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 unstably, allowing their separation and forming 2 antigen-binding sites, so that the bisppecific 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. Antinflammation: 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 (junctiional protein) and a third of patients with membranous glomerulonephritis, in whom IgG4 interacts with phospholipase A2 receptor type M of podocytes. There are antimeteloproteinase ADMA73 IgG4 autoantibodies role in thrombotic thrombocytocypenic purpura.1,6
3. Autoantibody reaction: IgG4 interactions with other antibodies.

The clinical expression of IgG4-RD is almost universal1–5; 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 disease 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, stori-form 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 relaxes; 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 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
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-α.

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. IgG4-RD (Churg Strauss disease), despite being suggestive of anti-ADAMTS13 antibodies in patients with acquired thrombotic thrombocytopenic purpura J Thromb Haemost 2009;7:170–110.

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References