

Pulmonary alveolar proteinosis induced by X-linked agammaglobulinemia: A case report

Ting Zhang, Ming Li, Li Tan, Xin Li

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Polat SE, Turkey

Received: October 20, 2023

Peer-review started: October 20, 2023

First decision: January 5, 2024

Revised: January 20, 2024

Accepted: March 1, 2024

Article in press: March 1, 2024

Published online: March 26, 2024



Ting Zhang, Ming Li, Li Tan, Department of Respiratory Medicine, Kunming Children's Hospital, Kunming 650228, Yunnan Province, China

Xin Li, Department of Emergency, Kunming Children's Hospital, Kunming 650228, Yunnan Province, China

Corresponding author: Xin Li, MM, Doctor, Kunming Children's Hospital, No. 288 Qianxing Road, Kunming 650228, Yunnan Province, China. 546918754@qq.com

Abstract

BACKGROUND

Pulmonary alveolar proteinosis (PAP) and X-linked agammaglobulinemia (XLA) are rare diseases in children. Many theories infer that immunodeficiency can induce PAP, but these reports are almost all review articles, and there is little clinical evidence. We report the case of a child with both PAP and XLA.

CASE SUMMARY

A 4-month-old boy sought medical treatment due to coughing and difficulty in breathing for > 2 wk. He had been hospitalized multiple times due to respiratory infections and diarrhea. Chest computed tomography and alveolar lavage fluid showed typical PAP-related manifestations. Genetic testing confirmed that the boy also had XLA. Following total lung alveolar lavage and intravenous immunoglobulin replacement therapy, the boy recovered and was discharged. During the follow-up period, the number of respiratory infections was significantly reduced, and PAP did not recur.

CONCLUSION

XLA can induce PAP and improving immune function contributes to the prognosis of children with this type of PAP.

Key Words: Pulmonary alveolar proteinosis; X-linked agammaglobulinemia; Children; Immunodeficiency; Alveolar lavage; Case report

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Pulmonary alveolar proteinosis (PAP) and X-linked agammaglobulinemia (XLA) are both rare diseases in children. This article shares the diagnosis and treatment process of a special case to confirm that XLA was a secondary cause of PAP which improved with intravenous immunoglobulin treatment.

Citation: Zhang T, Li M, Tan L, Li X. Pulmonary alveolar proteinosis induced by X-linked agammaglobulinemia: A case report. *World J Clin Cases* 2024; 12(9): 1644-1648

URL: <https://www.wjgnet.com/2307-8960/full/v12/i9/1644.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v12.i9.1644>

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) and X-linked agammaglobulinemia (XLA) are rare diseases in children. Many studies have suggested that immunodeficiency can induce PAP. However, only two cases of PAP induced by immune deficiency have been reported[1-3], and the remaining studies are almost all review articles. Therefore, more clinical data are needed to prove the correlation between PAP and immunodeficiency.

XLA is an X-linked recessive genetic disease. This is due to a defect in Bruton's tyrosine kinase (BTK). The differentiation of primitive B lymphocytes to mature B lymphocytes is impaired. There is a lack of B lymphocytes and plasma cells in the peripheral blood, and this leads to insufficient immunoglobulin synthesis. Therefore, children with XLA are prone to repeated bacterial infections and autoimmune diseases[4,5].

According to the etiology, PAP can be divided into congenital, acquired and idiopathic PAP[6]. Congenital PAP is an autosomal recessive disorder. It is caused by a defect in the surface-active substance protein or the gene encoding granulocyte-macrophage colony-stimulating factor (GM-CSF)[7,8]. Idiopathic PAP is caused by a large amount of GM-CSF self-neutralizing antibodies in the body, which block the function of GM-CSF. Therefore, the function of alveolar macrophages is severely affected, resulting in decreased alveolar surfactant clearance[9]. The pathogenesis of acquired PAP is unclear. It is currently believed to be related to various autoimmune, infectious, malignant and environmental etiologies[10].

CASE PRESENTATION

Chief complaints

The 4-month-old male patient had an acute cough, expectoration and difficulty breathing for > 10 d.

History of present illness

The child developed paroxysmal cough and phlegm 2 wk previously, along with difficulty breathing, runny nose, diarrhea, and cyanosis around the mouth. The symptoms did not improve after receiving penicillin infusion at the local hospital.

History of past illness

The child is gravida 2 para 2 and was a full-term birth. The birth process was smooth, with no asphyxia or respiratory distress. His birth weight was ~3 kg. He has suffered pneumonia and diarrhea many times since birth. However, no abnormalities were found on chest imaging except for pulmonary infection.

Personal and family history

There was no other relevant personal or family history.

Physical examination

The patient's body temperature was 36.5°C, heart rate 136 bpm, respiratory rate 62 breaths/min, fingertip oxygen saturation (SpO₂) 86%, and body weight 7.2 kg. Upon examination, his lips were cyanotic, no swollen superficial lymph nodes were noted throughout the body, respiratory sounds in both lungs were rough, and fine moist rales were heard in both lungs. Physical examination of the heart, abdomen and nervous system did not reveal any abnormalities.

Laboratory examinations

Blood tests revealed that his erythrocyte sedimentation rate, liver and kidney function, and C-reactive protein level were normal. The myocardial enzyme spectrum was normal except for lactate dehydrogenase (704 U/L). Humoral immunity showed the following: Ig 14.0 g/L, IgG 0.93 g/L, IgM 0.29 g/L, IgA 0.0 g/L, complement C3 0.40 g/L, complement C4 0.11 g/L, and total IgE 1 U/mL. Lymphocyte subpopulation determination was as follows: CD3⁺ 95.49%, CD3⁺CD4⁺ 65.58%, CD16⁺CD56⁺ 3.58% and CD19⁺ 0.03%. No pathogens were found in blood and sputum tests.

His bronchoalveolar lavage fluid was milky white and Periodic acid-Schiff staining was positive (Figure 1). Genetic testing [whole exome sequencing revealed that the BTK gene (located at chrX:100608340) had a hemizygous mutation (c.1751-1g>A)]. Thus, he was diagnosed with PAP and XLA. Genetic testing did not find gene mutations related to PAP [2] [such as surfactant protein B, surfactant protein C, ATP-binding cassette subfamily A member 3 (ABCA3), Nkx homeobox-1 gene (NKX2-1), and granulocyte-monocyte colony stimulating factor receptor genes]. No respiratory pathogens were detected in blood, sputum and alveolar lavage fluid.

Imaging examinations

Chest spiral computed tomography plain scan showed a significant decrease in the transparency of both lungs, with ground glass or butterfly-shaped changes in both lungs, and a large bubble in the upper lobe of the right lung (Figure 1). Tracheoscopy revealed that his alveolar lavage fluid was pale milky white.

FINAL DIAGNOSIS

PAP and XLA.

TREATMENT

The patient received ceftriaxone, total lung lavage, and infusion of intravenous immunoglobulin (IVIG).

OUTCOME AND FOLLOW-UP

After discharge, the patient received regular IVIG replacement therapy. During 1 year of follow-up, his respiratory tract infection frequency significantly decreased, and all were mild infections. He did not exhibit symptoms of PAP such as excessive phlegm or difficulty breathing, and there were no special features on chest imaging. Therefore, the child has not yet undergone a second bronchoscopy examination.

DISCUSSION

Current studies suggest that PAP is related to a decrease in macrophage clearance. The Toll-like receptor (TLR) pathway is an important signal pathway regulating the function of macrophages. BTK is an important regulatory molecule in the TLR pathway, which is involved in the regulation of cytokine production, phagocytosis, differentiation and the function of macrophages after TLR activation[11,12]. Therefore, XLA may directly induce PAP. At the same time, XLA children can be prone to repeated pulmonary infections, leading to PAP. Based on the above theory, we believe that XLA is one of the potential causes of PAP. Therefore, improving immune function may benefit the prognosis of children with PAP caused by immunodeficiency.

The child in this report had a history of multiple respiratory infections and diarrhea. Based on his genetic examination, chest imaging, and alveolar lavage fluid examination, he met the diagnostic criteria for PAP and XLA. In addition, his laboratory test results did not find GM-CSF autoantibodies, and genetic testing did not identify gene mutations related to PAP[2] (such as surfactant protein B, surfactant protein C, ABCA3, NKX2-1, and GM-CSF receptor genes). No respiratory pathogens were detected in blood, sputum and alveolar lavage fluid. His mother, brother, father and neighbors did not have PAP-related symptoms. Moreover, his residence was free from industrial pollution. Based on a previous analysis of the etiology of PAP, this patient's PAP was considered to be secondary to immunodeficiency.

At present, the most effective treatment for PAP is massive whole lung lavage[13]. Large volume whole lung lavage can directly remove the protein-like substances deposited in the alveoli, reduce macrophage inhibitory factors in the alveoli and distal bronchioles, improve the function of alveolar macrophages, and thus improve lung ventilation and function. However, for acquired PAP, we believe that the treatment of primary disease might be equally important. Tanaka-Kubota *et al*[3] studied children with PAP secondary to immunosuppression. In their study, the children only received lung lavage at the beginning, and the children's PAP symptoms improved, but soon relapsed. After cell transplantation, long-term relief of the symptoms of PAP was achieved. All cases (our report and Tanaka-Kubota's studies) suggest that XLA was a secondary cause of PAP which improved with IVIG treatment.

CONCLUSION

We describe a child with XLA and PAP. It is suggested that XLA may cause PAP, and immunotherapy was helpful in improving the prognosis of this child with PAP acquired due to immunodeficiency.

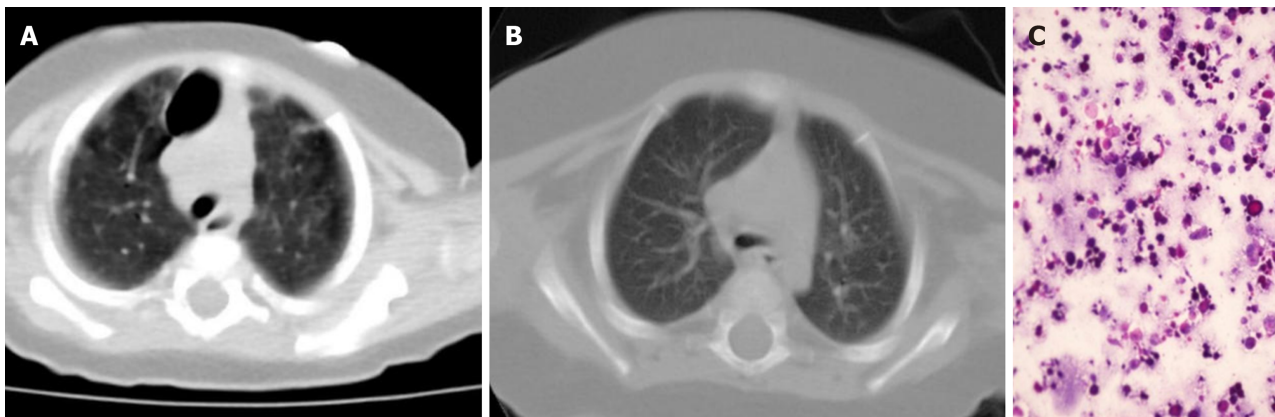


Figure 1 Lung imaging before and after treatment. A: Before treatment, the transparency of both lungs decreased, presenting as ground glass or butterfly-shaped changes, with a large bubble in the right upper lung; B: After alveolar lavage, there was a significant improvement in bilateral lung lesions; C: Periodic acid-Schiff staining of bronchoalveolar lavage fluid was positive.

FOOTNOTES

Co-first authors: Ting Zhang and Ming Li.

Author contributions: Zhang T managed the case, wrote and corrected the manuscript; Li X assisted with writing, correction, and reconstruction of the manuscript; All authors have read and approved the final manuscript.

Supported by Sanitation Research Project of Kunming Municipal Health Commission, No. 2020-06-01-119.

Informed consent statement: Written informed consent was obtained from the patient. A copy of the written consent is available for review from the Editor of this journal.

Conflict-of-interest statement: The authors declare that they have no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist statement, and the manuscript was prepared and revised according to the CARE Checklist statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Xin Li [0000-0003-0337-5740](https://orcid.org/0000-0003-0337-5740).

S-Editor: Luo ML

L-Editor: Kerr C

P-Editor: Cai YX

REFERENCES

- Zhang FZ, Yuan JX, Qin L, Tang LF. Pulmonary Alveolar Proteinosis Due to *Pneumocystis carinii* in Type 1 Hyper-IgM Syndrome: A Case Report. *Front Pediatr* 2020; **8**: 264 [PMID: [32596190](https://pubmed.ncbi.nlm.nih.gov/32596190/) DOI: [10.3389/fped.2020.00264](https://doi.org/10.3389/fped.2020.00264)]
- Gallagher J, Adams J, Hintermeyer M, Torgerson TR, Lopez-Guisa J, Ochs HD, Szabo S, Salib M, Verbsky J, Routes J. X-linked Hyper IgM Syndrome Presenting as Pulmonary Alveolar Proteinosis. *J Clin Immunol* 2016; **36**: 564-570 [PMID: [27324886](https://pubmed.ncbi.nlm.nih.gov/27324886/) DOI: [10.1007/s10875-016-0307-0](https://doi.org/10.1007/s10875-016-0307-0)]
- Tanaka-Kubota M, Shinozaki K, Miyamoto S, Yanagimachi M, Okano T, Mitsui N, Ueki M, Yamada M, Imai K, Takagi M, Agematsu K, Kanegane H, Morio T. Hematopoietic stem cell transplantation for pulmonary alveolar proteinosis associated with primary immunodeficiency disease. *Int J Hematol* 2018; **107**: 610-614 [PMID: [29185156](https://pubmed.ncbi.nlm.nih.gov/29185156/) DOI: [10.1007/s12185-017-2375-1](https://doi.org/10.1007/s12185-017-2375-1)]
- Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer* 2018; **17**: 57 [PMID: [29455639](https://pubmed.ncbi.nlm.nih.gov/29455639/) DOI: [10.1186/s12943-018-0779-z](https://doi.org/10.1186/s12943-018-0779-z)]
- Ochs HD, Smith CI. X-linked agammaglobulinemia. A clinical and molecular analysis. *Medicine (Baltimore)* 1996; **75**: 287-299 [PMID: [8982147](https://pubmed.ncbi.nlm.nih.gov/8982147/) DOI: [10.1097/00005792-199611000-00001](https://doi.org/10.1097/00005792-199611000-00001)]
- Jouneau S, Ménard C, Lederlin M. Pulmonary alveolar proteinosis. *Respirology* 2020; **25**: 816-826 [PMID: [32363736](https://pubmed.ncbi.nlm.nih.gov/32363736/) DOI: [10.1111/resp.13831](https://doi.org/10.1111/resp.13831)]

- 7 **Hildebrandt J**, Yalcin E, Bresser HG, Cinel G, Gappa M, Haghighi A, Kiper N, Khalilzadeh S, Reiter K, Sayer J, Schwerk N, Sibbersen A, Van Daele S, Nübling G, Lohse P, Griese M. Characterization of CSF2RA mutation related juvenile pulmonary alveolar proteinosis. *Orphanet J Rare Dis* 2014; **9**: 171 [PMID: 25425184 DOI: 10.1186/s13023-014-0171-z]
- 8 **Al-Haidary AS**, Alotaibi W, Alhaider SA, Al-Saleh S. A newly identified novel variant in the CSF2RA gene in a child with pulmonary alveolar proteinosis: a case report. *J Med Case Rep* 2017; **11**: 122 [PMID: 28464852 DOI: 10.1186/s13256-017-1285-4]
- 9 **Trapnell BC**, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, Wang T, Morgan C, Cottin V, McCarthy C. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers* 2019; **5**: 16 [PMID: 30846703 DOI: 10.1038/s41572-019-0066-3]
- 10 **Patel SM**, Sekiguchi H, Reynolds JP, Krowka MJ. Pulmonary alveolar proteinosis. *Can Respir J* 2012; **19**: 243-245 [PMID: 22891182 DOI: 10.1155/2012/841530]
- 11 **Xu B**, Luo Q, Gong Y, Li J, Cao J. TLR7 Expression Aggravates Invasive Pulmonary Aspergillosis by Suppressing Anti-Aspergillus Immunity of Macrophages. *Infect Immun* 2021; **89** [PMID: 33495270 DOI: 10.1128/IAI.00019-21]
- 12 **Bush A**, Pabary R. Pulmonary alveolarproteinosis in children. *Breathe (Sheff)* 2020; **16**: 200001 [PMID: 32684993 DOI: 10.1183/20734735.0001-2020]
- 13 **Smith BB**, Torres NE, Hyder JA, Barbara DW, Gillespie SM, Wylam ME, Smith MM. Whole-lung Lavage and Pulmonary Alveolar Proteinosis: Review of Clinical and Patient-centered Outcomes. *J Cardiothorac Vasc Anesth* 2019; **33**: 2453-2461 [PMID: 31307910 DOI: 10.1053/j.jvca.2019.03.047]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

