ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2023 November 24; 14(11): 445-548

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Monthly Volume 14 Number 11 November 24, 2023

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCO* as 2.8; IF without journal self cites: 2.8; 5-year IF: 3.0; Journal Citation Indicator: 0.36.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiang-Di Zhang*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Xu Guo*.

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
November 24, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 November 24; 14(11): 544-548

DOI: 10.5306/wjco.v14.i11.544

ISSN 2218-4333 (online)

CASE REPORT

Calcitriol induced hypercalcemia - a rare phenomenon in lung cancer: A case report

Amulya Prakash, Farhan Khalid, Ahmad Alalwan, Husam Bader, Doantrang Du, Trishala Meghal

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Haddadi S, Algeria; Musetti C, Italy

Received: July 26, 2023
Peer-review started: July 26, 2023
First decision: September 4, 2023
Revised: September 20, 2023
Accepted: October 23, 2023
Article in press: October 23, 2023
Published online: November 24, 2023

Amulya Prakash, Department of Internal Medicine, Haywood Regional Medical Center, Clyde, NC 28721, United States

Amulya Prakash, Farhan Khalid, Ahmad Alalwan, Husam Bader, Doantrang Du, Department of Internal Medicine, Monmouth Medical Center, Long Branch, NJ 07740, United States

Trishala Meghal, Department of Hematology-Oncology, Monmouth Medical Center, Long Branch, NJ 07740, United States

Corresponding author: Farhan Khalid, MD, Chief Physician, Department of Internal Medicine, Monmouth Medical Center, 200 Second Avenue, Long Branch, NJ 07740, United States. farhan.khalid.md@gmail.com

Abstract

BACKGROUND

Calcitriol-induced hypercalcemia has been rarely reported in cases of lung cancer; however, it is frequently reported in cases of lymphoid malignancy and granulomatous disease. We present a rare case of hypercalcemia associated with squamous cell cancer of the lung with elevated calcitriol level.

CASE SUMMARY

A 61-year-old Caucasian female with severe hypercalcemia of 15 mg/dL, which led to a new diagnosis of metastatic lung cancer. Since the parathyroid hormone-related peptide (PTHrP) level was minimally elevated at 2.1 pmol/L, we believe excessive calcitriol production by tumor cells was the underlying mechanism for hypercalcemia. Calcitriol was significantly elevated at 130 pg/mL with a low 25-hydroxyvitamin D level of 25.9 ng/mL and suppressed PTH level of 8 pg/mL. Corticosteroids are generally used to treat calcitriol-induced hypercalcemia, but we successfully treated our patient with bisphosphonate, highlighting the further utility of bisphosphonates in hypercalcemia treatment.

CONCLUSION

We believe that the underlying cause of hypercalcemia, in this case of metastatic squamous cell lung carcinoma, was elevated calcitriol, which was likely produced by the tumor cells. In addition to PTHrP, calcitriol levels should be included in the workup for hypercalcemia in cases of lung cancer. However, the pathophysiology and prognostic significance of dysregulated calcitriol production in solid tumors remain unclear and warrant further research. Bisphosphonate may be used as a steroid-sparing therapy even in cases of calcitriol-induced hypercalcemia and

warrants further investigation.

Key Words: Hypercalcemia associated malignancy; Lung cancer; Denosumab; Calcitriol; Vitamin D; Case report

Core Tip: Our case report illuminates a rare mechanism of hypercalcemia in lung malignancies, characterized by elevated calcitriol. Despite its rarity, it sheds light on the pathophysiology of hypercalcemia in solid malignancies, notably lung cancers. To the best of our knowledge, this is the first documented case in medical literature to present this mechanism. Moreover, the successful management of this condition with bisphosphonates highlights the potential efficacy of this treatment approach for future cases involving similar symptoms. By emphasizing this novel observation, our report contributes to the expanding body of knowledge regarding hypercalcemia in lung cancers and paves the way for the development of novel therapeutic strategies for the treatment of such cases.

Citation: Prakash A, Khalid F, Alalwan A, Bader H, Du D, Meghal T. Calcitriol induced hypercalcemia - a rare phenomenon in lung cancer: A case report. *World J Clin Oncol* 2023; 14(11): 544-548
URL: https://www.wjgnet.com/2218-4333/full/v14/i11/544.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i11.544

INTRODUCTION

Hypercalcemia associated with malignancy (HAM) is a common clinical finding and may even present as an oncologic emergency. It has been found in up to 30% of cases of malignancy[1]. The estimated yearly prevalence of hypercalcemia for all cancers is 1.46% to 2.74%[2]. Calcitriol overproduction is a rare etiology of HAM and accounts for merely 1% of cases of HAM[3]. It has been frequently reported in cases of Hodgkin and non-Hodgkin lymphoma and also in some cases of ovarian dysgerminoma, pancreatic neuroendocrine tumors, seminomas, and renal cell carcinoma[4-6]. In our extensive literature search, we came across just one case report of squamous cell lung cancer by Akai *et al*[7], where calcitriol overproduction was exclusively responsible for hypercalcemia and treated with tumor resection. We present a rare case of squamous cell lung carcinoma with hypercalcemia and elevated calcitriol levels, which was treated successfully with bisphosphonate. To the best of our knowledge, bisphosphonates have never been reported for the treatment of calcitriol-induced hypercalcemia in the case of squamous cell lung carcinoma.

CASE PRESENTATION

Chief complaints

Hypercalcemia on routine blood work investigation.

History of present illness

The patient didn't complain of any significant symptoms at the time of presentation. However, during detailed history taking, she reported vague complaints of nausea, fatigue, and generalized weakness but denied any other symptoms like constipation, palpitation, confusion, *etc.*

History of past illness

She has a past medical history of diabetes, hyperlipidemia, and depression.

Personal and family history

The patient has a remote history of tobacco smoking more than 15 years ago. She denies any supplementation with vitamin A, vitamin D, or calcium, frequent use of antacids, or excessive consumption of dairy products. Her current medications include atorvastatin and sertraline. Patient denies any significant family history.

Physical examination

Her vital signs and physical exam were within normal limits.

Laboratory examinations

Three months prior to the presentation, her calcium level was noted to be within the normal range of 10.1 (range: 8.6-10.3 mg/dL). In a routine lab work performed one week before the presentation, her corrected serum calcium was noted to be elevated first time at 13 mg/dL. She was asymptomatic at that point so decision was made to monitor with serial labs.

Our patient presented for repeat lab draw a week later and now her corrected serum calcium was 14.3 mg/dL, so she was instructed to visit the emergency department for further evaluation. She was admitted 12 h later on the same day and her corrected serum calcium further worsened to 15 mg/dL with an ionized calcium value of 7.5 mg/dL (range: 4.5-5.6). Her albumin was 3.4 mg/dL, creatinine 0.5 mg/dL, estimated glomerular filtration rate > 60 mL/min/1.73 m^2, magnesium 1.9 mg/dL (range: 1.8-2.4), phosphorus 2.4 mg/dL (range: 2.5-4.9). 25-hydroxyvitamin D was noted to be low: 25.9 ng/mL (30-100 ng/mL), with elevated calcitriol level: 130 pg/mL (24.8-81.5 pg/mL) and suppressed intact parathyroid hormone (PTH) level: 8 pg/mL (15-65 pg/mL) and minimally elevated PTH-related peptide (PTHrP) 2.1 pmol/L (normal < 2.0 pmol/L). Complete blood count and urinalysis were within normal limits.

Imaging examinations

Chest X-ray reveals a left hilar opacity, which was concerning for lung neoplasm. Upon further investigation with contrasted pan-computed tomography, the patient was noted to have a left lower lobe mass with an epicenter in the left lower lobe bronchus with invasion into the mediastinum and multiple hepatic metastases. No metastasis to bones, brain or spleen was noted. A core biopsy was performed on one of the liver metastases. Histopathology findings were consistent with metastatic squamous cell carcinoma, moderately differentiated. Immunohistochemistry of biopsied tissue sample was positive for markers p63, cytokeratin 5/6 heterogeneously positive; negative for thyroid transcription factor, cytokeratins 7, caudal-related homeobox transcription factor 2 and GATA binding protein 3. Thus, immunohistochemistry findings were also consistent with squamous cell carcinoma of lung. The tissue sample shows high programmed cell death ligand 1 expression (Figure 1).

FINAL DIAGNOSIS

Calcitriol induced hypercalcemia.

TREATMENT

Our patient was paucisymptomatic but had rapid rise in serum calcium level so we decided to treat her hypercalcemia. The patient was managed with intravenous normal saline, subcutaneous calcitonin administered twice, and a single infusion of zoledronic acid 4 mg during the course of the hospital stay. Her calcium level improved rapidly to 9.8 mg/dL within 48 h and she was discharged from the hospital. Her calcium level 2-wk later was noted to be elevated again at 13 mg/dL and was given another dose of zolendronic acid. Four weeks after discharge, her calcium level was noted to be within the normal range at 9.9 mg/dL.

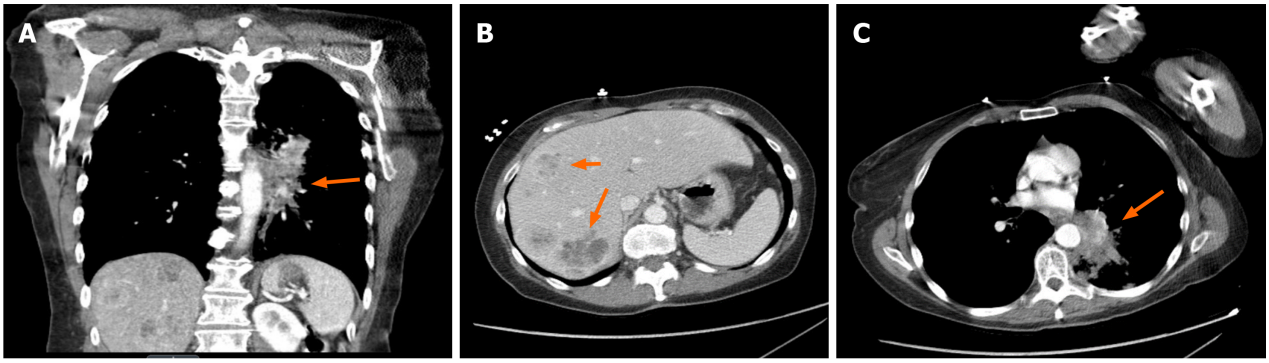
OUTCOME AND FOLLOW-UP

The patient is scheduled to receive infusion of zolendronic acid once every month to manage hypercalcemia. She is planned to undergo chemotherapy with carboplatin, paclitaxel and pembrolizumab.

DISCUSSION

Hypercalcemia results from dysregulation between normal bone formation and the degradation cycle. The pathophysiology of HAM can be broadly classified into: (1) Local osteolytic hypercalcemia; (2) Humoral hypercalcemia mediated through PTHrP; and (3) Excess production of 1,25-dihydroxy vitamin D (calcitriol).

In the current case, calcitriol level was noted to be significantly elevated with suppressed PTH level and minimal elevation of PTHrP. The question is about what's causing the calcitriol elevation in this case. Squamous cell cancer of the lung is usually associated with hypercalcemia driven by PTHrP elevation. In granulomatous disease such as sacrcoidosis, there is extrarenal production of calcitriol *via* autonomous 1-α-hydroxylase activity in tissue macrophages. PTHrP can also upregulate 1-alpha hydroxylase activity and calcitriol production in mice models, but it does not increase calcitriol production in humans[8,9]. In this patient, we tend to believe that hypercalcemia was due to a PTHrP-independent mechanism since PTHrP was minimally elevated. Additionally, extrarenal synthesis of calcitriol is dependent on its substrate 25-hydroxyvitamin D, which was low in this case, thus excluding extrarenal calcitriol production as an underlying mechanism. It's very possible that it was being ectopically produced by tumor cells in an autonomous fashion [10]. Although staining of the biopsy sample for 1,25-dihydroxy vitamin D and 1-alpha-hydroxylase was not done to confirm calcitriol's ectopic production, the treatment response further solidifies our hypothesis. Increased calcitriol level in cases of granulomatous disease is believed to be due to the upregulation of 1-alpha hydroxylase activity, and its autocrine regulation is sensitive to corticosteroid therapy. Hence, corticosteroid is indicated in the treatment of hypercalcemia in such cases[11,12]. However, in our case, hypercalcemia responded remarkably to treatment with bispho -sphonate and didn't require any steroid treatment, making us doubtful of any increased 1-alpha-hydroxylase activity.



DOI: 10.5306/wjco.v14.i11.544 **Copyright** ©The Author(s) 2023.

Figure 1 Computed tomography images. A: Computed tomography (CT) showing left lower lobe mass involving left bronchus; B: CT abdomen with contrast showing liver metastases; C: CT chest showing left lower lobe mass invasion into mediastinum.

The standard treatment approach for HAM is aimed at: (1) Promoting renal calcium excretion through intravenous normal saline administration and even loop diuretics, sometimes; and (2) Reducing bone absorption through the use of bisphosphonates and denosumab in refractory cases. Calcitonin can also be used as an adjunctive therapy with bisphosphonates, but tachyphylaxis develops within 48 h. Corticosteroids are the first-line agents for the treatment of calcitriol-mediated hypercalcemia by inhibiting the transcription of 25-hydroxyvitamin D-1-hydroxylase; however, it was not required in our case. That being said, bisphosphonates may have more of a role in the treatment of HAM. Bisphosphonate may inhibit the adhesion of osteoclast precursors to stromal osteoblasts through the increased expression of intercellular adhesion molecule-1, which is promoted by calcitriol[13,14]. In a case series reported by Rizzoli *et al*[15], bisphosphonate was more effective than steroids in the treatment of hypercalcemia, probably due to its bone anti-resorptive effect. Bisphosphonates may have additional effects, including induction of apoptosis, inhibition of invasion, and antiangiogenic properties, as seen in some preclinical studies[16]. It would be worthwhile to conduct further research to investigate the cellular effects of calcitriol and bisphosphonate in patients with lung cancer.

CONCLUSION

We believe that the underlying cause of hypercalcemia, in this case of metastatic squamous cell lung carcinoma, was elevated calcitriol, which was likely produced by the tumor cells. In addition to PTHrP, calcitriol levels should be included in the workup for hypercalcemia in cases of lung cancer. However, the pathophysiology and prognostic significance of dysregulated calcitriol production in solid tumors remain unclear and warrant further research. Bisphosphonate may be used as a steroid-sparing therapy even in cases of calcitriol-induced hypercalcemia and warrants further investigation.

FOOTNOTES

Author contributions: Alalwan A conceived the idea, did the literature search, managed the case on medical floor, contributed to case presenrtation and the introduction; Khalid F and Bader H contributed the discussion; Du D and Meghal T edited and revised the manuscript.

Informed consent statement: Informed consent was obtained by the patient.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: United States

ORCID number: Farhan Khalid 0000-0002-8456-5118.

S-Editor: Wang JJ

L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Stewart AF**. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; **352**: 373-379 [PMID: 15673803 DOI: 10.1056/NEJMcp042806]
2 **Jick S**, Li L, Gastanaga VM, Liede A. Prevalence of hypercalcemia of malignancy among cancer patients in the UK: analysis of the Clinical Practice Research Datalink database. *Cancer Epidemiol* 2015; **39**: 901-907 [PMID: 26520619 DOI: 10.1016/j.canep.2015.10.012]
3 **Goldner W**. Cancer-Related Hypercalcemia. *J Oncol Pract* 2016; **12**: 426-432 [PMID: 27170690 DOI: 10.1200/JOP.2016.011155]
4 **Rodríguez-Gutiérrez R**, Zapata-Rivera MA, Quintanilla-Flores DL, Camara-Lemarroy CR, Lavalle-Gonzalez FJ, González-González JG, Villarreal-Pérez JZ. 1,25-dihydroxyvitamin D and PTHrP mediated malignant hypercalcemia in a seminoma. *BMC Endocr Disord* 2014; **14**: 32 [PMID: 24721620 DOI: 10.1186/1472-6823-14-32]
5 **Shivnani SB**, Shelton JM, Richardson JA, Maalouf NM. Hypercalcemia of malignancy with simultaneous elevation in serum parathyroid hormone--related peptide and 1,25-dihydroxyvitamin D in a patient with metastatic renal cell carcinoma. *Endocr Pract* 2009; **15**: 234-239 [PMID: 19364692 DOI: 10.4158/EP.15.3.234]
6 **Hibi M**, Hara F, Tomishige H, Nishida Y, Kato T, Okumura N, Hashimoto T, Kato R. 1,25-dihydroxyvitamin D-mediated hypercalcemia in ovarian dysgerminoma. *Pediatr Hematol Oncol* 2008; **25**: 73-78 [PMID: 18231957 DOI: 10.1080/08880010701774033]
7 **Akai PS**, Wong T, Chang-Poon V, Green F, Whitelaw WA, Hanley DA. Resectable bronchogenic carcinoma presenting with hypercalcemia: tumor-associated granulomatous reaction and probable production of 1,25-dihydroxyvitamin D. *Clin Invest Med* 1989; **12**: 212-216 [PMID: 2743640]
8 **Horwitz MJ**, Tedesco MB, Sereika SM, Syed MA, Garcia-Ocaña A, Bisello A, Hollis BW, Rosen CJ, Wysolmerski JJ, Dann P, Gundberg C, Stewart AF. Continuous PTH and PTHrP infusion causes suppression of bone formation and discordant effects on 1,25(OH)2 vitamin D. *J Bone Miner Res* 2005; **20**: 1792-1803 [PMID: 16160737 DOI: 10.1359/JBMR.050602]
9 **Schilling T**, Pecherstorfer M, Blind E, Leidig G, Ziegler R, Raue F. Parathyroid hormone-related protein (PTHrP) does not regulate 1,25-dihydroxyvitamin D serum levels in hypercalcemia of malignancy. *J Clin Endocrinol Metab* 1993; **76**: 801-803 [PMID: 8445039 DOI: 10.1210/jcem.76.3.8445039]
10 **Chukir T**, Liu Y, Hoffman K, Bilezikian JP, Farooki A. Calcitriol Elevation Is Associated with a Higher Risk of Refractory Hypercalcemia of Malignancy in Solid Tumors. *J Clin Endocrinol Metab* 2020; **105**: e1115-e1123 [PMID: 31841590 DOI: 10.1210/clinem/dgz278]
11 **Fuss M**, Pepersack T, Gillet C, Karmali R, Corvilain J. Calcium and vitamin D metabolism in granulomatous diseases. *Clin Rheumatol* 1992; **11**: 28-36 [PMID: 1582115 DOI: 10.1007/BF02207080]
12 **Kallas M**, Green F, Hewison M, White C, Kline G. Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review. *J Clin Endocrinol Metab* 2010; **95**: 3111-3117 [PMID: 20427501 DOI: 10.1210/jc.2009-2673]
13 **Mateo RCI**, Ortiz R, Rosen HN. BISPHOSPHONATES FOR THE TREATMENT OF CALCITRIOL-INDUCED HYPERCALCEMIA. *AACE Clin Case Rep* 2019; **5**: e316-e320 [PMID: 31967061 DOI: 10.4158/ACCR-2019-0101]
14 **Okada Y**, Morimoto I, Ura K, Watanabe K, Eto S, Kumegawa M, Raisz L, Pilbeam C, Tanaka Y. Cell-to-Cell adhesion *via* intercellular adhesion molecule-1 and leukocyte function-associated antigen-1 pathway is involved in 1alpha,25(OH)2D3, PTH and IL-1alpha-induced osteoclast differentiation and bone resorption. *Endocr J* 2002; **49**: 483-495 [PMID: 12402981 DOI: 10.1507/endocrj.49.483]
15 **Rizzoli R**, Stoermann C, Ammann P, Bonjour JP. Hypercalcemia and hyperosteolysis in vitamin D intoxication: effects of clodronate therapy. *Bone* 1994; **15**: 193-198 [PMID: 8086237 DOI: 10.1016/8756-3282(94)90707-2]
16 **Clezardin P**. Potential anticancer properties of bisphosphonates: insights from preclinical studies. *Anticancer Agents Med Chem* 2012; **12**: 102-113 [PMID: 21864232 DOI: 10.2174/1871520127990149777]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com