

Presentation of latent tuberculosis with elevated calcitriol as the first-presenting sign: A case report

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Abstract

This case report sheds light on an unusual clinical presentation of elevated calcitriol levels and low cholecalciferol, serving as a potential early indicator of latent tuberculosis infection (LTBI). While hypercalcemia, along with the same vitamin D3 picture, has been notably associated with active tuberculosis (TB). What sets this case apart is mildly elevated calcium levels and high calcitriol, all occurring within the context of LTBI. This case report presents a 52-year-old male with mild hypercalcemia and elevated 1,25-dihydroxy vitamin D3 and low 25 hydroxy vitamin D3, revealing a unique biochemical profile. An insignificant chest x-ray with a positive QuantiFERON TB test ultimately confirmed LTBI. The patient was subsequently initiated on a four-month rifampin regimen for LTBI treatment. This case underscores the importance of recognizing elevated calcitriol levels as a potential early sign of latent TB infection.

Keywords: Latent Tuberculosis; 1,25-dihydroxy vitamin D3; QuantiFERON TB test; low 25 hydroxy vitamin D3; Hypercalcemia; Rifampin

1. Introduction

Hypercalcemia can present in several diseases, including primary hyperparathyroidism, familial hypercalcemia, multiple myeloma, malignancy, Vitamin D (VitD) intoxication, and granulomatous diseases. In several studies and case reports, active pulmonary and disseminated Tuberculosis (TB) has been linked with hypercalcemia [1]. The literature has shown hypercalcemia presented along with elevated calcitriol and low 25-(OH) Vitamin D (cholecalciferol) in patients with active TB [2]. However, mildly elevated calcium levels and increased calcitriol levels with low cholecalciferol have never been reported in latent TB Infection (LTBI). In this article, we present a rare case of a 52-year-old man who came for a routine physical examination and was found to have mild hypercalcemia. Investigations revealed elevated calcitriol and low cholecalciferol. On further investigation, no abnormality was found except LTBI. Through this case, we highlight elevated calcitriol as a possible first-presenting sign of latent LTBI.

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2. Case presentation

A 52-year-old man presented to the outpatient clinic to establish primary care. He was healthy with no significant past medical history. He had no complaints at that visit. Physical examination was within normal limits. Routine blood tests were ordered, which included a complete blood count (CBC) and a complete metabolic panel (CMP).

His lab results were within normal limits except for a serum calcium level of 10.5 milligrams per deciliter (mg/dL) (normal- 8.5 to 10.2 mg/dL). It was repeated along with PTH and vitamin D 3 immunoassay to confirm. Repeat calcium and PTH intact came back within normal limits at 10.1 mg/dL and 31 pg/ml, respectively. However, 1,25-Dihydroxyvitamin D3 (calcitriol) was elevated at 77 pg/ml. This discovery led to further investigation with 25 hydroxy vitamin D3 (cholecalciferol) and 24-hour urine calcium levels. 25 OH D report revealed a low level of 20 ng/ml, and 24-hour urine calcium was within the normal range at 125mg/24 hour.

The discrepancy between calcitriol and cholecalciferol warranted further investigation as granulomatous disease was suspected. ACE levels, Interferon-gamma, and chest x-ray were done. ACE levels were normal at 50U/L. However, the QuantiFERON TB test came back positive. Chest x-ray revealed insignificant findings showing mildly hyperexpanded lungs with flattening hemidiaphragm and no focal consolidation (Figure 1). Thus, LTBI infection (formerly called latent TB) was diagnosed.

The patient was started on rifampin 600 mg daily for four months to treat latent TB.



Figure 1 Chest X-ray showing no significant abnormalities indicating Latent TB Infection

3. Discussion

TB remains a global health challenge, with the World Health Organization (WHO) setting ambitious targets in its End TB Strategy. The strategy aims to reduce TB incidence by 90% and TB-related deaths by 95% by the year 2035 [3]. To achieve these goals, it is essential to not only focus on active TB case detection but also to address LTBI through preventative approaches. Preventing LTBI from progressing to active TB is a vital public health objective that can significantly reduce TB transmission. Central to the End TB Strategy is the targeted treatment of individuals infected with LTBI and those at risk of developing active TB disease.

TB, caused by *Mycobacterium tuberculosis*, is a chronic infectious disease characterized by granulomas. It is notably widespread among individuals in lower socioeconomic strata in developing and underdeveloped nations [4]. Elevated levels of calcium in the blood, known as hypercalcemia, often accompanied by increased calcitriol levels, have been observed as a frequent complication in individuals with tuberculosis, whether it affects the lungs (pulmonary) or other parts of the body (extrapulmonary) [2]. The occurrence of hypercalcemia among TB patients can vary considerably, ranging from as low as 2.3% to as high as 28% [5,6]. These variations are thought to be influenced by factors like

differences in Vitamin D and calcium consumption, the amount of exposure to sunlight, and the severity of the disease. It is noteworthy that most TB patients with hypercalcemia, approximately 88%, do not exhibit noticeable symptoms related to elevated calcium levels [7]. Instead, hypercalcemia is often only detected through routine screenings or when complications arise, including neuropsychiatric disturbances, kidney dysfunction, cardiovascular issues, or musculoskeletal problems.

LTBI is a widespread global issue affecting around 25% of the world's population. The duration of LTBI's latent phase can vary greatly, with some individuals harboring the infection for their entire lives. In a minority, estimated at approximately 5% to 15%, LTBI can transition from dormant to active tuberculosis (TB) within the first 2 to 5 years post-infection. This process, known as reactivation, is a crucial concern as it transforms individuals with LTBI into a significant reservoir for new cases of active TB. The reasons underlying LTBI reactivation are multifaceted and involve a complex interplay of bacterial, host, and environmental factors. While the overall risk of reactivation among healthy individuals with LTBI is estimated at 5% to 15%, certain comorbidities and risk factors substantially heighten the likelihood of progression to active TB. Notably, the most significant risk factor is co-infection with the human immunodeficiency virus (HIV). Chronic renal failure requiring hemodialysis, immune-suppressed transplant recipients, and other immunosuppression states increase the risk of active TB disease by over 100-fold. Moderate-risk individuals include those receiving treatment with tumor necrosis factor-alpha (TNF- α) inhibitors, individuals with diabetes, and young children recently infected. Slightly increased risk is linked to alcohol consumption, smoking, and being underweight or malnourished. These conditions share the common feature of compromised immunity, contributing to the heightened risk of LTBI reactivation and a higher incidence of TB within these specific groups compared to the general population [8].

However, this elevated calcium and calcitriol level presentation has not been seen in LTBI so far. In active TB, one plausible hypothesis for the elevated calcium levels could be attributed to the high calcitriol concentrations. This could lead to increased calcium absorption in the intestines and heightened osteoclastic bone resorption. Such an elevation in calcitriol concentrations might be linked to the stimulated activity of 1- α -hydroxylase in macrophages within the granulomatous reaction sites observed in patients with TB or sarcoidosis [9]. However, this phenomenon is not understandable when LTBI is considered as the disease is not widespread and active. We also searched with the terms "Latent TB", "Elevated calcium AND latent TB", and "Latent TB AND elevated calcitriol" on PubMed, Google Scholar, and Web of Science. There was no literature available to talk about these findings in LTBI. Physicians should be aware of this association of elevated calcitriol and mild hypercalcemia in patients with LTBI.

4. Conclusion

In conclusion, tuberculosis (TB) remains a pressing global health challenge, with the World Health Organization's (WHO) End TB Strategy setting ambitious targets to reduce TB incidence and related deaths by 2035. Achieving these goals necessitates a multifaceted approach encompassing the prevention of latent TB infection (LTBI) progression to active disease. TB, caused by *Mycobacterium tuberculosis*, predominantly affects lower socioeconomic strata in developing nations, with hypercalcemia often linked to active TB cases. In contrast, the intricate mechanisms underlying LTBI reactivation are less understood. While elevated calcium and calcitriol levels have been noted in active TB, their presence in LTBI remains underexplored. This knowledge gap highlights the need for further research and heightened physician awareness to comprehend and manage the nuances of LTBI, underscoring the importance of addressing LTBI as a latent TB reservoir to combat this persistent global infectious disease.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest of any kind.

Statement of informed consent

The signed consent from the patient was obtained. We retain the informed signed consent form.

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