

Severe Hypercalcemia From Inhalation Pneumonitis via Activation of 1,25 Dihydroxyvitamin D

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Abstract

Among the many causes of hypercalcemia are inflammatory conditions, particularly involving granulomatous disease. We present a case of a previously healthy woman who arrived at the emergency department with severe symptomatic hypercalcemia. Workup revealed elevated levels of 1,25-dihydroxyvitamin D along with pneumonitis on computed tomography (CT) imaging. The patient revealed frequent use of eucalyptus oil in her home essential oil diffuser and after removal of the offending agent her hypercalcemia, elevated 1,25-dihydroxyvitamin D, and pneumonitis on CT imaging all resolved.

Key Words: eucalyptus oil, inflammation, pneumonitis, vitamin D, hypercalcemia

Abbreviations: CT, computed tomography; PTH, parathyroid hormone.

Hypercalcemia can be a life-threatening condition, and understanding the underlying etiology of hypercalcemia is key for long-term management as both benign and malignant diseases can be a cause. Symptoms of mild hypercalcemia can range from asymptomatic to fatigue, osteoporosis, and renal dysfunction/nephrolithiasis. In more severe cases of hypercalcemia, symptoms can advance to psychosis and fatal arrhythmia. Workup should differentiate parathyroid hormone (PTH)-mediated hypercalcemia from PTH nonmediated hypercalcemia as the differential diagnosis and subsequent workup is dictated by PTH level. Our patient presented with non-PTH-mediated hypercalcemia in the setting of isolated elevation of 1,25-dihydroxyvitamin D level. The patient was ultimately diagnosed with hypersensitivity pneumonitis suspected to be due to inhalation of eucalyptus oil from an essential oil diffuser causing unregulated 1 α -hydroxylase activity leading to severe hypercalcemia [1, 2].

Case

A 69-year-old woman was in her usual state of health when she presented to the emergency department with a 1-week history of progressive weakness, gait instability, confusion, and hypoxia.

The patient had a medical history significant for psoriatic arthritis, treated with secukinumab for the past 5 years and severe spinal degenerative disc disease with spinal stenosis. Many years before presentation, she had surgical procedures, including T12 to L3 osteotomies with T10 to S1

posterior spinal fusion. Her surgeries were complicated by implant hardware infection with *Pseudomonas aeruginosa*, for which she was on lifelong antibiotic suppression therapy with levofloxacin. Despite her extensive back issues, she was able to ambulate a half mile unassisted up until the onset of these new symptoms. Routine laboratory tests dating back many years revealed normal serum calcium, and 8 before this presentation her total calcium was 9.9 mmol/L (albumin 3.8 g/dL).

At presentation, the patient required a walker to ambulate, was confused, and was hypoxic with SpO₂ 87% on room air and required 2 L nasal canula oxygen to treat her hypoxemia. She was found to have a total calcium of 16.1 mmol/L (albumin 4.1 g/dL). She received intravenous fluids in the emergency department as initial management for her hypercalcemia and was admitted to the hospital for further workup and treatment of her severe hypercalcemia.

Hypercalcemia workup included a PTH of 16 pg/mL (reference range, 12–72 pg/mL), PTH-related peptide 0.6 pmol/L (reference range < 4.2 pmol/L), 25-OH vitamin D 56.1 ng/mL (reference range, 20–80 ng/mL), 1,25-dihydroxyvitamin D 113 pg/mL (reference range, 19.9–79.3 ng/mL), unremarkable serum and urine protein electrophoresis, lactate dehydrogenase 222 U/L (reference range, 116–250 U/L), erythrocyte sedimentation rate 85 mm/h (reference range < 30 mm/h), C-reactive protein 8.6 (reference range < 0.5), negative QuantiFERON gold, and negative hepatitis panels. Table 1 shows the laboratory values.

The patient was initially treated with intravenous fluids and zoledronic acid leading to improved calcium levels and

Table 1. Laboratory values for our patient prior to admission, during admission and after discharge.

Laboratory value	Reference range	8 mo before admission	Time of admission	3-5 mo after discharge	12 mo after discharge
Glucose	74-99 mg/dL	88	110	91	92
BUN	8-23 mg/dL	19	31	15	14
Creatinine	0.60-1.10 mg/dL	0.59	1.43	0.65	0.67
BUN/creatinine ratio	8-20	32	22	23	21
Sodium	136-145 mmol/L	141	139	136	137
Potassium	3.7-4.8 mmol/L	4.8	3.9	5	4.5
Chloride	97-107 mmol/L	101	97	102	101
CO ₂	22-29 mmol/L	28	31	24	26
Anion gap	6-16 mmol/L	12	11	10	10
Calcium, plasma	8.9-10.2 mmol/L	9.9	16.1	9.1	9.9
AST, plasma	9-36 U/L	44	37	25	28
ALT, plasma	8-33 U/L	36	44	19	24
Alkaline phosphatase	46-142 U/L	132	114	93	77
Total bilirubin, plasma	0.2-1.1 mg/dL	0.3	0.2	0.4	0.5
Total protein	6.3-7.9 g/dL	7.1	7.7	7.1	7.1
Albumin	3.5-5.2 g/dL	3.8	4.1	4.4	4.7
eGFR	> 60	> 60	36	> 60	> 60
PTH	12-72 pg/mL		18	52	40
Ionized calcium	4.6-5.1 mg/dL		7.9	4.9	5.1
Total protein	6.2-7.7 g/dL		6.3		
Albumin electrophoresis, serum	3.6-4.7 g/dL		3.3		
Alpha 1 globulin electrophoresis, serum	0.2-0.4 g/dL		0.4		
Alpha 2 globulin electrophoresis, serum	0.5-0.9 g/dL		1		
Beta 1 globulin electrophoresis, serum	0.3-0.5 g/dL		0.4		
Beta 2 globulin electrophoresis, serum	0.2-0.5 g/dL		0.4		
Gamma globulin electrophoresis, serum	0.5-1.5 g/dL		0.8		
C-reactive protein	0.00-0.50 mg/dL	0.12	8.6	< 0.30	2.1
ESR	< 30 mm/h		85		30
25-Hydroxyvitamin D	20-80 ng/mL		56.1	36.8	58.4
1,25 Dihydroxyvitamin D	19.9-79.3 ng/mL		113	35.6	38.9
TB Nil	Negative			0.01	
QuantiFERON NIL	Negative			0.01	
QuantiFERON Mitogen Minus Nil	Negative			7.88	
QuantiFERON TB1 Ag Minus Nil	Negative			Negative	
Hepatitis B surface Ag	Negative		Negative		
Hepatitis C Ab	Negative		Negative		
Hepatitis A Ab IgM	Negative		Negative		
External Hepatitis B Core IgM	Negative		Negative		

Abbreviations: Ab, antibody; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; PTH, parathyroid hormone.

improved clinical symptoms with return to her baseline on hospital day 4. Given the elevated 1,25-dihydroxyvitamin D without elevation of 25-OH vitamin D, attention was focused on workup of granulomatous disease and lymphoma. A computed tomography (CT) of the chest, abdomen, and pelvis was performed to evaluate for granulomatous disease and showed scattered ground-glass opacifications in the bilateral upper lobes but was otherwise unremarkable for acute processes or lymphadenopathy (Figs. 1 and 2 with arrows highlighting representative ground-glass opacities). Although she had spinal osteomyelitis in the distant past, there were no concerning changes of her spine or signs of recurrent osteomyelitis. Owing to clinical improvement and a relatively un-

revealing workup while an inpatient, she was discharged with outpatient follow-up to further investigate the etiology of hypercalcemia.

Three weeks after her initial presentation, a positron emission tomography/CT whole-body scan was performed to look for any areas of inflammation to further direct workup and showed no evidence of FDG (¹⁸F-fluorodeoxyglucose)-avid primary malignancy, metastasis, or granulomatous disease but did show improving ground-glass opacification throughout the lungs.

Since the patient's hypercalcemia had resolved along with her symptoms, further history was obtained specifically regarding her pneumonitis. For approximately 6 months leading up to her initial presentation, the patient used an essential



Figure 1. Computed tomography of the chest without intravenous contrast performed at the time of hospital admission. Arrows indicate representative areas of ground-glass opacities in the bilateral upper lobes.



Figure 2. Computed tomography of the chest without intravenous contrast performed at the time of hospital admission. Arrows indicate representative areas of ground-glass opacities in the bilateral upper lobes.

oil diffuser in her bedroom for 5 to 6 hours every evening with eucalyptus oil. Her biochemical workup in conjunction with imaging, exposure history, and removal of exposure with clinical improvement led to the diagnosis of hypersensitivity pneumonitis-induced hypercalcemia. Because her condition had improved rapidly, even by the time the elevated 1,25-dihydroxyvitamin D resulted, the patient was not treated with steroids, which would have been the treatment of choice for hypersensitivity pneumonitis-induced hypercalcemia. The patient declined bronchoscopy, which is the gold standard for further workup of hypersensitivity pneumonitis [3], because of clinical improvement with return to her baseline functional status. Laboratory tests 4 months after discharge and at 1-year follow-up demonstrated sustained normocalcemia, normalization of 1,25-dihydroxyvitamin D level, and normalization of her C-reactive protein. Repeat CT chest at 1 year after discharge revealed resolution of the ground-glass opacities that were seen at time of presentation (Figs. 3 and 4). the patient remains well 1 year after presentation.

Discussion

New-onset hypercalcemia should be worked up in a stepwise fashion. In the outpatient setting PTH-mediated hypercalcemia is the most common etiology of hypercalcemia with the overwhelming majority due to primary hyperparathyroidism, and in the inpatient setting hypercalcemia of ma-

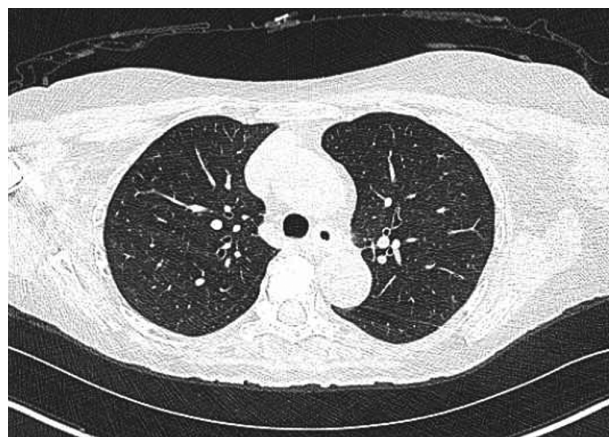


Figure 3. Computed tomography of the chest without intravenous contrast performed 1 year after discharge showing resolution of ground-glass opacities.

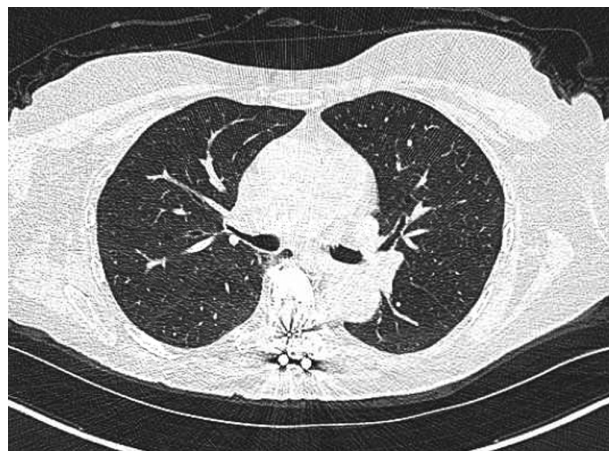


Figure 4. Computed tomography of the chest without intravenous contrast performed 1 year after discharge showing resolution of ground-glass opacities.

lignancy is most common. Given this information, the most useful test in differentiating etiologies of hypercalcemia is a PTH level. If a patient presents with inappropriately normal or elevated PTH with hypercalcemia, the workup is straightforward with primary hyperparathyroidism or tertiary hyperparathyroidism being most likely and in much more rare cases parathyroid carcinoma. A suppressed PTH in the setting of hypercalcemia requires additional evaluation as the differential remains broad. In the setting of patients with known malignancy, particularly squamous cell carcinoma and renal cell carcinoma, PTH-related peptide is most likely causative. Other evaluation in non-PTH-mediated hypercalcemia includes vitamin D metabolites with 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to differentiate hypercalcemia due to vitamin D toxicosis (elevated 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) vs granulomatous disease and lymphoma (normal or low 25-hydroxyvitamin D and elevated 1,25-dihydroxyvitamin D) [1]. Other diagnostic considerations include lytic bone disease from metastatic cancer or multiple myeloma, medication induced hypercalcemia, prolonged thyrotoxicosis, adrenal insufficiency, and acromegaly. Patients with mild hypercalcemia and prolonged bedrest could have hypercalcemia of immobility on the differential although this is a diagnosis of exclusion [4].

Our patient presented with a suppressed PTH, no known history of malignancy, normal 25-hydroxyvitamin D, elevated 1,25-dihydroxyvitamin D, and an elevated erythrocyte sedimentation rate leading to further workup for granulomatous disease and lymphoma as the etiology of hypercalcemia. The most common granulomatous diseases presenting with hypercalcemia include infection (tuberculosis, histoplasmosis, and coccidioides, and disseminated candidiasis), sarcoidosis, and foreign-body lung disease such as silicosis and berylliosis [1]. Less commonly, hypersensitivity pneumonitis can cause hypercalcemia.

Hypersensitivity pneumonitis is a diffuse granulomatous lung disease involving the lung parenchyma and terminal airways that results after inhalation of a causative antigen to which the patient has previously been sensitized [2, 3, 5]. Hypersensitivity pneumonitis leads to hypercalcemia in a similar manner that other granulomatous disease processes do, which is due to unregulated 1- α -hydroxylase activity in macrophages converting 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D [1, 2]. In hypersensitivity pneumonitis the granulomas that contain the macrophages are small and loosely formed, following a pattern along the interstitial and bronchiolocentric distributions [2, 3, 6].

Our patient did not have radiologic evidence of significant lymphadenopathy concerning for sarcoidosis, had a negative QuantiFERON gold test, negative beta glucan, and CT chest findings more suggestive of hypersensitivity pneumonitis than invasive infection from endemic mycosis due to the pattern of basal-sparing, scattered, ground-glass opacities with centrilobular nodules [2, 5]. She had no exposure to silica or beryllium. With radiologic evidence for hypersensitivity pneumonitis, further clinical history was taken to determine if there were any new antigen exposures, leading to the discovery that she had recently been using a eucalyptus essential oil diffuser at night. It is unclear if our patient had hypersensitivity due to chemical irritation from the aerosolization of oils or if there was a contaminant in the diffuser due to improper cleaning. Ideally in cases of unknown etiology of hypersensitivity pneumonitis, bronchoscopy should be performed [3, 7].

Diagnosis of hypersensitivity pneumonitis should be considered in patients with cough, dyspnea, fatigue, anorexia, and weight loss with imaging findings showing small centrilobular nodules, ground-glass attenuation, and lobular areas of decreased attenuation and vascularity [2, 5], particularly in the setting of known exposure to a provocative antigen. The most common causes include avian antigens and hot tub-related *M avium* complex; however, in up to 25% of patients the antigen is not identified [2, 5].

On withdrawal of the inhaled eucalyptus oil her hypoxia, abnormal CT chest findings, and hypercalcemia resolved with

normalization of her 1,25-dihydroxyvitamin D levels, and all have remained in the normal range without further interventions at 1-year posthospitalization follow-up.

Conclusion

In cases of hypercalcemia with suppressed PTH and no known active malignancy, vitamin D metabolites can be helpful to identify the etiology of hypercalcemia [1, 8]. In the setting of isolated 1,25-dihydroxyvitamin D elevation, a thorough workup for granulomatous and inflammatory conditions should be undertaken including a careful history of pulmonary exposures to help identify the underlying cause of hypercalcemia [7, 8].

Disclosures

The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

References

1. Zhang JTW, Chan C, Kwun SY, Benson KA. A case of severe 1,25-dihydroxyvitamin D-mediated hypercalcemia due to a granulomatous disorder. *J Clin Endocrinol Metab.* 2012;97(8):2579-2583.
2. Donato J, Phillips CT, Gaffney AW, VanderLaan PA, Mouded M. A case of hypercalcemia secondary to hot tub lung. *Chest.* 2014;146(6):e186-e189.
3. Lacasse Y, Selman M, Costabel U, et al; HP Study Group. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med.* 2003;168(8):952-958.
4. Carroll MF, Schade DS. A practical approach to hypercalcemia. 2003. Accessed August 8, 2021. <https://www.aafp.org/afp/2003/0501/p1959.html>
5. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc.* 2007;82(7):812-816.
6. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of hypersensitivity pneumonitis in adults. an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med.* 2020;202(3):e36-e69.
7. Calhoun K, Duke J, George N, Akkanti B. When oil meets air: a new cause of hypersensitivity pneumonitis. *Chest.* 2019;156(4 Suppl):2184A.
8. 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(7):3111-3117.