Molecular Features of Three Children Diagnosed With Early T-Cell Precursor Acute Lymphoblastic Leukemia

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Dear Editor,

We describe the diagnostic characteristics of three pediatric patients with early T-cell precursor (ETP)-ALL. All three patients had hyperleukocytosis with a white blood cell (WBC) count of more than 100.0×10⁹/L, showed immunophenotypic findings consistent with ETP-ALL, and were positive for FLT3 mutations. The clinical and laboratory findings, including immunophenotyping results (Fig. 1), T-cell receptor (TCR) rearrangements, Fms-related tyrosine kinase 3 (FLT3) mutations, and karyotype results, for the three patients are summarized in Table 1. The aim of this report is to provide information on ETP-ALL and reveal the immunophenotypic and molecular characteristics of ETP-ALL in pediatric patients.

A 14-yr-old boy presented with dizziness, vomiting, and otalgia lasting for several weeks. Laboratory tests showed WBC count of 402.2×10⁹/L, Hb of 8.4 g/dL, and platelet count of 78×10⁹/L. A peripheral blood (PB) smear revealed a very high number of blasts (94% of nucleated elements). Bone marrow (BM) aspirates revealed 100% cellularity with 97% blasts. He received induction chemotherapy (vincristine, l-asparaginase, daunorubicin, dexamethasone, and intrathecal methotrexate) and achieved complete remission (CR).

A 12-yr-old boy presented with left tibia pain for 14 days. Laboratory tests revealed WBC count of 130.1×10⁹/L, Hb of 7.4 g/dL, and platelet count of 33×10⁹/L. A PB smear revealed that 75% of nucleated elements were leukemic blasts. BM aspirates revealed 100% cellularity with 99% blasts. After ALL induction chemotherapy, he achieved CR and received consolidation chemotherapy.

A 12-yr-old boy presented with fever, cough, and petechiae of both tibiae for several weeks. Laboratory tests revealed WBC count of 169.5×10⁹/L, Hb of 8.7 g/dL, and platelet count of 194×10⁹/L. A PB smear revealed a markedly high number of blasts (89% of nucleated elements). He achieved CR after ALL induction chemotherapy.

ETP-ALL is a T-ALL subtype with a very high risk of remission induction failure, relapse, and overall poor prognosis; it is characterized by a specific immunophenotype, i.e., CD1a(-), CD8(-), CD5 weak, with one or more stem cell or myeloid-associated markers [1, 2]. Our three patients showed very similar immunophenotypic patterns, with common expression of cCD3, T-cell markers (e.g., CD2 and CD7), and stem cell or myeloid/stem cell markers (e.g., CD34 and CD117) (Table 1). The myeloid marker CD13 was expressed in two patients and the myeloid/monocytic marker CD64 was expressed in one patient. Although weak or negative CD5 was initially a part of the diagnostic criteria for ETP-ALL [1], the optimal aggregate of immunophenotypic markers for ETP leukemic cell identification is unknown. In a re-

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cent study, for example, CD4 and CD8 double negativity, in addition to CD34 or CD13/CD33 expression predicted 10 out of 13 cases with an ETP-ALL gene signature [3].

T-ALL shows a very high incidence of clonal rearrangements of TCR genes [4]. In our case series of ETP-ALL patients, TCR rearrangement was found in one (TCRγ) of the three patients, in contrast to a previous study that found TCR rearrangements in eight of nine ETP-ALL patients [1]. The development of the pro-T-cell, including the ETP stage, may be independent of TCR rearrangement because it is involved in the initial phase of T-cell differentiation, which is coordinated by the migration of distinct thymic microenvironments [5]. CD4 and CD8 double negative
(DN) thymocytes can be classified into four developmental stages (DN1, 2, 3, and 4) on the basis of CD44 and CD25 expressions [6]. TCR rearrangement starts at DN2 with the TCRβ locus, followed by TCRγ and TCRδ, and rearrangement is completed during DN3 [7].

FLT3 mutations, such as internal tandem duplications (ITDs), are the most common somatic alterations in AML and predict a poor prognosis [8]. FLT3 mutations were detected in all three patients, consistent with a previous study that reported a high frequency (35%) of FLT3 mutations in ETP-ALL and found that FLT3 mutations are less strongly associated with TCR rearrangements than wild-type FLT3 in ETP-ALL [9]. The coexistence of FLT3 mutations and CD117/KIT expression in our patients was consistent with previous results that T-ALL patients with CD117/KIT expression tend to harbor FLT3 mutations [10].

Although the three patients responded well to remission induction chemotherapy and have maintained CR (Table 1), we emphasize the need for close follow-up because ETP-ALL has a high risk of relapse, especially in children [2]. ETP-ALL has recently been recognized as a distinct entity within ALL; accordingly, literature on the diagnosis and treatment of ETP-ALL is limited. The morphological, immunophenotypic, and molecular characterization of three pediatric ETP-ALL patients in this study may aid in the diagnosis of this rare, but important subtype of acute leukemia.

**Authors’ Disclosures of Potential Conflicts of Interest**

No potential conflicts of interest relevant to this article were reported.

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