

## CASE REPORT

# Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: Successful treatment with granulocyte-macrophage colony stimulating factor after a partial response to whole lung lavage

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### **Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: Successful treatment with granulocyte-macrophage colony stimulating factor after a partial response to whole lung lavage**

JAMALUL AZIZI AR, MOODLEY YP, PHILLIPS MJ. *Respirology* 2004; 9: 419–422

**Abstract:** Pulmonary alveolar proteinosis (PAP) is a rare lung disease. Although whole lung lavage is considered the most effective treatment, not every patient shows a complete response. The case of a young man with PAP in association with psoriasis who underwent frequent whole lung lavage but only achieved remission following treatment with granulocyte-macrophage colony stimulating factor (GM-CSF) is reported. His lung problem was complicated by atypical mycobacterial infection, which resolved with treatment. The role of GM-CSF is discussed.

**Key words:** atypical mycobacterium, granulocyte-macrophage colony stimulating factor, psoriasis, pulmonary alveolar proteinosis.

## INTRODUCTION

A patient with pulmonary alveolar proteinosis (PAP) who had a background history of psoriasis and a partial response to repeated whole lung lavage, but who was successfully treated with granulocyte-macrophage colony stimulating factor (GM-CSF) is reported here. The occurrence of PAP in association with psoriasis suggests that a common pathogenesis might exist in these two conditions.

## CASE REPORT

A 44-year-old man with no known history of respiratory illness was transferred to Sir Charles Gairdner

Hospital, Perth, Western Australia, in December 2001 for further management of PAP. He had been initially admitted to another hospital 1 week earlier with complaints of increasing exertional dyspnoea over 6 months associated with dry cough and weight loss of 5 kg. There was no history of haemoptysis, chest pain, wheezing or fever.

A transbronchial biopsy performed at the referring hospital had resulted in a left-sided pneumothorax. He had suffered psoriasis from the age of six but only sought treatment for 2 years between the ages of 11 and 13 years. He did not remember the nature of the treatment he received for his psoriasis. Over the years, there was no progression of the skin disorder in spite of a lack of treatment. He smoked 40 cigarettes per day, worked as a swimming pool builder and had exposure to concrete dust. There was also a history of work in opencast mining for 6 months.

Physical examination revealed a fit-looking man who was tachypnoeic (respiratory rate 22 breaths/min) at rest. His oxygen saturation was 94% on oxygen (4 L/min) via a nasal cannula. Psoriatic lesions were noted on his elbows and knees. Respiratory examination revealed reduced air entry on the left side. The rest of the examination was normal.

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Received 23 May 2003; revised 22 September 2003; accepted for publication 10 February 2004.

Routine blood tests were normal. The erythrocyte sedimentation rate was 15 mm/h. Epstein-Barr serology was indicative of past infection. Mycoplasma, toxoplasma and cytomegalovirus serology was negative as was other viral serology. Bronchial washing for acid-fast bacilli and *Pneumocystis carinii* was negative.

The transbronchial biopsy revealed mild proliferation of type II pneumocytes together with variable thickening of alveolar walls associated with an intra-alveolar, slightly granular, acellular amorphous infiltrate. The amorphous material was moderately Periodic acid-Schiff positive. On arrival at Sir Charles Gairdner Hospital, a chest X-ray (CXR) showed a small left-sided pneumothorax and bilateral perihilar pulmonary infiltrates.

The patient was discharged from hospital after 2 days and the pneumothorax was managed conservatively. He was readmitted for a left lung bronchoalveolar lavage (BAL) in mid-December followed by a right lung BAL in the first week of January 2002. The BAL (left, 15 L; right, 18 L) was performed under general anaesthesia via a double lumen tracheal tube. Both procedures were uneventful.

The patient's symptoms improved for approximately 6 weeks. However, he had become breathless again when reviewed in the clinic in March 2002. CXR revealed bilateral pulmonary infiltrates that were worse on the left side. Pulmonary function testing at this time revealed a total lung capacity (TLC) of 4.29 L (predicted  $5.99 \pm 0.91$  L), vital capacity (VC) of 3.26 L ( $4.14 \pm 0.58$  L), residual volume (RV) of 1.03 L ( $1.79 \pm 0.39$  L), DLCO of 10.2 mL/min per mmHg ( $25.16 \pm 4.84$  mL/min per mmHg) and KCO of 2.67 ( $4.25 \pm 0.73$ ). Spirometry revealed a forced expiratory volume in 1 s ( $FEV_1$ ) of 2.75 L and a forced vital capacity (FVC) of 3.28 L (predicted 3.30 and 4.14 L, respectively). Arterial blood gas measurements while the patient was breathing room air revealed a pH of 7.46, a partial arterial carbon dioxide concentration ( $PaCO_2$ ) of 37 mmHg, a partial arterial oxygen concentration ( $PaO_2$ ) of 39 mmHg and an alveolar-arterial oxygen gradient of 64.8 mmHg (predicted 11.7 mmHg).

The patient underwent a second set of BAL in April 2002, after which he reported a significant improvement in his breathing. The initial fluid during BAL was milky but the fluid was clear at the end of the procedure. In May 2002, his  $FEV_1$  and FVC increased to 2.98 and 3.37 L, respectively. Several cavitating lesions in the right upper lobe were noted on his CXR at this time. A computed tomography (CT) scan of the chest (Fig. 1a) showed widespread ground glass abnormalities in both lungs, as well as some areas of soft-tissue mass with cavitation. Surprisingly, *Mycobacterium kansasii* (an atypical mycobacterium) was isolated from the BAL fluid.

In light of these new lung lesions, the patient was treated with isoniazid (300 mg daily), rifampicin (600 mg daily) and ethambutol (1800 mg daily) for 12–18 months. The treatment regimen was subsequently switched to rifabutin, clarithromycin and ethambutol. After 1 month of antimycobacterial treatment, the patient's breathing was stable and he tolerated the



**Figure 1** (a) Pre-granulocyte-macrophage colony stimulating factor (GM-CSF) computed tomography (CT) scan showing widespread ground glass appearance and consolidation; (b) post-GM-CSF CT scan showing resolution of ground glass appearance.

treatment with no side-effects. A repeat CXR showed resolution of the cavities. His spirometry improved further with  $FEV_1$  and FVC increasing to 3.06 and 3.40 L, respectively, and oxygen saturation on room air was approximately 90%.

The patient underwent a third set of BAL in July 2002, as he was feeling breathless again. He felt well again after the BAL. However, in September 2002, he became increasingly short of breath and his  $FEV_1$  and FVC had fallen to 2.54 and 2.86 L, respectively. The CXR again showed a recurrence of the pulmonary infiltrates and, in addition, he had coughed up milky fluid. He underwent a fourth set of BAL in late September 2002, after which he was commenced on GM-CSF at 240  $\mu$ g/day (3  $\mu$ g/kg per day subcutaneously) for the next 3 months in order to prevent recurrence.

After 2 months of GM-CSF treatment, the patient experienced no further dyspnoea and he tolerated the treatment well. There was only a marginal increase in his neutrophil count during treatment. The serum

lactate dehydrogenase level 1 day before GM-CSF treatment was only slightly elevated at 296 U/L (normal 125–250 U/L), but it declined to 255, 206 and 172 U/L during treatment and remained normal after treatment (211, 223 and 218 U/L).

On completion of GM-CSF treatment, pulmonary function testing revealed a TLC of 5.96 L (predicted  $5.97 \pm 0.90$  L), VC of 4.15 L ( $4.11 \pm 0.58$  L), RV of 1.81 L ( $1.80 \pm 0.39$  L), DLCO of 23.20 mL/min per mmHg ( $24.93 \pm 4.84$  mL/min per mmHg) and KCO of 4.06 ( $4.22 \pm 0.73$ ). Post-treatment arterial blood gas measurements on room air revealed a pH of 7.40, PaCO<sub>2</sub> of 41.9 mmHg, PaO<sub>2</sub> of 82.0 mmHg, oxygen saturation of 96.0% and alveolar–arterial oxygen gradient 15.63 mmHg (predicted 11.7 mmHg). Anti-GM-CSF antibody was not measured as the test was not available at Sir Charles Gairdner Hospital.

Figure 1b shows an image of a CT scan of the chest performed in April 2003 (taken at the same thoracic level as Fig. 1a), which demonstrates almost complete resolution of the ground glass appearance and consolidation. The patient has remained well for more than 6 months since GM-CSF treatment was stopped. GM-CSF did not, however, have any effect on his psoriasis.

## DISCUSSION

Pulmonary alveolar proteinosis is characterized by the accumulation of large amounts of a phospholipoproteinaceous material in the alveoli and is thought to be associated with abnormal surfactant homeostasis.

Only one case of secondary PAP associated with psoriasis has been reported previously.<sup>1</sup> In some cases, there has been a history of exposure to chemicals and mineral dusts.<sup>2</sup> The occurrence of PAP in this patient with psoriasis raises the possibility of a common pathogenesis for these disorders. A possible explanation is that a cytokine imbalance occurs in both conditions. Psoriatic lesions are characterized by infiltration of the skin with activated T cells, with CD8<sup>+</sup> cells predominating in the epidermis. Cytokines such as interleukin (IL)-2 from activated T cells elaborate growth factors that stimulate keratinocyte hyperproliferation.<sup>3</sup> Animal models suggest that IL-10 production is low in psoriatic lesions and treatment with recombinant IL-10 given subcutaneously results in improvement in psoriatic lesions in affected patients.<sup>4</sup> These data suggest that the pro-psoriatic effect of IL-2 can be counter-regulated by IL-10 administration.

Evidence from murine models and the occurrence of PAP in haematological malignancy suggest that, in common with psoriasis, imbalances in cytokines, particularly IL-10 and GM-CSF, might lead to abnormal surfactant homeostasis. Investigations in one patient with PAP suggested that expression of messenger RNA for GM-CSF was normal but there was a failure to secrete GM-CSF.<sup>5</sup> That study demonstrated high basal levels of IL-10, a potent inhibitor of cytokine expression at the transcriptional level,<sup>6,7</sup> and treat-

ment with IL-10 antibody normalized secretion of GM-CSF.<sup>5</sup> Therefore, it can be inferred that high levels of IL-10 are therapeutic in at least some cases of psoriasis but have the opposite effect on GM-CSF production and theoretically can worsen PAP. Based on these data, it was not expected that GM-CSF would have any therapeutic effect on psoriasis in the present case. Treatment with IL-10 might improve psoriasis but could also theoretically worsen PAP.

Pulmonary alveolar proteinosis is traditionally treated with whole lung lavage. Some studies have shown improvement after lavage, followed by a gradual decline and subsequent improvement following a repeat lavage,<sup>8</sup> as was clearly seen in the patient in the present report. A small proportion of patients (<15%) require lavage every 6 months,<sup>9</sup> and fewer than 10% do not respond. Serum carcinoembryonic antigen (CEA) was not measured in the patient in the present report, although it has been reported to be raised in PAP.<sup>10</sup> CEA is also raised in other pulmonary diseases such as pulmonary fibrosis.<sup>11</sup> Surfactant protein-A could not be measured at Sir Charles Gairdner Hospital.

The occurrence of anti-GM-CSF antibodies in idiopathic PAP has been reported by several researchers in the past.<sup>12–14</sup> It has been suggested that these antibodies are the causative agent in idiopathic PAP. By inhibiting endogenous GM-CSF activity, anti-GM-CSF antibodies impair the ability of alveolar macrophages to clear surfactant, resulting in excess surfactant accumulation in the alveolar spaces. Anti-GM-CSF antibodies were not measured in the present case as the test was not available at Sir Charles Gairdner Hospital.

Previous reports have suggested a potential role for GM-CSF in the treatment of PAP.<sup>15–17</sup> Improvement in pulmonary symptoms following treatment with GM-CSF further reinforces the hypothesis that a defect in GM-CSF production is important in the pathogenesis of PAP. Although successful use of GM-CSF in the treatment of idiopathic PAP has been reported in cases with elevated levels of anti-GM-CSF antibody, at least one previous report demonstrated successful use of GM-CSF in a patient with no anti-GM-CSF antibody.<sup>18</sup> This suggests that other factors such as IL-10 might play a role in inhibiting endogenous GM-CSF activity.

The patient in the present report had secondary PAP associated with psoriasis and showed a good response to GM-CSF. Although his anti-GM-CSF antibody status was unknown, this case provides evidence that a defect in GM-CSF production could also occur in some cases of secondary PAP, regardless of the presence of anti-GM-CSF antibody. There are at least two possible mechanisms that can impair endogenous GM-CSF activity leading to PAP: high levels of IL-10 (in patients with no anti-GM-CSF antibody) and the presence of anti-GM-CSF antibody.

The present case provides further evidence that GM-CSF is an effective alternative to whole lung lavage in some cases of secondary PAP, with or without anti-GM-CSF antibody. This gives hope to patients who have failed to achieve remission despite undergoing repeated whole lung lavage.

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