Editorial Commentary

Importance of diagnostic methods for round ligament leiomyomas in clinical practice

Takuma Hayashi[1,2]^, Nobuo Yaegashi[2,3], Susumu Tonegawa[4], Ikuo Konishi[1,2,5]

[1]National Hospital Organization Kyoto Medical Centre, Kyoto, Japan; [2]Medical R&D Promotion Project, The Japan Agency for Medical Research and Development (AMED), Tokyo, Japan; [3]Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Miyagi, Japan; [4]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, USA; [5]Kyoto University Graduate School of Medicine, Kyoto, Japan

Correspondence to: Takuma Hayashi. National Hospital Organization, Kyoto Medical Centre, Mukaihatake-cho, Fushimi-ku, Kyoto City, Japan. Email: yoyoyo224@hotmail.com.

Comment on: Wei L, Qin T, Chu J, Chong X, Chu J, Wang W, Li P. A large leiomyoma of the round ligament: a case report and literature review. Quant Imaging Med Surg 2022. doi: 10.21037/qims-22-311.

Keywords: Round ligament leiomyoma; leiomyoma; diagnostic method; cotyledonoid dissecting leiomyoma; mesenchymal tumor

Submitted Nov 18, 2022. Accepted for publication Dec 14, 2022. Published online Jan 10, 2023.
doi: 10.21037/qims-22-1276
View this article at: https://dx.doi.org/10.21037/qims-22-1276

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).

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

^ ORCID: 0000-0002-7525-2048.

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).

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 40 and 50 s (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).

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.

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 (9,14). 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/β1i, 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/β1i-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.

Conclusions

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.

Acknowledgments

We sincerely appreciate the technical assistance of the research staff at the National Hospital Organization Kyoto Medical Center.

Funding: This work was supported by the following agencies: Japan Society for the Promotion of Science (JSPS) for TH (grant No. 19K09840), START-program of Japan Science and Technology Agency (JST) for TH (grant No. STSC20001), National Hospital Organization) multicenter clinical study for TH (grant No. 2019-Cancer in general-02), and Japan Agency for Medical Research and Development (AMED) (grant No. 22ym0126802j0001).

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1276/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Wei L, Qin T, Chu J, Chong X, Chu J, Wang W, Li P. A large leiomyoma of the round ligament: a case report and literature review. Quant Imaging Med Surg 2022. doi: 10.21037/qims-22-311.
2. Uterine leiomyoma. Female Genital Tumours WHO Classification of Tumours, 5th ed., Vol.4. WHO Classification of Tumours Editorial Board. World Health Organization 2020:272-276.
3. Zaloudek CJ, Hendrickson MR, Soslow RA. Mesenchymal tumors of uterus. In: Kurman, RJ, Ellenson, LH, Ronnett, BM, eds. Blaustein's Pathology of Female Genital Tract. New York, NY: Springer; 2011:453.
4. Weiss SW, Goldblum JR. Benign tumors of smooth muscle. In: Weiss, SW, Goldblum, JR, eds. Enzinger and Weiss's Soft Tissue Tumors. Philadelphia, PA: Mosby Elsevier; 2008:520-521.
5. Ip PP, Tse KY, Tam KF. Uterine smooth muscle tumors other than the ordinary leiomyomas and leiomyosarcomas: a review of selected variants with emphasis on recent advances and unusual morphology that may cause concern for malignancy. Adv Anat Pathol 2010;17:91-112.
6. Toledo G, Oliva E. Smooth muscle tumors of the uterus: a practical approach. Arch Pathol Lab Med 2008;132:595-605.
7. Uterine leiomyosarcoma. Female Genital Tumours WHO Classification of Tumours, 5th ed., Vol.4. WHO Classification of Tumours Editorial Board. World Health Organization 2020:283-285.
8. Hayashi T, Yaegashi N, Tonegawa S, Konishi I. Potential biomarkers associated with malignancy in uterine mesenchymal tumors. European Journal of Gynaecological Oncology 2021;42:824-8.
9. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. (eds): WHO Classification of Tumours of Female Reproductive Organs, 4th ed, IARC Press, Lyon, 2014.
10. Zaloudek CJ, Hendrickson MR, Soslow RA. Mesenchymal tumors of the uterus. In Kurman R (ed): Blaustein's Pathology of the Female Genital Tract, 6th ed. Springer, New York, 2010:453-527.
11. Makharoblidze E, Goishvili N, Mchedlishvili M, Khakhutaishvili I, Jangavadze M. Unusual types of smooth muscle tumors of uterine corpus: case reports and literature review. Georgian Med News 2013;(216):7-11.
12. Dolscheid-Pommerich RC, Keyver-Paik M, Hecking T, Kuhn W, Hartmann G, Stoffel-Wagner B, Holdenrieder S. Clinical performance of LOCI™-based tumor marker assays for tumor markers CA 15-3, CA 125, CEA, CA 19-9 and AFP in gynecological cancers. Tumour Biol 2017;39:1010428317730246.
13. Babacan A, Kizilaslan C, Gun I, Muhcu M, Mungen E, Atay V. CA 125 and other tumor markers in uterine leiomyomas and their association with lesion characteristics. Int J Clin Exp Med 2014;7:1078-83.
14. Tamura S, Hayashi T, Ichimura T, Yaegashi N, Abiko K, Konishi I. Characteristic of Uterine Rhabdomyosarcoma by Algorithm of Potential Biomarkers for Uterine Mesenchymal Tumor. Curr Oncol 2022;29:2350-63.
15. Mehine M, Kaasinen E, Mäkinen N, Katainen R, Kämpjärvi K, Pitkänen E, Heinonen HR, Bützow R, Kilpivaara O, Kuosmanen A, Ristolainen H, Gentile M, Sjöberg J, Vahteristo P, Aaltonen LA. Characterization of uterine leiomyomas by whole-genome sequencing. N Engl J Med 2013;369:43-53.
16. Mäkinen N, Mehine M, Tolvanen J, Kaasinen E, Li Y, Lehtonen HJ, Gentile M, Yan J, Enge M, Taipale M, Aavikko M, Katainen R, Virolainen E, Böhling T, Koski TA, Launonen V, Sjöberg J, Taipale J, Vahteristo P, Aaltonen LA. MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. Science 2011;334:252-5.
17. Berta DG, Kuisma H, Välimäki N, Räisänen M, Jäntti M, Pasanen A, et al. Deficient H2A.Z deposition is associated with genesis of uterine leiomyoma. Nature 2021;596:398-403.
18. Matsubara A, Sekine S, Yoshida M, Yoshida A, Taniguchi H, Kushima R, Tsuda H, Kanai Y. Prevalence of MED12 mutations in uterine and extrauterine smooth muscle tumours. Histopathology 2013;62:657-61.
19. Hayashi T, Horiuchi A, Sano K, Yaegashi N, Konishi I. Uterine Leiomyosarcoma Tumorigenesis in Lmp2-deficient Mice: Involvement of Impaired Anti-oncogenic Factor IRF1. Anticancer Res 2015;35:4665-79.

20. Jonsson P, Bandlamudi C, Cheng ML, Srinivasan P, Chavan SS, Friedman ND, et al. Tumour lineage shapes BRCA-mediated phenotypes. Nature 2019;571:576-9.
21. Seligson ND, Kautto EA, Passen EN, Stets C, Toland AE, Millis SZ, Meyer CF, Hays JL, Chen JL. BRCA1/2 Functional Loss Defines a Targetable Subset in Leiomyosarcoma. Oncologist 2019;24:973-9.

Cite this article as: Hayashi T, Yaegashi N, Tonegawa S, Konishi I. Importance of diagnostic methods for round ligament leiomyomas in clinical practice. Quant Imaging Med Surg 2023;13(3):2033-2037. doi: 10.21037/qims-22-1276

