New tests for tuberculosis: local immune responses have greater specificity

Graham H Bothamley

We all want a good test for tuberculosis. Sputum smears are negative in half of those with lung involvement. How can we detect tuberculosis if there are <10³ bacilli per ml of sputum? We could use either a more sensitive test for something the tubercle bacillus produces or use the host’s response to amplify the signal. Mycobacterial culture, DNA-based amplification, breath tests for volatile organic chemicals⁴ and lipid profiles⁵ exhibit the first approach. Chest radiographs, non-specific inflammatory markers and tests based on the specific immune response (such as tuberculin testing) exploit the second option.

Local immune responses have previously been shown to have greater potential for diagnostic assays than systemic responses from peripheral blood.⁶ Studies using cells isolated from human granulomas have demonstrated the importance of early secretory antigen target-6 (ESAT-6) in the CD4+ T cell response,⁷ as have bronchoalveolar lavage (BAL) cells with ESAT-6, culture filtrate protein-10 (CFP-10) and a number of other proteins.⁸ New tests for tuberculosis have exploited the ESAT-6 and CFP-10 antigens found in region of difference 1 (RD1), which is deleted in BCG but found in all pathogenic strains of the Mycobacterium tuberculosis complex. Two papers which have studied BAL in patients with suspected but smear-negative pulmonary tuberculosis have therefore excited much interest. The earlier paper examined BAL cells from 37 patients with suspected tuberculosis.¹⁰ Eight culture-positive and four culture-negative patients who responded to antituberculosis treatment all gave positive responses (≥5 cells stained per 200 000 cells) when incubated with the peptides from ESAT-6 and CFP-10. Although false-positive responses were found in peripheral blood from those with previous tuberculosis, pneumonia or lung cancer in concurrent tests, there were no false-positive results from BAL fluid. Even if the higher cut-off value suggested by other workers were used,¹¹ the sensitivity of the
ELISPOT would have fallen from 100% to 92% and those with previously treated tuberculosis would have remained below the diagnostic threshold.

In this issue of Thorax, Breen et al. take a slightly different approach using tuberculin testing and flow cytometry (see page 67). BAL fluid was taken from a substantially larger group of patients (n = 250) in whom tuberculosis was suspected but the sputum smear was negative for auramine-positive bacilli, of whom 111 gained a diagnosis of active tuberculosis. The cells were first sorted for CD45 (common leucocyte antigen) and CD4 markers and 50 000 of these cells were cultured with the mixture of antigens found in tuberculin-purified protein derivative (PPD). Flow cytometry was then used to measure the percentage of CD4+ cells which expressed interferon-γ after stimulation with PPD. Although ESAT-6 was also used in 71 subjects, the specificity was not increased: all those who were positive with PPD but who did not have tuberculosis were also positive after stimulation with ESAT-6. The high false-positive rating in this assay (24%) was a significant problem. Breen et al suggest that many of these should have been treated for tuberculosis as 2 of 34 developed active disease within the period of follow-up. Several could well have had self-healed tuberculosis, as noted by the presence of apical shadowing and/or calcified mediastinal lymphadenopathy, and some had known contact with tuberculosis. The convenience of flow cytometry may have lost out to the specificity of the ELISPOT.

Should we use the new tests for latent tuberculosis in the examination of BAL fluid? The answer remains unclear, but the excitement is palpable. Many questions remain. Might sputum induction provide a similar sensitivity? Can the ELISA-based tests perform as well as the ELISPOT assays? At last the investment made during the last decade may begin to pay dividends in the clinical management of patients with suspected tuberculosis.

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REFERENCES


Non-invasive ventilation for the treatment of hypercapnic respiratory failure in cystic fibrosis

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Median survival for patients with cystic fibrosis (CF) has improved steadily over the past several decades as a result of a multifaceted treatment approach to the disease. Despite this aggressive care, many patients with classic disease eventually develop respiratory failure from progressive airways obstruction and bronchiectasis. At this stage, treatment strategies may focus on alleviating both the symptomatic and physiological effects of respiratory failure. Initially respiratory failure may be mainly hypoxic (type 1: arterial oxygen pressure (PaO2) < 8 kPa (or 60 mm Hg), with normal arterial carbon dioxide pressure (PaCO2)), and supplemental oxygen during sleep and/or exercise may be effective. However, when the disease becomes more severe, hypercapnia may ensue (type 2: PaCO2 > 6 kPa (or 45 mm Hg)). Such patients with chronic respiratory failure usually have obvious clinical signs and symptoms, and blood gas analysis demonstrates a compensated respiratory acidosis. Thus it is important to periodically measure arterial blood gases in all patients with severe CF lung disease, to monitor for this serious complication of the disease.

When CF patients develop chronic respiratory failure, symptoms include the usual clinical sequelae of hypoxia and hypercapnia, as well as worsening dyspnoea associated with the increased work of breathing, sleep fragmentation and daytime fatigue, and reduced activities of daily living. Hypoxia with hypercapnia, and an elevation in serum bicarbonate, can support the need for adjunctive treatments. If oxygen treatment alone is judged insufficient, non-invasive ventilation (NIV) may be considered. Patients with CF may suffer acute respiratory failure during an exacerbation of moderate to severe disease, or indeed without any identified specific acute insult. A 2002 British Thoracic Society Standards of Care document listed the criteria for the use of NIV in acute respiratory failure. Of note,
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