

# A Patient with Bronchial Asthma in Whom Eosinophilic Bronchitis and Bronchiolitis Developed during Treatment

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## ABSTRACT

A 56-year-old woman was referred to our hospital because of dyspnea, wheezing, and a productive cough. Eight years before presentation, bronchial asthma was diagnosed and the patient received inhaled corticosteroids plus antiasthmatic agents (a long-acting inhaled  $\beta_2$ -agonist, leukotriene modifiers, and theophylline). Chest radiography showed small diffuse nodular shadows, and a computed tomographic scan showed thickening of the bronchi and bronchioles, with diffuse centrilobular nodules in both lung fields. A blood test and microscopic examination of the bronchoalveolar fluid revealed marked eosinophilia. Transbronchial lung biopsy and transbronchial biopsy showed eosinophilic bronchitis and bronchiolitis. After treatment with oral prednisolone (40 mg daily) and inhaled corticosteroids, the symptoms, blood eosinophilia, and radiographic findings improved. Recently, several similar cases of eosinophilic bronchiolitis have been reported. Studies of further cases and elucidation of the pathophysiology of eosinophilic bronchiolitis are necessary to establish a concept for this disease and to determine whether it should be classified as a subtype of bronchial asthma or as a distinct entity.

## KEY WORDS

bronchial asthma, bronchiolitis, eosinophilic bronchiolitis, eosinophilic lung disease

## ABBREVIATIONS

TBLB, transbronchial lung biopsy; TBB, transbronchial biopsy; eNO, exhaled nitric oxide concentration; HFA, hydrofluoroalkane; DPB, diffuse panbronchiolitis.

## INTRODUCTION

Eosinophilic lung disease shows diverse pathological characteristics and chest imaging findings. It can be caused by various factors, including parasitic and fungal infections, allergies, drugs, radiation, hazardous materials, smoking, vasculitis, or can be idiopathic. Among potential causes, allergic bronchopulmonary mycosis and allergic granulomatous vasculitis/Churg-Strauss syndrome are also associated with bronchial asthma. In 2001, chronic eosinophilic bronchiolitis was proposed as an atypical eosinophilic lung

disease.<sup>1</sup> Subsequently, similar cases have been accompanied by asthma-like symptoms and dyspnea, suggesting an association with bronchial asthma.<sup>2-5</sup> We describe a case of bronchial asthma that showed diffuse centrilobular granular shadows and airway thickening on computed tomography (CT) of the chest and was diagnosed as eosinophilic bronchitis/bronchiolitis on histopathological examination.

## CLINICAL SUMMARY

The patient was a 56-year-old woman. Her main symptoms were dyspnea, wheezing, and a productive

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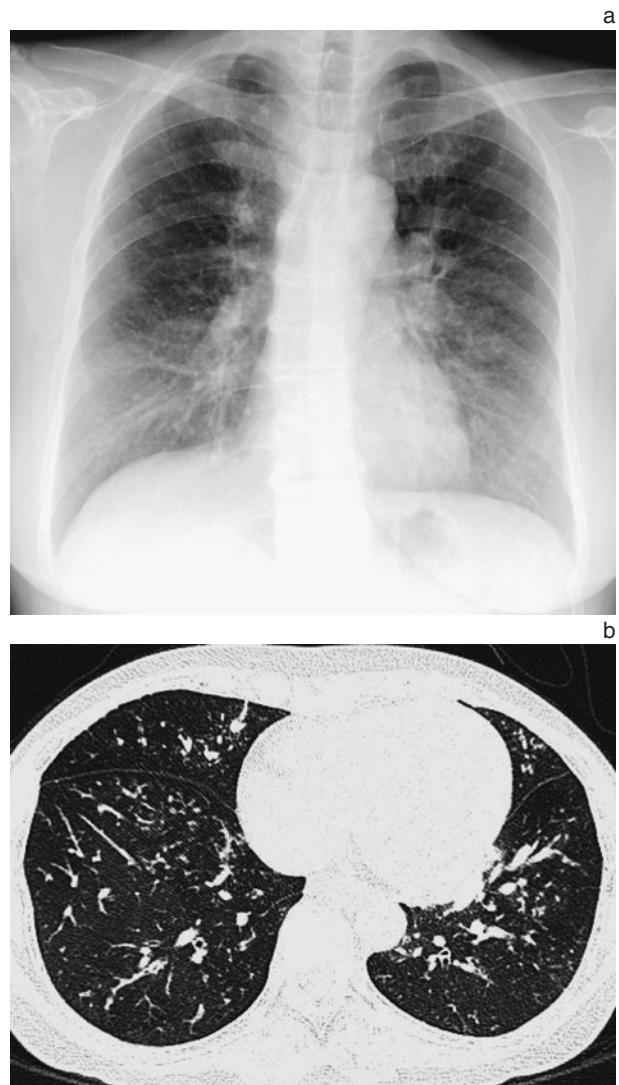
cough. The patient had a history of acute appendicitis at 20 years of age and sinusitis at 52 years. The family history was not relevant to the present disorder. As for lifestyle, the patient did not smoke or drink alcohol. She kept two dogs as pets outside of her home and was employed as an office worker.

Bronchial asthma was diagnosed 8 years previously and the patient had been treated by a local physician. She had been hospitalized 4 times for asthma attacks. Since November 2005, the patient received inhaled corticosteroids, a long-acting inhaled  $\beta_2$ -agonist, leukotriene modifiers, and theophylline in accordance with guidelines for the treatment of asthma.<sup>6</sup> Because the patient had frequent exacerbations, she was referred to our hospital in July 2006.

The physical findings on admission were as follows: height, 155.1 cm; body weight, 57.0 kg; body mass index, 23.7; body temperature, 36.8°C; blood pressure, 120/80 mmHg; pulse rate, 80 beats/minute; respiratory rate, 24 times/minute; and SaO<sub>2</sub>, 94%. The patient's consciousness was clear. Grade III wheezing was present in both lung fields, with no cardiac murmur. The abdomen was flat and soft, with no tenderness. There was no edema in the extremities. The neurological findings were normal.

The results of blood tests were as follows: white cell count,  $8.2 \times 10^9/L$  (neutrophils, 40.9%; eosinophils, 35.4%, lymphocytes, 19.3%; and monocytes, 4.0%); hemoglobin, 13.7 g/dL; hematocrit, 41.1%; platelets,  $329 \times 10^9/L$ ; serum total protein, 7.4 g/dL; serum aspartate aminotransferase, 16 U/L; serum alanine aminotransferase, 10 U/dL; serum lactate dehydrogenase, 190 U/L; C-reactive protein, 0.44 mg/dL; antinuclear antibody titer, 1 : 80; myeloperoxidase antineutrophil cytoplasmic antibody titer, <10 EU; proteinase 3-antineutrophil cytoplasmic antibody titer, <10 EU; and IgE, 411 IU/mL. Anti-SS-A/B antibody, aspergillus antibody, aspergillus-precipitating antibody, and human T-cell leukemia virus type-1 antibody were all negative. Radioallergosorbent testing showed that specific IgE antibodies to house dust, *Dermatophagoides pterynsinus*, aspergillus, candida, alternaria, cedar, ragweed, wormwood, orchard grass, cat dander, dog dander, and moth were negative. Blood gas values while the patient was breathing room air were as follows: pH, 7.43; PaCO<sub>2</sub>, 31.8 Torr; and PaO<sub>2</sub>, 69.8 Torr. Sputum cultures showed normal flora.

The results of lung function tests were as follows: VC, 1.84 L (74.1%); FEV<sub>1</sub>, 0.72 L (35.1%); FEV<sub>1</sub>% (G), 47.4%; and %DLCO, 77.1%. On airway hyperreactivity testing (acetylcholine inhalation test), the PC20 was 2800  $\mu\text{g}/\text{mL}$ . The exhaled nitric oxide concentration (eNO) was 184.4 ppb. The CXR and the HRCT findings on admission are shown in Figure 1. On bronchoscopy the numbers of cells in the bronchoalveolar lavage (BAL) fluid were as follows: total cell count,  $12.6 \times 10^5/\text{mL}$ ; monocytes, 22.9%; neutrophils, 0.4%;

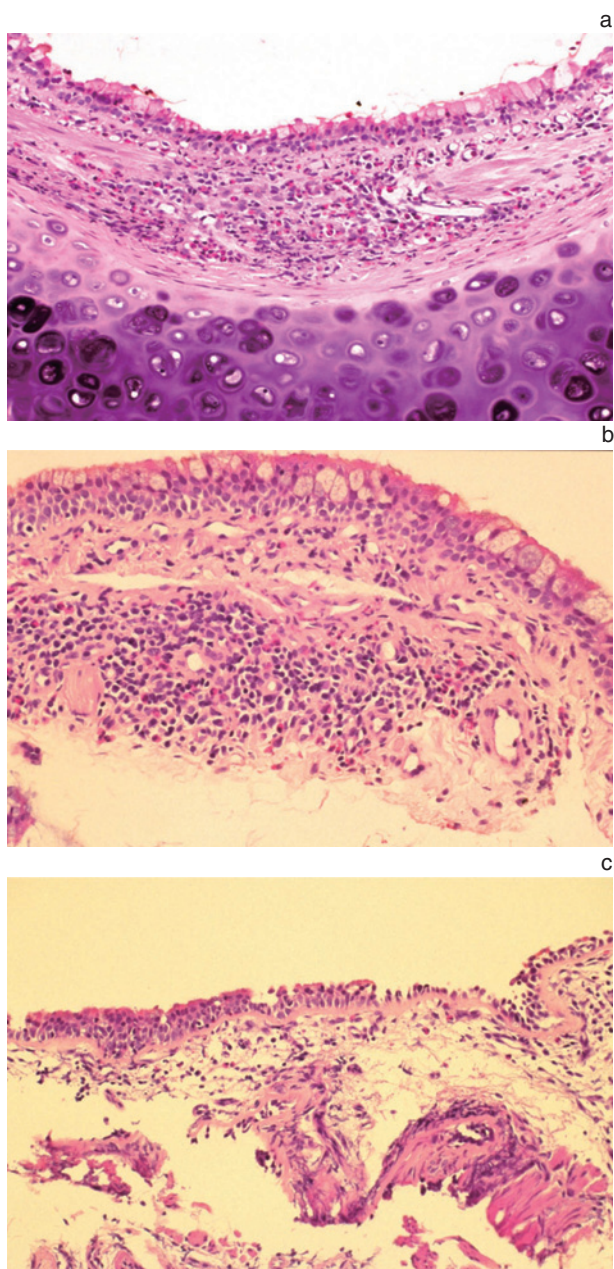


**Fig. 1** a. CXR on admission showed diffuse granular shadows in bilateral lung fields. b. Chest HRCT scan obtained on admission showed diffuse centrilobular nodules in both lung fields in association with thickening of the bronchi and bronchioles.

lymphocytes, 7.4%; and eosinophils, 68.7%. Histopathological findings of transbronchial lung biopsy (TBLB) specimens and transbronchial biopsy (TBB) specimens are shown in Figure 2.

### COURSE AFTER ADMISSION

The patient had symptoms of bronchial asthma such as dyspnea, wheezing, and hypoxemia on admission. Chest imaging studies showed bronchial and bronchiolar lesions. Since the patient had peripheral-blood eosinophilia, a diagnosis of eosinophilic bronchiolitis, recently proposed as a distinct clinical entity, was suspected. Bronchoscopy was performed on the 6th day. There was an increased total cell count in the BAL fluid, and the proportion of eosinophils had risen by



**Fig. 2** Photomicrographs of TBB and TBLB specimen. **a.** Significant infiltration of eosinophil is observed in the bronchial mucosal and submucosal membrane region (HE staining  $\times 100$ ). **b.** Goblet cell metaplasia is observed in the bronchiolar epithelium, and eosinophil/monocyte infiltration is observed in the subepithelial region (HE staining  $\times 200$ ). **c.** Epithelial detachment, basal membrane thickening, and eosinophil/mononuclear lymphocyte infiltration are observed in the membranous bronchiole (HE staining  $\times 200$ ).

68.7%. TBLB and TBB suggested bronchitis/bronchiolitis with eosinophilic infiltration. There was no evidence of allergy to aspergillus or other fungi and no peripheral neuritis or vasculitis. Allergic bron-

chopulmonary mycosis and allergic granulomatous vasculitis were thus unlikely. Since airway hyperreactivity was confirmed on an acetylcholine inhalation test, bronchial asthma associated with eosinophilic bronchiolitis was diagnosed. The patient received fluticasone (400  $\mu\text{g}/\text{d}$ ) since the date of admission, and prednisolone (40  $\text{mg}/\text{d}$ ) was started immediately after bronchoscopy. After starting treatment, symptoms improved dramatically. Dyspnea and wheezing decreased in several days and oxygen inhalation was stopped after 5 days of prednisolone treatment. The peripheral eosinophil count decreased from  $2902 \times 10^6/\text{L}$  to  $47 \times 10^6/\text{L}$  after 7 days of treatment. There was also improvement in the shadows on the chest images, as well as lung function. The eNO level decreased from 184.4 to 42.9 ppb. The dose of prednisolone was tapered, and hydrofluoroalkane (HFA)-beclomethasone (200  $\mu\text{g}/\text{d}$ ) was added to fluticasone. The condition of the patient improved substantially, and she was discharged.

## DISCUSSION

Recently, several cases of eosinophilic bronchiolitis have been reported in Japan (Table 1). Common characteristics include bronchiolitis with eosinophilic infiltration (on imaging studies and histopathological examination), obstructive ventilatory impairment, airway hyperreactivity, and blood and BAL-fluid eosinophilia. Clinically, eosinophilic bronchiolitis must be differentiated from various other diseases associated with eosinophilic infiltration and from various types of bronchiolitis and bronchial asthma. Although the radiographic findings in our patient, who had a history of sinusitis, resembled those in diffuse panbronchiolitis (DPB), the histological findings were not consistent with DPB, which is characterized by accumulations of mononuclear cells (predominantly lymphocytes, plasma cells and foamy histiocytes) in the walls of respiratory bronchioles. The histological evaluation of TBLB specimens such as those obtained in our patient has inherent limitations as compared with lung biopsy specimens obtained surgically, in which the walls of bronchioles can undergo complete microscopic examination. Inhaled steroids alone are not adequately effective in many patients; a moderate dose of oral steroids is usually very effective. However, decreasing the dose of steroids often triggers a recurrence, suggesting that long-term therapy with a maintenance dose of steroids is necessary.

Our patient did not respond to guideline-based treatment for asthma<sup>6</sup> at other clinics. However, the patient showed airway hyperreactivity, and the eNO level had increased to 184.4 ppb at admission.<sup>7</sup> The clinical features and the results of laboratory and histopathological examinations led to a diagnosis of bronchial asthma associated with eosinophilic bronchiolitis. In 5 previously reported cases (Table 1), not including the present one, biopsy specimens of the



**Table 1** Clinical characteristics of patients with EB reported in previous studies, including our patient †

Case	Signs and symptoms	Bronchial asthma	Time to EB onset	Radiologic findings (CT)	Method of biopsy	Therapy	Outcome	Year Author
1 46 M	Dyspnea, wheeze, cough	— (Airway hyper reactivity +)	3 years	Centrilobular nodules Thickening of bronchi, bronchioles	Surgical	Oral PSL 40 mg	Recurrence Dose of PSL decreased	2001 Takayanagi <i>et al</i> <sup>1</sup>
2 23 M	Dyspnea, wheeze, cough	— (Airway hyper reactivity +)	3 months	Centrilobular nodules Thickening of bronchi, bronchioles	Surgical	Oral PSL 30 mg ICS	Recurrence Dose of PSL decreased	2003 Nakagome <i>et al</i> <sup>2</sup>
3 62 F	Dyspnea, cough	+	4 years	Centriacinar nodules Thickening of bronchi, bronchioles	Surgical	mPSL 80 mg d.i.v. Oral PSL, ICS	Recurrence Dose of PSL decreased	2004 Nagata <i>et al</i> <sup>3</sup>
4 50 F	Chest shadow	+	5 years	Centrilobular nodules Bronchiectasis Mucoid impaction	Surgical	Hydrocortisone 300 mg d.i.v. Oral PSL 30 mg	No recurrence	2006 Tsuburai <i>et al</i> <sup>4</sup>
5 42 M	Dyspnea, cough	+	6 months	Centrilobular nodules Thickening of bronchi	Surgical	Oral PSL 30 mg	Recurrence Dose of PSL decreased	2006 Morimoto <i>et al</i> <sup>5</sup>
6 † 56 F	Dyspnea, wheeze, cough	+	8 years	Centrilobular nodules Thickening of bronchi, bronchioles	TBLB	Oral PSL 40 mg ICS	No recurrence	Present case

EB, eosinophilic bronchiolitis; PSL, prednisolone; mPSL, methylprednisolone; ICS, inhaled corticosteroids; d.i.v., drip intravenous infusion.

lung were obtained under video-assisted thoracoscopic guidance. This is a very useful technique for obtaining a sufficient quantity of peripheral lung lobules for histological examination, but is more invasive than bronchoscopic lung biopsy. Fortunately, we could make a diagnosis by bronchoscopic TBLB and TBB. The patient responded to treatment with 40 mg of oral prednisolone and is currently also receiving fluticasone and HFA-beclomethasone (considering delivery to the peripheral airways). The dosage of oral prednisolone was decreased to 2.5 mg on alternative days.

Since the late 1990's, eosinophilic airway inflammation, a cardinal sign of bronchial asthma, has been confirmed in the peripheral as well as the central airways.<sup>8,9</sup> The bronchiolar region may also be involved in asthma.<sup>10</sup> However, cases showing centrilobular granular shadows on chest CT scans have not been studied in detail. Eosinophilic bronchiolitis was first reported in 2001,<sup>1</sup> and several other similar cases were subsequently reported in Japan.<sup>2-5</sup> The present case was introduced because we believe that it satisfies the proposed diagnostic criteria. Studies of additional cases of eosinophilic bronchiolitis are necessary to establish the concept for this disease and to further elucidate its pathophysiology and thereby determine whether eosinophilic bronchiolitis should be classified as a subtype of bronchial asthma or as a distinct entity.

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