No Tumor-Free Waiting Period after Treatment of Multilocular Cystic Renal Cell Carcinoma: A New Case and Review of the Literature

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\textbf{Introduction}

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD) [1]. It requires extensive pretransplant evaluation, and often is deferred for many reasons. Malignancy, both known and newly diagnosed, is one of the most common causes of a delay in transplantation. Renal cell carcinoma (RCC) is more prevalent in ESRD patients and needs to be under control before kidney transplantation can be considered [2]. However, multilocular cystic RCC (MCRCC), one subtype of clear cell RCC, has low malignant potential and may not require a tumor-free waiting period. We report a case of newly diagnosed MCRCC that was found during routine pre-kidney transplant evaluation. A plan for kidney transplantation within 6 months of successful tumor removal by nephrectomy was made. The literature regarding MCRCC in kidney transplantation is reviewed.

\textbf{Case Report}

A 50-year-old African American man with a history of ESRD secondary to focal segmental glomerulosclerosis (FSGS) presented for a renal transplant evaluation. He had been well until 1.5 years earlier, when he presented with flu-like symptoms and acute shortness of breath. His serum creatinine was elevated at 18 mg/dl; 2
months earlier it was normal. Following emergent hemodialysis, a renal biopsy was performed and revealed collapsing FSGS in the setting of stage 3–4 membranous glomerulonephritis. There was moderate tubulointerstitial scarring with foci of microcystic tubular dilatation and superimposed diffuse, severe acute tubular injury. After 7 months, dialysis was discontinued. However, 8 months later, hemodialysis had to be reinitiated following a further decline in renal function. At the time of his transplant evaluation, he still made urine and a urinalysis revealed 600 mg/dl of protein. Hemoglobin was 14.3 g/dl. On examination, he was obese despite an intentional weight loss of 70 lbs in 1.5 years. Abdominal and pelvic computerized tomography (CT) scan showed a 4.2 × 4.1 × 4.2 cm rounded contour asymmetric lesion involving the inferior pole of the left kidney which was concerning for a solid renal mass. Abdominal magnetic resonance imaging (MRI) was performed for better detail and revealed a 3.8 × 4.4 × 4.7 cm cystic lesion in the interpolar left kidney with a thickened septation and mild mural nodularity along the medical aspect of the lesion, without any definite enhancing soft tissue elements (fig. 1). As CT scan without contrast revealed a solid renal mass, the Bosniak classification, which is used for the determination of the possibility of malignancy in renal cystic lesions, could not be utilized in this case. However, by using MRI with contrast which showed a renal cyst, this lesion was classified as a category III cystic renal lesion by the Bosniak classification. Because of concern for renal cancer, he underwent left laparoscopic radical nephrectomy. Pathology revealed a 3.0 × 2.3 × 2.2 cm MCRCC, clear cell type, Fuhrman nuclear grade 1, T1A NX with negative surgical margins (fig. 2–4). He returned for 6-month follow-up and was deemed eligible to be listed as a kidney transplant candidate after repeated imaging showed no evidence of recurrence or metastatic disease.

**Discussion**

With improvement in short-term renal graft survival, long-term complications increase. Although cardiovascular disease is the most common complication in the post-kidney transplant period, malignancy still remains a major cause of morbidity and mortality and often leads to death with a functioning graft [3]. ESRD patients have an increased risk of cancer in the kidney-ureter-bladder system. Cancer of the kidneys has an incidence rate ranging from 3.3 to 9.9% depending on age and causes of renal failure [2]. Although RCC in ESRD patients tend to have more favorable pathologic features and outcomes [4], immunosuppressive medications after transplantation increase the risk of tumor growth, and there is a higher incidence of certain malignancies in ESRD patients. Therefore, most pretransplant malignancies are a contraindication for kidney transplantation, and pretransplant screening for malignancy is mandatory.

At one institution where an ipsilateral native nephrectomy was done at the time of renal transplantation, 4.3% of ESRD patients had RCC [5]. One prospective study
demonstrated that the prevalence of RCC from screening renal ultrasound during pre-kidney transplant evaluation was up to 3.4% with the positive predictive value of a solid lesion on ultrasound of 100% [6]. In one series, the most common histopathology of these tumors was acquired cystic kidney disease-associated RCC followed by clear cell RCC and papillary RCC [7]. The 2001 American Society of Transplantation guidelines suggest that high-risk patients for RCC should be screened with both radiographic imaging and urine cytology [8]. Three common imaging modalities include ultrasound, CT scan, and MRI. Ultrasound is a noninvasive tool and is routinely used in pre-kidney transplant evaluation, but it is operator dependent and is not sensitive enough to detect renal cysts of <5 mm [9]. To differentiate malignant from benign solid renal masses, tumor enhancement is the most important criterion, and abdominal CT scan with intravenous contrast is required [10]. In addition, CT scan is better than ultrasound in the detection of complex cysts [11], and the Bosniak classification of renal cysts can further assist the workup and management [12]. MRI is more sensitive in detecting renal lesions than ultrasound and provides further information regarding renal mass, local growth, and vena cava involvement. It is also used in patients who are allergic to contrast or are pregnant [13].

RCC is classified by morphologic, immunohistochemical, and molecular features into more than 40 subtypes. Clear cell RCC is the most common malignant tumor of renal epithelial origin in adults, accounting for more than 60% of all renal tumors. It has a highly malignant behavior. However, MCRCC, which is one of the clear cell subtypes of RCC, has an excellent prognosis and a low potential for metastasis. It comprises just 4% of all clear cell RCC [14]. Commonly, it is an incidental finding in up to 90% of the cases, and is usually a unilateral solitary lesion [15, 16]. This type of clear cell RCC is found more in middle-age adults with a male-to-female ratio of 1.2–2.1:1 [16, 17]. MCRCC has a characteristic gross appearance, being a well-circumscribed mass composed exclusively of cysts of variable size. The tumor is separated from the kidney by a fibrous capsule, and the cysts are separated by thin septa [14]. Microscopic exam reveals cysts lined by a single layer of low-grade clear cells with abundant clear cytoplasm and small nuclei without nucleoli [14]. The septa consist of fibrous tissue containing clusters of tumor cells. These form small collections but not expansive nodules [18]. MCRCC has similar genetic abnormalities with clear cell RCC: chromosome 3p deletions (74%) and von Hippel-Lindau mutations (25%) [19, 20]. MCRCC can be differentiated from typical clear cell RCC by an absence of necrotic changes and large solid areas of tumor cells [21]. Immunohistochemical features are frequently characterized by diffusely positive cytokeratin 7 and less frequently by positive CD10 [22].
To analyze the tumor characteristics in post-kidney transplantation, it is essential to understand the presence of malignancy in the transplanted organ. The tumor characteristics can be categorized as follows: Tumor size, tumor grade, and tumor stage. The recurrence of RCC in post-kidney transplant recipients is concerning. Pathogenesis of malignancy in posttransplant recipients is (1) de novo occurrence in the recipient, (2) recurrent malignancy in the recipient and (3) transmission of malignancy from the donor [31]. In one reported case of known clear cell RCC, the patient successfully underwent living-related renal transplantation 10 years after a right radical nephrectomy. There was no tumor transmission from donor or tumor recurrence in donor after 10-year follow-up [30].
no evidence of tumor recurrence 9 years after kidney transplantation (table 1) [32]. However, in kidney transplant recipients, the prevalence of RCC in native kidneys was 1.25–3.9% (up to 100 times greater risk than general population) [33, 34] of and de novo RCC in renal grafts it was 0.25–0.5% [33, 35]. Therefore, routine screening renal ultrasonography or other imaging modalities even in asymptomatic post-kidney transplant recipients is strongly recommended in order to detect early small RCC in both native kidneys and renal grafts and to allow possible conservative management by nephron-sparing surgery [34, 35].

There is no consensus regarding the best diagnostic imaging for screening for RCC in kidney transplant recipients. Some studies showed a higher sensitivity to detecting RCC by MRI than by ultrasound (6% vs. 2%). This is especially important in acquired cystic kidney disease, which is an underlying risk factor of RCC in ESRD [11]. However, MRI is not superior to renal ultrasound for detecting solid renal masses [9].

The onset of tumor occurrence in our patient is unclear. Like our patient, most MCRCC are incidentally found from radiological workup for other reasons, and the majority of the patients with MCRCC are asymptomatic. However, a higher hemoglobin level as found in our patient versus the usual level for ESRD patients, may suggest a high erythropoietin state from RCC.

Because we lacked previous imaging studies at the time of kidney biopsy, we cannot confidently identify evidence of tumor progression in our patient. One retrospective study showed that around one third of cystic RCC had an average increase in size of 10.5 mm during 6 months of follow-up and the remaining tumors did not significantly increase in size [36]. Our patient had a kidney biopsy around 1.5 years before undergoing left radical nephrectomy, and the pathology revealed MCRCC measuring 3 cm in greatest diameter. If we assume that the imaging at the time of kidney biopsy did not reveal any renal lesion, the rate of tumor growth in our patient would be approximately 1 cm in 6 months or 3 cm in 1.5 years. This is the same rate as seen in the above study. Our patient likely had MCRCC more than 1.5 years but no evidence of local invasion or distant metastasis. This is consistent with the benign nature of this cancer. Given the clear surgical margins, a decision to wait after radical nephrectomy before the patient would be eligible for kidney transplantation seems unnecessary.

There is an unclear relationship between RCC in renal transplant recipients and prior immunosuppressive medications. Type of induction immunosuppressive therapy showed no difference in the incidence of de novo malignancies; however, conversion to mammalian target of rapamycin inhibitors as maintenance immunosuppression reduced the incidence of malignancies compared to calcineurin inhibitors [37, 38]. Further studies are needed to address the recommended immunosuppressive medications for kidney transplant recipients with RCC.

**Conclusion**

Our case illustrates the effect of malignancy on pre-kidney transplant evaluation and tumor-free waiting periods. MCRCC is a malignancy with benign nature and may not need a tumor-free waiting period. This could lead to an increase in the eligibility of kidney transplant recipients or even donors with MCRCC. However, close follow-up in the post-kidney transplant period is required as immunosuppressive medications may potentially cause recurrent malignancy or de novo occurrence in these recipients.

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