Cystic degeneration of uterine leiomyoma during ulipristal acetate treatment

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Uterine fibroma, leiomyoma or myoma, is both the most common solid tumor, as well as the most frequent smooth muscle tumor in women [1, 2]. It occurs in about 50% of women of reproductive age, and although many leiomyomas are asymptomatic, they may well lead to perturbing symptoms such as heavy menstrual bleeding, pelvic pressure symptoms and infertility [3]. Consequently, this benign uterine tumor is the single most common indication for hysterectomy [2, 4].

Leiomyoma is typified by increasing myometrial cell proliferation and a disproportionate accumulation of extracellular matrix [1, 2]. A great deal of evidence supports that its growth is dependent on ovarian sex steroids (estradiol and progesterone) hormonal activity through local cytokines and growth factors [5].

Generally, asymptomatic fibroids can be monitored simply through regular follow-up visits. However, myomectomy should be considered for patients with symptoms or for those who have large or growing tumors and want to preserve fertility. In women who have complete childbearing, to the contrary, hysterectomy is the standard treatment for symptomatic leiomyomas [4, 6].

Recent lines of attack to deal with uterine fibroid symptomatology involve hormone therapy (oral contraceptives, GnRHa), uterine artery embolization and a levonorgestrel-releasing intrauterine device (LNG-IUD) [3]. Additionally, the current introduction of several new potential therapeutic options (mifepristone, asoprisnil, ulipristal acetate, proellex, aromatase inhibitors, epigallocatechin gallate, and pirfenidone) has enriched our pharmacological arsenal for the management of leiomyomas [3, 4, 7-12].

Recently, the potential therapeutic role of selective progesterone-receptor modulators (SPRMs), an additional class of progesterone-receptor (PR) ligands displaying tissue-selective agonist/antagonist/mixed activity, has been introduced into clinical practice for the treatment of uterine leiomyomas [3, 9, 10]. Ulipristal acetate (UPA) is an orally active synthetic SPRM, characterized by a tissue-specific partial progesterone antagonist effect [8]. As a progesterone antagonist, UPA both inhibits the proliferation of leiomyoma cells, as well as induces apoptosis [5, 14]. Moreover, UPA
regulates the expression of angiogenic growth factors, matrix metalloproteinases and collagen deposition in the extracellular spaces, which, consequently, impairs fibroid tissue integrity by reducing vascularization, cell proliferation and survival in leiomyoma [4, 5, 12-14].

The clinical efficacy and tolerability of UPA in the treatment of symptomatic leiomyomas has been reported recently [4, 12, 13]. UPA has been shown to be useful for several clinical conditions. It might be administered to patients waiting for surgery in order to achieve clinical control of the symptoms (in particular, because it prevents the worsening of anemia). Furthermore, a reduction in uterine fibroid volume is achieved [4, 12, 13]. Finally, UPA may be a good option for women seeking pregnancy. Since it reduces the invasiveness of surgery, it expands woman’s fertility and improves the obstetric outcome [4, 15]. In contrast, the most recurrent adverse events were amenorrhea (although this is actually a goal to reach instead of an adverse event), headache, flushes, dizziness, discomfort, and tenderness in the breast [8, 12, 13]. Altogether, 94% of the patients reported adverse effects, describing their intensity as reasonable. Even so, such events resolved themselves spontaneously at the end of the treatment, and only 1% of the patients had to withdraw from the therapy because of undesirable side effects [8, 12, 13]. We describe three cases of complete cystic degeneration of uterine myomas in patients treated with UPA. This rare phenomenon had not been previously described among these patients, and it illustrates that UPA exerts, at least in part, its action on fibroids, via an anti-angiogenic effect.

Patient 1

A 43-year-old Caucasian woman, gravida 2, para 2, presented in our outpatient clinic with a history of a polymyomatous uterus associated with several months of heavy menstrual bleeding and an intense asthenia, despite the use of oral contraceptives and the posterior insertion of a LNG-IUD. Her blood pressure was 105/59 mmHg, with a pulse rate of 83 beats/min and a temperature of 36.8ºC. She had no significant personal or family medical history. Major laboratory findings at admission were a hematocrit level of 28.7%, hemoglobin of 8.6g/dL and a Ferritin of 12 ng/mL. Transvaginal ultrasound revealed a polymyomatous uterus with 3 intramural myomas measuring 3, 4 and 6 cm at the largest diameter and a pedunculated subserosal leiomyoma measuring 6 cm at the largest diameter. The patient was counseled regarding the different possible treatments. After counseling, the patient opted for uterine hysterectomy. The patient was prescribed UPA (Esmya®) 5mg/day and iron supplements for three months in order to control uterine bleeding and to restore hemoglobin and hematocrit levels before the surgery.

At 42 days after the initiation of UPA the patient attended our department because of markedly increased abdominal girth and moderate abdominal discomfort. A bimanual pelvic examination showed a mobile, 15cm mass in the left region. Transvaginal 2D/3D ultrasound revealed a polymyomatous uterus with the 3 intramural myomas measuring 2, 3 and 5 cm at the largest diameter. Moreover, a 15 cm cystic mass arising from the left side of the pelvis and extending into the upper abdomen was ascertained (Fig. 1A). The pedunculated subserosal leiomyoma was not observed. A cystic fibroid degeneration was considered in the differential diagnosis. Magnetic resonance imaging (MRI) was performed, and it supported our initial diagnosis (Fig. 1B).

The patient underwent laparotomy and a hysterectomy was performed. The histopathological examination corroborated the diagnosis of a complete cystic degeneration in the pedunculated leiomyoma (Fig. 1C).

Patient 2

A 39-year-old African American female patient, gravida 4, para 3, attended our gynecology outpatient department with complaints of lower abdominal pelvic pain, dyspareunia, and difficulty in passing urine for the last 6 months. The patient had regular menstrual cycles occurring at every 28 days with
normal bleeding lasting for 3-4 days. There was no previous illness or surgical intervention. Patient was a nonsmoker with normal bowel habits. Examination of her abdomen revealed a fixed suprapubic mass. She was referred for an ultrasound (US) examination which revealed an enlarged uterus with two intramural myomas measuring 12 and 5 cm at the largest diameter (Fig. 2A). The patient was counseled regarding the different possible treatments. After counseling, the patient opted for uterine hysterectomy. The patient was prescribed UPA (Esmya®) 5mg/day for three months in order to achieve a reduction in uterine fibroid size and to make surgery less invasive.

The patient presented in our outpatient clinic because of a significant increase in abdominal girth 51 days after the initiation of UPA. A MRI examination revealed a large, predominantly cystic mass of approximately 20x15x12 cm, arising from the middle of the pelvis and extending into the upper abdomen (Fig. 2B). The cystic mass revealed continuity with the remainder of the uterine myometrium. On the basis of these findings, a cystic degeneration of the uterine fibromyometrium was considered.

The patient underwent a laparotomy. A large cystic degenerated myoma arising from the anterior uterine body was observed. A hysterectomy was performed and histopathological examination confirmed the diagnosis of a leiomyoma with extensive cystic degeneration (Fig. 2C).

**Patient 3**

A 29-year-old nulliparous Caucasian woman, visited our hospital with complaints of menorrhagia and dysmenorrhea of seven months duration.

Her past medical history was unremarkable. A 3D-transvaginal US revealed a normal uterus with a uterine cavity distorted by a 3x3x3 cm submucosal myoma. This myoma was cataloged as G2 using the European Society for Gynecological Endoscopy (ESGE) classification system [16], meaning that it had its largest part (>50%) inside the myometrium. A hysteroscopic myomectomy was proposed to the patient and she accepted. The patient was prescribed UPA (Esmya®) 5mg/day for three months in order to achieve a reduction in the uterine fibroid size and make the surgery less invasive.

After completing the UPA therapy, the patient presented in our outpatient clinic for a pre-surgical US examination. She referred to amenorrhea and slight pelvic pain throughout the treatment period. 3D-transvaginal US examination, revealed a 4cm cystic mass inside the myometrium (Fig. 3A). A cystic degeneration of the submucosal uterine fibroma was suspected. A MRI was performed in order to complete the study, and it confirmed the initial US diagnosis. After counseling, the patient decided on an expectant management. Two months later, a 3D-transvaginal US revealed a significant reduction in the volume of the degenerated myoma (Fig. 3B). Five months later the US examination revealed a normal uterus with no sign of the fibroma (Fig. 3C).

**Discussion**

Leiomyomas have an atypical vasculature, characterized by a considerably well-vascularized peripheral area known as the “vascular capsule” and a progressively reduced vascularization throughout the epicenter of the tumor [14, 19]. Moreover, small myomas are nearly avascular, bordered by a condensed myometrial vascular complex constituted predominantly of capillaries [14, 19]. In contrast, larger fibroids comprise a disordered arrangement of blood vessels, mostly capillaries and venules [14, 19]. Once again, large fibromas are delimited by a dense peripheral vascular capsule [14, 19]. This distinctive vasculature harmonizes with the previously suggested pattern of angiogenesis in growing tumors. The pre-existing vasculature is first co-opted by the growing tumor. Subsequently, it undergoes degeneration and neo-angiogenesis begins at the periphery of the tumor leading to an invasion of new vessels into the tumor which support its future growth [20]. Furthermore, accumulating molecular evidence proposes that the expression of several angiogenic factors is dysregulated in fibroid tissue. Vascular
endothelial growth factor (VEGF) and adrenomedullin (ADM), major regulators of angiogenesis, are found in increasing concentration in uterine fibroids from the central zone to the periphery of the tumor \[14, 21\]. In addition, hypoxia-inducible factor-1α (HIF-1α) expression, which is typically up-regulated in hypoxia, forcing expression of numerous angiogenic factors and coordinating the tissue adaptations to hypoxia, was not identified in fibroid tissue \[14\]. This significant finding supports an anomalous reaction of fibroids to hypoxia and, therefore, a diminished tumoral vasculature \[5, 14, 17\].

Consequently, researchers are seeking out new therapeutic strategies for uterine fibromas and an enhanced understanding of local angiogenic growth factors \[5, 16, 17\]. The recent advent of UPA in clinical practice has led to a significant reduction of tumoral volume in uterine leiomyomas \[8, 12, 13\]. This effect is related, at least in part, to both the down-regulation of the angiogenic factors VEGF and ADM and their receptors, as well as to TGF-β and EGF and their receptors \[14\]. Additionally, a significant reduction in fibroid vascularization has been recently described by means of 3D power Doppler ultrasound after 3 months of UPA treatment \[22\]. Moreover, a moderate reduction in uterine artery blood flow was also reported following treatment with SPRMs \[14\]. These data suggest that UPA may induce leiomyoma shrinkage through an anti-angiogenic mechanism \[14\].

Conversely, numerous degenerative changes do take place habitually in uterine leiomyoma, such as hyaline, hydropic, myxoid, red, cotyledonoid, and dystrophic calcification \[23, 24\]. These changes are thought to be the consequence of relative ischemia involving regions of the myoma \[24-26\]. The apparition of edema in these tumors is considered to be an additional degenerative process, often referred to as hydropic degeneration. Whereas local hydropic degeneration is a relatively common process, the complete cyst transformation of a myoma is an exceptionally rare event \[24-26\].

It is of remarkable relevance that patient 3 had a myoma regression, and that the myoma completely disappeared after its cystic degeneration during UPA treatment. It illustrates the medical treatment of uterine leiomyomas as a realistic option for the future. This case is in consonance with a recent report in which two patients avoided surgical treatment as the myomas almost completely disappeared during treatment with UPA \[15\].

In conclusion, leiomyoma cystic degeneration in the context of UPA treatment is a phenomenon that can be expected. Patients and physicians need to be aware of this possible outcome since this degenerative process may lead to the inaccurate diagnosis of an adnexal malignant pathology \[24-26\]. Moreover, these cases illustrate the relevancy of vascular modulation in the myoma shrinkage under UPA treatment and open the door to the pharmacological treatment of myomas.

Conflicting interests

The authors have declared that no competing interests exist.

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