



## Optimal age for genetic cancer predisposition testing in hereditary *SMARCA4* Ovarian Cancer Families: How young is too young?

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### ABSTRACT

Small cell carcinoma of the ovary, hypercalcemic type is a rare, aggressive, and typically fatal ovarian cancer that primarily affects young women less than 40 years of age. It is caused by a pathogenic variant in the *SMARCA4* gene, with nearly half of patients found to have germline pathogenic variants and the remainder demonstrating somatic *SMARCA4* pathogenic variants. This case report discusses an illustrative case and explores the existing data and potential recommendations to optimize timing of genetic testing in family members, given the presence of a familial germline pathogenic variant.

### 1. Introduction

Ovarian cancer is the second most common gynecologic cancer in the United States. Ovarian cancer traditionally affects older women (mean age at diagnosis of 63) and is epithelial in origin and only 5.3% of ovarian cancers are diagnosed in women younger than 35 years (@NCICancerStats, 2019). Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare and extremely aggressive type of undifferentiated ovarian cancer that predominantly affects young women with a mean age of diagnosis of approximately 24 years (range of 5–46 years) and dismal long-term survival (50% at 1 year). (Callegaro-Filho et al., 2016; Witkowski et al., 2016). SCCOHT is caused by a germline (43%) or somatic (57%) pathogenic variant of the *SMARCA4* gene which is presumed to act as a tumor suppressor gene (Witkowski et al., 2014; 2016). The *SMARCA4* gene, located on chromosome 19p, forms a catalytic subunit with other proteins to make an ATP-dependent switching and sucrose non-fermenting complex (SWI/SNF), which is crucial to gene transcription (Witkowski et al., 2014; Agaimy and Foulkes, 2018). SCCOHT is morphologically and genetically similar to rhabdoid tumors in other organ systems based on microscopic appearance and mutations in members of the SWI/SNF family. These tumors are exceedingly rare, which makes it difficult to determine the optimal management; both surgical and adjuvant

chemoradiation (Agaimy and Foulkes, 2018).

Several studies have shown a grim prognosis for patients with SCCOHT, with recurrence rates as high 75%, regardless of age or stage at diagnosis, and median overall survival of 14.9 months. (Callegaro-Filho et al., 2016; Young et al., 1994) The objective of this case report and review of the literature was to evaluate reported outcome data in this rare tumor and make recommendations for optimal timing of cascade germline genetic testing in families harboring a potential *SMARCA4* pathogenic variant to enable prevention of this deadly cancer.

### 2. Case

A 24 year-old G1P1 presented to the emergency department with abdominal pain, nausea, and diarrhea. A CT scan demonstrated a 23 cm heterogeneous cystic and solid pelvic mass with internal vascularity and multiple contact points with the superior uterus, descending and sigmoid colon, as well as multiple foci along the spleen concerning for metastases (Fig. 1). At the time of presentation, CA-125 was elevated to 280 (normal < 35 U/mL), calcium was elevated at 11.9 (normal 8.5–10.5 mg/dL), LDH was slightly elevated at 279 (normal 125–250 U/L) and CEA, CA19-9, HCG and AFP were normal. She underwent exploratory laparotomy, left salpingo-oophorectomy, optimal tumor

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**Fig. 1.** (A) Coronal contrast enhanced CT image demonstrates a large mass centered in the pelvis with extensive interface with the uterus along the inferior margin of the mass. (B) Axial contrast enhanced CT image of the same mass clearly demonstrates the engorged left gonadal vasculature supporting this tumor.

debulking, omentectomy, and multiple biopsies. Pathology revealed a 1.5 kg solid ovarian tumor composed of sheets of poorly differentiated tumor cells with areas demonstrating follicle-like spaces and foci of tumor cells with a rhabdoid appearance. Immunohistochemical studies revealed focal cytokeratin expression, focal synaptophysin and CD56 expression, and complete loss of BRG-1 (protein product of the SMARCA4 gene) (Fig. 2). These findings confirmed the diagnosis of Stage IIIC small cell carcinoma of the ovary, hypercalcemic type. Of note, PD-L1 was negative with no tumoral or immune cell expression.

The patient's paternal cancer family history was notable for an aunt

who died in her 20 s from ovarian cancer and a grandmother who died in her 30 s from ovarian cancer and several other distant relatives with ovarian cancer diagnosed at unknown ages. However, prior to her cancer diagnosis, the patient had minimal contact with the paternal side of her family and this history was essentially unknown. Genetic testing for 35 genes associated with hereditary predisposition to ovarian cancer confirmed a pathogenic variant in *SMARCA4*, c.1189C > T (p.Arg397\*).

The patient received 4 cycles of adjuvant chemotherapy of carboplatin and etoposide. A CT scan at completion of therapy and at three months showed no definitive evidence of recurrence and calcium, Ca-125, LDH remained normal. At the six month point, she had some abdominal pain, her calcium was elevated and CT scan confirmed widespread and extensive recurrence (Fig. 3). She was subsequently treated with multiple chemotherapy regimens (carboplatin/etoposide, nivolumab/ipilimumab, paclitaxel); however, unfortunately her disease continued to rapidly progress and she died within 4 months of her recurrence and a year from primary diagnosis.

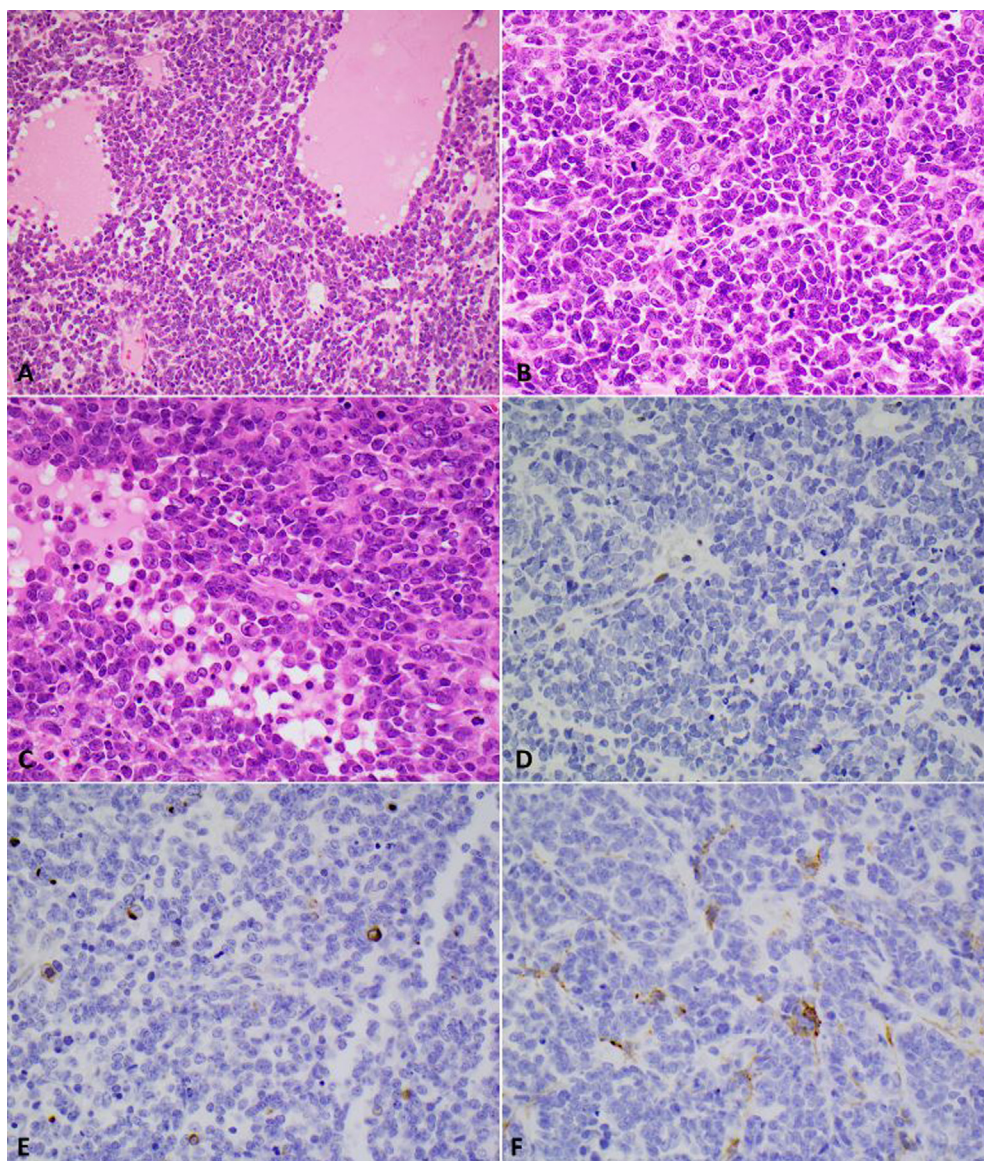
One of the main concerns of the patient and her family was to determine the best time to perform genetic testing in the patient's four year old daughter and what optimal recommendations would be for timing of risk reducing surgery if the familial variant were identified.

### 3. Discussion

Small-cell carcinoma of the ovary, hypercalcemic type is an extremely rare and aggressive type of ovarian cancer with dismal outcomes. While further investigation of the optimal adjuvant chemotherapy options are needed and ongoing, these efforts are hampered by the rarity of this disease. Thus, the best way to improve survival and outcomes would be to identify at risk families and individuals to allow for early intervention with risk reducing surgeries given the high preponderance of germline *SMARCA4* pathogenic variants as the causative factor.

As this cancer affects young women in their 20 s and 30 s, physicians must be more vigilant in identifying at risk individuals/families. Timing of first intervention (e.g. cancer screening) for patients with traditional hereditary breast and ovarian cancer predisposition syndromes is well after age 18 or even age 21 and thus at risk families can wait to allow individuals to make an informed choice as an adult about undergoing genetic testing. For example, in *BRCA1* carriers the earliest recommended intervention is breast MRI at age 25 and surgery to reduce ovarian cancer risk is not recommended before the age of 35. The recommendations for ovarian cancer risk reduction surgery have even been pushed back to 40 or 45 for other deleterious variants (e.g. *BRCA2* and Lynch Syndrome) (Genetic/Familial High Risk, 2019). Yet in a family with a known *SMARCA4* pathogenic variant, waiting for adulthood for genetic testing could miss the window for an effective risk reducing surgery.

*SMARCA4* deleterious variants are so rare that the most updated NCCN publication on Genetic/Familial High Risk Assessment: Breast/Ovarian/Pancreatic guidelines reports that there is insufficient evidence to make any recommendations regarding the time for genetic testing, screening or risk reducing surgery (Genetic/Familial High Risk, 2019). Similar to all genetic diseases, the decision of when to offer genetic testing should be tied to when a specific action (e.g. more intensive screening or treatments to reduce cancer risk) would be recommended and can be implemented. It is well established that current screening modalities for ovarian cancer have not improved outcomes although they can be considered in high risk populations (Genetic/Familial High Risk, 2019; Screening for Ovarian Cancer, 2019). The American Academy of Pediatrics and the American College of Medical Genetic and Genomics have the following opinion, "Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic



**Fig. 2.** Microscopic examination of the large ovarian neoplasm reveals sheets of medium to large pleomorphic tumor cells with areas demonstrating follicle-like spaces, a characteristic morphologic finding often seen in these tumors (A). The tumor cells have irregular nuclear membranes with scant cytoplasm and abundant mitotic figures (B). Some areas demonstrate eccentric nuclei with abundant eosinophilic cytoplasm consistent with a rhabdoid morphology (C). An immunohistochemical stain for BRG-1 (*SMARCA4* protein product) demonstrates complete loss in the tumor cells; a central vessel serves as a positive internal control (D). Focal cyokeratin expression is seen (E), as well as patchy synaptophysin (not pictured) and CD56 neuroendocrine markers (F).

uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.” (Bioethics et al., 2013).

Given that the mean age of diagnosis for women with SCCOHT is 24 years and the range of diagnosis is 5–46 years, a strong argument for prophylactic surgery at an early age can be made. This would necessitate doing genetic testing in at risk women before age 18 to enable both early surgical interventions as well as to allow time for potential fertility preservation in the form of assisted reproductive technology. Some similarities can be made to patients with Swyer syndrome (46, XY gonadal dysgenesis) and Li Fraumeni Syndrome (*TP53* pathogenic variants). Patients with Swyer Syndrome, generally diagnosed as teenagers when they are found to have delayed puberty and amenorrhea, have an increased risk of developing dysgerminoma (Michala et al., 2008). The current recommendation for patients with Swyer Syndrome is gonadectomy at time of diagnosis, usually when they are teenagers; which is younger than the age of majority but after physiologic growth has been completed. (Hughes et al., 2006) In patients with Li Fraumeni Syndrome, the current Clinical Cancer Research recommendations are to begin screening for many of the predisposed-cancers in childhood, as soon as the diagnosis is established, including annual body and brain MRIs. (Kratz et al., 2017)

Surgical intervention for risk reduction in the form of a bilateral salpingo-oophorectomy, for females carrying the deleterious *SMARCA4* variant could be considered after puberty in the teenage years (likely completed by age 18) which would also allow time for fertility preservation if desired while minimizing cancer risks. The potential for such early surgical Intervention would warrant genetic testing between the ages of 9 and 15, a much earlier age than typically recommended for individuals with a hereditary predisposition to developing ovarian cancer. Following testing, referral to reproductive endocrinology for discussion of the potential for oocyte preservation should be offered prior to embarking on surgery. Genetic testing (and potential oocyte retrieval) at such an early age would require informed consent from parents/guardians as well as assent from the child to proceed. We emphasize the importance of a thorough consent and assent process to include a discussion of benefits versus potential harms.

As genetic testing becomes more prevalent and is used to manage disease, difficult conversations and decisions will need to be made for testing offspring of known carriers of pathogenic variants. It is important for patients and their families to have informed discussions with the genetic counselors and oncologists to reach the best decision for each patient.

Written informed consent was obtained from the patient’s mother,



**Fig. 3.** Coronal contrast enhanced CT image demonstrates significant interval increase in tumor burden in the right lower quadrant. Consistent with recurrent tumor.

her next of kin, for this case report.

#### Author contribution statement

Dr. Modesitt was responsible for ideas and coordination. Dr. Podwika performed the chart review, literature review and writing. Dr. Erickson provided the images. Dr. Jenkins provided the slides as well as editing. Ms. Khokhar, MS, provided genetics information as well as editing.

#### Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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