and vice versa. In fact minor TCCs were identified in cases with normal TCP. Thus, normal CD3+ CD4+ (or CD8+) subsets may harbor a clonal cell population just like the more atypical CD3− CD4− or CD3+ CD4− CD8− lymphocytes can do. Whether this reflects oligoclonality of CD3− CD8− (or CD4+) cells, as sometimes reported in elderly healthy controls, or is the very early phase of an eosinophilia-associated T-cell disorder has yet to be determined. Further monitoring of these patients is indicated. In the single case with expanded, Vβ-unreactive CD3+ cells, Southern blotting or PCR may be required to rule out clonality and eventually confirm a concurrent CD3− NK cell increase (about 40%, data not shown).

The diagnostic technique described by Langerak et al. appears sufficiently sensitive for an accurate assessment of individual amounts of circulating TCC in patients with hyper-eosinophilic disorders. Although the formal proof of a clonal T-cell disease rests on molecular biology techniques and about 30% of known Vβ rearrangements are not covered by this method, flow cytometric analysis allows fast screening and could be useful, in patients with associated TCC, in the monitoring of treatment response and disease progression.

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Key words: immunophenotype, T-cell receptor rearrangements, hyper-eosinophilic syndrome.

References

Chronic Myeloproliferative Disorders

A further case of myeloproliferative syndrome with reciprocal translocation (8;13)(p11;q12)

The 8p11 myeloproliferative syndrome is an aggressive stem cell disorder characterized by eosinophilia, lymphadenopathy and rapid progression to acute leukemia, caused by FGFR1 fusion proteins resulting from translocations at chromosome band 8p11. We report a new case initially responsive to aggressive chemotherapy, who progressed to acute leukemia despite allogeneic stem cell transplantation.

Several subtypes of eosinophilic leukemia have been recently identified. These rare disorders are associated with specific cytogenetic and molecular genetic abnormalities. A chronic eosinophilic leukemia which often evolves into T-lymphoblastic lymphoma or acute myeloid leukemia (AML) is characterized by translocations with a chromosome 8p11-12 breakpoint and is, therefore, known as 8p11 myeloproliferative syndrome (EMS). This disorder is extremely aggressive: only allogeneic stem cell transplantation seems effective in eradicating the neoplastic clone. We report a patient with EMS who initially responded to aggressive chemotherapy, but soon evolved to AML despite allogeneic peripheral blood stem cell transplantation.
A 40-year-old man presented in May, 2002, with asthenia, night sweats and weight loss. On physical examination he had diffuse adenopathy and conspicuous hepatosplenomegaly. CT scan showed hepatomegaly, splenomegaly and extensive retroperitoneal, iliac and femoral adenopathy. No mediastinal mass was observed. A complete blood count revealed mild thrombocytopenia (87×10^9/L) and leukocytosis (381×10^9/L) with a differential count of 60% neutrophils, 12% eosinophils, 11% lymphocytes, 8% monocytes, 4% metamyelocytes and 5% myelocytes (Figure 1). Bone marrow aspirate was hypercellular with erythroid hypoplasia and myeloid hyperplasia with increased eosinophils and precursors. Eosinophils were morphologically normal. There were also 20% agranular blasts showing a high nucleocytoplasmic ratio, rather condensed chromat and irregular nuclear shape (Figure 1). Aspiration cytology and biopsy of a cervical lymph node showed mature lymphocytes, many blasts similar to bone marrow blasts and scattered eosinophils and precursors (Figure 1). Thus, whereas the peripheral blood picture was consistent with the diagnosis of a chronic myeloproliferative disorder with eosinophilia, the bone marrow and lymph node features rather suggested an acute disorder; on the other hand, a diagnosis of blast crisis of chronic myeloid leukemia at onset could not be ruled out. Immunophenotype of bone marrow and lymph node blasts was: CD1a, CD2, CD3, CD45, CD99 and TdT positive, CD7, CD10, CD14, CD20, CD68, CD79a, MPO and lysozyme negative. Therefore, a diagnosis of precursor T-lymphoblastic leukemia/lymphoma was made. The cytogenetic analysis of peripheral blood and bone marrow showed a reciprocal balanced translocation (8;13)(p11;q12), whereas BCR-ABL rearrangement was not detected by polymerase chain reaction. On the basis of these findings EMS was diagnosed. The patient was treated with aggressive chemotherapy according to an AML treatment protocol and achieved a complete remission. Soon after, he underwent allogeneic peripheral blood stem cell transplantation from an identical sibling. In June, 2003, he relapsed as AML.

EMS is a distinct biphenotypic hematologic disorder arising from a pluripotent stem cell able to differentiate into B and T lymphoid lineages as well as myeloid lineages, therefore termed also stem cell leukemia/lymphoma syndrome and stem cell myeloproliferative disorder. It is characterized by the association of lymphoblastic lymphoma usually of the T lineage, but, rarely, also of the B lineage, a myeloproliferative disorder with eosinophilia and a chromosomal translocation with an 8p11-12 breakpoint. So far, some thirty cases have been reported with a median age of 32 years at presentation and a slight male predominance. Characteristic clinical features include systemic symptoms, diffuse lymphadenopathies at diagnosis, as in our case, or appearing during the course of the disease, in the absence of a mediastinal mass, frequent splenomegaly, and leukocytosis with neutrophilia, eosinophilia, monocytosis and circulating myelocytes and metamyelocytes. Survival is usually short, because the disorder evolves into AML or, rarely, to acute lymphoblastic leukemia within 1 or 2 years of diagnosis. Since chemotherapy alone cannot eradicate the neoplastic clone, only allogeneic stem cell transplantation appears to offer a chance of cure. Of 8 reported cases who underwent allogeneic stem cell transplantation, 5 survived in complete remission.

Recently, the molecular abnormalities caused by t(8;13) and by variant translocations have been identified. The most common translocation in EMS is t(8;13), which results in the fusion of the N-terminal half of zinc-finger 198 (ZNF198) at 13q11-12 to the entire catalytic domain of fibroblast growth factor receptor 1 (FGFR1) at 8p11-12. The FGFR1 gene is constantly disrupted also in the variant translocations observed in rare cases of EMS: t(8;9) (p11; q33), t(6;8)(q27;p11) and t(8;22)(p11q22) which form the fusion genes CEP110–FGFR1, FOP–FGFR1 and BCR–FGFR1, respectively. The products of the fusion genes show constitutive tyrosine kinase activity and activate multiple pathways of signal transduction, which cause apoptotic and proliferative defects and may play an essential role in the pathogenesis of the disorder. Therefore, the identification of specific inhibitory drugs of the constitutive tyrosine kinase activity or of the critical signaling pathways would be very important for the treatment of EMS patients. The disappointing results of conventional therapy urge the need for this novel approach.

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Chronic Myeloid Leukemias

c-myc expression in cell lines derived from chronic myeloid leukemia

We analyzed proliferation and c-myc expression in three chronic myeloid leukemia (CML)-derived cell lines treated with interferon-α, hydroxyurea, busulfan and imatinib. We found that c-Myc levels did not universally correlate with CML cell proliferation and that c-Myc down-regulation correlated to imatinib activity but not to imatinib-induced apoptosis.

Key words: myeloproliferative syndrome, eosinophilia, lymphoblastic lymphoma, 8p11

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References


Table 1. Effects of interferon-α, hydroxyurea, busulfan and imatinib on c-myc expression and cell proliferation of CML-derived cells.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>c-myc</th>
<th>Hydroxyurea</th>
<th>Busulfan</th>
<th>Imatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>KU812</td>
<td>Growth arrest</td>
<td>+ reversible</td>
<td>++ reversible</td>
<td>++ irreversible</td>
</tr>
<tr>
<td>MEG01</td>
<td>Growth arrest</td>
<td>+ reversible</td>
<td>++ irreversible</td>
<td>++ irreversible</td>
</tr>
<tr>
<td>KS62</td>
<td>Growth arrest</td>
<td>+ reversible</td>
<td>++ irreversible</td>
<td>++ irreversible</td>
</tr>
</tbody>
</table>

** denotes a faster or more profound inhibition of cell growth than +, as assessed by thymidine incorporation and cell counting. The data are summarized from three independent experiments in each case. ↓ denotes c-myc down-regulation, as assessed by Northern blot analysis. "Reversible" refers to the recovery of c-myc mRNA levels after removal of the corresponding drug by cell washing. NT: not tested.