ORIGINAL RESEARCH

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Clinicopathological Comparison of Leiomyoma Variants and Leiomyosarcomas: A Retrospective Analysis

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ABSTRACT Objective: To compare leiomyoma variants and leiomyosarcoma (LMS) in terms of clinicopathological characteristics. **Material and Methods:** We evaluated the clinical and pathology outcomes of 57 patients who underwent myomectomy or hysterectomy between September 2013 and August 2022 and were diagnosed with cellular leiomyoma (CL), mitotically active leiomyoma (MAL), leiomyoma with bizarre nuclei (LBN), or LMS. Intraoperative frozen results were compared with the final pathology results. Leiomyoma variants (CL, MAL, and LBN) were compared with each other and with LMS. **Results:** Patients in the LMS group were older than those in the leiomyoma variants group ($p<0.001$). Frozen results in the variant group was 6.7% malignant, whereas 100% in the LMS group. Age ($p=0.207$), menopausal status ($p=0.347$), fibroid size ($p=0.432$), and number ($p=0.598$) did not differ between CL, MAL, and LBN groups. The median follow-up of leiomyoma variants and LMS groups was 61 months (4-105 months) and 20.5 months (6-85 months), respectively. No recurrence was observed in leiomyoma variants group whereas, recurrence was observed in 5 patients, and 3 patients died after recurrence in the LMS group. **Conclusion:** In this study, no recurrence was observed in the leiomyoma variants groups during the follow-up period and the prognosis is favorable. Not all tumors in the group of leiomyoma variants already meet the diagnostic criteria for LMS. Therefore, the detailed naming of the leiomyoma variants by subgroups does not seem to be of additional benefit for patient follow-up.

Keywords: Cellular leiomyoma; leiomyoma with bizarre nuclei; leiomyosarcoma; mitotically active leiomyoma

Uterine fibroids are tumors composed of smooth muscle, fibroblast, and dense extracellular matrix.[1] Uterine fibroids are classified as benign, malignant, or uncertain malignant potential based on clinical, histological, and molecular characteristics. Each tumor type has variants with different histological and molecular profiles. Of these, leiomyomas and leiomyoma variants are the most frequent uterine smooth muscle cell tumors in women. Variant tumors include mitotically active leiomyoma (MAL), cellular leiomyoma (CL), and leiomyoma with bizarre nuclei (LBN).[2] Leiomyosarcomas (LMS) are malignant tumors with a clinically aggressive course and a high recurrence rate.[3]

The malignant potential of fibroids is evaluated histopathologically by cytological atypia, mitotic index, and the presence of coagulative tumor cell necrosis.[4] In accordance with Stanford criteria, the existence of at least 2 of cytological atypia, mitotic index ≥10/10 high power fields (HPF), and coagulative necrosis is sufficient to qualify the tumor as LMS.[5] When the mitotic index is ≥10/10 HPF in the non-existence of the other 2 criteria, the tumor is classified as MAL.[6] CL may mimic mesenchymal malig-

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nancies in histopathological evaluation, but they can be distinguished by the absence of tissue necrosis, cytological atypia, and increased mitotic activity.[7] LBN is a term used for focal or diffusely distributed multinuclear giant cell smooth muscle tumors without increased mitotic activity and coagulative necrosis.[8]

The definitive diagnosis of uterine smooth muscle cell tumors is made by pathological examination after myomectomy and hysterectomy. To our knowledge, there is no clear consensus in the literature on the point of distinction between leiomyoma variants and LMS. Therefore, we sought to compare the clinical and pathological features of patients with leiomyoma variants and LMS treated in our clinic over a 10-year period.

MATERIAL AND METHODS

This retrospective study was conducted on patients who underwent surgery for CL, MAL, LBN, or LMS at the Zeynep Kamil Women's and Children's Disease Training and Research Hospital, between September 2013 and August 2022 were reviewed. A total of 57 patients with CL, MAL, LBN, or LMS were identified. The present study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Local Ethics Committee of the Zeynep Kamil Training and Research Hospital (date: November 9, 2022; no: 113).

Abstracted data included age, menopausal status, surgical information, results of the intraoperative frozen section, and final pathology findings. Leiomyoma variants and LMS were defined according to the World Health Organization (WHO) 2020 classification of tumors of the female genital tract.[9] All specimens were re-examined by gynecological pathologists with more than 10 years of experience. Pathology results were reviewed for tumor size, mitotic index, presence of necrosis, and degree of atypia. Leiomyoma variants were divided into groups: CL, MAL, and LBN. Intraoperative frozen results were compared with the final pathology results. In addition, leiomyoma variants were compared with each other and with LMS.

The patients were followed up until October 2022. Followed-up data were obtained from electronic records and by telephone contact with the patients. In the LMS group, follow-up evaluation consisted of pelvic examination and ultrasonography every 3 months for the first 2 years subsequently, every 6 months. In the leiomyoma variants group, annual pelvic examination and pelvic ultrasonography were performed every 6 months for the first 2 years. Pelvic and thoracic computed tomography were performed when necessary. Relapse status, time to relapse, relapse histopathology, disease-free status, and overall survival rates were analyzed.

STATISTICAL ANALYSIS

Statistical analysis was completed using IBM SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality was checked with the Shapiro-Wilk and Kolmogorov-Smirnov tests. Descriptive statistics were given as mean±standard deviation for normally distributed variables and as a number of cases and percentage (%) for nominal variables. Mean differences between groups for parametric variables were analyzed using the independent samples t-test or the one-way analysis of variance test. Further, distribution of the variables was tested using Pearson's chi-squared text or Fisher's exact test. A p-value of <0.05 was assessed statistically significant.

RESULTS

A total of 57 patients with a mean age of 43.2±1.4 years were included in the study. Forty-two (73.7%) of the patients were premenopausal and 15 (26.3%) were postmenopausal. Thirty patients (52.6%) underwent myomectomy and 27 patients underwent hysterectomy. The frozen examination was performed in 26 (45.6%) patients. The clinicopathological characteristics are presented in Table 1.

According to the clinicopathological data, group of LMS patients were remarkably older than those in the leiomyoma variants group ($p<0.001$). The LMS group had a higher proportion of postmenopausal women contrasted to the leiomyoma variant group ($p<0.001$). The frozen results were malignant in 13.4% of the variant group, and 100% of the LMS group. The frozen results were consistent with the final pathology results ($p<0.001$). The size ($p=0.351$)

TABLE 1: Baseline characteristic (n=57).

	n	%
Menopausal status		
Pre-menopausal	42	73.7
Post-menopausal	15	26.3
Type of surgery		
Myomectomy	30	52.6
Hysterectomy	27	47.4
Procedure		
Laparotomy	46	80.7
Laparoscopy	5	8.8
Vaginally	4	7.0
Hysteroscopy	2	3.5
Number of fibroids		
1	51	89.5
1<	6	10.5
Degree of atypia		
No atypia	23	40.4
Mild	6	10.5
Moderate	11	19.3
Severe	17	29.8
Distrubution of atypia		
No atypia	23	40.4
Focal	17	29.8
Diffuse	16	28.0
Multifocal	1	1.8
Presence of necrosis		
No	43	75.4
Yes	14	24.6
Frozen section results		
None	31	54.4
Benign	13	22.8
Borderline	1	1.8
Malign	12	21.0
Final pathology results		
Cellular leiomyoma	14	24.6
Mitotically active leiomyoma	13	22.8
Leiomyoma with bizarre nuclei	16	28.0
Leiomyosarcoma	14	24.6

TABLE 2: Comparison of LVs and LMS by clinicopathological characteristics (n=57).

	LV (n=43)	LMS (n=14)	p value
Age (years)[£]	39.8±1.3	53.4±2.4	<0.001[a]
Menopausal status			
Premenopausal	38 (88.4)	4 (28.6)	<0.001
Postmenopausal	5 (1.6)	10 (71.4)	
Number of leiomyomas			9
1	38 (88.4)	13 (92.9)	0.53
2≤	5 (11.6)	1 (7.1)	
Diameter of myoma (mm)[£]	82.1±5.9	94.3±14.2	0.351[a]
Presence of atypia			
No	23 (53.5)	0 (0.0)	<0.001[b]
Yes	20 (46.5)	14 (100.0)	
Grade of atypia[¥]			
Mild	6 (30.0)	0 (0.0)	0.002
Moderate	9 (45.0)	2 (14.3)	
Severe	5 (25.0)	12 (85.7)	
Distribution of atypia[¥]			
Focal	17 (85.0)	0 (0.0)	<0.001
Diffuse	2 (10.0)	14 (100.0)	
Multifocal	1 (5.0)	0 (0.0)	
Presence of necrosis			
No	41 (95.3)	2 (14.3)	<0.001
Yes	2 (4.7)	12 (85.7)	
Mitotic count (per 10 HPF)[£]	3.7±0.7	27.8±3.0	<0.001[a]
Frozen section results[Ω]			
Benign	13 (86.6)	0 (0.0)	<0.001
Borderline	1 (6.7)	0 (0.0)	
Malign	1 (6.7)	11 (100.0)	

LVs: Leiomyoma variants, LMS: Leiomyosarcoma

and number (p=0.539) of the fibroids did not differ between the groups (Table 2).

In the subgroup analysis, the CL, MAL, and LBN groups did not differ in terms of age, menopausal status, fibroid size, and number (p=0.207; p=0.347; p=0.432; p=0.598, respectively). LBN variants had a higher rate of atypia (p<0.001) and frozen mismatch (p=0.029). In addition, the MAL group (9.0±1.4) had a higher mitotic count than the CL (1.5±0.2) and LBN (1.2±0.3) groups (p<0.001) (Table 3).

Median follow-up period was 61 months (4-105 months) in the leiomyoma variants group (n=43). Median follow-up time for CL, MAL, and LBN were 64.5, 62, and 43 months, respectively. There were no relapses in any subgroup during follow-up. Median follow-up period was 20.5 months (6-85 months) in the LMS group (n=14). In this group, a total of 5 patients experienced recurrences, and 3 patients died.

DISCUSSION

Benign smooth muscle cell tumors of the uterus are called leiomyomas. Within this group, there is a het-

TABLE 3: Subgroup analysis of LV (n=43).

	LV CL (n=14)	MAL (n=13)	LBN (n=16)	p value
Age (years)[£]	41.6±1.9	36.4±2.3	41.1±2.3	0.207[a]
Menopausal status				
Premenopausal	12 (85.7)	13 (100.0)	13 (81.3)	0.347
Postmenopausal	2 (14.3)	0 (0.0)	3 (18.7)	
Number of leiomyomas				
1	13 (92.9)	12 (92.3)	13 (81.3)	0.598
2≤	1 (7.1)	1 (7.7)	3 (18.7)	
Diameter of myoma (mm)[£]	86.9±10.5	89.6±12.1	72.5±8.6	0.432[a]
Presence of atypia				
No	12 (85.7)	11 (84.6)	0 (0.0)	**<0.001**[b]
Yes	2 (14.3)	2 (15.4)	16 (100.0)	
Presence of necrosis				
No	13 (92.9)	13 (100.0)	15 (93.8)	1.000
Yes	1 (7.1)	0 (0.0)	1 (6.2)	
Mitotic count (per 10 HPF)[£]	1.5±0.2	9.0±1.4	1.2±0.3	**<0.001**[a]
Frozen section results[Ω]				
Benign	6 (100.0)	6 (100.0)	1 (33.3)	**0.029**
Borderline	0 (0.0)	0 (0.0)	1 (33.3)	
Malign	0 (0.0)	0 (0.0)	1 (33.3)	

LV: Leiomyoma variant, LV CL: Leiomyoma varian cellular leiomyoma, MAL:mitotically active leiomyoma, LBN:Leiomyoma with bizarre nuclei.

erogeneous group of lesions with some, but not all, features of a malignant disease called leiomyoma variants. Malignant smooth muscle cell tumors of the uterus are called LMS. Regardless of the group, the definitive diagnosis of fibroids is made as a result of the comprehensive evaluation of the pathological sample, with reference to the 2020 WHO criteria.[9]

The categorization of leiomyomas that exhibit remarkable atypia in the absence of an increased mitotic index or coagulative necrosis has been a matter of discussion for decades. Bell et al. named this group "atypical leiomyoma with low malignant potential".[4] This group is termed "LBN" among the benign variants of leiomyomas in the current WHO classification.[9] In line with this, numerous research has regarded LBN as a synonym for atypical leiomyoma.[10-12] In our study, cellular atypia was present in all the LBN group. A systematic review of atypical leiomyomas showed that the risk of recurrence was 5.5%. In studies involving LBN, this rate was 1.9%.[13] No recurrence was reported in the LBN group, except for the pelvis. In a retrospective study involving 51 LBN patients, recurrent bizarre leiomyoma was reported in the retroperitoneum in only one case.[8] In a study conducted in our country, it was shown that there was no recurrence in 26 LBN cases for an average of 58 months.[14] In our study, there was no relapse case in the LBN group during the median 43-month follow-up period. These outcomes show that the biological nature of LBN is compatible with a benign lesion. In addition, there is no concern about distant spread, and there is a low risk of local recurrence.

CLs are tumors with dense cellular fascicles, insufficient or incomplete intervening collagen, and thick-walled blood vessels. CL may be similar to low-grade endometrial stromal sarcomas, and immunohistochemical staining is often needed for differential diagnosis.[15] A study on CL found it to be more common in the younger age group.[16] In addition, the researchers announced a case of benign metastasizing leiomyoma 120 months after hysterectomy. Similarly, in our study, the mean age of the patients was 41.6 years, and there was no relapse in the CL group during the median follow-up period of 64.5 months. As a result, these tumors can be managed as benign leiomyomas without the need for further follow-up.

MAL is detected by the presence of increased mitosis in the absence of cellular atypia or coagulative necrosis. Leiomyomas in this group are almost always benign and have no potential for recurrence.[6] In our study, there was no case of relapse in the MAL group during the median 62-month follow-up period.

Uterine LMS is rare and represents only 1% of all uterine malignancies. Despite their low frequency, LMS is still the most common uterine sarcoma.[17] LMS is usually solitary and has an average diameter of 100 mm. The incidence of LMS increases significantly over the age of 40.[18] In our study, while the mean diameter was 94.3 mm in the LMS group, it was 82.1 mm in the leiomyoma variants group. While the mean age was 53.4 years in the LMS group, it was 39.8 years in the variant group. LMS can also be diagnosed in tumors with nuclear atypia, more than 10 mitoses per HPF, and any 2 of the features of coagulative tumor necrosis.[4] In our study, atypia, the presence of more than 10 mitoses in HPF, and necrosis were notably higher in the LMS group than those in the leiomyoma variants group. In addition, diffuse atypia was present in all cases in the LMS group, whereas focal atypia was found in 85% of the leiomyoma variants group. Furthermore, CL, MAL, and LBN groups did not differ in age, presence of necrosis, fibroid size, and number. Therefore, a detailed naming of these groups may not be necessary.

Frozen examination may not be reliable to exclude uterine sarcoma in cases of fibroids. While multiple sites should be sampled to obtain an accurate diagnosis, the frozen result typically depends on a limited tissue sample. Therefore, there is a high probability of false negative results even if sarcoma is present. Surgical decision is clearly affected only in cases with sarcoma as a result of frozen section.[19] In our study, sarcoma was also detected in the frozen examinations of all cases whose final result was LMS.

The key strengths of this study are that it represents a comprehensive analysis of the pathological features of myoma variants and has a long-term follow-up. However, given the small sample size, caution must be applied. We believe that the present study is important in furthering our understanding of the LMS and leiomyoma variants. More information on these subjects would help us to establish a greater degree of accuracy on this matter.

CONCLUSION

This study indicated that the prognosis was poor in patients with LMS, and close follow-up of these cases should be done. Another major finding was that no recurrence was observed during the follow-up in the leiomyoma variants and the prognosis was favorable. Amongst the leiomyoma variants, not all met the diagnostic criteria for LMS. Therefore, we believe that detailed naming of the leiomyoma variants group by dividing them into subgroups will not provide any additional benefit in terms of patient follow-up.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Uğur Kemal Öztürk;* ***Design:*** *Uğur Kemal Öztürk, Esra Keleş;* ***Control/Supervision:*** *Uğur Kemal Öztürk, Esra Keleş, Sami Acar;* ***Data Collection and/or Processing:*** *Uğur Kemal Öztürk, Erman Çiftçi;* ***Analysis and/or Interpretation:*** *Uğur Kemal Öztürk, Esra Keleş, Sami Acar, Serkan Akış, Erman Çiftçi, Murat Api;* ***Literature Review:*** *Uğur Kemal Öztürk, Esra Keleş, Sami Acar, Serkan Akış, Erman Çiftçi, Murat Api;* ***Writing the Article:*** *Uğur Kemal Öztürk, Esra Keleş, Sami Acar, Serkan Akış, Erman Çiftçi, Murat Api;* ***Critical Review:*** *Uğur Kemal Öztürk, Esra Keleş, Sami Acar, Serkan Akış, Erman Çiftçi, Murat Api;* ***References and Fundings:*** *Uğur Kemal Öztürk.*

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