

THORAX

Editorials

Tuberculous pleurisy and adenosine deaminase

Adenosine deaminase (ADA) activity has been proposed as a diagnostic test for tuberculous pleurisy since 1978.¹ Two papers in this issue of *Thorax* (pp 600-603 and 672-674) support the case for using this test in regions where the incidence of tuberculosis is high (the Western Cape in South Africa - 670 per 100 000)² or moderately high (Galicia, Spain - 95 per 100 000).³

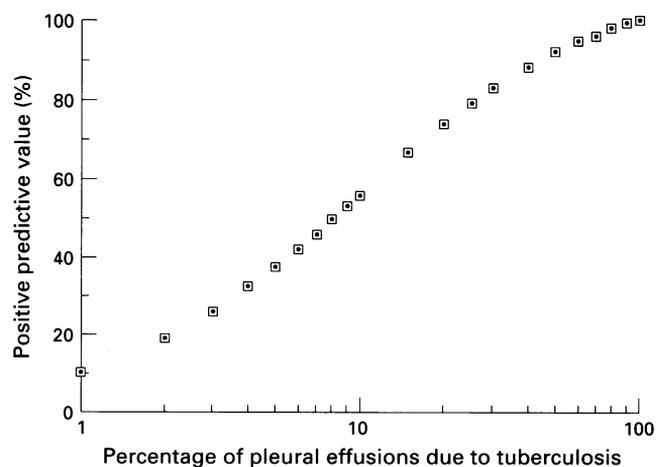
Investigation of a pleural effusion demands a pleural aspiration and biopsy.⁴ The pleural fluid is sent for measurement of protein and glucose content, cytological and microbiological examination, which includes culture for mycobacteria. Cytology and microbiology benefit from testing as large a quantity of fluid as possible; a "diagnostic" tap of 10-20 ml of pleural fluid without a pleural biopsy is inadequate. In as many as 20% of all pleural effusions this basic testing does not establish the diagnosis, and even a thoracotomy or thoracoscopy may not reveal the cause of the effusion.⁵

Tuberculous pleural effusions have until recently been a feature of primary disease, but as many as 50% now occur in conjunction with pulmonary infiltrates typical of post-primary tuberculosis.⁶ Although bilateral effusions may occur in miliary tuberculosis, unilateral effusions are more usual and arise from the rupture of a caseous sub-pleural focus of tuberculosis into the pleural space.⁷ The fluid collects as a result of a delayed hypersensitivity reaction to tuberculous proteins.⁸ The number of bacteria are few, and smear and culture have a low diagnostic yield (<25%).⁹ However, most tuberculous pleural effusions are exudates (a pleural fluid/serum protein ratio of >0.50) and have a low glucose concentration, although the latter does not discriminate tuberculosis from malignancy, parapneumonic effusions or rheumatoid disease. Lymphocytes constitute >50% of the cellular material in most (93%) tuberculous pleural effusions and two thirds of malignant effusions^{11,12}; the presence of a large number of mesothelial cells is against the diagnosis of tuberculosis.¹³ A pleural biopsy specimen will contain granulomas in about 60% and the yield apparently increases to 80% if three separate pleural biopsy specimens are examined and 90% if specimens are cultured^{14,15}; a lower diagnostic yield is more common in clinical practice. Using these several criteria, only seven of 70 patients in a recent series required a presumptive diagnosis of a tuberculous pleural effusion, made on the basis of a positive tuberculin skin test, a lymphocytic effusion, and successful treatment with anti-tuberculosis chemotherapy.⁶ The identification of tuberculous pleurisy is important; although tuberculous pleural effusions often resolve spontaneously, 43-65% of patients will develop active tuberculosis within the next five years.^{16,17}

Adenosine deaminase is an enzyme involved in purine catabolism found in most cells, but particularly in lymphocytes where its concentration is inversely related to the degree of differentiation. One of the earliest references to

this group of enzymes evaluated its role in the diagnosis of lung cancer.¹⁸ High levels of ADA activity were subsequently found in patients with tuberculous pleurisy.¹ Levels of ADA activity show a significant correlation with the number of CD4+ lymphocytes in the pleural effusion¹⁹; false positive tests are therefore found in patients with rheumatoid disease, chronic lymphatic leukaemia, and undifferentiated lymphoma.^{20,21} Neutrophils contribute to the high levels of ADA activity found in empyema fluid. Using the data of Burgess *et al.*,² the variation in the positive predictive value with prevalence is shown in the figure. Clearly, where the incidence of tuberculosis greatly exceeds any other cause of a lymphocytic pleural effusion, ADA activity will have a high positive predictive value.

Two questions remain unanswered by these papers. Firstly, would ADA activity be helpful in deciding which patients should receive empirical antituberculosis chemotherapy in the 20% of pleural effusions where even a thoracoscopy or thoracotomy has not achieved a diagnosis? Such a study would require a reasonable incidence of tuberculous pleurisy and the random assignment of patients with high ADA activity in their pleural fluid to treatment or placebo; the frequency of active tuberculosis over the subsequent five years would be the end point. Secondly, how does ADA activity compare with other potential diagnostic tests for tuberculous pleurisy? Interferon-gamma is produced by lymphocytes actively engaged in delayed hypersensitivity responses and is almost as good as ADA activity in terms of sensitivity and specificity, but accurate measurement is more demanding and more expensive.²¹⁻²³ Antibody levels to antigen 60 in pleural fluid have a sensitivity of about 50% depending on the incidence of tuberculosis.²⁴ Serum levels of antibody to a 38 kDa antigen have been helpful in establishing the diagnosis of tuber-



Effect of the prevalence of tuberculosis on the positive predictive value of adenosine deaminase activity. Derived from data from Burgess *et al.*²

culous pleurisy²⁵ but antibody levels in pleural fluid to this and other tuberculosis-specific antigens, as well as levels of mycobacterial antigens measured by reverse passive haemagglutination or latex beads, have been disappointingly low (unpublished data). Detection of mycobacterial DNA by the polymerase chain reaction has the advantage of specificity and no requirement for an intact immunity; a sensitivity of 81% has been achieved using a repetitive DNA sequence and 60% (9/15) using the standard IS6110 probe.^{26,27} Pleural effusions may become an increasingly common presentation of tuberculosis in HIV infected individuals and detection of mycobacterial DNA could have a more prominent role in the diagnosis of tuberculous pleurisy.²⁸

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