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IgG4-related diseases

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Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a fascinating condition recognised as a systemic disease in 2003 [1,2]. The first link between autoimmunity affecting the pancreas, elevated serum IgG4 concentrations and large numbers of IgG4-positive plasma cells in pancreatic tissue was described only 2 years earlier [3]. Since then, many diseases that have long been viewed organ-specific are now considered within the spectrum of IgG4-RD. Practically any organ can be affected, having in common a key pathological feature consisting in dense lymphocyte and plasma cell infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and often an elevated serum IgG4 concentration. While good clinical response to steroid therapy is observed, immunosuppressive or B-cell depleting therapy can be required. It is important to distinguish the IgG4-RD from traditional organ-specific autoimmune disease to guide therapy.

What we know about immunoglobulin G4

Many terms have been used to describe immunoglobulin G4 related disease (IgG4-RD), including IgG4-related sclerosing disease, IgG4-related autoimmune disease, systemic IgG4 plasmacytic syndrome (SIPS), IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS) and IgG4-associated multifocal systemic fibrosis [4]. IgG4 is the common factor of all these names, although its contribution as a specific pathogenic molecule is uncertain (reviewed in Refs. [5–9]). IgG4 has been long viewed as an anti-inflammatory immunoglobulin, and although an increase of IgG4+ plasma cells

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is critical for the diagnosis of these conditions, increased levels of IgG4 could be an epiphenomenon rather than an effector molecule.

IgG4 is a unique antibody in both structure and function, and the least common of the four subclasses of IgG. It accounts for only 3–6% of total IgG in normal serum, and IgG4 concentrations are normally stable. The IgG4 subclass was distinguished early on from the other IgG subclasses, as it exhibits negligible binding to the C1q protein complex and is unable to activate the classical complement pathway. IgG4 also has greatly reduced binding to the low-affinity Fc-gamma receptors (FcgRIIa and FcgRIIIa) and a 10-fold reduction in binding to the high-affinity FcgRI compared with other isotypes. The differences between IgG1 and IgG4 for binding to C1q and Fc receptors have been localised to a few amino acid differences in the CH2 domain, notably P331S for C1q binding [10] and L234F and P331S for Fc receptor binding [11].

The amino acid sequence of the core IgG4 hinge is also distinct from other IgGs, which increases susceptibility of the two core hinge inter-heavy chain disulfide bonds to chemical reduction [5,6]. This change allows the heavy chain to separate and recombine randomly, so that asymmetric antibodies with two different antigen-combining sites can be formed. This unique characteristic of IgG4 is called half-antibody exchange reaction [5,6]. The resulting bispecific IgG4 molecules are unable to crosslink antigen, thus losing the ability to form immune complexes.

Other characteristics of the IgG4 subclass are that can bind the Fc portion of other IgG antibodies, particularly other IgG4 molecule. IgG4 and IgG interaction occurs between Fc constant domains and might contribute to the molecule's anti-inflammatory function. Also, IgG4 is a T-helper cell 2-dependent isotype that plays a significant role in allergic reactions, as physiologic IgG4 response can be induced by repeated antigen exposures. Thus, autoimmunity and infectious agents are potential immunologic triggers in IgG4-related disease. Th2 cytokines such as interleukins 4, 5, 10, and 13 and transforming growth factor β (TGF-β) contribute to the eosinophilia, elevated serum IgG4 and IgE concentrations, and progression of fibrosis that are characteristic of IgG4-related disease. Massive infiltration by inflammatory cells leads to enlargement of the affected sites and results in organ damage [8,9]. Finally, IgG4 tends to have relatively low-affinity for target antigens [5,6].

The antigen specificity for IgG4 antibody in IgG4-RD has not been defined. It is important then to distinguish this syndrome from certain immune-mediated conditions in which autoreactivity plays a central role. In these diseases, IgG4 antibodies recognise a specific antibody and they are distinct from IgG4-RD, including clinical and pathological manifestations [8]. Examples of these disorders are IgG4 antibodies against desmoglein 1 in patients with pemphigus vulgaris and foliaceus; the M-type phospholipase A2 receptor expressed in podocytes in patients with idiopathic membranous glomerulonephritis; the metalloproteinase ADAMTS13 in patients with thrombotic thrombocytopenic purpura; MuSK protein in myasthenia gravis; and IgG4-containing immune complexes damage renal glomeruli in a subset of childhood membranous glomerulonephritis.

Epidemiology of the IgG4-RD

IgG4-RD affects mostly middle-aged and elderly men. This marked male predominance, with the possible exception of those patients with predominantly head and neck involvement, in whom the male and female ratio is balanced, contrasts with other autoimmune diseases that mimic IgG4-RD such as Sjögren's syndrome (SS) and primary biliary cirrhosis (PBC), which have female predominance [4].

Few data exist on the incidence and prevalence of IgG4-RD. Many medical conditions that have long been viewed as conditions affecting individual organs are now considered as a part of the spectrum of IgG4-RD (Table 1). Most epidemiologic studies come from Japan and focus on autoimmune pancreatitis. The estimated prevalence of autoimmune pancreatitis is 0.8 cases per 100,000 persons in Japan. The incidence of this disease throughout Japan was estimated to be 0.28–1.08/100,000, with 336–1300 patients newly diagnosed per year and approximately 6700–26,000 patients who developed IgG4-RD over the past 20 years [4].