Primary Peritoneal Carcinoma in a BRCA1/2-negative, PALB2-positive patient

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1. Introduction

Primary Peritoneal Carcinoma (PPC) is a cancer of the abdominal peritoneal lining without involvement of the ovaries or identifiable primary tumor. Its estimated annual incidence in the United States is 0.46 per 100,000 women (Goodman et al., 2009). The actual incidence of low-grade serous PPC is much lower (<1/150,000) (Rothacker et al., 1995). Most cases are serous subtype with cellular origin identical to that of epithelial ovarian carcinoma. PPC often mimics ovarian and fallopian tube cancers. It accounts for roughly 10% of ovarian carcinomas that have been presumably misdiagnosed (Rothacker et al., 1995).

Women undergoing prophylactic bilateral salpingo-oophorectomy (BSO) can still develop PPC years later, suggesting that certain epithelial peritoneal cancers do not originate from the ovarian surface. Instead, ovarian epithelial tumors and PPC are hypothesized to share a common embryologic origin with similar germline and somatic mutations. In current literature, nearly all PPC cases have been reported in women with a known BRCA1/2 germline mutation. However, there have been minimal studies on genetic testing outside of BRCA1/2 mutations in patients with PPC. Here, we report a case of a BRCA1/2-negative patient who had undergone prophylactic BSO and presented years later with PPC and was subsequently found to carry a mutation in PALB2.

2. Case report

A 60-year-old nulligravida woman of British descent presented for evaluation of an incidental finding of aortocaval lymphadenopathy. The patient has a history of estrogen receptor positive, poorly differentiated, invasive ductal carcinoma diagnosed at age 51. Her family history is remarkable, ovarian cancer in her mother at age 52, breast cancer at age 80 in a maternal aunt, pancreatic cancer in a maternal cousin at age 60, and a paternal aunt with breast cancer at age 50 (Fig. 1). The patient had previously tested negative for mutations in BRCA1/2. However, due to her family history she underwent a total abdominal hysterectomy with BSO for risk reduction at age 41. The pathology was benign.

An abdominal computed tomography CT without contrast, done initially for renal stone evaluation, demonstrated a 2.9 × 2.6 × 1.5 cm lobulated right retroperitoneal mass anterior to the inferior vena cava at the level of L3–L4 with both hypo-enhancing and cystic components (Fig. 2A). Subsequent positron emission tomography (PET) scan showed a partially calcified 2.3 × 1.3 cm hypermetabolic distal aortocaval lymph node, standard uptake value 6.5 (Fig. 2B). CT guided biopsy showed papillary adenocarcinoma with psammoma bodies. The tumor was positive for CA-125, PAX8, and ER. This immunophenotype and histomorphology were consistent with a serous carcinoma rather than a breast primary.

The patient underwent a robotic lysis of adhesions, right periaortic node dissection, and omentectomy for suspected PPC. Intraoperative findings included a 4 cm right periaortic lymph node and omental adhesions to the upper abdomen. No gross residual disease nor evidence of carcinomatosis were noted. Pelvic washing and omentum pathology were negative for malignancy. The right periaortic lymph node was positive for metastatic papillary carcinoma in a background with numerous psammoma bodies (Fig. 3A, B). Immunohistochemistry demonstrated that the tumor cells were positive for p53 (heterogeneous, “wild-type” pattern), WT1, ER (diffuse, strong pattern) and PAX8 (Fig. 3C, D). The tumor cells showed a low mitotic index and relatively uniform cytomorphology, with <3 times variation in size. Based on the morphologic and immunohistochemical findings, the diagnosis of a low-grade serous carcinoma, of likely peritoneal origin, was established.

Given the patient’s strong personal and family history of cancer, she underwent genetic counseling and further genetic testing for a multi-
gene panel by next generation sequencing and aCGH or MLPA for the following genes: ATM, BARD1, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53, and XRCC2. A pathogenic variant was identified in PALB2, denoted c.3113G > A, and a variant of uncertain significance (VUS) was identified in BRIP1, denoted c.2220G > T.

3. Discussion

The mutation in PALB2 is denoted c.3113G > A (W1038X) and results in a change from tryptophan to a premature stop codon. This mutation has been widely reported in literature and is considered to be a founder mutation originating in the United Kingdom (Southey et al., 2010; Casadei, 2011; Slater et al., 2010). It is shown to produce three different transcripts, all of which are damaging to the protein, either through protein truncation or nonsense-mediated mRNA decay (Casadei, 2011).

The increased risk of breast cancer conferred by truncating mutations in PALB2 has been demonstrated in population-based studies of women with breast cancer (Southey et al., 2010), as well as in family studies (Antoniou et al., 2014). Women with a PALB2 mutation are estimated to have a 2 to 4-fold increased breast cancer risk, with the level of risk dependent on the strength of the family history (Antoniou et al., 2014). Interestingly, the c.3113G > A PALB2 founder mutation is estimated through modified segregation analysis to have a 91% cumulative risk of breast cancer to age 70.

Although an increased risk of pancreatic cancer has been associated with PALB2 mutations, the exact risk has not yet been well established (Slater et al., 2010), an increased risk for ovarian cancer in PALB2 mutation carriers has been proposed as well (Walsh et al., 2011).

It is estimated that one in five ovarian carcinomas are associated with loss-of-function mutations in a tumor suppressor gene (Kanchi et al., 2014). In a study of 360 unselected primary ovarian, peritoneal, and fallopian tube cancer genes, BRCA1 and BRCA2 mutations were detected in 18% of patients and 6% had germline mutations in 10 additional tumor suppressor or DNA mismatch repair genes (Walsh et al., 2011). Among these included PALB2, which co-localizes with BRCA2 in the nucleus, promotes its stability, and facilitates its repair functions (Xia et al., 2006). Thus, mutations in PALB2 disrupt BRCA2 tumor suppression function and predispose carriers to similar cancers.

PPC is a relatively rare classification of serous cancers. A large prospective study of female BRCA1/2-mutation carriers estimated that the risk of PPC in 20 years following prophylactic BSO is 3.9% for BRCA1 mutation carriers and 1.9% for BRCA2 mutation carriers. On average, PPC is diagnosed 6.1 years after surgery and the 5-year survival rate is 38.4% (Finch et al., 2014). The risk of PPC was higher among women who underwent BSO between the ages of 40 and 50 compared to women who underwent BSO before the age of 40. PPC after BSO has also been reported in patients with Lynch syndrome (Schmeler et al., 2010). Of 48 patients with PPC reported in Walsh et al. (Walsh et al., 2011), 13 (27%) carried germline mutations in one of the 12 genes studied. One patient was reported to carry a mutation in PALB2, further implicating PALB2 as an ovarian cancer predisposition gene.

To our knowledge, this is the first report of PPC diagnosed in a woman 19 years post TAH-BSO in a BRCA1/2 negative, PALB2-mutation carrier. Given the rarity of PALB2 mutations and since prophylactic BSO

Fig. 1. Pedigree of family with PALB2 mutation and BRIP1 VUS. Circles = females; squares = males; filled symbols = affected with cancer; slashed symbols = deceased; + = mutation carrier; d. = death, number denotes age, arrow denotes proband.

Fig. 2. (A) Abdominal CT without contrast showing a 2.9 × 2.6 × 1.5 cm lobulated right retroperitoneal mass anterior to the inferior vena cava at the level of L3-L4 with both hypo-enhancing and cystic components. (B) PET scan partially calcified 2.3 × 1.3 cm hypermetabolic distal aortocaval lymph node, SUV 6.5.
is not generally recommended in PALB2 mutation carriers, this adds more information to the mounting data that PALB2 may be a significant risk gene in ovarian cancer predisposition(Daly et al., 2016).

Deleterious germline mutations in BRIP1 are associated with a moderate increase in ovarian cancer risk of 5.8%13. The BRIP1 variant of uncertain significance (VUS) identified in our patient is c.2220G > T, leading to a substitution of glutamine with histidine at codon 740 of the BRIP1 protein (Q740H). This variant was found to be more common in patients with ovarian cancer compared to controls (Ramus et al., 2015). However, the variant that occurs is observed with allele frequencies of 0.1% in the NHLBI Exome Sequencing Project. Therefore, when VUS are identified, patient recommendations should be based on that individual's personal and family history, not the VUS14.

This patient’s presentation of PPC 19 years after prophylactic BSO and BRCA1/2-negative testing raises awareness for the importance of further genetic characterization. As sequencing technologies and medical guidelines continue to advance, testing for a wider array of germline mutations can be critical in today’s clinical practice. With increased availability and rapidly decreasing costs, there are clear advantages to simultaneous multi-gene testing in ovarian cancer patients (Norquist et al., 2016). Multi-gene testing will have an important role in advancing screening strategies to evaluate for carcinoma predisposition (Kanchi et al., 2014). It will improve risk assessment and advance targeted therapy while minimizing unnecessary treatments. Currently, there is minimal literature regarding the association of PALB2 and additional cancer risks such as ovarian, fallopian tube and PPC. More studies are needed to further evaluate the cancer risk spectrum associated with this and other tumor suppressor genes.

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