Gastric Leiomyoma and Hyperplastic Polyposis Coli in a Patient with Multiple Cutaneous and Uterine Leiomyomatosis

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Background: Cutaneous leiomyomatosis has been associated with multiple uterine myomas and, more recently, with germline heterozygous mutations of the FH gene and certain types of renal cancer. Despite the growing amount of knowledge concerning this genodermatosis, its clinical spectrum remains incompletely characterized.

Objective: We report the observation of a patient with multiple cutaneous and uterine leiomyomatosis (MCUL) with unusual gastrointestinal manifestations.

Methods and Results: A gastric leiomyoma was diagnosed on a 38-year-old female MCUL patient on endoscopy performed because of mild dyspepsia. Furthermore, routine colonoscopy disclosed hyperplastic polyposis. Genetic testing revealed a previously not reported mutation of the FH gene.

Conclusion: Gastrointestinal lesions such as the present ones are frequently asymptomatic and probably underdiagnosed. As the phenotypical spectrum associated with mutations of the FH gene keeps expanding, clinicians should keep in mind that, besides renal cancer, other unexpected tumors could also arise in this setting.

MULTIPLE CUTANEOUS AND UTERINE LEIOMYOMATOSIS1–3 (MCUL; OMIM #150800) has been associated with renal cancer,4 uterine leiomyosarcomas,5,5 and, more recently, macronodular adrenocortical disease.6 These recent publications support the concept that the clinical spectrum of this syndrome is still expanding.9 We report the observation of a MCUL patient with a gastric leiomyoma and colonic polyposis carrying a new mutation of the fumarate hydratase (FH) gene.10

Case Report

A 44-year-old female patient presented with several long-standing, occasionally painful, erythematous papules and nodules in her trunk and upper limbs (Figure 1) that started to appear around age 20. A diagnosis of piloleiomyomas was confirmed on histopathology.
Her past medical history was significant for several conditions and surgical treatments. Due to dysmenorrhea and bleeding, multiple uterine leiomyomas were diagnosed at age 37, and a hysterectomy was performed thereafter. Later, at age 38, a submucosal tumor of the gastric corpus was diagnosed on esophagogastroduodenoscopy for minor dyspeptic symptoms (Figure 2). Surgical local excision revealed a gastric leiomyoma (actin positive, c-Kit negative). By the age of 39, a colonoscopy showed more than 20 sessile polyps, hyperplastic in multiple biopsies, located mostly on the ascending colon, some featuring a laterally spreading morphology with dimensions ranging from 10 to 30 mm in diameter. Considering this, the criteria for the diagnosis of hyperplastic polyposis according to the World Health Organization classification, as proposed by Jass and Burt in 2000, were fulfilled.

Given the potential for malignant degeneration and the uncertainties of endoscopic management, the patient decided on a surgical approach (a prophylactic colectomy).

Her family history was not contributory but could not be completely assessed as her father died at a young age, after an accident, and her grandparents’ medical history is unknown.

Genetic testing revealed a nonsense mutation in exon 4 of the FH gene (c.422G>A, p.Trp141X). This mutation generates a premature stop codon and has not yet been reported to the Leiden Open Variation Database of FH mutations.

A diagnosis of MCUL associated with a gastric leiomyoma and colonic hyperplastic polyposis was established. Periodic renal and rectal cancer screening has been negative, and the patient remains healthy.

Discussion

Piloleiomyomas can present as solitary or, more frequently, multiple lesions. In the latter case, they usually represent an autosomal dominant inherited condition associated with uterine myomas: MCUL. A subset of MCUL families has individuals affected with certain types of aggressive renal cancer, namely, type 2 papillary renal cell carcinomas and collecting duct carcinomas: hereditary leiomyomatosis and renal cell cancer (HLRCC; OMIM #605839). Mutations of the FH gene are present in both MCUL and HLRCC patients. As no significant genotype-phenotype correlation has been established, identification of families with renal cancer risk cannot rely on genetic testing.

The FH gene encodes fumarate hydratase, an enzyme of the tricarboxylic acid (Krebs) cycle. Its role as a tumor suppressor gene is now widely accepted. Putative mechanisms through which FH promotes tumorigenesis include oxygen-independent stabilization of hypoxia-inducible transcription factor and activation of cellular hypoxia response pathways (a pseudohypoxic drive), as well as
downregulation of serum response factor–regulated transcripts, particularly the FOS-JUNB pathway.

In this case, a MCUL patient presented with a gastric leiomyoma and colonic hyperplastic polyposis, two previously unreported pathologic associations to the best of our knowledge. The common smooth muscle origin of gastric, cutaneous, and uterine tumors supports the contention that this is not a casual occurrence, and it is conceivable that the neoplastic predisposition associated with a mutated FH could justify the development of these lesions.

Lamba and colleagues reported the case of a woman with MCUL and a gastrointestinal stromal tumor (GIST) diagnosed by the age of 36 years. Although GISTs share a mesenchymal origin with leiomyomas, there are several morphologic and biologic aspects suggesting that GISTs derive from a different cell type, namely, the precursors of the interstitial cells of Cajal.

On the other hand, FH mutations have not been associated with hyperplastic polyposis, a rare condition whose malignant potential has been acknowledged since the late 1980s. Its genetic basis is still far from understood but has been linked to the serrated neoplastic pathway of colorectal carcinogenesis. Although this case could merely consist of an association by chance, one might also consider a possible role for FH in colonic polyposis.

The gastrointestinal lesions described in this case are frequently asymptomatic and probably underdiagnosed. As the clinical spectrum associated with cutaneous leiomyomatosis keeps expanding, clinicians following these patients should bear in mind that other unexpected tumors could arise in this setting. Future research should clarify the implications of FH mutations and improve the management of these patients.

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