

Comments on “An overview of the relation between tuberculosis and autoantibodies: a systematic review”

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Dear Editor,

I read with interest the systematic review by Mohamadzadeh *et al.* (1), which synthesized evidence on autoantibodies associated with rheumatic diseases in active tuberculosis. With respect to the antibodies reviewed, the anti-neutrophil cytoplasmic antibody (ANCA) literature appears particularly difficult to interpret. The authors appropriately note geographical, disease-stage, methodological, and treatment-related differences. I would further emphasize that “ANCA positivity” has not represented a uniform laboratory or clinical entity across studies.

A central distinction is between indirect immunofluorescence (IIF) patterns and antigen-specific antibodies. Although IIF reveals fluorescence patterns, including cytoplasmic (c-ANCA) and perinuclear patterns, it does not establish antigen specificity, whereas antigen-specific immunoassays detect antibodies directed against defined antigens. PR3-ANCA and MPO-ANCA are the principal antigen-specific ANCAs used in the diagnostic evaluation of ANCA-associated vasculitis (AAV) (2). Other neutrophil antigens, including bactericidal/permeability-increasing protein (BPI), elastase, and lactoferrin, have similarly been studied in tuberculosis. However, these non-PR3/MPO reactivities should not be interpreted as being equivalent to PR3- or MPO-ANCA.

This distinction may help explain some of the apparently conflicting results. Flores-Suárez *et al.* detected ANCA in 44.4% of 45 patients *via* IIF and antigen-specific reactivity in 40.0% *via* enzyme-linked immunosorbent assay, predominantly PR3 (3). Contrastingly, Teixeira *et al.* detected IIF positivity in only 10% of 67 patients and found no evidence of combined c-ANCA/PR3 reactivity in sera (4). Esquivel-Valerio *et al.* detected IIF positivity in 4.4% and 28.8% of patients before and after treatment initiation, respectively, with post-treatment reactivity being predominantly directed against BPI, whereas PR3- and MPO-ANCA remained absent (5). Thus, an IIF-defined pattern in tuberculosis should not be assumed indicative of the same biological or clinical phenomenon as PR3- or MPO-ANCA positivity. Even among studies assessing antigen-specific PR3- and MPO-ANCA, reported frequencies vary substantially: Flores-Suárez *et al.* found PR3-ANCA more frequently than MPO-ANCA by ELISA (3), whereas Cheng *et al.* detected each specificity in only 1.3% using a standardized chemiluminescent immunoassay on pretreatment samples (6). Although the relative distributions of MPO-ANCA and PR3-ANCA vary across populations with AAV (7), whether comparable geographic or ethnic variation exists in tuberculosis-associated ANCA remains uncertain. Importantly, apparent geographical differences across tuberculosis studies are difficult to disentangle

from differences in assay methodology and treatment timing.

Future reviews may therefore be more informative if ANCA findings are stratified by IIF pattern, PR3/MPO specificity, non-PR3/MPO targets, and treatment timing, with explicit n/N denominators. Findings across these strata should not be compared as though they represented a single uniform outcome of “ANCA positivity”. Separating these laboratory categories and testing contexts may help distinguish underlying biological heterogeneity from that attributable to assay methodology and study design. I commend the authors for highlighting this important interface between infection and autoimmunity and hope that these distinctions may help refine the interpretation of ANCA findings in tuberculosis.

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