Best Practice & Research Clinical Rheumatology 30 (2016) 261–278

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

4

IgG4-related disease: Advances in the diagnosis and treatment

Pilar Brito-Zerón [a, b, c], Xavier Bosch [d], Manuel Ramos-Casals [b, c, e, *], John H. Stone [f]

[a] *Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA Sanitas, Barcelona, Spain*
[b] *Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Barcelona, Spain*
[c] *Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain*
[d] *Department of Internal Medicine, ICMiD, Hospital Clínic, Barcelona, Spain*
[e] *Department of Medicine, University of Barcelona, Barcelona, Spain*
[f] *Harvard Medical School and Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Boston, MA, 02114, USA*

Keywords:
IgG4-related disease
Autoimmune pancreatitis
Cholangitis
Fibrosis
Plasmablasts
Rituximab

A B S T R A C T

IgG4-related disease is a rare immune-mediated systemic disease with the capability of involving essentially any organ. Although the presenting clinical features vary substantially according to the speciality to which patients present first, perhaps the most common clinical presentation is that of single or multiple organ enlargement, arousing suspicion of cancer. The disease is frequently diagnosed unexpectedly in pathological specimens or on imaging studies. The diagnostic approach is complex and includes not only IgG4-related tests (serum levels, circulating plasmablasts, and specific immunohistochemical studies), but also clinical, laboratory, and imaging tests as well as the typical histopathological features (lymphocytic infiltration, storiform fibrosis, eosinophilic infiltration, and obliterative phlebitis). IgG4-related tests should not be considered as diagnostic in the absence of an appropriate clinical scenario. Therapeutic approaches reported to date pertain primarily to glucocorticoids, but the use of these medications has not been studied in a controlled or prospective

* Corresponding author. Servei de Malalties Autoimmunes Sistèmiques, Hospital Clínic, C/Villarroel, 170, 08036, Barcelona, Spain. Fax: +34 93 2271707.
E-mail address: mramos@clinic.ub.es (M. Ramos-Casals).

http://dx.doi.org/10.1016/j.berh.2016.07.003
1521-6942/

manner. The most current investigational treatment approaches have focused on targeting cells of the B-cell lineage, including B-cell-depleting agents (rituximab) and a non-depleting homodimer monoclonal antibody targeting CD19 and Fc-gamma RIIIb.

Introduction

IgG4-related disease (IgG4-RD) is a chronic, immune-mediated systemic disease first described in Japan [1]. In 2001, Hamano et al. [2] reported unexpectedly high serum levels of IgG4 in patients with type 1 autoimmune pancreatitis (AIP). Two years later, Kamisawa et al. [3] were the first to propose the term 'IgG4-related autoimmune disease' after discovering that patients with AIP also had the involvement of organs other than the pancreas. The key pathological feature of the disease is the infiltration of IgG4-bearing plasma cells [4]. IgG4-RD has now been reported in nearly every organ of the human body. However, it is not a new disease, because many diseases previously considered 'idiopathic' are now included into the clinical IgG4-RD spectrum (Mikulicz disease, Küttner tumour, Riedel thyroiditis, and Ormond disease, among others) [4]. In 2012, an international multidisciplinary study group proposed the name 'IgG4-RD' in preference to other names such as 'IgG4-related systemic disease', 'IgG4-related sclerosing disease', or 'IgG4-positive multiorgan lymphoproliferative syndrome' [5].

The epidemiology of IgG4-RD has not been characterized thoroughly, due in part to its relatively low prevalence and incidence but also due to continuing under-recognition of the disease by both clinicians and pathologists. Although nearly 75% of reported patients are Japanese [1], the disease has been described in nearly all racial and ethnic groups. In the last 2 years, the largest reported series of patients are from China ($n = 248$, $n = 118$) [6,7], Japan ($n = 158$, $n = 235$) [8,9], the USA ($n = 125$) [10], Spain ($n = 55$) [11], and Italy ($n = 41$) [12]. A recent review [1] of nearly 3500 reported patients found a mean age at diagnosis of 61 years with a clear male predominance (73% of patients). Although the youngest patient identified was 14 years at presentation, some paediatric cases have recently been reported [13].

This review addresses current advances in the diagnostic and therapeutic management of patients with IgG4-RD.

Diagnostic approach

Clinical presentation

The key for clinical suspicion of IgG4-RD is a patient presenting with tumefactive lesions in one or more organs (40% of patients have single organ involvement) [1]. The enlarged organs may be visible on the physical examination (salivary or lacrimal gland swelling, lymphadenopathy, and thyroid enlargement) or detected as an incidental finding in imaging diagnostic tests (enlargement of the pancreas, liver, spleen or kidneys) [14]. Some patients also have organ-specific symptoms, including abdominal pain, sicca features, respiratory symptoms, pruritus, and diarrhoea [1]. Lymphadenopathy has been reported in 25% of patients with systemic presentations, while a history of allergy/atopy, manifested primarily by asthma, is reported in 10–20% of patients. Specific IgG4-related skin involvement has been reported in only 1% of patients, but eczema is a frequently reported concurrent condition [1]. The presenting features of IgG4-RD vary substantially according to which speciality the patient present first, but the physicians most frequently involved are gastroenterologists [15], ophthalmologists [16], otolaryngologists [17], nephrologists [18,19], urologists [20], dermatologists [21], neurologists [22], and rheumatologists/internists. Rheumatologists tend to receive patients presenting with multiorgan systemic involvement that mimics a systemic autoimmune disease. The prevalence of specific organ involvement varies widely among studies, and is principally influenced by the nature of patient collection (unselected or selected by organ).