Gynecologic Oncology Reports 22 (2017) 45–47

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

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

Reshma Muppala[a], Talia Donenberg[b], Marilyn S. Huang[c], Matthew P. Schlumbrecht[c,*]

[a] University of Miami Miller School of Medicine, Miami, FL, United States
[b] Division of Clinical Cancer Genetics, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, United States
[c] Division of Gynecologic Oncology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, United States

ARTICLE INFO

Keywords:
SMARCA4
Serous ovarian cancer
Susceptibility

ABSTRACT

Background: *SMARCA4* is 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 salpingoopherectomy, 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

* Corresponding author at: Division of Gynecologic Oncology, Sylvester Comprehensive Cancer Center, University of Miami, 1475 NW 12th Ave, Suite 3510, Miami, FL 33136, United States.
E-mail address: mschlumbrecht@miami.edu (M.P. Schlumbrecht).

http://dx.doi.org/10.1016/j.gore.2017.09.010
Received 15 August 2017; Received in revised form 22 September 2017; Accepted 23 September 2017
Available online 28 September 2017

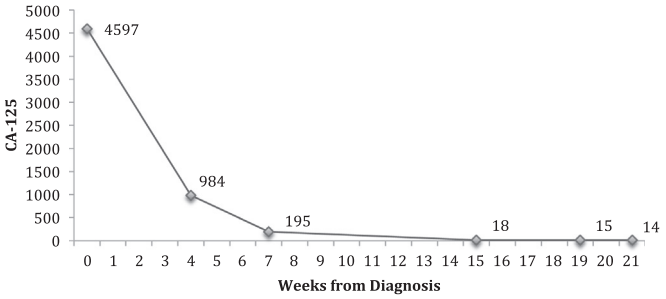

Fig. 1. Patient's CA-125 trend.

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.

Table 1
Patient's somatic tumor testing.

Biomarker	Method	Result
BRAF	NGS	Mutation not detected
BRCA1	NGS	Mutation not detected
BRCA2	NGS	Mutated, variant of unknown significance Exon 16|T25-42M
ER	IHC	Positive|2+, 85%
Her2/Neu (ERBB2)	NGS	Amplification not detected Mutation not detected
PD-L1	IHC	Negative|2+, 1%
PIK3CA	NGS	Mutation not detected
TP53	NGS	Mutated, pathogenic Exon 7|R248W

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-defecient 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 serous 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

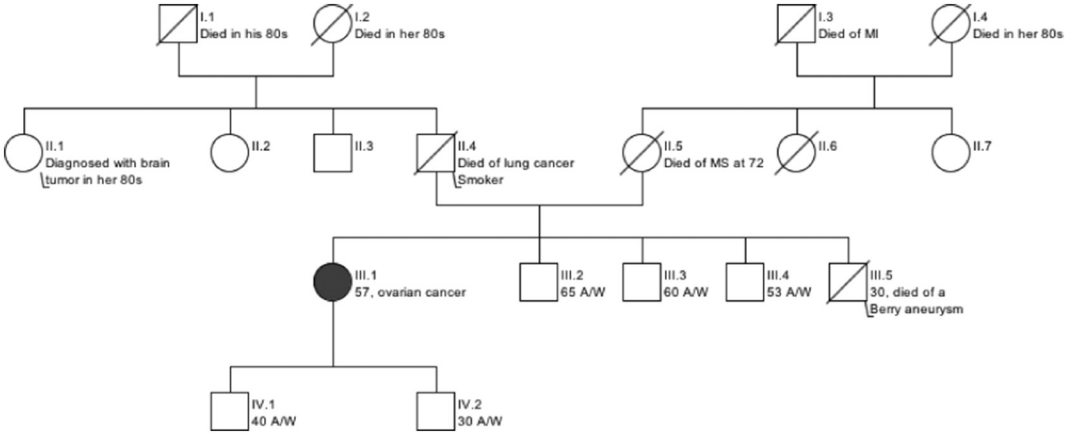

Fig. 2. Pedigree of patient's family medical history. MI—myocardial infarct; MS— multiple sclerosis; A/W— alive and well.

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 born to *SMARCA4* mutation-carrying parents, may be at increased risk for such rhabdoid tumors. To date, no additional family members have 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.

References

Bell, E.H., Chakraborty, A.R., Mo, X., Liu, Z., Shilo, K., et al., 2016 May 15. SMARCA4/BRG1 is a novel prognostic biomarker predictive of cisplatin-based chemotherapy outcomes in resected non-small cell lung cancer. Clin. Cancer Res. 22 (10), 2396–2404.

Bitler, B.G., Fatkhutdinov, N., Zhang, R., 2015. Potential therapeutic targets in ARID1A-mutated cancers. Expert Opin. Ther. Targets 19 (11), 1419–1422.

Borg, A., Haile, R.W., Malone, K.E., Capanu, M., Diep, A., et al., 2010 Mar. Characterization of BRCA1 and BRCA2 deleterious mutations and variants of unknown clinical significance in unilateral and bilateral breast cancer: the WECARE study. Hum. Mutat. 31 (3), E1200–40.

Hasselblatt, M., Gesk, S., Oyen, F., Rossi, S., Viscardi, E., et al., 2011 Jun. Nonsense mutation and inactivation of SMARCA4 (BRG1) in an atypical teratoid/rhabdoid tumor showing retained SMARCB1 (INI1) expression. Am. J. Surg. Pathol. 35 (6), 933–935.

Hasselblatt, M., Nagel, I., Oyen, F., Bartelheim, K., Russell, R.B., et al., 2014 Sep. SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. Acta Neuropathol. 128 (3), 453–456.

Herrera-Mullar, J., Horton, C., LaDuca, H., Castillo, A., 2017 June. Role of SMARCA4 Mutations in Ovarian Carcinoma: Preliminary Data from a Laboratory-based Multigene Panel Testing Cohort. Poster presented at: 2017 Western Association of Gynecologic Oncologists Meeting. (Rancho Mirage, CA).

Hill, D.A., de la Serna, I.L., Veal, T.M., Imbalzano, A.N., 2004 Apr 1. BRCA1 interacts with dominant negative SWI/SNF enzymes without affecting homologous recombination or radiation-induced gene activation of p21 or Mdm2. J. Cell. Biochem. 91 (5), 987–998.

Jelinic, P., Mueller, J.J., Olvera, N., Dao, F., Scott, S.N., et al., 2014 May. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. Nat. Genet. 46 (5), 424–426.

Jones, S., Wang, T.L., Shih, IeM, Mao, T.L., Nakayama, K., et al., 2010 Oct 8. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science 330 (6001), 228–231.

Kerl, K., Holsten, T., Fruhwald, M.C., 2013 Oct. Rhabdoid tumors: clinical approaches and molecular targets for innovative therapy. Pediatr. Hematol. Oncol. 30 (7), 587–604.

Ledermann, J.A., Drew, Y., Kristeleit, R.S., 2016 Jun. Homologous recombination deficiency and ovarian cancer. Eur. J. Cancer 60, 49–58 (PubMed PMID: 27065456).

Medina, P.P., Carretero, J., Fraga, M.F., Esteller, M., Sidransky, D., et al., 2004 Oct. Genetic and epigenetic screening for gene alterations of the chromatin-remodeling factor, SMARCA4/BRG1, in lung tumors. Genes Chromosom. Cancer 41 (2), 170–177.

Moes-Sosnowska, J., Szafron, L., Nowakowska, D., Dansonka-Mieszkowska, A., Budzilowska, A., et al., 2015 Mar 15. Germline SMARCA4 mutations in patients with ovarian small cell carcinoma of hypercalcemic type. Orphanet J. Rare Dis. 10, 32.

Oike, T., Ogiwara, H., Tominaga, Y., Ito, K., Ando, O., et al., 2013 Sep 1. A synthetic lethality-based strategy to treat cancers harboring a genetic deficiency in the chromatin remodeling factor BRG1. Cancer Res. 73 (17), 5508–5518.

Schneppenheim, R., Frühwald, M.C., Gesk, S., Hasselblatt, M., Jeibmann, A., et al., 2010 Feb 12. Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. Am. J. Hum. Genet. 86 (2), 279–284.

Witkowski, L., Carrot-Zhang, J., Albrecht, S., Fahiminiya, S., Hamel, N., et al., 2014 May. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. Nat. Genet. 46 (5), 438–443.

Witkowski, L., Donini, N., Byler-Dann, R., Knost, J.A., Albrecht, S., et al., 2017 Jul. The hereditary nature of small cell carcinoma of the ovary, hypercalcemic type: two new familial cases. Familial Cancer 16 (3), 395–399.