



A case of severe hypercalcemia with arterial and venous thrombosis

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ABSTRACT

We present a case of severe hypercalcemia with extensive venous and arterial thrombosis that led to the patient's demise in the setting of possible multiple endocrine neoplasia (MEN) type 2a. A 35-year-old female presented to the emergency with nausea and vomiting for one week. Physical examination revealed dry mucous membranes, a thyroid nodule on left side and epigastric tenderness. Initial investigations revealed evidence of renal impairment and hypercalcemia. Parathyroid hormone (PTH) level was very high. Ultrasound of the thyroid showed a solitary left thyroid nodule with mixed cystic and solid isoechoic echogenicity. The patient developed progressive dyspnea and hypoxemia, which mandated mechanical ventilation. Dialysis was initiated via the right femoral catheter and stopped due to extensive venous thrombosis of the right lower limb. Pulmonary emboli were excluded and pulmonary edema was confirmed by computed tomography. The patient was subsequently intubated for persistent respiratory distress. The same condition occurred in the right upper limb. Fine needle biopsy of the left thyroid nodule revealed medullary thyroid cancer. The consulting team preferred to manage her conservatively as she was rapidly-deteriorating. She developed progressive shock and multi-organ failure and expired.

Key words: Hypercalcemia; Hyperparathyroidism; Thrombosis; Limb ischemia; Medullary thyroid cancer; Multiple endocrine neoplasia

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INTRODUCTION

Hypercalcemia is a common medical condition. Patients usually present with mild symptoms like fatigue, abdominal pain, and constipation; but rarely, they can present as an endocrine emergency with convulsions, confusion or coma.¹ It can be caused by a variety of disorders, like hyperthyroidism and hyperparathyroidism, both solid and hematologic malignancies, granulomatous diseases and renal diseases; or they can simply be due to exogenous calcium intake or drug induced. It has been reported that severely-elevated levels of ionized calcium can very rarely lead to vascular hypercoagulability and thrombosis.²⁻⁷

Herein, we present a case of severe hypercalcemia with extensive venous and arterial thrombosis that led to the patient's demise in the setting of possible multiple endocrine neoplasia (MEN) type 2a.

CASE REPORT

A 35-year-old female patient presented to the emergency department with a history of nausea and vomiting for one week. Her past medical history only was significant for an abortion. Upon presentation, she was alert and oriented and her vital signs were significant for a postural drop in blood pressure and tachycardia. Physical examination was remarkable for dry mucous membranes, a left thyroid nodule and epigastric tenderness. Initial investigations revealed evidence of renal impairment and hypercalcemia. Creatinine was 228 $\mu\text{mol/L}$, urea 7.9 mmol/L , phosphate 1.93 mmol/L , calcium 4.28 mmol/L , and albumin 27 g/L . Other laboratory investigations showed a normal blood count, sodium 136, and potassium 3.3 mmol/L , with normal serum amylase and lipase levels of 50 U/L and 204 U/L (Normal levels 0-137 and 12-70 U/L), respectively. Urine Na and creatinine were consistent with a renal cause of renal failure as fractional excretion of sodium (FENa) >

hypercalcemia with thrombosis

2%). Parathyroid hormone (PTH) level was very high at 232 pmol/L. Thyroid stimulating hormone (TSH) level was normal at 0.409 mU/L and a pregnancy test was negative. Urine analysis was positive for WBC 45/hpf and RBC 6/hpf, but negative for nitrites.

The patient was admitted to the medical floor and was commenced on aggressive intravenous (IV) hydration and ciprofloxacin with a presumptive diagnosis of PTH-dependent hypercalcemia complicated by acute kidney injury and possible urinary tract infection. Ultrasound of the abdomen and pelvis was normal, apart from gallbladder sludge with mild distension. Both kidneys were normal in size and echotexture. Neither obstruction nor hydronephrosis was reported. Urine and blood cultures came back negative, so ciprofloxacin was discontinued. The patient received one dose of denosumab.

Ultrasound of the thyroid showed a solitary left thyroid nodule (Figure 1a) measuring 4.8 x 2.7 cm with mixed cystic and solid isoechoic echogenicity, and a fine needle aspiration (FNA) biopsy of this nodule was planned. However, on the fourth admission day, the patient developed progressive dyspnea and needed to be maintained on supplemental oxygen via a nasal cannula. Chest radiographs (Figure 1b) demonstrated mild diffuse alveolar opacities. The patient was kept on IV fluids because of severe hypercalcemia, but received intermittent furosemide doses and a ventilation/perfusion (V/Q) scan was arranged, which was interpreted as a low probability of pulmonary embolism.

Nevertheless, the patient continued to deteriorate with progressive dyspnea and hypoxemia, along with severe tachycardia requiring intensive care unit (ICU) admission and mechanical ventilation support. IV fluids were held as the patient had evidence of pulmonary edema. Diuretics and broad-spectrum antibiotics were started. Calcitonin was started at 200 iu every 12 h BID and increased to 400 iu BID. Echocardiography was normal.

However, the serum calcium level remained severely elevated at 4.66 mmol/L; thus, a decision to initiate dialysis via a right femoral catheter was made. A few hours following the end of dialysis, the patient's right lower limb was seen to show swelling and discoloration and the patient started complaining of severe pain. Bedside ultrasound confirmed right femoral vein deep venous thrombosis (DVT) (Figure 2a). The catheter was removed promptly, and a heparin infusion was initiated. The patient was subsequently intubated for persistent respiratory distress. Computed tomography (CT) pulmonary angiography (CTPA) was negative for pulmonary emboli, but revealed diffuse ground glass opacities suggestive of pulmonary edema (Figure 2b). Computed tomography of the right lower limb showed extensive venous thrombosis involving the bifurcation of the inferior vena cava (IVC), right

common iliac vein, and right external iliac vein and its branches. Extensive soft tissue edema also was noted. The arterial system was patent.

To continue the dialysis sessions to overcome refractory hypercalcemia, a dialysis catheter was placed in right internal jugular, and the patient had her second dialysis session. A few hours after this second session, she was noted to have progressive cyanosis of the distal right upper limb and a weak radial pulse (Figure 2c). CT angiogram of the right upper limb confirmed total occlusion of the right proximal radial artery and right mid ulnar artery. The patient was still on heparin with a therapeutic partial thromboplastin time (PTT). A thrombophilia screen including antiphospholipid antibody syndrome (APAS) was requested. The vascular surgery service elected not to intervene, due to the critical condition of the patient and multiple vessels involvement.

Following a multidisciplinary team discussion involving the ICU, endocrinology, hematology, rheumatology and vascular services, a tentative diagnosis of catastrophic anti-phospholipid antibody syndrome (APAS) was made, on a background of undiagnosed malignancy, like thyroid or parathyroid malignancy. Pulse steroid (inj methylprednisolone 1 g) daily for three days and plasma exchange sessions daily were initiated.

Both the right upper and lower limbs continued to get worse with extensive swelling and discoloration, despite the therapeutic PTT targets upon heparin infusion. The patient developed compartment syndrome in her right lower limb. Her total creatinine kinase (CK) reached above 14000 u/L. Orthopedic surgeons decided to manage conservatively, due to the patient's rapidly-deteriorating course.

During her ICU stay, her calcium level came down to normal ranges on dialysis. Thrombophilia screen and APAS antibodies were negative. Fine needle biopsy of the left thyroid nodule yielded malignant cells, which were interpreted as likely medullary thyroid cancer, but also potentially parathyroid malignancy. RET oncogene and calcitonin testing were postponed, due to the patient's critical condition.

She remained in the ICU intubated for a week afterwards and was shifted from dialysis to continuous renal replacement therapy. Her condition continued to deteriorate further, including progressive shock and multi-organ failure. Death later ensued.

DISCUSSION

Our case was a patient with medullary thyroid carcinoma (MTC) based on FNA, who presented with severe hypercalcemia that required sessions of dialysis, complicated by upper and lower limb venous/arterial thrombosis. Unfortunately, she experienced a

rapidly-deteriorating course with progressive shock and multi-organ failure, ultimately leading to death.

MTC is one of the neuroendocrine tumors that grows out of specialized thyroid cells called parafollicular or C cells, which synthesize a hormone called calcitonin. Calcitonin levels are used to help diagnose medullary thyroid cancer and as a marker for recurrence. Most MTCs are sporadic; but between 5 and 25% are familial, as part of multiple endocrine neoplasia type 2 (MEN2) syndrome.³⁻⁶ The diagnosis of MTC usually requires a combination of blood tests, imaging with ultrasound, and confirmation by histopathology of thyroid nodules by FNA biopsy.

In normal homeostasis, we need free ionized calcium for the initial steps of platelet plug formation and its use in multiple processes along the blood coagulation cascade. Calcium ions have known roles during clot formation and acceleration, combining with prothrombin to form thrombin, a proteolytic enzyme that, in turn, acts on fibrinogen to form fibrin monomers, the aggregation of which will form a final insoluble fibrin clot.

The link between hypercalcemia and thrombosis is still not completely understood and, due to the rarity of such cases, data are scarce. Possible mechanisms that have been proposed start with the coagulation cascade and its role in fibrin clot formation.⁷ However, calcium also can effect blood vessels via calcification and vasoconstriction, triggering vascular smooth muscle contraction due to increased intracellular free calcium levels. Furthermore, direct renal vasoconstriction can lead to dehydration and a further hypercoagulable state.⁸⁻⁹

A hypercoagulable state is common with malignancies, but how much this risk is altered if it is accompanied by severe hypercalcemia remains unknown. A review of published case reports about the correlation between severe hypercalcemia and thromboembolism showed that there is an increased risk of thrombosis. The search uncovered just five case reports, however, illustrating thrombosis in different sites with an underlying parathyroid adenoma and severe hypercalcemia, as well as a single case due to an underlying parathyroid carcinoma.

To the best of our knowledge, there is no report on the development of upper and lower limb thrombosis

in a patient with hypercalcemia. Other cases reported in the literature were those five patients with an underlying parathyroid adenoma, all of whom had calcium levels above 3 mmol/L, in addition to high PTH levels. Some of them, like our patient, had very acute hospital course which ended in patient demise. Two of the patients had a lower DVT, one of them catastrophic femoral DVT which led to muscular necrosis and subsequent multi-organ failure and death.¹⁰ Another patient presented with acute right-sided chest pain, in whom pulmonary CT angiography confirmed pulmonary emboli. One patient presented with left-sided hemiplegia and a right gaze palsy, while brain MRI revealed a cerebral infarction.² The last patient presented with unilateral visual loss, which ultimately was attributed to optic neuropathy secondary to arterial ischemia.¹¹ All these patients underwent surgical treatment of their hyperparathyroidism and, following surgery, had their PTH and calcium levels return to normal. A sixth report described a patient with bone pain, constipation and polyuria; on examination had a fixed neck mass. The patient was confirmed to have a parathyroid carcinoma. A pre-operative CT scan of the neck and chest revealed incidental filling defects in the right subclavian vein and in a branch of the left pulmonary artery indicating right subclavian vein thrombosis and a left pulmonary artery embolism, respectively. As with the others, this patient went for surgical resection of his tumor, which resulted in cure.¹²

CONCLUSIONS

Severe hypercalcemia is one of the rare causes of arterial/venous thrombosis, though the mechanism behind hypercoagulability from hypercalcemia is still not well understood. We suggest checking calcium levels in patients with an unexplained hypercoagulable state. Prompt recognition and management of such cases is crucial.

Competing Interests:

The authors declare that they have no competing interests.

Authors' contributions:

All authors took part in the management, and wrote and approved the final manuscript.

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