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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-postive 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.

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.

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