Hypereosinophilic Obliterative Bronchiolitis Clinically Mimicking Diffuse Panbronchiolitis: Four-year Follow-up

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Abstract

A 73-year-old man with a known history of asthma presented with dyspnea, worsening wheezing and a productive cough complicated by chronic sinusitis. Chest computed tomography showed bronchial wall thickening with centrilobular nodules and ground-glass opacity in the right lower lobe. Features meeting the diagnostic criteria for diffuse panbronchiolitis (DPB) were identified, and lobectomy confirmed the presence of lung cancer. Over the subsequent four years, the patient’s symptoms worsened. We reevaluated a lung lobe specimen, which showed hypereosinophilic obliterative bronchiolitis (HOB). A transbronchial lung biopsy also indicated bronchitis with eosinophilic infiltration. Our initial diagnosis of DPB was subsequently changed to HOB after four years. We herein describe this case of HOB, which was initially diagnosed as DPB primarily based on high-resolution computed tomography, with a focus on the histopathology and long-term clinical course. This is the first report to document the long-term clinical course of HOB.

Key words: hypereosinophilic obliterative bronchiolitis, follow-up, diffuse panbronchiolitis


Introduction

Eosinophilic lung disease exhibits diverse pathological characteristics. This condition may be idiopathic or caused by various factors, including drugs, infection, allergies, hazardous materials, smoking and vasculitis. Some eosinophilic disorders, such as allergic bronchopulmonary aspergillosis and eosinophilic granulomatosis with polyangiitis, can involve both parenchymal and airway structures (1). Eosinophilic bronchiolitis was first proposed to be an atypical eosinophilic lung disease in 2001 (2). Similar cases have reportedly been accompanied by asthma-like symptoms and exertional breathlessness, suggesting an association with bronchial asthma. Most cases have been documented in Japan (2-4). In 2013, Cordier et al. described several cases of hypereosinophilic obliterative bronchiolitis (HOB) (5) and suggested the following criteria for HOB: (1) a blood eosinophil count of >1G·L⁻¹ and/or bronchoalveolar lavage (BAL) eosinophil count of >25%; (2) persistent airflow obstruction based on lung function tests despite treatment with four to six weeks of inhaled corticosteroid therapy (2,000 μg/day of beclomethasone or equivalent); and (3) lung biopsy findings showing inflammatory eosinophils and/or characteristic direct high-resolution computed tomography (HRCT) features of bronchiolitis (poorly defined centrilobular nodules, branching opacity and a tree-in-bud pattern), similar to the radiological characteristics of diffuse panbronchiolitis (DPB). Due to these similarities, HOB may be underdiagnosed and even misclassified as DPB complicated by bronchial asthma. We herein describe a case of HOB that was initially diagnosed as DPB primarily based on HRCT.

Case Report

A 73-year-old man was referred to our hospital in June 2009 with complaints of dyspnea, worsening wheezing, a productive cough and postnasal discharge. He was an ex-smoker who had smoked one pack a day from 20 to 40 years of age. In 2008, he was diagnosed with bronchial asthma for which he received inhaled corticosteroids and a long-acting beta 2 agonist in 2008, as the local physician considered his symptoms to be asthmatic. HRCT findings revealed ground-glass opacity, and we suspected lung cancer...
and DPB (Fig. 1). We subsequently performed video-assisted left lower lobectomy in September 2009, and a biopsy of the resected specimen confirmed the diagnosis of lung cancer (adenocarcinoma, pT1aN0M0, stage 1A), although we did not evaluate the background lung. HRCT examinations were conducted postoperatively and regularly thereafter.

The patient also exhibited chronic eosinophilic sinusitis, and a diagnosis of chronic eosinophilic sinusitis (CES) was confirmed on a paranasal sinus specimen by an otorhinologist. Diffuse panbronchiolitis was also diagnosed, as the patient met the diagnostic criteria (6), without an evaluation of the pathological criteria. He then received clarithromycin (200 mg per day) for DPB and inhaled corticosteroids for asthma in 2008; however, the symptoms of bronchial asthma, including dyspnea and wheezing, continued to worsen. The patient subsequently experienced an asthma attack and received betamethasone intravenously from a local physician approximately once a month for an entire year. The symptoms of bronchial asthma improved spontaneously due to the steroid treatment.

In September 2013, during routine follow-up, the patient was found to have hypoxemia and admitted to the hospital. The physical examination findings included a height of 155 cm, body weight of 64 kg, temperature of 36.5°C, blood pressure of 140/62 mmHg, pulse rate of 80 beats/min, respiratory rate of 24/min and SaO2 of 92%. His consciousness was clear. Grade 2 wheezing was present in both lung fields, although no peripheral neuropathy was detected. The blood test results were as follows: white cell count=7.3×10^9/L (33.8% neutrophils, 24.9% lymphocytes, 4.2% monocytes and 17.6% eosinophils), hemoglobin=13.0 g/dL, hematocrit=40.1%, platelet count=240×10^9/L, serum aminotransferase=30 U/dL, serum aspartate aminotransferase=56 IU/L, serum lactate dehydrogenase=60 U/L, serum total protein=7.0 g/dL, albumin=4.0 g/dL, blood urea nitrogen=90 mg/dL, serum creatinine=0.84 mg/dL, anti-SSA antibodies= negative, anti-SSB antibodies= negative, myeloperoxidase antineutrophil cytoplasmic antibody titer=<10 EU, proteinase 3-antineutrophil cytoplasmic antibody titer=<10 EU and IgE=467 IU/mL. Radioallergosorbent testing was negative for specific IgE antibodies for house dust mite, Aspergillus, Candida, Alternaria, cedar, ragweed, wormwood, orchard grass, cat dander and moths. A sputum culture showed normal flora. Lung function testing showed a vital capacity of 1.85 L (51.7%), forced vital capacity of 1.85 L (53.2%), forced expiratory volume in 1 second (FEV1) of 0.80 L (28.7%), forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) of 43.2% and peak flow of 2.66 L. A reversibility test was negative.

Follow-up CT scans showed that the centrilobular and branched linear areas of high attenuation had increased in number and size (Fig. 2).

**Course after admission**

We reevaluated a lung lobe specimen obtained in 2009, which provided a diagnosis of HOB. Bronchoscopy was performed in September 2013, and a transbronchial lung biopsy showed features of bronchitis with eosinophilic infiltration, diagnosed as HOB (Fig. 3), which had not changed significantly from the specimen resected in 2009. There was no evidence of allergies to Aspergillus or other fungi. Following bronchoscopy, the patient received prednisolone (40 mg/day), and his symptoms improved significantly. Moreover, the pulmonary function was significantly ameliorated (Table), and follow-up HRCT revealed an improvement in the lung shadows and marked decrease in the number and size of centrilobular and branched linear areas of high attenuation (Fig. 2).
Figure 2. Follow-up CT examinations. (a) The initial CT scan showed centrilobular areas of high attenuation. (b) Four years later, the centrilobular and branched linear areas of high attenuation had increased in both number and size. (c) Following treatment with prednisolone, the peripheral areas of lung attenuation decreased.

Figure 3. Eosinophil infiltrations was observed in the (a) subepithelial regions, (b) alveoli and (c) vessels (Hematoxylin and Eosin staining x200).

Table. The Clinical Course of His Spirometry in Four Years

<table>
<thead>
<tr>
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<th>2009 / Sep</th>
<th>2013 / Sep</th>
<th>2013 / Oct</th>
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<tbody>
<tr>
<td>VC , L</td>
<td>2.64</td>
<td>1.85</td>
<td>2.96</td>
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<td>%VC , %</td>
<td>79.5</td>
<td>89.4</td>
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<td>FVC , L</td>
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<tr>
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<td>FEV1.0 , L</td>
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<td>1.78</td>
</tr>
<tr>
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<tr>
<td>PEF , L</td>
<td>4.65</td>
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<td>5.17</td>
</tr>
</tbody>
</table>

VC: vital capacity, FVC: forced vital capacity, FEV1 / FVC: forced expiratory expiratory volume in 1 second / forced vital capacity, FEV1.0: forced expiratory volume in 1.0 second, PEF: peak expiratory flow

Discussion

To the best of our knowledge, this is the first report to document the long-term clinical course of HOB. In this case, we reevaluated a lung lobe specimen that had been considered to be indicative of typical DPB and subsequently diagnosed the patient with HOB four years after lobectomy. Initially, this case of HOB was diagnosed as DPB primarily based on HRCT.

Akira et al. reported HRCT follow-up findings for DPB in 1993, in which they documented that the follow-up CT scans showed centrilobular areas of high attenuation progressing to dilatation of the proximal airways in some patients in the untreated group (7). DPB is a chronic inflammatory disease of the airways with a high mortality rate despite treatment with a combination of antibiotics and supportive therapies, such as oxygen. In contrast, the administration of macrolides is associated with a significant improvement in the survival rates of patients with DPB (8). However, some DPB patients respond poorly to macrolides, and others exhibit poor mortality due to complications of severe or persistent bronchial asthma. Nevertheless, the pathological characteristics of DPB complicated with bronchial asthma remain unknown.

In some cases of severe or persistent bronchial asthma, obstructive impairment becomes fixed following the use of steroids or bronchodilators. In patients with chronic asthma,
eosinophils in the lung tissue and blood may be increased, with HRCT showing abnormalities in 68-90% of cases (9). The concept of severe or persistent asthma is poorly understood. Cordier et al. suggested defining the characteristics of patients with severe asthma versus some form of as yet not well defined and new concept of bronchiolitis (6).

HOB is considered to be idiopathic and is reported to be a form of chronic eosinophilic sinusitis associated with asthma (3). Cases of eosinophilic bronchiolitis have been reported in Japanese patients with airflow obstruction (2). Treatment with inhaled steroids alone is not adequate in many of these patients, whereas a moderate dose of oral steroids is usually very effective. HRCT findings reveal diffuse defined centrilobular nodules with thickening of the bronchial and bronchiolar walls and mild bronchiectasis, similar to the features of DPB (2).

HOB possesses the characteristics of both DPB and bronchial asthma, and, as a result, some patients with HOB may be misdiagnosed with DPB. Most cases of severe DPB meeting the criteria for diagnosis without evaluating lung specimens pathologically may actually be HOB.

The authors state that they have no Conflict of Interest (COI).

References