Early T-cell precursor acute lymphoblastic leukemia with *KRAS* and *DNMT3A* mutations and unexpected monosomy 7

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ABSTRACT

Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL) is a recently recognized subgroup of T lymphoblastic leukemia/lymphoma thought to be derived from lymphocytes at the ETP differentiation stage that have not irreversibly committed to the T-cell lineage. The definition of ETP-ALL is based on a unique immunophenotype that also expresses at least one myeloid or stem cell marker other than myeloperoxidase and monocytic markers. Correspondingly, ETP-ALLs are often found to express myeloid-associated mutations and have stem cell gene expression profiles. Because its morphology is nonspecific, recognizing the immunophenotype of this uncommon entity is important to separate it from other closely related acute leukemias. We report a case of ETP-ALL with *KRAS* and *DNMT3A* mutations and monosomy of chromosome 7 that did not initially respond to conventional ALL therapy but eventually responded to acute myeloid leukemia-type therapy, underscoring the interesting characteristics of this leukemia. Little information is available regarding monosomy 7 in this entity for the adult population.

KEYWORDS Early precursor; ETP-ALL; *KRAS/DNMT3A*; leukemia; lymphoblastic; mixed phenotype; monosomy 7

Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL) is a recently recognized high-risk T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) subgroup in the World Health Organization classification. ETP-ALL is thought to be derived from thymic lymphocytes at the early T-cell precursor differentiation stage. It is believed that because of their early stage, they have not irreversibly committed to T-cell lineage and thus retain the ability for a certain degree of myeloid/dendritic cell differentiation.¹ As such, ETP-ALL has a somewhat specific immunophenotypic profile that can be elucidated via flow cytometric and immunohistochemical evaluation. Previously thought have to worse outcomes than T-ALL/LBL at later stages of differentiation, this prognostic difference may no longer be significant with current therapeutic modalities.¹

CASE PRESENTATION

A 51-year-old man presented with marked leukocytosis, skin rash, bilateral cervical lymphadenopathy, night sweats,

fevers, and shortness of breath. His complete blood count showed an elevated white blood cell count of 97.4 K/ μ L, anemia with a hemoglobin level of 7.9 g/dL and a hematocrit level of 23.5%, and thrombocytopenia with a platelet count of 53 K/ μ L. There were 75% circulating blasts, 18% lymphocytes, 6% neutrophils, and 1% eosinophils. He received a blood transfusion with packed red blood cells and platelets while awaiting further hematologic workup.

A morphologic review of the peripheral blood and bone marrow aspirate smear showed large blasts with a high nuclear-to-cytoplasmic ratio, an ovoid nucleus with immature chromatin, a single nucleolus, and absent cytoplasmic granules (*Figure 1*). The core biopsy showed sheets of immature cells comprising >95% of the marrow cellularity. Flow cytometric analysis demonstrated cytoplasmic CD3, CD5, CD7 (bright), CD11b (dim), CD13, CD33, CD34, CD38, CD45 (dim), and CD117. The blasts were negative for CD2, surface CD3, CD4, CD8, CD10, CD14, CD15, CD19, CD56, CD64, CD123, human leukocyte antigen–antigen

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Figure 1. (a) Bone marrow aspirate smear showing numerous medium to large-sized blasts (Giemsa-Wright stain). (b) Bone marrow core biopsy with sheets of blasts (hematoxylin and eosin stain). (c) Strong diffuse CD7 immunohistochemistry positivity. (d) Chromosome analysis demonstrated monosomy 7 (arrow) in 20 of 20 metaphases examined.

D related, myeloperoxidase, and terminal deoxynucleotidyl transferase. By immunohistochemistry, they were positive for CD3, CD5, CD7, CD34, and terminal deoxynucleotidyl transferase (variable) and negative for myeloperoxidase, CD4, and CD1a.

ALL and acute myeloid leukemia (AML) fluorescence in situ hybridization (FISH) panels were negative for *PML/RARA*, *CBFB*, *MLL*, *RUNX1T1/RUNX1*, *ETV6/RUNX1*, and *BCR/ABL1* gene rearrangements and negative for trisomies 6 and 21. However, conventional karyotyping identified monosomy 7 in 20 out of 20 metaphases examined. Additionally, AML mutational analysis revealed pathogenic *KRAS* (G12V) and *DNMT3A* (splice site 2173 + 1G > A) mutations by next-generation sequencing; *FLT3* mutation was not detected.

DISCUSSION

The definition of ETP-ALL relies on its early T-cell precursor immunophenotype, which is typically CD1a[−], CD8[−],

CD5[−] (dim), with expression of one or more of the following myeloid or stem cell markers: CD117, CD34, human leukocyte antigen–antigen D related, CD13, CD33, CD11b, or CD65.^{1,2} Importantly, absence of myeloperoxidase or monocytic expression is required to exclude classification as mixed phenotype acute leukemia. Not surprisingly, this entity is often found to overexpress genes associated with myeloid or stem cell profiles. Its mutational profile is also closer to myeloid leukemias than to other T-cell leukemias, with increased frequency of *FLT3*, *RAS* gene family, *DNMT3A*, *IDH1*, and *IDH2* mutations.¹ In keeping with this, our case demonstrated both *KRAS* and *DNMT3A* mutations. An unexpected finding was the presence of monosomy 7, an abnormality commonly seen in myeloid neoplasms and a subset of pediatric ALLs where they are associated with worse outcomes.³ However, there is limited literature information on monosomy 7 specifically in regards to ETP-ALL in adults.⁴ Altogether, ETP-ALL is uncommon and has been reported in 11% to 12% of childhood T-ALL/LBL and 7.4% of adult T-ALL/LBL.⁵

Though ETP-ALL was thought to have a particularly poor prognosis, recent studies with more effective therapy have shown less significant differences in outcomes. Nevertheless, it is noted that minimal residual disease rates in ETP-ALL are higher than those seen in other T-ALL cases.¹ Our patient had virtually no response to hyper-CVAD (cyclophosphamide, vincristine, Adriamycin, dexamethasone) therapy. He was subsequently switched to a clofarabine/cytarabine regimen more commonly used in acute myeloid leukemia, and repeat biopsy demonstrated <5% marrow cellularity with marked chemotherapeutic effect. However, some residual blasts were present with persistence of monosomy 7 in 11% of cells by FISH studies. A follow-up biopsy 1 week later showed marrow recovery with trilineage hematopoiesis, 6.5% myeloblasts (CD34⁺, myeloperoxidase⁺, CD3⁻), and negative monosomy 7 FISH studies. With absence of monosomy 7, it was hoped that these blasts represented regenerative myeloblasts, though the possibility of residual leukemic blasts with antigenic shift toward AML phenotype could not be completely excluded given the potential for myeloid differentiation in ETP-ALL cells. The patient eventually underwent bone marrow trans-

plant with no evidence of recurrence. Because there is limited literature information regarding monosomy 7 in regards to this entity in adults, its significance in our case is not entirely clear.

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