INTERNAL MEDICINE

□ CASE REPORT □

Pathologically Confirmed, Early-onset, Severe Chronic Obstructive Pulmonary Disease

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Abstract

A 27-year-old man who had been a smoker since 14 years of age presented with exertional dyspnea. Approximately three years earlier, he had been occupationally been exposed to an organic solvent and felt dyspnea during its use. He later developed severe dyspnea and received treatment for asthma. He had no relevant family history. Chest auscultation revealed decreased breath sounds without rales. Spirometry and high-resolution computed tomography scans suggested a diagnosis of chronic obstructive pulmonary disease (COPD). Video-assisted thoracoscopic surgery performed to obtain a pathological diagnosis confirmed the presence of centrilobular emphysema. High susceptibility, smoking from an early age and organic solvent exposure may have caused early-onset COPD in this case.

Key words: COPD, emphysema, early onset

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Introduction

Chronic obstructive pulmonary disease (COPD) is a representative chronic inflammatory disorder of the lungs that generally develops in the elderly in association with cigarette smoking (1). Physiologically, it is characterized by airflow limitation that is not fully reversible. Early onset COPD is defined as disease onset before the age of 50 years, irrespective of smoking history (2). Severe disease is further defined as dyspnea higher than Fletcher Hugh Jones (FHJ) class II and a forced expiratory volume in one second (FEV_1) <50%. The case of a patient with early-onset, severe COPD who developed COPD before the age of 30 is presented. In addition to a history of smoking from an early age, occupational gas exposure may have been associated with the development of COPD in this case.

Case Report

A 27-year-old man visited our hospital with FHJ class III dyspnea. He had no history of low birth weight or severe infectious or allergic diseases in childhood. His father had smoked; however, his mother was not a smoker. He had been healthy and without respiratory problems up to the age of 23. Between 23 and 24 years of age, he first felt dyspnea during use of an organic solvent for his interior decorating business. While at work at the age of 24, severe dyspnea occurred and the patient was admitted to the hospital. Following a routine examination, the dyspnea subsided for the most part and he was discharged from the hospital, even though the cause of the dyspnea remained unknown. Since then, the dyspnea has persisted. The patient consulted various family physicians and was treated for bronchial asthma without showing any significant improvement. Ultimately, he visited our institute. He had smoked 20 cigarettes/day since the age of 14; however, he quit smoking at the age of 26. He had neither a personal nor a family history of respiratory disorders. He had a good build; however, he was slightly lean (body mass index: 18.9 kg/m^2). He had tachypnea along with tachycardia. He had a barrel chest and diminished respiratory sounds without rales accompanied by hyper-resonance on percussion. Cardiac and abdominal examinations showed no abnormalities, and leg edema was ab-

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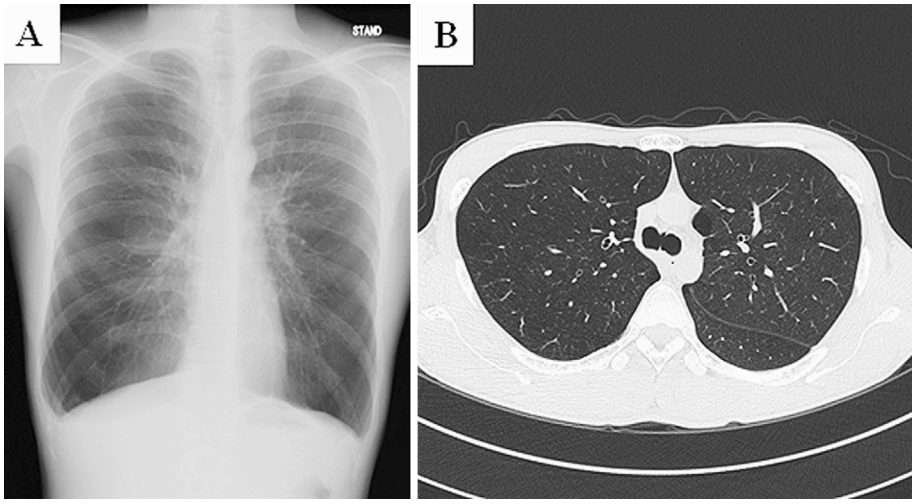

Figure 1. **Posterior-anterior chest radiograph (A) and high-resolution computed tomography (HRCT) of the thorax (B). Chest radiograph showed hyperinflated lung fields with a low-lying diaphragm and a tear drop heart. HRCT showed diffuse low attenuation areas throughout the lung fields.**

Table. **Pulmonary Function Test Results**

Age (years)	27 (at admission)	28	29
VC (L)	3.42	2.00	1.59
%VC	81.8	48.5	38.8
$FEV_{1.0}$ (L)	0.97	0.55	0.59
$FEV_{1.0}$ %	28.8	31.6	38.8
% $FEV_{1.0}$	24.5	14.2	15.4
FRC (L)	4.81	4.52	4.84
RV (L)	3.26	3.88	4.35
RV/TLC (%)	48.2	65.0	71.7
DLco (mL/min/mmHg)	15.99	9.92	7.25
%DLco	62.4	41.2	30.0
DLco/VA (mL/min/mmHg/L)	2.92	2.08	1.51
%DLco/VA	51.0	36.3	26.4

VC: vital capacity, $FEV_{1.0}$: forced expiratory volume in one second, FRC: functional residual capacity, RV: residual volume, TLC; total lung capacity, DLco: carbon monoxide diffusing capacity, VA: alveolar volume

sent. The results of a full blood count and biochemical tests were within normal limits. The serum α1 anti-trypsin level was 148 mg/dL (normal range 94-150 mg/d) determined with nephelometry (SRL Inc., Tokyo, Japan). An arterial blood gas analysis revealed a pH of 7.40, a PaO_2 of 75.1 Torr and a $PaCO_2$ of 40 Torr while breathing room air. A posterior-anterior chest radiograph showed hyperinflated lung fields with a low-lying diaphragm and a tear drop heart (Fig. 1A). High-resolution computed tomography (HRCT) of the thorax showed diffuse low attenuation areas throughout the lung fields (Fig. 1B). Echocardiography did not show any pulmonary hypertension. Pulmonary perfusion and ventilation scintigraphy showed diffuse matched defects, especially in the right lower lobe. Postbronchodilator spirometry results indicated the presence of a severe airflow limitation and a reduced carbon monoxide transfer coefficient, as shown in Table. To determine whether the airflow limitation was reversible, systemic corticosteroids (prednisolone: 30 mg/day) were administered for two weeks; however, the postbronchodilator $FEV_{1.0}$ remained low (960 mL), thus indicating that the airflow limitation was fixed.

Since the patient was too young to develop COPD, video-assisted thoracoscopic surgery was performed from the right S2 to obtain pulmonary tissue for pathological examination in order to exclude other diseases, including bronchiolitis obliterans. No pulmonary cystic diseases, including pulmonary Langerhans cell histiocytosis and Birt-Hogg-Dubé syndrome, were found on a histopathological examination of the obtained pulmonary tissue. Although smoking-associated desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis (RB) were scattered in some areas, marked centrilobular emphysematous changes were predominantly observed, in accordance with the CT findings (Fig. 2). Given these findings, the patient was diagnosed with early-onset, severe COPD, and treatment with inhaled corticosteroids in addition to a long-acting β2 agonist (Adoair diskus®, GlaxoSmithKline, Tokyo, Japan) and an inhaled long-acting muscarinic antagonist (Spiriva®, Nippon Boehringer Ingelheim, Tokyo, Japan) was initiated in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Nonetheless, the airflow limitation and dyspnea continued to rapidly progress, as shown in Table. Currently, the patient is on long-term oxygen therapy and is registered as a recipient for lung transplantation.

Discussion

Smoking is the most significant risk factor for the development of COPD, and the onset of COPD generally occurs in the 6th to 8th decades of life (1). Meanwhile, early-onset pulmonary emphysema is defined as disease onset before the age of 50, irrespective of smoking history. Although the exact prevalence of early-onset COPD has yet to be deter-

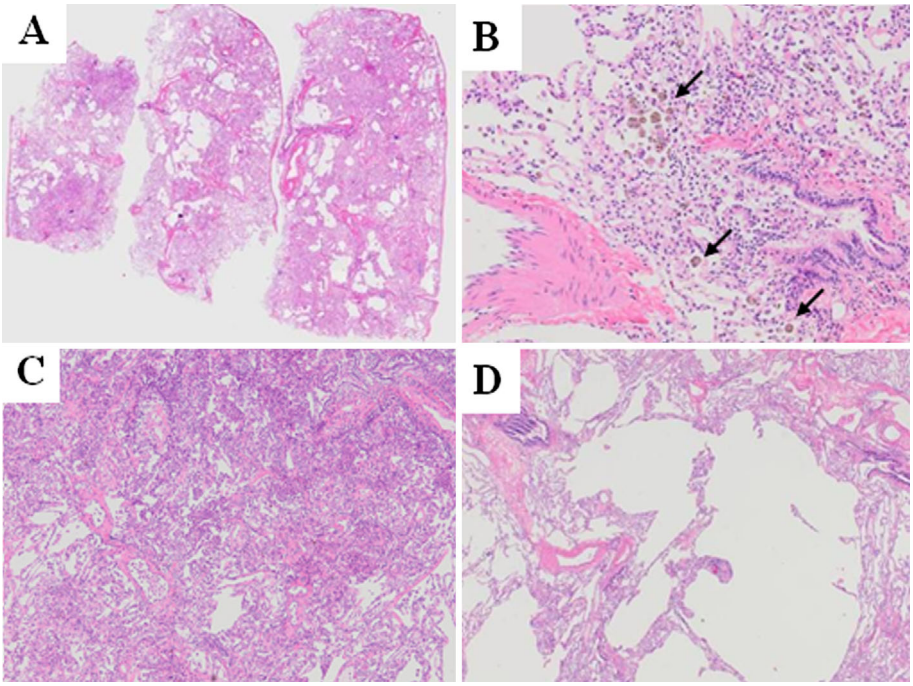

Figure 2. **Lung pathology. (A) Scanning magnification demonstrated centrilobular emphysema. (B) Respiratory bronchiolitis with smoker's macrophages (arrows) was found (×100). (C) Locally, alveolar macrophages were found in the alveolar spaces, suggesting a diagnosis of desquamative interstitial pneumonia (DIP) (×40). (D) Marked centrilobular emphysematous changes were predominantly observed (×20).**

mined, its prevalence in Japan is estimated to be less than 100 patients (2). Furthermore, patients with characteristics similar to those of the present case presenting before the age of 30 are extremely rare, and only a few cases have been reported (3-5). The present patient had begun to smoke cigarettes at 14 years of age and continued to smoke for 12 years.

Besides smoking, a deficiency of alpha-1-antitrypsin is the other established risk factor for COPD. A deficiency of alpha-1-antitrypsin is a rare genetic defect, and the serum level of alpha-1-antitrypsin was normal in the present case.

In addition to smoking, the present patient had another risk factor: occupational exposure. He had begun to use an organic solvent and subsequently developed dyspnea. The relevance of occupational exposure to the development of COPD is controversial (6). Good evidence has been presented linking the inhalation of cadmium fumes to the development of emphysema (7). The pathology of emphysema caused by other types of occupational exposure is less clear. There are two ways in which an occupational agent may act: 1) by promoting the deleterious effects of smoking; or 2) by acting in a manner similar to tobacco smoke. Further examinations excluded the presence of rare causes of emphysema, including Marfan syndrome, Ehlers-Danlos syndrome, intravenous drug abuse and human immunodeficiency virus infection. Ultimately, the diagnosis of COPD was pathologically confirmed following the results of a surgical lung biopsy. Therefore, early initiation of cigarette smoking and concomitant occupational exposure could have played important roles in the development of emphysema in the present case, and the patient may have had a high susceptibility to smoking.

It remains unclear why a subset of patients are so susceptible to smoking and develop COPD at an early age. Milara et al. reported that blood neutrophils are highly activated in patients with early-onset, severe COPD (8). Kelleher et al. detected a gene variant in early-onset COPD patients (9). Therefore, currently unknown biological pathways associated with genetic alterations are involved in the pathogenesis of early-onset COPD. Studies involving additional similar patients could clarify this pathogenesis in the future.

In young patients, chronic airflow limitations are usually diagnosed as bronchial asthma, since bronchial asthma is the most prevalent chronic respiratory disorder. However, in rare cases, a careful examination may show that the airflow limitation is caused by COPD. Since the effects of therapy are limited in established cases of severe COPD, providing education that stresses the significance of not starting to smoke is especially important.

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

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