The Outcome of Large B-Cell Lymphoma Evolving in a Hematopoietic Stem Cell Transplant Patient During Treatment of Chronic Graft-Versus-Host Disease

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ABSTRACT

Immunosuppression is a risk factor for the development of posttransplant lymphoproliferative disorder. This type of malignancy developed in an immunocompromised man. The patient presented with focal convulsion starting from right face and right arm followed by two generalized convulsions with one minute interval. Diagnosis was made by computed tomographic (CT) scan of the cranium following oral and intravenous administration of contrast dyes which revealedmass leisons in the frontotemporal lobe and by stereotaxic biopsy. Tissue sections showed a malignant tumor cell infiltration with large areas of necrosis and many mitoses. Many tumor cells were positive for CD 20 and CD 10. These findings were consistent with large B-cell lymphoma. Central nervous system radiation with a dose of 56 Gy was given with clinical and radiological improvement. The patient died due to multiorgan failure. Finally, the immunocompromised patients should be closely followed for the development of lymphoproliferative disorder.

Key Words: Immunosuppression, Lymphoproliferative disorder, Primary cerebral lymphoma, GVHD, AML.

ÖZET

Hematopoietik Kök Hücre Nakli Yapılan Bir Hastada, Kronik Graft-Versus-Host Hastalığı Tedavisi Sırasında Ortaya Çıkan Büyük B-Hücreli Lenfoma

İmmünsüpresyon nakil sonrası lenfoproliferatif hastalık gelişmesi için risk faktörüdür. AML nedeni ile nakil yapılan bir erkek hastada sağdan başlayan ve iki jeneralize konvülziyon gözlenmesinin ardından çekilen BT taramada kitle lezyonlu saptanmış ve yapılan stereotaksik biyopsi ile CD20 ve CD10 pozitif büyük B-hücreli lenfoma tanısı konmuştur. 56 Gy dozunda SSS ışınlaması yapılan hastada klinik ve radyolojik düzelme saptanmış, ancak hasta multiorgan yetmezliği ile kaybedilmiştir.

Anahtar Kelimeler: İmmünsüpresyon, Lenfoproliferatif hastalık, Primer beyin lenfoması, GVHH, AML.

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INTRODUCTION

The risk for posttransplant lymphoproliferative disorder (PTLD) in hematopoietic stem cell transplant (HSCT) recipients is lower than solid organ transplant recipients and it occurs in the former group particularly when T-cell depleted marrow or anti-T cell antibody treatment was given[1,2]. PTLD are a diverse group of pathologic entities that vary from reactive-looking morphologies to a picture indistinguishable from that of immunoblastic non-Hodgkin's lymphoma (NHL)[3]. We describe a patient with acute myeloid leukemia (AML) who received unmanipulated allogenic HSCT and developed central nervous system (CNS) lymphoma during treatment of chronic graft-versus-host disease (GVHD).

A CASE REPORT

A 36-year-old man was referred for HSCT as being AML (FAB; M2), in September 1997. He achieved complete remission after induction chemotherapy with idarubicin and cytarabine. This was followed by two cycles of the same regimen as consolidation. After two months from the last chemotherapy he received unmanipulated peripheral blood stem cells from his HLA-identical brother, in March 1998. The conditioning regimen consisted of busulphan and cyclophosphamide. Cyclosporine (CsP) and short-term methotrexate were given as acute graft-versus-host disease (GVHD) prophylaxis. His early post-transplant course was remarkable only for upper gastrointestinal bleeding due to an old duodenal peptic ulcer. Full hematological recovery was achieved and chimerism analysis revealed complete chimerism which was determined with polymorphic DNA markers by amplifying of these with PCR.

On day +104, he was readmitted with constitutional symptoms and bilateral enlargement of cervical nodes. A mild lymphocytosis with atypical mononuclear cells were detected on peripheral blood smear. He was commenced on nonsteroid antiinflammatory drugs. Bacterial infection was excluded by sterile cultures of blood and throat. Before transplantation, both patient and the donor were seropositive for herpes simplex virus, Epstein-Bar virus (EBV) and cytomegalovirus. They were HIV seronegative and had no known risk factors for HIV infection. During that time a seroconversion was not documented for these. The clinical picture was accused to an unidentified viral infection. These symptoms and signs completely disppeared in a couple of days without any specific treatment.

In July 1998, lichenoid lesions on oral mucosa, patchy hyper pigmentation, reticular mottling in the skin, mild hair and nail loss, with a gradual increase in serum cholestase enzyme level (ALP: 861U/L, GGT: 361U/L) were noted on his rotuine examination. Serum ALT and AST levels were less than one times elevated. Hepatitis C virus RNA and hepatitis B virus RNA were negative. The clinical picture was interpretated as chronic GVHD as extensive form. CsP's dose was increased to the full dose (12.5 mg/kg/day) depending on renal function as indicated by serum creatinine level. The patient failed to response to the escalating of CsP's dose and methylprednisolone was added to the treatment at a dose 2 mg/kg/day for two weeks followed by rapid tapering to 1 mg/kg/day on alternated days when GVHD had improved as returning of enzyme levels to normal. On the first month of this treatment, day +169, a focal convulsion started from right face and right arm followed by two generalized convulsions with one-minute interval complicated the clinical picture. The neurological examination did not reveal any focal deficit. The cerebrospinal fluid (CSF) protein content, cell counts and computed tomography (CT) of the brain were normal. The combined administration of CsP and corticosteroid was thought to be the probable cause of convulsions related to metabolic shifts, hypertension and fluid retention as well as direct CsP related toxicity and cerebral edema. T_2 sequence abnormalities on magnetic resonance imaging, which may occur as CsP caused CNS toxicity was not evaluated. Was withheld and restarted at reduced dosage with phenytoin prophylaxis. The patient gave up phenytoin on himself after 75 days. Chronic GVHD manifestations showed apparent regression. Consecutively, steroid dose tapered gradually and stopped. Subsequently CsP's dose was started to decrease.

On day +302, impairment of concentration, a mild confusion for names and faces were noticed by his family, which was followed by a new episode of seizure.

DISCUSSION

Although primary CNS lymphomas are relatively rare tumors in general population, they are the most common intracranial lesions in all organ transplant re-

cipients, so that CNS lymphomas should be suspected whenever a transplant patient has neurological symptom however minor, and prompt work-up is essential to eliminate other possible causes[2,4]. There are few reports about the natural history and the outcome of the PTLD after HSCT. Unlike our patient, patients reported as having PTLD after-HSCT had usually developed acute steroid resistant GVHD and received therefore anti-T cell therapy[2]. In our case, the immunsuppression induced by chronic GVHD itself and its long-term treatment with CsP and steroid, are the probable contributing factors to the lymphoma genesis as reported previously[5]. CNS involvement at presentation of a PTLD is mainly seen as part of very extensive disease similar to the clinical picture seen in systemic non-Hodgkin's lymphoma and the most of lesions seen in PTLD involved the brain parenchyma whereas meningeal involvement was uncommonly seen in transplant recipients[3,4]. The most successful treatment is not defined yet. Reduction in immunosuppression is generally the first step. After that, surgical resection, local radiation therapy (for anatomically limited disease) and/or chemotherapy (systemic or intrathecal), alpha-interferon can eradicate the disease. In HSCT setting, there are reports of long term remission with donor derived EBV-specific T cells or monoclonal antibody treatment against B-cells[5].

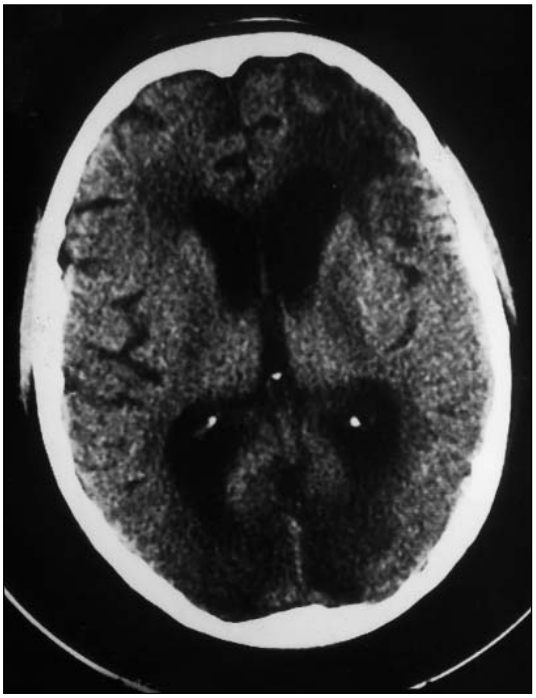

Figure 1. Computed tomography of the brain revealing a two contrast-enhancing mass lesion in the left frontotemporal area.

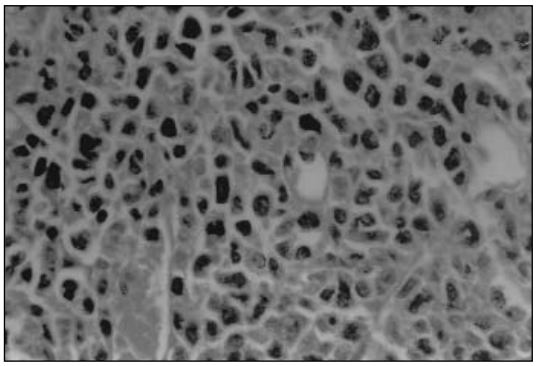

Figure 2a. Biopsy specimen from the mass lesion showing atypical neoplastic lymphoid infiltration (hematoxylin eosin stain, original magnification x 600).

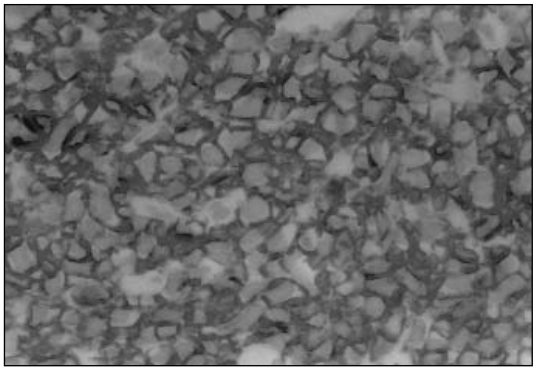

Figure 2b. Immunohistochemical analysis on paraffin-embedded sections of the mass lesion showing tumor cells expressing the CD20 molecule (AEC, X 600).

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