

# Bilateral Whole Lung Lavage in Hereditary Pulmonary Alveolar Proteinosis in a 4-year-old Child Using Extracorporeal Membrane Oxygenation

Prahlad Prabhudesai<sup>1</sup>, Indu Khosla<sup>2</sup>, Satish Kulkarni<sup>3</sup>, Manish Kumar Arya<sup>4</sup>, Abha Pandey<sup>5</sup>, Namrata Yadav<sup>6</sup>

## ABSTRACT

The hereditary form of pulmonary alveolar proteinosis (PAP) is an uncommon entity. We report a case of PAP due to colony-stimulating factor 2 receptor alpha (CSF2RA) gene mutation. The standard of care includes whole lung lavage (WLL). We faced two challenges: Firstly, a severely hypoxemic patient, and secondly, the nonavailability of appropriate size of double-lumen endotracheal tube for pediatric patients for a WLL while permitting single-lung ventilation. Hence, we performed WLL using venovenous extracorporeal membrane oxygenation (VV ECMO) with a successful outcome. The patient has been discharged and is off oxygen support since more than a year. There are only a few case reports of children having hereditary PAP treated with WLL using ECMO in Indian and Western literature.

**Keywords:** Extracorporeal membrane oxygenation, Pulmonary alveolar proteinosis, Whole lung lavage.

*Indian Journal of Critical Care Medicine* (2021): 10.5005/jp-journals-10071-23968

## INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a disorder of altered production or removal of surfactant from the lungs leading to its abnormal accumulation within the alveoli, which results in progressive hypoxemia and respiratory failure.<sup>1</sup> The estimated prevalence of PAP is 1 per million individuals.<sup>2</sup>

The most likely causes of PAP in infants and young children are either genetic errors of surfactant metabolism or immune deficiencies, whereas in adults, it is autoimmune or secondary in origin.

We report a pediatric case of hereditary PAP due to colony-stimulating factor 2 receptor alpha (CSF2RA) gene mutation with a favorable outcome to therapeutic whole lung lavage (WLL) using extracorporeal membrane oxygenation (ECMO).

## CASE DESCRIPTION

A 4-year 8-month-old girl born of third degree of consanguinity presented with cough and progressive breathlessness for 3 months. She was hypoxic for 2 weeks prior to presentation requiring oxygen support. She was admitted twice in the past 1 year for cough and breathlessness wherein a diagnosis of viral respiratory tract infection was made. Her birth, immunization, developmental, and family history were unremarkable. There was no significant family or personal history of asthma or allergy or any other respiratory illness.

Clinical examination on presentation to our hospital revealed the child with failure to thrive, with a weight of 12.1 kg (<first centile) and a height of 97 cm (<third centile). She was afebrile, had tachycardia (heart rate of 120/minute), and was tachypneic (respiratory rate of 46/minute). She had marked subcostal and intercostal retraction and a SpO<sub>2</sub> of 93% on 10 L/minute of oxygen by a non-rebreathing mask. On systemic examination, the child had pectus excavatum with bilateral coarse crackles on auscultation, with the rest of the examination being normal.

Basic hematological workup done during her previous admission was normal. Arterial blood gas (ABG) on O<sub>2</sub> of 10 L/minute

<sup>1,5,6</sup>Department of Chest Medicine, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

<sup>2</sup>Department of Pediatrics, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

<sup>3</sup>Department of Anaesthesiology, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

<sup>4</sup>Department of Pediatric Critical Care, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

**Corresponding Author:** Manish Kumar Arya, Department of Pediatric Critical Care, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India, Phone: +91 9867779565, e-mail: wildbluewind@gmail.com

**How to cite this article:** Prabhudesai P, Khosla I, Kulkarni S, Arya MK, Pandey A, Yadav N. Bilateral Whole Lung Lavage in Hereditary Pulmonary Alveolar Proteinosis in a 4-year-old Child Using Extracorporeal Membrane Oxygenation. *Indian J Crit Care Med* 2021;25(9): 1069–1072.

**Source of support:** Nil

**Conflict of interest:** None

showed PaO<sub>2</sub>—104 mm Hg, PaCO<sub>2</sub>—45.8 mm Hg, pH—7.31, and HCO<sub>3</sub>—22.4 mmol/L. Her thyroid function tests, electrocardiogram, and 2D echo were within normal limits. Human immunodeficiency virus was negative. Serum lactate dehydrogenase (LDH) was raised—694 U/L (140–280 U/L). X-ray of the chest showed bilateral reticular infiltrates, which showed a progressive worsening in serial X-rays (Fig. 1) over the past 1 year, and computed tomography (CT) of the chest showed diffuse intralobular and interstitial thickening with ground-glass opacities (crazy-paving pattern) suggesting interstitial lung disease (Figs 2A and 2B). Clinical and radiological features were suggestive of PAP, and further investigations were done to confirm the diagnosis.

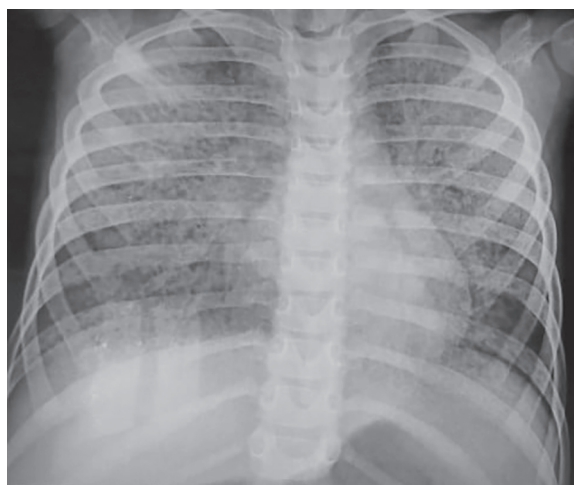
The bronchoscopy and bronchoalveolar lavage done in her previous hospital admission were inconclusive. It was negative

for acid-fast bacilli, *Pneumocystis carinii*, and aerobic cultures, and galactomannan test was also negative. An autoimmune etiology was ruled out as an antibody against granulocyte-macrophage colony-stimulating factor (GM-CSF) was negative, and serum GM-CSF concentration was raised. Next-generation sequencing showed contiguous homozygous deletion encompassing exonic regions 1 to 5 of *CSF2RA* gene, suggestive of pulmonary surfactant metabolism dysfunction 4, an X linked disorder confirming a diagnosis of PAP.

She was treated with steroids, antibiotics, and other supportive care. With a confirmed diagnosis of PAP due to *CSF2RA* gene mutation and the presence of severe respiratory insufficiency, a decision was made to perform a therapeutic WLL on ECMO.

## PROCEDURE

Getting an appropriate size of double-lumen endotracheal tube (the smallest size available is 28 Fr, which can be used for the patient weighing more than 30 kg) for our patient was a challenge. Furthermore, she was hypoxic with significant respiratory distress. Hence, we decided to do bilateral WLL in one session with ECMO to ensure the adequacy of oxygenation and better outcome.



**Fig.1:** Chest X-ray showed widespread bilateral reticular shadowing air space disease (Pre-procedure)

A dedicated team comprising pulmonologist, anesthesiologist, pediatric intensivist, perfusionist, ECMO specialist, and physiotherapists carried out the procedure.

Patient was intubated with a 3.5-mm uncuffed endotracheal (ET) tube and mechanically ventilated. The right internal jugular vein was cannulated with a 16-French Avalon Elite bicaval dual lumen ECMO cannula. Once the patient was stabilized on ECMO, lung lavage procedure was started through the uncuffed ET tube. Initially, aliquots of 50 to 70 mL of prewarmed (37°C) 0.9% saline was used. Post-instillation physiotherapy was given, and the fluid was gradually drained with gravity. As the child tolerated the procedure well, the aliquots were increased to 150 mL. Lavage was done in both supine and prone positions to ensure adequate clearance of the surfactant from the lungs. A total of 6000 mL of saline was instilled, and 6600 mL was drained out in the procedure that lasted for 6 hours (Fig. 3). A flexible fiberoptic bronchoscope (2.8 mm) was negotiated through the ET tube intermittently to check the position of the ET tube. Adequate suctioning was done with due precautions so as to avoid trauma to the airways.

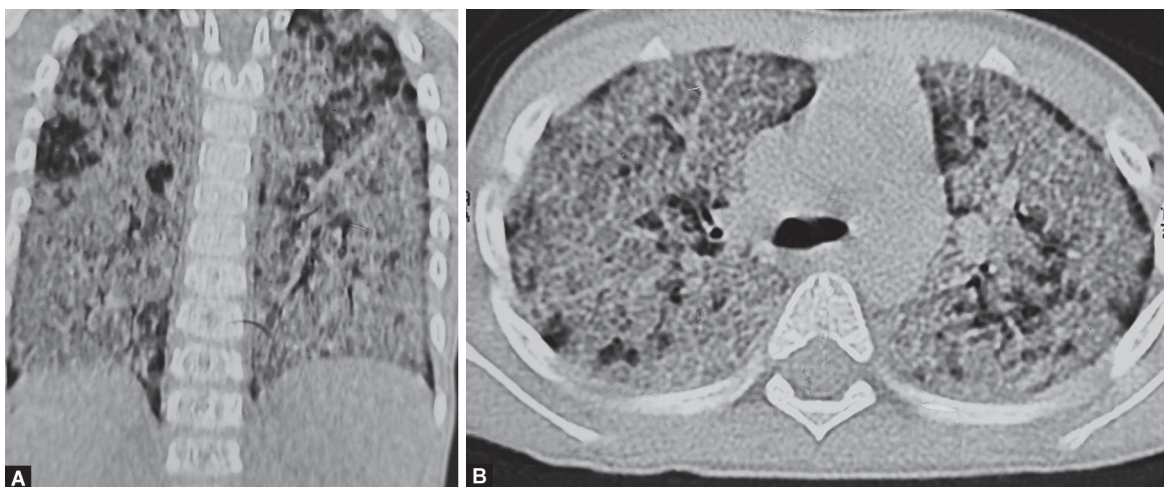
The child was hemodynamically stable and maintained saturation throughout the procedure. The patient was shifted to the pediatric intensive care unit on ECMO and mechanical ventilation. Post-procedure the patient was weaned off from ECMO and was extubated on the subsequent day.

Post-extubation, ABG on room air showed pH—7.41, PaCO<sub>2</sub>—40.9 mm Hg, PaO<sub>2</sub>—105 mm Hg, and HCO<sub>3</sub>—25.5 mmol/L. The child returned to normal physical activity with an excellent response both clinically and radiologically within 3 to 4 days of the procedure (Figs 4 and 5). The child is off oxygen for more than a year and is thriving well with a weight gain of 3 kg.

## DISCUSSION

PAP is due to abnormal collection of lipoproteinaceous insoluble amorphous substance (surfactant) within the alveoli, which impairs gas exchange and further results in progressive respiratory insufficiency. It is secreted by type 2 pneumocytes and is routinely cleared by alveolar macrophages.<sup>3</sup>

Four forms of PAP are recognized in children: Congenital, primary (encompassing autoimmune and hereditary PAP), secondary, and idiopathic. The congenital forms of PAP are due to



**Figs 2A and B:** (A) CT scan of the chest showing ground-glass opacification and interlobular septal thickening (crazy-paving pattern) (A) upper lobe; (B) CT scan of the chest showing ground-glass opacification and interlobular septal thickening (crazy-paving pattern) (B) lower



Fig. 3: Gradual clearing of fluid from the proteinaceous material



Fig. 4: Chest X-ray after WLL with marked radiological improvement

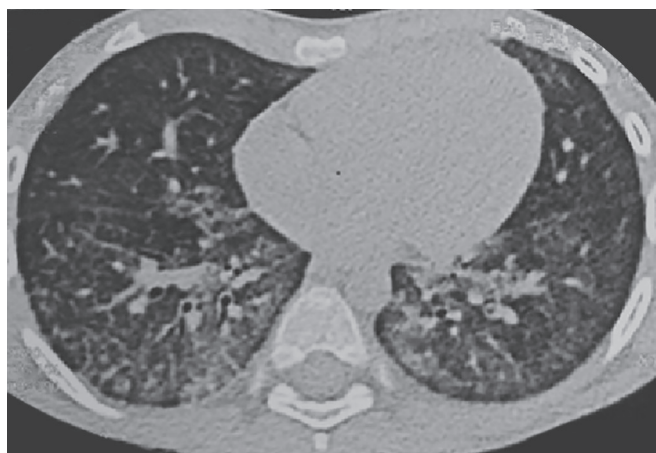


Fig. 5: CT scan of the chest after WLL with significant radiological improvement

the disorders of surfactant production or metabolism caused by a variety of genetic defects, including deficiencies in surfactant proteins B and C (SP-B and SP-C, which are encoded by the *SFTPB* and *SFTPC* genes, respectively), and variants of ATP-binding

cassette, subfamily A (*ABCA3*).<sup>2,3</sup> The majority of cases of hereditary PAP are due to the disruption of GM-CSF signaling. Two recessive variants of the genes for GM-CSF receptor, alpha and beta subunits (*CSF2RA* and *CSF2RB*), have been described.<sup>4,5</sup> Our patient had the *CSF2RA* defect, and these children develop progressive dyspnea, effort intolerance, and hypoxia at a median age of 3.5 years. Fifty-five percent of these children have growth failure.<sup>5</sup> Two case reports due to *CSF2RB* mutations<sup>6,7</sup> and a case series of 13 cases caused by *CSF2RA* gene defects have been published recently.<sup>6</sup> The GM-CSF level is elevated in cases with hereditary PAP due to functional defects of its receptor, while in patients with autoimmune PAP, the level of GM-CSF is typically low.<sup>8,9</sup> WLL is a standard of care for the treatment of hereditary PAP due to *CSF2RA* gene mutation.<sup>5</sup>

In children less than 8 years of age in whom a double-lumen endotracheal tube cannot be passed, maintaining oxygenation and ventilation becomes a challenge while doing WLL. The advantage of ECMO is being able to maintain adequate oxygenation during the entire procedure.<sup>10,11</sup> Hiratzka et al. in 1983 performed bilateral simultaneous lung lavage utilizing membrane oxygenator for PAP in an 8-month-old infant.<sup>12</sup>

Hence, we opted to put our patient on venovenous ECMO (VV ECMO) for the procedure and could carry out a successful WLL.

## CONCLUSION

WLL with ECMO is better tolerated especially in patients who are unable to tolerate single-lung ventilation. ECMO also has an advantage compared to the conventional double-lumen tube, lavaging both lungs simultaneously in a single session.

## ACKNOWLEDGMENTS

We are thankful to Cincinnati Children's Hospital Research Foundation and University of Cincinnati College of Medicine, United States, for providing us a platform for GM-CSF analysis.

## ORCID

Prahlad Prabhudesai  <https://orcid.org/0000-0003-4070-8639>

Indu Khosla  <https://orcid.org/0000-0002-4929-8835>

Satish Kulkarni  <https://orcid.org/0000-0002-3454-1003>

Manish Kumar Arya  <https://orcid.org/0000-0002-8098-5254>

Abha Pandey  <https://orcid.org/0000-0002-6833-7537>

Namrata Yadav  <https://orcid.org/0000-0002-8635-3282>



## REFERENCES

1. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *New Engl J Med* 2003;349(26):2527–2539. DOI: 10.1056/NEJMra023226.
2. Bush A, Pabary R. Pulmonary alveolar proteinosis in children. *Breathe* 2020;16(2). DOI: 10.1183/20734735.0001-2020.
3. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, et al. Pulmonary alveolar proteinosis. *Eur Respir Rev* 2011;20(120):98–107. DOI: 10.1183/09059180.00001311.
4. Martinez-Moczygemba M, Doan ML, Elidemir O, Fan LL, Cheung SW, Lei JT, et al. Pulmonary alveolar proteinosis caused by deletion of the GM-CSFR $\alpha$  gene in the X chromosome pseudoautosomal region 1. *J Exp Med* 2008;205(12):2711–2716. DOI: 10.1084/jem.20080759.
5. Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, et al. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. *J Exp Med* 2008;205(12):2703–2710. DOI: 10.1084/jem.20080990.
6. Hildebrandt J, Yalcin E, Bresser HG, Cinel G, Gappa M, Haghghi A, et al. Characterization of CSF2RA mutation related juvenile pulmonary alveolar proteinosis. *Orphanet J Rare Dis* 2014;9(1):171. DOI: 10.1186/s13023-014-0171-z.
7. Suzuki T, Maranda B, Sakagami T, Catellier P, Couture CY, Carey BC, et al. Hereditary pulmonary alveolar proteinosis caused by recessive CSF2RB mutations. *Eur Respir J* 2011;37(1):201–204. DOI: 10.1183/09031936.00090610.
8. Tanaka T, Motoi N, Tsuchihashi Y, Tazawa R, Kaneko C, Nei T, et al. Adult-onset hereditary pulmonary alveolar proteinosis caused by a single-base deletion in CSF2RB. *J Med Genet* 2011;48(3):205–209. DOI: 10.1136/jmg.2010.082586.
9. Hamvas A, Deterding RR, Wert SE, White FV, Dishop MK, Alfano DN, et al. Heterogeneous pulmonary phenotypes associated with mutations in the thyroid transcription factor gene NKX2-1. *Chest* 2013;144(3):794–804. DOI: 10.1378/chest.12-2502.
10. Ramirez JR. Bronchopulmonary lavage: new techniques and observations. *Dis Chest* 1966;50(6):581–588. DOI: 10.1378/chest.50.6.581.
11. Sihoe AD, Ng VM, Liu RW, Cheng LC. Pulmonary alveolar proteinosis in extremis: the case for aggressive whole lung lavage with extracorporeal membrane oxygenation support. *Heart Lung Circ* 2008;17(1):69–72. DOI: 10.1016/j.hlc.2006.11.007.
12. Hiratzka LF, Swan DM, Rose EF, Ahrens RC. Bilateral simultaneous lung lavage utilizing membrane oxygenator for pulmonary alveolar proteinosis in an 8-month-old infant. *Ann Thorac Surg* 1983;35(3):313–317. DOI: 10.1016/S0003-4975(10)61565-2.