Case report

SMARCA4 germline gene mutation in a patient with epithelial ovarian: A case report

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ABSTRACT

Background: SMARCA4 is a gene whose protein product participates in chromatin remodeling. Somatic mutations in this gene are associated with non-small cell lung cancer and malignant rhabdoid tumors, and both germline and somatic mutations are seen with small cell carcinoma of the ovary, hypercalcemic type. To date, there are no data identifying an association with more common epithelial carcinomas of the ovary.

Case: The patient is a 57-year-old female without any significant family history of cancer, diagnosed with high-grade serous carcinoma of the ovary. Per guideline, she underwent genetic testing, and was found to have a deleterious germline SMARCA4 mutation. She was treated with standard chemotherapy and an optimal tumor reduction, with a complete response to treatment.

Conclusion: The etiology of this patient's high-grade serous carcinoma is unknown. If the SMARCA4 gene plays a role in serous ovarian carcinoma it is with variable expressivity. Further investigation into the role of SMARCA4 as a susceptibility gene for epithelial ovarian cancer is warranted.

1. Introduction

Germline genetic testing has become an invaluable tool in determining the need for prophylactic interventions to prevent disease and determine the utility of targeted agents, such as PARP-inhibitors. While the most common germline aberrations predisposing to ovarian cancer occur in genes BRCA1/2, other more rare genetic mutations also contribute to a woman's ovarian cancer risk. One such gene is SMARCA4. Associated with non-small cell lung cancer and yolk sac tumors, alterations in the function of the SMARCA4 gene product also predispose to small cell carcinoma of the ovary. To our knowledge, there have been no reported cases of a high-grade serous carcinoma in a patient with a germline SMARCA4 mutation. We present here a patient where this was, in fact, the case.

2. Case

The patient is a 57-year-old female with a past gynecologic history of adenomyosis, status post hysterectomy at age 42 for pelvic pain, and 15 years of oral contraceptive use. She was in her usual state of health until she experienced abdominal pain at which time a CT scan of the abdomen/pelvic noted ascites and carcinomatosis. At the time, her CA-125 was found to be 4597. She underwent a diagnostic laparoscopy that revealed confluent carcinomatosis, small bowel mesenteric studding and retraction of the mesentery, and extensive diaphragmatic disease. Pelvic biopsies were performed, with final pathology finding high-grade serous carcinoma of the ovary. She underwent three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel (Fig. 1). She subsequently underwent an exploratory laparotomy, bilateral salpingooopherectomy, supracolic omentectomy, and appendectomy for an optimal tumor reduction to R0 disease. She completed three additional cycles of carboplatin and paclitaxel, and post-treatment imaging noted no evidence of disease. She remains without evidence of disease six months after completion of adjuvant therapy.

The patient had genetic counseling and testing, which consisted of a multigene next generation sequencing panel (NGS) panel. The pedigree obtained at the visit is shown in Fig. 2. The only family history of cancer was lung cancer in her father and a brain tumor in a paternal aunt. No family members had breast, ovarian, endometrial, pancreatic, or colon cancer. Germline testing was significant for a pathogenic mutation at c.4180_4181delGGinsC in the SMARCA4 gene. Multi-gene NGS panel testing was also performed on the tumor obtained from her interval
debulking (Table 1). As expected, there was a mutation in TP53. However, there was also a variant of undetermined significance in the BRCA2 gene at exon 16|T25-42M.

3. Discussion

The SMARCA4 gene is found on chromosome 19p and its product is part of the SWI/SNF (mating type Switching defective/Sucrose Non Fermenting) chromatin-remodeling complex. This product disrupts helicase and ATPase activity, histone-DNA contacts, and can bind BRCA1. Inactivating somatic mutations at this site have been reported in many cancer cell lines, including non-small cell lung cancer and malignant rhabdoid tumors (Medina et al., 2004; Jelinic et al., 2014; Hasselblatt et al., 2014; Schneppenheim et al., 2010). More recently, numerous cases of small cell carcinoma of the ovary, hypercalcemic type have been described with a germline mutation in SMARCA4 expression. Germline truncating mutations in SMARCA4 and somatic loss of the wild-type allele result in loss of SMARCA4/BRG1 protein expression in the tumors (Moes-Sosnowska et al., 2015; Hasselblatt et al., 2011). Both mutations have been found in small cell carcinoma of the ovary, hypercalcemic type, which has been shown to have clinical, molecular, and genetic similarities to rhabdoid tumors (Witkowski et al., 2014). These similarities include large cells with eccentric nuclei and abundant eosinophilic cytoplasm, hypercalcemia, which is present in some rhabdoid tumors, and epithelial to mesenchymal transition. Due to the high prevalence of the SMARCA4 gene mutation in small cell carcinomas of the ovary, hypercalcemic type, the loss of the SMARCA4 protein could play a valuable role as a diagnostic marker in a very lethal disease affecting young women. While there are insufficient data to determine the long-term responsiveness to treatment and therefore overall prognosis in women with small cell ovarian carcinoma, in non-small cell lung cancers, it has been shown that low expression of SMARCA4/BRG1 is associated with increased sensitivity to platinum-based chemotherapy (Bell et al., 2016). If this finding is also true in ovarian carcinomas, the SMARCA4 mutation may confer a survival benefit, much like BRCA.

The role of the SMARCA4 gene product differs from those of BRCA1 and BRCA2, which are more commonly associated with serous ovarian carcinomas; the former plays a role in chromatin remodeling and epigenetics while the latter two play a role DNA repair and tumor suppression. SMARCA4 protein also binds BRCA1 with a dominant negative effect though a study showed that this binding does not affect the efficacy of DNA repair started by BRCA1 (Hill et al., 2004). It has been found that chromatin-modifying genes are characteristic of specific tumors; for example, ARID1A was found to play a role in the pathogenesis of ovarian clear cell carcinoma (Jones et al., 2010). The ARID1A gene is also a part of the SWI/SNF chromatin remodeling complex and has the highest mutation rate among the SWI/SNF subunits (Bitler et al., 2015). A study conducted to find a potential therapeutic target in ARID1A found that inhibiting EZH2 might play a valuable role in combination therapy for ovarian clear cell carcinoma. Targeted therapy has also been studied in SMARCA4 deficient non-small cell lung carcinomas, finding that BRM-ATPase inhibitors suppress BRGA1/SMARCA4-deficient xenografts (Oike et al., 2013). With new therapies targeting specific chromatin-remodeling gene mutations, further study into the prevalence and pathogenesis of SMARCA4 gene in serious ovarian cancer is valuable.

This patient also demonstrated a BRCA2 VUS mutation of exon 16|T25-42M on her somatic testing. BRCA variants of unknown significance play a debated role in cancer risk and clinical outcomes with very little significant data on the exon 16 T25-42M mutation specifically. BRCA VUS frequency varies by ancestry and the majority of germline VUSs found in BRCA screening represent neutral alleles of no or little significance in the etiology of breast cancer (Borg et al., 2010). Somatic BRCA VUSs may play a larger role in the treatment of ovarian cancer with the introduction of PARP inhibitors in the treatment of ovarian carcinomas, the SMARCA4 mutation may confer a survival benefit, much like BRCA.
ovarian cancer, though this has yet to be definitively elucidated (Ledermann et al., 2016).

This patient's family history was not suggestive of a deleterious SMARCA4 mutation. Her father died of lung cancer and, while many lung tumors display loss of SMARCA4, whether the patient's father had a germline or somatic SMARCA4 mutation will never be known (Witkowski et al., 2017). Given the high incidence of lung cancer among American men and the history of smoking and late age of diagnosis, the significance of the father's cancer is unclear. Her paternal aunt died of a brain tumor in her 80s. While deleterious SMARCA4 mutations have been identified in rhabdoid tumors of the brain, these usually occur in the pediatric population (Kerl et al., 2013). It would thus be unlikely that the patient's aunt had a hereditary malignancy due to a SMARCA4 mutation. The patient was recommended to advise her family regarding germline genetic testing, as subsequent generations, if undergone testing.

It has been reported that SMARCA4 mutations do not predispose to epithelial ovarian cancer (Herrera-Mullar et al., 2017). In this case, however, a patient with high-grade serous ovarian carcinoma was found to have a pathogenic SMARCA4 mutation. This finding is of unclear significance in not just the etiology of her disease, but also her prognosis. If the SMARCA4 gene plays a role in serous ovarian cancer, and not just small cell ovarian cancers, it is with variable expressivity. Further studies on the prevalence of this gene mutation in serous ovarian cancers may guide further study of the pathogenesis of this disease, and help determine the clinical value of the SMARCA4 gene in both cancer prevention and treatment.

Patient has provided consent for this manuscript. The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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