Anti-Neutrophil Cytoplasmic Autoantibodies and Patterns of Pulmonary Disease

A Spectrum of Pathologic Findings

In this issue of the American Journal of Clinical Pathology, Gaudin and colleagues report on their investigation of the spectrum of pulmonary lesions associated with anti-neutrophil cytoplasmic autoantibodies (ANCA). As various investigations have previously detailed, ANCs are actually a heterogeneous collection of autoantibodies, which are for the most part directed at neutrophil granule enzymes. The two major target antigens are proteinase 3 (PR3), which produces a cytoplasmic pattern of staining by indirect immunofluorescence (C-ANCA), and myeloperoxidase (MPO), which produces a perinuclear pattern with this assay (P-ANCA). The study group of cases presented by Gaudin and colleagues consisted of 25 open lung biopsies and 2 autopsies, originating from 27 patients tested for ANCA. Thirteen of these 27 patients expressed C-ANCA, of which 12 of 12 tested were confirmed to have anti-PR3 specificity. However, the 14 P-ANCA patients were all confirmed by ELISA assay to have anti-MPO antibodies. Capillaritis was common, and occurred with equal frequency in both P-ANCA and C-ANCA patients. Although airway lesions, necrotizing granulomas, and non-specific inflammation were more commonly seen in the C-ANCA patients, no single lesion was specific for either C-ANCA or P-ANCA. This study raises several interesting points, as detailed below:

1. In a review of all P-ANCA positive tests from the Mayo Clinic, only 10 of 16 specimens demonstrated MPO specificity. However, all patients with alveolar hemorrhage were MPO-positive. Thus, although P-ANCA is associated with a wide spectrum of disease, and such antibodies may be directed against MPO, PR3, lysozyme, lactoferrin, elastase and other granule antigens, it seems that pulmonary disease, and in particular small-vessel vasculitis, is a feature that is strongly linked with MPO antibodies. Similar results were also noted by Bosch and colleagues in a study of patients presenting with pulmonary hemorrhage. The current study, in which all P-ANCA patients with lung disease by definition were MPO-specific, also supports that notion. The study provides a rationale for determining the antigen specificity of P-ANCA because antigen specificities other than MPO are much less likely to be related to active vasculitis.

2. These autoantibodies are highly linked to small vessel vasculitis. As such, they provide a unified pathogenesis for the different clinical entities, such as Wegener's granulomatosis (WG), microscopic polyarteritis (MPA), and Churg-Strauss syndrome (CSS), which of course have quite variant clinical manifestations. Although P-ANCA tended to be seen in MPA, whereas WG was more likely to demonstrate C-ANCA, P-ANCA and C-ANCA were not entirely specific for any entity. This also is in accordance with previous studies.

3. As a group, histopathologists, myself included, tend to be a rather paranoid lot, particularly in these days of cost-containment and other economic fears. Yet, given the lack of complete specificity of either P-ANCA or C-ANCA for a particular disease entity, the fear that somehow these serologic tests will obviate the need for histopathologic assessment seems unfounded. In other words, we do not yet have a test that will distinguish MPA and WG, although some may interpret the results of this paper simplistically as such. Rather, ANCA analysis appears to be most well-suited to function in a strong adjuvant role. For example, knowledge that a patient has a C-ANCA, with a biopsy that shows only capillaritis, and thus suggests MPA, should lead to some caution in interpretation, since the association of C-ANCA and WG suggests that the fully developed lesions of WG may become manifest at some point.

4. The broad range of findings disclosed in this paper include diffuse alveolar damage, bronchiolitis obliterans-organizing pneumonia, chronic inflammation and scarring of the interstitium, large and small vessel vasculitis, granulomatous lesions, alveolar hemorrhage, and pleuritis. They point out again a major theme of pulmonary pathology. Namely, there are a limited number of histopathologic responses to pulmonary insults. Thus, the pathologist must be ready to consider ANCA-associated disease at times when only seemingly non-specific biopsy findings are present. As such, one may have a major impact on therapy if the diagnosis is not suspected clinically. Along the same theme, one should not be surprised by this seemingly endless array of pathologic changes when examining a biopsy in a patient with a known positive-ANCA titer.

5. The pathogenesis of these antibodies remains somewhat mysterious. By immunofluorescence, there is no evidence of antibody deposition. Some authors have questioned whether these antibodies are pathogenetic, or are simply induced following vascular inflammation. However, several lines of evidence now point to the direct involvement of these anti-neutrophil granule antibodies in producing disease. Partially activated neutrophils may express these target antigens near the cell surface, and following reaction with the antibody, can become fully activated, thus triggering degranulation and a respiratory burst. If this occurred within small vessels, the release of toxic metabolites and lytic enzymes would appear to be capable of producing the lesion recognized as capillaritis, and would seem to go along with the extensive expression of this pathologic lesion in both P-ANCA and C-ANCA cases.

6. Perhaps more difficult to explain are the differences disclosed by this study. For example, why is C-ANCA more likely to produce necrotizing granulomatous inflammation
of either airways or vessels than P-ANCA, if a similar pathogenetic mechanism is operating with both antibodies?

7. The therapeutic implications relating to separation of P-ANCA and C-ANCA, and the various ANCA-associated vasculitic processes, are currently minimal, as most patients are treated similarly with steroids and/or cytotoxic agents. Nonetheless, as some of the authors of the current paper noted in a recent editorial review of ANCA, emerging therapies such as anti-idiotype antibodies, as well as delineation of differences in the pathogenesis of P-ANCA and C-ANCA related diseases, may make the distinction more important.

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REFERENCES