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An update on IgG4-related lung disease

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ABSTRACT

IgG4-related disease (IgG4-RD) is an autoimmune disorder characterized by substantial infiltration of plasma cells with IgG4 in target organs. Lung manifestations predominantly present as inflammatory pseudotumor, interstitial pneumonitis, organizing pneumonia, and lymphomatoid granulomatosis. There is no specific diagnostic test for IgG4-related lung disease (IgG4-RLD), and excluding diseases that mimic IgG4-RLD is important. Corticosteroids with or without disease-modifying anti-rheumatic drugs are recommended for treatment. The long-term prognosis of IgG4-RLD remains unknown. In this review, we summarized the current diagnostic algorithms and discussed potential biomarkers for future investigation.

1. Introduction

Immunoglobulin G4 (IgG4) is unique among all the subclasses of IgG constituting only 3–6% of total IgG fraction [1]. Immunoglobulin G4-related disease was reported first in the late 1990's. One of the first reports was a patient of AIP Immunohistochemical study of AIP revealed dense plasma cell infiltration with IgG4 [2]. After observing the association between various analogous symptoms and IgG4 tissue infiltration, the term "IgG4-related disease (IgG4-RD)" was coined. By definition, IgG4-RD is a systemic fibroinflammatory process characterized by substantial infiltration of plasma cells with IgG4 in target organs, regardless of plasma IgG4 level [3]: in fact, only about 50% of patients have elevated IgG4 levels in serum [4]. Histologically, IgG4-RD is characterized by a lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis and variable tissue eosinophilia [5]. Although this disease was initially found to affect mainly the pancreas, the spectrum of involved organs varies from the orbit to the retroperitoneum.

IgG4-related lung disease (IgG4-RLD) was first reported in 2004 [6]. IgG4-RLD is primarily composed of four clinical pulmonary syndromes: inflammatory lung pseudotumor, central airway disease, interstitial pneumonia, and pleuritis. Characteristic radiologic manifestations in the lung include nodules, ground glass opacities, alveolar and interstitial disease, and bronchovascular bundle thickening [5]. There are very few published reviews on pulmonary IgG4-RD in recent years. Here, we review the epidemiology, clinical presentations, different diagnostic criteria, histopathology, imaging, and treatment modalities of IgG4-RLD.

2. Methods

A literature search was performed for articles published between 1995 and 2018 using the search terms 'IgG4-RD', 'IgG4 related disease', 'lung', 'pulmonary', 'cancer', 'autoimmune pancreatitis', 'AIP', 'epidemiology', 'symptoms' 'diagnosis', 'treatment' as previously performed [7]. PubMed, Scopus and the Cochrane Library were reviewed. Titles of interest were further reviewed by abstract. Reference lists of relevant studies were hand-searched for additional studies.

Inclusion criteria for this review were: study populations of IgG4-RD, full reports, case reports or reviews, and articles that were published in English peer-reviewed journals.

2.1. Pathophysiology

IgG4-RD is classified as an fibroinflammatory disorder, with both adaptive and innate immune systems involved in its pathophysiology [8]. However, the exact mechanism remains to be understood. IgG4 antibodies are considered to have anti-inflammatory activity given the fact that they can undergo Fab-arm exchange and limit immune complex formation. These elements make IgG4 antibodies less likely to be the responsible for the pathology of this disease. IgG1 could be

Abbreviations: AIP, autoimmune pancreatitis; BALF, The bronchoalveolar lavage fluid; COPD, Chronic obstructive pulmonary disease; IgG, Immunoglobulin G; IgG4-RD, IgG4-related disease; IgG4-RLD, IgG4-related lung disease; SUV, Standardized uptake value

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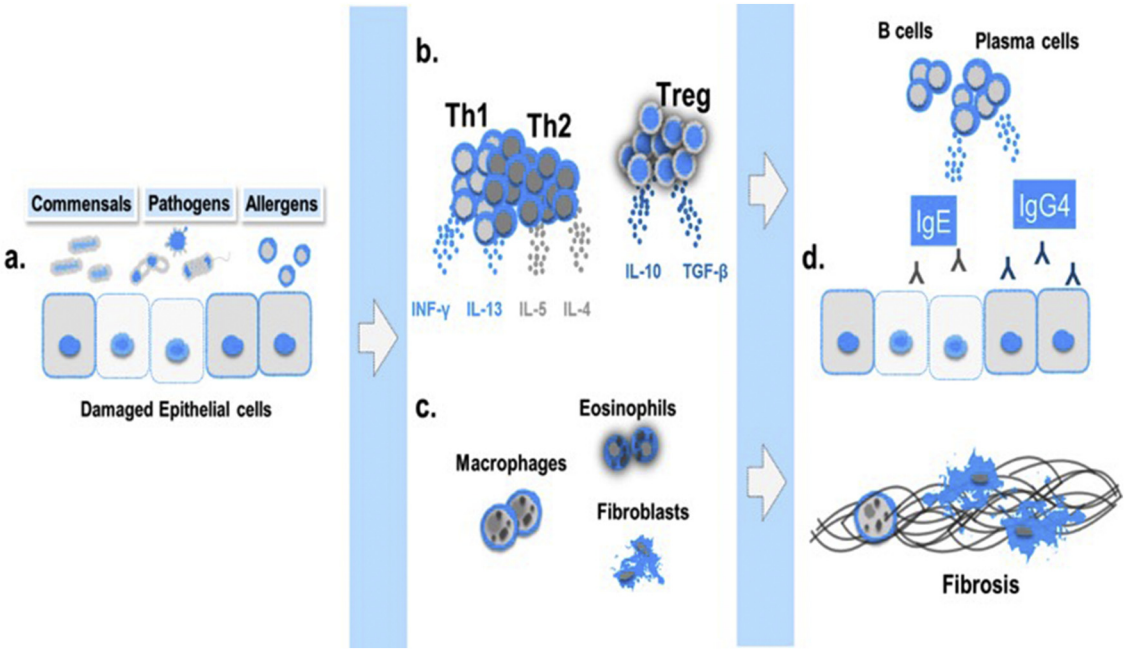

Fig. 1. Immunoglobulin G4-related disease (IgG4-RD) pathogenesis model. *a)* An anomalous immune response to tissue damage, allergens, commensal or pathogenic microbes may potentially trigger IgG4-RD. *b)* Activated Th1, Th2, Treg cells may produce IFN-y, IL-4, IL-5, IL-13, IL-10 and TGF-β. IL-4 and IL-10 may drive the activation of autoreactive B cells to produce IgG4 and IgE and induce IgG4+ plasma cells differentiation and replication. *c)* IL-5, IL-13, and TGF-β may activate fibroblast and recruit eosinophils. IFN-y may also contribute to the activated macrophages and fibrosis process. *d)* IgG4 and IgE antibodies may be cross-react to self-antigen. Activated self-reactive T cells may facilitate germinal center formation and recruit increasing numbers of autoreactive B cells. IFN: interferon, IL: interleukin, TGF: transforming growth factor, Th: T helper cell, Treg: regulatory T cell.

associated with IgG4 and be responsible for the inflammatory changes in IgG4-RD. Actually, IgG4 antibodies can oppose the inflammatory activity of IgG1 [9].

B cells maintain the memory CD4+ T cells, including the "pathogenic" clones [10]. The T helper (Th2-type) cells accumulate in one third of the patients, indicating a possible relation with allergic responses since IL-4, IL-5, and IL-13 are induced by Th2 cells. CD 4+ cytotoxic cells are seen in higher quantities in this population, resulting in an increased production of IL-1β, TGF-β1, and IFN-γ [9]. A subset of T-regulator cells produces certain interleukins such as IL-4, IL-10, and IL-13 that activate macrophages which produce fibrogenic factors [11] [12]. The secretion of these elements recruit other immune effectors such as macrophages, neutrophils, dendritic cells, among others, which contribute to the fibrotic lymphoplasmacytic infiltrate [13]. IL-5, IL-13 produced by Th cells and TGF-β from T-reg cells induce recruitment of eosinophils and activate fibroblasts [5]. Fig. 1 shows an illustration of potential pathophysiology of IgG4 related disease.

2.2. Epidemiology

The prevalence and incidence of IgG4-RD is undetermined, due to its misdiagnosis and unfamiliar pathophysiology [3]. In general, IgG4-RD is predominantly seen in adults, mostly older males (70–80%) [14]. A male to female ratio in Japan is reported as 3:1 [3]. Many of patients with IgG4-RD had been reported to have an increased serum IgG4 level (> 140 mg/dl) [14] but this finding has low sensitivity (63%), and acceptable specificity (94%) for IgG4-RD [15,16]. Normal serum IgG4 concentrations reported in 3–30% of patients [17]. AIP type I is the only disease subtype that has been studied in detail in relation to its epidemiology [18]. Its incidence varies from 0.28 to 1.08/100,000 and the prevalence is around 0.8/100,000 population [19]. In the United States, 11% of benign pancreatic resections were related to IgG4-RD [20]. Many studies report lung involvement in IgG4-RD but most of them lack a biopsy to confirm the diagnosis [21]. Lung specific involvement in AIP is reported in 9.5% to 51.2% of patients [22,23]. In general, Intrathoracic findings in IgG4-RD occur from 14% to 35% of patients [24,25]. There is a subgroup of patients that experienced IgG4-RD in lungs without involvement of other organs. A Japanese survey study on patients with IgG4-RD found 354 (8%) out of 4304 patients had IgG4-RLD without pancreas involvement [19].

3. Clinical presentation

Clinical features related to IgG4-RLD are ambiguous. Overall, the clinical scenarios can be classified as inflammatory pseudotumor, interstitial pneumonitis, organizing pneumonia, and lymphomatoid granulomatosis [26]. Patients may present with cough (dry), chest pain, exertional dyspnea while others may present with abnormal finding in chest imaging, with a lack of respiratory findings [27,28]. Interestingly, up to 75% of patients are asymptomatic and identified only by imaging [26]. Other presentations include asthma like symptoms including wheezing, nasal congestion, rhinorrhea and occasionally a nasal mass [29–31]. Inoue and associates reported 13 patients with IgG4-RLD. Among them 7(53%) complained of cough, 4(30%) fever, 2(15%) dyspnea on exertion, 1(7%) chest pain, and 3(23%) were asymptomatic [32]. A similar distribution was found by Sun et al. in 2016, where out of 17 patients with lung involvements, 11 (64%) presented with cough, 7(41%) with fever, 5(29%) with dyspnea, 4(23%) with chest pain, 2(11%) with hemoptysis, and 2(11%) were asymptomatic [16] [21]. In addition, they also found 4 (23%) patients had either allergies or asthma, 4(23%) had an autoimmune condition, and 1(5%) with chronic obstructive pulmonary disease (COPD) [16]. A correlation between AIP and allergic diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis and medication allergies was reported previously [33]. Lymphadenopathy is a common presentation in IgG4-RLD. It often presents while a fibrosing inflammatory process affecting extranodal sites [34].

Environmental risk factors for IgG4-RLD including smoking and occupational exposures have not been studied and might be an interesting avenue for future research.

Table 1
The japanese comprehensive clinical diagnostic (CCD) criteria for IgG4-RD.

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (> 135 mg/dl)
3. Histopathological examination shows:
    1. Marked lymphocyte and plasmacytic infiltration and fibrosis
    2. Infiltration of IgG4 + plasma cells: ratio of IgG4 + /IgG + cells > 40% and > 10 IgG4 + plasma cells/HPF

Definite: 1 + 2 + 3
Probable: 1 + 3
Possible: 1 + 2

- Consider always in the differential of IgG4-RD any malignant tumors (solid organ and blood malignancies).
- Consider similar diseases as Castleman's disease, granulomatous diseases or autoimmune diseases like Sjogren's syndrome.
- When CCD criteria are not met, patients may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

3.1. Diagnosis

IgG4-RLD implies a series of clinical, radiological, and histopathological characteristics. Patients do not always present with clinical symptoms, which makes its diagnosis more challenging. Since 2015, the international consensus recommends a tissue biopsy to confirm the diagnosis [17]. However, there are two major systems for diagnosis of IgG4-RD, the Japanese and the Boston criteria (Tables 1 and 2). The nomenclature for this disease was first accepted in 2011 in the first international symposium of IgG4-RD (Boston, Massachusetts). They initiated the term of IgG4-RD for this condition and developed the first diagnostic system [35]. A third diagnostic system is the 2012 International Consensus (Table 3). They include inflammation, fibrosis, and phlebitis which are commonly found aspects on histopathology (Table 4). Most of the lymphocytic infiltrates are T cells and plasma cells, often with germinal centers. Eosinophilic infiltrates in involved tissue are not rare. The term 'storiform fibrosis' alludes to beaded-arranged collagen and fibroblasts [4]. IgG4-RLD can sometimes exhibit sarcoid-like epithelioid granulomatous in histopathology [36]. Each organ has its own criteria for IgG-RD and they might have their own cut-off numbers per HPF for IgG4 + plasma cells, although these numbers haven't been verified yet. The serum levels of IgG4 lack specificity and sensitivity for diagnosis of disease. The Japanese guidelines are based on a philosophy that very detailed criteria are not suitable for general clinicians, hence they based the diagnosis mainly on serum IgG4 levels and infiltration of the tissue by B cells. The Japanese Criteria includes a clinical criterion, serum IgG4 elevation and histopathological findings that should include plasmacytic infiltration, fibrosis and/or an elevated ratio of IgG4 cells compared to IgG in general. The Boston Criteria focuses in the histological findings (same as Japanese features plus obliterative venulitis). The Boston criteria should be described as a non-organ specific criteria for histopathology diagnosis of IgG4-RD [26,35]. The International consensus is a mix of both clinical and histopathologic findings (both serum and tissue are studied). These criteria should be used by caution due to their lack of sensitivity and specificity [26].

In 2017 the diagnostic criteria for IgG4 related respiratory disease was published by Umehara et al. [26]. They focused on chest imaging, serology and histology, as well as other organ involvements (Figs. 2, and 3). Among the CT images one can find hilar or mediastinal lymphadenopathy, bronchovascular bundle thickening, nodules, and pleural disease. Serology and histology are similar findings to the ones for general IgG4-RD diagnostic with some lung orientation as shown in Table 4. Arteritis can be found often in the lung, along, with phlebitis. The presence of the disease in other organs increases the yield for diagnosis. As in the kidney the presence of hypocomplementemia contributes to the diagnosis [37] [26].

Table 2
The Boston consensus criteria.

Requires the presence of the triad of histological features in IgG4-RD
1. Lymphoplasmacytic inflammation;
2. Fibrosis, usually with a storiform pattern; and
3. Obliterative venulitis

Plus, support through the demonstration of prominent IgG4+ plasma cells within the lymphoplasmacytic infiltrate, using immunohistochemistry.

The bronchoalveolar lavage fluid (BALF) levels of IgG4 might be a promising tool to diagnose IgG4-RLD. Tsushima and co-workers measured IgG4 levels in BALF and compare with subjects with pulmonary sarcoidosis [38]. They found IgG4 mean (SD) 2132 (1932) $\mu g dL^{-1}$, and 9 (0.5) $\mu g dL^{-1,}$ respectively in IgG4- RLD and sarcoidosis. Further study is needed before recommending BALF IgG4 levels for routine practice.

KL-6, a mucin-like high-molecular-weight glycoprotein was first found by Kohno and colleagues in patients with lung adenocarcinoma [39]. In 1995, Kobayashi and Kitamura found higher levels of KL-6 in the serum of patients with interstitial pneumonitis [40]. Hirano et al. found higher levels of KL-6 in the serum of 4 patients with IgG4-RLD. Yamakawa and colleagues reported a case with IgG4-RLD who had desquamative interstitial pneumonia and high levels of KL-6 in the serum [41]. Recently, Kono et al. reported a case of IgG4-RLD with combined pulmonary fibrosis and emphysema and high serum levels of KL-6 [42]. The sensitivity and specificity of serum KL-6 in IgG4-RLD has not been studied yet. It is also interesting in learning the functionality of BALF KL-6 in diagnosis of IgG4-RLD.

The role of pulmonary function tests (PFT) in the diagnosis of pulmonary IgG4-RLD remains unknown Fig. 3.

3.2. Differential diagnosis

Some other lung diseases can mimic IgG4-RLD. They may have similar IgG4 plasma cell elevation, CT findings, or histopathology similarities to IgG4-RLD. Therefore, diagnosis of IgG4-RLD is a diagnosis of exclusion. Recently, Clerc et al. reported elevated IgG4 serum levels in patients with cystic fibrosis, which may be due to an association with colonization and infection by *Pseudomonas aeruginosa* [43]. Ebbo et al. reported IgG4 elevations associated with repeated infections, autoimmune diseases, malignancies, immunodeficiencies, vasculitis and idiopathic interstitial pneumonitis [44]. Other differential diagnosis are Castleman's disease, Rosai-Dorfman disease, granulomatous diseases including sarcoidosis, malignancies (lung neoplasia and lymphoma) and many other benign lung tumors [45,46]. Terasaki et al. described the difference between idiopathic multicentric Castleman's disease (iMCCD) and IgG4-RLD. Both diseases possess a lymphoplasmacytic infiltrate, the lung of IgG4-RLD patients presents with fibrosis and eosinophilic infiltrates in the perilymphatic stromal area accompanied by obliterative phlebitis, versus iMCCD lung, in which lesions are seen in the alveoli adjacent to the perilymphatic stromal area [47]. Commonly, IgG4-RLD is initially mistaken with malignancy. IgG4-RLD resembling a pseudotumor can be thought to be malignant until pathology results are negative for malignancies and positive for fibrosis, inflammatory infiltrates with plasma cells and positive staining for IgG4 cells [48]. Rosai-Dorfman disease can present with lymphadenopathy whose histopathology shows a predominance of histiocytes with large amount of cytoplasm in which lymphocytes are engulfed (also known as emperipolesis or Rosai-Dorfman cells). This pathology also shows positive staining for S-100 protein and negative CD1a marker. This disease can be present in different tissues outside of the lymph nodes as well as inside the lung. There is hypergammaglobulinemia in Rosai-Dorfman disease and there is a degree of speculation of an overlap between IgG4-RLD and Rosai-Dorfman disease [49]. Table 5 summarizes a list of common differential diagnoses of IgG-RLD.

Table 3
Diagnostic criteria of the 2012 international consensus.

Clinical suspicion that correlates histopathologic findings:		
A. Lymphoplasmacytic infiltrate in biopsy and/or storiform fibrosis and/or coronary/obliterative phlebitis	Highly Suggestive: 2 or more items of A + B	
B. IgG4 plasma cells (10–200 cells by HPF) infiltrates in biopsy. Cell count IgG4 + /IgG > 0.4	Probable: At least 1 item of A + IgG4 plasma cells that do not meet B criteria Insufficient: Not included in highly suggestive or probable categories	Confirmation of Probable requires IgG4 > 135 mg/DL levels and or involvement of another typical organ(s) of IgG4RD demonstrated by images or histopathologic analysis.

3.3. Case series

Wang et al. reported a compilation of > 130 cases of IgG4-RLD. Interestingly, twenty-five (25%) of those patients had salivary and submandibular gland involvements, and thirty-two (32%) had pancreatic involvement. Forty (40%) patients had a smoking history, conversely where sixty-one (61%) patients had no documented smoking history. Only five(5%) patients had a documented history of dust inhalation and seven (7%) patients had concomitant history of lung cancer, two (2%)of gastric cancer, and three (3%) of colon cancer [50]. Nagashima and coworkers suggested a correlation between IgG4-RD and autoimmune hepatitis. They reported a patient with Grave's disease, elevated liver enzymes, high serum IgG4 levels, and positive antinuclear antibodies (ANA). The chest CT scan showed bilateral multiple masses up to 3.5 cm in size, bilateral pleural thickening with right pleural effusion, and increased FDG uptake on PET/CT scan in the pleura and lung masses. Histologically, the mass biopsy demonstrated evidence of IgG4-RLD and the patient was treated with steroids therapy [48]. Sekiguchi and co-workers observed an association between constrictive pericarditis and lung entrapment. The patient they reported was a young woman with history of chronic pleuropericarditis. Biopsy of the pleura showed lymphoplasmacytic infiltration with IgG4 positive cells. The patient responded well to steroids therapy [36]. Sun et al. found 3 out of 17 patients had allergies, one had asthma, and 4 had an autoimmune disease as Sjogren syndrome or psoriasis [21]. Others reported association with hematologic malignancies i.e. lymphoma, and solid organ malignancies such as pancreatic and lung cancer with IgG4-RLD [21,51]. An association between IgG4-RLD and lung cancer was reported as well. Zen and colleagues reviewed 21 subjects of IgG4-RLD, found one case of concomitant lung adenocarcinoma [28]. Yamamoto et al. followed 106 patients with IgG4-RLD for 3 years and found 11 patients (10%) developed malignant lesions in colon, lung, breast, ovary, renal, prostate, lingual, non-Hodgkin's lymphoma, and MALT. The adjusted incidence ratio for malignancy in patients with IgG4-RD was 383 in 100,000 population which is much higher than for the general population [52]. IgG4-RLD has been proposed as part of a paraneoplastic syndrome based on a case report by Krause and coworkers. An elderly man was reported with weight loss and pleural effusion complicated with dyspnea who was diagnosed with IgG4-RLD by thoracentesis and needle biopsy. His respiratory illness improved on steroids although he continued to lose weight. PET/CT scan revealed a mass in the sigmoid colon which on resection was confirmed an adenocarcinoma of the colon [53].

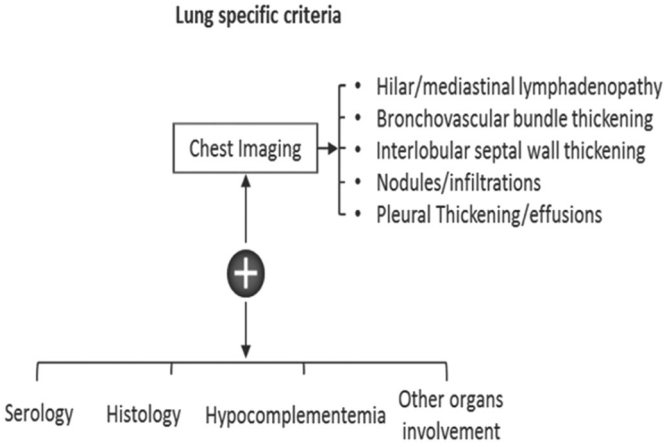

Fig. 2. Immunoglobulin G4-related lung disease (IgG4-RLD) specific criteria.

3.4. Treatment and prognosis

There is a large lack of knowledge on the IgG4-RLD treatment options and current recommendations are based on a treatment score for granulomatosis with polyangiitis disease (IgG4 Responder Index, see table S1) [54]. This score was designed to detect changes in the disease's activity and identify improvement or worsening in an organ or different new organ or systems, the higher the score the worse the course of the patient. The reason why this index is based on the one for ANCA-associated vasculitis is that both pathologies share a multi-organ involvement, they have a broad range of disease activity, they have a high frequency of disease-related damage and there are no reliable biomarkers to assess the patients.

The mainstay treatment for IgG4-RD is corticosteroids. Lung involvement tends to respond favorably to prednisone treatment (20-50 mg daily) and improvement is noticed in both symptoms as well as imaging [25]. Continued low dose steroids can be used to prevent long term relapse [14]. In 2015, a panel of experts created a consensus guideline on the treatment of IgG4-RD. Overall, 94% of the experts agree that glucocorticoids are the first line treatment and that after the induction therapy some patients need maintenance therapy. A vast majority, 87% of them affirm that symptomatic patients require treatment, sometimes urgently and that some asymptomatic patients also require treatment. 46% of the experts suggested that some patients require both glucocorticoids and steroid-sparing immunosuppressive drugs from the start of the treatment because the steroids might fail or have strong side effects [17].

Table 4
Variability of findings in the lung.

Inflammation	Fibrosis	Phlebitis	Others
Small aggregates of neutrophils may be present in alveolar spaces or within the inflammatory infiltrates	Sometimes lacks storiform fibrosis, particularly in non-solid lesions (eg, interstitial pneumonia)	No unique features	Obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions

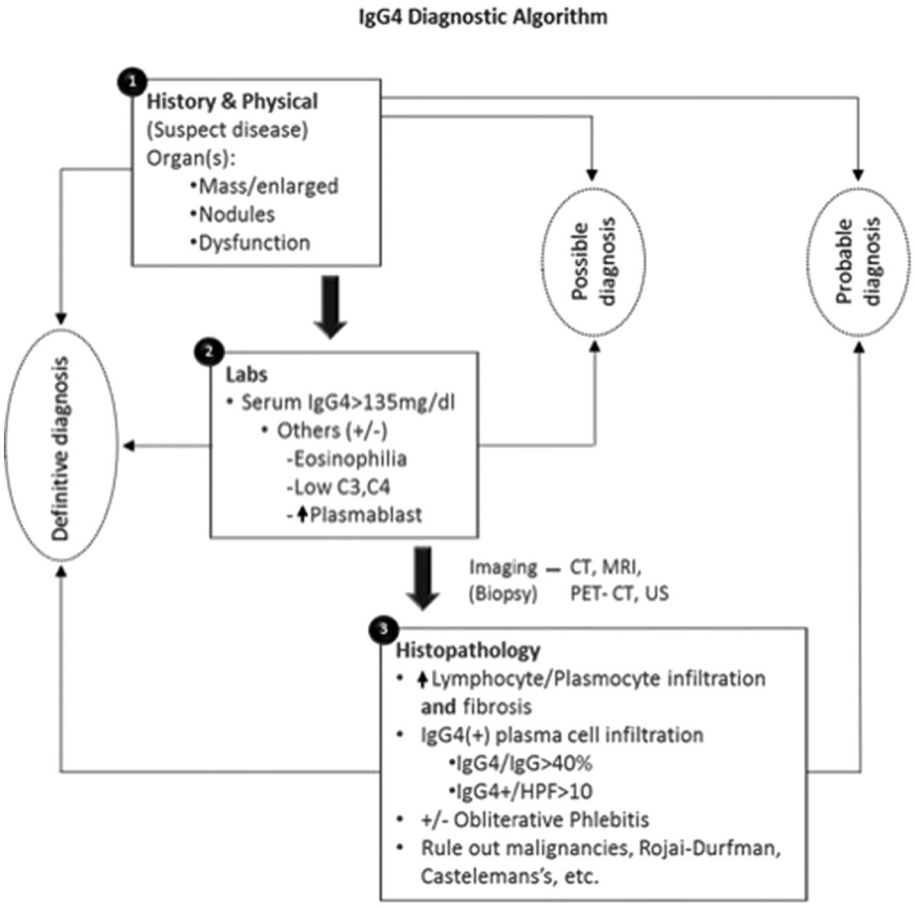

Fig. 3. Immunoglobulin G4-related lung disease (IgG4-RLD) specific criteria.

Bortezomib (protease inhibitor) and cyclosporine has been used in addition to steroid in recurrent diseases [55,56]. The effectiveness of bortezomib against multiple myeloma indicates that it might be beneficial for autoimmune or plasmocytic disorders like IgG4-RD [56]. There has been a case reported to achieve clinical and symptomatic improvement using bortezomib based combination therapy (Cy-BORD) [56]. Patients who do not respond to corticosteroids were treated with cyclophosphamide, azathioprine, and mycophenolate mofetil and

Table 5
Common differential diagnosis of IgG4 related disease that affects the lungs, airway of mediastinum.

Disease	Diagnosis
Multicentric castleman's disease (MCD)	Non-clonal lymphoproliferative disorder. Systemic inflammatory symptom; can mimic autoimmune diseases. Multicentric one is systemic and associated with HIV/HSV8. MCD lung, lesions are seen in the alveoli adjacent to the perilymphatic stromal area vs IgG4 where they locate in the perilymphatic stroma
Rosai-Dorfman	Presents with lymphadenopathy Predominance of histiocytes (Rosai-Dorfman cells). (+) S-100 protein and (−) CD1a. Different tissues outside of the lymph nodes, as in the lung. Hypergammaglobulinemia Possible overlap between IgG4 RD and Rosai-Dorfman disease
Granulomatosis with polyangiitis	Necrotizing granulomatous inflammation in upper and lower respiratory tract. Multinucleated giant cells. Necrotizing vasculitis affecting small to medium vessels.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. Necrotizing arteritis involving small and medium arteries Necrotizing glomerulonephritis is very common. Pulmonary capillaries often affected. No granulomatous inflammation.
Eosinophilic granulomatosis with polyangiitis (EGPA)	Eosinophilic and necrotizing granulomatous inflammation often found in the respiratory tract, and necrotizing vasculitis affecting small to medium vessels. Associated with asthma and eosinophilia. ANCA positive frequently.
Erdheim-Chester disease	Rare. Non-Langerhans cells histiocytosis with multiorgan involvement. Adult male in their 5th decade are usually more frequently involved. Mutations in the proto-oncogene BRAF or MAPK activation pathway. Clinical feature is extremely variable, and the disease can involve any organ.
Malignancy	Evidence of malignant cells vs fibrosis in IgG4 disease

showed histopathologic evidence of remission [21]. Rituximab has been used as an alternative to steroids and showed a rapid decline in serum IgG4 levels. This agent works by depleting the pool of B cells that replenish the IgG4-secreting plasma cells [57]. Among 17 patients who were treated with steroid and other medications reported by Sun and associates, only one patient expired due to respiratory failure [25].

4. Conclusion

Pulmonary involvement of IgG4-RD is a relatively new and unique clinical entity. It is barely understood. Even though the disease seems to be a relatively benign condition and well responsive to steroids, the prognosis of the disease is unclear. More prospective and multicenteric studies are needed to find better answers about its etiology, risk factors, disease staging long-term complications and prognosis. The role of biomarkers in diagnosis and prognosis of disease should be further investigated. The role of pulmonary function tests in pulmonary IgG4-RD remained unclear. It might be a useful tool in following up a known IgG4-RD patient. Long-term longitudinal study on a large cohort of patient is essential to understand the natural history and mortality of IgG4-RD.

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Conflict of interest

All authors report no conflict of interest.

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