CASE REPORT

Acute hypercalcemia and hypervitaminosis D associated with pulmonary tuberculosis in an elderly patient: A case report and review of the literature.

Toshihiro Wada1, Masaki Hanibuchi2, and Atsuro Saijo2

1Department of Internal Medicine, 2Department of Respiratory Medicine, Shikoku Central Hospital of the Mutual Aid Association of Public School teachers, 2233 Kawanoe-cho, Shikoku-Chuo, 799-0193, Japan

Abstract: An 80-year-old man was referred to our hospital for further examination of fever, cough and left pleural effusion. The laboratory findings showed acute inflammation, the elevation of albumin-corrected serum calcium and 1,25-dihydroxyvitamin D3. A chest CT revealed centrilobular particulate opacity in the bilateral lung fields and left pleural effusion, indicating acute hypercalcemia and hypervitaminosis D associated with pulmonary tuberculosis. By the confirmation of Mycobacterium tuberculosis on polymerase chain reaction and cultures of the sputum and pleural effusion, a diagnosis of pulmonary tuberculosis was made. The patient successfully completed a 9-month course of the anti-tuberculosis treatment, and bilateral infiltrative shadows and left pleural effusion in chest X-ray disappeared. Symptoms progressively improved and serum level of albumin-corrected calcium and 1,25-dihydroxyvitamin D3 eventually normalized. While pulmonary tuberculosis is an infrequent cause of hypercalcemia, it should be considered in patients with hypercalcemia and elevated serum level of 1,25-dihydroxyvitamin D3 and hypervitaminosis D.

Keywords: pulmonary tuberculosis, hypercalcemia, 1,25-dihydroxyvitamin D3

INTRODUCTION

The most important causes of hypercalcemia in the elderly are hyperparathyroidism, malignant disease and prolonged immobilization. Medications, such as thiazide diuretics and lithium, as well as excessive supplementation with calcium/vitamin D, may precipitate hypercalcemia (1). Granulomatous disorders, such as sarcoidosis and tuberculosis, can also potentially present with hypercalcemia. Although hypercalcemia is known to be associated with pulmonary tuberculosis, it is relatively uncommon (2, 3). We herein report an elderly case of pulmonary tuberculosis with hypercalcemia and hypervitaminosis D. In the present report, we highlight pulmonary tuberculosis as a potential cause of hypercalcemia and hypervitaminosis D, as well as discuss the prevalence and the putative mechanisms of tuberculous hypercalcemia through the review of the literature.

CASE REPORT

An 80-year-old man was referred to our hospital for further examination of left pleural effusion. On admission, low grade fever and productive cough had persisted for approximately nine months. His medical history included hypertension, vibration disease and fracture of left clavicle. No significant social or family history was reported. His body temperature was 36.7 °C, a blood pressure of 110/74 mmHg, a pulse of 60 beats per minute and an oxygen saturation of 97% on room air. There were no evident cervical, supraclavicular and axillary lymphadenopathies. The cardiovascular examination was unremarkable. Respiratory sounds were decreased in the left lower lung field. The remainder of the physical examination was normal. The laboratory findings on admission indicate acute inflammation (white blood cell count 6500/μL, C-reactive protein 4.55 mg/dL) and renal dysfunction (urea nitrogen 27.8 mg/dL, creatinine 2.94 mg/dL). The albumin-corrected serum calcium (corrected Ca) and 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) were elevated at 12.4 mg/dL and 151.0 pg/mL, respectively, but intact parathyroid hormone (PTH), PTH-related protein and angiotensin converting enzyme were within normal range. The remainder of laboratory test results is shown in Table 1. A chest X-ray demonstrated bilateral infiltrative shadows and left massive pleural effusion (Fig. 1A). A chest CT revealed centrilobular particulate opacities and consolidations in the bilateral lung fields and left massive pleural effusion (Fig. 1B). Several differential diagnoses were considered at this juncture. In our patient, there was neither a reported history of excessive calcium/vitamin D intake nor consumption of thiazides. Laboratory tests and systemic radiological scans excluded any malignancies and endocrinopathies. In view of the radiological findings, a diagnosis of hypercalcemia and hypervitaminosis D secondary to pulmonary tuberculosis was formulated. By the confirmation of Mycobacterium tuberculosis on polymerase chain reaction and cultures of the sputum and pleural effusion, a diagnosis of pulmonary tuberculosis (M. tuberculosis) was made. The isolated strain was susceptible to all anti-tuberculosis drugs. Immediately after diagnosis, the patient received an anti-tuberculosis treatment comprising daily dosing of isoniazid (INH), rifampicin (RFP), ethambutol (EB), andrifampicin (RFP), rifampicin (RFP), ethambutol (EB), and interferon gamma (IFN-γ).

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Address correspondence and reprint requests to Masaki Hanibuchi, Department of Respiratory Medicine, Shikoku Central Hospital of the Mutual Aid Association of Public School teachers, 2233 Kawanoe-cho, Shikoku-Chuo, 799-0193, Japan and Fax: +81-896-58-3464.
of isoniazid (INH) 300 mg and rifampicin (RFP) 450 mg, and alternate-day administration of ethambutol (EB) 750 mg for two months followed by daily dosing of INH and RFP for seven months. The dose of EB was adjusted according to the degree of renal dysfunction. In terms of treatment for hypercalcemia, intravenous saline was also administered. After receiving these treatments, the patient’s symptoms progressively improved and serum level of corrected Ca and 1,25-(OH)₂D₃ eventually normalized at 9.0 mg/dL and 29.6 pg/mL, respectively. Finally, the patient successfully completed a 9-month course of the anti-tuberculosis treatment, and bilateral infiltrative shadows and pleural effusion in chest X-ray and chest CT disappeared (Fig. 2A, B).
DISCUSSION

The present case reminds us of the importance of pulmonary tuberculosis as a cause of hypercalcemia especially in elderly patients. While pulmonary tuberculosis is an infrequent cause of hypercalcemia (4), it should be considered in patients with hypercalcemia and elevated serum level of 1,25-(OH)_{2}D_{3}. Whenever pulmonary tuberculosis is suspected, timely diagnosis and treatment are mandatory.

Main causes of hypercalcemia include primary hyperparathyroidism, malignancies, drugs and granulomatous diseases, although relative frequency is different between various regions (5). Primary hyperparathyroidism is the most frequent cause, but cancer and drugs have been recently identified as the causes with increased frequency, especially in elderly patients because of the greater risk for malignancy and increased use of vitamin D supplements. However, following these three major causes of hypercalcemia, granulomatous diseases remain important causes for hypercalcemia and these include sarcoidosis, histoplasmosis, coccidioidomycosis and candidiasis in addition to tuberculosis. Finally, other rare causes include hyperthyroidism. Investigations for causes of hypercalcemia include detailed history-taking, physical examination and logical use of laboratory tests. The use of vitamin D or calcium should be sought and physical examination should be performed for looking for a clue suggestive of possible malignancy or granulomatous diseases.

The prevalence of hypercalcemia in patients with tuberculosis is quite variable between countries, varying from approximately 2.3% in some studies (3) to 14.7-50.6% in other studies (6-14) (Table 2). This variation has been largely attributed to disparity in vitamin D and calcium intake, the degree of sunlight exposure as well as the criteria for the diagnosis for hypercalcemia (4). Generally, studies using the albumin-adjusted serum calcium concentration have reported higher prevalence rates compared with patients who did not use correction (7, 9). In the elderly patient with tuberculosis, the frequency of hypercalcemia has not been well documented. Although clinically significant hypercalcemia from tuberculosis is relatively uncommon, the elderly patient seems to be particularly susceptible, given their advanced age, comorbidities, polypharmacy as well as the frequent use of calcium/vitamin D supplements. In the present case, serum level of corrected Ca and 1,25-(OH)_{2}D_{3} eventually normalized with a continued treatment of tuberculosis, as reported previously (1). Although hypercalcemia associated with pulmonary tuberculosis is relatively uncommon and is rarely symptomatic, prompt diagnosis and appropriate treatment is very important.

The mechanism of tuberculous hypercalcemia remains unclear, but has been largely attributed to vitamin D dysregulation. Patients presenting with tuberculosis tend to have lower levels of vitamin D than healthy individuals (15). In patients with tuberculosis, extrarenal synthesis of active vitamin D, 1,25(OH)_{2}D_{3}, occurs via 1-α-hydroxylase produced by interferon

Table 2. Summary of the prevalence of hypercalcemia in pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Prevalence</th>
<th>Methodology*</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbasi AA</td>
<td>1979</td>
<td>U.S.A.</td>
<td>79</td>
<td>27.8%</td>
<td>Ionized calcium</td>
<td>6</td>
</tr>
<tr>
<td>Need AG</td>
<td>1980</td>
<td>Australia</td>
<td>89</td>
<td>50.6%</td>
<td>Albumin-adjusted calcium</td>
<td>7</td>
</tr>
<tr>
<td>Sharma SC</td>
<td>1981</td>
<td>India</td>
<td>94</td>
<td>15.5%</td>
<td>Ionized calcium</td>
<td>8</td>
</tr>
<tr>
<td>Kitrou MP</td>
<td>1983</td>
<td>Greece</td>
<td>50</td>
<td>48.0%</td>
<td>Albumin-adjusted calcium</td>
<td>9</td>
</tr>
<tr>
<td>Lind L</td>
<td>1990</td>
<td>Sweden</td>
<td>67</td>
<td>25.4%</td>
<td>Ionized calcium</td>
<td>10</td>
</tr>
<tr>
<td>Tan TT</td>
<td>1993</td>
<td>Malaysia</td>
<td>43</td>
<td>2.3%</td>
<td>Ionized calcium</td>
<td>3</td>
</tr>
<tr>
<td>Chan TY</td>
<td>1994</td>
<td>China</td>
<td>34</td>
<td>5.9%</td>
<td>Ionized calcium</td>
<td>11</td>
</tr>
<tr>
<td>Chan TY</td>
<td>1994</td>
<td>China</td>
<td>34</td>
<td>14.7%</td>
<td>Albumin-adjusted calcium</td>
<td>11</td>
</tr>
<tr>
<td>Liam CK</td>
<td>1998</td>
<td>Malaysia</td>
<td>120</td>
<td>27.5%</td>
<td>Albumin-adjusted calcium</td>
<td>12</td>
</tr>
<tr>
<td>Roussos A</td>
<td>2001</td>
<td>Greece</td>
<td>88</td>
<td>25.0%</td>
<td>Albumin-adjusted calcium</td>
<td>13</td>
</tr>
<tr>
<td>Dosumu EA</td>
<td>2006</td>
<td>Nigeria</td>
<td>120</td>
<td>27.5%</td>
<td>Albumin-adjusted calcium</td>
<td>14</td>
</tr>
</tbody>
</table>

*Methodology for the diagnosis of hypercalcemia
gamma (IFN-γ)-activated T lymphocytes and alveolar macrophages (16, 17), which results in increased enteric absorption of calcium. In vitro, vitamin D promotes mycobacterial killing in macrophages through production of nitric oxide (18), as well as the antimicrobial peptide cathelicidin LL-37, after activation of macrophages via either Toll-like receptor or IFN-γ release (19, 20), and by inducing phagolysosome fusion and autophagy (20, 21). These effects have been shown to be local (22) and does not normally affect overall calcium homeostasis. In addition, 1,25-(OH)2D3 induces 24-(OH) hydroxylase expression, which deactivates 1,25-(OH)2D3 to calcitriol. However, it is believed that if large quantities of 1,25-(OH)2D3 are produced, a ‘spillover’ effect may occur in the circulation and potentially result in hypercalcemia (23). It should be also kept in mind that RFP and INH may alter concentrations of serum 25-hydroxyvitamin D3 and 1,25-(OH)2D3 and thereby reduce the degree of hypercalcemia. RFP induces several enzymes (CYP3A4, CYP24A1, and uridine 5'-diphospho-glucuronyltransferases) that degrade 25-hydroxyvitamin D3 and, by reducing substrate, reduce 1,25-(OH)2D3 concentrations (24). In contrast, INH inhibits 1,25-(OH)2D3 synthesis (19). Further study is warranted to elucidate the appropriate mechanism of tuberculous hypercalcemia.

In conclusion, we herein report a case of pulmonary tuberculosis with hypercalcemia and hypervitaminosis D and discuss the prevalence and the putative mechanisms of tuberculous hypercalcemia through the review of the literature. While pulmonary tuberculosis is an infrequent cause of hypercalcemia, it should be considered in patients with hypercalcemia and elevated serum level of 1,25-(OH)2D3 especially in the elderly.

CONFLICT OF INTEREST DISCLOSURE

The authors have stated that we have no conflicts of interest.

REFERENCES