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Pulmonary alveolar proteinosis due to heterozygous mutation in *OAS1*: Whole lung lavages for long-term bridging to hematopoietic stem cell transplantation

Elias Seidl[1] | Dirk Schramm[2] | Carola Schön[1] | Karl Reiter[1] | Ingo Pawlita[1] | Matthias Kappler[1] | Simone Reu-Hofer[3] | Fabian Hauck[1] | Michael Albert[1] | Matthias Griese[1,4]

[1]Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany

[2]Department of General Pediatrics, Neonatology and Pediatrics Cardiology, University Children's Hospital, Heinrich-Heine-University, Düsseldorf, Germany

[3]Department of Pathology, Würzburg University, Würzburg, Germany

[4]Comprehensive Pneumology Center-Munich (CPC-M), Member of the German Center for Lung Diseases DZL, Munich, Germany

Correspondence
Elias Seidl and Matthias Griese, Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-University Munich, Lindwurmstrasse 4, Munich 80337, Germany.
Emails: Elias.seidl@med.uni-menchen.de (E.S.)
Matthias.Griese@med.uni-menchen.de (M.G.)

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Abstract

Introduction: Pulmonary alveolar proteinosis (PAP) is defined by increased accumulation of surfactant in the alveolar space. PAP has been reported to be associated with a large number of clinical conditions and diseases. Whole lung lavages (WLLs) can be helpful to stabilize the clinical course of PAP until the underlying condition is identified, which may enable more specific treatment. Recently, heterozygous *OAS1* gain-of-function variants were described as cause in patients with infantile-onset PAP combined with hypogammaglobulinemia.

Case presentation: At age 4 months, a female infant born to term was diagnosed with hypogammaglobulinemia and treated with monthly immunoglobulin injections. At age 15 months, the girl needed supplemental oxygen at night, and at age 18 months, also during the day. At age 2 years, PAP of unknown etiology was diagnosed by computed tomography scan and open lung biopsy. Subsequently, monthly WLLs were started, which stabilized the clinical course for over 2 years until a disease-causing *OAS1* variant was diagnosed and the patient was successfully treated by hematopoietic stem cell transplantation (HSCT).

Conclusion: Here, we describe the successful management of a female patient with severe PAP caused by a heterozygous *OAS1* gain-of-function variant until a definitive diagnosis was made and cured by HSCT.

KEYWORDS
genetic defect, OAS1, pulmonary alveolar proteinosis, stem cell transplantation, therapeutic lung lavage, children's interstitial lung disease, chILD, chILD-EU, whole lung lavage

1 | INTRODUCTION

Pulmonary surfactant is a complex mixture of surfactant proteins and lipids that lowers surface tension and regulates innate immune functions.[1] Impaired removal of surfactant from the alveolar space[2] increases the surfactant pool size and impairs gas exchange,[3] causing pulmonary alveolar proteinosis (PAP).

PAP typically starts insidiously at various ages, ranging from infancy to adolescence. The primary presenting symptoms include respiratory failure, exercise-induced non-productive cough, exercise intolerance, weight loss, and failure to thrive.[4] PAP has been reported to be associated with a large number of clinical conditions and diseases. Several pediatric cases of PAP can be attributed to defects in a variety of genes involved in surfactant metabolism, others are due to impaired function or reduced numbers of alveolar macrophages.[4,5] In late adolescence and adulthood PAP is most commonly caused by autoantibodies that block GM-CSF signaling.[6]

Here, we describe the successful management of a female patient with severe PAP caused by a heterozygous *OAS1* gain-of-function variant.[7] The patient's clinical condition was stabilized for over 2 years until a diagnosis was made and the patient was successfully treated by hematopoietic stem cell transplantation (HSCT). The pathomechanism of *OAS1* gain-of-function variants was recently published; the child described here was part of that analysis (as "Patient 1"), but the publication did not provide details of the pulmonary disease course.[8]

TABLE 1 Relevant laboratory findings before hematopoietic stem cell transplantation

White blood cell count	
Absolute leucocyte count	Within reference range
Absolute lymphocyte count	Within reference range
Immunological tests	
IgG	Decreased
IgG1	Decreased
IgG2	Not detectable
IgG3	Decreased
IgG4	Decreased
Polio vaccination antibodies	Not detectable
Tetanus vaccination antibodies	Not detectable
Hemophilus influence type B vaccination antibodies	Not detectable
Diphtheria vaccination antibodies	Not detectable
CD4/CD8 ratio	Increased
Active T and B cells (absolute and relative)	Decreased
Natural killer cells	Within reference range
Switch memory cells	Decreased
CD40L expression and staining	Within reference range

2 | CASE PRESENTATION

The patient was the second of two living children delivered via repeat cesarean section. Except for bronchial asthma in the children's mother and lung emphysema in the maternal grandmother, the family history was unremarkable for pulmonary or other diseases. The parents are nonconsanguineous and are both of German descent. Apart from an episode of unexplained respiratory distress after birth that required high-flow ventilation (FiO_2 max 0.43; flow max, 6 L/min) for 2 days and supplemental oxygen for an additional 4 days, the neonatal period was unremarkable. Within the first 12 weeks of life, two hospital admissions were necessary for respiratory infections with fever and cough. During the first episode, no pathogens were identified, but during the second episode, pneumonia caused by *Pneumocystis jirovecii* was diagnosed and treated with cotrimoxazole followed by prophylactic treatment with cotrimoxazole. At age 3 months, hypogammaglobulinemia was noted (Table 1), and immunoglobulins were subsequently given by subcutaneous injection every 4 weeks.

From age 3 months to 2 years, the patient was hospitalized seven times for five respiratory infections (bocavirus was the cause of one infection and coronavirus of the another, but no pathogenic germ was detected in the remaining three infections) and two gastrointestinal tract infections (one each due to norovirus and *Clostridium difficile*). After the bocavirus infection, at age 15 months, supplemental oxygen was required at night, and at age 18 months, during the day (Figure 1). At age 2 years, PAP was diagnosed by computed tomography scan and open lung biopsy (Figure 2a–e). No underlying cause of the PAP was identified at that time.

After PAP was diagnosed and because oxygen demand was increasing, monthly therapeutic WLLs were started (see next section and Figure 2f). Over 2 years, 14 WLLs were performed. The need for supplemental oxygen decreased after all except one WLL. Because the underlying cause of PAP was unknown, empirical treatments were started. Colchicine, ambroxol hydrochloride, subcutaneous GM-CSF (sargramostim), and hydroxychloroquine (which was given when the child was participating in a clinical trial[9]) had no effect on the PAP. Because of a lack of cooperation due to the patient's young age, inhaled GM-CSF treatment could not be used.

At age 4 years, whole-exome sequencing identified a novel de novo heterozygous mutation in *OAS1* (p.Ala76Val). Consequently, allogeneic HSCT appeared to be a suitable treatment and was performed with a matched, unrelated donor after myeloablative treatment. In the first few days after HSCT, oxygen demand increased, making another WLL (day +10 after HSCT) and noninvasive ventilation necessary. Thereafter, the pulmonary clinical course improved rapidly every day until normal gas exchange was established on day 15 after HSCT. At the time of writing, 3 years after HSCT, the girl is 7 years old and has no respiratory conditions or severe pulmonary exacerbations.

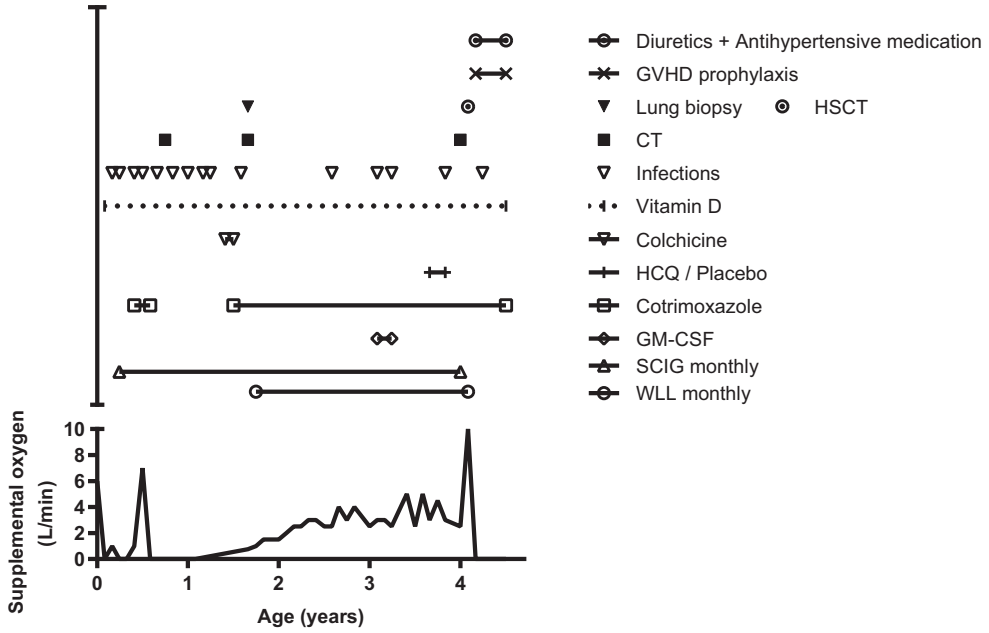

FIGURE 1 Long-term clinical course and treatments in a young girl with pulmonary alveolar proteinosis within the first year of life, supplemental oxygen was required for three respiratory infections. At age 12 months, the girl needed supplemental oxygen at night, and at age 18 months, also during the day. Within the first 2 years of life, a total of nine severe respiratory and gastrointestinal tract infections were diagnosed. After pulmonary alveolar proteinosis of unknown cause was diagnosed, monthly whole lung lavages (WLLs) were started at 2 years of age. When whole-exome sequencing revealed an *OAS1* variant, allogeneic hematopoietic stem cell transplantation (HSCT) was performed at the age of 4 years. One more WLL was necessary thereafter, and then the clinical course improved rapidly. CT, computed tomography; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-host disease; HCQ, hydroxychloroquine; SCIG, subcutaneous immunoglobulin

3 | WHOLE LUNG LAVAGE

WLL was performed under general anesthesia. We used a previously described technique[10,11] to isolate one lung by placing a balloon catheter (5–7 Fr, Arrow) in one of the main stem bronchi through a cuffed endotracheal tube (internal diameter, 4.0–5.0 mm). The correct position of the catheter was checked (Olympus Bronchoscope, BBFN20; outer diameter, 1.8 mm), and 0.9% NaCl warmed to body temperature was used as the lavage fluid and manually injected with a 50-ml syringe. The recovered lavage fluid was collected via a two-way stop cock into 2-L transparent bottles to evaluate turbidity. At start of the procedure, small lavage portions of 20 ml were injected, which were increased to 50 ml. Lavages were repeated until the recovered fluid changed from milky to transparent. The amount of fluid required to clear both lungs ranged from 3.3 to 6.7 L (median, 4.7 L). Over time, the recovered lavage fluid contained increasing amounts of protein (Figure S1). Both lungs were treated at each WLL, which took a total of 4–6 h.

4 | DISCUSSION

A recent report described a case of infantile-onset PAP, with the onset of respiratory symptoms within the first 6 months, combined with hypogammaglobinemia due to heterozygous *OAS1* gain-of-function variants.[7] Magg et al.[8] described four de novo heterozygous *OAS1* gain-of-function variants in six patients resulting in dysfunction and apoptosis of macrophages, most probably leading to PAP. The disorder, termed OAS1-associated polymorphic autoinflammatory immunodeficiency (OPAID), was cured by HSCT.[8] OPAID is part of a growing group of disorders of immune activation in which pulmonary symptoms and findings are prominent.

Here, we reported on one of the index cases, a patient with severe PAP and hypogammaglobulinemia in whom the underlying molecular cause was diagnosed during the course of illness, enabling successful treatment by HSCT. The patient was only able to survive the interim period because her severe clinical condition with chronic respiratory failure was stabilized by monthly WLLs for 2 years. A major strength of this case is that it demonstrated the feasibility of performing technically demanding, repetitive WLLs in a young child with PAP of unknown cause until the definite molecular diagnosis was established and HSCT was deemed feasible. In PAP, WLL is an important therapeutic option. Because WLL is a complicated and invasive treatment, it must be performed in specialized centers by a trained team of pneumologists, anesthesiologists, and intensive care physicians. Any less invasive alternative treatments should be utilized if availbale.

5 | CONCLUSION

We show that WLL is feasible for stabilizing the clinical condition of a patient with PAP, even in small children, until a definitive diagnosis is made. Interdisciplinary collaboration and dissemination of knowledge

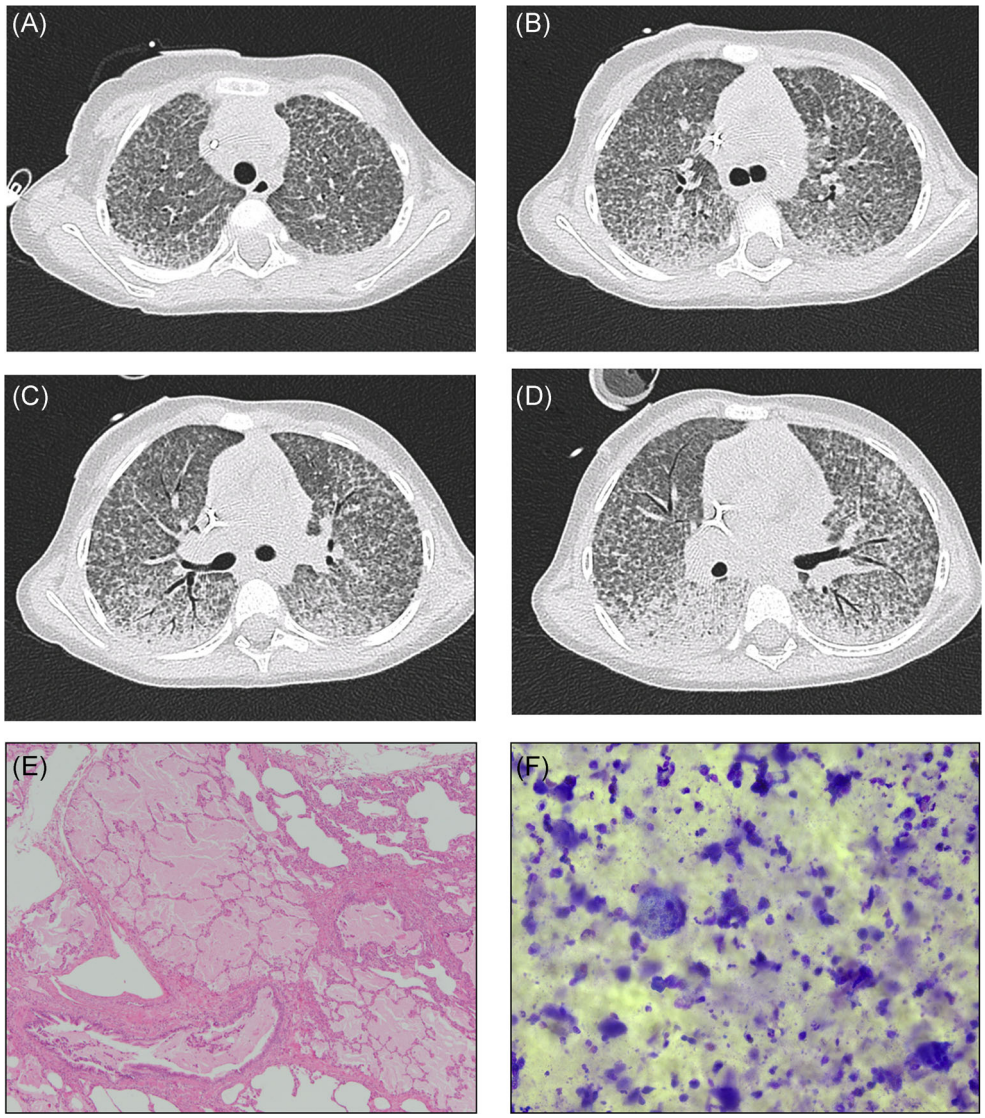

FIGURE 2 Computed tomography scan, lung biopsy, and recovered lavage fluid (pooled) in a young girl with pulmonary alveolar proteinosis. (A–D) High-resolution computed tomography scans at age 2 years showing crazy paving pattern (diffuse ground-glass opacification, inter- and intralobular thickening). (E) Histology of the lung biopsy showing accumulation of periodic acid-Schiff reaction-positive material in the alveolar space, indicating pulmonary alveolar proteinosis (hematoxylin and eosin staining 100×). (F) Pooled recovered lavage fluid from a whole lung lavage showing abundant proteinaceous material, a macrophage, and a few neutrophil granulocytes (May-Grünwald-Giemsa staining 20×) [Color figure can be viewed at wileyonlinelibrary.com]

are the keys to progress in the proper diagnosis and treatment of PAP and other rare diseases.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Elias Seidl: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review & editing (equal). **Dirk Schramm**: Investigation (equal); resources (equal); writing – review & editing (equal). **Karl Reiter**: Investigation (equal); writing – review & editing (equal). **Ingo Pawlita**: Investigation (equal); writing – review & editing (equal). **Matthias Kappler**: Investigation (equal); writing – review & editing (equal). **Simone Reu**: Investigation (equal); writing – review & editing (equal). **Fabian Hauck**: Investigation (equal); writing – review & editing (equal). **Michael Albert**: Investigation (equal); writing – review & editing (equal). **Matthias Griese**: Conceptualization (equal); data curation (equal); funding

acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); writing – review & editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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