CLINICAL VIGNETTE

Peritoneal Tuberculosis Causing Elevated Parathyroid Hormone-Related Protein: A Case Report

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Abstract

Peritoneal tuberculosis (TB) is a relatively rare manifestation of TB in the United States, although it is more common among foreign-born or immuno-compromised patients. Signs and symptoms of the disease are often non-specific and can mimic other processes such as spontaneous bacterial peritonitis or malignancy, which can delay diagnosis. Here, we report a case of peritoneal TB in a patient with end-stage renal disease who had hypercalcemia, elevated parathyroid hormone-related protein (PTHrP), peritoneal carcinomatosis, and a negative work up for malignancy. To our knowledge, this is the first case of clinically elevated PTHrP due to tuberculosis and it could have implications for expediting diagnosis in the future.

Case Report

A 48-year-old Korean-born man with end-stage renal disease secondary to hypertension, on hemodialysis, presented to the emergency department with a one-month history of diffuse abdominal pain, increasing abdominal girth, and a low-grade fever. The patient did not report change in skin color, bowel patterns, or lower extremity edema. On admission he was in no distress with temperature of 37.9^{o}C, heart rate 106 beats per minute, and blood pressure of 131/90 mmHg. He was anicteric, with normal cardiac and lung exams except for mild tachycardia. Abdomen was non-tender and was free of organomegaly. He had bilateral 1+ pitting edema to the knee. The remainder of the exam was unremarkable. Chest radiography showed bilateral, basilar pleural effusions. Labs revealed a white blood cell (WBC) count of 5.44x10^{3}/μL, hemoglobin of 8.9 g/dL, platelets of 373x10^{3}/μL, albumin of 3.1 g/dL, and corrected calcium of 11.7 mg/dL. The patient's liver panel, lipase, and lactate were within normal limits. Ascitic fluid analysis revealed WBC count of 405/mm^{3} (with 3% neutrophils, 33% lymphocytes, and 61% monocytes), albumin of 2.0 g/dL, adenosine deaminase (ADA) of 9.7 U/L, lactate dehydrogenase (LDH) of 181 U/L, and negative Gram stain and culture. Acid fast bacteria (AFB) stain, mycobacterial culture, mycobacterial polymerase chain reaction (PCR), and cytology from the ascitic fluid were all negative. 1,25-dihydroxy vitamin D (1,25-vit D) was elevated at 91 pg/mL, PTHrP was elevated at 65 pg/mL (normal range 14-27 pg/mL), parathyroid hormone (PTH) was in the normal range at 45 pg/mL, and 25-hydroxy vitamin D (25-vit D) was low at 14 ng/m. Thyroid studies, angiotensin converting enzyme level, *Histoplasma* serum antigen, and *Coccidioides* enzyme immunoassay were negative or within normal limits. He had a positive QuantiFERON-TB Gold test and negative purified protein derivative (PPD).

Abdominal computerized tomography (CT) revealed ascites and peritoneal enhancement of infectious, inflammatory, or neoplastic etiology. Alpha-fetal protein, carcinoembryonic antigen, and cancer antigen 19-9 were within normal limits. Cancer antigen 125 was elevated at 203 U/mL. A peritoneal biopsy was performed and revealed granulomatous inflammation. The patient was empirically started on four-drug therapy for tuberculosis with resolution of his fever, abdominal pain, and hypercalcemia. PTHrP and 1,25-vit D levels improved with treatment to 44 pg/mL and 18 pg/mL respectively. PCR results from the biopsy returned two weeks later revealing that the sample was positive for *Mycobacterium tuberculosis* DNA. Respiratory cultures, while all negative on AFB stain, eventually grew out *Mycobacterium tuberculosis* and *Mycobacterium gordonae* weeks after presentation. On follow up one week after discharge the patient reported that his symptoms had continued to resolve and he was feeling well.

Discussion

Patients with end-stage renal disease have a 6.9 to 52.5-fold increased risk of TB due to impaired cellular immunity that is a result of both end-stage renal disease and dialysis. Furthermore, peritoneal TB alone makes up 37% of the total number of TB cases in this patient population[1]. Diagnosis can often be a challenge as abdominal pain, fever, weight loss, or ascites may be present in only 59-73% of cases[2]. In addition, PPD tests are often falsely negative due to anergy, and symptoms that are commonly associated with TB, such as cough and hemoptysis, are less common in patients with end-stage renal disease[1-3]. Other commonly reported laboratory findings include elevated erythrocyte sedimentation rate, anemia, lymphopenia, thrombocytosis, and hypoalbuminemia, are all non-specific and can also present in bacterial peritonitis[2, 3].

Ascitic fluid analysis is similarly non-specific. WBC count can range from 10-4700/mm^3 with a median value of 310/mm^3, and tends to be lymphocyte predominant, although neutrophil predominance has also been reported[2-4]. LDH level greater than 90 U/L has been reported to be 90% sensitive but only 14% specific for peritoneal TB[2]. AFB stains are positive in only 3% of patients and ascitic cultures are only 35% sensitive. Moreover, when the AFB stain is negative, *Mycobacteria tuberculosis* PCR is only 48% sensitive[2, 3]. The most promising ascitic fluid diagnostic test is the ADA level, whose sensitivity and specificity are both greater than 90% when using cut off values of 30 U/L[2]. Furthermore, a recent meta-analysis showed that ADA values of greater than 39 U/L are 100% sensitive and 97% specific for peritoneal tuberculosis[5].

Imaging studies can give diagnostic clues but are neither sensitive nor specific for peritoneal TB. Chest x-ray has been shown to be abnormal in only 38% of cases[2]. Abdominal CT can reveal ascites, peritoneal thickening, omental caking, and lymphadenopathy[3, 4]. However, the sensitivity of CT is only 69%, and the CT can often be confused for peritoneal carcinomatosis[2].

Peritoneal biopsy with AFB stain and AFB culture is the only definitive diagnostic test for peritoneal TB[4]. Histologic findings of caseating granulomatous disease have a sensitivity and specificity of 85-100% and 98% respectively[2, 4]. Reliance on ascitic fluid culture alone not only has low yield, but can delay treatment[5]. One study showed peritoneal TB mortality was as high as 60% when treatment was started 30 days after symptom onset[6]. Thus, early peritoneal biopsy is advantageous, but because patients present with non-specific symptoms and signs, time to biopsy is often delayed[1].

Peritoneal tuberculosis remains difficult to diagnose with significant morbidity and mortality due to delayed treatment. This patient was no exception. The patient had low ascitic fluid ADA and did not meet diagnostic criteria of peritoneal TB. He also had elevated PTHrP, which diverted focus from infectious to malignant etiologies. The final diagnosis was not established until peritoneal biopsy revealed caseating granulomas and *Mycobacterium tuberculosis* DNA weeks after presentation.

To our knowledge, this is the first report of elevated serum PTHrP due to peritoneal tuberculosis. PTHrP is classically associated with paraneoplastic syndromes, particularly in lung cancer, breast cancer, and lymphoma[7]. However, evidence from case reports and case series suggests that PTHrP can be secreted with inflammation or granulomatous disease. PTHrP can be secreted from the liver with inflammation from the endotoxemia and from the synovium in the setting of rheumatoid arthritis [8]. Additionally, in some cases of renal failure with subsequent parathyroid gland hyperplasia, the parathyroid gland has been shown to secrete PTHrP in addition to PTH[7], and the kidney itself has been shown to secrete PTHrP[9]. Granulomas have been shown to secrete PTHrP[7, 10, 11] in cases of sarcoid and serratia marceseus. One study demonstrated PTHrP in pulmonary tuberculosis granulomas although there was no correlated elevation in serum PTHrP or demonstrated clinical significance[12]. Thus, to our knowledge elevated serum PTHrP resulting from tuberculosis has not been described to date.

In our patient, the PTHrP elevation could be related to chronic renal failure and/or possible hyperparathyroidism. However, given that his serum PTHrP levels decreased significantly and calcium normalized with tuberculosis treatment, it is likely that the PTHrP was associated with tuberculous disease. Additionally, no malignancy was found during workup, further supporting the conclusion that the tuberculous granulomas were secreting PTHrP themselves.

The clinical significance of elevated PTHrP in granulomatous disease has yet to be established, but the possible link to granuloma formation and inflammation make it a potential marker of disease. Future work could determine if elevated PTHrP is

found in other cases of peritoneal tuberculosis, and if it can aid in diagnosis and monitoring treatment.

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