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CASE REPORT

Hypoparathyroidism: An Uncommon Complication Associated With Immune Checkpoint Inhibitor Therapy

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Abstract

As immune checkpoint inhibitor drugs are being used in the treatment of some cancers, unusual adverse events are being reported, labeled as immune-related adverse events. Various endocrinopathies related to immune-related adverse events have been described, among which hypoparathyroidism is exceedingly rare. We report a case of hypoparathyroidism induced by immune checkpoint drugs, highlighting the need for awareness of this emerging complication.

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Immune checkpoint molecules such as cytotoxic T-lymphocyte–associated protein 4 and programmed cell death protein 1 (PD-1) have been identified as critical factors in cancer pathogenesis, leading to a revolution in cancer therapy with the use of immune checkpoint inhibitor (ICI) drugs.[1] Immune checkpoint inhibitor drugs are currently being used to target these molecules to modulate T-cell function and employ the immune response in the treatment of several solid and hematological malignancies.[2] However, as immune checkpoints are closely involved in the maintenance of immunological tolerance to self-antigens, ICIs have been associated with autoimmune-like manifestations, referred to as immune-related adverse events (irAEs).[3] Endocrinopathies including hypothyroidism, hyperthyroidism, hypophysitis, primary adrenal insufficiency, and autoimmune diabetes mellitus are among the more commonly reported events.[4] As the use of ICIs increases, the incidence of such events is expected to rise and the spectrum of described irAEs may broaden to include other rarely reported conditions.[5] Hypoparathyroidism with ICI use is an exceedingly rare endocrine complication with only 3 previous cases reported.[6-8] We report a case of hypoparathyroidism along with hypophysitis in the setting of ipilimumab (anti–cytotoxic T-lymphocyte–associated protein 4 therapy) and nivolumab (anti–PD-1 therapy) use, illustrating the need for clinicians to consider this complication vigilantly and call for further research to focus on its management, including identification of those patients at highest risk.

CASE REPORT

A 76-year-old man presented to the emergency department with symptoms of weakness, anorexia, and confusion of 1 week in duration. His history was remarkable for widespread metastatic melanoma to the pericardium, lung, liver, and lymph nodes for which he had been receiving combination immunotherapy with ipilimumab plus nivolumab 7 months earlier. Within 2 months of the initiation of this therapy, he developed irAEs of colitis and pneumonitis for which immunotherapy had been held. Approximately 4 months later, he was switched to nivolumab monotherapy. He received 2 infusion cycles, with the last dose given 28 days before our evaluation (Figure).

On presentation, his vital signs were significant for a blood pressure of 93/48 mm Hg. Physical examination was unremarkable with negative Chovstek and Trousseau signs.

Laboratory evaluation found severe hypocalcemia with a total serum calcium level of 5.7 mg/dL (reference range, 8.8-10.2 mg/dL), a serum albumin level of 3.0 g/dL (reference

range, 3.5-5.0 g/dL), an albumin-corrected calcium level of 6.5 mg/dL, hyperphosphatemia with a serum phosphorus level of 5.1 mg/dL (reference range, 2.5-4.5 mg/dL), and a normal serum magnesium level of 1.7 mg/dL (reference range, 1.7-2.3 mg/dL). The serum creatinine level was 1.18 mg/dL (reference range, 0.74- 1.35 mg/dL). The serum ionized calcium level was 3.01 mg/dL (reference range, 4.57-5.43 mg/dL), further confirming hypocalcemia. In addition, he was found to have hyponatremia with a serum sodium level of 118 mmol/L (reference range, 135-145 mmol/L).

Electrocardiogram was remarkable for a prolonged QT-corrected interval (corrected using the Bazett formula) of 492 ms. He was immediately treated with a total of 3 g of intravenous calcium gluconate and normal saline infusion.

Further workup found an undetectable serum parathyroid hormone (PTH) level of less than 6.0 pg/mL (reference range, 15-65 pg/mL) and a normal serum total 25-hydroxyvitamin D level of 31 ng/mL. A 1,25-dihydroxyvitamin D level was not measured. He was diagnosed with primary hypoparathyroidism. He denied any history of neck surgery or head and neck radiation. Anti-parathyroid antibody, a clinically available test performed by radiobinding assay (Quest Diagnostics), previously recognized in some cases of autoimmune hyopoparathyroidism, was undetectable in this case. Anti—calcium-sensing receptor (CaSR)—activating antibodies were not measured. Notably, his calcium level had been within the normal range until this presentation (Figure). The median serum calcium and creatinine levels over a time period of 5 years before any ICI therapy was 9.3±0.23 and 1.29±0.27 mg/dL, respectively. The parathyroid hormone level 6 years before presentation was normal at 49 pg/mL.

Given concerns for other endocrinopathies, particularly adrenal insufficiency due to noted hyponatremia, the morning cortisol level was checked, which was low at 2.0 μg/dL (reference range, 7-25 μg/dL). Additionally, the serum corticotropin level was inappropriately normal at 8.3 pg/mL (reference range, 7.2-63 pg/mL). Magnetic resonance imaging of the brain did not reveal any pituitary or hypothalamic abnormalities. Both thyroid-stimulating hormone and free T4 levels were normal at 2.9 mIU/L (reference range, 0.3-4.2 mIU/L) and 1.1 ng/dL (reference range, 0.9-1.7 ng/dL), respectively. Other hypothalamic-pituitary hormones were not assessed.

The patient began treatment with 500 mg of calcium carbonate (elemental calcium) 3 times daily and 1000 IU of cholecalciferol daily, with improvement in his serum calcium level over the course of 3 days (Figure). Given the absence of PTH and the resultant impairment of 1-alpha-hydroxylation of 25 hydroxyvitamin D, 0.25 μg of calcitriol twice daily was also initiated concurrently. Hydrocortisone replacement was initiated with good clinical response in blood pressure, sodium levels, and symptoms. After 22 days of initiating this regimen, the serum calcium level was 8.1 mg/dL with a serum albumin level of 4.0 g/dL and a 24-hour urine calcium level of 198 mg/24 h.

DISCUSSION

Acute hypocalcemia is a potentially life-threatening metabolic disturbance that requires prompt recognition and treatment. Because calcium in serum is 40% protein bound, with albumin accounting for 90% of protein binding, measurement of the albumin level is essential in the assessment of hypocalcemia. In cases in which the albumin level is abnormal, as in this case, the serum calcium level can be corrected for the albumin level by using a standard formula whereby each 1 g/dL reduction in the serum albumin concentration will lower the total calcium concentration by approximately 0.8 mg/dL. In practice, however, some observational evidence suggests that the diagnostic accuracy of uncorrected calcium is superior to corrected calcium in reflecting true calcium status.[9] Measurement of the ionized calcium level can also be used as a more direct evaluation of calcium status, although limitations include difficulties in accurate analysis, lack of standardization, and need for special handling of specimens. Despite correction and measurement of the ionized calcium level, the serum calcium level remained low by both measures in this patient, confirming true hypocalcemia. Once hypocalcemia is confirmed, PTH levels should be measured. In the absence of PTH or in circumstances of low to normal PTH levels despite hypocalcemia, hypoparathyroidism

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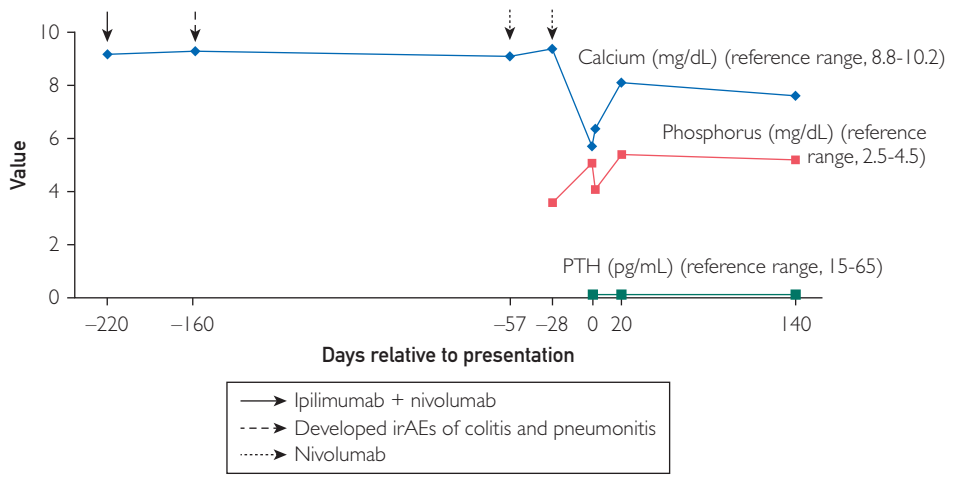

FIGURE. Serum levels of calcium, phosphate, and parathyroid hormone (PTH) over the course of immune checkpoint inhibitor therapy. Time expressed as days relative to presentation. irAE = immune-related adverse event.

must be considered.[10] Hypoparathyroidism should be distinguished from pseudohypoparathyroidism or hypocalcemia secondary to hypomagnesemia, both of which can also be characterized by a low serum calcium level. However, these can be distinguished by PTH levels. In pseudohyoparathyroidism, PTH levels may be elevated because of PTH resistance, whereas hypomagnesaemia may impair PTH secretion, leading to low PTH levels.[11,12] Hypoparathyroidism is a rare disorder with an estimated incidence of 23 to 37 cases per 100,000 person-years. The condition is most commonly seen as a complication of anterior neck surgery (75% of cases), but increasingly other etiologies including genetic and autoimmune causes are being reported.[11,12] Conventionally, autoimmune hypoparathyroidism can occur as an isolated endocrinopathy or as a component of autoimmune polyendocrine syndrome type 1.[12] With use of ICI in the treatment of cancer, the condition is being seen in association with ICI blockade but has been described only 3 times previously.[6-8]

Given the lack of other associated causes of hypoparathyroidism, late age of onset, and absence of other autoimmune polyendocrine syndrome features, combined with the temporal relationship between ICI therapy and other associated irAEs including hypophysitis with secondary adrenal insufficiency, we believe this case illustrates hypoparathyroidism as a rare complication associated with ipilimumab and nivolumab therapy. Although his pituitary on magnetic resonance imaging was unremarkable, pituitary enlargement can be seen in ICI drug—associated hypophysitis combined with headache and hypopituitarism.[13] Although this combination of drugs has been found to improve progression-free survival in melanoma, it may be associated with an increase in irAEs, specifically in 1 meta-analysis at an incidence of 55%, compared with 27% or 16% for nivolumab or ipilimumab monotherapy, respectively.[14] With regard to hypophysitis, which our patient also developed, there is a 2.2-fold increased risk of developing this complication when receiving combination therapy compared with monotherapy.[5] Moreover, endocrine complications present earlier with combination therapy (30 days) in comparison to 76 days in those treated with a single agent (ipilimumab).[15] Other PD-1 inhibitors have been associated with hypocalcemia in a meta-analysis as a rare complication affecting 11 of 604 patients.[16] Our patient also had previously reported irAEs (colitis and pneumonitis), which may be of importance as a predictor of developing additional irAEs.[17] Whether this patient's course of combination therapy followed by nivolumab monotherapy created a cumulative toxicity

effect is difficult to ascertain on the basis of the current literature.

The mechanism of irAE-related hypoparathyroidism remains unclear, but it is postulated that autoantibodies may play a role. Anti-parathyroid and CaSR-activating autoantibodies have been implicated in autoimmune hypoparathyroidism.[18] Indeed, CaSR-activating autoantibodies were detected in a patient with primary hypoparathyroidism receiving nivolumab.[6] Anti-parathyroid antibodies have been described in patients with autoimmune endocrine conditions such as Addison disease and Hashimoto thyroiditis as well as in cases of idiopathic hyoparathyroidism[19] and animal models of autoimmune hypoparathyroidism.[20] However, in the previously reported case, when common autoantibody targets of autoimmune polyendocrine syndrome type 1 were assessed in the same individual with anti—CaSR-stimulating autoantibodies, they were undetectable. Notably, anti-parathyroid antibodies were also negative in our patient but anti-CaSR antibodies were not measured. Further research is needed to elucidate the role of these various antibodies and whether ICI-associated hypoparathyroidism may be due to a destructive immune process as may occur in other endocrinopathies.

Unlike other irAEs, endocrinopathies often require lifelong treatment with permanent hormone replacement for unclear reasons. In 1 study of patients who received ipilimumab, 85% required long-term treatment, primarily with thyroid and corticosteroid hormone replacement.[21] In our case, 77 days after ICI use, PTH remained undetectable and the patient continues to require 500 mg of elemental calcium 3 times daily and 0.25 μg of calcitriol twice daily to maintain his serum calcium within a satisfactory range. Persistence of hypoparathyroidism despite discontinuation of ICI drugs has been previously recognized.[8]

SUMMARY

- Immune checkpoint inhibitor drugs are currently being used to employ the immune response in the treatment of several solid and hematological malignant neoplasms and are associated with improved survival. However, they are associated with autoimmune-like manifestations, referred to as immune-related adverse events (irAEs).
- Hypoparathyroidism is a rare but emerging irAE of immune checkpoint inhibitor drugs, which clinicians need to recognize in patients with acute hypocalcemia.
- Multiple irAEs can occur simultaneously, and diagnosis of 1 irAE should heighten the surveillance for other irAEs.

PATIENT'S PERSPECTIVE

"My battle with cancer started 7 years ago and as it got worse I am happy these drugs [ICI] kept me alive for the last year. I remember when they wanted me to start them they gave me 10 pages on the side effects. You just say yes because you are desperate. Now I am alive but unhappy with what these drugs left me with. I wish my case can show others what can happen and teach them to look out for this."

CONCLUSION

In an era of novel immuno-oncology treatments, one needs to consider ICI blockade—mediated hypoparathyroidism in those presenting with hypocalcemia. Particular attention may be needed for patients who received combination ICI and have had previous irAEs. Future studies should focus on understanding the mechanism of ICI-associated hypoparathyroidism, predicting factors, and long-term outcome with such events.

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Abbreviations and Acronyms: **CaSR** = calcium-sensing receptor; **ICI** = immune checkpoint inhibitor; **irAE** = immune-related adverse event; **PD-1** = programmed cell death protein 1; **PTH** = parathyroid hormone

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