

# IgG4-Related Disease and Eosinophilic Granulomatosis with Polyangiitis: Similarity or Coexistence?

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**I**mmunoglobulin G4-related disease (IgG4-RD) is a systemic, chronic, inflammatory disorder characterized by tumor-like swelling of involved organs, a lymphoplasmacytic infiltrate enriched in IgG4+ plasma cells, and a variable degree of fibrosis [1]. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of multisystemic diseases characterized mainly by necrotizing small-vessel vasculitis and/or granulomatous inflammation. The autoantibodies associated with this disease are directed against either proteinase-3 (PR3) or myeloperoxidase (MPO) [2].

It was recently demonstrated that IgG4-RD and AAV may mimic each other and, in rare cases, a true overlap between these two diseases may occur [3–6]. Thus, IgG4-RD and granulomatosis with polyangiitis (GPA) may result in similar clinical manifestations such as orbital mass or pachymeningitis that may lead to organ- or life-threatening complications [3]. In addition, biopsies from GPA patients may show IgG4+ plasma cell infiltrate, one of the major histopathological features of IgG4-RD [4,5]. For example, a recent study observed increased IgG4+ plasma cell concentrations in 8 of 26 sinonasal or orbital/

periorbital biopsies from GPA patients [4]. In another study, IgG4+ plasma cell infiltration was found in 6 of 15 biopsies from pauci-immune necrotizing glomerulonephritis patients [5]. These data suggest that IgG4+ plasma cell infiltration alone is not sufficient to confirm the diagnosis of IgG4-RD, and other histological features such as storiform fibrosis, dense obliterative phlebitis, and/or mild-to-moderate eosinophil infiltrate are required.

In rare cases, IgG4-RD shares some symptoms with eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome), and vice versa: EGPA patients may present some features compatible with IgG4-RD. For example, it has been demonstrated that patients with IgG4-RD have an increased prevalence of allergic rhinitis, bronchial asthma, peripheral eosinophilia, and increased IgE levels [7,8]. At the same time, although high serum concentrations of IgG4 may be a useful tool for the diagnosis of IgG4-RD, elevated levels of IgG4 are not specific to this disease and may be present in patients with EGPA [9]. Moreover, it has been reported that IgG4 levels were markedly higher in patients with active EGPA than in patients with inactive EGPA, patients with GPA, as well as healthy subjects [10]. The study found that serum IgG4 levels were correlated with disease activity and with the extent of organ involvement, and in some patients IgG4 levels decreased following immunosuppressive treatment.

Recently, a European multicenter observational study reported 18 cases with concomitant diagnosis of IgG4-RD and AAV, with the predominant AAV phenotype

being GPA [6]. All patients fulfilled the criteria for AAV and had a possible, probable or definite diagnosis of IgG4-RD, according to the comprehensive diagnostic criteria for IgG4-RD [6]. A definite diagnosis of IgG4-RD was made in 5 patients (28%). IgG4-RD manifestations in patients with AAV included chronic peri-aortitis in 9 patients (50%), orbital mass and tubulointerstitial nephritis in 4 (22%), prevertebral fibrosis in 3 (17%), and pachymeningitis and autoimmune pancreatitis in 2 (11%). Remarkably, in two cases, both the presence of granulomas related to GPA, and storiform fibrosis and IgG4+ plasma cell infiltration related to IgG4-RD were found in the same tissue sample. It was concluded that the coexistence of AAV and IgG4-RD may represent a new clinical entity, and that AAV patients with atypical clinical manifestations including chronic peri-aortitis, tubulointerstitial nephritis, and prevertebral fibrosis may have concomitant IgG4-RD [6].

In the current issue of *IMAJ*, an interesting case report by Meridor and Levy illustrates the clinical features that may be related to both EGPA and IgG4-RD [11]. The patient described had clinical features compatible with GPA, including sinusitis, spastic bronchitis, leukocytoclastic vasculitis, fever, pericardial and pleural involvement, and prominent eosinophilia. The patient also had an increased concentration of IgG4 (four times the upper limit of normal) and suspected esophageal involvement, which raised the possibility of IgG4-RD disease. Histopathological examination of involved organs was not performed, but elevated levels of blood plasmablasts were reported – which is compatible with

active IgG4RD. Based on these findings, the authors concluded that the diagnosis was consistent with IgG4-RD, without excluding the possibility of overlap with GPA.

Plasmablasts are derived from the B-cell lineage and represent an intermediate stage between activated B-cells and plasma cells. These cells are rarely found in the peripheral blood of healthy individuals [12]. Patients with active IgG4-RD have an increased count of circulating plasmablasts regardless of their serum IgG4 concentrations, and this may be useful in confirming the diagnosis of IgG4-RD [13,14]. In addition, a direct correlation was found between higher plasmablast counts and the number of organs involved and IgG4-RD responder index (IgG4-RD RI) [13]. Moreover, treatment with glucocorticoids and B-cell depletion therapy decreases plasmablast counts, and this decrease is correlated with improvement in IgG4-RD RI [13,14].

In conclusion, the report by Meridor and Levy [11] demonstrates that GPA and IgG4-RD may be characterized by similar clinical manifestations such as allergic features, eosinophilia, and increased con-

centration of IgE and IgG4. Although increased plasmablast counts may be a potential tool for the diagnosis of IgG4-RD, histopathological findings are required for a definite diagnosis.

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**Capsule**

**Critical amino acid variations in HLA-DQB1\* molecules confer susceptibility to autoimmune thyroid disease in south India**

The HLA-DQB1\* region exhibits complex associations with autoimmune thyroid disease (AITD). **Ramgopal** et al. checked AITD patients [Hashimoto's thyroiditis (HT) n=180, Graves' disease (GD) n=55], and age/sex-matched controls (n=235) were genotyped for DQB1\* alleles by PCR-SSP. Alleles DQB1\*02:02, \*06:03, \*06:09, \*03:02, and \*03:03 showed an increased risk and \*02:01, \*05:02, and \*06:02 showed a protection toward AITD. Multiple sequence alignment was used to determine the amino acid variations within the peptide-binding pockets of susceptible and/or protective DQB1\* alleles. The authors observed susceptible associations for amino acids 'Glu86 ( $P < 0.0007$ )' and 'Leu87 ( $P < 3.8 \times 10^{-4}$ )'

in P1, 'Leu26 ( $P < 4.0 \times 10^{-12}$ )' in P4, 'His9 ( $P < 5.0 \times 10^{-4}$ )' and 'Ala57 ( $P < 3.6 \times 10^{-4}$ )' in P9 toward HT; and 'Gly86 ( $P < 0.0004$ )' in P1 and 'Asp57 ( $P < 1.9 \times 10^{-4}$ )' in P9 towards GD. Protective associations were observed for amino acids 'Ala86 ( $P < 8.2 \times 10^{-6}$ )' and 'Tyr87 ( $P < 0.0003$ )' in P1, 'Gly26 ( $P < 4.9 \times 10^{-5}$ )' and 'Ser74 ( $P < 4.9 \times 10^{-5}$ )' in P4, 'Phe9 ( $P < 0.0007$ )' and 'Ser57 ( $P < 0.0016$ )' in P9 towards HT. Thus, the present study revealed that DQB1\* alleles and putative amino acid residues play an important role in susceptibility toward AITD in south India.

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Eitan Israeli

**“In everyone’s life, at some time, our inner fire goes out. It is then burst into flame by an encounter with another human being. We should all be thankful for those people who rekindle the inner spirit”**

Albert Schweitzer (1875–1965), French theologian, organist, writer, humanitarian, philosopher, and physician. He won the Nobel Peace Prize for his philosophy of “Reverence for Life,” which was expressed in many ways, but most famously in founding and sustaining the Albert Schweitzer Hospital for lepers in Lambaréné, in Gabon, Africa