Centrilobular Opacities in the Asthmatic Lung Successfully Treated with Inhaled Ciclesonide and Tiotropium: With Assessment of Alveolar Nitric Oxide Levels

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ABSTRACT

Background: Despite the fact that bronchioles are involved in asthma, there have been limited asthmatic cases showing marked centrilobular opacities on computed tomography (CT) chest scans. Systemic corticosteroids have been administered in such cases, but the efficacy of extra-fine particle inhaled corticosteroids has not been assessed.

Case Summary: A previously healthy 64-year-old man presented with a four-month history of productive cough and progressive dyspnea despite a combination therapy with inhaled salmeterol (50 μg bid) and fluticasone (500 μg bid), sustained-release theophylline, and pranlukast because of suspicion of asthma. Physical examination revealed wheezing at the end of forced expiration. High resolution CT chest scan showed diffuse centrilobular opacities, bronchiectatic changes, and bronchial wall thickening. Transbronchial lung biopsy, bronchoalveolar lavage fluid, and transbronchial biopsy all showed predominant eosinophil infiltrates, suggesting that eosinophilic inflammation across the entire airway tree caused the abnormal CT findings. Alveolar fraction of exhaled nitric oxide level, a non-invasive marker of eosinophilic peripheral airway inflammation, was also elevated. Because he refused systemic corticosteroids, inhaled ciclesonide (400 μg bid) and inhaled tiotropium were added on to his current medication under careful observation. His symptoms, pulmonary function and CT findings promptly improved, and he had fully recovered at follow-up.

Discussion: Extra-fine particle inhaled corticosteroids could be an alternative approach in centrilobular opacities caused by eosinophilic peripheral airway inflammation.

KEY WORDS
alveolar nitric oxide, asthma, centrilobular opacities, eosinophilic bronchiolitis, extra-fine particle inhaled corticosteroids

INTRODUCTION

In 2001, Takayanagi et al. have proposed a new disease entity of eosinophilic bronchiolitis that shows centrilobular opacities on computed tomography (CT) scans,1 which was followed by several similar reports of eosinophilic bronchiolitis with or without asthma.2 Accumulation of such cases may provide deeper understanding of links between peripheral airway dysfunction and eosinophilic inflammation. In the previous cases, however, details of peripheral airway function and its responses to treatment have been poorly described. In addition, the efficacy of extra-fine particle inhaled corticosteroids that may allow better access to the peripheral airways has not been assessed. We here report that the addition of an...
A previously healthy 64-year-old man presented with a four-month history of productive cough and progressive dyspnea despite a combination therapy with inhaled salmeterol (50 μg) and fluticasone (500 μg bid), sustained-release theophylline, and pranlukast because of suspicion of asthma. These medications did not sufficiently improve his symptoms. He had a smoking history of 20 pack-years, but had quit smoking before. He had experienced allergic rhinitis symptoms during Japanese cedar pollen season for 8 years. Physical examination revealed wheezing at the end of forced expiration. Blood tests showed eosinophilia (13.1%), elevated IgE (630 IU/mL), and mild hypoxemia while breathing room air (PaO2 = 66.5 mmHg). He was sensitized to multiple inhaled allergens. Other serological tests showed no remarkable findings. Pulmonary function tests revealed severe airflow limitation (pre- and post- bronchodilator FEV1 of 0.88 L and 0.89 L, respectively), inhaled allergens. Other serological tests showed no remarkable findings. Pulmonary function tests revealed severe airflow limitation (pre- and post- bronchodilator FEV1 of 0.88 L and 0.89 L, respectively), inhaled allergens. Other serological tests showed no remarkable findings.

**CLINICAL SUMMARY**

A previously healthy 64-year-old man presented with a four-month history of productive cough and progressive dyspnea despite a combination therapy with inhaled salmeterol (50 μg) and fluticasone (500 μg bid), sustained-release theophylline, and pranlukast because of suspicion of asthma. These medications did not sufficiently improve his symptoms. He had a smoking history of 20 pack-years, but had quit smoking before. He had experienced allergic rhinitis symptoms during Japanese cedar pollen season for 8 years. Physical examination revealed wheezing at the end of forced expiration. Blood tests showed eosinophilia (13.1%), elevated IgE (630 IU/mL), and mild hypoxemia while breathing room air (PaO2 = 66.5 mmHg). He was sensitized to multiple inhaled allergens. Other serological tests showed no remarkable findings. Pulmonary function tests revealed severe airflow limitation (pre- and post- bronchodilator FEV1 of 0.88 L and 0.89 L, respectively), increased residual volume and increased slope of the alveolar plateau during single-breath nitrogen washout test (ΔN2) (Table 1). The alternative indices of small airway caliber and reactance measured using the impulse oscillometry system (MasterScreen™; Erich Jaeger, Hoechberg, Germany) were also impaired; The frequency dependence of respiratory resistance (Rrs) between 5 and 20 Hz, i.e., Rrs5-Rrs20, was 0.25 kPa · L·1·s; the reactance at 5 Hz, i.e., Xrs 5, was -0.34 kPa · L·1·s; and the reactance area, i.e., the integral of Xrs from 5 Hz to the resonant frequency AX was 3.39 kPa · L·1. On admission methacholine challenge test was not performed because of the severe airflow limitation. Sputum showed predominant eosinophils and yielded no growth of microorganisms, including fungi and *Mycobacteria*.

High resolution CT chest scan showed diffuse centrilobular or tree-in-bud opacities, bronchiectatic changes, and bronchial wall thickening, but no airspace consolidation or emphysematous changes (Fig. 1a-c). Sinusitis was not observed on a CT scan of the sinuses. The exhaled NO level was measured at three flow rates, 50 ml/s, 100 ml/s, and 200 ml/s, using a chemiluminescence analyzer (NOA280, Sievers, CO, USA), and alveolar fraction of exhaled NO level was determined by a trumpet model with axial diffusion (CNO,TMAD). CNO,TMAD level was numerically higher than median (3.9 ppb) or average (5.5 ppb) of the measured values of 70 patients with stable asthma in our institution. The elevation of CNO,TMAD strongly suggested the presence of eosinophilic inflammation in the peripheral airways.

Transbronchial lung biopsy (TBLB) revealed eosinophilic infiltration into alveolar septa (Fig. 2a), and eosinophils (60%) were predominant in bronchoalveolar lavage fluid (BALF). Transbronchial biopsy obtained at the bifurcation of anterior basal segmental bronchus and lateral basal segmental bronchus of the right lung also showed eosinophil infiltrates, basement membrane thickening, and an increased area of airway smooth muscle (Fig. 2b).

Based on these clinico-pathophysiological findings, we speculated that eosinophilic inflammation associated with asthma might have involved the bronchiolites, which could explain the centrilobular opacities on a CT scan. Because he refused systemic corticosteroids use, inhaled ciclesonide (400 μg bid), an extra-fine particle inhaled corticosteroid, and inhaled tiotropium were added on to his current medication under careful observation. Within 2 weeks, the patient’s symptoms and pulmonary function promptly improved. One year later, he had fully recovered (Ta-
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Table 1 and Fig. 1d, showing improvement of airway impedance; an Rrs5-Rrs20 of 0.03 kPa · L⁻¹ · s, Xrs5 of -0.13 kPa · L⁻¹ · s, and A X of 0.37 kPa · L⁻¹. On subsequent evaluation, he showed airway hyperresponsiveness to inhaled methacholine (Astograph¹⁸; Chest, Tokyo, Japan; Dmin, 10.4 Units).

DISCUSSION

Despite the fact that the bronchioles are involved in asthma⁵ there have been a limited number of cases with asthma or eosinophilic lung disease that showed marked centrilobular opacities on chest CT scans, except for recent reports of eosinophilic bronchiolitis with or without asthma.¹² Here we presented an asthmatic case showing diffuse centrilobular or tree-in-bud opacities on a CT scan that was successfully treated with an extra-fine particle inhaled corticosteroid and an inhaled tiotropium. Although a definitive lesion involving bronchioles was not obtained in this case due to technical issues with the transbronchial approach, the presence of eosinophilic bronchiolitis was highly suspected as eosinophil infiltrates were observed across the entire airway tree (i.e., in TBLB, BALF and bronchial biopsy samples).

To the best of our knowledge, this is the first report showing that the addition of an extra-fine particle inhaled corticosteroid, as well as inhaled tiotropium, was effective for treating asthma with marked centrilobular opacities on a CT scan. We carefully observed the patient’s condition to avoid under-treatment, because previous cases with eosinophilic bronchiolitis with or without asthma consis-tently used medium to high doses of systemic corticosteroids. Previously we have also found that inhaled chlorofluorocarbon-beclomethasone dipropionate alone failed to treat chronic eosinophilic pneumonia.⁶ Despite these concerns, our patient promptly responded to medications without the administration of systemic corticosteroids and did not deteriorate thereafter. The addition of inhaled ciclesonide to the medication may have exerted anti-inflammatory effects, possibly because its particle size was adequately small for it to reach the peripheral airways, but also because of its delivery system. This patient might have had reduced inspiratory flow rates, in which case the use of the aerosol formulation, such as of ciclesonide, may be advantageous over the dry powder formulation. In addition, the increase in the total amount of inhaled corticosteroids may have suppressed the remaining inflammation throughout the airways. The additive effects of inhaled tiotropium should also be acknowledged, since cholinergic tone increases particularly in asthmatics.
Fig. 2 Transbronchial lung biopsy (a) and transbronchial biopsy (b). Arrow heads indicate eosinophil infiltrates.

with moderate to severe disease. Further studies are necessary, since we did not use any placebo control in this case; nonetheless, from the results obtained we can conclude that extra-fine particle inhaled corticosteroids may be an alternative approach for treating eosinophilic peripheral airway inflammation.

Unlike previous reports of eosinophilic bronchiolitis, we have clearly shown physiological abnormalities in the peripheral airways and their responses to treatment. Peripheral airway obstruction and ventilation heterogeneity at baseline as expressed in elevated RV/TLC and ΔN2 were improved in parallel with the improvement of symptoms and CT findings after intensifying the treatment. Moreover we showed improvement of alveolar NO level, a non-invasive marker of eosinophilic peripheral airway inflammation, after intensifying the treatment. Alveolar NO level determined by a two compartment model (CANO) has been used as a non-invasive tool to assess eosinophilic inflammation of peripheral airway/ alveolar regions. Recently corrected models of CANO, i.e., CANO,TMAD that incorporated trumpet shaped airways and axial diffusion have been developed to correct the effect of axial contamination by small airway NO diffusion on CANO. Changes in CANO,TMAD levels in our case may suggest the usefulness of multiple expiratory flow measurements of NO to determine alveolar NO levels particularly when eosinophilic peripheral airway inflammation is suspected.

NO level at an expiratory flow of 50 ml/s (FeNO50) before intensifying the treatment was unexpectedly low (Table 1). The low FeNO50 level can be explained by an elegant simulation model that shows that increased ventilation heterogeneity and predominant NO production in the peripheral airways decreases FeNO50 levels when compared to levels under uniform ventilation and NO production. Indeed, the FeNO50 level paradoxically increased when ventilation heterogeneity was partially resolved.

It was important to determine whether or not this patient had asthma. On admission to the hospital, 200 μg of inhaled salbutamol was administered, but it did not change his FEV1 level. We believe that the reason for this was the dose of salbutamol administered, which was insufficient to be delivered throughout the airways, since his airways were severely obstructed because of inflammation accompanied by airway edema and mucus plugging. After bronchoscopic examination, when the wheezing and dyspnea worsened, 300 μg salbutamol followed by 50 μg nebulized procaterol was administered, and the patient’s condition improved. This may suggest that the airway obstruction in this patient was reversible with bronchodilators. Furthermore, airway hyperresponsiveness to inhaled methacholine, eosinophilic inflammation in the central airway, and partial improvement of symptoms by asthma medication, including sustained-release theophylline and pranlukast, suggest that this patient had asthma.

In conclusion, we have comprehensively reported a rare case of asthma that presented with centrilobular opacities on a CT scan. The presence of eosinophilic peripheral airway inflammation was suspected due to an elevated alveolar NO level, which was confirmed by the findings of TBLB and BALF. Addition of extra-fine particle inhaled corticosteroids may attenuate eosinophilic peripheral airway inflammation.

REFERENCES


