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B-cell lymphoma in transplanted liver

Clinical, histological and radiological manifestations

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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

It has been estimated that patients given immunosuppressive therapy have an approximately 100-fold higher incidence of neoplastic disease than an age-matched control population [12]. Most commonly seen are non-Hodgkin's lymphomas (10%–20% of neoplastic tumors). Lymphomas in immunocompromised patients are more often of high-grade malignancy and with extranodal localizations than lymphomas in the normal population. In transplant patients the risk of developing neoplastic disease is greater when several immunosuppressive drugs are used concomitantly, especially if the patients are overimmunosuppressed due to repeated antirejection treatments. The risk also varies with the kind of graft transplanted [1, 11, 15], since this determines the immunosuppressive regimen administered. Thus, heart–lung transplant recipients seem to have the highest overall incidence (33%) of lymphoproliferative disorders compared with patients who have had liver (4%) or kidney (2%) transplants [13].

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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

2 mg/kg i.v. was introduced. One week later AZA had to be discontinued because of leucopenia due to cytomegalovirus (CMV) infection and *Candida albicans* fungemia. During the second month AZA was again administered at a low dose. *Pneumocystis carinii* pneumonitis developed at 2 months and during the subsequent months 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 γ-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 γ-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 absess 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 λ and μ types in the tumor cells. The cells were also positive for HLA-DR-(Ia)-region (LN3, Biotest, FRG). Stainings with monoclonal antibodies to T lymphocytes (UCHL1, Dakopatts, Denmark), monocytes/macrophages (MAC, South General Hospital, Department of Pathology, South Laboratory, Southampton, England), muramidase, α-1-antitrypsin and α-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, antivirus 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 epirubicin- and etoposide-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 necrotic 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.

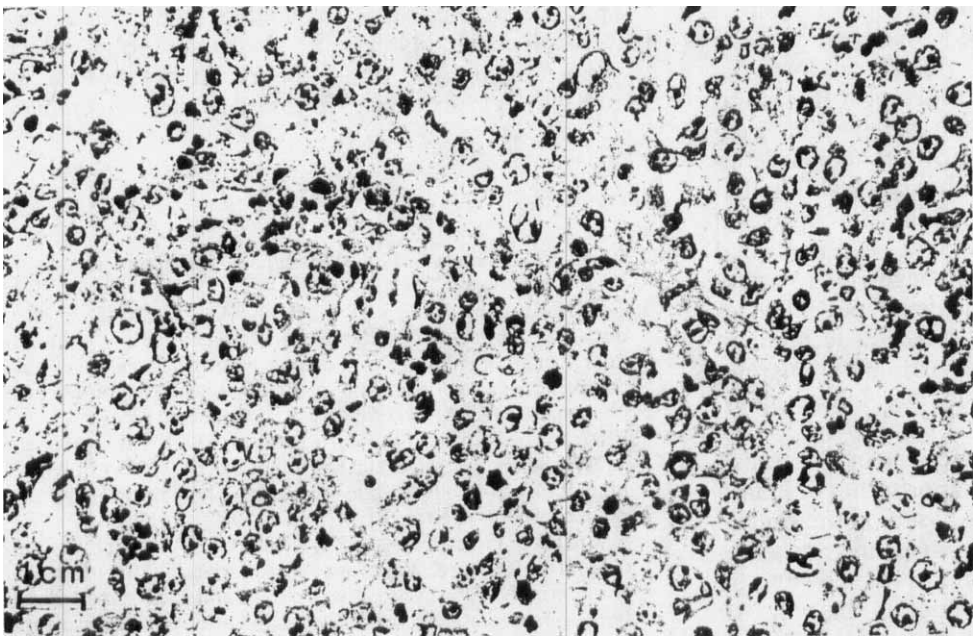

Fig. 1. Light microscopic findings demonstrating a centroblastic, polymorphic lymphoma (Hematoxylin and Eosin stain, × 440). (Courtesy of Finn Reinholt, MD, Department of Pathology, Karolinska Institute, Huddinge Hospital, Stockholm)

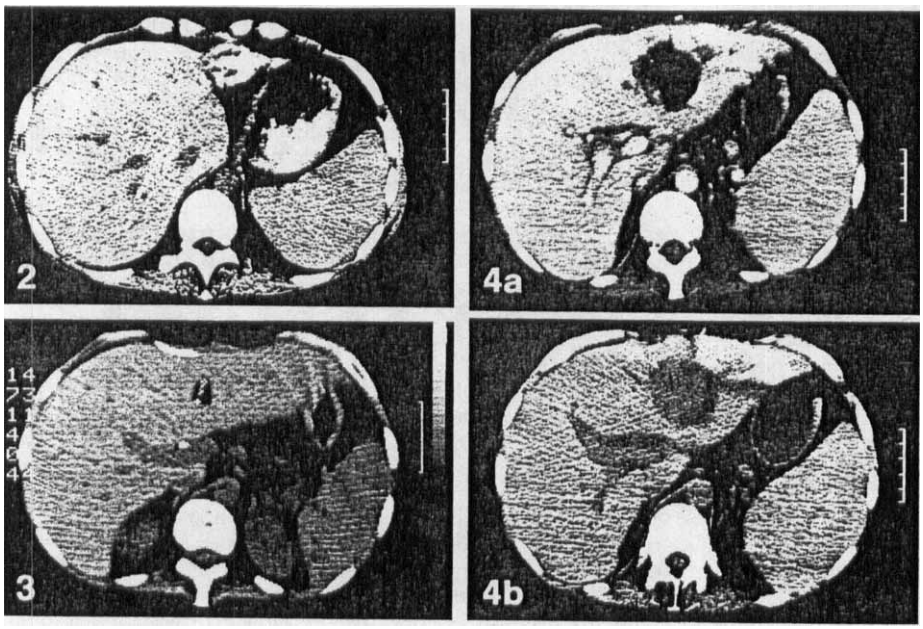

Fig. 2. CT scan with intravenous contrast demonstrating the liver transplant 4 months after a left hemihepatectomy without any recurrence of malignancy

Fig. 3. CT scan with intravenous contrast 2 months after liver transplantation demonstrating a lesion in the left lobe which was later diagnosed as a malignant B-cell lymphoma

Fig. 4. CT scans demonstrating the large lymphoma in the liver graft 9 months after transplantation. **a** With intravenous contrast; **b** without contrast. There is a central zone of necrosis which does not enhance with contrast

Discussion

Transplant patients treated in the pre-cyclosporin era were more prone to developing lymphoproliferative lesions in the central nervous system [16]. However, since cyclosporin combined with steroids became the standard immunosuppressive therapy in the late 1970s, the lymph nodes, the GI tract and the lungs have become the most common locations, and frequently there is involvement of several organs in combination with lymph node disease [6, 13]. In this regard our patient was an exception with an isolated solid lesion located in the liver.

According to previous reports [16], the time interval from transplantation until clinical attention to a lymphoproliferative disorder averages 44 months. However, in cyclosporin-treated patients, many such lesions have been radiologically diagnosed approximately 4–6 months after transplantation [6]. This could be due to better radiological investigation methods, or may be a consequence of the more potent immunosuppressive effect of cyclosporin. When the first CT scan performed 1 week post-transplantation was reviewed, it was found that a small lesion, 2 cm in diameter, was situated at the site of the neoplastic lesion. The nature of this lesion could not be established; it may have been a small lymphatic nodule, although focal fatty changes resembling this lesion have been described [17] (Fig. 3). After 10 weeks the lesion began to grow very slowly; later it grew more rapidly and developed into a lesion with a central necrotic zone which did not accumulate intravenous contrast. However, the surrounding margin, where the atypical, large polymorphic cells of the lymphoma were located, did stain (Fig. 4 a, b).

The histopathological features described by Frizzera et al. [3] together with the therapeutic approaches of Hanto et al. [4, 5] and Starzl et al. [13] are based on the central role of EBV and the development from a benign to a malignant lesion. The tumor in our patient was shown to be EBV associated, and had also developed in this way. An unusual feature was that the lesion was isolated to one side, while multifocal, extranodal lymphomas are the rule in immunocompromised patients. The rapid development of the tumor impaired its vascularization leading to a necrotic, central lesion. Rapidly growing tumors are often sensitive to chemotherapy, and B-cell lymphomas are generally chemosensitive. Interestingly, this tumor was totally replaced by necrotic tissue at the time of removal, despite the abbreviated chemotherapy program. Thus, this lymphoma might have been sterilized by the short cytotoxic treatment. In general the initial treatment of rapidly growing, but still isolated, tumors is a brief chemotherapy program to treat the minimal spread of the disease, followed by radiotherapy to cure the main lesion. While irradiation of the liver graft may be hazardous, and since the patient did not tolerate more chemotherapy, a surgical extirpation was considered to be a safer treatment.

Thus, we conclude that an isolated, high-grade malignant, B-cell derived lymphoma of recipient origin which developed in a liver transplant could be successfully treated with cytotoxic drugs followed by surgical removal.

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