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Concurrent renal-cell carcinoma and cutaneous leiomyomas: A case of HLRCC

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A 51-year-old Caucasian female presenting with renal-cell cancer and cutaneous leiomyomas was later diagnosed with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome. HLRCC is an autosomal dominant condition caused by a mutation in the fumarate hydratase gene, which encodes for an enzyme in the citric acid cycle. This syndrome has been reported in over 100 families throughout the world, the majority of whom are of Eastern European descent. Those with this syndrome have a significantly increased risk of developing renal-cell carcinoma, cutaneous leiomyomas, and uterine leiomyomas, and a smaller chance of developing uterine leiomyosarcomas. This syndrome has a relatively poor prognosis, with tumor metastasis occurring in approximately 50% of patients. However, more aggressive prophylactic measures and recent studies have shown potential to improve patient prognosis.

Case report

A 51-year-old Caucasian female initially presented to the emergency department in April 2010 with complaints of urinary retention. She had a past medical history significant for lupus, hypertension, stage III chronic renal failure, multiple painful skin lesions (Figs. 1, 2), and severe uterine fibroids requiring hysterectomy at age 23. Ultrasound (US) and noncontrast computed tomography (CT) evaluation showed a cortically based, partially exophytic mass, involving the lower pole of the right kidney, that demonstrated peripheral calcifications concerning for neoplasm (Fig. 3). A magnetic resonance imaging (MRI) scan performed one month later revealed two enhancing lesions in the right kidney that were concerning for neoplasm, one of which corresponded to the partially calcified lesion seen on CT.

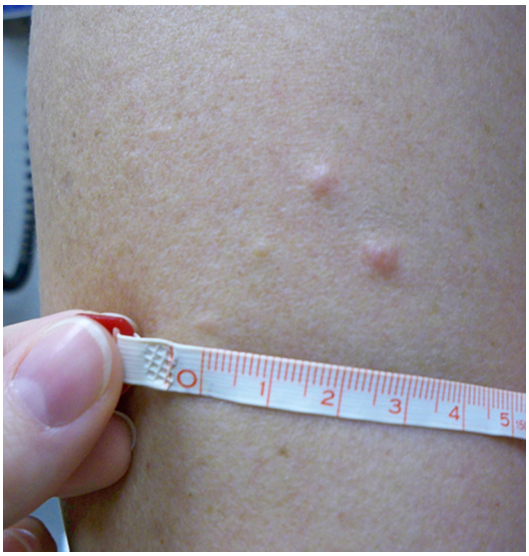

Figure 1. Two cutaneous leiomyomas visible on the patient's right arm.

The patient underwent partial nephrectomy for the right renal lesions in October 2010. Pathological exam revealed

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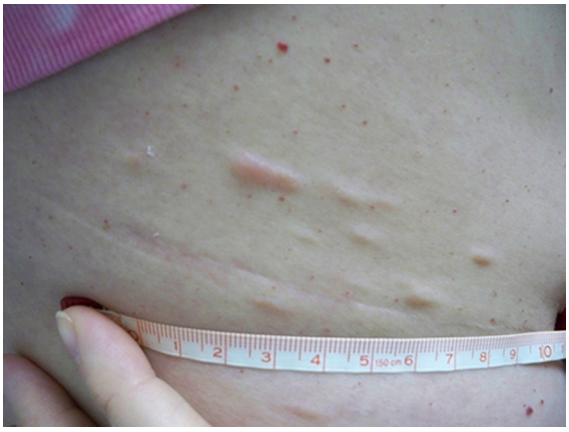

Figure 2. Multiple cutaneous leiomyomas of varying size and shape on the patient's right flank.

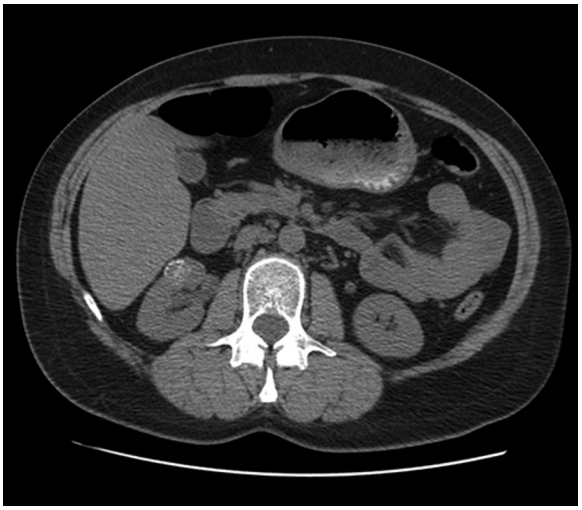

Figure 3. Right renal mass is present containing calcifications (CT without contrast, 2010).

two renal tumors, 2.2 and 1.0 cm in size. The larger showed a mixed solid and tubular histologic pattern (Fig. 4). Tumor cells were predominantly oncocytic, with abundant granular cytoplasm and Furhman grade 3 to 4 nuclei. Eosinophilic macronucleoli were present, but perinucleolar haloes were inconspicuous. The 1.0-cm tumor displayed morphologic features of type 2 papillary renal-cell carcinoma (Fig. 5). The surrounding renal tissue showed an additional 1-mm papillary lesion and a <1-mm focus of incipient papillary neoplasia (Fig. 6).

The patient had multiple followup MRIs of the kidneys in the following years. Although the surgical margins were microscopically positive on the 2.2 and 1.0 cm tumors, neither showed radiographic evidence of recurrence. A new, solid, enhancing left renal lesion was seen in October 2013, which was suspicious for neoplasm (Fig. 7). A positron emission tomography (PET) scan demonstrated this lesion to be fludeoxyglucose (FDG)-avid, with a standardized uptake value (SUV) of 4.9 (Fig. 8); it was new (as compared to the PET performed two years before). Around the same time, the patient's family doctor also identified a cutaneous leiomyoma, which was excised. Pathology showed minimal cytologic atypia and no mitotic activity but did show an infiltrative border, extending into subcutaneous fat (Fig. 9).

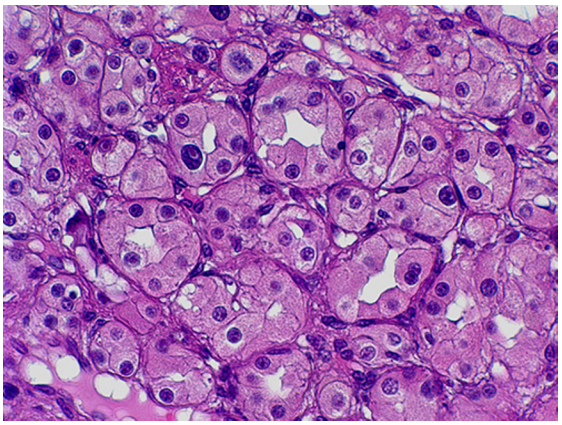

Figure 4. Renal tumor showing tubular pattern with oncocytic cells (H&E, 400x).

In January 2014, left partial nephrectomies were performed, yielding 4 renal tumors ranging in size from 0.6 to 1.6 cm. These showed papillary and cribriform features, with focal areas showing marked nuclear pleomorphism. Multiple smaller (<1 mm) papillary lesions were also identified in the surrounding renal tissue.

A cancer geneticist confirmed a clinical diagnosis of HLRCC Syndrome. Genetic testing for a germline mutation in the fumarate hydratase (FH) gene was positive. Physical findings supporting this diagnosis included the renal cancer, cutaneous leiomyoma, and history of uterine leiomyomas.

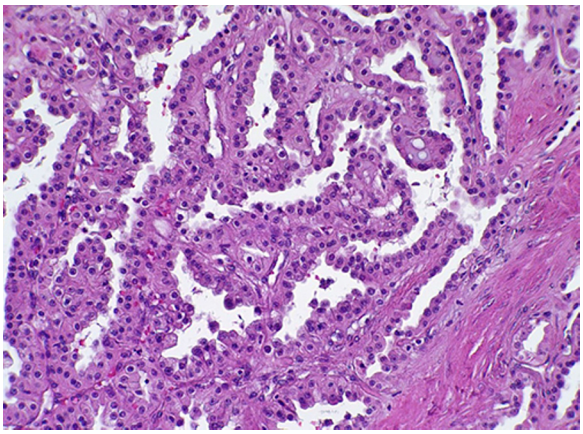

Figure 5. Smaller tumor showing papillary type II morphology (H&E, 400x)

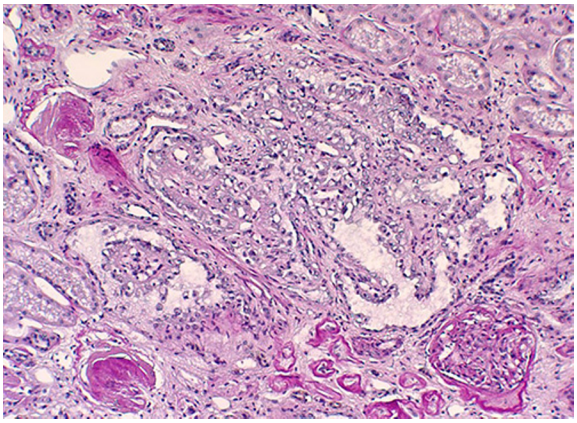

Figure 6. Renal tissue with incipient neoplasia (PAS, 400x).

Discussion

HLRCC is an autosomal dominant (AD) condition in which individuals are predisposed to benign leiomyomas of the skin and uterus. In addition, such individuals are at increased risk for aggressive, early-onset renal-cell carcinoma. The syndrome is caused by a germline mutation in the fumarate hydratase gene, which encodes for an enzyme in the citric acid cycle (1). At least 100 families have been identified worldwide with HLRCC, the majority being of Eastern European descent (2, 3). In a subset of families

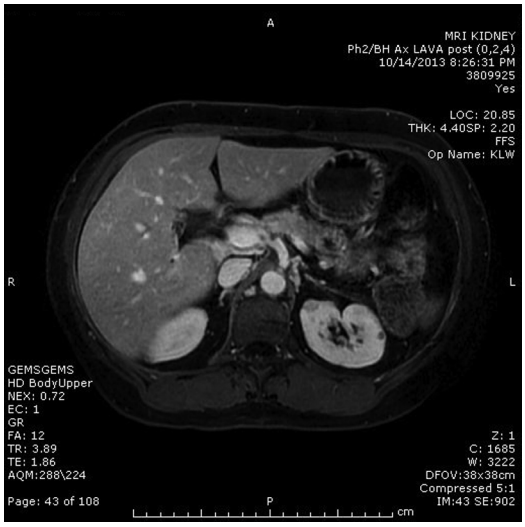

Figure 7. New mass in the superior pole of the left kidney demonstrates heterogeneous enhancement (fat-saturated T1 post contrast, 2013).

with the germline FH mutation, over 75% had cutaneous leiomyomas, more than 60% had renal-cell carcinoma, and all of the female carriers had uterine leiomyomas (3).

Patients may present with cutaneous leiomyomas, which are firm, tan to reddish-brown papules arising primarily from arrector pili muscles surrounding hair follicles. These lesions are often found on the trunk or extremities and can cause pain or paresthesias. Female patients normally develop numerous, large, symptomatic uterine leiomyomas, occurring at an earlier age than in the general population; these often require hysterectomy. In addition to uterine leiomyomas, several patients have also developed leiomyosarcomas (4).

Cutaneous leiomyomas are rare in the general population. Therefore, any patient who presents with these should

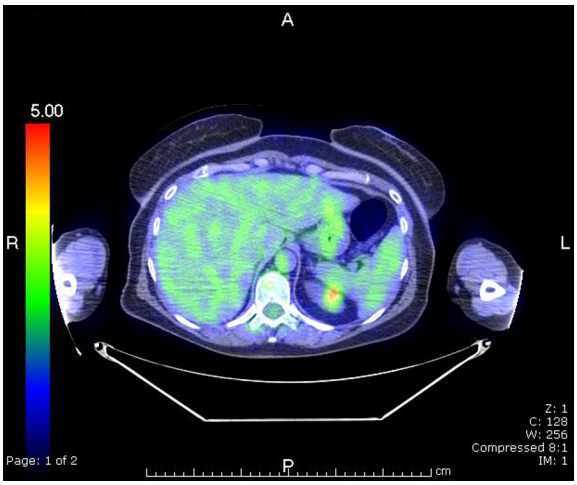

Figure 8. Mass in the superior pole of the left kidney demonstrates abnormally increased FDG uptake (FDG-PET, 2013).

undergo a thorough physical exam and history and be screened for renal tumors (3). Single cutaneous leiomyomas can be excised, but they commonly recur after removal. Cryotherapy and electrocoagulation may be considered with multiple lesions, but can cause extensive scarring (3, 4). Female patients with HLRCC should be evaluated for uterine disease. Myomectomy can be performed in patients with uterine leiomyomas. Nevertheless, most of the tumors are large and recurring, requiring hysterectomy. Any uterine leiomyosarcomas should be removed via hysterectomy (4). Patients with confirmed renal tumors and FH germline mutations should be managed with surgical strategies due to the aggressive nature of this renal cancer and the potential for early metastasis (1).

Renal tumors in HLRCC have been reported to occur relatively early in life and behave aggressively. They typically present as a solitary unilateral mass, with multiple or bilateral tumors occurring infrequently (4). HLRCC most commonly shows type II papillary renal-cell carcinoma histology, but tubulopapillary, solid, collecting-duct, and mixed types have been reported (1, 5). Merino et al. have described a series of 40 tumors in which the common histological feature was large, inclusion-like nucleoli with perinucleolar haloes (6).

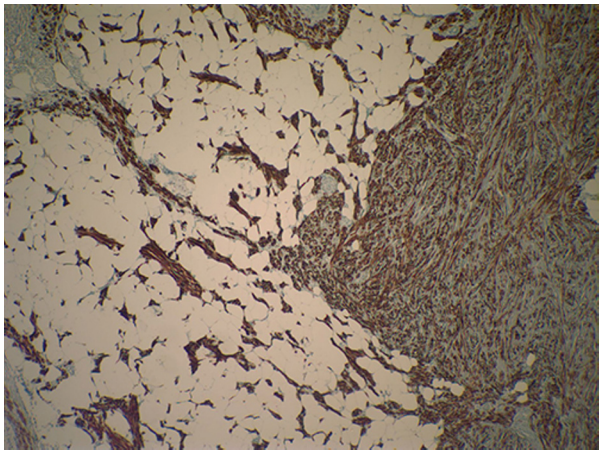

Figure 9. Cutaneous leiomyoma with infiltration of subcutaneous fat (Desmin, 100x).

The pathologic findings in our case are unusual in several respects. Multiple synchronous primary tumors were found in both kidneys, with incipient neoplasia in the surrounding renal tissue. The tumors showed a range of histologic patterns, including oncocytic, solid, tubular, cribriform, and papillary. Perinucleolar haloes were inconspicuous.

CT with and without contrast is the modality of choice for kidney screening, as papillary renal cancers are often isoechoic on US, making them difficult to distinguish from the surrounding parenchyma (1, 7). Renal tumors often enhance 20 HU or more with addition of contrast (1). However, noncontrast CT may pick up calcifications within the mass that would be obscured by contrast, as seen in this case (Fig. 3). In a subset of HLRCC patients, the average tumor size was around 8 cm, with some as large as 20 cm. These tumors often metastasize to retroperitoneal and mediastinal lymph nodes, bones, and liver (1).

Patients with HLRCC have a relatively poor prognosis, as the tumors are highly aggressive, metastasizing in approximately 50% of patients (1). In one study, the 5-year survival rate of patients with diagnosed renal-cell carcinoma was around 30%, with the cause of death attributed to metastatic disease (7). However, aggressive surgical treatment may significantly reduce the rate of metastasis (1). Recent studies have shown optimistic results after employing pharmaceutical and molecular techniques to reduce aerobic glycolysis in tumor cells (8, 9). Inhibition of lactate dehydrogenase-A in cells with an FH mutation significantly decreases tumor growth in a mouse model (8). The National Institute of Health (NIH) is currently performing a phase II study on the effect of bevacizumab and erlotinib on metastatic renal cancer in HLRCC (10). These therapies may be used as first-line treatment of HLRCC in the future.

In conclusion, HLRCC is a rare, AD condition that presents with cutaneous and uterine leiomyomas and renal-cell cancer. The degree of renal involvement determines the prognosis of the patient, as the renal cancers tend to be aggressive. CT is the preferred modality for kidney screening, as the tumors are isoechoic on US. Currently, this diagnosis carries a poor prognosis, but recent studies provide hope for better survival in the future.

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