Brief report

Acquired pure red cell aplasia associated with lymphoproliferative disease of granular T lymphocytes

Ronald S. Go, Chin-Yang Li, Ayalew Tefeferi, and Robert L. Phyliky

Acquired pure red cell aplasia (PRCA) can be associated with lymphoproliferative disease of granular T lymphocytes (T-LDGL), also known as T-cell large granular lymphocyte leukemia. Fifteen adult patients with PRCA associated with T-LDGL comprise this study. Neutropenia and rheumatoid arthritis were uncommon. All patients responded to immunosuppressive therapy. The 2 most commonly used treatments were prednisone and cyclophosphamide ± corticosteroids, producing overall response rates of 50% and 60%, respectively. Treatment with cyclophosphamide was associated with a more durable remission (median, 60 versus 7.5 months). After a median follow-up of 67 months, 2 patients died of treatment-related complications, one from myelodysplasia and another from cyclophosphamide-induced renal failure. The clinical course and treatment responses of PRCA associated with T-LDGL in this series were similar to the general group of PRCA. Because T-LDGL is frequently underdiagnosed, it is likely that a significant proportion of idiopathic or primary PRCA is in fact secondary to T-LDGL.

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Introduction

Common to the pathophysiology of bone marrow failure syndromes, including aplastic anemia, pure red cell aplasia (PRCA), and a subset of myelodysplastic diseases, is an immune-mediated suppression of marrow progenitor cells by cytotoxic T lymphocytes.1-5 Lymphoproliferative disease of granular T lymphocytes (T-LDGL) is a clonal disorder of cytotoxic T lymphocytes that usually manifests as neutropenic infections and is associated with autoimmune disorders, most commonly rheumatoid arthritis. T-LDGL can present as failure of hematopoiesis or immune-mediated destruction in any one or a combination of the several myeloid cell lines, including red cells, neutrophils, and platelets. The frequent associations of these bone marrow failure syndromes with T-LDGL and recent findings on pathogenic mechanisms of T-LDGL suggest that T-LDGL may share a similar pathology to these other syndromes.6,7 We have previously reported that T-LDGL is a disorder frequently associated with PRCA.8 In our institutional series of 203 patients with T-LDGL, 15 (7%) patients presented as PRCA.6 This report reviews our clinical experience in 15 patients with PRCA in the setting of T-LDGL. This series included an update on 9 patients previously reported.8

Study design

After receiving the approval of the institutional review board of the Mayo Foundation, our database of patients with T-LDGL was reviewed for associated PRCA. A diagnosis of PRCA was made on the basis of clinical and bone marrow findings. Anemia with reticulocyte count of less than 1% had to be present. On bone marrow examination, there was almost complete absence of erythroid precursors or maturation arrest at the pronormoblastic stage. Maturation of other hematopoietic cell lines was normal. Other known causes of PRCA were excluded. Published criteria for T-LDGL was used.9 Complete response (CR) was defined as normalization of hemoglobin. Partial response (PR) was defined as an increase in hemoglobin level by 2 g/dL or more or by a 50% reduction in transfusion requirements. Any response less than partial was considered no response (NR). The percentage and absolute counts of granular lymphocytes in the peripheral blood were calculated as previously reported.10 Multiparametric flow cytometry of the peripheral blood or bone marrow and immunohistochemical staining of bone marrow biopsy was used to study lymphocytic immunophenotype. T-cell receptor gene rearrangement study was performed by using either the Southern blot analysis or polymerase chain reaction.

Results and discussion

We found 15 patients having PRCA associated with T-LDGL. In all cases, the diagnosis of PRCA was made concurrently with T-LDGL. Of those 15 patients, 8 were women. The median age at diagnosis was 66 years (range, 28-88 years). Associated medical conditions included B-cell non-Hodgkin lymphoma (2), B-cell chronic lymphocytic leukemia (1), thymoma (1), porphyria cutanea tarda (1), rheumatoid arthritis (1), inflammatory bowel disease (1), and polyendocrine failure (1). In the patient with a history of thymoma, thymectomy was performed 6 years before the diagnosis of T-LDGL and PRCA. All patients presented with symptoms because of anemia and were transfusion dependent. Except for pallor, there were no other physical findings. Laboratory findings are shown in Table 1. Absolute lymphocytosis in the peripheral blood was noted in only 6 patients. In the rest of the patients without absolute lymphocytosis, increase in granular lymphocytes could be identified by examination of the peripheral blood or the bone marrow.

Seven patients were initially treated with prednisone (3 CR, 4 NR), and 5 patients received a combination of cyclophosphamide and corticosteroids (4 CR, 1 NR). Other initial treatments included chlorambucil/prednisone (1/1 NR), methotrexate (1/1 NR), and cyclophosphamide/doxorubicin/vincristine/prednisone (1/1 CR). The treatment outcome from initial therapy until a response was obtained is outlined in...
Table 1.  Laboratory findings of 15 patients with pure red cell aplasia associated with lymphoproliferative disease of granular T lymphocytes

<table>
<thead>
<tr>
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<th>Median (range)</th>
<th>Normal values</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.8 (5.0-10.5)</td>
<td>12.0-17.5</td>
</tr>
<tr>
<td>Mean corpuscular volume (fL)</td>
<td>90 (83.0-117.9)</td>
<td>81.2-98.3</td>
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<tr>
<td>White cell count ($\times 10^9$/L)</td>
<td>6.6 (3.4-37.0)</td>
<td>3.5-10.5</td>
</tr>
<tr>
<td>Absolute neutrophil count ($\times 10^9$/L)</td>
<td>3.09 (0.12-5.41)</td>
<td>1.70-7.0</td>
</tr>
<tr>
<td>Absolute lymphocyte count ($\times 10^9$/L)</td>
<td>2.31 (1.06-29.97)</td>
<td>0.90-2.90</td>
</tr>
<tr>
<td>Absolute granulocyte count ($\times 10^9$/L)</td>
<td>0.45 (0.30-7.21)</td>
<td>0.10-0.50</td>
</tr>
<tr>
<td>Granulocyte percentage (%)</td>
<td>31 (10-59)</td>
<td>5-25</td>
</tr>
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Clonal T-cell receptor gene rearrangement, 15 of 15 patients; positive direct antithymocyte globulin, 1 of 10 patients; positive antinuclear antibody test, 4 of 6 patients; rheumatoid factor, 1 of 4 patients; antineutrophil antibody, 0 of 2 patients. Cytogenetic studies, (n = 10 patients). Normal (8); loss of Y chromosome (1); complex abnormality (1). Peripheral blood flow cytometry, (n = 12 patients). CD3/CD8 (8); normal (4). Immunophenotypes studied include CD2, CD3, CD5, CD7, CD3/CD8, and CD3/CD4.

Bone marrow immunohistochemistry, (n = 9 patients). Increase in CD3+ and CD8+ cells (9); increase in CD57+ cells (8).

were modified to reflect this recognition.15 Nevertheless, we believe that T-LDGL remains a disease that is underdiagnosed.

The 2 most commonly used treatments in our series were prednisone alone and cyclophosphamide with or without concurrent low-dose corticosteroids. As initial therapy, cyclophosphamide ± corticosteroids produced a better overall response rate (CR + PR) than prednisone alone (80% versus 43%). When used as initial and salvage therapies were considered together, the overall response rates for cyclophosphamide ± corticosteroids and prednisone were similar (60% and 50%, respectively). Treatment with cyclophosphamide was, however, associated with a longer duration of response, 60 months (range, 22-117 months) versus 7.5 months (range, 5-43 months). Cyclosporine and methotrexate were used in the setting of treatment failure from other agents, with responses noted in 2 of 3 and 1 of 3 patients, respectively. These responses were durable, but, in each case, the treatment had to be maintained to achieve continued remission. All patients achieved remission after sequential immunosuppressive therapy. This finding suggests that T-LDGL association may be prognostic of a good response to immunosuppression. Considering that the clinical course and treatment responses of PRCA associated with T-LDGL are similar to the general group of PRCA and that T-LDGL is probably an underdiagnosed disorder, it is likely that a significant proportion of idiopathic or primary PRCA is, in fact, secondary to T-LDGL.

Acknowledgments

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References


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