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Case Report

A Case of Germline Mutation Fumarate Hydratase-Deficient Uterine Leiomyoma and Literature Review

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Abstract

Diagnosis and management of cavernous sinus thrombosis can be challenging, but several clinical clues can aid in a more time-efficient and cost-effective approach. This condition is rare which can delay diagnosis and be fatal due to the several important neurovascular structures that run through the cavernous sinus. This report discusses a case of cavernous sinus thrombosis in a male with substance use disorder whose signs, symptoms, and diagnostic findings were classic for the condition. Prompt recognition of these can lead to a more rapid diagnosis and early initiation of adequate treatment. There are limited evidence-based guidelines regarding diagnosis and treatment. This report will also review some of the more recent literature on the topic to aid healthcare providers in giving proper care for their patients and thereby increasing knowledge and awareness of the subject.

ABBREVIATIONS

FH: Fumarate Hydratase

INTRODUCTION

Uterine leiomyoma, a benign tumor, is the most common tumor in the female reproductive system. Fumarate hydratase (FH) deficiency is a rare finding in uterine leiomyomata patients, which represents 1% of all uterine leiomyomas [1]. FH gene is located on the q-arm of chromosome 1(char1q43) and encodes the FH key enzyme in the tricarboxylic acid (TCA) cycle, which acts as a tumor suppressor [2,3]. Heterozygous germline mutations in FH genes lead to the deficiency of FH enzymes, which can lead to the accumulation of fumarate and produces a variety of oncogenic mechanism [3]. The accumulation of fumarate can enhance the antioxidant capacity of cells and promote cell proliferation, which is associated with the formation of tumors. Moreover, it can enhance the antioxidant capacity of cells by activating transcription factors such as HIF and FOXM1, and promote cell proliferation by activating downstream genes related to cell survival and proliferation. In addition, the deficiency of FH can also play a carcinogenic role by promoting the transition from epithelium to mesenchymal.

As a result, the inhibitory effect of FH on tumor is reduced. Eventually, mutations in the FH gene lead to fumarate hydratase-deficient uterine leiomyoma. Moreover, germline variant in the FH gene is an increased risk of developing renal cell carcinoma [4] leading to patients suffering from Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. HLRCC syndromes are autosomal dominant diseases caused by germline mutations in the FH gene, with cutaneous leiomyomas, early-onset uterine leiomyomas, and renal cancer as clinical symptoms. It often presents initially with uterine leiomyomas. Therefore, patients with FH-deficient uterine leiomyoma need to be monitored for kidney cancer.

The patient reported in this case is a 33-year-old woman who is married with one son. Ultrasound reports multiple uterine fibroids (subserosal and intermural muscular). For this patient, we performed laproscopic myomectomy. The patient was discharged with stable vital signs, a soft abdomen without tenderness, and normal mental status and diet and sleep. Postoperative pathological examination combined with pathological immunohistochemistry showed fumarate-dehydrogenase-deficient leiomyoma and excluded hereditary leiomyomatosis and renal cell carcinoma syndrome. The

whole exon sequencing verfiy the diagnosis again. This article will introduce this case of FH-deficient uterine leiomyoma in detail, discuss the diagnosis and treatment of FH-deficient uterine leiomyoma, and review its clinical manifestations and morphological features.

CASE PRESENTATION

A 33-year-old married woman presented to our hospital with complaints of a 6-year history of uterine fibroids. Patient complains that uterine fibroids gradually grew and has increased significantly in the past six months. Patients now experience frequent urination and occasionally urgency and bloating. She had unremarkable anamnesis and no significant family history. Physical examination revealed no significant abnormalities except for an enlarged, hard, and poorly active uterus located at the level of the navel. A recent computer tomography (CT) evaluation revealed uterine occupying lesions (14.5*7.5 cm). Ultrasound shows abnormal uterine morphological, inner diameter of the section of the uterine body measured 10.2*10.2*14.6cm, which is greater than normal. Several hypoechoes can be seen in the muscle wall, and the larger one is located at the bottom of the left side, with well-defined borders and protruding outward, and band-like blood flow signals are displayed around it. Ultrasound shows endometrial thickening, and multiple small anechoes can be seen in the cervix. Ultrasonography revealed multiple uterine myomas (subserosal and intermuscular wall). Preoperative blood routine examination revealed lower levels of hemoglobin, mean RBC volume, mean hemoglobin content, mean hemoglobin concentration and RBC distribution width SD, suggesting the patient moderately anaemic. Laparoscopically, hysterectomy, wide ligamentectomy, and pelvic adhesiolysis were performed. Intraoperative exploration shows extensive adhesions between the left omentum and the abdominal wall, and after separating the adhesions, an enlarged irregular uterus can be seen. The well-delimitated fibroid that sticked out the surface was located at the bottom of the left side of the uterus, which measured 11cm*9cm and clearly. The anterior wall of the uterus is clearly demarcated from the uterus. Several subserosal fibroids can be seen at the base of the posterior wall of the uterus. The left broad ligament has a deep fibroid, about 6*5 cm in size. Postoperative pathological examination revealed uterine leiomyomas, and singular nuclear cells could be seen in some areas which combined with immunophenotyping suggested fumarate dehydrogenase-deficient leiomyoma. Clinically, examination of relevant sites such as kidneys and detection of related molecules excludes the possibility of HLRCC syndrome.Immunohistochemistry indicated high expression levels of SMA(+), DES(+), and Caldesmon(+) and revealed the loss of FH expression. SMA is used to mark smooth muscle and Caldesmon can be used to label whether the tissue comes from smooth muscle cells, and their positivity should be caused by leiomyomas. DES is the desmin expressed by muscle tissue tumor cells whose positivity indicates a greater likelihood of leiomyoma. Obviously, negative expression of FH indicates fumarate dehydrogenase deficiency. Immunohistochemistry also showed ER (little+), ER (Positive control) + CD10 (-), P53 (Scattered +, Hint for wild type), Ki-67(LI about 3%) 。 Estrogen receptor ER is both a predictor and a prognostic factor used to assess whether endocrine therapy can be performed, and the higher its expression, the better the effect of endocrine therapy. CD10 can be used for the diagnosis and differential diagnosis of endometrial interstitial nodules or endometrial stromal sarcoma, and has certain reference value in the diagnosis and differentiation of renal cell carcinoma. A negative result means that no abnormalities have been found yet. The possibility of HLRCC is therefore excluded. P53 is normally negative for tumor suppressor gene, and the positive result is scattered, indicating a wild type, which can inhibit tumor proliferation. Ki-67 is a marker to detect cell proliferation, the higher the positive rate, the faster the tumor multiplies, so the higher the degree of malignancy, and the patient's Ki-67 (Li about 3%) indicates that cancer cells are less active.

After the patient's informed consent, whole exome sequencing was performed on genomic DNA from blood and cancerous tissue. The results showed that there were heterozygous missense mutations known to be pathogenic in the EX5 gene subregion of the FH gene (p.K223Rfs*26, reference transcript NM_000143.3). The mutation is the deletion of two adenylate deoxynucleotides at positions 668-669 of the encoding DNA. And this FH germline variant is autosomal dominant. In addition, the report of genetic testing showed the presence of somatic variants in five genes, including TP53, CCND1, HRAS, RBM10 and KMT2D, of which three were clinically significant variants and the other two had not yet been clinically significant. Targeted drugs Ribociclib (D), pezopanib (D), pezopanib + Voristat (D), sorafenib (D), and Pipercilib (D) may benefit patients. The patient's final diagnosis was uterine leiomyoma (fumaric acid-deficient leiomyoma) with moderate anaemia. At discharge, the patient was unwell and showed normal mental status and diet and sleep. The patient's vital signs were stable and there were no obvious abnormalities in the heart and lungs. The patient's abdomen is flat and non-tender. Patients are advised to take care of rest and nutrition, and to exercise moderately. The woman needs to continue oral blood supplementation, prohibit sexual life for one month and strict contraception for more than two years after surgery, and regularly visit the hospital for follow-up visits.

DISCUSSION

Mutations in the FH gene lead to a deficiency of FH enzymes, which activates the hypoxia pathway and induces carcinogenesis [5]. The FH enzyme plays the role of catalyzing the conversion of fumarate to malate, so defects in the enzyme lead to the accumulation of fumarate, which is thought to be related to the activation of HIF and the activation of downstream cellular survival and proliferative genes [6,7]. On the one hand, the accumulation of fumarate can lead to the accumulation of HIF by competitively inhibiting the degradation of HIF-1α by proline hydroxylase。HIF is a transcription factor that promotes the survival and growth of cells under low oxygen conditions by regulating cellular oxygenation responses [8]. Therefore, cells mutated in the FH gene are in a state of pseudohypoxia due to elevated HIF levels which explains the growth of the tumor

[9,6]. On the other hand, an increase in fumarate can lead to the activation of the transcription factor FOXM1, which promotes the multiplication of cells as well as the antioxidant response [10-12]. In addition, the deficiency of FH can also play a carcinogenic role by promoting the transition from epithelium to mesenchymal [13].

In addition, studies have shown that uterine leiomyoma may receive a second blow due to somatic loss or mutation of the wild-type FH allele, which means that the inactivation of both alleles of FH leads to the loss of FH enzyme activity in the target tissue. But if germline mutations are present in both copies of the FH gene, it will lead to severe autosomal recessive fumaly enzyme deficiency, characterized by encephalopathy and psychomotor retardation, and often fatal in infancy or childhood [14,15].

FH-deficient leiomyoma is a specific type of uterine leiomyoma that generally develops ten years earlier than uterine leiomyoma and can be caused by systemic mutations and germline mutations. Germline mutations, as the main mode of mutation, are also clinically associated with HLRCC syndrome. HLRCC syndrome includes symptoms of cutaneous leiomyoma and kidney cancer in addition to uterine leiomyomas, and occasionally, uterine leiomyoma may be the initial manifestation of HLRCC syndrome [16,17]. Uterine leiomyoma caused by FH germline mutations are clinically different from sporadic cases, they are present in the early stages and are usually multiple and aggressive [7], and women with FH mutations have an increased risk of uterine sarcoma [18]. Young women from their teens to twenties may have noticed progressively worsening symptoms, which may include menorrhagia, abdominal pain, and abnormal bleeding, and leiomyoma may progress to malignancy before menopause [19]. Almost all reports occur in young women, not postmenopausal women. For these women, myomectomy or hysterectomy is required and there are generally no alternatives, and surgical intervention occurs at an average age of 35 years [18].

FH-deficient leiomyoma is mostly soft and invisible to the naked eye, unlike typical uterine fibroids. Microscopically, germline mutant uterine leiomyoma exhibits unique morphological features. Tumors are eosinophilic epithelioid cells with bundle-like growth patterns arranged in chains or fences. The nucleus is large and oval to round, with eosinophilic inclusion body-like nucleoli and a clear perinuclear halo [20,21]. The cytoplasm is fibrous and aggregates to form pink globules, with antler-like blood vessels. Due to the atypia of the nucleus and the difference in appearance and morphology, leiomyosarcoma may be diagnosed. However, leiomyosarcoma basically does not have FH gene defects, so it can be identified by immunohistochemical staining of FH, which is meaningful to avoid misdiagnosis as leiomyosarcoma or leiomyomyoma with uncertain malignant potential.

Fumarate hydratase (FH) and 2succinocysteine (2-SC) are two immunohistochemical biomarkers highly correlated with FH-deficient uterine leiomyomas. Defects in the FH gene cause fumarate accumulation, which in turn reacts with cysteine to form 2SC. As a result, a positive immunohistochemical staining of 2succinocysteine (2-SC) can demonstrate neoplastic FH deficiency. But because its antibodies are not yet commercial, 2SC has not been routinely applied to the clinic [22,23].

For patients with obvious uterine leiomyoma symptoms, the patient's past and family history should be fully understood, and histopathological and immunohistochemistry examination should be performed. Patients with abnormal FH expression should be aggressively tested for molecular genetics to confirm the diagnosis.Clinical diagnosis can be made by microscopic identification of characteristic morphological features of FH-deficient uterine leiomyomas, such as deer antler-shaped blood vessels, smooth muscle cells distributed in chains or fences, and atypia of the nucleus under low magnification, large nucleoli and clear perinuclear halo under high magnification. However, morphology lacks specificity, and morphology alone is insufficient to identify FH-deficient leiomyomas. IHC has higher sensitivity and specificity, so immunohistochemical markers such as FH and 2-SC need to be detected for further diagnosis. Diagnosis can then be confirmed by genetic testing for tumors.

FH-deficient uterine leiomyoma is primarily differentiated from other tumors with smooth muscle differentiation, including leiomyosarcoma and perivascular epithelioid cell tumors. Differential diagnosis is distinguished primarily by morphological features. Leiosarcoma is severely nuclear atypia and presents diffuse. Epithelioid leiomyoma show true epithelioid cells, whereas FH-deficient leiomyoma cells are pseudoepithelioid and can also be distinguished by eosinophils and apparent nucleoli from perinuclear halos [22]. The case that uterine leiomyoma developed into uterine sarcoma due to germline mutations in the FH gene is uncommon, and no studies have shown a particular association with an increased risk of malignancy [24]. Due to the large size and number of tumors of FH-deficient uterine leiomyomas, hysterectomy is recommended. However, myomectomy is usually preferred to protect uterine function [14]. Anti-hormonal therapy can be performed before surgery to shrink the tumor and temporarily relieve pain. Epidemiological studies have shown that FH-deficient uterine leiomyoma occurs an average of ten years earlier than ordinary uterine leiomyomas, mostly in young women. Once germline FH mutations or decreased enzyme activity are demonstrated, a definitive diagnosis can be made. Patients and their families should also be offered genetic counseling, and ongoing kidney monitoring and regular screening for kidney cancer should be planned.Conservative management is also possible, and the risk of fibroid recurrence needs to be determined by testing for relevant immune markers. It is also clear that leiomyoma has a clear genotype/phenotypic relationship. Studies have shown that both the size and location of leiomyoma are related to their karyotype, and studies of recurrence after myomectomy have also suggested that karyotype may be involved in recurrence risk. Therefore, understanding the different phenotypes and genotypes is clinically meaningful [18]. However, for now we still recommend hysterectomy as the treatment of choice.

For uterine leiomyomas, clearer genetic mechanisms may contribute to the generation and development of innovative management methods and prevention strategies, and help to achieve individualized treatment. Epidemiological studies will lay the groundwork for studying prevention strategies and predicting the risk of relapse in young girls receiving conservative treatment [18].

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