

Pulmonary Nocardia infection in child with idiopathic pulmonary hemosiderosis: case report and literature review

Qin Lu

Zhejiang University School of Medicine Children's Hospital

Feizhou Zhang

Zhejiang University School of Medicine Children's Hospital

Xiaofen Tao

Zhejiang University School of Medicine Children's Hospital

Lanfang Tang (✉ 6195007@zju.edu.cn)

Children's Hospital of Zhejiang University School of Medicine <https://orcid.org/0000-0002-7994-7066>

Case report

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Abstract

Background

Idiopathic pulmonary hemosiderosis (IPH) encompasses a rare and agnogenic group of diffuse alveolar capillary hemorrhagic diseases. Corticosteroid treatment is the globally preferred therapeutic strategy for IPH. However, its long-term administration can cause immunodeficiency. *Nocardia* infection often occurs in immunocompromised patients and primarily involves the pleura and lungs. Herein, we describe a case of pediatric pulmonary *Nocardia* infection complicated by IPH.

Case presentation

A 7-year-old girl presented with chief complaints of pale complexion persisting for 1 year and a cough for 20 days. Abundant hemosiderin-laden macrophages were detected in the gastric juice during the last hospitalization. Uninterrupted small doses of corticosteroids (1–2 mg/kg/day) were administered to the patient to treat the IPH. After nearly two months of corticosteroids therapy, the children began to cough. Next-generation sequencing of the bronchoalveolar lavage fluid (BALF) sample revealed the presence of *Nocardia abscessus* (*N. abscessus*) DNA and confirmed IPH again. Linezolid was administered to treat the *N. abscessus* infection. She recovered well and was discharged after 18 days of hospitalization. After 1 month of follow-up, her pulmonary lesions exhibited gradual resorption, the iron deficiency anemia had resolved, and the IPH appeared to be well-controlled.

Conclusions

This pediatric case of *N. abscessus* infection complicated by IPH, including the nonspecific clinical manifestations, time-consuming diagnosis, and timely adjusted treatment, provided considerable clinical experience and enlightenment.

Background

Idiopathic pulmonary hemosiderosis (IPH) is characterized by the copious deposition of hemosiderin-laden macrophages in the lung, has an incidence of approximately 0.24–1.23 per million people, and predominantly affects children¹. However, the exact pathogenetic mechanism of IPH remains unclear. Hemoptysis, lung infiltration, and iron deficiency anemia (IDA) is the generally recognized triad of symptoms in pediatric patients with IPH, and the typical earliest clinical manifestation in children with IPH is unexplained anemia². Corticosteroid (CS) therapy is the choice treatment for IPH³. *Nocardia* is an aerobic actinomycete, and is not part of the normal flora of the human body. Pulmonary nocardiosis is a well-described infectious disease in immunosuppressed patients (ISPs) as well as in immunocompetent patients (ICPs)⁴. It is similar to acute bacterial pneumonia, and approximately 90% of cases are caused by *Nocardia stellate*⁵. Herein, we describe a case of pediatric pulmonary *Nocardia* infection complicated by IPH.

Case Presentation

A 7-year-old girl was admitted to our hospital with chief complaints of pale complexion persisting for 1 year and a cough for 20 days. According to her medical history, her presentation of pale complexion exhibited no apparent signs of progression or aggravation. She was previously diagnosed with IDA at the local hospital because of dizziness and complaints of abdominal pain at presentation. Two months ago, based on the manifestation of diffuse fine granular shadows in both lungs on chest computed tomography (CT), presence of hemosiderin-laden macrophages in the gastric juice, aggravation of her pale complexion, apathy, poor appetite, occasional emesis of gastric contents without bile and blood, absence of hematuria, and presence of black stool, she was diagnosed with IPH at our hospital (Fig. 1A 2019/2/25). From then on, uninterrupted small doses of corticosteroids (1–2 mg/kg/day) were administered to the patient to treat the IPH. The patient is the second child of a healthy couple, and her 16-year-old sister presented in good health.

Physical examination revealed a pale complexion and Cushing's syndrome appearance. The liver was located 2 cm below the ribs and the spleen did not extend below the costal region. Moist rales, wheezing, hemoptysis, chest pain, and dyspnea were absent. Neurological examinations revealed no apparent abnormalities. There was no rash, no clubbed fingers, no bruises on the lips and extremities.

Laboratory investigations revealed a white blood cell count of $7.32 \times 10^9/L$ (reference range, $4-10 \times 10^9/L$), platelet count of $352 \times 10^9/L$ (reference range, $100-400 \times 10^9/L$), hemoglobin level of 33 g/L (reference range, 110–155 g/L), mean erythrocyte volume of 60.9 fL (reference range, 75–92 fL), and average hemoglobin content of 14.3 pg (reference range, 26–31 pg). Bone marrow biopsy revealed active erythroid hyperplasia, primarily in the late juvenile erythrocytes, and the central globus pallidus of some mature erythrocytes was enlarged, which was consistent with the myelogram of iron deficiency anemia. (Fig. 2A). The anti-tuberculous antibody test, enzyme-linked immunospot assay, tuberculin test, ANA, P-ANCA, C-ANCA, MPO + PR3, and anti-GBM were negative. Viral nasopharyngeal swab tests, test for *Mycoplasma pneumonia* RNA in the sputum, antibody tests for *Mycoplasma pneumonia* and *Chlamydia pneumonia*, 16S rRNA screening for the presence of gram-positive and gram-negative bacteria, and multiple blood cultures (e.g. for the detection of L form bacteria, anaerobic bacteria, fungus etc.) were negative.

Fiberoptic bronchoscopy revealed bronchoinflammatory changes and diffuse alveolar hemorrhage. The lymphocyte, neutrophil, and macrophage counts in the bronchoalveolar lavage fluid (BALF) were approximately 3, 2, and 95%, respectively. Eosinophils were absent. Multiple erythrocytes and large numbers of hemosiderin-laden macrophages were observed (Fig. 2B). The BALF culture was negative. To detect the presence of pathogens in the BALF, next-generation sequencing (NGS) (BGISEQ-50) was performed and the sequencing results were compared to the sequences of pathogens in the four Microbial Genome Databases, including 3,446 species of bacteria, 206 species of fungi, 4,152 viruses, and 140 species of parasites (note: If one sequence of pathogenic microorganism is detected, it will be determined as positive detection. A 96% match was found with the reference sequence of *N. abscessus*.

The treatment for IDA was initiated when she was diagnosed with IPH. CS therapy was used to treat the IPH, and the dose was gradually tapered. When she was referred to our department, her hemoglobin and ferritin levels were within the normal range. Therefore, the administration of therapeutic iron agents was ceased. After admission, the galactomannan test and (1, 3) β -D glucan test suggested the presence of fungal infection; oral voriconazole was administered as an antifungal treatment, but exhibited no efficacy. The transmittance of the disease into the bilateral lung decreased unevenly; however, fine particles were still present in both lungs. The right lung was scattered in circular lesions and the boundaries were clear on chest CT performed on the day of admission (Fig. 1B, 2019/5/16). Compared to the chest CT performed on the day of admission, the lesions in the lower lobe of the right lung exhibited improvement. However, cavity formation was observed, new lesions appeared in the left lung, and bilateral pleural thickening was observed (Fig. 1C, 2019/5/29). Therefore, linezolid therapy was initiated for *N. abscessus* infection (Fig. 3). Chest radiography performed after 1 month of follow-up indicated significant improvement of the pulmonary lesions compared to that at the time of admission, and oral linezolid was discontinued (Fig. 1D, 2019/7/3).

Discussion And Conclusions

IPH is a pulmonary hemorrhagic disease with an unknown pathogenetic mechanism and with typical manifestations of cough, hemoptysis, and IDA; chest images of patients with IPH typically demonstrate pulmonary infiltrating shadows⁶. Our patient was misdiagnosed with IDA because of the primary manifestation of anemia at disease onset. The most effective diagnostic method for IPH is the pathological observation of hemosiderin-laden macrophages in the sputum, alveolar lavage fluid, or gastric juice of indicated patients⁷. Due to the aggravation of anemia and occasional manifestation of abdominal pain, a large number of hemosiderin-laden macrophages were found in the patient's gastric juice and BALF samples, based on which a final diagnosis of IPH was made. The diagnosis of IPH was delayed by one year, resulting in deferred treatment. At the time of admission to our unit, the diagnosis of IPH was clear, and the hemoglobin and ferritin levels were within normal ranges; therefore, the administration of iron agents was discontinued. Currently, there is no specific treatment plan for cases of IPH; the main therapeutic strategy involves the use of CS, which increases the stability of the cell membrane, reduces blood vessel exudation, and rapidly improves bleeding symptoms⁸. Systemic CS administration reduces the morbidity and mortality of patients with acute onset alveolar hemorrhage and controls the progression of pulmonary fibrosis⁹. Besides, studies have reported that when use prednisolone for induction and maintained remission, early addition of HCQ plus azathioprine/cyclophosphamide may reduce disease flare and steroid toxicity without serious adverse effects¹⁰. Accordingly, adequate CS was administered for 2 months.

However, the patient was experiencing a cough, cough thick sputum, occasionally chest pain and the prophylactic use of voriconazole for 20 days yielded no improvement in symptoms. Laboratory tests suggested increased leucocytes and neutrophils. Three days after admission, NGS of the BALF sample was indicative of *N. abscessus* infection. The diagnosis of *Nocardia* infection depends on the results of

pathological examination. The most common infection site of *Nocardia* is the lung; however, infections can also be found in other organs, such as the brain, liver, skin, etc¹¹. Pulmonary *Nocardia* infection is clinically rare and serious, and is common in immunosuppressed individuals, such as patients on long-term CS administration and those with human immunodeficiency virus infection¹². However, it can also occur in individuals with normal immune function, particularly in patients with structural lung diseases, such as bronchiectasis and pulmonary cystic fibrosis¹³. *Nocardia* infection may lead to acute necrotic inflammatory responses followed by cavitation or pulmonary nodules, pneumonia and progression to empyema. Lung injury is characterized by necrosis but does not form fibrous encapsulation, which is easy to spread and cause multiple infections¹⁴. Pulmonary *Nocardia* has nonspecific clinical manifestations; however, the disease can be characterized by the presence of lobar pneumonia, lung abscess, or pulmonary nodular symptoms, similar to the symptoms of a fungal infection. The main symptoms of pulmonary *Nocardia* are fever, cough, initial dry cough, gradual occurrence of purulent sputum or hemoptysis, and severe dyspnea¹⁵.

Clinical symptom onset in our patient began with a cough, cough thick sputum, and occasionally chest pain. Her condition did not improve despite the prophylactic use of oral voriconazole for 20 days. Radiological imaging of patients with pulmonary *Nocardia* has revealed the following characteristics: infection is generally focused under the pleura, occasional presence of pulmonary consolidation, pulmonary infiltration, solitary or multiple nodules and other changes, and easy formation of voids¹⁶. The circular lesions observed on the patient's chest CT suggested positive bacterial infection, which was considered first. Owing to the inconspicuous cavities, prolonged application of voriconazole, and expansion and progression of lesions, there was insufficient evidence for a fungal infection. The round diseased focus grew rapidly, and the possibility of a tumor was therefore not taken into consideration. In addition, the patient had no fever, no history of tuberculosis, and negative immunospot and tuberculin tests; hence, tuberculosis was not considered. The ANA, P-ANCA, C-ANCA, MPO + PR3, and anti-GBM tests were negative; therefore, connective tissue diseases, such as antineutrophil cytoplasmic antibody-associated vasculitis, were not considered. However, since the child had a long history of hormone use, clinical manifestations include cough, thick sputum, imaging findings of new nodular lesions, and uneven reduction of transmittance in both lungs, we administered linezolid to cover the possibility of bacterial infection, and the effect was apparent. Unfortunately, this treatment could not be switched to amoxicillin clavulanate potassium quickly after the diagnosis of *Nocardia* infection, because we consider that linezolid has a significant effect in children. The administration of linezolid was thus continued; the patient exhibited gradual improvement and was eventually discharged after 18 days of hospitalization. In the subsequent outpatient follow-up, the imaging manifestations of the children's lungs gradually subsided, and the clinical symptoms improved significantly, without obvious adverse reactions.

Although in vitro susceptibility results suggest an increased resistance rate of *Nocardia* to sulfanilamide, currently, sulfonamides are still used as the first line drug for pulmonary *Nocardia* infection. In addition, aminoglycosides, carbapenems, quinolones and some cephalosporins are sensitive to *Nocardia* and can be

used alone or in combination. Linezolid is effective against multi-drug resistant *Nocardia* and can be used to treat resistant strains¹⁷.

In conclusion, patients receiving CS therapy for IPH should be monitored for immunosuppression and infection of specific pathogens, such as *Nocardia*. The possibility of pulmonary *Nocardia* infection should be considered in immunosuppressed individuals with unexplained cough, thick sputum, fever and other respiratory manifestations, rapid development of pulmonary lesions, realistic changes, nodules, cavities, masses and other lesions accompanied by pleural involvement. In indicated cases, NGS should be used to quickly identify the presence of *Nocardia*. In addition, the treatment course of pulmonary *Nocardia* is long and the prognosis of the disease is poor, so early diagnosis and rational combination of drugs is very important.

Abbreviations

IPH
idiopathic pulmonary hemosiderosis
N. abscessus
Nocardia abscessus
CS
corticosteroid
NGS
next-generation sequencing
BALF
bronchoalveolar lavage fluid
IDA
iron deficiency anemia
CT
computer tomography

Declarations

Ethics approval and consent to participate

This study was approved by the parents and the ethics committee of the children's hospital affiliated to Zhejiang university school of medicine.

Consent for publication

The children's parents have informed and consented to the publication.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

There is no any competing interest.

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Authors' contributions

LQ completed the first draft, FFZ and XFT have participated to the data collection and improved the later revision of the article, LFT revised the manuscript to ensure the authenticity and practicability. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

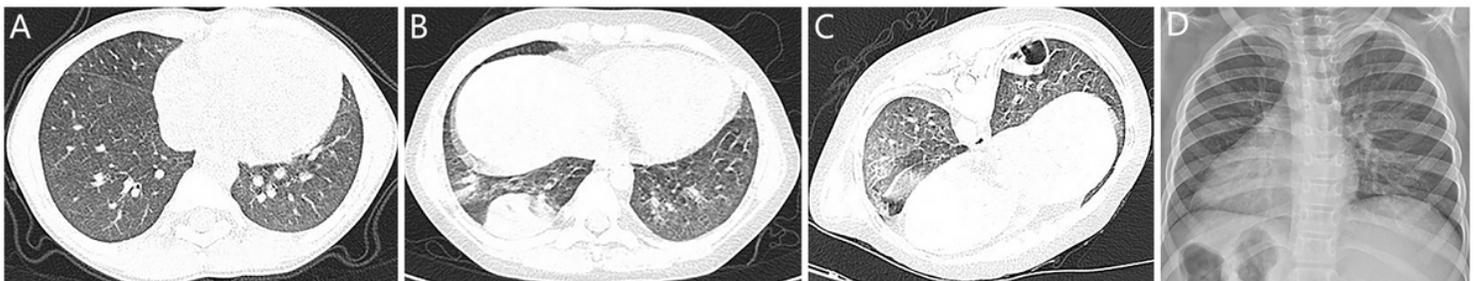


Figure 1

Changes in chest imaging of the patient. (A) Diffuse fine granular shadows were observed in both lungs (2 months ago). (B) The transmittance of the disease into the bilateral lung decreased unevenly, and there were still fine particles in the lungs. The right lung was scattered in circular lesions and the boundaries were clear (on the day of admission). (C) The lesions in the lower lobe of the right lung were improved, but cavity formation, new lesions in the left lung, and bilateral pleural thickening were observed (on the 9th day of admission). (D) The pulmonary lesions were significantly improved (1 month later).

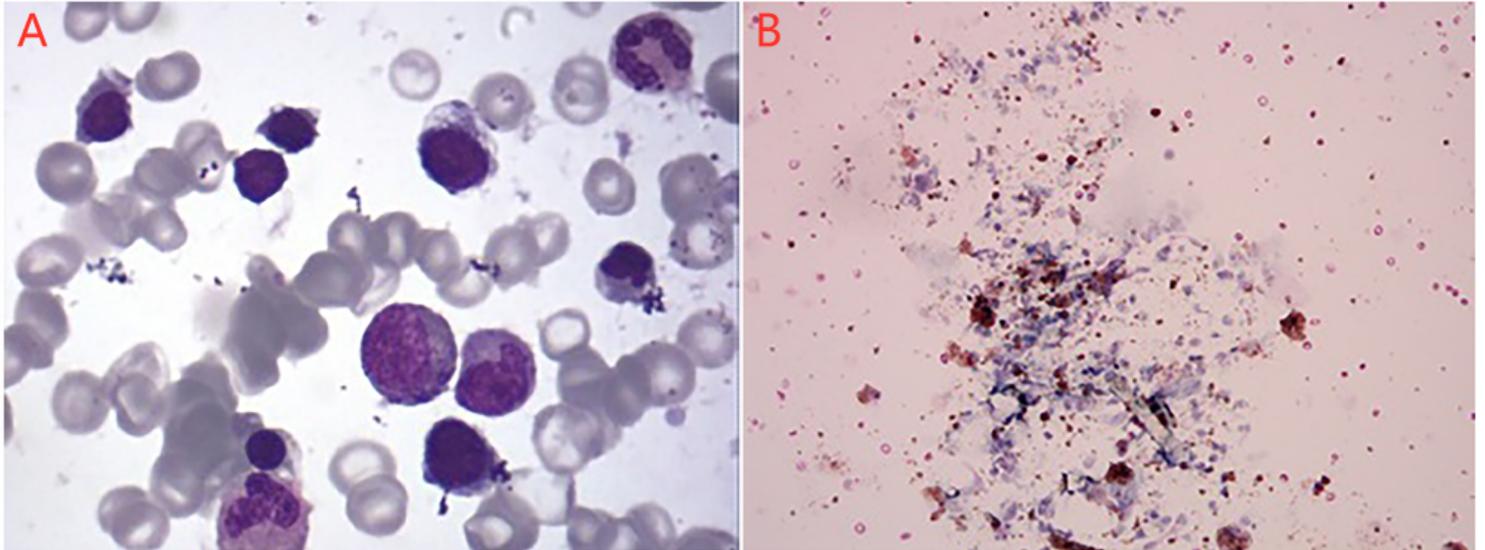


Figure 2

Pathological analysis. (A) Active erythroid hyperplasia, primarily in the late juvenile erythrocytes, was observed and the central globus pallidus of some mature erythrocytes was enlarged. (B) Multiple erythrocytes and large numbers of hemosiderin-laden macrophages were observed.

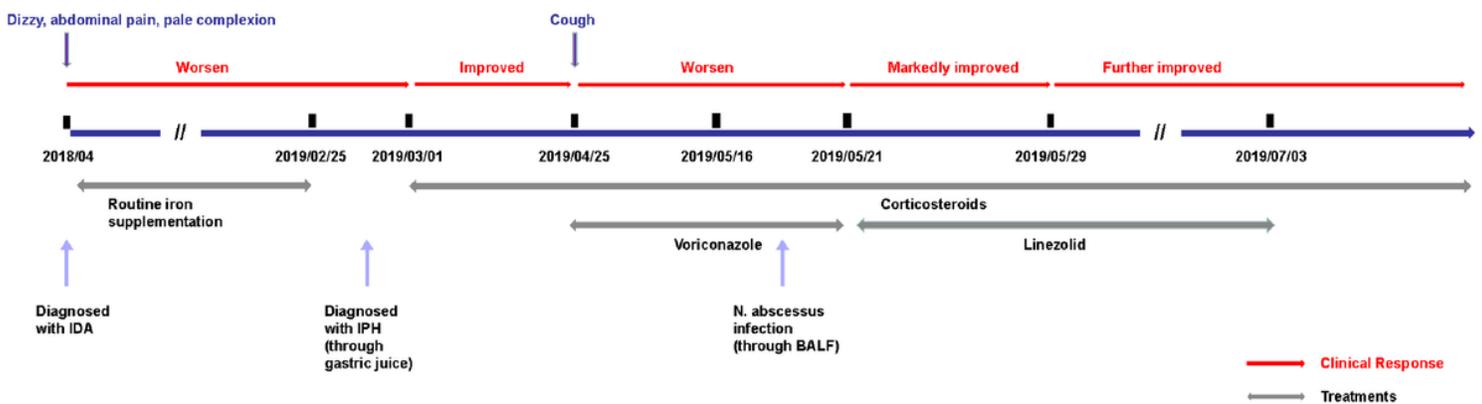


Figure 3

Diagrammatic representation of the treatment and outcome.