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Diagnostic and Therapeutic Challenges in Small Cell Carcinoma of the Ovary, Hypercalcemic Type: A Case Report

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ABSTRACT:

Background: Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT) is an uncommon and aggressive cancer predominantly affecting younger women, often linked with poor outcomes. This case elucidates the pivotal diagnostic value of hypercalcemia in young women presenting with ovarian masses, particularly in the context of challenging presentations like primary infertility.

Case Presentation: We report the case of a 30-year-old woman with primary infertility, who was diagnosed with SCCOHT following the identification of symptomatic hypercalcemia. Initially, the hypercalcemia was not evident; however, it became a significant diagnostic clue as the disease progressed. The patient underwent diagnostic evaluations including ultrasonography and contrast-enhanced CT scans. Histopathological and immunohistochemical findings from the adnexal resection specimen, which measured 4 x 3 x 2 cm and exhibited a characteristic small cell morphology with marked nuclear atypia and high mitotic activity, confirmed the diagnosis of SCCOHT.

Discussion: This case delineates the diagnostic intricacies of SCCOHT, spotlighting hypercalcemia as a critical indicator, especially in patients with ambiguous symptoms like infertility. The presence of hypercalcemia in young females with ovarian masses should heighten the suspicion for SCCOHT, emphasizing the necessity for prompt and thorough evaluation. This report enriches the understanding of SCCOHT's clinical and histological manifestations, underlining the imperative for heightened clinical vigilance and swift investigative processes to improve patient outcomes in this aggressive disease.

Introduction

Small cell carcinoma of the ovary (SCCO) is a rare and aggressive tumor type, broadly categorized into two subtypes: the pulmonary type (SCCOPT) and the hypercalcemic type (SCCOHT). While SCCOPT, with fewer than 20 documented cases, shows neuroendocrine

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differentiation akin to small cell carcinoma of the lung and affects a broader age range (28 to 85 years) [1], SCCOHT is notably the most common undifferentiated ovarian malignancy in women under 40. It is characterized by an aggressive clinical course, with a relatively higher incidence rate, more dismal prognosis, and a distinct age distribution, primarily affecting young females between 20 to 39 years [2,3,4].

SCCOHT not only poses a significant challenge in terms of its clinical management but also in its diagnostic and histological characterization. It is distinguished by a grim prognosis, with survival rates starkly lower compared to other ovarian malignancies [2]. Despite its rarity, the incidence of hypercalcemia in SCCOHT is noteworthy, present in about two-thirds of cases, yet clinically evident in a small fraction, manifesting through a spectrum of symptoms [5,6]. The histopathology of SCCOHT, featuring small round cells with scant cytoplasm, complicates its differentiation from other small round blue cell tumors, necessitating advanced immunohistochemical and molecular diagnostic approaches [7,8].

The differential diagnosis of SCCOHT includes consideration of its large cell variant, which can resemble other large-cell neoplasms, adding to the diagnostic challenge [9]. The role of next-generation sequencing has been pivotal in unraveling the genetic underpinnings of SCCOHT, with mutations in the SMARCA4 gene playing a central role in its pathogenesis [10,11]. These genetic insights underscore a potential monogenic predisposition to SCCOHT, enhancing our understanding of its etiology and aiding in the differential diagnosis.

Management strategies for SCCOHT remain underdeveloped, largely based on individual case reports and small case series due to the lack of comprehensive clinical trials. The current approaches, including primary cytoreductive surgery, radiotherapy, and chemotherapy, reflect the necessity for tailored therapeutic strategies, given the absence of standardized treatment protocols [12,13]. The ongoing challenges in early detection, coupled with the limitations of risk-reducing strategies, highlight the critical need for continued research and development of effective management guidelines for this rare ovarian malignancy.

Case presentation

In May 2021, a 30-year-old woman presented at the First Affiliated Hospital of Wenzhou Medical University with a complaint of one-month amenorrhea, which led to the discovery of an ovarian mass. Subsequent surgical intervention on June 18, 2021, encompassed a left salpingo-oophorectomy, omentectomy, and pelvic lymphadenectomy. The intraoperative frozen section analysis revealed a malignant entity within the left ovary, initially postulated to be a germ cell tumor or clear cell carcinoma. However, the clinical indication of hypercalcemia nuanced the diagnosis towards the small cell carcinoma of the ovary, hypercalcemic type (SCCOHT).

Postoperative care included six chemotherapy cycles from July 27 to November 14, 2021, which the patient tolerated well, showing no recurrence initially. Nevertheless, the detection of a lung tumor in December 2021 necessitated a right thoracoscopic radical resection and pleural adhesion lysis, pointing towards metastatic progression, as depicted in Figure 1. The patient's oncological journey continued with the recurrence of ovarian cancer and secondary abdominal malignancies, leading to extensive cytoreductive surgery on September 23, 2022.

The patient underwent rigorous diagnostic procedures. Multi-slice CT scanning delineated a clearly defined pelvic mass with heterogeneous density, measuring 105×93×94 mm, and displayed mild to pronounced enhancement, particularly at the periphery, as detailed in the CT report (Figure 2 c and d). Enhanced ultrasonography complemented these findings, revealing a hypoechoic mass with an irregular contour and heterogeneous internal echogenicity, characteristics crucial for surgical and therapeutic planning (Figure 2a and b).

Immunohistochemical profiling was integral to refining the diagnosis. It revealed robust positivity for CAM5.2 and CD99, while markers like CgA were negative, aiding in distinguishing the tumor's pathology (Table 1). Microscopic examination further detailed the tumor's architecture, displaying small, hyperchromatic cells with rhabdoid features and signet-ring cells, characteristics aligned with the large cell variant of SCCOHT, as demonstrated in Figure 3.

Gross pathological examination provided additional context, with the adnexal resection specimen revealing

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distinct morphological features detailed in the pathology report, contributing to the comprehensive diagnostic understanding of the patient's condition. The extensive immunohistochemical findings, documented in Table 1, confirmed the diagnosis, elucidating a clear cell sarcoma profile with diffuse positivity for several markers, pivotal for establishing the SCCOHT diagnosis.

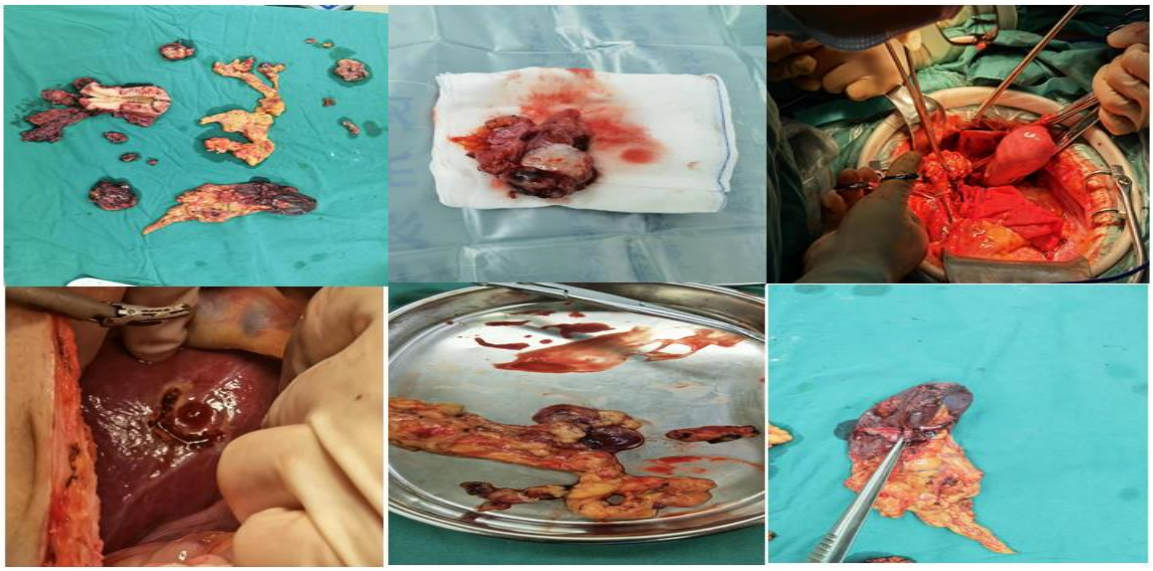

Figure 1. Various Malignant Tumors Detected Post-Surgical Approaches

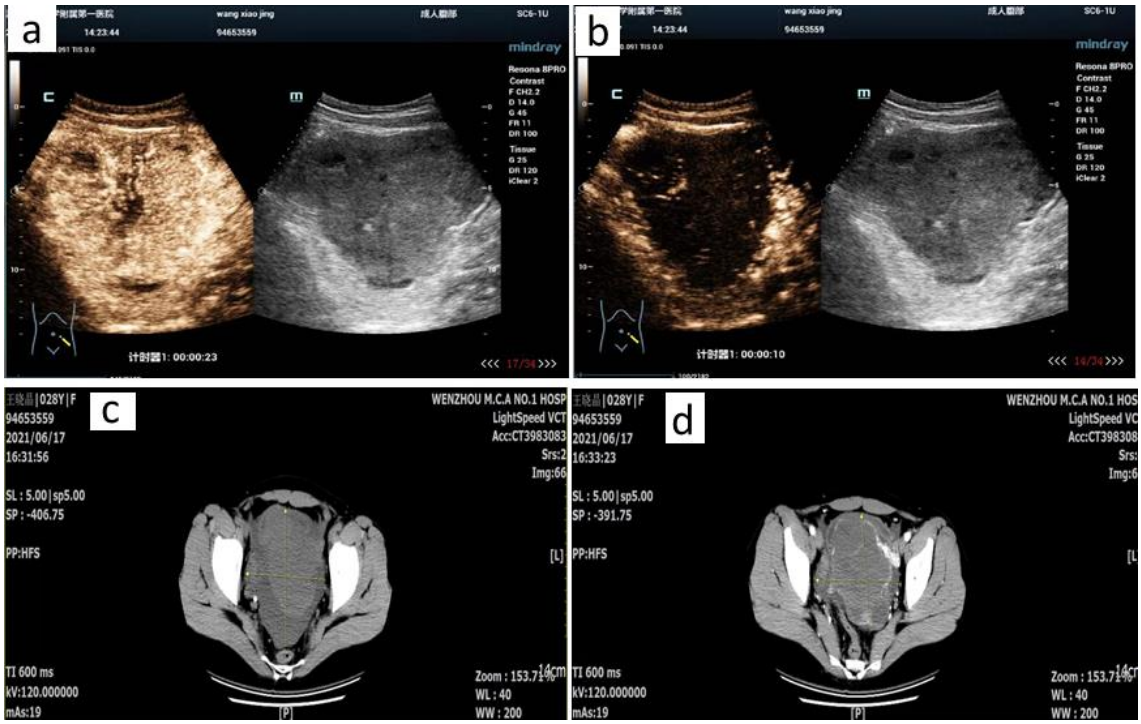

Figure 2. Ultrasound images (a) and (b) depict a hypoechoic mass located on the left ovary, (c) and (d) CT scans reveal a pelvic soft tissue mass with clearly defined boundaries and uneven density.

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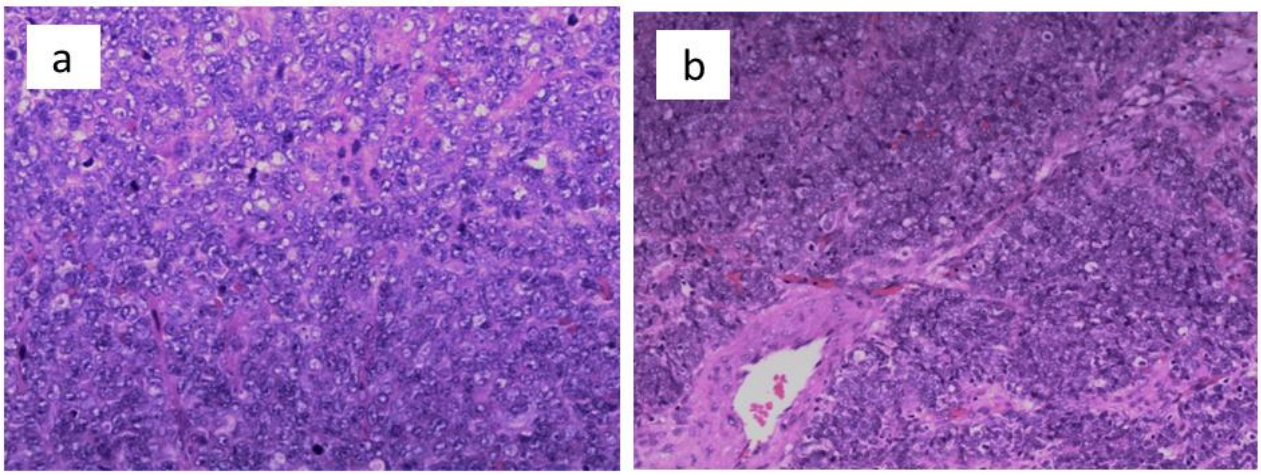

Figure 3. Microscopic examination in (a) and (b) Showing a diffuse growth pattern consisting of closely packed small cells with eccentric nuclei and prominent nucleoli.

Table 1. Immunohistochemical analysis and microscopic examination results of biopsy specimen

Marker	Positivity	Signal	Positivity
CAM5.2	+++	strong	Positive
CD99	+++	Strong	Positive
CgA	-	Negative	Negative
CK	+	Weak	Positive
EMA	++	Moderate	Positive
Inhibin	-	Negative	Negative
P16	++	Moderate	Positive
P53	++	Moderate	Positive
Syn	+++	Strong	Positive
VIM	++	Moderate	Positive

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Marker	Positivity	Signal	Positivity
WT-1	+++	Strong	Positive

Discussion

The discussion of this case report contributes significantly to the existing body of knowledge on Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT), linking specific clinical observations with established research findings. This case resonates with the demographic and clinical features typically associated with SCCOHT, notably aligning with the documented age range and the presence of hypercalcemia, a hallmark finding in such cases, which serves as a vital diagnostic clue, especially in young women with ovarian masses [14]. In our examination, the application of a suite of immunohistochemical markers—CAM5.2, CD99, CK, EMA, P16, P53, Syn, VIM, and WT-1—was pivotal in delineating the tumor's characteristics, supporting its identification and reinforcing the diagnostic approach that is well-documented in the literature on SCCOHT [15, 16]. These markers not only facilitated the confirmation of the SCCOHT diagnosis but also provided valuable insights into the tumor's behavior and potential responsiveness to therapeutic interventions.

Despite advancements in diagnosing and managing SCCOHT, the disease prognosis remains unfavorable, particularly when diagnosed in advanced stages, as reflected in the literature [15]. The treatment strategy employed in our case, encompassing surgical intervention and chemotherapy, adheres to established protocols yet highlights the aggressive nature of SCCOHT and its tendency for recurrence and metastasis.

The histopathological findings in our patient, exhibiting a classic small cell pattern with notable nuclear atypia and the presence of rhabdoid and signet ring features, offer a microscopic view into the tumor's aggressive pathology, which is consistent with previous descriptions in the scientific literature [16, 17]. These observations underscore the complexity and heterogeneity of SCCOHT, further emphasizing the need for a nuanced therapeutic approach.

As we look to the future, it is evident that there is a profound need for continued research into SCCOHT. Delving into its molecular landscape to identify novel biomarkers and potential therapeutic targets remains a priority. The goal is to foster research that can elucidate the molecular drivers of SCCOHT, improve the precision of therapeutic regimens, and ultimately, enhance prognostic accuracy for affected patients. By advocating for expanded research collaborations and innovative studies, the medical community can aspire to advance the care paradigms for patients facing this formidable challenge, moving towards more personalized and effective treatment strategies [14,15,16,17,18].

Conclusion

Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT) is an aggressive ovarian malignancy predominantly affecting reproductive-age women, characterized by hypercalcemia and a challenging prognosis. The intricate relationship between SCCOHT and hypercalcemia underscores a critical area for deeper scientific exploration to enhance our understanding and treatment approaches. Diagnostic clarity for SCCOHT relies heavily on detailed pathological evaluation, where immunohistochemistry is indispensable in differentiating SCCOHT from other ovarian tumors, ensuring accurate diagnosis and informed management. The rarity and complexity of SCCOHT demand concerted research efforts to elucidate its pathophysiology, improve diagnostic accuracy, and develop more effective therapeutic strategies, thereby aiming to improve outcomes for patients afflicted with this aggressive disease.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Availability of data and materials

All data and materials are fully presented in the manuscript.

Competing interests

The authors declare that they have no conflict of interest.

Author contributions

The study plan and experiment design were done by All authors who read and approved the final version of the manuscript.

Finding

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