

Hereditary leiomyomatosis and renal cell carcinoma: Case report and review of the literature

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Abstract

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a rare genetic disorder in which the affected individuals tend to develop cutaneous leiomyomas, uterine leiomyomas, and renal cell cancer (RCC). Within the spectrum of this syndromic disease, RCC is the most severe manifestation, occurring at a younger age compared to the sporadic form. Pathological suspicion or diagnosis of HLRCC is critical for appropriate clinical management and genetic counseling of the affected family members. In this study, we report the case of a 27-year-old misdiagnosed carrier of HLRCC phenotype, who presented with a large solitary Type II papillary RCC.

Keywords: Fumarate hydratase, hereditary cancer syndromes, leiomyomatosis, papillary renal cell carcinoma

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INTRODUCTION

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal-dominant syndrome in which the affected individuals tend to develop cutaneous leiomyomas, uterine leiomyomas, and renal cell carcinoma (RCC). This syndrome is rare and is caused by heterozygous mutations in the fumarate hydratase (FH) gene, a Krebs cycle enzyme.^[1]

RCC, the most aggressive manifestation of the disease, occurs in about 10%–16% of patients and is frequently classified as Type II papillary RCC. Since it can present at a young age and is usually more aggressive than the sporadic form, close cancer surveillance is recommended in carriers of HLRCC.

Here, we describe the case of a young adult with RCC as the first clinical manifestation of HLRCC.

CASE REPORT

We describe the case of a 27-year-old African woman who presented to the emergency room with a 2-week history of right-sided flank pain and sporadic hematuria. Her medical history also revealed complaints of long-standing menorrhagia and dysmenorrhea. The patient had no history of trauma, surgery, or childbearing. Routine laboratory testing was unremarkable.

An ultrasound was performed to assess the renal tract, which revealed a large heterogeneous solid mass in the right kidney [Figure 1].

Additional evaluation with contrast-enhanced abdominopelvic computed tomography (CT) confirmed a heterogeneously enhancing solid tumor of 7 cm in diameter at the upper pole of the right kidney, with small intratumoral hypodense areas due to necrosis/cystic

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degeneration [Figure 2]. No calcification or fat tissue was observed within the lesion. There were neither signs of tumor extension into the renal vein nor invasion of the adrenal gland.

The patient had no evidence of nodal or distant metastasis.

Additional CT findings of uterine leiomyomas were found. The uterus was largely replaced by multiple varying size and well-demarcated leiomyomas, mostly subserosal and intramural [Figure 3].

The patient underwent open retroperitoneal radical nephrectomy, without intra- or post-operative complications. Pathology of the specimen revealed a papillary renal cell carcinoma, Type II, with negative surgical margins (pT2a).

Taken into account the histological type of carcinoma and the patient's age, the hypothesis of HLRCC was considered and further genetic analysis was performed. Genetic testing was not conclusive for mutations in the FH gene in this patient.

Since the most common manifestation of HLRCC is cutaneous leiomyomas, the patient underwent a thorough dermatological examination later on, which revealed a few small, painless, skin-colored nodular lesions distributed mainly on the trunk, compatible with cutaneous leiomyomas.

The patient was referred to a gynecologist for evaluation of the uterine leiomyomas. A few months after the nephrectomy, an open myomectomy was performed to remove two large subserosal leiomyomas.

The patient remains asymptomatic, with no evidence of cancer recurrence at 1-year follow-up.

DISCUSSION

First described by Launonen *et al.* in 2001,^[2] HLRCC is an autosomal-dominant inherited renal cancer syndrome in which the affected individuals are at risk for the development of cutaneous leiomyomas, symptomatic early-onset uterine leiomyomas, and an aggressive form of type II papillary kidney cancer.

It is caused by heterozygous mutations in the FH gene that encodes an enzyme involved in the Krebs cycle, which catalyzes the conversion of fumarate to malate.^[3] Germline mutations in the FH gene are diagnostic for HLRCC, therefore genetic testing should be offered to any individual who presents with clinical manifestations of HLRCC or has a family history of HLRCC.^[3]

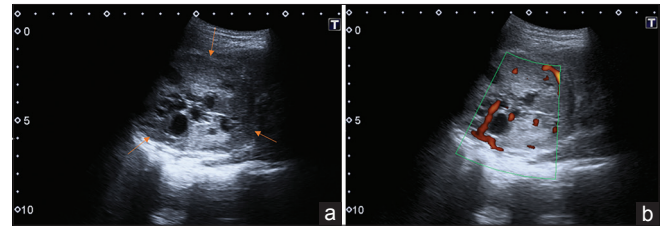


Figure 1: B-mode ultrasound image (a) depicting a large heterogeneous mass occupying the upper pole of the right kidney (arrows). Doppler US (b) detecting flow in the solid components in contrast to the small areas of cystic/necrotic degeneration within the mass

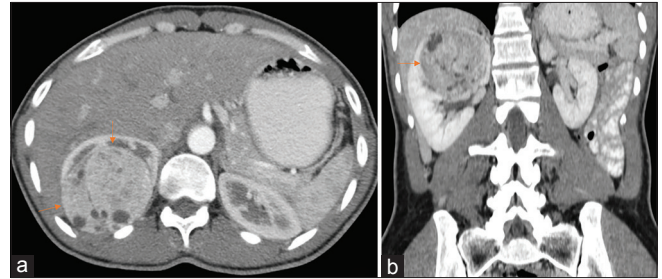


Figure 2: Axial (a) and coronal (b) postcontrast computed tomography images demonstrating a fairly well-defined solid tumor with heterogeneous enhancement in the right kidney (arrows). Neither signs of invasion of the hilum vessels nor hydronephrosis was observed



Figure 3: Axial (a and b) postcontrast computed tomography images of the pelvis showing an enlarged uterus with multiple large leiomyomas (arrows), predominantly in subserosal and intramural locations

The patient in this study did not reveal any mutation in the FH gene. The literature review shows some

families who are phenotypically characterized as being affected with HLRCC, but test negative for germline FH mutation, therefore detection rate is not currently 100%.^[3] Wei *et al.* have reported germline FH mutations in 52 of 56 families (93%) screened at the National Cancer Institute,^[4] while other researchers have identified FH mutations in 25 of 42 probands (60%).^[5] Those without identifiable FH mutations may have a novel mutation causing reduced fumarate enzyme activity.^[4]

When questioned about family oncologic history, the patient was not aware of further cases of RCC neither skin lesions. Medical records of her relatives were not available. When this genetic disorder is not found in either parent, it may represent a sporadic or mosaic case.^[1]

The most common manifestations of HLRCC are cutaneous leiomyomata, occurring in 76%–100% of patients.^[3] These cutaneous lesions generally present in the second to fourth decades and tend to increase in size and number with age.^[6] They appear as skin-colored to light brown dermal nodules, frequently involving the trunk, extremities, face, and neck.

A few nonsymptomatic cutaneous leiomyomas were identified in the trunk of our patient after careful dermatological examination. She was not able to precise the exact moment those lesions appeared.

Almost 85% of the affected women develop uterine leiomyomas with clinical onset at a younger age, more numerous and larger than women in the general population.^[6] Median age at diagnosis is about 30 years and up to 70% of HLRCC carriers underwent myomectomy or hysterectomy at or before the age of 40 years.^[6]

Our patient presented a very early diagnosis of large symptomatic uterine leiomyomas, which motivated open myomectomy by the age of 28 years, few months after the right nephrectomy.

Within the spectrum of this syndromic disease, RCC is the most severe manifestation, occurring in about

10%–16% of patients.^[6] HLRCC-associated RCCs are more aggressive and present at a younger age (median age of detection is 44 years) compared to the sporadic form.^[7] These tumors typically show an aggressive clinical course, even at a size <1 cm, and they are more frequently classified as Type II papillary renal cancer or collecting duct carcinoma.^[6] Although most of the cases present as high-stage disease, our patient did not show evidence of nodal or distant metastasis.

Specific screening guidelines do not exist and are often individual and treatment center dependent.^[7] Due to the potentially aggressive nature of renal cell carcinomas that develop as early as in childhood, most authors recommend close annual cancer surveillance in carriers of HLRCC.^[1]

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Conflicts of interest

There are no conflicts of interest.

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