Letters to the Editor

Relevant in determining the poor outcome observed in patients with trisomy 11.

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References


Acute Lymphoblastic Leukemia

γδ and ζ T-cell acute lymphoblastic leukemia: comparison of their clinical and immunophenotypic features

γδ-T-cell acute lymphoblastic leukemia (ALL) is a rare variant of ALL. The comparison of some clinical and laboratory features in children and adults with γδ-T-ALL or ζγ-ALL showed that in γδ-T-ALL the CD45RA--/CD45RO+ phenotype was predominant, the hemoglobin concentration was lower in children and the presence of splenomegaly and the white cell counts was higher in adults.
T-cell acute lymphoblastic leukemia (T-ALL) expresses the $\gamma\delta$- or $\alpha\beta$- T-cell receptor (TCR) in less than 35% of the T-ALL revealed that only the hemoglobin-based T-cell receptor (TCR) complex provides valuable biological, clinical and prognostic information. Based on morphological, cytochemical and immunophenotypic criteria, we diagnosed 202 cases of T-ALL (from 961 ALL cases), and compared some clinical and laboratory features of 19 cases of $\gamma\delta$-T-ALL (9 children, 10 adults) with those of 22 selected cases of $\alpha\beta$-T-ALL (11 children and 11 adults). Bone marrow malignant cells were studied by flow cytometry with the panel of monoclonal antibodies listed in Table 2. Results were considered positive if 20% or more of the cells expressed a particular antigen.

The overall incidence of T-ALL in Brazil is 12.5 cases/10^5 people-years: 25.5 cases/10^5 for children and 6.2 cases/10^5 for adults. T-ALL represents about 20% of all ALL cases (21% in this series), and about 35% of the T-lineage ALL have the TCR complex on membrane$^1$ (20% in this series), whereas only 2% of all ALL cases express the $\gamma\delta$ TCR (2% in this series). Among our 202 T-ALL cases, we found 19 $\gamma\delta$-T-ALL (9%), a proportion similar to those in the series presented by Macintyre et al.$^2$ (9%) and Schott et al.$^3$ (12%). These proportions are high compared to the low percentage (about 1%) of $\gamma\delta$ T cells in the normal thymus.$^4$ This finding remains unexplained, raising the possibility that some $\gamma\delta$ leukemic T-cells derive from extrathymic pathways of T-cell differentiation or, alternatively, that these cells have an increased potential for malignant transformation.$^4$

Comparison of the clinical and laboratory data from the $\gamma\delta$- and $\alpha\beta$-T-ALL revealed that only the hemoglobin concentration was lower in children with $\gamma\delta$-T-ALL, as previously shown by Schott et al.$^3$; whereas in adults, both the presence of splenomegaly and the white cell counts were higher in $\gamma\delta$-T-ALL (Table 1). Together, these findings suggest an increased tumor burden in $\gamma\delta$ T-ALL.

The immunophenotypic profile was similar in $\gamma\delta$- and $\alpha\beta$-T-ALL for children and adults (Table 2), except for the expression of the CD45 isoforms. The CD45RA/CD45RO$^+$ phenotype was the most common in $\gamma\delta$-T-ALL.

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**Table 1. Clinical and laboratory characteristics of the children and adult subgroups with $\alpha\beta$- and $\gamma\delta$-T-ALL.**

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Children (n=20)</th>
<th>Adults (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha\beta$-T-ALL (n=11)</td>
<td>$\gamma\delta$-T-ALL (n=9)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/9</td>
<td>7/2</td>
</tr>
<tr>
<td>Medialmass</td>
<td>8/11 (73%)</td>
<td>3/9 (33%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8/11 (73%)</td>
<td>7/9 (80%)</td>
</tr>
<tr>
<td>WBC, 10$^9$/L</td>
<td>114.0 (85.9-200.0)</td>
<td>150.0 (70.9-384.0)</td>
</tr>
<tr>
<td>Blasts in BM (%)*</td>
<td>78.5 (58.9-98.0)</td>
<td>93 (70.9-98.0)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>11.0 (7.0-13.0)</td>
<td>7.9 (6.6-11.1)</td>
</tr>
<tr>
<td>Platelets x10$^9$/L</td>
<td>94.0 (30.2-299.0)</td>
<td>71.5 (24.0-95.0)</td>
</tr>
<tr>
<td>Overall survival (5 years)</td>
<td>11/11 (100%)</td>
<td>5/9 (60%)</td>
</tr>
</tbody>
</table>

*p values represent median (range). B.M.: bone marrow.* n = 15 for $\alpha\beta$-T-ALL and n = 10 for $\gamma\delta$-T-ALL. Individuals with 14 years-old or less were considered to be children.

**Table 2. Immunophenotypic features of TCR positive cases.**

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Children (n=20)</th>
<th>Adults (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha\beta$-T-ALL (n=11)</td>
<td>$\gamma\delta$-T-ALL (n=9)</td>
</tr>
<tr>
<td>CD2</td>
<td>7/11 (64%)</td>
<td>8/9 (90%)</td>
</tr>
<tr>
<td>CD3*</td>
<td>11/11 (100%)</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>CD5</td>
<td>11/11 (100%)</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>CD7</td>
<td>11/11 (100%)</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>CD1</td>
<td>4/11 (36%)</td>
<td>6/9 (67%)</td>
</tr>
<tr>
<td>CD2+CD3*</td>
<td>1/11 (9%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>CD4+CD8*</td>
<td>1/11 (9%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>CD4+CD8*</td>
<td>5/11 (45%)</td>
<td>4/9 (44%)</td>
</tr>
<tr>
<td>CD4+CD8*</td>
<td>4/11 (36%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>CD56</td>
<td>7/10 (70%)</td>
<td>8/9 (90%)</td>
</tr>
<tr>
<td>CD34</td>
<td>4/11 (36%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>CD45</td>
<td>9/9 (100%)</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>CD45RA/CD45RO*</td>
<td>5/11 (45%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>CD45RA/CD45RO*</td>
<td>2/11 (18%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>CD45RA/CD45RO*</td>
<td>3/11 (27%)</td>
<td>1/5 (20%)</td>
</tr>
<tr>
<td>CD45RA/CD45RO*</td>
<td>1/11 (9%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>CD10</td>
<td>9/11 (82%)</td>
<td>5/9 (56%)</td>
</tr>
</tbody>
</table>

Notes: Antigens (clone): CD1a (SK9), CD2 (55.2), CD3 (SK7), CD4 (SK3), CD5 (L17F12), CD7 (4H9), CD8 (SK1), CD10 (W8E7), CD34 (BG12), CD45 (2D1), CD45RA (L4B), CD45RO (UCHL1), TCR $\alpha\beta$ (WT31), TCR $\gamma\delta$ (11F2) and anti-TdT (HT-6). NA: not applicable. *cCD3 and/or mCD3.
in both children and adults, whereas the CD45RA/CD45RO phenotype predominated in γδ T-ALL. There is a scarcity of data about the CD45 isoforms in γδ and γδ T-ALL, and the only two studies describing the predominance of the CD45RO isoform in T-ALL did not evaluate the γδ or γδ TCR status of leukemic cells. Since most normal thymocytes express the CD45RA/CD45RO phenotype, the finding that CD45RA/CD45RO was the most common phenotype in γδ, T-ALL was unexpected. Although CD45RA and CD45RO expression discriminates as naive and memory subsets of T-cells, respectively, this differentiation holds best for peripheral blood T cells. In the thymus, where the normal counterparts of T-ALL are found, the expression of these CD45 isoforms is associated with functions related to thymic maturation. Clinically, the CD45 isoform status had no prognostic value when overall survival of patients whose blasts expressed the CD45RA or CD45RO antigens were compared (data not shown).

The expression of membrane CD3 (mCD3), expected to be always detected in TCR T-ALL, was negative in two cases of γδ T-ALL, whereas cytoplasmic CD3 was present in all cases. Asnafi et al. recently described some T-ALL cases with negativity for mCD3, but with cytoplasmic expression of the TCRβ antigen, which they called pre-TCR T-ALL. We have no explanation for these TCRβ+/mCD3−/mCD3+ cases observed in our series. Although normal γδ T-cells represent a very small proportion of normal thymocytes, this subset is enriched among CD4 and CD8 double-negative T cells. Malignant γδ T-cells, however, expressed CD4 and CD8 or both of them in 74% of the cases. Similar results have been previously described, contradicting the intuitive acceptance that the γδ T-ALL blasts should not express CD4 and CD8, as their normal counterparts. Van Dongen et al. described a small subset of normal γδ T-cells in the peripheral blood which was either CD4 or CD8 positive, in addition to the vast majority of double negative cells. Therefore, perhaps this small subset of normal CD4 or CD8 γδ T-cells is particularly prone to malignant transformation. Alternatively, the expression of CD4 or CD8 antigens in γδ T-cells may represent a phenomenon related to the neoplastic transformation. In total, these data give support to the concept that γδ T-ALL represents a distinctive subtype of leukemia, with peculiar clinical, laboratory, and immunophenotypic characteristics.

References


Chronic Lymphoproliferative Disorders

Absence of surface CD27 distinguishes hairy cell leukemia from other leukemic B-cell malignancies

Surface expression of CD27 was evaluated in 75 mature leukemic B-cell neoplasms. All cases other than hairy cell leukemia (HCL) expressed CD27. Intensity was significantly higher in chronic lymphocytic leukemia. Lack of CD27 in 17/17 HCL contrasted with expression of this marker in 5/5 plasmacytomas/myelomas. Lack of CD27 is a new distinctive feature of HCL among B-cell malignancies.

CD27 is a member of the tumor necrosis factor (TNF)-receptor family induced on B lymphocytes after antigen challenge and interacts with CD70 to differentiate mature B cells into plasma cells. CD27 was originally defined as a memory B-cell marker, mainly because of its expression on B-cells with mutated VH-genes. However, CD27 is induced in centroblasts and centrocytes of the germinal center (GC) and retained by post-GC memory B cells. CD27 is generally conserved after neoplastic transformation on mature B-cell neoplasms, but, differently from the normal situation, is independent of VH-gene status. In chronic lymphocytic leukemia (B-CLL), CD27 is also present as a soluble molecule correlating with tumor load. Immunohistochemistry has confirmed expression of CD27 in mantle cell lymphoma (MCL), Burkitt’s lymphoma, marginal zone lymphoma (MZL) and plasmacytomas/myelomas.