Case Report

Hereditary leiomyomatosis and renal cell carcinoma syndrome: a case report and implications of early onset*

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Abstract: Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant manifestation of cutaneous and uterine leiomyomas together with renal cancer due to autosomal dominant germline mutations of fumarate hydratase gene. A twenty-year-old female patient presented with type-II segmental piloleiomyoma and increased menstruation due to uterine leiomyomas, with a history of bilateral nephrectomy performed at 13 and 16 years of age for type 2 papillary renal cell carcinoma. This case represents one of the very early onsets of hereditary leiomyomatosis and renal cell carcinoma syndrome. As genetic anticipation for renal cancer is a well-documented entity for HLRCC syndrome, early recognition is crucial for both the patient and her family in order to provide appropriate counseling and initiation of surveillance.
Keywords: Anticipation, genetic; Fumarate hydratase; Kidney neoplasms; Leiomyomatosis; Mutation

INTRODUCTION

The leiomyomas of the skin were first described by Virchow in 1854 as rare, slow growing, benign, smooth muscle tumors on the skin. The association between the leiomyomas and the inherited susceptibility to renal cancer could be first recognized in 2001. Up to date there have been only 180 families identified with hereditary leiomyomatosis and renal cell carcinoma (HLRCC).[1] The common mechanism beneath the HLRCC syndrome is the heterozygous germline mutations encountered in fumarate hydratase (FH) gene located at 1q42.3-43.[2]

We present the case of a 20-year-old patient with HLRCC, who initially presented with renal cancer at 13 years of age without a supportive family history. As the literature shows genetic anticipation, all of the recommended protective measures are mainly centered on the assessment of the siblings in the affected families. In contrast, here we questioned the presence of HLRCC in the older generations.

CASE REPORT

A 20-year-old female patient presented with multiple light brown-reddish grouped papules and nodules symmetrically distributed on both the trunk and limbs (Figure 1). The patient complained of pain on some of these lesions mainly related with increased sensation of pressure and change in temperature. She had a history of bilateral nephrectomy performed when she was 13 and 16 years of age due to histologically confirmed bilateral papillary type 2 renal cell carcinoma (Figure 2). She was the first member of her family who had renal carcinoma. A biopsy was taken from one of the skin lesions which demonstrated typical histologic features of cutaneous leiomyomas and a diagnosis of piloleiomyoma with a type 2 segmental distribution was made (Figures 3 and 4). Due to the high suspicion of HLRCC syndrome, subsequent gynecological consultation of the patient revealed the presence of unrecognized multiple intramural small leiomyomas. In her gynecologic family history, she mentioned

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that both her aunt and mother underwent hysterectomies before the ages of 35 due to symptomatic leiomyomas. Renal tumor could not be detected with magnetic resonance imaging (MRI) in the family members and they were offered annual screening for possible renal involvement.

DISCUSSION

Cutaneous leiomyomas are benign neoplasms arising from smooth muscles and are the most common and earliest manifestation of HLRCC, seen in over 80% of cases. Piloleiomyomas derived from the arrector pili muscle of hair follicles are the most common type of leiomyomas seen in HRLCC.[3]

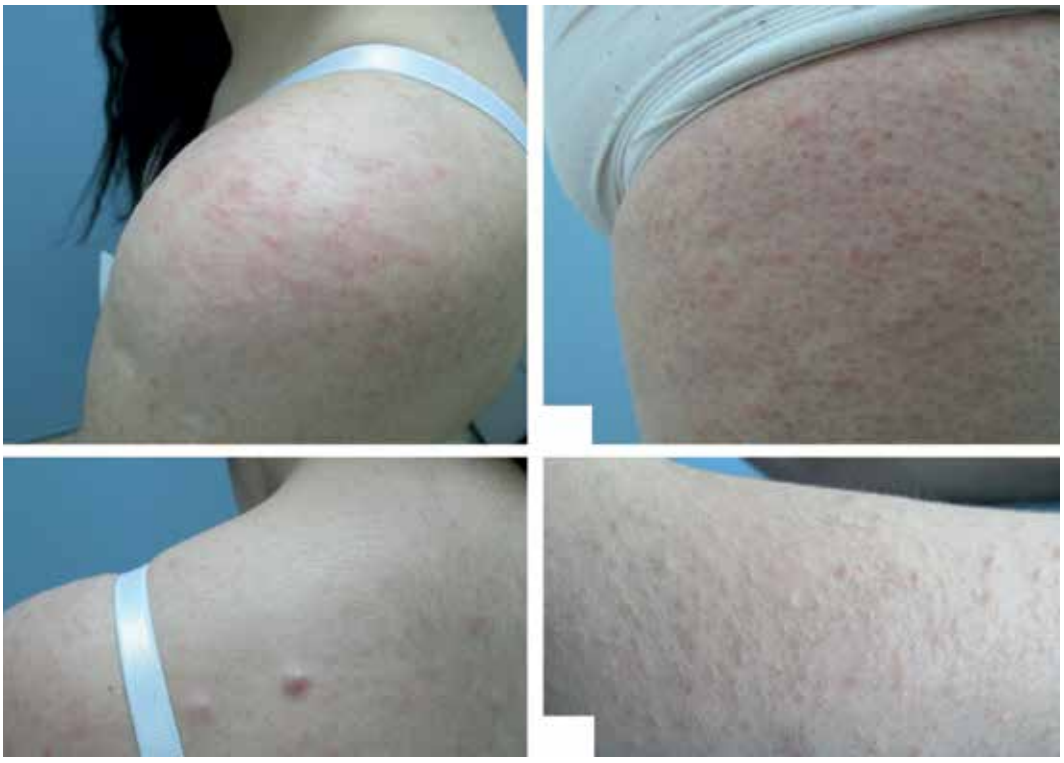

Figure 1:
Multiple light brown-reddish grouped papules and nodules on the trunk, back and extremities

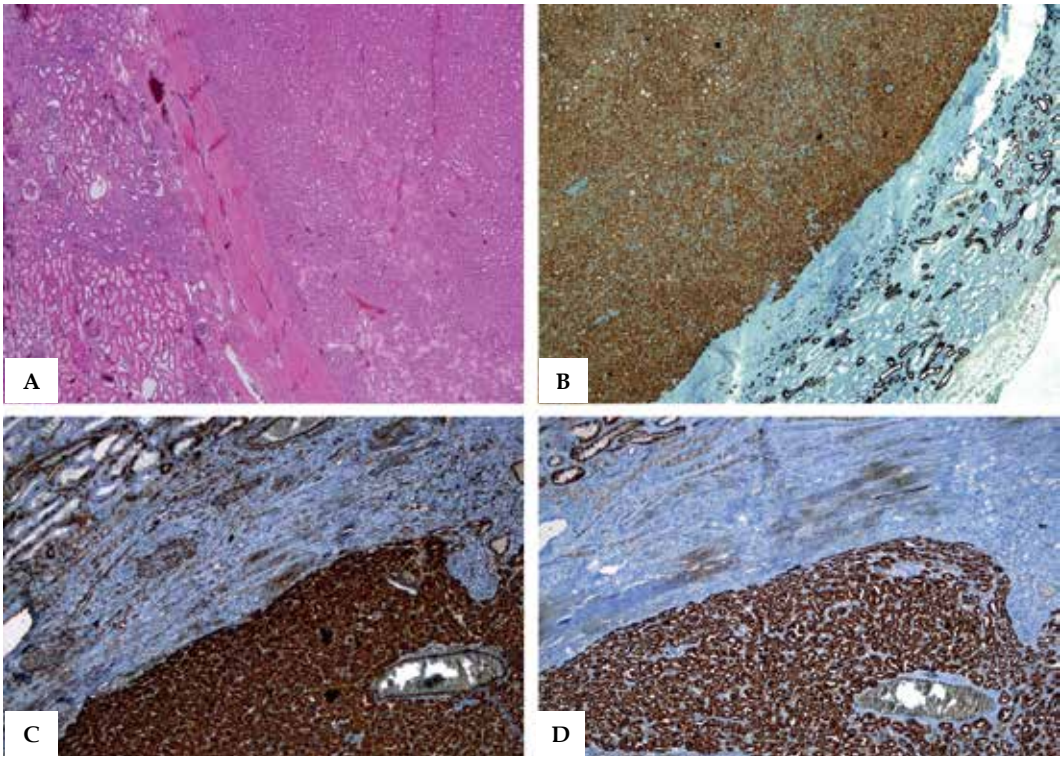

Figure 2:
A - Partially encapsulated epithelial tumor is seen on the right side and normal renal parenchyma on the left side (Hematoxylin & eosin, X40); Immunohistochemically, the tumor is positive for **B -** pancytokeratine, (x40) **C -** vimentine (x100) and **D -** Anti-mitochondrial antibody (x100)

Even though there is lack of a consensus about the prevalence/penetrance of renal carcinoma, it could be accepted as between 20-25%, among the affected families with FH mutation. Wong *et al.* showed the existence of genetic anticipation in HLRCC cases, with an approximately 18 years of mean difference in age at diagnosis of renal carcinoma between consecutive generations.[4] The youngest age at diagnosis of renal cancer is 11 years, found after screening of an asymptomatic child with confirmed FH gene mutation.[5] In the literature, there have been a few additional cases diagnosed around 16-18 years of age with metastatic renal carcinomas and deceased by the age of 20.[6]

Renal cell carcinoma develops approximately in 15.6% of the FH mutant individuals according to an American cohort.[7] HRLCC-associated renal neoplasms are known as early onset, solitary, unilateral and aggressive tumors which can cause death within five years of diagnosis, at a mean diagnostic age of 44. Only 7% of HLRCC patients are diagnosed with renal carcinoma before the age of 20.[8] To date, there have been only a few cases of bilateral renal cancer described associated with HLRCC.[9] Here we present one of the unique cases of HLRCC, as our patient had bilateral, very early onset type-2 papillary renal cancer.

Since the uterine leiomyomas are common in the general population, if the symptoms are severe enough to cause hysterectomy before the age of 30 and/or associated with cutaneous lesions, the possibility of HLRCC or Reed's syndrome should be raised.

The following criteria were advocated by Pithukpakorn and Toro for diagnosis of HLRCC. The presence of histopathologically confirmed multiple cutaneous lesions or solitary cutaneous leiomyoma plus family history of Reed's syndrome or HLRCC, was accepted as the major criterion. They described three minor criteria in addition to heterozygous mutation in the FH gene: 1) renal cell carcinoma 2) cutaneous leiomyoma 3) histologically confirmed multiple uterine leiomyomas.[10]

Wong *et al* reported genetic anticipation in HLRCC families which refers to earlier onset of disease in each succeeding generation. While the onset of renal cell carcinoma was found to be 18 years earlier between the generations, no evidence of anticipation for uterine leiomyomas was noticed in HLRCC syndrome.[4] According to them, the demonstrated anticipation supports the need to initiate surveillance programs at younger ages. Van Spaendonck-Zwarts *et al.* proposed that renal surveillance should be started from the age of 10 by using non-invasive techniques, since renal cancer is the major life-threatening feature of the syndrome.[6] As the most common type-2 papillary renal cell carcinoma is often isoechoic on ultrasound, MRI would be more appropriate for screening.

Also, genetic counseling is very important in patients with a family history of HRLCC, because there is potential for diagnosis in an asymptomatic state. Genetic evaluation could not be performed due to technical difficulty. We believe that our patient was potentially the second generation of HRLCC in her family, as her mother and aunt were still in the third decade. To us, these family

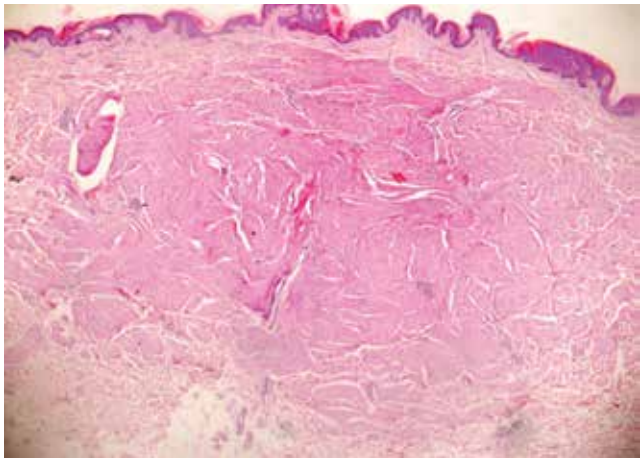

Figure 3: A well-demarcated tumor composed of intersecting smooth muscle bundles is seen beneath the epidermis (Hematoxylin & eosin, X40 magnification).

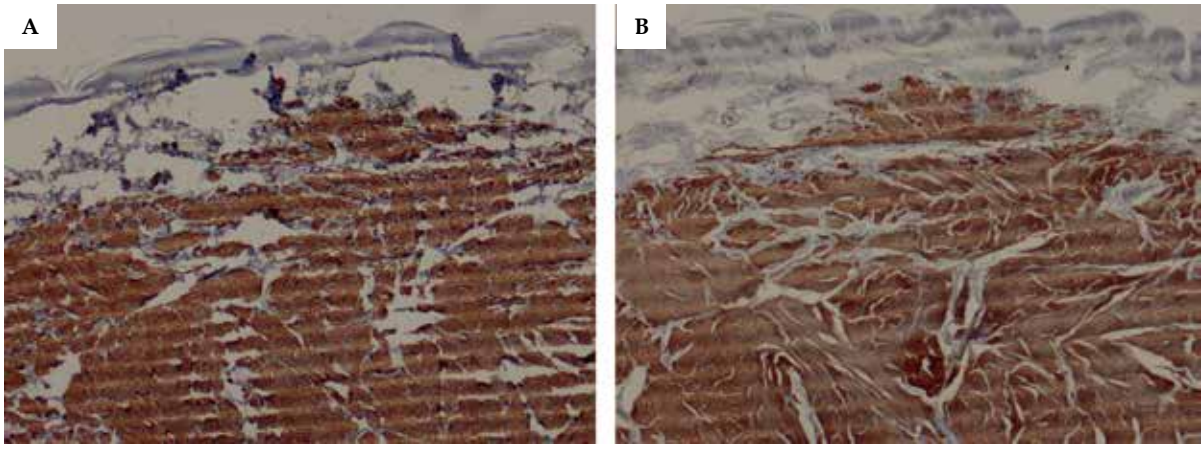

Figure 4: Immunohistochemistry study showed that the lesion was positive for desmin (**A) -** and smooth muscle antibidy (**B) -** Desmine antibody X40, Smooth muscle antibody X40)

members could be the undiagnosed first generations who were still at the risk for renal cell carcinoma. The screening with MRI did not show any renal tumors in neither relative. This could be due to the very low penetrance of renal cell carcinoma among the individuals with HLRCC. At-risk members of HLRCC families who test positive for the family's germline FH mutation should undergo annual MRI surveillance beginning at the age of 8 years. Early detection and immediate surgical intervention for HLRCC-associated kidney tumors, rather than active surveillance, are critical in preventing the metastatic spread of this malignancy.❑

REFERENCES

1. Tolvanen J, Uimari O, Ryynänen M, Aaltonen LA, Vahteristo P. Strong family history of uterine leiomyomatosis warrants fumarate hydratase mutation screening. Hum Reprod. 2012;27:1865-9.
2. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30:406-10.
3. Badeloe S, van Geel M, van Steensel MA, Bastida J, Ferrando J, Steijlen PM,et al. Diffuse and segmental variants of cutaneous leiomyomatosis: novel mutations in the fumarate hydratase gene and review of the literature. Exp Dermatol. 2006;15:735-41.
4. Wong MH, Tan CS, Lee SC, Yong Y, Ooi AS, Ngeow J, et al. Potential genetic anticipation in hereditary leiomyomatosis-renal cell cancer (HLRCC). Fam Cancer. 2014;13:281-9.
5. Alrashdi I, Levine S, Paterson J, Saxena R, Patel SR, Depani S, et al. Herediatary Leiomyomatosis and renal cell carcinoma: very early diagnosis of renal cancer in pediatric patient. Fam Cancer. 2010;9:239-43.
6. van Spaendonck-Zwarts KY, Badeloe S, Oosting SF, Hovenga S, Semmelink HJ, van Moorselaar RJ, et al. Hereditary leiomyomatosis and renal cell cancer presenting as metastatic kidney cancer at 18 years of age: implications for surveillance. Fam Cancer. 2012;11:123-9.
7. Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, et al. Mutations in fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003;73:95-106.
8. Refae MA, Wong N, Patenaude F, Bégin LR, Foulkes WD. Hereditary leiomyomatosis and renal cell cancer: an unusual and aggressive form of hereditary renal carcinoma. Nat Clin Pract Oncol. 2007;4:256-61.
9. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. Am J Surg Pathol. 2007;31:1578-85.
10. Pithukpakorn M, Toro JR. Hereditary Leiomyomatosis and Renal Cell Cancer. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2006 Jul 31 [updated 2010 Nov 02]. p. 1993-2015. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1252/

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