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Case Report: Co-Existence of BRCA2 and PALB2 Germline Mutations in Familial Prostate Cancer With Solitary Lung Metastasis

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Background: Mutation-caused loss-of-function of factors involved in DNA damage response (DDR) is responsible for the development and progression of ~20% of prostate cancer (PCa). Some mutations can be used in cancer risk assessment and informed treatment decisions.

Methods: Target capture-based deep sequencing of 11 genes was conducted with total DNA purified from the proband’s peripheral blood. Sanger sequencing was conducted to screen potential germline mutations in the proband’s family members. Targeted sequencing of a panel of 1,021 genes was done with DNA purified from the tumor tissue.

Results: Two previously unreported germline mutations in the DDR pathway, BRCA2 (c.8474_8487delCATACCCTATACAG, p.A2825Vfs*15) and PALB2 (c.472delC, p.Q158Rfs*19) were identified in a patient with metastatic PCa. A specific therapeutic regimen including androgen deprivation therapy, locally radical radiotherapy, and systemic platinum chemotherapy worked well against his cancer. In addition, the metastatic ovarian cancer in the proband’s half-sister harboring the same BRCA2 germline mutation also responded well to platinum chemotherapy.

Conclusions: The newly identified germline mutations in DDR plays important role in PCa development. Since specific regimen worked well against this cancer, screening of DDR mutation could provide better management for patients with these mutation-mediated PCa.

Keywords: BRCA2, PALB2, prostate cancer, platinum-based chemotherapy, radiotherapy, case report
INTRODUCTION
Prostate cancer (PCa) is the most prevalent cancer in men and the second leading cause of cancer-related death worldwide. It has been estimated that in the United States there will be 191,930 new PCa diagnoses and 33,330 PCa-related deaths in 2020 (1). Compared with the general population, first-degree relatives of men with PCa have approximately twice the risk of developing PCa (2) and genetic mutations are responsible for ~42% of this disease (3). Genome-wide association studies have identified more than 100 common variants that account for approximately 33% of familial PCa risk (4). Multiple lines of evidence suggest that mutation in genes involved in DNA damage response (DDR) plays a rather important role in cancer development and progression (5–7).

It has been estimated that the mutation of genes in DDR is responsible for at least 19% of localized PCa (6) and 23% of metastatic castration-resistant PCa (7). Proteins encoded by BRCA2, ATM, CHEK2, PALB2, and mismatch repair (MMR) genes including MSH2 and MSH6 play important role in DDR (7). Mutations in some of these genes have already been used for risk assessment and treatment decision-making (8). For example, germline mutation of BRCA usually confers a more aggressive PCa with higher Gleason scores (9), a higher probability of nodal involvement, distant metastasis, and shorter overall survival (10). More importantly, patients with advanced PCa harboring DDR gene mutations generally respond well to poly (ADP) ribose polymerase (PARP) inhibitors and platinum-based chemotherapy (11, 12). The U.S. Food and Drug Administration (FDA) recently approved two poly-ADP ribose polymerase (PARP) inhibitors, olaparib (11, 12), and rucaparib (14), as treatments for patients with metastatic castration resistant adenocarcinoma of the prostate harboring deleterious or suspected deleterious germline or somatic HRR gene-mutations. Therefore, the stratification of PCa patients with mutations in DDR pathway may lead to more informed therapies.

We here report a patient with metastatic PCa carrying previously unreported germline mutations in BRCA2 and PALB2, two important players in DDR. More importantly, this patient responded well to a specific therapeutic regimen including androgen deprivation therapy, locally radical radiotherapy, and systemic platinum chemotherapy. In addition, his half-sister carrying the same BRCA2 mutation with metastatic ovarian cancer responded equally well to platinum chemotherapy.

RESULTS
Case Presentation
The proband is a 48-year-old Chinese male who presented to our department on July 4, 2018 after having hematuria for 2 months. Digital rectal examination found the right lobe of his prostate is hardened with irregularities. Laboratory tests showed a relatively normal level of total serum PSA (prostate-specific antigen, 3.03 ng/ml). Pelvic magnetic resonance imaging (MRI) showed a lesion (3.1 × 4.3 cm) in the peripheral zone of the right lobe of his prostate with a low-intensity signal on T2 weighted imaging (Figures 1A, upper panel). Ultrasound-guided transrectal prostate biopsies were conducted and pathological examination showed prostate adenocarcinoma in 4 of the 14 cores, with an average Gleason score 4 + 4. Computed tomography (CT) chest scan also revealed two small lesions in his right lung (Figures 1B, C, upper panel). Whole body positron emission tomography (PET-CT) scan found hypermetabolic lesions in both his prostate and right side of lung, but not in the bone or other organs. Immunohistochemistry of the lesions from the right lung showed positive staining of PSA and negative staining of CDX-2 and TTF-1 (data not shown). Therefore, his diagnose was a primary PCa with lung metastasis (T2cNxM1c).

Identification of Germline and Somatic Mutations
Given that (i) the relative early-onset and high aggressiveness of cancer, (ii) his father died of lung cancer at the age of 70, and (iii) his half-sister suffered from metastatic ovarian cancer with severe ascites in her early 60s, we decided to screen potential germline mutations. To do so, DNA extracted from the patient’s leukocytes was used for sequencing 11 genes involved in the DDR pathway.

MATERIALS AND METHODS

Patients
All procedures involving human participants were carried out in accordance with ethical standards of the institutional research committee at the Army Medical University in Chongqing, China and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients provided written, informed consent for review of their medical record and sequence of their primary and/or metastatic PCa tissue. The research was conducted with Army Medical University IRB approval.

Abbreviations: DDR, DNA damage response; PCa, Prostate cancer; MMR, mismatch repair; PARP, poly (ADP) ribose polymerase; PSA, prostate-specific antigen; MRI, magnetic resonance imaging; CT, Computed tomography; PET, Positron emission tomography; ADT, androgen deprivation therapy; EBRT, External Beam Radiation Therapy; HR, homologous recombination; DSBR, double strand break repair.
including ATM, BRCA1, BRCA2, MLH1, MLH3, MSH2, MSH3, MSH6, PALB2, PMS1, and PMS2. Two previously unreported germline mutations of BRCA2 (c.8474_8487delCATACCCTATACAG, p.A2825Vfs*15, Figure 2A) and PALB2 (c.472delC, p.Q158Rfs*19, Figure 2B) were identified. These deletions result in the expression of truncated BRCA2 and PALB2. Next, leukocyte DNA was isolated from the other 10 immediate family members of the proband and used for Sanger sequencing of the BRCA2 and PALB2 genes. The characteristics of the family members and their genetic mutations were summarized in Table 1. Based on the pedigree (Figure 2C), we postulated that the proband inherited his mutant BRCA2 allele from his father and the mutant PALB2 from his mother and therefore the proband carries a heterozygous mutation of both BRCA2 and PALB2. We then decided to screen any potential somatic mutations. Total DNA extracted from both his prostate and lung cancer tissues was used to sequence a panel of 1021 genes highly involved in PCa. In addition to the germline mutant BRCA2 and PALB2, 10 and 9 additional somatic mutations were identified in his prostate and lung lesions, respectively (Supplementary Table S2). Of note, the six mutations with the highest frequency (>10%) including PAG1 (c.702A>T, p.K234N), KDM5C (c.1869G>C, p.L623F), CDH11 (c.1048G>A, p.A350T), AFF2 (c.124_141delGATCTC TTCTTCAGGC, p.D42_G47del), FOXA1 (c.753_764delCA ATGTTCGA, p.M253_N256del), and HCLS1 (c.2_7dupTGT GGA, p.M1_W2dup) were identical in both the lung and the prostate lesions. These data strongly suggest that the lesions in his right lung were metastasized from his PCa.

**Treatments and Responses**

The treatment regimen for the proband is shown in Figure 3A. Based on the recommendation from the NCCN guideline for M1

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**TABLE 1 |** The characteristics of the patient and his family members.

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Gender</th>
<th>Age (years old)</th>
<th>Carrying mutations</th>
<th>With Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proband</td>
<td>Male</td>
<td>48</td>
<td>BRCA2 and PALB2</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>His father</td>
<td>Male</td>
<td>Died at 70</td>
<td>BRCA2</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>His mother</td>
<td>Female</td>
<td>80</td>
<td>PALB2</td>
<td>Not yet</td>
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<tr>
<td>His son</td>
<td>Male</td>
<td>16</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>His daughter</td>
<td>Female</td>
<td>19</td>
<td>BRCA2</td>
<td>Not yet</td>
</tr>
<tr>
<td>The proband's half-sister</td>
<td>Female</td>
<td>60</td>
<td>BRCA2</td>
<td>Ovarian cancer</td>
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<tr>
<td>Her son</td>
<td>Male</td>
<td>36</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>The proband’s older brother</td>
<td>Male</td>
<td>54</td>
<td>BRCA2 and PALB2</td>
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</tr>
<tr>
<td>His son</td>
<td>Male</td>
<td>31</td>
<td>BRCA2</td>
<td>Not yet</td>
</tr>
<tr>
<td>The proband’s younger brother</td>
<td>Male</td>
<td>45</td>
<td>PALB2</td>
<td>Not yet</td>
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<tr>
<td>His son</td>
<td>Male</td>
<td>24</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>His daughter</td>
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<td>9</td>
<td>PALB2</td>
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<td>The proband’s sister</td>
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<td>No</td>
</tr>
<tr>
<td>Her son</td>
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<td>Predicted No</td>
</tr>
<tr>
<td>Her daughter</td>
<td>Female</td>
<td>22</td>
<td>Predicted No</td>
<td>Predicted No</td>
</tr>
</tbody>
</table>
castration-naive PCa (15), primary ADT (androgen deprivation therapy) with Goserelin (10.8mg sc 1/3months) started on the date of diagnosis and continued for the rest of the treatment. Between June 29, 2018, and November 20, 2018, six cycles of chemotherapy with the combination of nedaplatin (130 mg, formula: 75 mg/m² × body surface area) and docetaxel (130 mg, formula: 75 mg/m² × body surface area) were administrated. His body surface area was about 1.75 m² based on the formula 0.0061 × height (167 cm) + 0.0124 × weight (60 kg)-0.0099. In addition, EBRT (External Beam Radiation Therapy; 66 Gy/30 F, 2.2 Gy/F) was applied to the local primary PCa between June 4th and June 25th. Only mild adverse events such as slightly reduced leucocyte count were seen during the whole regimen. Workup to evaluate the treatment included the levels of serum PSA and testosterone (Supplementary Table S3), bone imaging, Chest CT and pelvic MRI without contrast. Figure 3B showed that the level of serum testosterone decreased to castrated level 4 months after the beginning of ADT. The levels of serum TPSA became and remained nearly undetectable 5 months after the start of ADT. The concentration of TPSA was 0.01 ng/ml 15 months

FIGURE 2 | Identification of mutations in the proband and his family members. (A, B) Sequencing reads of BRCA2 (A) and PALB2 (B) are shown by the Integrative Genomic Viewer. (C) The pedigree of mutations.

(A) BRCA2 mutation: c.8474_8487delCATAACCTATACAG, p.A2825Vfs*15

(B) PALB2 mutation: c.472delC, p.Q158Rfs*19

(C) Prostate Cancer, 48 year old

Lung Cancer, deceased at 70 year old

Ovarian Cancer, 60 year old

BRCA2

PALB2

?
after the start of the treatment. Pelvic MRI (March 2, 2019) revealed that the prostate volume shrank markedly and the tumor was barely detectable (Figure 1A, bottom panel) 10 months after the start of ADT. Chest CT scans conducted on September 26, 2018 (Figures 1B, C, middle panel) and March 1, 2019 (Figures 1B, C, bottom panel) and PET-CT examination on October 3, 2019 (data not shown) found that the lesions in his right lung disappeared completely. ADT has been continued without any sign of disease progression up to the preparation of this report. In addition and according to the recommendation of the NCCN guideline (16), we have also treated his half-sister’s metastatic ovarian cancer with platinum-based chemotherapy. After six cycles of chemotherapy, her general vital signs including appetite and physical energy improved greatly. More importantly, the ascites disappeared, and the tumors in her ovaries and abdominal cavity did not progress as of the preparation of this report.

**DISCUSSION**

We report in this study a PCa patient carries previously unreported germline mutation of **BRCA2** and **PALB2** and the same **BRCA2** mutation was found in his half-sister who suffered from metastatic ovarian cancer. In addition, the PCa in the proband has also metastasized to his right lung. The DNA sequencing of the proband’s family members showed that the proband’s brother carries the same **BRCA2** and **PALB2** mutations. In addition, six individuals carry either the mutant **BRCA2** (three individuals) or **PALB2** (three individuals) in his first- and second-degree relatives (Figure 2C). The proband underwent ADT and platinum-based chemotherapy as well as local radiation for his PCa, and his half-sister with metastatic ovarian cancer was treated with standard platinum-based chemotherapy. Both patients responded extremely well to the regimens, although the follow-up duration is relatively short. Particularly, the proband was found with an undetectable level of PSA, barely detectable PCa, and totally disappeared lung metastases after the systemic treatments.

Germline mutation in genes involved in Lynch syndrome (**MSH2**, **MSH6**, and **MLH1**) and those in homologous recombination (**BRCA1**, **BRCA2**, **ATM**, **PALB2**, and **CHEK2**) increase not only the incidence but also aggressiveness of multiple cancer types including prostate, breast, and ovarian cancer. Cancers with these mutations usually also have poorer outcomes (17, 18). Consistent with the findings that mutations of genes in the DDR pathway such as **BRCA2**, **PALB2**, and **ATM** play important roles in PCa (19), we report a PCa patient with **BRCA2** and **PALB2** double mutations. Germline **BRCA2** mutations were found in 5.35% of PCa patients from Caucasian (4) and 6.3% from the proband's family.
Chinese population (20). BRCA2 is a protein comprised of 3418 amino acid residues and functions as a scaffold to form a multiprotein complex with Rad51, BRCA1. This complex acts as a caretaker of genome integrity by enabling HR (homologous recombination)-based double-strand DNA break repair and intra-S phase DNA damage checkpoint control. The germline mutant BRCA2 (c.8474_8487delCATACCTATACAG, p.A2825Vfs*15) identified in this research encodes a truncated protein with 2840 amino acid and lack the 578 residuals at its C-terminus. Since the function of BRCA2 is severely affected when the 110 residuals at its C-terminus are lost (21), the truncated BRCA2 identified in the current report likely encode a loss-of-function BRCA2. Previous studies have demonstrated that loss of heterozygosity (LOH) occurred in most of BRCA carriers, including 100% ovarian cancer with germline BRCA1 mutation (22) and 67% PCa with germline BRCA2 mutation (23). Therefore, we evaluated the LOH of BRCA2 and PALB2 in our case by using allele frequency comparisons (22). Based on the HE staining of the biopsy specimens, we estimated the percentage of tumor cells in the biopsy specimens and found that ~80% of the lung biopsy tissue is composed of tumor cells. However, only about 50% of the prostate biopsy sample is tumor cells. We have also noticed that the variant allele frequencies (VAF) of the mutation in both tissues, we showed favorable clinical outcomes to first-line ADT treatments. Although ADT is the gold standard for patients with metastatic PCa, a universally accepted regimen for these kinds of patients is lacking. Based on the report that (i) mCRPC in patients with biallelic mutant BRCA2 responded well to platinum chemotherapy (33) and (ii) localized PCa with mutant BRCA can be treated with radiotherapy effectively (34, 35), we carefully crafted a regimen tailored to the proband (Figure 3A) and the patient responded to the treatment well (Figure 3B). In addition, his half-sister with metastatic ovarian cancer and the same germline mutation of BRCA2 also responded to platinum-based chemotherapies particularly well. Since cells with HR-deficiencies cannot repair DNA-damage efficiently, the cancer cells in the patients reported here would be more prone to chemo- and/or radiotherapy-mediated cancer cell apoptosis (36–38). We do acknowledge that an 18-month follow-up for PCa is too short to make any solid conclusion for the long-term effect of this regimen. The finding reported here are the first of its kind. We believe that longer follow-up and further research on a larger cohort of patients with these mutations will undoubtedly provide a more solid conclusion for the long-term effect of our therapeutic regime. In addition, we could not simply attribute the current therapeutic effect to platinum chemotherapy, because ADT and docetaxel might also result in favorable outcomes during such short follow-up (32). Even so, the therapeutic effect of platinum chemotherapy on this patient should be highlighted. Just as Mark M. Pomerantz et al. showed that carboplatin-based chemotherapy could render better prognosis in patients with BRCA2 germline mutations than those without (39).
although BRCA2 mutations are associated with more aggressive PCa. Given that PARP inhibitor olaparib and rucaparib can improve progression-free survival for mCRPC patients with mutations in DNA-repair genes (11), olaparib and rucaparib could be an alternative treatment for patients with BRCA2 and/or PALB2 mutations. TOPARP-A (11) and TOPARP-B (13) trails have revealed that olaparib, an orally bioavailable inhibitor of the catalytic activity of PARP1 and PARP2, has antitumor activity against metastatic castration-resistant PCa with specific DDR gene aberrations. More recently, the phase II TRITON2 study has found that the PARP inhibitor rucaparib has antitumor activity in mCRPC patients with a deleterious BRCA alteration (14) and specific non-BRCA DDR gene (e.g., PALB2) alteration (40). In addition, additional clinical trials are in progress for talazoparib, velinarib and niraparib (41).

In summary, we identified two previously unreported germline mutations in the DNA double-strand repair pathway, BRCA2 and PALB2 in a PCa patient with solitary lung metastasis but without bone lesion (T2cNxM1c). Since there is no consensus treatment for these patients, we designed a therapeutic regimen including androgen deprivation therapy, systemic platinum chemotherapy and locally radical radiotherapy specifically tailored to his prostate tumor and the patient responded well. These findings support the guidelines and consensus statements from international clinical organizations (42, 43) that recommend DDR mutation screening for the management of particular PCa patients. More importantly, these newly identified mutations in DDR are associated with PCa and can serve as the base for designing personalized treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

REFERENCES


ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Army Medical University IRB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conception/design: JJ and QL. Provision of study material or patients: TT and L-aW. Collection and/or assembly of data: TT, L-aW, PW, DT, GL, and GY. Data analysis and interpretation: JZ, YZ, ND, and JJ. Manuscript writing and revising: TT, L-aW, QL, KG, DZ, and JJ. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.564694/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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