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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 100.0×10^9/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 402.2×10^9/L, Hb of 8.4 g/dL, and platelet count of 78×10^9/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 130.1×10^9/L, Hb of 7.4 g/dL, and platelet count of 33×10^9/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 169.5×10^9/L, Hb of 8.7 g/dL, and platelet count of 194×10^9/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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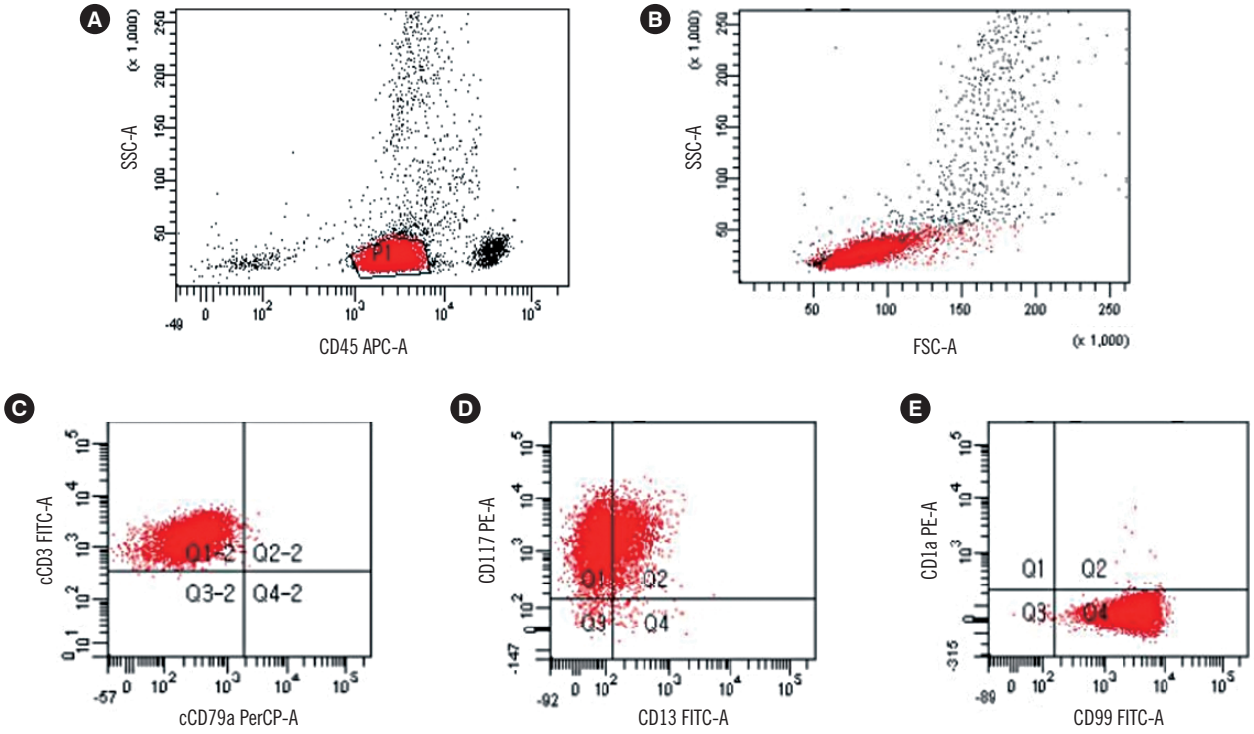

Fig. 1. Immunophenotyping of early T-cell precursor-ALL bone marrow sample (case 3). (A) CD45/SSC dot plot with the blast population highlighted. (B) FSC/SSC plot of the sample. Blasts are positive for cCD3 (C); CD13, CD117 (D); CD99 (E) and negative for CD1a (E). Please refer to Table 1 for the immunophenptyping results of cases 1 and 2.

Table 1. Clinical and laboratory characteristics of the three patients with early T-cell precursor (ETP)-ALL at initial presentation

No. case	Sex/Age (yr)	Mediastinal mass	WBC count ($\times 10^9$/L)	Immunophenotyping Positivity/Negativity	TCR rearrangement			FLT3 mutation	Karyotype	Treatment/ Relapse-free survival
					TCRβ	TCRγ	TCRδ			
1	M/14	No	402.2	CD2, cCD3, CD7, CD13, CD34, CD99, CD117, and HLA-DR/CD1a, CD5, and CD8	No	No	No	ITD mutation	47,XY,+4[5]/46,XY[15]	Chemotherapy: CR/6 months
2	M/12	No	130.1	CD2, cCD3, CD7,CD34, CD64, CD99, CD117, and HLA-DR/CD1a, CD5, and CD8	No	No	No	ITD mutation	45,XY,del(6)(q21q23), -21[3]/46,XY[9]	Chemotherapy: CR/8 months
3	M/12	No	169.5	CD2, cCD3,CD7, CD13,CD34, CD99, and CD117/CD1a, CD5, and CD8	No	Yes	No	TKD mutation	46,XY[20]	Chemotherapy: CR/8 months

Abbreviations: WBC, white blood cell; TCR, T cell receptor, ITD, internal tandem duplication; TKD, tyrosine kinase domain; CR, complete remission.

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 *TCRδ* locus, followed by *TCRγ* and *TCRβ*, 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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