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Case reports in renal cell carcinoma

Edited by
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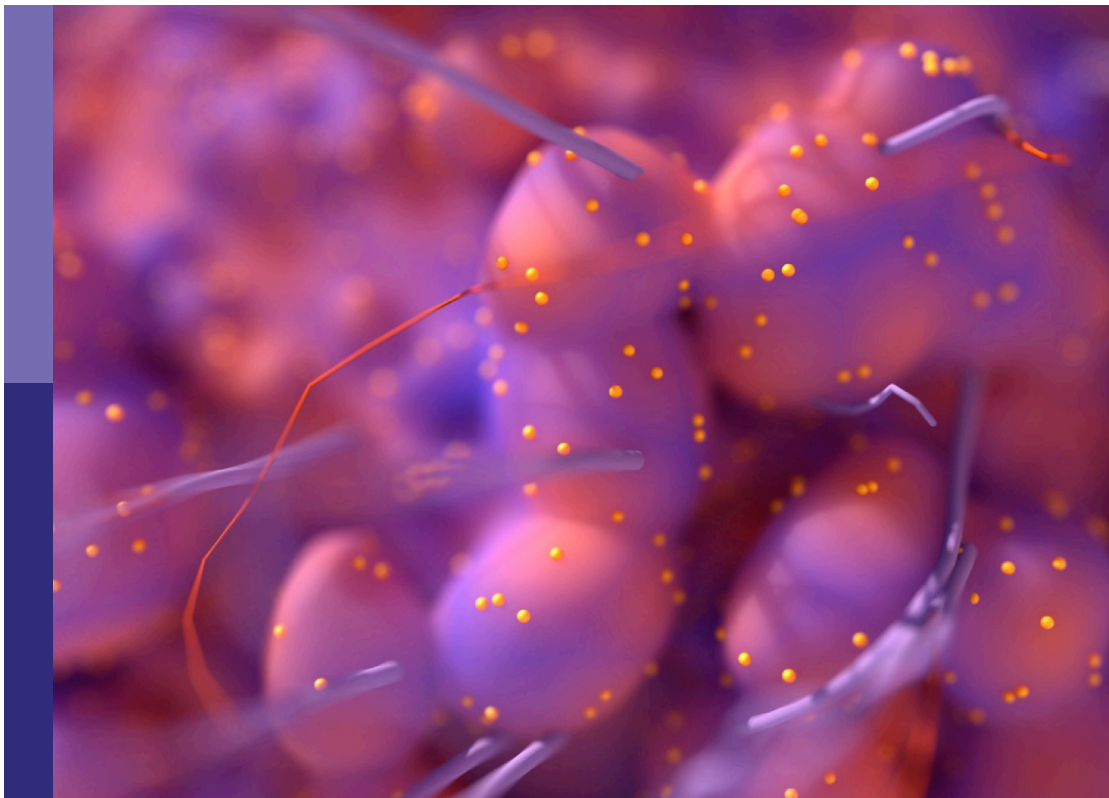
Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-83251-925-7
DOI 10.3389/978-2-83251-925-7

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Case reports in renal cell carcinoma

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Citation

Beckermann, K., Bilen, M. A., eds. (2023). *Case reports in renal cell carcinoma.* Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-925-7

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frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 01 March 2023
DOI 10.3389/fonc.2023.1165013

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

RECEIVED 13 February 2023
ACCEPTED 16 February 2023
PUBLISHED 01 March 2023

CITATION
Zhuang TZ, Mustafa SM, Beckermann KE and Bilen MA (2023) Editorial: Case reports in renal cell carcinoma. *Front. Oncol.* 13:1165013. doi: 10.3389/fonc.2023.1165013

Editorial: Case reports in renal cell carcinoma

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KEYWORDS

renal cell carcinoma, biomarker, immunotherapy, next-generation sequencing cytoreduction

Editorial on the Research Topic
Case reports in renal cell carcinoma

Background

Renal cell carcinoma (RCC) is one of the most common malignancies worldwide with nearly 81,000 new cases and 15,000 deaths annually (1). Clear cell RCC (ccRCC) is the most common histologic subtype. Immune checkpoint inhibitors (ICI) have been approved as a frontline treatment in recent years, with nivolumab/cabozantinib, pembrolizumab/levantinib, and pembrolizumab/axitinib approved for all risk groups, while nivolumab/ipilimumab is reserved for intermediate-to-poor risk disease (2–7). While the presentation of case reports and series may not represent practice-changing data, we believe it can spark new thoughts regarding biology, mechanisms, therapeutic options, and responses. Despite significant advances in immunotherapy and the discovery of novel biomarkers, the management of RCC is complex, owing to its heterogeneity, with multiple histological and genomic subtypes. This brief review describes 12 unique cases presented by 87 authors exploring the role of next-generation sequencing in treatment selection, rare disease and treatment complications, and the management of oligometastatic disease.

The role of next-generation sequencing in management of RCC

Mikhaylenko et al. and Huang et al. present cases of papillary RCC. The first patient developed multiple, bilateral type 1 papillary RCC tumors with a germline heterozygous missense variant in *MET*, which promotes unchecked cellular division in hereditary papillary renal cell carcinoma (Mikhaylenko et al.). They discuss oncogenic drivers in SWI chromatin complex disruption and explore the importance of next-generation sequencing for the development of an adjuvant treatment selection. The other patient was found to have an incidental large type 2 papillary carcinoma measuring 15 centimeters, underwent surgical resection, and recovered well without recurrence (Huang et al.). Given

that PRCC is a complex tumor with varying genetic and molecular heterogeneity, the selection of targeted therapy with NGS for relapsed/refractory cases may prove to be beneficial.

Lian et al. describe PARP inhibition in a patient with BAP1 mutation as a potential treatment in ccRCC, progressing after TKI/mTOR therapy and intolerance to ICI therapy. The patient originally achieved partial response with a 28-month sequenced regimen of TKI-TKI-mTOR and cytoreductive nephrectomy but later developed CNS and pulmonary metastasis. Next-generation sequencing revealed a frame shift pathogenic mutation in BAP1 (3p21.1) in ccRCC, and niraparib was subsequently started, achieving a partial response of five months. BAP1 mutations across cancer types were identified in RCC, pleural mesotheliomas, cholangiocarcinoma, and ocular melanoma. BAP1 acts as a tumor suppressor and inhibits E3 ligase activity in BRCA1/BARD1. This process inhibits ubiquitination and promotes deubiquitination of existing ubiquinated chains. Wang et al. present a patient with asymptomatic Birt–Hogg–Dube syndrome and a history of spontaneous pneumothorax. She was found to have a concurrent germline and novel somatic mutation in the folliculin gene (FLCN). The authors posit the clinical relevance of a somatic FLCN mutation in conferring familial risk by conducting correlative studies on FLCN, TFEB/TFE3, mTOR, and cilia length. TFEB was found to be constitutively expressed in the nucleus of the FLCN germline-mutated tissue, whereas TFE3, phosphorylated mTOR, and cilia were highly expressed in FLCN-deficient tissue. The authors emphasize the potential role of FLCN inactivation on TFEB/TFE3 migration in the tumor microenvironment. These case reports highlight the growing role of molecular studies in understanding ccRCC disease progression.

Martini et al. and Miroński et al. describe a rare diagnosis of translocation-associated RCC (tRCC), typically seen in the pediatric and younger adult population. Mutations in TFE3 and TFEB define this aggressive, rare RCC variant that lacks targeted treatments. One patient achieved an exceptional response to nivolumab and ipilimumab (Martini et al.). The authors then highlight intratumoral niches rich in TFC1+ CD8+ T cells and lymphovascular invasion as potential biomarkers of response. In another rare case of this, a patient with metastatic RCC underwent left radical nephrectomy and adrenalectomy with adjuvant temsirolimus, resulting in 10-month DFS until palliative radiation was required for spinal decompression (Miroński et al.). These cases highlight poor outcomes in this aggressive variant, with a recent retrospective study reporting mOS of 17.8mo in dual ICI and VEGF treatment (8).

Rare cases of RCC complications and treatment events

Recent case reports have emerged that describe rare and atypical presentations of RCC. Nkengurutse et al. describe an atypical case of metastatic RCC to the left atrium without IVC involvement complicated by coronary sinus invasion. Surgical resection and coronary sinus repair allowed for complete tumor removal, with the patient recovering well. Yang et al. present a rare diagnosis of anti-N-methyl-D-aspartate (NMDA) encephalitis as a paraneoplastic manifestation of ccRCC. The patient's symptoms resolved with pulse steroids and IVIG. Billon et al. highlight the development of vitiligo in the setting of a durable complete response with immunotherapy. The patient had progressed on frontline sunitinib for metastatic RCC and achieved a pCR to nivolumab after six months of treatment that was complicated by hyperthyroidism and vitiligo. The authors discuss the rarity of vitiligo as an irAE, which has been associated with a positive response marker, and the unanswered role of immunotherapy discontinuation in pathologic complete response.

Schmeusser et al. describe a complex case in balancing management of solitary kidney tumors and renal function preservation. The patient had a history of childhood Wilm's tumor treated with right nephrectomy and adjuvant chemotherapy, but they later developed a new malignant left solitary renal mass. A core needle biopsy was unable to differentiate between benign oncocytoma and chromophobe RCC. A complex open partial nephrectomy was performed for tissue sampling and the symptoms of mass effect. The renal function was preserved with perioperative nephrology guidance.

Management of oligometastatic RCC

Zhuang et al. and Qin et al. report cases of oligometastatic involvement in RCC. The first patient is a Jehovah's witness who responded to two cycles of nivolumab and ipilimumab and subsequently underwent a successful cytoreductive nephrectomy and a left pulmonary metastatectomy with minimal intraoperative blood loss (Zhuang et al.). The patient continues to demonstrate a complete durable response. The authors then discuss the CARMENA and SURTIME trials and explore the role of secondary cytoreductive nephrectomy in the immunotherapy era. The other patient developed a rare muscle metastasis in RCC involving the masseter (Qin et al.). The patient was able to be observed until the mass effect required surgical resection. The surgical resection was successful, with negative surgical margins and no evidence of disease at follow-up.

In summary, this Research Topic provides a selection of cases highlighting the complexity of RCC diagnosis and treatment in relation to surgical management, rare disease, treatment complications, and the emerging role of next-generation sequencing in the immunotherapy era. We thank the authors for their contributions to this Research Topic.

Author contributions

TZ and SM drafted the editorial. MB and KB edited the manuscript. All authors contributed to this work and gave approval to the final version.

Conflict of interest

MB has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Calithera Biosciences, Genomic Health, Nektar, EMD Serono, SeaGen, and Sanofi, and his institution has received grants from Merck, Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, SeaGen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer for work performed outside of the current study. KB has acted as a paid consultant for and/or as a member of the advisory boards of LCFA-BMS-IASLC for Young Investigator Award, Alpine Biosciences, Aravive, Astrazeneca, Aveo, BMS, Exelexis, Merck, Sanofi, and Seagen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Oncology

CASE REPORT
published: 07 August 2019
doi: 10.3389/fonc.2019.00738

Renal Cell Carcinoma Metastasizing to Left Atrium With Coronary Sinus Invasion: A Rare Site of Metastasis Mimicking Myxoma

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Renal cell carcinoma (RCC) metastasizing to the heart with inferior vena cava (IVC) involvement is well-documented. However, its metastasis to the right heart without venous involvement is very rare. To the left atrium, metastasis is even rarer with only a few cases reported in medical literature. Herein, we report a case of a 56-year-old man who presented to our department for the treatment of a right renal mass and a right adrenal mass discovered on a follow-up plain computed tomography (CT) 13 years after left laparoscopic radical nephrectomy. During the workup, a transthoracic echocardiography (TTE) revealed a left atrial mass with a suspicion of a myxoma. This finding prompted a cardiac surgery consult which proposed a surgical removal of the mass. Intraoperatively, the tumor was found to invade the coronary sinus as well. The entire tumor was successfully removed and surgical repair of the unroofed coronary sinus was performed. Pathological examination of the tumor along with immunohistochemistry–showing positivity for CAIX, CD10, Vimentin, and PAX-8–pointed to a diagnosis of metastatic clear cell RCC. Eight months postoperatively, he was free of any symptom. In conclusion, RCC metastasizing to the left atrium is extremely rare. A comprehensive search revealed only nine reports in the literature. We report, to our knowledge, the first case of RCC metastasizing to the left atrium with concomitant invasion of coronary sinus. Surgical resection combined with unroofed coronary sinus repair allowed a complete removal of the tumor. In patients with a history of RCC, a metastasis should be thought of when a left atrial mass is present.

Keywords: renal cell carcinoma, RCC, left atrium, coronary sinus, metastasis, myxoma

OPEN ACCESS

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *29 May 2019*
Accepted: *23 July 2019*
Published: *07 August 2019*

Citation:
Nkengurutse G, Wang Q, Tian F, Jiang S, Zhang L and Sun W (2019) Renal Cell Carcinoma Metastasizing to Left Atrium With Coronary Sinus Invasion: A Rare Site of Metastasis Mimicking Myxoma. Front. Oncol. 9:738. doi: 10.3389/fonc.2019.00738

INTRODUCTION

Renal cell carcinoma (RCC) is an aggressive malignancy representing 2–3% of all cancers, and it is the most lethal of all urologic cancers. In 2018, there were approximately 136,500 new cases of renal cancer and 54,700 kidney-cancer-related deaths in Europe (1).

RCC is a highly metastatic malignancy with 20–30% of patients having a metastatic or a locally advanced disease at the time of diagnosis (2). While metastasis can occur almost anywhere, the most common sites of metastasis are the lungs, the liver, bones and the brain.

Cardiac metastases from RCC are uncommon. In most cases, cardiac metastases are concomitant with IVC tumor thrombus where a further extension reaching the right atrium is

found in approximately 1% of all patients (3). However, metastasis to the right heart without IVC involvement is very rare. To the left atrium, metastasis is even rarer with only a few reports in the literature.

Herein, we report a rare case of left atrial metastasis with coronary sinus invasion 13 years after left laparoscopic radical nephrectomy for RCC and provide a review of the relevant literature.

CASE PRESENTATION

A 56-year-old Chinese male presented to our department in September 2018 with a right renal mass and a right adrenal mass discovered on a follow-up plain CT half a month before. The patient had left radical nephrectomy 13 years before for left RCC and he had a regular follow-up without any sign of recurrence or metastasis. Physical examination was unremarkable and the patient was otherwise doing well without any symptom. He had type 2 diabetes mellitus for 9 years wherein metformin and insulin were used to control blood glucose. A radical operation for rectal cancer was performed 7 years before. He had a history of heavy cigarette smoking with an average of 20 cigarettes per day for 60 years and a 60-year history of alcohol drinking (average 1 bottle of beer per day).

Work-up: An abdominal and pelvic non-contrast CT revealed a 36 × 31-mm, ellipsoid, and hypodense mass in the external branch of the right adrenal region (**Figure 1A**). It was well-demarcated with a CT value of about 27 Hounsfield units (HU). Hypodense lesions with a diameter of 15 mm and 39 mm were discovered in the upper and lower poles of the right kidney, respectively (**Figures 1B,C**). Their mean CT attenuation value was 39 HU. No renal vein or IVC tumor thrombus was visualized. Routine blood tests (including LDH, calcium) were unremarkable.

During the patient evaluation phase, a non-contract CT of the chest revealed multiple nodules in both lungs, the largest one being located in the middle lobe of the right lung (**Figure 1D**). Compared with findings of a follow-up chest CT taken in February 2016, some of the nodules were enlarged, suggesting a metastasis. No abnormality was found on the heart and big vessels; and no mass or enlarged lymph nodes were seen in the mediastinum. A TTE was performed, revealing a 23.9 × 13.4-mm, hyperechoic mass with a smooth surface in the left atrium, close to the posterior leaflet of the mitral valve, and moving without extension to the outflow tract during the cardiac cycle (**Figure 2A**). This imaging modality suspected a diagnosis of myxoma. The ejection fraction was 62% and no abnormality was found on electrocardiography.

Prior to any other intervention, a cardiac surgery consult was sought, suggesting surgical removal of the mass due to the risk of it to detach. The patient was then transferred to cardiac surgery department where a repeat TTE showed a 27.7 × 16-mm isoechoic mass attached to the posterior leaflet annulus of the mitral valve in the enlarged left atrium (**Figure 2B**). While the mass was following the mitral annulus moving toward the left atrial side during early diastole, it was tending to move toward the mitral valve orifice during late diastole and systole. Transesophageal echocardiography (TEE) revealed an enlarged left atrium and a 27.7 × 16-mm, isoechoic atrial mass of inhomogeneous echogenicity. It was attached with a broad base between the posterior leaflet of the mitral valve and the coronary sinus. A part of the atrial wall was protruded outwards and there was no clear margin between the protrusion and the coronary sinus. A capsule could be visualized around the mass. Despite the metastatic status of the patient, surgical removal of the atrial mass was scheduled since there was a risk of it to detach and cause embolism.

Through a median sternotomy, cardiopulmonary bypass (CPB) was established by cannulating the ascending aorta and the superior and inferior vena cava. The plan was a hypothermic CPB with cold cardioplegia. After and through right atriotomy, an incision was made in the fossa ovalis, exposing a yellow mass close to the posterior leaflet of the mitral valve. It was a mass with a broad base rather than a pedicle. When the part of the tumor protruding inwards was entirely removed, the remaining part of the tumor was found to be in immediate vicinity of the coronary sinus. Via a longitudinal incision in coronary sinus, the tumor was entirely removed with its intact pseudocapsule. An exploration of the left atrium and the opening of pulmonary veins did not reveal any residual tumor. An artificial pericardial patch was applied to the incised part of the coronary sinus and the latter was successfully repaired without causing any leakage. Pericardial patch was also used to close the fossa ovalis and the right atriotomy was closed. Post-operative TEE did not reveal any residual tumor or abnormality in coronary sinus drainage. Two specimens of 2.7 × 1.5 × 1.5 cm and 2 × 1.7 × 0.7 cm were obtained (**Figure 3A**). They were yellowish and cystic-solid with a tumor pseudocapsule (**Figures 3B,C**). Microscopically, the tumor cells were of clear cytoplasm with an acinar architecture (**Figure 4D**). Immunohistochemical staining showed positivity for CAIX, CD10,Vimentin, and PAX-8 and negativity for CK7, calretinin, WT1, WT1,CK5/6, CK20, Villin, and CDX2 (**Figure 4**). The postoperative period was uneventful. The patient was discharged with a recommendation to consult the department of cardiac surgery after 1, 3, and 6 months, and the departments of urology and oncology to ensure a multidisciplinary treatment. Four months postoperatively (on 2019 January 31st), he was contacted by telephone and he reported not seeking any further treatment because he was free of any symptom. We contacted the patient for the second time after 8 months (on 2019 May 27th). He was doing well and was going to his daily activities without any symptom. He denied any targeted therapy or immunotherapy use. We recommended him again to recheck and seek management for the renal and adrenal masses.

DISCUSSION

RCC is an aggressive disease accounting for 3% of all human malignancies and it is the most lethal of all the urologic cancers. In 2018, there were ∼136,500 new cases of renal cancer and 54,700 kidney-cancer-related deaths in Europe (1). Its incidence

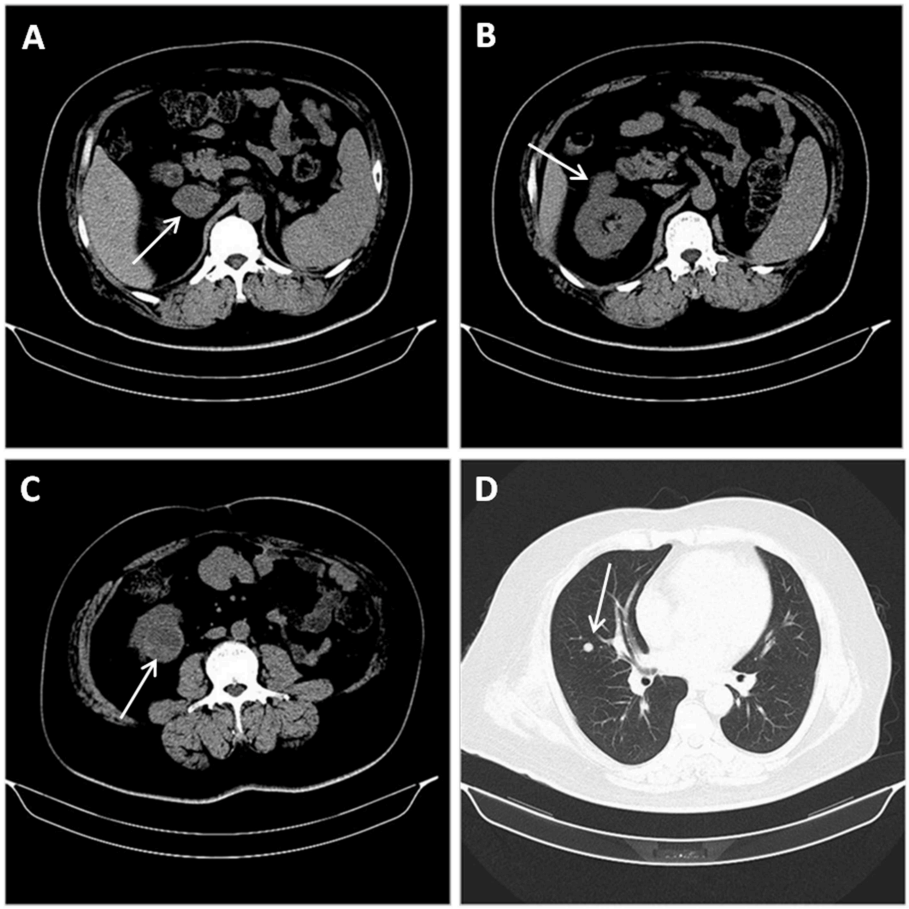

FIGURE 1 | Abdominal and pelvic non-contrast CT revealing a 36 × 31-mm, well-demarcated, ellipsoid and hypodense mass with a CT value of about 27 Hounsfield units (HU) in the external branch of the right adrenal region. **(A)** Hypodense lesions with a diameter of 15 mm and 39 mm discovered in the upper **(B)**, and lower **(C)** poles of the right kidney, respectively. Non-contract CT of the chest suggesting lung metastasis: multiple nodules in both lungs, the largest one being located in middle lobe of the right lung **(D)**.

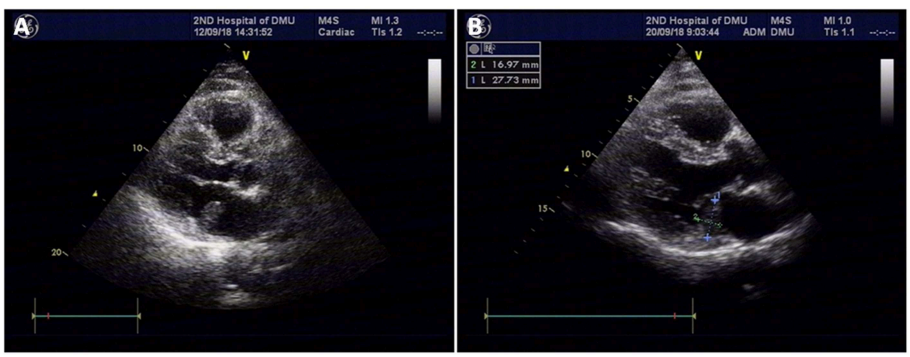

FIGURE 2 | TTE revealing a 23.9 × 13.4-mm, hyperechoic mass with a smooth surface in the left atrium, close to the posterior leaflet of the mitral valve, and moving without extension to the outflow tract during the cardiac cycle; the mass was suspected to be a myxoma **(A)**. Repeat TTE showing a 27.7 × 16-mm isoechoic mass attached to the posterior leaflet annulus of the mitral valve in the enlarged left atrium **(B)**.

has been increasing due in part to lifestyle factors and the widespread use of imaging studies, allowing many RCC to be discovered incidentally. Indeed, the classical presentation of RCC—the triad of gross hematuria, flank pain and palpable abdominal mass—is nowadays not common. This triad has been recently sometimes described as the "too late triad."

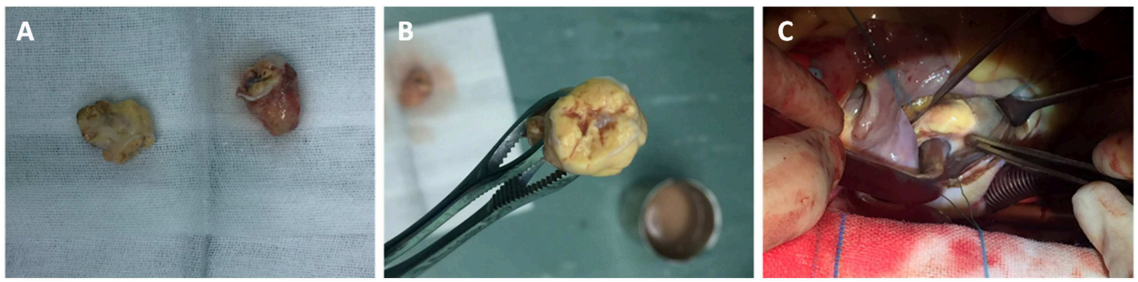

FIGURE 3 | Two specimens of 2.7 × 1.5 × 1.5 cm, and 2 × 1.7 × 0.7 cm **(A)**. They were yellowish and cystic-solid with a tumor pseudocapsule **(B,C)**.

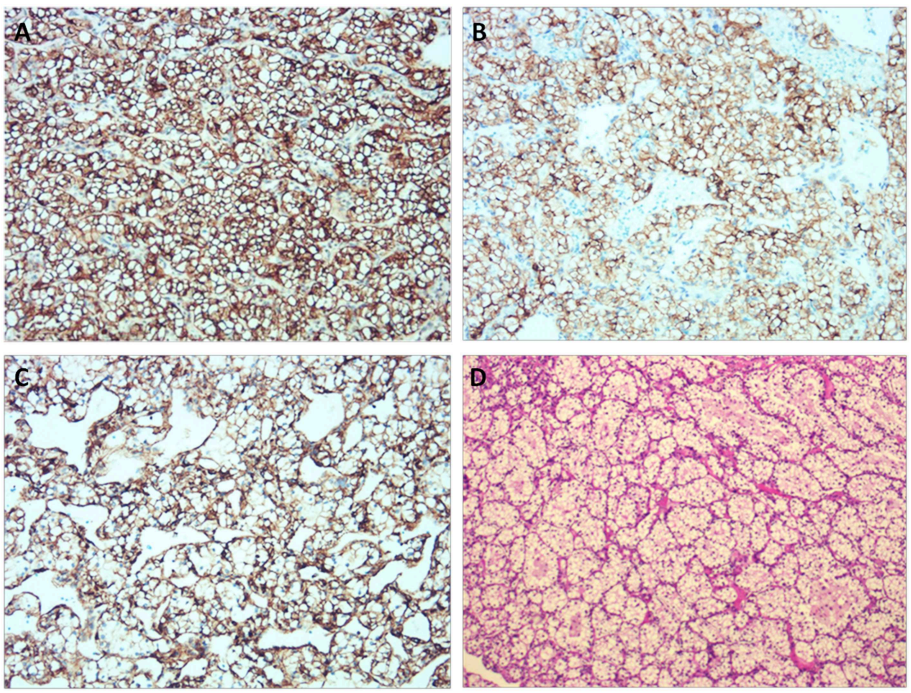

FIGURE 4 | Immunohistochemical staining showing positivity for CAIX, CD10, and Vimentin. **(A)** CAIX (×200). **(B)** CD10 (×200). **(C)** Vimentin (×200). **(D)** Histological examination of the tumor using Hematoxylin & Eosin stain.

RCC is characterized by a high propensity to metastasis. On presentation, 25% of patients already have a metastatic or a locally advanced disease. The most common sites of metastasis are the lungs, the liver, bones, the brain and the adrenal glands. However, metastatic RCC to the heart are very rare, most of which occurring concomitantly with IVC involvement. Without IVC involvement, cardiac metastases in general and left atrial metastases in particular, are even rarer, with only a few cases reported in the literature. Herein, we present a case of LA metastasis from RCC in a patient who had undergone left laparoscopic radical nephrectomy 13 years before. We further reviewed previously published cases and summarized the findings in **Table 1**.

A comprehensive search in PubMed and Web of Science was conducted using keywords and Boolean operators as follows: [(metastasis OR metastatic) AND (renal cell carcinoma OR renal cancer)] AND (atrial OR atrium). The search was updated till February 24th, 2019 without any language restriction to detect LA metastases from RCC without IVC involvement. A hand search in Google scholar was also performed. To date, only 9 cases are available in the literature (4–12). The present report is the 10th case of LA metastasis from RCC. We did not find any previous report describing LA metastasis with concomitant coronary sinus invasion.

Due to the risk of sudden death, embolism, and intraoperative or perioperative events in every patient with an intracardiac mass (11), it is wise to seek a cardiovascular or cardiothoracic surgery consult in such patients before any other intervention. Myxoma will be suspected first as it is the most common primary cardiac tumor (5). In fact, in the biopsy of 266 patients with cardiac masses, only 1.1% were RCC (13). In our patient, imaging study (TTE) pointed to a myxoma (see **Figure 2**),

TABLE 1 | Patients' characteristics and the course of disease in all reported LA metastases from RCC.

References	Age(years)/ Sex	Presentation	Other sites of metastasis	Treatment	Years from nephrectomy	Diagnostic tools	IHC	Follow-up (months) and outcome
Patane et al. (4)	58/F	asymptomatic	Left lower lobe of the lung, PV	Resection of the LA mass through sternotomy, video-assisted left lower lobectomy	ND	ND	ND	No recurrence, 13 months
Fogel et al. (5)	77/M	dizziness, syncope, dyspnea, atrial fibrillation	Left lung, PV	Left pneumonectomy, partial atrectomy through left thoracotomy	8	History, TTE, MRI, intraoperative findings	ND	Died postoperatively of respiratory complications
Miyamoto et al. (6)	56/M	Syncope	Mediastinal LN, right inferior PV, previously in lungs, intra-abdominal, spine.	Resection of the LA mass through sternotomy, lymphadenectomy	3	History, chest CT, TEE, histopathology	ND	No recurrence, 4 months
Cochennec et al. (7)	42/F	asymptomatic	Left lower lobe of the lung, left inferior PV	Resection of LA mass and of the left lower lobe though sternotomy associated with left anterolateral thoracotomy	4 and 2 from left and right nephrectomies respectively	History, chest CT, TEE, PET, histopathology, IHC	(+): cytokeratin AE1/AE3, vimentin and CD10. (–): CK 7 and CK20.	No recurrence, 8 months
Seker et al. (8)	37/M	Numbness, cerebellar and thalamic acute ischemic lesions	Left lung, muscle, cerebellar tentorium, left inferior PV	Tyrosine kinase inhibitor (axitinib)+ anticoagulant	6	History, PET, TEE, cardiac MRI, coronary CT,	ND	ND
Tolay et al. (9)	56/F	dyspnea	Right hilar LN, right PV, previously in both lungs	mTOR inhibitor (Temsirolimus)	3	History, chest CT	ND	11 months, stable disease
Tabakci et al. (10)	48/F	cough and hemoptysis	Left lower lobe of lung, left inferior PV	Tyrosine kinase inhibitor (sunitinib)	8	Chest CT, PET, lung and LN biopsy, IHC	CD10 (+)	ND
Ohba et al. (11)	75/M	consciousness disturbance	Both lungs, lymph nodes, right superior PV, pubic bone	Complete surgical resection of the LA mass, Interferon-alpha, sorafenib then everolimus for lung metastasis, radiotherapy for pubic bone metastasis	4	History, TTE, histopathology	ND	Died from progressive disease 4 months postoperatively.
Strauch et al. (12)	51/F	Dyspnea, hypertension, atrial fibrillation	Right lower PV	Tumor removal through left atriotomy+ Tyrosine kinase inhibitor (sunitinib)	1/4	History, chest CT,MRI, histopathology	pancytokeratin-expressing areas of the previously resected RCC	Continued to do well at 6 months with unobtrusive chest CT
Present case	56/M	asymptomatic	Both lungs, coronary sinus, right kidney, right adrenal gland	Resection of the atrial mass through sternotomy, Surgical repair of the unroofed coronary sinus	13	History, TTE, TEE, histopathology, IHC	(+): CAIX, CD10, vimentin and PAX-8. (–): CK7,calretinin,WT1, WT1,CK5/6, CK20, Villin and CDX2	No recurrence, Free of symptoms, 8 months

LA, left atrium; IHC, Immunohistochemistry; PV, pulmonary vein; NS, Not stated; CT, computed tomography; MRI, Magnetic resonance imaging; PET, Positron emission tomography; LN, lymph node; TTE, Transthoracic echocardiography; TEE, Transesophageal echocardiography; ND, No data available.

prompting a cardiac surgery consult that suggested a surgical removal of the mass. During the operation, the tumor was found to invade the coronary sinus and a longitudinal incision in the coronary sinus allowed an entire removal of the tumor with its intact pseudocapsule. Unroofed coronary sinus repair was then performed. A postoperative TEE did not reveal any mass. Immunohistochemical staining pointed to RCC and the diagnosis was confirmed given the patient's history.

Cardiac metastases from RCC are thought to occur via two mechanisms: The venous hematogenous spread through renal vein to the right heart and the lymphatic spread via carinal lymph nodes and parasternal lymph vessels. It has been reported that hematogenous spread is the most commonly involved pathway in metastasis to the right heart while the lymphatic spread is frequently involved in metastasis to the left heart (11). Left heart metastasis from RCC is frequently associated with metastasis to other sites. The present case is in line with this pattern because the patient was hospitalized for the management of right renal and right adrenal masses which were thought to be metastases. Moreover, pulmonary metastasis was considered since chest CT revealed masses that increased in size compared to previous CTs of 2016.

RCC has a characteristic feature of a high propensity to venous invasion. On review of literature, except the present case, all the previously reported cases of LA metastasis from RCC revealed pulmonary veins involvement. Apart from the report by Miyamoto et al. (6) where a direct invasion of pulmonary vein from a mediastinal lymph node was confirmed, most reports mentioned the lung as the source of pulmonary vein, and LA metastasis (4, 5, 7, 8), or could not rule out such source (9). While previous reports may apparently suggest a hypothesis that all LA metastases from RCC occur via pulmonary veins (although the small sample size cannot allow to draw further conclusions), the coronary sinus invasion in the present case and the absence of pulmonary vein tumor thrombus may raise a suspicion of another pathway in which LA metastasis can occur via coronary sinus—coronary sinus tumor thrombus invading the LA. However, intraoperative findings could not clearly support such a pathway. Moreover, the presence of lung metastasis and the absence of any mass or enlarged lymph nodes in mediastinum in the present case favor the pulmonary vein as the route of metastasis to left atrium. A diagnosis of lung metastasis from RCC—either concurrently or previously—was present in most cases (8 out of 9). Moreover, no isolated LA metastasis from RCC has been reported thus far. The time from nephrectomy to LA metastasis ranged from 3 months to 13 years, our present case having the longest time. There are no specific signs and symptoms for LA metastasis from RCC. Patients may be asymptomatic (3 out of 9) or may present with non-specific symptoms like dyspnea (3 out of 9), syncope (2 out of 9), consciousness disturbance or cough.

There is no established standard management for cardiac metastases from RCC. That said, metastasectomy is still playing an important role in RCC treatment and it has been shown to improve both overall survival and cancer-specific survival (14). Metastasectomies either synchronous or metachronous with nephrectomies are described especially in the liver and lungs in selected patients. Given the paucity of data regarding treatment of such cardiac metastases, management of RCC with cavoatrial extension—where radical surgical intervention is the only option to potentially result in curative treatment—may constitute a relatively better source of data. Due to the fear of cardiac sudden death, most cardiac masses are removed as soon as possible. Most of the cardiac metastases from RCC reported thus far were treated with surgical removal (4–7, 11, 12). Cardiopulmonary bypass (CPB) with or without hypothermia—usually performed through a sternotomy approach—is the most commonly used surgical technique. While a number of surgical strategies for the management of RCC with cavoatrial extension are available without a clear evidence of superiority of one technique over the others, Gaudino, and associates (15) reported in their systematic review that CPB with Deep Hypothermic Circulatory Arrest (DHCA) is the more commonly used technique when the level of invasion is above the diaphragm and it has the advantages of possible organ preservation and an excellent exposure with bloodless operative field, thus aiding in complete resection. However, in addition to its disadvantages—longer operative time, coagulopathy, complexity—the common belief that CPB with DHCA increases the operative risk and major complication rate (though not proven by the Gaudino and associates) may be a factor for surgeons to prefer CPB without DHCA. It is worth noting that these techniques' safety and treatment outcomes were primarily studied on RCC extending to IVC and right heart and thus will not necessarily yield the same results when applied on left atrial metastases without IVC involvement. In our case, successful extirpation of the tumor from the coronary sinus was followed by repair of the unroofed coronary sinus. When cardiac metastases are deemed inoperable, conservative approach with molecular targeted therapy is a treatment option although it has been rarely reported. Tyrosine kinase inhibitors (especially sunitinib and pazopanib) are reported to result in partial response or stable disease in such setting (16, 17). Mammalian target of rapamycin (mTOR) inhibitors were also reported with a stable disease as the main outcome (9, 18). The well-documented report by Tolay et al. (9) describes significant regression of cardiac metastasis from RCC and improvement of symptoms after 14 weeks of mTOR inhibitor therapy.

Currently, there is limited evidence regarding the efficacy and safety of immune checkpoint inhibitors in patients with intracardiac metastases. To date, only one report by Ansari et al. (19) described an excellent response to nivolumab (a programmed death-1 (PD-1) receptor inhibitor) where 12 months of treatment with this drug resulted in 70% reduction in the size of the intracardiac RCC metastasis on enhanced chest CT. However, no studies have compared long-term outcomes of these different treatment modalities in this subpopulation.

In conclusion, RCC metastasizing to the left atrium is extremely rare with only 9 reports in the literature. We report the 10th case of LA metastasis of RCC occurring 13 years post radical nephrectomy. This case highlights the need for a metastatic RCC to be considered when a left atrial mass is present in a patient with a history of renal cancer. To our knowledge, this is the first case of RCC metastasizing to the left atrium with concomitant invasion of coronary sinus. Surgical resection combined with unroofed

coronary sinus repair allowed a successful removal of the entire tumor. In the absence of standard therapy for such cardiac metastasis, surgical removal appears to be both a diagnostic and therapeutic tool, preventing the risk of heart failure and sudden death. In surgically unresectable cases, conservative therapy with molecular targeted therapy (either tyrosine kinase inhibitors or mTOR inhibitors) constitutes a treatment option. Despite the limited evidence regarding the efficacy and safety of immune checkpoint inhibitors for patients with intracardiac RCC metastases, these agents may improve outcomes in this subpopulation.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript/supplementary files.

INFORMED CONSENT

A written informed consent to publish the report and associated medical images was obtained from the patient.

AUTHOR CONTRIBUTIONS

GN and QW collected and analyzed the patient's clinical data and designed the research. GN performed the review of literature and drafted the manuscript. QW, FT, SJ, WS, and LZ revised the manuscript. WS and SJ supervised the report and the publication process. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors thank Li Lv, MD, PhD, Chief Physician (department of pathology) for her contribution during immunohistochemistry slides reading and preparation of related pictures. The authors also thank Miss Maria Jose Gonzalez Mendez, Msc and Mahmoud B.M. Hethnawi, Doctor of Dental Surgery for their contribution to the revision of the manuscript. The authors are greatly indebted to Haibo Wu, MD, Chief physician and Dr Liang Di (department of cardiac surgery) who performed the operation and provided intraoperative pictures.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 09 October 2019
doi: 10.3389/fonc.2019.01033

Vitiligo Adverse Event Observed in a Patient With Durable Complete Response After Nivolumab for Metastatic Renal Cell Carcinoma

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OPEN ACCESS

Edited by:
Walter J. Storkus, University of Pittsburgh, United States

Reviewed by:
Takeshi Yuasa, Japanese Foundation for Cancer Research, Japan
Sheldon L. Holder, Penn State Milton S. Hershey Medical Center, United States

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *18 July 2019*
Accepted: *24 September 2019*
Published: *09 October 2019*

Citation:
Billon E, Walz J, Brunelle S, Thomassin J, Salem N, Guerin M, Vicier C, Dermeche S, Albiges L, Tantot F, Nenan S, Pignot G and Gravis G (2019) Vitiligo Adverse Event Observed in a Patient With Durable Complete Response After Nivolumab for Metastatic Renal Cell Carcinoma. Front. Oncol. 9:1033. doi: 10.3389/fonc.2019.01033

Background: Renal cell carcinoma is the third most prevalent urological cancer worldwide and about 30% of patients present with metastatic disease at the time of diagnosis. Systemic treatments for metastatic renal cell carcinoma have improved recently. Vascular endothelial growth factor targeting therapies were the previous standard of care. However, immune checkpoint inhibitors used in second line therapy have now been shown to improve patient survival. We report a case of metastatic renal cell carcinoma with nivolumab as a second-line therapy after progression with tyrosine kinase inhibitor therapy. Unusual adverse events in metastatic renal cell carcinoma, such as vitiligo, were observed in this patient who developed a remarkable documented pathological complete response to his renal tumor.

Case presentation: A 60-year-old caucasian male was diagnosed with a pulmonary metastatic clear cell renal cell carcinoma. Sunitinib was used as first line treatment without success. He received nivolumab in second-line treatment. He developed several immune-related adverse events, most notably vitiligo. The patient had a radiological complete response on metastatic sites, with a significant decrease of renal tumor volume and underwent cytoreductive nephrectomy after 2 years of treatment, confirming the pathological complete response. The patient remains disease-free for 10 months without further systemic therapy after nivolumab discontinuation.

Conclusions: Pathological complete response with nivolumab in metastatic renal cell carcinoma is rare. This case further highlights the potentially predictive role of immune-related adverse events during nivolumab therapy for metastatic renal cell carcinoma and raises questions concerning the role of nephrectomy after immune checkpoint inhibitor therapy. Further studies are needed to better identify predictive factors for treatment response to immunotherapy in metastatic renal cell carcinoma, and to better understand the role of nephrectomy after nivolumab treatment.

Keywords: renal cell carcinoma, nivolumab, immunotherapy, complete response, immune adverse events, vitiligo, thyroid dysfunction, nephrectomy

BACKGROUND

Renal cell carcinoma is the third most prevalent urological cancer worldwide with 380,000 new cases diagnosed every year (1). Of these, about 30% of patients present with metastatic disease at the time of diagnosis (2). Over the past decade, remarkable progress has been made in the treatment of metastatic clear cell renal cell carcinoma. Tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors have been shown to improve survival (3–5), though immune checkpoint inhibitors were developed as a second-line treatment after TKI failures (6). Furthermore, the administration of immune checkpoint inhibitors therapy in untreated metastatic clear cell renal cell carcinoma demonstrated improved survival for patients with intermediate and poor-risk diseases [CheckMate-214 trial (7)], while the combination of checkpoint inhibitors plus vascular endothelial growth factor receptor inhibition improved both overall survival (OS) and progression free survival (PFS) over TKI therapy alone (8, 9).

Based on the phase III Checkmate 025 study, the PD-1 checkpoint inhibitor nivolumab was approved by the U.S. Food and Drug Administration and the European Medicines Agency for advanced metastatic clear cell renal cell carcinoma patients previously treated with TKIs. Nivolumab demonstrated benefits to both OS and the objective response rate (ORR) when compared to everolimus (6), while the side-effects (grade 3–4 Adverses Events 19 vs. 37%, respectively) and quality of life scores also favored patients treated with nivolumab. Nivolumab treatment improved median OS by 5.4 months, with an ORR of 25% and a complete response rate of 1% (6). Nivolumab's safety profile is different from conventional therapy and was responsible for several immune-related adverse events (irAEs), such as interstitial pneumonia, diarrhea, autoimmune hepatitis, and endocrine dysfunction (6, 10).

We report a case of metastatic renal cell carcinoma in a clinical trial (GETUG–AFU 26-NIVOREN, NCT03013335) with nivolumab as a second-line therapy after progression with TKI therapy. Unusual AEs in renal cell carcinoma were observed, and the patient developed a remarkable documented pathological complete response to his primary renal cell carcinoma.

CASE PRESENTATION

In February 2015, a 60-year-old Caucasian male with a seven-month history of chronic cough and macroscopic hematuria and no history of tobacco use was diagnosed with a pulmonary metastatic clear cell renal cell carcinoma. The patient also had a personal history of hyperthyroidism (Graves' disease, laboratory assays were performed before the start of any antitumoral therapy and indicated normal thyroid function), which was originally treated in 2013 with neomercazole, which was then replaced by 100 μg per day of levothyroxine. A computerized tomography (CT) scan revealed a 110 mm mass on the left kidney, as well as the presence of bilateral pulmonary lesions. Analysis of the kidney tumor biopsy further revealed a clear cell renal carcinoma, Fuhrman grade II.

In March 2015, the patient was randomized in the CARMENA trial (NCT00930033) and received sunitinib (50 mg per day), without nephrectomy. By February 2016, the patient's disease had progressed with new lung, pleural (**Figures 1A–C**), and bone metastases, and he was therefore offered inclusion in the GETUG–AFU 26-NIVOREN trial (NCT03013335). After inclusion, the patient received anti-PD-1 therapy with nivolumab (3 mg/kg every 2 weeks) in March 2016. Upon the third injection of nivolumab, the patient developed lower back pain and required the use of morphine whose perfusion duration was then increased for each subsequent administration.

After 3 months of treatment, the patient developed clinical and biological signs of hyperthyroidism with palpitations and tremors associated with low TSH (0.005 mUI/L) serum levels and high fT3 and fT4 (11 pmol/L and 39 pmol/L, respectively) serum levels. Thyroid scintigraphy did not detect any ^{123}I fixation, and the levels of anti-thyroid peroxidase and anti-thyroglobulin antibodies had not increased, thereby confirming the presence of a nivolumab-related, thyroid-related adverse event. Propranolol 120 mg per day was prescribed to counter symptoms caused by the hyperthyroidism. Because it was not being efficient enough, Neomercazole, 60 mg per day, was introduced and was quickly stopped for clinical and biological normalization; this was followed by the reintroduction of hormone replacement therapy.

We observed a partial response after 3 months of treatment and complete response in the lungs (**Figures 1D–F**) and bone after 6 months. After 8 months of treatment with nivolumab, the patient developed a depigmentation of his eyebrows and hair that was suspected to be indicative of vitiligo (**Figures 2A,B**). As nivolumab was maintained the vitiligo spread further, affecting the eyelashes and skin over the entire body (**Figure 2C**).

After 2 years of treatment, complete response was confirmed in the lungs by CT scan, with only the primary lesion of the left kidney remaining (65 vs. 110 mm at the diagnosis). The possibility of a cytoreductive nephrectomy was discussed with the patient and with a multidisciplinary urologic oncology team. In May 2018, a partial nephrectomy was initially planned but surgeons described difficulties in finding dissection planes because of major adhesions and inflammatory reactions in the kidney and surrounding tissue. The extent of surgery has been changed during the procedure because it was impossible to identify tumor boundaries (switch from partial to radical nephrectomy, in order to avoid potential positive surgical margins). Pathological analysis (**Figure 3**) revealed a lesion of 6 cm at the superior pole of the kidney with fibrosis, focally calcified, and without residual tumor cells.

The final nivolumab administration was performed on May 2018. As of the time of last follow up (April 2019) the patient was in complete response.

Abbreviations: CT, Computerized Tomography; ICI, Immune Checkpoint Inhibitor; irAEs, immune-related Adverse Events; HLA, Human Leukocyte Antigen; mCCRCC, metastatic Clear Cell Renal Cell Carcinoma; ORR, Objective Response Rate; OS, Overall Survival; PD-1, Programmed Death 1; PDL-1, Programmed Death Ligand 1; PFS, Progression Free Survival; TKI, Tyrosine Kinase Inhibitor.

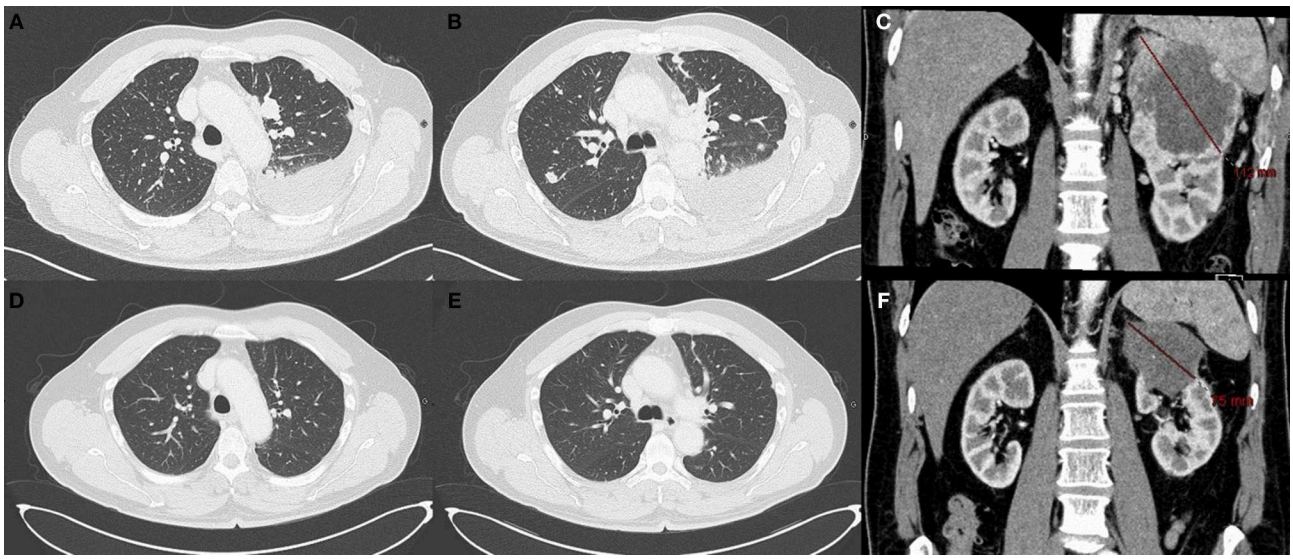

FIGURE 1 | CT scan after sunitinib therapy and while under nivolumab Pulmonary metastasis **(A,B)** and renal lesion **(C)** after progression under sunitinib. Radiological complete response of the pulmonary metastasis **(D,E)** under nivolumab therapy at 6 months. The CT scan showed only a 75 mm mass on the left kidney **(F)**.

DISCUSSION

We report a case of metastatic clear cell renal cell carcinoma with histological complete response after nivolumab administration as a second-line therapy, which resulted in an uncommon (in renal cell cancer) vitiligo side effect.

Immune-related adverse events commonly result from the use of immune checkpoint inhibitors. Vitiligo itself is an acquired pigment disorder in which depigmented macules result from the loss of melanocytes from the involved regions of skin and hair. Vitiligo occurs worldwide with an estimated prevalence rate of 0.5–1% and could be associated with several autoimmune diseases such as thyroid disease, rheumatoid arthritis, and type 1 diabetes (11). However, the incidence of vitiligo in the immune checkpoint inhibitor-treated population is not precisely known. In a meta-analysis of immunotherapy in patients with stage III and IV melanomas, the cumulative incidence of vitiligo was 3.6% (95% CI [2.64, 4.78]) and was significantly associated with a decreased risk of disease progression (one-half) and death (one-quarter), for patients with vitiligo compared to patients without vitiligo (12). A systematic review and meta-analysis of randomized clinical trials investigated the toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors (nine randomized trials and 5,353 patients were included). Cases of vitiligo were reported in five out of the nine studies and only among patients with a diagnosis of metastatic melanoma with a strong correlation between irAEs and improvement in ORR and survival. A pooled analysis of 576 patients treated with nivolumab found that irAEs of any grade were associated with higher ORRs without any difference in PFS (13).

Thyroid dysfunction, such as the thyroid-related adverse events observed with our patient, was reported to be an independent predictive factor of favorable outcomes for OS and PFS in a prospective trial with 58 patients with non-small cell lung cancer treated with PD-1 blockade (14). In our case, the patient had a history of Grave's disease and developed thyroid dysfunction. However, laboratory assays and the scintigraphy were not compatible with Graves' disease but confirmed nivolumab induced adverse event. Experience concerning the impact of checkpoint inhibitors on patients with preexisting autoimmune diseases is limited because these patients were usually excluded from clinical trials. Two retrospective studies described the use of PD-L1 inhibitors for metastatic melanoma in patients with pre-existing autoimmune disorders (15, 16). In these two series, of, respectively, 52 and 17 patients, a flare of the pre-existing autoimmune disorder was observed in 40% of patients. Response rates were above 30% in the two population and were in the range expected from clinical studies in patients without preexisting immunity disorders (21–32% for pretreated patients (17, 18) and 33–43% for untreated patients (19, 20). In a cohort of 56 patients treated with immune checkpoint inhibitors for non-small cells lung cancer, 23% developed flare of their pre-existing immune disorder, with a response rate of 22%. In this study, the incidence of irAEs was like reported rates in clinical trials where patients with immune disorders were excluded (21).

Our patient developed lumbar pain during the third nivolumab infusion. Lower back pain has been previously described as a possible rheumatic irAE, and a recent publication observed a high ORR to anti-PD1 correlation in the melanoma subgroup in association with rheumatic irAEs (22).

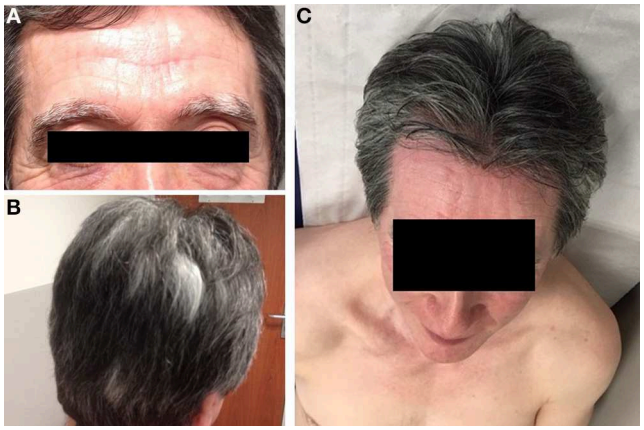

FIGURE 2 | Vitiligo lesions. Depigmentation of eyebrows **(A)**, hair **(B)**, and skin **(C)** observed after 8 months of treatment with nivolumab. Depigmentation affected the whole skin but preferentially the chest.

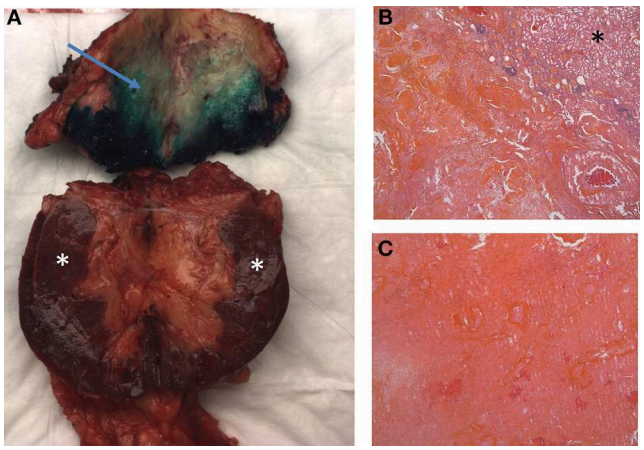

FIGURE 3 | Macroscopic and microscopic examination. Macroscopic examination **(A)**: fibrosis alterations on upper pole of the kidney (arrow) Microscopic examination **(B,C)**: fibrosis alterations with calcifications and without residual tumor cells. Stars indicate normal parenchyma.

Certain HLA genotypes, such as HLA DQ2/DQ8 or HLA DQA1, might be associated with immune disorders (23) and could be consequently associated with irAEs (24) or tumor response to ICIs. However, these genotypes were not detected in our patient after HLA typing. Recent studies suggest that HLA expression may affect the response to immune checkpoint inhibitors in advanced melanoma (25) and Hodgkin's lymphoma (26). Patients with MHC class II-positive and MHC class I-low expression tumors might have better responses and improved OS.

The role of nephrectomy is still unclear for patients who have a complete response to nivolumab in renal cell carcinoma. Approximately 90% of patients in the Checkmate 025 trial had a prior nephrectomy before systemic therapy, yet only a few (1%) had a complete response to treatment (6). Two other cases of total nephrectomy after radiological complete response with nivolumab were also described (27, 28), where both cases observed complete pathological responses without any viable malignant cells. These two cases, such as our, indicate that total nephrectomies could be safely carried out for metastatic clear cell renal cell carcinoma after nivolumab therapy, however, in our case, a partial nephrectomy was impossible due to significant post-immunotherapy fibrosis. Also, it is important to note that, in the case of pathological complete response, a biopsy is required before surgery in order to avoid an unnecessary nephrectomy.

The question of nivolumab discontinuation remains unanswered in metastatic clear cell renal cell carcinoma for patients treated for 2 years with pathological complete response. In metastatic melanomas, retrospective and prospective data indicated excellent results with immune checkpoint inhibitor therapy, even after discontinuation. In the phase III Checkmate 067 study, 159/314 patients treated by the combination nivolumab + ipilimumab were still alive at 4 years, and 113 (71%) of them are free from study treatment and have never received subsequent systemic therapy (29). For patients who received nivolumab alone, 138/316 patients were still alive after 4 years, and 69 stopped the treatment for any reason and never received other systemic therapy. In contrast, in the phase III Checkmate 017 and Checkmate 057 studies, 20/83 patients responding to nivolumab for non-small cell lung cancer maintained an objective response after 3 years (26/418 patients continued nivolumab at 3 years) (30). Furthermore, in a retrospective study of 19 patients with non-small cell lung cancer responding to immune checkpoint inhibitor therapy, for those who stopped immune checkpoint inhibitor treatment due to AEs (31) the median PFS after discontinuation depended on the confirmed response during administration, as PFS was not reached for partial response patients (4/19) vs. 4.9 months for stable patients (12/19). Additionally, in a retrospective analysis of 262 patients treated with immune checkpoint inhibitor therapy in phase I studies for all types of cancer, immunotherapy was discontinued in 39 cases for reasons other than progression, while 24 patients were still responding to treatment and 39 were in complete response (32).

Nivolumab discontinuation was not documented in mCCRCC, and the decision, in our case, was made in concert with the patient.

CONCLUSION

We reported herein a case of metastatic clear cell renal cell carcinoma with radiological and pathological complete response after nivolumab therapy and the associated irAEs. This case further highlights the potentially predictive role of irAEs during nivolumab therapy for mCCRCC. Further studies are needed to better identify predictive factors for treatment response to immunotherapy in metastatic renal cell carcinoma, and to better understand the role of nephrectomy after nivolumab treatment.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GG and EB: conception and design and manuscript writing. EB, JW, SB, JT, NS, MG, CV, SD, LA, FT, SN, GP, and GG: final approval. JT: pathological explorations. SB: radiological exploration. GG, JW, and GP: patient's management.

FUNDING

This work was supported by the Institut Paoli-Calmettes, Marseille, France.

ACKNOWLEDGMENTS

The authors wish to gratefully acknowledge the patient and his family for allowing us to publish the report of his case.

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Conflict of Interest: GP serves as board member for BMS. GG and SD receive travel grants from BMS and Pfizer. SD receives travel grants from AMGEN and ASTRAZENECA. JW participate to speaker's bureau for ASTRAZENECA, JANSSEN, TAKEDA, and BLUE EARTH DIAGNOSTICS.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 21 January 2020
doi: 10.3389/fonc.2019.01566

Case of Hereditary Papillary Renal Cell Carcinoma Type I in a Patient With a Germline *MET* Mutation in Russia

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OPEN ACCESS

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: 16 October 2019
Accepted: 24 December 2019
Published: 21 January 2020

Citation:
Mikhaylenko DS, Klimov AV, Matveev VB, Samoylova SI, Strelnikov VV, Zaletaev DV, Lubchenko LN, Alekseev BY and Nemtsova MV (2020) Case of Hereditary Papillary Renal Cell Carcinoma Type I in a Patient With a Germline MET Mutation in Russia. Front. Oncol. 9:1566. doi: 10.3389/fonc.2019.01566

Hereditary papillary renal carcinoma (HPRC) is a rare autosomal dominant disease characterized by the development of multiple papillary type I renal cell carcinomas. This hereditary kidney cancer form is caused by activating mutations in *MET*. Descriptions of patients with HPRC are scarce in the world literature, and no cases have been described in open sources in Russia. Here, we describe a 28-year-old female Russian patient with 7 and 10 primary papillary renal cell carcinomas in the left and right kidneys, respectively. The patient did not have a family history of any of the known hereditary cancer syndromes. A comprehensive medical examination was performed in 2016 including computed tomography and pathomorphological analysis. The observed tumors were resected in a two-step surgical treatment. In February 2019, no sign of disease progression was detected in follow-up medical examination. Molecular genetic analysis revealed the germline heterozygous missense variant in *MET*: c.3328G>A (p.V1110I; CM990852). We have discussed the biological effects of the detected mutation and the utility of DNA diagnostics for treating patients with HPRC.

Keywords: kidney cancer, papillary renal cell carcinoma, hereditary cancer syndrome, *MET* gene, germline mutation

INTRODUCTION

Renal cell carcinoma (RCC) shows the 9th highest incidence among all cancers worldwide and is a pressing problem in modern oncology (1). RCC due to germline mutations is a hereditary cancer syndrome accounting for only a few percent of all RCC cases, but has several unique features, both from the clinical (early manifestation, bilateral or multifocal tumors, and characteristic tumor type) and molecular genetics perspectives. Detection of a germline mutation in a proband is the main diagnostic test in the medical genetic counseling of patients with hereditary RCC. Thus, it is important to accumulate and systematize information on the relevant mutations and their phenotypic expression. Approximately 10 monogenic hereditary RCC forms have been described to date and can be diagnosed by direct DNA testing (2). Particularly, hereditary papillary renal

carcinoma (HPRC, or PRCC1, OMIM 605074) is an autosomal dominant disease characterized by the development of multiple papillary type I renal cell carcinomas. This hereditary RCC form is caused by activating mutations in the *MET* proto-oncogene on chromosome 7q31 (3, 4). *MET* encodes for a receptor of the hepatocyte growth factor (HGF), which affects many cell types despite its name. *MET* mutations cause constitutive activation of the cytoplasmic domain of the receptor and stimulate cell division, which is considered as the main event in the carcinogenesis of papillary carcinomas in HPRC (5). Direct DNA diagnosis in HPRC is based on identifying mutations in *MET* exons 15–21, which code for the cytoplasmic domain of the receptor (6, 7). Studies of HPRC and germline *MET* mutations in Russian patients have not been described to date in the available literature. Here, we report the first clinical case of HPRC in Russia and its characteristics in terms of genetic diagnosis and treatment.

CASE PRESENTATION

Case History

A 28-year-old female patient (K.) was admitted to N. N. Blokhin National Medical Research Center of Oncology in June 2016 after being referred from another hospital for further diagnosis and being treated for multiple renal cell tumors. Patient K. gave informed consent to undergo diagnostic procedures and treatment, as well as to participate in the study, and for the presentation of relevant clinical and molecular data in this paper. This case report was approved by the local Ethics Committee at Sechenov University. Based on the medical records, the patient had pituitary adenoma with endo-, supra-, infra-, and latero-sellar growth with partial descending optic atrophy on the left in 2012. At that time, the disease was clinically manifested by broadening of the feet and fingers, increased sweating, cysts and diffuse changes in the thyroid gland, and an increase in the level of growth hormone. The pituitary adenoma was partly removed via endoscopic transsphenoidal surgery in 2012, and she was treated with somatostatin analogs. At the time of the follow-up examination in 2016, no pituitary adenoma recurrence was detected; she was recommended to continue taking the somatostatin analog (octreotide depot) 20 mg intramuscularly once every 28 days in combination with bromocriptine 2.5 mg per day. At the same time, multiple neoplasms were detected in both kidneys. Family history was negative. The patient and her immediate family had no oncological diseases at a young age or other signs suggesting any known cancer syndrome. At the time of the hospitalization of patient K. in the N. N. Blokhin National Medical Research Center of Oncology, her parents and the child did not have cancer symptoms.

Instrumental Diagnosis

Patient K. was examined at Blokhin National Medical Research Center of Oncology. Computed tomography with intravenous contrast detected three 1–2 cm tumor lesions with the active accumulation of the contrast agent in the right kidney. In the left kidney, there were four tumor lesions: a 3.5 × 3.0-cm mostly cystic tumor with a soft-tissue component, with parietal accumulation of the contrast dye in the middle one-third portion; a tumor with a diameter of 1.3 cm at the upper pole; a tumor with a diameter of 1 cm in a subcapsular location in the middle one-third; and a tumor of 1.3 cm in diameter at the lower pole; these tumors similarly accumulated the contrast dye. Various tests were performed, including skeletal scintigraphy, computed tomography of thoracic organs, and ultrasound of the abdominal and pelvic organs, which showed no sign of distant tumor process. Blood count, chemistry, and clotting tests were carried out prior to surgery and showed no clinically significant abnormalities. Complex renal scintigraphy revealed an insignificant decrease in radionuclide clearance; preoperative creatinine clearance was 84 mL/min.

Surgery

Based on the obtained diagnostic data, a multidisciplinary board was held, with the participation of surgical oncologist, oncologist, pathomorphologist, a specialist in radiation diagnostics and urologist. Taking into account the current recommendations of the European Association of Urology (8) and the current standards of medical care of the Ministry of Health of Russia for patient K. with bilateral localized kidney cancer, the tactics of stepwise tumor resection with preliminary examination using computed tomography with contrast was chosen.

Partial nephrectomy was performed in two steps. The right kidney was resected during the first step. Intraoperative findings included four tumors of 0.5–1.3 cm in dimension in the lower one-third, three tumors of 0.5–1.0 cm in the middle one-third, and three tumors of up to 1.5 cm in the upper one-third of the right kidney. Through hilar occlusion, all detectable tumors were consecutively removed with a margin of visually unchanged tissue and adjacent pararenal fat under intraoperative ultrasound guidance. The sides of each resection site were sutured together. The kidney ischemia time was 28 min, total surgery duration was 135 min, and blood loss was 300 mL. Postoperative complications did not occur; serum creatinine increased insignificantly to 118 μmol/L. Patient K. was discharged in satisfactory condition on day 13 after surgery.

Two months later, in August 2016, patient K. was again admitted to Blokhin National Medical Research Center of Oncology to undergo a second surgery. Computed tomography scanning of the abdomen with intravenous contrast was performed before surgery and showed a deformed right kidney with two low-density sites that had uneven outlines and were 3.0 × 2.2 cm in total (postoperative changes). At least seven contrast-accumulating nodular masses were detected in the left kidney. Compared to the previous scan, which was performed 2 months earlier, one large mass had increased to 4.0 × 3.2 cm (previously 3.7 × 3.0 cm) at the posterior surface, whereas the other masses remained unchanged (**Figure 1**). Complex testing showed no findings suggesting metastasis. In surgery, nine tumors were consecutively removed with a margin of visually normal tissue from the left kidney with hilar clamping (ischemia time 28 min). Blood loss was 300 mL, and surgery duration was 150 min. The patient developed a fever (38°C) 9 days after the surgery. Due to the dilation in the collecting system of the right kidney, a JJ ureteric stent was placed. The inflammatory

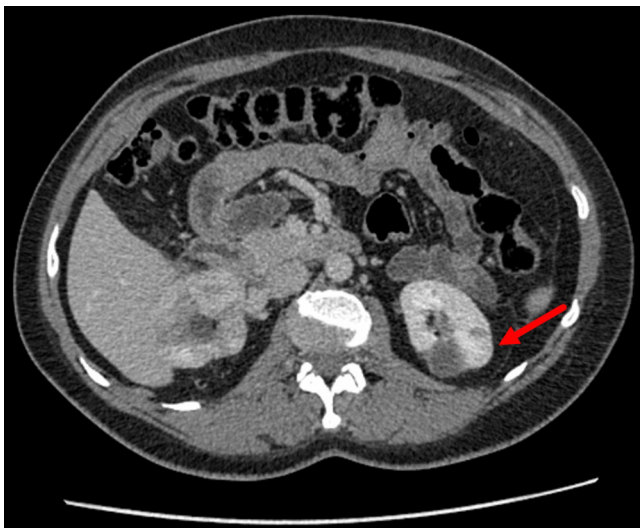

FIGURE 1 | Contrast-enhanced CT of the kidneys in patient K. The left kidney examined prior to the second surgery is indicated.

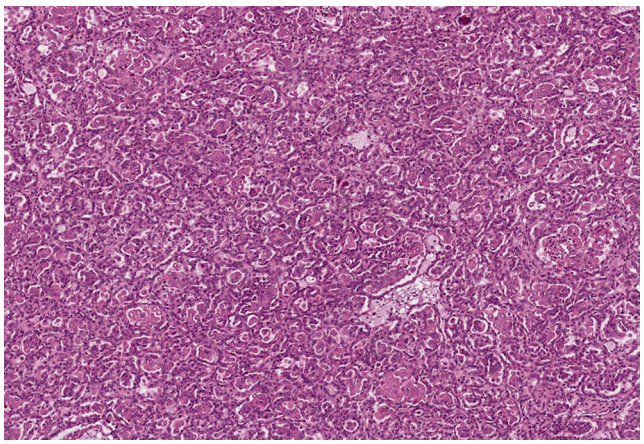

FIGURE 2 | Pathomorphological examination of the mass excised from the right kidney of patient K. Type I papillary RCC. Hematoxylin–eosin staining, magnification ×100.

infection worsened, warranting a change in the antibacterial therapy and a nephrostomy tube was placed on the right. Signs of acute pyelonephritis were eliminated. The nephrostomy tube was removed 18 days after the surgery. By the end of the surgical treatment, the creatinine clearance was 32 mL/min, and serum creatinine was 168 μmol/L. Patient K. was discharged in a satisfactory condition. Regular follow-up tests were performed in subsequent years. In February 2019, no sign of relapse or disease progression was detected in control complex testing, which included magnetic resonance imaging of the abdominal organs.

Pathomorphological Diagnosis

All tumor masses were removed from the right kidney during the first surgery. Microscopic examination revealed that they were structurally similar, and the tumors were identified as type I papillary RCC, Fuhrman grade 2 (**Figure 2**). Tumor cell growth was not detected in the pararenal fat. The nine tumors removed from the left kidney during the second surgery were also structurally consistent with type I papillary RCC, Fuhrman grade 2 by histology.

Molecular Genetic Diagnosis

Because multiple type I papillary RCC tumors developed synchronously and bilaterally and affected a young patient, molecular genetic testing was carried out for patient K. in the period between the first and second surgeries. Note that it would be more advisable to do this before the first stage of the surgical intervention, so that in case of a positive test result, there would be an extra argument in favor of organ-preserving treatment, but the organizational peculiarities of the hospital care and the time frame for molecular genetic diagnostics made it possible to conduct a genetic study only during the first stage of treatment.

Genomic DNA was isolated from a peripheral blood sample with a DNA-sorb-B kit (NextBio, Moscow, Russia). Fragments of *MET* exons 15–21 were PCR-amplified using primers with previously published sequences (9). The reaction mixture contained 50–100 ng of genomic DNA, 2.5 mM $MgCl_2$, 1.5 mM each dNTP, 2 pmol of the forward and reverse primers, 1 unit of thermostable Taq polymerase, and 5 μL of 5x PCR buffer (Interlabservice, Moscow, Russia); the total volume was 25 μL. Amplification was performed as follows: 95°C for 1 min; 35 cycles at 95°C for 45 s, 61°C for 25 s, and 72°C for 30 s; and final elongation at 72°C for 50 s. After amplification, the PCR product was treated with 1 unit of alkaline phosphatase and 4 units of *Escherichia coli* exonuclease I to eliminate free primers and dNTPs. The product was then subjected to Sanger sequencing using a BigDye Terminator v. 3.1 Cycle Sequencing kit and 24-capillary 3500xl sequencer (Thermo Fisher Scientific, Waltham, MA, USA).

The single-nucleotide substitution c.3328G>A was found in exon 16 in a heterozygous state (**Figure 3**). This substitution causes the missense mutation p.V1110I (Human Genome Mutation Database accession no. CM990852, http://www.hgmd.cf.ac.uk/ac/index.php). The germline mutation has been described as a cause of HPRC, occurs in the ATP-binding site of the HGF receptor, leads to its activation, and exerts a transforming effect in fibroblast cultures *in vitro* (10). The somatic p.V1110I mutation has similarly been found in a sporadic type 1 papillary RCC (Catalog of Somatic Mutations in Cancer accession no. COSM3724572, http://cancer.sanger.ac.uk/cosmic) and is considered as a pathological factor associated with activation of the HGF receptor (11, 12). These results confirmed the diagnosis of type I HPRC (OMIM 605074) in patient K. Following the results of the analysis, genetic counseling was carried out and mutation carriage testing was recommended for family members of the first line of kinship. Patient K. was also advised to consult a geneticist and a urologist once every 6–8 months. At the time of writing, there is no information about a confirmed mutation in any of the relatives of patient K. Together with a negative family cancer history, this suggests that the identified germline mutation can be classified as *de novo*.

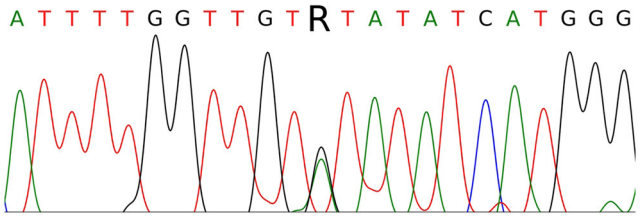

FIGURE 3 | Sanger sequencing of part of *MET* exon 16 in patient K. The c.3328G>A (p.V1110I) mutation is indicated by the letter R.

DISCUSSION

The timing and extent of surgery in hereditary RCC are important as the timely excision of the tumor is essential considering that the patients are at a high risk of developing tumors in the same or contralateral kidney, which might then require repeated surgery and cause chronic kidney failure at a relatively young age. For example, up to 600 cysts and neoplastic growth microfoci may be found in the kidney of a patient with von Hippel Lindau syndrome (hereditary clear cell renal carcinoma). Currently, the standard method of treating patients with von Hippel Lindau syndrome confirmed by molecular genetic testing is removing the primary tumor via nephrectomy as soon as the tumor reaches 3 cm in the largest dimension, with certain contraindications (6, 13). However, early metastasis is possible in other hereditary RCC forms, warranting surgery immediately after diagnosis. For example, type II papillary RCC in hereditary leiomyomatosis and RCC (HLRCC, OMIM 150800B) often develop as a solitary unilateral tumor but are characterized by rapid progression and early metastasis; thus, the surgical treatment strategy in this disease is the same as in sporadic RCC. HLRCC is associated with mutations in *FH*, which is on chromosome 1q42 and codes for fumarate hydratase, a Krebs cycle enzyme. The same strategy is possible in type I HPRC because of the germline *MET* mutations. However, type I HPRCs are less malignant than type II tumors, enabling physicians to choose the proper surgical strategy (3, 14).

Type 1 multiple papillary carcinomas developed in the patient's kidneys at the age of 28. This is consistent with previous publications describing multiple lesions and early manifestation of HPRC as hereditary cancer, compared with a later age of manifestation of solitary unilateral sporadic papillary kidney carcinomas (2, 4, 6, 7). Apart from the differences in age of manifestation, HPRCs and sporadic papillary carcinomas of the kidney present several significant differences at the molecular genetic level. Even though *MET* germline mutations are the cause of type I HPRC, similar somatic *MET* mutations are found in sporadic tumors in no more than 20% of cases. At the same time, amplification of the 7q31 locus harboring *MET* occurs in 45%, and MET overexpression occurs in 90% of type I sporadic papillary carcinomas of kidney, which indicates its significant role in carcinogenesis of both hereditary and sporadic kidney tumors of this type (11). To date, the results of several large-scale studies of sporadic papillary renal cancer involving NGS methods have been published. In one of them, *MET* mutations were detected in 17% of type I tumors, and of the 17 detected mutations, 3 were not somatic but germline, which once again indicates the advisability of diagnosing HPRC in young patients with papillary RP even without a clearly traceable family history of the disease. As with clear cell renal cell carcinoma, papillary renal cell carcinoma in these studies demonstrated high mutation frequency in chromatin remodeling genes in both type I and type II tumors. Mutations in *SMARCB1*, *SETD2*, *ARID2*, *PBRM1,* and some other genes involved in the formation of SWI complex, and other chromatin modifiers were found in papillary RP with a frequency of 10–38% of cases. It is possible that mutations in genes that affect chromatin state increase genome instability and can be considered as driver mutations that act in the initial stages of carcinogenesis of type 1 papillary renal cell carcinoma (15–17).

Patient K. had a history of pituitary adenoma and acromegaly. Significant extrarenal clinical signs of the syndrome have not been observed in patients with HPRC according to recent reviews, in contrast to von Hippel Lindau syndrome, Birt–Hogg–Dube syndrome, and HLRCC (6, 13). It remains unclear whether the two conditions were associated with *MET* mutation in patient K.

Because *MET* activation is a key event in the pathogenesis of HPRC, its therapeutic potential has been suggested for targeted therapy with MET inhibitors in metastatic HPRC. Clinical studies of the various disease phases are currently underway to evaluate several targeted drugs, such as the synthetic MET inhibitors foretinib (XL880), tivantinib (ARQ197), and volitinib (HMPL-504), and anti-HGF monoclonal antibody rilotumumab (AMG-102). Studies of papillary RCC will be carried out with cabozantinib (XL184) and the ALK/MET/ROS/RET inhibitor crizotinib (5, 18). Promising results have been reported for foretinib as a targeted therapy for treating metastatic HPRC in ten patients; treatment efficacy was comparable or even higher than that in sporadic type I papillary RCC. The specific details of *MET* mutation in the ATP-binding site are an important consideration because subclass 1 inhibitors, such as crizotinib, do not affect certain mutant variants of the receptor, particularly the Y1230H variant (6, 19). The targeted MET inhibitor savolitinib led to a 4-fold increase in relapse-free survival in papillary RCC with *MET* mutation (20). Multikinase inhibitors (sunitinib, sorafenib, and axitinib) have been observed to induce more objective responses when used as targeted therapies to treat various non-clear cell RCCs, including papillary RCC, in the multicenter clinical study setting, and their combinations with MET or mTOR kinase inhibitors have been evaluated in clinical studies (21, 22). MET inhibitors may be applicable in targeted therapy of HPRC; especially foretinib, which has been shown to be effective in papillary carcinomas of the kidney harboring germline *MET* mutations (23).

CONCLUSIONS

Diagnosis, including molecular genetic testing, and treatment of HPRC were performed in a Russian patient for the first time. The heterozygous germline p.V1110I activating mutation was identified in *MET* exon 16 in the patient. A positive result in molecular genetic testing for germline *MET* mutations may be considered as a weighty argument in favor of the choice of nephron-sparing surgery, in case genetic testing is performed

prior to surgical treatment. In addition, detection of a germline mutation is necessary for a diagnosis of HPRC as it helps to provide further advice on regular examinations, allows for simpler testing of the mutation in the patient's close relatives, and may be important for planning targeted therapy with those with the mutation. Such testing can be advised to all young patients with multiple papillary carcinomas of the kidneys, even in the absence of a previous family cancer history and/or known frequencies of *MET* mutations in the population in question.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in the web portal of the Laboratory of Epigenetics, Research Centre for Medical Genetics at http://www.epigenetic.ru/projects/renal-cancer/16r-1190_D07_10.ab1.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee at Sechenov University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DM performed molecular genetic diagnosis of patient K. and wrote abstract, introduction, and part of the case description in this manuscript. AK performed instrumental diagnosis, surgical treatment of patient K. and wrote clinical part of the case description. VM performed surgical treatment of patient K. SS provided pathomorphological examination of the removed tumors. VS prepared the illustrations. DZ wrote discussion in this manuscript. LL performed genetic counseling of patient K. BA supervised the clinical part of case study. MN wrote conclusion and supervised the laboratory part of case study.

FUNDING

The research was carried out within the state assignment of the Russian Federation.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 27 March 2020
doi: 10.3389/fonc.2020.00350

Anti-N-Methyl-D-Aspartate Receptor Encephalitis Associated With Clear Cell Renal Carcinoma: A Case Report

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Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a cause of autoimmune encephalitis and is characterized by epileptic seizures, psychosis, and consciousness impairments. It mostly affects young adults with ovarian cancers. We herein reported a case of anti-NMDAR encephalitis associated with clear cell renal carcinoma.

Case Presentation: A 54-year-old male with headache for 1 week and mood and behavioral changes for 3 days was presented, but his clinical presentation and poor response to antiviral treatment did not support a diagnosis of viral encephalitis. Positive anti-NMDAR antibodies in serum and cerebrospinal fluid confirmed autoimmune encephalitis. A subsequent evaluation revealed a paraneoplastic etiology of a renal mass, and this was then resected and pathologically confirmed as clear cell renal carcinoma. The patient's symptoms showed improvement after resection of the mass. The patient relapsed 6 months after discharge, and the symptoms completely disappeared after treatment with corticosteroids and intravenous immunoglobulin.

Conclusion: Our findings suggested that NMDAR encephalitis might be associated with clear cell renal carcinoma. When patients present with unexplained seizures, neuropsychiatric disorder, or other brain symptoms, clinicians should be careful with paraneoplastic neurological disorders. Early diagnosis and treatment of primary tumors might show improvement.

Keywords: anti-N-methyl-D-aspartate receptor encephalitis, autoimmune encephalitis, paraneoplastic syndrome, clear cell renal cancer, recurrence, seizure

OPEN ACCESS

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *30 August 2019*
Accepted: *27 February 2020*
Published: *27 March 2020*

Citation:
Yang J, Li B, Li X and Lai Z (2020) Anti-N-Methyl-D-Aspartate Receptor Encephalitis Associated With Clear Cell Renal Carcinoma: A Case Report. Front. Oncol. 10:350. doi: 10.3389/fonc.2020.00350

INTRODUCTION

Autoimmune encephalitis was first described more than 50 years ago (1), and a flood of novel clinical syndromes associated with neuronal autoantibodies has been recognized in the past 10 years. Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is mostly characterized by psychosis and memory impairment with abnormal movements in the early stage, and seizures and a depressed level of consciousness emerge as latter symptoms. Anti-NMDA receptor encephalitis is diagnosed by a blood or cerebrospinal fluid (CSF) test, imaging techniques, and electroencephalography (EEG). The identification of NMDAR antibodies in CSF or serum is currently the mainstay of diagnosis (2, 3). Magnetic resonance imaging (MRI) and CSF analysis might appear normal during the early stage of the disease. MRI, computed tomography (CT), and pelvic and transvaginal ultrasounds are necessary to confirm the underlying malignancies if

NMDAR encephalitis is suspected (4). To date there are no estimates regarding the prevalence rates, but more than 500 cases have been reported, and anti-NMDA receptor encephalitis was found in the reproductive system of women with ovarian cancers in most of these cases (5). Cases have also been reported in older patients, predominantly men, but cancer is less frequent in this age range. Tumors other than teratoma are rare. We report here a case of anti-NMDAR encephalitis associated with clear cell renal cancer.

The removal of underlying tumors and subsequent immunotherapy with corticosteroids, intravenous immunoglobulins (IVIg), or plasma exchange were considered as first-line treatment, and rituximab or cyclophosphamide was used as second-line treatment (4). About 75% of patients with NMDAR antibodies benefited from tumor removal and immunotherapy, which thus resulted in full recovery or having a mild sequelae, while other patients were either severely disabled or died (2).

CASE PRESENTATION

A 54-year-old male farmer belonging to Han nationality, with unremarkable medical history, was admitted to the Affiliated Ganzhou Hospital of Nanchang University, Department of Neurology, on April 9, 2017 for evaluation of headache for 1 week and mood and behavioral changes for 3 days. A neurological examination revealed mental disorder including dysphoria, excitement, gibberish, and nuchal rigidity. EEG and cerebral MRI revealed normal results. Lumbar puncture was then performed. A CSF analysis demonstrated leukocytic pleocytosis of 80,000 cells/ml, glucose levels of 4.76 mmol/L (normal range, 2.8–4.5 mmol/L), and protein levels of 16.4 mg/dl (normal range, 8–43 mg/dl). Antiviral treatment with acyclovir (0.5 g per 8 h, intravenously, for 3 days) was initiated for viral encephalitis, but the symptoms showed no improvement. He became agitated, confused, and disoriented 3 days after admission. Mildazolam (0.8 mg/h, intravenously) was used as a sedative treatment. On April 12, 2017, another lumbar puncture was performed, which showed positive anti-NMDAR antibodies in the serum as well as in CSF (antibody titer of 1:32) and negative anti-AMPA1, AMPA2, LGI1, Caspr2, and GABA-B antibodies (the antibody testing was performed by Kindstar Global Company). These diagnostic tests confirmed anti-NMDAR encephalitis. High doses of corticosteroids (methylprednisolone, 1 g/day for 3 days) and intravenous immunoglobulin (0.4 g/kg body weight) were administered.

As autoimmune encephalitis is cancer-related, CT scans of the chest, the abdomen, and the pelvis were performed on April 19, 2017, which revealed an exophytic mass on the left kidney and enhanced abdomen CT scans confirmed it as clear cell renal carcinoma (**Figure 1**). Laparoscopic partial nephrectomy was then performed with tracheal intubation and mechanical ventilation. The patient then had pneumonia and pleural effusion as surgical complications, so he was transferred to the intensive care unit. The pathology report showed renal cell carcinoma, clear cell type, and Fuhrman grade of 2, 5.5 × 5.0 × 4.0 cm

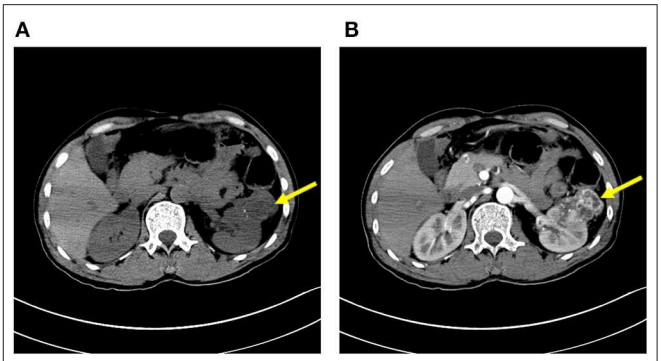

FIGURE 1 | Plain CT **(A)** and contrast-enhanced scan **(B)** of the kidney. The arrow shows a mass of 5.5 × 5.0 × 4.0 cm on the left side.

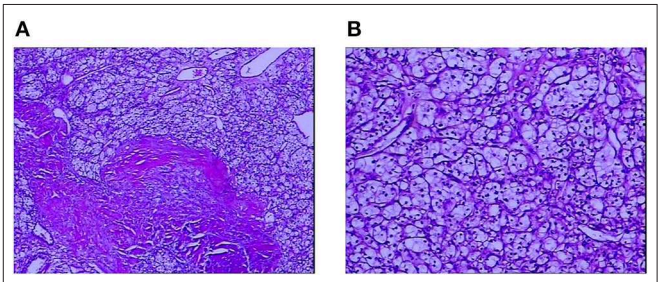

FIGURE 2 | A pathological study of the mass on the left kidney confirmed it as renal cell carcinoma, clear cell type. **(A)** Low magnification. **(B)** High magnification. The cells have a clear cytoplasm, surrounded by a distinct cell membrane, and contain round and uniform nuclei.

(**Figure 2**). After resection of the mass, the sedative drugs and intubation were discontinued. After corticosteroid (1 g per day, intravenously, for 5 days, 500 mg per day for 3 days, 250 mg per day for 3 days) and cyclophosphamide (0.4 g, intravenously, once a week for a month) treatment, his consciousness was significantly improved, and neurophysiologic examination, EEG, and cerebral MRI were completely unremarkable; the patient was discharged after 1 month of hospitalization. He was hospitalized again due to mood and behavioral changes on October 15, 2017. Lumbar puncture was performed, which showed that the titer of the anti-NMDAR antibody was 1:32 in CSF. MRI and routine CSF analysis appeared normal. Melthyprednisolone pulse therapy (1 g/day for 3 days) and intravenous immunoglobulin (0.4 g/kg body weight/day for 3 days) were then given. The symptoms of mood and behavioral changes then disappeared. Oral administration of prednisone (20 mg) was suggested after discharge. The patient was persuaded to take the medicine every day. The titer of the anti-NMDAR antibody was decreased to 1:1 in CSF on June 26, 2018 and medication was discontinued. The patient remained free from recurrence for 11 months without receiving any medication. The patient was also advised to regularly observe follow-up visits to his doctor. His last visit was on December 12, 2018, and he had normal mental status.

DISCUSSION

We reported a case of anti-NMDAR encephalitis associated with clear cell renal carcinoma. The case reported herein had a classical clinical pattern of anti-NMDAR encephalitis characterized by initial psychiatric symptoms followed by loss of consciousness within a few weeks. The brain MRI and EEG appeared normal, while the anti-NMDAR antibodies were detected in serum as well as in CSF. However, this case showed several unusual features. Firstly, a 54-year-old male was affected with encephalitis. Generally, NMDAR encephalitis occurs in young adults and children with or without teratomas (2, 6). Secondly, the associated tumor was clear cell renal cancer. Finally, the patient was cured after undergoing immunotherapy and tumor resection. To our knowledge, this is the first report with regard to the detection of NMDAR antibodies in clear cell cancer.

Renal cell carcinoma is not usually associated with paraneoplastic neurological syndromes (PNS), and its association with autoimmune encephalitis is rare (7). Few cases with limbic encephalitis in association with renal cell carcinoma have been reported (5), but no autoimmune antibodies in serum or CSF were detected in these cases, so this is the first case of NMDAR encephalitis associated with renal cell carcinoma, which was cured with nephron-sparing surgery.

Anti-NMDAR encephalitis is an immune-mediated disorder that is associated with IgG antibodies against the GluN1 subunit of NMDAR (2). It was first described by Dalmau in 2007 and shown to have an association with ovarian teratoma in a young woman (8). The understanding of this disorder has greatly increased and more cases have been reported since its initial description in 2007; however, clinicians in this field are unaware of the disease features. It is vital for psychiatrists to be aware of this condition in a wide age spectrum and to contact neurology colleagues more promptly, thus facilitating early screening and diagnosis.

The pathological relationship between renal carcinoma and production of pathogenic autoantibodies (NMDA-R antibodies) remains unclear. The anti-neuronal antibodies associated with PNS are divided into two broad categories: antibodies that target intracellular neuronal antigens that are expressed by the cancer and the other antibodies that target proteins or receptors residing on neuronal cell surface or in the synapse. The NMDA-R antibody belongs to the latter category, and it is the antibody that mediates neuronal dysfunction by direct interaction with target antigens in the central nervous system (9). Thus, the patients often fully recovered or have shown significant improvement with immunotherapy or tumor resection if present. This presents the opportunity for early diagnosis and early treatment and it is clear that early identification and treatment might have serious prognostic implications. Delayed treatment with immunosuppressive therapy probably results in worse outcomes.

Ovarian teratoma is most commonly reported in young females. Besides tumors of the reproductive system, NMDAR encephalitis also showed an association with hepatic carcinoma, small cell lung carcinoma, thymic carcinoma, pancreatic cancer, breast cancer, Hodgkin's lymphoma, etc. (2, 4, 10, 11). According to the previous literature, anti-NMDAR encephalitis occurs in association with any neuroendocrine carcinoma. Hepatic and renal carcinomas are solid cancer types. Compared with hepatic carcinoma (11), both patients presented with psychiatric manifestations, but no epilepsy and motor manifestations occurred, which improved with early immunotherapy. This might be due to the fact that the patients were either diagnosed early with access to early treatment or had expressed a milder form of disorders. In order to clarify the relationship between tumor antigen exposure and anti-NMDAR encephalitis, it should bring benefit to conduct experiments that would determine which subunit of the NMDAR, N1 or N2b, is expressed in tumor tissues. However, we have not tested the NMDAR subunit in this patient yet, which is a limitation of this case.

PNS is an important tumor biomarker of renal cell carcinoma. The recognition and the early management of PNS can improve the prognosis of patients, although its underlying pathomechanisms are not fully understood. Physicians should assist in improving the understanding of this disease.

This case adds to the current literature of yet another tumor association (renal neuroendocrine carcinoma) of anti-NMDAR encephalitis in an elderly person. This case suggests that when patients present with unexplained seizures, neuropsychiatric disorder, or other brain symptoms, it is crucial for clinicians to be aware of PNS, so it is necessary to evaluate the presence of NMDAR antibodies and perform CT scans of the chest, the abdomen, and the pelvis when autoimmune encephalitis is suspected.

DATA AVAILABILITY STATEMENT

The datasets used/analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Affiliated Ganzhou Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study and to the publication of this case report.

AUTHOR CONTRIBUTIONS

JY and BL carried out the studies, participated in collecting data, and drafted the manuscript. XL participated in its design. ZL participated in the acquisition and analysis or interpretation of data. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 16 December 2021
doi: 10.3389/fonc.2021.793808

Case Report: Exceptional Response to Nivolumab Plus Ipilimumab in a Young Woman With TFE3-SFPQ Fusion Translocation-Associated Renal Cell Carcinoma

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: 12 October 2021
Accepted: 22 November 2021
Published: 16 December 2021

Citation:
Martini DJ, Jansen CS, Harik LR, Evans ST, Olsen TA, Master VA, Kissick HT and Bilen MA (2021) Case Report: Exceptional Response to Nivolumab Plus Ipilimumab in a Young Woman With TFE3-SFPQ Fusion Translocation-Associated Renal Cell Carcinoma. Front. Oncol. 11:793808. doi: 10.3389/fonc.2021.793808

Translocation-associated renal cell carcinoma (tRCC) is a rare, aggressive malignancy that primarily affects children and young adults. There is no clear consensus on the most effective treatment for tRCC and there are no biomarkers of response to treatments in these patients. We present a case of a 23 year-old female with metastatic tRCC to the lungs who was started on treatment with nivolumab and ipilimumab. She had a complete radiographic response to treatment and has been progression-free for over 18 months. Immunofluorescence imaging performed on the baseline primary tumor sample showed significant intratumoral immune infiltration. Importantly, these cells are present in niches characterized by TCF1+ CD8+ T cells. Histopathologic investigation showed the presence of lymphocytes in the fibrovascular septae and foci of lymphovascular invasion. Furthermore, lymphovascular invasion and intratumor niches with TCF1+ CD8+ T cells may predict a favorable response to treatment with nivolumab and ipilimumab. These findings have significant clinical relevance given that immune checkpoint inhibitors are approved for several malignancies and predictive biomarkers for response to treatment are lacking. Importantly, the identification of these TCF1+ CD8+ T cells may guide treatment for patients with tRCC, which is a rare malignancy without a consensus first-line treatment option.

Keywords: translocation-associated RCC, combination immune checkpoint therapy, exceptional responder, intratumoral immune niche, TCF1+ CD8+ T cells, rare malignancy

INTRODUCTION

Translocation-associated renal cell carcinoma (tRCC) is an uncommon, aggressive subtype of non-clear cell renal cell carcinoma (nccRCC). It was first identified in 2004 with technological advancements in genetic profiling, which showed that the malignancy disproportionately affects young patients and has a very poor prognosis (1). Chromosomal translocations involve TFE3

(Xp11.2) or, much less commonly, TFEB (6p21), and these two variants are commonly grouped and referred to as "MiT Family Translocation RCC" (1). SFPQ-TFE3 tRCC accounts for 20-75% of pediatric RCC and approximately 1-4% of adult RCC, with a slight female predominance at 1.6:1. While agents targeting vascular endothelial growth factor (VEGF) have shown efficacy in retrospective studies, there is no consensus first-line systemic therapy for metastatic tRCC (2). Recent studies have demonstrated similar activity of immune checkpoint inhibitors (ICI) in metastatic tRCC, indicating potential therapeutic benefits of PD-1 and VEGF inhibition for non-clear-cell renal cell carcinoma (nccRCC) (3). There is limited data investigating dual ICI therapy in tRCC. In this report, we present a case of a young female with tRCC who experienced an exceptional response on nivolumab and ipilimumab combination therapy. We also present immunofluorescence (IF) imaging and histopathologic staining of the patient's primary tumor specimen, wherein we specifically probe for the presence of TCF1+ CD8 T cells. The importance of these TCF1+ CD8 T cells for the endogenous immune response to RCC has been demonstrated (4), and others have reported a critical role for these TCF1+ cells in the response to ICI in other tumor types (5–9), but the role of these cells in the response to ICI has been suggested (10), but not definitively established in RCC, particularly in rare subsets of RCC such as tRCC.

METHODS

Patients and Clinical Data

We collected clinical data for one patient with TFE3-SFPQ fusion tRCC from the electronic medical record. Data regarding histologic diagnosis was obtained from the pathology report and PD-L1 status was determined from a Foundation One immunohistochemical (IHC) test. Radiographic response rate was determined using response evaluation criteria in solid tumors version 1.1 (RECISTv1.1) (11).

Sample Collection, Preparation, and Storage

Samples for immunofluorescence (IF) analysis were formaldehyde fixed and embedded in paraffin (FFPE) blocks by Emory Pathology. Unstained stained sections of FFPE blocks were obtained from Emory Pathology.

Deparaffinization and Antigen Retrieval

Sections were deparaffinized in successive incubations with xylene and decreasing concentrations (100, 95, 75, 50, 0%) of ethanol. Antigen retrieval was achieved using Abcam 100x TrisEDTA Antigen Retrieval Buffer (pH = 9) heated to 115°C under high pressure. Sections were washed in PBS + 0.1% Tween20 before antibody staining.

Immunofluorescence Antibody Staining

Immunofluorescence staining and analysis was performed in a research laboratory at Emory University. Sections were blocked for 30 min with a 10% goat serum in 1x PBS + 0.1% Tween20. Sections were then stained with appropriate primary and secondary antibodies. Primary antibodies were used at concentrations of 1:100 (MHC-II) or 1:150 (CD8, TCF1) and incubated for 1 h at room temperature (**Supplemental Table 1**). Secondary antibodies were used at concentrations of 1:250 (A488, A568) or 1:500 (A647) and incubated for 30 min at room temperature.

Image Capture and Analysis

The selected fluorophore panel allowed for simultaneous visualization of three targets and a nuclear stain (DAPI). A For Leica SP8 confocal microscope with a motorized stage was used for tiled imaging, and a 40x, 1.3NA, 0.24 mm WD oil immersion objective was used, allowing for highly resolved, smoothly tiled images. Fluorophores were excited with the 496, 561, and 594 laser lines or with a multiphoton Coherent Chameleon Vision II laser, tuned to 700nm (DAPI). Emission-optimized wavelength ranges informed specific detector channels, which were used to detect fluorescence. Leica LASX software was used to create a maximum projection image, allowing for acquisition of large, tiled images regardless of a varying focal plane across each tissue section.

RESULTS

Case Presentation and Histologic Description

A 23-year-old female patient presenting with right-sided flank pain underwent a right radical nephrectomy and was diagnosed with a pT1bNxM1 melanotic translocation-associated renal cell carcinoma with TFE3-SFPQ fusion. Caris report found no significant mutations for clinical biomarkers and patient physical exam had no clinically significant findings. A CT scan of the chest showed numerous bilateral lung nodules concerning for metastasis. Four months later, the patient was started on dual ICI therapy with ipilimumab 1mg/kg and nivolumab 3 mg/kg given the patient's young age and the possibility of a durable radiographic response to immunotherapy, which has been seen in RCC patients treated with ICI-based treatment regimens. She received 4 cycles of dual therapy and has now received 22 cycles of nivolumab 480 mg q28d monotherapy. She experienced diffuse myalgias and arthralgias starting after cycle 5 of treatment which improved with 5mg prednisone. She also experienced adrenal insufficiency requiring hydrocortisone and hypothyroidism controlled on levothyroxine. Although the myalgias, arthralgias, adrenal insufficiency, and hypothyroidism were deemed as likely related to her ICI-regimen, no dose adjustments were required. She otherwise endorsed favorable tolerance with her therapy and felt positively about her treatment course. Her first restaging chest CT scan after cycle 4 showed a complete response, which has been maintained for over 18 months. At the time of this report, the patient is alive and well.

Correlative Data

Outside PD-L1 IHC staining identified a tumor proportion score of 1%. A Caris molecular intelligence tumor profiling report showed a low TMB, stable MSI, and no detected mutations in BAP1, FH or PBRM1. Germline testing was negative.

Pathologic Description

The right nephrectomy specimen included a well-defined nodular mass confined to the renal parenchyma measuring 5.7 x 4.6 x 4.3 cm (**Figure 1A**). The renal mass showed a relatively homogenous microscopic appearance composed of nests of optically clear polygonal cells separated by fibrovascular septae which contained occasional small reactive lymphocytic inflammation (**Figure 1B**). Some cells contained fine dark brown intracytoplasmic melanin pigment (**Figure 1C**), and the tumor was positive for HMB45, a melanocytic marker (**Figure 1D**). Foci of multinucleated tumoral cells consistent with a WHO/ISUP nuclear grade 4 were present. There were also foci of lymphovascular invasion present.

Immunofluorescence Imaging

Immunofluorescence imaging reveals presence of CD8+ and MHC-II+ cells in tumor tissue. CD8+ T-cells are found throughout the tumor issue, as well as in dense aggregations, or immune niches, with MHC-II+ antigen presenting cells (**Figure 2A**). Many CD8+ T-cells found in these niches are TCF1+ (**Figure 2B**).

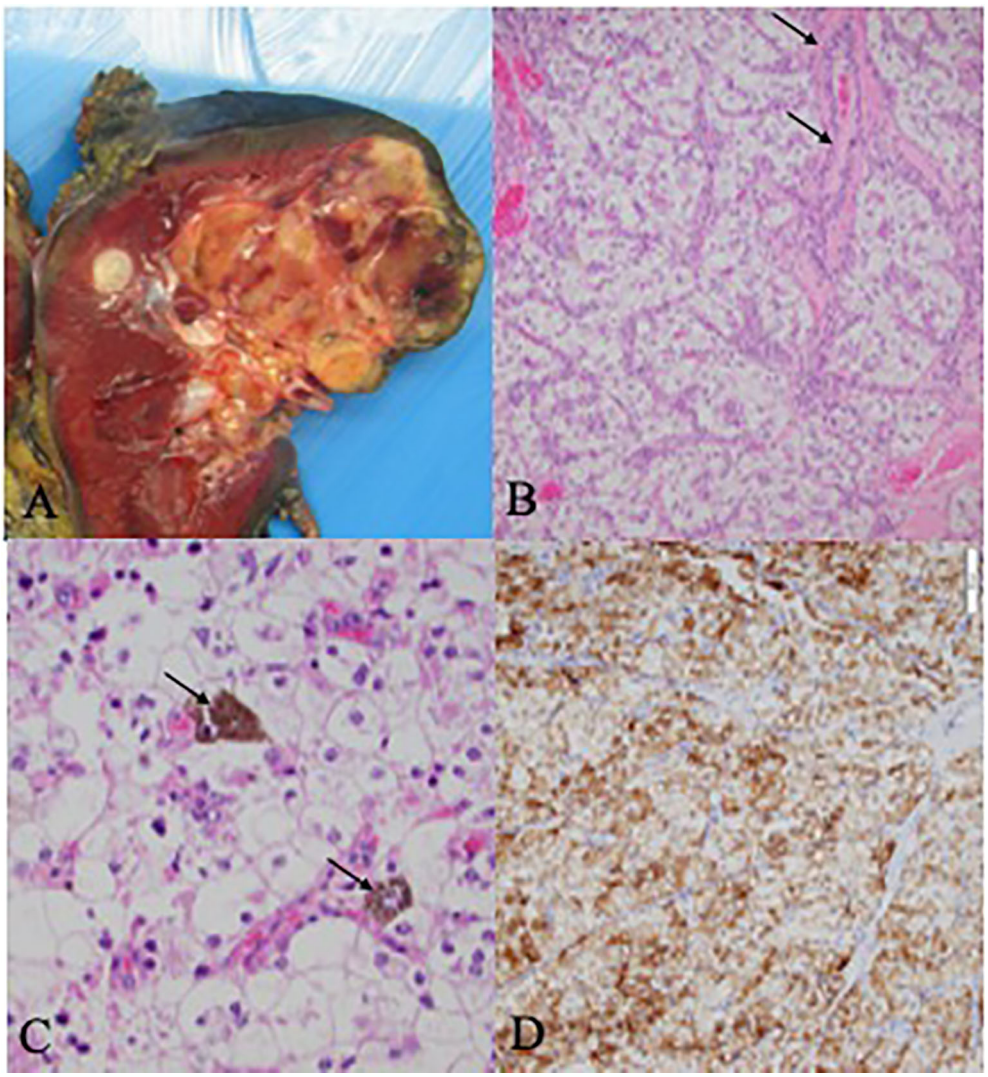

FIGURE 1 | Pathology and Histology Samples **(A)** Gross kidney specimen demonstrating a superior pole multi-nudular, well-defined yellow cream mass with areas of hemorrhagic degeneration and necrosis. **(B)** Histologic examination shows solid nests of polygonal clear cells with prominent neclei with nucleoli. The intervening fibrovascular septae contain small lymphocytic infiltrates (black arrows). **(C)** Unique intra-cytoplasmic melanin pidment which may be seen in melanotic translocation-associated renal cell carcinoma (black arrows). **(D)** The carcinoma was positive for HMB45, a melanocytic marker which can be positive in melantonic translocation-associated renal cell carcinoma.

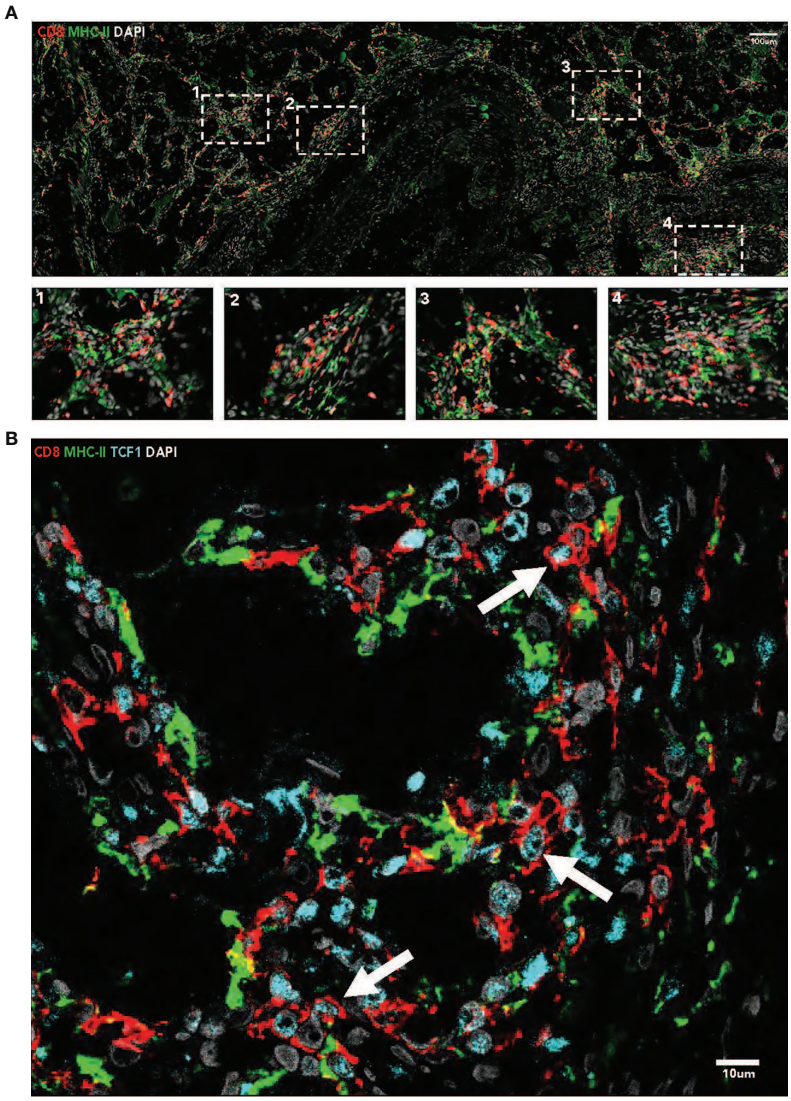

FIGURE 2 | **(A)** Immunofluorescence imaging (40x, tiled) demonstrates the presence of intratumoral immune niches containing CD8+ and MHC-11+ cells. Nuclei are stained with DAPI. **(B)** Immunofluorescence imaging (40x) demonstrates the presence of TCF 1+ CD8+ T cells in MHC-11+ antigen presenting cell dense niches. Nuclei are stained with DAPI.

DISCUSSION

In this report, we present a case of a young woman with metastatic TFE3-SFPQ fusion translocation RCC who had a durable complete response on nivolumab and ipilimumab combination therapy. Targeted therapy with mTOR or VEGF inhibitors was also under consideration based on clinical trials showing efficacy in tRCC (2, 12, 13). However, ICI-based therapy was selected as first-line therapy for this young woman based on the promise of a durable response (14, 15), especially in the context of recent reports suggesting promising activity for ICIs in nccRCC, and specifically tRCC (14, 16, 17). Ongoing trials continue to explore the efficacy of immune checkpoint inhibitors in tRCC (16).

We showed that intratumoral immune niches were present in the primary tumor specimen, which were characterized by TCF1+ CD8+ T-cells. This was supplemented by the histologic finding of the presence of lymphovascular invasion and lymphocytic infiltration in fibrovascular septae between tumor cells. These correlations have significant clinical implications because: (1) there is no consensus standard-of-care treatment for tRCC, (2) there are no validated predictive biomarkers of response to ICI in tRCC, and (3) these findings may be generalizable to other rare, aggressive malignancies which ICI are not currently FDA approved for if validated in larger, prospective studies.

Non-clear cell RCC is a heterogeneous group of malignancies that have no consensus standard-of-care treatments. A few small, retrospective studies have suggested VEGF inhibitors may have

efficacy for treatment of metastatic tRCC, identifying similar PFS and objective responses compared to patients with clear-cell RCC (2). Given the high recurrence rates in tRCC patients treated with targeted therapy or chemotherapy, immunotherapy is an attractive option for these young patients, particularly given that these agents offer the promise of a possible durable response. This is particularly true for tRCC, which disproportionately affects younger patients and has an aggressive course and a very poor prognosis. Recent data has suggested that ICIs have efficacy in treating nccRCC, including tRCC (14, 17). Given that there is limited data on treatment options for tRCC patients, this report has significant clinical value for medical oncologists because it provides a possible predictive marker of response to ICI and a potential mechanism by which patients with rare RCC histology respond to ICI. Furthermore, it is unclear whether specific subtypes of tRCC are more likely to respond to ICI and this report provides hypothesis-generative data regarding the sensitivity of TFE3-SFPQ fusion tRCC to ICI.

There has been an expanding effort to identify biomarkers of response to ICI given their increasing prevalence in the treatment of many malignancies including RCC. Miao et al. identified an association between loss of the PBRM1 gene and clinical outcomes, arguing for absence of this gene as a prognostic marker for improved response to ICI-based regimens (18). Although PD-L1 expression has value as a predictive biomarker in some solid tumors, there is no clear association in RCC patients treated with ICI (19). The limitation of PD-L1 expression as a biomarker is highlighted in our patient's case, as the IHC score was 1% and, despite this low expression, the patient experienced a complete response to treatment. A potential contributing factor could have been the degree of T-cell infiltration in the tumor's histology, which is a finding that has been associated with improved patient outcomes in many tumor types and clinical settings (20–25), and specifically in RCC patients receiving immunotherapy (24).

Subsequent study has suggested that TCF1+ CD8 T cells are the subset of the tumor infiltrating lymphocytes that are critical for the response to ICI in those tumors where CD8 T cell infiltration predicts patient outcomes (5–9). TCF1 is a transcription factor which defines a stem-cell like population of CD8+ T cells, and furthermore these cells have demonstrated increased proliferative potential, expression of survival-related genes such as IL7R, and generation of co-stimulatory molecules such as CD28 when compared to CD8+ T cells without TCF1 (4–9). In other tumor types, such as melanoma, the number of these TCF1+ CD8 T cells correlates with therapeutic response. This suggests that the presence of intratumoral TCF1+ CD8 T cells are critically important to the response to ICI in several tumor types (4–9). Thus, in the context of the findings that these TCF1+ stem-cell like CD8+ T cells reside in immune niches with a high density of antigen presenting cells in RCC (4), we looked for the presence of these cells in these dense immune niches in this patient with tRCC, given the patient's exceptional response.

Interestingly, these cells were identified in the baseline tumor sample of the patient presented in this report and appeared in close association with MHC-II+ antigen presenting cells, similar to what was reported in Jansen et al. (4). Additionally, lymphocytes were identified in the fibrovascular septae with foci of lymphovascular invasion on histopathologic investigation. This hypothesis-generating data may suggest that further study of these TCF1+ stem-like T cells and antigen presenting niches may reveal a prognostic and predictive biomarker for tRCC patients treated with ICI, especially given that recent reports have associated TCF1 enrichment with response to ICI in other RCC subtypes (10). While this case report is only a preliminary view into the role of TCF1+ CD8 T cells in the response to tRCC, and in RCC in general, it provides an interesting and important foundation for future, more comprehensive study into these cells as both a biomarker of and as a key mechanistic player in the response to ICI in RCC.

The strength of this case report is that it offers a unique anecdote of the potential for combination ICI therapy in patients with tRCC and highlights the potential for the presence of TCF1+ CD8+ T cells as a biomarker in this rare malignancy. Further investigation is needed regarding the potential predictive and prognostic of this biomarker to predict responses to immunotherapy. The main limitation of this study is that this is a case report which limits the generalizability of this finding without validation in larger, prospective studies. Additionally, the relatively short follow-up including in this case report limits our ability to assess the durability of the patient's response. However, as of October 2021, over 18 months after the initiation of therapy, the patient has maintained a complete response on follow-up imaging studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DM, CJ, and LH drafted the manuscript. DM collected the clinical data for the patient included in this study and provided administrative support. CJ provided the immunofluorescence images and LH provided the histopathologic images. MB oversaw the study. VM was the urologic surgeon that performed the patient's nephrectomy and provided samples used in the biopsy slides. All authors edited the manuscript and approved the final version of the manuscript.

FUNDING

Research reported in this publication was supported in part by the Breen Foundation and the Biostatistics Shared Resource of Winship Cancer Institute of Emory University. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.793808/full#supplementary-material

Supplementary Table 1 | Immunofluorescence Antibodies.

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Conflict of Interest: MB has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Calithera Biosciences, Genomic Health, Nektar, and Sanofi and has received grants to his institution from Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, Seattle Genetics, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer for work performed as outside of the current study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Oncology

CASE REPORT
published: 20 January 2022
doi: 10.3389/fonc.2021.826325

Case Report: TFE3 Positive Xp11.2 Translocation Renal Cell Carcinoma (TRCC) – A Case Study and Review of the Literature

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Microphthalmia-associated transcription factor renal cell cancer, also known as translocation renal cell cancer, belongs to the group of extremely rare non-clear-cell kidney neoplasms. Their incidence is lower in adulthood than in childhood. The only known risk factor for the development of this tumor is prior chemotherapy. In the operable stage of the disease, the prognosis depends on the status of regional lymph nodes. Interestingly lymph node positivity worsens the prognosis only in the adult patient population. Radical surgical excision is the best therapy in the early stage. The optimal treatment strategy for locally advanced and metastatic disease has not been established, given the lack of evidence in such a rare disease. We present the case of a patient with an aggressive course of this neoplasm treated with temsirolimus, who achieved 10-month control of this neoplasm accompanied by a discussion on other therapeutic possibilities.

Keywords: translocation renal cell cancer, TFE3, TRCC, non-clear renal cell carcinoma, microphtalmia-associated transcription factor

OPEN ACCESS

Edited by:
Mehmet Asim Bilen,
Emory University, United States

Reviewed by:
Bassel Nazha,
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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *30 November 2021*
Accepted: *16 December 2021*
Published: *20 January 2022*

Citation:
Miroński I, Zaucha JM. Kowalski J and Zaucha R (2022) Case Report: TFE3 Positive Xp11.2 Translocation Renal Cell Carcinoma (TRCC) – A Case Study and Review of the Literature. Front. Oncol. 11:826325. doi: 10.3389/fonc.2021.826325

INTRODUCTION

Malignant tumors of the kidneys are diagnosed in 3–15 per 100,000 people yearly (1). In addition to the clear cell cancers that account for 80%–85% of all renal cell cancer (RCC) cases, the World Health Organization (WHO) classification of RCC incorporates 12 rare non-clear-cell entities, including acquired cystic disease-associated, clear cell papillary, fumarate hydratase-deficient, succinate dehydrogenase-deficient, tubulocystic, and microphthalmia-associated transcription factor (MiT) family translocation RCC (TRCC) (2, 3). TRCC was established as a separate entity in 2004 after the discovery of a distinct molecular signature characterized by mutations in the transcription factor 3 or B (*TFE3* or *TFEB*) genes (3–5). Several recognized types of *TFE3* rearrangements are responsible for a wide range of morphologies in TRCC, which frequently make TRCC similar to more common RCC subtypes or neoplasms such as perivascular epithelioid cell tumor or epithelioid angiomyolipoma of the kidney (6). Although the histopathologic and genetic features of these uncommon neoplasms have been described, data on clinical behavior, optimal systemic therapy, and prognosis are limited. In children, TRCC accounts for about 20%–25% of all RCC cases. Although they are rare in adulthood, some cases have been misdiagnosed (5–9). Kuthi et al. found 28 cases of TRCC among 2,804 malignant kidney tumors (10). The incidence is

higher in women than in men at a ratio of 1.4–2:1, and the peak age is 20 to 30 years (7, 8). These tumors are usually found incidentally in asymptomatic patients. While radical surgical excision is the best therapy in the early stage, the optimal treatment strategy for locally advanced and metastatic disease has not been established. Therefore, the only way to choose the optimal treatment is based on data collected from small studies or even case reports. In the advent of improved personalized therapies for patients with clear cell renal cancer, detailed case descriptions on the type and effect of various therapies are of utmost importance.

To broaden the knowledge about this infrequent neoplasm, we report a case of an adult patient with advanced TRCC that rapidly progressed after surgical removal of the tumor. The informed consent for publishing this case was obtained from the patient.

CASE REPORT

In May 2019, after a several-month history of nausea and vomiting and self-resolving episodes of hematuria, two weeks of severe left flank pain motivated a 68-year-old woman to visit her primary physician who ordered a computed tomography (CT) evaluation. CT showed a large (13 × 17 × 19 cm) mass in the left kidney that caused hydronephrosis of the left renal pelvis. The perinephric tissue left renal vein and left suprarenal gland were infiltrated. Several enlarged retroperitoneal lymph nodes (LNs) and a small lesion in the first lumbar vertebra (L1) were not typical but suspected of metastasis. In June 2019 the patient was admitted to the hospital for further evaluations and treatment. The chest X-ray image was normal. Laboratory blood tests showed microcytic anemia with 7.7 mg/dL hemoglobin (Hb), 24% hematocrit (Hct), 78fL Mean Corpuscular Volume (MCV), 1.58 mg/dL serum creatinine, and an impaired creatinine clearance (CrCl) rate of 33 mL/min. All other laboratory results were within normal ranges. The patients' performance status was reasonably good (PS1). Comorbidities included well-controlled hypertension and hypercholesterolemia. The medical history included endometrial polypectomy and left submandibular gland removal for a benign adenoma, and about seven pack-years of smoking. There was no history of alcohol use, drug abuse or incidence of cancer in the family.

The patient was qualified for surgical treatment to obtain a pathological diagnosis and enable systemic therapy, which is available only for patients after at least partial nephrectomy in our country. In June 2019, a radical operation removed the left kidney with the tumor, the left adrenal gland, and, to increase the chance for obtaining clear surgical margins, with the spleen. The tumor, necrotic in more than 50%, vastly infiltrated the perinephric fat tissue and veins. A single metastatic nodule was found in the left adrenal gland. The renal pelvis, artery, and vein and all surgical margins were free of cancer. No LNs were observed in the specimen. The tumor was composed of epithelioid clear cancer cells that formed papillary and tubular structures. There was profound nuclear atypia. Immuno-histochemical (IHC) evaluation showed that the tumor was CD10+, vimentin+, TFE3+, and CK7- (**Figure 1**), which led to the final diagnosis of TRCC further confirmed as the Xp11 translocation subtype by fluorescence *in situ* hybridization (FISH) at the pathological stage T3aNxM1 (according to the TNM classification of malignant tumors, 8th edition).

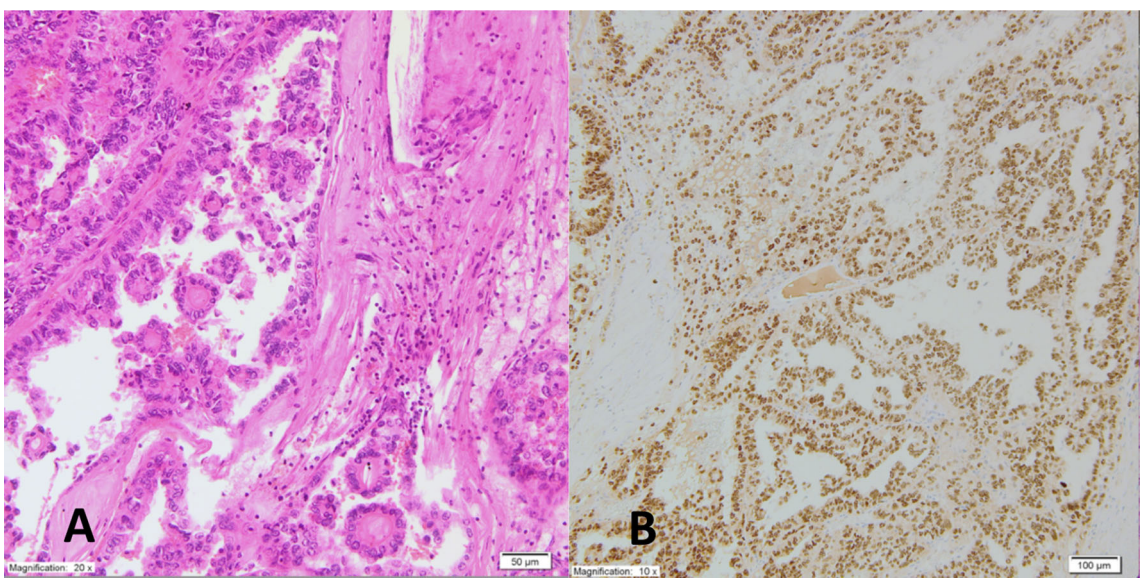

FIGURE 1 | Pathomorphologic picture of the tumor shows **(A)**. on HE examination epithelioid clear cancer cells with nuclear atypia forming papillary and tubular structures; **(B)** on IHC evaluation positive TFE3+ expression.

The early postoperative period was complicated by acute gastrointestinal bleeding; however, neither endoscopy nor CT revealed the bleeding site. The patient recovered after transfusion (with two packs of red blood cells, Hb level increased from 6.7 to 9.1 mg/dL). Echocardiography showed a distended inferior vena cava almost entirely obstructed by a large thrombus. An electrocardiogram, Doppler ultrasonography of the leg veins and the left ventricular ejection fraction (57%) were normal. Beta-blockers (25 mg QD metoprolol) and daily subcutaneous injections of low molecular weight heparin (enoxaparin at a dose adjusted for the decreased CrCl, 40 mg QD) were administered. During the first postoperative visit, the patient reported persistent fatigue and exacerbation of lumbago-like back pain uncontrolled by non-steroidal anti-inflammatory medications. A postoperative CT scan revealed an extensive inoperable, disseminated recurrence with multiple metastases in both lungs, peritoneum, intraabdominal and retroperitoneal LNs and the spine (Th12, L1, and L2). Neoplastic thrombus almost completely obstructed inferior vena cava from L2/L3 to the right atrium with by-pass circulation below and above the diaphragm and perfusion changes in the liver (**Figure 2**). Palliative radiotherapy (RTH) was administered to the affected spine (Th12-L2, 20 Gy in 5 fractions) with symptomatic improvement. Two weeks later, the patient started systemic therapy. Due to the lack of treatment guidelines for rare RCC subtypes, intravenous temsirolimus (25 mg weekly) was initiated as the only available in the country therapy for the non-clear-cell RCC. Metoprolol was switched to carvedilol and amlodipine, and furosemide was added to control exacerbated hypertension. However, mucositis, nausea, diarrhea, appetite decrease, and hypertriglyceridemia led to one-level dose de-escalation (to 20 mg weekly). Anemia was managed with packed RBC transfusion (Hb level increased from 5.7 to 9.0 mg/dL). Thirty-four cycles of therapy were administered and were associated with stabilising the disease (per RECIST 1.1 criteria on CT) without significant complications. Ten months after the start of treatment, a subsequent CT scan showed progression of preexisting lesions and new metastases. A tumor mass in the spine (Th3) caused spinal compression that required urgent palliative radiotherapy (20 Gy in 4 fractions), accompanied by symptomatic improvement. Thus, temsirolimus was withdrawn.

Standard second-line therapy for non-clear cell RCC has not been established. Therefore, in our country, such therapy is regarded as experimental and is not reimbursed. The patient was offered the best supportive care and died in May 2021.

DISCUSSION

The MiT family of TRCC is one of the five main subtypes of miscellaneous non-clear cell RCC originating from the proximal convoluted tubule of the kidneys. It is characterized by different histological features and clinical behavior related to a unique genetic alteration. The rarity of non-clear-cell RCC precludes the completion of prospective clinical trials, all of which have been prematurely closed due to slow accrual. We report a case of aggressive TRCC in a 68-year-old woman who achieved 10-month progression-free survival (PFS) on temsirolimus. Unlike 15% of the cases with the Xp11.2 translocation subtype of TRCC, our patient had no history of prior chemotherapy (11). The patient deferred evaluation for intermittent hematuria that lasted for several months. The diagnosis was triggered by lumbago-like symptoms caused by the enormous size of the primary tumor, which microscopically infiltrated the spine. Not surprisingly, the disease was discovered at an advanced stage. The histological proof of TRCC was established based on positive IHC expression of TFE3 and CD10 and negative expression of CK7 (11, 12). TFE3 is ubiquitously expressed in normal human cells, although its levels are undetectable. The translocation of the *TFE3* gene becomes detectable after it causes overexpression of the TFE3 protein (12). Vimentin expression is usually negative in TRCC; thus, its positivity in our patient required additional molecular analysis using next generation sequencing to rule out the risk of a false diagnosis.

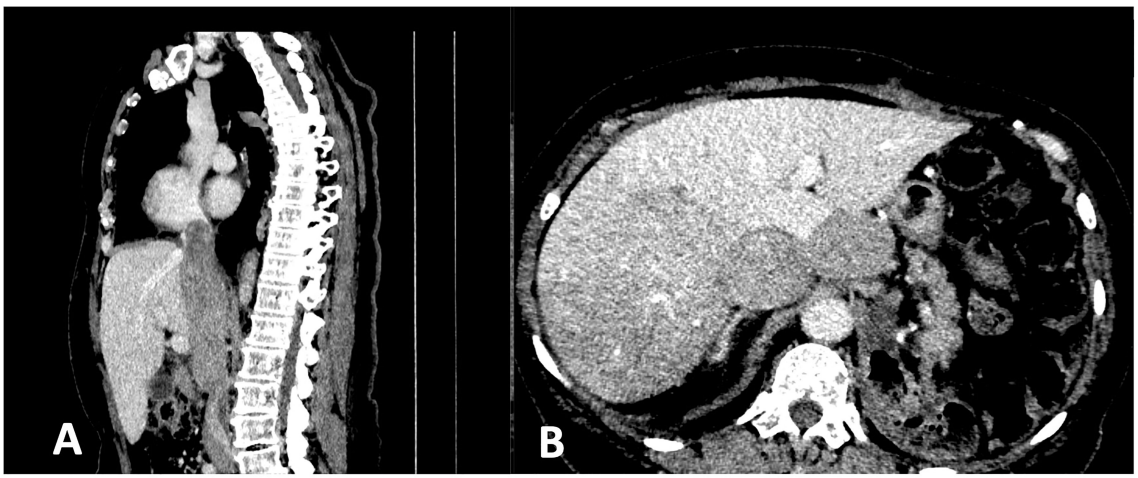

FIGURE 2 | CT scan shows **(A)** the neoplastic thrombus almost completely obstructing inferior vena cava from L2/L3 to the right atrium; **(B)** perfusion changes in the liver.

The histomorphology of adult-onset TRCC has been described in over 400 molecularly proven cases. The involvement of chromosome X (Xp11.2) suggests female preponderance; however, insufficient data confirms this hypothesis. Diverse genetic aberrations such as translocations or inversions of various genes (most frequently PRCC, ASPL, and SFPQ) lead to fusion genes responsible for the histological and clinical differences (6, 9–12). None of the numerous chimeric TFE3 fusion proteins has been useful as therapeutic targets. In addition, their types do not explain the differences in incidence rates and prognoses between children and adults. In a large study by Ma et al. that included 8,001 adults and 82 children, the proportion of pediatric and adult Xp11.2 TRCCs was 20.7% (17 of 82 children) and 0.9% (73 of 8001 adults), respectively. The five-year overall survival (OS) and PFS rates in children were significantly better than those in adults (OS: 75.0% vs. 40.3%, p <0.01; PFS: 64.8% vs. 0%, p=0.04) (4, 8, 9). Interestingly Malouf et al. have found a subgroup with 17q gain responsible for activating the cytotoxic T lymphocyte-associated protein 4 (CTLA4) pathway (13). It is also essential to emphasize the frequent expression of programmed death ligand 1 (PD-L1) in tumor-infiltrating immune cells present in 90% of TRCC cases (14).

LN positivity (LN+) is more common in children (58.8%) than in adults (28.8%, P=0.02) (4). Interestingly, LN+ is associated with significantly shorter PFS (Hazard ratio [HR]=0.10, 95% confidence interval [CI] 0.02–0.51, p=0.01) and OS (HR=0.11, 95% CI 0.01–0.98, p=0.04) but had no impact on prognosis in children (4). In our case, the postoperative specimen did not contain any LNs. The first post-resection CT scan revealed multiple LN metastases.

We noted acute clotting disorders with life-threatening mucosal gastric hemorrhage in our patient apart from diagnostic and staging difficulties.

However, the most critical problem was establishing an optimal treatment plan, given the lack of effective methods and the presence of enormous, possibly neoplastic thrombus in the VCI.

There are various therapeutic options for advanced or metastatic clear cell RCC (clear RCC), which include monotherapy or combinations of immune, antiangiogenic, and signal transduction-blocking agents. Treatment choice depends on the patient's general status, parenchymal organ function, intensity and evolution of symptoms, and comorbidities. Adjuvant treatment with pembrolizumab has been approved in the USA for high-risk clear RCC, including completely resected metastatic disease because of the significant positive impact on disease-free survival (15). Despite the poor prognosis of TRCC and high expression of PDL-1 in most of cases, adjuvant systemic immunotherapy is not recommended. Moreover, the evidence for the efficacy of available systemic therapies for non-clear RCC is not very strong. The results of the ARCC trial, one of the first randomized controlled phase III trials that included non-clear RCC patients, compared temsirolimus and interferon treatments and favored temsirolimus. However, this agent should be considered with caution because of the low number of non-clear RCC patients (73 of 626 patients with poor-risk non-clear RCC or unconfirmed histology) and suboptimal efficacy of the interferon treatment as a comparator (16).

Other studies, which included patients with non-clear cell histologies, have demonstrated that first-line anti-VEGF therapy with sunitinib offers better outcomes than the mammalian target of the rapamycin (mTOR) inhibitor everolimus (**Table 1**) (17–24). Two studies, ESPN (19) and ASPEN (20), were explicitly conducted in non-clear RCC and confirmed improved PFS and OS with frontline sunitinib therapy. Sequential therapies with sunitinib followed by everolimus or vice versa were evaluated in a trial called RECORD-3 (25). The outcomes favored initial therapy with sunitinib. The three studies showed a median PFS of 6.1, 7.2, and 8.3 months, respectively, much shorter than the median PFS of approximately 11–12 months observed with sunitinib treatment for clear RCC. In a phase II trial of pazopanib the disease control rate for treating non-clear RCC was 81%, and partial responses were observed in 10 of 37 (27%) patients (26). The median PFS and OS were 15.9 and 17.2 months, respectively. The International Metastatic RCC Database Consortium evaluated the outcomes of anti-VEGF therapy in 337 non-clear RCC cases (27). The median OS was 15.7 months in non-clear RCC and 20.2 months in clear RCC. The intermediate- and poor-risk patients predominantly contributed to the differences in OS outcomes between the groups. Outcomes were similar in the favorable group. Single-agent studies of everolimus, c-Met inhibitors, and chemotherapy have also demonstrated modest efficacy. Non-clear RCC, similar to other neoplasms, is driven by various factors such as the MET pathway in papillary kidney cancer or alterations in mitochondrial DNA in chromophobe cancer. However, no essential biological pathway was found in translocation-associated subtypes until 2018. The first study by Argani et al. (28) showed upregulation of the mTOR and HIF-1α pathways. Damayanti et al. (29) repeated these results eight years later. They showed that the TFE3/IRS-1/PI3K/AKT/mTOR pathway is altered in TRCC, suggesting a potential benefit from inhibiting this axis with a dual PI3K/mTOR inhibitor. However, the findings of these studies are limited by the low number of TRCC cases diagnosed annually around the world.

The most current non-clear cell RCC treatment results were released as conference presentations. Lee C-H et al. (30) used nivolumab with cabozantinib in patients who were treatment-naïve or previously treated with either a VEGF-R TKI or mTOR inhibitor for papillary RCC, MiT family TRCC, or unclassified RCC. Patients showed an overall response rate (ORR) of 48% (95% CI 31.5%–63.9%), a median PFS of 12.5 (95% CI 6.3–16.4) months, and an OS of 28 (95% CI 16.3–not established NE) months with an acceptable toxicity profile. The second cohort (for the chromophobe subtype) was closed early due to a lack of efficacy (ORR 0%), as previously suggested by the KEYNOTE 427 trial (31).

It is impossible to conclude ICI efficacy from other clinical trials as TRCC was not explicitly addressed; however, patients with TRCC may have been included among the unclassified cases.

Among other targets, the highest level of evidence has been shown for the efficacy of MET inhibitors in non-clear RCC. The results of the SWOG 1500 study (32) comparing sunitinib against three MET inhibitors (cabozantinib, crizotinib, and savolitinib)

TABLE 1 | Treatment results in clinical trials including patients with TRCC.

Study (type)	Agent	Prior treatmentsN	Patients with TRCC/totalN	Ageyears (range)	OSmedian (95%CI) (months)	PFSmedian (95% CI)(months)	Response RECIST 1.1N	ORR %	DCR %
Lee et al. (Retrospective) (17)	Sunitinib	0-1	1/31	53 (18-76)	NA	NA	SD:1	0	100
Tannir et al. (Prospective) (18)	Sunitinib	0-≤2	1/57	57 (22-85)	NA	1.0	PD:1	0	0
Tannir et al. (RCT) (19)	Sunitinib	0-1	3/33	60 (28–76)	16.2 (8.8–NA)	6.1 (6.0–8.8)	NA	NA	NA
	Versus Everolimus		4/35	58 (23-73)	8.1 (5.5–23)	3.0 (1.3–NA)	NA	NA	NA
Armstrong et al. (RCT) (20)	Sunitinib	0	6/51	59 (24–100)	13.2 (9.7-37.9)	5.5 (3.2-19.7)	NA	NA	NA
	Versus Everolimus		2/64	64 (29–90)	31.5 (14.8-NR)	11.4 (5.7-19.4)	NA	NA	NA
Koshkin et al. (Retrospective) (21)	Nivolumab	0-3	1/41	58 (33–82)	NR	NA (3.5)	PD:1	0	0
McKay et al. (Retrospective) (22)	PD-1/PD-L1	0-3	3/43	57 (24-75)	12.9 (7.4-NR)	NA	PR:1 SD:1 PD:1	33	66
Campbell et al. (Retrospective) (23)	Cabozantinib	≥0	2/30	58.4 (25-81)	25.4 (15.3-35.4)	8.6 (6.1 - 14.7)	PD:1 SD:1	0	50
Boilleve A et al. (Retrospective) (24)	ICIs (anti-CTLA4, anti-PD-1, anti-PDL-1, (monotherapy or combined)	1	24/24	34 (3-79)	24 (4-84.6)	2.5 (1-40)	PR 4 SD 3	29	NA

RCT, randomized clinical trial; N, number; OS, overall survival; PFS, progression free survival; ORR, objective response rate; DCR, disease control rate; NA, not assessed; NR, not reached; PR, partial remission; SD, stable disease; PD, disease progression.

favored cabozantinib, which was suggested as the preferred frontline treatment. However, the study exclusively involved patients with papillary RCC, so the results cannot be extrapolated to other subtypes (32). Treatment with cabozantinib (40 mg QD orally) in combination with atezolizumab (1200 mg iv Q3W) assessed in the COSMIC-021 study (33) was associated with an ORR of 27% (95% CI 19%–36%) across all non-clear RCC histologies (of 112 patients, 66 (59%) had papillary RCC, 17 (15%) had TRCC, 15 (13%) were unclassified, ten (9%) had the chromophobe subtype, and four (4%) had collecting duct histology). Among the 54 patients with available next-generation sequencing data, the most frequently altered somatic genes were CDKN2A (22%) and MET (20%), and responses were seen irrespective of mutational status. At a median follow-up of 11 months, the median time to treatment failure, median PFS, and median OS were 6.7 (95% CI 5.5–8.6) months, 7.0 (95% CI 5.7–9.0) months, and 12.0 (95% CI 9.2–17.0) months, respectively, with relatively good tolerance and no treatment-related deaths. Unfortunately, TRCC cases were not included in this study. Thus, cabozantinib seems to have the most significant impact on patient outcomes in MET-driven disease.

The interaction between RCC and the immune system was noticed many years ago. Studies on the "immune escape" mechanisms have led to investigating PD- 1/PD-L1- and CTLA-4-targeted immune checkpoint inhibitors (ICIs) to treat RCC. While ICIs have been studied in clear RCC since 2015, their effects in non-clear cell subtypes have only recently been highlighted in the 2021 phase II KEYNOTE 427 trial (31). With over 100 non-clear RCC patients, the response rate to anti-PD-1 treatment was 25%. This was similar to the 29% disease control rate and 16,7% objective responses in the international, multicenter retrospective study of 24 patients with metastatic MITF family TRCC treated with ICIs (24). Currently, the activity of nivolumab with or without ipilimumab is being studied in non-clear cell histotypes (UNISoN, NCT03177239, SUNIFORECAST, and NCT03075423). Several other immunotherapeutic strategies are being investigated and include combinations of anti-PD-1 antibodies with modified NK cells (NCT04551885), D-CIK cells (a heterogeneous subset of ex-vivo expanded T lymphocytes; NCT03987698), agonists or inhibitors of cytokines (polyethylene glycosylated IL-2; NKTR-214), dendritic cell-based immunotherapy, anti-LAG-3, anti-Tim-3, anti-CD27 mAb, metabolism-related molecules, individualized cancer vaccines, and several other agents.

Promising data from single-arm phase 2 studies warrant randomized evidence. Therefore, next-generation studies will probably be based on combinations of anti-Met agents with immunotherapy for an additive, if not synergistic effect.

Our case is unique because of a long time of stabilization of the disease achieved by temsirolimus - the only medication available in our country for non-clear RCC. Based on published reports, sunitinib is superior to mTOR inhibitors like temsirolimus or everolimus. However, there were significant medical contraindications for anti-VEGF therapies, including sunitinib. Keeping all those factors in mind, everolimus/temsirolimus or ICIs, if available, were the best.

These treatment options are not correlated with such frequent adverse events as clotting disorders.

We provided the only treatment that was available for non-clear cell kidney cancer. We regret that the patient did not have a chance to benefit from other promising treatment options like ICIs.

CONCLUSION

Continued international collaborations and ongoing prospective studies focusing on TRCC cases with specific molecular alterations are warranted to improve clinical outcomes for this rare disease, with few evidence-based treatment options.

Because prospective studies including rare RCC subtypes, including TRCC, will take years to produce results, retrospective studies or case reports can inform treatment decisions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Students IM and JZ: collected data, searched the literature and wrote the manuscript. JK: prepared histopathological examination and illustrations. RZ: conceived the manuscript, consulted the treatment plan, reviewed the topic presentation, structure of the manuscript, illustrations and photographs. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.826325/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 02 February 2022
doi: 10.3389/fonc.2022.830195

Masseter Muscle Metastasis of Renal Cell Carcinoma: A Case Report and Literature Review

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *06 December 2021*
Accepted: *12 January 2022*
Published: *02 February 2022*

Citation:
Qin F, Zhang X, Zhang J, Liu S, Wang Z, Xie F, Zhang M, Zhang T, Wang S and Jiao W (2022) Masseter Muscle Metastasis of Renal Cell Carcinoma: A Case Report and Literature Review. Front. Oncol. 12:830195. doi: 10.3389/fonc.2022.830195

Background: Patients with renal cell carcinoma are often troubled by metastases, but masseter muscle metastases are particularly rare.

Case Presentation: We reported a 76-year-old male who did not show any recurrence and metastasis after the nephrectomy until 5 years later. The metastatic mass was found with the protrusion of masseter muscle area. Computed tomography and ultrasonography indicated a hypervascular mass, and pathology confirmed the masseter muscle metastasis of renal cell carcinoma. Complete metastasectomy was performed with the preserval of facial function and appearance. No local recurrence or distant metastasis was found in follow-up.

Conclusion: Our report indicates masseter muscle can be a metastatic site of renal cell carcinoma, regardless of its rarity. Long-term comprehensive surveillance is needed for patients with renal cell carcinoma. Muscle metastases can disguise as benign mass, while multiple imaging and pathology are important in identifying their sources. If possible, complete metastasectomy with function retention is recommended for masseter muscle metastases.

Keywords: masseter muscle, muscle metastasis, renal cell carcinoma, case report, literature review

INTRODUCTION

Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system, with the highest mortality in urologic tumors (1). It is known that metastasis is an important factor contributing to death. About 16% of patients with RCC had distant metastases at the time of discovery (2), and about a quarter of patients with localized RCC eventually had distant metastases after the nephrectomy (3). Lungs, bones, lymph nodes, liver, adrenal glands, and brain were common metastatic sites (4), while skeletal muscles were rare sites, accounting for 0.4% in all metastatic sites (5). According to bodies literature, skeletal muscle metastases involved lower limbs (37.2%), upper limbs (25.6%), trunk (20.9%), and neck and head (16.3%), while muscle metastases in head and neck were the least (6).

We reported a case of masseter muscle metastasis five years after the nephrectomy. We reviewed relevant bodies of literature, to collect clinical characteristics and provide reference for the diagnosis and treatment of those patients.

CASE PRESENTATION

A 76-year-old male was hospitalized in our hospital due to asthma in July 2019 and found a mass in the right masseter area without symptoms. Ultrasonography (US) showed a mass of 17 mm × 17 mm × 10 mm which could be detected in the muscle layer of the masseter area, with hypoechogenicity, clear boundary and high vascularity (**Figure 1**). A diagnosis of "fibroma" was made. The patient chose close follow-up rather than any treatment, because of concomitant asthma and painless mass.

The mass increased gradually, so he went to our hospital in June 2021. In the area of masseter muscle, a round protrusion with a diameter of 3 cm was touched and local skin was complete. It was a little tough in texture, with no tenderness and poor mobility. Computed tomography (CT) demonstrated that the solitary mass of 38.4 mm × 22.3 mm existed at the surface of masseter muscle and the boundary with the masseter muscle was unclear (**Figure 1**). There was no other mass found in CT.

The patient had a history of laparoscopic radical nephrectomy in September 2014. The tumor was located at the pole of the kidney. There was no invasion of vascular system, lymphatic system, broken end of ureter and renal capsule. The post-operative pathology demonstrated clear-cell RCC (ccRCC, T1N0M0, Furhman grade 2) of the left kidney. It is possible that the mass is a metastatic lesion from RCC. Other history included asthma with stable condition. The patient and his family had no history of tumor.

The patient asked to remove the mass. Then the patient underwent a surgery in June 2021, for diagnosis and treatment at the same time. The mass was found at the surface of the masseter muscle. The mass and part of the masseter muscle were removed. The superficial lobe of parotid gland was also removed due to partial involvement. The mass was gray and yellow in section, and about 30 mm × 30 mm × 25 mm in size. Frozen sections were positive for malignancy and negative for

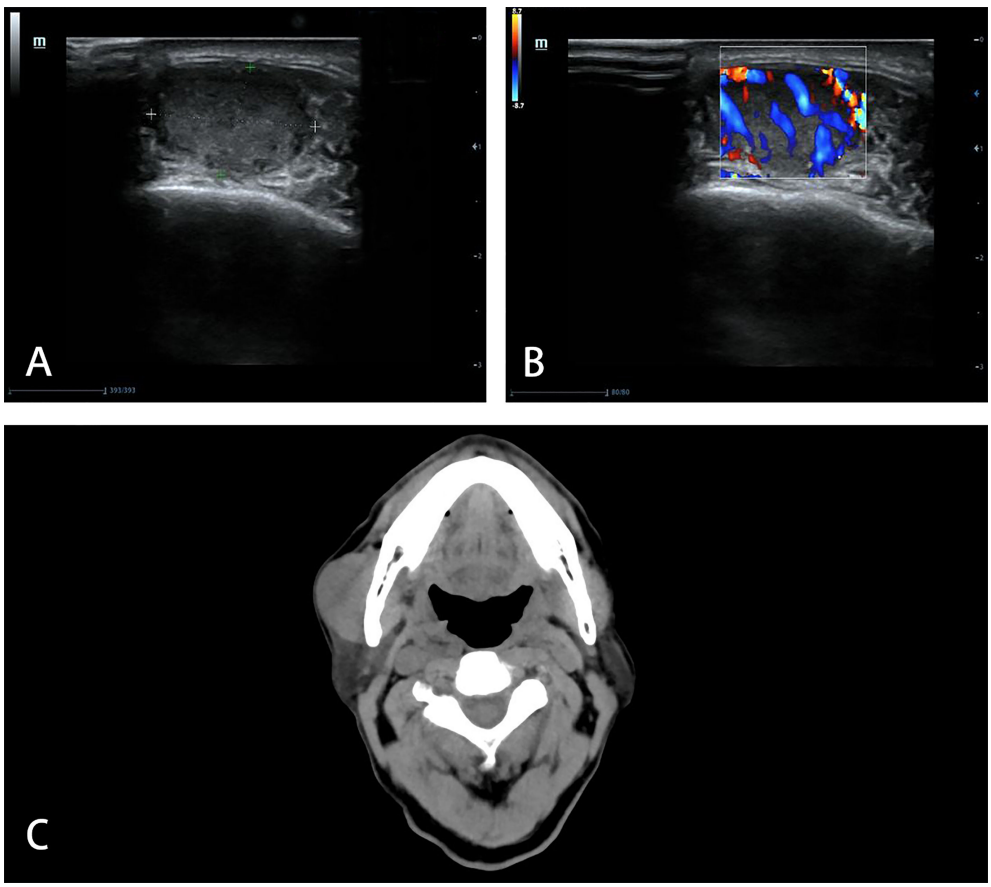

FIGURE 1 | Imaging manifestations of masseter muscle metastasis in US and CT. US shows a hypoechoic **(A)**, hypervascular **(B)** mass in the muscle layer of the masseter area in 2019. CT shows unclear boundary between the mass and right masseter muscle in 2021 **(C)**.

surgical margin. Post-operative pathology showed tumor cells had same morphology of clear cytoplasm, and tumor tissue infiltrated in striated muscle tissue, with rich blood sinuses. Immunohistochemistry revealed positive reactivity to Pax-8, CD10, CA IX, Ki-67 (5%), PD-L1 (22c3, CPS ≈ 1), and negative reactivity to CK7, CK19, p63, calponin, CD117, S100 (**Figure 2**). Combining morphology, immunohistochemistry and previous medical history, we made the diagnosis of masseter muscle metastasis of RCC.

There was no local recurrence and distant metastasis in follow-up positron emission tomography/computed tomography (PETCT) one month later. The patient did not complain about any abnormality of facial function or appearance.

DISCUSSION

The biological behavior of RCC is difficult to predict. Metastases often exist at the time of initial diagnosis or following surveillance. However, muscle metastases of RCC are very rare, which is consistent with high resistance of muscle to cancer. We reported a case of masseter muscle metastasis of RCC. According to what we had known, there were only 5 similar cases, which

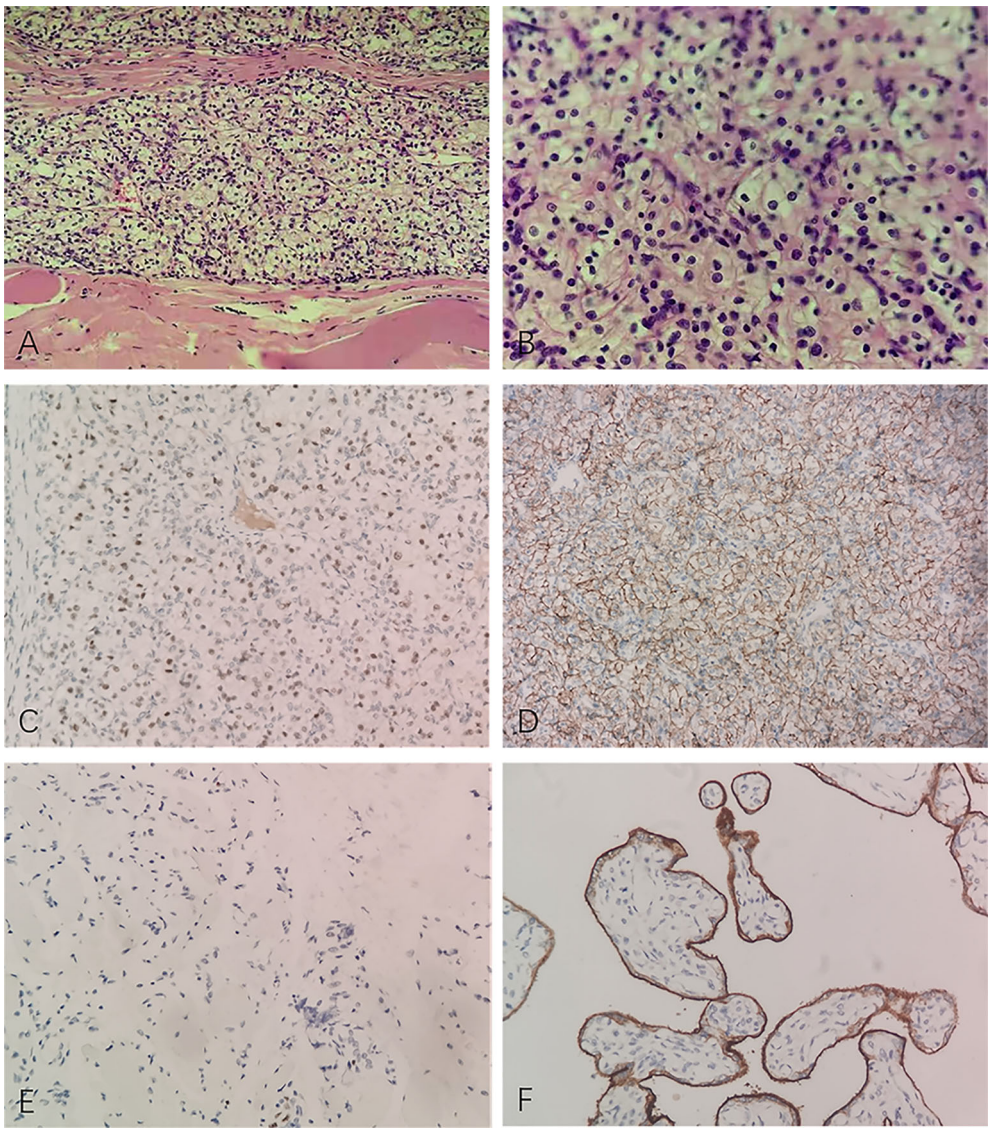

FIGURE 2 | Pathological manifestations of masseter muscle metastasis. Hematoxylin–eosin staining (×200): tumor tissue infiltrates in striated muscle tissue, with rich blood sinuses **(A)**. Hematoxylin–eosin staining (×400): tumor cells share the morphology of clear cytoplasm **(B)**. Immunohistochemistry: Pax-8 **(C)**, CA IX **(D)**, Ki-67 (5%) **(E)** and PD-L1 (22c3, CPS ≈ 1) **(F)** are positive. The figure was obtained in 2021.

were not collected and overviewed before. We gathered their clinical characteristics in **Table 1**. Because of limited reports of masseter muscle metastases, cases with skeletal muscle metastases of RCC were searched and reviewed in PubMed and related references (**Supplementary Figure 1**), especially focusing on their diagnoses and treatments. The key words were "muscle", "renal cell carcinoma" and "metastasis/metastases", with the limit to English articles and the deadline of August 31, 2021. We collected more clinical characteristics and listed them in (**Supplementary Table 1**).

Masseter muscles are rare but are possible sites of metastatic RCC. Similar to previous bodies of literature (6), we find that muscle metastases of RCC are more common in lower limbs and trunk, while upper limbs, head and neck are less reported. Compared with thyroid gland, parotid glands, and paranasal sinus, masseter muscles are less common sites involved by RCC at head and neck (9, 12). The rarity of masseter muscle metastases of RCC can be explained such that skeletal structures limit the development of metastatic lesions, which can only develop in natural cavities and loose glands. Besides, the high resistance of muscle to cancer is another reason for the rarity. The resistance may be explained by high tissue pressure, rapid blood flow, lactic acid production, antitumor activity of lymphocytes and natural killer cells, inhibition from skeletal muscle derived peptic factors and protection inhibitors (13, 14). Nevertheless, the special location and surrounding structures of masseter muscles also determine special metastatic pathways. It is considered that, in addition to conventional arterial pathway and lymphatic pathway, vertebral venous plexus may be a special pathway of metastases at head and neck (15). Vertebral venous plexus connects with inferior vena cava and mesenteric vein. Malignant tumors from abdomen and pelvis, like RCC, can be transferred to masseter muscles through this way. The round-trip blood flow and the absence of venous valves also help malignant cells spread in this way. Comprehensive surveillance for patients with RCC is needed, including unusual sites like masseter muscles.

Males seem to be more prone to muscle metastases of RCC, and 88.06% of reviewed patients are males. In particular, all of masseter muscle metastases of RCC are reported in males. This is associated with the male-to-female ratio of about 2:1 in patients with RCC (2). But male predominance is greater in patients with muscle metastases, suggesting that differences in sex hormones may play a role in muscle metastases of RCC. Muscle metastases mainly exist in the elderly, but a few young patients may be related to special types such as Xp11.2 translocation renal cell carcinoma (16) and renal medullary carcinoma (17).

Muscle metastases can be the premonitory or synchronous sign of RCC, but 70.15% of muscle metastases are found after RCC, with a median delay of 60 months. Usually, metastases of RCC occur within 5 years (18), but muscle metastases seem to have a longer delay. Angelini et al. reported a rare muscle metastasis of RCC found more than 40 years later (18). Early dissemination and dormancy are considered to play a role in the delayed metastases of RCC (19). After early dissemination, RCC cells are dormant due to local inappropriate environment and awaken under the stimulation of some factors. Muscles are usually not suitable environment for tumor cells, just as what have been discussed, so it may take more time to wait for awakening. So surveillance for patients with RCC is needed for a long time.

Muscle metastases of RCC tend to be single. All metastatic lesions of RCC in masseter muscles are single. The diameter of muscle metastases is limited to a median of 4.05 cm, because they are usually superficial and easy to be detected. In masseter muscles, limited space may be another reason for limited diameter, with a median of 2.90 cm.

The initial detection and further identification of muscle metastases from RCC are important in diagnosis. Most masseter muscle metastases of RCC are usually superficial and

TABLE 1 | Clinical characteristics of cases with masseter muscle metastasis of RCC.

Ref.	Age (years)/ Gender	Interval* (months)	Initial examination	Further examination	Number/ Side	Size (cm)	Combined metastasis	Treatment	Outcome** (months)
Nakagawa et al. (7)	57/M	48	Angiography	Angiography/CT/US/Galium-citrate scintigram	1/L	1.0	Brain and lung	Intravascular embolization + Metastasectomy + Interferon	No progression (N/A)
Gal et al. (8)	49/M	Premonitory sign	Symptoms	CT/MRI	1/R	4.0	Adrenal gland	Metastasectomy	Metastasis (25)
Yiotakis et al. (9)	60/M	2	Physical examinations	CT	1/L	1.5	N	Metastasectomy + Interleukin-2 + Interferon	No progression (N/A)
Kang et al. (10)	71/M	144	Physical examinations	MRI/PETCT	1/R	4.1	N	N/A	N/A (N/A)
Landström et al. (11)	59/M	N/A	N/A	CT	1/R	4.3	N/A	Electrochemotherapy	Death (4)
Present case	74/M	58	Physical examinations	US/CT	1/R	1.7	N	Metastasectomy	No progression (1)

**The interval from the discovery of RCC to the discovery of muscle metastasis.*

***Observation time was analyzed in cases without progression. PFS was analyzed in cases with progression. Progression consisted of the state of recurrence, metastasis and death. RCC, renal cell carcinoma; Ref., reference; M, male; CT, computed tomography; US, ultrasonography; MRI, magnetic resonance imaging; PETCT, positron emission tomography/computed tomography; L, left; R, right; N, no combined metastasis; N/A, not available; cm, centimeters; PFS, Progression-free survival.*

easy to be detected with symptoms or physical examinations such as swelling. Only one masseter muscle metastasis was incidentally found in carotid angiography (7). Muscle masses include a large variety of benign and malignant soft tissue lesions of diverse histological nature (20). In further identification, US is often used as the first imaging examination, for its convenience, free of radiation, and ability to detect blood supply of lesions. In 2019, the characteristics of regular shape and clear boundary in US were not consistent with malignant masses. Benign masses such as hemangioma, lipoma, fibroma and neurogenic tumor, are usually more common than primary and metastatic malignant masses in masseter muscles (21). So a benign mass was considered. Then with clear boundary, high vascularity and absent of neurological symptoms, fibroma was chosen in benign masses as the preliminary consideration. Increased diameter and unclear boundary in CT showed malignant characteristics in 2021. So the mass was removed and pathology finally identified the nature and source of it. In the specimen of present case, Pax-8 was positive, which is related to RCC. The clear cells under microscope, with positive of CA IX, further supported the diagnosis of ccRCC. A lesion from the misdiagnosis can be drawn: 1) the metastatic mass may be regular and well-defined in the early stage, which is easy to disguise as benign mass; 2) the history of malignancy should be considered, though the interval is long; 3) single examination is limited, and multiple examinations are needed for sufficient characteristics of the mass; 4) conclusion from pathology is essential for accurate diagnosis.

For metastases of RCC excepting brain and bone metastases, local complete metastasectomy, systemic immunotherapy and targeted therapy are recommended (22). Complete metastasectomy can lead to better survival and symptom control than incomplete or no metastasectomy (23, 24). According to our review, the most common treatment for muscle metastases is complete metastasectomy. However, structures in masseter area are essential in maintaining facial functions and appearance. In present case, measures were taken to preserve normal function and facial appearance when removing metastases: 1) trying to preserve the masseter muscle on the premise of negative margin; 2) dissecting and preserving the branches of facial nerve; 3) transferring sternocleidomastoid flap to restore facial appearance; and 4) preventing Frey Syndrome with patch and transferred muscle flap. The first two measures had been mentioned to protect masseter muscles and facial nerve (9, 11). We emphasized the restoration of facial appearance and maintaining normal function of sweat glands for the first time with the last two measures. The present patient recovered after complete metastasectomy without malfunction of masseter muscles and other facial structures. Immunotherapy and targeted therapy are often used as adjuvant treatment of surgery or alternative treatment when complete metastasectomy is not suitable. Interferon and interleukin are the main immunotherapeutic agents initially, but they are gradually replaced because of poor effectiveness and tolerance (25). Recently, immune checkpoint inhibitors is the standard form of immunotherapy (26). Among the 28 patients who received any treatment in our review, 14 patients did not have progression with a median observation time of 13.63 months, while 14 patients had final progression with a median progression-free survival (PFS) of 6 months. Most of patients with progression are troubled by combined metastases, leading to worse survival.

We reported a rare case of masseter muscle metastasis of RCC, and collected the clinical characteristics from reviewed literatures of muscle metastases, to provide reference for the diagnosis and treatment. The article is prepared and revised according to the CARE checklist (**Supplementary Table 2**). There are still some limitations in this report. Clinical and molecular characteristics of the primary tumor are insufficient, which may cause deviation in the judgment of metastatic mechanism and process. Because of limited reports of masseter muscle metastases, more cases are needed to collect and summarize their characteristics. Most of the cases reviewed in this paper come from case reports, which are difficult to share a unified standard, leading to several limitations of our conclusions. Further observational and comparative studies are still needed.

CONCLUSION

Masseter muscle can be a metastatic site of RCC, and vertebral venous plexus is a possible pathway. Comprehensive surveillance is needed for a long time. Muscle metastases can disguise as a benign mass, while multiple imaging and pathology are important in identifying their sources. If possible, complete metastasectomy with function retention is recommended for muscle metastases.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Affiliated Hospital of Qingdao University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SW was the patient's surgeon. FQ and JZ reviewed the literature and contributed to manuscript drafting. XZ and SL analyzed statistical data and contributed to manuscript drafting. ZW and TZ interpreted the imaging and pathological findings. FX, MZ and WJ were responsible for the revision of the manuscript for important intellectual content. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This research was funded by the Science and Technology Program in Chinese Medicine of Shandong Province (No. 2020M074).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.830195/full#supplementary-material

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CASE REPORT
published: 12 May 2022
doi: 10.3389/fonc.2022.876217

Giant Polycystic Papillary Renal Cell Carcinoma: A Case Report and Literature Review

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Introduction: Giant, cystic renal tumors are generally considered relatively contraindicated for laparoscopic surgery. We report on a 19-year-old male, where polycystic lesions in the left kidney were accidentally noted by enhanced computed tomography (CT) by focusing on the diagnostic, clinical, and surgery to the patient.

Case Report: Enhanced CT scan revealed solid component in multiple cystic lesions of Bosniak IV, which was enhanced after injection of contrast agent and the left kidney lost normal profile and enlarged with maximal diameter more than 18cm. Positron emission tomography-computed tomography (PET-CT) showed SUVmax 4.8 of the lesion and suggested malignant disease. A retroperitoneal laparoscopic radical left nephrectomy was performed successfully without cyst burst and the lesion was 17×17×18 cm in size. Pathological examination revealed that the lesions were consistent with papillary renal cell carcinoma (type 2, WHO grade II), no renal capsule invasion, no renal pelvis and renal sinus fat involvement, no abnormality in ureter and renal arteriovenous end, no abnormality in a few adrenal tissues, chronic inflammation of hilar lymph nodes (0/1). After surgery, no specific treatment was initiated and at a follow-up visit 1 year after surgery, no local recurrence or metastasis was found.

Conclusion: It is the largest cystic renal cell carcinoma that has ever been reported for laparoscopic resection. The selection of surgery for giant cystic renal cell carcinoma should be individualized. Retroperitoneal laparoscopy may be an option for such lesions.

Keywords: papillary renal cell carcinoma, laparoscopic surgery, PET-CT, Bosniak classification, pathology

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *15 February 2022*
Accepted: *11 April 2022*
Published: *12 May 2022*

Citation:
Huang Z, Wang H and Ji Z (2022) Giant Polycystic Papillary Renal Cell Carcinoma: A Case Report and Literature Review. Front. Oncol. 12:876217. doi: 10.3389/fonc.2022.876217

BACKGROUND

As a malignant renal parenchymal tumor type, papillary renal cell carcinoma (PRCC) is the second most common form of renal cell carcinoma (RCC) and the most common non-clear cell RCC (1), accounting for approximately 15%-20% of all kidney cancers, and is associated with poor outcomes (2). More than 30% of RCC patients with localized disease will develop metastases after nephrectomy with an expected 5-year survival rate below 10% (3). Besides risk factors associated with RCC (smoking, hypertension, obesity, male, and family history), PRCC is uniquely related to renal dysfunction of different stages (4).

For the diagnosis of PRCC, typical PRCC radiographically appear as homogeneous, solid masses (5), while cystic lesions can be seen in around 25% of papillary tumors (6). Also, the characteristics of hypovascular in PRCC contributes to distinguish it from benign lesions on imaging examinations (7, 8). Based on computed tomography (CT) imaging criteria allowing for the analysis of renal cysts' contour and contents, presence of septations and/or calcifications, and enhancement after contrast agent injection, the Bosniak classification system has been used to categorize renal lesions in an order of malignancy as follows: simple (I); minimally complicated (II); minimally complicated requiring follow-up (IIF); indeterminate (III); or cystic neoplasm (IV) (9). Complex renal cysts or solid components may be identified which requires more detailed characterization to determine the differential diagnosis and, thus, the appropriate treatment and prognostic evaluation. The low level of enhancement has led to tumors being misdiagnosed as renal cysts. As PRCC tumors are generally hypovascular, imaging with a single contrast phase displays lower enhancement compared to clear cell RCC (10). With multi-phase renal imaging, enhancement kinetics may provide additional discriminatory power. For instance, PRCC tumors tend to have peak enhancement in the later nephrographic phase of quadriphasic CT, whereas clear cell and chromophobe RCC show peak enhancement in the corticomedullary phase (11). Conventional imaging modalities, such as CT and MRI, have limitations, especially in terms of low sensitivity for early metastatic disease. Metastatic PRCC lesions may show similar enhancement characteristics to the primary tumor (5). However, dual-phase ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) showed better usefulness for predicting cell proliferation in RCC compared with single-phase imaging alone (12) and the potential to estimate the patient's survival according to the accumulation measured maximum standardized uptake value (SUVmax) (13). A high SUVmax has demonstrated to correlate with disease aggressiveness in RCC and can improve detection of recurrent and metastatic RCC (14), and pretreatment max SUVmax assessed by FDG PET/CT was a useful prognostic marker for patients with advanced RCC (15).

Characterizing the molecular basis of PRCC and determining the main therapy goal is imperative for selecting the best strategy. Several mutated genes associated with PRCC have been identified including MET, NF2, SETD2, and Nrf2 pathway genes (16). Different molecular mechanisms are involved in PRCC biology. Mutations in the MET oncogene is present in the pathogenesis of hereditary PRCC forms found in a low rate of sporadic cases. Regarding the treatment of PRCC, localized sporadic PRCC can be managed with partial or radical nephrectomy, ablation, or active surveillance (17). There are few standard forms of treatment options available to patients with advanced PRCC, which has evolved to molecular targeted therapies and checkpoint inhibitors in the modern era. Several agents, including anti-VEGF drugs and mTOR inhibitors are possible options in treating advanced and metastatic PRCC (18), showing promising efficacy for PRCC (19, 20). In addition, MET inhibitors and checkpoint inhibitor therapy are highly anticipated based on the knowledge of hereditary papillary RCC and may be effective in advanced PRCC treatment (21).

In the study, we aimed to report a case of giant polycystic papillary renal cell carcinoma that underwent retroperitoneal laparoscopic radical nephrectomy by focusing on the diagnostic, clinical, and surgery to the patient. A 19-year-old male with polycystic lesions in the left kidney which was accidentally noted by enhanced CT (Bosniak IV, maximal diameter more than 18cm), underwent preoperative ^{18}F-FDG PET-CT examination suggestive of malignancy with the SUVmax 4.8 of the lesion. The patient then underwent a retroperitoneal laparoscopic radical left nephrectomy successfully without cyst burst and no local recurrence or metastasis was found during the 1 year follow-up visit after surgery. Details follow.

CASE PRESENTATION

On December 7, 2020, a 19-year-old male was admitted to our hospital for polycystic lesions in the left kidney accidentally noted by computed tomography (CT). Three weeks prior, on November 17, 2020, enhanced CT, revealed solid component in multiple cystic lesions, which was enhanced after injection of contrast agent (**Figure 1**). According to Bosniak criteria (22), the lesion was classified into category IV.

The swollen kidney was palpable on the left abdomen and no other obvious abnormality was found in the physical examination. There was no previous personal or family medical history.

After admission, positron emission tomography-computed tomography (PET-CT) using 18F-Fluorodeoxyglucose as the imaging agent (December 2, 2020) found the left kidney was significantly enlarged and a large cystic-solid mass was seen in the upper pole with uneven increase in radioactivity uptake. The maximum cross section was about 13.8×10.9cm and the lesion SUVmax was 4.8, suggesting malignant disease (**Figure 2**). No cysts or other abnormalities were observed in the contralateral kidney or other organs such as the liver. Imaging of renal blood flow showed only the upper part of the renal parenchyma was visible in the left kidney and the mass in the left kidney had a lack of blood supply. The kidney function was normal, with serum creatinine 71 μmol/L, blood urea nitrogen 3.58 mmol/L.

Given the young age of the patient, related gene tests were recommended to exclude genetic diseases or mutations but the patient refused to accept.

On December 10, 2020, laparoscopic radical resection of left kidney tumor was performed under general anesthesia without cyst rupture. During the surgery, the irregular enlargement of the left kidney was seen, the upper and lower diameter was about 15cm, and the transverse diameter was about 10cm. The left kidney and tumor were successful resected, with little intraoperative bleeding. One renal fossa drainage tube and one urinary tube were reserved during the operation. The removal of urinary tube was successful and the vital signs were stable after surgery.

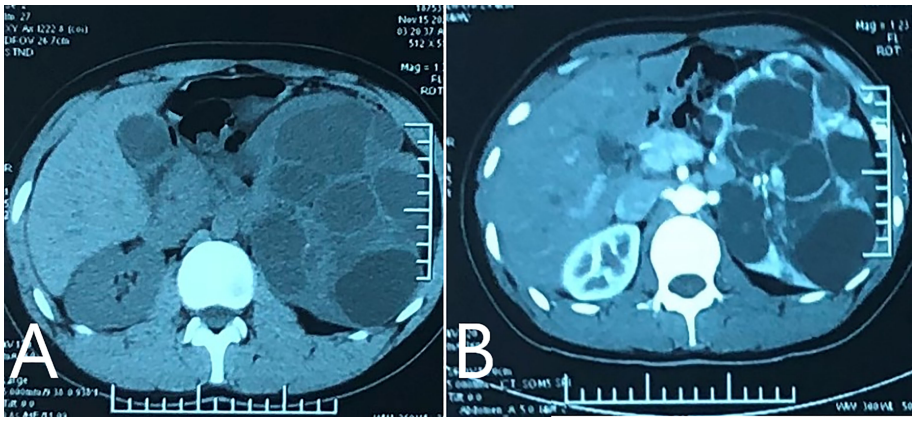

FIGURE 1 | Enhanced CT performed on November 17th 2020. **(A)** CT plain scan revealed multiple cystic lesions in left kidney, with solid component inside. The left kidney lost normal profile and enlarged significantly; **(B)** enhanced scan showed.

Pathology: (left kidney) Combined with immunohistochemical, the lesions were consistent with papillary renal cell carcinoma (type 2 PRCC, WHO grade II), no renal capsule invasion, no renal pelvis and renal sinus fat involvement, no abnormality in ureter and renal arteriovenous end, no abnormality in a few adrenal tissues, chronic inflammation of hilar lymph nodes (0/1). Immunohistochemical results: PAX-8 (+), AE1/AE3 (+), CD10 (portion +), CK7 (-), EMA (+), P504 (portion +), CC (-), TFE3 (-), Vimentin (+), CA9 (-), CD117 (-). Next-generation sequencing of blood sample was performed after surgery, indicating no pathogenic/possibly pathogenic variation of TSC1/2 gene and other solid tumor susceptibility genes was detected.

The patient healed well and was discharged on December 15, 2020, without any complications. He received no further treatment after surgery. During a 1 year regular follow-up, the kidney function was normal, and no local recurrence or metastasis was found.

The patient signed informed consent for publication of this case report and accompanying images.

DISCUSSION

PRCC can be divided into two subtypes on the basis of histomorphologic features (23), namely, type 1 and type 2, with different clinical and genetic features (24, 25). Compared with type 1 PRCC, type 2 is more often associated with a greater stage, higher Fuhrman grade, higher frequency of necrosis and sarcomatoid features with worse outcome and more aggressive disease (18, 26). However, previous studies indicated that WHO/ISUP grade and tumor size were associated with the prognosis, rather than histologic subtype (24, 27). Based on preoperative imaging, this case was classified as Bosniak category IV and considered malignant. Further PET-CT examination also indicated a malignant lesion, which was proved by post-operative histological examination. Similar to these findings, despite pathologic findings of type 2 PRCC, there was no recurrence at 1 year of follow-up after surgical resection of the lesion due to its WHO grade 2 classification.

Surgery is the basic treatment of PRCC. Immunotherapy and cytotoxic chemotherapy are the treatment options other than

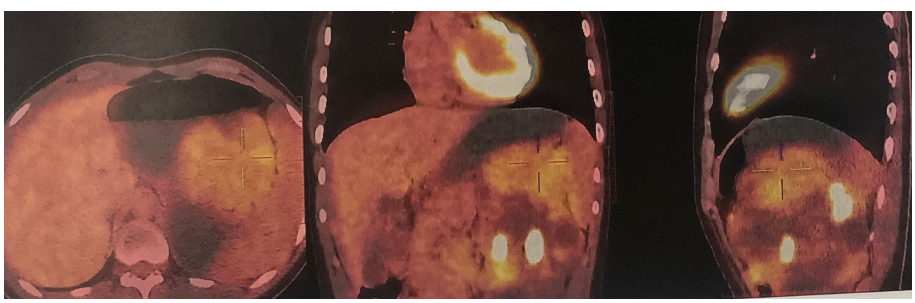

FIGURE 2 | PET-CT found the left kidney was markedly enlarged, and there was a large cystic solid mass at the upper pole of the left kidney with uneven increased radiation uptake. The maximum cross section was about 13.8×10.9cm and the lesion SUVmax was 4.8, suggesting malignant disease. Multiple cysts of the left kidney were also seen.

surgery before the introducing of targeted therapy. A retrospective study that included 64 patients with metastatic non-clear-cell RCC histology analyzed the curative effect of immunotherapy and cytotoxic chemotherapy (28). The results showed metastatic non-clear-cell RCC patients are resistant to systemic therapy and poor survival, with the median overall survival time being 9.4 months (95% confidence interval, 8 to 14 months) (28). Type 2 PRCCs represent a heterogenous group with different genetic and molecular make up, making it difficult to apply effective targeted therapies (29). A previous study revealed that PRCC patients who underwent partial nephrectomy showed 5- and 10-year recurrence free survival of 95.8% and 73%, respectively (30). Given the increased recurrence rate more than 5 years after surgery, the patient still needs regular follow-up and imaging examinations for a longer time.

Giant cystic renal tumors are generally considered relatively contraindicated for laparoscopic surgery. The lesion size of this patient we present here was 18×17×17cm, with multiple cystic lesions. To our knowledge, this is the largest cystic renal cell carcinoma ever reported for successfully treated by laparoscopic surgery. The reasons for choosing laparoscopic surgery for this case are as follows: first, based on the patient's age and imaging characteristics, the possibility of benign lesions cannot be ruled out, thus treatment with less invasive surgery is necessary and second, to explore the feasibility of retroperitoneal laparoscopy in the treatment of such huge polycystic kidney disease. Compared with open approach surgery, laparoscopic surgery can be performed under direct vision, the exposure of the operative area is more clear, and ligation and other surgical procedures are more reliable, ensuring the safety of surgery. Although the surgical procedure is relatively difficult, it indicates the possibility of successful retroperitoneal laparoscopic surgery for such lesions, providing an additional option.

CONCLUSION

The selection of surgery for giant cystic renal cell carcinoma should be individualized. Retroperitoneal laparoscopy may be an option for such lesions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the participant for the publication of this case report.

AUTHOR CONTRIBUTIONS

ZH designed the study. ZH and HW collected the data and initially drafted the manuscript. ZJ review and revise the manuscript. All authors read and approved the final manuscript.

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CASE REPORT
published: 19 May 2022
doi: 10.3389/fonc.2022.877470

Concurrent Germline and Somatic Mutations in FLCN and Preliminary Exploration of Its Function: A Case Report

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OPEN ACCESS

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *16 February 2022*
Accepted: *22 April 2022*
Published: *19 May 2022*

Citation:
Wang T, Yang Y, Feng H, Cui B, Lv Z, Zhao W, Zhang X and Ma X (2022) Concurrent Germline and Somatic Mutations in FLCN and Preliminary Exploration of Its Function: A Case Report. Front. Oncol. 12:877470. doi: 10.3389/fonc.2022.877470

Birt–Hogg–Dube syndrome is an autosomal dominant condition that arises from germline folliculin (FLCN) mutations. It is characterized by skin fibrofolliculomas, lung cysts, pneumothorax, and renal cancer. Here, we present the case of a 36-year-old woman with asymptomatic, multiple renal tumors and a history of spontaneous pneumothorax. Genetic analysis revealed a hotspot FLCN germline mutation, c.1285dupC (p.H429fs), and a novel somatic mutation, c.470delT (p.F157fs). This information and the results of immunohistochemical analysis of the renal tumors indicated features compatible with a tumor suppressor role of FLCN. Two transcription factors, oncogenic TFEB and TFE3, were shown to be regulated by FLCN inactivation, which results in their nuclear localization. We showed that a deficiency in the tumor suppressor FLCN leads to deregulation of the mammalian target of rapamycin signaling (mTOR) pathway. A potential link between FLCN mutation and ciliary length was also examined. Thus, the mutation identified in our patient provides novel insights into the relationship among FLCN mutations, TFEB/TFE3, mTOR, and cilia. However, an in-depth understanding of the role of folliculin in the molecular pathogenesis of renal cancer requires further study.

Keywords: Birt-Hogg-Dube (BHD) syndrome, folliculin (FLCN), mutation, renal cancer, TFEB/TFE3

INTRODUCTION

Birt–Hogg–Dube (BHD) syndrome is characterized by the development of fibrofolliculomas, lung cysts, and renal carcinoma. It is caused by germline mutations in the folliculin (FLCN) gene (1), a tumor suppressor gene that has been mapped to chromosome 17p11.2 (2). FLCN is currently the only gene associated with BHD. The spectrum of FLCN mutations has been outlined in several reports and summarized in a database (http://www.lovd.nl/flcn) (3). A hypermutable hotspot has been localized to a mononucleotide tract of eight cytosines within exon 11, and the most frequently observed mutation is the cytosine insertion c.1285dupC (2, 4).

The energy-sensing mammalian target of rapamycin (mTOR) pathway has been implicated in the pathogenesis of BHD (5, 6). The loss of functional folliculin caused by genetic mutations of FLCN may activate mTOR signalling that leads to the development of symptoms of BHD syndrome (6). TFEB and TFE3 are crucial transcription factors belonging to the MiTF/TFE family. FLCN plays a crucial role in mTORC1-mediated phosphorylation of TFEB (7). TFEB is activated by its nuclear localization, which occurs as a result of FLCN inactivation. The latter is correlated with reduced phosphorylation of TFEB. Overexpression of TFEB leads to kidney cysts and renal cell carcinoma (RCC) (8–10). FLCN inactivation also induces the transcriptional activity of TFE3 by promoting its nuclear localization and increased TFE3 activity is likely to be important for renal tumor development (11).

In their non-cycling resting state, most eukaryotic cells possess microtubule-based membranous protrusions from the cell surface referred to as primary cilia (12). FLCN is essential for ciliary localization and regulates mTOR signaling through primary cilia (13). Single point mutations within FLCN may disrupt these functions and cause cilia-related diseases (14).

In a sequencing analysis, we identified a hotspot germline variant of FLCN. We also confirmed a novel somatic mutation in tumor tissue that may confer additional familial risks. In the present study, we examined the associations among FLCN mutations, TFEB/TFE3, mTOR and cilia in a patient.

MATERIALS AND METHODS

Immunohistochemistry (IHC) Staining

Tissue microarray were collected from 210 clear cell RCC (ccRCC) and 75 papillary RCC (pRCC) patients who underwent surgery at the Urology Department of the Chinese People's Liberation Army (PLA) General Hospital (Beijing, China) from January 2012 to December 2020. This study was approved by the ethics committee of the Chinese PLA General Hospital.

The standard IHC staining protocols were followed as previously described (15). Slides were scanned using Axio Image Z2 Microscope (Zeiss) and TissueFAXS imaging system (TissueGnostics GmbH, Austria). The information of antibodies was listed in **Supplementary Table 3**.

Immunofluorescence Staining

Tissue sections were first subjected to gradient dehydration and washed three times with PBS, fixed with 4% paraformaldehyde for 15 min, permeabilized with 0.5% Triton X-100, and then blocked with 5% goat serum for 30 min. Tissues were stained with primary antibodies (ARL13B, proteintech, 17711-1-AP) at 37°C for 1h and were incubated with AlexaFluor488-conjugated secondary antibodies (1:400). Nuclei were counterstained by 0.2 mg/mL DAPI. Samples were imaged with an Axio Image Z2 fluorescence microscope (Zeiss) and analyzed by using Image J (NIH) software to determine the percentage of ciliated cells, cilium length, and fluorescent signal intensity. The information of antibodies was listed in **Supplementary Table 3**. Prior to manually counting cilia, parameters were established by which putative cilia were to be included or excluded: 1) size; the cilium needed to be a thin structure, intensely stained broad structures were considered background; 2) elongation; the cilium needed to be a continuous thin extending structure, square or dot-like structures were excluded. Cilia is considered positive when the cilia ratio is greater than 1%.

Sequencing

Genomic DNA was isolated using the Genomic DNA purification kit from Gentra Systems (Minneapolis, MN, USA). According to the manufacturer's recommendations. Whole exome sequencing (WES) of genomic DNA from cancerous tissue was performed after the patient had provided informed consent, with effective sequencing depth of 300x.We then verified it with sanger sequencing and confirmed the germline mutation with paracancer tissue.

Paired samples of 3 papillary renal cell carcinomas and 3 clear cell carcinomas (cancer and paracancer) were used for control. The tumor tissues of these 6 patients were sequenced in the next generation, and no FLCN mutations were found.

CASE PRESENTATION

A 36-year-old woman underwent ultrasonography and magnetic resonance imaging, which revealed multiple, asymptomatic renal tumors (**Figures 1A, B**). No apparent cutaneous lesions were found by careful inspection and palpation of the skin.

Retroperitoneal laparoscopic radical resection of the left kidney was performed with the patient under general anesthesia. Histopathologic examination (H&E staining) revealed that the large (3.5 cm × 3.5 cm × 3 cm) tumor in the left kidney was clear-cell RCC(image not available), nuclear grade WHO/ISUP II, and that the small (1.0 cm × 1.0 cm × 0.6 cm) tumor in the left kidney was chromophobe RCC, nuclear grade WHO/ISUP II (**Figure 1C**). In summary, the patient's TNM stage was T1aN0M0, stage I. Due to limited sampling conditions, we only sequenced and analyzed the small tumor in the left kidney.

A search for germline mutations revealed a single nucleotide frameshift duplication, c.1285dupC, within the polycytosine tract located in exon 11, resulting in a change in amino acid 429 from histidine to proline (p.H429fs) in the FLCN product (**Figure 1D**). A search for somatic mutations revealed a base (T) deletion at nucleotide c.470 in exon 6 (c.470delT) of the FLCN gene (**Figure 1E**), which caused a frameshift mutation starting at amino acid 157 (p.F157fs). These results were consistent with a diagnosis of BHD.

In addition to the renal tumor, the patient had a history of spontaneous pneumothorax. Her family history was notable, as her sister, father, and grandfather had been diagnosed with lung cysts. No other family members had found skin abnormalities despite not being examined by a professional dermatologist. And they did not be diagnosed kidney tumors during routine physical

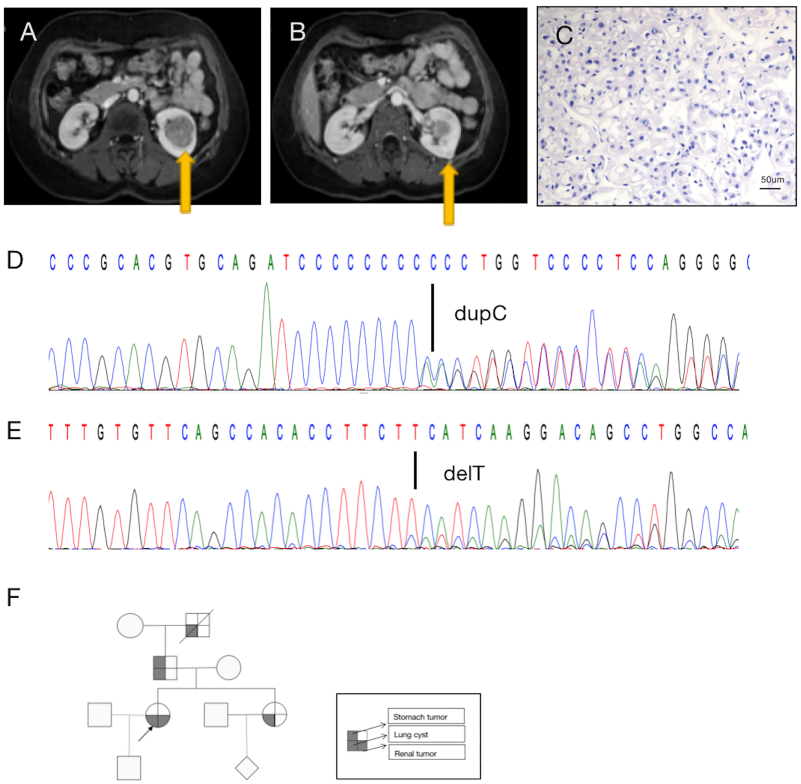

FIGURE 1 | A diagnosis of BDH syndrome was confirmed in the patient. **(A)** Abdominal magnetic resonance imaging (MRI) revealed a renal mass in the lower middle part of the left kidney (arrow). **(B)** MRI with intravenous contrast revealed a renal mass in the posterolateral surface of the left kidney (arrow). **(C)** Histopathology of the small tumor in the left kidney shows cells with classic plant-like architecture, perinuclear clearing (chromophobe cell carcinoma). **(D)** Germline mutation: base C duplication at nucleotide c.1285dupC in exon 11 (c.1285dupC) of the FLCN gene. **(E)** Somatic mutation: a base T deletion at nucleotide c.470 in exon 6 (c.470delT) of the FLCN gene. **(F)** Pedigree summarizing the family history of the proband (arrowhead). Different symbols indicate different diseases.

imaging examination. There was a history of benign tumor of the cardia on the father's side, and her grandfather had died of silicosis (**Figure 1F**). Unfortunately, the patient's family members did not consent to genetic testing.

FUNCTIONAL ANALYSIS

To determine the function of the FLCN protein, immunohisto chemistry/immunofluorescence staining was performed both on the patient's tumor and adjacent tissues and on renal tissues from patients without FLCN mutations. FLCN immunostaining was markedly weaker in the renal tumor and adjacent tissue than in tissues without FLCN mutations (**Figures 2A–C**). TFEB was constitutively expressed in the nucleus and was active in tissues carrying the FLCN mutation (**Figures 2D–F**). TFE3 was highly expressed in whole cells of the FLCN-deficient tumor tissue, mainly in the nucleus, was weakly expressed in the adjacent tissue, and was not expressed in non-mutated tissues (**Figures 2G–I**). Phosphorylated mTOR (p-mTOR) was highly expressed in FLCN-deficient cancer and adjacent tissue, and negative in control tissues (**Figures 2K–L**). The cilia are rarely expressed in FLCN-deficient cancer tissue and cilia length was reduced in the adjacent tissue. By contrast, cilia were normally present in the tissues without the FLCN mutation (**Figures 3A–C**).

GENETIC ANALYSIS

Somatic mutations in the ERF gene were also detected (exon4 c.911_913delCCT p.S304del). The mutation abundance is 6.4%. The **Supplementary Table 1** provides additional information that we sequenced for filtering out variations in genes with frequencies greater than 1% of a thousand genomes, variations with synonymous mutations, and variations that are benign and potentially benign.

DISCUSSION

Genetic studies have revealed several tumor suppressor genes responsible for the development of RCC, such as VHL, FH, TSC, SDHB, and FLCN, the focus of this study (16). Sequencing analysis revealed a hotspot germline variant of FLCN in our

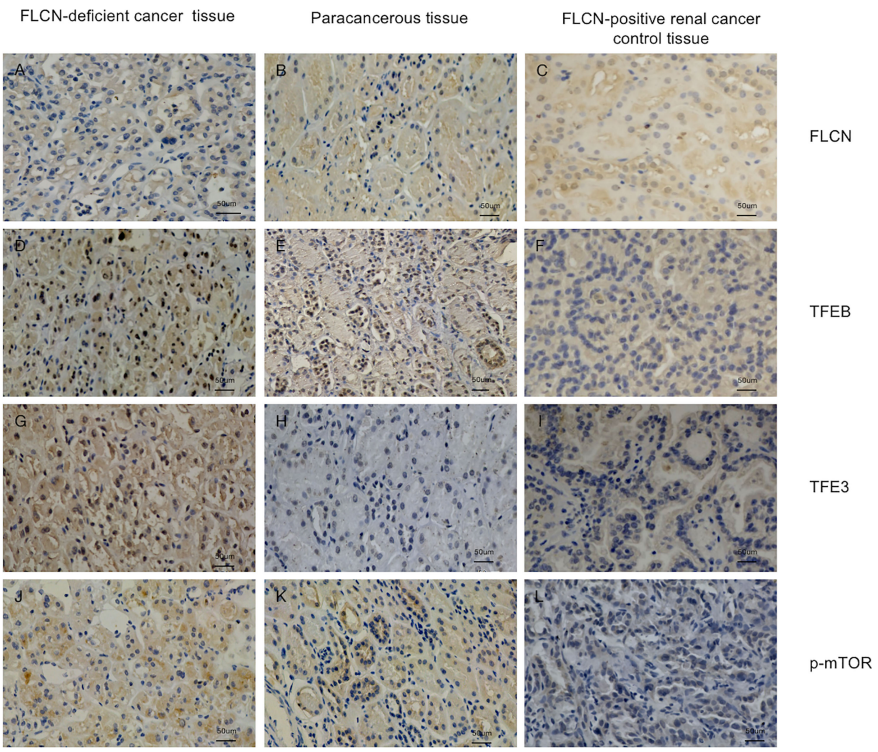

FIGURE 2 | Immunostaining of the patient's tumor tissue **(A, D, G, J)** and paracancerous tissue **(B, E, H, K)** and FLCN-positive control cancer tissue **(C, F, I, L)**. **(A–C)** Immunostaining of FLCN confirmed the loss of FLCN protein expression in patient-derived tumor tissue. **(D–F)** Immunostaining of TFEB confirmed that the protein was constitutively expressed in the nucleus and active in FLCN mutated tissue. **(G–I)** TFE3 was highly expressed in whole cells of tumor tissue, mainly in the nucleus. **(J–L)** p-mTOR was highly expressed in tumor and paracancer tissue, but negatively expressed in control tissues.

patient. We also identified a novel somatic mutation that merits attention as it may confer additional risks to family members.

Chromophobe RCC and a mixed pattern of chromophobe and oncocytic renal tumors are typical of patients with BHD, but RCCs with other histological subtypes can also occur (17). In our patient, H&E staining revealed that the large mass was ccRCC and the small mass chromophobe RCC. The presence of renal masses of different pathological types may suggest a relationship between the mutation hotspot and the pathology, but this awaits confirmation.

Normally, TFEB is located in the cytoplasm, and its phosphorylation by mTOR inhibits its function (18, 19). When FLCN is mutated, TFEB is dephosphorylated and freely enters the nucleus, where it participates in the transcription of its target genes (7). mTOR hyperactivity induced by TFEB is a key step in kidney cystogenesis and tumorigenesis. Recently, Ballabio and colleagues confirmed that TFEB promotes mTORC1 activity by transcriptionally regulating the levels of RagC and RagD GTPases (18). This sequence of events was consistent with our

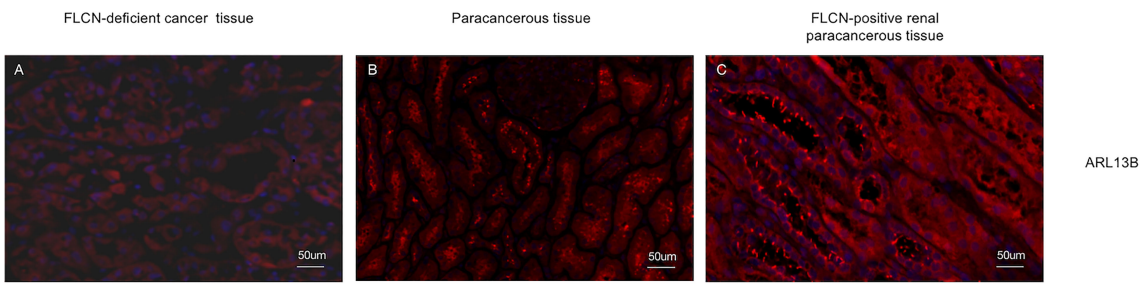

FIGURE 3 | The cilia are rarely expressed in tumor tissue **(A)** and cilia length was reduced in the adjacent tissue **(B)** and cilia were normally present in the tissues without the FLCN mutation **(C)**.

immunohistochemical results. Hong SB et al. (11) reported that FLCN inactivation was correlated with the post-translational modification and nuclear accumulation of TFE3. However, TFE3 was demonstrated by immunohistochemistry to be strongly expressed in cancer tissues but only weakly expressed in adjacent tissues in our data, which may due to the complexity of the tumor microenvironment.

Several studies have proposed that BHD is a novel ciliopathy (13, 14, 20). Single point mutations within FLCN can disrupt its ciliary location and cause cilia-related diseases (14). Basten et al. (21) evaluated renal tumor tissue cores from 110 RCC patients by immunofluorescent staining of cilia and showed reduced cilia frequency in RCC subtypes relative to adjacent non-tumor tissue suggesting that ciliary loss is common in renal cancer generally. Our study also supports this conclusion. Cilia staining was performed positive in 67/210 patients with clear cell RCC tissues, 35/75 patients with papillary RCC tissues, 274/285 patients with adjacent non-tumor tissues (**Supplementary Table 2**; **Supplementary Figure 1**). Besides, we discovered an interesting phenomenon in the patient: the cilia were abnormally shaped, forming short rods in the adjacent tissues, although it showed normal abundance. Normal cilia were found in tissues without FLCN mutations. This suggests that mutations in FLCN may affect the normal level and morphology of cilia. However, whether this is an accidental discovery or a general rule still requires large findings and mechanism exploration.

CONCLUSIONS

In conclusion, the case is presented from a clinical perspective, providing personal and family history of BHD manifestations, genetic results for FLCN gene testing, and a second hit FLCN mutation in the patient tumor. A hotspot FLCN germline mutation, c.1285dupC (p.H429fs), and a novel somatic mutation, c.470delT (p.F157fs) were identified in the case presented with renal tumors and spontaneous pneumothorax. We explored the link between FLCN mutation and TFE3/TFEB expression, mTOR and primary cilia dysfunction *in vivo*. However, the role of folliculin in the molecular pathogenesis of renal cancer awaits further clarification.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Chinese PLA General Hospital. The patients/ participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TW and YY: performed the research and wrote the article. HF and ZL: performed the experiments and collected patient data. BC, WZ, and XZ: assisted with laboratory experiments and produced radiology images. XM: contributed to patient samples and treated patients. All authors contributed to the article and approved the submitted version.

FUNDING

The present work was financially supported by the National Natural Science Foundation of China (No. 81900718 and No. 81970665) and Chinese Postdoctoral Science Foundation (No. BSH47933-JD).

ACKNOWLEDGMENTS

We would like to thank the patient who agreed to participate in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.877470/full#supplementary-material

Supplementary Figure 1 | The loss of cilia in tumor tissues accounts for a large proportion either ccRCC or pRCC (data seen in **Supplementary Table 2**).

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CASE REPORT
published: 06 July 2022
doi: 10.3389/fonc.2022.927250

Clinical Benefit of Niraparib to TKI/mTORi-Resistance Metastatic ccRCC With *BAP1*-Frame Shift Mutation: Case Report and Literature Review

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Edited by:
Katy Beckermann, Vanderbilt University, United States

Reviewed by:
Ruhee Dere, Baylor College of Medicine, United States
Scott Haake, Vanderbilt University Medical Center, United States

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *24 April 2022*
Accepted: *06 June 2022*
Published: *06 July 2022*

Citation:
Lian B-J, Zhang K, Fang X-D, Li F, Dai Z, Chen W-Y and Qi X-P (2022) Clinical Benefit of Niraparib to TKI/mTORi-Resistance Metastatic ccRCC With BAP1-Frame Shift Mutation: Case Report and Literature Review. Front. Oncol. 12:927250. doi: 10.3389/fonc.2022.927250

Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cancer. The top four mutant genes affecting the occurrence and progression of ccRCC are *VHL, PBRM1, BAP1*, and *SETD2*, respectively. Tyrosine kinase/mammalian target of rapamycin inhibitors (TKI/mTORis) with or without immunotherapy are the standard and effective therapy to metastatic ccRCC. Once TKI/mTORis fail to ccRCC, there is still a lack of other effective therapies. In this study, we reported a case in which a metastatic ccRCC patient (T2aN1M1) presented resistance after a 28-month treatment by sorafenib–axitinib–everolimus (TKI-TKI-mTORi). Subsequently, a frame shift pathogenic mutation, c.799_800del (p.Q267fs) in the exon10 of *BAP1* in ccRCC, was revealed by targeted sequencing. Oral administration of nilapanib (PARP inhibitor) was further given, which may provide a new therapy for TKI/mTORi-resistance metastatic ccRCC. Fortunately, a partial response has been achieved and lasted for 5 months. Since the frequency of *BAP1* mutations in ccRCC patients was approximately 10%–20%, as reported previously, we also tried to explore the potential mechanisms benefitting from the nilapanib. Moreover, the literature concerning *BAP1* mutation and associated cancers including ccRCC is reviewed.

Keywords: clear cell renal cell carcinoma, resistance, BAP1 mutation, niraparib, case report

INTRODUCTION

Clear cell renal cell carcinoma (ccRCC) is the most common pathological subtype of renal cell cancer, with a proportion of more than 75%. CcRCC is characterized by a high frequency, more than 90%, of von Hippel–Lindau (*VHL*) gene inactivation, which plays a key role in regulating angiogenesis through a hypoxia-driven pathway and affects the expression of multiple genes, such as

the vascular endothelial growth factor (*VEGF*) and its receptor (*VEGFR*) (1–3). Due to the lack of effective chemotherapy, interferon, and cytokines, the tyrosine kinase inhibitor (TKI), which target those pathways including *VEGF* and *VEGFR* genes, played an important role in the treatment of advanced ccRCC in the past 20 years (4). With the development of immunotherapy, especially since 2019, TKI alone is instead by the TKI combined with immunotherapy for the metastatic ccRCC as the first-line therapy (5, 6). Alhough TKI with or without immunotherapy did prolong metastatic ccRCC patients' progression-free survival (PFS) time. The second line therapy is limited to change one TKI to another (TKI to TKI) or the mammalian target of rapamycin inhibitor (mTORi), and in the absence of precision medicine based on gene sequencing.

Actually, *VHL* is not the only inactivation gene that appeared in ccRCC. Secondarily mutated genes, including *PBRM1*, *BAP1*, and *SETD2*, are also involved in the formation of ccRCC, with a frequency up to 30%–41%, 10%–20%, and 10%–20%, respectively (7–9). Here, we present a metastatic ccRCC patient with a somatic mutation *BAP1* detected by targeted genes and next-generation sequencing (targeted sequencing; range 808 genes®). After a 28-month treatment of TKI to TKI to mTORi, the patient presented resistance and tumor progression based on RECIST v1.1 (10). Subsequently, nilapanib [poly ADP-ribose polymerase inhibitor (PARPi)] was further given, and partial response was achieved, which has not been reported before. This may provide a new insight and drug therapy for advanced-resistance ccRCC. Moreover, we also systematically reviewed the previous literature, and assessed the *BAP1* alteration frequency and possible mechanism in cancers, particularly in ccRCC.

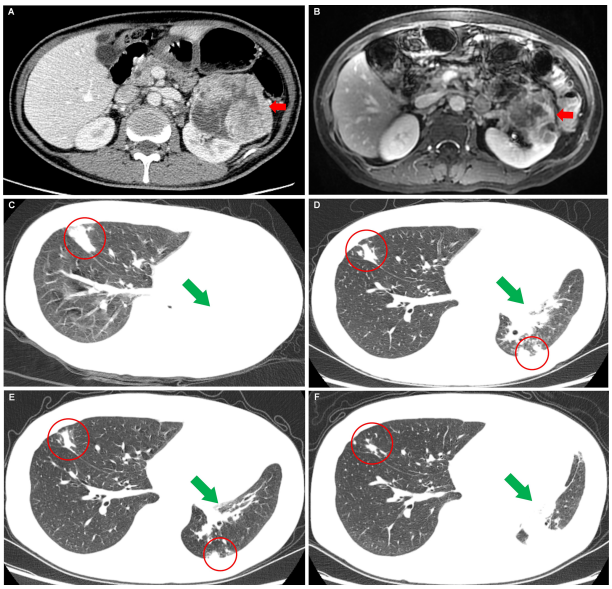

FIGURE 1 | Images of the left renal carcinoma and the changes of metastases when the patient took nilapanib. **(A)** Computed tomography image examination showed an enhancing mass measuring 9.3 cm × 8.2 cm × 7.7 cm (red arrow) in the left renal. **(B)** Magnetic resonance image examination revealed a significantly reduced mass [7.3 cm × 6.8 cm × 7.0 cm (red arrow)] in the left renal after sorafenib-targeted therapy for 14 months. **(C)** Before nilapanib; **(D)** After nilapanib for 2 months; **(E)** After nilapanib for 4 months; **(F)** After nilapanib for 5 months. Chest CT showed metastases in the lungs (red circle) and atelectasis in the left lung (green arrows) due to the tumor invasion of the left bronchus, received continuous remission in the first 4 months after nilapanib **(C–E)**. **(F)** showed that new metastases appeared in the hilus of the left lung, resulting in atelectasis.

CASE DESCRIPTION

A 49-year-old man without urologic symptoms and renal cancer family history received a conventional physical examination in a local hospital in May 2018. A huge hypoechoic mass in the left renal was occasionally showed by urologic Doppler ultrasound (US) examination. Computed tomography (CT) revealed an enhancing mass measuring 9.3 × 8.2 × 7.7 cm in the left renal (**Figure 1A**), multiple enlarged lymph nodes in the retroperitoneal, and a quasi-circular mass (maximum size 3.0 cm) in the liver but normal alpha-fetoprotein levels (1.54 ng/ml; normal <5.0 ng/ml). Afterwards, a US-guided fine-needle aspiration (FNA) was performed on the left renal mass. The histological Hematoxylin-Eosin (H&E) examination of biopsy specimens showed features positive for malignancy, and immunohistochemistry revealed that the tumor cells were positive expressions of PAX-8, CAIX, CD10, and negative for CK7, suggesting ccRCC [$T_{2a}N_1M_1$ (11)]. Meanwhile blood routine testing showed the patient with a lower serum hemoglobin of 97 g/L, an elevated platelet of 393 × 10^9/L, and Ca^{2+} 3.05 mmol/L, respectively. Based on these blood markers and less than 1 year from diagnosis to treatment, the patient was classified as a poor-risk group according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (11). Sorafenib (400 mg, bid) was subsequently taken as the first-line therapy based on the European Association of Urology (EAU) Guidelines–2018 (11). In July 2019, after the patient achieved a partial response confirmed by magnetic resonance imaging (MRI) after sorafenib-targeted therapy for 14 months (**Figure 1B**) (10), cytoreductive nephrectomy (CN) was further performed. Histopathological examination revealed ccRCC with lymph node metastases. Two weeks later, a radiofrequency ablation of liver metastases was also conducted. After 2 months of the CN operation, sorafenib was replaced by axitinib (5 mg, bid) due to an adverse event of grade 3 maculopapular erythroderma, and the disease was stable continuously. In May 2020, the patient began to lose weight and have a headache. Chest CT identified the areas of new abnormal metabolism in both lungs and brain MRI showed a mass in the right optic canal. Everolimus (10 mg per day; mTORi) was subsequently given as the third line but showed ineffective treatment.

In September 2020, the patient came to our hospital with a severe headache and dyspnea. The admission assessment showed a 4-grade Eastern Cooperative Oncology Group (12) and an 8-grade Visual Analogue Scale (VAS) Pain (13). Chest CT showed atelectasis in the left lung due to the tumor invasion of the left bronchus and metastases in the right lung (**Figure 1C**). Brain MRI showed a mass in the right optic canal. Targeted genetic

testing was further performed on a ccRCC specimen from nephrectomy [formalin-fixed paraffin-embedded (FFPE)] by utilizing the Illumina HiSeq 4000 platform. A frame shift pathogenic mutation c.799_800del (p.Q267fs) in the exon 10 of *BAP1* (https://www.ncbi.nlm.nih.gov/clinvar/variation/1070749/) was found. Owing to the patient's worse performance status and high cost of drugs, immune checkpoint inhibitors (PD-1/PD-L1/CTLA-4/LAG-3/CD47) were not a priority treatment option and should be refused. On the contrary, based on *BAP1* mutation detected in the tumor in the patient, PARPi should be recommended. In October 2020, niraparib (200 mg per day) was taken after obtaining the patient and his family's full informed consent, followed by CyberKnife radiosurgery (25 Gy; 5 cycles) for the treatment of intracranial metastatic lesion and supplemented nutritional support therapy. To our excited, the patient displayed a partial response in both lungs after niraparib for 2 months (**Figure 1D**). The intracranial lesion also shrunk due to radiotherapy and the headache were totally released. The Lactate Dehydrogenase (LDH) and Carcino-Embryonic Antigen (CEA), which elevated to abnormal when the patient admitted to our hospital, returned to normal again (**Figure 2**). In the following 2 months, the patient received continuous remission (**Figure 1E**). However, in March 2021, 5 months after taking niraparib, new metastases appeared in the brain and the hilus of the left lung, resulting in atelectasis (**Figure 1F**). Then, the patient began to suffer from breathing difficulties and refused any further treatment, except palliative care. Eventually, the patient died in June 2021 according to his family's message.

Moreover, we clustered data that were identified from other patients with cancer and *BAP1* alteration by the "cBioPortal" (http://www.cbioportal.org). This identified a total of 32 large-scale TCGA PanCancer Atlas Studies containing 10,967 samples. The data from these publications are clustered for analysis as shown in **Figure 3A**.

DISCUSSION

BAP1, which is located on the chromosome 3p21.1, is a ubiquitin carboxy-terminal hydrolase (14). It was recognized as a tumor suppressor, and a mass of processes including chromatin modification, programmed cell death, cell cycle control, DNA damage repair, and the immune response were regulated by its deubiquitinating activity (14, 15). *BAP1* can undergo germline or somatic alterations, and tumors that are relevant to germline are semblable to those with somatic *BAP1* alterations (15). The inactivation of the *BAP1* gene (either germline or somatic form) often led to the development of a number of cancers, such as melanoma, malignant mesothelioma, and ccRCC (14, 16). This may indicate the common mechanisms of tumorigenesis and the potential target therapies to *BAP1* in these highly relevant tumors (15). CcRCC with a *BAP1* mutation often showed clinicopathologic features as a high pathological stage, high renal vein involvement rate, and high metastasis rate and always had a worse prognosis, even in patients with low-risk tumors (17–19). In this study, the presence of the patient by physical examination showed that the occasional ccRCC had advanced and distant (bone and liver) metastasis (T2aN1M1), implying a worse prognosis. Moreover, the traditional targeted therapy for ccRCC with *BAP1* mutation, for example, antiangiogenic therapy-TKI, might also show a poor outcome (20). In contrast, this patient received a 24-month PFS time in total by the two TKI (sorafenib to axitinib) therapies, showing a certain degree of efficacy. On the contrary, mTORi

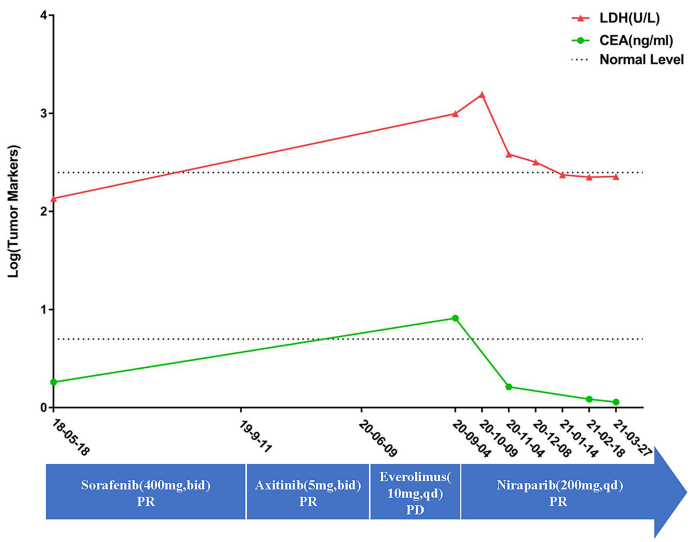

FIGURE 2 | The patient's detailed treatment process and the tumor marker changes. The curve showed that the tumor markers is still in the normal level upon first diagnosis. However, they were already higher than normal when the patient was admitted in our hospital. However, after taking nilapanib, the tumor markers returned to normal again. The blue arrow showed the detailed medication information along the treatment. On the other hand, there is still the lack of specific tumor markers for ccRCC. The changes of LDH and CEA may be inconsistent with changes in the tumors.

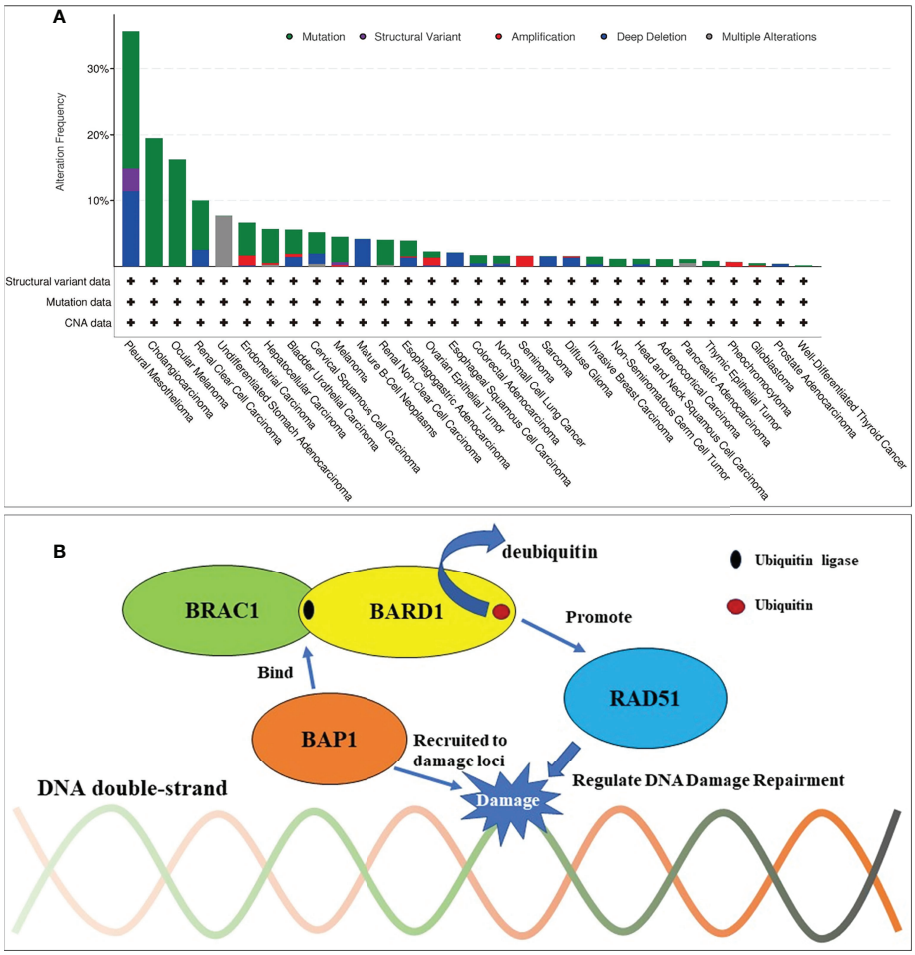

FIGURE 3 | Frequencies of BAP1 alteration across cancer types and mechanism of BAP1 in DNA damage repairment. **(A)** *BAP* mutations most commonly occurred in pleural mesotheliomas, cholangiocarcinoma, ocular melanoma, and renal clear cell carcinoma from a total of 32 large-scale TCGA PanCancer Atlas Studies that contained 10,967 samples. **(B)** Mechanism of BAP1 in DNA damage repairment. BRCA1/BARD1 complex is an E3 ubiquitin ligase and interacts with the recombinase RAD51 to regulate the homologous recombination repairment. BAP1 can be recruited to DNA damage loci and bind to the BRCA1/BARD1 complex. By this, BAP1 can inhibit the E3 ligase activity of BRCA1/BARD1 to protect against additional ubiquitination and deubiquitinate preexisting ubiquitin chains (bent arrow).

(everolimus) was used but not effective, lasting 3 months continuously. The treatment options for ccRCC patients regardless with or without the *BAP1* alterations are limited to traditional therapies. TKI with or without immunotherapy was still the main treatment method. Once TKI failed, the optimal further treatment is scanty. Immunotherapy was an option for a subsequent treatment; however, patients' poor performance status and the high cost of immune checkpoint inhibitors always prevented its application, such as this patient. It is interesting that several therapies targeting the *BAP1* alterations showed a positive potential in cancers, according to the recent studies (21, 22). The enhancer of zeste homolog 2 inhibitor (EZH2i) and histone deacetylase inhibitors (HDACis), which target the mechanism of BAP1 in transcriptional regulation and chromatin modification, respectively, are potential targeted therapies (21, 22). An EZH2i study had positive results obtained in a phase 2 trial conducted in *BAP1*-altered malignant pleural mesothelioma *in vivo* (22), as well as HDACi warrants further exploration whether *BAP1* aberrations modulate response in VANTAGE 014 study (21), although BAP1 downregulation increases the sensitivity to HDACi *in vitro* (23). Unfortunately, EZH2i and HDACi were not available in China, potentially, PARPi should be chosen as the further treatment for this TKI/mTORi-resistance advanced ccRCC.

BAP1 is first known as a protein interacted with *BRCA1*, which is the famous homologous recombination repair gene (24, 25). Nowadays, research has also reported that BAP1 regulates the DNA damage repair in many ways, for instance, binding the BRCA1/BARD1 complex. The BRAC1/BARD1 complex, which functions as an E3 ubiquitin ligase, is known to play a significant role in the DNA damage response through recruiting RAD51 to the damaged loci and so on (26, 27). Jensen et al. showed that BAP1 can interact with BRCA1 and augment the tumor

TABLE 1 | Studies of PARPi in tumors with BAP1 alteration.

Tumor phenotype	PARPis	Study type	Comments
Malignant mesotheliomas	Olaparib, niraparib	*In vitro*	PARPis at clinically relevant concentrations result in significant cytotoxicity in malignant mesotheliomas (31).
Osteosarcomas	Talazoparib	*In vitro*	Osteosarcoma cells with genetic signatures of BRCAness are susceptible to the PARPi talazoparib (32).
Malignant mesothelioma	Olaparib	*In vitro*	The response to PARPi could be demonstrated in the BAP1-mutated NCI-H2452 cells (33).
Malignant mesothelioma	Olaparib	*In vitro*	Patients with a high expression of BAP1 may be responsive to PARPi (34).
Malignant mesotheliomas	Olaparib	Phase 2 clinical trial (n=23)	Olaparib is safe with no new safety concerns and has limited activity in previously treated mesothelioma (35).
Malignant mesotheliomas	PARPi	Retrospective cohort study (n=4)	No responses were observed with PARPi (36).
Malignant mesotheliomas	Rucaparib	Phase 2 clinical trail	Rucaparib in patients with BAP1-negative or BRCA1-negative mesothelioma met the prespecified criteria for success (37).
Intrahepatic cholangiocarcinoma	Olaparib	Case report	Following 11.0 months on olaparib treatment, sustained stable disease control is ongoing (38).

PARPi, poly ADP-ribose polymerase inhibitor.

suppressor activity of BRCA1 (28). Nishikawa et al. showed that BARD1 is the major binding partner of BAP1 (29). By binding to the BRCA1/BARD1 complex, BAP1 can inhibit the E3 ligase activity of BRCA1/BARD1 to protect against additional ubiquitination and deubiquitinate preexisting ubiquitin chains (29). The dual role of BAP1 toward BRCA1/BARD1 could be important to ensure the inhibition of ubiquitination in cellular pathways, though the interacting mechanism of these molecules between BAP1 and BRCA1/BARD1 needs further study (**Figure 3B**) (24–30). Thus, PARPi would have a synthetic lethal effect on *BAP1*-mutated tumors, theoretically. Given the known experiment of *BAP1*-mutated cancers, PARPi was effective in the treatment of malignant neoplasm—pleural mesotheliomas, osteosarcomas *in vitro* (31–34) and mesotheliomas, intrahepatic cholangiocarcinoma *in vivo* (35–38), and so on (**Table 1**). The ongoing phase II clinical studies of niraparib and olaparib also react to the safety and feasibility of PARPi in treating patients with *BAP1* alterations (NCT03207347, NCT03531840, NCT03786796). As long as the mutated genes are identical, the same targeted drugs are feasible for different diseases (39). To control tumor progression, PARPi may have the potential to target *BAP1*-altered ccRCC. Based on these findings, niraparib was taken after obtaining the patient's full informed consent. The exciting part is that the tumors in the lungs achieved a partial response for 5 months, suggesting that niraparib is a relatively effective treatment for TKI-refractory metastatic ccRCC with *BAP1* alteration. Although owing the lack of specific tumor markers for ccRCC, the effect of the treatment cannot always be reflected by tumor markers. The reduction of LDH and CEA, which elevated to abnormal when the patient was admitted to hospital, may indicate that niraparib worked to some extent. Moreover, for ccRCC patients with a *BAP1* alteration, immunotherapy and/or immunocombination therapy may improve efficacy. Recent reports revealed that *BAP1* alterations in cancer confer distinct immunogenic phenotypes that may be particularly susceptible to novel cancer immunotherapies (40). *BAP1* mutations in ccRCC correlate with increased CCR5 expression and immunosuppression (41). These studies speculated that both PARPi and immunotherapy seemed to show enormous potential in treating ccRCC with *BAP1* alteration. Unfortunately, the patient never received the immunotherapy from the beginning to the end.

CONCLUSION

This study demonstrates that PARPi may be another potential therapy for TKI/mTORi-resistance ccRCC with a *BAP1* mutation, and, additionally, immunotherapy and/or immunocombination may also have effect on ccRCC with a *BAP1* mutation, although this warrants further validation in clinical studies. An individualized comprehensive approach for advanced ccRCC with *BAP1* mutation is beneficial.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The 903rd Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conception/design: X-PQ and B-JL; Provision of study material or patients: KZ, W-YC, FL, and X-DF; Data collection and analysis: B-JL, KZ, W-YC, X-DF, and ZD; Manuscript

writing: B-JL and X-PQ; All authors have read and approved the manuscript.

FUNDING

This work was supported by the National Natural Science Foundation of China (81472861), the Key Project of Zhejiang Province Science and Technology Plan, China (2014C03048-1), and Hangzhou Municipal Commission of Health and Family Planning Science and Technology Program (B20210355, OO20190253).

ACKNOWLEDGMENTS

The authors thank the patient and family members who agreed to publish the case in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.927250/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 03 August 2022
DOI 10.3389/fonc.2022.971341

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

RECEIVED 16 June 2022
ACCEPTED 14 July 2022
PUBLISHED 03 August 2022

CITATION
Schmeusser B, Palacios AR, Midenberg E, Nabavizadeh R, Master VA and Joshi SS (2022) Case report: Important considerations for a renal mass on a solitary kidney in an adult with history of childhood wilms tumor. *Front. Oncol.* 12:971341. doi: 10.3389/fonc.2022.971341

Case report: Important considerations for a renal mass on a solitary kidney in an adult with history of childhood wilms tumor

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Adult survivors of childhood Wilms tumor are at an increased risk of secondary malignant neoplasms. The presence of a solitary kidney further complicates clinical management in this population. Herein, we present the case of a 37 year old female with a history of childhood Wilms tumor presenting with a secondary renal neoplasm. We highlight important clinical considerations for renal function preservation and present a finding of predisposition to kidney stone formation due to urinary stasis from distorted ureter architecture secondary to tumor mass effect.

KEYWORDS

Wilms tumor, solitary kidney, partial nephrectomy, secondary malignant neoplasm (SMN), ureter abnormalities

Introduction

Adults with a history of childhood Wilms tumor (WT) and chemoradiation are at an increased risk of secondary malignant neoplasms (1–4). Termuhlen et al., in their study looking at 25-year outcomes of childhood Wilms tumor survivors in the Childhood Cancer Survivor Study, reported an increased incidence of soft tissue sarcomas, adenocarcinomas, lymphomas/leukemias, and other malignant neoplasms in this population (2). Renal Cell Carcinoma (RCC) has also been observed in adults with a history of WT (1, 4). Here we report a case involving a patient with a history nephrectomy for childhood WT presenting with a new solitary kidney mass.The clinical evaluation, diagnostic process, and surgical management are first discussed. Additionally, distortion of ureter architecture secondary to tumor mass effect refractory to treatment and resulting long-term management considerations is also presented.

Case description

A 37 year old female was referred to the urology clinic for evaluation of a renal mass in the setting of a left solitary kidney. Past medical history is significant for a right Wilms tumor (WT) status post nephrectomy at three years of age, followed by adjuvant chemotherapy and radiation for two years. The patient states the contralateral kidney was not included in her radiation. History regarding treatment and management of this patient's childhood WT is otherwise limited by time and access to records. However, the patient was able to recall that routine monitoring revealed no signs of recurrence, radiotherapy associated complications (i.e.soft tissue dystrophy), or evidence of ureteral anomalies. Additional surgical history includes two remote cesarean sections. She initially presented with 2 weeks of abdominal pain and pressure, nausea, and constipation. Review of systems was negative for hematuria, vomiting, diarrhea, and constitutional symptoms such as fever, fatigue, night sweats, or weight loss. Physical exam revealed a palpable mass in the left upper abdomen but was otherwise soft and nontender. Creatinine (Cr) was 0.7mg/dL, eGFR=120mL/min/m^2, and hemoglobin was 10.1g/dL. Laboratory workup was otherwise non-significant.

A CT-abdomen revealed a 7.5 x 8.3 x 10.0cm heterogeneous solid mass of the left solitary kidney with compression on the renal hilum and resulting hydronephrosis (Figure 1). Additionally, a 1.2cm stone was seen in the anterior lower pole. Subsequent imaging of the brain and chest revealed no evidence of metastatic disease.

Following tumor board consensus, a retroperitoneal percutaneous core needle biopsy of the mass was obtained. Biopsy pathology revealed an oncocytic neoplasm, indicating likely benign oncocytoma versus chromophobe renal cell carcinoma (RCC). Given unlikely improvement with neoadjuvant therapy, a complex open partial nephrectomy was planned. Nephrology was consulted to assist with perioperative management given the patient's history of unilateral nephrectomy. Intraoperatively, after achieving adequate exposure, a bulldog clamp was placed across the renal artery and the kidney was surrounded by ice slush. Following ten minutes of cold ischemia, tumor enucleation began; however, the bulldog clamp did not appear to sufficiently control the patient's renal arterial supply. It was decided to instead place a Satinsky clamp across the renal vein and artery, leading to a bloodless field. The enucleation was completed, and the collecting system was entered in several places which was oversewn with 4-0 vicryl sutures. Importantly, the kidney was surrounded by ice during the excision and reconstruction with a total clamp time of 120 minutes. Following clamp removal, a few venous bleeders were controlled with 5-0 monofilament suture. No significant arterial bleeding was visualized. Hemostatic materials were placed into the defect, and renorrhaphy was completed with sliding V-loc barbed sutures in standard fashion. Omentum from the transverse colon and stomach was harvested, pediculated off the left gastroepiploic artery, and tunneled into the left gutter to fill the defect. A 19Fr blake drain was placed in the left lower abdomen. A 16Fr foley catheter and ureteral stent were additionally placed. Prior to closure, retroperitoneal

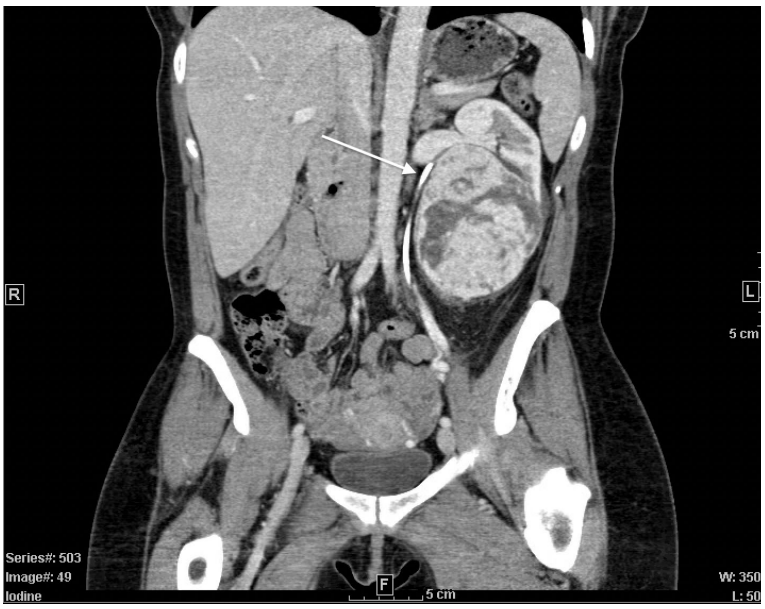

FIGURE 1
CT-Abdomen with IV contrast. Coronal view demonstrating large, 7.5x8.3x10.0cm heterogeneous solid mass in solitary left kidney. Stent in place *(white arrow)*, indicating compressed and arched ureter superior to the mass.

ultrasound revealed good renal blood flow. Total operation time was 270 minutes. Estimated blood loss was 500mL and no transfusion was required. On post-op day 3, the patient's drain was removed and she was discharged home with a foley catheter and ureteral stent in place. The foley catheter was removed two-weeks post-discharge, and the stent was removed one-month postoperatively. Final pathology of the mass confirmed oncocytoma. Postoperative imaging revealed continued arching of the ureter in the absence of the mass (Figure 2). The patient's renal function remained stable (Cr=0.7mg/mL, eGFR=107mL/min/m^2) without need for dialysis.

Short-term recovery was uncomplicated. Nine months after the surgery, she presented with nausea and left flank pain without fevers, chills, hematuria, or dysuria. Her Cr was increased to 1.4 mg/dL from 0.7 mg/dL. There was no leukocytosis and the urinalysis was benign. CT-abdomen revealed multiple left sided nonobstructing stones and a 5mm obstructing stone at the ureteropelvic junction (UPJ) with hydronephrosis (Figure 3). Laser lithotripsy was completed without complication. Stone composition was 90% uric acid. Intraoperative retrograde pyelogram revealed a distorted, superior malrotation of the left ureter. The patient's propensity for urinary stasis secondary to her superiorly arched ureter is the likely cause of her stone formation. To monitor, manage, and prevent further stone development, the patient was scheduled to follow-up with endourology where she was encouraged to maintain hydration to express at least 2 liters of urine per day.

Discussion

Renal masses in solitary kidneys are complex cases that require multidisciplinary care. As an absolute indication for nephron sparing interventions, the simultaneous optimization of renal function and oncologic control becomes crucial for maximizing patient outcomes (5, 6). In this particular case, a patient with history of childhood WT presenting with a new renal mass of the solitary kidney and subsequent anatomic distortion of the ureter secondary to mass effect, further complicates clinical management. In the following discussion, lessons learned and important considerations in this case are explored.

WT, or nephroblastoma, is the most common renal malignancy in childhood (7). The pathogenesis of childhood WT is closely tied to gene mutations and resulting disruptions in embryologic nephrogenesis (7). Most often unilateral, WT can be bilateral in up to 5-9% of cases (8). Treatment for WT is usually nephrectomy with adjuvant chemotherapy and radiation, as in our case, though neoadjuvant chemotherapy to monitor response can be considered (7). Survival rates for WT have been reported to be around 90%, though more aggressive histology can be associated with only 50% survival (8). Recurrence, associated with only a 50% survival rate, occurs in 20% of patients, typically within the first 2 years (8). Although extremely rare, delayed WT recurrence, defined as 5 years after initial diagnosis, have been reported in the literature (9, 10). Secondary renal neoplasms arising in adults with history of childhood WT have also been reported and include ccRCC and other RCC subtypes, oncocytomas, metanephric adenomas, and atypical cysts (1, 4).

Renal masses in young adults (17-45 years old), have been demonstrated to be benign in up to 20% of cases (11, 12). However, given the patient's history of WT and chemotherapy/radiation, which increases her risk for a secondary malignant renal neoplasm, a preoperative percutaneous biopsy of the mass was done to prevent unnecessary surgery and best direct treatment (1, 4). The result of the biopsy in this case was oncocytic neoplasm. Although reassuring that WT was not the cause and negating the need for systemic therapy, an oncocytic

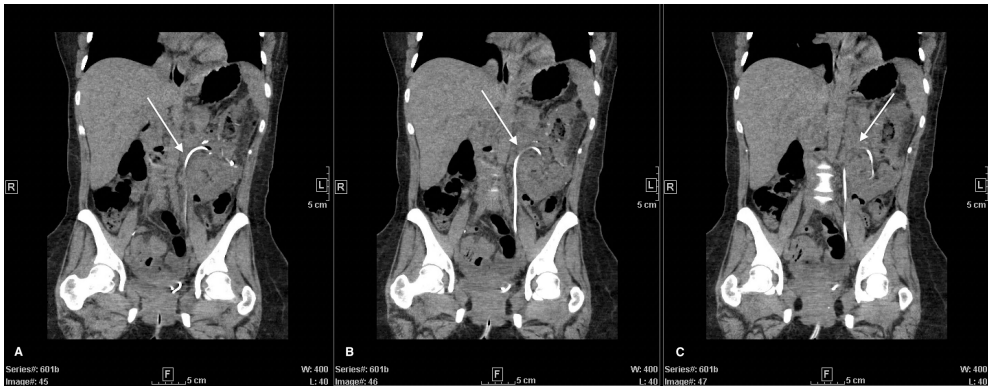

FIGURE 2
Post left partial nephrectomy CT-abdomen with IV contrast. Coronal view of 3 continuous images from left to right **(A–C)**. Ureteral stent *(white arrows)* displaying continued arching trajectory superiorly despite removal of mass.

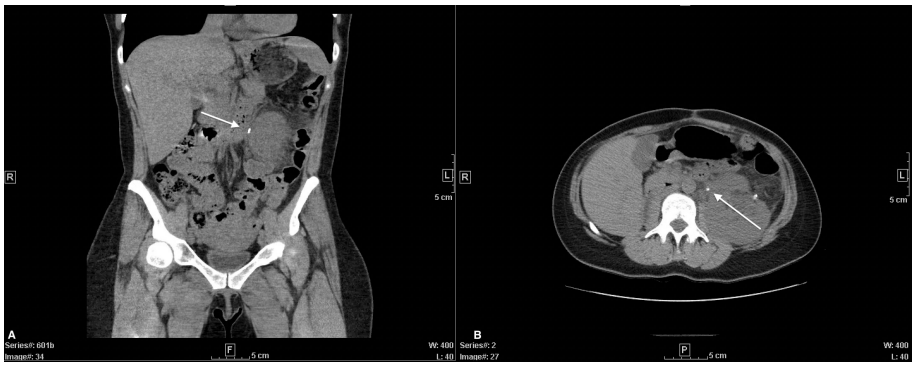

FIGURE 3
CT-Abdomen without contrast. Coronal **(A)** and axial **(B)** views displaying left-sided obstructing UPJ stone.

neoplasm on the pathology report fails to differentiate between a benign renal oncocytoma and chromophobe RCC (13). Chromophobe RCC, though a lower grade and more favorable subtype of RCC, is still recommended to be treated with nephrectomy for optimal oncologic control (14, 15).

Due to the potential for malignancy and symptoms of mass effect, partial nephrectomy was selected as the treatment choice. However, partial nephrectomy in solitary kidney patients presents additional long-term postoperative challenges and considerations for kidney function due to absence of contralateral compensation. A preoperative nephrology consult is recommended in these cases for optimal management and in preparation for worst-case scenarios, such as renal replacement therapy given the anatomic complexity inherent in this case (16). Predictors of better renal recovery postoperatively include younger age, higher preoperative eGFR, and greater renal parenchyma preservation (16, 17). Although ischemia time–both cold and warm–during partial nephrectomy has long been proposed as negative predictor of postoperative eGFR, studies suggest it has a minimal contribution with renal parenchymal preservation and preoperative eGFR having a more significant effect (16–19). Ching et al. examined patients that underwent partial nephrectomy in a solitary kidney at 5 and 10 years postoperatively, and found that patients who eventually required permanent dialysis or transplantation had a median eGFR of 26.1mL/min/1.73m^2 compared to 46.7mL/min/1.73m^2 for patients not requiring such interventions (17). Nevertheless, following partial nephrectomy in a solitary kidney, eGFR is expected to decline immediately postoperatively but then plateau around one month afterwards and remain relatively stable for at least 10 years (16, 17, 20, 21).

Interestingly, in this case, the patient had continued distortion and arching of the ureter at the UPJ despite removing the mass. The superior arching path of the ureter has resulted in urinary stasis, which predisposes her to form kidney stones. The patient had no past evidence of malrotation or history of nephrolithiasis. No similar reports have been found in the literature. The patient now has an endourologist managing this anomaly. Active surveillance of these patients is essential for maximizing renal function, and ultimately minimizing long term morbidity and mortality.

Conclusions

This case illustrates a patient with a solitary kidney secondary to nephrectomy for childhood Wilms tumor presenting with a large renal mass. Important considerations on the diagnosis and management in these patients must be made to ensure preservation of renal function and adequate oncologic control.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BS and SJ conceived and designed the study. SJ, VM, and RN played a critical role in the patient's care and decision making, as outlined in the case report. All authors contributed to the

writing, editing, and revision of the manuscript. All authors approved of the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 02 December 2022
DOI 10.3389/fonc.2022.949400

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Genitourinary Oncology,
a section of the journal
Frontiers in Oncology

RECEIVED 20 May 2022
ACCEPTED 14 November 2022
PUBLISHED 02 December 2022

CITATION
Zhuang TZ, Harik L, Force S, Hadadi A, Bilen MA, Brown JT, Carthon BC, Goldman J, Kucuk O, Master VA and Nazha B (2022) Durable complete response for oligometastatic renal cell carcinoma with immune checkpoint inhibition and cytoreductive nephrectomy in a Jehovah's witness: A case report.
Front. Oncol. 12:949400.
doi: 10.3389/fonc.2022.949400

Durable complete response for oligometastatic renal cell carcinoma with immune checkpoint inhibition and cytoreductive nephrectomy in a Jehovah's witness: A case report

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The role of cytoreductive nephrectomy in patients with metastatic renal cell carcinoma is a subject of debate. We report a durable complete response in a 62-year-old man Jehovah's Witness with metastatic clear cell renal cell carcinoma who received two cycles of nivolumab/ipilimumab followed by radical nephrectomy and metastasectomy of known pulmonary disease site, both without a clinical need for perioperative blood transfusions. The patient continues to be without evidence of disease and without additional need for systemic therapy over a year after his radical nephrectomy. The case highlights that cytoreductive nephrectomy continues to play a role in the era of immune checkpoint inhibitors.

KEYWORDS

renal cell carcinoma, nivolumab, ipilimumab, cytoreductive, oligometastatic, TKI (tyrosine kinase inhibitor)

Introduction

Renal cancer is the eighth most common cause of cancer worldwide, responsible for over 13,000 deaths annually (1). Clear cell renal cell carcinoma (ccRCC) is the dominant histological group, accounting around 75% of RCC cases (2). Upfront surgical resection is the gold standard treatment in patients with non-metastatic disease. Around 16% of renal cancers involve metastases at initial diagnosis with a 5-year survival rate of approximately 14%. The IMDC (International Metastatic RCC Database Consortium) predicts survival in patients with metastatic renal cell carcinoma (mRCC) and was originally validated in patients receiving vascular endothelial growth factor receptor inhibitors (VEGFRi).

With the incorporation of new systemic therapy, namely, immune checkpoint inhibitors (ICI) with or without VEGFRi, the role and timing of cytoreductive nephrectomy (CN) are debated in patients who do not have mass-related symptoms such as ongoing hematuria or uncontrolled pain (3, 4). Nevertheless, it remains an enduring facet in the treatment landscape especially in patients where complete resection of known disease sites can be achieved. We present a case of patient with oligometastatic RCC who received upfront ICI doublet and subsequently underwent CN. We explore the role of CN in the expanding treatment landscape of metastatic ccRCC.

Objective

We present a case of cT3aN0pM1G4 renal cell carcinoma with sarcomatoid differentiation (IMDC intermediate risk) with biopsy-proven pulmonary oligometastatic disease, in a Jehovah's Witness man.

Case description

A 62-year-old man who is a Jehovah's Witness presented to an outside hospital in July 2020 and received antibiotics for presumed urinary tract infection (Figure 1). Imaging showed a large left renal centrally necrotic mass with tumor thrombosis without adenopathy, concerning for renal cell carcinoma. His past medical history included hypertension and gouty arthritis. He had no major prior surgical history. The patient was chronically on allopurinol. He drank wine socially and did not smoke or use recreational drugs. His family history includes heart disease and diabetes mellitus (parent).

The patient underwent urologic evaluation. Upfront nephrectomy was deferred due to suspicion of metastatic disease. In addition, the procedure was felt to be too high risk for perioperative bleeding which would require blood transfusions, a supportive procedure that would go against his faith. An MRI of the abdomen and pelvis revealed a 12-cm left kidney mass with extension into the left renal vein. Additionally, CT chest imaging demonstrated a 1.3-cm right lower lobe (RLL) and a 1.1-cm left upper lobe (LUL) nodule. There was no evidence of other metastatic involvement.

The patient underwent a left-lung CT-guided biopsy of the LUL nodule which showed pathological findings consistent with poorly differentiated carcinoma of renal primary. After meeting with medical oncology, he then received his two cycles of systemic therapy consisting of nivolumab and ipilimumab starting September 2020 which he tolerated well and without gouty arthritis flares.

The patient subsequently presented to our institution for a second opinion. On initial evaluation, his vital signs were within the normal range. The physical exam was non-contributory, and the patient's performance status was excellent (ECOG 0, Karnofsky 100%). The IMDC score was 1 (intermediate, <1 year from time of diagnosis to systemic therapy) (Table 1).

At a multidisciplinary tumor board discussion, a surgical resection of his known sites of disease was felt to be feasible given oligometastatic disease status and repeat CT imaging demonstrating pulmonary nodule interval improvement following two cycles of ICI.

The patient then underwent an open left radical nephrectomy end of September 2020, with left adrenalectomy, opting for only bloodless products as needed. There was a tumor thrombus in the left renal vein. Hemostasis was carefully maintained with Bovie electrosurgery and argon beam plasma coagulation, along with hemostatic products achieving minimal intraoperative blood loss of 150 cc. Therefore, there was no clinical need for bloodless product transfusion. The patient tolerated his procedure well; an image of the resected mass is

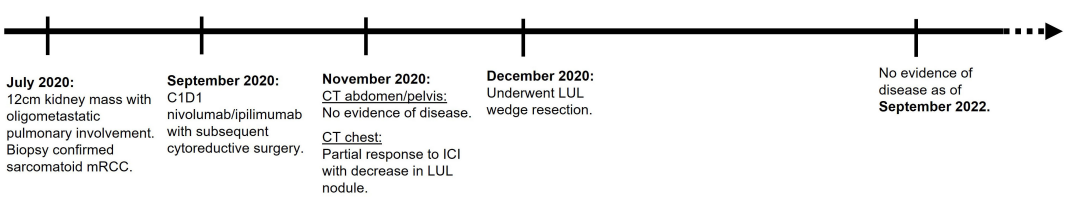

FIGURE 1
Timeline of disease.

TABLE 1 Baseline characteristics.

Initial characteristics	Values (normal range)
Time from diagnosis to systemic therapy	<1 year
ECOG/Karnofsky Performance Score	ECOG 0/KPS100
Sodium level	139 mmol/l (136–145 mmol/l)
Chloride level	102 mmol/l (98–107 mmol/l)
Creatinine level	0.80 mg/dl (0.7–1.3 mg/dl)
Calcium level	9.6 mg/dl (8.6–10.3 mg/dl)
Lactate dehydrogenase (LDH)	346 unit/l (140–271 unit/l)
Hemoglobin A1c (HbA1c)	5.8% (≤5.6%)
Aspartate aminotransferase level (AST)	22 unit/l (7–52 unit/l)
Alanine aminotransferase level (ALT)	27 unit/l (13–39 unit/l)
Hemoglobin level (Hgb)	12.6 gm/dl (12.9–16.1gm/dl)
Postoperative Hgb level	10.8 gm/dl (12.9–16.1gm/dl)
MCV (mean corpuscular volume)	83.9 fl (79.0–92.2 fl)
White blood cell count (WBC, 10^3)	6.8 cells/μl (4.2–9.1 cells/μl)
Absolute neutrophil count (ANC, 10^3)	4.59 cells/μl (0.67–6.4 cells/μl)
Platelet count (10^3)	336 cells/μl (150–400 cells/μl)

shown in Figure 2. Pathology revealed a WHO nuclear grade 4 with necrosis measuring 13.0 cm in greatest dimension and invading into the renal vein (Figure 2). Surgical margins were negative. An incidental papillary renal cell carcinoma mixed type 1–2 measuring 3 mm in greatest dimension.

About 6 weeks post-nephrectomy, a CT abdomen/pelvis in November 2022 revealed no evidence of disease (Figure 3) and the patient had recovered without major difficulties. Repeat CT chest imaging in November 2020 also demonstrated a continued decrease in the LUL pulmonary nodule and resolution of the previously noted RUL nodule. Subsequently, the patient underwent an incomplete left upper lobe wedge resection of the previously biopsy-proven metastatic LUL nodule, with pathology showing a 3-mm nodular scar and no residual malignant cells (Figure 4).

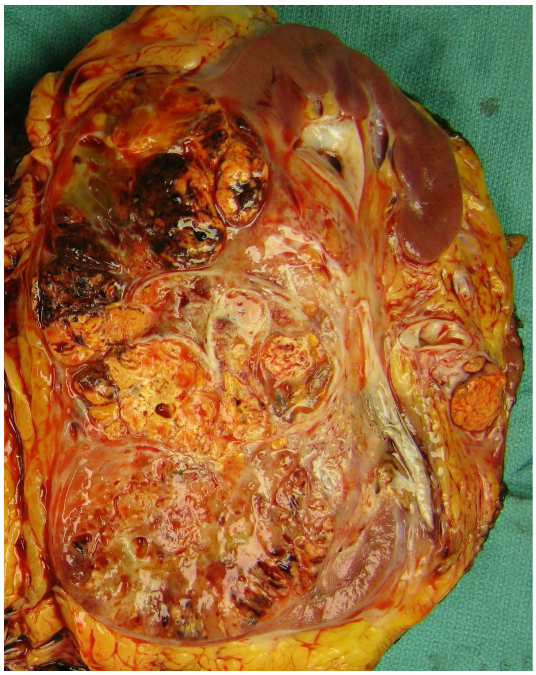

FIGURE 2
Gross examination revealed a 13.0-cm mass arising from the inferior renal pole with involvement of the interpolar region. The mass is multilobulated and variegated yellow-tan in color with areas of hyalinization and hemorrhage. It extends into the renal vein as a tumor thrombus.

Given the absence of disease sites on post-ICI, post-nephrectomy, and post-wedge resection imaging, the patient was followed with active surveillance only. At the time of manuscript writing, the patient had remained for 24 months post-nephrectomy with no evidence of disease, off any systemic therapy, and without new relevant symptoms.

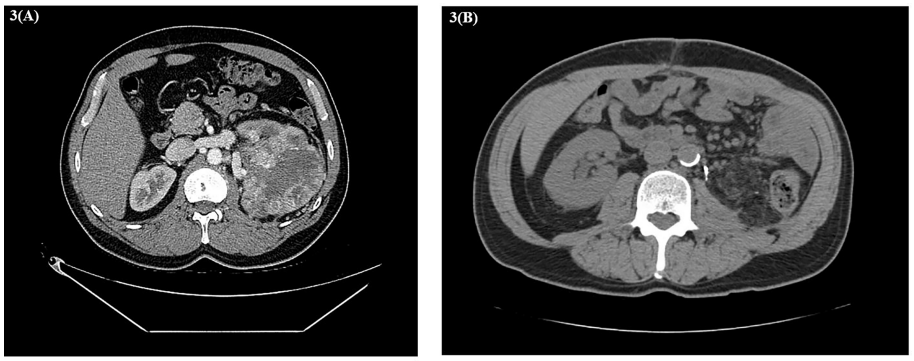

FIGURE 3
(A) Baseline CT abdomen and pelvis with left renal cell carcinoma. **(B)** CT abdomen 2 months after left radical nephrectomy.

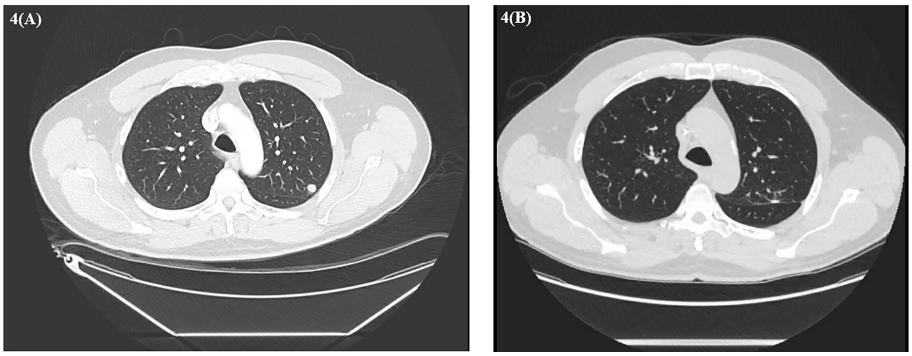

FIGURE 4
(A) Baseline CT chest demonstrating left upper lobe nodule. **(B)** CT chest after left thoracoscopic wedge resection.

Discussion

We present a case of a 62-year-old man who is a Jehovah's Witness achieving ongoing complete response following ICI and cytoreductive surgery of oligometastatic renal cell carcinoma. The presented patient had complete surgical resection of his primary RCC tumor and complete resolution of a known metastatic pulmonary site that is attributed to nivolumab/ipilimumab therapy plus subsequent wedge resection. The case is an argument for secondary cytoreductive nephrectomy, especially in patients who could have resection of all sites of disease and who have had a disease response on initial ICI therapy. Further, our work highlights the potential for safe radical nephrectomy at tertiary centers with a high case load and where a bloodless transfusion or cell saver program exists if needed.

Several case reports highlight the use of bloodless transfusion programs to lower the risk of hemorrhage in surgical resection of vascular-rich tumors. There is a wide spectrum of blood-conserving approaches including circulatory bypass, intraoperative cell saver therapy consisting of antifibrinolytics, fibrinogen cryoprecipitate, or prothrombin concentrate (5, 6). The bloodless transfusion approach at our institution is based on informed consent and discussion of each specific product the patient would and would not be willing to receive. In this case, he was amenable to receiving cell saver, cryoprecipitate, albumin, Arista, Surgicel, and Floseal and opted against receiving fresh frozen plasma and packed red cells. Ciancio et al. presented a case series of seven patients with renal or adrenal cancer who underwent a surgical resection using techniques derived from transplantation surgery that allow for optimal intraoperative exposure and vascular control. All patients recovered well without major blood loss or perioperative complications, similar to our patient's case. Those findings along with our case highlight the feasibility of such complex oncological surgeries without the need for blood transfusions in patients who are Jehovah's Witnesses (7).

Two previous randomized trials cemented CN as a standard of care for patients with metastatic RCC in the cytokine era of interferon-alpha or IL-2 therapies, both of which are rarely used now and much less effective compared with the currently available systemic therapy ICI-based options. In the EORTC 30947 and SWOG 8949 trial pooled analysis, OS was significantly higher within the nephrectomy group (13.6 months) than when treated with interferon (7.8 months) (8, 9).

The role and timing of CN in the VEGFi era was once again revisited with the SURTIME and CARMENA trials. SURTIME (EORTC 30073) was a prospective trial comparing nephrectomy with sunitinib and sunitinib for three cycles with delayed cytoreductive nephrectomy (10). The two arms demonstrated an equivalent progression-free rate (PFR) at 28 weeks. OS favored deferred cytoreductive nephrectomy (32.4 months) when compared with immediate surgical intervention (15.1 months, HR 0.57, 95% CI 0.34–0.95). CARMENA (Clinical Trial to Assess the Importance of Nephrectomy) was the largest prospective, randomized, open-label, non-inferiority trial comparing patients who received sunitinib alone with those who received a nephrectomy and received adjuvant sunitinib (11). The results showed that sunitinib alone was non-inferior to nephrectomy followed by sunitinib for OS. There was no observed difference (23.6 months in sunitinib alone vs 22.7 months in adjuvant sunitinib). In the subgroup analysis, there were worsened patient outcomes in those receiving cytoreductive nephrectomy (16.6 months) vs sunitinib only [(31.2 months, HR 0.61, 95% CI 0.41–0.91)] in the setting of intermediate- or poor-risk disease. However, the trial is often criticized for having had poor accrual, having had frequent crossovers between the arms, and having been

completed at a time when the treatment landscape of RCC was already shifting toward ICI-based therapies that are more effective than sunitinib (12).

Data are limited on the role and timing of CN in the current era of ICI. Proponents of the CN approach argue that the majority of patients enrolled in the IO/IO or IO/VEGF randomized clinical trials had undergone nephrectomy prior to initiation of systemic therapy (13–16). For example, 82% of patients in the Checkmate 214 of ipilimumab plus nivolumab in metastatic RCC had a prior nephrectomy. Further, CN offers the theoretical benefit of reducing the tumor burden of the primary, which could otherwise serve as a highly vascular and immunogenic sink for the administered systemic therapy drugs. Opponents to the CN approach shed concerns on the retrospective or *post-hoc* nature of data in favor of CN and the potential for major complications from a nephrectomy. In addition, *post-hoc* data have mixed results. For instance, a *post-hoc* analysis of the CLEAR trial showed that patients with mRCC who had an intact primary (a minority of patients in the trial) had a relatively improved clinical benefit (OS, PFS, ORR) from lenvatinib and pembrolizumab vs sunitinib that is similar to the one observed in the overall trial population (17).

A balanced viewpoint favors multidisciplinary collaboration as key to appropriate patient selection. Expert guidelines continue to support CN for patients with a favorable-intermediate IMDC risk score, low-volume or oligometastatic disease, and absence of brain metastases. In patients with intermediate- or poor-risk disease, CN can still be considered in patients with a positive response to systemic therapy, especially when all disease sites can be resected. A contemporary study by Esdaille et al. consisting of 937 patients across five centers demonstrated a 10% major complication rate with 1% mortality within 30 days after CN. Systemic therapy prior to CN was not significantly associated with risk of complications or mortality, supporting the approach followed in our presented case (18). Another multicenter study assessed overall survival in 1,163 patients across five different centers who underwent upfront CN. There were 79% treated without neoadjuvant systemic therapies. Most patients were either intermediate or poor risk on preoperative IMDC stratification. Of the 245 patients stratified into poor-risk IMDC, OS was not associated with comorbidity or age. Median overall survival was 21.8 months in poor-risk patients significantly exceeding that in the cohorts examined in CARMENA and SURTIME (19).

Prospective clarification is ongoing for the role of deferred CN in the ICI era. Phase III trials include the NORDIC-SUN (NCT03977571) trial of nivolumab/ipilimumab with or without CN and the PROBE (NCT04510597) of standard-of-care first-line therapy with or without CN. Nivolumab and cabozantinib with or without CN is also being evaluated in the Cyto-KIK trial (NCT04322955). ICI without or without stereotactic body radiation therapy (SBRT) is also explored as treatment of the primary in the CYTOSHRINK (NCT04090710, phase II) trial.

Conclusion

Cytoreductive nephrectomy is an important and often debated facet in treatment of metastatic renal cell carcinoma. With a rapidly expanding treatment landscape of ICI/ICI and ICI/VEGF, its definitive role and timing are less well defined. We hope more prospective and real-world data will benefit our understanding regarding the timing and role of ICI-based therapy and CN in patients with metastatic RCC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BN and VM have contributed equally to this work and share senior authorship. All authors contributed to the article and approved the submitted version.

Conflict of interest

BN has acted as a paid member of the advisory board of Exelis and paid participant in a case discussion for IntrinsiQ Specialty Solutions—AmerisourceBergen. MB has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Calithera Biosciences, Genomic Health, Nektar, EMD Serono, SeaGen, and Sanofi and has received grants to his institution from Merck, Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, SeaGen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer for work performed as outside of the current study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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