The Histopathological Classification of ANCA-associated Glomerulonephritis Comes of Age

The antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are multisystem disorders characterized by necrotizing inflammation of blood vessels, and are associated with an untreated mortality of around 90%¹. These disorders include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal limited vasculitis (RLV)².

Renal manifestations of AAV, which commonly include rapidly progressive glomerulonephritis, result in endstage renal failure or death in 40% of patients³. Despite the introduction of newer biological therapies, treatment continues to cause significant morbidity and mortality, and has been associated with more deaths at 1 year than the disease process itself⁴. A major challenge in the management of patients with renal AAV remains the identification of factors, both clinical and histopathological, which are predictive of response to therapy, risk of relapse, and renal and patient survival. Recognition of such factors would aid the implementation of patient-tailored therapy.

Clinical factors that have been demonstrated to correlate with the prognosis of renal AAV include age, with increasing age correlating with poorer outcome; and presenting creatinine, with a better prognosis in patients presenting with a lower serum creatinine⁵. These clinical factors cannot, however, be considered in isolation. The “gold standard” for diagnosis of renal AAV remains the renal biopsy. A number of histopathological factors have been reported to correlate with renal prognosis⁶. A higher percentage of normal glomeruli has been well established as being predictive of better renal outcome^{6,7}. A greater percentage of cellular crescents has been reported as predictive of a better response to therapy⁷. Increasing percentage of tubular atrophy and glomerular sclerosis have been associated with poorer renal outcomes⁷.

In 2010, an international working group of renal pathologists proposed a histological classification for renal AAV

based on these findings. This classification divides patient biopsies into 4 classes: focal (> 50% normal glomeruli), crescentic (> 50% cellular crescents), sclerotic (> 50% sclerotic glomeruli), and mixed (any other combination)⁸. A validation study was carried out using the biopsies of 100 patients enrolled in various European Vasculitis Study Group trials⁸. This confirmed the prognostic value of the classification system over a 1- and 5-year followup period, with patients in the focal class experiencing the best outcomes in terms of estimated glomerular filtration rate (eGFR) and renal survival followed in order by those in the crescentic, mixed, and sclerotic classes⁸.

A number of validation studies have since been published worldwide. These studies have varied in size and, to our knowledge, 7 studies have included over 100 biopsies^{9,10,11,12,13,14,15,16}. The first 6 of these studies have been summarized in publications by Rahmattulla, *et al*¹⁷ and van Daalen, *et al*¹⁸. The largest and most recent was carried out by Bjørneklett, *et al*¹⁶ in Norway, and included 250 patients with AAV. The study agreed with the general consensus that the classification is a useful predictor of renal outcome, with patients in the focal class experiencing the best and patients in the sclerotic class the worst renal outcomes¹⁶. There was no significant difference in renal outcome between the mixed and crescentic classes. Bjørneklett, *et al* also calculated the prognostic accuracy of the classification system using receiver-operator curve characteristics, and determined it to be of moderate quality¹⁶.

In this issue of *The Journal*¹⁹, Chen, *et al* report the results of their own validation study and in addition, the results of a metaanalysis they performed to assess the predictive values of the histopathological classification system. A retrospective analysis was carried out on 186 patients with ANCA-associated glomerulonephritis in Shanghai, China. As expected for this part of the world, the majority of patients (154; 83%) had a diagnosis of MPA. There were 10 patients with GPA, 4 with EGPA, and 18 with

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RLV. Of the biopsies, 24.7% were classified as focal, 19.4% as crescentic, 19.4% as sclerotic, and the remainder (36.6%) as mixed. Interestingly, the majority of patients in the study who were proteinase 3 (PR3)-ANCA-positive were included in the focal class. This is consistent with the recent publication from Cornec, *et al*, which reported less severe renal involvement in PR3-positive patients than those with MPO positivity²⁰.

Tubulointerstitial injury was also scored and assessed by class. Consistent with previous studies, the focal class had the least and the sclerotic class the most tubulointerstitial injury. There were statistically significant differences across the groups with regards to serum creatinine and proteinuria, with the lowest serum creatinine and level of proteinuria detected in patients in the focal class, followed by the crescentic, mixed, and sclerotic classes, respectively.

The best renal survival was in the focal class and the worst in the sclerotic class up to around 100 months. There was no significant difference in renal survival between the crescentic and mixed classes up to this timepoint. These findings are consistent with previous studies. At around 140 months, it seems from the survival curve that there was a poorer prognosis in the mixed than the sclerotic class; however, as discussed by the authors, this may be because of the longer followup of patients in the mixed class.

Patient survival by class at 1 year followed a similar pattern to that of renal survival, but this was lost on followup. The lack of a consistent relationship between class and patient survival is consistent with the literature, including the 250 patients in Bjørneklett, *et al*'s study, for whom there was no difference in patient survival across the classes at 1 year¹⁶. This could be (as explained by the authors) due to the multifactorial characteristic of patient survival in AAV, and the fact that morbidity and mortality cannot be solely attributable to renal involvement. In addition, worldwide differences in the efficiency of renal replacement therapy provided could contribute to variations in patient survival across the validation populations.

Chen, *et al* also carried out an interesting metaanalysis. With the varying numbers of patients in previous validation studies, and the difficulties of carrying out multivariate analysis on small numbers, combining the results and carrying out a metaanalysis of these studies was extremely useful. Their metaanalysis included 1601 patients from 16 different worldwide studies and confirmed the outcome in the different classes as per the 2010 classification, with the best outcome in the focal class, intermediate outcomes in the crescentic and mixed classes, and the worst outcome in the sclerotic class. Results were similar for both the Eastern and Western populations, with the implication that the classification can be applied across different ethnic groups.

As discussed by the authors of the paper, the study is limited by its retrospective design and variations between centers with regard to eGFR assessment, as well as the avail-

ability of treatment data and Birmingham Vasculitis Activity Score. Despite these limitations, this is the second largest validation study and the only metaanalysis of the various validation studies, and adds much weight to the current literature.

The histopathological classification has truly come of age and become widely accepted in populations across the globe, especially for patients classified as focal or sclerotic. Because there are discrepancies as to whether mixed or crescentic classes have a better prognosis, and as outcomes are similar in many series, there is some argument to consider combining these 2 classes. Further prospective studies are needed to accurately assess the response to different types of treatment in the different classes, particularly the crescentic and mixed classes.

There are successful histopathological classification systems in clinical use for diabetic and immunoglobulin A nephropathy. Six years on from the initial proposal of the classification for renal AAV and many validation studies later, perhaps we are one step closer to achieving the goal of using the classification system together with clinical features to provide patients with a realistic prognosis and to tailor their therapy accordingly. This would represent a major advance in the management of this disorder.

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