# A case with diffuse uterine leiomyomatosis and review of the literature

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**Summary**

Leiomyomas and diffuse uterine leiomyomatosis are smooth muscle tumors of the uterus. Diffuse uterine leiomyomatosis is a benign and extremely rare condition in which the uterus is symmetrically enlarged as a result of the almost complete replacement of the myometrium by innumerable poorly defined, confluent nodules. The etiology of these neoplasms is not completely understood. Initial symptoms of the diffuse uterine leiomyomatosis usually are abdominal pain and abnormal uterine bleeding. Similar to uterine leiomyomas, patients with leiomyomatosis present with menorrhagia, dysmenorrhea, abdominal pain, infertility, and pelvic pressure. Hormonal treatment usually fails to control the symptoms, anemia, or tumor growth after treatment is stopped. As a result, despite patients being in the third or fourth decades of life, hysterectomy has been the only permanent treatment option offered to patients for treatment of the symptoms related to uterine fibroids in diffuse leiomyomatosis. A case of a patient with a huge uterine mass (2,650 g in weight) who underwent hysterectomy due to diffuse uterine leiomyomatosis is presented together with a review of the literature.

*Key words:* Diffuse uterine leiomyomatosus; Leiomyoma; Management.

## Introduction

Leiomyomas or benign fibroids are smooth muscle tumors of the uterus. They are encountered in up to 25% of women in active reproductive life. The etiology of these neoplasms is not completely understood, however, their high prevalence among premenopausal women and regression in postmenopausal years suggest an association with hormones [1].

One of the other smooth muscle tumors of the uterus is diffuse uterine leiomyomatosis. Both leiomyoma and diffuse uterine leiomyomatosis are thought to be neoplastic processes [2]. Diffuse leiomyomatosis is a rare condition in which the uterus is symmetrically enlarged as a result of the almost complete replacement of the myometrium by innumerable poorly defined, confluent nodules [3]. The previously reported cases were described as “diffuse leiomyomatosis”, “complete fibromyomatosis”, “myomatosis”, or “diffuse myomatous tendency” [1].

Leiomyomas have been studied cytogenetically and have been shown to be clonal neoplasms with consistent cytogenetic alterations. In multiple leiomyomata, the tumors have been shown to have originated from different neoplastic clones independently, rather than representing spread of the same tumor in the uterus [4, 5].

Baschinsky *et al*. have reported that various tumor sites within the diffuse uterine leiomyomatosis were of different clonal origin, and this supports the independent origin of the neoplastic clones. They suggested that diffuse uterine leiomyomatosis may be an exuberant example of multiple uterine leiomyomas budding into each other and blending imperceptibly to the extent that the single nodules could not be readily identified by gross examination [1]. The nodules blend with each other and merge imperceptibly with the surrounding less-cellular normal myometrium. On microscopic examination the nodules are said to be compact fascicles and interweaving bundles of benign smooth muscle cells [6].

Initial symptoms of diffuse uterine leiomyomatosis are usually abdominal pain and abnormal uterine bleeding [3]. Similar to uterine leiomyomas, patients with leiomyomatosis present with menorrhagia, dysmenorrhea, abdominal pain, infertility, and pelvic pressure [1, 7]. It usually presents clinically between the third and fourth decades of life.

Hormonal treatment usually fails to control the symptoms, anemia, or tumor growth after treatment is stopped [8].

As a result, despite patients being in the third or fourth decades of life, hysterectomy has been the only permanent treatment option offered to patients for treatment of the symptoms related to uterine fibroids in diffuse leiomyomatosis [6].

Domnitz *et al.* and Grignon *et al*. reported cases of pregnancy in the presence of this disorder [9, 10]. The course may be complicated by cervical incompetence, spontaneous premature rupture of membranes, delivery by cesarean section, and intrapartum hemorrhage necessitating hysterectomy [10].

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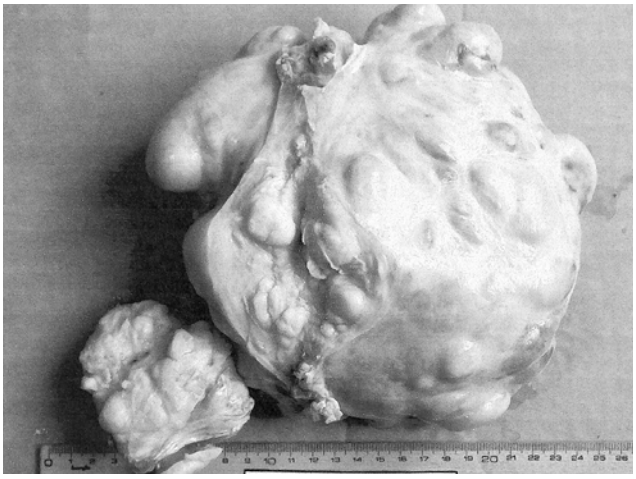

Figure 1. — Macroscopic view of the uterus with multiple intramural and subserosal myomatous nodules.

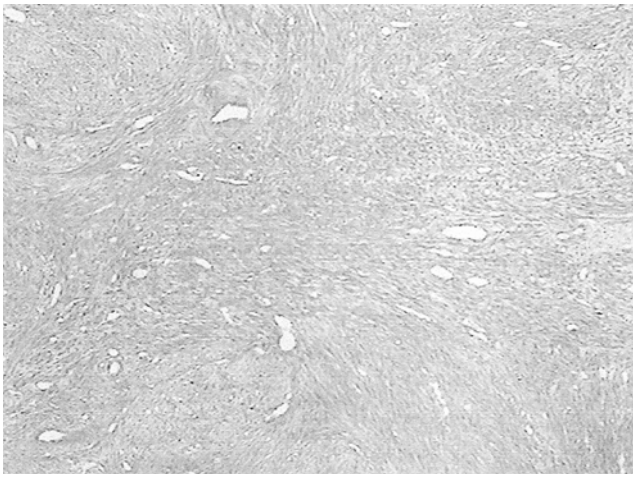

Figure 2. — Microscopic section of the nodule consisting of smooth muscle fibers crossing each other (H&E 10 x).

## Case Report

A 23-year-old woman (gravida 1, para 1) was referred to our hospital because of abnormal uterine bleeding of several years duration. Her symptoms included severe hypermenorrhea, dysmenorrhea, abdominal distension, and pelvic pain. The physicians she attended previously recommended she undergo hysterectomy with the diagnosis of uterine myomatosis but the patient did not have the operation. In that time interval she had been intermittently treated with innumerous courses of hormonal therapy such as progesterone, combined oral contraceptives, GnRH analogs, and various kinds of non-steroid anti-inflammatory drugs. She had also been taking iron supplements for anemia for a long time. Uncontrolled menstrual bleeding and severe anemia were noted, and because of these her daily life was affected very badly. In addition her pelvic pain had worsened over the previous three months. Finally she and her husband decided on hysterectomy and they came to our clinic.

Pelvic ultrasound scan showed a pelvic mass. The uterus was enlarged symmetrically and had a dimension of 20 x 18 cm. There were multiple myomas with undetermined borders. We decided to perform laparotomy. In the intraoperative observation, the uterus was on the midline, 20 x 20 x 10 cm in size (Figure 1), and the color was pinkish-white. The uterus had a multinodular appearance and soft consistency, and it was symmetrically enlarged as a result of the almost complete replacement of the myometrium by innumerable but hardly defined nodules. The other pelvic organs, parametrium and ovaries were normal. Because of the very enlarged uterus and limited surgical field it was impossible to reach the cervix. First we performed a subtotal hysterectomy and then we took out the cervical portion. The uterus weighed 2,650 g postoperatively.

At pathologic examination the cervical portion was 8 x 7 x 7 cm, and the corpus was 20 x 20 x 10 cm in dimension. Section surfaces were grayish, yellowish-pink, and included multiple intramural and subserosal myomatous nodules. In the histologic sections of these nodules there were neoplastic structures containing smooth muscle fibers which were crossing each other and benign neoplastic parts which had focal hyalinization and degeneration (Figure 2).

## Discussion

Diffuse uterine leiomyomatosis is a benign and extremely rare condition. In 1979 Lapan *et al.* claimed that diffuse leiomyomatosis of the uterus prevents myomectomy [11]. In 2000, Baschinsky *et al.* [1] found 14 well documented cases of diffuse uterine leiomyomatosis in the literature. Patient ages ranged from 22 to 39 years. Eleven of them were treated with total abdominal hysterectomy. The weights of the hysterectomy specimens of the patients ranged from 300 to 1200 g. In the case presented by Baschinsky *et al*. the hysterectomy specimen weighed 3,800 g. Kido *et al.* mentioned about 31 cases which had been reported till 2003 [12]. Two of these 31 cases included concomitant parametrial and pelvic or bilateral ovarian involvement [13, 14]. None of the diffuse leiomyomatosis cases recurred after hysterectomy. In subsequent years 11 more cases were added to the literature [7, 15-18]. The heaviest operation specimen in the English literature we found was the case presented by Baschinsky *et al*. [1].

There are few data on the metastasizing ability of uterine leiomyomatosis. Two cases of benign metastasizing leiomyomatosis that appeared in the bone and lungs have been reported [16, 17].

In a few families and isolated patients with Alport syndrome (about 5%), with proven alpha 5 chain type IV collagen (COL4A5) gene mutation, an association with leiomyomatosis of the esophagus, tracheobronchial tree and female genitals has been reported [19].

It is necessary to differentiate leiomyomatosis microscopically from diffuse uterine adenomyosis and diffuse endometrial hypertrophy. These two entities could be rejected by initial histologic examination [13].

The differential diagnosis of leiomyomatosis includes multiple leiomyomas, intravascular leiomyomatosis and endometrial stromal sarcoma [1, 3, 6, 7].

Leiomyomatosis can be distinguished from leiomyoma due to the uniform symmetrical involvement of the entire

myometrium by smooth muscle nodules without distinct borders between the nodules, whereas cases of multiple leiomyomas tend to have asymmetrical involvement of the uterus and sharp circumscription of the individual leiomyomas [1, 7].

Intravascular leiomyomatosis has a creamy to yellowish color, and there are intravascular extensions of worm-like smooth muscle tumor with multinodular irregular or indistinct margins. Intravascular leiomyomatosis can be distinguished histologically from diffuse leiomyomatosis by the presence of some or all of the neoplastic smooth muscle within the vascular channels.

Endometrial stromal sarcoma is characterized by its invasive growth having an abrupt transition with the normal myometrium, and it has a sheetlike, rather than fascicular, growth pattern. In contrast to diffuse leiomyomatosis, small neoplastic cells with round to oblong nuclei and scant cytoplasm separate the thick walled vessels. In addition, endometrial growth and intravascular growth are usually present [7].

Nisolle *et al*. have reported that estrogen receptors (ERs) and progesterone receptors (PRs) were significantly higher in leiomyoma than in the adjacent myometrium [20]. Kim SJ *et al.* found that the ER level was equal in both normal myometrium and leiomyomatosis areas but PR level was higher in leiomyomatosis tissue, so they suggested that diffuse leiomyomatosis lesions might be under the influence of progesterone, which might play a major role in their growth. They proposed an antiprogestin agent as a treatment alternative for diffuse uterine leiomyomatosis according to their results [7]. However hormonal treatment usually fails to control the symptoms, anemia, or tumor growth after treatment is stopped [8].

As a result, despite patients being in the third or fourth decades of life, hysterectomy has been the only permanent treatment option offered for treatment of the symptoms related to uterine fibroids in diffuse leiomyomatosis [6].

Aki Kido *et al.* presented a case of diffuse leiomyomatosis treated by uterine arterial embolization (UAE) as an alternative to hysterectomy for the treatment of leiomyomas and reported that UAE successfully controlled the symptoms and reduced uterine volume with no major complications in their patient [12]. Fedele *et al*. treated only medically with GnRH analogues (GnRH-a) one of three premenopausal women with diffuse uterine leiomyomatosis associated with persistent menorrhagia. The patient conceived spontaneously as soon as medical treatment was discontinued; at 34 gestational weeks, an emergency cesarean section followed by hysterectomy was performed for vaginal bleeding and a healthy 2,400 g baby was born. In the other two cases they performed an "extreme" myomectomy, including the removal of a large portion of corporal myometrium. Regular menses were restored in these two patients: one had no pregnancy desire and the other was not able to conceive after two IVF- ETs in 2004 [15].

Women with early-stage diffuse uterine leiomyomatosis can be treated by hysteroscopic resection, which has the benefit of successfully preserving the uterus. Yen *et al.* described five cases of successful hysteroscopic resection for early-stage diffuse uterine leiomyomatosis. The uterus was successfully preserved and a normal amount of menstruation was restored in all (5/5) patients. All (3/3) patients who wished to conceive had successful conceptions, with four healthy deliveries [18].

In the presented case, the patient had two aunts who had undergone operations for uterine myoma in her family history. Clinical presentation, symptoms and family history of our case was consistent with the literature. In comparison with most cases reported in the literature, our case had a large uterus that weighed 2,650 g. We think that medical treatment failure was due to the extremely enlarged uterus. Surgery was in August 2003 and there has been no any recurrence in four years of follow-up.

In the case of medical treatment failure, the symptoms of the patient may be resolved with surgical resection of the nodules by protecting the normal anatomic structure of the uterus, and even pregnancy may be possible. But in huge masses associated with diffuse uterine leiomyomatosis if protecting the normal anatomic structure is not possible, hysterectomy may be a treatment modality after the patient's approval.

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