



CASE REPORT

Pathologic Complete Response After Preoperative Ipilimumab and Nivolumab in an HLRCC Patient with Stage III Renal Cell Carcinoma

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Abstract

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a rare, aggressive hereditary cancer syndrome caused by germline mutations in the *fumarate hydratase (FH)* gene. Affected patients typically present with renal cell carcinoma (RCC) at a young age and often experience rapidly progressive disease and poor outcomes. Mean survival is significantly shorter for stages III and IV than for stages I and II (15.8 vs 80.7 months), underscoring the need for more effective therapeutic strategies. Here, we report an HLRCC patient with stage III RCC who achieved a pathologic complete response following one cycle of dual immune checkpoint blockade with nivolumab and ipilimumab and remains disease-free 15 months later. This case extends findings from previous reports and suggests that dual checkpoint blockade may result in clinically meaningful activity in a subset of patients.

Keywords: HLRCC; fumarate hydratase-deficient RCC; Immunotherapy; Germline; Kidney

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Introduction

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) (OMIM #150800) is a rare syndrome with an autosomal dominant pattern of inheritance, characterized by cutaneous and uterine leiomyomas and an aggressive form of renal cell carcinoma (RCC) with papillary or collecting

duct-like morphology (1–4). It is caused by germline mutations in the *fumarate hydratase (FH)* gene, a two-hit tumor suppressor gene located on chromosome 1q42.3–q43 (2–5). These patients are predisposed to other tumors such as pheochromocytoma and paraganglioma, and more recently, the disease was renamed FH Tumor Predisposition Syndrome (6).

The *FH* gene encodes fumarate hydratase, an enzyme that catalyzes the conversion of fumarate to malate in the tricarboxylic acid (TCA) cycle (5). As a result, *FH*-deficient tumors have impaired oxidative phosphorylation and depend on aerobic glycolysis for survival and proliferation. Fumarate is also an oncometabolite that causes posttranslational cysteine residue modifications and succination, which can be detected by immunohistochemistry for S-(2-succino)cysteine (2SC) (7, 8). A key target is KEAP1, an enzyme implicated in redox homeostasis, which, when succinated, is inactivated, resulting in NRF2 stabilization and the induction of stress response genes (9).

HLRCC-associated RCC tends to occur at a young age, with a mean age of diagnosis around 40 years (range 11–90 years) (10). The lifetime risk of RCC in affected carriers is estimated at 10–20% (11–15). Even small primary tumors (<2 cm) have a propensity for early nodal and distant metastasis (16). The prognosis is poor, with fewer than 30% of patients surviving 5 years after diagnosis (17). Surveillance of at-risk family members is therefore critical for early detection (8, 16).

Histologically, tumors show a papillary to tubulocystic architecture. Tumor cells exhibit an eosinophilic cytoplasm with large viral inclusion-like nucleoli with perinucleolar halos. However, the morphologic spectrum is broad, requiring immunohistochemistry for *FH* and 2SC for definitive diagnosis (18, 19). In the 2016 WHO classification of renal tumors, HLRCC-associated RCC was recognized as a distinct entity, and in the 2022 update, it was incorporated under the broader category of *FH*-deficient RCC, which includes sporadic cases with biallelic somatic *FH* mutations without family history (16).

Therapeutic advances for HLRCC have been limited. While *FH* inactivation interrupts the TCA cycle, resulting in increased reliance on glycolysis for cell survival and proliferation, glycolysis inhibition failed to show significant activity in an earlier report (20). Conventional therapies for clear cell RCC (ccRCC), the most common RCC subtype, have also shown limited benefit. Tyrosine kinase inhibitors (TKIs) such as pazopanib and cabozantinib have shown modest activity in case reports, but no FDA-approved therapy exists specifically for *FH*-deficient RCC. A recent multicenter Phase II trial showed that bevacizumab plus erlotinib achieves an objective response rate of 72%, with a response duration of 19.3 months (95% CI, 12.9–35.9), but complete responses were observed in only two patients (~5%) (21, 22). Immune checkpoint inhibitors (ICIs), in particular, the combination of nivolumab plus ipilimumab, have resulted in overall survival rates for metastatic ccRCC of ~50% at 5 years, with up to 25% of patients with long-term survival. However, their role in the context of HLRCC is limited. Although prospective data are lacking, *FH*-deficient RCC frequently demonstrates PD-L1 expression and an inflamed tumor

microenvironment (23–25). Clinically, responses have been reported with nivolumab plus ipilimumab (26) and with pembrolizumab monotherapy (27). Gao et al. reviewed published HLRCC cases treated with immunotherapy and concluded that benefit may occur across different *FH* germline variants (28), while Howells et al. described three patients with metastatic *FH*-deficient RCC, that responded to nivolumab plus ipilimumab (29). Together, these observations suggest that a subset of *FH*-deficient RCC may be sensitive to immune checkpoint blockade.

Herein, we describe a patient with HLRCC-associated RCC who developed regional nodal metastases while undergoing surveillance and received perioperative therapy with nivolumab plus ipilimumab, with no evidence of disease 15 months later. This case adds to the limited literature, raising the possibility that a subset of patients may derive substantial benefit from checkpoint blockade.

Case Report

A 40-year-old White male with a family history of HLRCC presented for genetic counseling and surveillance to the UTSW Kidney Cancer Program. His mother had been diagnosed with papillary RCC at the age of 67 and died within a year. His twin brother (diagnosed at age 39) and older brother (diagnosed at age 43) were also recently diagnosed with papillary RCC with molecularly confirmed diagnosis of HLRCC (Figure 1). On physical examination, he had multiple cutaneous leiomyomas. Germline testing confirmed a pathogenic *FH* mutation (c.698G>A [p.Arg233His]). In addition, a variant of uncertain significance in *DICER1* (c.3416-3418delGAA [p.Arg1139del]) was also found.

Baseline abdominal MRI showed bilateral, small cortical renal cysts without solid masses. He was followed with annual MRIs for 3 years until a 9 mm hypoenhancing lesion was detected in the left lower pole (Figure 2A). Initially managed with surveillance at 6-month intervals, the lesion remained stable for 2 years (Figure 2B). However, 6 months later, an MRI revealed a new area of restricted diffusion next to the nodule in the adjacent parenchyma and a left periaortic lymph node conglomerate (Figure 2C). Core biopsy of a lymph node confirmed the diagnosis of metastatic HLRCC-associated RCC.

Given the aggressive biology of HLRCC-associated RCC and the newly detected regional nodal metastasis, the patient was given one cycle of nivolumab and ipilimumab prior to nephrectomy. The patient underwent a left radical nephrectomy with regional lymph node dissection. Gross examination revealed a small, well-circumscribed tan lesion in the lower pole measuring 0.6 × 0.4 × 0.4 cm (Figure 2D). In addition, a 4.0 × 2.5 × 1.7 cm conglomerate of hilar lymph nodes was provided along with additional interaortocaval and periaortic lymph nodes.

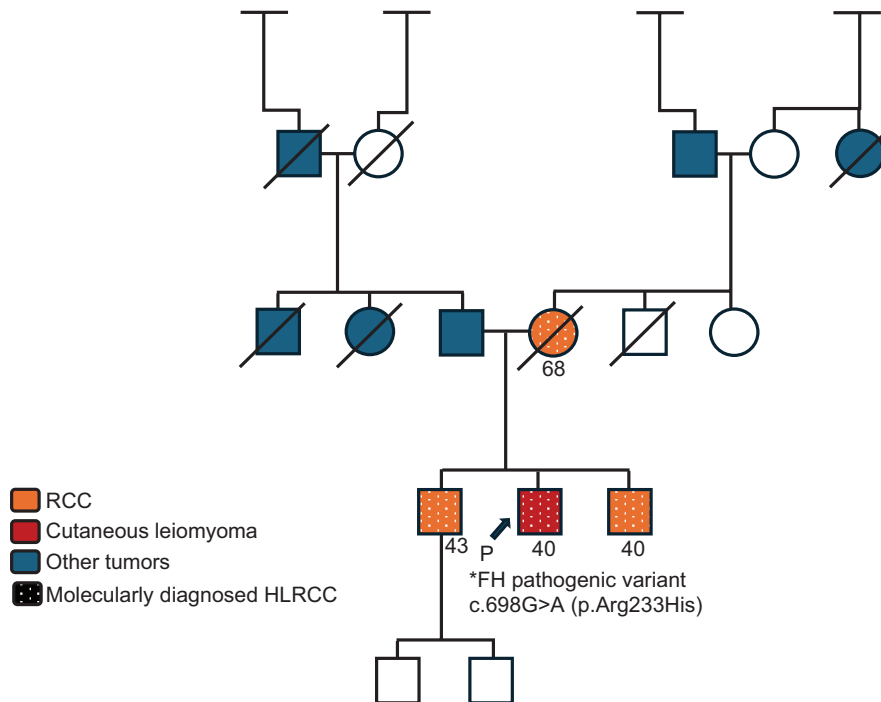


Figure 1: Family pedigree and genomic findings. Pedigree chart showing the proband (arrow) with a pathogenic *FH* germline mutation and affected family members, including his mother and two brothers with HLRCC-associated RCC.

Microscopically, the entirely submitted tumor bed showed only fibrous scar tissue and chronic inflammation without viable carcinoma, consistent with a pathologic complete response (CR) (Figure 3). Seven lymph nodes (three hilar and four interaortocaval) also showed similar treatment-related changes with fibrosis, biopsy-site effect, and granulomatous inflammation, but no apparent residual tumor (Figure 3).

The pretreatment biopsy from the left periaortic lymph node was concurrently reviewed and showed a PAX8-positive papillary RCC with morphologic features compatible with HLRCC, including multilayered neoplastic cells, eosinophilic cytoplasm, and characteristic viral inclusion-like nucleoli with perinucleolar halos (Figures 3A and 3B). Immunohistochemistry showed loss of FH in tumor cells with preserved staining in stromal and inflammatory elements (Figure 4). Given the remarkable response, PD-L1 IHC was performed (22C3 clone, Dako). This revealed strong membranous PD-L1 reactivity in >70% of tumor cells and ~5% of immune cells (Figure 4C).

Given the pathological complete response and the generally poor outcomes of FH-deficient RCC with lymph node involvement, dual immunotherapy was resumed postoperatively. Following his surgery, he received an additional three

cycles of nivolumab and ipilimumab and subsequently 10 cycles of maintenance nivolumab. At 15 months since surgical resection, he remains without radiographic evidence of recurrence.

Discussion

HLRCC-associated RCC is one of the most aggressive forms of hereditary kidney cancer, with a median overall survival of 16–21 months (17, 25, 30, 31). As our case illustrates, even small primary tumors carry a high metastatic potential, underscoring the importance of vigilant surveillance and the urgent need for timely intervention.

To date, therapeutic options for unresectable FH-deficient RCC remain limited. Retrospective analyses and case reports have described responses to VEGFR TKIs such as pazopanib and cabozantinib, although the durability of response is modest (30, 32). More recently, a prospective Phase 2 study showed that bevacizumab plus erlotinib was associated with an objective response rate of 72%. However, complete responses were observed in only 5% of patients (2 out of 41 patients enrolled) (21). Based on these data, NCCN guidelines recommend bevacizumab plus erlotinib as the preferred

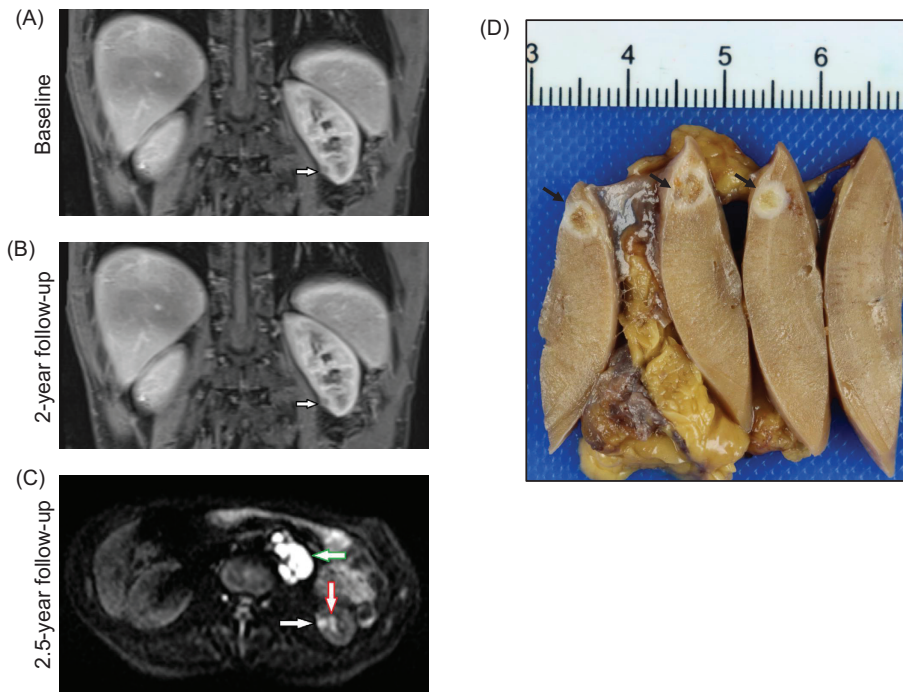


Figure 2: Radiological and macroscopic findings. (A) Coronal post-contrast T1 weighted MR image showing a 9 mm hypoenhancing lesion at the lower pole of the left kidney (white arrow). (B) Coronal post-contrast T1-weighted MR image at 2-year follow-up showing no significant change in size of the hypoenhancing lesion at the lower pole of the left kidney (white arrow). (C) Axial diffusion-weighted MR image at 2.5-years showing restricted diffusion in the same left lower pole lesion (white arrow) and new restricted diffusion (arrow outlined in red) as well as new retroperitoneal lymphadenopathy with restricted diffusion (arrow outlined in green). (D) Macroscopic examination of the left nephrectomy specimen revealed a well-circumscribed tan lesion with a thick fibrotic capsule, in the lower pole measuring $0.6 \times 0.4 \times 0.4$ cm.

regimen for patients with HLRCC-associated RCC (33). However, responses remain short-lived for many patients, highlighting the need for alternative strategies.

Immunotherapy, particularly the combination of nivolumab and ipilimumab, represents a therapeutic avenue with the potential for long-term benefit in a subset of patients with ccRCC. The rationale for using these drugs in HLRCC-associated RCC is supported by the frequent expression of PD-L1 in FH-deficient RCC. In a cohort of 13 cases, Alaghebandan et al. reported PD-L1 positivity in 69% of tumor cells (23), while Yu et al. found high PD-L1 expression in 63% of tumors ($n = 19$) (24). Somewhat surprisingly PD-L1 expression may be associated with better responses to TKI therapy (34). The combination of nivolumab and ipilimumab has demonstrated durable survival benefit in advanced ccRCC, as shown in the Phase III CheckMate 214 trial (35, 36), but its role in HLRCC remains largely unexplored (26–29).

A review of the literature identified a handful of Stage IV cases of HLRCC-associated RCC achieving durable

complete responses with ICIs. Iribe et al. described a patient with metastatic HLRCC who achieved a CR with nivolumab plus ipilimumab (26), and Wang et al. reported a CR with pembrolizumab monotherapy (27). Both tumors exhibited high PD-L1 expression by IHC.

Our case adds to the limited literature and is unique in the pathologic CR after only one cycle of induction immunotherapy in a patient with stage III disease. The optimal management of patients similar to ours is unclear. In clinical practice, most patients with stage III disease are managed surgically. Arguably, the role of surgery is accentuated for non-ccRCC, where systemic therapy has a less-established role. However, HLRCC patients with stage III RCC often develop metastatic disease. Thus, an argument can also be made to explore ICI while the primary tumor is in place, along with infiltrating immune cells. Because the patient had demonstrated substantial response (as shown by a pathologic CR) and tolerated treatment well, postoperative completion of induction combination immunotherapy followed by nivolumab maintenance was chosen.

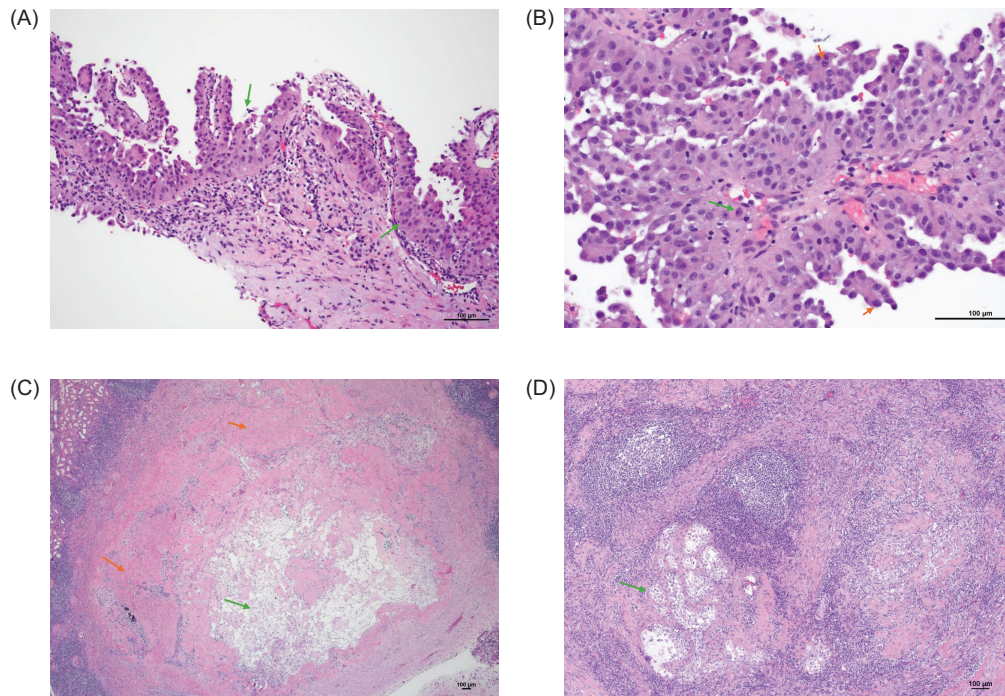


Figure 3: Microscopic features of HLRCC-associated RCC. (A) Core biopsy specimen showing a papillary renal tumor with multilayered neoplastic cells, abundant eosinophilic cytoplasm (green arrow), and prominent eosinophilic nucleoli with perinucleolar clearing (Hematoxylin and eosin (H&E), x100). (B) High-power magnification highlighting the characteristic viral inclusion-like nucleoli (green arrow) with perinucleolar halos (orange arrow) (H&E, x200). (C) Nephrectomy specimen demonstrating fibrosis (orange arrow) and chronic inflammation, including histiocytic reaction (green arrow), in the tumor bed without residual viable carcinoma, consistent with a pathologic complete response (H&E, x20). (D) Interaortocaval lymph node showing complete response with replacement by fibrosis and histiocytic reaction (green arrow) (H&E, x40).

This case also provides important translational insights. The pretreatment biopsy showed strong PD-L1 expression in >70% of tumor cells, consistent with reports that FH-deficient RCC frequently overexpress PD-L1 (23, 24, 34). The pathologic CR observed in the renal tumor bed and regional lymph nodes underscores the immunogenicity of these tumors and highlights the potential of checkpoint blockade to induce deep and durable remissions in this lethal disease.

Together with previous reports, our report raises the possibility that a subset of FH-deficient RCC may be responsive to ICI, in particular nivolumab and ipilimumab, and we speculate that these tumors may be enriched among those with PD-L1 expression.

Conclusion

We report a pathologic CR of a stage III HLRCC-associated RCC with regional nodal involvement after a single preoperative cycle of nivolumab plus ipilimumab. Together with prior case reports (26, 27), this case suggests that immune checkpoint blockade may induce deep and potentially durable responses in

a subset of patients with FH-deficient RCC. Whether PD-L1 expression enriches for benefit remains unknown and should be considered hypothesis-generating. However, one limitation is reporting bias and how often immunotherapy fails for these patients is unknown. Systematic multi-institutional evaluation of ICI for perioperative and metastatic FH-deficient RCC cases may help define the role of immunotherapy in this disease. While clinical trials in patient populations with rare subtypes are challenging, together with results in the literature, our data supports a more systematic evaluation of ipilimumab and nivolumab in patients with FH-deficient RCC, starting perhaps in the metastatic setting with concomitant evaluation of PD-L1 expression, which could be used as an enrollment criterion or stratification factor.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

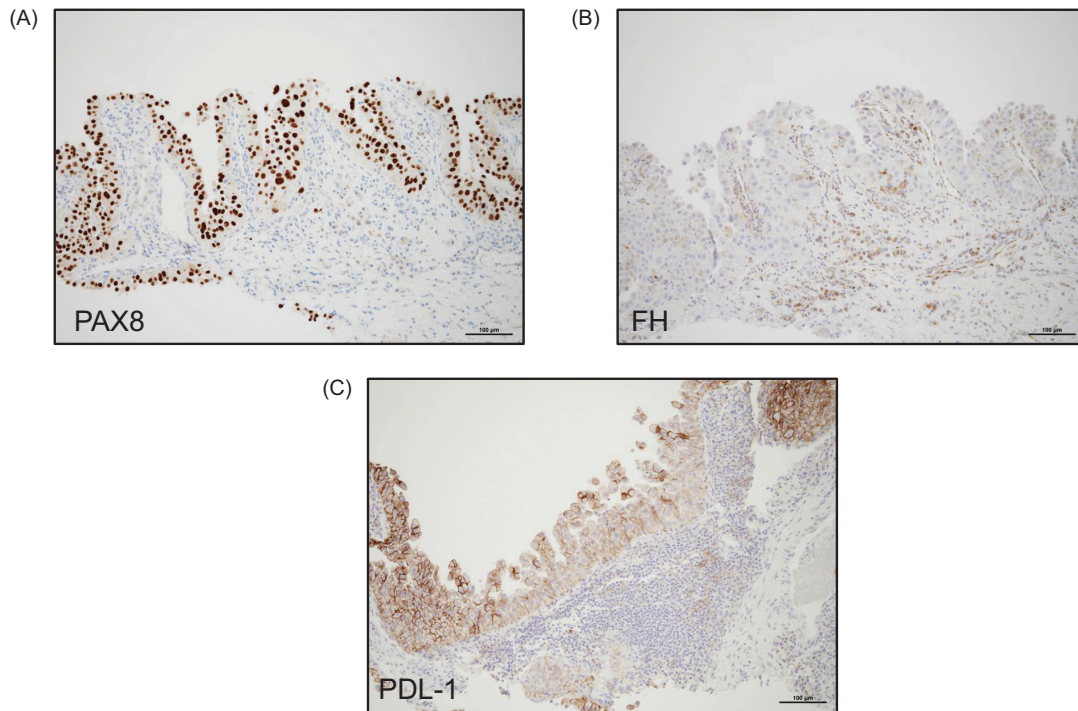


Figure 4: Immunohistochemical profile of HLRCC-associated RCC in core biopsy. (A) Tumor cells showing strong nuclear expression of PAX8, confirming renal epithelial origin (x100). (B) Loss of FH protein expression in tumor cells, with intact staining in surrounding stromal and inflammatory cells (internal positive control; x100). (C) Tumor cells with strong membranous PD-L1 expression in >70% of cells (22C3 antibody; x100).

Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

None

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