

## Case 2 – Ovarian small cell carcinoma: a case report and review of the literature

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### Abstract

Ovarian small cell carcinoma is a rare tumor associated with poor prognosis. Although combination chemotherapy remains the cornerstone of treatment due to the rarity of these tumors, there is no evidence-based consensus for a standard treatment, although in the majority of cases platinum-based regimens are used. A case of small cell carcinoma of the ovary, hypercalcemic-type (SCCOHT), in a 22 year-old patient is reported.

**Key words:** ovarian cancer, small cell carcinoma of the ovary, hypercalcemic-type, hypercalcemia

### Introduction

Small cell carcinoma of the ovary is a rare histotype of ovarian cancer; hypercalcemic type (SCCOHT) is characterized by a very aggressive behavior and generally occurs in young women [1].

First described by Dickersin et al. [2] patients with small cell carcinoma of the ovary typically present with a unilateral large tumor and the majority of patients (62%) also present with hypercalcemia [1] probably due to parathyroid hormone like proteins produced by cancer cells; for this reason calcemia and parathyroid hormone could be used as biomarkers of response to chemotherapy [1, 3, 4].

Young et al. have presented a large series of cases (including 150 patients) describing the histologic features of this tumor type [1]; the genesis of small cell carcinoma of the ovary is unknown, in fact the tumor cells can not be classified into surface epithelium, germ cell, sex cord or neuroendocrine cells (Table 1) [5]. The differential diagnosis includes germ cells tumors, granulosa tumors, malignant lymphoma, desmoplastic small round cell tumor of the ovary, metastatic small cell carcinoma [1], in this context a very expert pathologist is crucial, due to extreme rarity of the disease. About 80% of small cell carcinomas of the ovary overexpress p53 protein, suggesting that a p53 mutation may involve in tumor genesis and progression [6], however further investigation is needed to clarify its role and prognostic significance.

Optimal management of patients is not well defined; in literature several and different treatment strategies and chemotherapy are reported but in few cases due to the rareness of the disease, Harrison et al. presented a review of the management of 17 cases in a Gynecological Cancer Intergroup (GCIg) study, with poor results

showed [7]. In this context there are no evidence based recommendations nor guide lines (Table 2) [1, 3, 8-14]. We present and discuss a case of SCCOHT in a young patient, as well a review of the literature about ovarian small cell tumors treatment.

### Case description

On June 2014 a 22 year-old patient was admitted to the Gynecologic Emergencies for abdominal pain and volume increase in the last month. Abdominal and pelvic transvaginal ultrasound showed a right ovary solid inhomogeneous mass of 120 × 97 mm, and ascitic fluid.

Abdominal computed tomography (CT) scan showed a right pelvic mass of 120 × 100 mm, with a calcific area of 22 mm, ascitic fluid, peritoneal irregularities and abdominal lymphadenopathies.

She underwent a planned exploratory laparoscopy with evidence of hematic abdominal ascites, a pelvic mass of 12 cm and pelvic peritoneal carcinosis. Therefore, patient was submitted to laparotomy, right salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and peritoneal biopsies. The uterus and left ovary appeared normal so they were not removed, considering the young age of the patient. She was op-

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timely debulked with no evidence of residual disease. Intraoperative pathology reported indifferantiated carcinoma of the ovary. Final pathology showed SCCOHT, with metastases to the omentum, peritoneum and pelvic and paraaortic lymph nodes, FIGO stage IIIC. Immunohistochemistry was notable for EMA, CAM5.2 e vimentin positivity, negative staining for cytokeratin 7, cytokeratin 20, LCA, S100, TTF1, inhibin. Hystology was review and confirmed by the expert Gyneco Pathologist of the Istituition. Postoperative cancer antigen (Ca)-125 was 65 U/mL, lactate dehydrogenase (LDH) remained elevated at 507 UI/L. Adjuvant chemotherapy was planned, consisting of cisplatin, cyclophosphamide, bleomycin (PEB) for six cycles (bleomycin was stopped after four cycles).

A chest-abdominal CT scan performed 20 days after surgery showed a diffuse peritoneal carcinosis and ascitic fluid, and Ca-125 was 214.6 U/mL. After three cycles of chemotherapy, chest abdomen CT scan showed reduc-

tion of peritoneal carcinosis, ascitic fluid disappeared, Ca-125 was 109 U/mL and LDH was 105 UI/L.

She completed other three cycles of chemotherapy with grade 4 neutropenia; granulocyte colony-stimulating factors support was given.

After six cycles of chemotherapy patient experimented abdominal pain, volume increase and distension. Chest-abdominal CT scan with contrast showed large pelvic mass, ascites, diffuse peritoneal carcinosis and mediastinal lymph nodes of 25 mm. Ca-125 rose to 334 U/mL and LDH was 800 UI/L.

The patient began treatment with weekly paclitaxel. She completed two cycles of treatment before increasing pain, ascites and hydronephrosis, and bowel subocclusion necessitated inpatient admission. The ascites continued to accumulate despite multiple paracentesis and abdominal catheter; pain and bowel occlusion worsened. She died shortly thereafter, seven months from her date of diagnosis.

**Table 1.** World Health Organization (WHO) histological classification of tumors of the ovary (modified from [5]).

Surface epithelial-stromal tumors	Germ cell tumors
Serous tumors	Dysgerminoma
Mucinous tumors	Yolk sac tumor
Endometrioid tumors including variants with squamous differentiation	Embryonal carcinoma
Malignant Müllerian mixed tumor (carcinosarcoma)	Non-gestational choriocarcinoma
Adenosarcoma	Biphasic or triphasic teratoma
Endometrioid stromal sarcoma (low grade)	Immature teratoma
Undifferentiated ovarian sarcoma	Mature teratoma
Clear cell tumors	Monodermal teratoma and somatic-type tumors associated with dermoid cysts
Transitional cell tumors	Thyroid tumor group
Malignant	Struma ovarii
Transitional cell carcinoma (non-Brenner type)	Carcinoid group
Malignant Brenner tumor	Neuroectodermal tumor group
Borderline Brenner tumor 9000/1	Ependymoma
Brenner tumor 9000/0	Primitive neuroectodermal tumor
Metaplastic variant	Melanocytic group
Squamous cell tumors	Malignant melanoma
Mixed epithelial tumors (specify components)	
Undifferentiated and unclassified tumors	
<b>Sex cord-stromal tumors</b>	<b>Miscellaneous tumors</b>
Granulosa cell tumor group	<i>Small cell carcinoma, hypercalcaemic type</i>
Thecoma-fibroma group	<i>Small cell carcinoma, pulmonary type</i>
Fibrosarcoma 8810/3	Large cell neuroendocrine carcinoma
Sclerosing stromal tumor 8602/0	Hepatoid carcinoma
Signet-ring stromal tumor	Primary ovarian mesothelioma
Sertoli-Leydig cell tumors	Wilms tumor
Gynandroblastoma	Gestational choriocarcinoma
	Ovarian Wolffian tumor

**Table 2.** Literature review of the treatment of ovarian small cell carcinoma.

Author	N. of patients	Chemotherapy regimen
Young et al. [1]	150	Vincristine, vinblastine, cyclophosphamide, doxorubicin, etoposide, and cisplatin
Chen et al. [3]	1	Paclitaxel/carboplatin followed by consolidation paclitaxel
Tewari et al. [8]	1	Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide
Benrubi et al. [9]	1	Cyclophosphamide, doxorubicin, cisplatin, vincristine, and etoposide
Rana et al. [10]	1	Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide
Distelmaier et al. [11]	11	Cisplatin, etoposide, ifosfamide (n=4 pts) carboplatin, etoposide, vincristine, actinomycin, ifosfamide, and doxorubicin (adriamycin) (n=2 pts) carboplatin/paclitaxel followed by cyclophosphamide/paclitaxel (n=1 pt)
Dykgraaf et al. [12]	1	Bleomycin, etoposide, and cisplatin
McCormick et al. [13]	1	Cisplatin and etoposide
Nelsen et al. [14]	1	Two cycles of intensive cyclophosphamide, etoposide, and cisplatin regimen, followed by three cycles of ifosfamide, carboplatin and etoposide and an autologous peripheral blood stem cell transplant

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## Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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## Commentary

*The case presented by Vanda Salutari refers to a young patient with a stage IIIC ovarian small cell carcinoma (SCCO) of hypercalcemic type (SCCOHT). Despite an aggressive complete surgery and chemotherapy based on an etoposide and cisplatin association, the disease relapsed shortly after the beginning of the therapy and the patient died rapidly.*

*These tumors are highly undifferentiated, and recent data suggest they may simply be an ovarian variant of malignant rhabdoid tumors [1, 2]. Mutations in the SWItch/Sucrose Non Fermentable (SWI/SNF) chromatin-remodeling gene, SMARCA4, have now been shown to be a frequent event occurring in 76% to 100% of SCCOHT tumors [3-5]. Germline mutations in SMARCA4 or SMARCB1 were already known to predispose to the development of pediatric tumors, namely atypical teratoid/rhabdoid tumors [6, 7]. SMARCA4 immunohistochemistry is highly sensitive and specific for a diagnosis of SCCOHT (loss of SMARCA4 protein expression [BRG1]) and is now of clinical utility in the differential diagnosis of poorly differentiated ovarian tumors [8].*

*Prognosis is poor, with only 30% to 40% of patients achieving long-term survival with standard treatment. There is no international consensus regarding the optimal treatment of SCCO, and a multimodal approach including chemotherapy, radical surgery and possibly radiotherapy is often proposed. However, no randomized studies have been conducted and the available published data are composed of case reports or small retrospective series with very heterogeneous management strategies.*

*To optimize the practical use of anticancer chemotherapy in these young patients with initially good tumor response, some groups have opted for an aggressive strategy with extensive surgery to lower the tumor burden on the one hand, and dose intensive chemotherapy to circumvent cell mutations. The only prospective clinical trial reported in SCCOHTs was a prospective trial testing combination intensive therapy for stage-I to IV tumors [9]. Patients received multimodality therapy with aggressive debulking surgery, chemotherapy with a platinum etoposide-based regimen (PAVEP, cisplatin, doxorubicin [adriamycin], etoposide [VP-16] and cyclophosphamide), and one cycle of high-dose consolidation chemotherapy followed by autologous stem cell support in case of complete response. Eighteen patients among 27 achieved a complete remission, and 10 proceeded to high-dose chemotherapy with stem cell support. The only long-term survivors had complete surgical resection. This procedure induced an encouraging 3-year survival rate of 49% for the entire population. This study also used neoadjuvant chemotherapy in a small number of cases, who went on to undergo delayed primary surgery. In a review of all published and a series of unpublished 290 SCCOHT cases with collected information on possible prognostic factors, high-dose chemotherapy with autologous stem cell rescue is a positive prognostic factor [10].*

*Even with intensive regimens and despite frequent initial responses to chemotherapy, relapses are frequent and tend to be refractory to second-line chemotherapy. The management of relapsed disease is often very challenging, and prolonged remissions are never achieved, with second-line chemotherapy regimens usually used in small cell lung carcinomas. A number of schedules have been reported, including the combination of cyclophosphamide, doxorubicin, and vincristine. There are anecdotal reports on carboplatin and paclitaxel, including dose-dense regimes, and topotecan has also shown some modest activity, as in small cell lung cancers. To date, no targeted therapies have been tested in SCCO. Second-line treatment is likely to achieve short remission rates, and beyond that, patients should be considered for phase-I trials if they remain of good performance status. The future probably requires a better understanding of the molecular drivers.*

*In conclusion, all suspected cases should benefit from a review by an expert pathologist and be discussed in a specialized tumor board. Optimal treatment with a multimodal approach including chemotherapy, radical surgery, high dose chemotherapy and radiotherapy has to be discussed. Efforts should be made to treat patients in a more homogeneous way through national and international networks [11].*

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