Papillary Renal Cell Carcinoma with Sarcomatoid Differentiation in a Native Kidney of Transplant Recipient: A Case Report and Review of Literature

Abstract
Renal cell carcinoma (RCC) developing in a transplant recipient is about 5–20 times higher than the general population. It is more common in native kidneys than allograft kidney, and incidence varies between 0.3% and 4.8%. Clear cell and papillary types are more frequently reported. Most RCC of allograft recipient is usually low-grade with favorable prognosis. We present a case of papillary RCC with sarcomatoid differentiation (SD) in a native kidney of renal transplant (RT) recipient. The coexistence of sarcomatoid variant with papillary RCC, as in our case, makes it a high grade (WHO/ISUP grade 4) and portends a poor prognosis. Relative aggressiveness and rarity of this variant histology in transplant recipients prompted us to report this case and carry out an extensive search of the available literature.

Keywords: Renal cell carcinoma, renal transplantation, sarcomatoid differentiation

Introduction
Renal cell carcinoma (RCC) is the third most common malignancy after skin and hematopoietic cells in the renal transplant recipient.[1] Papillary RCC is more commonly reported than clear cell carcinoma in native kidneys, and are usually low-grade with a favorable prognosis. Although sarcomatoid differentiation rarely coexists, its presence makes papillary RCC a highly aggressive disease with a propensity for distant metastasis (70–80%). Sarcomatoid differentiation (SD) is not a distinct histological subtype; rather it arises from epithelial-mesenchymal transition.[2] Recently, the International Society of Urological Pathology (ISUP/WHO 2016) recognized this as a grade 4 RCC (validated for clear cell and papillary), which consists of extreme nuclear pleomorphic, multinucleated giant cells, and/or rhabdoid and/or sarcomatoid differentiation.[1] These features are found in 5–8% of clear cells, 8–9% of chromophobe, and 2–3% of papillary RCC.[4,5] Current case report reinforces the role of regular screening of not only the transplant kidney but also the native kidneys, which is usually missed.

Case Details
A 45-year-old, known diabetic and hypertensive male was incidentally diagnosed with a solid–cystic mass, around 5 cms in size, in the right native kidney on ultrasonography of abdomen. He had a history of right renal transplantation ten years (2009) back, followed by left transplant four years (2015) ago [Figure 1a]. He was on triple immunosuppression drugs i.e., Tacrolimus, Mycophenolate mofetil, and Prednisolone for ten years. Although he was on regular ultrasound screening for graft kidney, yet screening of native kidneys were somehow missed. Considering his comorbidity and low creatinine clearance (Crcl) of <45 ml/minute, he underwent noncontrast MRI of abdomen and pelvis for further characterization of incidentally detected right native kidney mass. MRI revealed bilaterally small native kidneys with few subcentimetric renal cortical cyst and a well-defined solid exophytic lesion from upper and middle pole of right side approximately 5.1 × 5.4 × 4.9 cm in size. The lesion was hypointense on T1WI and iso-hyperintense on T2WI images, highly suggestive of RCC [Figure 1b]. HRCT thorax

How to cite this article: Ranjan SK, Mittal A, Kumar S, Kishore S, Narain TA, Mammen KJ. Papillary renal cell carcinoma with sarcomatoid differentiation in a native kidney of transplant recipient: A case report and review of literature. Indian J Nephrol 2021;31:386-9.
showed no evidence of metastasis. Patient underwent robot-assisted right radical nephrectomy [Figure 2a and b]. Histopathology showed papillary RCC with sarcomatoid differentiation (PRCCs) of 10-15%, WHO/ISUP grade 4(pT1N0Mx) [Figure 2c and d]. Because of the high propensity for metastasis and poor prognosis of sarcomatoid differentiation, bone scan was done, and it showed subtle osteoblastic active suspicious lesion involving right 9th rib and right iliac bone, which was mildly FDG avid (SUV 3.2) on PET CT. Role of adjuvant therapy, i.e., tyrosine kinase inhibitors and immune check inhibitors were discussed in multidisciplinary tumor board. In view of the limited proven role and risks of the development of acute rejection, an informed decision was made to keep him on close surveillance.[6] He continues with the same triple immunosuppressive therapy as before.

Discussion

Malignancy after transplantation is not a rare occurrence. The meantime of occurrence for lymphomas, skin, and endocrine cancers, and respiratory tract malignancies were six and eight years respectively.[7] However, for leukemia, breast and genitourinary cancers, and the cancers of the alimentary tract it was nine and 10 years post-transplantation.[7] It was difficult to comment on the time of occurrence in our case as he was routinely screened for cancer in the graft kidneys only and was incidentally diagnosed with right native kidney mass, approximately 9–10 years of first renal transplantation. More than 90% of patients are diagnosed incidentally, only a handful of patients present with haematuria, flank pain, and lump abdomen.[8,9] Thus, active screening of both native and graft kidney for early detection and management is warranted.

An immunocompromised status, deficient immune surveillance against malignant cells, susceptibility for oncogenic viruses, and chronic urinary tract infection are hypothesized to play a significant role in genitourinary cancers in these patients.[7,10] Male sex, African-American race, pre-transplant dialysis interval >4.6 years, age of recipient >65 yrs, age of donor >50 years and allograft rejection within 1 year of transplantation were independent predictors of RCC in transplant recipients in a study by Hurst FP et al.[11] Renal cysts, congenital (polycystic disease) or acquired renal cystic disease (ARCD) during dialysis were also identified as risk factors but often within 6 months of transplantation.[11,12] Several researchers have specified risk factors for specific histological subtypes. They have shown an increased risk for papillary RCC among blacks, dialysis vintage and patients with hypertensive nephrosclerosis and vascular diseases.[13]

The most common variant in a transplant recipient is clear cell, but the incidence of papillary type is more common than in nontransplant.[14] True incidence and prognosis of RCC with SD in a transplant recipient is still not known. In a large series of RCC of 101 patient in nontransplant patients, SD was found in about 8%.[5] Long term prognosis of even localized disease of SD is very poor, reported overall survival is only 50% at 2 years and recurrence of about 77%.[15] Hence, patients even with the localized disease with sarcomatoid variant should be advised strict surveillance for disease progression.

Limited studies have been reported in the literature on RCC with SD in the native kidney of transplant recipients. Kitajima et al. reported the sarcomatoid clear cell RCC in a 60-year-old male in the left native kidney, about 12 years after renal transplantation. The patient had multiple lung metastasis at the presentation, and he also had a long history of dialysis (16 years) with the acquired renal cystic disease before transplantation. So the author concluded that long term dialysis and immunosuppression may be considered as risk factors.[16] In another retrospective series of 43 RCC in the native kidney by Vegso et al., only one patient (2.4%) had SD, highlights the rarity of this variant.[17] The exact nature of the disease in the transplant recipient is least...
understood, and most of the data is extrapolated from the sarcomatoid variant from the non-transplant population. Regular follow up and imaging of native kidneys along with graft kidney is probably the key to diagnose RCC in the native kidney as well as in the graft. Although there is no good evidence that mortality is reduced, several United States, European, and Asian centers are doing regular screening for renal cell carcinoma after transplant. Most of the international guideline recommendations are based on retrospective studies, observational cohort studies, registry-based studies, or modeling analyses. The European renal association-European dialysis and transplant association-2002 (ERA-EDTA) recommends yearly ultrasonography of graft and native kidneys, after the first year. The KDIGO guideline (2020) recommends screening for RCC in high-risk patients, i.e., patients with a family history of RCC, long duration of hemodialysis before transplantation (>3 years), history of the acquired renal cystic disease and analgesic nephropathy. In a follow-up study with annual ultrasonography by Chiang et al. of 326 transplant recipient, abnormal USG (benign as well as malignant disease) were found in 105 patients in native and 45 patients in graft kidneys. With this brief review of the literature we suggest annual USG screening of graft as well as native kidneys after the first year of transplantation and further cross-sectional imaging if any suspicious lesion (complex cyst, renal mass with calcification, rapid increase in size of existing cyst) is found in USG.

Radical nephrectomy is the standard of care for the patient with a papillary carcinoma with sarcomatoid variant and no metastases. There are limited studies on Immune checkpoint inhibitor (ICI) and Tyrosine kinase inhibitors (TKI) as adjuvant therapies in non-clear cell RCC with anecdotal results. A study on ICI has shown that tumoral PD-L1 and PD-1 expression was higher in RCC with SD than pure RCC in 54% and 96% versus 17% and 62%, respectively. These findings suggest that blockade of the PD-1/PD-L1 axis could be an attractive therapeutic approach in the SD of RCC. Other studies have shown risks of the development of acute rejection with ICI. Similarly, TKIs have shown modest response rate in RCC, whereas metastatic sarcomatoid-variant RCC responds poorly to systemic therapy. Thus safety and efficacy of these drugs in immunosuppressed patients either in adjuvant or palliative setting need further larger prospective study. Trials with tyrosine kinase inhibitors and immune checkpoint inhibitors are the need of the hour to answer questions revolving around the appropriate management of such patients.

**Conclusion**

Papillary RCC with sarcomatoid differentiation is a rare clinicopathological finding in transplant recipients and has a poorer prognosis than pure RCC. We hereby suggest a regular annual screening by ultrasonography of both native and graft kidneys post-transplantation that could be beneficial in early detection of renal cell carcinomas.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Stewart JH, Buccionati G, Agodoa L, Gellert R, McCredie MR, Lowenfels AB, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: Analysis of data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol 2003;14:197-207.
2. Mikami S, Katsube K, Oya M, Ishida M, Kosaka T, Mizuno R, et al. Expression of Snail and Slug in renal cell carcinoma: E-cadherin repressor Snail is associated with cancer invasion and prognosis. Lab Invest 2011;91:1443-58.
3. Moch H, Cubilla AL, Humphrey PA, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs—part A: Renal, penile, and testicular tumours. Eur Urol 2016;70:93-105.
4. Pichler R, Compérat E, Klatte T, Pichler M, Loidl W, Lusuardi L, et al. Renal cell carcinoma with sarcomatoid features: Finally new therapeutic hope? Cancers (Basel) 2019;11:422.
5. De Peralta-Venturina M, Moch H, Amin M, Tamboli P, Hailemariam S, Mihatsch M, et al. Sarcomatoid differentiation in renal cell carcinoma: A study of 101 cases. Am J Surg Pathol 2001;25:275-84.
6. Perazella MA, Shirali AC. Immune checkpoint inhibitor nephrotoxicity: What do we know and what should we do? Kidney Int 2020;97:62-74.
7. Sheil AGR. Cancer report 1997. In: Disney APS, editor. The Twentieth Annual Report: Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia: Queen Elizabeth Hospital; 1997. p. 138.
8. Klatte T, Marberger M. Renal cell carcinoma of native kidneys in renal transplant patients. Curr Opin Urol 2011;21:376-9.
9. Kim DY, Abouljoud M, Parasuraman R. The role of microscopic hematuria in the evaluation of urologic malignancy in renal transplant recipients. Transplant Proc 2010;42:1641-2.
10. Bumet FM. Immunological aspects of malignant disease. Lancet 1967;1:1171-4.
11. Hurst FP, Jindal RM, Graham LJ, Falta EM, Elster EA, Stackhouse GB, et al. Incidence, predictors, costs, and outcome of renal cell carcinoma after kidney transplantation: USRDS experience. Transplantation 2010;90:896-904.
12. Doublet JD, Peraldi MN, Gattegno B, Thibault P, Sraer JD. Renal cell carcinoma of native kidneys: Prospective study of 129 renal transplant patients. J Urology 1997;158:42-4.
13. Karami S, Yanik EL, Moore LE, Pfeiffer RM, Copeland G,
Gonsalves L, et al. Risk of renal cell carcinoma among kidney transplant recipients in the United States. Am J Transplantat 2016;16:3479-89.

14. Sun IO, Ko YM, Kim EY, Park KS, Jung HS, Ko SH, et al. Clinical characteristics and outcomes in renal transplant recipients with renal cell carcinoma in the native kidney. Korean J Intern Med 2013;28:347-51.

15. Merrill MM, Wood CG, Tannir NM, Slack RS, Babaian KN, Jonasch E, et al. Clinically nonmetastatic renal cell carcinoma with sarcomatoid dedifferentiation: Natural history and outcomes after surgical resection with curative intent. Urol Oncol 2015;33:166.e21-9.

16. Kitajima T, Ubara Y, Marui Y. Sarcomatoid carcinoma in the native kidney of a renal transplant recipient. Ther Apher Dial 2012;16:376-8.

17. Végô G, Toronyi E, Hajdu M, Piros L, Görög D, Deák PA, et al. Renal cell carcinoma of the native kidney: A frequent tumor after kidney transplantation with favorable prognosis in case of early diagnosis. Transplant Proc 2011;43:1261-3.

18. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1-155.

19. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV. 1. Organization of follow-up of transplant patients after the first year. Nephrol Dial Transplant 2002;17(Suppl 4):3-4.

20. Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation 2020;104 (4S1 Suppl 1):S11-103.

21. Chiang YJ, Chu SH, Liu KL, Lai WJ, Wang HH, Chen HW, et al. Kidney ultrasound is useful tool in posttransplant follow-up. Transplant Proc 2006;38:2018-9.

22. Joseph RW, Millis SZ, Carballido EM, Bryant D, Gatalica Z, Reddy S, et al. PD-1 and PD-L1 expression in renal cell carcinoma with sarcomatoid differentiation. Cancer Immunol Res 2015;3:1303-7.

23. Molina AM, Tickoo SK, Ishill N, Trinos MJ, Schwartz LH, Patil S, et al. Sarcomatoid-variant renal cell carcinoma treatment outcome and survival in advanced disease. Am J Clin Oncol 2011;34:454-9.

24. Kammerer-Jacquet SF, Deleuze A, Saout J, Mathieu R, Laguerre B, Verhoest G, et al. Targeting the PD-1/PD-L1 pathway in renal cell carcinoma. Int J Mol Sci 2019;20:1692.