Desquamative Interstitial Pneumonia Complicated with IgG4-related Lung Disease

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Abstract

As an idiopathic interstitial pneumonia, desquamative interstitial pneumonia (DIP) is an uncommon form of interstitial lung disease and is considered to be a smoking- or dust inhalation-related interstitial pneumonia in the majority of cases. However, the details regarding immunoglobulin G4 (IgG4)-related lung disease remain unclear and controversial. We herein report the first case of DIP complicated with IgG4-related lung disease. Even if a patient has a smoking history, we emphasize the importance of exploring the association between DIP and IgG4-related lung disease to clarify the pathogenesis of these two disorders.

Key words: IgG4-related respiratory disease, desquamative interstitial pneumonia, autoimmune disorder

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Introduction

Desquamative interstitial pneumonia (DIP) is a rare form of interstitial lung disease first described in adults by Liebow et al. in 1965 (1). This disease has been linked to smoking frequency and carries a relatively favorable prognosis (2). In contrast, IgG4-related disease, which is a newly recognized fibro-inflammatory condition characterized by several features and previously referred to as IgG4-related sclerosing disease or hyper-IgG4 disease, may occur in the lung and involve the alveolar parenchyma, airways, and pleura (3). Various pulmonary manifestations of IgG4-related disease have been reported. Inoue et al. found that the radiologic features of IgG4-related lung disease could be classified into four types: solid nodular, round-shaped ground-glass opacity, alveolar interstitial, and bronchovascular (4). However, if the IgG4-related lesion is present only in the lung, with no lesions in other organs, the reliability of the diagnosis of IgG4-related lung disease is controversial.

To our knowledge, the complication of IgG4-related lung disease with DIP has not been reported previously. We recently encountered a case of DIP with IgG4-positive plasma cell infiltration in the alveolar septa, interlobular septa, and pleura.

Case Report

The patient was a 65-year-old Japanese man in whom an abnormal shadow on chest X-ray had been noted in January 2012 during a routine medical examination. He was later referred to our hospital in September 2014 because of progression of the abnormal shadow. He had no symptoms but was a current smoker (1 pack/day for 46 years), and he had no obvious history of exposure to any dust or extrinsic allergens. Chest auscultation revealed slight bilateral inspiratory fine crackles in the lower zone. The physical examination did not reveal clubbed fingers, Raynaud’s phenomenon, eruptions, swelling, or pain in any joints.

Computed tomography (CT) of the chest showed changes typical of emphysema in the upper lung and bilateral ground-glass opacities appearing with thin-walled cysts pre-
Figure 1. Chest computed tomography showed emphysema and bilateral ground-glass opacities with tiny, thin-wall cysts predominantly in the peripheral area of the lower lung. The tiny, thin-walled cysts formed within the regions of ground-glass opacities without honeycombing.

Figure 2. Histological images. (A) The lesion was characterized by an accumulation of large macrophages in the alveoli with inflammatory cell infiltration in the alveolar septa, pleura, and interlobular septa (Hematoxylin and Eosin (H&E) staining, ×100). (B) The lesion was an accumulation of pigmented eosinophilic macrophages in the alveolar spaces with infiltrating plasma cells and lymphocytes (H&E staining, ×200). (C) IgG immunohistochemical staining revealed that most of the infiltrating plasma cells were positive (×300). (D) IgG4 immunohistochemical staining revealed that approximately 75% of the IgG-positive plasma cells were positive for IgG4 (×300).

Laboratory examinations revealed significantly high serum levels of IgG (2,031 mg/dL), IgG4 (907 mg/dL), and IgE (2,376 IU/mL). The serum KL-6 and C-reactive protein levels were elevated to 756 U/mL and 0.45 mg/dL, respectively. The test results for the autoantibodies examined were all negative. The bronchoalveolar lavage (BAL) fluid contained 5.9×10^5 cells/mL, 85% macrophages, 6% lympho-
cytes, 1% neutrophils, and 8% eosinophils. The respiratory function tests showed evidence of a reduced diffusing capacity with a forced vital capacity (FVC) of 3.6 L (100.8%, % predicted), a forced expiratory volume in 1 second (FEV1) of 2.88 L (101.7%, % predicted), a FEV1/FVC ratio of 77.8%, a diffusing capacity of carbon monoxide (DLCO) of 11.05 mL/min/Torr (76.3%, % predicted), and a DLCO/alveolar volume ratio of 62.2% (% predicted). An 18F-fluorodeoxyglucose (FDG)-PET/CT scan showed slight FDG accumulation only in the pulmonary lesion and subcarinal lymph node. There were no other findings suggestive of IgG4-related disease. At 6 months after the patient had stopped smoking, there was almost no change in the abnormal pulmonary shadow and serum IgG4 and KL-6 levels. Thus, a video-assisted thoracoscopic biopsy of the lung was performed from the right S2 and S9 for diagnostic purposes. Histologically, the lesion was well defined, mainly by the interlobular septum, and showed an accumulation of large eosinophilic macrophages in the alveolar space with inflammatory cell infiltration in the alveolar septa, pleura, and interlobular septa (Fig. 2A, B). This lesion was histologically compatible with DIP. Furthermore, an immunohistochemical examination revealed that most of the infiltrating plasma cells were positive for IgG and IgG4. The ratio of IgG4+ to IgG+ plasma cells was approximately 75% (Fig. 2C, D).

Based on the clinical and histological findings, the patient was diagnosed as having IgG4-related respiratory disease with DIP, and treatment with prednisolone (PSL) 30 mg/day (0.5 mg/kg/day) was started. The PSL dosage was gradually tapered, which led to an improvement in the radiological findings and normalization of the KL-6 and IgG4 levels.

**Discussion**

We experienced a case of DIP complicated with IgG4-related lung disease. DIP is thought to be a smoking-related interstitial pneumonia in the majority of cases (5). The radiological findings include widespread, patchy ground-glass opacifications with a predilection for the lower-lung zone and cyst formation. The main histological feature is the accumulation of numerous pigmented macrophages within most of the distal airspace of the lung (6). Our patient was diagnosed with DIP based on the presence of features compatible with this characterization.

The clinicopathological features of IgG4-related disease in the lung have been gradually clarified over time and usually manifest as inflammatory pseudotumors or interstitial pneumonia (7). Umehara et al. reported the comprehensive diagnostic criteria for IgG4-related disease as follows: a clinical examination showing characteristic diffuse/localized swelling...
or masses in single or multiple organs, elevated serum IgG4 concentrations (≥135 µg/dL), and a histopathological examination showing marked lymphocyte and plasmacyte infiltration and fibrosis, with infiltration of IgG4+ plasma cells and a ratio of IgG4+/IgG- cells of >40% and >10 IgG4+ plasma cells/HPF (8). The features of our case met all of these criteria, and thus the diagnosis of IgG4-related lung disease was reasonable. To our knowledge, the present report presents the first case of IgG4-related lung disease with DIP.

A few cases of IgG4-related interstitial pneumonia have been newly reported (4, 9-12). Bilateral ground-glass opacities were the most common radiological findings, followed by reticular shadows (4, 12). Based on the most recent guidelines on idiopathic pulmonary fibrosis (13), most cases have a non-specific interstitial pneumonia (NSIP) pattern and are inconsistent with the usual interstitial pneumonia (UIP) pattern due to the presence of wide-ranging ground-glass opacities, as in our case. Pathologically, the majority of cases have been NSIP, with only very rare cases of UIP and organizing pneumonia reported (9-12). Although storiform fibrosis and obliterator phlebitis are the major histopathological features of IgG4-related disease were not seen in our case, Ikeda et al. (12) and Deshpande et al. (14) reported that these two features may be inconspicuous or absent in cases of IgG4-related interstitial pneumonia. However, the complication of IgG4-related interstitial pneumonia with DIP has not been reported previously.

The pathogenesis of IgG4-related disease is assumed to be from autoimmune and allergic responses, as serum autoantibodies such as anti-lactoferrin, rheumatoid factor, allergic disorder, and elevated levels of serum IgE are often detected (15, 16). In contrast, DIP is sometimes present in nonsmokers and has been reported in patients with autoimmune disorders (e.g., connective tissue disease, rheumatoid arthritis) (17). Kawabata et al. reported that the association of organ-specific immunological diseases, elevated erythrocyte sedimentation rate and IgG and IgE levels, and high BAL eosinophilia in DIP suggests that the pathogenesis is immunologically mediated as an allergic response (6). We therefore hypothesized that the genesis of DIP in our case might have been associated not only with the patient’s smoking habit, but also IgG4 immunity and/or an allergic response.

In conclusion, we herein described the first known case of DIP complicated with IgG4-related lung disease. Even if a patient has a smoking history, the cause of DIP may not be explained solely by smoking. Although the pathogenesis of these two disorders remains unknown, and they may have been only coincidentally associated in our patient, this is an important consideration, given the undetermined association of DIP and IgG4-related disease. Further studies are needed to clarify the details of these two disorders and their association.

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

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