripheral blood revealed a population of neoplastic cells which were: positive for surface (s) and

Figure 1.



(A) Abnormal lymphoid cells in peripheral blood showing small size and relatively condensed chromatin, 100x magnification. (B) Bone marrow aspirate showing evident blast morphology of the cells, 100x magnification. Abnormal T-cells were strongly positive for CD99 (C), and partially positive for TdT (D), 20x magnification. PAX5 was used to confirm that the pattern of distribution of TdT+ cells was different from B-cells (picture not shown).

cytoplasmic (c) CD3, $\gamma\delta$ T-cell receptor CD5, CD7 and CD52; variably positive for CD45; dimly positive for CD8; and negative for CD4, CD2, CD25, CD16, CD56, CD57, $\alpha\beta$ T-cell receptor, CD1a, TdT, CD10, CD117, CD34, and B-cell and myeloid markers.

Bone marrow examination showed a markedly hypercellular marrow, packed with abnormal lymphoid cells that showed variability in size, mainly comprised of small to intermediate forms, and demonstrated blast morphology with dispersed chromatin, some with distinct nucleoli, and scant

amount of a blue-gray agranular cytoplasm. The chromatin of the cells was considerably more delicate than what was observed on the peripheral blood (Figure 1B). Additional flow cytometric analysis of the bone marrow indicated that the neoplastic T-cells were negative for CD48 (determined by testing at a reference laboratory), while approximately 15% of cells tested positive for TdT, as confirmed by immunohistochemistry (IHC) (Figure 1D). The remaining markers displayed expression patterns consistent with those observed in the peripheral blood (Figure 2A-F). Notably, the cells

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The differential diagnosis of a $\gamma\delta$ T-cell neoplasm includes T-ALL, hepatosplenic T-cell lymphoma (HSTCL), T-cell large granular lymphocytic leukemia (T-LGL), and non-hepatosplenic nodal and extra nodal T-cell lymphomas.³ This case presented in a leukemic phase, with an aggressive clinical course and no lymph node, cutaneous, or GI involvement. Rare leukemic cases of HSTCL have been reported,⁴ however, the main sites of involvement are spleen (with significant splenomegaly contrary to this case), liver, and bone marrow. Furthermore, the IHCs

It was difficult to definitively establish the stage of maturation of the abnormal T-cells by morphology and immunophenotype of the cells in the peripheral blood. However, morphology of the cells in the bone marrow was suggestive of blasts rather than mature T-cells. In addition, further immunophenotyping of the cells in the marrow confirmed their immature nature as they were strongly positive for CD99, with a subset of cells positive for TdT, while negative for CD48. CD99 is a nonspecific marker; however, in the

The patient is currently receiving maintenance chemotherapy consisting of oral mercaptopurine and weekly methotrexate, and remains in remission.

setting of a T-cell neoplasm, it is mainly seen in T-lymphoblastic leukemia, anaplastic large cell lymphoma (ALCL), and peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS).^{5,6} Regardless of other markers, ALCL was not a morphological concern in this case; additionally, leukemic presentation in PTCL, NOS is extremely rare, and most of the cases express $\alpha\beta$ T-cell receptor.^{7,8} Reduced expression of CD48 is a marker for immaturity, differentiating mature T-cells from blasts in T-ALL, and is recognized as a useful marker to assess MRD in T-ALL after therapy.⁹⁻¹¹

The diagnosis of $\gamma\delta$ T-ALL was made based on the morphological characteristics of the neoplastic cells observed in the bone marrow and their immunophenotypic profile. Involvement of the central nervous system was confirmed by morphologic examination (CNS3 positive status). Cytogenetic analysis identified *MLLT4(AFDN)/MLL(KMT2A)* fusion and a *TP53* deletion (at17p13) in approximately 85% of nuclei. Additional FISH analysis to evaluate common chromosome abnormalities associated with specific T-cell lymphoma subtypes including the *TCL1A* gene region, chromosome 7, and chromosome 8 was within normal limits. Genetic alterations specific to the $\gamma\delta$ T-cell lineage that result in fusion transcripts, such as *SET-NUP214* and *CALM-AF10*, were not identified. *SET-NUP214* and *CALM-AF10* have been demonstrated to affect clinical outcomes and are implicated in chemotherapy resistance and poor prognosis in T-ALL patients.^{2,12,13}

The patient underwent induction therapy as per Children's Oncology Group (COG) protocol AALL1231.¹⁴ Subsequently, post-induction therapy was as per COG study protocol

AALL0434, including the use of nelarabine.¹⁵ The patient is currently receiving maintenance chemotherapy consisting of oral mercaptopurine and weekly methotrexate, and remains in remission.

CONCLUSION

This report represents a case of a $\gamma\delta$ T-ALL, a rare entity, with challenging morphologic findings in the peripheral blood that required extended immunophenotyping to reach final diagnosis. The clinical and pathologic findings underscore the complexity of diagnosing and managing such cases. Further studies are required to assess the prognostic significance of the identified genetic alterations and their potential therapeutic implications in $\gamma\delta$ T-ALL.

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