Case Report

Post-transplant lymphoproliferative disorder after kidney transplantation: time to adopt monitoring of Epstein-Barr virus?

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Although post-transplant lymphoproliferative disorder is a classical complication encountered after kidney transplantation, its diagnosis can still be challenging and its outcome life-threatening. Most cases are related to Epstein-Barr virus (EBV) infection and occur mainly in the first year post-transplant, favoured by the seronegative EBV status of the recipient transplanted with a kidney from a seropositive donor, and strong immunosuppression. We report the case of a young kidney-pancreas transplant recipient who developed post-transplant lymphoproliferative disorder (PTLD) early after transplantation, with a rapid fatal issue. We review the pathogenesis, clinical presentation, and management of PTLD with a focus on prevention.

Keywords: PTLD, Lymphoma, Transplantation, Epstein-Barr virus, EBV

Background

Kidney transplantation is the preferred treatment option for patients with end-stage renal disease.[1] With increasingly potent immunosuppressive therapy, the incidence of acute rejection has decreased over the past years, leading to better graft and patient survival. However, strong immunosuppression after transplantation is associated with high morbidity and mortality related to increased susceptibility to infections and cancers. Post-transplant lymphoproliferative disorder (PTLD) is a classical complication encountered after transplantation that can be life-threatening. Most cases are associated with Epstein-Barr virus (EBV) infection. Indeed, impaired T-cell immunity resulting from immunosuppressive treatment is unable to restrain proliferation of B cells infected by EBV, leading to uncontrolled proliferation of EBV-infected lymphocytes.[2]

We report the case of a young kidney-pancreas transplant recipient who developed PTLD early after transplantation, with a rapid fatal issue. We review the pathogenesis, clinical presentation, and management of PTLD with a focus on prevention.

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Case Report

A 32-year-old woman was transplanted in October 2012 with a combined kidney-pancreas graft from a deceased donor for end-stage renal disease secondary to diabetic nephropathy. Her past medical history was mainly characterized by type 1 diabetes diagnosed at age 12, complicated with retinopathy, neuropathy, dysautonomia (orthostatic hypotension and gastroparesis), and chronic kidney disease requiring haemodialysis from February 2012. Her serostatus at transplantation was negative for both EBV and CMV. The serostatus of the donor was positive for EBV and negative for CMV. At transplantation, she was administered an induction therapy with thymoglobulin. Serum creatinine and glycemia rapidly normalized. At discharge, treatment included tacrolimus (14 mg q.d), mycophenolate mofetil (MMF) (500 mg b.i.d), methylprednisolone (4 mg q.d), trimethoprim-sulfametoxazole (800 mg 3 × /week), acetylsalicylic acid (100 mg q.d) and ranitidine (150 mg q.d).

Fifteen days after transplantation, she was hospitalised for fever (38.3°C) with chills, and complained of diarrhoea and abdominal pain. Her blood tests were normal, including C-reactive protein level at 0.4 mg/dl. A complete evaluation including abdominal and chest computed tomography with contrast injection was not contributory. Stool culture revealed *Clostridium difficile* for which metronidazole was prescribed.

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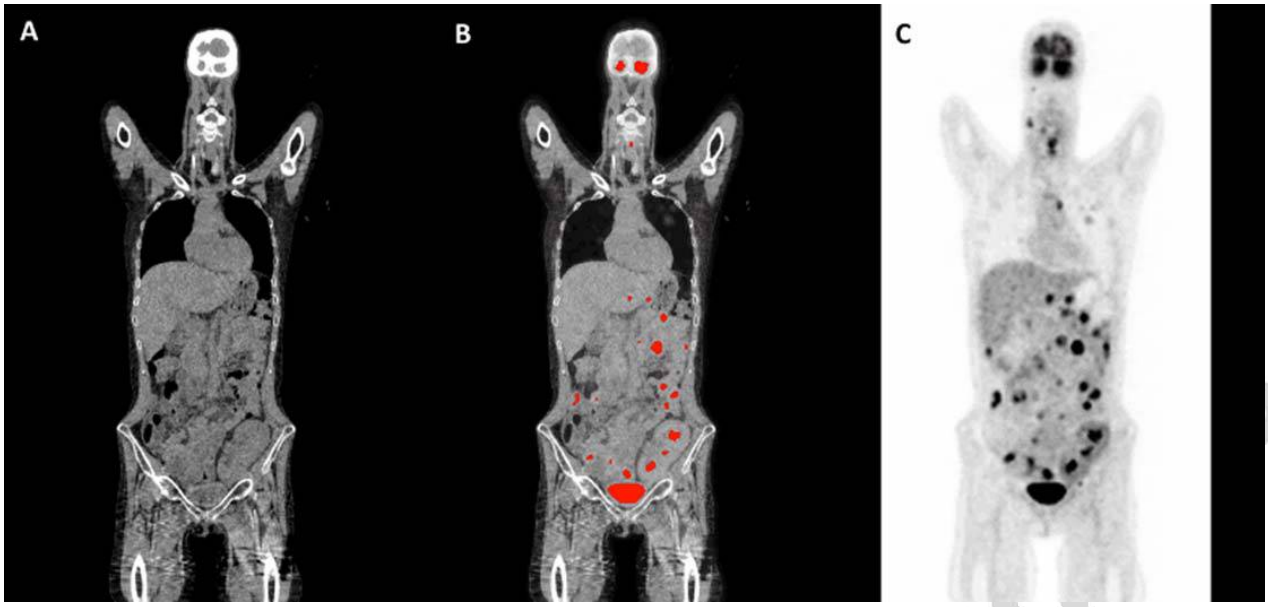

Figure 1 Positron emission computed tomography imaging after intravenous injection of ^{18}F-fluorodeoxyglucose (^{18}FDG). Coronal views (non-enhanced low-dose CT (A), FDG positron emission tomography (C) and fused images (B)) show multiple scattered foci of pathological accumulation of ^{18}FDG (arrow) in the native kidneys, liver, abdomen, lungs, upper part of the oesophagus suggestive of stage IV lymphoma.

Fever disappeared and the patient was discharged. At the outpatient clinic, she continued to complain of persistent diarrhoea. MMF was replaced by MMF delayed-release tablets, with no improvement. She was hospitalised 2 weeks later for a check-up. Stool cultures remained sterile. Laboratory results as well as CMV polymerase chain reaction (PCR) were unremarkable. MMF dosage was in the therapeutic range. Colonoscopy and colonic biopsies were normal; gastroscopy showed a fungal infection for which fluconazole was started. A celiac disease and malabsorption were ruled out. She was discharged but readmitted 3 weeks later for intermittent fever (37.5°C), sore throat, dysphagia, arthralgias and persistent diarrhoea with abdominal pain. Clinical examination was unremarkable, although the patient condition was altered. Blood tests showed increased C-reactive protein level (11.3 mg/dl), hypoalbuminemia, normal liver enzymes, and cholestasis (a twofold increase in gamma-glutamyl transferase and alkaline phosphatase values). Lactate dehydrogenase was increased (363 UI/l; normal value (NV) <240). A positron-emission computed tomography showed pathological fluoro-deoxy-glucose (FDG) uptake in the abdomen, liver, lungs, bones, retroperitoneal, cervical and in both kidneys (Fig. 1) suggestive in that context of stage IV lymphoma. EBV PCR showed a viral load of 28 924 copies/μg DNA. Excision of a 2 cm inguinal lymph node was performed. Grossly, the lymph node was necrotic. Microscopic examination identified a monomorphic B-cell PTLD with histological and immunophenotypic aspects of a diffuse large B-cell lymphoma CD20+ related to EBV (Fig. 2).[3] It was staged IVBb according to Ann Arbor, and the age-adjusted international prognostic index was calculated at III. MMF was immediately stopped and tacrolimus doses were reduced by half. An R-CHOP like chemotherapy including rituximab, cyclophosphamide and adriamycin was scheduled; it was decided to avoid vincristine because of the existing neuropathy. Unfortunately, the patient developed acute abdominal pain secondary to intestinal perforation of tumours requiring resection of part of the small intestine (Fig. 3). Severe sepsis consecutive to peritonitis contributed to acute renal function deterioration. Chemotherapy was nevertheless started, complicated by febrile neutropenia. Pulmonary aspergillosis and systemic candidemia were diagnosed and treated, but the patient rapidly succumbed at the intensive care unit.

Discussion

Post-transplant lymphoproliferative disorder encompasses a wide spectrum of lymphoproliferative disorders that range from infectious mononucleosis-like lesions and plasmacytic hyperplasia (early lesions) to highly invasive malignant lymphoma (monomorphic PTLD or classical Hodgkin lymphoma-type PTLD).[3] It is a relatively common malignancy after transplantation, ranking first in children and second in adults after skin cancer.[4,5] Although EBV-negative PTLD does occur, most cases are related to EBV infection and occur mainly in the first year post-transplant, in response to either primary infection with EBV or to re-activation of previously acquired EBV. Decreased T cell immune surveillance induced by immunosuppression favours

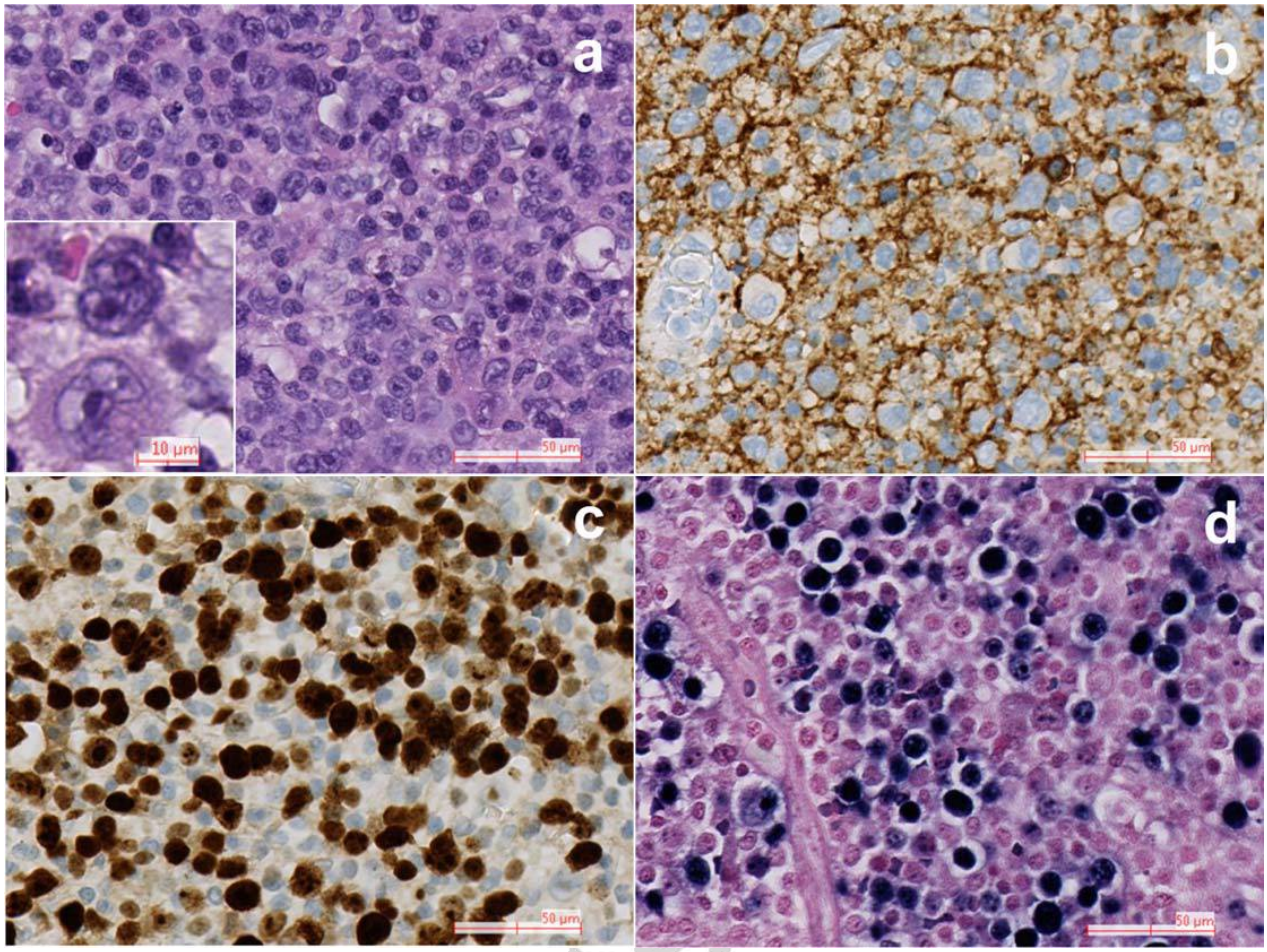

Figure 2 Monomorphic B-cell PTLD with histological and immunophenotypic aspects of a diffuse large B-cell lymphoma CD20+ related to EBV. Microscopic examination of the excised lymph node showed large areas of coagulative necrosis and a proliferation of polymorphic lymphoid cells of medium to large size with a voluminous nucleus containing one or more nucleoli (a). The tumour cells expressed CD20 (b), Bcl2, MUM1, c-Myc and occasionally CD30. Bcl6, CD15 and CD3 were negative. The proliferation index based on the Ki-67 immunostaining was 70% (c). Positive signals of EBV were detected in neoplastic cells by *in situ* hybridization with EBER probe (d).

proliferation of EBV-infected B lymphocytes.[6] The main risk factors for PTLD include EBV serostatus of the recipient and the degree of T-cell immunosuppression.[7–10] Our patient had both risk factors: heavy immunosuppression due to induction therapy and to the early post-transplant intense immunosuppression, and EBV-negative serostatus receiving kidney and pancreas organs from an EBV-positive donor.[2]

The clinical presentation of patients with PTLD varies from non-specific symptoms such as fatigue, weight loss, night sweats, and fever to more severe organ dysfunction or infectious complications. Commonly, patients present a mononucleosis-like syndrome associating lymphadenopathy, weight loss, fever and increased transaminase levels, or with gastrointestinal symptoms ranging from diffuse abdominal discomfort, loose bowel movement or diarrhoea to gastrointestinal bleeding or bowel perforation. Up to two-third of patients have extranodal organ involvement at presentation, that can involve the gastrointestinal tract, lungs, skin, liver, allograft, and central nervous system (CNS). In this latter case, the CNS can be the only site of the disease. Not infrequently, infiltration of the allograft can lead to allograft dysfunction.[8] Our patient presented with abdominal complaints and diarrhoea within the first month post-transplantation. A total digestive evaluation including abdominal computed tomography, colonoscopy and colon biopsies failed to diagnose PTLD, until she presented a few weeks later with a fulminant disseminated disease.

The cornerstone of therapy for PTLD is a reduction of immunosuppression. This strategy helps restoring T-cell-mediated immune response with the development of cytotoxic T lymphocytes against EBV-infected cells. As in our patient, mycophenolate mofetil is usually discontinued first, and calcineurin inhibitors doses reduced.[7] Rituximab, a humanized chimeric anti-CD20 antibody targeting B cells is used as an adjunct to reduction of immunosuppression or chemotherapy.[11] Risk factors for a poor response to anti-B cell therapy include late-onset PTLD (>1 year after transplant), CNS involvement, involvement of multiple viscera, and PTLD that lack expression of CD20.[12]

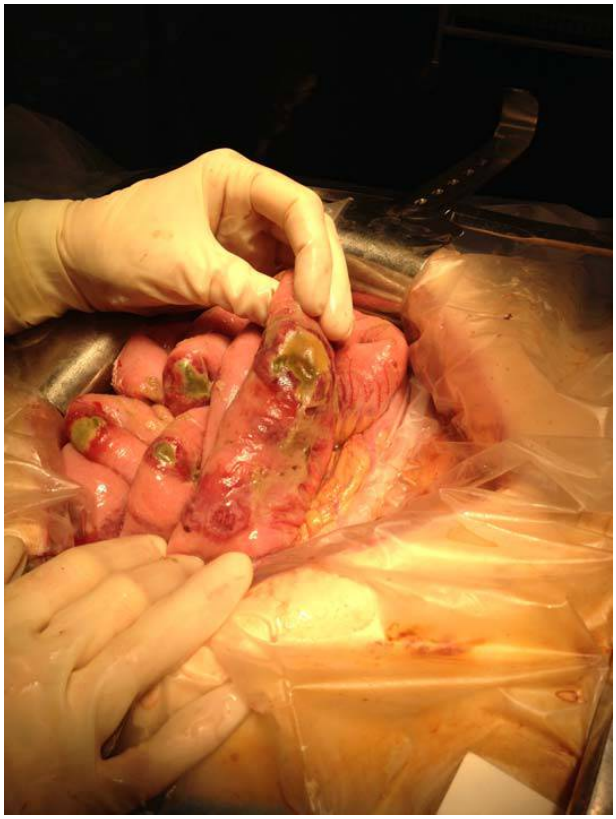

Figure 3 Disseminated small bowel lymphoid tumors with necrosis and perforation.

In patients with rapidly progressive or life-threatening disease, chemotherapy is used with regimens including among others CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) with or without rituximab. Though effective, these chemotherapies increase the risk of infections and other complications, resulting in significant morbidity and mortality.[8] Our patient prognosis was poor given the disseminated disease involving multiple organs complicated by intestinal perforation and she died from sepsis in a context of chemotherapy-induced neutropenia.

Would the monitoring of EBV viral loads after transplantation have changed the course of events in our patient? Kidney Disease Improving Global Outcomes suggests monitoring high-risk kidney transplant recipients (donor EBV seropositive/recipient seronegative) for EBV by quantitative PCR at least monthly for the first 3–6 months after transplantation, then every 3 months until the end of the first post-transplant year, and, additionally, after treatment for acute rejection.[13] Because EBV viral load becomes positive 4–16 weeks prior to development of PTLD,[14] a rising EBV load would help identify patients in whom intervention may prevent PTLD.[15] In these patients, pre-emptive reduction of immunosuppression has resulted in a decreased incidence of EBV disease and PTLD compared to historical controls and, as suggested by Kidney Disease Improving Global Outcomes guidelines,[13] is currently the optimal available preventive strategy.[2] Thus our high-risk patient would probably have benefited from EBV load surveillance in the context of persistent diarrhoea, altered physical condition, with a possible milder PTLD onset in response to preventive reduction of immunosuppression. This dramatic case brought us to implement monitoring for EBV by quantitative PCR in high-risk seronegative kidney transplant recipients. Because the assay is not reimbursed by our national medical insurance, we have opted to monitor EBV PCR at 1, 3, 6, 9 and 12 months post-transplantation. Monitoring is performed in our academic hospital to avoid interlaboratory variability. Conditions of reimbursement of the assay vary in different countries and are probably the current bottlenecks in the implementation of EBV viral load monitoring.

Conclusion

In conclusion, this case highlights the following points regarding PTLD occurring after renal transplantation.

1. Post-transplant lymphoproliferative disorder can be a life-threatening complication and is an important cause of mortality after transplantation.
2. Kidney transplant recipients seronegative for EBV who receive organs from EBV seropositive donors are at high risk for EBV disease and PTLD.
3. Epstein-Barr virus disease can present with several non-specific manifestations before the onset of PTLD, leading to delayed diagnosis.
4. Monitoring high-risk kidney transplant recipients for EBV by quantitative PCR during the first post-transplant year and in case of altered condition would probably help to diagnose PTLD early, and should be adopted whenever possible. An immediate decrease in immunosuppression may then prevent disseminated fatal disease.

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