

Hypercalcemia and Granulomatous-Like Lesions in a Patient with Melanoma after Treatment with Immunotherapy: Case Report

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Abstract

Checkpoint inhibitors, a subset of immunotherapies, are effective treatment modalities for cancers such as melanoma. However, they are not without possible adverse effects. Drug-induced reactions may present with similar symptoms of sarcoidosis. We present the case of a 73-year-old female with a recent diagnosis of anorectal melanoma treated with checkpoint inhibitors who developed subsequent episodes of hypercalcemia. Her clinical symptoms along with her surgical cytology and radiologic results are characteristic of a drug-induced sarcoidosis-like reaction. With the increasing usage of immunotherapies in cancer treatment, it is important for clinicians to be aware of which patient population they are ideal for and possible adverse effects.

Keywords

Hypercalcemia, Immune Checkpoint Inhibitors, Drug-Induced Sarcoidosis-Like Reaction, Ipilimumab, Nivolumab

1. Introduction

Immunotherapy is a therapy that involves activating or suppressing the body's natural defenses to eliminate cancerous cells, infections, or diseases [1]. Though immunotherapy has been around for centuries, it was not until the last decade that significant advances have been made eliciting clinically efficacious results [2].

Though there are different types of immunotherapies, checkpoint inhibitors specifically have been used to treat advanced melanoma and replaced some of the standards of care approaches to cancer. They release the checkpoint breaks

in the immune system that cause T cells to have reduced function and allow cancerous cells to go unchecked [2] [3].

Checkpoint inhibitors block programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and transcription factor (TF) on immune cell surfaces [1] [3]. Ipilimumab, a CTLA-4 inhibitor, nivolumab, and a PD-1 inhibitor are among the most common checkpoint inhibitors used. However, these immunotherapies do not come without possible immune-related adverse events. Skin involvement such as dermal hypernasality and immunobullous reactions and granulomatous and sarcoid-like lesions are adverse events that may occur [2]. Sarcoidal granuloma histopathological findings can be present in the lungs, lymph nodes, cardiovascular system, central nervous system, and skin. Diagnosis requires a tissue biopsy, radiological imaging, and observation of clinical symptoms, such as fever, fatigue, shortness of breath, and weight loss [2]. To date, 29 patients (including the one from this report) have been reported with granulomatous and sarcoid-like lesions after checkpoint inhibitor immunotherapy usage [2] [4]. Of these patients, 76% had primary melanoma [2] [4]. Though sarcoid-like symptoms are rare with these checkpoint inhibitors, the objective of this case report is to raise awareness among clinicians about these adverse effects and how to manage their patients who develop them.

2. Case Report

A 73-year-old white female with a medical history of anorectal melanoma, hypertension, type 2 diabetes, chronic kidney disease stage 3, and recent hypercalcemia presented to the emergency department for intermittent shortness of breath and right pleuritic chest pain that began that morning after taking a shower. At presentation, she reported loss of appetite, weight loss, and fatigue, but denied fever, chills, nausea, vomiting, or abdominal pain. She drinks alcohol socially but denied a history of smoking or illicit drug use.

Of importance, the patient was recently diagnosed with grade III ulcerated internal hemorrhoids and treated with hemorrhoidectomy. Pathology results of hemorrhoid specimen showed invasive mucosal melanoma with positive margins. Her diagnosis was followed up with a PET scan that did not show signs of metastatic disease. She received six weeks of immunotherapy with ipilimumab and nivolumab to reduce the melanoma. A transanal excision was needed to remove the remaining melanoma. At the time of hospitalization, the patient had an elevated blood calcium level of 14.8 and ionized calcium of 1.77. The patient's chlorthalidone medication was stopped and her hypercalcemia workup was begun in an outpatient setting. Labs were drawn to analyze parathyroid hormone (PTH), parathyroid hormone-related peptide (PTH-RP), 25-hydroxy vitamin D, 1,25-Dihydroxyvitamin D, and serum protein electrophoresis (SPEP) levels. Her past surgical history includes multiple colonoscopies, hemorrhoidectomy, and transanal excision.

On admission, patient was afebrile with a blood pressure of 163/67mmHg, heart rate of 86 beats per minute, respiration of 18 breaths per minute, and oxygenation saturation of 94% on room air. On physical examination, she had tenderness to palpation of the right upper quadrant and negative Murphy's and Homan's signs. Her exam was otherwise unremarkable. At the time of hospitalization, lab results from ten days prior were reviewed. Her PTH was appropriately suppressed at <6.3 pg/ml, 25-hydroxy vitamin D and PTH-RP levels were within normal range at 61 ng/ml and 10 pg/ml, respectively (**Table 1**). No M spike was seen on SPEP. Her level of 1,25-dihydroxyvitamin D was elevated at 97 pg/ml.

Her basic metabolic panel showed elevated blood calcium at 13.3 mg/dl. She was given pamidronate, resulting in a drop of her blood calcium to 12.5 mg/dl. Her angiotensin-converting enzyme (ACE) level was normal at 36 U/l. Her QuantiFERON TB test and COVID PCR were negative. Surgical cytology was positive for granulomatous lymphadenitis and negative for malignancy or metastatic disease. Chest CT angiography with contrast showed a small acute pulmonary embolus in the right lower lobe without right heart strain, bibasilar pulmonary consolidations concerning for pneumonia, moderate bilateral pleural effusions, right hilar and mediastinal lymphadenopathy, and scattered prominent mediastinal lymph nodes (**Figure 1**). Since her ipilimumab and nivolumab therapy had previously been discontinued, apixaban was prescribed for her pulmonary embolus but no further treatment was needed. She was found to be hemodynamically stable and discharged home with a nephrology follow-up scheduled to monitor her hypercalcemia and chest CT to monitor her hilar and mediastinal lymphadenopathy and mediastinal lymph nodes.

3. Discussion

Hypercalcemia can be associated with multiple pathophysiological causes. Most of the time, it results from excess PTH and is associated with diseases like parathyroid adenoma/hyperplasia, familial hypocalciuric hypercalcemia and multiple endocrine neoplasia syndromes [5]. The next most important etiology to consider is malignancy associated with the PTH-RP.

Hypervitaminosis D can also lead to elevated calcium levels because of iatrogenic causes, excessive milk intake, tuberculosis (TB), fungal infections, and

Table 1. Patient's PTH, PTH-RP, inactive and active Vitamin D lab values in comparison to the reference range.

Lab	Patient Value	Reference
PTH, intact	<6.3 pg/mL	18.4 - 88.0 pg/mL
PTH-rp	10 pg/mL	11 - 20 pg/mL
25-Hydroxy Vitamin D	61 ng/mL	30 - 100 ng/mL
1,25-dihydroxyvitamin D	97 pg/mL	18 - 72 pg/mL

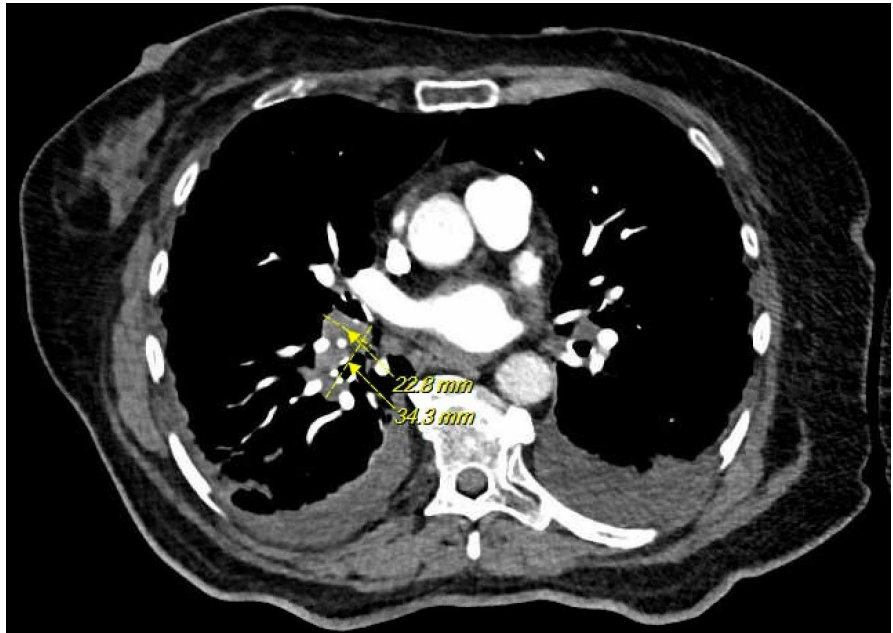


Figure 1. The patient's chest CT angiography with contrast shows small pulmonary embolus in the right lower lobe, right hilar lymphadenopathy, mediastinal lymphadenopathy, and scattered mediastinal lymph nodes.

granulomatous diseases like sarcoidosis [5]. Miscellaneous causes like thiazide diuretics or lithium and milk-alkali syndrome can also be associated with hypercalcemia [5].

Initially, our patient's chlorthalidone, a thiazide diuretic, was discontinued, but her blood calcium level remained elevated. Her PTH level was suppressed, excluding possible causes associated with excess PTH. Due to her history of anorectal melanoma, there was concern for a possible malignancy; however, her PTH-RP was within normal range and her PET scan did not detect cancerous sites. Pamidronate is used to treat hypercalcemia in the presence of a tumor [6]. Our patient initially responded to the medication but continued to have elevated calcium levels despite continued usage of it. Her TB test was negative, and her white blood cell count was within normal range, making infectious causes unlikely. Additionally, even though her inactive vitamin D, 25-hydroxy vitamin D, was normal, her active vitamin D, 1,25-dihydroxyvitamin D, was elevated, raising concerns for a granulomatous disease, such as sarcoidosis.

In approximately 75% of patients with sarcoidosis, an elevated serum ACE is observed, aiding in the diagnosis [7] [8]. It can correlate with extensive pulmonary involvement [7] [8]. Our patient's normal ACE level was most likely due to her early presentation of the disease. Her chest CT angiography showed right hilar and mediastinal lymphadenopathy with scattered mediastinal lymph nodes, which are thoracic radiological abnormalities observed in about 90% of sarcoidosis cases [9].

Drug-induced sarcoidosis-like reaction is a systemic granulomatous reaction that is hard to differentiate from sarcoidosis [10]. It results from starting an of-

fending drug, like a checkpoint inhibitor or antiretroviral [10]. There have been 28 other cases with granulomatous and sarcoid-like lesions after checkpoint inhibitor immunotherapy usage with 22 of them involving patients with primary melanoma [2] [4]. Treatment is usually not required because cessation of therapy usually resolves symptoms. If symptoms continue, standard anti-sarcoidosis treatment is effective [10]. Our patient was started on the immune checkpoint inhibitors ipilimumab and nivolumab for six weeks after her initial diagnosis of anorectal melanoma. Within weeks of starting these immunotherapies, she developed hypercalcemia followed by cytology and radiographic findings consistent with sarcoidosis. At the time of her shortness of breath, pleuritic chest pain, and pulmonary embolus diagnosis, the patient had discontinued this therapy regiment. She was discharged in stable condition with a nephrology follow-up to monitor her hypercalcemia. Though her sarcoidosis is not life-threatening at this time, hypercalcemia can result in multiple adverse effects, such as abdominal and bone pain, fatigue, muscle weakness, loss of appetite, weight loss, and mental confusion. Evaluating the mechanism that leads to drug induced sarcoidosis-like reactions will aid in the understanding of sarcoidosis' immunopathogenesis.

4. Conclusion

With the increasing use of checkpoint inhibitors, such as ipilimumab and nivolumab, physicians will be encountering more of these rare adverse events. Clinician education, proper diagnosis, and management of melanoma patients taking this therapy are essential.

Availability of Data and Materials

There are no specific data sets used in this case report. The clinical file of this patient is confidential information from a private clinic but available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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