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Case report

Anti-Ku antibody-positive desquamative interstitial pneumonia

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ABSTRACT

A 66-year-old man, an ex-smoker, was referred to our hospital for slightly progressive respiratory symptoms of cough and dyspnea on exertion and chest abnormal shadow. Chest high-resolution computed tomography showed wide-ranging ground-glass attenuation and reticulation with lower lobe predominance. Bronchoalveolar lavage (BAL) fluid revealed a marked increase in lymphocytes (53.0%), and a surgical lung biopsy revealed a pattern of desquamative interstitial pneumonia (DIP) with hyperplasia of the lymphoid follicles. His serum was positive for anti-Ku and anti-SS-A antibodies, and he had signs (such as Raynaud's phenomenon, joint pain, and mechanic's hand) suspicious of connective tissue disease (CTD) although a definitive diagnosis of CTD had not been established. On the basis of the findings in our patient obtained from the serologic domain, BAL, and pathological examination, clinicians should consider the important correlation of DIP with CTD as well as with smoking.

1. Introduction

Desquamative interstitial pneumonia (DIP) is a rare interstitial lung disease characterized by the accumulation of numerous pigmented macrophages within the alveolar airspace and mild to moderate fibrosis of the alveolar septal walls [1,2]. DIP in most patients is caused by smoking and exposure to inorganic particles. On the other hand, some previous reports showed that 10–42% of patients with DIP are never-smokers [3–7]. Interstitial pneumonia is commonly encountered in patients with connective tissue disease (CTD), and a few cases of DIP associated with CTD have been reported [6,7]. Anti-Ku antibody is a rare, wide-spectrum autoantibody that is especially present in scleroderma-polymyositis overlap syndrome, but there are few reports of its association with pathological findings of interstitial lung disease [8,9]. The cause of DIP might be considered as not only smoking but autoimmune response.

2. Case report

The patient was a 66-year-old Japanese man in whom a primary care doctor had noted an abnormal shadow on chest radiography in January 2017. He did not have any pulmonary symptoms. He was later referred to our hospital in July 2017 because of the appearance of cough, dyspnea on exertion, and progression of the abnormal shadow. He was an ex-smoker (1 pack/day for 42 years) and worked in a sewage treatment plant, but he had no obvious history of exposure to dust or drugs. The physical examination did not reveal crackles on chest auscultation or clubbed fingers, eruptions, or dry eyes/mouth, but it did reveal Raynaud's phenomenon, slight finger joint pain, and mechanic's hand.

Chest high-resolution computed tomography (HRCT) revealed emphysema in the upper lung and wide-ranging ground-glass attenuation and reticulation with lower lobe predominance. The ground-glass attenuation was distributed mainly in peripheral areas and partially along the bronchovascular bundles (Fig. 1A and B). Respiratory function testing showed evidence of moderately restrictive ventilation with a forced vital capacity (FVC) of 2.87 L (% predicted, 72.8%), forced expiratory volume in 1 second (FEV_1) of 2.02 L (% predicted, 86.2%), FEV_1/FVC ratio of 70.4%, and reduced diffusing capacity of carbon monoxide of 10.72 mL/min/Torr (% predicted, 58.5%). Laboratory examinations revealed the following: immunoglobulin G (2339 mg/dL), immunoglobulin E (28.1 IU/mL), anti-nuclear antibody positivity (× 40 with a speckled and cytoplasmic pattern), and anti-SS-A antibody (> 240 U/mL), but no other autoantibodies were detected. Renal

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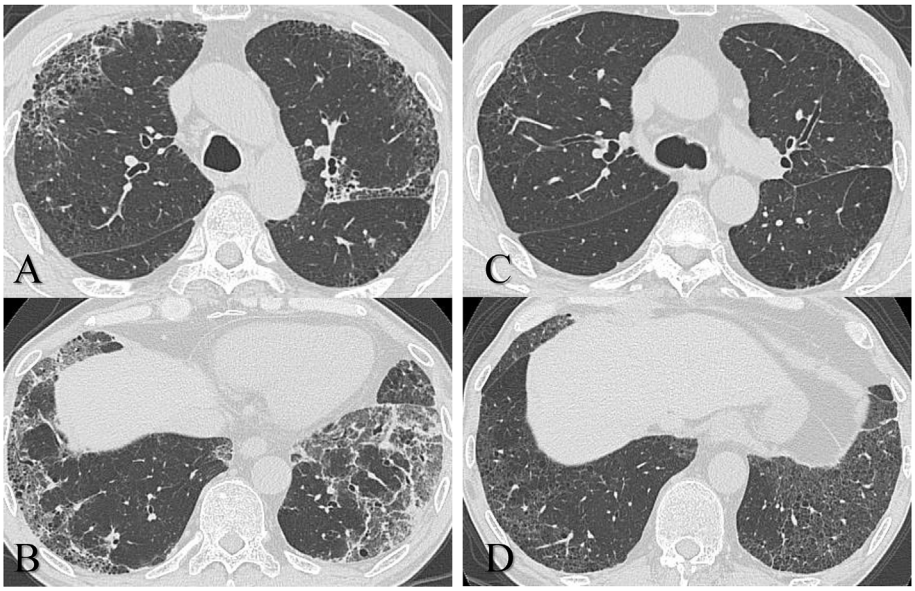

Fig. 1. High-resolution computed tomography findings. (A, B) Chest computed tomography showed emphysema in the upper lung and wide-ranging ground-glass attenuation and reticulation with lower-lobe predominance. Ground-glass attenuation was distributed mainly in the peripheral areas and partially along the bronchovascular bundles. (C, D) At 3 months following the diagnosis of DIP, immunosuppressive treatment with prednisolone had led to an improvement in the radiological findings.

and liver functions were within normal range. His C-reactive protein was elevated at 1.33 mg/dL, and his creatine kinase value was slightly elevated at 233 IU/L. The patient's serum KL-6 and surfactant protein-D levels were elevated to 798 U/mL and 237 ng/mL, respectively. Additional immunoassay analysis of sera for 11 different myositis-specific and associated autoantibodies (EUROLINE; Myositis profile 3) detected anti-Ku antibody. Although he had pain in his digital joints and Raynaud's phenomenon, a rheumatology consultation did not result in a definitive diagnosis of CTD such as rheumatoid arthritis, myositis, systemic sclerosis, or Sjögren's syndrome.

Bronchoalveolar lavage (BAL) fluid from the right middle lobe (B5a) showed a total cell count of 10.7×10^5 cells/mL (21.5% macrophages, 53.0% lymphocytes, 13.0% neutrophils, and 12.0% eosinophils). Thereafter, a video-assisted thoracoscopic biopsy of the lung was performed from the left S1 + 2 and S8. 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–D). Macrophages and multinucleated giant cells were positive for periodic acid-Schiff staining. Many lymphoid follicles were observed in the interstitial and peribronchial areas (Fig. 2B). The fibrosis was mild, and the alveolar architecture was relatively well maintained. This lesion was compatible with the histological diagnosis of DIP. Afterwards, we started immunosuppressive treatment with prednisolone (30 mg/day; 0.5 mg/kg/day), with gradual tapering of the dose, which led to an improvement in pulmonary symptoms. Moreover, findings from HRCT performed 3 month later confirmed this improvement (Fig. 1C and D).

3. Discussion

We experienced a rare case of anti-Ku antibody-positive DIP. The main histological feature of DIP is the accumulation of numerous pigmented macrophages within the alveolar airspace and mild to moderate fibrosis of the alveolar septal walls [1,2,10]. In addition, the main radiological feature of DIP is widespread, patchy ground-glass opacification, with a greater predilection for the lower-lung zone and, sometimes, peripheral predominance [7,11]. Our patient was diagnosed as having DIP based on the presence of features compatible with these characterizations. Interestingly, this case highlighted the following two clinical implications.

First, with regard to the BAL findings of DIP, elevated eosinophils in

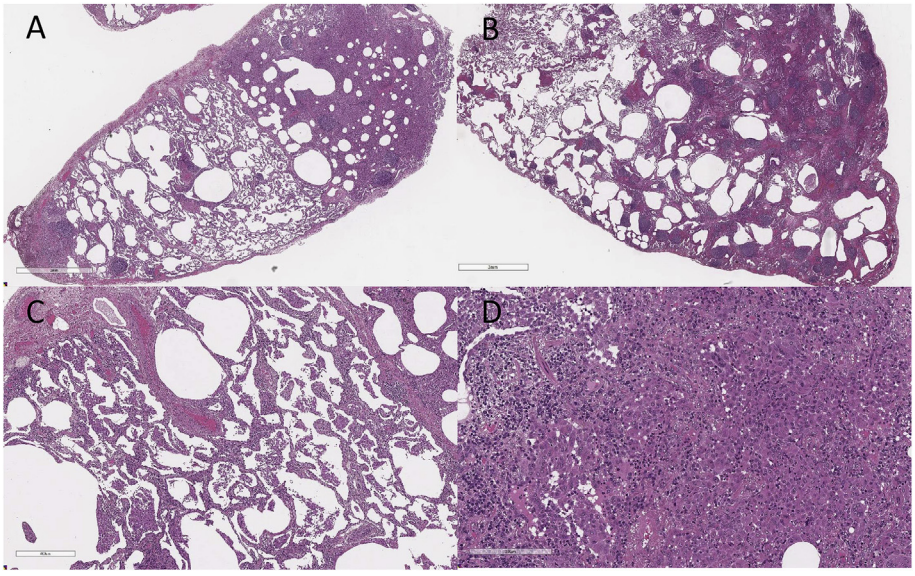

Fig. 2. Histological findings of the lung. (A) The alveolar architecture was relatively maintained, although chronic inflammatory infiltrate was present within the interstitium. Interstitial fibrosis was mild. The severity of the lesions varied from one lobe to another (Hematoxylin and eosin [HE] staining, × 12.5). (B) Many lymphoid follicles were observed in interstitial and peribronchial areas (HE staining, × 12.5). (C) This lesion was characterized by an accumulation of large macrophages in the alveolar space with inflammatory cell infiltration in the alveolar septa, pleura, and interlobular septa (HE staining, × 100). (D) This lesion showed an accumulation of pigmented eosinophilic macrophages in the alveolar spaces with infiltrating plasma cells and lymphocytes (HE staining, × 200).

BAL as found in our patient have often been reported. Kawabata et al. reported that eosinophils tended to increase (mean ± SD, 18 ± 18%) in 17 patients with DIP [10]. However, most DIP patients showed no increase of lymphocytes in BAL, and a few patients showed only a slight increase (mean ± SD; 10 ± 23%) [6,10]. In contrast, our patient with DIP showed a marked increase in the number of lymphocytes in BAL compared with that in previous reports.

Second, the histological findings of our patient showed a high incidence of lymphoid follicles with DIP. Lymphoid follicles are commonly seen in lung tissue of patients with CTD, particularly those with rheumatoid arthritis and antisynthetase syndrome [12,13]. Moreover, prominent lymphoid follicles with germinal center formation were included in the histological features of lung-dominant CTD proposed by Fischer et al. and this term emphasizes the important correlation between CTD and interstitial pneumonia [14]. However, whether hyperplasia of lymphoid follicles leads to CTD in DIP is unclear because little has been reported on DIP associated with CTD.

On the basis of these findings of an increase of lymphocytes in BAL and the abundant lymphoid follicles in lung tissue, we considered the possibility that CTD contributed to the etiology of DIP in our patient unlike common causes of DIP such as smoking and dust inhalation.

Our patient had positive results of anti-Ku and anti-SS-A antibodies in serum. Anti-Ku antibody is found in a wide spectrum of CTDs including overlap syndromes with systemic sclerosis and myositis, and systemic lupus erythematosus [8,9,15,16]. Raynaud's phenomenon and muscular and joint involvement are the most frequent clinical features associated with anti-Ku antibodies, which are frequently detected in association with the presence of anti-Ro/SS-A antibody, as in our case [17]. Our patient had signs suspicious of CTD such as Raynaud's phenomenon, joint pain, and mechanic's hand particularly in association with anti-Ku antibody, although he could not be definitively diagnosed as having CTD. We thus thought that he might have occult CTD.

Lung involvement in anti-Ku-positive patients has rarely been noted. It has been reported in only 3 studies at a frequency of 8–43% [8,9,18]. Rigolet et al. reported that interstitial pneumonia was detected in 11 of 30 patients (37%), and the radiologic pattern on CT varied, with findings such as nonspecific interstitial pneumonia, usual interstitial pneumonia, and a sarcoidosis-like pattern [9]. To our knowledge, however, there are no report on the pathological findings of interstitial lung disease associated with anti-Ku antibody.

In conclusion, we described the first known case of DIP with anti-Ku antibody whose etiology may not be explained solely by smoking. Although the pathogenesis of DIP remains unknown, when an increase of lymphocytes in BAL and of lymphoid follicles in lung tissue is observed in patients with DIP, we probably should consider the onset of DIP to be related not only to smoking but also to CTD. Further accumulation of studies is needed to clarify the pathogenetic mechanism of DIP.

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Conflicts of interest

The authors declare no Conflicts of Interest (COI) in association with this article.

List of abbreviations

BAL	bronchoalveolar lavage
CTD	connective tissue disease
DIP	desquamative interstitial pneumonia
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HRCT	high-resolution computed tomography

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.12.007.

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