

SOLELY LUNG-INVOLVED IgG₄-RELATED DISEASE: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT. By analyzing the clinical data of 1 case of IgG₄-related lung disease (IgG₄-RLD) and the review of literature, the author investigated the clinical characteristics of IgG₄-RLD. IgG₄-RLD is a rare disease characterized by significant elevation of serum IgG₄ and infiltration of a large number of IgG₄⁺ plasma cells. The clinical manifestations of the disease were nonspecific, and the imaging features were mixed with several types. The disease can only be involved in the lung, but also multiple organ involvement. Solely lung-involved IgG₄-RD is not only extremely rare but also easily misdiagnosed as tuberculosis, lung cancer, lymphoma and other common pulmonary diseases. Histopathological examination is the key to the diagnosis of the disease. Corticosteroids are the first choice of treatment, and the overall prognosis is good. (*Sarcoidosis Vasc Diffuse Lung Dis* 2016; 33: 398-406)

KEY WORDS: IgG₄-related disease, immunoglobulin G₄, lung

INTRODUCTION

Immunoglobulin G₄ (IgG₄)-related disease (IgG₄-RD) is a comparatively new concept (1) and has lately attracted clinical and research attention. IgG₄-RD is a chronic progressive disease characterized by significantly elevated serum IgG₄ level and IgG₄-positive plasma cell infiltration of involved tissues (2). IgG₄-RD has been recognized as occurring in nearly all major organs, including the pancreas, bile duct, salivary glands, lacrimal glands, retroperitoneum and lung (3-5). IgG₄-related lung disease (IgG₄-RLD) is usually accompanied by multi-organ involvement including the pancreas, however,

solely lung involved IgG₄-RD is extremely rare. The complete picture of this disease is not currently well understood and further investigation is thus needed. Herein, we report a case of solely lung involved IgG₄-RLD, and review the relevant literatures.

CASE REPORT

A 46-year-old male patient had intermittent cough and slight thoracalgia while cough six months ago with no reasons. He was a businessman and no history of smoking or dust inhalation. He was admitted into the local hospital and the chest CT scan on admission showed large scale consolidation of the lower and upper lobes with air bronchograms in right lung, enlarged mediastinal and bilateral hilar lymph nodes and small right pleural effusions. He was then considered as bacterial pneumonia. Antibiotics including ceftriaxone and moxifloxacin were administered. The symptoms had been alleviated, but reexamined chest CT showed the lesions in lung had

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no changes (Figure 1A and B). Ten days ago, due to high fever at 39 °C, aggravating cough and yellow phlegm, he was admitted into our hospital.

Laboratory examination revealed an elevated erythrocyte sedimentation rate (ESR) (55 mm/h) and C-reactive protein (CRP) (32.5 mg/L). Blood cell counts showed that white blood cells (WBC) $10.71 \times 10^9/L$; neutrophils 78.0%; hemoglobin (Hb) 116 g/L, platelet counts (PLT) $324 \times 10^9/L$. Arterial

blood gas analysis showed that: pH 7.46; pCO₂ 34 mmHg; pO₂ 76 mmHg; FiO₂ 40%. Serum electrolytes, amylase, renal function, and liver function were normal. Other laboratory tests showed decreased albumin (32.3g/L) and significantly increased globulin (55.0 g/L). Total IgG levels were increased (28.50 g/L), including serum IgG4. IgA, IgM, IgE, C3 and C4 were within normal range. Tumour markers including CEA, CA-125, CA-153 and CA-199 were

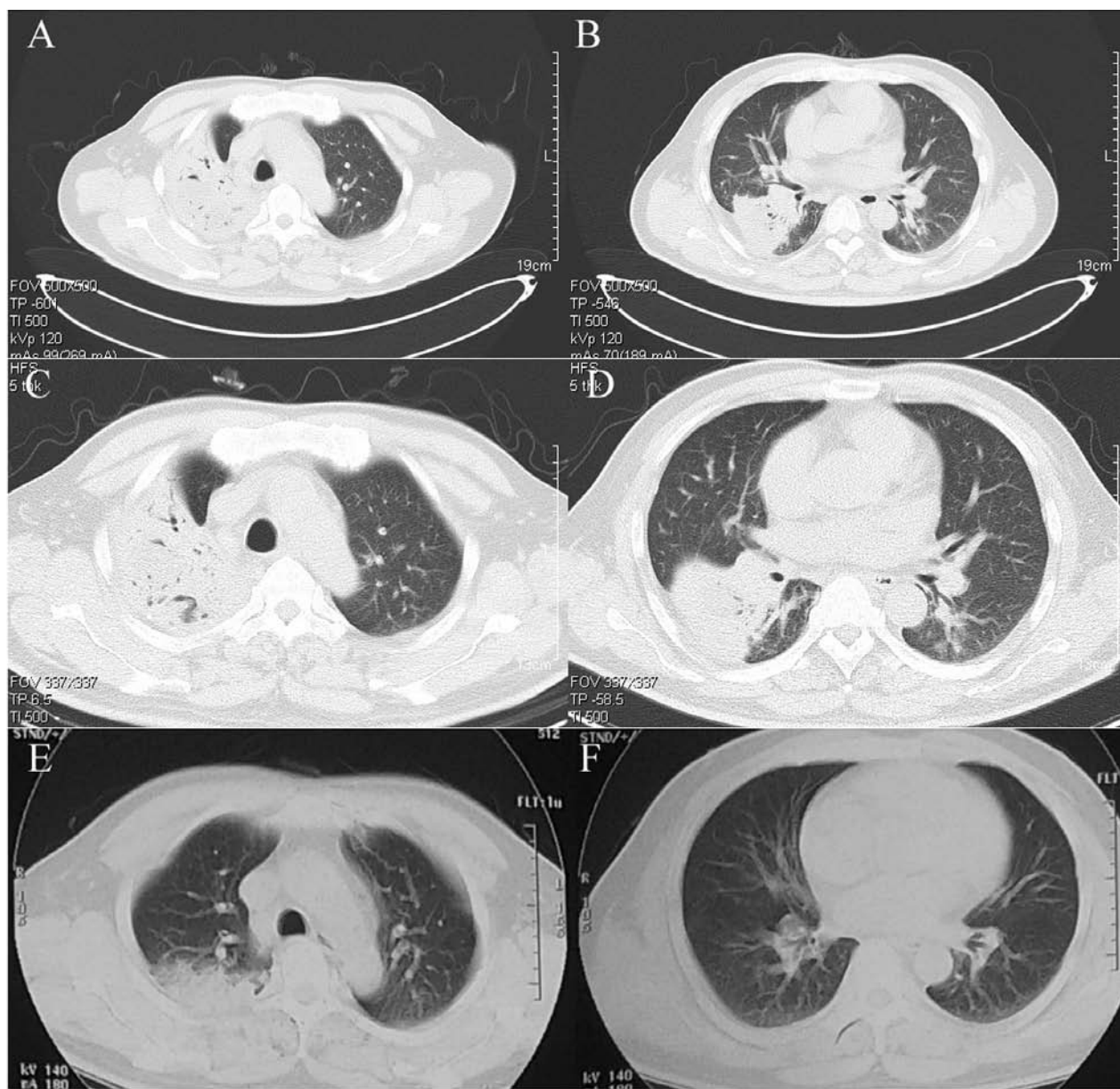


Fig. 1. Chest CT view: large scale consolidation of the lower and upper lobes with air bronchograms in right lung before hospitalization (A, B). There was no obvious progress compared with the pre hospital (C, D). The abnormal shadows were absorbed obviously after treatment (E, F).

all normal. And autoimmune markers including anti-nuclear antibodies, rheumatoid factor and ANCA were negative, too. The pulmonary function test results were normal, with a vital capacity 83.6% of predicted, a forced expiratory volume 1.0% (FEV1.0%) of 75.7% and a diffusion lung capacity for carbon monoxide (DLCO) of 92.4% of predicted. PPD skin-test and T-SPOT TB were negative; blood tuberculosis antibody was negative. After admission, the chest CT was reexamined, and there was no ob-

vious progress in the lesions than before (Figure 1C and D). Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET) revealed an intense FDG accumulation corresponding to the infiltrative shadows in the lung and a mild to moderate FDG accumulation in the right clavicle, the right hilar and mediastinal lymph nodes. The FDG accumulation in these lesions further increased after a delay. There was no FDG accumulation in any other organs, such as the pancreas (Figure 2).

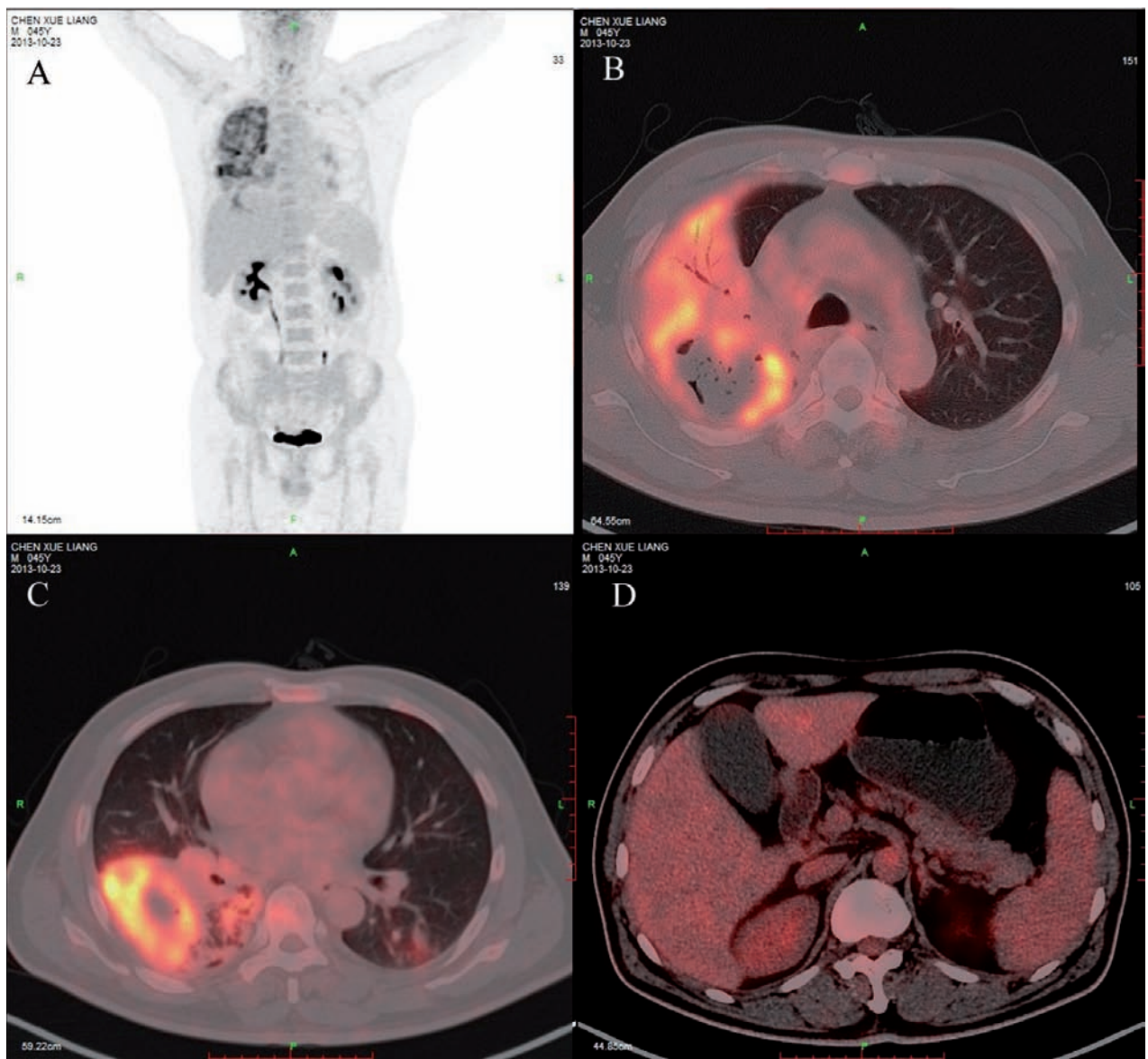


Fig. 2. FDG-PET view: an intense FDG accumulation corresponding to the infiltrative shadows in the lung(A, B, C). No FDG accumulation in any other organs including the pancreas(A, D).

Considering the possibility of partial necrosis of lung cancer with lymph nodes metastasis, the biopsy of high metabolic lesions was suggested. The bronchoscopy examination showed new organisms of the right upper lobe and right lower back segment obstructed bronchuses (Figure 3). The pathological result of transbronchial lung biopsy was local inflammatory granulation tissue proliferation, the infiltration of large number of lymphatic plasma cells and small amount of neutrophils in the stroma. Because the histopathological examination of the transbronchial lung biopsy samples revealed only a non-specific fibrotic thickening of the alveolar septa and an infiltration of inflammatory cells, a percutaneous lung biopsy was performed. The histopathological findings were alveolar consolidation and destruction, inflammatory fibrous hyperplasia, large number of lymphocytes and plasma cells infiltration, and focal tissue cells proliferation. Immunostains demonstrated an increased number of IgG4-positive plasma cells and an increased IgG4/IgG ratio. The mean number of IgG4+ plasma cells per high power field (HPF) was more than 10 (Figure 4). Immunostains for CD20, CD3, CD138, CD38, CD4 and CD8 were all positive; stains for desmin, PAX5, MPO and EBER were negative. Special staining: PAS (-), acid-fast staining (-) and PASM (-). Then the serum concentration of

IgG4 was detected, and it was elevated at 325 mg/dL (the reference value: 8-140 mg/dL).

According to the above clinical data, the diagnosis was considered as solely lung-involved IgG4-RLD. Once the diagnosis was confirmed, the medical treatment by steroid was recommended. After given urbason 80 mg/day intravenously half a month, the symptoms were relieved, and IgG4 decreased to 205 mg/dL, but the absorption of lesion in imaging was not obvious. After discharge, the oral administration of medrol tablets was started at a dose of 60 mg/day, and the dose monthly reduced by 10 mg until the withdrawal. The abnormal shadows on the chest radiography were absorbed obviously within six months (Figure 1E and F). the serum concentration of IgG4 was 162 mg/dL. The patient is currently in a stable condition without recurrence, and is still in the follow-up visit.

DISCUSSION

Since the first report of lung involvement in a patient with IgG4-RD in 2004 (6), some similar cases had been described. IgG4-RLD usually involved multiple organs or tissues, mostly affecting pancreas, biliary ducts, salivary glands and orbits. It was quite

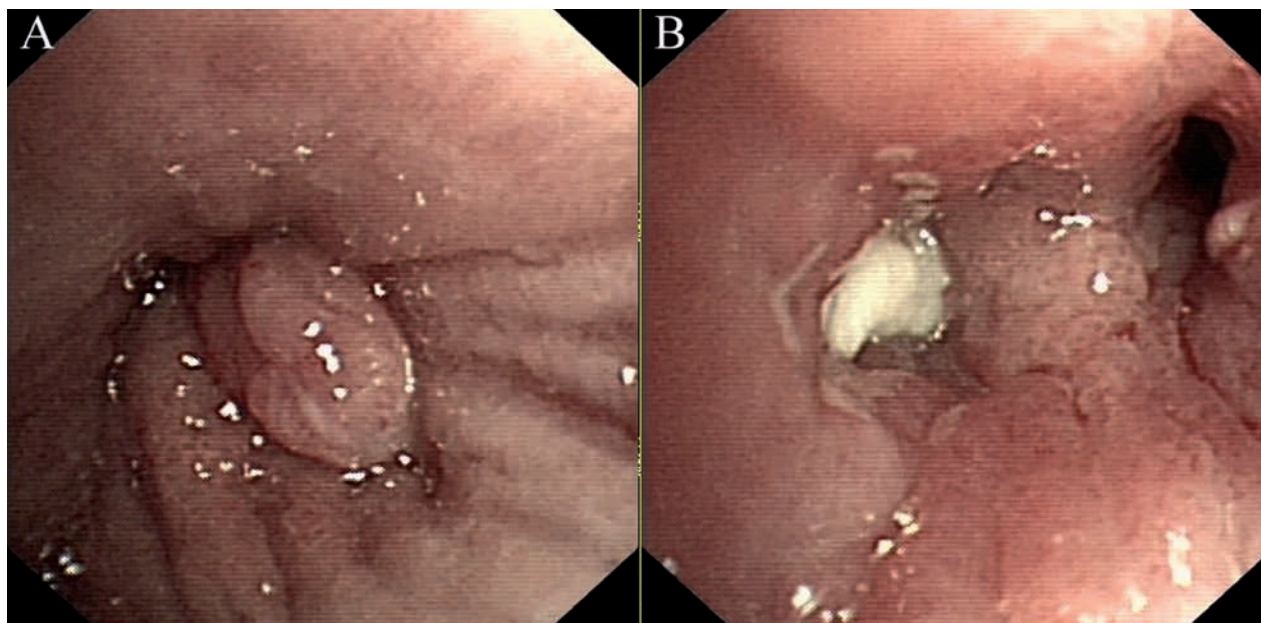


Fig. 3. Bronchoscopy performance: new organisms of the right upper lobe(A) and right lower back segment(B) obstructed bronchuses.

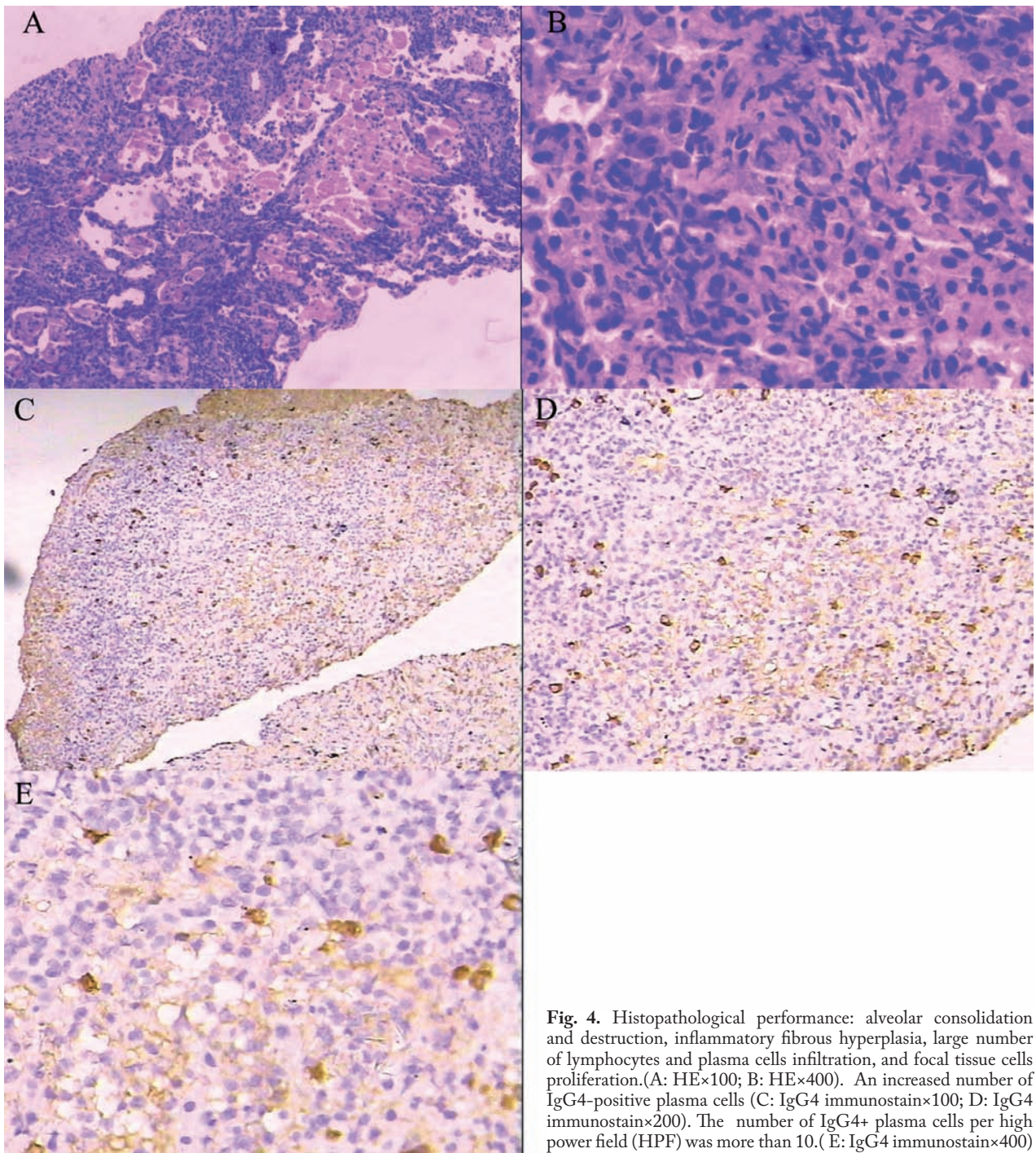


Fig. 4. Histopathological performance: alveolar consolidation and destruction, inflammatory fibrous hyperplasia, large number of lymphocytes and plasma cells infiltration, and focal tissue cells proliferation.(A: HE×100; B: HE×400). An increased number of IgG4-positive plasma cells (C: IgG4 immunostain×100; D: IgG4 immunostain×200). The number of IgG4+ plasma cells per high power field (HPF) was more than 10.(E: IgG4 immunostain×400)

rare that an IgG4-RLD only affected the lung. The case we reported was considered as solely lung involved IgG4-RD, because there was no evidence of extra-pulmonary organ involvement through the examination of PET-CT. IgG4-RLD had lately at-

tracted considerable attention. However, the clinical and pathological features of IgG4-RLD were not understood in detail. It was thus important to accumulate typical cases to reveal the precise characteristics of IgG4-RLD.

From January 2001 to January 2015, with “IgG4 related disease” [All Fields] AND “lung” [MeSH] in Pubmed search, a total of 25 articles in English were retrieved, and there were 89 cases of complete clinical data. Most of the articles reported only one case, and the 7 involved more than 2 cases. A review of the literature (Table 1) described the many facets of this disease through a number of case reports and case series, although there was yet insufficient information to comment on the disease’s epidemiology.

Pathogenetic mechanisms of IgG4-RD were not yet clear. Stone JH et al proposed that potential triggering factors were certain bacterial infection and subsequent formation of antibodies acting on self antigens through a molecular mimicry mechanism or autoimmunity (31). A related theory had proposed that *Helicobacter pylori* infection triggered autoimmune antibody production through molecular mimicry in genetically susceptible individuals (32). In genetically predisposed persons, these triggers provoked an immune reaction which was mediated predominantly by type 2 helper T (Th2) cells and activated regulatory T (Treg) cells in affected organs. Overexpression of Th2 cytokines, including interleukin (IL)-4, IL-5, and IL-13 and transforming growth factor- β (TGF- β) which were produced by activated Treg cells gave rise to eosinophilia, elevated serum IgG4 and IgE levels, and characteristic infiltration of IgG4-positive plasma cells and fibrosis in the tissue (31,33-34).

Imaging manifestations of IgG4-RLD were varied. Inoue et al (10) collected 13 cases of IgG4-RLD, and reported that it could be categorized into four major subtypes: 1) the solid nodular type, where a solitary nodular mass lesion was present (four cases); 2) the round ground-glass opacity (GGO) type, characterized by multiple round GGOs (two cases); 3) the alveolar interstitial type, with honeycombing, bronchiectasis, and diffuse GGO (two cases); and 4) the bronchovascular type, where there was thickening of bronchovascular bundles and interlobular septa (five cases). These 4 types of lesions can be either alone or in combination, and some cases may be accompanied by pulmonary hilar lymph nodes enlargement and pleural effusion(10-11). The CT findings in this case were also diverse, and which were consistent with those reported in the current literature.

Japanese scholars put forward the following diagnostic criteria of IgG4-RD in 2011(35): a

clinical examination showing characteristic diffuse/localized swelling or masses in either single or multiple organs; a hematological examination showing elevated serum IgG4 concentrations (>135 mg/dL) and a histopathological examination showing 1) marked lymphocyte and plasmacyte infiltration and fibrosis and 2) infiltration of IgG4+ plasma cells, a IgG4+/IgG+ cell ratio >40% and >10 IgG4+ plasma cells/HPF. The reported patient satisfied all three of the comprehensive diagnostic criteria for IgG4-RLD. Thus, a definitive diagnosis was made. The diagnosis of IgG4-RLD relied on a combination of the clinical symptoms, imaging findings, laboratory indicators and histopathological examination. The histopathological changes were especially important for the diagnosis. The clinical symptoms and imaging manifestations of the disease were nonspecific, and serum IgG4 levels were not detected routinely. Therefore, its diagnosis was very difficult. Due to lack of attention, the disease had long been missed diagnosis or misdiagnosis. So the clinicians need to raise awareness of this disease. The cases which lung tissue by biopsy contained more lymphocytes should be suggested to give IgG4 plasma cells immunohistochemical staining examination. Although IgG4-LD associated lung disease may occur alone, it may subsequently occur in other organs. So solely lung-involved IgG4-RLD should be followed up for a long period of time, and particular attention was paid to other organs.

Long-term follow-up data on IgG4-RD was still lacking. Some patients had malignant diseases (such as pancreatic cancer, non-hodgkin lymphoma) during the follow-up(36-38). The relationship between IgG4-RLD and lung cancer was not clear, and there was no report of IgG4-RLD secondary to lung cancer and other malignant tumors of the lung such as lymphoma. It was necessary to follow the history of patients with IgG4-RLD for longer to accurately reveal the risk of lung cancer and other malignant tumors.

An association between IgG4-RLD and atopic diseases such as bronchial asthma and allergic rhinitis had also been reported (7, 9, 11, 15, 21). And some of the patients often had a history of drug allergy (11, 22). In the pathogenesis of IgG4-RLD, IL-4, IL-13 and IL-5 secreted by Th2 cells and Treg cells can promote B cells to produce IgE. There is often eosinophilic infiltration in involved tissues, and IgE

Table 1. Literature review of clinical characteristics of IgG4-RLD

Year	First author	Number of cases	Age	Gender	Allergic diseases	Symptom	Extrapulmonary diseases	The level of IgG4	Treatment	Prognosis
2013	Matsui S (7)	18	62	14 M, 4 F	Rhinosinusitis (n=1) Asthma (n=1)	Cough (n=5)	AIP (n=12), CSS (n=9), RPF (n=3), lacrimal gland (n=5), bile duct (n=2), renal (n=3), prostate (n=3)	1635 mg/dL	Corticosteroid therapy (n=15)	Good response to corticosteroids
2013	Kitada M (8)	2	62	1 M, 1 F	NR	Bloody sputum (n=1)	AIP (n=1)	335 mg/dL	Corticosteroid therapy (n=1)	The densities noted on chest scans disappeared
2012	Matsui S (9)	13	61	11 M, 2 F	Rhinitis/sinusitis (n=6) Asthma (n=5) Both of them (n=4)	Cough (n=5), Dyspnea (n=1)	AIP (n=3), nephritis (n=3), RPF (n=1), hypophysitis (n=1)	926 mg/dL	Corticosteroid therapy (n=11)	All responded to steroids, one relapse after 3 years
2009	Inoue D (10)	13	70	9 M, 4 F	NR	Cough (n=7), fever (n=4), dyspnea (n=2), chest pain (n=1)	AIP (n=3), CSS (n=3), periaortitis (n=2), renal (n=3), prostate (n=1)	752 mg/dL	NR	NR
2009	Zen Y (11)	16	69	12 M, 4 F	Rhinitis/sinusitis (n=2) Asthma (n=6) drug allergy (n=1)	Cough or bloody sputum (n=10)	AIP (n=3), CSS (n=4), RPF (n=2), renal (n=1), bile duct (n=1)	690 mg/dL	Surgical resection (n=8) Corticosteroid therapy (n=6)	Resected with no recurrence; Good response to corticosteroids
2009	Shrestha B (12)	6	69	5 M, 1 F	NR	Cough (n=2)	AIP (n=6), renal (n=1), bile duct (n=1), periaortitis (n=1)	765 mg/dL	Corticosteroid therapy (n=1); NR (n=5)	Pulmonary shadow dissipated, relapse after 1 year
2008	Yamashita K (13)	3	72	3 M	NR	Dyspnea (n=2)	NR	196 mg/dL	Surgical resection (n=1) Corticosteroid therapy (n=2)	Resolved with steroid; resected with no recurrence
Single case reports	(6,14-30)	18	65	13 M, 3 F Others NR	Rhinitis/sinusitis (n=2); Asthma (n=2) drug allergy (n=2)	Cough (n=9), fever (n=4), dyspnea (n=7), Bloody sputum (n=6), chest pain (n=1)	AIP (n=12), CSS (n=8), RPF (n=4), lacrimal gland (n=4), bile duct (n=3), renal (n=3), prostate (n=2), periaortitis (n=2)	712 mg/dL	Surgical resection (n=5) Corticosteroid therapy (n=12)	Steroid generally effective
Total		89								

M male; FM female; NR Not reported; AIP Autoimmune pancreatitis; CSS Chronic sclerosing sialadenitis; RPF Retroperitoneal fibrosis

levels and eosinophils increase in peripheral blood. Rituximab can treat refractory IgG4-RLD, and the serum IgE level of patients after treatment decreased faster than IgG4 (31,39). So it was considered that chronic allergic reaction may also be involved in the occurrence of IgG4-RLD.

At present, most of the reports considered that corticosteroids therapy is effective for the treatment of IgG4-RLD, so systemic corticosteroids are the first line of treatment. Although the optimal dose and duration of treatment for IgG4-RLD are still to be studied. Significant elevation of serum IgG4 level is common in patients with IgG4-RLD. After hormone therapy, it may decline or even return to the normal level, which can be used as an indicator of the effect of the therapy. However, the IgG4 levels of 2 cases were normal among 89 cases in the literature review (21,29). So the normal level of IgG4 can not rule out the diagnosis of IgG4-RD, and it is unclear whether there is any causal relationship with the etiology. The overall prognosis of this disease is good, but there are also cases recur after stopping treatment (23,27). In nonresponsive or recurring cases, other immunosuppressives such cyclosporine are suggested (40,41). More recently, some small sample studies carried out demonstrated some therapeutic prospects of rituximab (31,39).

In summary, IgG4-RLD is relatively rare. The clinical manifestations of the disease are nonspecific, and the imaging features are mixed with several types. The disease can only be involved in the lung, but also multiple organ involvement. Solely lung-involved IgG4-RD is not only extremely rare but also easily misdiagnosed as tuberculosis, lung cancer, lymphoma and other common pulmonary diseases. Histopathological examination is the key to the diagnosis of the disease. Corticosteroids are the first choice of treatment, and the prognosis is good.

Authors' Contribution: Xiao-Qin Zhang and Guo-Ping Chen contributed equally to this work.

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