Leptomeningeal carcinomatosis in small cell carcinoma of the prostate

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Abbreviations & Acronyms
CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
MRI = magnetic resonance imaging
NSE = neuron-specific enolase
PCI = prophylactic cranial irradiation
ProGRP = pro-gastrin-releasing peptide
PSA = prostate-specific antigen
RT = radiation therapy
SCCP = small-cell carcinoma of the prostate

Introduction: Leptomeningeal carcinomatosis in small cell carcinoma of the prostate is rare.

Case presentation: A 69-year-old man visited our hospital due to dysuria and edema. Bilateral hydronephrosis and lymph node metastases due to a pelvic tumor were observed. Although the prostate-specific antigen level was normal, the tumor was suspected to originate from the prostate. He underwent percutaneous nephrostomy and prostate biopsy. Histopathology revealed small cell carcinoma accompanied by increased pro-gastrin-releasing peptide and neuron-specific enolase levels. After receiving systemic chemotherapy with carboplatin and etoposide and radiation therapy for prostate, these lesions gradually decreased in size, and tumor markers normalized. Ten months after the initial diagnosis, he developed consciousness disorder and seizure. Magnetic resonance imaging revealed leptomeningeal carcinomatosis without any other recurrences and elevated tumor markers. He died 4 weeks after these symptoms appeared.

Conclusion: Careful monitoring of the central nervous system should be considered in small cell carcinoma of the prostate patients.

Key words: brain metastasis, leptomeningeal carcinomatosis, prostate carcinoma, small cell carcinoma of the prostate.

Keynote message
Leptomeningeal carcinomatosis in small cell carcinoma of the prostate is extremely rare. It shows a poor prognosis once appeared. So we should observe carefully even with no evidence of disease progression.

Introduction
Small cell carcinoma of the prostate (SCCP) is rare and accounts for 0.5–2% of prostate tumors.1 Although SCCP has high response rate to chemotherapy,2,3 it has a poor prognosis because it tends to be refractory and relapsing. Leptomeningeal carcinomatosis is known to be the metastatic spread of tumor cells to the pia mater, arachnoid, and subarachnoid space. Leptomeningeal carcinomatosis in SCCP is rare and associated with rapid progression and poor prognosis.4 Here, we reported a case of leptomeningeal carcinomatosis in SCCP.

Case presentation
A 69-year-old man visited our hospital due to oliguria and edema. Computed tomography (CT) revealed bilateral hydronephrosis, multiple lymph node swelling, and a pelvic tumor (Fig. 1a,b). Laboratory data showed acute post-renal failure (creatinine, 13.48 mg/dL) due to the large pelvic tumor. His renal failure improved after percutaneous left nephrostomy. Colonoscopy was performed to exclude the possibility of advanced rectal cancer, but no suspicious lesion was found (Fig. 1c). Although prostate-specific antigen (PSA) level was normal
(2.39 ng/mL), we suspected the prostate as the origin of the tumor, and prostate biopsy was performed. Histological findings revealed proliferation of small cells with a high nuclear-to-cytoplasmic ratio (Fig. 2a), with immunohistochemical staining results (Fig. 2b-e), and pro-gastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) levels were elevated (ProGRP, 17,000.0 [normal limit, < 81.0] pg/mL; NSE, 51.2 [normal limit, < 16.3] ng/mL). Therefore, SCCP was diagnosed (clinical stage T4N1M1a). His clinical course is shown in Figure 3. He received systemic chemotherapy with carboplatin (area under the concentration–time curve, 4) and etoposide (100 mg/m²), and radiation therapy (RT) for the pelvic tumor (30 Gy). After 6 cycles of chemotherapy and RT, these lesions gradually decreased in size (Fig. 4a,b), and serum tumor marker levels normalized (Fig. 3), but chemotherapy was discontinued due to febrile neutropenia and fatigue. Ten months after the initial diagnosis, he was transferred because of consciousness disorder and seizure. Although no recurrence was observed on CT and serum tumor markers remained within normal levels, magnetic resonance imaging (MRI) revealed leptomeningeal carcinomatosis and brain metastases (Fig. 4c,d). For analysis, cytological evaluation in the cerebrospinal fluid (CSF) was negative (class 2), but tumor marker levels in the CSF were elevated.

Fig. 1 Results of abdominal computed tomography (CT) (a, b) and endoscopic ultrasonography by colonoscopy (c) at the initial diagnosis. (a) CT reveals bilateral hydronephrosis, para-aortic lymph node swelling (yellow arrow), and (b) a pelvic tumor involving the prostate and rectum (yellow arrows). Oliguria was caused by the tumor. (c) Although there were no lesions on colonoscopy, mosaic patterns in prostate was found by endoscopic ultrasonography.

Fig. 2 Histopathological findings at prostate biopsy specimen. Since PSA level was normal, we thought an atypical tumor unlike prostate adenocarcinoma at first. (a) Hematoxylin and eosin staining. The tumor cells appeared oval to spindle-shaped with a high nuclear/cytoplasmic ratio and scattered rosette pattern (yellow arrows). Histological findings strongly suggestive of small cell carcinoma. (b-e) Immunoistochemical staining. (b) Synaptophysin and (c) chromogranin A was diffusely positive. (d) The Ki-67 labeling index was about 100%. (e) NKX3.1 was negative. Immunohistochemical results confirmed the diagnosis of pure SCCP.
(ProGRP, 76.7 pg/mL; NSE, 363.0 ng/mL). He died within 4 weeks due to rapid progression.

**Discussion**

Histologically, SCCP is classified into three types: (i) pure SCCP (35.4%); (ii) mixed type, comprising adenocarcinoma, and small cell carcinoma (17.7%); and (iii) development of SCCP during the treatment of adenocarcinoma (46.9%).

All three types of SCCP have a poor prognosis, with a median survival period ranging from 5 to 17.5 months. Although the elevated PSA level in SCCP accounts only for 25%, the levels of serum tumor markers, such as ProGRP and NSE are frequently elevated and useful for confirming the diagnosis and monitoring disease progression. Thus, to diagnose SCCP, evaluating serum neuroendocrine markers is necessary as well as the histologic confirmation when serum PSA level does not reflect the disease state or when atypical visceral metastases are found. In our case, he had pure SCCP at the initial diagnosis, and serum tumor marker levels helped in confirming histopathologic findings.

Since SCCP has demonstrated similarity to small cell lung carcinoma in morphologic features, the current recommended chemotherapy regimens for SCCP are platinum-based, similar to those used for small cell lung carcinoma. In our case, he received systemic chemotherapy with carboplatin and etoposide due to mild renal dysfunction.

The proportion of brain metastasis in SCCP was 10–16%, whereas that of prostate adenocarcinoma was 0.8%. Leptomeningeal carcinomatosis in prostate cancer is also rare (<5%), which is usually observed in patients with end-stage disease. Additionally, the prognosis of leptomeningeal carcinomatosis from solid tumors is extremely poor, as the median overall survival periods are approximately 4 weeks without treatment and 2–4 months even with intensive treatment. He died 4 weeks after the symptoms appeared due to his poor performance status which caused his avoidance of intensive treatment such as chemotherapy, prophylactic percutaneous nephrostomy.
cranial irradiation (PCI), and surgery. Typical symptoms of abnormal neurological findings include consciousness disorder and seizure. To diagnose leptomeningeal carcinomatosis, CSF cytology by lumbar puncture is required, but the sensitivity of a single procedure is only 50–70%. Moreover, occasionally, repeated examinations are required to increase the sensitivity. Regarding neuroimaging, gadolinium-enhanced MRI is a useful examination because its sensitivity is 76–87%, which is higher than a single CSF examination. According to the report of other cancers, 28.3% of patients with intracranial metastasis with lung or breast cancer did not show elevated serum tumor marker levels. Thus, leptomeningeal carcinomatosis appeared despite the absence of disease progression and the presence of normal tumor marker levels because chemotherapeutic agents might not effectively cross the blood–brain barrier. Since chemotherapeutic agents cannot affect the central nervous system (CNS) while concomitantly enhancing tumor control outside the CNS, viable tumors might reach intracranial sites. Since data on the efficacy of PCI for SCCP are lacking, previous reports do not recommend routine use. To the best of our knowledge, this is the first case in which leptomeningeal carcinomatosis in pure SCCP was confirmed without evidence of disease progression and within normal serum tumor marker levels. The results of our case suggest that CNS metastasis can occur even in cases without evidence of organ metastases other than CNS or without the elevation of tumor markers, and if suspicious symptoms occur, prompt examination with gadolinium-enhanced MRI is required to make a diagnosis. Further studies are required to improve their prognosis.

Conclusion
In conclusion, since leptomeningeal carcinomatosis in SCCP shows a poor prognosis, careful observation is required even with no evidence of disease progression.

Author contributions
Kyotaro Fukuta: Conceptualization; data curation; visualization; writing – original draft. Keito Shiozaki: Investigation. Ryoichi Nakanishi: Investigation. Hirofumi Izaki: Supervision. Eiji Kudo: Conceptualization; writing – review and editing. Tomoya Fukawa: Conceptualization; writing – review and editing. Kunihisa Yamaguchi: Methodology. Yasuyo Yamamoto: Methodology. Masayuki Takahashi: Supervision. Hiro-omi Kanayama: Supervision.

Conflict of interest
The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board
Not applicable.

Informed consent
Written informed consent was obtained.

Registry and the Registration No. of the study/trial
Not applicable.

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