Case report

Small cell carcinoma of the ovary, pulmonary type: A role for adjuvant radiotherapy after carboplatin and etoposide?

Anase S. Asom a, Ricardo R. Lastra b, Yasmin Hasan c, Lori Weinberg d, Gini F. Fleming e, Katherine C. Kurnit f,*

a University of Chicago Pritzker School of Medicine, Chicago, IL, United States
b University of Chicago, Department of Pathology, Chicago, IL, United States
c University of Chicago, Department of Radiation Oncology, Chicago, IL, United States
d Minnesota Oncology, Coon Rapids, MN, United States
e University of Chicago, Department of Medicine, Chicago, IL, United States
f University of Chicago, Department of Obstetrics & Gynecology, Chicago, IL, United States

A B S T R A C T

Background: Primary small cell ovarian cancer of pulmonary type (SCCOPT) remains a rare ovarian tumor. Its aggressive nature is associated with poor survival outcomes. Current treatment algorithms rely on systemic chemotherapy, primarily involving platinum agents. However, given its low incidence, less is known about the potential benefits of other treatments.

Case Presentation: We report a case of an 80-year-old woman who was found to have a complex pelvic mass with a mildly elevated CA-125. She underwent a laparotomy for staging with tumor debulking; she had bulky unresectable adenopathy and pathology was consistent with stage IIIC SCCOPT. Postoperative imaging revealed progression of disease. She received six cycles of carboplatin and etoposide followed by consolidative radiation therapy to her para-aortic lymph nodes. She remains disease-free for over four years after completion of adjuvant therapy.

Discussion: Histologically, SCCOPT resembles small cell carcinomas of the lung, which are treated with a combination of chemotherapy and radiation therapy. New approaches that build upon the current treatment approaches and incorporate strategies from non-gynecologic tumor types could be beneficial.

1. Introduction

Small cell carcinoma of the ovary pulmonary type (SCCOPT) remains an unusual and highly aggressive malignant neoplasm (Kurasaki et al., 2013). The majority of cases are diagnosed at stage III-IV and it often affects older women (Stewart et al., 2016). Current reports suggest a high case fatality rate regardless of stage at diagnosis (Kurasaki et al., 2013; Stewart et al., 2016).

SCC OPT represents less than 1% of all ovarian cancers (Chun, 2015), and there have been fewer than 30 cases reported in the literature to date. Its histology (neuroendocrine differentiation) mimics small cell carcinoma of the lung. Thus, at diagnosis, the differential must include both metastatic lesions as well as other rare ovarian neoplasms: e.g., small cell carcinoma of the lung with metastasis to the ovary, small cell carcinoma of the cervix with metastasis to the ovary, Sertoli-Leydig cell ovarian tumors, desmoplastic small cell round ovarian tumors, and Ewing sarcoma of the ovary (Chun, 2015).

The current recommendations for management of SCCOPT involve primary surgical resection with adjuvant chemotherapy using a platinum agent. However, the average survival from diagnosis is under two years (Tsolakidis et al., 2012). Here we report a case of prolonged survival of an 80-year-old woman with primary SCCOPT treated with adjuvant platinum-based chemotherapy followed by consolidative radiation. We also discuss the current spectrum of treatment options and additional pathologic considerations of this rare tumor type.

2. Case Presentation

An 80-year-old woman presented to her primary care physician with a three-month history of recurrent abdominal pain, distention, and weight loss. CT imaging demonstrated an 8 cm heterogeneously lobulated mass of the right adnexa. A subsequent transvaginal ultrasound confirmed the mass, detailing a large right echogenic adnexal area with increased vascularity, suspicious for an ovarian neoplasm. Further metastatic work-up revealed a 1.4 cm anterior pericardial lymph node on CT imaging of the chest without any suspicious pulmonary nodules or masses. Laboratory evaluation was notable for a mildly elevated Cancer Antigen (CA) 125 of 40 u/mL. The pre-operative differential diagnosis...
included primary ovarian malignancy versus metastatic disease from another primary site, versus a benign mass.

The patient underwent a laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy with removal of the pelvic masses, and tumor debulking of the diaphragm and falciform ligament. Intraoperative findings included: 1) a small post-menopausal uterus; 2) an 8 cm nodular mobile right ovarian mass; 3) a left diaphragm mass; 4) a falciform mass; 5) nodularity on the dome of the liver extending over segment IV to the coronary ligament; and 6) matted para-aortic lymph nodes that were densely adherent to both the aorta and inferior vena cava with disruption of the usual planes. Given the extent of her disease, a radical dissection would have been required to achieve an optimal debulking, the risks of which were thought to outweigh the benefits in light of the patient’s advanced age. Further cytoreduction efforts were aborted, and her tumor debulking was therefore suboptimal.

At the completion of the case, the patient had residual carcinoma-atosis in the upper abdomen as well as enlarged paraaortic lymph nodes. Histologic evaluation demonstrated a high-grade carcinoma composed of cohesive tumor cells with a solid and nested growth pattern, with nuclear molding, brisk mitotic activity, and apoptotic debris. Immunohistochemical stains demonstrated the tumor cells to be positive for keratins (with ‘dot-like’ perinuclear expression of Cam 5.2), chromogranin, synaptophysin, neuron specific enolase, and CD56, consistent with neuroendocrine differentiation (Fig. 1). In combination, the morphology and the immunohistochemical staining pattern was consistent with a small cell carcinoma, pulmonary type. Based upon the overall clinical picture including review of the radiologic chest imaging and the absence of an identifiable pulmonary primary, the final pathology was determined to be consistent with at least a stage IIIC small cell carcinoma of the ovary, pulmonary type.

She recovered well post-operatively. A CT abdomen and pelvis performed four weeks after surgery demonstrated progression of disease, including retroperitoneal and cardiophrenic lymphadenopathy (3.0 × 1.9 cm), peritoneal nodularity, paraaortic lymphadenopathy (3.8 × 3.9 cm), and a subdiaphragmatic nodule (3.8 × 2.9 cm) (Fig. 2). Her postoperative bloodwork demonstrated an elevated CA-125 of 98 u/mL, and continued normal calcium levels.

Her case was discussed at our institutional, multidisciplinary tumor conference and it was recommended that she be treated with platinum-based adjuvant chemotherapy using a small cell carcinoma-type regimen. Given the histology and disease distribution, consideration of radiation therapy after completion of chemotherapy was also discussed. The patient was amenable and received carboplatin (AUC 5) on day 1 and etoposide (80 mg/m²) on days one, two, and three repeated every three weeks for six cycles. She was treated prophylactically with pegfilgrastim and did not have issues with bone marrow toxicity during treatment. During adjuvant therapy, the patient sought input from two Traditional Chinese Medicine providers and also started several herbal supplements on their recommendation. After three cycles of chemotherapy, imaging demonstrated marked improvement of metastatic disease with regression of the falciform ligament mass, and decreased size of the cardiophrenic and paraaortic nodes.

Upon completion of the six cycles of chemotherapy, she remained in good health and was without any significant side effects from chemotherapy. A PET scan showed no FDG-avid lesions, but there was still concern for residual paraaortic disease based on the CT imaging findings (after three cycles of chemotherapy, the paraaortic lymph node decreased to 3.0 × 1.6 cm, and improved further to 2.0 × 0.9 cm after six cycles). Of note, her cardiophrenic lymph node normalized in size after six cycles (nonmeasurable on imaging). She was amenable to radiation therapy and began consolidative and simultaneous integrated boost treatment. She was treated to a limited paraaortic field with simultaneous integrated boost, to 36 and 44 Gy, in 1.8 and 2.2 Gy per fraction, respectively, using volumetric modulated arc therapy technique (Fig. 3). The boost was delivered to the enlarged lymph node and doses were moderated to account for radiosensitive histology.

Repeat CT abdomen and pelvis four months after the completion of radiation therapy showed no evidence of recurrent or metastatic disease, and the reference paraaortic lymph node now measured 0.6 × 0.6 cm. The patient was followed with clinical exams, serial CA-125 levels, and CT chest, abdomen, and pelvis every six months for two years, at which time intensive follow-up was discontinued. She remains without

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**Fig. 1.** A) Representative image of the tumor morphology, demonstrating solid sheets of tumor cells with high nuclear to cytoplasmic ratio, nuclear molding, brisk mitotic activity, and extensive apoptotic debris (H&E, 200x). B) Cam 5.2 immunohistochemical stain demonstrating positive staining in the neoplastic cells with characteristic perinuclear ‘dot-like’ positivity (200x). C) Synaptophysin immunohistochemical stain showing strong and diffuse expression (200x).

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3. Discussion

SCCOPT is a rare subtype of ovarian cancer, notable for its high five-year fatality rate. Imaging and pathology findings, with the associated clinical features, are used to confirm this diagnosis (Kurasaki et al., 2013; Reed et al., 2014). Current treatment options primarily include surgical resection and postoperative adjuvant platinum-based therapy, frequently using regimens also used for small cell lung cancer (Kurasaki et al., 2013; Reed et al., 2014). However, recurrence often still occurs within the first twelve months even for individuals diagnosed at an early stage of disease (Kurasaki et al., 2013). No chemotherapy regimens have consistently shown a survival benefit for this aggressive subtype of ovarian cancer, although data are limited (Nakazawa et al., 2012; Kalampokas et al., 2018).

SCCOPT pathologically resembles small cell lung cancer (SCLC), which is primarily treated with a combination of concomitant chemotherapy and radiation or surgery and adjuvant chemotherapy (Früh et al., 2013). The current standard of care for limited stage disease specifies twice-daily curative-intent radiation therapy for five weeks given currently with cisplatin and etoposide chemotherapy (Früh et al., 2013). For this SCLC patient population, this treatment modality has been shown to improve survival (Früh et al., 2013).

SCLC primarily metastasizes to the liver (20.3%), bone (18.3%), brain (15.5%), and adrenals (6.0%) (Nakazawa et al., 2012). It also metastasizes to the ovary in 0.4% of reported cases (Kitazawa et al., 2019). Given how rare SCCOPT is in the population, once a high-grade neuroendocrine neoplasm is suspected on adnexal pathology, metastasis from a primary SCLC must be excluded. As such, SCLC and SCCOPT are often differentiated by clinical factors, such as pulmonary lesions on imaging and a significant history of smoking (Kurasaki et al., 2013; Früh et al., 2013).

Epithelial ovarian cancer is often confined to the pelvic and abdominal cavities even when diagnosed at advanced stages. In general, the use of radiation therapy in the treatment of epithelial ovarian cancer is relatively limited, with its most notable potential benefit being in the treatment of early-stage clear cell carcinoma (Prendergast et al., 2017). Whole abdominal radiation has been evaluated and is associated with high rates of acute and late toxicity, particularly to the gastrointestinal tract. For all these reasons, it is no longer recommended as a treatment modality (Kalampokas et al., 2018). Instead, platinum-based chemotherapy regimens are currently the standard of care for epithelial
ovarian cancer. However, in less common epithelial ovarian cancer histologies, particularly those that mirror traditionally radiation-responses histologies from other organs, the role of radiation is less clear. Based on the role of radiation in SCLC and the histologic similarities between SCLC and SCCOPT, we included consolidative radiation therapy in our adjuvant treatment plan. Given the rarity of this tumor, the size of her para-aortic nodes on imaging, and the patient’s favorable clinical status at baseline, evidence from the SCLC data was extrapolated to decrease her nodal burden. This patient’s excellent survival might be explained by the increased susceptibility of this tumor type to combined modality treatment.

In the largest available case series, Kalampokas et al. identify nine previously reported patients who had been diagnosed with SCCOPT (Kalampokas et al., 2018). The average survival was of about 24 months (range: 0 to more than 36 months) (Kalampokas et al., 2018). In this series, there was no consensus on the postoperative adjuvant therapy regimen, and the eight patients for whom data was available received six different combinations of chemotherapy. However, all but one patient received a platinum-based chemotherapy doublet (Kalampokas et al., 2018). Of note, two other advanced stage patients (e.g., stage III-IV) who also received platinum and etoposide treatment, lived for over 21 months, but no longer-term follow-up is noted.

For the patient presented here, her rapid clinical progression in the peri-operative period strongly suggests that the combination of postoperative adjuvant carboplatin and etoposide was critical to her treatment plan. Novel to her treatment was the additional use of radiation therapy. Although she had CA-125 normalization after chemotherapy, there was concern regarding residual lymphadenopathy which resolved after her radiation therapy, and the tendency of SCCOPT to recur even in the setting of a clinical complete response. We believe that the use of radiation therapy significantly contributed to the long-term survival of this patient. Our patient’s five-year postoperative survival, particularly in the context of her age and disease burden, represents an outlier in the SCCOPT literature and suggests that consideration of a consolidative radiation approach for patients with this rare tumor may be beneficial.

4. Conclusion

Primary small cell ovarian carcinoma of pulmonary type is a rare and aggressive subtype of ovarian cancer. Though surgical resection and adjuvant, platinum-based chemotherapy is the current standard treatment, the low incidence of SCCOPT has prevented detailed study on the optimal therapeutic management for this important subset of patients. The patient described in this report represents one of the longest surviving individuals with metastatic SCCOPT noted in the literature to date. We propose that consideration of consolidative radiation therapy after completion of a neuroendocrine-type chemotherapy regimen may have contributed to her prolonged survival. Further investigation of novel treatment approaches for these patients is necessary to continue to improve outcomes for these patients, but will likely require significant collaborative efforts given the rarity of this tumor type.

Author Contribution Statement

The authors confirm contribution to the paper as follows: Case conception and draft manuscript: A.A., G.F., and K.K.; Analysis and interpretation of imaging and pathology: A.A., R.L., Y.H., L.W., G.F., K.K.; Interpretation of findings: A.A., R.L., Y.H., L.W., G.F., and K.K. All authors reviewed the results and approved the final version of the manuscript.

Informed Consent Statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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