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Review

IgG4-related disease☆

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ABSTRACT

IgG4-related disease is a recently described clinicopathological entity showing a wide spectrum of clinical manifestations that share a common pathology. Its most characteristic feature is the formation of inflammatory tumors in different organs, which makes differentiation mainly with neoplastic diseases fundamental. The inflammatory process is typically comprised of IgG4 lymphoplasmacytic cells. The pathophysiological role of the immunoglobulin is not clear. The treatment of choice is corticosteroids. This article aims to summarize the main features of the disease.

Enfermedad relacionada con IgG4

Palabras clave:
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RESUMEN

La enfermedad relacionada con IgG4 es una entidad clínico-patológica descrita recientemente con un amplio espectro de manifestaciones clínicas que comparten una histopatología en común. Su manifestación más característica es la formación de tumores inflamatorios en diferentes órganos, lo que hace fundamental la diferenciación principalmente de enfermedades neoplásicas. Este fenómeno inflamatorio está compuesto característicamente por linfoplasmocitos productores de IgG4. El papel fisiopatogénico de la inmunoglobulina no está aclarado. El tratamiento de elección son los glucocorticoides. Este trabajo pretende resumir las principales características de la enfermedad.

Introduction

IgG4-related disease (IgG4-RD) is a clinicopathological entity recently described with a wide spectrum of clinical manifestations.[1] The presence of high serum IgG4 levels was associated with many IgG4-positive lymphoplasmacytic cells in samples from patients with autoimmune pancreatitis (AIP)[2] in 2001. Since then, there is growing interest in the participation of this molecule in various autoimmune/inflammatory disease. A Japanese group first suggested the IgG4-RD as a new clinicopathological entity with systemic involvement when they observed 8 AIP patients with the same histopathological pattern in other organs such as bile ducts, gastric mucosa, salivary glands or lymph nodes.[3] In recent years the number of publications related to the disease has been growing exponentially. Although several names have been used (Table 1), the nomenclature most widely accepted is IgG4-RD.[4]

Involvement of virtually any organ has been reported,[5] being involvement of healthy tissue by swollen masses characteristic and they can often be confused with malignant processes.

The purpose of this review is to approach the clinician to the fundamental concepts of the etiopathogenesis and histopathology of the IgG4-RD and describe the clinical features and treatment strategies.

Etiopathogenesis

The etiopathogenesis of IgG4-RD remains poorly elucidated, and one of the great unknowns is the role of the immunoglobulin associated with the disease. IgG4 is the rarest immunoglobulin G subtype, comprising 1–4% and its role is poorly understood. Its capability to activate the classical complement pathway is poor,

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Table 1
Different nomenclature used for IgG4 related disease.

IgG4-related systemic disease
IgG4-related sclerosing disease
IgG4-related disease
IgG4 syndrome
IgG4-related systemic sclerosing disease
IgG4-related autoimmune disease
Hyper-IgG4 disease
Systemic IgG4-related plasmacytic syndrome
IgG4 positive multiorgan lymphoproliferative syndrome

Source: Modified from Stone et al.[4]

and thus effective inflammatory response is low.[6] The potential anti-inflammatory role of IgG4 suggests that its presence is a response to an unknown inflammatory stimulus, although its potential to generate an inflammatory response has not been ruled out.[1]

Although it has not been fully proven, the hypothesis that IgG4-RD is induced by autoimmune phenomena appears to be the most accepted. Autoreactivity of IgG4 molecule against the epithelial tissue of pancreatic, bile and salivary gland ducts in patients with AIP has been reported, as well as several autoantibodies against several targets (carbonic anhydrase, lactoferrin, trypsinogens)[7,8] in AIP patients, with uncertain meaning in the pathophysiology of the disease.

The immunological mechanism involved in the pathogenesis of IgG4-RD appears to be mediated by a Th2 lymphocyte response. Cytokines released by these cells have increased in tissues involved, including interleukins 4, 5, 10 and 13.[9] The presence of eosinophilia and elevated serum IgE levels, present in up to 40% of patients with IgG4-RD, is also mediated by Th2 cytokines.

Another immunological feature in IgG4-RD is activation of regulatory T cells[9] unlike other autoimmune diseases in which the activity of these cells is decreased.[10] These cells have been associated with increased expression of transforming growth factor β which might play a core role in causing fibrosis in IgG4-RD.[11]

Histopathology

Histopathology represents the cornerstone for the diagnosis of IgG4-RD and has played a key role in the recognition of IgG4-RD as a systemic disease. There are 3 major morphological features (dense lymphoplasmacytic infiltrate, storiform pattern fibrosis and obliterative phlebitis), which sometimes can be accompanied by a mild or moderate eosinophilic infiltrate and non-obliterative phlebitis.[12] The inflammatory infiltrate consists predominantly of T lymphocytes, although there are also B lymphocytes, occasionally organized in germinal centers.[12] The presence of plasma cells is characteristic and sometimes they can be predominant.[12] Two extraordinary findings virtually rule out IgG4-RD: the presence of granulomas and the presence of neutrophilic infiltrate.[12]

Table 2
Other pathologies with presence of IgG4-positive plasma cells.

Inflammatory diseases
Primary sclerosing cholangitis
ANCA-associated vasculitis
Rheumatoid arthritis
Inflammatory bowel disease
Autoimmune atrophic gastritis
Lymphomas
Mainly from low-grade B cells
Other neoplasms
Pancreatobiliary
Oral cavity
Genitourinary
Colon

ANCA: antineutrophil cytoplasmic antibodies.

Histological analysis must be accompanied by an immunohistochemical confirmation. Since in other processes cells positive to IgG4 immunostaining[12] have been reported (Table 2), it is important to perform a quantitative analysis of these cells. The number of IgG4-positive cells found in tissues with IgG4-RD ranges from >10 and >200 cells per field and depends on the tissue analyzed.[12] Another tool that has been suggested for diagnosing the disease is the IgG4 positive plasma cell/IgG positive plasma cell ratio. A ratio >40% would be suggestive of IgG4-RD.[13] During the International Symposium on IgG4-RD in Boston in 2011 a consensus was reached on the histopathology of the disease and the histopathological terminology for IgG4-RD[12] was proposed, as summarized in Table 3.

Clinical manifestations

The type patient with IgG4-RD is a middle-aged and elderly male with, either simultaneous or progressive systemic involvement.[1] Clinical presentation is subacute, and constitutional symptoms such as fever or weight loss are rare. Many patients report a history of rhinitis, asthma, nasal polyps or atopy[1] and involvement of virtually every organ has been reported[5,14] (Table 4).

Pancreatic involvement was first described, considering today type 1 autoimmune pancreatitis the prototype disease.[2] It occurs in 41% IgG4-RD patients.[5] The symptoms most frequently reported are jaundice, abdominal pain, pruritus, steatorrhea and diabetes.[15]

Involvement of salivary glands is also frequent.[5] Both forms of presentation are those previously known as Mikulicz disease and Küttner tumor. The first form has been reported as painless, idiopathic, bilateral and symmetrical inflammation of lacrimal, parotid and submandibular glands.[16] The second presentation form

Table 3
Terminology recommended to describe the histopathological patterns of IgG4-related disease (IgG4-RD).

High suspicion of IgG4-RD (must meet each one of the 3 criteria)	(1) ≥2 of the major histopathological criteria[a]	Dense lymphoplasmacytic infiltrate Storiform fibrosis Obliterative phlebitis
	(2) Quantification of IgG4 cells: 10–200 cells per field depending on tissue[b]	
	(3) IgG4/IgG cell ratio > 40%[c]	
Probable IgG4-RD[d] (either 3 situations)	(a) A major histological criterion and consistent immunohistochemistry	
	(b) Those biopsies with fine needle	
	(c) Meningeal and cutaneous disease (little data published)	
Insufficient evidence of IgG4-RD	Cases not included in the above groups	

[a] Except in lacrimal gland where only one finding is required because there is usually no fibrosis and no obliterative phlebitis.

[b] >10 in meninges, pancreas (biopsy), bile ducts (biopsy), liver (biopsy) and kidney (biopsy); >20 in lung (biopsy); >30 in kidney (surgical specimen) and retroperitoneum; >50 in lung (surgical specimen), pleura, pancreas (surgical specimen), bile ducts (surgical specimen), liver (surgical specimen), aorta; >100 in salivary and lacrimal glands and lymph nodes; >200 in skin.

[c] Except in aorta where ratio is considered as >50%.

[d] Data such as serum IgG4 > 135 mg/dl or involvement of any other organ (through radiological technique or physical examination) would support the diagnosis.