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Case Report: Resolution of Hypercalcemia and Acute Kidney Injury After Treatment for Pulmonary Tuberculosis Without the Use of Corticosteroids

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Abstract. Hypercalcemia caused by tuberculosis is rare and it is usually asymptomatic. Tuberculosis (TB) -related hypercalcemia associated with acute kidney injury (AKI) is rarely reported. We report a case of a 22-year-old immunocompetent man with 1-month history of daily fever, asthenia and weight loss. Laboratory findings on admission included serum calcium 14.9 mg/dL, urinary Ca^{2+} 569.6 mg/24 hours, low level of parathyroid hormone, serum creatinine = 2.2 mg/dL and sodium fractional excretion (FeNa) 2.73%. The result of the tuberculin skin test was 17 mm. A chest X-ray revealed micronodular pulmonary infiltrate in the apex of the right lung, which was confirmed by computed tomography scan. The patient was diagnosed with hypercalcemia associated with pulmonary TB and AKI. A general improvement of the hypercalcemia and renal function was observed in the first 2 weeks after effective hydration and treatment of TB without corticosteroids. The patient was discharged with normal calcium levels and renal function.

INTRODUCTION

Tuberculosis (TB) is a serious public health concern that has historically been closely associated with poverty and poor income distribution.[1] Granulomatous disorders, such as TB, are rarely associated with hypercalcemia and hypercalciuria and are usually asymptomatic.[2]

Hypercalcemia in TB associated with acute kidney injury (AKI) is more rarely reported,[3] although a few cases of hypercalcemia in TB patients have been described.[4] The purpose of this study was to report the case of a previously healthy young male with pulmonary TB associated with hypercalcemia and acute deterioration of renal function who recovered with treatment of TB without corticosteroids and discuss the possible pathogenic mechanisms involved.

CASE REPORT

A previously healthy 22-year-old male farm employee who was non-human immunodeficiency virus (HIV) -infected presented with an 8-week history of unplanned weight loss (about 7 kg), low-grade fever, dry cough, persistent nausea, vomiting, and shortness of breath with mild exertion. The patient had been treated for pneumonia on two occasions without clinical improvement. One month later, he was admitted with hypercalcemia and azotemia. On examination, the patient presented with normal blood pressure, low-grade fever (37.8°C), weight loss, dehydrated appearance, mucocutaneous pallor (3+/4), and crackles in the lower chest on both sides. The remaining physical findings were unremarkable. On admission, the laboratory findings included white blood cell count $7.9 \times 10^2/mm^3$, differential test result of 60% neutrophils, 25% lymphocytes, 10% monocytes, 16% eosinophils, and 9% basophils, platelets $495 \times 10^2/mm^3$, erythrocyte sedimentation rate 70 mm in the first hour, hemoglobin 12.4 g/L in the first hour, plasma C-reactive protein (CRP) 5.7 mg/dL, and albumin 4.5 g/dL. The biochemical findings included serum calcium 14.9 mg/dL, reference value (RV) 8.6–11.0, urinary Ca^{2+} 569.6 mg/24 hours, serum phosphate 4.6 mg/dL, parathyroid hormone (PTH) 4.4 pg/mL (RV: 14–72 pg/mL), alkaline phosphatase 211 UI/L (RV: 40–129 UI/L), serum creatinine 2.2 mg/dL, and serum urea 54 mg/dL. Plasma sodium, potassium, chloride, and magnesium concentrations were normal. The urine 24-hour collection measured 3,130 mL, and the sodium fractional excretion (FeNa) was 2.73%. The findings of the dipstick chemical urinalysis included pH of 6.0, specific gravity of 1.015, positive leukocyte esterase, and negative nitrite. On microscopic examination, the urine sediment presented numerous white blood cells, granular casts, calcium oxalate crystals, and moderate bacteria. The 24-hour urine collection test yielded 218 mg protein. Arterial pH and blood gases were normal. The induration on the Mantoux TB skin test, purified protein derivative research tuberculin 23 (PPD RT 23) measured 17 mm. The chest X-ray revealed micronodular pulmonary infiltrate in the apex of the right lung and a small pleural effusion in the same side (Figure 1). A computed tomography (CT) scan of the chest confirmed a diffuse micronodular pattern at the level of the lung, which was suggestive of acute inflammation (Figure 2). On renal ultrasonography, kidneys presented normal shape and volume, with increased echogenicity. The patient was started on effective hydration and furosemide. Despite negative sputum smears, a clinical diagnosis of pulmonary TB was established, and the patient was submitted to rifampicin, isoniazid, pyrazinamide, and ethambutol treatment (RIPE). After 2 weeks of treatment, renal function and serum calcium levels returned to the normal range (Figure 3). Diagnosis was confirmed on week 6 through positive sputum culture for *Mycobacterium tuberculosis*. Investigation for renal TB with the search and culture for *M. tuberculosis* in urine samples was negative.

DISCUSSION

Slow, gradual loss of kidney function associated to genitourinary system TB contributes to chronic kidney disease in immunocompetent patients.[5,6] Pulmonary TB associated with severe hypercalcemia and AKI as observed in the present

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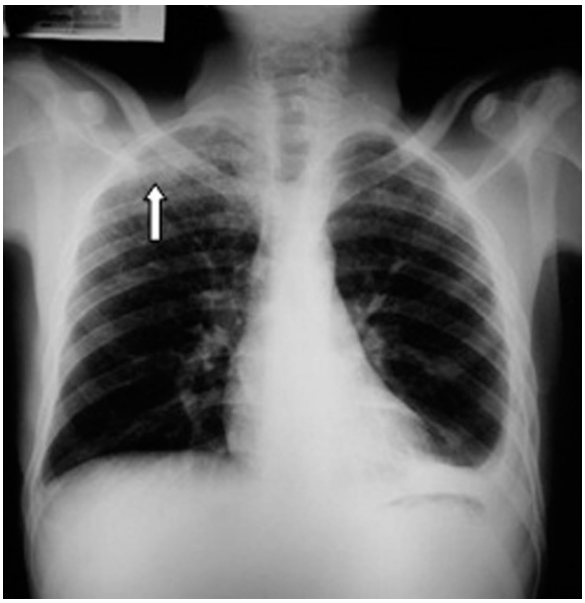

FIGURE 1. Postero-anterior chest X-ray showing pulmonary infiltrate in the apex of the right lung.

case is very rare and still poorly understood.[7,8] In patients with TB, hypercalcemia is usually mild and asymptomatic.[3,9] Another mechanism implicated in calcium and PTH disorders in patients with pulmonary TB involves cellular inflammatory response and immune mediators that suppress the parathyroid gland.[10,11] Some TB patients experience abnormal regulation of 1,25(OH2)D_3 with spontaneous production of the vitamin D metabolite by alveolar macrophages, contributing to hypercalcemia.[12] *In vitro* studies have shown that vitamin D metabolites play an important role in regulating the ability of macrophages to inhibit mycobacterial growth and influence granulomatous reactions.[13] Thus, low vitamin D levels seem to increase the risk of TB infection.[8] Several epidemiological studies have linked decreased vitamin D levels to increased susceptibility to immune-mediated disorders, including chronic

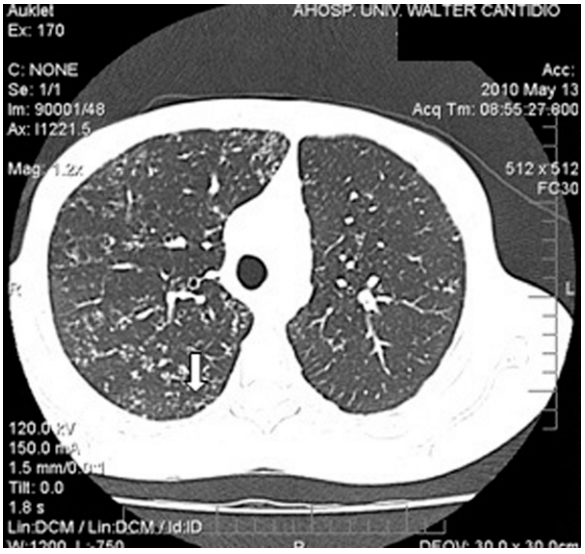

FIGURE 2. Chest CT scan showing diffuse pulmonary micronodules.

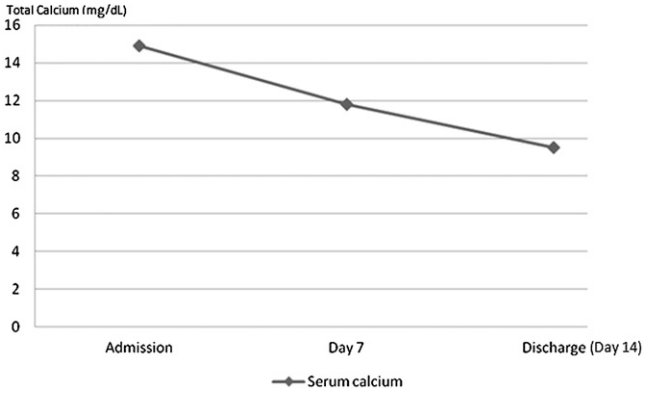

FIGURE 3. Decrease of calcemia during hospitalization of a patient with pulmonary TB and AKI associated to hypercalcemia.

infections and autoimmune diseases. Available data suggest that 1,25$(OH)_2D_3$ plays a role in the maintenance of immune homeostasis.[14] Moreover, hypercalcemia seems to be related to disease activity and vitamin D sufficiency status. Patients with granulomatous disorders living in areas with low rates of hypercalcemia have been shown to have either low dietary calcium intake or low vitamin D intake, whereas patients living in regions with high rates of hypercalcemia display relatively high levels of dietary calcium and vitamin D.[2] The patient described in this report was young, fairly light-skinned, and regularly exposed to intense sunlight with no risk factors for vitamin D (25-OH vitamin D) insufficiency.[15] Absorptive hypercalciuria, as observed in our patient, may be related to inappropriately high serum calcitriol levels.[16] Hypercalciuric TB patients tend to have reduced plasma PTH levels, and our patient was no exception.

Moreover, the development of renal insufficiency in individuals with hypercalcemia is related to the degree and duration of hypercalcemia. Long-standing hypercalcemia and hypercalciuria can lead to nephrogenic diabetes insipidus, nephrolithiasis, nephrocalcinosis, tubular atrophy with interstitial fibrosis, and thus, chronic kidney disease. Hypercalcemia causes nephrogenic diabetes insipidus decreasing delivery of solute to the loop of Henle (reduced glomerular filtration rate), inhibition of NaCl transport in the thick ascending limb, and inhibition of vasopressin-mediated water permeability in the terminal collecting duct.[17] Hypercalcemia has been shown to down-regulate the expression of aquaporine 2 protein in the medulla of rat kidneys, interfering with the patient's ability to concentrate urine.[18]

Our patient presented renal failure but no nephrocalcinosis or hydronephrosis, ruling out acute obstructive uropathy. Serum calcium values of 12–15 mg/dL (3–3.75 mmol/L) can lead to a reversible decrease in the glomerular filtration rate mediated by direct renal vasoconstriction and natriuresis-induced volume contraction. In fact, in this setting, renal disease can have acute and chronic outcomes. Early treatment generally restores renal function, but long-standing hypercalcemia and hypercalciuria may lead to calcification, degeneration, tubular cell necrosis, tubular atrophy, interstitial fibrosis, and calcification (nephrocalcinosis).[19] Granulomatous interstitial nephritis (GIN) is an uncommon form of acute interstitial nephritis, involving massive proteinuria (not observed in the present case), AKI, and granulomatous interstitial lesions. Several cases of

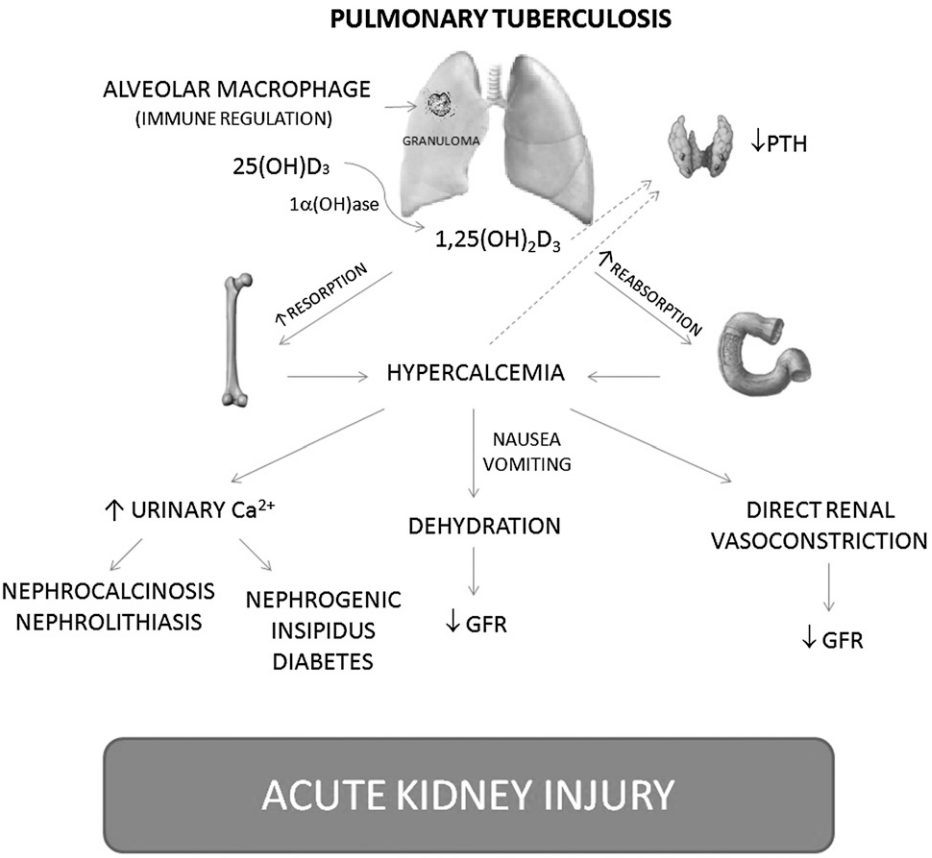

FIGURE 4. Possible basic mechanisms involved in the pathophysiology of AKI associated with hypercalcemia and pulmonary TB.

AKI associated with rifampicin, a drug widely used in the treatment of TB, have been reported.[20–24] Immune complex-mediated diffuse proliferative glomerulonephritis with crescentic formation is also described.[22,25] In a study in which the authors report a case of AKI in an individual with pulmonary TB, a review of literature yielded 48 cases of AKI associated with rifampin.[20] The cases were allocated according to their clinical characteristics and evolution in groups compatible with acute tubular necrosis (ATN) with hemolytic anemia and thrombocytopenia, rapidly progressive glomerulonephritis, acute interstitial nephritis, and light-chain proteinuria. The demonstration of rifampicin-dependent antibodies with anti-I specificity, which is known to be present on the surface of erythrocytes, leukocytes, and platelets and in body secretions, is also expressed on tubular epithelial cells but not in the glomeruli, and it provides a possible explanation for the AKI.[20] Correct diagnosis requires renal biopsy (currently the gold standard) but may not be necessary when clinical improvement is rapid after removal of the offending agent.

The possible basic mechanisms involved in the pathophysiology of AKI associated with hypercalcemia and pulmonary TB are presented in Figure 4.

Our study has important limitations, including the lack of measurement of serum calcitriol, α-1-microglobulin/urinary creatinine levels and urinary osmolality, for technical reasons. In addition, renal biopsy was not performed, because the patient presented general improvement of signs and symptoms and normalization of serum creatinine levels when started on hydration and furosemide, supporting the notion that the effect of tubular injury was transient and reversible. Calcium serum levels normalized as early as 2 weeks after treatment of pulmonary TB. Unlike most cases of hypercalcemia described in the literature, our patient recovered without the use of corticosteroids.

In conclusion, we report a case of hypercalcemia and AKI associated with pulmonary TB reverted by hydration, furosemide, and anti-TB treatment without the use of corticosteroids.

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