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UNVEILING THE UNCOMMON:RARE PRESENTATIONS OF FEMALE GENITAL TRACT TUMOURS

Pathology

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ABSTRACT

The female reproductive tract harbors many neoplastic conditions of which the most common type being leiomyomata and ovarian cysts with genital cancers like cervical, ovarian and endometrial carcinoma being the next common. The tumours of fallopian tubes vulva and vagina are very rare and STUMP presenting as endometrial polyp and labial mass is extremely rare. Likewise choriocarcinoma presenting as myometrial mass and high grade endometrial sarcoma presenting as a myometrial mass in 19 year old female are rare presentations. In this case series we are presenting these 4 female genital tract lesions with unusual presentations.

KEYWORDS

Choriocarcinoma, STUMP, trophoblast, endometrial stromal sarcoma

INTRODUCTION

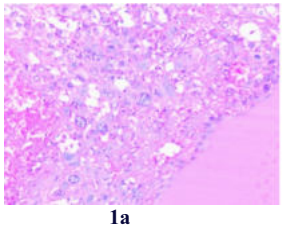
The female genital system is comprised of uterus, cervix, fallopian tubes, ovaries, vagina and vulva. Though these are prone for variety of inflammatory, cystic, benign and malignant lesions, the most common tumours are leiomyomata of the uterus, cystic lesions of the ovary and ectopic pregnancies of the tube with most common malignant tumours being squamous cell carcinoma of the cervix, endometrioid adenocarcinoma of the endometrium and germ cell tumours and surface epithelial tumours of the ovary. Germ cell tumours are common in FGT of which choriocarcinoma presenting as myometal mass is rare. Likewise endometrial stromal sarcoma presenting in a 19 year girl as an intramural mass and STUMP presenting as an endometrial polyp and labial mass is extremely rare and hence taken for publication. These 4 cases are presented for their unusual presentation and rarity of the lesions.

METHODS

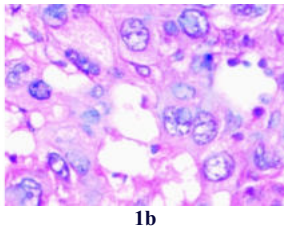
This study is a retrospective study of interesting female genital tract lesions over a period of one year from July 2023 to July 2024.As this is a case series, we chose to describe cases received during this period at Histolab Coimbatore.3 of these cases presented as mass myometrium, endometrial polyp and labia majora with the fourth case – known case of choriocarcinoma cytoreductive surgery post treatment presenting as myometrial mass.

Case1

29 year old female had a history of choriocarcinoma uterus following normal childbirth 2 years back who presented initially with multiple metastasis in the lungs and brain with a βHCG level of 2.5 lakh mIU/ml.(WHO high risk score) and Stage IV:22 disease. After 8 cycles of chemotherapy with multiple drug regimen she was free of metastasis and tumour size also was downgraded. She was taken up for cytoreductive surgery and uterus with adnexae was sent for HPE. Myometrium showed a hemorrhagic and necrotic mass measuring 8x8 cms with features of choriocarcinoma comprising of triphasic cell population of syncytiotrophoblasts, cytotrophoblasts and intermediate trophoblasts.(Figure 1a,1b) Her βHCG was 365 mIU/ml before the surgery and she will be followed up with serum βHCG levels.



1a

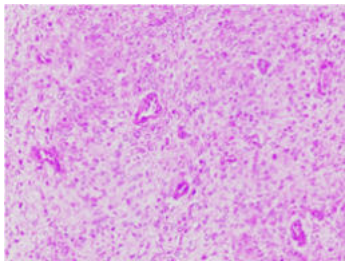


1b

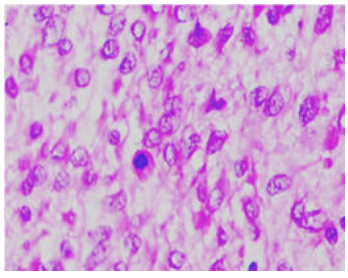
Fig 1a)Low power view of tumour with hemorrhage and necrosis.1b) High power view showing cytotrophoblasts and syncytiotrophoblasts

Case2

19 year old female presented with abdominal pain and radiologically there was a submucosal mass with intramural component, with a radiological and clinical diagnosis of leiomyoma, myomectomy was done and sent for HPE. Grossly the mass measured 12x10 cms which on sectioning appeared greyish and fleshy with necrotic areas. Histologically uterine wall with irregular dense islands of tumour cells with diffuse growth permeating the myometrium with tongue like appearance was seen. Tumour cells were spindly with oval to spindle nuclei with moderate atypia, moderate cytoplasm and mitotic count of 6 to 7/10 HPF. (Figure 2a,2b)Necrosis was also seen. Tumour tissue was taken up for IHC and was diffusely positive for Cyclin D, which may suggest YWHAE mutation rearranged HG-ESS. CD10 showed weak staining which may signify BCOR rearranged HG-ESS with SMA, CD34 and H-Caldesmin negativity and desmin showing weak positivity. With these findings, a diagnosis of High Grade Endometrial Stromal Sarcoma was made. Molecular study was not done.



2a



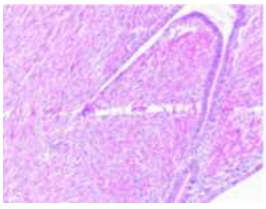
2b

Fig 2a&2b)Low and high power view of neoplastic stromal cells with blood vessels

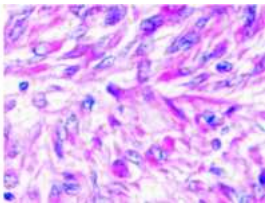
Case 3

50 year old female presented with AUB and radiology showed multiple

intramural fibroids and submucosal mass ?submucosal fibroid ? endometrial polyp. Hysterectomy was done and sent for HPE and intramural leiomyoma was confirmed. Endometrial polyp showed spindle cell proliferation which focally showed high nucleocytoplasmic ratio, moderate to marked pleomorphism, condensed chromatin and conspicuous nucleoli with a mitotic count of 1/10 hpf. No necrosis seen.(Figure 3a,3b) Using the morphological criteria in relation to atypia, mitotic count, presence /absence of necrosis, a diagnosis of STUMP was made on the endometrial polypoid mass.



3a

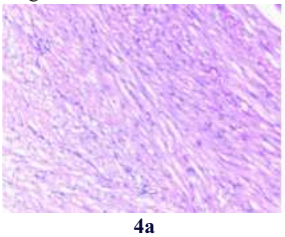


3b

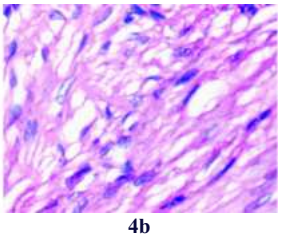
Fig 3a and 3b)Low and high power of tumour cells appearing spindly with moderate atypia

Case 4

39 years female presented with a mass in left labia of 8 months duration and MRI showed a mass lesion measuring 4.3x2.5x3.3 cm at the level of the introitus towards the left side, which was protruding into the labia majora –suggestive of leiomyosarcoma. The mass was excised and sent for HPE which showed spindle cell proliferation with moderate nuclear atypia and a mitotic count of 1-2/10hpf with no necrosis.(Figure 4a,4b)Tissue was taken up for IHC and showed positivity for desmin and H-Caldesmin and negativity for P53 with Ki67 proliferation index of 1-2%. With the above findings, size of the mass 4x3.5x3 cms,mitosis of 1-2/10hpf, presence of nuclear atypia(moderate and focal) and absence of geographic necrosis , a diagnosis of STUMP was made.



4a



4b

Fig 4a and 4b)Low and high power of tumour cells appearing spindly with moderate atypia

DISCUSSION

Choriocarcinoma

Choriocarcinoma is an aggressive form of gestational trophoblastic triphasic neoplasm composed of syncytiotrophoblasts , cytotrophoblasts and intermediate trophoblasts with elevated human chorionic gonadotropins(1)Etiology is from the trophoblastic cells of previous pregnancy and uterus is the commonest site. Our case presented with residual myometrial mass in cytoreductive surgery specimen following 8 cycles of chemotherapy for choriocarcinoma.

WHO classification of gestational trophoblastic disease(2)

Premalignant
Complete hydatidiform mole (C M)
Partial hydatidiform mole (PM)
Malignant (Gestational Trophoblastic Neoplasia)
Non metastatic
• Invasive mole
• Placental site trophoblastic tumor (PSTT)
• Epithelioid trophoblastic tumor (ETT).
Metastatic
• Choriocarcinoma

WHO prognostic scoring system(3) :

- **Low risk**: ≤ 6
- **High risk:** ≥ 7
- **Ultra high risk:** > 12

FIGO anatomic staging(4) :

- I: confined to uterine corpus
- II: extending to adnexa and vagina
- III: extending to lung
- IV: other metastatic sites

Prognostic factors of poorer outcome(4):

- Older age
- Arising from nonmolar pregnancy
- Long interval between index pregnancy and diagnosis
- Markedly elevated hCG
- Large tumor burden
- Metastasis to brain and liver
- Chemoresistance

WHO scoring system based on prognostic factors					*Our case*
	0	1	2	4	
Age, years	<40	>40	-	-	0
Antecedent pregnancy	Mole	Abortion	Term	-	2
Interval months from index pregnancy, months	<4	4-6	7-12	>12	4
Pretreatment serum hCG (mIU/ml)	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$	4
Largest tumour size (including uterus), cm	<3	3-4	> 5	-	2
Site of metastasis	Lung	Spleen,kidney	Gastrointestinal	Liver, brain	4
Number of metastasis	-	1-4	5-8	>8	4
Previous failed chemotherapy	-	-	Single drug	>2 drugs	0
Total					20

Our patient had an ultrahigh risk score of >12 and was FIGO Stage IV on initial diagnosis. As per WHO Scoring system based on prognostic factors our patient score was 20.

This prognostic scoring and staging system was later modified by WHO and was adopted by FIGO As per the international gynecologic cancer society and FIGO co ordinated by Dr. E. Kohorn one of the recommendation is, the use of 2 risk grading instead of 3 as recommended by WHO. (5)A total score of 6 or less is considered as low risk. Also full reassessment of spread and previous chemotherapy response are used in restaging .Molecular study-STR analysis is useful in diagnosing gestational trophoblastic neoplasia as, comparison of the allelic patterns at STR loci between the tumour and paired normal tissue identifies the presence or absence of paternal alleles in the tumour allowing for diagnostic separation of a gestational tumour from its non gestational mimics like non gestational choriocarcinoma which usually presents in prepuberty or in post menopausal state.(6)

Our case ,though was in stage IV and in high risk category , has responded very well to chemotherapy with the only residual tumour in the myometrium during cytoreductive surgery.

High Grade Endometrial Stromal Sarcoma

Mesenchymal tumors of the uterus(2)

- smooth muscle tumors
- uterine leiomyoma
- intravenous leiomyomatosis
- smooth muscle tumor of uncertain malignant potential (STUMP)
- metastasizing leiomyoma
- uterine leiomyosarcoma
- endometrial stromal and related tumors
- endometrial stromal nodule
- low-grade endometrial stromal sarcoma
- high-grade endometrial stromal sarcoma
- undifferentiated uterine sarcoma
- miscellaneous mesenchymal tumors
- uterine tumor resembling ovarian sex cord tumor
- perivascular epithelioid cell tumor (PEComa)
- inflammatory myofibroblastic tumor
- other mesenchymal tumors of the uterus: rare (includes vascular tumors, lipomatous tumors, alveolar soft part sarcoma, solitary fibrous tumor, nerve sheath tumors, NTRK sarcomas, giant cell tumor)

Mixed epithelial and mesenchymal tumors

- adenomyoma

- atypical polypoid adenomyoma
- adenosarcoma of the uterus

High Grade Endometrial Stromal Sarcoma (undifferentiated endometrial sarcoma uniform type) is a malignant stromal neoplasm usually occurring primarily in the uterine body and accounts for less than 1% of all uterine malignancies and is the second most common uterine malignant mesenchymal tumour.(7) They are classified as endometrial stromal nodule, low grade ESS, high grade ESS and undifferentiated uterine sarcoma. Though the common etiology is endometriosis, several alterations have been described like BCOR fusions, BCOR ITD,YWHAE::NUTM2A/B fusion. It appears that all genes found to be rearranged in ESS have a role in epigenetic regulation, through polycomb mediated gene slicing or post translational covalent modification of histone proteins. (8)Immunohistochemistry is required to differentiate between ESS and smooth muscle tumour. Cyclin D1 positivity may support YWHAE rearranged HG-ESS. (9)Though CD10 expression is in favour of BCOR rearranged ESS, negativity for SMA, CD34 and Caldesmin will make the diagnosis easy. Our case was diagnosed based on histology and IHC and genetic marker was not done. Detection of specific genetic alterations may become very pivotal in the diagnosis and probable treatment.In future Undifferentiated sarcomas have complex karyotype and no known recurring genetic alterations.(9,10)

STUMP(Smooth Muscle Tumour of Uncertain Malignant Potential)

STUMP is a smooth muscle tumour with morphologic features exceeding diagnostic criteria for leiomyoma but insufficient for the diagnosis of leiomyosarcoma. They are diagnostically challenging and generous sampling is essential for microscopic examination and it usually occurs in reproductive age or in postmenopausal women(our patients were 50 and 39 years). The types of STUMP are (i) Spindle cell STUMP(ii) Myxoid STUMP and (iii)Epitheloid STUMP with each having a specific diagnostic criteria.

Diagnostic criteria of STUMP (WHO Classification of tumour of female genital tract online version) Generous sampling advised for microscopic examination.(11)

General diagnostic criteria:

- 1 of the 3 criteria for leiomyosarcoma (coagulative tumor cell necrosis, cytologic atypia, elevated mitotic activity) should be present
- Other useful parameters include atypical mitoses, vascular involvement and infiltrative / irregular margins (12,13,14)

General guidelines for spindled smooth muscle tumors:

1) Tumors with focal / multifocal or diffuse cytologic atypia and 2 - 4 mitoses / mm2 (6 - 9 mitoses / 10high power fields [HPF] of 0.55 mm field of diameter [FD] and 0.24 mm2
in area) but lacking coagulative necrosis (15)

- 12 - 17% of STUMPs have these features
- Some STUMPs with fewer mitoses have recurred

2) Tumors with unequivocal coagulative necrosis but lacking cytologic atypia or elevated mitotic activity:

- 28% (5/18) of reported cases have recurred (16)
- Distinguishing between coagulative necrosis and early infarct type necrosis can be difficult (7)

3) Tumors with elevated mitotic activity at > 6 mitoses / mm2or > 15 mitoses / 10 HPF (FD = 0.55, 0.24
mm2 in area) but lacking coagulative necrosis or cytologic atypia:

- 0% (0/42) of reported cases have recurred (17)

4) Tumors with diffuse cytologic atypia and uncertain mitotic count, often due to prominent karyorrhexis but lacking coagulative necrosis:

- PHH3 immunohistochemistry may be helpful for accurate assessment of mitotic figures.(18)

Epithelioid STUMP:

Tumors exceeding the criteria for epithelioid leiomyoma (rounded or polygonal cells with eosinophilic granular or clear cytoplasm lacking cytologic atypia, < 0.8 mitoses / mm2 or < 2 mitoses / 10 HPF, FD = 0.55, 0.24 mm2 in area) but falling short of a diagnosis of epithelioid leiomyosarcoma (moderate to severe cytologic atypia or coagulative necrosis or ≥ 1.6 mitoses / mm2 or ≥ 4 mitoses / 10 HPF, FD = 0.55, 0.24 mm2 in area) (19)

Myxoid STUMP:

- Tumors exceeding the criteria for myxoid leiomyoma (circumscribed, hypocellular and myxoid tumor lacking cytologic atypia or mitotic activity) but falling short of a diagnosis of myxoid leiomyosarcoma (moderate to severe cytologic atypia or coagulative necrosis or > 0.4 mitoses / mm2/ > 1 mitosis / 10 HPF, FD = 0.55, 0.24 mm2 in area or infiltrative / irregular borders) (20)

Also STUMP has to be differentiated from Lieomyoma with bizarre nuclei(LBN) FH associated leiomyomas and leiomyosarcoma and the diagnostic criteria to be followed is

Practical Classification of Smooth Muscle Tumors With Typical Spindle Cell Differentiation

Diagnosis	Geographic Tumor Necrosis	Mitotic Rate: Mitoses/10 hpf	Atypia
Leiomyosarcoma	Present	Any rate	Present or absent
	Absent	≥10	Diffuse or multifocal; moderate to severe
Smooth muscle tumor of uncertain malignant potential (STUMP)	Questionable	Any rate	Present or absent
	Absent	>15	None
	Absent	Approaching, but less than 10	Diffuse or multifocal; moderate to severe
Atypical leiomyoma	Absent	≤10	Diffuse or multifocal; moderate to severe
Leiomyoma with increased mitotic activity	Absent	≤15	Absent

Table 5.1 Uterine smooth-muscle tumours with spindle-cell differentiation of uncertain malignant potential

Tumour cell necrosis	Moderate-to-severe atypia	Mitotic count (per 10 HPF)	Mean mitotic count in tumours with recurrence (per 10 HPF)	Cases with recurrence
Absent	Focal/multifocal	< 10	4 (range 3-5)	13.6% (3 of 22 cases) (68 ,811)
	Diffuse	< 10	4.3 (range 2-9)	10.4% (7 of 67 cases) (129,145,1865,1981)*
Present	None	< 10	2.8 (range 1-4)	26.7% (4 of 15 cases) (41,68,129)
Absent	None	≥ 15	Not applicable	0% (0 of 39† cases) (129,811)

*One of the four tumours also had epithelioid cells
†Three had ≥ 20 mitotic figures per 10 HPF, an unknown proportion also had counts between 10 and 14 (129).

CONCLUSION

Prognosis of choriocarcinoma depends on the risk factors like site, size, H/o previous pregnancy, βHCG levels, metastatic foci and response to chemotherapy. The high risk group of choriocarcinoma do poorly when treated with first line chemotherapy and hence multiple agent chemotherapy is preferred with salvage therapies wherever possible. Our patient responded well to chemotherapy with βHCG falling to 365 mIU/ml from 2.5lakhs mIU/ml and also the metastatic foci melted away. High grade uterine endometrial sarcoma is treated with chemotherapy after surgery. However recurrence and metastasis are more common in HGESS and hence some patients are given radiotherapy too. Unfortunately our patient was lost to follow up. STUMP patients are closely followed up for recurrence and both our patients are free of recurrence until now.

Abbreviation

FGT-Female Genital Tract, STUMP-Smooth Muscle Tumour of Uncertain Malignant Potential, IHC-Immunohistochemistry, LBN-Leiomyoma with bizarre nuclei, WHO-World Health Organization, STR-Short Tandem Repeat, HPE-Histopathological examination, ESS-Endometrial Stromal Sarcoma, LG-Low grade, HG-High Grade, AUB-Abnormal Uterine Bleeding

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