Long-term complete remission of early hematological relapse after discontinuation of immunosuppressants following allogeneic transplantation for Sezary syndrome

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Abstract

Sezary syndrome (SS) is a leukemic form of cutaneous T-cell lymphoma and is chemo-resistant. Allogeneic hematopoietic stem cell transplantation is a promising therapy for SS; however, relapse is common. Therapeutic options after relapse have not been established. We managed an SS patient with hematological relapse within one month after transplantation. After discontinuation of immunosuppressants, she achieved complete remission and remained relapse-free. The chimeric analyses of T-cells showed that the full recipient type became complete donor chimera after immunological symptoms. This clinical course suggested that discontinuation of immunosuppressants may result in a graft-versus-tumor effect, leading to the eradication of lymphoma cells.

Introduction

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphoma.[1,2] Most patients with MF show an indolent clinical course, although one-third of MF patients are in an advanced stage. Sezary syndrome (SS) is a leukemic form of cutaneous T-cell lymphoma, and has systemic features, such as lymph node swelling and liver involvement, in addition to skin involvement. SS presents an aggressive clinical course. Advanced MF and SS are incurable with skin-directed therapies or conventional chemotherapies.

Allogeneic hematopoietic stem cell transplantation may be a promising treatment for advanced MF and SS.[3,4] However, there is no established consensus on management after transplantation. A previous report showed that the rate of progression or relapse 1 year after transplantation was 50% and found that relapse is most common in the first year post-transplantation.[5] Another report showed that disease relapse occurred at a median of 3.8 months after transplantation.[6] Therefore, it is important to manage the relapse that occurs early after transplantation. The disease relapse documented in these reports was local, mostly in skin lesions. Some reports demonstrated that disease relapse in local lesions can be managed by immunomodulation.[7] However, hematological relapse after transplantation showed extremely poor prognosis.[6] The relapsed patients of other hematological disease require re-transplantation for cure. In SS, the management of hematological relapse after transplantation has not yet been established because there has been no report of successful treatment after hematological SS relapse after transplantation.

We managed an SS patient exhibiting hematological relapse within one month after myeloablative allogeneic stem cell transplantation. Interestingly, in spite of hematological relapse, she achieved complete remission after the discontinuation of immunosuppressants, and remained relapse-free. Here, we report the clinical details and discuss a possible mechanism of tumor reduction.

Case Report

A 31-year-old woman was referred for erythroderma. The patient noticed erythroderma with scales and enlarged cervical and inguinal lymph nodes three months before her visit. At the first visit to our hospital, her white blood cell count was 16.2 x 10^9/L, with 29% abnormal lymphocytes. Immunophenotyping by flow cytometry revealed that the abnormal lymphocytes were positive for CD3 and CD4, and negative for CD7. Southern blot analysis using a T-cell receptor C probe showed clonal rearranged bands. Skin biopsy showed that lymphocytes with constricted nuclei infiltrated the dermis. The patient was diagnosed as SS stage IVA (T4NxM0B2) and received CHOP therapy consisting of cyclophosphamide, adriamycin, vincristine and prednisolone. After the second cycle of chemotherapy, she had stable disease with residual abnormal lymphocytes in the peripheral blood, which indicated that her disease was resistant to chemotherapy. She received allogeneic peripheral blood stem cell transplantation from an HLA-matched sibling. The myeloablative condition regimen was cyclophosphamide (60 mg/kg, 2 days) and 12 Gy of total body irradiation. GVHD prophylaxis consisted of cyclosporine and short-term methotrexate. On day 11, neutrophil engraftment was achieved (Figure 1). The percentage of aberrant lymphocytes in peripheral blood smears gradually decreased. Five days after the engraftment, the patient developed skin rash and diarrhea (Figures 1 and 2). Considering acute GVHD (skin stage 1, gut stage 1, liver stage 0, total grade 2), prednisolone 1 mg/kg was administered on day 18 following transplantation. However, skin biopsy revealed the infiltration of Sezary cells instead of acute GVHD. Chimerism analysis of peripheral blood recognizing short tandem repeats in sorted T-cells showed that the proportion of donor cells in the T cell fraction was only 30% on day 30 (Figure 1). Subsequently, the Sezary syndrome relapsed, not only in skin lesions, but also in peripheral blood. Chimerism analysis showed the split chimera on day 42, in which there were no donor chimeras in the T cell fraction, but there were complete donor chimera in the granulocyte fraction (Figure 2). The administration of cyclosporine was discontinued, and the dose of prednisolone was rapidly reduced.

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Three days after the discontinuation of cyclosporine, intermittent fever developed without infection. Concurrently, her serum ferritin level increased to 1131 ng/mL by immunological reaction. On day 59 after transplantation, chimerism analysis showed that 71% of T cells were donor type. We considered that a graft-versus-lymphoma effect reduced the tumor cells after immunological fever after discontinuation of immunosuppressants. On day 64, she received cyclosporine again because of the sustained fever, which subsequently subsided. Chimerism analyses of peripheral blood on day 80 showed donor types in both T cell and granulocyte fractions (Figure 1). Abnormal lymphocytes disappeared and the erythema gradually subsided (Figure 2). The administration of cyclosporine was tapered and eventually stopped on day 730 after transplantation. At her last follow-up visit, the patient had maintained complete remission for 7 years without any complications.

Discussion and Conclusions

We managed an SS patient with early hematological relapse after allogeneic transplantation. Chimerism analyses showed that the donor cells in the T cell fraction decreased one month after transplantation. After discontinuation of cyclosporine, the percentage of donor T cells increased after immunological fever.

Allogeneic stem cell transplantation may provide long-term remission in advanced MF and SS. A graft-versus-lymphoma effect is key for allogeneic transplantation.[8] Previous reports showed that disease relapse after transplantation can be managed by reduction of immunosuppressants or infusion of donor lymphocytes, especially in regional relapse.[7,9,10] However, hematological relapse after transplantation has poor outcome. The detailed clinical course after early hematological relapse following transplantation in SS has not been reported. Withdrawal of immunosuppressants and infusions of donor lymphocytes have limited efficacy on hematological relapse in other hematological malignancies.[11] In this patient, the discontinuation of cyclosporine led to the reduction of tumor cells and achieved complete donor chimera. After discontinuation of cyclosporine, a sustained fever developed. She did not have physiological evidence of infection. Thus, the fever was likely due to immunological response. The serum ferritin level was also elevated during the sustained fever. Causes of elevated serum ferritin levels include iron overload, inflammation and immunological responses.[12] In this patient, the elevated serum ferritin level suggests acute inflammation associated with immunological responses. The fever subsided with the use of immunosuppressants. Simultaneously, the ferritin level decreased. Therefore, we considered that the fever and elevated ferritin level were due to immunological responses associated with a graft-versus-lymphoma effect. Discontinuation of immunosuppressants resulted in complete remission, and she was relapse-free for more than seven years.

It is necessary to immediately treat the patient after relapse in SS. However, the detection of disease relapse is sometimes difficult because abnormal lymphocytes associated with SS are indistinguishable from reactive lymphocytes after transplantation. Indeed, in spite of the percentage of aberrant lymphocytes decreasing morphologically, the SS in this patient relapsed (Figure 1). Chimerism analysis is useful for revealing the proportion of tumor cells. To assess the disease progression in detail, it is necessary to analyze each component of chimerism after separating blood cells into T lymphocytes and granulocytes.[13] A previous report demonstrated that 14% of patients had mixed chimera in the T-cell compartments in transplantation of cutaneous T-cell lymphoma.[14] The donor chimera in the T cell fraction decreased early at relapse of SS. Moreover, the assessment of the analysis of chimerism in T cell fraction over time enabled the understanding of the clinical course. In our patient, the donor chimera in the T cell fraction decreased. Subsequently, the chimerism of T-cells and granulocytes were distinct; all T-cells were derived from the host and all granulocytes from the donor. After discontinuation of immunosuppressants, complete donor chimera in the T-cell fraction was achieved. This clinical course demonstrated

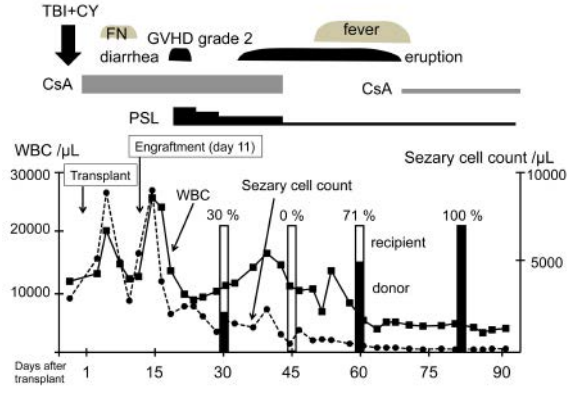

Figure 1. Clinical course. After tapering prednisolone and discontinuing cyclosporine, Sezary cells gradually decreased. Bars indicate the result of chimerism analyses of T-cell fraction. The black bar indicated the percentage of donor type. The white bar indicated the percentage of recipient type. After reducing the dose of immunosuppressants, the percentage of donor chimera in T-cell fraction increased. TBI, total body irradiation; CY, cyclophosphamide; FN, febrile neutropenia; GVHD, graft-versus-host disease; CsA, cyclosporine; PSL, prednisolone; WBC, white blood cell.

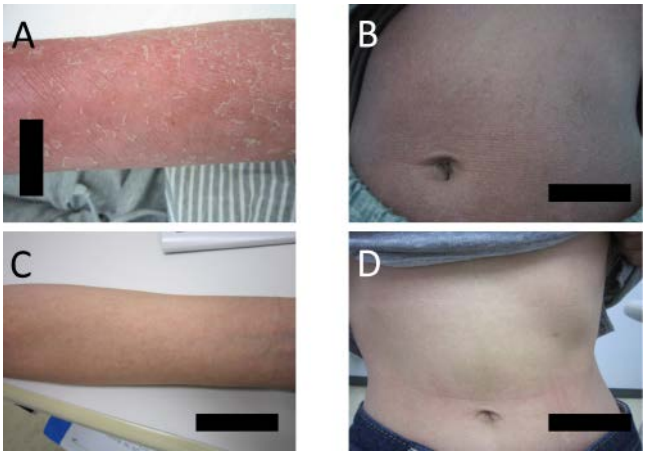

Figure 2. Skin feature. At relapse, the patient suffered from erythroderma. At complete remission, the erythroderma disappeared. A) The skin of antebrachium at relapse after transplantation. B) The skin of abdomen at relapse after transplantation. C) The skin of antebrachium at complete remission after discontinuation of immunosuppressants. D) The skin of abdomen at complete remission after discontinuation of immunosuppressants.

that the chimerism analyses in the T-cell fraction were useful for the disease status.

In conclusion, discontinuation of immunosuppressants may be one of the effective strategies for early hematological relapse of SS after allogeneic transplantation.

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