A multilocular B-cell neoplasia presenting as multiple myeloma and polymorphic lymphoma of recipient origin 2 months after kidney transplantation in a heart-transplant recipient

M. Haas¹, Ch. Mannhalter², R. Ullrich³, I. Schwarzinger², A. Zuckermann⁴, K. Derfler¹ and U. Jäger⁵

1Internal Medicine III, Division of Nephrology, ²Institute of Molecular Biology, ³Institute of Clinical Pathology, ⁴Department of Cardiothoracic Surgery, ⁵Internal Medicine I, Division of Hematology, University of Vienna, Vienna, Austria

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Introduction

Lymphoproliferative disorders and other malignancies occur with a frequency of nearly 20% in immunosuppressed patients. Recent studies published by the Cincinnati Transplant Tumor Registry (CTTC), the Australian and New Zealand Dialysis and Transplantation Centre, the Collaborative Transplant Study Group, and the Leeds Transplantation Centre [1-4] report a significant increase of neoplasias in transplant recipients. Although the pattern of malignancies differs widely between the studies the appearance of non-Hodgkin lymphomas (NHL) in transplant recipients is closely related to the duration and dose of immunosuppression [5-8]. Patients requiring intensive immunosuppression, as in heart, lung or liver transplantation, are therefore at significantly higher risk of the development of lymphomas than kidney transplant recipients [1].

Weintraub et al. described a dramatic increase in post-transplant lymphomas for patients being transplanted more than once in comparison to single transplant patients (4% of recipients versus 4.3%) which probably is due to the high cumulative doses of immunosuppressive drugs [5].

We report the case of a heart recipient with end-stage renal failure 6 years after transplantation, who developed a multiple myeloma and polymorphic lymphoma shortly after kidney transplantation and antithymocyte globulin (ATG) therapy for an episode of acute renal rejection.

Case report

The patient was a 55-year-old man who had been suffering from non-insulin-dependent diabetes mellitus (NIDDM) for over 30 years. He presented at the hospital with ischaemic heart disease and acute myocardial infarction in 1988. One year later heart transplantation was performed. The immunosuppressive induction therapy consisted of perioperative OKT-3 (5 mg/day over 14 days), high-dose cortisone, and azathioprine.

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During this time kidney function decreased continuously. In July 1994 the patient underwent kidney transplantation (mismatch 2-1-1). Forty days later a kidney biopsy revealed acute transplant rejection. Administration of 100 mg prednisolone/day over 3 days had no influence on kidney function; hence ATG (200 mg/day for 14 days) and two additional cortisone bolus were given. The creatinine was decreased to 1.9 mg%, and the patient was dismissed shortly thereafter. Two weeks later the patient presented at our outpatient clinic with hepatosplenomegaly, fever, LDH of 620 U/l, haematocrit 28.4%, WBC 9.6 G/l, platelets 130 G/l and a creatinine of 1.93 mg/dl. The differential blood count showed reduced granulocytes (40%) and lymphocytes (6%), with increased atypical lymphocytes (24%). In the following days LDH increased to a maximum of 1300 U/l and WBC to 42 G/l. Electrophoresis showed a gamma globulin peak with normal alpha 1, alpha 2 and beta globulins. Immunofixation in the serum revealed an IgA lambda paraprotein, but was negative in urine. The serum IgA
concentration was increased sixfold (2600 mg/dl), IgG reduced to a third of the normal concentration (370 mg/dl) and IgM was within normal range. The lambda chain showed an increase (837 mg/dl; normal 110–240 mg/dl), kappa chain a marked decrease (94 mg/dl; normal 200–440 mg/dl), which made a $\kappa/\lambda$ ratio of 0.11.

Bone marrow biopsy was performed and showed diffuse infiltration with plasmacytic cells corresponding to a plasmocytoma. Immunohistochemical studies where positive for B cells and showed CD38, CD19, IgA and lambda chains. There were no osteolytic lesions detectable on radiological examination.

Gastroscopy revealed a CMV associated acute gastritis which was negative for EBV hybridization. Computer tomography on brain and chest were normal, but abdominal tomography showed hepatosplenomegaly and enlarged lymph nodes. Chemotherapy with CHOP (1 m$^2$ dose (dl: cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, vincristin 1.4 mg/m$^2$, and d1–d5: prednisolone 100 mg)) was started, but shortly thereafter the patient developed agranulocytosis and died from septicemia.

Post-mortem examination showed a polymorphic B-cell lymphoma in the transplanted kidney and lymph nodes, while atypical plasmacytic cells were still present in the bone marrow (Figure 1). The intestine, central nervous system, and heart transplant were free of malignant cells.

CDR3-PCR showed an immunoglobulin (Ig) rearrangement in tumour-affected material (lymph node and bone marrow) [9]. In order to determine the origin of the lymphoma, von Willebrand factor (VWF)—VNTR PCR was performed on heart, kidney, brain, and lymph nodes [10]. This technique allows the discrimination of tissue origins by the use of a hypervariable region with variations in up to 75% of individuals. The CDR-3 positive material was clearly of recipient origin. The transplanted kidney showed a different pattern (Figure 2).

**Discussion**

Post-transplant lymphoproliferative disorders (PTLPDs) are described as a morphological heterogeneous group of lymphoid neoplasms of different clonal composition driven by Epstein–Barr virus [11]. We show the development of a post-transplant lymphoma in a patient with heart and kidney transplantation. The patient had received OKT-3 and CsA at the time of his heart transplant and received additional ATG after kidney transplantation.

Opelz et al. reported 317 cases of non-Hodgkin lymphomas in 52775 transplant recipients (heart and kidney) and described an increasing risk of NHL in the first year after transplantation in patients with a higher cumulative dose of OKT-3 or ATG. Not the kind of antibody but the cumulation of immunosuppression seemed to be important for developing lymphomas [3]. An underlying EBV infection and impairment of T-cell-mediated regression [12,13] seemed finally to be the cause for lymphoproliferation and selection of malignant cells.

The lymphoma arose in a perirenal lymph node adjacent to the kidney transplant. The histology of this lymph node showed a polymorphic B-cell lymphoma. Interestingly the patient also had a clonal
Willebrand factor gene. The data clearly demonstrate post-transplant lymphoproliferative disorders can be divided into three categories: (1) plasmacytic hyperplasia, (2) polymorphic B-cell hyperplasia or polymorphic B-cell lymphoma, and (3) multiple myeloma or immunoblastic lymphoma [11].

Since the plasmacytic infiltration of the bone marrow was clearly clonal by CDR3-PCR, it corresponded to multiple myeloma rather than to plasmacytic hyperplasia.

The tumour cells in the lymph node were positive for EBNA and therefore represent the pattern of an EBV-associated post-transplant lymphoproliferative disorder. We have also determined the origin of the tumour in the lymph node by PCR for a variable number of tandem repeats (VNTR) region in the von Willebrand factor gene. The data clearly demonstrate the recipient origin. This is in accordance with the observations of Weissmann et al. who showed that the tumour usually arises from the host lymphocytes [14], although lymphomas of donor origin have been reported [15]. Weissmann presumed that the aggressiveness and spreading of the tumour relates to the alloantigens on the donor cells. Due to the high antigenicity of these cells the immune system may respond more effectively to tumours from donor origin. Therefore tumours from donor origin mostly remain local and respond more often to reduction of immunosuppression.

The mortality in patients with post-transplant lymphoproliferative disorder receiving chemotherapy is high. Morrison et al. described a total mortality of 81% in 26 patients receiving immunosuppression and different kinds of chemotherapeutic regimens [16]. No correlation was found between survival and type of lymphoma and the extranodal manifestations appeared to be irrelevant for prognosis.

The utmost effort must therefore be taken in preventing lymphomas, particularly in patients undergoing a second transplantation. Prophylactic acyclovir therapy might be promising in patients with known high total immunosuppression.

To prevent chronic antigenic stimulation, which is thought to induce Non-Hodgkin lymphomas in malaria and other chronic diseases, the graft match in repeated transplantations will be important and might impede lymphomas. Witherspoon et al. found a correlation between HLA mismatch and Non-Hodgkin lymphomas in bone-marrow recipients, and explained the post-transplant lymphoproliferative disorders as being induced by chronic antigenic stimulation due to inadequate HLA matching [17].

The present case stresses the fact that patients with double transplants are at particularly high risk for the development of lymphomas of recipient origin. In addition, the example also shows that lymphomas derived from one B-cell clone may present with various morphology at different locations.

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References

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Editor's note
Please see also the Editorial Comment by Opelz (pp. 1952–1954 in this issue).