Case Report

Lethal disseminated intravascular coagulation induced by primary and metastatic neuroendocrine prostate cancer

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Abbreviations & Acronyms
ADT = androgen deprivation therapy
ALT = alanine aminotransferase
AST = aspartate aminotransferase
AT-III = antithrombin III
Cre = creatinine
CRP = C-reactive protein
CT = computed tomography
DIC = disseminated intravascular coagulation
FDP = fibrin degradation product
Hb = hemoglobin
Hct = hematocrit
LDH = lactate dehydrogenase
NEC = neuroendocrine carcinoma
NEDPC = neuroendocrine differentiation of prostate cancer
NEPC = neuroendocrine prostate cancer
NSE = neuron-specific enolase
PCa = prostate cancer
Plt = platelet
PSA = prostate-specific antigen
PT-INR = prothrombin time-international normalized ratio
RBC = red blood cells
TAT = thrombin–antithrombin complex
T-Bil = total bilirubin
TP = total protein
WBC = white blood cells

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Introduction: Neuroendocrine prostate cancer has a poor prognosis. Although disseminated intravascular coagulation associated with malignancy can be lethal, it very rarely occurs among patients with primary neuroendocrine prostate cancer.
Case presentation: An 80-year-old man presented to our hospital with bloody sputum. Blood examination indicated disseminated intravascular coagulation. Serum levels of prostate-specific antigen and neuron-specific enolase were 44.274 and 176 ng/mL, respectively. Core needle biopsies of an irregular mass in the prostate and a metastatic tumor in the left iliac bone showed similar neuroendocrine carcinoma cells. Hence, the patient was diagnosed with disseminated intravascular coagulation associated with primary and metastatic neuroendocrine prostate cancer. Unfortunately, he passed away 3 weeks after the biopsies.
Conclusion: Given the difficulty of effectively treating metastatic neuroendocrine prostate cancer among patients in poor physical condition due to disease progression, identifying a new well-tolerated treatment modality is imperative.

Key words: biopsy, case reports, disseminated intravascular coagulation, neoplasm metastasis, neuroendocrine carcinoma, neuroendocrine carcinoma prostate cancer.

Keynote message

An 80-year-old man was diagnosed with disseminated intravascular coagulation (DIC) associated with primary and metastatic neuroendocrine prostate cancer (NEPC). Although extremely rare, primary NEPC-associated DIC can be lethal. Considering the challenges associated with effectively treating metastatic NEPC in patients with a poor physical condition due to DIC, identifying a new well-tolerated treatment modality is imperative.

Introduction

NEDPC often results from ADT, a condition called treatment-related NEPC.[1] However, primary NEPC is a rare subtype of PCa that accounts for <1% of newly diagnosed PCa cases.[1–3] NEPC has a poor prognosis, and metastatic NEPC can be lethal.[1–3] Several malignancies can cause DIC, which can be lethal in cases with advanced malignancies.[4] ADT treatment can often cause DIC in patients with advanced PCa depending on its progression. However, DIC rarely occurs in patients with primary NEPC. We herein report a case involving an 80-year-old man who developed DIC due to primary and metastatic NEPC.

Case presentation

An 80-year-old man presented to the respiratory medicine department at our hospital with bloody sputum. Initial examination revealed hypertension, hypercholesterolemia, and hyperuricemia, but the patient and his family did not have any history of malignancies. Chest CT found no cause for his bloody sputum, and no otorhinolaryngological bleeding was detected by an otorhinolaryngologist. Blood examination results revealed pancytopenia, suggesting malignancy (Table 1). The patient's serum PSA level 2 years prior to presentation was

Table 1 Laboratory test findings

	Normal range		5 months ago	2 months ago	3 weeks ago	1 week ago	At visit urology department	DIC score
T-Bill	0.4–1.5	mg/dL	0.4	0.4	0.8	0.9	1.4	
AST	13–30	U/L	24	37	111	113	103	(Liver failure)
ALT	10–42	U/L	21	16	12	11	11	0
LDH	124–222	U/L	181	282	888	1003	1005	
Cre	0.65–1.07	mg/dL	1.03	0.97	1.04	1.16	1.12	
TP	6.6–8.1	g/dL	7.6	7.3	7.1	7.4	7	
CRP	0–0.14	mg/dL				0.49	1.4	
WBC	33–86	/μL	7700	7700	6500	6500	5300	
RBC	435–555	$\times 10^4$ /μL	463	422	354	350	310	
Hb	13.7–16.8	g/dL	14.1	13.1	10.8	10.7	9.5	
Hct	40.7–50.1	%	24.8	38.5	31.7	31.9	27.8	
Reticulocyte	3–11	%				30	29	
Plt	15.8–34.8	$\times 10^4$ /μL	24.8	17.6	9.5	8.6	8.2	1
FDP	0–4.9	μg/mL					382.5	3
Fibrinogen	200–400	mg/dL					161	0
PT-INR							1.38	1
AT-III	80–120	%					89	0
TAT	0–3.9	ng/mL					102.7	1
D-dimer	0–1	μg/mL					136.4	
								Total score 6

DIC score based on the diagnostic criteria established by the Japanese Society on Thrombosis and Hemostasis (2017 edition).

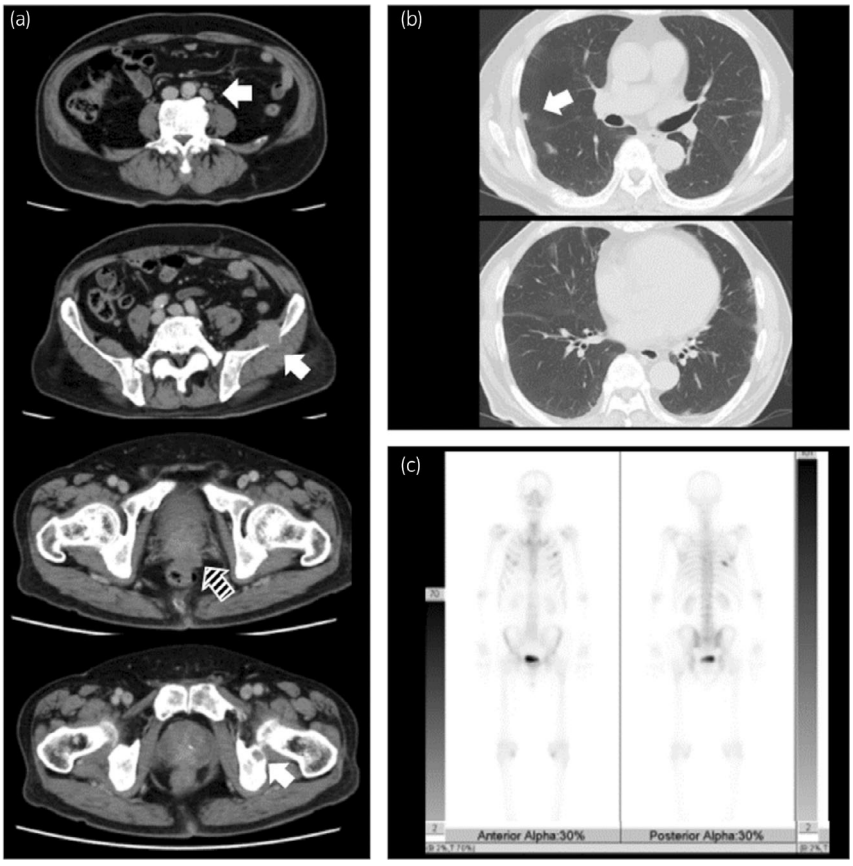

Fig. 1 CT and bone scan. (a) Axial abdominal and pelvic CT images obtained upon hospitalization. An irregular mass was identified at the base of the prostate (striated arrow). Para-aortic lymph node metastases and bone metastases were visualized (white arrows). (b) Axial chest CT images obtained upon hospitalization revealed lung metastasis (white arrow). Inflammatory changes could be visualized at the lung periphery. (c) A whole-body bone scan demonstrated no hot spots. The hot spots on the ribs suggested old fractures.

2.168 ng/mL but increased to 15.0 ng/mL during a local medical examination 1 month prior to presentation and then again to 44.274 ng/mL upon presentation to our internal medicine department, which prompted referral to our urology department. His serum NSE and soluble interleukin-2 receptor levels were 176 ng/mL and 694 U/mL, respectively.

Further examinations revealed normal levels of serum carcinoembryonic antigen, squamous cell carcinoma, carbohydrate antigen 19-9, and pro-gastrin-releasing peptide. Laboratory data suggested the presence of DIC based on the diagnostic criteria established by the Japanese Society on Thrombosis and Hemostasis (2017 edition) (DIC score = 6 [cutoff value, ≥6]; Table 1).[4] A rectal examination detected a deep, hard, and irregular mass in the prostate. Abdominal and pelvic CT revealed an irregular mass at the base of the prostate and multiple metastatic lesions in the lymph nodes, bone, and lungs (Fig. 1a,b). A bone scan found no significant tracer accumulation (Fig. 1c).

The patient was advised admission for core needle biopsies of the prostate and left iliac bone tumor. The biopsies were performed without any severe adverse events using 12,800 units of thrombomodulin alfa per day, which was administered before each biopsy for a total of two doses. A total of 10 core samples, including four cores from the irregular mass, were obtained from the prostate. Biopsies of the irregular prostatic mass and metastatic mass at the left iliac bone revealed similar small cell NEC, whereas biopsy of the mid-prostate revealed typical adenocarcinoma (Gleason score 3 + 4) (Fig. 2). Immunostaining characteristics determined from the biopsies suggested that left iliac bone metastasis from a primary NEPC (Fig. 3). The patient was ultimately diagnosed with DIC due to primary and metastatic NEPC. Unfortunately, invasive endoscopic examinations, such as a gastroscopy, colonoscopy, and bronchoscopy, could not be performed owing to his physical condition. A comprehensive explanation regarding the disease, its prognosis, and treatment options (ADT, platinum-etoposide chemotherapy, and supportive care) was provided to the patient and his family. However, the patient opted for only supportive care without ADT, stating that he had lived long enough and had suffered from shortness of breath. Accordingly, pain relief treatment using morphine was initiated, with the patient passing away 3 weeks after the biopsies. The family did not consent to an autopsy. At the time of death, the patient's serum PSA and NSE levels were 148.7 and 255 ng/mL, respectively.

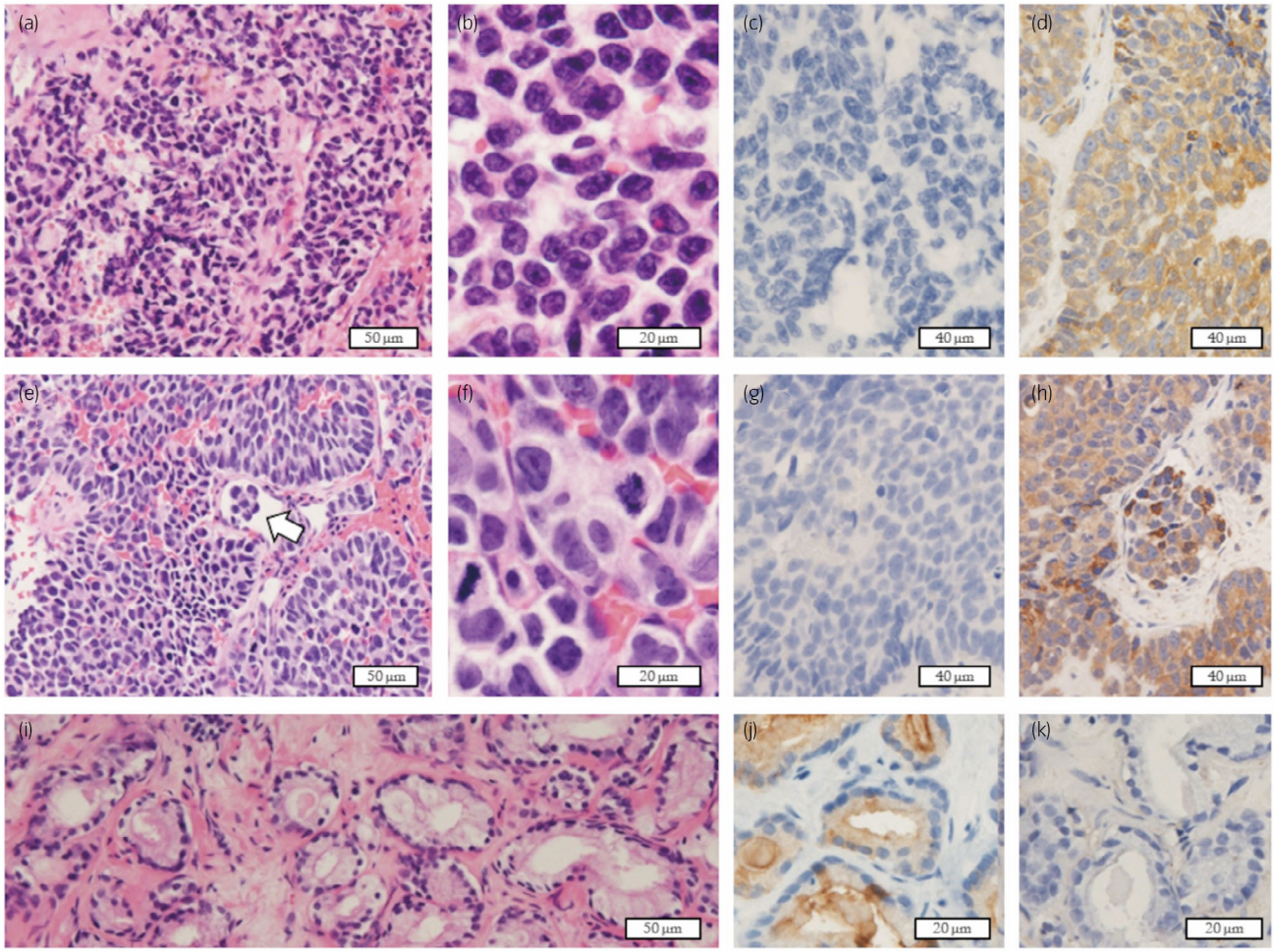

Fig. 2 Pathological findings I. Pathological findings of the core needle biopsy samples obtained from the tumors (a–d) at the base of the prostate, (e–h) left iliac bone, and middle of the prostate (i–k). Samples were stained with hematoxylin and eosin (a, b, e, f, and i) and immunostained for PSA (c, g, and j) and NSE (d, h, and k). Similar small cell carcinomas were detected in the prostate and left iliac bone tumors (a, b, e, and f). The arrow shows the carcinoma cells present in the blood vessels (e). Given the negative immunostaining findings for PSA and positive findings for NSE, an immunostaining marker for NEC, these carcinoma cells were diagnosed as NEC (c, d, g, and h). The tumor at the mid-prostate was found to be a typical adenocarcinoma, with a Gleason score of 3 + 4 (i), PSA positivity (j), and NSE negativity (k).

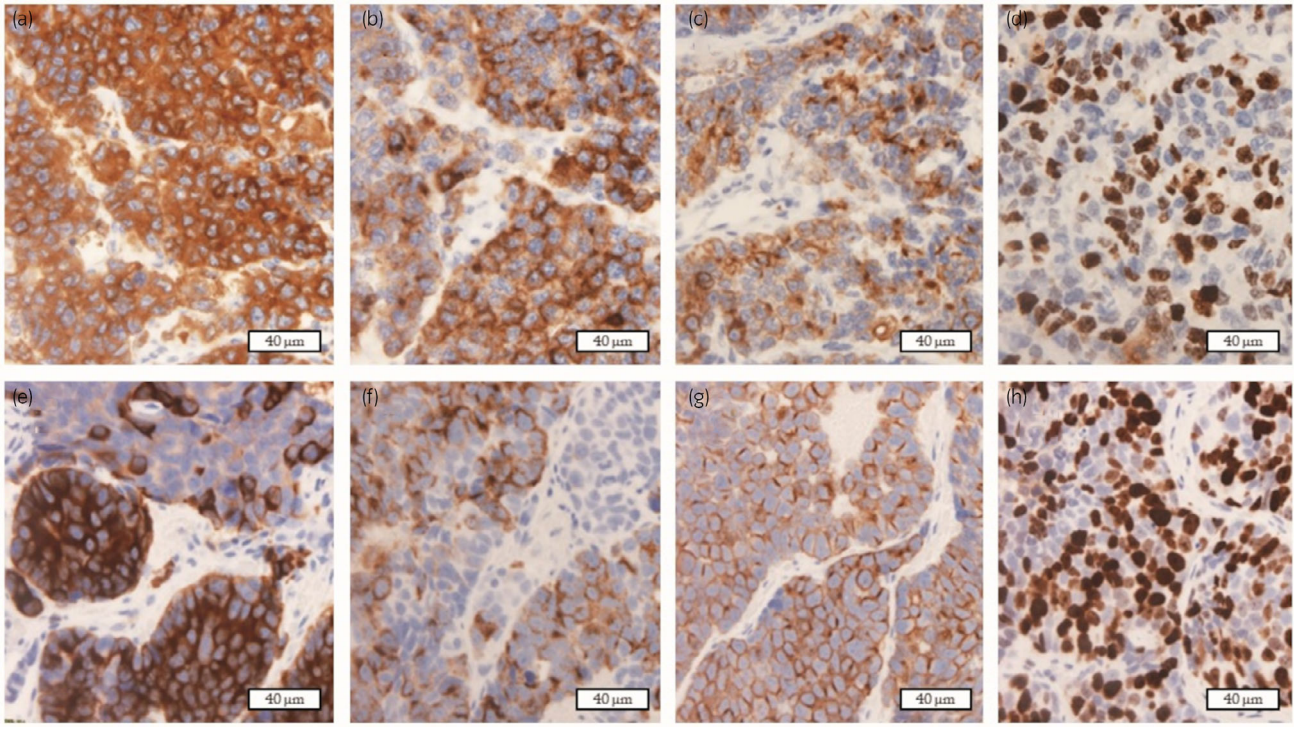

Fig. 3 Pathological findings II. Pathological findings of the core needle biopsy samples obtained from the tumors (a–d) at the base of the prostate and (e–h) at the left iliac bone. The samples were immunostained for synaptophysin (a, e), chromogranin A (b, f), CAM5.2 (c, g), and Ki67 (d, h). Immunostaining for markers of NEC, such as synaptophysin, chromogranin A, and CAM5.2, came back positive (a–c and e–g). These characteristics were similar for prostate and bone mass. These findings suggest that the bone tumor was a metastatic lesion, with the primary NEC originating from the prostate. The immunostaining positivity rate for Ki67 was >50%, suggesting highly proliferative NEC cells (d, h).

Discussion

Although rarely detected in every organ, NEC is most frequently observed in the lungs, followed by the small intestines, rectum, pancreas, stomach, appendix, and colon. NEPC is a very rare disease often diagnosed in its advanced stages given that routine prostate examinations frequently overlook this disease. Furthermore, reports have shown that NEPC progresses more rapidly than does typical adenocarcinoma in the prostate.[1] Moreover, serum PSA levels do not reflect the status of NEPC, which is androgen-independent, considering that PSA is a product of prostatic androgen metabolism.[1] Although NSE is a marker of NEC, its sensitivity for detecting early-stage NEC remains insufficient. Therefore, no effective approach exists for detecting early-stage NEPC. Our patient underwent a regional medical PSA examination, which revealed no remarkable findings until 2 years ago. His serum PSA levels increased rapidly within a few weeks. We hypothesize that the NEC could have destructively infiltrated the prostate, triggering an increase in PSA levels resulting from prostate cell destruction, or that the adenocarcinoma had spread throughout the patient's body, worsening his condition. Unfortunately, we could not confirm either of our hypotheses given that an autopsy could not be performed.

DIC can be classified into three subtypes according to its mechanism: "suppressed fibrinolysis," "balanced fibrinolysis," and "enhanced fibrinolysis."[4,5] DIC with suppressed fibrinolysis affects several organs and has been mainly associated with sepsis, whereas DIC with enhanced fibrinolysis causes several bleeding symptoms and has been mainly associated with leukemia, vascular diseases, and PCa. However, other solid cancers can cause balanced fibrinolysis. The decrease in our patient's Plt cell counts and fibrinogen levels, as well as the evaluation of his fibrinogen levels, FDPs, and prothrombin time, indicated DIC with enhanced fibrinolysis. Furthermore, alveolar hemorrhage, which caused hemoptysis, was determined to be a symptom of DIC.

Treating the cause of malignancy-associated DIC is imperative considering the correlation between DIC prognosis and direct treatment of the cause. Localized malignancies can be treated via resection or radiation; however, metastatic malignancies are challenging to treat. Moreover, only a few cases of DIC with untreated metastatic PCa have been reported.[6] ADT has been shown to improve the prognosis in these patients given its remarkable effectiveness as a systemic therapy for typical PCas, such as adenocarcinoma, which is androgen-dependent. Therefore, DIC associated with ADT-naïve PCa may not necessarily be lethal, at least in the short term. Following the patient's rejection of ADT after a thorough discussion, we could not strongly recommend ADT considering that immunostaining for PSA suggested that the NEC cells obtained from the bone metastasis had almost no sensitivity to ADT.

The prognosis of NEPC remains poor, with a median progression-free survival and overall survival of 2–8 and 8–19 months, respectively.[7] Platinum- and etoposide-based

chemotherapy is commonly administered as first-line treatment for NEPC.[7-9] Fujimoto *et al*. summarized the available second-line agents, which included amrubicin, irinotecan, docetaxel, everolimus, and olaparib, with several ongoing clinical trials being conducted on NEPC.[7] Given the lack of an established second-line treatment, physicians should consider personalized treatment approaches for each patient with NEPC. However, chemotherapy places a considerable strain on patients with already poor physical condition due to disease progression. Therefore, no standard treatment has currently been established for patients with DIC caused by primary and metastatic NEPC, which can be lethal.

Conclusion

The treatment of DIC caused by primary and metastatic NEPC remains challenging given the current lack of satisfactory treatments for metastatic NEPC. Hence, a well-tolerated treatment regimen for patients with metastatic NEPC in poor physical condition is urgently needed.

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Author contributions

Takashi Ando: Conceptualization; investigation; resources; writing – original draft. Taro Sasaki: Investigation; resources. Makoto Naito: Investigation; resources; writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Consent for the publication of this case report was acquired from the patient's family.

Registry and the Registration No. of the study/trial

Not applicable.

References

1 Yamada Y, Beltran H. Clinical and biological features of neuroendocrine prostate cancer. *Curr. Oncol. Rep.* 2021; **23**: 15.
2 Apostolidis L, Nientiedt C, Winkler EC *et al*. Clinical characteristics, treatment outcomes and potential novel therapeutic options for patients with neuroendocrine carcinoma of the prostate. *Oncotarget* 2019; **10**: 17–29.
3 Fine SW. Neuroendocrine tumors of the prostate. *Mod. Pathol.* 2018; **31**: S122–32.
4 Wada H, Takahashi H, Uchiyama T *et al*. The approval of revised diagnostic criteria for DIC from the Japanese society on thrombosis and hemostasis. *Thromb. J.* 2017; **15**: 17.
5 Asakura H, Takahashi H, Uchiyama T *et al*. Proposal for new diagnostic criteria for DIC from the Japanese society on thrombosis and hemostasis. *Thromb. J.* 2016; **14**: 42.
6 Umemoto T, Tokunaga M, Miyakita H, Miyajima A. A case of non-treated prostate cancer with disseminated intravascular coagulopathy. *Hinyokika Kiyo. Acta Urol. Jpn.* 2019; **65**: 473–7.
7 Fujimoto N, Tsubonuma Y, Nagata Y *et al*. Second-line systemic therapy for highly aggressive neuroendocrine prostate cancer. *Anticancer Res.* 2023; **43**: 3841–7.
8 Alabi BR, Liu S, Stoyanova T. Current and emerging therapies for neuroendocrine prostate cancer. *Pharmacol. Therap.* 2022; **238**: 108255.
9 Conteduca V, Oromendia C, Eng KW *et al*. Clinical features of neuroendocrine prostate cancer. *Eur. J. Cancer* 2019; **121**: 7–18.