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CASE REPORT

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Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement

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Abstract Although T-prolymphocytic leukemia (T-PLL) is characterized by organ infiltration, small-intestinal involvement is rare. We performed an unrelated allogeneic bone marrow transplantation in a patient with T-PLL who had multiple lymphomatous polyposis of the small intestine refractory to combination chemotherapy (cyclophosphamide, vincristine, and prednisolone [COP] and fludarabine plus cyclophosphamide). The patient developed no graft-versus-host disease (GVHD) and remains in complete remission 16 months after the transplantation. T-PLL is usually refractory to chemotherapy and is a T-cell malignancy with poor prognosis. There have been several reports on allogeneic hematopoietic stem-cell transplantation (allo-HSCT) for T-PLL, but none on allo-HSCT for T-PLL patients with intestinal involvement. It is suggested that allo-HSCT may improve the prognosis in patients with T-PLL involving the small intestine.

Key words T-prolymphocytic leukemia · Allogeneic bone marrow transplantation · Small-intestinal involvement

Introduction

T-prolymphocytic leukemia (T-PLL) is a rare hematological malignancy that is an aggressive subtype of chronic lymphocytic leukemia (CLL). Although responses are sometimes observed to agents such as alkylating agents;[1] 2-deoxycoformycin;[2] and cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP);[3] the prognosis is generally poor, particularly in patients with refractory disease. Here, we report a case of primary refractory T-PLL in a patient with small-intestinal involvement successfully treated by an unrelated allogeneic bone marrow transplantation (BMT).

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Case report

A 28-year-old man was admitted to our hospital on July 19, 1999, with abdominal pain, diarrhea, and weight loss. Lymphadenopathy was not noted. He had only mild splenomegaly. The white cell count was 19.6×10^9/l, the hematocrit was 37%, and the platelet count was 15.1×10^9/l. Seventy-five percent of the white cells had a prolymphocytoid appearance (Fig. 1A), being fairly uniform lymphoid cells, with fairly dense chromatin, scant cytoplasm, and nuclei with a single prominent nucleolus. Flow-cytometric analysis showed that the cells had the phenotype of post-thymic $CD8^+$ T cells ($CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, $CD8^+$, $CD4^-$, $CD10^-$, $CD34^-$, TdT^-; myeloid and B-lymphoid markers were negative). A bone marrow smear also suggested T-PLL, because 32% of the nucleated cells were prolymphocytes (Fig. 1B). Cytogenetic analysis of peripheral blood and bone marrow showed 46, XY, t(1;3)(p34;p21). Southern blot analysis disclosed T cell receptor (*TCRcβ1*) gene rearrangement in peripheral blood and bone marrow. Colonoscopy showed multiple lymphomatous polyposis (MLP) in the small intestine (Fig. 2A), extending from the end of the ileum to about 35 cm into the oral side of the ileum. Biopsy of the MLP revealed infiltration by atypical lymphocytes (Fig. 1C,D), consistent with leukemic infiltration. Based on these data, the patient was diagnosed with T-PLL with ileal involvement. In October 1999, the patient was initially treated with six courses of COP (cyclophosphamide, vincristine, prednisolone), which led to transient leukopenia, resolution of karyotypic abnormality in the peripheral blood and bone marrow, and shrinkage of the MLP.

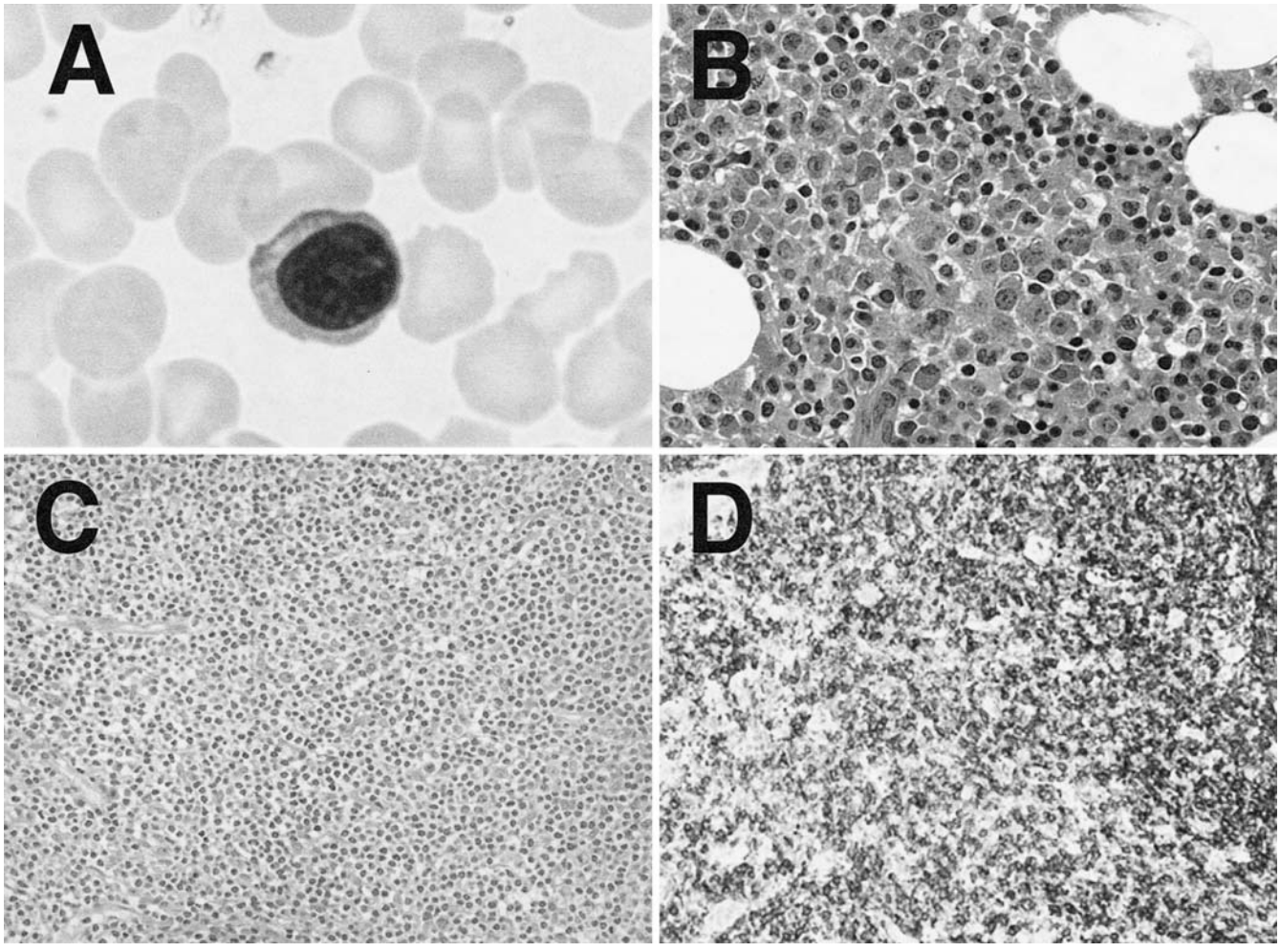

Fig. 1A–D. **A** Peripheral blood finding on admission, showing increased numbers of prolymphocytes. **B** Biopsy specimen from the bone marrow, showing infiltration of prolymphocytes. **C** Biopsy specimen from multiple lymphomatous polyposis (MLP), showing infiltration of atypical lymphocytes (prolymphocytes). **D** Immunoperoxidase staining for CD8 of biopsy specimen from MLP, showing infiltration of CD8-positive cells. **A** May-Grünwald-Giemsa, × 1000; **B** H&E, × 400; **C** H&E, × 200; **D** × 200

In April 2001, although the patient's white blood cell count remained within the normal range and karyotype was normal, the MLP had enlarged. The patient received two courses of combination chemotherapy consisting of fludarabine (50 mg i.v. daily for 3 days) and cyclophosphamide (500 mg i.v. daily for 3 days), which led to shrinkage of the MLP, but not to complete resolution (Fig. 2B). In November 2001, he received an allogeneic BMT. The conditioning regimen consisted of busulfan (240 mg/day p.o. daily for 4 days) and cyclophosphamide (3600 mg/day i.v. daily for 2 days). He received bone marrow (nucleated cell dose, 2.53×10^8/kg) from an HLA-identical unrelated donor. FK506 and short-course methotrexate were used for acute graft-versus-host disease (GVHD) prophylaxis. The posttransplant course was complicated by mild liver dysfunction and gram-positive bacteremia, but the patient did not develop acute GVHD. On day +18, the white cell count had recovered to 1.7×10^9/l and neutrophil count to 1.1×10^9/l. On day +91, bone marrow examination showed trilineage engraftment, and cytogenetic and Southern blot analysis of peripheral blood and bone marrow revealed complete resolution of the karyotypic abnormality and the *TCRcβ1* gene rearrangement. Chimerism analysis of peripheral blood $CD3^+$ cells on day +114 by a Short Tandem Repeats-polymerase chain reaction (STR-PCR) method showed that over 90% of the cells were donor cells. Colonoscopy on day +118 revealed complete resolution of the MLP (Fig. 2C), indicating complete remission. At the time of this writing, 16 months after the transplantation, the patient remains in complete remission with no chronic GVHD.

Discussion

T-prolymphocytic leukemia (T-PLL) is seen predominantly in the elderly patient population, and is characterized by leukocytosis, splenomegaly, lymphadenopathy, hepatomegaly, and skin involvement; infiltration of the small intestine

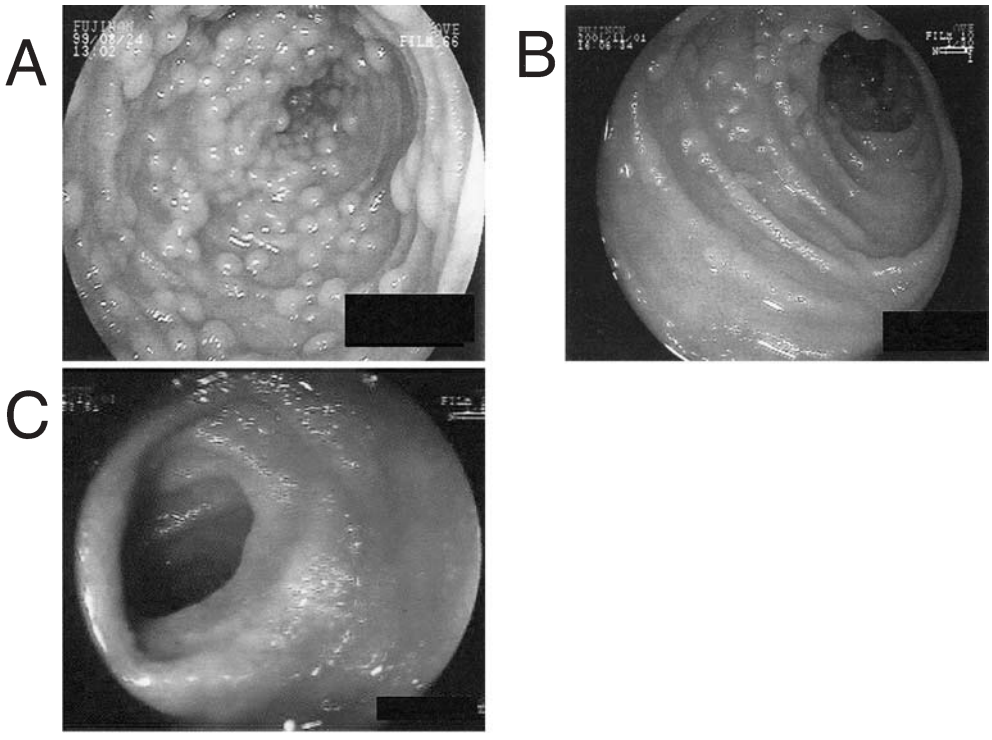

Fig. 2A–C. Colonoscopic findings of MLP in the ileum. **A** On admission. **B** Before transplantation. Although MLP were shrunken by chemotherapy, complete resolution was not obtained. **C** After transplantation. Complete resolution of the MLP was obtained by bone marrow transplantation

is rare.[1] Leukemic cells are positive for pan T-cell markers and are often positive for postthymic markers such as CD2, CD3, CD5, and CD7.

Responses have been observed in T-PLL patients treated with alkylating agents used as single-agent treatment; 2-deoxycoformycin; or CHOP, which have had response rates of only 29%, 33%, and 49%, respectively.[1,2] A high response rate, 76%, was recently reported with the anti-CD52 antibody.[4,5] As the response induced by these drugs is transient, and the median survival duration is only 7.5 months, the disease is considered essentially incurable by these means.[5]

Thus, in T-PLL, potent definitive consolidation therapy is required after achieving a response, and in recent years there have been case reports of six patients[5–7] who have undergone allogeneic hematopoietic stem-cell transplantation (allo-HSCT). Collins et al.[7] treated a 47-year-old man with skin and spleen involvement by BMT from an HLA-matched sister, with cyclophosphamide and total body irradiation as the conditioning regimen. Cyclosporine plus corticosteroid were used for GVHD prophylaxis, but the patient developed grade II acute GVHD. This patient remained in complete remission 36 months after transplantation. Garderet et al.[6] treated a 52-year-old patient, who had splenic involvement, with a nonmyeloablative conditioning regimen of busulfan plus fludarabine, followed by peripheral blood stem-cell transplantation (PBSCT) from an HLA-matched brother. The GVHD prophylaxis was cyclosporine and short-course methotrexate, and no GVHD was observed. The patient died 5 months after transplantation due to recurrence in the central nervous system. Dearden et al.[5] treated four patients with the anti-CD52 antibody, after which allo-HSCT was performed as salvage therapy. The four patients were a 50-year-old man with skin and spleen involvement, a 51-year-old man with spleen involvement, and a 57-year-old man and a 40-year-old man with no extramedullary involvement. The two patients with extramedullary involvement received a nonmyeloablative conditioning regimen of fludarabine plus melphalan (L-PAM), followed by PBSCT from a sibling donor. In the other two patients, the conditioning regimen was cyclophosphamide plus total body irradiation, followed by BMT from a sibling donor. GVHD was not noted in these four patients. One patient, the 57-year-old man who had undergone BMT, died of treatment-related toxicity. The other three patients obtained complete remission and showed long-term survival (2 months, 11 months, and 24 months, respectively). In summary, of the seven reported T-PLL patients, including the patient reported here, who received various conditioning regimens and bone marrow or peripheral blood as a source of stem cells, five patients showed long-term relapse-free survival; thus, allo-HSCT appears to be useful in the treatment of T-PLL. In addition, it is suggested that the type of conditioning regimen and the source of the stem cells does not affect the therapeutic effect of allo-HSCT in T-PLL.

We have reported the first T-PLL patient with small-intestinal involvement to have undergone allo-HSCT and achieved complete remission. Allo-HSCT seems to be effective in patients with refractory T-PLL with small-intestinal involvement.

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