

Case Report

Castration-resistant prostate cancer diagnosed during leuprorelin treatment for spinal and bulbar muscular atrophy

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Abbreviations & Acronyms

ADT = androgen deprivation therapy

AR = androgen receptor

CT = computed tomography

IMRT = intensity modulated radiation therapy

PSA = prostate-specific antigen

SBMA = spinal and bulbar muscular atrophy

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Introduction: We report a prostate cancer case diagnosed during leuprorelin treatment for spinal and bulbar muscular atrophy which is a X-linked recessive, lower motor neuron disease.

Case presentation: A 64-year-old man who had received leuprorelin treatment over 3 years for his spinal and bulbar muscular atrophy presented with an enlarged prostate accompanied by abdominal pain and constipation. An abnormally high serum prostate-specific antigen of 17.7 ng/mL and a low (castration level) serum testosterone level of 0.23 ng/mL were measured. Prostate needle biopsy revealed adenocarcinoma of the prostate. Orchiectomy, darolutamide, and radiation therapy for the prostate were initiated, resulting in a favorable response which was maintained at 12 months of treatment.

Conclusion: Prostate cancer can occur even when leuprorelin is used for spinal and bulbar muscular atrophy; therefore, checking serum prostate-specific antigen to screen for prostate cancer before leuprorelin administration should be considered.

Key words: androgen receptor, leuprorelin acetate, motor neuron disease, prostate cancer, spinal and bulbar muscular atrophy.

Keynote message

Prostate cancer can occur even when leuprorelin is used for spinal and bulbar muscular atrophy. Leuprorelin masks serum PSA levels. Therefore, there was room for consideration of serum PSA evaluation prior to leuprorelin administration to men with spinal and bulbar muscular atrophy.

Introduction

SBMA, otherwise known as Kennedy's disease, is a rare X-linked recessive, lower motor neuron disease, caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the first exon of the AR gene.^{1–3} In Japan, leuprorelin acetate is approved to inhibit the progression of this disease. We report here a 64-year-old man who was diagnosed with prostate cancer during leuprorelin treatment for SBMA.

Case presentation

A 64-year-old man was referred to our hospital with irregularly enlarged prostate; this was found during an examination in which his chief complaints were of abdominal pain and constipation. He had already been administered leuprorelin acetate as a treatment for SBMA for the past 3 years.

The patient had been aware of arm tremors since age 35, with gradual onset of dysarthria and dysphagia. At the age of 54, a genetic test revealed that the number of CAG repeats in his AR gene was abnormally long (46), and he had been diagnosed with SBMA. His older brother had also been diagnosed with SBMA. At age 55, the patient participated in a randomized controlled trial of leuprorelin acetate treatment, however, he was assigned to the placebo

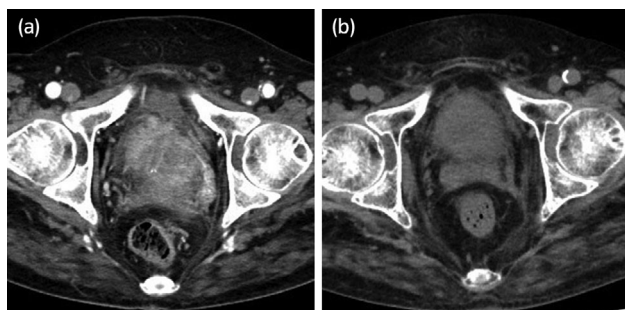


Fig. 1 Pelvic CT scans at diagnosis (a) and after initiation of treatment for prostate cancer (b). (a) The contrast-enhanced CT scan at the diagnosis revealed that the prostate was irregularly enlarged with a diameter of 84 mm, suggesting left seminal vesicle invasion of prostate cancer accompanied by a swelling right obturator lymph node. (b) The simple CT scan showed a significant decrease in size of prostate cancer after initiation of dalolutamide intake and radiation therapy to the prostate.

group. At the age of 60, he began receiving the actual drug, and his neurological symptoms stopped progressing thereafter. His serum PSA had never been measured at this point.

After the visit to our hospital, a laboratory test revealed that his serum PSA level was abnormally high at 17.7 ng/mL, even though his serum testosterone level had dropped to the castration level of 0.23 ng/mL (reference value, 1.31–8.71 ng/mL). Contrast-enhanced CT scan showed that his prostate was irregularly enlarged with a diameter of 84 mm, suggesting left seminal vesicle invasion of prostate cancer accompanied by a swelling right obturator lymph node (Fig. 1a). No evidence of distant metastasis was detected by CT scan and bone scintigraphy. Whole-body MRI was not performed. Based on the clinical history, the patient was diagnosed with castration-resistant prostate cancer without distant metastasis (m0CRPC). The patient underwent prostate needle biopsy and bilateral orchiectomies simultaneously, and the pathological results showed adenocarcinoma of the prostate (Fig. 2). The Gleason score could not be determined because the patient had already received leuprolerin acetate for several years. For treating m0CRPC, dalolutamide intake and radiation therapy to the prostate were initiated, resulting in a significant decrease in serum PSA levels and reduction in the size of the prostate (Fig. 1b). This favorable response was maintained at least 12 months of treatment.

Discussion

SBMA, also known as Kennedy's disease, is an adult-onset, X-linked recessive, lower motor neuron disease, characterized by an abnormal expansion of a CAG triplet repeat in the first exon of the AR gene. In healthy individuals, the number of CAG repeats in the AR gene ranges usually between 9–36, while patients with SBMA have between 38–62 CAG repeats.^{1–3} SBMA affects only males, and its incidence is 1–2 per 100 000 males.² Abnormal accumulation of mutant AR proteins in the nuclei of motor neurons leads to slowly progressive limb muscle paralysis, muscle atrophy, and ball paralysis. A randomized controlled trial, JASMITT study, was executed to evaluate the efficacy of a leuprolerin acetate

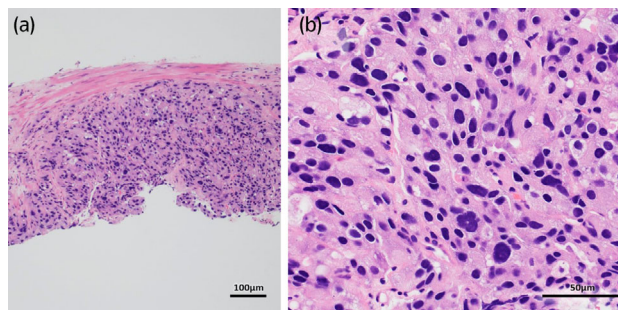


Fig. 2 Hematoxylin–eosin staining of the prostate biopsy. Adenocarcinoma with collapsed ductal structure is observed. Gleason score cannot be determined because of post-androgen deprivation therapy. (a) 10 \times . (b) 40 \times .

11.25 mg injection in inhibiting the progression of the disease.^{2,3} Based on the results of the JASMITT study, leuprolerin acetate 11.25 mg injection was approved for SBMA treatment in 2017 in Japan.

In the general population, several reports mentioned the association between the number of CAG repeats and prostate cancer. An inverse relationship between the number of repeats and the risk of developing prostate cancer was suggested; the shorter the number of CAG repeats, the more likely a man is to develop prostate cancer.^{4,5} It is also well known that there are racial/ethnic differences in the incidence and prognosis of prostate cancer,⁶ and there is a theory that the variation in the number of CAG repeats by race/ethnicity could affect the racial/ethnic differences in prostate cancer profiles. Irvine *et al.*⁷ reported that those with CAG repeats of less than 22 were found in 75% of African Americans at high risk of prostate cancer, in 62% of non-Hispanic whites at intermediate risk, and 49% of Chinese and Japanese at low risk. It has also been suggested that males with shorter CAG repeats tend to be diagnosed with prostate cancer at a younger age with a worse grade.⁸ Conversely, males with prostate cancer with longer CAG repeats tend to respond better to androgen deprivation therapy.⁸

This evidence suggests that SBMA patients with abnormally long CAG repeats are less likely to develop prostate cancer. To corroborate the evidence, a literature search for prostate cancer development among SBMA patients in PubMed (MEDLINE) and Ichushi-web (Japanese medical literature) revealed that only six cases, including our case, had been reported (Table 1). Moreover, other than our case, no report was found that mentioned prostate cancer diagnosis during preceding leuprolerin treatment for SBMA. In two of these cases, germline *BRCA2* mutations with neuroendocrine differentiation pathology were identified. Considering that germline *BRCA2* variants are found in only 1.1% of Japanese prostate cancer patients, this is a very high frequency.¹⁵ Hongo *et al.*¹³ suggested that genomic instability caused by *BRCA2* mutations could cause androgen-independent prostate cancer clones. In this case, we plan to perform cancer genomic profiling testing when distant metastases appear in the future.

In this case, at the first time of oncological diagnosis, the prostate cancer was already castration-resistant due to

Table 1 Previously reported cases of prostate cancer development among males with SBMA

No.	Author	Year	Age	PSA at diagnosis (ng/mL)	Treatment for prostate cancer	The number of CAG repeat	Complement
1	Yasui <i>et al.</i> ⁹	1999	63	72.0	Fosphestrol	52	
2	Yoshida <i>et al.</i> ¹⁰	2002	75	97.5	Orchiectomy with bicalutamide	n/a	Died of prostate cancer after 15 months
3	Sugahara <i>et al.</i> ¹¹	2011	66	n/a	Radical prostatectomy	n/a	
4	Kosaka <i>et al.</i> ¹² Hongo <i>et al.</i> ¹³	2012	54	148.0	(i) ADT with flutamide (ii) Enzalutamide (iii) Carboplatin and etoposide	46	Survival at 16 years BRCA2 mutation
5	Conteduca <i>et al.</i> ¹⁴	2018	57	53	(i) ADT with docetaxel (ii) Enzalutamide (iii) Talazoparib	49	Survival at 31 years BRCA2 mutation
6	Our case	2021	64	17.7	Orchiectomy with darolutamide and IMRT	46	Survival at 12 months Preceding leuporelin use for SBMA

androgen deprivation therapy for SBMA. The exact timing of prostate cancer development is unknown due to the lack of previous PSA measurements. As the use of leuporelin in patients with SBMA masks PSA levels, there was room for consideration of serum PSA evaluation prior to leuporelin administration.

Conclusion

We had the rare experience of diagnosing castration-resistant prostate cancer in a man receiving leuporelin for the treatment of SBMA. This case showed that prostate cancer can occur even when leuporelin is used for SBMA, and that prostate cancer screening by checking serum PSA before leuporelin administration should be considered.

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Author Contributions

Atsushi Yanase: Writing – original draft. Toru Sugihara: Conceptualization; writing – original draft. Takahiro Akimoto: Writing – review and editing. Hirotaka Yokoyama: Writing – review and editing. Jun Kamei: Writing – review and editing. Akira Fujisaki: Writing – review and editing. Satoshi Ando: Writing – review and editing. Tameto Naoi: Conceptualization; supervision. Mitsuya Morita: Conceptualization; supervision. Tetsuya Fujimura: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project was approved by a suitably constituted Institutional Reviewer Board at Jichi Medical University Hospital (Approval number, A19-199).

Informed consent

Informed consent was obtained from the subject.

Registry and the Registration No. of the study/trial

Not applicable.

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Editorial Comment

Editorial Comment to Castration-resistant prostate cancer diagnosed during leuprorelin treatment for spinal and bulbar muscular atrophy

Androgen receptor (AR) is the main mediator of androgen signaling. Androgens are sex steroid hormones released into the bloodstream in response to activation of the hypothalamic–pituitary–target endocrine gland axis. Free androgens enter the cells and bind to AR in the cytosol. In response to ligand binding, AR shuttles to the nucleus and works as a ligand-activated transcription factor. AR is widely expressed, from reproductive organs to skeletal muscle and brain. Hundreds of AR mutations have been linked to androgen insensitivity syndrome and prostate cancer. The expansion of a microsatellite CAG tandem repeat is the only AR mutation linked to neurodegeneration. SBMA symptoms fully manifest in males due to high circulating androgen levels. Androgen deprivation therapy (ADT) has shown promise in SBMA patients.^{1,2} ADT however is associated with side effects, spanning from muscle atrophy to sexual dysfunction and depression. ADT can also suppress hormone-naïve prostate cancer until a status of castration resistance is selectively established by mechanisms not entirely understood, comprising AR point mutations or overexpression, altered androgen biosynthesis, and constitutively active AR splice variants.

The case report from Atsushi *et al.* reignites a long-standing debate whether the size of the CAG microsatellite expansion in the AR gene influences development and progression of prostate cancer, the second most prevalent malignancy in men worldwide.³ It has been observed that the size of the CAG repeats inversely correlates with the AR transcriptional activity and the risk of developing prostate cancer,⁴ therefore suggesting that SBMA patients are less at risk compared to the general population.

With only a handful of reported cases and lack of solid epidemiological data, this question remains open. Additional mechanisms that may drive cancer initiation and progression beyond AR include age and loss of DNA repair, which are both a feature of SBMA and other polyglutamine disease. Those may be responsible for the insurgence of androgen-independent and more clinically aggressive prostate cancers in SBMA patients.⁵ As long-term ADT is currently in clinical

use in Japan for patients with SBMA, the links between microsatellite expansion in AR, androgen deprivation, and prostate cancer requires investigation to optimally balance benefits and harms of such treatment strategies for patients.

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Conflict of interest

The authors have no conflict of interest to report.

Author contributions

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Monica Montopoli: Conceptualization; writing – original draft.
Carlo Rinaldi: Conceptualization; writing – original draft.

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