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Case Report

BRCA2 Frameshift Mutation in de novo Small-Cell Neuroendocrine Carcinoma of the Prostate: A Case Report

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Keywords
BRCA2 · Neuroendocrine differentiation · Prostate cancer · Small-cell carcinoma

Abstract
A 66-year-old male was diagnosed with cT4N0M1b small-cell neuroendocrine carcinoma of the prostate. Four months after the administration of combined androgen blockade, multiple novel metastatic regions in the lung and liver and progression of bone metastasis were observed. The patient was referred to our hospital because of biochemical and radiographic progression after four cycles of docetaxel as a first-line therapy for castration-resistant prostate cancer. Transurethral resection of the prostate and hepatic biopsy revealed small-cell carcinoma with positive expression of neuroendocrine markers. The FoundationOne CDx next-generation sequencing test revealed several pathogenic variants, including *BRCA2* (W1692fs*3), *KEAP1* (R320W), and *TP53* (C2385) mutation. After four cycles of chemotherapy with carboplatin plus etoposide (CE), the metastatic regions regressed markedly. The prostate-specific antigen (PSA) and neuron-specific enolase (NSE) level decreased by 96.9% and 91.6%, respectively. However, 2 months after the completion of four cycles of CE, elevation of tumor marker levels, and re-growth of the metastatic regions were observed. Although olaparib, a poly (ADP-ribose) polymerase inhibitor (PARPi), achieved a 45.2% decrease in NSE, the patient rejected to continue therapy because of G2 adverse events. After receiving an additional two cycles of CE and one cycle of cabazitaxel, the patient died because of cancer progression 24 months after the initial treatment for prostate cancer. Here, we present a case of *BRCA2*-altered small-cell neuroendocrine prostate cancer treated with both platinum-containing chemotherapy

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and PARPi. Both therapies achieved an initial response; however, durable responses were not obtained. Additional discussion regarding the optimal treatment strategy for *BRCA*-altered small-cell/neuroendocrine prostate cancer is required.

Introduction

Pure small-cell/neuroendocrine prostate cancer (SCPC/NEPC) is a relatively rare disease with an incidence of 0–2%; moreover, it is an aggressive variant characterized by poor prognosis [1, 2]. Furthermore, the incidence of treatment-related NEPC has been increasing because of the widespread use of androgen receptor (AR) pathway inhibitors [3]. BRCA2 is a key molecule in the homologous recombination DNA repair pathway that causes several cancers, including breast, ovarian, and prostate cancer [4]. A phase III study demonstrated that the poly (ADP-ribose) polymerase inhibitor (PARPi) olaparib improved overall survival in patients with metastatic castration-resistant prostate cancer (CRPC) who had tumors with at least one alteration in the *BRCA1*, *BRCA2*, or *ATM* gene and whose disease had progressed during previous treatment with a next-generation hormonal agent [5]. Furthermore, several studies reported *BRCA*-altered SCPC/NEPC in recent years; however, the exact clinical courses of, and optimal treatment options for those patients remain largely unknown. Here, we reported a case of a patient with de novo SCPC/NEPC carrying a *BRCA2* frameshift mutation who was treated with both platinum-containing chemotherapy and an inhibitor (PARPi). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531134).

Case Presentation

A 66-year-old male with a past history of hypertension and fatty liver presented to another hospital with complaints of dysuria. No familial history of cancer was observed. Digital rectal examination revealed indurations in both robes of the prostate. The serum prostate-specific antigen (PSA) level was 17.6 ng/mL. Transrectal prostate biopsy revealed SCPC/NEPC in two-thirds of the cancerous regions of the prostate, and acinar adenocarcinoma in the residual one-third of the regions (Fig. 1a–c), which as diagnosed a mixture of SCPC and acinar adenocarcinoma. The patient was eventually diagnosed as having cT4N0M1b prostate cancer based on further radiographic examinations. Combined androgen blockade with an LH-RH agonist and bicalutamide at 80 mg was initially administered, and a nadir PSA level of 1.27 ng/mL was achieved at 1 month of therapy. Four months after the administration of combined androgen blockade, multiple novel metastatic regions were observed in the lung and liver, as well as progression of bone metastasis. Despite the subsequent administration of chemotherapy using docetaxel (60 mg/m^2 every 4 weeks, four cycles), progression of lung, liver, and bone metastases as well as novel lymph node metastasis with neuron-specific enolase (NSE) elevation occurred during the administration of docetaxel. The effect of docetaxel administration was considered as progressive disease at 3 months, and the patient was referred to our hospital because of a change in residence. At the time of admission to our hospital, his serum PSA, NSE, progastrin-releasing peptide (proGRP), and testosterone levels were 0.314 ng/mL, 43 ng/mL, 47.9 pg/mL, and <0.07 ng/mL, respectively. Contrast-enhanced

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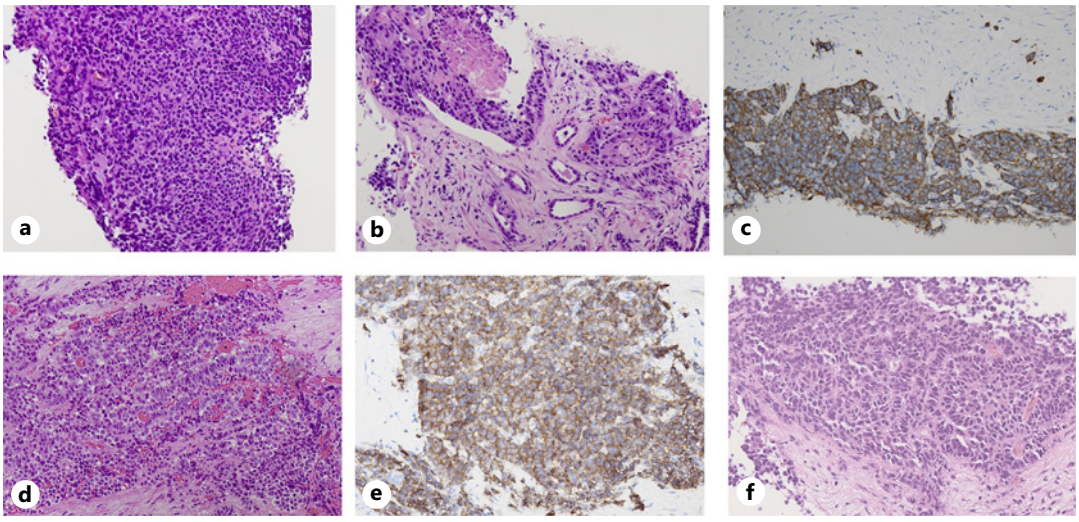

Fig. 1. Histopathological findings of the present case. Prostate biopsy revealed a mixture of small-cell carcinoma (**a**) and acinar (**b**) components of the prostate. Hematoxylin and eosin staining. **c** Immunohistochemistry (IHC) for synaptophysin in the initial prostate biopsy. **d** Prostate tissue resected using transurethral resection (TUR) of the prostate after castration-resistant prostate cancer. **e** IHC for synaptophysin in the TUR specimen. **f** Liver biopsy specimen after CRPC.

computed tomography revealed multiple lung, liver, and lymph node metastases, aggressive progression of bone metastasis, and an enlarged prostate (Fig. 2). The patient underwent transurethral resection of the prostate and liver biopsy for treatment of urinary retention and pathological diagnosis, respectively. The pathological diagnoses of prostate (Fig. 1d, e) and liver tissues (Fig. 1f) were small-cell neuroendocrine carcinoma with positive expression of neuroendocrine markers (including chromogranin A and synaptophysin), suggesting that the primary region of the metastases was the prostate. In immunohistochemistry of tumor tissues, while PSA was partially positive in the initial biopsy of the prostate, it was not expressed in the recurrent prostate tissue or the liver metastasis. A FoundationOne CDx next-generation sequencing test (F1CDx) was carried out using the prostate tissues from transurethral resection of the prostate; the results of the variations found are described in Table 1. Microsatellite instability and high tumor mutation burden (1 mutations/Mb) were not identified, and *BRCA2* (W1692fs*3), *KEAP1* (R320W), and *TP53* (C238S) mutations were detected as pathogenic variants. The molecular tumor board suspected that the *BRCA2* mutation was of germ-line origin, based on the allele frequency (VAF: 0.7306); however, the patient refused further confirmation testing for germ-line *BRCA2*. The time course of the treatment is summarized in Figure 3. The patient was treated with combination chemotherapy with carboplatin plus etoposide (CE; CBDCA, AUC 5, day 1; etoposide, 80 mg/mL, days 1–3) every 4 weeks. After four cycles of this chemotherapy, the metastatic regions regressed markedly (Fig. 2). Moreover, the PSA and NSE levels decreased to 0.330 ng/mL (96.9% decrease relative to the level detected before CE administration) and 8.8 ng/mL (91.6% decrease), respectively (Fig. 3). Nevertheless, 2 months after the completion of the chemotherapy, elevation of tumor marker levels and re-growth of lung and lymph node metastases were observed (Fig. 2, 3). Olaparib (600 mg per day) was then administered according to his mutation signature, as assessed using comprehensive genetic testing. A maximal 45.2% decrease in NSE level without any radiographic progression was observed during the 40 days of administration of PARPi, whereas the PSA increased from 2.044 to 3.986 ng/mL. Because

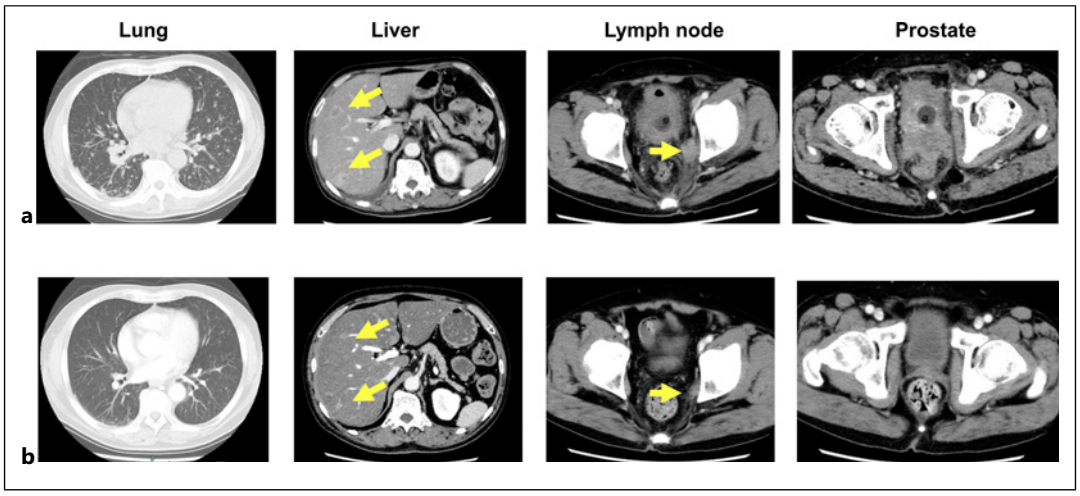

Fig. 2. Longitudinal changes in radiographic findings before and after (4 months) chemotherapy with carboplatin and etoposide or a poly ADP-ribose polymerase inhibitor. CE, carboplatin and etoposide; PARPi, poly ADP-ribose polymerase inhibitor.

Table 1. Observed variations by the FoundationOne CDx gene test

No	Gene	Ref Seq	Variant type	Exon	Mutation (AA)	Mutation (DNA)	Allele frequency
1	BRCA2	NM_000059	Frameshift	N/a	p.W1692fs*3	c.5073_5074insA	0.7306
2	KEAP1	NM_012289	Missense	N/a	p.R320W	c.958C>T	0.3078
3	TP53	NM_000546	Missense	N/a	p.C238S	c.713G>C	0.0086
4	BRIP1	NM_032043	Missense	N/a	p.I952V	c.2854A>G	0.1764
5	CIC	NM_015125	Missense	N/a	p.N702S	c.2105A>G	0.4918
6	MAP3K13	NM_004721	Missense	N/a	p.V72I	c.214G>A	0.1585
7	MST1R	NM_002447	Missense	N/a	p.P411L	c.1232C>T	0.304
8	SDHD	NM_003002	Missense	N/a	p.L77Q	c.230T>A	0.7103
9	TSC2	NM_000548	Missense	N/a	p.R1159W	c.3475C>T	0.4533

the patient suffered from CTCAE grade 2 adverse events, such as anemia, general fatigue, and stomatitis, PARPi was withdrawn based on the patient's preference. An additional two cycles of CE and one cycle of cabazitaxel were not effective. The patient died because of cancer progression 24 months after the initial treatment for prostate cancer.

Discussion

This was the first report of a patient with *BRCA2*-altered small-cell neuroendocrine carcinoma of the prostate who received both platinum chemotherapy and PARPi therapy. Four cycles of initial consecutive CE achieved a near-complete response and a tumor marker decrease >90%, whereas the rechallenge with two-cycle CE followed by PARPi failed to achieve disease control, with progressive disease being detected based on radiographic examinations. Moreover, PARPi administration for 40 days was considered to delay cancer

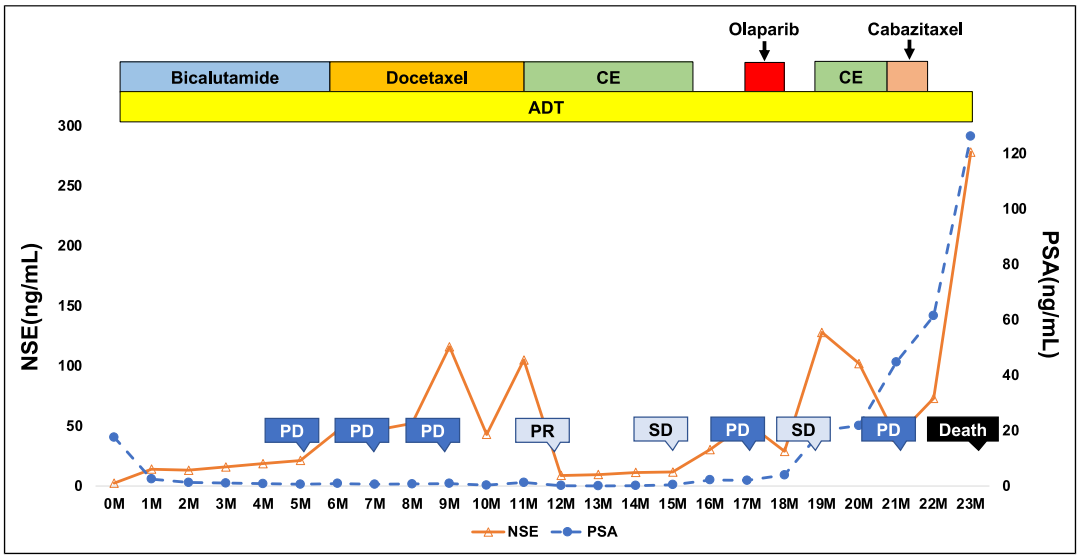

Fig. 3. Clinical patterns with changes in tumor markers and treatment responses. CBDCA, carboplatin; VP16, etoposide; ADT, androgen-deprivation therapy; PR, partial response; SD, stable disease; PD, progressive disease.

progression, with a 45.2% decrease in tumor marker levels; however, the patient refused to continue this therapy because of the presence of grade 2 adverse events.

Several previous studies reported *BRCA2* alterations in patients with neuroendocrine/small-cell carcinoma of the prostate [6–8]. Symonds et al. [6] identified 8 patients (2.3%) with concurrent biallelic *BRCA* inactivation and NEPC/SCPC among 354 patients with prostate cancer who underwent next-generation sequencing via UW-OncoPlex, which assesses the mutation status of over 350 genes, including single-nucleotide variants, small insertions and deletions, gene amplification, and selected gene fusions. Those authors found that 8 (26%) out of 31 patients with NEPC pathology carried biallelic *BRCA2* alterations, which represented a *BRCA2* mutation incidence that was significantly higher than that observed in patients without NEPC (29 out of 323, 9%, $p = 0.003$). Considering these findings together with the results of the present study, the presence of *BRCA2* mutation should be carefully assessed in patients with NEPC/SCPC. Three patients with de novo small-cell carcinoma of the prostate with *BRCA2* alterations were reported previously [6]. That study included two germ-line *BRCA2* mutations and a homozygous *BRCA2* copy loss, with the initial PSA levels ranging from 2.2 to 3.22 ng/mL. Because there is no further information regarding the 3 patients included in that report, additional studies are required to assess the characteristics and clinical outcomes of de novo small-cell neuroendocrine carcinoma of the prostate using a larger number of cohorts.

The optimal treatment sequence for de novo small-cell neuroendocrine carcinoma of the prostate with *BRCA2* alteration remains to be elucidated. A platinum-based chemotherapy has been widely used for NEPC/SCPC, and several regimens, including carboplatin and etoposide, cisplatin and docetaxel, cisplatin, and etoposide and doxorubicin have been proposed [3]. Conversely, genetic alterations of DNA damage repair genes, including *BRCA2*, sensitize tumors to PARPi or platinum chemotherapy [9]. Therefore, it is important to clarify to the best approach regarding the selection of the first-line therapy in patients with *BRCA2*-altered NEPC/SCPC. Slootbeek et al. conducted a retrospective analysis of 71 patients with mCRPC who received platinum chemotherapy. In that study, the authors evaluated the clinical

response to carboplatin and PARPi in a small cohort of the patients treated with the two drugs. All 4 patients with *BRCA2* mutation achieved an initial response of PSA (50% decrease from the baseline) to carboplatin and exhibited a PSA response to subsequent PARPi. In addition, all *BRCA2*-mutated patients had a radiographic response to initial carboplatin, and 3 out of 4 patients had a partial response (PR; based on the RECIST criteria) to PARPi. The authors also performed a literature-based survey of *BRCA2*-altered patients who received PARPi followed by platinum-based chemotherapy. None of the 5 patients, including 2 patients with PRs during PARPi administration, had a response in subsequent platinum-based chemotherapy for the treatment of *BRCA2*-altered CRPC. Therefore, platinum chemotherapy followed by PARPi may be an option; however, the optimal therapeutic sequence should be clarified in future studies in light of the paucity of evidence. Although platinum-based chemotherapy may be an option as a first-line therapy for CRPC in patients with *BRCA2*-altered small-cell neuroendocrine carcinoma of the prostate, novel treatment strategies are required to achieve a durable response.

There are several limitations in this study. First, there is a fact that the impact of other pathogenic variants, such as those of *TP53* and *KEAP1*, on the clinical outcomes was not considered. One of the key features of NEPC/SCPC is an aberrant p53 signaling pathway [3]. The impact of p53 alteration on the response to PARPi among patients with prostate cancer remains unclear, whereas previous studies showed that homozygous *BRCA2* deficiency-induced cell death by activating the p53-dependent checkpoint [10, 11]. Previous studies showed that Kelch-like ECH-associated protein-1 (Keap1) alteration was highly frequent in patients with SCLC-like LCNEC and LCC [12, 13]. Inactivation of Keap1 is known to induce the NF-E2-related factor 2 (Nrf2); in turn, Nrf2 is associated with a master regulator pathway of the antioxidants and cellular stress responses involved in neoplastic progression and resistance of tumor cells against chemotherapy and radiotherapy [14]. The impact of pathogenic variants observed in this study should be investigated in future studies. Second, since we conducted comprehensive genetic testing on just a recurrent tumor in the primary region, clonal differences among tumors from metastatic sites and primary tumor in these patients were not investigated. The impact of the intra-patient heterogeneity on response of each therapy should be assessed in future studies. Finally, we did not confirm germ-line BRCA2 alteration due to his refusal of further genetic testing.

In conclusion, we present a case of *BRCA2*-altered SCPC/NEPC treated with platinum-containing chemotherapy and PARPi. Both therapies achieved an initial response and a 24-month survival based on substantial lines of treatment. Additional discussion of the optimal treatment strategy of *BRCA*-altered NEPC/SCPC is required, while novel biomarkers and treatment options for NEPC-SCPC and PARPi-resistant BRCA2 alteration are warranted.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images because the patient had already died.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

K.O. managed the case, redaction, and correction of the manuscript. S.N., A.K., Y.T., R.Sa., K.M., R.So., H.S., S.K., M.K., R.Y., T.N., K.N., M.S., and T.H. assisted with redaction, correction, and reconstruction of the manuscript. H.N. was responsible for the pathological diagnosis. All authors read and approved the final manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this case report. Further inquiries can be directed to the corresponding author.

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