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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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POTENTIAL LIFE PROGNOSTIC MARKER FOR MESENCHYMAL TUMOR RESEMBLING UTERINE LEIOMYOSARCOMA

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Abstract.

Background/Aim: Benign uterine leiomyoma (U.LMA) and malignant uterine leiomyosarcoma (U.LMS), both uterine mesenchymal tumors, are distinguished by the number of cells exhibiting mitotic activity. However, uterine mesenchymal tumors contain tumor cells with various cell morphologies; therefore, making a diagnosis, including differentiating between benign and malignant tumors, is difficult. For example, cotyledonoid dissecting leiomyoma (CDL) or uterine smooth muscle tumors of uncertain malignant potential (STUMPs) are a group of uterine mesenchymal tumors for which a differential diagnosis is challenging. To date, a standardized classification system for uterine mesenchymal tumors has not yet been established. Furthermore, definitive preoperative imaging techniques or hematological examinations for the potential inclusion of CDL or STUMP in the differential diagnosis have not been defined. Several clinical studies have reported that there is no correlation between biomarker expression and mitotic rate or tumor recurrence. The immunohistochemical biomarkers reported so far cannot effectively help determine the malignant potential of CDL or STUMPs in patients who wish to become pregnant in the future.

Materials and Methods: The establishment of gene expression profiles or detection of pathogenic variants by using next-generation molecular techniques can facilitate disease prediction, diagnosis, treatment, and prognosis. We examined the oncological properties of STUMP in adults using molecular pathological techniques on tissue excised from patients with uterine mesenchymal tumor.

Result: In a clinical study conducted by our medical team, the results of gene expression profiling indicated factors that may be associated with malignancy of uterine mesenchymal tumors.

Conclusion: We herein describe the problems in diagnosing uterine mesenchymal tumors along with the results of the latest clinical studies. It is expected that the establishment of a diagnostic method targeting the characteristics of mesenchymal tumor cells will lead to the treatment of malignant tumors with a low risk of recurrence and metastasis.

Key words. STUMP, uterine mesenchymal tumor, leiomyoma, leiomyosarcoma.

Introduction.

Uterine leiomyomas (U.LMAs) are benign tumors that develop in the smooth muscle tissue of the uterus [1]. The walls of the uterus are made up of muscle cells called smooth muscle; thus, benign tumors derived from smooth muscle cells are called leiomyomas. The prevalence of U.LMA in adult women up to the age of 50 is approximately 70%, indicating that it is a common gynecologic tumor [2,3]. In many cases, U.LMAs do not rapidly grow in size or spread to other tissue sites while destroying surrounding tissue, as do malignant tumors. However, they can gradually grow in size and cause pain in the lower abdomen or abnormal bleeding that interferes with daily life [4]. Therefore, the onset of U.LMA often causes anemia and other conditions. Drug therapy such as Leuprin (Gonadotropin releasing hormone (GnRH) agonist preparation), Relumina tablets (GnRH antagonist formulation), or surgical treatment may be necessary to alleviate the symptoms U.LMA [5,6].

U.LMAs express female hormone receptors and are therefore known to increase in size due to female hormones [7]. Therefore, the onset of U.LMAs is observed from around the age of 20 when female hormone secretion increases. U.LMA is also known to gradually shrink after the age of 50 when menopause occurs and the amount of female hormone secretion sharply drops. However, the location and symptoms of U.LMA differ depending on each case, and there are many cases in which it is difficult to diagnose using contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT). Cotyledonoid dissecting leiomyoma (CDL), which occurs in the uterine smooth muscle layer within the uterine corpus, proliferates in the broad ligament of the uterus, making diagnosis via imaging examinations difficult [8] (Supplementary Figure 1). Furthermore, tumor cells derived from uterine smooth muscle cells, such as U.LMA cells, have various cell and nuclear morphologies. Thus, in many cases, it is not easy to make a surgical pathological diagnosis using tissue removed by surgical treatment. Uterine smooth muscle tumors of unknown malignancy are called uterine smooth muscle tumors of uncertain malignant potential (STUMPs), making it difficult to decide on treatment options postoperatively [9,10].

To elucidate the characteristics of various uterine smooth muscle tumors, our clinical team employed molecular histopathological techniques to determine the molecular biological characteristics of various uterine smooth muscle tumor cells, including U.LMA and uterine leiomyosarcoma (U.LMS) cells. The analysis results indicated that the malignancy of uterine smooth muscle tumor cells may be correlated more with the expression level of Ki-67 than with the positive rate of Ki-67-positive cells. In this report, we used cases of CDL and STUMP to explain the points to be noted in the diagnosis using contrast-enhanced MRI or CT and pathological examinations.

Materials and Methods.

1. Tissue Collection

A total of 101 patients aged between 32 and 83 years and diagnosed with smooth muscle tumors of the uterus were selected from pathological files. For hematoxylin and eosin staining and immunostaining, serial sections were cut from at least two tissue blocks from each patient.

2. Immunohistochemistry

Immunohistochemistry (IHC) staining for Caveolin 1, Cyclin B, Cyclin E1, large multifunctional peptidase 2/□1i (LMP2/□1i), Ki-67, desmin, and myogenin was performed using serial sections of human uterine mesenchymal tumor obtained from patients with uterine mesenchymal tumor.

3. Ethical approval and consent to participate

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) and Shinshu University (Nagano, Japan). Ethical approval was obtained on August 17, 2019 (approval no. NHO H31-02).

Details of Materials and Methods are indicated in Supplementary Materials.

Case 1: Molecular pathological features of cotyledonoid dissecting leiomyoma

Another clinical group recently reported the case of a 49-year-old woman with CDL diagnosed via molecular pathological examination using a paraffin-embedded postoperative tissue section [11]. In routine clinical gynecologic practice, uterine mesenchymal tumors are among the most common gynecologic tumors. U.LMA is a benign mesenchymal tumor that develops from the uterine smooth muscle layer. It accounts for approximately 75% of all uterine tumor tissues resected from patients by surgical treatment [12]. Uterine mesenchymal tumors mainly occur in women of reproductive age; the prevalence rate of U.LMA in women in their 50s is approximately 70% [12,13]. However, its incidence is low in postmenopausal women (The age at which menopause occurs is generally between 50 and 51 years old.). Because U.LMA expresses hormone receptors in many cases, female hormone secretion affects its proliferation, and its size and growth slightly varies depending on the sexual cycle. In the World Health Organization (WHO) classification of gynecologic tumors, the histomorphology of typical U.LMA is similar to that of spindle cell leiomyoma, cellular leiomyoma, epithelioid leiomyoma, intravenous leiomyomatosis, and leiomyoma with bizarre nuclei [14-17]. A CDL is an U.LMA with a very rare placental lobed tissue morphology [12] that can be misdiagnosed as a malignant mesenchymal tumor, i.e., U.LMS, owing to its rarity and characteristic appearance on gross examination.

In one such case, contrast-enhanced CT showed a mass that was continuous with the myometrium of the uterine corpus, suggesting that it has arisen from there [18]. However, no invasion of tumor cells into the vein and smooth muscle layer was observed. Therefore, U.LMA growing outside the uterus corpus and exhibiting a morphology similar to that of the placental leaf is called a CDL [18]. CDL, which extends into the myometrium and broad ligament as well as extrauterinally in a beaded manner, is accompanied by marked edematous changes and macroscopically resembles a placental lobe cotyledon [14,18,19].

Another clinical group reported the case of a 49-year-old woman with CDL diagnosed via molecular pathological examination using a postoperative paraffin-embedded tissue section [11]. She presented with a history of progressive constipation that lasted for 6 months and a palpable left lower abdominal mass for 1 month [11]. Contrast-enhanced CT revealed no enlarged pelvic or para-aortic lymph nodes. The result of her blood test showed normal serological tumor markers, namely, cancer antigen (CA) 125, CA19-9, carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) levels. Transvaginal ultrasonography showed a massive mass comprising two subserous fibroids measuring 9.9 × 6.9 × 6.3 cm and 8.1 × 6.6 × 6.8 cm, respectively, with peripheral and internal probing blood flow signals [11]. Rapid examination using intraoperative frozen sections showed an angioleiomyoma with edema [11]. Truncal CT performed 6 months postoperatively revealed no abnormal findings.

The patient in case 1: our clinical team recently experienced treatment for a patient with CDL (Supplementary Figure 2). In November 2020, a 57-year-old woman visited a hospital due to abnormal vaginal bleeding, and the development of a chocolate cyst was suspected. MRI showed a mass in the patient's pelvis that could not be adjudged as malignant or benign. However, ovarian cancer was suspected because a solid component was identified on MRI. Therefore, the patient was referred to our hospital that has a gynecologic team for thorough examination. Transvaginal ultrasonography showed a solid mass measuring 115 × 57 mm with an indistinct margin in the right ovary. The area of origin of the mass suggested ovarian cancer or a retroperitoneal tumor. In March 2021, the patient underwent simple hysterectomy and bilateral salpingectomy. A degenerative U.LMA measuring 110 × 80 mm was found growing within the broad ligament attached to the right round ligament. No gross abnormalities were detected in the bilateral fallopian tubes and ovaries. Surgical pathological examination of the resected tissue showed a CDL. There was no evidence of malignancy in the endometrial, cervical, or bilateral oviduct tissue. The patient is currently being followed up on an outpatient basis. Similar to the detection of a suspicious malignant mass during MRI examination by our medical staff, other healthcare professionals must understand the characteristic appearance of a CDL.

CDL is an extremely rare benign uterine mesenchymal tumor. It is often misdiagnosed as malignant in appearance in gross examination during surgical treatment, which can lead to overtreatment. The levels of serological tumor markers for gynecologic tumors, such as CA125 and CA19-9, are elevated in many cases of gynecologic malignancies [20,21]. Moreover, elevated levels of CEA, gastrointestinal malignancy markers, are not observed in many cases of gynecologic malignancies. Contrarily, blood test results for U.LMAs show normal serological tumor marker levels. If medical staff are aware of the appearance and oncological features of CDL, unnecessary surgical procedures, such as total abdominal hysterectomy and bilateral salpingo-oophorectomy, can be avoided in patients of reproductive age.

Figure 1

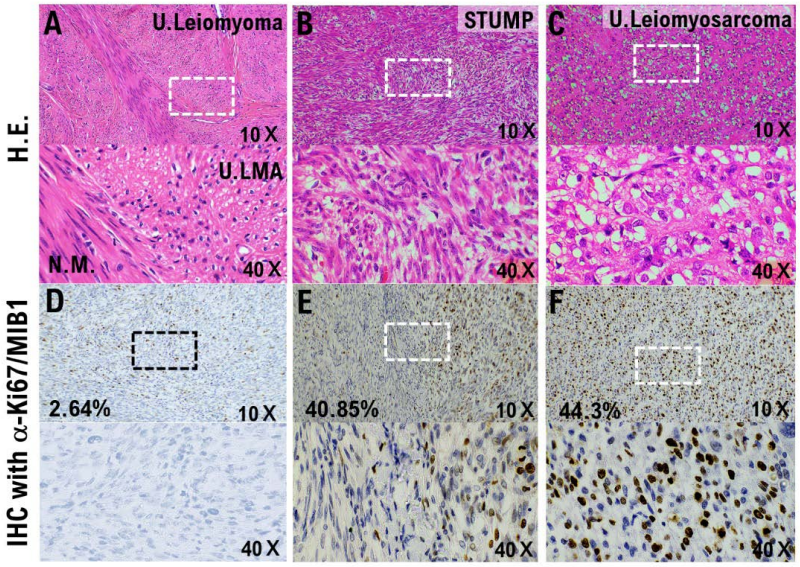
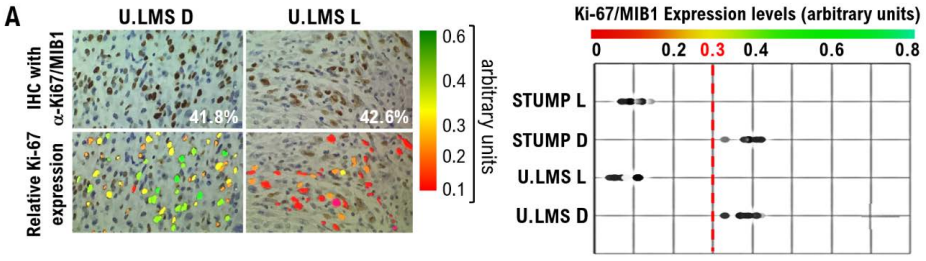


Figure 1. Cell morphology of uterine leiomyoma, STUMP, and uterine leiomyosarcoma.
(A,D) *Uterine leiomyoma (spindle cell leiomyoma). Low-power view (10×) shows a well-circumscribed tumor nodule in the myometrium comprising broad fascicles of spindle cells. High-power view (40×) shows spindle cells with bland cytological features, elongated nuclei, and fine nuclear chromatin.* ***(B,E)*** *Epithelioid smooth muscle tumor of uncertain malignant potential. Low-power view (10×) shows a tumor with multinodular growth at its periphery that might recur. The tumor has an irregular border with the surrounding myometrium. High-power view (40×) shows tumor recurrence in the peritoneum as multiple nodules.* ***(C, F)*** *Uterine leiomyosarcoma (spindle cell leiomyosarcoma). Low-power view (10×) shows a cellular tumor with fascicular growth and enlarged hyperchromatic nuclei. High-power view (40×) shows epithelioid leiomyosarcoma with round tumor cells having eosinophilic granular cytoplasm and irregularly shaped nuclei.* ***(A,B,C)*** *The photographs show tissue sections stained with hematoxylin and eosin.* ***(D,E,F)*** *The photographs show the tissue sections stained by IHC with anti-Ki-67/MIB1 monoclonal antibody. N.M., normal myometrium; STUMP, smooth muscle tumors of uncertain malignant potential; U.LMA, uterine leiomyoma.*

Figure 2



B

Ki-67/MIB1 positive cells/total cells (%)		
U.Liomyoma	STUMP	U.Leiomyosarcoma
02.48% – 04.61%	38.54% – 44.75%	40.78% – 45.68%

	Relative Ki-67/MIB1 expression (arbitrary units)	
	≤ 0.3	> 0.3
STUMP	Survival over 5 years after surgery	Death within 5 years after surgery
U.LMS	Survival over 5 years after surgery	Death within 5 years after surgery

Figure 2. Importance of the expression level of Ki-67/MIB on uterine mesenchymal malignancy.
(A) *The photographs show the results of IHC using an anti-human Ki-67 monoclonal antibody (clone; MIB1) on the sections of uterine leiomyosarcomas. The Ki-67/MIB1 positivity rate (%) in uterine leiomyosarcomas is indicated in the upper photographs. The expression levels of Ki-67/MIB1 were quantified by an image analysis device, Mantra 2™ Quantitative Pathology Workstation (Akoya Biosciences, Inc. Marlborough, MA, USA).* ***(B)*** *The table presents the Ki-67/MIB1 positivity rate (%) in uterine mesenchymal tumors: uterine leiomyoma, STUMP, and uterine leiomyosarcoma. These values are approximately 40.78%–45.68%, 02.46%–04.61%, and 38.54%–44.75% in uterine leiomyosarcoma, uterine leiomyoma, and STUMP tissues, respectively. Relative Ki-67/MIB1 expression (arbitrary units) in uterine mesenchymal tumors. As a result, it was demonstrated that in patients with uterine leiomyosarcoma or STUMP, those with a Ki-67/MIB1 expression level of 0.3 (arbitrary units) or higher died within 5 years postoperatively whereas those with a Ki-67/MIB1 expression level of less than 0.3 (arbitrary units) lived for more than 5 years postoperatively. N.M., normal myometrium; STUMP, smooth muscle tumors of uncertain malignant potential; U.LMA, uterine leiomyoma; STUPM L or U.LMS L, survival over 5 years postoperatively; STUMP D or U.LMS D, death within 5 years postoperatively.*

All CDLs reported to date were clinically diagnosed as benign gynecologic tumors, and only one case had recurrence 5 years after the initial segmental resection [22]. This case involved a 33-year-old woman who underwent incomplete resection to preserve fertility [22]. In this case, it is natural to think that the remaining tumor cells, even if they are benign tumors, proliferate again after being stimulated by estrogen or the like. However, tumor recurrence or advanced tumor has not been reported in cases where complete resection (hysterectomy) for CDL was performed. In the case reported by other clinical groups, there was no evidence of recurrence or advanced tumor in the patient 18 months after hysterectomy [11]. Recently, other research facilities have reported the cases of epithelioid CDL variants and CDLs with intravenous leiomyomatosis [23,24]. Histologically, CDL-derived neoplastic mesenchymal cells form the disorganized bundles, contrary to the organized pattern observed in common U.LMAs [25].

In many cases of uterine mesenchymal tumors, differentiation between U.LMA and U.LMS is difficult. U.LMA is the most frequently occurring uterine sarcoma and accounts for 1%–2% of all uterine malignant tumors [18]. Moreover, U.LMS mostly occurs in women aged >40 years. Unlike uterine benign smooth muscle tumors, U.LMS frequently occurs in postmenopausal women [26]. The rapid growth of uterine mesenchymal tumors that develop from the uterine smooth muscle layer does not immediately suggest U.LMS development. However, in postmenopausal women who are not undergoing hormone replacement therapy, malignancy should be suspected by medical staff when uterine mesenchymal tumors are growing or recurring. However, in the case reported by Ye H et al., neither an epithelioid pattern nor an intravascular neoplastic component was detected [11]. Therefore, tumor recurrence postoperatively will presumably not occur in this patient.

In conclusion, a CDL is a rare variant of U.LMA [25,27]. Its gross appearance and ultrasonographic features may indicate malignancy. Furthermore, it exhibits >10 increases in mitotic activity/10 high-power field (HPF), tumor cell necrosis, and no evidence of cellular atypia. Thus, histologically, CDL is a benign tumor. To date, recurrence and metastasis have not been reported in majority of the cases. Therefore, prognosis is considered favorable in clinical practice. Clinicians and pathologists must understand the oncologic features of CDL to prevent misdiagnosis of malignancy and consequent overtreatment.

Case 2: Molecular pathological features of STUMP

A recent clinical study reported an analysis of immunohistochemical examination findings of STUMPs, which are considered difficult to pathologically diagnose based on prognosis (28)]. Uterine smooth muscle tumors are the most common uterine mesenchymal tumors that have the properties of uterine smooth muscle cells. Uterine mesenchymal tumors are classified into three major types according to their malignant potential: benign leiomyoma (also called uterine fibroid), malignant U.LMS, and STUMP, whose degree of malignancy has not yet been elucidated [29]. U.LMS has a poor prognosis, and surgery is the only treatment for it. Therefore, it is important to determine the malignancy of uterine mesenchymal tumors. In clinical practice, Determination of malignancy is carried out by histopathological analysis based on the observation of indicators such as nuclear atypia, mitotic count, and coagulative necrosis. Uterine smooth muscle cells are characterized by proliferation of spindle-shaped cells consisting of obtuse, elongated nuclei at both ends and eosinophilic cytoplasm, which are oriented perpendicular to each other and multiply in bundles.

Our clinical team recently experienced treatment for a patient with CDL (Supplementary Figure 3). In October 2020, a 47-year-old woman visited a hospital due to abnormal vaginal bleeding, and the development of endometrial stromal sarcoma or U.LMS was suspected. In many cases, U.LMAs and U.LMSs exhibit the same morphological characteristics as those of uterine smooth muscle cells [30] (Figure 1A,C,D,F). Therefore, mesenchymal tumors are diagnosed based on the morphological features of the uterine smooth muscle cells [31]. However, U.LMAs and U.LMSs have similar morphological characteristics; thus, differentiating between them is a key challenge. During surgical pathological examination, including malignancy determination, the cell morphologies of STUMP and that of U.LMS are very similar, making differential diagnosis difficult (Figure 1B,C,E,F). A recent clinical research report showed that the Ki-67/MIB1 positivity rates in U.LMS and U.LMA tissues were approximately 40.78%–45.68% and 02.46%–04.61%, respectively [31] (Figure 2A, Table 1). Contrarily, the Ki-67/MIB1 positivity rate in STUMP tissues was approximately 38.54%–44.75% (Figure 2A, Table 1). However, the relationship between Ki-67/MIB1 positivity rate and prognosis has not been elucidated. In other words, among uterine mesenchymal tumors with more mitotic numbers than U.LMAs but fewer ones than U.LMSs, those without clear tumor-induced coagulative necrosis are identified as STUMPs [32].

In a recent clinical study, of the 54 cases of U.LMS, 43 were included in the cohort that died within 5 years postoperatively and 11 in the cohort that survived for more than 5 years postoperatively (Table 1). Furthermore, of the 12 cases of STUMP, 5 were included in the cohort that died within 5 years postoperatively and 7 in the cohort that survived for more than 5 years postoperatively (Table 1). In this clinical study, the expression level of Ki-67/MIB1 was quantified by an image analysis device, Mantra 2™ Quantitative Pathology Workstation (Akoya Biosciences, Inc. Marlborough, MA, USA) (Supplementary Materials and Methods). As a result, it was shown that in patients with U.LMS or STUMP, those with a Ki-67/MIB1 expression level of 0.3 (arbitrary units) or higher died within 5 years postoperatively (Figure 2A). Furthermore, those with a Ki-67/MIB1 expression level of less than 0.3 (arbitrary units) lived for more than 5 years postoperatively (Figure 2A). Rather than the Ki-67-/MIB1-positive rate, the expression level of Ki-67/MIB1 is considered to be associated with the malignancy of uterine mesenchymal tumors (Figure 2B). Therefore, the expression level of Ki-67/MIB1 is considered to be a useful candidate for prognostic marker for patients who develop uterine mesenchymal tumors. STUMPs typically occur in women of reproductive age or postmenopausal women with a mean age of approximately 43 years, which is a decade less than that of patients with U.LMS [33]. U.LMAs are sensitive to female hormones, and female hormones induce U.LMA cell

Table 1. *Differential expressions of SMA, Caveolin1, Cyclin B, Cyclin E, LMP2, NT5DC2, CD133, and Ki-67 in human uterine mesenchymal tumors and uterine LANT-like tumor.*

Mesenchymal tumor types	Age years	n	Protein expression*							
			SMA	CAV1	CCNB	CCNE	LMP2	NT5DC2	CD133	Ki-67
Normal	30s-80s	**74**	+++	-	-	-	+++	-	-	-
Leiomyoma (LMA)	30s-80s	**40**	+++	++	-/+	-/(+)	+++	-/+	-	+/-
(Ordinally leiomyoma)		(30)	+++	++	-/+	-	+++	-/+		+/-
(Cellular leiomyoma)		(10)	++	++	-/+	-/(+)	++	-/+		+/-
Cotyledonoid dissecting leiomyoma (CDL)	50s	**2**	+++	++	+	+	++	-/+	-	++
STUMP	40s-60s	**12**	++	++	+	-/+	-/+	-/+	NA	+/++
Lipoleiomyoma	40-50s	**2**	NA	++	-/+	+	+++	NA	NA	++
Bizarre Leiomyoma	40s-50s	**4**	++	++	-/+	+	Focal+	+	NA	+
Intravenous LMA	50s	**3**	++	++	+	+	-	NA	++	+
Benign metastasizing	50s	**1**	++	++	+	++	-	NA	NA	++
Leiomyosarcoma	30s-80s	**54**	-/+	+	++	+++	-/+	++	++	++/+++
Rhabdomyosarcoma	10s,50s	**2**	NA	++	-/+	+++	+++	NA	NA	NA
U.LANT[#]-like tumour	40s	**1**	++	+	NA	++	-	NA	NA	-

**Staining score of expression of SMA, CAV1 (Caveorin 1), CCNB (Cyclin B), CCNE (Cyclin E), LMP2 (low molecular protein 2), NT5DC2 (5'-Nucleotidase Domain Containing 2) and Ki-67 from results of IHC experiments. Protein expression*; estimated-protein expressions by immunoblot analysis, immunohistochemistry (IHC) and/or RT-PCR (quantitative-PCR),-/+; partially positive (5% to 10% of cells stained), Focal+; Focal-positive (focal or sporadic staining with less than 5% of cells stained),++; staining with 5% or more, less than 90% of cells stained, +++; diffuse-positive (homogenecus distribution with more than 90% of cells stained), -; negative (no stained cells). U.LANT-like tumour; uterine leiomyomatoid angiomatous neuroendocrine tumour-like tumour, LMP2, cyclin E, caveolin1, NT5DC2, CD133, Ki-67. STUMP (Smooth muscle tumor of uncertain malignant potential). Cyclin E, LMP2, Caveolin1 are potential biomarker for human uterine mesenchymal tumors. LANT#, leiomyomatoid angiomatous neuroendocrin tumour (LANT) is described as a dimorphic neurosecretory tumor with a leiomyomatous vascular component. NA; no answer.*

proliferation. However, the growth of U.LMS cells is female hormone independent. It is unclear how this 10-year difference affects the development of U.LMS, a malignant tumor.

An increased mitotic rate in U.LMA-like uterine mesenchymal tumors is highly suggestive of U.LMS. However, uterine mesenchymal tumors with poor nuclear atypia and no tumor-induced coagulation necrosis are diagnosed as U.LMAs with increased nuclear mitotic activity, and these tumors are benign [31]. In many of these cases, the mitotic rate is approximately 5–9/10 HPF, although mitotic rates as high as 10–20/10 HPF also occurs. A uterine mesenchymal tumor with a mitotic rate of ≥20/10 HPF in the absence of nuclear atypia and tumor coagulation necrosis is diagnosed as STUMP. U.LMA with nuclear atypia is referred to as U.LMA with bizarre nuclei that was considered a benign tumor until recently. However, in new clinical studies, the foci of atypical cells with nuclear atypia have been found, and recurrence has been observed in cases of uterine mesenchymal tumors with low mitotic numbers [34]. According to the latest WHO classification, U.LMA with bizarre nuclei is categorized as STUMP [29,34].

A meta-analysis of the results of 11 clinical studies involving the follow-up of patients with STUMP revealed a 10% postoperative recurrence rate (15/150 cases) [35]. However, uterine STUMP is a significantly rare uterine mesenchymal tumor among gynecologic tumors. Therefore, there is no standardized pathologic classification or definitive preoperative contrast-enhanced CT, MRI, or hematological examination for STUMP.

A Taiwanese clinical research group recently examined the medical history, etiology, risk factors, and prognosis of six patients with STUMP to establish a standardized pathologic classification [28]. Immunohistochemistry examination with the use of appropriate monoclonal antibodies showed a marked expression of cyclin-dependent kinase inhibitor 2A (CDKN2A), tumor protein p53 (TP53), and tumor antigen Ki-67/MIB1 in all six patients [11]. The expression rates of estrogen receptor (ER) and progesterone receptor (PgR) in this series were 50.0% (3/6) and 33.3% (2/6), respectively. Furthermore, no correlation was observed between the expression of these immunohistochemical biomarkers and mitotic count or tumor recurrence, which led to the conclusion that the expression status of current immunohistochemical biomarkers is ineffective in determining malignant potential in patients with STUMP who wish to conceive [11]. The identification of STUMP pathogenic variants by genome sequencing and gene expression profiling using next-generation molecular techniques may facilitate malignant potential prediction, surgical pathological diagnosis, clinical treatment, and prognostic assessment.

Previous clinical studies have reported immunohistochemical positivity for CDKN2A and TP53 in STUMP cases with postoperative recurrence [36,37]. However, in recent years, cancer genome testing in clinical practice has also revealed pathogenic variants in cell cycle regulators, such as CDKN2A, TP53, CDKN1A, and CDKN1B, in gynecologic tumors, including uterine carcinosarcoma and endometrial stromal sarcoma [38]. Thus, the immunohistochemical findings related to CDKN2A, TP53, CDKN1A, CDKN1B, ER, and PgR have limited application in the differentiation between U.LMAs and U.LMSs [39,40].

Discussion.

Owing to its high incidence, many patients present with the typical features of U.LMA. Thus, it can be easily identified by surgical pathological examination. However, smooth muscle tumor cells have various cell and nuclear morphologies and may proliferate into the broad ligament of the uterus, so diagnosing smooth muscle tumors is not always easy [41]. Furthermore, determining the malignancy of uterine mesenchymal tumors that exhibit atypical features is difficult [42]. The results of this study suggested that the morphological characteristics and expression level of Ki-67 are better indicators of malignancy of uterine smooth muscle tumor cells than the Ki-67 positivity rate.

The 5-year survival rate for U.LMS is thought to be less than 20% [43,44]. In this clinical study, we compared the Ki-67-positive cell rate and Ki-67 expression levels in each tissue of U.LMS obtained from patients who died within 5 years postoperatively and those who survived for more than 5 years postoperatively. As a result, no correlation was observed between the percentage of Ki-67-positive cells and tumor grade in the two groups. The expression of Ki-67 was significantly higher in the U.LMS tissues obtained from patients who died within 5 years postoperatively compared with those obtained from patients who survived for more than 5 years postoperatively. In addition, a correlation was observed between survival prognosis and Ki-67 expression levels in each tissue obtained from patients with STUMP.

To date, many medical researchers have investigated the expression status of various factors in uterine smooth muscle tumors to develop new diagnostic and therapeutic methods for such tumors, particularly U.LMS [45]. In cases of U.LMA, which has a high morbidity rate in actual clinical practice, a diagnostic exclusion method for U.LMS has not yet been established [46]. Therefore, an in-depth investigation of the relationship between the cell morphology and prognosis of various uterine mesenchymal tumors, including U.LMA, is key to understanding the oncological characteristics of these tumors. In clinical practice, STUMP should be conclusively diagnosed.

In actual clinical practice, endometrial stromal sarcoma and carcinosarcoma are recognized as tumors of uterine smooth muscle cells that arise in the uterine smooth muscle layer. At present, there is no established method for differentiating between these malignant tumors, STUMP, and U.LMS. Detailed pathological findings and clinical information about uterine mesenchymal tumors must be documented to establish a more appropriate pathological concept of STUMP or U.LMS.

Conclusion.

Surgical pathological diagnosis of uterine mesenchymal tumors is often difficult due to the lack of a standardized classification for uterine mesenchymal tumors, By using a next-generation sequencer to identify key biomarkers, i.e., pathogenic variants involved in the progression and tumorigenesis of various uterine mesenchymal tumors, the prediction of survival among patients with STUMP may be possible. In the future, the establishment of personalized treatment in clinical practice for uterine mesenchymal tumors, including STUMPs, is expected.

Abbreviations: AFP: Alpha-Fetoprotein; CA: Cancer Antigen; CDKN2A: Cyclin-Dependent Kinase Inhibitor 2A; CDL: Cotyledonoid Dissecting Leiomyoma; CEA: Carcinoembryonic Antigen; ER: Estrogen Receptor; Gnrh: Gonadotropin Releasing Hormone; IHC: Immunohistochemistry; HPF: High-Power Field; MRI: Magnetic Resonance Imaging; Pgr: Progesterone Receptor; STUMP: Smooth Muscle Tumors Of Uncertain Malignant Potential; TP53: Tumor Protein P53; U.LMA: Uterine Leiomyoma; U.LMS: Uterine Leiomyosarcoma; WHO: World Health Organization.

Supplementary Materials: Supplementary Materials: 1. Materials and Methods, 2. Patient #1 findings on contrast-enhanced MRI imaging, 3. Patient #2 findings on contrast-enhanced MRI imaging.

Author Contributions: S.N. and T.H. performed most of the clinical work and coordinated the project. T.H. and T.U. conducted the diagnostic pathological studies. T.H. conceptualized the study and wrote the manuscript. T.H., K.A. and I.K. carefully reviewed this manuscript and commented on the aspects of medical science. I.K. shared information on clinical medicine and oversaw the entirety of the study. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 08, 2019, and Shinshu University (Nagano, Japan) on August 17, 2019, with approval codes NHO H31-02 and M192. The completion numbers for the authors are AP0000151756, AP0000151757, AP0000151769, and AP000351128. As this research was considered clinical research, consent to participate was required. After briefing regarding the clinical study and approval of the research contents, the participants signed an informed consent form.

Informed Consent Statement: The applicable for studies involving humans. We have obtained Informed Consent Statements from people participating in clinical studies.

Data Availability Statement: The study did not report any data.

Conflicts of Interest: The authors declare no conflict of interest.

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