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Two Pathological Patterns in Different Stages of the Same Disease

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Abstract

This paper reports a case of a patient with IgG4-related lung disease who presented with two distinct pathological manifestations during the disease course. The first biopsy indicated an early inflammatory stage with mainly inflammatory exudation, while the second biopsy two years later showed a fibrotic stage with more fibrocyte foci and organizing pneumonia-like changes. By integrating relevant research, this study explores the reasons for the differences in the two pathological results, their impacts on prognosis, and their guiding significance for clinical treatment. It emphasizes that IgG4-related diseases may exhibit different pathological changes at different disease stages, and pathology is more likely to detect the trend of pulmonary fibrosis compared to imaging. Further research on its mechanism is needed.

Keywords

IgG4-Related Lung Disease, Pathological Progression, Pulmonary Fibrosis, Glucocorticoid Therapy, Informed Consent, Interstitial Lung Disease

1. Introduction

IgG4-related disease (IgG4-RD) is a newly defined immune-mediated chronic inflammatory disease with fibrosis in recent years. The disease can affect almost all parts of the body. A few patients only have a single organ involved, while most patients have multiple organ lesions simultaneously or successively. Significantly elevated serum IgG4 levels and mass-like lesions are the most common clinical symptoms of this disease [1]. Due to its unique clinical characteristics, it has become a hot spot in the international medical community in recent years.

Histopathology plays an extremely important role in disease diagnosis. One of

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the characteristic histopathological features of IgG4-RD is dense infiltration of lymphocytes/plasma cells and fibrosis; another characteristic pathological feature is the presence of large numbers of IgG4-positive plasma cells in affected organs [2]. In general, a disease corresponds to its own unique histopathological changes. Here we report a patient with IgG4-related lung disease who presented with two different pathological manifestations during the course of the disease.

2. Methods

A 56-year-old female patient developed symptoms of cough, sputum, and shortness of breath after catching a cold. Chest CT showed bilateral lung flakes. After anti-infective treatment, chest CT showed increased pulmonary lesions. Then, CT guided percutaneous lung biopsy was performed, and the lung tissue histopathology showed (**Figure 1**): (right upper lobe of the lung) the alveolar septum was slightly widened, and a large number of plasma cells and lymphocytes infiltrated in the septum and perivascular areas, and aggregation foci were observed. Inflammatory exudate and tissue cell aggregation were observed in the alveolar cavity. A few fibroblasts were seen in the local alveolar lumen. Immunohistochemistry showed positive IgG plasma cells, and the number of IgG4 positive cells > 10/HPF, however, it is difficult to count the IgG4/IgG ratio because of the obvious exudation in the tissue. Informed consent was obtained from the patient for the publication of this case report and accompanying images, in compliance with ethical guidelines. Combined with the level of peripheral blood IgG4 > 3.53 g/L (reference value 0.03 g/L - 2.01 g/L) and PET-CT results, and also some other exclusive diagnoses, such as negative results in the screening of immune related antibodies and tumor markers, IgG4 associated lung disease with thyroid and lymph node involvement was

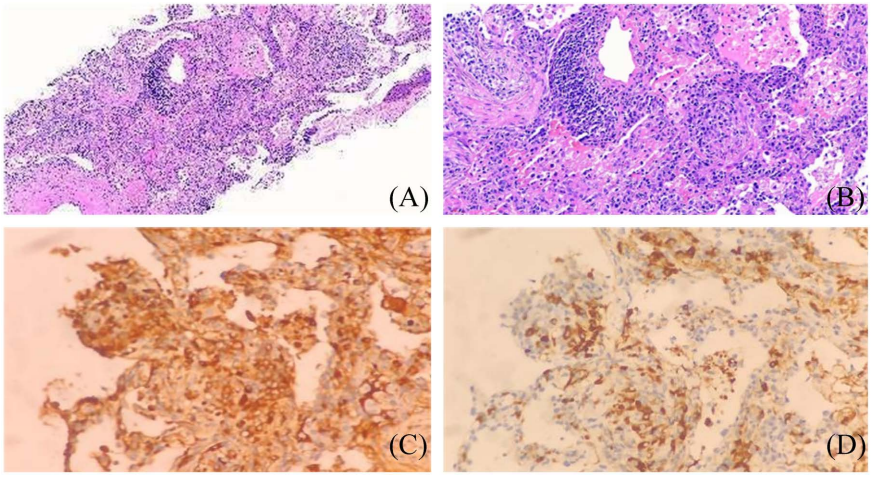

Figure 1. (A) (B) HE staining showed slight widening of the alveolar septum, with a large number of plasma cells and lymphocytes infiltrating in the septum and perivascular areas and foci of aggregation.Inflammatory exudate and tissue cell aggregation were observed in alveolar cavity. A few fibroblasts were seen in the local alveolar cavity ((A) × 200, (B) × 400). (C) (D) Immunohistochemistry showed positive IgG plasma cells, the number of IgG4 positive cells > 10 /HPF, IgG4/IgG < 40% (it was difficult to count clearly due to excessive exudation of lesions) (×400).

diagnosed. After hormone treatment, the symptoms and pulmonary imaging were significantly improved. The hormone was gradually reduced to a minimum of 7.5 mg QD for maintenance treatment. The glucocorticoid tapering regimen, starting at 40 mg daily and decreasing by 5 mg every two weeks until reaching a maintenance dose of 7.5 mg daily over a 3-month period, was implemented in accordance with standard clinical practice.

Immunohistochemistry suggests that CK7 (alveolar epithelium), SMA (blood vessels), CD68 (histiocytes) and CD38 (plasma cells) were all positive, IgG was positive, and IgG4 was partially positive. The positive expression of IgG4 > 10/hpf as well as IgG4/IgG > 40% (Figure 2). gh Immunohistochemistry: Both IgG and IgG4 were positive, and the number of IgG4 positive cells was >10/hpf, and the proportion of positive expression was igg4/igg > 40% (×400). At this time, serum level of IgG4 increased to 4.20 g/L (reference value 0.03 g/L - 2.01 g/L) again. The symptoms, pulmonary imaging and pulmonary function were better after glucocorticoid therapy again. The changes in mMRC, pulmonary function and imaging before and after treatment are shown in Figure 3 and Table 1.

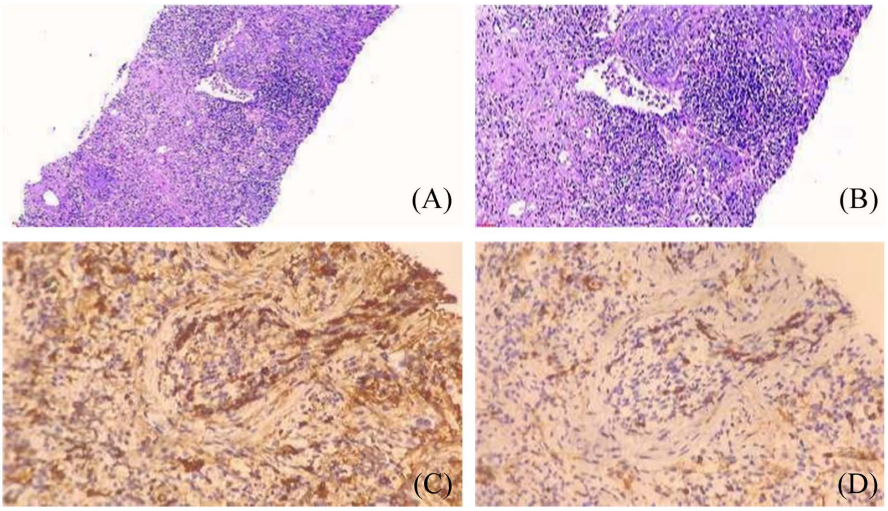

Figure 2. (A) (B) HE staining showed alveolar structure destruction with fibrous tissue hyperplasia in some areas, in which a large number of plasma cells, lymphocytes and some eosinophils were infiltrated, and inflammatory cells clustered. A large number of fibroblast clusters were seen in some alveolar cavities, showing organized pneumonia like changes ((A) ×200, (B) ×400). (C) (D) Immunohistochemistry: Both IgG and IgG4 were positive, and the number of IgG4 positive cells was >10/hpf, and the proportion of positive expression was igg4/igg > 40% (×400).

Table 1. Changes in lung function.

	2019-11-29 Before treatment	2020-1-9 Glucocorticoid therapy for 45 days	2020-9-14 Glucocorticoid therapy for 10 months*	2021-9-10 Relapse during glucocorticoid reduction	2022-3-22 6 months after adjustment of glucocorticoids
FVC (L/% predicted)	2.01 (72%)	2.71 (98%)	3.04 (103%)	3.70 (79%)	4.54 (102%)

Continued

FEV1 (L/% predicted)	1.61 (70%)	2.0 (87%)	1.93 (80%)	1.62 (68%)	1.99 (88%)
FEV1/FVC (%)	80	74	63	71	71
MV (L/min)	33.77	46.23	34.10	24.25	34.03
DLCO (smmol/min/kPa/% predicted)	5.38 (73%)	6.13 (84%)	5.82 (77%)	6.02 (80%)	6.35 (88%)
DLCO/VA (mmol/min/kPa/L)	1.29	1.17	1.45	1.69	1.44

FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, MV: maximum ventilation DLco: diffusing capacity of the lung for carbon monoxide, VA alveolar volume. *The patient was reexamined 6 months after drug withdrawal (due to COVID-19).

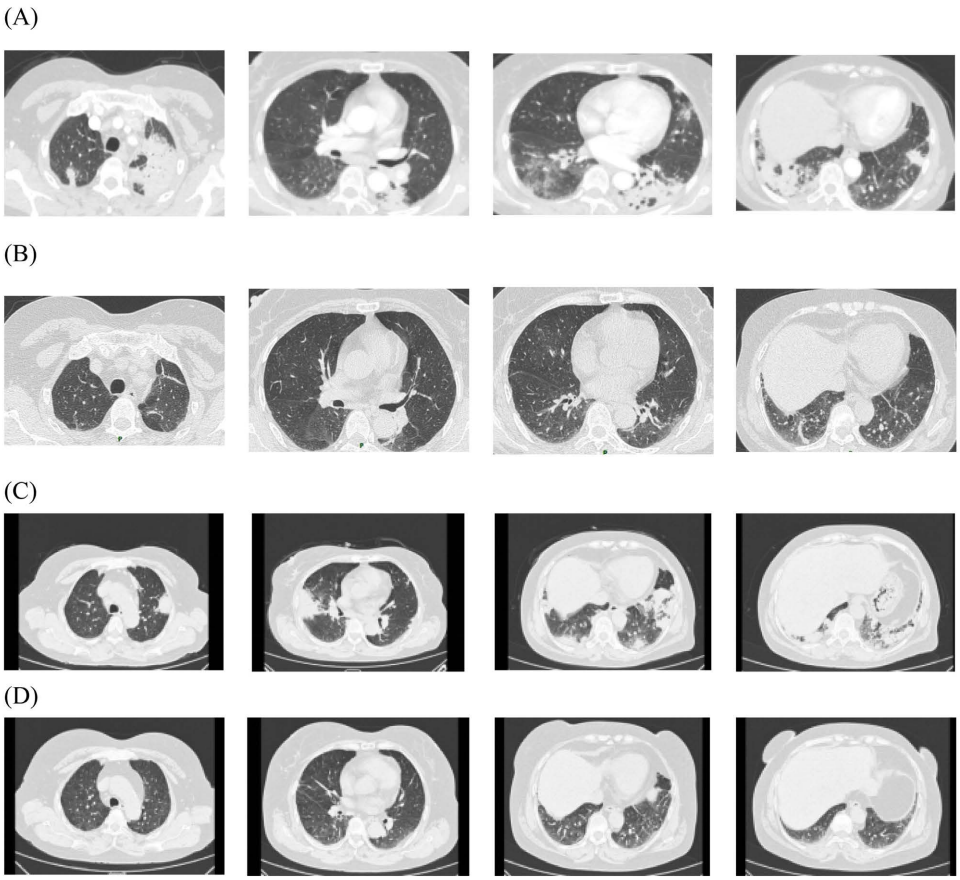

Figure 3. Imaging changes before and after glucocorticoid therapy (A) Chest CT scan before glucocorticoid therapy (B) Chest CT scan after nearly 2 months of glucocorticoid therapy (C) Chest CT scan when the condition worsens after 10 months of glucocorticoid maintenance therapy (D) Chest CT scan after 6 months of adjusting the glucocorticoid therapy regimen.

3. Discussion

IgG4-RD is a fascinating clinical entity that was reported in Japan for the first time in this century. It includes a variety of diseases such as Mikulitz's disease (MD),

autoimmune pancreatitis (AIP), interstitial nephritis, prostatitis, and retroperitoneal fibrosis [3]. There are two main criteria for the diagnosis of IgG4-RD, the Japanese criteria and the Bostoncriteria. In 2011, Japan published the first diagnostic criteria for IgG4-RD, namely, comprehensive diagnosis (CD) criteria [4]. It includes clinical criteria, elevated serum IgG4, and histopathological findings, among which histopathological findings: ① Marked lymphocyt and plasmacytic infiltration and fibrosis; ② Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG + cells > 40% and > 10 IgG4+ plasma cells/HPF. The Boston criteria can be described as the histopathological diagnosis of IgG4-RD: requires the presence of the triad of histological features in IgG4-RD: ① lymphoplasmacytic inflammation; ② Fibrosis, usually with a storiform pattern; ③ Obliterative venulitis. Both diagnostic systems emphasize the importance of histopathology in the diagnosis of IgG4-RD.

In this case, the first pathological report of the patient was mainly inflammatory exudation, but a little fibrous tissue was visible. The chest imaging was mainly exudative lesions, which was consistent with the pathological results. In the second pathology, in addition to a large number of inflammatory cell infiltration, there were more fibrocyte foci, and even organic pneumonia changes. The chest imaging was mainly composed of multiple patchy and large consolidation shadows, mostly located in the subpleura. This suggests that our pathology can detect the tendency of pulmonary fibrosis earlier. Meanwhile, a question arises: Why are the pathological results of the same disease different for two times? Does it suggest a different prognosis? What is the guiding significance of different pathological results for clinical treatment?

At present, the pathogenesis of IgG4-RD has not been thoroughly studied. However, it has been reported in literature [5] that IgG4-RD follows a two-stage development process, characterized by an "inflammatory" phase that eventually culminate in a "fibrotic" outcome. The first inflammatory phase of IG4-RD is characterized by the appearance of antigen-experienced B and T lymphocytes that accumulate at the disease sites, engage in mutual activating antigen driven interactions, and secrete pro-fibrotic molecules such as interleukin-1, interleukin-6, interferon γ, and transforming growth factor β [6]-[8]. In the fibrosis phase of IGG4-RD, lymphocytes and innate immune cells are replaced by a dense matrix reaction, gradually leading to tissue distortion and organ damage [9]. However, the role of IgG4 antibody is still unclear. Although the pathogenesis of IgG4-RD is not completely clear yet, some existing research results seem to be able to explain the difference between the two pathological results of the patient reported in this case. At the time of the first biopsy, the patient was in the early stage of the disease, namely the inflammatory stage. Two years later, at the second biopsy, the patient began to progress to the fibrosis stage of the disease, which also suggested that the patient's condition might be progressing. At the same time, it also verified the correctness of the two-stage development process of IgG4-RD "inflammation" and "fibrosis". From the follow-up results of the patients, we can see that compared with the second glucocorticoid therapy after relapse, the treatment effect of

the first two months of glucocorticoid therapy is obviously comparable to the treatment effect of the latter 10 months, and even the overall treatment effect is better (Table 1). This was also demonstrated by repeated chest CT findings (Figure 1). This also suggests that timely treatment in the early stage of inflammation has the best effect. Even if the disease begins to change to the fibrosis stage, it still has considerable therapeutic effect, and anti-inflammatory treatment should be carried out in time. At the same time, it also shows that glucocorticoid have therapeutic effects both on patients with initial diagnosis of IgG4-RD and patients with relapse. But for this patient's poor disease control, it is likely caused by the patient's withdrawal of drugs during the treatment. Reviewing the diagnosis and treatment of this patient, if the patient's imaging or pathology shows increased fibrosis, is the combined use of glucocorticoid and anti fibrosis drugs beneficial to the patient? Whether it can delay the fibrosis process of patients' lungs needs to be confirmed by more cases and studies on the pathogenesis.

For differential diagnosis, other interstitial lung diseases (e.g., idiopathic pulmonary fibrosis, which features usual interstitial pneumonia on pathology) and organizing pneumonias (e.g., cryptogenic organizing pneumonia, which lacks IgG4-positive plasma cell infiltration) were explicitly ruled out based on histopathological findings. Negative results for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and tumor markers (e.g., CEA, NSE) further supported the diagnosis of IgG4-RLD.

4. Conclusion

In summary, IgG4-RD may have different pathological changes in different stages of the disease course. Compared with imaging, pathology may find the tendency of pulmonary fibrosis changes earlier. Its mechanism remains to be further studied, so as to better guide the diagnosis and treatment of IgG4-RD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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