

A case of extrapulmonary tuberculosis in a patient with end-stage renal disease with elevated parathyroid hormone–related protein

SAGE Open Medical Case Reports
JCMS Case Reports
Volume 8: 1–4
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2050313X20926421
journals.sagepub.com/home/sco



Shreya Podder¹ , Katarina Fleckenstein² and Zehra Gaudiano¹

Abstract

The diagnosis of extrapulmonary tuberculosis in patients with end-stage renal disease can be challenging as the signs and symptoms are often non-specific. In this study, we present a case of extrapulmonary tuberculosis in an Ethiopian woman with end-stage renal disease who had subcarinal and right hilar lymphadenopathy, moderate sized right pleural effusion, hypercalcemia, and elevated parathyroid hormone–related protein in the setting of an elevated 1,25-dihydroxyvitamin D. After being started on appropriate tuberculosis treatment, patient's parathyroid hormone–related protein level decreased and calcium level normalized. Our literature review showed that the elevation of parathyroid hormone–related protein in extrapulmonary tuberculosis has not been well studied, and it is our aim to explore the role of parathyroid hormone–related protein in extrapulmonary tuberculosis.

Keywords

Infectious diseases, respiratory medicine, extra pulmonary, end-stage renal disease, parathyroid hormone–related protein

Date received: 23 September 2019; accepted: 21 April 2020

Introduction

About one-quarter of the world's population is infected with tuberculosis, with over 9000 cases reported in the United States in 2018. Patients with end-stage renal disease (ESRD), especially those undergoing hemodialysis or peritoneal dialysis, are at an increased risk of developing tuberculosis due to immune depression and dysfunction related to uremia.¹ The clinical manifestations of tuberculosis in patients with ESRD are often non-specific as these patients frequently have extrapulmonary infection. Moreover, there is significant overlap in laboratory test abnormalities in patients with ESRD and patients with extrapulmonary tuberculosis (EPTB); both can present with hypercalcemia, low or normal parathyroid hormone, and variable 1,25-dihydroxyvitamin D levels. In our report, we discuss a case of EPTB with elevated parathyroid hormone–related protein (PTHrP) which has been a useful diagnostic tool in differential diagnosis for humoral hypercalcemia of malignancy, but not well-described in other disease processes.

Case presentation

Our patient is a 42-year-old female who had presented in Ethiopia with vague symptoms of a few months of fatigue,

weakness, and unintentional weight loss of 3–4 kg. She was subsequently diagnosed with renal failure, requiring hemodialysis. The etiology of her renal failure was unclear. She went to India to see if she could obtain another explanation for her symptoms and continued hemodialysis there. Due to a lack of improvement in her symptoms, she came to the United States for different treatment options.

She presented initially to an American hospital with dyspnea and volume overload. She underwent a chest X-ray for dyspnea (Figure 1) which was largely unremarkable. A computed tomography (CT) angiography of her chest was negative for pulmonary embolism, but notable for non-specific lymphadenopathy and small right-sided pleural effusion. She also underwent CT imaging of her abdomen and pelvis which noted multiple small renal cysts bilaterally, which were too small to characterize. Her symptoms were thought

¹Department of Internal Medicine, Inova Fairfax Medical Campus, Falls Church, VA, USA

²Inova Fairfax Medical Campus, Falls Church, VA, USA

Corresponding Author:

Shreya Podder, Department of Internal Medicine, Inova Fairfax Medical Campus, Falls Church, VA 22003, USA.
Email: podder.shreya123@gmail.com





Figure 1. Mild atelectasis at the right base.

to be secondary to ESRD, and she was advised to continue outpatient hemodialysis.

She presented again to the hospital two-and-a-half months later with progressive dyspnea on exertion and right-sided chest pain. The patient denied any hemoptysis, nausea, vomiting, diarrhea, or prior exposure to tuberculosis. Patient had a negative cardiac workup. She underwent another CT angiography of her chest which showed no pulmonary embolism, but now showed loculated right pleural effusion (Figure 2(a)), subcarinal and right hilar adenopathy (Figure 2(b)). Thoracentesis was performed. Analysis of the pleural fluid revealed it was an exudative effusion (pH 7.8, white blood cells 1083 cells/mm³, 24% lymphocytes, <25% polymorphonuclear cells, glucose 84 mg/dL, and Lactate dehydrogenase 270 U/L) with moderately elevated adenosine deaminase (ADA, 57.6 U/L) level. Fungal culture and gram stain of pleural fluid did not reveal any fungal or bacterial organisms. She produced two sputum samples which were both negative for acid fast bacilli smear and culture. Patient was also found to have persistent hypercalcemia (11.7–12.8 mg/dL), elevated 1,25-dihydroxyvitamin D (131 pg/mL), normal parathyroid hormone level (53.8 pg/mL), and surprisingly elevated PTHrP (52 pg/mL). At this point, there was concern for malignancy such as lymphoma, but the pleural fluid did not show any malignant cells and peripheral flow cytometry did not show any abnormal T or B cells. Endobronchial ultrasound was performed with biopsy of lymph node showing necrotic tissue, with insufficient cells to send for lymphoma stains. She was also found to have a positive quantiferon, but negative acid fast stain of bronchoalveolar lavage and sputum samples. She underwent a right pleural biopsy as well, with results pending when patient was

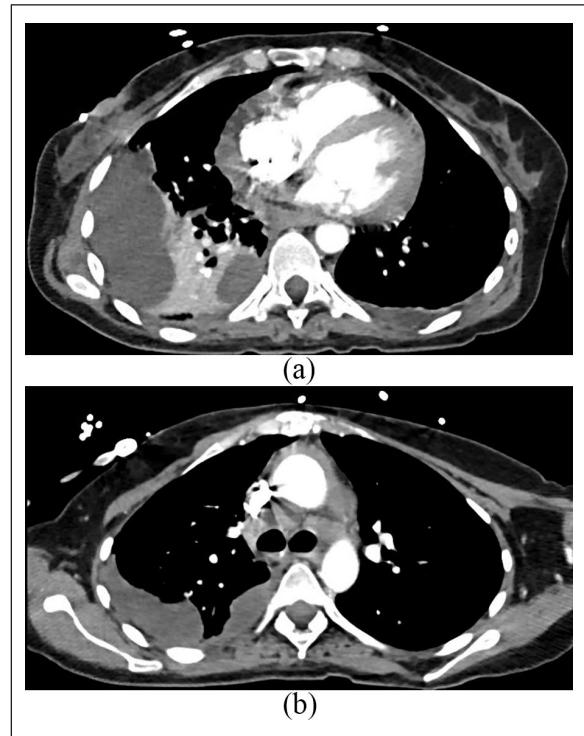


Figure 2. (a) Loculated right pleural effusion. (b) Subcarinal and right hilar lymphadenopathy.

discharged from the hospital. Patient was hemodialyzed, treated with 9-day course of piperacillin-tazobactam for fevers of unknown origin, and advised to follow-up in clinic.

She presented a week later with similar complaints and worsening tachycardia during her hemodialysis sessions. Chest radiograph showed moderate right pleural effusion with consolidation throughout right lung base. Serum leukemia/lymphoma panel was negative. Patient underwent mediastinoscopy with excisional lymph node biopsy as her previous fine needle aspiration was non-diagnostic. The biopsy of the lymph node showed necrotizing granulomas (Figure 3). Eventually, the acid fast stain of the pleural biopsy sample resulted and showed growth of mycobacterium tuberculosis. Patient was started on medications that were weight-based (patient's weight 48.1 kg), which included oral rifampin 600 mg daily, isoniazid 300 mg daily, pyrazinamide 1500 mg three times a week after dialysis, and ethambutol 1200 mg three times a week after dialysis. Drug susceptibility testing indicated that the mycobacteria was sensitive to the medication regimen. One week after starting therapy, patient's PTHrP decreased to 35 pg/mL and normalization of serum calcium concentration (9.9 mg/dL) occurred. Patient's fevers, tachycardia, and chest pain improved on these antibiotics.

Discussion

The risk of developing EPTB is more prevalent in patients with ESRD compared to the general population. Patients undergoing chronic hemodialysis are about 6–16 times more

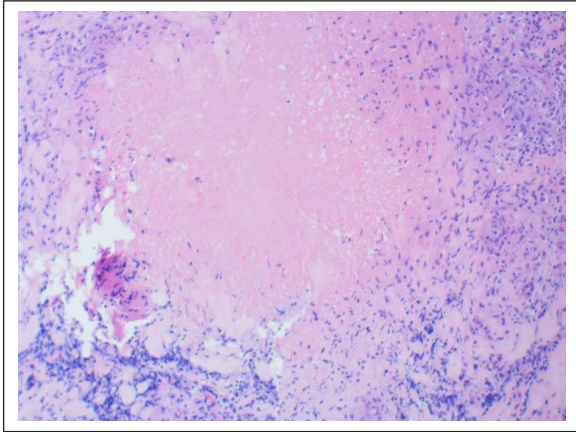


Figure 3. Necrotizing granuloma found on pleural biopsy.

likely to develop tuberculosis due to impaired cellular immunity.² Patients with EPTB often present with nonspecific symptoms, making the diagnosis of EPTB very challenging. The most common presentations of EPTB include non-tender lymphadenopathy, gastrointestinal symptoms, pleural effusions, pericardial effusions, and fevers of unknown origin.³ Currently, culture confirmation of tuberculosis remains the gold standard for diagnosis, and growing the bacteria is required to perform drug-susceptibility testing and genotyping, with the most common source being a sputum sample. Patients with EPTB typically lack a productive cough, thus obtaining sputum samples for acid-fast bacilli (AFB) stains is often not a feasible task. Even when patients can produce sputum, the AFB stain is usually negative. Laboratory findings are also non-specific and include elevated erythrocyte sedimentation rate (ESR), anemia, lymphopenia, thrombocytosis, and hypoalbuminemia.⁴ Under these circumstances, it can take weeks before disease confirmation.

The Mantoux tuberculin skin test (TST) measures the delayed-type hypersensitivity response to intradermal injection of tuberculin purified protein derivative (PPD), and is commonly used as a screening tool and as a diagnostic aid for tuberculosis. TST, however, may fail to detect tuberculosis infection in high-risk groups, such as patients with ESRD undergoing dialysis due to the prevalence of anergy. Given the poor sensitivity of the test in immunocompromised patients, a negative TST cannot be used to rule out the possibility of latent or active tuberculosis infection.⁵ Different strategies have been proposed to improve the sensitivity of the TST in patients undergoing dialysis, including lowering the TST threshold for a positive test in these patients and two-step testing with repeat PPD injection to induce booster effect to reduce the number of false negative TST.⁶ Unfortunately, this improvement in sensitivity comes at the expense of the specificity of TST. T-cell-based interferon-gamma release assays (IGRAs), such as the T-SPOT.TB assay and the QuantiFERON-TB Gold test, have better specificity for the diagnosis of active tuberculosis in patients

undergoing dialysis,⁷ but are comparable to TST for detecting latent tuberculosis infection. Studies have also suggested that QuantiFERON-TB Gold test can show indeterminate results in up to 40% of cases.⁸

Our patient had initially complained of right chest discomfort and received CT imaging of her chest, which showed lymphadenopathy and right-sided pleural effusion. Patients with EPTB often undergo radiological investigations with the recommended imaging modality being CT and magnetic resonance imaging. A common finding on imaging is lymphadenopathy. Tuberculous lymphadenopathy most commonly affects cervical, mediastinal, and axillary lymph nodes. However, imaging alone cannot distinguish between causes of lymphadenopathy, as was the case in our patient.⁹

Pleural effusion is a common finding in patients with EPTB and ESRD. Our patient's right-sided pleural effusion was exudative in nature. It is important to note that uremia is the most common cause of exudative pleural effusions in patients with ESRD, even in countries with endemic tuberculosis. ADA is a protein produced by various cells in the body and is associated with the activation of lymphocytes. Thus, infections such as tuberculosis which trigger the immune system can lead to increased levels of ADA. In fact, the ADA level in pleural effusions are sometimes used in the diagnosis of tuberculosis infection, but low ADA levels are not enough to rule out tuberculosis infections.¹⁰ Per our institution's laboratory test, patients with tuberculosis had mean ADA level of 92.1 U/L. Though our patient's ADA level was elevated, it was well below this mean. This could be explained by the routine hemodialysis. In patients with chronic kidney disease, hemodialysis was found to be a confounding factor as it reduces ADA levels.¹¹ Thus, the diagnosis was unable to be made based upon our patient's ADA levels.

The outstanding laboratory findings in our patient were the elevated calcium and PTHrP levels. Severe hypercalcemia, although rare, is a manifestation of pulmonary tuberculosis.¹² In these cases, hypercalcemia is due to an over-abundance of extra-renal 1-alpha hydroxylase activity, which increases conversion of 1 vitamin D to 1,25-vitamin D, thus increasing calcium absorption in the gut. Inappropriate PTHrP production has been generally associated with malignancies, where it acts as the primary contributor of hypercalcemia and also has prognosis value in non-metastatic solid tumors.¹³ Case reports also show PTHrP as a mediator of hypercalcemia in granulomatous disease such as sarcoidosis.¹⁴ PTHrP and parathyroid hormone share similar mechanisms of actions including enhancing bone resorption, renal calcium reabsorption, and stimulates 1 α -hydroxylase resulting in increased 1,25-OH vitamin D concentrations. The regulation of PTHrP by macrophages in infectious granulomatous states is unclear. To our knowledge, there is only one recorded case of peritoneal tuberculosis presenting with hypercalcemia secondary to elevated PTHrP, with eventual decrease in PTHrP level and normalization of calcium levels after starting tuberculosis treatment.¹⁵

Conclusion

It is possible that the elevated PTHrP in our patient was related to her renal failure. However, given that the patient's PTHrP level and serum calcium level decreased after starting tuberculosis treatment, it is likely that her PTHrP is associated with tuberculosis. Moreover, patient had a negative malignancy workup, which strengthens our argument for her elevated PTHrP. Our case highlights the possibility of PTHrP as a marker for diagnosis and response to tuberculosis treatment. Further work is needed to establish the clinical significance of PTHrP in EPTB.

Acknowledgements

The authors thank Drs Chad Zik and Tejasri Chandrabhatla for providing care for this patient. The authors thank Dr Dan Qi for the pathology image.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

Shreya Podder  <https://orcid.org/0000-0001-6035-5637>

References

- Shankar MSR, Aravindan AN, Sohal PM, et al. The prevalence of tuberculin sensitivity and anergy in chronic renal failure in an endemic area: tuberculin test and the risk of post-transplant tuberculosis. *Nephrol Dial Transplant* 2005; 20(12): 2720–2724.
- Wauters A. The value of tuberculin skin testing in haemodialysis patients. *Nephrol Dial Transplant* 2004; 19: 433–438.
- Abdelrahman M, Sinha A and Karkar A. Tuberculosis in end-stage renal disease patients on hemodialysis. *Hemodial Int* 2006; 10: 360–364.
- Yang W-F, Han F, Zhang X-H, et al. Extra-pulmonary tuberculosis infection in the dialysis patients with end stage renal diseases: case reports and literature review. *J Zhejiang Univ Sci B* 2013; 14(1): 76–82.
- Chau T, Leung V, Wong S, et al. Diagnostic challenges of tuberculosis peritonitis in patients with and without end-stage renal failure. *Clin Infect Dis* 2007; 45(12): e141–e146.
- Dogan E, Erkoc R, Sayarlioglu H, et al. Tuberculin skin test results and the booster phenomenon in two-step tuberculin skin testing in hemodialysis patients. *Ren Fail* 2005; 27(4): 425–428.
- Inoue T, Nakamura T, Katsuma A, et al. The value of QuantiFERON®TB-Gold in the diagnosis of tuberculosis among dialysis patients. *Nephrol Dial Transplant* 2009; 24: 2252–2257.
- Thiers B. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with mycobacterium tuberculosis: a prospective study. *Lancet* 2006; 367: 1328–1334.
- Gambhir S, Ravina M, Rangan K, et al. Imaging in extrapulmonary tuberculosis. *Int J Infect Dis* 2017; 56: 237–247.
- Kumar S, Agarwal R, Bal A, et al. Utility of adenosine deaminase (ADA), PCR & thoracoscopy in differentiating tuberculous & non-tuberculous pleural effusion complicating chronic kidney disease. *Indian J Med Res* 2015; 141: 308–314.
- Ahluwalia G. Exudative pleural effusion in chronic kidney disease: an aetiological dilemma. *Indian J Med Res* 2015; 141(3): 269–270.
- Rajendra A, Mishra A, Francis N, et al. Severe hypercalcemia in a patient with pulmonary tuberculosis. *J Family Med Prim Care* 2016; 5(2): 509–511.
- Wysolmerski JJ. Parathyroid hormone-related protein: an update. *J Clin Endocrinol Metab* 2012; 97: 2947–2956.
- Krikorian A, Shah S and Wasman J. Parathyroid hormone related protein: an unusual case of hypercalcemia in sarcoidosis. *Endocr Pract* 2011; 4: e84–e86.
- Melamed K, Reid W and Martinez D. Peritoneal tuberculosis causing elevated parathyroid hormone-related protein: a case report. *Proc UCLA Healthcare* 2012; 16: 1–3.