INTERNAL MEDICINE

□ CASE REPORT □

Desquamative Interstitial Pneumonia (DIP) in a Patient with Rheumatoid Arthritis: Is DIP Associated with Autoimmune Disorders?

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Abstract

Desquamative interstitial pneumonia (DIP) is a rare pattern of diffuse parenchymal lung disease known as one of the idiopathic interstitial pneumonias and is considered to be a smoking- or dust inhalation-related interstitial pneumonia in the majority of cases. This report presents the first case of DIP in which the pulmonary manifestation preceded the onset of rheumatoid arthritis. This case and our review of twenty-four DIP cases (nineteen cases previously-reported from Japan, plus five cases in our departments) indicate the possibility that the DIP pattern is an additional form of diffuse interstitial pneumonia that may develop in association with autoimmune diseases.

Key words: autoimmune disorders, desquamative interstitial pneumonia, rheumatoid arthritis, smoking

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Introduction

Desquamative interstitial pneumonia (DIP) is a rare pattern of diffuse parenchymal lung disease known as one of the idiopathic interstitial pneumonias. DIP was reported first by Liebow et al in 1965 (1). In 1978, it was reported that DIP responds well to steroid therapy resulting in a good prognosis, in comparison to idiopathic pulmonary fibrosis (IPF) (2). The main pathological diagnostic criteria (3) were a homogeneous distribution, large numbers of macrophages accumulated in the airspaces, a small to moderate number of interstitially infiltrating cells with mild to moderate fibrosis and widespread cuboidal cell metaplasia. Although DIP was originally thought by some to represent an early phase of IPF (4), it is now accepted as being a different entity (3, 5, 6) and considered to be a smoking-related interstitial pneumonia in the majority of cases, more closely related to respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (7, 8).

This report presents the first case, to our knowledge, of DIP in which the pulmonary manifestation preceded the onset of rheumatoid arthritis (RA). A review of 24 DIP cases (19 cases previously-reported from Japan, plus 5 cases in this department) indicates that DIP may be associated with a high incidence of autoimmune disorders.

Case Report

In 1998, a 49-year-old Japanese man with a 30-yr smoking history of 2 packs a day was admitted to the hospital because of the identification of bilateral reticular infiltrates on a chest roentgenogram. High-resolution computed tomography (CT) of the chest showed bilateral ground-glass opacities without a honeycomb appearance predominantly in the middle and lower lungs (Fig. 1a). A serum examination showed a positive rheumatoid factor (RF) and antinuclear antigen (ANA) (Table 1). Pulmonary function tests demonstrated neither a restrictive impairment nor airway obstruction, however, a reduced percent diffusion capacity for carbon monoxide (DLCO) was observed (Table 1). No signs or symptoms of arthritis or other collagen-vascular diseases

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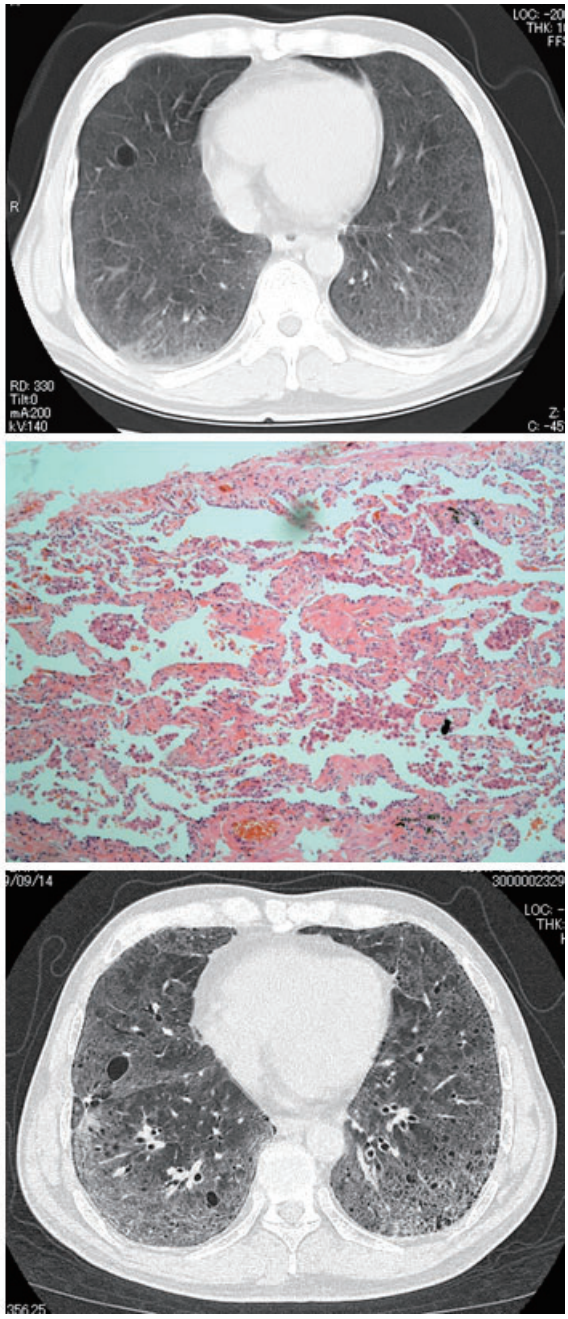

Figure 1. **(a) Chest computed tomography obtained before a surgical lung biopsy, revealing areas of ground-glass opacity in both lower lobes. (b) A surgical lung biopsy specimen (Hematoxylin and Eosin staining, ×100), showing an accumulation of macrophages in the alveoli and cuboidal cell metaplasia with mild interstitial fibrosis. (c) Chest computed tomography obtained 9 years after the lung biopsy, demonstrating areas of diffuse ground-glass opacity and multiple small cystic lesions in both lower lobes.**

were present at that time. A surgical lung biopsy specimen revealed evidence of DIP (Fig. 1b) and RB-ILD. The radiological findings partially improved as a result of giving up smoking, and steroid therapy for a year provided additional efficacy. Thereafter, the patient's condition remained stable without any treatment.

However, in 2007, the patient developed RA at the age of 58, concurrently with an exacerbation of the interstitial pneumonia. The patient had already quit smoking by this time. There was no finger clubbing, but fine crackles were detected in the lower lung fields. Swelling was seen in the finger and bilateral ankle joints without deformation. The serum levels of C-reactive protein, RF, ANA, immunoglobulin (Ig)-G, IgE and KL-6 were higher than those in 1998 (Table 1). An arterial blood gas analysis revealed no hypoxemia, but pulmonary function tests demonstrated a lower percent DLCO than that observed in 1998. Although the anti-cyclic citrullinated peptide antibody and other autoantibodies in the serum were negative, the joint symptoms had been present for over 6 weeks and he met the 1987 Criteria for the Classification of Acute Arthritis of RA as established by the American College of Rheumatology. There were bilateral reticular infiltrates on a chest roentgenogram and homogeneous ground-glass opacities with small cysts on CT (Fig. 1c). A bronchoalveolar lavage (BAL) fluid analysis revealed eosinophilia (9.3%) and neutrophilia (39.0%) without evidence of bacterial infection. These findings suggested the exacerbation of DIP.

Table 1. **Laboratory Findings at the Onset of DIP (1998) and RA (2007)**

	1998	2007
white blood cell count (/μL)	10,770	13,400
neutrophils (%)	68.8	69.9
lymphocytes (%)	21.3	21.3
monocytes (%)	7.0	6.2
eosinophils (%)	2.0	2.2
basophils (%)	0.9	0.4
C-reactive protein (mg/dL)	0.69	4.06
rheumatoid factor (U/mL)	124.6	282.0
antinuclear antigen	×80	×320
immunoglobulin-G (mg/dL)	1,061	2,340
immunoglobulin-E (IU/mL)	188.2	557.0
KL-6 (U/mL)	834	1,210
diffusion capacity for carbon monoxide (%)	55.1	38.0
bronchoalveolar lavage fluid		
macrophages (%)	75.0	50.2
neutrophils (%)	11.0	39.0
lymphocytes (%)	11.0	1.5
eosinophils (%)	3.0	9.3

Discussion

DIP was considered to be a smoking-related interstitial pneumonia in the majority of cases, more closely related to RB-ILD (7, 8). Meanwhile, according to the recent report by Kawabata et al (9), one of the 21 cases that were pa-

thologically diagnosed as having a definite DIP pattern developed systemic lupus erythematosus, while the other 20 cases were considered to be idiopathic. However, of these 20 cases, mild to moderate increases in IgG were seen in 59% and IgE in 45%. Interestingly, positive findings for some kind of autoantibodies (e.g. ANA, RF, ribonucleoprotein, SS-A, centromere) or high serum levels of IgG (1,700-4,440 mg/mL) were observed in 19 cases (79%) by our reviewing 24 pathologically definite DIP cases. These 24 cases included some previously reported cases and cases from our departments (9-11), which were all previously assayed for collagen-vascular diseases. Although Kawabata et al (9) demonstrated BAL eosinophilia and neutrophilia in DIP, this tendency was more noteworthy in the above 19 cases [eosinophil; median: 9.3 (range: 0-51.0)%, neutrophil; 7.2 (0-62.5)%] than the other cases [eosinophil; 1.3 (0-5.8) %, neutrophil; 0.6 (0-56.0)%]. However, that difference was not statistically significant. Mild tissue eosinophilia was observed both in the alveolar wall and lumen in the previous series (2, 9, 12, 13). It was thought that there is active eosinophil emigration caused by unknown intra-alveolar stimuli (9), but the cause of the discrepancy between obvious BAL eosinophilia and slight intra-alveolar eosinophilia is still unknown.

The association of organ-specific immunological diseases, elevated ANA, IgG and IgE levels and BAL eosinophilia/neutrophilia in DIP suggests that the pathogenesis is immunologically mediated with the participation of a type I allergic reaction to some kind of exogenous dust including cigarette smoke, or an immunologically altered state such as an autoimmune disorder. However, there may also be racial differences that could explain these findings, because all of the patients were Japanese descent, as well as those in the report by Kawabata et al (9). Although some patients with DIP show either an improvement or at least no progression without any treatment, steroid therapy provides additional effect and the long-term follow-up data showed continuation of the preserved PaO_2 in recent reports (5, 6). Conversely, this suggests that some autoimmune diseases may not become clinically evident during steroid therapy for a certain period of time, as in the present case, because DIP patients may be treated early with steroids.

In this case, the occurrence of RA was 9 years after the detection of the pulmonary lesion. It has been known for some time that the pulmonary manifestations of collagen-vascular diseases occasionally precede the more typical systemic manifestations by either month or years, especially in RA, systemic lupus erythematosus, and polymyositis/dermatomyositis (14). In a study of 18 patients with RA-related interstitial pneumonia reported by Lee et al (15), interstitial pneumonia preceded the RA diagnosis in three patients by 1.6, 2.5 and 7 years, respectively, whereas, in another three patients, the diagnosis of interstitial pneumonia and RA occurred simultaneously. However, there has so far been no report of RA-related DIP, and therefore precisely how long it takes to recognize RA after the detection of DIP still remains to be elucidated.

In conclusion, this report described the first case of DIP in RA, although these two disorders may have only been coincidentally associated. This case and a review of the previous pertinent case reports, including our own, therefore indicate the possibility that the DIP pattern is an additional form of diffuse interstitial pneumonia that may develop in association with autoimmune diseases, including RA. The ultimate impact of interstitial pneumonia, including DIP, on patients with autoimmune diseases, therefore remains to be clarified.

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