Rapid Response to Cyclosporine Therapy and Sustained Remission in Large Granular Lymphocyte Leukemia

To the Editor:

Considering the recent interest in large granular lymphocyte (LGL) proliferation and the frequent association of severe granulopenia ("T-γ neutropenia") with T-LGL leukemia leading to intractable and often fatal infections, we wish to describe a case of T-LGL leukemia with absolute agranulocytosis which showed an excellent, rapid, and sustained response to nontoxic doses of cyclosporine after failing steroid and growth-factor therapy.

CASE REPORT

A 36-year-old woman was admitted to Cedars-Sinai Medical Center in Los Angeles in December 1993 because of agranulocytosis associated with intractable fever and resistant staphylococcus septicaemia not responding to polyantimicrobial therapy. Nine months before admission, she developed a severe upper respiratory infection associated with myalgia, arthralgia, weakness, fatigue, and other systemic symptoms. Repeated blood counts were within normal range (white blood cell [WBC] count 6.5 to 7.7 X 10^9/L) with slight lymphocytosis. The absolute neutrophil count (ANC) was between 2.9 and 3.6 X 10^9/L. There was no evidence of rheumatoid arthritis or other collagen diseases. Five months before admission, she developed shaking chills, 104°F fever, and pneumonia that required prolonged antibiotic therapy. Anemia and absolute neutropenia (ANC decreasing from 1.9 to 0.8 X 10^9/L) was observed, and she was treated with ferrous sulfate and prednisone without hematologic response. From this point on, the patient experienced increasingly frequent episodes of respiratory infections, sepsis, aseptic meningitis, abscesses, and other infectious problems.

One month before admission, the patient was again hospitalized at a community hospital with fever, chills, pneumonia associated with chest-wall pain, generalized muscle aches, and joint pain diagnosed as fibromyalgia. Blood counts showed the ANC persistently below 500; the bone marrow showed markedly reduced granulocyte precursors. Treatment with high-dose prednisone, granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, and antibiotics had no effect. She became febrile, all antibiotics were withdrawn, and within 13 days, she showed full clinical and hematologic recovery (Table 1). Large granular lymphocytes disappeared from the blood, the WBC increased to 14,900, the ANC rose to 11,324 with the differential count showing 20% polys, 26% bands, 24% myelocytes, and 6% metamyelocytes. The platelet count increased to 982,000; the hemoglobin rose to 10.6 g, and the hematocrit to 34.2%. The cyclosporine blood level initially reached a maximum of 860 ng/L, which was quickly reduced to 500 to 600 ng/L and stabilized at 200 to 250 ng/L.

Subsequently, the WBC count settled at 4,800 with ANC between 2.9 and 3.5 X 10^9/L. LGL was reported between 0% and 5%; a mild anemia persisted. She was discharged on 100 to 200 mg cyclosporine/d maintaining a blood level between 10 to 70 ng/L, resulting in a sustained WBC count between 5.0 to 6.2 and ANC of 2.1 to 4.1 X 10^9/L and normal hemoglobin, hematocrit, and platelet counts (Table 1). She continued to show mild lymphocytosis with only 0% to 1% LGL on blood smears; however, immunophenotyping continued to demonstrate the persistence of a T-LGL type pattern (Table 1).

Except for a brief episode of febrile infection responding to antibiotic therapy 2 months later, she had no further infectious or febrile diseases over the past 10 months. She remains well and working, but she requires analgesics for lower extremity pains. Her hemogram remains normal. A repeat bone marrow study on August 22, 1995 (at 20 months) showed normal trilineage maturation and no evidence of LGLs. At no time did the patient develop neuropathy, elevated creatinine, or other toxic effects of cyclosporine.

DISCUSSION

Large granular lymphocyte leukemia (T-LGL-L) is a lymphoproliferative disorder characterized by monoclonal expansion of CD3^-CD57^ large granular lymphocytes similar to those seen on the peripheral smear.

Based on these findings, T-LGL leukemia ("T-γ neutropenia") was diagnosed and confirmed by immunophenotyping, which showed a T-cell phenotype: CD2^ (92%), CD3^ (88%), CD8^ (60%). The natural killer (NK) cell markers CD16 and CD56 were only slightly increased (Table 1).

The patient was started on cyclosporine 12 mg/kg/d (700 mg total dose), which was tapered to 5 mg/kg/d (total dose 300 mg/d) within 8 days. Initially, GM-CSF (5 μg/kg/d) and dexamethasone (20 mg/d) were also administered but discontinued after 8 days. Within 3 days, the patient's WBC count increased to 3.3 X 10^9/L and her ANC to 800. She became afebrile, all antibiotics were withdrawn, and within 13 days, she showed full clinical and hematologic recovery (Table 1). Large granular lymphocytes disappeared from the blood, the WBC increased to 14,900, the ANC rose to 11,324 with the differential count showing 20% polys, 26% bands, 24% myelocytes, and 6% metamyelocytes. The platelet count increased to 982,000; the hemoglobin rose to 10.6 g, and the hematocrit to 34.2%. The cyclosporine blood level initially reached a maximum of 860 ng/L, which was quickly reduced to 500 to 600 ng/L and stabilized at 200 to 250 ng/L.

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**Table 1. Hemograms and Lymphocyte Phenotyping**

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 13</th>
<th>Day 30</th>
<th>18 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC X 10^9</td>
<td>0.6</td>
<td>3.3</td>
<td>14.9</td>
<td>22.8</td>
<td>5.8</td>
</tr>
<tr>
<td>ANC X 10^9</td>
<td>0</td>
<td>0.8</td>
<td>11.3</td>
<td>17.4</td>
<td>3.5</td>
</tr>
<tr>
<td>LGL %</td>
<td>70</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelet</td>
<td>130</td>
<td>767</td>
<td>962</td>
<td>266</td>
<td>371</td>
</tr>
<tr>
<td>CD3 %</td>
<td>88</td>
<td>59</td>
<td>78</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>CD8 %</td>
<td>60</td>
<td>46</td>
<td>51</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>CD16/56*</td>
<td>20</td>
<td>14</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD57*</td>
<td>31</td>
<td>30</td>
<td>38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Hb, hemoglobin; HCT, hematocrit.
* Dual staining.
or, less frequently, CD3+ NK lymphocytes. Severe neutropenia leads to intractable and often fatal infections due to agranulocytosis in 80% of patients with typical T-LGL-L. The condition is often associated with other hematologic and immunologic disorders. Arthralgia and myalgia have been frequently observed. The mechanism of suppression of granulopoiesis remains controversial and is probably multifactorial.

The clinical entity of T-LGL leukemia was first described by McKenna et al in 1977 and recently reviewed by Loughran, who defined two immunophenotypically different groups of monoclonal T-cell proliferation: The CD3+ T-LGL leukemia and the CD3+, CD56+ NK-LGL leukemia which is mostly seen in Asia, especially in Japan. Both types may have a similar polyclonal (reactive ?) preleukemic ?) variety and a monoclonal leukemic form that can be differentiated on the basis of TRC gene rearrangement studies. The Asian form of NK cell LGL leukemia appears to be more aggressive with early fatalities, but milder, chronic forms of this variant were also described.

The importance of morphologic features, severity of neutropenia, rheumatoid pain, as well as the diversity of symptoms and variability of immunophenotypic features were emphasized by Scott et al, who studied a large cohort of patients with this condition. LGL-leukemia appears mostly resistant to traditional antileukemic therapy, high-dose steroids, splenectomy, or cytokine therapy, although transient responses to toxic doses of GM-CSF have been described. Good response to prolonged, low-dose, oral methotrexate therapy was published recently. Responses were seen after 2 weeks to 4 months of therapy before attaining a neutrophil count greater than 500. Responders required methotrexate maintenance therapy. Interestingly, the combination of methotrexate and cyclosporine yielded good results in the treatment of resistant, severe cases of rheumatoid arthritis. Good response to cyclosporine in ankylosing spondylitis with severe neutropenia has been also reported. In addition, a search of the literature revealed an abstract describing good response to cyclosporine in agranulocytosis associated with LGL proliferation in three other cases.

We attempted to treat our patient with cyclosporine because of its reported ability to selectively block the activation of T-helper and cytotoxic lymphocytes and its selective inhibition of T-cell growth factor gene expression. The decision was also based on the experience of one of the investigators who observed complete remission and normalization of the blood count using cyclosporine in a case of near-fatal, accelerated, chronic lymphocytic leukemia associated with brisk autoimmune hemolysis (unpublished data, February 1992).

Although TCR gene rearrangement could not be studied initially in our patient, the morphologic features, the severity of agranulocytosis, and the associated hematologic and immunologic abnormalities suggests typical T-LGL leukemia. The dramatic and sustained response to cyclosporine over the past 2 years in this treatment-resistant and critically ill patient calls for further clinical investigation of this compound in the treatment of T-LGL-L.

NOTE ADDED IN PROOF

T-beta clonal gene rearrangement was recently identified after withholding cyclosporine therapy for 1 month, using JH and T-beta/ JB 1, 2 probes, confirming the monoclonality of T-cell proliferation in this patient.

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REFERENCES


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