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Case Study

PRIMARY NEUROENDOCRINE TUMOR OF THE ENDOMETRIUM, A RARE TUMOR: CASE SERIES

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ABSTRACT

Objective: Endometrial NET is a rare disease with a poor prognosis. Due to its rarity, there are no evidence-based standards or international guidelines for the diagnosis and treatment of endometrial NETs.

Methods: In this study, we present our experience with four cases of NETs of the endometrium to describe these rare tumors' clinical characteristics and behaviour. The clinicopathological characteristics, treatment and prognosis, were analysed.

Results: Most common age group for presentation was 50 to 70 y. Irregular vaginal bleeding was most common symptom at presentation. Three patients underwent surgery followed by adjuvant chemoradiation while one patient with metastatic disease underwent chemotherapy. Overall prognosis was poor with two patients died 12 mo and 24 mo, respectively. One patient was lost to follow-up after 39 mo and one patient was disease free till last follow-up.

Conclusion: Given the aggressive nature of the disease, patients should be carefully observed and followed up regularly. More studies with a higher number of cases are required to establish a standard therapeutic protocol.

Keywords: Neuroendocrine tumor, Endometrial NETs, Small cell neuroendocrine carcinoma

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INTRODUCTION

Endometrial NET is a rare disease with a poor prognosis. Given its extremely low incidence, the most effective methods for treating endometrial NETs and the most important factors for determining prognosis remain unknown, making clinical management difficult [1, 2]. In addition, due to its rarity, there are no evidence-based standards or international guidelines for the diagnosis and treatment of endometrial NETs. In this study, we present our experience with 4 cases of NEC arising in the endometrium to describe the clinical characteristics, histopathologic and immunophenotypic features, and behaviour of these rare tumours. This study is carried out at Adyar Cancer Institute Chennai; consents were taken, during admission of patients.

CASE 1

A 60-year-old female presented with vaginal bleeding for the past 1 mo. Ultrasound of the abdomen and pelvis was done which was suggestive of a hypoechoic mass of size 6 x 5 cm seen in the endometrial cavity. A contrast-enhanced CT scan of the abdomen and pelvis was done, which was suggestive of a heterogeneously enhancing mass lesion of size 6x6 cm seen in the endometrial cavity with loss of endomyometrial junction. An endometrial biopsy was done, which was suggestive of poorly differentiated carcinoma. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection. Histopathological examination showed endometrium infiltrated with tumor with features of adenocarcinoma mixed with poorly differentiated tumor. The tumor also involved one ovary. Ten lymph nodes dissected were free of tumor. Immunohistochemistry was done, which confirmed it as a large cell neuroendocrine tumor. Tumor cells stained positive for synaptophysin, chromogranin, CD56, P63, and Neuron-specific enolase. The patient was diagnosed with large cell neuroendocrine carcinoma endometrium admixed with adenocarcinoma FIGO stage IIIA.

She received adjuvant chemoradiation 50Gy/25# with 200cGY/# (5 d a week) with concurrent cisplatin 50 mg/m2 at week 1 and week 4 followed by weekly Intravaginal brachytherapy 7GyX 2#.

She received carboplatin (400 mg) and etoposide (150 mg) adjuvant chemotherapy for 4 cycles with three weekly intervals.

After 5 mo of completing treatment, she had a recurrence with left supraclavicular lymphadenopathy and liver metastasis. Due to poor general condition and altered liver function profile, she was on supportive care. She died after 7 mo of recurrence.

CASE 2

A 79-year-old female presented with a complaint of vaginal bleeding for 4 mo. Ultrasound of the abdomen and pelvis was done which showed an increase in endometrial thickness to 16 mm. She underwent upfront staging laparotomy. Histopathological examination revealed large cell neuroendocrine carcinoma of endometrium infiltrating serosa, FIGO stage IB. Immunohistochemistry was done. Tumor cells stained positive for synaptophysin, CD56, P63, and Neuron-specific enolase.

She received adjuvant RT 50 Gy/25# with 200cGY/# (5 d a week) with concurrent cisplatin 50 mg/m2 at week 1 and week 4 followed by weekly intravaginal brachytherapy 7GyX 2#.

She received adjuvant chemotherapy with carboplatin (240 mg) and etoposide (100 mg) for 4 cycles. She was on follow-up till 39 mo after treatment, then she lost to follow-up.

CASE 3

A 53-year-old female presented with vaginal bleeding for 6 mo. On per vaginal examination, endocervical growth was palpable. Contrast-enhanced CT scan of the abdomen and pelvis revealed heterogeneously enhancing mass lesions in the endometrial cavity involving the cervix with multiple liver metastases. Histopathological examination after endocervical curettage showed small cell neuroendocrine carcinoma. Immunohistochemistry was done. Tumor cells stained positive for synaptophysin, chromogranin, and CD56; the Patient received 6 cycles of palliative chemotherapy with cisplatin (120 mg) and etoposide (100 mg). Complete response was seen after 4 w of completion of chemotherapy. The patient died after 24 mo of completion of treatment.

CASE 4

A 59 y old female presented with complaints of vaginal bleeding for 3 mo. USG abdomen showed an increase in endometrial thickness to 18 mm. An endometrial biopsy was done which was suggestive of poorly differentiated carcinoma.

She underwent a total abdominal hysterectomy with salpingo-oophorectomy and pelvic lymph node dissection. Histopathological examination confirmed large cell neuroendocrine carcinoma of endometrium involving cervical stroma. It was staged as FIGO stage II. Immunohistochemistry was done. Tumor cells stained positive for synaptophysin, chromogranin, CD56, and P63. All margins were free and the twelve lymph nodes dissected were free of tumor.

She also received adjuvant RT 50Gy/25# with 200cGY/# (5 d a week) with concurrent cisplatin 50 mg/m2 at week 1 and week 4 followed by weekly intravaginal brachytherapy 7GyX 2#.

The patient received four cycles of adjuvant chemotherapy with carboplatin (420 mg) and etoposide (160 mg). The patient was disease-free for 48 mo and then she lost to follow up. Table 1, Showing summary of patients of each case with age, presenting symptoms, histology, stage treatment and follow-up of patients of all 4 above cases.

Table 1: Shows summary of patients of each case with age, presenting symptoms, histology, stage treatment and follow-up of patients

Case No.	Pt age (y)	Presenting symptom	Histology	% NE component	FIGO stage	Surgical treatment	Adjuvant therapy	Follow Up
1	60	Vaginal bleeding	LCNEC admixed with adenocarcinoma	60	IIIA	Hysterectomy BSO	Chemo RT followed by chemo	Recurrence after 5 mo, died after 12 mo
2	79	Vaginal bleeding	LCNEC	100	IB	Hysterectomy BSO	Chemo RT followed by Chemo	Disease-free till 39 mo, then LFU
3	53	Vaginal bleeding	SCNEC	80	IV	NO	Chemotherapy	Died after 24 mo
4	59	Vaginal bleeding	LCNEC	90	II	Hysterectomy BSO, LND	Chemo RT followed by chemo	Disease-free till 48 mo

Table 1 shows summary of patients of each case with age, presenting symptoms, histology, and stage treatment and follow-up of patients.

DISCUSSION

In our series, endometrial NEC presented in patients with an age range of 50 to 80 y with predominance in the sixth and seventh decades. While vaginal bleeding was the most frequent presentation, which has not previously been reported in endometrial NEC. The tumors in this series tended to be large, with a median size of 6 cm. We found that the most common form of NEC in this study was the large cell type, detected in 3 out of 4 cases. This finding was somewhat unexpected, given the predominance of reports of endometrial SCNEC over LCNEC in the published literature [3, 4]. LCNEC is most likely under-reported due to its tendency to be associated with other histotypes of endometrial cancer, which can make its recognition somewhat difficult. This common association of NEC with other histotypes of endometrial cancer has been reported by other investigators [5-7].

Regarding the immunohistochemical profile of our cases, synaptophysin was the most commonly expressed neuroendocrine marker. This finding is in concordance with the results of others where both synaptophysin and chromogranin IHC were obtained; synaptophysin was slightly more sensitive than chromogranin. SCNEC can be designated as such as long morphological features resembling small cell carcinoma of the lung are displayed (i. e. the expression of NE markers is not required). In contrast, the diagnosis of LCNEC requires the expression of at least one NE marker, in addition to the presence of the histological features associated with NE differentiation (i. e., nesting, trabecular, or ribbon-like formations) [8-10].

Surgery should be the main treatment strategy for all patients with localized disease. In addition, our results suggest that early-stage postoperative treatment with chemoradiation and adjuvant chemotherapy may improve OS and DFS. For stage IV disease systemic therapy may improve PFS.

Based on the treatment plan for pulmonary NETs, platinum-based CT is often used for adjuvant treatment in patients with NETs of the endometrium. Currently, the most common regimen is EP (cisplatin or Carboplatin+etoposide) followed by Paclitaxel and Carboplatin. Some researchers have suggested that chemotherapy is also required in the early stage, given the aggressive nature of NETs of the endometrium. NETs of the endometrium often present with disseminated disease, indicating that radical surgery with chemotherapy would be appropriate for both early and advanced cases. Combined treatment with CT and somatostatin-like octreotide has also been reported in patients with NETs of the endometrium. The inhibitory effect of somatostatin analogs on tumor growth has been demonstrated [11].

CONCLUSION

Due to the aggressive nature of neuroendocrine tumors of endometrium, patients should be kept on careful observation with regular follow-up. More studies with a higher number of cases are required to establish a standard therapeutic protocol.

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AUTHORS CONTRIBUTIONS

This work was carried out in collaboration with authors. Author Dr Prateek Tiwari and Dr Shreena Patidar were the principal investigators of the study and were involved in the design, clinical treatment protocol, conduct, and analysis of the study and author Dr V Pal contributed in applying Histological and Anatomical concepts, report wrote, reviewed and edited the manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

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