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Use of Corticosteroid as an Adjunct with Antitubercular Therapy in the Management of Miliary Tuberculosis Associated with Organizing Pneumonia- A Case Report

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Abstract

In miliary TB, the role of steroid remains to be unclear. Till date, extremely limited studies have been conducted to evaluate corticosteroids' role in miliary TB.

We report a patient with miliary TB and co-existing organizing pneumonia (OP), a condition that was managed successfully by anti-TB chemotherapy in adjunct with the corticosteroid. To the best of our knowledge, this association has not been reported or extremely infrequently reported in the existing literature.

The adjunctive use of corticosteroids does not appear to diminish the efficacy of 'adequate' anti-tuberculosis therapy. The use of corticosteroids has significant short- and long-term benefits in most forms of tuberculosis.

Keywords: ***Tuberculosis; Miliary; Organizing pneumonia; Corticosteroid***

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Introduction

Multidrug-resistance tuberculosis (TB) requires long-term anti-tubercular chemotherapy, and to oppose these inflammatory reactions, corticosteroids are employed as an adjunct with anti-TB treatment. However, the use of steroids can increase the susceptibility of other infections [1].

A recent systematic review and meta-analysis of 41 trials described that the application of corticosteroids as an adjuvant therapy with anti-TB medications resulted in a significant reduction in mortality, regardless of the organ group affected. The overall reduction in mortality from steroid use was found to be 17% (RR 0·83, 95% CI 0·74-0·92) [2].

In miliary TB, the role of steroid remains to be unclear. Till date, extremely limited studies have been conducted to evaluate corticosteroids' role in miliary TB. A study was performed by Sun et al. in 1981 with 55 miliary TB patients, which evaluated corticosteroid's effect. They concluded that the addition of corticosteroid compounded by anti-TB chemotherapy facilitated the control of infection as well as reduced toxic adverse effects [1,3].

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In this study, we report a patient with miliary TB and co-existing organizing pneumonia (OP), a condition that was managed successfully by anti-TB chemotherapy in adjunct with the corticosteroid. To the best of our knowledge, this association has not been reported or extremely infrequently reported in the existing literature.

Case Presentation

A 76-year-old male presented to our accident and emergency unit with a three-week history of generalized fatigability, loss of appetite, weight loss, and fever that had been deteriorating in the past week. He was a known case of type 2 diabetes mellitus who was on an oral hypoglycemic agent. His surgical history was significant for the transurethral resection of bladder tumor and intravesical BCG (Bacillus Calmette–Guérin); the surveillance was found negative for recurrence.

On examination, the patient was found to be conscious and alert; he did not exhibit any respiratory distress. He was emaciated, but no pallor, jaundice, cyanosis, clubbing, or lymphadenopathy was observed. He was afebrile with other vital parameters as stable.

Chest examination revealed bilateral fine crepitation, while the other systemic examination was unremarkable. The CXR (X-ray chest) displayed diffused bilateral military opacities (Figure 1). Inflammatory markers were high: ESR (erythrocyte sedimentation rate), 43 mm in the first hour and CRP (C-reactive protein), 94 mg/L. The complete blood count, renal and hepatic functions, and electrolytes were within their normal limits. The patient underwent a bronchoscopy; the transbronchial lung biopsy was conducted with bronchoalveolar lavage (BAL). The BAL revealed 76% lymphocyte in cell differentials and was found negative for malignant cells. BAL stain was also found negative for acid-fast bacilli (AFB), fungal, and PCP. The transbronchial biopsy revealed poorly formed granulomatous inflammation and staining, while AFB and fungi were negative (Figure 2). The PPD (purified protein derivative) test and 3 sputa AFB were also negative.

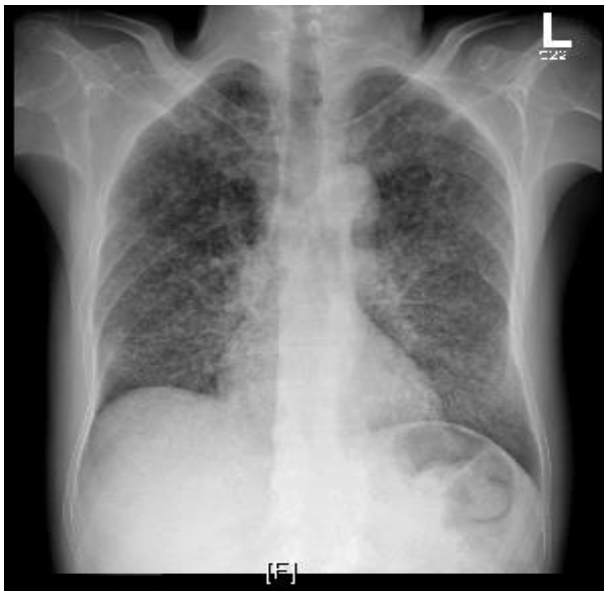

Figure 1: Chest X ray (PA view) demonstrates wide spread small (2-4mm) nodular opacities distributed throughout both lungs.

The provisional diagnosis was reported as miliary TB, and the patient was entered into quadruple antitubercular chemotherapy that included Isoniazid, Rifampin, Ethambutol, and Pyrazinamide, and an adjunct tab. The administration of prednisolone 20 mg daily was also started.

The patient remained in the hospital for three weeks and showed clinical and symptomatic improvement. He was discharged with four anti-TB regimens and advised prednisone, to be tapered gradually over two weeks and subsequently terminated.

In the following four weeks, the patient's condition continued to deteriorate, and he had a high-grade fever of up to 39°C, suffered weight loss, reduced appetite, and overall weakness. He was compliant with the anti-TB medications.

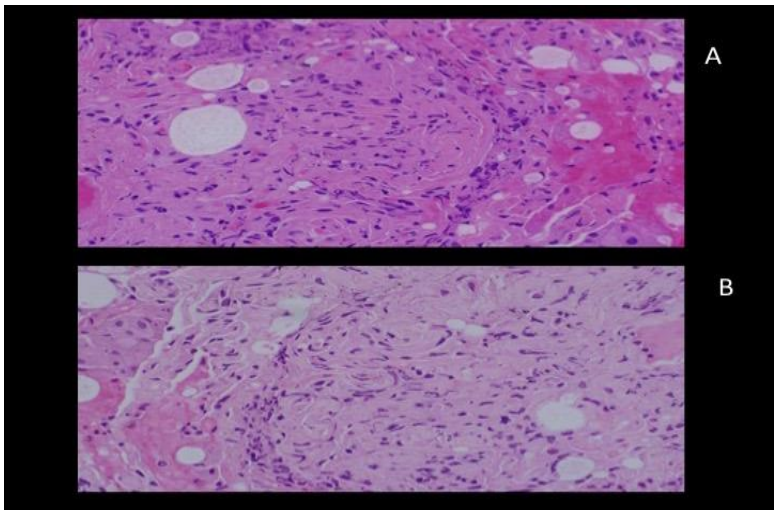

Figure 2A & 2B: Transbronchial lung biopsy report: Poorly Formed granulomatous inflammation and Staining for AFB and Fungi was Negative.

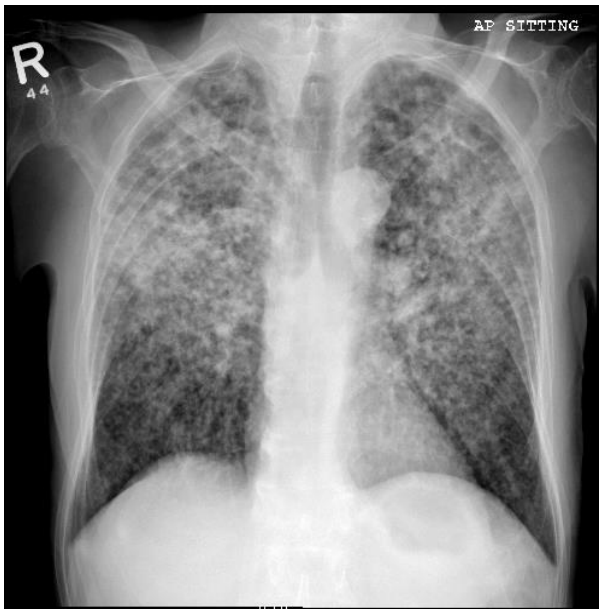

Figure 3: Follow up PA chest radiograph (sitting position) demonstrates progression of the nodular opacities compared to previous radiograph.

On examination, he was found to have a low-grade fever (37.4°C), O2 saturation of 95% with the oxygen mask, the pulse rate was 80 beats per minute, blood pressure was 101/55 mmHg, and the respiratory rate was 20 per minute. The chest examination revealed scattered crepitation.

The laboratory examination revealed an increased white cell count (16 × 109) with neutrophilia, raised ESR (120 mm/hr). CXR demonstrated progression in the bilateral airspace disease (Figure 3).

The CT chest revealed diffuse miliary shadows with airspace consolidation, mainly in the upper lobes with multiple, mildly enlarged lymphadenopathy in the upper mediastinum, paratracheal, and the aortopulmonary window, and inferiorly to the carina (Figure 4).

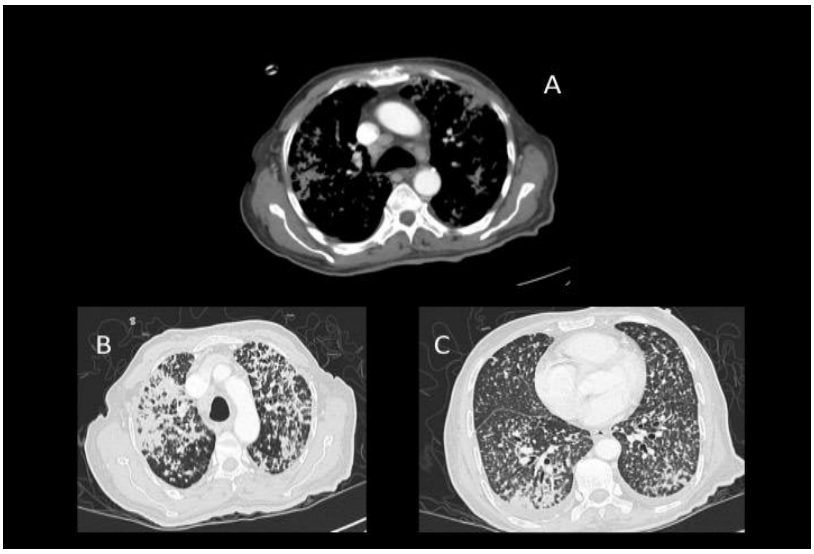

Figure 4A, 4B & 4C: CT chest (mediastinal and lung algorithms) confirms the presence of innumerable small pulmonary nodules, which have a centrilobular predilection and dependent changes are also present.

Repeated bronchoscopy revealed BAL 54% lymphocyte in cell differentials and was found to be negative for malignant cells. The BAL stain yielded negative AFB, fungal, and PCP. The transbronchial biopsy demonstrated bronchopneumonia with organization and staining; AFB and fungi were negative (Figure 5). Blood culture and sputum for acid-fast bacilli were found to be negative. The workup for Aspergillus, blastomycosis, coccidiosis, Histoplasma, and HIV all yielded negative results. Tumor markers, as well as the autoimmune study (ANA, pANCA, cANCA), were also found to be negative.

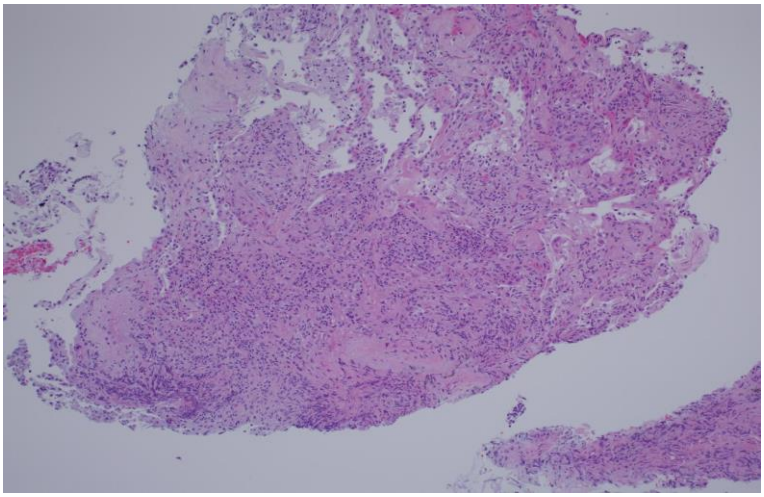

Figure 5: Repeat transbronchial lung biopsy report: Bronchopneumonia with organization and staining for fungi, PCP & AFB negative.

Our surmise was the presence of drug-resistant tuberculosis, superimposed bacterial infection, malignancy (bladder, lymphoma), vasculitis, sarcoidosis, or adverse drug reaction.

He was entered on a course of intravenous antibiotic Tazobactum and vancomycin. Additionally, 20 mg of prednisone was administered twice daily to treat OP diagnosed from the transbronchial biopsy.

The patient was discharged in an improved condition with anti-TB medications in addition to a tapering daily dosage of tab prednisolone 40 mg.

Unfortunately, the patient returned to us three weeks later with high-grade fever and unstable vitals (pulse: 124 beats per minute; blood pressure: 100/44 mmHg; respiratory rate: 30 per minute; O_2 saturation: 93% on 4 L/min of oxygen by the facial mask).

The sputum AFB was positive, and PCR for Mycobacterium from sputum was also reported as positive.

The differential diagnosis was made as follows: drug-resistant tuberculosis (MDR), aggravation of TB due to steroids, relapse of BOOP (Bronchiolitis obliterans organizing pneumonia), or paradoxical reaction.

The prednisolone administration was stopped; anti-TB medications INH and Rifampicin were continued sequentially, and other medications in the regimens were stopped. He was also entered on a course of Amikacin and Moxifloxacin. However, the fever continued to increase; his condition did not show improvement.

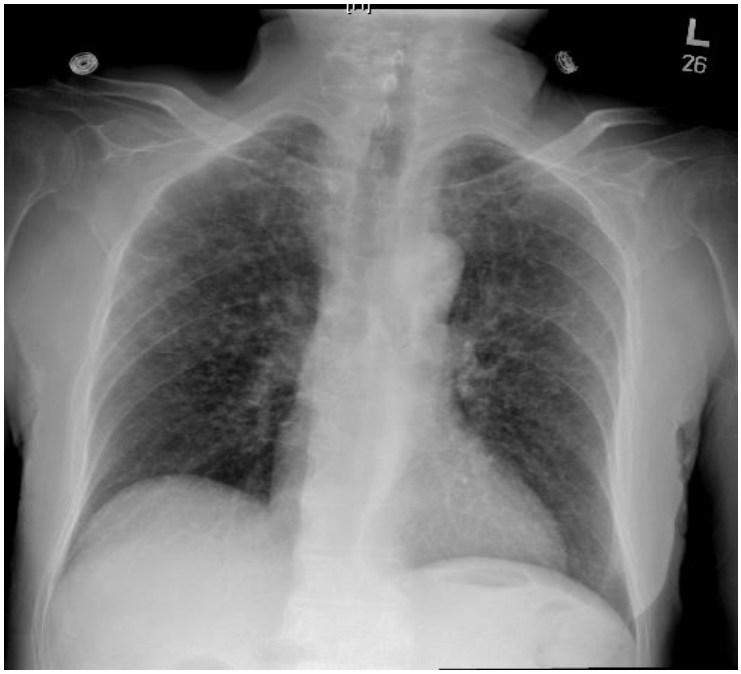

Figure 6: Follow up PA chest radiograph after treatment demonstrates complete resolution of the miliary nodules.

It was observed that when the steroid dosage was tapered, the patient suffered a relapse. Therefore, the prednisone 20 mg dosage twice daily was restarted. The patient showed symptomatic and clinical improvement, and the body temperature tended to shift toward normal. He was discharged after he showed improvement with the intake of INH, Rifampicin, and prednisone. The anti-TB medications were continued for a total of 12 months. The prednisone dosage was tapered gradually and

discontinued after eight weeks. He remained healthy, regular follow-ups were done, and no further relapses were observed. Follow up chest radiograph showed complete resolution of the miliary nodules (Figure 6).

Discussion

The paradoxical deterioration during anti-TB therapy, defined as the clinical or radiological deterioration of pre-existing TB lesions or the development of new lesions in a patient who initially shows improvement, remains a diagnostic dilemma for the researchers [4]. It has been reported for HIV-positive patients with pulmonary TB under retroviral therapy. In the literature, a case of miliary TB with a fever lasting for more than two months in spite of the provision of anti-TB treatment was found [5].

In an analysis of 75 patients, the mean time for the resolution of fever was found to be 16 days, while the fever response was recorded until 109 days after the onset of anti-TB treatment. The treatment of the contradictory response included surgical intervention and administration of steroids in this group [6].

In the case noted here, we continued the empirical anti-TB therapy in spite of radiological deterioration and persistent fever and observed the clinical and laboratory response.

Transient deterioration on radiography was observed in 45% of 31 HIV-positive patients with pulmonary TB under retroviral therapy and improvement occurred between two weeks and three months later in another study [7].

In another study, the paradoxical response was reported in two HIV-infected patients with TB after the initiation of anti-TB therapy: one of them also received anti-retroviral therapy [8].

For these cases, the authors suggest that an improved immune function leads to a greater inflammatory reaction that contributed to the paradoxical deterioration.

Regarding our experience with this patient, we do not advise radiological examination to evaluate response early in the course of treatment, because it may mislead the physician. More importantly, with the observation of the paradoxical response in our patient, we hypothesize that anti-TB therapy may lead the patient to regain immune function suppressed by miliary TB and a related increase in inflammatory response. The paradoxical response should also be recognized for non-HIV miliary TB patients so that one does not interrupt the anti-TB treatment due to transient deterioration. Our patient presented a picture highly suggestive of miliary TB, for which, anti-TB medications were started immediately. One of the differential diagnoses on the top of the list was bladder cancer metastasis. Indeed, this differential has been ruled out based on the transbronchial biopsy report and the follow-up surveillance cystoscopy; the biopsy was negative merely four weeks prior to the presentation.

Our reported case had miliary TB and co-existing OP

OP is a non-specific repair process seen in a variety of clinical settings. It has been reported secondary to numerous infectious agents. Other secondary associations include several connective tissue and autoimmune diseases, vasculitis, various drugs, malignancies (especially hematological), and lung radiotherapy. The potential mechanisms by which Mycobacterium and OP are associated are interesting. Mycobacterium is known to induce the production of cytokines such as interleukin-8, which shows an increased presence in bronchoalveolar lavage fluid of patients with Mycobacterium infection. It has been reported that both interleukin-8 and fibronectin genes undergo increased expression in OP, suggesting a role of cytokine activation through alveolar macrophages in the inflammatory process [9].

Corticosteroids are currently the standard therapy for both variants of OP, although spontaneous remission is known to occur. Recent British Thoracic Society (BTS) guidelines recommend initial doses of prednisolone 0.75-1 mg/kg, decreasing over 12 months. Clinical response is frequently dramatic, with improvement observable within 48 hours of therapy, while radiographic improvement usually lags behind by several weeks. However, relapse is common as corticosteroid doses are reduced but seldom occur when the maintenance dose of prednisolone exceeds 20 mg/day [10].

The above fact may explain the deterioration in the condition of our patient that required recurrent admissions and prolonged fever. This compels us to consider other differential diagnosis and modify anti-TB medications throughout the course of the disease.

Conclusion

In our case, the adjunctive use of corticosteroids does not appear to diminish the efficacy of 'adequate' anti-tuberculosis therapy. The use of corticosteroids has significant short- and long-term benefits in most forms of tuberculosis. Large studies are recommended to further investigate this matter.

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