Received: 11 December 2023 | Accepted: 19 February 2024

DOI: 10.1002/ppul.26946

CLINICAL CORRESPONDENCE

WILEY

Successful atorvastatin treatment of pulmonary alveolar proteinosis in a child with GM-CSF receptor deficiency

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KEYWORDS
child, interstitial lung disease, statin

Funding information
None

To the editor,

Pulmonary alveolar proteinosis (PAP) is characterized by the accumulation of surfactant within alveoli. Underlying aetiologies might be autoimmune, genetic (hereditary, secondary, and congenital), and secondary to other disorders.[1] There is no standard treatment, and there are no consensus recommendations on how to treat pediatric PAP. Among the available treatments, whole-lung lavages (WLL) are the cornerstone of treatment, and other treatment options, such as inhaled granulocyte–macrophage colony-stimulating factor (GM-CSF) and hematopoietic stem cell transplantation (HSCT), depending on the cause and severity.[2,3] Few cases using statins as a novel pharmacotherapy approach have been reported in adults, but not in children. Here, we present a school-age girl with a history of PAP due to a homozygous deletion in the CSF2RA gene and successful atorvastatin treatment during a follow-up period of almost 2 years.

1 | CASE REPORT

Seven years ago, she initially presented to another center with dyspnea and a dry cough. She was term-born with a nonremarkable pregnancy. There was parental first-degree consanguinity. There was no chronic lung disease in family history. Physical examination on admission showed a resting oxygen saturation of 85% in room air, tachypnoea, digital clubbing, and failure to thrive. Thoracic deformities were not observed. Her respiratory sounds were fine rales and wheezing in both lungs. Chest x-ray showed bilateral ground-glass opacities (Figure 1A). Bronchoalveolar lavage fluid was macroscopically milky, no bacterial growth was detected, and extracellular globular hyaline material was found homogeneously positive for periodic acid–Schiff staining (Figure 1B). Chest computed tomography showed a "crazy-paving" appearance (Figure 1C,D). With these examinations, the diagnosis of PAP was confirmed.

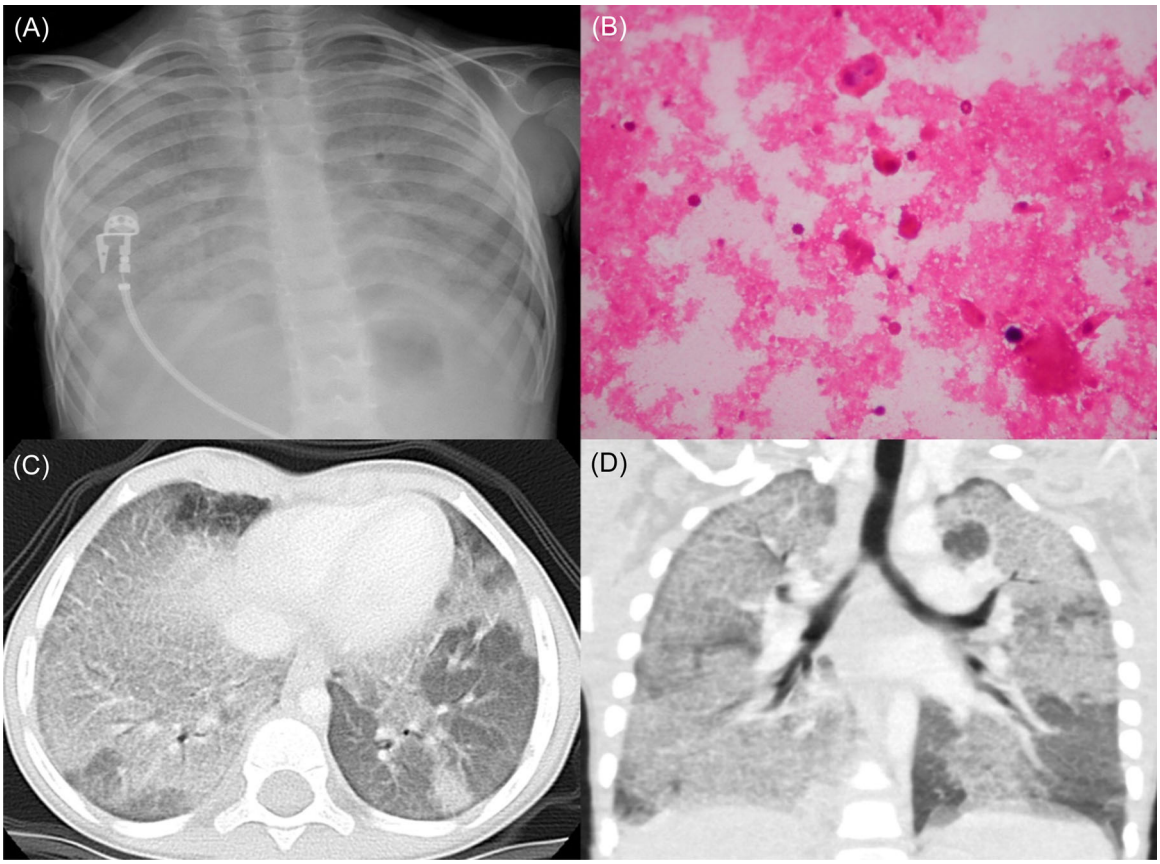


FIGURE 1 (A) PA chest X-ray demonstrates bilateral diffuse ground-glass opacities. (B) Amorphous eosinophilic hyaline material with macrophages in bronchoalveolar lavage fluid. (C) CT at the level of the lower lobes shows crazy-paving pattern, combining smooth interlobular septal thickening and ground-glass opacities. (D) Coronal reformatted CT image shows that the right lung has diffuse pattern of disease, whereas the left lung has somewhat geographic pattern with spared areas of upper and lower lobes. CT, computed tomography; PA, posterior anterior.

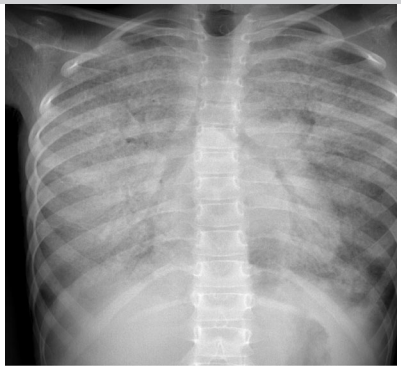
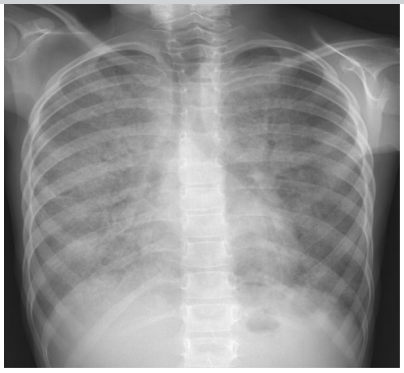
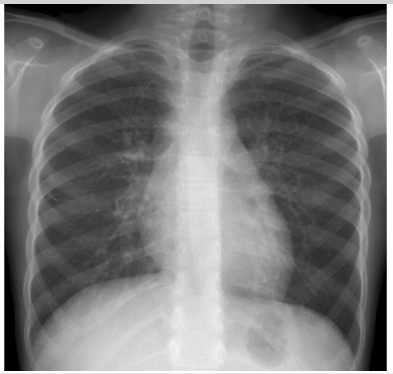
Serum anti-GM-CSF antibodies were negative. No infectious cause and no inhalation exposure could be identified. Whole exome analysis did not reveal any single nucleotide variants in known PAP-causing genes (*SFTPB*, *STFPC*, *ABCA3*, NKX2.1, *CSF2RA*, *CSF2RB*, *GATA2*, *OAS1*, *IRF8*, *SLC7A7*, *ADA*, *MARS*, *NPC2*). However, copy number variant analysis indicated a homozygote multiexon deletion within *CSF2RA*: chrX:1419223-1428583, affecting Exon 10–13 in the canonical transcript (NM_172245.4: ΔEx10-13) in the patient. The deletion was found in heterozygous fashion in both parents. Since the CSF2RA locus is part of the pseudoautosomal region 1 present on both sex chromosomes, the father has an unmutated CSF2RA copy on his Y-chromosome explaining his status as an unaffected mutation carrier.

During the 5-year follow-up period, WLL, which is an invasive procedure and requires general anesthesia, was performed 19 times. In the last 2 years, she was hospitalized four times for respiratory distress and required respiratory support. Noninvasive ventilation support was started 2 years ago. Meanwhile, since we did not yet know the etiology, we could not plan a treatment method such as HSCT. However, due to deterioration of the clinical status and unresponsiveness to WLL, atorvastatin, which has a safe and effective record for patients with unclassified PAP in the literature, was started at 5 mg/day after the parents provided written informed consent. Cholesterol levels were checked before starting the medication, and they were found within normal range. During the first 8 months of treatment, she had no respiratory symptoms, no need for supplemental oxygen, gained 6 kg of weight, had a normal physical examination, and was without any adverse drug reactions. Exceptional improvement of chest x-rays and clinical condition are shown in Table 1. She is now in the 20th month of statin treatment. She is followed up in a local hospital. Currently, she has no symptoms, complaints, or hospitalization history.

2 | DISCUSSION

Statins have been suggested as a potential treatment option for PAP in adults. Statins are thought to increase cholesterol excretion from alveolar macrophages and decrease alveolar cholesterol levels. The first patient with PAP and treated with statins was a 58-year-old woman with autoimmune PAP.[4] Her symptoms were refractory to treatment with nebulized GM-CSF and multiple WLL. However, her symptoms improved after treatment for coincident

TABLE 1 Radiological and clinical outcomes during first 8 months follow-up of after statin treatment.

Time of statin treatment	Just before starting statin	40th day	8th month
Chest x-ray			
Comments on chest x-ray	Bilateral diffuse ground-glass opacities	Somewhat improvement of the left lung	Lungs are almost clear with peribronchovascular thickening
Symptoms	Dyspnea Dry cough	No cough Decreased dyspnea	No symptoms
Physical examination	Bilateral fine rales	Bilateral fine rales	Breath sounds are normal
Respiratory support	On noninvasive ventilation	Oxygen requirement 5 L/min	No need for oxygen for the past 2 months, Spo2%98
Others	Hypercapnia in venous blood gas	Impairment hypercapnia No adverse reaction	Gained 6 kg No adverse reaction

hypercholesterolemia over a 42-month period. The same report also reported that statins reduced both bronchoalveolar lavage turbidity and cholesterol in alveolar macrophages from CSF2RB−/− mice with a resultant improvement in symptoms. Bush et al.[2] suggested that when combining these findings, drugs targeting cholesterol homeostasis may be beneficial for all types of PAP.

In another uncontrolled study, the same group evaluated prospectively the safety and efficacy of oral statin therapy for PAP without hypercholesterolemia.[5] They included 47 patients older than 18 years old who were nonresponsive to WLL or GM-CSF treatment. Forty patients completed the study, and 26 had improvements in arterial blood gas measurement, pulmonary function, and radiographic assessment with no severe side effects. The authors conclude that oral statin therapy is a promising therapeutic option for PAP.

In the present case, the significant improvement in the clinical status suggests that statins may be a promising therapeutic option in children with PAP, but controlled studies are needed to provide solid evidence.

AUTHOR CONTRIBUTIONS

Manuscript written by Halime Nayır Büyükşahin and Ebru Yalçın. All images reported by Mithat Haliloglu and Diclehan Orhan. Genetic analyses done in Germany by Matthias Griese, Florian Gothe, Sandra Gräfin v. Hardenberg, and Christina Rapp. Additionally, Ali Özdemir, İsmail Güzelkaş, Nagehan Emiralioğlu, Sehend Debbağ, Deniz Doğru, Uğur Özçelik, and Nural Kiper authors have made significant contributions to the editing of this manuscript and each has approved this final version.

ACKNOWLEDGMENTS

The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Griese M. Pulmonary alveolar proteinosis: a comprehensive clinical perspective. *Pediatrics*. 2017;140(2):e20170610.
2. Bush A, Pabary R. Pulmonary alveolarproteinosis in children. *Breathe*. 2020;16(2):200001.
3. Nayir Buyuksahin H, Kiper N. Childhood interstitial lung disease. *Pediatr Allergy Immunol Pulmonol*. 2023;36(1):5-15.
4. McCarthy C, Lee E, Bridges JP, et al. Statin as a novel pharmacotherapy of pulmonary alveolar proteinosis. *Nat Commun*. 2018;9(1):3127.
5. Shi S, Gui X, Ding J, et al. Assessment of statin treatment for pulmonary alveolar proteinosis without hypercholesterolemia: a 12-month prospective, longitudinal, and observational study. *BioMed Res Int* 2022;2022:1-9.

How to cite this article: Nayır Büyükşahin H, Yalçın E, Özdemir A, et al. Successful atorvastatin treatment of pulmonary alveolar proteinosis in a child with GM-CSF receptor deficiency. *Pediatr Pulmonol*. 2024;59:1777-1780. doi:10.1002/ppul.26946