Pulmonary Tuberculosis and Disease-Related Pulmonary Apical Fibrosis in Ankylosing Spondylitis

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ABSTRACT. ***Objective***. We investigated the etiological association and clinical characteristics of apical pulmonary fibrosis in ankylosing spondylitis (AS).

Methods. We reviewed medical records of 2136 consecutive patients diagnosed with AS at a tertiary medical center. Clinical and radiographic characteristics were analyzed for evidence of apical lung fibrosis on chest radiographs.

Results. Of 2136 patients with AS, 63 (2.9%) developed apical lung fibrosis, of which chronic infections were the cause in 41 and AS inflammation predisposed the fibrosis in 22 patients. Tuberculosis (TB) infection was considered to be the cause of apical lung fibrosis in 40 patients (63.5%) including 19 with bacteriologically-proven TB and 21 with chest radiographs suggestive of TB. Two were identified as having non-TB mycobacterial infection and one as *Aspergillus* infection. Lung cavity lesion appeared to be a crucial differentiator (p = 0.009, odds ratio 7.4, 95% CI 1.5–36.0) between TB infection and AS inflammation-induced apical fibrosis.

Conclusion. Our study suggests that TB, instead of *Aspergillus*, is the most common pulmonary infection in patients with AS presenting with apical lung fibrosis. AS-associated apical lung fibrosis may mimic pulmonary TB infection. Thus, bacteriological survey and serial radiological followup of lung fibrocavitary lesions are critical for accurate diagnosis and treatment. (First Release Jan 15 2009; J Rheumatol 2009;36:355–60; doi:10.3899/jrheum.080569)

Key Indexing Terms:
PULMONARY TUBERCULOSIS APICAL PULMONARY FIBROSIS
ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease principally affecting the axial skeleton, joints, and entheses. Extraskeletal involvements of the eye, chest, heart, kidney, prostate, and nervous system in patients with AS also have been described[1]. Inflammatory chest pain due to involvement of costosternal and costovertebral joints and insertional muscles is the most common thoracic manifestation in AS. As the disease progresses, restriction of the thoracic cage can be identified, and pulmonary function tests usually show decreased vital capacity (VC) and total lung capacity (TLC) and an increased residual volume along with closing volume/vital capacity ratio[1,2]. Involvement of lung parenchyma was incidentally found in patients with AS. In 1949, Hamilton first described 2 patients with AS who developed chronic infiltrative and fibrotic changes in the upper lobes of the lungs[3]. They clinically presented productive cough and chest tightness and later hemoptysis. Serial radiographs revealed cavity formation and parenchyma destruction that mimic tuberculosis (TB) infection. Such fibrocavitary or fibrobullous disease was well recognized as a pulmonary complication of AS in many other reports[1,4-11].

The precise mechanisms of AS that predispose to respiratory infection remain incompletely understood. Rosenow, *et al*[7] reviewed 2080 patients with AS and found pulmonary infections were increased in patients with fibrocavitary lung disease. The secondary infection of cavities or bullae usually colonized by specific aspergilla with mycetoma formation results in morbidity and mortality, whereas TB or non-TB mycobacterium infection was rarely reported[7]. To our knowledge, around 20 cases of AS with bacteriologically-proven pulmonary TB have been reported[7,9,12-14].

Pulmonary TB has been well recognized as a serious pub-

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lic health issue worldwide despite all medical efforts[15-17]. Fibrocavitary disease of AS and pulmonary TB may share several clinical and radiological characteristics. Based on these observations, we speculated that patients with AS may concurrently be infected with pulmonary TB that requires prompt differentiation from AS-related lung disease. Indeed, our study demonstrated high incidence of pulmonary TB infection in patients with AS along with apical pulmonary fibrosis.

MATERIALS AND METHODS

Patients. We reviewed the medical records of 2136 AS patients for detection of pulmonary TB and fibrocavitary disease. All patients fulfilled the 1984 revised New York diagnostic criteria for AS[18] confirmed by rheumatologists, and were followed longitudinally at Chang Gung Memorial Hospital between July 1991 and March 2006. The study excluded patients who presented with psoriatic spondylitis, reactive arthritis, and enteropathic arthropathy. Finally, we compared and analyzed the fibrocavitary apical lung lesions and clinical and radiological characteristics of specific AS patients with lung involvement.

Methods. We analyzed clinical information of AS patients including sex, age at onset of AS, fibrocavitary apical lung disease, associated chest symptoms, microbiological findings, history of anti-TB drug therapy, medications prescribed for AS disease, extraskeletal manifestation of AS such as uveitis, peripheral arthritis including hip and shoulder joint involvements, and HLA-B27 antigen survey.

Of 2136 AS patients, 794 received chest radiography examinations for lung lesions. Two independent observers including rheumatologists, pneumonologists, and radiologists reviewed and confirmed the presentations of pulmonary fibrosis, cavitations, and other abnormalities on chest radiographs. Regarding radiological findings, we further analyzed the locations of fibrocavitary lung lesions, the number of lung lobes involved, and the presence of pleural diseases, spontaneous pneumothorax and bronchiectasis. Pulmonary TB infection was defined as bacteriologically-proven TB and/or anti-TB treatment that demonstrated healed and/or arrested lung lesions in patients with cavitary, fibrocalcified lesions, or tuberculoma on chest radiographs[12,19-20].

The ethics committee of Chang Gung Memorial Hospital approved the study.

Statistical analysis. Mann-Whitney test was used for quantitative variables after we had verified the assumptions. Chi-square analyses were applied to clinical characteristics and abnormalities on chest radiographs between AS-associated apical lung fibrosis and pulmonary infections. The SPSS v10 statistics package for Windows (SPSS, Chicago, IL, USA) was used for all analyses. The null hypothesis was rejected at 5% level of significance ($p < 0.05$).

RESULTS

Demographic features in AS patients with apical pulmonary fibrosis. Chest radiography disclosed apical lung fibroses in 63 of 2136 (2.9%) patients with AS. As shown in Table 1, the study consisted of 53 men and 10 women with AS, with a mean age of 28.7 ± 9.1 years (range 12–48) at onset of AS disease, and a mean age of 44.9 ± 15.7 years (range 17–73) at development of lung disease. TB infection was considered to be associated with apical lung disease in 40 of 63 (63.5%) patients, including 19 (30.2%) with bacteriologically-proven pulmonary TB and 21 (33.3%) with apical lung fibrosis and calcification or calcified tuberculoma suggestive of TB infection although with no bacteriological confirmation of infection. Two patients (3.2%) were identified with non-TB mycobacterium infection including one with *Mycobacterium abscessus*, and the other displayed arrested pulmonary TB after complete anti-TB treatment, verified as *M. kansassi* infection. One (1.6%) patient developed coincidental TB and *Aspergillus* infection. The remaining 22 patients (34.9%) were diagnosed with AS and chronic inflammatory apical lung disease. All but one of 63 (98.4%) patients were HLA-B27 antigen-positive. Thirty-four of the 63 (54%) patients with pulmonary TB and/or disease-related pulmonary apical fibrosis were smokers. Notably, spontaneous pneumothorax occurred in 3 patients with apical lung fibrosis at 19, 26, and 27 years of age, and the onset of AS occurred at 16, 21, and 18 years of age, respectively. All 3 patients displayed a slender build, and 2 had history of cigarette smoking. None of the 3 had bacteriologically-proven TB infection, but one revealed apical fibrosis along with calcification, and received anti-TB treatment.

Table 1. Demographic features of 63 patients with AS presenting with apical lung fibrosis.

Characteristics	Total N = 63 n (%)
Male to female	53:10
Mean age at onset, yrs	28.7 ± 9.1 (12–48)
Mean age of lung disease	44.9 ± 15.7 (17–73)
AS preceded lung disease, duration, yrs	17.6 ± 12.6 (0.5–49)
AS preceded lung disease	60 (95.2)
Lung disease preceded AS	3 (4.8)
AS associated with TB	40 (63.5)*
Culture positive	19 (30.2)
Chest radiograph diagnosis	21 (33.3)
AS associated with atypical TB	2 (3.2)
AS associated with fungus	1 (1.6)
AS inflammation	22 (34.9)
Pneumothorax	3 (4.8)

* One coexisted with atypical TB and the other with fungus infection.

Clinical characteristics of AS apical fibrosis associated with pulmonary TB infection. In the 40 AS patients (32 men) with suspected pulmonary TB infection the mean age of AS onset was 29.8 ± 8.8 years (range 14–48) while the mean age at diagnosis of pulmonary TB was 44.5 ± 16.9 years (range 17–73). Thirty-seven patients were diagnosed with pulmonary TB an average of 17.0 ± 13.0 years (range 0.5–49) after the onset of AS. However, 3 patients had been diagnosed with pulmonary TB that preceded the onset of AS by 10, 12, and 13 years, respectively (Table 1). The cardinal clinical symptoms consisted of cough in 30 patients (75%), dyspnea in 18 (45%), hemoptysis in 12 (30%), fever in 11 (27.5%), chest pain in 24 (60%), malaise in 4 (10%), anorexia in 3 (8.5%), and night sweats in 3 (8.5%). In addition, 19 (47.5%) presented with peripheral arthritis and 9 (22.5%) had a history of uveitis. Regarding medical treatment of patients with AS, 7 (17.5%) received corticosteroid therapy, one (2.5%) methotrexate, and 16 (40%) received sulfasalazine for disease control. Radiographic findings revealed apical fibrosis in 40 (100%) patients, cavity formation in 17 (42.5%), blunting costo-

phrenic angle suggestive of pleural effusion in 17 (42.5%), pulmonary calcification in 33 (82.5%), tuberculoma in 4 (10%), bronchiectasis in 13 (32.5%), pleural thickening in 11 (27.5%), and pneumothorax in one (2.5%). Thirteen (32.5%) patients had pulmonary fibrosis involving one upper lobe, 16 (40%) had 2 upper lobes involved, and 11 (27.5%) had lower or middle lobe involvement in addition to upper lung fibrosis. Thirty-three patients (82.5%) received anti-TB drugs and demonstrated resolved or arrested progression of TB lesions. We further analyzed the clinical symptoms and signs in 21 patients with apical lung fibrosis that were radiologically suggestive of pulmonary TB, finding cough in 16 patients (66.7%), dyspnea in 12 (57.1%), hemoptysis in 4 (19.1%), fever in 4 (19.1%), chest pain in 11 (52.4%), pleurisy in 9 (42.9%), lung cavity in 6 (28.6%), and bronchiectasis in 8 (38.1%), and 14 (66.7%) received anti-TB treatment. No significant differences ($p < 0.05$) were found in comparison with 19 AS patients with bacteriologically-proven pulmonary TB.

Clinical characteristics in AS apical fibrosis associated with an inflammatory entity. Of the 22 subjects presumed to have AS-associated apical lung disease, 20 were male and 2 female (ratio 10:1). Thirteen demonstrated bamboo spine (undulating extensive syndesmophytosis) and 2 revealed 2 and 3 separate syndesmophytes, respectively. Mean age at onset of AS was 27.9 ± 8.5 years (range 12–48) while the mean age at diagnosis of AS-associated apical lung disease was 45.4 ± 14.0 years (range 26–71). The average interval between onset of AS and documentation of AS-associated apical lung disease was 17.6 ± 11.8 years (range 3–41) (Table 2).

Comparison of clinical characteristics and radiographic findings between AS patients with pulmonary TB infection and AS-related lung disease. As shown in Table 2, pulmonary TB infection in AS patients shared several similar clinical characteristics and radiographic findings with AS-related lung disease. Importantly, lung cavity lesion proved to be a crucial differential feature between patients with AS with pulmonary TB infection and patients with AS-related lung disease ($p = 0.009$, odds ratio 7.4, 95% confidence interval 1.5–36.0).

DISCUSSION

For 5 decades the prevalence of pulmonary TB infection in patients with AS has been assumed to be more frequent than in the general population[21,22]. However, these results should be interpreted cautiously because most cases lacked bacteriological confirmation of *M. tuberculosis*. Moreover, the radiological and clinical similarities of fibrocavitary disease of pul-

Table 2. Comparison of clinical and radiographic characteristics between patients with AS with pulmonary TB infection and AS-related lung disease.

	AS TB Infection, n = 40 (%)	AS Inflammation, n = 22 (%)	p
Male:female	32:8	20:2	
Mean age at onset, yrs (range)	29.8 ± 8.8 (14–48)	27.9 ± 8.5 (12–48)	
Mean age of lung disease, yrs (range)	44.5 ± 16.9 (17–73)	45.4 ± 14.0 (26–71)	
AS preceded lung disease, yrs (range)	17.0 ± 13.0 (0.5–49)	17.6 ± 11.8 (3–41)	
Cough	30 (75)	17 (77.3)	0.343
Dyspnea	18 (45)	11 (50)	0.706
Hemoptysis	12 (30)	3 (13.6)	0.150
Fever	11 (27.5)	2 (9.1)	0.112
Chest pain	24 (60)	14 (63.6)	0.779
History of peripheral arthritis	19 (47.5)	9 (40.9)	0.855
Uveitis	9 (22.5)	5 (22.7)	0.984
Lung fibrosis			
Upper lobe	13 (32.5)	10 (45.5)	0.312
Lower lobes	16 (40)	6 (27.3)	0.316
Diffused*	11 (27.5)	6 (27.3)	0.985
Lung calcification	33 (82.5)		
Pleurisy	17 (42.5)	7 (31.8)	0.409
Pleural thickening	11 (27.5)	3 (13.6)	0.212
Lung cavity	17 (42.5)	2 (9.1)**	0.009†
Bronchiectasis	13 (32.5)	6 (27.3)	0.669
Pneumothorax	1 (2.5)	2 (9.1)	0.285
Anti-TB therapy	33 (82.5)	5 (18.2)	< 0.0001
Corticosteroid therapy	7 (17.5)	1 (4.6)	0.240
Sulfasalazine	16 (40)	8 (36.4)	0.779
Bamboo spine	19 (47.5)	13 (59.1)	0.382

* Lower and/or middle with apical lung fibrosis. ** Lung cavity attributed to AS inflammatory entity due to persistent lung cavity lesions despite anti-TB treatment. † Significant difference in lung cavity incidence in apical lung fibrosis caused by pulmonary TB infection as compared with AS inflammation entity ($p = 0.009$, OR 7.4, 95% CI 1.5–36.0).

monary TB and inflammation-associated pulmonary fibrosis from AS could result in the previously reported high frequency of pulmonary TB diagnosed in patients with AS. Anti-TB agents have often been given to these patients[10-12]. Our study suggests that pulmonary TB infection in patients with AS and AS-related lung diseases may share common clinical and radiological characteristics.

In an analysis of 2080 patients with AS, Rosenow, *et al*[7] reported positive association of infections in 26 patients who demonstrated fibrobullous apical lung disease. Among them, 5 demonstrated aspergillomas, 2 had a nontuberculous mycobacterial infection, and one patient had bacteriologically-proven infection with *M. tuberculosis*[7]. Hillerdal, in a literature review focusing on AS with fibrocavitary apical lung disease, found *Aspergillus fumigatus* was suggested to be the most common infectious agent, followed by TB infection, in the population with AS with fibrocavitary apical lung disease[13]. To our surprise, AS patients with bacteriologically-proven pulmonary TB were rarely described in the ensuing 24 years after Hillerdal's report[9,14].

The growing global burden of TB is well recognized[15-17], possibly due to increased incidence of acquired immunodeficiency syndrome (AIDS), multidrug-resistant TB, and unsatisfactory performance of the directly observed treatment short course (DOTS) program[23,24]. About 1.8 million patients die of TB worldwide every year. In the year 2002, an estimated 8.8 million (141/per 100,000) new cases of TB occurred, of which 3.9 million (63/per 100,000) were smear-positive for TB[25]. The World Health Organization (WHO) has suggested a set of targets for TB control efforts to achieve a prevalence rate of 0.14% for adults and an annual TB fatality rate of less than 2 cases per 100,000 in the population[15]. TB infection remains a serious public health problem in Taiwan. A nationwide survey showed a TB prevalence rate of 0.65% and the death rate due to TB was 5.8 per 100,000 in the Taiwan population, higher than the WHO recommendation[26-28]. Our study reveals that the prevalence of pulmonary TB in AS patients was 3 times that in the general population in Taiwan (0.65%). TB infection accounted for 63.5% of AS patients with apical lung fibrosis, whereas *Aspergillus* accounted for only 1.6%. Together, these findings suggest that AS with thoracic complications may predispose to pulmonary TB infection and require careful surveillance for chronic TB infection.

Medications augmented with immunosuppressive functions to interfere with AS disease activity may predispose to infection. Increased opportunistic infections including TB have been observed in patients treated with corticosteroid or methotrexate. Sulfasalazine has been reported to induce leukopenia or neutropenia and suppress activated lymphocytes, with significantly decreased production of tumor necrosis factor-α (TNF-α)[29]. Our study showed no significant influence of sulfasalazine on TB infection. However, TNF-α plays a major role in the defense against microorganisms by activating the formation of granulomas to prevent dissemination of microorganisms[30]. Application of anti-TNF-α therapy to patients with AS requires screening for early latent infections to prevent the development of chronic lung infections, especially TB.

Clinically, the onset of AS has preceded the pleuropulmonary abnormalities with predominately apical lung fibrosis by an average of 15 years[1,7,9,31]. However, apical or diffuse interstitial lung disease may occur at varied stages in the disease course of AS[31-35]. Our study demonstrated the higher incidence (3.0%) of pleuropulmonary changes accompanied by a high incidence of infections. Accordingly, use of high resolution computerized tomography (HRCT) is recommended for detecting early lung changes in patients with AS, whereas plain chest radiographs show normal or unremarkable findings[14,36-38].

The precise pathogenesis of the fibrocavitary pulmonary disease in AS remains unclear. Pathologic findings in lung specimens have shown elastic degeneration of collagen, pneumonitis with foci of lymphocytic infiltrations, intraalveolar fibrosis, areas of hyalinized connective tissue and scarring, fragmented elastic tissue, dilated bronchi, and interstitial fibrosis but no evidence of vasculitis or granulomatous disease[5,14,36,37,39]. Wendling, *et al* found that bronchial IgA deposits are common in patients with AS[40]. Other theories concerning fibrocavitary lung disease in patients with AS include diminished upper lung ventilation due to thoracic rigidity, altered apical mechanical stress due to restricted chest wall expansion, recurrent pulmonary infection due to impaired cough, repeated aspiration pneumonia secondary to esophageal muscle dysfunction, cricoarytenoid joint disease, and previous thoracic irradiation[41-44].

Hemoptysis in patients with AS may be attributed to lung infections such as TB, *Aspergillus*, and AS-related lung disease; it also can be caused by bronchiectasis[11]. Bronchiectasis is found in some AS patients with apical fibrocavitary lung disease, probably secondary to distortion and destruction of the advanced lung disease of AS[7,11,32,34,35], based mainly on histology findings of dilated bronchi[5,35]. In addition, necrotizing suppurative pneumonia caused by *Staphylococcus* and TB may contribute to the development of bronchiectasis[19,20,45]. The relationships between bronchiectasis and AS lung remain to be fully elucidated.

Spontaneous pneumothorax with recurrence has been reported in AS patients with fibrocavitary lung diseases[7,46,47]. The inflammatory process of fibrocavitary lung disease with concurrent smoking and pulmonary infections, especially TB, may predispose to the development of spontaneous pneumothorax and is speculated to be an extraskeletal manifestation of AS[46]. Moreover, patients with AS may develop idiopathic spontaneous pneumothorax and chronic obstructive pulmonary disease-related spontaneous pneumothorax[46-50]. Similarly, we observed spontaneous pneumothorax that developed in 3 patients, with 2 who displayed recurrence.

Patients with AS may develop apical pulmonary fibrosis

during the disease course. Chronic lung infections, especially TB, should be excluded first in Chinese patients with AS, especially in Taiwan, which has a high prevalence of TB. Our study emphasizes the critical role of serial images for the followup and prompt identification of the precise etiology in order to prevent the spread of TB and further pleuropulmonary complications in Taiwanese patients with AS.

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