Research Article ISSN 2639-9342

Gynecology & Reproductive Health

Uterine Leiomyoma in Postmenopausal Women: Possible Reasons for Growth and Differential Diagnosis

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Received: 26 September 2021; **Accepted:** 01 November 2021

Citation: Shigeta H, Asano R, Oi Y, et al. Uterine Leiomyoma in Postmenopausal Women: Possible Reasons for Growth and Differential Diagnosis. Gynecol Reprod Health. 2021; 5(6): 1-8.

ABSTRACT

Background: *Uterine leiomyomas appear after menarche, typically grow during the reproductive years, and then stabilize or regress after menopause. However, there have been several reports of a considerable number of patients who have undergone surgery for uterine leiomyomas during the postmenopausal period. In this paper, we discuss two issues: the possible reasons for the growth of uterine leiomyomas and the differential diagnoses of presumed leiomyomas in postmenopausal women.*

Methods: *PubMed was searched for studies about uterine leiomyomas and sarcomas with a focus on postmenopausal women.*

Main findings: *Several hypotheses exist for the growth of postmenopausal leiomyomas. Among these, we propose the following as an important candidate: estrogen and progesterone do not necessarily work in a positive way. In addition, in postmenopausal patients, the incidence of malignant tumors is very high, and it is generally difficult to diagnose uterine sarcoma prior to surgery.*

Conclusion: *We propose that in cases in which uterine sarcomas cannot be ruled out, physicians should proactively consider surgery, particularly for postmenopausal patients.*

Keywords

Leiomyoma, Postmenopausal, Progesterone, Sarcoma, Uterine Neoplasms.

Introduction

Uterine leiomyomas, also referred to as fibroids, are common, benign tumors of the reproductive tract. Although they are generally benign, uterine leiomyomas are responsible for significant morbidity in a large proportion of women [1,2]. Uterine leiomyomas appear after menarche, typically grow during the reproductive years, and then stabilize or regress after menopause [3]. However, several reports have included a considerable number of patients who have undergone surgery for uterine leiomyomas during the postmenopausal period [4,5]. Few studies have examined leiomyoma growth over time and have determined their significance in the postmenopausal period. Moreover, the preoperative diagnosis of uterine sarcoma is very difficult, and its diagnostic accuracy is not currently satisfactory [6]. In addition, the incidence of malignant tumors is very high in postmenopausal patients and very low in premenopausal patients. Thus, physicians should carefully manage presumed uterine leiomyoma, particularly in postmenopausal patients [7]. The objectives of this review are to survey the significance of uterine leiomyomas with a focus on postmenopausal patients and to assess the characteristics of patients with uterine sarcomas with a focus on the postmenopausal period.

Possible reasons for uterine leiomyoma growth in postmenopausal women

Incidence of patients who underwent surgery for uterine leiomyomas stratified by patient age

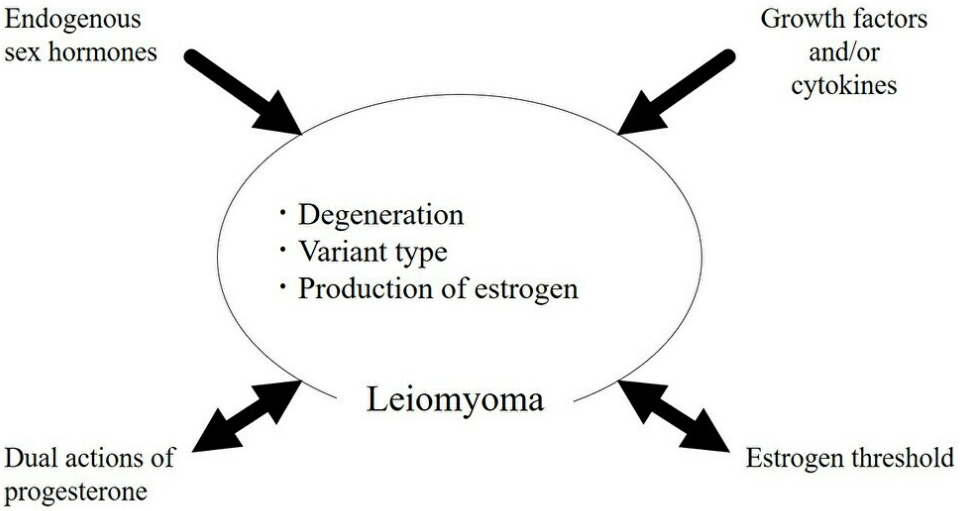
A Japanese study reported that the highest incidence of leiomyomas occurred in women aged 40–49 years (63.9%), followed by those aged 30–39 years (17.4%), 50–59 years (13.4%), and ≥60 years (3.4%) [8]. In a previous report evaluating 1790 participants with a diagnosis of surgically treated fibroids in the United States, the highest incidence was reported in women aged 40–49 years (46.7%), followed by those aged 50–59 years (35.3%) and 30–39 years (7.5%). In patients >60 years, the incidence was 10.3% [4]. In a Romanian study that analyzed 959 cases of surgically treated uterine myomas, the highest incidence was observed among women aged 41–50 years (62.4%), followed by those aged 31–40 years (16.9%). The incidence for women >60 years was 0.7% [5]. These observations show that a considerable number of elderly patients undergo surgery for uterine leiomyomas.

Therefore, the incidence of patients undergoing surgery for uterine leiomyomas during the postmenopausal periods is not low. In one study, among 471 patients who underwent surgery for uterine leiomyomas, 441 (93.4%) were premenopausal and 30 (6.4%) were postmenopausal [5].

Possible reasons for uterine leiomyoma growth in postmenopausal women

Ovarian steroids are believed to play a central role in uterine leiomyoma growth, and it has been reported that progesterone rather than estrogen plays a vital role in promoting growth of leiomyomas [9]. In fact, uterine leiomyomas have been shown to grow in postmenopausal women taking hormone replacement therapy [10]. Sommer et al. reported that uterine fibroids continue to develop in postmenopausal women, and obesity and hormone therapy were cited as important modifiable risk factors [11]. Tamoxifen is also known to increase leiomyoma volume in postmenopausal patients. Schwartz et al. reported that more than half (13/21) of leiomyomas in their study increased in volume among postmenopausal patients with breast cancer who received postoperative tamoxifen [12]. Furthermore, one report noted that a postmenopausal woman had a growing leiomyoma that was related to a high intake of soy products [13]. These findings raise the following question: why do uterine leiomyomas grow without the administration of hormones in postmenopausal women? We present the following seven hypotheses: 1) endogenous sex hormones, 2) estrogen threshold, 3) degeneration of leiomyomas, 4) existence of estrogen and progesterone in a local area, 5) growth factors and/or cytokines working in a local area, 6) leiomyoma variants, and 7) estrogen and progesterone do not necessarily work in a positive way (Figure 1).

Many studies have measured sex steroid hormone levels in postmenopausal women. Zhao et al. studied 2,834 postmenopausal women with an average age of 64.9 years and reported that their average estradiol level was 0.07 (0.05–0.16) nmol/L [14]. Sriprasert et al. studied 596 postmenopausal women and reported that the average estradiol level was 8.3 ± 5.3 pg/mL (7.9 ± 4.8 pg/mL in women within 6 years of menopause and 8.5 ± 5.7 pg/mL in women 10 years or longer after menopause) [15]. Missmer et al. examined postmenopausal women with breast cancer (n = 322) and control subjects (n = 643). They observed a statistically significant direct association between breast cancer risk and estrogen levels: values of 7 (4–15) and 6 (4–13) pg/mL were reported in breast



Seven possible reasons for growth of uterine leiomyomas in post menopausal women.

cancer patients and control subjects, respectively. They did not find any statistically significant associations between this risk and progesterone levels (4.0 [1.5–10.0] and 4.0 [1.5–10.0] ng/dL in breast cancer patients and control subjects, respectively) [16]. In the study by Xu et al., 164 postmenopausal women with an average age of 62.43 ± 5.87 years were studied, and the average age at menopause was 49.26 ± 4.05 years. They reported that the serum estradiol levels were 61.34 ± 5.48 pg/mL in the nonosteoporotic vertebral compression fracture (OVCF) group and 43.21 ± 4.37 pg/mL in the OVCF group, and a significant difference was noted in the serum estradiol levels between the two groups. The serum progesterone level was 1.62 ± 0.42 nmol/L in the non-OVCF group and 1.43 ± 0.31 nmol/L in the OVCF group, and this difference was statistically significant [17]. Heshmati et al. assessed the effect of a blockade of estrogen synthesis on bone turnover markers by the potent aromatase inhibitor letrozole in 42 normal women (mean ± SD age, 69 ± 5 years) and suggested that in late postmenopausal women, even low serum estrogen levels exert a restraining effect on bone turnover. This finding provides support for the concept that variations in these low levels may contribute to differences in the bone loss rate [18]. These observations suggest that measurable amounts of sex steroid hormones affect biological activities, including the growth of uterine leiomyomas in postmenopausal women.

Barbieri first proposed the estrogen threshold hypothesis, which stated that the sensitivity of tissues to estradiol varies [19]. He speculated that the most sensitive to least sensitive estrogen-responsive disease processes are (1) breast cancer, (2) leiomyoma, and (3) endometriosis. From this point of view, leiomyomas may have their own estradiol therapeutic windows. If each myoma has its own suitable estradiol concentration in which to grow, some myomas may grow in low estradiol levels of the postmenopausal period.

Fibroids have been reported to contain a large percentage of interstitial collagens [20]. Jayes et al. reported that collagen content is highly variable within and among fibroids. They suggested that in addition to systemic hormonal milieu, local conditions and mechanotransduction determine fibroid development, growth, and regression [21]. Flake et al. hypothesized that progressive developmental changes in many uterine fibroids occur as follows: the developmental phases are related to the ongoing production of the extracellular collagenous matrix, which eventually exceeds the degree of angiogenesis, resulting in the progressive separation of myocytes from their blood supply and a condition of interstitial ischemia. The consequence of this process of slow ischemia with deprivation of nutrition and oxygen is progressive myocyte atrophy (or inanition), culminating in cell death, a process that the authors referred to as inanosis. They also suggested that some tumors continue to proliferate and grow to a large size, with relatively little collagen production. Other tumors, by contrast, may produce abundant collagen early in development, resulting in interstitial ischemia with an associated reduced rate of proliferation and subsequent involution while still retaining the same size [22,23]. Conversely, Okamoto et al. reported the case of a postmenopausal woman with a rapidly growing leiomyoma with hyaline degeneration [24]. There have also been several reports of uterine swelling caused by cystic degeneration after menopause. This swelling is understood to occur as a result of liquid accumulation, without any cell proliferation [25,26]. Microarray analyses have shown that specific collagen isoforms and veriscan, which contains high levels of proteoglycans that absorb water, are overexpressed in leiomyoma cells, and the addition of GnRH analogs can reduce their expression [3]. Although the degeneration and/or accumulation of liquid may lead to the growth of uterine leiomyomas, the significance of this is not yet clear.

Leiomyoma tissue can be a source of estrogen. Leiomyoma tissue produces its own aromatase, which is a microsomal enzyme that catalyzes the conversion of androgens to estrogen, whereas normal myometrium does not [27]. In addition, aromatase levels are significantly higher in leiomyomas than in myometrial tissue [28,29]. These findings suggest that in situ estrogen synthesized in leiomyomas plays a role in the promotion of leiomyoma growth via an autocrine/paracrine mechanism [9]. However, Grings et al. reported that the protein expressions of ERα, ERβ, and aromatase were similar in leiomyomas and the normal adjacent myometrium of premenopausal women [30]. Therefore, whether this hypothesis is correct requires further consideration.

Estrogen and progesterone influence leiomyoma growth by regulating growth factors, cytokines, and their signaling pathways [31]. The mitogenic action of steroids in their target tissues is considered to be mediated by the local production of growth factors that act through paracrine and/or autocrine mechanisms [32,33]. Furthermore, different growth factors, such as epidermal growth factor (EGF), transforming growth factor (TGF), heparin-binding EGF, acidic fibroblast growth factor, basic fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor, and platelet-derived growth factor, perform actions in leiomyomas [32]. EGF has been shown to play a crucial role in regulating leiomyoma growth as a local growth factor. Progesterone upregulates the expression of EGF in leiomyoma cells [32]. Moreover, estrogen's effect is mediated by EGF in the murine uterus, and EGF may be able to replace estrogen action [34]. Ciebiera et al. reported that the effect of progesterone on uterine fibroid growth is determined by the overexpression and increased concentration of various growth factor genes, including TGF-β [35]. Many cytokines, including interleukin (IL)-1, IL-6, IL-11, IL-13, IL-15, interferon-α, tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, and erythropoietin, have been documented in leiomyomas [32]. Among them, the mRNA expression of erythropoietin was reported to be significantly higher in premenopausal than in postmenopausal leiomyomas [36]. These results suggest that factors other than sex steroid hormones stimulate the expression of growth factors and/or cytokines, which may result in leiomyoma growth (Table 1).

Table 1: Growth factors and Cytokines as possible mediators of sex hormones.

Growth factors	Cytokines
epidermal growth factor	interleukin-1
transforming growth factor	interleukin-6
heparin-binding epidermal growth factor	interleukin-11
acidic fibroblast growth factor	interleukin-13
basic fibroblast growth factor	interleukin-15
vascular endothelial growth factor	interferon-α
insulin-like growth factor	tumor necrosis factor-α
platelet-derived growth factor	granulocyte-macrophage colony-stimulating factor
	erythropoietin

Table 2: WHO Classification of Tumors of the Uterine Corpus.

Leiomyoma
Cellular leiomyoma
Leiomyoma with bizarre nuclei
Mitotically active leiomyoma
Hydropic leiomyoma
Apoplectic leiomyoma
Lipomatous leiomyoma (lipoleiomyoma)
Epithelioid leiomyoma
Myxoid leiomyoma
Dissecting (cotyledonoid) leiomyoma
Diffuse leiomyomatosis
Intravenous leiomyomatosis
Metastasizing leiomyoma

Table 2 shows the classification of leiomyoma variants based on the World Health Organization Classification of Tumors of Female Reproductive Organs [37]. Among 471 patients with uterine leiomyomas, postmenopausal patients had a higher incidence of variants (7/30, 23.3%) as compared with premenopausal patients (14/441, 3.2%) [8]. In postmenopausal women, lipoleiomyomas are the most common uterine variants requiring surgery [8]. Sieiński noted that lipoleiomyomas primarily occur in the uterine corpus of postmenopausal women. He reported that lipomatous neometaplasia constituted 0.42% of hysterectomy cases of uterine myomas in patients aged 41–74 years (mean, 56.6 years) [38]. In an analysis of 70 consecutive women with 76 lipoleiomyomas, 58 (82.8%) patients were reportedly postmenopausal [39]. Wang et al. reported that 2.1% of patients (mean age, 54 years; median age, 51 years; range, 29–92 years) who had uterine leiomyomas had a lipoleiomyoma [40]. However, they also reported that because most leiomyomatous uteri contained multiple leiomyomas and because all lipoleiomyomas in their study were solitary, the proportion among all uterine smooth muscle tumors was much lower than 1%. In their study of patients with an average age of 59.9 years (range, 45–74 years), Aung et al. reported that uterine lipoleiomyomas were observed in 0.35% of uterine myomatous tumors [41]. These reports suggest that it is common for lipoleiomyomas to grow even after menopause.

Rothmund et al. reported that 6 of 76 cases of cellular leiomyomas were postmenopausal [42]. Hodge et al. reported that cellular leiomyomata with chromosome 1P deletions were more likely to occur in postmenopausal women with higher cellularity and hyaline necrosis as compared with women without 1P deletions. They suggested that the investigation of the genetic changes in cellular leiomyomas is important and that cellular leiomyomas have malignant potential [43]. In a recent report, one postmenopausal woman was reported to have a rapidly enlarging uterine cellular leiomyoma with a KAT6B-KANSL1 fusion. The patient had a history of ductal carcinoma in situ of the breast that was treated with tamoxifen. Microscopic examination showed a hyaline extracellular matrix throughout the tumor [44]. Therefore, the mechanism of tumor enlargement seems complicated.

Mitotically active leiomyomas are rarely observed in postmenopausal women, except under the influence of exogenous hormones [45]. On study reported a case of a mitotically active leiomyoma in a postmenopausal woman taking tamoxifen [46]. Most patients with intravenous leiomyomatosis are of reproductive age, although some cases have described patients in their 80s [45]. Patients with benign metastasizing leiomyomas are usually of late reproductive age, but they are occasionally postmenopausal [45]. Funakoshi et al. reported a woman with benign metastasizing leiomyomas who underwent hysterectomy with oophorectomy for uterine leiomyomas at the age of 65, in whom pulmonary metastases were detected at the age of 77 [47]. Griffin et al. reported that women of similar, but overall younger, reproductive age were more commonly affected by hydropic leiomyoma than usual-type leiomyoma [48]. The findings of these cases indicate that the occurrence of leiomyoma variants might not be rare among postmenopausal women.

Progesterone is known to play a vital role in promoting the growth of leiomyomas [9]. However, Phelan reported that in the course of pregnancy, most leiomyomas identified early in gestation had the same size or even shrank despite increased circulating concentrations of estrogen and progesterone [49]. Maruo et al. also reported that the effect of the levonorgestrel-releasing intrauterine system (LNG-IUS) on the size of leiomyomas varies remarkably: in one-third of the examined cases, the size of uterine leiomyomas in women using LNG-IUS was noted to increase, remain the same, or decrease [50]. These observations suggest that progesterone has dual actions on leiomyoma growth: one action stimulates growth, and the other action inhibits leiomyoma growth [50]. Peddada et al. reported that fibroids can grow at different rates over time, and spontaneous regression can occur at any age, not merely after menopause [51]. Furthermore, Ciarmela et al. reported that abnormal bleeding related to fibroids is likely to persist during the perimenopausal phase and after menopause [52]. In addition, Kawamura et al. reported a case of the transient rapid growth of a uterine leiomyoma after menopause with a pathological finding similar to that of a typical leiomyoma [53]. These reports also support the idea that progesterone may have dual actions. On the basis of these observations, the growth of leiomyomas after menopause can be attributed primarily to the dual action of progesterone and the fact that estrogen and progesterone do not necessarily work in a positive way. Moreover, both estrogen and progesterone have positive and negative effects on the growth of postmenopausal leiomyomas [8].

Among these hypotheses, the degeneration of leiomyoma and leiomyoma variants, particularly lipoleiomyoma, could be clear reasons for the mechanism of uterine leiomyoma growth in postmenopausal women. The significance of the other hypotheses is not yet clear. However, progesterone's dual action may be the primary reason why surgical treatment is required for uterine leiomyomas in the postmenopausal period [7].

Differential diagnosis between leiomyoma and sarcoma

Incidence of sarcoma in postmenopausal patients who require surgery for uterine corporeal mesenchymal tumors

In the management of presumed uterine leiomyomas, the differential diagnosis between leiomyoma and sarcoma must be considered. Some studies have assessed the frequency of sarcomas in postmenopausal women. For example, in a report of 487 patients undergoing surgery for uterine corporeal mesenchymal tumors, 447 women (92%) were premenopausal, and 40 (8%) were postmenopausal. Among the 487 patients, malignant tumors were observed in 16 cases (3.3%), including 10 leiomyosarcomas, 5 endometrial stromal sarcomas, and 1 undifferentiated sarcoma. The authors also found that the incidence of malignant tumors was very high in postmenopausal patients (11/40, 28%) and very low in premenopausal patients (5/447, 1.1%) (Table 3) [7].

However, according to a study that examined the estimated age-stratified risk of uterine sarcomas among women undergoing surgery for presumed uterine leiomyomas, the incidence of malignant tumors was 0.17% in 25- to 29-year-olds, which gradually increased to 1.0% in 75- to 79-year-olds and decreased to 0.56% in 80- to 84-year-olds [54]. Mao et al. studied 241,114 patients who underwent a hysterectomy or myomectomy with any diagnosis and reported that the estimates of sarcoma prevalence were highly dependent on age, with the lowest prevalence noted for women younger than 50 years (0.08%-0.13%) and the highest for women older than 60 years (0.36%–1.53%). The authors concluded that there was more than 10-fold higher prevalence of uterine sarcoma among women older than 60 years as compared with women younger than 50 [55]. Therefore, careful observation is necessary to operate on patients with uterine tumors if the patient is postmenopausal.

Difficulty of differential diagnosis

Clinical characteristics, tumor markers, and diagnostic imaging are commonly used for the diagnosis of uterine sarcomas, but it is generally not easy to diagnose them, and they are often diagnosed only after surgery for tumors suspected to be benign [54]. Nagai et al. reported that abnormal vaginal bleeding tended to be more common in patients with sarcomas than in patients with benign tumors, and no significant differences were observed in the maximum diameter of the tumors [6].

Rapid growth of the tumor

Rapid tumor growth is sometimes thought to be related to malignancy. However, among 371 women operated on for rapidly growing leiomyomas, only one case of uterine sarcoma was found. In that study, none of the 17 postmenopausal women admitted for rapid uterine growth was shown to have a sarcoma, and 10 of the 17 women were receiving estrogen replacement therapy. The authors concluded that among patients with presumed leiomyomas, the incidence of uterine sarcoma, even if growing rapidly, was extremely low [56]. Another study showed that rapid growth of uterine tumors was significantly more common in benign cases than in sarcoma cases [57]. On the basis of these observations, rapid tumor growth is not useful for the diagnosis of uterine sarcomas even if it occurs during the postmenopausal period.

Tumor markers

Whether cancer antigen 125 (CA125) and lactate dehydrogenase (LDH) are useful for the differential diagnosis of leiomyomas and leiomyosarcomas remains controversial. Yilmaz et al. reported that preoperative CA125 levels were not predictive of sarcomas [58]. Conversely, Juang et al. reported that the values of preoperative serum CA125 were significantly higher in patients with uterine leiomyosarcomas than in those with uterine leiomyomas [57]. Another report showed that the serum LDH value significantly predicted uterine sarcomas, whereas CA125 values did not [6]. Duk et al. reported that uterine sarcoma cells were completely negative for CA125. They speculated that in patients with uterine sarcomas, mesothelial cells might be the source of the elevated serum CA125 levels [59].

Table 3: Comparison of the characteristics of postmenopausal patients with sarcomas and leiomyomas who underwent surgery for uterine mesenchymal tumors. Abnormal signal on MRI was the only characteristic that was useful for distinguishing sarcomas from myomas.

	Total		Sarcoma		Benign		p-value
Number of patients	40	100%	11	27.5%	29	72.5%	
Age (yr)	62.5	(50-81)	66	(50-80)	60	(51-81)	0.12
Age at menopause (yr)	51	(49-57)	52	(49-55)	51	(49-57)	0.523
BMI	22.6	(15.4-39.4)	22.4	(19-27.8)	22.6	(15.4-39.4)	0.654
Tumor size (cm)	10	(2.6-30)	10	(6-30)	9	(2.6-24)	0.2
Serum CA125 (U/ml)	13	(5.6-234.1)	18.3	(11-234.1)	11.5	(5.6-44.2)	0.054
Serum CA19-9 (U/ml)	6.4	(1.2-303)	6	(2-19.9)	6.5	(1.2-303)	0.94
Serum CEA (ng/ml)	1.45	(0.4-6.3)	1.5	(0.5-4.9)	1.4	(0.4-6.3)	0.598
Serum LDH (IU/l)	203	(125-629)	225	(156-629)	202	(125-300)	0.08
Abnormal bleeding	7	17.5%	3	27.3%	4	13.8%	0.399
Abnormal signal on MRI	22	55%	11	100%	11	37.9%	<0.001*

Values are presented as the median (range) or number (%). BMI: Body Mass Index; CA125: Cancer antigen 125; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging.

Magnetic resonance imaging (MRI) and other imaging modalities for diagnosis

MRI has been shown to be one of the most useful imaging modalities for the preoperative differentiation between tumors, but even with MRI, it is difficult to distinguish between uterine sarcomas and uterine leiomyomas with degeneration [7,60-62] (Table 3).

Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) has been useful for this purpose [63], but researchers have also reported that FDG PET alone cannot be used to differentiate leiomyosarcomas from leiomyomas [64].

The expression of estrogen receptor (ER) coupled with glucose metabolism using ER imaging agents for PET, such as 16α-[^{18}F]-fluoro-17β-estradiol and FDG PET, is useful for the differential diagnosis of leiomyomas and leiomyosarcomas, but some overlapping cases exist [65].

Biopsy and scoring system

Kawamura et al. attempted to obtain a diagnosis of uterine sarcomas using transcervical needle biopsies and a scoring system that included the mitotic index, cytologic atypia, and coagulative tumor cell necrosis [66]. The authors suggested that the scoring system was effective but not definite. They recommended performing surgery when uterine sarcoma cannot be excluded.

Malignant transformation

Uterine leiomyosarcomas have been considered to arise de novo. However, several reports have noted that leiomyomas undergo transformation into leiomyosarcomas [67,68]. Bertsch et al. examined the somatic gene mutations in the mediator complex subunit 12 (MED12) gene among 178 uterine leiomyomas and 32 uterine leiomyosarcomas and found mutations in 74.7% (133/178) of leiomyomas and 9.7% (3/32) of leiomyosarcomas. The authors suggested that, because there are far fewer MED12 mutations in leiomyosarcomas than in leiomyomas, most leiomyosarcomas have tumorigenic pathways that are independent from their benign counterpart [69].

In conclusion, uterine leiomyomas may grow or persist after menopause. In particular, unusual types of leiomyomas might not be rare among postmenopausal women. We propose that the reason for this is that estrogen and progesterone do not necessarily work in a positive way. Moreover, the pathophysiology of uterine leiomyomas is not yet fully understood. Further studies are needed to understand uterine leiomyomas and to explore new treatment strategies that do not involve the surgical removal of the uterus or leiomyoma.

In addition, the incidence of malignancy is much higher in postmenopausal patients undergoing surgery for uterine corporeal mesenchymal tumors as compared with premenopausal patients. Thus, because it is difficult to diagnose uterine sarcomas before surgery, physicians should proactively consider surgery in cases in which uterine sarcomas cannot be ruled out, particularly for postmenopausal patients.

Acknowledgments

The authors would like to thank Enago (www.enago.jp) for the English language review.

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