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Case Report

J Med Cases. 2024;15(8):180-185

Primary Hyperparathyroidism and Pulmonary Embolism in Patients With a Fractured Neck of Femur

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Abstract

Two patients aged 82 and 77, with a fractured neck of the femur, were found to have primary hyperparathyroidism, characterized by hypercalcemia and hypercalciuria. Post-surgery, both developed pulmonary embolism (PE), highlighting a possible link between hypercalcemia and increased hypercoagulation risk. There have been few case reports suggesting the association between hypercalcemia due to hyperparathyroidism and the increase in tendency of hypercoagulation and subsequent risk of venous thromboembolism (VTE). This case series offers insights into how ionized calcium influences thrombin formation, platelet activation and aggregation, and activation of clotting factors such as factor VII and factor X, raising questions about the role of chronic hypercalcemia in VTE. Further research is needed to 1) establish whether chronic hypercalcemia in the absence of fracture can modulate the risk of hypercoagulation; 2) determine whether chronic hypercalcemia in individuals with bone fracture may represent a significantly higher hypercoagulability risk during the postoperative periods.

Keywords: Primary hyperparathyroidism; Pulmonary embolism; Hypercalcemia; Fracture neck of the femur

Manuscript submitted April 27, 2024, accepted July 1, 2024
Published online July 18, 2024

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doi: https://doi.org/10.14740/jmc4235

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder whereby the parathyroid gland secretes excessive parathyroid hormone (PTH). It affects approximately four in 1,000 individuals in the UK [1] and is twice as common in women than in men.

The condition arises from various etiologies, including solitary adenomas (85% of cases), multiglandular disease (10-15%), and parathyroid carcinoma (< 1%) [2]. PTH acts on the bones, kidneys, and intestines to increase serum calcium levels. In bones, PTH stimulates osteoclast activity, causing bone resorption and releasing calcium into the bloodstream, which further enhances intestinal calcium absorption [3]. Thus, patients with PHPT suffer from chronic hypercalcemia. Ionized calcium, as the coagulation factor IV, participates in the coagulation process and is necessary for thrombin formation. Calcium is also crucial for the activation of various clotting factors, such as factor VII and factor X, as well as for platelet activation and aggregation [4]. Studies have shown that patients with parathyroid adenoma have increased protein S activity and fibrinogen levels [5].

This puts patients with PHPT in a hypercoagulable state, therefore possibly multiplying the risk of thrombotic events, including pulmonary embolism (PE). While the incidence of PE in the UK is estimated to be around eight per 10,000 individuals annually [6], the association between PHPT-induced hypercalcemia and PE remains an area of interest and ongoing investigation. Understanding the potential link between hypercalcemia and PE in patients with PHPT is crucial for early recognition, diagnosis, and appropriate management of this rare but serious complication. In this case series, we present two challenging cases of PHPT-induced hypercalcemia and explore its potential association with PE.

Case Reports

Case 1

The first case is an 82-year-old male who presented to the emergency department (ED) with left knee pain and difficulty to mobilize due to a fall. His past medical history included stroke, deep vein thrombosis (DVT) and very high risk of falls and fractures.

Table 1. PTH, Adjusted Calcium, Calcium-Creatinine Ratio and Vitamin D Levels for Both Cases

Parameter	Case 1 (82 years old)	Case 2 (77 years old)	Reference range
PTH	15.2	9.2	1.6 - 6.9 pmol/L
Adjusted calcium	2.9	3.05	2.1 - 2.6 mmol/L
Urine calcium/creatinine ratio	0.39	0.42	0.07 - 0.28
Vitamin D	50.3	55	50.0 - 150.0 nmol/L

PTH: parathyroid hormone.

Prior to this incident, the patient was independent, mobilizing with a stick and living with his wife. Atorvastatin and apixaban were the two regular medications he was taking.

On examination he was unable to weight bear with his left leg, had reduced leg extension and a swollen left knee. He was pyrexial and had raised inflammatory markers. Initial investigations showed hypercalcemia with calcium levels of 2.9 (normal reference range: 2.1 - 2.6 mmol/L) and raised PTH with levels of 15.7 (reference range: 1.6 - 6.9 pmol/L) (Table 1). Following a computed tomography of chest/abdomen/pelvis (CT CAP), multiple incidental findings came to light: parathyroid nodule suspicious of adenoma (Fig. 1), intracapsular left neck of femur fracture (Fig. 2) and acute small volume PE (Fig. 3). In view of the findings, the patient had a left hip hemiarthroplasty, was started on therapeutic dose low-molecular-weight heparin (LMWH) (dalteparin) for PE, then switched to apixaban. The diagnosis of hyperparathyroidism was made in light of the presence of parathyroid adenoma, raised urinary calcium/creatinine ratio, as well as high level of calcium and PTH. Patient was referred to the ear, nose and throat (ENT) department to be assessed and found not suitable for surgery and advised to manage medically, in consideration of multiple comorbidities and frailty. He was discharged with an endocrinology follow-up.

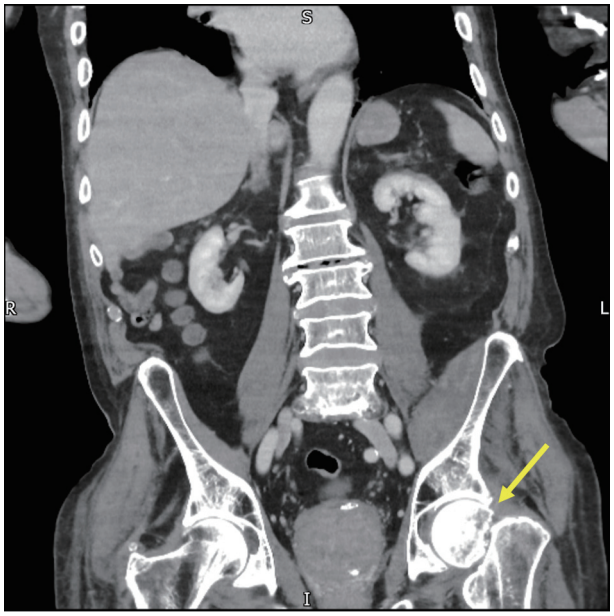

Figure 2. Sagittal view of computed tomography (CT) scan showing left intracapsular neck of femur fracture (yellow arrow).

Case 2

The second patient, a 77-year-old female, presented to the ED with right hip pain following a fall on ice. Examination re-

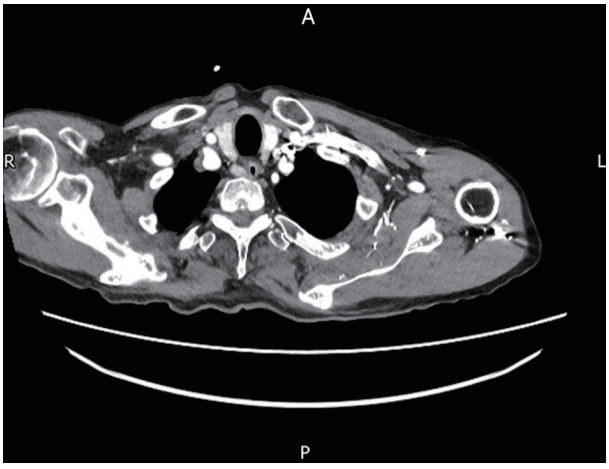

Figure 1. Axial view of computed tomography (CT) scan showing parathyroid nodule suspicious of adenoma.

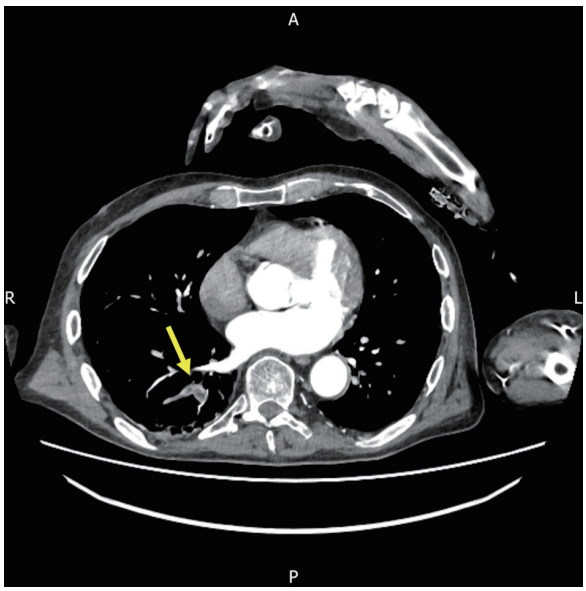

Figure 3. Axial view of computed tomography (CT) scan showing incidental finding of acute small volume PE in the right lobe (yellow arrow). PE: pulmonary embolism.

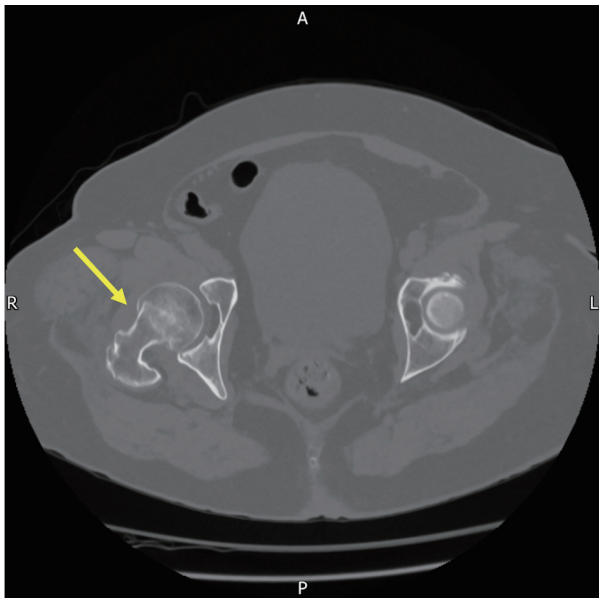

Figure 4. Subcapital proximal femoral fracture of the neck of the femur (yellow arrow) in computed tomography (CT) scan.

vealed external rotation of the right leg. A plain radiograph and subsequent CT scan confirmed an impacted right subcapital proximal femoral fracture (Fig. 4). Further preoperative evaluation through magnetic resonance imaging (MRI) confirmed the fracture diagnosis with no lytic lesions (Fig. 5).

The patient's medical history included hypertension, multiple episodes of DVT treated with edoxaban, hypothyroidism, and breast cancer managed with letrozole and adjuvant radiotherapy in 2019. A hemi-arthroplasty was planned for the patient. During the perioperative workup, hypercalcemia was detected, raising concerns about an underlying malignancy as the possible cause. A CT CAP scan was performed, revealing bilateral lower lobe PE without evidence of malignancy (Fig. 6). Intraoperative histology samples of the head of the right femur did not indicate any malignancy.

Treatment for the PE included LMWH, with discontinuation of edoxaban. To address hypercalcemia, the patient was

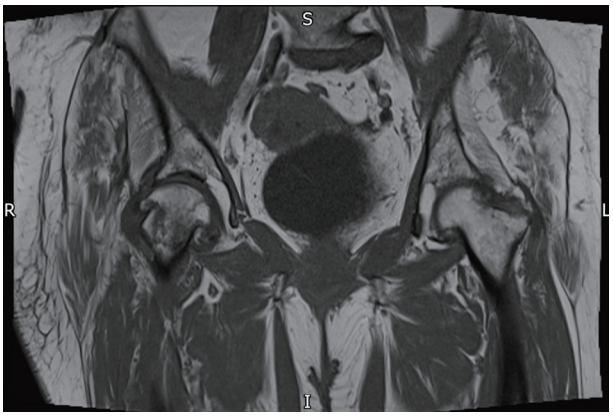

Figure 5. MRI confirming fracture diagnosis of right neck of femur with no lytic lesions. MRI: magnetic resonance imaging.

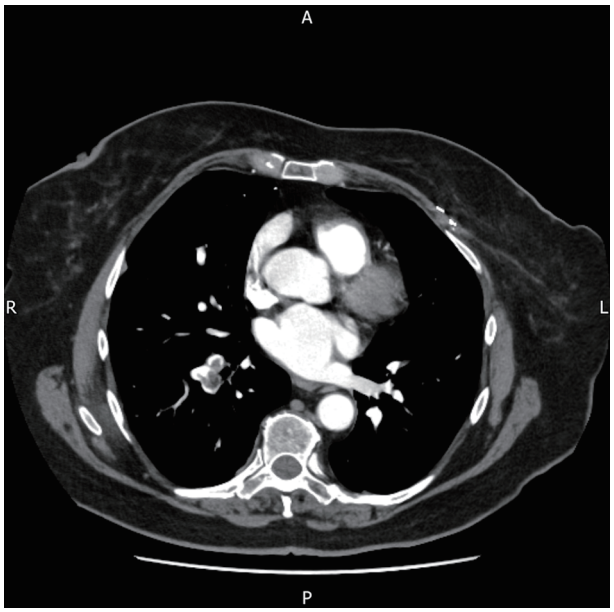

Figure 6. A CT chest/abdomen/pelvis scan was performed, revealing bilateral lower lobe pulmonary emboli without evidence of malignancy. CT: computed tomography.

advised to discontinue calcium supplements and increase oral fluid intake. Referral to the endocrinology department was made due to suspicion of PHPT based on the blood test results (Table 1). Following fracture treatment, the patient recovered well. Calcium levels are being monitored by the primary care physician, and calcium supplementation was discontinued. The hematology clinic conducted a thrombophilia screen, which showed negative anticardiolipin and beta-2 glycoprotein 1 antibodies, normal protein C and protein S levels, and no evidence of factor V Leiden or prothrombin gene mutations. At yearly follow-up, the patient demonstrated good mobility without signs of PE recurrence or hypercalcemia.

Discussion

This case series explores the potential association between PHPT and PE in patients with a fracture of the neck of the femur, a subject that, despite being understudied, may have important effects on patient care. By examining two elderly patients who presented with a fracture of the neck of the femur and were subsequently found to have high calcium, high PTH, and high urinary calcium levels indicative of PHPT, we have uncovered clinical presentations that support the pre-existing body of research that suggests a potential link between these two illnesses. Both patients developed PE postoperatively, diagnosed via CT imaging.

The potential for improved patient outcomes through early detection and care, should a solid link be unquestionably proven, highlights the significance of this work. We will explore the potential relevance of our findings, interpret them, and examine how they fit with existing medical knowledge in this debate.

From the late 20th century, evidence has suggested possible connections between hypercalcemia and an increased risk of thromboembolic events. A study published in 1979 demonstrated that hypercalcemia could lead to a hypercoagulable state and therefore, increase the risk of thromboembolic diseases [7]. Further to this, Gorelick et al reported six patients with hypercalcemia among 502 stroke patients in the mid-1980s, all of whom had elevated PTH levels, having said that, parathyroid adenoma and hyperplasia were detected in only two cases [8]. These findings suggested that hypercalcemia, often a result of PHPT, could have significant vascular implications.

A study conducted in 2008 provides further evidence supporting the presence of a hypercoagulable state in patients with PHPT. It was observed that there were increased platelet count, factor VII and factor X activities, as well as elevated D-dimer levels in patients with PHPT, compared to healthy controls [9]. These findings suggest that the hypercoagulable state associated with PHPT may heighten the risk of atherosclerotic and atherothrombotic complications, potentially contributing to the elevated mortality rate attributed to cardiovascular disease in patients with PHPT. Moreover, a separate study from 2021 provides similar support for this conclusion. It indicates that hyperparathyroidism can induce a hypercoagulable state, which can be successfully assessed using modified rotation thermoelectrometry [10]. Considering these findings, it is plausible to infer that the hypercoagulable state linked with PHPT could have contributed to the development of PE in our patients, especially in the presence of a fractured neck of the femur. In more recent investigations into the coagulation profile of PHPT patients, abnormal coagulation tests have been reported, and coagulopathy has been frequently linked with hyperparathyroidism secondary to vitamin D deficiency [11]. These reports further support the hypothesis of a potential hypercoagulable state in patients with hyperparathyroidism in line with the findings presented in this case series. Factors such as reduced mobility, multimorbidity, and the presence of cancer can significantly impact the risk of thrombosis in patients [12]. Additional considerations include weight, gender, the development of frailty, and calciphylaxis [13]. Moreover, PTH levels tend to increase with age [14], which may further enhance the hypercoagulability risk in elderly patients with PHPT.

An additional proposed mechanism contributing to the hypercoagulability observed in PHPT is the direct activation of platelets induced by elevated calcium levels. Studies have suggested that increased calcium can directly trigger platelet activation, leading to platelet aggregation and clot formation. This calcium-induced platelet activation further exacerbates the prothrombotic state associated with PHPT [15, 16]. Nevertheless, it is essential to acknowledge that some studies have reported conflicting findings regarding the impact of PHPT or secondary hyperparathyroidism (SHPT) and serum calcium levels on platelet functions, specifically when evaluated through aggregation tests [17]. These inconsistent results indicate a potential variation in the relationship between PTH, hypercalcemia, and platelet function. This may suggest the need for more research to explore whether bone fracture in association with hypercalcemia may lead to an increase in activation of platelets and hence risk of coagulation. Moreover, calcium is crucial for vascular smooth muscle cell activity and can help prevent altered blood flow patterns. These altered patterns are often associated with hypercoagulability due to flow disruption and the release of prothrombotic substances by the endothelium [18].

Importantly, the "Tromso Study" which included 27,712 subjects, showed that high levels of both calcium and PTH were associated with an increased risk of VTE compared to subjects with normal levels [19]. It is significant to note that both our patients had a history of DVT and experienced PE. Interestingly, in case series of three patients, it was shown that surgical treatment of hyperparathyroidism was associated with significant decrease in recurrence of thrombotic events (stroke, PE, DVT) [20]. The unique part in our case series is the fact that the presence of a fractured neck of femur in association with hypercalcemia led to the association of the development of PE. Several studies showed an increased tendency of risk of coagulation in elderly patients with a fractured neck of femur [21-23].

Conclusions

Further research is needed to 1) establish whether chronic hypercalcemia in absence of fracture can modulate the risk of hypercoagulation; and 2) whether chronic hypercalcemia in individuals with bone fracture may represent significant hypercoagulability risk during the postoperative periods. The potential interplay between bone fracture, hypercalcemia, comorbidities, and high PTH is shown in Figure 7.

Learning points

Despite the fact that hypercalcemia is not frequently acknowledged as a characteristic precipitant of venous thrombotic events, our case series emphasizes the significance of taking it into account in patients with bone fracture who come with thrombotic symptoms, such as PE. As a result, we recommend including checks for thromboembolic events in the evaluation of patients who are diagnosed with PHPT and other chronic causes of hypercalcemia admitted to orthopedic wards. Additionally, calcium levels, particularly ionized calcium, should be measured in all elderly patients with hip fractures.

This proactive strategy makes it easier to identify potential thrombotic risks quickly and to start taking precautions through simple measures such intravenous or oral rehydration.

Acknowledgments

Yashar Mashayekhi and Sara Baba-Aissa are grateful for their parents for their unlimited support during their study at the Medical School in the University of Buckingham, UK. The first case was presented in the Endobridge conference in Istanbul, Turkey (2023), and only abstract was published (Yashar Mashayekhi, Sara Baba-Aissa, Amina Adil Al-Qaysi, Henry Owles, Maria Panourgia, Mohamed H. Ahmed, P-11 Case report of Primary Hyperparathyroidism and PE, JCEM Case Reports, Volume 2, Issue Supplement_1, January 2024, luad146.016).

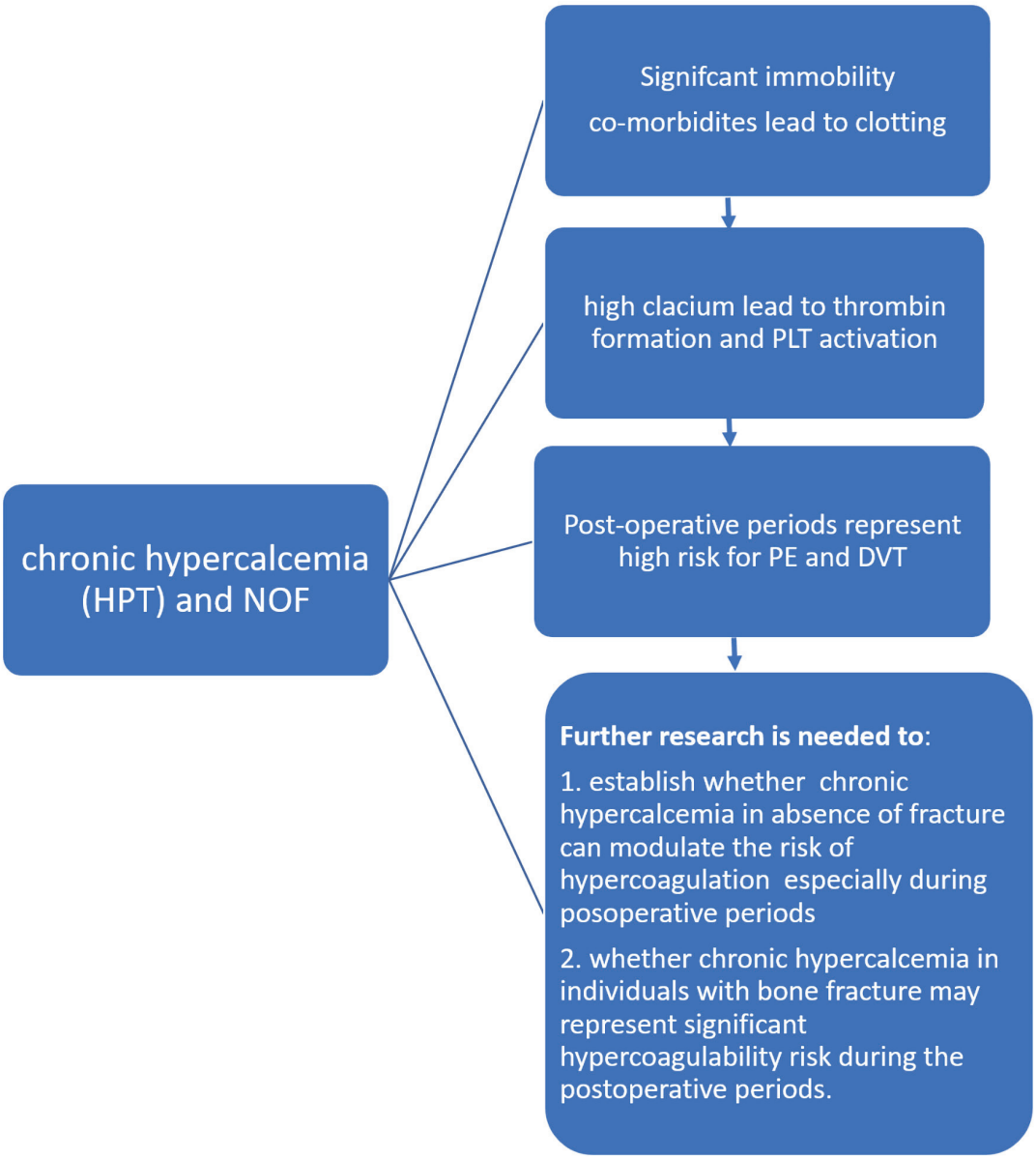

Figure 7. The potential interplay between bone fracture, hypercalcemia, comorbidities, and high PTH. DVT: deep vein thrombosis; PE: pulmonary embolism; HPT: hyperparathyroidism: PLT: platelets; NOF: fracture neck of femur; PTH: parathyroid hormone.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent has been obtained from the patients.

Author Contributions

Conception and design: MHA. Administrative support: all authors. Provision of study materials or patients: all authors. Collection and assembly of data: MHA, YM, and SBA. Data analysis and interpretations, manuscript writing, and final approval of manuscript: all authors.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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