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Case Report

An atypical case of Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)-associated renal cell carcinoma identified by next-generation sequencing

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ABSTRACT

Germline mutations in the *fumarate hydratase* (*FH*) gene classically lead to Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome. Patients with HLRCC typically exhibit multiple cutaneous and uterine leiomyomas at a young age. They also display a 20–30% lifetime risk for renal carcinomas, which commonly present before 40 years of age, have a distinct papillary morphology, and an aggressive phenotype. However, the clinical presentation of HLRCC and the morphology of HLRCC-associated renal cell carcinomas (RCCs) can be variable and thereby evade diagnosis. Here, we present two cases of HLRCC-associated RCC to emphasize this point. The first case is typical of HLRCC, involving a 29-year-old man with multiple cutaneous leiomyomas and a renal tumor with characteristic papillary morphology. Next, we describe a 48-year-old man presenting with metastatic cancer of unknown primary origin and no skin findings. Interestingly, next-generation sequencing of his metastatic tumor identified two unique *FH* mutations. In both cases, *FH* mutations were confirmed as germline. These cases highlight the variable presentations of HLRCC-associated RCC and underscore the importance of screening tumors of unknown origin for *FH* mutations using next-generation sequencing.

1. Introduction

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome is an autosomal dominant genetic disease caused by mutations in the *fumarate hydratase* (*FH*) gene [1–3]. Patients with HLRCC develop cutaneous and uterine leiomyomas at a young age and display a 20–30% lifetime risk for renal cell carcinomas (RCCs) [4–6]. HLRCC-associated RCCs are reported to have a Type II papillary architecture, with large eosinophilic nucleoli and perinucleolar clearing [7,8]. They commonly present before the age of 40, often metastasize early, and exhibit an aggressive phenotype. However, the presentation of HLRCC and HLRCC-associated RCC can be highly variable with outlier cases being difficult to diagnose [8]. HLRCC patients may develop aggressive renal tumors with collecting duct, tubular, or papillary histology, or present with metastatic tumors of unknown primary origin. Next-generation sequencing (NGS) panels are increasingly utilized as a diagnostic tool in these situations and inclusion of *FH* on these panels can serve as an effective tool to screen for *FH* mutations and HLRCC. The results can help to direct patient treatment and also provide an opportunity to identify additional affected family members. In this report, we relate two cases from our pathology service to illustrate this point. One case constitutes a textbook presentation of this entity, whereas a second case represents an atypical presentation that only came to light after NGS.

2. Case report

Hematoxylin and eosin (H&E) sections were analyzed in each case. Briefly, immunohistochemistry (IHC) was performed on formalin-fixed paraffin-embedded (FFPE) tissue sections with anti-PSA (Cell Marque), anti-TTF1 (Ventana), anti-CK7 (Ventana), anti-GATA3 (Cell Marque), anti-p63 (Biocare), anti-Uroplakin II (Biocare), anti-Thyroglobulin (Ventana), anti-CK20 (Ventana), anti-Vimentin (Ventana), anti-high molecular weight keratin (Ventana), and anti-PAX8 (Ventana) antibodies. IHC was performed on an automated system (Ventana) and sections were counterstained with hematoxylin. The

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FoundationOne panel is manufactured by Foundation Medicine and the latest version targets the full coding regions of 315 genes plus select introns from 28 genes [9,10]. Our in-house *FH* panel covers all exons of *FH*, *EGFR*, and *POLE* and consists of multiplex PCR followed by next generation sequencing on a Personal Genome Machine (Thermo Fisher Scientific) as previously described [11]. Sanger sequencing was performed on an ABI 3500 XL sequencer. Genomic DNA for all in-house assays was extracted on a Maxwell 16 instrument (Promega) from unstained FFPE tissue sections.

2.1. Case 1

The patient was a 29-year-old Caucasian man with a recent medical history of urinary tract infection. He presented for a routine physical after moving to the area. He complained of lightheadedness and urinalysis revealed a mildly elevated creatinine (1.22 mg/dL). He also requested a referral to dermatology after noting soreness over a mole on his chest. A punch biopsy of the mole revealed a cutaneous leiomyoma with focal nuclear atypia which extended to the margins. A complete re-excision was performed. A follow-up urinalysis confirmed an elevated creatinine (1.39 mg/dL) and the patient was referred for ultrasound. Abdominal ultrasound revealed a mass in the left kidney. Follow-up MRI demonstrated a 3.0 cm interpolar exophytic mass with a dominant enhancing mural nodule. The patient underwent robot-assisted laparoscopic partial nephrectomy.

Grossly, the specimen was received as a fragment of kidney with attached adipose (4.0 × 2.5 × 1.7 cm, 8.9 g). Sectioning revealed a firm white mass (2.4 × 2.2 × 1.3 cm) that was limited to the kidney. Microscopically, the tumor exhibited a papillary architecture (Fig. 1a) with large irregular nuclei, prominent eosinophilic nucleoli, and perinucleolar halos (Fig. 1b–c). A diagnosis of papillary renal cell carcinoma was rendered. Noting the patient's relatively young age and recent diagnosis of cutaneous leiomyoma, the pathologist recommended genetic testing for suspected HLRCC. Genomic DNA was isolated from the patient's tumor and sequenced using an in-house NGS panel that included all exons of the *FH* gene. The findings revealed a single base-pair duplication in exon 2 of the *FH* gene (c.221dupC) and no additional pathologic mutations. Sanger sequencing of genomic DNA isolated from matched normal tissue revealed an identical mutation indicating germline origin.

2.2. Case 2

This patient was a 48-year-old African American man with a history of hypertension, depression, alcoholism, and pancreatitis. He also had a 25 pack-year smoking history. He presented to the emergency room with neck pain and facial numbness. On review of systems, he reported night sweats during the past 2 to 3 months concurrent with a 10-lb weight loss. MRI revealed a soft tissue mass surrounding the C7 and T1 vertebral bodies with areas of bony destruction. The mass was biopsied, revealing an infiltrative gland-forming carcinoma with high-grade nuclei (Fig. 2a–b). The carcinoma was strongly positive for the marker PAX8 (Fig. 2c), which stains tumors of renal, Müllerian, thyroid, and thymic origin. In contrast, it was mostly negative for the breast and urothelial marker GATA3 (Fig. 2d), and completely negative for the prostate marker PSA, lung and thyroid marker TTF1, and Type II keratin marker CK7 (Fig. 2e–g). A diagnosis of metastatic adenocarcinoma (favor high-grade collecting duct carcinoma of the kidney) was rendered. The mass was later shown to be diffusely positive for vimentin, patchily positive for high molecular weight keratin, and completely negative for p63, Uroplakin II, CK20, and thyroglobulin, supporting the initial diagnosis. No primary tumor was identified despite extensive imaging performed at regular intervals over an 18-month period, which included a full-body CT scan, CT urography, multiple MRIs of the spine, and ten CT scans of the abdomen with IV contrast. Shortly after the initial diagnosis the patient's tumor tissue was sent to Foundation Medicine, which develops and performs NGS panels, where it was subjected to the FoundationOne panel. The results revealed two mutations in the *FH* gene, including a single base pair duplication in exon 2 (c.239dupT) that was predicted to be germline and a single base pair deletion in exon 4 (c.450delA) that was predicted to be somatic. No additional pathologic mutations were identified. We confirmed these *FH* mutations using an in-house NGS assay that covered all exons of *FH*. We then performed Sanger sequencing of genomic DNA isolated from a peripheral blood sample which identified the exon 2 duplication (c.239dupT) as a germline mutation, while the exon 4 deletion was not detected indicating it was acquired.

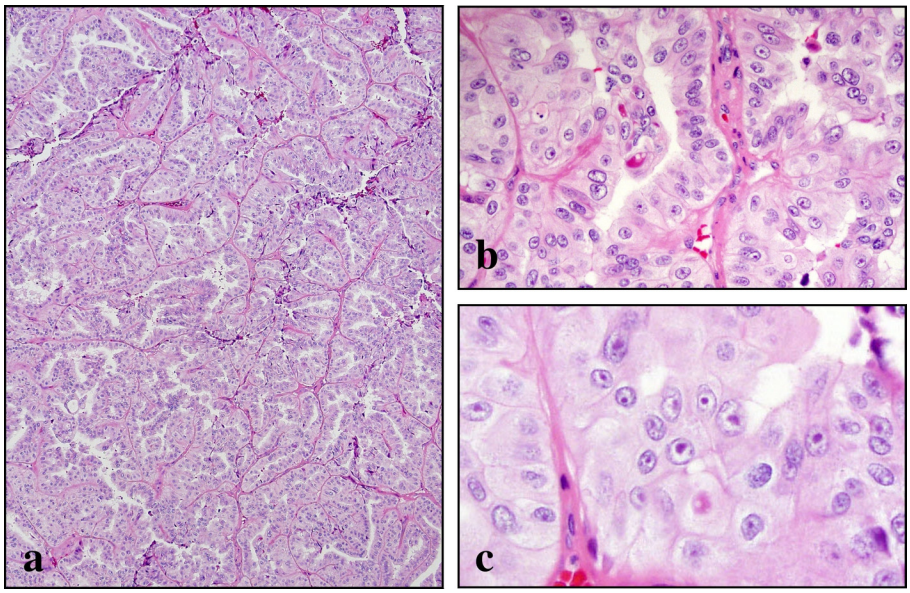

Fig. 1. Representative sections from the renal tumor in Case 1. (a) Low power view showing papillary architecture. (b–c) Higher power images demonstrating eosinophilic nuclei and perinucleolar clearing. All images are H & E. (a): 100×; (b): 400×; (c) 600×.