

# Pleural Effusion Adenosine Deaminase (ADA) Level and Occult Tuberculous Pleurisy

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**Background:** We investigated the incidence of tuberculous pleurisy among patients with adenosine deaminase (ADA) levels of 50 IU/L or less in a pleural effusion, and without a previous diagnosis of carcinomatous pleurisy or *Mycobacterium tuberculosis*.

**Subjects and Methods:** Subjects were selected from patients who had undergone pleural biopsy by thoracoscopy at National Hospital Organization Tokyo Hospital from January 1995 to November 2004, and who had ADA levels of less than 50 IU/L in pleural fluid obtained preoperatively by thoracentesis. In all subjects, smear, culture, and polymerase chain reaction for *Mycobacterium tuberculosis* were negative.

**Results:** Of 138 patients who underwent thoracoscopic pleural biopsy, a total of 50 had effusions with ADA levels of less than 50 IU/L. Six (12%) of these patients were diagnosed with tuberculous pleurisy after biopsy. Three patients with an effusion ADA level of 35 IU/L or less were diagnosed with tuberculous pleurisy.

**Conclusions:** Occult tuberculous pleurisy is significantly common in patients with pleural effusion ADA levels of 50 IU/L or less and who may otherwise be diagnosed with nonspecific pleurisy. (*Ann Thorac Cardiovasc Surg* 2009; 15: 294–296)

**Key words:** tuberculous pleurisy, pleural effusion, adenosine deaminase

## Introduction

Along with malignancy and heart failure, tuberculous pleurisy is a major cause of pleural effusion. In tuberculous pleural effusion, *Mycobacterium tuberculosis* is rarely found in the pleural fluid obtained from thoracentesis and pleural drainage. Therefore tuberculous pleurisy is more often diagnosed clinically by adenosine deaminase (ADA) levels and lymphocyte to neutrophil ratios. The measurement of ADA levels is a useful test with good

sensitivity and specificity<sup>1–3</sup>; however, diagnosis in some patients has been reported to be impossible if only their ADA levels alone.<sup>4,5</sup> In this study, we examined patients who had ADA levels of 50 IU/L or less and in whom carcinomatous pleurisy or *Mycobacterium tuberculosis* was not found. These patients would normally be determined to have nonspecific pleurisy, and their clinical course would be monitored and untreated. We investigated how many of them actually had tuberculous pleurisy as confirmed by pleural biopsy.

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## Subjects and Methods

The subjects were selected from patients with pleural effusion who underwent thoracoscopic biopsy at National Hospital Organization Tokyo Hospital from January 1995 to November 2004 and who had ADA levels of less than 50 IU/L in pleural fluid obtained by preoperative thoracentesis. In these patients, a diagnosis of tuberculous pleurisy was not possible by smear, culture, or polymerase

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**Table 1. Patient characteristics**

Age	24–87 (62.4)
Gender M:F	48:2
Location R:L	32:18
ADA (mg/L)	
≤37	43
37–50	7

M, male; F, female; R, right; L, left; ADA, adenosine deaminase.

chain reaction (PCR) for *Mycobacterium tuberculosis*. Patients with malignant tumors, heart failure, or liver disease were excluded. They underwent pleural biopsies because of indeterminate diagnosis or the need for definitive diagnosis. Thoracoscopy under local anesthesia was performed using an Olympus LTF-240 scope. The method of thoracoscopic examination was as described in a report by Sakuraba et al.<sup>6)</sup> The official cutoff point of ADA level in pleural fluid for a diagnosis of tuberculous pleurisy is a minimum of 50 IU/L at the Tokyo Hospital. Informed consent was obtained from each participant.

## Result

A total of 138 patients underwent thoracoscopy under local anesthesia from January 1995 to November 2004. In 50 of these patients (48 males and 2 females), a diagnosis of tuberculous pleurisy was indeterminable using smear, culture, or PCR, and ADA levels in the pleural fluid were less than 50 IU/L. The age range was 24–87 years (mean 62.4). The right side was involved in 32 patients and the left side in 18 (Table 1). Six of the 50 (12%) were diagnosed with tuberculous pleurisy, using pleural biopsy by thoracoscopy under local anesthesia (Table 2). Forty-three patients had ADA levels of 35 IU/L or less, and 3 (7%) of them were diagnosed with tuberculous pleurisy. All patients with tuberculous pleurisy were smear, PCR, and culture negative for *Mycobacterium tuberculosis* (Table 3).

## Discussion

The clinical diagnosis of tuberculous pleurisy is often made by ADA level and lymphocyte to neutrophil ratio in pleural fluid. In practice, many patients are borderline cases in terms of ADA value, and there are some in whom pleural fluid is not manageable by monitoring without drainage. Since the treatment period for tuberculous pleurisy is long, it is desirable to provide treatment only

**Table 2. ADA levels and tuberculous cases**

ADA (mg/L)	n	Tuberculosis confirmed with biopsy
≤37	43	3
37–50	7	3
Total	50	6 (12%)

ADA, adenosine deaminase.

after obtaining a definitive diagnosis established histologically or with a positive culture.

The measurement of the ADA level in pleural fluid is reportedly a useful test with good sensitivity and specificity. However, it has been reported that there are patients with tuberculous pleurisy who have low ADA levels in the pleural fluid.<sup>4,5)</sup> In some reports, the diagnosis of tuberculous pleurisy is made with an ADA level in the pleural fluid of more than 37–50 IU/L.<sup>7–9)</sup> In the present study, 6 patients (12%) with confirmed tuberculous pleurisy had ADA levels in the pleural fluid of less than 50 IU/L; the ADA levels in 3 (7%) were less than 37 IU/L. Normally, with no histological or bacteriological abnormalities, they would be diagnosed with nonspecific pleurisy, and the clinical progress of these patients is usually simply monitored. Since the oral regimen of antituberculosis drugs has side effects, it is difficult to justify continued administration of these drugs without a definitive diagnosis from pleural biopsy. Furthermore, in some patients the accumulation of pleural fluid does not improve during the follow-up period, and the outcome of pleurisy treatment can be unsatisfactory, thereby warranting diagnostic or therapeutic thoracoscopy. It is possible that some of these patients have tuberculous pleurisy.

Sugiyama and Horiguchi<sup>10)</sup> reported that the diagnostic yield from the pleural biopsy by thoracoscopy is 90.1%. Our diagnostic yield was similar at 93.8%.<sup>6)</sup> According to previous reports,<sup>11,12)</sup> the mortality rate associated with thoracoscopy is low, ranging from 0.001%–0.6%. Our method resulted in no major complications and no mortalities. It was also safe to perform and provide reliable diagnoses. Our method was considered an essential element in reliably diagnosing tuberculous pleurisy.

Another diagnostic tool involves interferon-gamma (INF- $\gamma$ ), which has been used as a biological marker. Hiraki et al.<sup>13)</sup> reported that INF- $\gamma$  is a specific biological marker with the highest specificity for tuberculous pleurisy. However, it cannot be measured in all pleurisy cases because of its high cost relative to ADA measurement. In

**Table 3. Tuberculous pleurisy cases with ADA levels in the pleural fluid of less than 50 IU/L**

Case	Age	Gender	Location	ADA	Pleural smear	Effusion culture	Pleural biopsy histology
1	82	M	L	33.7	Negative	Negative	Epithelioid granuloma
2	48	M	R	30.6	Negative	Negative	Epithelioid granuloma
3	78	M	R	18.3	Negative	Negative	Epithelioid granuloma
4	24	M	R	44.6	Negative	Negative	Epithelioid granuloma
5	28	M	R	45.2	Negative	Negative	Epithelioid granuloma
6	76	M	L	43.9	Negative	Negative	Epithelioid granuloma

ADA, adenosine deaminase; M, male; L, left; R, right.

a great many pleural effusion cases, pleural biopsy by thoracoscopy could be an accurate and useful diagnostic and therapeutic method if performed with drainage. Pleural biopsy by thoracoscopy has a high diagnostic yield and is very safe. Therefore it is a good tool in the diagnosis of tuberculous pleurisy, but its invasiveness is a drawback.

The subjects of this study were those patients seen at the hospital up until November 2004. Therefore the cases were not very recent, and INF- $\gamma$  testing was not available to be assessed in these patients. In the future, measurements of both ADA and INF- $\gamma$ , as well as pleural biopsies in certain cases, can be performed in combination for accurate diagnoses. Future studies are required to investigate the incidence of occult tuberculous pleurisy among patients with negative INF- $\gamma$  testing.

## Conclusion

Tuberculous pleurisy was found in 12% of the patients who had pleural effusion ADA levels of 50 IU/L or less, and who would otherwise have been diagnosed with non-specific pleurisy. In addition to measuring ADA levels, the performance of pleural biopsy by thoracoscopy under local anesthesia or the measurement of biological marker INF- $\gamma$  may be necessary to provide a definitive diagnosis in patients with unexplained pleural effusion.

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