Case Report

De novo large-cell neuroendocrine carcinoma of the prostate: A case report and literature review

Eri Fukagawa,[1,2] Takeshi Yuasa,[1] Kentaro Inamura,[3] Kosuke Hamada,[1] Motohiro Fujiwara,[1] Yoshinobu Komai[1] and Junji Yonese[1]

Departments of [1]Urology and [3]Pathology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, and [2]Department of Urology, St. Luke's International Hospital, Tokyo, Japan

Abbreviations & Acronyms
AC = adenocarcinoma
ADT = androgen deprivation therapy
AR = androgen receptor
CT = computed tomography
LCNEC = large-cell neuroendocrine cell carcinoma
LH-RH = luteinizing hormone-releasing hormone
LUTS = lower urinary tract symptoms
MRI = magnetic resonance imaging
N/R = not reported
PBx = prostate biopsy
PSA = prostate-specific antigen
SCLC = small cell lung cancer
SCNEC = small cell neuroendocrine carcinoma
TURBT = transurethral resection of the bladder tumor
TURP = transurethral resection of the prostate
ULN = upper limit of normal range
WHO = World Health Organization

Correspondence: Eri Fukagawa M.D., Department of Urology, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan. Email: fukaeri@luke.ac.jp

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Introduction: Prostatic large-cell neuroendocrine carcinoma is poorly studied. Although several case reports are available, information on the clinicopathological characteristics of this disease is limited, particularly for the *de novo* (hormone-naive) type. Herein, we report an extremely rare *de novo* case of this disease with a good prognosis despite a multi-metastatic status.

Case presentation: An 83-year-old male patient presented with a high serum prostate-specific antigen level and was found to have *de novo* prostatic large-cell neuroendocrine carcinoma with an adenocarcinoma component upon pathological examination. Diagnosed with stage pT4cN1cM1c, he underwent chemo-hormonal therapy using a luteinizing hormone-releasing hormone antagonist and combined etoposide and cisplatin, which achieved a partial response. The patient has survived for 20 months without progression.

Conclusion: Although prostatic large-cell neuroendocrine carcinoma is known for its aggressive clinical behavior, the *de novo* type with an adenocarcinoma component may be sensitive to hormonal therapy and achieve a good prognosis.

Key words: adenocarcinoma, cell differentiation, large cell carcinoma, neuroendocrine carcinoma, prostate cancer.

Keynote message

De novo large-cell neuroendocrine carcinoma (LCNEC) of the prostate has been known to exhibit aggressive clinical features; however, information on its clinicopathological characteristics is limited. *De novo* LCNEC with an adenocarcinoma component may be sensitive to androgen deprivation therapy, which may result in a relatively good prognosis.

Introduction

Prostate cancer is one of the most common cancers in men. Pathologically, >95% of prostate cancer cases are acinar AC. LCNEC was described as a rare histological variant since the 2004 WHO classification.[1] Although several case reports are available, information on its clinicopathological characteristics is limited, particularly for the *de novo* (hormone-naive) type. Herein, we reported an extremely rare case of *de novo* prostatic LCNEC with a good prognosis, despite a multi-metastatic status.

Case presentation

An 83-year-old male patient presented to our hospital due to an elevated serum PSA level detected during a routine health checkup. His initial PSA level was 22.47 ng/mL (Fig. 1), and his prostate was irregularly enlarged, stony, and hard upon palpation during the digital rectal examination. Imaging studies, including multi-parametric MRI, whole trunk CT scan, and bone scintigraphy, revealed a prostatic tumor with seminal vesicle invasion and multiple metastases to the para-aortic lymph nodes, bones, and bilateral lungs (Fig. 2a,b). The imaging

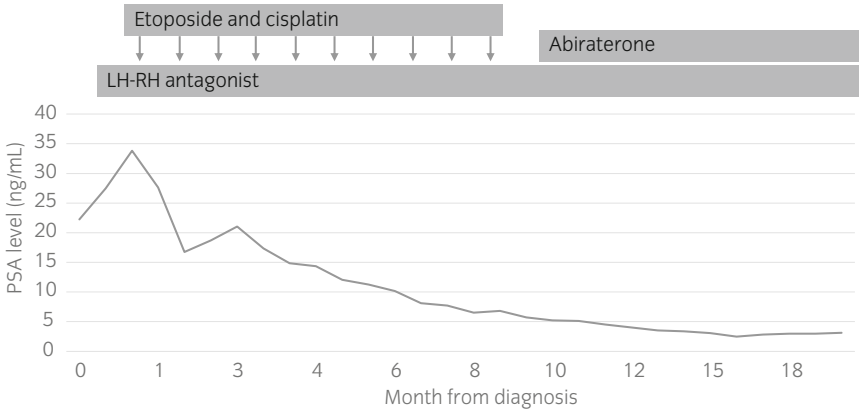

Fig. 1 Clinical course and serum level of the PSA (ng/mL).

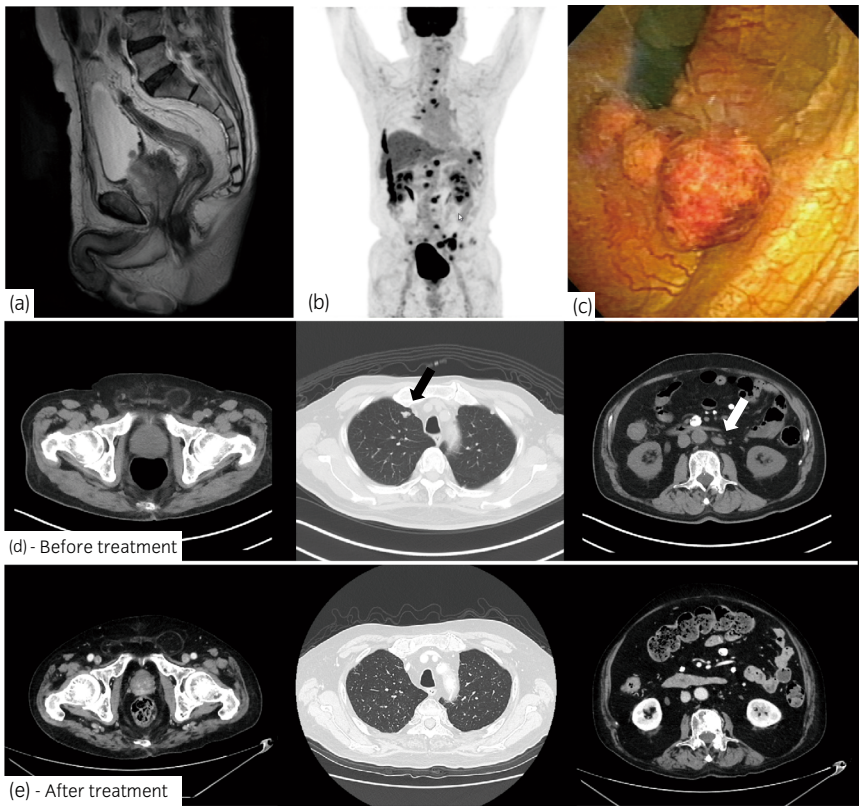

Fig. 2 Imaging studies. (a) MRI revealed a prostatic tumor protruding into the bladder, with seminal vesicle invasion, and (b) positron emission tomography revealed multiple metastases to the para-aortic lymph nodes, bones, and bilateral lung. (c) Cystoscopy revealed a non-papillary tumor on the bladder neck. CT (d) before and (e) after treatment (10 months after completing 10 cycles of chemotherapy with etoposide and cisplatin) showed a partial response to both primary and metastatic lesions (arrow).

studies also showed a tiny mass in the bladder, and cystoscopy revealed a non-papillary tumor on the bladder neck (Fig. 2c). Figure 2d,e show the results of the imaging studies before and after treatment. Prostatic biopsy and TURBT were performed. Histologically, the tumor specimens from both procedures showed similar neuroendocrine morphology, including peripheral palisading and rosettes (Fig. 3a). Immunohistochemical examinations revealed positive staining for NKX3.1, synaptophysin, and chromogranin A, with a Ki-67 labeling index of 70% (Fig. 3b,d). Although the LCNEC component of the tumor was not immunostained for PSA, immunoreactivity was observed for prostate-specific acid phosphatase, prostate-specific membrane antigens, and ARs (Fig. 3c). The tumor also contained an AC component with a Gleason score of 4 + 5 (Fig. 3e), with positive staining for AR and negative for synaptophysin (Fig. 3f,g). The other serum tumor markers were pro-gastrin-releasing peptide 56.8 pg/mL (ULN: 50 pg/mL), neuron-specific enolase 5 ng/mL (ULN: 16.6 ng/mL), and carcinoembryonic antigen 8.9 ng/mL (ULN: 2.5 ng/mL).

The patient was diagnosed with combined LCNEC with AC of the prostate, which was staged as pT4cN1cM1c. He started chemo-hormonal therapy with a LH-RH antagonist and combined etoposide and cisplatin, resulting in a partial response to both primary and metastatic lesions (Fig. 2d,e). After 10 courses, chemotherapy was terminated due to myelosuppression. Subsequently, abiraterone therapy was initiated because of high metastatic risk. Since then, the patient has been followed up by monthly PSA exams and CT scans every 3 months. PSA has remained at a low level, and the patient has survived without disease progression, 20 months after the diagnosis.

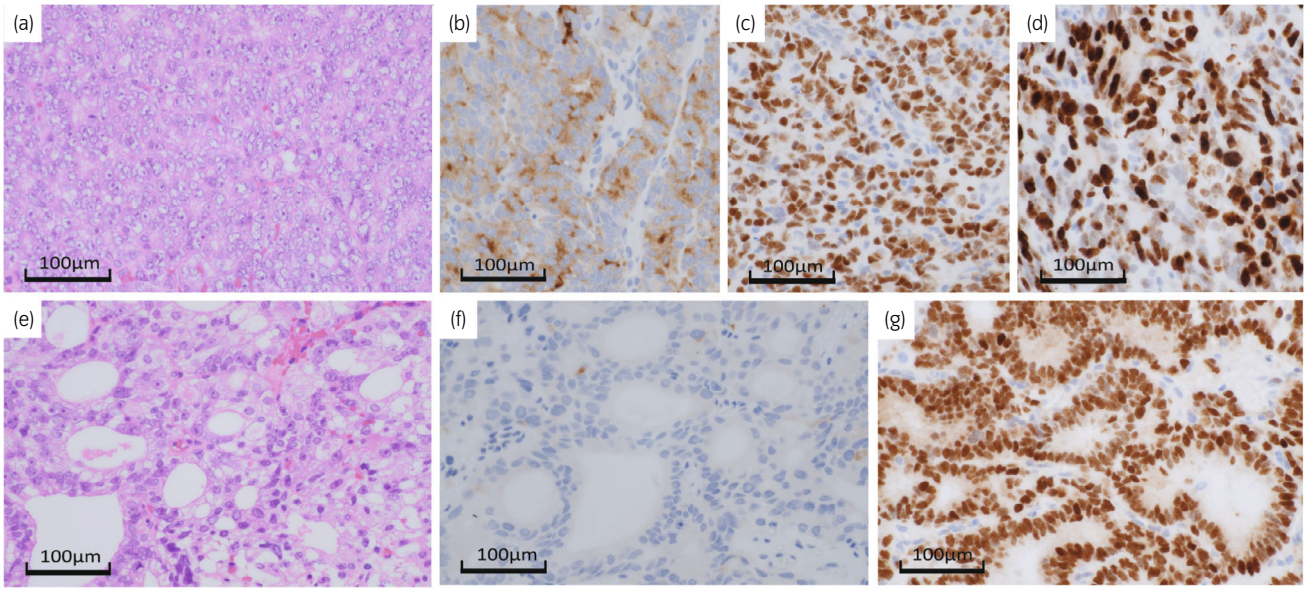

Fig. 3 Histopathological findings of specimens showing large-cell neuroendocrine carcinoma (LCNEC) and AC of the prostate, all at 400× magnification (scale bar: 100 μm). LCNEC component (a–d); (a) Hematoxylin and eosin staining. Immunohistochemical examinations demonstrating positive staining for (b) synaptophysin and (c) AR, with a (d) Ki-67 labeling index of 70%. AC component (e–g); (e) hematoxylin and eosin staining. Immunohistochemical examinations showing negative staining for (f) synaptophysin, and positive for (g) AR.

Discussion

LCNEC is a tumor entity first observed in lung cancer by Travis *et al*. in 1991.[2] It was added as a histological subtype of large-cell carcinoma in the 1999 WHO classification of lung tumors.[3] LCNEC is a large-cell carcinoma with neuroendocrine morphology. The confirmation of neuroendocrine differentiation by immunohistochemistry or electron microscopy is mandatory for its definitive diagnosis.

In 2006, Evans *et al*. reported the first and largest case series for prostatic LCNEC.[4] To date, only 23 of these cases have been reported, including ours (Table 1).[4–18] Of these cases, half had a history of long-standing ADT for conventional-type prostate AC, suggesting acquired neuroendocrine differentiation. The rest is considered as *de novo* LCNEC, which can be classified into two types: pure and combined with AC.

In all reported cases, serum PSA levels varied but showed type-dependent trends. For cases of *de novo* LCNEC with available data, five with PSA immunoreactivity showed a high serum PSA level (3.3–170 ng/mL, mean: 58.3 ng/mL) regardless of the presence of the AC component. In contrast, there are four without PSA immunostaining, three of which were pure LCNEC with a normal serum PSA level (0.09–3.9 ng/mL, mean: 2.1 ng/mL) and the remaining one (our case), which has AR-positive LCNEC admixed with hormone-naive AC, showed a high serum PSA level (22.47 ng/mL).

Many patients with prostatic LCNEC reportedly presented with LUTS, hematuria, or hydronephrosis, which were possibly associated with direct tumor invasion beyond the prostate (10/11 cases were T4). In addition, almost all cases showed metastasis upon diagnosis (12/14 cases were N1, and 10/16 cases were M1). These data indicate that LCNEC has a highly aggressive clinical behavior, with rapid progression at both local and distant sites.

LCNEC is known to have a dismal prognosis. In the study by Evans *et al*., six cases with available follow-up data had rapid disease progression and died at a mean of 7 months after platinum-based chemotherapy.[4] In all previously reported cases, five patients were alive at the time of reporting; four of which, including our case, had *de novo* LCNEC admixed with typical AC and underwent ADT. In addition, all these cases had similar pathology with positive immunostaining for either PSA or AR in the LCNEC component. Patients with pure LCNEC (one PSA/AR positive case was reported; however, the outcome was unknown) and those with mixed hormone-naive AC and PSA/AR negative LCNEC have not been reported to survive. Although LCNEC with acquired differentiation from AC through exposure to long-term ADT generally lacks AR expression resulting in an ADT-refractory tumor, combined LCNEC with hormone-naive AC, especially with AR expression in the LCNEC, may have a good prognosis with ADT.

A treatment strategy for LCNEC has not been established due to the small number of reported cases. Existing case reports of LCNEC rarely mention treatment options, but the reports that discuss treatment strategies pertain to the treatment for SCNEC, which is more prevalent and more widely reported than LCNEC.[10,12] SCNEC has no standard treatment; however, due to its similarity with SCLC, platinum-based chemotherapy is administered as first-line chemotherapy, and sometimes platinum is combined with taxanes, etoposide, and irinotecan.[19] An initial response is observed in some cases, but it is short-lived. Combining chemotherapy and immunotherapy to treat SCLC has improved survival compared to chemotherapy alone. However, no benefit has

Table 1 Characteristics of reported cases of prostatic large-cell neuroendocrine carcinoma

Case	Author	Age	PSA (ng/mL)	Prior ADT	Pathology	PSA	PAP/PSAP	AR	Chief compliant	Diagnosis	Tumor stage	Treatment after LCNEC diagnosis	Outcome
1	Evans *et al.*[4] (2006)	71	3.66	Yes	–	+	+	–	N/R	TURP	N/R	Chemotherapy: palliative mitoxantrone	Died of disease; bone, lymph nodes, mets
2		81	<0.05	Yes	–	–	–	–	N/R	TURP	N/R	Chemotherapy: carboplatin, VA-16	Died of disease; lung, liver, brain, mets
3		75	N/R	Yes	–	–	–	N/R	N/R	Biopsy of pelvic mass	N/R	Radiation	Lost to follow-up
4		64	<0.2	Yes	–	–	+	–	N/R	TURP	N/R	Chemotherapy: carboplatin and etoposide	Died of disease; bone mets
5		65	<0.2	Yes	–	–	+	–	N/R	TURP	N/R	Chemotherapy: carboplatin and etoposide	Died of disease; bone mets
6		69	<0.1	No	Pure	N/R	N/R	N/R	N/R			Prostatectomy Chemotherapy: carboplatin and etoposide	N/R Died of disease; pelvic mass post-prostatectomy and brain mets
7	43	9.9	Yes	–	–	+	–	N/R	TURP	N/R		Chemotherapy: carboplatin, etoposide and palliative mitoxantrone	Died of disease; bone mets
8	Moratalla *et al.*[5] (2013)	81	0	Yes	–	N/R	N/R	N/R	hematuria	PBx	T4N0M1b	Chemotherapy: docetaxel and carboplatin	Died of disease 10 days after starting chemotherapy
9	Azad *et al.*[6] (2014)	70	9.6	No	Mixed	+	N/R	N/R	LUTS	PBx	T3N1M0	ADT	Survival
10		71	170	No	Mixed	+	N/R	N/R	LUTS, swollen left leg	PBx	T4N1M1b	ADT	Survival
11	Lin *et al.*[7] (2014) T4N1M0	84	N/R	No Palliative care	Pure Died of	N/R	N/R	N/R	hematuria disease 1 year after			obstructive renal failure discharged	TURP 12
	Okoye *et al.*[8] (2014)	48	N/R	No	Mixed	–	–	N/R	LUTS	TURP	TxN1M0	Chemotherapy: paclitaxel, etoposide and cisplatin with ADT	Died of disease 13 months after prostatectomy
13	Acosta-Gonzalez *et al.*[9] (2014) T4N1M0	66 N/R	97 N/R	No	Pure	+	++	++	bilateral			hydronephrosis	TURP
14	Patel *et al.*[10] (2015)	75	<0.01	Yes	–	N/R	N/R	N/R	LUTS, hematuria	TURP	T4NxM1c (lung)	Chemotherapy: Platinum and etoposide	Survival
15	Zafarghandi *et al.*[11] (2017)	71	0.09	No	Pure	–	N/R	N/R	LUTS	TURP	T4N1M0	Radiation	N/R
16	Tzou *et al.*[12] (2018)	66	2.44	No	Pure	–	N/R	–	LUTS	TURP	T4N1M1	Chemotherapy: cisplatin and etoposide	N/R
17	Miyakawa *et al.*[13] (2018)	87	3.3	No	Mixed	+	N/R	+	LUTS, hematuria	TURBT	T4N0M0	ADT	Survival
18	Papagoras *et al.*[14] (2018)	69	11.49	No	N/R	+	+	N/R	facial swelling and	PBx	TxN1M1b	N/R	Died of disease 4 months after the diagnosis

Table 1 (Continued)

Case	Author	Age	PSA (ng/mL)	Prior ADT	Pathology	PSA	PAP/PSAP	AR	Chief compliant	Diagnosis	Tumor stage	Treatment after LCNEC diagnosis	Outcome
									redness fatigue				
19	Acar *et al.*[15] (2019)	70	<0.2	Yes	Mixed	N/R	N/R	N/R	N/R	N/R	TxN1M1b	Radiation: 177Lu DOTATATE headache, dizziness extremity weakness	N/R
20	Aljarba *et al.*[16] (2020)	79	12.3	Yes	–	+	N/R	N/R	LUTS,				Removal of brain tumor
	TxNxM1c (brain)			Palliative care	Died of				disease 43 days after the surgery				
21	Basatac *et al.*[17] (2020)	70	3.9	No	Pure	–	N/R	N/R	LUTS, hematuria	TURP+PBx	T4N1M1c (brain)	Chemotherapy: cisplatin and etoposide	Died of disease 7 months after the surgery
22	Schepers *et al.*[18] (2020)	75	90	Yes	–	–	N/R	N/R	muscle weakness emotional lability	PBx	TxN1M1b	Palliative care	Died of disease within several weeks after diagnosis
23	Our case (2022)	83	22.47	No	Mixed	–	+	+	LUTS	TURBT+PBx	T4N1M1c (lung)	Chemotherapy: cisplatin and etoposide with ADT	Survival

been reported for prostate SCNEC.[20] More clinical information is necessary to establish the prostate LCNEC and SCNEC treatment strategy.

Conclusions

The early introduction of combined androgen deprivation and platinum-based chemotherapy may have beneficial effects in patients with *de novo* LCNEC of the prostate, especially with AR expression. AR immunoreactivity should be confirmed to ensure an appropriate treatment strategy when de novo LCNEC of the prostate is observed.

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Author contributions

Eri Fukagawa: Conceptualization; data curation; investigation; project administration; visualization; writing – original draft; writing – review and editing. Takeshi Yuasa: Conceptualization; data curation; project administration; supervision. Kentaro Inamura: Data curation; writing – review and editing. Kosuke Hamada: Data curation. Motohiro Fujiwara: Data curation. Yoshinobu Komai: Data curation. Junji Yonese: Data curation; 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 has been approved by a suitably constituted Ethics Committee of Cancer Institute Hospital of Japanese Foundation for Cancer Research (Approval No. 2012–1008). The protocol also conforms to the provisions of Declaration of Helsinki.

Informed consent

Informed consent was obtained from the subject.

Registry and the Registration No. of the study/trial

Not applicable.

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