Case Report

# Prominent response to platinum-based chemotherapy in a patient with *BRCA2* mutant-neuroendocrine prostate cancer and *MDM2* amplification

Tatsuaki Daimon,[1] Takeo Kosaka,[1] Hiroshi Hongo,[1] Eriko Aimono,[2] Kohei Nakamura,[2] Shuji Mikami,[3] Hiroshi Nishihara[2] and Mototsugu Oya[1]

[1]Department of Urology, Keio University School of Medicine, [2]Genomics Unit, Keio Cancer Center, Keio University School of Medicine, and [3]Division of Diagnostic Pathology, Keio University Hospital, Tokyo, Japan

**Abbreviations & Acronyms**
AR = androgen receptor
*BRCA2 = breast cancer susceptibility gene*
CN = copy number
CRPC = castration-resistant prostate cancer
HRR = homologous recombination DNA repair
LOH = loss of heterozygosity
*MDM2 = Murine Double Minute 2*
NEPC = neuroendocrine prostate cancer
PSA = prostate-specific antigen
*RB1 = retinoblastoma 1*
*SPOP = speckle-type bric-a-brac, tramtrack, broad complex/pox virus and zinc finger protein*
VAF = variant allele frequency

**Correspondence:** Takeo Kosaka M.D., Ph.D., Department of Urology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Email: takemduro@gmail.com

**How to cite this article:** Daimon T, Kosaka T, Hongo H *et al*. Prominent response to platinum-based chemotherapy in a patient with *BRCA2* mutant-neuroendocrine prostate cancer and *MDM2* amplification. *IJU Case Rep*. 2021; **4**: 216–219.



Received 11 January 2021; accepted 15 March 2021.
Online publication 5 May 2021

**Introduction:** Genomic profiling provides useful information for diagnosis, treatment, and prognosis, and detection of certain defects, such as DNA repair gene aberrations or microsatellite instability, can possibly lead to optimal treatment, but this testing has not been widely used to inform prostate cancer treatment.
**Case presentation:** A 55-year-old man sequentially treated for prostate cancer was diagnosed as neuroendocrine prostate cancer from prostate specimens resected because of urinary retention. Subsequently, he received five cycles of platinum-based chemotherapy in total and responded well. We also performed next-generation sequencing of a sample from the prostate specimen and identified a *breast cancer susceptibility gene* mutation with *Murine Double Minute 2* amplification and loss of heterozygosity in *retinoblastoma 1*.
**Conclusion:** We report a neuroendocrine prostate cancer patient with *Murine Double Minute 2* amplification who experienced an aggressive course and for whom platinum-based chemotherapy was effective, and one of the reasons for the good response might be the *breast cancer susceptibility gene* mutation.

**Key words:** *MDM2*, *BRCA2*, neuroendocrine prostate cancer, genomic profiling.

## Keynote message

Next-generation sequencing identified a *BRCA2* mutation, *MDM2* amplification, and LOH in the *RB1* gene, although there was no tumor protein p53 mutation. This patient with NEPC was treated with platinum-based chemotherapy and experienced good response to the chemotherapy, and one of the reasons for the good response might be the *BRCA2* mutation. One of genetic features of NEPC is inactivation of p53 and, in this case, p53 was inactivated due to *MDM2* amplification.

## Introduction

Genomic profiling is useful for diagnosis, treatment, and prognosis of various diseases and conditions, such as DNA repair gene aberrations or microsatellite instability, and the information can possibly lead to optimal treatment for cancer patients. However, it has not been widely used to inform prostate cancer treatment. We report a case of an NEPC patient with *MDM2* amplification and LOH in *RB1* who exhibited an aggressive course and responded well to platinum-based chemotherapy.

## Case presentation

The patient was a 55-year-old man who presented to a nearby hospital with a symptom of frequent urination. He had no family medical history. His serum PSA level was 426.9 ng/mL. Pathological analysis revealed prostate adenocarcinoma with a Gleason score of 4 + 5.

Magnetic resonance imaging revealed that the prostate cancer had grown outside of the prostate. Computed tomography and bone scans showed pelvic lymph node swelling and multiple bone metastases at the lumbar vertebra and ilium. Imaging examination revealed stage cT3aN1M1b prostate cancer. Subsequently, the patient underwent androgen deprivation therapy and denosumab. He was sequentially treated with therapeutic agents (Fig. 1a). During cabazitaxel treatment, his PSA level gradually increased, and imaging examination revealed new metastases in the pubic bone and right external iliac lymph nodes (Fig. 1b). Moreover, he then developed urinary retention due to local progression of prostate cancer. Subsequently, he was referred to our hospital for further treatment. First, he received transurethral resection of the prostate to relieve his urinary retention. The pathological diagnosis of the prostate specimens was adenocarcinoma with neuroendocrine differentiation (Fig. 2a). Immunohistochemical analysis showed positivity for synaptophysin, chromogranin A, and androgen receptor, although PSA was only partially positive. However, serum neuron-specific enolase level was within normal limits before the operation.

Therefore, the patient received chemotherapy using carboplatin (area under the curve = 5) with etoposide (100 mg/m$^2$ intravenous infusion on days 1–3). He received five cycles of platinum-based chemotherapy in total. The patient was free from a urothelial catheter, and the prostate volume and lymph node sizes were reduced remarkably on radiography after the chemotherapy (Fig. 1c), and his PSA level gradually went down (Fig. 1a).

In addition, we performed targeted next-generation sequencing of the resected prostate specimen by applying certain algorithms and the list of 160 genes examined (Appendix S1 and Table S1). A *BRCA2* frameshift mutation (p.N2346Qfs*20) with LOH was detected as a pathogenic variant in the tumor. The VAF% in this case was 55.4%; however, this patient did not have a family history, such as of hereditary breast and ovarian cancer or prostate cancer. *MDM2* amplification (estimated CN: 4.6) and *myc proto-oncogene, basic helix-loop-helix transcription factor* amplification (estimated CN: 4.0) were observed. LOH was observed in *RB1* and *Fanconi anemia complementation group A*. The tumor mutation burdens calculated from our pipeline were 5.4 single-nucleotide variants/Mbp in the samples. The CN variation box and VAF plots (Fig. 2b,c) indicated a high LOH frequency and scattered allelic imbalance, which are often detected in homologous recombination-deficient tumors.

## Discussion

Although a variety of new therapeutic agents, such as enzalutamide, abiraterone acetate, and cabazitaxel, are used to treat CRPC patients, only a few CRPC patients achieve remission, and most experience disease progression. Although platinum-based chemotherapy is sequentially not used for the treatment of CRPC, it has been reported to be effective for some CRPC patients. In a systematic review, Leal and García-Perdomo found that platinum-based chemotherapy was effective for patients with CRPC to some extent,[1] and Aparicio *et al.* reported that patients with some variants of CRPC and an atypical and aggressive clinical course were characterized by sensitivity to platinum-based chemotherapy.[2] We have also reported that CRPC patients with genetic alterations, such as *SPOP*[3] and *BRCA2*[4] mutation, showed drastic responses to cisplatin-based chemotherapy. However, there is no

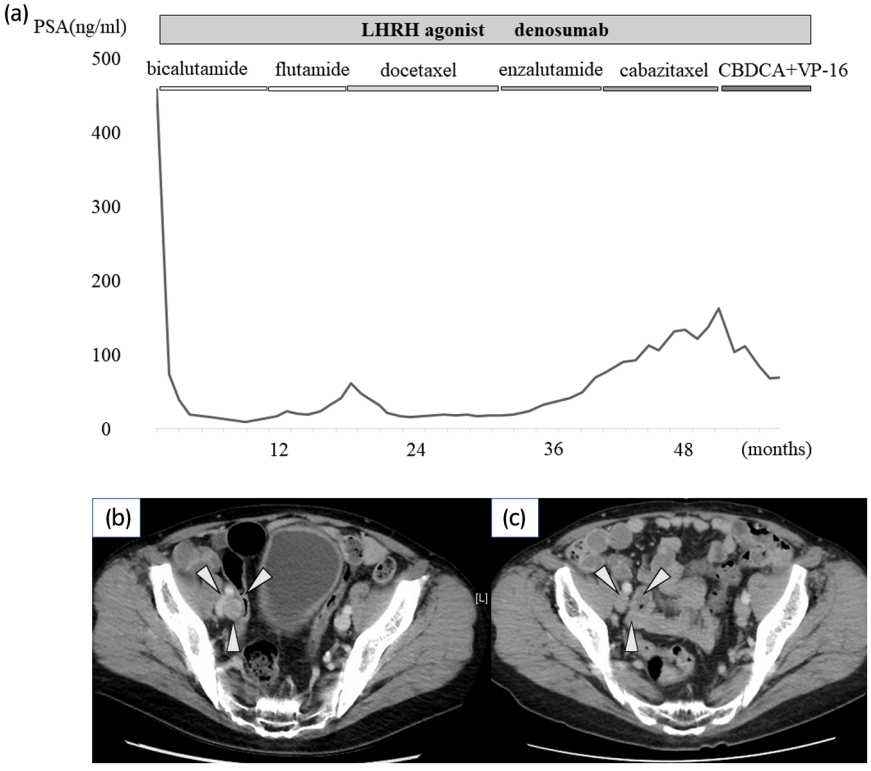


**Fig. 1** (a) The graph illustrates time-course changes in serum PSA levels and therapeutic agents. Computed tomography imaging before (b) and after five cycles of carboplatin (CBDCA) + etoposide (VP-16) chemotherapy (c). The lesions of lymph node metastasis are indicated by triangles surrounding them.

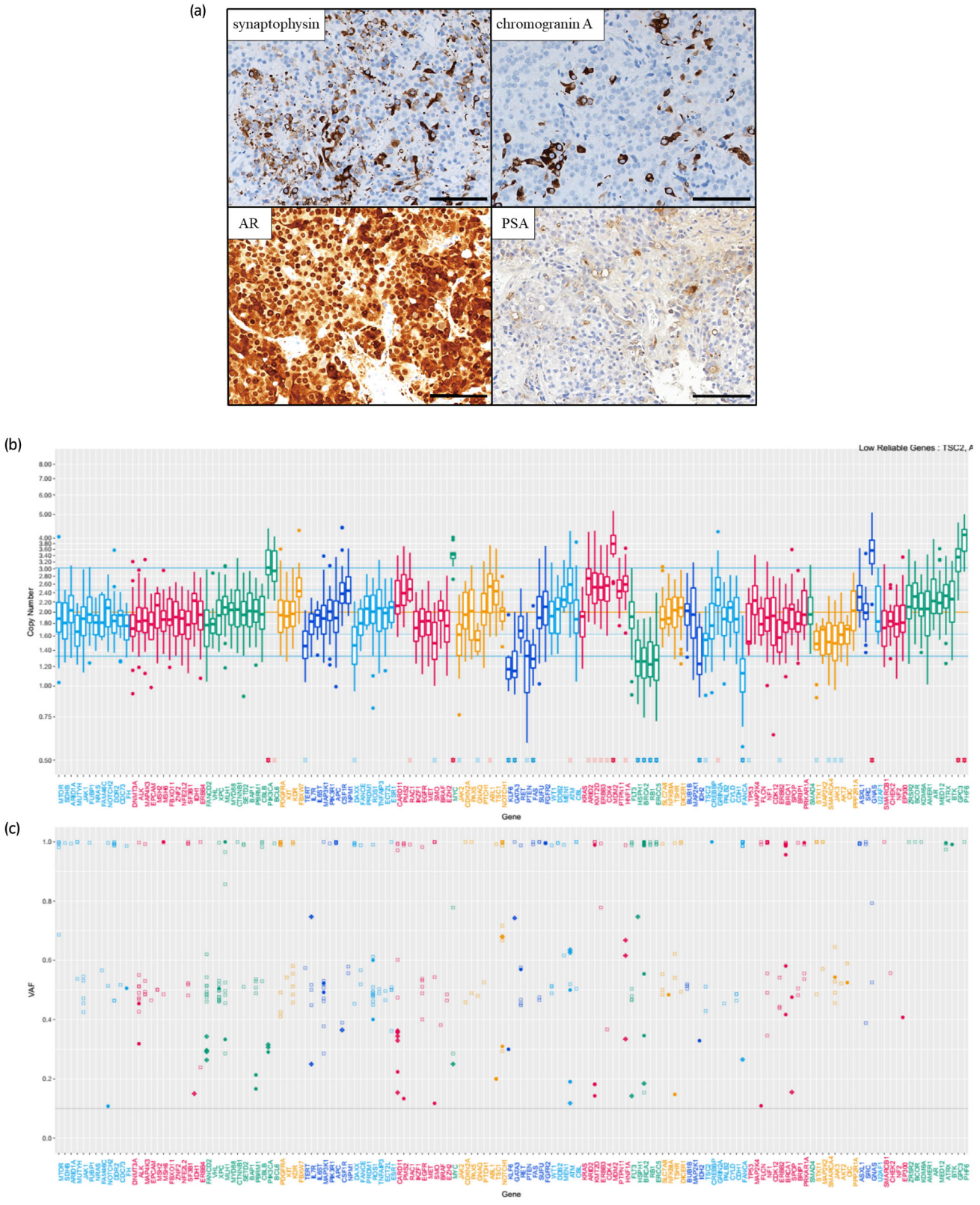


**Fig. 2** (a) Representative images of immunohistochemistry of the transurethral resection of prostate specimens for synaptophysin, chromogranin A, AR and PSA. Bars indicate 100 μm. (b, c) The horizontal axis corresponds to the examined genes, and the vertical axis corresponds to (b) the CN or (c) variant allele frequency.

consensus on what kind of CRPC patients can benefit from platinum-based chemotherapy.

Recently, some studies have shown that DNA repair gene aberrations, such as mutations of *BRCA1/2* and *ataxia telangiectasia mutated*, are biomarkers for the higher likelihood response of platinum chemotherapy and poly(adenosine diphosphate-ribose) polymerase inhibitor. Those genetic mutations are present in 20% of metastatic CRPCs.[5] In this case, a *BRCA2* mutation was identified, and VAF plots (Fig. 2b) indicated the potential of a high LOH frequency and scattered allelic imbalance. Recently, three independent DNA-based measures of genomic instability reflecting underlying tumor HRR deficiency have been developed on the basis of LOH, telomeric allelic imbalance, and large-scale state transitions. However, we could not determine the homologous recombination deficiency score because the relevant test did not undergo, and therefore, could not prove this. However, we can hypothesize that the *BRCA2* mutation results in an HRR deficiency subsequently causes a high LOH frequency and scattered allelic imbalance, which potentially results in a good response to platinum chemotherapy.

Furthermore, some reports have indicated that genetic features of NEPC are inactivation of the RB and p53,[6,7] and some researchers have reported MDM2 as one of the regulators of p53. Overexpression of MDM2 inhibits p53 activity thorough p53 ubiquitination and inhibition of p53 interaction with DNA and leads to tumor progression.[8] MDM2 is upregulated in almost 30% of prostate cancer patients and associated with distant metastasis.[9] However, the association between NEPC and MDM2 has rarely been reported to date. In this NEPC case, next-generation sequencing identified a *BRCA2* mutation, *MDM2* amplification, and LOH in the *RB1* gene, although there was no *tumor protein p53* mutation. In this case, LOH was observed in the *RB1* gene. Thus, we believe that the other allele may be inactivated by *RB1* promoter methylation or epigenetic change, which induced the loss of *RB1* functionality. Genetic analysis suggested that *RB1* inactivation and p53 inactivation due to *MDM2* amplification after sequential treatment could have led to the NEPC of this patient.

Testing DNA alterations and checking those DNA repair gene aberrations might be beneficial to patients with aggressive CRPC from the point of view of precision oncology. In this case, a *BRCA2* mutation had already been detected by genetic testing; therefore, we planned to use a poly(adenosine diphosphate-ribose) polymerase inhibitor after platinum-based chemotherapy. Here, we report an NEPC patient with *MDM2* amplification who experienced an aggressive course and for whom platinum-based chemotherapy was effective because of a *BRCA2* mutation.

## Conflict of interest

The authors declare no conflict of interest.

## References


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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Table S1**. 160 genes examined in the PleSSision-Rapid test.
**Appendix S1**. Materials and methods.

## Editorial Comment

### Editorial Comment to Prominent response to platinum-based chemotherapy in a patient with *BRCA2* mutant-neuroendocrine prostate cancer and *MDM2* amplification

In this issue, Daimon *et al*.[1] reported on the efficacy of platinum-based chemotherapy in patients with neuroendocrine prostate cancer harboring *BRCA2* mutations. Docetaxel administered after progression to castration-resistant prostate cancer (CRPC) initially suppressed disease progression, but prostate-specific antigen (PSA) levels remained constantly elevated during the subsequent administration of enzalutamide and cabazitaxel. Eventually, the patient was pathologically diagnosed as adenocarcinoma with neuroendocrine differentiation. After



 