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REVIEW ARTICLE

Histopathologic classification of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis: achievements, limitations, and perspectives

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Abstract Clinical and histological factors have been identified as predictors of early and late renal outcome in ANCA-associated vasculitides (AAV). The presence and severity of kidney involvement at diagnosis are associated with poor prognosis in both patient and renal survival. Histologic findings remain the gold standard for diagnosing patients with AAV. In order to quantify the extent of the morphological parameters in the renal biopsies and to identify the histopathological lesions that predict renal outcome, several scoring systems have been proposed to systematically assess kidney biopsies in AAV. Renal pathologists from an international working group proposed in 2010 a new histopathological classification. This scheme comprises four general categories, based on the predominance of the glomerular histological lesions: focal (≥50% normal glomeruli); crescentic (≥50% glomeruli with cellular crescents); mixed (<50% normal, <50% crescentic, <50% globally sclerotic glomeruli), and sclerotic (≥50% globally sclerotic glomeruli). This article reviews the background and the main studies that have validated the histopathologic classification of ANCA-associated glomerulonephritis, the conclusions derived from these studies, and the perspectives for the assessment of renal outcome in AAV.

Keywords ANCA · Glomerulonephritis · Histological classification · Renal pathology · Vasculitis

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Introduction

The philosophy of classification addresses the questions: *How should we classify the world's entities? What is the relationship between classification and the world itself?* Classifications tell us whether two species belong to the same genus, or whether a genus is part of a particular family. They provide information for understanding the course of evolution and about evolutionary relations among biological traits [1]. In Medicine, classification schemes have been developed in all fields and are used to understand the nature of the diseases, to categorize groups of patients for epidemiological, prognostic, or interventional studies, but more important, to assist in the clinical management of individual patients [2]. Histopathological classifications represent a good example of this.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of diseases characterized by inflammation of small blood vessels, often leading to tissue destruction and organ failure. The main phenotypes of AAV are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Multisystem involvement is the hallmark of these diseases, being renal, in the form of glomerulonephritis, a common complication present in 38–70% of patients with GPA and 80–100% of MPA [3, 4].

Renal involvement is important in AAV because of its frequency and the impact on prognosis, especially in patient and kidney survival [5]. Clinically, it presents as rapidly progressive glomerulonephritis (RPGN), and histologically as a pauci-immune necrotizing crescentic glomerulonephritis. Positivity for ANCA may influence clinical and histological presentation in patients with pauci-immune glomerulonephritis [6, 7]. Also, variations in renal histology exist according to clinical and serologic subgroups. MPA patients present with glomerulonephritis characterized by more chronic injury

compared to GPA patients, probably due to a delayed diagnosis, while MPO-ANCA positive patients present more abundant active and chronic histological lesions compared to PR3-ANCA positive patients [8].

A descriptive study of 74 American patients with ANCA-negative and ANCA-positive pauci-immune crescentic glomerulonephritis showed that ANCA-negative patients had lower estimated glomerular filtration rate (eGFR) and higher degree of interstitial fibrosis at presentation compared to ANCA-positive patients, with similar rates of end-stage renal disease (ESRD) at 1 year and comparable response to treatment in both groups [9].

Histopathological findings may vary among patients, and inter- and intraobserver variability may also exist [10]. Renal biopsy is useful to distinguish treatment-responsive active disease from treatment-unresponsive chronic states. For example, endocapillary lesions, glomerular tuft necrosis, and cellular and fibrocellular crescents represent acute and active lesions, whereas fibrous crescents, adhesion/synechia, and global or segmental glomerulosclerosis are chronic lesions [11]. Interstitial infiltrate consisting of mononuclear inflammatory cells and neutrophils, and less frequently, eosinophils are also characteristic [12]. Destruction of the basement membrane of Bowman's capsule, interstitial fibrosis and tubular atrophy, vasculitis, fibrinoid necrosis, and periglomerular granulomatous inflammation are other renal histological findings in AAV [11, 12].

In this article, we review the background and the main studies that have emerged since the development of the histopathologic classification of ANCA-associated glomerulonephritis in 2010, the conclusions derived from these studies and the perspectives for the assessment of renal outcome in AAV.

Predictors of renal outcome in AAV

Clinical and histological factors have been identified as predictors of early and late renal outcome in AAV. The presence and severity of kidney involvement at diagnosis are associated with poor prognosis in both patient and renal survival.

Clinical predictors of renal outcome include older age (>65 years), female gender, diagnosis of MPA and renal limited vasculitis, serum creatinine at diagnosis, proteinuria ≥500 mg/day, arterial hypertension, treatment resistance, and relapses [5, 13, 14].

Among the histological factors, the percentage of normal glomeruli at diagnosis is the strongest predictor of GFR, showing a positive correlation [5]. Active lesions are associated with renal recovery and may be reversible, while chronic lesions, such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy, are associated with poor renal prognosis [5, 15]. Moreover, recovery of renal function in patients initially dialysis dependent is associated with the amount of chronic lesions and arteriosclerosis, while long-term renal function correlates with chronic and acute tubulointerstitial lesions, tubular atrophy, and intraepithelial infiltrate [16–18].

Background

Histologic findings remain the gold standard for diagnosing patients with AAV. Renal biopsy in patients with GPA and evidence of active renal disease defined by urinary sediment demonstrates extracapillary proliferation in more than 91.5% of patients [12]. Repeat kidney biopsy is also helpful in differentiating patients with chronic damage from those with treatment-responsive active disease.

In the past, comparison between studies assessing renal outcome in patients with AAV was difficult due to differences in inclusion criteria, the type of histological lesions evaluated, and the definitions of renal outcome.

In order to quantify the extent of the morphological parameters in the renal biopsies and to identify the histopathological lesions that predicted renal outcome, several scoring systems were proposed to systematically assess kidney biopsies in AAV.

In 1996, Bajema et al. proposed the European Vasculitis Study Group (EUVAS) histological scoring system [10], based on a selected number of glomerular parameters (i.e., fibrinoid necrosis, extracapillary proliferation, sclerosis, periglomerular infiltrate, and granulomatous reaction) that were scored quantitatively as a percentage of the total number of glomeruli in the biopsy (quantitative data), while interstitial, tubular, and vascular parameters were scored either as dichotomous data or semi-quantitatively. The inter- and intra-observer agreement was good for quantitative glomerular parameters and less consistent for dichotomous data. When this system was validated in a multicenter European study comprising 157 patients with systemic vasculitis, the histologic parameters that correlated with renal outcome were the following: the percentage of normal glomeruli, glomerular sclerosis, diffuse interstitial infiltrates, tubular necrosis, and tubular atrophy [19]. Moreover, using this system in patients with repeated kidney biopsies, the mean percentage of normal glomeruli did not change over time, while the percentage of glomeruli with crescents decreased and glomerulosclerosis increased, independent of diagnosis, gender, age, time interval between biopsies, and treatment [20].

When the EUVAS histological scoring system was used to assess renal outcome in patients with ANCA-negative pauci-immune vasculitis, the histological findings and prognosis were comparable to those with ANCA-positive disease. Renal outcome was related to initial serum creatinine and to vasculitis-related organ involvement, but not to any histological parameter [7].

In 1998, Shigematsu et al. [21] proposed a histologic grading (acute activity index) and staging (chronicity index) for glomerular and interstitial lesions, in an effort to produce guidelines for the treatment of rapidly progressive nephritic syndrome. This system focused on the characterization of acute and chronic lesions among intracapillary, extracapillary, and interstitial lesions, using a sum score in each glomerular lesion and then calculating a mean score by dividing the sum score by the total number of glomeruli. This system was complicated, not suitable to select each glomerular and tubulointerstitial parameter for distribution as a prognostic marker, and did not consider the vascular lesions.

In 2003, Vergunst et al. [22] analyzed the predictive value of clinical, serological, and histological parameters for renal outcome in 160 patients with ANCA-associated glomerulonephritis and proposed an index for clinical use. The histological parameters included the following: normal glomeruli, fibrinoid necrosis, extracapillary proliferation, granulomas, interstitial edema, focal and diffuse infiltrates, fibrosis, tubular casts, tubular atrophy, tubular necrosis, sclerosis, mesangial proliferation, mesangial matrix expansion, arteriosclerosis, and infiltrates in arterioles. The proposed index is as follows:

$$\begin{aligned}\text{GFR at 1 } year = {} & 36.96 + 0.65^{*}(\text{GFR at } time\ of\ renal\ biopsy) \\ & + 10.52\ (if\ normal\ glomeruli\ present) \\ & + 7.72\ (if\ fibrinoid\ necrosis\ present) - 0.42^{*}(\text{age}).\end{aligned}$$

This index shows that renal function (GFR) at the time of biopsy is the best predictor for renal function at 1 year, and that together with normal glomeruli, fibrinoid necrosis, and age, it explains more than 60% variation in GFR at 1 year.

In 2008, Joh et al. [11] proposed the Japanese scoring system for renal pathology in AAV, adding to the EUVAS score the assessment of the destruction of the tubular basement membrane, the basement membrane of Bowman's capsule, the presence of granulomatous lesions in the arteries as well as the interstitium, and vasculitis including endarteritis. This score evaluates quantitatively not only the glomerular lesions, but also tubulointerstitial and vascular lesions in percentages. Moreover, vascular lesions are scored based on the most severe lesions, and arcuate artery, interlobular artery, arteriole, venule, and peritubular capillary are evaluated with reference to sclerosis, necrosis, vasculitis, and thrombosis.

The histological classification of ANCA-associated glomerulonephritis

In order to assess the prognosis of patients with ANCA-associated glomerulonephritis at the time of renal biopsy and to facilitate uniform reporting worldwide, renal pathologists from an international working group proposed in 2010 a new histopathological classification. The aim was to design a classification scheme that would provide valuable information for clinicians and be easily adopted by pathologists in daily practice [23].

This classification derived from clinicopathological studies conducted within the EUVAS by an expert panel of renal pathologists known as the RENHIS (Renal Histology) group, consisting of experts from European centers in France, Italy, Germany, and the Netherlands [2]. Among the EUVAS studies that served as background for the classification were the CYCAZAREM (Cyclophosphamide versus Azathioprine as Remission Maintenance therapy for ANCA-associated vasculitis) and the MEPEX (Randomized trial of Plasma Exchange or High-dosage Methylprednisolone as adjunctive therapy for severe renal vasculitis) trials [24, 25].

The classification proposed by Berden et al. [26] is based on glomerular pathology as assessed by light microscopy and suggests a minimum of 10 whole glomeruli as adequate for evaluation. Hematoxylin and eosin, methenamine silver, and periodic acid-Schiff stainings are minimally required, while Masson trichrome staining or one of its variants can be helpful to visualize fibrinoid necrosis, acute tubular necrosis, and interstitial fibrosis.

The classification scheme comprises four general categories, based on the predominance of the glomerular histological lesions [26]:

- Focal: ≥50% normal glomeruli.
- Crescentic: ≥50% glomeruli with cellular crescents.
- Mixed: <50% normal, <50% crescentic, <50% globally sclerotic glomeruli.
- Sclerotic: ≥50% globally sclerotic glomeruli.

The classification does not take into account comorbid diseases or overlap syndromes and provides definitions for the main histological lesions (normal glomeruli, cellular or fibrous crescents, global glomerulosclerosis). Because the classification is based on glomerular lesions only, it suggests that tubulointerstitial and vascular lesions are scored according to the previous EUVAS scheme [10].

Validation studies

Geographical differences in the incidence and expression of AAV have been demonstrated in Japan, Europe, and North America [27]. African Americans with pauci-immune glomerulonephritis are younger and more often MPO-ANCA positive compared to Caucasians [28]. Differences in clinical phenotypes also exist, with lower frequency of renal involvement in Japanese patients with GPA (12–63%) compared to over 70% in patients with GPA from Germany and USA [27]. The severity of kidney damage and differences in therapy

Table 1 Validation studies from 2010 to 2013

Study Study design	Berden et al. [26] EUVAS clinical trials	Berden et al. [49] EUVAS clinical trials	Chang et al. [29] Retrospective	Ellis et al. [30] Retrospective cohort	Iwakiri et al. [31] Retrospective	Togashi et al. [36] Retrospective
Number of patients	100	30	121	76	102	54
Age—years	62.6 (20.4–80.7)[a]	63.3 (16.8)[b]	57.2 (14.7)[b]	58[b]	66.3 (11.3)[b]	66.9 (36–85)[b]
Gender—*n* (%)						
Male	54 (54)	16 (53)	64 (53)	43 (57)	54 (53)	28 (52)
Female	46 (46)	14 (47)	57 (47)	33 (43)	48 (47)	26 (48)
Geographical area	Europe (multicenter)	Europe Australia	China (single-center)	U.S. (single-center)	Japan (multicenter)	Japan (single-center)
Diagnosis—*n* (%)						
GPA	39 (39)	15 (50)	49 (41)	43 (57)	3 (3)	0
MPA	61 (61)	15 (50)	68 (56)	31 (41)	97 (95)	25 (46)
EGPA	0	0	0	0	2 (2)	1 (2)
RLV	0	0	4 (3)	2 (3)	0	28 (52)
ANCA—*n* (%)						
pANCA/MPO	47 (47)	13 (43)	108 (89)	32 (42)	86 (84)	54 (100)
cANCA/PR3	45 (45)	17 (57)	13 (11)	30 (39)	5 (5)	0
Negative	2 (2)	0	0	14 (18)	11 (11)	0
Missing	3 (3)	0	0	0	0	0
Histological class—*n* (%)		26/30				
Focal	16 (16)	10 (38)	33 (27)	20 (26)	46 (45)	17 (31)
Crescentic	55 (55)	10 (38)	53 (44)	18 (24)	32 (31)	8 (15)
Mixed	16 (16)	6 (23)	24 (20)	27 (36)	18 (18)	19 (35)
Sclerotic	13 (13)	0	11 (9)	11 (14)	6 (6)	10 (19)
Conclusion	Phenotypical order of the classes corresponded to the order of severity of renal function impairment during follow-up.	Significant association between renal biopsy class and baseline eGFR. Association between tubulointerstitial lesions and renal function.	Histological classification reflected the severity of the initial renal impairment and predicted renal response to treatment and development of ESRD.	Association between histologic class and renal function at baseline and 1 year. Dialysis-dependent patients with sclerotic class on presentation had no response to therapy.	Histopathological classification was associated with eGFR at one year. Immunohistochemical staining for α-SMA expression might be useful to estimate renal outcome.	Phenotypical order of classes corresponded to severity of renal function impairment. No difference in patient survival among the four groups.

GPA granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *RLV* renal-limited vasculitis, *ANCA* anti-neutrophil cytoplasmic antibodies, *pANCA/MPO* perinuclear ANCA/myeloperoxidase, *cANCA/PR3* cytoplasmic ANCA/proteinase 3, *EUVAS* European Vasculitis Study Group, *ESRD* end-stage renal disease, *α-SMA* α-smooth muscle actin, *eGFR* estimated glomerular filtration rate

[a] Median (range)

[b] Mean (SD or range)

Table 2 Validation studies from 2013 to 2014

Study Study design	Unlu et al. [37] Retrospective	Hilhorst et al. [38] Retrospective cohort	Muso et al. [39] Retrospective	Hilhorst et al. [40] Retrospective cohort	Tanna et al. [41] Retrospective	Quintana et al. [42] Retrospective	Nohr et al. [33] Retrospective cohort
Number of patients	141	164	87	181	104	136	67
Age—years	49 (16.4)[b]	61 (14.6)[b]	63 (17–85)[a]	61.4 (14.4)[b]	62.2 (17–3-87.2)[a]	62.1[b]	60 (14–89)[b]
Gender—*n* (%)							
Male	80 (57)	113 (69)	37 (43)	129 (71)	58 (56)	71 (52)	41 (61)
Female	61 (43)	51 (31)	50 (57)	52 (29)	46 (44)	65 (48)	26 (39)
Geographical area	Turkey (multicenter)	Netherlands (single-center)	Japan (multicenter)	Netherlands (single-center)	London (single-center)	UK, Spain	Canadian
Diagnosis—*n* (%)		NA		NA	NA		NA
GPA	55 (39)	-	0	-	-	44 (32)	-
MPA	20 (14)	-	87 (100)	-	-	80 (59)	-
EGPA	0	-	0	-	-	0	-
RLV	39 (28)	-	0	-	-	8 (6)	-
Unknown	27 (19)	-	0	-	-	4 (3)	-
ANCA—*n* (%)							
pANCA/MPO	61 (43)	81(49)	76 (87)	92 (51)	49 (47)	76 (56)	39 (58)
cANCA/PR3	60 (43)	83 (51)	0	89 (49)	49 (47)	51 (37)	21 (31)
Double-positive	5 (4)	0	0	0	0	0	0
Negative	25 (18)	0	0	0	6 (6)	9 (7)	7 (11)
Missing	0		11 (13)	0	0	0	0
Histological class—*n* (%)							
Focal	31 (22)	81 (49)	40 (46)	51 (28)	23 (22)	35 (26)	15 (22)
Crescentic	69 (49)	43 (26)	7 (8)	77 (43)	26 (25)	31 (23)	25 (37)
Mixed	29 (21)	39 (24)	26 (30)	52 (29)	48 (46)	53 (39)	20 (30)
Sclerotic	12 (8)	1 (1)	14 (16)	1 (0.1)	7 (7)	17 (12)	7 (11)
Conclusion	Percentage of full moon glomeruli should be noted in the pathology report; cases with >50% at increased risk of dialysis requirements.	Patients classified as crescentic or mixed had worse survival when the percentage of normal glomeruli was <25%. Adding the percentage of normal glomeruli improves the predictive value of the classification.	Mixed class showed heterogeneity of histological activity and chronicity, which shows the insufficiency of the classification for predicting progression to ESRD.	The focal group had the best renal survival and the crescentic group had the worst. Histological groups were significantly related to renal but no to patient survival.	It may be of value to combine the histological classification with tubular atrophy and percentage of normal glomeruli.	Confirmed predictive value of histological classification. Worse renal outcome in patients with MPO-ANCA, tubulointerstitial fibrosis and atrophy.	The classification validated the association between cellular crescents and improvement in eGFR, and between globally sclerotic glomeruli and reduced eGFR.

GPA granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *RLV* renal-limited vasculitis, *ANCA* anti-neutrophil cytoplasmic antibodies, *pANCA/MPO* perinuclear ANCA/myeloperoxidase, *cANCA/PR3* cytoplasmic ANCA/proteinase 3, *NA* not available, *eGFR* estimated glomerular filtration rate

[a] Median (range)

[b] Mean (SD or range)

Table 3 Validation studies from 2014 to 2016

Study Study design	Naidu et al. [43] Retrospective	Ford et al. [46] Retrospective	Andreiana et al. [34] Retrospective	Córdova et al. [47] Retrospective	Diaz-Crespo et al. [44] Retrospective	Kristensen et al. [45] Retrospective
Number of patients	86	120	75	62	151	87
Age—years	42.5 (15.2)[b]	66 (8–87)[a]	60 (53–68)[a]	52 (34–61)	60 (22–85)[b]	62.9 (22–86)[b]
Gender—*n* (%)						
Male	42 (49)	72 (60)	36 (48)	24 (39)	85 (56)	54 (62)
Female	44 (51)	48 (40)	39 (52)	38 (61)	66 (44)	33 (38)
Geographical area	India (single-center)	Australia (single-center)	Romania (single-center)	México (single-center)	Spain (multicenter)	Denmark (single-center)
Diagnosis—*n* (%)		NA	NA			NA
GPA	34 (40)	-	-	34 (55)	10 (6)	-
MPA	36 (42)	-	-	20 (32)	60 (40)	-
EGPA	1 (1)	-	-	0	0	-
RLV	0	-	-	8 (13)	81 (54)	-
Unknown	15 (17)	-	-	0	0	-
ANCA—*n* (%)	53 (62)					
pANCA/MPO	NA	75 (63)	57 (76)	21 (34)	96 (64)	49 (56)
cANCA/PR3	NA	28 (23)	18 (24)	35 (56)	21 (14)	38 (44)
Atypical	-	17 (14)	0	0	0	0
Negative	33 (38)	0	0	6 (10)	34 (22)	0
Missing	0	0	0	0	0	0
Histological class—*n* (%)	84/86			55/62		Unknown 9 (10)
Focal	13 (16)	34 (28)	4 (5)	5 (9)	32 (21)	21 (24)
Crescentic	43 (51)	33 (27)	39 (52)	1 (2)	62 (41)	24 (28)
Mixed	16 (19)	33 (27)	24 (32)	25 (45)	36 (24)	30 (34)
Sclerotic	12 (14)	20 (17)	8 (11)	24 (44)	21 (14)	3 (4)
Conclusion	Histopathological class correlated with the initial SCr and proteinuria levels. The probability of worsening renal outcome and mortality increased with sequence of focal, crescentic, mixed and sclerotic groups.	Reproducibility of the classification was seen only in patients with sclerotic patterns of glomerular injury. Interstitial injury, sclerotic pattern and decreased kidney function predicted poor outcomes.	Neither response to therapy nor outcome was influenced by ANCA specificity or by the histopathological class.	Histopathological classification predicted response to therapy and 2-year eGFR, with poorer remission rate for sclerosing group and those with <25% normal glomeruli, but did not predict renal nor patient survival.	Confirmed that the histopathological classification has prognostic value and is a useful tool for renal survival. Suggests a subdivision of crescentic category (< and ≥75% of crescents) based on the different survival rates.	Histopathologic groups were not associated with eGFR at 3 years. More patients in the crescentic group than in the mixed and focal groups developed ESRD (33%, 13% and 5% respectively). Age and baseline eGFR predicted renal function at 3 years.

GPA granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *RLV* renal-limited vasculitis, *ANCA* anti-neutrophil cytoplasmic antibodies, *pANCA/MPO* perinuclear ANCA/myeloperoxidase, *cANCA/PR3* cytoplasmic ANCA/proteinase 3, *NA* not available, *SCr* serum creatinine, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease

[a] Median (IQR)

[b] Mean (SD or range)

influence the distribution of the renal histopathological classes among populations.

Single-center and multicentric studies worldwide have validated the renal histopathologic classification proposed by Berden et al. in different ethnic groups. The distribution of the four renal histological categories is similar in Europe, Canada, India, and China, with crescentic class being the dominant, whereas in Japan, the focal class predominates, and in USA and in UK, the mixed class is more prevalent [26, 28–45]. Of special interest are geographical regions such as Australia, where equal distribution of the focal, crescentic, and mixed histological classes is seen, and Mexico, where mixed and sclerotic classes are the more prevalent [46, 47].

The histological classification has also been validated in 40 pediatric patients with ANCA-associated glomerulonephritis from a single-center in Canada, demonstrating that the most frequent histological class in this group was crescentic (50%), and supporting the clinical utility of the classification and its ability to discriminate renal outcomes in children with AAV [48].

Tables 1, 2, 3 summarize the main studies that have validated the histological classification.

Perspectives

The renal histological classification of ANCA-associated glomerulonephritis has raised the conduction not only of validation studies, but also of other studies focused on specific clinical correlations. An example of this is a study from the EUVAS group that found that ear, nose, and throat involvement in AAV patients was associated with favorable renal biopsy findings (less interstitial fibrosis and tubular atrophy and a more favorable histological class), as well as better renal function [50].

The studies that have validated the histological classification have provided information regarding its predictive value with respect to renal survival, but only few studies have addressed the interobserver variation. Another question that remains unanswered is whether the classification identifies specific lesions most likely to respond to one or more specific immunosuppressive agents [32]. In this regard, it should be considered that classifications are likely of greater value for evaluating the appropriateness and equivalency of patient cohorts for clinical studies rather than for use in routine clinical practice.

It also remains to be determined the impact of the lack of inclusion of the tubulointerstitial parameters in the classification, since these factors have shown to be of predictive value in the long-term renal outcome [49]. In this regard, the recently published Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of glomerulonephritis [51] suggest reporting additional features besides the prognostic class, such as clinicopathological features (e.g., GPA), percentages of focal glomerulosclerosis, tubular atrophy and interstitial fibrosis, as well as the gravity (mild, moderate or severe) of vascular changes (arteriosclerosis and arteriolosclerosis).

Despite these unsolved issues, the classification has achieved the goals of any classification system: it enhances the communication between experts in the field; provides a logical structure for the categorization of groups of patients for epidemiological, prognostic, or interventional studies; it assists in the clinical management of individual patients and includes categories that are mutually exclusive and predictive of the disease prognosis [52].

Conclusions

The renal histopathologic classification for ANCA-associated glomerulonephritis provides a logical structure for the categorization of patients into four classes defined according to glomerular lesions. The validation studies have demonstrated its reproducibility, its utility as a clinical tool, and the predictive value with respect to renal outcome.

Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest. The manuscript does not contain clinical studies or patient data.

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