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IgG4-related disease of the lung: a case series of 6 patients and review of the literature

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Abstract. IgG4 related disease has been recently proposed as a unifying term for a group of inflammatory conditions previously referred to by a plethora of other names. The common denominator for these entities is the histopathologic finding of lymphocytic infiltrates rich in IgG4 producing plasma cells, often accompanied by storiform fibrosis and obliterative phlebitis. Many medical conditions have been attributed to IgG4-related disease, but few reports of IgG4-related lung disease have been published, and it remains a rare condition about which little is known. In this report, we describe the clinical and pathologic features of six patients with IgG4-related disease of the lung. Patients were followed 1 - 5 years following their diagnosis. We describe unique features of IgG4-related lung disease, including one patient who presented with alveolar hemorrhage and a positive anti-neutrophil cytoplasmic antibody and two patients whose disease improved after treatment with mycophenylate mofetil. Two patients presented with pulmonary pseudotumor. We conclude that the clinical presentation of IgG4-related lung disease varies widely, and histopathology remains the key to diagnosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 360-367)*

Key words: interstitial lung disease, autoimmune pancreatitis, pulmonary IgG4

Introduction

IgG4 related disease (IgG4-RD) has been recently proposed as a unifying term for a group of inflammatory conditions previously referred to by a plethora of other names. Originally described in Japan in association with autoimmune pancreatitis, a comprehensive approach for the varied clinical presentations has been created, along with some organ specific pathologic criteria (1,2). The common denominator for these entities is the histopathologic characteristics of the inflammatory process. We report here a series of 6 patients with IgG4-RD of the lung with varying clinical presentations and unique features that have not been reported previously.

Methods

Patients were identified by reviewing the Interstitial Lung Disease database at the University of Minnesota and during case review at a community hospital. Five patients were diagnosed and treated at the University of Minnesota Medical Center-Fairview in Minneapolis, Minnesota. The sixth was treated at HealthPartners Medical Group in Saint Paul, Minnesota. Data collection was approved by

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institutional review boards at the respective hospitals and subjects consented to their inclusion. We performed chart reviews to abstract clinical data. Chest computerized tomography (CT) scans were reviewed with a chest radiologist, and lung biopsies were reviewed with a pathologist. The cases exhibit pathologic features highly suggestive of IgG4-RD based on proposed IgG4-RD diagnostic criteria in the appropriate clinical setting (1,2).

Results

The demographic characteristics of the 6 patients with pulmonary IgG4-RD are reviewed in Table 1. Mean age was 55.2 years, and 5 of the 6 patients were male. Only one patient had pancreatitis.

Table 1. Patient characteristics

Age	55.2±11.7
Sex - Female	1\6
Tobacco Use	2\6
Pancreatitis	1\6
Prior COPD Diagnosis	1\6
Ethnicity	
Asian	1\6
African American	2\6
Caucasian	3\6
ANCA +	2\6

Five of the 6 patients were treated with corticosteroids (see patient descriptions below). Chest computed tomography scan findings varied (Table 2). Four patients had mediastinal adenopathy, 2 patients had ground glass opacities, and 4 patients had a lung mass or nodules (one patient had a solitary mass, while the others had multiple findings). Laboratory and histologic descriptions are listed in Table 3.

Patient 1

A 38 year-old male with a history of ulcerative colitis presented with fatigue, jaundice, and hemoptysis. He was diagnosed with autoimmune hepatitis and diffuse alveolar hemorrhage. High resolution CT scan revealed patchy ground glass opacities with interlobular septal thickening and mediastinal adenopathy. Serum anti-neutrophil cytoplasmic antibody (ANCA) was positive (1:320) with an elevated anti-serine protease 3. Serum IgG level was increased at 1710 mg/dL (695-1620 mg/dL) and IgG4 level was 150 mg/dL (11-86 mg/dL).

A wedge biopsy of the lung showed diffuse expansion of the interstitium by dense lymphoplasmacytic inflammation with a lymphangitic distribution (Fig. 1). There were numerous IgG4 staining plasma cells (more than 100 per high power field) (Fig. 2). Transmural inflammation with various degrees of

Table 2. Chest computed tomography findings

Patient	Chest computed tomography findings
1	Patchy ground glass with interlobular septal thickening, mediastinal lymphadenopathy
2	Patchy ground glass, mediastinal and subcarinal lymphadenopathy
3	Scattered pulmonary nodules, diffuse lymphadenopathy
4	Spiculated right upper lobe mass
5	Multiple nodules, right upper lobe mass
6	Septal thickening, small nodules, mediastinal lymphadenopathy

Table 3. Pathologic findings

Patient	Biopsy Tissue	Histologic Findings	Serum IgG or IgG4 level (mg/dL)
1	lung, kidney	interstitial plasma cells, lymphoplasmacytic nephritis	IgG 1710 IgG4 150
2	lung	vasculitis, incl venules, plasma cells	IgG 3190, IgG4 831
3	Inguinal lymph node, parotid gland	lymphocyte and plasma cell inflammation	IgG4 4280
4	lung	lymphoplasmacytic inflammation, vasculitis	IgG 1200, IgG4 37
5	FNA lung mass	fibrosis and lymphoplasmacytic inflammation	IgG 1090, IgG4 54
6	open lung	dense lymphoplasmacytic hyperplasia	IgG 1120, IgG4 162

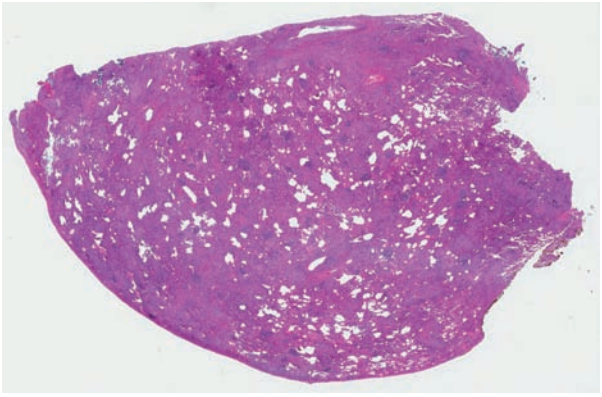

Fig. 1. Wedge biopsy of the lung showing interstitial inflammation with lymphoid aggregates with a lymphangitic distribution (Hematoxylin and eosin stain, panoramic view)

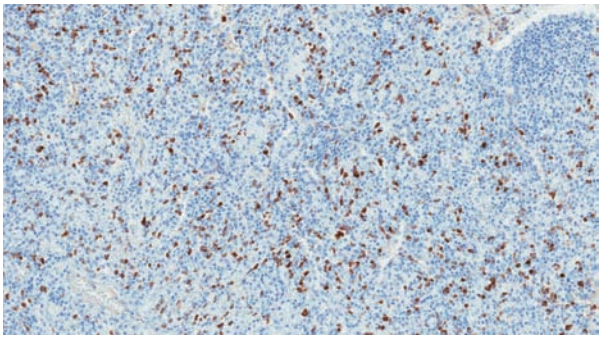

Fig. 2. The interstitial inflammation contains numerous IgG4 positive cells (IgG4 immunostaining)

luminal obliteration was present in numerous medium sized to small arteries and veins as well as peribronchiolar inflammation (Figg. 3 and 4). There were no granulomas, necrotizing vasculitis, neutrophilic capillaritis or parenchymal necrosis. The explanted liver showed severe chronic active hepatitis with submassive necrosis with portal and lobular inflammation containing abundant plasma cells many of which were IgG-4 positive.

The patient ultimately underwent a successful liver transplantation. Post-transplant, his hemoptysis resolved, and his chest x-ray normalized. The improvement was felt to be secondary to immunosuppression following his liver transplant. The patient has been stable for three years on mycophenylate mofetil (MMF) and low dose prednisone for his liver allograft without pulmonary symptoms.

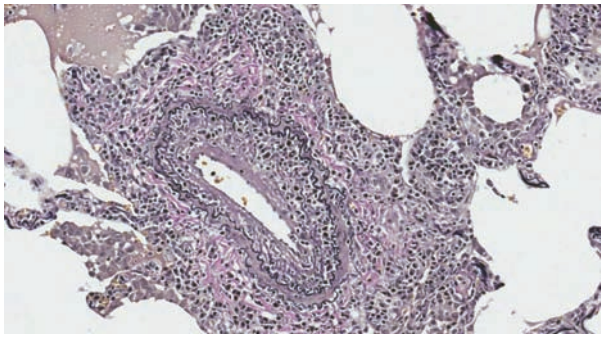

Fig. 3. Intimal inflammation in a small muscular artery (Verhoeff Van Gieson stain)

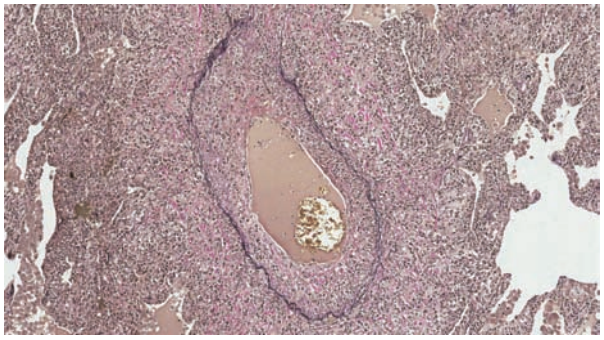

Fig. 4. Obliterative venulitis (Verhoeff Van Gieson stain)

Patient 2

A 65 year-old male with a 30 year history of colitis was evaluated for fatigue, weight loss, cough, parotid enlargement and generalized lymphadenopathy. Chest CT scan showed ground glass opacities and mediastinal and subcarinal adenopathy. Serum IgG and IgG4 levels were elevated at 3190 mg/dL and 831 mg/dL, respectively. A wedge biopsy specimen of the lung revealed patchy interstitial lymphoplasmacytic inflammation with numerous IgG-4 immunoreactive cells (more than 50 per high power field), non-necrotizing vasculitis and patchy interstitial fibrosis.

He was treated with prednisone 40 mg daily with a slow taper over several months. On therapy, he gained weight and had improvement in diffusing capacity, CT findings, and salivary gland size. Symptoms recurred with prednisone dose taper, and MMF was added as a steroid-sparing agent. Pred-

nisone was tapered off, and he has been clinically stable on MMF for several years.

Patient 3

A 59 year-old male presented with weight loss and parotid hyperplasia. Chest CT scan showed scattered pulmonary nodules and diffuse lymphadenopathy. Serum IgG4 was 4280 mg/dL. Parotid gland biopsy showed chronic sialadenitis rich in IgG-4 plasma cells (more than 100 per high power field), acinar atrophy and fibrosis.

Prednisone was initiated at 30 mg daily, with improvement in parotid gland swelling and fatigue. IgG4 level decreased to 1282 mg/dL. His prednisone dose was slowly tapered to 20 mg daily over several months. Chest CT two months later showed decreased adenopathy and pulmonary nodule size. IgG4 level decreased to 476 mg/dL.

Patient 4

A 61-year old female with past medical history of juvenile rheumatoid arthritis presented with a spiculated 3 cm mass found incidentally on chest CT (Fig. 5). The patient had no additional systemic or pulmonary symptoms. Wedge biopsy of the lung showing interstitial inflammation with a non-specific interstitial pneumonia-like pattern (Fig. 6), extensive peribronchiolar and perivascular lymphoplasmacytic inflammation with abundant IgG-4 immunoreactive cells (more than 50 per high power field) (Figg. 7,8) obliterative venulitis (Fig. 9) and focal storiform fibrosis. There was no evidence of malignancy. Serum IgG and IgG4 levels were within normal limits. She received no further treatment and remained asymptomatic over three years.

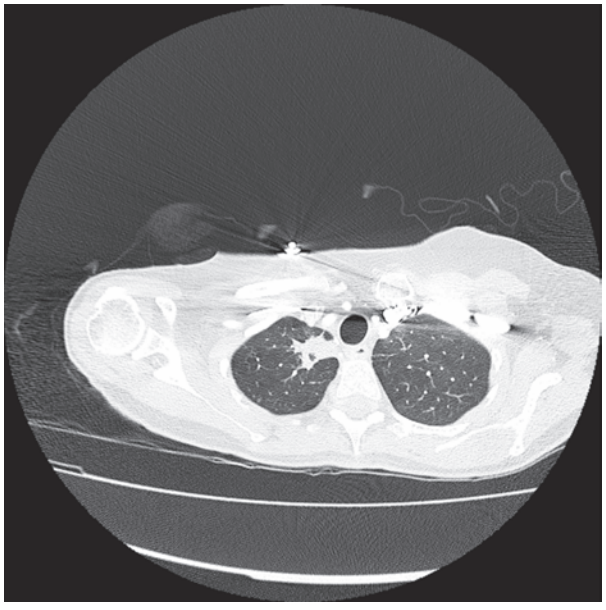

Fig. 5. Chest computed tomography image of spiculated mass in right upper lobe

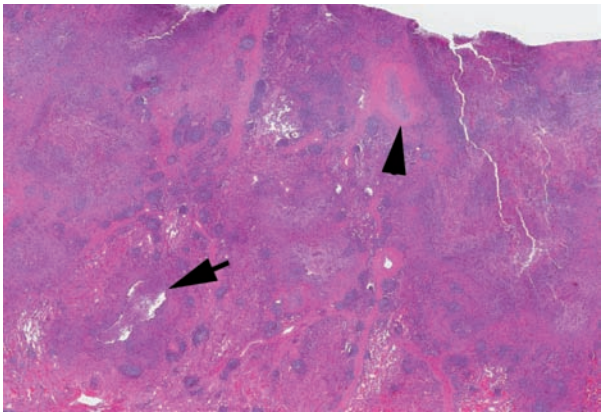

Fig. 6. Interstitial inflammation a non-specific interstitial pneumonia pattern, bronchiolitis with peribronchiolar lymphoplasmacytic inflammation (arrow) and obliterative venulitis (arrowhead) (Hematoxylin and eosin stain, panoramic view)

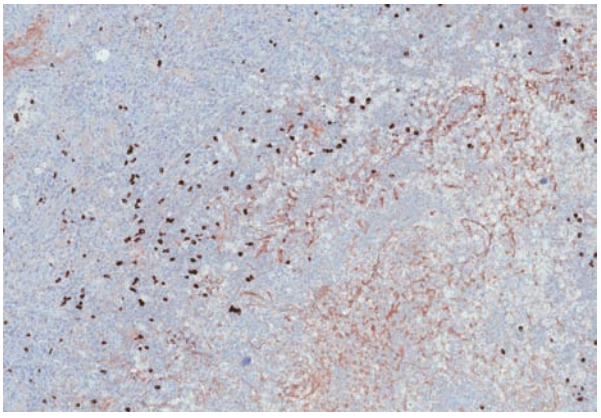

Fig. 7. The interstitial inflammation contains numerous IgG4 positive cells (IgG4 immunostaining)

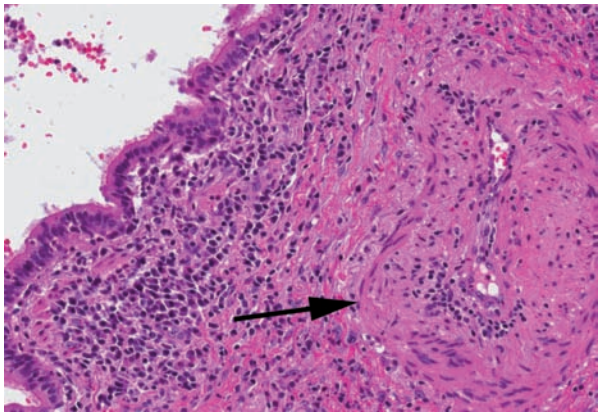

Fig. 8. High power image showing peribronchiolar inflammation and intimal inflammation and obliteration on an adjacent artery (Hematoxylin and eosin stain)

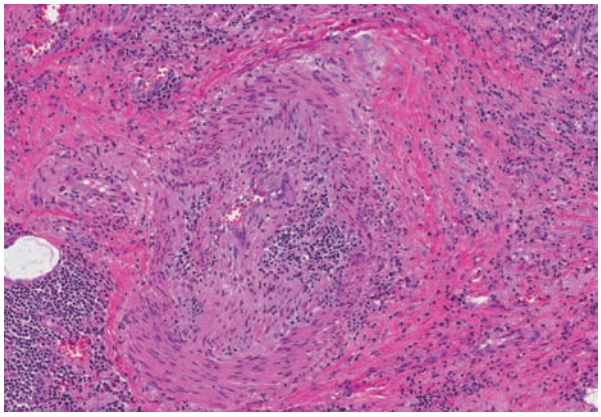

Fig. 9. Obliterative venulitis (Hematoxylin and eosin stain)

Patient 5

A 65 year old male with history of tobacco use was evaluated for dyspnea, dysphagia, and 100-pound weight loss over two years. CT chest showed a 4 cm rounded mass in the medial right upper lobe along with multiple smaller lung nodules (Fig. 10). Serum IgG levels with subclasses were within normal limits. Microscopic examination of the material obtained by fine needle aspiration of the mass showed numerous plasma cells (more than 50 per high power field) with an IgG4/IgG ratio of 40%, histiocytes and eosinophils.

He was incidentally treated with prednisone for a COPD exacerbation. A non-contrast chest CT showed the mass had mildly decreased in size over one month. Given the patient's relative lack of symptoms, his prednisone was not restarted. The patient remained relatively stable by spirometry and symptoms.

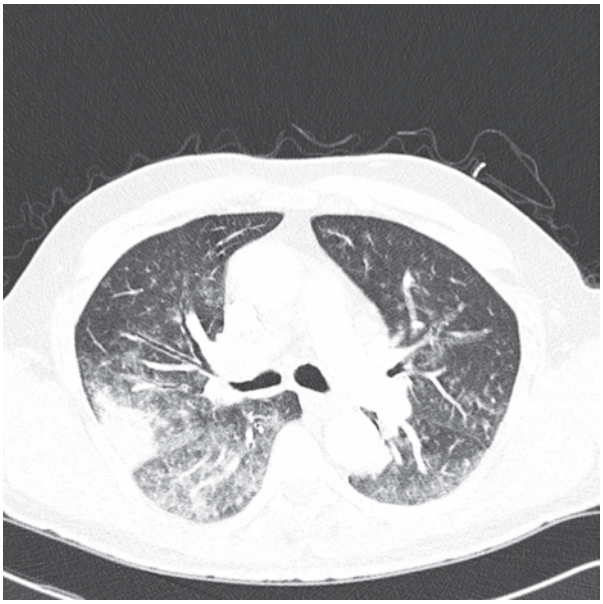

Fig. 10. Chest computed tomography image of right upper lobe mass, ground glass infiltrates, and left hilar lymphadenopathy

Patient 6

A 43 year old man with a history of chronic pancreatitis and tobacco use was evaluated for cough and weight loss. Chest CT scan showed new biapical interlobular septal thickening, one focal consolidation, diffuse small nodules, and mediastinal lymphadenopathy. Biopsies from the lung and lymph nodes revealed lymphoplasmacytic hyperplasia with numerous IgG4 plasma cells (more than 100 per high power field).

Serum IgG level was 1120 mg/dL and serum IgG4 level was 162 mg/dL. Prior to prednisone therapy, the patient had positive tuberculin skin test, but all cultures were negative. He was treated for latent tuberculosis infection (LTBI) with daily isoniazid, and prednisone was started at 40 mg daily. Due to a variety of patient social factors, his use of prednisone varied between none and 60 mg daily. He stopped smoking after 6 months. His serum IgG4 level at that time had decreased to 62.5 mg/dL. Over the year following diagnosis, his dyspnea progressed, and chest CT showed increased cystic changes and infiltrates.

Discussion

The frequency of lung involvement in IgG4-RD varies. Incidence was 14% in an IgG4-RD cohort (3) and 54% of patients with autoimmune pancreatitis (4). Manifestations are wide-ranging. Parenchymal lung involvement presents as single or multiple nodules or masses, or as more diffuse interstitial lung disease. Airway disease has been described as tracheobronchial stenosis or due to extrinsic compression (5). Clinical pleural disease is commonly due to nodular lesions (6), and incidental pleuritis and fibrinous exudate are noted commonly on lung biopsy (7). Mediastinal and hilar adenopathy are frequent. Fibrosing mediastinitis has been described rarely.

Systemic symptoms such as fever and weight loss have not been commonly reported (5) but fatigue and weight loss were present in six of the seven patients in our series.

Respiratory symptoms occur in approximately one-half of patients with pulmonary IgG4-RD (6,8). Pulmonary function tests are not specific and depend on the pulmonary manifestation of the disease.

Radiographic findings in IgG4-RD vary. Parenchymal nodules or masses can be solid or ground-glass in appearance. They occur both in isolation and as multi-focal disease. HRCT findings of interstitial disease include ground-glass or reticular opacities, consolidation, honeycombing, or bronchovascular and interlobular septal thickening (4-15). In our series 2 of the 6 patients had ground glass opacities on CT, while the other four had pulmonary nodules or a mass.

The characteristic laboratory finding is an elevated serum IgG4 level (>140 mg/dL) in the majority of patients with pulmonary IgG4-RD (6-8). However, it is not required for diagnosis. There are no other specific laboratory findings for IgG4-RD of the lung. In our series, five out of six patients had elevated IgG4 serum levels.

Bronchoalveolar lavage fluid has characteristic findings of lymphocytosis and elevated IgG4 level, but it is not currently part of the IgG4 related lung disease diagnostic criteria (9).

Histopathologic examination remains the gold standard for the diagnosis of IgG4-RD. However, since the lesional patterns vary in different organs, a presumptive diagnosis needs close clinical and pathological scrutiny (16). Lymphoplasmacytic infiltrates rich in IgG4 producing plasma cells, a definitive requirement for this diagnosis, are often accompanied by storiform fibrosis and obliterative phlebitis (17). This "triad" is diagnostic of IgG4-RD and was first described in patients with autoimmune pancreatitis, the prototype of IgG4-RD (17,18). However, in other organs such as lymph nodes, minor salivary glands, lacrimal glands and lungs, one or two components of the triad may be absent making the diagnosis of this entity less certain (16).

Previous studies of the pulmonary lesions in IgG4-RD have described several patterns, which include organizing pneumonia (bronchiliolitis-obliterans organizing pneumonia-like), nonspecific interstitial pneumonia, small airway lymphoplasmacytic inflammation, grade 1 lymphomatoid granulomatosis-like lesions, vasculitis, and inflammatory pseudotumors (plasma-cell granuloma) (8). A recent report of pulmonary lesions of patients presumed to have IgG4-RD with and without associated autoimmune pancreatitis described as the main findings lymphoplasmacytic infiltrates with a prominent lymphangitic distribution, non-necrotizing lymphoplasmacytic vasculitis involving arteries and veins, peribronchial inflammation and fibrosis which included collagen deposits and fibroblast-rich, active foci. The concentration of IgG4 staining plasma cells were generally scored as 3 meaning more than 30 cells per high power field (19).

Glucocorticoids are typically the first line treatment (17). The exact dose and duration are unclear. A consensus statement from 17 referral centers in 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 (20-22). Glucocorticoids are effective in most cases of IgG4-RD, but flares and intolerance to tapering are common (21). Methotrexate, azathioprine, and MMF have been used as steroid-sparing agents or maintenance medications. For patients with refractory or recurrent disease, successful use of rituximab has been described (23,24). Clinical experience suggests that the patient's response to treatment depends on the degree of fibrosis of the involved organ.

In this series, we report six patients with pulmonary IgG4-RD. Findings of our case series not described elsewhere for IgG4-related lung disease include MMF used as steroid sparing maintenance therapy, remission of pulmonary disease following liver transplant with its accompanying immune suppression, a patient with concomitant LTBI, and notably one patient with alveolar hemorrhage and a positive ANCA and clinical features similar to granulomatosis with polyangiitis (GPA). Two of our patients presented with localized "pseudotumor" in the lungs. Only one of our patients clinically had a history of pancreatitis. The variability in symptoms and frequent multi-organ system involvement are consistent with the wide array of clinical presentations in previous reports.

Elevation of IgG4 in GPA has been reported for several decades, and may play a pathogenic role (25). High tissue IgG4 levels have been noted on retrospective review of the pathology of patients with GPA (26). Cases of GPA initially diagnosed as IgG4 related disease have been reported (27). A case of ANCA positive nephritis with IgG4 positive mediastinal mass has been described, but it is not explicit that it met formal pathologic criteria for diagnosis (28). According to a recent review, there have been no previous reports of elevated ANCA in confirmed IgG4 related disease diagnosed on histopathology (5). Our patient with positive ANCA had histopathology that met the proposed criteria for IgG4 related disease.

The five patients in our series treated with corticosteroids had clinical improvement or response on imaging, consistent with previous reports (22). The only patient not treated was asymptomatic on presentation and had focal disease that was excised. The only patient who had clinical and radiographic disease progression had variable adherence to prednisone. Three patients were able to stop corticosteroid treatment: two tolerated it well, while the third had recurrence of symptoms that responded well to the addition of MMF.

IgG4-related lung disease is an emerging clinical entity forming a subset of IgG4 -RD. While the diagnosis remains controversial, affected organs share similar histopathologic features. Additional studies are needed to determine the pathogenesis, establish diagnostic criteria, and optimize treatment of pulmonary IgG4-RD.

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