

Original Article

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT): a challenge for clinicopathological diagnosis

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Abstract: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is an extremely aggressive ovarian tumor, with a poor prognosis and high mortality for young women. This paper aims to inform clinical physicians of new clinical improvements and further understanding of SCCOHT. Two cases diagnosed with SCCOHT from our medical database were reconfirmed and immunohistochemically stained with vimentin, CK, EMA, S-100, ER, PR, and SMARCA4. Diffuse small, round cells with scant cytoplasm, small nucleoli, hyperchromatic nuclei, and active nuclear divisions were detected in the microscopy. The immunohistochemical markers indicated minor positive but notably were SMARCA4 negative, which led to the final diagnosis. SCCOHT is a rare and lethal ovarian tumor in young women. The loss of SMARCA4 or the presence of SMARCA2 is a specific marker for the disease. Susceptibility to CDK4/6 inhibitors associated with downregulation of SMARCA4 targeted cyclin D1 may be a probable therapeutic mechanism for the disease.

Keywords: SCCOHT, SMARCA4, ATRT, PD1, CDK4/6

Introduction

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is an aggressive ovarian malignancy. It's important to distinguish it from other mimics because of its dismal prognosis, highly likely recurrence, and early onset age [1]. It was first reported by Robert Scully in 1979, who named it for its morphology and hypercalcemic features [2]. Generally, in microscopy, the tumor cells are mainly small, round cells that diffuse into a sheet, but it also presents with rhabdoid morphological large cells in some rare cases [3, 4]. And in a digital analysis, about two-thirds of patients may show elevated serum calcium, which can return to a normal level after tumor resection [5]. Epidemiologically, young females are mainly affected, with a median age of 23 years, and many patients are admitted for a unilateral accessory mass with an average diameter of 15.3 cm [1, 2, 6]. Meanwhile, the disease-free survival rate is approximately one-third for stage IA disease, with exponentially poorer prognoses for about 10% of patients in the more advanced stages

[7]. Also, more than 70% of SCCOHT cases present with a recurrence within 6 months, according to Young's report [5]. For its rarity, only about 350 cases have been described worldwide, and half of these were reported in Young's retrospective research [5]. The origin of SCCOHT is still obscure. Neither an epithelial origin nor a germ cell neoplasm etiology has been confirmed, and the World Health Organization (WHO) still classifies it as a "miscellaneous tumor [3]".

We report two clinical cases of unilateral SCCOHT that presented in our hospital. And we also review a possible rationale, a current study of the immunochemotherapy, as well as some treatment options for the disease. The paper aims to inform clinical physicians of new clinical improvements and further knowledge of SCCOHT.

Patients and methods

Collected from the First Affiliated Hospital of Bengbu Medical College, the only two cases in

Table 1. The sources of the antibodies used in the immunohistochemical analysis

Source	Antibody
CK	Monoclonal, clone AE1/AE3
CA125	Monoclonal, clone TA347
EMA	Monoclonal, clone E29
PLAP	Monoclonal, clone 8A9
CD30	Monoclonal, clone Ber-H2
S-100	Monoclonal, clone 4C4.9
Inhibin-a	Monoclonal, clone R1
Ki-67	Monoclonal, clone MIB-1
SMARCA4	Rabbit Polyclonal Antibody
WT1	Monoclonal, clone WT49
Desmin	Monoclonal, clone D33
Vimentin	Monoclonal, clone V9
ER	Monoclonal, clone SP1
PR	Monoclonal, clone P2
MyoD	Monoclonal, clone 5.8A

All antibodies were obtained from Maixin Biotech, Inc. (Fuzhou, China) and were ready to use.

Table 2. The results of the immunohistochemical features

Immunohistochemical markers	Result (+/-)
CK	-/+
CA125	-
EMA	-
PLAP	-
CD30	-
S-100	-
Inhibin-a	-
Ki-67	+, about 70%
SMARCA4	-
WT1	-
Desmin	-
Vimentin	+
ER	-
PR	-
MyoD	-

our database were aged 26 and 44 years when diagnosed with SCCOHT. Surgical specimens were taken regularly and HE-stained sections were examined by our experienced pathologists. Immunohistochemical staining was performed using the EnVision two-step method. The antibody used and its results are shown in **Tables 1** and **2** respectively. The clinical records were obtained from the patients' medical records. The study was conducted according to

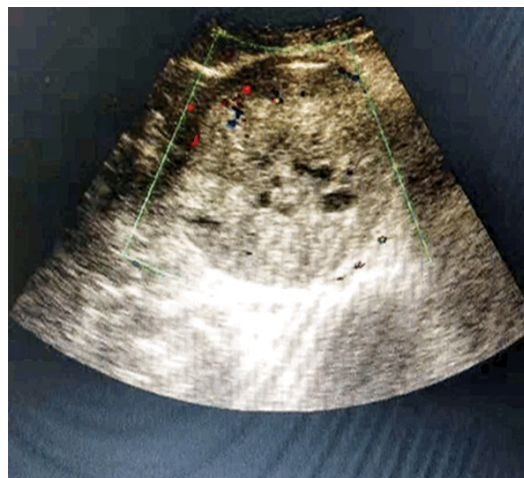


Figure 1. Imaging figures (case 1). Ultrasound of the pelvis demonstrating a 10 cm × 7.1 cm mixed echo figure in the right ovary.

the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College.

Results

Clinical features

Both of the patients were admitted to our hospital with persistent abdominal pain lasting for one year or more. A small pelvic mass and abdominal pain during menstruation were not apparent until the condition became aggravated. In case 1, a soft mass of about 10 cm diameter was examined in the right groin area, and ultrasound verified it had a mixed echo figure of 10 cm × 7.1 cm in the right accessory (**Figure 1**). No obvious abnormality was found in the preoperative examinations other than the serum CA125 of about 57.5 IU/ML. Most notably, the blood calcium was 2.41 mmol/L, a normal level which prevented us from making a morphological diagnosis. In case 2, there was a 14 cm × 18 cm lump in the left ovary, and the preoperative examination showed the CA125 at about 233 U/ML, while the serum calcium was about 3.53 mmol/L.

A clinical operation of the total uterus, a bilateral oophorectomy, a greater omentum resection, and a pelvic lymph node dissection were performed. A TP (paclitaxel + carboplatin) regimen was given to the patients monthly as post-operative adjuvant chemotherapy.

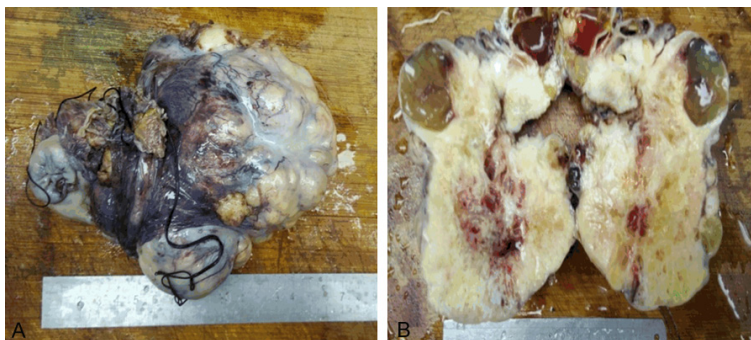


Figure 2. A: Gross image of the external surface of the left ovary (Case 2). B: Representative cut surfaces of the left ovary (Case 2). The tumor mass is lobulated, with cystic degeneration, hemorrhage, necrosis, and mucus.

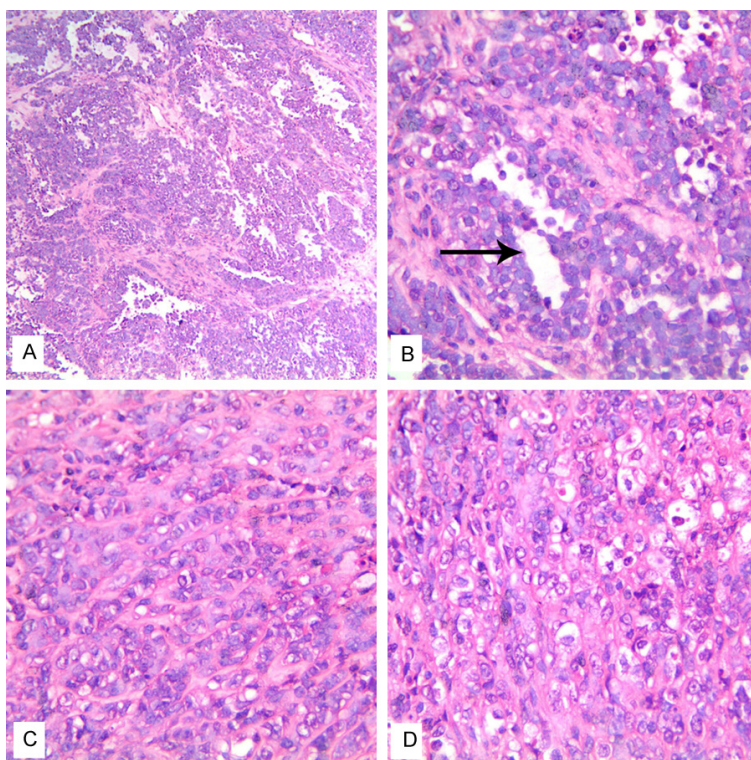


Figure 3. HE stained photomicrograph of the right ovary (case 1). A. Diffuse sheet-like architecture of small cells (H&E staining, $\times 100$). B. The follicular architecture of the neoplastic tissue (Black arrow) (H&E staining, $\times 400$). C and D. The scant cytoplasm, small nucleoli, hyperchromatic nuclei, and nuclear division of the neoplastic cells (H&E staining, $\times 400$).

Gross and histological features

Generally, the tumor mass is nodular or lobulated, with cystic degeneration, hemorrhage, necrosis, and mucus [5]. In case 2, the external surface of the tumor was gray and partly purplish red, and it was lobulated with a maximum dimension of 18 cm (**Figure 2A**). The representative cut surface was mainly solid and yellow,

with the foci of hemorrhage, cystic degeneration, and necrosis (**Figure 2B**). In the HE stain photomicrograph of the right ovary, the neoplastic cells were mainly diffusing sheets of small round cells, punctured by follicular-like architecture (**Figure 3A, 3B**). The follicles of various sizes were mainly empty, and few contained any eosinophilia fluid (**Figure 3B**). The tumor cells predominately had scant cytoplasm, small nucleoli, hyperchromatic nuclei, and active nuclear division (**Figure 3C, 3D**). The nucleoli could be observed but were rarely prominent. The mitotic figures were about 18 per every 10 high-power field. Finally, all the lymph nodes selected from the omentum and pelvic cavity were negative.

Immunohistochemical features

The immunohistochemical features were similar between the two cases. The tumor cells merely were positive for vimentin and partially positive for CK (**Figure 4C**). Other makers, such as EMA, S-100, ER, and PR, were all negative. The proliferation index, Ki-67, was greater than 50% (**Figure 4A, 4B**). Notably, a negative expression of SMARCA4 leads to the exactly diagnosis of SCCOHT (**Figure 4D**). The antibody used and its results are shown in **Tables 1** and **2** respectively.

Discussion

SCCOHT is a rare, undifferentiated ovarian cancer named for its morphological appearance and notable presence of hypercalcemia [2]. Currently, it is generally believed that the loss of SMARCA4, either alone or with SMARCA2, is highly sensitive and specific for SCCOHT [1, 6, 8]. SMARCA4 (BRG1) and SMARCA2 (BRM) are two vital and exclusive components of the SWI-SNF chromatin remodeling complex, which are

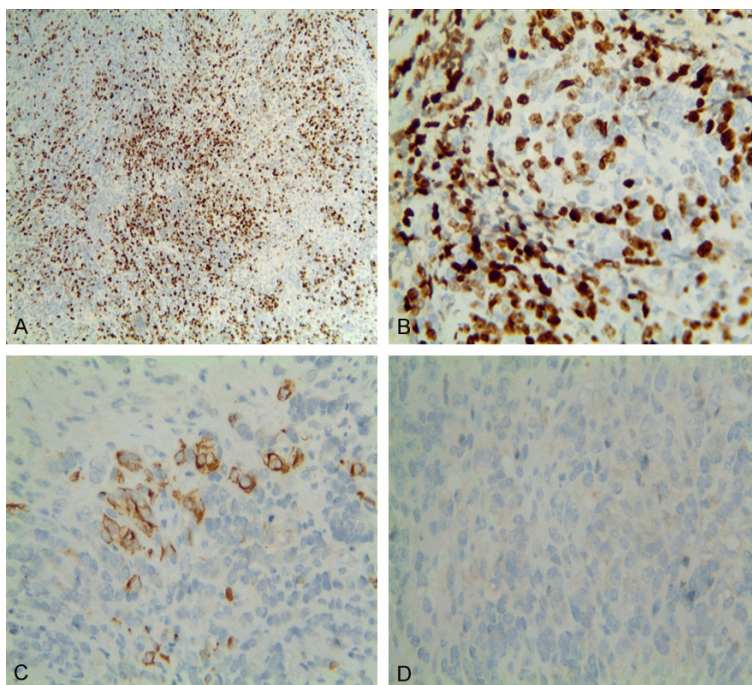


Figure 4. Immunohistochemical features of the tumor. The proliferation index (Ki-67) of the tumor is about 70% positive. (magnification $\times 100$, magnification $\times 400$, (A and B) Respectively). (C) CK is partially positive in the tumor cells. (magnification, $\times 400$). (D) SMARCA4 is negative which leads to the final diagnosis for SCCOHT (magnification, $\times 400$).

involved in the growth, differentiation, and infiltration of various tumors [9, 10]. With the genetic mutation of SMARCA4 in most cases, the loss of SMARCA2 may refer to the epigenetic silencing or mRNA degradation, confirmed by the lack of mutations or deletions involving SMARCA2 [1]. And with the mutually exclusive functions between SMARCA2 and SMARCA4 [8, 9], there may be an epigenetic recombination to support the residual functions of the remaining SMI/SNF complex.

In addition, current research from Yibo *et al.* demonstrated a remarkable susceptibility to CDK4/6 (cyclin-dependent kinase 4/6) inhibitors in SCCOHT cell lines [11]. For the molecular mechanism of the susceptibility, Yibo declared a deficiency of cyclinD1 and retinoblastoma (RB) phosphorylation, which are caused by the inactive mutation of SMARCA4 [11]. The “SMARCA4-cyclin D1-CDK4/6” mechanism may give a proper interpretation of SCCOHT, but this interpretation still needs more supporting evidence in clinical and immunopathology.

Moreover, some researchers are predisposed to reclassify SCCOHT as MRT0 (malignant rhab-

doid tumor of the ovary) due to its resemblance to ATRT. ATRT (atypical teratoid/rhabdoid tumor) is a rare, malignant CNS tumor that occurs mainly in infants and children [12]. There are many similarities between SCCOHT and ATRT [3, 4]. First, in some SCCOHT cases, large cells with rhabdoid morphology can be detected [13]. Second, the dual loss of SMARCB1 and SMARCA4 in ATRT closely resembles those in SCCOHT [3, 14]. Third, both present with an aggressive malignancy and hypercalcemia in clinical features. And last, their similarities are shown by other clues found in clinical examinations and immunochemistry or in whole exome sequencing studies [1, 14].

Moreover, studies of immunotherapy, like anti-PD1 immunotherapy, have also been encouraged and focused on SCCOHT. Programmed death 1 (PD-1) is a vital immune-checkpoint inhibitory receptor expressed by activated T cells. It could be blocked in the peripheral tissue by the immunosuppressive PD-1 ligands PD-L1 and PD-L2, which are expressed by tumor cells, stromal cells, or both [15]. The interaction between PD-L1 and PD-1 could significantly suppress the infiltration of tumors and enhance T-cell responses in vitro [16, 17]. And it has been confirmed that the PD-L1 expressions and TILs (tumor-infiltrating lymphocytes) in tumors are associated with its mutational burden, which also links the clinical responses to anti-PD1 immunotherapy [15, 18].

Contrasted with its low burden in mutation, SCCOHT shows an unexpectedly high expression of PD-L1 and is strongly statistically correlated with the infiltration of T cells, according to the experiments of Jelinic [18]. Also, the clinical feasibility of anti-pd1 immunotherapy is also shown in his study, in which 3 of 4 cases didn't recur for over 1.5 years after additional anti-pd1 immunotherapy [18]. Thus, it may be possible to treat patients diagnosed with SCCOHT

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with anti-PD1 immunotherapy [18, 19]. More clinical analyses and further molecular studies are still needed.

Regarding therapy, there are no targets or efficient therapies now. A useful regimen for SCCOHT is complete surgery followed by radiation, stem cell rescue, and high-dose chemotherapy [7, 20]. Furthermore, as indicated above, anti-PD1 immunotherapy such as CDK4/6 inhibitors may also prove favorable [18]. More clinical care has also been shown to lead to a better prognosis and treatment for patients. First, it's confirmed that ponatinib, a member of RTK (receptor tyrosine kinase) inhibitors, could delay tumor double time fourfold and decrease final tumor volumes by 50% and may also be efficient in SMARCB1 mutations in ATRT tumors [21]. Secondly, the target epigenetic regulator TSA (the HDAC inhibitor trichostatin A) could reactivate SMARCA2 expression in SCCOHT cell lines, which lead to a depression in tumors [1]. In addition, it's also been proved clinically that patients are sensitive to the histone methyltransferase EZH2 [4, 10, 22].

Conclusion

In general, SCCOHT is a rare but highly aggressive disease in young women. The loss of SMARCA4 alone or together with SMARCA2 is the only sensitive marker for its diagnosis, considering that there is no specific clinical manifestation or other features. Druggable vulnerability to CDK4/6 inhibitors may also be a molecular mechanism for further study. SCCOHT's resemblance to atypical teratoid rhabdoid tumors is also generally understood now. Up to now, many studies have demonstrated that SCCOHT greatly resembles AT/RT. And currently, further studies have confirmed a notable expression of PD-L1 associated with the clinical efficacy of anti-PD1 immunotherapy. Many other novel treatments like ponatinib, TSA, and EZH2 are also mentioned. Physicians and pathologists should have a new understanding of the SCCOHT's etiology and clinical therapy.

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Disclosure of conflict of interest

None.

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