*The Korean Journal of Pathology 2011; 45: 523-528*
*http://dx.doi.org/10.4132/KoreanJPathol.2011.45.5.523*

# Ovarian Large Cell Neuroendocrine Carcinoma Associated with Endocervical-like Mucinous Borderline Tumor – A Case Report and Literature Review –

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**Received:** July 22, 2010
**Accepted:** January 6, 2011

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Ovarian large cell neuroendocrine carcinoma is a rare tumor that is usually associated with surface epithelial tumors. Mucinous tumors are most common surface epithelial component identified in reported cases. Ovarian mucinous tumor associated with large cell neuroendocrine carcinoma is almost always an intestinal type. However, large cell neuroendocrine carcinoma associated with pure mucinous borderline tumor of endocervical-like type has not been described previously. The present case report describes a large cell neuroendocrine carcinoma associated with endocervical-like mucinous borderline tumor of the ovary in a 35-year-old woman. The tumor was confirmed by histopathology and immunohistochemistry. A review of the pertinent literature is included.

**Key Words:** Ovary; Large cell neuroendocrine carcinoma; Mucinous tumor

Primary ovarian large cell neuroendocrine carcinoma (LCNEC) is a rare tumor with a very poor prognosis and is included in the miscellaneous group category of the World Health Organization tumor classification.[1] Most of these tumors are associated with other epithelial neoplasm. To the best of our knowledge, 30 cases have been reported in the English literature.[2-4] LCNEC associated with a pure mucinous borderline tumor of endocervical-like type has previously not been described. Here, we present a case of LCNEC of the ovary associated with endocervical-like mucinous borderline tumor.

## CASE REPORT

A 35-year-old woman with a previous medical history of myomectomy presented with a 5-month history of lower abdominal distension. She had an obstetric history of G2P1Aa1Sa0Lf1. On pelvic computed tomography, a malignant appearing, 15×10×7 cm, right-sided ovarian mass was identified. Multiple hepatic and lymph node metastases were apparent upon positron emission tomography scan (Fig. 1A). The initial levels of carbohydrate antigen (CA) 19-9 and CA 125 were high (360 U/mL and 473.93 U/mL, respectively); however, postoperative levels were not measured. Total abdominal hysterectomy with bilateral salpingooophorectomy, partial omentectomy, appendectomy, and multiple peritoneal biopsies were performed. On gross examination, the right ovary was almost completely replaced by a huge mass composed of multi-cystic or pale-to-yellow solid portions. The cysts contained yellow and sticky mucinous fluid, and a solid portion displayed multifocal granular necroses (Fig. 1B). The uterus and left ovary were normal.

Microscopically, two components composed of neuroendocrine and mucinous tumor in an isolated or admixed pattern including transitional foci were identified (Fig. 2). The neuroendocrine tumor component consisted of irregularly shaped and closely packed solid islands of highly atypical cells with high mitotic rates and necroses. The cells were generally medium to large-sized, oval to round cells. Also noted were a few smaller cells with a rosettoid configuration. The cells had hyperchromatic nuclei with coarse, but even, chromatin and variable amounts of occasionally eosinophilic cytoplasm. Occasionally, tumor cells had vesicular nuclei with prominent nucleoli. These tumor cells

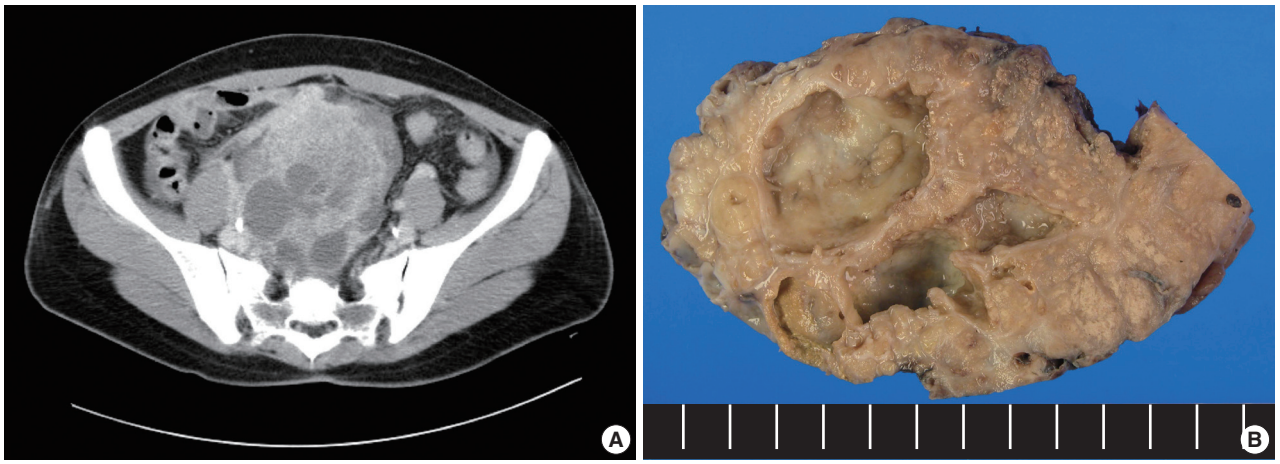

**Fig. 1.** Pelvic computed tomography shows a huge multiloculated mass in pelvic cavity (A). The cut sections of the right ovary disclose solid and multi-cystic mass, measuring 15×10×7 cm in size (B).

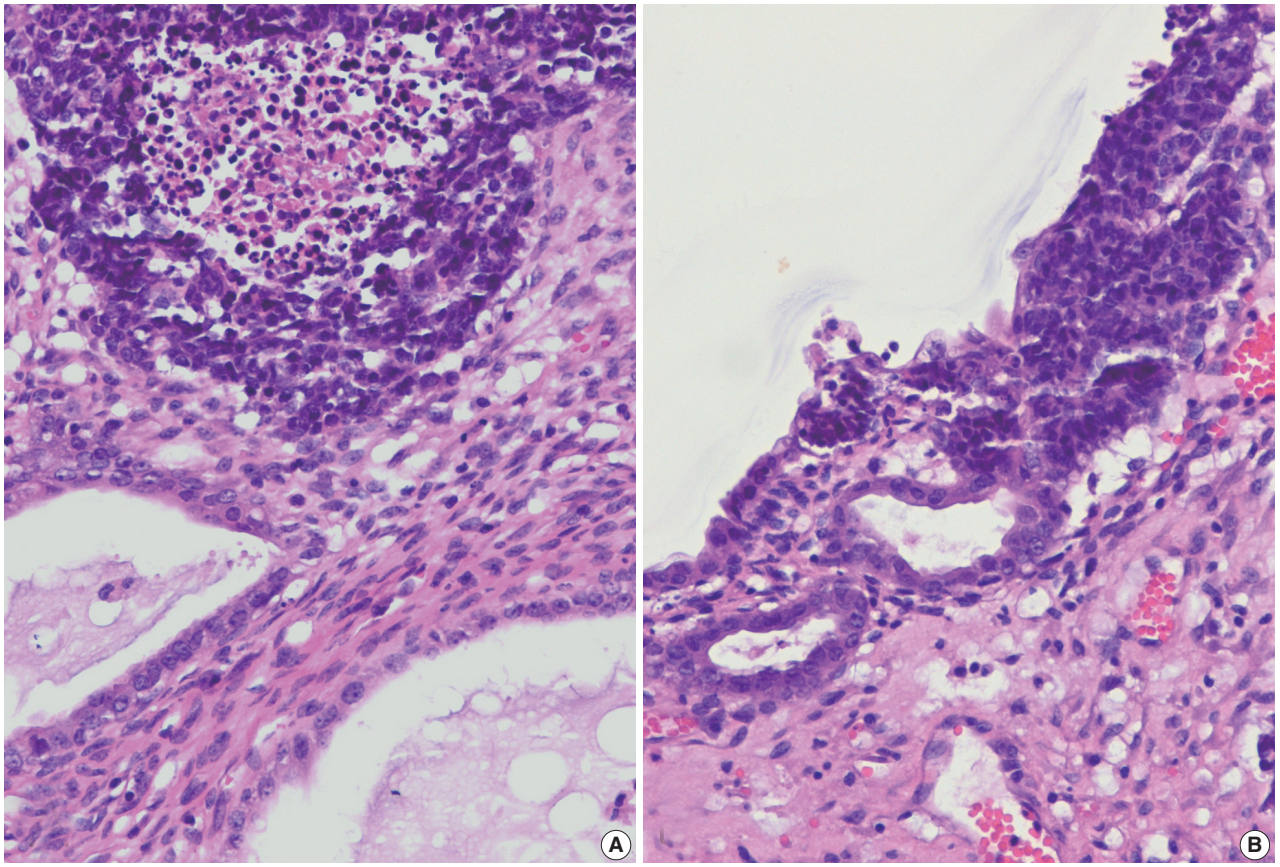

**Fig. 2.** The tumor consists of two components of neuroendocrine carcinoma and mucinous tumor in an isolated (A) or admixed pattern including transitional foci (B).

were immunoreactive for epithelial membrane antigen (1:60, Dako, Glostrup, Denmark), synaptophysin (1:120, Dako), chromogranin (predilution, Dako), and CD56 (1:60, Novocastra, Newcastle, UK) (Fig. 3). The mucinous tumor component was a papillary growing borderline tumor composed of a mixture of two types of epithelium – tall colmnar mucinous cells and stratified eosinophilic cells – with pronounced neutrophilic infiltration within the stroma of the papillae and in extracellular spac-

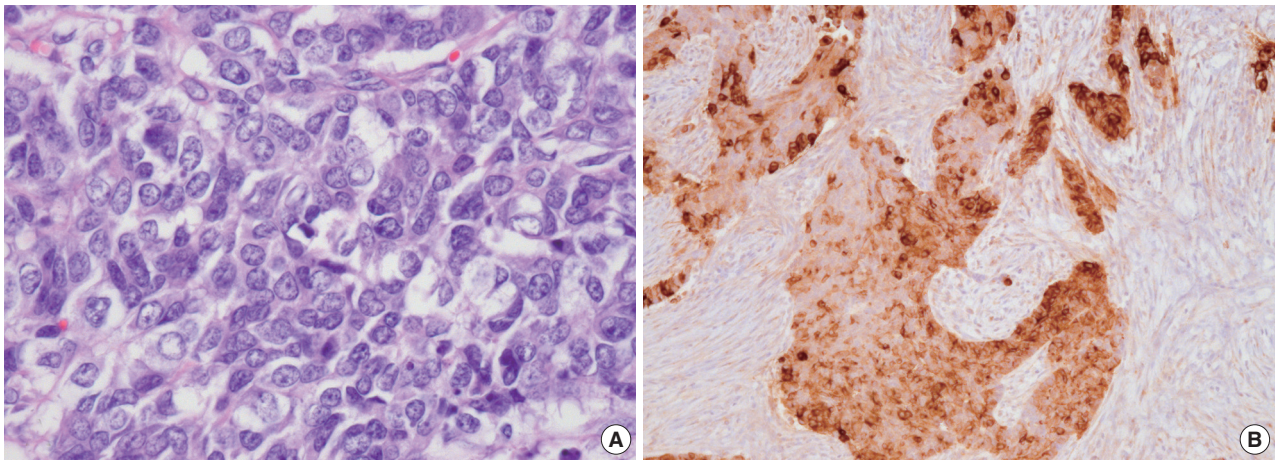

**Fig. 3.** Neuroendocrine carcinoma shows solid sheets of medium to large cells with moderate amount of cytoplasm and round to oval nuclei with even chromatin and occasionally prominent nucleoli (A). These cells are positive for synaptophysin (B).

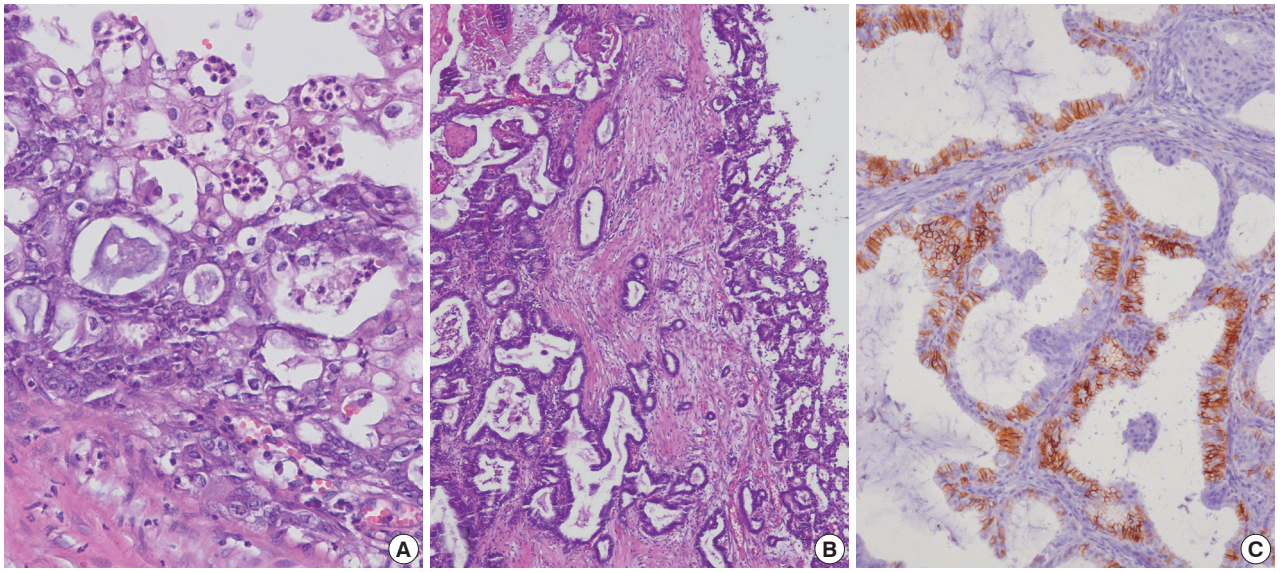

**Fig. 4.** Mucinous tumor shows endocervical-like borderline tumor characterized by papillae lined by atypical mucinous and eosinophilic cells and neutrophilic infiltration (A). There are small focus of irregular glands embedded within densely fibrotic stroma, deceptive of invasion, but frankly invasive mucinous adenocarcinoma is not found (B). The mucinous borderline tumor cells have scattered CD56-positive neuroendocrine cells (C).

es, suggestive of endocervical-like or seromucinous type (Fig. 4A). No apparent stromal invasion was identified, although there was a region of irregular glands embedded within densely fibrotic stroma mimicking invasive growth (Fig. 4B). Immunohistochemically, these cells were positive for cytokeratin 7 (CK7; 1:250, Dako), estrogen receptor (predilution, Ventana, Tucson, AZ, USA), progesterone receptor (predilution, Ventana), and CA 125 (1:40, Dako). The mucinous component also had scattered positive cells for neuroendocrine marker (Fig. 4C). Appendix and omentum were not involved by the tumor, but there were multiple peritoneal metastases containing the LCNEC element only. The patient was transferred to another medical center and received chemotherapy, but died of the disease 4 months postoperatively.

## DISCUSSION

There are infrequent ovarian tumors with neuroendocrine differentiation including surface epithelial tumors with neuroendocrine cells, Sertoli-Leydig cell tumors with heterologous neuroendocrine elements, teratomas with neuroendocrine cells,

carcinoids, small cell carcinomas of pulmonary or hypercalcemic type, and LCNEC.[5]

Primary ovarian LCNEC is synonymous with undifferentiated carcinoma of non-small cell neuroendocrine type, according to the World Health Organization classification.[1] Since the first case report of this type,[6] 35 cases including five pure LCNEC have been reported (summarized in Table 1).[2,3,6-20] Most of these cases were associated with ovarian surface epithelial neoplasia. The majority of these tumors were associated with mucinous tumor component, (19 cases out of 30 cases, 63.3%) including three cystadenoma,[7,10,12] one borderline tumor,[3] and 15 adenocarcinomas with or without a borderline tumor.[2-4,18,19] In the case of LCNEC mixed with mucinous adenocarcinoma, all had a mucinous borderline tumor of intestinal type. However, LCNEC associated with a pure mucinous borderline tumor of the endocervical-like type has not been reported previously. Mixed LCNEC and endocervical-like type mucinous tumor was described in two cases; one case[6] arose from a 34-year-old woman, presented with weight loss and had mucinous component ranged from usual mucinous cystadenoma of endocervical-like type to a larger portion of typical mucinous borderline tumor and mucinous adenocarcinoma of intestinal type; the other[16] was from 36-year-old woman, presented with abdominal distension, and were accompanied by mucinous endocervical borderline tumor with intraepithelial carcinoma. The current case showed endocervical-like mucinous borderline tumor only with no definite mucinous adenocarcinoma component.

Another associated tumor components identified in the re-

**Table 1.** Clinicopathological features of large cell neuroendocrine carcinoma of the ovary in previously reported cases and the present case

| No. | Reference | Age (yr) | Symptom | Size (cm)/ Location | Associated component | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|
| 1 | Collins *et al.*[6] | 34 | Weight loss, abdominal distension | 16, left | MBT with focal mucinous adenocarcinoma | TAH/BSO/OMT/CHE | Died in 8 mo |
| 2 | Khurana *et al.*[20] | 22 | Abdominal pain | 21, right | MBT with focal mucinous adenocarcinoma | RSO/APP/CHE | Died in 3 mo |
| 3 | Jones *et al.*[7] | 65 | Abdominal distension | 16.5, left | Mucinous cystadenoma | TAH/BSO/OMT | Died in 10 mo |
| 4 | Eichhorn *et al.*[8] (5 cases) | 36-77 | Pelvic mass/pain/fever | 10-30, R>L | Endometrioid/mucinous adenocarcinoma/MBT with foci of IECA/MBT with focal mucinous adenocarcinoma | TAH/BSO/RAD/OMT/ CHE | Died in 8 mo-3 yr |
| 5 | Chen[2] | 73 | Abdominal mass | 11, left | Microinvasive mucinous tumor | BSO/OMT/TAH/CHE | Died in 4 mo |
| 6 | Chen[2] | 44 | Dyspnea, abdominal distension and pain | 25, left | Mucinous IECA | TAH/BSO/OMT/CHE | Died in 4 mo |
| 7 | Ohira *et al.*[9] | 44 | Abdominal pain | 11, left | Endometrioid carcinoma | LSO/OMT/CHE | Died in 6 mo |
| 8 | Hirasawa[10] | 56 | Abdominal pain | NA | Mucinous carcinoma and dermoid cyst | TAH/BSO/CHE | Died in 10 mo |
| 9 | Hirasawa[10] | 35 | NA | 18, NA | Mucinous adenoma | TAH/BSO/OMT/NA | NED 10 yr |
| 10 | Choi *et al.*[11] | 71 | Abdominal distension | 6.5, right | Serous carcinoma | TAH/BSO/CHE | NED 8 mo |
| 11 | Ahmed *et al.*[12] | 30 | Ovarian mass | 15, NA | Mucinous cystadenoma | NA | NA |
| 12 | Behnam *et al.*[13] | 27 | Pelvic mass | 11, left | None | LSO/OMT/CHE | NED 10 mo |
| 13 | Lindboe[14] | 64 | Abdominal discomport | 14, right | None | TAH/BSO/OMT/CHE | NED 9 mo |
| 14 | Dundr *et al.*[15] | 73 | NA | 9, left | None | NA | NA |
| 15 | Veras *et al.*[3] (11 cases) | 22-63 | Abdominal pain/distension/ bleeding | 5-26, R>L | Mucinous/endometriod carcinoma, mature cystic teratoma, MBT with IECA/mucinous carcinoma | TAH/BSO/APP/CHE | Died in 2 mo/ NED 28 mo |
| 16 | Aslam *et al.*[16] | 76 | Abdominal pain | 35, left | None | TAH/BSO/OMT | Died soon |
| 17 | Tsuji *et al.*[17] | 46 | Abdominal distension | 12, right | None (focal suqmous differentiation) | TAH/BSO/OMT | Died in 4 mo |
| 18 | Yasuoka *et al.*[18] | 36 | Abdominal distension, pain | 26, right | MBT with IECA | TAH/BSO/OMT | NED 6 mo |
| 19 | Chenevert *et al.*[19] | 53 | Abdominal mass | 20, left | MBT with focal carcinoma and teratoma | TAH/BSO/OMT/CHE | Died in 24 days |
| 20 | Chenevert *et al.*[19] | 53 | Abdominal distension | 21, left | Mucinous carcinoma and teratoma | TAH/BSO/OMT/CHE | Died in 7 mo |
| 21 | Draganova-Techeva *et al.*[4] | 68 | Abdominal distension | 7, right 5, left | Serous carcinoma with mucin production | BSO/OMT | Died in 7 mo |
| 22 | Present case | 35 | Abdominal distension | 15, right | MBT with microinvasive mucinous adenocarcinoma | TAH/BSO/OMT/APP/ CHE | Died in 4 mo |

MBT, mucinous borderline tumor; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; OMT, omentectomy; CHE, chemotherapy; RSO, right salpingo-oophorectomy; APP, appendectomy; RAD, radiation; IECA, intraepithelial carcinoma; LSO, left salpingo-oophorectomy; NA, not applicable; NED, no evidence of disease.

ported studies include endometrioid adenocarcinoma,[3,8,9] adenocarcinoma, not otherwise specified,[3] admixed mucinous and endometrioid carcinoma,[3] serous adenocarcinoma,[4,11] and teratoma with or without mucinous tumor.[3,10,19] The pure form of LCNEC of the ovary is extremely rare; only five cases have been reported previously.[4,13-17] These tumors displayed a solid and cystic appearance, but other epithelial tumor components were not identified microscopically, except one case of squamous differentiation.[17]

In the review of three large studies,[2-4] an average age of the patients was 50.5 years (range, 22 to 77 years), and the most common presenting symptom was abdominal or pelvic pain (12 cases). The average size of the tumor was 14.8 cm (range, 5 to 30 cm) and the tumor was unilateral in 24 cases. Twenty patients died of disease in times ranging from 2 months to 3 years. Immunohistochemically, these tumors were positive for neuroendocrine markers, such as CD56, chromogranin A, and synaptophysin. Synaptophysin was known to be more sensitive than chromogranin A.[3] Our case also showed immunoreactivity for synaptophysin and CD56.

A pathophysiological hypothesis regarding the origin of LCNEC of the ovary is not clear and several hypotheses have been suggested. One posits that LCNEC may arise from neuroendocrine cells present in epithelial ovarian neoplasms.[5,6] This has the backing of the presence of neuroendocrine cells in the ovarian epithelial tumors associated with LCNEC, as in the present case, as well as not associated with LCNEC.[5] The occurrence of surface epithelial tumors in the ovary associated with carcinoid or small cell carcinoma[21] explains the possibility of this hypothesis. Moreover, with respect to the monoclonality of two components,[21] it is considered likely to arise from the neuroendocrine cells in the surface epithelial stromal tumors. The existence of pure LCNEC raises the possibility that LCNEC may arise directly from the ovarian tissue.

Another hypothesis proposes that LCNEC is of teratomatous orign. This is supported by the fact that ovarian carcinoids are rarely associated with surface epithelial tumors, but frequently associated with teratomas. It has been also suggested that LCNEC probably arises from primitive endodermal cells or stem cells capable of differentiating into endocrine or other cell types.[6] Finally, it has also been proposed that ovarian neuroendocrine tumors may develop from non-neuroendocrine cells by activation of a gene that promotes neuroendocrine differentiation.[6]

The differential diagnoses include small cell carcinoma of pulmonary or hypercalcemic type, metastatic neuroendocrine carcinoma, anaplastic carcinoma arising in mucinous tumor, and primitive neuroectodermal tumor. Small cell carcinomas of the pulmonary type are differentiated from LCNEC by their smaller size of cells with molding and less intense immunohistochemical reaction for CK and chromogranin. The ovarian small cell carcinomas of hypercalcemic type may have a significant number of large cells, but these cells often have pale intracytoplasmic hyaline globules that are not seen in LCNEC. The tumor cells often show follicle-like spaces and are associated with hypercalcemia. Metastatic neuroendocrine carcinomas may have bilateral involvement, mutinodular growth, vascular invasion, and, ultimately, clinical history, and are microscopically almost never admixed with ovarian surface epithelial tumors. Careful consideration of the histological and immunohistochemical features excludes the possibility of other types of ovarian carcinomas and helps to avoid under-recognition or misdiagnosis of this type of tumor.

Patients with this type of tumor usually have a poor prognosis. Survival period after the surgery ranges from 3 to 36 months in most reported cases.[2] Our patient was transferred to another medical center and received chemotherapy with taxol-carboplatin, but died of the disease 4 months postoperatively. Like the previously reported case,[2] only the neuroendocrine component of the carcinoma was identified in metastatic sites.

In summary, LCNEC of the ovary is a rare entity and is frequently associated with ovarian surface epithelial tumor, especially mucinous tumor. Furthermore, its association with pure endocervical-like mucinous borderline tumor has not been described previously. Here, we present a case of an ovarian LCNEC associated with endocervical-like mucinous borderline tumor.

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