

Oncology

Hypercalcemia due to parathyroid hormone-related peptide secreted by neuroendocrine dedifferentiated prostate cancer

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ARTICLE INFO

Keywords:

Androgen deprivation therapy
Hypercalcemia
Neuroendocrine dedifferentiated prostate cancer
Parathyroid hormone-related peptide

Introduction

Hypercalcemia is a paraneoplastic syndrome and can be caused by several malignancies, such as breast or lung cancer, multiple myeloma, and renal cell carcinoma, but it is rarely caused by prostate cancer (PC).¹ It has been known that neuroendocrine carcinoma (NEC) of the prostate and neuroendocrine dedifferentiated prostate cancer (NEDPC) can secrete parathyroid hormone-related peptide (PTHrP) which may occur hypercalcemia.^{2,3} NEDPC has been often diagnosed in patients with prostate adenocarcinoma receiving long-term androgen deprivation therapy (ADT). Here we report the case of a patient with hypercalcemia due to PTHrP secretion by NEDPC that developed from an adenocarcinoma after receiving long-term ADT.

Case presentation

An 85-year-old male visited our department with symptoms such as fatigue and pain in the trunk for 1 month. He had been diagnosed with PC (adenocarcinoma, cT4N0M0, Gleason score 3 + 4, initial prostate-specific antigen 52.2 ng/mL) 16 years before the visit. He had received an external-beam radiation therapy 70 Gy 8 years prior when the PC advanced to castration-resistant prostate cancer (CRPC) without metastasis after receiving ADT for 8 years. The treatments were considered effective as the serum prostate-specific antigen (PSA) level was consistently < 0.5 ng/mL for 8 years after the radiation and no metastasis was detected by computed tomography (CT) until 1 year before the visit (Fig. 1). Laboratory test results showed substantially elevated serum levels of corrected calcium (16.3 mg/dL, normal range 8.8–10.1 mg/dL), PTHrP (4.5 ng/mL, normal limit < 1.0 ng/mL), and neuron-

specific enolase (NSE; 3120 ng/mL, normal limit < 16.3 ng/mL) along with liver dysfunction (Table 1). However, serum levels of PSA (0.22 ng/mL) and parathyroid hormone (207 pg/mL, normal range 74–273 pg/mL) were within the normal range. CT revealed the existence of locally recurrent prostate tumor invading the rectum and multiple bone, liver, and lymph node metastases (Fig. 2). Clinical diagnosis was hypercalcemia due to PTHrP secretion by NEDPC with metastasis, and the patient was admitted to our department. The patient opted for palliative care using morphine rather than continuous treatments to hypercalcemia and died 7 days after admission. To investigate the histopathological cause of the disease, we recommended performing an autopsy, but it was not performed because his family did not consent to it.

Discussion

Neuroendocrine dedifferentiation (NED) is considered as a mechanism of castration resistance for PC that possibly develops in response to ADT.² Primary NEC is detected in a small percentage of prostate biopsies; however, NED of PC will be caused in major cases of CRPC as the result of long-term ADT.² The influence of radiation therapy on NED is unclear. Prostate biopsies of castration-resistant tumors are uncommon and rarely detect NEDPC. Most NEDPCs are diagnosed after they develop into a metastatic disease and have a poor prognosis. Given the current knowledge, we cannot predict who will develop NEDPC and when; therefore, NED detection in the early phase of CRPC is important. Periodic PSA measurement was insufficient because it did not reflect NEDPC progression and performing image inspection frequently was unrealistic; it could only detect changes

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Received 19 October 2018; Received in revised form 1 November 2018; Accepted 6 November 2018

Available online 09 November 2018

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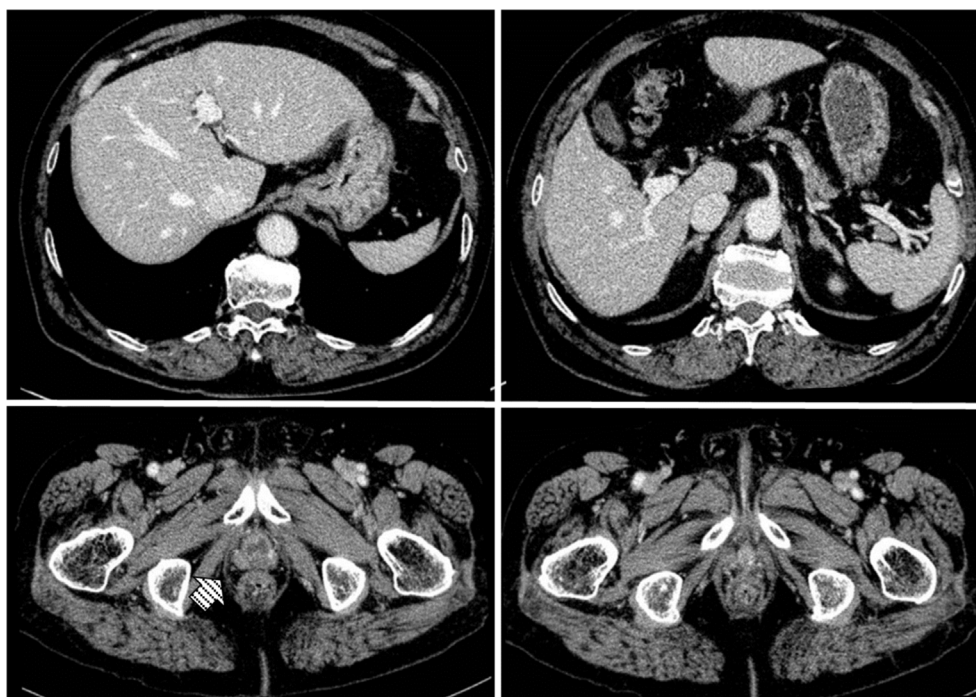


Fig. 1. Abdominal computed tomography 1 year prior to admission. Any metastases were not revealed, but a small locally recurrent tumor in the prostate was retrospectively noted (lined arrow).

Table 1
Changes of laboratory data.

		1 year before admission	3 months before admission	Upon admission
Calcium	(mg/dL)	9.2	9.4	15.4
AST	(IU/L)	22	29	420
ALT	(IU/L)	16	21	68
ALP	(IU/L)	298	460	872
LDH	(IU/L)	200	197	1138
TP	(g/dL)	7.0	7.3	6.0
albumin	(g/dL)	4.3	4.1	3.1
PSA	(ng/mL)	0.42	0.46	0.22
PTH	(pg/mL)			207
PTHrP	(pg/mL)			4.5
NSE	(pmol/L)			3120

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; TP, total protein; PSA, prostate-specific antigen; PTH, parathyroid hormone; PTHrP, PTH-related peptide; NSE, neuron-specific enolase.

associated with disease progression. NSE is a generic marker of NEC with high sensitivity but low specificity. Periodic NSE measurement can monitor NEDPC progression and may be considered for early detection in patients with CRPC, although the routine use of neuroendocrine markers in early stage PC is not recommended.^{2,4} In our patient, periodic PSA assays per 3 or 6 months and CT scan per 1 or 2 years did not detect disease progression; however, elevated serum NSE level reflected disease progression. Chemotherapy is a preferred treatment, and its early adaptation may improve the prognosis of NEDPC.

Hypercalcemia is rare in CRPC even in the presence of multiple bone metastases because they are osteoblastic in nature. Previous studies have reported that NEDPCs secrete PTHrP, a neuroendocrine-derived peptide that can promote PC cell growth and operate as a humoral factor for hypercalcemia.^{3,5} Although there are few studies reporting hypercalcemia in patients with CRPC, to the best of our knowledge, this is the first study to report the case of a patient who demonstrated high serum PTHrP levels as a cause of hypercalcemia.

Hypercalcemia due to humoral PTHrP secretion can be lethal if it is

caused by a metastatic malignancy, because the secretion by the tumor may not be effectively ceased.⁵ Hypercalcemia is categorized according to the total serum calcium level: mild, 10.5–11.9 mg/dL; moderate, 12.0–13.9 mg/dL; and severe, ≥ 14.0 mg/dL. Severe hypercalcemia may be lethal, causing neurocognitive symptoms such as epileptic seizures or coma, acute renal failure, and acute heart failure. Fluid replacement and the use of loop diuretics, glucocorticoids, calcitonin, zoledronic acid, and denosumab are recommended for hypercalcemia treatment. We started those treatments such as the use of loop diuretics, calcitonin, and zoledronic acid, for the patient upon admission, but he opted for palliative care rather than those treatments.

The lack of histopathological confirmation of NEDPC is a major limitation of our report. However, CT findings of the locally recurrent prostate tumor invading the rectum, substantially elevated serum NSE level, and the absence of gastrointestinal cancers indicate the presence of NEDPC.

Conclusion

NEDPC developed from PC as the result of ADT and could worsen rapidly. It caused hypercalcemia due to PTHrP secretion, which was lethal. Early detection and treatment of NEDPC would improve prognosis; therefore, periodic monitoring of neuroendocrine markers such as NSE should be considered.

Consent

Verbal informed consent was obtained from the patient's family for the publication of this case report.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding

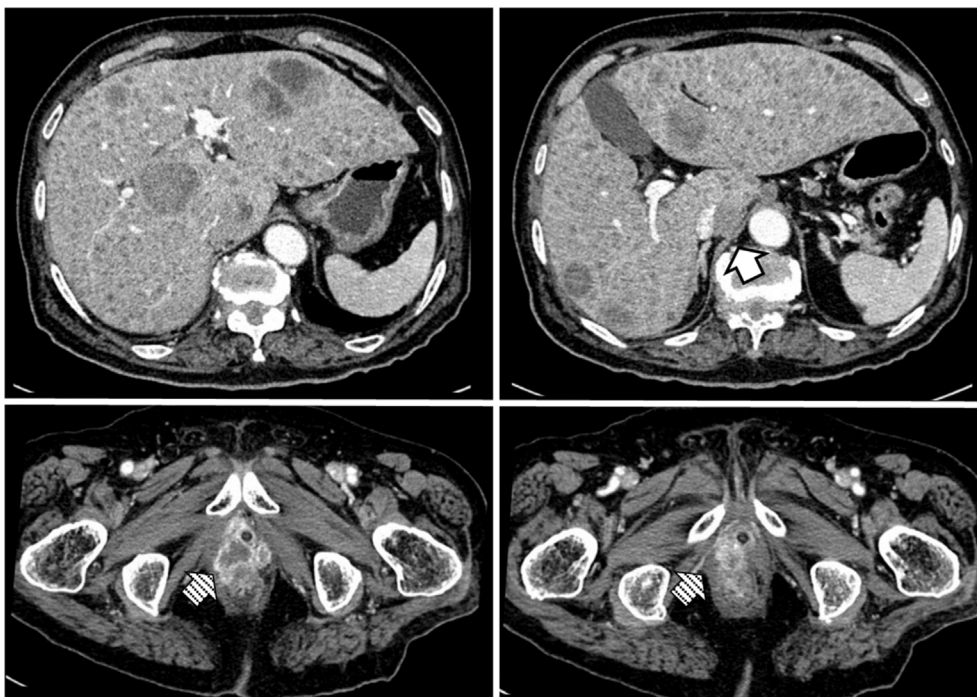


Fig. 2. Abdominal computed tomography upon admission. Multiple metastases of liver, lymph nodes (white arrows), and bone (not shown) and a locally recurrent prostate tumor invading the rectal wall (lined arrows) were revealed.

agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English language review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eucr.2018.11.001>.

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