Case Series

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Pathology Section

Rare Diagnoses and Diagnostic Pitfalls in Female Genital Tract Neoplasms: A Case Series

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ABSTRACT

There is a wide spectrum of disorders that may originate from different parts of the female genital tract. They are often unique and rare, posing a diagnostic challenge for reporting pathologists. Their uniqueness lies in the rare histomorphologic picture and challenging clinical scenarios, accentuated by a paucity of available literature. Sometimes, histomorphology alone may not be sufficient for diagnosis, and ancillary studies like Immunohistochemistry (IHC) may help arrive at a definitive diagnosis. Present article represents a series of six unique cases. The first case presented with virilising features and menstrual irregularities. Gross examination of the adnexal neoplasm showed solid yellowish-orange areas, which were diagnosed as Steroid Cell Tumour (SCT), Not Otherwise Specified (NOS) based on histomorphology. This diagnosis was further substantiated by diffuse and strong Inhibin positivity on IHC. The second case presented with huge abdominal distention and markedly raised CA-125 levels. It was diagnosed as mucinous carcinoma with a focus of Benign Brenner Tumour. The third case presented with postmenopausal bleeding and underwent radical hysterectomy. Gross examination revealed simultaneous involvement of the unilateral adnexa, and it was finally diagnosed as endometrioid carcinoma with adnexal metastasis, International Federation of Gynaecology and Obstetrics (FIGO) stage IIIA. The fourth case was a cervical carcinoma with histomorphology suggestive of high-grade, but it did not fit into any of the known subtypes of adenocarcinoma. Therefore, it was reported as Adenocarcinoma NOS with focal mucinous differentiation. The fifth case was a rare cervical Adenosquamous Carcinoma (ASCC) with both malignant squamous and glandular components. The sixth case was of mesenchymal origin in the vulva, namely Aggressive Angiomyxoma (AA). All these cases highlight the fact that pathologists should be well aware of these entities to make an appropriate diagnosis.

Keywords: Adenosquamous, Angiomyxoma, Brenner tumour, Endometrioid, Mucinous carcinoma, Steroid cell tumour

INTRODUCTION

The female genital tract comprises of bilateral ovaries, fallopian tubes, uterine corpus, cervix, vaginal tract, and vulva. Numerous pathological conditions arise from these sites of epithelial and/or mesenchymal origin and can be of benign, borderline, or malignant nature. Clinical presentation, radiological data, and histopathological study are the cornerstones in the diagnosis of these pathologies. Sometimes, histopathology alone may not be sufficient for diagnosis, and differentials are provided with advice for IHC or molecular genetic studies for precise categorisation and management. Ovarian cancer is the sixth most common cancer and the seventh leading cause of cancer-related deaths among women [1]. Ovarian tumours may originate from surface epithelium, sex cord-stroma, or germ cells. Certain mesenchymal tumours can also occur rarely. Mixed histologic patterns may also be seen in unilateral ovarian neoplasms. Here, two unique ovarian neoplasms are discussed along with possible pitfalls in their diagnosis. Recently, there has been marked advancement in the field of endometrial carcinoma with comprehensive genomic analysis and significant prognostic significance. Molecular classification of endometrial carcinoma has now been incorporated into management guidelines [2]. Molecular studies are also helpful in identifying the origin of tumours, as it might be an issue in some cases where ovaries are simultaneously involved. One such interesting entity has been discussed in this series.

Cervical adenocarcinomas are heterogeneous groups of tumours with varying histomorphology, molecular drivers, and aetiologies, comprising almost 25% of cervical cancers [3]. There are several known histomorphological types of cervical adenocarcinomas. Some of them may not fall into any of the defined categories. One such case with atypical histomorphology has been presented in this series. Adenosquamous Carcinoma (ASCC) of the cervix is a rare malignant epithelial neoplasm of the cervix showing the presence of both glandular and squamous differentiation. There is a paucity of knowledge and published literature regarding survival outcomes and prognostic factors of this neoplastic entity [4]. One such case is described in this series. Vulvar tumours are relatively rare with non specific clinical manifestations and mainly fall into two categories- cystic and solid neoplasms [5]. Solid vulvar masses may be squamous, glandular, or mesenchymal in origin [6]. Here, a solid vulvar tumour of mesenchymal origin is presented.

The uniqueness of this series lies in the fact that the lesser-known entities, which are rarely encountered in daily reporting, have been discussed here. Differentials based on clinical and preoperative investigations have been provided, with the final diagnosis based on histomorphology and ancillary studies. The details of these are enumerated below.

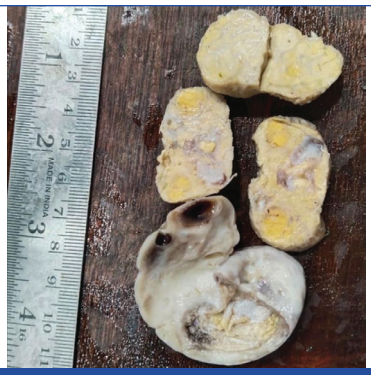
CASE SERIES

Case 1

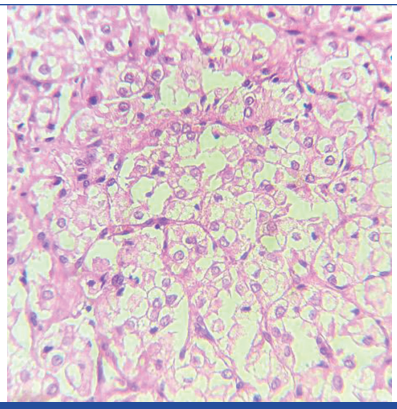
A 38-year-old female patient presented to the gynaecological Outpatient Department (OPD) with complaints of irregular menstruation for 8-9 months. On examination, virilising features were observed, such as excessive facial hair and deepening of the voice. An ultrasound examination of the pelvis was advised, which showed a unilateral solid-cystic ovarian Space-Occupying Lesion (SOL) measuring around 6 cm in its largest dimension in the left adnexa. The CA-125 level was within the normal range (value=12 units/mL). Based on the clinical and radiological presentations, a possibility of a functioning ovarian tumour was considered. Unilateral salpingo-oophorectomy was performed, and the specimen was sent for histopathological examination.

During gross examination, an ovarian cyst measuring 6 cm in its largest dimension was received. The cut section showed a solid-cystic appearance, and clear serous fluid was drained out. The solid

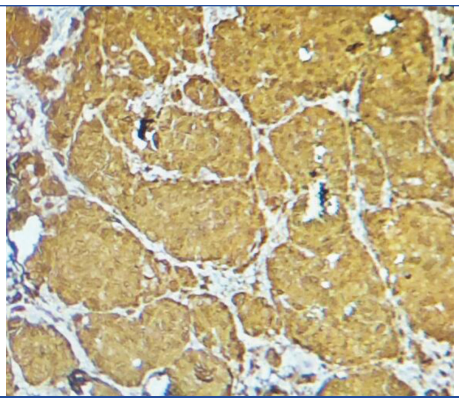
area had a yellowish-orange colour with no areas of necrosis [Table/Fig-1a]. Multiple sections were submitted for histopathological study. The sections showed sheets and nests of polygonal cells with abundant clear to eosinophilic granular cytoplasm, monomorphic central nuclei, and occasional prominent nucleoli embedded in scant fibromatous stroma [Table/Fig-1b]. There was no area of necrosis, marked pleomorphism, or atypical/brisk mitosis. The provisional diagnosis was a sex cord stromal tumour, favoring SCT, NOS. IHC for inhibin was advised for confirmation, and the sample was outsourced. The inhibin test came out strongly positive [Table/Fig-1c]. Thus, the diagnosis of SCT NOS was confirmed. On a six-month follow-up, the patient is doing well with regression of virilising features and menstrual irregularities.



[Table/Fig-1a]: Gross appearance of Steroid Cell Tumour (SCT), NOS with yellowish-orange cut section.



[Table/Fig-1b]: Histomorphology of Steroid Cell Tumour (SCT) showing nests of polygonal cell with clear-to-eosinophilic cytoplasm (H&E, 400x magnification).



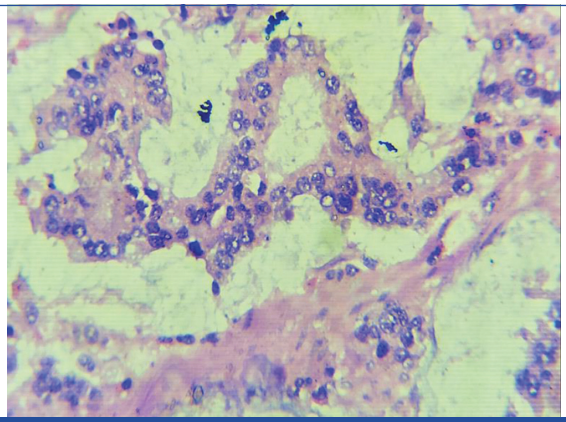
[Table/Fig-1c]: Diffuse Inhibin positivity in Steroid Cell Tumour (SCT), NOS (100x magnification).

Case 2

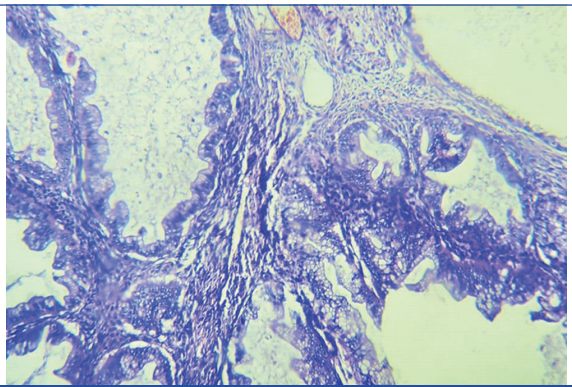
A 60-year-old female presented to the surgical OPD with features of huge abdominal distension, fatigue, and weight loss for the past three months. An urgent Computed Tomography (CT) scan study was advised, which showed a unilateral right-sided huge adnexal complex SOL measuring 30 cm in its maximum dimension, along with moderate ascites and a few prominent pre and para-aortic lymph node enlargements. CA-125 levels were elevated (>200 units/mL, normal range: 0-35 units/mL). A provisional diagnosis of malignant ovarian neoplasm was made. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, along with pelvic lymph node dissection, was planned, and the specimen was sent for histopathological examination.

The received specimen showed a right-sided ovarian tumour measuring 28×20×15 cm with a smooth outer capsule without any breach. The attached fallopian tube, contralateral adnexa, uterine corpus, and cervix were unremarkable. The cut section of the ovarian SOL showed a multiloculated tumour with mucinous fluid [Table/Fig-2a] and focal solid areas. Multiple sections were submitted, and the received pelvic nodes were also fully processed for histopathological examination. The sections showed pools of mucin with floating dysplastic glands, isolated cells, and signet ring cells in tumour areas [Table/Fig-2b]. Definite areas of stromal invasion were also seen. Areas of borderline mucinous tumour were also noted [Table/Fig-2c]. A section from one solid area showed a benign Brenner tumour [Table/Fig-2d]. One para-aortic lymph node showed metastasis of mucinous carcinoma [Table/Fig-2e]. The final histopathological report was right ovarian mucinous carcinoma with foci of benign Brenner tumour, FIGO stage IIIA1. The patient was then treated in the radiotherapy department with Platinum-based adjuvant therapy, with no signs of recurrence in a four-month follow-up period.

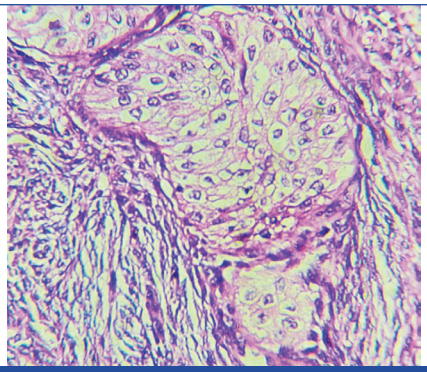
[Table/Fig-2a]: Gross image showing cut-section of ovarian mucinous neoplasm.



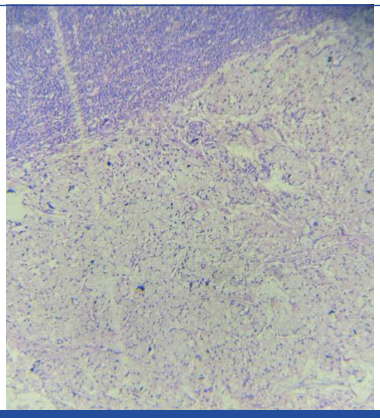
[Table/Fig-2b]: Mucinous carcinoma of ovary (H&E, 400x magnification).



[Table/Fig-2c]: Area of borderline mucinous tumour in mucinous carcinoma (H&E, 100x magnification).



[Table/Fig-2d]: Foci of benign Brenner tumour (H&E, 400x magnification).

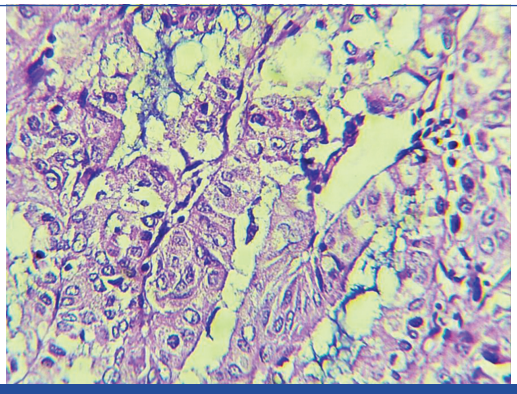


[Table/Fig-2e]: Metastatic mucinous carcinoma showing signet ring cells in para-aortic lymph node (H&E, 100x magnification).

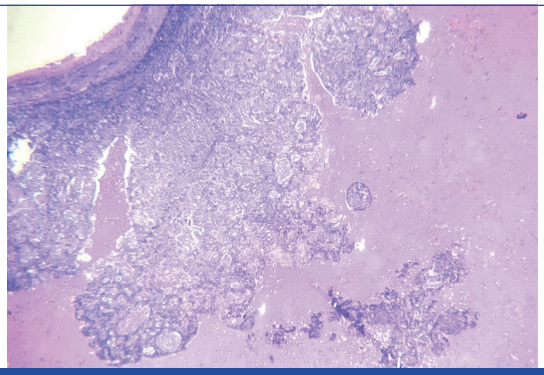
Case 3

A 55-year-old woman presented to the gynecological OPD with postmenopausal bleeding for the last four months. A cervical Papanicolaou (Pap) smear study was advised, which was reported as Negative for Intraepithelial Lesion and Malignancy (NILM). The Ultrasound (USG) study showed irregular thickening of the endometrium with a polypoid mass lesion. A colposcopy-guided endometrial biopsy was reported as atypical endometrial hyperplasia, followed by radical hysterectomy, and the specimen was sent for histopathological examination.

The specimen, on cut section, showed a polypoid growth involving almost the whole endometrial cavity measuring 6×4×2 cm, with involvement of the Lower Uterine Segment (LUS). Grossly, the cervical stroma was uninvolved. The left-sided adnexa showed haematosalpinx with whitish multiple foci of tumour within the tubal lumen, the largest measuring around 1 cm in diameter. The contralateral adnexa and grossly unremarkable serosa were unremarkable. Multiple sections were submitted for histopathological study. The study showed well-defined glands as well as focal solid areas, along with areas of squamous morules with >50% myometrial invasion [Table/Fig-3a], indicating involvement of the Lower Uterine Segment (LUS). The findings were consistent with endometrioid endometrial carcinoma, NOS. The left-sided fallopian tube was also involved, confirming the gross findings and providing evidence of direct spread through the uterine cavity [Table/Fig-3b]. The final diagnosis was Endometrioid Carcinoma, NOS, FIGO grade 2, and stage IIIA. The patient is currently undergoing chemo-radiation therapy in the three-month follow-up period after surgery.



[Table/Fig-3a]: Endometrioid carcinoma, NOS (H&E, 400x magnification).

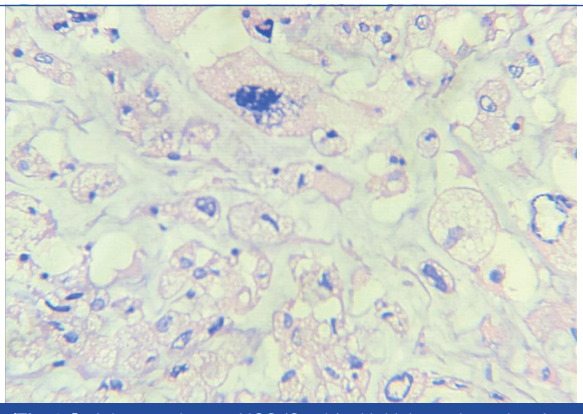


[Table/Fig-3b]: Adnexal metastasis of endometrioid carcinoma in the background of haematosalpinx (H&E, 100x magnification).

Case 4

A 45-year-old woman presented to the Gynaecological OPD with complaints of irregular menstruation. A PAP smear examination was advised, which was reported as atypical glandular cells, NOS. The USG examination revealed an irregular, heterogeneous, hypoechoic mass lesion measuring 4×3×1.5 cm in the cervical canal without parametrial, adnexal, or vaginal invasion. A cervical biopsy was reported as a poorly differentiated malignant neoplasm, and radical hysterectomy was planned. The received specimen showed an ulcerated mass involving all the cervical lips, measuring 3.5×3.3×1.5 cm with focal mucinous areas. The endomyometrium, LUS, parametrium, vaginal cuff, and bilateral adnexae were grossly free.

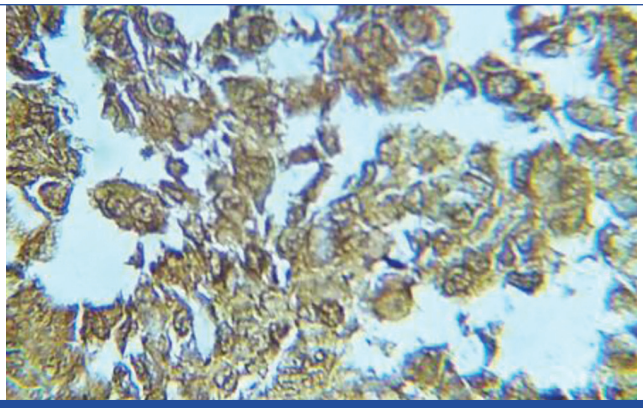
Histopathological examination showed tumour cells arranged in sheets, glands/acini, and a dispersed population floating in mucin pools. Individual tumour cells were highly pleomorphic, with irregular nuclear membranes, vesicular chromatin, occasional prominent nucleoli, and abundant foamy cytoplasm. Multiple tumour giant cells were seen along with atypical/bizarre mitosis [Table/Fig-4a]. The report was signed out as adenocarcinoma NOS with focal mucinous differentiation - Grade 3, FIGO stage IB2. The diagnosis was confirmed by intense positive immunohistochemical expression for monoclonal Carcinoembryonic Antigen (mCEA), which was outsourced and the slide was reviewed in the department [Table/Fig-4b]. Considering the early stage of the carcinoma, the patient was put under follow-up with no signs of recurrence in the four-month postsurgical period.



[Table/Fig-4a]: Adenocarcinoma, NOS (Cervix) with high-grade nuclear features and prominent bizarre mitosis at places (H&E, 400X magnification).

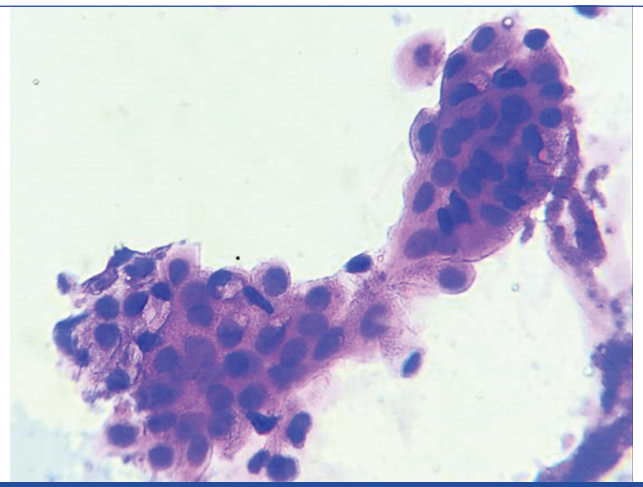
Case 5

A 65-year-old woman complained of postmenopausal bleeding for the last month. A per vaginal examination showed an irregular surface of the cervix with obliteration of the external os. She was

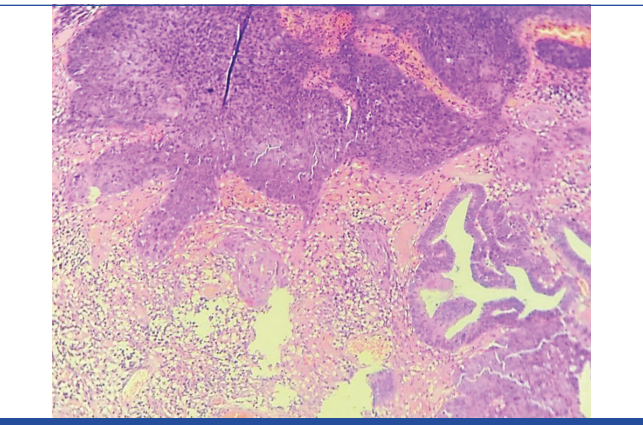


[Table/Fig-4b]: Intense positivity for mCEA (IHC, 400x magnification).

advised a cervical PAP smear examination, which was reported as High-grade Squamous Intraepithelial Lesion (HSIL) [Table/Fig-5a]. Imaging showed an irregular, heterogeneous mass lesion measuring 3.5×3×2 cm, involving the cervical canal, with the bilateral adnexae being free. A cervical biopsy was performed, which was reported as moderately differentiated Squamous Cell Carcinoma (SCC) with areas of glandular dysplasia. A radical hysterectomy procedure was performed. On gross examination, the specimen showed an irregular, corrugated mass in the cervical canal measuring 3.5×2×2 cm without any gross involvement of the uterine corpus, bilateral adnexae, and vaginal cuff. Sections were submitted from all representative areas for histopathological study. The sections showed a tumour composed of infiltrating dysplastic glands as well as foci of atypical squamous epithelium intermixed with one another [Table/Fig-5b]. There were foci of HSIL and high-grade endocervical glandular dysplasia in the adjacent area with involvement of the parametrium. Thus, the final diagnosis was Adenocarcinoma of the Cervix, FIGO stage IIB. In the four-month follow-up period, the



[Table/Fig-5a]: High-grade Squamous Intraepithelial Lesion (HSIL) in exfoliative cytology (PAP, 100X magnification).

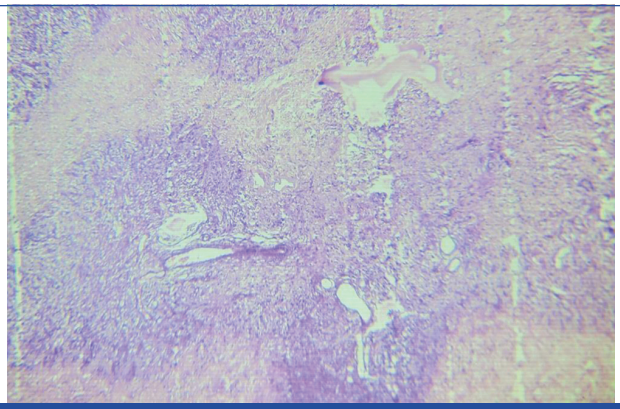


[Table/Fig-5b]: Adenosquamous Carcinoma (ASCC) (Cervix) showing glandular and squamous components (H&E, 100x magnification).

patient was being treated in the Radiotherapy department with chemo-radiation.

Case 6

A 40-year-old female presented with a painless mass in the vulva for the last four months along with increased urinary frequency. An ultrasound revealed a locally infiltrative lesion measuring 4×3×2.5 cm in the vulva with increased vascularity. A biopsy was performed and reported as a spindle cell lesion with myxoid change. A wide local excision was performed, and the specimen was sent for histopathological study. Gross examination showed a lobulated mass measuring 3.5×3×2 cm with infiltration into the surrounding soft tissue. The mass appeared tan-gray in colour with focal myxoid areas. Multiple sections were submitted for histopathological study. The study showed a tumour composed of bland spindle-to-stellate cells in a myxoid background with delicate rich vasculature [Table/Fig-6]. No areas of necrosis or mitosis were seen. The histopathology was suggestive of an Angiofibroma (AA). Unfortunately, no follow-up details were available the case was lost to follow-up. The findings of all the cases have been summarised in [Table/Fig-7].



[Table/Fig-6]: Histomorphology of aggressive angiomyxoma (H&E, 100x magnification).

DISCUSSION

Steroid Cell Tumours (SCT) make up 0.1% of ovarian neoplasms, with 80% belonging to the group of SCT, NOS (Steroid Cell Tumor, Not Otherwise Specified) [7]. These are SCTs that cannot be categorised as either stromal luteomas or Leydig cell tumours [8]. These often come to attention due to their androgenic effects, leading to menstrual irregularities and virilising features [9], as seen in our case. There are no definitive ultrasound characteristics of SCT, and they may often be too small to be misinterpreted as follicular growth [10]. Suspicion for high-grade malignant ovarian neoplasms can be ruled out by normal CA-125 levels [11], as seen in the first case of this series. The majority of these tumours are benign, but a few may exhibit malignant behaviour with metastatic potential [12]. In a paper by Hayes MC and Scully RE, predictive markers for malignancy were abundant mitosis, necrosis, hemorrhage, nuclear atypia, and gross tumour size [13]. SCT, NOS can be differentiated from Leydig Cell Tumours by the absence of Reinke's crystals in the cytoplasm. The former stains strongly and diffusely for Inhibin [14]. In this case, strong and diffuse Inhibin positivity was observed. Follow-up of these cases includes estimation of sex hormone levels.

Epithelial tumours of the ovary are the most common ovarian neoplasms and can show heterogeneous collections of neoplasms, namely Mucinous and Brenner tumours [7]. Mucinous tumours account for 10-15% of ovarian neoplasms and are classified as benign, borderline, or malignant [15]. On the other hand, Brenner tumours are relatively rare, accounting for 1.4-2.5% of all ovarian tumours, with 99% being benign [16]. Mixed epithelial tumours are significant only when all components are present in a significant amount (10%). Mucinous cystadenomas are known to occasionally contain a component of Brenner tumour, with a reported incidence of 1.3-4% [17]. However, the coexistence of mucinous carcinoma

Case no.	Age (years)	Site of tumour	Preoperative investigations	Histopathological diagnosis	Postoperative investigations	Follow-up
1.	38	Left ovary	CA-125- 12 units/mL (normal level)	Steroid cell tumour, NOS	IHC for Inhibin-positive	6 months follow-up- regression of virilising features and menstrual irregularities.
2.	60	Right ovary	CA-125- >200 units/mL (high levels)	Mucinous carcinoma with benign brenner tumour	--	4 months follow-up- Platinum- based chemotherapy with no signs of recurrence.
3.	55	Endometrium	1. Cervical PAP- NILM 2. Endometrial biopsy- atypical endometrial hyperplasia	Endometrioid carcinoma, NOS with left adnexal metastasis	--	3 months follow-up- patient was on chemo-radiation.
4.	45	Cervix	1. Cervical PAP- atypical glandular cells, NOS 2. Cervical biopsy- Poorly differentiated malignant neoplasm	Adenocarcinoma, NOS with focal mucinous differentiation	--	4 months follow-up- no signs of recurrence.
5.	65	Cervix	1. Cervical PAP- HSIL 2. Cervical biopsy- Moderately differentiated squamous cell carcinoma with areas of glandular dysplasia	Adenosquamous Carcinoma (ASCC)	--	4 months follow-up- patient was put on chemo-radiation.
6.	40	Vulva	Biopsy- Spindle cell lesion with myxoid change	Aggressive angiomyxoma	--	No follow-up details available.

[Table/Fig-7]: Table summarising age, histomorphological diagnosis and ancillary investigations of all cases of the series.

with a benign Brenner tumour is unique, as there have been very few cases reported in the literature. In a case report by Khadang B and Omeroglu A, a rare combination of Malignant Brenner tumour and Mucinous carcinoma with signet ring cell morphology was described [18]. The case discussed here is one such unique case in this series. The pathological staging in this case is influenced by the mucinous carcinoma component of the tumour, and further prognosis and treatment of the case are also dependent on this.The awareness of the pathologist regarding the coexistence of these two entities may lead them to perform more rigorous sampling from solid areas of the tumour. This is particularly important when both components are borderline/malignant entities.

Endometrioid adenocarcinoma is the typical histologic type of endometrial cancer, and stage being an important prognostic factor [19]. Staging depends on multiple factors such as the depth of myometrial invasion, cervical stromal involvement, adnexal involvement, serosal and parametrial invasion, vaginal cuff involvement, and others. Risk factors for adnexal involvement are particularly important in younger cancer patients where preservation of the ovary for fertility preservation is considered [20]. It is essential to weigh the risks and benefits of such procedures on the long-term outcome of the patients. Another important aspect of synchronous involvement of the endometrium and ovary is Synchronous Endometrial and Ovarian Cancer (SEOC), especially in younger women with Hereditary Non Polyposis Colon Cancer syndrome (HNPCC) [21]. It is critical to differentiate between adnexal metastasis in cases of primary endometrial carcinoma versus dual primary sites of cancer, i.e., adnexa and endometrium. This distinction is difficult but important as it may completely change the therapeutic protocol for management. IHC is often helpful in these cases, such as PAX-8, which is positive in ovarian primaries but not in ovarian metastasis [22]. Molecular genetic studies are also helpful in difficult cases. However, in the case discussed in this series, the gross finding was sufficient to make a diagnosis of adnexal metastasis. It was a result of direct and contiguous spread of endometrial carcinoma through the endometrial cavity. Thus, careful gross and histologic assessment of bilateral adnexa is crucial for accurate staging and management.

There are many known histologic variants of adenocarcinoma of the cervix, such as mucinous, intestinal, signet ring-like, villoglandular type, etc. In a case reported by Frías-Sánchez Z et al., high-grade endocervical adenocarcinoma was associated with heterologous elements like rhabdomyosarcoma [23]. The case discussed in this series is unique as its histomorphological features are high-grade and do not fit the defined histologic criteria of all known subtypes of cervical adenocarcinoma. The main diagnostic difficulties in this case were the high-grade cytologic features that led to various differentials, such as cervical metastasis of Poorly Differentiated Neoplasm from an Unknown Primary [24], high-grade sarcoma, etc. A detailed history was evaluated along with imaging, which ruled out the possibility of an unknown primary. The typical presence of mucin and occasional foci of dysplastic glands helped in confirming the final diagnosis. Monoclonal CEA (mCEA) is a potential marker that is positive in almost all cases of adenocarcinoma arising from the cervix [25], and it was strongly positive in this case.

ASCC is a very rare entity of cervical malignancy, with only a few small retrospective analyses based on small sample sizes and markedly inconsistent results [26]. They may often be missed in small biopsies where only the squamous or glandular component may be sampled, but complete excision specimens and histopathological examination make their identification easier. They must not be missed in the diagnosis, as some studies suggest that SCC and ASCC have a poorer prognosis compared to adenocarcinoma, regardless of the clinical stage of the disease [27]. They may also have an association with Human Papillomavirus (HPV), as demonstrated by Xu J and Zhang W [28]. There are also a few differences in the management of ASCC, as adjuvant chemo and radiotherapy have been shown to have no proven benefits in the very early stage of the disease [29]. AA is a rare myofibroblastic tumour that predominantly affects young women. In a study conducted by Haldar K et al., there were only seven cases over a period of eight years [30]. The common pitfall in diagnosing AA is that they may clinically simulate a vulvo-vaginal cyst or vulvar hernia [31]. Hence, a proper radiological evaluation is essential before any operative procedure is planned, as the treatment protocols for all the differentials are completely different. AA is characterised by local infiltration, and therefore, wide local excision with margin clearance is essential to prevent multiple recurrences [32]. Hence, following excision, this requires follow-up to rule out recurrence.

Many of the above cases presented with several pitfalls. The diagnosis of ovarian mucinous carcinoma with foci of benign Brenner tumour would have been missed if proper and adequate representative sections were not provided, highlighting the importance of ample sections to establish the heterogeneous nature of the tumour. In cases of synchronous involvement of the endometrium and ovary, the pitfall lies in determining the primary site of origin. This was the scenario in the third case of the series, where the primary site was determined by large tumour foci in the endometrium that were six times the size of the adnexal foci. The dilemma in the fourth case was the high-grade morphology of the tumour in the cervix, which raised the possibility of metastasis from an unknown primary. However, this pitfall was resolved by the immunohistochemical expression of mCEA, confirming the cervical origin of the adenocarcinoma. The pitfall in ASCC was the initial missed diagnosis in the cervical Pap smear study, which only highlighted the dysplastic squamous component. The histopathological examination of the specimen further delineated the concurrent dysplastic glandular component as well. Despite these several pitfalls, there were certain pointers that helped in arriving at a particular diagnosis in each of the above-mentioned cases.

CONCLUSION(S)

The case series highlights some unique cases of female genital tract pathologies with their diagnostic dilemmas and pitfalls. The case of SCT, NOS was unique in terms of its rare occurrence. The case of mucinous carcinoma with benign Brenner tumour highlighted the fact that mixed histomorphological types of ovarian neoplasms may be missed due to a lack of adequate and representative sectioning. On the other hand, high-grade adenocarcinoma, NOS was difficult to diagnose based on histomorphology alone, due to its unique histomorphological appearance. All these cases emphasised the importance of a wider and expanded insight into these areas, which may help in proper orientation and appropriate diagnosis of these lesser-known entities and lesser-explored domains of histopathology.

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