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Melanoma and basal cell carcinoma in the hereditary leiomyomatosis and renal cell cancer syndrome. An expansion of the oncologic spectrum.

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Abstract

Background: Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is an autosomal dominant syndrome due to mutation in fumarate hydratase. Patients with HLRCC frequently develop cutaneous and uterine leiomyomata and are at risk for renal cell carcinoma. Rarely, other malignancies have been reported.

Main observations: We report the development of basal cell carcinoma and melanoma in two siblings with genetically-confirmed HLRCC.

Conclusions: It is unclear whether the development of melanoma and basal cell carcinoma in our patients is due directly to their mutations in the gene encoding fumarate hydratase, or genetic susceptibility at another unrelated locus, or whether these are incidental lesions. However this observation has implications for careful and routine skin surveillance in patients with HLRCC for lesions other than cutaneous leiomyomata. (*J Dermatol Case Rep*. 2016; 10(3): 53-55)

Introduction

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is an autosomal dominant tumor predisposition syndrome due to germline mutations in the fumarate hydratase (*FH*) gene. HLRCC is characterized by cutaneous and uterine leiomyomas in association with renal cell carcinoma (RCC). Most often type 2 papillary RCC develops at a young age with a propensity for early metastasis, thus warranting careful surveillance. We are the first to report the development of basal cell carcinoma and melanoma in two siblings with HLRCC. This observation has implications for careful visceral as well as cutaneous surveillance for all patients with HLRCC.

Case reports

A 67-year-old Caucasian female (*Patient 1*) presented to establish care given a history of basal cell carcinoma (BCC) on her nose two years prior. On routine examination she was found to have several small, firm, pink-to-skin-colored papules clustered on the right back (Fig. 1). Past medical history was significant for hypothyroidism and multiple uterine fibroids requiring hysterectomy at age 32. Family history was significant for a younger sister (*Patient 2*) and five paternal aunts with uterine fibroids requiring hysterectomy. Her father died at age 82 years of possible metastatic bladder cancer; one paternal aunt died of presumed cancer complications. Suspecting leiomyomas, a representative skin lesion

was biopsied. Histopathology revealed fascicles of smooth muscle interweaved in the dermis with scattered atypical nuclei (Fig. 2). Patient 1 was then referred for a genetics evaluation and for MRI of the chest, abdomen, and pelvis to evaluate for HLRCC.

Patient 1 referred her younger sister, *Patient 2*, for cutaneous examination. Patient 2 was a 63-year-old female with a history of hypothyroidism, uterine fibroids requiring hysterectomy at age 45 years, BCC of the nose, and melanoma *in situ* of the right leg diagnosed at age 44 years. On examination, Patient 2 was found to have several pink-to-skin-colored, firm papules clustered on the left upper back. A representative lesion was biopsied, also showing a leiomyoma with atypical features. Patient 2 was also referred to genetics and for MRI of the chest, abdomen, and pelvis. Patient 2 underwent genetic testing which revealed a heterozygous missense mutation, c.952C>T (H318Y), in the *FH* gene.

Both patients have maintained ongoing skin examinations. Patient 1 was subsequently found to have a melanoma *in situ* of the right shoulder. At the present time, six years after diagnosis, Patient 1 is followed by urology for a small, minimally complex cyst in the interpolar region of the left kidney and a 3.6 cm complex cyst in the lower pole. Patient 2 is followed for a stable 6 cm, minimally septate cyst in the left lower pole of the kidney and a small cyst in the right kidney.

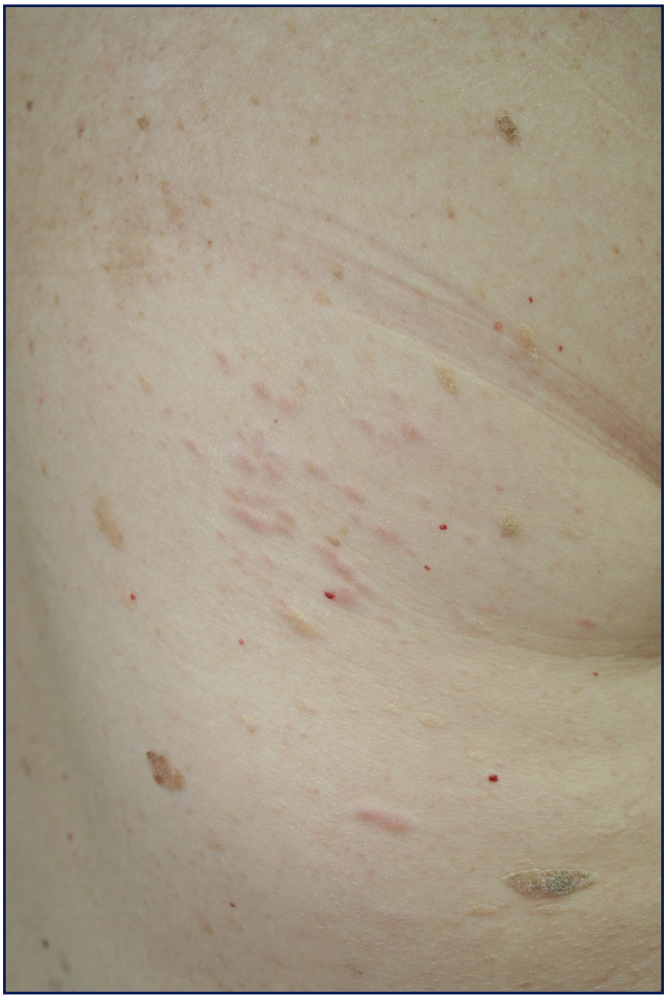

Figure 1

Multiple firm, slightly tender pink papules clustered on the back.

Discussion

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC), formerly known as Reed syndrome, is an autosomal dominant tumor predisposition syndrome characterized by cutaneous and uterine leiomyomas in association with renal cell carcinoma (RCC). HLRCC is due to germline mutations in fumarate hydratase (*FH*), an enzyme that catalyzes the conversion of fumarate to malate in the Kreb cycle.

Though rare, over 200 families worldwide have been reported to carry germline mutations in *FH*. A multitude of heterozygous, predominantly missense, mutations have been identified.[1] Homozygous mutations in *FH* are even more rare and result in fumarate hydratase deficiency, which presents with a different phenotype characterized by severe neonatal encephalopathy, poor feeding, failure to thrive, hypotonia, lethargy, seizures, and frequently, early death.[2]

Nearly all patients with HLRCC develop cutaneous leiomyomas by age 40; however; a novel missense mutation in *FH* was recently identified in a father and son with HLRCC who developed papillary type 2 RCCs in the absence of cutaneous leiomyomas.[3] Cutaneous leiomyomas can range from a few asymptomatic leiomyomas to hundreds of painful lesions. Histopathologic analysis has suggested that cutaneous leiomyomas associated with HLRCC present with a higher degree of nuclear atypia compared to sporadic leiomyomas.

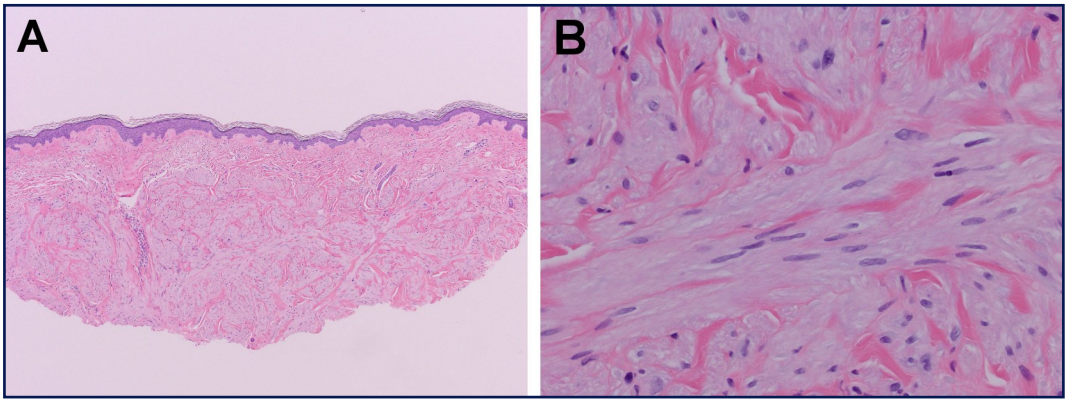

Figure 2

Fascicles of smooth muscle interwoven in the dermis. Some cells demonstrate scattered, atypical nuclei [hematoxylin and eosin, (A) 50X and (B) 400X].

In addition, they demonstrate negative or weakly positive immunostaining for fumarate hydratase.[4] Uterine leiomyomas develop in 80% of women with HLRCC, often with an early age of onset and severe symptoms. Rarely, uterine and cutaneous leiomyosarcomas have been reported.[5]

The overall lifetime risk of RCC is about 15%, with a mean age of 41 years at diagnosis (range 11 to 90 years).[6] Most often the renal tumors are unilateral and solitary, consisting of papillary type 2 RCC with a propensity for early metastasis. Collecting duct and clear cell carcinomas as well as oncocytic renal tumors and Wilms' tumor have also been reported. Primary management of patients with HLRCC is aimed at prevention of disease and death due to RCC. There is no consensus for screening; however, some suggest periodic renal imaging beginning at age 8. While neither of our patients, now 69 and 72 years of age, have been diagnosed with RCC, they both have complex renal cysts that are being carefully monitored and probably remain at risk for the development of renal malignancy.

It is interesting to note, that there are three previously reported families with the same His318Tyr missense mutation (previously designated as His275Tyr) identified in our siblings. The mutation is located in a semi-conserved residue in a functional domain of the encoded FH protein.[7] In a North American family, the mutation was associated with RCC as well as uterine fibroids.[8] In a large Tunisian Jewish pedigree, the mutation was associated with reduced penetrance for skin and uterine lesions in carrier females, but RCC was noted.[9,10] In a Dutch family, the mutation was associated with cutaneous and uterine leiomyomas but not RCC.[1] Now, with a fourth reported family with the same mutation (this report), it is apparent that penetrance of all key features, including RCC, may depend on other genetic or environmental factors.

Smit *et al*. 2011 proposed criteria for the clinical diagnosis of HLRCC.[1] The major criterion is histopathologic confirmation of multiple cutaneous piloleiomyomas. Minor criteria include: (1) surgical treatment for severely symptomatic uterine leiomyomas before age 40, (2) type 2 papillary RCC before age 40, and (3) a first-degree family member who meets one of the above criteria. The diagnosis is likely when a patient meets the major criterion. HLRCC may be suspected when a patient meets at least two minor criteria.

In a retrospective study of 14 Dutch families with genetically confirmed HLRCC, Smit *et al*. 2011,[1] reported BCC in two patients from two families harboring two distinct *FH* missense mutations. We are the first to report the development of BCC as well as melanoma in siblings with a third *FH* missense mutation. While it is unclear whether the development of melanoma and basal cell carcinoma in our patients is due directly to mutations in *FH*, genetic susceptibility at another unrelated locus, or are only incidental lesions, this observation implies a possible association and attests to the necessity for careful and routine skin surveillance in patients with documented HLRCC for lesions other than cutaneous leiomyomata. Additional studies are warranted to further elucidate a possible causal link between HLRCC and BCC and/or melanoma.

Conclusion

Patients with mutations in *FH* are at an increased risk for the development of RCC and require ongoing surveillance, initiated at a young age and continued into the geriatric population, for tumor development. Our observations indicate that there may be an association of *FH* mutations with the development of BCC and/or melanoma. It is imperative that patients with HLRCC not only receive careful renal surveillance but ongoing cutaneous surveillance as well.

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