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Case Report

Post-transplant lymphoproliferative disorder: case report and review of susceptibility to EBV in the Scottish adult renal transplant pool

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Abstract

We report a case of high-grade non-Hodgkin's lymphoma following Epstein-Barr virus (EBV) infection in a 38-year-old renal transplant recipient who was successfully treated with rituximab and remains alive 6 years later with reasonable graft function. We subsequently undertook a survey showing that 1.8% of the Scottish adult transplant pool are susceptible to EBV infection. Though a vaccine for EBV is currently not yet available, routine screening of potential renal transplant recipients for EBV should help identify those at increased risk of post-transplant lymhoproliferative disorder (PTLD), while tailoring of immunosuppression and antiviral prophylaxis with Ganciclovir may help reduce the emergence of this potentially life-threatening disease.

Keywords: EBV; CMV; PTLD; renal; transplantation

Background

Renal transplantation prolongs survival and improves quality of life for most patients who require renal replacement therapy. Complications include cardiovascular disease, opportunistic infections and tumours. Epstein-Barr virus (EBV), cytomegalovirus (CMV) and varicella zoster virus (VZV) can all cause serious illnesses in transplanted patients. The spectrum of illness caused by EBV ranges from an acute infectious mononucleosis-like illness to a highly malignant B cell tumour. We describe a patient who developed a lymphoma after her second transplant in whom long-term remission has been achieved by reduction in immunosuppression and the use of rituximab, a monoclonal antibody with activity against B lymphocytes. This prompted us to test for susceptibility to EBV infection in the Scottish Adult Renal Transplant Pool.

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Case report

A 38-year-old woman presented with left leg, tiredness, sore throat and sweats, 16 months after a second cadaveric renal graft. Positive anti-VCA IgM and negative EBNA IgG supported a diagnosis of glandular fever. Her underlying diagnosis was focal segmental glomerulosclerosis, an early recurrence of which had led to the loss of her first graft. Her second transplant was perfectly matched, but highly sensitized, so she had been given basiliximab as induction therapy followed by prednisolone, tacrolimus and mycophenolate. Serum creatinine was 127μmol/l. Imaging by ultrasound and CT showed a 6 cm soft tissue mass inferior to the transplanted kidney, encircling the femoral vessels. There were no other sites involved. A diagnosis of monoclonal polymorphic high-grade non-Hodgkin's lymphoma was made by a CT-guided biopsy (Figure 1). The cells in this tumour were confirmed immunohistochemically as lymphocytes of B-cell origin by their CD20 and CD79a positivity. *In situ* hybridization for EBV-encoded RNA (EBER) was strongly positive. Withdrawal of tacrolimus and mycophenolate followed by infusion of rituximab 375 mg/m^2 once weekly for 4 weeks led to a significant reduction in tumour size. When last seen at the clinic 6 years after her initial presentation with post-transplant lymphoproliferative disorder (PTLD), serum creatinine was 137 μmol/l with the estimated GFR of 38 mls/min and the urine protein:creatinine ratio of 86.5 mg/mmol. She remains on prednisolone 5 mg daily for immunosuppression. The lymphoma was no longer visible on ultrasound.

This patient's case prompted us to test for susceptibility to EBV infection in the Scottish Adult Renal Transplant Pool. We obtained a list of patients who were active on the renal transplant waiting list in July 2007 through the Scottish Renal Registry and UK Transplant, and then tested their most recent stored blood for EBV IgG Viral Capsid Antigen and CMV IgG VCA if not already known. We obtained results for 492 (91.3%) of 539 active patients. Nine (1.8%) of these were EBV IgG VCA negative and one was equivocal. There were seven men and two women in the EBV-negative group. The median age was 43 years

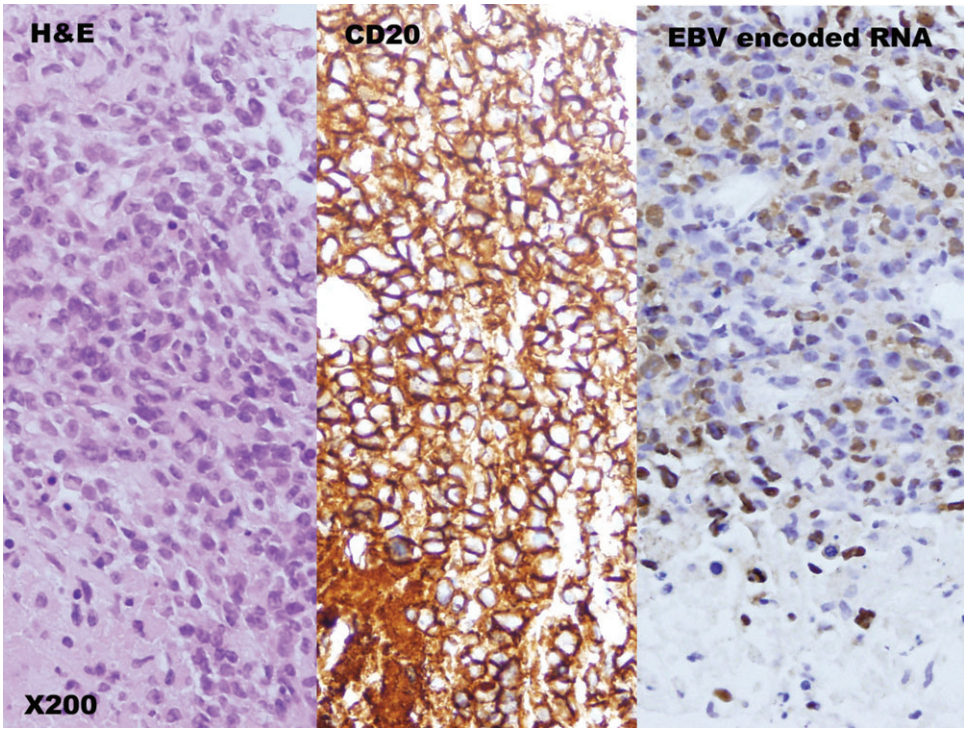

Fig. 1. Biopsy showing monoclonal polymorphic high-grade non-Hodgkin's lymphoma.

(range 20–67 years). Seven (78%) of the nine patients who were EBV-negative were also CMV negative.

Discussion

Our survey showed that 1.8% of Scottish patients awaiting renal transplantation are susceptible to EBV infection, and therefore, at risk of PTLD. This is comparable to population studies showing EBV seronegativity in up to 5% of European adults [1] and also to a small Canadian survey showing 2 EBV seronegative patients amongst 40 adult transplant recipients (5%) [2]. The main risk factors for the disease are EBV seronegativity and the degree of immunosuppression [3,4]. PTLD is more common in children than in adults because more children are seronegative, and therefore, susceptible to primary EBV infection at the time of transplantation [5]. The incidence of PTLD has increased following the introduction of ciclosporin, tacrolimus and newer immunosuppressive agents such as OKT3 [5,6]. The risk of PTLD is also 4-fold greater in EBV-negative recipients if they are CMV negative [7]. This is either because CMV acts as a cofactor in the development of PTLD or could simply reflect the level of immunosuppression [5].

Milder forms of the disease may respond simply to a reduction in immunosuppression although there is no consensus on which drugs to target first [3–5]. Some recommend cutting the dose of calcineurin inhibitors by half and stopping antimetabolite drugs while continuing prednisolone at <10 mg/day [4]. Patients with more severe forms of PTLD are unlikely to respond to a reduction in immunosuppressive therapy alone. Previously, chemotherapy and radiotherapy were used with variable results, but recently it has been shown that treatment with rituximab 375 mg/m^2 by once weekly infusion for 4 weeks may induce complete remission [8]. Chemotherapy should now be reserved for patients not responding to antibody treatment [3]. Despite these advances in therapy, outcome studies suggest a 5-year patient survival of only 51.4% from time of transplantation in renal patients who develop PTLD [9].

What then can be done to prevent the emergence of PTLD in high risk (donor EBV positive, recipient EBV negative) patients? Serial EBV monitoring, tailoring of immunosuppression and antiviral prophylaxis have all been reported to reduce the incidence of PTLD [5,10,11]. Unfortunately, none of these strategies has been tested by randomized trials. The American Society of Transplantation nevertheless recommended in 2006 that donor and recipient EBV status should be ascertained prior to kidney transplantation and that EBV viral load should be checked monthly for at least 1 year thereafter in patients who are EBV seronegative [6]. The purpose of this is to allow early detection of first-time EBV infections. Similar recommendations were made for checking CMV status. In patients at risk by virtue of their EBV seronegativity, reducing the overall burden of immunosuppression and the avoidance of OKT3 has been advised [6].

The strong association between EBV infection and PTLD risk suggests a possible prophylactic role for antiviral therapies, though this remains controversial as these drugs affect replicating viruses only. In PTLD most of the viral genome is in the non-replicative phase [3,5]. The incidence of PTLD is too low to test antiviral therapies by randomized trial, but a large multicentre, case-control study has suggested up to

83% reduction in risk of PTLD depending on the antiviral agent. Ganciclovir was more effective than acyclovir in this study [10]. Others have shown similar results [11]. In EBV-seronegative patients, primary prevention might also be achieved through the use of immunization against EBV prior to the commencement of immunosuppression [4]. A vaccine using the gp350 EBV envelope protein is currently in phase I/II clinical trials in the UK [4].

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Conflict of interest statement. None declared.

References

1. Pariente M, Bartholome J, Santiago L *et al*. Age distribution of serological profiles of Epstein-Barr virus infection: review of results from a diagnostic laboratory. *Enferm Infec Microbiol Clin* 2007; 25: 108–110
2. Shahinian V, Muirhead N, Jevnikar A *et al*. Epstein-Barr virus seronegativity is a risk factor for late-onset posttransplant lymphoproliferative disorder in adult renal allograft recipients. *Transplantation* 2003; 75: 851–856
3. Everly MJ, Bloom Roy D, Tsai ED *et al*. Posttransplant lymphoproliferative disorder. *Ann Pharmacother* 2007; 41: 1850–1858
4. Dharnidharka VR, Araya CE. Posttransplant lymphoproliferative disease—educational feature. *Paediatr Nephrol*, Epub Sep 2007.
5. Taylor AL, Marcus R, Bradley JA. Post transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Clin Rev Oncol/Haematol* 2005; 56: 155–167
6. Humar A, Michaels M. On behalf of the AST ID Working Group on Infectious Disease Monitoring. *Am J Transplant* 2006; 6: 262–274
7. Walker RC, Marshall WF, Strickler JG *et al*. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis* 1995; 20: 134–153
8. Elstrom RL, Andreadis C, Aqui NA *et al*. Treatment of PTLD with rituximab or chemotherapy. *Am J Transplant* 2006; 6: 569–476
9. Saadat A, Einollahi B, Ahmadzad MA *et al*. Posttransplantation lymphoproliferative disorders in renal transplant recipients: report of over 20 years of experience. *Transplant Proc* 2007; 39: 1071–1073
10. Funch DP, Walker AM, Schneider G *et al*. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. *Am J Transplant* 2005; 5: 2894–2900
11. Malouf MA, Chhajed PN, Hopkins P *et al*. Anti-viral prophylaxis reduces the incidence of lymphoproliferative disease in lung transplant recipients. *J Heart Lung Transplant* 2002; 21: 547–554

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