Case of relapsed AIDS-related plasmablastic lymphoma treated with autologous stem cell transplantation and highly active antiretroviral therapy

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Abstract

Plasmablastic lymphoma is a rare and aggressive malignancy strongly associated with HIV infection. The refractory/relapsed disease rate is high, and the survival rate is characteristically poor. There are no satisfactory salvage regimens for relapsed cases. We successfully performed autologous stem cell transplantation using a regimen consisting of MCNU (ranimustine), etoposide, cytarabine, and melphalan in a Japanese patient with relapsed AIDS-related plasmablastic lymphoma of the oral cavity. Highly active antiretroviral therapy continued during the therapy. Therapy-related toxicity was tolerable, and a total of 40 Gy of irradiation was administered after autologous stem cell transplantation. The patient has remained in complete remission for 16 months since transplantation.

Introduction

Plasmablastic lymphoma (PBL) was proposed in 1997 as a new distinct subtype of diffuse large B-cell lymphoma (DLBCL).[1] PBL has a strong predilection for the oral cavity of HIV-positive patients, predominantly in males. The response duration is generally short, and the refractory/relapsed disease rate is high.[2,3] Previously, we reported that a MEAM [MCNU (ranimustine), etoposide, cytarabine, melphalan] regimen with autologous stem cell transplantation (ASCT) was effective and well tolerated in 3 patients with refractory or relapsed AIDS-related lymphoma, even though the patients were infected with HIV.[4] Here, we report a case of relapsed PBL treated with high-dose chemotherapy using a MEAM regimen followed by ASCT.

Case Report

A 51-year-old Japanese man was diagnosed with HIV infection 8 years previously presented with night sweats, fever, weight loss, and a gingival ulcer. Gingival biopsy showed PBL [LCA$^+$, CD20$^-$, CD79a$^-$, CD38$^+$, CD138$^+$, MUM-1$^+$, CD30 (partially$^+$), CD10$^-$, CD3$^-$, CD5$^-$, CD56$^-$, IgG$^+$, IgA$^-$, IgM$^-$, lambda$^+$, kappa$^-$, EBER-ISH$^+$, LMP-1$^-$, and HHV-8 LANA-1 (latency-associated nuclear antigen-1)$^-$, Mib-1 index 40-90%; Figure 1], and computed tomography (CT) confirmed stage IBE PBL. The patient's performance status was 1, and his serum LDH level was above normal. No bone marrow involvement was detected in the biopsy sample. His age-adjusted IPI (International Prognostic Index) was a low intermediate. The patient's HIV viral load was less than 50 copies/mL, and his CD4 count was 520 cells/μL. The patient was treated with 3 courses of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone every 21 days, but not given G-CSF routinely), 36 Gy of involved-field radiation, and highly active antiretroviral

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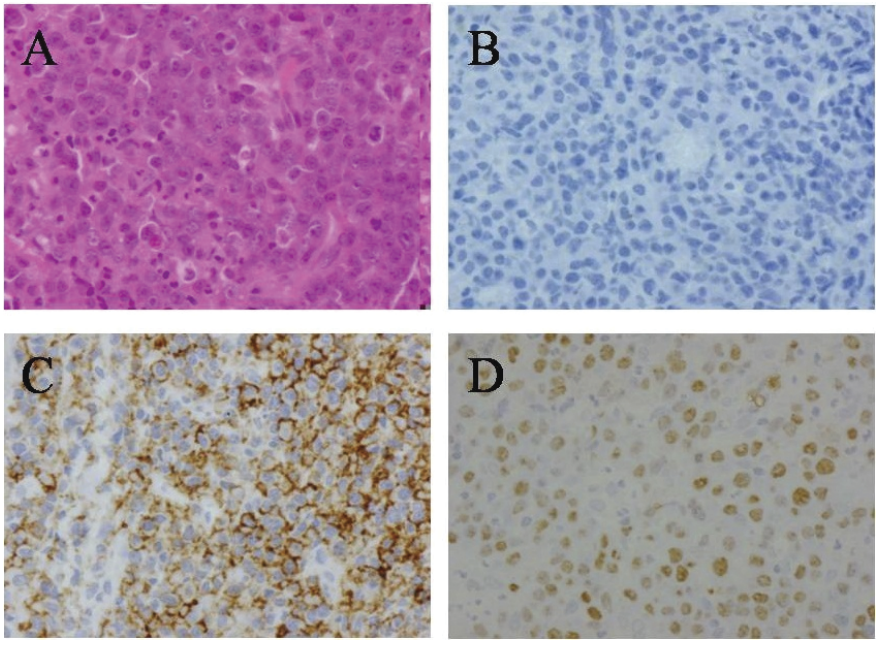

Figure 1. Pathologic findings in the oral cavity (× 400). (A) Hematoxylin and eosin staining showing large cells with plasmablastic morphology. (B) The cells were negative for CD20. (C) The cells expressed CD138, which is a plasma cell-related antigen. (D) EBV-encoded RNA *in situ* hybridization (EBER-ISH) was positive.

therapy (HAART) with abacavir/lamivudine/nelfinavir concurrently. He achieved a complete remission (CR) confirmed by a CT scan and was followed up at our outpatient clinic for 1 year after the completion of treatment. However, the patient subsequently discontinued regular visits and HAART. Two years later, he developed an oral cavity tumor (Figure 2) and was readmitted to our hospital. A CT scan showed a gingival tumor with destruction of the maxillary bone. A fluorodeoxyglucose positron emission tomography (FDG-PET) scan (Figure 3a) showed increased uptake of FDG in the tumor lesion. The initial diagnosis was confirmed by a biopsy. The patient's HIV viral load was 1.2×10^5 copies/mL and his CD4 count was 90 cells/μL at the time of relapse. First, the patient was administered modified-ESHAP (etoposide, methylprednisolone, cytarabine, and carboplatin) as salvage chemotherapy, but there was no significant change in the tumor lesion after one course of modified-ESHAP. Next, he was treated with two courses of ICE (ifosfamide, carboplatin, and etoposide), and a reduction in tumor was achieved. We performed intrathecal administration of 15 mg methotrexate and 20 mg prednisolone on the day preceding each course. HAART with abacavir/lamivudine/raltegravir was administered concurrently with the chemotherapy. He was also treated with prophylactic agents such as sulbactam/ampicillin for aerobic and anaerobic bacteria in his oral cavity, acyclovir for herpes simplex and zoster, fluconazole for fungal infection, sulfamethoxazole/trimethoprim for Pneumocystis jiroveci (discontinued on day 1 of ASCT and restarted when the engraftment was confirmed), and azithromycin for Mycobacterium avium-intracellulare complex (MAC). At the time of hematological recovery from modified-ESHAP, a CD34-positive cell count of 28.3×10^6 cells/kg was obtained by G-CSF (2.5 μg/kg lenograstim subcutaneously every 12 hours for 6 days). The patient achieved a partial response (PR) after completion of salvage therapy, and he was subsequently treated with MEAM followed by infusion of $CD34^+$ cells at 4.7×10^6 cells/kg (Table 1). Nine days after transplantation, he achieved complete hematological recovery, and the regimen-related toxicity was mild showing grade 1 nausea, grade 2 diarrhea, and grade 3 febrile neutropenia. HIV control was optimal throughout transplantation, and the CD4 count rapidly increased after stem cell transplantation. At the time of relapse, the CD4 count was less than 100 cells/μL; however, 1 year after transplantation it increased to more than 400 cells/μl (Figure 4). The patient achieved CR after ASCT (Figure 3b). Subsequently, 40 Gy of irradiation was administered to the oral cavity and the left maxillary sinus. The patient has remained in complete remission for 16 months after transplantation.

Discussion

Plasmablastic lymphoma is a distinctive B-cell neoplasm that manifests diffuse proliferation of large atypical lymphoid cells, most of which resemble B-immunoblasts and have the immunophenotype of plasma cells.[5] PBL is uncommon and accounts for 2.6% of all AIDS-related lymphomas.[6] The clinical course is very aggressive. A retrospective analysis of 112 published cases showed that the refractory/relapsed disease rate was 54%; mortality rate was 53%, and the median overall survival rate was 15 months.[3] Initially, our patient achieved a CR by chemoradiotherapy combined with HAART. However, the lymphoma relapsed 20 months after discontinuation of HAART. A meta-analysis showed that the prognosis of PBL was statistically better in patients who received HAART in addition to chemotherapy and/or radiotherapy than in patients who received chemotherapy and/or radiotherapy alone.[7] Francischini *et al*. reported a case of PBL that recurred after interruption of HAART thus substantiating the findings.[8] Immunologic and virologic control with HAART may be beneficial for treating PBL and may possibly maintain continued CR.[9] In our case, HAART was initiated with chemotherapy concurrently. We avoided the use of zidovudine and stavudine because of its associated bone marrow toxicity and neurotoxicity. The use of protease inhibitors was also avoided because of their inhibitory effect on CYP3A4. No serious side effects associated with HAART were noted in this patient.

Epstein-Barr virus (EBV) is identified in the neoplastic cells of approximately 40% of HIV-related lymphoma cases, and human herpesvirus (HHV)-8 is specifically associated with primary effusion lymphoma and Castleman disease.[10] We detected the EBV genome in atypical cells by in situ hybridization, and it is considered to play a vital role in the pathogenesis of PBL.[1] Our case was negative for HHV-8 LANA-1. Previous studies have shown the absence of HHV-8 in oral PBL cells, but Cioc *et al*. reported the presence of HHV-8 in oral PBL cells using reverse transcriptase *in situ* PCR method.[11] It is possible that some cases of PBL are associated with HHV-8.

Recently, high-dose chemotherapy and ASCT as a salvage therapy for relapsed or

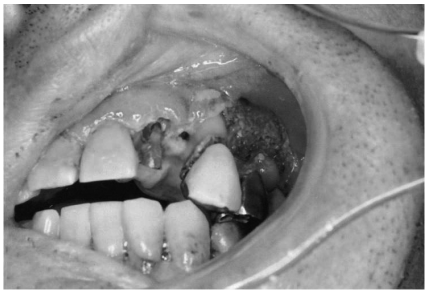

Figure 2. Clinical appearance of the lesion at relapse.

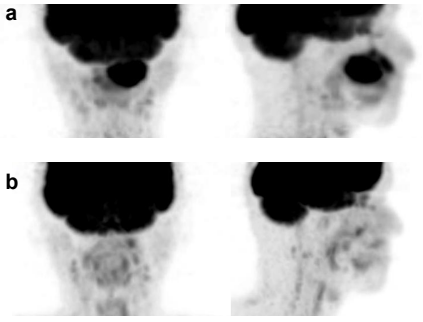

Figure 3. (a) Fluorodeoxyglucose positron emission tomography scan of the oral cavity prior to salvage therapy. FDG uptake was shown in the tumor. (b) Fluorodeoxyglucose positron emission tomography scan of the oral cavity after autologous stem cell transplantation. No abnormal uptake was present in this region.

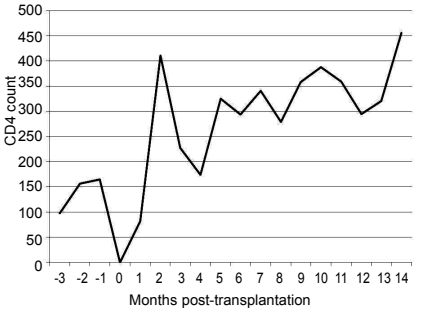

Figure 4. Transition of $CD4^+$ cell counts (/μL) before and after autologous stem cell transplantation.

Table 1. MEAM regimen.

	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
MCNU 300 mg/m²	○						
Etoposide 200 mg/m²		○	○	○			
Cytarabine 200 mg/m²		○	○	○			
L-PAM 140 mg/m²					○		SCT↓

refractory AIDS-related lymphoma was shown to be feasible and effective.[12,13] However, its role in relapsed AIDS-related PBL was unclear. We found that at least 7 cases of AIDS-related PBL were treated with ASCT,[3,12,14-17] but the efficacy of ASCT has not yet been analyzed. In this case, we performed ASCT using a MEAM regimen based on a BEAM regimen by replacing BCNU (carmustine) with MCNU. The regimen-related toxicity was mild. The patient developed febrile neutropenia but it was not caused by Pneumocystis pneumonia, MAC infection, or any other serious infection. He had an ulcer with necrotic tissue in his oral cavity which seemed to be related to a severe infection. The use of sulbactum/ampicillin as prophylaxis was effective. High-dose chemotherapy using a MEAM regimen with HAART followed by ASCT seemed to be well tolerated.

Re *et al*. showed that a low CD4 count, a poor performance status, and bone marrow involvement were negative prognostic factors in patients treated with ASCT.[16] In our patient, the CD4 count was less than 100 cells/μL, the performance status was 1, and no bone marrow involvement was detected at the time of relapse. The patient is currently alive with no relapse or major opportunistic infection. The CD4 count increased rapidly after transplantation. Recently, some studies showed that immune recovery after ASCT for HIV-related lymphoma was similar to that observed in HIV-negative patients.[18,19] High-dose chemotherapy followed by ASCT for relapsed AIDS-related PBL seems to be feasible and effective.

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