RESIDENT'S CORNER

Advanced fumarate hydratase-deficient renal cell carcinoma responding to combination immune checkpoint inhibitors

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Fumarate hydratase deficient (FHdef) renal cell carcinoma (RCC) is rare, highly aggressive and is believed to arise mostly in the setting of hereditary leiomyomatosis RCC (HLRCC) syndrome with a germline mutation of fumarate hydratase (FH) gene. There is currently little evidence regarding the most effective systemic treatment for advanced FHdef RCC. We present three cases of metastatic FHdef RCC, all achieving tumor response with combination immunotherapy ipilimumab and nivolumab (Ipi/Nivo). A 50-year-old male, a 27-year-old male and a 48-year-old female. The clinical features, diagnosis and medical imaging are reviewed.

Key Words: fumarate hydratase deficient renal cell carcinoma, ipilimumab and nivolumab, immunotherapy, checkpoint inhibitors, hereditary leiomyomatosis renal cell cancer syndrome

Introduction

Fumarate hydratase deficient (FHdef) renal cell carcinoma (RCC) is a rare subtype of non-clear cell RCC (nccRCC) associated with hereditary leiomyomatosis RCC (HLRCC). HLRCC occurs due to loss of function mutations in the FH tumor suppressor gene and is associated with uterine leiomyomas as well as FHdef RCC in at least 15% of patients with the syndrome.[1] FHdef RCC can also occur in the absence of a detectable germline mutation, presumed to be due to sporadic somatic mutation. Hereditary and sporadic forms seem to have similar histological and clinical features.

Morphologically, FHdef RCC can present as several different histological subtypes, commonly a type 2 papillary RCC.[1] It is identified with immunohistochemistry (IHC) by a lack of FH protein expression and/or positive 2-succinocysteine (2-SC) expression.[2] Clinically, FHdef RCC is often diagnosed around 40 years of age.[3] It is an aggressive form of RCC that is usually metastatic at or soon after diagnosis and has an overall poor prognosis.[3] Due to its rarity, there is limited high-level evidence on effective treatments.

Like other nccRCC, the management of FHdef RCC is often extrapolated from evidence in clear cell RCC (ccRCC). Key randomized trials have established the role of immune check-point inhibitors and anti-angiogenic agents in the treatment of ccRCC[4] but trials in nccRCC are limited and often study this heterogenous group of diseases as one entity. Amongst the available evidence there has been mixed reports of FHdef RCC response to immunotherapy.

We present three cases of FHdef RCC treated with combination ipilimumab and nivolumab (Ipi/Nivo) all resulting in tumor response.

Case 1

A 48-year-old previously well woman presented with 3 weeks of nausea, loss of weight and left loin pain. A computed tomography (CT) scan demonstrated a large left renal mass directly invading the left renal vein with tumor thrombus extending into the inferior vena cava as well as para-aortic and paracaval

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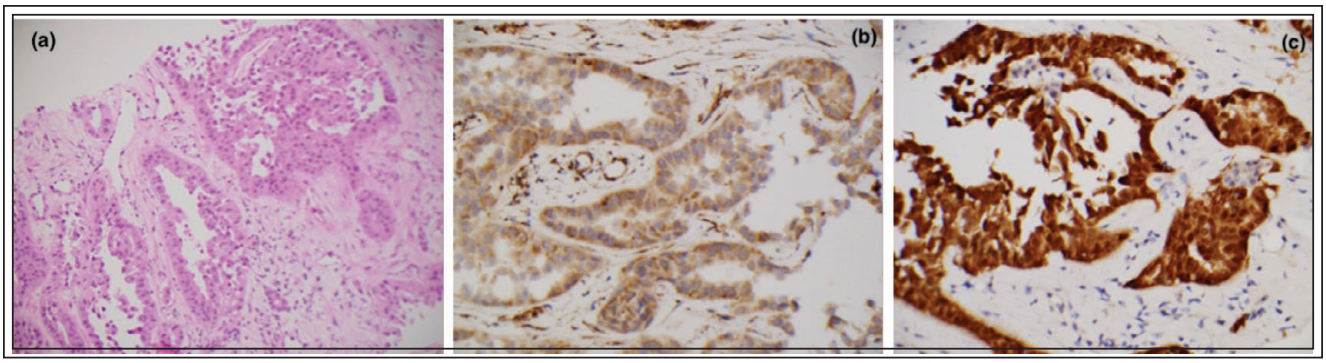

Figure 1. Liver biopsy case 1. **(a)** FH-deficient RCC showing papillary growth pattern. **(b)** On IHC neoplastic cells demonstrate FH- negative staining. **(c)** 2SC shows diffuse strong staining in the neoplastic cells.

lymphadenopathy, a left adrenal gland metastasis, T12 and L2 bone metastases, small pulmonary metastases, and multiple hepatic metastases. The CT scan also reported a bulky uterus with fibroids. Her serum calcium, albumin, hemoglobin, and renal function were normal. Liver biochemistry was deranged with alkaline phosphatase 258 U/L (20-105), gamma-glutamyl transferase 663 U/L (5-35), alanine aminotransferase 123 U/L (5-30), bilirubin normal. Serum lactate dehydrogenase (LDH) was elevated at 820U/L (120-250). A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan confirmed an FDG avid diffusely enlarged left renal mass with multiple sites of FDG avid nodal activity including retroperitoneal and intrathoracic nodes, and extensive metastatic disease in left adrenal, liver, and multiple bony sites, but no uptake within the uterus or lower urinary tract.

An ultrasound guided biopsy of a liver lesion revealed features metastatic carcinoma, favoring renal cell origin based on paired box gene 8 (PAX8) expression. The morphology was in keeping with FHdef RCC with prominent nucleoli and variable architecture with papillary growth and areas of solid and cribriform pattern. IHC for FH showed weak nonspecific expression and the 2SC immunostaining was positive. The patient was referred to a genetics counselor and germline testing confirmed a pathogenic mutation in the FH gene, confirming HLRCC, Figure 1.

Her past medical history was significant only for pre-eclampsia during her first pregnancy requiring caesarean section complicated by intraoperative bleeding and at the time she was noted to have a multi-fibroid uterus. She has a paternal uncle with colorectal cancer and a maternal uncle with metastatic cancer of unknown primary site. Her mother and sister also have uterine fibroids.

The patient commenced Ipi/Nivo induction therapy in March 2022. She tolerated the treatment well, with

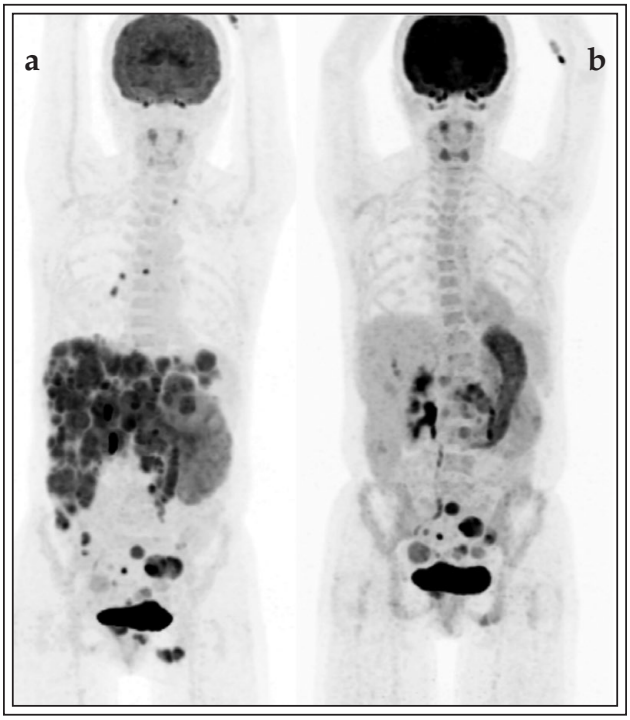

Figure 2. FDG-PET for case 1 at initial diagnosis and 6 weeks later after 2 cycles of Ipi/Nivo. Initial diagnosis **(a)** showing diffuse involvement of the left kidney and adrenal with FDG avid tumor and extensive FDG avid left renal vein involvement. There are retroperitoneal, intrathoracic and left supraclavicular nodal metastases, extensive hepatic metastases and several skeletal metastases. Follow up scan 6 weeks later post 2 cycles of induction combination immunotherapy **(b)** showed considerable improvement in the disease. Residual pelvic activity is considered likely related to fibroids.

fatigue and grade 1 pruritus being the only side effects. Her liver biochemistry improved and LDH normalized. A FDG PET scan after two cycles of induction Ipi/Nivo showed a substantial reduction, Figure 2, in uptake in previously avid lesions in the left kidney, liver, left adrenal gland and lymph nodes. She completed the four cycles of induction immunotherapy and commenced maintenance nivolumab monthly. She regained her lost weight and her performance status returned to premorbid level. A follow up FDG PET scan, Figure 2, in May 2022 reported all previously demonstrated metastatic lesions showed marked reduction in metabolic activity; the primary renal tumor had markedly reduced in size with no significant ongoing metabolic activity. A CT scan also showed a partial response and the patient continues with maintenance nivolumab without adverse effect.

Case 2

A 50-year-old otherwise well male presented with a 12-month history of intermittent fevers, renal colic, shortness of breath, cough, chest and back pain in late 2018. He was not on any regular medications and there was no family history of malignancy. A CT scan revealed a left cystic renal mass, left hydronephrosis, retroperitoneal and mediastinal lymphadenopathy and a lytic scapula metastasis. No bony metastases were discovered on whole body bone scan (WBBS); noting that purely lytic bone lesions are often not well visualized on WBBS. Ureteroscopy and insertion of a left ureteric stent was performed in January 2019. Cytology from the ureteroscopy was negative.

Left nephrectomy confirmed papillary RCC and endobronchial ultrasound with nodal aspiration revealed an unclassified metastatic cancer within the enlarged mediastinal node. The patient was mildly anemic but calcium and other biochemistry tests were normal.

The patient initiated Ipi/Nivo on an access program in February 2019. Four induction cycles were completed without adverse effects in May 2019. Re-staging CT scan post the induction treatment confirmed a partial response with improvement in the bone metastases and lymph nodes, however, a new pelvic soft tissue mass was evident. Concurrently, the patient reported left iliac fossa pain. The oligo-progressive metastatic disease was biopsied, and pathology confirmed reviewed in a multidisciplinary meeting was suggestive of FHdef RCC. The patient was referred to the Familial Cancer Centre and the diagnosis of HLRCC was confirmed on germline testing. He underwent radiotherapy 20 Gray (Gy) in 5 fractions to the area of oligo-progressive pelvic metastatic disease whilst continuing nivolumab maintenance therapy. In July 2019 CT imaging confirmed complete response.

The patient continues with maintenance monthly nivolumab 3 years after commencement of immune checkpoint inhibitors with the most recent imaging in April 2022 continuing to show complete response.

Case 3

A 27-year-old male nursing student with a known heterozygous FH germline mutation and HLRCC presented with left flank pain and multiple metastasis detected by FDG-PET scan in June 2020. He is a non-smoker and does not consume alcohol. His only relevant history was a laparoscopic partial left nephrectomy for a papillary renal cell carcinoma in September 2019. He developed further disease within the left kidney and surgical port site recurrence in February 2020 requiring completion nephrectomy and resection of the port site recurrence. In May 2020, FDG-PET scan revealed multiple sites of metastatic disease and he developed significant pain related to abdominal wall metastases. Two symptomatic subcutaneous metastases were resected.

The patient commenced Ipi/Nivo in June 2020. Following two cycles a CT scan demonstrated new metastases inferior to his spleen and in the nearby left posterior deep intramuscular soft tissue of his erector spinae. He went on to receive radiotherapy, 36Gy in 12 fractions to this area and then completed the four cycles of Ipi/Nivo. Following radiotherapy, he had 10 months of disease control on maintenance nivolumab until he developed progressive disease in April 2021 with a new soft tissue mass in his pelvis and a left upper quadrant peritoneal metastasis.

He was transitioned to second line treatment with erlotinib and bevacizumab combination. The patient experienced the typical rash anticipated from the use of erlotinib which was treated effectively with minocycline and a topical corticosteroid cream. A CT scan performed after four treatment cycles revealed that the patient had an excellent response to the second line treatment and the most recent imaging in May 2022 confirmed ongoing complete response to this therapy.

Discussion

There is limited evidence available for the treatment of FHdef RCC despite key trials establishing the role of Ipi/Nivo and anti-angiogenic treatments in ccRCC. Trials in nccRCC include a heterogenous group of

diseases, with small numbers of FHdef RCC included in some of these trials. Evidence specific to FHdef RCC treatment is limited to one phase II study as well as a handful of retrospective analyses and case reports.

Retrospective analyses in management of FHdef RCC have only small patient numbers but report better response rates to anti-angiogenic treatments compared with single agent or doublet checkpoint inhibitors.[2,3] A French retrospective review reported on 21 patients with FHdef RCC across all lines of therapy. All but one patient received one line of anti-angiogenic treatment. The median time to treatment failure with cabozantinib, sunitinib and combination bevacizumab and erlotinib was 14, 11.6 and 5.6 months respectively, compared to 2.7 months with immune checkpoint inhibitors used as monotherapy or in combination. Only four patients received first line Ipi/Nivo with an objective response in only one patient.[3]

Another retrospective analysis of 26 patients with FHdef RCC reported higher objective response rates (ORR) and disease control rates with combinations of mechanistic target of rapamycin (mTOR) inhibitors and anti-angiogenic agents compared to immune checkpoint inhibitors. Only eight patients received checkpoint inhibitors, with two receiving Ipi/Nivo in the first line setting, four receiving nivolumab in the second or third line and two patients receiving atezolizumab. Of these eight patients, three achieved stable disease and five had progressive disease.[2]

A phase II study of bevacizumab and erlotinib combination recruited patients with HLRCC or sporadic papillary RCC. A third of patients recruited had at least one prior treatment. Of the 42 patients with HLRCC, the ORR was 64% and the median progression free survival (mPFS) was 21.1 months. Overall, the combination was well tolerated. Adverse effects of grade 3 or higher occurred in 47% but were primarily hypertension (34%) and proteinuria (13%) with one patient with a grade 5 gastrointestinal haemorrhage possibly related to bevacizumab.[5]

A Korean retrospective analysis of ten patients with HLRCC-associated RCC who received bevacizumab and erlotinib supported the use of this combination with an ORR of 50%, mPFS of 13.3 months and overall survival of 14.1 months.[6]

Available evidence for the use of immunotherapy in FHdef RCC includes a phase II trial of cabozantinib and nivolumab in nccRCC which included five patients with FH-def RCC all of whom obtained an objective response. Two previous case reports of FHdef RCC describe complete responses to combination Ipi/Nivo, one of which had HLRCC, the other without a detectable FH germline mutation.[7]

Alaghebandan et al found in an evaluation of 13 FHdef RCC cases that most tumors did not strongly express PD-1 or PDL-1. All tumors contained tumor infiltrating lymphocytes (TILs) although the majority demonstrated mild TILs intensity and none or rare isolated lymphoid aggregates. TILs were mostly PD-1 and PDL-1 negative or weakly positive.[8] This may in part explain why single-agent immune checkpoint inhibition is ineffective. However, Ipi/Nivo recruits T-cells into tumours and induces T-cell responses.[9] Our three cases add to the evidence that at least some patients with FHdef RCC have excellent responses to dual checkpoint inhibition. The complete explanation as to why some cases respond whilst others do not is likely to be much more complicated, however clearly more studies are required to further define the role of combination immune checkpoint inhibition in the treatment of FHdef RCC. □

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