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Case Report

Nonfamilial Bilateral Synchronous Renal Cell Carcinoma with Discordant Histology with Eventual Complete Response to Dual Immunotherapy

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Abstract
Bilateral synchronous renal cell carcinoma (RCC) is rare, especially in sporadic rather than familial cases. While immunotherapy has improved prognosis, RCC remains a diagnosis with significant morbidity and mortality, particularly pronounced in patients with sarcomatoid RCC (sRCC). We describe a case of a patient with bilateral, synchronous, nonfamilial RCC, with and without sarcomatoid features and differing genetic markers, who demonstrated a pathologic response after neoadjuvant nivolumab and ipilimumab. The patient then had radical left nephrectomy and partial right nephrectomy followed by adjuvant nivolumab and cabozantinib, after which the patient had no evidence of disease. Our patient's illustrative case shows the potential therapeutic value of immunotherapy even in sRCC, the disease's most aggressive clinical subtype.

Introduction

Bilateral, synchronous renal cell carcinoma (RCC) is exceptionally rare, occurring in less than 5% of cases of RCC [1]. RCC with sarcomatoid features is the most aggressive clinicopathologic phenotype of RCC, and prior to the recent advent of immunotherapy, portended a median overall survival of less than 12 months [2, 3]. Recent meta-analyses have suggested an emerging role for immune checkpoint blockade (ICI) as single agent and in immuno-

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oncology combinations as a suitable treatment with an increased chance of achieving complete remission in patients with RCC [4, 5]. We describe a case of a patient with bilateral, synchronous, nonfamilial RCC, with and without sarcomatoid features, treated with dual ICI.

Case Report

A 47-year-old male with a past medical history including benign prostatic hyperplasia, right renal cyst, and chronic low back pain presented to the Emergency Department for 1 month of persistent, nonproductive cough with associated exertional dyspnea and fatigue. He was noted to be mildly tachycardic but not hypoxic; further review of systems was notable for chronic intermittent hematuria for over 10 years (prior imaging suggestive of right renal cyst), although no episodes within the preceding 6 months. His family history was notable for his mother and maternal cousin with polycystic kidney disease, without a history of malignancy.

Work-up at the time revealed leukocytosis (10.1×10^3) with neutrophilic predominance, serum calcium 9.6 mg/dL (nmL 8.6–10.2), elevated CRP (6.44 mg/dL), elevated fibrin d-dimer (0.90 μg/mL), and normocytic anemia (Hgb 10.2 g/dL) with a negative respiratory viral panel and unremarkable chest radiograph. Given his elevated d-dimer, a CT angiogram of the chest was performed, which was negative for pulmonary embolism but was notable for a right renal mass.

Further dedicated imaging with a contrast MRI of the kidneys re-demonstrated the right renal mass (10.4 × 7.8 × 6.1 cm) and showed hypoenhancement of the inferior aspect of the left kidney and corresponding enhancement of the left renal vein, suggestive of infiltrative process/malignancy (Fig. 1a). CT with contrast corroborated these findings and showed no concerning masses in other organs. Interventional radiology then obtained biopsies of both masses. The right renal mass was consistent with grade 4 RCC unclassified, noted to have sarcomatoid features. In contrast, the left renal mass was diagnostic of grade 4 RCC unclassified without a sarcomatoid component.

Next-generation sequencing (NGS) was ordered using an OmniSeq Insight panel. Results from the right RCC showed no actionable genetic mutations, microsatellite stable, with tumor proportion score (TPS) of 80%; this result was available before systemic therapy. Next-generation sequencing testing of the left RCC showed genetic variants in NF2 D281fs and von-Hippel Lindau R167Q, microsatellite stable, with TPS 10%. Germline genetics evaluation was unremarkable, suggesting both mutations to be sporadic. The differentiation of tumor characteristics is summarized in Table 1.

His case was presented at a multidisciplinary tumor board. Dual ICI was recommended, with a plan for left radical and right partial nephrectomy versus bilateral radical nephrectomy after the initial immunotherapy. The patient was informed of these recommendations and agreed with the plan, and subsequently received four cycles of nivolumab 3 mg/kg and ipilimumab 1 mg/kg administered every 21 days. During cycle 2 of treatment, the patient developed a mild COVID infection managed with Paxlovid. During cycle 3, he developed localized edema of the right eyelid and face without airway compromise, managed with oral prednisone and levofloxacin. He completed four planned cycles of ICI without delay or dose reduction. After neoadjuvant treatment, a repeat MRI demonstrated an interval decrease in the size of the right renal mass (7.0 × 6.2 × 8.2 cm) but an unchanged size of the left renal mass with persistent thrombus in the left renal vein (Fig. 1b). There was no evidence of metastasis on CT chest or MRI abdomen.

Approximately 6 weeks after his last cycle of ICI, he underwent left radical and right partial nephrectomies with retroperitoneal lymph node dissection. Results from these

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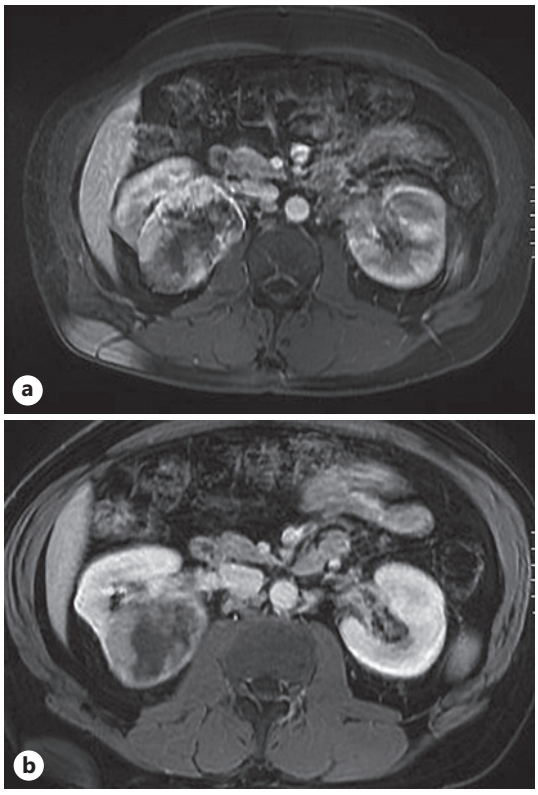

Fig. 1. a Contrast MRI of kidneys prior to treatment. Initial MRI demonstrated a heterogeneously enhancing large right renal mass (10.4 × 7.8 × 6.1 cm) and hypoenhancement of the inferior aspect of LT kidney with enhancement of LT renal vein. **b** Contrast MRI post-neoadjuvant immunotherapy. Repeat MRI demonstrated interval decrease in size of the right renal mass (7.0 × 6.2 × 8.2 cm) but unchanged size of the left renal mass with persistent thrombus in left renal vein.

surgical specimens demonstrated no residual malignancy in the left kidney, i.e., pathologic complete response, suggesting the visualized mass on preoperative MRI was post-immunotherapy residual scar tissue rather than persistent neoplasm. The right kidney specimen demonstrated residual malignancy – grade 4 with rhabdoid and sarcomatoid features and lymphovascular invasion, positive margins, and lymph node involvement in the retrocaval, right peri-hilar, and right retrocrural regions, ypT2ap N1p M1, total 4/85 positive lymph nodes. The patient's postoperative course was complicated by urinoma requiring left ureteral stent placement, retroperitoneal abscess, and dysautonomia. Approximately 1 month after surgery and recovery from postsurgical complications, and 15 weeks since the last ICI treatment, he was started on adjuvant nivolumab 480 mg IV every 4 weeks.

Before cycle 2 of adjuvant nivolumab, the patient was admitted for enterococcus bacteremia with enlarging fluid collections in the perinephric space, right psoas muscle, and concurrent right retroperitoneal lymphadenopathy. The perinephric space and psoas muscle biopsies showed metastatic RCC with sarcomatoid features. Given progressive disease on single agent nivolumab, cabozantinib 40 mg daily was added. Short interval response imaging at 6 weeks after initiation of combination therapy showed decreased size of known metastatic burden and subjective symptom improvement from the patient. Repeat imaging after 3 months of combination therapy showed no evidence of disease.

Discussion

Bilateral synchronous RCC occurs in an estimated 2–5% of patients with RCC; in one large-scale study of 41,000 patients with RCC, only 31 individuals presented with bilateral malignancies [6]. Of these, the vast majority are associated with familial hereditary

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Table 1. Summary of right and left renal tumor characteristics: tumor size, staging, histologic and genetic features

	Right kidney	Left kidney
Tumor characterization		
Size (at diagnosis)	10.4 × 7.8 × 6.1 cm	5.7 × 3.7 cm
Size (post-neoadjuvant)	7.0 × 6.2 × 8.2 cm	4.2 × 3.4 cm
TNM stage	T2b N0 M0	T3a N0 M0
Immunostaining		
PAX8	Strong nuclear	Nuclear
CA IX	Strong cytoplasmic	Complete membranous
CD10	Strong, diffuse nuclear, and cytoplasmic	Positive within cells
CK7	Negative	Negative
HMB45	Negative	Negative
GATA-3	Negative	Negative
p63	Negative	Negative
Sarcomatoid features	Present	Absent
Next-generation sequencing		
TMB	–	TMB 0
NF2 mutation	NF2 D281 fs	–
MSI	–	Low
VHL mutation	VHL R167Q	–
PDL1 TPS, %	10	80
Germline mutation	None	None

VHL, von-Hippel Lindau.

syndromes, including von-Hippel Lindau, hereditary papillary RCC (HPCC), and Birt-Hogg-Dubé syndrome [7]. Clear cell carcinoma is the predominant histologic subtype in over 80% of cases, with papillary, chromophobe, and undifferentiated RCC comprising a much smaller proportion of cases [8]. Discordant histology in bilateral RCC is less commonly observed.

Tumor grade and patient age, but not laterality, have been shown to impact overall survival when comparing patients with unilateral versus bilateral malignancy [9]. In particular, sarcomatoid differentiation, irrespective of tumor histology, has been shown to be an independent predictor of poor prognosis [10]. While no explicit guidelines exist for the management of bilateral RCC, in clinical practice, bilateral nephron-sparing surgery (NSS) with partial nephrectomy is preferred over bilateral nephrectomy, with systemic therapy as indicated for higher grade tumors [11]. Neoadjuvant immunotherapy with dual ICI has become a first-line option [12] in advanced RCC; immunotherapy with concurrent tyrosine kinase inhibitor (TKI) is another first-line option [12]. In a recent phase III study of 651 patients with previously untreated advanced RCC comparing nivolumab 240 mg q2 weeks + cabozantinib with sunitinib monotherapy, which included patients with sarcomatoid histology, median progression-free survival was 16.6 months in the combined ICI + TKI group as compared to 8.8 months with Sunitinib alone [13].

Other studies have also cited improvements in progression-free survival and health-related quality of life when ICI therapy is part of the upfront treatment regimen for RCC [14]. Although NCCN guidelines recommend cabozantinib or sunitinib as the two preferred

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treatment regimens in non-clear cell RCC, we selected single-agent nivolumab postoperatively, given our patient's initial robust response to dual ICI [15, 16]. Postoperative single-agent nivolumab was unsuccessful in this case, which was unexpected due to the high PDL-1 in the left renal mass. However, the lack of response was expected for the right RCC tumor with low PDL-1. The difference in initial response could be explained by the limitations of knowing the complete architecture of the tumor based on a single biopsy which is a snapshot of a particular region of the tumor. The initial responding area could have corresponded to a section of the tumor with high PDL-1 expression that was not uniform throughout the tumor. The subsequent addition of cabozantinib to nivolumab resulted in a strong clinical and radiographic response that has since been sustained.

Overall, this case reiterates the increased role that immunotherapy will play going forward in RCC treatment, its benefit in a patient with particularly aggressive, bilateral RCC, and its potential use in the neoadjuvant setting, either combined ICI or combination ICI + TKI in an attempt to promote nephron-sparing surgery and preserve renal function. Note that the CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533936).

Statement of Ethics

This research was developed in an ethical manner with respect to patient's right to self-determination, privacy, and confidentiality. Ethics board approval is not required for this case report in accordance with local guidelines. Written informed consent was obtained from the patient for publications of medical case and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

Ian J. Robertson was the primary author who wrote up the initial case report, performed literature review, and incorporated edits of the secondary authors. Sierrah G. Grigsby assisted with secondary revisions as well as response to reviewer comments and constructing provided table. John C. Mattingly contributed to case write-up, provided proofreading/edits, and was the primary provider involved in the treatment of this patient. Dean K. Park provided critical review of the details of the case and discussion, as well as editing/proofreading.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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