AACE Clinical Case Rep. 10 (2024) 45–48

Clinical Case Reports™
www.aaceclinicalcasereports.com

Case Report

An Unusual Case of Hypercalcemia Due to Graft-Versus-Host Disease

Paras Fatima, MBBS [1,*], Vincent Czerwinski, BS [2], Sujata Panthi, MBBS [3], Chitra Choudhary, MD [4]

[1] Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas
[2] University of Kansas School of Medicine, Kansas City, Kansas
[3] Department Endocrinology, University of Indiana Medical Center, Indianapolis, Indiana
[4] Division of Endocrinology, Metabolism and Clinical Pharmacology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

ARTICLE INFO

Article history:
Received 15 July 2023
Received in revised form
4 December 2023
Accepted 11 December 2023
Available online 13 December 2023

Key words:
GVHD
hypercalcemia
bone marrow transplant

ABSTRACT

Background/Objective: Hypercalcemia is a common disorder with a wide differential and is most commonly related to malignancy and hyperparathyroidism. Hypercalcemia is a rarely reported consequence of graft-versus-host disease (GVHD) and may be related to a granulomatous manifestation of the common stem cell transplantation procedure.
Case Report: A 67-year-old woman with a history of allogenic stem cell transplantation due to myelodysplastic syndrome presented to the bone marrow transplant clinic with dysphagia, muscle aches, and rash. She was found to have an extremely increased calcium and 1,25-dihydroxyvitamin D levels, which were ultimately corrected with administration of steroids and zoledronic acid.
Discussion: While uncommon, granulomatous disease can lead to hypercalcemia via the activation of 1α-hydroxylase within macrophages, which, in turn, activates 1,25-dihydroxyvitamin D leading to an increased serum calcium level. GVHD is a common, variably presenting complication of bone marrow transplantation. Granulomatous processes related to GVHD may mediate hypercalcemia in patients with both increased calcium and 1,25-dihydroxyvitamin D levels.
Conclusion: This is a rare cause of calcitriol-mediated hypercalcemia associated with GVHD. There have been cases of granulomas associated with GVHD, and this could potentially lead to ectopic production of calcitriol. We deemed GVHD to be a likely cause of the patient's calcitriol-mediated hypercalcemia because we did not find another etiology that fit the clinical findings. Physician awareness of this complication and the appropriate workup will allow future researchers to properly elucidate the etiology of this rare complication.

Introduction

Hypercalcemia is frequently observed in both community and hospitalized patients, with an incidence of 0.2% to 4%.[1] Primary hyperparathyroidism and malignancy are common etiologies of hypercalcemia. An increased 1,25-dihydroxyvitamin D level due to lymphoma and granulomatous diseases such as sarcoidosis, tuberculosis, and fungal diseases can also cause hypercalcemia. Hypercalcemia may be noted in approximately 20% to 30% of malignancy cases.[2] Because hematopoietic stem cell transplants are being performed more frequently, this brings attention to graft-versus-host disease (GVHD) as the leading cause of morbidity and mortality after allogeneic hematopoietic cell transplantation. We describe an unusual case of hypercalcemia in a patient with GVHD.

Case Report

A 67-year-old woman with myelodysplastic syndrome underwent an allogeneic stem cell transplantation in September 2019. The patient presented to the bone marrow transplant (BMT) clinic in September 2020 with dysphagia, generalized muscle aches, and skin changes for 2 weeks. She reported diffuse muscle aches in her

Abbreviations: AML, acute myeloid leukemia; BMT, bone marrow transplant; GVHD, graft-versus-host disease; PTH, parathyroid hormone; PTHrP, PTH-related protein.

* Address correspondence to Dr Paras Fatima, Department of Internal Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160.
E-mail address: pfatima@kumc.edu (P. Fatima).

https://doi.org/10.1016/j.aace.2023.12.002

arms, legs, and back. She had dry and rough/leathery skin of the neck, dysphagia, dry eyes, and dry mouth. She was taking cholecalciferol 2000 units daily before presentation and denied taking calcium supplements, oral/parenteral steroid medications, or medications that can cause hypercalcemia. She had normal vital signs, and examination showed dry skin and conjunctival injections bilaterally. A neurologic examination did not reveal muscle weakness. The other examination results were within the normal limits. The laboratory tests showed increased levels of serum calcium at 14.3 mg/dL (normal range, 8.5-10.6 mg/dL), ionized calcium at 1.91 mmol/L (normal range, 1.0-1.3 mmol/L), CPK at 316 U/L (normal range, 21-215 U/L), and albumin at 3.3 g/dL (normal range, 3.5-5.0 g/dL) and a corrected calcium level at 14.9 mg/dL. Other laboratory tests showed an alkaline phosphatase level of 176 U/L (normal range, 25-110 U/L), AST level of 97 U/L (normal range, 7-40 U/L), ALT level of 37 U/L (normal range, 7-56 U/L), and creatinine level of 1.6 mg/dL (0.4-1.00 mg/dL). The parathyroid hormone (PTH) level was low at 4.2 pg/mL (normal range, 10-65 pg/mL). The laboratory tests showed a PTH-related protein (PTHrp) level of <0.4 pmol/L, thyroid-stimulating hormone level of 0.47 mcu/mL (normal range 0.35-5.0 mcu/mL), phosphorus level of 3.2 mg/dL (normal range, 2.0-4.5 mg/dL), and normal 1,25-dihydroxyvitamin D level at 43.4 ng/mL (normal range, 30-80 ng/mL). The patient had an increased 1,25-dihydroxyvitamin D level at 102.0 pg/mL (normal range, 19.9-79.3 pg/mL). The chest radiography result was normal and did not show abnormal lymphadenopathy.

Rheumatology was consulted to rule out autoimmune myositis. Because of the absence of rash and only a modest increase in the creatine kinase level, an autoimmune cause was deemed less likely. With the features of myositis, transaminitis, and hypercalcemia, chronic GVHD was diagnosed, and she was admitted to the hospital for further management. Treatment was started with intravenous hydration and prednisone 1 mg/kg (60 mg) daily. In addition, the patient received an infusion of calcitonin 200 units every 12 hours for 2 days and 1 dose of zoledronic acid 4 mg. Follow-up laboratory tests after treatment initiation showed a downtrend in the calcium levels. The calcium level improved to 11.7 mg/dL (corrected calcium level, 12.7 mg/dL) in <24 hours, as depicted in the Figure. On the day of discharge after 3 days of hospital admission, the calcium level was normal at 9 mg/dL (corrected calcium level, 10 mg/dL). She was discharged on prednisone 60 mg once daily. At the outpatient follow-up, the 1,25-dihydroxyvitamin D level improved to 28 pg/mL in a month, and the corrected calcium level remained stable at approximately 8.9 mg/dL. Her symptoms of myalgias, dry mouth, and dry skin also improved. The prednisone was tapered off slowly over 8 months. The angiotensin-converting enzyme (ACE) level was normal at 57 U/L (normal range, 16-85 U/L) at the 2.5-year follow-up. No previous ACE level was available for comparison in this patient. The laboratory test results on hospital admission and at follow-up are summarized in Table 1.

Highlights

- Graft-versus-host disease (GVHD) can manifest with multiple sign and symptoms
- Case report of calcitriol-mediated hypercalcemia in a patient with GVHD
- Calcitriol-mediated hypercalcemia in GVHD may be due to granuloma formation

Clinical Relevance

Bone marrow transplant is an increasingly common procedure in the treatment of hematologic malignancies. Graft-versus-host disease (GVHD) is an exceedingly common complication of this procedure and may manifest in a highly variable fashion. This is a rare cause of calcitriol-mediated hypercalcemia associated with GVHD. Here, we demonstrate that the hypercalcemia due to GVHD may be mediated by an increased 1,25-dihydroxyvitamin D level, suggesting a possible granulomatous etiology.

Discussion

Mild hypercalcemia can be asymptomatic or cause symptoms including lethargy and constipation. Severe hypercalcemia can present with life-threatening symptoms, such as dehydration, encephalopathy, and renal failure. Calcium homeostasis is regulated by an equilibrium between intestinal absorption, bone resorption, and renal excretion. Factors that play a role to maintain calcium homeostasis are PTH, 1,25-dihydroxyvitamin D, calcitonin, serum calcium, and serum phosphorus. PTH leads to direct and indirect stimulations of osteoclasts and can lead to increased renal calcium reabsorption and decreased renal phosphate reabsorption. PTH also increases intestinal calcium absorption by activating 1,25-dihydroxyvitamin D production in the kidney.[3] Calcitonin inhibits both

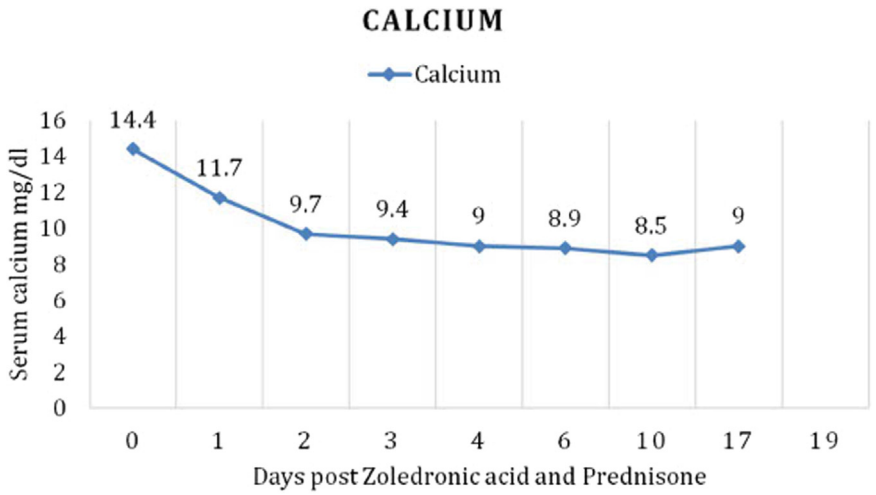

Fig. Serum calcium level after zoledronic acid and prednisone therapy.

Table 1
Laboratory Values at Time of Admission and Follow-up

Laboratory test	Reference range	Results at admission	Results at follow-up after 5 wk of prednisone treatment
Serum calcium	8.5-10.6 mg/dL	14.3	8.5
Creatine phosphokinase	21-215 U/L	316	…
Albumin	3.5-5.0 g/dL	3.3	3.5
Ionized calcium	1.0-1.3 mmol/L	1.91	…
Phosphorus	2.0-4.5 mg/dL	3.2	…
Creatinine	0.4- 1.0 mg/dL	1.6	0.88
PTH	10-65 pg/mL	4.2	…
PTHrp	<4.2 pmol/L	<0.4	…
25-Hydroxyvitamin D	30-80 ng/mL	43.4	39
1,25-Dihydroxyvitamin D	30-80 ng/mL	102	28
AST	7-40 U/L	97	25
ALT	7-56 U/L	37	41
Alkaline phosphatase	25-110 U/L	176	134

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; PTH = parathyroid hormone; PTHrp = parathyroid hormone–related protein.

renal reabsorption and intestinal absorption of calcium. It also acts on osteoblasts to increase bone deposition of calcium.[4]

Hypercalcemia of malignancy can occur due to multiple factors such as bone destruction by tumor cells through increased osteoclastic activity or by increased 1,25-dihydroxyvitamin D, PTH, or PTHrP by the tumor cells. Among solid cancers, breast and renal cancers are the leading cause of hypercalcemia, followed by squamous cell carcinoma.[5] Humoral hypercalcemia of malignancy is also referred to as PTHrP-mediated hypercalcemia. PTHrP stimulates PTH receptors in the bone and kidney and results in osteoclast activation and osteoblast suppression.[6] PTHrP also uncouples bone resorption from formation. This process of uncoupling is mediated by cytokines such as interleukin-1, prostaglandin, lymphotoxin, and tumor necrosis factor.[7] In addition, PTHrP enhances renal proximal tubule phosphorous excretion, resulting in phosphaturia and low/normal serum phosphorus levels.[5] However, PTHrP does not activate 1,25-dihydroxyvitamin D because of the differences in structure between PTH and PTHrP.[8] Calcitriol-mediated hypercalcemia can be observed in Hodgkin and non-Hodgkin lymphomas along with granulomatous diseases. Calcitriol-mediated hypercalcemia is prevalent in <1% of all malignancy-associated hypercalcemia.[2] It is associated with normal to high phosphorous levels compared with PTHrP-mediated hypercalcemia and primary hyperparathyroidism.[9]

GVHD in the acute or chronic form is a frequent complication after hematopoietic stem cell transplant. Up to 30% to 50% of patients who undergo allogeneic transplantation develop acute GVHD.[10] Acute GVHD usually occurs within 100 days, whereas chronic GVHD develops after 100 days. Acute GVHD manifestations typically include maculopapular rash, hepatic dysfunction, and gastrointestinal (GI) symptoms, such as vomiting, abdominal pain, and diarrhea.[10] Chronic GVHD affects multiple organs and can present in several different ways including sicca, dry eyes, polymyositis, skin rash, and bronchiolitis obliterans.[11] The first-line therapy for both acute GVHD and chronic GVHD is corticosteroids.[12] Few cases of relapse of acute myeloid leukemia (AML) after BMT have been described in pediatric patients with AML presenting with hypercalcemia.[9,13,14] In adults, only 1 case of hypercalcemia that was associated with relapse of AML after BMT has been reported.[15] Sarcoidosis can lead to hypercalcemia due to activation of the 1,25-dihydroxyvitamin D level, and sarcoidosis after stem cell transplant has been described in the literature. The most common site of sarcoidosis after stem cell transplant is the lung, followed by the skin, liver, musculoskeletal system, and bone marrow.[16]

The association between GVHD in post-BMT transplant and calcitriol-mediated hypercalcemia has not been widely reported. Our case is unique because the patient was admitted with GVHD and subsequently found to have hypercalcemia with an increased 1,25-dihydroxyvitamin D level. No other cause for an increased 1,25-dihydroxyvitamin D level was identified. Sarcoidosis associated with GVHD can cause hypercalcemia; however, our patient did not have any clinical, imaging, or histologic evidence of sarcoidosis. The chest radiography result was normal during admission, and the ACE level collected at outpatient follow-up was also normal. Some cases in the literature have granulomas associated with GVHD. One case of cutaneous granuloma in GVHD has been reported in the literature.[17] It may be possible that GVHD can cause granulomas in a similar manner to sarcoidosis because both are characterized by immune response to antigens. Cutaneous GVHD specimens have revealed the presence of proinflammatory markers such as tumor necrosis factor-alpha, interferon-gamma, and interleukin-1, similar to those found in sarcoid granulomas.[17] In addition, another study found rare cases of granulomas on GI biopsies of patients with GI GVHD.[18] An additional possibility is granulomatous myositis as a complication of GVHD because the patient presented with muscle aches. Granulomatous myositis has been described in association with both sarcoidosis and GVHD.[19] The case reports of GVHD causing granulomatous myositis are presented in Table 2.[20] Two cases described in Table 2[20] had hypercalcemia with low PTH and 1,25-dihydroxyvitamin D levels, suggesting a granulomatous cause; however, data on 1,25-dihydroxyvitamin D are lacking. Limited data in the literature prevent definitive comparisons from being drawn.

The decreased 25-hydroxyvitamin D level with an increased 1,25-hydroxyvitamin D level observed in our case suggests a possible granulomatous etiology of hypercalcemia. Our patient was started on prednisone for GVHD, and the 1,25-dihydroxyvitamin D and serum calcium levels improved on the steroid therapy. At 1-year follow-up, the patient did not have a recurrence of

Table 2
Case Reports of Graft-Versus-Host Disease Causing Granulomatous Myositis

Underlying disease	Calcium (mg/dL)	PTH (pg/mL)	25-Hydroxyvitamin D (ng/mL)	Treatment	Source
Allogenic hematopoietic stem cell transplantation due to CLL	12.99	Decreased	Decreased	Calcitonin, pamidronate, prednisone, and azathioprine	Roy et al[20]
Allogenic hematopoietic stem cell transplantation due to B-ALL	12.38	Unreported	Slightly decreased	Prednisone and rituximab	Roy et al[20]

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia.

myelodysplastic disease, and the calcium level remained normal after stopping prednisone.

Conclusion

This case is an example of GVHD presenting with 1,25-dihydroxyvitamin D–mediated hypercalcemia. Few previous case reports have described a similar presentation, limiting the determination of frequency of this condition. The pathophysiology of 1,25-dihydroxyvitamin D–mediated hypercalcemia in patients with GVHD after stem cell transplant remains unclear but may be related to granulomatous activation of 1α-hydroxylase. We deemed GVHD to be a likely cause of the patient's calcitriol-mediated hypercalcemia because we did not find another etiology that fit the clinical findings.

Disclosure

The authors have no conflicts of interest to disclose.

References

1. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. *Endocr Rev*. 2016;37(5):521–547. https://doi.org/10.1210/er.2016-1070
2. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;352(4):373–379. https://doi.org/10.1056/NEJMcp042806
3. Trehan A, Cheetham T, Bailey S. Hypercalcemia in acute lymphoblastic leukemia: an overview. *J Pediatr Hematol Oncol*. 2009;31(6):424–427. https://doi.org/10.1097/MPH.0b013e3181a1c12b
4. Yu E, Sharma S. Phyisology, Calcium. In: *Statpearls [Internet]. Treasure Island (FL)*. StatPearls Publishing; 2023.
5. Sternlicht H, Glezerman IG. Hypercalcemia of malignancy and new treatment options. *Ther Clin Risk Manag*. 2015;11:1779–1788. https://doi.org/10.2147/TCRM.S83681
6. Bender RA, Hansen H. Hypercalcemia in bronchogenic carcinoma. A prospective study of 200 patients. *Ann Intern Med*. 1974;80(2):205–208. https://doi.org/10.7326/0003-4819-80-2-205
7. Adami S, Rossini M. Hypercalcemia of malignancy: pathophysiology and treatment. *Bone*. 1992;13(Suppl 1):S51–S55. https://doi.org/10.1016/s8756-3282(09)80010-0
8. Nakayama K, Fukumoto S, Takeda S, et al. Differences in bone and vitamin D metabolism between primary hyperparathyroidism and malignancy-associated hypercalcemia. *J Clin Endocrinol Metab*. 1996;81(2):607–611. https://doi.org/10.1210/jcem.81.2.8636276
9. Goldner W. Cancer-related hypercalcemia. *J Oncol Pract*. 2016;12(5):426–432. https://doi.org/10.1200/JOP.2016.011155
10. Zeiser R, Blazar BR. Acute graft-versus-host disease - biologic process, prevention, and therapy. *N Engl J Med*. 2017;377(22):2167–2179. https://doi.org/10.1056/NEJMra1609337
11. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet*. 2009;373(9674):1550–1561. https://doi.org/10.1016/S0140-6736(09)60237-3
12. Garnett C, Apperley JF, Pavlů J. Treatment and management of graft-versus-host disease: improving response and survival. *Ther Adv Hematol*. 2013;4(6):366–378. https://doi.org/10.1177/2040620713489842
13. Kounami S, Yoshiyama M, Nakayama K, Hiramatsu C, Aoyagi N, Yoshikawa N. Severe hypercalcemia in a child with acute nonlymphocytic leukemia: the role of parathyroid hormone-related protein and proinflammatory cytokines. *Acta Haematol*. 2004;112(3):160–163. https://doi.org/10.1159/000079728
14. Muler JH, Valdez R, Hayes C, Kaminski MS. Acute megakaryocytic leukemia presenting as hypercalcemia with skeletal lytic lesions. *Eur J Haematol*. 2002;68(6):392–396. https://doi.org/10.1034/j.1600-0609.2002.02715.x
15. Montoliu J, Maciá J, Salamero P, Parra R, Gallart M. Severe hypercalcemia indicating relapse of acute myelocytic leukemia after bone marrow transplantation. *Nephron*. 1992;62(3):357–358. https://doi.org/10.1159/000187073
16. Wurm-Kuczera RI, Buentzel J, Koenig JFL, et al. Sarcoidosis following hematopoietic stem cell transplantation: clinical characteristics and HLA associations. *Front Immunol*. 2021;12:746996. https://doi.org/10.3389/fimmu.2021.746996
17. Tsunemi Y, Ihn H, Saeki H, Tamaki K. Epithelioid granulomas in post-transplantation chronic graft-vs.-host disease. *Br J Dermatol*. 2003;149(4):898–899. https://doi.org/10.1046/j.1365-2133.2003.05581.x
18. Wong NACS, Marks DI. The diagnostic and clinical significance of granulomas in gastrointestinal biopsies from haematopoietic transplant patients. *Histopathology*. 2021;78(5):772–777. https://doi.org/10.1111/his.14303
19. Kaushik S, Flagg E, Wise CM, Hadfield G, McCarty JM. Granulomatous myositis: a manifestation of chronic graft-versus-host disease. *Skelet Radiol*. 2002;31(4):226–229. https://doi.org/10.1007/s00256-001-0469-5
20. Roy C, Lai EJ, Lee AHA, et al. Granulomatous myositis as a manifestation of chronic graft-versus-host disease: a case series and review of the literature. *Clin Lymphoma Myeloma Leuk*. 2022;22(7):e459–e462. https://doi.org/10.1016/j.clml.2022.01.004