Gynecologic Manifestations of Less Commonly Encountered Hereditary Syndromes

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KEYWORDS

• Hereditary leiomyomatosis renal cell carcinoma syndrome • Tuberous sclerosis • von Hippel-Lindau • Nevoid basal cell carcinoma syndrome • Cowden syndrome • Ollier disease • Maffucci syndrome • Carney complex

ABSTRACT

This review covers gynecologic manifestations that may occur in rare hereditary syndromes. Recent advances in disorders, such as hereditary leiomyomatosis, renal cell carcinoma syndrome and tuberous sclerosis complex, are discussed as well as lesions that occur in von Hippel-Lindau syndrome, nevoid basal cell carcinoma syndrome, Cowden syndrome, Ollier disease/Maffucci syndrome, and Carney complex. Characteristic clinicopathologic features of each of these syndromes are discussed with an emphasis on the key features that enable pathologists to identify patients at highest risk for these diseases.

HEREDITARY LEIOMYOMATOSIS RENAL CELL CARCINOMA SYNDROME

Hereditary leiomyomatosis renal cell carcinoma syndrome (HLRCC) is an autosomal dominant syndrome due to a germline mutation in the *fumarate hydratase* (*FH*) gene located on chromosome 1q42.3. The syndrome predisposes patients to an aggressive form of renal cancer as well as uterine and cutaneous leiomyomas that have underlying *FH* abnormalities[1–3] (**Table 1**). The incidence of the syndrome is not definitively known but is estimated to be 1 in 10,000 to 50,000 individuals.[4] Virtually all women with HLRCC develop uterine and cutaneous leiomyomas whereas the penetrance for renal cell carcinoma (RCC) is approximately 20% to 30%.[5] Although leiomyomas with *FH* abnormalities (L-FHs) occur in almost all patients with HLRCC, they can also be sporadic and can occur in patients without the syndrome.[6]

CLINICAL FEATURES

The median age at diagnosis for L-FHs in HLRCC is approximately 30 years compared with sporadic leiomyomas, which usually present a decade later. Patients often have multiple, large, and symptomatic leiomyomas, which often lead to hysterectomy at an early age.[7–9] Occasionally, a patient may present with uterine leiomyomas as the initial manifestation of the syndrome.[2,8] Frequently, patients do not have a family history suggestive of HLRCC because the penetrance is incomplete and variable.[5]

GROSS/MICROSCOPIC FEATURES AND DIAGNOSIS

There have been a handful of studies that have examined the morphologic features that are present in L-FHs.[4,7,10,11] Grossly, L-FHs are similar to leiomyomas without FH abnormalities but are often multiple and large. Microscopically, the tumors have an eosinophilic, epithelioid, and sometimes cellular appearance at low power. The cells show a fascicular growth pattern and the background vasculature is staghorn or pericytomatous. The nuclei are ovoid to round with a vesicular appearance and optical clearing and have inclusion-like nucleoli with perinuclear halos (**Fig. 1**A). Usually the cells have little to no atypia; however, the atypia may be severe and diffuse,

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Table 1
Diagnostic criteria for proposed for hereditary leiomyomatosis renal cell carcinoma syndrome as proposed by Smit and colleagues[3]

Major Criteria	Minor Criteria
Multiple cutaneous leiomyomas	Surgical resection of severely symptomatic uterine leiomyomas before age 40 Type 2 papillary or collecting duct RCC before age 40 First-degree family member with any major or minor criteria

The diagnosis requires 1 major criteria or 2 minor criteria.
From Smit DL, Mensenkamp AR, Badeloe S, et al. Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. Clin Genet 2011;79(1):49–59.

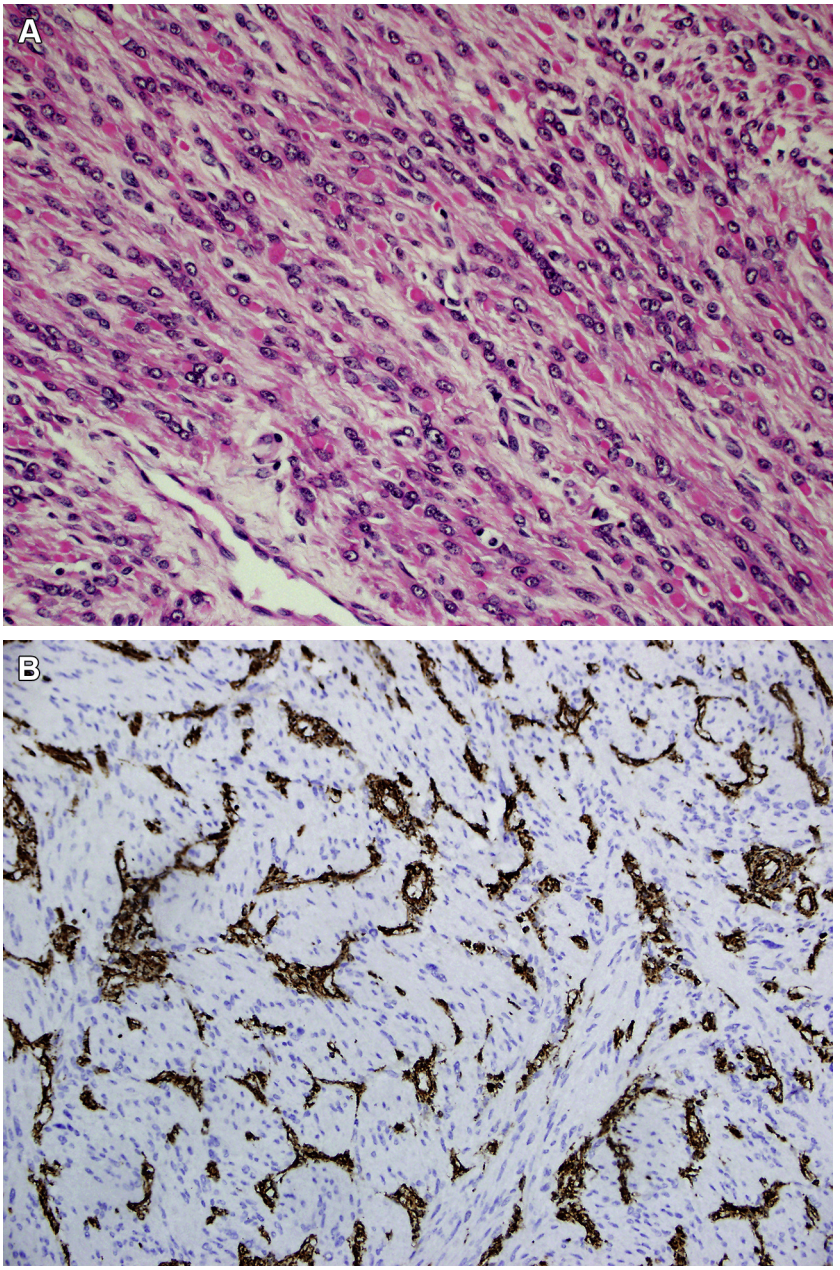

Fig. 1. (*A*) Uterine leiomyoma with FH abnormality. Morphologic features include an epithelioid appearance, prominent nucleoli with perinucleolar halos, and fibrillary cytoplasm with pink globules. (*B*) Leiomyoma with immunohistochemistry for fumarate hydratase. Loss of staining indicates an *FH* abnormality. Note the internal control in the form of vessels. (*Courtesy of* Dr Karuna Garg, University of California, San Francisco.)

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