Abstract

Myoma is the most common benign neoplasm that can occur in the female reproductive system, most frequently seen in women in their 50s. Although the majority of myomas are asymptomatic, some patients have symptoms and/or signs of varying degrees. Typical myoma-related symptoms or signs include: (1) menstrual disturbances like menorrhagia, dysmenorrhea and intermenstrual bleeding, (2) pelvic pain unrelated to menstruation, (3) compression symptoms, similar to a sensation of bloatedness, urinary frequency and constipation, (4) subfertility status such as recurrent abortion, preterm labor, dystocia with an increased incidence of Cesarean section, and postpartum hemorrhage, and (5) cosmetic problems due to increased abdominal girth. However, there are undoubtedly some clinical presentations secondary to uterine myomas that are not so specific, such as: (1) uncommon compression-related symptoms, (2) cardiac symptom and atypical symptoms secondary to vascular involvement or dissemination, (3) abdominal symptoms mimicking pelvic carcinomatosis, (4) dyspnea, (5) pruritus, (6) hiccup or internal bleeding, and (7) vaginal protruding mass or uterine inversion. Familiarization with these symptoms and awareness of other unusual or atypical presentations of uterine myomas will remind clinical practitioners of their significance, and of the necessity of follow-up examinations and individualized management to fit the needs and childbirth desires of the patients.

Keywords: fibroids; leiomyomas; myomas; symptomatic; uterus

1. Introduction

The incidence of myoma can vary from 20%–50% in different study populations and surveys. The diagnosis of uterine myoma is the most frequently seen reason for hospital admission, and hysterectomy is performed on three-quarters of those women hospitalized, approximately 30%–60% of patients from different communities. Therefore, this common disorder among women of reproductive age is considered to be a major burden on the health care system.

The correct assessment and diagnosis of a possible clinical presentation of myoma relies on an understanding of the etiology, risk factors and development of leiomyomas. For
example, due to the slow-growing characteristic of this disease, affected women are most commonly asymptomatic. However, in around 20%—50% of patients, myoma induces problems that affect quality of life. Although nearly all myomas initial arise from the uterine myometrium layer, these tumors develop into one of three categories, intramural, subserous, and submucous types, and the severity of symptoms seems to correlate with the number, size, and location of the tumors.

2. Pathogenesis

The precise cause of myoma development and growth is not fully understood, but molecular studies have revealed that each tumor is unicellular in origin and about 40% have nonrandom and tumor-specific chromosomal abnormalities that may affect growth rates. In addition, women with a positive family history of myomas have a 1.5- to 3.5-fold higher risk of developing similar lesions than those women without a family history. African-American women have a two- to 9-fold greater likelihood of developing myomas than Caucasian women. All evidence supports an ethnic or genetic predisposition for the occurrence of myomas.

The importance of steroid hormones in the pathogenesis of myomas is supported by the observation that myomas are never found in preadolescent girls, that the prevalence of myomas increases throughout the reproductive years, peaking in the fifth decade, and that their prevalence is markedly reduced after menopause. In addition, early age at menarche and obesity, which are associated with a greater exposure to endogenous estrogens, contribute to a two-fold increased risk of uterine myomas. By contrast, increased parity and cigarette smoking, which might decrease endogenous estrogen levels, showed a nearly 50% reduced risk compared with nulliparous women and nonsmoking women, respectively. Myomas are reported to show higher concentrations of estrogen receptors, progesterone receptors, and aromatase, an enzyme important for local estrogen production, than normal myometrium.

However, the relationship between orally administered hormones and the prevalence of uterine myomas is controversial. For example, the use of oral pills seems to be unrelated to the development of uterine myomas, and low-dose pills do not stimulate the growth of existing uterine myomas in most women. However, the use of progestins, such as depot medroxyprogesterone acetate, may reduce the risk of developing uterine myomas. On the other hand, agents which are modified from the original form of progesterone, for example, selective progesterone receptor modulators (SPRM), might also be involved in the growth of uterine myomas, since SPRM has been tested in recent clinical trials.

3. Typical symptoms of uterine myomas

The symptoms of this disease are mainly related to the physical changes in the pelvic organs arising from the onset of this tumor and may present in women of any age but usually in women between menarche and menopause. When a female of reproductive age presents with symptoms like menorrhagia, dysmenorrhea, fainting, pallor, dyspnea, urinary frequency, and constipation, it may be common to quickly assume a diagnosis of uterine fibroids. On the other hand, some unusual or atypical symptoms like acute abdominal pain, and pain between periods or internal bleeding do occur in patients with a well-established diagnosis of uterine fibroids that may be ignored, leading to a misdiagnosis and further delay in medical management. Here, we would like to discuss these symptoms in detail.

3.1. Compression symptoms

The symptoms related to myomas are primarily those of physical changes to the pelvic organs due to the presence of an enlarging mass. These symptoms, similar to those of an enlarged pregnant uterus, may lead to a suspicion of conception in some premenstrual victims. Pelvic heaviness or a dull aching sensation, such as that experienced by women in early pregnancy, might be the only symptom of this slow-growing tumor.

Increased urinary frequency and urgency can also develop, especially when these tumors arise from the anterior wall of the uterus. In addition, these symptoms might worsen with the onset of menses, thereby aggravating menses-related symptoms.

3.2. Menses-related symptoms

Abnormal menstruation, including excess or prolonged bleeding, is believed to be the most common symptom and is experienced by about 30% of women with myomas. However, the most common menses-related symptom is menorrhagia. Since the exact cause—effect relationship between myoma and excess menstrual bleeding is poorly understood, women with this disease are more likely to report gushing-type bleeding, even if the uterine myoma was small. Controversy exists as to whether a submucous myoma is associated with a higher incidence of heavy bleeding. In women who do not seek gynecological care, leiomyoma-related menstruation problems are often neglected. Blood vessels in uterine fibroids are abnormal in distribution and appearance, suggesting that altered angiogenesis might be the cause of menstrual disturbance. Nonetheless, the old theory of an expanded surface area of the endometrium has been disproven, and local compression of veins in the interior uterine layers was proposed as a possible mechanism.

Other symptoms of anemia, including pallor, fainting, dyspnea, and fatigue might result from massive blood loss whenever menses begins, and could worsen during menses. In addition to the general discomfort caused by symptoms of acute and colic pain during menses, these symptoms substantially interfere with the health and life quality of women, often leading to surgical intervention.

3.3. Pain-related symptoms

About one-third of women with myomas experience pelvic pain. Dysmenorrhea seems less common in this group of
patients than in those with adenomyosis. Secondary dysmenorrhea is still one of the most frequently heard complaints related to fibroids. However, in a noncare-seeking population study, dyspareunia and noncyclic pelvic pain, but not dysmenorrhea, increased in severity with the presence of uterine fibroids.

Pain-related symptom varies in degree, from dull pelvic pain to severe and colic pain. However, intractable pelvic pain noticed during the intermenstrual period is unusual. The changed status of the uterine myomas with a compromised blood supply often results in painful symptoms. For example, cases of myoma degeneration or torsion of pedunculated myomas can be found in the literature. Torsion of a pedunculated uterine myoma represents a surgical emergency, with expedited intervention necessary to improve symptoms and avoid consumptive coagulopathy. Severe pain accompanied with fever is another warning sign of possible red degeneration of myoma during pregnancy.

3.4. Subfertility status

Since myomas have such a high incidence, they may sometimes be the only identifiable abnormality after a detailed infertility investigation. In these situations, the focus remains on the position of the tumor. Evidence suggests that only submucous myomas appear to interfere with fertility, and only very rarely do myomas affect the pregnancy outcome, such as by recurrent abortion or obstructed labor. Therefore, surgical intervention should be the last option to be considered for an infertile patient with a uterine myoma. Though full-term pregnancy rates of 40%–50% have been reported following a myomectomy, the success of such an operation depends on a lot of other confounding factors that affect the couple’s fertility.

3.5. Cosmetic problem

Though the occurrence of uterine myoma seems correlated with higher body mass index in premenstrual women, an increase in abdominal girth without appreciable change in body weight tends to bother slender patients more than others. A protruding mass from an otherwise flat abdominal wall compromises their body image and encourages these patients to seek help, though no other symptoms are noticed.

4. Atypical symptoms of uterine myomas

Other atypical or unusual presentations of this disease might be encountered in well-established or new cases, and represent either the existence of a special form of leiomyomatosis or a changed status of this disease; immediate treatment may be necessary.

4.1. Uncommon compression-related symptoms

Other atypical compression symptoms are also found in women with uterine myomas. For example, the masses arising from the posterior wall might cause rectal symptoms like tenesmus, back pain or constipation, though they appear to be less common. These symptoms might worsen when menses comes and can aggravate the symptoms related to menses. Flank pain, especially on the right side, is an atypical symptom of the uterine myoma, and is due to compression of the ureter, although its incidence is far below our expectation. Transient relief after lying on the opposite side might be reliable evidence of the existence of this compression.

4.2. Cardiac symptom and atypical symptoms secondary to vascular involvement or dissemination

Cardiac symptoms like chest pain might occur in a rare condition known as intravenous leiomyomatosis. Benign smooth muscle fibers invade the venous channels of the pelvis and, even though they grow slowly, they might grow into the vena cava and right heart and cause these unusual symptoms. Surgical intervention with primary excision and follow-up antiestrogen therapy for prevention is recommended to treat these cases. This mechanism might explain the occurrence of distant myomas with more unusual symptoms like urination difficulty and urethral obstruction from a leiomyoma of the bladder, and visual impairment from an orbital leiomyoma.

4.3. Abdominal symptoms mimicking pelvic carcinomatosis

Multiple pelvic growths with various compression symptoms with or without ascites will raise the suspicion of pelvic carcinomatosis. However, another rare benign condition, leiomyomatosis peritonealis disseminata (LPD), which is caused by the direct seeding of myomatous cells on the surface of the peritoneum, could be the possible diagnosis. It is believed that LPD is associated with recent pregnancy or previous operation for myoma using a morcellator.

4.4. Dyspnea

Dyspnea with pleural effusion, pelvic mass and ascites mimicking Meigs syndrome is another rare carcinoma-like presentation of this disease. Leiomyoma arising from the uterus, ovary, or fallopian tube might be the only diagnosis.

4.5. Pruritus

Pruritus with multiple raised skin lesions on the limbs is unusual and is the only symptom of piloleiomyoma. However, the coexistence of uterine myoma and cutaneous leiomyoma nodules might be the initial symptom of piloleiomyoma. Renal evaluation should be done first in cases of piloleiomyoma, before conservative follow-up is recommended, because piloleiomyoma is often accompanied with renal carcinoma.
4.6. Hiccup or internal bleeding

Unusual symptoms like hiccup or internal bleeding might result from a subserosal myoma with rapid growth. While the former might be irritation of the vagus or phrenic nerve and deserve a more thorough evaluation before operation, the latter might be due to rupture of superficial vessels and deserve prompt diagnosis and emergency management.49,50

4.7. Vaginal protruding mass or uterine inversion

Sometimes submucous myoma induces uterine inversion, which results in hemorrhage.51 If this rapid growth occurs in a menopausal woman, then malignant change must be highly suspected, and imaging might help to distinguish benign and malignant uterine masses.53,54

5. Symptoms and medical treatment

If menstruation symptoms are the only patient complaint, medical treatment can be prescribed first. At present, many effective drugs are available in routine clinical practice, though some are still under investigation.8 Tranexamic acid, nonsteroidal anti-inflammatory drugs, high-dose estrogen, progesterin, gonadotropin-releasing hormone agonists (GnRH agonists), contraceptives or levonorgestrel-releasing progestin, gonadotropin-releasing hormone agonists (GnRH antagonist, or mixed agonist antagonist actions, depending on receptor A and progesterone receptor B) and can have agonist, antagonistic, and corepressors.59 SPRMs have been used, in molecular complex including coregulators, such as coactivators and corepressors, levo- norgestrel-releasing intratuterine system have all been proven to reduce menstrual bleeding and restore the hemoglobin level.23 Spontaneous expulsion of a submucosal myoma after GnRH agonist treatment has even been reported.57 Mifepristone, danazol, and tamoxifen show modest overall benefit, but they need more thorough evaluation.8,16,17,58 Therefore, medical therapy seems a reasonable option for women with symptomatic myomas who prefer non-surgical treatment, are concerned about fertility preservation, or expect a less aggressive operation after shrinkage of the uterine volume.3

SPRMs have been developed since the late 70s when mifepristone was first described.15 SPRMs act through nuclear progesterone receptors (two isoforms, including progesterone receptor A and progesterone receptor B) and can have agonist, antagonist, or mixed agonist antagonist actions, depending on the cell and tissue.59 However, the mechanisms underlying some of these effects remain unknown, although they follow the rule of nuclear receptors. Following the binding of the ligand to the specific ligand-binding domain, nuclear receptors interact with the transcriptional machinery through a large molecular complex including coregulators, such as coactivators, and corepressors.59 SPRMs have been used, in particular, for the inhibition of ovulation, the transformation of endometrial morphology, and the apoptosis of myoma cells.59 Mifepristone has unique major antagonist properties which are conducive to its use for pregnancy termination.60,61 Ulipristal acetate has been marketed in 2009 for emergency contraception.14 The oral SPRM, ulipristal, proved highly effective as a treatment for symptomatic uterine fibroids, according to two randomized studies published in the New England Journal of Medicine.16,17 In both studies, this universal SPRM rapidly reduced excessive bleeding, and reduced the size of uterine fibroids.

The Uterine Fibroid Symptoms and Quality of Life (UFSQOL) questionnaire, which consists of eight symptom questions and 29 health-related quality of life questions with six subscales, was proposed as a useful tool in evaluating the change in symptoms after follow-up,52 medical treatment, or even after an operation.64 An electronic version of the questionnaire called the Fibroid Symptom Diary (FSD), containing eight items that assess bleeding severity, menstrual cramping, and fibroid-related fatigue, with three pain-specific items (i.e., abdominal pain, low back pain, and pain during intercourse), is another option for assessing changes in symptoms and treatment benefit.65

6. Symptoms and operation

Persistent symptoms like pain or menorrhagia after medical treatment are classic indications that surgical intervention may be necessary. The choice between a myomectomy and hysterectomy is usually determined by the patient’s age, parity, and, most important, future reproductive plans. Hysterectomy addresses more than 90% of symptoms, and might be an appropriate back-up plan for myomectomy, which treats about 80% of symptoms. However, the fact that one-fourth of patients suffered from recurring symptoms after myomectomy and received a follow-up hysterectomy within 20 years makes the choice more difficult for a patient with a complete family.5 Since the value of myomectomy for subfertile patients is not well-established, the possible damage and adhesion related to the adverse reproductive outcome after operation should be emphasized before operation and prevented during surgery. For this reason, a variety of options, which further enhance the myomectomy procedure have been proposed in recent years. Instead of laparotomy, laparoscopy with careful multilayer closure and the use of antiadhhesive barriers has been recommended as the surgery of choice.66–69 Vaginal myomectomy is considered a feasible and safe surgical procedure, with low morbidity and a short hospital stay.70 A hysteroscopic myomectomy via the cervical canal is a reasonable choice for a submucous myoma.71 Magnetic resonance imaging-guided focused ultrasound surgery (MRLgFUS) is another noninvasive treatment for symptomatic uterine myomas.31 Sustained symptom relief after this operation relies on careful selection of patients.72 Uterine embolization is an option with substantial symptom improvement noted for most patients, and with hysterectomy required in only 2.9% of patients in the first 12 months after therapy.73,74 Uterine artery embolization (UAE) reduced fibroid volume and provided significant relief of menorrhagia.75–77 However, a smaller baseline leiomyoma size and submucosal location seemed more likely to result in a positive imaging outcome and symptom relief after UAE.78 Combined with laparoscopic myomectomy (LM), UAE demonstrated superiority in treating recurrent symptomatic myomas with less blood loss and recurrence rate.78–81 Therefore, uterine artery occlusion (UAO) combined with myomectomy was considered a good
option for treating pregnant women with uterine leiomyomas who are undergoing Cesarean section, with increased operative time but similar surgical morbidity.\textsuperscript{82}

Another similar option is laparoscopic uterine vessel occlusion (LUVO), which was believed to be more effective in treating symptomatic fibroids than UAO.\textsuperscript{83–86} In fact, the uterine vessel occlusion (which some papers call uterine artery occlusion) procedure can be further classified into two different strategies, based on the literature.\textsuperscript{83–86} One is UAO alone, without simultaneous blockage of the uterine vessels and the anastomotic sites between the uterine vessels and the ovarian vessels. The other is uterine artery occlusion with simultaneous blockage of the uterine vessels and the anastomotic sites between the uterine vessels and the ovarian vessels (UVO). However, women treated with UVO were associated with a greater risk of a significant increase in the follicle-stimulating hormone (FSH) level during the first month after operation than those treated with UAO.\textsuperscript{85} Symptoms related to the diminished ovarian function should be followed after UVO.\textsuperscript{86} When combined with LM, UVO was more effective, with a longer period of symptom control in most women with symptomatic myomas and prevented reoperation in most patients.\textsuperscript{78–81}

Ultra minilaparotomy (UMLT), a new procedure, resulted in a better recovery than conventional laparotomy when treating uncomplicated uterine myomas, but with a similar rate of symptom relief, especially for uterine fibroids less than 8 cm in size and fewer than five in number.\textsuperscript{6,32,33} When compared to the laparoscopic approach for UVO procedure (LUVO), the UMLT approach for UVO procedure is also an acceptable option with similar therapeutic outcomes, although LUVO might yield a faster recovery. Since LUVO and UMLT myomectomy combination might require less operation time and achieve a higher success rate, this approach might be a more reasonable choice in the management of symptomatic uterine fibroid than the combination of LUVO and LM.\textsuperscript{81}

Because of its reduced impact on ovarian function, combined LUAO and UMLT myomectomy seem to be a feasible option for women who wish to preserve the uterus. The best choice of operation for a subfertile woman or those who want to maintain fertility remains a subject of debate and requires further evaluation, although LM is suggested and recommended in many studies.\textsuperscript{4}

### 7. Symptoms and differential diagnosis

After an inquiry about symptoms, the diagnosis of uterine myomas may be provisionally made by palpating an enlarged, firm, irregular uterus during pelvic examination. However, a distorted uterine cervix alignment that is difficult to expose during speculum manipulation might also raise the suspicion of a uterine mass. The establishment of the diagnosis of uterine myomas requires the assistance of special tools. For example, imaging studies, especially ultrasound through the vaginal route (transvaginal ultrasound), will help physicians make a differential diagnosis with other benign or malignant uterine masses. Sometimes, a more powerful tool, such as color Doppler ultrasound, computed tomography, magnetic resonance imaging, or positron emission tomography, may help to distinguish benign uterine masses from malignant tumors.

In conclusion, familiarity with the typical and atypical clinical presentations of women with uterine myomas aids the discussion between the physician and the woman. Although tumor size is regarded as an important factor in deciding the treatment regimen, symptoms and signs might have a greater effect on the choice of management. Because of the extremely low incidence of malignant change, asymptomatic patients require only routine follow-up between 6 months and 12 months regularly, although the recommended interval is still inconclusive. To establish the best policy for the management of women with uterine myomas, a detailed study of symptoms and/or signs is encouraged.

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