A first case of ductal adenocarcinoma of the prostate having characteristics of neuroendocrine phenotype with PTEN, RB1 and TP53 alterations

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Abstract

Background: Ductal adenocarcinoma (DCa) of the prostate is a rare morphologic subtype, occurring in less than 1% and up to 5% in cases of acinar adenocarcinoma (ACa), defined histologically by elongated cells and papillary or cribriform architecture [1–3]. Since DCa often presents at an advanced clinical stage with local or distant metastases and no effective treatment has been established, the prostate-specific mortality is significantly worse than that of ACa [1]. In contrast, neuroendocrine prostate cancer (NEPC) is an extremely rare entity with poor prognosis and limited therapeutic options [4]. The pathological characteristics of NEPC include staining with immunohistochemical markers (CD56, synaptophysin, chromogranin A, and NSE), high proliferative rate (Ki67 > 50%), and the presence of TMPRSS2-ERG rearrangement. Synaptophysin is the most sensitive marker, NSE is also sensitive but not specific, and chromogranin A is the most specific marker [5, 6]. Little is known regarding the genetic and specific histopathological characteristics of DCa and NEPC, and to date, few studies have investigated the genetic profile of these tumors.

Case presentation:

A 63-year-old man presented with gross hematuria and urinary retention, and his serum prostate-specific antigen level was 4.58 ng/mL. We performed transurethral resection of the prostate, and the diagnosis was ductal adenocarcinoma with a Gleason score of 5+4 for acinar adenocarcinoma. Magnetic resonance imaging showed local invasion of left lobe of the prostate and bone metastasis of the left trochanteric section of the femur. Multidisciplinary treatments such as androgen deprivation therapy, chemoradiation therapy, and surgery for metastatic lesions have led to long-term survival. Since next-generation sequencing revealed PTEN and RB1 co-loss and TP53 mutations, we re-evaluated the immunohistochemistry and he was found to be positive for synaptophysin.

Conclusions: This is the first Japanese case of ductal adenocarcinoma with a neuroendocrine phenotype. Genetic analysis may help not only guide the therapeutic strategies, but also sometimes with the diagnosis.

Keywords: Ductal adenocarcinoma, Neuroendocrine prostate cancer, Next-generation sequencing, Case report
Therefore, the accumulation of case reports and genetic or histopathological analyses is expected to add to our understanding to this disease entity. Herein, we report a case of a DCa mixed with ACa with a neuroendocrine phenotype.

**Case presentation**

A 63-year-old man presented with gross hematuria and urinary retention. He had no remarkable medical or family history. His serum prostate-specific antigen (PSA) was 4.58 ng/mL, and urine cytology was class 3 (atypical urothelial cells). Since cystoscopy revealed a papillary tumor in the prostatic urethra, we performed transurethral resection of the prostate. The pathological diagnosis was poorly differentiated adenocarcinoma with Gleason score of 5 + 4 = 9 with DCa (Fig. 1). Magnetic resonance imaging showed local invasion of the left lobe of the prostate and bone metastasis of the left trochanteric section of the femur (Fig. 2). Although he was treated with androgen deprivation therapy (ADT), 10 months later, the disease became castration-resistant prostate cancer. At this point, the PSA level was 3.66 ng/mL and serum NSE was 9.6 ng/mL. Then, we administered three courses of docetaxel (75 mg/m²) as the second-line therapy. Since the serum PSA level was decreased to 0.54 ng/mL, the patient was treated with a combination of 160 mg of enzalutamide and intensity-modulated radiation therapy (IMRT) consisting of 78 Gy administered in 39 fractions for the prostate and 40 Gy administered in 14 fractions for the left femur as the third-line therapy, which decreased the PSA level to be nadir of 0.03 ng/mL. After the combination therapy, enzalutamide was continued for 13 months, and when the serum PSA increased to 0.35 ng/mL, four courses of cabazitaxel (25 mg/m²) were administered as the fourth-line therapy. Despite multimodal therapy, positron emission tomography/computed tomography (PET/CT) showed viability of the left trochanteric section of the femur. Thus, we performed left femoral head replacement, and we confirmed the absence of viable cancer cells pathologically. After 1 year, he was treated with local radiation of 60 Gy administered in 25 fractions because the PSA level increased to 0.76 ng/mL and pelvic lymph node metastasis was noted. At this point, we performed targeted genome sequencing of the tumor specimen from the transurethral resection and re-evaluated the immunohistochemistry findings. We identified *PTEN* p. R233fs*10, *RB1* loss exons 18–27, and *TP53* p.R249G mutations by genome sequencing (Table 1), and the patient was found to be positive for synaptophysin by immunohistochemistry (Fig. 1F). Currently, he is undergoing chemotherapy with cabazitaxel, and his PSA/NSE level was around 0.20/9.0 ng/mL.

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Fig. 1 Representative images of A hematoxylin and eosin staining and B PSA, C loss of PTEN, D loss of RB1, E TP53 and F synaptophysin immunohistochemical staining of transurethral resection of prostate specimens. Bar = 0.1 mm
Discussion and conclusions

Patients with metastatic ACa are currently best treated with palliative drug treatments, such as ADT plus androgen receptor-targeted agents or chemotherapy [7]. Recent studies have demonstrated that early detection and aggressive treatment of metastatic lesions with surgery or radiation therapy appears to be a feasible strategy in patients with newly diagnosed oligometastatic ACa [8–10]. On the other hand, DCa has no established treatment strategy, and palliative ADT or chemotherapy alone cannot be expected to have a long-term prognosis even though a significantly greater frequency of men with DCa had local or distant metastasis at diagnosis. In our case, the patient was aggressively treated with ADT and chemotherapy with IMRT and local radiation therapy, while the initial diagnosis was a DCa with a Gleason score of 5 + 4 = 9 of ACa and bone metastasis. When PET/CT revealed revitalization of the left trochanteric section of the femur, we decided to perform the operation and confirmed the absence of viable cancer cells. Based on these aggressive multidisciplinary treatments made for the long-term survival.

Currently, in Japan, we can perform genome sequencing of tumor specimens in order to find the next treatment target drug in rare cancer patients in which the typical treatment effect becomes less remarkable. In this case, we identified PTEN and RB1 co-loss and TP53 mutations by next-generation sequencing. PTEN loss, RB1 loss,

**Table 1** Results of FoundationOne® companion diagnostic (F1CDx) assay

| Biomarker findings | Genomic findings |
|--------------------|------------------|
| MSI                | Cannot be determined, PTEN R233fs*10, splice site 480_492 + 2delCAGAGACAA AAAGGT |
| TMB                | 3Muts/Mb, RB1 Loss, TP53 R249G |

MSI, microsatellite instability; TMB, tumor mutational burden
and TP53 mutations are common genomic alterations in many cancers. Vinceneux et al. reported that a complete loss of PTEN expression was more frequent in DCa (34%) than in ACa (11%) by immunohistochemistry [11]. Some reports have also indicated that PTEN loss occurring in DCa is associated with multiple markers of poor prognosis and has recently been associated with cribriform morphology similar to that of ductal histology [12–14]. In fact, there were some scattered areas of complete loss of PTEN expression (Fig. 1C). Similarly, loss of function of the tumor suppressive function of TP53 and RB1 are the common mutant genes in ACa and are associated with aggressive tumor progression or metastatic ACa [15–17], while there was no confident evidence about the correlation between RB1 or TP53 mutation and DCa. Tarjan et al. reported that the combination of TP53 and chromogranin A expression in cancer cells is associated with ductal differentiation of ACa [18]. On the other hand, we performed immunohistochemistry for chromogranin A and synaptophysin staining, and the patient was found to be positive for synaptophysin (Fig. 1F) because these three genomic mutations are often found in patients with NEPC [19]. These results indicated that we could have the treatment option to perform the administration of a platinum agent for the future.

In conclusion, to the best of our knowledge, there are few case reports of genomic analysis for DCa, which is the first Japanese report of DCa with PTEN and RB1 co-loss and TP53 mutation. Genetic analysis may help not only guide the therapeutic strategies, but also sometimes with the diagnosis.

**Abbreviations**

DCa: Ductal adenocarcinoma; ACa: Acinar adenocarcinoma; NEPC: Neuroendocrine prostate cancer; PSA: Prostate-specific antigen; ADT: Androgen deprivation therapy; IMRT: Intensity modulated radiation therapy; PET/CT: Positron emission tomography/computed tomography.

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**Authors’ contributions**

Conception and design: TK, HN, and MO. Acquisition and analysis of data: TK, KN, KS, HH, and HN. Drafting the manuscript and figures: HK, TK, SM, HN, and MO. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed in this study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethical Committee of Keio University Hospital (20160084).

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**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report. A copy of the consent form is available for review by the Editor of this journal.

**Competing interests**

The authors declare that they have no competing interests.

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