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Case Report

Recurrent Pleural Effusion in Drug Sensitive Extrapulmonary Tuberculosis: Marker of Immune Dysregulation!

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Abstract: Pleural effusion secondary to tuberculosis is second most common manifestation of extrapulmonary tuberculosis. Tuberculous pleural effusion is more frequently documented in India due to high TB burden setting and usually cured with universally available ATT as per NTEP program. Very few cases showed inadequate treatment response and these cases require addition of steroids to relive symptoms. Addition of steroids in management of TB pleural effusion is not routinely indicated and not recommended by NTEP as well. Clinical deterioration during antituberculosis therapy in patients whose cases have initially improved is known as a "paradoxical reaction." In this case report, a 54-year teacher male presented with constitutional symptoms with right upper lobe nodular opacity with infiltrates treated empirically for community acquired pneumonia and progressed to left massive pleural effusion with respiratory distress diagnosed as case of Tuberculous pleural effusion by reporting raised ADA level and CBNAAT test results with MTB genome and negative Rifampicin (rpo-b) mutation. He is treated according to NTEP guided ATT schedule as per weight band in line with drug sensitive tuberculosis. He has shown good clinical and radiological response in first six weeks to ATT and later showed clinical and radiological worsening. We further reassessed and confirmed drug sensitive tuberculosis and continued same regimen. We have further evaluated for possibility of immune dysregulation in present case by doing TH1 and TH2 markers and observed TH1-TH2 dysregulation and also significantly raised IgE level. We have started oral steroids which were contoured till six weeks in tapering order along with ATT and documented significant improvement in clinical and radiological response. We have observed near complete resolution of pleural effusion after seven months and documented clinical and radiological cure after eight months of ATT. Paradoxical reaction is not uncommon, but needs prompt workup to rule out underlying drug resistant tuberculosis. Short course of steroids will give symptomatic relief in drug sensitive tuberculosis along with ATT. We recommend to rule out immune dysregulation in cases with drug sensitive recurrent pleural effusion in spite of acceptable adherence with good quality drugs for adequate duration which have showed excellent initial response to ATT.

Keywords: Tuberculous pleural effusion, Immune dysregulation, Drug sensitive tuberculosis, AFB, Gene Xpert MTB/Rif.

INTRODUCTION

Mycobacterium tuberculosis (M. tuberculosis) is a pathogenic bacterial species in the family Mycobacteriaceae and the causative agent of most cases of tuberculosis (TB) (1). Despite being isolated by Robert Koch in 1882, as well as the availability of effective treatment and the use of a live attenuated vaccine in many parts of the world, TB remains one of the deadliest communicable diseases. Although TB affects the lungs in the majority of patients, extrapulmonary TB serves as the initial presentation in about 25% of adults, and primarily involves the lymph nodes and pleura [1]. Pleural is second only to lymphatic involvement as a site of extrapulmonary TB, and may occur in either primary or reactivation disease. The gold standard for the diagnosis of tuberculous pleuritis remains the detection of Mycobacterium tuberculosis in pleural fluid, or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli (AFB). In high burden settings, however, the diagnosis is frequently inferred in patients who present with a lymphocytic predominant

exudate and a high adenosine deaminase (ADA) level, which is a valuable adjunct in the diagnostic evaluation. ADA is generally readily accessible, and together with lymphocyte predominance justifies treatment initiation in patients with a high pre-test probability. Still, false-negative and false-positive results remain an issue during management of these cases [1].

Pulmonary tuberculosis can have diverse presentations ranging from cavitation, consolidation, tumorous lesions, coin lesions, lower lung filed tuberculosis and endobronchial and miliary nodules [2-12]. Similarly, non-tuberculous pathologies can present with abnormalities such as consolidations, nodules, cavitations mimicking tuberculosis [2-14]. Bronchoscopy is a very crucial interventional pulmonology technique in evaluating these cases [2-14]. High risk factors for tuberculosis would be advanced age, malnutrition, pregnancy, steroids exposure, diabetes mellitus and immunosuppression [9-14]. Tuberculosis in advanced stage may cause cardiac dysfunction and systemic effects which will have poor outcome if timely treatment not received [15-17]. Final outcome in delayed treatment initiation may lead to destroyed lung as post tuberculosis sequel and proportionate number of cases may have lung function abnormalities irrespective of radiological outcome [18-24]. Tuberculosis may be misdiagnosed due to confusing or overlapping clinical and radiological features in high burden setting like India [25-28]. In children extrapulmonary tuberculosis can present like tuberculous meningitis and with or without mediastinal adenopathy which is usually missed due to vague presentations like bronchitis and asthma and cases with failure to thrive [29, 30]. In present case report we have reported tuberculous pleural effusion with paradoxical clinical and radiological worsening after starting ATT as per NTEP program in India and we have conformed as drug sensitive tuberculosis before initiation of ATT and during reassessment of paradoxical worsening by doing pleural fluid MTB CBNAAT or Gene Xpert MTB/RIF which is the best available diagnostic modalities in NTEP program and offered 8 month course of universally acceptable and freely available treatment for tuberculosis and documented clinical and radiological cure.

Case Summary:

54-year-old male, teacher by occupation, tobacco addict, normotensive and non-diabetic with history of progressive shortness of breath over a period of two weeks duration referred by family physician for further treatment.

Further clinical details-

1. Fever for three months weeks, low grade without chills and rigors associated with bodyache, intermittent, more during evening hours, responding to antipyretics
2. Cough for three weeks, dry, intermittent, no diurnal or postural variation.
3. Shortness of breath for two weeks, progressive, more during lying down position, decreased during recumbent position, and more in left lateral position. Initially, he was having grade I and progressed to grade IV one day before hospitalization.

We have recorded complete medical history and observed clinical issue of low-grade fever of chronic onset with associated minimal intermittent dry cough and fatigability and weakness. He was evaluated chest x-ray and HRCT thorax and diagnosed to have community acquired pneumonia and bronchitis. He was offered oral antibiotics and cough suppressant for a tend days. His symptoms were partially responding to oral antibiotics with persistent fever. Then treating physician decided to start intravenous antibiotics consisting beta-lactum and macrolides for three days.

Chest X-ray PA view documented inhomogeneous, well defined round opacity in upper zone just above the horizontal fissure, and inhomogeneous infiltrates in right upper zone [Image 1].

HRCT thorax documented well defined opacity in posterior segment of right upper lobe with multiple discrete well defined to ill-defined nodular opacities in right upper lobe with parenchymal bands [Image 2].

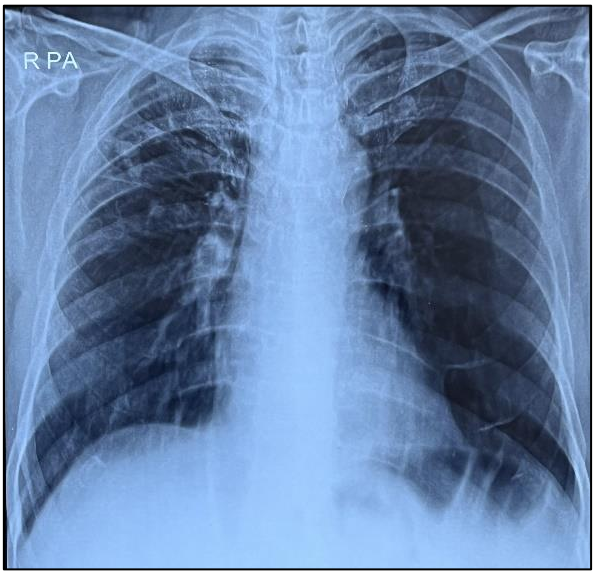

Image 1: Chest x-ray PA showing tiny airspace consolidation in right upper zone

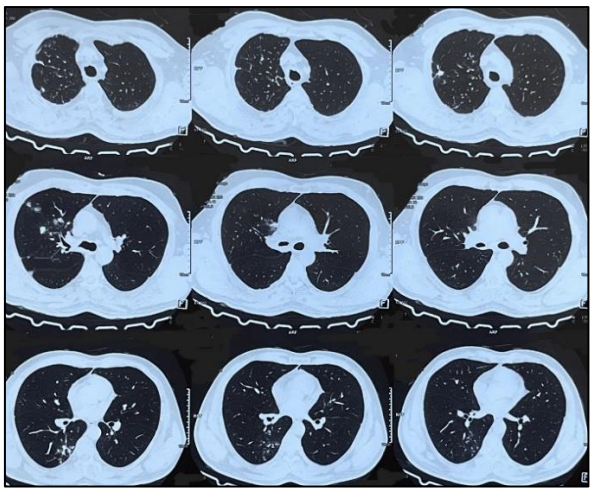

Image 2: HRCT Thorax showing abnormalities in right lung upper lobe anterior and posterior segment infiltrates and inhomogeneous opacities

Chest radiological findings were underestimated and half-heartedly evaluated and treated as tropical community acquired infection with partial response to medical treatment. His clinical deterioration is the reason for referral to our center especially progressive breathlessness.

Clinical examination documented as-

Thin built, febrile, no pallor or cyanosis or clubbing.
Heart rate-128/min Respiratory rate: 28/bpm, BP-90/60 mmhg
PsO2: 90% resting & 88% on routine walk @ room air

Respiratory system examination revealed- left thoracic volume is increased with intercostal fullness and sift of trachea to right side. Trail sign is positive. Stony dull note heard over left thoracic areas in left thoracic cavity in all areas form anterior to posterior clavicular, mammary, axillary, intrascapular and infrascapular area during percussion. Decreased to absent breath sounds in left thoracic cavity in all areas form anterior to posterior clavicular, mammary, axillary, intrascapular and infrascapular area. Decreased vocal resonance on auscultation in mentioned areas.

Cardiovascular, gastrointestinal & nervous system examination were normal.

Laboratory Examination during hospitalization documented as-

Hemoglobin-11.0 gm% total white blood cells-9000/mm3 Polymorphs-68%, Platelet count-270000/uL
CRP-230 mg/L (0-6 mg/L), random blood sugar level-134 mg% HbA1C-5.60 %
LDH-656 IU/L (70-470 IU/L)
Serum electrolytes: Sodium-138 meq/L (135-145 meq/L) Potassium-3.7 meq/L (3.5-5.5 meq/L) Ionic calcium-1.39 meq/L (1.09-1.36 meq/L)
D-dimer-423 ng/ml (<500 ng/ml)
IL-6-26.98 pg/ml (0.00-7.00 pg/ml)
Serum creatinine-1.1 mg/dL (0.7-1.4 mg/dL)
Liver function tests- normal
Thyroid functions-normal
ECG was showing sinus tachycardia.
Pro-BNP- 96 pg/ml (<125 pg/ml)
CPK-MB- 10.33 IU/L (0-25 IU/L)
Trop-I- (cardiac troponin)-12 ng/L (0-19 ng/L)
COVID-19 RT PCR test and results documented Negative for SARS-CoV-2
Viral markers such as HIV-II and HIV-II antibody negative and Australia antigen negative

Chest x-ray examination revealed opacification of left thoracic cavity with complete homogenous opacification in upper, middle and lower zones with obliteration of costophrenic and cardio phrenic angles with shift of mediastinum to right side [Image 3]. Upper mediastinum (trachea) and lower mediastinum (cardiac silhouette) is shifted to right side [Image 3].

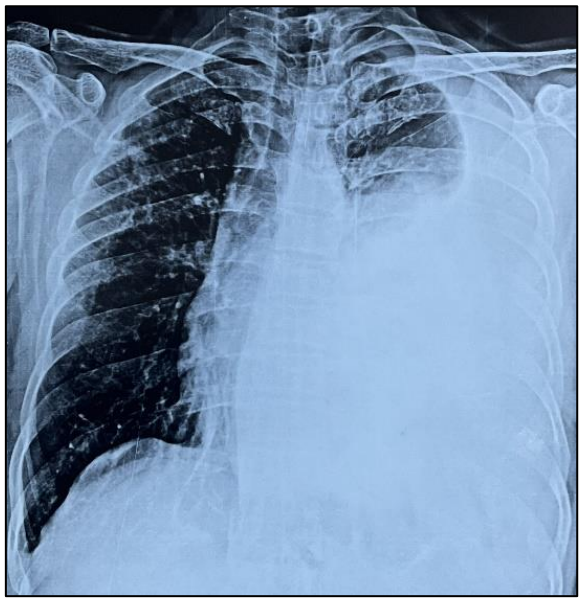

Image 3: Chest x-ray PA showing massive pleural effusion left side with nodular opacity in right upper zone

We have pleural fluid aspiration of 1600 ml of straw-colored pleural fluid from left pleural cavity in posterior axillary line in sixth intercostal space under ultrasound guidance.

Pleural fluid analysis-

Volume- 1600 ml
Color-Yellow straw colored
Cobweb- Present
Proteins- 5.7 gram%
Sugar-52mg%
Cells- 6800/mm^3
Lymphocytes- 90% Neutrophils-5% Mesothelial cells-2%
Malignant cells = negative
Pleural fluid cell block- negative for malignant cells

Pleural fluid CBNAAT (Cartridge based nucleic acid amplification) test- MTB (mycobacterium tuberculosis) positive, Rifampicin mutation (Rpo-b) Negative.

We have performed chest x-ray to document lung expansion and any obvious lung parenchymal or mediastinal abnormalities after pleural fluid removal. We have observed normal lung parenchyma with moderate residual pleural effusion left side, Interestingly, pressure effects due to pleural fluid reversed with shift of mediastinum and observed central trachea and cardiac silhouette [Image 4].

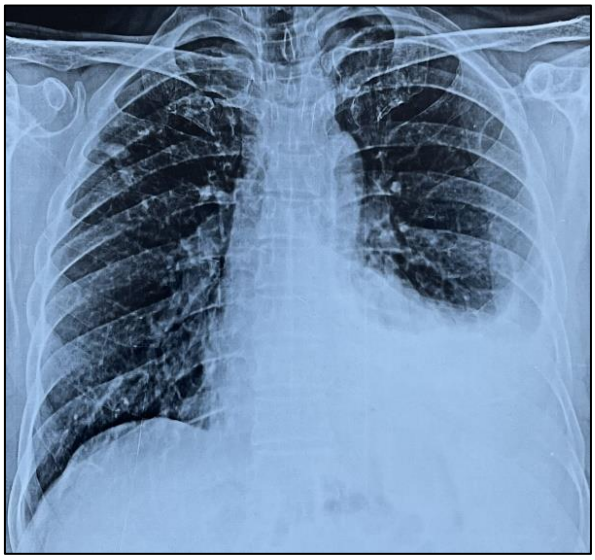

Image 4: Chest x-ray PA showing moderate pleural effusion left side with nodular opacity in right upper zone

We have started anti-tuberculosis treatment (ATT) as per the NTEP (National tuberculosis elimination program) protocol according to weight band containing four drugs isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). He was discharged to home with advice for strict anti-TB treatment as four drugs in the first 2 months (HRZE) and three drugs in the next 4 months (HRE) as per the NTEP national guidelines for TB treatment. During routine follow-up in outdoor after one month, his clinical parameters were improved with improvement in weight and appetite. He was not having fever or any chest discomfort. We have advised for continuation of second moth of intensive phase of ATT and guided follow-up for shift to continuation phase. He visited outdoor unit after two months of ATT with worsening of symptoms as more cough with reappearance of breathlessness and decreased appetite in last one week. We have repeated chest x-ray PA view and documented increase in pleural effusion left side with moderate to massive type and shift of mediastinum to right side [image 5].

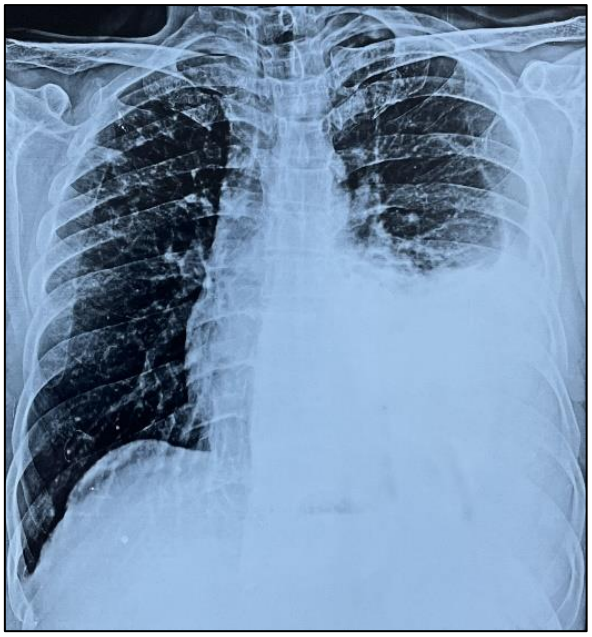

Image 5: Chest x-ray PA showing massive pleural effusion left side with nodular opacity in right upper zone

We have performed ultrasound and performed aspiration of 1000 ml straw colored pleural fluid form left pleural cavity and conformed drug sensitive tuberculosis by doing CBNAAT for MTB with negative rifampicin mutation. Pleural fluid cytology for malignant cells were negative.

Due to clinical and radiological worsening in extrapulmonary tuberculosis in spite of drug sensitive scenario conformed two times and in setting with good quality drugs with appropriate dosage according to weight band, we have further evaluated for possibility of immune dysregulation in this patient with recurrent pleural effusion.

We have performed, TH1 and TH2 cell mediated immune balance or harmony by analyzing markers for immune dysregulation.

CD4 counts-756/mm^3 (range 500-1200/mm^3)
CD4 counts- 698/mm^3 (range 150-1000/mm^3)
IgE-6800IU/ml (range 50-300)

We have confirmed as Immune dysregulation is the reason for clinical and radiological worsening in setting with drug sensitive tuberculosis. We have treated with oral steroids as omnacrotil with dose of 60 mg daily for 5 days and 40 mg daily for 5 days and 20 mg daily for additional five days. After two weeks, we have continued omnacrotil 10 mg daily for two more weeks and 5 mg daily for two weeks. Thus, we have given steroids for 6 weeks in total to document clinical and radiological response.

We have repeated chest x-ray after two months i.e., after two weeks of completion of 6 weeks of completion of steroids and observed significant

improvement in radiological abnormality. Pleural effusion is decreased and there was no any lung parenchymal abnormality [Image 6].

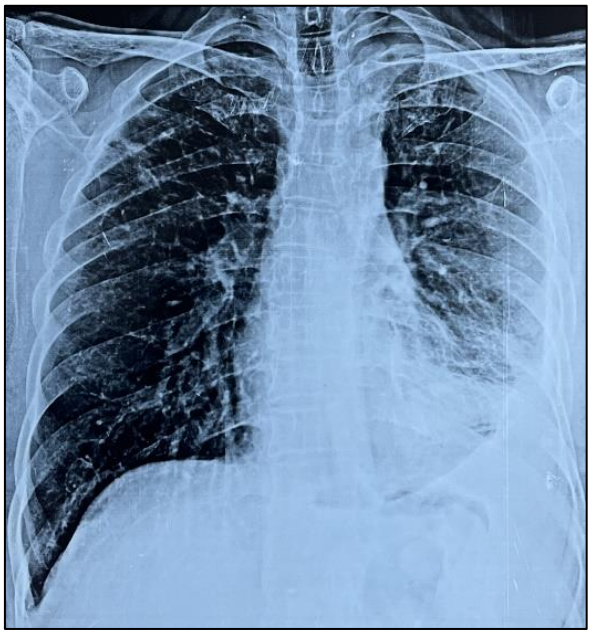

Image 6: Chest x-ray PA showing moderate pleural effusion left side with decreased thoracic volume with nodular opacity in right upper zone

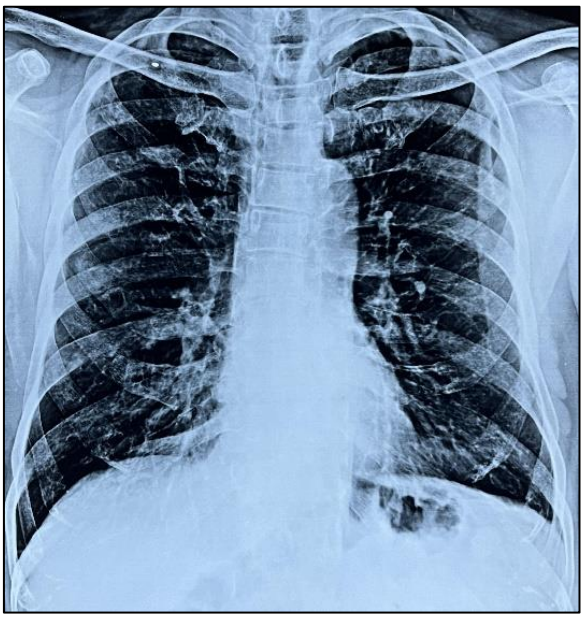

Image 7: HRCT Thorax showing complete resolution of left pleural effusion with compete resolution of right upper zone lung opacity

We have decided to continue ATT containing three drugs HRE for more two months till eight months. Radiological resolution of pleural effusion has documented after seven months of ATT treatment. We have documented weight gain and general health improvement with best compliance to anti-TB treatment and observed the importance of counselling. He was regularly monthly followed for 8 months; clinical and radiological assessment was done in every visit. We have documented clinical, microbiological and radiological 'cure' after eight months of treatment [Image 7].

DISCUSSION

Tuberculosis (TB) is a major public health problem in developing countries. Although the majority of patients with TB have pulmonary TB, extrapulmonary TB affecting mainly the lymph nodes and pleura serves as the initial presentation in about 25% of adults. It is important to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion. A pleural effusion as an isolated manifestation of TB has been likened to a primary chancre as a manifestation of syphilis. Both are self-limited and of little immediate concern, but both may lead to serious disease many years later. Tuberculous pleuritis is thought to represent primarily a hypersensitivity reaction to tuberculous protein and the bacillary burden in the pleural space is low [31].

Pathogenesis of tuberculous pleural effusion:

A tuberculous pleural effusion that occurs in the absence of radiologically apparent TB may be the sequel to a primary infection 6–12 weeks previously or it may represent reactivation TB. In industrialized countries, it is thought that more pleural effusions are due to reactivation than follow a primary infection [32]. The pathogenesis of a tuberculous pleural effusion is thought to be related to the rupture of a subpleural caseous focus in the lung into the pleural space. The basis for this is the observation by Stead *et al*., [33] that they could demonstrate a caseous tuberculous focus in the lung contiguous to the diseased pleura in 12 of 15 patients with tuberculous pleuritis. The three other patients in this study had parenchymal disease although they did not have caseous foci adjacent to the pleura.

It is believed that delayed hypersensitivity plays a large role in the pathogenesis of tuberculous pleural effusion. The hypersensitivity reaction is initiated when tuberculous protein gains access to the pleural space. Evidence for the role of hypersensitivity includes the following: (i) When tuberculous protein is injected into the pleural spaces of guinea pigs sensitized to purified protein derivative, an exudative pleural effusion rapidly develops. (ii) When the sensitized guinea pigs are given antilymphocyte serum, the development of the pleural effusion is suppressed. (iii) The mycobacterial cultures of the pleural fluid from most patients with tuberculous pleural effusions are negative [34].

The tuberculous pleural effusion develops when the delayed hypersensitivity reaction increases the permeability of the pleural capillaries to protein and then the increased protein levels in the pleural fluid result in a much higher rate of pleural fluid formation. In addition, the lymphocytic pleuritis obstructs the lymphatics in the parietal pleura, which leads to decreased pleural fluid clearance from the pleural space. The pleural effusion

results from the combination of the increased pleural fluid formation and the decreased pleural fluid removal [35].

Clinical Presentation:

The most frequent symptoms are cough (~70%), which is usually non-productive and chest pain (~70%), which is usually pleuritic in nature. If both cough and pleuritic pain are present, the pain usually precedes the cough. Most patients are febrile but approximately 15% will be afebrile. Patients with tuberculous pleural effusions may be dyspneic if the effusion is large. On occasions the onset of tuberculous pleuritis is less acute with mild chest pain, at most a low-grade fever, a non-productive cough, weight loss and easy fatigability [31]. The pleural effusions secondary to tuberculous pleuritis are usually unilateral and can be of any size.

TB was the third leading cause of large or massive pleural effusion (12%) after malignancy (55%) and pneumonia (22%) Approximately 20% of patients with tuberculous pleural effusions have coexisting parenchymal disease on chest radiograph. However, if chest CT scans are performed, more than 80% may have parenchymal abnormalities. The parenchymal disease is almost always on the side of the pleural effusion and is invariably active. On rare occasions, pleural TB can present with pleural-based nodules and thickening [36-38].

Natural history of untreated Tuberculous pleuritis:

Without treatment, tuberculous pleuritis usually resolves spontaneously, but the patient frequently develops active TB at a later date. In one study Patiala followed for at least 7 years all 2816 members of the Finnish Armed Forces who developed pleural effusion between 1939 and 1945 [39] He reported that 43% of this large group of young men developed TB during the follow-up period. A second study followed 141 military personnel first seen in the USA between 1940 and 1944 with a pleural effusion and a positive tuberculin skin test [40] Although the effusions resolved and all other symptoms disappeared within 2–4 months, 92 of the 141 individuals (65%) subsequently developed some form of active TB. The subsequent incidence of TB was comparable in these whose pleural fluid cultures were initially positive for TB (60%) and those in whom the initial cultures were negative (65%) [40] Moreover, the size of the original effusions and the presence or the absence of small radiological residual pleural disease were not correlated with the subsequently development of active TB. These two studies underline the importance of making the diagnosis of tuberculous pleuritis if that is what the patient has.

Diagnosis of tuberculous pleural effusion:

The diagnosis of tuberculous pleuritis depends upon the demonstration of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimens, or the demonstration of granulomas in the pleura. The diagnosis can also be established with reasonable certainty by demonstrating elevated levels of adenosine deaminase (ADA) or γ-interferon in the pleural fluid.

Routine smears of the pleural fluid for mycobacteria in immunocompetent individuals are not indicated because they are almost always negative unless the patient has a tuberculous empyema. Smears should be obtained in immunocompromised hosts. Smears are positive in approximately 20% of HIV-positive individuals. However, pleural fluid cultures for mycobacteria should be obtained in any patient with an undiagnosed pleural effusion. In most series of immunocompetent patients with tuberculous pleuritis, the cultures are positive in less than 40% [31].

The tuberculin skin test is being utilized less and less in patients suspected of having tuberculous pleuritis. This is primarily because a negative test does not rule out the diagnosis of tuberculous pleuritis. If a patient with a negative tuberculin skin test and tuberculous pleuritis is skin tested more than 8 weeks after the development of symptoms, the skin test will almost always be positive. However, if the patient is markedly immunosuppressed with HIV infection or is severely malnourished, the skin test may remain negative [31].

Adenosine deaminase in tuberculous pleural effusion:

Testing for pleural fluid ADA levels is an easy and inexpensive method for establishing the diagnosis of TB pleuritis.1 ADA, a predominant T-lymphocyte enzyme, catalyses the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. A recent meta-analysis of 63 studies including 2796 patients with tuberculous pleuritis and 5297 with non-tuberculous effusion reported that the sensitivity and specificity of ADA in the diagnosis of pleural TB were 92% and 90%, respectively [41] The most widely accepted cut-off value for pleural fluid ADA is 40 U/L. The higher the level, the greater the chance of the patient having TB while the lower the level the lesser the chance of the patient having TB.

The main disease other than TB that causes an elevated pleural fluid ADA is empyema. Roughly one-third of parapneumonic effusions and two-thirds of empyemas have ADA levels that exceed 40U/L [42] However, tuberculous pleuritis and parapneumonic effusions are easily distinguished by the clinical pictures and the fact that parapneumonic effusions have predominantly polymorphonuclear leucocytes instead of the lymphocytes typical of TB. Less commonly high pleural fluid ADA has been reported in malignancies (5%, particularly lymphomas), infectious diseases (e.g. brucellosis, Q fever) and connective tissue diseases such as rheumatoid arthritis.

The pleural fluid ADA level can be used to exclude the diagnosis of tuberculous pleuritis in patients with undiagnosed pleural effusions. Ferrer and associates followed 40 patients with undiagnosed pleural effusions and a pleural fluid ADA level below 43U/L for a mean of 5 years and reported that none developed TB [42] Lymphocytic pleural effusions not due to tuberculous pleuritis usually have pleural fluid ADA levels below 40 U/L. Castro *et al*., measured the pleural fluid ADA levels in 410 lymphocytic non-tuberculous pleural fluids and found that the ADA was above 40 IU/L in on seven (1.7%) [43].

Adenosine deaminase has two molecular forms, ADA1 and ADA2. ADA1 is found in all cells and has it greatest activity in lymphocytes and monocytes while ADA2 is found only in monocytes. Most of the ADA in tuberculous pleural fluid is ADA2 which seems paradoxical as ADA1 comes from lymphocytes and lymphocytes predominate in pleural fluid from patients with TB pleuritis. Although a ratio of the ADA1 to the total ADA of less than 0.42 will slightly increase the sensitivity and specificity of the ADA measurement in diagnosing tuberculous pleuritis, the separation of ADA into its isoenzymes is not necessary in the vast majority of cases [44].

Role of Xpert MTB/RIF in diagnosis of tuberculous pleural effusion:

Xpert MTB/RIF assay is a rapid, automated PCR test endorsed by WHO for TB. It is a box-based nucleic acid amplification method, which merely takes a very short time in detecting the Mycobacterium tuberculosis. What's more, Xpert MTB/RIF can detect both MTB and rifampicin resistance in respiratory specimens simultaneously. Rifampicin is a crucial drug for the treatment of patients who suffer from tuberculosis. Xpert MTB/RIF assay has the advantages of high sensitivity, specificity, simple operation, low contamination risk, and short turnaround time [45].

Although Xpert MTB/RIF for tuberculous pleural effusion was found to be a method with less sensitivity that fails to meet the clinical requirements, its high specificity (100%) suggests it is a specific tool for diagnosis of tuberculous pleural effusion. If the MTB/RIF system result is positive, it indicates Mycobacterium tuberculosis in the pleural effusion. The operation of this technique is simpler than conventional laboratory diagnostic methods. For pleural tuberculosis with a large sample size but low diagnostic rate and microscopic examination positive rate, the technique can still be a method to improve the positive rate of tuberculosis diagnosis [45].

Recommended Diagnostic Approach:

When a patient with an undiagnosed pleural effusion is initially evaluated, the diagnosis of tuberculous pleuritis should always be considered because if the diagnosis is not made, the patient will subsequently develop TB. At the time of the initial thoracentesis, the pleural fluid should be analysed for the ADA level and differential cell count and the fluid should be cultured for mycobacteria. If the fluid ADA is above 70 U/L and the pleural fluid has a lymphocyte-to-neutrophil ratio greater than 0.75, the diagnosis of tuberculous pleuritis is virtually established. If the pleural fluid ADA is between 40 and 70 U/L and the patient has a lymphocyte-to-neutrophil ratio of more than 0.75, one can make a presumptive diagnosis of tuberculous pleuritis. In this situation, if the patient's clinical picture is not typical for tuberculous pleuritis, consideration can be given to performing a needle biopsy of the pleura or thoracoscopy. If the patient's pleural fluid ADA level is below 40 U/L, the diagnosis of TB is unlikely. Nevertheless, if the patient has a clinical picture typical of tuberculous pleuritis and particularly, if the pleural fluid has a high percentage of lymphocytes, the possibility of tuberculous pleuritis can be further evaluated with needle biopsy of the pleura or thoracoscopy [31].

Treatment of Tuberculosis pleural effusion:

The recommendations for the treatment of all pulmonary and extrapulmonary TB are as follows. The initial phase of a 6-month regimen should consist of a 2-month period of isoniazid (INH), rifampin and pyrazinamide. Ethambutol should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance. The second phase of the treatment should be INH and rifampin given for 4 months [31].

With treatment, the patient's symptoms and radiological abnormalities gradually abate. The typical patient becomes afebrile within 2 weeks, but temperature elevations may persist as long as 2 months. If a therapeutical thoracentesis is performed at the same time that antituberculous therapy is initiated, most patients become afebrile within 5 days. The mean time for the complete resorption of pleural fluid is approximately 6 weeks, but it can be as long as 12weeks. There is no reason to keep the patient at bed rest and the patient needs to be isolated only if their sputum is positive for mycobacteria [46].

Approximately 50% of patients will have some residual pleural thickening 6–12 months after the initiation of treatment. The pleural thickening may result in a reduction in the VC. The incidence of residual pleural thickening is slightly more common in patients with a low pleural fluid glucose, a high pleural fluid LDH level and high pleural fluid cytokine levels. The residual pleural thickening is more common if the pleural effusion is initially loculated. Complete removal of the pleural fluid does not appear to decrease the amount of residual pleural thickening [31].

The administration of a fibrinolytic may decrease the degree of residual pleural thickening in

patients with loculated tuberculous pleural effusions. Kwak *et al*., randomized 43 patients with loculated pleural effusions to receive 100000 urokinase daily administered through a pigtail catheter starting when the pleural fluid drainage was less than 100 mL/day and finishing when the amount of pleural fluid was less than 50 mL/day or only antituberculous therapy. They reported that the mean width of the pleural thickening was 0.46 cm in the urokinase group and 1.86 cm in the control group [47].

Paradoxical reaction in tuberculous pleural effusion:

PR is a form of tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) that may occur during or after completion of anti-TB therapy. It represents either a paradoxical worsening/recurring of pre-existing tuberculosis lesions or a development of new lesions in patients after effective anti-tuberculosis treatments. Several criteria are needed to be taken into consideration for diagnosis of PR, including the initial response to anti-tuberculosis treatments, paradoxical deterioration of TB-related symptoms and/or radiological findings, exclusion of alternative explanations for clinical deterioration such as drug resistance, poor adherence, drug side effects and other infections [48].

Paradoxical response can occur with a variety of systems including CNS, respiratory system, skin and soft tissue, lymph node, abdomen, bone and tendon. Paradoxical reaction following anti-tuberculous treatment is common in both HIV and non-HIV infected individuals. Patients with disseminated tuberculosis, extra-pulmonary tuberculosis or tuberculosis co-infected with HIV are more likely to develop paradoxical reactions. Risk factors for paradoxical reactions in patients without HIV include baseline anaemia, hypoalbuminemia and lymphopenia. The mechanism for paradoxical reaction after starting tuberculosis treatment is not well understood but it is very likely immune mediated. At the time of paradoxical deterioration, a concomitant increase in the lymphocyte counts and conversion of the tuberculin skin test is observed [49] Differential diagnosis of a paradoxical reaction would include secondary infections, adverse drug reactions, drug resistance and poor compliance. Diagnosis of paradoxical reaction is by exclusion; therefore, investigations should be directed to exclude the above conditions. The clinical severity of a paradoxical reaction is probably determined by the magnitude and timing of the immune response; an overwhelming response may produce excessive immunopathological damage at the tissue level. The median time to development of paradoxical reaction is 60 days (range 14–270 days) in HIV negative individuals [49].

The mechanisms of PR remain elusive. A few hypotheses have been proposed. Since HIV-seropositive individuals are more vulnerable to PR and low baseline lymphocyte counts is a widely recognized risk factor in HIV-negative patients, host immunodeficiency may contribute to the development of Sun *et al.*, [50] have conducted a systemic study among 64 consecutive solid organ transplant recipients with tuberculosis. Nine (14.1%) recipients developed PR which was similar to the frequency of other HIV-negative hosts. How immunodeficiency is involved in the pathogenesis of PR needs to be investigated. Rapid killing of bacilli with antibiotics may lead to the release of large amounts of microbial components, which could stimulate an exuberant inflammatory response. Higher baseline numbers of bacilli may potentiate this process and lead to PR. PR might also result from the recovery from tuberculosis-induced immunosuppression which might have led to a local hypersensitive response against massive mycobacterial antigens exposure following anti-tuberculosis treatments [51, 52].

Paradoxical worsening of the pleural effusion occurs in a few patients after the initiation of antituberculous therapy. A second report suggested that such paradoxical responses might be due to INH-induced lupus pleuritis. An occasional patient with tuberculous pleuritis will also develop a peripheral lung nodule while being treated for the pleuritis. Such nodules almost always represent pulmonary TB and disappear when the antituberculous therapy is continued [31].

***Immune dysregulation in tuberculosis*:**

T cells play a fundamental role in conferring protection against Mtb infection, while NK cells are increasingly regarded as an important component of the innate immune response to Mtb, linking adaptive and innate immunity. However, persistent exposure or overexposure of antigens to T and NK cells can elicit a state of impairment in their function, referred to as immune exhaustion. Among the CD4+T subsets, Th1 cells, which plays a key role in controlling Mtb infection, underwent exhaustion in severe TB patients and this was evidenced by (i) high exhaustion response and exhaustion scores; (ii) elevated expression of multiple inhibitory receptors; (iii) decreased cytokine production (IFN-γ, TNF); (iv) augmented expression of exhaustion-related transcription factors. As with Th1-cells, CD8+T and NK cells also underwent exhaustion in severe TB patients, and displayed typical exhaustion features. It is noteworthy that exhausted Th1, CD8+T and NK cells secreted lesser quantities of IFN-γ in severe TB patients. IFN-γ can activate macrophages and promote bacterial killing by permitting phagosomal maturation and production of reactive oxygen intermediates and antimicrobial reactive nitrogen intermediates. It has been reported that the higher number of inhibitory molecules co-expressed by exhausted cells (T and NK cells), the more severe is the exhaustion. Interestingly, these co-expression patterns are mechanistically relevant, as simultaneous blockade by multiple inhibitory molecules in severe TB patients might result in synergistic reversal of T and NK cell exhaustion. There are several mechanisms by which inhibitory receptors and their

ligands stimulate inhibitory signaling pathways: first, through the induction of inhibitory genes; second, by ectodomain competition, which involves inhibitory molecules sequestering target ligands and/or preventing the optimal formation of lipid rafts and microclusters; and third, through modulation of intracellular mediators, which can lead to local and transient intracellular attenuation of positive signals from activating receptors (e.g. TCR and its co-stimulatory receptors). Hence, an in-depth understanding of the molecular mechanism by which T- and NK-cells undergo exhaustion during Mtb infection is critical in exploring novel therapeutic targets to protect the host from Mtb-induced damage [53]. Myeloid-derived suppressor cells (MDSCs) are a population of heterogeneous immature myeloid cells which expand during inflammatory conditions and has the capacity of suppress T cell responses. Interestingly, we identified a class of monocytic MDSCs in the peripheral blood of severe TB patients which significantly increased. Several monocytes, NK and CD8+T subsets may be the main contributors of a diverse set of pro-inflammatory cytokines that were significantly increased in TB patients with severe disease progression [53].

Among the T cell subsets, Th1 cells are thought to play a key role in controlling Mtb infection by secreting cytokines such as IFN-γ and TNF. The expression of Th1 cytokine IFN-γ was significantly higher in mild, moderate and TBI conditions than in healthy controls, while the upregulated expression of IFN-γ was not observed in patients with severe disease. Similar results for IFN-γ expression were also observed in NK cells, which are another source of IFN-γ. Besides IFN-γ, TNF is involved in granuloma formation, and plays a crucial role in killing intracellular Mtb through reactive nitrogen intermediates together with IFN-γ. In severe TB, the expression of TNF in Th1 and NK cells was not significantly upregulated compared to healthy controls, while its expression was significantly elevated in mild and moderate TB [53].

Th17 cells secrete IL17, IL-17F, IL-21 and IL22 cytokines which stimulate defensin production and recruit monocytes and neutrophils to the site of inflammation. We did not observe elevated expression of Th17 cytokines and Th17 gene signatures in severe TB patients compared to these with mild and moderate disease, implying a potential dysfunction of Th17 response in severe disease. Th2 cells produce cytokines IL-4, IL-5, IL-13 and IL-25 which promote antibody generation but suppresses the Th1 immune response. We did not find significant differences in Th2-cytokine expression between active TB and healthy controls. Treg cells secrete IL-10 and TGF-β to downregulate CD4+ T cell responses, inhibit T cell cytokine production, suppress the effector-immune response, and can induce Mtb dissemination and disease manifestation. These results suggest that depleted Th1 and Th17 immune response in severe patients may be not associated with Th2 and Treg immune suppression.

Mtb infection and the anti-Mtb host immune response interact in vivo and shape disease severity as well as clinical outcomes, especially for severe TB cases. One of the major barriers in devising effective strategies to prevent and control Mtb infection is our incomplete understanding of the host-Mtb interaction. Thus, a comprehensive immune landscape, which characterizes the anti-Mtb and pathogenic immune responses in TB patients as well as dissect the potential changes related to disease severity, is urgently needed.

Treatment of paradoxical reaction and role of steroids in Paradoxical reaction and tuberculous pleural effusion:

The role of corticosteroids in the treatment of tuberculous pleurisy is controversial. In two controlled studies in which therapeutical thoracentesis was performed there were no benefits. In a third study in which no therapeutical thoracentesis was performed, the duration of fever and the time required for fluid resorption were decreased. The administration of corticosteroids did not decrease the degree of residual pleural thickening and 6 or 12 months after therapy was initiated in any of the three studies. In one randomized study of 197 patients with HIV-associated pleural TB, the administration of prednisolone was associated with an increased risk of Kaposi sarcoma. A recent Cochrane review concluded that there are insufficient data to support evidence-based recommendations regarding the use of adjunctive corticosteroids in people with tuberculous pleurisy [31].

The recommended approach to the patient with tuberculous pleuritis is as follows. If the patient is more than mildly symptomatic, a therapeutical thoracentesis is recommended. If the patient continues to have severe systemic symptoms (fever, malaise, pleuritic chest pain) after the therapeutical thoracentesis, the administration of 80 mg of prednisone every other day until the acute symptoms have subsided is recommended. Thereafter the corticosteroids are rapidly tapered [31].

Currently, there is no guideline regarding management for PR. A short course of oral corticosteroids, which is tapered off, can be considered. As many patients have exacerbated symptoms, a combination therapy of corticosteroid and anti-tuberculosis is recommended. The use of corticosteroid is systemic and short term. There are no severe steroid-related complications reported [52]. Currently, much of the evidence available evaluating the efficacy of corticosteroids in treating PR assesses this within the context of TB IRIS (immune reconstitution inflammatory syndrome) in HIV cases. In cases with HIV with or without immunosuppression, the preventative value of early administration of prednisone in the development of PR has recently been demonstrated

[54]. This intervention is yet to be applied to those that do not belong to this risk group of patients with IRIS following antiretroviral therapy.

CONCLUSION

In the present case report, we have reported a case of progressive pulmonary tuberculosis with history pf parenchymal lesion on right side and pleural effusion on left side of tuberculous etiology which is confirmed by analyzing raised pleural fluid ADA and positive MTB genome in CBNAAT test and drug sensitive disease with negative Rpo-b mutation analysis. He was treated as per NTEP schedule and weight band with four drug ATT and showed paradoxical worsening after in initial clinical and radiological response in 8 weeks of ATT treatment. We have documented immune dysregulation by doing IgE and treated with systemic steroids as omnacortil in tapering doses over six weeks. He is cured of tuberculosis disease and documented clinical and radiological cure after eight months of ATT as per NTEP.

Learning points:

1. The possibility of tuberculous pleuritis should be considered in every patient with an undiagnosed pleural effusion, for if this diagnosis is not made the patient will recover only to have a high likelihood of subsequently developing pulmonary or extrapulmonary tuberculosis Between 3% and 25% of patients with tuberculosis will have tuberculous pleuritis. The incidence of pleural tuberculosis is higher in patients who are HIV positive. Tuberculous pleuritis usually presents as an acute illness with fever, cough and pleuritic chest pain. The pleural fluid is an exudate that usually has predominantly lymphocytes. Pleural fluid cultures are positive for Mycobacterium tuberculosis in less than 40% and smears are virtually always negative.
2. The easiest way to establish the diagnosis of tuberculous pleuritis in a patient with a lymphocytic pleural effusion is to generally demonstrate a pleural fluid adenosine deaminase level above 40 U/L. Lymphocytic exudates not due to tuberculosis almost always have adenosine deaminase levels below 40 U/L.
3. Paradoxical reaction after the initiation of tuberculosis treatment is defined as increased inflammation following effective antimycobacterial treatment. This is a phenomenon that can severely complicate a patient's recovery, potentially leading to further morbidity and residual deficits. Paradoxical reaction remains poorly understood regarding its pathophysiology and management.
4. The exact pathophysiology of paradoxical reaction is not known and why only selective patients develop needs more research. Whether immune dysregulation and altered TH1-TH2 interplay may be the predominant pathway for paradoxical reaction as we have documented in our case.
5. Although paradoxical reaction is more frequently reported in HIV secondary to immunosuppression and other conditions causing immune dysregulation, it is also documented in immunocompetent host irrespective of immunosuppression which gives thought provoking facts to consider possibility of immune dysregulation resulted from MTB-Host interaction causing paradoxical reaction.
6. Immune dysregulation is documented in selected cases of pulmonary and extrapulmonary tuberculosis irrespective of drug sensitivity patterns needs further global research which will prevent distress in patients and health professionals in wasting time in ruling out drug resistant tuberculosis and doing more invasive tests and microbiological workup.
7. Paradoxical reaction in Tuberculous pleural effusion in immunocompetent case is less common, usually underestimated and less predicted, but it should be predicted early in cases with recurrent pleural effusion which has showed clinical and radiological response to ATT.
8. Blood investigations such as IgE is simple bed side test which will help in predicting paradoxical reaction is the underlying pathological mechanism for recurrent pleural effusion. IgE analysis is cost effective, and sensitive for paradoxical reaction. IgE analysis also decrease unnecessary evolution in line with alternative diagnosis including workup for to rule out MDR TB.
9. Paradoxical reaction is easily managed with therapeutic aspiration of pleural fluid to decrease respiratory symptoms including respiratory discomfort and systemic steroids for short course. Systemic steroids with undercover of standard four drug ATT as per NTEP guidelines will give successful treatment outcome without residual pleural sequel such as thickening, fibrosis and restrictive lung pathology resulting into long term impaired quality of life due to this easily treatable disease.

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