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Case Report

Metastatic Renal Cell Carcinoma Arising in a Renal Allograft after Two Transplants: Case Report and Implications for Screening

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ABSTRACT

Background: Renal cell carcinoma (RCC) arising in a transplanted kidney is rare, accounting for 0.2–0.5% of grafts, but poses serious risks of graft loss and cancer-related mortality.

Case Presentation: We report a 50-year-old kidney transplant recipient who developed metastatic RCC six months after his second living-related transplant. He presented with cough and dyspnea, and imaging revealed multiple pulmonary nodules and a metabolically active cystic lesion in the renal allograft. Ultrasound-guided biopsies of the allograft lesion and a pulmonary nodule confirmed clear cell RCC on histology, supported by immunohistochemistry (PAX8, CD10, and Vimentin positive). Despite the initiation of lenvatinib, his condition deteriorated rapidly, and he died one week after treatment initiation.

Conclusion: This case underscores the difficulty of early detection and management of allograft RCC. It demonstrates the probable value—but uncertain benefit—of a risk-based, rather than universal, surveillance strategy in kidney transplant recipients.

KEYWORDS: Renal cell carcinoma; Kidney transplant; Calcineurin inhibitor

INTRODUCTION

Renal transplantation is the treatment of choice for end-stage kidney disease, offering superior survival and quality of life compared with dialysis. However, longer post-transplant survival and lifelong immunosuppression have led to an increased burden of malignancies. Among these, renal cell carcinoma (RCC) is of particular concern. Kidney transplant recipients (KTRs) have a markedly elevated risk of RCC compared with the general population, largely due to impaired immune surveillance, dialysis-associated renal changes, and oncogenic effects of immunosuppressive regimens. Large registry linkages such as the U.S. Transplant Cancer Match study report a 4–5-fold increased standardized incidence ratio (SIR) for RCC in KTRs, with the vast majority (~90%) of tumors arising from native kidneys rather than the graft [1]. Similarly, analyses from ANZDATA and USRDS confirm that kidney cancer incidence in both dialysis and transplant recipients is roughly 10-fold higher than in the general population [2, 3]. More recent international multi-registry studies estimate the overall post-transplant RCC incidence at ~0.7%, with allograft RCC accounting for ~0.2–0.5% of cases [4, 5]. Although rare, RCC in the renal allograft is clinically significant, carrying the dual risk of graft loss (necessitating return to dialysis) and cancer-related mortality. Reported risk factors include older donor age, male sex, deceased donor transplantation, smoking, acquired cystic kidney disease, and prolonged calcineurin inhibitor exposure [6]. The diagnosis is challenging, as tumors may remain asymptomatic until advanced stages,

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and distinguishing donor-derived RCC from de novo tumors can be difficult. Some studies suggest a two-year post-transplant threshold as a practical discriminator [7].

Management strategies for allograft RCC are heterogeneous and largely based on case series: graft nephrectomy, nephron-sparing surgery, and ablative therapies are considered in localized disease, whereas metastatic cases carry a dismal prognosis with no standardized treatment pathway [8]. Given this risk landscape, screening assumes critical importance. Registry data indicate a cumulative RCC risk of ~0.5% at 5 years and ~1% at 10 years post-transplant [1, 4]. This situation justifies integrating periodic ultrasound or cross-sectional imaging into post-transplant surveillance protocols, particularly in high-risk patients, to enable early detection and potentially curative intervention.

In this context, we present the case of a middle-aged male who developed metastatic renal cell carcinoma in a renal allograft after two kidney transplants, underscoring the difficulties of early detection, diagnostic attribution, and management in the absence of definitive international guidelines.

CASE PRESENTATION

A 50-year-old man with type 2 diabetes mellitus and end-stage kidney disease underwent two sequential renal transplants. His first transplant, performed 4 years before the current presentation, was a living-related, ABO-compatible kidney transplant from his 34-year-old wife, who had no comorbidities. The donor's blood group was B+, with 6/12 HLA mismatch and a cold ischemia time of 24 minutes. Pre-donation evaluation, including renal ultrasonography, revealed no structural renal lesions. Induction immunosuppression consisted of antithymocyte globulin (ATG) 3 mg/kg and methylprednisolone 1.5 g over 3 days, followed by maintenance therapy with tacrolimus, mycophenolate mofetil, and prednisolone.

The initial graft functioned for four years, after which progressive graft dysfunction developed and immunosuppression was appropriately modified. The patient subsequently returned to maintenance hemodialysis and was evaluated for repeat transplantation.

A second living-related transplant was performed 6 months before the current presentation, with his 52-year-old brother as the donor. The donor had no comorbidities, blood group B+, 4/12 HLA mismatches, and cold ischemia time of 26 minutes. Comprehensive donor and recipient assessment, including recipient ultrasound of native kidneys and the first graft, demonstrated no cysts, masses, or suspicious renal lesions. Induction immunosuppression included ATG 3 mg/kg and methylprednisolone 1.5 g. The postoperative course was uneventful, and the patient was discharged with stable graft function.

At 6 months following the second transplant, the patient presented with a two-week history of progressive shortness of breath and persistent dry cough. He denied fever, hemoptysis, or weight loss. Examination revealed only bilaterally diminished breath sounds. Laboratory evaluation showed stable allograft function (serum creatinine 1.4 mg/dL), normal liver enzymes, and mild normocytic anemia.

A chest radiograph demonstrated multiple rounded pulmonary opacities consistent with "cannonball" metastases (Fig. 1A), so an HRCT chest was done, which revealed multiple large randomly distributed nodules of varying sizes in bilateral lung fields, with many of them being pleural-based, suggestive of malignant etiology (metastases) (Fig. 1B, 1C, & 1D). 18F-FDG PET-CT revealed a heterogeneous exophytic cystic lesion in the transplanted kidney in the right iliac fossa, with focal metabolic activity suggestive of an infected renal cyst versus renal cell carcinoma (RCC). Numerous hypermetabolic bilateral pulmonary nodules were also noted, with post-transplant lymphoproliferative disorder (PTLD) and metastatic RCC as differentials (Fig. 1E).

To establish a diagnosis, ultrasound-guided

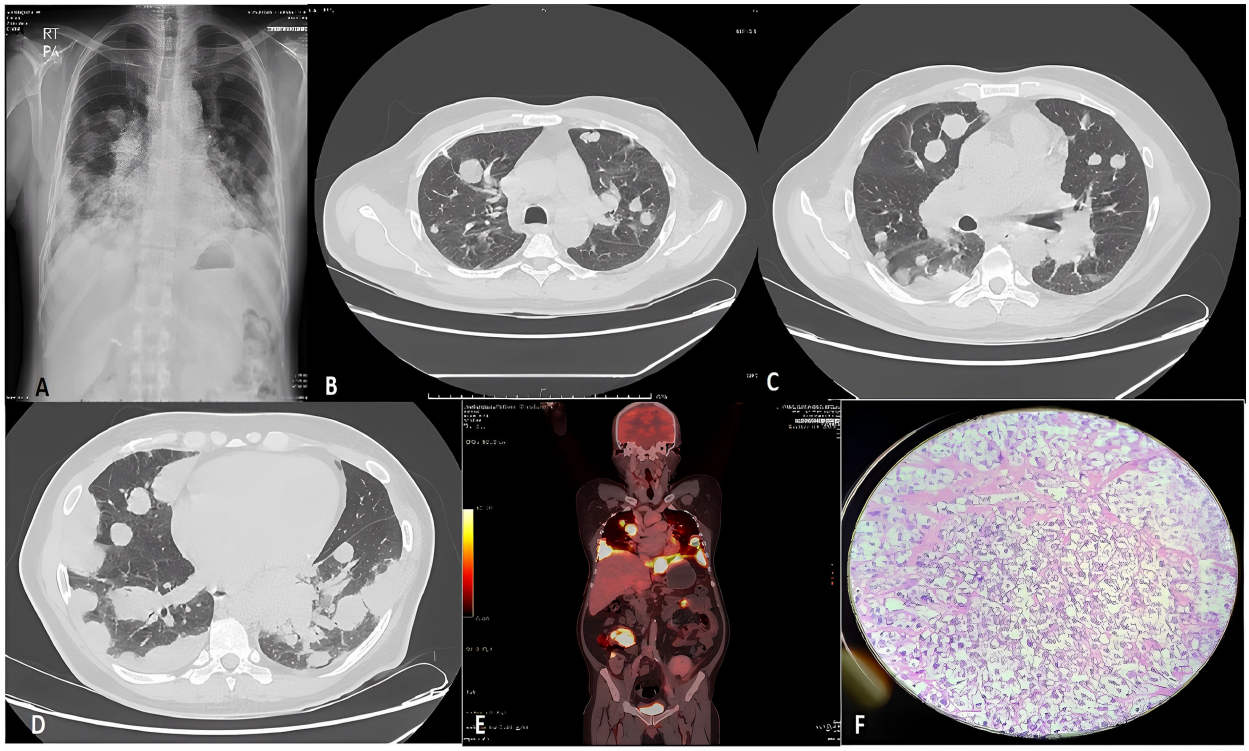

Figure 1: (**A**) Posteroanterior (PA) chest radiograph demonstrating multiple bilateral pulmonary nodules and confluent air-space opacities. There is patchy consolidation in both lower zones with blurring of the costophrenic angles, suggestive of an infective/inflammatory process. Cardiomediastinal contours are within normal limits. No pleural effusion or pneumothorax is evident. Image quality is adequate with proper exposure and full inspiratory effort. (**B**) HRCT chest revealing randomly distributed nodules in bilateral lung fields likely malignant (slice thickness 1/10 mm obtained on Discovery 750 HD 64-row spectral scanner). (**C**) HRCT chest revealing randomly distributed nodules in bilateral lung fields likely malignant (slice thickness 1/10 mm obtained on Discovery 750 HD 64-row spectral scanner). (**D**) HRCT chest revealing randomly distributed nodules in bilateral lung fields with a pleural-based nodule likely malignant (slice thickness 1/10 mm obtained on Discovery 750 HD 64-row spectral scanner). (**E**) F-18 FDG PET-CT (coronal fused image) demonstrating multiple hypermetabolic pulmonary nodules in both lung fields, the largest measuring approximately 5.2 x 3.2 cm, with intense FDG uptake (SUVmax 22.7) in the left lung lower lobe. Additional foci of increased metabolic activity are noted in the right lower lobe, mediastinal nodes, and paratracheal regions. The transplanted kidney shows focal FDG uptake in a heterogeneous-density exophytic cyst measuring 15 x 16 mm in the upper pole. No FDG-avid primary renal mass is visualized in the native renal fossa. PET-CT parameters: F-18 FDG dose 10 mCi, imaging performed at 45-60 minutes post-injection, slice thickness 3.3 mm. (**F**) Hematoxylin and eosin (H&E)–stained section of the renal allograft biopsy. Low-power micrograph showing nests and sheets of tumor cells with abundant clear cytoplasm, distinct cell borders, and delicate branching fibrovascular septa, features characteristic of clear cell renal cell carcinoma. The nuclei show moderate pleomorphism with variably prominent nucleoli. Magnification: low-power field.

core biopsies were performed from both the renal allograft lesion and a representative pulmonary nodule. Histopathological examination of the renal allograft core biopsy demonstrated a malignant epithelial neoplasm arranged in solid nests, alveolar structures, and focal acinar patterns. The tumor cells exhibited abundant clear to pale eosinophilic cytoplasm, distinct cell borders, and moderately pleomorphic nuclei with prominent nucleoli. Foci of tumor necrosis and increased mitotic activity (4–5 mitoses/10 HPF) were identified (Fig. 1F). No papillary, chromophobe, or sarcomatoid features were observed. The pulmonary nodule biopsy showed an identical morphology, supporting a metastatic process. Immunohistochemical staining was performed using the Ventana Benchmark XT automated platform (Ventana Medical Systems), with appropriate antigen retrieval and detection protocols. The following antibodies were used: PAX8 (clone MRQ-50, Ventana; dilution pre-optimized) – strong nuclear positivity, CD10

(clone 56C6, Novocastra; 1:50 dilution) – diffuse membranous positivity, Vimentin (clone V9, Dako; 1:200 dilution) – strong cytoplasmic positivity, CXCR7 (polyclonal, Abcam; 1:100 dilution) – focal cytoplasmic positivity. Internal controls (renal tubular epithelium) and external positive controls were satisfactory. Negative controls run for each marker showed no background staining. PAX8 and CD10 were included as standard markers to confirm renal epithelial origin and are routinely used in distinguishing RCC from urothelial carcinoma, metastatic carcinomas, and PTLD. Vimentin positivity supported the diagnosis of an RCC of clear cell phenotype. CXCR7 was incorporated as part of the extended renal carcinoma panel available at our institution. While not a routine diagnostic marker, it was used as a supportive marker because it is reported to be expressed in metastatic clear-cell RCC. Its expression was interpreted only in conjunction with the primary diagnostic markers.

Based on the combined clear cell morphology, WHO/ISUP grade, and confirmatory immunoprofile, the findings were diagnostic of metastatic clear cell renal cell carcinoma (RCC) originating from the transplanted kidney.

Given the diagnosis of metastatic clear cell RCC with extensive bilateral pulmonary involvement, systemic therapy was considered the only feasible oncologic option. Immune checkpoint inhibitors were avoided because of the extremely high risk of precipitating acute allograft rejection in a recently transplanted recipient. Combination regimens involving immunotherapy (e.g., pembrolizumab–lenvatinib or nivolumab–cabozantinib) were therefore contraindicated. Among available tyrosine kinase inhibitors, lenvatinib was selected due to its relatively favorable toxicity profile in frail patients, its once-daily dosing, and its suitability in individuals with multiple comorbidities. Sunitinib and pazopanib were avoided because of their higher rates of gastrointestinal toxicity, hypertension, and cytopenias in people with diabetes. At therapy initiation, the patient had an ECOG performance status of 3, tachypnea with a respiratory rate of 26/min, oxygen saturation of 89% on room air, serum creatinine of 1.6 mg/dL, hemoglobin of 9.8 g/dL, and no laboratory features of sepsis. Lenvatinib was started at 14 mg orally once daily during the same admission. Surgical options were deemed inappropriate. Graft nephrectomy was not pursued because the renal lesion was small (15 × 16 mm), non-resectable without major morbidity, and metastatic disease was already widespread. Palliative radiotherapy was not considered beneficial given the diffuse bilateral pulmonary metastases and absence of a dominant symptomatic mass. The best supportive care was discussed; however, the patient and family opted for an attempt at systemic therapy.

Following initiation of Lenvatinib, the patient exhibited rapidly progressive respiratory distress. Over the next several days, he developed worsening hypoxemia, requiring escalating oxygen support. Repeat imaging showed an interval increase in pulmonary metastatic burden without evidence of infection, drug toxicity, or hemodynamic instability. His condition deteriorated to ECOG 4, and he succumbed to progressive metastatic disease on Day 7 of therapy.

The chronological sequence of the patient's clinical course, diagnostic workup, therapeutic interventions, and outcomes is summarized in Table 1.

Ethical Considerations

Well-informed written consent for publication, including images, was obtained from his wife.

DISCUSSION

Renal transplantation remains the most effective therapy for patients with end-stage kidney disease, offering survival and quality-of-life benefits compared with dialysis. However, the increasing number of transplants and longer patient survival have been accompanied by a rising burden of post-transplant malignancy [1]. Among these, renal cell carcinoma (RCC) is particularly noteworthy, not only for its elevated incidence in transplant recipients but also for its complex implications in graft

Table 1: Timeline of clinical events, diagnostic evaluation, treatment, and outcomes.

Time relative to presentation	Clinical event/course	Key findings	Diagnostic or therapeutic intervention	Outcome/clinical significance
4 years before presentation	First living-related kidney transplantation	—	Living-related renal transplantation	Initial functioning renal allograft
4 years to 6 months before presentation	Progressive deterioration of the first renal allograft	Initially stable graft function followed by progressive dysfunction	Clinical and laboratory follow-up	Progressive graft dysfunction culminating in graft failure
6 months before presentation	Second living-related kidney transplantation	—	Second living-related renal transplantation	Successful transplantation with subsequent stable graft function
Post-transplant months 1–5	Stable function of the second renal allograft	Nadir serum creatinine approximately 1.4 mg/dL	Routine post-transplant monitoring	No apparent evidence of graft dysfunction during this period
2 weeks before presentation	Development of respiratory symptoms	New-onset cough and dyspnoea	—	Prompted subsequent clinical evaluation
At presentation	Evaluation of respiratory symptoms	Imaging demonstrated multiple pulmonary nodules and a lesion within the renal allograft.	Radiological assessment	Findings raised suspicion for a malignant process involving the renal allograft with pulmonary metastases.
During the same admission	Histopathological evaluation of the renal and pulmonary lesions	Biopsies of the renal allograft lesion and a pulmonary nodule were consistent with metastatic renal cell carcinoma	Ultrasound-guided renal allograft biopsy and lung nodule biopsy	Diagnosis of metastatic RCC established
Approximately 1 week later	Rapid clinical deterioration following diagnosis	Progressive clinical decline	Initiation of lenvatinib	Patient died approximately one week after treatment initiation

and patient survival. Population-based registries have consistently shown that KTRs face a 4–10-fold increased risk of RCC compared to the general population [1-3]. The majority of these tumors (~90%) develop in the native kidneys, often in association with acquired cystic kidney disease (ACKD) after prolonged dialysis [2]. In contrast, RCC arising from the allograft is relatively rare, with an estimated incidence of 0.2–0.5% of grafts, yet it carries disproportionately grave consequences 4, 5. Risk factors include older donor age, deceased donor transplantation, male gender, smoking, ACKD, and chronic exposure to calcineurin inhibitors [6].

The pathogenesis of RCC in the allograft remains incompletely understood. Some cases may transmit donor-derived malignancy with the graft, while others experience de novo tumor development due to chronic immunosuppression. Distinguishing between these mechanisms is difficult. A retrospective study indicated that tumors manifesting within two years post-transplant are more likely to be donor-derived, whereas those emerging subsequently are generally de novo [7]. Genetic typing of tumor versus donor tissue can provide definitive attribution, though such an analysis is rarely feasible in routine practice.

Allograft RCC is often asymptomatic and detected incidentally on surveillance imag-

ing. However, symptomatic cases, particularly with metastases at presentation—as in our case—portend a poor prognosis [8]. Imaging findings may mimic other post-transplant complications such as post-transplant lymphoproliferative disorder (PTLD) or infected cysts, necessitating histological confirmation. The lack of standardized surveillance protocols across transplant programs contributes to delayed detection [6].

The therapeutic approach to allograft RCC is challenging and individualized. For localized disease, options include:

Radical nephrectomy of the graft, which eliminates the tumor but results in graft loss and a return to dialysis [4].

Nephron-sparing surgery or minimally invasive ablative techniques (radiofrequency ablation, cryoablation), which aim to preserve graft function when feasible [5].

In cases with metastatic disease, as in our patient, the prognosis is poor. Systemic therapies such as tyrosine kinase inhibitors (e.g., sunitinib, pazopanib, lenvatinib) have been used, though efficacy is limited in immunosuppressed hosts and toxicity may be accentuated [8]. Immunotherapy with immune checkpoint inhibitors (anti-PD-1/PD-L1 or CTLA-4 antibodies), now standard in advanced RCC, is generally avoided in transplant recipients due to the risk of allograft rejection. Limited case reports indicate heterogeneous outcomes, with certain patients exhibiting tumor response at the expense of graft loss [9].

The prognosis is contingent upon the tumor stage and metastatic status. Localized disease treated surgically can achieve favorable survival, but metastatic cases are associated with dismal outcomes, as illustrated in our report [8]. In the absence of consensus guidelines, screening strategies are increasingly advocated. Several authors recommend annual ultrasonography of the graft and native kidneys in high-risk recipients, with cross-sectional imaging for suspicious findings [6]. The rationale is supported by registry data showing a cumulative RCC risk of ~0.5% at 5 years and ~1% at 10 years post-transplant [1]. Early detection may permit curative treatment while preserving graft function.

A limitation of our report is that molecular genotyping to determine the donor versus recipient origin of the RCC was not performed. Techniques such as short tandem repeat (STR) profiling, XY fluorescence in situ hybridization (FISH) in sex-mismatched transplants, or next-generation sequencing–based chimerism analysis provide definitive attribution of tumor origin and are increasingly recommended in transplant-oncology evaluations. These assays were not available at our center at the time of diagnosis, and the patient's rapid clinical deterioration precluded referral for external testing. Nevertheless, future cases would benefit from incorporating such molecular analyses, as they help clarify whether a malignancy is donor-derived, donor-transmitted, or de novo, thereby guiding surveillance strategies and informing transplant safety practices.

In conclusion, this case highlights the clinical challenges posed by renal cell carcinoma arising in a renal allograft, an uncommon but consequential complication of kidney transplantation. Early detection remains difficult because allograft RCC may be asymptomatic and lacks standardized surveillance recommendations. While several registries suggest that targeted imaging may facilitate earlier diagnosis, the benefits of routine screening must be weighed against potential limitations—such as false positives, cumulative testing costs, and the absence of validated intervals or modality-specific protocols. In view of these uncertainties, a cautious, risk-stratified approach appears most appropriate. Existing literature supports consideration of periodic ultrasound or cross-sectional imaging in high-risk groups, such as recipients with older donors, prolonged dialysis vintage, acquired cystic kidney disease, smoking history, or long-term calcineurin inhibitor exposure. However, evidence remains insufficient to endorse universal screening. Given the absence of universal guidelines and limited prospective data, surveillance should be individualized using a risk-based frame-

work. This approach balances early detection against the risk of overdiagnosis, costs, and procedural burden. Larger multi-center studies are needed to determine which subgroups derive the greatest benefit and to establish evidence-based intervals.

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