Positive antineutrophil cytoplasmic antibody serology in patients with lupus nephritis is associated with distinct histopathologic features on renal biopsy

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Class IV-S lupus nephritis is often associated with more necrosis and fewer subendothelial immune deposits compared to class IV-G lupus nephritis, suggestive of necrotising glomerular inflammation found in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. ANCAs are present in a significant proportion of patients with lupus nephritis. Here we determine whether ANCAs are associated with distinct clinical and histopathologic features of lupus nephritis. Thirty-two ANCA-positive biopsies were compared to 222 ANCA-negative biopsies from patients with lupus nephritis. The majority (82%) of ANCA-positive patients had antimyeloperoxidase antibodies. Class IV-S lupus nephritis and glomerular necrosis were significantly more common (36% vs. 16% and 35% vs. 15%, respectively) and isolated Class V lupus nephritis significantly less common (10% vs. 29%) in the ANCA-positive group. ANCA-positive patients had significantly higher dsDNA titers (335u/ml vs. 52u/ml), significantly lower serum C4 concentrations (0.125g/L vs. 0.15g/L) and significantly higher serum creatinine (130μmol/L vs. 84μmol/L) at the time of biopsy. Hence ANCAs appear to influence the histological pattern of lupus nephritis and are associated with worse baseline renal function and more active lupus serology. There was no significant difference in outcome between groups when matched for severity of disease and treatment using propensity scoring. Thus, further studies are needed to examine whether ANCAs in patients with lupus nephritis have a pathogenic role and whether they are associated with worse renal outcomes or are simply a marker of more severe disease.

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The classification of lupus nephritis (LN) was revised with the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification in 2003,[1] which subdivides Class IV LN into segmental (IV-S) and global (IV-G) subclasses based on whether endocapillary involvement in diffuse proliferative LN is predominantly segmental (involving <50% of the glomerular tuft) or global (involving >50% of the glomerular tuft). Part of the rationale for this subdivision of Class IV LN was based on a study by the Lupus Nephritis Collaborative Study Group, which found that patients with "severe" focal segmental glomerular inflammation (involving >50% of glomeruli in the biopsy specimen) tended to have different histopathologic features on biopsy and worse clinical outcomes, with lower 5-year remission rates and poorer renal survival at 10 years (despite similar baseline clinical parameters and similar treatment).[2] In that study, diffuse segmental glomerular inflammation was associated with more necrosis and fewer subendothelial immune deposits compared with diffuse global glomerular inflammation. The observed difference in the extent of subendothelial immune deposits between these 2 groups led the authors to suggest that the pathogenic mechanisms mediating segmental as opposed to global glomerular inflammation in diffuse proliferative LN may be distinct.

Class IV LN was therefore divided into Class IV-S (when >50% of involved glomeruli have segmental inflammation) and Class IV-G (when >50% of involved glomeruli have global inflammation) in the revised ISN/RPS Classification 2003. A number of centers have used this revised classification to perform retrospective reviews of their patient cohorts, and some have reported that patients with Class IV-S LN have more necrosis and fewer subendothelial immune deposits compared with those with Class IV-G LN.[3,4]

Controversy exists as to whether there is a difference in the clinical outcome associated with each of these subclasses.[5]

It has been suggested that the more necrotic and pauci-immune glomerular inflammation seen in some patients with Class IV-S LN may be associated with patients having antineutrophil cytoplasmic antibodies (ANCAs).[2–4] However, in many of these studies, ANCA testing at the time of biopsy was not available. ANCAs are more common in patients with systemic lupus erythematosus (SLE) compared with the general population and more common still in those with LN compared with other clinical manifestations of SLE.[6–8] A small number of case series in the literature have looked at ANCA serology in patients with focal and segmental LN characterized by necrosis without prominent subendothelial immune deposits. Some report an association between this histopathologic phenotype and ANCA positivity,[9,10] but others found no association.[11,12] None of these studies systematically studied ANCA serology in their cohorts of patients with LN. Hence, as yet, there is no convincing evidence in the literature that ANCA positivity in patients with LN is associated with different histopathologic features of glomerular inflammation.

The aim of this study was to perform a retrospective review of our cohort of patients with LN in order to compare those patients who were ANCA positive (ANCA+ve) at the time of biopsy with those who were ANCA negative (ANCA−ve), with respect to histopathologic features of LN, serologic SLE activity, and renal outcomes. In particular, we wanted to determine whether Class IV-S LN was more common in those patients with positive ANCA serology and whether this was associated with more necrosis and fewer immune deposits, akin to the pauci-immune focal necrotizing glomerulonephritis seen in ANCA-associated vasculitis.

In our center, we screen the majority of our patients with biopsy-confirmed LN for ANCA, and thus we have a large cohort of patients for whom ANCA status at the time of renal biopsy is known. We were therefore able to examine systematically our cohort to determine whether there are particular histopathologic and serologic features of SLE associated with ANCA positivity. This contrasts with existing studies in this field that have tended to report ANCA status for patients with LN who have more necrotic and pauci-immune glomerular inflammation on biopsy, which naturally introduces bias into any assessment of an association of this histopathologic phenotype with positive ANCA serology.

RESULTS

In this retrospective analysis, a total of 254 biopsy specimens from 203 patients with a histologic diagnosis of LN identified in our hospital renal biopsy database (covering the time period 1997–2013) had ANCA serology assessed within 6 months of biopsy. Thirty-two biopsy specimens were from 29 patients who were ANCA+ve, and this group was compared with the remaining 222 biopsy specimens from 174 patients in our cohort who were confirmed to be ANCA−ve at the time of biopsy. There were no cases of drug-induced lupus.

Demographic characteristics of the patient population

There was no significant difference between the ANCA+ve and ANCA−ve groups with respect to age at biopsy, male:female ratio, ethnicity, duration of LN, or reason for biopsy (Table 1). This was a young and predominantly female patient population, with a distribution of ethnicity representative of the local population in West London.

ANCA serology

The majority of patients in the ANCA+ve group had anti-myeloperoxidase (MPO) antibodies (82%) at the time of biopsy, 7% had antiproteinase-3 (PR3) antibodies, and 11% had both anti-MPO and anti-PR3 antibodies (Table 1). In the majority of patients, ANCA antibody titers fell rapidly during the first 6 months post-biopsy (Figure 1), such that the median titers of both anti-MPO (18 IU/ml) and anti-PR3 (20 IU/ml) antibodies were within the normal range by 6 months post-biopsy.

One patient developed increasing anti-PR3 antibody titers during the first 6 months post-biopsy (Figure 1b). This patient had a long-standing history of SLE with multiple disease flares, and her previous treatment included cyclophosphamide and rituximab. ANCA developed at the time of her last renal biopsy when she had had a disease flare with increasing proteinuria and progressive renal impairment. She was poorly adherent to treatment and, hence, unfortunately received suboptimal immunosuppression. She progressed to end-stage renal failure and required hemodialysis 14 months post-biopsy.

Table 1 | Patient characteristics at the time of renal biopsy

Demographic data	ANCA-positive group (n = 32)	ANCA-negative group (n = 222)
Median age (range) at biopsy, yr	37.5 (16–78)	34 (16–75)
Median (range) duration of LN, yr	0 (0–24)	0.1 (0–28)
Sex (M:F)	1:4	1:3.5
Ethnicity, %	White: 25 Asian: 31.2 Black: 34.4 Other: 9.3	White: 30.6 Asian: 25.7 Black: 27.5 Other: 16.3
ANCA serology, %	MPO: 82 PR3: 7 MPO and PR3: 11	
Reason for biopsy, %	First presentation: 56 Flare: 34 Failure to respond: 9 Routine: 0	First presentation: 48 Flare: 35 Failure to respond: 8 Routine: 9

ANCA, antineutrophil cytoplasmic antibody; F, female; LN, lupus nephritis; M, male; MPO, myeloperoxidase; PR3, proteinase 3.
No significant difference between the 2 patient groups for all parameters shown.