Clinical Case Report

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# Failure of ulipristal acetate treatment as an indication for uterine malignancy

## Two case reports

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**Abstract**

**Introduction:** To study the clinical, pathological and therapeutic implications of ulipristal acetate (UPA) treatment failure in patients affected by uterine smooth muscle tumors.

**Case Presentation:** Two patients affected by uterine leiomyosarcoma were preoperatively diagnosed as uterine leiomyomas and, thus, treated conservatively with UPA and morcellation. Both patients experienced a worsening of symptoms (persistent bleeding) after 3 month of treatment with UPA. Therefore a myomectomy with morcellation of tumor specimens was performed. Pathological examination of morcellated specimens revealed the unsuspected diagnosis of leiomyosarcoma based on the presence of severe nuclear atypia, tumor necrosis and increased mitotic activity. Unfortunately after 6 month of follow-up, 1 patient died for multiple peritoneal recurrences and lung metastases. The other patient is still alive after 3 month of follow-up and shows no local recurrences or metastases.

**Conclusion:** Our reported cases emphasize that the poor or absent response to UPA treatment in addition to the instrumental evidence of a single mass may be indicative of the presence of an unsuspected leiomyosarcoma clinically and radiologically misdiagnosed as leiomyoma. The awareness of this possibility would avoid a delay in the diagnosis as well as unuseful and potentially dangerous treatments such as morcellation.

**Abbreviations:** FDA = Food and Drug Administration, GnRH = gonadotropin releasing hormone, LMS = leiomyosarcoma, MRI/US = magnetic resonance imaging/ultrasonography, PAEC = PRM-associated endometrial changes, PRM = progesterone receptor modulators, ULM = uterine leiomyoma, UPA = ulipristal acetate.

**Keywords:** esmya, leiomyoma, leiomyosarcoma, morcellation, ulipristal acetate

## 1. Introduction

Hysterectomy has long been considered the treatment of choice for symptomatic uterine leiomyoma (ULM), despite the consequences on fertility in women of reproductive age.[1] Nowadays, minimally invasive surgical approaches such as myomectomy through the laparoscopic or the hysteroscopic route, mini-invasive laparotomy, and robotic assisted surgery are more often proposed especially in women who wish to preserve their fertility.[2] Power morcellation represents a useful approach that facilitates minimally invasive surgery of even large uterine masses.[3] This technique involves the use of a whirling blade to generate small fragments that can pass through laparoscopic ports. However, if a malignant tumor is preoperatively misclassified as benign and morcellated there is a significant risk of dispersing microscopic tumor fragments in the peritoneal cavity.[4]

As an alternative to surgery, women with symptomatic fibroids who wish to preserve their fertility can be treated with gonadotropin releasing hormone (GnRH) analogues and ulipristal acetate (UPA).[5]

Currently, UPA is emerging as a novel approach indicated for intermittent, long term, and preoperative treatment of symptoms related to uterine fibroids.[6] The reversible blocking of the progesterone receptor induced by UPA inhibits the proliferation of the myoma cells and also induces an inhibition of the ovulation reducing, thus, the heavy menstrual bleeding related to ULM.[7]

However, about 5% of patients do not benefit from this treatment and the possible explanations for this phenomenon are still debated.[8] Recently, some authors emphasized the presence of unsuspected leiomyosarcoma (LMS) as a possible cause of poor response to UPA.[9,10]

We herein report 2 cases of LMS, which were preoperatively diagnosed as ULMs and, thus, treated with UPA followed by morcellation. The present cases emphasize the importance of the early detection of a LMS in cases in which UPA treatment is ineffective in order to avoid a delay in the diagnosis as well as potentially dangerous surgical approaches such as morcellation.

## 2. Case report

### 2.1. Methods

Tissue samples analyzed in the present study were collected from patients receiving 5 mg/d of UPA for 12 weeks.

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For pathological examination of resected specimens, sections (4–5 μm in thickness) were cut from paraffin blocks using a microtome, mounted on sialinate-coated slides (Dako, Glostrup, Denmark) and stored at room temperature. The sections were stained with hematoxylin and eosin (H&E) and examined using a Zeiss Axioplan light microscope (Carl Zeiss, Oberkochen, Germany) for general morphological characterization and to highlight the presence or absence of structural alterations

The histological diagnosis of leiomyosarcoma was rendered on the basis of the presence of severe nuclear atypia, increased mitotic activity (>10 mitoses/10 high power fields), atypical mitotic figures and tumor necrosis.

### 2.2. Ethics statement

The study was approved by the ethics committee of our hospital

### 2.3. Case 1

A 46-year-old woman, with a medical history of uterine bleeding was referred to our hospital for persistent dysmenorrhea and pelvic pain. Imaging (magnetic resonance imaging/ultrasonography, magnetic resonance imaging/ultrasound [MRI/US]) revealed a single mass, located on uterine posterior wall. The patient underwent preoperative treatment with UPA to control menorrhagia. This treatment was stopped after 3 months because of persistent bleeding. In March 2016, she underwent a laparoscopic myomectomy and morcellation. Histologic evaluation of morcellated specimens revealed scattered foci of vial tumor cells in a background of coagulative type necrosis. Tumor cells were arranged in long intersecting fascicles, showed a spindled morphology and severe cytologic atypia with cigar shaped nuclei and prominent nucleoli (Fig. 1A). Moreover, a brisk mitotic activity of 58/10 HPF was encountered. Based on the above mentioned findings, a diagnosis of LMS, spindle cell variant was rendered.

Given the unsuspected diagnosis of LMS a hysterectomy with adnexectomy was performed and the pathological examination revealed residual foci of LMS within the uterine wall. The patient underwent chemotherapy and 6 month later she died for peritoneal and lung metastases.

### 2.4. Case 2

A 47-year-old woman, secundigravida para 2, with a medical history of Hashimoto thyroiditis and no other relevant general health problems, was referred to our hospital for a symptomatic ULM causing heavy menstrual bleeding. A diagnosis of a ULM has been made in 2006, during the first pregnancy. She did not undergo any follow-up until September 2017, when, due to the appearance of hypermenorrhea and menorrhagia since April 2017, she underwent an ultra-sonographic pelvic exam documenting an intramural fibroid, 6.5 cm in diameter, and 1.9 cm subserosal myoma. At the time of the first visit, in October 2017, she was on UPA treatment since a few days, and the medical board suggested her to go on with the treatment while completing her diagnostic work-up. During the first period of UPA administration, the patient experienced an improvement of her symptoms. Concomitantly, she reported the recurrence of very heavy menstrual bleeding despite UPA intake. The patients then underwent a hysteroscopy with intrauterine morcellation and the pathological examination revealed a uterine leiomyosarcoma and an endometrial polyp.

Because the unexpected diagnosis of malignancy a robotic hysterectomy with adnexectomy was performed. Pathological examination of the hysterectomy specimen revealed a 4 cm grey-white nodule with scattered areas of hemorrhage and necrosis located within the uterine wall. Histologically the nodule was highly cellular and consisted of intersecting fascicles of spindle cells with eosinophilic cytoplasm. Tumor cells showed a severe nuclear atypia and the mitotic index was 30 per 10 high-power fields. Areas of hemorrhage and ischemic necrosis were encountered; however, coagulative necrosis was not present. Based on the severe nuclear atypia and the brisk mitotic activity, a diagnosis of LMS, spindle cell variant was rendered (Fig. 1 B). After three months of follow-up the patient is still alive and shows no tumor recurrences or metastases.

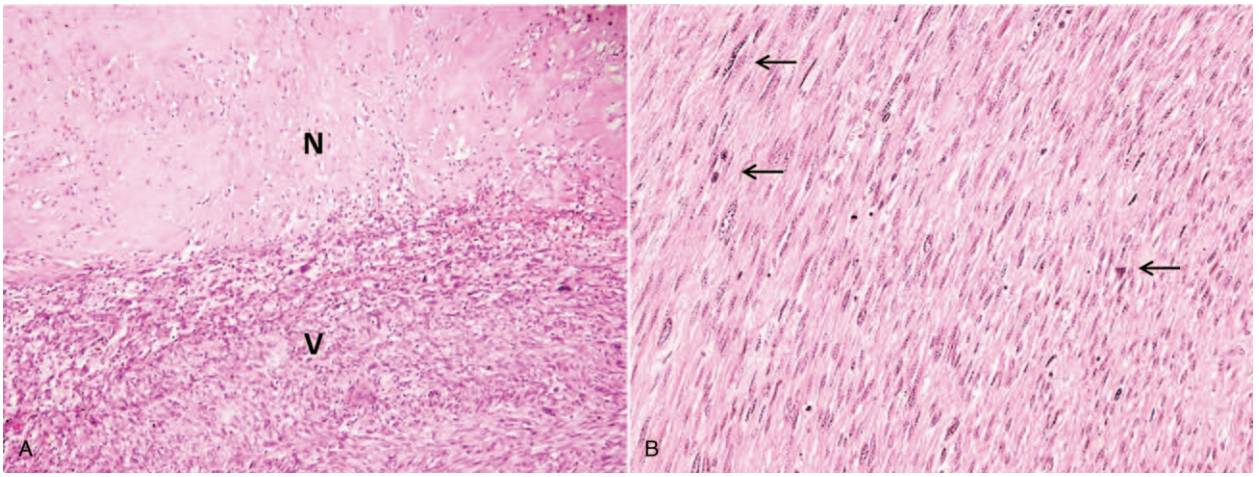


**Figure 1.** Pathological examination of leiomyosarcoma cases preoperatively diagnosed as leiomyomas: Hematoxilyn and eosin stained sections (H & E). A, Case 1: The interface between vial tumor cells (V) and tumor necrosis (N) is depicted. Tumor cells are arranged in long intersecting fascicles, and show a spindled morphology with cytologic atypia (H & E, 10 ×). B, Case 2: highly cellular neoplasm composed of intersecting fascicles of spindle cells with eosinophilic cytoplasm. Tumor cells show a severe nuclear atypia (arrows) (H & E, 20 ×).

## 3. Discussion

UAP is a selective progesterone receptor modulator that has recently been approved for intermittent, long term, and preoperative treatment of moderate-to-severe symptoms associated with ULM in adult women of reproductive age.[6–8]

The reversible blocking of the progesterone receptor induced by UPA explains it's anti-proliferative, anti-fibrotic and pro-apoptotic effects which are responsible of the reduction of ULM size. Moreover, due to its interaction with endometrial progesterone receptors, UPA induces amenorrhea reducing thus the severe bleeding related to ULM.[6–8]

An interesting finding described in endometrial biopsies from patients treated with progesterone receptor modulators (PRM) is the occurrence of endometrial changes known as PRM-associated endometrial changes (PAECs).[11,12] These are reversible changes induced by hormonal depletion as well as estrogenic or progesterone stimulation and include the development of cystic changes and the increase in endometrial thickness, that tends to disappear after the cessation of treatment and do not determine any long-term implications.[11,12] Pathologists must be aware of these specific changes in order to avoid confusion with other entities such as disordered proliferative endometrium, unopposed estrogen effect, or endometrial hyperplasia.[11,12]

Moreover, a considerable small percentage of patients (4.8%) has been reported to not benefit from UPA treatment and the possible motivations for this inefficacy are still debated.[8] In this regard, a recent study identified the following predictive parameters of UPA treatment failure: young age (<35 years), absence of previous pregnancy and the size of the dominant fibroid ≥ 80 mm.[13] Hence, the persistence of heavy bleeding and pelvic pain during UPA treatment is not to be considered specific for the diagnosis of LMS.

Similarly, our reported LMS cases were preoperatively misdiagnosed as benign smooth muscle tumors (ULM). Therefore, the treatment with UPA revealed to be ineffective or only partially beneficial, so that both patients experienced a rapid increase of symptomatology.

To the best of our knowledge, a total of 6 cases of LMS treated with UPA for suspected ULM have been reported in the literature. In detail, Kadhel et al[10] recently reported two LMS cases in which UPA treatment for a presumed ULM revealed to be ineffective. A similar case of LMS inadvertently treated with UPA has been described in a European multi-centre, prospective study of patients undergoing a pre-operative treatment with UPA for suspected ULM.[14] Another case of LMS initially treated as a ULM with UPA has been described by Laursen et al.[15] In this report, the final diagnosis of LMS was achieved only after a laparoscopic hysterectomy using contained power morcellation. Istre O described the case of a symptomatic ULM treated at first with UAP for 6 months and then, due to the worsening symptoms, with a laparoscopic hysterectomy with morcellation.[9] Also in this case the pathology report showed a malignant leiomyosarcoma and a postoperative positron emission tomographic scan revealed 4 metastatic processes in the lungs.

In another recent paper, Modaffari et al[16] presented the case of a woman with hereditary fibrinogen deficiency, exclusively treated with UPA for myoma-related menorrhagia and abdominal pain. Because of clinical worsening, hysterectomy was performed and a FIGO IB uterine leiomyosarcoma was found among multiple myomas. Similarly, our cases, preoperatively treated with UPA, were diagnosed as LMS following a laparoscopic morcellation of the tumor. This minimally invasive surgical approach has gained increased attention in recent times because in case of unsuspected LMS there is a significant risk of dissemination of the morcellated tumor within the abdomino-pelvic cavity.[3,4]

This event automatically leads to upstaging of the cancer to International Federation of Gynecology and Obstetrics stage IIA and affects the long-term survival of patients. Therefore, the US Food and Drug Administration (FDA) has estimated the risk of diagnosing LMS after hysterectomy of presumed ULM to be 1/350 and advanced a warning against the use of power morcellation.[17] Unfortunately, given the lack of pathognomonic clinical and radiological signs, the differential diagnosis between benign and malignant uterine smooth muscle tumors still represents a challenging topic in gynecologic oncology. Therefore, the pathological examination of the surgically resected specimen remains the gold standard for the diagnosis of LMS.

Our reported cases, similarly to previous publications, emphasize that the poor or absent response to UPA treatment in addition to the instrumental evidence of a single mass may be indicative of the presence of an unsuspected LMS clinically and radiologically misdiagnosed as ULM.

Therefore, the gynecologists and radiologists must pay attention to any unusual evolution of the symptomatology during UPA treatment such as increasing pelvic pain and persistent bleeding in order to identify as earlier as possible the presence of a LMS. Moreover physicians should always consider a clinical and instrumental careful re-evaluation when planning to repeat UPA treatment cycles. This strategy would avoid a delay in the LMS diagnosis as well as unnecessary and potentially dangerous treatments such as morcellation that may cause an upstaged or metastatic tumor.

## Author contributions

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**Writing – review & editing:** Angela Santoro, Giuseppe Angelico, Gian Franco Zannoni.

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