CASE STUDY

Plasmapheresis for treatment of pulmonary alveolar proteinosis

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ABSTRACT: Whole lung lavage (WLL) is currently the standard therapy for pulmonary alveolar proteinosis (PAP). Nevertheless, some PAP patients respond poorly to WLL or require it frequently. The present paper reports a patient with autoimmune PAP with persistent disease despite three WLL treatments over 10 months.

Plasmapheresis with ten 1.5-L plasma exchanges was performed, which lowered the serum granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody level from 250 μg mL⁻¹ to 156 μg mL⁻¹ but did not improve respiratory impairment. Further WLL therapy was required and transiently effective. Serum GM-CSF autoantibody levels declined progressively, reaching a value of 56 μg mL⁻¹ 80 weeks after completion of plasmapheresis. However, this decrease was not accompanied by clinical improvement and the patient required additional WLL therapy.

The results confirm that minor reductions in serum granulocyte-macrophage colony-stimulating factor autoantibody levels from plasmapheresis are not reflected in clinical improvement in the severity of lung disease in pulmonary alveolar proteinosis.

KEYWORDS: Autoantibodies, granulocyte-macrophage colony-stimulating factor, surfactant, whole lung lavage

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterised by accumulation of surfactant lipids and proteins within airspaces that can result in respiratory failure. The most common form of the syndrome, autoimmune PAP, is specifically associated with high levels of neutralising granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies that are thought to mediate pathogenesis by eliminating GM-CSF bioactivity in vivo, thereby impairing GM-CSF-dependent surfactant catabolism in alveolar macrophages and reducing pulmonary surfactant clearance [1]. Whole lung lavage (WLL), the current standard of care for treating autoimmune PAP, is effective in physically removing the accumulated surfactant and is effective in most patients [2]. However, in some patients WLL is ineffective, despite repeated WLL treatments [1]. Theoretically, plasmapheresis may be effective in removal of the presumably pathogenic neutralising GM-CSF autoantibodies and this approach has been described in one patient, in whom plasmapheresis resulted in improvement in symptoms, blood oxygen saturation and radiographic appearance of the lungs [3]. Based on the latter report, the present authors undertook the use of repeated plasmapheresis to treat a patient with autoimmune PAP who was poorly responsive to WLL.

CASE REPORT

A 40-yr-old man received a diagnosis of autoimmune PAP in 2004 based on lung biopsy, high resolution computed tomography (CT) of the chest, and an elevated serum neutralising GM-CSF autoantibody level. Progressive respiratory failure developed and the patient was treated with WLL in October 2004. A total of 30 L of normal saline was used for each lung and was combined with mechanical chest percussion during infusion and drainage to improve the physical removal of the accumulated alveolar surfactant. Lung function improved, as evidenced by a change in the gas exchange after the WLL therapy. The therapeutic effects of WLL were transient and lasted only a few months, in contrast to most PAP patients treated by WLL at our centre using the same technique [4]. Respiratory impairment progressed and WLL therapy was repeated 4 and 10 months later (February and August 2005), again with only
minimal and transient improvement. At this point, the patient was regarded as a poorly responsive to WLL therapy and other therapies were considered.

After obtaining approval from the Pavia Hospital Ethics Committee (Pavia, Italy), treatment of the patient was attempted by removal of GM-CSF autoantibodies using plasmapheresis, as recently described [3]. The patient received 10 treatment sessions during February and March of 2006, each of which involved a plasma exchange volume of 1.5 L. This relatively low-intensity regimen was chosen to minimise the potential plasmapheresis complications, represented by a slight increase of infections due to the loss of immunoglobulins, and the induction of a pro-thrombotic state. Plasmapheresis decreased the serum GM-CSF autoantibody level from an initial value of 250 µg·mL⁻¹ to 130 µg·mL⁻¹ after the third session; however, the level did not decrease further despite seven additional sessions and was 153 µg·mL⁻¹ after a total of 10 sessions (fig. 1). Importantly, this treatment did not improve the patient’s clinical condition.

Since neither lung function nor the chest CT abnormalities characteristic of PAP deteriorated during plasmapheresis, serial WLLs therapy was re-instituted. Since completion of plasmapheresis, three WLL treatments have been required (in March 2006, July 2006 and May 2007). Although the lung manifestations of PAP are still present, WLL therapy has been required less frequently after plasmapheresis therapy than before it. Interestingly, the serum GM-CSF autoantibody level has continued to decline from its value of 153 µg·mL⁻¹ at the completion of plasmapheresis to 56 µg·mL⁻¹.

DISCUSSION

Here, the use of serial WLLs and plasmapheresis is reported for the treatment of a PAP patient who responded poorly to WLL alone compared to other similar patients followed at the current authors’ center in Pavia, Italy. The rationale for plasmapheresis was based on the concept that GM-CSF autoantibodies appear to be pathogenic in PAP [1], and that plasmapheresis may reduce autoantibody levels sufficiently to improve surfactant clearance by restoring surfactant catabolism in alveolar macrophages [3].

While the patient’s initial serum GM-CSF autoantibody level was quite high, plasmapheresis clearly reduced the concentration, in a similar manner to results reported by BONFIELD et al. [3]. However, it was unable to reduce levels to <130 µg·mL⁻¹, despite 10 sequential plasmapheresis treatments over a 2-month period. This resulting concentration is higher than the mean±SEM serum GM-CSF autoantibody level in 158 autoimmune PAP patients with active lung disease (113±7 µg·mL⁻¹) [1] measured using the same ELISA method [5]. It is also considerably higher than the critical threshold predicted to increase the risk of developing the lung manifestations of autoimmune PAP [6]. Since at high levels of GM-CSF autoantibodies the actual autoantibody level does not correlate with the severity of PAP lung disease [6], it is not surprising that plasmapheresis was not associated with clinical improvement, since it did not reduce the level below the critical threshold. Thus, the present results suggest that small reductions in GM-CSF autoantibody levels from plasmapheresis are not expected to have a therapeutic effect. Further studies are required to determine if greater reductions in autoantibody concentration may be therapeutic; this could be theoretically achieved with more aggressive plasmapheresis regimens, at <3-day intervals,

FIGURE 1. a) Behaviour of granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody serum level (●) and arterial oxygen tension (P\textsubscript{a}O\textsubscript{2}, □) in the study patient over a period of 2 yrs including 10 plasmapheresis sessions and three whole lung lavages (WLLs). Changes in chest computed tomography image features can be seen b) before and c) after the 10 plasmapheresis sessions, and improvements can be seen d) after the March 2006 WLL. e) A worsening of the crazy paving can be seen before the July 2006 WLL following plasmapheresis. f) After the third (May 2007) WLL improvements can be seen.
with five or more exchanges over a period of 7–14 days [7]. However, risk/benefit must be carefully evaluated in view of the intrinsically increased susceptibility to infections displayed by PAP patients [1].

It is interesting that the serum GM-CSF autoantibody concentration continued to decline for 24 months after completion of plasmapheresis to less than half the value present at the end of these treatments. The reason for this is unclear. It is possible that the sequential WLLs removed a substance that stimulates the production of GM-CSF autoantibodies. Alternatively, WLL may remove significant numbers of the antibody-producing cells themselves, thereby reducing the circulating GM-CSF autoantibody levels. In either case, it is possible that the combination of a systemic treatment (plasmapheresis) and a local treatment (WLL) may act synergistically to lower the production of GM-CSF autoantibodies. While neither WLL nor plasmapheresis alone were sufficient to produce sustained benefit in this case, the combination of the two may have been beneficial.

Further studies are needed to determine the utility of lowering the granulocyte-macrophage colony-stimulating factor autoantibody levels to values lower than the threshold associated with development of pulmonary alveolar proteinosis.

REFERENCES