CASE REPORT

Hypercalcemia Owing to Overproduction of 1,25-Dihydroxyvitamin D_3 in Fetal Lung Adenocarcinoma: Case Report

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Received 18 February 2021; revised 12 June 2021; accepted 27 June 2021
Available online - 5 July 2021

ABSTRACT

Hypercalcemia is a common electrolyte abnormality in malignancy and is largely caused by activation of parathyroid hormone (PTH) pathways. We report the case of a 76-year-old man with hypercalcemia primarily owing to 1,25-dihydroxyvitamin D_3 overproduction from a high-grade fetal lung adenocarcinoma. Histologically, the tumor itself and tumor-adjacent macrophages were positive for the CYP27B1 protein, a key enzyme that generates 1,25-dihydroxyvitamin D_3. Suppression was observed in serum PTH and PTH-related hormone levels, suggesting hypercalcemia is independent of the PTH pathway. Serum calcium level returned to normal after surgical resection of the lung cancer, supporting extrarenal overproduction of 1,25-dihydroxyvitamin D_3 elicited by the tumors is the cause of hypercalcemia in this patient.

Keywords: Hypercalcemia of malignancy; Lung cancer; 1,25-Dihydroxyvitamin D_3; Case report

Introduction

Hypercalcemia of malignancy (HCM) is an oncological emergency, occurring in approximately 10% of patients with lung cancer. The two major etiologies of HCM are the tumor production of parathyroid hormone-related peptide (PTHrP) (~80%) and osteolytic bone metastasis (~10%).[1] Hypercalcemia by extrarenal overproduction of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) accounts for less than 1% of HCM and is typically found in lymphomas.[1] Recently, simultaneous up-regulation of serum $1,25(OH)_2D_3$ and PTHrP has been observed in squamous cell lung carcinoma.[2] Nevertheless, to our knowledge, a solitary $1,25(OH)_2D_3$-mediated hypercalcemia, independent of PTHrP up-regulation, has yet to be reported in lung cancer. We report a case of high-grade fetal lung adenocarcinoma (H-FLAC) with hypercalcemia from the overproduction of $1,25(OH)_2D_3$, but not PTHrP.

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Disclosure: The authors declare no conflict of interest.

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Cite this article as: Saito T, Ishida M, Kusabe M, et al. Hypercalcemia owing to overproduction of 1,25-dihydroxyvitamin D_3 in fetal lung adenocarcinoma: case report. *JTO Clin Res Rep*. 2021;2:100204.

Some data in this manuscript were presented in an abstract submitted to the 60th annual meeting of The Kansai Thoracic Surgical Association in Osaka, Japan, on June 22, 2017.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2021.100204

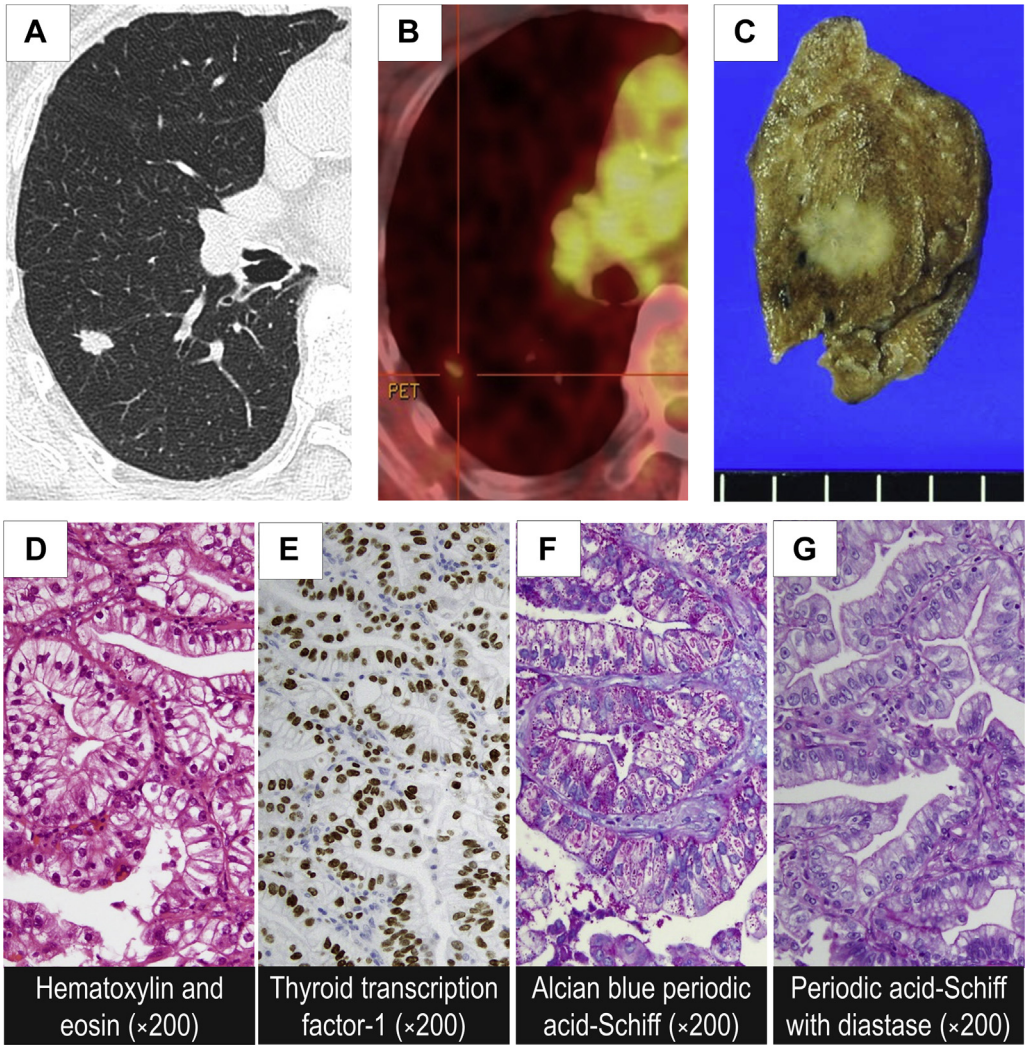

Figure 1. Imaging and pathologic findings of the pulmonary tumor. (*A*) Chest computed tomography revealed a lobulated, solid 14-mm pulmonary nodule with a clear border at S6 of the right lower lobe. (*B*) 18-Fluorodeoxyglucose uptake was found in the S6 nodule with the maximum standardized uptake value of 1.3. (*C*) Macroscopically, a 9-mm nodule was found. Microscopically, papillary growth of high columnar cells with (*D*) clear cytoplasm, (*E*) thyroid transcription factor-1 positivity, and (*F, G*) glycogen granules, which were positive for Alcian blue periodic acid-Schiff and digested by diastase, was observed.

Case Presentation

A 76-year-old man with a pulmonary nodule on computed tomography results and elevated carcinoembryonic antigen (8.5 ng/mL) was referred to our department. The patient had a lobulated 14-mm solid pulmonary nodule in the S6 segment of the right lower lobe revealing increased 18-fluorodeoxyglucose uptake (Fig. 1*A* and *B*). No nodal or distant disease was detected, and surgery was scheduled for possible cT1bN0M0 disease. Preoperative corrected calcium level was 8.6 mg/dL (reference range: 8.5–10.3 mg/dL), and serum creatinine level was 1.82 mg/dL (reference range: 0.6–1.0 mg/dL). After three and a half weeks, the patient presented with a one-week history of fatigue and anorexia. Blood tests revealed the following: corrected calcium level, 14.5 mg/dL; serum creatinine level, 2.67 mg/dL; and $1,25(OH)_2D_3$, 121 pg/mL (reference range: 20–60 pg/mL) (Fig. 2). The patient was not taking vitamin D supplements. The levels of intact PTH, PTHrP, angiotensin-converting enzyme, and proteinase 3 antineutrophil cytoplasmic antibodies were within the reference ranges. Hypercalcemia was treated with intravenous hydration and elcatonin, followed by alendronate. After four and a half weeks, the patient underwent video-assisted thoracoscopic right lower lobectomy with dissection of lobe-specific lymph nodes (stations 7, 8, and 9 and hilar lymph nodes). The resected 9-mm nodule had a papillary growth of high columnar cells with clear subnuclear vacuoles and moderate nuclear atypia (Fig. 1*C* and *D*), thyroid

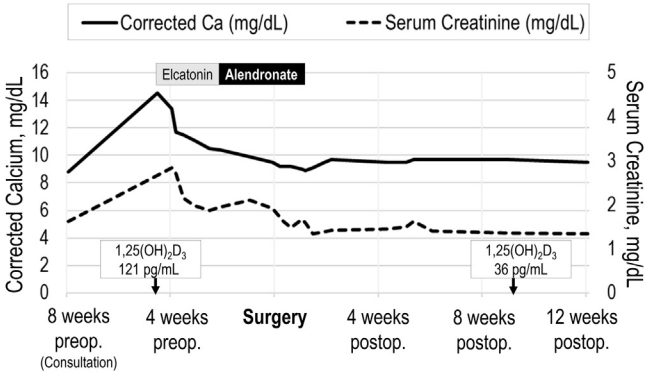

Figure 2. Time course of changes in laboratory data. Serum-corrected Ca and $1,25(OH)_2D_3$ levels were most remarkably elevated at four and a half weeks preoperatively with concomitant deterioration of renal functions as indicated by the rise in serum creatinine. The serum Ca, vitamin D, and creatinine levels gradually declined in response to the treatment with elcatonin alone (for 10 d), which was replaced by alendronate (for 4 wk), and the levels subsequently returned to normal after the surgical removal of the pulmonary tumor. $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; Ca, calcium; Postop., postoperative; Preop., preoperative.

transcription factor-1 positivity (Fig. 1*E*), and glycogen granules (Fig. 1*F* and *G*), but it was negative for hepatocyte nuclear factor 4β, α-fetoprotein, Sal-like protein 4, and glypican-3. Dissected lymph nodes had non-necrotizing granulomas, suggesting sarcoid-like reactions. Nevertheless, the patient had no other clinical manifestations suggestive of concurrent systemic sarcoidosis. Immunostaining for 1α-hydroxylase, also known as CYP27B1, revealed strong positivity for alveolar macrophages and weak positivity for tumor cells and macrophages in nodal granulomas (Fig. 3*A* and *B*), which was distinct from the control case (Fig. 3*C*). The final pathologic diagnosis was pT1aN0M0 H-FLAC. The serum calcium levels dropped after the surgery, allowing discontinuation of alendronate on the sixth postoperative day (Fig. 2). The serum $1,25(OH)_2D_3$ levels returned to normal (36 pg/dL) at eight postoperative weeks. Neither tumor recurrence nor hypercalcemia was noted for 13 months.

Discussion

Hypercalcemia mediated through $1,25(OH)_2D_3$ production typically occurs in granulomatous diseases, such as sarcoidosis and tuberculosis, lymphomas, and ovarian tumors.[1,3] In sarcoidosis, alveolar macrophages may cause hypercalcemia by metabolizing 25-hydroxyvitmin D_3 to $1,25(OH)_2D_3$ by means of up-regulated CYP27B1 activity.[1] Macrophage CYP27B1 activity is regulated by cytokines, such as interferon-γ.[4] In solid tumors, the mechanism of $1,25(OH)_2D_3$-mediated hypercalcemia remains unclear but is presumed to be similar to that in sarcoidosis. A case series of ovarian dysgerminoma with $1,25(OH)_2D_3$-mediated hypercalcemia revealed an increased expression of CYP27B1 mRNA in both tumor cells and tumor-associated macrophages.[3] Thus, in solid tumors, up-regulated CYP27B1 in tumor-associated macrophages and tumor cells could play a pertinent role in $1,25(OH)_2D_3$-mediated hypercalcemia (Fig. 3*D*).

In NSCLC, up-regulation of CYP27B1 mRNA in alveolar macrophages has been reported, but no remarkable association with calcium metabolism has been found.[5] This might be explained by the difference in the magnitude of CYP27B1 mRNA overexpression. NSCLC, sarcoidosis, and ovarian dysgerminoma were reported to reveal a twofold, fivefold, and 222-fold increase, respectively, in CYP27B1 mRNA expression compared with controls.[3,5] This case revealed the ectopic overexpression of CYP27B1 in both tumor cells and alveolar macrophages, including in nodal granulomas. Nevertheless, we could only evaluate the right lower lung lobe and the lobe-specific lymph nodes (stations 7, 8, and 9 and hilar lymph nodes) but neither the other lung parenchyma nor other thoracic lymph nodes. This made it difficult to differentiate whether the nodal granuloma was a tumor-associated, sarcoid-like reaction or a part of the manifestation of subclinical systemic granulomatous disease. Nevertheless, hypercalcemia and up-regulation of $1,25(OH)_2D_3$ seemed of acute onset and were entirely normalized after resection of the tumor and adjacent lymph nodes. These findings indicate that hypercalcemia in the presented case is mediated by extrarenal overexpression of CYP27B1 in both tumors and the surrounding tumor microenvironment (Fig. 3*D*). Thus, surgical resection could be considered a fundamental treatment of hypercalcemia when overproduction of $1,25(OH)_2D_3$ from tumor cells and surrounding immune cells is suspected.

Conclusion

In summary, we report a case of H-FLAC with $1,25(OH)_2D_3$-mediated hypercalcemia, independent of PTH and PTHrP secretion. Our histologic analysis reveals that extrarenal activation of vitamin D is caused by CYP27B1 overexpression in both the tumor (H-FLAC) and adjacent environments, including macrophages in nodal granulomas.

CRediT Authorship Contribution Statement

Tomohito Saito: Conceptualization, Methodology, Software, Writing—original draft, Writing—review and editing, Visualization.

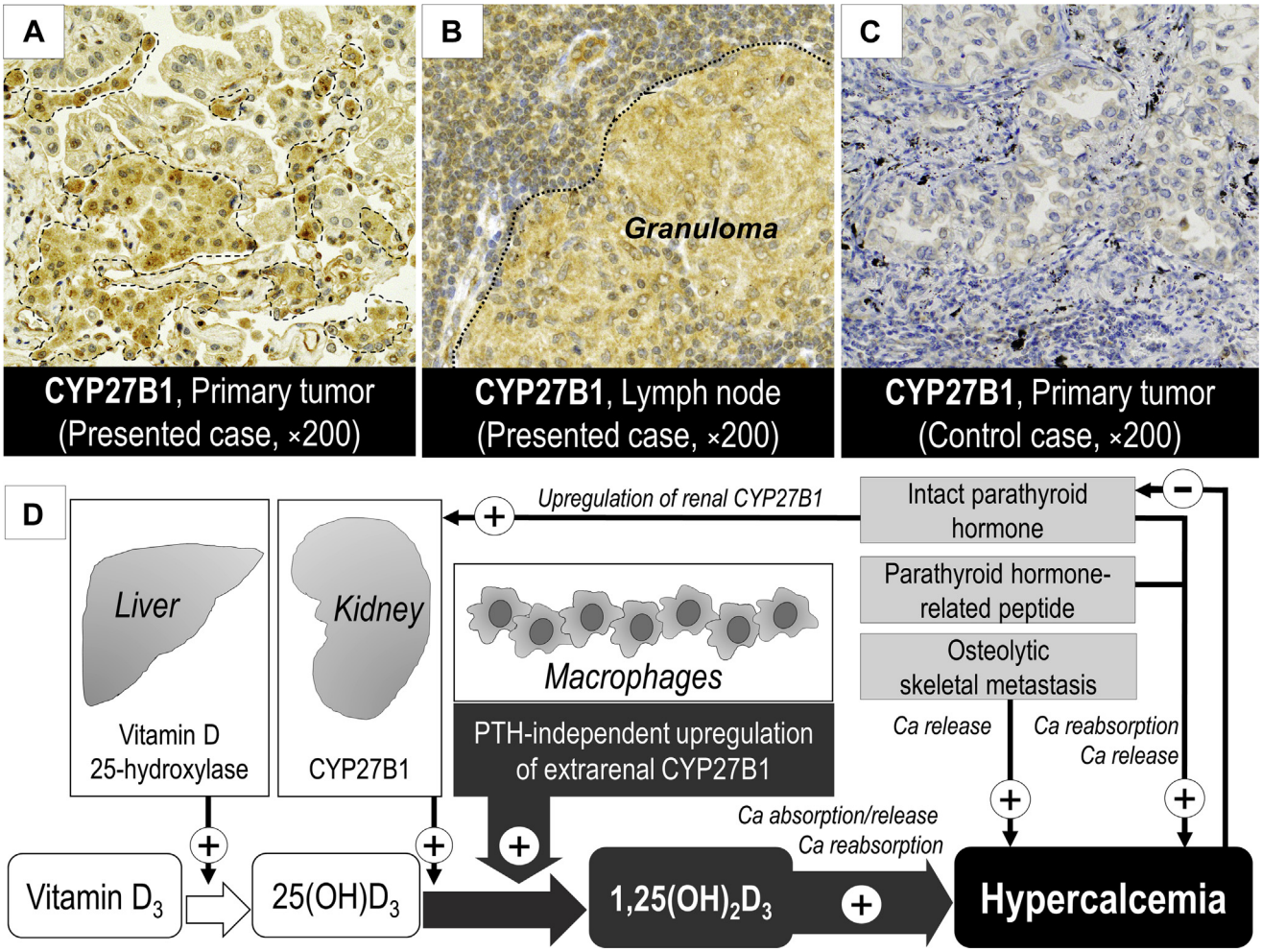

Figure 3. Immunohistochemical staining of CYP27B1 and schematic presentation of the pathophysiology of vitamin D_3-mediated hypercalcemia. Immunostaining for CYP27B1 (PA5-26065, Thermo Fisher Scientific, Rockford, IL) revealed a strong positivity in alveolar macrophages (surrounded by broken line), (*A*) weak positivity in tumor cells, and (*B*) strong positivity in macrophages in granulomas within the dissected lymph nodes (below the dotted line). (*C*) Another control case with pulmonary adenocarcinoma revealed CYP27B1 negativity. (*D*) In the presented case, hypercalcemia might be induced by extrarenal CYP27B1-mediated $1,25(OH)_2D_3$ overproduction (thick gray arrows). $1,25(OH)_2D_3$, 1,25-dihydroxyvitaminD_3; $25(OH)D_3$, 25-hydroxyvitamin D_3; Ca, calcium.

Mistuaki Ishida: Methodology, Validation.

Makiko Kusabe, **Takahiro Utsumi**, **Natsumi Maru**, **Hiroshi Matsui**, **Yohei Taniguchi**, **Takahiro Imada**: Validation.

Takayasu Kurata, **Koji Tsuta**: Supervision.

Hiroaki Kurokawa: Validation, Supervision.

Hiroyasu Tsukaguchi: Supervision, Writing—review and editing.

Tomohiro Murakawa: Supervision, Project administration.

Acknowledgments

This study was approved by the Kansai Medical University Hospital Research Ethics Board (approval number: 2015630). Consent for publication was obtained from the patient. The authors thank Ms. Sayuri Yamamoto and Ms. Yoko Oda for facilitating this study and Editage (www.editage.com) for the English-language editing. This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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