Large Cell Neuroendocrine Carcinoma of the Ovary and Its Skin Metastases

A Case Report and Review of the Literature

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ABSTRACT

Large cell neuroendocrine carcinoma in the gynaecological organs affects the uterine cervix and ovary. Large cell neuroendocrine carcinoma of the ovary is extremely rare, and prognosis is quite poor even when diagnosed at an early stage. These tumours respond poorly to standard chemotherapy regimens. The clinical observation of skin metastasis in patients with epithelial ovarian cancer is relatively uncommon, occurring in only 3.5% of patients. These lesions are observed mostly in skin of the abdominal wall adjacent to the primary ovarian tumours. Metastatic skin lesions on extremities are much more rare; it is reported that only 12% of epithelial ovarian carcinoma skin metastases occur on the limbs. Skin metastasis due to large cell neuroendocrine carcinoma of the ovary has not been previously reported. We report the case of a large cell neuroendocrine tumour of the ovary with skin metastases on extremities appearing two months after surgery in a 68-year old woman.

Keywords: Large cell, neuroendocrine carcinoma, ovary, skin metastasis

El Carcinoma Neuroendocrino de Células Grandes de Ovario y Sus Metástasis Cutáneas: Reporte de un Caso y Revisión de la Literatura

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RESUMEN

El carcinoma neuroendocrino de células grandes en los órganos ginecológicos afecta el cuello del útero y el ovario. El carcinoma neuroendocrino de células grandes del ovario es extremadamente raro, y el pronóstico es muy pobre, incluso cuando se diagnostica en una etapa temprana. Estos tumores responden pobremente a los regímenes de quimioterapia estándar. La observación clínica de metástasis de la piel en pacientes con cáncer epitelial de ovario es relativamente poco frecuente, ocurriendo sólo en el 3.5% de los pacientes. Estas lesiones se observan principalmente en la piel de la pared abdominal adyacente a los tumores ováricos primarios. Las lesiones cutáneas metastásicas en las extremidades son mucho más raras. Se reporta que sólo el 12% de las metástasis cutáneas de carcinoma ovárico epitelial ocurre en las extremidades. La metástasis cutánea a causa del carcinoma neuroendocrino ovárico de células grandes no ha sido reportada con anterioridad. Reportamos el caso de una mujeres de 68 años con tumor neuroendocrino ovárico de células grandes, que presentó metástasis cutáneas en las extremidades dos meses después de la cirugía.

Palabras claves: Células grandes, carcinoma neuroendocrino, ovario, metástasis cutánea

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INTRODUCTION

Large cell neuroendocrine carcinoma was first described in the lung (1). Ovarian large cell neuroendocrine carcinoma (LCNEC) is an exceedingly rare tumour (2). To date, approximately 48 cases have been reported (3−25), and the prognosis is very poor (2−25). Generally, in epithelial ovarian cancers, the most common sites of distant metastasis are the pleura, liver, lung and lymph nodes (26). The clinical observation of skin metastasis in ovarian cancer cases is uncommon, occurring in only 3.5% of patients (26, 27). The incidence of skin metastasis from large cell neuroendocrine ovarian tumours is unknown, because none of the 45 reported cases of LCNEC of the ovary had skin metastases (Table). We report a rare case of LCNEC with skin metastasis for the first time.

Table: Pathological and clinical features of large cell neuroendocrine carcinoma cases in the literature

Reference	Age (years)	Epithelial stromal component	Recurrence sites	Outcomes
(3)	40	Mucinous carcinoma	None	NED (8 months)
(4)	46	Pure large cell neuroendocrine carcinoma of ovary	N/A	Died in 4 months
(5)	44	Mucinous intraepithelial carcinoma	None	NED (6 months)
(6)	68	Serous carcinoma	Abdomen	DOD (7 months)
(7)	39	Mucinous adenocarcinoma	Unclear	AWD (8 months)
(7)	55	Mucinous LMP with intraepithelial carcinoma	None	NED (68 months)
(7)	42	Benign cyst and teratoma in contralateral ovary	Unclear	DOD (20 months)
(7)	53	Endometrioid adenocarcinoma	None	NED (37 months)
(7)	47	Adenocarcinoma, NOS and teratoma	None	NED (11 months)
(7)	25	Mature cystic teratoma	Unclear	DOD (36 months)
(7)	55	Mucinous LMP	Unclear	DOD (2 months)
(7)	54	Mucinous carcinoma, endometrioid adenocarcinoma	None	NED (66 months)
(7)	63	Endometrioid adenocarcinoma	Unclear	DOD (9 months)
(7)	59	High-grade adenocarcinoma, NOS	None	NED (28 months)
(7)	22	Endometrioid adenocarcinoma	N/A	N/A
(8)	73	Microinvasive mucinous adenocarcinoma	Retroperitoneal space, bone, liver	DOD (8 months)
(8)	44	Mucinous intraepithelial carcinoma	Retroperitoneal space	DOD (4 months)
(9)	76	Pure large cell neuroendocrine carcinoma of ovary	N/A	Died
(10)	71	Serous carcinoma	None	NED (8 months)
(11)	65	Mucinous cystadenoma	Liver, abdomen	DOD (10 months)
(12)	27	Pure large cell neuroendocrine carcinoma of ovary	None	NED (10 months)
(13)	77	Endometrioid adenocarcinoma	Abdomen, bone, lung	DOD (19 months)
(13)	36	Mucinous adenoma		Recent
(13)	45	Mucinous cystadenoma and partial intraepithelial carcinoma	Unclear	DOD (36 months)
(13)	68	Mucinous adenocarcinoma	Unclear	LTF
(13)	58	Mucinous cystadenoma and partial intraepithelial carcinoma	Unclear	DOD (8 months)
(14)	34	Mucinous cystadenoma and mucinous adenocarcinoma	Liver, brain, PAN, pelvis	DOD (8 months)
(15)	22	Mucinous cystadenoma and mucinous adenocarcinoma	Liver	DOD (3 months)
(16)	33	Endometrioid adenocarcinoma	PAN	DOD (4 months)
(17)	56	Mucinous adenocarcinoma and teratoma	Unclear	DOD (10 months)
(17)	35	Mucinous adenoma	None	NED (10 years)
(18)	31	Mucinous adenoma	Unclear	Unclear
(19)	64	Pure large cell neuroendocrine carcinoma of ovary	None	NED (9 months)
(20)	73	Pure large cell neuroendocrine carcinoma of ovary	Brain	NED (12 months)

(21)	65	Endometrioid adenocarcinoma with squamous differentiation	Pelvis, liver, lymph node	DOD (2 months)
(21)	66	Pure large cell neuroendocrine carcinoma of ovary	Brain	NED (64 months)
(21)	42	Endometrioid adenocarcinoma	None	NED (32 months)
(21)	80	Endometrioid adenocarcinoma	None	NED (40 months)
(22)	40	Pure large cell neuroendocrine carcinoma of ovary	None	NED (6 months)
(23)	69	Mature cystic teratoma	Abdomen	DOD (6 months)
(24)	77	Undifferentiated non-small cell neuroendocrine carcinoma	None	DOD (45 days)
(24)	58	Undifferentiated non-small cell neuroendocrine carcinoma	PAN	DOD (17 months)
(24)	67	Non-small cell neuroendocrine carcinoma	None	NED (5 months)
(25)	53	Mucinous adenocarcinoma	Lymph node, bone, lung	DOD (24 days)
(25)	53	Teratoma	Liver, brain	DOD (7 months)
Present case	68	Adenocarcinoma	Skin, lung, liver, lymph node	DOD (7 months)

AWD: alive with disease; N/A: no information available; NED: no evidence of disease; DOD: dead of disease; LTF: lost to follow-up; PAN: para-aortic lymph node; LMP: low malignant potential; NOS: not otherwise specified.

CASE REPORT

A 68-year old, nulligravida, postmenopausal woman presented with progressive abdominal distension and pain over a period of six months. Physical examination revealed a firm irregular mass in the lower abdomen. Computed tomography confirmed a 20 cm abdominal tumour. Extensive pelvic and paraaortic lymphadenopathies were also identified. A solid left ovarian mass with tumour deposits on the capsule was observed by the surgeon during the operation. A total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and retroperitoneal lymph node biopsy were performed. The tumour involved the myometrium, endometrium, serosa of the bladder, sigmoid colon and omentum.

Microscopically, the tumour was composed of large pleomorphic cells with a moderate amount of cytoplasm and coarse nuclear chromatin that was organized in trabecular and rosette-like patterns and showed a high mitotic rate (Fig. 1A, B). Immunohistochemical analysis demonstrated that the tumour cells were diffusely positive for chromogranin (Fig. 1C) and synaptophysin (Fig. 1D). The tumour cells were also oestrogen receptor (ER) positive (Fig. 1E). The histological and immunohistochemical findings described above confirmed the final diagnosis of ovarian LCNEC.

A whole-body positron emission tomography-computed tomography scan (FDG-PET/CT) was performed in the postoperative period, revealing increased fluorodeoxyglucose (FDG) uptake in the lungs and multiple lymph nodes in the mediastinum, abdomen and bones (Fig. 2A). The patient received palliative radiation therapy for weight-bearing vertebrae (T8) over the course of 10 days. Approximately two months after the initial diagnosis, the patient presented with a 2 cm nodular skin lesion on the right

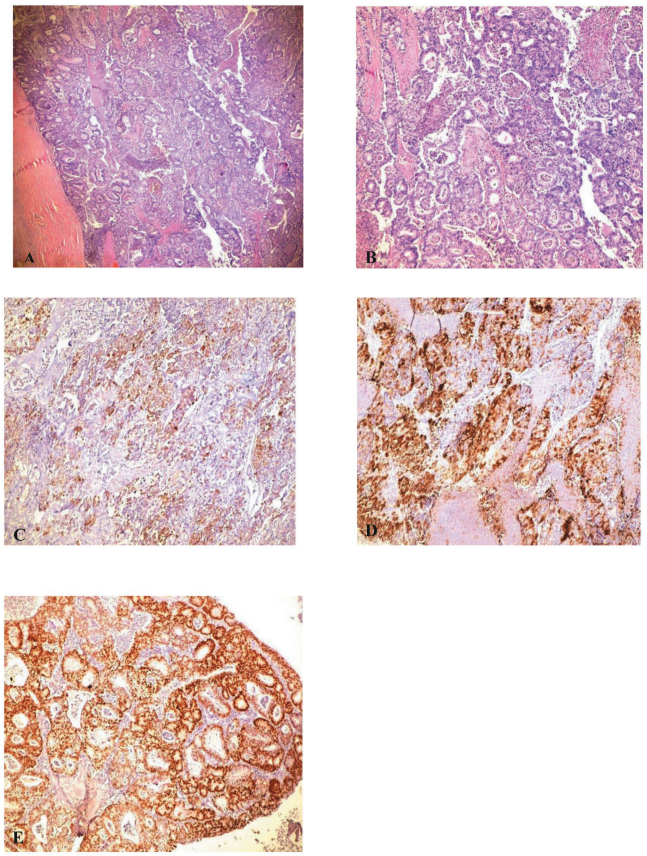

Fig. 1: Immunohistochemical analysis. **A** and **B**: Neoplastic cells arranged in rosette-like, palisading, or adenoid patterns (H/E, ×40). **C:** Positive immunohistochemical expression of chromogranin (100×). **D:** Neoplastic cells positive staining for synaptophysin (200×). **E:** Oestrogen positivity in tumour cells (ER, ×100).

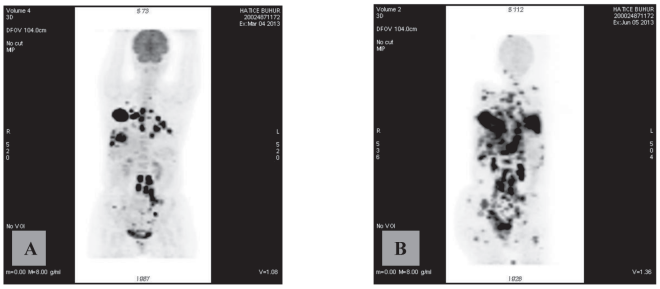

Fig. 2: **A:** The whole body positron emission tomography-computed tomography (PET-CT) appearance before the chemotherapy. **B:** The whole-body PET-CT appearance after the chemotherapy.

lower leg (Fig. 3). An excisional biopsy of the lesion revealed a metastatic large cell neuroendocrine tumour (Fig. 4). The patient was then treated with etoposide and carbo-

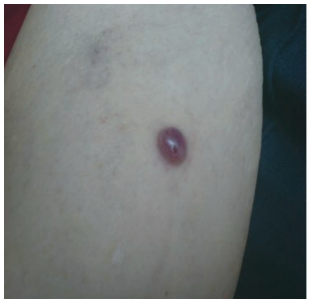

Fig. 3: A nodular skin lesion due to metastatic LCNEC of the ovary in the right thigh.

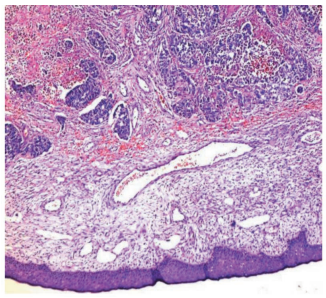

Fig. 4: Multiple lymphatic spaces in the dermis infiltrated by tumour (H/E, ×10).

platin for two cycles. However, by the time she was due for her second course of chemotherapy, a skin metastasis on the left upper extremity was noted. Based on the evidence from a PET/CT scan, significant disease progression had occurred in the cervical, axillary and subcarinal lymph nodes, in the retroperitoneum of the upper abdomen, mesentery and pelvic cavity, and in the soft tissues of the scalp (Fig. 5A), the right lower extremity (Fig. 5B) and the left lower extremity (Fig. 5C), which were not observed in the PET-CT that was performed before treatment was initiated (Fig. 2A). The administration of second-line chemotherapy was considered, but due to a worsening of the patient's condition, active treatment was impossible, and the patient died seven months after the initial diagnosis.

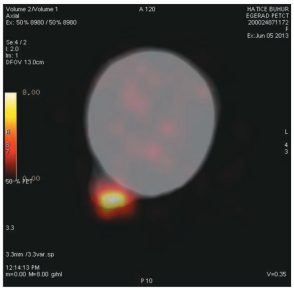

Fig. 5A: Skin metastasis in skull.

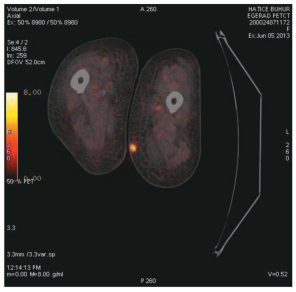

Fig. 5B: Skin metastasis in right leg.

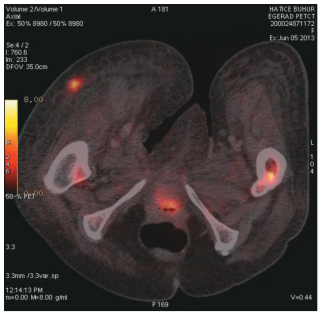

Fig. 5C: Skin metastasis in left lower extremity.

DISCUSSION

Large cell neuroendocrine carcinoma was first described by Travis *et al* (1). The most frequent regions are the lungs, intestine, pancreas, skin, salivary glands, prostate, urinary tract, genitals and biliary tract (1−3). Large cell neuroendocrine carcinoma, irrespective of localization, is a tumour with poor prognosis. Generally, LCNEC in the gynaecological organs affects the uterine cervix and ovary. According to the definition from the World Health Organization, primary ovarian large cell neuroendocrine carcinoma is synonymous with "undifferentiated carcinoma of the non-small cell neuroendocrine type" (2, 3). Ovarian LCNEC is an aggressive neoplasm, and most patients die of disseminated disease within one year of primary operation even after undergoing chemotherapy (4−7).

The origin and natural history of LCNEC are unknown. Histopathologically, these tumours are composed of solid islands of tumour cells (5). The tumour cells are large and the nuclei are hyperchromatic or granular, some having prominent nucleoli. Mitotic activity is usually significant, and abnormal mitoses are present (2, 5, 7). Immunohistochemically, the tumour cells are positive for cytokeratins and the neuroendocrine markers chromogranin, synaptophysin and neuron specific enolase (6, 7, 28). Large cell neuroendocrine carcinoma of the ovary is generally accompanied by ovarian surface epithelial-stromal tumours (28). It has been reported that the presence of surface

epithelial-stromal components distinguishes this neoplasm from ovarian carcinoma of the small cell pulmonary type and from metastatic small cell carcinomas of the ovary (7). In light of this information, in our patient, where we detected surface epithelial-stromal adenocarcinoma, the existence of a neuroendocrine tumour of a primary ovarian origin was supported, leading us away from our initial prospect of ovarian metastases of a small-cell carcinoma in another region. In addition, the tumour cells were ER positive (Fig. 1E) and the patient had no tumours of the breast or uterus. This evidence was further proof of an ovarian tumour.

The associated surface-epithelial components identified in the reported cases include a mucinous borderline tumour, mucinous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenoma/cystadenoma, adenocarcinoma not otherwise specified, admixed mucinous and endometrioid carcinoma, and serous carcinoma (8, 28). The epithelial components in 45 cases of ovarian LCNEC, excluding the seven pure-type LCNEC cases, were as follows: 18 mucinous tumours (benign, borderline malignancy and malignancy), eight endometrioid adenocarcinomas, four mature cystic teratomas, two adenocarcinomas, not otherwise specified, two serous adenocarcinomas, one benign ovarian cyst and three undifferentiated non-small cell neuroendocrine carcinoma [Table] (3−25). Of these, only two cases of adenocarcinoma as surface-epithelial components have been described (4, 9). Our patient is important as she is only the third case in which adenocarcinoma as surface-epithelial components is present. However, a more interesting feature of this case was the skin metastases observed. Generally, the clinical observation of skin metastasis in epitelial ovarian cancer is uncommon; its incidence ranges from 1.9% to 5.1% (26). Most metastatic skin lesions occur in skin adjacent to the primary ovarian cancer including the abdominal wall (27, 28). Several mechanisms may explain the occurrence of skin metastasis in the abdominal wall, such as the direct spread of tumour cells from the underlying growth, accidental implantation associated with surgery, or the contiguous spread of tumour cells through lymphatic or haematogenous routes (26, 28).

Metastatic skin lesions on extremities are even more rare; it has been reported that only 12% of epithelial ovarian carcinoma skin metastases occur on the limbs (27, 29). Skin metastasis due to LCNEC of the ovary has not been previously reported. Our reasons for reporting this case are the unique metastasis area (skin) of this rare histological subtype (LCNEC) and the site of this rarely observed metastasis (lower extremity). In the patient, skin lesions first appeared on the lower right extremity within eight weeks of primary surgery despite no detection at the time of diagnosis (Fig. 3), and these lesions showed extremely rapid progression with skin metastasis on the left lower extremity, and then the skull, even with carboplatin-etoposide chemotherapy. As seen in the patient, non-abdominal skin lesions may have resulted from tumour embolus through the lymphatic or haematogenous spread. In the literature, it has been reported that the time between the diagnosis of ovarian cancer and the documentation of cutaneous involvement is the most important prognostic factor affecting survival (26, 27). We lost our patient following the skin metastasis that emerged soon after she was diagnosed due to the progression of the disease.

There is no consensus on the management of skin metastases, as this tumour is very rare. The patient was treated with surgical excision and systemic chemotherapy. In general, the literature on ovarian cancer has suggested that a combined modality approach including surgical excision and chemotherapy may be useful in the management of skin metastases (27, 29). Hence, surgery and chemotherapy may be recommended for palliation in patients with LCNEC of the ovary.

In conclusion, we reported the first case of metastatic skin lesions on the lower extremities due to LCNEC of the ovary. In the patient, there was a recurrence not only in the abdominal cavity but also to unexpected sites that differed from the usual ovarian cancer distribution. This evidence suggests that LCNEC may have a much stronger predisposition for systemic spread compared with typical epithelial ovarian cancer, which tends to metastasize intra-abdominally.

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