

Recent advances in knowledge regarding the head and neck manifestations of IgG4-related disease



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ABSTRACT

IgG4-related disease (IgG4-RD) is a chronic inflammatory disorder, characterized by elevated serum IgG4 levels as well as abundant infiltration of IgG4-positive plasmacytes and fibrosis in various organs, including the head and neck region. In particular, the salivary glands, orbit, and thyroid are common sites of disease involvement. IgG4-RD is diagnosed based on various clinical, serological, and histopathological findings, none of which are pathognomonic. Hence, various differential diagnoses, which exhibit elevated serum IgG4 levels and infiltration of IgG4-positive cells into tissues, need to be excluded, especially malignant diseases and mimicking disorders. Systemic corticosteroids are generally effective in inducing IgG4-RD remission; however, recurrent or refractory cases are common. In addition, although the pathogenic mechanisms of IgG4-RD remain unclear, an antigen-driven inflammatory condition is believed to be involved. Recent studies have indicated the important pathogenic role of B cell/T cell collaboration and innate immunity in this disease. Nevertheless, additional research and discussions are needed to resolve many remaining questions. In this review, we provide an overview of the recent insights on the history, clinical features, diagnosis, and treatment of IgG4-RD in the head and neck region. Furthermore, we have also addressed the pathogenesis of this disease.

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1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibro-inflammatory condition characterized by the enlargement of the affected organs, elevated serum immunoglobulin (Ig)-G4 levels, and abundant IgG4-positive plasma cell infiltration in the affected organs [1–4]. Although the pathogenesis of this disease remains unclear, patients with IgG4-RD often present with systemic organ dysfunction and immunological abnormalities [2–5]. IgG4-RD involving the head and neck is a common manifestation of this disease [1,2,5]. In this article, we provide an overall review of IgG4-RD in the head and neck region.

2. History of IgG4-related disease

Table 1 illustrates the history of IgG4-RD. In 1888, Mikulicz-Radecki, a surgeon, first reported a case of what was subsequently termed as Mikulicz's disease (MD) [6]. The patient exhibited symmetrical bilateral edema and enlargement of the salivary and lacrimal glands, which showed lymphocytic infiltration on microscopic examination. Subsequent studies described this syndrome as MD, and the clinical features included benign and chronic dacryoadenitis with bilateral painless swelling of the lacrimal and salivary glands and decreased lacrimation associated with dry mouth and dry eyes, without any arthritis or blurred vision. In the 1930s, Henrik Sjögren, a Swedish ophthalmologist, summarized the findings of 19 cases with keratoconjunctivitis sicca; swelling of the major salivary glands was observed in 2 of these cases [7]. The

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Table 1
History of IgG4-related disease.

Year	Authors	Contents	Journal
1892	Mikulicz J. et al.	Mikulicz's disease	Z Chir Fesrschr
1961	Sarles H et al.	Hyper-gammaglobulina in chronic pancreatitis	Am J Dig Dis
1967	Comings DE et al.	Familial multifocal fibrosis	Am Intern Med
1972	Räsänen O et al.	Küttner tumor	Acta Otolaryngol
1989	Konno A et al.	Proposed an independent entity of Mikulicz's disease	J Jpn Saliv Gl
1995	Yoshida et al.	Autoimmune pancreatitis (AIP)	Dig Dis Sci
2001	Hamano et al.	High IgG4 levels in AIP	N Engl J Med
2003	Kamisawa et al.	Concepts of IgG4-associated autoimmune disease	J Gastroenterol
2006	Yamamoto et al.	IgG4-related plasmacytic disease	Mod Rheumatol
2008	Masaki et al.	IgG4-multiorgan lymphoproliferation syndrome (MOLPS)	Am Rheum Dis
2012	Umehara Okazaki et al.	United name: IgG4-related disease (IgG4-RD)	Mod Rheumatol
2012	Umehara Okazaki et al.	Comprehensive diagnostic criteria for IgG4-RD	Mod Rheumatol
2012	Stone H et al.	International consensus for IgG4-RD	Arthritis Rheum
2012	Deshpande V et al.	International pathological consensus for IgG4-RD	Mod Pathol

concept of Sjögren's syndrome (SS) was established thereafter. In 1953, Morgan and Castleman examined specimens obtained from 18 patients with MD, and concluded that the histological findings in MD and SS were similar, and that most patients with MD could also be considered to have SS [8].

MD was then recognized as a subtype of SS, and there were no major disagreements regarding the 2 illnesses for >50 years. However, cases were frequently reported in Japan. In fact, prior to the establishment of the IgG4-RD concept, Konno et al., analyzed certain clinical cases in detail in 1984, and proposed that MD was an independent entity [9]. In 2000, Tsubota et al. reported that the extent of apoptosis in the salivary glands was significantly lower in MD than in SS [10]. Furthermore, Yamamoto et al. reported a series of cases of MD, wherein some cases exhibited elevated serum IgG4 levels and others exhibited the infiltration of IgG4-positive plasmacytes in swollen lacrimal and submandibular glands [11,12]. Thus, MD was recognized as a clinical and pathological entity distinct from SS in 2006 [13].

In contrast, Küttner's tumor (KT), which was first described as chronic sclerosing sialadenitis by Küttner in 1896 [14], is a rare and chronic inflammatory disorder of the salivary glands and most commonly affects the submandibular glands. Patients with KT present with firm swelling of the salivary glands, and the clinical differentiation of KT from other neoplasms is difficult [15,16]; hence, it has been termed as Küttner's "tumor" [17]. KT is occasionally associated with similar sclerosing lesions in extrasalivary glandular tissues, such as those of the bile duct (sclerosing cholangitis) and the retroperitoneum (retroperitoneal fibrosis) [18–20]. The concomitant occurrence of such lesions is referred to as multifocal fibrosclerosis, and hence, KT can be considered as a manifestation of multifocal fibrosclerosis. Recent studies have shown that patients with KT exhibit high serum levels of IgG4 as well as infiltration of IgG4-positive plasma cells [21–23], and KT is now considered to belong to the spectrum of IgG4-RD. However, the term "Küttner's tumor" should not be used at present, because it is not a tumor but an inflammatory disease.

3. Organ involvement in the head and neck region

3.1. Salivary glands

The enlargement of the major salivary glands is a common hallmark of IgG4-RD. The enlargement of the lacrimal and salivary glands (IgG4-related dacryoadenitis and sialadenitis [IgG4-DS]) in this condition was found to be elastic, painless, and persistent (occurring for >3 months). Although the submandibular glands are most frequently involved, the parotid, sublingual, and labial salivary glands may also be affected (Fig. 1) [5]. In contrast, in SS, the enlargement of the parotid gland is predominant. With regard to salivary gland function in patients with this disease, the secretion is normal or slightly reduced, but improves with steroid treatment. The sialography findings were also normal, and the "apple-tree sign", which is typical in SS, was not observed in patients with IgG4-RD [1,11–13]. As mentioned below, differentiation from lymphoma is important and requires histological examination.

3.2. Lacrimal gland and orbit

IgG4-related orbital lesions comprise 22.5% of cases of orbital lymphoproliferative disorders [24]. The primary sites of involvement include the lacrimal glands, extraocular muscles, and orbital nerves [25,26]. Patients with IgG4-related dacryoadenitis often exhibit swelling of the upper eyelids and bilateral ptosis (Fig. 1). In this condition, echography examination of the lacrimal gland shows a lowly echogenic swollen gland with partitioning, whereas neuroimaging studies indicate lacrimal gland enlargement [27]. Nevertheless, as it is difficult to evaluate whether the lesion is benign or malignant only via imaging, histopathological examination is essential, particularly in cases of unilateral involvement and without signs of additional organ dysfunction (salivary or pancreatic lesions) [5]. Furthermore, keratoconjunctivitis sicca is apparent in a small number of cases with IgG4-related dacryoadenitis.

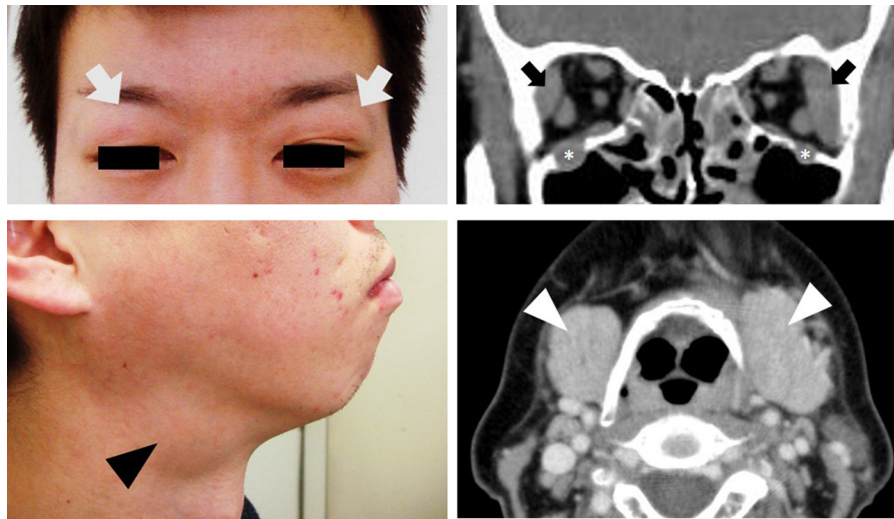


Fig. 1. Facial views and computed tomography images of patients with IgG4-dacryoadenitis and sialadenitis. The patients show persistent symmetrical enlargement of the lacrimal (arrows) and submandibular glands (arrow heads). Symmetrical infraorbital nerve swellings (asterisks) were also observed.

The branches of the supraorbital and infraorbital nerves may be affected in IgG4-RD (Fig. 1) and may occasionally cause sensory impairment in the area of innervation [24,26,28,29]. Infraorbital nerve swelling has been reported to be observed in approximately 30% of patients with IgG4-DS [26]; however, this inflammatory response may represent perineuritis, as biopsy specimens have shown an abundant infiltration of IgG4-positive cells not into the nerve fiber, but into perineural connective tissue. In contrast, optic nerve involvement has been reported to lead to permanent visual loss [30,31].

3.3. Sinonasal region

Allergic features may develop in a substantial subset of patients with IgG4-RD, and many patients have longstanding histories of allergy, such as allergic rhinitis, nasal polyps, and asthma [4]. Mild to moderate peripheral eosinophilia and high serum IgE concentrations are also common in these cases.

Several recent reports have described the nasal manifestations associated with IgG4-RD [32–39]. Although patients with atypical massive or tumorous sinonasal lesions were considered to have IgG4-RD, it has been confirmed that rhinosinusitis is beyond the IgG4-RD spectrum, because inflammatory disease conditions, potentially associated with an elevated number of IgG4-positive plasma cells in tissue, include rhinosinusitis [32,40,41]. Hence, careful consideration is required when diagnosing sinonasal lesions as IgG4-RD; in contrast, it is possible that patients with rhinosinusitis complicated with IgG4-RD exhibit characteristic features [32,42]. Our recent study indicated that rhinosinusitis is common in patients with IgG4-RD, and that patients with IgG4-RD and serum eosinophilia also tend to develop sinonasal lesions, with a similar pathogenesis as in eosinophilic chronic rhinosinusitis [42].

Patients with IgG4-RD often complain of olfactory disturbance, even in the absence of nasal and paranasal sinus obstructive or inflammatory disease [43,44]. Although the detailed mechanisms underlying olfactory dysfunction remain

unclear, the dysfunction of the nasal gland is mild and shows a good response to treatment [44].

3.4. Thyroid

IgG4-RD is infrequently found to affect the thyroid gland. IgG4-related thyroiditis reportedly includes Riedel's thyroiditis (RT) [45], Hashimoto's thyroiditis (HT) [46–50], and IgG4-related thyroiditis [51]. Cases of Grave's disease, associated with IgG4-RD, have also been reported [52,53]; however, recent histologic examinations indicated that the thyroid of Graves' disease patients with persistent hyperthyroidism show diffuse lymphoplasmacytic infiltration of IgG4-positive plasma cells, without any concomitant fibrosis or obliterative phlebitis [54].

RT was first reported in 1896 by Riedel as a hard, infiltrative lesion in the thyroid gland [55]. RT is a chronic fibrosing disorder of unknown etiology that remains poorly understood even >100 years after it was first described. RT shows several features consistent with the spectrum of IgG4-RD, including the fibroinflammatory nature of the infiltrate, the presence of obliterative phlebitis, and its association with other forms of fibrosclerosis, including sclerosing cholangitis [45]. Dahlgren et al. indicated that elevated numbers of IgG4-positive plasma cells and the morphologic features of IgG4-RD are found in RT patients [45]. RT is now firmly considered as an IgG4-RD variant, and has long been known to be associated with systemic fibrosclerosing diseases, many of which are now included within the spectrum of IgG4-RD.

HT shows a partial overlap with IgG4-related thyroiditis. Kakudo et al. identified a variant of HT that shows elevated numbers of IgG4-positive plasma cells, and found significant differences between patients with IgG4-positive thyroiditis and IgG4-negative thyroiditis. In particular, patients with IgG4-related thyroiditis tend to be young men with a shorter disease duration; higher anti-thyroglobulin levels, anti-thyroid peroxidase levels, and antibody titers; and diffuse low echogenicity on ultrasonography [48,49]. Moreover, a study has indicated

that 90% of cases classified as the fibrosing variant of HT were associated with high IgG4 levels [50].

3.5. Pituitary gland and dura mater

Intracranial lesions of the pituitary gland [56,57] and dura mater [58,59] rarely develop, and are infrequently involved in IgG4-RD. IgG4-related hypophysitis of the anterior pituitary may cause headache, visual field loss, and galactorrhea. The symptoms of hypopituitarism include general malaise and amenorrhea. Magnetic resonance imaging (MRI) findings show sellar enlargement and thickening of the pituitary stalk. In contrast, IgG4-RD is one of the most common causes of hypertrophic pachymeningitis (HP), which is an inflammatory condition involving the thickening of the dura mater of the cranium or spine, that can lead to symptoms resulting from mass effect, nerve compression, or vascular compromise [59]. A recent survey study in Japan showed that among 159 patients with HP, antineutrophil cytoplasmic antibody (ANCA)-related HP was the most frequent form (34%), followed by IgG4-related HP (9%) [60].

3.6. Ear and mastoid

Takagi et al. reported 5 cases of suspected otologic involvement, including otitis media with effusions, eosinophilic otitis media, and sensorineural hearing loss, in patients with biopsy-proven IgG4-RD at other sites [61]. The otologic manifestations were responsive to steroid therapy; however, it is unclear whether these manifestations should be included in the spectrum of IgG4-RD because they have not been confirmed by biopsy. In contrast, cases of IgG4-RD involving the mastoid and middle ear have shown characteristic histopathological features of IgG4-RD [62,63]. Although these patients reported long-standing disease at this site and multiple surgical interventions and recurrences, steroids and/or rituximab therapy led to the stabilization of the disease and resolution of the symptoms [63]. Furthermore, Deshpande et al. histopathologically examined 162 consecutive mastoiditis cases, and found that some cases fulfilled the histopathological features of IgG4-RD due to severe acute or chronic infection [63]. Therefore, the diagnosis associated with IgG4-RD at the ear and mastoid should be discussed by experts, and every effort should be made to exclude an infectious etiology, prior to initiating immunosuppressive therapy.

3.7. Lymph node

The enlargement of the regional lymph nodes are commonly observed around affected organs [64]. In the head and neck region, the involvement of the cervical, supraclavicular, and submandibular nodes is often found to be non-tender. The biopsy of the enlarged lymph nodes for the diagnosis of IgG4-RD is not recommended, as they are unlikely to show the histological features observed in other organs affected with IgG4-RD [4]. Moreover, patients with systemic lymphadenopathy as a result of IgG4-RD should be distinguished from those with Castleman's disease.

3.8. Other sites

IgG4-RD may also involve the pharynx, larynx, and Waldeyer's ring, and frequently presents with mass lesions in these cases [65,66]. It is essential to consider whether these mass-forming lesions can lead to the destruction of the underlying bone, which is usually observed in malignant lesions [67]. Eosinophilic angiocentric fibrosis (EAF), which is an uncommon and enigmatic disease affecting the lacrimal gland, nasal cavity, nasal sinuses, and lower respiratory tract, is also considered as part of the spectrum of IgG4-RD [68]. Although EAF may respond to immunosuppression therapy, the surgical removal of the lesion is the current standard therapy.

4. Methods of diagnosis

IgG4-RD can be diagnosed based on clinical imaging, serological, and pathological findings. The currently proposed diagnostic criteria include enlarged or hypertrophic organs, elevated serum IgG4 levels, and pathological findings [41]. A definitive diagnosis requires that all criteria are met, whereas a probable diagnosis is considered when the clinical and histopathological criteria are met.

4.1. Clinical suspicion

Most patients with IgG4-RD present with the disease subacutely. The clinical manifestations of IgG4-RD depend on the pattern of organ involvement and the severity of disease activity. IgG4-RD typically affects middle-aged to elderly men; however, the sex-ratio of patients with IgG4-RD of the head and neck region is roughly equal [1,69]. Moreover, patients with IgG4-RD generally show persistent swelling (>3 months) of the affected organ, such as the submandibular gland, lacrimal gland, and lymph node, or show mass-forming lesions, including those in the sinonasal sinuses or laryngopharyngeal subsites. The proposed diagnostic algorithm for IgG4-RD in the head and neck region is shown in Fig. 2.

4.2. Serological findings

Although most patients with IgG4-RD exhibit elevated serum IgG4 concentrations, this parameter is neither sufficiently sensitive nor specific for diagnosis [70]. Normal serum IgG4 concentrations are noted in 3–30% of IgG4-RD patients [71], particularly in those with single-organ disease. However, elevated serum IgG4 concentrations are also noted in patients with various other disorders, including atopic dermatitis, pemphigus, asthma, and multicentric Castleman's disease [41,70]. Hence, serum IgG4 concentrations may be useful for screening, but cannot be used as the sole diagnostic marker. Most patients with IgG4-RD can often be identified based on the high serum IgG4 concentrations, and can then be diagnosed in combination with other diagnostic components such as imaging and histological examination. The degree of serum IgG4 elevation tends to correlate with the number of organs involved and a higher serum concentration is associated with a greater number of organs involved [70].

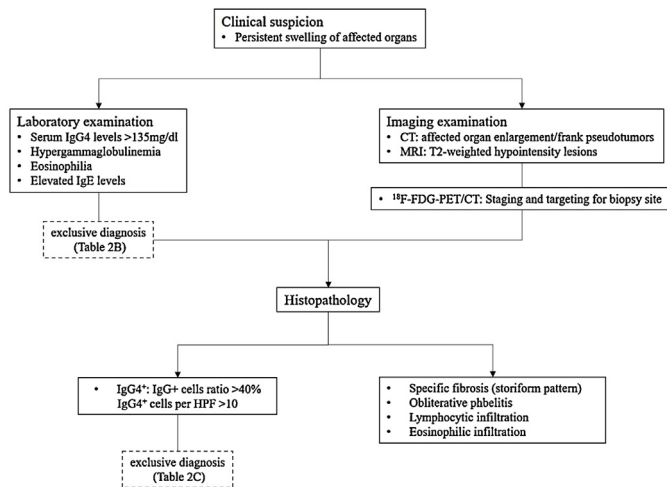


Fig. 2. The diagnosis of IgG4-related disease is made on the basis of clinical imaging, serological, and pathological findings. The proposed diagnostic criteria include enlarged or hypertrophic organs, elevated serum levels of IgG4 (>135 mg/dL), and pathological findings (infiltration of IgG4-positive plasmacytes and specific findings such as fibrosis).

Elevated C-reactive protein levels, hypergammaglobulinemia, serum positive antinuclear antibody, rheumatoid factor, and soluble interleukin-2 receptor are often detected in patients with IgG4-RD [1,69,72]. Peripheral eosinophilia and elevated serum IgE levels are also often observed among patients with this disease [42,73]. A recent study indicated that the levels of circulating plasmablasts are elevated in active IgG4-RD and in patients with normal serum IgG4 concentrations; hence, plasmablasts could serve as a useful biomarker for diagnosis [74].

4.3. Imaging findings

Since IgG4-RD frequently presents with organ enlargement and massive lesions, imaging can be useful in diagnosing

whether the component is malignant, and is usually employed as the main modality for differential diagnosis. On computed tomography (CT), the organ affected by IgG4-RD frequently exhibits organ enlargement or frank pseudotumors. On T2-weighted MRI, IgG4-RD lesions usually exhibit low signal intensity [75]. However, these imaging examinations do not provide specific findings for IgG4-RD. ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET)/CT may be useful for staging patients with IgG4-RD, for evaluating their response to treatment, and for targeting specific biopsy sites [76,77]. Because tissue infiltration by inflammatory cells and lymphocytes is associated with an increased uptake of ^{18}F -FDG by patients with IgG4-RD [76], ^{18}F -FDG-PET/CT imaging enables diagnosis by indicating a characteristic pattern of organ involvement (Fig. 3). Moreover, ^{18}F -FDG uptake by the parotid glands was observed in patients with abundant IgG4-positive plasma cell infiltration into the labial salivary gland tissue [72]. An increased uptake of ^{18}F -FDG by the parotid gland may be associated with IgG4-RD activity in all the major and minor salivary glands.

4.4. Histopathological findings

Histopathology is a hallmark in the diagnosis of IgG4-RD, with central pathological features such as lymphoplasmacytic tissue infiltration of dominant IgG4-positive plasma cells, accompanied by fibrosis, obliterative phlebitis, and dacryoadenitis (Fig. 4) [40]. Tissue biopsy of the affected organ is the gold standard for the diagnosis of IgG4-RD [4], and a rigorous histopathological examination is necessary to confirm the diagnosis, particularly in cases of malignant disease. The hallmark characteristics of IgG4-RD include tissue infiltration by numerous IgG4-positive plasma cells [1–4]; however, these cells are also found in other inflammatory and malignant disorders [40,41,77]. Hence, IgG4-RD should not be diagnosed based on infiltration by IgG4-positive cells alone. In the head

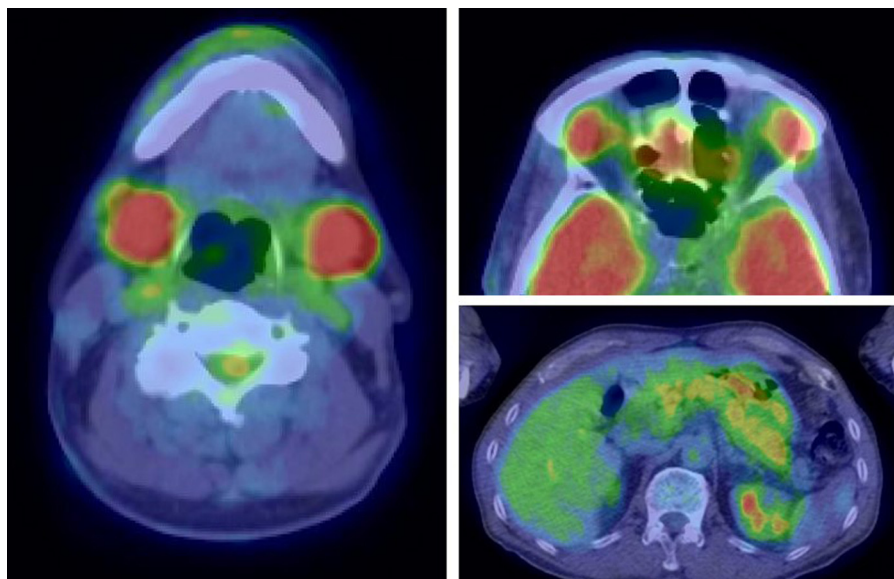


Fig. 3. Axial fused PET/CT image of a patient with biopsy-proven IgG4-related disease. Increased uptake ^{18}F -FDG in the bilateral submandibular glands, lacrimal glands, and pancreas.

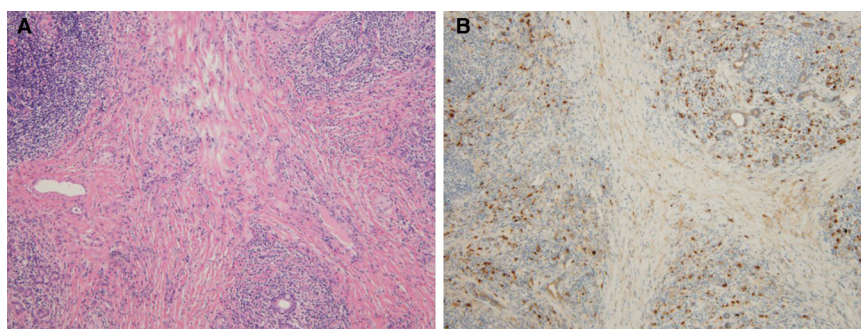


Fig. 4. (A) Hematoxylin and eosin staining and (B) immunostaining for IgG4 in submandibular gland (SMG) biopsy specimens obtained from patients with IgG4-related disease (A, B; magnification $\times 100$). Extensive infiltration by inflammatory cells (lymphocytes and plasma cells) is evident, and the infiltration of IgG4-positive plasma cells is observed in SMG specimens. An irregularly whorled pattern of fibrosis, so-called “storiform fibrosis,” may be observed in SMG.

and neck region, submandibular gland (SMG) or labial salivary gland (LSG) biopsies are generally performed in cases with possible IgG4-RD to achieve an accurate definitive and differential diagnosis. However, an SMG biopsy may be more invasive and has been associated with greater complications, as compared to an LSG biopsy, which is a minimally invasive and convenient procedure for obtaining tissues for diagnostic analysis. There are 3 major pathological features: (1) lymphoplasmacytic infiltration, (2) fibrosis arranged at least focally in a storiform pattern, and (3) obliterative phlebitis [40]. Although the first 2 features are thought to be present in most cases, LSG fibrosis is inconspicuous or absent in most cases of IgG4-RD, whereas LSG tissue infiltration by IgG4-positive plasma cells is observed in <60% of patients with IgG4-RD [78,79]. LSG biopsy is a minimally invasive and a convenient procedure; however, its sensitivity for the diagnosis of IgG4-RD is very low [78,79]. Moreover, based on the findings of a case of marginal zone B-cell lymphoma that produced IgG4 [80,81], a western blot analysis of immunoglobulin heavy-chain gene rearrangement is recommended and a certain amount of tissue volume is needed for diagnosis. Therefore, SMG biopsy is recommended to achieve an accurate diagnosis of IgG4-RD and to exclude the possibility of malignant diseases. Moreover, SMG biopsy may be used for diagnosis in cases with possible type-1 AIP with sialadenitis involvement [82].

4.5. Differential diagnosis

The differentiation of IgG4-RD from not only malignant diseases but also common conditions mimicking IgG4-RD is important (Table 2). In the head and neck region, it is essential to exclude common conditions mimicking IgG4-RD, including head and neck cancer, metastatic cancer, malignant lymphoma, granulomatosis with polyangiitis (Wegener’s), eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and multicentric Castleman’s disease, because extensive IgG4-positive plasma cell infiltration has been described in these conditions [77,83,84]. Although these conditions lack the characteristic histopathological features of IgG4-RD such as storiform fibrosis and obliterative phlebitis [40], the clinico-pathologic correlation is always important. The differential diagnosis of patients with suspected IgG4-RD in the head and neck region, associated with elevated serum IgG4 concentrations and/or tissue infiltration by IgG4-positive cells, is illustrated in Table 2.

5. Treatment and prognosis

IgG4-RD is primarily treated with systemic corticosteroids. However, no randomized clinical trials or formal treatment guidelines for IgG4-RD have been established. The use of early intervention to prevent complications related to progressive

Table 2

Differential diagnosis of IgG4-related disease in the head and neck region.

A. Diseases to be excluded or differentiated	
Malignant disease	Cancer, malignant lymphoma
Mimicking disease	Sjögren syndrome (SS), multicentric Castleman’s disease (MCD), ANCA associated vasculitis (AAV), Sarcoidosis
B. Not IgG4-RD associated with elevated serum IgG4 Levels	
SS, MCD, hypereosinophilic syndrome, Behçet disease, asthma, AAV, cancer, healthy individuals	
C. Not IgG4-RD associated with tissue infiltration by IgG4-positive cells	
Inflammatory/infectious disease	AAV, chronic rhinosinusitis, mastoiditis, Epstein–Barr virus related lymphadenopathy, histiocytosis (Rosai–Dorfman disease)
Lymphoma	Extranodal marginal zone B-cell lymphoma, follicular lymphoma, angioimmunoblastic lymphoma
Cancer	IgG4-positive cell infiltration was found in cancer tissue as well as regional lymph nodes

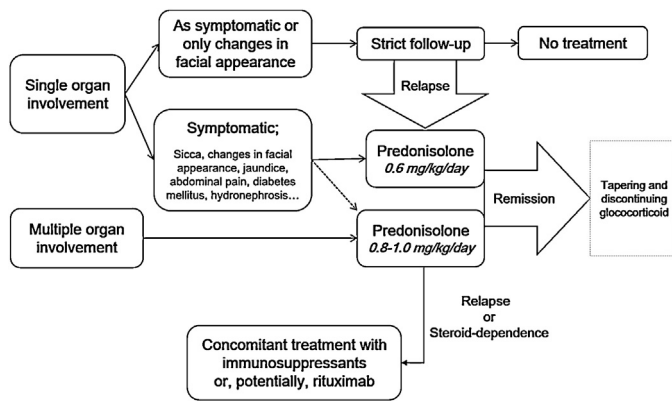


Fig. 5. Treatment protocol for IgG4-related disease.

fibrosis in the salivary glands has also been reported [85]. The treatment protocol of our institution is illustrated in Fig. 5. Initiation of treatment with prednisone at 0.6 mg/kg/day is appropriate for single organ failure, but should be increased to 1.0 mg/kg/day for multiple organ failure [1,5]. Prednisone is continued at the initial dose for 2–4 weeks, followed by a tapering of the dose by 10% at 2-week intervals. The treatment led to rapid improvements in glandular swelling, and gland secretion also gradually increased with treatment. Maintaining the prednisone dose at 5–10 mg/day is recommended due to the high relapse rate of IgG4-RD. Approximately 50% of the relapse patients with IgG4-RD present with lesions in other organ systems [86]. However, not all manifestations of IgG4-RD require immediate treatment; instead, a “watchful and waiting” approach is often appropriate in certain cases, such as patients with asymptomatic lymphadenopathy or mild submandibular glandular swelling.

Although conventional steroid-sparing agents such as azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, tacrolimus, and cyclophosphamide have all been used [4,71], the efficacies of these agents have not been prospectively assessed, and the evidence for their efficacy is poor. Rituximab (RTX), an anti-CD20 antibody, has been shown to be effective in inducing remission and achieving steroid-sparing effects, and has been frequently used since its first related report in 2010 [87]. Carruthers et al. [88] conducted a prospective open-label trial of RTX, and reported on its efficacy as induction therapy for IgG4-RD without short-term glucocorticoid use. Yamamoto et al. [89] reported on the outcomes of long-term treatment with RTX in IgG4-RD patients, and suggested that RTX should be indicated in cases with a definitive diagnosis on histological examination, having a younger age, and wherein increasing the glucocorticoid dose is difficult due to complications. In other patients, 1 or 2 administrations of RTX would not induce or maintain complete remission of IgG4-RD, whereas some others would present with fading of the RTX effect [89]. Although the polyclonal populations of lymphocytes and plasma cells increase, these increases are not etiologic, but are instead the result of other types of stimulation; hence, the RTX may serve as an effective treatment mechanism.

The surgical approach may be an option for IgG4-RD involvement; for example, some cases with orbital diseases,

such as highly fibrotic orbital pseudotumors, are more amenable to surgical interventions than to medical therapy [71]. Moreover, submandibular resection in patients with IgG4-RD has been shown to lead to the spontaneous disappearance of lung lesions [90].

Even with the use of glucocorticoid maintenance therapy, relapses of IgG4-RD are not uncommon. Our data showed that the clinical remission rate was 73.8% and annual relapse rate was 11.5%; moreover, 50% of the cases experienced relapses within 7 years of the initial treatment [69]. In the case of disease relapse, the corticosteroid dose needs to be increased or another immunosuppressants need to be administered. Although the prognosis of patients with IgG4-RD is good, the incidence of cancer development within 3 years of IgG4-RD diagnosis is higher in the general population [91]. The cause for this association remains unclear, and careful patient follow-up is needed.

6. Pathogenesis

Although the pathophysiological mechanisms driving IgG4-RD remain unclear, an antigen-driven inflammatory condition or infection has been suggested, based on the features of this disease, including the chronic clinic course, effectiveness of steroid treatment, specific organ involvement, and common histopathological features shared by different unrelated organs. Elevated serum IgG4 concentrations, based on which IgG4-RD was named, is a distinctive feature of this disease. Nevertheless, IgG4 itself is not considered as a disease driver, because it is traditionally believed to be non-inflammatory, and its primary function is the inhibition rather than the induction of chronic immune activation; moreover, elevated serum IgG4 concentrations have been found in other allergic conditions [2–4]. However, Shiokawa et al. recently reported that the injection of IgGs from IgG4-RD patients, but not control subjects, into neonatal mice led to the induction of pancreatic and salivary gland injuries [92]. Although this finding may improve our understanding of the pathogenic role of IgG4 antibodies in this disease, additional research is required to further elucidate its role in IgG4-RD.

The central role of B-lymphocytes in the pathogenesis of IgG4-RD is reportedly important because of the abundant infiltration of IgG4-positive plasma cells into the affected organ and the effectiveness of treatment with B-cell depletion by RTX. Recent studies have shown that the levels of circulating plasmablasts, CD19⁺CD20⁺CD27⁺CD38⁺, were found to be increased in IgG4-RD patients [74,93]. These cells imply a stage of B-lymphocyte development between activated B cells and plasma cells, as well as oligoclonal expansion and somatic hypermutation, indicating the presence of an immune response to a common antigen [94].

IgG4-RD has been proposed to involve a Th2/T regulatory-driven condition [95,96]. The production of Th2 cytokines (IL-4 and IL-13) and Treg cytokines (IL-10 and TGF- β) has been observed in affected tissue [95,96]. IL-13 and TGF- β reportedly induce the deposition of the extracellular matrix by activating fibroblasts; however, IL-4 and IL-10 are considered the major inducers of IgG4 class switching in naive B

lymphocytes [95]. Moreover, the infiltration of cytotoxic T lymphocytes (CTLs) was found to be similar in IgG4-DS and SS, although the features differed, including the presence of cytotoxic granules and higher expression of programmed death-1 in IgG4-DS [97]. A more recent study showed that the clonal expansion of CD4⁺CTLs, which secrete interferon- γ , TGF- β , and IL-1 β , and their infiltration into tissue in IgG4-DS, may be associated with the pathogenesis of IgG4-DS [98,99]. However, the reactivation of CD4⁺CTLs may require antigen presentation by plasmablasts or other activated B cells in the affected lesion, and the activated CD4⁺CTLs may then contribute to fibrosis by activating macrophages and fibroblasts and to inflammation via cytokine secretion or induction of cell apoptosis [99].

T cells may also contribute to IgG4-RD pathogenesis through dysregulated follicular T helper cell (Tfh) activity. The number of circulating Tfh2 cells is increased in the peripheral blood of patients with IgG4-RD, in correlation with elevated serum IgG4 levels and the number of plasmablasts [100]; these Tfh2 cells induce the differentiation of naïve B cells into plasmablasts and the production of IgG4 in patients with IgG4-RD, and may also be correlated with IgG4-RD disease activity

[101]. In contrast, the elevated mRNA levels of IL-21, which is secreted from Tfh or Th2 cells, have been linked to ectopic germinal centers within lacrimal and salivary glands, derived from patients with IgG4-DS [102]. IL-21 is thought to induce the class switching of IgG4, in correlation with IL-4 and IL-10. Epithelial cell-derived cytokines, including thymic stromal lymphopoietin, IL-25, and IL-33, can control immune cells, such as dendritic cells and T cells, and can thus act as “master switches” for allergic inflammatory diseases. These epithelial cell-derived cytokines may also induce Th2-dominant immune responses in IgG4-RD.

Recent studies have highlighted not only the T-cell-driven model, but have also described the involvement of innate immunity. Activated macrophages are known to contribute to fibrosis in IgG4-RD by secreting profibrotic factors such as TGF- β and the platelet-derived growth factor [103]. Indeed, a correlation has been observed between CD163⁺ M2 macrophage infiltration and the amount of tissue fibrosis in biopsies of patients with IgG4-DS [104]. Toll-like receptors and nucleotide-binding oligomerization domain-like receptors on macrophages may lead to class-switch recombination via B-cell activating factor, and may lead to the further activation and

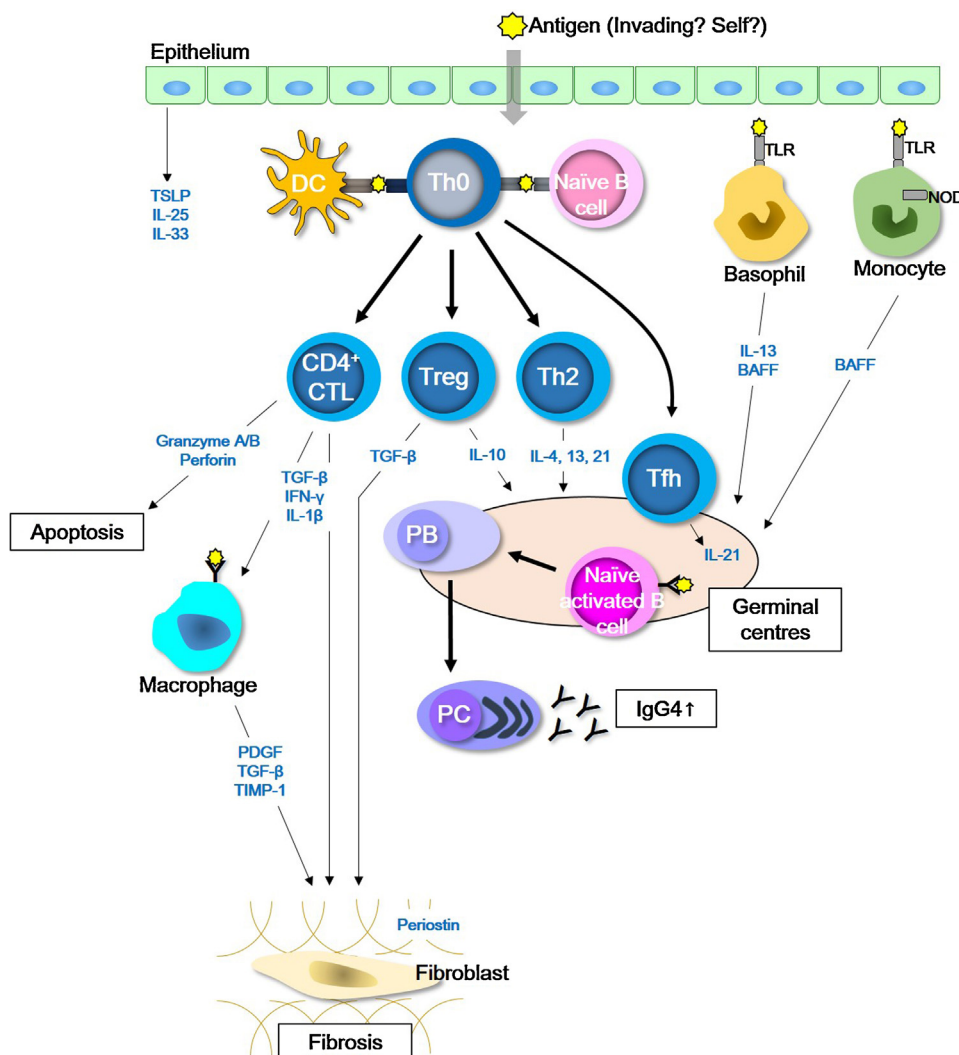


Fig. 6. Schematic pathogenic model of IgG4-related disease.

proliferation of IgG4-positive B-cells [105]. The assumed pathogenic mechanisms in this disease are summarized in Fig. 6.

7. Conclusion

IgG4-RD was only recognized at the start of the 21st century, but has been identified in nearly every organ system, including the head and neck region. Examination for systemic organ failure and screening for underlying malignant diseases are important in caring for patients with this systemic fibroinflammatory disorder. Although novel manifestations of IgG4-RD continue to be reported, the pathophysiology of this disease remains unclear. Therefore, we need to conduct further research regarding the epidemiology, pathophysiology, diagnosis, and effective treatment of IgG4-RD.

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References

- [1] Himi T, Takano K, Yamamoto M, Naishiro Y, Takahashi H. A novel concept of Mikulicz's disease as IgG4-related disease. *Auris Nasus Larynx* 2012;39:9–17.
- [2] Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366:539–51.
- [3] Yamamoto M, Takahashi H, Shinomura Y. Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. *Nat Rev Rheumatol* 2014;10:148–59.
- [4] Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015;385:1460–71.
- [5] Yamamoto M, Hashimoto M, Takahashi H, Shinomura Y. IgG4 disease. *J Neuroophthalmol* 2014;34:393–9.
- [6] Mikulicz J. Über eine eigenartige symmetrische Erkrankung der Thranen und Mundspeicheldrüsen. Stuttgart: Beitr Chir Fortsch Gewidmet Theodor Billroth; 1892. p. 610–30.
- [7] Sjögren H. Zur Kenntnis der Keratoconjunctivitis Sicca (Keratitis filiformis bei Hypofunktion der Tranendrüsen). *Acta Ophthalmol* 1933;(Suppl. II):1–151.
- [8] Morgan WS, Castleman B. A clinicopathologic study of "Mikulicz's disease". *Am J Pathol* 1953;29:471–503.
- [9] Konno A, Ito E, Okamoto Y. The clinical, histopathological and electronmicroscopical study of chronic parotitis, Sjögren syndrome and Mikulicz disease. *J Jpn Saliv Gl* 1984;25:1–33 [in Japanese].
- [10] Tsubota K, Fujita H, Tsuzaka K, Takeuchi T. Mikulicz's disease and Sjögren's syndrome. *Invest Ophthalmol Vis Sci* 2000;41:1666–73.
- [11] Yamamoto M, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H, et al. Elevated IgG4 concentrations in serum of patients with Mikulicz's disease. *Scand J Rheumatol* 2004;33:432–3.
- [12] Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. *Rheumatology (Oxford)* 2005;44:227–34.
- [13] Yamamoto M, Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006;16:335–40.
- [14] Küttner H. Ueber entzündliche tumoren der submaxillar-speicheldrüse. *Beitr Klin Chir* 1896;15:815–34.
- [15] Ellis GL, Auclair PL. Tumor-like conditions. In: Ellis GL, Auclair PL, editors. *Tumors of the salivary glands*. Washington, DC: Armed Forces Institute of Pathology; 1996. p. 412–9.
- [16] Isacson G, Ahlner B, Lundquist PG. Chronic sialadenitis of the submandibular gland: a retrospective study of 108 cases. *Arch Otorhinolaryngol* 1981;232:91–100.
- [17] Chan JK. Küttner tumor (chronic sclerosing sialadenitis) of the submandibular gland: an underrecognized entity. *Adv Anat Pathol* 1998;5:239–51.
- [18] Nieminen U, Koivisto T, Kahri A, Färkkilä M. Sjögren's syndrome with chronic pancreatitis, sclerosing cholangitis, and pulmonary infiltrations. *Am J Gastroenterol* 1997;92:139–42.
- [19] Sekine S, Nagata M, Watanabe T. Chronic sclerosing sialadenitis of the submandibular gland associated with idiopathic retroperitoneal fibrosis. *Pathol Int* 1999;49:663–7.
- [20] Tsuneyama K, Saito K, Ruebner BH, Konishi I, Nakanuma Y, Gershwin ME. Immunological similarities between primary sclerosing cholangitis and chronic sclerosing sialadenitis: report of the overlapping of these two autoimmune diseases. *Dig Dis Sci* 2000;45:366–72.
- [21] Takano K, Yamamoto M, Takahashi H, Shinomura Y, Imai K, Himi T. Clinicopathologic similarities between Mikulicz disease and Küttner tumor. *Am J Otolaryngol* 2010;31:429–34.
- [22] Geyer JT, Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY, et al. Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010;34:202–10.
- [23] Furukawa S, Moriyama M, Kawano S, Tanaka A, Maehara T, Hayashida JN, et al. Clinical relevance of Küttner tumour and IgG4-related dacryoadenitis and sialoadenitis. *Oral Dis* 2015;21:257–62.
- [24] Oshima K, Sogabe Y, Sato Y. The usefulness of infraorbital nerve enlargement on MRI imaging in clinical diagnosis of IgG4-related orbital disease. *Jpn J Ophthalmol* 2012;56:380–2.
- [25] Takahashi H, Yamamoto M, Suzuki C, Naishiro Y, Shinomura Y, Imai K. The birthday of a new syndrome: IgG4-related disease constitute a clinical entity. *Autoimmun Rev* 2010;9:591–4.
- [26] Takano K, Yajima R, Seki N, Abe A, Yamamoto M, Takahashi H, et al. A study of infraorbital nerve swelling associated with immunoglobulin G4 Mikulicz's disease. *Mod Rheumatol* 2014;24:798–801.
- [27] Yamamoto M, Takahashi H, Shinomura Y. Mikulicz's disease and the extraglandular lesions. *Curr Immunol Rev* 2011;7:162–71.
- [28] Wallace ZS, Khosroshahi A, Jakobiec FA, Deshpande V, Hatton MP, Ritter J, et al. IgG4-related systemic disease as a cause of "idiopathic" orbital inflammation, including orbital myositis, and trigeminal nerve involvement. *Surv Ophthalmol* 2012;57:26–33.
- [29] Katsura M, Morita A, Horiuchi H, Ohtomo K, Machida T. IgG4-related inflammatory pseudotumor of the trigeminal nerve: another component of IgG4-related sclerosing disease? *AJNR Am J Neuroradiol* 2011;32:E150–2.
- [30] Kawakami Y, Yamamoto M, Tabeya T, Yajima H, Shimizu Y, Ishigami K, et al. IgG4-related orbital tumor with eye enucleation – infra-orbital nerve enlargement (IONE). *Rheumatology (Oxford)* 2014;53:610.
- [31] Takahashi Y, Kitamura A, Kakizaki H. Bilateral optic nerve involvement in immunoglobulin G4-related ophthalmic disease. *J Neuroophthalmol* 2014;34:16–9.
- [32] Moteki H, Yasuo M, Hamano H, Uehara T, Usami S. IgG4-related chronic rhinosinusitis: a new clinical entity of nasal disease. *Acta Otolaryngol* 2011;131:518–26.
- [33] Ishida M, Hotta M, Kushima R, Shibayama M, Shimizu T, Okabe H. Multiple IgG4-related sclerosing lesions in the maxillary sinus, parotid gland and nasal septum. *Pathol Int* 2009;59:670–5.
- [34] Ikeda R, Awataguchi T, Shoji F, Oshima T. A case of paranasal sinus lesions in IgG4-related sclerosing disease. *Otolaryngol Head Neck Surg* 2010;142:458–9.
- [35] Sasaki T, Takahashi K, Mineta M, Fujita T, Aburano T. Immunoglobulin G4-related sclerosing disease mimicking invasive tumor in the nasal cavity and paranasal sinuses. *AJNR Am J Neuroradiol* 2012;33:E19–20.
- [36] Chen BN. IgG4-related disease presenting with destructive sinonasal lesion mimicking malignancy. *Eur Arch Otorhinolaryngol* 2016;273:4027–9.

- [37] Inoue A, Wada K, Matsuura K, Osafune H, Ida Y, Kosakai A, et al. IgG4-related disease in the sinonasal cavity accompanied by intranasal structure loss. *Auris Nasus Larynx* 2016;43:100–4.
- [38] Ohno K, Matsuda Y, Arai T, Kimura Y. Nasal manifestations of IgG4-related disease: a report of two cases. *Auris Nasus Larynx* 2015;42:483–7.
- [39] Piao Y, Wang C, Yu W, Mao M, Yue C, Liu H, et al. Concomitant occurrence of Mikulicz's disease and immunoglobulin G4-related chronic rhinosinusitis: a clinicopathological study of 12 cases. *Histopathology* 2016;68:502–12.
- [40] Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25:1181–92.
- [41] Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;22:21–30.
- [42] Takano K, Abe A, Yajima R, Kakuki T, Jitsukawa S, Nomura K, et al. Clinical evaluation of sinonasal lesions in patients with immunoglobulin G4-related disease. *Ann Otol Rhinol Laryngol* 2015;124:965–71.
- [43] Takano K, Yamamoto M, Kondo A, Himi T. A case of reversible hyposmia associated with Mikulicz's disease. *Otolaryngol Head Neck Surg* 2009;141:430–1.
- [44] Takano K, Yamamoto M, Kondo A, Takahashi H, Himi T. A clinical study of olfactory dysfunction in patients with Mikulicz's disease. *Auris Nasus Larynx* 2011;38:347–51.
- [45] Dahlgren M, Khosroshahi A, Nielsen GP, Deshpande V, Stone JH. Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 2010;62:1312–8.
- [46] Li Y, Zhou G, Ozaki T, Nishihara E, Matsuzuka F, Bai Y, et al. Distinct clinical, serological, and sonographic characteristics of Hashimoto's thyroiditis based with and without IgG4-positive plasma cells. *J Clin Endocrinol Metab* 2010;95:1309–17.
- [47] Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, Mori I, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathol Int* 2009;59:636–41.
- [48] Kakudo K, Li Y, Taniguchi E, Mori I, Ozaki T, Nishihara E, et al. IgG4-related disease of the thyroid glands. *Endocr J* 2012;59:273–81.
- [49] Li Y, Zhou G, Ozaki T, Nishihara E, Matsuzuka F, Bai Y, et al. Distinct histopathological features of Hashimoto's thyroiditis with respect to IgG4-related disease. *Mod Pathol* 2012;25:1086–97.
- [50] Deshpande V, Huck A, Ooi E, Stone JH, Faquin WC, Nielsen GP. Fibrosing variant of Hashimoto thyroiditis is an IgG4 related disease. *J Clin Pathol* 2012;65:725–8.
- [51] Watanabe T, Maruyama M, Ito T, Fujinaga Y, Ozaki Y, Maruyama M, et al. Clinical features of a new disease concept, IgG4-related thyroiditis. *Scand J Rheumatol* 2013;42:325–30.
- [52] Takeshima K, Inaba H, Furukawa Y, Nishi M, Yamaoka H, Miyamoto W, et al. Elevated serum immunoglobulin G4 levels in patients with Graves' disease and their clinical implications. *Thyroid* 2014;24:736–43.
- [53] Nishihara E, Hirokawa M, Takamura Y, Ito M, Nakamura H, Amino N, et al. Immunoglobulin G4 thyroiditis in a Graves' disease patient with a large goiter developing hypothyroidism. *Thyroid* 2013;23:1496–7.
- [54] Nishihara E, Hirokawa M, Ito M, Fukata S, Nakamura H, Amino N, et al. Graves' disease patients with persistent hyperthyroidism and diffuse lymphoplasmacytic infiltration in the thyroid show no histopathological compatibility with IgG4-related disease. *PLoS One* 2015;10:e0134143.
- [55] Riedel BM. Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse. *Verh Dtsch Ges Chir* 1896;25:101–5 [in German].
- [56] Yamamoto M, Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. *Scand J Rheumatol* 2006;35:410–1.
- [57] Leporati P, Landek-Salgado MA, Lupi I, Chiovato L, Caturegli P. IgG4-related hypophysitis: a new addition to the hypophysitis spectrum. *J Clin Endocrinol Metab* 2011;96:1971–80.
- [58] Chan SK, Cheuk W, Chan KT, Chan JK. IgG4-related sclerosing pachymeningitis: a previously unrecognized form of central nervous system involvement in IgG4-related sclerosing disease. *Am J Surg Pathol* 2009;33:1249–52.
- [59] Wallace ZS, Carruthers MN, Khosroshahi A, Carruthers R, Shinagare S, Stemmer-Rachamimov A, et al. IgG4-related disease and hypertrophic pachymeningitis. *Medicine (Baltimore)* 2013;92:206–16.
- [60] Yonekawa T, Murai H, Utsuki S, Matsushita T, Masaki K, Isobe N, et al. A nationwide survey of hypertrophic pachymeningitis in Japan. *J Neurol Neurosurg Psychiatry* 2014;85:732–9.
- [61] Takagi D, Nakamaru Y, Fukuda S. Otolitic manifestations of immunoglobulin G4-related disease. *Ann Otol Rhinol Laryngol* 2014;123:420–4.
- [62] Schiffenbauer AI, Wahl C, Pittaluga S, Jaffe ES, Hoffman R, Khosroshahi A, et al. IgG4-related disease presenting as recurrent mastoiditis. *Laryngoscope* 2012;122:681–4.
- [63] Deshpande V, Zane NA, Kraft S, Stone JH, Faquin WC. Recurrent mastoiditis mimics IgG4 related disease: a potential diagnostic pitfall. *Head Neck Pathol* 2016;10:314–20.
- [64] Cheuk W, Chan JK. Lymphadenopathy of IgG4-related disease: an underdiagnosed and overdiagnosed entity. *Semin Diagn Pathol* 2012;29:226–34.
- [65] Reder L, Della-Torre E, Stone JH, Mori M, Song P. Clinical manifestations of IgG4-related disease in the pharynx: case series and review of the literature. *Ann Otol Rhinol Laryngol* 2015;124:173–8.
- [66] Khoo JF, Batt M, Stimpson P, Safdar A. Supraglottic immunoglobulin-G4 related plasma cell granuloma: case report and literature review. *Head Neck* 2014;36:E57–9.
- [67] Della-Torre E, Mattoo H, Mahajan VS, Deshpande V, Krause D, Song P, et al. IgG4-related midline destructive lesion. *Ann Rheum Dis* 2014;73:1434–6.
- [68] Deshpande V, Khosroshahi A, Nielsen GP, Hamilos DL, Stone JH. Eosinophilic angiocentric fibrosis is a form of IgG4-related systemic disease. *Am J Surg Pathol* 2011;35:701–6.
- [69] Yamamoto M, Yajima H, Takahashi H, Yokoyama Y, Ishigami K, Shimizu Y, et al. Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: results from the SMART database. *Mod Rheumatol* 2015;25:199–204.
- [70] Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis* 2015;74:14–8.
- [71] Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;67:1688–99.
- [72] Abe A, Takano K, Seki N, Jitsukawa S, Yamamoto M, Takahashi H, et al. The clinical characteristics of patients with IgG4-related disease with infiltration of the labial salivary gland by IgG4-positive cells. *Mod Rheumatol* 2014;24:949–52.
- [73] Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy* 2014;69:269–72.
- [74] Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2015;74:190–5.
- [75] Fujita A, Sakai O, Chapman MN, Sugimoto H. IgG4-related disease of the head and neck: CT and MR imaging manifestations. *Radiographics* 2012;32:1945–58.
- [76] Ebbo M, Grados A, Guedj E, Gobert D, Colavolpe C, Zaidan M, et al. Usefulness of 2-[(18)F]-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography for staging and evaluation of treatment response in IgG4-related disease: a retrospective multicenter study. *Arthritis Care Res (Hoboken)* 2014;66:86–96.
- [77] Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011;64:237–43.

- [78] Takano K, Keira Y, Seki N, Abe A, Yamamoto M, Takahashi H, et al. Evaluation of submandibular versus labial salivary gland fibrosis in IgG4-related disease. *Mod Rheumatol* 2014;24:1023–5.
- [79] Takano K, Nomura K, Abe A, Kamekura R, Yamamoto M, Ichimiya S, et al. Clinicopathological analysis of salivary gland tissue from patients with IgG4-related disease. *Acta Otolaryngol* 2016;136:717–21.
- [80] Yamamoto M, Tabeya T, Naishiro Y, Yajima H, Ishigami K, Shimizu Y, et al. Value of serum IgG4 in the diagnosis of IgG4-related disease and in differentiation from rheumatic disease and other disease. *Mod Rheumatol* 2012;22:419–25.
- [81] Sato Y, Takata K, Ichimura K, Tanaka T, Morito T, Tamura M, et al. IgG4-producing marginal zone B-cell lymphoma. *Int J Hematol* 2008;88:428–33.
- [82] Takano K, Yamamoto M, Ichimiya S, Takahashi H, Himi T. Assessing the usefulness of salivary gland biopsy for diagnosis of type-1 autoimmune pancreatitis. *Mod Rheumatol* 2016 [Epub ahead of print].
- [83] Yamamoto M, Takahashi H, Suzuki C, Tabeya T, Ohara M, Naishiro Y, et al. Analysis of serum IgG subclasses in Churg-Strauss syndrome – the meaning of elevated serum levels of IgG4. *Intern Med* 2010;49:1365–70.
- [84] Shimizu Y, Yamamoto M, Naishiro Y, Sudoh G, Ishigami K, Yajima H, et al. Necessity of early intervention for IgG4-related disease: delayed treatment induces fibrosis progression. *Rheumatology (Oxford)* 2013;52:679–83.
- [85] Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. Beneficial effects of steroid therapy for Mikulicz's disease. *Rheumatology (Oxford)* 2005;44:1322–3.
- [86] Yamamoto M, Takahashi H, Ishigami K, Yajima H, Shimizu Y, Tabeya T, et al. Relapse patterns in IgG4-related disease. *Ann Rheum Dis* 2012;71:1755.
- [87] Khosroshahi A, Bloch DB, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010;62:1755–62.
- [88] Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis* 2015;74:1171–7.
- [89] Yamamoto M, Awakawa T, Takahashi H. Is rituximab effective for IgG4-related disease in the long term? Experience of cases treated with rituximab for 4 years. *Ann Rheum Dis* 2015;74:e46.
- [90] Seki N, Yamazaki N, Kondo A, Nomura K, Himi T. Spontaneous regression of lung lesions after excision of the submandibular gland in a patient with chronic sclerosing sialadenitis. *Auris Nasus Larynx* 2012;39:212–5.
- [91] Yamamoto M, Takahashi H, Tabeya T, Suzuki C, Naishiro Y, Ishigami K, et al. Risk of malignancies in IgG4-related disease. *Mod Rheumatol* 2012;22:414–8.
- [92] Shiokawa M, Kodama Y, Kuriyama K, Yoshimura K, Tomono T, Morita T, et al. Pathogenicity of IgG in patients with IgG4-related disease. *Gut* 2016;65:1322–32.
- [93] Mattoo H, Mahajan VS, Della-Torre E, Sekigami Y, Carruthers M, Wallace ZS, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. *J Allergy Clin Immunol* 2014;134:679–87.
- [94] Wallace ZS, Stone JH. An update on IgG4-related disease. *Curr Opin Rheumatol* 2015;27:83–90.
- [95] Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. *Annu Rev Pathol* 2014;9:315–47.
- [96] Moriyama M, Tanaka A, Maehara T, Furukawa S, Nakashima H, Nakamura S. T helper subsets in Sjogren's syndrome and IgG4-related dacryoadenitis and sialoadenitis: a critical review. *J Autoimmun* 2014;51:81–8.
- [97] Tabeya T, Yamamoto M, Naishiro Y, Ishigami K, Shimizu Y, Yajima H, et al. The role of cytotoxic T cells in IgG4-related dacryoadenitis and sialadenitis, the so-called Mikulicz's disease. *Mod Rheumatol* 2014;24:953–60.
- [98] Mattoo H, Mahajan VS, Maehara T, Deshpande V, Della-Torre E, Wallace ZS, et al. Clonal expansion of CD4+ cytotoxic T lymphocytes in patients with IgG4-related disease. *J Allergy Clin Immunol* 2016;138:825–38.
- [99] Maehara T, Mattoo H, Ohta M, Mahajan VS, Moriyama M, Yamauchi M, et al. Lesional CD4+ IFN- γ + cytotoxic T lymphocytes in IgG4-related dacryoadenitis and sialoadenitis. *Ann Rheum Dis* 2016 [Epub ahead of print].
- [100] Akiyama M, Suzuki K, Yamaoka K, Yasuoka H, Takeshita M, Kaneko Y, et al. Number of circulating follicular helper 2 T cells correlates with IgG4 and interleukin-4 levels and plasmablast numbers in IgG4-related disease. *Arthritis Rheumatol* 2015;67:2476–81.
- [101] Akiyama M, Yasuoka H, Yamaoka K, Suzuki K, Kaneko Y, Kondo H, et al. Enhanced IgG4 production by follicular helper 2 T cells and the involvement of follicular helper 1 T cells in the pathogenesis of IgG4-related disease. *Arthritis Res Ther* 2016;18:167.
- [102] Maehara T, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Tanaka A, et al. Interleukin-21 contributes to germinal centre formation and immunoglobulin G4 production in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Ann Rheum Dis* 2012;71:2011–9.
- [103] Wynn TA, Barron L. Macrophages: master regulators of inflammation and fibrosis. *Semin Liver Dis* 2010;30:245–57.
- [104] Furukawa S, Moriyama M, Tanaka A, Maehara T, Tsuboi H, Iizuka M, et al. Preferential M2 macrophages contribute to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Clin Immunol* 2015;156:9–18.
- [105] Watanabe T, Yamashita K, Fujikawa S, Sakurai T, Kudo M, Shiokawa M, et al. Activation of toll like receptors and NOD-like receptors is involved in enhanced IgG4 responses in autoimmune pancreatitis. *Arthritis Rheum* 2012;64:914–24.