A first Japanese Case of Intraductal Cancer of the Prostate with CHEK2 Mutation

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Case Report

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Abstract

Background: Genomic profiling of tissue biopsies can be used to investigate genomic alterations. Although genomic analysis is also useful for precision medicine of prostate cancer, it is unclear whether to apply the results of this analysis to treatment.

Case presentation: A 62-year-old man underwent docetaxel therapy and enzalutamide for castration-resistant prostate cancer. However, he developed urinary retention and radiological images showed progression of prostate cancer. We performed prostate biopsy and trans-urethral resection of the prostate. Pathological examination showed acinar adenocarcinoma with intraductal carcinoma. Although docetaxel rechallenge and cabazitaxel therapy were attempted, the tumor expanded to the rectum and his systemic condition worsened gradually (Fig. 1). Palliative care was started and the patient was transferred to another hospital. We performed next-generation sequencing using DNA from FFPE tissue of the TUR-P specimen. We identified 4 genetic variants within the FFPE tissue sample. Remarkably, CHEK2 alteration was known to be associated with some solid cancer progression.

Conclusions: The results of genetic analysis suggested that modification of tumor suppressor pathways might be associated with refractory nature of his cancer.

Introduction

Prostate cancer is the most prevalent cancer and second leading cause of cancer among American men. Several drugs are now approved for the treatment of castration-resistant prostate cancer (CRPC). Although CRPC initially responds to these drugs, acquired resistance is inevitable.

The accumulation of somatic mutations cause prostate cancer development and progression by altering important pathways of cell proliferation, invasion, and metastasis[1–3]. Genomic profiling of tissue biopsies can be used to investigate genomic alterations. Although genomic analysis is also useful for precision medicine of prostate cancer, it is unclear whether to apply the results of this analysis to treatment.

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 PCa. However, the molecular profile or clinical character of IDC-P in progressive CRPC were not fully characterized yet.

Here we report our experience of genetic analysis of the first Asian case of intraductal carcinoma of the prostate with CHEK2 mutation.

Case Presentation

A 62-year-old man visited our hospital for further evaluation of serum prostate specific antigen (PSA) elevation of 7.81 ng/mL. Prostate needle biopsy revealed a Gleason score of 3 + 4 = 7 prostatic

adenocarcinoma. Magnetic resonance imaging (MRI) showed an extracapsular extension of prostate cancer. He underwent external beam radiation therapy. Although his PSA concentration decreased to 2.61 ng/ml, it started increasing within a year. Combined androgen blockade with goserelin acetate and flutamide was started and his PSA concentration dropped temporarily. Recurrent cancer developed as CRPC within a year. He sequentially received docetaxel therapy and enzalutamide. However, he developed urinary retention during enzalutamide therapy, and MRI and computed tomography scans showed a diffusely spread prostate tumor and an internal iliac lymph node metastasis (Fig. 1). We performed prostate biopsy and trans-urethral resection of the prostate for releasing retention and diagnosing whether these tumors were adenocarcinoma or neuroendocrine tumors. Pathological examination showed intraductal carcinoma and acinar adenocarcinoma with PTEN deficiency (Fig. 2). Although docetaxel rechallenge and cabazitaxel therapy were 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.

To understand the aggressiveness of the disease in this patient, we analyzed the genetic profile of this patient (Fig. 2). We performed next-generation sequencing using a custom panel using DNA from FFPE tissue of the TUR-P specimen as previously shown (Sup methods, sup table 1, 2)[4]. We identified six genetic variants in the FFPE tissue sample including *PTEN* p.R233*, *CHEK2* p.V498F, *MTOR* p.R32W, *SMARCA4* p.G1162D, *ATRX* p.G2075V and *FANCA* p.R756C. *PTEN* alterations were detected pathogenic variants in the tumor. 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 nonsynonymous SNPs’ functional predictions)[5]. Furthermore, *FANCA* mutations is determined to be of unknown significance. The detailed information is provided in Fig. 3. 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 /Mbp in the samples.

Discussion

We previously reported genomic analysis of tumor biopsy tissue of prostatic adenocarcinoma cases, which suggested *FANCA* and *BRCA2* loss might be associated with tumor aggressiveness[6, 7]. In this case, we investigated genomic feature of intraductal carcinoma of the prostate (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 damaging with LOH, indicating that these genes would be loss of function.

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 prostate cancer, frequency of IDCP increases after androgen deprivation therapy and presence of IDC-P is associated with higher risk of cancer progression[8]. Genomic feature of IDC-P is higher percentage of genomic alteration including *PTEN*, *RB1*,

TP53 and CHEK2[9, 10]. However, Asian cases of IDC-P with CHEK2 mutations have not been reported previously.

CHEK2 is one of the most important regulator of DNA repair and it activates TP53. CHEK2 gene alteration are known to increase the risk of breast cancer and ovarian cancer[11]. Loss of CHEK2 function was also reported in the NGS cohort of prostate cancer[3]. A previous study identified incidence of CHEK2 germline mutations was significantly higher in prostate cancer cases than unaffected cases[12]. In addition, mutations in DNA-repair genes including CHEK2 were significantly more frequent in metastatic prostate cancer cases than localized cases[13]. Although CHEK2 mutations are suggested to contribute prostate cancer development and progression, there have been no reports on Asian prostate cancer 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[14].

Frameshift mutation of PTEN p.R233* was reported to be associated with malignancy in a genotyping study of over 5000 patients with various cancers[15]. The loss of PTEN function is a risk for prostate cancer progression[16]. 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[17, 18]. PTEN R233* mutation was a poor prognostic factor for glioblastoma[19] and was also reported in several prostate cancer cohorts[2]. Moreover, PTEN deficient prostate cancer as this case was reported to be vulnerable to PARP inhibitors[20]. Considering the above, PARP inhibitors may be effective to our case while these are not yet approved for prostate cancer.

Conclusions

We report Asian first case of IDC-P with CHEK2 mutation. Genetic mutation involving major tumor suppressor pathways including PTEN and CHEK2 may be associated with tumor aggressiveness in our case. PARP inhibitors may be expected for such refractory cancer with genetic variants.

Abbreviations

CRPC = castration-resistant prostate cancer

IDC-P = intraductal carcinoma with the prostate

PSA = prostate specific antigen

Declarations

Ethical approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Availability of data and material

Not applicable

Authors' contributions

Hongo H: Collection and assembly of data, data analysis and manuscript writing

Koska T: Collection and assembly of data, data analysis, provision of study material and manuscript writing

Nakamura K: Collection and assembly of data and data analysis

Mikami S: Collection and assembly of data and provision of study material

Nishihara H: Collection and assembly of data and data analysis

Oya M: Conception and design, and manuscript writing

Compliance with Ethical Standards

This study was approved by the by the Ethics Committee of Keio University Hospital (Approval number 20150285, 20160084). Written informed consent for this study was obtained from the patient.

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Figures

Figure 1

Figure 1

Clinical course of our case.

Figure 2

Figure 2

a, Hematoxylin-Eosin staining of TUR specimen showed poorly differentiated carcinoma. b, 34βE12 + p63 staining of TUR specimen showed the presence of basal cells at the duct periphery. c, PTEN staining of TUR specimen showed PTEN-null lesion.

Figure 3

Figure 3

a, CHEK2 missense mutation at 498th valine into phenylalanine. b, PTEN frameshift mutation at 233rd arginine. c, MTOR missense mutation at 23rd arginine into tryptophan. d, SMARCA4 missense mutation at 1162nd glycine into aspartic acid. e, ATRX missense mutation at 2075th glycine into valine.

Supplementary Files

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