Case Report

A case of metastatic treatment-emergent small cell/neuroendocrine prostate cancer with *BRCA2* mutation diagnosed by liver biopsy

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Abbreviations & Acronyms
ADT = androgen deprivation therapy
CRPC = castration-resistant prostate cancer
CT = computed tomography
HE = hematoxylin–eosin staining
MRI = magnetic resonance imaging
NEPC = neuroendocrine prostate cancer
NSE = neuron-specific enolase
PARP = poly (ADP-ribose) polymerase
PCa = prostate adenocarcinoma
PSA = prostate-specific antigen
PSMA = prostate-specific membrane antigen
t-SNPC = treatment-emergent small cell/neuroendocrine prostate cancer

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Introduction: Treatment-emergent small cell/neuroendocrine prostate cancer occurs predominantly in advanced or metastatic castration-resistant prostate cancer that arises when prostate adenocarcinoma is transformed after androgen deprivation therapy. The clinical course for the pathogenesis involved or associated genetic information have not been clearly elucidated.

Case presentation: A Japanese male, 63-year-old, underwent a para-aortic lymph biopsy due to sudden severe bilateral leg edema, with a final diagnosis of stage IV prostate adenocarcinoma. He was initially responsive to upfront abiraterone with androgen deprivation therapy; however, relapse occurred in the liver and bone 10 months after initial treatment, with serum neuron-specific enolase elevation and without prostate-specific antigen elevation. Pathological findings of liver tumor revealed treatment-emergent small cell/neuroendocrine prostate cancer. FoundationOne® CDx was used for cancer-related gene profiling of liver tumor specimen; a *BRCA2* mutation was identified.

Conclusion: Early detection of this transformation and pathological diagnosis can improve patient survival when genetic mutations, including *BRCA 1/2*.

Key words: *BRCA2* mutation, castration resistant, treatment-emergent small cell/neuroendocrine prostate cancer.

Keynote message

Especially in Asian country, the clinical course for the pathogenesis involved or associated genetic information of t-SNPC have not been clearly elucidated. A use of PARP inhibitor as a result of FoundationOne CDx® in early stage would likely be promising treatment for this disease in the future.

Introduction

Almost all treatment-naïve PCa initially proliferate depending on androgen receptor signaling. Therefore, the basic treatment strategy for advanced or metastatic PCa has been the deprivation of androgen. However, emergence of CRPC following ADT has been a major clinical problem. NEPC, an aggressive prostate cancer subtype that can arise de novo, accounts for 1% of untreated prostate cancers at diagnosis.[1–4] In addition, recent data described how t-SNPC likely arises after ADT, which transforms ordinary CRPC.[5] t-SNPC is mainly characterized by a low serum PSA level, rapid resistance to treatment, and high tumor metastasis burden that seems to be an aggressive variant of CRPC.[5] For pathological classifications in total PCa with neuroendocrine differentiation, Epstein et al. outlined categories,[6] however, on the transformation to t-SNPC, the analysis of biology or a clinical prognosis of patients according to those categories and clinical data are lacking, and choice of treatment is very limited. We described a case of a patient with t-SNPC, diagnosed by biopsy of liver metastasis, accompanied by a *BRCA2* mutation and review the relevant literature.

Case report

An Asian male, aged 63 years, presented with sudden severe bilateral leg edema. His past medical history included hypertension that was made stable by medication for over 10 years. Abdominal CT showed various lymph node swellings, including in the left subclavian, para-aortic, and intrapelvic regions (Fig. 1a,b). Biopsy of the para-aortic lymph node was performed; histopathological findings revealed a poorly differentiated adenocarcinoma (Fig. 1c). Immunohistochemical staining was positive for AE1/3 (Fig. 1d), PSA (Fig. 1f), and negative staining for TTF1 (Fig. 1e), synaptophysin (Fig. 1g), and chromogranin A (Fig. 1h). The patient was referred to our department since such results indicated the primary tumor occurred in the prostate. The serum PSA level of the patient was 20.3 ng/mL. Various serum tumor markers were within normal range, including NSE. MRI of the prostate showed an indistinct hypo-intensity in the left peripheral zone on T2-weighted images (Fig. 2a) with a focal area of diffusion restriction (apparent diffusion co-efficient 0.63×10^{-3} mm^2/s; Fig. 2b), diagnosed as prostate cancer of PI-RADS-v.2 category 4. MRI-fusion ultrasound-guided prostate biopsy showed PCa with a Gleason score of 4 + 3 (Fig. 2c,d). The final diagnosis was prostate cancer of stage IV (T2N1M1a) with aggravation in the short term. After informed consent, the patient agreed to be treated with a combination of surgical castration and abiraterone acetate. As a result, his serum PSA quickly decreased to 1.34 ng/mL and adverse events did not occur; all lymph node swellings gradually reduced on CT by 4 months after the initiation of treatment.

However, 10 months after the initiation of treatment, serum NSE was elevated to 27.4 ng/mL (normal range: 0–10 ng/mL), without elevation of serum PSA. Furthermore, CT revealed multiple liver nodules (Fig. 3a) and bone metastasis in the fourth lumbar vertebra. Pathological findings of the specimen obtained by biopsy of liver tumor, on HE staining, nests of round to polygonal cells with scant cytoplasm and infiltrated necrosis were observed (Fig. 3b) as shown in Figure 4a. The cells were immunohistochemically positive for PSMA (Fig. 3c), CD56 (Fig. 3d), synaptophysin (Fig. 3e), and negative for chromogranin A (Fig. 3f). Consequently, the patient was diagnosed with t-SNPC, and combination chemotherapy of etoposide and cisplatin was

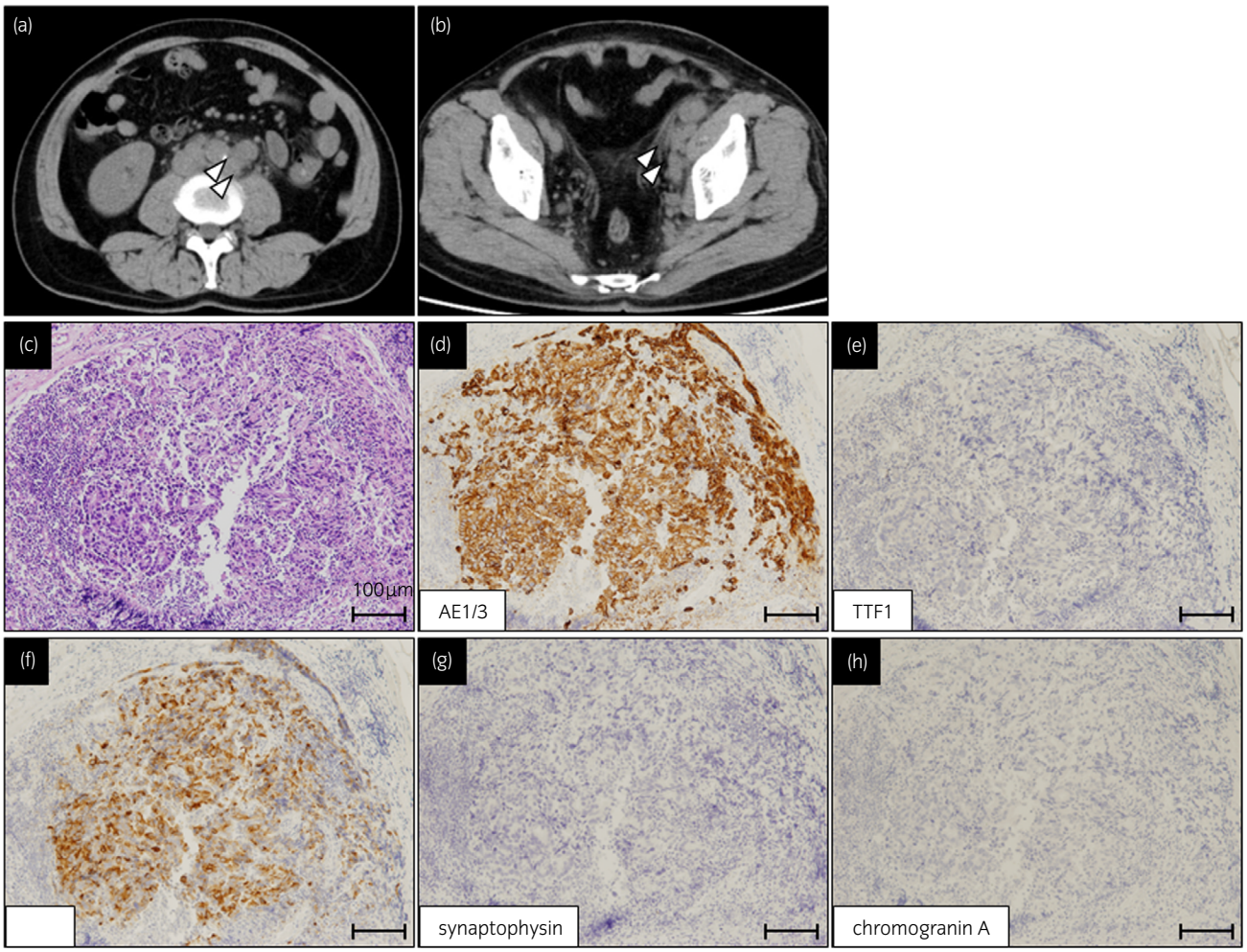

Fig. 1 (a, b) CT revealed multiple lymph node swellings (white arrows). A lymph node was surgically removed and HE (c) revealed a poorly differentiated adenocarcinoma; immunohistochemical staining was positive for AE1/3 (d), PSA (f), and negative for TTF1 (e), synaptophysin (g), and chromogranin A (h).

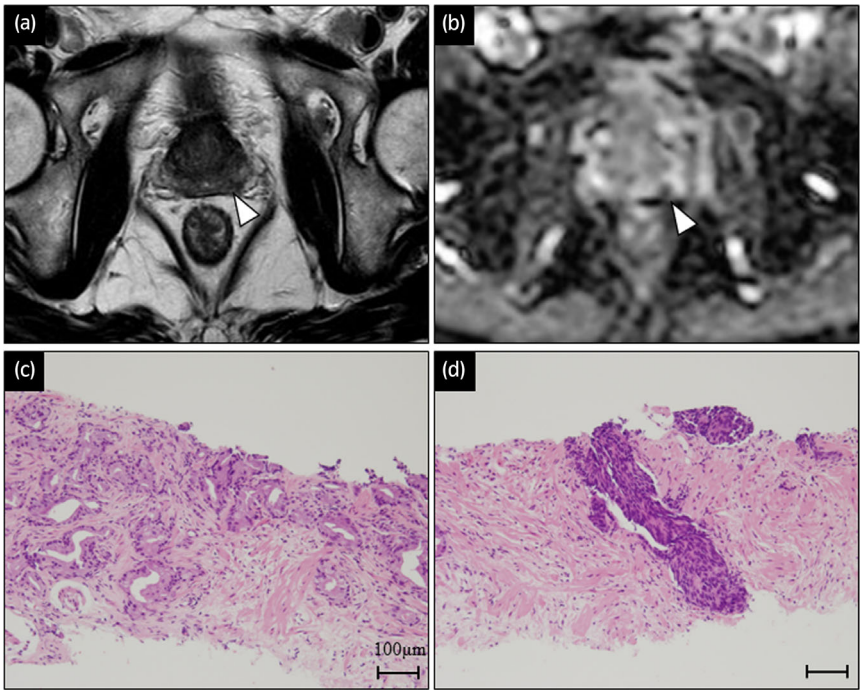

Fig. 2 MRI of the prostate showed an indistinct hypo-intensity in the left peripheral zone on T2-weighted images (a) with a focal area of diffusion restriction (Apparent diffusion coefficient, 0.63×10^{-3} mm^2/s; b), diagnosed as prostate cancer of PI-RADS-v.2 category 4 (white arrow). By MRI-fusion ultrasound-guided prostate biopsy, HE staining of the specimen revealed PCa with a Gleason score 4 + 3 (c, d).

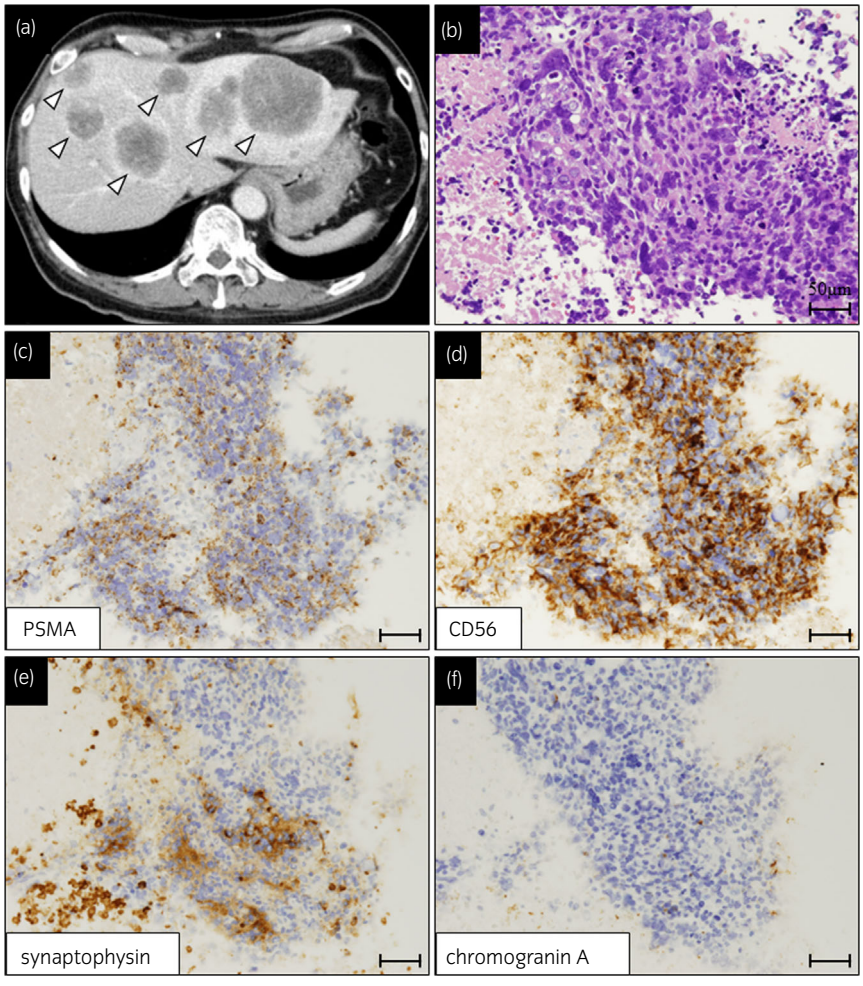

Fig. 3 CT revealed multiple liver nodules (a). Pathological findings of a biopsied specimen from liver tumor revealed t-SNPC in HE (b) that immunostained positive for PSMA (c), CD56 (d), synaptophysin (e), and negative for chromogranin A (f).

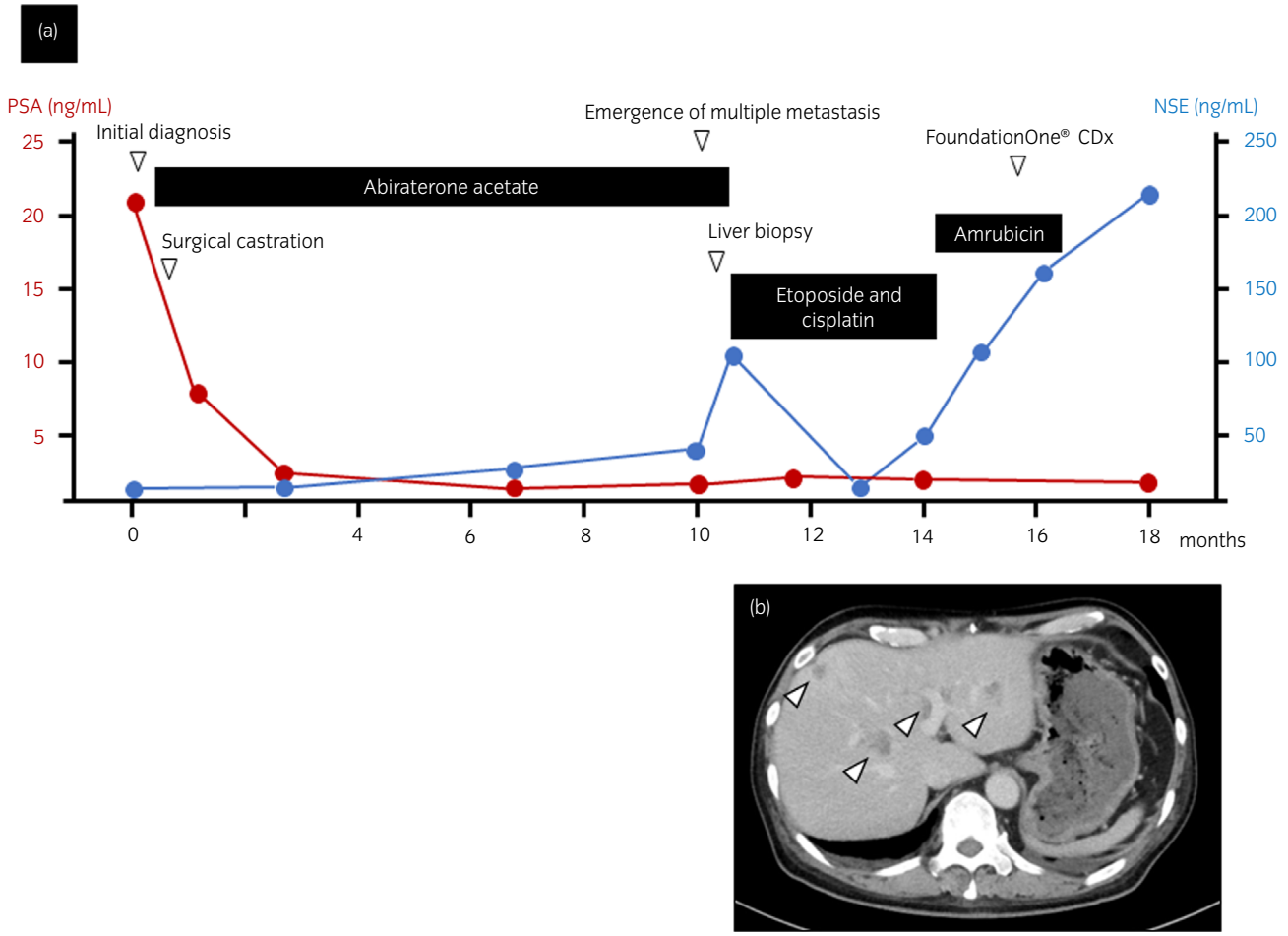

Fig. 4 (a) Clinical course of this case. (b) CT 3 months after initiation of chemotherapy.

administered. The serum NSE levels quickly decreased to a nadir level of 7.9 ng/mL and metastatic sites uniformly reduced (Fig. 4b) at 3 months after the initiation of chemotherapy; however, those increased after seven cycles of treatment. After informed consent, second-line amrubicin treatment was administered but the reduction in tumor growth was insufficient. FoundationOne® CDx (Foundation Medicine Inc, Cambridge, MA, USA) was used for cancer-related gene profiling of a formalin-fixed paraffin-embedded liver tumor specimen that identified a *BRCA2* mutation at H1223fs*9. Considering this result, a PARP inhibitor was promising drug, however, progression of the tumor was very rapid, and finally, the patient died because of cancer-related disseminated intravascular coagulation 10 months after the initiation of first-line chemotherapy.

Discussion

Previous articles in Western countries described how, for patients with NEPC, the combined chemotherapy strategy of etoposide plus cisplatin/carboplatin or amrubicin monotherapy was effective. However, the prognosis for such treatment was less than 1 year, and severe adverse events, including myelosuppression, occurred.[4] Based on further accumulated data as to the prevalence and characteristics of this treatment on emergent differentiation, novel treatment strategies including the genome analysis need to be established.

It became evident that a *BRCA1/2* mutation was a strong risk factor for the development of prostate cancer; PARP inhibitor has recently been made available for such patients on the basis of the excellent PROfound trial.[7] In addition, in searching for a new target gene, recent accumulating evidence describes the molecular mechanisms of NEPC, especially in a Western patient cohort.[5,8] In Aggarwal et al., 202 newly diagnosed patients with prostate cancer, whose consecutive pathological specimens could be evaluated, were prospectively analyzed: The incidence of t-SNPC was found to be 17% (27/160 patients), and 61 genes (including E2F Transcription Factor 1) were identified as being highly expressed in patients with t-SNPC.[5] Furthermore, compared with CRPC without t-SNPC, the presence of mutations in DNA repair genes, including *BRCA1/2*, was significantly lower in patients with t-SNPC (1/12 [8%] biopsy specimens with t-SNPC *vs* 29/73 [40%] without t-SNPC; $P < 0.05$). However, in Asian countries, only two case reports were published describing the existence of the *BRCA* mutation in patients with NEPC or t-SNPC.[9,10] Similar to above patient, a use of PARP inhibitor as a result of FoundationOne CDx® in early stage would be promising treatment for this disease, including for our patient. The underlying relationship

between t-SNPC and *BRCA1/2* mutations should be further clarified in future. In addition, capturing more precise molecular data would allow tracing the molecular evolution of this disease and therefore, hopefully, lead to earlier detection and intervention.

Conclusion

t-SNPC is a very aggressive phenotype and the early detection of this transformation and pathological diagnosis may improve patient survival when genetic mutations, including *BRCA 1/2*, are detected.

AUTHOR CONTRIBUTIONS

Taku Naiki: Conceptualization; data curation; writing – original draft. Aya Naiki-Ito: Conceptualization; writing – original draft. Tatsuya Kawai: Data curation; writing – review and editing. Hirokazu Komatsu: Data curation; writing – review and editing. Ryutaro Nishikawa: Data curation; writing – review and editing. Masakazu Gonda: Data curation; writing – review and editing. Maria Aoki: Data curation; writing – review and editing. Yosuke Sugiyama: Data curation; writing – review and editing. Yoshihiko Tasaki: Data curation; writing – review and editing. Takahiro Yasui: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The ethics committees of Nagoya City University Graduate School of Medical Sciences gave approval for this study (#60-22-0134) and written informed consent was obtained in accordance with the World Medical Association Helsinki Declaration.

Informed consent

Written informed consent was obtained from the patient for publication of this article and accompanying images.

Registry and the Registration No. of the study/trial

Not applicable.

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Editorial Comment

Editorial Comment from Dr Sekino and Dr Hinata to A case of metastatic treatment-emergent small cell/neuroendocrine prostate cancer with BRCA2 mutation diagnosed by liver biopsy

Treatment-emergent small cell/neuroendocrine prostate cancer (t-SNPC) mainly occurs in the advanced or metastatic castration-resistant prostate cancer that is caused by the transformation of prostate adenocarcinoma after androgen deprivation therapy (ADT).[1] t-SNPC is an aggressive disease with a poor prognosis. The ADT treatment is ineffective, and the combined chemotherapy strategy of etoposide plus cisplatin/carboplatin was effective for patients with t-SNPC.[2] Therefore, early diagnosis and treatment play an important role in the survival in the patient with t-SNPC. This case report by Naiki *et al*. showed that metastatic t-SNPC with BRCA2 mutation diagnosed by liver biopsy.[3]

In this case report, the patient was diagnosed as t-SNPC by the pathological findings of liver metastasis. The