REVIEW

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Tuberculous Pleurisy: An Update

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Tuberculous pleurisy is the most common form of extrapulmonary tuberculosis in Korea. Tuberculous pleurisy presents a diagnostic and therapeutic problem due to the limitations of traditional diagnostic tools. There have been many clinical research works during the past decade. Recent studies have provided new insight into the tuberculous pleurisy, which have a large impact on clinical practice. This review is a general overview of tuberculous pleurisy with a focus on recent findings on the diagnosis and management.

Keywords: Tuberculosis; Pleural Effusion; Adenosine Deaminase

Epidemiology

Tuberculous pleurisy is the first or second most common form of extrapulmonary tuberculosis as well as the main cause of pleural effusion in many countries[1]. The relative incidence of tuberculous pleurisy is usually expected to be higher in a high tuberculosis prevalence setting. Tuberculous pleurisy accounts for about 4% of all tuberculosis cases in the United States and Brazil, while 20% of those in South Africa[2-4]. In Korea, 2,884 new tuberculous pleurisy cases were notified in 2012, which accounted for 7.3% of a total of 39,545 new tuberculosis cases and 34% of all extrapulmonary tuberculosis cases[5]. Tuberculous pleurisy is the most common form of extrapulmonary tuberculosis in Korea.

Immune status can also influence the incidence of tuberculous pleurisy. Because the main mechanism is a delayed hypersensitivity reaction, one might hypothesize that the immunocompromised hosts are less likely develop tuberculous pleurisy than the immunocompetent host. However, incidence of tuberculous pleurisy is higher in human immunodeficiency virus (HIV)-infected patients than in non-infected patients[6]. On the other hand, higher incidence is not observed in renal transplant and dialysis patients[7].

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Pathogenesis

Rupture of a subpleural caseous focus in the lung into the pleural space is thought to be the initial event in the pathogenesis of primary tuberculous pleurisy[8]. This hypothesis is based on the observation by Stead et al.[9] that they could demonstrate a caseous focus in the lung contiguous to the diseased pleura in 12 of 15 patients with tuberculous pleurisy. The three other patients in this study had parenchymal disease. Mycobacterial antigens enter the pleural space and interact with T-cells previously sensitized to mycobacteria, then result in a delayed hypersensitivity reaction.

Clinical Manifestations

Tuberculous pleurisy usually presents as an acute illness. The most common presenting symptoms are nonporoductive cough and pleuritic chest pain. Other symptoms include fever, night sweats, weight loss, malaise, and dyspnea varying in severity according to the size of effusion. As a general rule, an acute illness is more likely to occur in younger patients who are more immunocompetent[10].

Patients with tuberculous pleurisy tend to be younger

than patients with pulmonary tuberculosis (TB). However, in industrialized countries the mean age of patients with tuberculous pleurisy tends to be older. In a study from the United States, the mean age of 14,000 patients reported between 1993 and 2003 was 49.9 years[2]. In Korea, the age distribution of patients with tuberculous pleurisy notified in 2011 was as follows: less than 20 years, 4.9%; 20–39 years, 29%; 40–59 years, 25.3%; 60–79 years, 28.6%; more than 80 years, 12.2%[11]. This data showed similar incidence across all age groups. Therefore, tuberculous pleurisy should be considered in any adult or elderly patient with a unilateral pleural effusion.

Diagnosis

The definitive diagnosis of tuberculous pleurisy depends upon the demonstration of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimens[12]. The diagnosis can also be established with demonstration of classical granulomas in the pleura or reasonable certainty by demonstrating elevated levels of adenosine deaminase (ADA) or interferon-gamma (IFN-γ) in the pleural fluid.

1. Pleural fluid examination

The tuberculous pleural fluid is usually clear and straw colored, but may be turbid or serosanguinous. The effusion is virtually always an exudate, with lymphocytic predominance in about 90% of cases. Polymorphonuclear cells may predominate during the first 2 weeks following the onset of symptoms, but a shift towards lymphocytic predominance was observed at repeat thoracentesis[13]. In a retrospective study of 214 patients with tuberculous pleurisy, polymorphonuclear cells were predominate in 11% of cases[14]. Compared with those whose pleural fluid was predominantly lymphocytic, these patients showed a higher yield of mycobacteria in culture of pleural fluid (50% vs. 10%) and had shorter duration of symptoms[14].

2. Radiology

Chest radiography usually reveals a small-to-moderate unilateral pleural effusion. Various studies report the prevalence of coexisting parenchymal lesions to range from 20% to 50%[15,16]. Chest computed tomography (CT) scan improves the diagnostic accuracy by documenting associated parenchymal lesions and lymphadenopathy. A prospective study using chest CT showed coexisting parenchymal lesions were observed in 86% of patients with tuberculous pleurisy[17]. CT can also help to rule out other diseases and to detect complications associated with tuberculous pleurisy. Ultrasonography helps by demonstrating fibrin bands, septations, and loculated pleural effusion.

3. Mycobacterial stain and culture

1) Sputum: It has been suggested that patients with tuberculous pleurisy without coexisting parenchymal lesion are sputum negative and, therefore, noncontagious. The mycobacterial culture of spontaneous sputum has low sensitivity with a range from 0% to 30%[18]. In the absence of pulmonary infiltration, the sensitivity will be in the range of 4–7%[18]. However, Conde et al.[19] reported higher yield of mycobacterial culture (52%) in a single specimen of induced sputum. Even in patients with normal lung parenchyma on chest radiography, the yield of sputum culture in induced samples approached 55%. Therefore, in patients with suspected tuberculous pleurisy it is important to obtain sputum, even in the absence of parenchymal involvement.

2) Pleural fluid: Microscopy of the pleural fluid for acid fast bacilli (AFB) is positive in fewer than 10% of tuberculous pleurisy cases, except for HIV-infected patients and tuberculous empyema[12]. Mycobacterial culture of pleural fluid has also low sensitivity with a range from 12% to 70%, with the majority of series showing diagnostic yields of 30%[12]. It is also limited by lengthy delays of up to 8 weeks in obtaining results if solid culture media are used.

The use of liquid culture media with bedside inoculation of the pleural fluid can provide higher yields and faster results than do conventional methods[20]. The volume of fluid used for inoculation in liquid culture did not seem to influence the proportion of positive cultures[21]. The lymphocyte percentage in pleural fluid was negatively associated with the probability of a positive effusion culture[22]. Microscopic-observation drug susceptibility culture was associated with greatly increased diagnostic sensitivity and shorter time to diagnosis, compared with solid culture[23].

4. Pleural biopsy

Histological analysis and mycobacterial culture of pleural biopsied tissue have traditionally been the gold standard diagnostic method. A blind needle biopsy of pleura using Cope's or Abraham's needle has been the most sensitive diagnostic test for tuberculous pleurisy. In one study of 248 patients with tuberculous pleurisy who underwent needle biopsy of the pleura, the biopsy showed granulomas in 198 patients (80%), the AFB stain of the biopsy was positive in 64 (25.8%) and the culture of the biopsy tissue was positive in 140 (56%)[16]. In this study at least one of the three tests was positive in 227 (91%). Even when granulomas are not visualized, the biopsy specimen should always be examined for AFB (in 10%, only organisms may be seen in the biopsy)[16]. Although other disorders including fungal diseases, sarcoidosis, tularemia and rheumatoid pleuritis may produce granulomatous pleuritis, more than 95% of patient with granulomatous pleuritis have tuberculosis[8].

The introduction of thoracoscopy has had a very important impact on diagnosis. Diacon et al.[24] performed a direct comparative study and found that the sensitivity of histology, culture and combined histology/culture was 66%, 48%, and 79%, respectively, for closed-needle biopsy and 100%, 76%, and 100%, respectively, for thoracoscopy. In addition, both were 100% specific. Thoracoscopy can be medical or video-assisted. It helps visualize the entire pleural surface and allows interventions such as target biopsy, breaking the septae, adhesionolysis, and efficient drainage of effusion. Thoracoscopy could also provide superior opportunity for drug susceptibility testing because of biopsing larger area and higher culture yields.

5. Molecular tests

1) Nucleic acid amplification test: A pooled analysis of the data from 20 studies assessing the use of pleural fluid nucleic acid amplification (NAA) tests concluded that these tests demonstrated reasonably high specificity (97% for commercial and 91% for in-house tests), but generally poor and variable sensitivity (62% for commercial and 76.5% for in-house tests)[25]. An earlier meta-analysis of 40 studies came to very similar conclusions[26]. Pai et al.[26] reported that commercial NAA tests have a potential role in confirming tuberculous pleurisy because of high specificity. However, these tests had low and variable sensitivity and, therefore, were not useful in excluding the disease. The low test sensitivity is mainly the result of the technical aspects of nucleic acid extraction, the presence of inhibitors in the pleural fluid, and the paucibacillary nature of the disease[27].

2) Xpert MTB/RIF assay: The Xpert MTB/RIF assay (Xpert, Cepheid, Sunnyvale, CA, USA) is a rapid, WHO endorsed, automated polymerase chain reaction test optimized for respiratory specimens that can detect both *Mycobacterium tuberculosis* and rifampicin resistance[28]. Several studies have evaluated the performance of Xpert using pleural fluid. Overall, these studies show limited accuracy with sensitivity ranging from 15% to 44%[29-31]. Recent study using pleural tissue sample showed that Xpert did not detect any of the identified TB cases[32].

6. Biomarkers

Because conventional diagnostic tests have known limitations, newer and more rapid diagnostic tests are needed. Although numerous potential markers have been evaluated in pleural effusion, the majority have limited diagnostic accuracy. The two most reliable biomarkers of tuberculous pleurisy are ADA and IFN-γ.

1) Adenosine deaminase: ADA is the enzyme catalyzing the conversion of adenosine to inosine and deoxyadenosine to deoxyinosine. There are two main isoenzymes of ADA: ADA1 and ADA2. ADA1 is a ubiquitous enzyme present in many cells, whereas ADA2 is produced mainly by monocyte/macrophages and responsible for most of the increase in ADA activity in tuberculous pleurisy.

Since 1978, when Piras et al.[33] reported the utility of ADA measurement in pleural fluid, numerous studies have evaluated the diagnostic performance of ADA in tuberculous pleurisy. Four meta-analyses[34-37], including 77 studies in total, were performed in the last few years. All meta-analyses demonstrated uniformly high diagnostic performance of pleural fluid ADA. The largest of these four meta-analyses, evaluating 2,796 patients with tuberculous pleurisy and 5,297 patients with non-tuberculous pleurisy, showed 92% of sensitivity and 90% of specificity[34]. The most widely accepted cutoff value for pleural fluid ADA is 40 U/L[10]. Higher ADA levels are associated with a greater chance of a patient having tuberculosis, while persistent low level on repeated thoracentesis strongly argue against tuberculosis[10].

The diagnostic usefulness of ADA depends not only on its sensitivity and specificity but also on the local prevalence of tuberculous pleurisy. This imply the practical use of the test in different populations[38]. In populations with a high prevalence of tuberculous pleurisy, elevated ADA level might be considered as a confirmatory test justifying treatment initiation. In contrast, in countries with a low prevalence of tuberculous pleurisy, the negative predictive value remains high even though the positive predictive value of pleural ADA declines. Therefore, a negative ADA test may justify abandoning further diagnostic procedures for tuberculosis.

There are two major concerns about the interpretation of ADA level, false-negative and false-positive result. Some patients in the early phase of tuberculous pleurisy may have low pleural fluid ADA levels, but subsequent elevated ADA level could be demonstrated in virtually all patients at repeat thoracentesis[39]. It has been suggested that in immunocompromised patients ADA might be a less sensitive marker of tuberculous pleurisy. However, later studies demonstrated that ADA is a reliable marker of tuberculous pleurisy in HIV-infected patients with a low CD4 T-cell count[40] and in renal transplant recipients[41].

An important issue is also that of false-positive results in patients with non-tuberculous pleural effusion. The main disease are parapneumonic effusion and empyema. Roughly one-third of parapneumonic effusions and two-thirds of empyemas have ADA levels above 40 U/L[10]. High pleural fluid ADA has also been reported in malignancies (e.g., lymphomas, bronchoalveolar carcinoma, mesothelioma), infectious diseases (e.g., mycoplasma and chlamydia pneumonia, psittacosis, paragonimiasis, infectious mononucleosis, brucellosis, mediterranean fever, histoplasmosis, coccidioidomycosis), and connective tissue diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus)[10].

Two approaches have been proposed to increase the speci-

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ficity of the ADA test[38]. The first is the measurement of ADA isoenzymes, ADA1 and ADA2. In two earlier studies, ADA isoenzyme measurement increased the specificity from 91% to 96%[42] and 92.1% to 98.6%[43], respectively. However, as the test is more expensive and does not add much to routine clinical practice, its use is so far limited. The second approach is to combine ADA level and other clinical and laboratory data.

2) Interferon-gamma: The concept of applying IFN-γ as a marker of tuberculous pleurisy is based on the important role of this cytokine in the immunologic response to *M. tuberculosis* infection. Numerous studies have demonstrated that an elevated level of IFN-γ in pleural effusion is a reliable marker of tuberculous pleurisy. Greco et al.[35] analyzed 13 studies and found the mean sensitivity and specificity of 87% and 97%, respectively. A later meta-analysis of 22 studies revealed that the mean sensitivity and specificity were 89% and 97%, respectively[44]. As in the ADA assays, hematologic malignancies and empyema can cause increased IFN-γ levels in pleural fluid[45].

Studies that have directly compared ADA and IFN-γ in patients with tuberculous pleurisy have reported a slightly higher accuracy of IFN-γ[38,44]. However, from the clinical point of view, the differences seem to be irrelevant. Because ADA is both cheaper and simpler, ADA is considered to be the preferred test.

Both pleural fluid ADA and IFN-γ are still the most useful biomarkers of tuberculous pleurisy. Their use allows the reduction of the number of more invasive diagnostic procedures, but in some cases biopsy methods still play an important role[38].

(1) IFN-γ release assay: Although interferon-gamma release assays (IGRAs) were primarily designed to detect latent tuberculosis, it is expected that it might also contribute to the diagnosis of tuberculous pleurisy. However, they are much less useful than unstimulated IFN-γ levels in diagnosing tuberculous pleurisy[46,47]. In a meta-analysis of 7 publications, the sensitivity and specificity for pleural IGRAs in diagnosing tuberculosis were 75% and 82%, respectively[48]. Based on the evidence so far, the IGRAs are not recommended to make a diagnosis of tuberculous pleurisy.

3) Other biomarkers: Numerous potential markers have been evaluated in tuberculous pleurisy, which include neopterin, leptin, lysozyme, fibronectin, interleukin-2, tumor necrosis factor-α, interleukin-1β, CD4+ T-cell count, complement activation, and serum antibodies[49]. Unfortunately, the majority have limited diagnostic accuracy. None of these tests have been found to be superior to pleural fluid ADA or IFN-γ levels.

7. Combination of tests

Combinations of tests, especially combinations that include ADA, seem to perform better than any single test[50-53]. A decision tree analysis that contained simple clinical (age, fever) and laboratory (pleural fluid ADA) data allowed differentiation between tuberculous and malignant effusion with high accuracy[50]. The combination of elevated ADA and pleural fluid lympocyte/neutrophil ratio greater than 0.75 is a more specific than a high ADA level alone[51]. Further work is necessary to identify the best combination that will be most useful in clinical practice.

8. Diagnostic approach

Figure 1 suggests an algorithmic approach for diagnosing tuberculous pleurisy. The first diagnostic step always includes the processing of pleural fluid for biochemical and microbiological studies as well as examination of the sputum for mycobacteria. If an exudative pleural effusion of lymphocytic predominance and negative cytology, pleural fluid ADA can be used as a screening test.

If the fluid ADA is above 70 U/L, the diagnosis of tuberculous pleurisy is virtually established and antituberculous chemotherapy can be initiated. If the pleural fluid ADA is between 40 and 70 U/L, one can make a presumptive diagnosis of tuberculous pleurisy. In this situation, if the patient's clinical picture is not typical for tuberculous pleurisy, further diagnostic procedures such as a needle biopsy or thoracoscopy should be considered. If the patient's pleural fluid ADA level is below 40 U/L, the diagnosis of tuberculosis is unlikely and further diagnostic procedures for tuberculosis would not be necessary. Nevertheless, if the patient has a typical clinical picture of tuberculous pleurisy, the possibility of tuberculous pleurisy can be further evaluated with needle biopsy of the pleura or thoracoscopy.

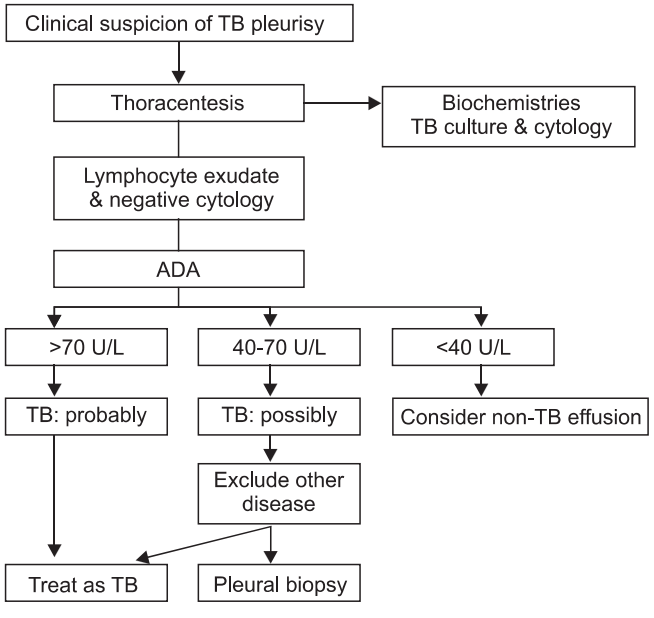

Figure 1. Algorithmic approach to tuberculous pleurisy. TB: tuberculosis; ADA: adenosine deaminase.

Treatment

Tuberculous pleurisy usually resolve spontaneously without treatment, but active tuberculosis develops in 43–65% of patients over the several next years[54,55]. These data from the observation studies in pre-antibiotic era emphasize the importance of proper diagnosis and treatment of tuberculous pleurisy. The treatment of tuberculous pleurisy has three goals 1) to prevent the subsequent development of active tuberculosis, 2) to relieve the symptoms of the patient, and 3) to prevent the development of a fibrothorax[8].

1. Chemotherapy

A standard, 6-month short course regimen composed of isoniazid and rifampicin, intensified with pyrazinamide for the first 2 months, is considered adequate in most uncomplicated cases. Ethambutol should be included in the initial regimen until the results of drug susceptibility tests are available. Although patients with tuberculous pleurisy were successfully treated with only isoniazid and rifampicin for 6 months[56,57], it must be taken into account that such a regimen can only be applied in areas with low drug resistance. The drug resistant pattern of tuberculous pleurisy broadly reflects that of pulmonary tuberculosis[2]. In a epidemiological analysis of tuberculous pleurisy in the United States, 9.9% of patients had isolates resistant to at least one first-line drug. Furthermore, multidrug-resistant tuberculosis was detected in 1% of cases[2].

With treatment, the patient usually becomes afebrile within 2 weeks, but fever may persist as long as 2 months[58]. Paradoxical worsening of the pleural effusion occurs in a few patients after the initiation of chemotherapy. In a retrospective study of 459 patients with isolated tuberculous pleurisy, paradoxical response developed in 16% of the patients approximately 2 months after initiation of treatment, mostly presenting with aggravation of pre-existing pleural effusion[59].

The mean time for the complete resorption of pleural fluid is approximately 6 weeks, but it can be as long as 12 weeks[58]. As many as 50% of patients with tuberculous pleurisy develop pleural thickening 6–12 months after the beginning of the treatment[60]. Residual pleural thickening decreases with time even after the completion of chemotherapy up to 24 months[61], and many of them has negligible functional consequences[62]. Repeated thoracocentesis[63] or corticosteroids[64] does not appear to alter the degree of residual pleural thickening.

2. Local therapy

If the patient is dyspneic from a large pleural effusion, a therapeutic thoracentesis should be performed. However, routine complete drainage of pleural fluid at the time of diagnosis does not appear to improve mid- and long-term outcomes[63]. In patients with loculated tuberculous pleural effusion, the administration of a fibrinolytic may decrease the degree of residual pleural thickening. Two small prospective studies suggest that pigtail drainage and instillation of fibrinolytics, in addition to anti-tuberculosis medication, in patients with symptomatic loculated tuberculous effusions may hasten the resolution of pleural effusion and reduce the incidence of residual pleural thickening[65,66].

3. Corticosteroids

The rationale of using corticosteroids is that corticosteroids through their antiinflammatory action may hasten fluid resorption and prevent pleural thickening. Three randomized trials showed early resolution of clinical symptoms and signs, but there was no difference in residual lung function and incidence of residual pleural thickening[67-69]. A recent Cochrane review concluded that there are insufficient data to support evidence-based recommendations regarding the use of adjunctive corticosteroids in people with tuberculous pleurisy[64]. Nevertheless, in selected patients who continue to have severe systemic symptoms (e.g., fever) after 2 weeks of chemotherapy and therapeutic thoracentesis, a short course of corticosteroids may be beneficial[1,10].

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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