Atypical presentation of disseminated tuberculosis

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Abstract

Disseminated Tuberculosis is a potentially lethal disease if not diagnosed and treated early. Therefore a high index of clinical suspicion for early diagnosis and timely institution of anti-tuberculosis treatment is important. We report a case of an elderly female who presented with complaints of weight loss, generalised fatigue, altered sensorium and moderate hypercalcemia. Investigations excluded multiple myeloma and hyperparathyroidism. A PET scan to rule out occult malignancy showed suspicious uptake in juxtaphrenic nodes and terminal ileum. Biopsy of lymph nodes showed granulomatous inflammation with detection of Mycobacterium tuberculosis by GeneXpert. Culture of the tissue yielded Mycobacterium tuberculosis. The patient showed good clinical response to anti-tuberculosis treatment.

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Introduction

Tuberculosis can present in different ways which may pose difficulties in diagnosis. Extra pulmonary tuberculosis infections often lack typical clinical symptoms and imaging features. It can potentially be easily misdiagnosed leading to a delay in treatment.

Case Presentation

A 72-year-old female, with no known comorbidities, presented with complaints of 8kg weight loss in the last two months, loss of appetite, generalised fatigue and a recent onset of altered sensorium which lasted for one week. The patient did not report fever, cough, shortness of breath, haemoptysis, swelling of legs or abdominal symptoms. On clinical examination, the patient was confused (Mini mental state examination score of 14; normal score 24-30), but haemodynamically stable. A respiratory system examination revealed dull note and decreased breath sounds in both lung bases.

Initial investigations showed total leukocyte count 5.7K/ul (normal range 4-10K/ul), raised ESR of 100 mm/hr (normal range 20-35mm/hr), raised serum protein 9.2g/dl (normal range 6.4-8.3g/dl), hypoalbuminemia of 2.8g/dl (normal range 3.6-5.1 g/dl), hyperglobulinemia of 6.0g/dl (normal range 2-3.5 g/dl) with albumin/globulin (A/G) ration reversal of 0.5. Serum Lactate dehydrogenase of 162 U/L (normal range 135-214 U/L). Serum Calcium was elevated at 13.5 mg/dl (normal range 8.6 -10.2mg/dl) and CT Thorax shows bilateral pleural effusion (Figure 1). A diagnostic thoracentesis and pleural fluid analysis showed protein 5.7g/dl (normal range 1-2 g/dl), sugar 104 mg/dl (normally similar to plasma), Lactate dehydrogenase 167.3 U/L (normally less than 50% of serum LDH). Pleural fluid adenosine deaminase level (ADA) level was of 20.8 U/L (normal range 0-40U/L). Cytology revealed 85% lymphocytes (normal less than 50%). This low ADA was inconclusive to consider the possibility of tuberculosis despite being a lymphocytic exudative effusion. Thus further evaluation was carried out.

Figure 1 CT thorax (axial plane) showing bilateral pleural effusion (black arrows)

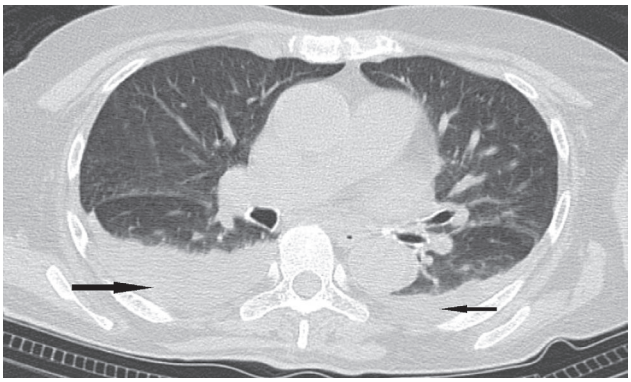

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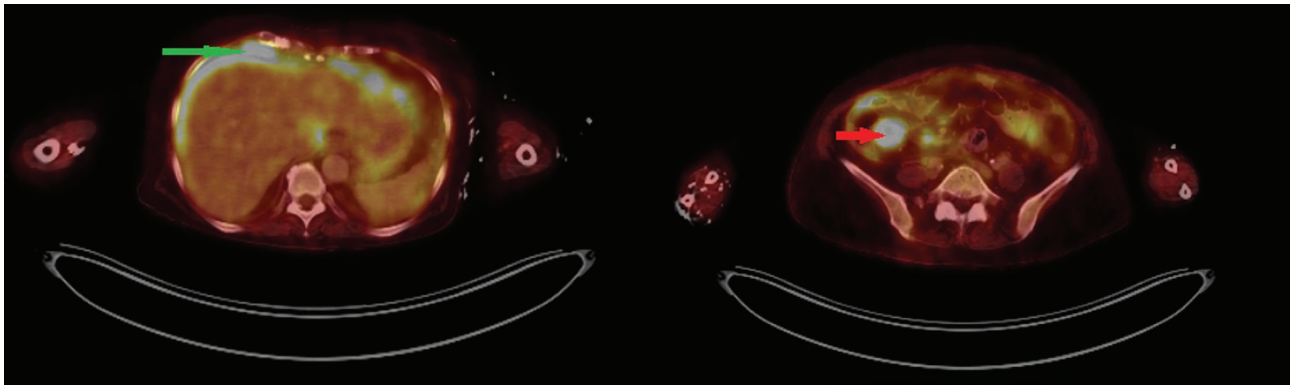
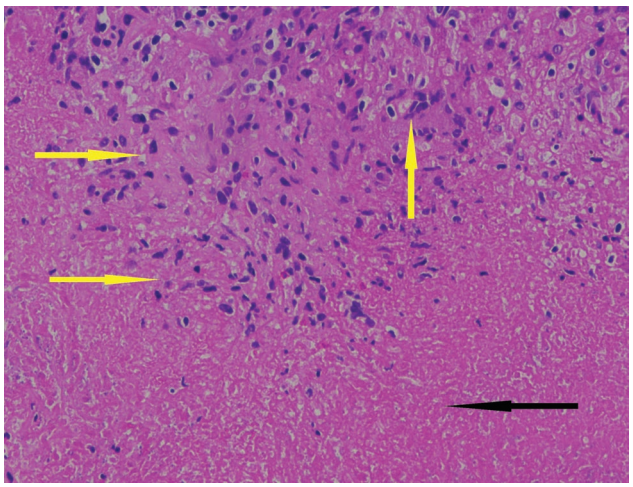
Figure 2 PET scan showing uptake in diaphragmatic nodes (green arrow), terminal ileum (red arrow)



As serum intact PTH was low at 7.3pg/ml (normal range 14.0-72pg/ml), hyperparathyroidism was ruled out. Her hypercalcaemia was managed with intravenous hydration and Zoledronic acid. Serum electrophoresis showed polyclonal gammaglobulinemia but no paraproteins. Multiple myeloma panel (by FISH technique) was negative for any chromosomal abnormalities. Bone marrow biopsy showed trilineage haematopoiesis with few scattered plasma cells. Urine Bence Jones proteins was negative. Serum free kappa/lambda ratio was normal. The patient underwent a whole body PET scan which revealed FDG avid multiple supra and infra-diaphragmatic, paracardiac lymph nodes and diffuse peritoneal uptake with multiple pericolic necrotic lymph nodes with circumferential wall thickening and luminal narrowing of terminal ileum (Figure 2). CT guided biopsy from PET avid lesion from juxtaphrenic lymph nodes was performed. Examination of biopsy specimen showed features of granulomatous inflammation with extensive necrosis (Figure 3). Rapid molecular test for tuberculosis, Xpert MTB/RIF assay of lymph node biopsy also detected mycobacterium tubercle bacillus which was sensitive to rifampicin. We initiated anti-tubercular treatment (two months of intensive phase with Isoniazid 300mg, Rifampicin 450mg, Pyrizinamide 1200mg, Ethambutol 800mg and four months of continuation phase with Isoniazid 300mg, Rifampicin 450mg and Ethambutol 800mg).

Figure 3 Histopathologic examination of lymph node showing granulomatous inflammation (yellow arrow) with necrosis (black arrows).



After six weeks, AFB culture of the biopsy specimen by Mycobacterial Growth Indicator Tube (MGIT) liquid culture technique also showed the growth of Mycobacterium Tuberculosis. The patient showed good clinical response to antitubercular treatment. Her altered sensorium can be attributed to hypercalcaemic status, which showed improvement in two weeks with correction of serum calcium. Her appetite improved in four weeks with a weight gain of 6kg with six months of antitubercular treatment.

Discussion

Disseminated tuberculosis is defined as having two or more non-contiguous sites resulting from lympho-haematogenous dissemination of Mycobacterium tuberculosis. Extrapulmonary involvement occurs in one-fifth of all Tuberculosis cases and it may occur in the absence of histological and radiological evidence of pulmonary infection.

In this case, the patient had hypercalcaemia as a metabolic abnormality and minimal pleural effusion as a radiological abnormality. As pleural fluid results were of low ADA and a lymphocytic exudative effusion, it presented a diagnostic dilemma. Measurement of the ADA level in pleural fluid is diagnostically useful because it tends to be higher in pleural effusion of tubercular origin. In this case, a negative ADA report would have justified abandoning further diagnostic procedures for TB, and pursuing alternative diagnoses.

The evaluation for hypercalcaemia was suggestive of a parathyroid independent hypercalcaemia. Possibility of paraproteinemia was ruled out. Though the PET scan was carried out with the aim of ruling out malignancy, the unexpected detection of suspicious lesions and a timely intervention with biopsy resulted in confirmatory diagnosis of TB.

The Xpert MTB/RIF is a cartridge based nucleic acid amplification test for simultaneous rapid tuberculosis diagnosis and a rapid antibiotic sensitivity test. It is an automated diagnostic test that can identify mycobacterium tuberculosis DNA and resistance to rifampicin. The diagnostic accuracy of Xpert in lymph node samples showed sensitivities ranging from 83 to 96% and specificities ranging from 86 to 94%[1]. This test has higher specificity for the diagnosis in smear negative and extrapulmonary specimens.

Hyperparathyroidism and malignancy account for 80–90% of cases of hypercalcaemia. Hypercalcaemia is known to occur in granulomatous disease, most commonly in sarcoidosis and has also been reported in tuberculosis[2,3]. The incidence of hypercalcaemia in TB has been variably reported as ranging from 2% to 25% depending on multiple factors including geographical area, Vitamin D and calcium intake and exposure to sunlight[4]. Hypercalcaemia in TB is usually mild and asymptomatic. Mechanism of hypercalcaemia in TB is considered to be due to the extra-renal production of 1,25(OH)2D3 by alveolar macrophages and T lymphocytes possibly CD8 T lymphocytes[5]. However hypercalcaemia independent of the aforementioned mechanism has also been reported. Activated Vitamin D plays an important role in the regulation of granulomatous inflammation and influences the cell-mediated immunity to tuberculosis. Treatment of hypercalcaemia in patients with TB is aimed at controlling tuberculosis infection to decrease calcitriol synthesis and directly lower blood calcium levels. Initial treatment should involve aggressive hydration with a loop diuretic such as furosemide, avoidance of thiazide diuretics, use of calcitonin and bisphosphonates. Low-dose glucocorticoid therapy also plays a role in hypercalcaemia treatment especially if it is severe or refractory hypercalcaemia associated with mycobacterium tuberculosis[6].

Conclusion

Tuberculosis is a common disease with various atypical presentations. Hypercalcaemia is commonly caused by hyperparathyroidism and malignancy. However, granulomatous diseases, especially tuberculosis, must be considered as one of the probable causes in patients who present with hypercalcaemia with coexistent pleural effusion. This case report highlights the need to consider rare presentations of a common disease in difficult case scenarios.

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