Case Reports in Oncology

Case Rep Oncol 2024;17:900–905
DOI: 10.1159/000540418
Received: May 13, 2024
Accepted: July 10, 2024
Published online: August 12, 2024

Case Report

Parathyroid Hormone-Related Protein-Producing Adenocarcinoma Suspicious of Lung Cancer: A Case Report

Masahiro Hirabayashi[a] Tomonobu Koizumi[a, b] Daichi Nakajima[a]
Shuko Azegami[a] Hajime Midorikawa[a] Nami Kitagawa[a]
Hideaki Hamano[a] Tatsunori Chino[c] Maki Ohya[d]

[a]Department of Medicine, Nagano Prefectureal Kiso Hospital, Kiso, Nagano, Japan; [b]Shinshu Cancer Center, Shinshu University Hospital, Nagano, Japan; [c]Department of Surgery, Nagano Prefectureal Kiso Hospital, Kiso, Nagano, Japan; [d]Department of Pathology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan

Keywords
Parathyroid hormone · Hypercalcemia · Lung cancer · TTF-1 · CK7/CK20

Abstract
Introduction: Lung adenocarcinoma with parathyroid hormone (PTH)-related hypercalcemia is uncommon. ***Case Presentation:*** A 69-year-old man was admitted to our hospital due to anorexia and fatigue. Serum calcium (15.0 mg/dL) and carcinoembryonic antigen (361.7 ng/mL) were extremely high, and PTH-related protein (PTH-rP) also elevated (16.7 pmol/L). Systemic computed tomography revealed multiple enlarged lymph nodes and disseminated peritoneal nodules, with irregularly shaped nodules in the upper lobe in the left lung. Ultrasound-guided biopsy from the axillary lymph node revealed adenocarcinoma. Immunohistological staining showed the tumor cells to be positive for cytokeratin 7 and PTH-rP and negative for cytokeratin 20 and thyroid transcription factor-1. Although the primary origin remains undetermined despite detailed examinations, possible primary tumor was considered to be lung adenocarcinoma in the present case. The serum calcium level was reduced by denosumab, but the patient died 20 days after admission. ***Conclusion:*** The present case demonstrated the importance of considering oncological emergency, such as hypercalcemia and/or PTH-rP-producing hypercalcemia, in patients with adenocarcinoma.

Correspondence to:
Tomonobu Koizumi, tomonobu@shinshu-u.ac.jp

Case Rep Oncol 2024;17:900–905
DOI: 10.1159/000540418

Introduction

Hypercalcemia is a common complication in patients with malignancy. Parathyroid hormone-related protein (PTH-rP) is one of the main causative peptides associated with hormonal hypercalcemia in patients with malignancies [1, 2]. Hypercalcemia associated with PTH-rP secretion has been observed in squamous cell tumors, hepatocellular carcinoma, kidney, and hematological malignancies [1–4] but is unlikely in adenocarcinoma. Based on a previous report by Lin et al. [3] summarizing 27 cases of PTH-rP-producing adenocarcinoma, which consisted of 11 cases of bile duct cancer, followed by breast cancer (5 cases), pancreatic cancer (3 cases), stomach cancer (3 cases), etc. In addition, several PTH-rP-related adenocarcinomas arising from various organs have been reported [4–10], but lung adenocarcinoma is uncommon [3–6]. We encountered a case of PTH-rP-producing adenocarcinoma with extremely rapid progression. Although the primary site remained unclear, radiological and immunohistological findings suggested the primary disease to be lung adenocarcinoma. We present this case and a review of PTH-rP-producing adenocarcinoma in the literature. The present case demonstrated the importance of considering oncological emergency, such as hypercalcemia and/or PTH-rP-producing hypercalcemia, in patients with adenocarcinoma.

Case Report

A 69-year-old man was admitted to the hospital due to loss of appetite and fatigue for 1 month, as well as a decrease in muscle strength and increasing difficulty in walking. He was admitted to hospital in a wheelchair. His medical history included diabetes and smoking 7 cigarettes/day for 29 years. Eastern Cooperative Oncology Group (ECOG) performance status was 3 at admission. Laboratory testing revealed an increased white blood cell count (17,600/μL, neutrophils; 88.8%), C-reactive protein level (13.5 mg/dL), and calcium level (15.0 mg/dL; 15.3 mg/dL after correction for serum albumin) and a decreased phosphorous level (2.9 mg/dL). The serum PTH-rP level was markedly elevated (16.7 pmol/L; normal range <0.6 pmol/L), and the PTH level was reduced (5.3 pg/mL; normal range 14–66 pg/mL). The carcinoembryonic antigen (CEA) level was also extremely high (361.7 ng/mL; normal range <5 ng/mL). Systemic computed tomography revealed multiple enlarged lymph nodes in the bilateral neck, left axilla, left hilum, and mediastinum; an irregularly shaped nodule in the upper lobe of the left lung; left pleural effusion; and peritoneal dissemination (Fig. 1a–c). Endoscopic examinations, including esophagogastroduodenoscopy and colonoscopy, did not reveal any causative abnormal findings. Ultrasound-guided needle biopsy of the axillary lymph node was performed, and the histological findings indicated poorly differentiated adenocarcinoma (Fig. 2a). Immunohistochemical analysis showed diffuse positivity for cytokeratin (CK) 7 but negative for CK 20, thyroid transcription factor-1 (TTF-1), and napsin A (Fig. 2b–e). The tumor cells also showed strong expression of PTH-rP (Fig. 2f). In addition, the Oncomine Dx Target Test Multi-CDx System (Oncomine DxTT) using biopsy samples from the axillary lymph node revealed no genetic alterations, including *EGFR*, *ALK*, *ROS1*, *BRAF*, and *KRAS*.

After admission, saline and denosumab, a fully human monoclonal antibody for receptor activator of nuclear factor (NF)-κB ligand (RANKL), were administered to improve hypercalcemia. The serum calcium level was reduced to 8.3 mg/dL (9.9 mg/dL after correction for serum albumin), but the patient's general condition, including consciousness disorder due to brain metastasis (Fig. 3a) and increased ascites and bilateral pleural effusion, worsened (Fig. 3b, c). He died due to cardiorespiratory failure 20 days after admission. Autopsy was not performed.

Case Rep Oncol 2024;17:900–905
DOI: 10.1159/000540418

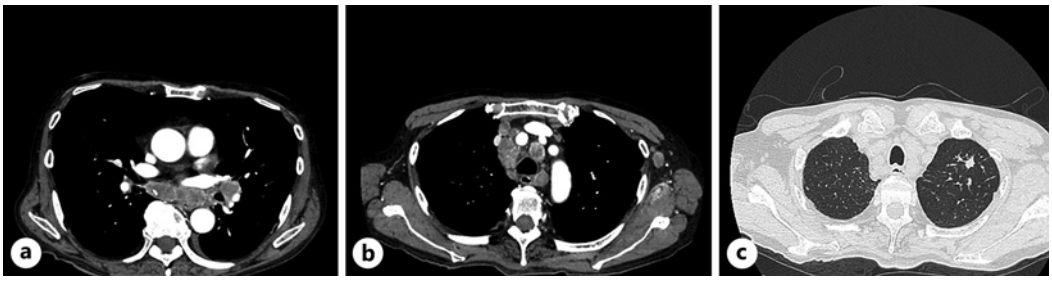

Fig. 1. Chest enhanced CT detected left hilar (**a**) and mediastinal lymphadenopathy (**b**) and an irregularly shaped nodule in the left upper lobe (**c**). CT, computed tomography.

Discussion

We described a case of initially presenting PTH-rP-producing hypercalcemia that showed systemic involvement and poor prognosis. PTH-rP-producing adenocarcinoma has been reported in various organs [3–10]. Donovan et al. [4] collected data on patients showing hypercalcemia concomitant with an elevated PTH-rP level using a database of all public hospitals in Queensland, Australia, from 1999 to 2010, and identified 138 cases of PTH-rP-related hypercalcemia. They identified 38 (27.5%) adenocarcinomas, which was almost equivalent to the rate of squamous cell carcinoma (39 cases, 28.2%). Although the frequency of adenocarcinoma was higher than in other studies [1–3], the reason remained unclear. Interestingly, 11 of the 38 adenocarcinomas were of unknown primary origin, followed by breast cancer (10 cases). These findings indicated that adenocarcinoma should be recognized as an important issue in PTH-rP-producing carcinoma and adenocarcinoma of unknown primary origin should also be considered as a PTH-rP-producing carcinoma. It has been shown that survival in patients with PTH-rP-related hypercalcemia is extremely poor [1–4]. In a case series reported by Lin et al. [3], 50% of the patients died within 1–2 months, consistent with our case. It was also possible that insufficient diagnostic examinations due to the rapid progression and short survival period may have been related to the diagnosis of cancer of unknown primary origin.

A suspected primary lesion was detected in the left lung, and the tumor increased in size during the clinical course in the present case. However, the lesion and changes were too small compared with other clinical manifestations, including systemic lymphadenopathy and thoracoabdominal dissemination. For diagnostic pathology, the patterns of CK7 and CK20 immunohistochemical staining are relatively specific in adenocarcinoma and useful for identification of the primary origin in cases of unknown primary origin [11]. In addition, it is well known that TTF-1 and napsin A are specific for lung adenocarcinoma, but TTF-1-negative lung adenocarcinoma accounts for approximately 20–30% of cases [11–13]. In a cohort of 70 TTF-1-negative patients with lung cancer, Court et al. [12] reported $CK7^+/CK20^-$ staining in 61 patients (87.1%), $CK7^-/CK20^-$ in 4 patients (5.7%), $CK7^+/CK20^+$ in 3 patients (4.3%), and $CK7^-CK20^-$ in 2 patients (2.8%). Therefore, the $CK7^+/CK20^-$ pattern, observed in the present case, supported lung carcinoma as the primary lesion, but this is not always specific for lung adenocarcinoma. Taken together, a possible primary lesion in the present case was observed in the left lung, and primary lung adenocarcinoma was the most likely diagnosis based on the radiographical and immunohistological findings. However, it was difficult to confirm the diagnosis of primary lung carcinoma.

We examined the genetic alterations in tumor cells considering the possibility of lung adenocarcinoma. However, no specific biomarkers were found in the present case. The lack

Case Rep Oncol 2024;17:900–905
DOI: 10.1159/000540418

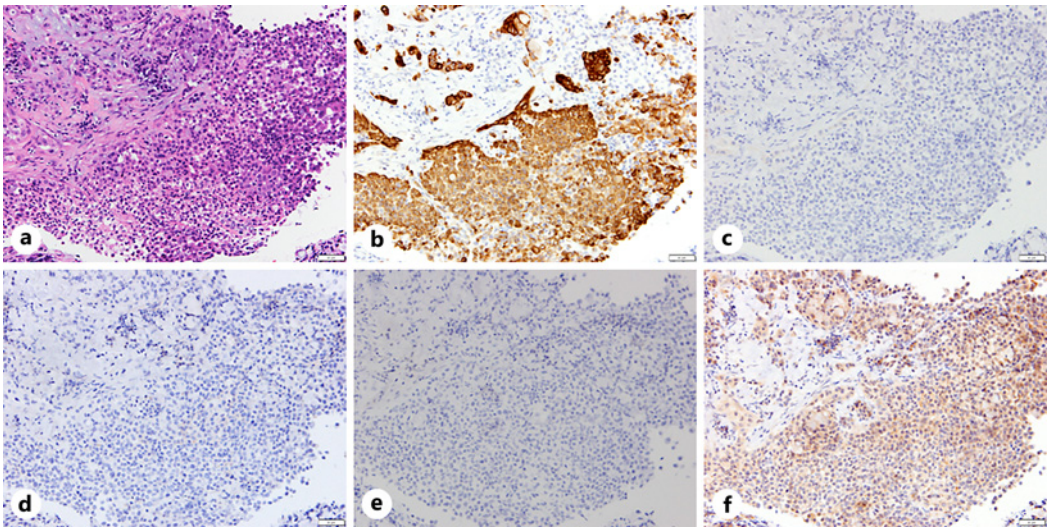

Fig. 2. a Pathological examination of needle biopsy taken from the axillary lymph node revealed poorly differentiated adenocarcinoma. Immunohistochemical staining indicated diffuse expression of CK 7 (**b**) but negative for CK 20 (**c**), TTF-1 (**d**) and napsin A (**e**). **f** The tumor cells were also positive for PTH-rP.

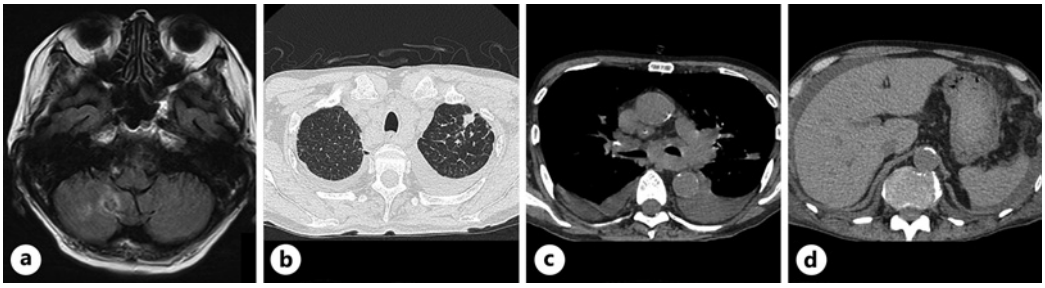

Fig. 3. a Magnetic resonance imaging showed brain metastasis. Chest and abdominal CT showed increased size of the nodule in the upper lobe of the left lung (**b**), bilateral pleural effusion (**c**), and ascites (**d**) 15 days after admission. CT, computed tomography.

of genetic biomarkers, rapid progression, and poor prognosis in our case were also consistent with those in TTF-1-negative lung adenocarcinoma [11–14].

Our patient exhibited an inflammatory reaction along with a continuous high neutrophil level and CRP concentration. Several cases of PTH-rP-producing malignancies showing increased serum granulocyte-colony stimulating factor and inflammatory cytokine levels have been reported [5–7]. These factors were not examined in our case, but these associations may be related poor prognosis in patients with PTH-rP-producing carcinoma concomitant with hypercalcemia.

In conclusion, PTH-rP-producing adenocarcinoma is a rare clinical finding and could exhibit a variety of clinical features with poor prognosis. Although the primary tumor may have been lung adenocarcinoma in the present case, the primary origin remains undetermined. The present case demonstrated the importance of considering oncological emergency, such as hypercalcemia and/or PTH-rP-producing hypercalcemia, in patients with adenocarcinoma. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540418).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from his legal guardian (wife) for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

M.H., T.K., D.N., S.A., H.M., N.K., and H.H. treated the patient. T.C. contributed to surgical resection of axillar lymph node. M.O. was responsible for the pathological analysis and interpretation. M.H. collected the relevant clinical data of the present case and wrote the manuscript. T.K. checked the manuscript and provided suggestions for revision. All the authors contributed equally to this work and have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

References

1 Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005;352(4):373–9. https://doi.org/10.1056/NEJMcp042806
2 Burtis WJ, Brady TG, Orloff JJ, Ersbak JB, Warrell RP Jr, Olson BR, et al. Immunochemical characterization of circulating parathyroid hormone-related protein in patients with humoral hypercalcemia of cancer. N Engl J Med. 1990;322(16):1106–12. https://doi.org/10.1056/NEJM199004193221603
3 Jin J, Chung JO, Chung MY, Cho DH, Chung DJ. Clinical characteristics, causes and survival in 115 cancer patients with parathyroid hormone related protein-mediated hypercalcemia. J Bone Metab. 2017;24(4):249–55. https://doi.org/10.11005/jbm.2017.24.4.249
4 Donovan PJ, Achong N, Griffin K, Galligan J, Pretorius CJ, McLeod DS. PTHrP-mediated hypercalcemia: causes and survival in 138 patients. J Clin Endocrinol Metab. 2015;100(5):2024–9. https://doi.org/10.1210/jc.2014-4250
5 Nobata K, Fujimura M, Ishiura Y, Shirasaki H, Myou S, Yasui M, et al. A case of adenocarcinoma complicated with massive leukocytosis and hypercalcemia. Nihon Kokyuki Gakkai Zasshi. 2000;38(7):530–5.
6 Sakamoto A, Katakami H, Mukae H, Taniguchi H, Maki H, Ashitani J, et al. Simultaneous production of parathyroid hormone-related protein (PTHrP) and granulocyte colony-stimulating factor (G-CSF) in lung cancer patients with hypercalcemia and leukocytosis. Nihon Kyobu Shikkan Gakkai Zasshi. 1995;33(1):34–8.
7 Sohda T, Shiga H, Nakane H, Watanabe H, Takeshita M, Sakisaka S. Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein. Int J Clin Oncol. 2006;11(3):246–9. https://doi.org/10.1007/s10147-006-0560-y

Case Rep Oncol 2024;17:900–905
DOI: 10.1159/000540418

8 Yamada R, Tanaka K, Inoue H, Sakuno T, Harada T, Yoshizawa N, et al. Pancreatic adenocarcinoma producing parathyroid hormone-related protein. Case Rep Oncol Med. 2017;2017:5656130. https://doi.org/10.1155/2017/5656130
9 Yamamoto M, Nakano S, Mugikura M, Tachibana I, Ogami Y, Otsuki M. Pancreatic cancer and hypercalcemia associated with von Recklinghausen's disease. J Gastroenterol. 1996;31(5):728–31. https://doi.org/10.1007/BF02347625
10 Hori Y, Uechi M, Kanakubo K, Sano T, Oyamada T. Canine ovarian serous papillary adenocarcinoma with neoplastic hypercalcemia. J Vet Med Sci. 2006;68(9):979–82. https://doi.org/10.1292/jvms.68.979
11 Dennis JL, Hvidsten TR, Wit EC, Komorowski J, Bell AK, Downie I, et al. Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. Clin Cancer Res. 2005;11(10):3766–72. https://doi.org/10.1158/1078-0432.CCR-04-2236
12 Court A, Laville D, Dagher S, Grosjean V, Dal-Col P, Yvorel V, et al. Anti-CK7/CK20 immunohistochemistry did not associate with the metastatic site in TTF-1-negative lung cancer. Diagnostics. 2022;12(7):1589. https://doi.org/10.3390/diagnostics12071589
13 Rodriguez EF, VandenBussche CJ, Chowsilpa S, Maleki Z. Molecular genetic alterations in thyroid transcription factor 1-negative lung adenocarcinoma in cytology specimens: a subset with aggressive behavior and a poor prognosis. Cancer Cytopathol. 2018;126(10):853–9. https://doi.org/10.1002/cncy.22048
14 Ding X, Shi W, Han B, Chen H, Li J, An J, et al. Thyroid transcription factor 1 (TTF-1) negativity as a predictor of unfavorable response to EGFR-TKI therapy in advanced lung adenocarcinoma patients with EGFR mutations. Thorac Cancer. 2023;14(29):2934–40. https://doi.org/10.1111/1759-7714.15079