Combined immunoradiotherapy induces long-term remission of CNS relapse of peripheral, diffuse, large-cell lymphoma after allogeneic stem cell transplantation: Case study

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Relapse of peripheral non-Hodgkin's lymphoma (NHL) in the central nervous system commonly has a poor prognosis. Graft-versus-leukemia effects (GvL) contribute substantially to eradication of hematological malignancies after allogeneic stem cell transplantation. Few data are available describing GvL activity within the brain. We report the case of a man allografted for peripheral NHL. On day +83 after transplantation a CNS relapse of the lymphoma occurred. The brain was irradiated with 44 Gy, anti-CD20 antibodies were given, and the immunosuppression was withdrawn. Subsequently, limited-stage, chronic graft-versus-host disease occurred. The lymphoma regressed completely, and the patient has been in continuous complete remission for 30 months. The favorable course suggests substantial contribution of immunomodulation to excellent outcome. *Neuro-Oncology 7, 508–510, 2005 (Posted to Neuro-Oncology [serial online], Doc. 05-025, August 11, 2005. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152851705000256)*

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[2]Abbreviations used are as follows: BSCT, blood stem cell transplantation; EBV, Epstein-Barr virus; GvHD, graft-versus-host disease; GvL, graft-versus-leukemia effects; NHL, non-Hodgkin's lymphoma.

We report the case of a man who received an allogenic blood stem cell graft for peripheral high-grade non-Hodgkin's lymphoma (NHL).[2] After a CNS relapse of the lymphoma, the brain was irradiated with 44 Gy, and anti-CD20 antibodies were given. Limited-stage, chronic graft-versus-host disease occurred. However, the lymphoma regressed completely, and the patient has been in continuous complete remission for 30 months.

Case Study

A 24-year-old male suffering from a stage IV, diffuse, large-cell lymphoma ($CD20^+$, $CD79a^+$) with gastric (Fig. 1), hepatic, mediastinal, and pulmonary manifestations

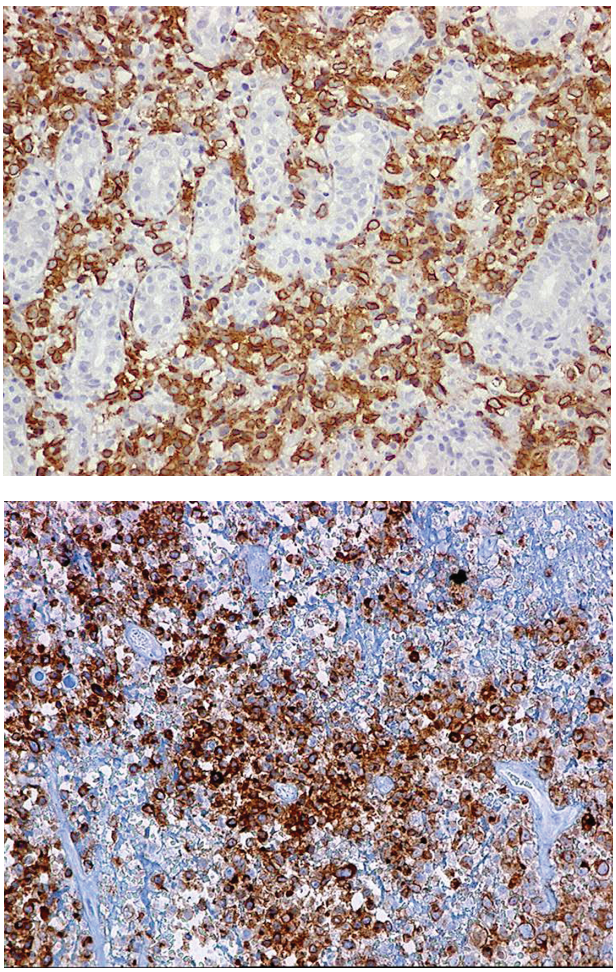

Fig. 1. Immunohistology (HE/anti-CD79a) stain of the primary lymphoma (top, biopsy from the stomach, obtained by endoscopy) and of the cerebral biopsy (bottom) obtained on day +83 after transplantation

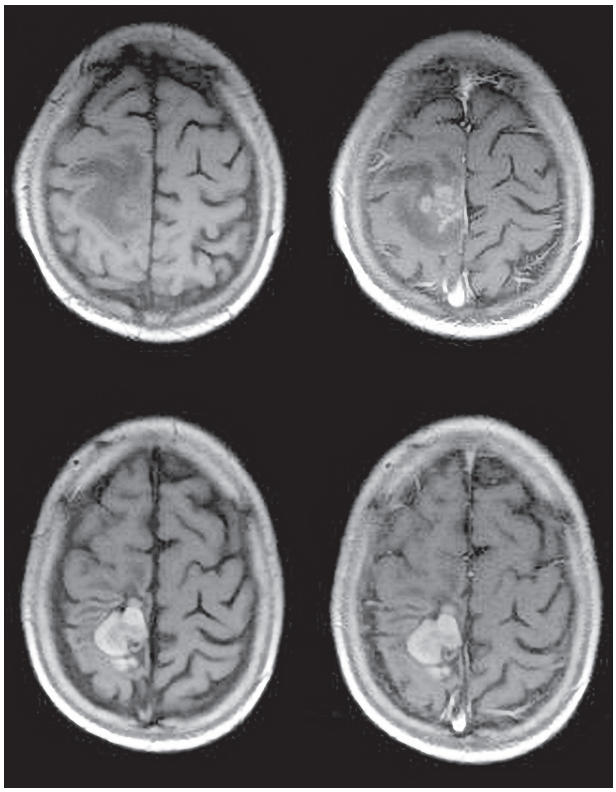

Fig. 2. MRI examination from day +50 (top) after transplantation and 18 months after transplantation (bottom). Left: Axial T1-weighted sequence. Right: Postgadolinium sequence.

was treated with six cycles of rituximab/CHOP (cyclophosphamide [750 mg/m^2; i.v., day 1] + doxorubicin [50 mg/m^2; i.v., day 1] + vincristine [1.4 mg/m^2; maximal 2 mg absolute, i.v., day 1] + prednisone [100 mg per day absolute; p.o., days 1–5]). Cytostatic therapy had to be reduced because of renal impairment, and autologous stem cells could not be harvested. CNS involvement was excluded at diagnosis and prior to hematopoietic stem cell transplantation by MRI. Since only a partial remission was reached, the patient was allografted from his serologically human leukocyte antigen–matched sister. He was conditioned with treosulfan/fludarabine and grafted with 4.5×10^6 CD34$^+$ cells/kg body weight (Casper et al., 2004). Cyclosporin A and methotrexate were given for chronic graft-versus-host disease (GvHD) prophylaxis. Leukocytes engrafted on day +8 after transplantation, and the patient was discharged on day +36.

On day +50 the patient was readmitted because of seizure and paresthesia. MRI examination showed a tumorlike lesion in the right parietal subcortex with contrast enhancement and perifocal edema (Fig. 2, top). Examination of blood and cerebrospinal fluid gave no evidence for atypical cells or infection, and peripheral relapse of NHL was excluded. Biopsy was not performed because of the localization of the lesion. Under the assumption of an infectious complication, an empiric antimicrobial therapy was started.

On day +83 intracerebral bleeding occurred in the area of the lesion requiring neurosurgical intervention. Immunohistology of a biopsy showed an Epstein-Barr virus (EBV)–negative, high-grade NHL positive for CD20 and CD79a, histologically identical to the primary manifestation (Fig. 1). The clonal identity of the intracerebral and the primary lymphoma was demonstrated by homology of the CDR-3 sequences amplified from both lesions (Dolken, 2001).

Cyclosporin A was discontinued, two i.v. doses of rituximab were given, and the neurocranium was irradiated with 44 Gy. Limited GvHD occurred, and the hemiplegia regressed nearly completely. Eighteen months after transplantation a continuous remission of lymphoma was documented by cranial MRI and whole-body CT scan. On T1-weighted images there is a hyperintense bleeding in the resection area. The postgadolinium T1 sequence shows no enhancing lesion and regression of perifocal edema (Fig. 2, bottom).

Discussion

NHL after allogeneic stem cell transplantation is in the majority of cases a manifestation of the so-called EBV-associated lymphoproliferative disease and positive for viral proteins and nucleic acids (Curtis et al. 1999). The CNS lymphoma reported in this case could be clearly be identified by molecular and immunological methods as identical with the primary peripheral lymphoma and was negative for EBV.

CNS relapse of successfully treated peripheral high-grade NHL after allogeneic blood stem cell transplantation (BSCT) is rare and usually associated with an aggressive course of the disease, including infiltration of the bone marrow and a poor prognosis (van Besien et al., 1998). Graft-versus-leukemia/lymphoma effects are essential for the eradication of residual hematological malignancies after allogeneic BSCT (Kolb et al., 1990), but very limited information is available about graft-versus-leukemia activity within the CNS. One case of a primary CNS NHL treated with allogeneic peripheral BSCT has been described: The manifestation of acute GvHD could be correlated with the disappearance of intracerebral lymphoma (Varadi et al., 1999). In addition, donor-derived lymphocytes have been detected in the cerebrospinal fluid after transplantation (Hibi et al., 1997). Furthermore, the successful treatment by allogeneic BSCT of patients with isolated CNS relapse of acute leukemia has been published (Classen et al., 2003). Usually, multimodal therapy is not sufficient to cure an intracerebral relapse of lymphoma (van Besien et al., 1998). The favorable outcome observed in our patient, that is, a complete remission after CNS relapse of a highly malignant NHL lasting now for more than 30 months, seems to be due to the combined effects of radiotherapy, anti-CD20 application, and graft-versus-leukemia reactivity.

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