American Journal of Transplantation 2006; 6: 419–422
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01170.x

Case Report

Postrenal Transplant Non-EBV Multiple Myeloma of Donor Origin

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Multiple myeloma occurring after solid organ transplantation is a rare condition, with only a few case reports found in the literature. We report a case of Epstein-Barr virus-negative, posttransplant multiple myeloma in a 67-year-old female, presenting 18 months after renal transplantation. Interestingly, fluorescence *in situ* hybridization analysis of the tumor revealed a Y chromosome in the majority of the cells, indicating that the neoplasm was derived from the donor kidney. To our knowledge, this represents the first reported case with these features.

Received 29 July 2005, revised 19 September 2005 and accepted for publication 3 October 2005.

Introduction

Multiple myeloma occurring after solid organ transplantation is an extremely rare condition, with only a few case reports found in the literature. These cases have generally been reported in association with renal or cardiac transplantation (1–8), and have been associated with Epstein-Barr virus (EBV), suggesting that they originated from the host B-lymphoid cells latently infected with EBV. We report a case of postrenal transplant plasmablastic myeloma in a 67-year-old female, which presented as a pararenal mass along with multifocal marrow involvement, 18 months after the renal transplant. Interestingly, this neoplasm was of donor origin, and was unrelated to EBV, despite the relatively short interval between the transplant and the presentation of the mass.

Case Report

A 67-year-old female with end-stage renal disease, believed to be secondary to oxalate nephrolithiasis, underwent cadaveric renal transplantation from a male donor. Post-transplant, the patient was placed on steroid-free immunosuppression with Tacrolimus, Rapamycin and Sirolimus, although the latter was eventually discontinued after the patient developed impaired renal function. Mycophenolate mofetil was added later. There was a single episode of acute cellular rejection, 1 month post-transplant, which was treated effectively with pulsed methylprednisone.

Approximately 18 months posttransplant, the patient developed ureteral stricture and hydronephrosis, requiring a stent placement. Due to persistent hydronephrosis and elevated renal function parameters, open surgical correction of the stricture was undertaken. Intra-operatively, a large, solid tumor was seen between the lower pole of the kidney and the iliac vessels. Intraoperative ultrasound demonstrated the mass to be 8.5 × 5.9 cm, iso- to hypoechoic, and vascular (data not shown), with apparent origination at the lower pole of the transplant kidney. The mass encased the ureter and stent. Surgery was terminated at this stage, to enable further characterization of the mass before definitive treatment was planned.

Postoperatively, magnetic resonance imaging (MRI) of the pelvis confirmed a large (9 × 6.6 × 5.7 cm), lobulated mass arising from the transplant kidney (Figure 1). FDG-PET imaging suggested the possibility of multifocal abnormalities in the bone marrow, with the pelvis and femoral heads demonstrating areas of hypermetabolic activity.

Ultrasound (US)-guided biopsy of the pararenal mass was performed. Hematoxylin and eosin (H&E)-stained sections of the biopsy demonstrated a diffuse infiltrate of frankly neoplastic, discohesive cells showing intermediate to large size, generally open chromatin with frequent nucleoli, a moderate amount of amphophilic cytoplasm, readily identifiable mitotic and apoptotic forms, and scattered cells with the appearance of mature plasma cells (Figure 2A and B). By immunohistochemistry, the neoplastic cells uniformly expressed CD45 (leukocyte common antigen, not shown), CD138 (syndecan-1, a plasma cell-associated antigen, (Figure 2C)) and lambda-restricted cytoplasmic light chains (Figure 2E), with variable CD56 (neural cell adhesion molecular, which is aberrantly expressed by a subset of plasma cell neoplasms, not shown). The neoplastic cells did not express kappa light chains (Figure 2D), the B cell-associated antigens CD20 and Pax-5, the T cell-associated antigens CD3 and CD5, pancytokeratin (positive in

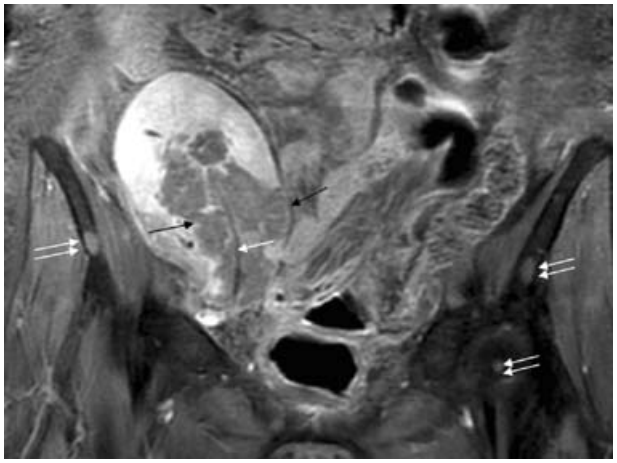

Figure 1. MR image showing a large lobulated heterogeneous mass (black arrows) on the post-contrast image, with extensive hypointense areas and a few tiny hyperintense foci. The stent is seen to traverse through the mass (white arrow). The bone involvement is seen as hyperintense areas in the iliac bone and the left femoral bone (double arrows).

carcinoma), or S-100 protein (positive in melanoma). In addition, there was no evidence of EBV by *in situ* hybridization studies with an EBV probe (Figure 2F). The overall histologic and immunohistochemical findings were diagnostic of a plasmacytoma with plasmablastic features.

Importantly, fluorescence *in situ* hybridization (FISH) analysis of the paraffin-embedded tissue from the mass, which was entirely replaced by tumor, revealed the presence of the Y chromosome in the majority of the cells. This finding indicated that the tumor cells were derived from the male donor.

The random iliac crest bone marrow biopsy performed in the course of clinical staging demonstrated scattered collections of frankly neoplastic cells with histologic features similar to those in the renal mass, representing about 5–10% of the marrow cells (Figure 3A and B). These cells were confirmed to represent plasma cells by virtue of their uniform expression of CD138 (Figure 3C). In addition, concurrent flow cytometric evaluation of the marrow aspirate revealed an abnormal plasma cell population with monoclonal lambda cytoplasmic light chain restriction, strongly suggesting that the neoplastic plasma cells in the marrow represented the same clonal process as the renal mass.

Other laboratory data obtained at the time of diagnosis were consistent with a systemic plasma cell dyscrasia. Serum protein electrophoresis showed decreased total protein, hypoalbuminemia, decreased beta-globulins, low-normal gamma-globulins and monoclonal free lambda light chain by immunofixation. Although dipstick evaluation of the urine did not reveal increased total protein, urine protein electrophoresis did reveal a monoclonal band representing 52% of the total protein, which immunofixation demonstrated to be lambda Bence-Jones protein. Neither total serum calcium nor ionized calcium was increased. Concurrent peripheral blood counts demonstrated moderate normocytic anemia (hemoglobin of 8.6 g/dL and MCV of 91 fL), moderate leucopenia (white blood count of

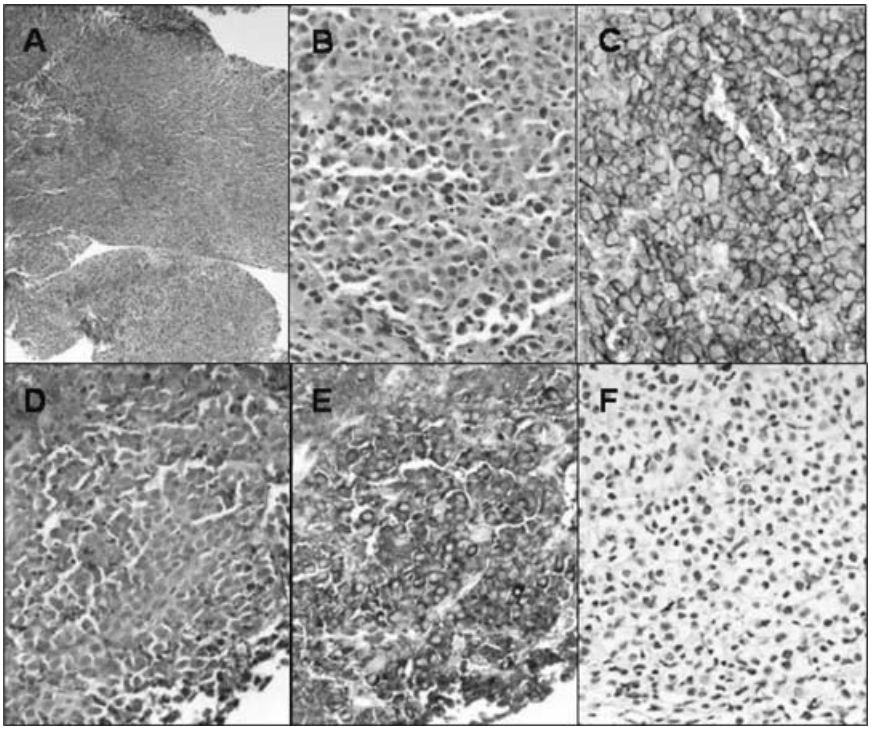

Figure 2. Renal mass biopsy. (A) Low power H&E-stained section (34× magnification) shows the sheet-like arrangement of the neoplastic infiltrate. (B) Higher power H&E-stained section (170× magnification) shows open chromatin, prominent nucleoli and relatively abundant cytoplasma in many the neoplastic cells, as well as frequent apoptotic cells (dark staining, dot-like material). The neoplastic cells uniformly express the plasma cell-associated antigen CD138 (C) and lambda light chains (E), while lacking kappa light chains (D) and showing no evidence of EBV infection by *in situ* hybridization (F).

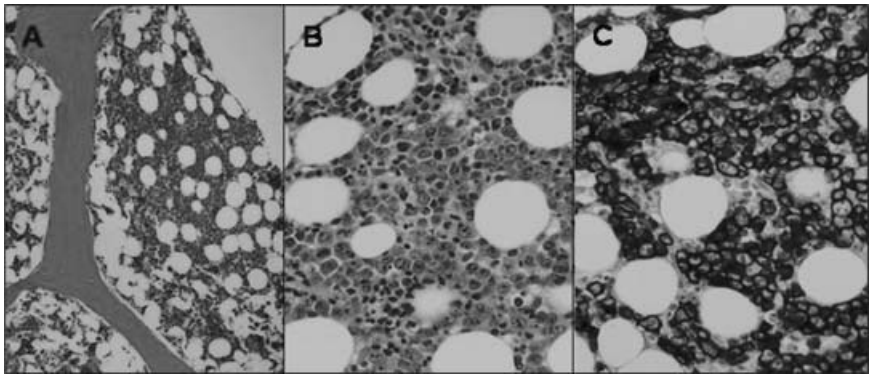

Figure 3. Bone marrow biopsy. (A) Low power H&E-stained section (34× magnification) shows the sheet-like arrangement of the neoplastic infiltrate. (B) Higher power H&E-stained section (170× magnification) shows the similar cytologic appearance of the neoplastic cells to those in the renal mass biopsy. (C) The neoplastic cells uniformly express CD138.

2.5 K/uL) with mild absolute neutropenia (neutrophil count of 1.5 K/uL) and a normal platelet count (224 K/uL). There was no evidence of rouleaux formation or circulating plasma cells in the peripheral blood smear.

Because the presence of a plasmacytoma fulfilled a major criterion for the diagnosis of plasma cell myeloma (multiple myeloma) under the World Health Organization classification system (8), and because the presence of lambda Bence-Jones protein in the urine fulfilled a minor criterion for this diagnosis, the overall features of the case satisfied criteria for the diagnosis of multiple myeloma under the WHO system (fulfillment of one major and one minor criterion). Therefore, given the clinical history of solid organ transplantation, the overall classification of this case under the WHO system was "monomorphic posttransplant lymphoproliferative disorder, plasma cell myeloma type" (8).

The patient was treated with two cycles of VAD chemotherapy (vincristine, adriamycin and prednisone). A follow-up abdominal ultrasound approximately 2 months after the start of therapy demonstrated persistence of the mass, with an increase in size. Morphologic and flow cytometric evaluation of the bone marrow at that time also demonstrated persistence of the lambda-restricted plasma cell population. Following the failure of chemotherapy, there was rapid progression of the tumor with extensive involvement of the pelvic organs, and radiographic evidence of peritoneal and cutaneous involvement. Terminally, the patient developed candidemia, DVT and pulmonary embolism, and expired a few weeks later.

Discussion

The WHO classification of PTLD relies primarily on the clinical history of organ transplantation, rather than whether the process is of host or donor origin. Therefore, this case is appropriately classified as a PTLD under the WHO system. Among the recognized forms of PTLD, multiple myeloma (MM PTLD) is very rare, accounting for less than 4% of PTLD, and less than 1% of posttransplant malignancies (1,6). However, MM PTLD appears to be relatively common in renal transplant recipients; of the 21 cases of MM PTLD reported in literature, 12 were in renal transplant recipients (1). MM PTLD has been reported to occur at a variety of sites, including the oral cavity, maxillary antrum, scalp, thigh, abdominal and chest walls, skull base and bone marrow, as well as the allograft itself (6,7,9–12).

Nearly all of the reported MM PTLDs have been of recipient origin. There has been only one case of donor-origin MM PTLD reported in literature until now; however, no mention was made of the EBV status in this case (13). Therefore, our case appears to be the first such case of donor-origin with documented EBV negativity. The one other reported case of donor-origin plasma cell neoplasm involved a solitary plasmacytoma occurring in a renal allograft (14). The exact incidence of EBV negativity is not well established in multiple myeloma PTLD; of the 21 cases of MM PTLD found in literature, 3 were EBV negative compared to 6 EBV positive cases and the EBV status has not been documented in the rest of them (15).

While EBV status would not be expected to significantly impact therapy in donor-origin cases such as ours, in recipient-origin cases knowledge of EBV status is critical, since EBV-positive cases often respond well to decreased immunosuppression alone. Finally, although the renal graft was cadaveric in this case, for non-cadaveric organ grafts it is important to determine whether a PTLD is of donor vs. recipient origin, since the development of PTLD of donor origin in the setting of non-cadaveric graft would warrant screening of the organ donor for evidence of lymphoma.

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