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Editorial

IgG4 (IgG4-RD) Related Diseases, With a Horizon Not Limited to Mikulicz's Disease☆

Enfermedades relacionadas con IgG4 (IgG4-RD), con horizonte no limitado a la enfermedad de Mikulicz

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The IgG4-RD is characterized by pseudotumoral inflammatory lesions caused by lymphoplasmocytic infiltration of IgG4+ cells and elevated serum IgG4. For decades, Mikulicz's disease and Sjögren's syndrome were considered identical conditions.[1–5]

IgG1 immunoglobulin is most prevalent (>50%) and the IgG4 variety constitutes less than 5%. IgG4 has disulfide bonds linking the heavy chains unsteadily, allowing their separation and forming 2 antigen-binding sites, so that the bispecific antibody is asymmetric with an unclear in vivo role. IgG4 interacts with the Fc portion of IgG1–3 and not through the Fab-Fc, as occurs with other immunoglobulins, and has rheumatoid factor activity. Therefore, IgG4 has little or no cross-reactivity between antigens and rarely forms immune complexes having no complement activation capacity.[1]

IgG4 is characteristically protagonic in:

1. *Antiinflammation*: through binding with soluble antigens blocks interaction with IgE and mast cells, with subsequent inhibition of the allergic response.
2. *Physiopathogeny*: as in pemphigus foliaceus, where IgG4 is directed against desmoglein (junctional protein) and a third of patients with membranous glomerulonephritis, in whom IgG4 interacts with phospholipase A2 receptor type M of podocytes. There are antimetelloproteinase ADMATS13 IgG4 autoantibodies role in thrombotic thrombocytopenic purpura.[1,6]
3. *Autoantibody reaction*: IgG4 interactions with other antibodies.

The clinical expression of IgG4-RD is almost universal[1–5]; the 2 presentations classically described are salivary and lacrimal gland disease (Mikulicz's disease) and pancreatic disease, which may occur alone or accompanying other organic problems, such as biliary disease and salivary gland problems associated with a fibrosing inflammatory process of the pancreas.[7–9]

Most presentations of IgG4-RD occur between 55 and 60 years of age, predominantly in women. Characteristically, it causes growth or thickening of the affected organ and pseudotumor formation, which can lead to organ dysfunction (e.g., xerostomia and xerophthalmia due to salivary and lacrimal gland disease, chronic diarrhea, pancreatitis, dyspnea, interstitial pneumonitis, etc.).

The differential diagnosis between Mikulicz's disease and Sjögren's syndrome is of great interest,[10–12] with some overlap of clinical and serological manifestations. The first occurs typically in the sixth decade of life in females and glandular growth is persistent, with high levels of IgG4 and IgG4/IgG index, with lower prevalence of antinuclear antibodies (ANA) (≤30%), seronegative for anti-Ro and anti-La (SSA, SSB), glandular preservation, storiform fibrosis (from the center to the periphery) in advanced stages, venular obliteration (obliterative phlebitis) and excellent response to steroids, whereas Sjögren's is more common in the fifth decade of life in women, with more xerostomia and xerophthalmia, ANA (90%) and anti-SSA (50%), being able to evolve to glandular destruction and be unresponsive to steroids.

Immunohistochemistry allows for an accurate diagnosis and helps exclude other entities such as lymphomas. In case of liver affection there is portal inflammation; in renal disease, tubulointerstitial infiltration may be found and, less frequently, glomerular disease (membranous nephropathy)[13] and when lymph nodes are affected there are 5 subtypes that might pose a histological diagnosis challenge when differentiating with Castleman's disease or hyperplasia.[14]

IgG4-RD has ethnic predilections; the Japanese are associated with DRB1 *04015 and 0405, and Koreans with DQB1 and relapses; other, different genes have been described for Chinese patients and for selected clinical expressions. Recognized initiator mechanisms are autoantigens in autoimmune pancreatitis, such as lactoferrin and carbonic anhydrase autoantibodies II of another IgG subclass.[15] Yamamoto et al. identified a 13.1 Kd antigen bound to an IgG4 molecule in patients with autoimmune pancreatitis and Mikulicz disease, not present in Sjögren patients or in healthy controls.[16]

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Additionally, we have documented changes in the activation and regulation of Toll-like and NOD type receptors. Activation of Toll-like receptor 4 in patients with IgG4-RD leads to increased IL-10, an increased Th2 response and increased production of IgG4, but in healthy patients leads to an increased production of interferon and tumor necrosis factor.[17–29]

The primary response modulator in IgG4-RD are Th2 lymphocytes (leading to an overproduction of IgG4 and eosinophils); it elevates the production of various cytokines 18- to 45-fold in patients with autoimmune pancreatitis, with lesser titers in autoimmune cholangitis and primary biliary cirrhosis.[18–20] T regulatory cells (Tregs, CD25+ FoxP3+) are elevated in number or functionally, unlike what is characteristically observed in other rheumatic diseases, where they are diminished and increase after treatment. In IgG4-RD, increased conventional and memory Tregs are responsible for the production of IL-10, which in turn is responsible for the change to the IgG4 subclass. All this leads to the activation and infiltration of plasma cells, eosinophils and fibroblasts, with subsequent tissue damage in conjunction with the release of cytokines and, on occasion, immune complexes and complement activation, which typically depends on the coparticipation of IgG1; transforming growth factor beta participates in the formation of fibrosis.[1,20–22]

The diagnosis is usually one of exclusion against common diseases, such as infections (viral, bacterial, mycobacterial and fungal) and neoplasia (lymphoma). Its recognition has increased due to its distinctive characteristics and classification criteria: (a) dysfunction of one or more organs, (b) radiographical evidence of involvement by IgG4-RD (e.g., pseudotumor, peripancreatic inflammation, interstitial pneumonitis), (c) serological: IgG4≥135 mg/dl, and (d) pathological: lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, eosinophilia, immunohistochemistry showing IgG4+ (≥10 cells IgG4 in a high power field and/or IgG4+/IgG+ of 40%), with sensitivity of 92% and 88%–95% specificity. Eosinophilia occurs in 15%–20% of cases.[1,2,4]

Despite its low prevalence, which puts them in the condition of an exclusion diagnosis, and sometimes constitute part of associated comorbid conditions, the clinician should consider IgG4-RD in the differential diagnosis of any disease with glandular, pulmonary, retroperitoneal, thyroid, biliopancreatic, eye, aortic, mediastinal, renal, urogenital and neurological manifestations. Thus, a third of vasculitis associated with antineutrophil cytoplasmic antibodies, such as granulomatous polyangiitis (PG) and GP with eosinophilia (Churg Strauss), occurs with increased IgG4 and almost 10% of the IgG4-RD meet criteria or are associated with Sjögren's syndrome, vasculitis, cancer, etc.[1,11,13,21–31]

Although not *a prerequisite* for diagnosis, we must consider elevated levels of IgG4 (normal up to 30%). Of 3300 IgG4 determinations made by clinically suggestive signs, 158 (4.8%) had high titers (>140 mg/dl) and only 29 (18.4%) had IgG4-RD in possible or definitive titers,[22] a fact that evidences that most patients with clinical manifestations indicative of IgG4-RD, even with high levels of IgG4, have other diseases responsible for manifestations, such as vasculitis.[22–31] According to the above criteria, we analyzed 23 712 biopsies performed from January 2011 to June 2012 and selected 34 cases potentially compatible with IgG4-RD according to conventional histopathology (granulomatous mastitis 17, sialadenitis 8, thyroiditis [2 and one of each: dacryoadenitis, pleomorphic parotid tumor, pericarditis, inflammatory lung tumor, or sclerosing myofibroblastic tumor, aortitis lymphoplasmacytic ileum tumor and SLE with inflammatory autoimmune pancreatitis and chronic sialadenitis]), and only in 10% did we confirm an IgG4-RD.

The response to low-dose steroids is distinctive of the IgG4-RD, although it is of interest that up to 30% of patients with IgG4-RD have spontaneous resolution and a similar percentage is refractory or have relapsed; Rituximab is generally suitable for B cell depleting therapy,[32] although one can also use methotrexate, mycophenolic acid and azathioprine. There is evidence that treatment modifies the natural course of the disease, both in normalizing the organic functions and preventing fibrosis.[33]

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