Reply of the Authors: The Waldo of fibroids under the microscope: fumarate hydratase-deficient leiomyomata

We appreciate the interest and comments of Drs. Punjabi and Thomas in our publication entitled "How a woman's myomectomy saved her father's life: evidence of fumarate hydratase-deficient uterine leiomyoma and early detection of germline variants in fumarate hydratase" where we identified a woman with fumarate hydratase–deficient leiomyomas with the characteristic morphological features, immunohistochemistry confirmation, and molecular testing, which revealed a pathogenic germline variant in *FH*, gene encoding fumarate hydratase. This set of events resulted in familial risk assessment, screening, and early identification of renal carcinoma in the patient's father (1). We understand the points Drs. Punjabi and Thomas presented and partially agree.

In our case, the morphological features in the leiomyomas including hemangiopericytoma-like vasculature, alveolar edema, multinucleated cells, and cells with prominent cherry red nucleoli and perinucleolar halo suggested fumarate hydratase deficiency, and immunohistochemistry against *FH* showed loss of expression in tumor cells confirming the diagnosis (2). Given that the loss of expression can be seen in the setting of both germline and somatic *FH* mutations, the patient underwent molecular testing. We are aware that a subset of cases with the classical morphological features and missense mutations in *FH* may show retained expression of the protein and lead to misinterpretation (3, 4). However, in our case, the tumor cells showed loss of *FH*, and we further confirmed the findings with germline testing. The sensitivity and specificity of *FH* immunohistochemistry are 91% and 100%, respectively; thus, it is critical to be aware of the possibility of missense mutations and retained expression resulting in false-negative results. There are 2 other immunohistochemical markers, S-(2-succino)-cysteine and aldo-keto reductase family 1 member B10, with higher sensitivity and specificity for fumarate hydratase–deficient leiomyomas; however they are not widely available for commercial use at the time of writing (4). Overall, identification of classical morphological features followed by genetic testing to identify germline variants is the optimal workflow, and loss of FH on immunohistochemistry can be helpful to identify patients at risk of hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, as was the case for this patient.

With regard to the patient's father's kidney tumor, the case was evaluated at an outside institution, and morphological details are unavailable. However, there are some emerging studies proposing that HLRCC-associated renal cell carcinoma histopathologic features have diverse and complex characteristics. In fact, up to 40% of HLRCC-associated renal cell carcinomas have different morphological patterns from those observed in papillary type 2 renal cell carcinoma (5). Overall, in this case, the family benefited from identification of the germline *FH* variant for cancer screening and genetic counseling. Familial risk assessment led to early detection and treatment of a kidney tumor in the patient's father. We agree that there is the possibility of another sporadic tumor given the clear cell histopathology; however, identification of the mutation led to,screening which resulted in identification of this tumor.

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