The pulmonary physician in critical care • Illustrative case 2: Interstitial lung disease

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The case history of a patient admitted to the ICU with interstitial lung disease deteriorating to respiratory failure is presented. Problems in distinguishing between infection and disease progression are discussed and the role of transplantation in ventilated patients is examined.

CASE REPORT

A 31 year old man with a 5 month history of Jo-1 negative dermatomyositis was admitted to the intensive care unit (ICU) with respiratory failure. Five months previously he had developed severe myositis which responded to corticosteroid treatment (prednisolone 1 mg/kg) with symptomatic improvement and a fall in creatine kinase. Six weeks later he developed chest radiographic infiltrates, extensive ground glass opacification on high resolution computed tomographic (HRCT) scanning (fig 1) and hypoxaemic respiratory failure despite maintenance treatment with prednisolone 20 mg daily. He deteriorated despite antimicrobial and increased corticosteroid treatment, requiring mechanical ventilation. A thoracoscopic biopsy specimen taken while on the ventilator disclosed diffuse alveolar damage admixed with organising pneumonia. Intravenous methylprednisolone (750 mg daily for 3 days) allowed weaning from ventilatory support and eventual discharge from hospital on prednisolone (0.5 mg/kg) and azathioprine (200 mg once daily). One month later he was readmitted with increasing dyspnoea and was treated for cytomegalovirus (CMV) pneumonitis diagnosed on the basis of a positive urinary detection of early antigen fluorescence foci (DEAFF) test and bronchoalveolar lavage (BAL) immunofluorescence. After a good initial response, progression of interstitial lung disease became evident radiologically and a single dose of intravenous cyclophosphamide (1.4 g) was administered.

One week later he developed increasing dyspnoea associated with increasing oxygen requirements and a low grade fever, but there were no major changes in chest radiographic abnormalities or inflammatory indices which were only mildly increased. Broad spectrum antibiotic treatment was instituted with cotrimoxazole to cover pneumocystis pneumonia (PCP) and intravenous ganciclovir to cover reactivation of CMV pneumonitis. However, all cultures, including specific testing for CMV antigen, were negative. Continued deterioration prompted transfer to the ICU 48 hours after admission.

Examination of bronchoalveolar lavage (BAL) samples revealed no evidence of infection. Having failed to identify an infective agent and in the presence of broad spectrum antimicrobial treatment, the patient’s continued decline was treated with three further daily doses of intravenous methylprednisolone and a further dose of intravenous cyclophosphamide. The transplantation investigation protocol was initiated and cyclosporin was added in the hope of decreasing steroid requirements. However, intermittent noninvasive support was increasingly necessary and tracheal intubation and mechanical ventilation were required 7 days after admission to the ICU. Despite vasopressor support, adjustment of antimicrobial treatment (including the empirical addition of liposomal amphotericin), and the use of granulocyte colony stimulating factor to treat pancytopenia, he continued to deteriorate and died 30 days after admission to the ICU. No clear evidence of underlying infection was obtained. Overall, the balance of probability strongly favoured inexorable progression of underlying interstitial lung disease.

MANAGEMENT OF PATIENTS WITH DIFFUSE INTERSTITIAL LUNG DISEASE IN THE ICU

Use of diagnostic techniques

This case illustrates important management difficulties in patients with diffuse interstitial lung disease (DILD) who progress to respiratory failure. Clinically, the differential diagnosis usually consists of deterioration of the underlying disease demanding increased immunosuppression, and infection requiring antimicrobial treatment and a reduction in immunosuppressive treatment. The distinction is important, whatever the likely outcome. Young patients with connective tissue disease may have an excellent long term outcome if they survive an acute episode—be it infective or due to inflammatory DILD—and prolonged aggressive intervention is appropriate. By contrast, major progression of fibrotic disease generally denotes a very poor outcome once mechanical ventilation has been instituted in idiopathic and connective tissue disease alike; prolonged ventilation is inappropriate.

Unfortunately, in most connective tissue diseases and other forms of DILD no serological marker correlates closely with pulmonary disease activity. The distinction between the onset of infection and progression of disease is complicated by the marked similarities in clinical presentation (fever, cough, increased breathlessness, and increased radiographic shadowing). Similarly, laboratory indices of infection (white
ventilator associated pneumonia in ARDS, between infection and progression of DILD in patients requiring immunosuppressive therapy, BAL makes a crucial contribution before SLB (fig 2).

However, in cases in which the underlying diagnosis is known and the problem is one of distinguishing between infection and disease progression, a more calibrated approach is usually appropriate including BAL and transbronchial biopsy (TBB) before SLB (fig 2). In a case where pulmonary infiltrates are associated with immunosuppressive therapy, BAL makes a crucial contribution to the detection of opportunistic infection. The spectrum of likely infective organisms depends on a variety of factors including the presence of neutropenia, the nature of the underlying disease process and immunosuppressive therapy, the prior administration of antimicrobial treatment, and the timing of the BAL relative to hospital admission and the onset of ventilation. Bacterial pathogens are isolated most commonly, but staining and cultures should be undertaken to exclude fungal, mycobacterial, and viral infections. In addition, non-infectious causes of diffuse radiographic shadowing including malignancy and alveolar haemorrhage may be identified. New diagnostic techniques applicable to BAL fluid include antigen detection (e.g. Aspergillus spp, Cryptococcus neoformans, Legionella pneumophila), antibody detection (e.g. antipneumolysin for pneumococcal pneumonia), special methods for culture (BACTEC radiometric culture for mycobacteria), and techniques from molecular biology such as the polymerase chain reaction. However, the appropriate use of new diagnostic tests is often difficult to rationalise; their clinical usefulness is likely to be heavily dependent upon the quality of specimen, BAL technique, and population studied. It is advisable for clinicians to seek microbiological advice before performing BAL if the use of novel diagnostic procedures is contemplated.

BAL is generally safe in immunosuppressed patients including those with haematological dysfunction and in critically ill patients requiring mechanical ventilation. However, deterioration in respiratory mechanics and gas exchange is well recognised and may be clinically significant. Thus, BAL should be performed in the ICU in high risk patients; occasionally it is appropriate to institute mechanical ventilation before BAL is undertaken.

The diagnosis of CMV pneumonitis was unexpected but illustrates the diagnostic usefulness of BAL. CMV pneumonitis is probably rare outside transplant patients and those

### Figure 1
Thin section CT image through the upper lobes showing patchy consolidation, some of which is peribronchial. There is a generalised non-specific increase in attenuation of the lung parenchyma. The consolidation could represent autoimmune organising pneumonia associated with connective tissue disease (in view of its bronchocentric distribution), but an infective cause for the changes (or a coexisting infective component) cannot be excluded. Poor quality images are also a major constraint in the patient with severe dyspnoea at rest. Some of the ground glass attenuation may be technical.

### Figure 2
An algorithm for the management of patients with diffuse interstitial lung disease (DILD) and acute respiratory failure (ARF). BAL=bronchoalveolar lavage; TBB=transbronchial biopsy; SLB=surgical lung biopsy.
in patients infected with HIV. In patients infected with HIV the clinical 

care to be discussed definitively with the relatives. 36 37 

Finally, immunocompromised patients with underlying DILD can be viewed as “special cases” with regard to the performance of SLB because of the unique difficulties in distinguishing between infection and progression of the primary disease.

Role of lung transplantation 

Mechanical ventilation is widely regarded as a strong relative 

43 However, in small populations from selected 

28 Several studies have demonstrated that a negative TBB result should prompt a repeat TBB 

29 The authors argue that TBB is safe in mechanically ventilated 

35 In patients with interstitial lung disease who deteriorate to 

36 37 The successful use of non-invasive ventilation as a bridge to transplantation in patients developing respiratory failure has been reported. 36 37 In view of the general scarcity of donor organs, the indications 

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31 In ventilated patients the mortality rate with SLB may be as high as 10% and operative complications, occurring in approximately 20%, may influence survival. 30 31 However, mortality after the initial postoperative period is probably largely ascribable to progression of the underlying condition rather than to the surgical procedure, although controlled clinical data are lacking. Factors predicting mortality in ventilated patients with pulmonary infiltrates undergoing SLB have included an immunocompromised status at the onset of respiratory failure or current immunosuppressive treatment, severe hyoxia, multorgan failure, and older age. 30 31 In immunocompromised patients in the ICU, high inpatient and 1 year mortality rates (50% and 90%, respectively) are often cited to suggest that SLB adds little to the management provided that broad spectrum antibiotic cover (including cotrimoxazole to cover PCP) and a trial of corticosteroid treatment are instituted. 30 31 However, “patient benefit” is not always synonymous with eventual survival. Inappropriate immunosuppressive therapy may be associated with infective complications. SLB may identify irreversible disease, allowing inappropriate support to be minimised 34 35 and withdrawal of care issues to be discussed definitively with the relatives. 36 37

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