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Raised ADA in exudative pleural fluid with positive exposure is not tubercular

[1]Swetha Narayanan, [1]Madhav Banjade, [1]Prasan Kumar Panda, [1]Rajat Ranka

Department of Medicine (ID Division)[1], All India Institute of Medical Sciences, Rishikesh, Uttarakhand 249203, India

Email ids: swethanarayanan26053@gmail.com, Madhav6541@yahoo.com, motherprasanna@rediffmail.com, ranka.rajat95@gmail.com

Corresponding Author: Prasan Kumar Panda, motherprasanna@rediffmail.com

Abstract

Parapneumonic effusions are more familiar with bacterial pneumonia than viral pneumonia. In a tuberculosis-endemic country like India, viral parapneumonic effusions can be misdiagnosed as tubercular effusions and unnecessarily treated with antitubercular therapy. Here, we present an observational single case study of a middle-aged female who presented with shortness of breath a few days following an episode of atypical pneumonia. On examination, she was in acute respiratory distress with reduced air entry on the right side of her chest. Chest radiograph showed right-sided pleural effusion, which was exudative with lymphocytic predominance on diagnostic thoracocentesis with raised ADA level. Workup on pleural fluid was negative for bacteria as well as tuberculosis. Therapeutic thoracocentesis was done to relieve dyspnea, and she was managed conservatively without any antimicrobial therapy. It was thus a case of simple parapneumonic effusion, which, if misdiagnosed as tuberculous effusion considering its endemicity, would have resulted in unwanted exposure of the patient to antitubercular drugs and the associated drug side effects. This case study proves that contact exposure and exudative pleural effusion are not pathognomonic of tuberculosis.

Keywords: Antitubercular drugs, Parapneumonic effusions, Therapeutic thoracocentesis, Viral pneumonia

Introduction

Parapneumonic effusions are common complications of bacterial pneumonia. Bacteria such as Streptococcus pneumonia, oral streptococci and anaerobes, and Staphylococcus aureus are the

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most common causes of parapneumonic effusions [1]. The reported prevalence of viral parapneumonic effusion is 10% [2]. Tuberculosis (TB), however, is the leading cause of pleural effusion in developing countries like India [3]. Tuberculous pleural effusions (TPE) occur due to the reactivation of the disease or primary tuberculosis. In endemic areas, for all patients with unilateral pleural effusion, TB should be appropriately considered and ruled out. However, given the high rates of TB in these areas, patients may be incorrectly assumed to have TB and treated based on clinical suspicion alone. In 2020, only 60% of the 4.8 million people diagnosed with pulmonary TB worldwide were microbiologically confirmed. Other patients were diagnosed and treated with antitubercular drugs based on symptoms or signs and radiological evidence [4]. Uncomplicated viral parapneumonic effusion can be managed conservatively without antimicrobial therapy or interventions.

Here, we present a viral parapneumonic effusion case study, which resolved with time.

Case Presentation

A middle-aged female from North India with a positive pulmonary TB contact history with her son for one month, 5-years before was admitted to our hospital one week before her current admission with a history of low-grade fever of one day duration, which was associated with myalgia and headache along with the history of insidious onset shortness of breath for four days. There were bilateral diffuse crepitations on chest examination at presentation, and CECT thorax showed consolidation and ground glass opacities in bilateral lungs. Bronchoalveolar lavage (BAL) sample workup during that admission was negative for microorganisms, including mycobacterium. She was diagnosed with community-acquired bacterial pneumonia and treated with antibiotics (ceftriaxone and azithromycin) and discharged in stable condition on the resolution of her symptoms. She presented to us again within a week with complaints of worsening shortness of

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breath for four days after discharge from the hospital. It was associated with a dry cough and sharp pleuritic-type right-sided chest pain. She also complained of orthopnea. There was no history of fever, rashes, joint pain, pedal edema, or decreased urine output. She had no history of night sweats, decreased appetite, or weight loss. She was a reformed bidi smoker and did not have any prior comorbidities.

On examination in the outpatient clinic, she was tachypneic, and tachycardia was present. There was reduced vocal fremitus, and stony dullness on percussion on the right side was felt. Air entry was reduced in the right infra-scapular, axillary, and mammary areas. The rest of the examinations were within normal limits. She was admitted for a detailed evaluation of pleural effusion.

The patient had presented with gradual worsening shortness of breath, one week after discharge from a tertiary hospital, associated with right-sided pleuritic chest pain. It was essential to rule out pulmonary thromboembolism, hospital-associated pneumonia, and heart failure. The patient had a contact history of tuberculosis, and being in a tuberculosis-endemic country, it had to be ruled out. It was an uncomplicated pleural effusion, and given the history of atypical pneumonia a few weeks back, viral parapneumonic effusion should also be kept as a possible differential and was considered the most likely diagnosis.

Her complete blood count, kidney function, and liver function tests were within normal limits. The chest radiograph revealed a right-sided pleural effusion (Fig 1A). CT pulmonary angiography was done to rule out pulmonary thromboembolism, which revealed only right-sided pleural effusion. 2D echocardiography, myocardial injury biomarkers, and brain natriuretic peptide (BNP) levels were within normal limits. Diagnostic pleural tapping was done, which was exudative as per Light's criteria, with monomorphic predominance with protein of 5.6g/dl corresponding serum

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protein of 7.7g/dl (normal range, 6-8g/dl) and LDH of 311 U/Lwith corresponding serum level 368 U/L (normal range, 14-280U/L). All three *Lights criteria* for exudative pleural fluid were present, and considering the high sensitivity and specificity, it supported the exudative effusion finding [5].

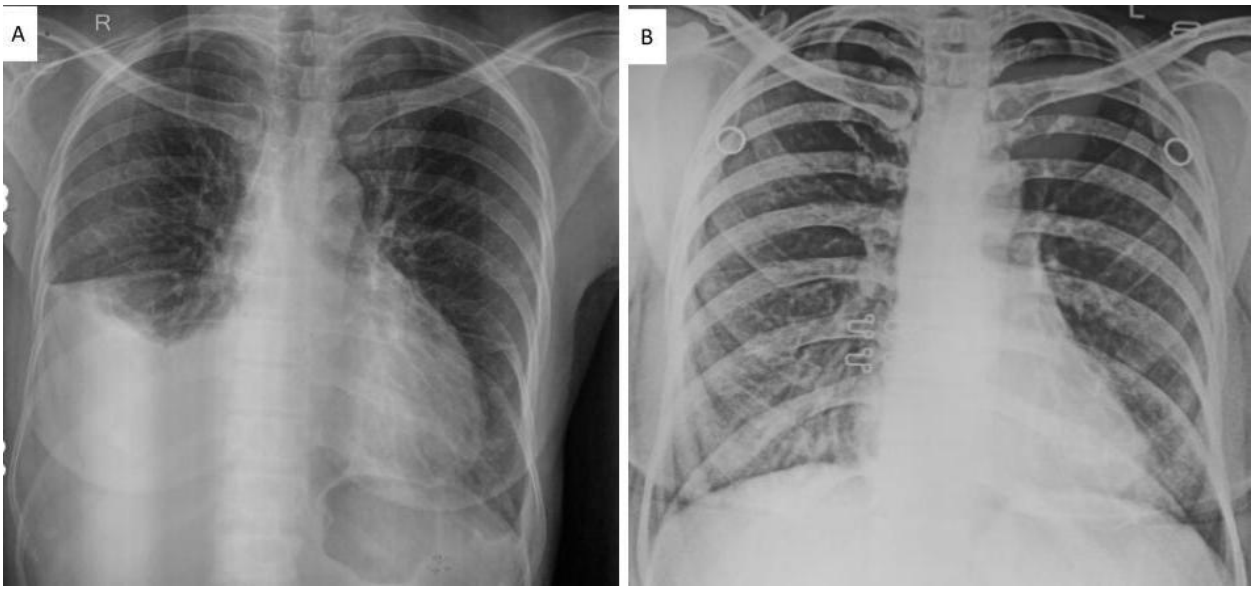

Figure 1. Radiological images of the thorax. Figure (A) shows chest X-ray findings of right-sided pleural effusion with normal lung parenchyma and mediastinum during the second hospital admission. Figure (B) shows a normal chest X-ray at 3 months of follow- up of the last admission.

Gram stain and cultures were sterile. Her pleural fluid adenosine deaminase (ADA) was 41 U/L (normal range, less than 40 U/L), but her pleural fluid cartridge-based nucleic acid amplification test (CBNAAT) for Mycobacterium tuberculosis was negative. Regrettably, PCR detection in the pleural fluid for common respiratory viruses and bacteria such as Streptococcus, Staphylococcus, Mycoplasma, and Chlamydia could not be conducted due to the lack of availability of necessary testing facilities within the institute. Compounding this challenge, the patient found it financially unfeasible to send the samples outside for testing, given the exorbitant costs of such procedures.

CECT thorax, which was done in her previous admission, had multiple ground glass opacities and consolidation in bilateral lungs. Bronchoalveolar lavage done in the previous week revealed a negative CBNAAT and BAL cultures were also sterile.

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The patient was managed conservatively, without any antimicrobial therapy. As the pleural effusion was significant and the patient had shortness of breath, therapeutic thoracocentesis was done. About 400ml of free-flowing serosanguinous fluid was removed, following which the patient had considerable relief in dyspnea.

It was decided to keep her in close follow-up for any new B symptoms (fever, night sweats, loss of appetite, or unintentional weight loss) or recurrence of pleural effusion. The same was explained to the patient, and she was discharged.

The patient has been on regular follow-ups for the last six months. She did not have a recurrence of pleural effusion, fever spikes, or any of the B symptoms. The last chest X-ray was normal (Fig 1B).

Discussion

Parapneumonic effusion is the accumulation of exudative pleural fluid associated with ipsilateral pneumonia. Though the most common cause of this is a bacterial infection, TPE is the most common cause in a TB endemic region [1,3,6]. Viral parapneumonic effusions are less common when compared to pyogenic and tubercular effusions. In our case, during the first admission for pneumonia, the patient had a low-grade fever of one-day duration followed by shortness of breath. CECT thorax showed consolidation and ground glass opacities in the bilateral lung, which was more suggestive of viral than bacterial pneumonia. BAL gram stain, cultures were sterile, and CBNAAT was also negative. The pleural fluid analysis during her next admission had lymphocytic predominance with cultures and gram stain negative. All these are more suggestive of a viral parapneumonic effusion rather than a culture of sterile bacterial parapneumonic effusion post-antibiotic treatment.

In approaching a case of tubercular effusion, fluid ADA has greater importance in a monocytic exudative fluid. The sensitivity and specificity of ADA for tuberculous pleural effusions are high (92% and 90%, respectively) [7-9]. Simultaneously, the ADA levels were significantly higher in the malignant effusions, parapneumonic effusions, post-CABG effusions, miscellaneous exudative effusions, and idiopathic effusions when compared with the transitive group [10]. In our case, it was a lymphocytic predominant unilateral pleural effusion with an elevated ADA level, reaching

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the cut-off of tuberculous effusion. Considering the TB endemicity as well as TB contact history, the patient could have been misdiagnosed as having tuberculosis and started on ATT.

Both tuberculosis and viral effusions have monocyte predominance. The level of mononuclear cells and macrophages was higher in uncomplicated parapneumonic effusion than in TPE [11]. Pleural fluid LDH is a frequently used biomarker to differentiate complicated parapneumonic effusion from uncomplicated, and a very high and isolated pleural fluid LDH level might be of specific diagnostic significance, especially for empyema [12]. The pleural fluid LDH level was found to be significantly lower in patients with TPE than in those with parapneumonic effusion ($P < .001$) [11].

Appropriate antibiotic therapy, together with drainage of pleural fluid if required in cases of bacterial parapneumonic effusions, is the treatment of choice [13]. Patients who need an invasive procedure for its resolution include the following: an effusion occupying more than 50% of the hemithorax or one that is loculated; a positive Gram stain or culture of the pleural fluid; and a purulent pleural fluid that has a pH below 7.20 or glucose below 60 mg/dl (3.3mmol/L) or has an LDH level of more than three times the upper normal limit for serum [14,15].

In our case, an uncomplicated viral parapneumonic effusion responded to conservative management. Therapeutic thoracocentesis was only done to relieve her of the dyspnea, and the patient was monitored for the recurrence of symptoms meticulously. The patient was thus prevented from unwanted initiation of antituberculous therapy and the drug side effects. The overall prevalence of adverse reactions with first-line anti-tuberculosis drugs is estimated to vary from 8.0% to 85% [16]. Adverse reactions of antitubercular drugs may cause morbidity and even mortality if not detected early. Such adverse events could be avoided if patients are diagnosed and managed appropriately with a cautious approach toward the initiation of ATT.

CONCLUSION

There is an increased concern about ATT-induced drug-induced liver injury in the community in patients in whom tuberculosis is diagnosed but with wrong clinical judgment. Viral parapneumonic effusion may present as pleural exudative effusion with raised fluid ADA level despite tubercular positive exposure. Hence, even in TB endemic areas, other potential causes should be considered and investigated thoroughly before initiating antituberculous therapy in cases of pleural effusion.

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However, drawing definitive conclusions based on a single case study poses challenges, and it is imperative to emphasize the need for further follow-up with additional cases before generalizing the findings.

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