Primary large cell neuroendocrine carcinoma arising from the uterine corpus

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SUMMARY

Large cell neuroendocrine carcinoma (LCNEC) of the endometrium is a rare high-grade malignancy with an aggressive course, the definitive preoperative diagnosis is difficult due to non-characteristic radiological and pathological findings. We report a case of pure endometrial LCNEC in an 82-year-old woman who presented with an ill-defined solid tumour originating from the endometrium and extending through the myometrium with ovarian, fallopian tube and omentum metastases. The tumour was highly pleomorphic with a high nuclear/cytoplasmic ratio and large nuclei, highly cellular with solid sheets of large cells and interspersed areas of extensive necrosis. Tumour cells expressed CD56, synaptophysin, chromogranin A, p53 and p16. Ki67 was 80%. The disease progressed and the patient died two weeks after surgery. To facilitate differential diagnosis in high-grade undifferentiated endometrial tumours lacking typical morphological features of neuroendocrine tumours, LNEC should be considered and neuroendocrine markers should be added to the immunohistochemical panel.

INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) of the uterine corpus is a rare high-grade entity of with an aggressive progression. Neuroendocrine carcinoma (NEC) arising from the endometrium make up less than 1% of all uterine endometrial carcinomas with early hematogenous/lymphogenous metastasis and poor prognosis. Uterine LCNEC is particularly rare with limited data to case reports.[1]

CASE PRESENTATION

An 82-year-old woman presented with abdominal pain and ascites. After radiological imaging with detection of heterogeneous mass and ascites, she underwent surgery (Figure 1). The uterine corpus was completely filled with an ill-defined, white, solid tumour arising from the endometrium, infiltrating the wall and extending through the myometrium. The surfaces of the ovaries and fallopian tubes were covered with small white tumour nodules. The surface of the omentum majus was covered with small white nodules and the sectioned surface was covered with numerous white solid tumour nodules. Microscopically, the tumour was highly cellular with solid sheets of large cells and interspersed areas of extensive necrosis. The tumour cells were highly pleomorphic with relatively abundant eosinophilic cytoplasm, high nuclear/cytoplasmic ratio and large nuclei (Figure 2). There were numerous abnormal mitotic figures and cell apoptosis. The mitotic count of tumour cells was >10 per 2 mm^2. Immunohistochemically, tumour cells showed expression of p53 and p16. The proliferation index with Ki67 was 80%. Vimentin and CK8/18 were only focally positive. There was no staining for panCK, CK7, ER, PR, PAX8, WT1 and CD45. The surfaces of the ovaries and fallopian tubes were infiltrated by the tumour. Due to unclear differentiation and marked nuclear atypia, staining with neuroendocrine markers was performed. The tumor cells were strongly positive for CD56, synaptophysin and chromogranin. The diagnosis of large cell neuroendocrine carcinoma of the endometrium was established. According to the American Joint Committee on Cancer (AJCC) staging system and the International Federation of Obstetrics and Gynaecology (FIGO), the tumour stage was pT3a N2a M1, FIGO IIIA (tumour involving serosa or adnexa with macrometastases in para-aortic lymph nodes). The patient died two weeks after surgery.

DISCUSSION

NECs are categorised into well or poorly differentiated grades and further subdivided into small cell neuroendocrine carcinoma (SCNEC) or LCNEC. These types of tumours are mainly found in the lungs and less commonly in the gastrointestinal or genitourinary tract. The incidence of NEC and LCNEC in the female genital tract is low, with the uterine cervix being the most common site. LCNEC of the endometrium is extremely uncommon.[2]

No diagnostic criteria have been proposed for endometrial neuroendocrine carcinoma. According to the WHO classification for lung tumours, LCNECs are diagnosed based on large cell size exhibiting low nuclear/cytoplasmic ratio, >10 mitotic figures in 2 mm^2, and by showing both neuroendocrine histology and at least one immunohistochemically positive neuroendocrine marker (chromogranin, synaptophysin or CD56).[3] Our case fulfils these criteria.

Little is known about the molecular characteristics of endometrial NECs and how they differ from lung NECs and more common endometrial cancer histotypes. Howitt et al.

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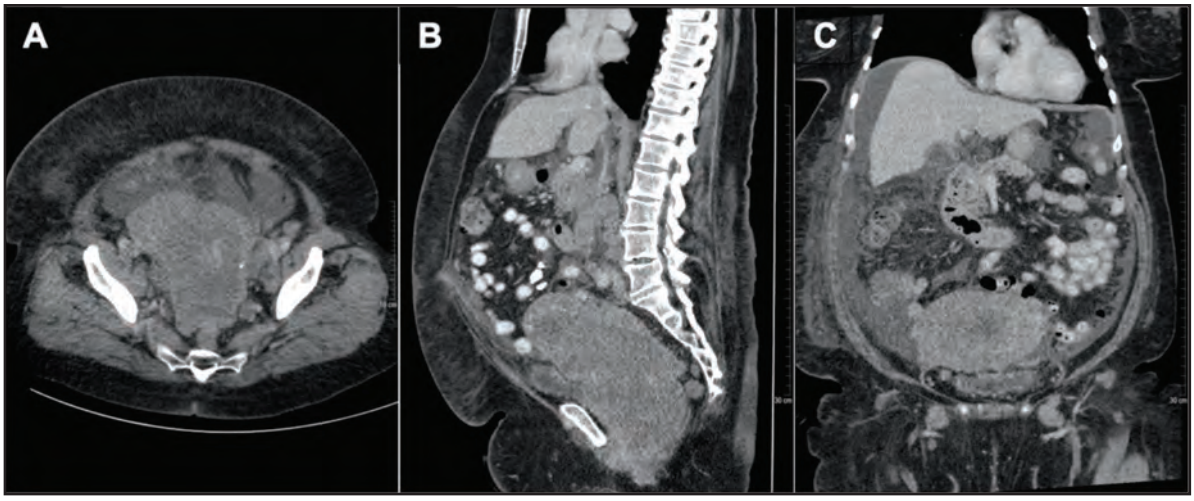

Fig. 1: Preoperative findings on computed tomography. (A) Axial reconstruction shows the giant mass lesion in the uterus with loss of normal architecture. (B) Sagittal reconstruction demonstrates the mass lesion with paraaortic lymph node metastasis and (C) coronal reconstruction shows the mass lesion in the uterus with bilateral inguinal lymph node metastasis and diffuse ascites

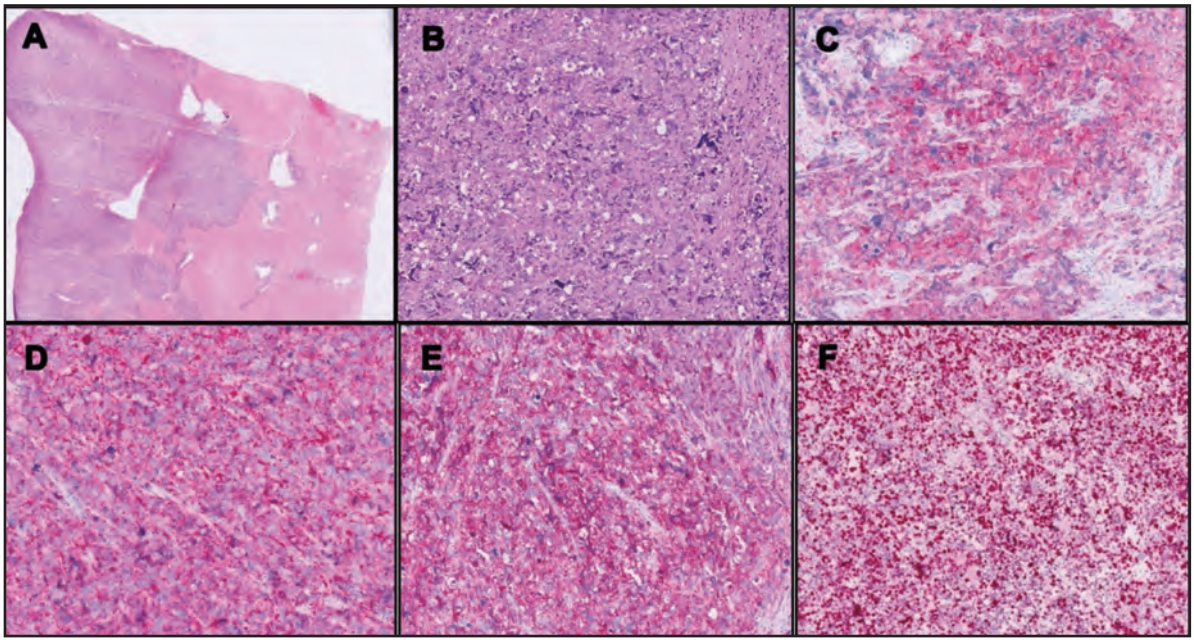

Fig. 2: Histology and immunohistochemistry. (A) Tumour with solid sheets of large cells and areas of extensive necrosis arising from the endometrium and extending through the myometrium. (B) The tumour cells are highly pleomorphic with a high nuclear/cytoplasmic ratio, large nucleoli and numerous mitotic figures and cell apoptosis. Immunohistochemically the tumour cells showed expression of (C) chromogranin A, (D) synaptophysin and (E) CD56. (F) The proliferation index with Ki67 was 80%

conducted a study to investigate the molecular changes in a series of 14 cases of pure NEC (including LCNEC and SCNEC) and mixed NEC with LCNEC or SCNEC components, along with endometrioid adenocarcinoma or carcinosarcoma, using a targeted next-generation sequencing panel known as 'Oncopanel'. The molecular analysis of the tumours identified four significant groups via the Cancer Genome Atlas: POLE mutated/ultramutated, microsatellite instability/hypermutated, TP53 mutated/high copy number or no specific molecular profile. It was discovered that half of the cases were either ultramutated or hypermutated. The different histological components of mixed carcinomas were sequenced separately. The molecular alterations between the two components were nearly identical, with the non-NEC component having a slightly increased tumour mutation burden. However, only carcinomas with pure SCNEC morphology exhibited a molecular profile that would be anticipated in typical pulmonary SCNEC (RB1 deletion and TP53 mutations). It has been recommended that immune checkpoint inhibition could be a viable treatment approach for microsatellite instability NEC. It is recommended that all endometrial NEC be tested for mismatch repair abnormalities through molecular or mismatch repair protein immunohistochemistry.[4] In our case, we performed

immunohistochemistry for MLH1, PMS2, MSH2, and MSH6 mismatch repair genes. This showed no loss of these markers, so no microsatelite deficiency was found by this immunohistochemistry.

The staging of endometrial cancer currently utilizes the FIGO system. The AJCC staging system aligns its tumour (T), lymph node (N) and metastasis (M) categories with the FIGO system. The NCCN guidelines for the management of uterine neoplasms use the 2018 FIGO staging criteria.[5] However, the 2023 update considers histological and molecular characteristics to generate sub-stages that are more accurately linked to prognosis and treatment options:

Stage I POLE mutated: POLE mutated endometrial cancer confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type.

Stage II p53 abnormal: p53 abnormal endometrial cancer confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type.[6] Management guidelines are expected to be updated soon.

However, there is limited data available to guide the management of uterine LCNEC, which is typically treated similarly to LNEC of the cervix. A multimodal approach involving surgery, chemotherapy, and radiotherapy is commonly used. LNEC of the uterus are managed initially with cytoreductive surgery. The standard surgical procedures consist of total hysterectomy and bilateral salpingo-oophorectomy. In cases with distant metastasis, lymph node dissection and omentectomy are also performed. Following surgery, there is presently no agreement on the optimal therapy. In the majority of cases, adjuvant chemotherapy comprising of platinum and etoposide, along with radiotherapy, are administered or planned. When LNEC is diagnosed on a preoperative curettage or endometrial biopsy, neoadjuvant therapy may be considered.[7]

CONCLUSION

LNEC of the endometrium is very rare, highly aggressive and difficult to diagnose. Prognosis is poor due to rapid progression and the absence of established therapy. The imaging findings lack specificity and no pathological criteria have been proposed. To facilitate the differential diagnosis of endometrial malignancies, especially in cases with unusual morphology and receptor negativity, it is necessary to assess neuroendocrine differentiation and perform appropriate immunohistochemical stains. However, in some high-grade undifferentiated tumours, as in our case, the morphological features are not typical of a neuroendocrine tumour and yet LNEC should be kept in mind and the neuroendocrine immunohistochemical markers should be added to the immunohistochemistry panel. Additional research is required to develop an effective therapy protocol.

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