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EDITORIAL

Pauci-immune glomerulonephritis: the ANCA-negative side of the coin

Anti-neutrophil cytoplasmic antibodies (ANCAs) were first described as 'tools for diagnosis and markers of disease activity' in a set of small vessel vasculitides characterized by frequent renal injury.[1] Since then, a first generation of seminal studies further enforced the clinical and pathogenic relevance of ANCA for granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA) and renal-limited pauci-immune vasculitis, which were thus grouped as 'ANCA-associated vasculitides (AAVs)'.[2–4] At the same time, diagnostic advances occurred with the introduction of more accurate quantitative methods (such as enzyme-linked or chemiluminescence assays) for the specific recognition of anti-myeloperoxidase (MPO) and anti-proteinase-3 (PR3) antibodies, besides conventional immunofluorescence. Recent genetic studies[5] pointed out that AAV subsets can be distinguished not only by clinical diagnosis and organ involvement, but also by ANCA status (i.e. a specific ANCA type was associated with a different genetic background), paving the way to a novel serological classification of AAV. Several additional studies confirm the usefulness of this ANCA-centred approach at a clinical level and support the contention that some pathogenic mechanisms may vary depending on presence and type of ANCAs. For example, ANCA-positive patients with EGPA have more prominent vasculitic manifestations.[6] In addition, anti-PR3-positive patients respond better to rituximab (RTX) than to cyclophosphamide,[7] but have a higher cardiovascular risk[8] and are more likely to experience relapse after renal transplant when compared to MPO-positive patients.[9] Finally, the ANCA titre could predict disease flares and indicate the optimal timing for RTX administration[10] (NCT01731561, MAINRITSAN-2 trial).

However, while a classification based upon an anti-MPO versus anti-PR3 dichotomy seems promising for an accurate clinical-pathogenic stratification of patients, the smaller, but clinically significant subset of ANCA-negative patients remains in an indefinite

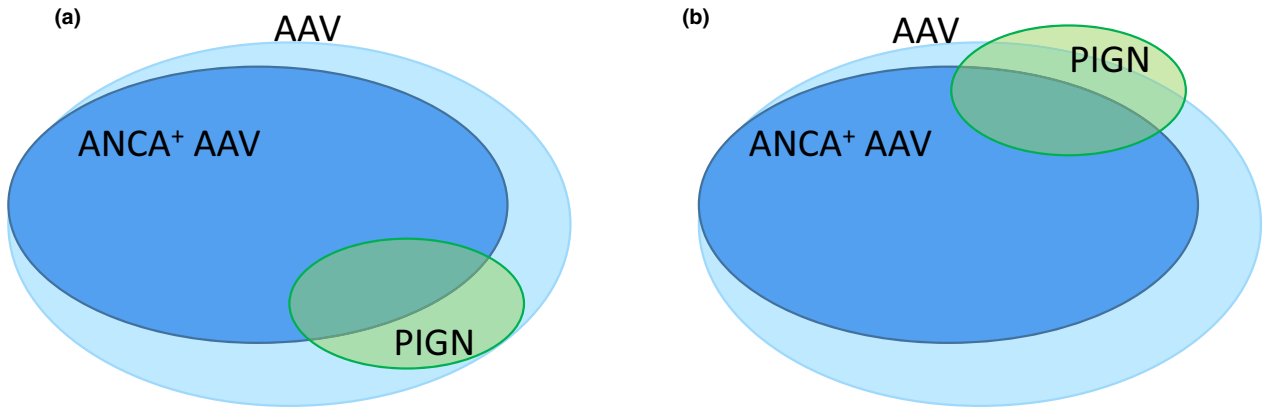

Figure 1 Possible logical relations between anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) and pauci-immune glomerulonephritis (PIGN). ANCA$^+$ AAV (blue elipses) and AAV (light blue elipses) are shown. The area within the AAV set but outside the ANCA$^+$ set represent ANCA-negative AAV patients. PIGN (green elipses) has a higher percentage of ANCA-negative patients. Further research on ANCA-negative patients with PIGN might determine whether (Panel a) or not (Panel b) all these patients belong to the AAV spectrum.

Limbo. Infact, ANCA-negative patients are characterized by the *lack* of specific clinical manifestations and are more frequently described (excluding EGPA) in nephrology series, since they often present with isolated pauci-immune glomerulonephritis (PIGN) without extra-renal manifestations of AAVs.[11–14] Despite this finding, the prognostic relevance of ANCA status in patients with crescentic PIGN is controversial.[11–14] The article by Sharma and colleagues,[15] in this issue of the *IJRD*, sheds light on this topic by investigating a monocentric cohort of 84 subjects with PIGN, including 33 ANCA-negative patients. The authors report that a significantly lower fraction of ANCA-negative patients experience an improvement in renal function or become dialysis-independent after therapy, despite lower Birmingham vasculitis activity scores at presentation. Sharma *et al.* also point out that ANCA-negative patients have fewer extra-renal manifestations despite a more severe active glomerular injury in terms of presence of cellular crescents, and more advanced interstitial fibrosis. Unfortunately, the authors stratified their sample only on the basis of immunofluorescence results, without taking into account the results of the anti-MPO and anti-PR3 enzyme-linked immunosorbent assays.

Taken together, these data suggest that ANCA-negative patients do not simply lack a diagnostic marker, but may more correctly lack a definite diagnosis. Specific and still unknown pathogenic mechanisms could be active in this group of patients and explain the phenotype discrepancy with anti-MPO/PR3-positive patients. For example, other autoantibodies have been previously associated with ANCA-negative patients, and it is possible that some of them will not exert an ANCA-like biological behavior. Consequently, the so-called ANCA-negative subset may be more heterogeneous than previously thought and mistakenly include pathologies that do not even belong to the AAV spectrum (Fig. 1). We believe that clarification of this point is crucial, and further studies are needed to address this issue.

In conclusion, ANCA status distinguishes between disease subsets both in AAV and PIGN. Recent data suggest that genetic predisposition, clinical phenotype, histology, response to therapy and possibly prognosis differ according to ANCA status. In the future, we should try to overcome the current definition of one subset of patients based on negation (i.e., ANCA-negative, without extra-renal manifestations). Further research should aim to clarify whether all patients with ANCA-negative PIGN should be included within the AAV spectrum and seek novel auto-antibodies. Finally, increased efforts are needed to identify more homogenous subsets of ANCA-negative PIGN, with the aim to improve knowledge of pathogenesis, hopefully paving the way to better therapies and outcomes.

Giuseppe A. RAMIREZ,[1,2] Justin C. MASON[3,4] and Enrico TOMBETTI[1,4]

[1]*Università Vita-Salute San Raffaele,* [2]*Unit of Internal Medicine and Clinical Immunology, San Raffaele Scientific Institute, Milan, Italy* [3]*Rheumatology Section, Vasculitis Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust, and* [4]*Vascular Science, National Heart and Lung Institute, Imperial College – Hammersmith Campus, London, UK*
Email: tombetti.enrico@hsr.it

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