Case Report

Cyberknife radiotherapy and anastrozole for the treatment of advanced progressive low-grade papillary serous ovarian carcinoma: A case report

Shandhini Raidoo a,⁎, Sareena Singh a, Raymond Redline b, Robert DeBernardo c

a Department of Obstetrics and Gynecology, University Hospitals Case Medical Center, Cleveland, OH, USA
b Department of Pathology, University Hospitals Case Medical Center, Cleveland, OH, USA
c Department of Obstetrics and Gynecology, Cleveland Clinic Foundation, Cleveland, OH, USA

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Introduction

Low-grade serous ovarian carcinoma represents a minority of ovarian cancers, and is distinct from high-grade serous ovarian carcinoma in its development, survival rates, and response to therapy. We present a case of advanced widely metastatic low-grade serous ovarian carcinoma successfully treated with Cyberknife radiotherapy followed by anastrozole at progression.

Case report

A 45 year-old morbidly obese (BMI 41) African–American woman presented with a new sensation of chest discomfort. Her initial workup was negative. A few months later, she presented with a new left-sided mass on her back. The mass was excised and was identified as a low-grade papillary serous carcinoma consistent with an ovarian origin (Fig. 1A). On further investigation, a CT scan identified an irregularly-shaped calcified chest mass along the right cardiac border, multiple pulmonary nodules, and a pelvic mass measuring 6 × 7 cm (Fig. 2). A PET/CT demonstrated a large right mediastinal mass with irregular calcification and increased uptake measuring 10 cm × 6.5 cm × 5.8 cm. Increased uptake was identified in multiple pulmonary nodules, bilateral axillary and inguinal lymph nodes, and soft tissue nodules in the abdomen suspicious for malignancy. An echocardiogram demonstrated compression of the right atrium by the mediastinal mass.

A right-sided video-assisted thoracoscopic surgery (VATS) was performed, and the mass was noted to involve the phrenic nerve and the superior vena cava, rendering it unresectable. A right middle lobe wedge resection was performed at the time of the VATS, and the pathology results revealed a low-grade papillary serous carcinoma. A few weeks later, the patient underwent a laparoscopic bilateral salpingo-oophorectomy, omentectomy, and diaphragmatic biopsy. The pathology of these specimens revealed bilateral serosal borderline ovarian tumors with microinvasion on the left (Fig. 1B), an omental implant indefinite for invasion, and positive peritoneal cytology. Her initial CA-125 at the time of surgery was 215.9. Histologic stains revealed the tumor to be estrogen and progesterone receptor positive, positive for CK7 and vimentin, and negative for CEA, CK20, CD10, and TTF-1. PAX8 and WT-1 immunostaining of tumor samples confirmed that the metastatic deposits were derived from the primary ovarian tumor. The patient was diagnosed with FIGO stage IV low-grade papillary serous carcinoma of the ovary.

The compressive effects of the tumor on the pericardium resulted in extreme exercise intolerance and shortness of breath at rest. The unresectable mediastinal mass was treated with Cyberknife radiosurgery at a dose of 36Gy in two fractions over four days. Following treatment of the cardiac lesion, the patient was started on tamoxifen 20 mg by mouth twice daily.

The patient’s disease remained stable on tamoxifen for five months, after which the metastatic nodule in her anterior abdominal wall was found to be increasing in size on a routine surveillance CT scan. Megestrol acetate 80 mg twice daily for one week was then added to her regimen, followed by three weeks of tamoxifen. On this regimen the patient’s disease remained stable for 8 additional months. Routine imaging demonstrated progression, with an increase in the size and number of pulmonary nodules, an increase in the size of an abdominal wall metastasis, and a rise in CA-125 from 33.1U/mL to 80.5U/mL. The patient also reported a new breast mass which, on core biopsy, demonstrated a papillary lesion confirmed to be low-grade papillary serous carcinoma consistent with metastatic disease by immunohistochemical staining for PAX8 and WT1 (Fig. 1C). Three months later, the patient underwent resection of the metastatic mass in her anterior abdominal wall, which demonstrated pathologic changes consistent with low-grade papillary serous carcinoma.

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⁎⁎ Corresponding author at: Department of Obstetrics and Gynecology, University Hospitals Case Medical Center, 11100 Euclid Ave Mac 5034, Cleveland, OH 44106, USA.
E-mail address: shandhini.raidoo@uhhospitals.org (S. Raidoo).
of the ovary with increased cytologic atypia compared to the primary tumor (Fig. 1D). The subjective impression of increased cytologic atypia in this abdominal wall lesion was verified by quantification of the proliferative fraction by Ki-67 immunostaining (proliferative fraction = 18.0% compared with 3.6% in the original serous borderline tumor, 8.3% in the localized area of microinvasive borderline tumor, and 9.3% in the 2008 metastatic focus of low grade papillary serous carcinoma in the lung). Tamoxifen and megestrol acetate were discontinued, and she was instead started on anastrozole 1 mg by mouth daily. She remains stable on anastrozole. Serial CT scans every 6 months have demonstrated no evidence of disease progression for 42 months.

Discussion

Low-grade serous ovarian carcinoma comprises 10 percent of all ovarian cancers (Schmeler and Gershenson, 2008). It is defined by mild to moderate nuclear atypia and up to 12 mitoses per high-power field. High-grade serous carcinoma, in comparison, is defined by marked nuclear atypia and more than 12 mitoses per 10 high-power field (Schmeler and Gershenson, 2008).

Patients with low-grade serous carcinoma typically present at a younger age than patients with high-grade serous carcinoma: 45–57 years and 44–65 years, respectively (Vang et al., 2009). Although both types present at advanced stages, the median survival for low-grade serous carcinoma is 6.8 years, compared to 1.7 years for high-grade serous carcinoma (Vang et al., 2009).
Ovarian carcinomas are separated into Type I (low-grade serous, low-grade endometrioid, mucinous, clear cell, and Brenner tumors) and Type II (high-grade serous, high-grade endometrioid, carcinosarcoma, and undifferentiated tumors) (Lim and Oliva, 2013). Type I tumors are characterized by genetic stability, and develop from benign, borderline, or endometriosis precursors (Lim and Oliva, 2013). Serous borderline tumors are occasionally linked to low-grade serous ovarian carcinoma through the process of microinvasion, although this occurs in a small minority of cases (Hogg et al., 2007).

Ovarian cancer, both low-grade and high-grade, often presents at advanced stages with disease outside of the pelvis. When a patient’s presenting complaint is unrelated to pelvic or abdominal symptoms, as with this case, it is important to obtain an accurate diagnosis. PAX8 and WT1 are two immunohistochemical markers that are used in the identification of metastatic ovarian carcinoma: PAX 8 has a detection rate of 87 percent for carcinomas of Mullerian origin, while WT1 has a detection rate of 63 percent (Zhao et al., 2012). Combined testing for the two increases detection rate to 94 percent (Zhao et al., 2012). The tumor samples obtained from this patient were all positive for PAX8 and WT1.

Low-grade serous ovarian carcinomas have a poor response to traditional chemotherapy. Standard chemotherapy for high-grade ovarian cancer typically consists of platinum and taxane based combinations. In a study of neoadjuvant traditional chemotherapy in low-grade serous ovarian carcinoma, only 4 percent of patients responded with improvement in disease status (Schmeler et al., 2008). Adjuvant chemotherapy is associated with a similarly poor response rate (Schmeler and Gershenson, 2008; Vang et al., 2009). This characteristic poor response is attributed to the differences in molecular profiles and proliferative activity between low and high-grade serous carcinomas (Vang et al., 2009).

Estrogen (ER) and progesterone (PR) receptors are variably expressed in ovarian cancers and confer a survival advantage. In a large Danish study of ER/PR expression in ovarian tumors from 773 patients, 36 percent of tumors were found to be ER positive, and 20 percent of tumors were found to be PR positive (Hagdall et al., 2007). An analysis of survival data demonstrated that ER and PR positivity of 10 percent or higher was independently predictive of disease-specific survival (Hagdall et al., 2007). ER and PR receptors are also expressed at significantly higher levels in low-grade serous ovarian carcinomas than in high-grade (Schmeler and Gershenson, 2008).

Cyberknife stereotactic radiosurgery is image-guided robotically-controlled external beam radiation that enables highly conformal administration of radiotherapy to target lesions within the body; in this case, the chest. Both respiratory and cardiac motions are accounted for in real time by synchronous imaging just prior to delivery of the prescribed therapy (Kunos et al., 2012). This is the first report in the literature of Cyberknife stereotactic radiosurgery being used to treat low-grade serous ovarian carcinoma. This patient had an excellent response with resolution of her symptoms and improvement of her performance status.

Tamoxifen, a selective estrogen receptor modulator, is a widely-used agent for the treatment and prevention of breast cancer, particularly in the setting of estrogen-receptor positivity. A retrospective review of its use in the treatment of recurrent small volume ovarian, fallopian tube, and peritoneal cancers demonstrated that it may have some success in the management of recurrence of these gynecologic malignancies (Markman et al., 2004). This therapy was effective in our patient for five months, and then a combination of tamoxifen and megestrol acetate for eight additional months. At progression, she underwent resection of a symptomatic abdominal wall mass and began anastrozole therapy. She continues to enjoy stable disease after forty-two months of therapy.

Conclusion

Low-grade papillary serous ovarian carcinoma is a malignancy with unique features. It does not, in general, respond well to chemotherapy and there is no standard therapy to treat cases of advanced disease. Surgical resection was not feasible in this case. This case demonstrates the excellent long-term control of advanced, unresectable low-grade papillary serous ovarian carcinoma using Cyberknife radiotherapy and supports the use of anastrozole to prevent disease progression.

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

Conflict of interest statement

The authors do not have any potential conflicts of interest to disclose.

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