Case Report

Respiratory syncytial virus pneumonitis complicating immunosuppressive treatment for ANCA-positive vasculitis

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Introduction

We present a case of acute respiratory failure developing in a patient given immunosuppression for anti-neutrophil cytoplasm antibody (ANCA)-positive renal vasculitis. With these interventions, however, comes the increased risk of infective complications. This case highlights a highly unusual (but probably underdiagnosed) infection, respiratory syncytial virus (RSV), associated with severe pneumonitis. This pathogen is associated with bronchiolitis in infants and outbreaks of pneumonia in the elderly. Previous reports associating RSV with immunosuppression have virtually exclusively focused on lung and bone-marrow transplant recipients.

Case

A 66-year-old male had been referred for investigation of impaired renal function and symptoms of lethargy, nausea, loss of appetite and swollen ankles of 4 months duration. His plasma creatinine had been 100 μmol/l in 1996, rising to 372 μmol/l at the time of referral in October 2001 and to 501 μmol/l at his first outpatient appointment the following week.

The only past medical history of note was of chronic obstructive pulmonary disease not requiring hospital admission and for which he was taking regular inhaled beclomethasone. There was no history of cardiac disease. His normal exercise tolerance was 800 yards on the flat. He was a smoker of 20 cigarettes per day and occasionally drank alcohol.

Examination revealed a hypertensive gentleman with a blood pressure of 190/100 mmHg. He had leuko-nychia, but there was no evidence of clubbing, anaemia or rash. His jugular veins were not visible, heart sounds were normal and there was mild swelling of the ankles. There was no evidence of wheeze or crepitations on examination of his chest. Resting echocardiograph did not show any evidence of ischaemic heart disease. Echocardiography showed preserved left ventricular function with a left ventricular end-diastolic diameter of 5.0 cm [normal range (NR): 3.0–5.0 cm]. Left atrial diameter was at the upper end of the normal range (4.0 cm; NR: 2.0–4.0 cm) and left ventricular ejection fraction was 55% (NR: 50–65%). There was no diastolic dysfunction. Calculated pulmonary artery pressures were in the normal range, but the right atrium was mildly dilated.

Initial investigations revealed a normal full blood count. His renal function was impaired, as noted earlier, and his plasma albumin was 25 g/l. An abdominal ultrasound showed two normal-sized unobstructed kidneys and a normal liver. His chest X-ray was normal. A 24 h protein excretion was measured at 3.9 g. Serum immunoglobulin levels and protein electrophoresis were normal. The autoantibody screening showed him to be p-ANCA positive (MPO +ve) with a titre of 1:80. The C-reactive protein was elevated at 65 mg/dl and remained at or around this level for ~14 days, returning to normal after resolution of this illness (NR: <5 mg/l). He subsequently underwent a renal biopsy, which showed features consistent with pauci-immune crescentic glomerulonephritis (21% active or healing crescents, most glomeruli showing focal necrotizing glomerulonephritis; immunoglobulin deposition was not evident with immunoperoxidase, i.e. pauci-immune) and a diagnosis of ANCA-positive vasculitis was made.

He was treated with three 1 g pulses of intravenous methylprednisolone after which he was started on
60 mg prednisolone and 100 mg cyclophosphamide daily.

He was reviewed again 2 weeks later at which time the dose of prednisolone was reduced to 40 mg, but the cyclophosphamide was left unchanged. Four days later he presented with symptoms of breathlessness on exertion and reduced exercise tolerance. He denied any cough or haemoptysis. On examination he was afebrile and had an oxygen saturation of 90% on air. The jugular veins again were not visible, heart sounds were normal and there was no peripheral swelling. His chest revealed bilateral coarse crepitations to the midzone.

A full blood count revealed leukopenia with a white cell count of $1.1 \times 10^9$ (lymphocyte count: $0.1 \times 10^9$) and as a result cyclophosphamide was stopped. A course of granulocyte-colony stimulating factor (263 mg daily for 5 days) was given to boost his marrow response. Arterial blood gases now showed a $pO_2$ of 8.3 kPa and a $pCO_2$ of 3.63 kPa on air. His oxygen requirement increased over the next few days and on day 3 he had a $pO_2$ of 6.31 kPa on 35% oxygen. His chest X-ray showed bilateral mid/lower-zone shadowing (Figure 1).

Bronchoscopy showed a normal looking bronchial tree, with no evidence of pulmonary haemorrhage on direct vision. The bronchoalveolar lavage was positive for RSV (by immunofluorescence staining; Figure 2) and negative for red Pneumocystis carinii, acid-fast bacilli and fungi. The predominant cells were lymphocytes (detailed immunophenotyping was not carried out). There were no red cells. Acute and convalescent phase mycoplasma and legionella serology was negative (chlamydial serology was also negative). A CMV pp65 antigenemia test was weakly positive, but with just two nuclei. CMV was not detected in sputum samples by detection of early antigen fluorescent foci testing. CMV serology showed IgG positivity, but not IgM.

He was initially treated with amoxicillin and clarithromycin to cover a possible bacterial pneumonia. He was also started presumptively on a 10 day course of ganciclovir following the results of the CMV DAT. However, he failed to respond clinically to the antibiotics and ganciclovir and after 5 days required intermittent non-invasive ventilation and haemofiltration (for 5 days). In view of his continued clinical deterioration, aerosolized ribavirin (6 g daily for 5 days) and intravenous immunoglobulin (30 g every 2 days over 20 days) were prescribed. He made a good recovery over the next 7 days and was weaned off oxygen and eventually discharged. His chest X-ray and exercise tolerance had returned to status quo ante after 4 weeks. His renal function stabilized without significant further immunosuppression and he remains well and dialysis-independent some 12 months later.

**Discussion**

RSV infection has a predilection for the upper and lower respiratory tracts (LRT). The clinical manifestations are diverse, ranging from asymptomatic infection to pneumonia and death. The Institute of Medicine (Washington, DC, USA) estimated that 91 000 infants were hospitalized with RSV bronchiolitis in the United States in 1985 at an estimated cost of $300 million [1]. RSV pneumonia has been long established as a major cause of morbidity and mortality in the paediatric population, accounting for 25% of hospitalized pneumonias. In more recent years LRT RSV infection has been recorded in the elderly, often in seasonal outbreaks (autumn and winter) in residential homes for the elderly, and in immunosuppressed adults following bone marrow and lung transplantation [1–4].

Susceptibility to RSV infection seems to be enhanced by underlying cardiopulmonary disease. Radiological
findings can be diverse and in a recent computerized tomography (CT)-based study, findings in nine patients were ground-glass (seven), air-space (five) and tree-in-bud (four) opacities and acute bronchial dilatation (four) and wall thickening (four). Pleural effusions and lymph node enlargement did not feature. Five out of seven patients with follow-up imaging had new air trapping (three), persistent bronchial dilatation (three) and thickening (two). Three and two of the 10 patients developed bronchiolitis obliterans syndrome and obliterative bronchiolitis, respectively [5]. Our patient did not undergo CT chest investigation, but the chest X-ray showed bilateral lower and mid-zones reticulo-nodular shadowing.

RSV infection is diagnosed either by antigen detection using labelled antibody, by viral culture or by nucleic acid testing of respiratory specimens. Clinically, it can resemble ‘influenza’ in so far as adults get an influenza-like illness, but there is some evidence that the mortality from community-acquired RSV is higher than that seen with influenza virus (types A and B) [6].

Controversy surrounds the efficacy of therapy for RSV (as either pre-emptive therapy or disease treatment). Aerosolized ribavirin is common to both, but parenteral pooled immunoglobulin, or RSV-IvIg, is reserved for active disease. Many authorities would advocate the use of topical antiviral therapy and parenteral immunoglobulin for immunocompromised adults [4,7,8]. The importance of this therapy, which is both toxic and expensive, to overall recovery is not clear; reduction in contemporaneous immunosuppression also needs to be considered and evaluated.

Our patient is the second reported case of RSV LRT infection in association with the use of oral cyclophosphamide and steroids for the treatment of p-ANCA vasculitis [9] and the only one to survive. The reasons for the rarity of this diagnosis amongst immunosuppressed renal patients are not certain, although lack of clinical suspicion and diagnostic testing may contribute. In addition, the immunosuppressive regimes used for the treatment of renal vasculitis and for prevention of renal transplant rejection may not alone be sufficient to tip the balance in favour of severe LRT RSV infection. Interestingly, cyclophosphamide has been shown to increase susceptibility of mice to RSV infections. The susceptibility of our patient is likely to have been enhanced both by his age and his underlying pulmonary disease. A greater awareness of the diagnosis of RSV LRT infection in adults is needed. The successful outcome in this case may reflect early diagnosis and treatment.

Conflict of interest statement. None declared.

References


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