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Advanced small-cell ovarian carcinoma, hypercalcemic type: a challenging therapeutic entity

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ABSTRACT

Small-cell ovarian carcinoma (SCOC) is a rare and aggressive neoplasia, predominantly affecting young women who are frequently first diagnosed with advanced stage disease. Platinum-based chemotherapy (ChT) can provide high response rates and rapidly ameliorate symptoms in this scenario. However, progression after chemotherapy usually occurs quickly, leading to high mortality rates. In addition, ChT complications, such as tumor lysis syndrome (TLS) can also occur, jeopardizing the patient's outcome. We present a case of metastatic SCOC in a 47-year-old patient who achieved tumor response after platinum-based chemotherapy and developed TLS, from which she recovered with supportive treatment. After the second ChT cycle, she developed febrile neutropenia and died 8 weeks after the diagnosis of SCOC. Although SCOC is a chemo-sensitive tumor, short-lived responses and frequent chemotherapy complications lead to a dismal prognosis.

Keywords
Ovarian Neoplasms; Carcinoma, Small Cell; Tumor Lysis Syndrome; Drug Therapy.

INTRODUCTION

Small-cell ovarian carcinoma (SCOC) is a rare tumor, representing less than 1% of all ovarian carcinomas. It predominantly affects young women (average 23.9 years in a series of 150 patients).[1] Prognosis is poor, with a median survival of less than 6 months in stages III and IV disease.[2] The first detailed description of this disease was made in 1982, in a report of eleven cases by Dickersin et al.[3] The literature on this entity is comprised of small retrospective series, which quite often demonstrate a dismal prognosis. Although there is a lack of consensus on the best treatment, it is usually multimodal and includes surgery, chemotherapy, and radiotherapy. Recommendations are based on case reports and expert experiences. Herein, we report a case of this unusual tumor, and perform a literature review about SCOC.

CASE REPORT

A 47-year-old female patient was admitted to the oncology ward with a 2-month history of low abdominal pain, nausea, vomiting, hyporexia, dehydration, and weight loss. Physical examination disclosed a hypogastric mass with signs of ascites.

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A deep venous thrombosis (DVT) was suspected due to an asymmetric edema in her right calf, which was later confirmed by venous Doppler ultrasonography. Her Eastern Cooperative Oncology Group performance status (ECOG-PS) was 3. Laboratory findings included anemia (hemoglobin 10.6 g/dL, reference value [RV]: 12–16 g/dL), and normal electrolytes including ionic calcium. Renal and hepatic functions were preserved.

Computer tomography (CT) of the chest, abdomen, and pelvis revealed a pelvic mass (21 × 11 × 16 cm) in the right adnexal region, infiltrating the left hepatic lobe, peritoneum (with ascites) and multiple para-aortic and iliac lymph nodes (Figure 1A). Bilateral pleural effusion was also present (Figure 1B). Both pleural and ascitic fluids were positive for neoplastic cells.

An image-guided biopsy of a peritoneal nodule was performed. Microscopy revealed a poorly differentiated small-cell neoplasia with a solid pattern. Immunohistochemistry analysis was positive for CD56 and vimentin, and was focally positive for cytokeratins 35BH11 (Figure 2). It was negative for WT1, estrogen receptor, TTF-1, and inhibin. These findings were suggestive of a carcinoma with neuroendocrine differentiation. Later on, an ovarian biopsy was performed when the patient underwent an emergency laparotomy due to acute peritonitis. Microscopy revealed a poorly differentiated small-cell neoplasia with extensive necrosis (this biopsy was performed after two cycles of chemotherapy). On immunohistochemistry, this second tissue specimen was positive for CD56, focally positive for CD99, and negative for estrogen receptors, and cytokeratins S-100, desmin, TTF-1, WT-1, and inhibin.

Based on this second biopsy, a diagnosis of primitive neuroectodermal tumor (PNET) was suspected (due to the negative cytokeratins and focally positive CD99). Recently, the assay to test for the FLI-1 protein on immunohistochemistry—a marker of PNET—became available at our institution. Both the peritoneal nodule and the ovarian specimens were tested; both were focally positive for FLI-1. This finding is not exclusive to PNET (other tumors can also express FLI-1).[4] The second specimen was obtained after ChT, and presented extensive necrotic areas, which could explain the negative cytokeratin expression. Despite FLI-1 focal staining, we do not consider that this finding alone is capable of changing our initial diagnosis of an undifferentiated carcinoma with neuroendocrine differentiation. Considering the clinical manifestations, morphological pattern, and immunohistochemistry findings, we concluded the diagnosis to be more consistent with SCOC of the hypercalcemic type.

The patient was started on venous hydration and anticoagulation with low-molecular weight heparin due to DVT. Since she already had metastatic disease at presentation, we started systemic chemotherapy with cisplatin (80mg/m^2 on day 1) and etoposide (80mg/m^2 on days 1, 2, & 3) every 21 days. She had a remarkable clinical response, with significant reduction of the abdominal mass and improvement of performance status. (ECOG: PS 2). Two days after the first cycle of chemotherapy, the patient's serum uric acid level was 13.1 mg/dL (RV: 2.4–5.7 mg/dL); serum potassium was 6.6 mEq/L (RV: 3.5–5.0 mEq/L) and serum phosphate was 9.7 mg/dL (RV: 2.7–4.5 mg/dL), leading to the TLS diagnosis according to the Cairo-Bishop criteria.[5] The

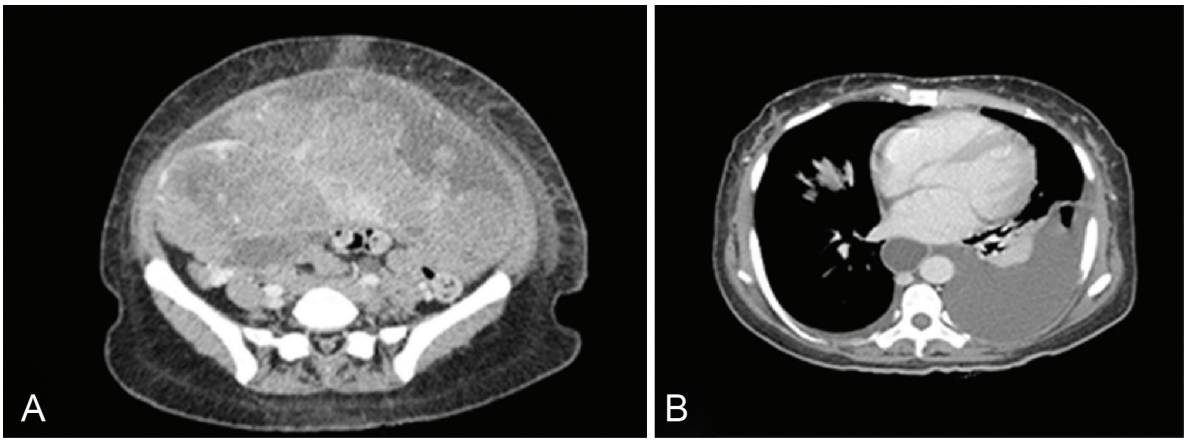

Figure 1. A - Pelvic axial computed tomography (CT) revealing a bulky heterogeneous pelvic mass in the right adnexal region. Note the presence of ascites; **B** - Chest axial CT showing a large pleural effusion.

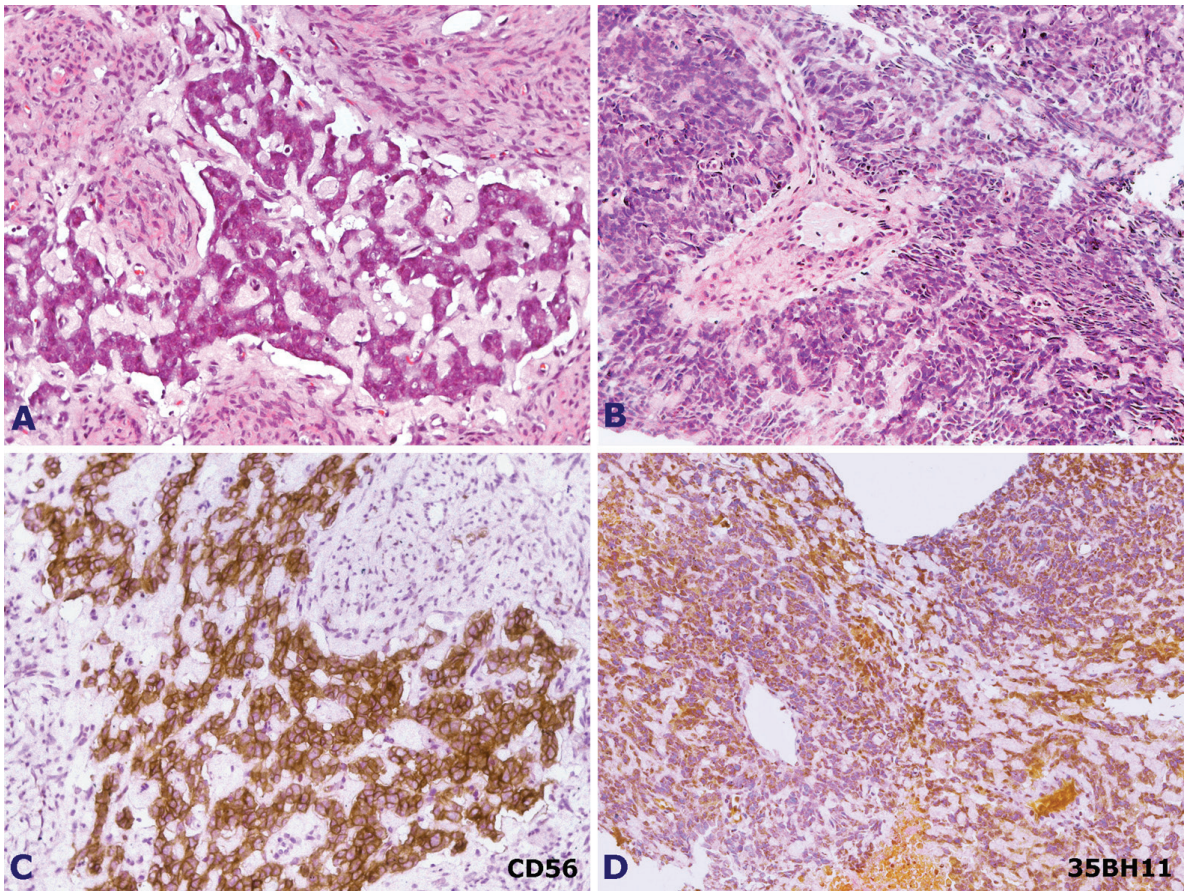

Figure 2. Photomicrography of the peritoneal nodule. **A** - A poorly differentiated carcinoma (H&E, 50X); **B** - Tumoral cell nests (H&E, 200X); **C** - Positive immunohistochemistry staining for CD56, a neuroendocrine marker (200X); **D** - Immunohistochemistry staining focally positive for cytokeratin (35BH11), a marker of epithelial differentiation usually found in carcinomas (200X).

outcome was favorable after 3 days of intravenous hydration with saline. The second chemotherapy cycle was administered 28 days after the first cycle. Seven days after this second cycle, the patient developed septic shock with febrile neutropenia and acute peritonitis. She was admitted to the Intensive Care Unit and promptly received a regimen of broad-spectrum antibiotics. On emergency laparotomy, no sign of bowel perforation was found, but a necrotic adnexal mass with an associated abscess was resected and submitted to analysis, as mentioned earlier. Unfortunately, the patient died on the seventh day after surgery, due to sepsis.

DISCUSSION

SCOC, hypercalcemic type, is a rare disease that predominantly affects women under 40 years of age**.** This tumor exhibits aggressive behavior, with a median survival of 6 months in stage III disease.[2] Patients usually present with pelvic and abdominal pain, fatigue, nausea, vomiting, weight loss, and ascites.[3]

About two-thirds of patients present hypercalcemia, which is likely related to tumoral secretion of parathyroid hormone related peptide (PTHrp). In 1994, Young et al.,[1] published a study where five of seven tumors investigated by immunohistochemical staining for PTHrp showed positive results. Hypercalcemia symptoms, such as vomiting, dehydration, diarrhea, polyuria, renal failure, cardiac arrhythmias, somnolence, confusion, and even coma, can prevail at disease presentation. The calcium determination can be used to monitor treatment response, as decreasing levels are associated with a favorable response.[3] Staging is usually performed with thoracic, abdominal, and pelvic CT scans. Brain imaging is recommended if neurologic symptoms are present.

Concerning thrombotic events, an analysis of the American Medicare database of hospitalized cancer patients showed a rate of 120 thrombotic events per

10,000 patients with epithelial ovarian carcinoma representing the neoplasm with the highest rate of this association.[6] However, no data specifically regarding the association of SCOC with thrombotic events has been reported. The presence of thrombosis increases morbidity, since the risk of embolic and new thrombotic events is augmented[7].

Due to the rarity of the disease, many treatment and management decisions are based on studies of small-cell lung cancer,[8,9] although there is no evidence that these two entities present the same response to treatment. In addition, there is still doubt about the exact origin of SCOC. Young et al.[1] proposed an epithelial origin for SCOC, based on their histopathologic and electronic microscopy findings, which showed cells with abundant and enlarged rough endoplasmic reticulum.

Therapeutic decisions should be guided by initial tumor staging and the degree of pelvic and abdominal involvement. Complete cytoreductive surgery is the treatment of choice in resectable small-volume disease.[2,3] However, the best surgical approach is debatable. In cases with unilateral involvement in future child-bearing patients, unilateral salpingo-oophorectomy can be performed,[10] although some authors argue that a bilateral oophorectomy and hysterectomy with lymphadenectomy would reduce the risk of relapse. However, there is a lack of evidence comparing these two approaches. In the presence of extensive pelvic disease or bilateral involvement, a radical approach should be favored. Although these recommendations are based on data from epithelial ovarian cancer, surgery seems to be the best way to reduce tumor burden and the only treatment capable of providing long disease-free intervals.[11]

Adjuvant treatment is controversial in terms of modality and benefits for the patients. Both radiotherapy (pelvic or abdominopelvic) and systemic ChT can be used to reduce the risk of local and distant relapses, and eliminate micro-metastatic disease. Reed[11] reported a favorable outcome with surgery followed by adjuvant radiotherapy and chemotherapy with cisplatin, etoposide and bleomycin in a 31-year-old woman who remained free of disease during 5 years of follow-up. Harrison et al.,[2] in a series of 17 patients with the diagnosis of SCOC submitted to surgery, observed that 5 out of 7 patients who received adjuvant radiotherapy survived more than 50 months. Among the patients who did not receive radiotherapy, three out of four with stage I tumors had recurrences and one remained alive without disease after 10 months of follow-up. Five out of six patients with stage III died, and the other was alive without disease after 5 months of follow-up. These data point towards a potential benefit of adjuvant radiotherapy.

There is no clinical trial demonstrating the superiority of adjuvant chemotherapy over observation alone, and there is no evidence supporting one specific chemotherapy regimen over another. In all case series reviewed,[2,3,10-15] patients received adjuvant chemotherapy—the vast majority with platinum-based regimens. The most prescribed drugs were cisplatin in combination with etoposide, with limited results in terms of survival outcomes. Few patients remained disease-free after 60 months of follow-up, and the majority experienced recurrences within 6 months after chemotherapy.

Since SCOC not only is an aggressive disease with high mortality and relapsing rates, but also is a chemo-sensitive tumor, there is a potential role for adjuvant chemotherapy and radiotherapy in preventing recurrences. This potential benefit may be specifically directed to patients with high disease burden at presentation. Other strategies, such as neoadjuvant chemotherapy or radiotherapy, as well as a second line treatment after relapse, have not been evaluated in randomized clinical trials.

Our patient, like most SCOC patients, presented metastatic disease, with peritoneal carcinomatosis, involvement of the pleural and lymph nodes, which favored our decision to start systemic treatment. The regimen of choice (cisplatin/etoposide) was based on data derived from studies of small-cell lung cancer, where response rates as high as 78% were observed in the first-line setting.[8,9] Taxanes, bleomycin, and cyclophosphamide were combined with a platinum agent in some reports of advanced disease.

Pautier et al.[14] published a series with 27 patients, out of which 17 presented stage III or IV disease. For these patients, he used a four-drug chemotherapy regimen (cisplatin, doxorubicin, etoposide, and cyclophosphamide) followed by autologous stem cell transplantation (ASCT) for those who achieved a complete remission after four to six cycles of chemotherapy. The majority of patients (18/27)

experienced complete responses and 10 successfully received ASCT. In this series, 49% of patients were alive after 3 years of follow-up.

Although SCOC is a chemo-sensitive tumor, responses obtained with chemotherapy are mild and not sustained. In the largest series from Young et al.,[1] after 2 years of follow-up only 33% of the patients with a stage IA tumor were alive and free of disease, but no patient with an advanced stage was alive, which confirms the poor prognosis of this disease. No direct comparisons of chemotherapy regimens for metastatic disease have been published to date. Reported outcome and response for CHT regimens in three series are shown in Table 1.

Generally, SCOC is very responsive to chemotherapy, and in almost all case series, at least partial responses were obtained.[13-15] In the case presented herein, a remarkable response was observed with cisplatin-based chemotherapy with evident reduction in ascites and the abdominal mass, as well as tumor lysis syndrome (TLS). The latter is characterized by massive tumor cell necrosis leading to electrolyte disturbances (hyperkalemia, hyperphosphatemia, and hypocalcemia), cardiac arrhythmias, renal failure, and often results in death.[5] Although a high response rate is anticipated with chemotherapy, there are no previous reports of TLS in SCOC.

As observed in several other case series and reports, despite the initial response to treatment, our patient had an unfavorable outcome, surviving 2 months after a stage IV SCOC diagnosis. Although the patient initially responded to therapy, high toxicity was observed after the second cycle—namely neutropenia and sepsis—which was responsible for the fatal outcome. Similar patterns of toxicity were observed by Pautier et al.[14] in their series, 19 febrile neutropenia events were observed in 11 patients, despite the regular use of granulocyte-colony stimulating factor. We found no reports of patients presenting with metastatic disease that remained disease-free for periods longer than 1 year, demonstrating the high mortality and relapse rates observed in SCOC.

In conclusion, SCOC is an uncommon neoplasm, which is extremely aggressive with a very poor prognosis, and high relapse and mortality rates. Not only the precise origin of this neoplasm remains unknown, but also there is no consensus about the ideal therapeutic strategy. In localized disease, cytoreductive surgery, followed by adjuvant chemotherapy and radiotherapy, is the current adopted strategy. In the metastatic scenario, chemotherapy regimens derived from SCOC studies show positive response rates, but unfortunately the survival rates are dismal. More studies about SCOC biology and genetics are necessary to provide better understanding of this tumor in order to develop new and more effective treatment strategies.

Table 1. Chemotherapy regimens previously described in the literature

Author	Patients with IFGO stage I or II disease	Patients with IFGO stage IIIc or IV disease	Chemotherapy regimen	Reponses	Percentage alive after 3 years
Rovithi et al.[12]	0	2	BEP	1 patient stable disease; 1 patient progressed during therapy	0
Shrimali et al.[15]	0	2	Carboplatin AUC 3 + paclitaxel 80mg/m^2 weekly	2 patients partial response	0
Pautier et al.[14]	10	17	Cisplatin 80mg/m^2 on day 1 + doxorubicin 40mg/m^2 on day 1 + etoposide 75mg/m^2 on days 1–3 + cyclophosphamide 300mg/m^2 on days 1–3	2 patients partial response; 18 patients with complete responses; 9 progressed during therapy	49

AUC = area under the concentration curve; BEP = bleomycin, etoposide, cisplatin; IFGO = International Federation of Gynecology and Obstetrics.

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