B-cell lymphoma in transplanted liver

Clinical, histological and radiological manifestations

Lisbeth Barkholt1, Hans Billing2, Gunnar Juliusson3, Anna Porwit4, Bo-Göran Ericzon1, and Carl-Gustav Groth1

1 Department of Transplantation Surgery, 2 Department of Radiology, and 3 Department of Medicine, Karolinska Institute, Huddinge Hospital, S-14186 Huddinge, Sweden
4 Department of Pathology, Immunopathology Laboratory, Karolinska Institute, Karolinska Hospital, S-10401 Stockholm, Sweden

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Abstract. An isolated, centroblastic lymphoma developed in a 25-year-old female liver transplant recipient in her liver graft a few months after transplantation. Her immunosuppressive therapy consisted of antithymocyte globulin, cyclosporin, corticosteroids and, periodically, azathioprine. Chromosome analysis showed the tumor to be of female origin, thus excluding the possibility of transfer from the male donor. The tumor cells expressed EBV nuclear antigen (EBNA). The tumor was located in the left lobe of the liver. It was successfully removed 11 months after transplantation by a hemihepatectomy following a very brief combined chemotherapy course, and was then found to be replaced by necrotic tissue. No further treatment for lymphoma was given, and the patient is now free from lymphoma 3 years after transplantation.

Key words: Liver transplantation - B-cell lymphoma - Liver transplantation

Viral infection is probably involved in the pathogenesis of the lymphomas seen in transplant patients. Epstein-Barr virus (EBV) seems to play a special role in this regard. EBV is B-cell lymphotropic with unique infectious and oncogenic properties. EBV causes infectious mononucleosis in humans, a benign self-limited polyclonal B-cell hyperplasia [7]. In immunosuppressed patients there is an increased oropharyngeal shedding of EBV [14]. EBV has also been strongly implicated as a cofactor in the pathogenesis of the B-cell lymphoproliferative diseases arising in organ transplant recipients [4]. There is a hypothesis of evolution from a polyclonal benign B-cell hyperplasia through an intermediate oligoclonal B-cell neoplasia into a monoclonal malignant lymphoma. The first may be reversible when immunosuppressive therapy is stopped, but the last is irreversible [4, 5]. Thus, in transplant patients many extranodal lymphatic tumor masses are associated with EBV, and the disease often occurs with unusual clinical and radiological manifestations [4, 8, 9]. Usually, the lesions are multifocal and appear about 4–6 months after transplantation [6].

Here we report an EBV-associated, isolated, monoclonal B-cell lymphoma in a liver graft which was successfully treated with brief combined chemotherapy followed by surgical removal.

Case report

A 25-year-old woman with a 13-year history of Wilson's disease developed an acute hepatic failure after general intravenous anesthesia for exeresis. The patient underwent orthotopic liver transplantation in July 1987. While waiting for a new liver the patient was in precoma and needed hemodialysis due to anuria. A few hours before the liver transplantation she had acute bleeding from esophageal varices.

For immunosuppression, prednisolone was given initially at 200 mg/day, which was tapered to 20 mg/day over a period of 6 days, together with 2 mg/kg azathioprine (AZA). During the first week, antithymocyte globulin (Fresenius, FRG) 3 mg/kg was added to the baseline therapy. An acute rejection episode was diagnosed on day 5, but it reversed. One week after transplantation, when renal function had improved, cyclosporin (CyA) at a dose of
prominent nucleoli (Fig. 1). Immunohistochemical staining, using clonal antibodies to T lymphocytes (UCHL1, Dakopatts, Denmark), HLA-DR-(Ia)-region (LN3, Biotest, FRG). Stainings with monoclonal antibodies of \( \lambda \) and \( \mu \) types in the tumor cells. The cells were also positive for the alkaline phosphatase-antialkaline phosphatase method [2], consisting of large cells with basophilic cytoplasm and one to three diffuse infiltrates of an anaplastic, malignant tumor, which consisted of several abdominal abscesses containing Candida were drained. Bone marrow suppression ensued and AZA was not used during months 4 and 5 after transplantation. Also CyA concentrations were kept low during this period and an acute biopsy-proven rejection of the graft occurred at 5 months. Solumedrone (1 g) was given and the prednisolone dose was tapered from 200 to 20 mg/day over 6 days, but serum bilirubin and \( \gamma \)-glutamyl continued to increase. Treatment was intensified with the OKT-3 monoclonal antibody (Ortho Pharmaceutical, NJ, USA), but this could only be given twice due to side effects. Hepatic enzymes, such as alanine and aspartate transaminases and \( \gamma \)-glutamyl transpeptidase then normalized within 1 week, and eventually bilirubin also normalized.

Diagnostic examinations, performed during months 4 and 5 because of a malfunctioning liver and remitting high fever (39°–40° C), revealed not only an acute rejection but also a focal intrahepatic lesion in the midline, expanding to the left liver lobe. This lesion was revealed by ultrasonography, computerized tomography (CT) (Fig. 3) and liver scintigraphy. A fungal abscess was suspected, but an ultrasound-guided puncture was unrevealing, and blood cultures were negative both for fungi and bacteria. When re-examined with CT scanning, the lesion was found to be growing at a rate of about 0.5–1 cm/month (Fig. 4).

Seven months post-transplantation a core biopsy was taken. Macroscopically the lesion had a pale, white-brownish soft appearance. Histologically there were areas of necrotic tissue with proliferation of large cells, and the findings were compatible with a fungal abscess or a malignant process. Two weeks later debridement was carried out, and a lump of partially encapsulated fibrotic tissue extirpated.

Histological examination of the extirpated liver tissue revealed diffuse infiltrates of an anaplastic, malignant tumor, which consisted of large cells with basophilic cytoplasm and one to three prominent nucleoli (Fig. 1). Immunohistochemical staining, using the alkaline phosphatase-antialkaline phosphatase method [2], showed the presence of monoclonal, cytoplasmic immunoglobulins of \( \lambda \) and \( \mu \) types in the tumor cells. The cells were also positive for HLA-DR-(Ia)-region (LN3, Biostest, FRG). Stainings with monoclonal antibodies to T lymphocytes (UCHL1, Dakopatts, Denmark), monococytes/macrophages (MAC, South General Hospital, Department of Pathology, South Laboratory, Southampton, England), muramidase, \( \alpha \)-1-antitrypsin and \( \alpha \)-1-antichymotrypsin (Dakopatts), cytokeratin (PKK1), vimentin (Labsystems OY, Finland), desmin and protein S100 (Dakopatts), were negative in the tumor cells. Thus, a high-grade malignant, B-cell derived lymphoma of the centroblastic polymorphic type (according to the Kiel classification [10]) was diagnosed.

Cytogenetic studies of the tumor cells showed the lesion to be of female origin, thus excluding the possibility of transmission with the graft from the male donor. Virological analysis revealed an association with EBV as demonstrated by the expression of EBV nuclear antigen (EBNA) in the tumor cells. Assay of the patient's IgG antibodies against EBV and EBNA before and after transplantation revealed stable titers.

Extensive radiological examinations failed to reveal any extrahepatic lymphoma. While waiting for the results of histopathological analyses of the tumor, antiviral treatment with acyclovir (5 mg/kg three times daily i.v. for 1 week, followed by 800 mg four times daily orally for 10 days) was started because of the hypothetical link between EBV infection and lymphoma. A weekly episcleritis and otoposipod-containing six-drug combination chemotherapy program for 12 weeks was intended, but after 2 weeks of therapy the patient refused further chemotherapy due to an acute psychic crisis. She had then developed a transient neutropenia and thrombocytopenia. In view of the high-grade malignant character of the tumor and the severe adverse reactions to the cytostatic therapy, it was decided to intervene surgically. Eleven months after transplantation the patient underwent a left-side hemihepatectomy with total extirpation of the lesion. No abnormal extrahepatic lymph nodes could be found. Histopathological examination of the liver specimen showed the lesion to consist of a neoplastic area with fibrotic granulated parenchyma along the margins but no malignant lymphatic tumor remained. No further anti-lymphoma treatment was given.

The patient was discharged 13 months after the transplantation. She is now, 3 years after the transplantation, mentally and physically well, with the exception of minor difficulties with walking because of a left-sided peroneus neuropathy. Postoperative chest X-ray and hepatic ultrasonography until the 3-year post-transplant control have not revealed any recurrence (Fig. 2). The patient's hepatic function parameters are also completely normal. At present, her immunosuppressive therapy consists of cyclosporin 10 mg/kg, azathioprine 1 mg/kg and prednisolone 10 mg per day.

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Fig. 1. Light microscopic findings demonstrating a centroblastic, polymorphic lymphoma (Hematoxylin and Eosin stain, \( \times 440 \)). (Courtesy of Finn Reinholt, MD, Department of Pathology, Karolinska Institute, Huddinge Hospital, Stockholm)