JMSR
Journal of Medical and Surgical Research

Case Report

ISSN: 2351-8200 JMSR 2023 Vol. X, n 1:

A P16 POSITIVE PLEOMORPHIC ENDOMETRIAL STROMAL SARCOMA: AN UNUSUAL CASE SCENARIO

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ABSTRACT

Endometrial stromal tumors are rare uterine malignancies, particularly in young women, and are divided into four types- Endometrial Stromal Nodules [ESN], Low Grade ESS [LGESS], High Grade ESS [HGESS] and Undifferentiated Uterine Sarcomas [UUS]. A fifth category of Endometrial Stromal Sarcomas – Not Otherwise Specified [ESS NOS] has also been kept for tumours with a predominantly high grade morphology showing significant LG ESS areas as well. Herein, we report a case of a 26 year old woman who presented with an abdominal mass and bleeding per vaginum. Abdomino pelvic ultrasound revealed a neoplastic polypoidal lesion. Post hysterectomy, histopathological examination revealed a tumour mass with features of a highly pleomorphic high grade endometrial stromal sarcoma [HGESS] along with concomitant features of low grade endometrial stromal sarcoma [LGESS] as well. Application of IHC panel further revealed that the tumor came out to be immuno reactive for vimentin, cyclin D1, INI1 and p-16 with focal positivity for Calretinin, Glypican 3 and CD99, the demonstration of p16 positivity being highly unusual for a HGESS. As the patient's condition deteriorated rapidly and she expired soon after the initial examination started, molecular profiling could not be done.

Key words: Endometrial sarcomas, stromal neoplasms of uterus, high grade endometrial stromal sarcomas, undifferentiated endometrial sarcomas

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******Published in March, 2023.*

doi: 10.46327/msrjg.1.000000000000----; doi url: https://doi.org/10.46327/msrjg.1.000000000000----

INTRODUCTION

Endometrial stromal tumors constitute less than 1% uterine malignancies and less than 10% uterine sarcomas. **[1]** These tumours have been classified on the basis of morphological and molecular profile into 4 types-Endometrial Stromal Nodules [ESN], Low Grade ESS [LGESS], High Grade ESS [HGESS] and Undifferentiated Uterine Sarcomas [UUS], the last one being a diagnosis of exclusion. **[2]** A miscellaneous category of Endometrial Stromal sarcomas – Not Otherwise Specified [ESS NOS] has also been kept for tumours with a predominantly high grade morphology showing significant LG ESS areas as well. **[3]** They usually exhibit round / spindle / epithelioid morphology with pseudo papillary, glandular, rhabdoid morphology, pseudorosettes **[4]** and sex cord like differentiation also sometimes present.

On immunohistochemistry, ESNs and LGESS are usually ER, PR, CD 10, CD56 positive with variable positivity for Desmin, SMA, MSA whereas HGESS and UUS are positive for Cyclin D1, BCOR, c- KIT and negative for Desmin, ER, PR and CD10. **[2]** INI 1 retention is seen in all cases of ESS. p 16 positivity is very unusual and mostly reported in the UUS, **[5]** though there's a case reporting it in a morphologically low grade ESS. **[6]** We present here a rare case scenario of a high grade and highly pleomorphic ESS with a concomitant low grade ESS component [ESS-NOS] in a young female which was p16 positive too.

CASE REPORT

A 26 year old woman (Parity-2) came to the gynaecology OPD in a low general condition with chief complaints of abdominal pain and heavy bleeding per vaginum. Physical examination revealed soft and slightly tender lower abdomen. Per speculum showed a bulging, fleshy, red polypoid mass protruding externally from the os.

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Routine investigations performed revealed that the patient was severely anaemic (Hb- 5.5gm/dl) with a low BMI (16.5 kg/m2). Abdomino - pelvic ultrasound of the patient revealed an enlarged uterus with solitary heterogeneous isoechoic polypoidal lesion, likely neoplastic. The patient was operated and the polyp mass was sent to us for further histopathological examination.

Grossly, we received two irregular, grey white to grey brown fragile pieces of tissue, both measuring approximately 3x2x1cm in size and were whole processed. On microscopy, a highly cellular tumour mass was seen with tumour cells mostly arranged in nests and separated by vascularized fibro connective tissue (Figure 1A).

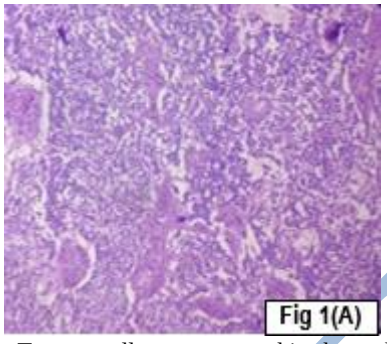

Figure 1(A) - Tumour cells seen arranged in sheets, lobules and nests separated by thick fibrovascular septae [H&E x10 X]

In almost all tumour nests, the cells were arranged radially around blood vessels, suggesting perivascular rosetting (Figure 1B).

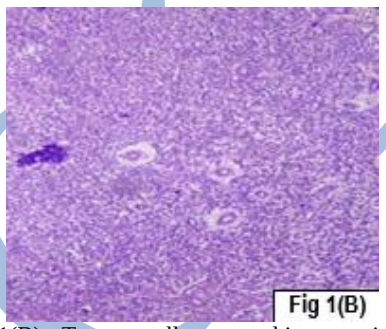

Figure 1(B) - Tumour cells arranged in an angiocentric pattern with perivascular pseudorossetting [H&E x10 X]

The tumour cells were loosely cohesive, large, moderately pleomorphic, round to epithelioid with eccentrically placed nuclei, vesicular chromatin, prominent nucleoli and moderate amount of clear to eosinophilic cytoplasm, mostly in a myxofibrillary background (Figure 1C).

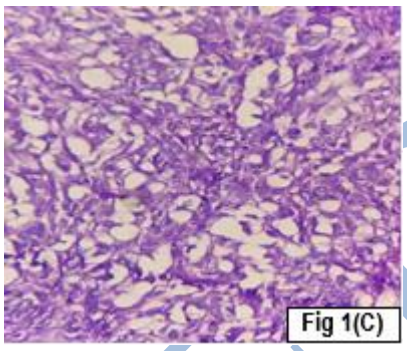

Figure 1(C) - Round to epithelioid tumour cells showing mild pleomorphism, vesicular chromatin, prominent nucleoli and eosinophilic to clear cytoplasm in a myxofibrillary background [H&E x40 X]

Some of the areas showed scattered large tumour cells with rhabdoid like morphology (Figure 1 D), some sex cord like areas (Figure 1E), some areas showing glomeruloid arrangement of tumour cells (Fig 1F) and some markedly hypercellular areas with increased mitotic activity (Fig 1G) with few multinucleate forms (Figure 1H).

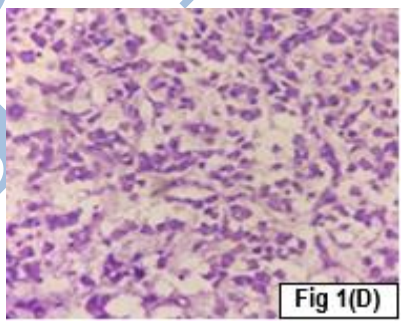

Figure 1(D): Large epithelioid cells displaying rhabdoid morphology [H&E x40 X]

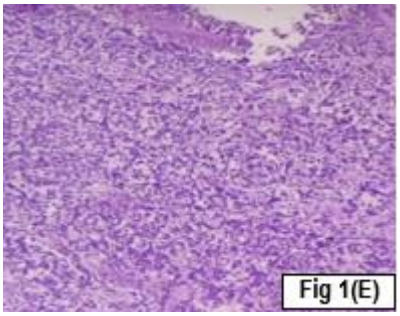

Figure 1(E): Tumour cells displaying sex cord like differentiation. [H&E x10 X]

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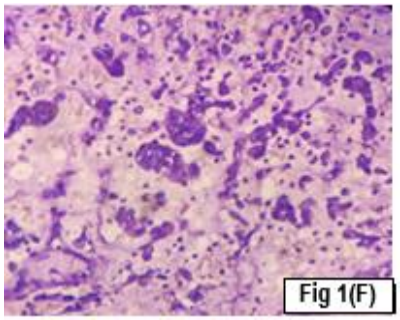

Figure 1(F): Foci of glomeruloid arrangement of tumour cells [H&E x40 X]

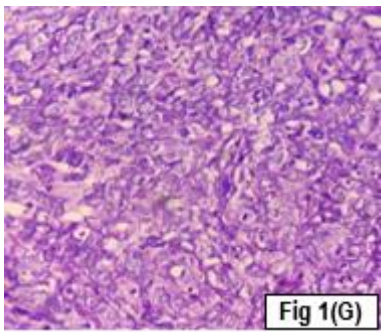

Figure 1(G): Hypercellular areas with increased mitosis {arrow head} [H&E x40 X]

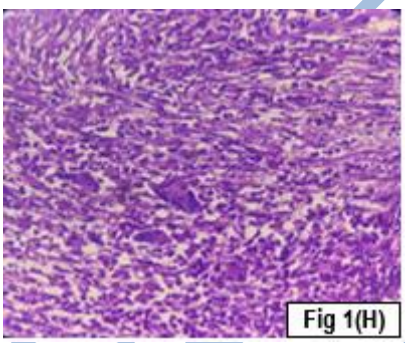

Figure 1(H): Multinucleate tumour cells in areas of high cellularity [H&E x40 X]

Areas of haemorrhage, inflammation and ischaemic necrosis were seen in the periphery. A foci of lymhovascular emboli was also noted (Fig. 1 I).

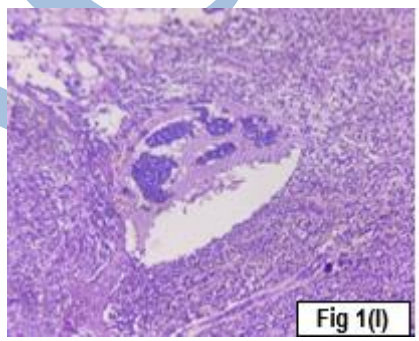

Figure 1 (I): A foci of tumour emboli in a vessel [H&E x10 X]

The differential diagnoses considered were- Endometrial Stromal Sarcoma / Epithelioid leiomyosarcoma / Undifferentiated or Dedifferentiated carcinomas / Malignant PEComa.

Based on the above differentials, a comprehensive IHC panel was applied comprising of Vimentin, WT-1, Cyclin D1, Inhibin A, INI1, p16, CD56, Calretinin, Glypican 3, CD99, Pancytokeratin (AE1/AE3), PAX8, EMA, SMA, MSA, Desmin, CD10, S100, Melan A and HMB 45. The tumour came out to be immuno reactive for Vimentin (Figure 2A), Cyclin D1 (Figure 2B), INI1 (Figure 2C) and p-16 (Figure 2D) with focal positivity for Calretinin, Glypican 3 and CD99.

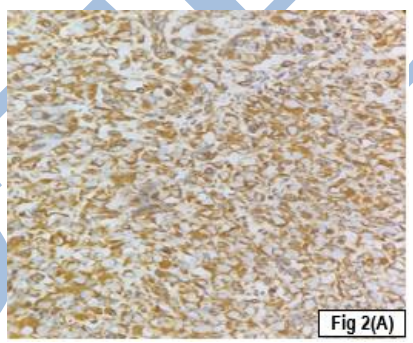

Figure 2(A): Tumour cells displaying cytoplasmic positivity for Vimentin [IHC x 10X]

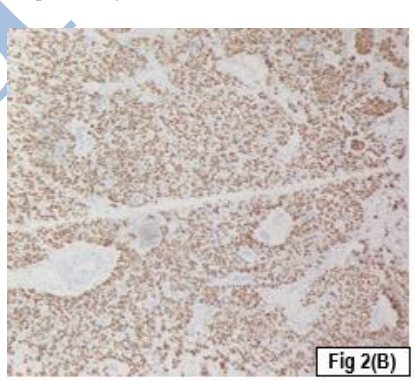

Figure 2(B): Tumour cells displaying nuclear positivity for Cyclin D1[IHC x 10X]

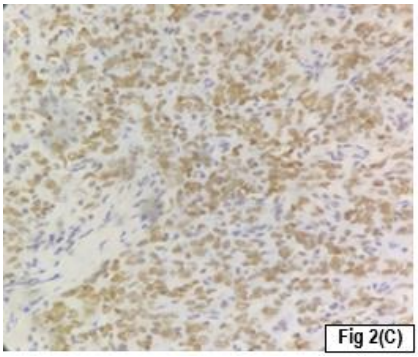

Figure 2(C) : Tumour cells displaying no loss of INI-1[IHC x 40X]

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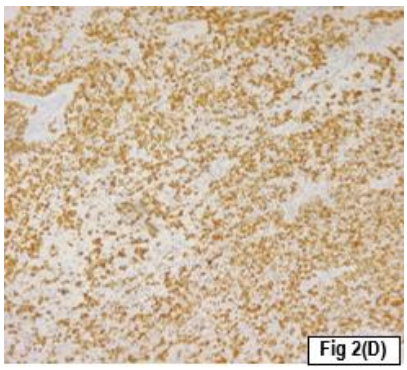

Figure 2(D): Tumour cells showing diffuse p16 positivity [IHC x 40X]

The remaining markers were negative, thus confirming it to be an ESS.
We could not perform further molecular classification of the tumour as by the time we arrived at the final diagnosis and reverted back to the gynaecology department, the patient had expired. So we had to leave our case as a p16 positive ESS-NOS.

DISCUSSION

Endometrial stromal tumors usually occur in patients from age group 14-71 years and constitute less than 10% of all the uterine sarcomas. The most common sites are uterus and cervix but may also occasionally occur in ovary, peritoneum or colon and are postulated to be associated with endometriosis. Macroscopically they are typically bulky, tan yellow, fleshy masses, often displaying haemorrhage and necrosis. The common presenting symptoms include pelvic pain, vaginal bleeding and palpable mass. **[2]** which were consistent with the clinical presentation of our patient.
These tumours have been classified on the basis of morphological and molecular profile into mainly 4 types:

- **ESNs**: These are benign tumours with proliferation of bland uniform cells resembling endometrial stromal cells of proliferative phase endometrium with prominent arterioles and pushing margins. Areas of necrosis may be seen but lymphovascular invasion {LVI} should be absent.
- **LGESS:** Morphologically these are like ESNs except for infiltrative/ permeative margins. Presence of LVI may be seen. Molecular profile of ESTs [ESNs and LGESS] usually show JAZF1-SUZ12 fusions.
- **HGESS:** These tumours can harbour mainly three types of fusions-
  a. YWHAE- NUTM2A/B fusions- These tumours typically display round cells with eosinophilic cytoplasm, irregular nuclear contours, vesicular chromatin, prominent nucleoli, brisk mitoses and delicate curvilinear blood vessels They may also occasionally show low grade stromal fibromyxoid component and variable morphology like pseudoglandular/pseudopapillary/ rhabdoid/ sex cord differentiation and rosette like formations.
  b. ZC3H7B - BCOR fusions- These tumours display haphazard fascicles of uniformly atypical spindle cells with scant to moderate and abundant eosinophilic to blue gray cytoplasm in an extensive myxoid stroma with brisk mitoses and conspicuous absence of low grade areas as well as perivascular whorling. Infarct type of necrosis is seen but nuclear pleomorphism is usually not overt. A few cases also show MDM2, CDK4 and FRS 2 amplification as well.
  c. BCOR ITDs show additionally a strong and diffuse pan Trk positivity with presentation mostly in young females.
- **UUS**: These include a variegated group of neoplasms with no specific lines of differentiation. They may be monomorphic or pleomorphic type. LVIs and necrosis are common findings. They can harbour simultaneously numerous gene fusions. They may also show YWHAE / BCOR fusions typically seen in HG ESS. They usually show p16 positivity with positive aberrant p53 expression. **[5]** Many of the UUS reported are now thought to be under recognised HGESSs. **[3]**

A miscellaneous category of ESS –NOS has also been kept for tumours with a predominantly HG ESS like morphology showing significant LG ESS areas as well and are somewhat intermediate between a LGESS and a HGESS. **[3]**
In our case, the tumour expressed morphological features favouring YWHAE- NUTM2 type of HGESS but since the patient was lost too soon on follow up, molecular profiling could not be done. Another unusual finding in our case was p16 positivity that has been so far reported in UUS only amongst all the ESS, **[5]** though there's a case report with a morphologically low grade ESS showing concomitant Cyclin D1 and p16 positivity where it was emphasised to test all the potential ESSs with CD 10 negativity for Cyclin D1 and p16 as they inadvertently carry a worse prognosis and may be an unrecognised variant of a HGESS rather than a UUS. **[6].** Though p16 is a negative regulator of cell proliferation and is considered a tumour suppressor protein, in cases of endometrial lesions it promotes the progression of endometrial cancers. [**7**]

The other uterine tumours displaying p16 positivity include uterine serous carcinomas, epithelioid leiomyosarcomas and undifferentiated/ dedifferentiated carcinomas**. [8]** Uterine serous carcinoma consist of complex papillary/ glandular architectural features, with irregular/ elongated glands. Multinucleation, marked nuclear pleomorphism and psammomatous calcifications can be seen. They show PAX8, WT1, p53 and p16 expression, with variable ER/ PR staining. Epithelioid leiomyosarcomas consist of round or polygonal cells with clear/ eosinophilic cytoplasm, with frequent rhabdoid cells. However, this tumour is positive for EMA, cytokeratin, p16, Desmin and negative for Cyclin D1. Poorly differentiated uterine sarcomas/ carcinosarcomas are high grade malignant tumours that lack evidence of specific lines of differentiation. These tumours typically display sheets of uniform/ pleomorphic epithelioid cells associated with brisk mitotic activity, necrosis and lympho vascular invasion. These tumours uniformly show INI1 loss. PEComa is a mesenchymal neoplasm composed of perivascular epithelioid cells arranged in nests and surrounded by delicate thin walled vessels and on IHC are Melan-A, SMA, Desmin and HMB 45 positive.
Prognostic factors for ESS include the grade and the stage. The standard treatment protocol entails cytoreductive surgery and multimodality therapy. **[9,10]** HGESS with YWHAE- NUTM2A/B fusions have found to benefit from anthracycline based therapy whereas there is potential role of MDM 2/ CDK4 inhibitors in BCOR rearranged sarcomas. **[2,5]**. The studies done so far lay stress on the fact that p16 positivity indicates poorer prognosis and such tumours should always be tackled with an aggressive approach. **[5]**

CONCLUSION

This case reports of a mixed high and low grade endometrial stromal sarcoma in a young female [ESS-NOS] with a highly pleomorphic picture that interestingly turned out to be p16 positive which has mostly been seen in undifferentiated ESSs only. It is very important for pathologists to be aware of the myriad histopathology of an ESS and to keep a very high index of its suspicion while reporting before signing it out as a dedifferentiated/ undifferentiated neoplasm. The presence of p16 should not misguide to label it as an UUS and molecular profiling should always be performed in an ESS to exactly delineate the type as this has significant prognostic as well as therapeutic implications.

ABBREVIATIONS

ESN	: Endometrial stromal nodule
LGESS	: Low Grade Endometrial Stromal Sarcoma
HGESS	: High Grade Endometrial Stromal Sarcoma
UUS	: Undifferentiated Uterine Sarcoma
ESS NOS	: Endometrial Stromal Sarcomas

There are no conflict of interest to declare.

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