Case Report

Squamous cell carcinoma of the prostate with *SMARCA4* alteration in a Japanese patient

Yuta Kaneko,[1] Takeo Kosaka,[1] Kohei Nakamura,[2] Shuji Mikami,[3] Hiroshi Nishihara[2] and Mototsugu Oya[1]

[1]Department of Urology, Keio University School of Medicine, [2]Genomics Unit, Keio Cancer Center, Keio University School of Medicine, and [3]Division of Diagnostic Pathology, Keio University Hospital, Tokyo, Japan

Abbreviations & Acronyms
GC = gemcitabine and carboplatin
PSA = prostate-specific antigen
SCC = squamous cell carcinoma

Correspondence: Takeo Kosaka M.D., Ph.D, Department of Urology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Email: takemduro@gmail.com

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Introduction: Squamous cell carcinoma of the prostate is very rare. Due to difficulty in diagnosis, it is often detected in advanced stages. Effective treatment of squamous cell carcinoma and the genetic profiling has not yet been established.
Case presentation: We experienced the case of a 79-year-old man who was diagnosed with primary squamous cell carcinoma of the prostate. He had multiple lymph node metastases, liver metastases, and lung metastases, and he was treated with gemcitabine and carboplatin. However, he had poor patient status: it became difficult to continue after one course, and best supportive care was provided. We also performed targeted next-generation sequencing of 160 cancer-related genes and detected *SMARCA4* mutation.
Conclusion: This is the first study reporting the genomic profiling of squamous cell carcinoma of prostate in Japan.

Key words: chemotherapy, gene profiling, *SMARCA4* mutation, squamous cell carcinoma of the prostate.

Keynote message

This is the first study reporting the genomic profiling of squamous cell carcinoma of prostate in Japan. We believe that further genetic analyses of SCC of the prostate will elucidate the carcinogenesis of this disease and will thereby provide a basis for developing novel gene-targeted therapy and precision medicine strategies.

Introduction

Adenocarcinomas are the most common prostate cancers, accounting for approximately 95% of cases, whereas squamous cell carcinomas (SCCs) account for only 0.5% to 1%.[1] The pathogenesis of SCC of the prostate has not yet been clarified. This disease is difficult to diagnose from images and prostate-specific antigen (PSA) measurements, and it is often not detected until it is at an advanced stage: the prognosis by then is poor because of the lack of standard treatments, including chemotherapy.

To date, genetic profiling for SCCs of the prostate has not been reported; thus, possible therapeutic options involving precision medicine are limited. We report a case of primary SCC of the prostate in which we performed targeted genome sequencing.

Case presentation

A 79-year-old man visited his previous physician for dysuria in September 2019. At that time, his PSA level was normal (1.12 ng/mL), and the estimated prostate volume was 100 mL. In October 2019, he underwent holmium laser enucleation of the prostate. The pathological results indicated SCC, and he was subsequently referred to our hospital for adjuvant chemotherapy. When he visited our hospital, his SCC antigen level was elevated (92.2 ng/mL), his PSA level was 0.12 ng/mL, and his neuron-specific enolase level was 16.4 ng/mL.

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Computed tomography (Fig. 1) showed a mass lesion 8 cm in diameter in the prostate. Dorsally, the mass crossed Denonvilliers's fascia and was in contact with the rectum. Bilateral closed lymph nodes, the right internal iliac lymph node, and the presacral lymph node were enlarged. Bilateral lung metastases and metastasis in segment 8 of the liver were also found.

Histopathological examination of the resected prostate specimen revealed substantial proliferation of atypical cells with a high degree of nuclear atypia, accompanied by extensive necrosis. The atypical cells were positive for cytokeratin 5/6 and p63, negative for GATA binding protein 3, and partially positive for cytokeratin 20 (Fig. 2). Therefore, we classified the tumor as prostate carcinoma with squamous differentiation.

After admission to our hospital, we initiated gemcitabine and carboplatin (GC) therapy. Although the SCC antigen level decreased to 68.7, computed tomography showed enlargement of the primary tumor and the appearance of mild hydronephrosis. The patient's general condition worsened, and chemotherapy was discontinued after one course.

Using an in-house assay[2] during the patient's treatment, we also performed targeted next-generation sequencing of 160 cancer-related genes in the resected prostate specimen. We detected a point mutation (p.Asp1235Glu [p.D1235E]) of the *SMARCA4* gene as an actionable variant in the tumor.

Discussion

We reviewed 25 cases of primary SCC of the prostate reported in Japan between 1959 and 2020(Table 1).[3-8] The median age of patients was 73 years (range: 54–90 years), and the most common complaints were dysuria, urinary retention, urinary frequency, and urinary urgency, in 24 cases (92%). Among the 20 PSA levels reported, 18 (90%) were normal, and prostate cancer was not initially suspected. SCC antigen levels were reported in 16 cases, of which 14 (88%) were high. In 10 (38%) of the 26 patients, SCC was diagnosed incidentally through transurethral resection of the prostate. The mean length of survival was 16 months: 3 patients with operable disease survived much longer. Imamura et al. reported a case of complete remission after chemotherapy with methotrexate, peplomycin, and cisplatin.[4]

Hutten et al.[9] reviewed the cases of primary SCC of the prostate diagnosed in the United States between 2004 and 2015. We compared their report with those of cases in Japan (Table 2). Hutten et al. summarized race and T stage; in the Japanese case reports, in addition to race and T stage, SCC antigen levels were described. In Japan, chemotherapy was used in combination with local treatment in 18 cases. The prognosis was better in patients who received chemotherapy, possibly because they had to be in good general condition to receive chemotherapy. In addition, the majority of cases in Japan were treated with chemotherapy, but no follow-up of cases has been reported in Japan.

With regard to chemotherapy, one patient in Japan was treated with a regimen of 5-fluorouracil and cisplatin with docetaxel[3] for multiple lymph node metastases 15 months after total prostatectomy, and complete remission was obtained after two courses of therapy. In our study, instead of immune checkpoint inhibitors and other agents, we initiated GC therapy, in view of the patient's PSA level and renal function. At the time of diagnosis, the disease had already progressed, and the patient could not tolerate chemotherapy. However, the SCC antigen level was decreased after that course, which suggests that the treatment was somewhat effective. Early diagnosis and prompt initiation of therapy are essential, and in patients with symptoms such as dysuria and

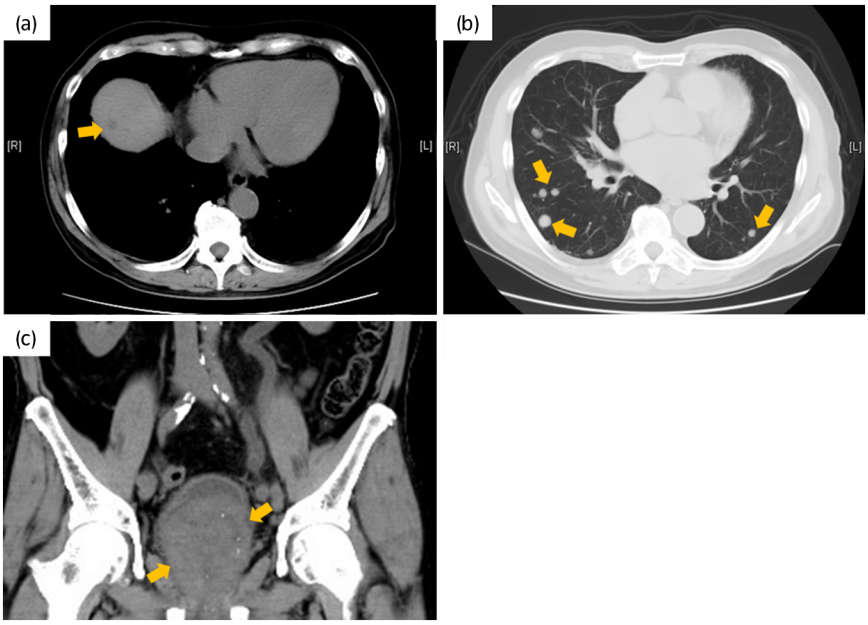

Fig. 1 (a) Metastasis in liver S8. (b) Bilateral lung metastases. (c) The prostate cancer invades the bladder, and dorsally, the mass crosses the Denon-villiers fascia and contacts the rectum.

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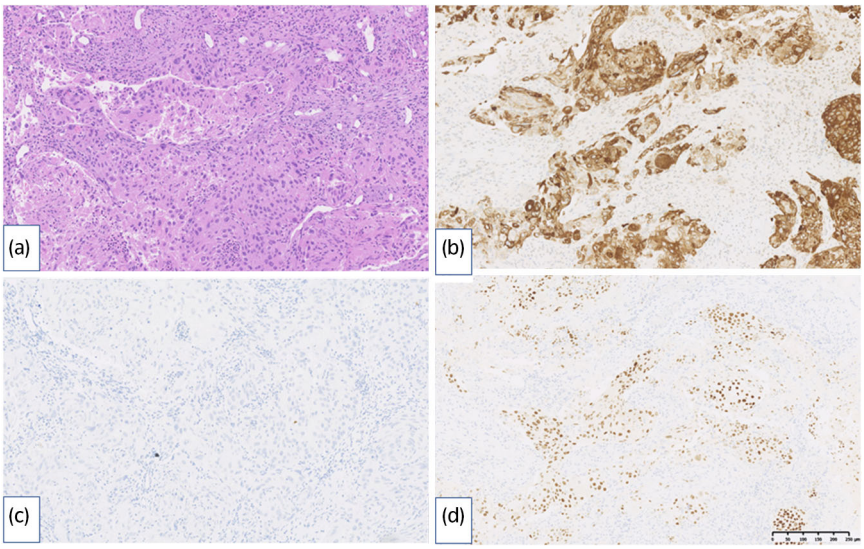

Fig. 2 Photomicrograph of prostate carcinoma with squamous cell differentiation (a). CD5/6(b) and p63(d) were positive. CK20(c) was negative in most of the area.

Table 1 Japanese case of primary squamous cell carcinoma of the prostate

No. of patient	26
Age	73 (54–90)
Chief complaint	
Dysuria	9
Urinary retention	11
Frequent urination	3
Urgency	1
Melena	2
PSA (ng/mL)	1.8 (0.1–14)
SCC antigen (ng/mL)	7.8 (1–92.2)
Prognosis (months)	11 (2–60)

SCC, squamous cell carcinoma.

urinary retention, this diagnosis should be considered even if the PSA level is low.

In sequencing of genes in the samples of SCC of the prostate, we detected a point mutation of the *SMARCA4* gene. Interest in the genetic characteristics of neoplasia has increased, partly because of promising developments in targeted therapies and personalized medicine. *SMARCA4* is one of the constituents of the SWI/SNF chromatin remodeling complex and functions as a catalytic subunit. By changing the chromatin structure in an adenosine triphosphate–dependent manner, this gene controls the binding of DNA-binding proteins such as transcriptional regulators to the target DNA region and is involved in the regulation of transcription and replication and in DNA repair. Among mutations of genes in the SWI/SNF chromatin remodeling complex, those of

Table 2 Clinical features in each treatment compared with those of the United States

	Local Therapy Alone			Local Therapy + Chemotherapy				
	Operation	Radiotherapy	United States(*)	Operation + Chemotherapy	Operation + Radiotherapy	Chemotherapy + Radiotherapy	Operation+Chemotherapy + Radiotherapy	United States(*)
patients	1	1	40	6	3	5	4	13
age(median)	90	85	80 (71–83)	68 (56–79)	78 (75–89)	65 (55–84)	72 (61–76)	65 (51–79)
PSA								
<2 ng/ml	0	0	10	4	2	4	4	4
2–10 ng/ml	1	1	7	0	1	1	0	4
10–20 ng/ml	0	0	1	1	0	0	0	0
>20 ng/ml	0	0	1	0	0	0	0	0
Unknown	0	0	-	0	0	0	0	-
SCC								
<1.5	0	0	-	1	0	0	1	-
≧1.5	1	0	-	3	3	5	2	-
Unknown	0	1	-	2	0	0	1	-
Prognosis (months)	3	10	-	16.5 (2–60)	5 (4–12)	10 (3–18)	13.5 (9–21)	-

*Data modified from Hutten et al.[9]

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SMARCA4 are the second most common in tumors, after *ARID1A*. Peng L et al.[10] reported that *SMARCA4* may correlate with tumor immunity. Few reports on prostate cancer, but depending on future research, treatment strategies with immune checkpoint inhibitors could be considered.

Our study is the first to reveal a genomic profile of SCC of the prostate in Japan. Because effective treatment has not yet been established and the prognosis is poor in advanced cases, we believe that further genetic analyses of SCC of the prostate will elucidate the carcinogenesis of this disease and will thereby provide a basis for developing novel gene-targeted therapy and precision medicine strategies.

Conclusion

In the gene sequencing of a primary SCC of the prostate, we found a mutation in *SMARCA4*.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an institutional reviewer board

The study was approved by the by the Ethics Committee of Keio University Hospital (Approval numbers: 20160084 and 20180015).

Informed consent

Consent to participate and for publication were acquired from the patient.

Registry and the registration no. of the study/trial

N/A.

Author Contributions

Yuta Kaneko: Investigation; project administration; visualization; writing – original draft. **Takeo Kosaka:** Conceptualization; funding acquisition; investigation; project administration; resources; writing – original draft; writing – review and editing. **Kohei Nakamura:** Data curation; methodology; writing – review and editing. **Shuji Mikami:** Formal analysis; methodology; validation; visualization. **Hiroshi Nishihara:** Data curation; methodology; project administration; validation. **Mototsugu Oya:** Supervision; validation.

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