Respiratory Medicine Case Reports 15 (2015) 62–65

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Successful treatment of chronic lower respiratory tract infection by macrolide administration in a patient with intralobar pulmonary sequestration and primary ciliary dyskinesia

Hironobu Tsubouchi*, Nobuhiro Matsumoto, Shigehisa Yanagi, Jun-ichi Ashitani, Masamitsu Nakazato

Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Kiyotake, Miyazaki, 889-1692, Japan

ARTICLE INFO

Article history:
Received 27 February 2015
Received in revised form
19 April 2015
Accepted 12 May 2015

Keywords:
Cilia
Macrolide
Alopecia
Bronchopulmonary sequestration

ABSTRACT

Primary ciliary dyskinesia (PCD) is a genetic disease associated with abnormalities in ciliary structure and function. Although recurrent respiratory infection associated with ciliary dysfunction is a common clinical feature, there is no standardized treatment or management of respiratory infection in PCD patients. Here, we report that respiratory infection with PCD and intralobar sequestration (ILS) were treated successfully with clarithromycin before the surgical resection of ILS. A 15-year-old non-smoking Japanese woman was admitted for productive cough and dyspnea on exertion. Chest CT scan on admission showed complex cystic LESIONS with air-fluid level in the right lower lobe, and diffuse nodular shadows in the whole lobe of the lung. On flexible bronchoscopy examination, sputum and bronchiolar fluid cultures revealed *Staphylococcus aureus* (*S. aureus*). An electron microscopic examination of the cilia showed inner dynein arm deficiency. Administration of clarithromycin improved the lower respiratory tract infection associated with *S. aureus*. CT angiography after clarithromycin treatment demonstrated an aberrant systemic artery arising from the celiac trunk and supplying the cystic mass lesions that were incorporated into the normal pulmonary parenchyma without their own pleural covering. Based on these results, the patient was diagnosed with PCD and ILS. Because of the clarithromycin treatment, resection of the ILS was performed safely without any complications. Although further observation of clarithromycin treatment is needed, we believe that clarithromycin may be considered one of the agents for treating PCD.

1. Introduction

Primary ciliary dyskinesia (PCD) is a relatively rare autosomal recessive disease associated with defective ciliary structure and function, in which defective cilia cause impairment of mucociliary clearance [1]. PCD is characterized by recurrent respiratory tract infections, sinusitis, bronchiectasis, male infertility and a randomization of the left–right (LR) body asymmetry. In addition, PCD occasionally coexists with other congenital diseases that require surgical treatment, such as congenital heart disease [2]. Although the non-infective condition is thought to be an important preoperative factor, there are no standardized treatments for recurrent respiratory infection in PCD patients.

Bronchopulmonary sequestration (BPS) is a congenital malformation characterized by a mass of non-functioning lung tissue separated from the normal bronchopulmonary tree and vascularized by an aberrant systemic artery [3]. Intralobar sequestration (ILS), a more common type of BPS, is an abnormal region within the normal pulmonary parenchyma without its own pleural covering [3]. In patients with ILS, surgical intervention is recommended to protect the lung parenchyma and to prevent possible complications, including hemoptysis [4], cardiovascular problems [5], and recurrent respiratory infections [3,6]. Here, we describe a patient with PCD and ILS in whom the respiratory tract infection was treated by clarithromycin before surgical resection of the ILS.

2. Clinical report

A 15-year-old non-smoking Japanese female was admitted to our hospital because of the symptoms of productive cough and

* Corresponding author.
E-mail address: hironobu_tsubouchi@med.miyazaki-u.ac.jp (H. Tsubouchi).

http://dx.doi.org/10.1016/j.rmcr.2015.05.008

dyspnea on exertion, which appeared 6 months before admission. She had been diagnosed with alopecia universalis as a 1-year-old, and was hospitalized for 1–2 weeks for recurrent lower respiratory tract infections at the ages of 1, 4, and 10 years old. At 12 years old, she was treated for chronic sinusitis by antibiotics and some mucolytic agents.

The physical examination on admission revealed a body temperature of 36.6 °C, blood pressure of 99/56 mmHg, and regular pulse of 87 beats/min. The skin was normal apart from the absence of hair, and lung auscultation revealed coarse crackles in the right chest. The results of the laboratory data, an arterial blood gas analysis on room air and a pulmonary function test on admission showed a white blood cell count of 8800/μL; hemoglobin, 9.7 g/dL; cold agglutinin × 64; pH, 7.43; $PaCO_2$, 42 Torr; PaO_2, 96 Torr; vital capacity (VC), 2.18 L; %vital capacity (%VC), 75.2%; forced expiratory volume in one second ($FEV_{1.0}$), 1.51 L; and forced expiratory volume % in one second ($FEV_{1.0\%}$), 67.9%. Reversibility of airway obstruction was not noted in the patient.

A chest X-ray revealed cystic changes with an air-fluid level localized in the right lower lung field (Fig. 1A). The chest CT scan on admission showed complex cystic lesions with an air-fluid level in the right lower lobe, and diffuse centrilobular nodules in the whole lobe of the lung (Fig. 2A). On flexible bronchoscopy examination, sputum and bronchoalveolar lavage fluid (BALF) cultures revealed methicillin-sensitive *Staphylococcus aureus (S. aureus)* which was sensitive to clarithromycin (the minimal inhibitory concentration is < 2.0 μg/mL). The differential cell counts of BALF obtained from the medial segmental bronchus and the CD 4/8 ratio were as follows: total cell count, 3.77 × 10^5/mL; alveolar macrophages, 2.46 × 10^5 (65.3%); neutrophils, 0.58 × 10^5 (15.4%); lymphocytes 0.73 × 10^5 (19.3%); and CD 4/8 ratio, 1.8. The pathologic examination of transbronchial lung biopsy (TBLB) specimens obtained from the lateral segmental bronchus demonstrated noncaseating granuloma in the alveolar spaces and neutrophil infiltration (Fig. 1B). No acid-fast bacilli were detected by Ziehl-Neelsen staining of TBLB specimens and culture of BALF. An electron microscopic examination of the biopsy specimens obtained from the bronchial mucosa showed deficiency of the inner dynein arm in the cilia (Fig. 1C). Left nasal polyps were detected by CT scan. Based on these findings, we diagnosed the patient with PCD.

Treatment with clarithromycin (400 mg/day) was commenced 2 weeks after admission and was continued for 6 months. As a result of the treatment, there was improvement in the patient's symptoms of productive cough and dyspnea on exertion, and in pulmonary function (VC, 2.59 L; %VC, 87.2%; $FEV_{1.0}$, 2.15 L; and $FEV_{1.0\%}$, 80.1%). In addition, the 6-month chest CT scan revealed that the diffuse nodular shadows and the fluid in cystic lesions were diminished (Fig. 2B), whereas CT angiography demonstrated an aberrant systemic artery arising from the celiac trunk and supplying the cystic mass lesions with systemic blood flow (Fig. 2C). The cystic lesions were located in the normal lobe and lacked their own pleural covering.

These results indicated that this patient, diagnosed with PCD, was also affected by ILS. A right lower lobectomy and closure of the anomalous systemic artery was performed by video-assisted thoracic surgery. The aberrant artery arising from the celiac trunk, and penetrating the right lower lobe, was detected in the right pulmonary ligament. After isolation and cutting of the aberrant artery, a right lower lobectomy was performed.

The diagnosis of ILS with PCD was based on the macroscopic and microscopic appearance of specimens obtained from the patient's resected lung that showed multiple cystic lesions without pleural covering and an aberrant artery penetrating the right lower lobe (Fig. 3A,B).

At present, 3 months after the surgery, the patient is free from respiratory symptoms such as dyspnea and cough.

3. Discussion

We report the case of a patient with PCD and ILS treated with long-term macrolides that improved her lower respiratory tract infection. Whereas ILS should be resected due to potential complications including hemoptysis, recurrent pneumonia, and congestive heart failure [7–9], a standard treatment for recurrent respiratory infections associated with PCD has not been defined [10]. In regard to the perioperative management of ILS, because the

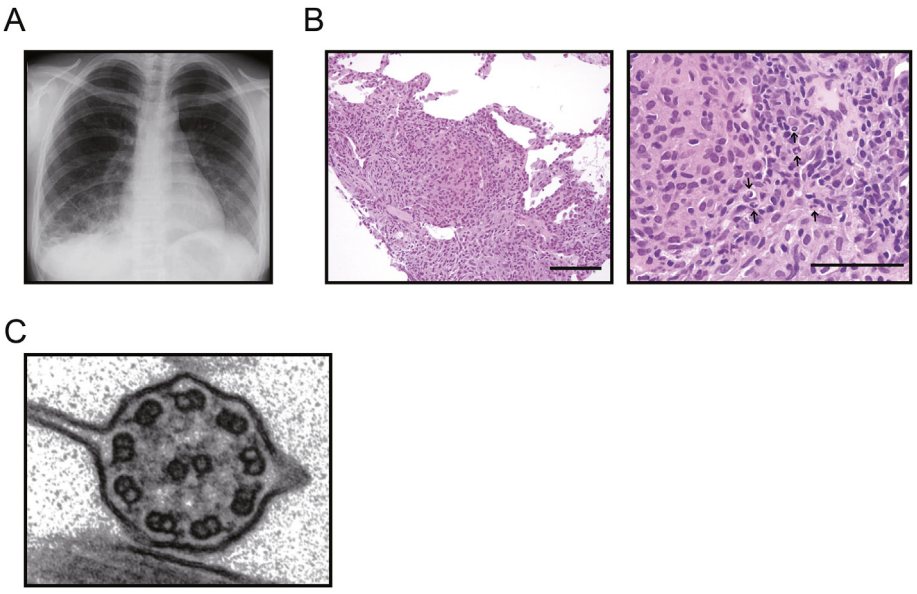

Fig. 1. Chest X-ray on admission, and light microscopic and electron microscopic examination of transbronchial lung biopsy specimens of the patient, a 15-yr-old female nonsmoker. (A) Chest X-ray shows cystic changes with an air-fluid level localized in the right lower lung field. (B) Light microscopic examination of the transbronchial lung biopsy specimen. Noncaseating granuloma in the alveolar space (left panel) and neutrophil infiltrations (arrowheads, right panel) are observed. Hematoxylin and eosin staining. Scale bars: 50 μm. (C) Electron microscopic examination of transbronchial lung biopsy specimens. The cross-section of cilia shows the absence of inner dynein arms.

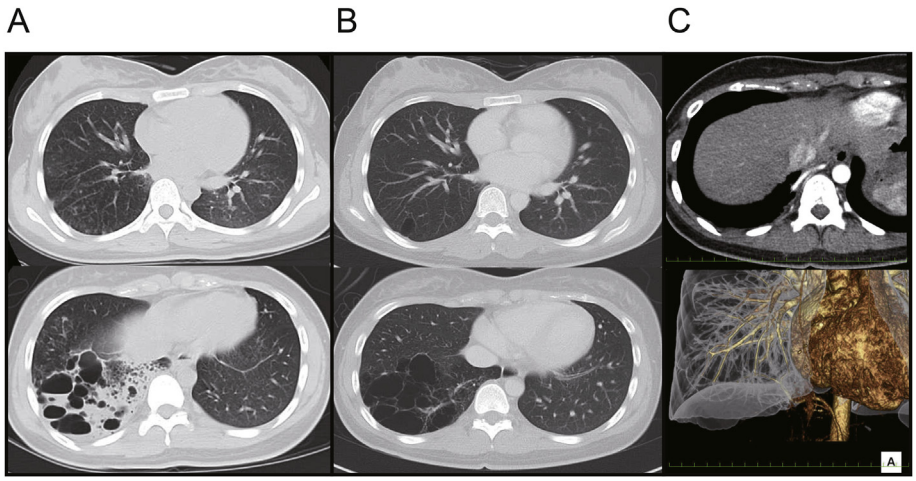

Fig. 2. High-resolution CT of the thorax and CT angiography. (A) Chest CT on admission. The chest CT shows complex cystic lesions with a high air-fluid level in the right lower lobe and diffuse nodular shadows in the whole lobe of the lung. (B) Chest CT after 6-month administration of clarithromycin. Reductions in both diffuse nodular shadows and the fluid in the cystic lesions are observed. (C) CT angiography after 6-month administration of clarithromycin. The CT angiography demonstrates an aberrant systemic artery arising from the celiac trunk and supplying the cystic mass lesions with systemic blood flow.

presence of a respiratory tract infection is related to adverse respiratory events perioperatively, the control of the respiratory infection is essential [11,12]. In the present case, we observed that long-term macrolide administration was useful for the management of the lower respiratory tract infection of a patient with PCD and ILS.

The appearance of cystic changes is a feature of both PCD and BPS including ILS [13,14]. With regard to the cause of cystic changes in the right lower lobe in this case, we concluded that the cystic changes in the right lower lobe were due to BPS, not due to PCD, because of the absence of the connections of cystic lesions to bronchioles in the gross appearance of the resected right lower lobe and the confinement of the cystic changes in the right lower lobe.

Bronchiectasis is a relatively frequent complication of lower respiratory tract infection and is one of the common features of PCD detected by chest CT. The presence of bronchiectasis in pediatric PCD patients has been reported to be approximately 56%–73% [15]. In regard to the absence of bronchiectasis in our 15-year-old patient, we considered the possibility that the degree of recurrent airway infections in PCD patients may be related to the type of ciliary defect. Chilvers et al. reported different ultrastructural defects responsible for ciliary malfunction. While the mean ciliary beat frequency of healthy children was found to be 12.8/sec, the mean ciliary beat frequencies were 8.1, 2.3, and 0.8 in patients with an isolated inner dynein arm defect, isolated outer dynein arm defect, and combined defects of inner and outer arms, respectively [16]. Mucociliary clearance is a critical determinant of the host airway defense against infection in PCD patients [17], and the clearance is dependent on ciliary beat frequency [18]; thus, in PCD patients with an isolated inner dynein arm defect, the degree and incidence of bronchiectasis may be less severe and less frequent compared to PCD patients with another type of ciliary defect.

Although a standard clinical approach to treatment of recurrent respiratory tract infection in PCD patients has not been defined, the use of antibiotic therapy against the most frequently isolated agents such as *S. aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* has been a common and effective treatment [19]. In the present patient, we observed the considerable effectiveness of clarithromycin against chronic lower respiratory infections. The reasons for the successful treatment of the patient are thought to be as follows: first, *S. aureus* detected in the airway was sensitive to clarithromycin (the minimal inhibitory concentration is < 2.0 μg/mL). Second, macrolides including clarithromycin have the mechanisms of inhibition of mucus secretion [20] and the production of proinflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) by suppressing the transcription factor nuclear factor-kappa B (NF-κB) [21]. The long-term administration of clarithromycin has been reported as an empirically effective treatment for respiratory tract infection in patients with PCD and has been expected to have antimicrobial and

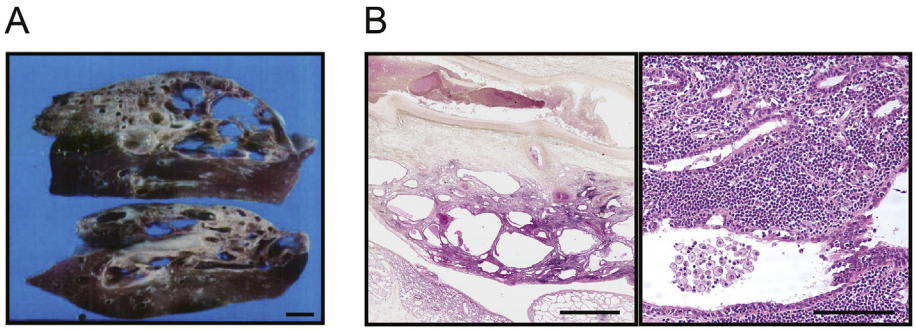

Fig. 3. The pathology of the resected lung specimens. (A) Gross appearance of the resected right lower lobe. Cut sections show multiple cystic lesions without pleural covering and an aberrant artery penetrating the right lower lobe. Bar scale: 10 mm. (B) Microscopic appearance of the resected right lower lobe. The multiple cystic lesions are located in the normal lobe and lacked their own pleural covering, and an aberrant artery was found in the cystic lesion (left panel, bar scale = 5 mm). The resected lung exhibited extensive infiltrations of inflammatory cells in the wall of the cystic lesion (right panel; bar scale = 200 μm).

immune-modulating functions that reduce inflammatory cytokines in the respiratory tract [22]. Furthermore, Kido et al. reported different ultrastructural defects responsible for clinical and radiological improvements provided by clarithromycin treatment [23]. In that study, the patients with only an inner dynein arm defect had a good response to clarithromycin treatment, but patients with defects of inner and outer dynein arms showed no response. The specific inner dynein arm defect of the cilia may also be the contributing factor for the high sensitivity to clarithromycin treatment in our patient.

Because of potentially serious late complications, including fungal infection [24], massive hemoptysis [4], cardiovascular problems [5], and recurrent respiratory tract infection, the surgical resection of ILS is recommended [6,7]. Due to the association of this surgery with adverse respiratory events, including airway obstruction, sustained cough, and oxygen desaturation (SpO_2 < 95%), the control and prevention of respiratory tract infection before the operation is essential [11,12]. In our patient, clarithromycin was useful for the chronic respiratory infection.

With regard to the histopathological findings of the TBLB specimen, we detected noncaseating granuloma formation with neutrophil infiltration in the alveolar spaces. Ziehl-Neelsen staining detected no acid-fast bacilli in the TBLB specimen, and the acid-fast culture of her sputum and BALF were also negative. Although we could not identify the pathogen, the noncaseating granuloma formation in this TBLB specimen might be reflect the chronic lower respiratory infection other than acid-fast bacilli. In regard to the differential diagnosis of sarcoidosis, lymphatic distributions of granulomas that are usually seen in the lung tissues in patients with sarcoidosis, were not detected in this case.

Alopecia universalis, diagnosed when our patient was 1 year old, is characterized by the rapid and total loss of scalp and body hair [25]. Alopecia universalis is the most severe form of alopecia areata caused by autoimmune abnormalities [25]. The genetic mutation for autoimmune polyendocrinopathy syndrome type 1, a monogenic autoimmune syndrome caused by a defect in the autoimmune regulator gene on chromosome 21, is also associated with a 29%–37% prevalence of alopecia areata [26], and a strong association between alopecia areata and trisomy 21 has been observed [27]. Thus, the genes on chromosome 21 may have an important association with the development of alopecia areata. To our knowledge, although some genes — i.e., the human homologous gene *HDHC7* (renamed *DNAH1*) as well as *DNAH5* and *DNAI1*, which are located on 3p21, 5p15–14, and 9p13–21 [28–30], respectively — were reported to be causative for PCD, there has been no report that gene mutations of a PCD patient are linked to chromosome 21. As no genetic test was performed in the present case, the correlation between alopecia universalis and PCD is unclear.

In conclusion, we describe a patient with PCD and ILS who was successfully treated with clarithromycin preoperatively. Although PCD is a rare disease, it is necessary to accumulate evidence of successful and unsuccessful treatments for recurrent respiratory tract infections in PCD patients.

Conflict of interest

The authors declare that there were no conflicts of interest.

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