Case reports

Commentary

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One of the inevitable consequences of success in a new clinical procedure would appear to be a slow but steady relaxation of strict guidelines pertaining to patient selection as familiarity increases. Nowhere has this been more evident than in the field of lung transplantation. After two decades of failure, the early 1980s were characterised by the cautious introduction of heart and lung transplantation for pulmonary vascular disease and single lung transplantation for fibrosing lung disease with clinical success.[1]

Transplant surgeons and, indeed, their physician colleagues were, however, blessed with a pioneering spirit and were keen to take on new challenges. This manifest itself by the development of a flood of ever increasing indications for lung transplantation. In this respect the decision to perform heart lung transplantation in a patient with respiratory failure due to cystic fibrosis was a milestone. The idea of transplanting an essentially septic recipient with a systemic disease flaunted the received wisdom at the time. Nevertheless, this brave decision has been proved an inspired one with the excellent results obtained offering hope for a new life for many patients with advanced cystic fibrosis.

The two case reports by Licker *et al*[2] and Hill *et al*[3] are based on a common theme and illustrate the points above because it is unlikely that either of the patients would have been considered for transplantation in the early 1980s. Results have been successful, at least in the medium term, and the transplant teams are to be congratulated on their success. What conclusions, however, can we draw? In essence both cases revolved around patients whose risk for a successful long term outcome would have to be estimated as less than average at the time the decision to transplant was made. Both cases have been reported as a direct result of success "in adversity" and this success has been used to justify the decision to transplant.

Would the cases have been reported if both patients had died? Lung transplantation has become a victim of it's own success by failing to deliver an adequate service for well characterised lower risk patients with respiratory failure due to cystic fibrosis, emphysema and pulmonary fibrosis. A shortfall in donor organs has led to most centres experiencing a 50% mortality amongst patients on the active transplant waiting list. Transplant centres must make the best use of a rare resource and, whilst a pioneering spirit must be allowed to flourish, it should not do so if the cost is failure to deliver a service for ever increasing numbers of patients with established indications for whom success is more likely. Perhaps one way forward is for more transplant centres to try to expand the donor lung pool by the use of marginal donors for high risk cases[4] and good donor lungs for recipients who represent a lower risk. The introduction of successful lung xenografting in the future remains a tangible but distant prospect.

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Single lung transplantation for adult respiratory distress syndrome after paraquat poisoning

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Abstract
Ventilator-dependent patients are considered poor candidates for lung transplantation. A 17 year old boy developed adult respiratory distress syndrome (ARDS) due to paraquat poisoning. A single lung transplantation was carried out with a successful outcome.
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Although ventilator dependence has traditionally been regarded as a relative contraindication for lung transplantation, candidates who deteriorate while on a waiting list and patients who develop acute respiratory failure in the absence of any associated organ dysfunction represent unique situations that merit cautious examination.[1] We report the perioperative management of a patient who developed adult respiratory distress syndrome (ARDS) after paraquat ingestion.

Case history
A 17 year old farmer with a recent history of diarrhoea and abdominal pain was admitted to the hospital because of worsening respiratory distress. The plasma creatinine level was raised (272 μM/l) and bilateral lung infiltrates were seen on the chest radiograph. Renal dysfunction and gastrointestinal signs resolved within one week. However, despite treatment with intravenous antibiotics, corticosteroid, and inhaled nitric oxide (NO), the patient's respiratory condition progressively deteriorated. A lung biopsy specimen had revealed obliterative bronchiolitis, few inflammatory cells, and extensive fibrosis associated with an intact alveolar framework. Several diagnoses were evoked including farmer's lung fibrosis, viral infection, and paraquat poisoning. After a multidisciplinary consultation he was accepted as a candidate for an urgent lung transplant since there was no evidence of a septic state or an associated organ failure, and the patient's relatives denied a suicidal attempt.

Mechanical ventilatory support was continued for five weeks until a suitable lung donor was found. After induction of anaesthesia a left-sided double lumen tracheobronchial tube was inserted. Conventional mechanical ventilation was applied selectively on the right lung with inhaled NO (8–15 ppm). High frequency jet ventilation was applied on the left lung until clamping of the pulmonary artery. Partial cardiopulmonary bypass was instituted and lung transplantation was performed through a standard thoracotomy in the fifth intercostal space. After a cold ischaemia time of 270 minutes the donor lung was reperfused and conventional mechanical ventilation was resumed on both lungs with the application of a PEEP of 5 cm H_2O. Weaning from cardiopulmonary bypass was successful with inotropic support (epinephrine 0.1 μg/kg/min). Although respiratory compliance and arterial oxygen tension were markedly improved, the pulmonary artery pressure remained elevated at 37 mm Hg. A trial of inhaled NO (2–20 ppm) was ineffective whereas an incremental infusion of nitroglycerin (1–5 μg/kg/min) induced a progressive fall in pulmonary artery pressure without any deterioration in oxygen exchange or in pulmonary shunting.

Postoperatively, despite signs of anaesthesia emergence and satisfactory chest radiographs and gas exchange, the patient failed to sustain spontaneous breathing as a result of generalised muscular weakness (with normal sensitivity) that was attributed either to prolonged immobilization, administration of corticoid related myorelaxants, or a toxic insult. The diagnosis of paraquat intoxication was confirmed by the patient himself and by immunoassay detection of paraquat in lung and muscle samples (134 μg/g and 328 μg/g, respectively) obtained 59 days after herbicide ingestion. No paraquat had been detected in several plasma samples obtained 4–24 days after the onset of gastrointestinal symptoms. On the 10th day after transplantation a 3 mm right bronchopleural fistula developed that was initially treated by stapling, pleural drainage, and antibiotics. A right pneumonectomy was finally performed 29 days after transplantation because of persistent air leakage and the risk of contralateral bronchopneumonia. Histological sections of the native lung revealed extensive and obliterative intra-alveolar and bronchiolar fibrosis with ectatic subpleural air spaces whereas the arteries and large bronchi were normal. After partial recovery of the neuromyopathy the patient was weaned from the ventilator 17 days after transplantation and he was discharged from the hospital 88 days after transplantation. Presently, he is able to lead an independent life. Thirteen months after the procedure pulmonary function tests showed the following values: FEV_1, 2.23 l; FVC, 3.3 l, and TLC, 4.9 l.

Discussion
Paraquat is a water soluble quaternary ammonium derivative, poorly absorbed by the oral route (5–10%) and unbound to plasma proteins. Peak plasma concentrations are reached within 1–4 hours and decrease rapidly thereafter as the compound is taken up by the tissues and cleared by the kidney.[2] In our case paraquat was undetectable in plasma obtained

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four days after the start of gastrointestinal symptoms whereas high levels were found on lung and muscle samples taken as late as nine weeks after herbicide ingestion. Indeed, paraquat is actively concentrated in alveolar pneumocytes and skeletal muscles. The acute pulmonary lesions have been attributed to the formation of oxygen derived free radicals and lipid peroxidation products whereas activation of "resident" macrophages are implicated in lung fibrosis.[3] All pharmacological treatments including free radical scavengers, iron chelators, cochicine or corticoids are of unproven value, but encouraging results have recently been reported with a combination of cyclophosphamide and methylprednisolone.[4]

In the most severe form the early mortality is related to respiratory, cardiac, renal and hepatic failure. In less severe poisoning a progressive bronchiolo-alveolitis develops and, once changes in the lung become apparent radiologically or if ventilatory assistance is required, the condition is invariably fatal.[3] Lung transplantation has been previously reported in five patients after paraquat intoxication, all of whom died (immediately and up to three months after transplantation) in relation to graft failure, infection, or massive haemorrhage.[5–8] In the present case the possibility of a suicide attempt was refuted by the patient's family and, after a multidisciplinary consultation, lung transplantation was advocated as the ultimate treatment of a respiratory insufficiency of unclear origin in the absence of sepsis and other organ failure.

At the time of the lung transplant partial cardiopulmonary bypass was instituted in order to improve blood oxygenation, to prevent right ventricular failure, and to maintain cardiac output after clamping of the right pulmonary artery. After reperfusion of the grafted lung a trial of inhaled NO failed to reduce pulmonary hypertension. In fact, rapid interaction of exogenous NO with superoxide generated during early pulmonary reperfusion may liberate far more toxic oxygen species, such as peroxynitrite and hydroxyl radicals,[9] than direct stimulation of the 3', 5'-cyclic guanosinemonophosphate (cGMP) pathway with a cGMP analogue, or an intravenous NO donor such as nitroglycerin might confer protective vascular effects while avoiding the release of toxic byproducts.[10]

Postoperatively, toxic myopathy and development of a right bronchopleural fistula led to difficulty in weaning the patient from the venti-lator. The myopathy can severely limit the ultimate recovery and repeated biopsies are advocated to document the extent of injured and regenerated muscle fibres.[6] Since muscles are important body stores for paraquat, progressive release may occur resulting in new injuries in the grafted lung and further destruction of the native lung. Ablation of the "remodelled" right lung contributed to the decrease in the risk of infection and to healing of the bronchopulmonary fistula. Fortunately, gas exchange and functional lung volumes remained good. In addition, the patient recovered sufficient muscle strength to lead an independent life and he was compliant with the post-transplant medical regimen and follow up examinations.

The present case illustrates the successful management of paraquat poisoning by a single lung transplantation and is the longest survival ever reported (more than 20 months). However, given the shortage of donor lungs, the unknown psychological state of some candidates, and the bad outcome of previously reported cases, the question of the desirability of lung transplantation as a treatment for acute lung fibrosis after paraquat intoxication should be raised. Such cases should remain exceptional since rare resources and expensive medical treatment should be utilised for eligible candidates accepted onto a transplant programme.

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Heart lung transplantation in a patient with end stage lung disease due to common variable immunodeficiency

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Figure 1   Thoracic CT scan showing emphysematous bullae and diffuse interstitial shadowing.

Abstract

The case history is presented of a patient with common variable immunodeficiency in whom heart lung transplantation has been carried out with success. Transplantation was the only long term therapeutic option in this patient due to the progressive respiratory failure resulting from bronchiectasis, emphysema, and granulomatous lung disease.

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Common variable immunodeficiency is a primary immunodeficiency characterised by hypogammaglobulinaemia and has an estimated prevalence ranging from 1:50 000 to 1:200 000.[1] The immunodeficiency affects men and women equally and the onset is usually in the second or third decade of life.[1] It is characterised by recurrent bacterial infections of the respiratory tract usually with nontypable *Haemophilus influenzae* and *Streptococcus pneumoniae*.[1] Recurrent bacterial infections can lead to irreversible chronic lung disease with bronchiectasis.[1]

Case report

A 37 year old man, an aircraft inspector, presented with a one year history of progressive dyspnoea, expectoration of a cupful of mucopurulent sputum daily, weight loss, and frequent sinus headaches. Past history included staphylococcal pneumonia at the age of six, pneumonia age of seven, delayed puberty, short stature, and frequent chest infections. He had a 10 year pack history of smoking, having stopped 10 years previously. His nephew had frequent infections including osteomyelitis as a child.

Pulmonary function tests were compatible with emphysema: forced expired volume in one second (FEV_1) 0.61 l (15% predicted), forced vital capacity (FVC) 2.66 l (55% predicted), total lung capacity (TLC) 8.05 l (125% predicted), residual volume (RV) 5.11 l (302% predicted), and gas transfer coefficient (K_{CO}) estimated using a 10 second breath hold met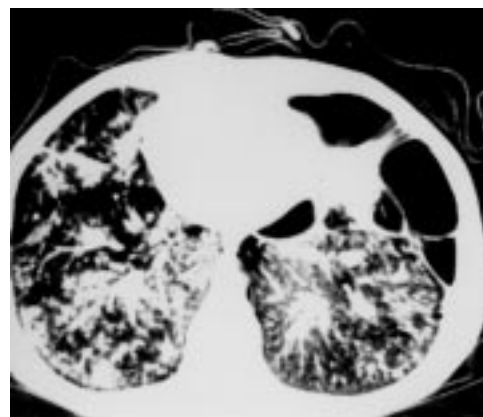hod at 10.77 (38% predicted). Sputum microbiology cultured *Haemophilus influenzae* (mycobacterial and fungal cultures were negative). Chest radiography revealed hyperinflated lung fields and bilateral basal cystic shadowing. Computed tomographic (CT) scanning of the lungs revealed emphysematous bullae and diffuse interstitial shadowing associated with structural lung and bronchial damage (fig 1). Although there was uncertainty whether there was bronchiectasis on the CT scan, a bronchogram carried out eight years earlier revealed bilateral bronchiectasis.

Full blood count and biochemistry were normal including angiotensin converting enzyme, α_1-antitrypsin, aspergillus precipitins, rheumatoid and antinuclear factor. A sweat sodium and chloride test to exclude cystic fibrosis was normal. Immunoglobulin screening prior to treatment revealed a low IgG at 4.6 g/l (normal range 6–16) but normal IgA at 1.8 g/l (0.75–4) and IgM 0.65 g/l (0.25–2). Immunoglobulin subclasses revealed IgG subclass 1 and 3 deficiency: IgG_1 3.5 g/l (4.2–12.9) and IgG_3 0.13 g/l (0.4–1.3). He had low antibody levels to the recall antigens of *Haemophilus* and pneumococcal polysaccharides, as well as diphtheria and tetanus toxoid, and the latter failed to normalise after vaccination. There were low numbers of both T and B lymphocytes with a low T4 level and a reversed T4/T8 ratio (CD4 0.12×10^9/l (healthy control 0.74×10^9) and CD8 0.69×10^9/l (0.77×10^9)). The lymphocytes also showed poor in vitro functional activity with subnormal lymphocyte proliferative responses to phytohaemagglutinin, concanavalin A, pokeweed mitogen, purified protein derivative, and *Candida albicans*.

Immunoglobulin replacement intravenous infusions (Sandoglobulin) at 150 mg/kg were commenced three weekly correcting the hypogammaglobulinaemia up to within the normal range (>6 g/l). Following replacement therapy the frequency of chest infections reduced. Despite this, over the next six years he progressively deteriorated becoming breathless on minimal exertion and requiring long term oxygen therapy, home nebulised bronchodilators, and cyclical antibiotics. At this stage his FEV_1 was 0.4 l and he was referred for heart lung transplantation.

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Seventeen months later he had a successful heart lung transplant. The macroscopic appearance of the explanted lung revealed extensive bronchiectasis and emphysema through all lobes. Microscopy revealed evidence of bronchiectasis and emphysema, but also evidence of interstitial fibrosis and less frequent granulomas in all lobes.

He was put on standard post-transplant immunosuppressive therapy with cyclosporin, azathioprine and prednisolone. Replacement immunoglobulin therapy was continued every three weeks with IgG levels maintained at >6 g/l and co-trimoxazole was used as prophylactic treatment against *Pneumocystsis carinii*. The CD4 T cell count was not monitored. Since transplantation he has had one minor episode of rejection at two months. Spirometric tests at two years showed that lung function was maintained with FEV_1 4.24 l (119% predicted) and FVC 4.96 l (114% predicted) and he is back at work.

Discussion

Patients with common variable immunodeficiency have hypogammaglobulinaemia leading to defects in humoral immunity.[1–4] The marked decrease in serum IgG is usually associated with depressed serum IgM and IgA levels[2] which was not seen in this case, reflecting the spectrum of disease that occurs. Defects in cell mediated immunity may also occur in common variable immunodeficiency and, rarely, patients can become infected with mycobacteria, fungi and *Pneumocystis*.[1–4] This patient had immunodeficiency in both the humoral and cellular arms, although he suffered mainly from bacterial infections and had no evidence of fungal or mycobacterial infection.

Multisystem involvement, resembling sarcoidosis, with non-caseating granulomas is recognised in common variable immunodeficiency.[1–6] The granulomas most commonly occur in the lung, lymph nodes, skin, bone marrow, and liver.[1–6] The aetiology of the granulomas is unclear and during their course they often undergo spontaneous expansion and regression without therapy.[1–4] Occasionally the granulomatous process will become aggressive and steroid therapy is useful in these cases.[1–5] The granulomatous lung disease was found diffusely in the explanted lung, but might have been picked up earlier by lung biopsy.

Immunoglobulin replacement was first commenced for hypogammaglobulinaemia in 1952.[1] The decision to replace immunoglobulins should be based on the frequency and severity of recurrent infections and a demonstrated inability to mount a functional antibody response.[2] Following replacement immunoglobulin therapy there was a reduced number of chest infections compared to preceding years, body weight improved, and the decline in lung function stabilised; however, this progressed to the point of requiring transplantation.

Heart lung transplantation has successfully been carried out in this patient with end stage lung disease due to common variable immunodeficiency. There was, however, initial reluctance by the transplant team to pursue transplantation, since it was felt that an immunodeficient patient would be at increased risk of chest and other infections with post-transplant immunosuppression. This does not appear to have been the case, and an important factor was the maintenance of adequate replacement immunoglobulins. It is possible that the degree of impairment in his cell mediated immunity, as evidenced by abnormal parameters of in vitro lymphocyte function, may have made it easier for the transplant to become established.

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