Clinicopathological changes of uterine leiomyomas after GnRH agonist therapy

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Summary

Objective: Gonadotrophin-releasing hormone agonist (GnRHa) has been commonly used for the medical treatment of prostate cancer, precocious puberty, endometriosis, adenomyosis and uterine leiomyomas. GnRHa therapy in cases of symptomatic uterine leiomyomas aims for the reduction of their size and remission of symptoms such as menometrorrhagia, causing a state of hypoestrogenemia. This is considered to be a helpful preoperative strategy in cases of large myomas, or anemia because of abnormal vaginal bleeding. The aim of this retrospective study was to examine the clinicopathological changes in uterine leiomyomas exposed to preoperative GnRHa therapy for two up to six months. *Materials and Methods:* The study group consisted of 10 premenopausal patients who were treated with GnRHa prior to surgery. *Results:* In all cases the size of leiomyomas was reduced after GnRHa therapy. A microscopic review of the surgical specimens showed increased cellularity and ischemic type of necrosis. *Conclusion:* Morphological changes of uterine leiomyomas are often associated with preoperative GnRH agonist therapy. The differential diagnosis from uterine leiomyosarcomas includes absence of mitotic activity.

Key words: GnRH agonist; Uterine leiomyomas; Morphological changes.

Introduction

With the advent of isolation and synthesis of the gonadotrophin-releasing hormone (GnRH) by Schally *et al*. (1971) in the early 1970s, interest in the clinical application of GnRH agonist (GnRHa) has grown [1]. GnRH analogues are a class of drugs that downregulate hypophyseal receptors, resulting in a direct refractoriness of the gland to new GnRH stimulus. That leads to a reduction of gonadotropins and ovarian steroid serum levels, with important changes in cell growth, cell cycle progression, apoptosis and expression of growth factors that determine regressive alterations in myometrial cells [2, 3].

Uterine leiomyomas are considered to be hormone-sensitive neoplasms, since estrogens have been shown to promote their growth as the concentration of receptors for estradiol is higher in leiomyomas compared to normal myometrium [4]. Chronic administration of GnRHa causes a 'medical oophorectomy' with a state of hypoestrogenemia through suppression of ovarian follicular activity. This is followed by reduction of the volume of the estrogen-sensitive uterine leiomyomas and by remission of symptoms such as menometrorrhagia.

From a surgical point of view the operation is easier after GnRHa treatment because of the reduction of both uterine volume and blood flow. The surgical field is better and there is less bleeding [5, 6]. This is very important in order to avoid hysterectomy in cases of young premenopausal women where myomectomy is the only surgical approach for fertility preservation reasons. GnRHa preoperative therapy is also helpful in cases of anemia due to symptomatic uterine leiomyomas, in order to decrease abnormal vaginal bleeding prior to surgery and the need for transfusion during the operation.

Although the endometrial morphology following GnRHa therapy has been described [7], the possible morphologic changes within leiomyomas have not been thoroughly studied [8-10]. The aim of this study was to analyze the clinical, surgical and histopathologic changes of uterine leiomyomas removed after GnRHa treatment.

Materials and Methods

From September 2009 to February 2011, ten patients who had received GnRHa therapy for two to six months prior to surgery, because of uterine leiomyomas, were seen in our Department. All women were premenopausal. They presented with either an asymptomatic pelvic mass diagnosed in a typical ultrasound (US) examination or with symptoms such as menometrorrhagia, menstrual disorders, infertility, and urine retention. The leiomyomas were resected by operative hysteroscopy, laparoscopic/abdominal myomectomy or hysterectomy. None of the patients had any history of recent pregnancy, other uterine surgery, or hormone replacement/contraceptive therapy.

This was a retrospective study. All necessary parameters (patient's age, symptoms, number and size of uterine leiomyomas prior and after GnRHa therapy, type of surgery, surgical findings, blood loss during surgery and need for transfusion, type-dosage-duration of GnRHa treatment and time between the last GnRHa dose and the operation) were collected from the hospital history records of the study group patients as well as from their surgical and histopathological reports.

In all cases the specimens were fixed in 4% neutral buffered formaldehyde, examined and sectioned, and blocks were selected and processed. Hematoxylin-eosin stained slides were examined. Mitotic activity, cellularity, fibrosis degree, edema between the smooth muscle cells, vascular changes and cytological atypia or necrosis – with cytoplasmic and nuclear changes – were studied during the histopathological examination.

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Results

Ten patients (27-48 years old, mean age 38.1 years), with prior surgical removal of their uterine leiomyomas and GnRHa treatment, were seen in our Department during this study period. The most common symptoms and signs were menometrorrhagia/menstrual disorders (50%), infertility (10%) and urine retention (10%). In the rest of the cases, typical gynecological and US routine examination revealed an asymptomatic pelvic mass.

Eight patients had been treated with triptorelin. Five out of these eight patients had received depot intramuscular injections of triptorelin (3.75 mg) administered every four weeks for periods varying from two months (two doses) to six months. Two patients received two doses, one patient three doses and in the other two cases the patients underwent six cycles. Three out of the eight patients who were treated with triptorelin received depot intramuscular injections of triptorelin pamoate (11.25 mg) administered every 12 weeks, from three months (one dose in one case) up to six months (two doses in another one patient). Two patients had been treated with another GnRH analogue, leuprorelin acetate, again using depot intramuscular injections (3.75 mg) at four weekly intervals for periods of two and three months, respectively.

All patients underwent surgery in a period of two up to five months after cessation of treatment with GnRH analogues. In one case hysteroscopic resection of a submucosal leiomyoma was perfomed. Seven patients underwent myomectomy and in two cases hysterectomy was necessary because of multiple large leiomyomas. In five cases a single leiomyoma was resected and examined, in three cases two leiomyomas, and in the last two cases multiple leiomyomas were removed within the surgical specimen of the uterus. In all cases leiomyomas maximum diameter at the time of surgery was reduced from 1.4 up to 3.2 cm in comparison with the US findings before GnRHa therapy. In only one case was there the need for transfusion during surgery.

The pathologic examination of the leiomyomas removed after GnRHa treatment showed cellular areas with moderate cellular and nuclear atypia of smooth muscle cells. Areas of ischemic type necrosis, hyalinization or hydropic degeneration of stroma were observed as well. No remarkable mitotic activity (0-1 mitoses/10 high-power fields HPF), or geographic type necrosis were observed (Figures 1, 2, 3). The morphology was consistent with the effects observed after GnRH therapy.

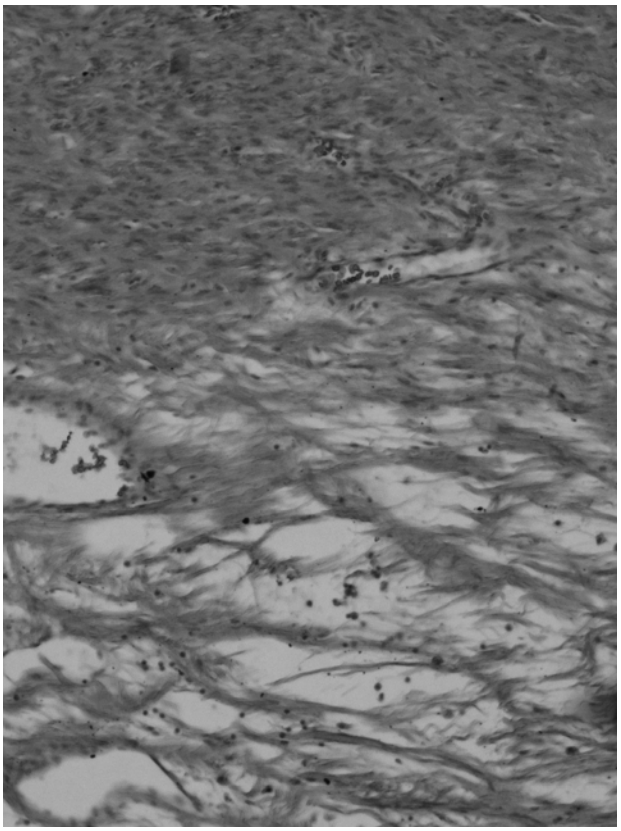


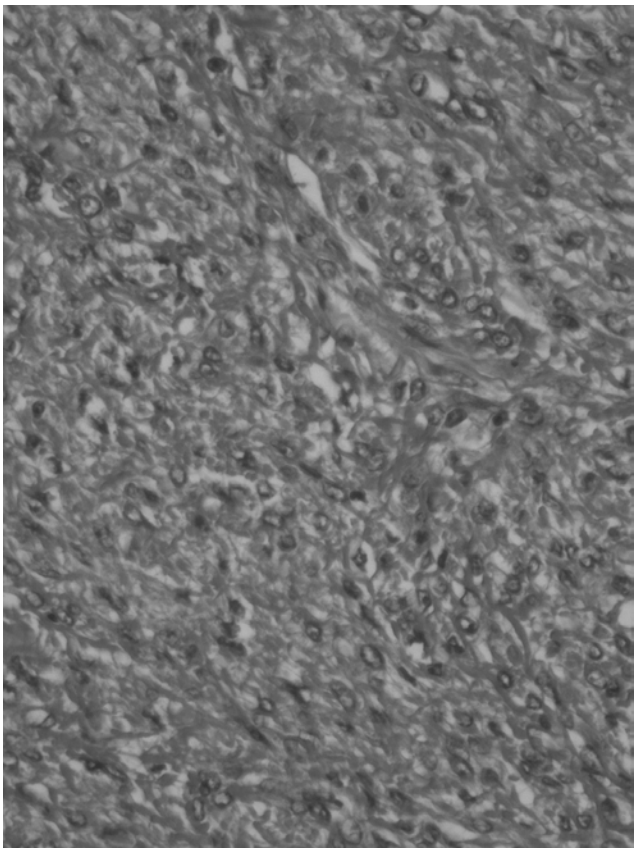
Figure 1. — Histological section showing stromal hydropic degeneration of a leiomyoma after GnRH agonist therapy (H-E x 120).

Discussion

GnRH agonists are commonly used as an adjunct to surgery since the need for transfusion during surgery may be reduced and leiomyoma shrinkage may lead to an easier and safer operation, avoiding hysterectomy [11]. Their use is also indicated in cases of perimenopausal women with leiomyomas as a temporary treatment to reduce menometrorrhagia and associated anemia prior to the onset of menopause. On the other hand, long-term treatment with GnRHa can cause osteopenia, osteoporosis and vaginal dryness due to prolonged hypoestrogenism. That is why patients under GnRHa treatment have to receive calcium in order to avoid osteopenia. None of our patients received GnRHa therapy for more than six months and all were under calcium during the treatment period. Response to intramuscular GnRHa therapy occurs within three weeks of the initiation of the treatment [12], and the maximal rate of reduction of uterine and leiomyoma size occurs during the first month of GnRH agonist treatment [10]. However it is also well known that most leiomyomas return to pretreatment size in cases of premenopausal women after cessation of treatment if it is not followed by surgical resection [13].

Many studies demonstrate that the reduction of uterine volume is caused by the reduction of both leiomyoma and nonleiomyoma components of the uterus [14]. It is believed that hypoestrogenism caused by GnRHa leads to a significant reduction in uterine blood flow in pathologic lesions or in surrounding myometrial tissues as Doppler US examinations have shown [10, 15, 16]. These findings as well as the severe decrease in micro-vessel density in leiomyomas after GnRHa treatment could give an explanation to the mechanism of action of GnRHa therapy in the reduction of uterine size. In all our cases the diameter of leiomyomas was reduced after GnRHa therapy.

Fig. 2



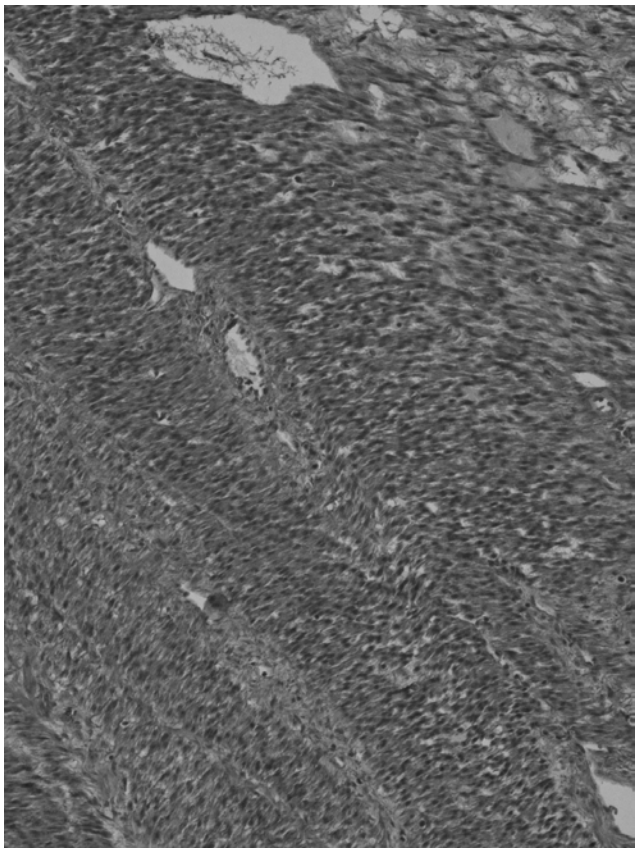


Fig. 3

Figures 2-3. — Histological sections of leiomyoma after GnRH agonist therapy showing increased cellularity and microcystic stromal degeneration (H-E x 120, Figure 2), (H-E x 25, Figure 3).

Also only in one case was transfusion necessary. This is probably because of reduced blood loss during myomectomy after GnRHa therapy.

In agreement with other studies [8, 9] we did not reveal any significant differences in mitotic activity, edema, fibrosis or vascular changes. The histopathologic findings of our study demonstrate hypercellularity and ischemic type of necrosis in leiomyomas that had been exposed to GnRHa therapy.

These results lead in many cases to diagnostic problems. However the absence of remarkable mitotic activity and cellular atypia is enough to exclude leiomyosarcomas from the differential diagnosis of these smooth muscle tumors.

In conclusion, pathologic changes in leiomyomas following GnRHa treatment, such as increased cellularity, ischemic type of necrosis, hyalinization or hydropic degeneration are often probably associated with this preoperative therapy. On the other hand this treatment leads to an easier surgery with less bleeding in order to avoid hysterectomy especially in young premenopausal women. Also in perimenopausal women it could be an ideal strategy to control menometrorrhagia and avoid the risks of an unnecessary surgery prior to menopause.

These are the main reasons for which the conclusion of many studies is that GnRHa therapy could result in a more cost-effective use of hospitalization and support services [9, 17].

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