AACE Clinical Case Rep. 10 (2024) 156–159

Clinical Case Reports™
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Case Report

Hypocalcemia and Hypoparathyroidism Associated With Critical Illness and Aplastic Anemia

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ARTICLE INFO

Article history:
Received 28 August 2023
Received in revised form
22 April 2024
Accepted 25 April 2024
Available online 3 May 2024

Key words:
hypocalcemia
hypoparathyroidism
aplastic anemia

ABSTRACT

Background/Objective: Severe hypocalcemia is common in critically ill patients. There are different mechanisms. To our knowledge, there are no data about the acute presentation of hypocalcemia at the time of diagnosis of aplastic anemia (AA). The objective of this case report was to describe the case of hypoparathyroidism with severe hypocalcemia in a critically ill patient with AA.
Case Report: A 60-year-old man presented with severe hypocalcemia with a calcium level of 6.1 mg/dL (reference range, 8.6-10.3 mg/dL) and hypoparathyroidism with a parathyroid hormone level of 11 pg/mL (reference range, 12-88 pg/mL). He developed a critical state caused by newly diagnosed AA and its complications, such as an acute decrease in the platelet value to a critically low level of 2×10^3/cmm, complicated by neutropenic fever and lower gastrointestinal bleeding. After the initiation of immunosuppressive therapy for AA, his parathyroid hormone-calcium metabolism improved and remained stable but did not normalize completely.
Discussion: In our patient, hypoparathyroidism with hypocalcemia may have been caused by cytokine-related upregulation of the calcium-sensing receptor in the setting of AA. On the other hand, given the severity of the initial hypocalcemia and only partial improvement in calcium homeostasis with residual mild hypocalcemia after treatment initiation for AA, autoimmune causes cannot be entirely ruled out, nor could a combination of cytokine-mediated and autoimmune causes.
Conclusion: It is essential to treat the underlying causes of hypocalcemia, which, in this case, were AA and hypoparathyroidism.

Introduction

Severe hypocalcemia is a well-known phenomenon in critically ill patients, with a prevalence of 15% to 88% in adults.[1,2] There are multiple causes of hypocalcemia in this population, including sepsis; hypomagnesemia; hypophosphatemia; alteration in the fatty acid, pH, and protein levels; kidney failure; and impaired parathyroid gland secretion.[3] Hypoparathyroidism with hypocalcemia has been shown in critically ill patients with sepsis and toxic shock; however,

Abbreviations: AA, aplastic anemia; CaSR, calcium-sensing receptor; ICU, intensive care unit; IL, interleukin; PTH, parathyroid hormone; TNF, tumor necrosis factor.

Funding Statement: This case report did not get any funding.

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https://doi.org/10.1016/j.aace.2024.04.007

the mechanism is unclear. One of the proposed mechanisms of calcium homeostasis derangements is an impairment of parathyroid hormone (PTH) synthesis.[2] A reported cause is activation of calcium-sensing receptor (CaSR) expression in the kidneys and parathyroid glands during inflammation, which can lower PTH secretion.

There are several reports of hypoparathyroidism due to iron deposition in patients with secondary hemochromatosis in the settings of multiple blood transfusions for aplastic anemia (AA).[4] However, to our knowledge, there are no data about the acute presentation of hypocalcemia at the time of diagnosis of AA. Our search in Ovid MEDLINE and PubMed did not show similar cases reported.

Case Report

A 60-year-old Caucasian man with a past medical history of duodenitis, chronic microscopic lymphocytic colitis, and gastroesophageal reflux disease presented with fatigue, weight loss, tingling, and numbness in the extremities for several months was found to have severe hypocalcemia with a calcium level of 6.1 mg/dL (reference range, 8.6-10.3 mg/dL) and low PTH level of 11 pg/mL (reference range, 12-88 pg/mL). The albumin, alkaline phosphatase, magnesium, and phosphorus levels were 3.7 g/dL (reference range, 3.5-4.8 g/dL), 94 U/L (reference range, 40-129 U/L), 2.0 mg/dL (reference range, 1.8-2.5 mg/dL), and 4.0 mg/dL (reference range, 2.4-4.7 mg/dL), respectively (Table 1). The patient had no family history of autoimmune conditions. He did not have a history of radiation exposure or neck surgery. The 25-hydroxyvitamin D level was 25.9 ng/mL. He had pancytopenia with a white blood cell count of 3.7 $\times$ 10^3/cmm, hemoglobin level of 13.6 g/dL, and platelet count of 136 $\times$ 10^3/cmm (Table 1). The peripheral blood smear was unremarkable.

Autoimmune workup was negative, including antinuclear antibody panel and anti-PTH antibodies (Table 2). CaSR gene sequencing was performed, and the result was negative for genetic abnormalities (Table 2). Human immunodeficiency virus and hepatitis panel were also negative. Although the patient did have weight loss given his age, lack of a history of mucocutaneous candidiasis, normal blood pressure (135/72 mm Hg), and electrolytes inconsistent with adrenal insufficiency, there was low concern for autoimmune polyglandular syndrome, and thus, adrenal function was not evaluated. Thyroid function was within normal limits.

Highlights

- Treatment of a primary cause is essential to manage hypocalcemia in critical illness
- Aplastic anemia may be associated with an immune-mediated hypoparathyroidism
- Hypoparathyroidism should be treated with calcium and calcitriol

Clinical Relevance

Hypocalcemia is common in critical illness. We report a case of hypocalcemia with aplastic anemia (AA). Hypocalcemia may have been caused by either cytokine-related upregulation of the calcium-sensing receptor in the setting of AA, an autoimmune process, or a combination of both immune mechanisms. Management requires treatment of the underlying illness.

Studies were performed to exclude infiltrative causes of hypocalcemia, such as malignancy, hemochromatosis, and sarcoidosis, and were unrevealing (Table 3).

The patient developed an acute decrease in the platelet value to a critically low level of 2 $\times$ 10^3/cmm, complicated by neutropenic fever and lower gastrointestinal bleeding. A bone marrow biopsy revealed a hypocellular bone marrow with <10% cellularity and no evidence of infiltration or granulomatous changes. A diagnosis of AA was made. He required multiple platelet transfusions, empirical dexamethasone treatment, intravenous immunoglobulin, and antithymocyte globulin infusion. Subsequent treatment for AA included eltrombopag and cyclosporine, after which the PTH and calcium levels improved (Table 4). Allogenic bone marrow transplantation or repeat antithymocyte globulin infusion is planned.

The hypocalcemia was initially treated with intravenous calcium gluconate, and then, the patient was switched to oral calcium carbonate 500 mg 3 times a day and calcitriol 0.5 μg twice daily, which was adjusted to the current dose. The patient is now off calcium supplements and receives calcitriol 0.25 μg twice a day and vitamin D3 2000 IU daily. The patient continues to follow-up with us since his initial presentation 4 years ago. His most recent PTH level was 26.9 pg/mL, and the calcium level was between 8.0 and 8.5 mg/dL. Ongoing

Table 1
Laboratory Results on Presentation

Laboratory test	Result		Reference range
Creatinine	(L) 0.69		0.9-1.3 mg/dL
GFR		>90	>60
Calcium	(L) 6.1		8.6-10.3 mg/dL
Magnesium		2.0	1.8-2.5 mg/dL
Phosphorus		4.0	2.4-4.7 mg/dL
Total protein	(L) 6.0		6.1-7.9 g/dL
Albumin		3.7	3.5-4.8 g/dL
Alkaline phosphatase		94	40-129 IU/L
25-Hydroxyvitamin D	(L) 25.9		30-100 ng/mL
TSH		1.07	0.34-5.6 uIU/mL
PTH	(L) 10.7		12-88 pg/mL
24-h urine calcium		176	55-300 mg/24 h
Ionized calcium	(L) 0.96		1.16-1.32 mmol/L
WBC	(L) 3.70		4.3-10.8 $\times$ 10^3/cmm
Hemoglobin	(L) 13.6		14.0-18.0 g/dL
Hematocrit	(L) 39.9		40.0%-52.0%
Plt	(L) 136		150-400 $\times$ 10^3/cmm

Abbreviations: GFR = glomerular filtration rate; L = low; Plt = platelet; PTH = parathyroid hormone; TSH = thyroid-stimulating hormone; WBC = white blood cell.

Table 2
Autoimmune and Genetic Screening

Laboratory test	Result
ANA screen	Negative
Centromere Ab	Negative
RNP Ab	Negative
Smith Ab	Negative
Double-stranded DNA Ab	Negative
Sjogren Ab SSA	Negative
Sjogren Ab SSB	Negative
IgA	Negative
Tissue transglutaminase IgA	Negative
JO-1 Ab	Negative
Scleroderma Ab	Negative
Chromatin	Negative
Ribosomal P	Negative
Smith, U1 ribonucleoprotein	Negative
PTH antibody	Negative
CaSR gene sequencing	Normal without mutations

Abbreviations: Ab = antibody; ANA = antinuclear antibody; CaSR = calcium-sensing receptor; DNA = deoxyribonucleic acid; IgA = immunoglobulin A; PTH = parathyroid hormone; RNP = ribonucleoprotein; SSA = Sjogren syndrome A; SSB = Sjogren syndrome B.

Table 3
Evaluation of the Causes of Hypoparathyroidism

Destruction of parathyroid tissue	
Postsurgical	No surgery
Postradiation	No radiation
Autoimmune	Autoimmune workup negative; no other endocrine insufficiencies
Heavy metal deposition	Ferritin level elevated at 530.9 ng/mL but normal saturation percentage
Reversible causes	
Hypomagnesemia	Magnesium level within normal limits
Genetic causes	No family history
Malignancy	CT of the chest with contrast, unremarkable; CT of the abdomen and pelvis with contrast, unremarkable; CT of the neck, unremarkable. PTH-rP level, 11 pg/mL (reference range, 14-27 pg/mL)
Sarcoidosis	CT of the chest and abdomen with no signs of lymphadenopathy; ACE level, 44 U/L (reference range, 9-67 U/L)

Abbreviations: ACE = angiotensin-converting enzyme; CT = computed tomography; PTH-rP = parathyroid hormone–related protein.

hypocalcemia may be explained by either mild hypoparathyroidism or eltrombopag use to treat his AA. Eltrombopag is similar to other iron chelators in that it can bind divalent cations, such as calcium.[5]

Discussion

Hypocalcemia is known to be a common finding among critically ill patients. Our patient's critical state was caused by AA and its complications. Sepsis is one of the most common causes of hypocalcemia in critically ill patients. Low calcium levels in nonseptic but severely ill patients have not been investigated well. Zivin et al[2] found that hypocalcemia is widespread in hospitalized patients (up to 88%) and is correlated with the severity of illness but not with a specific condition. Haghbin et al[6] found a negative correlation between ionized calcium and calcitonin level in pediatric intensive care unit (ICU) patients with hypocalcemia. Although the study did not show a correlation between the PTH and calcium levels, it was found that the PTH level was associated with the severity of illness: there was a positive correlation between the Pediatric Risk of Mortality III score and serum PTH level ($r = 0.291$, $P = .024$).[6] We did not check calcitonin in our patient; however, his hypocalcemia was associated with a low PTH level in a critical illness setting. Another study showed that pediatric patients in the ICU have a high prevalence of vitamin D deficiency. However, the parathyroid glands were proved to have diminished reaction to it in the settings of severe medical condition.[7] Although the 25-hydroxyvitamin D level was low in our case, we suspect that it was hypoparathyroidism that caused hypocalcemia, and therefore, secondary hyperparathyroidism was not expected.

Some studies have shown that uncorrected or ionized calcium is a better criterion than an albumin-adjusted calcium level to guide replacement therapy and overall prognosis.[8,9] The lack of accuracy of albumin-corrected calcium for estimation of ionized calcium can be explained by changes in pH, which can affect calcium-albumin binding, as well as changes in the citrate, fatty acid, and phosphate levels.[10,11] Given that ionized calcium is more expensive, uncorrected calcium levels may be used for follow-up after initial diagnosis.

Several research groups reported low survival rates in acutely ill patients with hypocalcemia. The mortality rate reaches 44% in patients with hypocalcemia versus 17% in those with a normal calcium level ($P < .05$).[12] Egi et al[13] demonstrated no association between a particular ionized calcium level and hospital or ICU mortality. However, only extreme abnormalities were independent predictors of mortality, particularly an ionized calcium level of <0.8 or >1.4 mmol/L.[13]

It is reported that proinflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNFα) upregulate CaSR expression in the kidneys and parathyroid glands in critical illness, which leads to a decrease in PTH secretion with subsequent hypocalcemia.[14] AA pathogenesis is very complex and includes several mechanisms. One of them is immune dysfunction, where abnormal activation of T lymphocytes results in an increase in the levels of TNFα and IL-6, among other cytokines.[15] The improvement in PTH-calcium homeostasis after initiation of immunosuppressive treatment in our patient supports an underlying immune mechanism for his hypocalcemia. We postulate that the increased levels of cytokines, such as TNFα and IL-6, may have been associated with the AA and cause upregulation of CaSR with resultant suppression of PTH secretion. However, the response to immune suppression could also represent an underlying autoimmune process. The patient had a history of 1 autoimmune condition—lymphocytic colitis. However, the workup for other autoimmune disorders was unrevealing, including negative PTH antibodies. Although given the fact that the PTH-calcium metabolism did not completely normalize with AA treatment and the patient still required calcitriol, autoimmune causes of hypoparathyroidism with hypocalcemia remain as a potential etiology. Given the severity of the initial hypocalcemia and the partial response to the initial treatment of the AA with residual mild hypocalcemia, dual underlying immune mechanisms due to both cytokines and autoimmune causes are also possible.

A report suggests that calcium supplementation does not improve the ionized calcium levels in critical conditions and that the calcium levels cannot be corrected by calcium therapy only; it is also not associated with improved outcomes in critically ill conditions.[8] In a systematic review by Forsythe et al,[16] there is no clear evidence that parenteral calcium supplementation impacts the outcome of critically ill patients. In our patient, anti-AA treatment was associated with improvement in the calcium and PTH levels;

Table 4
Timeline of the Parathyroid Hormone-Calcium Homeostasis, Platelet, Hemoglobin, and Leukocyte Changes

	Initial presentation	Acute critical pancytopenia In 1 mo	Initiation of ATG In 2 mo	On ATG In 3 mo	Initiation of eltrombopag In 4 mo	Initiation of cyclosporine In 14 mo	Continuation of cyclosporine and eltrombopag In 14 mo	Increase in the cyclosporine dose In 15 mo
Calcium, mg/dL (8.6-10.3)	6.1	8	9.8	8.2	8	7.9	7.7	7.9
Albumin, g/dL (3.5-4.8)	3.7	3.3	3.6	Not performed	Not performed	4.3	3.9	4.2
PTH, pg/mL (12-8)	11	Not performed	Not performed	Not performed	Not performed	Not performed	19.4	Not performed
Hemoglobin, g/dL (14.0-18.0)	13.6	10.2	7.9	6.9	8.2	9.5	6.5	7.4
Plt, $\times 10^3$/cmm (150-400)	135	2	31	10	11	62	21	30
WBC, $\times 10^3$/cmm (4.3-10.8)	3.7	1	2.3	0.4	1.3	6.8	2.6	3.4

Abbreviations: ATG = antithymocyte globulin; Plt = platelet; PTH = parathyroid hormone; WBC = white blood cell.

however, he still required calcitriol. Thus, it is important to treat the underlying causes of hypocalcemia, which, in our case, were AA and hypoparathyroidism.

In conclusion, in our patient, an immune mechanism of either cytokine-related upregulation of the CaSR, an autoimmune process, or a combination of both may be the cause of the acute parathyroid suppression with resultant hypocalcemia. Successful management requires identification and treatment of the underlying illness.

Disclosure

The authors have no conflicts of interest to disclose.

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