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Importance of diagnostic methods for round ligament leiomyomas in clinical practice

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Abstract

Benign uterine leiomyoma (U.LMA) and malignant uterine leiomyosarcoma (U.LMS), which are both uterine mesenchymal tumors, are distinguished by the number of cells with mitotic activity. However, uterine mesenchymal tumors contain tumor cells with various cell morphologies; therefore, making a diagnosis, including differentiation between benign tumors and malignant tumors, is difficult. For example, round ligament leiomyomas are uterine leiomyomas with a very rare placental lobed tissue morphology that can be misdiagnosed as a malignant uterine leiomyosarcoma because of its rarity and characteristic appearance on gross examination. Similar to the detection of a suspicious malignant mass during magnetic resonance imaging (MRI) examination by medical staff, healthcare professionals must understand the characteristic appearance of round ligament leiomyomas. Clinicians and pathologists must understand the oncologic features of round ligament leiomyomas to prevent misdiagnosis of malignancy and consequent overtreatment.

Short Review

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Editorial Comment

The incidence of large round ligament leiomyoma is rare. Wei *et al.* reported a rare case of mesenchymal primary leiomyoma in the round ligament of a 45-year-old woman [1]. In routine outpatient visits, magnetic resonance imaging (MRI) is performed for diagnostic purposes before surgical treatment, and round ligament leiomyoma is usually diagnosed based on the evaluation of the MRI reports. Patients have a favorable prognosis if the tumor can be completely resected. Wei *et al.* noted that in clinical practice, round ligament leiomyomas may be difficult to diagnose, and laparoscopic imaging is the best procedure for the management of symptomatic leiomyomas [1].

1. Classification of uterine smooth muscle tumors

Uterine smooth muscle tumors, which are the most common uterine tumors, are mesenchymal tumors that differentiate into smooth muscle cells. They are broadly classified into three types depending on their malignancy: leiomyoma (benign uterine mesenchymal tumors), leiomyosarcoma (malignant uterine mesenchymal tumors), and smooth muscle tumor of uncertain malignant potential (STUMP) [2]. The malignancy of uterine mesenchymal tumors is detected via histopathological examination and is based on indicators such as nuclear atypia, mitotic number, and coagulative necrosis. Uterine smooth muscle cells are morphologically characterized by mutually orthogonal fascicles of spindle-shaped cells with obtuse elongated nuclei and eosinophilic cytoplasm at both ends [2]. Both leiomyomas and leiomyosarcomas exhibit the same morphological characteristics as those of uterine smooth muscle cells. Therefore, these features are considered indicative of smooth muscle tumors during oncological diagnosis.

Among leiomyomas, in addition to typical smooth muscle tumors (usual type), those with distinctive characteristics (a special type) occur [2]. These variants include mitotically active leiomyoma (a variant with increased mitotic activity), cellular leiomyoma, atypical leiomyoma with bizarre nuclei, symplastic leiomyoma, atypical epithelioid leiomyoma, lipoleiomyoma (a lipomatous variant), diffuse leiomyomatosis, intravenous leiomyomatosis, benign metastasizing leiomyoma, and disseminated peritoneal leiomyomatosis. Diffuse uterine leiomyomatosis, intravascular leiomyomatosis, benign metastatic leiomyomatosis, disseminated peritoneal leiomyomatosis, and dissociative uterine fibroids are uterine leiomyomas in which special growth patterns are observed. Furthermore, a myxoid variant of epithelioid leiomyosarcoma

has been reported [2][3].

2. Incidence, symptoms, and progression of uterine leiomyomas and leiomyosarcomas

Among gynecologic tumors, uterine leiomyomas occur most frequently. They are commonly found in women in their 40s and 50s [2], affecting 20%–30% of women aged >30 years, 40% of women aged >40 years, and 70%–80% of women in their 50s, with some also exhibiting microscopic tumors [3][4]. The development of clinically relevant uterine leiomyomas is more common in women who have attained sexual maturity and is rarer in women aged <18 years [3][4]. Moreover, many uterine leiomyomas shrink after menopause. Therefore, the development of uterine leiomyomas is dependent on the female hormones, with rapid growth observed during pregnancy or with the use of oral contraceptives. Treatment with gonadotropin-releasing hormone (GnRH) analogs has been shown to shrink uterine leiomyomas [3]. Although many women with uterine leiomyomas are asymptomatic, some experience irregular vaginal bleeding, cramping, and pressure. Discomfort due to the development of uterine leiomyomas is noted while undergoing progesterone therapy or during pregnancy. The symptoms vary depending on the tumor size, tumor number, and location at onset. Women with submucosal leiomyomas suffer from abnormal bleeding, including menorrhagia. They also experience significant pain when acute intramyometrial hemorrhage occurs during pregnancy or stem torsion of pedunculated submembranous leiomyoma takes place. In rare cases, uterine leiomyomas adhere to the heart and great vessels of patients with intravenous leiomyomatosis [5]. Lung metastases are most common in patients with metastasizing leiomyoma. In clinical practice, intravenous leiomyomatosis and metastatic leiomyomas are difficult to diagnose.

Uterine sarcomas account for 1%–2% of all malignant uterine tumors. Among the smooth muscle tumors, uterine leiomyosarcomas are detected in approximately 0.1%–0.3% of all cases. The age of onset of leiomyoma is lower than that of leiomyosarcoma, which usually occurs in women aged >40 years [2][6][7], with postmenopausal women exhibiting a high incidence of uterine leiomyosarcoma. There is no association between the risk factors for uterine leiomyosarcoma and those for endometrial cancer (infertility, obesity, and diabetes). The symptoms of uterine leiomyosarcoma are irregular vaginal bleeding, lower abdominal pain, pelvic pain, and pelvic mass. Tumor rupture and metastatic lesions in distant organs are observed in the early stages of the disease [8]. It is common for uterine leiomyosarcomas to adhere to the gastrointestinal tract and bladder. Hematogenous metastasis to the lung also occurs commonly. Although there is no medical evidence that the rapid growth of uterine mesenchymal tumors indicates the development of uterine leiomyosarcoma, it should be suspected if tumor growth is observed in postmenopausal women who are not undergoing hormone replacement therapy. Uterine leiomyosarcoma has a poor prognosis (the 5-year survival rate is approximately 25%), even in stage I cases. Furthermore, the recurrence rate after surgical treatment is high (approximately 45%–75%) [6][7].

3. Characteristics of cotyledonoid dissecting leiomyoma

In a previously reported case, contrast-enhanced computed tomography revealed a mass that was continuous with the

muscular layer of the uterine corpus, suggesting that it originated from there. However, no tumor cell extension was observed in the vein and myometrium [9]. Therefore, a benign leiomyoma growing outside the uterus and exhibiting a morphology similar to that of the placental lobe is called cotyledonoid dissecting leiomyoma [9]. A uterine leiomyoma that spreads in a bead-like manner and penetrates the uterine smooth muscle layer and broad ligament outside the uterus is accompanied by marked edematous changes. Such smooth muscle tumors are also called cotyledonoid dissecting leiomyomas because of their gross resemblance to the placental lobed cotyledon [9][10][11]. The large primary leiomyoma in the round ligament of a 45-year-old woman reported by Wei *et al.* is considered a type of cotyledonoid dissecting leiomyoma [1].

Cotyledonoid dissecting leiomyoma is an extremely rare benign uterine mesenchymal tumor. Its appearance on gross examination during surgical treatment is often misinterpreted as malignancy, which may result in considering unnecessary procedures, including chemotherapy. Serum tumor markers, including cancer antigen (CA) 125 and CA19-9, are elevated in many cases of gynecologic malignancies [12][13]. However, uterine leiomyomas, which are benign tumors, demonstrate normal levels of serum tumor markers. Unnecessary surgical procedures, such as total abdominal hysterectomy and bilateral salpingo-oophorectomy, can be avoided in patients of reproductive age if medical staff are aware of the characteristics of cotyledonoid dissecting leiomyomas.

4. Chromosomal and genetic abnormalities in uterine leiomyoma and leiomyosarcoma

Chromosomal abnormalities occur in approximately 40% of all uterine leiomyoma cases. The main chromosomal abnormality, that is, t(12;14) (q15;p23-24), is a gene rearrangement involving the short arm of chromosome 6 and deletion of the long arm of chromosome 7 [14]. Recently, such chromosomal abnormalities, including chromothripsis, caused by genetic variations have been reported [15]. Moreover, 70% of all uterine leiomyoma cases include a pathogenic variant (also called oncogenic variant or druggable variant) in the mediator complex subunit 12 (*MED12*) gene [16][17].

Genetic abnormalities in uterine leiomyosarcomas are more complex than those in uterine leiomyomas. Although various chromosomal abnormalities have been reported in cases of uterine leiomyosarcoma, none that is specific to it has been identified. Chromosomal aberrations (except in *MED12*) that are frequently observed in uterine leiomyomas have not been observed in uterine leiomyosarcoma. Therefore, the transformation of uterine leiomyoma into uterine leiomyosarcoma is very rare [18]. Mice lacking the large multifunctional protease (LMP) 2/ 1i, which is one of the subunits of the immunoproteasome, have been reported to develop spontaneous uterine leiomyosarcoma [19]. However, there is no oncological evidence for the development of uterine leiomyoma in LMP2/ 1i-deficient mice [19]. Previous clinical studies have reported genetic defects and mutations (Previous clinical studies have reported pathogenic or druggable variants in uterine leiomyosarcomas) in uterine leiomyosarcomas. Antitumor agents that target genetic mutations are ineffective against them [20][21]. Therefore, further pharmacogenomics clinical studies are required to develop targeted drugs against uterine leiomyoma and leiomyosarcoma.

Conclusion

Inguinal hernia and edema of the canal of Nuck are suspected in women presenting with inguinal mass and pain. Tumors that develop in the round ligament of the uterus can also cause this symptom although their incidence is very low. Although uterine leiomyomas are relatively common in clinical practice, there are very few reports of leiomyomas originating from the uterine round ligament. Previously reported cotyledonoid dissecting leiomyomas were not malignant. Medical staff must understand the oncologic features of cotyledonoid dissecting leiomyoma, including round ligament leiomyoma, to prevent misdiagnosis of malignancy and consequent overtreatment. Therefore, the report by Wei *et al.* provides medical professionals important information regarding the diagnosis and treatment of gynecologic tumors.

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Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Informed Consent

We have received informed consent from participants in clinical studies.

Author Contributions

T.H. designed the research, and TH collected and analyzed data. S.T. provided genetically engineered mouse and critical comments. N.Y. and I.K. wrote and approved the final paper.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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