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Case report

Malignant Brenner tumor associated with a germline *BRCA2* mutation

Michael D. Toboni[a,*], Haller J. Smith[b], Sarah E. Dilley[b], Lea Novak[c], Charles A. Leath[b]

[a] University of Alabama at Birmingham, Department of Obstetrics & Gynecology, United States
[b] University of Alabama at Birmingham, Division of Gynecologic Oncology, United States
[c] University of Alabama at Birmingham, Department of Pathology, United States

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1. Background

Germline mutations in *BRCA1* and *BRCA2* account for at least 13% of invasive ovarian cancers, although some studies place their actual incidence closer to 20% (Zhang et al., 2011). Given this high mutation rate, since October 2014 the Society of Gynecologic Oncology (SGO) has recommended offering genetic testing to all patients diagnosed with epithelial ovarian, primary peritoneal, or fallopian tube carcinoma (SGO Clinical Practice Statement, 2014). The National Comprehensive Cancer Network (NCCN) guidelines make the same recommendation (Daly et al., 2016). While the majority of epithelial ovarian cancers associated with germline *BRCA1/2* mutations are high-grade serous carcinomas, other types of epithelial ovarian cancers have been noted to harbor deleterious *BRCA* mutations (Norquist et al., 2016). One rare type of epithelial ovarian cancer is the Brenner tumor, which represents < 1% of all ovarian cancers. The vast majority of Brenner tumors are benign, with malignant Brenner tumor representing < 5% of all Brenner tumors. Malignant Brenner tumor is characterized by atypical transitional cells, squamous or undifferentiated carcinoma with intervening stroma (Han and Soslow, 2011).

In 2013, Kuhn et al. suggested a fallopian tube origin for Brenner tumors based on morphologically identical cilia on the fallopian tube and ovarian surface, as well as a very similar immunohistochemistry profile in the two tissues (Kuhn et al., 2013). Although rare and thus difficult to characterize, fallopian tube cancers are estimated to be forty-eight times higher in *BRCA1* mutation carriers than in the general population (Brose et al., 2002). Furthermore, the fallopian tube has been found to be an important site of epithelial ovarian cancer precursors in women with germline *BRCA1/2* mutations (Kindelberger et al., 2007). Until recently, no identifiable connection had been made between malignant Brenner tumor and a *BRCA1/2* germline mutation; however, in 2016, Norquist identified a *BRCA1* mutation in a patient with malignant Brenner tumor. We present a case of a patient with a malignant Brenner tumor and a deleterious *BRCA2* germline mutation.

2. Case

A 54 year-old Caucasian female para zero originally presented in 2008 with a one-year history of vague gastrointestinal complaints and lower abdominal pain to a local emergency department (ED). The patient's medical history was significant for malignant melanoma in 1997, which was treated with surgical excision and did not require adjuvant therapy. Her family history was significant for colon cancer in her father and brother, as well as gallbladder cancer in her mother. Upon arrival to the ED, a CT scan demonstrated masses lateral to the ascending colon and anterior to the cecum. She underwent an exploratory laparotomy, hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. A postoperative CA-125 was 675 U/ml. Her surgical pathology was reviewed and was consistent with malignant Brenner tumor (Figs. 1 and 2) with immunohistochemical stains, including positive CK7, WT-1, and CA-125, and negative CDX2 and CK20, confirming primary ovary origin (Fig. 3). Negative MART-1 and S100 stains ruled out recurrence of her melanoma.

After her initial tumor cytoreductive surgery, she underwent six cycles of combined intravenous and intraperitoneal platinum and taxane therapy at our institution. After normalization of her CA-125 she remained in clinical remission for four years. After her first recurrence she was treated at an outside institution with two additional tumor reductive surgeries and an additional six cycles of taxane and platinum-based chemotherapy. While being treated for a fourth recurrence in 2016, she was referred to our genetics clinic for testing. Testing demonstrated a pathogenic mutation in *BRCA2*, specifically

* Corresponding author at: University of Alabama at Birmingham, 619 19th Street South, 176F Room 5329, Birmingham, AL 35249, United States.
E-mail address: mdtoboni@uabmc.edu (M.D. Toboni).

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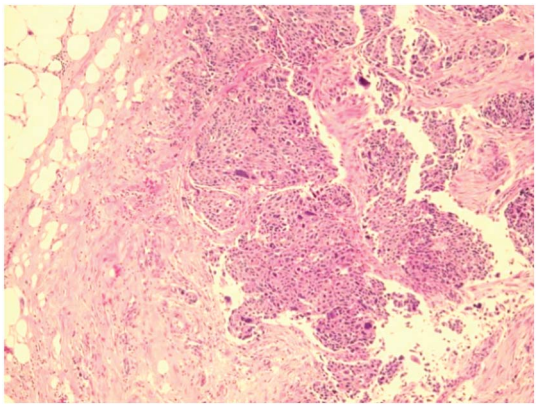

Fig. 1. Malignant Brenner tumor invading into stroma. This tumor had a background benign Brenner tumor – not shown here; 20 × magnification.

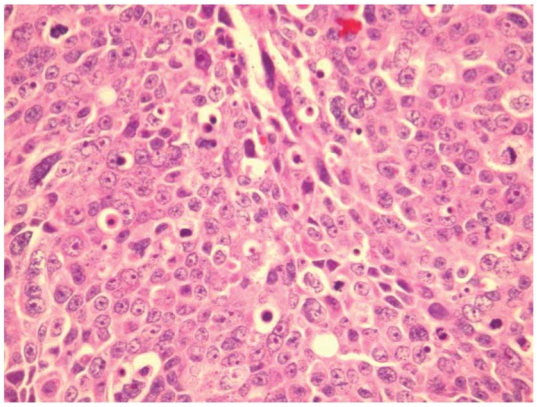

Fig. 2. Malignant Brenner tumor with high grade cytologic atypia and numerous mitoses; 200 × magnification.

c.4965C > G, which is a nonsense mutation that changes a Tyrosine to a premature stop codon and results in loss of function of the *BRCA2* protein. This nonsense mutation is also implicated in prostate cancer and was shown to be associated with a more aggressive phenotype and overall poorer survival in *BRCA2* carriers (Castro et al., 2013). After revelation of the *BRCA2* mutation, treatment with PARP inhibitors was considered but deferred as her current treatment regimen of carboplatin was working to treat her disease.

3. Comment

While individuals with serous epithelial ovarian cancers are more likely to harbor deleterious germline mutations, patients with other histologic subtypes warrant referral for genetic counseling and testing per national guidelines. In 2016, Norquist et al. further classified inherited deleterious mutations in ovarian carcinomas. Of the 1915 women evaluated, a total of 9 had transitional cell carcinomas. Of those 9 cases, one had an associated *BRCA1* mutation, with no cases having a *BRCA2* mutation. Although malignant Brenner tumors are substantially more rare, this mutation rate (11%) is similar to the mutation rate associated with the high-grade serous histology (Norquist et al., 2016). Relationships between the origins of fallopian tube epithelium and Brenner tumors, as well as between *BRCA1/2* mutations and fallopian tube origins of serous carcinoma have been shown. An extensive English literature search was performed to evaluate any previously described connection between *BRCA2* mutations and malignant Brenner tumors. PubMed search terms included *BRCA*, *BRCA1*, *BRCA2*, malignant Brenner tumor, and Brenner tumor, and a review of the references of relevant papers was performed. While one case of malignant Brenner tumor in an individual with a *BRCA1* mutation has been reported, to our knowledge our case represents the first known case of a malignant Brenner tumor associated with a *BRCA2* mutation. Interestingly, this patient also had a case of cutaneous melanoma in 1997, which can also be associated with familial *BRCA2* mutations (Moran et al., 2012).

Despite current guidelines, genetic risk assessment for patients with epithelial ovarian cancer remains underutilized, with some providers still relying more on family history than histology (Febbraro et al., 2015; Lheureux et al., 2016). Patients with uncommon histology or patients who were diagnosed prior to the recommendation for universal testing are likely at higher risk of not having undergone genetic testing. In addition, it is important to note that not all gynecologic oncology patients are taken care of by gynecologic oncologists, and some, especially in rural areas, are cared for by general surgeons. This, in combination with patients having multiple providers can be barriers to guideline adherence. In a 2017 study, Hayden et al. demonstrated that financial concerns were a barrier to proceeding with genetic testing after undergoing genetic counseling. Over 15% of those with private insurance and 36% of those with government-sponsored insurance cited financial concerns as a reason for not obtaining genetic testing. Continued attention for widespread insurance coverage of genetic testing

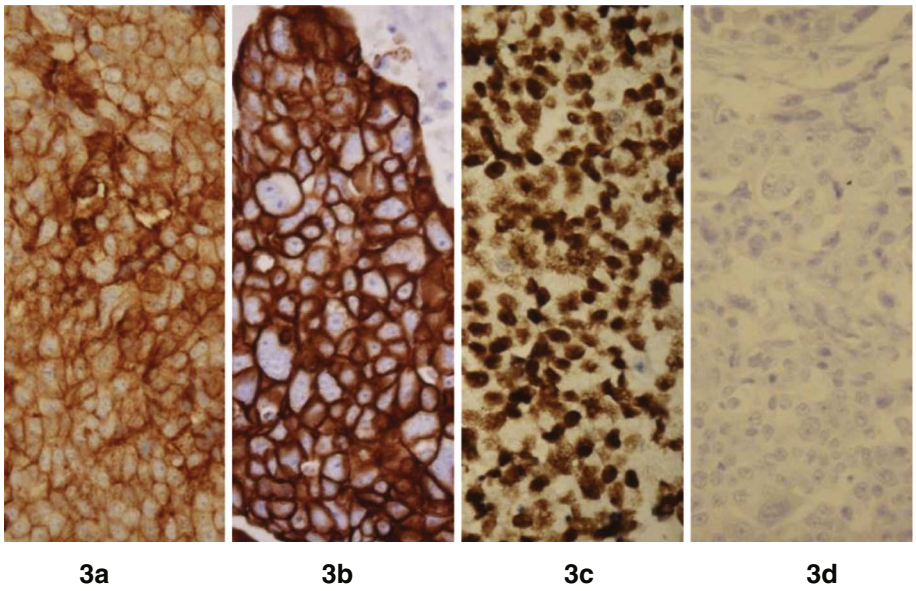

Fig. 3. Immunohistochemical stains were performed to rule out other tumors. CA125 (a), CK7 (b) and WT-1 (c) are positive. CDX2 (not shown) and CK20 (d) are negative. Controls were reactive. The results of the stain support the diagnosis of primary ovarian tumor consistent histologically with malignant Brenner tumor.

for those at high risk for familial cancer remains paramount (Hayden et al., 2017). The testing and discovery of germline *BRCA1/2* mutations for at risk patients is critical for medical decision-making for individual patients as well as their relatives. For the affected patients, the discovery of a harmful mutation may lead to more frequent cancer screening for other malignancies in addition to potential therapy options. Preventive therapies, such as mastectomy or tamoxifen for breast cancer and bilateral salpingo-oophorectomy or oral contraceptive pills for ovarian cancer, have been shown to decrease risk in high-risk populations (Iodice et al., 2010; Phillips et al., 2013; Domchek et al., 2010). For relatives, the knowledge of a deleterious germline mutation may offer the opportunity for enhanced surveillance or prophylactic surgery, which as mentioned above would substantially decrease their risk of developing a cancer in the future.

This finding affirms the recommendation that we should be counseling and testing all patients with non-mucinous epithelial ovarian, fallopian tube, or primary peritoneal cancers for germline mutations regardless of how common or rare the histology. Our finding is supported by the Norquist et al. study demonstrating similar rates of *BRCA1* mutations in high-grade serous carcinomas and malignant Brenner tumors (Norquist et al., 2016). Going forward, especially with the decrease in cost of genetic testing in recent years, a deliberate effort should be made to follow the established recommendation and refer all women with epithelial ovarian cancers for comprehensive genetic counseling and genetic testing.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Disclosures

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