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Case Report

Fumarate Hydratase-deficient Renal Cell Carcinoma: A Case Report and Literature Review

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Abstract

Fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) is a rare but aggressive subtype of renal cancer associated with germline or somatic mutations of the *FH* gene. The histology demonstrates a broad range of morphologic patterns with loss of FH immunostaining. There is no standard therapy approved for FH-deficient RCC, and treatment is often extrapolated from other subtypes of RCC. With a better understanding of the molecular mechanism and pathogenesis, more studies including this population are ongoing. We reported a 33-year-old man with no relevant family history diagnosed with locally advanced FH-deficient RCC and who later developed distant metastasis. He received erlotinib-bevacizumab combination therapy and achieved a partial response. We also performed a literature review of FH-deficient RCC.

Keywords: Fumarate hydratase, fumarate hydratase-deficient renal cell carcinoma, renal cell carcinoma

Introduction

Fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) is a rare but clinically aggressive disease. This subtype of RCC is related to germline or somatic mutations of the *FH* gene, which encodes FH, an enzyme involved in the tricarboxylic acid (TCA) cycle. Germline *FH* gene alterations are associated with hereditary leiomyomatosis and RCC (HLRCC), which is characterized by renal tumors as well as uterine and cutaneous leiomyomas. Patients typically present at a younger age (median age: 38-43 years), and 19%-82% have metastatic disease at diagnosis.[1-3] The lifetime RCC risk for *FH* mutation carriers is estimated to be 15%,[4] with a 6.5-fold increased risk compared to the general population.[5] The prognosis of metastatic disease is poor, and prior studies have reported a median survival of around 18-22 months.[1,2] FH-deficient RCC demonstrates various morphologic features, and a papillary pattern is the most frequently found subtype. Immunohistochemically, these tumors show loss of FH expression and are positive for

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S-(2-succino)-cysteine (2SC) staining. There is currently no standard therapy for FH-deficient RCC, and treatment is often extrapolated from studies of clear-cell RCC. Recently, one phase II trial included this population and showed promising results of erlotinib-bevacizumab combination therapy.[6]

Here, we report a case of metastatic FH-deficient RCC treated with erlotinib plus bevacizumab. We also performed a literature review of this uncommon disease entity.

Case Report

A 33-year-old man presented to the urology clinic with a 4-month history of a painless mass over the left flank. Contrast-enhanced magnetic resonance imaging showed a huge retroperitoneal tumor with left psoas muscle and kidney involvement. A biopsy of the tumor revealed RCC. He had no family history of malignancy. No evidence of distant metastasis was detected on positron emission tomography-computed tomography (CT) and a bone scan. He underwent a left radical nephrectomy with partial resection of the psoas muscle. Pathology of the specimen revealed RCC with mixed papillary, tubular, and cystic patterns. The neoplastic cells demonstrated prominent nucleoli and eosinophilic cytoplasm. Immunohistochemically, the tumor cells were diffusely and strongly positive for AMACR, but negative for CK7. FH staining showed loss of expression in tumor cells [Figure 1a-d]. A diagnosis of FH-deficient RCC (pT4) was made. One year after the surgery, a left subphrenic tumor was found on imaging. He received tumor excision and the pathology suggested local recurrence of RCC. Next-generation sequencing of the tissue confirmed pathogenic alterations of the *FH* gene. Eight months later, recurrent tumors developed at the left retroperitoneum with bone and cervical lymph node metastasis. He received target therapy with erlotinib plus bevacizumab. Adverse events included grade 2 folliculitis and skin rash. At the 4-month follow-up CT scan, the tumor showed a partial response and he was still treated with this regimen.

Discussion

FH-deficient RCC can be associated with germline HLRCC syndrome or biallelic somatic *FH* loss. The 2016 WHO classification of tumors classified HLRCC syndrome-associated RCC as a distinct entity and did not include those with somatic *FH* mutations and the absence of characteristic syndromes of HLRCC.[7] Systematic analysis showed similar clinical characteristics, histological results, and responses to therapy in FH-deficient RCC either with a germline or somatic *FH* mutation.[1] The underlying molecular biology of FH-deficient RCC is still not well understood. The *FH* gene encodes a TCA cycle enzyme which catalyzes the formation of L-malate from fumarate. FH deficiency results in fumarate accumulation and stabilization of hypoxia-inducible factor-1alpha, which activates downstream effectors such as vascular endothelial growth factor (VEGF), erythropoietin, epidermal growth factor, transforming growth factor beta-3 (TGFβ-3), and glucose transporters, and subsequently induces angiogenesis, tumor growth, and metastasis. An increased fumarate level also induces a metabolic shift to aerobic glycolysis. In addition, fumarate accumulation increases oxidative stress and activates the nuclear factor E2-related factor 2 (Nrf2) signaling pathway.[8] Prior studies of the genomic profiling of FH-deficient RCC have revealed that *NF2* is the most commonly co-occurring somatic mutation, which may also affect Nrf2 transcription activity.[1]

Due to the rarity of this disease, FH-deficient RCC has generally been excluded from prospective trials. Currently, treatment is mostly extrapolated from studies of clear-cell RCC, such as anti-VEGF and multitargeted tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and immune checkpoint inhibitors (ICIs). However, FH-deficient RCC demonstrates different molecular mechanisms and therapy responses. The phase II AVATAR trial enrolled patients with advanced papillary RCC to receive erlotinib plus bevacizumab. This is currently the only trial to include a subgroup of patients with HLRCC. The HLRCC cohort showed a 64% overall response rate (ORR) and median progression-free survival (mPFS) of 21.1 months, compared with 37% and 8.7 months in the sporadic cohort.[6] A real-world data analysis of 10 HLRCC patients from Korea treated with this regimen showed a 50% ORR, mPFS of 13.3 months, and 14.1 months survival.[9] Based on the promising results, the National Comprehensive Cancer Network guidelines recommend this regimen for HLRCC-associated RCC.

A retrospective study reported 26 patients with metastatic FH-deficient RCC receiving systemic therapies, and a combination of mTOR/VEGF inhibitors showed the best response (ORR 44%), followed by VEGF monotherapy (ORR

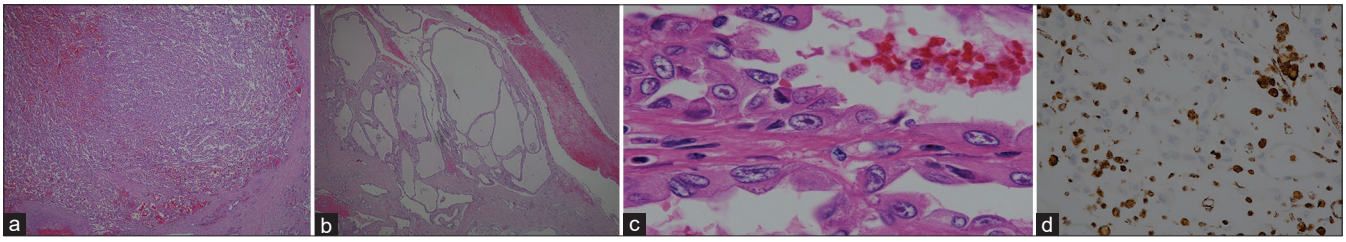

Figure 1: Histologic features of FH-deficient RCC arranged in (a) papillary pattern and (b) tubulocystic pattern (×40, H and E stain). The tumor cells showed eosinophilic cytoplasm, and macronucleoli (c, × 1000, H and E stain) with loss of FH expression (d, × 400, FH stain). The inflammatory cells represent internal controls, with preserved FH expression. FH-deficient RCC: Fumarate hydratase-deficient renal cell carcinoma

20%). No response was observed with mTOR inhibitors (ORR 0%) or ICIs (ORR 0%). Another European study of 21 patients showed a consistent response. Antiangiogenics showed stronger antitumor activity (ORR 49%) than ICIs (18%) and mTOR inhibitors (0%). Furthermore, an ORR of 50% was observed in the subgroup receiving cabozantinib, suggesting that it may be a potential therapeutic agent.[10] The treatment response to ICIs seemed to be poor in retrospective studies, but the sample sizes have been small. Although FH-deficient RCC has a lower mutation count compared to clear-cell RCC, it also has a higher fraction of genome alteration.[1] The role of immunotherapy still requires further investigation.

Excessive fumarate suppresses the homologous recombination DNA repair pathways, making FH-deficient tumor cells susceptible to poly (ADP-ribose) polymerase (PARP) inhibitors.[10] a response to PARP inhibitors has been shown in preclinical studies, however, more evidence is required to translate into clinical practice. Clinical trials with PARP inhibitors in HLRCC-associated RCC are ongoing.

In conclusion, clinicians should be aware of this distinct type of RCC. Further studies are required to guide the choice of treatment and identify potential novel therapies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest

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