CASE REPORT

IgG4-related Lung Disease: A Case Report and Review of the Literature

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ABSTRACT

IgG4-related disease (IgG4-RD) is a systemic autoimmune disease characterized by the infiltration of a large number of IgG4+ plasma cells, neoplastic lesions in the affected tissues, and a sharp increase in the concentration of serum IgG4. IgG4-RD is a rare and novel disease involving multiple organs with various clinical manifestations. Understanding and studying the pulmonary manifestations of IgG4-RD is critical for improving diagnosis, treatment, and prognosis. However, lung involvement alone is less common. Here we present a rare case of IgG4-related lung disease (IgG4-RLD) to show the variable manifestations of this disease in the lungs and review the relevant literature. (*Altern Ther Health Med.* 2023;29(8):320-323).

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INTRODUCTION

IgG4-related disease (IgG4-RD) is a rare chronic inflammatory autoimmune disease mediated by IgG4, common in middle-aged and older men. Involved organs primarily manifest as swelling or formation of inflammatory pseudotumor, with IgG4+ lymphoplasmacytic infiltration and elevated serum IgG4 levels.[1] IgG4-RD can affect almost any organ of the human body, and more than 90% of cases show multiple organ involvement. However, a few cases involve only the lungs. IgG4-related lung disease (IgG4-RLD) has a high rate of missed diagnosis due to the lack of clinical manifestations. Generally, diagnosis rests on the results of serum immunological and histopathological. IgG4-RLD responds well to glucocorticoid treatment and most patients receive a favorable prognosis after timely treatment. Therefore, the correct diagnosis and differentiation of this type of disease are critical for the treatment and prognosis of patients. This article reports on a case of IgG4-RLD with pneumonia and an intrapulmonary mass diagnosed in the researchers' hospital and reviews related literature to the case to improve the level of diagnosis and treatment of IgG4-RD.

CASE PRESENTATION

Following "fever with cough and expectoration for four days," the researchers' hospital admitted a 57-year-old male patient." Laboratory tests showed elevated inflammatory markers (erythrocyte sedimentation rate, C-reactive protein). He underwent a lung computed tomography (CT), which implied patchy shadows in the left lower and right upper lung (Figure 1a), indicating lung inflammation. Bronchoscopy manifested a large mass in the anterior and lateral basal segment of the left inferior lobe of the lung. The histopathologic showed chronic active inflammation of the bronchial mucosa (Figure 2); no tumor cells were present in the bronchoalveolar lavage fluid (BALF). The patient received symptomatic treatment with antibiotics and expectorants for more than a week. His coughing

Figure 1. Lung Computed Tomography Showed Patchy Shadows in the Left Lower and Right Upper Lung, Especially in the Left Lower Lung

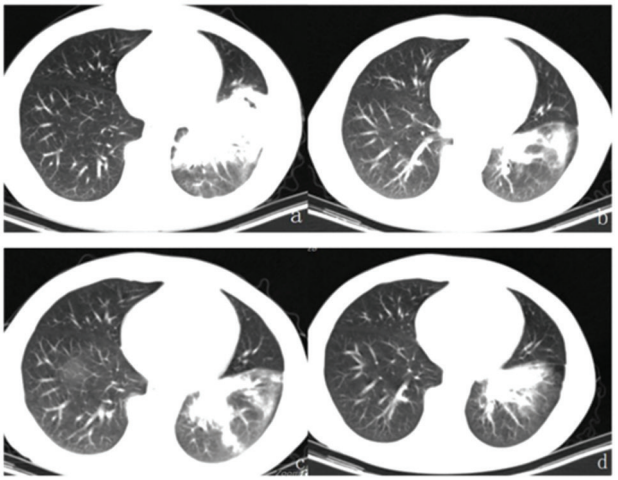


Figure 2. Bronchial Biopsy (First Time); Chronic Active Inflammation of the Bronchial Mucosa, with Squamous Metaplasia and Papillary Hyperplasia

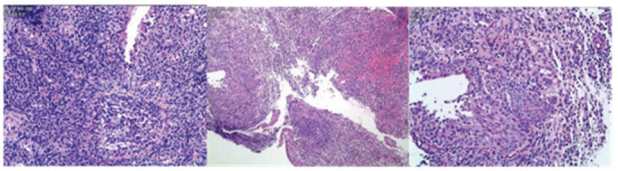


Figure 3. Enhanced Chest CT.

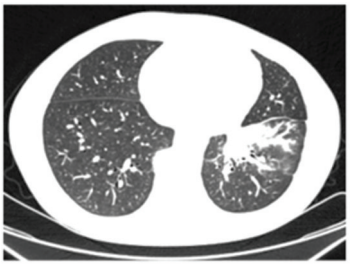
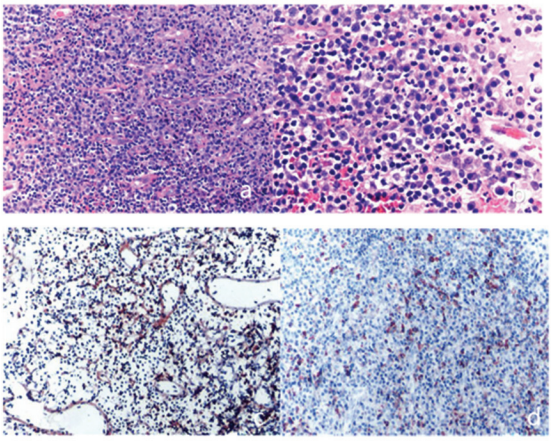
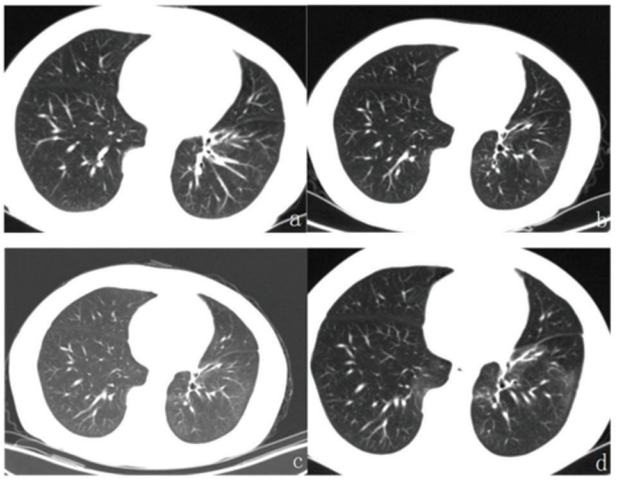


Figure 4. Bronchial Biopsy (Fourth Time); Infiltration of IgG4+ Plasma Cells, the Ratio of IgG4+/IgG+ Cells > 40%, and > 10 IgG4+ Plasma Cells/HPF (**A**. H&E Staining, Original Magnification ×100; **B.** H&E Staining, Original Magnification ×200; **C.** IHC for Igg; **D.** IHC for Igg4).



Abbreviations: H&E, Hematoxylin and Eosin; HPF, High-Power Field; IHC, Immunohistochemistry.

Figure 5. Regular Re-examination of Chest CT After Glucocorticoid Treatment



and fever symptoms subsided with decreased inflammatory markers. The re-examined chest CT (Figure 1b) suggested that the lung lesions were markedly absorbed. However, even four months after discharge, the patient still had recurrent cough and sputum, sometimes with blood. Of more significant concern was several CT re-examinations showed lung inflammation to be more severe than earlier (Figure 1c, 1d). The patient experienced poor results from conventional treatment, including anti-inflammatories and/or phlegm elimination.

The patient's infections were in the same site of the left lower lung. Malignant tumors could not completely rule out the possibility of post-obstructive pneumonia. After five months, the patient was re-admitted. The inflammatory markers at admission were as follows: white blood count, 8.39×10^{12}/L(3.5-9.0×10^9/L); Eosinophil count, 0.09×10^9/L (0.02-0.52×10^9/L); erythrocyte sedimentation rate, 33 mm/hour (<15 mm/hour); C-reactive protein, 25.9 mg/l (0-8 mg/l). There was no abnormality in the detection of tumor markers and t-lymphocyte subpopulation. Enhanced chest CT also showed left lower pneumonia; no observed signs of neoplasia existed (Figure 3). Four days after re-admission, a bronchoscopy revealed nodules under the tracheobronchial wall blocking the bronchial lumen in the lateral basal segment of the left inferior lobe of the lung. Biopsy pathology demonstrated mucosal tissue with inflammation, erosions, and granulation tissue proliferation. A 1,3-β-D-glucan test (G-test) was positive in BALF; serological tests showed the results of the G test, galactomannan (GM), aspergillus IgG, and IgM as all negative. The patient experienced poor effects of anti-infective therapy and other symptomatic treatment. The patient underwent a third and fourth bronchoscopy; special staining revealed no microorganisms. Pathology found no evidence of malignancy.

One month after admission, the fourth immunohistochemistry of the patient demonstrated a prominent IgG4+ plasma cell infiltration, an IgG4+/IgG+ cell ratio of > 40%, and IgG4+ plasma cells > 10/HPF in histopathological examination (Figure 4). In addition, serum IgG4 was remarkably elevated (2.410 g/L; reference, 0.08–1.40 g/L). Taken together, the physicians confirmed IgG4-RLD. Therapy began with an intravenous injection of 40 mg methylpred-nisolone for 14 days. The patient improved. Infusions preceded a maintenance, appropriately tapered treatment of oral prednisone for a year. After three months of treatment, the patient's total serum IgG4 level was normal (0.861 g/L). In a follow-up after a year, the patient had no recurrence, and a subsequent CT re-examination revealed that the lung lesions were markedly absorbed (Figure 5).

DISCUSSION

IgG4-RD is a newly discovered systemic immune-mediated disease with unknown incidence and prevalence. In 2001, Hamano et al.[2] first proposed a correlation between elevated levels of IgG4 and sclerosing pancreatitis. Researchers subsequently established that this autoimmune process was not exclusive to the pancreas and introduced the concept of "IgG4-related autoimmune disease."[3] Since then, incidents involving other organs has gradually been reported. Various case reports and cohort studies have demonstrated that IgG4-RD may affect any body organ, such as the liver, pancreas, thyroid, salivary gland, lung, bile duct, gastrointestinal tract, lacrimal gland, kidney, and retroperitoneum. However, pulmonary involvement of IgG4-RD is rare and challenging to diagnose.

IgG4-RLD lacks specific clinical manifestations. Some patients may first show respiratory symptoms such as cough or dyspnea, while 75% are asymptomatic. Due to non-specific clinical manifestations, the disease is easily misdiagnosed as other lung diseases, as abnormal shadows can be found incidentally on CT scans and chest X-rays.[4] The characteristic radiologic findings of the lung include solid nodules, ground-glass opacities, thickening of bronchovascular bundles and interlobular septa, honeycombing simulating pulmonary fibrosis, and enlarged hilar and mediastinal lymph nodes.[5] Sometimes, a variety of radiological features can be found in a single patient. IgG4-related lung disease should be highly suspected if chest CT shows pleomorphic features.

In most cases, doctors highly recommend a lung biopsy to confirm the diagnosis of IgG4-RD. Physicians are supposed to rule out IgG4-RLD to avoid misdiagnosis when patients with CT showing pulmonary inflammation experience poor effects from antibiotic therapy. It is noteworthy, however, that IgG4-related lung disease can mimic lung cancer on imaging findings, which is difficult to distinguish in the early stage. Moreover, cancer can coexist with IgG4-RD; they can serve as both cause and effect to each other. Discussions about the possible link between IgG4-RD and malignant tumors are ongoing. Fujimoto et al.[6] found that IgG4+ plasma cells infiltrated 11.9 percent of the non-small cell lung cancer surgical specimens. A retrospective study in the USA[7] found that compared to the general US population, the incidence of malignant tumors was 2.5 times higher in patients with IgG4-RD, and the frequency of malignant history in patients with IgG4-RD was > 3-fold higher than that in the matched controls. Those with a history of malignancy also developed IgG4-RD at an older age and had a higher serum IgG4 concentration than those without prior malignancy. In contrast, a large Japanese study demonstrated that the cancer incidence in patients with IgG4-RD has only a marginal increase. There seems to be no tendency for malignancy in IgG4-RD patients.[8] Researchers need to conduct a long-term follow-up prospective study for further evaluation.

Pathogenesis of IgG4-RD has been unclear, and the IgG4-RLD criteria are not presently well-established. No matter which organ is involved, the gold standard for the diagnosis of IgG4-RD is a significant IgG4+ plasma cell infiltration with typical histopathologic features (such as a rich lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis).[9]

In 2012, an IgG4-RD Research Group in Japan issued the first integrated clinical diagnostic criteria. The criteria emphasized diffuse/localized swellings or masses in single or multiple organs, elevated serum IgG4 concentrations (135 mg/dl), significant lymphocyte and plasmacyte infiltration, fibrosis, IgG4+ plasma cells infiltration, IgG4+/IgG+ cell ratio > 40%, and > 10 IgG4+ plasma cells/HPF in histopathological examination.[10] The diagnostic criteria are based on two important features: elevated serum IgG4 concentrations and IgG4+ cell infiltration. However, the serum IgG4 concentration is neither necessary nor sufficient to diagnose IgG4-RD. Some patients diagnosed with IgG4-RD may not have increased serum IgG4 concentrations. Wallace et al.[11] retrospectively studied the clinical and laboratory characteristics of 125 patients. Nearly 50% of the patients were diagnosed as IgG4-RD by biopsy but with normal serum IgG4 concentrations.[11] Compared to patients with normal serum IgG4 concentrations, the increase in IgG4 concentrations suggests multiple organs are more likely to be involved, and the disease is more refractory. Moreover, elevated serum IgG4 concentrations are common in 5% of normal adults and patients with other conditions, including autoimmune diseases, repeated infections, and cancer. Overemphasizing the role of serum IgG4 level in consideration of IgG4-RD may lead to an increase in the misdiagnosis rate.

Regarding the pathology of IgG4-RD, a growing consensus in the literature highly recommends[9] IgG4 immunostaining to provide confirmatory solid evidence for the diagnosis under any circumstances. Physicians should also evaluate IgG4+/IgG+ plasma cell ratios and IgG4+ plasma cell counts in evaluating the infiltration of IgG4+ plasma cells. However, due to the high background IgG stain, accurate IgG4+/IgG+ ratios are sometimes hard to calculate, and there is no accurate way to count IgG4+ plasma cells. Moreover, non-IgG4-related disease entities may be related to the increased IgG4+ plasma cell counts.[9,12] For example, in multicentric Castleman's disease, rheumatoid arthritis, B-cell lymphoma, or plasmablastic B-cell malignancies, sometimes there are great quantities of IgG4+

plasma cells in the tissue, as well as more than 40% of IgG4+/IgG+ plasma cells and elevated serum IgG4 concentrations. The international expert panel produced a consensus. In 2015, an international expert panel agreed that the most accurate evaluation of IgG4-RD should be on the basis of a complete clinical history, physical examination, radiology studies and laboratory investigations[13]. Thus, a physician should comprehensively analyze the patient's condition in establishing the diagnosis of IgG4-RD. Such an analysis may require repeated histopathological examinations.

In the above case, the first bronchial biopsy of the patient did not show any specific histopathological manifestation of IgG4-RD. One explanation is that the sample size was too small to show full histological images. The levels of IgG4 may be low in the given bronchoscopic lung biopsy specimen leading to an increase in the rate of missed diagnosis. A second possibility may relate to the degree and stage of the lesion in IgG4-RD. In a previous case report,[14] a patient biopsy shows marked lymphoplasmacytic infiltration accompanied by only a few IgG4-positive cells. The possible explanation for the patient's scarcity of IgG4 is that the disease had developed to a fibrosis stage with fewer plasma cells. Fibrosis may predominate in the affected tissue. In contrast, Satoshi Hara published a study of a case closely mimicking IgG4-RD, in which no obvious IgG4+ plasma cell infiltration appeared in multiple involved tissue biopsies[15]. The case did not meet the comprehensive diagnostic criteria of IgG4-RD or the recommended criteria for IgG4-related kidney disease. However, the T helper (Th2-type) cells and Treg-dominant immune response can be found in this case, contributing to the formation of IgG4-related kidney disease-like lesions, suggesting that the involved tissue is in an early phase with plasma cell (PC)-rich lesions. The activation of Th2 and Treg cells is a key feature of IgG4-RD.[16] IgG4 is a Th2-dependent immunoglobulin. Th2 may promote the formation of germinal centers and recruit increased numbers of eosinophils, mast cells, and increase the level of serum IgE, activating the production of IgG4 and infiltration of IgG4+ plasma cells. Treg cells may produce IL-10, which can drive B cells to differentiate into plasma cells and produce IgG4. Such events may explain the reason for no IgG4+ plasma cells in the histopathology of early-stage samples. However, it is presently unknown why the activation of Th2 and Treg cells does not induce IgG4 class switching. Previous studies have speculated that it may be related to abnormal IL-10 signaling pathways.[15]

Hormone therapy is the recommended first-line therapy for IgG4-RD. Research indicates that most hormone therapy patients have a good initial response. Practicing clinicians should not exclude IgG4-RD based on a lack of histopathologic evidence. When IgG4-RD is clinically suspected, it is necessary to consider early steroid treatment according to the clinical diagnosis. However, with the increase in IgG4-RD patients, studies have found that not all patients respond to glucocorticoid treatment. Many patients appear to develop disease recurrence, relapse, or corticosteroid intolerance during or after treatment, for whom immunosuppressants, and rituximab may be an important alternative treatment[17]. Many patients with IgG4-RD may develop other diseases. Thus, it is important to establish long-term follow-up with patients to observe clinical signs of other organ involvement. We have followed up with the patient in this case report for one year. After a year, the patient's symptoms subsided significantly, and a chest CT scan also showed a significant reduction in lung lesions.

Since most patients with IgG4-RD develop other diseases, the best course of action would be long-term follow-up to observe any clinical signs of other organ involvement. The study followed the patient in this case report for one year. The patient's symptoms subsided significantly after a year and a chest CT scan also showed significant reductions in lung lesions.

In conclusion, this case demonstrates that IgG4-related lung disease can manifest as a lung infection in structural and functional imaging in early stages and can mimic high-grade primary lung malignancy. Repeated biopsies of affected tissue are highly recommended to rule out malignancies and other similar diseases of IgG4-RD. Unexpectedly, the patient's situation was complicated by a renal malignant tumor during treatment. This complication emphasizes the importance of ruling out malignancy when examining for IgG4-RD.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

XZ and WZ contributed equally to this work. XZ, WZ, YS and JH designed the study and performed the experiments, SZ and JY collected the data, SZ, JY and ZB analyzed the data, XZ, WZ, YS and JH prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was supported by the Science and Technology Project of Fujian Province (Grant No. 2020J011134)

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