Rapid Occurrence of Lymphoproliferative Disease After Pancreas-Kidney Transplantation Performed During Acute Primary Epstein-Barr Virus Infection

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Generalized lymphoproliferative disease occurred in a 30-year-old woman 15 days after she underwent simultaneous pancreas-kidney transplantation. Because of the rapid progression of this disorder, it was necessary to remove the grafts and discontinue immunosuppression 19 days after transplantation. Serological analysis demonstrated that the patient, who was Epstein-Barr virus (EBV)—seronegative 3 months before, was seroconverting at the time of the transplantation. EBV therefore was acquired just before the transplantation, either by a blood transfusion 4 months earlier or from the patient’s EBV-positive boyfriend. The latter source appeared most likely, as concluded from the investigation of the EBV strains from the patient’s boyfriend and from the blood and organ donors. Donor origin of lymphoblastoid cells was excluded by sex chromosomal analysis. Initiation of immunosuppression during a primary EBV infection carries the risk of very rapid development of B-cell lymphoproliferative disease. This emphasizes the need for active monitoring of EBV infections in transplant recipients and for the development of preventive strategies.

Case Report

A 30-year-old woman received simultaneous pancreas and kidney transplants from a male donor because of end-stage diabetic nephropathy due to diabetes mellitus type 1 that had been diagnosed at 12 years of age. She had been well in the period preceding the transplantation and had received a pretransplantation blood transfusion 4 months before. Immunosuppression was started on the day of transplantation with prednisone (100 mg/d for the first 3 days and 25 mg/d thereafter), azathioprine (1.5 mg/[kg • d]), cyclosporine A (1 mg/[kg • d] iv until day 6 and 4 mg/[kg • d] po thereafter during OKT3 therapy, followed by 10 mg/[kg • d] po), and OKT3 (5 mg/d from day 1 after transplantation for 10 days). Acyclovir (3,200 mg/d po) was administered as prophylaxis against cytomegalovirus, starting on day 6 after the procedure.

After the transplantation, both grafts were functional, as the patient had good renal function and was normoglycemic. On day 11 she complained of a sore throat and muscle pains. Pharyngitis was noted, and during the following days the maximum temperature was between 37.8°C and 38.7°C. A urinary tract infection with Enterococcus faecalis was treated with a 7-day course of amoxicillin.

From day 15 onward, rapidly progressive generalized lymphadenopathy developed. The next day, an exanthematous skin reaction developed, which was explained as an allergic reaction to amoxicillin. On day 17 after the transplantation, a lymph node excision was performed. Two days later the pancreas was painful and appeared edematous on CT scan examination, ascites developed, and multiple perfusion defects were observed in the kidney.
The serum amylase level increased during these 2 days from 301 U/L to 1,010 U/L (normal upper limit, 300 U/L), and the serum creatinine level rose from 107 μmol/L to 305 μmol/L. In view of the rapid progression of the generalized lymphoproliferative disease, it was decided to cease immunosuppressive therapy, which necessitated removal of both grafts. In addition, therapy consisting of monoclonal antibody to CD19, gammaglobulin, acyclovir, and IFN-α [5] was initiated.

This indeed led to rapid reduction of the lymphoproliferation. The patient recovered quickly, was treated with hemodialysis and insulin again, and shortly afterward prepared for a new transplantation. She had had a sexual relationship with a seemingly healthy male friend during the period of the first transplantation procedure.

Pathological findings. A biopsy of the donated kidney before transplantation revealed no abnormalities. The excised lymph node showed lymphoblastoid cells with B-cell characteristics (CD19- and CD30-positive). EBV-encoded RNAs in situ hybridization were positive in these cells. Immunofluorescence analysis of heavy and light chains of immunoglobulins demonstrated polyclonality. Examination of the resected kidney showed diffuse infiltration of the pyelum by large lymphocytes. The pancreas was partly necrotic and contained infiltrates of polyclonal B lymphoblastoid cells, as observed in the lymph node. Several thrombi were present in the pancreas as well as in the kidney.

The pattern of lymphoid infiltration was not suggestive of rejection. In situ hybridization with X and Y chromosome-specific probes [6] demonstrated that the lymphoblastoid cells were of female origin, which rendered it unlikely that this proliferation originated from male donor lymphocytes (figure 1).

The diagnosis was polyclonal posttransplantation EBV-related B cell lymphoproliferative disorder with secondary thrombotic events in both organs. There was no sign of monoclonal or oligoclonal B cell proliferation accompanied by electrophoretically homogeneous immunoglobulin components [7] in serum specimens obtained after transplantation, which made the existence of a widespread B cell clonal expansion less likely.

Virological findings. All specimens available from before the transplantation indicated that the patient was seronegative for EBV; the most recent sample dated from 3 months before the procedure. In a specimen obtained on the day of the transplantation, both IgG and IgM antibodies against EBV viral capsid antigen (VCA) were detected by several techniques, which included immunofluorescence on a P3HR1 cell line, a Gull ELISA for EBV VCA IgG and IgM (Gull Laboratories, Salt Lake City), and an Organon Teknika ELISA for EBV VCA IgG and IgM (Organon Teknika, Boxtel, The Netherlands).

Reactivity of IgG and IgM assays increased in the following weeks. After 2 months the IgM titer gradually decreased again. There was an increasing titer of antibodies against the EBV

Figure 1. The origin of the lymphoid infiltration in the kidney, derived from a male donor and explanted from the female patient, was investigated by in situ hybridization with use of X and Y chromosome-specific probes. A, Hematoxylin-eosin staining of the kidney explant showed glomerulus and atypical lymphoid infiltrates between tubules (original magnification, ×100). B, In situ hybridization with an X chromosome probe revealed atypical lymphocytes showing two dots (recipient origin) and tubular epithelial cells showing one dot (donor origin) (original magnification, ×400). C, In situ hybridization with a Y chromosome probe revealed tubular epithelial cells showing one dot (donor origin) (original magnification, ×400).
Fig. 2. Pattern of EBV serology in the patient, based on ELISA results (ELISAs for antibodies to EBV viral capsid antigen [VCA] and early antigen [EA]; Gull Laboratories, Salt Lake City). Ratio of measured extinction (optical density) to the cutoff value is given for each ELISA result: EBV VCA IgG (■), EBV VCA IgM (♦), and EBV early antigen IgG (dashes). The horizontal axis indicates dates of assays and the time intervals (in days) from the date of transplantation.
The consequences of this infection were serious, with early onset of rapidly progressive lymphoproliferative disease. PTLD is rare in the first month after organ transplantation [12, 13, 16, 17]; most described cases have presented at 2 months or later after the procedure. The occurrence of PTLD is generally considered to be the consequence of suppression of the T cell response directed against the expanding EBV-infected B cell clones [2, 18].
The institution of immunosuppressive therapy with an intensive induction scheme may pose special risks if a primary EBV infection is in the phase of maximal B cell proliferation, before the generation of specific cytotoxic T cells. This coincidence could well explain why PTLD developed exceptionally rapidly in this case.

This type of EBV infection is potentially hazardous, as it is less predictable than infection transmitted by the engrafted organ. It is relevant to all EBV-negative recipients in relationships with EBV-seropositive persons, but this circumstance is hardly amenable to preventive strategies. In any case, the described complications support the need for an active diagnostic approach toward EBV in EBV-negative organ recipients, starting before the transplantation and including detection of IgM antibody to the virus.

The use of antiviral therapy probably is most relevant in the early stages of active viral replication [5, 17], as acyclovir inhibits the viral DNA synthesis in the lytic cycle and not in the latent phase associated with lymphocyte proliferation. In this case, acyclovir was given from day 6 after transplantation onward, which is relatively late after the actual infection, and it did not prevent the clinical manifestations of PTLD. Cases attributable to transmission of EBV with the donated organ are more likely to benefit from early antiviral treatment or prophylaxis.

With more intensive initial immunosuppressive regimens and a gradually increasing proportion of EBV-negative recipients of organ grafts, the potentially severe consequences of EBV acquisition during or just before immunosuppression may become increasingly relevant to the care of transplantation patients.

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References