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CASE REPORT

Polyomavirus interstitial nephritis and concurrent post-transplant lymphoma in a renal allograft: coincidence or more?

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Summary

We describe a case of an Epstein–Barr virus (EBV)-negative post-transplant large B-cell non-Hodgkin lymphoma located in the renal allograft, spleen, liver and left inguinal lymph node of a renal recipient and accompanied by a simultaneous polyomavirus-associated nephropathy. To our knowledge, this is the first report of a simultaneous polyomavirus infection and post-transplant lymphoproliferative disorder.

Case report

A 19-year-old White male patient underwent a first renal transplantation because of renal failure due to lupus erythematosus disseminatus. Fourteen years later, he lost his graft to chronic rejection with transplant glomerulopathy and returned to dialysis therapy. After 7 years, he received a second renal allograft. Immunosuppressive therapy consisted of mycophenolate mofetil (MMF), tacrolimus and steroids. A first renal biopsy was taken on day 17 because of a rise in serum creatinine to 1.86 mg/dl. Besides discrete chronic lesions of donor origin, no features of acute cellular or humoral rejection were seen, or were viral inclusions. Eight months post-transplantation the patient underwent a second renal biopsy because of a rise in serum creatinine to 3.13 mg/dl. This time the cortex contained a patchy mixed inflammatory infiltrate without tubulitis. The tubular epithelium showed intranuclear inclusions, suspicious for infection by cytomegalovirus (CMV) on light microscopy. In the medulla, a dense lymphocytic infiltrate was present, consisting of large lymphoid elements with marked nuclear atypia. Unfortunately, it was impossible to differentiate the infiltrate or to confirm the CMV infection because of longstanding fixation of the tissue in Bouin's fluid and absence of lymphoid infiltrate in the frozen tissue. Therefore only the suggestion of a post-transplant lymphoproliferative disorder (PTLD) and a concomitant viral infection could be made. Abdominal ultrasound imaging at that time showed two suspicious lesions in the spleen and one in the liver and thickening of the left lateral and posterior capsular rim of the graft. The latter was compatible with fibrosis on nuclear magnetic resonance scan (NMR). Whole-body positron emission tomography after intravenous injection of 18 F-fluorodeoxyglucose (FDG-PET) confirmed the diagnosis of a lymphoma based on the

presence of hepatic and splenic lesions of increased metabolic activity and 'hot spots' in the left groin and the upper pole of the renal graft. Bone marrow aspirate and trephine bone biopsy were tumor-free. Computerized axial tomography imaging of the thorax showed no evidence of malignancy, confirmed by FDG-PET. A repeat renal biopsy contained a clearly malignant lymphoid population with marked cytological atypia and immunohistochemical positivity for CD20 and CD30, diagnostic for a diffuse large B-cell non-Hodgkin lymphoma with anaplastic features in the context of a PTLD. Again the adjacent tubular epithelium showed numerous intranuclear inclusions that remained negative on (repeated) CMV stains. As the tumor had developed asymptomatically within the first year post-transplantation, it was decided to stop immunosuppression, to perform a transplantectomy within a week and to maintain careful follow-up of the hepatic and splenic lesions before starting adjuvant treatment. Histological and immunohistochemical analysis and PCR (IgH, heavy chain gene rearrangement) of the transplantectomy specimen confirmed the earlier diagnosis of PTLD. Withdrawal of immunosuppressive therapy resulted in complete remission 4 months later with disappearance of hepatic, splenic and nodal lesions both on NMR imaging and follow-up FDG-PET scans.

Recently all microscopic slides of renal tissue were retrospectively re-evaluated as part of an unrelated research project (approved by the Local Commission for Medical Ethics and Clinical Studies), and the diagnosis of PTLD 8 months post-transplantation was confirmed. All biopsies were this time also stained for polyomavirus (monoclonal SV40 T Ag; Oncogene Research Products, Nottingham, UK; dilution 1/10) and Epstein–Barr virus (EBV) (monoclonal LMP-1; Dako Cytomations, Glostrup, Denmark; dilution 1/50). *In situ* hybridization for EBV was carried out [EBV (EBER) PNA probe; Dako Cytomations]. The inclusions in the second and third biopsy as well as in the transplantectomy specimen stained strongly positive for polyomavirus (Fig. 1), while the first, tumor-free biopsy was both morphologically and immunohistochemically negative for polyomavirus. EBV immunohistochemistry as well as *in situ* hybridization was negative on all biopsies. The *posthoc* diagnosis of a concomitant polyomavirus interstitial nephritis was made, characterized by a typical histological pattern B2 according to Drachenberg *et al.* [1], in the presence of an EBV-negative PTLD.

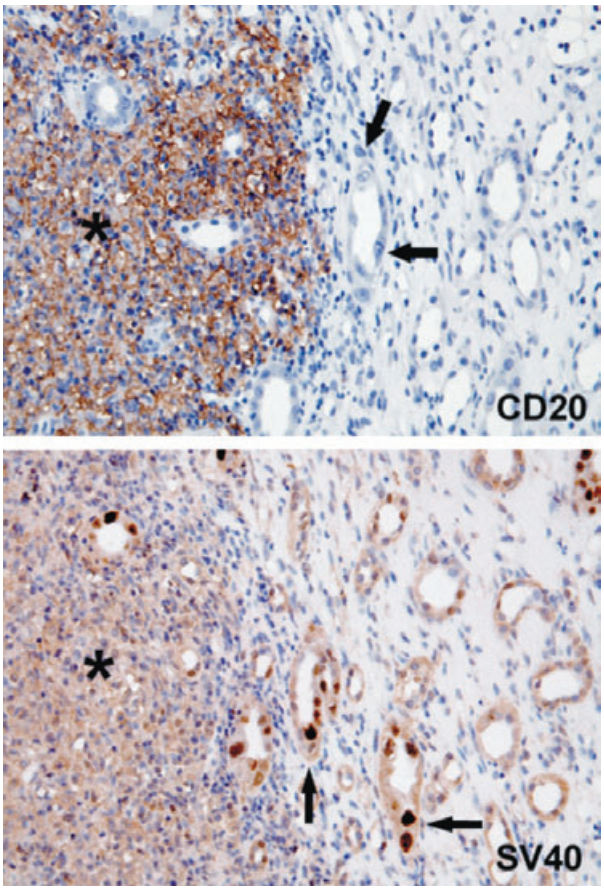

Figure 1 The post-transplant B-cell non-Hodgkin lymphoma (*) stains strongly positive for anti-CD20 (top panel), while the concurrent polyomavirus infection is demonstrated by strongly anti-SV40-positive intranuclear inclusions in the tubular epithelium. (original magnification 20×).

Discussion

Among solid organ transplants, renal allograft recipients are the least likely to develop PTLD (<1%), while the highest incidence occurs after intestinal transplantation, probably because of the large amounts of lymphoid tissue present in this type of allografts [2,3]. About 80–85% of PTLD are of B-cell lineage [3,4] and are usually EBV-related [5]. Immunosuppressive medication impairs EBV-specific cytotoxic T-cell responses, allowing viral replication and proliferation and ultimately malignant transformation of EBV-infected B-lymphocytes. Varying reports describe the type of immunosuppressive regimen, young recipient age, male gender, white race and simultaneous CMV infection as risk factors for PTLD, but the most important risk factor seems to be the EBV-seronegative status of the recipient, with a 20-fold higher relative risk in the first year post-transplantation compared with seropositive recipients [2].

In renal recipients, however, 50% of PTLD may be EBV-negative [3], as was the case in our patient. Serological EBV-IgM and -IgG testing at the time of diagnosis were both negative. This was confirmed by the negative EBV immunohistochemistry and *in situ* hybridization on

the tissue specimens. Due to the retrospective character of this report, confirmation by PCR is lacking.

As other viral agents have not been described in the etiology of PTLD, the simultaneous presence of polyomavirus-associated nephropathy exclusively in PTLD-containing biopsies, was an unusual finding. To our knowledge, polyomavirus has not been described in biopsies in the context of PTLD.

Polyomavirus was detected in the 1960s when murine leukaemia models developed a range of solid tumors [6,7]. For non-Hodgkin lymphoma particularly, several findings led to further research on a possible role for polyomavirus in its etiology: (i) it was known to infect man and to be oncogenic in mice, (ii) a substantial number of non-Hodgkin lymphomas were negative for EBV or HHV8, (iii) SV40, JCV and BKV DNA sequences were found in human B-lymphocytes suggesting lymphotropism of the virus [8–10]. Different groups confirmed the presence of SV40-specific DNA sequences in up to 42% of non-Hodgkin lymphomas, with the highest frequencies in large B-cell and follicular non-Hodgkin lymphoma [11–13]. One study reported JCV-specific DNA sequences [13], while no reports on BKV in non-Hodgkin lymphoma were found. However, these studies included different types of non-Hodgkin lymphomas, but none of them included PTLD. An interesting finding was that less HIV-infected patients with non-Hodgkin lymphoma carried the SV40-specific DNA sequences compared with HIV-uninfected lymphoma patients [11]. This could indicate that the presence of SV40 is not related to acquired immunodeficiency or it could mean that underlying mechanisms in the pathogenesis of HIV infection are competitive with polyomavirus infection. Nevertheless, the role of polyomavirus in the etiology of non-Hodgkin lymphoma remains controversial as a large British study failed to confirm the presence of these SV40 sequences [14].

Several risk factors have been associated with polyomavirus associated nephropathy. The most frequently reported cause of the sudden emergence of polyomavirus since 1995 [15] is the use of more potent immunosuppressive agents (such as tacrolimus and MMF) and high trough levels of tacrolimus, as the disease was absent in the cyclosporine era [16–22]. Our patient's tacrolimus trough levels varied between 9 and 14 mg/dl between transplantation and time of diagnosis of PTLD.

At our hospital, the first diagnosis of biopsy-proven polyomavirus-associated nephropathy was made in 2000 and up to now 31 cases have been described [including this (1999) and one other retrospective finding (1997)]. The anti-polyoma antibody we currently use is a 'pan-polyoma' antibody, cross-reacting with functional regions in the large T antigen of the virus, common to BKV as well as to JCV and SV40. Therefore we were unable to differentiate between the viral strains involved in this case. Serological or PCR detection methods for BK-polyomavirus were not available because of the retrospective nature of the report.

We cannot conclude from this case report whether polyomavirus plays a causal role in the development of PTLD or that it merely is a coincidental finding. However, the exclusive presence of polyomavirus interstitial nephritis in renal biopsies simultaneously containing lymphoma cells and the absence of the former in the first PTLD-free biopsy, suggests a possible association.

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