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Autoantibodies and COVID-19: Rediscovering Nonspecific Polyclonal B-Cell Activation?

To the Editor—In the search to explain advanced, prolonged, or post-coronavirus disease 2019 (COVID-19) disease, several investigative groups, including that of Acosta-Ampudia et al, have found presumed autoantibody activities, which at times have been linked to accentuated proinflammatory states or possible autoimmunity [1]. The mere association of coincident elevations of such antibodies or their intermediate-term persistence have tempted several hypotheses of pathogenesis, whether for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection directly or concomitant immunologically based phenomena. While it is certainly appropriate to focus on these findings as being coronavirus specific, are we only rediscovering nonspecific polyclonal B-cell activation?

The concept of nonspecific polyclonal B-cell activation and, hence, nonspecific antibody production, has been well known for nearly a half century [2–4]. Whether for acute or persistent infections, a wide variety of autoantibodies, usually immunoglobulin G (IgG) subsets having low specificity, may develop to bind nonspecific antimicrobial or self-antigens. Among the latter are autoantibodies to cytokines, classic connective tissue disease autoantigens, and many other but variable host targets. Most of these nonspecific responses either markedly diminish or disappear over time. Such timing may span weeks to well over 1 year.

The transient development of autoantibodies such as rheumatoid factor or cold agglutinins during acute *Mycoplasma pneumoniae* infections remains a classic example of such nonspecificity [5]. That a similar antibody production would arise with coronaviruses was heralded in the study of murine hepatitis virus [6]. Even more recent studies illustrate how such nonspecific events can follow many non–SARS-CoV-2 infections or vaccination ([7], Feng et al, unpublished). What has not been resolved, however, is whether these immune activations represent purposeful innate immunity tactics or aberrations supporting the microbial pathogen's disease process or, perhaps, neither. Yet unresolved is the extent, if any, that such a B-cell cascade truly induces an autoantibody with definitive and/or long-lasting immune dysfunction.

Theories of detrimental postinfection immunopathology abound for COVID-19. For example, common thrombotic events during infection, or rare ones after some vaccinations, have largely stimulated reconsideration of infection-associated antiphospholipid antibodies [8]. In the short term, and with the desire to better understand the complexity of an impactful pandemic, it is more common to assume that COVID-19–associated autoantibody production should somehow factor into either early and/or late disease. We must concede, however, that a mere attribution of autoantibody existence to functional autoimmune disease, including interinfection cytokine storm or advanced inflammatory states, may just be a rudimentary and/or preliminary association, as the nonspecific polyclonal B-cell activations that we have experienced with other infections and for which we continue to seek answers. For some patients, the finding of autoantibodies during active COVID-19 has the potential to bias the treating physician towards an assumption that the two are pathologically linked and, hence, may potentially elicit intervention. Just as unproven antiviral treatments may jeopardize patient status, so too may the assumptions that any such autoantibody may truly have a role in the disease course.

Notes

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