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IgG4 related lung disease- a rare and novel mimic of malignancy and infections-a case series of three patients with a brief review of updated literature

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ABSTRACT

IgG4-related lung disease is an extremely rare and novel entity which is still poorly understood. We reviewed the 16 patients diagnosed with IgG4-related disease from October 2014 through December 2019 at our institution. The three cases that showed pulmonary involvement are included in this series. Of these, two patients had cavitary lung disease and developed aspergilloma and chronic cavitating aspergillosis after a prolonged course of steroid therapy, and one had isolated pulmonary nodule and ground glass opacity. We reviewed the updated literature and briefly described disease epidemiology, clinical characteristics, diagnostic approaches, and management strategies for IgG4-related lung disease.

1. Introduction

IgG4-related disease (IgG4-RD) is a newly discovered etiology recognized in 2003 in Japan. It is an exceedingly rare and poorly understood systemic fibro-inflammatory disease which results from substantial infiltration of IgG4-positive plasma cells into end organs regardless of serum IgG4 levels [1,2]. Its underlying cause is postulated to be autoimmune or allergic. The condition has been described in all most every organ: pancreas, bile ducts, periorbital tissue, lungs, aorta, kidneys, salivary glands, lacrimal glands, prostate, thyroid, retroperitoneum and skin [3]. Isolated IgG4-related lung disease is also uncommon with eight cases described in literature to date [4]. Most of the data in regards to IgG4-RD has been reported in Asia. We present a case series of three patients with IgG4-RD with lung involvement at our institution, one of which describes isolated IgG4-related lung disease. We then briefly explained different clinical and radiological presentations of IgG4-related lung disease.

2. Case reports

2.1. Case 1

A 52-year-old Caucasian female with a 30 pack/year history of smoking was seen at an outside facility with complaints of productive cough, weakness and dyspnea on exertion for one month. A computed tomography (CT) chest revealed diffuse cavitary lung disease concerning for infectious etiology. She was started on broad-spectrum antibiotics including vancomycin, Levaquin, and Unasyn. Due to worsening shortness of breath, the patient was transferred to our hospital for a higher level of care. A repeat CT chest was performed which revealed diffuse bilateral cavitary lung disease in apices of both lungs, and numerous bilateral small cavitary masses, diffuse interlobular septal thickening, bilateral hilar lymphadenopathy and extensive pleural thickening with enhancement (Fig. 1).

Infectious workup for cavitary lung disease, including acid-fast bacilli stain and culture, fungal culture, Legionella culture, and mycoplasma pneumonia, was unremarkable. Rheumatologic workup was significant for rheumatoid factor 798 mg/dl and atypical P-ANCA

Abbreviations: IgG4-related disease, IgG4-RD.

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1:0640. The patient underwent bronchoscopy which was unremarkable. Transbronchial biopsies of the right lower lobe showed benign bronchial tissue with chronic inflammation. Due to unrevealing workup the patient underwent video-assisted thoracoscopic surgery (VATS) lung biopsy. Lung biopsy revealed perivascular and interstitial lymphoplasmacytic infiltrate along with IgG4 and IgG4 plasma cell consistent with IgG4-related lung disease (Fig. 2).

Serum IgG level was elevated to 2172 mg/dl (reference range 767–1590 mg/dl) and serum IgG4 was also increased up to 367 mg/dl (reference range 135–144 mg/dl). The patient was diagnosed with IgG4-related cavitary lung disease and discharged home. She was started on high dose prednisone along with PJP prophylaxis with Bactrim by Rheumatology as an outpatient. She remained stable on prednisone 10 mg daily for two years.

She was then admitted to the hospital again with shortness of breath and lower extremity edema. Diagnostic workup revealed biventricular failure with pulmonary hypertension. A repeat CT scan chest was performed which showed diffuse bilateral cavitary lung disease. Left apex cavitary lesion was noted to have intra luminal debris concerning for superimposed Aspergillus infection, as well as multiple cavitary lung nodules, diffuse interlobular thickening, and diffuse pulmonary nodules (Fig. 3).

The patient had worsening respiratory failure despite diuresis use ultimately requiring mechanical ventilation. A bedside bronchoscopy was performed which returned positive for Aspergillus fumigatus in bronchoalveolar lavage. She developed refractory septic shock requiring multiple vasopressors and persistent hypoxic respiratory failure leading to cardiac arrest without return of spontaneous circulation with cardiopulmonary resuscitation.

2.2. Case 2

A 78-year-old Caucasian female with a past medical history of seasonal allergies, asthma, chronic obstructive pulmonary disease and a 15 pack/year history of smoking was seen in the clinic with complaints of diplopia. A left orbital mass was noted on CT orbits. The patient underwent surgical anterior orbitotomy which showed reactive hyperplasia with marked plasmacytosis, and increased expression of IgG4 cells consistent with the diagnosis of IgG4-related orbital pseudotumor. Serum IgG and IgG4 levels were normal. Further workup showed cavitary lung disease on CT scan. Infectious workup for tuberculosis and fungal infections was unremarkable; hence it was presumed secondary to IgG4-related lung disease and no intervention was done. The patient was treated with prednisone followed by rituximab due to persistent diplopia and inadequate response to steroids. Diplopia resolved with rituximab. The patient was seen at our institution one year later. A repeat CT scan chest was performed which showed a cavitary lesion in left lung apex with associated bronchiectasis unchanged from the prior CT scan (Fig. 4).

Acid fast bacilli stain and culture, fungal culture, Aspergillus antibodies and Aspergillus galactomannan were negative. Positron emission tomography (PET) scan showed increased fluorodeoxyglucose (FDG) standardized uptake value (SUV) of 1.5 in the cavitary lesion. The patient remained off steroids and immunosuppressants. A repeat CT scan chest six months later showed a left apex cavitary lesion measuring 5.9 × 5.3-cm and retraction of left hilum. A 1.5-cm irregular nodular density was noted on the inferior portion of cavitary concerning for fungal ball (Fig. 5).

Repeat Aspergillus antibodies were positive for Aspergillus

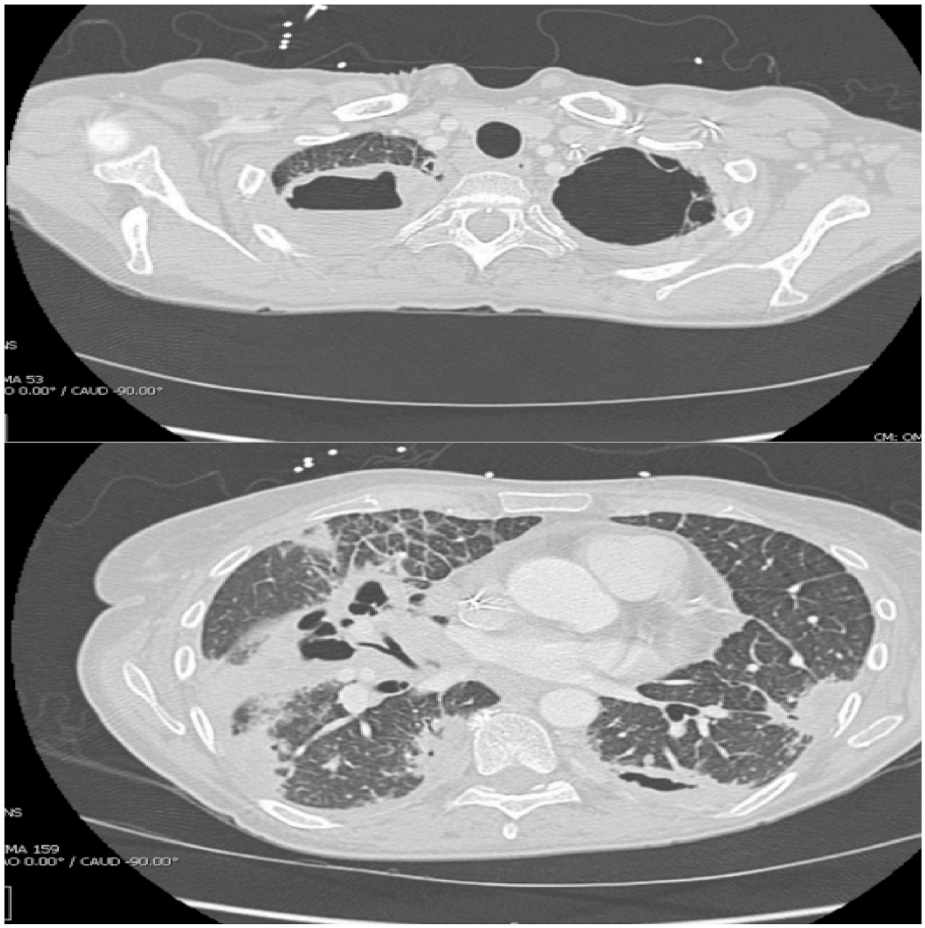

Fig. 1. CT chest shows diffuse bilateral cavitary lung disease in apices of both lungs (top panel), and numerous bilateral small cavitary masses, interlobular septal thickening, bilateral hilar lymphadenopathy and extensive pleural thickening with enhancement (bottom panel).

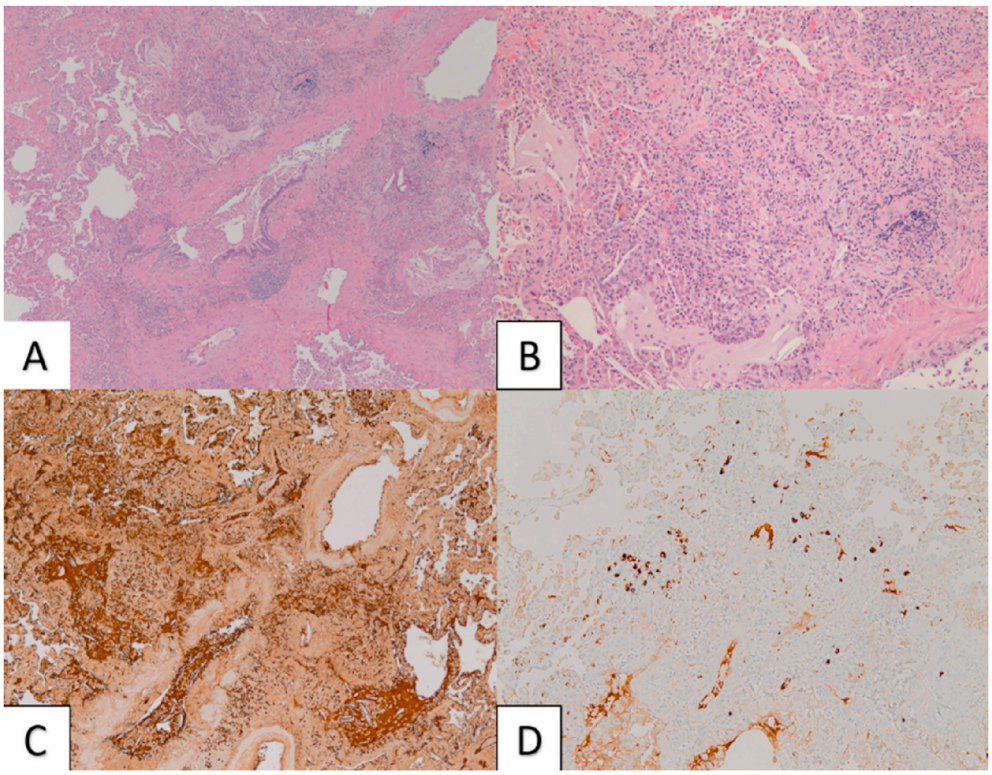

Fig. 2. Lung wedge biopsy on hematoxylin and eosin stain at 40X (Panel A) and at 100X (Panel B) shows perivascular and interstitial lymphoplasmacytic infiltrate. Immunohistochemistry highlights IgG plasma cells present up to 84/high power field (Panel C) and IgG4 plasma cells up to 61/high power field (Panel D).

fumigatus, which supported the diagnosis of superimposed aspergilloma and cavitating aspergillosis. The patient was started on voriconazole which was continues to date. A repeat CT scan chest after 6 months of voriconazole revealed decreased thickness of the cavity with minimal residual debris consistent with aspergilloma. Total IgG and IgG subclasses including IgG4 remained normal throughout the course of therapy. The patient is following up with rheumatology and pulmonology on regular basis.

2.3. Case 3

A 73-year-old non-smoking Caucasian female with a past medical history of recurrent sinusitis, osteoporosis, hypothyroidism and glaucoma was seen in the clinic with decreased appetite and a 30-pound weight loss over 6 months. The patient underwent CT chest and abdomen which showed a 1 cm solid and ground-glass right upper lobe pulmonary nodule along with borderline mild right hilar lymphadenopathy (Fig. 6).

A PET scan was obtained which showed an increased FDG SUV uptake of 3.2. The patient underwent VATS which did not show evidence of malignancy but did show organizing pneumonia, and immunohistochemistry revealed IgG-4-positive plasma cells 130 per hpf with total IgG positive cells at the same density. Storiform fibrosis and vascular sclerosis were also noted on biopsy (Fig. 7).

This constellation of findings was consistent with IgG4-related lung disease. The patient was not started on steroids due to history of osteoporosis. However, symptoms started improving without immunosuppressive therapy. A repeat CT scan chest at 1 year did not reveal any new nodules and patient remains stable without therapy for IgG4-related disease. Summary of IgG levels and disease course of our cases is tabulated in Table 1.

3. Discussion

Due to the rarity of IgG4-related lung disease, its true prevalence has yet to be elucidated [2]. The condition may arise as an isolated presentation of IgG4- RD or it may be accompanied by involvement of other organs. Intrathoracic involvement with IgG4 RD is observed in 14–35% of patients [5]. Based on limited epidemiologic data, the condition seems to affect males more than females (3:1) with median age greater fifty years [3,6]. A few case series have associated smoking with development of IgG4-related lung disease, as was seen in our patients' history [7]. Infiltration of IgG4-positive plasma cells into the lungs leads to tumefaction of pulmonary parenchyma and can result in interstitial pneumonitis, organizing pneumonia, pseudotumor, and lymphomatoid granulomatosis [2]. Clinical presentation exists on a spectrum from asymptomatic (53%) to cough, chest pain, hemoptysis, and shortness of breath [6]. The condition is seen more frequently in patients with allergies, asthma and sinusitis as observed in Patient 2 [2,8–10]. Autoimmune workup should be done to rule out associated disorders such as eosinophilic granulomatosis with polyangiitis which can show clinical and histopathologic resemblance to IgG4-RD [2,11]. Definitive diagnosis demands serological and pathological evidence in clinically suspected patients based on various criteria, i.e. Boston consensus criteria and Japanese comprehensive clinical diagnostic criteria for IgG4-RD [2]. Abnormalities on chest CT scan are usually seen at initial presentation. Other findings seen on CT scan in previous studies are summarized below in Table 2.

Findings such as cavitary lesions, GGO, nodules and lymphadenopathies demand exclusion of infectious and malignant etiologies such as lung cancers and Castleman disease. PET scan is often performed to characterize the disease and can show increased FDG uptake as seen in our series, though this measure can mislead the clinician toward malignancy [16]. Elevated serum IgG4 (>135 mg/dl) levels can support diagnosis; however, this parameter is nonspecific and is elevated in 5% of healthy population or could be normal in 30% of affected patients.

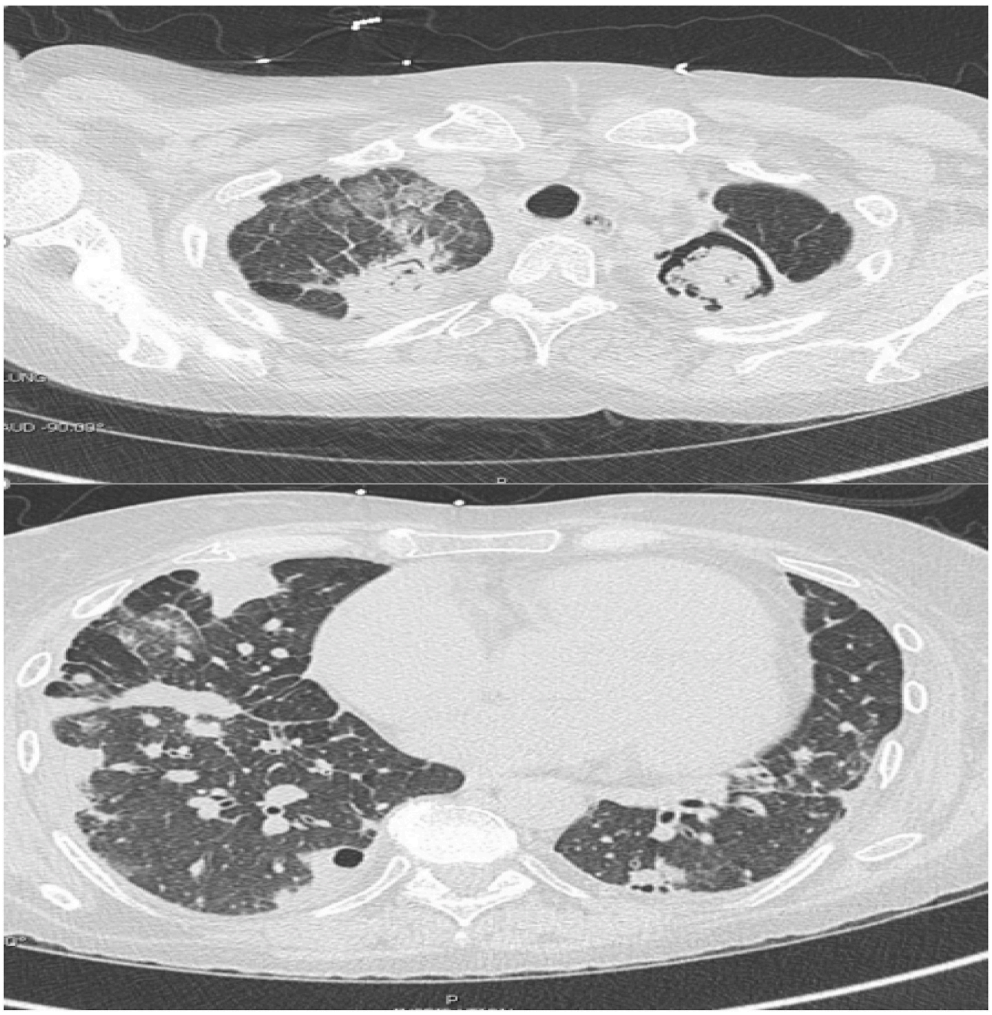

Fig. 3. CT chest shows diffuse bilateral cavitary lung disease, left apex cavity containing intra luminal debris concerning for superimposed Aspergilloma (top panel), multiple cavitary lung nodules, diffuse interlobular thickening, and diffuse pulmonary nodules (bottom panel).

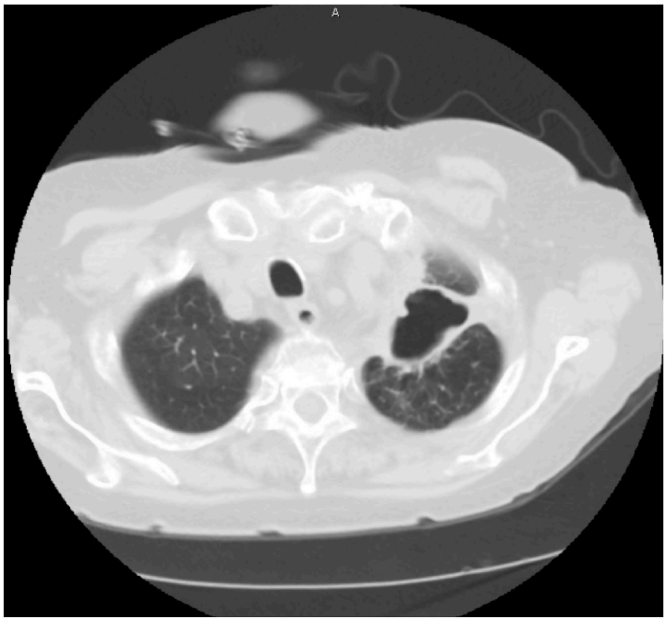

Fig. 4. CT scan chest shows cavitary lesion in left lung apex.

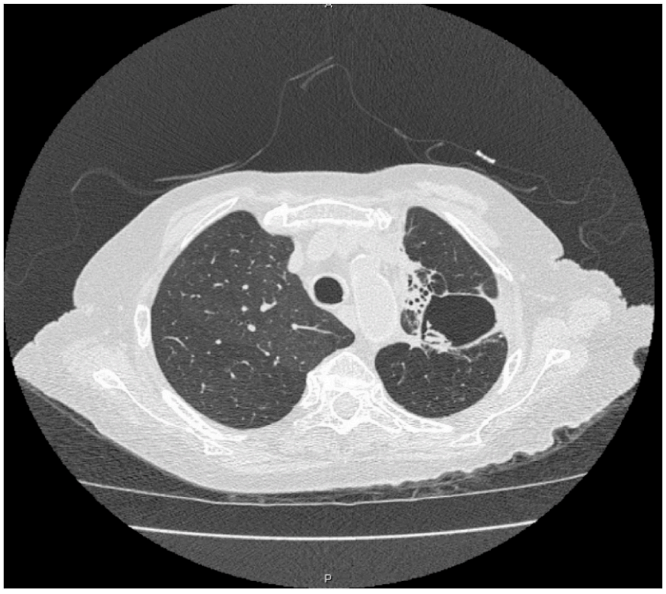

Fig. 5. CT scan chest shows left apex cavitary lesion, an irregular nodular density on the inferior portion of cavitary concerning for fungal ball.

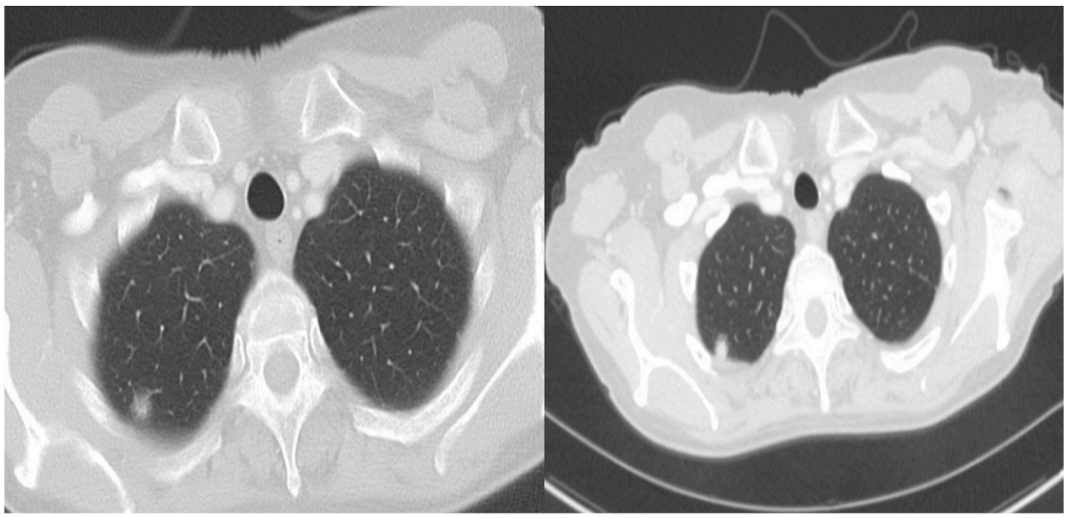

Fig. 6. CT chest solid and ground-glass right upper lobe pulmonary nodule.

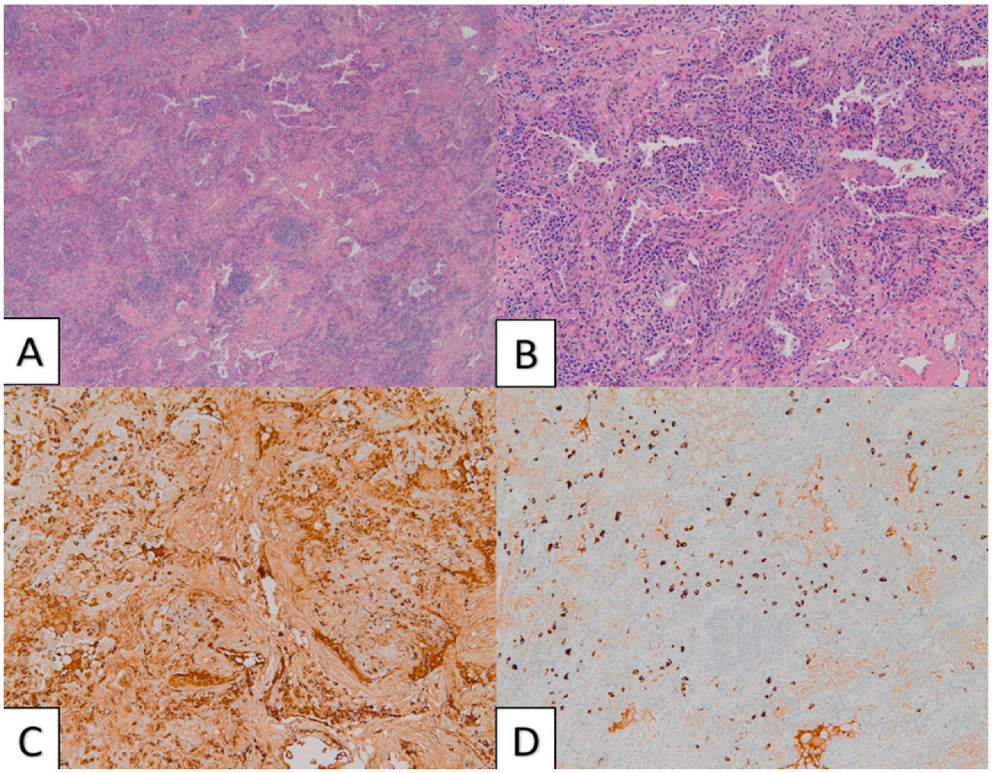

Fig. 7. Lung wedge biopsy on hematoxylin and eosin stain at 40X (Panel A) shows chronic inflammation, fibrosis and vascular sclerosis. Lymphoplasmacytic rich chronic inflammation and interstitial fibrosis is seen (Panel B). Immunohistochemistry highlights IgG plasma cells present up to 130/high power field (Panel C) and up to 130/high power field IgG4 plasma cells in (Panel D).

Indeed, a trend of inconsistent IgG and IgG4 levels was noted in our series [3,4,6]. Tissue biopsy is the only method of histopathologic confirmation and exclusion of IgG4-RD mimics such as fungal infections and malignancy. Different approaches can be utilized to obtain tissue biopsy including percutaneous needle biopsy, transbronchial biopsy or video-assisted thoracoscopic surgery (VATS) lung biopsy. Characteristic findings on biopsy include dense lymphoplasmacytic infiltrate (IgG4+ plasmacyte to IgG + cells ratio >40% and >10 IgG4 + plasma cells per hpf), storiform fibrosis, obliterative phlebitis and variable degree of tissue eosinophilia [11]. Obliterative phlebitis is the most common pattern observed in lung involvement [4]. Transbronchial biopsies have also been shown to support the diagnosis of IgG4-RD in 47% of cases with 94% specificity, though more longitudinal evidence is needed assess its utility in disease evaluation [17]. Although two of our patients had obstructive lung disease based on their pulmonary function tests (PFTs), there is no clear role of PFTs in IgG4-related lung disease yet. Bronchoscopy has been utilized to assess bronchoalveolar lavage fluid IgG4 levels, which may be notably high in IgG4-related lung disease patients with autoimmune pancreatitis [18].

The decision to treat is based on degree of organ dysfunction, as well as patient-associated risk factors. Asymptomatic disease can be managed with watchful waiting. In cases where organ dysfunction is noted,

Table 1
Illustrates a summary of different IgG levels and disease course.

Case	Pretreatment serum IgG4 levels (135–144 mg/dl)	Pretreatment serum IgG levels (767–1590 mg/dl)	Treatment	Post treatment Ig4 levels (135–144 mg/dl)	Post treatment CT	Follow up course	Status
1	367	2172	Steroids	350	Worsened at 2 years	Aspergillus fumigatus infection; CHF	Died due to respiratory failure
2	36	895	Steroids followed by Rituximab	Not obtained	Stable at 1 year	Aspergillus fumigatus on voriconazole	Alive
3	44	735	No steroids due to osteoporosis; symptoms improved post-resection	36	Stable at 1 year	Stable	Alive

Table 2
Lists various presentations of IgG4-related lung disease seen on CT scan chest [6,8,12–15].

Radiologic findings
1. Nodules
2. Cavitary lesions
3. Ground glass opacities
4. Hilar and or mediastinal lymphadenopathy
5. Thickening of bronchovascular bundles
6. Alveolo-interstitial infiltration
7. Interlobular septal thickening
8. Pleural thickening and effusion

glucocorticoids are the first line of therapy. Prednisone at 0.6 mg/kg daily for 2–4 weeks with a prolonged taper of 3–6 months has been used in some cases. In refractory cases immunosuppressants such as rituximab, mycophenolate mofetil, azathioprine and cyclosporine can be utilized as was prescribed for our patient 1 [2,6,13]. Therapy with rituximab often leads to a brisk decline in IgG4 levels which correlates with clinical improvement. With other therapies, IgG4 levels do not reliably drop post-treatment; moreover, IgG4 levels do not consistently predict relapse [3]. In patients with fibrosed target organs, immunosuppression is usually futile due to lack of active inflammatory milieu. In patients with IgG4-RD, age- and sex-appropriate screening should be performed as various studies have demonstrated its association with solid organ and hematologic malignancies [19]. While relapse is not uncommon, overall prognosis is yet to be determined due to the novelty and limited understanding of the disease. Our patient in case 1 had a biopsy proven IgG4 related lung disease which was complicated by aspergillus infection, while case 2 was diagnosed as IgG4-related cavitary lung disease due to constellation of findings consistent with IgG4 related disease and negative infectious work up. Case 2 did develop aspergillus infection prospectively as well, though it is difficult to decipher if it was a superimposed fungal infection or primary slow growing aspergillus infection. Hence, infectious etiologies must be thoroughly ruled out prior to diagnosing IgG4 related cavitary lung disease.

4. Conclusion

IgG4-related lung disease can have diverse clinical and radiological presentations. Due to the novelty and limited understanding of this disease, it is underdiagnosed and often misdiagnosed. In a clinically suspicious patients, a thorough history to assess associated conditions, coupled with consensus-based criteria, should be used to diagnose IgG4-related lung disease. Early diagnosis can result in timely institution of steroid therapy which has robust clinical response in the inflammatory phase of disease. More longitudinal studies are need to understand the natural history of this disease and the effectiveness of various diagnostic modalities and management strategies.

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Declaration of competing interest

All the authors have seen and approved the manuscript. The authors report no conflicts of interest.

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