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Case Report

L-Asparaginase Induced Durable Remission of Relapsed Nasal NK/T-Cell Lymphoma After Autologous Peripheral Blood Stem Cell Transplantation

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Abstract

A 60-year-old Japanese woman who presented with right nasal congestion and high fever was admitted to our hospital in March 1999. She was diagnosed with nasal NK/T-cell lymphoma clinical stage IVB. Because her NK/T-cell lymphoma was highly aggressive and chemo-resistant, she underwent autologous peripheral blood stem cell transplantation (PBSCT). The patient received a pretransplantation conditioning regimen of ranimustine, etoposide, carboplatin, and cyclophosphamide. On July 29, 1999, 1.0×10^6/kg $CD34^+$ cells were infused. The patient achieved first complete remission. In January 2000, NK/T-cell lymphoma relapsed in the skin and fever developed. CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone) was administered, resulting in partial regression of the skin lesions, but fever persisted. L-asparaginase (L-Asp) at a dose of 6000 U/m^2 per day was administered for 7 days, resulting in the complete disappearance of the skin lesions and resolution of the fever. The patient has been in second complete remission for more than 18 months since the completion of L-Asp treatment (as of July 2001). The effect of L–Asp in this patient was dramatic. Several cases have been reported describing the effectiveness of L-Asp in patients with nasal lymphoma and cutaneous T-cell lymphoma. A front-line chemotherapy regimen containing L-Asp for NK/T-cell lymphoma may warrant further evaluation. *Int J Hematol.* 2001;74:447-450.

Key words: NK/T-cell lymphoma; Nasal; L-asparaginase; Stem cell transplantation

1. Introduction

Nasal NK/T-cell lymphoma is a distinct clinicopathological entity [1,2] associated with Epstein-Barr virus (EBV) infection [3-5] and carries a poor prognosis with notorious chemo-resistance [2,6-8]. According to Nakamura et al [2], the overall survival rate for patients with nasal NK/T-cell lymphomas in Japan was 49% at 5 years, and all patients with stage IV disease died within 6 months. Dissemination to extranodal sites usually involves skin, lung, gastrointestinal tract, and bone marrow. To overcome the chemo-resistance, stem cell transplantation (SCT) has been used. Successful treatments with autologous [9,10] and syngeneic [11] SCTs have been reported; however, the number of reports is limited.

NK/T-cell lymphoma frequently expresses a P-glycoprotein (P-gp) that extrudes anti-cancer drugs from the cell against a concentration gradient. This can at least partially explain the lymphoma's resistance to chemotherapy [12,13]. CHOP, consisting of cyclophosphamide (Cy), vincristine (VCR), doxorubicin (ADR), and prednisolone (PSL), is the standard chemotherapy regimen for non-Hodgkin lymphoma (NHL) [14] and has been used as the front-line chemotherapy for nasal NK/T-cell lymphoma [2,6-8]. Theoretically, VCR and ADR can be affected by P-gp [15]. L-asparaginase (L-Asp) is a unique anti-cancer drug that hydrolyzes serum asparagine and deprives lymphoid malignant cells of this required amino acid [16]. Thus, the action of L-Asp does not seem to be affected by P-gp.

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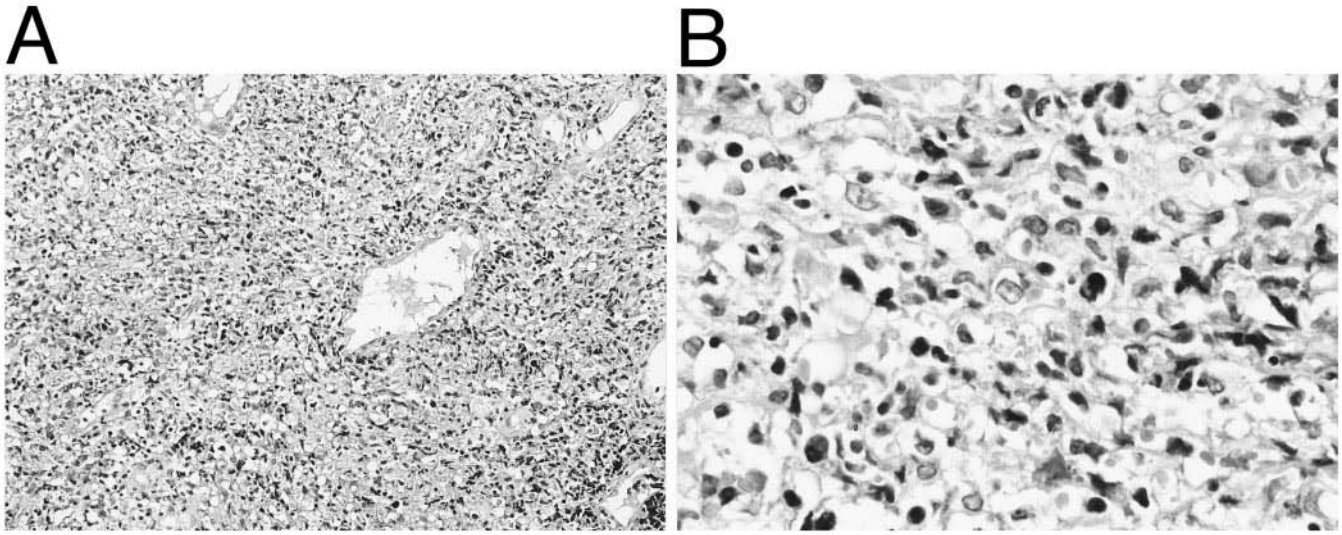

Figure 1. Nasal biopsy showing medium to large atypical lymphoid cells with round or indented nuclei and distinct nucleoli invading the blood vessel (hematoxylin-eosin stain; original magnification ×50[A], ×200[B]).

Here, we report the successful treatment of relapsed nasal NK/T-cell lymphoma with L-Asp after autologous peripheral blood SCT (PBSCT).

2. Case Report

A 60 year-old Japanese woman who presented with right nasal congestion and high fever was admitted to our hospital in March 1999. Physical examination revealed bilateral cervical lymphadenopathy and red, flat-topped nodules (3 to 5 cm) on her left shoulder, left forearm, and left anterior leg. Magnetic resonance imaging of the head and face revealed in the right middle nasal meatus a 6.5 cm × 4.5 cm × 4.0 cm tumor that had invaded the right ethmoid sinus. Biopsy was taken from the tumor in the nasal cavity. Histologic study showed medium- to large-sized atypical lymphoid cells, with round or indented nuclei with distinct nucleoli, that invaded the blood vessels (Figure 1). Results of an immunochemical study of paraffin-embedded specimens showed positivity for CD45RO, CD3, and TIA (T-cell restricted intracellular antigen) and negativity for CD20, CD56, and EBV–latent membrane protein (EBV-LMP). EBV small RNAs were detected by in situ hybridization [17]. EBV serology was as follows: viral capsid antigen (VCA)-IgG, 1:640; VCA-IgM, <1:10; VCA-IgA, 1:10; and EB nuclear antigen (EBNA), 1:40. The patient's skin lesions seemed to be an invasion of the lymphoma, but biopsy was not done. No malignant cells were found on bone marrow examination. The diagnosis of nasal NK/T-cell lymphoma clinical stage IVB was confirmed.

After 3 courses of CHOP (Cy, 750 mg/m^2; VCR, 2 mg/body; ADR, 50 mg/m^2; and PSL, 100 mg/body ×5) followed by the administration of human glycosylated granulocyte colony-stimulating factor (G-CSF), PBSCs were harvested in May 1999. The yield of CD34$^+$ cells was 1.0 × 10^6 cells/kg body weight. At this time, the nasal mass, cervical lymphadenopathy, and skin lesions had regressed. Two more courses of CHOP were administered. In June 1999, left ocular nerve palsy and fever developed. Cerebrospinal fluid tap showed the presence of lymphoma cells, and central nervous system (CNS) invasion by lymphoma was diagnosed. High-dose methotrexate (MTX) (3 g/m^2) was administered, resulting in partial improvement of the left ocular nerve palsy. Because her NK/T-cell lymphoma was highly aggressive and chemo-resistant, we decided to perform autologous PBSCT.

The patient received a pretransplantation conditioning regimen of ranimustine (MCNU) (200 mg/m^2 per day) on day –8 and day –3, etoposide (VP-16) (400 mg/m^2 per day) on days –6 to –4, carboplatin (CBDCA) (200 mg/m^2 per day) on days –7 to –4, and Cy (20 mg/m^2 per day) on days –3 and –2. PBSCs were infused on July 29, 1999. Trilineage engraftment was obtained, and the patient achieved first complete remission. In January 2000, 6 months after PBSCT, a red, flat-topped nodule with a crusted ulcer developed in the right sural region and was accompanied by fever; the skin lesions (2 to 5 cm) spread to the right upper arm, left cubitus, and left thigh. The biopsy specimen was diagnosed as invasive NK/T-cell lymphoma (Figure 2). CHOP was administered on January 27 with partial regression of the skin lesions but persistent tumor fever. Despite G-CSF administration, prolonged neutropenia was observed. Because of the significant bone marrow toxicity of CHOP, L-Asp at a dosage of 6000 U/m^2 per day for 7 days was administered from February 21, resulting in the complete disappearance of the skin lesions and fever resolution. Side effects of L-Asp treatment were minimal. Plasma fibrinogen was decreased from 429 mg/dL before L-Asp treatment to 313 mg/dL after, and pancreatitis did not occur. The patient has been in second complete remission without further chemotherapy for more than 18 months since the completion of L-Asp treatment (as of July 2001).

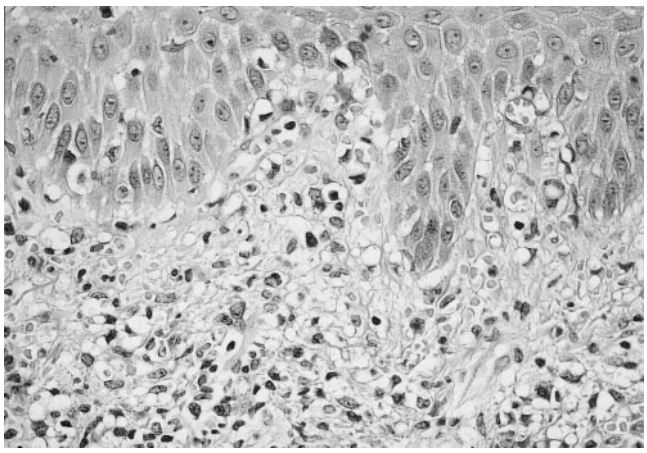

Figure 2. Skin biopsy showing medium to large atypical lymphoid cells with round or indented nuclei and distinct nucleoli with obvious epidermotropism (hematoxylin-eosin stain, original magnification ×100).

3. Discussion

Autologous PBSCT is an effective salvage therapy for NHL [18,19]. Successful autologous and syngeneic SCTs for NK/T-cell lymphoma have been reported [8-10]. It is desirable that PBSCs are harvested while lymphoma is under good control [20]. However, NK/T-cell lymphoma is very aggressive and is difficult to control with conventional chemotherapy. As in the case reported by Sasaki et al [10], PBSCs were harvested when the disease activity remained. In our case, autologous PBSCT induced a first complete remission lasting 6 months. Considering the very aggressive clinical course including CNS invasion in our patient, autologous PBSCT seems to be one of the effective treatments for nasal NK/T-cell lymphoma.

Because autologous PBSCT is a relatively safe procedure, lymphoma progression and relapse are the main reasons for treatment failure after autologous PBSCT for NHL. The prognosis of patients with relapsed lymphoma after SCT is ominous. Usually, the second transplantation has limited antitumor effects with a significant regimen-related toxicity, and chemotherapy cannot induce a good response.

Our patient's NK/T-cell lymphoma relapsed 6 months after autologous PBSCT, and a single course of L-Asp treatment has induced more than 18 months of continued second complete remission. The effect of L–Asp in our patient was striking.

The high level of functional P-gp expression is thought to contribute to the chemo-resistance of NK-cell tumors [12,13]. One of the ways to circumvent the chemo-resistance of NK/T-cell lymphoma is to use anti-cancer agents that are not affected by P-gp. Obviously, the anti-cancer effect of L-Asp, which is deprivation of serum asparagines, cannot be affected by P-gp. This may explain the effectiveness of L-Asp in patients with nasal lymphoma and cutaneous T-cell lymphoma that seemed to be associated with EBV [21-23]. However, the actual reason that L-Asp is sometimes very effective against multidrug-resistant lymphoma remains to be elucidated. L-asparagine synthetase (AS) is an enzyme that makes L-asparagine from L-asparatic acid and L-glutamine, and cells that can upregulate AS have been reported to be L-Asp–resistant [24]. Recently, taking advantage of complementary DNA microarrays, Sherf et al reported a moderately high negative correlation (–0.44) between AS messenger RNA expression and L-Asp sensitivity in leukemic and lymphoma cell lines [25]. Thus, it would be interesting to evaluate AS expression in NK/T-cell lymphomas to predict L-Asp sensitivity. The outcomes with conventional chemotherapy regimens such as CHOP for advanced NK/T-cell lymphoma are discouraging [2,6-8]. Therefore, a front-line chemotherapy regimen containing L-Asp for treatment of NK/T-cell lymphoma may warrant further evaluation.

The establishment of an effective chemotherapy regimen can dramatically improve the prognosis of lymphoid malignancies. This improvement of prognoses has been demonstrated in the treatment of acute B-cell lymphoblastic leukemia (B-ALL) and Burkitt's lymphoma [26]. B-ALL shows aggressive clinical behavior and a very poor prognosis. However, the introduction of short-duration, very intensive treatment containing Cy and MTX has made the prognosis favorable. According to the treatment outcome of chemotherapy, the indication for SCT can be altered. Because nasal NK/T-cell lymphoma is relatively common in Asian countries, establishment of an effective treatment regimen is sought in Asian countries. The integration of an effective chemotherapy regimen containing L-Asp and SCT for NK/T-cell lymphoma seems to be a promising avenue.

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