Case Report

Small-cell carcinoma of the ovary, hypercalcemic type: A report of two cases and review of related literature

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Abstract:

Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare and aggressive type of ovarian cancer. It generally presents in younger patients, is diagnosed at an advanced stage, and is associated with a dismal prognosis. Due to its rarity and morphologic similarity to more common ovarian tumors, diagnosis may be a challenge. A high index of suspicion followed by appropriate immunohistochemistry stains performed by an expert pathologist is essential to diagnosis. Two cases of SCCOHT are presented: 21 years old with rapidly progressive Stage IIIA1i disease who underwent surgery and succumbed to the illness after 3 months before adjuvant treatment could be given, and a 49 years old with Stage IIIB disease with tumor progression who is on adjuvant chemotherapy and apparently well, 21 months after her first symptoms appeared. Related literature is presented and compared to the features of the index cases. Diagnosis and treatment options are also discussed briefly.

Keywords:

Hypercalcemic type, ovarian cancer, small-cell carcinoma of the ovary, hypercalcemic type, small-cell carcinoma of the ovary

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Introduction

The importance of accurate histologic diagnosis of ovarian tumors cannot be overemphasized as it will dictate appropriate management. Diagnostic difficulties arise when rare tumors are encountered, especially when morphologic similarities with other tumors exist. Even in the hands of experts, these cases may pose diagnostic dilemmas, and among the adjunctive tests performed are immunohistochemistry (IHC) and molecular studies. Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a very rare type of ovarian tumor comprising only 0.01% of all ovarian malignancies, with <500 case reports to date. Here, we present two cases encountered in our institution.

Clinical Case Protocol

Patient 1 is a 21-year-old nulligravid who presented with a rapidly enlarging abdominal mass. On exploratory laparotomy, the right ovary was converted to a predominantly solid mass measuring 27 cm × 21 cm × 10.5 cm with a reddish brown smooth surface and 3 cm × 2 cm point of rupture at the posterior area [Figure 1]. She underwent peritoneal fluid cytology, right salpingo-oophorectomy with frozen section biopsy, bilateral pelvic lymph node dissection, infracolic omentectomy, and para-aortic lymph node sampling. The cut section of the ovary revealed cystic spaces filled with yellowish mucinous fluid. The rest of the mass was mostly yellowish in color and solid, with hemorrhagic and necrotic areas. Histopathologic diagnosis was granulosa cell tumor, juvenile type, of the right ovary, with an intact capsule and

no surface involvement. Peritoneal fluid, omentum, and pelvic lymph nodes were negative for malignancy, but para-aortic lymph node was positive for tumor with no extranodal extension. Postoperative stage was Stage IIIA1i. Whole abdominal ultrasound done postoperatively revealed a complex left parailiac focus measuring 5.3 cm × 1.8 cm × 2.2 cm, which could represent lymphadenopathy or a peritoneal implant. A review of the histopathology revealed a poorly differentiated round cell neoplasm with necrosis and increased mitotic activity with the considerations of granulosa cell tumor (adult-type/juvenile-type) versus small cell carcinoma. A panel of IHC stains revealed paranuclear cytoplasmic staining with pancytokeratin in a few scattered cells, nuclear staining with WT1 in >95% of tumor cells, and moderate nuclear staining in about 20% of tumor cells. The stains for CK7, LCA, SALL4, ER, PAX8, CD10, calretinin, and inhibin were all negative. The immunohistomorphologic findings were strongly suggestive of small-cell carcinoma, hypercalcemic type [Table 1]. CA125, antimüllerian hormone, and lactate dehydrogenase (LDH) were not elevated. Serum calcium was normal. She was advised chemotherapy with bleomycin (30 mg/m^2) D1, D8, and D15, etoposide (100 mg/m^2) D1–D5, and cisplatin (20 mg/m^2) D1–D5 for four cycles but was not able to comply.

Three months postoperatively, she noted a recurrence of abdominal distention. On examination, the abdomen was distended and a 7 cm × 5 cm solid, fixed cul-de-sac mass was noted on the pelvic examination. Pelvic ultrasound revealed a heterogeneous cul-de-sac mass measuring 10.9 cm × 7.2 cm × 7.5 cm, which on power Doppler showed moderate vascularity (color score = 3) [Figure 2a]. The mass was contiguous with surface implants at the left fallopian tube and ovary, and peritoneal implants seen within the abdominopelvic cavity: parietal peritoneum, uterus, bowel, and right kidney, the largest measuring 6.0 cm × 5.5 cm × 3.1 cm (volume = 53 cc) [Figure 2b]. A heterogeneous solid mesenteric mass measuring
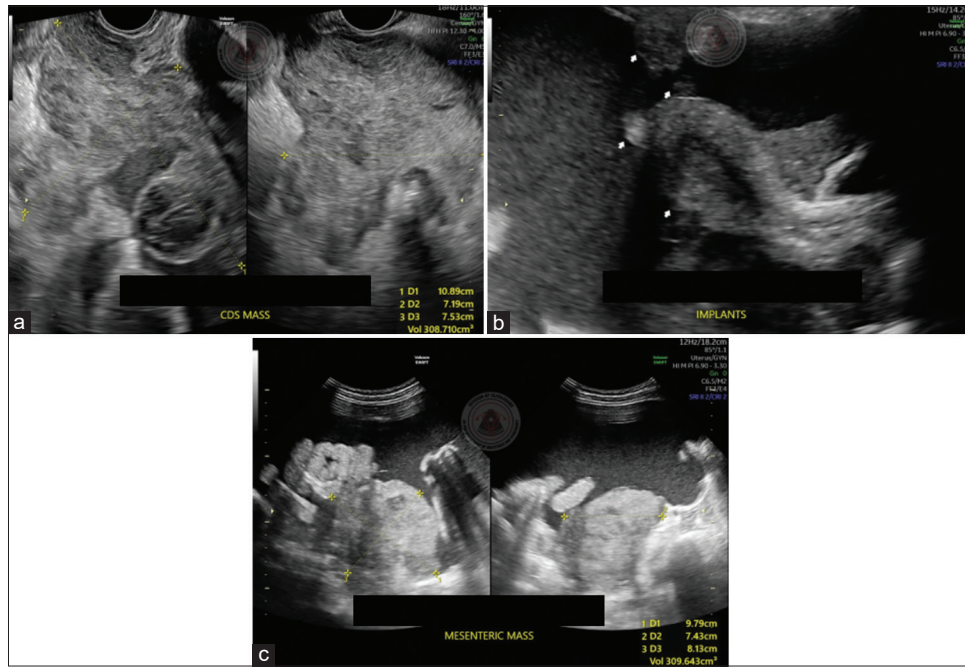
9.8 cm × 7.4 cm × 8.1 cm (volume 309 cc), with scant vascularity (color score 2), and massive ascites were also seen [Figure 2c]. The patient subsequently succumbed to death after 1 month.

Patient 2 is a 49-year-old G4P3 (2112) with a history of progressive hypogastric pain who underwent exploratory laparotomy with intraoperative findings, including the left ovary converted to a complex mass measuring 12 cm × 10 cm × 6 cm adherent to the sigmoid colon and segments of the ileum, with a point of rupture measuring 3 cm. A 1 cm seeding on the anterior lateral peritoneal wall was also noted. She underwent peritoneal fluid cytology, total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, excision of sigmoid colon tumor adhesion excision of ileal tumor adhesion, segmental ileal resection with end-to-end anastomosis. Histopathologic diagnosis was a mixed malignant germ cell tumor (dysgerminoma: 90%, embryonal rhabdomyosarcoma: 10%), ovary, left, with 20% tumor necrosis [Figure 3a-f]. Biopsies taken from the sigmoid adhesion and peri-ileal fatty tissue were positive

Table 1: Immunohistochemistry studies

	Case 1	Case 2
Pancytokeratin	Paranuclear cytoplasmic staining in few scattered cells	Positive, strong, diffuse, in cells of interest
PLAP		Positive, faint, in sporadic cells of interest
CK7	Negative	Positive
CK20		Negative
LCA	Negative	Negative
SALL4	Negative	Negative
ER	Negative	
PAX8	Negative	
CD10	Negative	
CD117		Negative
CD30		Negative
CD56		Negative
WT1	Nuclear staining in >95% of tumor cells	Positive, focal, nuclear, in cells of interest
Inhibin	Negative	Negative
Glypican 3		Negative
Calretinin	Negative	Negative
p53	Moderate nuclear staining in about 20% of tumor cells	Negative in cells of interest consistent with null phenotype
EMA		Positive
Synaptophysin		Negative
Chromogranin		Negative
GATA3		Negative
p63		Negative
SMARCB1/INI1		Noncontributory; retained nuclear expression in cells of interest

EMA: Epithelial membrane antigen, PLAP: Placental alkaline phosphatase, LCA: Leukocyte common antigen, ER: estrogen receptor

Figure 1: Case 1: (left) Right ovary converted to a predominantly solid mass measuring 27 cm × 21 cm × 10.5 cm with reddish brown smooth surface and 3 cm × 2 cm point of rupture at the posterior area (right). Cut section of the ovary revealed cystic spaces filled with yellowish mucinous fluid. The rest of the mass was mostly yellowish in color, solid with hemorrhagic and necrotic areas

Figure 2: Case 1: (a) Heterogeneous cul-de-sac mass measuring 10.9 cm × 7.2 cm × 7.5 cm (308.7 cc), contiguous with the surface implants at the left fallopian tube and ovary. (b) Peritoneal implants are seen within the abdominopelvic cavity: Parietal peritoneum, uterus, bowel, and right kidney the largest measuring 6.0 cm × 5.5 cm × 3.1 cm (volume = 53 cc). (c) A heterogeneous solid mesenteric mass measuring 9.8 cm × 7.4 cm × 8.1 cm (volume 309 cc)
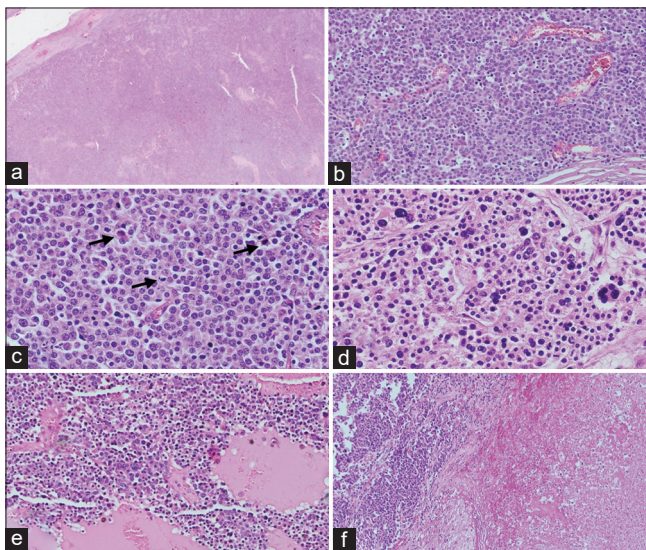

Figure 3: Case 2: left ovary: (a) Hematoxylin and eosin (H and E, ×40). On scanning magnification, the conversion of the ovary into a solid, cellular neoplasm is appreciated. (b). H and E, ×100. The tumor appears to be comprised of sheets of atypical round cells with vesicular to hyperchromatic nuclei, coarse chromatin, and eosinophilic cytoplasm. (c) H and E, ×400. Mitotic activity is brisk, as demonstrated by the arrows. (d) H and E, ×400. Large, multinucleated tumor cells with hyperchromatic nuclei and voluminous, eosinophilic cytoplasm are focally present in the tumor. (e) H and E, ×100. The tumor cells appear to take on a follicular architecture. (f) H and E, ×100. Foci of necrosis are interspersed between areas of viable tumor

for tumor involvement, hence staged as IIIB. She was advised chemotherapy but was lost to follow-up.

One year postoperatively, she underwent laparoscopic cholecystectomy. Multiple peritoneal implants were noted during this procedure, and a biopsy of the implants revealed round cell neoplasm. A series of IHC stains, including positive strong, diffuse staining with pancytokeratin, faint staining with PLAP, CK7, focal nuclear staining with WT1, and epithelial membrane antigen led to a diagnosis of SCCOHT [Table 1].

Imaging studies at this time included a magnetic resonance imaging of the whole abdomen [Figure 4], which revealed a cluster of enlarged, heterogeneously enhancing retroperitoneal lymph nodes in the para-aortic and aortocaval regions, with an aggregate measurement of 9.8 cm × 4.7 cm × 3.4 cm. Multiple T1W hypo/isointense and T2W-hyperintense marrow lesions were also seen scattered in the imaged vertebral bodies and right iliac bone. Whole body positron emission tomography-computed tomography scan [Figure 5] revealed confluent lymph nodes in the retroperitoneal para-aortic and aortocaval regions, with heterogeneous but generally intense fluorodeoxyglucose (FDG) uptake. The largest confluence was seen in the para-aortic region, measuring about 5.1 cm × 3.8 cm. Intense FDG-avid foci are also noted along the ileum as well as to the left and anterolateral to the urinary bladder. CA 125 was elevated, while serum alpha-fetoprotein and LDH were normal. Serum calcium was normal. She received three cycles of chemotherapy with bleomycin etoposide and cisplatin every 28 days and received zoledronic acid every 12 weeks and currently remains well 19 months postdiagnosis.
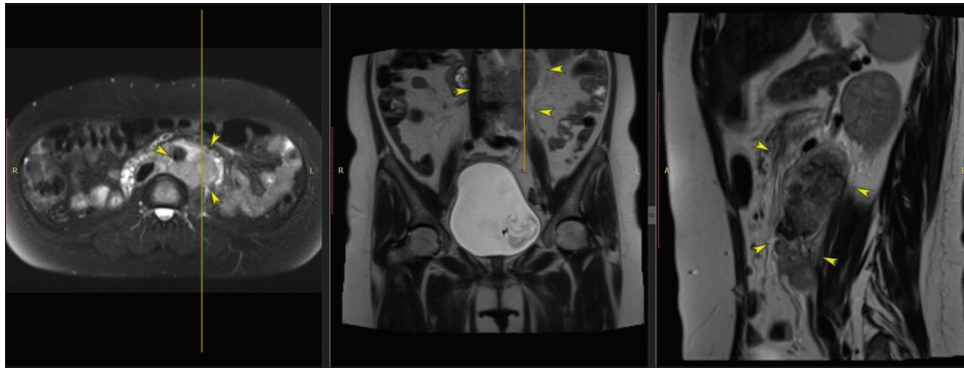
Figure 4: Case 2: Magnetic resonance imaging of the abdomen showing a cluster of enlarged, heterogeneously enhancing retroperitoneal lymph nodes in the para-aortic and aortocaval regions (arrowheads). It has an aggregate measurement of 9.8 x 4.7 x 3.4 cm slightly displacing the abdominal aorta anteriorly.
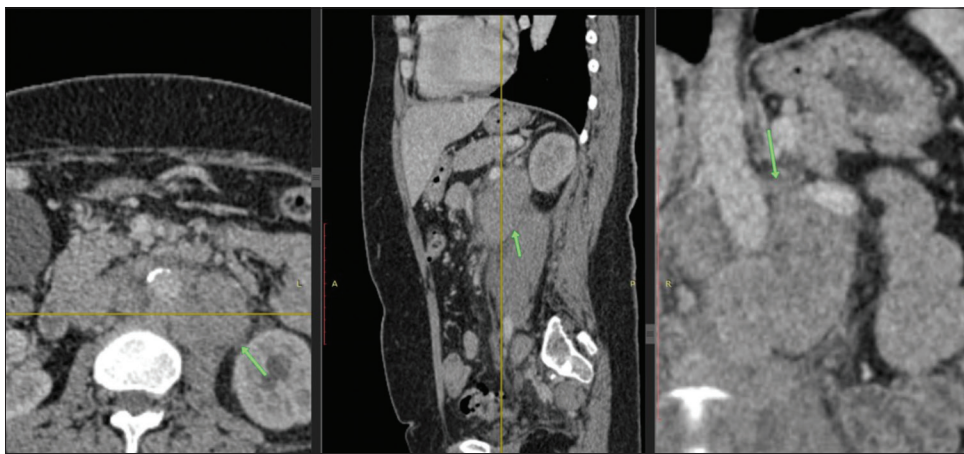
Figure 5: Case 2: Positron emission tomography scan image showing the largest confluence of lymph nodes seen in the para-aortic region measuring about 5.1 x 3.8 cm (arrows). Surrounding fat-stranding is still noted. This still displaces the abdominal aorta anteromedially, and shows no clear plane of cleavage from the left psoas muscle posteriorly

Case Discussion

SCCOHT is a very rare type of ovarian tumor comprising only 0.01% of all ovarian malignancies, with only <500 case reports to date.[1] This tumor is more frequently diagnosed in younger patients with a median age of 39 years at diagnosis.[1,2] Majority are diagnosed at an advanced stage, with only 20%–25% diagnosed at an early stage, confined to the ovary.[1,3] In both cases presented in this paper, the tumor involved only one ovary but had disseminated pelvic disease. This tumor is associated with a poor prognosis, with a 5-year overall survival rate of only 24.1% among patients who undergo surgery.[1] In one study, this poor prognosis is seen across all stages, with only 30%–40% long-term survivors among those with Stage IA disease.[4] In another study, almost all the patients with tumors of a stage higher than IA died of the disease within 2 years. Among patients with Stage IA disease, features that portend a favorable outcome include older age >30, normal serum calcium, smaller tumor size <10 cm, and absence of large cells on histopathology.[2] The poor prognosis associated with

this tumor is evident in both cases, with a short interval between initial diagnosis and progression or recurrence.

SCCOHT has no specific patterns of clinical presentation, hence it is challenging to distinguish it from other more common ovarian malignancies. Differential diagnoses include germ cell tumors, juvenile granulosa cell tumors, and sex cord tumors. Both cases described in this paper had an initial diagnosis of one of these more common ovarian tumors.

Clinical presentation is nonspecific, and patients usually complain of abdominal swelling and pain, vomiting, ascites, or, in rare cases, symptoms of hypercalcemia. In the study of Young *et al.*, tumor rupture occurred in 20%. The tumor surface was often lobular or nodular, and sections of the tumors revealed solid (33%) or solid with cystic degeneration (67%). These solid areas were described as tan, gray, cream-colored, or yellow. Hemorrhage or necrosis was present in the majority of cases. Almost all of these tumors are unilateral, with a median size of 13 cm.[1,2] Both patients discussed

presented with a complex solid-cystic unilateral ovarian mass, both with preoperative tumor rupture. Owing to the rarity of this tumor, the pathogenesis and mechanism of tumor spread are poorly understood but are likely to be similar to other ovarian epithelial tumors. Peritoneal spread is likely, and the risk of disseminated pelvic disease is further increased due to the propensity of these tumors for preoperative tumor rupture.

The diagnostic difficulties are compounded by the rarity of SCCOHT and the lack of a specific biomarker. Measurement of tumor markers should be carried out but may not be particularly helpful. About 60%–70% of cases may have hypercalcemia.[2,3] In both cases discussed, the tumor markers were of limited value. CA125 was only slightly elevated in the second case. Both cases had normal serum calcium levels.

In the original description of these tumors by Scully *et al.*, the key diagnostic elements were: (a) the presence of small, highly mitotic cells with hyperchromatic nuclei and scant cytoplasm; (b) an early age (<40 years) of onset; and (c) the presence of hypercalcemia.[4] The most common microscopic pattern of SCCOHT includes diffuse sheets of cells punctured by variable numbers of follicle-like spaces, which are usually filled with eosinophilic fluid. These tumor cells may also exhibit growth in nests, cords, or clusters. The neoplastic cells are small and round, with hyperchromatic nuclei. Mitotic activity within these cells is brisk.[4] Because morphologic similarity to other more common tumors exists, meticulous examination is essential, and additional tests with IHC are necessary to confirm the diagnosis. In a detailed immunohistochemical analysis of a series of SCCOHT, most cases were found to exhibit diffuse nuclear positivity with an antibody against the N-terminal of WT1. However, this marker is positive in many other tumors, including some in the differential diagnosis of SCCOHT, limiting its diagnostic value. In this study, all except one of the whole tissue sections of SCCOHT cases were positive for SALL4, while all cases were OCT3/4, AFP, and glypican 3 negative, except for focal glypican 3 staining in an occasional case.[5] As in this case, a definitive diagnosis may be difficult to achieve and may take a battery of many IHC tests. In the second case discussed, a total of 20 stains were performed before arriving at the diagnosis of SCCOHT.

The most recent advancement in the study of this rare tumor is the identification of bi-allelic inactivation of SMARCA4, which encodes a member of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex, as the defining molecular event in SCCOHT. This may occur either through two intra-genic mutations or a single intra-genic mutation and loss of heterozygosity on chromosome 19p. It has been shown that most cases have a loss of expression of the corresponding SMARCA4 protein, also referred to as BRG1. SMARCA4 is a highly sensitive and specific marker for SCCOHT. Loss of SMARCA4 has a sensitivity of 96.55% and specificity of 100%.[6] Rare cases of SCCOHT lacking molecular and immunohistologic evidence of SMARCA4 deficiency show alterations in SMARCB1, representing a mechanism of oncogenesis through alternate defects in the SWI/SNF complex.[7]

Owing to the rarity of this tumor, optimal treatment is difficult to identify. There is a paucity of prospective and randomized trials, and recommendations are mostly based on case reports. There is no clear evidence on the most appropriate surgical approach, especially in younger women. Recommendations on the acceptability of fertility-preserving surgery as well as routine lymphadenectomy are not available. As with other ovarian neoplasms, standard primary surgical debulking is the preferred treatment. For selected patients with advanced, bulky Stage III disease or Stage IV disease where optimal primary debulking surgery may not be achievable, neoadjuvant chemotherapy may be considered on an individual basis after consultation with a multidisciplinary team. The recommendation based on the ESGO-SIOPE guidelines for the management of adolescents and young adults with nonepithelial ovarian cancers states that when the pathological diagnosis of SCCOHT is certain, surgical treatment includes total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal staging and full pelvic and para-aortic lymphadenectomy, even for macroscopically Stage I patients. A conservative approach is not recommended due to the aggressive nature of this tumor.[8] In the first patient discussed earlier, only conservative surgery was performed since the initial biopsy was a granulosa cell tumor. This underscores the importance of accurate histologic diagnosis. Adjuvant chemotherapy is recommended for all stages, generally cisplatin- and etoposide-based combination regimens (e.g., bleomycin, etoposide, and cisplatin; vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide; and cisplatin, doxorubicin, and etoposide cyclophosphamide [PAVEP]).[9] The inclusion of paclitaxel in the platinum combination can be considered. Radiotherapy may also be considered in a multimodality approach following chemotherapy, but because of limited evidence, its role is still not well defined. In patients without evidence of disease after initial chemotherapy, dose-intensive chemotherapy with stem cell support may be used in a multimodality approach for consolidation. For advanced-stage disease, removal of peritoneal disease, including omentectomy and pelvic and para-aortic lymphadenectomy, if complete removal of the peritoneal disease can be

achieved, is recommended. This may be through a primary debulking surgery or interval debulking surgery after neoadjuvant chemotherapy. For the select patients who achieve complete remission after initial surgery and chemotherapy, a dose-intensive regimen followed by high-dose chemotherapy with stem cell support and pelvic radiotherapy may be considered.[8]

The evidence for chemotherapy for small-cell carcinoma of the ovary is generally extrapolated from its use in small-cell carcinoma of the lung, where the combination of a platinum drug and etoposide is considered most appropriate.[3] Adjuvant pelvic radiation may result in a lower relapse rate. In one study,[10] adjuvant radiotherapy with either pelvic and para-aortic radiotherapy, with an average dose 46.5 Gy, or pelvic and whole abdominal radiotherapy, with an average dose 45 Gy to pelvis and 25 Gy to abdomen, was given. In their study, of the seven patients who received radiotherapy, five were long-term survivors (>50 months). Only one patient with Stage III disease received radiotherapy, and she remained well at 6 months after completion of therapy. Given the pattern of peritoneal spread with positive washings in most patients at diagnosis, whole abdominal radiotherapy may be preferable to pelvic radiotherapy alone.

Another treatment option is a dose-intensive regimen with debulking surgery followed by 4–6 cycles of chemotherapy with cisplatin (P) 80 mg/m^2 day 1, adriamycin (A) 40 mg/m^2 day 1, vepesid (V) 75 mg/m^2/day days 1–3, cyclophosphamide (EP) 300 mg/m^2/day days 1–3, every 3 weeks, and granulocyte colony-stimulating factor with, in case of complete remission, high-dose chemotherapy with carboplatin, vepesid, cyclophosphamide, and stem-cell support resulted to an encouraging overall survival of 49% at 1 year and 58% at 3 years. The only long-term survivors had complete surgical resection.[11] In another study, an intensive treatment regimen with optimal cytoreductive surgery and chemotherapy protocol for 4–6 cycles (PAVEP) followed by high-dose chemotherapy with stem cell support and pelvic radiotherapy resulted in a significantly better overall survival albeit significant toxicity.[12]

Tumor recurrence in SCCOHT may occur after initial surgery and adjuvant treatment in the following sites: pelvis (most common), abdomen, small bowel mesentery, retroperitoneal nodes, ascites, pleural effusion, and supraclavicular node.[8] Based on limited case reports and series, SCCOHT is often chemosensitive initially, but a substantial risk for relapse exists. In most of these cases, the effectiveness of additional chemotherapy is limited. Available options for chemotherapy in the recurrent setting include combinations of cyclophosphamide, doxorubicin, and vincristine, or carboplatin in combination with paclitaxel and topotecan.[9,13] Management of these patients with tumor recurrence or relapse is often challenging, and the majority of cases only rarely achieve prolonged remission. A number of salvage chemotherapy regimens have been reported including cyclophosphamide, adriamycin, and vincristine with or without etoposide, ifosfamide, and carboplatin and paclitaxel including dose-dense regimens in a few case reports.[3,14]

SCCOHT is often difficult to distinguish from other epithelial ovarian carcinomas, and owing to its rarity, is often missed out. As with all other disease entities, a high index of suspicion is key to diagnosis. Expert pathological review is essential, and the diagnostic value of adjunctive IHC staining is highlighted in this paper. Because evidence on the most appropriate treatment is limited, management of these rare cases should be individualized, and discussion with a multidisciplinary team that involves gynecologic oncologists, sonologists, radiologists, radiation oncologists, pathologists, reproductive endocrinologists, pediatric oncologists among young patients, and genetic counselors, is desirable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/ have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Almaira S. Pagayao, MD - Involved in the conceptualization, methodology, data curation, writing of the original draft, review and editing, visualization/ data presentation.

Jericho Thaddeus P. Luna, MD - Involved in conceptualization, methodology, review and editing of the draft, supervision.

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Conflicts of interest
There are no conflicts of interest.

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