Clinical Case Report

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Diagnosis of pulmonary aspergillosis-related broncholithiasis in a child undergoing bronchoscopy

A case report

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Abstract

Rationale: Broncholithiasis is a rare disease and is characterized by calcification in the tracheobronchial tree. This disease has a predilection in the adult and occurrence is rare in children. Considering its infrequency, we report a rare clinical case, with the aim of sharing our experience during the diagnosis and treatment procedures.

Patient concerns: We report a 9-year- and 6-month-old girl who complained of chronic cough and recurrent wheeze for 2 months.

Diagnosis: Bronchialithiasis were found under bronchoscope. Pathologic examination revealed aspergillosis.

Interventions: The stone and surrounding granulation tissue were removed using a bronchoscope and the patient was treated with antifungal therapy.

Outcomes: The patient was in good general health without any clinical symptoms during the follow-up period.

Lessons: Pulmonary *Aspergillus* infection can cause bronchiolithiasis. Stones were removed under bronchoscope, and anti-*Aspergillus* therapy was effective.

Abbreviations: CRP = C-reactive protein, CT = computed tomography.

Keywords: aspergillosis, broncholithiasis, children

1. Introduction

Broncholithiasis refers to the irritating or obstructive symptoms of the airway caused by calcification or ossification in the bronchial lumen.[1–3] It was 1st reported by the Dutch physician Boerhave.[1–3] The morbidity of broncholithiasis is low, the average age of onset is 50 years, and it occurs in both sexes.[1–3] A broncholith is usually formed by the erosion and extrusion of a calcified adjacent lymph node into the bronchial lumen. Other causes of broncholithiasis include calcification of bronchial mucus and aspirated foreign material.[4] There are also reports in the literature that chronic inflammatory processes or granulomatous diseases, such as tuberculosis, histoplasmosis, coccidioidomycosis, nocardiosis, cryptococcosis, and aspergillosis, are common causes of broncholithiasis. In China, the cases of bronchial calculi reported are mostly caused by tuberculosis, and mostly in adults. The cases of children caused by *Aspergillus* are rare. Due to the rarity, the diagnosis of this disease is troublesome. Herein, we describe a broncholithiasis in a 9-year-old girl with aspergillosis infection.

2. Case study

This study presented the case of a 9-year and 6-month-old girl of the Han Chinese nationality. She was 1st treated in our ward 4 years and 6 months ago (January 12, 2013). She was admitted to the hospital for the "proposed treatment of interventional bronchoscopy 1 month after the reconstruction surgery of the right main bronchial stenosis." She underwent "hematopoietic stem cell transplantation" 8 years ago because she was diagnosed with "aplastic anemia." The disease was completely cured after the oral administration of "cyclosporin A" for 2 years. Her parents and twin sister were healthy, and a history of familial genetic diseases and infectious diseases was excluded. She was

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The patient provided informed consent for publication of the case.

The family members of the patient signed the informed consent form.

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The authors have no conflicts of interest to disclose.

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diagnosed with "contusion in the right main bronchus and right pneumothorax" in a local hospital due to "breathing difficulties after a car accident" 2 months before admission. Electronic bronchoscopy was immediately performed, revealing "granulation tissues in the right main bronchial lumen blocking the airway." Bronchoscopy showed the growth of granulation tissues in the airway (details were unknown) after 2 times therapy in a local hospital. The patient was transferred to the other hospital after 20 days of treatment for "reconstruction surgery of the right main bronchus" (the specific surgical method was unknown). She had smooth breathing and occasional morning cough 1 month after the surgery. Bronchoscopy showed the "growth of granulation tissues in the right bronchial lumen." The growth of granulation tissues in the ruptured right main bronchus and many secretions were still observed after about 20 times of interventional therapy, such as cleaning of granulation tissues under a bronchoscope, in a local hospital. Chest computed tomography (CT) suggested the progression of pulmonary lesions. On January 12, 2013, the patient was 1st admitted to the Department of Respiratory Intervention for electron bronchoscopy, which showed stenosis during right bronchial trauma. Therefore, a metal stent of $7.0 \times 15.0\,mm^2$ (Medtronic, Shanghai, China) was implanted (Fig. 1). Interventional therapy under a bronchoscope, such as cleaning of frozen tissues using laser and clamps, was performed more than 10 times under general anesthesia. The disease was stable within 2 years, and no pulmonary infection occurred. The parents of the patient were advised to get her metal stent removed because she had to undergo a regular review after stent implantation. Recurrent respiratory tract infection occurred after stent removal. She underwent electron bronchoscopy on January 21, 2015, which showed that the right main bronchial cartilage softened and stenosis occurred. Then, a silicone stent of $8.0 \times 25\,mm^2$ (Dumon) was implanted (Fig. 2). The patient was stable, and the silicone stent was removed after 6 months. She was frequently treated for "pneumonia" after stent removal in the local hospital.

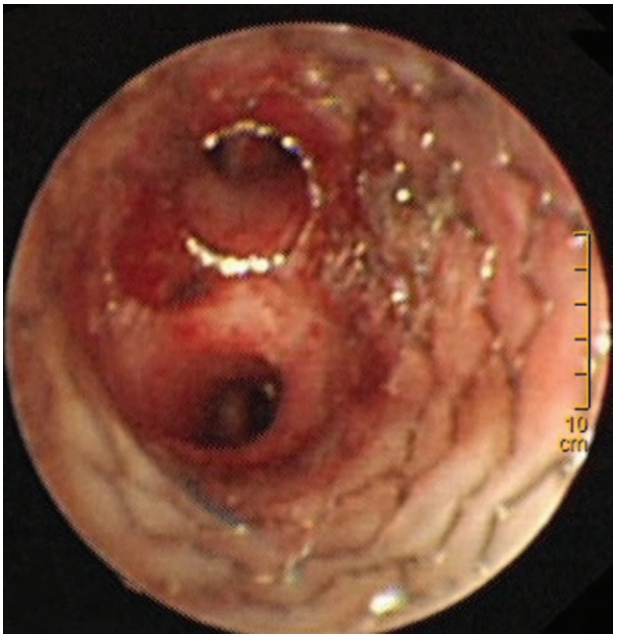

Figure 1. A metal stent was implanted in the patient, and the stent swelled better.

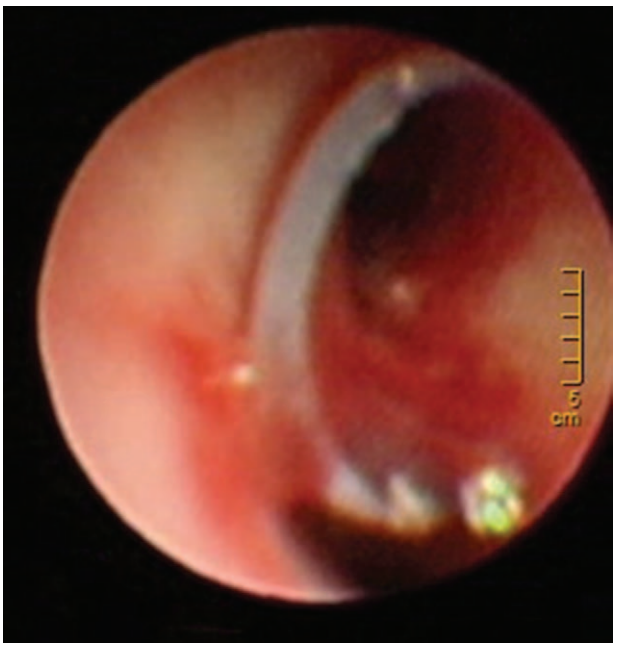

Figure 2. After implanting a silicone stent, the stent adhered to the wall well.

On March 17, 2017, she was treated at the Department of Respiratory Intervention of our hospital for "cough and polypnea for 2 months." The patient suffered from fever once in the initial stage of disease with a peak temperature of 38.0°C. Moreover, a small amount of white sputum was seen when coughing, but no chest tightness, chest pain, hemoptysis, dyspnea, or a history of foreign body inhalation was reported. Wheezing of the 2 lungs in the dual respiratory phase could be heard. No expiratory extension was present. She received antibiotics, inhaled steroid hormones, and underwent bronchodilator treatments in other hospitals, but the therapeutic effects were poor. After admission, the routine blood test showed that the leukocyte count was 4.61×10^9/L, neutrophils accounted for 54.5%, and C-reactive protein (CRP) was <3.14 mg/L. Chest CT revealed right-sided pneumonia, bronchial stenosis, a soft-tissue mass in the lumen, and scattered spot-like calcification (Fig. 3A). Furthermore, no calcified mediastinal lymph nodes were present, and a local biopsy did not reveal any lymph node structure. Electron bronchoscopy indicated the incarceration of bone-like substances at the distal end of the right main bronchus (Fig. 3B). Granulation tissues and necrotic proliferation were visible in the surroundings. After removing granulation tissues using laser and clamps, about 20 bone-like fragments were eliminated in multiple attempts (Fig. 4). The pathologic findings revealed that the detected substances were necrotic tissues, hyperplastic granulation tissues, fibrous tissues, and a small amount of metaplastic squamous epithelium. Moreover, neutrophils, plasma cells, lymphocytes, and a large number of fungi were found (Fig. 3). The culture of alveolar lavage fluid showed *Klebsiella pneumoniae*. Electron bronchoscopy 1 week later showed mucosal ulcers in the right middle bronchial lateral wall, scattered granulation tissues, necrotic tissue, and some "bone-like substances." The pathologic examination demonstrated that the detected tissues included bronchial mucosa and necrotic tissues. Moreover, lymph node and plasma cell infiltration in bronchial mucosa, vasodilation, hyperemia, and hemorrhage were observed. Necrotic tissues had a large number of *Aspergillus*

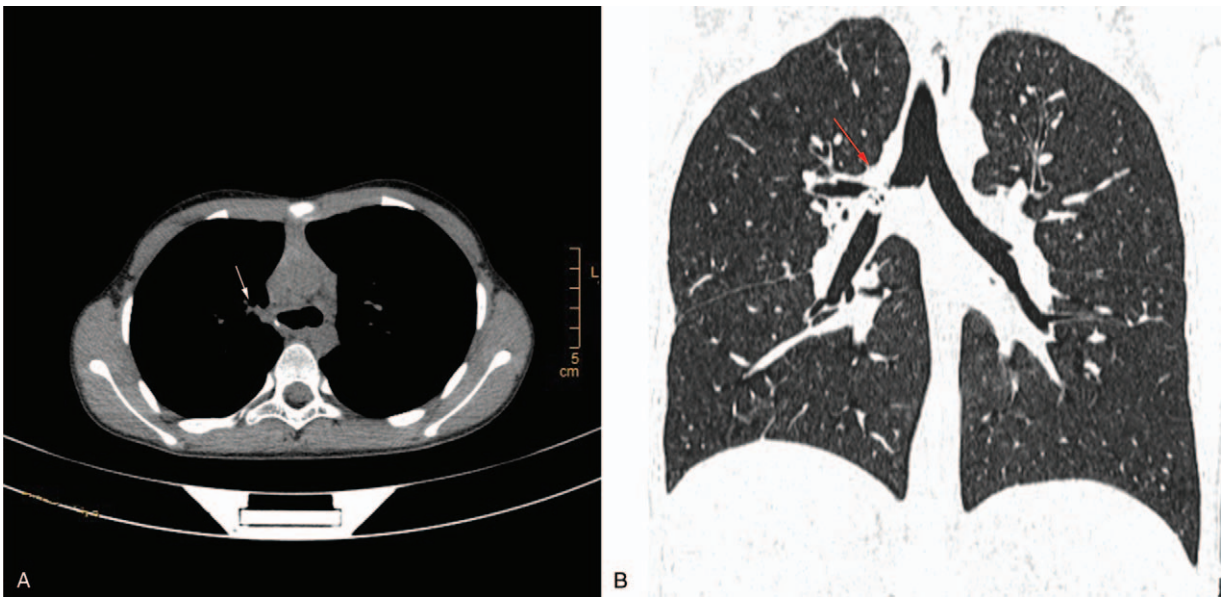

Figure 3. A soft-tissue mass in the lumen and scattered spot-like calcification on the wall were observed.

mycelia (Fig. 5A and B). Brushing under a bronchoscope and culture of alveolar lavage fluid showed the growth of *Staphylococcus aureus*.

The patient developed recurrent respiratory tract infection. She was treated for recurrent cough and polypnea. Treatments such as inhalation of steroid hormones and bronchodilators proved ineffective. The preliminary diagnosis revealed a barrier to secretion drainage after the airway cartilage was destroyed by trauma, and pathogenic infection by bacteria and fungi, based on the endoscopic and pathologic findings. However, the nature of "bone-like substances" in the lumen could not be determined. The "bone-like substances" were found to be gray-white and hard in texture when preparing pathologic sections. During staining, most of them chipped off and decalcified, and no tissue structure was observed. Chest CT and bronchoscopy showed it as "broncholithiasis (intraluminal type)" combined with scattered spot-like calcification. Therefore, the stone was removed under a bronchoscope, and oral administration of itraconazole (6.5 mL) was initiated for 2 months for antifungal treatment. The patient had no symptom of cough, polypnea, and so forth.

3. Discussion

Broncholithiasis is the presence of calcified substances in the trachea and bronchial tree. The main symptoms of broncholithiasis are cough, hemoptysis, obstructive pneumonia, and so forth.[2] Broncholithiasis usually occurs in the right lung. It is common at the proximal end of the right middle bronchus and the bronchial opening at the anterior end of the right superior bronchus.[3] Broncholithiasis is also accompanied by granulomatous diseases. In China, it is usually caused by tuberculosis infection. However, in European countries, it is correlated with histoplasmosis, *Actinomyces* infection, and tuberculosis.[1]

The clinical symptoms of broncholithiasis are not specific. Cough and hemoptysis are common in the development of multiple diseases, and the incidence rate is low with <10 cases reported in children.[3] The diagnosis of this disease is easy to be delayed and prone to be missed because of the lack of knowledge about this disease among medical staff. Chest CT of broncholithiasis can assist the diagnosis, but the final diagnosis depends on the discovery of calcified substances in the airway using bronchoscopy. During diagnosis and treatment of the patient in

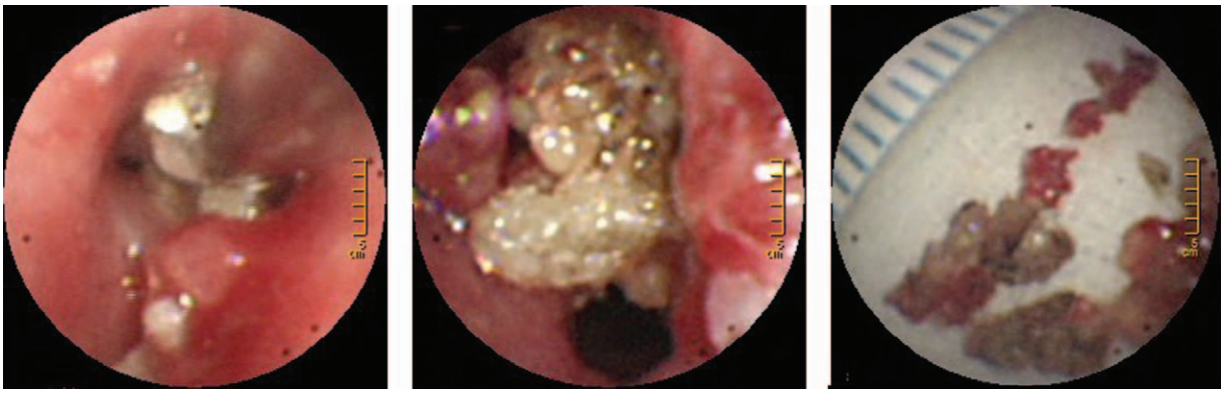

Figure 4. Granulation tissues and yellow-white calcified substances shown using endoscopy.

this study, the identification of stones using chest CT was not typical because the stones were inlaid in the granulation tissues. Bronchoscopy revealed incarceration of "bone-like substances" in the right superior lobe and the distal opening of the right middle bronchus. These substances had the characteristics of chipping off, easy dissolution, decalcification, and no tissue structure during preparation and staining, which were in line with the characteristics of stones. Furthermore, no bone manifestation occurred.

During broncholithiasis, usually mediastinal or hilar lymph nodes invade adjacent bronchial lumen through respiratory movement after tuberculosis and fungal infection. Broncholithiasis may also be caused by mucus in the diseased region, long-term inhalation of silicon dust and foreign bodies, and so forth.[4] The calcified lymph nodes in pulmonary mediastinal histoplasmosis need several months or even years to progress into acute inflammation of granulation tissues and then to fibrosis. However, the time from calcified lymph nodes to broncholithiasis is unclear.[3] Granulation tissue proliferation continuously occurred in the patient in this study during long-term stent implantation after trauma. Interventional bronchoscopy was performed multiple times, and no broncholithiasis occurred in the recent 4 years. Moreover, chest CT did not reveal calcification of mediastinal lymph nodes, and a local biopsy did not find lymph node structures. Pulmonary aspergillosis showed the same characteristics as stenosis and polyploid masses using bronchoscopy. Stone-like substances may be formed in some patients.[5,6] Jha et al reported that intrathecal aspergillosis combined with broncholithiasis was found in one case of allergic bronchopulmonary aspergillosis.[7] However, such studies have not been reported in children. Pathologic examination suggested a large number of *Aspergillus* mycelia in the diseased region in the patient in this study who had no history of long-term inhalation of silicon dust and foreign bodies, which was consistent with previous findings. Therefore, broncholithiasis was considered to be a result of the fungal infection in the diseased region, but its underlying mechanism needs further investigation.

The basic aim of broncholithiasis treatment is to remove stones, release obstruction, and relieve clinical symptoms, which usually depends on endobronchial lithotomy or surgery.[8] Bronchoscopy is superior because it can be used for not only diagnosis but also treatment. The patient in this study was treated using interventional bronchoscopy. A stent was implanted due to the damage of tracheal cartilage after trauma and luminal collapse, thereby improving local ventilation and secretion drainage. However, treatments against infection and polypnea were ineffective due to cough and polypnea for a long time. Multiple stones in granulation tissues in the diseased region found using bronchoscopy were removed with bronchoscopic laser treatment and clamping to avoid surgical trauma to the patient, thereby reducing the family burden to a large extent. Bronchoscopic lithotomy involved chances of stone fragments entering into the distal end of the bronchus, thus making the removal of these fragments difficult. However, massive hemorrhage was expected during lithotomy because large stones invaded the blood vessels. Surgical thoracotomy is usually used when bronchoscopic lithotomy fails or massive hemoptysis and tracheal fistula occur. However, it is associated with trauma. Lobectomy or segmentectomy should be performed if necessary.[3] Hiroki Nishine reported that the stones on the bronchial wall could be moved by injecting saline into the bronchial lumen.[4] Therefore, this method can be used in the future to reduce damage to the bronchial wall in patients with broncholithiasis. The culture of alveolar lavage fluid of the patient showed the growth of *K pneumoniae* and *S aureus*. Bronchoscopic specimen culture confirmed the presence of *S aureus*. The disease history showed that the patient had no fever. Bronchoscopic secretions reduced, related inflammatory indicators were basically normal, and the number of bacteria in the alveolar lavage fluid was low, which was considered to be *Bacteriopexia*. Therefore, anti-bacterial treatment was not performed. Previous studies indicated that antifungal agents should not be used when broncholithiasis was the only treatment for a pediatric patient with histoplasmosis because stones were usually formed after controlling fungal infection.[3] However, the patient in this study had invasive pulmonary aspergillosis, and cough and polypnea did not occur after 1 month of oral administration of itraconazole. Moreover, bronchoscopy showed a few granulation tissues, but no broncholithiasis (Fig. 5C). Thus, the treatment was considered to be effective. Cough and polypnea did not occur in the patient, and antifungal treatment with itraconazole was continuously given for 1 month.

The complications of broncholithiasis include recurrent respiratory tract infection, bronchiectasis, tracheal fistula, and so forth.[3] The primary complication of the patient in this study was a recurrent infection, which might be associated with luminal

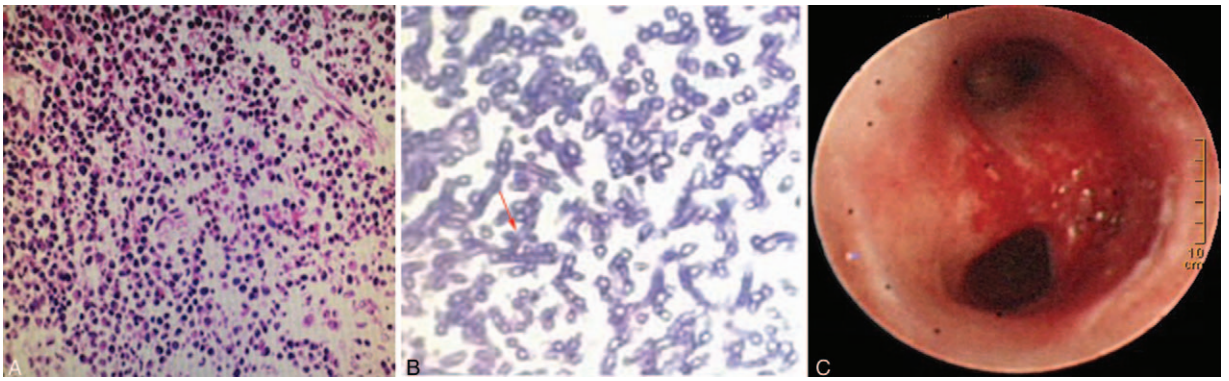

Figure 5. (A) Pathologic hematoxylin and eosin staining of pulmonary tissues. Figure H was magnified 10 × 20 times, showing a lymph node and plasma cell infiltration. Moreover, vasodilator congestion and hemorrhage occurred. A large number of *Aspergillus* mycelia were found in necrotic tissues. (B) The presence of *Aspergillus* mycelia and spores is demonstrated (magnified 10 × 40 times; indicated by arrows). (C) After 1 month of administering itraconazole, bronchoscopy showed a few granulation tissues, but no broncholithiasis.

obstruction and inhibited secretion drainage due to stones. Massive hemoptysis might occur if pulmonary blood vessels were invaded by broncholithiasis. Therefore, timely diagnosis and treatment are of great importance.

In summary, although the incidence rate of broncholithiasis is low in children, the possibility of broncholithiasis should be considered when symptoms, such as recurrent cough, polypnea, hemoptysis, and respiratory tract infection, are difficult to be controlled, especially combined with tuberculosis and *Aspergillus* infection. Chest CT has a certain limitation in diagnosing broncholithiasis. Bronchoscopy should be improved as soon as possible to confirm the diagnosis, and stone removal should be performed using interventional bronchoscopy. A larger number of previously unknown diseases have gradually entered into the field of vision with the improvement in diagnosis and treatment. Multidisciplinary collaboration is important in the diagnosis and treatment of these diseases. The Departments of Respiratory Intervention, Radiology, and Pathology collaborated to understand and report the case of combined pulmonary aspergillosis and broncholithiasis while diagnosing and treating the patient in this study. However, the number of cases was low. Therefore, further clinical observation and summary are needed. Moreover, the mechanism underlying broncholithiasis caused by pulmonary aspergillosis should be further studied.

Author contributions

Conceptualization: Chen Meng.
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Formal analysis: Zhongxiao Zhang.
Investigation: Na Liu, Jing Ma.
Methodology: Xiuli Yan.
Project administration: Xia Liu.
Resources: Chen Meng, Zhongxiao Zhang, Na Liu.
Software: Xiuli Yan, Chong Shi, Xinxin Wang Coll.
Supervision: Chen Meng.
Validation: Zhongxiao Zhang, Xia Liu.
Visualization: Chong Shi, Xinxin Wang Coll.
Writing – original draft: Chen Meng, Jing Ma.
Writing – review & editing: Jing Ma.

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