A graft-versus-tumor effect in a patient with ependymoma who received an allogenic bone marrow transplant for therapy-related leukemia

Case report

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Graft-versus-leukemia effect is an immune-mediated antitumor phenomenon associated with allogenic bone marrow transplants (BMTs) for hematological malignancies, and recent findings have indicated that a similar effect could occur in some solid tumors such as breast cancers. The authors report on a 42-year-old man with a recurrent ependymoma who received an allogenic BMT for therapy-related leukemia. After transplantation, the patient developed chronic graft-versus-host disease, which was controlled with steroid agents. Interestingly, the recurrent ependymoma regressed steadily over the next 21 months posttransplant, until the tumor became almost undetectable on magnetic resonance images. This case indicates that the graft-versus-tumor effect, mediated by cytotoxic T cells, may be able to target intraparenchymal neuroepithelial tumors, despite the brain’s generally recognized status as an immunoprivileged organ.

KEY WORDS • ependymoma • graft-versus-host disease • therapy-related leukemia

A llogenic BMTs can induce a GVL effect in patients with hematological malignancies. There is also anecdotal evidence of a GVT effect in patients with solid tumors such as breast cancers and renal cell carcinomas. The GVL or GVT effect is believed to be caused by allogenic T lymphocytes, because 1) the risk of relapse of leukemia is much lower in allogenic transplant recipients than in patients receiving syngeneic transplants; 2) T-cell depletion in allogenic donor grafts increases the relapse risk; and 3) donor lymphocyte infusion delivers the GVL or GVT effect. Although such a favorable immune response could open a promising new window for better control of malignant neoplasms, no similar effect has been reported in neuroepithelial tumors. In this report, we describe a patient with a recurrent ependymoma that showed steady, long-term regression after an allogenic BMT, most likely because of the GVT effect.

Case Report

This 42-year-old man underwent subtotal removal of a right temporal tumor on July 12, 1993; the lesion was diagnosed as an ependymoma without malignant features on histological studies (Fig. 1). Three months postsurgery, the patient suffered a generalized seizure, and computerized tomography scanning revealed tumor recurrence in addition to a massive intratumoral hemorrhage in the right temporal lobe. Although he recovered well from the hemorrhagic event, the tumor increased rapidly in size, and the patient was transferred to our institution 7 months later. The tumor was subtotally removed in an operation performed in two stages in August 1994, and the histologically confirmed diagnosis of the tumor was again ependymoma. The MIB-1 staining index was 5% (Fig. 2).

The patient underwent postoperative radiochemotherapy; the radiation therapy consisted of 65 Gy in 33 fractions, and the chemotherapy consisted of nimustine (80 mg/m² administered intravenously on Day 1) and etoposide (80 mg/m² administered intravenously on Days 2 and 3), which was repeated every 2 months for 13 cycles over 2 years. The cumulative dosage of nimustine and etoposide amounted to 1560 mg and 3120 mg, respectively. The residual tumor remained stable on serial MR images obtained during this period. The patient developed severe leukopenia (peripheral white blood cell count 1800/µL, myeloblasts 2%) in May 1997, 8 months after the last dose of chemotherapy, and he underwent bone marrow biopsy sampling. The specimen revealed numerous myeloblasts, which was in accordance with the diagnosis of acute myeloid leukemia with maturation (French–American–British classification M2; Fig. 3). Chromosomal analysis was unsuccessful. Intensive antileukemia chemotherapy

Abbreviations used in this paper: BMT = bone marrow transplant; GVHD = graft-versus-host disease; GVL = graft-versus-leukemia; GVT = graft-versus-tumor; MR = magnetic resonance.
consisting of one cycle of 100 mg/m² cytarabine and 12 mg/m² idarubicin induced complete remission in June 1997, and was followed by two more cycles of consolidation chemotherapy.

On November 4, 1997, the patient underwent BMT with tissue from a human leukocyte antigen–matched, unrelated donor. The residual tumor volume before the allogenic BMT was performed was 14.6 ml, based on the enhancing mass on MR imaging, and calculated using Image software obtained from the National Institutes of Health. Two months later, the patient developed Grade II acute GVHD limited to the skin, which was well controlled with oral prednisolone (1 mg/kg/day). The size of the residual ependymoma decreased gradually after the BMT, and 21 months later, only a trace amount of tumor was visible along the edge of the tentorium on MR imaging, with no sign of recurrence (Fig. 4). The volume of the tumor was 1.8 ml in August 1999. Chronic GVHD caused respiratory dysfunction, however, and the patient died of pneumonia 30 months after the BMT, 83 months after the initial surgery. An autopsy was not performed.

**Discussion**

The temporal profile of the tumor reduction following the allogenic BMT in this case indicates that a GVT effect might have played a primary role in tumor control, although there is no direct evidence. The residual tumor did not change in size for a long time, despite the chemoradiotherapy, or even after intensive chemotherapy was administered to treat the leukemia. Instead, the tumor reduction started after the development of GVHD, which occurred 2 months after the completion of chemotherapy for leukemia and the subsequent BMT. No further chemo- or radiotherapy was given after the GVHD developed, and yet the tumor steadily decreased in size. Therefore, it was most likely that the tumor shrinkage was induced by the GVT effect.

Recruitment of the immune system seems to be an important aspect in developing novel strategies for treating intracranial neuroepithelial tumors. The brain is generally recognized as an immunologically privileged organ, and the frequent failure in clinical trials to use the immune system for brain neoplasms has been attributed, at least in part, to this unique status of the brain. On the other hand, there are numerous case reports and experimental studies describing remarkable tumor reduction or disappearance of malignant brain neoplasms after stimulation of the host immune system by various measures, such as lymphokine-activated killer cells, interleukin-2 therapy, and dendritic cell vaccination. In peptide-pulsed dendritic cell vaccination for malignant glioma, peripheral
Cytotoxic T lymphocytes were histologically detected in the tumor. Therefore, immunotherapy is apparently effective for some intracranial neuroepithelial tumors.

The GVT effect is generally considered to be inseparable from GVHD, a major complication associated with allogenic BMT, as was the case in our patient. In some recent studies, however, it has been shown that these favorable and unfavorable effects may be regulated somewhat independently, raising the possibility of using allogenic BMT as an antitumor immunotherapy.

Conclusions

Our case raises the possibility that the GVT effect of allogenic BMT may be used to target intraparenchymal neuroepithelial tumors, despite the general recognition that the brain is an immunoprivileged organ.

Acknowledgments

We thank Drs. Akio Asai and Keisuke Ueki for their help in reviewing the manuscript.

References


Manuscript received September 11, 2001. Accepted in final form April 16, 2002.
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