The uncertain meaning of ANCA positivity in IgG4-related disease

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In this issue of *Rheumatology*, Martin-Nares et al. report the results of a retrospective study that investigates the prevalence and significance of antineutrophil cytoplasmic antibody (ANCA) in IgG4-related disease (IgG4-RD) **(1**).

IgG4-RD is a fibroinflammatory disorder characterized by lymphoplasmacytic tissue infiltration, rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. IgG4-RD potentially affects every organ; however, the most common manifestations include type I autoimmune pancreatitis, chronic periaortitis, and thyroid, salivary, or lachrymal gland involvement. Differential diagnosis includes malignancies, infectious diseases, and autoimmune disorders, including ANCA-associated vasculitis (AAV) **(2).** An overlap in organ involvement and histopathological features may occur between IgG4-RD and AAV. ANCA-positivity, when confirmed by both indirect immunofluorescence (IIF) and enzyme immunoassay (ELISA), strongly supports the diagnosis of AAV. However, the presence of ANCA in patients with IgG4-RD has increasingly been reported.

In the article by Martin-Nares *et al.* ANCA positivity in IgG4-RD had a higher prevalence than that revealed by previous studies, particularly when ANCA were detected by IIF. However, this greater frequency was not confirmed when they were detected using ELISA for traditional antigens. Among a cohort of 69 IgG4-RD patients, 25 underwent ANCA testing; of those, 56% showed ANCA by IIF with only 22% having anti-PR3 or anti-MPO antibodies by standard ELISA testing. Patients with positive ANCA by IIF more often had systemic symptoms, salivary glands, lymph node, and kidney involvement (other than rapidly progressive glomerulonephritis). Moreover, they displayed higher levels of total serum IgG, IgG1, and IgG4; lower levels of C3 and C4, and a higher prevalence of anti-nuclear antibodies (ANA) **(1).**

In IgG4-RD, IgG4 serum levels directly correlate with other IgG subclasses and with inflammatory markers, and inversely with complement levels. Moreover, elevated serum IgG4 antibodies denote a subset of patients with a greater likelihood of multiple organ involvement and systemic symptoms **(3).** In many clinical settings, the specificity of the ANCA IIF test for the diagnosis of AAV is low, as results may be positive in a wide range of conditions other than AAV **(4).** In IgG4-

RD too, ANCA detected only by IIF do not necessarily indicate an underlying AAV but might instead represent the result of an exuberant B-cell response.

Conversely, ANCA directed against myeloperoxidase (MPO-ANCA) or proteinase-3 (PR3-ANCA) were found to be more frequent in patients presenting clinical features shared with AAV even in the absence of histological elements suggestive for vasculitis. It would be of interest to determine whether ANCA in IgG4-RD are of the IgG4 subclass, as contradictory evidence exists regarding the pathogenicity of IgG4 autoantibodies. ANCA in AAV are mostly of the IgG1 and IgG4 subclasses. However, IgG4 in vasculitis contribute to tissue damage much less than other IgG subclasses. In keeping with this view is the observation that, while IgG1 and IgG3 PR3-ANCA elicit a vigorous neutrophil response, IgG4 PR3-ANCA are only weakly stimulatory to neutrophils **(9).**

Due to the retrospective nature of the study, no ANCA specificities other than MPO and PR3 were determined. In this regard, almost all the subjects testing positive for ANCA by IIF had a C-ANCA pattern, which is atypical for non-AAV ANCA (drug-induced ANCA, inflammatory bowel disease-associated ANCA, etc.) that usually display a P-ANCA pattern. Of the five subjects with ELISA-positivity, three had a C-ANCA pattern, one patient with anti-PR3 antibodies, and two with anti-MPO antibodies. Therefore, in some IgG4-RD patients, there appear to be unknown C-ANCA antigens. The identification of these antigens could improve the understanding of IgG4-RD biology. Indeed, lactoferrin (towards which ANCA may also be directed) has been detected in various epithelial tissues, such as salivary glands and the pancreatic acinus, and anti-lactoferrin antibodies were identified in sera from patients with autoimmune pancreatitis **(10).** However, anti-lactoferrin antibodies present a P-ANCA pattern at fluorescence assays, thus appearing not involved in the observed C-ANCA reactivity in this study.

A single case of AAV and IgG-RD overlap was identified by the authors, but not included in the study. To date, several cases of overlap between AAV and IgG4-RD have been described, with coexisting histopathological features of both diseases (**5**). Rarely, medium- to small-vessel vasculitis has been described in biopsies from patients with IgG4-RD; conversely, IgG4 levels may be increased

in the sera or tissue of patients with AAV. However, the typical histopathological lesions of the two conditions imply different pathogenic mechanisms. Inflammation in AAV is characterized by neutrophil-rich infiltrates, fibrinoid necrosis of the vessel walls, and extravascular granulomas (**6**). Pathological lesions of IgG4-RD include dense polyclonal lymphoplasmacytic infiltrate with an elevated number of plasma cells, storiform fibrosis, and obliterative phlebitis without evidence of necrotizing vasculitis (**2**). Based on these histological differences, a unifying pathophysiological mechanism appears unlikely.

Despite both IgG4-RD and AAV responding to B-cell depletion therapy (**7, 8**), which is an important clue to shared immune-mediated pathways, the idea that ANCA are the sole link between the two diseases could be too simplistic. Deregulation in T-follicular-helper cell activity has been demonstrated in both diseases, where T follicular helper cells are atypically polarized towards a type 2 phenotype, enhancing IgG4 production from plasmablasts **(5)**. Further additional mechanisms are to be uncovered.

Two speculative explanations may be proposed for cases of IgG4-RD and AAV overlap. First, one may think that the prominent IgG4 and IgG1 production in IgG4-RD may occur in parallel with autoantibody (namely ANCA) appearance, which may contribute to vasculitic manifestations. This hypothesis is weakened by the description of cases of AAV preceding IgG-RD **(5).** Alternatively, IgG4-RD lesions might represent the chronic, sclerotic evolution of vasculitis-related inflammation. The debate is still open, and questions exceed the answers: whether a histopathological link exists between IgG4-RD and AAV, or whether they are just a co-occurrent epiphenomenon; whether it is possible to identify an IgG4-RD subgroup of patients that, on account of clinical, serological, or genetic characteristics, are more prone to develop AAV; and whether ANCA-positivity needs to be retested during the follow-up of IgG4-RD affected patients to evaluate relapse or response to therapy. To date, ANCA testing in IgG4-RD is a tool to exclude a concomitant vasculitic process, waiting for experimental and longitudinal clinical studies to unravel the meaning of ANCA positivity in IgG4-RD.

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