A comparison study of IFN-γ, ADA, and CA125 as the diagnostic parameters in tuberculous pleuritis

Y. AOKI, O. KATOH, Y. NAKANISHI*, S. KUROKI, AND H. YAMADA

Department of Internal Medicine, Saga Medical School, 1-1, Nabeshima 5-chome, Saga 849, and
*Research Institute for Diseases of the Chest, Faculty of Medicine, Kyushu University, 3-1-1, Maidashi,
Higashi-ku Fukuoka 812, Japan

Adenosine deaminase in pleural fluid (pADA), CA125 in serum (sCA125), and IFN-γ in pleural fluid (pIFN-γ) were measured in patients with pleurisy of various causes to evaluate their diagnostic utility in tuberculous pleuritis (TBP). We studied 39 pleural fluid samples, including 11 TBP and 28 non-TBP. With both pADA and sCA125, although the median values were much higher in TBP than in non-TBP groups, there was considerable overlap between the two groups. The sensitivity, specificity, and diagnostic efficiency were 81.8%, 89.3%, and 87.2%, respectively, when pADA values of more than 45 U ml⁻¹ were considered, and they were 100%, 75.0%, and 84.2%, respectively, when sCA125 values of more than 35 U ml⁻¹ were considered. In contrast, pIFN-γ values were significantly higher in TBP patients (5.8 ± 3.0 IU ml⁻¹; mean ± s.d.) than those in non-TBP patients (<0.3 IU ml⁻¹), leading to both a sensitivity and a specificity of 100%.

Introduction

Tuberculous pleurisy has long been a subject of debate in the differential diagnosis of exudative pleural effusions. Several diagnostic approaches are generally employed by clinicians, but the diagnostic yields vary with the type of procedure involved. They are reported to be 25-70% for pleural fluid culture (1-3), 50-80% for histology of closed pleural biopsies, and 70-95% for combined histology and culture of biopsy specimens (2-5).

The measurement of adenosine deaminase levels in pleural fluid makes a major contribution to the diagnosis of TBP, and many investigators have reported on its diagnostic utility (6-9).

We have reported that CA125, widely known as a diagnostic marker for ovarian carcinoma, increased in the sera of both male and female patients with TBP. In our previous study, the mean serum CA125 levels in 8 TBP patients were significantly higher (P<0.01) than those in 12 benign non-TBP patients (10). Therefore, we have measured both pADA and sCA125 routinely in patients with pleurisy as diagnostic clues to TBP.

It has also been reported that IFN-γ levels in pleural fluids are significantly higher in TBP as compared with non-TBP patients (11,12).

To the best of our knowledge, however, there are no reports in which diagnostic efficiencies of these tests for TBP were compared. In the present study, we concurrently measured pADA, sCA125, and pIFN-γ in patients with pleurisy caused by various underlying disorders, and compared diagnostic utilities of these parameters in the patients with tuberculous pleuritis.

Patients and Methods

Patients

We studied pleural fluid samples from 39 patients with pleurisy (April, 1989 to August, 1991). In these 39 patients, the following underlying disorders were found: (1) tuberculous pleuritis in 11 patients, (2) malignant pleuritis in 11, (3) empyema in five, (4) parapneumonic effusion in five, (5) autoimmune disease in four (6) transudative pleural effusion in three (Table 1).

In 11 TBP patients, the diagnoses were confirmed by the isolation of Mycobacterium tuberculosis (seven patients), positive pleural biopsy (one patient), or both (three patients). One patient with biopsy evidence alone showed a positive PPD reaction, lymphocyte-rich fluid, and a favourable clinical response to anti-tuberculous agents.

In 11 malignant pleuritis patients, pleural fluid cytologies were all positive for malignant cells. Nine
Table 1 Characteristics of the patients with pleural effusions

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>11</td>
</tr>
<tr>
<td>Non-tuberculosis</td>
<td>28</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11</td>
</tr>
<tr>
<td>Empyema</td>
<td>5</td>
</tr>
<tr>
<td>Parapneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>4</td>
</tr>
<tr>
<td>Transdate</td>
<td>3</td>
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</tbody>
</table>

had histologically confirmed primary lung cancer (squamous cell carcinoma in five patients, adenocarcinoma in two, and small cell carcinoma in two), and another two patients had malignant effusions due to pleural metastases from gall bladder carcinoma and T cell lymphoma.

In four autoimmune disease patients, the pleurisies were caused by rheumatoid arthritis (RA), polymyositis (PM), polyarteritis nodosa (PN), and Wegener’s granulomatosis (WG) in one each. The predominant cell types were lymphocytic in RA and PM, and neutrophilic in PN and WG.

The transductive effusions were caused by congestive heart failure in two patients and liver cirrhosis in one.

SAMPLING AND ASSAY

Blood and pleural fluids were obtained before treatment, centrifuged immediately, and then kept at -30°C until assay.

pADA was measured by reduced nicotinamide adenine dinucleotide-linked kinetic assay (AD auto, Maruho, Japan), sCA125 by one step radiometric immunoassay (CA153 RIA kit, Centcor, Canada), and pIFN-γ by enzyme immunoassay (Human γ-IFN Test, CSL, Australia).

STATISTICAL ANALYSIS

Between the groups, the significance of the difference was examined by Student’s t-test. The degree of association between the parameters was examined by the coefficient of correlation.

Results

pADA values were measured in 11 TBP patients (eight male, three female) and in 28 non-TBP patients (male 18, female 10). The results are shown in Fig. 1. pADA values in TBP patients ranged from 35 to 75 U l⁻¹ with a median of 58.6 U l⁻¹. In 28 non-TBP patients, 25 showed the pADA values of less than 37 U l⁻¹, however, the values in the other three patients were 52 (empyema), 97 (empyema), and 412 U l⁻¹ (T cell lymphoma). Although the median

![Fig. 1](image-url)  

Fig. 1 pADA levels in TBP and non-TBP patients. Dotted line indicates cut-off value (45 U l⁻¹).
value in TBP was much higher than in non-TBP patients (25.9 U ml$^{-1}$), there was no significant difference between the two groups.

In the present study, sCA125 levels were available in seven TBP patients (five male, two female) and in 12 non-TBP patients (seven male, five female). In TBP patients, the values ranged from 35 to 600 U ml$^{-1}$. In nine out of 12 non-TBP patients (75%), the values were less than 35 U ml$^{-1}$ (7-32 U ml$^{-1}$), which is considered normal in our laboratory. In another three patients, however, the values showed marked increases; they were 880 (transdate due to liver cirrhosis), 463 (lung cancer), and 193 U ml$^{-1}$ (Wegener's granulomatosis). The median value in TBP (70 U ml$^{-1}$) was much higher than in non-TBP (20 U ml$^{-1}$); however, there was no significant difference between the two groups.

We examined whether the combined measurement of pADA and sCA125 is useful in the diagnosis of TBP. The results were obtained from seven TBP and 12 non-TBP patients in whom both values were available (Fig. 2). In six of seven TBP patients (85.7%), both of the pADA and sCA125 were increased, while both of these two parameters did not increase in eight of 12 non-TBP patients (66.6%). No TBP patients were found to have showed both of these two parameters being less than cut-off values, and conversely there were no non-TBP patients in whom these values were both increased. In the TBP patients, there was no correlation between the pADA and sCA125 values (data not shown).

pIFN-γ levels in 39 patients are shown in Fig. 3. In TBP patients, the values ranged from 2.0 to 12.1 IU ml$^{-1}$, with the mean ± SD of 5.8 ± 3.0 IU ml$^{-1}$. On the contrary, the values were all less than 0.3 IU ml$^{-1}$ in 28 non-TBP patients. There was a significant difference between the two groups ($P<0.01$). In the TBP patients, there was no correlation between the pIFN-γ and pADA values (data not shown).

The diagnostic utilities of pADA, sCA125, and pIFN-γ for TBP are shown in Table 2. For pADA, the sensitivity, specificity and the diagnostic efficiency were 81.3%, 89.3%, and 87.2%, respectively, when the value of more than 45 U l$^{-1}$ was considered. For sCA125, they were 100%, 75%, and 84.2% when the value of more than 35 U ml$^{-1}$ was considered. In contrast, pIFN-γ measurement
Table 2 Diagnostic utilities of the parameters in tuberculous pleuritis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Efficiency</th>
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<tbody>
<tr>
<td>pADA*</td>
<td>9/11 (81.8%)</td>
<td>25/28 (89.3%)</td>
<td>34/39 (87.2%)</td>
</tr>
<tr>
<td>sCA125†</td>
<td>7/7 (100%)</td>
<td>9/12 (75.0%)</td>
<td>16/19 (84.2%)</td>
</tr>
<tr>
<td>pIFN-γ</td>
<td>11/11 (100%)</td>
<td>28/28 (100%)</td>
<td>39/39 (100%)</td>
</tr>
</tbody>
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*cut-off; 45 U l⁻¹. †cut-off; 35 U l⁻¹

yielded both a sensitivity and a specificity of 100%, leading to the diagnostic efficiency also of 100%.

Discussion

Tuberculous pleuritis is still a major cause of pleural exudates, with the prevalence being reported to be nearly 10% of all pleural effusions (13). In order to make a definite diagnosis, pleural fluid culture and pleural biopsy are generally needed. However, evidence of tuberculosis cannot be obtained with these tests in 5–30% of the patients with TBP (2–5). Nowadays, the measurement of ADA in pleural fluid, in addition to conventional tests, has been widely employed as an useful diagnostic examination in the vast majority of patients suspected of having TBP (6–9). In the present study, although pADA measurement was considered to be of value, some patients with diseases such as lymphoma or empyema also showed substantial increase in pADA value, in agreement with previous investigators (8,12). It has been reported that pADA increases in rheumatoid pleurisy (8,14), but the value did not increase in one RA patient in our study. In the previous reports dealing with pADA, the cut-off values ran from 30 to 70 U l⁻¹ (6–9). No doubt the diagnostic utility varies considerably with the cut-off value employed. When the value was established at 45 U l⁻¹ in our study, the diagnostic efficiency of pADA for TBP was 87.2%. One may be reminded that the utility of pADA measurement depends partly on the prevalence of tuberculosis. Its elevation is considered not so diagnostic in a country with a low morbidity rate for tuberculosis (15); whereas it is considered very useful in a high prevalence area (9).

CA125 was originally described by Bast et al. (16) as an antigen which is recognized by the monoclonal antibody 'OC125' obtained by immunizing mice with a human ovarian cancer cell line. We previously reported that sCA125 is a good diagnostic marker for TBP for the following reasons: (1) CA125 was increased significantly in the sera of both male and female TBP patients as compared with non-TBP patients (P<0.01); (2) No evidences of female genital neoplasia were found in TBP patients; (3) sCA125 values returned to normal range following the treatment of TBP (P<0.01) (10). In the present study, the sensitivity was 100% for TBP with the cut-off value of 35 U ml⁻¹ (range; 35–600); however, the specificity was 75%, which was lower than that of our previous study. It is known that sCA125 increases not only in patients with ovarian cancer but also in those with liver cirrhosis, hepatoma (17), lung cancer (18), and other conditions. Therefore, the high specificity of sCA125 for TBP found in our previous study may be explained by the differences of the non-TBP population. Our previous study included neither malignancy nor liver cirrhosis in non-TBP group, whereas the present study included both of these causes of pleurisy. We do not know why sCA125 increased in one pleurisy associated with Wegener's granulomatosis. In the previous study, there was no correlation between the values of sCA125 and CA125 in pleural effusions (pCA125) measured on TBP patients, and there were also no differences at all in pCA125 values between TBP and non-TBP patients (10). Therefore, we can not explain the possible mechanism by which sCA125 increases in TBP patients. Although the specificity of sCA125 in the present study was not as good as the previous one, we expect that sCA125 could be one of the diagnostic clues to TBP, particularly when measured together with pADA; so far as our present study is concerned, the positive predictive value and the negative predictive value of the combined measurements proved to be 100% in the diagnosis of tuberculous pleuritis.

IFN-γ plays an important role in the local cell-mediated immune reaction at the site of active inflammation (11,19). In tuberculous pleurisy, PPD-specific T-lymphocytes are selectively present in pleural spaces where the disease activity is exclusively high (20,21). Barnes et al. (22) reported that CD4⁺/CDw29⁺ 'memory T cells' were concentrated in tuberculous pleural effusions, which proliferate vigorously and produce high levels of IFN-γ in response to the stimulation with PPD. It was recently reported by Shimokata et al. (11) and by Ribera et al. (12) that IFN-γ increased prominently in tuberculous pleural effusions. Also in our study, pIFN-γ values differed significantly (P<0.01) between TBP and non-TBP patients, and there was no overlap in the ranges between the two groups. We expect that pIFN-γ also increases to some extent in lymphocytic pleural effusions found in RA or PM, however, the values did not show any increase in our study. In this respect, we must further investigate with more
patients, especially of lymphocyte-rich autoimmune pleurisy, to know whether pIFN-γ measurement is invariably diagnostic for TBP.

In conclusion, we believe that the measurement of pADA and/or sCA125 are useful in the diagnosis of TBP. In addition, pIFN-γ measurement is recommended, if available, when clinicians are confronted with a pleurisy strongly suspected of TBP but as yet undetermined by any other means.

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References