Renal Cell Carcinoma in Kidney Allografts: Case Report Series and Review of the Literature

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Abstract
The overall incidence of malignancy after renal transplantation is three to five times higher than in the general population. As a result, malignancy is the third most common cause of death in renal recipients. Three cases are given below of de novo renal allograft tumor occurring after transplantation. Case 1 is about a 57-year old female patient who underwent kidney transplant (LRKT) with zero haplotype match from her cousin and the case 2 discuss about a 45-year old female who developed ESRD secondary to chronic glomerulonephritis v/s hypertensive sclerosis. Last case report discusses about 46-year old Caucasian male with a history of Ig A and Granulomatosis with polyangiitis received LRKT from his brother.

Introduction
The overall incidence of malignancy after renal transplantation is three to five times higher than in the general population. As a result, malignancy is the third most common cause of death in renal recipients [1]. Non melanoma skin cancer (NMSC) and lymphoma are the most common malignancies followed by renal cell carcinoma (RCC) [1]. The classic triad of hematuria, abdominal pain and flank pain is not a feature of RCC transplant. The median time lapse between transplantation and tumor diagnosis is between 3 and 19 years or longer as reported in literature. Most of the RCC are found in the recipient’s native kidneys and only few cases of RCCs in renal allograft have been reported so far. As a result allograft tumor is an unusual and rare complication. Obesity, analgesic abuse, tobacco, repeated pyelonephritis along with immunosuppression is the risk factors facilitating the development of allograft and native RCC [2]. Israel Penn Transplant Tumor Registry has reported only 45 cases of allograft RCC [3]. Genetic analysis and immunologic human leukocyte antigen typing should be assessed on the basis of tumor specimen to identify the donor or recipient origin of RCC. Treatment options for these cancers include radiofrequency ablation and partial or total nephrectomy, depending on the patient’s performance status and staging of the RCC. Three cases are given below of de novo renal allograft tumor occurring after transplantation.

Case Reports

Case 1
A 57-year old Hispanic female with a history of HTN and End Stage Renal Disease (ESRD) secondary to Systemic lupus Nephritis (SLE) in December 1994, underwent living related kidney transplant (LRKT) with zero haplotype match from her cousin. She had a baseline creatinine of 0.9-1.1 mg/dL. There was no history of malignancies in her family. She was placed on Imuran, Cyclosporine (CSA) and steroids. Due to steroid induced complications her Imuran was discontinued and Cellcept was started and steroids were tapered. In 2008, she had a CT of abdomen due to abdominal pain and a 10 mm enhancing mass in left native kidney was discovered. Interventional radiology (IR) guided biopsy was performed which was inconclusive and showed no discrete mass lesion with deeper cuts. The mass was later treated with cryoablation. Follow up MRI was performed in November 2011, which showed a 1.3 cm × 1.3 cm mass in the lower pole of the right allograft but no changes were noted in the prior ablation site of the left native kidney. CSA was switched to Rapamune. A repeat biopsy showed Conventional Clear type tumor- Grade1 and as result required allograft nephrectomy and was started on hemodialysis (HD). Left native nephrectomy was planned due to suspicion being the primary source. Unfortunately, her donor was also diagnosed with RCC (Figure 1).

Case 2
A 45-year old African American female with a history of coronary artery disease with stent, hypertension during pregnancy and proteinuria as a teenager developed ESRD secondary to chronic glomerulonephritis v/s hypertensive sclerosis. Patient had no family history of any malignancies. Initially, hemodialysis was started in October 1997, for about 3 years. Later, she underwent an LRKT from her sister with one haplotype match in July 2001. Her transplant was complicated with severe cellular rejection with necrotizing arteriolitis and thrombosis, and treated with Thymoglobulin, OKT3 and plasmapheresis. She later...
maintained good graft function with creatinine in the range of 1.5-1.6 mg/dl on steroids, Cellcept, Prograf and Rapamune. In 2003, her immunosuppressants (IS) were changed to Cellcept and Cyclosporine due to toxicities. Subsequent rejection occurred in 2010 and required intravenous steroids. She developed chronic intermittent microscopic hematuria which led to an ultrasound (U/S) finding of a 1.8 cm hyperechoic lesion on the lateral aspect of the graft in 2010. Due to unknown cardiac stent MRI was not performed. Urological workup showed normal cystoscopy and cytology. However, subsequent ultrasounds within 4-5 months showed a complex cyst of 1 x 1.2 cm along with the mass which had regressed to 1.3 cm. Radiology raised suspicion for post transplant lymphoproliferative disorder (PTLD), which requires biopsy of the graft showing papillary renal cell carcinoma with potential multifocality of the lesion. As a result, transplant nephrectomy of the right kidney was performed on September 2011. Her current status is that she is on hemodialysis but the status of the donor is unknown (Figure 2).

Case 3

A 46-year old Caucasian male with a history of Ig A and Granulomatosis with polyangiitis (Wegener’s, GPA) received LRKT from his brother in 1997, which was performed at the University of Michigan. GPA was treated with Cyclophosphamide, Cellcept and prednisone. Post transplant, he was administered with cyclosporine and Cellcept. His graft function was stable for the last 14 years with creatinine around 1.9-2.2 mg/dl. He visited the institute due to failing kidney function as his creatinine level increased from baseline 2.26 mg/dl to 6.8 mg/dl. His U/S and CT scan were indicative of a solid echoic lesion on the lateral aspect of the graft in 2010. Due to unknown abuse, tobacco use, cystic diseases, BK virus or dialysis. Even though a long-term follow up is not yet available but the clinical and radiological follow ups of the donors have not shown any signs of malignancy. This suggests the possibility that donor kidney harbored tumor at the time of transplantation which remained undiagnosed. However, the possibility of some genetic predisposition may be responsible to cause RCC in recipients suggested minimal risk factors for RCC such as analgesic abuse, tobacco use, cystic diseases, BK virus or dialysis. Even though a long-term follow up is not yet available but the clinical and radiological follow ups of the donors have not shown any signs of malignancy. This suggests the possibility that donor kidney harbored tumor at the time of transplantation which remained undiagnosed. However, the possibility of some genetic predisposition may be responsible to cause RCC in an allograft rather than native kidney. This could lead to malignant transformation of the cells of the graft along with low possibility of the unnoticed transplanted tumor.

Since these tumors are quite rare, therefore, no general consensus or guidelines have been implicated on the management of these
patients. Although partial graft nephrectomy less than 4 cm in diameter is encouraged by Ribal et al. [13] and Chambade et al. [14] with the advantage of preserving graft function and reducing the need to start HD again which is associated with poor survival [14]. However, surgical expertise is required as coexistence of renal and peri renal inflammations make it difficult to maneuver the parenchyma. As a result, risk of hemorrhage and urinoma and even secondary total nephrectomy is high with open or laparoscopic partial or radical nephrectomy.

Another approach is to perform percutaneous thermal ablation. This minimally invasive option leads to preservation of graft function and low morbidity. A recent multicenter retrospective analysis showed that percutaneous ablation is a safe and effective approach in treating de novo RCC in renal transplant [15]. This retrospective analysis has identified 24 tumors in 20 patients with maximal diameter of masses between 6-40 mm, treated mostly with radiofrequency ablation or with cryoablation. This technique has proved to be beneficial as only one patient had a new tumor in a different location after 2 years of follow up and in some cases multifocal RCC were also treated. In those cases where there was complex nature of the lesions and suspicion of the multifocality of the lesion, so transplant nephrectomy was preferred.

Table 1: The Clinical and Pathological Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Primary Disease</th>
<th>HD</th>
<th>IS</th>
<th>Tumor Location/ Size</th>
<th>Type</th>
<th>Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>57/F</td>
<td>SLE</td>
<td>-</td>
<td>Cyclosporine-Celecoxib-Ramapamune-Prednisone</td>
<td>RK/1.3 cm</td>
<td>Clear Cell Grade-1</td>
<td>LRKT/Cousin One Haplotype</td>
</tr>
<tr>
<td>45/F</td>
<td>GN?</td>
<td>36 m</td>
<td>Celecoxib-Cyclosporine</td>
<td>RK/1.3 cm</td>
<td>Papillary Cell Grade-3</td>
<td>LRKT/Sister One Haplotype</td>
</tr>
<tr>
<td>46/M</td>
<td>GPA</td>
<td>-</td>
<td>Cyclosporine-Celecoxib</td>
<td>LK/3.1 cm</td>
<td>Papillary Cell Grade-3</td>
<td>LRKT/Brother</td>
</tr>
</tbody>
</table>

References