

Case Report

Small cell carcinoma of the ovary hypercalcemic type (SCCOHT): report of three cases and literature review

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Summary

Background: Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT), is a rare ovarian tumor with hypercalcaemia mainly affecting young females, but its histogenesis remains largely unknown, which makes it a challenge for effective diagnosis and treatment. This report describes three cases of SCCOHT in young women aging between 23 and 31 years. **Material and Methods:** All three patients with SCCOHT were subjected to sex hormone and normal blood calcium test, B-ultrasound, and microscopic examination for diagnosis. Expression of low molecular weight Cytokeratin, Vimentin, INI1, WT1, and SMARCA4 were determined by immunohisto-chemistry. Morphological features of cancer cells were observed using electron microscopy, and gene mutation was analyzed by DNA sequencing. **Results:** All three SCCOHT patients were diagnosed by pathology examination, B-ultrasound, and increased blood calcium level, and underwent surgical resection followed by chemotherapy. Immunohistochemistry showed positive expression of WT-1, CK, INI1, Vimentin, EMA, CD10, and CD56 in tumor tissues of all three cases, but no expression of a-Inhibin, Bcl6, PLAP, Alk, SALL4, SMARCA4, OCT3/4, SF1, Calretinin, MPO, CD20, AFP, CD5, hCG-β, BCL2, ER, and S100. No mutations in FOXL2 gene were detected in these three SCCOHT cases. Two patients died within one year after surgery, and one was lost to follow-up. **Conclusion:** Three cases of young female SCCOHT patients were reported in this report, featured with poor prognosis even after surgery and chemotherapy.

Key words: SCCOHT; Small cell carcinoma of the ovary; Hypercalcaemia; INI1; SMARCA4.

Introduction

Small cell carcinoma of the ovary, hypercalcaemic type, (SCCOHT), is a rare ovarian tumor featured by hypercalcaemia, onset at early age and poor prognosis [1, 2]. This type of undifferentiated malignant tumor was first described early in 1979 with unknown histogenesis, based on the appearance of small and hyperchromatic cells [3]. SCCOHT accounts for 0.01% cases of ovarian tumors mainly in young females under the age of 40 with a median age of 24 years, usually causing unilateral pelvic masses, vomiting, infertility, and other systemic symptoms [1, 4]. Epithelial, neuroendocrine and sex cord-stromal origins, and various other hypothesis have been postulated over past decades about the etiology of SCCOHT, but none of them were fully supported and accepted [3]. Due to the lack of typical histological features, the diagnosis of SCCOHT is extremely challenging, difficult to distinguish it from other ovarian malignancies such as germ cell tumor, intra-abdominal desmoplastic small round cell tumor, and primitive neuroectodermal tumor [3, 5]. Recent investigations revealed various genetic mutations associated with SCCOHT development, such as SMARCA4 and SMACB1 genes [6-8]. More observations of the specific clinical and

molecular features are pressingly needed for SCCOHT early diagnosis and effective therapy.

In this report, the authors describe three cases of small cell carcinoma of the ovary hypercalcemic type (SCCOHT), followed by a literature review of its clinicopathological features, molecular basis, as well as clinical diagnosis and treatment.

Material and Methods

The expression of WT-1, CK, INI1, Vimentin, EMA, CD10, CD56, a-Inhibin, Bcl6, PLAP, Alk, SALL4, SMARCA4, OCT3/4, SF1, Calretinin, MPO, CD20, AFP, CD5, HCG-β, BCL2, ER, and S100 expression in tumor tissues were evaluated by immunohistochemistry as follows. Briefly, tissue sections were washed three times with xylene for five minutes, washed twice with 100% ethanol for ten minutes, washed twice with 95% ethanol for ten minutes, rinsed twice in dH₂O for five minutes, and boiled in 10 mM sodium citrate buffer (pH 6.0) for ten minutes. After being washed three times with dH₂O for five minutes, tumor tissue sections were then incubated with 3% hydrogen per-oxide for ten minutes, washed twice with dH₂O for five minutes, blocked with blocking solution for one hour at room temperature, incubated with primary antibody solution overnight at 4°C, washed three times with dH₂O for five minutes, and incubated with biotinylated secondary antibody at room temperature for 30

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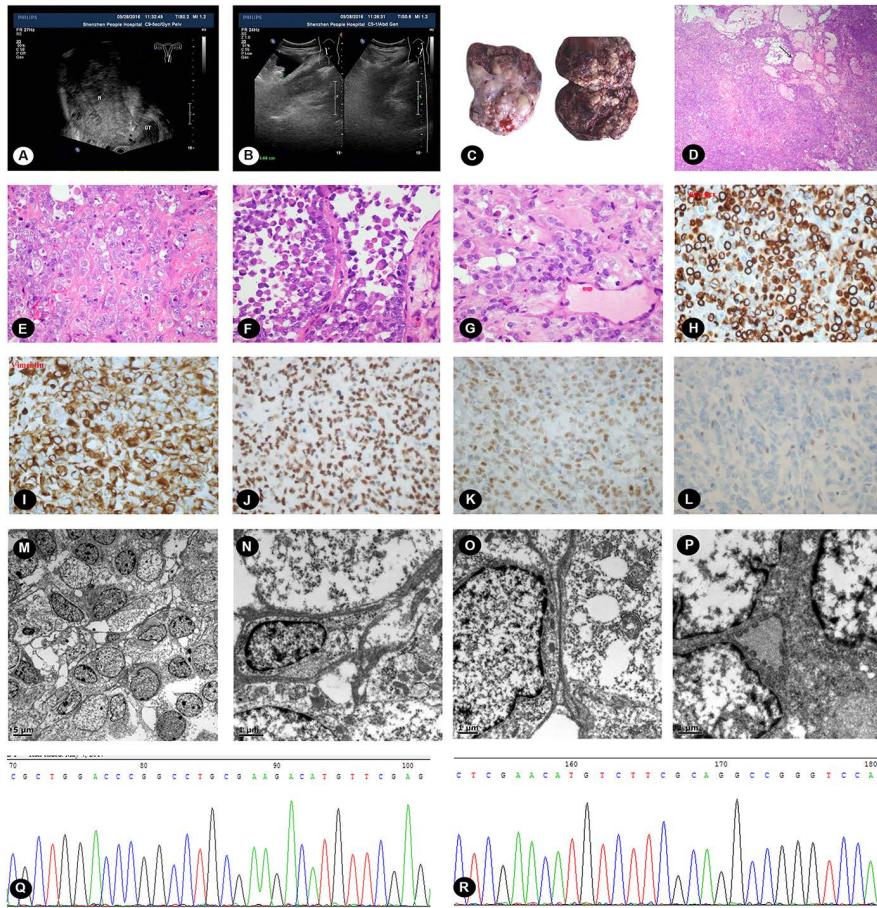


Figure 1. — Case 1 patient with small cell carcinoma of the ovary hypercalcemic type. (A) Solid space-occupying lesions in pelvic cavity by B-ultrasound. (B) Effusion in pelvic cavity and right iliac fossa by B-ultrasound. (C) General view of solid mass collected by surgical resection. (D) Follicular structures containing eosinophilic liquid under microscopy. (E) Eosinophilic basement membrane-like structure under microscopy. (F) Slightly enlarged cells with eosinophilic cytoplasm, eccentric nuclei, and striated muscle cell-like shapes. (G) Individual cells with eosinophilic spherule structures in cytoplasm. (H-L) Low molecular weight Cytokeratin (H), Vimentin (I), INI1 (J), WT1 (K), and SMARCA4 (L) expression by immunohistochemistry. (M, N) Undifferentiated cells showing clear nuclear membranes, condensed chromatin particles, and visible nucleolus without neurosecretory granules. (O, P) Gap junctions and desmosomes between tumor cells viewed under electron microscopy. (Q, R) No mutation in FOXL2 gene by DNA sequencing.

minutes. Finally, tissue sections were incubated with 200 μ l DAB or other substrate until being fully developed, immersed, and washed in dH₂O again, dehydrated by incubation with 95% ethanol for ten seconds and mounted for imaging under microscopy.

Results

Case 1

A 24-year-old female patient underwent cesarean section four months ago and presented with abdominal distension for two days before admission to hospital. B ultrasonography showed one solid mass (147×128×94 mm) linked with a fallopian tube in the pelvic cavity with irregular shape, significantly non-homogeneous echo and blood stream signals, which suggested teratoma of ovary (Figures 1A-1C). Multiple sonolucent spaces with a maximum size of 37×31 mm were observed in the mass, adjacent to left ovarian tissues. Examination on admission showed normal levels of sex hormones and normal blood calcium (2.24 mmol/l). Microscopic examination showed tumor cells in diffuse or stripe-like distribution, adenoid structures in local lesions, follicular structures containing eosinophilic liquid (Figure 1D), and basement membrane-like material between tumor cells (Figure 1E). Tumor cells in local areas were in spin-

dle shapes, with shrunken cytoplasm, hyperchromatic nuclei, condensed chromatin, and visible nucleolus. Slightly enlarged cells were observed in local areas with eosinophilic cytoplasm, eccentric nuclei, and striated muscle cell-like shapes (Figure 1F). Individual cells showed eosinophilic spherule structures in cytoplasm, significant apoptosis, recognizable nuclear division stages, and hemorrhagic necrosis (Figure 1G). Also observed in tumor mass were decreased and edematous stroma.

To provide a preliminary basis for molecular pathology and diagnosis, the authors detected the expression of major protein biomarkers closely associated with tumorigenesis by immunohistochemistry, which showed the expression of WT-1, CK, INI1, Vimentin, EMA, CD10 and CD56, rather than a-Inhibin, Bcl6, PLAP, Alk, SALL4, SMARCA4, OCT3/4, SF1, Calretinin, MPO, CD20, AFP, CD5, HCG- β , BCL2, ER, and S100 (Figure 1H-1L). Electron microscopic examination showed undifferentiated cells evidenced by clear nuclear membranes, condensed chromatin particles, and visible nucleolus, without neurosecretory granules (Figure 1M and 1N). Also shown by electron microscopic examination were gap junctions and desmosomes between cells, endoplasmic reticulum in uniform sizes with electron dense deposits in medium density, and microcavities in cytoplasm (Figure 1O and 1P).

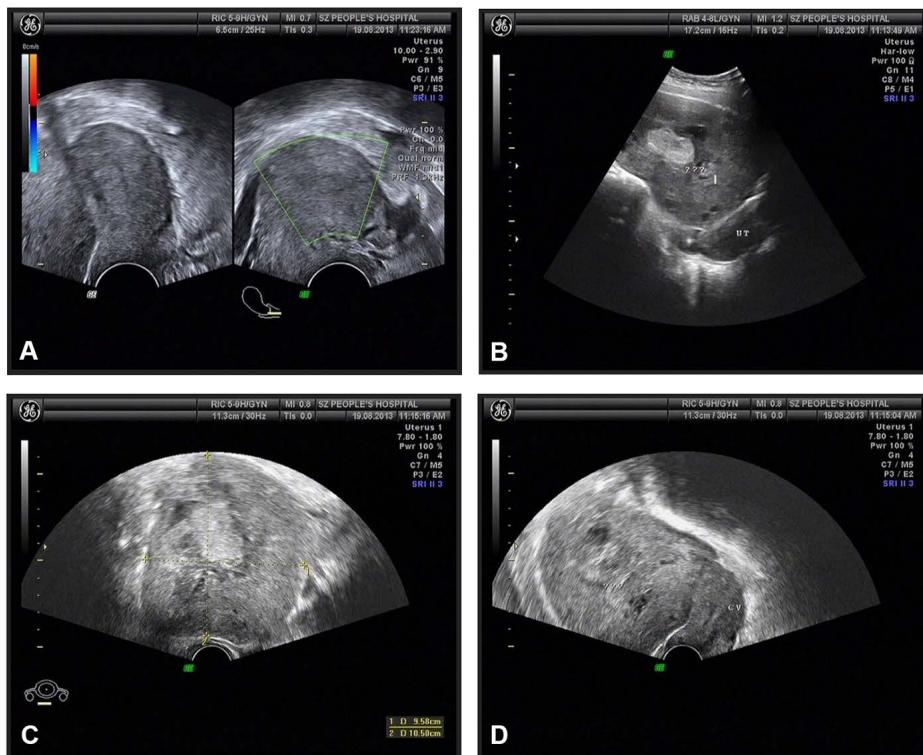


Figure 2. — Case 2 patients with small cell carcinoma of the ovary hypercalcemic type. A 23-year-old female patient was admitted to hospital due to recurrent hypogastralgia. B-ultrasound (A-D) showed an elliptic mass (104×128×94 mm) at anterior side of right ovary, anterior, and superior to the uterus. Also revealed were substantial echoes of uniform distribution, anechoic area inside, irregular hyperechoic sheets, clear and regular boundaries, and slight blood flow signaling inside the mass.

No mutation in FOXL2 gene were detected by DNA sequencing (Figure 1Q and 1R). The patient was finally diagnosed with SCCOHT, underwent surgical resection in June 2016, and received chemotherapy since September 2016. The patient had multiple metastasis in November 2016 and died in April 2017.

Case 2

A 23-year-old unmarried female patient was admitted to hospital due to recurrent hypogastralgia. Examination on admission showed normal cervix, vulva, and vagina. B ultrasonography examination showed normal uterus shape and size, with homogeneous echoes of uterus wall, centered endometria line, and an endometrial thickness of 2 mm. No abnormal echoes and blood flow signals were observed in uterine cavity. An elliptic mass (104×128×94 mm) was detected at anterior side of right ovary, anterior, and superior to the uterus, with substantial echoes of uniform distribution, anechoic area inside, irregular hyperechoic sheets, clear and regular boundaries, and slight blood flow signal inside the mass. Few fluid sonolucent areas suggesting effusion were observed in Douglas cavity at depth of 7 mm. No abnormal expressions of tumor biomarkers were detected. The patient was diagnosed with left ovarian juvenile granulosa cell tumor rupture and chronic inflammation of left fallopian tube by clinical examination, underwent surgical resection, and lost at follow-up. (Figure 2)

Case 3

This 31-year-old female patient had undergone surgery

for Stage IV ovarian juvenile granulosa cell tumor and was admitted to hospital for giant tumor in pelvic cavity detected following abdominal distension for 14 days. Examination on admission showed progressive accumulation of ascites and hydrothorax, significantly increased CA125 level (45.8 U/ml). B ultrasonography revealed solid cystic tumor in right ovary (150×120 mm) with a cauliflower-like surface and crevasses in tumor capsule, accompanied with slightly enlarged left ovary and normal uterus size with miliary nodules on surface. After surgery, the patient was given chemotherapy with bleomycin, vincristine, and cisplatin (BVP), combined with intraperitoneal chemotherapy (90 mg cisplatin in 500 ml normal saline). The blood calcium level was 1.69 mmol/L. Follow-up revealed that this patient had died two years ago.

Discussion

As a non-epithelial ovarian cancers (NEOC), the treatment for SCCOHT which mainly affects young females still remains a great challenge in clinics [9, 10]. SCCOHT is one type of rare ovarian cancers accounting for only 0.1% of all malignant ovarian tumors, which indicates low availability of epidemiological evaluation based on large-scale patient groups [1, 9], and makes understanding of the biological mechanisms a pressing need for timely diagnosis and effective treatment. Abnormally increased calcium content in patient blood samples has been viewed as one main characteristics of SCCOHT [11], but little is known about the pathophysiological processes

of hypercalcemia in spite of the possible involvement of parathyroid hormone [9]. Although multimodality treatment has been applied, the five-year OS rate for SCCOHT patients is still no more than 10% [12]. Effective prevention and treatment of such rare malignant disease calls for accumulation of clinical case reports, which might provide information for investigation of the underlying pathogenic processes and novel therapeutic agent development. In this study, the authors reported three cases of young females with SCCOHT, which is consistent with previous references, further confirming that women at young age are susceptible to SCCOHT development.

Biologically, the histogenesis of SCCOHT and pathogenic are still poorly understood. Recent investigations showed that the development of SCCOHT was associated with malignant rhabdoid tumor and mutation of SMACB1 gene (also known as INI1), which encodes a key component protein of the SW1/SNF (SMARCA2, SMARCA4) complex [6, 9, 13]. Through whole-exome sequencing (WES) of three patient families with SCCOHT, it has been recently disclosed that mutation of the SMARCA4 gene closely associating with chromatin remodeling was also detected in all tested SCCOHT cases [7], which has been supported by multiple reports [8, 14-16]. In light of the ubiquitous existence of SMARCA4 and SMACB1 gene mutations in atypical rhabdoid tumor and malignant rhabdoid tumors, it has also been proposed that SCCOHT should be renamed ‘malignant rhabdoid tumor in ovary’ [7]. However, the relationship between SCCOHT and malignant rhabdoid tumor, as well as the roles of SMACB1 and SMARC genes in pathogenesis of SCCOHT, deserve further investigations. In addition, several marker genes were reported to be associated with SCCOHT by immunohistochemistry, which could be used for accurate diagnosis. For instance, WT1 and TTF1 (thyroid transcription factor) expressional alterations were differentially detected between SCCOHT and other tumor types such as pulmonary small cell cancer [17]. Other tumor-related genes expressed in SCCOHT cancer tissues detected by immunohistochemistry include neuron-specific enolase (NSE), Equi Merozoite Antigen (EMA), and also the tumor suppressor gene TP53 [4, 17]. Here in this report, the authors showed also by immunohistochemistry that the low molecular weight Cytokeratin, Vimentin, INI1, WT1, and SMARCA4 genes were highly expressed in one of the reported SCCOHT patients, as a supporting evidence of these tumor marker genes in SCCOHT pathogenesis. However, the specific biological roles of these genes during initiation and progression of SCCOHT, as well as the associated signaling pathways and molecular mechanisms, are to be extensively studied. The interactions between various biological processes mediated by these key functional genes also deserved further investigations.

The diagnosis of SCCOHT remains a clinical challenge due to insufficient understanding of SCCOHT biology

and the lack of specific pathogenic features. Clinical diagnosis of SCCOHT should be based on the clear distinguishing from other confusing tumors such as juvenile granulosa cell tumor, undifferentiated carcinoma, small cell carcinomas of the ovary, pulmonary type (SCCOPT), adult granulosa cell tumors (GrCT), ovarian dysgerminoma, and rhabdoid tumor [1, 4]. For instance, the patients of SCCOHT and juvenile granulosa cell tumor share similar age distributions and similar follicular structures [1, 4]. The majority of patients with juvenile granulosa cell tumor in clinics were usually Stage 1 benign tumors at diagnosis, with significant estrogen secretion and positive expression of a-Inhibin, but with no hypercalcemia symptom and EMA expression [18, 19], which could be applied as major distinctions for pathologists and clinicians. As performed in this report, accurate diagnosis and classification of SCCOHT depends on combined analysis of clinical symptoms, cellular, and histological features, imaging examinations and immunohistochemical results. Unfortunately, there have no available consensus or standard guidelines for SCCOHT treatment so far. Recently, the main treatment modality for SCCOHT patients in clinics includes debulking surgery as the first choice, combined with chemotherapy and radiotherapy [9]. Because most SCCOHT cases were unilateral, the timely surgical resection has been successfully applied to relieve symptoms and produce desirable outcomes, which could spare the contralateral ovary and uterus [9]. Clinical study based on 17 SCCOHT patients from Australia, Europe, and Canada also highlighted the importance of multi-modality treatment approaches including surgery, adjuvant platinum-based chemotherapy such as carboplatin combined with paclitaxel and etoposide, and also adjuvant radiotherapy for favorable outcomes [20]. This report strikingly revealed the possible effect of adjuvant radiotherapy in elongating SCCOHT patients’ survival time, shown by the observation that most long-term survivors has been treated with adjuvant radiotherapy [20]. The beneficial effects of adjuvant chemo- and radio-therapy on survival and outcomes of SCCOHT patients were also supported by other clinical observations [21]. However, no specific treatments by targeting known tumor marker genes such as SMARCA4 are available for SCCOHT therapy in clinics. These three SCCOHT cases reported here could provide new pathogenic and molecular information for SCCOHT biology investigation and therapy development.

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