Lung and airway disorders in immunoglobulin G4-related disease

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Summary

IgG4-related disease (IgG4-RD) is an immune-mediated condition, characterized by the formation of fibroinflammatory tumefactive lesions that can cause progressive tissue damage and subsequent organ failure. Although initially described as a disease of unknown etiology confined to the pancreas, IgG4-RD has been realized over time as an important entity that has underlies numerous pathologic conditions such as autoimmune pancreatitis, Riedel thyroiditis, Mikulicz syndrome, inflammatory pseudotumors and many others. IgG4-RD can affect almost any organ. However, the most commonly affected are the pancreas, hepatobiliary system, exocrine glands (salivary, lacrimal), retroperitoneum, kidneys and intrathoracic structures. Within the thorax, involvement of the lung parenchyma, airways, mediastinum, and pleura have been reported. The pulmonary involvement, therefore, is very diverse and can present as pulmonary nodule(s) or mass(es), alveolar or interstitial infiltrates, airflow obstruction, lymphadenopathy, mediastinal fibrosis, and pleural thickening and/or effusion. It is therefore important to recognize the diverse manifestations of this condition, as it can involve multiple organs and have various forms of expression within the same organ. As a consequence, IgG4-RD has presented a fascinating diagnostic challenge for many different specialties. In this review, we focus on the diagnosis and management of the intrathoracic involvement in this multisystem disease.

KEY WORDS: immunoglobulin G4, IgG4, fibroinflammatory, interstitial lung disease, lymphadenopathy.

Introduction

The IgG4-related disease (IgG4-RD) is a multisystem disorder characterized by the formation of fibroinflammatory tumefactive lesions that can lead to progressive fibrosis, tissue destruction and subsequent organ failure (1, 2). It can present with involvement in one or multiple organs. Single-organ involvement is present in about 40% of patients at the time of presentation (3, 4). For those with multiorgan involvement, the lesions may present synchronously or metachronously. The two main features of IgG4-RD are tissue infiltration with IgG4-positive plasma cells and the elevation of serum IgG4 (not present in all patients) (1, 5).

IgG4-RD is a recently recognized disease process. In 1995, Yoshida et al. (6) described a form of chronic autoimmune pancreatitis that was associated with hyperglobulinemia and postulated an autoimmune mechanism as the cause of the pancreatic injury. In 2001, Hamano et al. (7), identified a relationship between high serum IgG4 levels and sclerosing pancreatitis. However, it was not until 2003 that Kamisawa et al. (8), designated for the first time the term "IgG4-related autoimmune disease". They recognized that patients who had autoimmune pancreatitis could have extensive injury in other tissues as well. These Authors comprise the pioneers in uncovering the existence of a previously unrecognized disease entity caused by underlying autoimmune mechanisms (8). Subsequently, several studies documented the association between the characteristic lesion of dense lymphoplasmacytic infiltrates containing IgG4-positive plasma cells in various organs including salivary gland (IgG4-related sialadenitis) (9, 10), lacrimal gland (IgG4-related dacryoadenitis) (9, 11), the bile duct (IgG4-related sclerosing cholangitis) (9, 12), liver (IgG4-related hepatopathy) (9), kidneys (IgG4-related kidney disease) (9, 11), aorta (IgG4-related aortitis/periaortitis) (9, 13), retroperitoneum (IgG4-related retroperitoneal fibrosis) (9, 10), lymph nodes (IgG4-related lymphadenopathy) (9, 10, 14)

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and lungs (IgG4-related lung disease) (9, 11, 15) with high serum IgG4 levels. In 2012, a consensus of experts with broad representation from different specialties officially recommended using the term "IgG4-related disease" and unified an appropriate nomenclature for this spectrum of diseases (previously also referred to as "hyper-IgG4 disease" and "IgG4-related sclerosing disease") (16). Herein, we summarize clinically relevant aspects of intrathoracic IgG4-RD, focusing on the point of view of the pulmonologists. This review describes the diverse intrathoracic manifestations, associated findings, diagnostic process, and treatment strategies. We also discuss the clinical course and prognosis.

General and epidemiologic aspects of IgG4-RD

IgG4-RD can be a diagnostic challenge as it mimics many other processes including neoplasms, infections, and autoimmune diseases. Overrepresentation in the literature of the most challenging and severe cases is a potential bias and has to be taken into consideration when evaluating epidemiologic aspects of this disease. IgG4-RD seems to be more common in men (Ratio of 1 to 0.7) (9, 17-19) with the possible exception of those with mainly head and neck involvement in whom the male to female ratio is nearly equal (9). It usually affects middle-aged to older individuals, with a median age of 60 to 65 years (2, 17) with only few sporadic cases under 18 years of age (2, 3).

The IgG4-RD is a condition described in all races although initially described predominantly in Asians. Successively, cases have been reported in subjects with differing ethnic backgrounds and various regions of the world. The predominance of Asians in the literature describing cases of IgG4-RD was likely due to the fact that Japanese physicians were the first to recognize these cases, and therefore had a broader experience in the diagnosis of this disease.

IgG4-RD may have an unpredictable clinical course whether one or multiple organs are involved at the time of diagnosis.

Symptomatology associated with IgG4-RD depends on the organ involved and includes abdominal pain (40%), sicca symptoms (15%), respiratory symptoms (13%), pruritus (13%), and diarrhea (6%) (4, 20). Patients may also present with constitutional complains such as weight loss, fatigue, and low-grade fevers (3, 4, 20). Additionally, some subjects may be asymptomatic at the time of diagnosis and present with only abnormalities on laboratory testing or imaging studies (2, 17).

IgG4-RD may have an unpredictable clinical course whether one or multiple organs are involved at the time of diagnosis. However, once the disease is recognized, it usually responds well to treatment. A minority of cases can progress to a life-threatening situation such as rupture of inflammatory aneurysms, coronary syndromes, and hypertrophic pachymeningitis or progressive organ damage despite immunosuppressive therapy (21-24).

Pathogenesis of IgG4-related disease

The pathogenesis of this disease remains an unfinished puzzle though several theories have been postulated. Herein, we review some of the hypotheses that have been proposed.

The genetic background is likely to influence how the individual responds to environmental exposures or lifestyle factors and it likely influences the evolution of autoimmune and other chronic inflammatory conditions. In the particular case of IgG4-RD, various genetic risk factors have been reported to play a role in the susceptibility to this disease, among which the HLA (human leukocyte antigen) serotypes DRB1*0405 and DQB1*0401 have been associated with increased predisposition in the Japanese population (25). Additionally, single-nucleotide polymorphisms in the tumor necrosis factor α, cytotoxic T-lymphocyte-associated antigen, and Fc receptor-like 3 have been implicated in susceptibility IgG4-RD to but study results have been inconsistent (17, 25-27).

IgG4 is the least abundant of the IgG family. It represents only 3 to 6% of the total IgGs; and presents in variable concentrations in healthy subjects, usually ranging from 0.01 to 1.4 mg/ml (1, 28). Among IgG4-RD patients, 70 to 90% of the patients have an elevated serum IgG4 level (>140 mg/dL). However, it should be noted that the serum IgG4 level is elevated in up to 5% of the normal population (28-30). The exact role of IgG4 in the pathogenesis of this disease is not well-understood and it is questionable whether IgG4 itself is the true driver of the inflammatory process.

IgG4 is a special form of IgG with respect to the structural, functional, and immunologic regulation. One of its unique characteristics is that IgG4 forms a dimer incorporating half of its own molecule and half from a different IgG4; this half-antibody exchange reaction is referred to as fragment antigen-binding (Fab)-arm exchange (2). This phenomenon occurs because, unlike other subclasses of IgG, the heavy chain has no covalent bonds and the disulfide bridges are incompetent (due to a single amino acid difference in the hinge region) (31, 32) allowing the IgG4 to randomly dissociate and regroup with other IgG4 molecules resulting in varying antigen-binding specificities. This half-antibody exchange can bind two different antigens but rarely associate with each other to form large immune complexes (33, 34). This is one of the reasons why IgG4 has traditionally been viewed as non-inflammatory component and whose primary function is to mitigate rather than accelerate or incite a chronic immune response.

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In addition to the individual genetic predisposition, several theories have been

postulated regarding infectious processes and autoimmunity as possible triggers for IgG4-RD. One is the observation that physiologic IgG4 responses can be induced by prolonged or repeated antigen exposures. Therefore, it is possible that the abundance of circulating IgG4 could be a reaction to an unidentified primary inflammatory stimulus. Second is that the formation of IgG4 antibodies directed against some microbial antigens could potentially act as autoantibodies to self-antigens through molecular mimicry in those who are genetically predisposed (1, 2). For instance, it has been shown that some patients with IgG4-related autoimmune pancreatitis have antibodies against the plasminogen-binding protein of *H. pylori* (35). Third, certain antibodies are directed to respond to autoantigens, some of which are expressed in exocrine glands such as lactoferrin, trypsinogens, pancreatic secretory trypsin inhibitor, and carbonic anhydrases. Reaction to these antigens may explain some of the IgG4-RD systemic manifestations (1, 36). However, these autoantibodies are not known to be a part of the IgG4 subclass nor specific for IgG4-RD (1, 37, 38).
Another important theory that may shedd some light into the pathogenesis of IgG4-RD comes from the observation that some of these patients respond well to B-lymphocyte depletion therapies (2, 39, 40). It is therefore possible that activated $IgG4^+$ B-lymphocytes and plasmablasts may drive the pathogenesis of IgG4-RD either directly through autoantibody assembly or indirectly through the activation of pathogenic $CD4^+$ T cells (2).

Overview of intrathoracic involvement in IgG4-RD

Even though IgG4-RD was beginning to be recognized in the late 1990s, it was not until 2004 that pulmonary involvement in this disease was documented. Taniguchi et al. reported a patient with autoimmune pancreatitis and bilateral interstitial infiltrates in the lower lung fields (41). Transbronchial lung biopsy showed marked thickening of the alveolar septae with infiltration of $IgG4^+$ plasma cells. Duvic et al. (42) reported a patient with pancreatic and retroperitoneal fibrosis, elevated serum IgG4 level, and nodular pulmonary opacities. Surgical lung biopsy demonstrated histopathologic features of organizing pneumonia. Both patients were treated with corticosteroids with a good response. Subsequent studies have reported a wide variety of intrathoracic findings. Interestingly, the most frequently affected intrathoracic component is the lymph nodes (17, 43-45). But involvement of other compartments including the lung parenchyma, airways, vasculature, and pleura and have also been reported. In 2005, Zen et al. reported inflammatory pseudotumour of the lung with $IgG4^+$ plasma cell infiltration and suggested that clinicopathological similarities exist between inflammatory pseudotumours and autoimmune pancreatitis (46). It seems, therefore, that the IgG4-related lung disease can manifest varying forms of involvement resembling many other disease processess in the lung.

There are two features of IgG4-related lung disease that continue to be incompletely understood and need further investigation. First, it is unclear how often pulmonary involvement occurs in patients with IgG4-RD. A cross-sectional study of 114 patients with the IgG4-RD, found that 16 (14%) patients had lung or pleural lesions (9). A retrospective multicenter study of 235 IgG4-RD patients reported only 13 (5.5%) patients to have lung involvement (47). Secondly, it is unknown whether the behavior of IgG4-RD in the lung may be modified by factors such a smoking or concomitant lung disease such as COPD or asthma.

Clinical features of intrathoracic IgG4-RD

Patients with intrathoracic IgG4-RD are often asymptomatic at presentation with incidental abnormalities detected by imaging studies performed for unrelated indications. Among patients with abnormal chest imaging studies related to IgG4-RD approximately 38% have respiratory symptoms, usually consisting of cough and exertional dyspnea (3, 15, 48). Less common symptoms include hemoptysis, chest pain, low-grade fever and weight loss (15, 48). Intrathoracic involvement in IgG4-RD can be classified according to anatomic compartments as shown in Table 1.

Parenchymal lung disease

Parenchymal lung involvement in IgG4-RD are mainly of two types: rounded opacities [nodules (≤3 cm in diameter) or masses (>3 cm in diameter)] and interstitial lung disease (ILD) (11, 15, 17, 43, 48-53). Rounded opacities may be solid or ground-glass density and can exhibit variable dimensions, from sub-centimeter (<1 cm) to pulmonary masses (>5 cm) (11, 15, 17, 43, 46, 48). Multiple or single rounded opacities can be observed on chest radiography or CT with no particular anatomical predilection (Figure 1) (15, 17, 43, 48, 49). Recently, a case of cavitating lung disease in

Table 1 - Patterns of intrathoracic involvement in IgG4-RD.

Parenchymal
Nodules or masses
Interstitial lung disease
Airways
Tracheobronchial stenosis
Extrinsic compression of large airways
Pleural
Pleural mass
Pleuritis/fibrosis
Pleural effusion
Mediastinal
Lymphadenopathy
Fibrosing mediastinitis
Pulmonary vascular disease
Pulmonary arterial hypertension

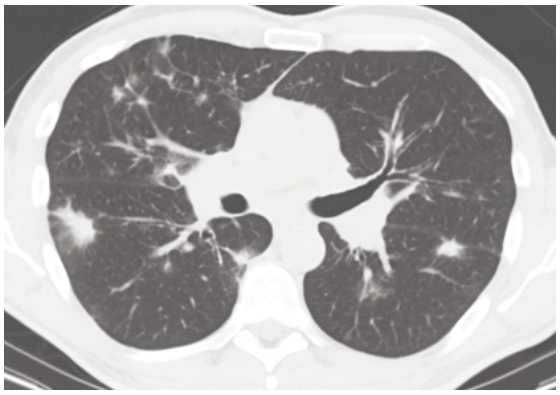

Figure 1 - Chest CT of a 55-year-old man with IgG4-related lung disease consisting of multiple solid irregularly margined nodules bilaterally. Transbronchial biopsy demonstrated interstitial and perivascular lymphoplasmacytic infiltrate with 30 IgG4+ plasma cells per high power field and 90% IgG4+/IgG+ plasma cell ratio. PET scan demonstrated FDG uptake in multiple organs including the lungs, mediastinal lymph nodes, salivary glands, lacrimal glands, and the pancreas.

IgG4-RD was reported (54). Rounded opacities usually raise suspicion of malignancy, particularly when associated with irregular margins (17, 43, 49). Thus, patients with these types of focal lung lesions not uncommonly undergo surgical resection (17).
The radiological features of interstitial involvement of IgG4-related lung disease are heterogeneous. Previous reports described bilateral interstitial pattern consisting in ground-glass opacities in the lower lung fields associated with honeycombing (17, 41). Subsequent reports have described widely varying radiological patterns including reticular opacities (irregular lines), patchy ground-glass opacities, alveolar consolidation, and thickening of the bronchovascular bundles and interlobular septa (11, 15, 17, 42, 43, 48, 49). Patients with these types of pulmonary involvement usually manifest a restrictive pattern along with a reduced diffusing capacity on pulmonary function testing (17).

Airway disease

Several cases of airway involvement in IgG4-RD have been reported. Ito et al. described a 63-year-old woman previously diagnosed with autoimmune pancreatitis that presented with a persistent cough and was noted to have irregular tracheobronchial stenosis on bronchoscopic inspection. Pulmonary function testing showed an obstructive pattern and chest CT revealed intrathoracic lymphadenopathy along with thickening of the bronchovascular bundle (17, 55). Inoue et al. (56) reported a 56-year-old woman who presented with exertional dyspnea. Chest radiography revealed stenosis of main bronchi bilaterally and spirometry demonstrates severe obstructive impairment. CT scanning in this patient revealed a diffuse mass in the mediastinum ("sclerosing mediastinitis") that involved the main bronchi bilaterally. A thoracotomy was performed with partial excision of the tissue mass which exhibited infiltration with many IgG4+ plasma cells (17, 56).

In IgG4-RD elevated serum IgE level and eosinophila are related to the immune response rather than to an underlying atopic condition.

Several patients diagnosed with IgG4-RD have been reported to present with asthma-like symptoms, peripheral blood eosinophilia and elevated serum IgE level (57, 58). However, it remains to be determined whether the findings represent mere coexistence of two diseases or pathogenically related entities. Zen et al. (15) reported a retrospective study of 21 patients among whom 9 (43%) had features of atopy and 6 (29%) had a diagnosis of asthma. In addition, Della Torre et al. (57) observed elevated serum IgE level in 35% of patients and peripheral blood eosinophilia in 27%. These Authors concluded that elevated serum IgE level peripheral eosinophilia are related to the immune response in IgG4-RD rather than to an underlying atopic condition (57).

Pleural disease

IgG4-related pleural disease can present alone, accompany parenchymal lung lesions, or with extrapulmonary involvement (17, 59, 60). Pleural manifestations in IgG4-RD mainly include three features: pleural mass, pleuritis with fibrosis, or pleural effusion (Figure 2). Zen et al. (15) reported pleural lesions in 24% of their 21 patients. The pleural lesions were nodular and involved the visceral and parietal pleura as well as the chest wall. All 5 patients had both parenchymal and pleural involvement (15). There have also been reports of patients presenting with symptomatic pleural effusions, sometimes bilateral and massive (49, 61, 62). A pleural fluid analysis demonstrated an exudative character with cellular constituents comprising mainly of lymphocytes and plasma cells (61).

Mediastinal disease

Most common intrathoracic manifestation is probably lymphadenopathy in the mediastinum and/or hilar regions and has been described in 40% to 100% of patients with IgG4-RD (10, 11, 15, 43, 44, 63). Matsui et al. (63) reported a retrospective review of 18 patients diagnosed with intrathoracic IgG4-RD among whom hilar lymphadenopathy was noted in all patients as detected by CT scanning, gallium-citrate or 18-fluorodeoxyglucose positron emission tomography.
Fibrosing mediastinitis is an uncommon manifestation of IgG4-RD but may respond to corticosteroid therapy (17, 56, 64). This is notable since fibrosing medias-

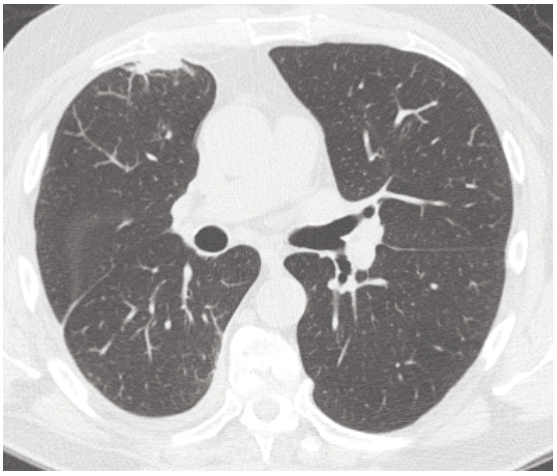

Figure 2 - Chest CT of a 70-year-old man with IgG4-related autoimmune pancreatitis and pleural fibrosis. Chest CT scan demonstrated multiple regions of pleural thickening within the right hemithorax including focal nodular thickening anteriorly and more diffuse thickening posteriorly. Thoracoscopic pleural biopsy demonstrated sclerosing pleuritis with dense lymphoplasmacytic infiltrates containing >30 $IgG4^+$ cells per high power field.

tinitis is generally considered a condition refractory to corticosteroid therapy (17).

Pulmonary vascular disease

Involvement of the pulmonary vasculature is rare in IgG4-RD, but recently, cases of pulmonary arterial hypertension associated with IgG4-RD have been reported (65, 66). In one such report of a 22-year-old woman, chest CT revealed multiple small pulmonary nodules along with thickening of bronchovascular bundles and interlobular septae (65). She was documented to have pulmonary hypertension by echocardiography and right heart catheterization. The pulmonary hypertension and CT abnormalities improved rapidly after beginning corticosteroid therapy. The Authors hypothesized the mechanism of pulmonary hypertension to be obliterative arteritis affecting the pulmonary arteries caused by IgG4-RD.

The mechanism of pulmonary hypertension is pulmonary obliterative arteritis caused by IgG4-RD.

Laboratory findings

Basic laboratory tests such as complete blood cell counts and biochemical profiles often provide nonspecific indications of organ impairment (67). Mild-to-moderate peripheral eosinophilia is found in 34% of patients with IgG4-RD (4). Serum IgG4 level is elevated (>140 mg/dL) in the majority of patients with intrathoracic IgG4-RD (29, 67-70). However, an elevated serum IgG4 level is a relatively insensitive and nonspecific biomarker in the diagnosis of IgG4-RD (29, 30, 67, 71).

Kerbs von den Lungen-6 (KL-6) is a circulating high-molecular weight glycoprotein (MUC1 mucin) expressed by type II pneumocytes in the lung (17). This biomarker has been reported to be elevated in patients with various ILDs including idiopathic pulmonary fibrosis (17, 72, 73). Hirano et al. (50) reported pulmonary involvement in 4 of 30 patients with autoimmune pancreatitis and the serum levels of KL-6 was elevated in all 4 patients. Additionally, the serum KL-6 level has been noted to decrease with glucocorticoid therapy in patients with IgG4-related lung disease (74). Nonetheless, the utility of serum KL-6 level in patients with intrathoracic IgG4-RD remains to be clarified.

The usefulness of other immunological markers such as rheumatoid factor, anti-nuclear antibody and inflammatory biomarkers such as erythrocyte sedimentation rate and C-reactive protein, is limited, considering that these nonspecific biomarkers tend to rise in many inflammatory disorders (49, 75). Recent studies suggest that circulating plasmablast levels are elevated in patients with IgG4-RD and may correlate with disease activity (76, 77). Additional studies are needed in assessing the role of plasmablast levels as a biomarker in this disease.

The IgG4 level in the bronchoalveolar lavage fluid (BAL) seems to correlate with the serum IgG4 level and patients with IgG4-related lung disease have higher levels of IgG4 in the BAL compared to patients with sarcoidosis (17, 43). As expected from histopathological findings, BAL cellularity consists predominantly of lymphocytes and the $CD4^+/CD8^+$ lymphocyte ratio tends to be normal (17, 43, 55, 63). However, the BAL data concerning to IgG4-related lung disease are sparse and the role of BAL in the evaluation of patients with IgG4-related lung disease remains to be clarified.

Histopathology

Histopathological findings remain the diagnostic keystone of IgG4-RD (4, 75). These findings are better depicted on surgical lung biopsy but can also be recognized on bronchoscopic biopsy (17). Transthoracic needle biopsy may be useful in excluding malignancies in patients with focal lesions, but may not provide sufficient tissue to confirm a diagnosis of IgG4-RD (4, 17, 75).

The key morphological points shared with extrapulmonary IgG4-related lesions include lymphoplasmacytic inflammation, increased numbers of $IgG4^+$ plasma cells, fibrosis and phlebitis.

Many of the histopathological features of pulmonary involvement in IgG4-RD are similar to those appreciated in those with extrapulmonary lesions but there are also some differences. The key morphological points shared with extrapulmonary IgG4-related lesions include lymphoplasma-

cytic inflammation, increased numbers of IgG4+ plasma cells, fibrosis and phlebitis (9, 17, 48, 78, 79). Eosinophilic infiltration into the interlobular septae, peribronchioles and pleura can be prominent but granulomas are seldom present and tend to be small and vague (9, 17, 63, 79). Plasma cells comprise the main cell type of the inflammatory infiltrates, followed by lymphocytes and histiocytes (9, 17).

In the lung, the collagenized fibrosis and active fibroblastic proliferation are more predominant than in autoimmune pancreatitis, whereas distinct storiform fibrosis is often not seen (4, 17, 79). Obliterative arteritis and/or phlebitis has been described in both pulmonary veins and arteries in contrast to the findings in the involved pancreas which show obliterative phlebitis with sparing of the arteries (17, 78, 79).

The appropriate cut-off values for the number of IgG4+ plasma cells per high-power field differ depending on the organ involved (60, 75, 80). Several studies report the IgG4+/IgG+ plasma cell ratio in tissue over 40% to have aproximatly 85% specificity for diagnosing IgG4-RD (60, 80). Nevertheless, numerous disorders, including multicentric Castleman's disease, rheumatoid synovitis, carcinoma-associated inflammatory response, and other nonspecific inflammatory responses can exhibit high IgG4+ plasma cell counts and IgG4+/IgG+ ratios.

Diagnosis of IgG4-RLD

In patients who already have an established diagnosis of IgG4-RD, concern regarding pulmonary involvement may arise when respiratory symptoms occur or intrathoracic abnormalities are noted on imaging. In 2015 an expert consensus panel agreed that the results of clinical evaluation, laboratory analysis, and imaging studies are generally insufficient to distinguish the lesions of IgG4-RD from other diseases. Therefore, diagnostic confirmation by histopathologic analysis of the intrathoracic lesion is recommended for the exclusion of malignancies and other processes that may present in a similar manner (81). Ryu et al. (17) proposed several criteria to diagnose IgG4-related lung disease (RLD) including the presence of a histopathologic lesion characterized by a fibroinflammatory process (in the absence of an infection), with or without nodular formation, and the presence of plasma cells that comprise >50% of inflammatory infiltrates with endothelialitis in the pulmonary arteries and/or veins (17, 78). Interlobular septal and pleural involvement is commonly present (17). IgG4+ plasma cells are increased with >50 IgG4+ plasma cells seen per high power field with IgG4+/IgG+ plasma cell ratio of >40% (75). The diagnosis of IgG4-RD can be reached in the presence of these histopathological findings along with compatible clinical and radiologic features that do not suggest an alternative disorder.

Diagnostic confirmation by histopathologic analysis of the intrathoracic lesion is recommended for the exclusion of malignancies and other processes that may present in a similar manner.

Differential diagnosis

The differential diagnosis for IgG4-RLD may include a large number of disorders due to its protean manifestations. Thus the disease entities that need to be considered in this regard depend on the abnormal feature being evaluated as outlined in Table 2.

Treatment

The primary goal for treatment of IgG4-RD is the prevention of irreversible fibrosis and organ damage which can occur within weeks or months (81). Intrathoracic IgG4-RD, similar to extrapulmonary lesions, responds well to corticosteroid therapy (1, 15, 17, 41, 42, 44, 48, 60, 63, 78, 81, 82). The optimal dose of corticosteroid therapy in the treatment of IgG4-RD is not exactly known, but most experts recommend oral prednisone at an initial dosage of 30 to 40 mg/day (81, 83). The dosage may be adjusted based on body weight. If the disease appears to be particularly aggressive in its behavior, 1 mg/kg per day can be used.

The initial corticosteroid dosage should be maintained for 2 to 4 weeks (81). Favorable response is typically seen by 2 weeks on treatment, after which it can be tapered gradually over the following weeks to months with close monitoring for possible recurrence

There is lack of consensus among experts and the evidence regarding the use of immunosuppressive therapy other than corticosteroids in the treatment of IgG4-RD is limited.

Table 2 - Differential diagnosis for IgG4-RLD.

Diseases with similar pulmonary presentations
Neoplastic disorders, including lymphoma (nodular opacities)
Infections, including lung abscess (nodular opacities ± cavitation)
Interstitial pneumonias (interstitial infiltrates)
Asthma (airway disease)
Diseases with multi-system involvement
Connective tissue diseases
Vasculitis, especially granulomatosis with polyangiitis (Wegener)
Sarcoidosis
Diseases with pulmonary inflammation and increased IgG4+ plasma cells
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatous with polyangiitis (Churg-Strauss)
Multicentric Castleman's disease
Rosai-Dorfman disease

(17). The practice at many centers is to discontinue corticosteroid use 3 to 6 months after the start of treatment while others advocate low-dose maintenance therapy for a longer period to reduce the risk of relapse (12, 81, 84-86). Optimal duration of maintenance therapy has not been determined.

Not all intrathoracic manifestations of IgG4-RD require immediate treatment. For example, "watchful waiting" may be appropriate, in patients with asymptomatic intrathoracic lymphadenopathy (63, 81).

Spontaneous remissions of IgG-RD, at least temporary, without treatment, have been reported (81, 87, 88). However, spontaneous improvement in intrathoracic IgG4-related lung disease has not been documented. While corticosteroid therapy is used commonly in patients with IgG4-related lung disease, it is not necessary in the management of patients who undergo complete surgical resection of a solitary pulmonary nodule or mass that represents the sole manifestation IgG4-RD (9, 15, 17).

There is lack of consensus among experts and the limited evidence regarding the use of immunosuppressive therapy other than corticosteroids in the treatment of IgG4-RD (81). The addition of steroid-sparing agents seems appropriate when the corticosteroid dosage cannot be decreased due to persistently active disease, particularly when adverse effects of corticosteroid therapy have occurred (81). In certain situations such as in patients known to be at increased risk of adverse effects from corticosteroids or situations requiring prolonged treatment, combining a steroid-sparing agent with corticosteroid therapy at the start of treatment can be considered (81). Steroid-sparing agents that have been used in the treatment of IgG4-RD include azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, tacrolimus, and cyclophosphamide (17, 81). The efficacy of these agents has not been assessed in prospective clinical trials.

The B cell depletion therapy with rituximab has shown promising results in retrospective studies, even in patients in whom treatment with other steroid-sparing agents has been unsuccessful (43, 89-92). Addition of rituximab therapy for patients on corticosteroids can facilitate reduction of corticosteroid dosage (40, 81). Recently, Carruthers et al. (40) reported the results of an open-label pilot trial of rituximab therapy in 30 patients with IgG4-RD. Favorable disease response that was maintained at 6 months was seen in nearly all patients and only 8 participants required prednisone treatment at any point in the trial (40). Optimal use of B-cell depletion therapy in IgG4-RD remains to be determined.

Prognosis

The outcome in IgG45-RD appears to depend on several parameters including patient-specific factors (age, sex) and disease-specific factors such as disease duration and extent of disease (e.g., single-organ *vs* multi-organ involvement) (93). Relapse of disease is relatively common during the steroid tapering process and may necessitate reescalation of the corticosteroid dose or and/or addition of a steroid-sparing agent (81, 93, 94). Thus, some experts have advocated the use of prolonged maintenance therapy, typically low-dose corticosteroids, to prevent relapses (1, 81, 95). In addition, the response to corticosteroid therapy seems to vary according to the affected organs and the stage of disease (degree of fibrosis). Some patients with IgG4-RD may not experience complete resolution of their disease and exhibit evidence of residual disease. For example, Zen et al. (15) reported residual radiologic abnormalities after treatment in 14% of patients with IgG4-related pleuro-pulmonary disease.

Conclusions

IgG4-related intrathoracic disease comprises varying patterns of involvement and can affect nearly all components in the thorax including the lung parenchyma, airways, pleura, pulmonary vasculature and the mediastinum. The diagnosis of IgG4-RD should be considered in patients presenting with a persistent or recurrent inflammatory process which appears to be characterized by lymphoplasmacytic infiltration of the tissue with fibrosis. IgG4-RD may account for a portion of various idiopathic fibroinflammatory disorders encountered in the thorax including inflammatory pseudotumors, idiopathic interstitial pneumonias, asthma-like airway disease, nodular pleural lesions, and fibrosing mediastinitis.

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