

# Cystic Degeneration of Submucous Uterine Leiomyoma After an Incomplete Course of Ulipristal Acetate Treatment

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Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) indicated for the medical treatment of myoma. Several theoretical mechanisms help explain how it induces apoptosis and cystic degeneration of a submucous myoma, leading to its expulsion. This paper presents the case of a young nulligravid diagnosed with heavy menstrual bleeding secondary to submucous myoma, who was started on UPA treatment but with very poor compliance. Despite the very short and incomplete course of treatment, degenerative changes still took effect, which led to the expulsion or prolapse of the pedunculated submucous myoma.

**Keywords:** ulipristal acetate, leiomyoma uteri, apoptosis

## Introduction

Uterine myomas are the most common pelvic tumors in women and are frequently responsible for heavy menstrual bleeding and pelvic pain. The most common treatment options include surgical interventions such as hysterectomy or myomectomy.<sup>1</sup> Recently, in 2017, ulipristal acetate (UPA) was introduced in the Philippine market as a potential medical treatment for leiomyoma uteri. UPA is an orally active synthetic selective progesterone receptor modulator (SPRM), characterized by a tissue-specific partial progesterone antagonist effect. As a progesterone antagonist, UPA both inhibits the proliferation of leiomyoma cells, as well as induces apoptosis. 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.<sup>2</sup> These mechanisms can, in theory, explain the cystic degenerative effect of UPA on leiomyoma uteri, even after an incomplete course of treatment.

Reported here is the case of a 25 year old nulligravid who suffers from heavy menstrual bleeding secondary to submucous myoma, who, after only 1 month of treatment with UPA, showed signs of cystic degeneration and expulsion of the endometrial mass. Also discussed here are the mechanisms on how cystic degeneration happens after UPA treatment. This case report may also suggest the possible significant apoptotic effects of UPA even after only a very short and incomplete course of treatment.

## The Case

This is a case of a 25 year old single nulligravid, who consulted at the outpatient department of a tertiary hospital due to heavy menstrual bleeding.

History started one year prior to admission when patient first experienced prolonged and heavy menstrual bleeding with blood clots, using up to 7 fully soaked regular pads/day, lasting for 14 days. No consultation was done and no medications were taken. Six months prior to admission, there was persistence of heavy menstrual bleeding which prompted the patient to consult at the outpatient

department. Transvaginal ultrasound showed a submucous myoma, measuring 2.95cm x 1.95cm x 2.80 cm. Her complete blood count showed severe anemia (hemoglobin of 47 g/l). She was admitted and transfused with 4 units of packed red blood cell. A sonohysterosalpingogram showed a grade 0 submucous myoma measuring 4.20cm x 2.95cm x 2.07cm, attached at the posterior middle-third, and a endometrial pedunculated polyp at the fundal area measuring 1.78cm x 2.62cm x 1.12cm. She refused hysteroscopic myomectomy during this time due to financial constraints, so she was started on ulipristal acetate 5mg OD, instead. Liver enzymes prior to treatment were all normal. She was advised to finish at least 2 courses of medical treatment (total of 6 cycles), but due to financial constraints, was not able to continue beyond the first 30 days of treatment with ulipristal acetate.

In the interim, her menstrual bleeding became normal in amount, duration and frequency, following her one month intake. She had no other subjective complaints. No consultations were done, and she was lost to follow-up. Until 3 months prior to admission, patient reported to experience a recurrence of heavy menstrual bleeding, using up 4-5 fully soaked regular pads/day, lasting for 14 days. No consultation was done and no medications were taken.

On the day of admission, patient presented at the OPD with persistent heavy menstrual bleeding, pallor, and a palpable mass inside her vagina, described as the size of a chicken egg.

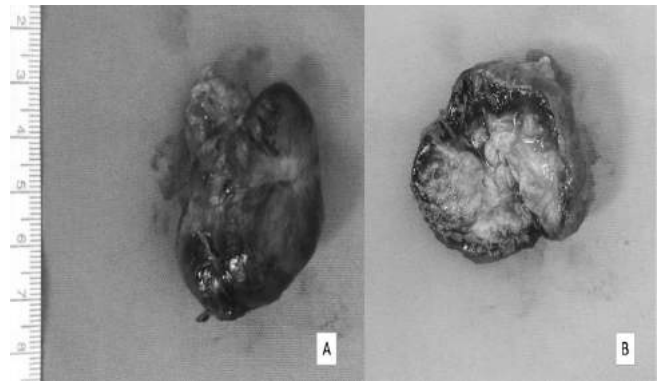
Patient has no known co-morbidities nor heredo-familial diseases such as hypertension, diabetes mellitus, asthma, cancer, cardiac, kidney, or thyroid problem nor previous surgical operations. She is a college graduate, a non-smoker, and an occasional alcoholic beverage drinker and does not use illicit drugs. She had her menarche at the age of 14 with subsequent menses occurring at regular intervals, lasting for 5 days, using 3-5 regular pads/day, moderately soaked with no associated dysmenorrhea. Her last menstrual period was approximately a month prior to admission.

On admission, patient was conscious, ambulatory, with stable vital signs, and normal BMI. She had pale palpebral conjunctiva, and normal cardiopulmonary and abdominal findings. On pelvic exam, she had normal external genitalia, and there was a 5cm x

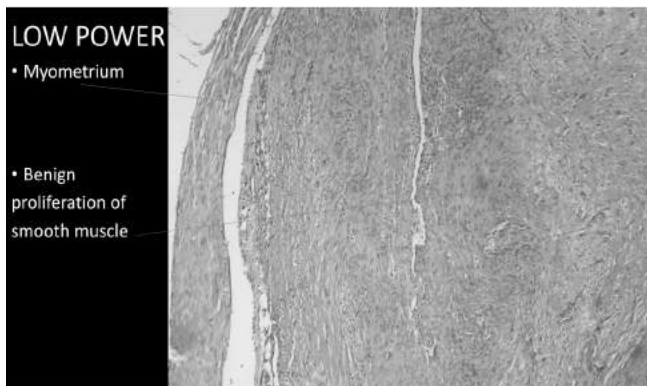
3cm, smooth, soft pedunculated mass occupying the vaginal vault, seemingly attached at the anterior uterine wall.

Admitting impression was Abnormal Uterine Bleeding – Leiomyoma (prolapsed submucous myoma); Anemia secondary to chronic blood loss.

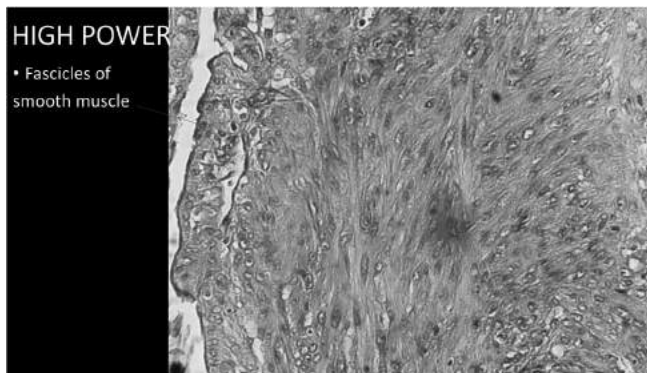
Complete blood count showed moderate anemia (hemoglobin level of 89 g/l). A transvaginal ultrasound showed a normal sized retroverted uterus, normal cervix and ovaries, with a hypoechogenic myoma-like structure at the endocervical canal extending to the lower uterine segment measuring 4.48cm x 3.57cm x 2.7 cm which could be a prolapsed submucous myoma. She was given tranexamic acid 500mg IV every 6 hours and mefenamic acid 500 mg/tablet every 8 hours to control her vaginal bleeding. She was transfused with 2 units packed red blood cell. Post-transfusion, the hemoglobin level improved to 101 g/l. She underwent vaginal myomectomy with diagnostic hysteroscopy and endometrial biopsy on hospital day 2. Upon visualization, a 4cm x 3cm, degenerated, violaceous, foul smelling endocervical mass was seen prolapsed at the external cervical os, with scanty vaginal bleeding (Figure 1). No endometrial masses were noted upon diagnostic hysteroscopy. Specimen was sent for histopathologic analysis and the patient tolerated the procedure well. On the third hospital day, the patient had stable vital signs and was subsequently discharged. Histopathologic results revealed Leiomyoma (Figures 2 & 3) and fragments of endometrial polyps.



**Figure 1.** A 4cm x 3cm, degenerated, violaceous, foul smelling endocervical mass was seen prolapsed at the external cervical os, with scanty vaginal bleeding (A); Cut section of the mass showed some indistinct whorled pattern (B)



**Figure 2.** Low power view of the cut section of myomatous mass showing benign proliferation of smooth muscles.



**Figure 3.** High power view of the myomatous mass showing fascicles of smooth muscle.

## Discussion

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) indicated for the medical treatment of myoma. Randomized controlled trials (PEARL I-IV) showed that UPA induces amenorrhea in 80% of patients after only 3.5 days of treatment, and it reduces myoma volume by 45%. It does not reduce the estrogen circulating rate.<sup>3</sup> The same trials showed that the 5-mg daily doses of ulipristal acetate was actually non-inferior to once-monthly leuprolide acetate in controlling uterine bleeding and were significantly less likely to cause hot flashes.<sup>4</sup>

Since its introduction to the Philippine market in 2017, ulipristal acetate (UPA) has become accepted as part of the limited therapeutic strategies Filipino gynecologists may offer symptomatic patients with leiomyoma uteri, especially those with abnormal uterine bleeding and pelvic pain. The Philippine FDA approved the use of ulipristal acetate for the

following indications: 1) for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; 2) for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Prior to its temporary product recall in April 2020 (due to an EMA review on a rare but serious liver injury case allegedly due to ulipristal acetate), Filipino gynecologists have reported various clinical findings about its efficacy in controlling heavy menstrual bleeding and reducing uterine volume. Ulipristal acetate 5mg is recommended to be taken once a day for at least 3 months (1 course), and most experts advise at least 2 courses of treatment for a more clinically-significant improvement in signs and symptoms.

For this report's index case, what could have caused the submucous myoma's cystic degeneration despite an incomplete course of therapy?

Myoma expulsions reported in the published literature are mainly expulsions secondary to postembolization necrosis, and after treatment with GnRH agonists. There is only one published report on myoma expulsion while under SPRM treatment.<sup>1</sup> The link between the administration of UPA and expulsion of the myoma may theoretically be explained by UPA's degenerative effects on the submucous myoma, that can be explained by various mechanisms: UPA induces apoptosis and 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- $\beta$  and EGF and their receptors.<sup>2,5,6</sup> Another theory states that UPA may effect a significant reduction in fibroid vascularization through an anti-angiogenic mechanism.<sup>2,7</sup>

Why then do some women manifest with no clinical response to UPA? A landmark study by Guillaume, et al. showed the first molecular distinction between myomas responsive or non-responsive to UPA treatment. Significant changes in expression of four genes were found in UPA-treated myomas: gene expression of integrin subunit beta 4 was repressed by UPA treatment, tenascin-C expression was downregulated in UPA-responsive patients, survivin was repressed in short-term UPA-responsive tumors and catenin delta 2 gene expression was upregulated in non-responsive myomas. This study lays out the genetic basis of

clinical response to UPA, and why some myoma are UPA-resistant, while others are UPA-sensitive. These molecular explanations as to the mechanism of action of UPA illustrate that the medical treatment of uterine leiomyomas is indeed a realistic option for the future. Whereas the genetic basis for a woman's clinical response to UPA may help identify the cohort of women where UPA may be the best option.

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