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Diagnosing tuberculous pleural effusion using clinical data and pleural fluid analysis
A study of patients less than 40 years-old in an area with a high incidence of tuberculosis

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Pleural effusion;
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Summary
Background: Tuberculous pleural effusions (TPE) are common. The diagnosis is often problematic. As the determination of ADA is often unavailable in some countries, the aim of this study was to evaluate the diagnostic usefulness of other data from pleural fluid analysis, in young patients from populations with high prevalence of tuberculosis (TB).
Methods: We analysed 218 patients with pleural effusion (165 tuberculous, 21 infectious, 11 neoplastic, 16 miscellaneous, 3 idiopathic). We performed two regression models; one included pleural fluid ADA values (model 1), and the other without ADA (model 2).
Results: Model 1 selected two variables (ADA >35 U/L) and lymphocytes (>31.5%) and correctly classified 216/218 effusions (1 false negative, 1 false positive). Model 2 (without ADA) selected three variables: lymphocytes (>31.5%), fever and cough, and correctly classified 207/218 effusions (8 false negatives, 3 false positives). The sensitivity of models 1 and 2 was 99.4% and 95.2%, specificity 98.1% and 94.3% and accuracy 99% and 95%.

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Conclusions: In geographic areas with high prevalence of TB and a low prevalence of HIV, in young patients (≤40 years), it is possible to confidently diagnose TPE with either of the two regression tree models, with the utility of ADA providing superior sensitivity, specificity, and accuracy.

Introduction

The diagnosis of a tuberculous pleural effusion (TPE) requires a positive culture (from pleural fluid or pleural tissue) or the presence of granulomas in the pleura.[1] However, we have demonstrated that with the high diagnostic yield of adenosine deaminase (ADA), in a region like ours, with a high prevalence of TPE,[2,3] and in a specific population (less than <35 years), it would be possible to establish the diagnosis of TPE without the need for a pleural biopsy. Pleural biopsy should be reserved for patients with a low pleural fluid ADA, negative cytology and a high suspicion of a neoplasm.[4]

Although making the clinical diagnosis is more likely with the measurement of ADA, its availability may be problematic in some countries [5] and pleural biopsy is not available in many hospitals. Therefore, the aim of this study was to evaluate whether in regions with a high prevalence of tuberculosis and, at least, in young patients (less than <40 years), a confident clinical diagnosis of TPE generated can be established from clinical data and standard pleural fluid analysis, with or without a determination of ADA.

Material and methods

We analysed, prospectively, all patients admitted to our health centre, a 1000-bed teaching hospital in Santiago de Compostela, Spain from January 2000 to December 2008.

Pleural fluid and peripheral blood samples were obtained at the same visit, with the patient fasting and the closed pleural biopsy was obtained by either a Cope[6] or Abrams[7] needle. Pleural fluid samples were sent to cytology, microbiology (for Ziehl—Neelsen stain and aerobic and anaerobic cultures in Lowenstein media), and biochemistry, which included total protein, lactate dehydrogenase (LDH), cholesterol, glucose, ADA, red cell count and total nucleated cell count with differential. The same testing was performed on blood samples. All biochemical measurements were performed on a clinical chemistry analyser (ADVIA 2400, SIEMENS HEALTHCARE DIAGNOSTICS) using standard methodology. The ADA activity (U/L at 37 °C) was determined colorimetrically by the method of Galanti and Giusti.[8] The NH_4^+ released by deamination of adenosine added to the samples was quantified by incubation with phenol nitroprusside in an alkaline medium, followed by measurement of absorbance at 628 nm. The within-run precision of this method in our hands was evaluated using 30 replicate high ADA samples and 30 replicate low ADA samples. The corresponding coefficients of variation were 2.24% for low ADA samples (mean ± SD: 22.93 ± 0.5 U/L) and 2.02 for high ADA samples (102.48 ± 2.04 U/L). Between-run precision was evaluated using 17 pairs of duplicates and a coefficient of variation of 2.51% (37.29 ± 0.94 U/L) was obtained.[4] Red cell and total nucleated cell counts were determined by a Haematology analyser (ADVIA 2120, SIEMENS HEALTHCARE DIAGNOSTICS). Neutrophilic and lymphocytic effusions were defined as effusions with a neutrophil or lymphocyte count >50% of the total nucleated cell count. An effusion was considered eosinophilic if the cell count was ≥10%. Only the first pleural fluid chemistry panel was used for statistical analysis in patients with more than one thoracentesis.

Clinical parameters recorded were age, sex, chest pain, cough, sputum, dyspnoea and fever. The radiological findings that were determined were: 1) pulmonary lesion and its location; 2) laterality of the effusion (right, left, or bilateral); 3) and the size of the effusion: (large if >2/3 of the hemithorax, medium if >1/3 and <2/3 of the hemithorax, or small if it was <1/3). A tuberculin skin test was performed with 2 U of RT-23 and was considered positive if the induration of the transverse axis of the forearm was ≥5 mm measured at 48—72 h. With suspected HIV, serology was also obtained. Thoracoscopy was not performed on any patient.

The pleural fluid was classified as tuberculous if the Ziehl—Neelsen stain or the Lowenstein culture was positive in pleural fluid or biopsy, or if granulomas were identified on biopsy.

An effusion was diagnosed as neoplastic only when confirmed by positive cytology in pleural effusion or pleural biopsy. An effusion was considered parapneumonic if there was bacterial pneumonia, a lung abscess or bronchiectasis or if the pleural fluid culture was positive. An empyema was diagnosed if the fluid was purulent. The other diagnoses were based on previously established criteria.[1]

Statistical analysis

Data are expressed as mean ± SD. The Student *t* test was used for the comparison of the continuous variables between TPE and the rest of the groups, and the Mann—Whitney test was used if the distributions were not normal. The chi-squared analysis was used for comparison of proportions. The results of the diagnostic tests were expressed as sensitivity, specificity, predictive values (positive and negative), positive likelihood ratio, negative likelihood ratio and accuracy, with 95% confidence intervals (95% CI). ROC (receiver operator characteristics) curve methodology was used to find the optimum cut-point.

We performed two regression tree models. The first included the ADA level in pleural fluid (model 1) while the second (model 2) did not include ADA. The statistical modelling used analysis adjusted for the following covariates: gender, fever, chest pain, dyspnoea, cough, sputum, size and location of the effusion, accompanying pulmonary lesions, tuberculin skin test, red and total nucleated cell