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Successful pregnancy following chemotherapy in a survivor of small cell carcinoma of the ovary, hypercalcemic type (SCCOHT): A case report and review of literature☆

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1. Introduction

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare neoplasm that mostly affects young women. Patients are usually diagnosed in their second or third decade of life, with a peak age between age 18 and 39 years (Young et al., 1994). The symptoms are usually nonspecific and include abdominal discomfort, pain or distension related to an abdominal or pelvic mass. Most patients are diagnosed at an advanced stage. Regardless of disease stage, most patients relapse and die of disease. The estimated overall survival rate is 50% at one year and less than 10% at five years (Young et al., 1994).

Several studies have reported familial cases of SCCOHT with an autosomal dominant pattern of inheritance. It is associated with germline or somatic mutation in the SMARCA4 gene, which encodes the BRG1 protein. A recent study showed that even in patients with no family history of SCCOHT, up to half of those tested were found to carry a germline mutation (Witkowski, 2016).

There is currently no standard protocol for treatment of SCCOHT and management remains a challenge. Previous studies have reported favorable results with a chemotherapy regimen consisting of vinblastine, cisplatin, cyclophosphamide, bleomycin, adriamycin and etoposide (VPCBAE) as an adjuvant treatment after surgery (Senekjian et al., 1989; Callegaro-Filho et al., 2016). Other treatments showing activity in SCCOHT include other platinum-based chemotherapy regimens, high-dose chemotherapy with stem cell transplant, radiation therapy and immunotherapy. Given the young age at diagnosis, many women with this disease desire preservation of fertility. There are limited data on fertility and pregnancy outcomes among women treated for SCCOHT. In this report, we present the case of a successful pregnancy following chemotherapy with VPCBAE.

2. Case presentation

A 26-year-old nulligravid Caucasian woman presented to her gynecologist in June of 2011 with abdominal pain, abdominal distension and emesis. Her physical examination revealed a large pelvic mass with tenderness on palpation. Transvaginal ultrasound showed a complex solid mass measuring 15.2 × 8.0 cm. She underwent surgery with a general gynecologist who performed a diagnostic laparoscopy converted to exploratory laparotomy with right salpingo-oophorectomy, with the ovary removed intact. Intraoperative findings included a 15 cm complex right ovarian mass. Frozen section was not performed.

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Her left ovary and uterus appeared normal. There was no evidence of metastatic disease in the abdomen or pelvis. Staging procedures were not performed. Final pathology showed apparent stage IA SCCOHT. Her postoperative tumor markers (CA125, CEA, CA19-9) were within normal limits. Calcium level was also normal. She then presented to MD Anderson Cancer Center where review of the surgical specimens by a pathologist with expertise in gynecologic cancers confirmed the diagnosis of SCCOHT. Computed tomography (CT) scan of the chest, abdomen and pelvis was negative. She was treated with 6 cycles of VPCBAE chemotherapy every 28 days at the following doses: vinblastine (6 mg/m^2 intravenous (IV) over 30 min on Day 1), cisplatin (90 mg/m^2 IV over 4 h on Day 1), cyclophosphamide (1000 mg/m^2 IV over 60 min on Day 2), bleomycin (15 units/m^2 IV over 24 h on Day 2), doxorubicin (45 mg/m^2 IV over 30 min on Day 3, and etoposide (200 mg/m^2 IV over 2 h on Day 3). All chemotherapy was administered on an inpatient basis and pegfilgrastim 6 mg was given following each cycle for the prevention of chemotherapy-induced neutropenia. She tolerated chemotherapy well and completed therapy in December 2011. Germline testing was negative for mutations in the SMARCA4 gene. Of note, the patient had no family history of ovarian cancer. At the completion of therapy, imaging with CT scans showed no evidence of disease.

The patient desired future fertility and was placed on surveillance with no further treatment. She underwent clinic visits with pelvic exam and CA125 level every 3–4 months during the first 2 years then every 6 months. Imaging with pelvic ultrasound and/or CT scan was performed periodically during the surveillance period and all tests were negative. She ceased having menstrual periods after her first cycle of chemotherapy, however she resumed having regular periods approximately 9 months after completing treatment. She was started on oral contraceptive pills at that time. Approximately six years after completing chemotherapy, she discontinued the oral contraceptive pills and was able to conceive naturally. She had a normal vaginal delivery of a term healthy baby boy. She remains without evidence of disease 8 years after completing therapy, and her son is currently 18 months of age.

3. Discussion

The rarity of SCCOHT has made it difficult to establish standard treatment guidelines. The primary therapy for early-stage disease is surgery. In women with stage IA disease, unilateral salpingo-oophorectomy has a reported 5-year disease-free survival rate of approximately 30% (Estel et al., 2011). However, even when diagnosed at an early stage, more than half of patients eventually die of their disease. Potentially favorable prognostic factors for women with stage IA disease include: age $>$ 30 years, normal preoperative calcium level, tumor size $\leq$10 cm, absence of large cell histologic finding, operation that included bilateral oophorectomy, and postoperative radiation therapy (Young et al., 1994).

The largest published series to date is by Young et al. (1994) and includes 150 women with SCCOHT, the majority of whom received adjuvant chemotherapy. However, only 7 of these patients had a response to chemotherapy which consisted of regimens including anthracyclines, etoposide, cisplatin and alkylating agents. Treatment with the VPCBAE chemotherapy regimen has shown promising results. The first report by Senekjian et al. (1989) included 5 patients and showed a disease-free interval of 29 months in one patient and survival of 11–18 months in four patients. A subsequent retrospective study from our group of 47 patients with SCCOHT demonstrated that VPCBAE was associated with a decreased rate of recurrence (Callegaro-Filho et al., 2016). In all reports, the major reported toxicities associated with VPCBAE were severe myeolosuppression, neutropenic fever/sepsis, polyneuropathy and moderate to severe nausea and vomiting.

The use of radiotherapy has also been described as adjuvant therapy as well as for the treatment of recurrent disease in women with SCCOHT. From the report by Young et al. (1994) of 150 cases, five of the fourteen patients with stage IA disease received adjuvant radiotherapy and four (80%) are long term survivors. A case report by Callegaro-Filho et al. (2015) described a patient with recurrent SCCOHT who had complete resection of a 8.2 cm para-aortic mass followed by radiotherapy; she is alive and without evidence of disease 15 years after treatment.

Several reports have also shown high-dose chemotherapy with stem cell transplantation to be effective treatment in SCCOHT. Qin et al. (2018) reported the case of a woman with stage IIIC SCCOHT treated with cytoreductive surgery, adjuvant chemotherapy, high-dose consolidation chemotherapy, autologous stem cell transplant and pelvic radiation with a disease-free interval of 8 years at the time of publication. Immunotherapy may also play a role in the treatment of SCCOHT. A recent study by Jelinic et al. (2018) reported responses to anti-PD1 immunotherapy in four patients with three patients remaining disease-free at 1.5 years, and one patient having a partial response at 6 months. The majority of the tumors demonstrated PD-L1 expression with strong associated T-cell infiltration.

Most early studies proposed a radical surgical approach for all women with SCCOHT, including hysterectomy and bilateral salpingo-oophorectomy. However, more recent reports have indicated that a less-invasive, fertility-sparing approach in combination with multiagent adjuvant chemotherapy may not compromise survival in women with early stage disease. However, if a germline SMARCA4 mutation is present, removal of both ovaries is still recommended due to the risk of developing SCCOHT in the contralateral ovary (Witkowski, 2016).

It is well known that infertility in cancer survivors may be temporary or permanent and is due to several factors including injury to the reproductive tract organs and injury to the hypothalamic-pituitary-gonadal axis by surgery, cytotoxic drugs and radiation therapy. Almost 50% of cancer patients report amenorrhea during treatment with chemotherapy; however, menses resume in approximately 70% of these women (Jacobson et al. 2016). The *American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on Fertility Preservation in Patients With Cancer* (Oktay et al., 2018) recommends that health care providers discuss the possibility of infertility with patients with cancer treated during their reproductive years or with parents/guardians of children as early as possible. Sperm, oocyte, and embryo cryopreservation are considered standard practice and are widely available. There is conflicting evidence to recommend gonadotrophin-releasing hormone agonists (GnRHa) and other means of ovarian suppression for fertility preservation during chemotherapy, and the Panel recommends that, when proven fertility preservation methods are not feasible, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency (Jacobson et al. 2016).

To our knowledge, this is the first reported case of pregnancy after treatment for SCCOHT. Fertility-sparing surgery may be considered in women with early stage SCCOHT who do not have a germline SMARCA4 mutation. However, given the aggressive nature of the disease and need for adjuvant therapy, the chances of future fertility for most women with SCCOHT remain limited. We recommend that all women of childbearing age diagnosed with SCCOHT be offered consultation with a reproductive endocrinology/infertility specialist for expert opinion. The findings in this report suggest that adjuvant VPCBAE is an effective adjuvant treatment for SCCOHT and that fertility is possible following this chemotherapy regimen.

CRediT authorship contribution statement

Natacha Phoolcharoen: Conceptualization, Data curation, Writing - original draft. **Terri Woodard:** Data curation, Writing - review & editing. **Deepthi James:** Data curation, Writing - review & editing. **Dina Patel:** Data curation, Writing - review & editing. **Sarah Roder:** Data curation, Writing - review & editing. **Deborah Holman:** Data curation, Writing - review & editing. **Mila Salcedo:** Writing - review & editing. **Michael Frumovitz:** Funding acquisition, Supervision, Writing

- review & editing. **David Gershenson:** Supervision, Writing - review & editing. **Kathleen Schmeler:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare there is no conflict of interest regarding this work.

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