



# Histopathological and Immunohistochemical Evaluation of 84 Uterine Sarcomas According to Current Literature

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## OBJECTIVE

It was aimed to reevaluate uterine sarcoma cases diagnosed in our institution within the last 20 years according to current information and to provide intra-departmental standardization in the differential diagnosis and reporting.

## METHODS

Totally 84 uterine sarcoma cases were re-examined. Recurrence, metastasis, and prognostic data were collected from the patient files. Immunohistochemistry panel consisting of CD10, h-caldesmon, and cyclin D1 was applied to the representative tumor tissues. The relationships between the parameters studied were evaluated statistically.

## RESULTS

Statistically significant differences were found between different histopathological types of uterine sarcomas (US) in terms of age distribution, tumor diameter, mitotic index, necrosis, depth of myometrial invasion, cervical, adnexial and/or omental involvement, lymphovascular invasion, lymph node metastasis, recurrence, and distant metastasis. Statistically significant correlation was determined between the prognosis of the patients and mitotic activity of their tumors and the presence of distant metastasis. The immunohistochemistry panel was found to have significant contribution to the histomorphological examination in the differential diagnosis.

## CONCLUSION

Routine use of CD10, h-caldesmon, and cyclin D1 in the histopathological evaluation of US and establishing an updated standard checklist was thought to be beneficial for the differential diagnosis and reporting prognostic parameters.

**Keywords:** Adenosarcoma; carcinosarcoma; endometrial stromal sarcoma; leiomyosarcoma; undifferentiated uterine sarcoma.

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## Introduction

Uterine sarcomas (US) consist of a malignant mesenchymal tumor group, representing 2-6% of all uterine malignancies.[1,2] The most common histopathological subtype is leiomyosarcomas (LMS) while the

second most common is endometrial stromal sarcomas (ESS). LMS has spindle cell, epithelioid and myxoid subtypes. Endometrial stroma and associated tumors are classified as endometrial stromal nodule, low-grade ESS (LGESS), high-grade ESS (HGESS), and undifferentiated uterine sarcoma (UUS). Remaining sub-

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types such as pure heterologous sarcomas, including perivascular epithelioid cell neoplasm (PEComa) and rhabdomyosarcomas, are much less common.[2-4] In addition to these, adenosarcomas (AS) and carcinosarcomas Malignant mixed Mullerian tumors (MMMT) are considered among other US.

Carcinosarcoma has been reclassified as a differentiated or metaplastic form of endometrial carcinoma based largely on its invasion pattern. However, since carcinosarcoma exhibits more aggressive behavior than classical endometrial carcinoma, besides being classified separately as mixed epithelial and mesenchymal tumors according to the 2014 WHO classification, it is still among USs in most retrospective studies.[5,6]

The strongest prognostic factor in USs is reported as stage. In addition, factors such as age, tumor diameter, mitosis and necrosis are also associated with prognosis. Due to the rarity of USs, their evaluation in prospective randomized studies is limited. There are limited case series in the literature that includes all USs.

Our retrospective study provides the advantage of redefining the cases between 1998 and 2014 in terms of subtyping. If this study was planned prospectively, the estimated time to reach statistically sufficient number of cases in terms of diagnosis and prognostic factors would be too long.[1,7] Therefore, we re-evaluated our case series of the last 20 years according to the current diagnostic criteria.

In our institution, immunohistochemical tests such as CD10, cyclin D1, h-caldesmon, p53 were not used routinely in subtyping USs. While evaluating these cases, we completed cases for which immunohistochemical examinations were incomplete. Thus, all the cases evaluated were classified as current and standardized.

While the treatment methods used were only surgery in the past, the guidance of the pathology report on this issue is more important with the inclusion of chemotherapy and radiotherapy among the current treatments. Immunohistochemical examinations may be more important not only for subtyping but also for future treatment of patients. According to the current literature, it was thought that such a study would contribute to the literature in terms of retrospective subtyping in USs, the place of immunohistochemical studies in differential diagnosis and the information that should be included in the pathology report as prognostic parameters.

## Materials and Methods

Eighty-four USs that were stored in our archive for the past 20 years under appropriate conditions were

included in the study. All of our cases that meet the study criteria were included in the study; the number of groups and samples that can be evaluated statistically has been reached.

Eighty-four cases were re-examined histomorphologically; tumor diameter, necrosis, mitosis, heterologous elements, myometrial invasion, cervix uteri, ovaries and tubas, omentum were evaluated. leiomyosarcomas (LMS), LGEES, HGEES, UUS, AS, and MMT cases were grouped as younger or older than 50 years of age.

While the tumor diameter was determined as <5 cm, between 5 and 10 cm and >10 cm; values of <10, 10-20 and >20/10 high power fields (HPF) were used for mitotic figures. When choosing these values, current literature information was taken into consideration.

A representative paraffin block of the tumor was selected from all cases for immunohistochemical examinations. Immunohistochemical studies were performed in the automated Ventana Benchmark XT closed device using h-caldesmon (caldesmon [monoclonal], CellMarque, 1: 100 dilution); anti-CD10 (anti CD10 [monoclonal], Ventana, 1: 100 dilution) and cyclin D1 (anti-Cyclin D1 [monoclonal], Ventana, 1: 100 dilution) antibodies.

Histopathological and immunohistochemical evaluation of the cases was made without knowing the diagnosis in order to prevent possible “bias.”

## Results

In our study, out of 84 cases, which were histopathologically re-evaluated according to the current literature, 19 were LGEES, nine were HGEES, 23 were LMS, 10 were UUS, 20 were MMT, and three were AS.

The average age of the patients included in the study was 55.9 (SD: 13.26). Patients were minimum 20-years-old and maximum 81-years-old. Of the cases; 29 of them were under the age of 50, 55 of them were in the age group of 50 and over. The highest mean age (65.4 years) was found in the group with MMT diagnosis ( $p=0.000$ ) (Table 1).

Tumor diameters varied between 1.3 and 18 cm for ESS, 4.5 and 68 cm for LMS, 4 and 22.5 cm for UUS, 1.7 and 15 cm for MMT, and 4 and 22 cm for AS. It was observed that 90% of the cases in the UUS group had a tumor diameter over 10 cm. The tumor diameter was <5 cm in 63.2% of the cases in the LGEES group ( $p=0.001$ ) (Table 1).

There was a statistically significant difference in mitotic count between LGEES and other high-grade

**Table 1** Statistically significant clinicopathological parameters between the histopathological types of uterine sarcomas

Clinico-pathological parameters	LGESS (%)	HGESS (%)	LMS (%)	UUS (%)	MMMT (%)	AS (%)	p
Age							
<50	68.4	11.1	34.8	30	10	66.7	0.001
≥50	31.6	88.9	65.2	70	90	33.3	
Tumor size							
≤5 cm	63.2	33.3	13	0	25	33.3	0.001
5-10 cm	15.8	55.6	34.8	10	45	33.3	
>10 cm	21.1	11.1	52.2	90	30	33.3	
Mitotic index							
≤10	84.2	0	26.1	10	15	33.3	0.008
10-20	5.3	33.3	17.4	30	25	0	
>20	10.5	66.7	56.5	60	60	66.7	
Necrosis							
Absent	68.4	33.3	13	0	60	66.7	0.000
Present	31.6	66.7	87	100	40	33.3	
Myometrial invasion							
≤1/2	62.5	12.5	22.2	10	35	0	0.024
>1/2	37.5	87.5	77.8	90	65	100	
Cervical invasion							
Absent	100	60	86.4	60	55	66.7	0.025
Present	0	40	13.6	40	45	33.3	
H-Kaldesmon immuno-reactivity							
Negative	100	100	52.2	90	95	100	0.008
Focally positive	0	0	13	0	0	0	
Diffusely positive	0	0	34.8	10	5	0	
CD 10 immuno-reactivity							
Negative	26.3	55.6	95.7	40	80	66.7	0.002
Focally positive	21.1	22.2	0	20	5	0	
Diffusely positive	52.6	22.2	4.3	40	15	33.3	
Cyclin D1 immuno-reactivity							
Negative	89.5	22.2	91.3	90	80	66.7	0.002
Focally positive	0	22.2	0	0	15	33.3	
Diffusely positive	10.5	55.6	8.7	10	5	0	

LGESS: Low grade endometrial stromal sarcomas; HGESS: High grade endometrial stromal sarcomas; LMS: Leiomyosarcomas; UUS: Undifferentiated uterine sarcomas; MMT: Malignant mixed Mullerian tumors; AS: Adenosarcomas

sarcomas. High-grade sarcomas had higher mitotic counts. Mitotic index was >20/10 HPF in 48.8% of our cases. In the LGESS group, it was noted that the mitotic index was ≤15/10 HPF in 89.5% of the cases (p=0.008) (Table 1).

Tumor necrosis was observed in 66.7% (51/84) of our cases. It was seen in all cases with UUS (100%) diagnosis, in 20 cases with LMS (87%), in eight cases with the diagnosis of MMT (40%), and in one of the cases with the diagnosis of adenosarcoma (33.3%). The sarcoma subgroup in which tumor necrosis was most common was UUS followed by LMS (p=0.000) (Table 1).

Histopathological evaluation in terms of myometrial invasion could be done in 73 cases. While deep myo-

metrial invasion was detected in 68.5% (50/73) of total cases; superficial myometrial invasion was observed in 62.5% (10/16) of the cases in the LGESS group. Deep myometrial invasion was found in 6 (37.5%) cases with LGESS; in 7 (87.5%) of the HGESS cases; in 14 (77.8%) of the LMS cases; in 9 (90%) of the UUS cases; in 13 (65%) of the MMT cases and in 1 of the cases diagnosed with adenosarcoma (p=0.024) (Table 1).

Cervix uteri involvement was observed in two of the cases diagnosed with HGESS; in three of the cases diagnosed with LMS; in four of the cases with UUS diagnosis; in 9 of the cases with MMT diagnosis; in one of the cases diagnosed with adenosarcoma. Cervical stromal invasion was detected in 45% (9/20) of our

MMMT patients and in 40% of our patients diagnosed with HGESS (2/5) and UUS (4/10). Cervical involvement was not observed in any of our patients with a diagnosis of LGESS ( $p=0.025$ ) (Table 1).

In terms of the stages of the cases versus histopathological diagnoses; our cases were in stage IV disease with a rate of 17.9% (15/84). It was observed that these patients were predominantly in the UUS, MMT and LMS groups ( $p=0.123$ ) (Table 1).

In our study, the follow-up periods of our patients ranged from 2 to 152 months; the average follow-up time was 27.5 months (SD: 32.7). Ten patients died during this follow-up period. While a mitotic figure of  $>10/10$  HPF was observed in histopathological examination in 10 of our patients who died, 9 of them had deep myometrial invasion.

A statistically significant difference was found between the mean survival time (114.9 months) of the patients in the stage I-II group and the mean survival time (91.5 months) of the patients in the stage III-IV group ( $p=0.026$ ) (Table 1).

Coming to the relationship between distant organ metastases and survival of the cases; a statistically significant correlation was found between the prognosis of the patients and the presence/absence of distant organ metastases ( $p=0.005$ ) (Table 2). Distant metastasis was present in 6 (60%) of 10 patients who died during the follow-up period. In the group of 57 cases without distant metastasis, only 4 patients (7%) died.

Lymphovascular invasion was observed in 17 (20.2%) cases. The diagnostic groups in which LVI was most frequently observed were MMT (35%) and LGESS (26.3%) ( $p=0.33$ ) (Table 1).

Last but not the least immunohistochemical findings were evaluated strong and diffuse immunoreactivity was detected with h-caldesmon in 34.8% (8/23) of the LMS cases, and focal positive immunoreactivity in 3 (13%) of them. H-caldesmon expression was observed in one case of each from the UUS and MMT

groups. No positivity was observed in any case of the ESS group ( $p=0.008$ ) (Table 1).

With CD10 staining, 52.6% (10/19) of LGESSs showed diffuse and strong positivity while 21.1% (4/19) showed focal positive immunoreactivity. CD10 expression was remarkable in 4 patients in the UUS group, 3 patients in the MMT group, and 1 patient of the each LMS and AS groups among other diagnosis groups ( $p=0.002$ ) (Table 1).

Cyclin D1 positivity was observed in 50% of the cases detected at advanced stage. With cyclin D1, 55.6% (5/9) of HGESS cases showed diffuse and strong ( $>70\%$  cells) positive immunoreaction. There were rare positive cases in other diagnostic groups ( $p=0.002$ ) (Table 1).

Diffuse/strong positive intranuclear immunoreactivity with p53 was detected in 50% (11/22) of the cases in the LMS group. However, no significant correlation was observed between p53 immunoreactivity and survival of the patients in this group.

The histopathological/immunohistochemical results of our cases that were found to be statistically significant are summarized in Table 1.

Examples of different histopathological subtypes of USs and immunohistochemical results are presented in Figures 1-6.

## Discussion

USs consist of an uncommon malignant mesenchymal tumor group representing 2-6% of all uterine malignancies.[1,2] The most common histopathological subtype is LMS, which constitutes 60% of US cases, and ESS the second most common with 20-25% of incidence.[2] In the present study, there were LMS cases in the first order and LGESS and HGESS cases were in the second order.

Most of the series in the literature consist of limited number of patients. This is because USs are rare. In two large reviews by D'Angelo and Prat (2010) and Gadducci et al. (2011),[5,8] it is reported that USs constitute 3-7% of uterine cancers. For this reason, in the current literature, there is no consensus yet on the prognostic factors of USs, hence clinical results and treatment strategies.

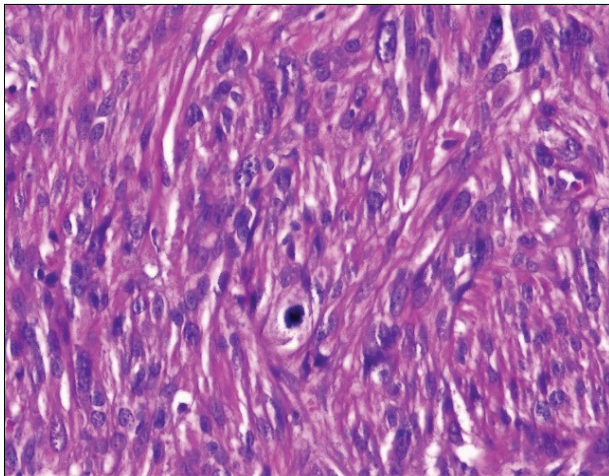
The largest series published to date on USs is the study of Nordal et al.[9] In this study, the incidence and survival of USs were investigated by following the Norwegian female population for 37 years. In another study of Norwegian origin, by Abeler et al.[10] publishing detailed histopathological and survival data of 419

**Table 2** Relationship between survival of the cases versus mitotic index and distant organ metastases

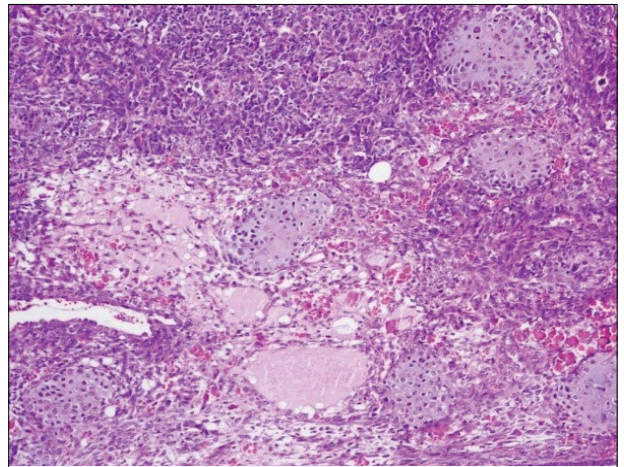
Clinico-pathological	Parameters	Alive (%)	Exitus (%)	p
Mitotic index	$\leq 10/10$ HPF	34.4	0	<b>0.028</b>
	$> 10/10$ HPF	65.6	100	
Distant metastasis	Absent	84.4	40	<b>0.005</b>
	Present	15.6	60	

HPF: High power fields

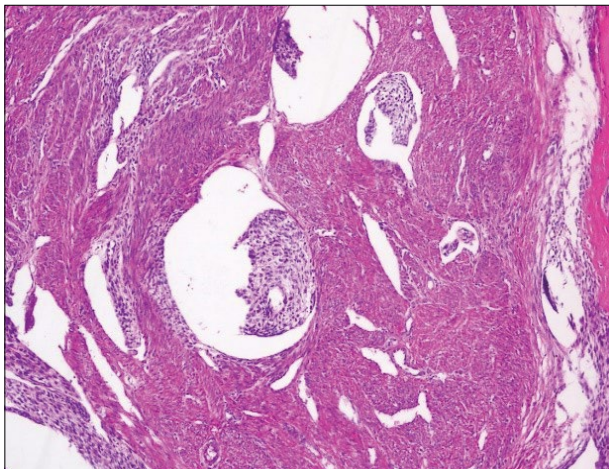




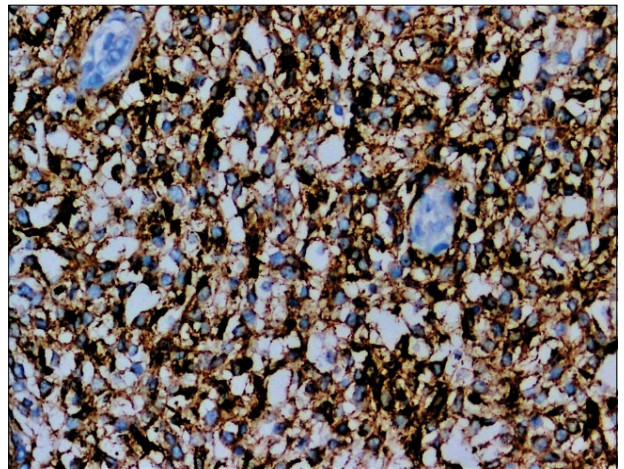
**Fig. 1.** Leiomyosarcoma, (H&E×400).



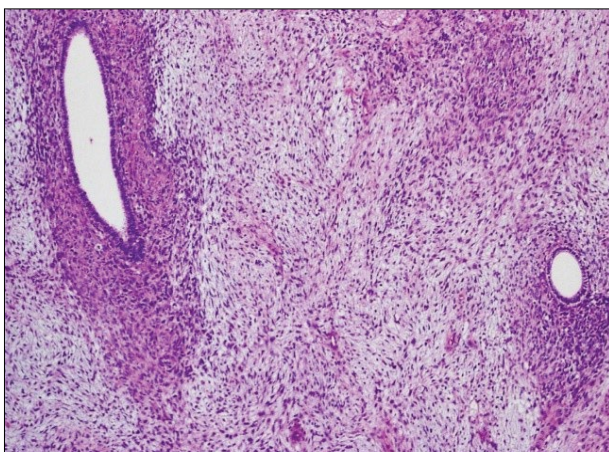
**Fig. 4.** Carcinosarcoma, (H&E×100).



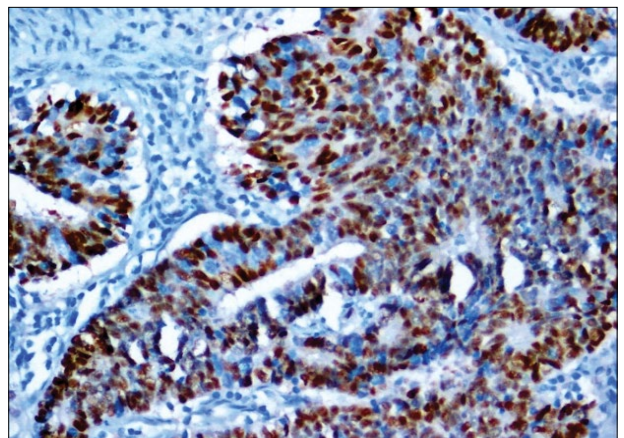
**Fig. 2.** Lymphovascular invasion in LGESS, (H&E×100).  
LGESS: Low grade endometrial stromal sarcomas.



**Fig. 5.** CD10 in LGESS (IHC×400).  
LGESS: Low grade endometrial stromal sarcomas.



**Fig. 3.** Adenosarcoma, (H&E×200).



**Fig. 6.** Cyclin D1 in HGESS (IHC ×400).  
HGESS: High grade endometrial stromal sarcomas.



cases with known prognosis and documenting the risk factors of each diagnostic group, they reported that stage was the strongest prognostic factor. In the present study, a statistically significant difference was found between the mean survival time 114.9 months of the patients in the stages I-II group and the mean survival time (91.5 months) of the patients in the stages III-IV group.

Considering the age distribution of USs, it is noteworthy that they generally occur in advanced ages. In the study conducted by Gao et al., the mean age in the premenopausal group of ESS was 45; MMMT has always been reported in the age of 50 or over.[7,11] In accordance with the literature, the mean age was 47.8 in our LGESS cases, 56 in the HGESS group, and 65.4 in the MMMTs out of 84 US cases we examined.

There are studies in the literature showing that tumor diameter is related to prognosis in USs.[10,12] It has been reported that the size of the tumor has a prognostic value, especially in stage I disease.[13-15] In our study, 33 out of all USs had a tumor diameter >10 cm. Tumor diameter was larger than 10 cm in 6 out of 10 patients who died. While cases with high tumor diameter may be at low stage, none of the cases with low tumor diameter were at advanced stage. As a matter of fact, FIGO staging took the tumor diameter <5 cm in USs as stage I criteria.

Both parameters are valuable for differential diagnosis when USs are evaluated in terms of the number of mitoses and necrosis they contain. High mitotic activity (>10/10HPF) is more common in UUS and LMS. High mitotic activity is a factor used for differential diagnosis in USs and associated with poor prognosis. Again, the absence of necrosis in LGESS is a valuable parameter used in the differential diagnosis of USs. In our study, all of the cases died during the follow-up period had high mitotic activity.

The depth of myometrial invasion has also an important effect on prognosis.[7,16] The depth of myometrial invasion is also included in FIGO staging of AS and carcinosarcomas. In terms of myometrial invasion in our series, deep myometrial invasion was detected in 68.5% (50/73) in cases with histopathological evaluation; superficial myometrial invasion was observed in 62.5% (10/16) of the cases in the LGESS group while deep myometrial invasion was present in 90% of the patients who died.

Most studies on USs highlight the stage as the most important prognostic factor.[7-9,17-21] Five-year survival rates have been reported to range from 29% to 74% for stage I and between 20 and 40% for other stages.[18,22,23] In the series presented by Kokawa et

al. in terms of prognosis by stage, there was a similar rate (52%) in stage III and IV, as in the data (50%) in the study by Gao et al.[7,24] In the study conducted by Gao et al. 63.6% of the patients in the LMS group were diagnosed at stage I-II; and those in the MMMT group at more advanced stages (stage III-IV, 66.6%). In our study, a statistically significant difference was found between the mean survival time (114.9 months) of the patients in the stage I-II group and that (91.5 months) of the patients in the stage III-IV group.

In the study of Pautier et al.[25] regardless of the stage and histopathological subtype, the diagnosis of US itself confirms the poor prognosis. It was stated that only LGESS has a favorable prognosis with surgery alone and does not require further therapeutic interventions. It was also emphasized that age, in addition to stage, is a strong prognostic factor for MMMT.

Comparison of IHC analysis in different studies on USs is still open to debate. The contradictions in immunoreactivity results reported in many studies might be the result of the variability of antibody clones, dilutions of antibodies, different staining techniques, and different patient populations. In addition, threshold values for positive immunoreactivity are not always clearly defined in the literature and therefore results may be variable.[26]

Lee et al.[27] in their works published in 2012, suggested that the presence of myopermeatic growth pattern in a uterine tumor consisting of cyclin D1 positive, non-CD10/ER/PR expressing, high grade, monomorphic round cells indicates ESS with YWHAE-FAM22 genetic fusion. In this study, diffuse (> 70%) and strong cyclin D1 immunoreactivity was also observed in the UUS with uniform nucleus (UUS-U) subgroup and rarely in cases of uterine leiomyosarcoma. However, YWHAE (or JAZF1/PHF1) regulations were not detected in these by FISH analysis. Importantly, cyclin D1 positive UUS-U cases also showed diffuse strong CD10 immunoreactivity, unlike round cell component of HGESS with the genetic fusion of YWHAE-FAM22, which is CD10 negative. Therefore, when cyclin D1 and CD10 immunohistochemistry staining is applied to a histopathologically high-grade but non-pleomorphic uterine sarcoma, it is argued that diffuse strong cyclin D1 staining in the absence of CD10 staining is highly sensitive and specific for HGESS harboring the YWHAE FAM22 genetic fusion.[27]

Emphasizing that the diffuse strong cyclin D1 immunoreactivity was observed in a correlated way in HGESS with YWHAE-FAM22 genetic fusion; a diagnostic algorithm including morphological and immu-

nophenotypic features is proposed to identify ESS with uterine YWHAE-FAM22 genetic fusion.[27] Following this study, in the WHO 2014 classification, ESSs were again divided into LGESSs and HGESSs.[28] On the other hand, the mechanism of cyclin D1 overexpression in ESS with YWHAE-FAM22 genetic fusion has not been explained.[27]

Cyclin D1 immunoreactivity has been previously evaluated by Kurihara et al.[29] in both endometrial stromal tumors and UUS. Cyclin D1 immunoreactivity has also been studied in uterine MMMT before.[30,31] De Jong et al.[30] found that 7 out of 31 MMMT cases had cyclin D1 positivity in the mesenchymal component; however, these authors used a much lower (10%) nuclear staining score threshold.

An important subgroup of Ewing sarcomas can also show diffuse strong nuclear cyclin D1 immunoreactivity.[32] ESS with YWHAE-FAM22 genetic fusion may also show diffuse strong CD99 immunoreaction.[33] This overlap in the immunophenotype creates difficulties in the differential diagnosis when a malignant round cell tumor is encountered in the biopsy of a pelvic mass. Molecular analysis (FISH or Real-time polymerase chain reaction) is required for the differential diagnosis of Ewing sarcoma from ESS with the genetic fusion of YWHAE-FAM22.[27]

In our study, one out of eight cases diagnosed with HGESS and whose prognostic information could be reached was lost during the follow-up period and this case showed negative immunoreaction with cyclin D1. Unfortunately, we have no facility for molecular genetic studies of our cases at our institution yet.

On the other hand, Koivisto-Korander et al.[26] showed that there was a statistically significant relationship between the p53, ERa and PRA markers and the survival of LMS patients. While p53 positivity was detected in 30% of MMMT, 26% of LMS and 12% of ESS cases; they reported longer survival in p53-negative LMS cases (median survival time of 123 months compared to 11 months in p53 positive patients).

In our study, diffuse/strong positive intranuclear p53 immunoreactivity was observed in 50% (11/22) of the cases in the LMS group. However, there was no statistically significant relationship between p53 immunoreactivity and survival of the patients in this group. The differences between these results might be due to the fact that the studies were performed with a small number of LMS cases and the dilution of antibodies used in immunohistochemical studies.

Chemotherapeutic agents are also used in addition to surgical treatment in Uss.[34] Performing genetic

analysis, especially in ESSs, might predict the use of different agents in treatment. The first bicentric study presented on this subject was by Hemming et al. Targeted immunotherapy has also been recently mentioned in the literature.[35,36]

The limitations of this study include the small number of cases, as in other studies, and the necessity to adhere to the incidence in histopathological diagnostic groups. Therefore, it might not be possible for significant prognostic factors found in larger case series to be evident in our case series.

In the light of the results we obtained in our study, an algorithm for the differential diagnosis and a report format for classification and reporting of these cases, which are quite rare in our daily practice, was prepared for the purpose of standardization in our department. In the commentary part of the report, it was recommended to re-emphasize the risk factors associated with case-specific recurrence and prognosis. In addition, a genetic study was planned for molecular investigation.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** All authors declared no conflict of interest.

**Ethics Committee Approval:** The study was approved by The Kocaeli University Non-Invasive Clinical Research Ethics Committee (No: KÜ GOKAEK 2018/20.18, Date: 26/12/2018).

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