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Uterine leiomyoma with fumarate hydratase deficiency A case report with literature review

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Abstract: *Uterine leiomyomas or uterine fibroids are the most common benign soft tissue tumor in reproductive-aged women. Fumarate hydratase deficient (FH-d) uterine fibroids are a rare subtype that is diagnosed only on pathologic evaluation. FH-d uterine fibroids may be the first indicator of hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. Therefore, identifying and understanding the clinical implication and diagnosis of FH-d uterine fibroids is critical for early diagnosis of HLRCC. This case report describes a woman with a uterine leiomyoma diagnosed with* FH *deficiency who further went on genetic screening for HLRCC.* ***Patient concerns:*** *A 31-year-old nullipara in genital activity woman visited a gynecological clinic for abnormal uterine bleeding consisting of heavy menstrual periods In the last 6 moths . An echography was performed and the discovery one a large type 2-5 leiomyoma of 9*4cm in size. She had a history of surgery for uterine leiomyoma in 2018 and resection of a Bartholin cyst in 2019 .* ***Diagnosis and Interventions:*** *The patient underwent successful transabdominal myomectomy with resection of one large leiomyoma . The pathological results showed a uterine leiomyoma with scattered large bizarre giant cells. Immunohistochemistry results demonstrated* FH *deficiency.* ***Outcomes:*** *On follow-up, the patient did not have any complications. She was finally referred to the nephrologists for follow-up and for genetic screening for HLRCC which came up negative.*

Keywords: uterine *leiomyoma, fumarate hydratase deficiency, hereditary leiomyomatosis and renal cell cancer (HLRCC)*

1. INTRODUCTION:

Uterine leiomyomas, or uterine fibroids (UFs), are extremely common. Moreover, 20% to 50% of women will develop uterine leiomyomas by 30 years of age, and more than 80% of females may have uterine leiomyomas by 50 years [1]. Fumarate hydratase-deficient (FH-d) UF is a rare subtype of UF characterized by its association with both somatic and germline FH gene mutations [2]. Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome secondary to germline fumarate hydratase (*FH*) mutation presents with cutaneous and uterine leiomyomas, and a distinctive aggressive renal carcinoma We reported a 31-year-old woman suffering from uterine leiomyoma and the pathology demonstrated FH negative uterine leiomyoma but did not present with HLRCC syndrome.

2. CASE PRESENTATION:

This is a 31-year-old patient, nulliparous, with history of myomectomy in 2018 in private Clinic without documentation and ablation of a Bartholin cyst in our hospital in 2019, was admitted for treatment of abundant menstrual bleeding (with a PBAC of 102) evolving for 4 months associated with a pelvic pain related to increase in abdominal pressure. in whom the clinical examination finds a stable patient, BMI at 21 presence of a well-demarcated firm pelvic mass arriving at 2cm below the umbilicus measuring 12 cm on large axis and vulvar inspection Presence of a small swelling of 2cm long axis at the base of the Bartholin gland, renitent, the rest of the examination, particularly breast, is unremarkable.

A transabdominal Pelvic ultrasound done on 07/12/2023 showed the Myometrium contained a rounded formation with peripheric vascularization on doppler measuring 9X11 cm in relation with a type 2-5 myoma, endometrium otherwise poorly explored (fig. 1). No obvious abnormality was found on ultrasonography of the urinary system. We offered the patient a hysteroscopy in order to explore the endometrium, the patient refused and preferred an MRI with a view to exploring the endometrium and taking progestin for regularization of the cycle. A pap smear was done discreetly inflammatory smear with absence of intravenous lesion epithelial.

A Pelvic MRI done in favor of 02 myometrial and cervico-isthmic masses of 98x 96 x 98 mm in diameter related to class myxoid degeneration myomas classified FIGO 4 and 8 another formation of 27x 22 mm in FIGO class 5 hyaline degeneration in the myometrium. Fine and regular endometrium. Absence of adenomyosis, Right ovary is the site of a large unilocular cystic mass which does not enhance after contrast measuring 64x46 mm in diameter classified ORADS 2 Left ovary unremarkable. Decision was to perform a myomectomy. Immunohistochemistry results demonstrated that cells of uterine leiomyoma were negative for FH, while adjacent vascular endothelial cells and vascular smooth muscle cells were positive for FH. Based on the combined results of immunohistochemistry and H&E staining, the woman was finally diagnosed with uterine leiomyoma with *FH* deficiency. On a follow-up visit, the patient was well without any discomfort. She was finally referred to the nephrologists for follow-up and for genetic screening for HRLCC which turned out negative.

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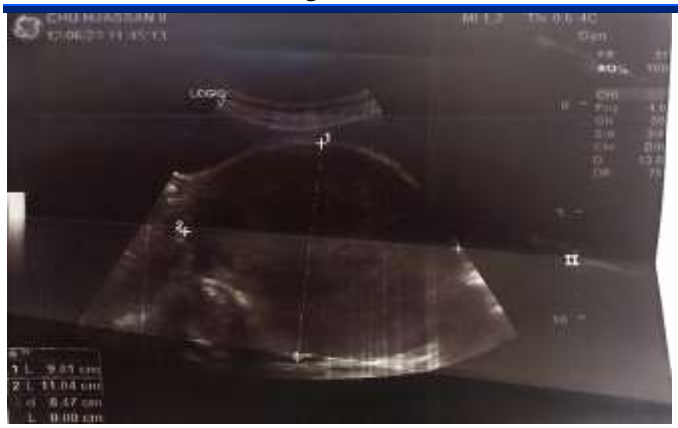

Figure 1: Multiple uterine leiomyomas by pelvic ultrasound. The size of the largest one was approximately 98 × 110 mm.

3. DISCUSSION:

The frequency of myomas with FH deficiency remains unknown. This entity is rare and little described in current practice. According to anatomo-pathological data, in a consecutive series of 534 non-atypical uterine leiomyomas, Siegler et al found FH deficiency in 0.4% of cases [3]. This relatively high-rate contrasts with data in the literature reporting a limited number of cases of myomas presenting FH deficiency [4]. Furthermore, if we take into account the French data from the 2012 PMSI published in 2014 by Fernandez et al, 46,126 patients were hospitalized for symptomatic fibroids, 16,070 of whom underwent total or subtotal hysterectomy and 16,384 of a myomectomy. If we consider that the patients were operated on for a single myoma, the number of patients with a myoma with FH deficiency in 2012 should be between 130 and 324 cases even though this entity is rarely reported. This could be explained by the non-recognition of diagnostic criteria in histology or by an overestimation of the incidence in published anatomopathological series. The phenotype of HLRCC syndrome, or Reed syndrome, is variable with multiple circumstances of discovery. Uterine myomas often appear before age 30, skin lesions before age 40, and kidney tumors before age 46 [5]. In addition, uterine leiomyomas in the context of HLRCC syndrome are symptomatic approximately 10 years earlier than sporadic cases and most often require surgical treatment from the age of 30 [6]. This timeline is remarkable because the discovery of a fibroid with FH deficiency makes it possible to offer real screening for renal cell carcinoma.

These carcinomas associated with HLRCC are more aggressive, with a risk 6.5 times higher than in the general population [7] and occur at a younger age than in the sporadic form [8] justifying annual screening from the age of 10 years [9.7] Although on MRI an appearance of hypercellular myoma was observed in our patient, there is no imaging description allowing us to suggest the diagnosis of leiomyoma with FH deficiency [10]. In histology, the diagnosis is difficult due to non-specific signs [11]. Harrison et al reported that leiomyomas with FH deficiency frequently present a very suggestive hemangiopericytoma appearance as in our case. Other histological features associated with FH-deficient leiomyomas have been reported such as hypercellularity, nuclear atypia, nucleolar inclusions or perinuclear halos and stromal edema but are more inconsistent [11]. Harrison et al reported that leiomyomas with FH deficiency frequently present a very suggestive hemangiopericytoma appearance as in our case. Other histological features associated with FH-deficient leiomyomas have been reported such as hypercellularity, nuclear atypia, nucleolar inclusions or perinuclear halos and stromal edema but are more inconsistent [11].

IHC finding a loss of expression in FH is the key element of diagnosis without being able to state whether it is a sporadic or germline mutation [3]. Most authors agree to consider the diagnosis of HLRCC syndrome in the presence of a myoma with FH deficiency. Smit et al and Schmidt et al proposed diagnostic criteria comprising major criteria (painful multiple cutaneous leiomyomas, one or more painful pilocutaneous leiomyomas) and minor criteria (single cutaneous leiomyoma and family history of hereditary syndrome of cutaneous leiomyomatosis and renal cancer, type 2 papillary kidney cancer before the age of 40, patient with very symptomatic myomas before the age of 40, a first-degree family member with one of the aforementioned minor criteria). The diagnosis of HLRCC syndrome is retained for one major criterion and suspected based on two minor criteria [12.13]. In our case, the patient did not present these criteria, raising the problem of the interest of a genetic study. The search for mutations in our patient was negative. One hundred and thirty mutations have been described but some families have a phenotype characteristic of HLRCC but without currently identified mutations [12.6].

4. CONCLUSION:

The interest of our clinical case is to raise pathologists' awareness of this entity as well as to request a search for FH expression in cases of hypercellular myomas in imaging.

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