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Case Report

Parathyroid Crisis and Thromboembolism: Association or Coincidence?

Zhanna Zavgorodneva, MD [1, *], Irving Guatemala, MD [2], Tooraj Zahedi, MD [3, 4], Fan Zhang, MD, PhD [5, 6]

[1] Department of Internal Medicine, Brookdale University Hospital Medical Center, One Brooklyn Health System, One Brooklyn Plaza, Brooklyn, New York
[2] Department of Internal Medicine, Brookdale University Hospital Medical Center, One Brooklyn Health System, One Brooklyn Plaza, Brooklyn, New York
[3] Diabetes & Metabolism, Brookdale University Hospital Medical Center, One Brooklyn Health System, One Brooklyn Plaza, New York, New York
[4] Division of Endocrinology, Diabetes and Metabolism, New York Presbyterian Hospital/Weill Cornell Medical Center, New York, New York, New York
[5] Division of Endocrinology, Diabetes & Metabolism, Brookdale University Hospital Medical Center, One Brooklyn Health System, One Brooklyn Plaza, Brooklyn, New York
[6] Department of Endocrinology, Diabetes & Metabolism, Suny Downstate Medical Center, Brooklyn, New York

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ABSTRACT

Background/Objective: The association between hypercalcemia and the risk of thromboembolic events is not clearly understood. Here, we present a unique case of a patient diagnosed with bilateral pulmonary thromboembolism in the setting of a parathyroid crisis due to primary hyperparathyroidism (PHPT). Our case may suggest a potential correlation between thromboembolism and PHPT with severe hypercalcemia. Nowadays just a few case reports provide support for this association, particularly in the settings of significant calcium and parathyroid hormone (PTH) derangement.
Case Report: A 70-year-old woman presented to the hospital with a few weeks' onset of fatigue, difficulty walking, and shortness breath. Laboratory investigations revealed significantly elevated serum calcium (19.2 mg/dL) and PTH (1156 pg/mL) levels. Her past medical history was significant for PHPT with mild hypercalcemia since 2014. Computerized tomography and thyroid ultrasound of the neck showed a high suspicion of a left parathyroid adenoma. A computerized tomography angiogram of the chest revealed a bilateral lower lobe pulmonary embolism. The patient underwent medical management for hypercalcemia and pulmonary embolism, followed by parathyroidectomy. Pathology reports confirmed the diagnosis of parathyroid adenoma.
Discussion: The clinical significance of hyperparathyroidism, leading to subsequent hypercalcemia and its association with the development of a procoagulable state, has been elucidated in a very limited number of case reports.
Conclusion: This case suggests that parathyroid crisis with hypercalcemia could potentially provoke thromboembolic events. However, this phenomenon could be explained by an extremely high level of PTH and calcium.

Introduction

The correlation between endocrinological pathologies and hemostasis alterations has been investigated for the last few decades[1]. It has been determined that data concerning for hyperparathyroidism and its influence on hemostasis is inconsistent. A limited number of studies showed coagulation factors elevation in patients with primary hyperparathyroidism (PHPT)[2,3]. Although Alay et al did not find significant differences in D-dimer, Activated Partial Thromboplastin time, International Normalized ratio, protein C,

Abbreviations: PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.
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* Address correspondence to Dr Zhanna Zavgorodneva, Department of Internal Medicine, Brookdale University Hospital Medical Center, One Brooklyn Health System, One Brooklyn Plaza, 1031 Thomas Boyland, Brooklyn, New York, 11212.
E-mail address: mdzavgorodneva@gmail.com (Z. Zavgorodneva).

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and antithrombin III level investigating homeostatic parameters of 28 women with parathyroid adenoma compared with 27 women of age-matched control group.[4] Similarly, no effect of hyperparathyroidism state was observed on platelet aggregation.[5,6]

Alteration in calcium concentration could potentially explain hemostatic abnormalities since calcium is essential in platelet functioning and coagulation cascade. It was shown that increase in ionized calcium could trigger platelet activation that is why maintaining a stable concentration of calcium is essential to keep platelets in resting state.[7] Calcium plays role in both platelet activation (that happens after the intracellular calcium reaches the threshold) and platelet aggregation——calcium serves to stabilize glycoprotein IIb/IIIa complex and promote its binding to dimeric fibrinogen.[8] Also, calcium catalyzes necessary protein transitions of factor IX, X, and prothrombin and is required for their binding to phospholipid.[9] Direct dependence of thrombin formation on free calcium activation was also highlighted.[10]

PHPT is an endocrinological disorder that represents excessive production of parathyroid hormone (PTH). The classical manifestations of PHPT are nephrolithiasis, osteoporosis, and hypercalcemia-related symptoms, such as abdominal pain, constipation, polydipsia, and polyuria. Parathyroid crisis is a rare life-threatening complication of PHPT, characterized by severe hypercalcemia and multiple organ failure. It is typically precipitated by immobilization, excessive calcium intake, acute illness, or infection. Here, we describe a rare case of parathyroid crisis and bilateral pulmonary embolism in a patient with previously chronic mild hypercalcemia due to PHPT.

Highlights

- The classical manifestations of PHPT are nephrolithiasis, osteoporosis, and hypercalcemia-related symptoms
- Parathyroid crisis is a complication of PHPT with severe hypercalcemia and acute organ damage
- Link between PHPT and thrombosis may be present when calcium level is severely disrupted

Clinical Relevance

Despite the increasing incidence and prevalence of PHPT in clinical practice, managing its presentation as a parathyroid crisis concurrent with venous thromboembolism can be challenging. We endeavored to address these complex issues, focusing on the rapid correction of calcium levels, appropriate anticoagulation therapy, and determining the optimal timing for surgical intervention.

Case Report

A 70-year-old female presented to the hospital with fatigue, difficulty walking, and shortness of breath on exertion over the course of 3 weeks. Her past medical history was notable for PHPT, likely attributed to a parathyroid adenoma, resulting in mild hypercalcemia since the year 2014, as depicted in Fig. 1. The recorded calcium levels consistently ranged from 10.3 to 11.9 mg/dL (2.57-2.97 mmol/L), with the established normal reference range being 8.6 to 10.5 mg/dL (2.13-2.55 mmol/L). Concurrently, PTH levels were elevated (Fig. 2), ranging from 156 to 380 pg/mL (156-380 ng/L), while normal level ranges from 14 to 65 pg/mL (14-65 ng/L). 24 urine calcium level was 290 mg/24 h. The patient had regular follow-ups with an endocrinologist and was informed about treatment options; conservative management was chosen by the patient. Upon presentation to the hospital, the patient denied any recent trauma, acute illnesses, immobilization, or long-distance travel; there was no personal or family history of venous thromboembolic events. A review of systems revealed the presence of polyuria, constipation, exertional dyspnea, and fatigue.

During the physical examination, the patient demonstrated increased work of breathing, which notably improved after the placement of a nasal cannula. Signs of dehydration, decreased turgor, increased deep tendon reflexes, and a confused state were also observed. The gait was slow, with no focal neurological deficit noted.

A computerized tomography chest angiogram, performed to evaluate dyspnea, revealed a bilateral lower lobe pulmonary embolism. Laboratory findings indicated severe hypercalcemia with a calcium level of 19.2 mg/dL (4.79 mmol/L), as shown in Fig. 1, alongside a normal 25-hydroxyvitamin D level. Notably, the PTH level registered at 1156 pg/mL (1156 ng/L), significantly higher than a previous measurement of 380.8 pg/mL (380.8 ng/L) a few months prior, as depicted in Fig. 2. Acute kidney injury was evident with

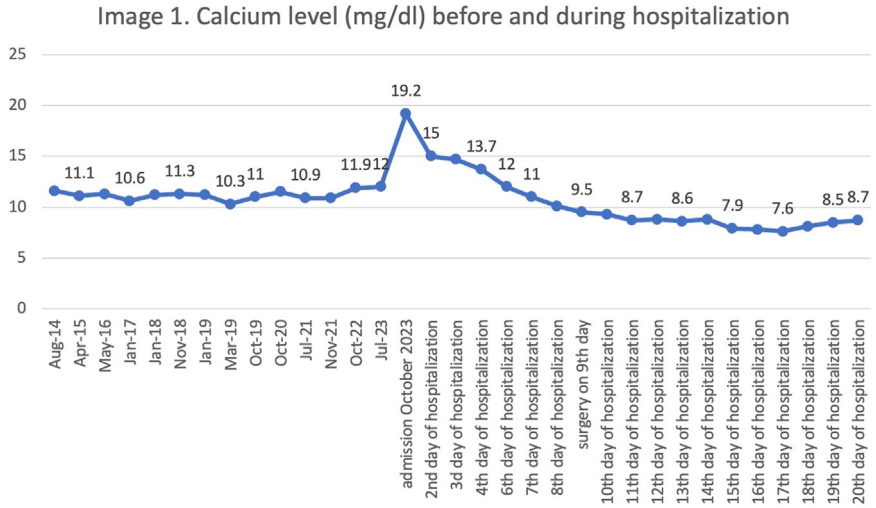

Fig. 1. Calcium level (mg/dl) before and during hospitalization.

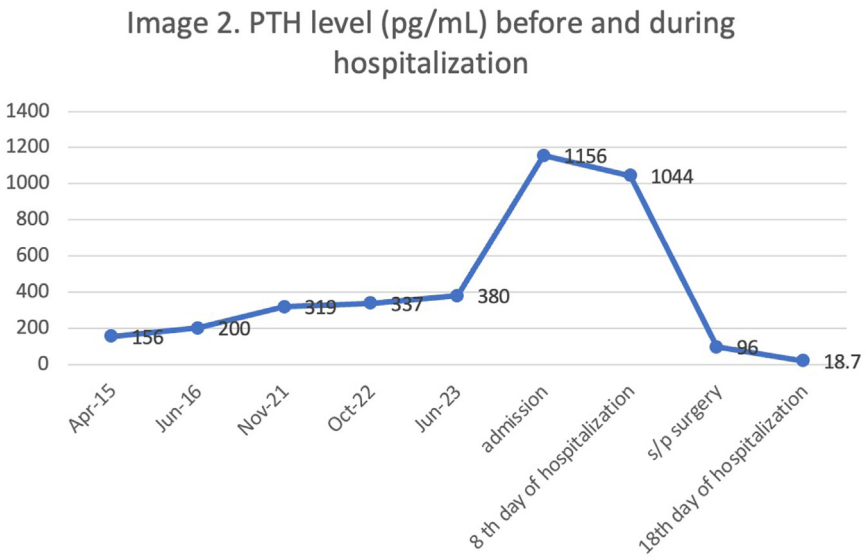

Fig. 2. PTH level (pg/ml) before and during hospitalization. *PTH*, parathyroid hormone.

creatinine level increased from a baseline 0.9 mg/dL (79.58 umol/L) to 2.8 mg/dL (247.58).

The 24-hour urine collection showed calcium level of 323 mg/d. Patient's albumin was 3.8 g/dL, (38 g/L), within the normal range of 3.4 to 5.4 g/dL (34-54 g/L). Thyroid function tests showed no abnormalities. Additional examinations revealed negative results for deep venous thrombosis on lower extremity duplex.

Thyroid ultrasound indicated a suspected left parathyroid adenoma measuring 2.1 × 2.1 × 1.4 cm (Fig. 3), while a computerized tomography of soft tissues in the neck revealed a 1.9 cm left posterior midpole thyroid nodule versus parathyroid adenoma (Fig. 4). A renal ultrasound was negative for renal calculi. Due to technical issues, thyroid scintigraphy could not be obtained. Bone density scan results showed osteopenia in the distal radial bone and lumbar spine.

Anticoagulation therapy was initiated. Following treatment with intravenous fluids, administration of calcitonin at a dosage of 4 U/kg every 12 h for 2 days, and injection of 60-mg denosumab, the calcium level improved to 10.1 mg/dL (2.52 mmol/L). The patient's symptoms ameliorated, and she subsequently underwent parathyroidectomy 9 days after hospitalization. Pathology examination confirmed a diagnosis of parathyroid adenoma, with no morphological evidence of malignancy. Immunohistochemical analysis showed a Ki-67 proliferation index of 1%, and the tumor was negative for thyroglobulin.

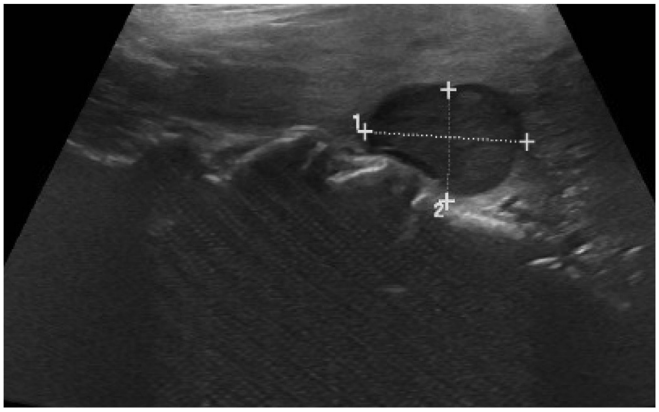

Fig. 3. US soft tissue of neck. *US*, ultrasound.

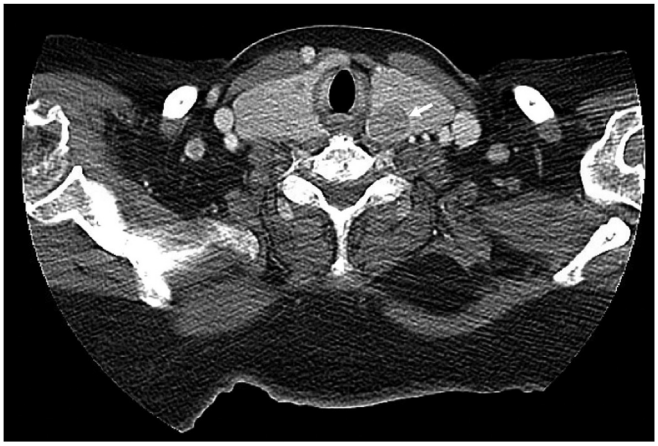

Fig. 4. CT soft tissue of neck with contrast. *CT*, computerized tomography.

Upon discharge, the patient's PTH and calcium levels were within the normal range. Close follow-up with the endocrinologist was recommended. Direct oral anticoagulation was prescribed for the next 6 months.

Discussion

In modern times, PHPT is often diagnosed in asymptomatic patients, and overall survival rates remain unaffected, particularly in mild cases and in the elderly, where definitive treatment is often unnecessary. However, we present a unique case here: a previously stable mild form of PHPT that was complicated by a parathyroid crisis and copresented with bilateral pulmonary embolism.

Unfortunately, our clinical knowledge about hyperparathyroidism with hypercalcemia and its correlation with a hypercoagulable state is primarily derived from case reports. Algethamy et al described a case of severe hypercalcemia with arterial and venous thrombosis that led to the patient's demise in the context of possible multiple endocrine neoplasia type 2a syndrome.[11] Previous reports by Koufakis et al have documented pulmonary

embolism, deep venous thrombosis and stroke in patients with hypercalcemia.[12] Routine calcium level assessment in patients with thrombosis was recommended.

Additionally, Chan et al, in their case report of hyperparathyroidism induced hypercalcemic crisis described the development of intracardiac thrombus.[13] Our case potentially adds to the body of evidence that this correlation may be present. The patient's age, absence of other risk factors for hypercoagulability, and the simultaneous manifestation of hypercalcemic crisis and acute pulmonary embolism make hypercalcemia a more likely pathogenetic origin of a hypercoagulable state.

The risk of hypercoagulability could be linked to the degree of hypercalcemia. Retrograde analysis of the patient's chart revealed persistent mild hypercalcemia that was present since 2014, when PHPT was diagnosed. However, a pulmonary embolism developed in 2023 when the patient's hypercalcemia reached a severely elevated level (Fig. 1). Similarly, other clinicians described thrombotic events in the presence of severe hypercalcemia.[12,14]

Two critical therapeutic objectives were prioritized in treating our patient: correcting the calcium levels and initiating anticoagulation therapy. Anticoagulation is a primary therapy for pulmonary embolism. As the direct link between hyperparathyroidism and venous thromboembolism is not established, there is no consensus on the optimal duration of anticoagulation therapy for such cases. Following guidelines for provoked pulmonary embolism (presumably by severe hypercalcemia), we decided to prescribe 6 months of direct oral anticoagulation therapy[15] upon discharge.

A hypercalcemic crisis is managed by aggressive hydration and the use of calcimimetic or antiresorptive agents. In our case, the calcium level was corrected by administering intravenous fluids and calcitonin, followed by the injection of denosumab. Bisphosphonates were not considered due to impaired renal function.

The question about the proper timing of the surgery could be difficult to answer. According to guidelines for PHPT,[16] the criteria for surgical treatment were met. However, the decision regarding whether to perform the surgery on an inpatient or outpatient basis can be discretionary. As per the patient's preferences, we opted to plan the surgery as an inpatient procedure. Furthermore, concern about parathyroid carcinoma was raised due to specific clinical indicators. These included a sudden rise in PTH and calcium levels despite previously mild elevations, markedly high PTH levels upon admission, and the identification of a single enlarged gland on imaging. Similarly, Gasparri et al, an expert in parathyroid surgical interventions, emphasized the urgency of surgical intervention in cases of parathyroid crisis.[17] However, the pathological report ultimately confirmed the diagnosis of a parathyroid adenoma.

Conclusions

Hyperparathyroidism-hypercoagulability association may not be present in mild persistent PHPT. In our case, it could be explained by an extremely high level of PTH and calcium.

Disclosure

The authors have no conflicts of interest to disclose.

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