Hypercalcemia and Unilateral Ovarian Mass in a Young Adult: A Case Report of Small Cell Ovarian Carcinoma

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Conflict of interest: None declared

Patient: Female, 31-year-old
Final Diagnosis: Small cell ovarian cancer • hypercalcemic type
Symptoms: Abdominal pain • bloating
Medication: —
Clinical Procedure: Surgery • adjuvant chemotherapy • adjuvant radiotherapy
Specialty: Oncology
Objective: Rare disease

Background: Small cell ovarian carcinoma, hypercalcemic type is an uncommon malignant ovarian tumor entity with an unfavorable prognosis and a short overall survival rate. It mainly affects women of childbearing age.

Case Report: We report a case in which a 31-year-old woman with small cell ovarian carcinoma, hypercalcemic type presented with unspecific symptoms. We emphasize the importance of treatment planning and address fertility-sparing surgical procedures, which remain a therapeutic dilemma.

Conclusions: The occurrence of unspecific abdominal symptoms, unilateral tumor masses, and hypercalcemia may indicate the presence of malignant ovarian neoplasm in young adults. Histopathological examination of the mass should be performed by an experienced gynecological pathologist. A misdiagnosis can lead to inadequate surgical and adjuvant treatment. Adjuvant multi-agent chemotherapy and high-dose chemotherapy with autologous stem cell rescue may prolong the progression-free interval and overall survival.

MeSH Keywords: Carcinoma, Small Cell • Chemotherapy, Adjuvant • Hypercalcemia • Ovarian Neoplasms • Young Adult

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Background

Small cell ovarian carcinoma, hypercalcemic type (SCCOHT) is an uncommon tumor with highly aggressive biological behavior. The clinical outcome is generally poor, with an overall survival (OS) of 1 to 2 years in the majority of cases. SCCOHT affects younger women (average age 24 years) [1,2], and the incidence is estimated to be 1 in 80 million women [3]. The majority of patients present with hypercalcemia (62–65%) and a characteristically unilateral ovarian tumor [1,2].

Case Report

A 31-year-old nulliparous woman without any past medical history presented with abdominal pain and bloating. Her mother was diagnosed with epithelial ovarian cancer at 55 years of age. The patient had undergone a large loop excision of the transformation zone at the age of 26 years.

A computed tomography (CT) scan of the abdomen showed a complex tumor of the left ovary with the dimensions 20×20×19 cm (Figure 1A, 1B). A midline laparotomy and a left salpingo-oophorectomy were performed. The intraoperative frozen section showed a malignant ovarian tumor. The patient wished to maintain fertility; therefore, no radical surgery was performed.

The final histopathological report showed small monotonous cells and some follicle-like spaces filled with eosinophilic fluid (Figure 2A, 2B). The SMARCA4 immunoreactivity was lost due to a mutation, which was consistent with SCCOHT. Based on the International Federation of Gynecology and Obstetrics (FIGO) staging system, the tumor was stage IA. Preoperative laboratory tests were normal, except for the slightly elevated serum calcium level of 2.97 mmol/L (reference range [RR] 2.10–2.60 mmol/L). The planned staging surgery was performed with a repeat laparotomy, peritoneal lavage specimen, right salpingooophorectomy, omentectomy, and peritoneal biopsies without visible disease. The patient refused a hysterectomy. All samples were negative for malignancy.

One month after staging surgery, adjuvant chemotherapy for 6 cycles began with a combination of carboplatin and paclitaxel. Before and during adjuvant chemotherapy, all tumor markers (cancer antigen [CA] 125, human epididymis protein 4 [HE4], carcinoembryonic antigen, CA 15-3, CA 19-9, CA 72-4, alpha-fetoprotein, human chorionic gonadotropin, neuron-specific enolase, and S100 proteins) were within the reference range, as was the serum calcium level. Twelve months after the completion of treatment, the patient was clinically free of disease. She underwent regular checkups at 3-month intervals with clinical examination and transvaginal ultrasound by an experienced gynecological oncologist. Fifteen months after the end of the treatment,

Figure 1. Computed tomography scan showing a left ovarian tumor (white arrows) with the size of 20×20×19 cm: (A) axial view and (B) coronal view.
an ultrasound examination of the abdominal cavity revealed a tumor mass behind the uterus. The patient did not experience any signs or symptoms of the disease. Tumor markers CA 125 and HE4 and the risk of ovarian malignancy algorithm (ROMA) index score were within normal ranges, but the serum calcium level was elevated (2.96 mmol/L). An abdominal CT scan confirmed a tumor with cystic and solid components, 8 cm in diameter, on the left side of the pelvis near the iliac vein (Figure 3A, 3B). Positron emission tomography revealed that this was the only suspected mass, and a biopsy of it confirmed recurrent SCCOHT. The serum calcium level rose to 4.65 mmol/L. A third surgery was performed on a fast-growing retroperitoneal mass, 24×14×4 cm in size, that was infiltrating the left ureter and the left common iliac artery and vein. A suboptimal cytoreduction was performed and a residual mass of 5×3×1 cm, which encased the iliac vessels and the ureter, was left in situ. Definitive histology confirmed recurrent SCCOHT. The patient’s recovery from surgery was uneventful, and the serum calcium levels were in the reference range.

Figure 2. Ovarian parenchyma with cells that have monomorphic round nuclei with vesicular chromatin and small nucleoli (hematoxylin and eosin stain). (A) Follicle-like spaces (white arrows) and (B) numerous mitotic figures (black arrows) are present.

Figure 3. Computed tomography scan showing recurrent tumor (white arrows) on the left side of the pelvis near the iliac vein with cystic and solid components: (A) axial view and (B) coronal view.
Adjuvant radiotherapy of the tumor bed was performed 8 weeks after surgery, with a total dose of 37.5 Gy in 15 fractions. One month after radiotherapy, an abdominal CT scan showed rapid progress of the disease, with an 8-cm-diameter retroperitoneal tumor, a 6-cm solid mass anterior to the space of Retzius, 2 para-aortic lymph nodes under the left renal vein (5 cm and 3.5 cm in diameter), and many intraperitoneal deposits, including a deposit 12 cm in diameter on the liver and a deposit 3 cm in diameter on the inferior pole of the spleen. Tumor markers were elevated for the first time 25 months after initial diagnosis: CA 125 was 60 kU/L (RR <35 kU/L), and HE4 was 151 pmol/L (RR <140 pmol/L). In addition, the serum calcium levels were elevated to 3.51 mmol/L.

The patient died 27 months after her initial diagnosis.

Discussion

SCCOHT is an uncommon malignant ovarian tumor in girls and young women. The youngest patient reported so far was 14 months old [4]. SCCOHT is characteristically unilateral, with tumor sizes ranging from 6 to 26 cm in diameter. Patients usually show unspecific symptoms such as abdominal pain, flatulence, nausea and vomiting, weight loss, or weight gain due to an enlarged waist [1,5].

The strongest determinant of survival is the stage at the time of diagnosis. In the largest study of patients with SCCOHT, Witkowski et al. [2] reported survival rates for 293 patients. They found a 5-year survival rate of 55%, 40%, and 29% for patients with FIGO stages I, II, and III, respectively. The longest survival time of patients with stage IV SCCOHT was 13 months. In the second largest study of patients with SCCOHT, which included 150 patients, Young et al. [1] found FIGO stage I disease in 50% of cases, stage II in 5%, stage III in 43%, and stage IV in 1%. After 5 years, 33% of patients with FIGO stage IA were alive without recurrence. Less than 10% of patients with FIGO stage IC were long-term survivors. This finding emphasizes the importance of avoiding artificial tumor rupture.

The second strongest determinant of survival is the treatment modalities, which depend on the stage at diagnosis. Radical surgery followed by chemotherapy is recommended for patients with early-stage disease, and adjuvant radiotherapy is a treatment option in selected cases [6,7]. Witkowski et al. [2] stratified 293 SCCOHT cases in 5 different treatment groups. The first group consisted of 24 patients treated surgically, the second group had 133 patients treated surgically and with adjuvant chemotherapy, the third group included 8 patients treated surgically and with adjuvant radiotherapy, and the fourth group comprised 39 patients treated surgically and with adjuvant chemotherapy and radiotherapy. A fifth group consisted of 28 patients treated with surgery and adjuvant chemotherapy and/or radiotherapy with high-dose chemotherapy with autologous stem cell rescue (HDC-aSCR). The worst outcome, with an OS of only 5 months, was observed in patients treated with surgery only. The importance of adjuvant chemotherapy was emphasized. Adjuvant chemotherapy extended OS to 14.5 months. The best response was observed in patients who also received HDC-aSCR. In the fifth group, 71.4% (20/28) of patients had a complete response to chemotherapy. The relapse rate in this group was 25% (5/20) [2,3,8]. Previously reported relapse rates were up to 65%, so it can be concluded that treatment with HDC-aSCR mainly influences the relapse rate by reducing it [9]. These data indicate the benefit of additional HDC-aSCR treatment in extending survival. In other cases, a possible cure has been reported in patients with SCCOHT who received HDC-aSCR treatment after a complete response to chemotherapy [10–12].

SCCOHT is considered to be highly aggressive, and extensive surgical resection is often performed, including total hysterectomy, bilateral oophorectomy, omentectomy, peritoneal lavage, and, in advanced cases, optimal debulking. This corresponds to the current treatment concepts for epithelial ovarian cancer, but the question of whether these concepts also apply to SCCOHT has not yet been answered [9]. Since many patients with SCCOHT are young and want to maintain their fertility, the extent of the surgery is a significant problem at the time of initial diagnosis. In a young woman with a tumor restricted to 1 ovary, fertility-sparing surgery can be performed after adjuvant therapy [11,13].

The overall results of Patibandla et al. [5] indicate the importance of multimodal treatment with radical surgery, adjuvant chemotherapy, and adjuvant radiotherapy as the best treatment option for SCCOHT patients. In most cases, platinum-based chemotherapy was administered [2,3,7], usually with cisplatin/carboplatin and etoposide and a multi-agent regimen with vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide [6,14].

Reports documenting the use of radiotherapy in SCCOHT provide contradictory results. Radiotherapy remains an option in an optimal, personalized treatment regimen [6]. In the study by Witkowski et al. [2], adjuvant radiotherapy did not prolong OS compared with chemotherapy alone. However, Harrison et al. [7] analyzed 17 women who were treated with radical surgery and platinum-based adjuvant chemotherapy due to SCCOHT. Seven patients received additional radiotherapy treatment, and 71.4% (5/7) were long-term survivors. Recurrent disease occurred in 75% of patients (3/4) with FIGO stage I disease who did not receive adjuvant radiotherapy [7]. Radiotherapy is also associated with gonadal failure, and major questions in patients who wish to preserve their fertility are whether radiotherapy...
should be given adjuvantly and whether it should be to the pelvis alone, the pelvis and para-aortic area, or the whole abdominal-pelvic region [13].

The most common sites of SCCOHT recurrence are the pelvis, the retroperitoneal lymph nodes, and the contralateral ovary, which occurred in our case [6,7,9].

In patients whose disease has relapsed, a maximum therapy that includes all 3 modalities is justified because the risks of not being cured are extremely high in SCCOHT relapses [13], which was also true in our case. Patients who are disease-free for 5 years after the initial diagnosis are most likely to be cured [2].

In more than 60% of cases, SCCOHT is associated with hypercalcemia and can present as a paraneoplastic syndrome [1,2,7]. However, only a small proportion of patients may have symptomatic hypercalcemia that causes hypertension, dysrhythmia, abdominal pain, hypotonia, polydipsia, and fatigue. Calcium levels can be used to assess the effectiveness of treatment and to measure disease progression. Calcium levels in SCCOHT usually spontaneously return to normal after tumor removal. Our case confirmed that calcium levels can be a marker for follow-up and a possible tumor marker for SCCOHT in young patients with large unilateral solid cystic tumors [1,15].

As in epithelial ovarian carcinoma, CA 125 could be an applicable tumor marker in SCCOHT. In a study by Estel et al. [9], CA 125 was elevated in 75% of patients at the time of diagnosis. In our case, CA 125 was not assessed at diagnosis but after primary surgery. It remained negative until the disease progressed rapidly, and it then became slightly elevated (60 kU/L). In our case, other tumor markers were checked and were all negative. Despite scarce evidence, the use of serum calcium and CA 125 levels as markers for recurrence and follow-up in patients with SCCOHT seems reasonable.

Due to the rarity of SCCOHT, the diagnosis is a challenge for pathologists and many cases are initially misdiagnosed. Callegaro-Filho et al. [16] and Pautier et al. [17] reported misdiagnosis in 14 of 47 patients (30%) and in 5 of 27 patients (19%), respectively. An ovarian tumor in a child or adolescent requires histopathological examination by an experienced pathologist in the field of germ cell tumors, sex cord stromal tumors, and SCCOHT [3]. An incorrect diagnosis of frozen sections taken intraoperatively can lead to an unsuitable surgical procedure [15]. A correct histopathological diagnosis is of crucial importance for an optimal adjustment of the adjuvant therapy.

Conclusions

We present a case of prognostically unfavorable SCCOHT, which predominantly affects younger women. Fewer than 500 cases have been reported in the literature. Standardized management has yet to be established, but the available data indicate an important role of multimodal treatment, including radical surgery and adjuvant multi-agent high-dose chemotherapy, and possibly autologous stem cell rescue.

Department and Institution where work was done

This study was done at the Department of Gynecological Oncology, Institute of Oncology, Ljubljana, Slovenia.

Conflicts of interest

None.
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