IgG4 Syndrome: Old Disease, New Perspective

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Editorial

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In the last few decades, the evolution of biomedical sciences has contributed to a better understanding of the pathogenesis of human disease, the description of new clinical entities, sorting out of disease subgroups, and development of targeted therapeutic interventions[1].

A new syndrome was identified recently, called IgG4 syndrome. Many terms such as "IgG4-related systemic sclerosing disease," "IgG4-related autoimmune disease," "IgG4-related systemic disease," "IgG4-positive multiorgan lymphoproliferative syndrome," and others have been used to identify the disease.

IgG4 syndrome has various clinical manifestations, such as sclerosing pancreatitis, sclerosing cholangitis, prostatitis, tubulointerstitial nephritis, interstitial pneumonia, and enlargement of salivary glands. In previous years, these clinical entities appeared to be unrelated. Recent studies, however, revealed that they share some common denominators, such as elevated serum IgG4 levels and tissue infiltration by IgG4-positive plasma cells, accompanied by tissue fibrosis and sclerosis[2]. These serological and histopathological features are considered hallmarks for diagnosis of IgG4 syndrome. Thus, the enlargement of salivary glands, accompanied by high serum IgG4 concentrations and IgG4-positive plasma cells in the infiltrates of the salivary glands, previously called Mikulicz's disease or Kuttner's tumor (sclerosing sialadenitis) and for many years considered a subgroup of Sjögren's syndrome (SS), has been recently recognized as one of the various clinical manifestations of IgG4 syndrome[3,4].

IgG4 syndrome affects mainly middle-aged men. Many organs and tissues are involved in these patients, including pancreas (the most commonly affected tissue), gall bladder, bile duct, salivary glands, retroperitoneum, kidneys, lung, prostate, lymph nodes, breast, thyroid, and pituitary glands[5]. Patients with IgG4 syndrome have clinical manifestations from 2 or more organs, simultaneously or sequentially, while rarely, the syndrome can be expressed at only one tissue. Recently, it was recognized that around one-third of patients with IgG4 syndrome also suffer from dry eyes and mouth, arthralgias, and they exhibit low titers of rheumatoid factor (RF), antinuclear autoantibodies (ANA), and decreased serum levels of complement, making the differential diagnosis of this syndrome from SS difficult[6]. Treatment strategies include administration of corticosteroids, to which IgG4 syndrome is highly responsive, while an open observational study revealed that anti-CD20 therapy can be effective in cases of IgG4 syndrome refractory to corticosteroids[7].

In this issue of *The Journal*, Masaki, *et al* review the main clinical, serological, and histopathological characteristics of IgG4 syndrome and delineate differences among IgG4 syndrome patients and SS patients[8]. In agreement with previous studies[2] the authors suggest that incidence of dry eyes, dry mouth, and arthralgias is lower in IgG4 patients, while incidence of allergic rhinitis, bronchial asthma, sclerosing pancreatitis, interstitial nephritis, and interstitial pneumonitis is higher compared with respective findings in SS patients. Further, it was found that total IgG, IgG2, IgG4, and IgE were significantly higher, while IgG1, IgG3, IgA, and IgM were lower compared with corresponding levels found in SS patients. Additionally, patients with IgG4 syndrome did not possess anti-Ro/SSA and anti-La/SSB autoantibodies, and only a few had low serum titers of RF and ANA.

This and other studies have raised questions: First, is IgG4 syndrome really an autoimmune disorder? Second, why are IgG4 levels increased in these patients? In the current study[8], the authors speculate that IgG4 syndrome might not be an autoimmune disorder, since neither target antigens nor disease-specific autoantibodies were found. Although there are controversial suggestions[9], many authors think that an allergic response is involved in the pathogenesis of IgG4 syndrome[10]. Observations that support this hypothesis include increased expression of Th2 cytokines in tissues affected by the syndrome, increased serum amounts of IgE and IgG4 antibodies (IgG4 is known to be associated with

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allergic reactions), and high incidence of allergic rhinitis and bronchial asthma.

On the other hand, T regulatory cells seem to play a major role in the pathogenesis of the syndrome. Cytokines produced by T regulatory cells (i.e., interleukin 10 and transforming growth factor-ß) are found to be increased in affected tissues in IgG4 patients, while in peripheral blood increased numbers of CD25-positive T regulatory cells are detected.

The role of IgG4 is still largely unknown; whether it is involved in the pathogenesis of the syndrome or is an epiphenomenon is unclear. Recently, it has been suggested that in patients with autoimmune pancreatitis, T regulatory cells may favor differentiation of B lymphocytes to IgG4 plasma cells[11]. In conjunction with increased Th2 cytokines in the affected tissues, this may provide an explanation for the high titers of IgG4 antibodies[12,13]. One should also note that IgG4 antibodies are not specific for this syndrome. These antibodies have been observed in many other diseases, such as multicentric Castleman's disease, idiopathic plasmacytic lymphadenopathy, Wegener's granulomatosis, pemphigus vulgaris, and pemphigus foliaceus[13,14,15].

Future studies may broaden the work of Masaki, *et al*[8]. First, the study was performed in a specific racial group; thus, it would be of interest for investigators from North America, Europe, and Africa to describe the clinical picture, serology, and histopathology of the IgG4 syndrome. Second, the number of patients examined was relatively low and their full clinical picture (i.e., the number having bilateral swelling of salivary, lachrymal, or submandibular glands) has not been presented. Third, a study using an experimental animal model is needed to delineate the role of IgG4 in the pathogenesis of the syndrome.

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