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Small Cell Carcinoma of the Ovary, Hypercalcemic Type: A Case Report

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ABSTRACT

Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT), first described by Dickersin et al. in 1982, is a rare and highly aggressive neoplasm that predominantly affects women between the ages of 10 and 40. It accounts for less than 1% of all ovarian cancers, making it an uncommon and challenging entity.

Case Report: *A 25-year-old woman presented with suprapubic pain for 3 days, worsening in intensity, and progressive abdominal distension over the past 2 months. On physical examination, she exhibited tenderness on palpation of the lower abdomen and a palpable hypogastric mass. Vaginal examination revealed a tender cervix upon mobilization. Imaging demonstrated a large, heterogeneous mass with ascites. Exploratory laparotomy was performed with resection of a solid left ovarian mass along with the adherent ipsilateral fallopian tube, total hysterectomy, right salpingo-oophorectomy, omentectomy, appendectomy, bilateral pelvic and retroperitoneal lymphadenectomy. Histopathology revealed a high-grade carcinoma, and immunohistochemistry confirmed SCCOHT. Chemotherapy cycles were initiated, but within three months the patient developed malignant bowel obstruction, ascites, and peritoneal carcinomatosis. Due to extensive disease and lack of therapeutic response, she died four months after diagnosis.*

Discussion: *This disease is typically unilateral, rapidly progressive, and life-threatening. Its histogenesis remains unproven. Pathologic diagnosis is not straightforward due to morphologic overlap with other tumor types. Clinical presentation is variable, often nonspecific, and may include hypercalcemia-related symptoms (up to 90% of cases), though some patients are asymptomatic. Treatment usually involves a multidisciplinary approach with radical surgery, chemotherapy, radiotherapy, and palliative care.*

Keywords

Ovarian neoplasms, Small cell carcinoma, Hypercalcemia.

Introduction

Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT), is a rare and highly aggressive neoplasm that predominantly affects young women between the ages of 10 and 40 (average age: 23 years). First described by Dickersin et al. in 1982, SCCOHT represents less than 1% of all ovarian cancers, making it an uncommon and challenging disease entity [1].

Its clinical presentation is variable, ranging from nonspecific symptoms such as abdominal or pelvic pain, fatigue, vomiting, dyspareunia, and changes in bowel habits, to manifestations

related to hypercalcemia, such as muscle weakness, polyuria, and polydipsia. In some cases, patients may remain asymptomatic [1]. Diagnosis is often challenging due to its rarity and overlapping features with other gynecologic conditions. Although tumorigenesis remains uncertain, some evidence suggests epithelial origin, while other studies argue against germ cell or epithelial derivation [2].

Treatment is frequently arduous, requiring a multidisciplinary approach. Aggressive cytoreductive surgery remains the mainstay, typically followed by adjuvant chemotherapy. However, in the absence of disease-specific randomized clinical trials, there is no consensus regarding the most effective chemotherapeutic regimen. Treatment response is often limited, recurrence rates are high, and prognosis is poor [2,3].

Case Report

A 25-year-old woman was referred to the Gynecology Department at Santa Casa de Misericórdia de Vitória with a 3-day history of progressive suprapubic abdominal pain. She reported abdominal enlargement over the previous two months, undocumented fever, whitish vaginal discharge with pruritus, and two episodes of dysuria. Upon initial physical examination, she was in good general condition but presented swelling in response to superficial and deep palpation of the lower abdomen and a poorly defined hypogastric mass extending 3 cm below the umbilicus. Vaginal examination revealed a mobile, closed cervix that was tender upon mobilization.

Laboratory results included: hemoglobin 14 g/dL, hematocrit 43.6%, leukocytes 14,630/mm³, β-hCG 2.4 IU/L, pancreatic amylase 39 IU/L, CEA 0.5 ng/mL, AFP 1.9 ng/mL, albumin 4.5 g/dL, CA-125 1,930 U/mL, LDH 434 U/L, CA 19-9 3.8 U/mL. Remaining lab testes were unremarkable.

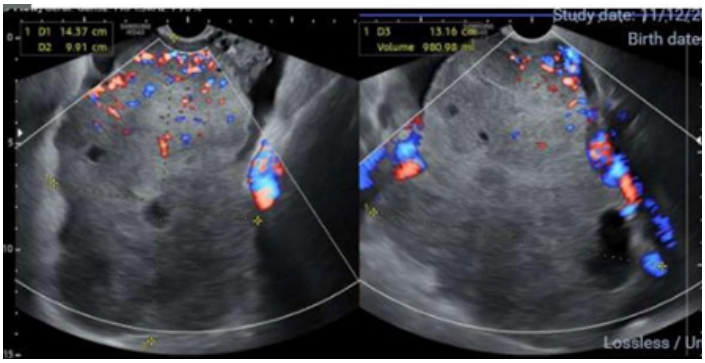

Figure 1: Transvaginal Doppler ultrasound showing a solid, intensely vascularized mass.

Surgical Findings

Exploratory laparotomy revealed a large, solid left ovarian mass with adherent ipsilateral fallopian tube. The procedure included total hysterectomy, right salpingo-oophorectomy, omentectomy, appendectomy, bilateral pelvic and retroperitoneal lymphadenectomy. Intraoperative frozen section suggested a malignant ovarian tumor consistent with dysgerminoma, with ovarian surface involvement. Ascitic fluid was collected for cytopathological analysis.

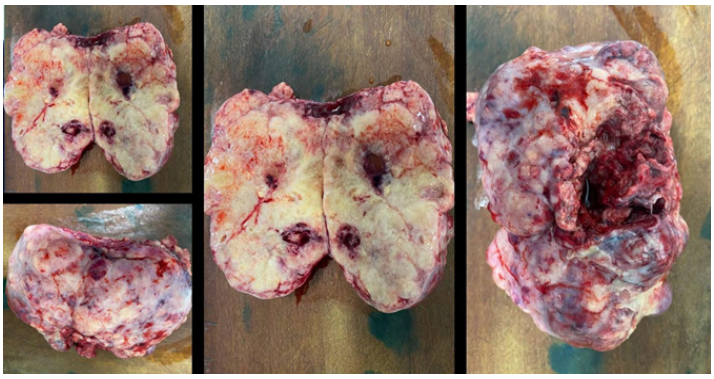

Figure 2: Resected left ovarian mass with adherent ipsilateral fallopian tube.

Following surgical procedures, the patient recovered in the intensive care unit, being discharged after 5 days.

Histopathology: final analysis confirmed high-grade carcinoma infiltrating the entire ovarian tissue with necrosis, without surface involvement or angiolymphatic invasion. Tumor cells displayed plasmacytoid morphology with "salt-and-pepper" chromatin

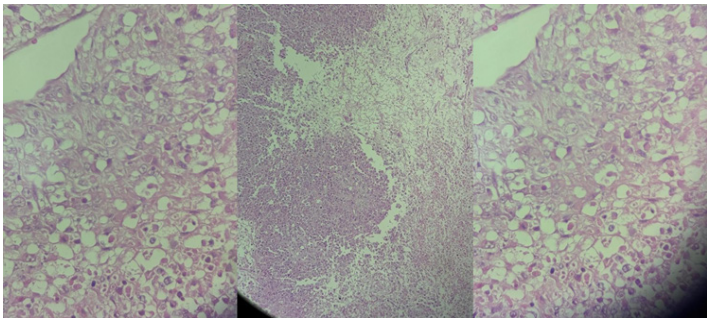

Figure 3: High-grade epithelioid neoplasm, predominantly composed of small plasmacytoid cells with "salt-and-pepper" chromatin.

Immunohistochemistry: revealed positivity for cytokeratins (see Table 1 below), neuroendocrine markers (synaptophysin, INSM1, CD56), and WT1. SMARCB1/INI1 expression was preserved, whereas SMARCA4 expression was lost — findings consistent with SCCOHT.

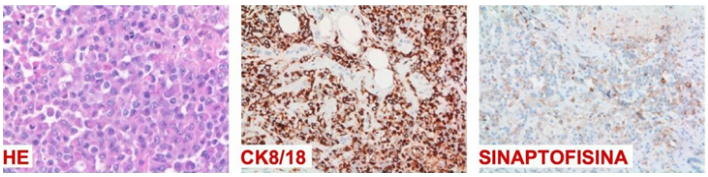

Figure 4: Immunohistochemistry panel.

Follow-up: Serum calcium was 12.4 mg/dL (normal 8.6–10.0). Chemotherapy was initiated with **carboplatin (AUC 5) plus paclitaxel 175 mg/m2**, followed by **etoposide–cisplatin**;

zoledronic acid was given for hypercalcemia.

Three months later, the patient developed right leg swelling; ultrasonography confirmed deep vein thrombosis of gastrocnemius veins, and anticoagulation was started. During the same admission, she developed malignant bowel obstruction. Abdominal CT showed large-volume ascites, peritoneal nodules (largest 2.1 cm), irregular solid-cystic pelvic lesions, and retrovesical infiltration. Despite further chemotherapy, disease progression continued, and the patient died four months after diagnosis.

Discussion

Ovarian cancer is the eighth leading cause of death from malignant neoplasms among women worldwide. Recent studies have revealed significant findings regarding its distribution and evolution: (1) the highest mortality rates are observed in low- and middle-income countries, reflecting inequalities in access to early diagnosis and treatment; (2) paradoxically, incidence is higher in high-income countries, possibly due to improved detection capacity; and a worrisome increase in incidence has been noted among younger women [4].

Although frequently treated as a single nosological entity, ovarian cancers comprise a heterogeneous group of neoplasms that differ in clinical, morphologic, immunohistochemical, and molecular-genetic features. Among these, Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT), stands out as a rare, highly aggressive neoplasm with a dismal prognosis. This article reports the case of a 25-year-old woman diagnosed with SCCOHT, highlighting the clinical, diagnostic, and therapeutic aspects of this oncologic entity.

SCCOHT predominantly affects young women, and early diagnosis is particularly challenging due to its nonspecific presentation and extremely low prevalence—factors that substantially contribute to poor prognosis [1].

Serum tumor markers, such as CA-125, may be useful tools in the evaluation of adnexal masses, aiding in the differentiation between benign and malignant ovarian lesions. Elevated CA-125 levels are most often associated with serous epithelial carcinomas, though they may also occur in other malignancies, inflammatory conditions, and benign diseases. Additionally, CA-125 is recognized as an important prognostic factor in epithelial ovarian tumors. However, its prognostic role in SCCOHT remains poorly defined, owing to the rarity of the disease and the limited data available in the literature [5]. In this case, the patient presented with markedly elevated CA-125 levels (1,930 U/mL), likely reflecting a high tumor burden at diagnosis.

Clinically, SCCOHT often presents with nonspecific manifestations that mimic other gynecologic conditions. In this case, the patient reported progressive suprapubic abdominal pain and abdominal distension.

Abdominal pain is a common finding and may be diffuse or localized, with variable intensity. Other typical signs include ascites, a palpable adnexal mass, and abdominal distension, often reported as bloating or enlargement due to tumor expansion. Gastrointestinal symptoms such as nausea, vomiting, constipation, or diarrhea may also occur from intra-abdominal compression by the tumor. A hallmark of SCCOHT is hypercalcemia, present in up to 90% of cases, serving as an important clinical marker [1,6,7].

The pathophysiology of hypercalcemia is not fully understood. In some cases, it may be mediated by secretion of parathyroid hormone–related protein (PTHrP), which mimics the action of parathyroid hormone (PTH). The presence of PTHrP can be confirmed by immunohistochemical techniques, and it constitutes an important marker for diagnosis [8].

The histogenesis of SCCOHT remains under debate. Hypotheses include epithelial, germ cell, stromal, and neuroendocrine origins.

Table 1: Immunohistochemical analysis.

Anticorpos	Clone	Resultado	Observação
• ARID1A	Polyclonal	Expressão Preservada	
• Receptor de Estrógeno	EP1	Negativo	
• Receptor de Progesterona	PgR636	Negativo	
• CK8/18	B22.1&B23.1	Positivo	
• PAX8 - fator de transcrição da família do gene - paired box (PAX)	ZR-1	Negativo	
• Produto do oncogene Wilms Tumor 1 (WT-1)	6F-H2	Positivo	
• Produto do gene supressor tumoral p16(INK4)	MX007	Positivo	forte e difuso
• Produto do gene supressor tumoral TP53	DO-7	Padrão selvagem	
• Desmina (filamento intermediário célula muscular)	D33	Negativo	
• Miogenina, antígeno de células musculares esqueléticas	F5D	Negativo	
• Alfa-inibina	R1	Negativo	
• Cromogranina A	LK2H10 + PHE5	Negativo	
• Sinaptofisina	DAK-SYNAP	Positivo	
• Produto do gene INI-1 (hSNF5; SMARCB1)	MRQ-27	Expressão Preservada	
• FOXL2	Policlonal	Negativo	
• Citoceratinas de 40, 48, 50 e 50,6 kDa	AE1/AE3	Positivo	
• insulinoma-associated protein 1	BSB-123	Focalmente positivo	raras células
• BRG1/SMARCA4	BSB-154	Negativo (controle interno +)	perda de expressão
• CD56 - antígeno de células NK e subpopulação de linfócitos T	MRQ-42	Positivo	

Dr. Robert E. Scully, who first described the entity, classified it under miscellaneous tumors, reflecting the complexity of its pathogenesis. More recently, genetic and molecular studies have pointed toward a distinct profile, particularly involving SMARCA4 mutations, which may clarify its histogenesis [1,6].

Pathologic diagnosis is particularly challenging due to morphologic overlap with other poorly differentiated malignancies. SCCOHT typically exhibits small cells arranged in nests or cords, with scant cytoplasm and hyperchromatic nuclei, showing high mitotic activity. Follicular spaces filled with eosinophilic fluid are characteristic. In approximately 50% of cases, larger cells with more abundant eosinophilic cytoplasm may be present, further complicating the differential diagnosis. Mucinous glands have also been reported in some cases [1,6]. In the present case, microscopy demonstrated small plasmacytoid cells with "salt-and-pepper" chromatin, extensive necrosis, and tubal epithelial invasion—findings consistent with classic SCCOHT.

In 2014, pivotal studies established SCCOHT as a monogenic neoplasm primarily associated with deleterious mutations in the **SMARCA4** gene, a tumor suppressor that is part of the SWI/SNF chromatin- remodeling complex. SMARCA4 inactivation is considered a central molecular event in SCCOHT pathogenesis, conferring a distinct genetic profile with diagnostic, prognostic, and therapeutic implications. This discovery marked a significant advance in the understanding of the disease [9].

Immunohistochemistry plays a crucial role in SCCOHT characterization, especially with the development of antibodies against SMARCA4 protein, which are highly sensitive and specific. This tool is fundamental to confirming diagnosis, distinguishing SCCOHT from other ovarian neoplasms, and guiding therapeutic decisions. Recommended immunohistochemical panels include inhibin, EMA, WT1, CD56, synaptophysin, and Ki-67, among others, to ensure accurate differential diagnosis [10].

In the immunohistochemistry panel, the neoplastic cells of small cell carcinoma of the ovary, hypercalcemic variant (SCCO-H), often show focal positivity for epithelial membrane antigen (EMA), broad-spectrum cytokeratins, Wilms tumor 1 protein (WT1), calretinin, and CD10 [6,9]. In the present case, the immunohistochemical study revealed positivity for cytokeratins and neuroendocrine markers, including synaptophysin, INSM-1, and CD56, as well as positive expression for WT1. The expression of INI-1 was preserved, while a loss of SMARCA4 expression was observed, a finding highly suggestive of the diagnosis of SCCO-H, as the mutation or deletion of this gene is present in most cases described in the literature.

In addition, they may express neuroendocrine markers, such as parathyroid hormone-related protein (PTHrP), and show diffuse nuclear positivity for p53 [6,9]. In contrast, these cells are consistently negative for desmin, S100, and inhibin, which helps in the exclusion of other ovarian tumors with similar morphological features [1,10].

Therapeutic management of SCCOHT is generally multimodal, requiring cytoreductive surgery, systemic chemotherapy, and, in select cases, radiotherapy. Because of the disease's rarity and lack of randomized trials, there is no consensus on optimal treatment, and most strategies are based on case series, individual reports, or regimens adapted from small cell lung carcinoma [3,6].

Standard therapy usually involves aggressive cytoreductive surgery followed by chemotherapy, often with etoposide combined with platinum agents (carboplatin or cisplatin) [3,7]. Despite this, treatment efficacy is limited: responses are frequently partial, recurrence rates are high, and prognosis remains poor [6,9]. In the reported case, the patient underwent surgery followed by carboplatin-paclitaxel chemotherapy and subsequently etoposide-cisplatin, with the addition of zoledronic acid for hypercalcemia. Nevertheless, disease progression was rapid and fatal.

Radiotherapy may be considered as an adjunctive modality in locally advanced or metastatic cases, particularly for palliation of symptoms such as pain. Emerging therapies, including immunotherapy and targeted agents, are under investigation but lack consolidated clinical guidelines [3].

In conclusion, SCCOHT presents major diagnostic and therapeutic challenges due to its rare incidence and aggressive nature. This case highlights the importance of early clinical suspicion, the role of cytoreductive surgery, and the urgent need for more effective treatment strategies to improve patient outcomes.

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