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Case Report

Respiratory Bronchiolitis-associated Interstitial Lung Disease with Unusual Histopathological Findings

Shinya TOMARI, Hiroto MATSUSE, Hiroshi MUKAE, Shigeru KOHNO

Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, JAPAN

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is a mild inflammatory reaction commonly seen in asymptomatic young male cigarette smokers. This report describes unusual pathological findings in a 63-year-old Japanese female with RB-ILD. She had a 40 pack-year smoking history. Chest computed tomography showed multiple patchy shadows, especially in the right lower lobe. Diagnosis could not be established by bronchoalveolar lavage and transbronchial lung biopsy. Thoracoscopic lung biopsy was performed from right S^5 and S^9, which demonstrated the typical pathological findings of RB-ILD, including the presence of pigmented macrophages within respiratory bronchioles, thickening of alveolar septa by fibrosis, accumulation of intrapulmonary blue bodies and lack of granulomatous changes. Our patient had atypical RB-ILD based on old age at presentation (commonly ~40 years of age), marked fibrosis and presence of numerous blue bodies.

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Introduction

Respiratory bronchiolitis associated interstitial lung disease (RB-ILD) usually occurs in cigarette smokers who are younger than 60 years of age, and the clinical features of this disease include productive cough, dyspnea, abnormal shadows on the chest roentgenogram, and abnormal lung function tests[1−5]. RB-ILD is, however, diagnosed pathologically by the presence of pigmented macrophages within the respiratory bronchioles and adjacent air spaces, associated with mild thickening of the peribronchiolar interstitium[2−5].

We describe here a case of atypical RB-ILD in a middle-aged woman with numerous intrapulmonary blue bodies, accumulation of pigmented macrophages within bronchioles, and thickening of alveolar septa by fibrosis.

Address Correspondence: Hiroto Matsuse, M.D.
Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
TEL: +81-95-849-7273, FAX: +81-95-849-7285
E-mail: hmatsuse@net.nagasaki-u.ac.jp

Case Report

A 63-year-old woman was referred to the outpatient clinic on August 2000 because of an abnormal shadow found on the chest X-ray on a routine medical examination. She complained of cough and sputum for 8 months prior to the visit. Chest computed tomography (CT) revealed that the abnormal shadow was a bone island, but it also showed multiple patchy shadows in both lung fields. For further examination of these multiple shadows, she was transferred to our hospital on September 2000.

She was a habitual smoker (40-pack-year smoking history) but there was no evidence of illicit drug use, allergy, or history of travel to a foreign country. She was a housewife and had kept a dog during the past 25 years. On admission to our hospital, chest auscultation revealed fine crackles at the base of the lung, bilaterally. Arterial blood gas analysis while breathing room air showed PaO_2 of 85.3 Torr, $PaCO_2$ 40.4 Torr, pH 7.472, and SaO_2 of 97.5%. Laboratory tests including leucocyte count, C-reactive protein, autoantibodies to deoxyribonucleic acid (DNA), double stranded DNA, rheumatoid factor, KL-6, surfactant protein-D, angiotensin converting enzyme, lysozyme, cartinoembryonic antigen and IgE were normal. Urinalysis and stool examination were also normal. Pulmonary function tests showed forced vital capacity (FVC) of 2.30 (99.6% pred); forced expiratory volume in one second (FEV1) 1.70 (87.8% pred); and a diffusing capacity for carbon monoxide

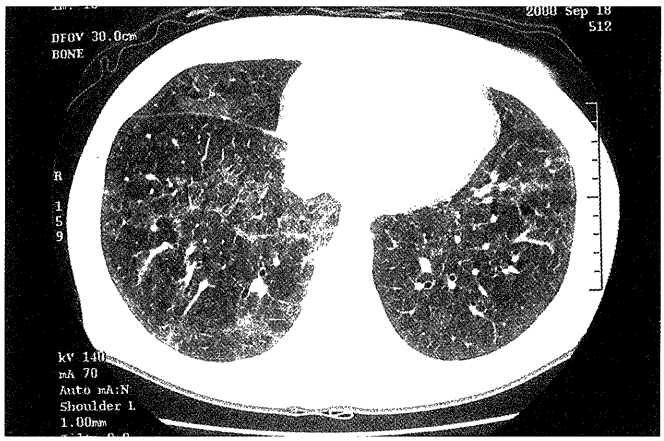

Figure 1. Chest CT scan taken on admission (September 2000), showing multiple ground glass opacities mainly in the middle and lower lobes bilaterally.

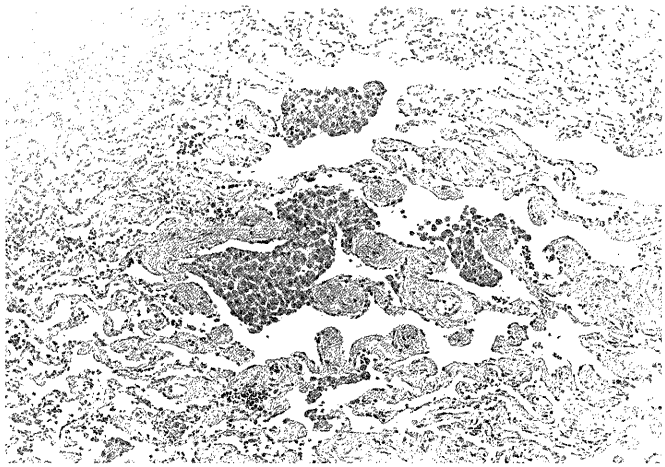

Figure 2. Low magnification of biopsy specimen from rt. S5 and S9 showing a collection of intra-alveolar macrophages in the centre of a bronchiole and alveolar duct, and fibrosis along the alveoli with hyperplasia of smooth muscles. These changes were not diffuse.

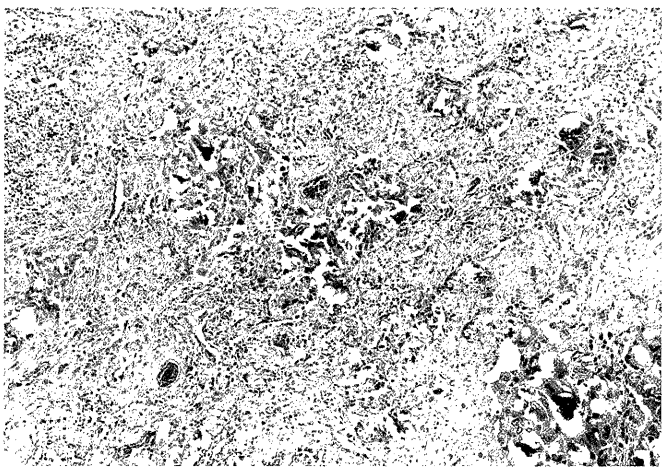

Figure 3. Biopsy specimen from rt. S5 and S9 showing blue bodies with fibrosis (low magnification). Inset: high magnification of blue body.

(DLCO) of 10.55 ml/min/mmHg (69.3% pred).

A chest radiograph revealed a small nodule (a bone island) at the left upper lung field. Chest CT scan showed multiple patchy ground glass opacities, bilaterally, especially in the middle and lower lobes (Fig. 1). On September 28, bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed. Analysis of BAL fluid showed total cell count of 412 cells/μL (differential: macrophages 90.0%, neutrophils 1.6%, lymphocytes 7.8%, and eosinophils 0.7%). These findings were compatible with chronic smoking and were considered to be non-specific. The pathological findings of TBLB showed the presence of blue bodies with no other specific findings. Because of persistence of symptoms and lack of definite diagnosis, on October 13, the patient underwent video-assisted thoracoscopic lung biopsy from rt. S^5 and S^9 to establish the diagnosis. The main pathological findings were the presence of macrophages containing brown or black pigments within the respiratory bronchioles and fibrosis along the alveoli with hyperplasia of smooth muscles. Based on the patchy distribution of the lesion (Fig. 2), the diagnosis of RB-ILD was established. However, this case was particularly different from typical cases of RB-ILD because of the marked fibrosis and the presence of numerous intrapulmonary blue bodies (Fig. 3).

The patient stopped smoking since admission, and her symptoms subsequently subsided. The multiple patchy shadows on chest CT also decreased 3 months later.

Discussion

Niewoehner *et al.*[1] were the first group to describe respiratory-bronchiolitis in autopsies of young cigarette smokers. The pathological findings of RB-ILD include the presence of pigmented macrophages within the respiratory bronchioles and adjacent air spaces associated with mild thickening of the peribronchiolar interstitium[2-5]. Therefore, the diagnosis of this disease cannot be established by chest roentgenogram, CT6, or BAL; rather, either open lung biopsy or video-assisted thoracoscopic lung biopsy is required to establish the diagnosis.

An important differential diagnosis of RB-ILD is desquamative interstitial pneumonia/alveolar macrophage pneumonia (DIP/AMP)[2-6]. Since DIP/AMP shows intrapulmonary pigmented macrophages and interstitial fibrosis, both of which are also commonly observed in RB-ILD, it is often difficult to distinguish RB-ILD from DIP/AMP. Previous reports indicated

that the pathological changes in the lung are restricted to the peribronchiolar areas in RB-ILD, whereas they are more diffuse throughout the alveolar septa of the lobules in DIP/AMP[3]. Another important feature that distinguishes RB-ILD from DIP/AMP is the good prognosis without corticosteroid therapy. In general, DIP/AMP is a progressive disease even in patients receiving treatment (*eg*, corticosteroids)[4]. In contrast, patients with RB-ILD show spontaneous improvement after cessation of smoking without any medications[2]. Thus, the final diagnosis in our case was RB-ILD since pigmented macrophages and interstitial fibrosis were restricted to peribronchiolar areas, and clinical symptoms and signs improved after cessation of smoking.

However, the histopathological findings in our case were different from those of previously reported cases, including the marked fibrosis of centrilobular distribution and the abundant intrapulmonary blue bodies. The latter are intra-alveolar basophilic concretions, and are often observed in DIP/AMP, pneumoconiosis, lung cancer, pulmonary fibrosis and pulmonary talcosis[7-10]. Although the exact aetiology of blue bodies is unknown, the relation between pulmonary inflammation and accumulation of blue bodies has been reported[7], although Kung *et al.*[9] failed to find a significant relation between pulmonary inflammation and intrapulmonary blue bodies. Since no inflammation was detected in the lung biopsy specimen in our case, it is not clear whether the marked fibrosis and numerous blue bodies were associated with pulmonary inflammation prior to the development of the disease. The present case was diagnosed as RB-ILD based on the patchy distribution of the lesion and clinical course. However, marked fibrosis and blue bodies may rather support the diagnosis of DIP/AMP. It is also possible that relatively long smoking history might cause marked fibrosis in the present case. Marked fibrosis may be associated with the presence of blue bodies.

Ryu *et al.*[5] reviewed smoking-related interstitial lung diseases. They indicated that RB-ILD usually occurs in smokers aged around 40 years. However, our patient was 63 years old, thus this case could be possibly labelled as atypical RB-ILD. To our knowledge, this is the first case of RB-ILD with marked pulmonary fibrosis and numerous intrapulmonary blue bodies. Identification of similar cases in the future may allow determination of the exact aetiology of intrapulmonary blue bodies of RB-ILD.

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