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Autoimmune Pulmonary Alveolar Proteinosis: Still Cloudy with a Chance of Understanding

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Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by the accumulation of phospholipids and surfactant apoproteins in the lower respiratory tracts; alveoli and terminal bronchioli [1]. Most cases originally diagnosed with primary or idiopathic PAP have been shown to be positive for granulocyte macrophage-colony stimulating factor (GM-CSF) autoantibody [2]. Strong evidence of causality in human idiopathic PAP was shown by the fact that GM-CSF autoantibodies reproduced the pathologic manifestations of idiopathic PAP in healthy macaques and that the autoantibodies were re-isolated from previously healthy macaques who were injected with them [3].Thus, the pathologically proven PAP with the autoantibody is termed autoimmune PAP (aPAP) at present, which constitutes 90% of PAP cases [4].

In the normal lung, GM-CSF binds to GM-CSF receptors on immature alveolar macrophages and initiates GM-CSF signaling in these cells. This triggers the terminal differentiation of alveolar macrophages into mature ones which incorporate and degrade surfactant lipids and proteins. Instead in the aPAP, GM-CSF autoantibodies prevent GM-CSF from binding to GM-CSF receptors on immature macrophages. Consequently, terminal differentiation of alveolar macrophages does not occur to impair surfactant catabolism in the lung, which causes gradual but progressive respiratory failure [5]. In the absence of any known cause of PAP, an elevated serum anti-GM-CSF autoantibodies titer is 100 percent sensitive and 91 to 98 percent specific for the diagnosis of aPAP [2,6]. However, GM-CSF autoantibody levels in serum did not correlate with duration of disease, disease severity, pulmonary function, or serum biomarkers, even in individuals with high GM-CSF autoantibody levels [4].

Observations about the natural history of the disease show a high rate of spontaneous remission. In the largest series, asymptomatic patients were most likely to have a stable to improving course with only 8 percent worsening during follow up. An experimental therapy with GM-CSF has been administered in some patients with aPAP. In an open label study of 35 adults with aPAP, inhalation of GM-CSF improved lung function and facilitated clearance of the GM-CSF-antibody complex from the lung [7]. Nevertheless, serum GM-CSF autoantibody levels were unaffected during observation as well as during inhalation period in both responders and non-responders. To elucidate the risk factors for recurrence of aPAP after GM-CSF inhalation, the 35 patients were followed up for 30 months [8]. During the observation, 23 patients remained free from additional treatments, and 12 patients required additional treatments. However, the serum levels of GM-CSF autoantibody were unchanged during the observation period except for three cases. The titers of anti-GM-CSF antibody in the bronchoalveolar lavage (BAL) fluid were reduced in responders.

The results of other therapies, treatment with plasmapheresis and rituximab are controversial. Plasmapheresis was performed to a patient with aPAP with persistent disease despite three whole lung lavage treatments over 10 months[9]. Serum GM-CSF autoantibody levels declined progressively during plasmapheresis. Nevertheless, this decrease was not accompanied by clinical improvement and the patient required additional whole lung lavage therapy. In an open-label, phase II study, 10 patients with aPAP were treated with rituximab [10]. Both PaO_2 and $AaDO_2$ in room air improved in seven out of the nine patients completing the study with improvement of both lung function and high-resolution computed tomography scans. Although the total anti-GM-CSF autoantibodies level and the capacity to neutralize GM-CSF activity decreased in the BAL fluid six months after treatment, no difference in either was seen in the pre- and post-treatment sera.

Since corticosteroid has been administered to treat successfully a number of autoimmune diseases, it is reasonable that the drug might also be effective to aPAP. To see the efficacy and safety of corticosteroid, clinical records of 31 patients with aPAP treated with corticosteroids were retrospectively reviewed [11]. The worsening rate was significantly higher in patients treated with high-dose prednisolone than treated with low-dose one. Infections newly emerged in six cases during corticosteroid therapy. Median serum GM-CSF autoantibody levels were similar to those in the previously reported data.

Anti-GM-CSF autoantibody, a form of anti-cytokine autoantibodies, is normally present in the serum of healthy human subjects with much lower concentrations than in the patients with PAP[6]. In addition, GM-CSF was far more abundant in healthy human serum than previously reported, but more than 99% was bound to and inactivated by GM-CSF auto antibodies. The critical threshold of GM-CSF autoantibodies associated with the development of PAP was also determined. These results demonstrate that free serum GM-CSF is tightly maintained at low levels even in a patient with aPAP and the reason why a healthy human does not develop PAP is not completely clarified.

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Authors	Publication year	Case n	Major findings	References
Seymour et al.	2002	146	Overall survival from the time of diagnosis of acquired PAP was significantly improved if patients had received therapeutic lavage at any time during their disease course.	1
Inoue et al.	2008	223	Asymptomatic patients were most likely to have a stable to improving course with only 8 percent worsening during follow up.	4
Luisetti et al.	2009	1	Plasmapheresis lowered the serum GM-CSF autoantibody level but did not improve respiratory impairment.	9
Tazawa et al.	2010	50	Of 35 patients completing the high- and low-dose GM-CSF inhalation therapy, 24 improved, resulting in an overall response rate of 62%.	7
Kavuru et al.	2011	10	Both PaO_2 and $AaDO_2$ in room air improved in seven out of the nine patients treated with rituximab.	10
Tazawa et al.	2014	35	In 35 patients completing GM-CSF inhalation therapy during 30 months observation, baseline %VC was higher among 23 patients who required additional treatment.	8
Akasaka et al.	2015	31	The worsening rate was significantly higher in patients treated with high-dose prednisolone than treated with low-dose one.	11

Table 1: Representative reports on treatment for autoimmune pulmonary alveolar proteinosis.
Abbreviations; PAP, pulmonary alveolar proteinosis; GM-CSF, granulocyte macrophage-colony stimulating factor.

There is no doubt that GM-CSF autoantibodies cause development of PAP in human subjects. Nonetheless, titers of the autoantibodies have no correlation with various clinical parameters, efficacy of treatment of both GM-CSF inhalation and rituximab, or corticosteroid administration. Like "milky" appearance of BAL fluid of the disease, aPAP is still cloudy with a chance of fully understanding its pathophysiology.

Competing Interests

The authors have no competing interests with the work presented in this manuscript.

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