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# Lung Manifestations of IgG4-related Disease. A multifaceted disorder. Presentation of two cases and short review of the literature

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**Abstract.** Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a recently described systemic inflammatory disease associated with elevated circulating levels of IgG4. IgG4-RD may affect one or more organs and lesions can present synchronously or metachronously in different organs. Pulmonary involvement of IgG4-related disease includes airway, lung parenchyma, pleura and mediastinum. In this article, we report two cases of IgG4-RD to show the multifaceted manifestations of this disease in the lungs. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 74-80)*

**Key words:** IgG4 related disease, lung, pleura

## Introduction

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a recently described systemic inflammatory disease associated with elevated circulating levels of IgG4 (1). Histopathologically, this disease is characterized by dense infiltration of IgG4-positive plasma cells and lymphocytes, storiform fibrosis and obliterative phlebitis in affected organs (2, 3).

IgG4-RD can affect many organs, including the biliary tract, pancreas, liver, kidney, salivary glands, lacrimal glands, retroperitoneum, aorta and lungs (2). Pulmonary involvement of IgG4-RD includes airway, lung parenchyma, pleura and mediastinum (4). The clinical presentation of the disease may be quite variable. Therefore, diagnosis requires a high index of suspicion. In this article we report two cases of IgG4-RD to show the multifaceted manifestations of this disease in the lungs.

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## Case 1

A 51-year-old man with a previous history of smoking (45 packs/year) presented to medical attention with dyspnoea and a dry cough. He underwent a chest X-ray, which showed massive pleural effusion in the left pleural cavity without parenchymal abnormalities (Fig. 1). Despite a course of antibiotics, his symptoms progressed and, accordingly, he was admitted to our ward. His medical history was significant for an antiphospholipid-antibody syndrome with pulmonary thromboembolism and deep vein thrombosis when he was 30 years old.

Physical examination revealed evident reduction in breath sounds at the bottom left lung and blood gas analysis showed moderate hypoxemia ($PaO_2$=62 mm Hg). Blood tests detected mild anaemia, increased inflammatory markers (erythrocyte

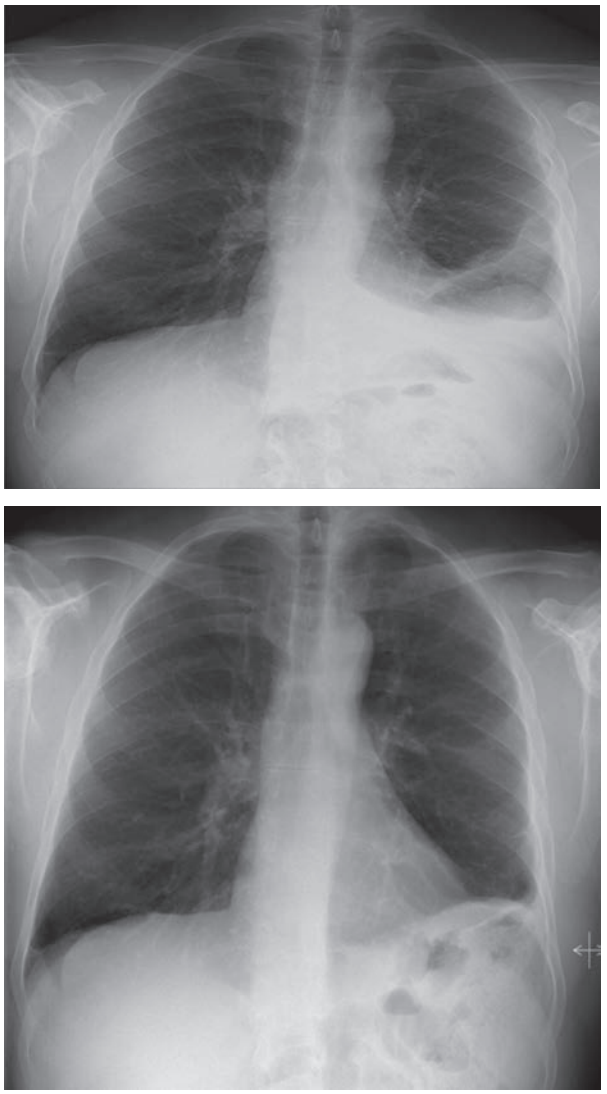

**Fig. 1.** Chest X-ray showing pleural left effusion without parenchymal abnormality (*upper*). Chest X-ray after one month of systemic corticosteroid therapy showing improvement (*lower*)

sedimentation rate, C-reactive protein) and an increase in plasma levels of IgG4 (230 mg/dL). The CT (computed tomography) scan showed partially organized left pleural effusion, small areas of atelectasis in the lingula and anterior basal segment of the left lower lobe and an increase in volume of some of the lymph nodes in the paratracheal and subcarinal stations (Fig. 2).

Multiple biopsies were performed under thoracoscopy and 850 cc of orange-citrine liquid were evacuated. The thoracoscopy pointed to the presence of two coarse adhesions to the lower lobe, a thickened visceral pleura with whitish appearance and a very thickened parietal pleura, with nodules showing a lardaceous appearance (Fig. 3).

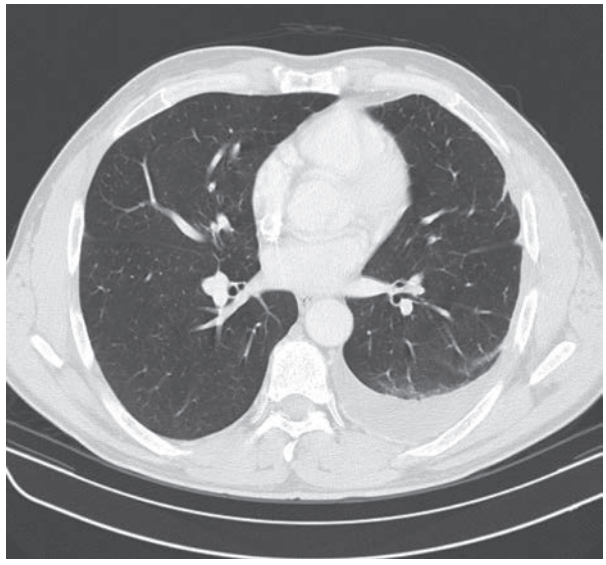

**Fig. 2.** Chest CT SCAN showing left pleural effusion

The cytology of the pleural fluid showed a reactive cytological framework with erythrocytes, lymphocytes, plasma cells, neutrophils, numerous eosinophils, alveolar macrophages and mesothelial cells with hyperplastic behaviour.

Histopathological examination of biopsy samples of the parietal pleura (Fig. 4) was characterized by a lymph plasmacellular inflammatory process, perivascular, interstitial and plasma cell infiltration (MUM1, CD138 +) with a typical discrete proportion of IgG4-positive cells (approximately 20%). These findings were attributable to IgG4 disease. The microbiological examination performed on the pleural fluid and pleural biopsy was negative.

The patient was treated with prednisone at a dose of 0.6 mg/kg/day for 4 weeks, which was then gradually reduced to a maintenance dosage of 10 mg/day. After a month of systemic corticosteroid therapy, a chest X-ray showed a significant improvement (Fig. 1).

## Case report 2

A 52-year-old man patient was admitted to our department with dyspnoea and limb weakness.

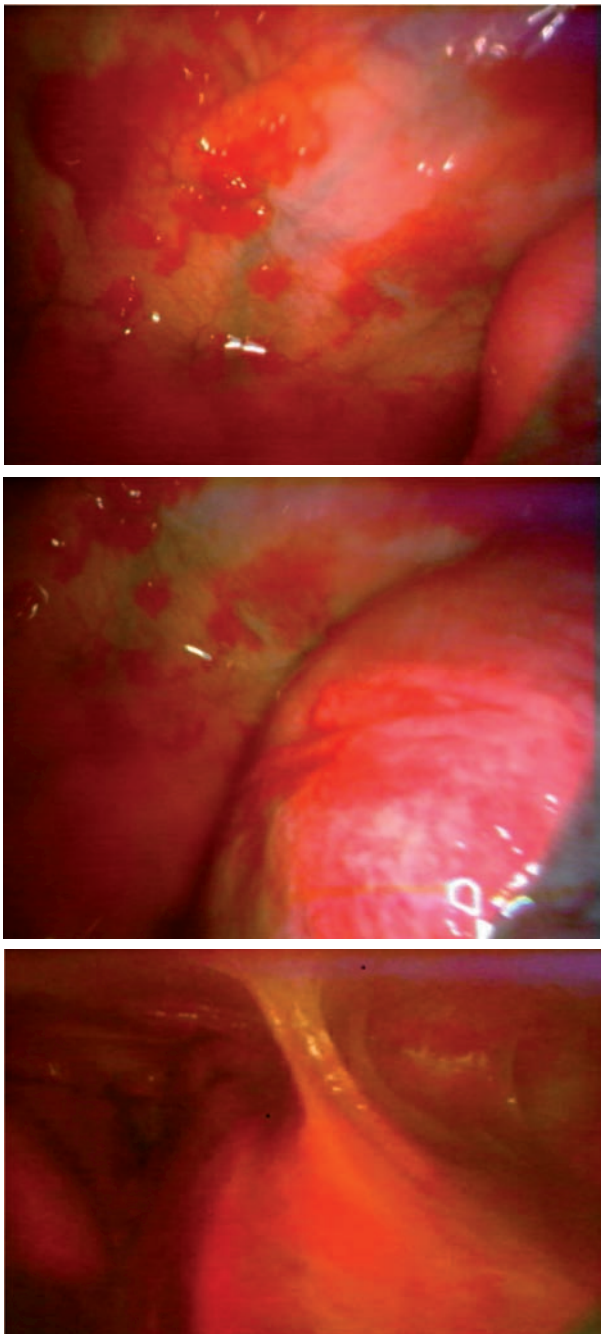

**Fig. 3.** Thoracoscopy: presence of two coarse adhesions at upper and lower lobe, a thickened and whitish visceral pleura, a very thickened parietal pleura, lardaceous with some detected areas

He had Type 2 diabetes mellitus and was a former smoker (20 packs year). Physical examination revealed light reduction in breath sounds and paraparesis. Blood tests showed an increase in plasma levels of IgG4 (318 mg/dL).

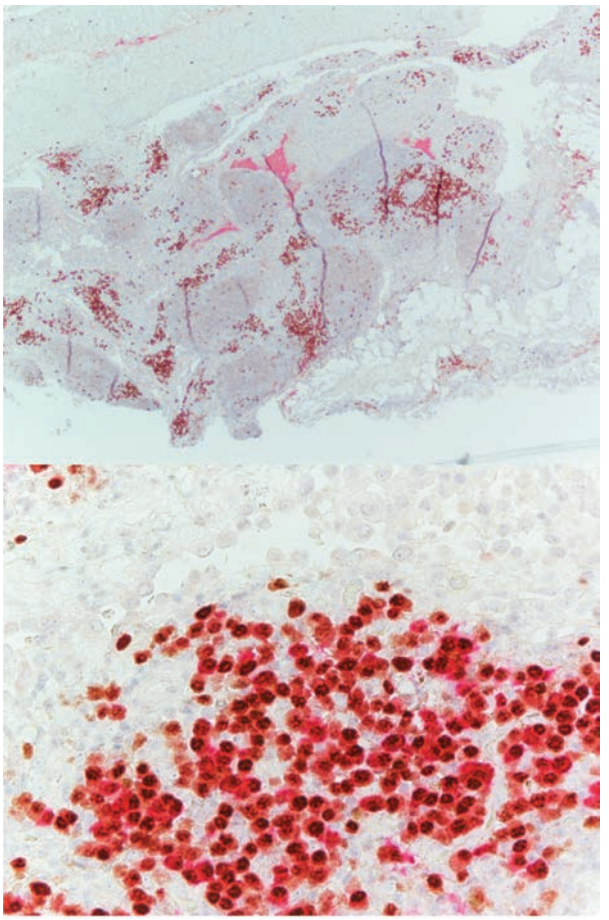

**Fig. 4.** Pleural biopsy. Marked pleural thickening by diffuse inflammation with dense fibrosis that extends into the subpleural fibrous and fatty tissue (Immunochemistry, 10X) (*upper*); lymphoplasmacytic infiltration within the fibrosis (lymphocytes and plasma cells of small size) and the presence of small lymphoid follicles; high ratio of IgG4-/IgG-positive plasma cells (MUM-1(Brown) –IgG4(Red) (Immunochemistry, 40X) (*lower*)

A CT scan showed patchy ground-glass consolidation associated with bronchiectasis and signs of fibrosis in the apical segment of the right upper lobe and the apical segment of the left lower lobe (Fig. 5).

Magnetic resonance imaging revealed central syringomyelia, which diffusely compressed the spinal cord from C2 through to T5 and a bulging disc marking the bone marrow area with bilateral foraminal stenosis in C5-C6 (Fig. 6).

Multiple biopsies performed under bronchoscopy showed almost complete stenosis of the right upper bronchus and right apical lower bronchus.

Histopathological examination of fragments of the bronchial wall (Fig. 7) was characterized by

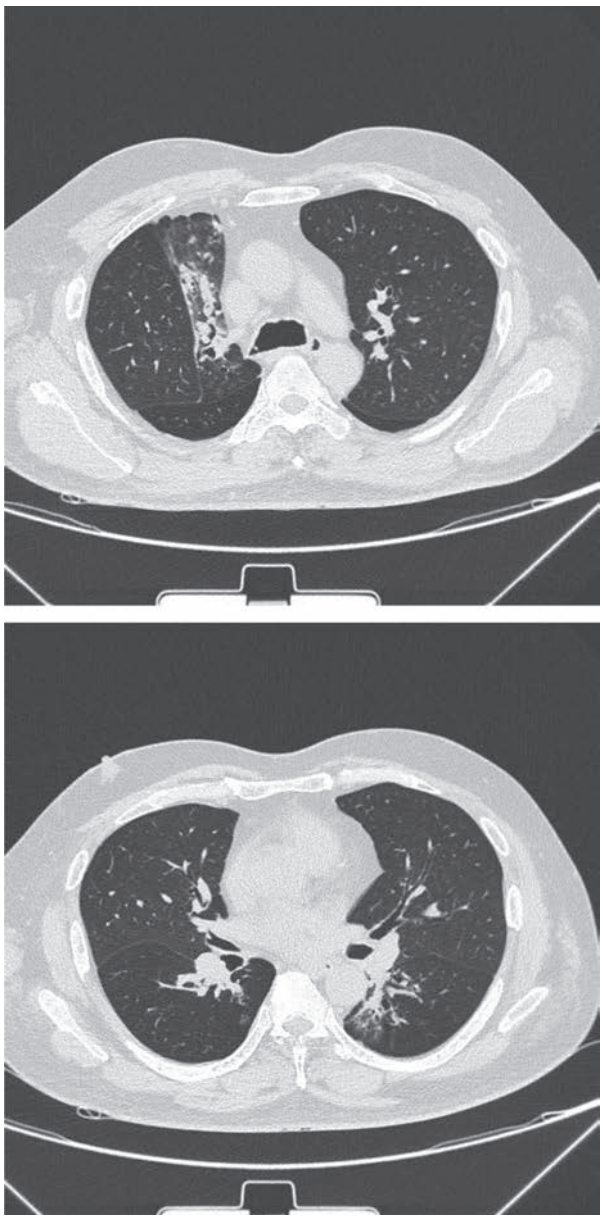

**Fig. 5a.** Chest CT SCAN: patchy ground-glass consolidation associated with bronchiectasis, and fibrosis of the apical segment of the right upper lobe and the apical segment of the left lower lobe

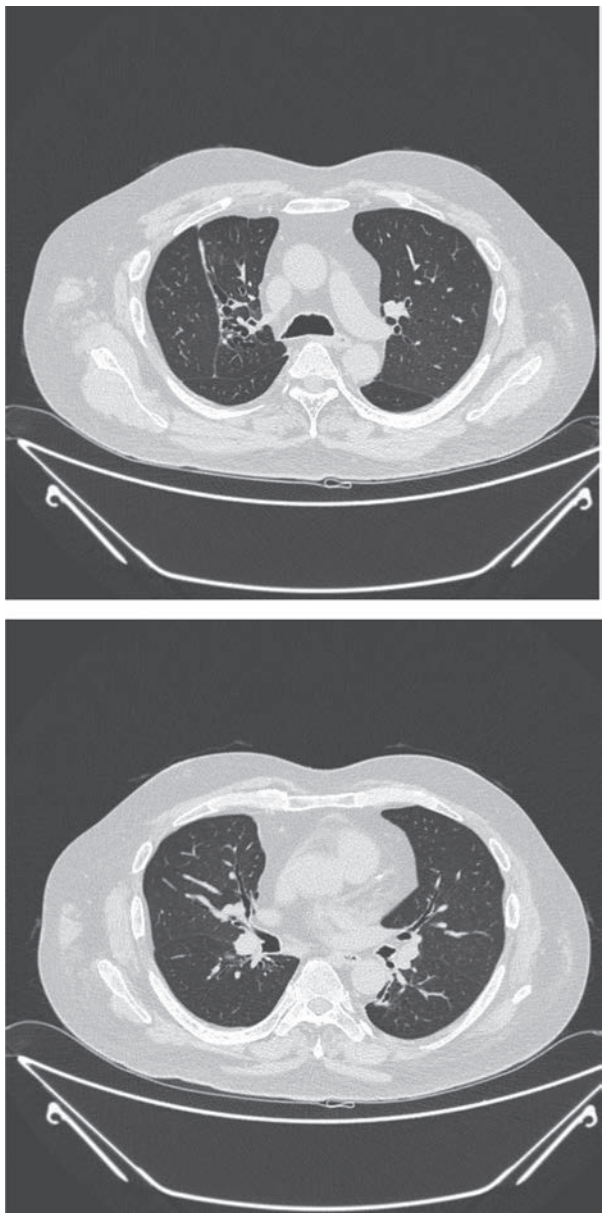

**Fig. 5b.** Chest CT SCAN: Reduction of consolidative areas in the right upper lobe and the left lower lobe after a month of systemic corticosteroid therapy

a dense lymphoplasmacytic infiltrate with >20/HPF IgG4 plasma cells and IgG4/IgG ratio >40% and mild fibrosis. These findings are consistent with IgG4-RD.

The microbiological examination performed on bronchial washing was negative. The patient was treated with prednisone at a dose of 0.6 mg/kg/day for 4 weeks, which was then gradually reduced to a maintenance dosage of 10 mg/day. After a month of systemic corticosteroid therapy, a chest CT scan showed an improvement with a reduction in the areas of consolidation in the right upper lobe and the left lower lobe (Fig. 8). Unfortunately, limb weakness progressed and the patient underwent laminotomy from C2 to T5. After two months of rehabilitation, the patient's neurologic symptoms improved.

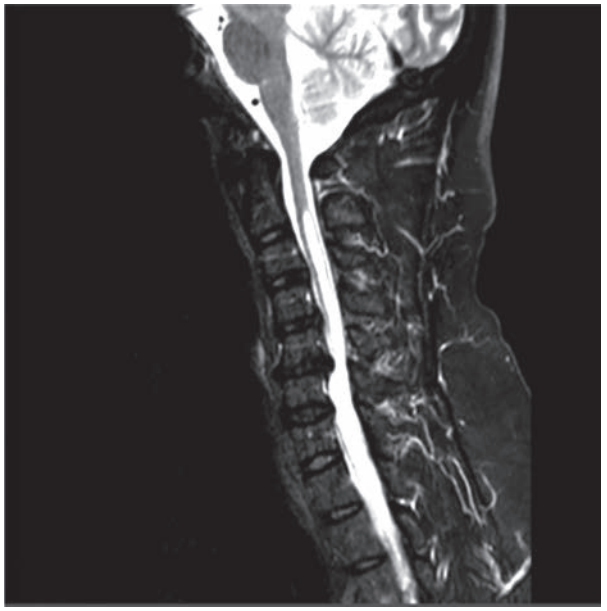

**Fig. 6.** Magnetic resonance imaging: central syringomyelia which diffusely compressed spinal cord along the C2 to T5 levels and bulging disc that mark the bone marrow area and to fix bilateral foraminal stenosis in C5-C6

## Discussion

IgG4-RD is a systemic inflammatory condition that is characterized by specific histological findings of the involved organs (lymphoplasma cell infiltration stained with IgG and IgG4, storiform fibrosis, and obliterative phlebitis) and increased serum IgG4 levels (1). Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, others show involvement of a single organ (1).

Recent investigations have focused on the interactions between cells of the B cell lineage and a novel CD4+ SLAMF7+ cytotoxic T cells capable of promoting fibrosis.

Plasmablasts appear to play a crucial role along with B cells in the presentation of antigen to this T cell (5).

Clinical symptoms vary depending on the affected organ and steroid therapy is often effective (1).

The first case of IgG4-RD was reported by Sarles et al. (6), who described a sclerosing pancreatitis with hypergammaglobulinemia. In 2001, Hamano et al. (2) revealed the association of high serum IgG4 concentration with autoimmune pancreatitis

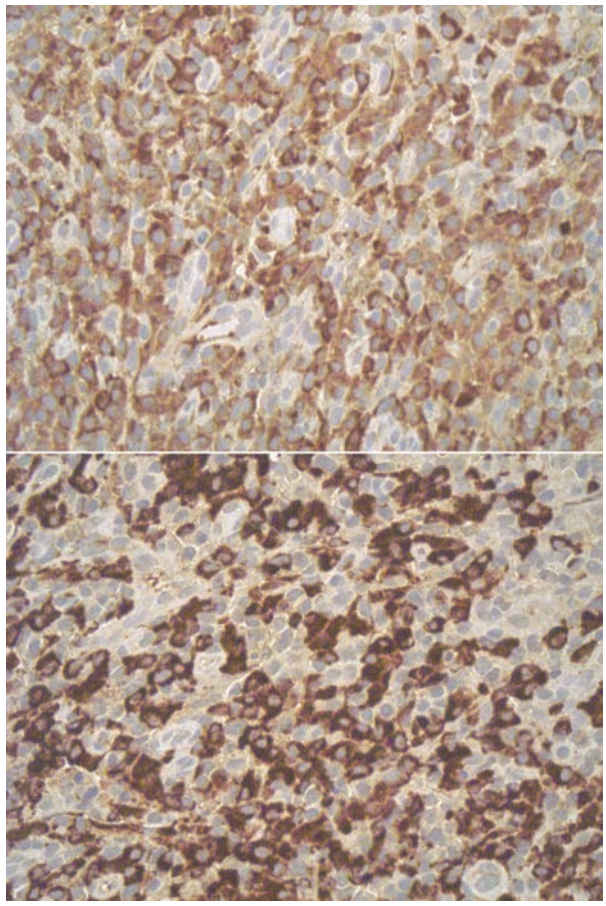

**Fig. 7.** Bronchial biopsy. Dense lymphoplasmacytic infiltrate, with > 20/HPF IgG4 plasma cells and IgG4/IgG ratio >40% (Immunochemistry, 10X)

(or sclerosing pancreatitis), and Kamisawa et al. (7) proposed autoimmune pancreatitis as a systemic disease based on the histological results of samples from multiple sites which were positive for IgG4.

The intrathoracic manifestations of IgG4-RD appear to be rather heterogeneous, resulting from involvement not only of the lung parenchyma, but also of the intrathoracic lymph nodes, mediastinum and pleura, as well as the airways (4) (Table 1).

Diagnosis is based on symptoms, biochemistry (serum IgG4 level ≥135 mg/dL) and histopathological characteristics (marked lymphocytic and plasmacytic infiltration and fibrosis) (8,9). The ratio of IgG4/IgG positive cells in tissue should be greater than 40% and more than 10 IgG4-positive plasma cells per high power field should be found on tissue sample (9). Based on symptoms, biochemistry and histopathological features, the IgG4-RD is classified

**Table 1**

| Patterns of intrathoracic involvement in IgG4 related disease |
|---|
| Airways |
| Tracheobronchial Stenosis |
| Parenchimal |
| Nodules (Rounded opacities) <3 cm solid or ground glass |
| Masses >3 cm |
| Interstitial lung disease (UIP-NSIP-COP) |
| Pleural |
| Pleural nodules |
| Pleural effusion |
| Pleuritis with fibrinous exudates |
| Mediastinal |
| Lymphadenopathy ( mediastinal and/or hilar lymphadenopathy) |
| Fibrosing mediastinitis |

into definite (symptoms and biochemical and histopathology), probable (symptoms and histopathology only) or possible (symptoms and biochemical markers only) disease (9). Accordingly, our cases can be classified as a definite IgG4-RD

Substantial overlap in the types of organ involvement and histopathological features occur in IgG4-RD and vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA). Elevation of IgG4 in granulomatosis with polyangiitis (GPA) has been reported for several decades, and may play a pathogenic role. High tissue IgG4 levels have been noted on retrospective review of the pathology of patients with GPA . Cases of GPA initially diagnosed as IgG4 related disease have been reported (10).

Recently, Keenan et al described a patient who presented with alveolar haemorrhage, a positive antineutrophil cytoplasmic antibody (anti-serine protease 3 pattern) and had histopathology that met the proposed criteria for IgG4 related disease (11).

IgG4-related lung disease can present in various forms according to involved sites: parenchyma (nodules or masses, or interstitial pneumonia); airway (tracheobronchial stenosis); pleura (pleural nodules or effusions); mediastinum (lymphadenopathy or fibrosing mediastinitis) (4). Although the exact proportion of pleural effusions among IgG4-related lung disease is uncertain, it may be a less common manifestation. Zen et al. (12) collected 21 cases of IgG4-related lung disease, and reported that 5 had pleural lesions. Matsui et al. (13) analysed 18 patients retrospectively based on their clinical, radiological and pathological features. They found that all 18 patients had hilar and mediastinal lymphadenopathy and nobody had pleural effusion (13).

The characteristic histopathological features of IgG4-related pleuritis are as follows: 1) the pleura is thickened by diffuse sclerosing inflammation, and extends into the subpleural fibrous and fatty tissue, 2) inflammation consists of lymphocytes and plasma cells, 3) eosinophilic infiltration is frequently seen, but neutrophilic infiltration is rare, 4) obliterative phlebitis is commonly found, and 5) abundant IgG4-positive plasma cell infiltration is observed, and the ratio of IgG4-/IgG-positive plasma cells is high (>40%) (10). The pleural biopsies of our case fulfilled most of these characteristics and, typically, our patient also showed improvement of clinical symptoms and radiological findings after systemic steroid treatment, which is considered the primary therapy for IgG4-related disease. The exact dose and duration are unclear. A consensus statement from Japan suggested prednisolone at 0.6 mg per kilogram of body weight per day for two to four weeks followed by a taper to 5mg per day over 3-5 months and maintenance 2.5 mg or 5 mg per day for up to three years. Methotrexate, azathioprine, and mycophenylate mofetil have been used as steroidsparing agents or maintenance medications.

More recently, excellent response rates have been recorded with the use of rituximab to deplete B cells (1, 14). The role of surgery is uncertain. In cases of isolated lung lesions refractory to immunosuppressive therapy, a surgical option may be considered if patients have significant symptoms and/or demonstrate significant organ impairment. Future studies will further inform our understanding of the pathogenesis, natural progression, treatment and prognosis. On the other hand, spinal cord involvement is rare and there are only few reports of IgG4-related sclerosing pachymeningitis (15). The majority of patients did not respond to steroid therapy and underwent surgical laminotomy (15) .

In conclusion, IgG4-RD is not common, but an increasingly reported disease entity with systemic involvement. Lung is also a target organ of IgG4-RD and their manifesting patterns are various and multifaceted. Detailed histopathological and immunohistochemical analyses and measurement of serum IgG4 are required for correct diagnosis and treatment. Clinicians should consider IgG4-RD as a

differential diagnostic disease in patient with systemic or localized inflammatory disease with unknown aetiology. Our cases also confirm the key role of the bronchoscopy and thoracoscopy in the diagnosis of pleural disorders.

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