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Case report

A case of autoimmune pulmonary alveolar proteinosis with severe respiratory failure treated with segmental lung lavage and oral statin therapy

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a diffuse lung disease characterized by the accumulation of alveolar surfactants due to dysfunction of granulocyte-macrophage colony-stimulating factor-dependent cholesterol clearance. Whole-lung lavage is the current standard of care for PAP, but it can lead to the exacerbation of hypoxia. A medication targeting cholesterol homeostasis is a promising therapy for refractory PAP. We present a case of autoimmune PAP with severe hypoxia that was successfully treated with segmental lung lavage (SLL). Following SLL for disease relapse, statin treatment for dyslipidemia was started. After initiating statin treatment, the patient did not require bronchoalveolar lavage for 10 months.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare diffuse lung disease characterized by the accumulation of surfactants in the alveoli [1,2]. PAP can lead to progressive hypoxia, secondary infections, and fibrosis. PAP can be classified as primary, secondary, or congenital. More than 90% of PAP cases are classified as primary PAP, and most primary PAP cases have autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) [3].

Homeostasis of alveolar surfactants is mainly regulated by secretion from type II alveolar epithelial cells and their removal by alveolar macrophages. Alveolar macrophages require constitutive GM-CSF stimulation to maintain their functions. In patients with autoimmune PAP, dysfunction of GM-CSF stimulation leads to cholesterol accumulation in macrophages and a secondary reduction in surfactant clearance from alveoli [2].

Whole-lung lavage (WLL) is currently the standard treatment for PAP. However, performing WLL exacerbates hypoxia and sometimes requires extracorporeal membrane oxygenation (ECMO) in cases of severe hypoxia [4,5]. Thus, its invasiveness is particularly important in patients with severe gas exchange impairments.

Although WLL results in significant clinical, radiological, and physiological improvement in no less than 80% of cases, it has been reported that more than 60% of PAP patients who had undergone WLL needed more than one additional lavage [6]. Non-invasive

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; GM-CSF, granulocyte-macrophage colony-stimulating factor; HOT, home oxygen therapy; PAP, pulmonary alveolar proteinosis; SLL, segmental lung lavage; WLL, whole-lung lavage.

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medications for refractory PAP have not been well established; however pharmacotherapy targeting pulmonary cholesterol homeostasis is a promising therapy. We present a case of severe hypoxia that was successfully treated with segmental lung lavage (SLL). Although the patient needed subsequent lavages for relapse, lavages were avoided after initiating statin treatment for dyslipidemia.

2. Case presentation

A previously healthy 50-year-old Japanese man (who smoked 1 pack per day for 35 years) was referred to our hospital for the examination of dyspnea and dry cough in December 2020. He was unemployed, although he had previously worked as a truck driver. He had never been exposed to occupational dust. On presentation, physical examination revealed an oxygen saturation of 78% on room air and a respiratory rate of 20/min. Laboratory tests showed elevated lactate dehydrogenase level of 427 IU/L, carcinoembryonic antigen level of 30 ng/ml, KL-6 level of 15,866 U/ml, surfactant protein D level of 454.8 ng/ml, and normal complete blood cell count and C-reactive protein levels.

Chest radiography revealed diffuse consolidation (Fig. 1A). Computed tomography revealed diffuse bilateral ground-glass opacities with a crazy-paving appearance (Fig. 2A). To establish a definite diagnosis, we performed bronchoalveolar lavage (BAL) under intubation because of severe hypoxia. The patient was diagnosed with PAP with milky-appearing BAL fluid (Fig. 3). Abnormal macrophages with PAS-positive intracellular inclusions were confirmed later by cytology. Judging from the oxygen saturation, the patient's disease severity score was 5. We performed successive SLL from right segments III, V, and VIII as a treatment for severe hypoxia just after confirmation of the gross finding of bronchoalveolar lavage fluid.

Next, we considered performing WLL, and given the severity of hypoxia, v-v ECMO was thought to be necessary for safe WLL. However, we could not find any nearby hospitals that could offer v-v ECMO during the COVID-19 pandemic. Therefore, we decided to perform SLL. We performed SLL in the right Segment VI, VIII, IX, and X on day 12, in left Segment VI, VIII, IX, and X on day 15, in the right Segment I, II, and III on day 19, and in the left Segment I+II, III, and V on day 22 of hospitalization under general anesthesia. After consecutive SLL, his oxygenation, radiological findings, and laboratory data had significantly improved (Figs. 1B and 2 B, Table 1), and he was discharged on day 39 with home oxygen therapy (HOT). He was diagnosed with autoimmune PAP with high anti-GM-CSF antibody (51.8 U/ml, normal <1.7 U/ml). We performed four consecutive SLLs for PAP recurrence in February and May 2021 (Fig. 1C and D). During the third administration in May 2021, he was able to stop HOT and started 2.5mg of rosuvastatin for dyslipidemia with a serum triglyceride level of 320 mg/ml and normal LDL-cholesterol level. One month after initiating treatment, his serum triglyceride level decreased to 112 mg/dl. After ten months, his symptoms and radiological findings were stable, and invasive treatment was not required (Fig. 1E and F).

3. Discussion

The standard therapy for patients with PAP with moderate-to-severe symptoms is WLL [7]. However, this procedure may lead to

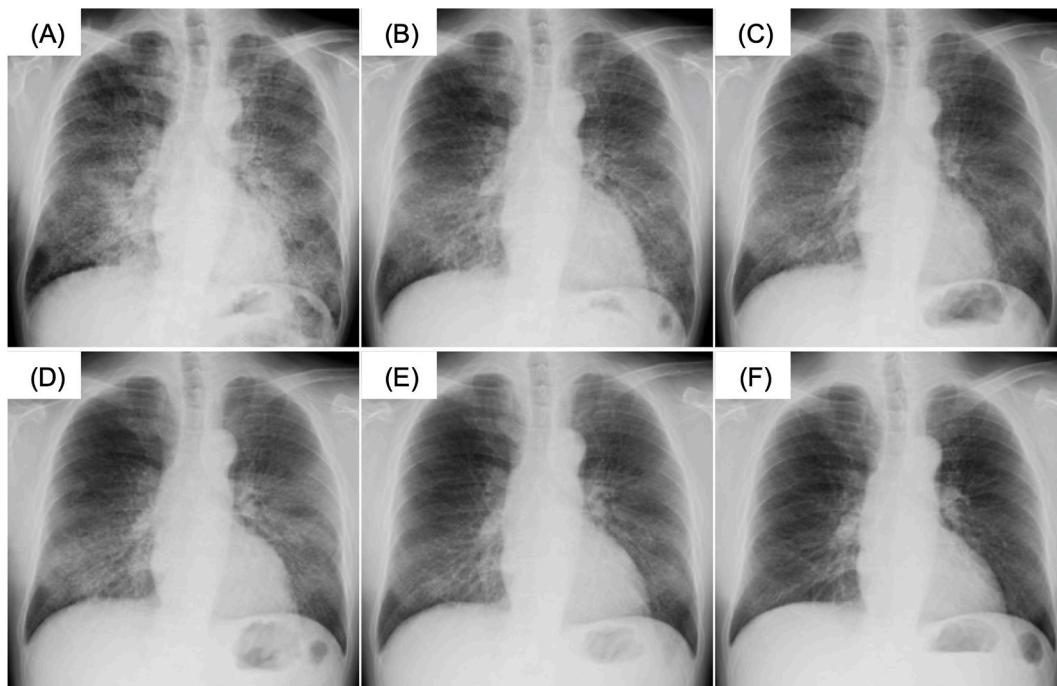


Fig. 1. Chest radiograph at first visit (A), first discharge (B), second administration (C), third administration (D), third discharge (E), and 10 months after statin initiation (F).

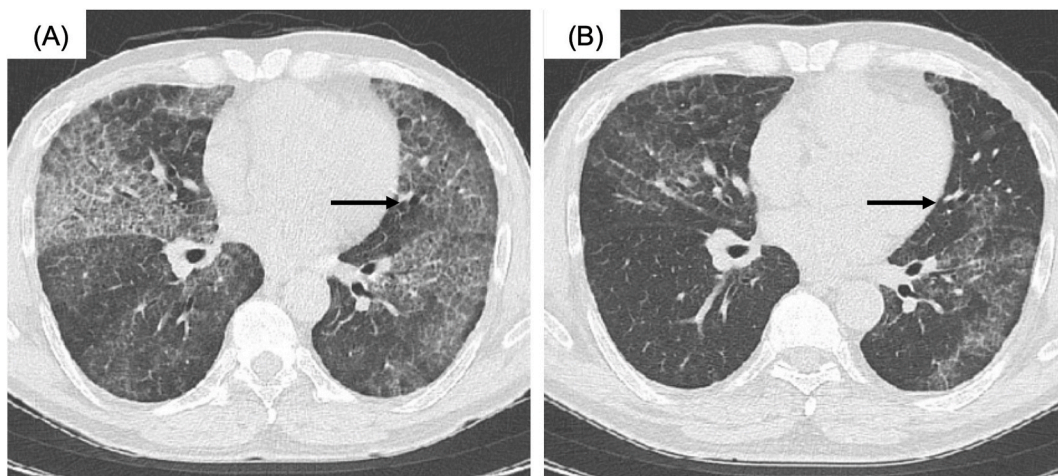


Fig. 2. High-resolution computed tomography at first visit (A) and at first discharge (B). Partial improvement was observed in both the lavaged and non-lavaged areas (left S4). Arrow shows left B4.

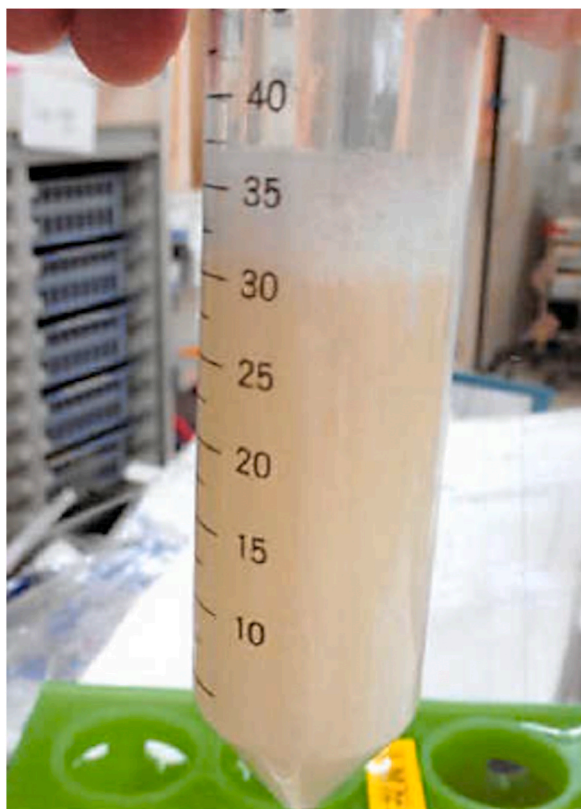


Fig. 3. Appearance of bronchoalveolar lavage fluid at the first bronchoalveolar lavage.

substantial worsening of hypoxia and sometimes requires ECMO support [4,5]. Thus, its invasiveness is particularly important in patients with severe gas exchange impairments. The effectiveness of SLL for PAP has not yet been established, but a considerable number of cases have been reported [8–17]. In the largest case series (74 patients), most of the cases were assumed to have mild symptoms, and SLL was performed [8]. In addition to this case series, most reported cases of SLL were mild. On the contrary, our literature search showed that only three cases with severe respiratory failure have been reported this far [15–17]. Compared with WLL, SLL is considered less effective because of the smaller amount of lavage, but it is safer in terms of procedure-induced exacerbation of hypoxia. Because we were unable to find a hospital that could offer ECMO during the COVID-19 pandemic, we performed consecutive

Table 1

Change in laboratory data from the administration to ten months after the initiation of statin treatment.

	November 2020	February 2021	May 2021	March 2022
LDH (U/L)	427	367	278	202
CEA (ng/mL)	30.4	17.6	NA	NA
KL-6 (U/mL)	15866	9402	NA	NA
SP-D (ng/mL)	454.8	394.7	NA	NA

CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; SP-D, surfactant protein D.

SLL safely with confirmed therapeutic benefit.

Interestingly, radiological findings of not only the lavaged area but also the non-lavaged area improved in this case (Fig. 2A and B). To the best of our knowledge, only three cases in which the non-lavaged area with SLL was confirmed to improve has been reported [9, 10,17]. Although the mechanism of improvement in non-lavaged areas and the reproducibility of this phenomenon are uncertain, this finding is beneficial for the choice of area to perform BAL.

More than 60% of patients who require WLL require repeat lavages [9]. Thus, long-term treatment, especially noninvasive treatment, for refractory patients needs to be established. Pathogenesis-based medications for refractory cases such as GM-CSF supplementation, rituximab, and plasmapheresis have been reported. In addition, medications targeting cholesterol homeostasis are prospective treatments.

GM-CSF stimulation induces cholesterol efflux in alveolar macrophages, mainly mediated by peroxisome proliferator-activated receptor- γ (PPAR γ) pathway. Absence of GM-CSF stimulation leads to cholesterol accumulation in alveolar macrophages and their consequent dysfunction. Statins treatment is thought to induce cholesterol efflux from alveolar macrophages, leading to improved function.

McCarthy et al. retrospectively reported that statin treatment ameliorated the clinical course of two patients with recurrent PAP [18]. They also reported that statin treatment reduced cholesterol accumulation in macrophages of patients with PAP ex vivo and ameliorated the symptoms in a mouse PAP model. In addition to statins, a phase I trial using PPAR γ agonists is currently in progress (NCT03231033). It has been reported that approximately 30% of PAP cases improved spontaneously [19]. Hence, although we cannot rule out the possibility of spontaneous remission of PAP, this case avoided BAL after the initiation of statin treatment. Our literature search revealed only three cases in which treatment with statins improved the clinical course [18,20]. Although the effectiveness of statins has only been reported in a few cases, it might be a promising treatment option for patients with recurrent PAP, considering its safety and low cost.

4. Conclusion

- For PAP patients with severe hypoxia, the standard treatment is WLL, which sometimes needs ECMO support to maintain oxygenation.
- SLL might be a treatment option to avoid the risk of further exacerbation of hypoxia and perform ECMO.
- Although further trials are needed, statins may be a treatment option for patients with recurrent PAP.

Declaration of competing interest

There are no conflicts of interest to declare.

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