Gynecologic Oncology Reports 18 (2016) 45–48

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Small cell ovarian carcinoma: Long term survival in juvenile case with poor prognostic features

Lauren Stewart, MD [a,*], Ruchi Garg, MD [b,*], Rochelle Garcia, MD [a,c], Elizabeth Swisher, MD [a]

[a] Department of Obstetrics and Gynecology, University of Washington Medical Center, Seattle, WA, USA
[b] Mid Atlantic Gynecology Oncology and Pelvic Surgery Associates, Annandale, VA, USA
[c] Department of Pathology, University of Washington Medical Center, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 12 September 2016
Received in revised form 1 November 2016
Accepted 5 November 2016
Available online 9 November 2016

Keywords:
Small cell
Ovarian
Chemotherapy
Ovarian preservation

ABSTRACT

Background: Ovarian small cell carcinoma is a rare, aggressive neoplasm that occurs in young women and has a poor long-term prognosis. Treatment involves surgical resection and chemotherapy. The required radicality of surgery is uncertain, balancing cytoreduction with fertility preservation. Various chemotherapy regimens are utilized due to confusion regarding the neoplasm's lineage.

Case

We describe an adolescent with small cell carcinoma, hypercalcemic type, stage IA. Surgery included left salpingo-oopherectomy, left pelvic/paraaortic lymphadenectomy, omentectomy and peritoneal biopsies. She received four cycles of bleomycin, etoposide and cisplatin, similar to high-risk germ cell cancers. She has received no further therapy and is eleven years from diagnosis without evidence of disease.

Conclusion: This is the first long-term juvenile survivor managed with both fertility-sparing surgery and BEP (bleomycin, etoposide, cisplatin).

1. Introduction

Small cell carcinoma of the ovary (SCCO), hypercalcemic type, is an aggressive, rare neoplasm that tends to affect young women, with an average age at diagnosis of 23 years. Long-term prognosis is poor, with overall survival of one to two years in most cases (Young et al., 1994). Patients with early-stage disease confined to the ovary may experience longer survival (Young et al., 1994; Harrison et al., 2006; Distelmaier et al., 2006). There are a few case reports of patients with stage II or III disease surviving several years (Young et al., 1994; Harrison et al., 2006; Sholler et al., 2005; Christin et al., 2008; Kanwar et al., 2008; Tewari et al., 1997; Woopen et al., 2012; Pressey et al., 2013) and no cases of long-term survival in stage IV disease.

Treatment usually includes a combination of surgical resection and chemotherapy (Young et al., 1994; Harrison et al., 2006; Distelmaier et al., 2006; Senekjian et al., 1989; Peccatori et al., 1993; Sholler et al., 2005; Christin et al., 2008; Kanwar et al., 2008; Tewari et al., 1997; Woopen et al., 2012; Pressey et al., 2013). The extent of surgery required is uncertain due to the need to provide aggressive treatment while attempting to preserve fertility in these young patients (Woopen et al., 2012). Fertility-sparing surgery is debated, as many patients are young with unilateral ovarian involvement; however, recurrences in the contralateral ovary have been reported and are usually fatal. Due to the rarity of SCCO, there are no randomized controlled trials that identify optimal treatment. The majority of recommended treatment plans are derived from case reports and small case series. The only prospective trial to date treated 27 patients on a phase II trial consisting of radical surgical resection followed by four to six cycles of chemotherapy with cisplatin, adriamycin, etoposide, cyclophosphamide, and, in case of complete remission, additional high-dose chemotherapy with carboplatin, vepeside, cyclophosphamide (Pautier et al., 2007). This intensive regimen demonstrated a 49% 3-year overall survival rate, which was consistent with previously published reports with less intensive chemotherapy (Pautier et al., 2007).

Various chemotherapy regimens have been proposed, in part due to uncertainty over what cell lineage SCCOs arise from (or differentiate towards); it is not certain whether the neoplastic cells in SCCO derive from ovarian epithelium, sex-cord stromal cells or germ cells (Young et al., 1994; Ulbright et al., 1987). Based on their histology, a number of neoplasms can be confused with SCCO including granulosa cell tumors, dysgerminomas, primitive neuroectodermal tumors, melanoma, lymphomas, round cell sarcomas, and small cell desmoplastic tumors (Distelmaier et al., 2006; McCluggage et al., 2004). Some of these may be excluded based on immunohistochemistry (IHC) protein expression profiles. However, IHC does not clearly distinguish between the possibilities of epithelial and stromal differentiation.

* Corresponding author at: University of Washington Medical Center, Department of Obstetrics and Gynecology, 1959 NE Pacific Street, Box 356460, Seattle, WA 98195, USA
E-mail address: stewart4@uw.edu (L. Stewart).

http://dx.doi.org/10.1016/j.gore.2016.11.002

Poor prognostic factors for SCCO include early age of onset, large tumor size, and elevated serum calcium (Young et al., 1994). We describe our experience with an adolescent patient diagnosed with early stage disease with multiple poor prognostic features who has done well with both conservative surgery and less intensive adjuvant chemotherapy.

2. Case report

In October 2004, a healthy 14-year-old girl presented to the emergency department complaining of abdominal pain following a sexual assault. Her past medical and surgical history was remarkable for drug and alcohol use. Physical exam revealed a large, firm, immobile mass extending from the pubic symphysis to the umbilicus. Pelvic ultrasound demonstrated a 16 × 10 × 17 cm mass and ascites (Fig. 1). Laboratory analyses showed beta HCG <3 mIU/mL, mildly elevated LDH at 202 U/L, CEA 1.1 ng/dL, AFP < 5 ng/mL, inhibin A < 10 pg/mL, inhibin B 25 pg/mL and CA-125 81 U/mL. Her calcium was mildly elevated at 10.9 mg/dL and ionized calcium was also high at 1.53 mmol/L. She was anemic with a hemoglobin of 9.8 g/dl. She underwent exploratory laparotomy. The left ovarian mass (17 × 15 × 12 cm, 1042 g) was removed and frozen section was reported as malignant neoplasm, possible granulosa cell tumor, favor small cell carcinoma. Complete surgical staging was performed including left pelvic and para-aortic lymph node dissection, infracolic omentectomy and peritoneal biopsies. There was no evidence of disease outside of the left ovary and the right ovary appeared normal. Final pathology returned as SCCO, hypercalcemic type, stage IA. By histologic examination, the neoplasm consisted of sheets of cells with small to moderate-sized, irregular nuclei and scant cytoplasm (Fig. 1). The cellular proliferation index was high, with numerous mitotic figures per high-powered-field, apoptotic cell debris and areas of geographic necrosis. Rare follicle formation was present. By IHC the neoplastic cells were negative for CD45, chromogranin, and inhibin and positive for vimentin and cytokeratin AE1/AE3 (Fig. 1).

The patient was treated with four cycles of BEP (bleomycin 30 U day 1, etoposide 100 mg/m^2 days 1–5, and cisplatin 20 mg/m^2 days 1–5, every 4 weeks) from November 2004 to February 2005. After completing chemotherapy, she was followed with serum ionized calcium, pelvic exam (PE), and transvaginal ultrasound (TVUS) of the retained ovary every three months, and CT scan of the chest, abdomen, and pelvis every six months for two years and then with decreased frequency. Her ionized calcium was normal immediately following chemotherapy, but upon recheck 3 months later it was slightly elevated. PE, TVUS, and CT scan were normal at that time. FDG-PET scan showed a focus with SUV 3.3 in the region of the right external iliac lymph nodes and in the upper abdomen posterior to the liver. These findings were concerning for disease recurrence. The patient was taken to the

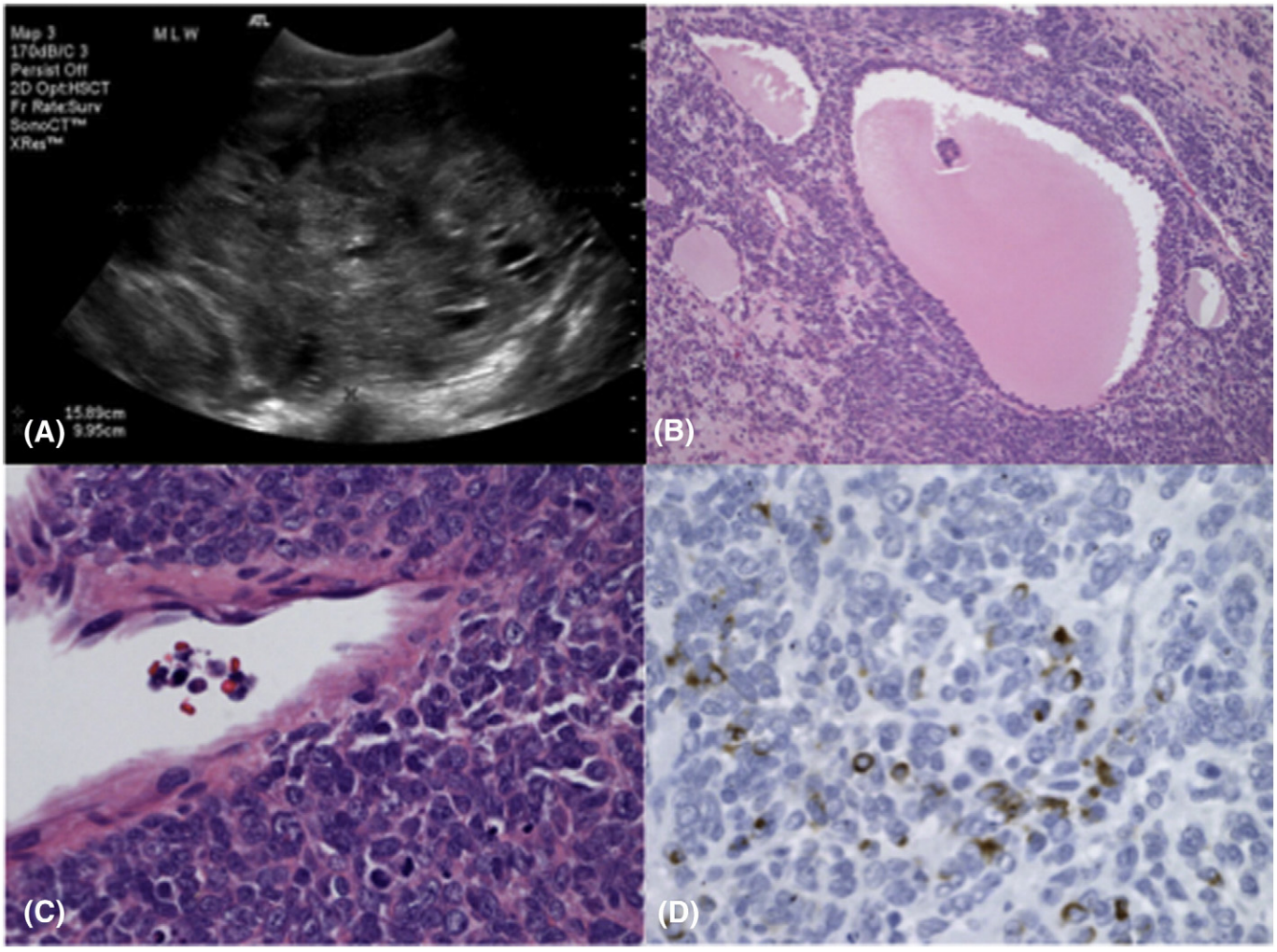

Fig. 1. Selected radiologic and histologic images. A) Transvaginal ultrasound demonstrating the cystic/solid nature of the large mass. B) H&E 100×. Sheets of neoplastic cells form follicles with pink eosinophilic secretions. C) H&E 600×. The neoplasm is composed of small to moderate sized cells with hyperchromatic nuclei and scant cytoplasm. Mitotic figures and apoptotic debris are easily visible. D) Immunohistochemical detection of cytokeratins (brown stain) using AE1/AE3 600×. Cytokeratin expression is common but often scanty in SCCOs as is seen in this case.

operating room, 9 months after initial surgery, for a second look laparotomy with a plan for salvage whole abdominal radiation if any evidence of disease was found and no further treatment in the absence of disease. At the time of surgery, there was no gross evidence of disease. Right pelvic lymph node dissection, peritoneal biopsies, omental biopsy, diaphragm biopsy, and intraoperative ultrasound of the liver were performed. Final pathology was negative for neoplasm. She received no further therapy and as of November 2015, she is eleven years from initial presentation without evidence of disease. She has since had regular monthly periods and one unintended pregnancy, which ended in termination. The only persistent effect from her therapy is right lower extremity lymphedema.

3. Discussion

Our patient has been disease-free for eleven years after treatment for a malignant neoplasm that is reportedly fatal in >50% of stage IA patients (Young et al., 1994). This remarkable survival is even more impressive considering that she had three of the four risk factors for a worse prognosis described by Young et al. in their analysis of 150 cases of SCCO (Young et al., 1994). These risk factors include stage, tumor size > 10 cm, age < 30 years, and an abnormal preoperative serum calcium. In considering an optimal surgical and adjuvant treatment plan for this patient, the goal was to optimize survival while maintaining fertility and ovarian function. Therefore, a conservative, fertility-sparing surgery with USO and complete staging was performed.

Table 1 contains a collection of reported cases of young women with SCCOHT/unspecified type who had a favorable response to therapy (NED at ≥24 months from initial diagnosis) and their treatment regimens. Supplementary Table 1 contains a collection of reported outcomes for young women with small cell carcinoma presenting at various stages. Even among patients presenting with stage IA disease, there are very few patients who have experienced long-term survival without disease recurrence (Table 1). The high incidence of unilaterality (96.4%) in small cell carcinoma of the ovary makes it amenable to conservative surgery (Young et al., 1994). However, several patients initially treated with conservative surgery, but without complete staging, experienced recurrence requiring further therapy. The retained ovary is a common site of recurrence, raising doubt about the safety of unilateral oophorectomy in women with SCCO.

Our patient was treated with cisplatin, etoposide, and bleomycin, a combination aimed at both carcinoma (cisplatin, etoposide) and possible germ cell and sex-cord stromal elements (all three agents). The choice of chemotherapy was based, in part, on the uncertain and possibly dual nature of SCCO. Authors have argued over the stem cell origin of SCCO (Young et al., 1994; Ulbright et al., 1987), although perhaps the more relevant question is which way those stem cells are differentiating. SCCOs have some features which suggest epithelial differentiation and some which suggest sex-cord stromal differentiation (Young et al., 1994; Ulbright et al., 1987). The microscopic appearance of SCCO with closely packed cells that grow in nests, cords or clusters with hyperchromatic nuclei and scanty cytoplasm resembles small cell carcinoma of the lung. However, the follicle-like structures present in 80% of SCCO (Young et al., 1994) and the early age of presentation is more akin to sex cord stromal neoplasms than ovarian carcinomas. By IHC, SCCOs express WT1, vimentin, and cytokeratins (AE1/AE3 or EMA). Expression of WT1 supports the possibility of ovarian origin (Woopen et al., 2012; McCluggage et al., 2004). Co-expression of vimentin and cytokeratins is seen in both epithelial and stromal ovarian neoplasms (Peccatori et al., 1993; Sholler et al., 2005; Christin et al., 2008; McCluggage et al., 2004). These protein expression patterns support the pluripotency of neoplastic cells in SCCO. Similarly, Ulbright et al. emphasized the pluripotency of neoplastic cells in the large cell variant of SCCO, which contains ill-defined pink intracytoplasmic globules, with bright eosinophilic hyaline bodies similar to those seen in many yolk sac tumors (Ulbright et al., 1987).

A variety of chemotherapy regimens have been tried, most of which incorporated some combination of platinum-based therapy and some adding adjuvant radiotherapy. Some of the longer reported survivals in advanced stage disease have been reported with the regimen utilizing a combination of vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide (Table 1). This regimen incorporates traditional germ cell agents with those shown to be effective against other solid tumors. However, it is associated with severe toxicities, including hematologic, gastrointestinal, pulmonary, renal, neurologic, some long-lasting hypomagnesemia, and hearing loss. In contrast, we used the traditional four cycles of bleomycin, etoposide, and cisplatin (BEP) recommended for advanced germ cell carcinomas. Our patient had minimal side effects and has retained fertility.

We described the first case of a patient with stage IA SCCO who underwent fertility preservation surgery and adjuvant treatment with BEP who achieved long term survival without disease recurrence.

Supplementary data to this article can be found online at doi:10.1016/j.gore.2016.11.002.

Table 1
Published cases of SCCOHT/unspecified type in patients <30 years at diagnosis[a] who had a favorable response to therapy (NED at ≥24 months from initial diagnosis) (Young et al., 1994; Harrison et al., 2006; Distelmaier et al., 2006; Senekjian et al., 1989; Peccatori et al., 1993; Sholler et al., 2005; Christin et al., 2008; Kanwar et al., 2008; Tewari et al., 1997; Woopen et al., 2012; Pressey et al., 2013; McCluggage et al., 2004).

Ref.	Age	Stage	Ovarian preservation	Post-op treatment	Site of recurrence (mos)	Status (mos)
Young et al. (1994)	10	IA	Y	P, V	Lymph nodes (5)	NED (53)
Young et al. (1994)	19	IA	Y	P, V, B	Pelvis/abd wall (4/18)	NED (45)
Woopen et al. (2012)	29	IA	N	Cb, T	–	NED (29)
Senekjian et al. (1989)	21	IA	N	V, C, A, E	–	NED (29)
Distelmaier et al. (2006)	11	IA	Y	Cb, E, C, T, VCR, Act-D for recurrence	Peritoneum (11)	NED (64)
Distelmaier et al. (2006)	9	IA	Y	Cb, E, C, T, VCR, Act-D, A Then HD-CT with Cb, E, Mel	–	NED (73)
Peccatori et al. (1993)	23	IB	N	P, V, B	–	NED (58)
Woopen et al. (2012)	18	IIB	Y	P, I, A, + ASCT	–	NED (47)
Young et al. (1994)	16	IIB	Y	E, P, C, A, VCR	Not specified (6)	NED (72)
Young et al. (1994)	19	III	N	E, P, A, VCR	–	NED (30)
Pressey et al. (2013)	6	IIIB	N	V, P, C, B, A, E then HD-CT with Cb, E, Mel + Rads	Pelvis (0)	NED (33)
Sholler et al. (2005)	11	IIIB	Y	V, P, C, B, A, E	–	NED (25)
Tewari et al. (1997)	26	IIIC	N	V, P, C, B, A, E	–	NED (66)
Kanwar et al. (2008)	17	IIIC	Y	V, P, C, B, A, E + Imatinib, Thalidomide, Celecoxib	–	NED (36)
Pressey et al. (2013)	10	IIIC	Y	V, P, C, B, A, E	–	NED (84)

Chemotherapy abbreviations: A: Doxorubicin; B: Bleomycin; C: Cyclophosphamide; Cb: Carboplatin; E: Etoposide; I: ifosfamide; P: Cisplatin; T: Paclitaxel; V: Vinblastine; VCR – vincristine; Act-D – Actinomycin D; Mel – Melphalan; HD-CT: High-dose Chemotherapy; ASCT: Autologous stem cell transplant.

[a] This table excludes patients ≥30 yrs. of age at diagnosis with the exception of cases from Young et al. (1994) in which ages were not linked with cases. In their cohort, 20% of patients were ≥30 yrs.

Conflicts of interests

None.

Acknowledgements

None.

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