Received: 27 March 2023 | Accepted: 29 April 2023

DOI: 10.1002/rcr2.1160

CASE REPORT

Respirology Case Reports OPEN ACCESS APSR WILEY

Pulmonary alveolar proteinosis after lung transplantation: Two case reports and literature review

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Funding information
Japan Society for the Promotion of Science KAKENHI, Grant/Award Number: jp21k08882

Associate Editor: Tracy Leong

Abstract

Pulmonary alveolar proteinosis (PAP) affecting transplanted lungs is not well recognized. Herein, we report two cases of PAP after lung transplantation (LTx). The first case was a 4-year-old boy with hereditary pulmonary fibrosis who underwent bilateral LTx and presented with respiratory distress on postoperative day (POD) 23. He was initially treated for acute rejection, died due to infection on POD 248, and was diagnosed with PAP at autopsy. The second case involved a 52-year-old man with idiopathic pulmonary fibrosis who underwent bilateral LTx. On POD 99, chest computed tomography revealed ground-glass opacities. Bronchoalveolar lavage and transbronchial biopsy led to a diagnosis of PAP. Follow-up with immunosuppression tapering resulted in clinical and radiological improvement. PAP after lung transplantation mimics common acute rejection; however, is potentially transient or resolved with tapering immunosuppression, as observed in the second case. Transplant physicians should be aware of this rare complication to avoid misconducting immunosuppressive management.

KEYWORDS
graft dysfunction, immunosuppression, lung transplantation, pulmonary alveolar proteinosis

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disease caused by abnormal accumulation of surfactant in the alveolar space. Secondary PAP is a minor subtype with a poorer prognosis than common autoimmune PAP.[1] It can reportedly complicate haematologic disorders, infections, and immunodeficiency. PAP after lung transplantation (LTx) is regarded as secondary PAP caused by alveolar macrophage dysfunction owing to immunosuppression and clinically and radiologically mimics acute rejection.[2] However, PAP is not well-recognized as a post-lung transplant complication. Herein, we report two cases of PAP after LTx.

CASE REPORT

Case 1

A 4-year-old boy with hereditary pulmonary fibrosis underwent bilateral LTx and subsequent immunosuppressive management with tacrolimus, prednisolone, and mycophenolate mofetil (MMF). The early post-transplant period was uncomplicated, with grade 1 primary graft dysfunction (PGD). On postoperative day (POD) 23, the patient complained of shortness of breath. Computed tomography (CT) revealed bilateral ground-glass opacities (GGO) and interstitial infiltrates (Figure 1A). The serum KL-6 level increased to 1629 U/mL, whereas C-Reactive Protein (CRP)

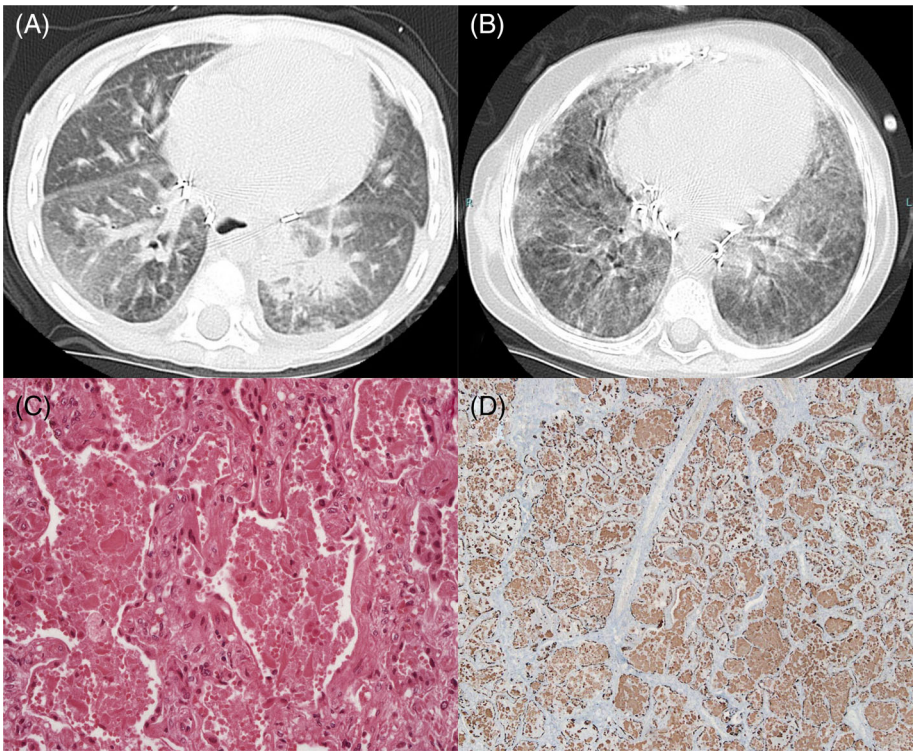

FIGURE 1 Computed tomography (CT) scan in case 1 displaying bilateral ground-glass opacities (GGO) and interstitial infiltrates (A: postoperative day [POD] 23) being exacerbated after increasing the dose of immunosuppression (B: POD 96). Histology of a lung specimen at autopsy showing diffuse intra-alveolar eosinophilic materials (C: haematoxylin-eosin stain; original magnification, ×200) stained by surfactant protein A (D; original magnification, ×40), indicating evidence of pulmonary alveolar proteinosis.

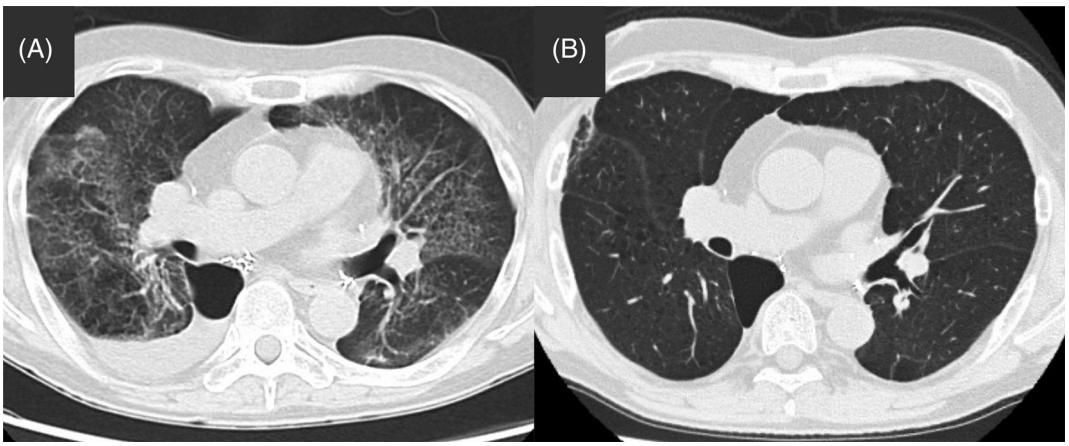

FIGURE 2 Computed tomography (CT) scan in case 2 displaying broadened bilateral centrilobular ground-glass opacities (GGO) (A: postoperative day [POD] 138) that disappeared after reduction of immunosuppressants (B).

levels were not elevated. Acute cellular rejection was clinically suspected because infection and heart failure were not evident. A high-dose bolus steroid was repeatedly administered without clinical response. Eventually, the patient underwent plasma exchange and thymoglobulin therapy for presumed antibody-mediated rejection caused by non-HLA antibodies. Despite these varied therapies, his respiratory condition progressively deteriorated without a definite diagnosis and response to treatment. Five months after transplantation, he required mechanical ventilation, which resulted in a recurrent pulmonary infection with *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (Figure 1B). The serum KL-6 (Krebs von den Lungen-6) level was over 5000 U/mL (normal range, 0–500 U/mL) at the time; however, CRP was not elevated. The patient ultimately died of sepsis associated with catheter-related bacterial infection and pneumonia on POD 248. Autopsy of the transplanted lungs led to the diagnosis

TABLE 1 Reported cases of PAP after LTx (patients' background, $n = 14$).

Age	57.5 (4–69)
Male/female	10 (72%)/4 (28%)
Primary disease	
IIPs/COPD/other	10 (72%)/2 (14%)/2 (14%)
PAP onset	99 days (23 days–5 years)
0–1 month	2 (14%)
1–6 month	7 (50%)
6–12 month	2 (14%)
>12 month	2 (14%)
Diagnosis	
Before initial treatment	3 (21%)
After initial treatment	6 (43%)
Post-mortem	3 (21%)
Immunosuppressive management	
Reduction	7 (50%)
Non-reduction	5 (38%)
NA	2 (12%)

Abbreviations: COPD, chronic obstructive pulmonary disease; IIPs, idiopathic interstitial pneumonias; LTx, lung transplantation; Not available, NA; PAP, pulmonary alveolar proteinosis.

of PAP, which was histologically characterized by intra-alveolar accumulation of surfactant phospholipids and apoproteins (Figure 1C, D).

Case 2

A 52-year-old man with interstitial lung disease (ILD) underwent bilateral LTx and a standard immunosuppressive regimen of tacrolimus, prednisolone, and MMF. Although PGD was determined to be grade 3, the subsequent early post-transplant period was uneventful. On POD 99, a routine chest CT scan showed slight bilateral centrilobular GGO without clinical symptoms or an inflammatory response. The diagnostic trial for steroid increase was ineffective. On POD 105, he complained of exertional dyspnoea and hypoxia with a broadened GGO on follow-up chest CT (Figure 2A). The serum KL-6 levels were elevated, whereas the inflammatory response was not. Bronchoalveolar lavage fluid (BALF) analysis and transbronchial biopsy revealed intra-alveolar eosinophilic materials stained with periodic acid-Schiff (PAS). He was diagnosed with PAP and followed up by tapering immunosuppression in a standard manner. Thirty-two months after the onset of PAP, the lung opacities completely disappeared, and the patient was doing well without any respiratory discomfort (Figure 2B).

DISCUSSION

The aetiology of PAP is currently divided into three categories: autoimmune (90%), secondary (7%–10%), and congenital

TABLE 2 Reported cases of PAP after LTx (outcomes, $n = 12$).

	Immunosuppressive management		
	Non-reduction $n = 5$	Reduction $n = 7$	*p*-Value
Prognosis			0.081
Improved	0 (0%)	4 (57%)	
Persisted or worsened	5 (100%)	3 (43%)	
Survival			0.576
Alive	1 (20%)	3 (43%)	
Dead	4 (80%)	4 (57%)	
Follow-up period	3 months (1–33)	13 months (2–44)	0.255

(<2%). In autoimmune PAP, neutralizing autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) are central to pathogenesis.[1] Secondary PAP is caused by dysfunction or a reduced number of alveolar macrophages. The pathology is related to diverse background complications, including haematological disorders, immunodeficiency disorders, infections, and toxic inhalation. Although LTx can cause secondary PAP, it is not well-recognized. However, the incidence of PAP after LTx remains unknown. In our institution, we have performed 215 LTx procedures since 1998, two of which (1%) developed PAP. However, this incidence might have been underestimated because we did not routinely perform BALF analysis and PAS staining for post-LTx surveillance.

To date, 14 cases of PAP after LTx, including the present two cases have been reported (Table 1).[2–8] The median age was 57.5 years (range, 4–69), and 71% were men. The patients received a single LTx (36%), bilateral LTx (57%), or heart-lung transplantation (7%) for interstitial pneumonia (IP) (71%), chronic obstructive pulmonary disease (14%), or others (14%). The median time from LTx to the onset of PAP was 99 days (range, 23 days to 5 years), while 64% of patients developed PAP within 6 months. Regarding the timing of diagnosis, nine (64%) cases were not diagnosed before the initial intervention, and three (21%) of them were diagnosed at autopsy. After the diagnosis of PAP, immunosuppression was adjusted in seven (50%) cases, GM-CSF was used in three (21%), and alveolar lavage was performed in two (14%) cases. Regarding clinical outcomes, three (21%) patients recovered, one (7%) suffered persistent PAP, and eight (57%) died at a median time of 7 months (range, 1–33 months) from PAP onset, mostly from infectious complications, accounting for seven (88%) of the total fatalities.

The onset mechanisms of PAP after LTx have been proposed to be alveolar macrophage (AM) dysfunction due to immunosuppressive therapy.[2] ILD was significantly more common (72%) as a primary disease for LTx. Some studies have suggested an association between immune cell dysfunction, including AMs, and pulmonary fibrosis.[9] Thus, recipients who undergo LTx for IP may be more susceptible to alveolar AM dysfunction. Immunosuppression after LTx may exacerbate the dysfunction of recipient-derived AM and lead to the development of PAP. The turnover rate of

AMs from donor to recipient is reported to be 40–90% per year, which is affected by lung damage.[10] This implies that PAP may occur when graft-resident AMs are replaced by recipient-derived AMs. Among the five patients who developed PAP after a single LTx in the retrieved literature, the majority (60%) exhibited unilaterally predominant development in the transplanted lung.[2,3,6,7] This suggests that some triggers derived from the transplanted lung, such as allorejection or impaired lymphatic drainage, may coexist with AM dysfunction as a cause of PAP.

The common clinical features of PAP are exertional dyspnoea and cough with patchy GGO and interlobular septal thickening known as the "crazy paving" pattern on a chest CT scan. These clinical findings can also commonly appear as signs of AR in post-LTx settings. Once PAP develops in LTx recipients, it is difficult to distinguish it from other causes of graft dysfunction, especially AR. Only three cases had been diagnosed with PAP before the initial intervention in previous reports. A delay in reaching an accurate diagnosis and intensifying immunosuppression with misdiagnosis of AR may lead to a worse prognosis. Among the 14 cases in the retrieved literature, 12 with a description of prognoses were subjected to subgroup analysis to compare outcomes with or without immunosuppressive reduction (Table 2). While no patient in the non-reduction group did not demonstrate any improvement, 57% of patients in the reduction group showed improvement of PAP ($p = 0.08$). A similar trend was observed in survival. The poor prognosis of the non-reduction group might have been caused by an exacerbation of macrophage dysfunction due to intensified immunosuppression, which not only exacerbated PAP itself but also increased vulnerability to infection. This could explain the high percentage of infectious complications as the cause of death. We would note that this case literature review of small-sized sample provides only a suggestion, and further research into future cases is necessary.

PAP after LTx can be potentially transient or slowly progressive, as observed in the second case; therefore, we should correctly distinguish PAP from AR, and may be better off tapering but not intensifying immunosuppression. Arai et al. reported that serum KL-6 was useful for the diagnosis of autoimmune PAP. The cut-off value of 2050 U/mL serum KL-6 levels was able to differentiate autoimmune PAP from other interstitial lung disease with a sensitivity of 75% and a specificity of 78%.[11] Lung opacity without an inflammatory response and markedly elevated KL-6 levels are potential signs of PAP. Once PAP is suspected, PAS staining of BALF should be considered to distinguish this rare pathology after LTx from common rejection and infection.

In conclusion, we have reported two cases of secondary PAP in LTx recipients, with successful and unsuccessful management. Transplant physicians should be aware of this rare but manageable complication of LTx.

AUTHOR CONTRIBUTIONS

Conceptualization: Kentaroh Miyoshi; formal analysis: Shinichi Kawana, Kentaroh Miyoshi. *Investigation*: Kentaroh Miyoshi, Shin Tanaka, Seiichiro Sugimoto, Dai Shimizu, Mikio Okazaki, Noboru Hattori, Shinichi Toyooka. *Writing-original draft*: Shinichi Kawana, Kentaroh Miyoshi, Shin Tanaka. All authors contributed to revisions of the manuscript, provided final approval for the final version to be published, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

This report was presented at the international Society for Heart and Lung Transplantation, the 42nd Annual Meeting and Scientific Sessions, Boston MA, USA.

FUNDING INFORMATION

This study was supported by JSPS KAKENHI [grant number jp21k08882] for data collection and publication.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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How to cite this article: Kawana S, Miyoshi K, Tanaka S, Sugimoto S, Shimizu D, Matsubara K, et al. Pulmonary alveolar proteinosis after lung transplantation: Two case reports and literature review. Respirology Case Reports. 2023;11:e01160. https://doi.org/10.1002/rcr2.1160