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Letter to the Editor

Airway clearance ameliorated the control of diffuse panbronchiolitis accompanied by asthma and leukocytoclastic vasculitis

Dear Editor,

Asthma is occasionally complicated with bronchiectasis or diffuse panbronchiolitis (DPB), which makes asthma or asthma-like symptoms difficult to control, potentially owing to subclinical infection or bacterial colonization.¹ Here, we present a case of difficult-to-treat asthma comorbid with DPB or protracted bacterial bronchiolitis that was resistant to macrolide therapy and resulted in cutaneous leukocytoclastic vasculitis (CLV). All conditions dramatically improved after the induction of Acapella®, an oscillating positive expiratory device, which facilitates airway clearance.

A 21-year-old non-smoker woman who developed asthma at 5 years of age was treated with ICSs, LABAs, and leukotriene receptor antagonists until 18 years of age, when she suffered from pneumococcal pneumonia and acute sinusitis. These acute infections were successfully treated with antibiotics; however, productive cough and mild sinusitis persisted. Former doctors diagnosed the patient with co-occurrence of DPB based on the symptoms, signs, and chest computed tomography (CT) findings that satisfied the following three major criteria: persistent cough, sputum, and exertional dyspnea; past history of recurrent chronic sinusitis; bilateral diffuse small nodular shadows on a plain chest radiograph or centrilobular nodular shadows on the chest CT images; and at least two of the following three minor criteria: coarse crackles; FEV₁/forced vital capacity (FVC) <70% and partial pressure of arterial oxygen <80 mmHg; cold agglutinin titer ≥64 as proposed by the Ministry of Health and Welfare of Japan (MHLW).² Laboratory results showed a white blood cell (WBC) count of 6030/μL (eosinophils 9.5%), C-reactive protein (CRP) level of 1.5 mg/dL, total IgE of 721 IU/mL with multiple sensitization to inhaled allergens, including house dust mites, cedar, *Aspergillus*, and *Alternaria*, titer of cold agglutinin of 128, and negative result for anti-neutrophil cytoplasmic autoantibodies. Pulmonary function tests revealed FEV₁ of 2.22 L (72% of predicted) and FVC of 2.81 L (81% of predicted). *Pseudomonas aeruginosa* was cultured, and prominent neutrophilic inflammation was observed in the sputum. Low-dose macrolide therapy with erythromycin (EM) or clarithromycin, which had been prescribed to the patient from 18 years of age, failed to improve her symptoms. However, omalizumab slightly reduced productive cough. At 20 years of age, palpable purpura and edema appeared with pain in both legs, leading to the diagnosis of CLV based on skin biopsy.

One year later, she was referred to our hospital. In the first examination, wheezes, coarse crackles, and squawk were auscultated

bilaterally. Percutaneous oxygen saturation (SpO₂) was 93% on room air. Chest CT showed an increase in centrilobular nodules and bronchiectatic changes (Fig. 1). Laboratory findings and pulmonary functions were as follows: WBC, 9730/μL (eosinophils 2.6%); total IgE, 306 IU/mL; CRP, 0.8 mg/dL; normal serum IgG, IgA, and IgM levels; negative for precipitins and specific IgG antibody to *Aspergillus fumigatus*; exhaled nitric oxide, 7 ppb; FEV₁, 2.13 L (70% of predicted); and FVC, 2.57 L (75% of predicted). *P. aeruginosa* and *Haemophilus parainfluenzae* were cultured, and prominent neutrophilic inflammation was observed in the sputum. New and old lesions of palpable purpura, petechiae, and edema extending from the thighs to the foot (Fig. 2) were observed under treatment with external steroid and diaphenylsulfone. Re-biopsy was performed from the purpuric lesion on the left lower leg that showed infiltration of the lymphocytes and neutrophils around the blood vessels in the superficial dermis without eosinophilic infiltration. We observed nuclear debris deposits in the surrounding stroma, swollen vascular endothelium, and extravasated erythrocytes (Fig. 2).

We speculated that chronic inflammation caused by bacterial colonization in the lower airways might have triggered CLV; therefore, Acapella® was introduced to facilitate airway clearance, and tiotropium mist was introduced at the same time. Further, 1 month after the regular use of Acapella® twice daily, which she preferred to tiotropium mist, productive cough decreased and symptoms of CLV were ameliorated. ICS doses were reduced gradually: fluticasone furoate/vilanterol (FF/VI) 200 μg daily to budesonide/formoterol (BUD/FM 160) twice daily. Additionally, 12 months after the first visit, all conditions significantly improved (Fig. 1): no wheezes or squawk; SpO₂, 99%; FEV₁, 2.66 L (90% of predicted); and FVC, 3.21 L (96% of predicted). Medications against CLV were discontinued. Six months later, sputum culture turned negative, and Acapella® was only necessary once every 2 days. Despite being in a good condition, she showed mild airway hypersensitivity to inhaled methacholine, and sputum cytology revealed 10% eosinophils with 90% neutrophils, although later sputum cytology showed prominent neutrophils again. Therefore, omalizumab and BUD/FM once daily with other anti-asthma medications were continued.

Considering DPB in the differential diagnosis or overlapping with asthma is important^{3–6} because clinical manifestations of DPB, such as productive cough, dyspnea, crackles, and wheezes, mimic those of asthma, and low-dose macrolide is a key therapy against these conditions. Unfortunately, however, this patient benefitted little from macrolide therapy and developed CLV. Because CLV is occasionally complicated with chronic lower airway infections,⁷ we introduced Acapella® to facilitate airway clearance, which improved all conditions remarkably and enabled reducing

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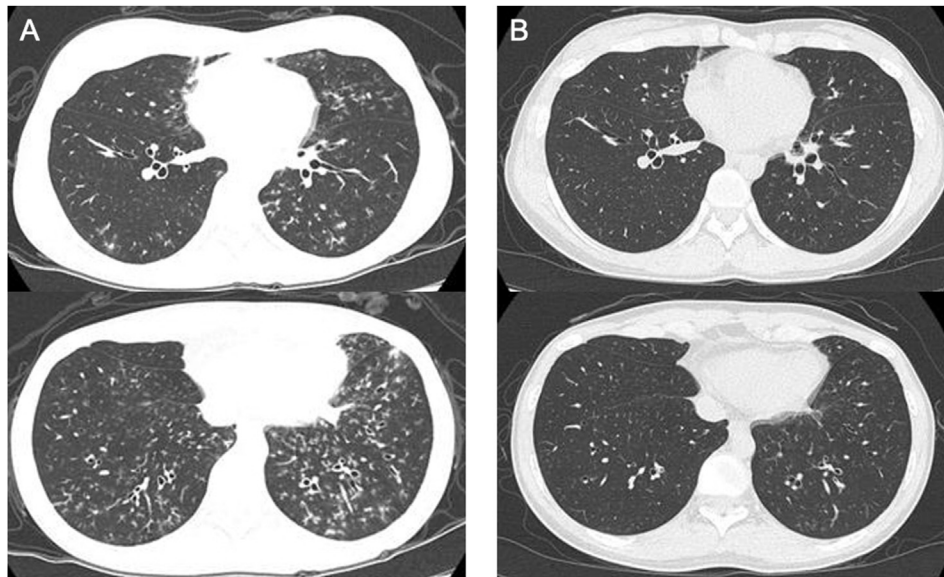


Fig. 1. A) Chest CT on the first visit to our hospital. B) CT showing improvements after 12 months.

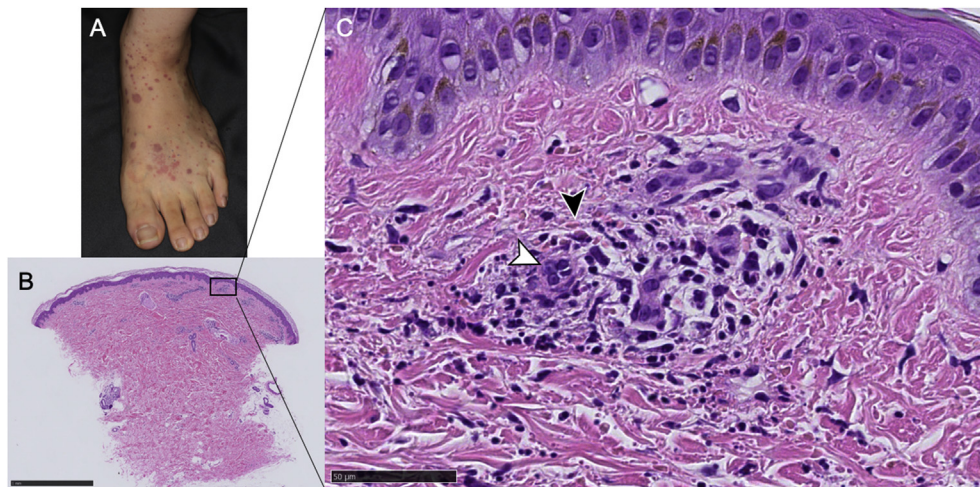


Fig. 2. A) Palpable purpura on the left foot. B) Low power view of hematoxylin and eosin stained skin biopsy from the purpuric lesion. C) High power view shows infiltration of the lymphocytes and neutrophils around the blood vessels with nuclear debris deposits in the surrounding stroma, swollen vascular endothelium (arrow white), and extravasated erythrocytes (arrow black).

ICS doses. The pathogenesis of CLV is poorly understood, but activated neutrophils due to chronic sub-clinical infections in the lower airways release cytokines and chemokines, along with free oxygen radicals, leading to vessel wall destruction.⁸ We speculated that a decrease in bacterial load and cytokines via improved airway clearance may have led to the remission of vasculitis.

The diagnosis of DPB was definite in this case, while satisfying the major and minor criteria proposed by the MHLW. Cystic fibrosis, which is a rare disease in Japan, was excluded because of absence of gastrointestinal symptoms or no family history. Meanwhile, the resolution of DPB merely through improvement of airway clearance and/or reduction of ICS doses was unexpected. Although we did not perform pathological examination, we speculated that protracted bacterial bronchitis⁹ or bronchiolitis might be the main feature of this case.

The presence of asthma in this patient could be argued. The lack of a history of chronic sinusitis with productive cough in her childhood may support the speculation that DPB/protracted bacterial

bronchiolitis had overlapped with preexisting atopic asthma. Furthermore, mild airway hypersensitivity and the presence of airway eosinophilia, albeit transient, may support the persistence of asthma. Previous cases of DPB–asthma overlap focused on a shift from neutrophilic/Th1 to eosinophilic/Th2 inflammation after macrolide therapy.^{3,4} In one case, respiratory symptoms and FEV₁ deteriorated despite successful resolution of radiologic abnormalities with macrolide therapy, which ameliorated with reduction in sputum eosinophil counts after administration of ICS.⁴ Meanwhile, sputum eosinophilia, a hallmark of asthma and robust target for ICS treatment could be observed and permissible in some cases of DPB alone; patients with DPB, who clinically presented with severe asthma but well responded to macrolide treatment while reducing ICS doses, initially showed sputum eosinophilia (2%–42%). Thus, making a diagnosis of DPB–asthma overlap or DPB/protracted bacterial bronchiolitis alone is important, but control of subclinical infections and monitoring eosinophils would be more important in these indistinguishable conditions. Cohort studies are warranted

to elucidate the role and management of airway eosinophilia in these conditions.

Conflict of interest

The authors have no conflict of interest to declare.

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