Small-Cell Carcinoma in Association With a Mature Cystic Teratoma of the Ovary: A Case Report With Literature Review

Karina E. Hew,1 Kimberley Studeman,2 Panayotis Ledakis,3 Arvind Bakhru,4 Neil B. Rosenshein1

Introduction

Malignant transformation of a mature cystic teratoma (MCT) is a well-documented event that occurs in 1% to 2% of cases. Small-cell carcinoma arising from an MCT is particularly rare, with only 3 other cases described in the English literature. We report a case of a 54-year-old para 1 female who was found to have advanced-stage small-cell carcinoma of the ovary in association with a MCT. The clinicopathological features, treatment regimen, and outcome of this patient were compared with the other cases described in the literature to evaluate the prognostic significance of this unusual subtype of ovarian cancer.

Small-cell carcinoma of the ovary arising from a mature cystic teratoma is a rare form of ovarian cancer. It is usually of the pulmonary subtype and is treated with the same chemotherapeutic regimen as small-cell lung cancer. The prognostic significance of this unusual cancer subtype remains uncertain.

Clinical Practice Points

- Malignant transformation of mature cystic teratoma (MCT) is a rare event, occurring in 1% to 2% of cases. Small-cell carcinoma arising from an MCT is particularly rare, with only 3 other cases described in the English literature.
- We report a case of a 54-year-old para 1 female who was found to have advanced-stage small-cell carcinoma of the ovary in association with a MCT. The clinicopathological features, treatment regimen, and outcome of this patient were compared with the other cases described in the literature to evaluate the prognostic significance of this unusual subtype of ovarian cancer.
- Small-cell carcinoma of the ovary arising from a mature cystic teratoma is a rare form of ovarian cancer. It is usually of the pulmonary subtype and is treated with the same chemotherapeutic regimen as small-cell lung cancer. The prognostic significance of this unusual cancer subtype remains uncertain.

Case Description

The patient is a 54-year-old gravida 1 para 1 married white female who originally presented in February 2010. She presented with a 1-month history of abdominal pain and increased abdominal girth. A computed tomography scan of her abdomen and pelvis revealed a 15 × 10 × 13-cm right pelvic mass and ascites. A paracentesis was performed resulting in 4 L of bloody, cloudy peritoneal fluid with atypical cells and increased nuclear cytoplasmic ratio. The hypercalcemic type is thought to be present in two-thirds of cases. They demonstrate aggressive biologic behavior and high rates of local and distant recurrence. These neuroendocrine carcinomas are thought to have poor prognoses.

It has also been put forward that malignant transformation of an MCT, particularly to squamous cell carcinoma, carries a worse prognosis than primary squamous cell carcinoma of the ovary. However, little is known about the natural history, optimal treatment regimens, or prognosis when an MCT undergoes transformation to a small-cell carcinoma of the ovary.

Address for correspondence: Karina E. Hew, MD, The Gynecologic Oncology Center, Weinberg Building, 6th Floor, Mercy Medical Center, 361 St Paul Place, Baltimore, Maryland 21202
E-mail contact: karinahew04@hotmail.com
diagnosis revealed an undifferentiated carcinoma arising from a mature cystic teratoma.

The final pathology report described a small-cell carcinoma arising in association with an 18-cm mature cystic teratoma of the right ovary. There was microscopic involvement of the diaphragm, omentum, and paraaortic nodes, and the cancer was classified as International Federation of Gynecology and Obstetrics stage IIIC. Angiolympathic invasion was present.

The patient had an uneventful postoperative course and received six cycles of adjuvant chemotherapy with carboplatin and etoposide. She did not suffer any significant toxicity from the chemotherapy, with the exception of grade 1 myelosuppression and neuropathy. The patient never exhibited any laboratory or clinical sign of hypercalcemia throughout her presentation. She currently exhibits no evidence of recurrence at 33 months since her surgery.

Pathologic Description

Gross Features

The right ovary and fallopian tube weighed 278 g and included an intact right ovary measuring 18.0 × 13.5 × 11 cm with a mottled pink-purple surface. Serial sections of the ovarian mass revealed a multiloculated and fleshy cut surface, with the cysts containing thin, clear fluid, yellow gelatinous material, and gray-white grumous material with associated strands of hair. Areas of softening consistent with necrosis were identified (Fig. 1).

Microscopic Description

The malignant neuroendocrine population comprised approximately 90% of the ovarian tumor mass. The residual teratomatous component consisted of ectodermally derived epithelium, skin adnexal structures, and intestinal epithelium. Definite bronchial epithelium was not identified. Immature teratomatous elements such as embryonic tissues or primitive neural tissue were not seen, nor were malignant transformed mature elements other than those described in Figure 2.

In sections from the ovarian mass, large areas of tumor necrosis were identified, and sheets of undifferentiated malignant cells with a high nuclear-cytoplasmic ratio, nuclear molding, and some larger cells with small nucleoli, in sheets, trabeculae, and islands, in a background of teratomatous elements were identified. Mitotic figures were abundant. Follicle-like structures were not seen. Within the fallopian tubal lumen, malignant neuroendocrine tissue fragments were identified. Small-cell carcinoma was also identified in the alcohol-fixed Papanicolaou-stained cytologic preparation from the diaphragmatic smear, the omentum, para-aortic lymph nodes, and the nodule on the right infundibular pelvic ligament. Of 3 paraaortic lymph nodes, 2 had metastatic deposits, the largest measuring 2.5 cm with extranodal tumor extension into soft tissue identified.

Immunohistochemical Features

The malignant cell population was labeled with CD56 (neural cell adhesion molecule [NCAM], the prototypic natural killer cell marker; most neuroendocrine cells and tumors with neurosecretory granules express NCAM protein) (Fig. 3), chromogranin, and synaptophysin (the latter with weak granular cytoplasmic staining) (Fig. 4A and 4B). Chromogranin A remains the single most specific marker of neuroendocrine differentiation, labeling the cytoplasmic chromogranin protein stored in secretory granules. Synaptophysin, a calcium-binding glycoprotein, is the most abundant membrane protein in synaptic vesicles of neurons, and is present in neuroendocrine neoplasms. The Ki-67 (mindbomb E3 ubiquitin protein ligase 1 [MIB-1]) index was high (> 90%), which is generally associated with aggressive clinical behavior (Fig. 5). Immunostain results were negative for intermediate filaments of cytokeratins 7 and 20 and thyroid transcription factor 1 (TTF-1).

Discussion

MCTs are a common neoplasm of the ovary accounting for 10% to 20% of all ovarian tumors and occur most commonly in the fifth to sixth decade of a patient’s life. However, only 1% to 2% of MCTs undergo malignant transformation, and the
majority of these are squamous cell carcinomas. However, there have been only 3 case reports in the English literature of small-cell carcinoma of the ovary arising from a MCT. In contrast, primary small-cell carcinomas of the ovaries are described more frequently in the literature and have been subclassified into pulmonary and hypercalcemic subtypes. These 2 subtypes have characteristic pathologic, ultrastructural, flow cytometric, and immunohistochemical features.

Attempts at distinguishing between ovarian small-cell carcinoma of the hypercalcemic type and pulmonary type utilizes clinical information including patient age, serum calcium levels, and whether tumor is unilateral or bilateral. Histologic features including the presence of follicular spaces; the presence of a large-cell component; and the presence of an associated endometrioid, mucinous, or Brenner tumor are utilized to help classify the 2 entities. Additionally, vimentin expression and DNA content are examined by flow cytometry.

This patient exhibited mixed features of both the pulmonary and hypercalcemic subtype. Her age, the absence of postoperative elevated serum calcium levels, and the lack of follicle-like spaces favored a pulmonary subtype. However, the presence of a population of large cells with prominent nucleoli and no associated Brenner or endometrioid component were more indicative of the hypercalcemic type. Although no bronchial epithelium was identified, it is postulated that small-cell carcinoma arose from a malignant transformation of a mature element within the teratoma. This was similar to the findings noted by Chang et al, where bronchial epithelium was also not identified among the mature teratomatous elements. In the case report by Ikota et al, it was postulated that the adenocarcinoma arose from an intestinal epithelium in the teratoma, which then differentiated into pulmonary type small-cell carcinoma among other types of carcinomas.

Primary small-cell carcinomas of the ovary have been well described in the literature and arise in the background of epithelial-stromal tumors. These tumors exhibit aggressive biological behavior with frequent relapses; they are usually treated with a multidisciplinary approach using combined surgery, chemotherapy, and occasionally radiation. There is no randomized study of these tumors, and the majority of data originate from institutional experience and case series. The actual optimal sequence of various treatment modalities such as adjuvant versus neoadjuvant systemic chemotherapy has not been determined. In most cases, patients have received multiple cycles of platinum-based
chemotherapy in the adjuvant setting, with or without concomitant radiation therapy.11,14,17,18 One study looked at a fertility-sparing approach to treating advanced-stage, primary, small-cell ovarian cancer with a disease-free survival of ≥ 60 months.17 Whereas most patients appear to have tolerated multiagent chemotherapy well, the risk of long-term toxicity, such as the incidence of myelodysplastic syndromes and secondary bone marrow neoplasias, is recognized in small-cell lung cancer and has not been studied in women with primary small-cell ovarian cancer.20

Because of the rarity of this type of malignant transformation, the treatment has been similar to that of primary small-cell carcinoma of the ovary. Clinicopathological characteristics, treatment regimens, and clinical outcomes of the 4 cases that have been reported are summarized in Table 1. All 4 patients, including our case, had a complete response to treatment and showed no evidence of disease with follow-up periods ranging from 10 to 84 months. Chen et al found that survival was significantly affected by cancer stage and optimal cytoreduction in patients with malignant transformation of MCT.13 However, there was no patient with small-cell carcinoma in their study population. More recent data from Sakuma et al, who studied 20 cases of transformed malignancies of the ovary retrospectively, suggested that postoperative chemotherapy with platinum and taxane combination could improve clinical outcomes.14 However, the majority of their patients had undergone transformation to a squamous cell carcinoma.

To our knowledge, our case of an exceedingly rare small-cell carcinoma transformed from MCT of the ovary demonstrates one of the longest reported remissions after cytoreduction and systemic chemotherapy with a platinum-based regimen. The combination of etoposide and carboplatin that was used, is the standard treatment for small-cell lung cancer. Though, in fact our patient did not have all the features of the pulmonary subtype.

The prognostic significance of this uncommon subtype of ovarian cancer is difficult to discern, as there are only 4 reported cases, including the case reported in this article. Therefore, large population-adjusted epidemiologic studies should be implemented to further evaluate the clinical impact of this rare entity.18,21

## Conclusion
Small-cell carcinomas of ovary arising from a malignant transformation of an MCT are very rare entities, with only a few cases reported. Whether there are any differences in clinical outcomes between primary and transformed small-cell carcinoma of the ovary remains uncertain. The optimal management of these tumors is not well defined, although in most centers they are treated with a multidisciplinary approach that includes multiagent platinum-based chemotherapy. Although optimal cytoreduction remains the main treatment modality, we report a long-term follow-up of a patient remaining in prolonged remission after postoperative chemotherapy with a small-cell lung cancer—like regimen. In the future, molecular characterization of these tumors may aid in the design and implementation of more effective therapies for this type of cancer.

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## Disclosure
The authors have stated that they have no conflicts of interest.

## References

## Table 1
### Small-Cell Carcinomas Arising in Association With a Mature Cystic Teratoma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Stage (FIGO)</th>
<th>Ovary Site</th>
<th>Size, cm</th>
<th>Histologic Subtype</th>
<th>Treatment</th>
<th>Survival, months</th>
<th>Prognosis</th>
</tr>
</thead>
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<tr>
<td>How et al</td>
<td>IIC</td>
<td>Right</td>
<td>18</td>
<td>Mixed</td>
<td>Surgery + etoposide/ carboplatin × 6 cycles</td>
<td>33</td>
<td>NED</td>
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<td>IA</td>
<td>Left</td>
<td>12</td>
<td>Pulmonary</td>
<td>Surgery</td>
<td>10</td>
<td>NED</td>
</tr>
<tr>
<td>Lim et al</td>
<td>IV</td>
<td>Left</td>
<td>28</td>
<td>Pulmonary</td>
<td>Surgery + etoposide/ bleomycin/cisplatin × 6 cycles</td>
<td>34</td>
<td>NED</td>
</tr>
<tr>
<td>Chang et al</td>
<td>IA</td>
<td>Left</td>
<td>20</td>
<td>Pulmonary</td>
<td>Surgery + cisplatin/ doxorubicin (Adriamycin)/ cyclophosphamide × 8 cycles</td>
<td>84</td>
<td>NED</td>
</tr>
</tbody>
</table>

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; NED = no evidence of disease.

*Index case.*