Severe hypercalcemia in elderly patient with asymptomatic pulmonary tuberculosis: a case report

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Abstract

Hypercalcemia presents itself as a challenging disorder in clinical practice, with hyperparathyroidism and malignancies accounting for 90% of the causes. The case report describes a married 78-year-old white rural male worker with low level of education. Given the social isolation brought on by the COVID-19 pandemic, the patient initially received antidepressants for a history of adynamia, muscle weakness, and inappetence for a year. Four months before admission, he had an aggravation of the clinical picture, presenting mental confusion, and becoming dependent for all daily life activities. He was hospitalized with adynamia and intense fatigue, muscle weakness, inappetence with weight loss, splenomegaly and severe hypercalcemia (15.9 mg/mL; corrected by serum albumin - reference value: 8.8 to 10.3 mg/dL) and low parathyroid hormone level. This is a rare case of severe hypercalcemia in an elderly patient with asymptomatic pulmonary tuberculosis with late diagnosis and renal impairment, possibly aggravated by hypercalcemia.

Introduction

Hypercalcemia presents itself as a challenging disorder in clinical practice, with hyperparathyroidism and malignancies accounting for 90% of the causes.[1] It is classified as mild, moderate, and severe, depending on calcium values: mild 10.5–12 mg/dL, moderate 12.1–14 mg/dL, and severe >14 mg/dL.[2]

Generally, values above 14 mg/dL cause severe symptoms, and after 15 mg/dL, there is a risk of cardiac arrest.[3]

It is known that calcium homeostasis is balanced because urinary excretion draws closer to food intake. About 200 mg of calcium is absorbed in the intestine per day through vitamin D-dependent transport mechanisms. Then, the calcium is absorbed by the bones or excreted via the kidneys. Body calcium homeostasis is regulated by three factors: calcitonin, vitamin D, and parathyroid hormone (PTH), which is the main regulator. It may result from increased bone resorption dependent or independent of PTH, from increased absorption secondary to vitamin D, or from drug causes.[4] Calcitonin is a hormone produced by thyroid parafollicular C cells, which is released into the circulation in response to an acute increase in calcium concentration.[5] The non-specific presentation provides a broad differential diagnosis.[4]

In response to a drop in serum calcium levels, PTH is released, leading to bone resorption and calcium release. In the kidney, PTH stimulates tubular reabsorption of calcium, in addition, it stimulates 1α-hydroxylase to convert vitamin D to its active form [1.25-dihydroxy vitamin D or 1.25(OH)2 D], which then, increases intestinal calcium absorption.[6]

The clinical presentation is varied and depends on the serum calcium value, corrected by albumin: corrected calcium = measured calcium (mg/dL)+[0.8×4–albumin (g/dL)]. Additionally, the evolution time of this elevation must be considered. The first step in the evaluation of a patient with hypercalcemia is the measurement of PTH. The second step is to determine its cause; correct diagnosis allows effective and often definitive treatment. Primary hyperparathyroidism leads to excessive PTH production. When total calcium is measured, the value should be corrected by serum albumin concentration, as albumin is the main protein that carries the ion. A low level of parathyroid hormone would signify a pathology independent of the parathyroid.[1] The next step is to dose 25 (OH), if it is high, consider exogenous vitamin D poisoning, if it is normal, dosing 1.25 (OH)2D, and if it is low, consider malignant disease producing hypercalcemia and high lymphomas or granulomatous diseases.[4]

Case report

The patient is a 78-year-old white, male rural worker who is married and has a low level of education. History of adynamia,

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Key words: Hypercalcemia; tuberculosis; elderly.

Acknowledgments: The authors would like to thank the patient and his family for fully trusting their work, and the interdisciplinary and multi-professional teams for the comprehensive care centered on the elderly.

Contributions: All authors contributed to the patient's management and discussed the case.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Ethical approval: Project approved by decision of the Research Ethics Committee (CEP). According to operational rule 001/2013. On 06/19/2022.

Informed consent: The privacy and confidentiality are guaranteed as only laboratory examinations, tomography image and histopathology are presented.

Availability of data and materials: Data and materials are available by the authors.

Received for publication: 23 August 2022.
Revision received: 5 January 2023.
Accepted for publication: 3 March 2023.

Licensee PAGEPress, Italy
Geriatric Care 2022; 8:10812
doi:10.4081/gc.2022.10812

muscle weakness, inappetence for a year was initially medicated with antidepressants - given the social isolation due to the COVID-19 pandemic. Four months before admission, there was an aggravation on his clinical picture, presenting mental confusion, and becoming dependent on others for all daily life activities. He was hospitalized with adynamia and intense fatigue, muscle weakness, inappetence with weight loss, splenomegaly, and severe hypercalcemia (15.9 mg/mL; corrected by serum albumin - reference value: 8.8 to 10.3 mg/dL) and low PTH level. He denied other symptoms.

He was hypertensive for a long time, using losartan irregularly, and had recently been diagnosed with non-dialytic chronic kidney disease, stage G4A2. He was a long-term smoker, but he experienced no fever, or respiratory symptoms. Relatives denied replacement of calcium or vitamin supplements.

He presented temporal and spatial disorientation, dehydrated and pale mucous membranes +/+++, and absence of palpable lymph nodes. He also presented cardiac auscultation with regular heart rhythm, with occasional extrasystoles, blood pressure of 130×80 mmHg, heart rate of 82 bpm, and pulmonary auscultation without alterations, respiratory rate of 18 bpm and 98% oxygen saturation, globular abdomen, presence of hydroaerial noises, painless palpable spleen with a rigid consistency (Boyd III). Laboratory tests (Table 1), tomography of the abdomen and lung (Figure 1A, B and Figure 2), and upper digestive endoscopy were normal.

Due to high risk, treatment for severe hypercalcemia was started with intravenous hydration, intravenous furosemide, and 4 mg zoledronic acid (single dose). Bronchoscopy and pleural biopsy were performed to clarify the diagnosis (Figure 3A and B). The patient evolved with laboratory improvement in serum calcium and relative improvement in muscle strength, but with worsening renal function and ventilatory failure, it was not possible to perform a splenectomy. The death occurred in the intensive care unit due to renal and pulmonary complications, without the possibility of treating the underlying disease.

Discussion

After excluding malignant and endocrine causes of hypercalcemia, granulomatous diseases and lymphoma remained the probable etiology, as it had low levels of parathyroid hormone (PTH) and high levels of 1.25 dihydroxy vitamin D.[4]

The patient in question was hospitalized with severe hypercalcemia and important symptoms, such as lethargy, an intense weakness that made it impossible to stand or walk, and delirium. In addition to the use of furosemide, intravenous hydration and zoledronic acid (4 mg with slow venous infusion) were necessary, despite the decline in renal

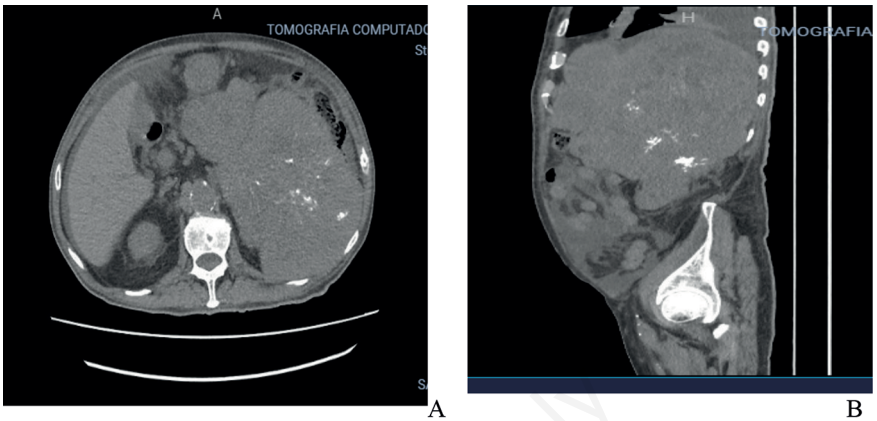

Figure 1. A,B) Abdominal tomography: voluminous heterogeneous expansive lesion, intermingled with amorphous calcifications, located in the topography of the splenic cavity, measuring approximately 19.6×13.1 cm, of probable splenic nature. The described lesion medially displaces the pancreatic tail and left kidney. A moderate amount of free fluid in the abdominal and pelvic cavity.

Table 1. Laboratory tests.

Tests (reference value)	Values found	After treatment
Hemoglobin (g/dL): (14.0 to 17.5)	11.3	10.4
Leukocytes (cell/mm^3): (4.4 to 11.0×10^3)	12.560	16.840
Platelets (cell/mm^3): (150,000 to 400,000)	129,000	192,000
Creatinine (mg/dL): (0.5 to 1.3)	2.4	4.8
Urea (mg/dL): (19 to 43)	64	118
Sodium (mEq/L): (135 to 145)	131	133
Potassium (mEq/L): (3.5 to 5.2)	3.7	5.2
Venous blood gas Ph: (7.32 to 7.43)	7.439	7.282
PaO2(mmHg): (35 to 40)	22.4	39.8
PCO2(mmHg): (38 to 50)	44.5	32.1
Bicarbonate (mmol/L): (22 to 29)	29.5	14.8
BE (mmol/L): (+2 to -2)	4.6	-10.6
Calcium corrected by albumin (mg/dL): (8 to 10.3)	15.9	9.84
Ionic calcium (mg/dL): (4.6 to 5.2)	8.0	4.7
Phosphorus (mg/dL): (2.7 to 4.5)	3.3	5.6
TSH (IU/mL); (0.340 to 5.600)	1.608	
Free T4 (ng/dL): (0.7 to 1.48)	0.94	
PTH (pg/mL): (12 to 72)	7.54	
1.25 hydroxy vit D (pg/mL):(9 to 79.3)	136	
Pleural Fluid	Xanthochromic color, cloudy, Red cells 147,000/mm^3, Leukocytes 3,200/mm^3, Polymorphonuclear 27%, Mononuclear 73%, Eosinophils 0%, T otal Proteins 3.1g/dL, DHL 269 U/L	
Albumin (g/dL): (3.5 to 5.5)	2.6	
Protein electrophoresis	Polyclonal Peak	

PaO2, partial pressure of oxygen; PCO2, partial pressure of carbon dioxide; BE, barium enema; TSH, thyroid stimulating hormone; T4, Thyroxine; PTH, parathyroid hormone; VIT, vitamin.

function (glomerular filtration rate 30 mL/min). It was to investigate the cause of the hypercalcemia (bronchoscopy with bronchial lavage and pleural biopsy) only after the eighth day of hospitalization, with stabilization of the clinical picture; splenectomy was not performed. The incidence of tuberculosis of the spleen is a rare entity and has occasionally been described in the literature; isolated splenic tuberculosis is an unusual phenomenon, especially in immunocompetent individuals.[7]

There are two major morphological subtypes of hepatosplenic tuberculosis: micronodular and macronodular. Calcifications may occur in late-stage disease.[8] However, splenic calcifications are nonspecific and may arise in many other diseases.

Among the causes of hypercalcemia independent of PTH, lymphoma, and ingestion of high doses of vitamin D were excluded, leaving granulomatous diseases, as they present severe hypercalcemia, reduced PTH, and high levels of 1.25 (OH)2 D3.

Severe hypercalcemia (corrected values ≥14 mg/dL) is a rare manifestation of pulmonary tuberculosis.[9] Despite enormous advances in diagnosis and treatment, tuberculosis remains an important cause of death worldwide. According to the World Health Organization, tuberculosis was the cause of death for 1.5 million people in 2020.[10]

The definitive mechanism that causes hypercalcemia in patients with tuberculosis is not fully understood. The increase in 1.25-dihydroxy vitamin D levels along with low or normal levels of 25-hydroxy vitamin D levels suggests an increase in the conversion of 25-hydroxy vitamin D to 1.25-dihydroxy vitamin D. This conversion is mediated by the 1-α-hydroxylase enzyme found in the kidney. Alveolar macrophages located in tuberculous granuloma are suggested as the site for extra renal 1-α-hydroxylase activity. Macrophage production of 1-α-hydroxylase is probably important for the immune response to tuberculosis infection. Most patients with tuberculosis infection-related hypercalcemia are asymptomatic.

Patients with tuberculosis rarely develop symptoms related to hypercalcemia, including polyuria, anorexia, nausea, weakness, and lethargy, and more severe central nervous system symptoms, such as delirium.

The diagnosis of tuberculosis in elderly people is a challenge when associated with atypical and little symptomatic manifestations. Symptoms of severe hypercalcemia, such as adynamia, mental confusion, and weakness, were initially confused with depression, delaying the correct diagnosis.[4] In a retrospective study in the United Kingdom, the less specific symptoms of dyspnea, lethargy, and reduced appetite were more common in elderly patients.[11]

Before the etiological diagnosis was established, the patient worsened with dialytic acute kidney injury and hospital infection, progressing to mechanical ventilation and death in the intensive care unit.

Among the limitations of the case, we can mention the impossibility of surgically approaching the splenomegaly due to the aggravation of the case (a splenectomy was scheduled), and the late hospitalization of the patient with renal impairment, making specific treatment of the underlying disease impossible. The lack of splenic histologic data couldn't exclude hematologic malignancies or other neoplastic conditions as the cause of hypercalcemia.

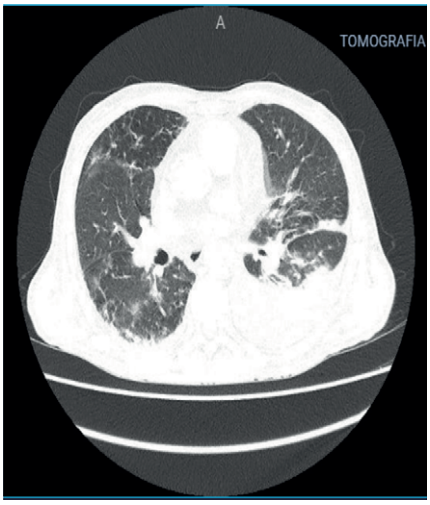

Figure 2. Chest tomography showed moderate pleural effusion on the left and small on the right. Bubbles of paraseptal and centrilobular emphysema sparsed bilaterally in both lungs, predominantly in the upper lobes. Fibroatelectasic striae associated with traction bronchiolectasis and minute and calcified nodules, in addition to architectural distortion of the parenchyma, affecting the upper lobes, notably on the right. Atelectatic bands/zones of consolidation compromising the inferior lingular segment. Diffuse thickening of the bronchial walls, inferring diffuse bronchopathy. Cardiomegaly. Aortic and coronary atheromatosis. Centered mediastinum, with no signs of masses or lymph node enlargement.

Conclusions

In conclusion, this is a rare case of severe hypercalcemia in an elderly patient with asymptomatic pulmonary tuberculosis with late diagnosis and renal impairment, possibly aggravated by hypercalcemia.

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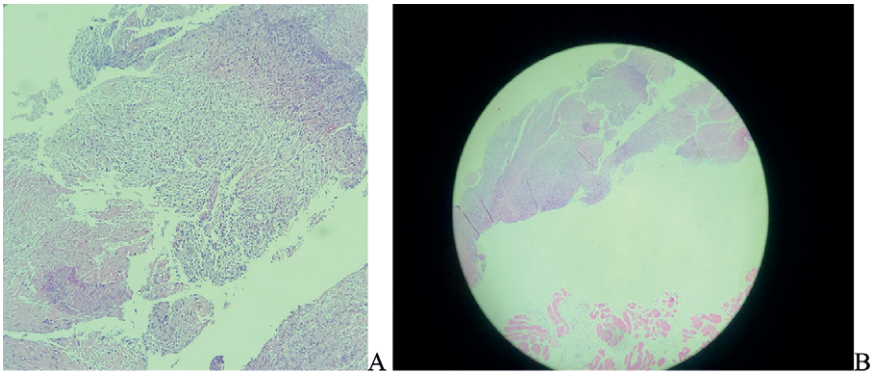

Figure 3. A,B) Pleural anatopathology: granulomatous pleuritis with caseous necrosis. Positive smear and rapid molecular test for mycobacterium tuberculosis from detectable bronchoalveolar lavage.

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