*Case Report***Multi-modality therapies for advanced small cell carcinoma of the ovary, hypercalcemic type (SCCOHT): three case reports and literature review**Qin Han^{1,*}, Hongyan Guo¹¹Department of Obstetrics and Gynecology, The Third Hospital of Peking University, 100191 Beijing, China*Correspondence: lmlfe_lynn@126.com (Qin Han)

Academic Editor: Enrique Hernandez

Submitted: 22 September 2021 Revised: 27 October 2021 Accepted: 1 November 2021 Published: 15 February 2022

Abstract

Background: Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare but highly undifferentiated, aggressive malignancy that primarily affects young women. Most SCCOHT patients present with advanced disease and have a very poor prognosis. Although several therapeutic regimens have been proposed, there is no consensus on the optimal treatment strategy. **Case:** Herein, we describe three cases of advanced-stage SCCOHT aged from 16 to 36 treated with cytoreductive surgery and chemotherapy with or without immune checkpoint blockade treatment. With different strategy, the patients showed utterly different outcomes. **Conclusion:** The cases highlight the importance of prompt diagnosis as well as early, aggressive, and combined modality treatment of SCCOHT. We believe that improved therapies could result in more young patients surviving SCCOHT.

Keywords: Small cell carcinoma of the ovary hypercalcemic type (SCCOHT); Advanced stage; Tumor immunotargeted therapy

1. Introduction

Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare, highly undifferentiated, aggressive ovarian malignancy of unknown cell origin, which usually occurs in young women. It was first described by Dickersin *et al.* [1] in 1982 as paraneoplastic hypercalcemia. Several therapeutic regimens have been proposed for SCCOHT; however, to date, there is no consensus on the optimal treatment strategy. With the development of high-throughput sequencing technology, molecular characteristics of SCCOHT have been gradually revealed, and new molecular targets have been proposed. Herein, we describe three SCCOHT cases with different clinical stages, different treatment approaches, and different outcomes and present an overview of the clinical and pathological features, molecular features, multimodality treatment or therapy, molecular targeting and immunotherapy, genetic counseling, and prevention of SCCOHT.

2. Cases presentation**2.1 Case A**

Patient A was a 36-year-old G2P1 female who was admitted to the Third Hospital of Peking University in December 2019 with acute abdominal pain, and abdominal distension accompanied by fever. Bilateral gynecological examination revealed a 9 cm cystic, solid mass in front of the uterus. Serum calcium and tumor markers were within normal limits. Pelvic abdominal computerized tomography (CT) indicated a 9.6 × 9.2 cm mass extending from the right ovary (Fig. 1). Emergent laparoscopy exploration was per-

formed. The right ovary had a solid but brittle enlargement of 10 cm with a rich blood supply (Fig. 1). In addition, a resection of the right adnexa was performed. The frozen section analysis suggested a poorly differentiated carcinoma. As metastatic cancer could not be excluded, only the right adnexa was removed. The postoperative pathologic diagnosis (on paraffin-embedded tissue) was of a small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) (Fig. 1).

After the operation she received, she received three courses of chemotherapy of TC (paclitaxel 135–175 mg/m² d1 and carboplatin AUC 5–6 d1, intravenous infusion) between January and March 2020. The regimen was given every 21 days. During the cytoreductive surgery in April 2020, we found several 1–2 cm masses on the surface of the left fallopian tube and appendix. The tumor was classified as stage IIIB. Next, a genetic test was performed by LIFE HEALTHCARE, showing a mutation of SMARCA4; germline testing was negative. The score of HRD and PD-L1 was 25 and 10–15%, respectively. According to the guidelines published by the International SCCOHT Consortium in March 2020, six courses of EP regimen (etoposide 100 mg/m² d1 to d3, cis-platinum 70 mg/m² d1, intravenous infusion) were given post-operatively. The regimen was given every 21 days.

In August 2020, a 1 cm mass in the right lower abdominal wall was found on the CT, just after the last chemotherapy cycle. The pathology suggested a metastatic lesion of SCCOHT. Considering the disease was not controlled during both the preoperative TC chemotherapy and postoperative EP chemotherapy, cancer-targeted drugs were pre-

Fig. 1. Pelvic abdominal CT, intraoperation view and paraffin pathological picture of patient A. (A–C) Pelvic abdominal CT. (A) A plain scan. (B) An arterial phase of enhancement, and (C) is a venous phase of enhancement. The density of the mass in the plain scan was not uniform. The lumen was soft tissue density, the extension of the vessels could be seen at the enhancement stage, the solid components of the mass at the venous stage were strengthened, the peripheral enhancement was high, suggesting that the mass could be malignant. (D) Laparoscopic exploration. The right ovary had a solid but brittle enlargement of 10 cm, a rich blood supply, and a 2 cm incision. Oozing blood was observed on the surface. (E) Monomorphic round cells with many mitoses ($\times 200$).

scribed. Five courses of anti-PD1 (sintilimab 200 mg injection, the regimen was given every 21 days) were given for 4 months. Ponatinib (protein receptor tyrosine kinase inhibitor) 45 mg qd was used as a maintenance treatment. Follow-up was performed every three months (laboratory tests and ultrasound). At the last follow-up (January 2021), the patient was still alive, showing no signs of recurrence.

2.2 Case B

Patient B was a 15 years old girl who was admitted to The Third Hospital of Peking University emergency department in October 2012 due to epigastric pain and a high fever (38°C). Physical examination revealed left abdominal tenderness and a large pelvic mass. Pelvic abdominal CT suggested a 25 cm cystic mass; thus, malignancy was suspected (Fig. 2). The CA125 was high at 345.7 U/mL (0–35 U/mL) and serum calcium was within normal limits. An emergent open exploratory operation was performed and a large cystic, solid mass from the left ovary filled the whole pelvic cavity. Multiple peritoneal nodules were found in the pelvic cavity. The frozen section examination suggested a poorly differentiated carcinoma. Cytoreductive surgery was performed immediately after the diagnosis was confirmed and after the signed informed content from the patient's parents was obtained. We performed a successful cy-

toreductive surgery (R1) with a 1 cm mass left in the cavity between liver, stomach, and pancreas, followed by an intraperitoneal chemoperfusion of 60 mg cis-platinum ten days after the surgery. The postoperative pathologic diagnosis (on paraffin-embedded tissue) was of a SCCOHT and were classified as stage IIIC.

Fourteen days after the operation, an abdominal ultrasound indicated a 7 cm nodule between the liver, stomach, and pancreas, which was considered a residual lesion, and a 1 cm lesion on the liver surface, which was considered a metastatic lesion. Six courses of EP regimen (etoposide 100 mg/m^2 d1 to d3, cis-platinum 70 mg/m^2 d1, intravenous infusion) were given post-operatively. The regimen was given every 21 days. Unfortunately, the abdominal mass increased in size (to 9 cm) (Fig. 2). Her parents refused further treatment, and the patient passed away due to multiple organ failure in July 2017. The survival time was nine months after diagnosis.

2.2 Case C

Patient C was a 33 years old girl who suffered from abdominal distension for two months. She was diagnosed with myoma or leiomyoma of the uterus and underwent laparoscopic hysterectomy in another hospital in November 2018. The pathological findings were initially diagnostic

Fig. 2. Pelvic abdominal CT. (A) Huge pelvic mass. (B) A 9 cm mass between the liver, stomach, and pancreas, increased during the chemotherapy.

of HGSC of the ovary. Based on this diagnosis, the patient received three-course chemotherapy of TC (paclitaxel 135–175 mg/m² d1 and carboplatin AUC 5–6 d1, intravenous infusion). Unfortunately, a rectovaginal fistula was found after the first course, and the tumor mass increased during chemotherapy with metastasis of peritoneum omentum and vaginal cuff. In February 2019, after pathology consultation in The Third Hospital of Peking University, she was diagnosed with SCCOHT, stage IVb. Considering the progression, immunity inhibitors and anti-angiogenesis factors were used. Three courses of chemotherapy with albumin taxol, cis-platinum, bevacizumab and anti-PD1 (albumin-bound paclitaxel 135–175 mg/m² d1, cis-platinum 70–75 mg/m² d1, bevacizumab 15 mg/kg d2, sintilimab 180 mg d3, intravenous infusion) were given before the second surgery. The regimen was given every 21 days. The tumor mass was reduced during chemotherapy. The second cytoreductive surgery was performed in June 2019, during which a 5 cm mass was identified on the vaginal stump. Luckily, the mass was removed without an enterostomy. The second cytoreductive surgery was R0. Five courses of chemotherapy of albumin-bound paclitaxel, cis-platinum, and anti-PD1 were performed after surgery. Currently, the patient has been taking anti-PD1 as maintenance treatment for the past 2 years. Follow-up was performed every three months (laboratory tests and ultrasound). At the last follow-up (January 2021), the patient was still alive with no signs of recurrence.

3. Discussion and literature review

3.1 Clinical and pathology features

The SCCOHT is a rare ovarian tumor with poor prognosis that was first described in 1982 [1]. In the landmark study by Young *et al.* [2], the clinical and pathological features of SCCOHT were analyzed. The minimum age of onset was 14 months. The tumor primarily affected young women with a median of 23 years. The clinical signs were nonspecific and mainly included abdominopelvic pain or distension, weight loss, nausea, and vomiting; approximately 60% of SCCOHT cases presented with paraneoplastic hypercalcemia [2,3]. The recurrence rate was 65.1%, and the average recurrence time was 11.5 months [4,5]. The three cases discussed in this report were all PD (progressive disease) after the initial treatment. Most patients are diagnosed at an advanced stage, and the overall long-term survival rate in SCCOHT patients is only 10% to 20% [4,6,7].

The tissue of origin of SCCOHT has been inconclusive. A small cluster of round or oval cells with sparse cytoplasm, hyperchromatic nuclei, prominent nucleoli, and active mitotic figures was found in all three cases presented in this study (Fig. 3). The pathological basis of SCCOHT still remains unclear. SMARCA 4 (SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily member 4) gene mutation and the relative BRG-1 protein deficiency is the important molecular feature of SCCOHT (Fig. 3) [8,9].

Fig. 3. Histological features of SCCOHT. (A,B) The tumor cells were found to be infiltrating and growing in a flaky, dense nest with small cells and fibrous cords ($\times 40$) (A) ($\times 200$) (B). (C) Under the microscope, the tumor cells were BRG-1 negative, while the background cells (endothelial cells) were BRG-1 positive ($\times 200$).

3.2 Clinical management

To date, there is no consensus on the optimal strategy for SCCOHT. Among three cases presented in this study, patient B was the youngest but the worst prognosis, which may be related to the lack of experience in the diagnosis and treatment of this rare disease at that time. Pautier *et al.* [10], reported a prospective study in which the patients underwent nonconservative debulking surgery, semi-intensive chemotherapy (cisplatin, adriamycin, etoposide and cyclophosphamide), high-dose consolidation chemotherapy (carboplatin, etoposide and cyclophosphamide) followed by autologous hematopoietic stem-cell transplantation, (AHSCT). The outcomes were better for early-stage patients although late-stage diseases remain difficult to manage. The understanding of pathogenesis and development of related targeted drugs has gradually brought certain benefits to the patients. Also, the International SCCOHT Consortium (ISC) presented guidelines for the diagnosis and management of SCCOHT in 2020 which make clinical strategy reasonable [11]. Resect primary ovarian tumor and base diagnosis on expert gynecologic pathology review are needful and chemotherapy should be followed. For recurrent disease, obtain biopsy as clinically indicated and encourage patients to participate in clinical trials. Genetic testing for patient and family members is recommended.

For newly diagnosed cases, primary ovarian tumor resection and diagnosis by gynecologic pathologist are necessary. In this report, cytoreductive surgery was performed in all three cases. Initiate cytotoxic chemotherapy included cisplatin and etoposide regimens (e.g., BEP or similar). For patient A, three courses of TC as neoadjuvant chemotherapy were used. As the disease progressed and tumor mass was found during the second surgery, chemotherapy was changed to EP. Radiation therapy may be considered after chemotherapy for the residual disease, but the efficacy remains uncertain.

For recurrent disease, the principles for recurrent ovarian cancer are applicable. As chemotherapy has limited effectiveness, surgery can be given after the administration of targeted drugs and immunotherapy. Chemotherapy with

cisplatin and etoposide regimens or alternative chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine; or carboplatin, paclitaxel; or topotecan; or similar) can be combined with other treatments. SCCOHT patients should be encouraged to participate in clinical trials if available and consider off-label immune checkpoint blockade treatment based on drug availability. In patient A, anti-PD1 and ponatinib were used; In patient C, anti-PD1 and Bevacizumab were used. Both patients benefited from the off-label drugs, which will be discussed in more detail.

3.3 Identification of SCCOHT therapeutic candidates

SMARCA4 is involved in many cellular processes, including transcriptional regulation, DNA damage repair, differentiation, and mitosis. The targeted drug should be focused on several approaches, including exploiting known synthetic lethal interactions of SMARCA4 loss and identifying novel targets through unbiased genetic screens (Table 1).

3.3.1 Epigenetic therapeutics (EZH2 inhibitor, LSD1 inhibitor, BET inhibitor, lysine-specific demethylase inhibitor)

Impaired function of the mSWI/SNF complex leads to histone-lysine N-methyltransferase (EZH2) abnormal recruitment to target genes [12]. Selective EZH2 inhibitor tazemetostat has shown an anti-tumor effect in a rat model. Recently, tazemetostat has been approved by the FDA for the treatment of epithelioid sarcoma. The arm accruing patients with SCCOHT in phase II multiarm trial (ClinicalTrials.gov identifier: NCT02601950) was stopped for futility. Of note, 1 patient with SCCOHT was reported to have a PR of 32 weeks [13,14]. One way to improve efficacy may be to combine EZH2 inhibitors with histone deacetylase inhibitors, such as panobinostat or quisinostat, which demonstrated a greater synergistic anti-tumor effect than monotherapy [13].

A similar approach is used with inhibitors of lysine-specific demethylase-1 (LSD1/KDM1), which is upregulated in SWI/SNF-mutated cancers. The LSD1 inhibitor seclidemstat (SP-2577) demonstrated anti-tumor activity in

Table 1. Potential treatments and trials for SCCOHT.

Class	Target	Drug	Clinical trial available for SCCOHT
Epigenetic therapeutics	EZH2	Tazemetostat	Phase II NCT02601950
	LSD1	Seclidemstat	Phase I, NCT03895684
	HDAC	Quisinostat	
Kinase inhibitors	RTK	Ponatinib	
	CDK4/6	Palbociclib	Phase II, NCT03297606
Immunotherapies	PD-1	Pembrolizumab	Phase II, NCT03012620

murine models. A phase I trial (NCT03895684) has been recently designed to investigate the clinical effect of seclidemstat, for patients with SWI/SNF-mutant gynecologic cancers, with an emphasis on SCCOHT, ovarian clear cell carcinomas, and endometrial carcinomas.

Bromodomain and extraterminal motif (BET) inhibitors are other potential drugs for SCCOHT. *In vivo* studies showed anti-proliferative effects of BET inhibition such as OTX015 in SMARCA4-deficient SCCOHT by downregulating the oncogenic HER3 and other receptor tyrosine kinases [15]. BET inhibitors can also promote an anti-tumor response, decrease regulatory T cells, increase TILs, and synergism *in vivo* with anti-PD1 therapy [16].

Targeting other histone modification complexes, HDACi has been clinically approved for the treatment of several hematologic malignancies. Several studies have shown that HDAC is in the context of SCCOHT results in re-expression of SMARCA2, which strongly suppresses the growth of SCCOHT cells [17]. One of these reports also showed *in vivo* sensitivity of SCCOHT cells to the HDACi Quisinostat.

3.3.2 Kinase inhibitors (RTK inhibitor, CDK4/6 inhibitor, c-Met inhibitor)

A previous study showed the SCCOHT cell line's dependence on a variety of protein receptor tyrosine kinase (RTK) [17]. Ponatinib, an RTK inhibitor approved for clinical use, was found to have a strong inhibitory effect both *in vitro* and *in vivo* preclinical models through its inhibition of multiple kinases [18]. Furthermore, inhibition of EGFR2, CSF1R, and VEGFR negatively affect the recruitment and survival of myeloid-derived suppressor cells, thus suggesting ponatinib has a role in modulating the immune microenvironment for anti-tumor effect [19].

Xue *et al.* [20] found that silencing cyclin-dependent kinase4/6 (CDK4/6) may significantly inhibit SCCOHT cell growth by screening short hairpin RNA (shRNA) library. *In vitro* and *in vivo* studies suggested that SCCOHT is sensitive to palbociclib, a CDK4/6 inhibitor that has been used in the clinical treatment of ER+ and HER2-breast cancer. The mechanism of action is related to the decrease of cyclin D1 expression and the restriction of CDK4/6 kinase activity due to SMARCA4 deficiency. The Canadian Profiling and Targeted Agent Utilization Trial (NCT03297606), a pan-Canadian phase II basket trial, has

recently approved a new match to treat SMARCA4-mutant tumors with the CDK4/6 inhibitor palbociclib based on the findings [20,21].

3.3.3 Immunotherapies (PD-1/PD-L1 inhibitor)

Although the low mutation burden of SCCOHT would not predict responsiveness to immune checkpoint blockade (ICB), anti-PD1-antibody including pembrolizumab have shown substantial and durable responses in selected patients with recurrent SCCOHT after prior treatment [22]. A French phase II basket trial AcSe program with pembrolizumab (NCT03012620) is currently open for women with rare ovarian tumors, including relapsed SCCOHT. The application of SCCOHT's immune microenvironment and PD-1/PD-L1 inhibitor needs further study.

3.3.4 Off-label drug discussion for the cases

To the best of our knowledge, this is the first study reporting on the use of ponatinib or combined antiangiogenic therapy bevacizumab and immune checkpoint blockade (ICB) in patients with SCCOHT. Although patient C was misdiagnosed at another hospital and suffered from rectovaginal fistula even progressed during chemotherapy, after full communication with the patient, she was treated with ICB and Bevacizumab, which put the progression of the disease under control, and the second tumor cell reduction was satisfactorily performed. Currently, ICB is performed as maintenance therapy. She is among rare stage IV patients who benefited from the targeted drugs and was still having a good quality of life. Although patient A was timely diagnosed and received standard treatment, despite the change of chemotherapy regimen, the relapse still occurred over a short time, which might be related to the laparoscopic surgery. Considering an uncontrolled condition, five courses of ICB were performed, and Ponatinib was used as a follow-up treatment, as was also reported in previous studies. Although there are some side effects such as low fever, body aches, and leukopenia, the patients still benefited from the targeted drugs.

Owing to the rarity of the tumor and a lack of large series evaluating therapeutic strategies, more case series reports and multicenter analyses are needed to further investigate this rare disease and optimize clinical treatments. Blocking of PD1/PD-L1 is being studied in several malignancies.

nancies, with good responses, including patients with SC-COHT, and some benefit has been reported, as it is also shown in our cases. Therefore, immunotherapy should be considered in the treatment of these devastating ovarian tumors. We hope that additional viable options will become available as more preclinical and translational studies are being reported and that more SCCOHT patients will benefit from them.

3.4 Genetic counseling

SMARCA4 germline variation is still possible in SC-COHT patients who do not have a family history of SC-COHT [5]. Therefore, patients diagnosed with SCCOHT, with or without a family history of SCCOHT, are advised to seek professional genetic counseling. If SCCOHT patients do not carry the SMARCA4 germline variant, unaffected ovaries' retention may be considered based on clinical conditions, tumor stage, and other factors. All patient relatives with germline mutations should undergo genetic counseling and mutation detection. Considering the early onset of SC-COHT, poor prognosis, and lack of an effective test, young women with SMARCA4 germline variant, may be considered for prophylactic ovariectomy. In order to achieve fertility preservation and genetic blocking of hereditary tumor families, the carriers may be considered for assisted reproductive technologies before prophylactic ovariectomy [23].

4. Conclusions

The SCCOHT is a rare disease with a poor prognosis. Due to the rarity and lack of large series evaluating therapeutic strategies, the clinical diagnosis and treatment experience are worth summarizing as its molecular characteristics are likely to guide the best prevention and treatment. To achieve the most reasonable treatment and genetic tumor prevention, attention should be paid to multidisciplinary cooperation, including gynecological oncology, pathology, genetic counseling, and assisted reproduction. One of the most important things is to pay attention to the mechanism of SMARCA4 driving tumor formation and the development of targeted drugs.

Abbreviations

SCCOHT, Small Cell Carcinoma of the Ovary, Hypercalcemic Type; CT, Computerized Tomography; SMARCA4, SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4; HRD, Homologous Recombination Deficiency; PD-1, Programmed cell Death 1; PD-L1, Programmed cell Death Ligand 1; PD, Progressive Disease; BEP, Bleomycin Etoposide Platinum; DNA, DeoxyriboNucleic Acid; EZH2, Enhancer of Zeste Homolog 2; LSD1, Lysine-specific Histone Demethylase 1; HDAC, Histone Deacetylase; RTK, Receptor Tyrosine Kinase; CDK, Cyclin-dependent Kinase; HGSC, High-grade Serous Carcinoma.

Author contributions

QH wrote the manuscript and designed the figures. HYG revised the draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects or their family members gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the Third Hospital of Peking University (approval number: IRB00001052-06058). All patients or their family members have consented to the submission of the case report.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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