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Case Report

The development of diffuse panbronchiolitis during the treatment with long-term, low-dose clarithromycin for chronic sinusitis☆

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ABSTRACT

Diffuse panbronchiolitis (DPB) is a progressive inflammatory airway disease characterized by a chronic cough, copious sputum expectation, dyspnea, and chronic sinusitis. Owing to the long-term treatment of low-dose macrolides, the prognosis has been remarkably improved. However, in some cases, patients are refractory to macrolides, and the subsequent treatment strategies are controversial. We herein present a patient with the onset of DPB during treatment with long-term, low-dose clarithromycin (CAM) for chronic sinusitis who was successfully treated by switching to long-term treatment with normal-dose CAM. We should recognize that DPB may develop in patients with chronic sinusitis despite treatment with a long-term, low-dose macrolide. We also propose that increasing the dose of macrolide may be a useful strategy for treating refractory patients.

1. Introduction

Diffuse panbronchiolitis (DPB) is a clinicopathologic entity characterized by chronic inflammation of the respiratory bronchioles [1]. The clinical features are chronic cough with intermittent purulent sputum and exertional dyspnea. More than 75% of the patients have a history of chronic paranasal sinusitis. DPB had a poor prognosis before 1985 when treatment with several antibiotics and life-saving supportive therapy was used; however, low-dose, long-term treatment with erythromycin (EM) has been shown to improve the symptoms, lung function, and computed tomography findings. Furthermore, the prognosis has been dramatically improved, and it is now recognized as a curable disease [2].

Clarithromycin (CAM) and roxithromycin (ROX), semisynthetic 14-member ring macrolides with modifications in their structures, have also been widely used in the treatment of DPB where EM was ineffective [3]. We herein report a man who developed DPB despite the long-term treatment with low-dose CAM but was successfully treated by increasing the dose of clarithromycin. To our knowledge, there have been no reports of patients who developed DPB during the treatment with long-term, low-dose CAM for chronic sinusitis.

2. Case report

A 37-year-old man presented with a 5-year history of productive cough and dyspnea on exertion. He was a never smoker. At the examination, his body height was 178 cm and body weight 90 kg. At 20 years of age, he had been diagnosed with chronic sinusitis. At 32 years of age, he had suffered from persistent cough and been diagnosed with bronchial asthma or post-nasal drip-induced cough. Inhaled Salmeterol/Fluticasone, carbosysteine and ambroxol were started, but his cough did not improve. At 33 years of age, chest high-resolution CT (HRCT) and pulmonary function tests demonstrated normal findings (Figs. 1, 2). A microbiological test of the sputum revealed the presence of *Streptococcus pneumonia* at $> 1 \times 10^8$ CFU/ml. Treatment with long-term, low-dose CAM was started for chronic sinobronchitis, but his nasal obstruction and productive cough continued. At 35 years of age, primary ciliary dyskinesia was speculated owing to the positive result of saccharin test; however primary ciliary dyskinesia was denied by electron

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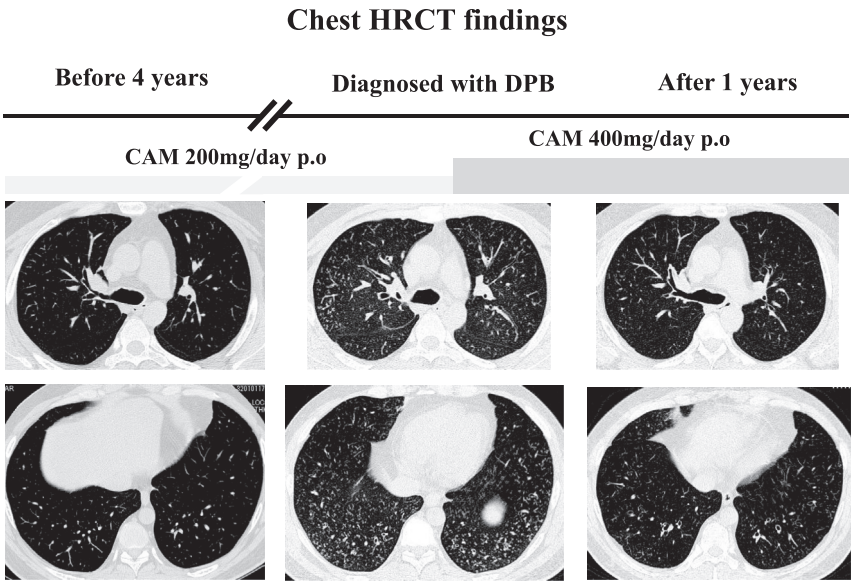

Fig. 1. Chest HRCT findings. At 4-years prior to the diagnosis with DPB, chest HRCT demonstrated normal findings. At the diagnosis, it demonstrated bilateral diffuse centrilobular granular shadows and bronchial wall thickenings. After 1-year treatment by switching to long-term treatment with normal-dose CAM, these abnormal findings decreased.

microscopy of the bronchial walls. Ten month later, dyspnea on exertion appeared, and bilateral diffuse centrilobular granular shadows and bronchial wall thickenings were identified on chest HRCT (Fig. 1). Auscultation revealed coarse crackles and wheezing. A complete blood count (CBC) revealed the following findings: red blood cell count, 597 × 10^4/μL (normal range: 386–492 × 10^4/μL), haemoglobin, 16.0 mg/dl (normal range: 11.6–14.8 mg/dl), white blood cell count, 8770/μL, (normal range: 3300–8600/μL). The serum levels of C-reactive protein (CRP) were 2.83 mg/dl (normal range: ≦0.37 mg/dl), serum level of IgG was 1234 mg/dl (normal range: 861–1747 mg/dl), and the titer of cold haemagglutinin was 256 (normal range: ≦64). Blood human leukocyte antigen typing was negative for the HLABw54 antigen. Arterial blood gases (ABGs) were as follows: pH 7.440, pO_2 55.0 Torr, pCO_2 38.0 Torr, HCO_3 25.8 mEq/l, BE 1.7 mEq/L. A pulmonary function test revealed an obstructive pattern, vital capacity of 4230 ml (86.3% of the predicted value), and FEV_1/FVC ratio of 60.0%. At this point, he was confirmed to have DPB based on the diagnostic criteria proposed by a working group of the Ministry of Health and Welfare of Japan [4]. We attempted to increase the dose of CAM from 200 to 400 mg/day instead of changing to another macrolide because no adverse effects were experienced while the patients was receiving long-term CAM treatment and because CAM (400 mg per day, orally) is recommended in the clinical guidelines on macrolide therapy for DPB (provided by the Ministry of the Health, Labour and Welfare of Japan.) After 1-year treatment, his nasal and respiratory symptoms had recovered, his pO_2 and FEV_1/FVC ratio increased (FEV_1%) (Fig. 2), and the diffuse centrilobular granular shadows and bronchial wall thickening on chest HRCT decreased (Fig. 1).

3. Discussion

DPB is a clinicopathologic entity characterized by chronic inflammation of the respiratory bronchioles [1]. Without treatment with several antibiotics and life-saving supportive therapy, it can progress to bronchiectasis, respiratory failure, and death [5]. In previous decades, the prognosis of DPB was poor, and the reported 10-year survival rate was only 33.2% in 1983; however, the long-term administration of low-dose EM treatment has remarkably improved the prognosis up to 90%. However, low doses of erythromycin were found to be ineffective in advanced cases of DPB [2]. Thus, the early diagnosis and treatment is crucial.

Despite widespread evidences supporting long-term EM treatment, attention must be paid to possible adverse events, such as the prolongation of the QT interval and the subsequent arrhythmia torsades de pointe, gastrointestinal side effects, and hearing loss. If administration must be stopped due to adverse effects, drug interactions, or a loss of efficacy, CAM or ROX is recommended as the second-line option. Intermittent administration of azithromycin (AZM) is also effective for patients in whom the CAM or ROX is ineffective [6]. In the present case, long-term treatment with low-dose CAM was ineffective, but changing to a normal dose (400 mg/day) turned out to be effective.

CAM is well distributed throughout the body and achieves higher concentrations in tissues than in blood. Kikuchi et al. demonstrated that the concentrations of CAM in the alveolar epithelial lining fluid and the alveolar macrophages were increased approximately 14-fold and 30-fold, respectively in comparison to serum [7]. On the other hand, CAM inhibited tumor necrosis factor alpha (TNF-α)-induced mucus secretion, which was accompanied by a reduction in the expression of MAC5AC mRNA in NCI-H292 cells (a human mucoepidermal cell line) as well as nasal epithelial cells in a dose- and time-dependent manner [8]. Furthermore, CAM has been shown to dose-dependently attenuate several cytokines and chemokines, such as TNF-α, IL-1β, IL-6, IL-8, IL-10 and CCL-18, which are produced by alveolar macrophages, in patients with bronchiolitis obliterans organizing pneumonia [9]. Thus, the concentration of CAM in the inflammatory lesions would warrant showing the immunomodulatory effects in patients with DPB. The absorption and metabolism affect the serum and tissue concentrations of CAM. As for the absorption, oral cimetidine prolongs the absorption of CAM as evidenced by the decreased peak concentrations [10]. With regard to the metabolism, enhancement of metabolic clearance by induction of CYP enzyme reduced the plasma level to below the therapeutic level. Inducers of CYP3A4 (eg. Efavirenz, rifampicin, St John's wort) may reduce the plasma concentrations of CAM because CAM is primarily metabolized by CYP3A4. The patient in the present case was not treated

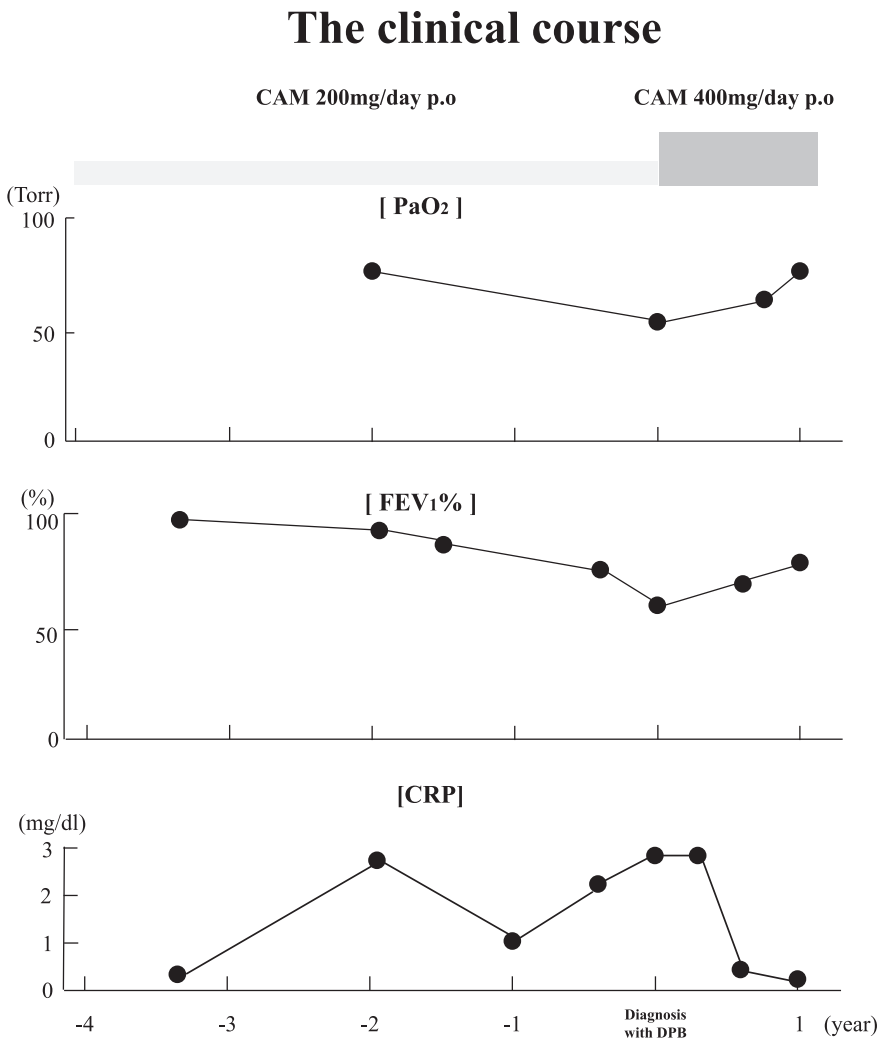

Fig. 2. Time course of PaO_2, $FEV_1\%$ and CRP. The PaO_2 and $FEV_1\%$ were decreased and the serum levels of CRP were slightly elevated despite the long-term treatment with low-dose CAM, whereas these levels recovered after switching to long-term treatment with normal-dose CAM.

with cimetidine or any medicines capable of CYP3A4 induction, We, therefore, hypothesize that the patient's large body size meant that the circulating concentration of CAM was insufficient to exert its activity, and that this was the most likely reason for why the low-dose treatment lost its efficacy.

Macrolide antibiotics are known for their efficacy in treating acute airway infections, but they are also effective anti-inflammatory and immunoregulatory agents [11,12]. The mechanism underlying macrolide therapy for DPB is thought to involve an anti-inflammatory effect rather than an antibacterial effect. Previous reports have shown that EM promotes the downregulation of proinflammatory chemical mediators, such as TNF-α, IL-8, IL-4, and IL-1 [13] and the chemotaxis of polymorphonuclear cells (PMAs) [14,15], lymphocytes and histiocytes [16,17]. Furthermore, EM dose-dependently reduces mucus secretion [18]. CAM and ROX have been reported to exert anti-inflammatory actions and inhibit bronchial secretion, showing equally efficacy against DPB [19]. Kadota et al. reported that the long-term treatment with low-dose CAM is effective and tolerable because of the lower incidence of adverse effects in the gastrointestinal tract than with EM in a prospective open trial [20]. Long-term, low-dose AZM treatment showed efficiency and few adverse effects [21] but was more costly for the treatment of DPB than EM, CAM and ROX.

Occurring in over 75% of patients, chronic sinusitis is exceedingly common and frequently precedes pulmonary symptoms. Before the diagnosis of DPB, patients suffer from years of nasal discharge or congestion, cough, dyspnea, and sputum production [1]. In the preset case, chronic sinusitis was diagnosed at 20 years of age. Afterwards, severe cough and dyspnea on exertion developed at 32 years of age, and he was diagnosed with bronchial asthma or postnasal drip-induced cough. However, his respiratory symptoms did not improve. One year later, the long-term treatment of low-dose CAM was started for the treatment of chromic rhinitis, but his symptoms did not improve. Two years and six months after the administration of CAM, diffuse small nodules appeared on chest HRCT, and DPB was ultimately confirmed. It is impossible to predict the occurrence of DPB in patients suffering from refractory cough when the typical findings of DPB are not apparent on chest imaging.

The administration of macrolides for the treatment of chronic sinusitis has become increasingly common. Patients with chronic sinusitis experience a reduction in mucus hypersecretion, alleviating symptoms such as postnasal drip, and a decrease in the size of nasal polyps, which reduce mechanical obstruction [22–24]. Macrolide therapy also benefits patient refractory to conservative medical management or aggressive surgical intervention. A recent epidemiological study showed a decreasing trend in both the

incidence and prevalence of DPB [25]. The popularization of macrolide treatment for the patients with chronic sinusitis may be related to this decreasing trend in DPB development. However, our case developed DPB during the disease course of chronic sinusitis despite long-term treatment with low-dose CAM.

The frequent use of any antibiotic increases the risk of bacterial resistance emerging. Kadota et al. reported that a four-year study of CAM for the treatment of DPB showed that there were no pulmonary infections caused by resistant bacteria [20]. Although 78% of *Streptococcus pneumoniae* are EM-resistant with cross-resistance to penicillins and fluoroquinolones, macrolides continue to be effective as antimicrobial agents [26]. Furthermore, CAM-related adverse effects on the gastrointestinal tract may be significantly less frequent EM-related ones [27]. We therefore suggest that CAM is more beneficial than EM and that CAM represents a better choice for DPB treatment. However, the prevalence of NTM in sputum was approximately 20%, which was higher than the previous surveillance of NTM in the general Japanese population [28]. CAM monotherapy is a risk factor for the development of CAM-resistant NTM [29,30]. Physicians should repeatedly check the sputum for NTM during treatment with CAM, as CAM is a key drug in the treatment of NTM.

In conclusion, the long-term treatment with low-dose CAM has been widely used in the patients with DPB. When treating patients with a background of chronic sinusitis, we should bear in mind that DPB may develop during the disease course despite the long-term treatment with low-dose CAM. For patients who develop refractive DPB while receiving long-term, low-dose CAM treatment, increasing the CAM dose may be an effective alternative to switching to other macrolides.

Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

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