

Case Report

Large Cell Neuroendocrine Carcinoma of the Ovary Associated with Serous Carcinoma with Mucin Production: A Case Report and Literature Review

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Abstract: Large cell neuroendocrine carcinoma (LCNEC) of the ovary is a rare entity and is frequently associated with ovarian surface epithelial tumors. However, its association with serous carcinoma has only been described recently in one case. We report another case of such with mucin production in a 68-year old woman. Immunohistochemistry and mucicarmine stain confirmed the diagnosis. Its clinicopathologic association is discussed and the literature is reviewed.

Keywords: Ovary, neuroendocrine carcinoma, non-small cell type, serous carcinoma, immunohistochemistry

Introduction

Large cell neuroendocrine carcinoma (LCNEC) of the ovary is a rare tumor and is now included in the World Health Organization tumor classification [1]. Its prognosis is generally very poor even when the diagnosis is made at an early stage. Since Collins *et al* [2] described the first case of mixed neuroendocrine and mucinous carcinomas, a few more cases of primary ovarian LCNECs have been reported. The majority of the tumors are associated with other epithelial neoplasms, among which only one case of serous carcinoma has been recently described [3]. Here we present another case of LCNEC of the ovary associated with serous carcinoma with mucin production.

Clinical History

A 68-year-old G1P0 woman presented with abdominal distension for 5 months. Her past medical history was remarkable only for hypertension. Physical examination was remarkable for ascites, bilateral inguinal lymphadenopathy, 3+ pitting leg edema and an 18 cm firm, fixed mass in the pelvis. A

chest radiograph showed no metastatic disease. There were bilateral small pleural effusions. Computerized tomography of the abdomen and pelvis confirmed the 18 cm pelvic mass with peritoneal and omental nodules and ascites. Inguinal lymphadenopathy measuring up to 4 cm was identified. The patient had shortness of breath at rest due to the massive abdominal distention. A paracentesis was performed and malignant cells consistent with papillary serous adenocarcinoma were identified. Her performance status was extremely poor and she was hypoalbuminemic. She received three courses of neoadjuvant chemotherapy (carboplatin/paclitaxel) with a decrease in serum CA125 from 1235 to 95 U/ml and clinical resolution of ascites. Exploratory laparotomy identified right and left ovarian tumors and multiple tumor nodules on the peritoneum, omentum, bladder and colon. The surfaces of the uterus, bladder peritoneum, sigmoid colon and diaphragm were coated by thick tumor plaques. The patient underwent tumor debulking including omentectomy and bilateral salpingo-oophorectomy. However, optimal debulking could not be achieved and the uterus was not removable. The liver,

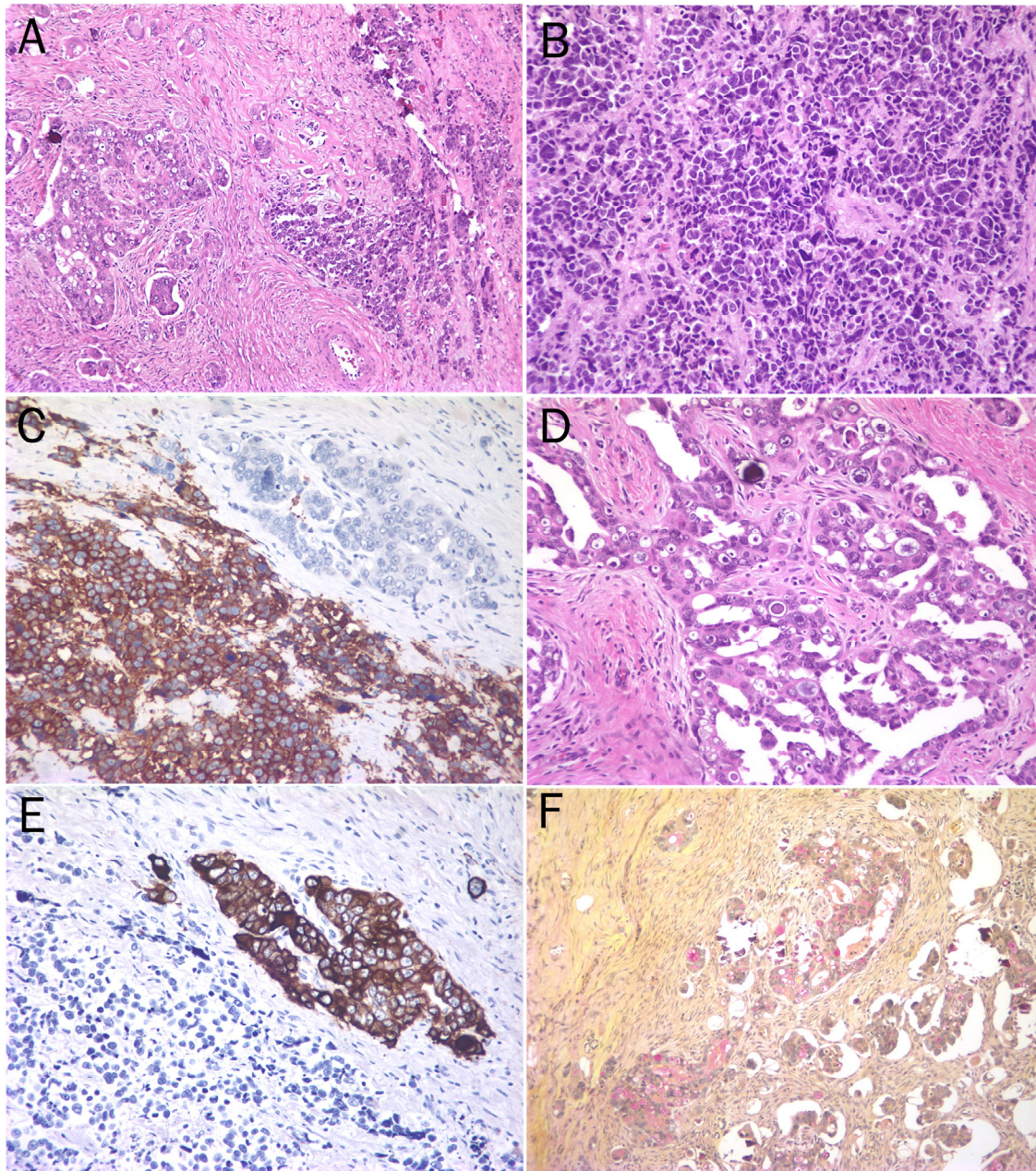


Figure 1 A. Low-power view of the tumor showing a combination of neuroendocrine carcinoma of the large cell type and serous carcinoma. B. High-power view of the neuroendocrine carcinoma showing solid islands of medium to large cells with a variable amount of amphophilic cytoplasm and large nuclei with stippled evenly distributed chromatin. C. Neuroendocrine component positive for synaptophysin, but not the serous component. D. High-power view of the serous carcinoma showing papillary configuration and glandular differentiation with marked nuclear atypia and abundant psammoma bodies. E. Pan-cytokeratin positive in serous component and negative in neuroendocrine component. F. Focal mucin production within the serous carcinoma component stained by mucicarmine.

stomach, bowel, gallbladder and appendix were normal. There was no evidence of intraluminal gastric or intestinal tumors. Postoperatively she received two additional courses of carboplatin and paclitaxel with the

serum CA125 dropping to 51 U/ml. However, by the time she was due for her sixth course of chemotherapy, an upper abdominal mass was noted and the serum CA125 had increased to 474 U/ml. The chemotherapy was switched to

Doxil of which she received two courses without response. She died seven months after the diagnosis of ovarian carcinoma.

Pathologic Findings

The gross pathology examination revealed that both ovaries were almost completely occupied by a 7 cm tumor on the right side and a 5 cm tumor on the left side. On cut surface the tumors consisted of white to tan solid soft tissue with focal necrosis. The peritoneal and omental tumors ranged in size from 1 to 2.5 cm in the greatest dimensions.

Histologically the tumor had two discernable but admixed cellular components: neuroendocrine carcinoma contributing to approximately 60% of the tumor mass, the remaining being ovarian carcinoma of the serous type (**Figure 1A**). The neuroendocrine

component of the tumor consisted of solid islands and cords of medium to large epithelial cells with a variable amount of amphophilic cytoplasm and large nuclei with stippled evenly distributed chromatin. There were numerous mitotic figures (**Figure 1B**). The tumor cells were positive for chromogranin and synaptophysin, and negative for CK7, CK20 and EMA (**Figure 1C**). The ovarian epithelial component of the tumor showed papillary configuration and glandular differentiation with marked nuclear atypia. Abundant psammoma bodies were present (**Figure 1D**). This component was positive for AE1/3, CK7 and EMA, and negative for chromogranin and synaptophysin (**Figure 1E**). Focal mucin secretion by the tumor cells was proven by mucicarmine stain (**Figure 1F**) (**Table 1**). The peritoneal and omental tumor nodules were histologically identical to the primary ovarian tumor.

Table 1 Immunohistochemistry of the neuroendocrine and serous components of the tumor

Markers	Source	Clone	Dilution	Neuroendocrine	Serous
Pan-keratin	Zymed	AE1/AE3	1:200	Positive (dot-like pattern)	Positive (membranous pattern)
EMA	DAKO	E29	1:800	Negative	Positive (membranous pattern)
CK7	DAKO	OV-TL12/30	1:100	Negative	Positive (membranous pattern)
CK20	DAKO	Ks20.8	1:400	Negative	Negative
Chromogranin	DAKO	DAK-A3	1:400	Positive (40-50% of tumor cells)	Negative (less than 5% tumor cells showing weak positivity)
Synaptophysin	Zymed	SY38	1:200	Positive (90-95% of tumor cells)	Negative

Dako Cytomation Nordern A/S, Glostrup, Denmark; Zymed Laboratories Inc., San Francisco, CA, USA

Discussion

Although recently listed in the WHO Classification of Tumors as a primary ovarian tumor, LCNEC of the ovary is an exceedingly rare neoplasm, and only twenty-nine cases have been reported in the literature so far (**Table 2**). Except for three cases of pure neuroendocrine carcinoma, all the remaining ones have been associated with ovarian epithelial tumors or germ cell tumors [4-6]. The only case of LCNEC admixed with low-grade serous carcinoma has recently been reported by Choi *et al* [3]. Here we present another case of LCNEC associated with papillary serous carcinoma showing focal mucin production.

Diagnosis of LCNEC in routine pathology practice relies on typical morphology and adjunctive immunohistochemistry. The tumor is composed of medium to large neuroendocrine cells forming solid sheets and cords with abundant eosinophilic or granular cytoplasm. The nuclei show condensation of nuclear material (salt and pepper chromatin) and there are often large prominent nucleoli. Foci of necrosis and frequent mitoses are common findings. The neuroendocrine differentiation can be confirmed by immunohistochemistry that is positive for chromogranin, synaptophysin or other neuroendocrine markers [1]. The associated surface-epithelial components identified in the reported cases include mucinous borderline

Table 2 Large cell neuroendocrine carcinoma of the ovary reported in the literature and the current case

Authors	Age	Associated Component	Size/Laterality	Stage	Treatment	Follow-up
Collins <i>et al</i> [2]	34	Mucinous borderline tumor with small foci of mucinous adenocarcinoma	16 cm, left	Ic	TAH/BSO/omentectomy/cisplatin and cyclophosphamide	DOD 8 m
Khurana <i>et al</i> [10]	22	Mucinous borderline tumor with small foci of mucinous adenocarcinoma	21 cm, right	Ic	RSO/carboplatin and cyclophosphamide	DOD 3 m
Jones <i>et al</i> [11]	65	Mucinous cystadenoma	16.5 cm, left	Ia	TAH/BSO/omentectomy	DOD 10 m
Eichhorn <i>et al</i> [8]	77	Endometrioid adenocarcinoma	15 cm, N/A	Ia	TAH/BSO/radiation	DOD 19 m
Eichhorn <i>et al</i> [8]	36	Mucinous adenocarcinoma	10 cm, right	Ia	RSO prior TAH	Unknown
Eichhorn <i>et al</i> [8]	45	Mucinous borderline tumor with small foci of mucinous adenocarcinoma	18 cm, right	Ib	TAH/BSO/omentectomy/chemotherapy	DOD 3y
Eichhorn <i>et al</i> [8]	68	Mucinous adenocarcinoma	9 cm, right	IIb	TAH/RSO/omentectomy/prior LSO	Unknown
Eichhorn <i>et al</i> [8]	58	Mucinous borderline tumor with small focus of mucinous adenocarcinoma	30 cm, left	IIIb	TAH/BSO/omentectomy/chemotherapy	DOD 8m
Chen <i>et al</i> [7]	73	Microinvasive mucinous adenocarcinoma	11 cm, left	IIIc	BSO/omentectomy/chemotherapy prior TAH	DOD 4m
Chen <i>et al</i> [7]	44	Mucinous intraepithelial adenocarcinoma	25 cm, left	Ia	TAH/BSO/omentectomy/chemotherapy	DOD 4m
Ohira <i>et al</i> [12]	33	Endometrioid adenocarcinoma	11 cm, left	Ic	LSO/omentectomy/chemotherapy	DOD 6m
Hirasawa [13]	56	Mucinous carcinoma and dermoid cyst	N/A	IIc	TAH/BSO/chemotherapy	DOD 10m
Hirasawa [13]	35	Mucinous adenoma	N/A	Ic	TAH/BSO/omentectomy/chemotherapy	NED 10y
Choi <i>et al</i> [3]	71	Serous carcinoma	6.5 cm, right	IIIb	TAH/BSO/chemotherapy	NED 8m
Ahmed <i>et al</i> [14]	30	Mucinous cystadenoma	15 cm, N/A	N/A	N/A	N/A
Behnam <i>et al</i> [4]	27	None	11 cm, left	Ic	LSO/omenntectomy/chemotherapy	NED 10m
Lindboe [6]	64	None	14 cm, right	Ia	TAH/BSO/omentectomy/chemotherapy	NED 9m
Dundr [5]	73	None	9 cm, left	N/A	N/A	N/A
Veras <i>et al</i> [9]	39	Mucinous adenocarcinoma	5 cm, right	IV	TAH/BSO/chemotherapy	AWD 8m
Veras <i>et al</i> [9]	55	Mucinous borderline tumor with intraepithelial cancer	26 cm, right	I	TAH/BSO/chemotherapy	NED 68m
Veras <i>et al</i> [9]	42	Benign cyst/dermoid cyst in contralateral ovary	N/A	IV	TAH/BSO/chemotherapy	DOD 20m
Veras <i>et al</i> [9]	53	Endometrioid carcinoma	14.5 cm, left	III	TAH/BSO/chemotherapy	NED 37m
Veras <i>et al</i> [9]	47	Adenocarcinoma, NOS and mature teratoma	14 cm, right	III	TAH/BSO/chemotherapy	NED 11m
Veras <i>et al</i> [9]	25	Mature cystic teratoma	5 cm, right	IV	BSO/omentectomy/chemotherapy	DOD 36m
Veras <i>et al</i> [9]	55	Mucinous borderline tumor	13.5 cm, right	III	TAH/BSO/chemotherapy	DOD 2m
Veras <i>et al</i> [9]	54	Mucinous and endometrioid carcinoma	14 cm, right	I	TAH/BSO/chemotherapy	NED 66m
Versa <i>et al</i> [9]	63	Endometrioid carcinoma	14 cm, left	IV	TAH/RSO/chemotherapy	DOD 9m
Veras <i>et al</i> [9]	59	High-grade adenocarcinoma, NOS	14 cm, left	I	BSO/chemotherapy	NED 28 m
Veras <i>et al</i> [9]	22	Mucinous low malignant potential and mucinous carcinoma	21 cm, right	I	RSO/appendectomy/chemotherapy	DOD 3m
Present case	68	Papillary serous adenocarcinoma with focal mucin secretion	7 cm, right and 5 cm, left	IIIc	BSO/omentectomy/tumor debulking/chemotherapy	DOD 7m

AWD=alive with disease; BSO=bilateral salpingo-oophorectomy; DOD=dead of disease; LSO=left salpingo-oophorectomy; N/A= No information available; NED=no evidence of disease; NOS=not otherwise specified; RSO=right salpingo-oophorectomy; TAH=total hysterectomy; m=months; y=years.

tumor, mucinous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenoma/cystadenoma, adenocarcinoma NOS, admixed mucinous and endometrioid carcinoma, and serous carcinoma.

The LCNEC component in our case had a morphology typical of neuroendocrine differentiation and an immunoprofile that was positive for neuroendocrine differentiation and negative for epithelial markers. However, the interesting feature of this case was that the intermingled ovarian epithelial tumor consisted of serous carcinoma showing focal mucin production. The high grade nuclear atypia, papillary configuration and glandular formation, and the psammoma bodies formed the classic morphology of a serous carcinoma. The reversed immunoprofile positive for epithelial markers and negative for neuroendocrine differentiation helped establish the diagnosis. Focal mucin secretion has been described in serous carcinomas and its prognostic significance is not established. Whether it modifies their clinical behavior remains to be determined.

The differential diagnoses of ovarian LCNEC are other primary and secondary neuroendocrine tumors. Small cell carcinoma has smaller cell size with molding and significant necrosis. Metastatic neuroendocrine carcinoma would almost never admix with ovarian surface epithelial tumors.

Most of the reported cases presented with stage I disease, with tumors confined to one ovary. In our case, the tumor was identified in both ovaries with extensive peritoneal disease. It is possible that the tumor started on one side and spread to the other ovary and the peritoneum. However, this assumption cannot be proven in a patient with such widespread disease. It is interesting to note that both Choi's patient [4] and the current patient with serous carcinoma components presented in advanced stage of disease.

Follow-up (2 months to 10 years) was available in 26 of the 30 reported cases (including ours). At the time of publication nine (6 stage I, 3 stage III) of the 30 patients had no evidence of disease. The three long-term survivors (60 months) had stage I disease and received adjuvant chemotherapy. Sixteen patients died of disease 2 months to three

years (median, 8 months) after diagnosis. Nine of these 16 patients were reported to have stage I disease and three of these nine did not receive adjuvant chemotherapy. One patient with stage IV ovarian LCNEC was alive with disease eight months after diagnosis at the time of the report.

LCNEC of the ovary appears to be highly aggressive. The presence of LCNEC component in an otherwise usual type epithelial tumor should be reported because of the potential negative prognostic impact of this histologic finding, although there are too few cases in the literature to determine the prognostic impact of the percentage of LCNEC component in an epithelial ovarian tumor. Prior to our report, only the neuroendocrine component of the carcinoma has been described in the metastatic sites when metastasis occurs [7]. Unlike the previously reported cases, our patient's peritoneal metastases contained both LCNEC and surface-epithelial components identical to those in the primary tumor. Most patients died of disease within 1 year of diagnosis despite extensive surgery and adjuvant chemotherapy [3, 4, 8, 9]. Our patient presented with widespread peritoneal disease and showed an initial response to the chemotherapy followed by rapid progression and death, which is typical of the aggressive behavior of these tumors.

In summary, we report a rare case of an ovarian neuroendocrine carcinoma, large cell type, associated with papillary serous carcinoma with mucin production.

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