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Exceptional Case

EBV-positive B cell cerebral lymphoma 12 years after sex-mismatched kidney transplantation: post-transplant lymphoproliferative disorder or donor-derived lymphoma?

Paul J. Phelan[1], Rory K.J. Murphy[2], Michael Farrell[3], Orna O'Toole[3], Josie Heffernan[3], Donncha O'Brien[2], Oscar Breathnach[4] and Peter J. Conlon[1]

[1]Department of Nephrology, Beaumont Hospital, Dublin, Ireland, [2]Department of Neurosurgery, Beaumont Hospital, Dublin, Ireland, [3]Department of Neuropathology, Beaumont Hospital, Dublin, Ireland and [4]Department of Oncology, Beaumont Hospital, Dublin, Ireland

Correspondence and offprint requests to: Paul J. Phelan; E-mail: paulphel@gmail.com

Abstract

We present a follow-up case report of possible transmission of lymphoma 12 years after deceased-donor renal transplantation from a male donor who was found at autopsy to have had an occult lymphoma. The female recipient underwent prompt transplant nephrectomy. However, 12 years later, she presented with cerebral B cell lymphoma. A donor origin for the cerebral lymphoma was supported by *in situ* hybridization demonstration of a Y chromosome in the lymphoma. There was a dramatic resolution of the cerebral lesions with tapering of immunosuppression and introduction of rituximab treatment. The finding of a Y chromosome in the cerebral lymphoma does not exclude a host contribution to lymphoma development.

Keywords: cancer transmission; lymphomatoid granulomatosis; post-transplant lymphoproliferative disorder (PTLD); renal transplantation

Introduction

The transmission of cancer *via* transplantation is a rare but recognized phenomenon with potentially devastating consequences [1]. A small number of lymphoma transmissions *via* bone marrow and solid organ allografts have been reported [2–4]. We present a follow-up case report of possible transmission of lymphoma 12 years after deceased-donor renal transplantation. The case was previously reported as being lymphoma-free 5 years after explantation [5].

Case report

Donor details

A 34-year-old man sustained head trauma during a motorcycle accident and died from his injuries near the end of 1996. His kidneys were the only organs recovered for transplantation. He had a good urinary output and a serum creatinine of 86 μmol/L before death. There was no past medical history of note and no evidence of cardiovascular compromise at the time of death. The donor underwent a post-mortem examination on Day 3 post-transplantation during which an occult lymphoma was found in a duodenal–jejunal lymph node. The lymphoma was described as a low-grade, centrocytic cell, B-cell lymphoma which was BCL-2 positive and Epstein–Barr virus (EBV) negative.

Recipient A

The first recipient was a 51-year-old woman with adult polycystic kidney disease (APKD). She was transplanted 14 h after organ recovery. She had spent only 6 weeks on the transplant waiting list and was maintained on CAPD. Her panel reactive antibody (PRA) was 0% and she received a 1:1:1 HLA-mismatched graft (for HLA-A, HLA-B and HLA-DR antigens). The left donor kidney was implanted onto the right external iliac vessels. The warm ischaemia time was 28 min. Anti-lymphocyte preparations were not given at induction. She had immediate allograft function with a sharp drop in serum creatinine. Initial immunosuppression consisted of cyclosporin (4 mg/kg twice daily), azathioprine (2 mg/kg daily) and prednisolone (20 mg).

The patient was informed of the donor post-mortem result and was admitted to the hospital where the patient opted for a graft nephrectomy 16 days post-transplantation. Lymphoma tissue was present in the explanted kidney. All immunosuppression was stopped but no specific anti-lymphoma treatment was administered. She was commenced on haemodialysis and was monitored with abdominal and thoracic CT scanning prior to re-listing on the transplant pool. Nineteen months after transplant nephrectomy, she was successfully re-transplanted despite now having a peak PRA of 95%. She received a 1:1:1 HLA-mismatched graft from a 42-year-old male donor. Despite being a re-

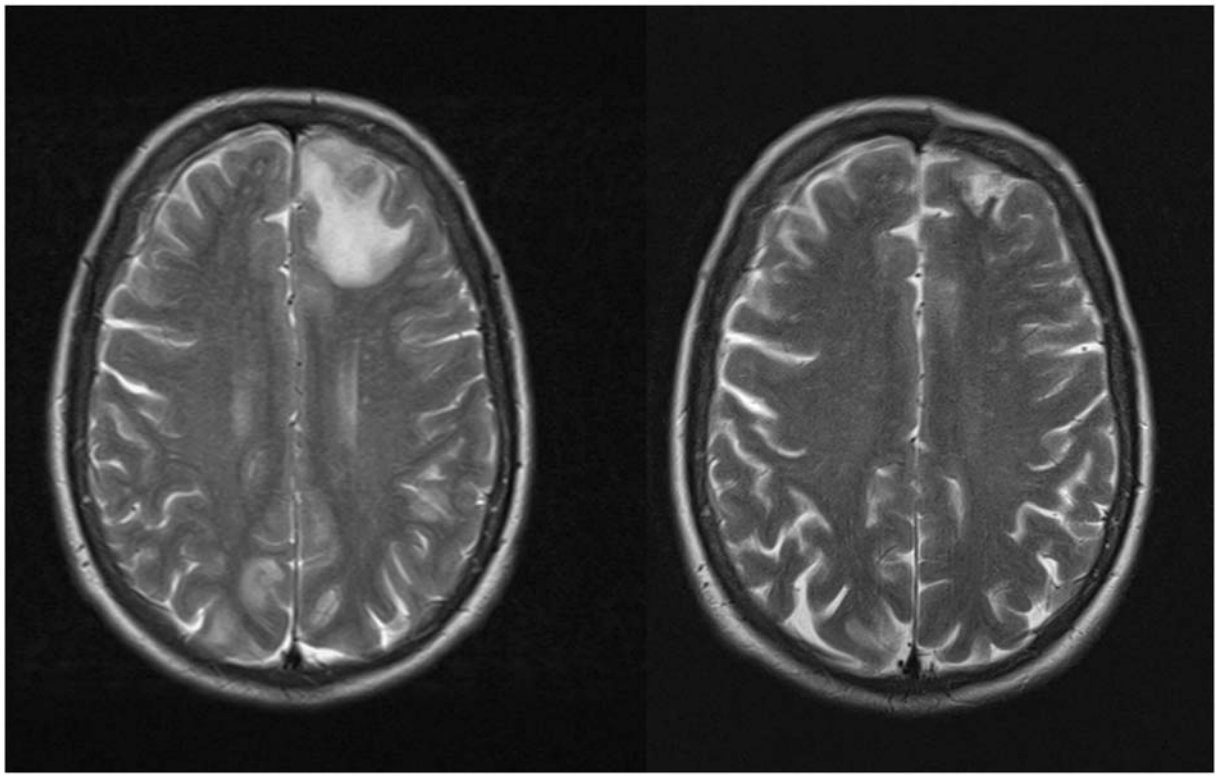

Fig. 1. T2-weighted MR brain scan at the time of diagnosis (left) showing large left frontal lesion and, 6 months later, showing resolution of lesion (right).

transplant, no anti-lymphocyte induction agents were used. Other than this modification to her regime, she was commenced on standard immunosuppression for that era (cyclosporine, azathioprine and prednisone). A period of close supervision including surveillance ultrasonography failed to reveal any suspicious lesions and the patient remained well over the years. At 10 years post-transplantation, the patient had a serum creatinine of 140 μmol/L and was maintained on cyclosporine 50 mg once daily (trough levels between 80 and 100 ng/ml) and mycophenolate mofetil 750 mg twice daily.

In 2008, the patient presented with a 3-week history of blurred vision and new left-sided headache. Clinical examination was unremarkable but MR cerebral angiography was performed to exclude intracranial aneurysm given the history of APKD. Several areas of vasogenic oedema, primarily involving the left frontal and both occipital lobes, were associated with small mass lesions. A CT and MR brain scan showed an enlarged enhancing mass in the left frontal lobe and multiple intracranial enhancing lesions at the grey/white matter junction which were suspicious for cerebral metastases (see Figure 1). A left frontal craniotomy with excision of the largest lesion was carried out. Microscopy demonstrated an immunoproliferative process characterized by large atypical CD20-positive B cells with occasional CD138-positive plasma cells which showed restricted kappa light chain clonality. Necrosis was extensive and multi-nucleate giant cells were prominent (see Figure 1, left). Tubercle bacilli were not present. *In situ* hybridization demonstrated EBV viral RNA in the patients' tumour but not in the donor lymphoma or in the explanted kidney. Given the extensive angiocentricity with giant cell formation, a diagnosis EBV-driven lymphomatoid granulomatosis was preferred to post-transplant lymphoproliferative disorder (PTLD). A staging PET CT scan was performed which showed no evidence of extra-cranial lymphoma. A male origin for the lymphoproliferative disease was supported by *in situ* hybridization for the human Y chromosome in the patients' lymphoma (see Figure 1, right).

Initial management consisted of withdrawal of immunosuppression and urgent oncology referral. CSF examination showed no evidence of lymphoma and treatment with the chimeric anti-CD20 monoclonal antibody rituximab was initiated. The patient initially received six cycles (every third week) at a dose of 375 mg/m^2 per infusion with three monthly treatments continued after this. A follow-up MR brain scan performed 6 months after presentation demonstrated entire resolution of the intracranial lesions (see Figure 2). Her renal function has gradually deteriorated since cessation of her immunosuppression. As of November 2009, she has a serum creatinine of >500 μmol/L and a return to haemodialysis is imminent.

Recipient B

This patient was a 47-year-old male who was described in previous reports [5,6]. He opted not to have his allograft removed after an allograft biopsy demonstrated no malignancy. He has remained lymphoma free over the years and his failed allograft remains *in situ*.

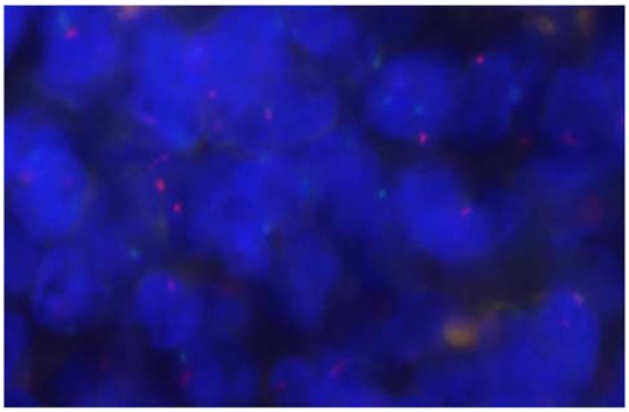

Fig. 2. FISH analysis of cerebral lymphoma using chromosome Xp11.1-q11.1 and chromosome Yq12 fluorescent-labelled DNA probes [red = X and green = Y] and showing rare Y-positive cells in lymphoma.

Discussion

In this report, we describe the development of a cerebral malignant B cell lymphoma 12 years after deceased-donor renal transplantation. We believe it possible that this cerebral lymphoma may be of donor origin given the previous history of the recipient having been inadvertently transplanted from a donor with a low-grade lymphoma together with the documented presence of donor lymphoma in the explanted kidney. Further evidence to support donor origin of the lymphoma is the *in situ* hybridization demonstration of Y chromosomes in the recipient's cerebral lymphoma. Although the donor's low-grade duodenal lymphoma and recipient's cerebral lymphoma differed morphologically and, in EBV status, both were of B-cell origin. Progression of low-grade lymphoma to high-grade lymphoma over time is well documented [7]. We cannot exclude the possibility of a recipient contribution to the development of the cerebral lymphoma. Indeed, many aspects of the case are more in keeping with PTLD and, in particular, with PTLD of cerebral origin, which has recently been reviewed [8]. Most PTLD is of host origin [9,10] and late presentations of PTLD are almost always seen in host-origin PTLD. Moreover, donor-derived PTLD is generally limited to the allograft in contrast to recipient-origin disease [10]. Furthermore, the second recipient is well with no evidence of lymphoma either systemically or in the non-functioning transplanted kidney which may well have been carrying lymphoma. The presence of EBV in the cerebral lymphoma and not in the explanted kidney or in the donor low-grade duodenal lymphoma is also supportive of PTLD. However, there remains the possibility that a clone or clones of donor-derived lymphoma remained occult, possibly in a sanctuary area, and when later exposed to EBV were triggered to proliferate. The more sustained immunosuppressive regime necessitated as a consequence of having to undergo a second renal transplant may, at least in part, have contributed to an outcome which differed from that in the other recipient who elected to retain the transplanted kidney and not undergo re-transplantation. Using a similar *in situ* hybridization strategy, Cheung *et al*. reported post-transplantation B-cell lymphoproliferative disorder of sex-mismatched donor origin in a renal allograft 5 months after transplantation [4].

Recipient lymphoma developed despite prompt transplant nephrectomy after the lymphoma was discovered at donor autopsy. According to registry data, 43% of patients who receive an allograft from a donor with malignancy will subsequently demonstrate cancer transmission [11]. Two hundred and seventy transplant recipients (238 of which were renal transplant recipients) were reported as at risk of transmitted malignancy. A significant proportion of the at-risk patients never developed malignancy. The consequences of cancer transmission are frequently catastrophic for the organ recipient and explantation of the cancer-bearing organ would usually be recommended. As reported by others, it might have been anticipated that transmission of lymphoma would have presented earlier in the recipient. In one report of a multiple organ donor, found on autopsy to have lymphoma, a liver recipient died at Day 116 from transmitted lymphoma [12]. The pancreas was explanted on Day 40 and showed lymphomatous infiltration as did both explanted kidneys.

Lymphomatoid granulomatosis is an angiocentric EBV-associated B-cell lymphoma in which the lung is the commonest site of involvement, but CNS disease is also described [8,12]. Overall, prognosis is poor, especially with CNS involvement [8,14]. There are previous reports in renal transplant patients [15,16] and good outcomes have been described following stepwise reduction in immunosuppression [16] and introduction of cyclophosphamide [1]. Recently, Ishiura *et al*. reported a non-transplant-related case of CNS lymphomatoid granulomatosis successfully treated with rituximab alone [18]. The patient received 375 mg/m^2 once weekly for four doses and stayed in remission for 18 months at the time of reporting.

The 12-year lymphoma-free interval following 'inadvertent' lymphoma transplantation in the subject of this report illustrates the continued risk of donor-transmitted malignancy well after the time period where one would have considered the patient had escaped cancer transmission and in spite of prompt transplant nephrectomy, but also raises questions about a possible host role in the expression of donor-derived malignancy.

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Conflict of interest statement. None declared.

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