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ORIGINAL ARTICLE

Differential diagnosis of tuberculous and malignant pleurisy using pleural fluid adenosine deaminase and interferon gamma in Taiwan

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Accurately differentiating tuberculous pleurisy from lung cancer is important for disease management but difficult using conventional laboratory methods. This study assessed the value of adenosine deaminase (ADA) and interferon gamma (IFN-γ) for differentiating the two conditions in a region of Taiwan with a high prevalence of tuberculosis. The study population comprised patients with lymphocytic exudative pleural effusions: tuberculous ($n = 24$) and malignant ($n = 42$). Mean levels of ADA and IFN-γ in pleural fluid, measured with commercial standardized kits, were significantly higher for tuberculous than for malignant pleurisy ($p < 0.001$ for both). For differentiating the two effusions, results for ADA versus IFN-γ were: sensitivity, 70.8% versus 91.7%; specificity, 95.2% versus 97.6%; positive predictive value, 89.5% versus 96.7%; and negative predictive value, 85.1% versus 95.3%. IFN-γ allows precise diagnosis of pleural tuberculosis, but ADA is easier to use, has a low cost, and results are quickly available. Our study confirms previous studies and extends the usefulness of these diagnostic methods to a wider group of clinical laboratories by showing the

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reliability of standardized relatively inexpensive commercial kits. We recommend that initial ADA screening be used in conjunction with IFN-γ measurements for differential diagnosis of tuberculous pleurisy.

Introduction

There are many causes of pleural effusion, and an effusion caused by tuberculous pleurisy may be difficult to distinguish from one caused by some form of cancer. A rapid precise diagnosis is important as the prognosis and therapy for these two diseases are markedly different. Unlike some other studies, we restricted our analysis to these two groups to mimic the common clinical situation. A definitive diagnosis of tuberculous pleural effusion can be difficult because of nonspecific clinical presentation and the relatively poor efficiency of traditional diagnostic methods. In clinical practice, the predictive value is an important measure of diagnostic validity. The positive predictive value (PPV) is the probability of the presence of a disease, given a positive test result. Likewise, the negative predictive value (NPV) is the probability of absence of a disease, given a negative test result.

Detection of *Mycobacterium tuberculosis* using primary culture or the polymerase chain reaction usually allows definitive diagnosis, although the positive rate of pleural fluid culture for *M tuberculosis* is low in tuberculous pleurisy.[1,2] Because of the long culture period, clinical and therapeutic decisions often have to be made before culture results become available. The sensitivities of pleural fluid culture, pleural biopsy culture, and histological examination of a pleural biopsy sample, are reported to be on the order of 23%, 55%, and 63%, respectively.[3] Another method, acid-fast staining of pleural effusion fluid, has the advantage of being rapid and inexpensive but lacks sensitivity and often produces negative results even in patients with a confirmed diagnosis of tuberculous pleurisy.

The inefficiency of conventional laboratory methods has resulted in the development and evaluation of alternative diagnostic strategies. In recent years, both adenosine deaminase (ADA) activity and interferon gamma (IFN-γ) concentrations have been reported as useful diagnostic markers of tuberculous pleurisy.[4–12] However, one limitation of predictive values is their dependence on disease prevalence.[13] If the sensitivity and specificity of a diagnostic test were constant, then the PPV would increase with disease prevalence, whereas the NPV would decrease with disease prevalence. Thus, the prevalence of tuberculosis (TB) has a strong impact on the predictive values of clinical diagnostic tests. The value of ADA in the diagnosis of tuberculous pleurisy in a country with a high burden of TB, such as Taiwan, has not been reported previously.

A previous prospective study showed that using ADA in combination with the lymphocyte/neutrophil (L:N) ratio increased the specificity of tuberculous pleurisy diagnosis.[4] In this report, the study population was restricted to one of the most diagnostically challenging categories of pleural effusions, namely, patients with lymphocyte-predominant exudative pleural effusions. The goal of the present study was to evaluate the diagnostic value of using rapid commercial ADA and IFN-γ quantification kits for differentiating between tuberculous pleurisy and malignant pleurisy in patients with lymphocytic exudative pleural effusions. Use of such kits would make these tests available to a wider range of clinical laboratories. We evaluated the sensitivity, specificity, and PPVs and NPVs of the ADA and IFN-γ tests in this setting and provided recommendations for routine clinical practice.

Materials and methods

Patients

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan. Informed consent was obtained from patients who participated in the study. Pleural effusions were collected from consecutive patients who were admitted to Kaohsiung Veterans General Hospital between July 2006 and January 2007. Samples from consecutive patients ($n = 177$) with lymphocytic exudative pleural effusions were screened for inclusion in this study. Patients with exudative effusion and lymphocyte counts less than 50% were excluded from further analyses ($n = 54$). Among the remaining 123 patients, patients with TB and malignancies were eligible for further analysis. Clinical signs and symptoms, demographic data, and radiologic results were recorded. Results of ADA and IFN-γ tests were blinded to the physicians to avoid bias in determination of patient clinical diagnosis.

Diagnostic criteria

Patients were included in the study if they had exudative pleural effusions with lymphocyte counts of 50% or more. Pleural effusions were classified as exudates if the pleural fluid-to-serum ratio of total protein was 0.5 or more, the pleural fluid level of absolute lactic dehydrogenase (LDH) was 200 IU/L or more, or the pleural LDH fluid-to-serum ratio was 0.6 or more.[1] A diagnosis of pleural TB was made if patients had one of the following clinical manifestations suggestive of TB: *M tuberculosis* isolated from pleural fluid or pleural tissue, granulomas in the pleural tissue that stained positive for acid-fast bacilli (AFB), or granulomas in the pleural tissue that did not stain positive for AFB but did show a response following antituberculous treatment. The diagnosis of malignant pleurisy was made