Letter

The first Japanese case of intraductal cancer of the prostate with checkpoint kinase 2 mutation

Dear editor:

Intraductal carcinoma of the prostate (IDC-P) is characterized by expansive growth of cancer cells in normal prostatic ducts with basal cell layer and associated with high grade invasive prostate cancer (PCa). However, the molecular profile or clinical character of IDC-P in progressive castration-resistant PCa (CRPC) was not fully characterized yet.

A 62-year-old man diagnosed with prostatic adenocarcinoma (Gleason score, 4+3=7) and serum prostate-specific antigen (PSA) of 7.81 ng/mL underwent external beam radiation therapy. Although his PSA concentration decreased to 2.61 ng/mL, it started increasing within 1 year. Combined androgen blockade was started and his PSA concentration dropped temporarily. Recurrent cancer developed as CRPC within 1 year. He sequentially received docetaxel therapy and enzalutamide. However, he developed urinary retention; magnetic resonance imaging and computed tomography scans showed a diffusely spread prostate tumor and an internal iliac lymph node metastasis (Fig. 1A). We performed prostate biopsy and transurethral resection of the prostate. Pathological examination showed intraductal carcinoma and acinar adenocarcinoma with phosphatase and tensin homolog (PTEN) deficiency (Fig. 1B and C). Although cabazitaxel therapy was attempted, the tumor expanded to the rectum and his systemic condition worsened gradually. Palliative care was started and the patient was transferred to another hospital. Written informed consent was obtained from the patient for the publication of this case report. This study was approved by the Ethics Committee of Keio University Hospital (Approval number 20150285, 20160084).

We performed next-generation sequencing using a custom panel using DNA from formalin-fixed paraffin-embedded tissue of the transurethral resection of the prostate specimen (Supplementary Methods and Supplementary Table 1). We identified six genetic variants in the tissue sample including PTEN p.R233*, checkpoint kinase 2 (CHEK2) p.V498F, mammalian target of rapamycin (MTOR) p.R32W, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4 (SMARCA4) p.G1162D, alpha thalassemia mental retardation syndrome X-linked (ATRX) p.G2075V, and Fanconi anemia complementation group A (FANCA) p.R756C (Supplementary Fig. 1).

PTEN p.R233* in the tumor was identified as the pathogenic variant. Regarding CHEK2, MTOR, SMARCA4, and ATRX mutations, there are no data in ClinVar database. However, the pathogenicity of all these variants was determined to be probably damaging by our mutation calling system “dbNSFP” (database for non-synonymous single nucleotide polymorphisms’ functional predictions) [1]. Furthermore, FANCA mutation was determined to be of unknown significance. Loss of genetic heterozygosity (LOH) with mutation was observed in PTEN, CHEK2, MTOR, SMARCA4, and ATRX. No gene amplification was detected. Tumor mutation burdens calculated from our pipeline were 9.3 single nucleotide variants per megabase pair in the samples.

The accumulation of somatic mutations cause PCa development and progression by altering important pathways of cell proliferation, invasion, and metastasis [2]. Genomic profiling of tissue biopsies can be used to investigate genomic alterations. Although genomic analysis is also useful for precision medicine of PCa, it is unclear whether the results of this analysis can be applied to treatment.

We previously reported that FANCA and breast cancer 2 (BRCA2) loss might be associated with PCa aggressiveness [3,4]. In this case, we investigated genomic feature of IDC-P and identified PTEN pathogenic mutations with LOH. Regarding CHEK2, MTOR, SMARCA4, and ATRX mutations, the pathogenicity of all these variants was determined to be probably damaged with LOH, indicating that these genes would be loss of function.

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Pathological characteristics of IDC-P are expansive growth of cancer cells in normal prostatic ducts with basal cell layer. Although IDC-P is relatively rare type among PCa, the frequency of IDC-P increases after androgen deprivation therapy and the presence of IDC-P is associated with higher risk of cancer progression. Genomic feature of IDC-P is higher percentage of genomic alteration including \( PTEN \), \( RB1 \), tumour protein p53 (TP53), and \( CHEK2 \)\[5\]. However, Asian cases of IDC-P with \( CHEK2 \) mutations have not been reported previously.

\( CHEK2 \) is one of the most important regulators of DNA repair and it activates \( TP53 \). \( CHEK2 \) gene alteration is known to increase the risk of breast cancer and ovarian cancer \[6\]. Loss of \( CHEK2 \) function was also reported in the next generation sequencing cohort of PCa \[2\]. A previous study reported mutations in DNA-repair genes including \( CHEK2 \) were significantly more frequent in metastatic PCa cases than localized cases \[7\]. Although \( CHEK2 \) mutations are suggested to contribute to PCa development and progression, there has been no report on Asian PCa cases with \( CHEK2 \) mutations. A previous phase III study for metastatic CRPC reported functional loss of DNA damage repair gene including \( CHEK2 \) variants was associated with the response to poly ADP-ribose polymerase (PARP) inhibitors \[8\].

The loss of \( PTEN \) function is a risk for PCa progression. \( PTEN \) R233* was reported to be a driver mutation of Cowden syndrome, which is an autosomal dominant inherited disease characterized by multiple hamartoma in the skin, mucosa, breast, and thyroid \[9\]. \( PTEN \) R233* mutation was a poor prognostic factor for glioblastoma and was also reported in several PCa cohorts \[2\]. Moreover, \( PTEN \)-deficient PCa as this case was reported to be vulnerable to PARP inhibitors \[10\]. Considering the above, PARP inhibitors may be effective for our case while they have not been yet approved for PCa.

Author contributions

**Study design**: Hiroshi Hongo, Takeo Kosaka, Mototsugu Oya.

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Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2022.02.002.

References

[1] Liu X, Jian X, Boerwinkle E. dbNSFP: a lightweight database of human nonsynonymous SNPs and their functional predictions. Hum Mutat 2011;32:894–9.

[2] Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011–25.

[3] Kosaka T, Hongo H, Aimono E, Matsumoto K, Hayashida T, Mikami S, et al. A first Japanese case of neuroendocrine prostate cancer accompanied by lung and brain metastasis with somatic and germline \( BRCA2 \) mutation. Pathol Int 2019;69:715–20.

[4] Hongo H, Kosaka T, Aimono E, Nishihara H, Oya M. Aggressive prostate cancer with somatic loss of the homologous
recombination repair gene FANCA: a case report. Diagn Pathol 2020;15:5. https://doi.org/10.1186/s13000-019-0916-z.

[5] Khani F, Wobker SE, Hicks JL, Robinson BD, Barbieri CE, De Marzo AM, et al. Intraductal carcinoma of the prostate in the absence of high-grade invasive carcinoma represents a molecularly distinct type of in situ carcinoma enriched with oncogenic driver mutations. J Pathol 2019;249:79–89.

[6] Lu HM, Li S, Black MH, Lee S, Hines R, Wu S, et al. Association of breast and ovarian cancers with predisposition genes identified by large-scale sequencing. JAMA Oncol 2019;5:51–7.

[7] Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.

[8] Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.

[9] Neychev V, Sadowski SM, Zhu J, Alligaeuer M, Kilian K, Meltzer P, et al. Neuroendocrine tumor of the pancreas as a manifestation of Cowden syndrome: a case report. J Clin Endocrinol Metab 2016;101:353–8.

[10] González-Billalbeitia E, Seitzer N, Song SJ, Song MS, Patnaik A, Liu XS, et al. Vulnerabilities of PTEN-TP53-deficient prostate cancers to compound PARP-PI3K inhibition. Cancer Discov 2014;4:896–904.

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