The Waldo of fibroids under the microscope: fumarate hydratase–deficient leiomyomata

To the editor: We read with interest the case report of Rivera-Cruz et al. (1) that illustrated the clinical implications of the identification of fumarate hydratase (*FH*)–deficient leiomyomata.

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant syndrome, caused by heterozygous germline mutations of *FH*, an enzyme of the tricarboxylic acid cycle (also known as the Krebs cycle). Syndromic manifestations can be summarized by the triad of *FH*-deficient uterine leiomyomata, cutaneous (pilar) leiomyomata, and HLRCC-associated renal cell carcinoma (RCC). Other neoplasms that have been rarely described in this context include malignant paragangliomas and pheochromocytomas, testicular Leydig cell tumors, and breast and bladder carcinomas (2).

In HLRCC, uterine leiomyomata develop in virtually all women, with its mean onset (second to third decade of life) predating that of HLRCC-associated RCC (fourth decade of life) (3). This, therefore, presents a unique opportunity where identification of a benign tumor with unusual morphological features (*FH*-deficient leiomyoma) allows early recognition of a syndrome (HLRCC) and facilitates surveillance of another syndromic tumor that is far more aggressive, albeit of lower penetrance (HLRCC-associated RCC). Because this is an autosomal dominant condition, a child of an affected parent has a 50% chance of inheriting the mutated gene, and Rivera-Cruz et al. (1) illustrate the role of preimplantation genetic testing in this context.

Histomorphological clues for the diagnosis of *FH*-deficient leiomyomata have become increasingly recognized and include low-power features of hemangiopericytoma-like blood vessels and alveolar pattern edema and high-power features of scattered bizarre nuclei, prominent eosinophilic nucleoli surrounded by perinucleolar halos, and eosinophilic cytoplasmic inclusions. More recently recognized features also include Schwannoma-like growth and chain-like arrangement of ovoid tumor nuclei (3). Rivera-Cruz et al. (1) state that the identification of such features should be followed by FH immunohistochemistry (IHC). However, the clinical utility of this immunostain is controversial because of several issues that limit its sensitivity. First, retained staining pattern may be observed in cases of missense mutation (which forms most *FH* mutations in HLRCC) because the protein product, although nonfunctional, may still be detected by IHC (3). Second, a loss of staining pattern does not distinguish between somatic and germline mutations. Third, it has been reported that even in patients carrying germline mutations, different uterine leiomyomata in the same patient may show varying results on IHC (4). Given these issues, some investigators recognize that in the presence of well-developed morphological features, FH IHC will not affect the eventual recommendation to correlate the suspicion with clinical and family history and consider genetic counseling (3). Formation of 2-succinocysteine (2-SC) occurs as a downstream event of loss of FH activity, and 2-SC IHC is a sensitive and specific surrogate marker for FH-deficient states. In practical terms, however, 2-SC IHC is not widely available (at the time of writing) (3). These issues, thus, give weight to making a recommendation on morphological grounds. This is further bolstered by results of comparative studies that favor morphology-based screening over IHC-based screening (5). Crucially, however, there is no strict or universal definition of what amounts to well-developed features, and this is fertile ground for subjectivity in reality. The sensitivity and specificity of morphological features and interobserver and intraobserver variabilities in interpretation require further study. Taking all of these into consideration, the evaluation of such cases will likely involve seeking consensus pathologist opinion and discussion in a multidisciplinary setting.

Rivera-Cruz et al. (1) list papillary type II RCC as an associated tumor in HLRCC. However, currently, HLRCC-associated RCC is considered an entity distinct from papillary RCC, owing to its unique etiology and clinical and pathological features (2). Morphologically, this tumor may show a variety of architectural growth patterns, including papillary growth, and show cytologic features reminiscent of benign *FH*-deficient uterine leiomyomata, including large nuclei with eosinophilic nucleoli and perinucleolar halos (inclusion-like nucleoli). This tumor often presents at advanced stage, pursues an aggressive clinical course, and is associated with a poor prognosis. Surveillance and early identification, thus, offer a theoretical chance of reducing morbidity and mortality. While Rivera-Cruz et al. (1) describe in their case report how identification of HLRCC led to early diagnosis of "clear cell renal carcinoma" in a first-degree relative, it is unclear if this was an *FH*-deficient RCC with clear cell morphology or a conventional clear cell RCC, the latter possibly representing a nonsyndromic tumor and incidental finding on surveillance.

To conclude, identifying *FH*-deficient leiomyoma is akin to finding Waldo because it requires dedicated attention to certain features, amid the vast and several faces of common variety leiomyomata. Its reward, however, is most certainly significant.

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