INTERNAL MEDICINE

□ CASE REPORT □

Primary Ciliary Dyskinesia that Responded to Long-Term, Low-Dose Clarithromycin

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Abstract

A 46-year-old man was referred to our hospital with hemoptysis. He had been diagnosed with chronic sinusitis since childhood, but had received no treatment. Chest CT showed a diffuse centrilobular granular shadow and thickened bronchial walls. Otitis media and decreased spermatic motor ability were identified. In addition, electron microscopy of a biopsy specimen of the nasal mucosa showed a deficiency of inner dynein. Based on these clinical findings, primary ciliary dyskinesia (PCD) was diagnosed and successfully treated with long-term, low-dose clarithromycin. Although the effects of macrolide therapy remain controversial, long-term treatment with low-dose clarithromycin might confer clinical benefits upon patients with PCD.

Key words: clarithromycin, immotile cilia syndrome, macrolide, primary ciliary dyskinesia

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Introduction

Primary ciliary dyskinesia (PCD) is a genetic condition associated with abnormal ciliary structure and function that was originally described as immotile cilia syndrome (1). The clinical manifestations of PCD include chronic bronchitis, bronchiectasis, chronic sinusitis, chronic otitis media from infancy and male infertility. Bronchiectasis and pulmonary fibrosis can lead to severe pulmonary dysfunction and death unless excessive and/or abnormal secretions are eliminated (2). However, a standardized treatment for PCD and the means by which to correct the ciliary dysfunction have not been defined, and most recommendations have been extrapolated from those for cystic fibrosis (CF) (3, 4). Here, we describe a patient with PCD in which pulmonary disease was improved by long-term, low-dose treatment with the 14-membered macrolide, clarithromycin.

Case Report

A 46-year-old Japanese man was referred to our hospital for further examination due to hemoptysis. He had been admitted to another hospital 1 month previously with fever and hemoptysis. Antimicrobial therapy and bronchial artery embolization improved these symptoms. He had been diagnosed with chronic sinusitis since childhood, but had received no treatment. A productive cough and occasional hemosputum had persisted since high school. He was not married and had no children.

A physical examination upon admission revealed a body temperature of 37.0℃, blood pressure of 116/72 mmHg and regular pulse of 72 beats/min. Lung auscultation revealed coarse crackles in both lungs. Laboratory findings were: white blood cell count, 5,100/μL; hemoglobin, 11.4 g/dL; cold agglutinin, ×512; mycoplasmal antibody, below ×40 and immunoglobulin-A, 946 mg/dL. Arterial blood gas analysis while breathing room air showed mild hypoxia and hypercapnia (pH 7.406; $PaCO_2$ 45.2 Torr; PaO_2 71.2 Torr). Sputum microbiology revealed methicillin-sensitive *Staphylococcus aureus*. Pulmonary function tests demonstrated restrictive (%VC 63.5%) and obstructive impairment ($\%FEV_1$ 50.0%). Chest CT showed a diffuse centrilobular granular shadow and thickened bronchial walls (Fig. 1a). Bronchoalveolar lavage fluid contained an increased cell count (7.7×10^5/mL) with high proportions of neutrophils (65.8%) and

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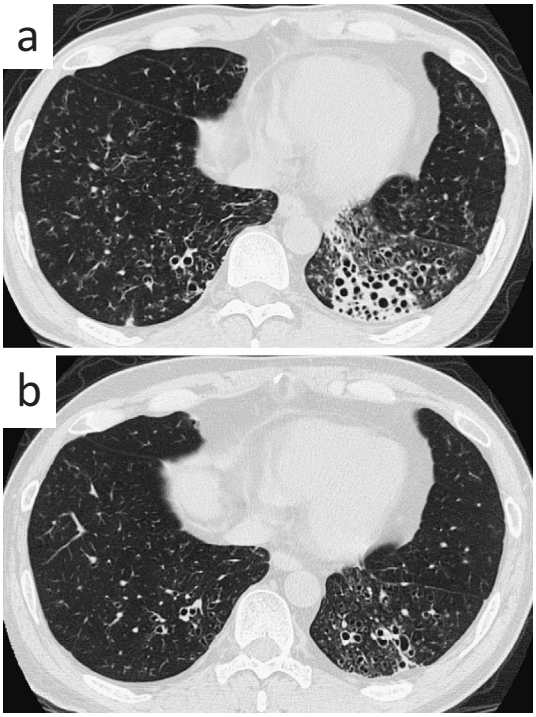

Figure 1. **Chest CT scans upon admission and after clarithromycin treatment. Upon admission (a): centrilobular small nodular shadows and bronchiectasis were evident. After two years of treatment (b): centrilobular small nodular shadows had improved.**

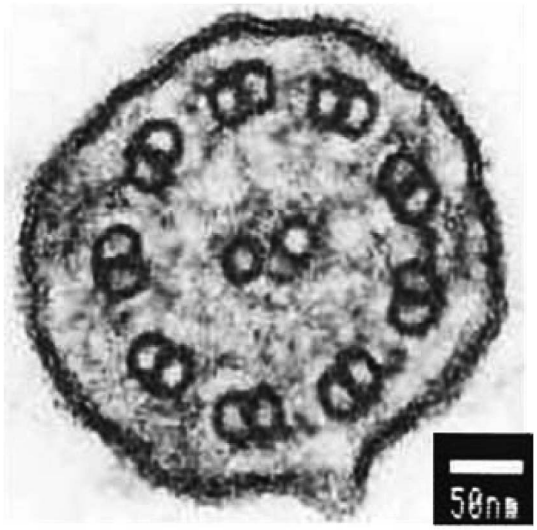

Figure 2. **Cross-section of cilia shows absence of inner dynein arms.**

lymphocytes (26.7%) and a low CD4/CD8 ratio of 0.22. Otitis media with effusion and chronic sinusitis were diagnosed. Spermatic motor ability was also decreased. Electron microscopy of a biopsy specimen from the nasal cavity mucosa revealed a deficiency of inner dynein (Fig. 2). These findings indicated a definitive diagnosis of PCD.

Treatment with clarithromycin (200 mg/day) was started and maintained for two years. No mucoactive drugs or bronchodilators were prescribed. This treatment strategy improved symptoms such as cough and sputum, chest CT findings (Fig. 1b), arterial blood gases (PaO_2 74.3 Torr) and pulmonary function (%VC 63.5%, $\%FEV_1$ 67.8%; Fig. 3). Symptoms of sinusitis such as nasal obstruction and secretion were also improved.

Discussion

Lung involvement in PCD is critical because respiratory failure can develop (5). Respiratory management for PCD consists of regular respiratory monitoring, airway clearance by combinations of physiotherapy and physical exercise, and aggressive treatment of upper and lower airway infections (3). Current PCD treatment mainly follows the recommendations for CF. Although drugs such as mucoactive agents, osmolar agents, ion-transport regulators and antibiotics are administered, no empirical evidence supports their effectiveness against PCD (3, 6).

Long-term, low-dose clarithromycin therapy improved productive cough and chest CT findings in the present patient. Macrolide antibiotics including clarithromycin are used as first-line agents to treat acute bacterial infections such as community-acquired pneumonia (7). However, low-dose clarithromycin is generally considered to be below the levels required to inhibit *Staphylococcus aureus*. In addition, one study in vitro has indicated that clarithromycin does not increase the beat frequency of cilia from rabbit cultured tracheal epithelium (8). Thus, we considered that clarithromycin improves the airway status of PCD patients through modifying the activities of the immune system. The 14-membered macrolide, erythromycin, radically improves the clinical outcomes of patients with diffuse panbronchiolitis (DPB) (9), and this report rekindled interest in the use of macrolides as a potential therapy for other inflammatory airway disorders such as CF, bronchiectasis, asthma, obliterative bronchiolitis, chronic obstructive pulmonary disease and chronic rhinosinusitis (10). The 15-membered macrolide azithromycin improves pulmonary function and reduces the rate of respiratory exacerbations in patients with CF (11). The mechanism of these macrolide actions is thought to be due to immune-modifying effects rather than to direct antimicrobial activity (10). Many immune-modifying effects have been reported (12) but we could not clarify which mechanism caused the favorable response in the present patient. Nonetheless clarithromycin decreased airway mucus secretion, inflammatory cytokine and chemokine production and inflammatory cell accumulation, which indicate improved lung involvement.

Homma et al described 8 patients with Kartagener's syndrome (a subset of PCD), in which 7 and 1 were treated with erythromycin and clarithromycin, respectively. However, sputum volume, pulmonary function tests and radiography images were not affected (13). On the other hand, two reports found that three patients with PCD responded to clarithromycin (14) and that one responded to a combination of clenbuterol hydrochloride and azithromycin but not to

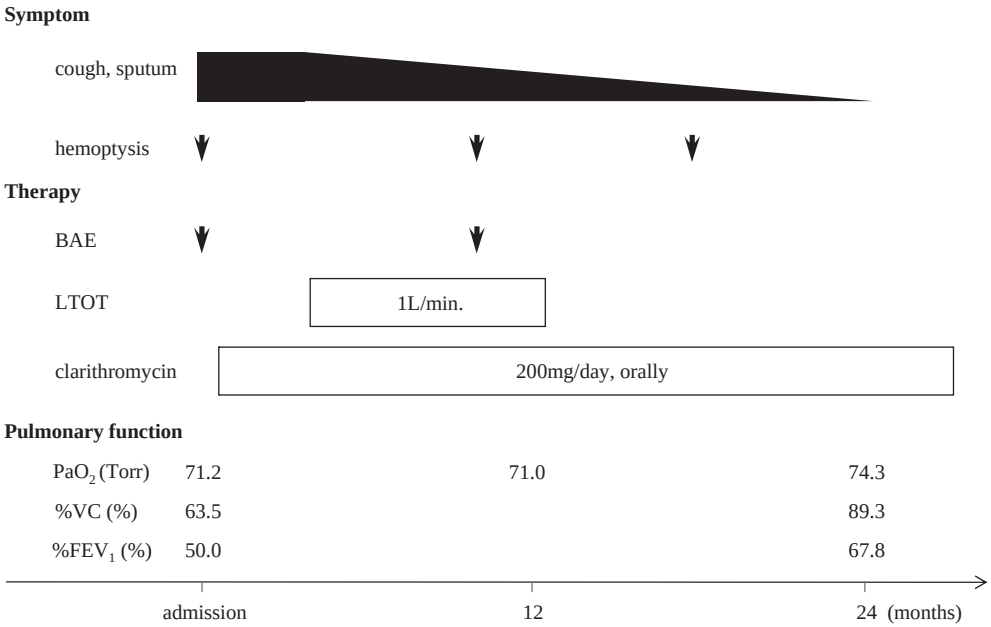

Figure 3. **Clinical course. BAE: bronchial artery embolization, LTOT: long-term oxygen therapy**

clarithromycin (15). Although the reasons for different responses to macrolides remain to be clarified, reports of patients with DPB or related conditions may suggest some possible mechanisms. Some patients with advanced DPB and extensive bronchiectasis or respiratory failure are refractory to macrolide therapy (9), indicating that disease severity might affect response. The present patient did not have severe symptoms or radiological findings, which might have contributed to his favorable response to macrolide therapy. Other reports (16, 17) have demonstrated that the clinical features of human T-cell lymphotrophic virus type 1- or rheumatoid arthritis-associated bronchiolitis are similar to those of DPB, suggesting that multiple disease processes induce the same clinical entity as DPB. However, macrolide therapy improves lung function less effectively in patients with these diseases than in those with DPB (16, 17). Furthermore, PCD is a genetically heterogeneous disorder (18), which might also explain the variation in responses to macrolide therapy among PCD patients.

In conclusion, we describe a patient with PCD pulmonary disease that was successfully treated with long-term and low-dose clarithromycin. Further studies are warranted since very few reports have described the effectiveness of this treatment strategy in PCD patients.

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