ORIGINAL ARTICLE

THE IMPORTANCE OF PREOPERATIVE LABORATORY EVALUATIONS IN THE DIFFERENTIAL DIAGNOSIS OF UTERINE LEIOMYOSARCOMAS FROM LEIOMYOMAS

Uterine Leiomyosarkomların Leiomyomlardan Ayırıcı Tanısında Ameliyat Öncesi Laboratuvar Değerlendirmelerinin Önemi

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ABSTRACT

Objective: This study investigates the role of preoperative clinical features and hematological parameters in the differential diagnosis of uterine leiomyosarcoma (ULMS), degenerated uterine leiomyoma (DULM), and uterine leiomyoma (ULM).

Material and Methods: A total of 272 patients diagnosed with benign uterine leiomyoma (benign), 43 patients in whom malignancy could not be ruled out (presumed malignant or DULM), and 21 patients with leiomyosarcoma (LMS) (malignant) were included in the study. In the ULMS group and control groups, data about demographic, clinical, pathological, and ultrasonography features, laboratory tests, and surgical methods used were obtained retrospectively. Ultrasonography features included the largest diameter of the uterus, the number of myomas, and the diameter of the largest myoma.

Results: According to the erythrocyte sedimentation rate (ESR) results, A statistically significant difference was found between Group I and II, and between Group I and III (Group I: 11.2 (6.4-29.2), Group II: 20.3 (8.5-32.2), and Group III: 22.8 (17.5-30.8) (p: <0.001 and <0.001, respectively). Lactate dehydrogenase (LDH) values were 182 (112-295) in Group I, 196 (126-381) in Group II, and 246 (164-373) in Group III, and a statistically significant difference was found between Group I and II, between Group I and III, and between Group II and III (p: <0.001, <0.001, and <0.001, respectively).

Conclusion: It should be kept in mind that preoperative ESR and LDH values are significant in the differential diagnosis of benign ULM, DULM, and malignant ULMS. Postoperative histopathological examination is the gold standard; however, the value of preoperative laboratory biomarkers may be revealed through multi-center prospective studies.

Keywords: *Uterine Leiomyoma; Degenerative Uterine Leiomyoma; Uterine Leiomyosarcoma; Lactate Dehydrogenase; Neutrophil Lymphocyte Ratio; Erythrocyte Sedimentation Rate*

ÖZET

Amaç: Bu çalışmanın amacı, uterine leiomyosarkoma (ULMS), dejenere uterin leiomyoma (DULM) ve uterine leiomyoma (ULM)'yı ayırt etmede preoperatif klinik özelliklerin ve hematolojik parametrelerin rolünü araştırmaktır.

Gereç ve Yöntemler: Uterin benign leiomyoma tanısı alan 272 (benign) (ULM) (grup 1), malignite dışlanamayan 43 (presumed malign or dejenere uterin leiomyoma) (DULM) (grup 2) ve 21 leiomyosarkoma (malign) (ULMS) (grup 3) olgu çalışmaya dahil edildi. Uterin leiomyosarkoma grubunda ve kontrol gruplarında (ULM, DULM) hastaların demografik, klinik, patolojik verileri, ultrasonografik özellikleri, laboratuvar testleri ve cerrahi operasyon yöntemleri retrospektif olarak alındı. Ultrasonografik özellikler arasında uterusun en büyük çapı, miyom sayısı ve en büyük miyom çapı yer aldı.

Bulgular: ESO (eritrosit sedimentasyon oranı) açısında grup I: 11,2 (6,4-29,2), Grup II: 20,3 (8,5-32,2) ve grup III ise 22,8 (17,5-30,8) değerleri açısından grup I ile II ve I ile III arasında istatistiksel olarak anlamlı farklılık izlendi (sırasıyla p değerleri: <0,001, <0,001). LDH (laktat dehidrogenaz) düzeyleri grup I de 182 (112-295), grup II de 196 (126-381) ve grup III te ise 246 (164-373) olup her üç grubun karşılaştırılmasında grup I ile II, I ve III ve II ile III arasında istatistiksel olarak anlamlı farklılık izlendi (sırasıyla p değerleri: <0,001, <0,001, <0,001).

Sonuç: Preoperatif dönemde Bening uterin leiomyomaları, dejenere uterin leiomyoma ve malign uterin leiomyosarkomalardan ayırıcı tanısında özellikle ESO ve LDH düzeylerinin ayırıcı tanıda önemli olduğu unutulmamalıdır. Cerrahi sonrası histopatolojik incelemenin altın standart olduğu ancak özellikle çok merkezli prospektif çalışmalar ile preoperatif laboratuar belirtleçlerinin de ayırıcı tanıdaki değeri daha net ortaya konulabilir.

Anahtar Kelimeler: *Uterine Leiomyoma; Dejenere Uterin Leiomyoma; Uterin Leiomyosarkoma; Laktat Dehidrogenaz; Nötrofil-Lenfosit Oranı; Eritrosit Sedimentasyon Hızı*

INTRODUCTION

Uterine leiomyomas (ULM) are common benign tumoral lesions that may be seen in 40-60% of women of reproductive age. They are usually asymptomatic, but uterine leiomyosarcomas (ULMS) that develop following malignant transformation are rare (1).

ULMS have a poor prognosis with a rate of 1-2% among all uterine malignant lesions and may occur incidentally between 1/354-1/500 after surgery, especially in cases where the diagnosis of benign leiomyoma is considered (2).

The differential diagnosis of leiomyoma and leiomyosarcoma (LMS) should be made well. It should be remembered that myomectomy or minimally invasive endoscopic approaches to malignant lesions mimicking benign leiomyoma lesions may result in a dissemination pattern due to non-intact mass removal or surgical procedures. It should also be remembered that diagnosis and correct surgical and medical treatment may be delayed. In addition, benign leiomyomas may be mistakenly thought to be LMS in clinical and radiological evaluations in degenerative changes due to advanced age, pregnancy, perfusion disorders, and unnecessary surgical and medical treatments may be applied, so the differential diagnosis of benign/malignant lesions should be made very well. Therefore, clinical, histopathological, and laboratory tests have been used in the differential diagnosis of LMS in all studies ongoing for years; however, a sufficient predictive preoperative test could not be determined. It is reported that advanced age, post menopause, tumor size, obesity, and clinical symptoms could be used in the differential diagnosis, however, they cannot indicate a definitive diagnosis (3,4).

Radiological findings, including tumor necrosis, intra-tumoral bleeding, and widespread inflammation, are also valuable for LMS. Serum markers are also reported to be useful (1).

Systemic inflammatory markers are reported to have a diagnostic role in epithelial ovarian and endometrial carcinoma, like uterine LMS, and in cervical intraepithelial neoplasia (5,6). However, hematological and biochemical parameters could not be put forward in the preoperative differential diagnosis of leiomyoma and LMS (7).

In 2014, the US Food and Drug Administration (FDA) did not recommend the removal of the mass outside the abdomen by power morcellation during myomectomy or hysterectomy performed due to ULM, especially during laparoscopic methods. Because it has been stated that, especially in atypical leiomyoma or LMS, the spread of atypical tumor cells into the abdomen may increase, and their prognosis is poor due to recurrence in a short time after the operation. Therefore, it is recommended that atypical ULM/ULMS should be diagnosed preoperatively, and necessary surgical procedures should be planned accordingly (8). In uterine masses, necrosis and hemorrhage within the mass are common, especially in atypical leiomyomas. We suggest that tumor necrosis is especially associated with intravascular thrombosis and strong inflammatory reactions; therefore, C-reactive protein (CRP), white blood cell (WBC), hemoglobin (HGB), hematocrit (HTC), neutrophil, lymphocyte, mean platelet volume (MPV), lactate dehydrogenase (LDH), platelet (PLT), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), erythrocyte sedimentation rate (ESR), thyroid stimulating hormone (TSH), fasting blood glucose (FBG), alpha-fetoprotein (AFP), carcino-embryonic antigen (CEA), cancer antigen 15-3 (CA15-3), cancer antigen 19-9 (CA-19-9), cancer antigen-125 (CA-125), and other similar laboratory marker values, which help our clinical pre-diagnosis in the preoperative period, should be considered to be reflexively elevated, and necessary treatments should be planned. Many researchers are trying to find gold standard methods to diagnose ULMS in the preoperative period. Most of the current methods have not been validated in the preoperative period.

Therefore, in our study, we aimed to discuss the diagnostic value of clinical, pathological, and laboratory markers in the preoperative period for the differential diagnosis of leiomyoma and LMS in light of the literature and to contribute to the correct diagnosis and treatment in clinical practice.

MATERIAL AND METHODS

Clinical records of 336 patients who underwent surgery due to uterine masses in gynecological oncology centers between 2022 and 2025 were retrospectively analyzed. A total of 272 patients diagnosed with benign ULM (Group 1, benign, ULM), 43 patients in whom

malignancy could not be ruled out (Group 2, presumed malignant or degenerated uterine leiomyoma (DULM)), and 21 patients with LMS (Group 3, malignant, ULMS) were included in the study. The study group included the patients who had uterine masses which are considered to be benign and/or suspected of malignancy or malignant, who did not have a history of surgery for uterine masses, and who were diagnosed with ULM, DULM, and LMS by histopathology examination. Those who had a gynecological inflammatory condition (i.e., pelvic inflammatory disease, tubo-ovarian abscess or endometriosis) or non-gynecological comorbidities like hepatobiliary, cardiac, urological, musculoskeletal or other systemic disorders, primary or metastatic gynecological cancers, or other cancers, who were receiving chemotherapy, radiotherapy, or systemic therapy were excluded due to potential negative or positive effects on laboratory test results. All patients were operated on with laparotomy. Morcellation was not used to remove the uterus or uterine mass from the abdomen.

Clinical and preoperative blood test variables were analyzed in experienced centers. Postoperative histopathological examinations were performed by experienced gynecopathologists in experienced centers.

This study was conducted in accordance with the ethical standards described in the Declaration of Helsinki, and ethics committee approval was obtained from the local ethics committee on 18/04/2025, number 4/6. Written informed consent was not obtained due to the retrospective nature of this study.

Demographic, clinical, pathological data, ultrasonographic features, laboratory tests, and surgical methods of the patients in the ULMS group and control groups (ULM, DULM) were retrospectively obtained. Ultrasonographic features included the largest diameter of the uterus, the number of myomas, and the largest myoma diameter.

Laboratory tests included hemoglobin (HGB), hematocrit (HTC), white blood cell (WBC), neutrophil count, lymphocyte, neutrophil/lymphocyte ratio (NLR), platelet count (PLT), mean platelet volume (MPV), thyroid stimulating hormone (TSH), fasting blood glucose (FBG), cancer antigen-125 (CA-125), carcino-embryonic antigen (CEA), C-reactive protein (CRP), cancer antigen 15-3 (CA-15-3), erythrocyte sedimentation rate (ESR), alpha-fetoprotein (AFP), cancer antigen 19-9 (CA-19-9), and serum lactate dehydrogenase (LDH) level. Ultrasonography and laboratory tests were performed within one month before surgery.

Adjuvant treatments and follow-up of all cases continue postoperatively. Patients diagnosed with malignant histopathology are receiving their adjuvant therapies, and they are being followed up.

Statistical Analysis

Data were analyzed using IBM SPSS version 26.0 (Armonk, NY: IBM Corp.) software, with the statistical significance level set at α=0.05. Categorical variables were presented as frequency (n) and percentage (%), and group comparisons were performed using Pearson's chi-square test. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, which revealed that none of the variables followed a "normal distribution." Therefore, descriptive statistics were reported as median (minimum-maximum) values. For between-group comparisons, the non-parametric Kruskal-Wallis test was employed. In cases where significant differences were detected ($p<0.05$), post-hoc analysis was conducted using Dunn's test with Bonferroni correction.

RESULTS

The study included a total of 336 cases, including 272 uterine leiomyomas (Group I), 43 degenerating uterine leiomyomas (Group II), and 21 uterine leiomyosarcomas (Group III).

The mean age was 47.2±12.6 years, and body mass index (BMI) was 26.1±6 kg/m2. The median gravida was 3 (0-14), and parity was 1 (0-12). The mean WBC values were 7420±2033, NLR 1.74±0.90, PLT 269±118, CRP 6.2±4.8, and LDH 181±40. Detailed measurements of tumor markers and laboratory test results are presented in Table 1.

In all three groups, 14% of the patients were smokers, and 46% were postmenopausal. the most common complaint at presentation was menorrhagia at a rate of 31%, followed by infertility (31%), asymptomatic (18%), pelvic pain (17%), and menstrual irregularity

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Table 1. Descriptive Statistics of Demographic and Laboratory Characteristics (n= 336).

	Valid N	Mean	S.D.	Median	Min.	Max.	Percentile	
							25%	75%
Age	336	47.2	12.6	46	23	91	36	56
BMI	336	26.1	6.0	24.5	16.8	43.3	21.6	30.3
Gravidity	336	3.2	2.9	3	0	14	1	5
Parity	336	2.0	2.5	1	0	12	0	3
HTC %	336	32.3	4.7	32.2	19.2	46.4	29.8	35.3
MPV fL	336	9.2	2.1	9.6	5.1	13.6	7.5	10.8
WBC $10^3/\mu L$	336	7496	2033	7420	3610	15090	6195	8540
Neutrophil $10^9/L$	336	4100	1605	3655	1560	12490	3210	4805
Lymphocyte $10^9/L$	336	2567	823	2410	870	6870	2100	3005
NLR	336	1.74	0.90	1.50	0.52	7.31	1.19	2.00
PLT $10^9/L$	336	269	118	253	96	652	177	336
PLR	336	117	69	101	23	416	67	148
CRP mg/dL	335	6.2	4.8	4.6	1.1	45.1	3.2	7.7
ESR mm/hr	336	13.7	5.1	11.6	6.4	32.2	10.3	17.7
TSH mIU/L	336	2.80	1.82	2.36	0.23	10.90	1.36	3.75
LDH U/L	336	181	40	186	112	381	147	201
FBG mg/dL	336	103	19	101	72	183	89	119
AFP ng/mL	336	2.45	1.35	2.32	0.33	8.92	1.39	2.94
CEA ng/mL	336	2.35	1.34	2.26	0.33	8.92	1.33	2.87
Ca 125 U/mL	336	36.7	25.2	27.1	2.9	145.6	18.4	46.0
CA 15-3 U/mL	336	18.9	7.7	18.0	5.7	49.2	12.5	24.2
CA 19-9 U/mL	336	29.8	23.2	23.2	2.1	145.6	15.4	38.4

BMI: Body mass index, HGB: Hemoglobin, HTC: Hematocrit, WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, PLT: Platelet, PLR: Platelet/lymphocyte ratio, MPV: Mean platelet volume CRP (C-reactive protein), ESR: erythrocyte sedimentation rate, LDH (lactate dehydrogenase), TSH (thyroid stimulating hormone), FBG (fasting blood glucose), AFP (alpha-fetoprotein), CEA (carcino-embryonic antigen), CA-125 (cancer antigen-125), CA15-3 (cancer antigen 15-3), CA-19-9 (cancer antigen 19-9).

Table 2. Demographic and Clinical Characteristics of Patients by Pathology Group

Characteristic	Group I (n= 272)	Group II (n= 43)	Group III (n= 21)	Total (n= 336)	p
Smoking Status					0.829
Non-smoker	233 (86%)	37 (86%)	19 (90%)	289 (86%)	
Current smoker	39 (14%)	6 (14%)	2 (10%)	47 (14%)	
Menopausal Status					0.702
Premenopausal	151 (56%)	21 (49%)	11 (52%)	183 (54%)	
Postmenopausal	121 (44%)	22 (51%)	10 (48%)	153 (46%)	
Presenting Symptom					na
Pelvic pain	45 (17%)	8 (19%)	3 (14%)	56 (17%)	
Menorrhagia	84 (31%)	11 (26%)	8 (38%)	103 (31%)	
Menstrual irregularity	31 (11%)	4 (9%)	4 (19%)	39 (12%)	
Infertility	61 (22%)	12 (28%)	3 (14%)	76 (23%)	
Asymptomatic	51 (19%)	8 (19%)	3 (14%)	62 (18%)	
Tumor Location					0.710
Local	130 (48%)	21 (49%)	12 (57%)	163 (49%)	
Central	142 (52%)	22 (51%)	9 (43%)	173 (51%)	
Leiomyoma Location					na
Submucosal	17 (6%)	3 (7%)	1 (5%)	21 (6%)	
Intramural	234 (86%)	33 (77%)	17 (81%)	284 (85%)	
Pedunculated	21 (8%)	7 (16%)	3 (14%)	31 (9%)	

na = not applicable

(12%). About location, 51% of the uterine masses were centrally located, and 85% were intramural, 9% were pedunculated, and 6% were submucosal (Table 2).

In post hoc analysis of all three groups in terms of age, BMI, gravida, and parity, statistically significant differences were observed between Groups I and III in terms of age, and between Groups I and II in terms of gravida and parity (p:<0.001, 0.019, and 0.037, respectively) (Table 3).

When hematological parameters were evaluated by post hoc analysis, statistically significant differences were observed between Groups II and III in hemoglobin [11.9 (7.5-13.3)/10.2 (6.8-13.8)] and hematocrit [35.2 (25.3-40.2)/30.2 (20.1-40.2)] (p:0.039 and 0.011, respectively). A statistically significant difference was observed between Groups I and II in terms of neutrophil count [3650 (1560-12150)/4200 (1990-12490)] and NLR [1.44 (0.52-7.31)/1.85 (0.74-6.51)] (p:0.029 and 0.004, respectively). No statistically significant difference was observed between the groups regarding WBC, lymphocyte, PLT, PLR, and MPV (Table 4).

In post hoc analysis of biochemical values between the three groups, CRP values were 4.6 (1.1-26.3) in Group I and 7.3 (1.8-45.1) in Group II, and a statistically significant difference was observed between the two groups (p:0.029). ESR was 11.2 (6.4-29.2) in Group I, 20.3 (8.5-32.2) in Group II, and 22.8 (17.5-30.8) in Group III, and a statistically significant difference was observed between Groups I, II, and III (p:<0.001 and <0.001, respectively). LDH levels were 182 (112-295) in Group I, 196 (126-381) in Group II, and 246 (164-373) in Group III and a statistically significant difference was observed between Groups I and II, between I and III, and between II and III (p:<0,001, <0,001, and <0,001, respectively).

AFP levels were 2.29 (0.33-7.87) in Group I, 2.6 (0.42-8.92) in Group II; a statistically significant difference was observed between the groups (p:0.020). CEA values were 2.23 (0.33-7.87) in Group I and 2.54 (0.42-8.92) in Group II, and a statistically significant difference was observed between the groups (p:0.022).

CA 19-9 values were 24.9 (2.1-145.6) in Group I and 15.6 (2.7-45.2) in Group II, and a statistically significant difference was observed between the two groups (p<0.001). No significant difference was observed between all groups in terms of TSH, FBG, CA15-3, and CA125 values in normal and post hoc analyses (Table 5).

The Raincloud plot graph, which is traditionally prepared by emphasizing more than one modality, showed a significant statistical difference between each pair of Groups I, II, and III in terms of LDH, between

Table 3. Comparison of Demographic/Clinical Parameters between Groups.

Variable	Group I (n = 272)	Group II (n = 43)	Group III (n = 21)	Overall	Post Hoc p (Bonferroni)		
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	p	I vs II	I vs III	II vs III
Age (years)	45 (23–72)	48 (31–84)	58 (37–91)	<0.001	0.210	<0.001	0.081
BMI (kg/m²)	24 (17–43)	24 (18–42)	28 (17–43)	0.246	1.000	0.292	0.725
Gravidity	3 (0–14)	2 (0–10)	3 (0–9)	0.019	0.019	1.000	0.124
Parity	1 (0–12)	0 (0–9)	1 (0–7)	0.034	0.037	1.000	0.160

BMI: Body mass index, kg/m²: kilogram/square meter

Table 4. Comparison of Demographic/Clinical Parameters between Groups.

Variable	Group I (n = 272)	Group II (n = 43)	Group III (n = 21)	Overall	Post Hoc p (Bonferroni)		
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	p	I vs II	I vs III	II vs III
HGB (g/dL)	10.5 (6.3–14.8)	11.9 (7.5–13.3)	10.2 (6.8–13.8)	0.016	0.031	0.875	0.039
HCT (%)	32.1 (19.2–46.4)	35.2 (25.3–40.2)	30.2 (20.1–40.2)	0.009	0.051	0.282	0.011
WBC ($10^3/\mu L$)	7225 (3610–15090)	7500 (4720–15090)	7640 (6230–14050)	0.037	0.320	0.097	1.000
Neutrophil ($10^9/L$)	3650 (1560–12150)	4200 (1990–12490)	4520 (2780–9850)	0.007	0.029	0.117	1.000
Lymphocyte ($10^9/L$)	2440 (870–6870)	2370 (1210–4780)	2310 (1450–3650)	0.248	0.860	0.497	1.000
NLR	1.44 (0.52–7.31)	1.85 (0.74–6.51)	1.72 (0.88–4.57)	<0.001	0.004	0.057	1.000
PLT ($10^9/L$)	245 (96–652)	300 (114–526)	304 (156–651)	0.015	0.070	0.132	1.000
PLR	96 (23–416)	132 (35–277)	123 (43–314)	0.008	0.052	0.077	1.000
MPV (fL)	9.6 (5.1–13.6)	9.7 (5.5–13.6)	10.1 (5.3–12.6)	0.790	1.000	1.000	1.000

HGB: Hemoglobin, HTC: Hematocrit, WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, PLT: Platelet, PLR: Platelet/lymphocyte ratio, MPV: Mean platelet volume.

Table 5. Comparison of Biochemical Parameters between Groups.

Variable	Group I (n = 272)	Group II (n = 43)	Group III (n = 21)	Overall	Post Hoc p (Bonferroni)		
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	p	I vs II	I vs III	II vs III
CRP (mg/dL)	4.6 (1.1–26.3)	7.3 (1.8–45.1)	6.3 (2.0–23.3)	0.016	0.029	0.396	1.000
ESR (mm/hr)	11.2 (6.4–29.2)	20.3 (8.5–32.2)	22.8 (17.5–30.8)	<0.001	<0.001	<0.001	0.192
LDH (U/L)	182 (112–295)	196 (126–381)	246 (164–373)	<0.001	<0.001	<0.001	0.030
TSH (mIU/L)	2.36 (0.23–10.90)	2.45 (0.42–8.92)	2.35 (0.82–7.20)	0.499	0.785	1.000	1.000
FBG (mg/dL)	101 (72–156)	102 (72–183)	98 (78–136)	0.749	1.000	1.000	1.000
AFP (ng/mL)	2.29 (0.33–8.20)	2.60 (0.42–8.92)	2.62 (2.00–3.74)	0.009	0.020	0.260	1.000
CEA (ng/mL)	2.23 (0.33–7.87)	2.54 (0.42–8.92)	2.12 (0.81–5.32)	0.028	0.022	1.000	0.513
CA-125 (U/mL)	27.3 (2.9–145.6)	24.1 (6.3–123.5)	37.4 (12.1–141.4)	0.066	0.080	1.000	0.222
CA 15-3 (U/mL)	16.9 (5.7–49.2)	18.4 (9.6–33.1)	19.8 (8.6–30.1)	0.447	0.966	1.000	1.000
CA 19-9 (U/mL)	24.9 (2.1–145.6)	15.6 (2.7–45.2)	22.3 (2.5–42.3)	<0.001	<0.001	0.308	0.437

CRP (C-reactive protein), ESR: erythrocyte sedimentation rate, LDH (lactate dehydrogenase), TSH (thyroid stimulating hormone), FBG (fasting blood glucose), AFP (alpha-fetoprotein), CEA (carcino-embryonic antigen), CA-125 (cancer antigen-125), CA15-3 (cancer antigen 15-3), CA-19-9 (cancer antigen 19-9).

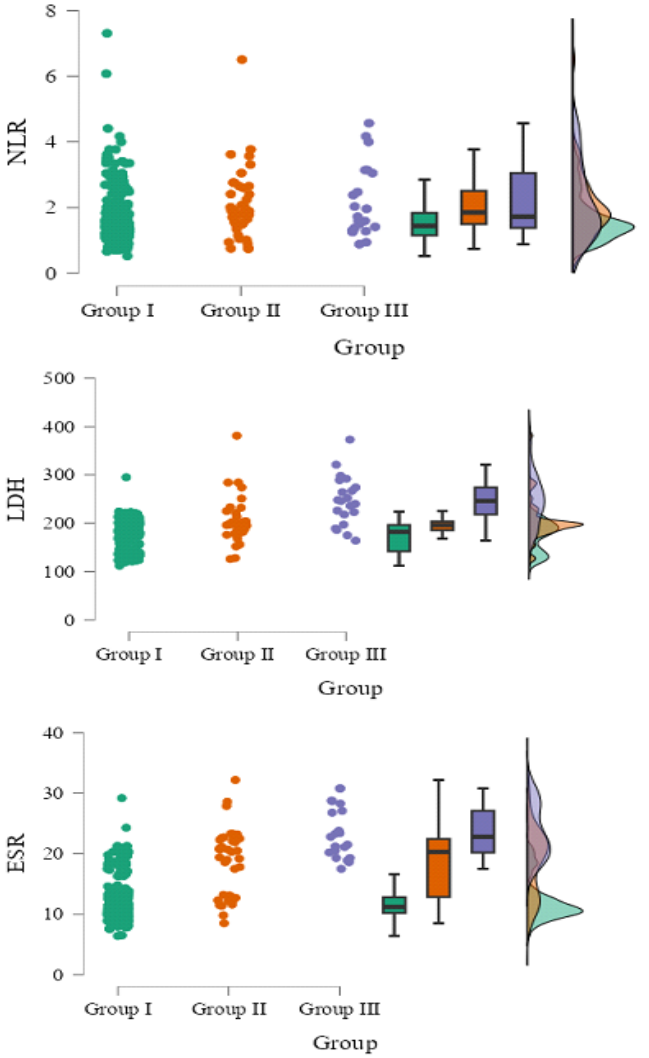


Figure 1. Raincloud plot graph showing the distribution of different levels of NLR, ESR and LDH levels among the groups.
NLR (neutrophil/lymphocyte ratio), ESR (erythrocyte sedimentation rate), LDH (lactate dehydrogenase).

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Groups I and II in terms of NLR, and between Groups I and II, and between I and III in terms of ESR (Figure 1).

DISCUSSION

The mean age was 47.2±12.6 years, and BMI was 26.1±6 kg/m². A statistically significant difference was observed between Groups I and II in terms of neutrophil count [3650 (1560-12150)/4200 (1990-12490)] and NLR [1.44 (0.52-7.31)/1.85 (0.74-6.51)] ratios (p: 0.029, 0.004, respectively). In post hoc analysis of biochemical values between the 3 groups, CRP values were 4.6 (1.1-26.3) in Group I and 7.3 (1.8-45.1) in Group II, and a statistically significant difference was observed between the two groups (p:0.029). ESR was 11.2 (6.4-29.2) in Group I, 20.3 (8.5-32.2) in Group II, and 22.8 (17.5-30.8) in Group III, and a statistically significant difference was observed between Groups I and II, and between I and III (p:<0.001 and <0.001, respectively). LDH levels were 182 (112-295) in Group I, 196 (126-381) in Group II, and 246 (164-373) in Group III, and statistically significant differences were observed between Groups I and II, between Groups I and III, and between Groups II and III (p:<0.001, <0.001, <0.001, and <0.001, respectively). The fact that there were significant statistical differences between benign groups and malignant sarcomas, especially in the pairwise mutual evaluation of ESR and LDH levels of ULM, DULM, and ULMS groups, is the strongest aspect of our study, and we can state that it may contribute to the literature with these results. When the literature is examined, it is seen that the differential diagnosis of leiomyoma and LMS is not easy, especially in the preoperative period, and therefore, poor prognostic conditions may occur for patients in the long term due to inadequate or excessive surgical and medical treatments. Therefore, studies requiring sufficient evidence seem to be necessary.

LMS is diagnosed incidentally during surgery for ULM. Especially if malignancy is diagnosed during fertility-sparing myomectomy, it may need to be managed conservatively since hysterectomy is not performed. Therefore, before all surgeries planned for benign leiomyoma, the risks of sarcoma should be explained in detail to the patient and her relatives and it should be stated that endoscopic methods used during the operation and morcellation used during the removal of the leiomyoma mass from the abdomen or recurrence that may be caused by tumoral spillage may worsen the prognosis (9).

Due to the aggressive malignant features of LMS, it is crucial to make a clear preoperative diagnosis to complete early diagnosis and treatment and has been the focus of many studies (10). In a cohort study, these rates are reported to be as low as 54% and insufficient for the completion of the correct surgical treatment because more rapid and sensitive methods are needed (11).

Although clinical findings such as abnormal uterine bleeding, severe groin and abdominal pain, and rapid enlargement of the pelvic uterine mass are usually seen in LMS lesions, it should be kept in mind that they can also be seen in leiomyoma lesions. Differential diagnosis methods are recommended with scoring systems developed based on ultrasonography findings and basic clinical features, especially in the preoperative period and including endometrial biopsy, serum LDH level, Doppler ultrasonography, or magnetic resonance imaging methods (12).

When the clinical presentations of the 336 patients were analyzed, it was seen that the most common complaint in all three groups was excessive menstrual bleeding followed by infertility and pelvic pain.

Uterine masses may increase in size between 18% and 120% within one year, especially if they grow more than the volume of 6 weeks of gestation within one year, it is considered rapid growth. It has been observed that the growth may vary depending on the localization and size of the leiomyoma mass, but especially in small lesions located intramurally, the average growth rate was 53.2%, and the average growth volume was 35.2%. It has also been stated that these growth rates can be estimated by hormonal effects (FSH, LH, LDL, cholesterol) and other hematological laboratory values, but it is difficult to predict the likelihood of malignancy due to clinical and subjective evaluations, and majority can only be diagnosed by postoperative histopathological evaluations (13-15).

In our study, intramural uterine mass was observed in 85% of the cases, and in ULM, DULM, and ULMS groups, the most common localization of leiomyoma was intramural and central localization, consistent with the literature. The frequency of LMS increases with age. Especially

after surgery, it continues to increase as 0% under 40 years of age, 0.15% between 40-49 years of age, and 1.2% over 49 years of age, indicating that age is important in terms of prevalence (16).

In our study group, the mean age was 47.2±12.6 [(median: 46 (23-91)]. When groups were compared in terms of age, it was observed that ULM [45(23-72)] and particularly the ULMS group consisted of elderly patients [58(37-91)], and a statistically significant difference was found between ULM and ULMS groups ($p<0.001$). Consistent with the literature, especially the ULMS group consisted of elderly patients and the risk of malignancy increased with increasing age.

In many studies, it has been reported that ULMS are especially seen in postmenopausal women over 50 years of age, and that advanced age and postmenopausal status are risk factors for LMS and the prognosis of these cases is poorer. The highest sarcoma risk was observed in 10 out of 1000 cases in the age range of 75-79 years and in 1 out of 500 cases under the age of 30 years. It is stated that the risk of sarcoma depends on age and postmenopausal status, and the most common clinical complaint is postmenopausal bleeding, so endometrial sampling should be performed preoperatively (11,17-19).

In terms of menopausal status, 54% of all cases were premenopausal and 46% were postmenopausal. The number of premenopausal cases was high in the benign group (56%), 54% were in the premenopausal period, and 46% were in the postmenopausal period in the malignant group. We can state that the reason for the low number of postmenopausal cases, especially in the ULMS group, compared to the literature is the low number of ULMS cases, and that the number of cases in the postmenopausal group may increase as the number of our cases increases.

LDH, the most important laboratory marker used in the preoperative diagnosis of LMS, is an enzyme that catalyzes the conversion of lactate to pyruvate in the glycolytic pathway. It is highly expressed, especially in tumor cells to use mitochondrial processes more to produce and consume more energy. This process, in which LDH is used as an enzyme for tumor cells regardless of the presence of oxygen, is particularly necessary for the excessive production of energy in many types of systemic cancer and thus for the proliferation, maturation, growth, structural change, and invasion of tumor cells (20,21).

In the early studies regarding LDH, Seki et al. reported that LDH levels increased to in 3 (42.8%) of 7 LMS a cases (22).

In another study from 2015, 9 out of 15 uterine sarcoma cases were diagnosed with ULMS, 6 other types of uterine sarcoma, 42 out of 48 benign uterine masses were diagnosed with ULM, and the cases were compared in terms of serum LDH levels. In 7 (46.7%) out of 15 uterine sarcoma cases, LDH level was 279 and above, but no LDH elevation was found in any cases diagnosed with benign uterine ULM (23). In another study, 6 ULMS cases and 19 ULM cases were compared, and the mean LDH levels were found to be 343 IU/L±188 in the ULMS group and 183.1 IU/L±44 in the ULM group. There was a significant relationship between the two groups in terms of LDH elevation (24). According to the results of the two studies, it was reported that LDH elevation in the diagnosis of ULMS was significantly higher in terms of differentiation from ULM and may help to organize the correct diagnosis and treatment in the preoperative period.

Goto et al., reported that LDH levels were increased in all 10 LMS cases (100%) and in 32 out of 130 degenerated leiomyoma cases (26.4%). Consequently, it has been stated that LDH increase is not a specific indicator only for ULMS and may be increased in ULM or DULM and other subtypes (25). In the studies conducted to detect malignancy at higher rates by combining LDH levels with D-dimer, CRP, Human epididymal factor (HE4), CA-125, 69 ULM, 36 ULMS, and 28 suspected malignant (presumed malignant) cases were evaluated by scoring in terms of preoperative LDH, D-dimer and CRP levels and sensitivity was found 35.3% and specificity 100% (1). In another scoring system using CA-125, LDH, and HE4 in the preoperative period, when 37 ULMS and 102 DULM cases were compared, 68.4% sensitivity and 95.1% specificity rates were reported (26). It has been stated that in the case of positive elevation of all parameters, all benign cases can be detected with 95.1-100% specificity, but they have a limited sensitivity in detecting malignant cases.

In a study conducted by Zhang Guoruj et al., 45 ULMS and 180 ULM cases were evaluated on the parameters of age 40 years and older, tumor diameter of 7 cm

and above, neutrophil/lymphocyte ratio ≥2.8, platelet count ≥298000/L and LDH ≥193, sensitivity was 80% and specificity was 77.8% and sensitivity rates were reported to be higher in the detection of ULMS at 4 points and above according to cut-off values (4).

In another study, 159 ULM and 31 ULMS cases were compared in a scoring system using postmenopausal status, clinical findings, neutrophil count ≥7500/L, hemoglobin level <11.8 g/dl, endometrial biopsy results, cellular atypia and neoplasia, and uterine mass ≥ 10 cm on radiological imaging, and significant differences were not found between groups with regard to sensitivity and specificity. It has been stated that LDH level may be elevated in malignant tumors other than ULMS, that the use of LDH alone has limited advantages, and that prospective studies consisting of more cases are needed to be considered as an auxiliary factor in the differentiation of ULM and ULMS (27). LDH, an enzyme found in somatic cells and necessary for energy production, plays a role in converting cellular glucose into energy. Tumor cells need this energy to proliferate. In our study, there was a statistically significant increase in LDH values between ULM and DULM (p<0.001), DULM and ULMS (p:0.030), and ULM and ULMS (p<0.001) groups. The increase in LDH values, especially as degeneration and malignancy progress, is consistent with the literature, and our study indicates that LDH levels are an important marker in the differential diagnosis of ULMS in the preoperative period.

It is aimed in many studies that other tumor markers like CEA, CA 19-9, and CA 15-3 can be used to differentiate ULMS and ULM, and that differential values can be used in clinical practice. Especially for sarcoma lesions developing in uterine smooth muscle mesenchymal cells, studies are potentially ongoing.

CEA levels are elevated in metastatic uterine sarcoma cases. Still, the histopathological differential diagnosis was not clear in this study, and no comparison was made with ULM cases regarding CEA levels. Besides, it should be noted that CA19-9 and CA-15-5 values were not analyzed in ULMS and ULM, and only uterine carcinosarcoma data were analyzed in studies consisting of a small number of cases. In the literature, many studies are not available on the use of CEA, CA19-9, and CA15-5 levels as markers in the differential diagnosis of ULM and ULMS (28,29,30). Since there is a need for studies consisting of a large number of cases for all sarcoma types, in our study, CEA, CA19-9, and CA15-3 values of three different groups of smooth muscle cell tumor lesions with different histopathological changes from benign ULM to malignant ULMS were compared. We suggest that the data will shed light on further studies since it is the first in the literature.

In our study, especially in the comparison of ULMS with the other two groups, no significant differences were found in terms of tumor markers, but especially CA19-9, AFP, CEA values were elevated due to organ compression resulting from degeneration, inflammatory reaction, peritoneal tension or uterine enlargement and different between ULM and DULM groups.

In a study consisting of 79 ULMS and 257 ULM, and investigating WBC, platelet, neutrophil, lymphocyte, monocyte, hemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), CRP, LDH, and CA-125 levels, significant differences were found in terms of WBC, neutrophil count, CRP, LDH, and NRL (31).

Especially CA-125 levels were found to be significantly higher, and when used together with NLR ratios, significant rates of NLR≥2.8 were found in ULMS cases (4, 32). In studies on NLR ratios in soft sarcoma cases, poorer prognostic results were obtained in terms of overall and disease-free survival, especially when significantly higher NLR ratios were detected. NLR ratios indicating an inflammatory reaction in the body are valuable for differentiating ULMS from ULM (33, 34).

Regarding preoperative laboratory data of our study, there was a significant statistical difference between ULM and DULM and between DULM and ULMS in terms of hemoglobin and hematocrit levels (p: 0.016 and 0.009, respectively), probably due to the likelihood of uterine bleeding and long-term clinical complaints in large degenerated and malignant masses, and this was consistent with the literature.

NLR levels were [median: 1.44(0.52-7.31)] in ULM, and [median: 1.85(0.74-6.51)] in DULM, and [median: 1.72(0.88-4.57)] in ULMS. There was a statistically significant difference between ULM and DULM, and

the difference between ULM and ULMS (p:0.057) was statistically limited because of the small number of cases. Consistent with the literature, it can be stated that inflammatory markers are statistically significantly increased in cases of degeneration and malignant change.

In the literature, there was a case with a diagnosis of large ischemic intramural leiomyoma who presented with elevated ESR, and it was concluded that ESR may be elevated as a result of ischemia due to gonadotropin analogue treatment in the postpartum period (35).

In another case of ULMS, it was diagnosed with secondary amyloidosis with elevated WBC, eosinophilia, and elevated ESR. The diagnosis of amyloidosis was made by endoscopic biopsy. Histopathological examination of the hysterectomy material revealed diffuse necrosis, and the diagnosis of low-grade ULMS was made. It was stated that elevated ESR and eosinophil values may have developed due to systemic inflammatory reaction related to amyloidosis (36).

Our study indicates for the first time in the literature that there may be a relationship between elevated ESR and degenerated ULM and ULMS in the absence of another inflammatory reactive condition.

Many laboratory markers used to differentiate ULMS from ULM in the preoperative period are inexpensive and easily accessible and are frequently used in daily medical practice. However, it should be remembered that many studies are retrospective with a small number of cases due to the rarity of ULMS cases, and it is difficult to distinguish malignant lesions from benign lesions in the preoperative period. Unfortunately, we cannot specify a specific scale or method to differentiate ULM and ULMS preoperatively, and histopathological examination is still the gold standard for the diagnosis of ULMS. This does not change the fact that the scales proposed by the researchers should be investigated in a larger number of patients and in more gynecological centers to evaluate their effectiveness.

The strengths of our study include its consisting of 3 different histopathological groups as ULM, DULM, and ULMS, a sufficient number of cases, and investigation of preoperative examinations that can be held even in medical centers with inadequate conditions.

Most importantly, it is the first study to demonstrate the value of ESR levels in the differential diagnosis of normal leiomyomas from degenerated and malignant forms. The strongest aspect of our study is that it is the first in the literature to evaluate three distinct groups—benign leiomyoma, degenerated leiomyoma, and malignant LMS. However, due to the retrospective nature of the study, the malignant-benign differentiation of our cases could not be made in the preoperative period, and since ULMS is a rare clinical diagnosis, our number of cases may be insufficient in terms of the accuracy of preoperative laboratory markers in predicting malignancy. As preoperative serum markers are non-specific for inflammation and patients with any inflammatory condition, such as adenomyosis or endometriosis, were excluded, laboratory test results may have been influenced by other unrecognized systemic inflammatory conditions.

CONCLUSION

In conclusion, it should be remembered that LDH and especially ESR values may be significantly elevated in ULMS in the preoperative period. Unfortunately, most of the known preoperative clinical, radiological, and laboratory methods have not been validated, and histopathological examination is still the gold standard for the diagnosis of ULMS. Multicenter studies with a larger number of cases are needed to demonstrate the efficacy of laboratory markers in the preoperative period.

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