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CASE REPORT

A Paradox of Pleural Effusion

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Abstract:

Paradoxical response is referred to an unusual expansion or formation of a new lesion during successful anti-tuberculous chemotherapy (ATT).In general tuberculosis is the most common cause of pleural effusion but development of pleural effusion during successful anti-tuberculous chemotherapy is uncommon.In our case, a young man was diagnosed as sputum smear negative pulmonary tuberculosis and ATT was started. He responded to treatment but 12 days later he developed right sided pleural effusion. A paradoxical pleural effusion was suspected. We continued ATT with addition of oral corticosteroid and the patient was under observation. Pleural effusion subsided over time and the patient was recovered completely without any further complication. Development of pleural effusion in patient getting ATT may be due to a paradoxical response having an immunological basis, and does not necessarily require nay modification in chemotherapy. Strong suspicion is needed to diagnose such case.

Key words: *Anti-tuberculous chemotherapy (ATT), Paradoxical effusion.*

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Case Report

A 35-year-old male Muslim from urban residency presented to us with the complaints of cough and fever for 2 months and heaviness in chest for 5 days. The patient stated that he had cough for 2 months which was present throughout day and night. Cough was mostly dry with occasional expectoration of sputum which was yellowish in colour.He also noticed low grade continued fever for last 2 months, more marked at evening and associated with night sweats. Cough had no diurnal variation. There was no history of wheeze, shortness of breath, hemoptysis, chest pain or palpitation.He had no history of contact with active TB patient. He consulted a chest physician and was diagnosed as a case of smear negative pulmonary tuberculosis.

Category-I anti TB drug was started. His fever and cough subsided within 07 days.On 12th day he felt heaviness on right side of chest and according to his physician's advice he got admitted into specialized hospital (NIDCH) for further

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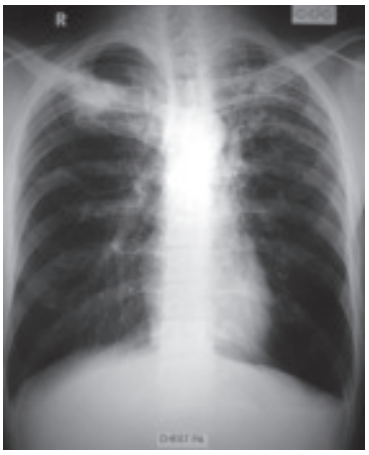

Fig-1: *A non- homogenous opacity in right upper zone.*

evaluation. He gave no history of weight loss, joint pain and abdominal pain, alteration of bowel habit, oral ulceration, hair loss, skin rash, and dryness of eye or mouth. He was normotensive and non-diabetic. His bowel and bladder habit and sleep pattern was normal. There was no significant history of past illness.

He was a businessman with middle-class family. He smoked cigarette with a history of 24 pack-year. He was alcoholic 06 years back. For last 1 year he used to take methamphetamine (as tab. Yaba).He was unmarried and gave history of multiple sexual exposures. His father died of geriatric diseases.

On examination, he was anxious and ill-looking with average body built. His pulse rate was 92/minute, blood pressure 110/70 mmHg, and respiratory rate 22/minute, temperature99^0F. There was no palpable lymph node or organomegaly. Chest examination revealed movement restricted on right side. Breath sound, vocal fremitus and vocal resonance diminished on right lower chest and percussion note dull over the same area. Examination of other systems revealed no abnormality. A clinical diagnosis of right-sided pleural effusion was made.

After admission at NIDCH, diagnostic procedures were done. His WBC count was 8500/cmm with 66% neutrophil, total platelet count 350000/cmm, ESR 25 mm in 1st hour and haemoglobin count 12gm/dl.Urine routine examination revealed trace albumin with 0-5 pus cell/HPF and no RBC. Random blood sugar 93mg/dl, serum creatinine 0.7mg/dl, serum albumin5.0gm/dl, SGPT 35U/L. Sputum AFB and GeneXpert was negative and Mantoux test revealed 12 mm induration. Chest radiograph showed right-sided pleural effusion with consolidation in right upper zone.

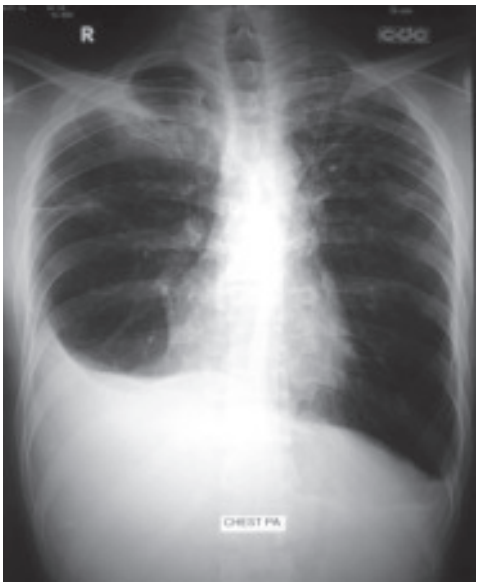

Fig-2: *Dense homogenous opacity with curvilinear upper border in right hemithorax with non-homogenous right apical shadow.*

Development of new pleural effusion in a patient getting ATT may be due to different phenomena. This may be an immunological response or drug induced hypersensitivity most likely INH. Keeping in mind the possible causes, further investigations were done. CT scan of chest revealed consolidation in right upper lobe with small right-sided pleural effusion. We decided to do diagnostic thoracentesis. About 80 cc pleural fluid was aspirated. Aspirate was straw colored, with 80mg/dl glucose and 5.3mg/dl protein. Total count 130/cmm with 92% lymphocytes. As there was small effusion, pleural biopsy was not taken. HBsAg and HIV screening was negative. ANA and anti-ds DNA was also negative.

Anti-Histone antibody was not done. Spirometry and echocardiography was normal. Surgical consultation was taken regarding pleuroscopy and decided against any intervention. We continued treatment with ATT and added short course oral corticosteroid and followed-up the patient. His

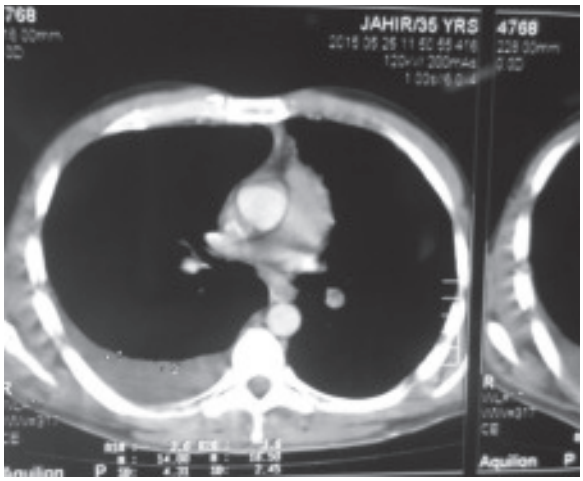

Fig-3: *CT scan of chest showing right-sided pleural effusion.*

condition was improving. Chest X-ray on 23rd day showed resolution of effusion. Further intervention was not done. Patient was discharged with ATT and tapering dose of oral corticosteroid. The clinical diagnosis of paradoxical pleural effusion was established. On subsequent follow-up, he was doing well without any new symptom.

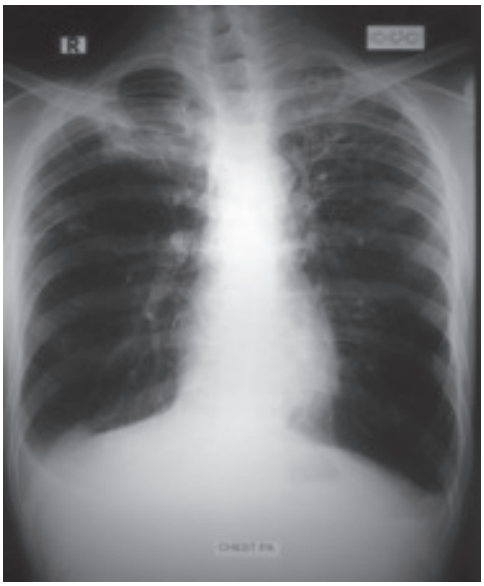

Fig-4: *Chest X-ray on 23rd day.*

Discussion:

Tuberculosis is one of the most common causes of pleural effusion andcan occur in any formof pulmonary tuberculosis. But development of new effusion in a patient on anti-tuberculous chemotherapy is a rare phenomenon. The first case of development of pleural effusion in a patient on ATT was reported by Trocme[1] on 1950. This may be due to a paradoxical response or drug-induced hypersensitivity. In most of the reported cases, pleural effusion developed between three to eight weeks of starting ATT[1-9]. The term "paradoxical response" refersto enlargement of old lesions or unexpectedappearance of new lesions during anti-tuberculoustherapy. Re-crudescence of fever, enlarging lymphadenopathies, worsening of pulmonary infiltrates,pleural effusion, ascites and appearance ofintracranial tuberculomas have all been described. An incidence of 16% of paradoxical worsening oftuberculous effusion following the start of antituberculoustreatment has been observed[6,10].

During active pulmonary tuberculosis, signs of both immune depression and immune activation are concomitantly present[11]. It has been observed that mycobacterial products induce the production of

tumour necrosis factor-alpha (TNF-á) which is involved in the expression of many of the local and systemic toxicities evident in tuberculosis. Kaplan *et al*[12]have recently shown that cytokines in newly diagnosed tuberculosis patients falls with ATT, except TNF, which increases to a maximum at 7-14 days. This temporary rise in TNF is associated with a transitory clinical deterioration. Interleukin-2 (IL-2) is also known to cause development of pulmonary infiltrates and pleural effusion[13]. The possible mechanism of development of pleural effusion during ATT seems to have an immunological basis. The possibility of a local hypersensitivity reaction to tuberculoprotein is further supported by Gupta and colleagues[14] who studied twenty nine cases of tuberculosis developing pleural effusion after starting ATT. Among them, 79.3% cases showed negative pleural fluid smear and/or culture for *M. tuberculosis* and 15 cases showed negative pleural biopsy for tuberculousp[athology.

Our patient developed pleural effusion on 12th day of starting ATT and subsided spontaneously after addition of stroid and continuing anti-TB drugs. Similar observation is noted by Gupta *et al* [14]. However, Al-Majed reported six patients who developed massive PE with respiratory distress requiring therapeutic aspiration and oral corticosteroid[6]. Endo *et al* [9]reported a case where recovery occurred after stopping all drugs and adding steroids.

Hypersensitivity reaction to isoniazid has also been implicated in development of pleural effusion during ATT. Isoniazid (INH) is known to be associated with lupus pleuritis causing chest pain, fever and arthritis[15]. The development of PE during ATT could be due to either INH-induced pneumonia's or INH induced lupus pleuritis[5,6].

There have been few cases of INH-induced pleural effusion documented in the literature.5 INH-induced pleural effusion usually begins 3 to 12 weeks after starting the medication and regresses after a change of therapy or introduction of steroids, or both[8].While the exact pathogenic mechanism ofINH-induced pleural effusion remains unclear, this indicatesthat the disease entity may have an underlying inflammatory component. Khattri S *et al*reported a case of INH-induced pleural effusion and lupus erythematosuswhere pleural fluid was eosinophilic and effusion subsided after discontinuing INH and addition of corticosteroid[16].

Development of tuberculouspleuritis or effusion during the early stages of chemotherapy does not imply failure of the current therapeutic regimen and no change in therapy is indicated unless there are other reasons, like progressive paraenchymal infiltrates or an unfavourable bacteriological response or drug-induced reaction[2]. In our case, we continued ATT with addition of corticosteroid and the patient recovered fully. Thus, there is no need to change drugs or increase treatment duration when pleural effusion occurs as a paradoxical response to ATT.

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