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Dr. Impana BD
Consultant Pathologist,
Central Reference Lab, Medall
Diagnostics, Chennai,
Tamil Nadu, India

Dr. Kavitha A
Consultant Pathologist,
Central Reference Lab, Medall
Diagnostics, Chennai,
Tamil Nadu, India

Dr. Varsha P
Consultant Pathologist,
Central Reference Lab, Medall
Diagnostics, Chennai,
Tamil Nadu, India

Corresponding Author:
Dr. Impana BD
Consultant Pathologist,
Central Reference Lab, Medall
Diagnostics, Chennai,
Tamil Nadu, India

Endometrial stromal sarcoma and variants: A study of four cases with review of literature and immunohistochemistry

Dr. Impana BD, Dr. Kavitha A and Dr. Varsha P

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Abstract

Endometrial stromal Sarcoma (ESS) is a rare malignant neoplasm of uterus occurring in perimenopausal age group. The annual incidence of ESS is 1–2 per million women. ESSs are morphologically heterogeneous. The distinction between uterine smooth muscle tumors such as myxoid leiomyosarcoma and low-grade ESS can be difficult when stromal sarcomas have abundant myxoid stroma. A definitive diagnosis of stromal sarcoma can be made if myometrial invasion is present, but hysterectomy is usually required for definitive diagnosis. We report four cases of ESS encountered in a period of one year all of which was confirmed by immunohistochemistry.

Keywords: Mesenchymal, endometrial stromal sarcoma, leiomyosarcoma, myxoid

Introduction

Endometrial stromal sarcomas are malignant tumors of the uterus. ESS accounts for 1% of all uterine malignancies and 15% of malignant mesenchymal neoplasms of the uterus [1]. They are composed of neoplastic cells resembling normal proliferative endometrial stromal cells [2]. Although ESS is a low grade tumor histologically, its prognosis is worsened by frequent recurrences [3]. The World Health Organization (WHO) [4] currently divides endometrial stromal tumors into four types based on tumor morphology, clinicopathological features and prognosis as endometrial stromal nodule (ESN), low-grade endometrial stromal sarcomas (LGESS), high grade endometrial stromal sarcomas (HGESS), and undifferentiated endometrial sarcoma (UUS). The term “myxoid” refers to a matrix rich in proteoglycans and glycosaminoglycans, particularly hyaluronic acid [5]. In the uterus, such finding is commonly seen in the context of a smooth muscle neoplasm. Sometimes, tumors with a prominent myxoid appearance obscures their cellular nature and make the distinction between smooth muscle and endometrial stromal tumors difficult [6]. The myxoid matrix is usually prominent, imparting a hypocellular appearance and a characteristic fleshy and soft consistency on macroscopic evaluation. The diagnosis of endometrial stromal tumor is based on the presence of a spiral arteriolar network, a CD10 positivity as well as the absence of smooth muscle markers [7]. We are presenting four cases of ESS which were clinically misdiagnosed with other smooth muscle tumors.

Case details: We studied four cases of endometrial stromal sarcomas in a period of one year which were confirmed by immunohistochemistry. The youngest was 26 years, gravida 2 para 2 and the oldest was a 66 years old lady. All the patients presented with abdominal pain and Total abdominal hysterectomy with bilateral salphingo oophorectomy (TAH with BSO) was done on all of them (Table 1). The first case showed enlargement of uterus by a mass lesion with infiltration of the perimetrium was noted intra operatively. A part of the small bowel was also adherent to the omentum, fragmented omental bits were also received along with the main specimen (Figure 1).

Table 1: Clinical features with the histopathological diagnosis of all cases

Case No.	Age (yrs)	Symptoms	Surgery	Histopathology Diagnosis
Case 1	26	Abdominal pain, bleeding per vaginum	TAH with BSO, adherent omental bits	Myxoid leiomyosarcoma
Case 2	46	Pain abdomen	TAH with BSO	ESS
Case 3	66	Pain abdomen	TAH with BSO	1. Leiomyosarcoma 2. ESS
Case 4	45	Pain abdomen	TAH with BSO	1. Malignant Perivascular epithelioid cell tumor (PECOMA) 2. ESS

Grossly, first 3 cases showed intramyometrial grey white lesion which was protruding into the endometrial cavity. Fourth case showed an ill-defined grey tan mass attached to myometrium measuring 12x10x5cm was away from endometrium.



Fig 1: Gross image of uterus with cervix and adherent omentum bits of case 1. A mass lesion in myometrium with grey white whorled areas and foci of yellowish area

Microscopy of only one case showed characteristic features of an endometrial stromal sarcoma like uniform oval to spindle shaped cells, with plexiform vasculature and minimal cytological atypia. Whereas in case one, extensive myxoid change, areas of necrosis and increased mitotic figures (10-12/10 high power field) were seen and lesion had an infiltrative growth extending beyond the inked perimetrium (Figure 2). The separately sent adherent omental bits also showed lobules of adipocytes with infiltration by these similar tumor cells. Hence owing to the infiltrative pattern, increased mitotic count and areas of necrosis a diagnosis of myxoid leiomyosarcoma was rendered and immunohistochemistry (IHC) was advised for

confirmation. The fourth case showed invasive sheets and clusters of round to polygonal cells having eosinophilic cytoplasm and round nucleus. Focal clear cell change, large areas of necrosis and increased atypical mitotic figures (12-14/ 10 hpf) were seen. Hence a differential of Malignant Perivascular epithelioid tumor (PECOMA) was given.

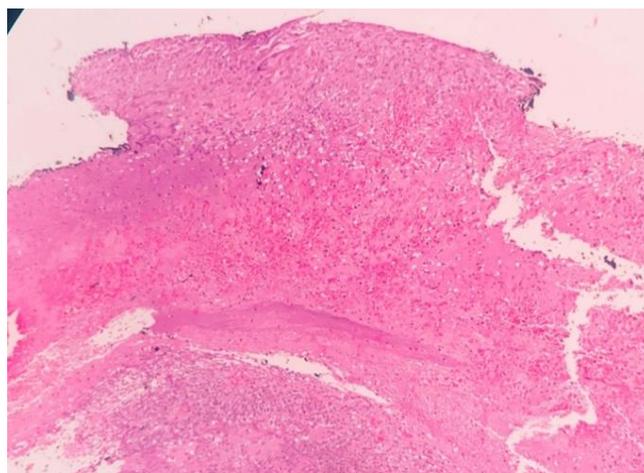


Fig 2: The lesion has an infiltrative growth extending beyond the inked perimetrium. (H&E, 100x). Inset showing tumor infiltrating the omentum. (H&E, 100x)

Immunohistochemistry panel comprised of vimentin, Smooth muscle actin (SMA), CD 10, ER, PR, Desmin and Ki 67 (Table 2). Additional markers HMB45 and cyclin D1 were added for fourth case as PECOMA was considered as a differential. First three cases showed Vimentin and CD 10 positive. Based on Ki 67 they were classified as low grade and high grade. In the fourth case ER, PR and CD 10 were negative whereas cyclin D1 was strongly diffusely positive. This has to be differentiated from undifferentiated uterine sarcomas which are positive for CD 10 and are absent in high grade round cell component of YWHAE-FAM22 ESS.

Table 2: Immunohistochemical results of all the four cases

Case No.	SMA	Vimentin	CD10	ER	PR	Cyclin D1	Desmin	HMB 45	Ki 67
Case 1	Negative	Positive	Positive	Negative	Negative	-	Negative	-	60%
Case 2	Negative	Positive	Positive	Negative	Negative	-	Negative	-	05%
Case 3	Negative	Positive	Positive	Negative	Negative	-	Negative	-	08%
Case 4	Negative	Positive	Negative	Negative	Negative	Positive	Negative	Negative	60%

The histopathological and IHC features favoured low grade ESS in two cases and one case was high grade ESS. The fourth case which showed cyclin D1 positivity was

characteristic of ESS with YWHAE-FAM22 translocation (Figure 3).

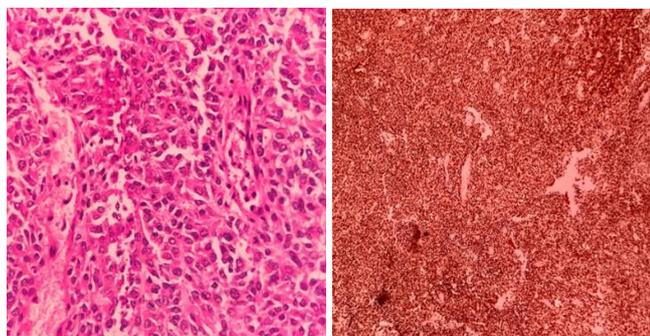


Fig 3(a, b): Microscopy showing plump to epithelioid like cells around blood vessels (H and E 400x). Immunohistochemistry showing strong positivity for cyclin D1 (IHC cyclin D1, 400x).

Table 3: Comparison of the histopathological diagnosis and final diagnosis given after immunohistochemistry.

Case No.	Histopathology Diagnosis	Final diagnosis
Case 1	Myxoid leiomyosarcoma	High grade ESS
Case 2	Endometrial stromal sarcoma	Low grade ESS
Case 3	1. Leiomyosarcoma 2. ESS	Low grade ESS
Case 4	1. Malignant Pecoma 2. ESS	High grade ESS with Ywhae-Fam22

Discussion

ESS originates from the endometrial stromal cells and occurs frequently in the uterine cavity. Extra uterine ESS is more rare, occurs in ovary, pelvic cavity, retro peritoneum, mesentery, and originates from malignant transformation of endometriosis or malignant transformation of pelvic primordial Mullerian cells [8]. Myxoid ESS were first described in 1999 by Oliva *et al.* [9]. Grossly, the tumors can be polypoid intracavitary masses, intramyometrial, or pedunculated tumors. Myxoid ESS retains most of the characteristics of its conventional counterpart: tongue-like invasive growth in the myometrium, spindle cells resembling endometrial stroma and uniformly distributed small thin-walled vessels. Once the myxoid nature of the lesion has been established, assessment of the tumor border is necessary. The presence of infiltrative tumor borders as seen in the first case has been related to potential for aggressive behaviour. The myxoid matrix can be prominent, often representing over 50% of the tumor volume. In contrast with conventional areas, myxoid tumor areas are hypocellular which can be a confounding factor. Overall, the nuclei are low grade with the typical spindle cell appearance. A uniformly distributed vascular network of small caliber vessels, typical of endometrial stromal tumors, is not a characteristic feature of smooth muscle or myofibroblastic neoplasms [10]. If present, endometrioid and sex cord differentiation are indicative of an endometrial stromal tumor.

IHC has long played an important role in the distinction between endometrial stromal tumors and smooth muscle neoplasia. A panel of CD10 and 2 smooth muscle markers including desmin has been recommended in the differential diagnosis of a conventional low grade ESS or endometrial stromal nodule and a highly cellular leiomyoma. The utility of IHC in assessing uterine mesenchymal tumors that exhibit predominant variant morphologic features particularly of the myxoid nature currently appears less informative as there is extensive overlap of CD10, desmin,

actin, h-caldesmon, ER, and PR among ESS, UUS, leiomyosarcoma, and inflammatory myofibroblastic tumor all of which may show myxoid change. Myxoid morphology can occur in low grade and HG ESS.

A recently described ZC3H7B-BCOR gene fusion seems to be a defining feature of a subset of high-grade ESS with myxoid features [9]. A study by Hoang *et al.* [11] described three cases of high-grade ESS harboring a novel ZC3H7B-BCOR gene fusion. Unlike high-grade ESS with other rearrangements, these tumors were characterized by an extensive myxoid matrix, fascicular growth pattern and pleomorphic nuclei morphologically mimicking myxoid leiomyosarcoma. As LG ESS is a highly hormone-dependent tumor which shows progesterone receptor isoform expression similar to normal endometrial stroma, surgical castration can be used to treat microscopic dissemination and prevent recurrence [3].

Lee *et al.* [12], described and characterized a series of ESS with YWHAE-FAM22 genetic fusion resulting from t(10;17)(q22;p13). Clinically, the majority of patients presented with evidence of extra uterine spread and had higher rate of recurrences in contrast to patients with JAZF1 ESS. These cases display a cellular high-grade round cell morphologic appearance with larger nuclei, more irregular nuclear contour, high mitotic activity and frequent necrosis with a fibromyxoid background. Although cyclin D1 immunostaining extent and intensity in YWHAE-FAM22 ESS is comparable to that in mantle cell lymphoma, the mechanism of cyclin D1 overexpression in YWHAE-FAM22 ESS has not been determined, but is a sensitive and specific marker for these cases.

Furthermore, YWHAE-FAM22 ESS also needs to be distinguished from other high-grade typically pleomorphic uterine sarcomas including UUS and leiomyosarcoma, which in contrast to YWHAE-FAM22 ESS, are highly aggressive with a five year survival of less than 50%. The consistent lack of ER and PR expression in the high-grade round cell component implies that hormonal therapy, which has been used as a systemic therapy for ESS, will likely be ineffective against YWHAE-FAM22 ESS [13].

Conclusion

- The diagnosis of endometrial stromal sarcoma with unusual morphologic features like myxoid appearance is difficult.
- Careful morphologic assessment and immunohistochemical study will contribute to their distinction from myxoid LMS.
- The distinction between myxoid LMS and ESS is clinically relevant, as the latter tends to have a more indolent course with long-term relapses, and is amenable to endocrine therapy.
- Given the availability of cyclin D1 readily, it can be included in the immunohistochemical panel as an indicator of YWHAE-FAM22 ESS while evaluating high grade endometrial stromal sarcomas.

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