CASE REPORT

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A challenging case of metastatic pulmonary calcification in a predialysis patient

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ABSTRACT

A 45-year old white female with personal history of psychiatric disorder, severe hypokalaemia, medullary sponge kidney and chronic kidney disease, not on dialysis, was admitted to the Emergency Department after syncope. She was hypotensive and dehydrated. Arterial blood revealed metabolic alkalosis and no hypoxaemia. Laboratory tests revealed altered renal function, hypokalaemia, hyperparathyroidism, normal calcaemia and slightly elevated phosphorus. Exuberant alterations on chest radiography led to performing a chest computed tomography, which was suggestive of pulmonary metastatic calcification. She also had signs of calcification of the kidney.

The main diagnoses were chronic kidney disease, medullary sponge kidney, hypokalaemia, dehydration, hypotension and pulmonary metastatic calcification.

Tissue calcification can be metastatic or dystrophic. Pulmonary metastatic calcification is most commonly due to chronic kidney disease. Risk factors for tissue calcification in this patient were chronic kidney disease, hyperparathyroidism and elevated phospho-calcium product. The hyperparathyroidism was most probably secondary.

Treatment aimed at correcting the water and electrolyte disturbances and admission to the psychiatric ward, with improvement of renal function, normalization of blood pressure and correction of the hypokalemia. To treat hyperparathyroidism, she was referred for parathyroidectomy.

Key words: Chronic Kidney Diseases; Hypokalemia; Lung; Medullary Sponge Kidney; Pathologic Calcification

INTRODUCTION

Calcification refers to the deposition of calcium salts. Pathologic soft tissue calcification can be metastatic or dystrophic, whether it occurs on intact tissue or superimposed on previously damaged tissue, respectively[1,2].

The mechanism of tissue calcification is not clear. It may be favored by an elevated phospho-calcium product (i.e. > 40 mg^2/dL^2), an increased activity of the tissue alkaline phosphatase, elevated levels of parathyroid hormone (PTH) or vitamin D, alkaline tissue pH, and uraemia. Acid-excreting organs such as the lung, the kidney and the stomach have an alkaline parenchyma which renders them more susceptible to calcification. The apical lobes of the lung, where ventilation to perfusion ratio is higher, are its most alkaline and hence susceptible portion[1,2].

Dystrophic pulmonary calcification can be seen on granulomatous disorders (e.g. tuberculosis and sarcoidosis), amyloidosis, silicosis and some parasitic and viral infections, amongst other causes. The most frequent cause of pulmonary metastatic calcification is chronic kidney disease (CKD), particularly when associated with secondary hyperparathyroidism. It is found

in 60-75% of haemodialysed patients at autopsy. It is thought that the pre-dialysis acidosis favors the release of calcium salts from the bone into the circulation, and the post-dialysis alkalosis favors the deposition of calcium salts on vasculature and other tissues. Other causes are less common and include primary hyperparathyroidism, vitamin D hypervitaminosis, intravenous calcium therapy and massive osteolysis from metastases or multiple myeloma[1,2].

Pulmonary metastatic calcification is an underdiagnosed condition. It is most often asymptomatic (even though the process may lead to fulminant respiratory failure and death) and usually goes unnoticed on conventional chest radiography, which appears normal or shows only poorly defined bilateral opacities without signs of calcification[1-3].

On computed tomography (CT) scans, it is characterized by centrilobular ground-glass nodular opacities measuring 3 to 10 mm in diameter. These show as a higher signal intensity than skeletal muscle on Magnetic Resonance Imaging (MRI), on T1 weighted imaging[3].

The histopathology features are calcium deposits located in the alveolar epithelial basement membranes, alveolar capillary walls, bronchial walls and media of the pulmonary arterioles[3].

Some authors believe that the clinical history associated with the characteristic high resolution CT findings is sufficient to establish diagnosis and avoid lung biopsy[3]. MRI has the advantage of not employing ionizing radiation, which is relevant for follow-up. However, the accuracy of MRI *versus* CT is yet to be tested[3].

Therapy for pulmonary metastatic calcification condition focuses on correcting the phospho-calcium product[1].

CASE REPORT

We report the case of a 45-year old white female of Portuguese ancestry, divorced, born in South Africa, unemployed, living in Portugal with her mother for four years.

She was brought to our hospital's Emergency Department after an episode of syncope with spontaneous recovery. She had had similar episodes in the past and denied trauma or other symptoms.

She had personal history of psychiatric disorder, known for about 20 years and characterized by anorexia nervosa, self-induced vomiting and medication abuse (namely laxatives and furosemide); hypokalaemia detected on several occasions; and medullary sponge kidney diagnosed 3 years before, accompanied by CKD stage 5 (plasma creatinine level 4.0 mg/dL for an estimated glomerular filtration rate of 13 mL/min/1.73 m^2, calculated with the Chronic Kidney Disease Epidemiology Collaboration – CKD-EPI equation). She was a smoker and denied abuse of alcohol and recreational drugs and exposure to occupational hazards such as smoke or dust. She did not acknowledge having an eating disorder in the present (though she referred having had anorexia and bulimia until her late twenties). She was not receiving any mental health support.

She attended our Nephrology clinic on an irregular basis (3 appointments in 3 years) and was not compliant with any prescribed medication. During this period, relevant tests and exams results were hyperparathyroidism (parathyroid hormone 840.3 pg/mL), serum calcium in the upper range of normal (9.5 mg/dL), high serum phosphorus (6.0 mg/dL), normal serum albumin (4.52 g/dL), high levels of serum 25-OH-colecalciferol (46.8 ng/mL), hypokalaemia (lowest result was 1.9 mmol/L), variable serum sodium (129-136 mmol/L), normal lipid profile, normal uric acid, bland urinary sediment, non-nephrotic range proteinuria (urine protein to creatinine ratio 1.1 g/g), normal plasma protein electrophoresis, normal complement factors C3 and C4 and negative antinuclear antibodies. She also tested negative for human immunodeficiency, hepatitis C and hepatitis B viruses. On renal ultrasound, both kidneys showed medullary cysts and signs of nephrolithiasis.

On admission, the patient was lucid, collaborative and asymptomatic. Blood pressure was 75/40 mmHg, heart rate was 87 beats per minute and body temperature was 36,6 ºC. She had low body mass index (16.4 Kg/m^2). She was dehydrated, with reduced skin turgor. Pulmonary and cardiac auscultations were normal. There was no oedema. The neurology exam was normal.

Arterial blood values (under no supplemental O2) revealed metabolic alkalosis and no hypoxaemia (pH 7,5; HCO3 28 mmol/L; PCO2 37 mmHg; PO2 110 mmHg).

Laboratory results showed anaemia, altered renal function, hyponatraemia, hypokalaemia, high serum phosphorus, normal serum calcium, hyperparathyroidism, normal serum levels of angiotensin converting enzyme (Table I). The electrocardiogram was normal.

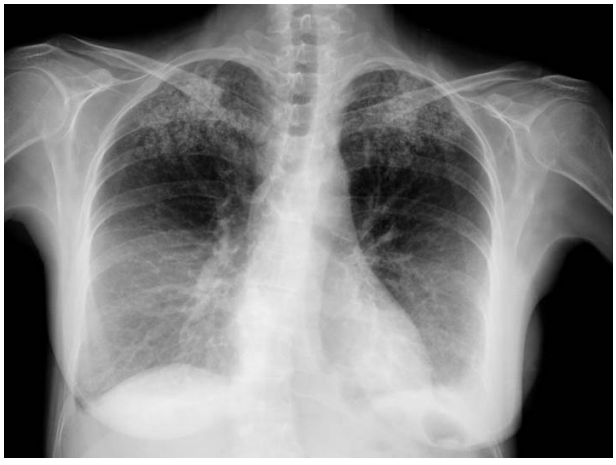
Table I

Blood tests

Haemoglobin	9 g/L [115-180]
Haematocrit	0.266 L/L [0.37-0.54]
Mean globular volume	78.8 fL [76-96]
Mean globular haemoglobin	26.6 pg [27-32]
Platelets	291*10^9/L [130-400]
Leucocytes	11.3*10^9/L [4-11]
Glucose	77 mg/dL [60-110]
Urea	116 mg/dL [16-48]
Creatinine	4 mg/dL [0.5-0.9]
Sodium	128 mmol/L [135-145]
Potassium	1.8 mmol/L [3.5-5]
Phosphorus	5 mg/dL [2.5-4.5]
Total calcium	9.3 mg/dL [8.1-10.2]
Magnesium	3.2 mg/dL [1.6-2.6]
Uric Acid	5.9 mg/dL [2.4-5.7]
Albumin	3.8 g/dL [3.5-5]
C Reactive Protein	2.6 mg/dL [<0.2]
Aspartate aminotransferase	23 UI/L [<32]
Lactate Dehydrogenase	236 UI/L [240-480]
Creatine Kinase	130 UI/L [<170]
Angiotensin Converting Enzyme	55 UI/L
25-OH colecalciferol	19.4 ng/mL [≥ 30]
Parathyroid hormone	1202 pg/mL [10-65]
Haemoglobin	9 g/L [115-180]
Haematocrit	0.266 L/L [0.37-0.54]
Mean globular volume	78.8 fL [76-96]
Mean globular haemoglobin	26.6 pg [27-32]
Platelets	291*10^9/L [130-400]
Leucocytes	11.3*10^9/L [4-11]
Glucose	77 mg/dL [60-110]

Figure 1

Chest radiography.



A routine conventional chest radiography was performed (Fig. 1). To better clarify the unspecific lesions found, a chest CT was performed (Fig. 2), which was suggestive of metastatic pulmonary calcification.

In collaboration with Pulmonologists, a bronchofibroscopy with bronchoalveolar lavage and lung biopsy were performed. The airways looked slightly inflamed. No microorganisms were isolated; there was no evidence of neoplastic cells or granulomas. There was alveolar calcification.

Renal ultrasound and abdominal CT revealed small, undifferentiated and hyperecogenic medullary sponge

Figure 2

Chest CT scan suggesting metastatic pulmonary calcification.

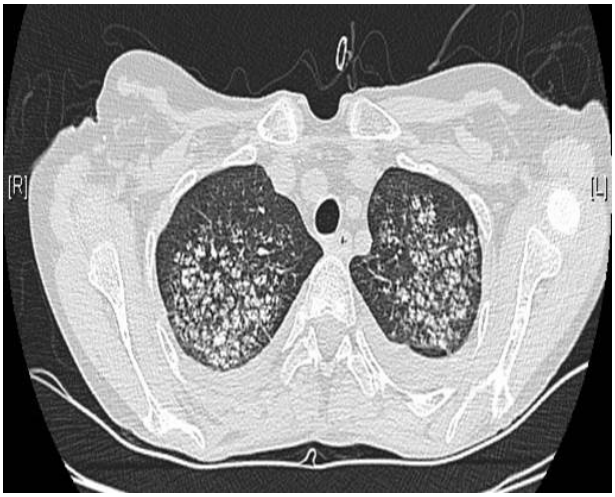
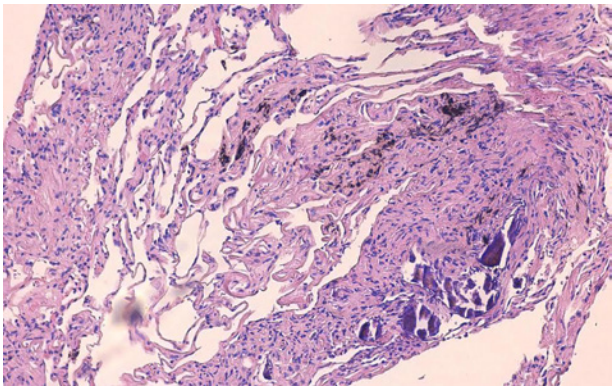


Figure 3

Lung biopsy showing alveolar calcification.



kidneys with nephrocalcinosis. There were no other significant alterations, namely the presence of tumours or adenopathies.

Neck ultrasound and thyroid plus parathyroid scintigraphy showed 2 nodules with increased activity next to the lower part of the left and right thyroid lobes.

DISCUSSION

The main diagnoses were chronic kidney disease, medullary sponge kidney, hypokalaemia, dehydration, hypotension and pulmonary metastatic calcification.

Syncope was probably a consequence of hypotension.

In addition to medullary sponge kidney, chronic hypokalaemia and chronic dehydration were contributors to the decline of renal function.

The causes of hypokalaemia included low intake of potassium, increased renal loss due to tubular dysfunction and loop diuretic abuse, and gastrointestinal losses due to vomiting and laxative abuse.

Risk factors for tissue calcification in this patient were chronic kidney disease, hyperparathyroidism and elevated phospho-calcium product.

The cause for hyperparathyroidism presented a difficult diagnosis. It was most probably secondary due to chronic kidney disease, since the patient presented with normal calcaemia, high phosphorus and a very high level of PTH[4].

However, since the patient used furosemide surreptitiously and possibly had low intake of calcium, we cannot exclude primary hyperparathyroidism with normal calcaemia or tertiary hyperparathyroidism.

In primary hyperparathyroidism, there is dysregulation of the secretion of PTH; in 94% of the cases the cause is parathyroid adenoma. It usually presents with hypercalcaemia, hypophosphataemia, hypomagnesaemia and only mildly elevated PTH (on the order of ~120 pg/mL), since there is partial inhibition of the secretion of PTH by the hypercalcaemia[4]. Against this hypothesis is the fact that the patient had higher levels of PTH.

In tertiary hyperparathyroidism, which can occur with much larger parathyroid adenomas and longstanding chronic kidney disease, PTH secretion becomes autonomous, reaching serum levels of more than 2000 pg/mL and severe hypercalcaemia[5]. Against this hypothesis is the fact that the patient had normal levels of calcaemia.

As therapy, we primarily attempted to correct the water and electrolyte disturbances, with normal saline and potassium supplementation (oral and intravenous), followed by a short curse of spironolactone due to refractoriness of hypokalaemia.

Blood pressure was normalized. There was improvement of the estimated glomerular filtration rate (the lowest measured serum creatinine was 2.0 mg/dL, for an estimated glomerular filtration rate of 30 mL/min/1.73 m^2, calculated with the CKD-EPI equation). Urinary output was stable, of about 1800 mL per day.

Surreptitious behaviors, such as vomiting and throwing away medication, were detected that could be preventing the normalization of serum potassium levels. The patient was evaluated by psychiatrists and afterwards was admitted to the psychiatry ward. Under stricter control of medication and food intake, serum potassium reached the highest level, which was 3.5 mmol/L.

After discharge, the patient was kept on oral potassium salts without spironolactone, due to risk of abuse. The patient was also informed about the short-term need to start some kind of renal replacement therapy. She opted for haemodialysis, so was referred to peripheral vascular access creation.

As treatment for hyperparathyroidism, even though we considered a calcimimetic, this was not a reasonable option in this patient. This drug is not yet recommended for pre-dialysis patients[5] and in this case, there was also high risk of misuse. Since the patient had very high levels of PTH, severe calcification and parathyroid lesions compatible with adenomas, we decided to refer for parathyroidectomy.

CONCLUSION

This was a challenging case in which a pre-dialysis patient presented with exuberant alterations in a routine chest radiography.

The psychiatric and renal prognoses are poor. In fact, the patient failed follow-up appointments with her

nephrologist and missed appointments with the vascular surgeon (for peripheral vascular access construction) and with the general surgeon (for parathyroidectomy).

Disclosure of potential conflicts of interest: none declared

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