Unveiling the Role of Additional Histological Parameters in ANCA-Associated Vasculitis

In their recent report, Boudhabhay *et al.*[1] demonstrated that the detection of arteritis in ANCA-associated vasculitis (AAV) at renal biopsy may improve the performance of the proposed renal risk score, predicting poor renal outcomes and mortality. Moreover, Aendekerk *et al.*[2,3] independently validated these findings in a large cohort of patients, confirming the higher risk of all-cause mortality in AAV with confirmed arteritis. However, other possible additional clinical/histologic parameters are involved in the deterioration of renal function. In this setting, we recently described the improvement of the already-established renal risk score[4] with the addition of a specific histologic feature, the Bowman's capsule rupture (BCR), in stratifying patients with higher risk of mortality and poor renal outcome.[5,6] Thus, we evaluated a selected series of 45 patients with biopsy specimen–proven AAV, diagnosed in a large Italian nephropathology center,[7] for the effect of arteritis and BCR on outcome with a 12-month follow-up. In this cohort, we confirmed the incidence of arteritis already reported by Boudhabhay *et al.* (six of 45 patients, 13%; Figure 1). All of the patients had demonstrated concurrent glomerular involvement in the form of pauci-immune crescentic necrotizing GN. The patients with AAV and arteritis were treated with high-dose steroids, cyclophosphamide (two patients), and rituximab (one patient), or without immunosuppressive therapy. On the basis of the renal risk score, patients with AAV and arteritis were classified as being at low ($n=1$), medium ($n=3$), or high ($n=2$) risk, although no statistically significant differences in the distribution of risk scores were noted compared with the AAV group without arteritis (Table 1). Interestingly, in our cohort, the presence of arteritis correlated with baseline serum creatinine ($P=0.0003$) and with the related renal outcome measures (dialysis at diagnosis, serum creatinine at 6 and 12 months, $P=0.002$, 0.02, and 0.05, respectively), confirming the correlation with renal outcomes already reported by Boudhabhay *et al.* Moreover, we found a correlation with overall mortality in our cohort ($P=0.005$), further confirming the predictive value of this histologic feature. Finally, the presence of arteritis in this subset of patients was correlated with evidence of BCR on the biopsy specimen ($P=0.05$; Figure 1), which has not yet been investigated and could suggest a complementary role for these two features in improving the predictive performance of the already existing risk scores. For these reasons, we agree with the authors that further investigation on prospective and multicentric cohorts with comprehensive clinical and histologic data will shed further light on the role of these underestimated morphologic features.

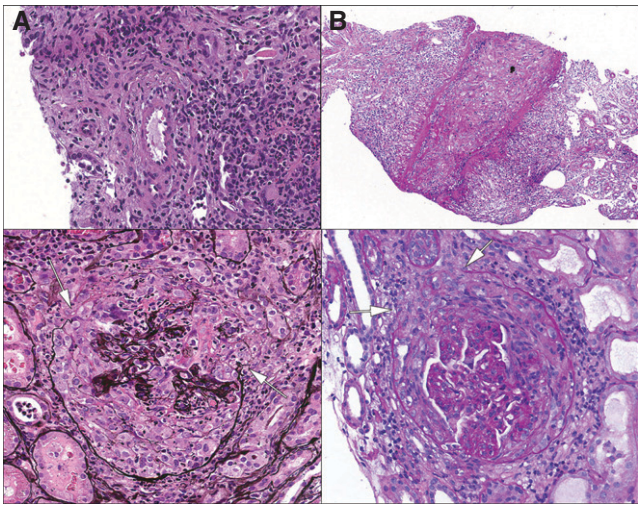

Figure 1. Concurrent renal arteritis and BCR. (A) A medium-sized artery with transmural inflammation, mainly composed of lymphocytes, plasma cells, and neutrophils (top; hematoxylin and eosin) is seen in association with BCR in a glomerulus with cellular crescent and fibrinoid necrosis (white arrows, bottom; Jones methenamine silver stain). (B) A different specimen of a large artery in cross-section demonstrating circumferential involvement of inflammation (top; Periodic acid–Schiff) along with BCR (white arrows, bottom; Periodic acid–Schiff). Original magnification, ×20 in (A) top panel, ×40 in (A) bottom panel, ×5 in (B) top panel, ×40 in (B) bottom panel.

DISCLOSURES

F. Pagni reports serving on speakers bureaus and in an advisory or leadership role for Amgen, MSD, Novartis, and Roche. The remaining author has nothing to disclose.

FUNDING

None.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Prof. Fabio Pagni, Pathology, Department of Medicine and Surgery, Università degli Studi di Milano-Bicocca, via Pergolesi 33, 20900, Monza, Italy. Email: fabio.pagni@unimib.it

Table 1. Clinical and histologic characteristics of the cohort, comparing patients with or without evidence of arteritis

Variables	ANCA-Associated Vasculitis A+	ANCA-Associated Vasculitis A−	*P* Value
Patients, *n* (%)	6 (13%)	39 (87%)	
Males, *n* (%)	6 (100%)	22 (56%)	—
Age, yr, (mean±SD)	71.5±8.5	62.4±13.6	0.12
Clinical features			
Proteinuria, g/d, (mean±SD)	1.2±0.8	1.8±1.5	0.30
Microhematuria, *n* (%)	6 (100%)	38 (97%)	—
Baseline serum creatinine, mg/dl, (mean±SD)	7.2±3.7	3.2±2	0.0003[a]
Hypertension, *n* (%)	4 (67%)	25 (64%)	0.90
ANCA specificity			
MPO, *n* (%)	5 (83%)	24 (62%)	0.32
PR3, *n* (%)	1 (17%)	14 (36%)	
Double positive	0	1 (3%)	
ANCA titer, U/ml, (mean±SD)	94.7±44.3	139.5±241.7	0.66
Complement level, mg/dl, (mean±SD)			
C3	106.8±15.3	109.8±17.6	0.70
C4	23.7±8.8	27.9±8.8	0.28
Berden class, *n* (%)			
Focal	2 (33%)	10 (26%)	0.79
Crescentic	0	7 (18%)	
Mixed	3 (50%)	18 (46%)	
Sclerotic	1 (17%)	4 (10%)	
ANCA renal risk score, *n* (%)			
Low	1 (17%)	10 (26%)	0.43
Medium	3 (50%)	24 (62%)	
High	2 (33%)	5 (13%)	
Histology features, %, (median (IQR))			
Normal glomeruli	35% (21%–49%)	25% (17%–48%)	0.28
Sclerosed glomeruli	11% (0%–24%)	13% (9%–33%)	0.49
BCR	19% (4%–30%)	0% (0%–7%)	0.05[a]
Interstitial fibrosis and tubular atrophy	20% (13%–20%)	15% (5%–35%)	0.30
Peritubular capillaritis	6 (100%)	14 (36%)	—
Outcome			
Dialysis at diagnosis, *n* (%)	4 (67%)	5 (13%)	0.002[a]
Serum creatinine at 6-month follow-up, mg/dl, (mean±SD)	4.8±2.9	2.5±2.0	0.02[a]
Serum creatinine at 12-month follow-up, mg/dl, (mean±SD)	4.5±3.1	2.5±2.2	0.05[a]
RRT at 12-month follow-up, *n* (%)	2 (33%)	7 (18%)	0.38
Mortality, *n* (%)	3 (50%)	3 (8%)	0.005[a]

Differences in continuous variables expressed as mean±SD were assessed using the independent samples *t* test; variables expressed as median (IQR) were compared using the Wilcoxon test. Differences in categoric variables were assessed using the chi-squared test. A+, patient with arteritis; A−, patient without arteritis; MPO, myeloperoxidase; PR3, proteinase 3; IQR, interquartile range.
[a]$P \leq 0.05$.

AUTHOR CONTRIBUTIONS

V. L'Imperio conceptualized the study, wrote the original draft, and was responsible for data curation and methodology; and F. Pagni reviewed and edited the manuscript, provided supervision, and was responsible for resources and visualization.

REFERENCES

1. Boudhabhay I, Delestre F, Coutance G, Gnemmi V, Quemeneur T, Vandenbussche C, et al.: Reappraisal of renal arteritis in ANCA-associated vasculitis: Clinical characteristics, pathology, and outcome. *J Am Soc Nephrol* 32: 2362–2374, 2021
2. Boudhabhay I, Coutance G, Karras A, Duong Van Huyen JP: Authors' reply. *J Am Soc Nephrol* 33: 458–459, 2022
3. Aendekerk JP, Timmermans SAMEG, Busch MH, van Paassen P; the Limburg Renal Registry: Arteritis status and renal involvement in ANCA-associated vasculitis. *J Am Soc Nephrol* 33: 457–458, 2022
4. Brix SR, Noriega M, Tennstedt P, Vettorazzi E, Busch M, Nitschke M, et al.: Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 94: 1177–1188, 2018
5. L'Imperio V, Vischini G, Pagni F, Ferraro PM: Bowman's capsule rupture on renal biopsy improves the outcome prediction of ANCA-associated glomerulonephritis classifications [published online ahead of print June 12, 2020]. *Ann Rheum Dis* 10.1136/annrheumdis-2020-217979
6. L'Imperio V, Vischini G, Ferraro M, Pagni F: Response to: 'Correspondence on 'Bowman's capsule rupture on renal biopsy improves the outcome prediction of ANCA-associated glomerulonephritis classifications'' by Hakroush and Tampe [published online ahead of print February 5, 2021]. *Ann Rheum Dis* 10.1136/annrheumdis-2021-219988
7. L'Imperio V, Brambilla V, Cazzaniga G, Ferrario F, Nebuloni M, Pagni F: Digital pathology for the routine diagnosis of renal diseases: a standard model. *J Nephrol* 34: 681–688, 2021

See related original article, "Reappraisal of Renal Arteritis in ANCA-Associated Vasculitis: Clinical Characteristics, Pathology, and Outcome," in Vol. 32, Iss. 9, on pages 2362–2374.

Vincenzo L'Imperio [1] and Fabio Pagni [1]

Pathology, Department of Medicine and Surgery, ASST Monza, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy

JASN 33: ●●●–●●●, 2022.
doi: https://doi.org/10.1681/ASN.2022020208