ANCA-associated Vasculitides and Classification: A Conundrum Solved?

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Editorial

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The discovery of the antineutrophil cytoplasmic antibody (ANCA) has brought us closer to understanding the mechanisms involved in the development of certain vasculitides. In spite of this, an ideal classification scheme for vasculitis has eluded the literature. This is especially true for those vasculitides that we believe are related to ANCA, a group of disorders sometimes referred to as ANCA-associated vasculitides, or AAV [Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MPA), and the occasionally referred to renal limited vasculitis]. In this issue of *The Journal*, Linder, *et al* from the University of Heidelberg once again tackle the issue of classification, specifically WG versus MPA, using an artificial neural network (ANN)[1].

There are many issues when assessing classification criteria. Historically, vasculitis was initially described histologically in a patient with necrotizing arteritis in 1866 by Kussmaul and Meir, who named the disease "periarteritis nodosa" (PAN). By the 1950s, many investigators realized that there were clinically and pathologically distinct forms of arteritis and that many if not all the vessels involved smaller arteries.

In 1952, Zeek proposed the generic term "necrotizing vasculitis" to designate 5 distinct types of systemic vasculitis defined by clinical and pathological findings[2]. All subsequent classifications are to some extent derived from Zeek's classification. Also by the 1950s two variant forms of vasculitis with associated granulomatosis inflammation had been recognized — WG and CSS. Churg and Strauss in 1951 described 13 patients with asthma, eosinophilia, granulomatous inflammation, necrotizing systemic vasculitis, and necrotizing glomerulonephritis[3]. The definitive description was provided in 1954 by Godman and Churg, who identified the triad of features: systemic necrotizing "angiitis," necrotizing inflammation of the respiratory tract, and necrotizing glomerulonephritis[4].

The American College of Rheumatology (ACR) classification criteria for vasculitides were created in 1990 from large retrospective cohorts and have been used in many research and clinical studies[5]. However, the criteria have not been widely validated in a prospective cohort. The criteria were also developed before the widespread introduction of ANCA testing, which now plays an important role in the diagnosis and classification of vasculitis. Finally, microscopic polyangiitis was not included in these ACR criteria.

In 1994, the Chapel Hill Consensus Conference (CHCC) nomenclature was created to clarify and standardize terms[6]. The CHCC restricted the use of the term PAN to a medium-vessel disease, and recognized MPA as a discrete condition. This definition was not intended as a classification structure but has been used as such by some.

However, the difficulty in classification in vasculitis is the complexity and heterogeneity of the diseases; this is particularly true for MPA and WG. Both MPA and WG have many similar features that can include pulmonary capillaritis, an indistinguishable renal biopsy, and the presence of ANCA. It has been stated by some that sinus and nasal involvement can be present in MPA[7], but others believe that the presence of upper respiratory tract involvement effectively excludes it[8]. Significantly, both these 2 AAV may run different courses, with WG tending to run a much more relapsing course than MPA and having some unique respiratory features such as subglottic/bronchial stenosis and orbital pseudotumors that can be active locally. Recent trials and longitudinal databases have found it necessary to modify the ACR criteria and to use the CHCC nomenclature conjointly, which illustrates the weakness in the current classification system.

Sorensen, *et al* have attempted to apply the CHCC nomenclature along with certain surrogate markers (proteinuria and hematuria, angiographic evidence of aneurysm or stenoses, radiological evidence of pulmonary infiltrates or cavitations, bloody nasal discharge and/or crusting/chronic sinusitis/otitis/mastoiditis/acute hearing loss) as diagnostic criteria of WG and MPA, in addition to other primary vasculitides[9]. Lane, *et al* found, by applying them to a group of their patients with primary vasculitis, the Sorensen criteria for WG may be useful (with the modifica-

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tion of including patients with tissue eosinophilia or low peripheral eosinophilia) but not for MPA[10]. However, they did recognize that the criteria proposed by Sorensen, *et al* were designed as diagnostic criteria rather than classification criteria. Watts, *et al* undertook a consensus method to develop a 4-step algorithm to categorize patients into a single classification of either WG, MPA, CSS, or PAN[11]. Using a known cohort, they put great weight into first identifying those patients with WG using the ACR and CHCC criteria along with surrogate markers for WG (upper airway — bloody nasal discharge/chronic sinusitis/saddle nose deformity/retro-orbital mass/subglottic stenosis). MPA was excluded if there were any upper airway surrogate markers. They concluded that the algorithm provided excellent face validity and inter-observer reliability.

The European League Against Rheumatism (EULAR) recently published "points to consider" for the development of classification and diagnostic criteria in systemic vasculitis, underlining that the terms disease definition, classification, and diagnostic criteria were often mistakenly used interchangeably[12]. They conclude that there is a need for development of future definitions and validated diagnostic and classification criteria.

Linder, *et al*[1] partly address the intricacy of classification of WG and MPA and the EULAR "points to consider" with the use of an ANN. The strength of their article is the high number of patients that are included in the study and use of an independent validation cohort. They studied 23 parameters and using a computerized non-directed classification software, they found that using an ANN might be a more efficient way to distinguish between MPA and WG than the ACR, CHCC, or Sorensen criteria. Ultimately though, they rely on 4 main parameters (pulmonary nodules and involvement of the nose, sinuses, and ears) to distinguish the 2 disorders, which in reality remain clinically debatable. The definition of nose/sinus involvement remains subjective. What really is nose or sinus involvement and how are they defined? If present in MPA, they are likely not significant to patient- or physician-reported outcomes or treatment decisions, whereas for WG, erosive and crusting nasal lesions are significant.

The importance of distinguishing WG and MPA vasculitis is also only partly addressed. Whether such a differentiation between the 2 has any overt therapeutic influence clinically remains debated, as opposed to WG/MPA versus CSS. Outcomes were not looked at in the report by Linder, *et al*, but future clinical trials will have to study this important point, as the ANCA type (proteinase-3 vs myeloperoxidase) has been suggested to have prognostic implications, possibly to a greater extent than does the differentiation between MPA and WG[13,14]. We await the report of a large multicenter study to develop a validated set of diagnostic criteria that will influence therapeutic outcomes.

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