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

Ronald S. Go, Chin-Yang Li, Ayalew Tefferi, 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 cyclosporine-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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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% was noted in only 6 patients. In the rest of the patients without 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 positive 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 positive 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 positive 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 positive 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 positive 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 positive 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 positive 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 positive findings, Laboratory findings are shown in Table 1.
Figure 1. In patients who initially responded to cyclophosphamide (5), the remission duration ranged from 22 to 120 months. All responded again to cyclophosphamide. In contrast, all prednisone responders (3) relapsed within 5 to 10 months of treatment. They were retreated with either oral cyclophosphamide (1 CR, 1 NR) or prednisone (1 CR). Salvage treatments used included cyclosporine, methotrexate, fluoroxymesterone, antithymocyte globulin, or combination chemotherapy. The usual dosages of immunosuppressive agents used were prednisone, 1 mg/kg/d; cyclophosphamide, 50-100 mg/d; cyclosporine, 10 mg/kg/d; and methotrexate, 7.5-15 mg/wk. In general, a specific treatment was tried for at least 2 to 3 months unless side effects were not tolerated. The use of cytotoxic agents was limited to a total of 6 to 12 months after a response was achieved, whereas noncytotoxic immunosuppressive agents were given as long as necessary to control the disease. After a median follow-up of 67 months (range, 22-113 months), 13 patients were alive; 10 patients had PR, and 3 patients were in unmaintained CR. Continued therapy was necessary in all of the patients in PR. The clinical course was characterized by frequent relapses, although durable responses could be achieved. Two patients died of treatment-related complications, one from acute myeloid leukemia arising from myelodysplasia after cyclophosphamide treatment and another from cyclosporine-induced renal failure.

It is now evident that a close association exists between T-LDGL and PRCA. In our experience, PRCA is the second most common hematologic disease found in T-LDGL patients, exceeded only by autoimmune hemolytic anemia. In this subset of T-LDGL with concomitant PRCA, it is notable that rheumatoid arthritis and neutropenia were infrequently associated (1 and 2 patients, respectively). A careful examination of the peripheral blood is always necessary as lymphocytosis was observed in less than half of our cases. Similarly, bone marrow involvement by granular lymphocytes was mostly subtle. Peripheral blood flow cytometry detected an abnormal T-cell population in only 8 of the 12 patients studied. This finding was probably because of the limited antibody panel we used (Table 1) for routine T-cell analysis. A more detailed analysis of the CD8 subset, including determinations of CD16, CD56, and CD57, might have provided us more information. Initial case reports and series of T-LDGL included only cases that were obvious on clinical grounds, i.e., those with evident lymphocytosis and symptoms, features consistent with a later diagnosis. As is true when there is a better awareness of a newly described disease, T-LDGL earlier in its natural history is being recognized in a more recent reported series. In fact, the diagnostic criteria for T-LDGL were modified to reflect this recognition. 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 uses such 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.

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References


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