Large cell neuroendocrine carcinoma arising in mature cystic teratoma: a case report and review of the literature

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Summary

Background: Malignant transformation of ovarian mature cystic teratoma is rare, and occurs in approximately 1% of all cases. The most common histology arising in mature cystic teratoma is squamous cell carcinoma. Less frequently, malignant transformation is represented by an endocrine tumor. To date, only five cases of large cell neuroendocrine carcinoma (LCNC) arising in a mature cystic teratoma of the ovary have been reported. *Clinical case:* A 69-year-old woman presented with a 15-cm left ovarian mass, and was diagnosed with Stage IV large cell carcinoma neuroendocrine carcinoma (LCNC) arising in mature cystic teratoma (MCT) of the left ovary. The patient received adjuvant chemotherapy with paclitaxel and carboplatin, however, residual tumors increased in size. Six months after the debulking surgery she succumbed to the disease. A literature review revealed LCNC of the ovary showed excessively aggressive phenotype in malignant transformation from ovarian mature cystic teratoma. *Conclusion:* The present case of LCNC arising in MCT had an exceedingly poor prognosis, which was suggested in the previous five cases reported.

Key words: Ovarian tumor; Mature cystic teratoma; Large cell neuroendocrine carcinoma; Paclitaxel; Carboplatin.

Introduction

Malignant transformation of mature cystic teratoma (MCT) has been reported to occur in about 1% of patients with MCT. More than 80% of malignant transformations were squamous cell carcinomas [1]. Other histological subtypes arising from a MCT include adenocarcinoma, and adenosquamous cell carcinoma [2], however, the frequencies of these tumors are extremely rare.

To date, only five cases of large cell neuroendocrine carcinoma arising in a MCT of the ovary have been reported [3-5]. In this study, we report a case with large cell carcinoma neuroendocrine carcinoma arising from a MCT together with review of the literature.

Case Report

The patient was a 69-year-old woman, gravida 2, para 2. She was diagnosed as having clinical Stage IIAE diffuse large cell lymphoma three years before, and received combination chemotherapy of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. She had been in complete remission for 26 months; however, her left ovarian tumor was detected by a routine screening with positron emission tomography and computed tomography (PET-CT). She complained of slight tenderness in the lower abdomen, and magnetic resonance (MR) images showed a 15-cm left ovarian tumor which had enhanced solid parts with fatty tissue (Figure 1a). CT suggested multiple metastases including left subclavian lymph nodes, paraaortic lymph nodes, and both lungs. Several tumor markers of her serum were elevated: CA125 37.5 U/ml, CA19-9 139 U/ml, CEA 5.7 ng/ml, SCC 1.3 ng/ml, IL-2R 900 U/ml, and NSE 170 ng/ml. Subsequently, she underwent left salpingo-oophorectomy and biopsy of peritoneal dissemination and subclavian lymph nodes. Approximately 500 ml of yellowish oily ascites was observed at laparotomy. A 15-cm pelvic tumor was derived from the left ovary the adhering to the pelvic wall tightly. The tumor had preoperatively ruptured with intraperitoneal dissemination. The left ovarian tumor was completely removed; however, several residual tumors including pelvic and paraaortic lymph nodes with a diameter more than 4 cm were left.

Macroscopically, the solid tumor showed a yellow and white appearance, and cystic lesion containing hair balls, sebaceous materials, bone, and fatty tissue (Figure 1b). Pathologically, large tumor cells showed solid growth in the benign teratoma (Figure 2a). Partially, tumor cells with solid growth had unclear nucleoli and a high nuclear/cytoplasmic ratio (Figure 2b), resembling pulmonary small cell carcinoma. However, in most solid growths, tumor cells showed strong atypia with large eosinophilic cytoplasm and clear nucleoli (Figure 2c). These cells were immunohistochemically positive for synaptophysin (Figure 2d) and CD56, and partially positive for chromogranin A (Figure 2e) and cytokeratin. Detailed microscopic examination revealed there were no other ovarian epithelial neoplasms such as mucinous tumor. The tumor was diagnosed as a large cell carcinoma neuroendocrine carcinoma arising in mature cystic teratoma. Also, these cells were observed in the subclavian lymph nodes; her disease was diagnosed as Stage IV.

She received two cycles of combination therapy with paclitaxel (175 mg/m^2) and carboplatin (AUC = 6) postoperatively. However, peritoneal disseminations and metastatic lymph nodes progressed in size. She and her family did not want additional chemotherapy, and she died six months after the first surgery.

Discussion

Primary large cell carcinoma neuroendocrine carcinoma (LCNC) of the ovary is an extremely rare disease. A search with MEDLINE over two decades showed that 27 cases with ovarian LCNC have been reported (Table 1). [3-12]. Including the present case, 27 cases were available for clinical staging: 11 cases (41%) with Stage I, two cases (7%) with Stage II, six cases (22%) with Stage III,

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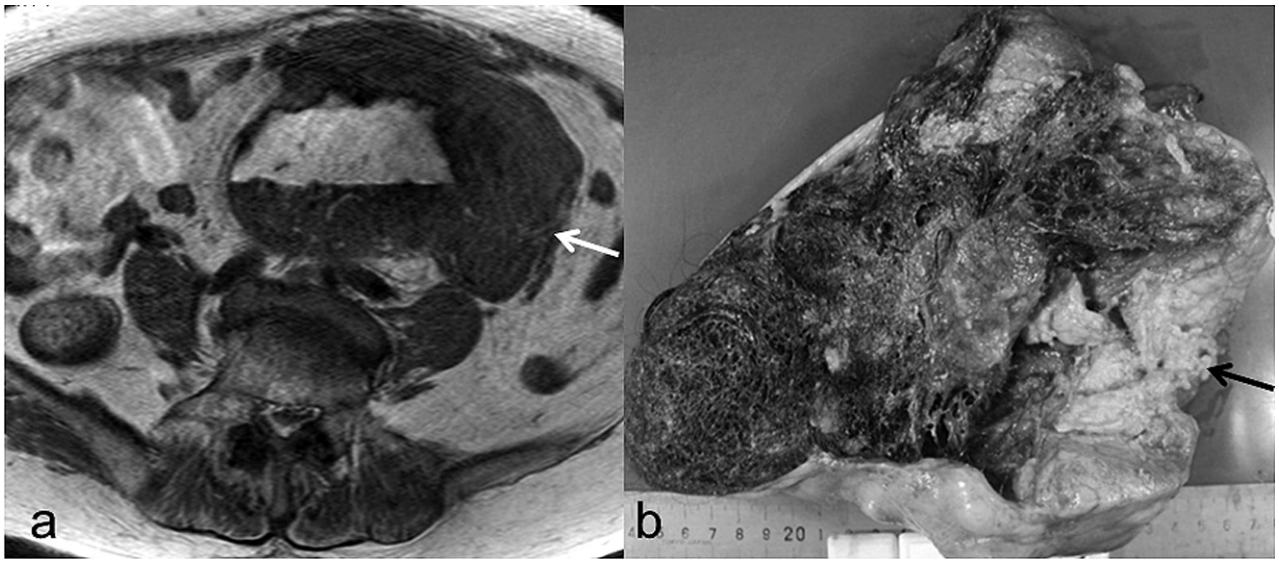

Figure 1. — Magnetic resonance (MR) images of the patient and macroscopic view of ovarian tumor. (a) T1-weighted image of ovarian tumor. The tumor had a solid part (arrow) and fatty tissue is shown by high intensity signal. (b) Solid part (arrow) shows a yellow and white appearance, and a cystic lesion containing hair balls, sebaceous materials, bone, and fatty tissue.

and eight cases (30%) with Stage IV. Seventeen cases died of disease within 36 months, and seven cases had no evidence of disease during the follow-up period ranging from 8-120 months. Among these seven cases with no evidence of disease, four cases had Stage I disease and three cases had Stage III disease. Three Stage III cases underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by platinum-based chemotherapy; however, the follow-up period of two cases was within a year. Seven (64%) of 11 cases with Stage I disease died of disease within three years, suggesting that prognoses of LCNC cases seems to be quite poor in comparison with epithelial ovarian cancers. Additionally, stage distribution was compared with the patients with squamous cell carcinoma (SCC) arising from MCT. According to the review of 277 cases that had a SCC component, clinical stage was available in 241 cases: 120 cases (50%) in Stage I, 45 cases (19%) in Stage II, 66 cases (27%) in Stage III, and ten cases (4%) in Stage IV [1]. The cases with a LCNC component had significantly advanced stage in comparison with patients with a SCC component ($p < 0.001$).

The origin or precursor of LCNC of the ovary remains unclear. Most LCNC cases have been associated with ovarian surface neoplasms, such as mucinous cystic tumors. The hypothesis is that LCNC arises from the neuroendocrine calls that are located in surface epithelial-stromal tumors or teratoma [3]. To our knowledge, five cases with LCNC arising in MCT have been reported in the literature. Including the present case, only six cases have been described in the English literature [3-5]. Four were associated mucinous adenocarcinoma, and two cases had a LCNC component only in mature cystic teratoma. Three cases presented with abdominal pain, and another three cases presented with abdominal distension. Stage distribution was as follows: one case (17%) with Stage II, one case (17%) with Stage III, and four cases (67%) with Stage IV. Five cases received systemic chemotherapy after surgery, and one case underwent surgery only. Four of these cases died of disease within 12 months, and another case died of disease within 36 months. Only one case showed no evidence of disease, although the follow-up period was 11 months. The prognosis of LCNC arising from teratoma is presumed to be extremely poor among LCNC tumors of the ovary, which might be explained by advanced stages at diagnoses. Our case was not associated with epithelial tumors by detailed pathologic examination, and we believe that she was the second case of LCNC arising from mature cystic teratoma that had no association with mucinous neoplasia. Considering a precursor lesion in the case, direct transformation existed from MCT to LCNC.

The present case revealed that a combination with paclitaxel and carboplatin was not effective against LCNC arising from MCT. Most ovarian LCNC cases received platinum-based chemotherapy; it can be concluded that there is no standard and effective regimen for these tumors.

Conclusion

We have reported a case with LCNC arising from teratoma with a review of the literature. The tumor seemed to be extremely aggressive, showing a high frequency of distant metastasis and chemo-resistant phenotype. An extremely rare case report as described here would be helpful for decision making, when a case with ovarian LCNC presents.

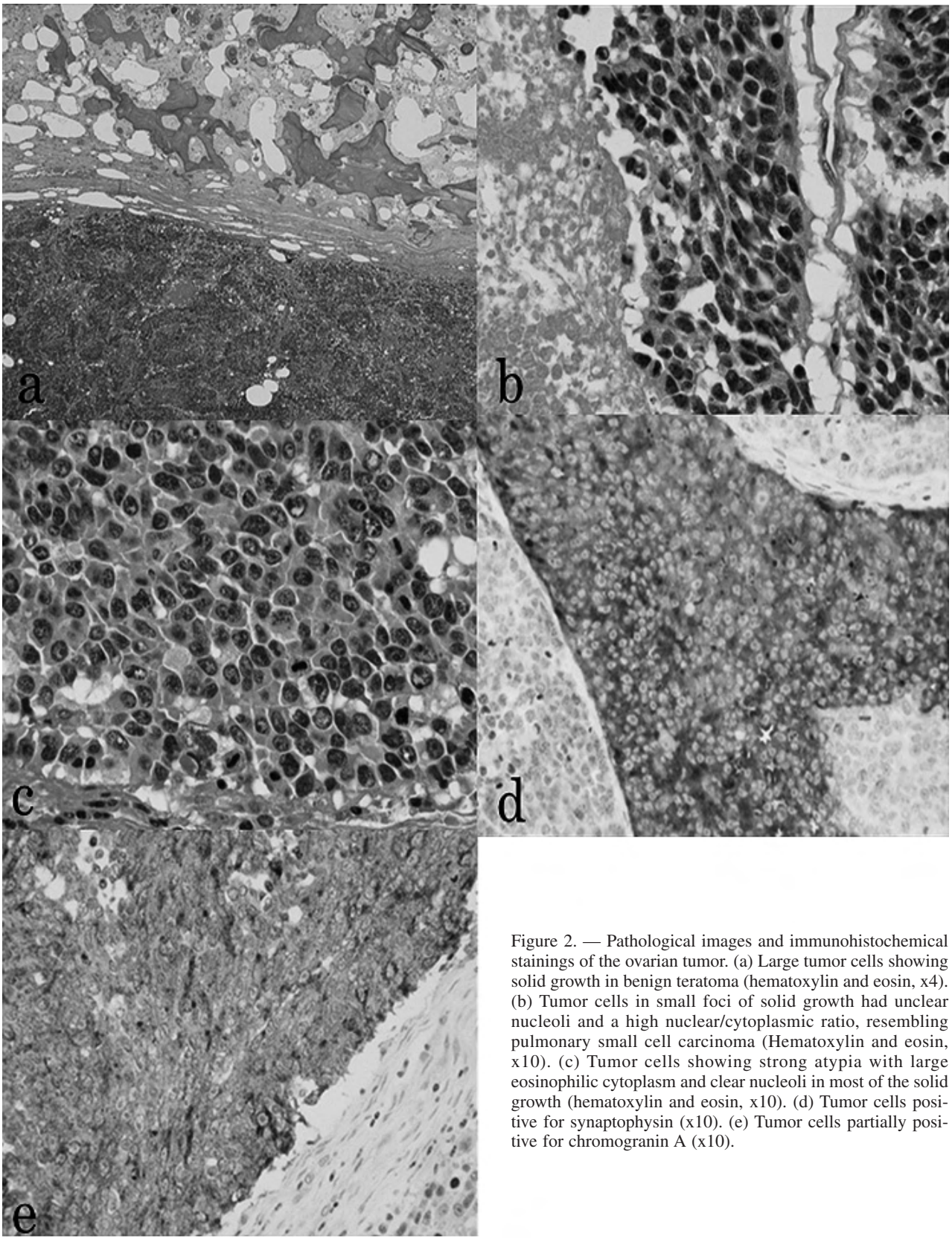

Figure 2. — Pathological images and immunohistochemical stainings of the ovarian tumor. (a) Large tumor cells showing solid growth in benign teratoma (hematoxylin and eosin, x4). (b) Tumor cells in small foci of solid growth had unclear nucleoli and a high nuclear/cytoplasmic ratio, resembling pulmonary small cell carcinoma (Hematoxylin and eosin, x10). (c) Tumor cells showing strong atypia with large eosinophilic cytoplasm and clear nucleoli in most of the solid growth (hematoxylin and eosin, x10). (d) Tumor cells positive for synaptophysin (x10). (e) Tumor cells partially positive for chromogranin A (x10).

Table 1. — *A literature review of non-small cell endocrine tumors of the ovary.*

Author	Age	Chief complaint	Associated component	Stage	Surgery	Adjuvant therapy	Outcome
With teratoma component							
Hirasawa [3]	56	Abdominal pain	Mucinous adenocarcinoma and teratoma	II	TAH+BSO+PN	not done	DOD 10 months
Veras, *et al*. [4]	47	Abdominal distention	Adenocarcinoma, NOS and mature teratoma	III	TAH+BSO	Cisplatin-based chemotherapy	NED 11 months
Chênevert, *et al*. [5]	53	Abdominal distention	Mucinous adenocarcinoma and teratoma	IV IV	TAH+BSO+Omx+PN sampling	Paclitaxel and Carboplatin	DOD 5 months
Chênevert, *et al*. [5]	53	Abdominal distention	Mucinous adenocarcinoma and teratoma	IV	TAH+BSO+Omx	Cisplatin and Etoposide	DOD 7 months
Veras, *et al*. [4]	25	Abdominal pain	Mature cystic teratoma	IV	BSO+Omx+App	Cisplatin-based chemotherapy	DOD 36 months
This study	69	Abdominal pain	Mature cystic teratoma	IV	LSO	Paclitaxel and Carboplatin	DOD 6 months
Without teratoma component							
Chen, *et al*. [6]	44	Dyspnea, abdominal distention	Mucinous intraepithelial adenocarcinoma	I	TAH+BSO+Omx	Paclitaxel and Carboplatin	DOD 4 months
Ohira, *et al*. [7]	33	Lower abdominal pain	Endometrioid adenocarcinoma	I	LSO+Omx	Irinotecan and Nedaplatin	DOD 6 months
Collins, *et al*. [8]	34	Weight loss and abdominal distention	Mucinous BT with small foci of mucinous adenocarcinoma	I	TAH+BSO+Omx	Cisplatin and Cyclophosphamide	DOD 8 months
Jones, *et al*. [9]	22	Abdominal distention	Mucinous cystadenoma	I	TAH+BSO+Omx	not done	DOD 10 months
Eichhorn, *et al*. [10]	77	Vaginal bleeding and pelvic mass	Endometrioid adenocarcinoma	I	TAH+BSO	Radiation	DOD 19 months
Eichhorn, *et al*. [10]	45	Abdominal distention and pain	Mucinous BT with small foci of mucinous adenocarcinoma	I	TAH+BSO+Omx	Cisplatin-based chemotherapy	DOD 36 months
Veras, *et al*. [4]	59	Abdominal pain	High grade adenocarcinoma, NOS	I	BSO	Cisplatin-based chemotherapy	NED 28 months
Veras, *et al*. [4]	54	Pelvic mass	Mucinous adenocarcinoma and endometrioid adenocarcinoma	I	TAH+BSO	Cisplatin-based chemotherapy	NED 66 months
Veras, *et al*. [4]	55	Abdominal pain	Mucinous BT with intra-epithelial adenocarcinoma	I	TAH+BSO	Cisplatin-based chemotherapy	NED 68 months
Hirasawa [3]	35	Unknown	Mucinous adenoma	I	TAH+BSO+Omx	Chemotherapy	NED 120 months
Eichhorn, *et al*. [10]	36	Right lower quadrant pain	Mucinous adenocarcinoma	I	RSO	N/A	N/A
Eichhorn, *et al*. [10]	68	Asymptomatic	Mucinous adenocarcinoma	II	TAH+RSO+Omx	N/A	N/A
Veras, *et al*. [4]	55	Vaginal bleeding	Mucinous BT	III	TAH+BSO	Cisplatin-based chemotherapy	DOD 2 months
Chen, *et al*. [6]	73	Abdominal mass	Microinvasive mucinous adenocarcinoma	III	TAH+BSO+Omx	Paclitaxel, Cisplatin and Adriamycin	DOD 4 months
Eichhorn, *et al*. [10]	58	Pelvic mass	Mucinous BT with small foci of mucinous adenocarcinoma	III	TAH+RSO+Omx	Cisplatin-based chemotherapy	DOD 8 months
Choi, *et al*. [11]	71	Pelvic mass	Serous carcinoma	III	TAH+BSO	Paclitaxel and Carboplatin	NED 8 months
Veras, *et al*. [4]	53	Ascites	Endometrioid adenocarcinoma	III	TAH+BSO	Cisplatin-based chemotherapy	NED 37 months
Veras, *et al*. [4]	22	Abdominal pain	Mucinous BT with small foci of mucinous adenocarcinoma	IV	RSO	Cisplatin-based chemotherapy	DOD 3 months
Veras, *et al*. [4]	63	Ascites	Endometrioid adenocarcinoma	IV	TAH+RSO	Cisplatin-based chemotherapy	DOD 9 months
Veras, *et al*. [4]	42	Pelvic pain	None	IV	TAH+BSO	Cisplatin-based chemotherapy	DOD 20 months
Veras, *et al*. [4]	39	Abdominal pain	Mucinous adenocarcinoma	IV	TAH+BSO	Cisplatin-based chemotherapy	AWD 8 months
Ahmed, *et al*. [12]	30	Asymptomatic	Mucinous cystadenoma	N/A	N/A	N/A	N/A

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RSO, right salpingo-oophorectomy; LSO, left salpingo-oophorectomy; PN, lymphadenectomy; Omx, omentectomy; App, appendectomy; BT, borderline tumor; DOD, dead of disease; NED, no evidence disease; AWD, alive with disease; N/A not available.

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