Risk Factors for Development of Paradoxical Response during Anti-Tuberculosis Treatment in HIV-Negative Patients with Pleural Tuberculosis

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Paradoxical response (PR) is the unusual expansion or new formation of a tuberculous lesion during anti-tuberculosis (TB) treatment. Pleural TB is the second most common form of extrapulmonary TB and has clinical importance because it occurs in a restricted space. Limited information is available for PR in HIV-negative patients with pleural TB. The aim of this study was to evaluate the clinical characteristics and risk factors of PR in HIV-negative patients with pleural TB. Patients diagnosed with pleural TB between 2003 and 2008 at Chung-Ang University Hospital and Yong-San Hospital, Seoul, South Korea were included. We evaluated the incidence and treatment outcome of PR in pleural TB, and compared baseline clinical characteristics and laboratory findings between TB patients with PR and those without PR. PR was present in 32 (23%) of 139 patients after mean 51.1 days following initiation of treatment. Out of 32 patients, 18 patients needed additional treatment for symptom control. PR patients had a high incidence of adverse drug reaction such as drug skin reaction or liver function abnormality ($P < 0.05$). The risk factors for PR are younger age, high serum albumin level, low proportion of lymphocyte, and high proportion of PMN in pleural fluid ($P < 0.05$). PR is not an uncommon problem in HIV-negative pleural TB and half of these patients need additional treatment. Therefore, physicians must pay more attention for PR during the management of pleural TB in the expected patients to develop PR.

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Pleural tuberculosis (TB) is estimated to constitute approximately 5-30% of all disease caused by *Mycobacterium tuberculosis* (Seibert et al. 1991; Ferrer Sancho 1996). The current recommendation for pleural TB is the same as for pulmonary TB (Bass et al. 1994). However, despite documented therapeutic successes, some patients show deterioration during anti-TB therapy. This deterioration is called paradoxical response (PR), and it remains a clinical challenge.

PR is the unusual expansion or new formation of a tuberculous lesion during TB treatment (Smith 1987). PR is one phenomenon of the immune reconstitution inflammatory syndrome and has been extensively reported in HIV-positive patients receiving highly active antiretroviral therapy (HAART) (Wendel et al. 2001; Cheng et al. 2002; Navas et al. 2002). However, PR can also occur in HIV-negative patients, especially in extra-pulmonary TB including pleural TB (Cheng et al. 2002; Cheng et al. 2007). Clinically, PR may be confused with treatment failure, drug

resistant TB, or other infection, especially in extra-pulmonary cases that have a low positive rate of pathogen culture (Baumann et al. 2007). However, only limited information is available on the clinical characteristics and risk factors for PR of pleural TB in HIV-negative patients (Al-Majed 1996; Kumar and Vasu 2001; Choi et al. 2002).

The aim of this study was to estimate the incidence and clinical course of PR in HIV-negative patients with pleural TB and to determine the parameters for predicting PR in HIV-negative patients with pleural TB.

Methods

Study design and patients

Patients diagnosed with pleural TB between January 2003 and December 2008 at Chung-Ang University Hospital and Yong-San Hospital were included in this retrospective study. We excluded patients who had pleural TB with HIV infection and also those younger than 15 years of age. Anti-TB medications including isoniazid, rifampicin, ethambutol and pyrazinamide were administered. We

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evaluated the incidence, clinical course, and treatment outcomes of PR in pleural TB. Demographic findings, adverse drug reactions, white blood cell (WBC) count, and pleural fluid parameters, including differential cell count, lactate dehydrogenase (LDH), total proteins, and adenosine deaminase (ADA) levels, were compared between patients with PR and patients without PR when available. The Institutional Review Board of Yong-San Hospital, Seoul, Korea, and Chung-Ang University Hospital, Seoul, Korea, approved this study.

Diagnostic criteria of pleural TB and PR

The diagnosis of pleural TB depended on 1) the demonstration of acid-fast bacilli (AFB) or the growth of *M. tuberculosis* in pleural fluid or pleural biopsy specimens; 2) the presence of classical caseating granulomas in the pleural tissue and a successful response to anti-TB therapy; or 3) a lymphocyte-predominant exudative effusion with ADA levels (> 401 U/L) and a successful response to anti-TB therapy (Gopi et al. 2007). The positive predictive value of lymphocyte predominant exudates with ADA levels (> 401 U/L) is 100% in the Korean population (Kim et al. 2006).

PR was defined as the worsening of radiological findings following the initiation of appropriate anti-TB treatment in the absence of evidence of disease relapse or the presence of another diagnosis (Breen et al. 2004). Whom onset of paradoxical response occurs within 14 days after initiation of anti-TB treatment are excluded in PR. Worsening of radiological findings was defined when pleural effusion increased or new parenchymal lesion developed. Two independent radiologists evaluated the radiographic findings in our study.

Statistical analysis

All tests of significance were two-sided and were conducted using the Statistical Package for the Social Sciences (SPSS) software (version 16.0; SPSS; Chicago, IL, USA). Values are expressed as mean $\pm$ standard deviation. Univariate comparisons between the PR-positive group and the PR-negative group were performed using the Pearson χ^2 test or Fisher Exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Multivariate analysis was performed using logistic regression to adjust other variables. A *P* value < 0.05 was considered statistically significant.

Results

Patients with pleural TB

Over the course of our study, 139 patients (80 males and 59 females) were diagnosed as having pleural TB (Table 1). The mean age was 46.6 years. Past medical history of tuberculosis was corresponded to 18 patients (12.9%). The 12 patients (8.6%) were suffered from diabetes mellitus and 7 patients were chronic alcoholics. Mean treatment duration and follow-up duration were 7.2 months and 14.7 months.

Clinical characteristics of the 32 patients with PR

PR occurred in 32 (23%) patients after they began anti-TB medication (Table 2). These PR patients included 18 males and 14 females with the mean age of 37.9 years. The mean onset time of PR was 51.1 days after starting anti-TB medication. The patients over half had no symptom. Out of 32 patients, 18 patients received additional

Table 1. Demographic and clinical characteristics of 139 patients with pleural tuberculosis.

Characteristic	N = 139
Age, years	46.6 $\pm$ 21.6
Male gender	80 (57.6%)
Body mass index	21.2 $\pm$ 3.0
Active smoker	44 (31.7%)
Past history of tuberculosis	18 (12.9%)
Comorbidity	
Diabetes mellitus	12 (8.6%)
Chronic alcoholics	7 (5.0%)
Malignancy	2 (1.4%)
Chronic renal failure	1 (0.7%)
Site of pleural effusion	
Right	55 (41.0%)
Left	77 (55.4%)
Both	5 (3.6%)
Treatment duration, months	7.2 $\pm$ 2.2
Follow-up duration, months	14.7 $\pm$ 10.2

Table 2. Clinical characteristics and outcomes of the 32 patients with paradoxical response.

Characteristics	N = 32
Age, years	37.9 $\pm$ 19.2
Male gender	18 (56.3%)
Time to onset of PR, days	51.1 $\pm$ 46.0
Readmission	15 (46.9%)
Main symptoms	
None	17 (53.1%)
Dyspnea	8 (25.0%)
Cough	3 (9.4%)
Chest pain	2 (6.3%)
Fever	2 (6.3%)
Treatments	
None	14 (43.6%)
Steroids	7 (21.9%)
Simple drainage	7 (21.9%)
Thoracotomy	4 (12.5%)
Residual pleural thickening	11 (34.4%)

treatment for symptom control and 15 patients (46.9%) required readmission. Of the 18 patients who needed additional treatment, 7 patients received simple drainage and 4 patients received thoracotomy and 7 patients received steroids because of dyspnea. Of 7 patients who received systemic steroid with 0.5 mg/kg of prednisolone, 5 (71%) showed improvement after a median of 14 days (7-28 days) of steroid therapy. The 14 patients who did not receive additional therapy also showed improvement after a median of 28.5 days (9-58 days). Steroid responder showed improvement more quickly than non treatment group (*P* = 0.03).

Table 3. Comparison of characteristics of patients with and without paradoxical response.

	Patients without PR <i>n</i> = 107	Patients with PR <i>n</i> = 32	<i>P</i> value
Age, years	49.2 ± 21.7	19.2 ± 3.4	0.007
Male gender	62 (57.9%)	18 (56.3%)	NS
Body mass index	21.1 ± 2.8	21.8 ± 3.5	NS
Comorbidity	13 (12.1%)	2 (6.2%)	NS
Loculated pleural effusion	24 (22.4%)	5 (16.1%)	NS
Site of effusion (right/left/both) (%)	38.3/57.0/4.7	50.0/50.0/0	NS
Presence of adverse drug reaction			
Skin reactions	11 (10.3%)	8 (25.0%)	0.033
Liver function abnormality	10 (9.3%)	8 (25.0%)	0.021
Peripheral neuropathy	2 (1.9%)	2 (6.3%)	NS
Drug fever	1 (0.9%)	2 (6.3%)	NS
Treatment outcome			
Duration of anti-TB medication	7.2 ± 2.0	7.1 ± 2.9	NS
Residual pleural thickening	34 (31.8%)	11 (36.7%)	NS

NS, not significant.

Table 4. Comparison of laboratory findings of patients with and without paradoxical response.

	Patients without PR <i>n</i> = 107	Patients with PR <i>n</i> = 32	<i>P</i> value
Hemoglobin, g/dl	12.5 ± 1.7	12.9 ± 1.5	NS
WBC count, /mm ³	6,476.9 ± 2,077.7	6,593.8 ± 1,874.5	NS
PMN count, /mm ³	4,481.1 ± 1,721.5	4,664.9 ± 1,710.4	NS
Lymphocyte count, /mm ³	1,167.1 ± 480.5	1,168.3 ± 501.2	NS
Protein, g/dl	6.5 ± 0.7	6.8 ± 0.7	0.028
Albumin, g/dl	3.4 ± 0.5	3.7 ± 0.4	< 0.001
Cholesterol, mg/dl	144.5 ± 31.8	138.4 ± 32.2	NS
LDH, IU/L	267.2 ± 183.4	236.5 ± 103.8	NS
Pleural effusion			
WBC count, /mm ³	3,268.1 ± 5,753.4	4,466.4 ± 3,087.6	0.001
PMN %	15.0 ± 21.5	23.5 ± 24.4	0.038
Lymphocyte %	83.7 ± 22.3	75.3 ± 25.4	0.040
Protein, g/dl	1.3 ± 6.8	0.9 ± 2.9	NS
LDH, IU/L	740.7 ± 490.0	731.3 ± 426.2	NS
ADA, IU/L	88.1 ± 23.4	86.7 ± 23.3	NS

NS, not significant.

Comparison of characteristics of patients with and without PR

Compared with the 107 patients without paradoxical deterioration after receiving anti-TB medication, PR patients had no differences in sex, body mass index (BMI) and underlying comorbidities, such as diabetes mellitus or malignancy (Table 3). Patients with PR were younger ($P = 0.007$), and had a higher incidence of adverse reactions to anti-TB medication such as drug hypersensitivity reaction of skin ($P = 0.033$; Odds ratio (OR) = 2.909, confidence interval [CI], 1.055-8.024) and liver function abnormality ($P = 0.033$; OR = 3.233, CI, 1.153-9.070) compared with patients without PR. There was no difference in duration of

anti-TB medication. After treatment, 11 (36.7%) showed residual pleural thickening and 34 (31.8%) patients showed in the non-PR group ($P = 0.783$).

Risk factors for development of PR

PR patients had no differences in hemoglobin, WBC count and lymphocyte count with patients without PR (Table 4). Patients with PR had higher baseline serum protein levels ($P = 0.028$) and high albumin level ($P < 0.001$). This difference in albumin level was maintained after adjusted by age, sex and BMI ($P = 0.010$). In analysis of pleural effusion, WBC count, proportion of polymorphonuclear cell (PMN) and proportion of lymphocyte was statisti-

Fig. 1. Comparison of cell proportion of effusion in patients with and without paradoxical response. The PR group had higher percents of patients present the proportion of lymphocyte in inflammatory cells of pleural effusion $\leq 90\%$ ($P = 0.021$; OR = 2.639, CI, 1.157-6.019), PMN $\geq 15\%$ ($P = 0.014$; OR = 2.820, CI, 1.238-6.424) and lymphocyte $\leq 90\%$ and PMN $\geq 15\%$ ($P = 0.008$; OR = 3.153, CI, 1.345-7.391) compared those of non PR group.

* $P < 0.05$

cally difference between PR negative group and PR positive group ($P < 0.05$).

Especially, the risk factors for PR were the proportion of lymphocyte in inflammatory cells of pleural effusion $\leq 90\%$ ($P = 0.021$; OR = 2.639, CI, 1.157-6.019) and the proportion of PMN $\geq 15\%$ ($P = 0.014$; OR = 2.820, CI, 1.238-6.424) (Fig. 1). The OR was 3.153 (CI, 1.345-7.391) with lymphocyte $\leq 90\%$ and PMN $\geq 15\%$ ($P = 0.008$).

Discussion

In our study, PR was present in 32 (23%) of 139 patients after a mean 51.1 days following initiation of treatment. The 18 patients (56.4%) with PR needed additional treatment such as simple drainage, thoracotomy and steroids for symptom control. PR patients had a high incidence of adverse drug reaction such as drug skin reaction or liver function abnormality as compared with patients without PR. The risk factors for PR were younger age, high serum albumin level, low proportion of lymphocyte, and high proportion of PMN in pleural fluid.

Modern chemotherapy regimens for the treatment of TB have a low rate of failure. Excellent results are also achieved when treating pleural TB (Dutt et al. 1986). However, tuberculosis can worsen despite effective chemotherapy; this troublesome condition is termed PR. PR during TB treatment has been explored mainly in HIV-infected patients when beginning highly active antiretroviral therapy (Chambers et al. 1984; Wendel et al. 2001; Navas et al. 2002; Breen et al. 2004). The development of HAART-associated immunity leads to a variety of new clinical manifestations, due to an increased CD4 T cell count in HIV-positive patients (DeSimone et al. 2000). The mechanism of this PR has been postulated to be an interaction between the host's immune response and the direct effects of mycobacterial products (Afghani and Lieberman 1994).

PR has been reported in HIV-negative patients (Cheng

et al. 2002; Breen et al. 2004; Cho et al. 2009). However, the incidence of PR is variable. Chen et al. found that only 2.4% of pulmonary TB patients developed PR (Cheng et al. 2007). However, a recent study reported that 23% of patients who had lymph-node TB had PR (Cho et al. 2009). We believe these differences may be due to the site of infection. In the present study, the incidence of PR in pleural TB with HIV-negative patients was 23% (32 of 137), which was consistent with a previous report on lymph-node TB (Cho et al. 2009). Therefore, the present study shows that PR was not an uncommon phenomenon in pleural TB with HIV-negative patients.

PR is usually a mild, transient and self-limited phenomenon. The mainstay of PR management is the continuation of anti-TB treatment without any modification of the drug regimen. However, PR may deserve special attention in pleural TB as respiratory function can be compromised in cases with massive pleural effusion. These patients often require additional treatments. In our cases, 7 patients received simple drainage of pleural fluid, 4 patients, thoracotomy and 7 patients, steroid medication. Steroid treatment has been used in the management of PR. Some case reports have described rapid recovery after initiation of corticosteroid therapy (Chambers et al. 1984; Hejazi and Hassler 1997). But, it did not show advantage in treating PR in patients with lymph node TB (Cho et al. 2009). In our series, 7 patients received systemic steroids. And the patients with steroids had shorter duration in improvement of pleural effusion compared with the patients who did not receive additional therapy ($P = 0.03$). Therefore, steroids could be used depending on the symptom.

Limited information about risk factors for PR is available in HIV-negative patients with pleural TB. Cheng et al. found that baseline anemia, hypoalbuminemia, lymphopenia, and a greater change in lymphocyte count were independent risk factors for developing PR in pulmonary TB

(Cheng et al. 2007). Another study reported that risk factors for developing PR in culture positive TB infection are lower baseline lymphocyte counts and a greater surge in lymphocyte counts during PR (Cheng et al. 2003). In contrast, Cho et al. found that younger age and male gender were risk factors for PR in lymph node TB. Our data showed that younger age and a high baseline albumin level were risk factors for PR in pleural TB. However, baseline anemia and lymphopenia were not risk factors for PR. The new finding of our study was that the presence of skin reaction or liver enzyme abnormality was related with PR. Drug hypersensitivity such as urticaria and rash is immune cell mediated hypersensitivity reaction to medication, and anti-TB drug-induced hepatotoxicity is an idiosyncratic reaction to drug metabolites by T cells (Tostmann et al. 2008). These mechanisms may be similar to that of PR. In active tuberculosis, mycobacterial protein-induced TGF- β in monocytes may be responsible for the well-established immunosuppressive response (Toossi et al. 1995). When anti-TB chemotherapy treatment begins, T-cell responses are gradually restored and cytokine levels (such as IFN- γ and TNF- α) normalize. The associated decline of live bacterial load and increase in components of dead mycobacteria may result in an increase in priming of monocytes/macrophages *in situ* and an enhancement of the production of inflammatory cytokines, such as TNF- α . Therefore, radiological and clinical worsening of a previous lesion or the development of a new lesion may occur after initial improvement during the process of antituberculous treatment (Marshall and Chambers 1998). In a series of this response, a mixed type-1 T helper cell and type-2 T helper cell response were found to be related (Grange et al. 1995). Pleural TB is thought to result from rupture of a subpleural pulmonary tuberculous focus into the pleural space, which allows tuberculo proteins to enter the pleural space and generate the hypersensitive reaction responsible for most of the clinical manifestations (Berger and Mejia 1973). Therefore, the presence of adverse drug reactions might be more common in the PR group.

In our study, the risk factors for PR were the proportion of lymphocyte in inflammatory cells of pleural effusion $\leq 90\%$ or the proportion of PMN $\geq 15\%$. In general, the fluid of TB pleurisy is an exudate, with lymphocytic predominance in about 90% of cases (Lin et al. 2009). In several study, the initial stage of illness, the differential cell count may reveal polymorphonuclear cell predominance with a subsequent change to a lymphocytic predominance within 1 week is seen (Batungwanayo et al. 1993; Lin et al. 2009). In light of these, it is supposed that ant-TB medication in early neutrophilic inflammation phase may trigger the restoration of immune response, and as a results, PR in pleural TB is induced. There was no study that investigated the condition of pleural effusion to evaluate the risk factors for PR in pleural TB. This study is the first study about the risk factors for PR in pleural TB.

Our study had limitations. Of 139 patients, only 28

patients were culture-positive for *M. tuberculosis*. Therefore, several patients could not be evaluated using the drug susceptibility test. In South Korea, the rate of multi-drug-resistant TB among newly diagnosed cases in 2003 was 2.4%, and the resistance to at least one drug was 12.8% (Kim et al. 2010). Based on these findings, some PR patients in our study may have had drug-resistant TB. However, all of the patients who showed PR improved after 7 to 58 days after initiation of PR. Therefore, the possibility of drug resistance was low. Second, our study is limited by its retrospective nature and relatively small sample size. However, few data are available for the PR in pleural TB with negative of HIV. Therefore, our data might be meaningful.

In conclusion, paradoxical response was not an uncommon problem in non-HIV-infected patients with pleural TB, and half of whom needed additional treatment. Therefore, physicians must pay more attention for PR during the management of pleural TB in the expected patients to develop PR.

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Conflict of Interest

The authors report no conflict of interest.

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