Small cell carcinoma of the ovary hypercalcemic type (SCCOHT): A review and novel case with dual germline SMARCA4 and BRCA2 mutations

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ABSTRACT
Small cell carcinoma of the ovary hypercalcemic type (SCCOHT) is a rare and aggressive disease. While classically linked to mutations in SMARCA4, we describe a case in a patient with both SMARCA4 and BRCA2 germline mutations. We describe her disease presentation, histopathology and treatment with adjuvant systemic chemotherapy, interval hyperthermic intraperitoneal chemotherapy, high dose chemotherapy with stem cell rescue, and maintenance with a poly-ADP-ribose polymerase inhibitor (PARPi). Additionally, we share spatial transcriptomics completed on original tumor.

1. Introduction
Small cell carcinoma of the ovary hypercalcemic type (SCCOHT) is a rare and aggressive disease. While classically linked to mutations in SMARCA4, we describe a case in a patient with both SMARCA4 and BRCA2 germline mutations. We describe her disease presentation, histopathology and treatment with adjuvant systemic chemotherapy, interval hyperthermic intraperitoneal chemotherapy, high dose chemotherapy with stem cell rescue, and maintenance with a poly-ADP-ribose polymerase inhibitor (PARPi). Additionally, we share spatial transcriptomics completed on original tumor.

2. Case presentation
A 35-year-old non-Hispanic white obese gravida 4 para 2 with known germline BRCA2 mutation presented to the emergency room for lower abdominal pain and chest tightness for 2 weeks. Computed tomography (CT) of the chest revealed a subsegmental pulmonary embolism in addition to ascites around the liver and spleen. Transvaginal sonography and CT of the abdomen and pelvis was notable for a midline mass measuring $11.3 \times 11.6 \times 10.3$ cm, heterogeneous and inseparable from the ovaries (Fig. 1A). A $2 \times 1.4$ cm aortocaval lymph node was also noted in addition to small volume pelvic ascites. Her serum CA-125 was $1695 (<35)$. Serum calcium was normal. Recommendation was made for primary debulking surgery after a four week delay due to diagnosis of pulmonary embolism, however the patient became increasingly symptomatic, prompting urgent surgical management for both diagnostic and therapeutic purposes.

2.1. Intervention
An exploratory laparotomy, bilateral salpingo-oophorectomy, infracolic omentectomy, right para-aortic lymph node debulking, total abdominal hysterectomy, Argon beam ablation of tumor deposits in the posterior cul-de-sac, and overall optimal cytoreductive surgery with no visible residual tumor was completed. Final pathology demonstrated stage IIIA1(ii) SCCOHT. On post-operative day 10, she required re-operation for evacuation of hemoperitoneum in the setting of therapeutic anticoagulation.
2.2. Pathology

Grossly, the right ovary was replaced by a 17 cm solid, nodular mass without external surface involvement. The heterogeneous cut surface was marbled with areas of black-red hemorrhage, yellow-white gelatinous tissue, and firm, granular foci (Fig. 2A). Hematoxylin and eosin (H&E) histologic sections revealed sheets and cords of monotonous, rounded to polygonal, discohesive cells with eccentric nuclei imparting a rhabdoid/plasmacytoid appearance in the background of extensive myxoid stroma. The nuclei showed prominent nucleoli and vesicular chromatin with high mitotic activity (Fig. 2B). Necrosis was geographically distributed. Occasional follicle-like structures were formed by tumor cells without a definitive epithelial component. SMARCA4 (BRG1) and SMARCA2 (BRM) were lost. Epithelial markers EMA and most keratins (AE1/3, CK7, and CK20) were negative, as was WT-1. Low molecular weight keratin CAM5.2 showed focal expression. SALL4, a transcription factor with a key role in embryogenesis often utilized as a germ cell tumor marker, was weak and patchy (McCluggage et al., 2017). See Table 1 for complete list of staining results.

The final diagnosis was ovarian small cell carcinoma, hypercalcemic type, large cell variant, FIGO stage IIIA1(ii) based on metastatic tumor in five of six para-aortic lymph nodes.

2.3. Genetic testing

Somatic tumor testing revealed the following mutations and alterations: BRCA2 G2748D, ARID1A R1262H, SMARCA4 (NM_003072 deletion intron 6 – intron 8), SMARCA4 I996fs*22. PDL-1 tumor proportion score (TPS) was 5 %. The tumor was microsatellite stable.

2.4. Treatment

Baseline echocardiogram, pulmonary function testing, and nuclear glomerular filtration rate were completed post-operatively. She then underwent 5 cycles of outpatient VPCBAE combination chemotherapy with pegfilgrastim support: vincristine (6 mg/m2), cisplatin (90 mg/m2), cyclophosphamide (1000 mg/m2), bleomycin (15units/m2), doxorubicin (45 mg/m2), and etoposide (200 mg/m2). Cycle 2 was dose reduced by 5 % given neutropenia. Echocardiogram, pulmonary function testing, and nuclear glomerular filtration rate were repeated after cycle 2. Stem cell collection was completed in collaboration with the bone marrow transplant team prior to cycle 3, with adequate collection of cells (>5 × 10^6/kg CD34+ cells). Cycle 3 completed with bleomycin dose reduced to 7.5units/m2 given decrease in her diffusion capacity of the lung for carbon monoxide (DLCO) on pulmonary function testing. On cycle 3 day 10 she was admitted for febrile neutropenia with an absolute neutrophil count of 0, hemoglobin of 5.8 and platelets of 8. Cycle 4 completed with cisplatin reduced 25 % (to 67.5 mg/m2) and etoposide reduced 50 % (to 100 mg/m2). Repeat echocardiogram and pulmonary function tests were reassuring. CT chest abdomen and pelvis was completed after cycle 4 with hypointensening focal lesions in the lesser sac, the aortocaval space, and the right rectus abdominis musculature. Subsequent positron emission tomography was completed with no significant FDG avidity in focal lesions, however there was low level uptake in bilateral external iliac lymph nodes. Right external iliac lymph node biopsy was performed with a nearly acellular sample with rare lymphocytes. Cycle 5 was then completed with the same dosing as cycle 4.

Following comprehensive management recommendations for SCCOHt by Pressey et al (Pressey et al., 2020), our patient subsequently underwent a second look with diagnostic laparoscopy, exploratory laparotomy, peritoneal biopsies and lymph node sampling with hyperthermic intraperitoneal chemotherapy with 100 mg/m2 of cisplatin. There was no appreciable disease on abdominal exploration and final
pathology demonstrated no residual disease in resected specimens. Cycle 6 was completed with a 50% reduction in vinblastine due to grade 2 neuropathy. One month following completion of VPCBAE, she was admitted for high-dose chemotherapy with busulfan 3.2 mg/kg daily for 3 days, melphalan 50 mg/m2 daily for 2 days, and thiotepa 250 mg/m2 daily for 2 days. This was followed by stem cell rescue. Treatment and recovery required a 21-day admission and was followed by recurrent outpatient labs to confirm normalization of counts.

CT scan was completed following treatment with no suggestion of persistent or residual disease. CA-125 was stable at 20. Approximately 3 months later she was started on olaparib maintenance therapy given germline BRCA2 mutation. She continues olaparib with no evidence of disease at the time of writing of this report, 16 months since stem cell rescue.

### 2.5. Spatial transcriptomic analysis

Given the unique nature of this tumor, spatial transcriptomics, an innovative method to understand the transcriptional heterogeneity while preserving spatial context within the tumor microenvironment, was performed (Maynard et al., 2021). The transcriptomic data is publicly available through National Center for Biotechnology Information Gene Expression Omnibus (GSE213699, sample GTFB170; [https://visium-shiny-9hylz00.ondigitalocean.app/](https://visium-shiny-9hylz00.ondigitalocean.app/)). There were 12 distinct clusters defined based on transcriptional profiles (Fig. 3A-B) and the cell type of each cluster was inferred based on existing Cell Type Signature gene sets (GSEA). There were five clusters with an FDR q-value of < 1 × 10⁻⁴ based on hypergeometric overlap, and these include “ovary putative early atretic follicle” (5.17 × 10⁻⁴⁹), “ovary angiogenic endothelial cells” (1.66 × 10⁻²⁹), “pancreatic mesenchymal stromal cells” (2.07 × 10⁻²⁹), “fetal retina fibroblast” (4.32 × 10⁻¹⁵), and “ovary mature smooth muscle cells” (1.42 × 10⁻¹³). Three of the 12 clusters are predicted to be involved in angiogenesis and endothelial cell biology. Two of the 12 clusters are immune-related. Consistent with the histology, SMARCA4 expression was relatively low across all the clusters compared to a SWI/SNF core subunit, SMARCB1 (Fig. 3C-D). Beyond a few sporadic cells, BRCA2 expression was undetectable in all the clusters.

| Table 1 | Immunohistochemical study results. |
|---------|-----------------------------------|
| Positive test result | Negative test result |
| Vimentin | AE1/3 |
| SALL4 (patchy, weak to moderate) | CAM5.2 (focal) |
| SATB2 (weak) | CK7 |
| Synaptophysin (patchy, weak) | CK20 |
| SMARCA4/BRG1* (lost) | EMA |
| SMARCA2/BRM* (lost) | PAX8 |
| WT-1 | p53 (wild-type) |
| p16 (patchy) | INI-1 |
| CD10 | OCT4 |
| SF-1 | Glypican-3 (focal) |
| HepPar (focal) | ERG |
| Calretinin | SOX10 |
| Inhibin | S100 |
| GATA3 | Chromogranin |
| CD34 | CD45 |
| CD99 | Estrogen receptor |
| Mismatch repair proteins (MLH1, PMS2, MSH2, MSH6) | *Performed at the University of California San Francisco (UCSF). All other stains performed at the University of Colorado unless otherwise noted. |

*Table 1: Immunohistochemical study results.*
A targetable vulnerability of SMARCA4-mutated SCCOHT is EZH2 (Wang et al., 2017) which was observed to be expressed in most of the cell clusters apart from “ovarian angiogenic endothelial cells” (Fig. 3F).

### 3. Discussion

SCCOHT is a rare histotype of ovarian carcinoma with the largest report consisting of 293 patients (Witkowski et al., 2016). The median age at diagnosis typically falls between age 20–30; however, cases have been reported between the ages of 1 and 71 (Witkowski et al., 2016; Callegaro-Filho et al., 2016; Young et al., 1994). Sixty percent of patients will present with paraneoplastic hypercalcemia (Karmezis, 2016). Multivariate analyses have demonstrated that tumor stage at diagnosis is the most significant determinant of prognosis (Witkowski et al., 2016). Reports demonstrate a five-year overall survival of 33–55 % in patients with stage I disease (Witkowski et al., 2016; Young et al., 1994) and as low as 10 % in advanced stage patients (Bittin et al., 2014; Harrison et al., 2006). Witkowski et al evaluated determinants of survival and found that after tumor stage, treatment modality was the second most significant factor impacting survival. The addition of high-dose chemotherapy with autologous stem cell rescue improved survival to over 70 % compared to systemic chemotherapy alone (Witkowski et al., 2016). Further, radiotherapy did not appear to alter survival compared to chemotherapy alone (Witkowski et al., 2016).

Given the aggressive nature of this histopathology, adjuvant treatment is recommended regardless of stage at the time of diagnosis. Due to a lack of prospective or randomized data informing specific treatments, a multi-agent regimen is recommended. This patient underwent treatment per Pressy et al with VP/CB: vinblastine (V), cisplatin (P), cyclophosphamide (C), bleomycin (B), doxorubicin (A), and etoposide (E) (Pressy et al., 2020). While limited to small cohorts and case reports, patients undergoing this regime have demonstrated objectively successful outcomes with disease free intervals greater than 5 years (Tewari et al., 1997; Wallbillich et al., 2012). Though this regimen appears effective in our experience, it required dose de-escalation to aid in tolerability in a patient with an otherwise excellent performance status.

Deviating from the traditional course of staging and treatment of patients with ovarian cancer, reports recommend limited diagnostic surgery with neoadjuvant chemotherapy followed by a second look or interval cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) using cisplatin between cycles 4 and 5 (Pressy et al., 2020). Our patient was staged primarily as a high-grade epithelial ovarian carcinoma, given that the diagnosis of SCCOHT was not made on intraoperative frozen section. Identification of SCCOHT on frozen section is often difficult, given the ancillary testing such as immunohistochemistry required for the diagnosis. In our patient’s case, in addition to her optimal primary cytoreduction, the decision was made to proceed with a second look operation with HIPEC between cycles 5 and 6 of VP/CB: following comprehensive management recommendations for SCCOHT by Pressy et al (Pressy et al., 2020).

Germline and somatic mutations in SMARCA4, a tumor suppressor, are hallmark of SCCOHT. SMARCA4 encodes a protein within the SNF/SWI chromatin remodeling complex. Only 0.4 % of SCCOHT tumors demonstrate retained expression of SMARCA4 on immunohistochemistry (Ramos et al., 2014). Our patient had a known BRCA2 germline mutation, with her mother and maternal aunt afflicted with epithelial ovarian cancer at the ages of 54 and 35 respectively. Germline mutations in SMARCA4 in her family are otherwise unknown. To date there is no targeted therapy for tumors that harbor mutations in SMARCA4. In a study of 294 patients with SCCOHT, 26 patients with germline SMARCA4 mutations were diagnosed at a younger age in comparison to those without. Interestingly, of patients diagnosed younger than age 18, the odds ratio of having a SMARCA4 germline mutation was over 20. SMARCA4 germline presence or absence did not appear to alter survival (Witkowski et al., 2016).

Histopathologically, SCCOHT is derived from an unknown cell of origin; “carcinoma” is a misnomer as it is not epithelial derived in the classical sense. In general, tumors are unilateral and grossly lobular. Cut surfaces frequently demonstrate hemorrhage and necrosis intermixed with fleshy viable tumor. On histologic evaluation, small neoplastic cells with high nuclear to cytoplasm ratio are distributed in nests, sheets, and cords with minimal intervening stroma. Follicle-like structures are often present and surround eosinophilic acellular material. Examination of the nuclei reveal prominent nucleoli and brisk mitotic activity. The large cell variant exhibits a predominant population of large rhabdoid cells with abundant eosinophilic cytoplasm and vesicular nuclei encompassed by myxoid stroma. Occasional SCCOHTs contain foci of benign-appearing mucinous epithelium. Antigen expression, highlighted by immunohistochemistry, demonstrate the following patterns: loss of SMARCA4/BRG1, variably positive WT-1, and variably positive EMA which is more often expressed in the large cell variant.

Single cell transcriptomics demonstrate the complexity of this unique SCCOHT tumor microenvironment. In terms of the SWI/SNF remodeling complex, SMARCA4 is clearly downregulated however the relatively high and ubiquitous expression of SMARCB1 suggests that an alternative SMARCA4-dependent SWI/SNF complex is still forming. SWI/SNF function is dependent on its composition, thus the alternative SWI/SNF complex being formed within these tumor cells may represent either a therapeutic vulnerability (Wang et al., 2017) or a mechanism of therapy resistance (Wu et al., 2018). The increased expression of EZH2 has been described in SCCOHT and EZH2 knockdowns and inhibitors in vitro and in vivo, respectively, have shown selective and significant anti-tumor response (Wang et al., 2017). While EZH2 overexpression is not specific to SCCOHT, prior research show there is increased response to EZH2 inhibition in SMARCA4-mutated SCCOHT cells, compared to other ovarian cancer cell lines (Wang et al., 2017). In terms of the identified cell clusters, while there were clusters with clear relationships to ovarian biology, most did not appear to align with previously described cell types. These poorly defined cell clusters possibly represent a novel cell type found within SMARCA4-mutated SCCOHT tumors.

### 4. Conclusions

We present a novel case of small cell carcinoma of the ovary hypercalcemic type in a patient with both SMARCA4 and BRCA2 germline mutations. This is the first case presented with maintenance treatment with a poly-ADP-ribose polymerase inhibitor (PARPI). Transcriptomic analysis of this patient’s tumor is a novel approach to further classify this rare histotype of ovarian cancer to identify unique signatures and potential therapeutic targets.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Author contributions**

BES, BGB and LWB conceived the idea and wrote the manuscript. RW and ED provided pathologic and histologic images and co-wrote the manuscript. BGB, KLW and DG performed spatial transcriptomic sequencing and analysis and co-wrote the manuscript. LK provided genetic expertise and co-wrote the manuscript. JGP contributed clinical expertise to the manuscript.

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**Supplement**

**Supplementary Methods:** Spatial Transcriptomic Analysis

Formalin-fixed paraffin-embedded (FFPE) tumor tissue was
sectioned onto a Visium Spatial Expression Slide (Serial Number: V10D007-67, 10X Chromium) and was visualized via H&E (Fig. 3A). RNA within the tissue was hybridized to barcoded probes (Visium Human Transcriptome Probes, Cat. # PN-1000364). The RNA-probe complexes were collected for library preparation using Visium Spatial Gene Expression Reagents (Cat. #CG000407). Quality of the libraries was confirmed via Bioanalyzer (Agilent) analysis and libraries were sequenced on a NovaSeq (Illumina) instrument in the University of Colorado Genomics Shared Resource. Sequencing files were inputted into the SpaceRanger (version 1.3.0) software to assign the tissue location and gene expression values using the GRCh38-3.0.0 transcriptome and GRCh38-2020-A probe set from 10× genomics.

Raw data generated by Spaceranger were then read into the Seurat Hao et al., 2021 version 4.0.4 R package. Data were normalized using the ‘SCTransform’ function with default values. Dimensionality reduction was run on the spots using ‘RunPCA’. Because each individual spot contains multiple cells, ‘BayesSpace’ Zhao et al., 2021 version 1.0.0 was used to perform deconvolution and identify spots that contained multiple cells. Briefly, ‘spatialPreprocess’ was using the top 2000 highly variable genes and ‘skip.PCA’ set to TRUE. Next, ‘spatialCluster’ was run to cluster the spots using 7 clusters and 33 PCs and gamma set to highly variable genes and ‘skip.PCA’ set to TRUE so only positive markers of each cluster were identified. ‘spatialEnhance’ was run to perform the deconvolution using the same parameters as ‘spatialCluster’. Any spots that had subspots assigned to multiple clusters were removed for the remainder of the analysis. Variable genes were computed after the spots containing multiple cell types were removed. The PCA was recomputed using ‘RunPCA’ from Seurat followed by performing UMAP dimension reduction (‘RunUMAP’ using the top 25 PCs) and clusters were identified (‘FindNeighbors’ using the top 25 PCs followed by ‘FindClusters’ using a resolution of 0.6). Markers for each cluster were identified using ‘FindAllMarkers’ with ‘only.pos’ set to TRUE so only positive markers of each cluster were identified. Transcriptomic data publicly available (GSE213699, sample: GTFB 1170).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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