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Dual Drama: Tumours in Tandem
A Rare Case of Large Cell Neuroendocrine Carcinoma of Endometrium

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INTRODUCTION

The most frequently occurring malignancy in the female reproductive system is endometrial carcinoma in developed countries.[1]

In developing countries, cervical cancer remains the leading gynaecological cancer, **though the incidence of endometrial cancer has been increasing.** The age-standardized incidence rate (ASIR) of endometrial cancer in India is 2.3/1,00,000 women.[2,3] **This rise is largely attributed to changes in lifestyle and reproductive patterns among women.**

Neuroendocrine neoplasms primarily develop in the lungs but can occasionally be found in the GI & GU tracts. They are classified into poorly-differentiated neuroendocrine carcinoma and well-differentiated neuroendocrine tumour. Poorly-differentiated NECs are further subdivided into small cell and large cell neuroendocrine carcinomas (SCNECs and LCNECs).

A LCNEC is a **malignant tumour composed of large cells exhibiting neuroendocrine differentiation**, commonly arising in the lungs.[4] In the female reproductive system, LCNECs are most often found in the uterine cervix and ovaries, with **rare occurrences in the endometrium**.[5]

In this report, we present a case of a 70-year-old woman diagnosed with large cell neuroendocrine carcinoma (LCNEC) of the endometrium

CASE HISTORY

A 70-year-old woman, P5L3D2 came to our hospital with complaints of **postmenopausal vaginal spotting** for the past 6 months along with **abdominal pain and non-foul-smelling white vaginal discharge**. Additionally, she mentioned a **weight loss of approximately 6 kg over the past year**. She had been in her usual state of health until 6 months ago, when she first noticed abnormal vaginal spotting, despite being **postmenopausal for 20 years**. The patient used one to two pads daily for the bleeding. She denied experiencing dizziness or shortness of breath during physical activity. Following her visit to our hospital, a tumour was detected in the endometrium and endocervix. **A biopsy of the endocervical tumour revealed moderately differentiated endometrial adenocarcinoma.**

IMAGING

Ultrasonography: The uterus was bulky, measuring 78 × 47 × 39 mm, with heterogeneous echotexture and myometrial calcification. A 54 × 37 mm heterogeneous hyperechoic lesion arising from the endometrium extending to the endocervical region, abutting and thinning the myometrium. **The lesion demonstrated vascularity on color doppler with loss of the endo-myometrial junction.**

MRI: The uterus measured 8 × 4.6 × 5.5 cm with a heterogeneous mass of 6.6 × 4.6 × 5.4 cm in the fundus, body, and upper cervix. The mass appeared hyperintense on T2, isointense on T1, and shows diffusion restriction. **It infiltrated the uterine serosa, abutting the small bowel and bladder anteriorly with loss of fat planes but no infiltration**. The parametrium and fascial planes surrounding the cervix were normal. Both ovaries were atrophic.
FIGO Stage IIIA was suggested.

EXAMINATION & INVESTIGATIONS

Ht: 150 cm Wt: 53 kg BP: 130/80 mmHg PR : 80 bpm.
Per Abdomen Examination: Abdomen was soft, non-tender. No evidence distension, dilated vein, scars, sinuses, stretch marks. No palpatory mass. No evidence of fluid thrill or shifting dullness. Bowel sounds : normal.
Per Speculum Examination : Bleeding from the cervix and vaginal discharge without malodour.
Bimanual Examination : Retroverted uterus~ 10 weeks size. Bilateral adnexal region was free and non tender. Mobility was Present.
Pre-operative laboratory investigations were within normal limits.

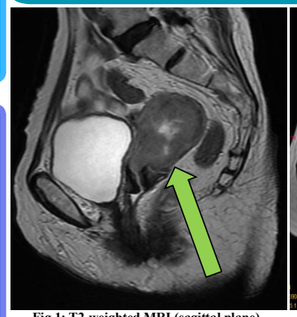

Fig 1: T2-weighted MRI (sagittal plane) demonstrating the lesion

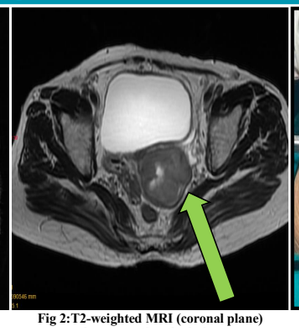

Fig 2:T2-weighted MRI (coronal plane) demonstrating the lesion

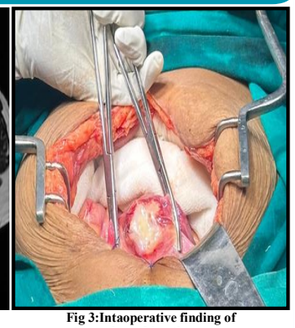

Fig 3:Intaoperative finding of tumor breaching the serosa

Sr. No.	Antibody	Endometrioid Component	Poorly Differentiated (Neuroendocrine Component)	Both Components
1	ER	Diffuse +	Negative	-
2	PR	Diffuse +	Negative	-
3	AE1/AE3	Diffuse +	Negative	-
4	CK7	Diffuse +	Negative	-
5	Vimentin	Diffuse +	Negative	-
6	Synaptophysin	Negative	Diffuse +	-
7	Chromogranin	Negative	Patchy strong +	-
8	INSM1	Focal patchy +	Diffuse +	-
9	SMA	Negative	Negative	-
10	Desmin	Negative	Negative	-
11	Myogenin	Non-contributary	Non-contributary	Non-contributary
12	MyoD1	Non-contributary	Non-contributary	Non-contributary
13	P53	Null Type	Mutation Type	-

Table 1 : Immuno-Histo Chemistry

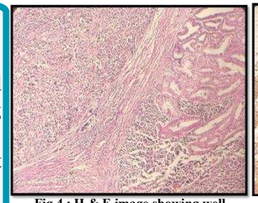

Fig 4 : H & E image showing well differentiated endometrioid carcinoma component and Large Cell Neuroendocrine Carcinoma component

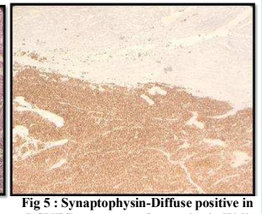

Fig 5 : Synaptophysin-Diffuse positive in LCNEC component & negative in Well differentiated Endometrioid Carcinoma component

MANAGEMENT

Surgical Procedure: Radical hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection. FIGO Stage: IIIa
Intraoperative Findings: Tumor invaded all uterine layers and breached the serosa.
Histopathology: Tumor comprised 80% LCNEC and 20% well-differentiated endometrioid adenocarcinoma (FIGO grade 2), with abrupt transitions, showing extensive areas of necrosis & focal calcification, **multiple intramural & extramural vascular emboli, lymphatic emboli & perineural invasion. The** tumor infiltrated >50% myometrial thickness and involved the lower uterine segment and cervix. Margins were <0.1 cm from the uterine walls. Ovaries, fallopian tubes, and pelvic lymph nodes were tumor-free.
Radiotherapy: The treatment plan included 50Gy /25 fractions external beam radiotherapy, along with brachytherapy 6Gy/2 fractions. Follow-up appointments were scheduled at 1.5,3, and 6 months.

DISCUSSION

Large-cell neuroendocrine carcinoma (LCNEC) is rare in the female genital tract, typically affecting the cervix or ovaries, **with endometrial involvement being uncommon**.[6] Endometrial LCNEC may occur alone or as part of composite tumors, often with endometrioid carcinoma. Pocrnich et al. reported 25 cases of endometrial neuroendocrine carcinoma, including 22 with LCNEC components and three with small cell neuroendocrine carcinoma. Rivera described LCNEC coexisting with low-grade endometrial stromal sarcoma. Most patients present with postmenopausal or aberrant bleeding. Tumors range from 0.8 to 12 cm, with a median of 6 cm; **in the present case, the tumor measured 4.5 x 6 cm**. Neuroendocrine morphology typically shows insular and diffuse growth patterns, with markers like CD56, synaptophysin, or chromogranin expressed. High Ki-67 proliferation index (>80%), vascular invasion, necrosis, and mitotic activity are common. [7] [8] **In our case, the tumor showed diffuse and strong positivity for synaptophysin, chromogranin A.**
Genetically, endometrial LCNEC and endometrioid carcinoma share mutations in PTEN, PIK3CA, and FGFR3, suggesting a common origin.[9] **Treatment, often surgery followed by chemotherapy, lacks standardization.**[10]Etoposide and platinum-based regimens are preferred.[11] Imaging features resemble other aggressive carcinomas, and staging remains critical for prognosis. Pure neuroendocrine carcinomas show worse outcomes than mixed types, with aggressiveness outweighing FIGO staging in prognostic significance.

CONCLUSION

Large-cell neuroendocrine tumor (LCNEC) of the endometrium is a challenging diagnosis, often confused with poorly differentiated carcinomas. Identifying the primary organ can be difficult due to metastatic sites, and histological confirmation relies on selecting appropriate neuroendocrine biomarkers. There are no specific diagnostic criteria for LCNEC of the endometrium, so guidelines are typically adapted from the WHO classification for lung tumors. Additionally, no clear recommendations exist regarding the preferred type of tissue sample for diagnosis. Once diagnosed, chemotherapy or radiotherapy options must be carefully considered, **though treatment guidance is limited due to the rarity of the disease**. **Accurate diagnosis is critical, as LCNEC of the endometrium is associated with rapid progression and a poor prognosis.**

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