A Case of Severe Leg Edema After High Intensity Focused Ultrasound Ablation for Adenomyosis - A Possible Side Effect of Gonadotrophin-Releasing Hormone Agonist Injection

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Abstract
Adenomyosis is a common gynecological benign disorder that deteriorates women’s quality of life. The efficacy and safety of high intensity focused ultrasound (HIFU) ablation for treating adenomyosis patients has been increasingly recognized. Regardless of this fact, there are still potential adverse events that may happen during and after the provision of HIFU treatment, leading to a severe adverse outcome. Patients after HIFU has always been under close observation since HIFU surgery. This paper reports a sudden development of severe leg edema in a patient after HIFU for adenomyosis. It mimics an urgent development of deep vein thrombosis (DVT), an urgent ultrasound scan, fortunately, excludes DVT. After exclusive investigations, the severe leg edema is found secondary to a side effect of gonadotrophin-releasing hormone agonist (GnRHa).

Introduction
Adenomyosis is a common gynecological benign disorder. The main symptoms of adenomyosis include menorrhagia and dysmenorrhea. Adenomyosis has a major adverse impact on a woman’s quality of life; it also greatly impacts the fertility of childbearing age women.

The treatment for adenomyosis is still an intense challenge. Traditionally treatment of adenomyosis was medication and/or surgical. Hysterectomy remains the only definitive cure for adenomyosis. As the adenomyotic lesion boundary is unclear, it is difficult to remove the lesion completely, and the recurrence rate after adenomyomectomy is very high. In addition, there is no specific treatment for patients who want to retain their uterus or wish to remain fertile. Thus, it is important to explore more effective and less invasive treatments for these patients.

Over the last decade, high intensity focused ultrasound (HIFU) ablation has been widely used to treat adenomyosis. As a non-invasive treatment, the efficacy and safety of HIFU ablation for treating adenomyosis patients have been increasingly recognized. Regardless of this fact, there are still potential adverse events that may happen during and after the provision of HIFU treatment, leading to severe adverse outcomes [1,2]. Patients after HIFU has always been under close observation since HIFU ablation. This paper reports a sudden development of severe leg edema patient after HIFU for adenomyosis.

Case report
A 39 years old lady suffered from dysmenorrhea with increasing severity. The pain was at Visual Analog Scale pain scoring 8/10. Increasing analgesic use, and no menorrhagia were noted over a year. She married for eight
years without any children. Her past health was good, with no relevant history. Ultrasound examination, followed by MRI imaging in January 2020, confirmed adenomyosis (Figure 1). HIFU or Focused Ultrasound Surgery (FUS) was recommended to relieve her pain symptoms and remove her adenomyosis lesion. One week before her HIFU treatment, she received an injection of GnRHa (Enantone 11.5 mg for a 3 months dose injection).

The HIFU ablation to her adenomyosis was then performed without difficulty. She was well after HIFU ablation treatment and was discharged home after 2 hours without hospital stay. She was fine for one week after returning home; then, she complained of rapid onset of severe swelling of her lower limbs with pain, with no respiratory distress. She returned for a medical consultation because of her severe leg swelling (Figure 2). Urgent ultrasound Doppler scan for both limbs venous system was performed. Other than subcutaneous edema of the lower legs, the ultrasound scan showed no evidence of deep vein thrombosis in posterior tibial veins, peroneal veins, and both external iliac arteries and veins are patent and normal. Her blood test showed sodium 138 mmol/L, blood urea 6.3 mmol/L, creatinine 65 mol/L, white blood cell count 6.6 x 10^9/L, hemoglobin 12.5 g/dL, platelet count 248 x 10^9/L, alanine transaminase 15 U/L, aspartate aminotransferase 11 U/L, and other investigations, all revealed normal findings. There was no laboratory finding of renal impairment. A diagnosis of suspected Enantone induced leg edema was then made. The patient recovered well without medication. The leg edema gradually subsided after days with mobilization and a low salt diet.

**Discussion**

HIFU represents a non-invasive method that causes ablation necrosis of adenomyosis by focusing a high-intensity sonication beam into the uterine lesion. The focused beam generates coagulative necrosis at a focal spot that destroys the adenomyosis lesion. It is an emerging treatment for adenomyosis with efficacy and safety proven through research and practice [3-5]. Nonetheless, some adverse events have been reported during and after HIFU treatment, which may lead to the above problem of leg edema in some patients. Acute renal failure and deep vein thrombosis are the two potential adverse events reported in the literature. Park et al. [6] reported that a case of HIFU induced tumor lysis syndrome. It occurred in a 35-year-old patient with a 14×10 cm leiomyoma who underwent HIFU ablation. Five days after HIFU treatment, she suffered from fever and pain, with blood tests showing hyperuricemia, hyperphosphatemia, and slight metabolic acidosis. An acute kidney insufficiency was then diagnosed. Chen et al. [1] found three (0.3%) cases of acute renal failure after HIFU ablation, and Liu et al. (2) also reported four patients (0.023%) who experienced acute kidney failure after HIFU treatment. For all of them, kidney function returned to normal levels after conservative medical treatment. As a result, after HIFU, acute renal failure causing bilateral leg edema has to be excluded. Liu et al. (2), in their study, also reported that two patients (0.011%) developed deep vein thrombosis after ablation. In an evidence-based study of MRI-guided focused ultrasound surgery (FUS) by Pron [7], it was found that risks of deep vein thrombosis increase due to long immobilization in a prone position, especially in patients with great uterine fibroids requiring prolonged ablation time.

Because both of these potential complications - acute renal failure and deep vein thrombosis can end up with a disastrous event that needs to be promptly investigated and
excluded, therefore close monitoring of HIFU/FUS procedure and postoperative recovery of patients after treatment are essential to ensure patients’ safety.

On the other hand, adverse vascular thermal injury at the HIFU far-field area (the zone behind the targeted lesion) may be possible, though it has not ever been reported. With the fast blood flow in the major pelvic vessels, it would be unlikely that severe damage to these big vessels could occur unless the HIFU beam directly targeted at them. Yet, thrombosis in the iliac vessels was studied in this lady. Any thermal injury leading to thrombosis was excluded by the ultrasound Doppler scan, which showed that both external iliac vessels are patent and normal.

Based on her medical history, she had no allergic to any medication or food. She reported no history of taking any other medication and complained of itching. The physical examination showed no rash on the skin. Therefore, her severe edema can not be explained by allergy.

Thromboembolism shortly after GnRHa injection had also been reported though rarely [8]. When the Doppler ultrasound scan excluded deep vein thrombosis in this lady, the severe leg edema could only be explained by the other uncommon side effect of GnRHa - i.e., GnRHa induced edema. Whether the severe edema is related to a higher dose being used in this woman cannot be excluded. This dosage of Enantone may cause prolonged estradiol (E2) peak for a while after injection, leading to retention of fluid in the body. Further immobilization after surgery can aggravate the development of severe lower limb edema.

In this article, we aim to describe this possible side effect of GnRHa, which indirectly raises awareness of some uncommon adverse complications that could arise after HIFU/FUS therapy for adenomyosis. Learning from this case and knowing the potential major complications, GnRH-a should be used with caution in adenomyosis patients who had recently used pills or other estrogenic drugs, with a coagulation profile check before HIFU treatment. We should also inform patients about the risk of thrombosis after any HIFU/FUS treatment. At the time of HIFU ablation, TED stocking to reduce the risks of thrombosis and early mobilization should be encouraged. Most importantly, frequent communications with patients during the recovery period after HIFU treatment are useful for ensuring safety and detecting any complications promptly and appropriately.

References


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