

Case report

Asymptomatic Hypercalcemia due to Cavitory Pulmonary Tuberculosis: A Case Report

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SUMMARY

Hypercalcemia in granulomatous diseases as tuberculosis (TB) is uncommon. We describe a case of a 21-year-old male whose serum calcium level was 14 mg/dL at the time of admission. Chest imaging revealed a cavity at the top of both lungs as well as the closure of the right laberal angle. The sputum smears and culture were evaluated regarding *Mycobacterium tuberculosis* and the findings of the smear and culture were reported as positive. As the values of creatinine were increased, renal failure had to be investigated. Both pathological mechanisms appear to affect the renal function. The anti-TB treatment included isoniazid 5 mg/kg, rifampicin 10 mg/kg and pyrazinamide 20 mg/kg once daily for two months and then the therapy continued with isoniazid and pyrazinamide up to eight months. The patient also received hydration, loop diuretics, and prednisolone (20 mg per day). One week after the introduction of the corticosteroid therapy, the patient's serum creatinine and calcium (Ca) levels decreased (4 mg/dL to 2 mg/dL, and 14 mg/dL to 10 mg/dL, respectively).

Hypercalcemia, renal failure, interstitial nephritis, and proteinuria are rare in pulmonary tuberculosis but should be considered as severe complications. Therefore, hypercalcemia should be first controlled by hydration or some steroids along with the treatment of TB, and introduction of loop diuretics and nutritional constraints.

Key words: hypercalcemia, renal failure, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a dangerous disease that threatens the health of a community (1). In rare cases, granulomatous diseases such as sarcoidosis, fungal infections and TB can be a secondary cause of hypercalcemia and hypercalciuria, which are asymptomatic in most cases (2, 3). The prevalence of hypercalcemia varies in different parts of the world, ranging from 2% to 30% (4). The prevalence of hypercalcemia is reported to be 16% in patients with TB, and in tropical areas such as Nigeria it amounts to 27.5% (5). However, this level depends on the level of total vitamin D and calcium intake. Hypercalcemia is unusual in patients with TB and patients with renal failure, and only a few such cases have been reported so far. The aim of this paper was to present a case without a history of a previous disease, with the symptoms of pulmonary TB, hypercalcemia and renal failure.

CASE REPORT

A patient was a 21-year-old male student, from Babol, northern Iran, and referred to the history of productive cough and fever in duration of six months. The patient also mentioned 10 kg weight loss during this period but had no sign of shortness of breath, night sweats, and chest pain. During this period, the patient had an outpatient visit to a doctor and was treated with oral antibiotics but did not recover. The patient did not mention the history of some previous disease, and was neither a smoker nor an addict.

The examination showed fever above 38 °C; the patient had high blood pressure (140/90 mmHg) and sinus tachycardia (PR = 98). Oxygen saturation without nasal oxygen was 98%. The conjunctiva was pale. In the lung-ear drum pathway, the loss of sound was noticed in the right lung. In the chest X-ray (CXR), a cavity was seen at the top of both lungs, and the right lateral angle was closed (Figure 1).



Figure 1. The chest X-ray (CXR) shows the cavity on the top of both lungs in which the right lateral angle was closed

Spiral computed tomography (CT) scan without contrast medium showed pleural calcification with pleural effusion and evidence of a decrease in the size of the

right hemithorax. Moreover, calcified lymph nodes were located in the right bronchovascular area. Two nodules, 18 mm and 37 mm in size, with corneal calcification,

were observed in the pleura, and large cavitary lesions were observed at the top of both lungs in addition to tree-in-bud opacities, patchy ground-glass opacities, and synthetic lobar nodules (Figure 2 and 3).

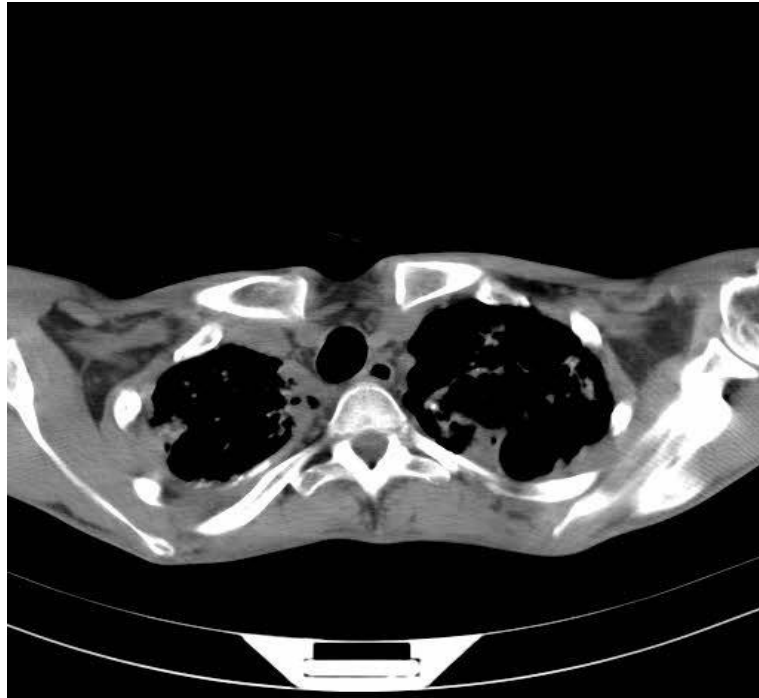


Figure 2. The spiral computed tomography (CT) scan without contrast shows a pleural calcification with pleural effusion and evidence of a decrease in the size of the right hemithorax

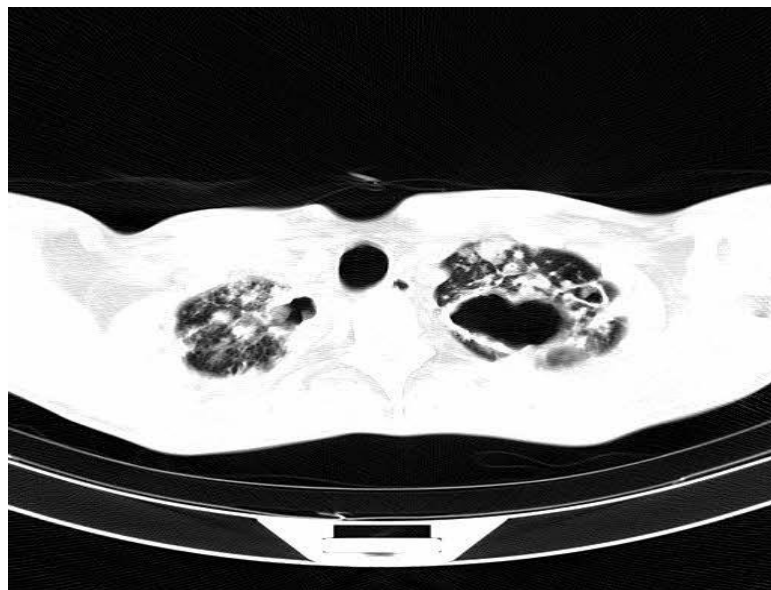


Figure 3. Computed tomography (CT) scan shows calcified lymph nodes in the right bronchovascular area, with corneal calcification in the pleura and large cavitary lesions on the top of both lungs, as well as tree-in-bud opacities, patchy ground-glass opacities, and synthetic lobar nodules

Based on the radiological patterns and epidemiological conditions, the findings strongly suggested the existence of tuberculosis. The patient's laboratory results were as follows: leukocytosis (WBC = 12.500 cells/mm³); anemia (Hb = 8.6 g/dL) with mean corpuscular volume (MCV) - 82; platelet count (PLT) - 478,000/mm³; C-reactive protein (CRP) - 68 mg/L; erythrocyte sedimentation rate (ESR) - 110 mm/hr; Na, 122 mmol/L and creatinine (Cr): 3.8 mg/dL. In the following tests, calcium (Ca), 10.05 mg/dL, phosphorus, 4.5 mg/dL; albumin (ALB), 3.8 g/dL; 25OHVitD₃, 71 nmol/L, and in the urinalysis, specific gravity (SG), 10.3 and pH 7 with proteinuria 2+ were reported. Due to the suspicion of pulmonary TB, the patient was hospitalized in an isolated room with negative pressure. The sputum smears and culture were evaluated regarding *Mycobacterium tuberculosis*, and the findings of the smear and culture were reported as positive. The anti-TB treatment included isoniazid 5 mg/kg, rifampicin 10 mg/kg and pyrazinamide 20 mg/kg once daily for two months and then therapy continued with isoniazid and pyrazinamide up to eight months, (with adjustments according to glomerular filtration rate (GFR)). Considering the increased values of creatinine, the patient was also examined for renal failure. In the ultrasound of the kidney and urinary tract, the right kidney and the left kidney were reported to be 100 mm and 105 mm in diameter, respectively; parenchymal echo patterns of both kidneys were increased. However, no evidence of nephrolithiasis was found. The 24-hour urine specimen results were as follows: protein - 909 mg, volume - 2,250 ml and Cr - 1100 mg/dL. The test results for HIV were negative. Smear examination of early morning urine specimen regarding AFB was also negative, which was confirmed in three consecutive analyses.

The patient was also examined regarding autoimmune diseases and the complement levels were normal. The antinuclear antibody (ANA), antiglomerular basement membrane (GBM), anti-double stranded DNA (anti-dsDNA), and anti-neutrophil cytoplasmic antibodies (ANCA) were also within the normal range. Ultimately, in a re-examination of the patient in terms of electrolytes, the patient's calcium level was 14 mg/dL; phosphorus - 3.5 mg/dL; 24-hour urine calcium - 390 mg/dL (normal, too); intact parathyroid hormone (iPTH) - 9 pg/mL and 25OHVitD - 1 ng/mL. Considering the unjustifiable high creatinine and proteinuria levels, and persistently high levels of creatinine after three weeks, the patient then underwent kidney biopsy. Therefore, chronic tubulointerstitial nephritis with mild inflammation was reported in pathological analysis. Considering high calcium levels, normal phosphor, low iPTH, high

urine calcium (hypercalcemia), and renal pathology, nephritis was considered in the context of granulomatous disease (tuberculosis), and in addition to anti-TB drugs, the patient received hydration, loop diuretics, and prednisolone at a dose of 20 mg per day. One week after starting the corticosteroid therapy, the patient's creatinine level decreased from 4 mg/dL to 2 mg/dL, and Ca decreased from 14 mg/dL to 10 mg/dL. For this reason, the patient was discharged with a recommendation to continue taking the corticosteroid therapy and have monitored the level of calcium for the next two months until the decrease of Ca; the use of anti-TB drugs including isoniazid and pyrazinamide was recommended for the next eight months.

DISCUSSION

The paper presents the case of a patient with smear-positive cavitary pulmonary tuberculosis, and there were some specific indicators in the patient's tests that pointed to renal failure, proteinuria, and hypercalcemia caused by secondary hyperparathyroidism. It should be noted that renal involvement in tuberculosis is more commonly caused by the hematogenous seeding of bacillus that leads to the destruction of renal glomeruli, the formation of abscess, descending release of the infection to the ureter and bladder, stenosis and obstruction, hydronephrosis, and ultimately renal dysfunction (6-9). As ultrasound examination showed no evidence of renal involvement, other mechanisms had to be considered. Since TB rarely causes glomerulonephritis and interstitial nephritis of the kidney, and although its pathogenesis is not completely clear, nephritis is an immunological phenomenon, at least in some patients (10). In other words, as biopsy was not done, it was not possible to determine the definitive cause. Two possible mechanisms for kidney involvement in the course of tuberculosis were expected. Direct involvement of parenchyma was unlikely due to the negative results obtained in the analysis of urinary smear (repeated for three times), i.e. if we had continued to treat tuberculosis, we would have got a curative treatment cover. However, by adding a corticosteroid to the regimen, significant changes in calcium levels were observed at the calcium level. In some studies, even the polymerase chain reaction (PCR) of kidney biopsy specimens of these patients was negative regarding TB (11). In our patient, interstitial nephritis was reported in the pathology of kidney biopsy, but *Mycobacterium tuberculosis* was not observed. Another finding in our patient was hypercalcemia, which was not justifiable with regard the interstitial strengthening.

It was proved that granulomatous diseases such as sarcoidosis, tuberculosis, and fungal infections may cause hypercalcemia due to the extrarenal production of 1, 25 (OH) 2D3 in activated macrophages in granulomas and CD8+ T-cells, which can suppress PTH (12-14). Subsequently, due to the low level of PTH and the presence of hypercalciuria, hypercalcemia was suspected. In other words, by induction of vasoconstriction on renal glomeruli, hypercalcemia may reduce GFR, which can induce nephrolithiasis and nephrocalcinosis in the kidney through hypercalcemia, if it persists. It could be postulated that the increase in creatinine in our patient may be caused by two mechanisms of hypercalcemia and interstitial nephritis. In some studies on the treatment of hypercalcemia using this mechanism, only anti-TB treatment and hydration were mentioned. However, avoiding Ca supplements, dairy products, exposure to sunlight, and ultimately loop diuretics contribute to the normalization of Ca levels. In some cases, it is necessary to introduce corticosteroids in order to control this disorder and restore Ca and Cr to the normal levels (15, 16).

CONCLUSION

Hypercalcemia, renal failure, interstitial nephritis, and proteinuria are rare manifestations of pulmonary

tuberculosis but should be considered as complications of tuberculosis. Although hypercalcemia is not usually symptomatic in these patients, it can lead to renal failure. Therefore, it should be controlled first by hydration in addition to treatment with anti-TB loop diuretics and nutritional constraints. If not controlled, treatment with steroids should be considered. In the case presented here, both hypercalcemia and interstitial nephritis appear to affect renal failure; thus, several mechanisms should always be taken into consideration.

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Conflicts of interests

There are no conflicts of interest.

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Asimptomatska hiperkalcemija usled kavitarne tuberkuloze pluća: prikaz slučaja

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SAŽETAK

Hiperkalcemija kod granulomatoznih bolesti poput tuberkuloze (TB) je retka. U radu je opisan slučaj dvadesetjednogodišnjeg muškarca kod koga je nivo kalcijuma u serumu iznosio 14 mg/dL u vreme prijema. Snimanje grudnog koša pokazalo je postojanje šupljina u gornjem delu oba plućna krila, dok je desni lateralni ugao bio zatvoren. Kultura i razmaz sputuma na mikroskopskoj pločici analizirani su na prisustvo bacila *Mycobacterium tuberculosis* i dobijeni rezultati bili su pozitivni. Kako su vrednosti kreatinina bile povećane, krenulo se sa ispitivanjem bubrežne insuficijencije. Oba patološka mehanizma uticala su na bubrežnu insuficijenciju. Anti-TB terapija uključila je primenu isoniazida u dozi od 5 mg/kg, rifampicina u dozi od 10 mg/kg i pirazinamida u dozi od 20 mg/kg jednom dnevno, u trajanju od dva meseca, a potom je terapija nastavljena isoniazidom i pirazinamidom narednih osam meseci. Pacijent je bio hidriran, primio je diuretike Henleove petlje i prednisolon (20 mg). Nedelju dana nakon uvođenja terapije kortikosteroidima nivoi serumskog kreatinina i kalcijuma su se smanjili (od 4 mg/dL na 2 mg/dL i od 14 mg/dL na 10 mg/dL).

Hiperkalcemija, bubrežna insuficijencija, intersticijalni nefritis i proteinurija retko se javljaju kod tuberkuloze pluća, ali ih treba razmatrati kao ozbiljne komplikacije. Stoga, hiperkalcemiju bi trebalo prvo kontrolisati hidratacijom ili steroidnim lekovima uz istovremeno lečenje tuberkuloze, kao i uvođenjem diuretika Henleove petlje i dijetetskog režima.

Ključne reči: hiperkalcemija, bubrežna insuficijencija, tuberkuloza