First Case of Ductal Adenocarcinoma of the Prostate with MAP3K1 Homozygous Deletion: A Case Report and Literature Review

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Case Report

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Abstract

Background: Ductal adenocarcinoma of the prostate is a rare prostate cancer variant and associated with higher stage and greater risk of recurrence and mortality. Optimal systemic therapy for metastatic ductal adenocarcinoma is not known. Many case reports are needed for further understanding of clinical and molecular features about it. Herein we report the first case of a man who was diagnosed with ductal adenocarcinoma of the prostate with mitogen-activated protein kinase 1 (MAP3K1, MEKK1) homozygous deletion.

Case Presentation: A 67-year-old man presented with ductal adenocarcinoma of the prostate accompanied by multiple lung metastases and advanced bone metastases. We performed channel transurethral resection of the prostate and confirmed the diagnosis of ductal adenocarcinoma of the prostate. DNA sequencing identified a TP53 somatic point mutation (p.Gly245Ser) as the pathogenic variant. Furthermore, a homozygous deletion was observed in MAP3K1 (MEKK1). The patient received enzalutamide but deceased five months after presenting to our institution.

Conclusion: To our knowledge, this is the first report of ductal adenocarcinoma of the prostate with a MAP3K1 homozygous deletion. Accumulation of whole-exome sequencing data is expected to inform future advances in therapy development.

Background

Ductal adenocarcinoma of the prostate (DAP) was first reported in 1967.[1] DAP is a rare prostate cancer variant and the incidence of DAP accounts for 0.5–6% of prostate cancers.[2, 3] Several studies reported that ductal adenocarcinoma is a more aggressive disease than acinar carcinoma and associated with higher stage and greater risk of prostatic specific antigen (PSA) recurrence and mortality. Although ductal adenocarcinoma is characterized by distinct pathological features, it is often under-recognized and overlooked in both the laboratory and the clinic.[4]

In recent years, new technologies such as whole genome sequencing have assisted in revealing detailed molecular profiles of DAP,[4] and case reports using these technologies are needed to increase the understanding of the clinical and molecular features of DAP.

Herein we report the first case of a Japanese man who was diagnosed with DAP with mitogen-activated protein kinase 1 (MAP3K1, MEKK1) homozygous deletion.

Case Presentation

A 67-year-old Japanese man presented to another institution for urinary retention in 2017. At that time, his serum PSA concentration was 5.06 ng/mL. Silodosin therapy was initiated, and a few months later, his PSA level rose to 14.16 ng/mL. He underwent transrectal ultrasound-guided prostate biopsy. Pathological analysis of his prostate revealed DAP (Fig. 1a) corresponding to clinical stage T4N0M1b

disease and he was administered a combined androgen blockade in October 2018. After reaching its nadir (0.32 ng/mL) in April 2019, PSA levels gradually began to re-increase.

He was readmitted to hospital due to acute urinary retention. Computed tomography showed multiple lung metastases and advanced bone metastases, and so he was referred to our institution for treatment.

His PSA concentration was 9.73 ng/mL in January 2020, and we performed channel transurethral resection of the prostate (TURP). Pathologic analysis confirmed the diagnosis of DAP (Fig. 1b).

The results of immunohistochemistry tests revealed that the tumor cells exhibited partial positive expression of androgen receptor, negative expression of PSA chromogranin, and synaptophysin, and a high Ki-67 labeling index (Fig. 1c–g).

In addition, we performed targeted next-generation sequencing of the prostate specimen obtained by channel TURP (Document S1 and Table S1). Moreover, a *TP53* somatic point mutation (p.Gly245Ser) was detected as a pathogenic variant in the tumor. A *RB1* somatic point mutation (p.Ser485Phe) was detected as a variant of unknown significance. No gene amplification was observed among 160 genes we examined. Furthermore, a homozygous deletion was observed in *MAP3K1* (Fig. 3a). The tumor mutation burden calculated by our pipeline was 5.4 single nucleotide variants/Mbp.

His PSA levels soared to 123.73 in April 2020, and he was treated with enzalutamide. However, the patient deceased in June 2020.

Discussion

The most common type of prostate cancer is acinar adenocarcinoma, whereas DAP is rare. DAP is characterized by large glands lined by tall, pseudostratified, columnar, neoplastic epithelial cells, typically arranged over fibrovascular cores or cribriform glands, and approximately 3% of all prostate cancers have some component of ductal histology.[5, 6] Because DAP may be less sensitive to androgen deprivation therapy and is enriched for targetable mutations, patients with DAP should be offered next-generation sequencing of DAP biopsies to guide standard-of-care treatment [4, 6] Schweizer et al. reported that 49% and 16% of patients with DAP exhibited DNA damage repair gene alterations and mitogen-activated protein kinase (MAPK) pathway alterations, respectively.[6]

In the present case, three alterations were detected. TP53 and RB1 alterations are relatively common and co-occurring in metastatic castration-resistant prostate cancers and moreover occur at high frequencies in neuroendocrine cancers.[7] However, the present patient tested negative for chromogranin A and synaptophysin. We speculate that this might be because the RB1 variant is a variant of unknown significance and associated with intact function. Moreover, MAP3K1/JNK signaling increases TP53 stability and transcriptional activation and potentiates the ability of TP53 to initiate programmed cell death.[8] The combination of a TP53 mutation with a MAP3K1 homozygous deletion might have inhibited programmed cell death in this particular case.

The aggressive disease course in the present patient may reflect the fact that he had TP53 alteration and MAP3K1 loss-of-function mutation.

It has been observed that TP53 alteration is significantly associated with poor survival and shorter time of treatment with next-generation androgen receptor signaling inhibitor.[7, 9] Meanwhile, the frequency of MAP3K1 alterations observed in prostate cancer is low, and data on this are generally limited. Alterations of MAPK pathways such as BRAF, KRAS, and MAP2K1 have been detected in DAP.[6] To our knowledge, this is the first report of DAP with a MAP3K1 homozygous deletion.

Aberrant activation of the MAPK pathway is a major and highly prevalent oncogenic event in many human cancers.[10] MAP3K1 plays a significant role in promoting cell survival or apoptosis and activates androgen-regulated gene expression in an androgen receptor-dependent fashion.[11] Abreu-Martin et al. demonstrated that expression of constitutively active MAP3K1 induces apoptosis in androgen receptor-positive but not in androgen receptor-negative prostate cancer cells, and the apoptotic effect in prostate cells occurs only when the androgen receptor signaling pathway is intact.[11] Because the androgen receptor was only partially positive in this case, apoptosis of prostate cancer cells by MAP3K1 may have been limited.

Androgen receptor-staining of almost all naïve DAP shows positive staining, but previous studies on the immunohistochemical profile of DAP upon androgen deprivation therapy are limited..[12] In this case, the androgen receptor might gradually have turned negative after androgen deprivation therapy, and the MAP3K1 loss-of-function mutation and negative androgen receptor phenotype resulted in the aggressive behavior of the tumor.

Next, we investigated the prognostic significance of MAP3K1 gene alteration in prostate cancer using the TCGA cohort data. [13] Recurrence-free survival and genetic characteristics were extracted from cBioPortal (<http://www.cbioportal.org/>). As a result of survival analysis, the loss of MAP3K1 of heterozygosity is a poor prognostic factor (Fig. 3b). This suggests that MAP3K1 may play a significant role in prostate-cancer cell apoptosis.[13]

Radiotherapy is a suitable definitive treatment option in the management of DAP; however, the optimal systemic therapy for metastatic ductal adenocarcinoma remains to be established.[14–16]

Treatment for MAP3K1 loss depends on whether androgen receptor testing is positive or negative. When it is positive, MEK inhibitor therapy may be effective. Xue et al. showed that cancer cells that have inactivating mutations in MAP3K1 are sensitive to MEK inhibitor monotherapy by disabling the JNK-JUN-mediated positive feedback loop, which limits drug responsiveness.[17] MicroRNAs also play critical roles in the tumorigenesis of prostate cancer, and overexpression of miR-4735-3p, which is a MAP3K1-targeting microRNA, inhibited MAP3K1-mediated cell apoptosis upon docetaxel treatment. Inhibition of miR-4735-3p may improve the outcome of chemotherapy for some prostate cancers.[18]

Meanwhile, in cases of androgen-receptor negativity, reconstitution of the androgen receptor signaling pathway restores MAP3K1-induced apoptosis.[19]

Conclusions

To our knowledge, this is the first report of DAP with a MAP3K1 homozygous deletion. Accumulation of whole-exome sequencing data is expected to inform future advances in DAP therapy development.

Abbreviations

DAP: Ductal adenocarcinoma of the prostate; PSA: prostatic specific antigen; MAP3K1, MEKK1: mitogen-activated protein kinase 1; TURP: transurethral resection of the prostate; MAPK: mitogen-activated protein kinase

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Keio University Hospital (Approval number 20180015).

Consent for publication

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

Availability of data and materials

The datasets generated and analysed during the current study are available in the TCGA cohort data from cBioPortal (<http://www.cbioportal.org/>).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TK, KN, SM, and HN analyzed and interpreted the pathological and genomic data. TK, KS and HH investigated the prognostic significance of MAP3K1 gene alteration in prostate cancer. KS, TK, KN, HH

and MO was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

a: Hematoxylin–Eosin (HE) staining showing the papillary architecture, with tall, pseudostratified, columnar epithelial cells arranged over fibrovascular cores. b: HE staining showing the papillary architecture. Nuclear irregularities are evident. c: Androgen receptor-staining of tumor cells showing partial positive staining. d: Immunohistochemical analysis of tumor cells for prostatic specific antigen showing negative staining. e: Tumor cells stained with chromogranin showing absence of stain uptake. f: Tumor cells stained with synaptophysin showing absence of stain uptake. g: Tumor cells stained with Ki-67, showing a high labeling index.

Figure 2

Computed tomography and magnetic resonance imaging showed multiple lung metastases and advanced bone metastases

Figure 3

a: Copy number plot showing the MAP3K1 homozygous deletion, b: Kaplan–Meier curve reflecting recurrence-free survival for MAP3K1 loss of homozygosity (LOH)-negative vs. MAP3K1 LOH-positive patients with prostate cancer.

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