Case Report

Fulminant post-transplant lymphoproliferative disorder presenting with lactic acidosis and acute liver failure

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is the most common non-cutaneous malignancy in solid organ transplant recipients and is associated with significant mortality. In renal transplant recipients the incidence has been estimated to be between 0.2 and 2.3% [1,2]. Most PTLD is driven by Epstein–Barr virus (EBV) infection. The risk of lymphoma in transplant recipients is up to 40 times that of the general population [1]. A spectrum of severity is seen and this reflects the degree of additional oncogene activation and the associated transition from a polyclonal to a monoclonal disease [3]. Extra-nodal disease is common and as a consequence the presentation is often subtle and the diagnosis delayed.

There are two principle risk factors for the development of PTLD: the intensity of immunosuppression and the EBV status of the donor and recipient. High dose immunosuppression with ciclosporin, tacrolimus, or anti-lymphocyte antibodies are all associated with increased risk [1]. EBV naïve recipients receiving EBV positive grafts are at greatly increased risk [4,5]. Such patients acquire a primary infection in the context of high dose immunosuppression during the early post-transplant period when cytotoxic T-cell responses to EBV are undetectable [6].

This report describes a minimally immunosuppressed patient who developed PTLD very early in the post-transplant period. The clinical presentation was catastrophic and to the best of our knowledge has not been described before.

Case

A 59-year-old Caucasian man with Alport’s Syndrome on peritoneal dialysis received a primary cadaveric renal transplant. He was discharged on the eighth postoperative day when his serum creatinine was 170 μmol/l. Immunosuppression was with ciclosporin microemulsion 6 mg/kg (target whole blood trough level 200–250 ng/ml by immunoassay), azathioprine 1.5 mg/kg and prednisolone 20 mg tapered to 10 mg by 8 weeks. The donor organ was human leukocyte antigen mismatched at 1 A locus, 1 B locus, and 0 DR loci. The patient never required treatment for acute rejection. At the time of transplantation, donor and recipient were known to be cytomegalovirus (CMV) seronegative.

Two months post-transplant he was admitted with chest pain, diagnosed as a subendocardial myocardial infarction on the basis of characteristic electrocardiographic changes and a significant rise in Troponin T. This admission was complicated by pyrexia of unknown origin, leucopenia, and oral ulcers. Azathioprine was stopped, ciclosporin dose was reduced by 20% and he received a course of aciclovir. He responded to the above treatment and was discharged 10 days later. A CMV pp65 antigenemia test was negative.

A week later he was readmitted with general malaise, exertional dyspnoea, restlessness, and insomnia. On examination he had a pyrexia of 38°C, was normotensive and had mild pedal oedema. There was no lymphadenopathy. He was not tachypnoeic at rest but the pO2 breathing room air was 8.54 kPa. A chest radiograph showed alveolar shadowing at the left lung base that was not significantly different from a historical film. His serum creatinine was stable but the transaminases and bilirubin were mildly elevated. A septic screen was negative for bacterial infection and he was treated empirically with intravenous (i.v.) ganciclovir 5 mg/kg/day, although the CMV pp65 remained negative. Over the next 3 days his general condition deteriorated, with marked worsening of his
liver function (alkaline phosphatase 439 IU/l, aspartate transaminase 4939 IU/l, alanine transaminase 910 IU/l, bilirubin 58 μmol/l) and oliguria. Hypotension with severe metabolic acidosis (lactate 13.13 mmol/l, pH 7.27) required transfer to the general intensive therapy unit where his mean arterial pressure remained low despite volume expansion and inotropes. His immunosuppression was discontinued. The lactic acidosis deteriorated (lactate 21.5 mmol/l) despite continuous veno-venous haemofiltration with bicarbonate as buffer (lactate free). He developed a coagulopathy (prothrombin time 69.3 s, activated partial thromboplastin time 141.5 s, fibrinogen 0.83 g/l, D-Dimers 3000 ng/ml). Ultrasound scan showed a normal transplant kidney with patent vessels. Computed tomography with i.v. contrast did not demonstrate any evidence of a perforated or infarcted viscus. The clinical impression was that of acute liver decompensation with multiple organ failure. Despite renal, circulatory, and ventilatory support his condition continued to decline and he died 11 weeks post-transplant.

A post-mortem examination demonstrated that the cause of death was a widely disseminated PTLD. Atypical pleomorphic B-cell lymphoid infiltrates were seen in multiple extra-nodal tissues including liver, transplanted kidney, native kidneys, myocardium, coronary arteries, and lungs. EBV latent membrane protein (EBV-LMP) immunohistochemistry and in-situ hybridization for EBV-encoded small RNA were positive. These changes were attributed to a high-grade B-cell lymphoma, driven by EBV infection.

Subsequent microbiological investigations including those for respiratory and hepatitis viruses, toxoplasma, and CMV were all negative. However, a serum sample taken whilst on ITU was positive for EBV IgM (viral capsid antigen), but negative for EBV IgG (EBV nuclear antigen) indicating a primary infection. EBV DNA was detected at the same time by polymerase chain reaction (PCR) in the buffy coat. Retrospectively, it was confirmed that the donor had been EBV seropositive and the recipient seronegative pre-transplant. Kidney, liver, spleen, and lung tissues obtained at post-mortem were all positive for EBV DNA by PCR.

Discussion

This patient had an unusually aggressive PTLD only 2 months after transplantation of a well-matched kidney that did not require high dose immunosuppression or anti-rejection therapy. There is evidence that as well as a rise in the overall incidence of PTLD [2] there has been a trend towards diagnosis earlier in the post-transplant period in recent years [7]. Early onset disease is associated with a poor prognosis and this may be because of an association with primary EBV infection. One recently published single-centre series describes a rising incidence of early onset PTLD, presenting as soon as 4 months after transplantation [2]. The development of PTLD in the first 3 months after transplantation is rare but has been described [7,8]. However, presentation with fulminant liver failure has not been reported. Various hypotheses have been put forward to explain this evolution in the epidemiology of PTLD, including the introduction of more potent immunosuppression, better matching, and a reduction in the practice of pre-emptive blood transfusion [1,2].

This patient had not received intense immunosuppression but was nevertheless at high risk of PTLD because he was EBV naïve and received an EBV positive organ. One report describing early onset PTLD is a detailed virological study of four cardiothoracic transplant recipients [8]. Of the two cases, who were EBV naïve, both developed PTLD driven by EBV of donor origin in the first 3 months and both died. Conversely, in the two cases who had previously been exposed to EBV, the authors were able to confirm that PTLD was driven by the reactivation of recipient EBV rather than by super-infection with donor strain. Thus, both primary infection and reactivation of EBV can lead to PTLD, although the overall risk of PTLD is estimated to be between 6.8 and 24 times greater in naïve recipients [4,5]. This is particularly relevant in paediatric practice where the proportion of naïve recipients is greater. However, in adult practice, primary infections only account for 50% of PTLD, because the majority of recipients are not EBV naïve [8]. It is possible that the reduction in pre-transplant blood transfusion has increased the proportion of naïve adults [2].

We did not make a confident pre-mortem diagnosis of PTLD in this patient, but his immunosuppression was reduced and because of the clinical presentation he did receive anti-viral therapy even though CMV was excluded. These changes in therapy were appropriate for a patient with PTLD; however, this did not prevent progression of the disease. It is possible that the ‘subendocardial MI’ was an unusual manifestation of PTLD and the post-mortem finding of coronary artery involvement supports this. The subsequent hepatic failure might have been due to primary EBV itself, but again the post-mortem confirmed that PTLD was the predominant cause.

It is likely that prior knowledge of the recipient’s EBV status in this case would have led to an earlier diagnosis of primary EBV infection. Whether this would have changed the outcome is less clear, as the PTLD ran a relentless course despite the reduction in immunosuppression and use of anti-virals. Nevertheless, there is evidence that surveillance for primary EBV infection in naïve recipients can be useful and allow early institution of anti-viral therapy along with a reduction in immunosuppression [9,10]. Furthermore, early diagnosis might have allowed consideration of chemotherapy or novel therapies such as Interferon-alpha, anti-CD20 monoclonal antibodies, and passive immunization with allogeneic cytotoxic T-cells. Matching cadaveric donors and recipients for EBV status is probably not practical in adult practice and would greatly restrict the number of donors available to paediatric recipients. In live donor
transplantation EBV matching can be taken into account and knowledge of serological risk can be used to target surveillance. In the future, immunization may play a role in the work up of EBV naïve recipients, especially children.

Transplant physicians and surgeons should be aware of this devastating presentation of PTLD in an EBV naïve recipient. Knowledge of recipient EBV status should be used to inform clinicians of the risk of PTLD. This would allow consideration of surveillance and increase the chance of early diagnosis.

Conflict of interest statement. None declared.

References


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