Case Report

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PERSISTING ALVEOLITIS IN MILIARY TUBERCULOSIS DESPITE TREATMENT WITH SHORT-COURSE CHEMOTHERAPY

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Bronchoalveolar lavages in two patients with miliary tuberculosis have shown lymphocytic alveolitis. A 6-month regimen with an initial intensive 2-month phase resulted in remarkable clinical and radiographic improvement in both. However, bronchoalveolar lavage following treatment has shown that there was a persistence of lymphocytic alveolitis, though with reduced intensity. The significance of the persisting alveolitis, despite treatment, is not known at present. There is also a suggestion that compartment-alisation of lymphocytes may occur in miliary tuberculosis of the lung.

Miliary disease of the lung due to *Mycobacterium tuberculosis* poses diagnostic as well as therapeutic problems because of the radiographic similarity with diffuse lung diseases and also due to the seriousness of the disease. Miliary tuberculosis is essentially an interstitial lung disease and studies have reported lymphocytic alveolitis[1] at the diagnostic stage in these patients. Availability of potent chemotherapeutic agents[2] has made it possible to treat this condition successfully. Bronchoalveolar lavage (BAL) studies were carried out in 2 patients with radiological and bacteriological evidence of miliary tuberculosis, in order to study the response of the alveolitis to treatment with intensive short course chemotherapy.

Case Reports

Case 1. A 24-year-old female patient complained of dyspnoea, cough, chest pain and fever of one week duration. She was a housewife, denied any previous illness or history of tuberculosis in the family, and was a non-smoker. On physical examination, she had

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Table. *BAL in miliary tuberculosis*

	Pretreatment					Post-treatment (6 months)				
	Total cells ($x10^6$/100ml)	M %	L %	N %	E %	Total cells ($\times10^6$/100ml)	M %	L %	N %	E %
Case 1	51.3	17	82	0	1	22.8	62	37	1	0
Case 2	48.9	25	75	0	0	21.8	25	66	6	3

M = Macrophages; L = Lymphocytes; N = Neutrophils; E = Eosinophils

dyspnoea at rest, respiratory rate was 40/min, pulse rate 144/min, temperature 99 °F and blood pressure 100/70 mmHg. Fine rales were heard in both lung bases. Mantoux test with 1 TU PPD was 15 mm. Total leucocyte count was 11000 cells/mm^3 with differentials as polymorphs 81%, lymphocytes 17% and eosinophils 2%. There were albumin (+), 2-4 pus cells and occasional RBCs/HPF in urine and stool did not show any ova or cyst. Skiagram chest revealed diffuse miliary shadows in both lung fieldsespecially in the mid and lower zones. Two sputa examined by fluorescent microscopy were negative for AFB Pulmonary functions could not be done because of breathlessness, Blood gas studies showed a pH 7.53, PaO_2 42.4 mmHg, $PaCO_2$ 25.1 mmHg and HCO_3 +20.9 mmol/l. Bronchoalveolar lavage[3] using flexible fibreoptic bronchoscope showed an increase in cellularity in the lower respiratory tract (51.3 x 10^6/100 ml of the lavage fluid), with 82% lymphocytes, confirming the presence of lymphocytic alveolitis. The patient was provisionally diagnosed to be suffering from miliary tuberculosis based on clinical, radiological and lavage findings.

She was prescribed injection streptomycin 0.75 g, isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1 g and ethambutol 600 mg daily for the first 2 months, followed by rifampicin 450 mg and isoniazid 300 mg daily for the next 4 months. Meanwhile, the sputum, urine and lavage culture results were reported as positive for *M. tuberculosis* pre-treatment and the organisms were sensitive to streptomycin, isoniazid, rifampicin and ethambutol. Sputa became negative for *M. tuberculosis* by culture at 1st month of treatment. During the entire period of her 6 months chemotherapy, she had missed treatment only for a total of 16 days and she continues to be negative for *M. tuberculosis* by culture in sputum at the end of 6 and 12 months. She had also shown remarkable clinical and radiological improvement following the treatment. Pulmonary function tests at the end of treatment revealed a mild restrictive ventilatory defect (TLC% predicted 83%, RV% predicted 78%, FRC% predicted 83.4%) and diffusion defect (TLCO% predicted 76%). Arterial blood gases were normal (pH 7.4, PaO_2 104.2 mmHg and $PaCO_2$ 35.2 mmHg). There was a reduction in total cells (22.8 x 10^6/100 ml) and lymphocytes (37%) in BAL fluid following treatment (Table).

Case 2. A 45-year-old female patient was evaluated for cough, dyspnoea, chest pain and fever of 3 months duration. She was a housewife and non-smoker. She also denied any

previous illness or family history of tuberculosis. On physical examination, pulse rate was 92/min, respiratory rate 28/min, temperature 98.2 °F and BP 90/60 mmHg. There were no abnormal signs on auscultation. Mantoux with 1 TU PPD was 19 mm, and total leucocyte count was 10400/mm^3 with differentials as polymorphs 77%, lymphocytes 15% and eosinophils 8%. Urine and stool examinations were within normal limits. Skiagram chest showed miliary shadows in both lung fields. Out of a total of 6 sputa, one was positive for AFB by fluorescent microscopy. BAL showed that the total cells were 48.9 x 10^6/100 ml and lymphocytes were 75%, confirming the presence of lymphocytic alveolitis in this patient as well. She was given injection streptomycin 0.75 g, isoniazid 400 mg, rifampicin 450 mg and pyrazinamide 1.5 g thrice weekly for the first two months followed by streptomycin 0.75 g, isoniazid 600 mg and rifampicin 450 mg twice-weekly for the next 4 months. However, streptomycin was terminated at the end of 5th month due to giddiness. Her pre-treatment sputa and lavage cultures became positive for *M. tuberculosis* and the organisms were sensitive to streptomycin, isoniazid and rifampicin. Sputa became negative for *M. tuberculosis* by culture at 1st month of treatment. She had missed only one dose during the entire 6 months period of chemotherapy. She had also shown remarkable clinical and radiographic improvement following treatment and sputa continued to be negative for *M. tuberculosis* by culture at 6 and 12 months. BAL at 6 months had shown that total cells were 21.8 x 10^6/100 ml and lymphocytes were 66% (Table). Pulmonary function tests revealed that there was diffusion defect (TLCO% predicted 59.4%), with normal lung volumes.

Discussion

Clinical trials in tuberculous meningitis: pulmonary tuberculosis[2], spinal tuberculosis[5] and tuberculosis of lymphnodes[6] had shown that treatment with potent bactericidal and sterilising drugs for 6-9 months is adequate for remarkable therapeutic response. Though no controlled clinical trials in miliary tuberculosis of the lung have been reported, the highly satisfactory clinical response and complete radiographic resolution of the lesions in our patients suggest that 6 months treatment may be adequate for a bacteriological response in these patients.

Lymphocytic alveolitis in miliary tuberculosis prior to treatment has previously been reported[1]. Since the mean lymphocytes in BALF in our normal subjects[3] were 21 (SE ± 4%), the patients with lymphocytes ≥ 31% in BAL fluid was classified as having lymphocytic alveolitis. The persistence of lymphocytic alveolitis with reduced intensity in our patients even after treatment with potent chemotherapeutic regimen requires further indepth study. Will the alveolitis subside spontaneously as time passes or will it produce any deleterious effects on the lung parenchyma? Long term follow-up of such patients are essential to answer these questions. As it has been shown that lymphocytic alveolitis can cause lung injury and fibrosis in sarcoidosis and hypersensitivity pneumonitis[7], there is a possibility that alveolitis observed in miliary tuberculosis patients, despite treatment, may cause injury to lung parenchyma. In addition, the finding of reduced transfer factor at 6

month in our patients is also significant. Immunological investigations using BAL coupled with long term clinical and pulmonary function studies are required to unravel the mystery. If there is a possibility that these patients might develop interstitial fibrosis, the role of steroids in the management of miliary disease of the lung due to *M. tuberculosis* has to be critically evaluated, as it had been shown recently that anti-tuberculosis chemotherapy should be initially supplemented with steroids in patients with tuberculous constrictive pericarditis,[8] if there are no contra-indications. Another interesting finding in these patients is the occurrence of relative lymphopenia in peripheral blood, as opposed to lymphocytosis in BAL fluid, suggesting that there may be compartmentalisation of lymphocytes in miliary tuberculosis. An increased number of helper/inducer T-lymphocytes at sites of involvement had been previously reported in tuberculous pleural effusion[9], tuberculoid leprosy[10], pulmonary sarcoidosis[11], rheumatoid arthritis[12] and hypersensitivity pneumonitis[13]. It had been demonstrated in tuberculous pleural effusion that pleural T-lymphocytes, but not blood T-lymphocytes, released gamma interferon when exposed to PPD[14], suggesting that the immune response is also compartmentalised in tuberculous pleurisy. The observation of increased lymphocytes in BAL fluid and a simultaneous decrease in lymphocytes in periphera1 brood in our patients warrants further extensive immunological studies in miliary tuberculosis.

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