Case Report

Primary Large Cell Neuroendocrine Carcinoma of the Uterus: A Case Report and Literature Review

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Large cell neuroendocrine carcinomas (LCNEC) of the uterus is a rare and very aggressive neoplasm. Herein we report a case of large cell neuroendocrine carcinoma arising from the uterus with extensive carcinomatosis. The patient was a 51-year-old African-American female who presented with increasing worsening abdominal distension and abdominal pain over a period of one month. A computed tomography (CT) imaging study disclosed a 20 x 15 x 10 cm heterogeneous uterine mass with significant ascites and omental thickening. The patient subsequently underwent a total hysterectomy with bilateral salpingo-oophorectomy and omental resection. Histological examination showed a large cell neuroendocrine carcinoma with extensive necrosis and numerous abnormal mitosis. No associated surface epithelial component was identified. Immunohistochemical staining pattern was consistent with the neuroendocrine origin. The patient's condition rapidly deteriorated postoperatively, and she died one month later due to multi-organ complications. In light of the rarity of LNEC arising from the uterus, a comprehensive review of the literature is discussed.

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CASE REPORT

The patient was a 51-year-old African-American postmenopausal woman, gravida 4, para 4, who presented with increasing worsening abdominal pain and distension for one month. She denied vaginal bleeding, vaginal discharge, fever, chills, shortness of breath, or chest pain. Physical examination revealed a firm mass in the lower abdomen with a size equivalent to a small football. A computed tomography (CT) demonstrated a 20 x 15 x 10 cm heterogeneous mass in the location of the uterus, associated with significant ascites with omental thickening. Also noted was a small mass in the right adrenal gland, scattered enlarged retroperitoneal lymph nodes as well as bilateral inguinal lymph nodes, concerning for additional metastatic disease. Preoperative serum level of CA125 was elevated to 200 unit/ ml (normal range 0-21 unit/ml). Serum calcium level was within normal range. The patient subsequently had a total hysterectomy, bilateral salpingo-oophorectomy, resection of the omentum, and a drainage of 6 liters of ascites. Intraoperatively, the uterus measured approximately 20 x 15 x 10 cm and was relatively immobile. Both ovaries were adhered to the mass on each side. The right ovary was slightly enlarged, measuring about 5 cm in greatest dimension and partially cystic. Intraoperative assessment was notable for the observation of extensive extrauterine disease involving most peritoneal surfaces. Omental fat was replaced by a soft tumor that measured about 30 cm in diameter. Postoperatively, the patient's clinical course was complicated by sepsis. She was treated with antibiotics, drainage of malignant ascites, and respiratory support. The patient's condition deteriorated after surgery and expired one month later due to multiorgan failure secondary to her malignancy. No chemotherapy was administrated to the patient.

PATHOLOGY

On gross pathologic exam, the uterus weighed 1.4 kg and measured 20 x 15 x 10 cm. The specimen was remarkable for multinodular masses. The tumor extended to the cervix, fallopian tube and ovary, metastasize to the omentum and skin on the abdomen. The patient was staged as pT3NxMx. Microscopically, the tumor was highly cellular with admixed areas of extensive necrosis (**Figure 1A**). The neoplastic cells had relatively abundant cytoplasm, a high nuclear/cytoplasmic ratio and finely dispersed chromatin. In solid areas of the tumor, there were numerous abnormal mitotic figures (**Figure 1B**) and individual cell apoptosis. In some poorly preserved sections, crush artifacts are present. No associated malignant epithelial component was identified. Immunohistochemistry of the tumor showed the neoplastic cells to express only CD56 and vimentin, with only patchy

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expression for synaptophysin (**Figures 1C** and **1D**). The tumor cells were negative for chromogranin, smooth muscle actin, desmin, CD-10, ER, PR, CK7, CK20, pan-cytokeratin, CD-45, CD-117, and TTF-1 (**Table 1**). Taken together, the above morphological and immunohistochemical features were compatible with a large cell neuroendocrine carcinoma.

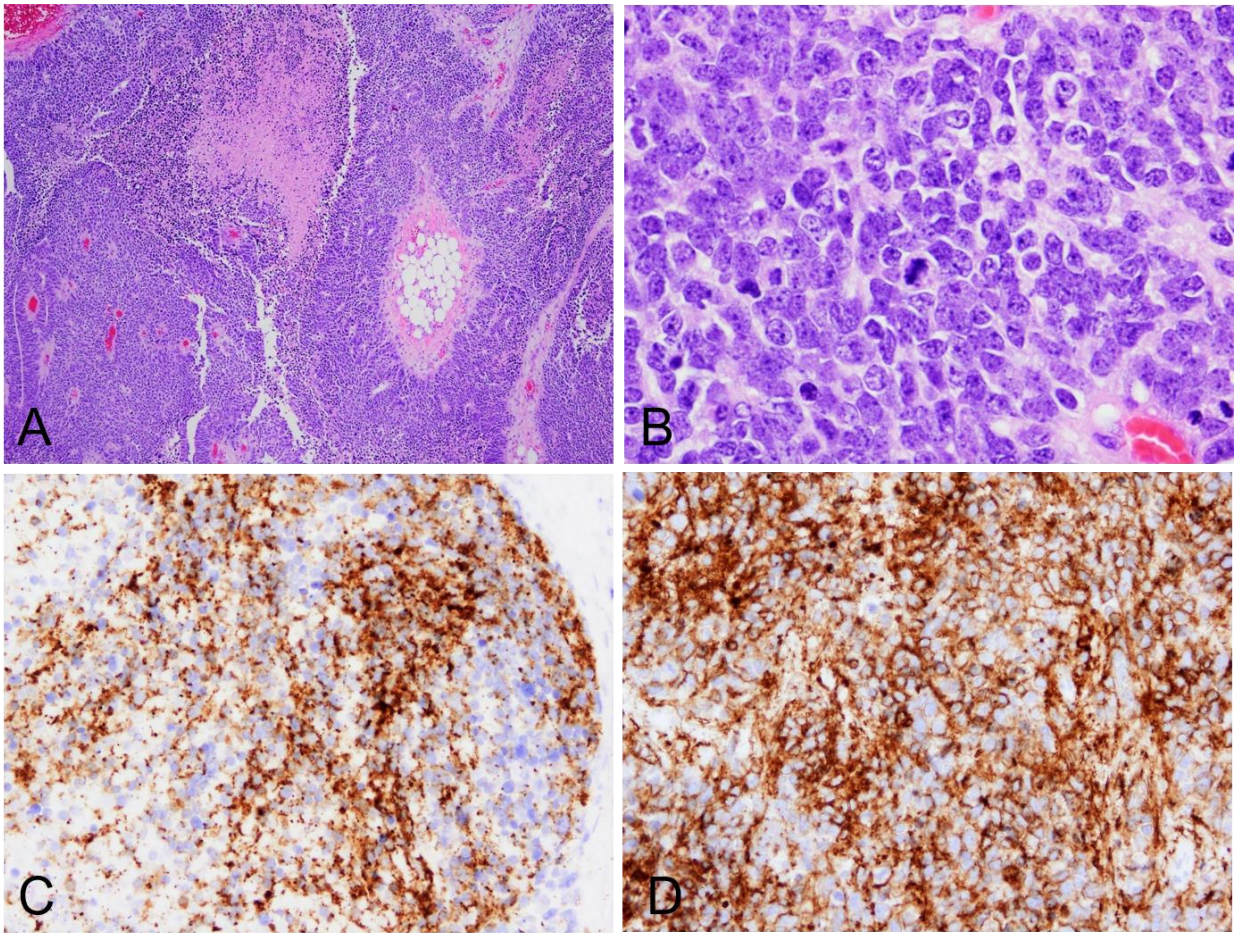

Figure 1. Histological and immunohistochemical examination of the tumor. **A** and **B.** H&E examination at low- and high- power views at 4x and 20x, respectively; **C.** Immunoreactivity of synaptophysin; **D.** Immunoreactivity of CD56.

Table 1. Primary antibodies used in this study with corresponding results.

Markers	Function	Results
pan-cytokeratin	Epithelial marker	Negative
CK7	Epithelial marker	Negative
CK20	Epithelial marker	Negative
ER	Hormone receptor	Negative
PR	Hormone receptor	Negative
TTF-1	Pulmonary origin marker	Negative
Synaptophysin	Neuroendocrine marker	Patchy positive
Chromogranin	Neuroendocrine marker	Negative
CD56	Neuroendocrine marker	Positive
Vimentin	Mesenchymal marker	Positive
Smooth muscle actin	Smooth muscle marker	Negative
Desmin	Smooth muscle marker	Negative
CD10	Endometrial stromal marker	Negative
CD45	Hematologic marker	Negative
CD117	GIST tumor marker	Negative

DISCUSSION

The 2014 WHO defines large cell neuroendocrine carcinoma (LCNEC) as undifferentiated large cells that lack cytological and architectural features of small cell neuroendocrine carcinoma (SCNEC) and glandular or squamous differentiation. There are many similar molecular features and immunostaining profiles between LCNEC and SCNEC, including mutations in the TP53 and RB1 genes, concomitant decreased TP53 and RB1 protein expressions, and high expression of p16 and Bcl-2. Generally, overexpression of Bcl-2 protein is less prevalent in LCNEC comparing to SCNEC, and a subset of LCNEC can harbor other mutations which are not seen in SCNEC such as KRAS and STK11.[1]

The human papilloma virus (HPV) infection has been frequently reported in the LCNEC of the female genital tract, especially those arising from the cervix. A systemic review and meta-analysis of nine studies of 45 LCNEC and 32 studies with 403 SCNEC showed 88% LCNECs and 85% SCNECs are associated with HPV infection.[2] Further specific HPV genotyping work showed cervical LCNEC and SCNEC have different prevalence of HPV-16 and HPV-18. Grayson et al. reported that HPV-16 was detected by NISH and/or PCR in 7 out of 12 cervical LCNECs, and HPV-18 was detected in 2 out of 12 cervical SCNECs.[3,4] Stoler et al. showed that HPV-18 messenger RNA was detected in 14 of 18 cervical SCNECs.[5,6] Integration of HPV-16 and to a lesser extent HPV-18 may be associated with the occurrence of LCNEC whereas HPV-18 may be closely correlated with the occurrence of SCNEC. It IS still unknown how the HPV infection contributes to the tumorigenesis in these highly aggressive neuroendocrine carcinomas.

LCNEC of the uterus is extremely rare. To our best knowledge, approximately 20 cases have been reported in English literatures so far. Patients with LCNEC of the uterus usually are at an advanced stage when the they present with symptoms. Rarely, patients may present with paraneoplastic symptoms due to ectopic hormone production. The diagnoses can be made by endometrium biopsy. However, the limited amount of tissue obtained from the biopsy may yield a diagnosis of poorly differentiated adenocarcinoma, or undifferentiated carcinoma. The neuroendocrine component is sometimes recognized following hysterectomy. Histologically, tumor exhibits a high-grade phenotype with scant stroma, ulceration, extensive tumor necrosis, with a trabecular, organoid, palisading or rosette-like growth pattern. In the majority of cases, the neoplastic cells show abundant cytoplasm with a granular eosinophilic or basophilic appearance, large nuclei, small but frequent nucleoli and mitotic rates at more than 10 per 10 high power fields (HPF).

LCNEC of the uterus is often mixed with endometrioid adenocarcinoma, serous adenocarcinoma and sarcomatoid tumor.[7,8,9] It also can occur in combination with SCNEC in the cervix and uterus, representing different morphologic expressions of the same neoplasm that is in keeping with the hypothesis of a common cell of origin. In this case, the tumor is composed purely large neuroendocrine carcinoma cells without associated malignant epithelial component. There are some studies regarding where the malignant neuroendocrine cells originate from. Yasuoka et al. reported a case of mixed LCNEC and mucinous adenocarcinoma in the cervix. They found that the two carcinomatous components demonstrated evidence of monoclonality using X-chromosome clonality assay, suggesting that the neuroendocrine component may have arisen from the invasive mucinous carcinoma.[10] Consistently, a recent study on 28 cases of squamous or adenocarcinomas with coexisting neuroendocrine differentiation components showed identical loss of heterozygosity (LOH) at 5 polymorphic microsatellite markers (D3S1300, D9S171, D11S914, D13S319, and TP53) and X-chromosome inactivation between the neuroendocrine and squamous or adenocarcinoma components. These concordant genetic alterations support a common clonal origin for neuroendocrine carcinomas, supporting the hypothesis of divergent differentiation in the tumorigenesis of this aggressive neoplasm.[11]

Like neuroendocrine tumors, LCNEC of the uterus is immunopositive for neuroendocrine markers including synaptophysin, chromogranin and CD56. TTF-1 is commonly positive, expressing in 50% of LCNECs. P16, a surrogate marker for the presence of high-risk of HPV infection, is almost always positive in cervical neuroendocrine carcinomas.[12] LCNEC of the uterus also tends to be PAX-8 positive. It can show aberrant mismatch-repair protein (MLH1/PMS2; MSH2/MSH6, MSH6) expression by immunohistochemistry in multiple studies.[7,13,14] Mhawech-Fauceglia et al. reported that MSI-H was found in all nine cases of LCNECs of endometrium and ovary for the 17 microsatellites markers and at variable frequency, indicating MSI is strongly involved in the development of LCNEC of the uterus and ovary. Additionally, the immunohistochemical expression of MLH1, MSH6, MSH2, PMS2 and MSI status correlates with their molecular alterations. This recognition of microsatellite their instability in LCNEC of female genital tract could explain resistance to chemotherapy and radiation therapy.[8,13,14]

The differential diagnoses for LCNEC of the uterus include undifferentiated carcinoma and endometrial stromal sarcoma. Undifferentiated carcinoma is characterized by non-cohesive small to large sized cells without glandular formation. Moreover, the undifferentiated carcinoma also has a focal expression of neuroendocrine markers in 41% undifferentiated carcinoma, usually less than 30% of the tumor. Endometrial stromal tumor typically has a spiral arteriole-like vascular component and lack brisk mitosis. These neoplastic cells show CD10 positivity but are negative for any neuroendocrine markers.

The prognosis of LCNEC of the uterus is very poor. Most patients die during the follow-up period. The survival rate is 46% at 1 year and 11% at 5 years after the diagnosis.[15] In the present case, the patient died one month after debulking

surgery. This rapidly progressive clinical course has been well documented.[16,17] The factors determining the prognosis of LCNEC of the uterus are not well documented due to limited cases. Staging probably is the most important prognostic factor as seen in SCNEC of the uterus. One study showed that a polypoid feature of the tumor[18] and CD10 positivity[19] may be associated with a better prognosis, but more studies are warranted for a confirmative conclusion.

Because of the rarity of this entity, no established guideline is given for the treatment of patients with LCNEC of the cervix and uterus. Most patients undergo primary surgery to obtain the definitive tissue diagnosis and staging and a tumor debulking operation. Various combinations of chemotherapy had been chosen, including cisplatin and cyclophosphamide followed by etoposide and cisplatin; or paclitaxel and carboplatin protocols. Patients with stage I and/or with platinum-bases therapy may have a more favorable prognosis, but stage III or IV cases with standard surgery that was followed by adjuvant platinum-based chemotherapy had the prognosis similar to that of the early stage.[20] The efficient treatment of platinum-based chemotherapy and paclitaxel–carboplatin-based chemotherapy has also been reported by others to improve survival. The effects of radiation therapy have not been proven yet, but it has been proposed that the combination of chemotherapy with aggressive surgery and adjuvant radiation therapy should be considered as a possible treatment strategy.

In conclusion, here we report a case of rare case of LCNEC of the uterus with extensive pelvic involvement. LCNEC of the uterus is a rare entity with an aggressive clinical course. It often coexists with epithelial malignancies and small cell neuroendocrine carcinoma. HPV infection is associated with the development of the LCNEC of the female genital tract, primarily in the cervix. Diagnosis of LCNEC sometimes can be challenging since it may lose typical epithelial markers and shows ambiguous neuroendocrine marker immunostaining. The current management is mainly debulking surgery followed by platinum-based chemotherapy. The recent recognition of the MSI status in the pathological changes of LCNEC may help understand the fundamental mechanisms underlying the resistance to treatment in this rare and aggressive entity.

CONFLICT OF INTEREST DISCLOSURE

The authors have no conflict of interest to disclosure.

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