On the pathogenesis and clinical outcome of ANCA-associated vasculitis

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Chapter IV

Histopathological classification of antineutrophil cytoplasmic antibody-associated glomerulonephritis: an update

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Abstract

Purpose of review

This review discusses the findings of studies validating the histopathological classification of antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, which was devised in 2010 by an international working group of pathologists and nephrologists in collaboration with the European Vasculitis Society.

Recent findings

So far, eight studies have validated the histopathological classification of ANCA-associated glomerulonephritis. The studies came from Japan, China, Australia, the United States, the Netherlands, and Turkey. These validation studies confirmed that the histopathological classification of ANCA-associated glomerulonephritis is of predictive value for renal outcome. This was especially the case for patients with either a focal or sclerotic-class renal biopsy, whereas the crescentic and mixed classes showed different results in the validation studies. These differences could be due to differences in patient populations or therapy, inter-rater reliability and lack of inclusion of tubulointerstitial lesions in the classification. Therapy is known to influence renal outcome, but due to the retrospective design of the to-date performed validation studies, this parameter could not be fully accounted for in these validation studies. Inter-rater reliability among three histopathologists was investigated in one study and was moderate.

Summary

The histopathological classification of ANCA-associated glomerulonephritis predicts renal outcome during follow-up, especially in patients with a focal or sclerotic-class renal biopsy. A large international validation study is currently being performed.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a systemic autoimmune disease affecting small and middle-sized blood vessels[1•]. Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are the major clinical syndromes of ANCA-associated vasculitis, whereas renal limited vasculitis (RLV) and eosinophilic GPA (EGPA) occur less frequently[2]. Approximately 90% of ANCA-associated vasculitis patients have circulating antibodies against proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA. These antibodies probably play a pathogenic role in the disease process and have recently been shown to represent genetically distinct subsets of patients with ANCA-associated vasculitis[3••, 4•, 5••, 6, 7••]. Renal involvement is a common and severe feature of ANCA-associated vasculitis, leading to end-stage renal failure (ESRF) and even death in a considerable number of patients[8-10].

ANCA-associated glomerulonephritis may show a variety of lesions, of which crescentic and focal necrotizing glomerulonephritis are the most prominent[11]. Clinicopathologic studies have demonstrated that the presence or absence of specific pathologic lesions in the renal biopsy is of important prognostic value for renal outcome, independently of baseline estimated glomerular filtration rate (eGFR). A high percentage of normal glomeruli is the strongest histological predictor of a favorable renal outcome; a high percentage of globally sclerotic glomeruli is associated with a worse renal outcome[12–14]. The percentage of cellular crescents is associated with recovery of renal function, irrespective of baseline eGFR[13]. Tubulointerstitial lesions, especially tubular atrophy, are associated with a worse renal outcome[12–14].

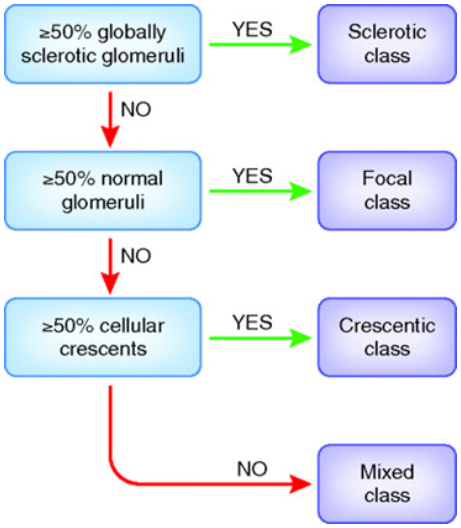
In 2010, the histopathological classification of ANCA-associated glomerulonephritis was devised by an international working group of pathologists and nephrologists in collaboration with the European Vasculitis Society (EUVAS)[15]. This review discusses the findings of studies validating the histopathological classification of ANCA-associated glomerulonephritis.

The histopathological classification of antineutrophil cytoplasmic antibody associated glomerulonephritis

The histopathological classification of ANCA-associated glomerulonephritis is built around glomerular pathology and encompasses four classes: focal, crescentic, mixed, and sclerotic-class renal biopsies[15]. The focal class is defined by the predominance of normal glomeruli (≥50%), the crescentic class by the predominance of cellular crescentic glomeruli (≥50%), and the sclerotic class by the predominance of globally sclerotic glomeruli (≥50%). The mixed class represents a heterogeneous glomerular phenotype in which no glomerular

feature predominates. A flowchart through which renal biopsies can be evaluated according to this classification system is depicted in Fig. 1. Tubulointerstitial lesions were not included in the classification system because these lesions did not improve the predictive value of the classification system in a first validation study incorporated in the publication by Berden *et al.*[15], and only increased its complexity.

Figure 1. Classification system flowchart



Biopsies are scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli and cellular crescentic glomeruli. Biopsies that do not fit into one of these classes will automatically be included in the mixed class. Reprinted, with permission from the *Journal of the American Society of Nephrology*.[15]

Baseline characteristics of the 100 patients of European descent included in the validation study incorporated in the publication by Berden *et al.* are depicted in Table 1. The phenotypical order of focal, crescentic, mixed, and sclerotic-class renal biopsies corresponded to the eGFR at baseline and at 1 and 5-year follow-up (Table 2). In addition, the histopathological classification and the baseline eGFR were the only independent predictors for eGFR at both 1 and 5 year follow-up in a multivariable analysis taking patient age, treatment, baseline eGFR, and the histopathological classification of ANCA-associated glomerulonephritis into account. The percentage of patients who developed ESRF increased with ascending class.

Table 1. Baseline characteristics of the patients included in the validation studies.

	Berden *et al.*[15]	**Iwakiri** *et al.*[16]	**Togashi** *et al.*[17]	**Muso** *et al.*[18]	**Chang** *et al.*[19]	**Hilhorst** *et al.*[20]	**Ford** *et al.*[21]	**Ellis** *et al.*[22]	**Unlu** *et al.*[23]
Number of patients	100	102	54	87	121	164	120	76	141
Age (median[a] or mean[b]; (SD[c] or range[d]))	62.6[a] (20.4 - 80.7[d])	66.3[b] (±11.3[c])	66.9[b] (36-85[d])	63.0[a] (17–85[d])	57.2[b] (15–81[d])	61.0[b] (±14.6[c])	66[b] (8-87[d])	58 (NR)	49.09[b] (7 – 80[d])
Male (n; (%))	54 (54)	54 (53)	28 (52)	37 (43)	64 (53)	113 (69)	72 (60)	43 (57)	80 (57 %)
Period	1995 - 2002	2000 - 2010	1990 - 2010	2001 - 2010	1997 - 2010	1979 - 2011	1993 - 2011	1995 - 2011	NR
Geographical area	Europe	Japan	Japan	Japan	China	Netherlands	Australia	US	Turkey
Number of glomeruli per biopsy (mediana or mean[b]; (rangec or SD[d]))	14.8[a] (10.0-49.0)[c]	19.0[b] (10-61)[c]	25.8[b] (10-64)[c]	26.5[a] (10-98)[c]	25.7[b] (±10.4)[d]	NR	22[a] (±14)[d]	NR	18.5[b] (7-60)[c]
Diagnosis						NR	NR		
GPA (n; (%))	39 (39)	3 (3)	28 (52)	0 (0)	49 (40.5)			43 (57)	55 (39)
MPA (n; (%))	61 (61)	97 (95)	25 (46)	87 (100)	68 (56.2)			31 (41)	20 (14)
EGPA (n; (%))	0 (0)	2 (2)	1 (2)	0 (0)	0 (0)			0 (0)	0 (0)
RLV (n; (%))	0 (0)	0 (0)	0 (0)	0 (0)	4 (3.3)			3 (3)	39 (28)
Unknown (n; (%))	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			0 (0)	27 (19)
ANCA-subtype									
PR3-ANCA (n; (%))	45 (45)	5 (5)	0 (0)	0 (0)	13 (11)	83 (51)	28 (23)**	30 (39)**	60 (43)**
MPO-ANCA (n; (%))	47 (47)	86 (84)	54 (100)	76 (87)	108 (89)	81 (49)	75 (63)**	32 (42)**	61 (43)**
Double positive (n; (%))	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	17 (14)	0 (0)	5 (4)
Negative (n; (%))	2 (2)	11 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	14 (18)	25 (18)
Missing (n; (%))	2 (3)	0 (0)	0 (0)	11 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 1. Baseline characteristics of the patients included in the validation studies. (Continued)

	Berden *et al.*[15]	Iwakiri *et al.*[16]	Togashi *et al.*[17]	Muso *et al.*[18]	Chang *et al.*[19]	Hilhorst *et al.*[20]	Ford *et al.*[21]	Ellis *et al.*[22]	Unlu *et al.*[23]
Histopathological class									
Focal class (n; (%))	16 (16)	46 (45)	17 (31)	40 (46.0)	33 (27.3)	81 (49)	34 (28)	20 (26)	31 (22)
Crescentic class (n; (%))	55 (55)	32 (31)	8 (15)	7 (8.0)	53 (43.8)	43 (26)	33 (28)	18 (24)	69 (49)
Mixed class (n; (%))	16 (16)	18 (18)	19 (35)	26 (29.9)	24 (19.8)	39 (24)	33 (28)	27 (36)	29 (21)
Sclerotic class (n; (%))	13 (13)	6 (6)	10 (19)	14 (16.1)	11 (9.1)	1 (1)	20 (17)	11 (14)	12 (9)

NR, not reported; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; RLV, renal limited vasculitis; ANCA, Antineutrophil cytoplasmic antibodies; PR3, against proteinase 3; MPO, myeloperoxidase. amedian; bmean; crange; dSD; ** C-ANCA and p-ANCA were reported instead of PR3-ANCA and MPO-ANCA, respectively.

Table 2. Outcomes of the validation studies performed up to date.

	Berden *et al.*[15]	Iwakiri *et al.*[16]	Togashi *et al.*[17]	Muso *et al.*[18]	Chang *et al.*[19]	Hilhorst *et al.*[20]	Ford *et al.21*	Ellis *et al.*[22]	Unlu *et al.*[23]
Renal function at baseline	*Mean eGFR (±SD)*	*Median eGFR (IQR)*	*Mean eGFR (±SD)*	*Mean serum creatinine (±SD)*	*Mean eGFR (±SD)*	*Mean eGFR (±SD)*	*Median eGFR (range)*	*Mean eGFR ± SD*	*NR*
Focal class	56.4 (36.8)	38.1 (22.5–57.4)	49.1 (26.2)	1.51 ± 1.49	55.3 (39.9)	39.3 (29.4)	31 (3.4-128)	50.2 (63.4)	
Crescentic class	11.2 (10.9)	12.0 (7.1–19.7)	12.4 (5.1)	2.42 ± 1.67	37.8 (63.7)	16.8 (14.7)	8 (2.5-108)	16.4 (10.3)	
Mixed class	15.4 (16.2)	16.5 (8.7–31.6)	17.4 (9.6)	3.37 ± 3.17	17.9 (17.7)	24.3 (19.5)	21 (5-60)	26.5 (23.3)	
Sclerotic class	10.8 (9.5)	12.4 (9.8–27.4)	13.3 (4.9)	7.52 ± 4.92	8.3 (8.1)	14.6	10 (1.9-45)	26.5 (15.0)	
eGFR 1-year	*Mean (±SD)*	*Median (NR)*	*Mean (±SD)*	*NR*	*NR*	*Mean (±SD)*	*Median (range)*	*Mean (±SD)*	*NR*
Focal class	63.3 (23.7)	45.7	52.9 (11.4)			54.5 (20.9)	42 (67.2-104)	70.8 (29.6)	
Crescentic class	32.8 (20.8)	24.5	25.5 (6.3)			41.0 (21.1)	26 (4.6-95)	42.1 (22.4)	
Mixed class	24.5 (21.4)	26.0	31.3 (20.4)			36.7 (18.6)	34 (6.1-102)	37.8 (19.8)	
Sclerotic class	16.6 (15.9)	16.9	15.5 (4.1)			-	8 (3.3-41)	32.7 (15.3)	

Table 2. Outcomes of the validation studies performed up to date. (Continued)

	Berden *et al.*[15]	**Iwakiri** *et al.*[16]	**Togashi** *et al.*[17]	**Muso** *et al.*[18]	**Chang** *et al.*[19]	**Hilhorst** *et al.*[20]	**Ford** *et al.*[21]	**Ellis** *et al.*[22]	**Unlu** *et al.*[23]
eGFR at 2- or 5-year follow-up	*5-year*	*NR*	*2-year*	*NR*	*NR*	*2-year*	*NR*	*2-year*	*NR*
Focal class	65.6 (20.3)		60.9 (17.6)			53.5 (20.8)		76.7 (29.5)	
Crescentic class	39.5 (22.5)		33.9 (9.4)			38.8 (22.3)		41.7 (18.1)	
Mixed class	29.9 (16.7)		29.1 (9.2)			38.3 (16.0)		42.9 (21.6)	
Sclerotic class	20.4 (15.1)		7.4 (3.4)			-		37.8 (16.8)	
Renal survival at 1-year follow-up		*NR*				*NR*	*NR*	*NR*	*NR*
Focal class (%)	93		2	100	100				
Crescentic class (%)	84		22	86	73				
Mixed class (%)	69		11	96	83				
Sclerotic class (%)	50		33	35	29				
Renal survival at 2- or 5-year follow-up	*5-year*	*NR*	*NR*	*5-year*	*5-year*	*5-year*	*NR*	*NR*	*NR*
Focal class (%)	93			100	93	91			
Crescentic class (%)	76			86	60	64			
Mixed class (%)	61			96	72	69			
Sclerotic class (%)	50			29	29	-			
Development of ESRF or death	*ESRF*	*ESRF*	*ESRF*	*NR*	*ESRF*	*NR*	*ESRF or death*	*NR*	*ESRF*
Focal class (n; (%))	1 / 14 (7%)	2 / 46 (4.3)	2 / 46 (4)		3 / 33 (9)		11 / 34 (32)		4 / 31 (13)
Crescentic class (n; (%))	11 / 45 (45%)	9 / 32 (28)	9 /32 (28)		15 / 53 (28)		14 / 33 (42)		20 / 69 (29)
Mixed class (n; (%))	6 / 13 (46%)	8 / 18 (44)	8 / 18 (44)		4 / 24 (17)		13 / 33 (39)		10 / 29 (34)
Sclerotic class (n; (%))	7 / 10 (70%)	4 / 6 (67)	4 / 6 (67)		8 / 11 (73)		16 / 20 (80)		8 / 12 (67)

eGFR, estimated glomerular filtration rate; ESRF, end-stage renal failure; IQR, interquartile range; NR, not reported.

Validation of the histopathological classification of antineutrophil cytoplasmic antibody-associated glomerulonephritis

So far, eight studies from Japan, China, Australia, the United States, the Netherlands, and Turkey have validated the histopathological classification of ANCA-associated glomerulonephritis[16–23]. Five of these studies included more than 100 patients[16,19–21,23]. The distributions of diagnoses and ANCA serotype varied and are depicted in Table 1. We will review these validation studies below.

Validation of the classification system in the Asian population

Four validation studies came from Asia, three of which were from Japan and one from China[16–19]. All these studies had a predominance of MPO-ANCA-positive patients. The diagnosis of GPA or MPA was equally distributed in two studies[17,19]. Two other studies consisted of 95 and 100% of MPA patients, respectively[16,18]. At baseline, eGFR levels in all four studies showed a similar distribution over the four classes, with the best eGFR levels for patients with a renal biopsy classified as focal class and worst levels for patients with a renal biopsy classified as sclerotic class. In all these studies, patients with renal biopsies classified as crescentic and mixed class showed intermediate eGFR levels. The outcome with respect to renal function during follow-up in relation to the histopathological class varied somewhat amongst the studies as discussed below in detail. This may have been influenced by the different end-points of the studies.

Iwakiri *et al.*[16] reported a significant relationship between the four histopathological classes and eGFR at baseline and 1-year follow-up, which was greatly determined by a relatively good eGFR in patients with a focal-class renal biopsy (Tables 1 and 2). A renal survival curve over 120 months showed a distribution pattern similar to that of the validation study in the publication by Berden *et al.*, with patients with focal and sclerotic-class renal biopsies having the best and worst renal survival, respectively. There was no significant difference in the eGFR of patients with renal biopsies classified as crescentic or mixed class. The authors comment that discrimination between these two classes was hindered because, in their cohort, both the proportion of normal and sclerotic glomeruli was higher in the mixed class than in the crescentic-class renal biopsies.

Togashi *et al.*[17] reported that the phenotypical order of focal, crescentic, mixed and sclerotic class corresponded to the severity of renal function impairment at baseline and 1 and 5-year follow-up in a cohort of Japanese MPO-ANCA-positive patients (Tables 1 and 2). However, at all time points, the eGFR of patients with crescentic and mixed-class renal biopsies was similar. Overall, renal survival was relatively good with only five of the 54 patients developing ESRF during the 5-year follow-up. Of the patients developing ESRF, two patients had a crescentic and three patients had a sclerotic-class renal biopsy.

Muso *et al.*[18] focused on baseline eGFR and the development of ESRF in a Japanese cohort (Tables 1 and 2). The phenotypical order of focal, crescentic, mixed, and sclerotic-class renal biopsies corresponded to the order of severity of renal function impairment at baseline. At 5-year follow-up, the risk of ESRF development was not increased in patients with focal and mixed-class renal biopsies. Patients with a renal biopsy classified as sclerotic had a highly increased risk to develop ESRF. Patients with focal, mixed and crescentic-class renal biopsies had similar renal survival curves, particularly after 10 months of follow-up.

Chang *et al.*[19] validated the histopathological classification of ANCA-associated glomerulonephritis in a Chinese cohort (Table 1). The phenotypical order of focal, crescentic, mixed, and sclerotic-class renal biopsies corresponded to the order of severity of renal function impairment at baseline (Table 2). Renal survival was best for patients with a focal-class renal biopsy and worst for patients with a sclerotic-class renal biopsy. Comparing patients with a mixed and crescentic-class renal biopsy, 5-year renal survival was 72 and 60%, respectively. The authors stated that the patients with a mixed-class ANCA-associated glomerulonephritis in this cohort had relatively milder lesions than patients with a mixed-class ANCA-associated glomerulonephritis in the Berden *et al.* cohort, with more normal glomeruli, fewer sclerosed glomeruli and fewer glomeruli with fibrous crescents. In addition, tubulointerstitial lesions were not independent predictors of ESRF in a multivariable analysis taking the histopathological classification of ANCA-associated glomerulonephritis into account.

Summarizing the data from the Asian studies, we conclude that all studies show a clear tendency for eGFR at baseline being related to the phenotypical order of focal, crescentic, mixed, and sclerotic-class renal biopsies. Patients with a focal-class renal biopsy had the best eGFRs and patients with a sclerotic-class renal biopsy had the worst eGFRs. Follow-up data varied in time periods and whether ESRF or eGFR was chosen as the end-point. It may be tentatively concluded that there was no clear-cut difference in the outcome of patients with crescentic and mixed-class renal biopsies. In some studies, there was a tendency for patients in the mixed-class to have a slightly better renal outcome than patients in the crescentic class. The Asian studies differed from the studies in the Caucasian population which we discuss below, in terms of ANCA-serotype distribution, diagnosis distribution, and a patient population from the Asian race.

Validation of the classification system in the Caucasian population

The largest validation study reported so far came from a Dutch cohort consisting of 164 patients with an equal distribution of PR3-ANCA and MPO-ANCA patients (Table 1)[20]. There was only one patient with a renal biopsy classified as being in the sclerotic class, therefore this class could not be part of the analysis. The histopathological classification of ANCA-associated glomerulonephritis

predicted eGFR at both 1 and 2-year follow-up (Table 2). At both time points, eGFR differed significantly between patients with a focal and crescentic-class renal biopsy, and between patients with a focal and mixed-class renal biopsy, but not between patients with a crescentic and mixed-class renal biopsy. In addition, 5-year renal survival was significantly higher in patients with a focal-class renal biopsy than in patients with a crescentic or mixed-class renal biopsy, whereas renal survival in these two latter groups was similar. Subdividing the crescentic and mixed-class renal biopsies on the basis of more or less than 25% normal glomeruli in the renal biopsy showed that patients with more than 25% normal glomeruli had a significantly better renal survival.

A recently published study by Ford *et al.*[21] is the only study so far which investigated the inter-rater reliability of the classification system, showing variability among three histopathologists scoring 145 renal biopsies (k=0.46). Good agreement was found for classifying the sclerotic class (k=0.70), but only moderate agreement for classifying the focal, crescentic, and mixed classes (k=0.47, k=0.23, and k=0.51, respectively). There was no significant difference in ANCA subtype between patients in the different classification groups (Table 2). Most tubulointerstitial lesions were found in the sclerotic class. Renal function at presentation was best in patients with a focal or mixed-class renal biopsy, and worst in patients with a sclerotic or crescentic-class renal biopsy. At 1-year follow-up, eGFR declined in the phenotypical order of focal, crescentic, mixed, and sclerotic-class renal biopsies. Patients with a sclerotic-class renal biopsy had a significantly increased risk of ESRF development or death compared with patients with a focal, crescentic, or mixed-class renal biopsy. When taking ESRF development or death as outcome, there was no difference in outcome between patients with focal, crescentic or mixed-class renal biopsies. A drawback of this study is that no minimum amount of glomeruli was required in the renal biopsies.

Ellis *et al.*[22] performed a validation study in 76 patients from the United States. Diagnosis and ANCA serotype were equally distributed in this cohort (Table 1). Renal function at baseline was best in patients with a renal biopsy classified as focal and did not differ between patients with renal biopsies classified as crescentic, mixed, or sclerotic (Table 2). At both 1 and 2-year follow-up, renal function was best in patients with a focal-class renal biopsy, worst in patients with a sclerotic-class renal biopsy, and intermediate in patients with a crescentic or mixedclass renal biopsy. In contrast to the study by Ford *et al.*, this study showed that patients in the crescentic class were significantly more often c-ANCA-positive with a GPA phenotype. Renal survival at 1-year follow-up did not differ significantly between the classes, but the histopathological class was an independent predictor of eGFR at 1-year follow-up in linear regression analyses.

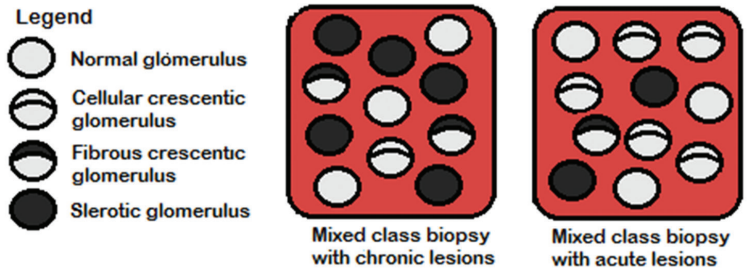
Unlu *et al.*[23] reported a study in Turkish patients that was not primarily focused on the validation of the histopathological classification for ANCA-associated glomerulonephritis, but evaluated the classification system with dialysis

as outcome in a subanalysis (Table 1). The classification system did predict for dialyses requirement in the log-rank test, but not in the Cox regression model (Table 2). Similar to the study performed by Ford *et al.*, in this study, no minimum amount of glomeruli was required in the renal biopsies.

Points of consideration and future perspectives

The studies validating the histopathological classification of ANCA-associated glomerulonephritis show that the classification system predicts clinical outcome, in particular, in patients with either a focal or sclerotic-class renal biopsy. There are conflicting outcomes with respect to the crescentic and the mixed-class renal biopsies. In a number of studies, the outcome of patients with a crescentic-class renal biopsy is similar to that of patients with a mixed-class renal biopsy. In other studies, patients with focal and crescentic-class renal biopsies seem to have similar outcomes. There is some evidence that the proportion of normal glomeruli is an important determinator of outcome and is taken as a parameter to subcategorize the classes. Whether additionally, the variation of study results is due to differences in patient populations, moderate inter-rater reliability, or other factors is currently unknown. Only one study investigated inter-rater reliability, showing moderate variability among histopathologists. In particular, the mixed-class renal biopsies may be 'suffering' from an 'identity crisis', as exemplified in Fig. 2. This figure shows that biopsies in this class may indeed show mixed findings as their denominator suggests, in which either an acute or chronic phenotype predominated. This may have important consequences for renal outcome if different phenotypes prevail in different studies. Renal outcome is also greatly influenced by the therapy a patient receives. However, due to the retrospective design of all to-date performed validation studies, it was not possible to fully account for this parameter in these studies. Another important issue is the influence of interstitial lesions on outcome, in addition to the classes which are primarily based on glomerular lesions. In a recent review by Haas *et al.*[24], it was questioned whether the lack of inclusion of tubulointerstitial changes would affect the value of the classification system. It was also questioned whether the classification system identified specific lesions most likely to respond to one or more immunosuppressive agents. These issues are being addressed in a large international validation study, which is currently being performed and incorporates histopathological, clinical, and therapeutical data.

Figure 2. Different phenotypes of mixed class ANCA-associated glomerulonephritis



Hypothetical example of how mixed class biopsies may represent quite different phenotypes of ANCA-associated glomerulonephritis in terms of activity and chronicity.

Conclusion

In general, validation studies supported the predictive value of the histopathological classification of ANCA-associated glomerulonephritis for renal outcome. This was especially the case in patients with a focal or sclerotic-class renal biopsy, whereas the crescentic and mixed classes showed different results in the validation studies. These differences could be due to differences in patient populations or therapy, moderate inter-rater reliability, and lack of inclusion of tubulointerstitial lesions in the classification system. To address these issues, a large international validation study is currently being performed.

Key points

- The histopathological classification of ANCA-associated glomerulonephritis predicts renal outcome during follow-up, especially in patients with either a focal or sclerotic-class renal biopsy.
- There are conflicting outcomes with respect to the crescentic and the mixed-class renal biopsies.
- This could be due to differences in patient populations or therapy, moderate inter-rater reliability, and lack of inclusion of tubulointerstitial lesions in the classification system.
- A large international validation study is currently being performed to address these issues.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest.

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