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Case report

Rituximab rescue therapy for autoimmune pulmonary alveolar proteinosis

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ABSTRACT

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disease characterised by abnormal alveolar surfactant accumulation due to macrophage dysfunction. Whole lung lavage (WLL) is the cornerstone of first-line aPAP therapy, but effective rescue treatments have not yet been well established. We report a case of a 41-year-old man with aPAP in whom further WLL is contraindicated. His diagnosis was established using a combination of classical radiological findings, positive serum GM-CSF IgG antibodies and bronchoalveolar lavage (BAL) findings. Following a literature review of emerging therapies, a decision was made to treat with a course of rituximab to suppress GM-CSF autoantibody production and restore alveolar surfactant-macrophage homeostasis. A significant clinical response was demonstrated within 6 months with improvements in arterial oxygenation, respiratory membrane gas diffusion, six-minute walk test and radiological findings.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterised by abnormal alveolar surfactant accumulation. Symptoms are generally non-specific, but dyspnoea is the most common. PAP has a variable clinical course, ranging from spontaneous resolution to death from respiratory failure. The majority of cases are autoimmune, characterised by the presence of granulocyte-macrophage colony stimulating factor (GM-CSF) autoantibodies. GM-CSF is a growth factor, integral to the development of functioning myeloid cells [1]. GM-CSF antibodies block the growth factor's activity, resulting in dysfunctional alveolar macrophages [1]. Consequently, the impaired surfactant clearance, poor gas exchange and disrupted innate immunity can result in respiratory failure and recurrent pulmonary infections.

Diffuse changes within the lungs, including septal and reticular thickening with ground glass opacities, are typical high-resolution CT findings. This is often described as a 'crazy-paving' appearance. Gold standard diagnosis is through lung biopsy. Cytology typically shows alveoli filling with Periodic Acid Schiff (PAS) positive granular and eosinophilic material [2]. Whole lung lavage is currently the only accepted first-line therapy, of which the clearest indications are hypoxia or severe symptoms. Second-line therapeutic considerations are not well established and include lung transplant and recombinant GM-CSF therapies. Multiple trials have demonstrated mixed results from the use of nebulised GM-CSF, of which the most recent, demonstrated a clinical and laboratory benefit from daily dosing over a period of 24 weeks [4,9]. Inhaled recombinant GM-CSF is an uncommon and expensive medication that requires good patient compliance and does not yet have an accepted dosage or duration.

Rituximab is a more readily available, cost-effective and easy to administer therapeutic option with a recent prospective case-series

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showing some clinical improvement [3]. Rituximab is a monoclonal antibody directed against the B lymphocyte antigen CD20 and is an effective therapeutic option in several autoimmune diseases such as rheumatoid arthritis. We present a patient with aPAP refractory to whole lung lavage and our experience of using rituximab as a second-line therapy.

2. Case presentation

A 41-year-old indigenous male initially presented to the emergency department with six months of recurrent chest infections, worsening exertional dyspnoea and intermittent bilateral pleuritic chest pains. Clinical examination revealed peripheral oxygen saturations of 89% on room air, digital clubbing and lower zone inspiratory crackles. Screening blood tests including inflammatory markers and connective tissue disease serology were all unremarkable.

The initial chest Xray demonstrated non-specific diffuse alveolar changes along with evidence of bullous disease [Fig. 1]. Computed tomography (CT) imaging of the chest confirmed bilateral mixed ground glass changes, alveolar infiltrates and 'classical' crazy paving in the left lower lobe, in addition to underlying bullous emphysema and congenital bronchial atresia of the right lower lobe [Fig. 2]. He was a smoker of both cannabis and tobacco with no other significant medical history and no significant occupational exposures.

Pulmonary function testing demonstrated a mixed ventilatory defect on spirometry (FEV1 1.86L, 49% predicted; FVC 2.81L, 61% predicted) and severe reduction in gas diffusion (DLCO 8.7mL/mmHg/min, 28% predicted). BAL fluid was turbid and milky brown in colour; cytological examination revealed abundant acellular globules which were positive on PAS staining and microbiological cultures were negative [Fig. 3]. Unfortunately, BAL samples were not sent for serological testing at the time, but serum IgG GM-CSF antibodies subsequently returned positive on an ELISA with 1.24 optical density units. GM-CSF neutralising index is not currently available to our pathology service and was not able to be requested. The combination of radiological findings, PAS-positive material in BAL fluid and positive GM-CSF antibodies confirmed the diagnosis of aPAP.

The primary treatment was sequential bilateral whole lung lavages (WLL), for which he only had a partial clinical response, requiring repeat WLL cycles every 6 months. During this time he had no oxygen requirement, a six-minute walk test (6MWT) of 330m and stable lung function. Unfortunately, his sixth and most recent WLL procedure was complicated by a hydropneumothorax requiring reintubation and intercostal catheter insertion in the context of his underlying structural lung disease. With further WLL now contraindicated and no established evidence-based second-line therapy, he had progressive clinical deterioration. Within two months he had a significantly reduced exercise tolerance, became oxygen dependent with an arterial oxygen partial pressure of 47 mmHg and was house bound. Ongoing cigarette smoking precluded lung transplantation assessment.

After a review of the available evidence, a decision to proceed with rituximab rescue therapy was made based on patient preference, drug availability, cost, relative ease of administration and predicted patient compliance. Two doses of 1 g of rituximab were administered intravenously, separated by 14 days. The patient showed an excellent clinical response. Six months after commencing treatment he no longer required domiciliary oxygen, his 6MWT had improved to 562m, and his lung function improved to FEV1 1.90L (51.4%), FVC 3.08L (67.5%) and DLCO 14.38mL/mmHg/min (46.1%). His serum GM-CSF IgG antibodies were still detectable but with a reduced optic density units of 0.69. As a result of the Rituximab, B-cell depletion was confirmed with a serum $CD19^{+}$ count of zero. There was significant improvement in 'crazy-paving' infiltrates on repeat CT [Fig. 4]. The patient's quality of life significantly improved including being able to walk his dog, an important milestone for him. Maintenance rituximab is planned in 6 month cycles, although duration of therapy and long-term benefit is still yet to be determined.

3. Discussion

Autoimmune pulmonary alveolar proteinosis is rare chronic lung condition whereby the alveolar-surfactant homeostasis is dysfunctional. IgG autoantibodies are produced against GM-CSF which is required in the signalling pathway to stimulate alveolar

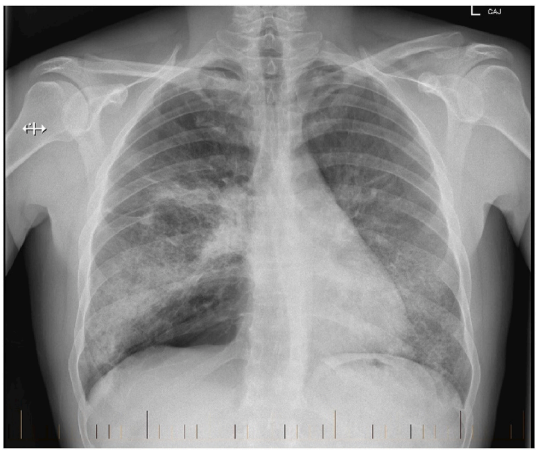

Fig. 1. Baseline Chest X-ray at time of presentation shows diffuse alveolar opacities in the bilateral mid and lower zones, along with bullous disease in the right base and apex consistent with a number of differentials.

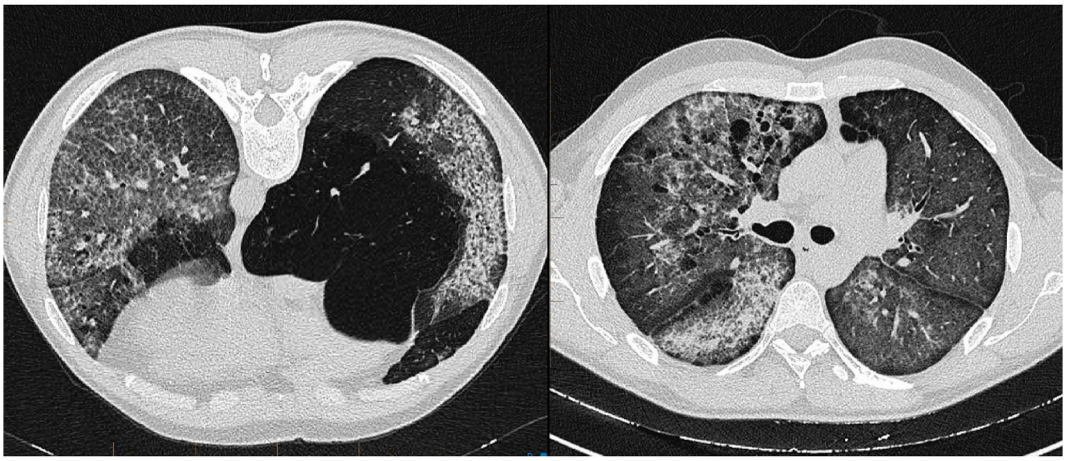

Fig. 2. High Resolution CT Chest (at diagnosis) showing diffuse septal and reticular thickening on a background of ground glass changes consistent with 'crazy paving'. Concurrent bullous centrilobular emphysematous changes.

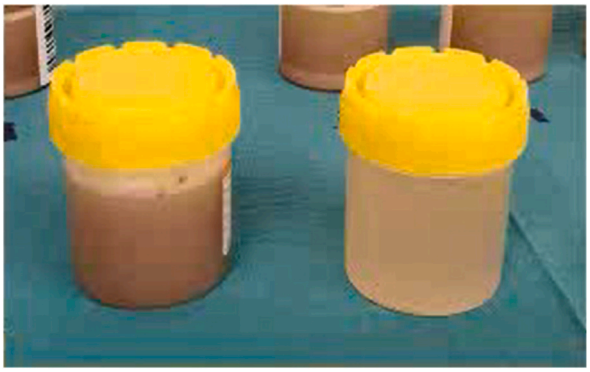

Fig. 3. BAL samples from the first Whole Lung Lavage. Samples become progressively transparent as the bronchopulmonary lavage continues.

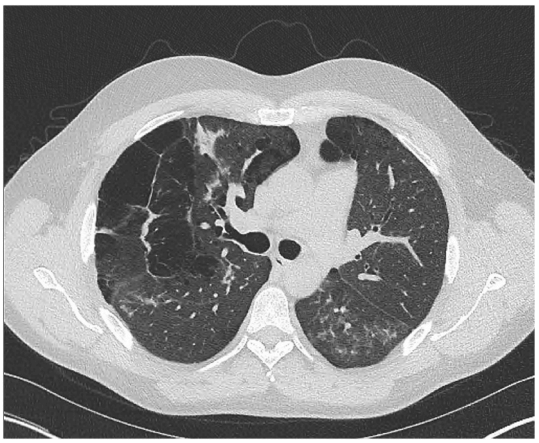

Fig. 4. CT Chest 6 months following first course of rituximab with significant improvement in septal, reticular and ground glass changes.

macrophages maturation and surfactant clearance [4]. This is demonstrated by the foamy, surfactant filled, alveolar macrophages on lung biopsy and milky lipo-proteinaceous BAL fluid. The dysfunctional alveolar macrophages and accumulation of lipo-proteinaceous material predisposes patients to pulmonary infections and disrupts the respiratory membrane, potentially leading to progressive respiratory failure [3,5]. The accepted standard of care is sequential whole lung lavage with no established second-line rescue therapy if this fails or is contraindicated.

Proposed rescue therapies in the literature are aimed at replacing the deficient GM-CSF via inhalation/subcutaneous administration or by blocking autoimmune inhibition of macrophages via CD20 suppression. It has been theorised that macrophage transplantation could even be a target for further research for aPAP therapy [5]. Recent studies of inhaled recombinant GM-CSF have had varying laboratory and clinical benefit, and to date this appears to have the largest body of evidence [4,6]. The barriers to inhaled GM-CSF that we experienced were in relation to its significant cost, difficulty in procuring and concern about patient compliance due to its daily dosing requirement.

Several case studies and small phase II trials have suggested effectiveness of rituximab for aPAP [3,7]. A recent study assessing serum and BAL cytokines responsible for B cell selection, activation, maturation and survival, which are commonly elevated in other autoimmune disorders, were significantly elevated in aPAP patients [8]. CD20-positive B cell depletion would inhibit the production of GM-CSF autoantibodies and allow alveolar macrophages to mature and function. This may restore alveolar-surfactant homeostasis, clear lipo-proteinaceous material from the alveolus and restore the respiratory membrane.

The effectiveness of rituximab to restore alveolar surfactant-macrophage balance was demonstrated in this patient by resolution of resting hypoxia, improvement in exercise tolerance and 6MWT, improvement in gas diffusion and decrease in ground glass changes and pulmonary infiltrates on CT imaging.

In summary we report a case of autoimmune pulmonary alveolar proteinosis with a significant clinical and radiological response to rituximab rescue therapy. We suggest that the role of rituximab as second-line therapy for aPAP be evaluated further in randomised controlled trials.

Author contributions

DB and JE have contributed equally in drafting the manuscript and CP has reviewed and edited the manuscript.

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Declaration of interest

None.

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Abbreviations

aPAP: autoimmune pulmonary alveolar proteinosis
WLL: whole lung lavage
BAL: bronchoalveolar lavage
GM-CSF: granulocyte-macrophage colony stimulating factor
PAP: pulmonary alveolar proteinosis
PAS: Periodic Acid Schiff
6MWT6 min: walk test