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Small cell carcinoma of the ovary hypercalcemic type (SCCOHT): Comprehensive management of a newly diagnosed young adult

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ABSTRACT

SCCOHT is an aggressive malignancy linked to alterations of *SMARCA4*. We describe the diagnosis and therapy of a 32 year old who received multi-agent chemotherapy and underwent a second look operation with HIPEC followed by high-dose chemotherapy with stem cell transplant. Supportive care, oncofertility, and genetic counseling are described.

1. Presentation and diagnosis

1.1. Original diagnosis

A 32 year old female presented with a complaint of several days of abdominal bloating that progressed to severe right lower quadrant pain. She denied fever, gastrointestinal symptoms, menstrual changes, or dysuria. Computed tomography (CT) of the abdomen and pelvis revealed a 13 × 9.9 cm heterogeneous pelvic mass without evidence of ascites, peritoneal carcinomatosis, or lymphadenopathy (Fig. 1). Laboratory studies were unremarkable with a calcium of 10.5 mg/dL and the following normal serum tumor markers (normal reference ranges indicted): quantitative human chorionic gonadotropin < 1 (0–5 IU/L), alpha-fetoprotein 7.1 (<8 mg/mL), carcinoembryonic antigen 1 (<5 mg/mL), inhibin B 59 (<290 pg/mL in premenopausal females over 18), CA125 12 units/mL (<35), and CA19-9 3 units/mL (<37). She underwent a laparoscopic right salpingo-oophorectomy with sampling of peritoneal washings. The salpingo-oophorectomy specimen revealed gross hemorrhages, giving the impression of hematosalpinx, with frozen section findings suggestive of an undifferentiated round cell sarcoma. A whole body 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT on post-operative day (POD) #21 demonstrated hypermetabolic activity within the contralateral (left) ovary with a maximum standardized uptake value (SUV) of 11.9 and mild hypermetabolic activity within left iliac lymph node chain. A transvaginal ultrasound visualized a normal remaining ovary with a single simple cystic lesion measuring 2.2 × 2.3 × 3.0 cm with fewer than 12 follicles in the ovary. The uterus was normal in morphology and echogenicity. A dedicated chest CT was negative for metastasis.

The patient's past medical history was significant for a right temple skin lesion that was shave biopsied and found to be a 0.34 mm deep malignant melanoma with a positive deep margin that required a wide re-excision (T1N0M0) at age 29. Her family history was significant for a sister with a history of cervical cancer and another sister with a history of choriocarcinoma following an ectopic pregnancy. There was no family history of other gynecologic malignancies, childhood cancers, or sarcoma.

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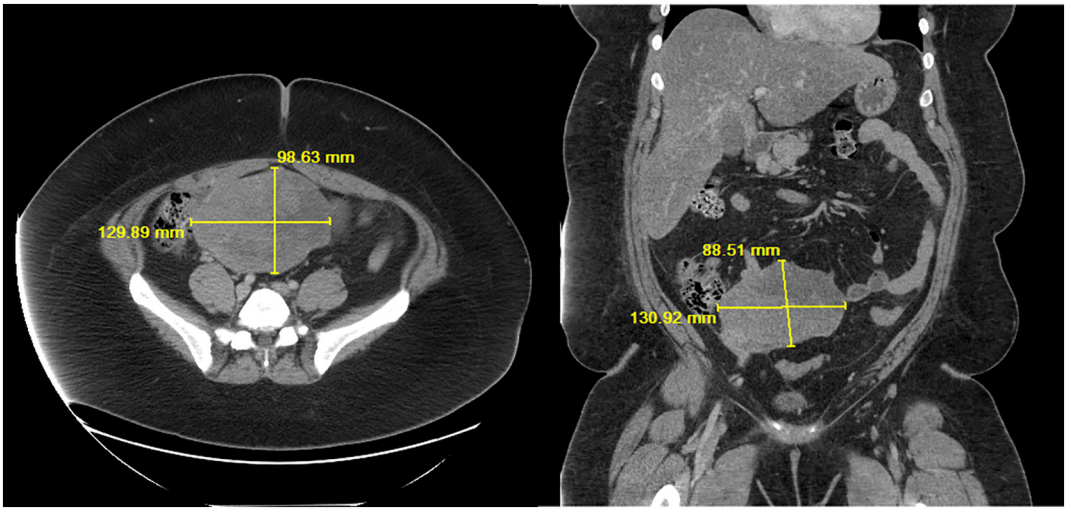

Fig. 1. Pre-therapy axial and coronal computed tomography (CT) imaging. Abdominal and pelvic CT scan with IV contrast at diagnosis revealed a 13 × 9.9 × 8.9 cm heterogeneous mass with well circumscribed margins. No mass was identified on a CT scan performed 21 months earlier. Small mesenteric lymph nodes noted on the prior CT scan were unchanged on the diagnostic scan. Moderate diffuse fatty infiltration of the liver was also noted.

1.2. Pathology

The focus of the differential workup (Fig. 2) was primary ovarian tumors, as well as various abdominal and extra-abdominal tumors. The diagnostic work up based on histomorphology, presentation, and adolescent and young adult (AYA) oncology is outlined in Table 1. Beside juvenile granulosa cell tumors (JGCT) and a range of sex cord-stromal tumors [1], poorly to undifferentiated round cell sarcomas entered the main differential, such as desmoplastic small round cell tumor (DSRCT) and other, much rarer entities including those of renal and uterine origin. Retention of normal INI-1 nuclear immunoreactivity excluded a malignant rhabdoid tumor (MRT), typically characterized by *SMARCB1* mutations. The loss of BRG1 nuclear immunoreactivity in this tumor, consistent with an inactivating mutation of the *SMARCA4* gene, was cardinal in the diagnosis of small cell carcinoma of the ovary hypercalcemic type (SCCOHT) [2]. Sampled peritoneal fluid was positive for malignant cells, rendering her disease pT1c3 per AJCC staging. Next generation sequencing (NGS) of the tumor tissue revealed *SMARCA4* splice site mutations 3952-1G>A and 4534-1G>A (Foundation Medicine, Cambridge MA).

1.3. Background

SCCOHT is an exceptionally rare malignancy with a peak incidence in young adulthood, although the age spectrum ranges from infancy to at least the fifth decade of life. Early descriptions of the tumor documented abysmal survival. In 1982, Dickersin and colleagues first described 11 cases of ovarian tumors characterized by poorly differentiated small cells with epithelial features that were associated with hypercalcemia [3]. Among the patients reported, ranging in age from 13 to 35 years, seven were dead of disease and only two were in remission at the time of publication. In 1994, Young et al. reported a retrospective cohort of 150 SCCOHT cases with a median age of 23 years, providing the first large scale description of SCCOHT [4]. There was no uniform treatment approach among the collected cases. The survival of patients with stage IA disease was only 33%, while patients with more advanced disease rarely survived.

As additional reports were published, common themes that emerged were that SCCOHT was a distinct tumor type often associated with hypercalcemia but with an ambiguous cell of origin. In order to distinguish the tumor from small cell carcinoma of the ovary pulmonary type (SCCOPT) that display neuroendocrine features, the SCCOHT designation was established. While the clinical phenotype was clearly virulent, with most patients dying of disease, there was some indication that multimodal therapy would at least delay progression [5]. Familial clustering of SCCOHT in rare cases also suggested a potential genetic predisposition [6]. In the subsequent decades several hundred additional patients were reported. The most comprehensive overview of SCCOHT outcomes included nearly 300 patients available mostly from the published literature [7]. A key finding indicated that disease stage was an important prognostic factor, with distant metastases predicting nearly uniform lethality with rare exception.

1.4. Molecular genetics

In 2014, mutations of *SMARCA4*, a tumor suppressor gene encoding an ATPase of the SWI/SNF chromatin remodeling complex, were identified by three independent teams as the only recurrent genetic alteration in SCCOHT [8]. *SMARCA4* encodes one of two mutually exclusive ATPase subunits of the SWI/SNF chromatin remodeling complex that plays a central role in regulation of transcriptional programs associated with differentiation. The alternative SWI/SNF ATPase, SMARCA2/BRM, is also often absent in SCCOHT due to epigenetic silencing [9,10]. Biologically, *SMARCA4* is closely related to *SMARCB1*, which also encodes a subunit of SWI/SNF complexes. Loss of *SMARCB1* is the driver of most renal and extra-renal MRT, atypical teratoid rhabdoid tumor (ATRT), and other tumor types including epithelioid sarcoma [11]. MRT and ATRT occur mainly in infants and children and are clinically aggressive malignancies [12]. With closely overlapping clinical and pathobiological features, established MRT therapeutic principles including choice of chemotherapy regimens and local control measures contributed to the therapeutic strategy utilized in the present case.

2. Treatment

2.1. Medical treatment

SCCOHT is considered a systemic disease for which regional or distant micrometastases are presumed to be present even when extra-ovarian disease is not evident radiologically or intra-operatively. Regardless of the extent of disease, all patients should receive chemotherapy. The rarity of SCCOHT and the dearth of prospective therapeutic

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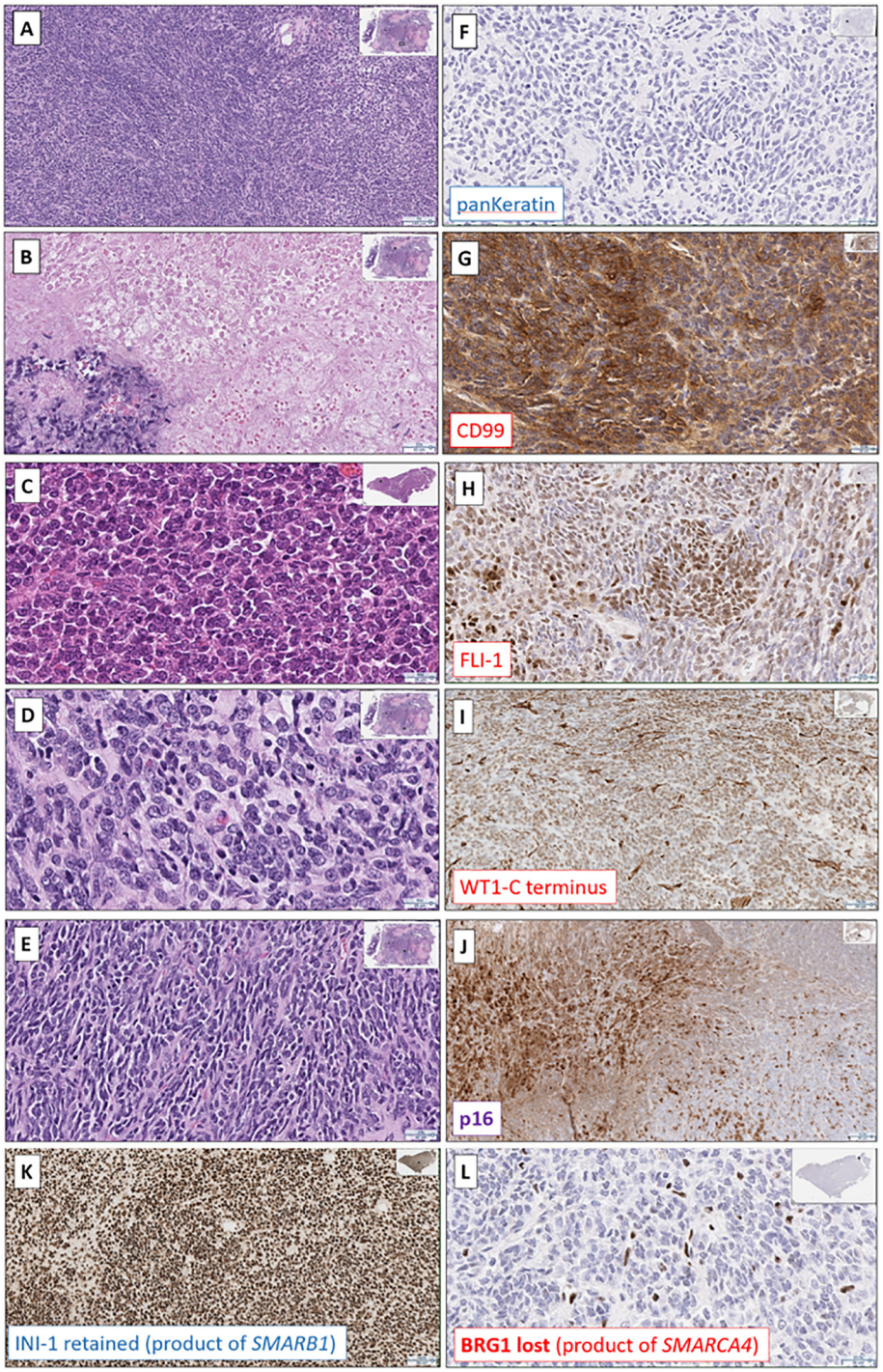

Fig. 2. Pathology. The tumor was highly cellular, relatively monotonous in solid sheets (A,K), and with frequent patches of ischemic necrosis (B). Classic cytomorphology reminiscent of primitive round cell sarcomas was evident (with round nuclei, small amount of cytoplasm, regional molding, in patternless cellular sheets, frequent mitoses) (C), along with nesting and cord-like patterns, delicate vascularity and stromal streaming along oval to polygonal cells with vesicular nuclei (D). Streaming ovoid to spindle cells (E) were predominant in this case (A, F). While this range of architectural patterns is common in SCCOHT, in this tumor, it was difficult to find other focal patterns that are otherwise frequent in SCCOHT — such as follicle-like spaces with eosinophilic or basophilic material, or rhabdoid cytomorphology. No large cell-morphology was seen. Diagnostically cardinal (at the bottom of the panel, K–L) were the normal nuclear retention of INI-1 and the abnormal diffuse loss of nuclear immunoreactivity for BRG1 — the product of the *SMARCA4* gene; (spotty positivity reflects normal retention in capillaries — an internal positive control). Additional immunostains (F–J): Epithelial stains and calretinin are variably (though frequently) positive in SCCOHT; this case was negative for panKeratin AE1/AE3 (F); CAM5.2 and calretinin was only focal spotty positive. Diffusely positive stains included CD99 (largely cytoplasmic, rather than membranous) (G), along with the frequent non-specific mimicker of FLI-1 (H), and WT1 (I). These are frequently variably positive in SCCOHT, but are not specific. Notable negative stains included inhibin and SF-1, in exclusion of other ovarian tumors, (mostly juvenile and adult granulosa cell tumors, and other sex cord-stromal tumors). In light of the patient's history of melanoma, the negative SOX10, S100 and BRAFV600E excluded metastatic recurrence. In consideration of potential further management: Cyclin D1 was only rare spotty positive (<1%); p16 was moderately (to spotty strong) positive in 40% of the tumor (J); PD-L1, ER and PR were negative.

trials have hindered the establishment of a standard medical therapy regimen. Given that SCCOHT tumors exhibit transient chemosensitivity, a tendency to progress rapidly, and limited capacity for retrieval in the setting of recurrence, intensive multi-agent chemotherapy is relied upon at diagnosis. Many chemotherapy regimens for SCCOHT have been reported with varying degrees of success; however, publications

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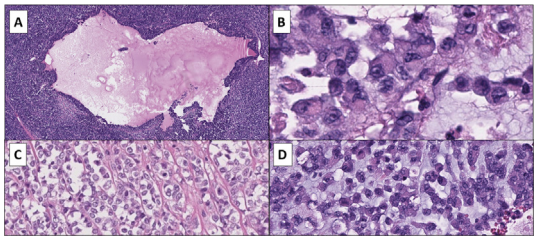
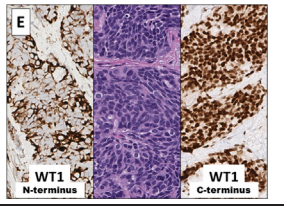
Table 1
Pathologic evaluation, step by step. The primary pathologic work-up starts with assessment of the spectrum of histologic patterns, presence or lack of specific features for a particular diagnosis (1) to narrow or broaden the workup, in the context of primary ovarian tumors (2), non-ovarian primary abdominal tumors in young adults (3), "Krukenberg tumor" phenomenon for distant primaries and tumor predisposition syndromes (4), and markers for clinical maintenance or other practical aspects of personalized management of patients (5).

Focus of diagnostic work-up	Select examples, rationale and practical points considered
1. Spectrum of histopathologic patterns in SCCOHT	 This patient's tumor was relatively monotonous, mostly lacking histologic patterns that are commonly seen in SCCOHT, including *follicle-like* structures (A), eosinophilic (pink) and basophilic (bluish) extracellular material (A, B, D), or frank *rhabdoid* morphologies (B). There were no features of the l*arge cell variant* of SCCOHT or any semblance to pulmonary large cell neuroendocrine carcinomas.
2. Primary ovarian tumor differential diagnosis	Juvenile granulosa cell tumor was high on differential diagnosis, given the patient's age, tumor cellularity, solid patterns and frequent mitoses, (coupled with microcystic features in other cases). Patterns mimicking (image C above) Sertoli cell tumors or other sex cord-stromal tumors were inconspicuous, and a panel of immunostains (including Inhibin, Calretinin and others) was supportive. Furthermore, these tumors retain immunoreactivity for BRG-1.
3. Abdominal (non-ovarian) tumor differential diagnosis	Given pelvico-abdominal location, age and tumor morphology, desmoplastic small round cell tumor (DSRCT) (E) was a top differential entity to exclude. Additional mimickers included malignant rhabdoid tumor (MRT) (with INI-1 loss) and other undifferentiated round cell sarcomas (URCS) of the kidney and uterus. 
4. Extra-abdominal/distant primary tumor differential diagnosis (Krukenberg tumor phenomenon)	The history of melanoma in this patient warranted ruling out a metastasis to ovary – in a practical approach with immunostains – though there is little data (no current evidence) of BRG1- (or SWI/SNF-) deficiency in melanomas. Sequencing the patient's tumor revealed both a germline mutation (confirmed) and a second (somatic) mutation in the *SMARCA4* gene – in line with known risks for Tumor Predisposition Syndrome in patients with SCCOHT.
5. Markers for personalized management	Finally, considering maintenance therapy, PD-L1, Cyclin D1 and p16 were performed, along with estrogen receptor and progesterone receptor, as markers for potential hormonal drivers of the tumor.

are often limited by small patient numbers, inherent selection bias, and inconsistency in the delivery of therapy and supportive care.

For our patient, we recommended 6 cycles of VPCBAE therapy consisting of vinblastine (V), cisplatin (P), cyclophosphamide (C), bleomycin (B), doxorubicin (A), and etoposide (E) administered on a 3 week schedule (Fig. 3). Many of the successfully treated SCCOHT cases in the literature received similar therapy. In the first report of patients receiving VPCBAE published in 1989, three of the five patients reported remained clinically free of disease after six cycles of VPCBAE. Two patients who demonstrated measurable pelvic disease prior to chemotherapy experienced objective responses [13]. Subsequently, a 26 year old with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC effectively treated with VPCBAE was reported, and numerous successful case reports of advanced stage patients have since been published [14–18]. In the largest contemporary retrospective series, among patients with FIGO stage I disease, only one of six treated with VPCBAE experienced recurrent disease, compared to all five treated with cisplatin and etoposide (CE) and both patients who received no adjuvant therapy ($P = 0.008$) [19].

A similar multi-agent regimen (PAVEP) consisting of cisplatin (P), doxorubicin (A), etoposide (V), and cyclophosphamide (EP) was used in the only prospective SCCOHT trial conducted to date. Patients with newly diagnosed disease were treated with 4 to 6 cycles of PAVEP therapy [20]. Encouragingly, 18 patients were found to be in a complete remission (CR) while eight experienced progressive disease prior to randomization to high dose chemotherapy with stem cell transplant (HDCSCT) consolidation. PAVEP or similar therapy has also been cited in case reports [21,22]. Among published SCCOHT regimens, VPCBAE and PAVEP particularly resemble intensive MRT regimens that include multi-agent therapy such as vincristine, cyclophosphamide, and doxorubicin (VDC) alternating with cyclophosphamide, carboplatin, and etoposide or VDC utilizing high dose cyclophosphamide [23,24]. The evidence for VPCBAE or PAVEP therapy in SCCOHT is relatively well established. Given the potential added benefit of bleomycin and vinblastine, our approach has been to recommend VPCBAE but with a low threshold to modify or hold bleomycin dosing in the face of pulmonary toxicity.

Other regimens that are cited in the literature include commonly used germ cell regimen bleomycin, etoposide, and cisplatin (BEP) which has been reported as successful [25]. Advantages of BEP (or similar PVB) are the relative tolerability as well as familiarity among pediatric, medical, and gynecologic oncologists who routinely treat germ cell tumors. On the other hand, these regimens lack alkylators or anthracyclines often used in MRT regimens. Other regimens that are cited include carboplatin combined with taxanes, reported less favorably in a retrospective multi-institutional study [26].

2.2. Surgery

After originally presenting with an ovarian mass of uncertain etiology, the patient underwent a right salpingo-oophorectomy with peritoneal fluid sampling at the referring hospital. Once the diagnosis of SCCOHT was confirmed, our team chose not to undertake a formal ovarian cancer staging procedure. Rather, a second look operation (SLO), with the intent of confirming/rendering the patient free of gross disease, as well as a course of Heated Intra-Peritoneal Chemotherapy (HIPEC) was scheduled between cycles 4 and 5 (Fig. 3). She underwent a midline exploratory laparotomy where the entirety of the small bowel and colon was examined. The only significant finding was a small sub-centimeter mesenteric nodule, which was resected. Nodularity of the right fallopian

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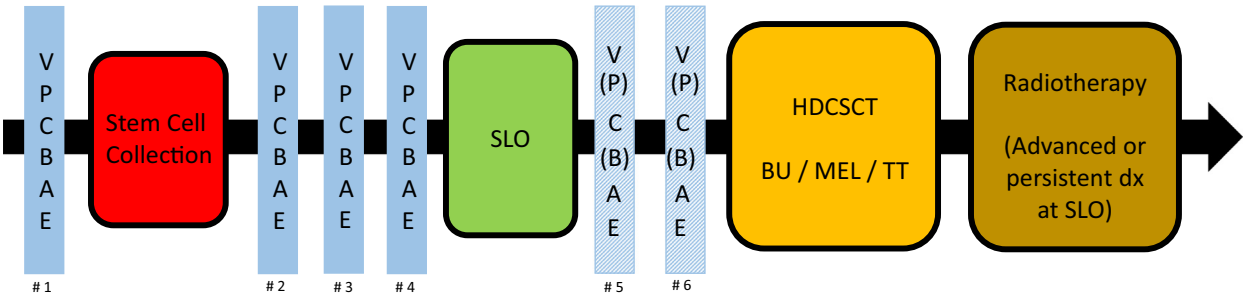

Fig. 3. Recommended treatment schema. VPCBAE therapy given as an inpatient consisting of Day #1 vinblastine (V) 6 mg/m^2 over 5 min and cisplatin (P) 90 mg/m^2 over 4 h, Day #2 cyclophosphamide (C) 1000 mg/m^2 over 60 min and bleomycin (B) 15 Units/m^2 over 10 min, and Day #3 doxorubicin (A) 45 mg/m^2 over 15 min [after dexrazoxane (450 mg/m^2)] and etoposide (E) 200 mg/m^2 over 120 min administered intravenously on an every 3 week schedule assuming bone marrow function has recovered adequately. Continuous intravenous fluids (including mannitol prior to cisplatin) and anti-emetics appropriate for a highly emetogenic chemotherapy regimen are given throughout. Organ function including pulmonary function testing (PFTs), echocardiogram (ECHO), glomerular filtration rate (GFR), and audiology is screened at diagnosis and again prior to cycles 3 and 5 and HDCSCT. If diffusing capacity (DLCO) and/or GFR significantly decrease, bleomycin and/or cisplatin, respectively, are decreased or even held in later cycles. Regardless of the surgical approach taken at diagnosis, a second look operation (SLO) or secondary cytoreduction is recommended prior to consolidative HDCSCT. If unresectable or progressive disease is documented, the patient should be considered for experimental medical therapy. Hematopoietic stem cell collection is recommended either after cycle #1 or #2 of VPCBAE. The preparative regimen for high dose chemotherapy with stem cell transplant (HDCSCT) includes busulfan, melphalan, and thiotepa. Busulfan is given every 24 h for three days (day −8 to −6) and the dosing is based on pharmacokinetics, with an area under the curve (AUC) of 3600–6000 μmol*min/L. Melphalan (total dose of 100 mg/m^2) is given daily on days −5 and −4, and thiotepa (total dose of 500 mg/m^2) is given daily on days −3 and −2. To minimize toxicity, radiotherapy is delivered following recovery from HDCSCT. Radiation therapy is reserved for patients with advanced disease at diagnosis or persistent disease detected at the time of SLO.

tube at the previously resected ovarian margin was debulked, and the left ovary had a firm nodule on its surface, which was also resected. No evidence of tumor was found. With all potential gross disease removed, the HIPEC portion of the case with 100 mg/m^2 (130 mg maximum dose) of cisplatin was performed over 90 min after warming the peritoneal cavity to 42 °C.

Given the rarity of SCCOHT, many patients will have already undergone an upfront surgical resection with extensive staging, prior to reaching the referral center where comprehensive therapy will be delivered. However, when possible, we recommend a limited diagnostic procedure such as a salpingo-oophorectomy. The rationale for limited surgery at diagnosis is supported by the concept that SCCOHT is a systemic disease often characterized by lymphatic invasion and hematogenous dissemination for which chemosensitivity is limited but seemingly most exquisite early in the disease process. An extensive surgical procedure, as is performed for an epithelial malignancy, may delay the delivery of chemotherapy and may interfere with fertility preservation. The choice of chemotherapy regimen generally does not vary based on staging/risk status. Finally, a second look operation (SLO) or secondary cytoreduction will ideally provide an opportunity to either confirm complete response to therapy or resect remnants of viable disease, rendering the patient with minimal residual disease prior to consolidative therapy. The extent of residual disease at the time of follow-up surgery will inform the plan for consolidative therapy including radiotherapy to sites of gross disease. On the other hand, a change of therapy would be indicated if extensive unresectable disease such as peritoneal carcinomatosis is detected. Furthermore, similar surgical principles exist for limiting extremely morbid procedures that may affect long term function in tumors such as rhabdomyosarcoma.

There is presently no published experience of HIPEC in SCCOHT, but the therapy is easily incorporated into SLO or secondary cytoreductive surgery. The role of HIPEC for epithelial ovarian tumors has been studied formally but remains controversial. A randomized trial of surgery with or without HIPEC following three cycles of neoadjuvant carboplatin and paclitaxel demonstrated longer recurrence-free and overall survival in epithelial ovarian patients who received HIPEC [28]. Given a similar age distribution, the utility and morbidity of HIPEC in SCCOHT may be most comparable to that in DSRCT, with similar intra-peritoneal spread and sensitivity to intensive systemic chemotherapy and multi-modal local control strategies. There appears to be a survival benefit for patients with DSRCT limited to the abdomen who undergo resection of all gross disease followed by HIPEC [30]. Clearly, further study into the risks and benefits of HIPEC for SCCOHT is needed to better delineate if there is a similar survival benefit.

2.3. HDCSCT consolidation

Myeloablative consolidation with HDCSCT is associated with improved outcomes over non-myeloablative regimens for extracranial MRT that generally fare dismally. In the Intergroup Rhabdomyosarcoma Study trial, 19 of 26 MRT patients died at a median of 6 months from the start of treatment [31]. In a description of 21 patients diagnosed with extracranial MRT at a single center from 1983 to 2012, survival was significantly higher in the four patients who received HDCSCT (100% survival with no disease recurrence). Importantly, all four of the patients had either stage III or IV disease. In those who did not undergo autologous transplant, only four of 17 survived without relapse. The authors concluded that treatment with high dose alkylator therapy, followed by consolidation with HDCSCT for those patients in radiographic complete remission, was beneficial [23].

The benefit of HDCSCT specifically in SCCOHT is also emerging. Among other successful reports in the literature, Qin et al. described a 19-year old female with stage IIIC disease who achieved a durable remission with chemotherapy, surgery, and HDCSCT with or without radiation therapy [21,32,33]. Further support for HDCSCT for SCCOHT is derived from a review of 293 patients diagnosed with SCCOHT. In those with FIGO stages II–IV SCCOHT, 5-year survival was 71% for patients who received HDCSCT, compared to 25% in patients who received conventional chemotherapy alone following surgery. Consolidation with HDCSCT was concluded to provide the best opportunity for long-term survival [7]. Finally, among 469 women with a diagnosis of "small cell carcinoma of the ovary" included in the National Cancer Data Base from 2004 to 2014, patients treated with high-dose chemotherapy followed by a "hematologic transplant procedure" had increased overall survival compared to those receiving chemotherapy alone [34].

Many of the published cases of SCCOHT undergoing HDCSCT received a preparative regimen which included an alkylating agent (*e.g.*, melphalan, busulfan, cyclophosphamide) and the others included a platinum-based chemotherapeutic agent (*e.g.*, carboplatin) [7,19–21,32,35]. Due to the heterogeneity of preparative regimens reported, there is no single regimen that has been shown to be superior

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to others. We recommend patients receive a preparative regimen which includes a high dose alkylating chemotherapeutic agent, which has been suggested in several reports [2,7,23]. For the patient described here, the recommended preparative regimen included busulfan, melphalan, and thiotepa given approximately 4 weeks after the last cycle of VPCBAE (Fig. 3).

Peripheral blood stem cells (PBSC) are the preferred stem cell graft for autologous stem cell transplant due to faster engraftment. Usually, stem cell mobilization is done using G-CSF in combination with chemotherapy; however, the success of mobilization depends on many factors, including the amount of previous chemotherapy and patient age [36,37]. Attempts to salvage PBSC harvests are possible but can be associated with prolonged hospitalization and resources. In patients that are unable to mobilize, HDCSCT is not possible. In the report from Pautier et al. [20], 3 of the 18 (17%) patients with SCCOHT who were intended to receive high dose chemotherapy were unable to harvest due to poor mobilization. We suggest PBSC harvest very early in treatment, no later than the second chemotherapy cycle and preferably after the first, to ensure a successful harvest.

2.4. Consolidative radiotherapy

Radiation treatment guidelines for SCCOHT are not presently established. The use of radiotherapy is well recognized as beneficial for tumor control in MRT and ATRT. In MRT of the kidney, radiotherapy has been associated with improved survival [38]. For ATRT, toxicity and long-term side-effects of the central nervous system are particularly problematic in a young population [39], but some adverse effects have been attenuated by the use of proton beam radiotherapy [40]. The use of radiotherapy in these biologically similar and better studied diseases has provided rationale for SCCOHT radiotherapy. Publications by Callegaro-Filho and colleagues have demonstrated activity in the relapse setting as well as possible association with survival in upfront treatment of SCCOHT [19,41].

Given the limited extent of disease in the present case, we did not recommend radiotherapy. Considering the potential benefit balanced with expected toxicities, we have generally recommended whole abdomen irradiation (WAI) in cases of advanced disease at diagnosis and/or residual disease identified at the time of SLO or secondary cytoreductive surgery. In cases of radiographically evident disease and/or persistent lymphadenopathy (LAD), we advocate for additional radiation boost following WAI. If there is no evidence of parenchymal metastases within visceral organs, liver and kidney doses are minimized *via* intensity-modulated radiotherapy technique and taken to tolerance levels if presence of parenchymal disease is noted. We have favored doses of 30.6 Gy in 1.8 Gy fractions for WAI and boost for an additional 14.4 Gy to a cumulative 45 Gy for residual LAD or radiographically visible lesions. WAI exposure typically takes intra-abdominal normal tissues to near tolerance levels. Utilization of intensity modulated radiotherapy or proton radiotherapy should be considered when feasible for boost to gross disease. Our approach is to sequence radiotherapy following HDCSCT to minimize overlapping toxicities, consistent with most common regimens containing both modalities in other oncologic disease (Fig. 3).

Common short-term toxicities related to abdomen and pelvis radiotherapy include fatigue, nausea, and bowel irritation. Long-term bowel obstruction, kidney and liver dysfunction are also risks and must be given additional consideration due to multimodality therapy with overlapping risks. Furthermore, ovarian failure and uterine dysfunction are well recognized toxicities in patients undergoing similar chemotherapy and radiotherapy exposures [42,43]. This is of particular interest and concern given the typical age range of this patient population. It should be noted that future pregnancy is possible in patients treated with pelvic radiotherapy, however rates of complication and low birth weight are higher [43].

3. Genetics, endocrinology, and survivorship

3.1. Genetic counseling

After identifying tumor *SMARCA4* splice site mutations 3952-1G>A and 4534-1G>A by NGS, the patient was subsequently found to carry a heterozygous germline *SMARCA4* variant 3952-1G>A (Invitae, San Francisco, CA). This previously unreported alteration was predicted to impact RNA splicing, resulting in a disrupted protein product. Pathogenic variants in the *SMARCA4* gene are associated with Rhabdoid Tumor Predisposition Syndrome Type 2 and are known to increase the risk of developing SCCOHT, as well as MRT and ATRT [44]. In addition to SCCOHT, an increased risk of developing undifferentiated uterine sarcoma (UUS) with germline *SMARCA4* mutation is now also recognized. Importantly, the median age of UUS in the setting of germline *SMARCA4* mutation is 49 years [45]. Somatic loss of *SMARCA4* is described in thoracic sarcomas but no association with germline predisposition has been established [46].

While the prevalence of *SMARCA4* variants is unknown, it is reported that approximately 35% of cases of SCCOHT are due to germline alterations [47]. Our institutional approach has been to offer all SCCOHT patients germline *SMARCA4* testing regardless of age at diagnosis or family history, typically after tumor NGS has identified one or more *SMARCA4* mutations. The penetrance of tumor development in individuals who carry a *SMARCA4* pathogenic variant is not well defined. Surveillance and management guidelines are not well established but suggest that women who carry germline *SMARCA4* pathogenic variants undergo a pelvic ultrasound every six months and prophylactic oophorectomy after childbearing [47]. Germline *SMARCA4*-associated SCCOHT develops at younger ages than do sporadic SCCOHT, rendering recommendations for prophylactic oophorectomy particularly challenging. There is a report of a female carrier undergoing prophylactic oophorectomy at age 13, following careful consideration of implications of the surgery and family history [48]. While the present patient's history of cutaneous melanoma is not easily linked to *SMARCA4* (note: her tumor specimen was not studied by our team), the patient will be routinely monitored for recurrence [50]. *SMARCA4* germline mutation testing was also recommended for the patient's parents and two sisters.

3.2. Oncofertility & reproductive endocrinology

At the time of presentation, the patient was 32 years old gravida 1 para 0010 with a history of an early pregnancy loss approximately three months prior. She and her husband had been attempting conception for greater than two years. Her reproductive history was significant for polycystic ovary syndrome by clinical hyperandrogenism and ultrasound findings. Regarding the function of her remaining ovary, the chemotherapy treatment plan of VPCBAE alone would place the patient at intermediate risk of premature ovarian insufficiency (POI) based on a cyclophosphamide equivalent dose of 6 g/m^2 [51]. The addition of the busulfan, melphalan, thiotepa preparative regimen for HDCSCT would place the patient at high risk (>80%) of POI [51]. The risk assessment and potential fertility preservation techniques including oocyte cryopreservation and ovarian tissue cryopreservation (OTC) were reviewed with the couple [52].

The approximate two week timeframe needed for ovarian hyperstimulation prior to oocyte collection and cryopreservation was discussed. The patient expressed that the initiation of treatment was most important to her, declining oocyte cryopreservation given the necessary time commitment. The patient was also counseled on the process of OTC, including removal of her remaining ovary with cryopreservation of the ovarian cortical tissue to use for future fertility. Current success rates for OTC are based on ovarian tissue transplantation (OTT). This process involves thawing the ovarian cortical strips and surgically placing them into the pelvis, typically in either peritoneal pocket (the only option for this patient) or sutured onto the remaining ovary (when

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present). The fertility preservation rate for this technique is approximately 30% [53]. Possible use of *in vitro* techniques with oocytes from frozen ovarian tissue for future pregnancy was also discussed, but this research presently remains only in pre-clinical development. The patient was counseled on the uncertain risk of microscopic SCCOHT cells within the remaining ovary and potential risk of cancer recurrence with OTT. After extensive discussion, the patient declined OTC and proceeded with VPCBAE therapy.

After documentation of the patient's germline *SMARCA4* mutation, she presented again to the fertility/gynecology team. Approximately five months after completion of HDCSCT, she sought additional counseling prior to possible left oophorectomy. At that time her serum follicular stimulating hormone level was 31.9 IU/L, estradiol level was 6.9 pg/mL, and her anti-mullerian hormone level was undetectable. These studies indicated that the remaining left ovary was in acute POI and that recovery of ovarian function post chemotherapy (<20% chance) may take 18 to 24 months or more. Counseling was provided on the following: (1) the risks and benefits of OTC/OTT given her acute POI and previous gonadotoxic therapy, (2) donor oocyte or embryo adoption for future pregnancy, and (3) the risks associated with POI, including cardiovascular disease and osteoporosis without hormone replacement therapy (HRT) [54]. While SCCOHT is not known to be hormonally driven, the original SCCOHT specimen was evaluated for estrogen (ER) and progesterone receptor (PR) expression and found to be negative, providing reasonable reassurance that neither HRT nor pregnancy would increase risk of tumor recurrence. Ultimately, while not quantifiable, the risk of a metachronous SCCOHT outweighed any desire to maintain the remaining ovary. The patient opted to proceed with left oophorectomy followed by HRT and plans to use third party reproduction in the future to achieve pregnancy. Nine months after HDCSCT, the patient underwent prophylactic left salpingo-oophorectomy. No evidence of malignancy was identified.

3.3. Surveillance

Suggested recommendations for monitoring of SCCOHT recurrence, development of new *SMARCA4*-related tumors, and organ dysfunction are given (Table 2). These recommendations are adapted from standard practices established for pediatric and young adult sarcomas and germ cell tumors. For the present patient we did not document tumor marker secretion at diagnosis. Unfortunately, the sensitivity and specificity of markers such as CA125 in SCCOHT are not described. Tumors that secrete CA125 at diagnosis may not necessarily do so in the presence of radiologically evident recurrent disease, diminishing confidence in such markers for disease surveillance.

4. Future considerations

4.1. AYA oncology

Many of the challenges of AYA oncology are particularly relevant to the SCCOHT population that peaks in the third decade of life. Defined by the National Cancer Institute (NCI) as including patients 15 to 39 years of age, AYA oncology patients have not experienced the same degree of improvement in survival in recent decades as have pediatric or older adult patients. For some pediatric cancers, AYA patients fare less favorably than children with the same diagnosis; distinct tumor and host biology and more prevalent comorbidities are theorized to hinder successful therapy in young adults. Unfortunately, AYA patients also have profoundly low rates of participation in clinical trials, slowing the development of therapeutic regimens, documentation of unique toxicities, and establishment of tissue repositories for investigation [55]. Among therapeutic trials for AYA acute lymphoblastic leukemia (ALL), pediatric regimens have generally been superior to adult ALL regimens [56]. Evidence also suggests that AYA patients fare better when treated at comprehensive cancer centers [57]. In response to these challenges, AYA oncology centers have been developed that cater to the needs of the AYA population including fertility preservation, behavioral medicine, and wellness/integrative medicine. Given the typical age range of SCCOHT patients, a potential model of care delivery would include intensive treatment regimens provided at cancer centers with relevant expertise, ability to anticipate and manage toxicities, and resources for the unique needs of the patient population.

4.2. Novel therapies

Newly diagnosed SCCOHT is potentially curable with intensive, albeit toxic, multi-modal therapy. For SCCOHT patients, standardized treatment regimens should be delivered in close consultation with cancer centers possessing expertise in the diagnosis, treatment, and supportive care of pediatric or adult SCCOHT. Any benefit of novel agents for newly diagnosed patients is unproven and should not be offered at the expense of effective upfront therapy. Arguably, the study of maintenance therapy may be the most sensible approach to investigating new agents in patients with otherwise potentially curable disease. On the other hand, with nearly uniform lethality, patients with distant metastasis or recurrent disease should be offered appropriate clinical trials when available. The identification of SMARCA4 loss as the key driver of SCCOHT tumorigenesis has opened the door to developmental therapeutics targeting alterations of the SWI/SNF complex, which are estimated to affect 20% of all cancers. Given the marked chemoresistance displayed by recurrent SCCOHT, novel single agent therapies may be of limited capacity to cure; hence, strategies combining novel agents together and/or with cytotoxic chemotherapy backbones will likely be necessary.

A variety of promising therapies are at various stages of investigation. Inactivation of SMARCA4 leads to over-expression of EZH2, the catalytic subunit of polycomb repressive complex 2 (PRC2) that catalyzes H3K27 methylation. Preclinical studies of EZH2 inhibitor tazemetostat demonstrated *in vitro* and *in vivo* anti-tumor effect in MRT and SCCOHT xenografts [58]. Tazemetostat is presently being studied in combination with doxorubicin (NCT04204941) in a phase 3 trial of newly diagnosed epithelioid sarcoma, supporting the exploration of EZH2 inhibitors in combination with other relevant cytotoxic chemotherapies. Despite the low mutational burden documented in MRT and SCCOHT, there is an emerging rationale for immune checkpoint inhibitor therapy. In a study of SCCOHT tumors, eight of 11 tumors expressed PD-L1 with associated T-cell infiltration [59]. Brief anecdotes of four patients with recurrent SCCOHT that seemingly benefitted from the PD1 inhibitor therapy were also reported. Interestingly, PD1 inhibitors were given following or in combination with radiotherapy in three of the patients, suggesting immune surveillance may have promoted a remission state and/or potentially interacted synergistically with radiotherapy. Combining PD1 inhibitors with EZH2 inhibition may also be a consideration [60]. However, exhausted immune systems in heavily pre-treated patients may be less amenable to immunostimulatory signals.

Other preclinical work in SCCOHT has focused on cyclin D–cyclin-dependent kinase CDK4/6 as a therapeutic target. SMARCA4 loss has been shown to lead to downregulation of cyclin D1, limiting the activity of CDK4/6 and promoting sensitivity to CDK4/6 inhibitors. Assays of SCCOHT cell lines revealed a retinoblastoma-proficient/p16INK4a-deficient profile reliant on CDK4/6 activity [61]. Several CDK4/6 inhibitors are commercially available, and combination data with cytotoxic chemotherapy agents are emerging. Other preclinical work demonstrated that effective dual blockade of fibroblast growth factor receptor (FGFR1) and platelet derived growth factor receptor alpha (PDGFRα) with commercially available receptor tyrosine kinase inhibitor ponatinib, led to synergistic apoptosis [62].

Given the dismal prognosis faced by SCCOHT patients, continued laboratory and clinical investigation is critically needed. Acquisition of tumor specimens at diagnosis and relapse for 'omics' studies and the

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Table 2
Recommended post-therapy observations.

Years off therapy	Radiology	Blood studies	Organ function
First and second	CT chest, MRI or CT of abdomen and pelvis, PET scan (particularly if any suspicious mass or adenopathy present) every 3 months	Routine blood count and chemistry, tumor markers (if secreted at diagnosis); repeat blood work at each monitoring visit *If pt. has a remaining ovary – serum FSH, estradiol, AMH at 18–24 months after last chemotherapy to determine ovarian function and fertility potential	ECHO, PFTs, audiology, renal function (nuclear GFR or cystatin C); repeat yearly
Third	CT chest, MRI or CT of abdomen and pelvis, PET scan (particularly if any suspicious mass or adenopathy present) every 4 months		
Fourth and fifth	CT chest, MRI or CT of abdomen and pelvis, PET scan (particularly if any suspicious mass or adenopathy present) every 6 to 12 months		
Year six and beyond (Yearly survivorship visit)	If germline *SMARCA4* mutated: pelvic ultrasound (every 6 to 12 months)	Routine blood count and chemistry, tumor markers (if secreted at diagnosis)	ECHO, PFTs, audiology, renal function (nuclear GFR or cystatin C)

establishment of patient derived xenografts should be undertaken at institutions that routinely treat such patients. The development of genetically engineered transgenic animal models will also provide valuable tools for biological and therapeutic studies. Finally, tumor registry and prospective trials of patients at either diagnosis or relapse will provide important data to drive therapeutic recommendations.

Author contributions

JGP conceived the idea for the Tumor Board presentation and wrote the manuscript. SS provided the histologic images and co-wrote the manuscript. CED, RD, LEP, JSR, and RS all co-wrote the manuscript. All authors participated in the care of the patient.

Declaration of competing interest

None.

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