Classifying and predicting outcomes in ANCA-associated glomerulonephritis

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Histopathological classification systems have been applied to a number of renal conditions, to allow clinicians to make useful predictions regarding patient and kidney outcome and to aid in comparing similar lesions across clinical trials and cohorts. This has been successful for lupus nephritis, focal segmental glomerulosclerosis and more recently for both IgA disease (the Oxford classification) [1] and anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) [the Berden or European vasculitis study group (EUVAS) classification] [2]. In IgA disease, numerous follow-up studies have now been published validating the classification, in different age groups and across different countries and ethnicities. The paper in Nephrology Dialysis Transplantation by Chang et al. [3] attempts to re-evaluate the Berden/EUVAS ANCA-associated glomerulonephritis classification in a Chinese population, and it therefore represents an important first step in assessing the general utility of the classification.

AAV frequently causes a focal segmental necrotizing glomerulonephritis, and renal involvement exerts a profound influence on patient morbidity and mortality. Indeed, disease severity in AAV is mostly assessed by the severity of renal involvement. A significant proportion of patients present with advanced renal failure and require dialysis. With modern treatment protocols, ~50–60% of those dialysis-dependant patients who survive the first year recover independent renal function. Previous studies by EUVAS investigators had demonstrated the prognostic value of the renal biopsy by defining lesions that were associated with favourable renal outcome and treatment response. They demonstrated that those patients recovering independent renal function had less glomerulosclerosis, arteriosclerosis and tubular atrophy while they were more likely to have received plasmaphaeresis as adjunctive treatment [4]. Additionally, by combining presenting renal function measurement (estimated glomerular filtration rate; eGFR) with histological parameters, they devised better predictors of renal function at 18 months than eGFR alone [5]. They found that the most inflammatory glomerular lesions, containing fibrinoid necrosis or cellular crescents, were the ones most likely to respond to treatment, being associated with the greatest improvement in renal function following 18 months of follow-up. By contrast, established sclerotic glomerular lesions were most predictive of final renal function at 18 months. These findings relied on assessment of cohorts who were treated in a relatively homogeneous manner (recruited from various EUVAS clinical trials), with pathologists who had demonstrated high degrees of concordance in defining the histopathological lesions [6]. However, despite the prognostic value of the biopsy, a formal histological classification system had been lacking, until recently.

The Berden/EUVAS histopathological classification of AAV was proposed in 2010 [2] by an international group of renal pathologists and was validated in 100 patients from two large multicentre European vasculitis trials (CYCAZAREM and MEPEX, which recruited patients with ANCA-associated glomerulonephritis of differing severities). Renal histology from patients originating in nine European countries, with at least 1-year follow-up, and including both MPO-ANCA and PR3-ANCA were analysed. Importantly, patients with other co-morbid conditions, such as concurrent anti-glomerular basement membrane disease, were excluded. The classification system was based on glomerular pathology assessed by light microscopy. Interestingly, tubulointerstitial fibrosis and tubular atrophy, generally predictive of long-term renal outcomes for many diseases, did not add any prognostic value and were thus excluded. The key aspect of the classification was that it was simple and was defined by four separate glomerular categories: focal, crescentic, mixed and sclerotic. Biopsies in the focal category were defined by having >50% normal glomeruli. Crescentic biopsies were those with ≥50% glomeruli with cellular crescents. Mixed referred to biopsies having <50% normal, <50% crescentic and <50% globally sclerotic glomeruli. The last category was sclerotic, which included biopsies with ≥50% globally sclerotic glomeruli. The biopsies included in this classification were all pauci-immune and contained at least 10 glomeruli, which are clearly important standards for applying the classification. The validation study was able to demonstrate that the different classes correlated with the
severity of renal impairment, assessed by eGFR during prolonged follow-up, with those patients with focal lesions having the best renal outcome, followed by crescentic, mixed and, lastly, sclerotic. Additionally, those patients with a sclerotic classification were at highest risk of death within the first year of diagnosis. Thus, a classification was established which could in the future allow biopsies from different centres to be compared directly and provide some insight into renal prognosis based on the renal histology, which is clearly of value in counselling patients. However, whether it should be used as a means of deciding on treatment, remained to be clarified, bearing in mind that the validation cohort of patients was of limited size and all subjects were treated in a similar manner in EUVAS studies, with induction therapy consisting of cyclophosphamide and corticosteroids. It is reasonable to assume that without therapy or with different, perhaps, less efficacious therapy to that used in the EUVAS studies, crescentic or focal lesions would not be associated with such good outcome but would lead to progressive renal failure. Recent data suggest that AAV patients in clinical trials may differ significantly with regards to their demographics and outcomes from those treated outside trials [7], with trial patients being older, having worse renal disease and higher early mortality. Clearly, this has to be borne in mind when extrapolating results of trials and prognostic tools derived from them to daily clinical practice. Therefore, validating the classification in other cohorts treated in different ways would be important to confirm that the classification could be widely applied.

The article by Chang et al., in this issue of Nephrology Dialysis Transplantation, evaluated the Berden/EUVAS classification using a Chinese population of patients with AAV. This was a retrospective study of renal biopsies from a large single referral centre, receiving patients from several areas within China. There were several differences between this Chinese cohort and the European patients in which the original classification was validated. The majority of the Chinese patients (89.3%) were positive for MPO-ANCA, unlike the European patients who were split equally between MPO-ANCA and PR3-ANCA, which is significant as the renal outcome for MPO-ANCA vasculitis differs from that of PR3-ANCA vasculitis [8]. Treatment regimens also differed between the two cohorts. In the Chinese population, cyclophosphamide therapy was delayed for 10–14 days after the initiation of corticosteroids unlike the European cohort, in which both were started together, and was continued every 3 months in half of the surviving cohort. Furthermore, fewer Chinese patients (5%) received plasma exchange, previously shown to have a significant benefit on renal function in the first year of follow-up. Therefore, it is conceivable that some mature active lesions may have failed to resolve or progressed to a more sclerotic phenotype, during the induction period. Finally, the Chinese cohort all came from one centre, whereas the Berden/EUVAS cohort was recruited from various European centres. The results in the Chinese cohort were broadly similar to the Berden/EUVAS study, in that the worst renal outcome was seen in the sclerotic group, and tubulointerstitial atrophy was not predictive of end-stage renal failure; however, a significant difference was that those patients with a crescentic classification had a worse outcome than those with a mixed renal classification. This may be a reflection of differences in ethnicity, the delayed initiation of cyclophosphamide therapy, the omission of plasmapheresis in some patients as well as the higher proportion of patients with MPO-ANCA. A previous study of Chinese patients demonstrated that those patients with MPO-ANCA-associated granulomatosis with polyangiitis (GPA, formerly Wegener’s) had more severe chronic lesions than those patients with PR3-ANCA-associated disease, exhibiting more fibrous crescents, interstitial fibrosis and tubular atrophy [9]. In addition, geographical variations in the incidence and outcomes of AAV have been described in different patient cohorts. For example, in a retrospective analysis of patients with microscopic polyangiitis from Korea, the clinical outcome seemed to be better compared to that reported in the (European American) literature [10], while in a cohort of patients from south-eastern USA, African-American race was a predictor of treatment resistance [11], demonstrating the potential importance of environment or ethnicity on outcome [12]. That the genetic background plays an important role in mediating some of these differences is highlighted by recent studies identifying different human leukocyte antigen (HLA) associations in Chinese and European populations [13, 14].

Chang et al. suggest that differences in outcome of the mixed category compared to Berden/EUVAS cohort were explained by their patients having fewer sclerotic glomeruli and a higher proportion of normal glomeruli. But this perhaps suggests that the mixed classification may be too heterogeneous to be of widespread prognostic use, while the more polarized biopsies may be of more utility in defining outcomes. However, apart from the mixed group doing better, the crescentic group did worse in the Chang compared to the Berden/EUVAS cohorts at 5 years.

The article by Chang highlights some important points regarding the histological classification of AAV in different patient populations. Significant variables existed between the group reported by Chang and the original Berden/EUVAS cohort, including the treatment regimens; however, the differences in autoantibody and clinical phenotype raise interesting questions about the application of a European histological classification to other populations with different disease characteristics. So, should we now use the classification to guide treatment? Not yet. Clearly, the sclerotic group tend to do badly in both these cohorts, and the focal group tend to do the best, having mostly normal glomeruli, however, the outcome for crescentic and mixed groups varies sufficiently for there to be some doubt about basing treatment plans on the currently available data. Moreover, even with a poor outcome in the sclerotic group as a whole, the 1- and 5-year renal survival following treatment was 50%. This suggests that for a significant number of patients, treatment stabilizes renal function and is beneficial. One would want to see these small cohort studies replicated in larger and more diverse groups of patients, perhaps incorporating patients from the six additional worldwide randomized vasculitis studies (RAVE, RITUXVAS, IMPROVE, REMAIN, MYCYC and PEXIVAS) as well as including some treated outside of clinical trials. This re-evaluation by Chang represents the first step and we should encourage further investigators to apply the classification to their AAV cohorts and report the clinical outcomes.
There is no doubt that the classification represents an important scaffold on which to build a greater understanding of how pathology translates to clinical end points in AAV.

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