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Case Report

First case of ductal adenocarcinoma of the prostate with MAP3K1 homozygous deletion

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Abbreviations & Acronyms
BRAF = v-raf murine sarcoma viral oncogene homolog B1
DAP = ductal adenocarcinoma of the prostate
HE = hematoxylin–eosin
KRAS = Kirsten rat sarcoma viral oncogene homolog
LOH = loss of homozygosity
MAP3K1 (MEKK1) = mitogen-activated protein kinase kinase kinase 1
MAPK = mitogen-activated protein kinase
NGS = next-generation sequencing
PSA = prostate-specific antigen
TURP = transurethral resection of the prostate

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Introduction: Ductal adenocarcinoma of the prostate is a rare prostate cancer variant and associated with higher stage and greater risk of mortality. Optimal systemic therapy for metastatic ductal adenocarcinoma is not known.

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 mitogen-activated protein kinase kinase kinase 1. The patient received enzalutamide but deceased 5 months after presenting to our institution.

Conclusion: To our knowledge, this is the first report of ductal adenocarcinoma of the prostate with a mitogen-activated protein kinase kinase kinase 1 homozygous deletion. Accumulation of whole-exome sequencing data is expected to inform future advances in therapy development.

Key words: ductal adenocarcinoma of the prostate, MAP3K1, next-generation sequencing, prostate cancer, TP53.

Keynote message

We described a case of the first report of DAP with a MAP3K1 homozygous deletion. DNA sequencing identified a homozygous deletion in MAP3K1 (MEKK1).

Introduction

DAP was first reported in 1967.[1] DAP is a rare prostate cancer variant and the incidence of DAP accounts for 0.5% to 6% of prostate cancers.[2,3] Several studies reported that ductal adenocarcinoma is a more aggressive disease than acinar adenocarcinoma and associated with higher stage and greater risk of 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 MAP3K1 homozygous deletion.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Board of Keio University Hospital (No. 20160084 and 20180015). Written informed consent was obtained from the participant.

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 the hospital due to acute urinary retention. Computed tomography showed multiple lung metastases and advanced bone metastases when his PSA level was 4.52 ng/mL in December 2019 (Fig. 2), and he was referred to our institution for treatment. His PSA concentration was 9.73 ng/mL in January 2020, and we performed channel TURP. Pathologic analysis confirmed the diagnosis of DAP (Fig. 1a,b).

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

In addition, we performed targeted NGS of the prostate specimen obtained by channel TURP (Appendix 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.

He had a vertebral compression fracture in March 2020. His PSA levels soared to 123.73 in April 2020, and he was

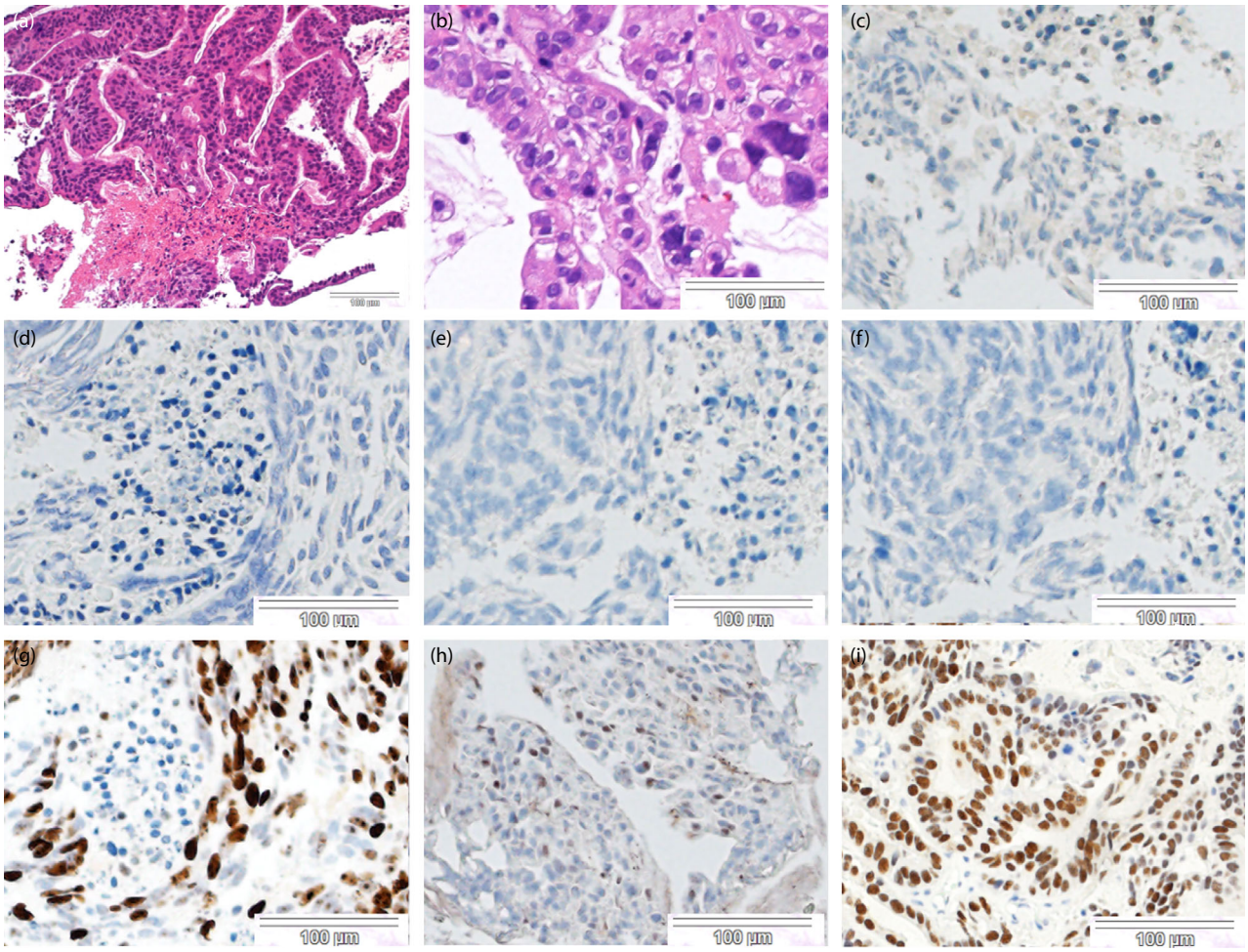

Fig. 1 (a) HE staining showing the papillary architecture, with tall, pseudostratified, columnar epithelial cells arranged over fibrovascular cores at initial diagnosis. (b) HE staining showing the papillary architecture. Nuclear irregularities are evident. (c) Androgen receptor staining of tumor cells showing partial positive staining. (d) Immunohistochemical analysis of tumor cells for PSA 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. (h) Immunohistochemical analysis of tumor cells for MAP3K1 showing reduced staining suggesting the loss of the expression at the protein level. (i) Immunohistochemical analysis of tumor cells for TP53 showing diffuse nuclear positivity.

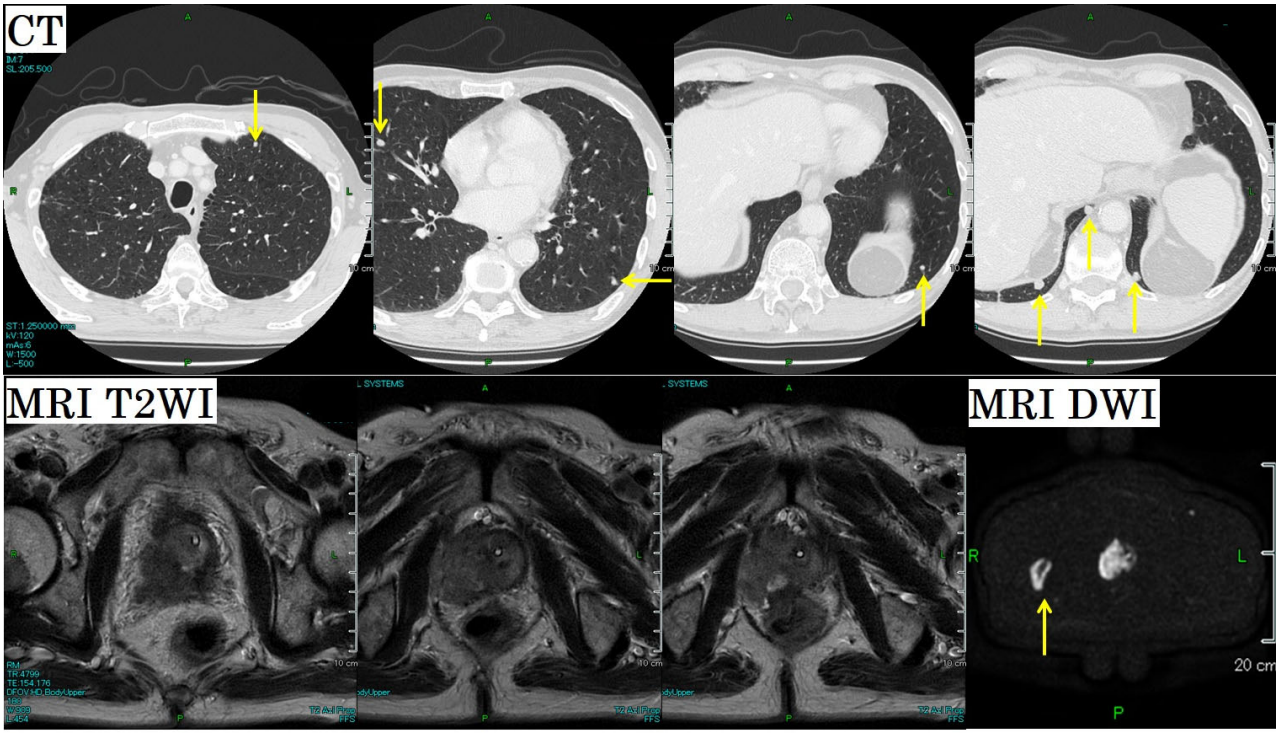

Fig. 2 Computed tomography and magnetic resonance imaging showed multiple lung metastases and advanced bone metastases.

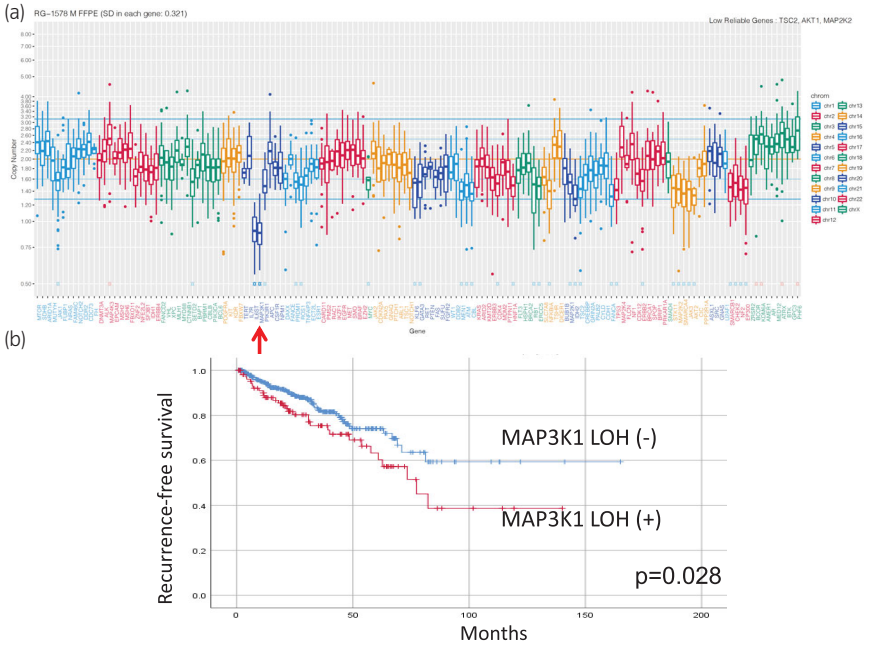

Fig. 3 (a) Copy number plot showing the MAP3K1 homozygous deletion, (b) Kaplan–Meier curve reflecting recurrence-free survival for MAP3K1 LOH-negative versus MAP3K1 LOH-positive patients with prostate cancer.

treated with enzalutamide. However, liver metastases emerged, and the patient died in June 2020.

Discussion

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 NGS 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 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. We examined the expression of MAP3K1 and TP53 by immunohistochemical analysis to validate NGS analysis. Tumor cells for MAP3K1 showed reduced staining, suggesting the loss of the expression at the protein level (Fig. 1h), and tumor cells for TP53 showed diffuse nuclear positivity (Fig. 1i). Meanwhile, the frequency of MAP3K1 alterations observed in prostate cancer is low, and data on this are generally limited. Alterations in 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.[9] MAP3K1 plays a significant role in promoting cell survival or apoptosis and activates androgen-regulated gene expression in an androgen receptor-dependent fashion.[10] 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.[10] 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 after androgen deprivation therapy are limited.[11] 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.[12] 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.[12]

Also, genome-wide association studies of breast cancer have identified a MAP3K1 mutation.[13] The MAP3K1 mutation in breast cancer is likely inactivating.[14] MAP3K1 may be associated with cancer cell apoptosis.

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.

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Conflict of interest

The authors declare no conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. 160 genes examined in the PleSSision-Rapid test.
Appendix S1. Methods of next-generation sequencing of the specimen.