

CASE REPORT

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Repeated intermittent use of ulipristal acetate associated with rapid growth and multilocular cystic hydropic degeneration of a uterine fibroid: A case report

Synnöve Maaria Staff, Sami Kristian Saarelainen, Marita Aino Laurila

ABSTRACT

Introduction: Uterine fibroids or leiomyomas are common benign tumors often associated with menorrhagia, pressure symptoms and dysmenorrhea. Selective progesterone receptor modulators (SPRMs) such as ulipristal acetate (UPA) have been proven a safe and effective treatment resulting in significant volume reduction of uterine fibroids and amenorrhea. Safety concerns of long-term use of UPA have mainly focused on endometrial changes, which have been proven to be benign and self-resolving. **Case Report:** A 44-year-old woman presented with symptomatic subserosal fibroid of 7.5 cm in diameter and was prescribed UPA for three months. After a positive initial treatment response, a repeated three-month course of UPA was started. At the end of the second course the patient became symptomatic presenting with cyclic abdominal pain. Ultrasound imaging revealed a large multilocular cystic pelvic mass sized 10x11 cm suspicious of a malignant tumor and abdominal hysterectomy was performed.

The uterine specimen weighed 1066 g and consisted mainly of a large multicystic tumor, which was confirmed a benign fibroid with cystic hydropic degeneration by histopathological analysis. **Conclusion:** Ulipristal acetate treatment has been suggested to inhibit fibroid growth partly by down-regulation of local angiogenic factors, which is the hypothetical pathogenetic mechanism for cystic degenerative tumor growth in the present case. It is important to bring about awareness to clinicians about this SPRM-induced benign condition in order to avoid misdiagnosis of a malignant process.

Keywords: Cystic degeneration, Selective progesterone-receptor modulator (SPRM), Ulipristal acetate, Uterine fibroid

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INTRODUCTION

Treatment modalities of symptomatic uterine fibroids include hysterectomy, myomectomy, hysteroscopic resection, uterine artery embolization and various medical treatments [1]. Traditional options for medical

treatment are gonadotropin-releasing hormone agonists, progestins and the levonorgestrel-releasing intrauterine system, which all have certain limitations and side effects [2]. More recently, targeting progesterone receptor (PR) signaling using selective progesterone-receptor modulators (SPRMs) such as asoprisnil, mifepristone, telapristone, and ulipristal acetate have been shown potentially beneficial treating patients with fibroids [3]. A large randomized placebo-controlled trial showed UPA to be effective in the treatment of symptomatic uterine fibroids without causing marked side effects [4]. A 5-mg daily dose of UPA led to a significant reduction in fibroid volume and rapid development of amenorrhea [4]. Repeated courses and long-term use of UPA have also been proven safe and effective in bleeding control and size-reduction of symptomatic fibroids [5]. The concerns associated with long-term use of SPRMs have mainly focused on endometrial histological changes. To our knowledge, there is only one previous report on changes induced by UPA on uterine fibroid architecture or histology [6]. We report a case of sizeable multilocular cystic hydropic degeneration in a uterine fibroid, which evolved during a repeated course of UPA.

CASE REPORT

A 44-year-old woman was referred to our hospital's gynecological outpatient clinic due to menorrhagia and sensation of pressure in the pelvic area. Patient's medical history included only systemic lupus erythematosus of the skin. She had a history of three uncomplicated vaginal deliveries and no previous abdominal surgery. Patient used no regular medication. Ultrasound (US) imaging revealed a typical subserosal fibroid of 7.5 cm in diameter in the anterior wall of the uterus, a hyperechogenic solid 5 cm sized cystic mass in the left ovary suspicious of a benign endometrioma, normal appearing right ovary, normal endometrium and no sign of ascites. CA12-5 measured 82 Units/L (normal range 0–35 units/L) and HE4 34 pmol/L (normal range 0–70 pmol/L in premenopausal women). HE4, a human epididymis protein 4, is a useful marker in ruling out malignancy when CA12-5 is elevated e.g., in endometriosis. Endometrial sampling showed normal histology. Since the patient refused hysterectomy, laparoscopic left adnexectomy and right-sided salpingectomy were performed. Left ovarian mass was histologically proven as benign endometrioma. Patient's recovery from the laparoscopic surgery was uneventful.

A three-month course of UPA (5 mg daily) was started after surgery because the patient suffered from menorrhagia and feeling of pressure most probably due to the uterine fibroid. A follow-up visit was scheduled at the end of the treatment course. At the three-month follow-up visit a response to UPA treatment was confirmed. The subserosal fibroid measured 5.5 cm in diameter by US imaging and the patient had reached amenorrhea. The

patient was counseled to continue with UPA for a three-month course after two menstrual periods. However, at the end of the repeated course of UPA, patient started to suffer again from cyclic pelvic pain and was referred to our outpatient clinic prior to the pre-scheduled appointment. By 2D-US imaging the fibroid was found enlarged, as an 11 cm-sized multilocular cystic mass with moderate blood flow by Power Doppler (Figure 1A–B). The right ovary was not clearly visualized and no ascites was detected. CA12-5 and HE4 measurements were normal and HCG was negative. Endometrium was thickened by UPA treatment but histological sampling showed normal proliferation. Due to alarming US findings, open surgery was recommended and hysterectomy was performed from midline lower vertical incision under general anesthesia. The uterine specimen weighed 1066 g and its body consisted mainly of a large multilocular cystic mass of 10.5 cm (Figure 2). Histopathological evaluation revealed benign multilocular fluid-filled cystic structures with marked degeneration (Figure 3). No areas of necrosis, cell atypia or aberrant mitotic activity were detected. Final histological diagnosis was cystic hydropic degeneration in leiomyoma. Postoperative healing was complicated by a mild infection and intra-abdominal hematoma, which yielded drainage in the operating theater.

DISCUSSION

To our knowledge, this is the first report of UPA-induced multicystic hydropic degeneration of a uterine fibroid evolved during a repeated course of treatment. Notably, a positive initial response to the first course of UPA treatment was observed. A single case report has been published recently describing unilocular cystic degeneration of a uterine fibroid during the three-month preoperative course of UPA [6] implying that cystic and rapid growth induced by UPA may still be a somewhat uncharacterized phenomenon.

Data on the specific mechanism of action of SPRMs are limited. It likely involves modulation of transcriptional activity of PR by modifying the interaction of PR complex with its corepressors and coactivators [7]. UPA has been shown to inhibit proliferation, induce apoptosis and reduce collagen synthesis in cultured leiomyoma cells, but having no effect on normal myometrial cells [3]. In



Figure 1: (A) Transabdominal ultrasound image showing uterine tumor with multicystic structures, (B) Moderate blood flow in a cyst septum detected by power Doppler.

addition, UPA has been shown to inhibit fibronectin and VEGF-A expression in an activin A-dependent manner [8]. These results imply that the mechanism of UPA action in fibroid shrinkage may be, at least to a certain extent, due to downregulation of local angiogenic factors.

The extensive uterine fibroid growth results in a degenerative process, which is usually due to inadequate blood supply [9]. Several variants of fibroid degeneration such as hyaline, cystic, myxoid and dystrophic calcification have been described [10]. We hypothesize that the development of the large mass with cystic hydropic

degeneration described here was due to compromised vascular supply promoted by repeated course of UPA. However, why this particular patient finally responded in this manner after a clear initial response to UPA therapy, remains unclear.

Uterine fibroids are benign tumors and usually routinely diagnosed with US or magnetic resonance imaging. However, this case report highlights that the UPA-induced degenerative and cystic changes can lead to diagnostic misinterpretation.

CONCLUSION

Ulipristal acetate (UPA) has been suggested to exert its inhibitive effect on fibroid growth by down-regulation of angiogenic factors. A degenerative process due to inadequate blood supply is the most likely pathogenetic mechanism for cystic tumor growth in the present case. Finally, as UPA is being more widely used, it is important to bring about awareness to clinicians of this SPRM-induced benign condition in order to avoid misdiagnosis of a malignant process.

Author Contributions

Synnöve Maaria Staff – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Sami Kristian Saarelainen – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Marita Aino Laurila – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published.

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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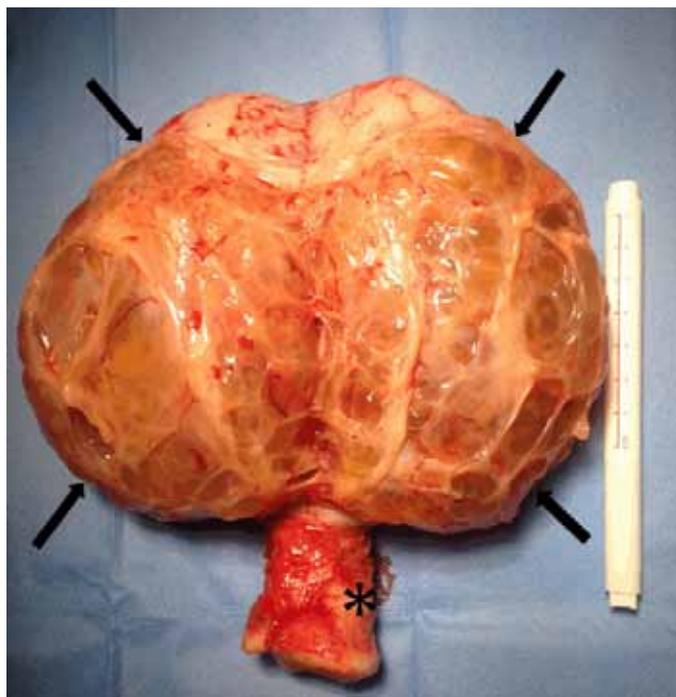


Figure 2: Uterine specimen obtained from abdominal surgery. Uterine body mostly consisting of multicystic hydropic tumor is incised in the midline leaving only the cervix intact. Cervix is marked with an asterisk and the borders of the multicystic tumor are indicated by arrows.

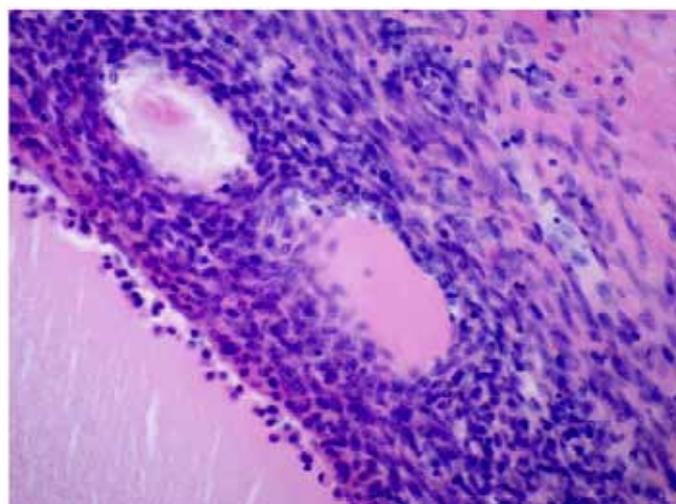


Figure 3: The uterine tumor morphology with multiple fluid-filled cystic structures (H&E stain, x200).

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