Case Report

Acute Respiratory Distress Syndrome Secondary to Pulmonary Tuberculosis: A Case Report and Literature Review

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Acute respiratory distress syndrome (ARDS) is an unusual and rare manifestation of pulmonary tuberculosis (TB). The mortality rate of TB with respiratory failure is high. We report a patient who had an initial manifestation mimicking severe bacterial pneumonia with ARDS not responding to antibacterial therapy. Acid-fast bacilli and *M. tuberculosis* isolates were identified from tracheal aspiration and bronchoalvelolar lavage. Intensive respiratory care and early anti-tuberculosis therapy provided a good clinical outcome.

Keywords: Pulmonary tuberculosis, *Mycobacterium tuberculosis,* Acute respiratory distress syndrome

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Tuberculosis (TB) remains a major public health problem in several countries, including Thailand[1]. The 2016 Global TB report by WHO estimated the TB prevalence and mortality rates in Thailand were 172/100,000 population and 12/100,000 population, respectively[1]. Several studies have demonstrated that a number of medical conditions are associated with mortality; these include liver cirrhosis, extrapulmonary involvement[2], malignancy, HIV infection[3], receiving immunosuppressive agents[4], and radiographic findings, such as miliary infiltration, pneumonic pattern, and cavitary lesion[2]. *Mycobacterium tuberculosis* (MTB) is transmitted to humans by inhalation of infected aerosol. Thus, the lungs are the most affected site of infection, and pulmonary TB usually manifests as a chronic productive cough, fever and constitutional symptoms. Radiographic findings typically show reticulonodular infiltration, cavitary lesions or occasionally patchy consolidations. However, acute respiratory distress syndrome (ARDS) is an unusual and rare manifestation of pulmonary TB. The rate of ARDS secondary to pulmonary TB ranged between 1.3%-1.5% in previous studies[5,6]. The mortality rate of TB with respiratory failure is high, at approximately 60%-70%[7,8]. We report on a patient who suffered from pulmonary TB complicated by ARDS who had a good outcome after anti-tuberculosis therapy.

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Case Report

A previously healthy, 16-year-old woman presented with fever and a non-productive cough of 2-week duration. Initially, she received oral amoxicillin (2 grams/day) from a private hospital, but her symptoms did not improve. One week later, she felt more febrile and developed a frequent cough with yellowish sputum production. A chest radiograph revealed a patchy infiltration in the left upper and middle lung areas suggestive of pneumonia. After admission to the private hospital, she intravenously received cefepime (6 grams/day) and azithromycin (500 milligrams/day). A sputum culture was overgrown by oropharyngeal flora. Her shortness of breath worsened, and she was transferred to Siriraj Hospital, Bangkok, Thailand, after receiving the antibiotics for 3 days. A physical examination revealed a body temperature of 38°C, heart rate of 110 beats/minute, respiratory rate of 25 times/minute, blood pressure of 100/60 mmHg and room-air oxygen saturation of 82%. A chest examination found dullness on percussion and decreased breath sound over the left lung. There was no hepatosplenomegaly or lymphadenopathy.

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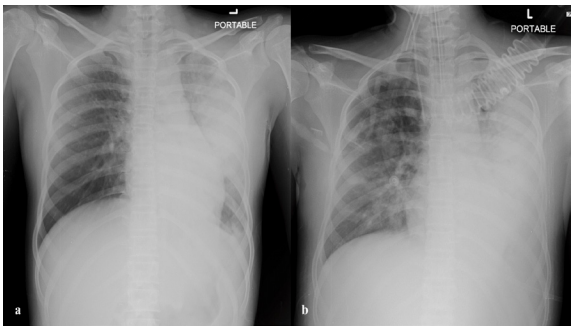

Figure 1. (a) Chest radiograph initially revealed consolidation of left upper lung and left lingular lobe, and (b) subsequent chest radiograph revealed significant increase of consolidation with air bronchogram involved almost entire left hemithorax and new alveolar infiltrates at right lung.

The results from other physical examinations were unremarkable. A chest radiography showed consolidation of the left upper lung and the left lingular lobe (Figure 1a). Intravenous piperacillin-tazobactam (4.5 grams) every 6 hours was initially prescribed to treat severe bacterial pneumonia. Soon after admission, however, the patient developed respiratory failure, necessitating endotracheal intubation and mechanical ventilatory support. A chest radiograph post intubation showed a progressive increase of the consolidation with air bronchogram involving almost the entire left hemithorax, and with new patchy infiltrations in the right lung (Figure 1b). The arterial blood gas revealed a pH of 7.36, $PaCO_2$ of 35.6 mmHg, PaO_2 of 90.5 mmHg, HCO3 of 19.7 mEq/L, and PaO_2/FiO_2 ratio of 150, which are compatible with moderate ARDS as defined elsewhere[9]. An endotracheal aspiration sent for a Gram stain and routine bacterial culture, including a commercial multiplex real-time PCR assay for respiratory pathogens (Allplex Respiratory Panels, Korea), found no organisms. Bronchoalvelolar lavage (BAL) was performed after 2 days of intubation. An acid-fast stain of the BAL fluid and subsequent endotracheal aspiration samples demonstrated positive acid-fast bacilli (AFB), and a direct real-time polymerase chain reaction assay (rt-PCR; Anyplex MTB/NTM, Korea) was positive for MTB complex. Cultures on Lowenstein-Jensen media grew MTB complex, identified by using biochemical testing and INNO-LiPA Mycobacteria v2 assay (Innogenetics, Ghent, Belgium). The patient denied having close contact with a TB patient, or having consumed cigarettes, alcohol or illicit drugs. Other laboratory investigations showed a hemoglobin of 9 g/dl, hematocrit of 30%, white blood cell count of 2,780/mm^3 (neutrophils, 83%; lymphocytes, 7%; bands, 10%), platelet count of 125,000/mm^3, blood sugar of 101 mg/dL, BUN of 4.5 mg/dL and creatinine of 0.53 mg/dl. Anti-HIV was non-reactive, and immunological studies were negative for the anti-IFN gamma autoantibody, IFN-gamma receptor, and interleukin-12 receptor. The CD4 and CD8 T-cell counts were 245 cells/μl (56.13%) and 71 cells/μl (16.25%), respectively. Anti-tuberculosis agents, namely, isoniazid (INH; 300 mg/day), rifampicin (RFP; 450 mg/day), pyrazinamide (PZA; 1,000 mg/day) and ethambutol (ETB; 800 mg/day) were promptly commenced after knowing of the AFB smear-positive sputum result.

The patient was progressively weaned from the mechanical ventilator and was extubated after 7 days of intensive respiratory care. Anti-tuberculosis susceptibility testing by broth microdilution method ensued, and demonstrated that the isolate was susceptible to all, first-line anti-tuberculosis agents. On the seventh day of anti-tuberculosis therapy, the pulmonary infiltration gradually resolved, including defervescence of the fever. The patient was discharged home without complications. At the 2- and 4-month follow-ups, the patient had no fever, no dyspnea, and a reduced productive cough; on both occasions, a chest radiograph revealed markedly decreased pulmonary infiltrations (Figure 2, a and b), and her sputum acid fast stain was negative. The patient complied well with the anti-tuberculosis therapy, and there were no complications. As the patient showed complete resolution of chest radiographic findings after 9 months of treatment, the therapy was discontinued.

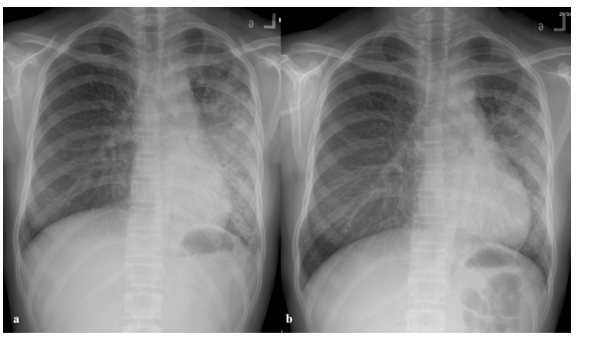

Figure 2. Chest radiograph following anti-tuberculosis therapy for 2 (a) and 4 months (b) showed decrease of consolidation of left hemithorax and markedly resolved infiltration at right lung

Discussion

Pulmonary TB presenting as a rapidly progressive pneumonia with ARDS is very unusual because tubercle bacilli have a slow multiplication rate [10]. The pathogenesis of ARDS secondary to pulmonary TB has not been clearly defined. The acquisition of massive tubercle bacilli and the subsequent release of mycobacteria into the pulmonary circulation, thereby causing severe inflammation, endothelial injury and alveolocapillary membrane damage[11], has been hypothesized as the mechanism of ARDS in TB patients. In addition, lipoarabinomannan, a component of the mycobacterial cell wall, may activate macrophages to release inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1b (IL-1b)[12]. The activation of the macrophages and the secretion of the cytokines are also thought to be central in causing lung injury[12].

The rapid progression of pulmonary TB can mimic bacterial pneumonia. Patients can have systemic toxicities, a productive cough, the presence of pulmonary consolidation in chest radiographs, and AFB-positive sputum[13]. Patients also have a shorter duration of symptoms (approximately 2–6 weeks) than with classical pulmonary TB[8,13–16]. This condition is often seen in advanced age, HIV-infected persons, and in patients who are receiving immunosuppressive agents or corticosteroids[8]. The authors also reviewed previous case reports of ARDS secondary to pulmonary TB. The ages of the previous cases ranged between 15–81 years; some patients had predisposing conditions, such as alcoholism, diabetes mellitus, cirrhosis, Addison's disease, and rheumatoid arthritis[11,17–20]. A previous study found approximately 21% and 3% had immunosuppressed conditions and HIV infections, respectively, whereas 28% had no predisposing conditions[21]. Onset of ARDS following the pulmonary-TB diagnosis varied among a few days to several weeks[11,17–20] . The present case had a temporal duration and clinical manifestations similar to those in the previous studies, but the patient was younger and has no predisposing or apparent immunodeficiency conditions. The reviewed cases of ARDS secondary to pulmonary TB had non-specific and varying chest-radiographic features, such as diffuse alveolar infiltration, reticulonodular infiltration, mixed alveolar and interstitial infiltration, military infiltration, and predominated unilateral infiltration[11,17–21]. In the case of patients who had a unilateral pulmonary infiltration which progressed rapidly to respiratory failure without responding to antibacterial therapy, pulmonary TB with ARDS should be included as a differential diagnosis. A sputum examination was the optimal diagnostic method for pulmonary TB with ARDS for almost all of the previous case reports. WHO recommends that sputum for acid-fast stain, a mycobacterial culture, and molecular testing be considered as mandatory for the early diagnosis of TB[22]. It is difficult to differentiate rapidly progressing pulmonary TB from severe bacterial pneumonia. Lee et al demonstrated approximately 70% of patients who had TB with ARDS were diagnosed pneumonia without causative pathogens other than MTB [21]. Approximately 30% of TB patients with respiratory failure received delayed anti-tuberculosis treatment[23]. Acid-fast staining and direct molecular detection from the patient's sample can assist in early diagnosis and treatment. Samples other than respiratory specimens such as gastric fluid, urine, bone marrow, lymph nodes, or tissue biopsy might assist in the diagnosis of TB from previous studies[11,20-21].

Treatment of ARDS whether due to pulmonary TB or other causes is similar. Pressure and volume limitation, which uses low tidal volume and limited plateau pressure, is strongly recommended to treat this condition[24,25]. The prompt administration of combined anti-tuberculosis agents, such as INH, RFP, PZA and ETB, is also appropriate when pulmonary TB with ARDS is suspected. The presented case received the early anti-tuberculosis regimen after learning of the AFB smear-positive sputum result. Early and optimal anti-tuberculosis treatment can improve the outcome. The WHO guidelines recommend the use of adjunctive corticosteroids in the treatment of TB meningitis and pericarditis[26]. However, the beneficial effect of corticosteroids in the treatment of pulmonary TB with ARDS is still inconclusive. Pharmacologically, corticosteroids are considered to reduce the severe pulmonary inflammation causing pulmonary gas exchange impairment[26,27]. A previous study demonstrated that a combined anti-tuberculosis and prednisolone regimen for patients with pulmonary TB provided rapid clinical and radiological improvement[28]. However, Lin et al found adjunctive corticosteroids did not alter the survival rate of patients with severe pulmonary diseases[29]. Monitoring for adverse effects, such as gastrointestinal bleeding or increased opportunistic infections, should be considered when prescribing corticosteroids for severely ill patients. We suggest the use of corticosteroids in the treatment of severe pulmonary TB should be decided on a case-by-case basis, weighing

the risks and benefits of this agent. The presented case received standard anti-tuberculosis agents without adjunctive corticosteroid, and a good outcome ensued. Duration of treatment is not different form treatment of pulmonary TB based on clinical and radiological responses. The present case required a 9-month anti-TB regimen because of delayed radiological response. The hospital mortality rate of patients with pulmonary TB who need mechanical ventilatory support is significantly higher than that for patients with non-tuberculous pneumonia[17]. ARDS secondary to pulmonary TB is more commonly found in miliary TB and is associated with a high fatality rate[30,31]. APACHE II score, serum sodium and PaO_2/FiO_2 ratio[20] including higher Sequential Organ Failure Assessment (SOFA) score[21] were determinant factors associated with mortality.

In conclusion, TB should be considered as a possible cause of ARDS, particularly in countries with high endemicity. ARDS, an unusual manifestation of pulmonary TB, can occur in patients without apparent immunodeficiencies. Clinical findings of pulmonary TB with ARDS can mimic severe bacterial pneumonia. Severe pneumonia with ARDS which is not responsive to antibacterial treatment or has no microbiological evidence of bacterial infection, *M. tuberculosis* should be included in probable etiologies. Early diagnosis, the use of combined anti-TB agents and intensive respiratory care are the mainstays of treatment for this condition.

What is already known on this topic?

Clinical findings of pulmonary tuberculosis with acute respiratory syndrome (ARDS) can mimic severe bacterial pneumonia. Severe pneumonia which is not responsive to antibacterial treatment or has no microbiological evidence of bacterial infection, *M. tuberculosis* should be included in probable etiologies.

What this study adds?

Pulmonary tuberculosis should be considered as a possible cause of ARDS, particularly in countries with high endemicity. It can also occur in patients without apparent immunodeficiencies.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. Global tuberculosis control: WHO report 2016. Geneva: WHO; 2016.
2. Lin CH, Lin CJ, Kuo YW, Wang JY, Hsu CL, Chen JM, et al. Tuberculosis mortality: patient characteristics and causes. BMC Infect Dis 2014;14:5.
3. Sterling TR, Zhao Z, Khan A, Chaisson RE, Schluger N, Mangura B, et al. Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors. Int J Tuberc Lung Dis 2006;10:542-9.
4. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis 2011;15:871-85.
5. Magazine R, Rao S, Chogtu B, Venkateswaran R, Shahul HA, Goneppanavar U. Epidemiological profile of acute respiratory distress syndrome patients: A tertiary care experience. Lung India 2017;34:38-42.
6. Levy H, Kallenbach JM, Feldman C, Thorburn JR, Abramowitz JA. Acute respiratory failure in active tuberculosis. Crit Care Med 1987;15:221-5.
7. Ryu YJ, Koh WJ, Kang EH, Suh GY, Chung MP, Kim H, et al. Prognostic factors in pulmonary tuberculosis requiring mechanical ventilation for acute respiratory failure. Respirology 2007;12:406-11.
8. Kim YJ, Pack KM, Jeong E, Na JO, Oh YM, Lee SD, et al. Pulmonary tuberculosis with acute respiratory failure. Eur Respir J 2008;32:1625-30.
9. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
10. Erbes R, Oettel K, Raffenberg M, Mauch H, Schmidt-Ioanas M, Lode H. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. Eur Respir J 2006;27:1223-8.
11. Piqueras AR, Marruecos L, Artigas A, Rodriguez C. Miliary tuberculosis and adult respiratory distress syndrome. Intensive Care Med 1987;13:175-82.
12. Zhang Y, Doerfler M, Lee TC, Guillemin B, Rom WN. Mechanisms of stimulation of interleukin-1 beta and tumor necrosis factor-alpha

by *Mycobacterium tuberculosis* components. J Clin Invest 1993;91:2076-83.
13. Schwartz WS, Moyer RE. The management of massive tuberculous pneumonia; a therapeutic review of seventy-five cases. Am Rev Tuberc 1951;64:41-9.
14. Calix AA, Ziskind MM, Leonard AJ, Anderson HS, Block J, Jacobs S. Acute tuberculous pneumonia in the Negro. Am Rev Tuberc 1953;68:382-92.
15. Septimus EJ, Awe RJ, Greenberg SD, Raleigh JW. Acute tuberculous pneumonia. Chest 1977;71:774-5.
16. Zahar JR, Azoulay E, Klement E, De Lassence A, Lucet JC, Regnier B, et al. Delayed treatment contributes to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure. Intensive Care Med 2001;27:513-20.
17. Dyer RA, Potgieter PD. The adult respiratory distress syndrome bronchogenic pulmonary tuberculosis. Thorax 1984;39:383-7.
18. Raina AH, Bhat A, Bhat FA, Changal KH, Dhobi GN, Koul PA, et al. Pulmonary tuberculosis presenting with acute respiratory distress syndrome (ARDS): A case report and review of literature. Egypt J Chest Dis Tuberc 2013;62:655-9.
19. Omote N, Kondoh Y, Taniguchi H, Kimura T, Kataoka K, Hasegawa R, et al. Acute respiratory distress syndrome due to severe pulmonary tuberculosis treated with extracorporeal membrane oxygenation: A case report and review of the literature. Respir Med Case Rep 2016;19:31-3.
20. Sharma SK, Mohan A, Banga A, Saha PK, Guntupalli KK. Predictors of development and outcome in patients with acute respiratory distress syndrome due to tuberculosis. Int J Tuberc Lung Dis 2006;10:429-35.
21. Lee K, Kim JH, Lee JH, Lee WY, Park MS, Kim JY, et al. Acute respiratory distress syndrome caused by miliary tuberculosis: a multicentre survey in South Korea. Int J Tuberc Lung Dis 2011;15:1099-103.
22. World Health Organization. Framework of indicators and targets for laboratory strengthening under the End TB Strategy. Geneva: WHO; 2016.
23. Penner C, Roberts D, Kunimoto D, Manfreda J, Long R. Tuberculosis as a primary cause of respiratory failure requiring mechanical ventilation. Am J Respir Crit Care Med 1995;151:867-72.
24. Ryu YJ. Diagnosis of pulmonary tuberculosis: recent advances and diagnostic algorithms. Tuberc Respir Dis (Seoul) 2015;78:64-71.
25. Claesson J, Freundlich M, Gunnarsson I, Laake JH, Vandvik PO, Varpula T, et al. Scandinavian clinical practice guideline on mechanical ventilation in adults with the acute respiratory distress syndrome. Acta Anaesthesiol Scand 2015;59:286-97.
26. World Health Organization. Treatment of tuberculosis: guidelines. Geneva: WHO; 2010.
27. Schlossberg D. Acute tuberculosis. Infect Dis Clin North Am 2010;24:139-46.
28. Marcus H, Yoo OH, Akyol T, Williams MH Jr. A randomized study of the effects of corticosteroid therapy on healing of pulmonary tuberculosis as judged by clinical, roentgenographic, and physiologic measurements. Am Rev Respir Dis 1963;88:55-64.
29. Lin SM, Wang TY, Liu WT, Chang CC, Lin HC, Liu CY, et al. Predictive factors for mortality among non-HIV-infected patients with pulmonary tuberculosis and respiratory failure. Int J Tuberc Lung Dis 2009;13:335-40.
30. Shneerson JM. Respiratory failure in tuberculosis: a modern perspective. Clin Med (Lond) 2004;4:72-6.
31. Kim JY, Park YB, Kim YS, Kang SB, Shin JW, Park IW, et al. Miliary tuberculosis and acute respiratory distress syndrome. Int J Tuberc Lung Dis 2003;7:359-64.