Epstein-Barr Virus-Negative Lymphoproliferative Disorders after Liver Transplantation

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Abstract: Lymphoproliferative disorders following liver transplantation are often Epstein-Barr virus (EBV)-related high-grade B cell lymphomas. EBV-negative and low-grade lymphoma is a very rare condition after cadaveric as well as living donor liver transplantation (LDLT). Herein we report a case of follicular lymphoma with negative EBV viral capsid antigen (VCA), IgM, IgG and Epstein-Barr virus-encoded small RNA (EBER), which developed after LDLT, and review the literature pertaining to EBV-negative post-transplantation lymphoproliferative disorder (PTLD) after liver transplantation.

Key Words: Follicular lymphoma, living donor liver transplantation, positron emission tomography with computed tomography, Epstein-Barr virus, lymphoproliferative disorders.

INTRODUCTION

Among lymphomas that develop after transplantation, post-transplantation lymphoproliferative disorder (PTLD) is well known. PTLD is mostly of B-cell origin and is often associated with active infection by Epstein-Barr virus (EBV), an oncogenic herpes virus observed in most patients with PTLD. With the rise in the number of patients undergoing organ transplantation, the incidence of PTLD has also increased, with a reported incidence of 2-4% and a mortality exceeding 50% [1]. The etiology of this disease varies depending on the extent of immunosuppression and the type of organ transplanted. Heart, liver, lung, and intestine allografts are at greater risk for PTLD than renal allografts. Also, primary EBV infection in young solid-organ transplant patients and treatment with cyclosporine are risk factors for PTLD development. As many as 90% of all PTLD cases are triggered by primary EBV. EBV infection occurring in the first 3-5 months after transplantation in patients with pretransplant seronegativity for EBV infection is a risk factor for development of PTLD.

Although the majority of lymphomas developing after solid organ transplantation are EBV-associated, high-grade, B-lineage lymphoid neoplasms, a recent increase in EBV-negative PTLD has been noted [1, 2]. Most cases of PTLD occurring after organ transplantation belong to the polymorphic and diffuse large B-cell type that is related to EBV. Low-grade B-cell lymphomas, such as follicular lymphoma, are very rare [3].

With the aim of characterizing the clinical features and outcomes of non-EBV-related low-grade B-cell lymphoma after liver transplantation (LT), we report a case encountered at our department, and review the literature pertaining to all reported cases of this type of neoplasm. No cases in living donor liver transplantation (LDLT) recipients have been identified up to now.

CASE REPORT

Under a diagnosis of primary biliary cirrhosis, a 60-year-old woman underwent LDLT (left lobe graft) in February 2002. On the 23rd postoperative day, she developed tacrolimus-induced encephalopathy and the immunosuppressive agent was therefore switched to CsA (Neoral; Novartis, Basel, Switzerland). Her recent medical record indicated that abdominal CT conducted in October 2004 had demonstrated swollen lymph nodes around the upper abdominal aorta. Positron emission tomography with computed tomography (PET/CT) showed marked accumulation of the radionuclide at the para-aortic lymph nodes in the upper abdomen (Fig. 1). The blood soluble IL2 receptor content had increased to 659 U/ml (normal: 135 to 483 U/ml, Fig. 2), suggesting the
The presence of a malignant lymphoma. The patient showed negativity for EBV VCA, IgM, and IgG before transplantation and positivity for those parameters (×160) after. Similar results were also obtained from the donor. The dosage of Neoral (120 mg to 80 mg) was reduced to give a blood concentration of less than 100 ng/ml, and steroid (Medrol 4 mg) administration was discontinued. The IL2 receptor level was determined and PET/CT was conducted periodically while the patient was placed under observation. Although the tumor did not seem to increase in size, the soluble IL2 receptor level rose to 1,350 U/ml. Patient lowest white cell count was 3.50 x 10^9 /l pre LDLT. Post LDLT level of white cells was range 7.0 to 8.0 x 10^9 /l until time of lymph node development. There was not differential white cell counts time of LDLT, post LDLT and lymph node development. Tumor extirpation was contemplated, but the patient developed cholangitis due to choledocholithiasis in September 2005. In October, she underwent choledocholithotomy with T-tube drainage and para-aortic lymph node resection (Fig. 3). An immunohistological examination showed that the lymph nodes had been affected by a low-grade follicular lymphoma (Fig. 4a, b and c). However, Epstein-Barr virus-encoded small RNA (EBER) was negative (Fig. 5). One year after the operation, no hot spot was evident in the abdomen by PET/CT and the soluble IL2 receptor level was reduced to 706 U/ml. For postoperative adjuvant therapy, administration of rituximab (MabtheraR, Hoffman-La Roche AG, Grenzach-Whylen, Germany) was considered but rejected because the lymphoma was of low-grade malignancy and the patient did not wish to undergo this mode of chemotherapy. She is currently under observation.

**LITERATURE REVIEW**

A medline search was conducted to identify reported cases of EBV-negative PTLD in liver transplant patients.
from January 1963 to August 31, 2007 using, “EBV-negative” and “liver transplant” as index terms. A secondary search was performed to include references cited in the articles obtained by the initial search. Recently diagnosis of EBV infection has been made by EBER in situ hybridization (ISH) [4], positive reactions. It has been said that histological grade 3 indicates a poor prognosis in comparison with grade 1 or 2. The literature lists two previous cases of follicular lymphoma that developed after liver transplantation [4], but the present case is the first reported to have developed after LDLT.

PTLD is a lymphoma observed after transplantation, and occurs particularly frequently among young children after kidney or heart transplantation [11]. Although various etiological factors have been considered, the use of antilymphocyte antibodies and EBV infection are commonly cited. PTLD develops particularly frequently in EBV-seronegative recipients who have received organs from EBV-seropositive donors. With the recent increase in the frequency of transplantation, PTLD has begun to occur occasionally in EBV-negative patients, the increase amounting to 20% of this population group. For diagnosis, PTLD is classified morphologically as follows: 1) early lesion; 2) polymorphic PTLD; 3) monomorphic PTLD of diffuse large cell lymphoma or Burkitt-like lymphoma; and 4) T-cell type lymphoma [12]. Furthermore, EBER or the Epstein-Barr virus latent protein (LMP) is used for immunohistological diagnosis [11]. Recently, however, there have been reports of cases such as the present one that do not belong to any of these four categories and are EBER- or LMP-negative. There is no clear-cut diagnostic standard determining whether this B-cell-type lymphoma should be categorized as a common malignant lymphoma or as PTLD.

The treatment of a lymphoma that occurs after transplantation starts with reduction in the dosages of immunosuppressants, and if the patient is EBV-positive, antiviral therapy is instituted. If the lymphoma is aggressive, chemotherapy is added. For the treatment of non-Hodgkin’s lymphoma, rituximab, a chimeric monoclonal anti-CD20, recently introduced as a first-line therapy, has proven to be effective [11]. For the present case, postoperative use of rituximab was considered but subsequently rejected because the lymphoma showed low-grade malignancy and the patient refused its use.

To confirm the presence of PTLD, CT or PET has been employed. McCormack et al. reported that PET/CT was effective for localizing PTLD that had developed after liver transplantation. The use of CT simultaneously with PET, in particular, pinpoints the anatomical site of the lesion by radionuclide accumulation. This is considered to be very effective for pinpointing the site of a biopsy [13]. The efficacy of post-transplantation PET/CT is expected to improve further.

REFERENCES


