CLINICAL VIGNETTE

Hypercalcemia from Sarcoidosis-like Granuloma after Pembrolizumab

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Introduction

Immune checkpoint inhibitors (ICI) are increasingly essential treatment of advanced cancers. However, use can be associated with a number of side effects, including hypercalcemia. The mechanism through which hypercalcemia arises is not well established. One proposed mechanism involves sarcoidosis-like reactions, as illustrated below.

Case Presentation

A 75-year-old female with stage IV endometrial adenocarcinoma was admitted to the hospital with generalized fatigue, difficulty ambulating, slow movements, and slow speech. Initial labs revealed extremely elevated calcium 13.8 mg/dL (8.6-10.4 mg/dL) with ionized calcium 1.64 mmol/L (1.09-1.29 mmol/L). Previous treatment included total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy followed by nine months of adjuvant chemotherapy. Past medical history includes type 2 diabetes and hypertension.

Evaluation for hypercalcemia revealed the process was PTH-independent, and that elevated 1,25 (OH)2 vitamin D levels were responsible (Figure 1). PTH level was appropriately suppressed at 7 pg/mL (11-51 pg/mL), 1,25(OH)2 vitamin D and angiotensin converting enzyme (ACE) levels were elevated to 114 pg/mL (19.9-79.3 pg/mL) and 90 U/L (12-69 U/L). Other labs included normal PTHrP pmol/L 2.7 pmol/L (0.0 - 3.4 pmol/L) and 25-OH vitamin D 19 ng/mL (20-50 ng/mL). Two months prior to admission and seven months after starting PD-1 receptor blocker pembrolizumab, surveillance CT found improvement in tumor burden but with presence of new intrathoracic lymphadenopathy (Figure 2). Bronchosopic lymph node biopsy identified non-caseating granulomas suggestive of a sarcoidosis-like reaction. Infectious testing including respiratory cultures for nocardia, legionella, mycoplasma pneumoniae, acid fast culture, fungal culture were negative. Repeat CT during hospitalization showed stable intrathoracic lymphadenopathy, decreased size of pulmonary metastases and no lytic or blastic bone lesions. The overall clinical picture suggested that 1,25(OH)2D-mediated hypercalcemia was caused by the biopsy-proven sarcoidosis-like reaction of the mediastinal lymph nodes. The patient's moderate hypercalcemia was treated with intravenous fluids, calcitonin, and zoledronic acid 4 mg with normalization of calcium levels (Figure 1).

One month after discharge the patient developed hypercalcemia of 11.1 mg/dL. Although glucocorticoid therapy is typically recommended for sarcoidosis-medicated hypercalcemia, it was initially deferred to avoid counteracting the effect of pembrolizumab. However, given recurrent hypercalcemia, prednisone 10 mg daily was started and tapered off over 8 weeks as her calcium and 1,25(OH)2D levels normalized. She then restarted pembrolizumab, but after the third month she developed recurrent hypercalcemia (calcium 10.8 mg/dL) with elevated 1,25(OH)2D (89.5 pg/mL). She was again treated with prednisone 10 mg daily which was tapered off over 6 weeks with resolution of hypercalcemia. Subsequently pembrolizumab was stopped due to elevation in creatinine. Two years after the last dose of pembrolizumab, her calcium level and tumor burden remained stable. The temporal correlation in this patient strongly suggests that pembrolizumab administration caused sarcoidosis-like granulomas and hypercalcemia.

Discussion

Pembrolizumab is a PD-1 receptor blocker that induces antitumor action by blocking T-cell suppression. It belongs to the family of immune checkpoint inhibitors (ICI) which have enhanced treatment of various advanced hematologic and solid tumors. The same mechanism through which ICI exerts antitumor action can also lead to side effects known as immune-related adverse events (irAE), affecting all organ systems.[1] Common endocrine irAEs include thyroiditis and hypothyroidism. Other rare but important endocrine irAE include hypophysitis, primary adrenal insufficiency, and type 1 diabetes mellitus.[1]

Most cases of hypercalcemia in malignancy are caused by humoral hypercalcemia via PTHrP secretion and osteolytic activity from skeletal metastasis. 1,25(OH)2D mediated hypercalcemia is a less common cause, and sarcoidosis-like granuloma (SLG) from pulmonary irAE is an even rarer subtype. It is reported that SLG occurs in 5-6.7% of patients treated with anti-CTLA-4 and <0.5% of patients treated with anti-PD-1 antibodies.[2] The mechanism is not well established. One proposed mechanism is through the shift towards T helper 1 and T helper 17 immune pathways, thought to be crucial in the development of sarcoid granulomas.[2] Certain genetic

variants near the interleukin 23 receptor have also been implicated, which can promote the response of T helper 17 cells.[2]

The most common sites affected by SLG are lymph nodes (71% of cases), lungs (60% of cases) and skin (35% of cases).[1] SLG occurs within a mean of 9 months after initiation of ICI and resolves within a mean of 4 months.[1] Because it can be difficult to distinguish between SLG and tumor progression, biopsy is often needed for definitive diagnosis.[1] Our patient presented exactly 9 months after initiation of pembrolizumab with radiographic mediastinal lymph node and pulmonary changes, consistent with the current literature. The diagnosis was based on radiographic progression and lymph node biopsy after pembrolizumab initiation, lack of sustained normocalcemia despite receiving zoledronic acid, as well as the temporal correlation between hypercalcemia recurrence and pembrolizumab rechallenge.

Our case also highlights the challenge associated with treatment of SLG and the factors that impact the treatment decision. Currently there are no randomized controlled studies addressing this topic and most recommendations are professional societies consensus statements and case reports or case series.[1-4] ICI can be continued without interruption in asymptomatic patients who demonstrate clear improvement in disease burden.[3] SLG specific treatments can be considered in symptomatic patients with progressive radiographic changes, pulmonary function deterioration, critical extrapulmonary organ involvement, or sarcoid-related hypercalcemia.[4] Treatment involves corticosteroid </= 0.5-1mg/kg followed by a 2–4-month taper and resuming ICI after recovery from irAE.[3-5] Most patients will respond to corticosteroid treatment or cessation of ICI.[3,5] Notably, the presence of SLG is associated with better cancer response to ICI therapy.[2]

This case illustrates SLG as a cause of hypercalcemia due to irAE from PD-1 receptor blocker pembrolizumab. Though this is a rare cause of hypercalcemia in patients with cancer, a high index of suspicion is warranted as prompt evaluation and accurate diagnosis allows for prompt treatment and potential continuation of a class of life-saving medication.

Figures

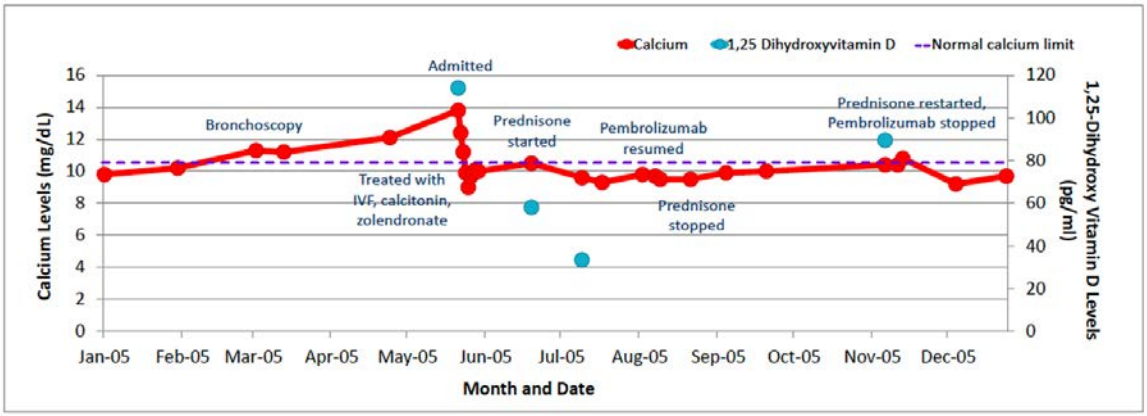

Figure 1. Clinical course: Calcium level, 1,25-dihydroxy vitamin D level, and interventions.

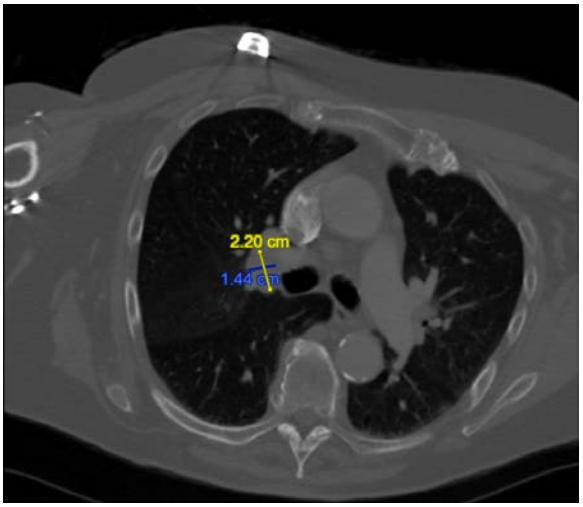

Figure 2. Mediastinal lymphadenopathy on CT chest.

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