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Review

Update in ethiopathogeny, diagnosis and treatment of the IgG4 related disease☆

Fernando Martínez-Valle[a,b,*], Olimpia Orozco-Gálvez[a], Andreu Fernández-Codina[a,b,c]

[a] Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna, Hospital Universitario Vall Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Vall d'Hebron Institut de Recerca, Barcelona, Spain
[c] Rheumatology Division, Department of Medicine, University of Western Ontario, London, Ontario, Canada

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ABSTRACT

IgG4 related disease (IgG4-RD) is probably an autoimmune pathology of unknown aetiology. Diverse interactions participate in its pathogen between the adaptive and innate immune systems, activating lymphocytes B and T which trigger the inflammatory cascade, which culminates in fibrosis of the organs and their malfunction. It can affect a multitude of organs simultaneously. The diagnosis is based on the correlation of clinical findings with anatomopathological results (lymphoplasmocitary infiltrate, storiform fibrosis, obliterative phlebitis and IgG4+ plasmatic cell count) and with the presence of elevated IgG4 in serum, depending on the criteria used. Corticoids and rituximab are among the few validated treatments available. There are multiple biomarkers and treatments in development. In this review, we aim to go over the principal pathogenic and clinical characteristics of IgG4-RD, as well as its handling, in accordance with the available scientific evidence.

Etiopatogenia, diagnóstico y tratamiento de la enfermedad relacionada con la IgG4

Palabras clave:
Enfermedad relacionada con IgG4
Diagnóstico
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RESUMEN

La enfermedad relacionada con la IgG4 (IgG4-RD) es una afección probablemente autoinmune, de etiología desconocida. En su patogenia participan diversas interacciones entre los sistemas inmunes adaptativo e innato, activando linfocitos B y T que desencadenan la cascada inflamatoria, que culmina en fibrosis de los órganos y disfunción de los mismos. Puede afectar a multitud de órganos simultáneamente. El diagnóstico está basado en la correlación de hallazgos clínicos con los resultados anatomopatológicos (infiltrado linfoplasmocitario, fibrosis estoriforme, flebitis obliterativa y recuento de células plasmáticas IgG4+) y con la presencia de IgG4 elevada en el suero, dependiendo de los criterios utilizados. Entre los escasos tratamientos validados disponibles se encuentran los corticoides y rituximab. Existen múltiples biomarcadores y tratamientos en desarrollo. En esta revisión pretendemos repasar las características patogénicas y clínicas principales de la IgG4-RD, así como su manejo, de acuerdo con la evidencia científica disponible.

Introduction

IgG4-related disease [IgG4-RD] was first described in the early years of the XXI century, which can mimic malignant, inflammatory or infectious diseases.[1,2] For this reason, the histological diagnosis is essential, characterized by the presence of a lymphoplasmacytic infiltrate rich in plasma cells, storiform fibrosis and obliterative phlebitis (pylephlebitis) and, quite often, a mild or moderate eosinophil infiltrate.[3] The disease was initially described as affecting the pancreas in what is now known as type I autoimmune pancreatitis (AIP-I). A key fact for the discovery of this disease were the observations made by Kamisawa et al.[4] in reference to patients with AIP-I having extrapancreatic fibroinflammatory lesions rich in plasma cells that were positive for IgG4

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* Corresponding author.
E-mail address: ferranmartinezvalle@gmail.com (F. Martínez-Valle).

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staining, as well as the fact that other apparently different entities shared the characteristic of high IgG4 serum levels with similar histological findings. The fact that the serum levels of the subunit 4 of IgG (IgG4) were increased in these patients was initially interpreted as having an important value in the diagnosis. However, subsequently, it has been observed that only about 50% of patients have elevated IgG4 levels in serum. In addition, many other diseases may incidentally show high levels of IgG4 in peripheral blood.[5]

Knowing the epidemiology of the disease is complicated because the first publications date from 2003,[4] reason why many professionals still do not know about its existence. The only disease subtype that has been studied in detail in relation to the epidemiology is AIP-I.[6] The prevalence of AIP-I in Japan is estimated to be 2.2 cases per 100,000 population; however, there are no data regarding the involvement of other organs. As a result of the growing interest in this disorder, several cohorts from different geographical locations have recently been published.[7–11] According to the data provided by these cohorts, most patients are male. The average age of affected individuals is around 60 years, being this average higher in Eastern countries (Japan and China), although the age range varies between 12 and 86 years. An interesting fact is that in the Japanese cohort,[9] up to 30% of the subjects included (70 out of 235 patients) were incidentally diagnosed with IgG4-RD by means of a routine medical check-up or during the follow-up of other processes, being the symptomatology attributable to a mild or non-existent IgG4-RD.

Etiopathogenesis

Genetic risk factors

At present there is little data available on possible genetic risk factors in IgG4RD. These factors vary depending on the populations studied. Thus, Japanese patients affected by AIP-I show an association with HLA-DRB1*0405 and DQB1*0401.[12] In Korea, DQB1-57 without aspartic acid has been linked to a tendency to develop recurrences.[13] Some polymorphisms of genes unrelated to the HLA system, which encode proteins that include antigen 4 associated with cytotoxic lymphocytes, tumour necrosis factor alpha (TNFα) and the Fc segment of *Toll-like receiver* 3 may be involved in disease susceptibility.[14]

Cellular immune response

The production of IgG4 and IgE is characteristic of Th2-type immune response, so it was initially thought that this type of response was the most important in this disease. At first, an increase in the expression of cytokines with Th2 expression was described in the characteristic lesions of the disease, however, the specific presence of Th2-type cells had not been isolated, since this requires the use of the latest multiple-colorimetric staining techniques. Recently it has been described that these Th2-type cells accumulate only in 30% of patients. This percentage coincides with the presence of atopy manifestations in this disease,[15] so the presence of these cells may be secondary to the occurrence of allergic phenomena. Likewise, it has been described that CD4+cytotoxic lymphocytes (CTL) accumulate in the blood of patients with active disease, as well as in affected tissues, with Th2 cells being scarce.[16] Through analysis of the TCR receptors, these CD4+CTL manifest a clonal expansion.[16] This cell subtype found in tissues secretes interleukin 1 beta (IL-1β), interferon gamma and tumour growth factor beta (TGF-β) *in vivo* in the tissues.[17] These data indicate that specific CD4+CTL and with clonal expansion infiltrate the affected tissues, possibly being reactivated locally by activated B cells, which capture local antigens through the receptors (*B cell receptors*), internalizing them and presenting them to CD4+CTL. These, in turn, will produce the inflammatory and fibrotic processes characteristic of the disease. In addition, the interaction between B cells and CD4+CTL can mediate the death of parenchymal cells that express the antigens responsible for the disease.

A characteristic of this disease is the activation of regulatory T cells (Treg) Foxp3+, unlike what occurs in classical autoimmune diseases, in which Treg function is decreased, which are responsible for the production of IL-10 and TGF-β. The presence of ectopic germinal centres, composed of IgG4+ B lymphocytes and plasma cells, can be explained by the increased production of IL-21 by T follicular *helper* cells (Tfh).[18] Tfh collaborate with B cells during T-dependent immune responses and contribute to *isotype switching* of somatic hypermutation present in IgG4 and IgG1, formation of germinal centres, as well as the selection of germinal centres with high affinity B cells. Some Tfh cell subtypes (Tfh2) secrete Il-4 after *in vitro* stimulation and may contribute to immunoglobulin isotype switching to IgA, IgE and all IgG subtypes, including IgG4.[17]

By means of new generation sequencing methods and flow cytometry the presence of oligoclonal expansions of plasmablast cells $CD19^{low}CD20^{-}CD38^{+}CD27^{+}$ of IgG4 and non-IgG4 type has been demonstrated in peripheral blood of patients affected with IgG4-RD, as well as in tissues with lesions.[19,20] Plasmablasts end up differentiating into short-lived plasma cells (producers of antibodies) or long-lived (with the ability to circulate in blood for a long time) and it is suspected that in this entity they are generated by B-cell activation in the germinal centers.[19] These plasmablasts express large numbers of class II HLA molecules on its surface and it is believed that it is possible that these cells or other activated B cells can play an important role in the reactivation of CD4+CTL, inducing them to the production of cytokines that include IL-1β, TGF-β1, IFN-β and other factors that stimulate innate and adaptive immunity.[16,21] The presence of an increase in plasmablast cells is very specific for this disease, and has not been described in other autoimmune diseases or in controls.

The tissue damage associated with IgG4-RD occurs due to the expansion of fibroblasts that, in advanced phases of the disease, will lead to a significant fibrosis. The fibrosis that characterizes IgG4-RD is the storiform-type, which represents an unusual pattern of collagen deposition. This type of fibrosis is often found in neoplastic diseases, being uncommon in inflammatory disorders. The mechanism of fibrosis production in this disease is not clear, although it is thought that IL-4, IL-10 and IL-13 from Treg could cause the activation of macrophages, which in turn would produce profibrogenic factors such as TGF-β and growth factors derived from platelets.[22] On the other hand, IL-5 can promote fibrosis by the recruitment of eosinophils, which in turn would also produce TGF-β, growth factors derived from platelets and IL-13.[23]

Role of IgG4 antibodies

IgG4 antibodies have anti-inflammatory functions, since they do not bind to receptors for the Fc fraction of Ig. In addition, Ig4 molecules usually show a change in the Fab segment of immunoglobulin, which converts them into bispecific antibodies, conferring them a low antigen-binding capacity. This characteristic makes them unable to activate the complement and, therefore, unable to produce an inflammatory response. However, all these observations have been made *in vitro*, so it might be possible that some IgG4 could participate forming immunocomplexes *in vivo*. The fact that no specific subtypes of these antibodies have been found in patients with IgG4-RD, suggests that the presence of these antibodies can be a protective mechanism in the presence of a certain inflammatory stimulus. IgG4 antibodies are usually synthesized in response to environmental allergens and food, requiring a long exposure to antigens before the produc-