

IgG4 Related Disease

A Challenge for Pneumonologist

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ABSTRACT

IgG4-related disease (IgG4-RD) includes a wide spectrum of inflammatory and fibrous procedures that affect a variety of issues and organs and are accompanied by elevated serum IgG4 levels. The clinical presentation is quite heterogeneous as almost every organ can be influenced. Clinical, laboratory and histopathological features and criteria must be taken into account and both malignancies (solid tumors and lymphomas) and benign disorders be excluded for the diagnosis to be established. Intrathoracic involvement in IgG4-RD varies and includes the lung parenchyma causing nodules, masses, ground-glass opacities, infiltrates resembling consolidation and thickened bronchovascular bundles, the central airways resulting in stenosis, obstruction and bronchiectasis as well as the pleura with effusion and nodular lesions and the mediastinum. Hilar and mediastinal lymphadenopathy are the most common intrathoracic manifestation while fibroid mediastinitis is much more rare. Corticosteroids are the cornerstone of therapy and most of cases present complete or partial response. However, rates of recurrence after treatment termination are high. In addition, patients may develop IgG4-related extrathoracic disease during the next months or even years after the initial diagnosis.

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INTRODUCTION

The term IgG4 Related Disease (IgG4-RD) includes a wide spectrum of inflammatory and fibrotic procedures that take place in multiple organs and tissues and are related to increased blood levels of IgG4 immunoglobulin. First reports of the disease in 2001, refer to cases of autoimmune pancreatitis. Ever since, our knowledge on pathogenesis, clinical features, histopathology and treatment of this lympho-hyperplastic disorders have been enhanced leading to increase of cases diagnosed.

Recent studies suggest that this entity should be defined as a systematic disease due to simultaneous or metachronous lesions in more than one

organs with characteristic infiltrations of IgG4-positive plasmacytes and various degree of fibrosis in combination with elevated serum levels of IgG4¹⁻⁵.

IgG4-RD can affect any organ and tissue resulting in heterogeneous clinical appearance. The disease may be single or multiple sited and be presented as a tumor-like or a diffuse infiltrative lesion. However, most of patients have a multi-organ involvement and only 10-20% of them experience a solitary organ affection^{5,6}.

1. GENERAL

There are few studies, mainly from Asian populations, with reports on IgG4-RD epidemiology. A cross-sectioned study in 2009, estimated that approximately 8,000 individuals in Japan were suffering from IgG4-RD accounting for a prevalence of about 60 affected persons per million of inhabitants⁷.

In literature, IgG4-RD has been mainly described in male (70-80%) adults of 17 to 80 years-old (median age 60-65 years) with the probable exception of those patients presenting head and neck disease in whom male to female ratio seems to be equal. There are no data on the prevalence of IgG4-RD in Europe but is thought to be much more rare than in Asia^{8,9,10}.

The organs known to be affected include the central nervous system, the lacrimal and salivary glands, the thyroid gland, the lung, the pancreas, the liver, the gastrointestinal tract, the kidney, the prostate gland, the skin, the arteries and the lymph nodes. Although clinical symptoms are relatively mild, some patients develop serious complications such as obstructive jaundice due to hepatic, gall bladder or pancreatic lesions, hydro-nephrosis due to retroperitoneal fibrosis and respiratory impairment due to pulmonary involvement².

Patients with IgG4-RD may present a variety of symptoms depending on the organs affected or may be completely asymptomatic with only imaging or laboratory abnormal findings. Constitutional symptoms like fever and weight loss are uncommon^{8,9,11}. Most of IgG4-RD patients (70-90%) have an elevated serum IgG4 level which is also found in 5% of healthy population.

Involvement of immunological mechanisms, possibly of autoimmune nature, may be implicated in IgG4-RD pathogenesis but the exact role of IgG4 in this disorder remains unclear. It is also uncertain whether IgG4 represents a protective response against a pathogen or is a bystander to the inflammatory process^{9,12-14}.

Common histopathological findings in IgG4-RD are lympho-plasmacytic inflammation, fibrosis, phlebitis and infiltrates of IgG4(+) plasmacytes. Although combination of these features is characteristic for the disease, none of them of its own is absolutely specific for the diagnosis^{15,16}.

Studies published over the past few years, have documented the association between high serum IgG4 values and characteristic lympho-plasmacytic infiltration of IgG4(+) plasmacytes in various organs including the bile duct (sclerosing cholangitis), salivary and lacrimal glands (sclerosing sialadenitis and dacryoadenitis, respectively), liver (IgG4 hepatopathy), kidney (inflammatory pseudotumor), retroperitoneum (retroperitoneal fibrosis), aorta (inflammatory aneurysm), lymph nodes or lung^{9,17-26}.

Umehara et al, propose three major diagnostic criteria (clinical, laboratory and histopathological) for disease diagnosis²⁷. Physical examination and imaging on Ultra Sound, Computed Tomography and Magnetic Resonance Imaging can reveal localized or diffused swelling, masses or thickness in one or more organs. Increased serum levels of IgG4 are usually observed. IgG subclass analysis demonstrates high IgG4 levels in many but not all of patients. It should be underlined that IgG4 level can be substantially misleading when used as the only criterion for diagnosis of the disease. A number of other diseases, such as cancer, infections and autoimmune disorders including vasculitis, are associated with increased IgG4 value. On the other hand, some of IgG4-RD patients may have normal IgG4 level. Thus, sensitivity, specificity and positive predictive value of elevated serum IgG4 was found to be 90%, 60% and as poor as 10% respectively, in relative studies²⁸⁻³⁰.

The most particular histological features of the disease are:

- dense lympho-plasmacytic infiltration,
- storiform fibrosis (resembling the spokes of a car wheel) and
- obstructive phlebitis.

Other histopathological findings include phlebitis without obstruction of the vein and increased number of eosinophils in tissues. In locations such as lymph nodes, lungs and lacrimal glands, storiform fibrosis and obstructive phlebitis may be absent. According to the above, Umehara et al suggest that the ratio of IgG4/IgG (+) cells and grade of IgG4(+) plasmacytic infiltration should be taken into account with values of >40% and >10/High Power Field (HPF) respectively, to be consistent with diagnosis²⁷.

In contrary, presence of neutrophils, granulomas, neu-

trophilic micro abscesses and necrotic vasculitis strongly argues against IgG4-RD³¹.

Inflammatory markers, like ESR and CRP, may be elevated but can also be normal despite disease activity. Anti-nuclear antibodies, anti SS-A as well as anti SS-B antibodies are negative in the majority of cases while low complement level (C3 and C4) are not uncommon^{32,33}. Polyclonal hyper-gamma globulinemia is often found in IgG4-RD. Increased serum IgE level and allergic disorders are present in about one third of patients³⁴.

Differential diagnosis includes malignancies, such as solid tumors and lymphomas, and benign diseases like Sjogren syndrome, primary sclerosing cholangitis, Castleman's disease, idiopathic retroperitoneal fibrosis, granulomatosis with polyangiitis (Wegener's granulomatosis), sarcoidosis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)³⁵.

2. INTRATHORACIC DISEASE RELATED TO IGG4

Intrathoracic manifestations of IgG4-RD are rather heterogeneous as not only lung parenchyma but also intrathoracic lymph nodes, mediastinum and pleura may as well be involved. In this context, it seems plausible that IgG4-RD may account for a significant proportion of fibro-inflammatory disorders of unknown origin such as inflammatory pseudotumors of the lung, idiopathic interstitial pneumonia like cryptogenic organizing pneumonia and fibrosing mediastinitis.

It is not precisely known how often lungs are affected in patients with IgG4-RD. In a study of 114 patients, 16 (14%) were found to have parenchymal or pleural lesions. In another retrospective analysis of 90 patients with autoimmune pancreatitis, 54% of them were found to experience lung parenchymal involvement. Intrathoracic lymphadenopathy seems to be common enough and can be detected in more than one half of patients with IgG4-RD^{9,19,20,24}. Intrathoracic disease lesions can be combined with one or more extrapulmonary ones^{15,23,25,35}.

2a. Pulmonary involvement

First reports on IgG4-related lung disease were about patients with autoimmune pancreatitis and diffuse interstitial pneumonia or pulmonary nodules. Since then, a wide and heterogeneous spectrum of intrathoracic disorders have been reported, with mediastinal and hilar lymphadenopathy being the most common.

In a recent study, IgG4-related lung disease was cat-

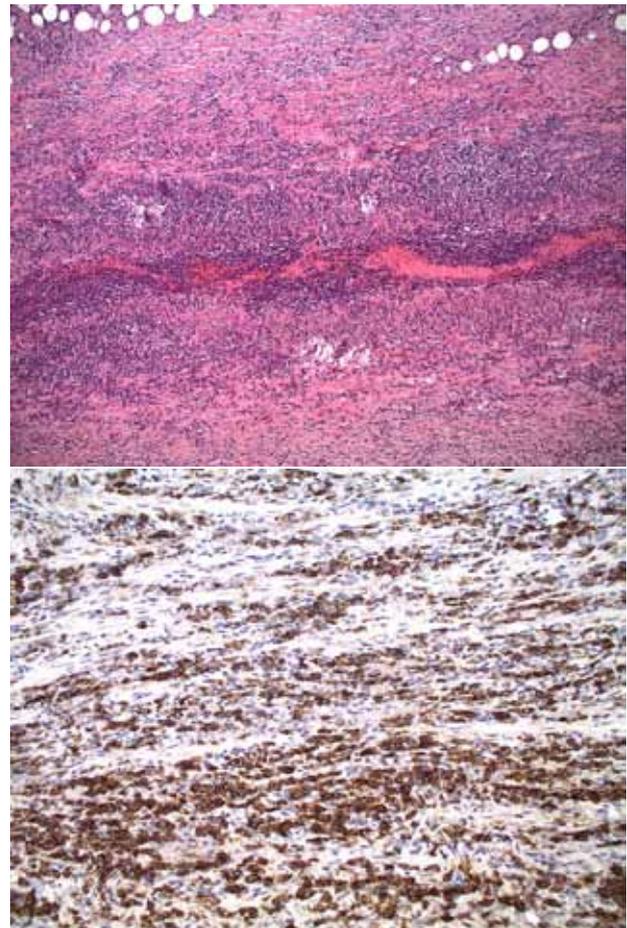


FIGURE 1. Biopsy of mediastinum mass. A) Lymphoplasmacytic infiltration, fibrosis and obstructive phlebitis (hematoxylin-eosin stain, magnification $\times 100$). B) Diffuse infiltration of IgG4 positive plasmacytes with >50 /high power field (immunohistochemical stain, magnification $\times 200$).

egorized into four types, according to thoracic computed tomography findings:

- solid nodular type (solitary nodule including a mass)
- bronchovascular type (with thickening of bronchovascular bundles and interlobular septa)
- alveolar-interstitial type (with bronchiectases, honeycombing and diffuse ground-glass opacities) and
- round-shaped ground-glass opacity type (with multiple round-shaped ground-glass opacities)

Lung parenchymal involvement mainly consists of nodules (up to 3cm in diameter) or masses (of >3 cm in diameter) and interstitial lung disease. Nodular lesions may be single or multiple, of solid or ground-glass opacity and are revealed in chest X-ray or chest computed tomography. They usually raise suspicions of malignancy,

especially when their margins are speculated whereas, ground-glass lesions may resemble to broncho-alveolar carcinoma³⁶⁻⁴².

IgG4-related lung disease should be suspected in patients with extrapulmonary IgG4-RD.

Pulmonary involvement occurs in 12-50% of patients with IgG4-RD. This great variation is attributable to the different methods used for identification of lung affection and the relatively small number of patients enrolled^{19,40}.

As previously reported, intrathoracic involvement include lung parenchyma, airways and pleura as well as lymph-nodes with hilar and mediastinal lymphadenopathy being the most frequent type (up to 80%)^{19,21,22}.

Nodular lesions and bronchovascular involvement are the most common pulmonary manifestations but, various combinations of pulmonary abnormalities are often found in the same patient^{26,30}. Interstitial lung disease due to IgG4-RD has been described but, it is unclear if IgG4-RD is the underlined cause or whether these cases represent patients with interstitial lung disease unrelated to IgG4 disorder⁴³.

Respiratory symptoms include cough, dyspnoea and chest pain but they can also be completely absent in about one half of the patients⁴⁴.

Diagnosis is based on clinical presentation, laboratory measurement of IgG4 >135mg/L or IgG4/IgG ratio >40%, and characteristic histopathological findings and is classified into definite (patients with clinical, biochemical and histopathological evidence), probable (patients with clinical and histopathological evidence only) and possible (patients with clinical and laboratory evidence only)^{26,45} (Table 1).

A variety of disease can mimic IgG4-related lung disease including lung cancer, idiopathic interstitial pneumonia and sarcoidosis²⁶.

2b. Pleural involvement

Pleural affection in patients with IgG4-RD is uncommon

and mainly consists of nodular lesions in the visceral or parietal pleura. Cases with exudative lymphocytic effusion and even chylothorax have been described^{46,47}.

2c. Mediastinal involvement

Localized or systemic lymphadenopathy is common in IgG4-RD and differential diagnosis is broad including lymphomas, metastatic lymph nodes disease, Castleman's disease and other immune mediated or hematological disorders²².

Symptoms like fever, weight loss and night sweats are not common in IgG4-RD. Of note, histopathological features differ from those usually seen, as storiform fibrosis and obliterative phlebitis are often absent in affected lymph nodes^{48,49}.

It is important to recognize that, histopathological examination of lymph nodes in suspected IgG4-RD cases is not sufficient to establish diagnosis when used as a solitary criterion. Thus, it may be difficult to clearly distinguish IgG4-related lymphadenopathy from other diseases.

- Mediastinal and Hilar Lymphadenopathy

Mediastinal and/or hilar lymphadenopathy are the most common intrathoracic manifestations of IgG4-RD and have been described in 40-90% of patients^{18-20,22-24}. In a study of 65 patients with autoimmune pancreatitis, Hamano et al, reported that hilar lymphadenopathy, detected by chest Computed Tomography and Gallium-67 scintigraphy, was the most frequent extrapancreatic lesion being occurred in 80% of cases²⁰. In other surveys intrathoracic lymphadenopathy has been identified in the majority of patients with IgG4-RD who underwent 18-Fluoro-2-deoxy-D-glucose Positron Emission Tomography (18-FDG-PET)^{50,51}.

- Fibrosing Mediastinitis

Fibrosing mediastinitis (FM), also called sclerosing

TABLE 1. Diagnostic Criteria for IgG4-RD

Diagnosis	Compatible clinical and imaging findings (diffuse or localized edema, mass)	Serum IgG4 >135mg/dl	Compatible Histopathological findings (IgG4+ lymphoplasmacytic infiltrate, fibrosis, obstructive phlebitis)
Definite	+	+	+
Probable	+	-	+
Possible	+	+	-



FIGURE 2. Chest computed tomography that reveals solid mass next to the aortic arch due to fibrotic mediastinitis caused by IgG4-RD.

mediastinitis, is commonly combined with retroperitoneal fibrosis but rarely with IgG4-RD. It is characterized by an aggressive inflammatory process and progressive fibrosis within the mediastinum that frequently results in compression and functional impairment of vital structures⁵²⁻⁵⁴.

Consequently, FM can lead to substantial morbidity and perhaps even to increased mortality.

Although pathogenesis of FM remains unknown, radiographic, serologic or histopathologic evidence of prior *Histoplasma Capsulatum* infection can often be documented. In endemic areas of North America, the majority of FM cases are thought to represent a rare hyper-sensitivity reaction to this infection^{54,55}.

Additional infections triggers that are implicated in the pathogenesis of FM include other fungal and mycobacterium associated with granuloma mediastinitis.

Finally, there are rare immune-mediated (idiopathic) and drug-induced (e.g.: methysergide) reported cases of FM^{54,55}.

Interestingly, patients with idiopathic immune-mediated FM frequently have other disease manifestations such as retroperitoneal fibrosis or Riedel's thyroiditis, and they all have been associated with the IgG4-RD spectrum⁵⁴⁻⁵⁶.

Up to date only a single case of FM attributed to IgG4-RD has been reported in the literature^{57,58}. However, based on fibro-inflammatory changes associated with the local accumulation of plasmacytes, it can be hypothesized that a subset of FM cases may belong to the IgG4-RD spectrum and demonstrates consistent histopathological and immunological features. Peikert et al, retrospectively studied 15 cases of histologically confirmed FM and found out that three of them were consistent with IgG4-RD

after re-examination of biopsy specimens underlining a probable underestimation of disease⁵⁹. This is of great importance as the majority of FM is not responsive to common treatments^{53,54} whereas, IgG4-related FM is sensitive to corticosteroids^{9,11,56,57}.

Consequently, identification of this subgroup of FM patients is proposed to be based upon the presence of elevated serum IgG4 level >140mg/L and/or characteristic histopathological findings with accumulation of IgG4(+) plasmacytes within the mediastinal lesions.

Of note, diagnostic criteria for most of disease locations, including the mediastinum, are exclusively based on experts opinion and consensus or extrapolated from observations in pancreas, salivary and lacrimal glands^{61,62}.

2d. Airway Disease

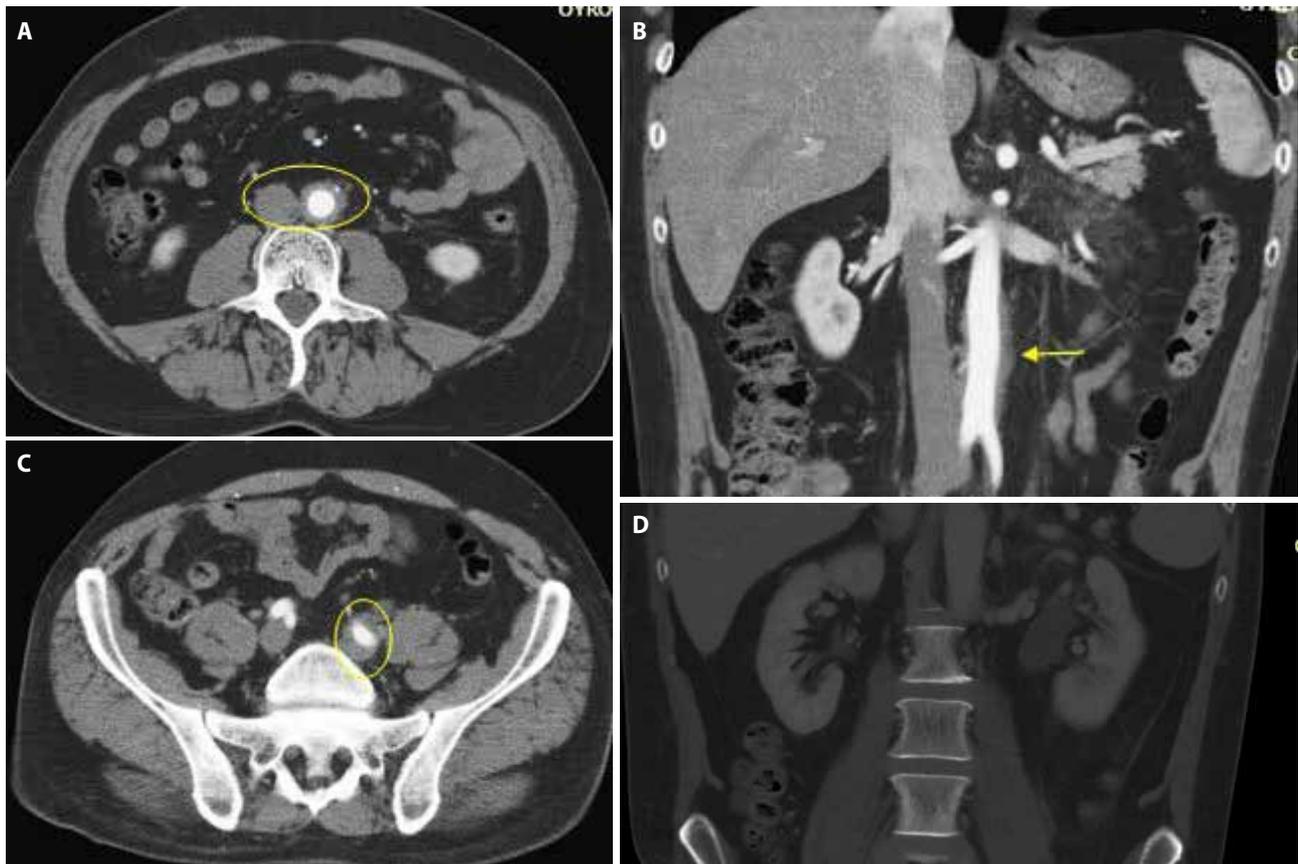
There have been rare reports on airway disease associated to IgG4. Ito et al, describe the case of a 63-year old female with autoimmune pancreatitis who was presented with cough⁶². Bronchoscopic examination revealed a tracheobronchial stenosis with oedematous and hyper-vascular bronchial mucosa resembling sarcoidosis. An obstructive pattern was seen in pulmonary function tests while chest computed tomography revealed intrathoracic lymphadenopathy and thickening of the bronchovascular bundles also resembling sarcoidosis features.

Another airway manifestation described in IgG4-RD is extrinsic compression of the central airways mainly due to fibrotic mediastinitis and bronchiectases, probably associated also with parenchymal fibrosis of the peripheral zones of lung (traction bronchiectasis) rather than involvement of the proximal large airways^{23,25,58}.

Features shared with extrapulmonary IgG4-related lesions include lymph-plasmacytic inflammation, fibrosis, phlebitis and increased number of IgG4 (+) plasmacytes.

Plasmacytes represent the predominant cell population found in the inflammatory infiltrates followed by lymphocytes and histiocytes. Eosinophilic infiltration can be detected but granulomas are rare and usually of small size^{9,15}. These changes are better recognized in surgical lung biopsies but can also be found in bronchoscopic and fine needle biopsies. In surgical lung biopsies lymphangitic distribution involving the interlobular septa and visceral pleura is seen.

Characteristic storiform fibrosis is not common in lungs where fibrosis rich to collagen and active fibroblastic proliferation are more predominant. In addition, both pulmonary arteries and veins are involved with intimal and mural inflammation, whereas in pancreas, obliterative



EIKONA 3. Abdomen computed tomography that reveals solid mass around A, B) the aorta, C) the common iliac artery and D) left ureter with distention of its upper part in patient with IgG4-RD.

phlebitis is observed without arteries affection¹⁵. Necrotic vasculitis is not usually detected while histopathological findings of organizing pneumonitis and non-specific interstitial pneumonia have been described in patients with IgG4-related pulmonary disease.

3. CLINICAL FEATURES

Respiratory symptoms including cough, exertional dyspnea and chest pain have been described in almost one half of patients with pulmonary IgG4-RD while the rest of them present abnormal radiologic intrathoracic findings in the absence of respiratory symptoms. Constitutional symptoms like fever and weight loss are not common^{23,26}. There are no studies assessing potential risk factors for pulmonary involvement in IgG4-RD. For example, it is unknown whether tobacco smoking or exposure to other inhaled factors may increase the risk for pulmonary affection^{15,36,39}.

4. LABORATORY TESTS

Serum IgG4 value is elevated $>140\text{mg/L}$ in the majority of patients with intrathoracic disease^{15,23,25}.

Analysis of bronchoalveolar lavage (BAL) fluid shows increased levels of IgG4 when compared to specimens obtained from patients suffering of sarcoidosis²⁴. IgG4 level in BAL seems to be correlated to that in serum. Cellular analysis of BAL typically reveals increased lymphocytes as expected based on histopathological findings. Overall, existing data are insufficient and the role of BAL in evaluation of patients with IgG4-RD remains to be clarified⁶².

Even though the presence of IgG4 positive lymphoplasmacytic infiltrations characterizes the disease, it is not entirely specific for the diagnosis¹⁵.

In addition, there is not a single specific histopathological parameter that could distinguish IgG4-related pulmonary disease from other disorders of similar appearance. According to published data, histopathological lesion of intrathoracic IgG4-RD is characterized by a non-infectious,

inflammatory plus fibrosing process, with or without nodule formation, infiltrates consisting of plasmacytes at more than 50% and affection of pulmonary arteries and/or veins endothelium¹⁵. IgG4(+) plasmacytes are increased reaching the 30% of all IgG(+) cells in immunohistochemical staining^{15,23,25}. Interlobular septal and pleural involvement is commonly present.

As these histological findings are not specific for diagnosis, they must be correlated with clinical, laboratory and imaging context.

In conclusion, presence of typical histopathological features and compatible clinical and radiological findings that do not suggest another disorder, is crucial for the diagnosis to be established.

It must be noted, for once more, that, although serum IgG4 value is increased in the majority of patients with IgG4-RD, including those having intrathoracic disease, absence of elevation does not exclude the diagnosis.

5.THERAPY

Intrathoracic location of IgG4-RD generally responds well to corticosteroid therapy, weather lungs, airways, pleural or mediastinum is involved^{15,20,22,23,25,36,39,40,42,62}. Exact regimen, dose and treatment schedule is not specified but in most studies typically consists of oral prednisone at an initial dose of 30mg/day to 1mg/kg/day. Response is usually observed after 2 weeks of therapy. 1 to 2 weeks later, prednisone dose is tapered over the following several months under monitoring for complete resolution or recurrence during the interval. Use of bortezomib, a proteasome inhibitor, and addition of cyclosporine to corticosteroid therapy, have been reported in two cases of recurrent IgG4-related pulmonary disease and appeared to be beneficial^{39,63}.

In extrathoracic IgG4-RD azathioprine, mycophenolate, methotrexate and cyclophosphamide have been occasionally used to prevent long term relapse^{17,64}. Recently, rituximab has been reported to result in rapid decline of serum IgG4 value and improve clinical condition of four patients with systemic IgG4 disease⁶⁵. In the above study, rituximab was used as a corticosteroid-sparing agent.

Typically, systemic corticosteroids are the first line of treatment. Although there is no universal consensus on the dose or the duration of treatment, experts suggest 0,5mg/kg/day to 1mg/kg/day for 2 to 4 weeks followed by dose tapering over 3 months. As illustrated in relative studies, most of IgG4-RD cases present partial or com-

plete response to corticosteroids, even though the rates of recurrence after discontinuation of therapy are high.

The role of surgery is uncertain. In cases of isolated lung lesions refractory to immunosuppressive therapy, a surgical option may be considered in patients presenting significant symptoms and/or demonstrate notable organ impairment.

6. PROGNOSIS

Even though the response to corticosteroid therapy is favourable in most patients with intrathoracic IgG4-RD, long-term follow-up data are currently not available. Patients may develop extrathoracic lesions of IgG4-RD over months or even years after initial diagnosis⁹. Furthermore, some patients with intrathoracic involvement may not experience complete disease resolution and have persistent radiological irregular findings. Zen et al, described residual imaging abnormalities in 3 of 21 patients with IgG4-related pulmonary and preural disease²³.

Association between IgG4-RD and malignancy such as lymphoma, pancreatic and lung cancer has been referred but if IgG4-RD truly is a risk factor for cancer development needs further clarification^{9,22,23,66,67}.

CONCLUSION

IgG4-related disease (IgG4-RD) is a clinical entity characterized by elevation of serum IgG4 and issues infiltration of lymphocytes and plasmacytes that produce IgG4.

Usually more than one organ is involved and clinical presentation is relative to disease localization. Diagnosis is based on consistent clinical, imaging, laboratory and histopathological findings and exclusion of benign disorders and malignancies with similar manifestations.

Respiratory system is often affected and lung parenchyma, pleura and airways involvement has been reported. Hilar and mediastinum lymphadenopathy are the most common intrathoracic forms of disease while fibrosing mediastinitis is rare as well as thoracic aortitis and compressive pericarditis.

Cornerstone of therapy are corticosteroids while other immunosuppressive regimens have been also used either in combination to corticosteroids or as a second-line treatment.

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