Letter to the Editor

Uterine leiomyosarcoma diagnosis after treatment of presumed uterine fibroid with the high-intensity focused ultrasound: a case description

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Submitted Aug 16, 2021. Accepted for publication Mar 21, 2022.
doi: 10.21037/qims-21-814
View this article at: https://dx.doi.org/10.21037/qims-21-814

Introduction

Uterine leiomyosarcoma is a rare and aggressive gynecologic malignancy that is difficult to diagnose before surgery; it has high recurrence rates and metastatic potential through blood and lymph nodes (1). Unintentional dissemination of uterine sarcoma may occur in the case of preoperative misdiagnosis, such as when the lesion is thought to be a fibroid or when the sarcoma is found within a "fibroid" uterus. However, preoperative diagnosis of sarcoma has remained difficult despite the implementation of various modalities, such as advances in ultrasound image resolution, magnetic resonance imaging (MRI), or the application of different sequences, biochemical and molecular markers, and preoperative core needle biopsies (2-4). Sometimes, pathology-based postoperative diagnosis is also unclear. Clinical symptoms of sarcoma are often elusive and develop slowly. Some patients are randomly screened for uterine fibroids during routine physical check-ups, and the slow growth of fibroids that are thought to be benign is followed up.

Ultrasound-guided high-intensity focused ultrasound (USgHIFU) is a noninvasive technology that causes thermal ablation-induced cellular protein necrosis within the focus area without causing damage to the surrounding tissue (5). Each of sonication procedure treats one spot at a time, line by line, in a uniform pattern that conforms to the shape of the lesion being treated, and the non-perfusion volume is evaluated with echo contrast-enhanced ultrasound (CEUS) imaging. The CEUS aims to assess tissue micro-vascularization (6).

High-intensity focused ultrasound (HIFU) is used to treat malignancies such as hepatic cancer, pancreatic cancer, bone sarcoma, pelvic primary malignancy or metastatic tumors, parenchymal neoplasms, and some cystic neoplasms (7). The application of HIFU thermal ablation to the cervical stump to treat advanced cervical cancer after radiotherapy and HIFU ablation of middle or advanced carcinoma of the vulva are effective and safe (8). While HIFU directly ablates lesions, the ablated tissue induces the production of anti-tumor antibodies against the released tumor antigens, which has subsequent antitumor immune effects. However, at present, there are few reports on the application of HIFU ablation of uterine sarcoma before surgery (9,10).

Case description

A 39-year-old woman was admitted to the Department of Minimally Invasive Gynecological Surgery, Capital Medical University, Beijing Obstetrics and Gynecology Hospital. The patient declined a laparotomy and then underwent USgHIFU with the JC200D therapeutic system (Chongqing Haifu Medical Corporation Ltd., Chongqing, China) of a presumed large uterine leiomyoma. A routine ultrasound check-up 5 years prior, she had been diagnosed with a leiomyoma with a diameter of 2 cm. Nearly a year prior to this admission, she had been diagnosed with an enlarged fibroid (11.5 cm × 12.8 cm × 5.7 cm) accompanied by symptoms of frequent urination.

Before treatment, on ultrasonic images, the volume of the uterus was 6.2 cm × 5.7 cm × 3.6 cm with an almost clearly

defined margin of the posterior lesion (11.5 cm × 12.8 cm × 8.7 cm). The lesion was found to have semicircular blood flow signals on color Doppler images during transabdominal ultrasound. All laboratory test results were normal except for measurements of 249 U/L for lactate dehydrogenase (LDH; standard 135–214 U/L).

During HIFU treatment, the greyscale image did not obviously change until the end, after 166 min of total treatment time, 2,473 s of sonic time, 94,456.0 kJ of total energy, and 350.8 s/cm3 of effective factor (EFF). The intraprocedural visual analogue scale (0–10) was reported to be a 9 due to sacrococcygeal regional pain.

After treatment, a non-perfused area of 8.6 cm × 7.3 cm × 8.3 cm was observed on CEUS imaging. The non-perfused volume rate was noted as 59.3%. After treatment, there was a slight color change of the skin in the treatment area; however, the skin returned to normal at 15 days post-treatment. During the 3-month follow-up, the patient felt pressure in her pelvis, and the volume of the leiomyoma decreased, especially in the transverse diameter. Moreover, color Doppler blood flow in the area around the ablated lesion was evident. We advised her to undergo an MRI scan including contrast-enhanced images. The MRI showed that the size of the posterior lesion was 13.6 cm × 11.7 cm × 14.2 cm, and necrosis was present within the lesion, which was expected after HIFU ablation (*Figure 1*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Outcomes

A 39-year-old woman underwent HIFU ablation of a presumed uterine leiomyomata that had been diagnosed 5 years prior. The volume of the lesion was reduced by 31% at the 1-month follow-up postoperatively compared to the pretreatment size; 3 months after HIFU treatment, the lesion volume was reduced by 21% compared to pretreatment. The features on the MRI showed iso-intense signals on T1-weighted images (T1WI) interspersed with hyperintense signals on T2-weighted images (T2WI) and heterogeneous enhanced diffusion-weighted images (DWIs) (*Figure 2*).

Therefore, she was readmitted, and then she had 2 more operations for the diagnosis with pathologic malignancy. Her levels of LDH returned to normal after surgery (from 263 to 221 U/L). First, the patient underwent myomectomy. During the operation, the general view of the lesion showed no obvious abnormalities, and rich thick blood vessels appeared on the tumor surface. The intraoperative frozen pathology results showed no abnormalities. The gross sample was identified as leiomyosarcoma accompanied by poor differentiation and vascular tumor emboli. The results of pathology were as follows: extensive necrosis, several obvious mitoses in the 3–5 high power field, nuclear atypia, tumor emboli in parts, and the tumor had invaded the surrounding smooth muscle tissue. The 3 main features of uterine leiomyosarcoma are poor differentiation, coagulative necrosis of the tumor, and vessel carcinoma embolus.

Following a pathologic diagnosis of a malignancy of the uterus, the patient underwent bilateral salpingo-oophorectomy with full staging procedures shortly thereafter. Computed tomography (CT) revealed multiple metastases in the bilateral lung. Positron emission tomography-computed tomography (PET-CT) revealed lung and bone metastases. Radioisotope scans also detected bone metastases. During the second operation, panhysterectomy and pelvic lymph node removal were performed.

After surgery, the patient underwent chemoradiotherapy; she was discharged after achieving partial remission with gemcitabine-docetaxel chemotherapy. Currently, the patient visits our department regularly and is taking self-prescribed traditional Chinese medicine for long-term maintenance. The patient's last follow-up visit was 1 year after HIFU treatment, at which time her general condition was good.

Discussion

Uterine leiomyosarcoma is a rare but aggressive group of uterine malignancies with nonspecific clinical features, making up 1–3% of all gynecologic malignant tumors (1,5). It has the potential for high recurrence and metastasis.

In benign fibroids, T2WI show a well-defined round mass with uniformly reduced signal intensity (SI) compared to the ectopic myometrium, while T1WI show near-iso-SI to the ectopic myometrium and relatively uniform enhancement after contrast administration. In contrast, for leiomyosarcoma, T2-weighted pelvic MRI shows a heterogeneous ovoid mass in the corpus uteri, although some of these features overlap with those of fibroids (for example, the mass may be ovoid and well-defined, which

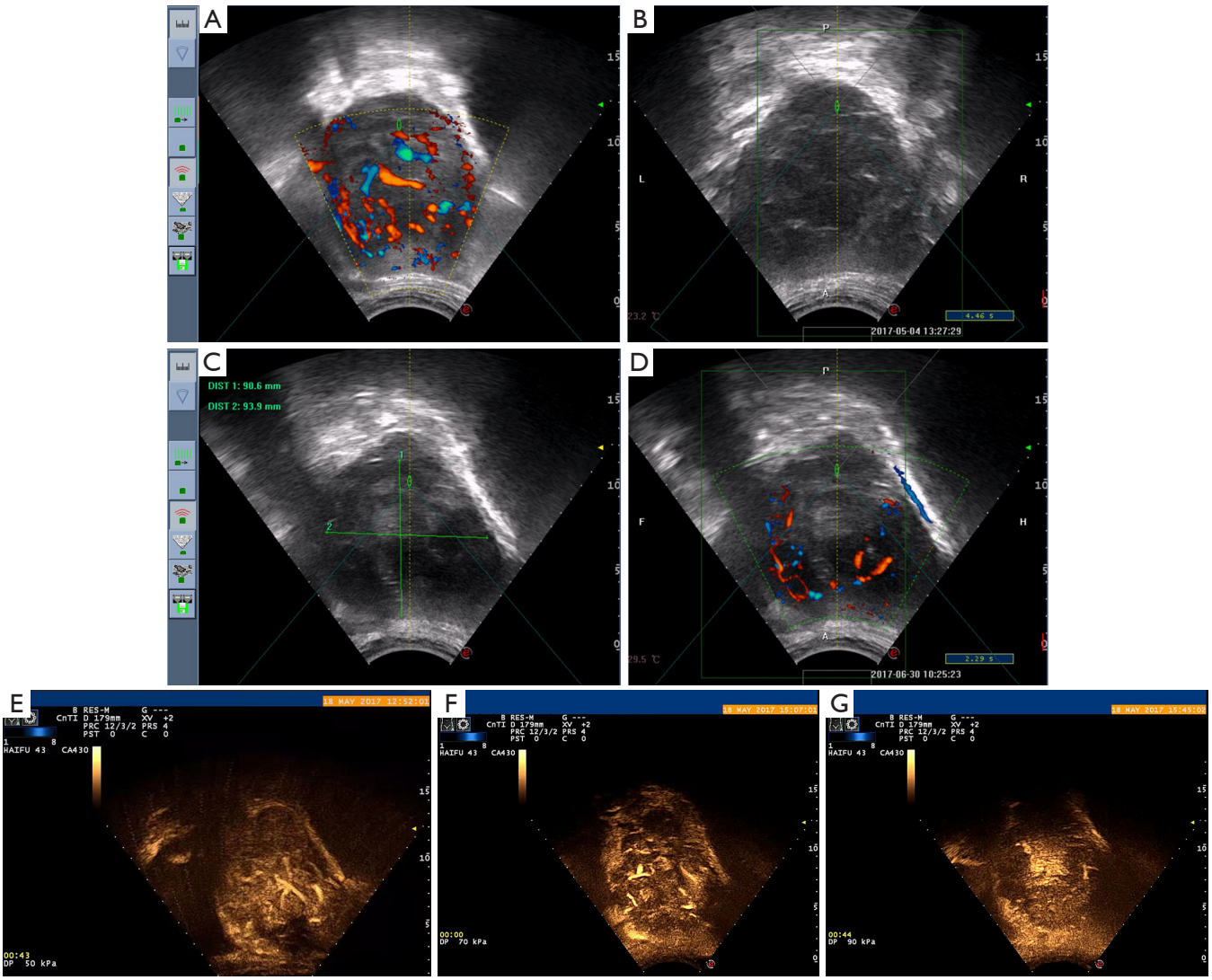

Figure 1 CDFI and CEUS imaging of the lesion. (A,B) CDFI and 2D imaging of the lesion before HIFU treatment. (A) Before HIFU treatment, CDFI showed abundant blood flow around and inside the lesion and a coarse vascular network. (B) 2D imaging showed heterogeneous hypoecho and a blurred boundary. (C,D) CDFI and 2D imaging of the lesion 1 month after HIFU treatment. (C) One month after HIFU treatment, on 2D imaging, heterogeneous hyperechoism emerged, with the apparent shrinkage of the volume of the lesion ablated. (D) On CDFI, color blood flow presented around the lesion. (E) CEUS of the lesion before HIFU treatment. Before HIFU treatment, on CEUS imaging, the perfusion of the lesion was significantly enhanced compared with the uterine muscle wall. CEUS showed that most lesions appeared as hyperperfused regions, and some were hypoperfused fractions before HIFU. (F) CEUS of the lesion after HIFU treatment. CEUS revealed that a residual large blood supply existed in the hyperperfused area at 135 min during the HIFU process. (G) Immediately after HIFU treatment, CEUS imaging showed non-perfusion in the ablated lesion. Generally, angiographic sonograms showed that the center of the hyperperfused region of the neoplasm basically lacked a blood supply, and there was still perivascular perfusion in the periphery. CDFI, ultrasound color doppler flow imaging; CEUS, contrast-enhanced ultrasound; 2D, two-dimensional; HIFU, high-intensity focused ultrasound.

Figure 2 MRI at 3 months after HIFU treatment. (A) T2WI of lesions at 3 months after HIFU treatment. T2WI showed an oval-shaped clear boundary of the lesion with an uneven intermediate-to-hyperintensity signal in the posterior wall of the uterus. (B) DWI of lesions at 3 months after HIFU treatment. DWI displayed an uneven hyperintensity signal in the lesion area. (C) Enhanced imaging of lesions at 3 months after HIFU treatment. Enhanced imaging on T1WI with fat saturation showed uneven significant enhancement in the lesion with an internal non-perfusion zone. MRI, magnetic resonance imaging; HIFU, high-intensity focused ultrasound; T2WI, T2-weighted images; DWI, diffusion-weighted image; T1WI, T1-weighted images.

is more typical of benign normal or degenerative fibroids). The DWI is useful to differentiate malignant from benign lesions due to the irregular and ill-defined margins of the malignant lesions. Malignant lesions tend to be hypointense and heterogeneous on T1WI; they have an intermediate-to-high signal on T2WI and appear early and heterogeneous on contrast enhancement image, and they generally show more restriction than leiomyomas on DWI (11). However, the SI increases on T1WI images and is not enhanced after contrast administration, which is suggestive of necrosis. Furthermore, the high b-value (b =800 s/mm^2) DWI and apparent diffusion coefficients (ADC) show restricted diffusion (12). High SI shown in the high b-value DWI and correspondingly reduced SI in the ADC image raise concerns about leiomyosarcoma (2,12). A suspicion of leiomyosarcoma should also arise if imaging detects a neoplasm that is >8 cm large, solitary, highly vascularized, and heterogeneous myometrial with an absence of calcifications. However, the typical features that distinguish between uterine myoma and malignancy tend to be absent from ultrasonic imaging.

The HIFU is a noninvasive modality that has been widely applied for the ablation of malignancies, such as bone sarcoma, soft tissue sarcoma, and retroperitoneal sarcoma (7). Uterine leiomyosarcoma is clinically rare; it often lacks distinguishing symptoms, and is seldom diagnosed before surgery. At present, surgery is the primary choice; adjuvant therapies such as radiotherapy and chemotherapy are often ineffective, therefore the options for treating recurrences after surgery are restricted.

Keshavarzi *et al.* (13) tried to ablate lesions in a uterine sarcoma model of nude mice with HIFU. In that study, 30 subcutaneously implanted uterine sarcoma nude mice were randomly divided into 3 groups: the HIFU group (n=17), the sham treatment group (n=7), and the control group (n=6). After 3 weeks, a total of 16 sarcomas disappeared, and some residual lesions vanished after the second thermal ablation. At 3 months postoperatively, the results of the histological examination after the animals had been euthanized found no residual tumor cells in the ablated region and no occurrence of metastasis in the lung, liver, or kidney. There were no adverse events except first degree skin burns close to the tumor site and fat necrosis. Clinically, HIFU could be used as an effective auxiliary method to treat uterine sarcoma without increasing the risk of tumor metastasis. Until now, HIFU has only been reported as a means to ablate leiomyosarcoma that is presumed to be a fibroid in clinical gynecologic practice (10). The HIFU ablation may have a positive effect on the prognosis of uterine leiomyosarcoma and result in a lower risk of dissemination and improved survival outcomes (9).

Although it shows potential, we believe that HIFU should not yet be a standard treatment for uterine sarcoma. Uterine sarcoma is extremely malignant, has a poor

prognosis, and easily relapses, with a recurrence rate of 53–71%, 5-year survival rate of 15–25%, and a median survival time of only 10 months (14). However, according to the follow-up results of this case and the literature we reviewed, applying HIFU does not adversely affect patient survival. Uterine sarcoma is difficult to differentiate from benign myomas. At present, a reliable method of preoperative diagnosis is not available. Infrequently, in women who have undergone surgery to treat presumed uterine myomas, subsequent histopathologic examination can reveal uterine sarcoma. However, it is not easy to perform tissue biopsy before HIFU. Although the rate of malignant transformation of uterine fibroids is low, this is a concern for many clinicians who apply HIFU as a treatment for uterine fibroids. In this study, the effects of HIFU treatment on the prognosis of the patient were monitored through follow-up and can be provided as a reference for clinical treatment.

The effect and safety of HIFU in sonicated solid tumors, such as cervical and vulvar cancers, requires further clarification. In 4 patients with cervical stump recurrence of advanced cervical cancer after radiotherapy, the focal effective rate was 85.4%, and the pain relief rate was 86.1% (15). Furthermore, HIFU offers a new choice for middle-late gynecologic malignancy tumors as a palliative treatment (8). Among pelvic malignant primary and metastatic tumors that are thermally sonicated with HIFU, 522 solid organ tumors were found to be necrotic through a variety of modalities after HIFU therapy; these vanished at once without discharge channels and faded away slowly due to the processes of absorption, shrinking, and fibrosis after necrosis (4).

In summary, HIFU has clinical utility as a new kind of therapy to treat tumors (8). It also induces tumor immunity through a variety of mechanisms, however, these mechanisms are still unclear and require further investigation.

From the results of this case and after review of existing literature, guidelines regarding the treatment of leiomyosarcoma of the uterus do not exist because it is rare and constitutes only 1–3% of female reproductive system tumors. Studies reported that the risk of uterine sarcoma decreases with age and is higher for those aged below 45 years (16). In practice, preoperative conversations should aim to clarify that pathology information does not suggest a lesion, and regular follow-up must be performed in a timely manner. Another concern occurs when patients with uterine leiomyosarcoma are misdiagnosed as having a uterine fibroid and/or have an unfavorable prognosis due to unintentional HIFU ablation of a uterine leiomyosarcoma, which delays treatment. An MRI has the potential to delineate malignant lesions from the typical features on DWI.

Conclusions

Based on our experience with HIFU therapy for a patient with leiomyoma, the decision to apply conservative treatment requires careful consideration of whether the benign and malignant lesions need to be diagnosed before therapy. If conservative treatment is pursued strict follow-up must be observed, and patients must be informed of this requirement in advance.

Acknowledgments

We thank Zhan Yang for taking responsibility for the pathology results.
Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-814/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Wang S, Duan H, Zhang X, Li B. Uterine leiomyosarcoma diagnosis after treatment of presumed uterine fibroid with the high-intensity focused ultrasound: a case description. Quant Imaging Med Surg 2022;12(6):3489-3494. doi: 10.21037/qims-21-814

