Editorial

Significance of positive rheumatoid factor in ANCA-associated vasculitis

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Rheumatoid arthritis (RA) is a chronic, inflammatory multisystem disease characterised by the presence of symmetric polyarthritis with extra-articular manifestations that include a small- to medium vessel vasculitis (1). Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) are characterised by pauci-immune necrotising vasculitis, predominantly affecting the small vessels, and presence of ANCA (2). There is a well-recognised association between RA and AAV, with RA preceding the diagnosis of AAV in most cases (3-5). ANCA antibodies have been reported in patients with a clinical diagnosis of RA, and, conversely, rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibodies can be present in patients with AAV. In a study of 385 patients with RA, 16% had a positive ANCA; all p-ANCA (6) while in AAV, positive RF has been reported in 39–62% with CCP positivity of 5% in 1 study (7-9). At present, it is unclear whether the presence of other antibodies modifies disease presentation or prognosis of the primary disease, or are an incidental finding. Studies evaluating patients with RA and positive ANCA serologies have reported variable associations with increased disease activity, erosions, renal manifestations, vasculitic manifestations and pulmonary involvement (6, 10-13). In AAV, the presence of RF has been associated with cutaneous manifestations in (one study in eosinophilic granulomatosis with polyangiitis (EGPA)), neurologic involvement, more constitutional symptoms, higher disease activity, higher systemic inflammation, variable renal outcomes and mechanical ventilation (7-9). In a series comparing patients with RA and positive ANCA tests to patients with RA and a clinical diagnosis of AAV, the latter patients had a higher prevalence of positive RF, MPO-ANCA antibodies, rheumatoid nodules and inflammatory eye disease (5). Finally, RA and granulomatosis with polyangiitis (GPA, a form of AAV), share genetic polymorphisms within the CTLA4 gene (14).

The study by Öz *et al*. adds to our knowledge about the role of RF positivity in patients with GPA (15). The authors included 82 patients with GPA evaluated at a university-based rheumatology clinic between 2014 and 2024. Patients with concurrent systemic autoimmune conditions like RA were excluded as were patients with an active infection. The overall prevalence of RF in this cohort was 45% with 35% of those with positive RF exhibiting low tiers. Only 1 patient (3%) also tested positive for CCP antibodies. When comparing laboratory parameters of patients with GPA with and without RF, those with positive RF had higher ANCA levels (MPO or PR3 via Enzyme-Linked Immunosorbent Assay (ELISA) perhaps indicating a more robust autoimmune response. Patients with positive RF also had higher white blood cell counts, neutrophil to lymphocyte ratio consistent with a prior report (15). Despite this, in contrast to prior studies, there were no differences in the acute phase reactants erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) between the 2 groups (8, 9, 15).

The authors do not provide clarity on the differences of disease manifestations at baseline *versus* over time which makes it difficult to tease out the role of RF on clinical phenotypes. However, when evaluating disease manifestations (either at baseline or follow-up), a higher proportion of patients with arthritis had positive RF while those with cutaneous vasculitis and end stage renal disease (ESRD) had a lower number of RF positivity (9). Several other stud-

ies have also shown presence of RF in AAV to be protective against severe renal involvement though the frequency of renal disease did not differ in patients with and without RF in those studies (8, 9). Patients with positive RF also had higher disease activity as captured by the Birmingham Vasculitis Activity Score (BVAS) (15).

For reasons that are not evident, more patients with positive RF were treated with rituximab (n=24) than RF negative group (n=16) (15). While the authors conclude that the use of rituximab in RF positive patients precludes development of end stage renal disease, the absence of information on important variables like relapses, and, the lack of granularity on the timing of the different treatments during the disease course make it difficult to draw any conclusions on the treatment and outcomes (15). Finally, in univariate and multivariate analyses, RF positivity remained significantly protective against development of end stage renal disease (15).

The study had several limitations to consider when interpreting the results. It only included patients with GPA and whether these findings can be extrapolated to other forms of AAV, especially microscopic polyangiitis (MPA) where renal involvement is frequent, remains unclear. Patients with a diagnosis of RA were excluded. The authors noted that none of the RF positive patients met criteria for RA, though, that is unclear since at least 67% of the patients in the RF positive group had arthritis and no details are provided about the joints that are affected to allow one to draw conclusions. Finally, given the absence of granularity regarding clinical manifestations and treatment at baseline *versus* over time in a cohort with a disease duration of over 200 weeks (3.8 years), no conclusions can be made about the role of RF on the overall clinical phenotype. The study observations along with the previously published literature raise interesting questions about the role of RF formation in patients with AAV (7-9, 15). A recent study found that RF in patients bind with multiple citrulline- and homocitrulline containing IgG-derived peptides, whereas the RF in patients with Sjögren's disease sera had consistent binding to a single linear native epitope of IgG in the hinge region (16). Whether this may be a potential mechanism whereby RF in AAV modifies disease activity and renal involvement remains unclear. Further studies are needed to evaluate the reported overlap between RA, AAV and the presence of RF in patients with AAV.

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