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Original Article

Cyclin-D1 Utility in Classification of Endometrial Stromal Sarcomas and Segregation from other Uterine Sarcomas

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ABSTRACT

Context: Endometrial stromal sarcomas (ESSs) are rare mesenchymal tumors of uterus which accounts for less than 10% of all uterine sarcomas. Gene rearrangement studies unveil their genetic heterogeneity with the discovery of specific *YWHAE-FAM22 gene fusion.* According to recent WHO classification of endometrial stromal tumors all Endometrial stromal sarcomas with this fusion are labeled as high grade-Endometrial Stromal Sarcomas (HG-ESS). Immunohistochemically HG-ESSs with *YWHAE- FAM22* translocation express nuclear Cyclin D1 positivity which can be used as a surrogate immunohistochemical marker for this translocation.

Objective: Determine diagnostic utility of Cyclin D1 as a marker to segregate high grade- Endometrial Stromal Sarcomas (HG-ESS) from low grade-Endometrial Stromal Sarcomas (LG-ESS) and undifferentiated uterine sarcoma (UUS) and from other uterine sarcomas including leiomyosarcomas and carcinosrcomas.

Materials and Methods: Cases of Endometrial stromal sarcomas, leiomyosarcomas and carcinosarcomas received from Jan 2010- Jan 2015 were reviewed and immunostained with Cyclin D1, CD-10, ER, PR and Desmin. Nuclear positive or negative staining for Cyclin D1 was noted.

Results: Total 36 cases of uterine sarcomas including 10 cases of ESS, 20 cases of leiomyosrcoma and 6 cases of carcinosarcoma were retrieved from surgical database. Out of ten cases of endometrial stromal sarcomas, five were low grade, two were high grade and three were undifferentiated sarcomas. Cyclin D1 was expressed in three cases previously diagnosed as low grade, high grade and undifferentiated sarcomas respectively. Cyclin D1 positive undifferentiated uterine sarcoma (UUS) also revealed diffuse CD-10 positivity. Other two cases with a positive Cyclin D1 expression revealed a patchy CD-10 positivity. Negative expression of Cyclin D1 was noted in all cases of leiomyosrcoma and carcinosarcoma.

Conclusions: Endometrial stromal sarcomas are relatively uncommon tumors and can pose diagnostic problems for pathologists. Smooth muscle tumors (leiomysrcomas) and carcinosarcomas are among the top differentials. Final diagnosis usually requires immunohistochemistochemical analysis with a panel of immunomarkers. Cyclin D1 expression along with patchy CD-10 positivity favors HG-ESS over LG-ESS and UUS. Cyclin D1 positivity along with diffuse CD-10 expression favors Undifferentiated Uterine Sarcoma. Negative expression in other uterine sarcomas makes it a specific marker for ESSs. It is suggested that Cyclin D1 along with CD-10, ER, PR and Desmin should be added in immunohistochemical panel of high grade uterine sarcomas especially if patchy expression of CD-10 is noted. It is to make a provisional diagnosis of YWHAE-FAM22 associated HG-ESS when fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) are not available to make a final diagnosis.

Keywords: Endometrial Stromal Sarcoma (ESS), Low grade-Endometrial Stromal Sarcoma (LG-ESS), High grade- Endometrial Stromal Sarcoma (HG-ESS), Undifferentiated Uterine Sarcoma (UUS).

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Introduction

Endometrial stromal sarcomas (ESSs) are rare uterine tumors which accounts for about 0.2% of all genital tract malignancies and less than 10% of all uterine mesenchymal tumors.[1,] [2] Most of the information

available in literature is based on small series or case reports.[3] They arise from endometrial stroma and resemble to proliferative–phase endometrial architecture.[2, 4] As compared to other uterine malignancies, they affect slightly younger females of premenopausal age group with a mean age of 42-58 years.[3]

The classification and pathogenesis of these tumors has been debated widely.[5] Since their initial classification by Norris and Taylor in 1966 the classification of these neoplasms has evolved a lot.[6] In 2003 they were classified by WHO into endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), and undifferentiated endometrial sarcomas (UES) based on nuclear pleomorphism and necrosis.[7]

In 2014 a revised classification is proposed by WHO on the basis of recently recognized translocation t (10; 17) YWHAE-FAM22. HG-ESS is recognized as a separate entity along with endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS) and undifferentiated uterine sarcoma (UUS).[8] HG-ESSs > 70% of cases associated with this translocation show strong and diffuse nuclear positivity for Cyclin D1.[5]

Cyclin D1 (bcl-1) rearrangement t (11; 14) is frequently associated with mantle cell lymphoma but it is also commonly seen in other human cancers especially sarcomas.[9, 10]. It is a cell cycle regulatory protein which causes the cell to progress to G1 phase afterwards Cyclin D1/CDK4 complex usually leaves the nucleus. Oncogenic drive is achieved through retention of active cyclin D1/CDK4 complexes in the nucleus. It is usually up-regulated through increased transcription, translation, and protein stability.[11] Mechanism of it's over expression in YWHAE-FAM22 translocation associated ESS is yet to be determined.[9]

YWHAE-FAM22 associated HG-ESSs are more aggressive, recurrent and usually presented with extra uterine spread when compared with *JAZF1* associated ESN and LG-ESS. They also need to be distinguished from pleomorphic, undifferentiated sarcomas of uterus which are more furious with a 5year expectancy rate of < 50%. [9]

Objective of our study was to review morphologic and immunohistochemical features of ESS and to find the diagnostic utility of Cyclin D1 to segregate ESS in to in to various classes and from other uterine sarcomas based on new classification scheme proposed by WHO.

About 500,000 patients are hospitalized world widely with 25,000 deaths annually[1]. Dengue virus is flavivirus having four serotypes DENV1, DENV2, DENV3 and DENV4.Approxamately 75-80% of dengue virus infections are asymptomatic. In symptomatic cases, typically the symptoms develop between 4-7 days after the bite of an infected mosquito. The symptoms of dengue virus infection range from mild to incapacitating high grade fever, with severe headache, retro-orbital pain, myalgia, arthralgia, and rash. Dengue hemorrhagic fever is characterized by fever, abdominal pain, persistent vomiting, platelet depletion and bleeding leading to death.

In Pakistan, the first serologically confirmed case of Dengue Fever was reported in 2005 from Karachi[2]. In Lahore; there was a massive outbreak in 2011 in which over 14000 confirmed cases were registered out of which 300 cases lost their life.[3]

The total registered cases of dengue fever were 41311 from year 2012 to year 2016 in Pakistan. The incidence of dengue fever in Pakistan is increased during hot, humid and rainy season, while fewer cases are reported during winter and summer. The peak of dengue cases are reported during September and October. In the State of Azad Jammu and Kashmir, the first outbreak was reported in 2016, which affected mainly district Muzaffarabad.[4] Majority of the dengue fever cases were admitted in Abbas institute of Medical Sciences Muzaffarabad. Due to high influx of the patients, a separate "dengue ward" was established in the hospital.

This study was carried out to assess the magnitude of dengue fever and its description with respect to time, place and person, socio demographic and clinical characteristics of the dengue cases registered during 2016 across the State of Azad Jammu and Kashmir (AJ&K).

Material & Methods

All cases of ESSs, leiomyosarcoma and carcinosarcomas received from 2010 to 2015 were retrieved from surgical pathology database according to institutional review protocols. Available demographic record including age, symptoms and stage were re-evaluated. Original Hematoxylin-Eosin stain slides (as per the availability) and re-cuts were reviewed. Immunohistochemical stains were applied and the diagnosis was confirmed using standard diagnostic criteria.

Immunohistochemical studies were performed as per instructions of available kit of Novolink Leica Germany. Panel of antibodies used include CD-10, ER, PR, Cyclin D1 and Desmin. Heat-induced antigen retrieval was performed and slides were incubated with antibodies according to manufacturer's instructions.

Each case was considered "positive" if 1% or more of tumor cells expressed staining. Conversely, staining in less than 1% of tumor cells was considered to be "negative." For CD-10 and Desmin cytoplasmic staining and for ER, PR and Cyclin D1 nuclear staining was considered positive.

Results

Clinicopathologic Features of Endometrial stromal sarcoma cases:

Ten diagnosed cases of ESS were retrieved including five cases of low-grade endometrial stromal sarcoma (LG-ESS), two cases of high-grade endometrial stromal sarcoma HG-ESS and three cases of undifferentiated uterine sarcoma (UUS). Median age of patients was 45 years with an age range of 36-46 years for LG and HG-ESS and 48-52 years for UUSs.

All females diagnosed with LG-ESS and HG-ESS were in premenopausal age group with the most common symptoms of abnormal uterine bleeding, pain and pressure effect. All were multipara except one who presented with secondary infertility and clinical impression of leiomyoma. All females diagnosed with UUS were post menopausal, multipara and presented with pelvic pain and abnormal uterine bleeding. None had family history of gynecologic or other malignancies.

Microscopic Findings

Light microscopic examination of LG-ESSs revealed irregular tongue like growths infiltrating the myometrium. The tumor cells were oval to fusiform, imparting a monotonous appearance with low cytologic atypia and low mitotic activity. Interspersed rich network of spiral arterioles along with vascular invasion was also identified. Immunohistochemistry revealed diffuse membranous positivity for CD-10 and reciprocal negativity for Desmin.

Diffuse nuclear positivity for ER and PR was noted in four cases with patchy positivity in a single case. Cyclin-D1 was negative in 4 cases and showed a positive expression in one case only.

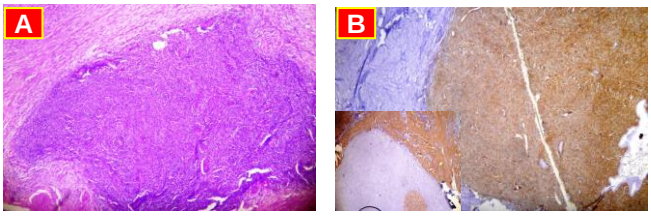

Figure-1: (A) Low grade endometrial stromal sarcoma (LG-ESS) A. Showing tongue like infiltration of myometrial stroma (H&E X 40), (B) Diffuse membranous positivity of CD-10 in tumor cells along with negative expression in myometrial stroma. Reciprocal negativity of Desmin in tumor cells along with positive expression in myometrial stroma. (inset) (IHC X40)

Table-1: Immunohistochemical profile of Endometrial Stromal Sarcomas

	Immunomarkers	Staining characteristics
Low grade endometrial sarcoma	CD-10	Diffuse positive expression in 4 cases, patchy positivity in 1 case
	Desmin	Negative expression in all cases
	ER, PR	Diffuse positive expression in 4 cases, patchy positivity in 1 case
	Cyclin D1	Negative expression in 4 cases, diffuse positivity in one case
High grade endometrial stromal sarcomas	CD-10	Patchy positivity in one case, diffuse expression in other
	Desmin	Negative in both cases
	ER, PgR	Negative in both cases
	Cyclin D1	Diffuse positivity in one case, negative in other
Undifferentiated Uterine Sarcomas	CD-10	Diffuse positive in all cases
	Desmin	Negative in all cases
	ER, PR	Negative in all cases
	Cyclin D1	Positive in one cases

Light microscopy of HG-ESS revealed advance nuclear atypia with larger nuclei showing irregular nuclear contours and hyperchromasia. Intervening stroma revealed rich capillary network and vascular space invasion. Areas of necrosis were also identified. Brisk mitotic activity was seen with >10 mitoses/10HPFs.

(Figure 2 A) Immunohistochemistry revealed patchy positivity for CD-10 in one case while diffuse positive expression in other. Negative expression of Desmin and ER, PR was noted in both cases. Positive expression of Cyclin D1was noted in the same case showing patchy CD-10 expression while it was negative in other.

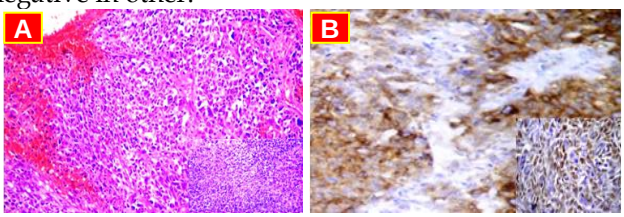

Figure 2: High grade endometrial stromal sarcoma A. Showing advance nclear atypia and mitotic activity (inset)(H&E x 100) B. Patchy positive expression of CD-10 along with diffuse positive nuclear expression of CyclinD1 in the same case.(inset) (IHC x 100)

Microscopic examination of undifferentiated stromal sarcomas revealed significant pleomorphism with highly atypical bizarre nuclei. Multinucleated giant cells and frequent atypical mitoses were also seen. Extensive areas of necrosis were also identified. (Figure-3A) Immunohistochemical examination of all cases revealed diffuse membranous positivity for CD-10, negativity for Desmin and ER, PR. One case expressed Cyclin D1 positivity while other cases showed negative reaction for Cyclin D1. (Figure-3B)

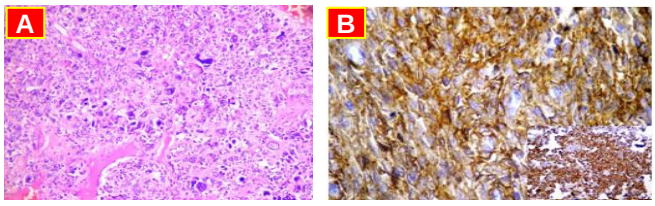

Figure-3: A: Undifferentiated uterine sarcoma (UUS) pleomorphic, bizarre nuclei. (H&E x 40)
B: Diffuse positive CD-10 expression along with diffuse Cyclin D1 positivity. (inset) (IHC x 100)

Apart from 10 cases of ESS, 20 diagnosed cases of leiomyosarcomas and six cases of carcinosarcomas were also retrieved from surgical data base. Median age of the patients was 55 years with an age range of 48-69 years. All females were postmenopausal, multipara and presented with common complaint of pelvic mass and irregular vaginal bleeding.

Most cases revealed characteristic morphologic features on light microscopy. When a panel of CD-10, ER, PR, Desmin and Cylin D1 was applied all of them were negative for CD-10 and Cylin D1. Variable expression of ER, PR and positive expression of Desmin was noted in leiomyoarcomas. Positive expression of Cytokeratins was observed in all cases of carcinosarcomas.

Table-2: Immunohistochemical profile of Leiomyosarcomas and Carcinosarcomas

Immunomarkers	Staining characteristics
CD-10	Negative in all cases
Desmin	Positive in all cases of Leiomyosarcomas
ER, PR	Variable expression
Cyclin D1	Negative in all cases

Discussion

Endometrial stromal sarcoma (ESS) is an uncommon malignancy; during last five years out of 40,000 surgical specimens and 15,000 gynecological specimens received in our setting, only 10 cases proved to be ESS. Besides, owing to rarity of disease, limited numbers of studies are available in literature regarding its clinic-pathologic behavior, prognosis and treatment.

The disease is mostly prevalent among younger females during the mean age of 42-58 years.[3] In this study the mean age for all patients with ESS was 44.5 years. For LG-ESS it was 41 years, for UUS it was 49 years and for HG-ESS it was of 45 years. Around 88% of cases belong to premenopausal age group.

Generally it is presented with irregular vaginal bleed and sometimes with a faulty clinical diagnosis of leiomyoma due to indolent behavior, especially for LG-ESS.[12, 13] Definitive diagnosis on curettage specimen is challenging for ESN and LG-ESS due to minimal pleomorphism, similarity to endometrial stroma and difficulty in commenting upon the invasion of myometrium, so final diagnosis is given on hysterectomy specimen.[14] In our study most common symptoms were abnormal uterine bleed, pelvic pain and pressure effects caused by the tumor. A case of LG-ESS was suspected as leiomyoma on radiology. For all the cases definitive diagnosis was made on hysterectomy specimen. For a single case of UUS with endometrial curettage specimen, an initial diagnosis of "Undifferentiated high grade tumor" was made which was later confirmed as UUS on

immunohistochemistry. No link had been found between parity and histologic subtype.

In 2003, Endometrial stromal tumors were classified by WHO in to Endometrial stromal nodule (ESN), Low-grade endometrial stromal sarcoma (LG--ESS) and Undifferentiated endometrial sarcoma (UES). HG-ESS was not recognized as a separate entity. Distinction between these three entities was based on myometrial invasion, pleomorphism, mitotic count and presence or absence of necrosis. LG-ESS was characterized by minimal atypia, occasional mitotic figures and scanty or absent necrosis, in contrast UES exhibit moderate to severe atypia, brisk mitoses with atypical mitotic figures and multiple areas of necrosis.[7] However, there were controversies regarding the classification criteria of ESS in this version.[13]

With advances in gynecologic pathology during recent years special attention had been given to Endometrial stromal tumors which led to emergence of new classification by WHO in 2014. HG-ESS is recognized as a separate entity in current classification and is separated from LG-ESS on the basis of specific translocation, morphology, immunohistochemistry and clinical behavior. Currently, four recognized entities include endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS). [8]

The translocation t (7; 17) (p15; q21) producing JAZF1-SUZ12 fusion gene is specific for a large proportion of ESN and LG-ESSs. HG-ESS is recognized by a specific translocation t (10; 17) (q22; p13) resulting in YWHAE-FAM22 gene fusion and as an entity with the morphological features and prognosis in between LG-ESS and UUS. This translocation is so specific for HG-ESSs that no other uterine tumor including ESN, LG-ESS, UUS, leiomyoma, leiomyosarcoma and carcinosarcoma exhibit it, so it forms the basis of segregation of HG-ESS from all the rest.[9]

These translocations can be detected through cytogenetics, fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction, but the HG-ESSs with YWHAE-FAM22 gene fusion also show (> 70% of cases) strong and diffuse nuclear positivity for Cyclin D1.[5] Thus Cyclin D1 can be used as a surrogate immunohistochemical marker for HG-ESS especially when the above mentioned tools cannot be applied to determine the molecular genetics of tumor.

Other immunohistochemical markers which aid in differentiating ESS from other uterine sarcomas and also among its own grades include CD-10, ER, PR and Desmin. In challenging cases h-caldesmon can also be used along with Desmin to rule ot leiomyosarcomas. LG-ESSs usually express diffuse and strong reactivity of CD-10, ER and PR. HG-ESSs with YWHAE-FAM22 gene fusion show a patchy expression of CD-10 and variable expression of ER, PR. UUSs can either show a diffuse positive or completely negative CD-10 expression if the loss their differentiation completely and are usually negative for ER, PR. Desmin can show a variable expression in both LG and HG-ESS with a negative expression in UUS.[5]

HG-ESSs with YWHAE-FAM22 translocation and Cyclin D1 positivity usually have same clinical presentation as other ESSs. Majority of them are presented in advance stage but have better prognosis than UUS.[5] Lee et al. compared clinicopathologic characteristics of 13 cases of ESS which had YWHAE-FAM22 rearrangement with 20 cases of ESS along with JAZF1 rearrangement. 90% of cases revealed high grade areas with nested round cells, brisk mitotic activity and focal areas of necrosis. 65% of the cases also revealed a bland, mitotically inactive spindle cell component with fibrous stroma. In contrast cases with JAZF1 rearrangement revealed comparatively bland cells with round to oval nuclei and low mitotic count. Spindle cell component of cases with YWHAE-FAM22 gene rearrangement showed diffuse positive expression of ER, PR and CD-10 while high grade round cell component was negative for all of them.[15]

Diffuse; moderate to strong Cyclin D1 positivity was seen in this high grade round cell component in all cases. Cyclin D1 positivity was not seen in other cases with JAZF1 and in other low-grade ESS with no genetic rearrangement. Its positivity in other uterine sarcomas is an extremely rare event. Lee et al. presented a case series of 243 uterine sarcomas and mixed tumors, only 5% of cases revealed its positivity with <1% cases of leiomysarcomas.[9]

For current study none of the cases with Cyclin D1 positivity revealed biphasic components in the form of bland spindle cells and high grade round cells on light microscopic examination. However immunohistochemistry revealed a patchy CD-10 positivity in two cases with patchy positivity of ER, PR in one case and negative expression in other case. These findings are coherent with the immunohistochemical profile of HG-ESS in which CD-10, ER and PR are either absent or show weak or focal

positivity. 3rd and last case showed a diffuse CD-10 positivity which coexisted with Cyclin D1 positivity and negative expression of ER and PR. Co-existence of diffuse CD-10 positivity with Cyclin D1 favors UUS, tumor pleomorphism can also aids in segregating two entities.

Due to variable immunohistochemical expression of CD-10, ER and PR in HG-ESS, Cyclin D1 can be extremely helpful to constitute a diagnosis. In absence of pleomorphism, diffuse strong Cyclin D1 staining with focal or negative CD-10 staining appears to be highly sensitive and specific for HG-ESS with *YWHAE-FAM22* translocation.

Conclusion

Endometrial stromal sarcomas (ESS) are infrequent mesenchymal tumors of uterus. Recently HG-ESS is recognized as a separate entity by WHO on the basis of specific YWHAE-FAM22 translocation. HG-ESSs with this translocation show strong and diffuse nuclear positivity for Cyclin D1, which can be used as a surrogate immunohistochemical marker to make a provisional diagnosis of YWHAE- FAM22, associated HG-ESS. It is also helpful in identifying a subset of tumors in between *JAZF1* associated ESS (ESN and LG-ESS) and pleomorphic uterine sarcomas, which is more aggressive and show frequent recurrences than JAZF1 associated ESS and is complaisant when compared with pleomorphic uterine sarcomas.

Further studies with a larger cohort and confirmation of YWHAE-FAM22 translocation by RT-PCR or FISH analysis warranted to establish its utility as an immunomarker for YWHAE-FAM22 associated HG-ESS.

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D. Manuscript Writing
E. Critical Review
F. Facilitated for Reagents/Material/Analysis

Ethical Policy of International Journal of Pathology

Acknowledgement: This policy is on the guidelines and "Recommendations on Publication Ethics Policies for Medical Journals" which is Prepared by the WAME Publication Ethics Committee. We are grateful to them.

Study Design and Ethics

Good research should be well justified, well planned, and appropriately designed, so that it can properly address the research question. Statistical issues, including power calculations, should be considered early in study design, to avoid futile studies that produce subject risk without enrollment sufficient to answer the research question. Outcomes should be specified at the start of the study. Research should be conducted to high standards of quality control and data analysis. Data and records must be retained and produced for review upon request. Fabrication, falsification, concealment, deceptive reporting, or misrepresentation of data constitute scientific misconduct.

Documented review and approval from a formally constituted review board (Institutional Review Board or Ethics committee) should be required for all studies involving people, medical records, and human tissues. For those investigators who do not have access to formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed. If the study is judged exempt from review, a statement from the committee should be required. Informed consent by participants should always be sought. If not possible, an institutional review board must decide if this is ethically acceptable.

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