Published in final edited form as:

Semin Arthritis Rheum. 2014 October ; 44(2): 198–201. doi:10.1016/j.semarthrit.2014.03.008.

Hematuria duration does not predict kidney function at 1 year in ANCA-associated glomerulonephritis

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Abstract

Objectives—Hematuria is considered a marker of active renal disease in ANCA-associated glomerulonephritis (ANCA-GN) with induction immunosuppression often continued until hematuria has resolved. We aim to determine whether longer hematuria duration is associated with lower estimated glomerular filtration rate (eGFR) at 1 year.

Methods—We conducted a retrospective study of 55 patients with biopsy-proven ANCA-GN. Linear regression models were constructed to determine predictors of eGFR at 1 year. The primary exposure was hematuria (>5 rbc/hpf) duration, defined as <90 days vs. ≥90 days following renal biopsy. Covariates included age, gender, ANCA type, baseline eGFR, and baseline proteinuria.

Results—Mean age at diagnosis was 58 years (53% male, 80% Caucasian, 38% PR3-ANCA, and 45% MPO-ANCA). At baseline, all patients had hematuria, 95% had proteinuria, and mean serum creatinine was 3.1 [standard deviation (SD) = 2.3] mg/dL. Overall, 93% were treated with steroids in combination with either cyclophosphamide or rituximab. Mean hematuria duration was 92 (SD = 77) days with 34 (62%) patients having hematuria resolution within 90 days. Older age and lower baseline eGFR were associated with lower eGFR at 1 year ($p = 0.03$ and $p < 0.001$, respectively). Hematuria resolution (<90 days vs. ≥90 days) was not predictive of eGFR at 1 year ($p = 0.93$).

Conclusions—In ANCA-GN, hematuria duration does not predict eGFR at 1 year. Our findings provide support that among individuals who are otherwise considered to be in clinical remission, the persistence of hematuria should not delay transition from induction to maintenance immunosuppression.

Keywords

ANCA; Glomerulonephritis; Hematuria; Renal function

Introduction

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis are small vessel vasculitides characterized by the presence of circulating anti-neutrophil cytoplasmic antibody (ANCA) [1]. Pauci-immune glomerulonephritis is a hallmark of ANCA-associated vasculitis (AAV) and often presents as microscopic hematuria and proteinuria, with or without an elevation in serum creatinine [2]. While persistent proteinuria is considered to be a marker of disease damage, persistent hematuria is generally considered to be a sign of disease activity. As such, it is possible that some patients may undergo a longer course of aggressive immunosuppressive therapy until their hematuria has completely resolved [3] (personal observation).

Even though hematuria is frequently used as both a diagnostic tool for glomerulonephritis and a marker of disease activity in AAV, little is known regarding the significance of prolonged hematuria and its impact on renal outcomes. Recent studies have suggested that the persistence of hematuria in patients with AAV, who are otherwise in clinical remission by all other criteria, is a sign of renal damage rather than active disease [3,4]. Since infection due to immunosuppressive agents remains the leading cause of early mortality in AAV, a better understanding of the consequences of persistent hematuria in AAV is necessary [5].

We aimed to determine whether longer hematuria duration is associated with lower estimated glomerular filtration rates (eGFR) at 1 year of follow-up among individuals with biopsy-proven ANCA-associated glomerulonephritis (ANCA-GN). We also aimed to identify clinical and laboratory predictors of hematuria resolution.

Methods

Study population

The study population consisted of individuals with GPA and MPA with renal involvement who had been treated at a tertiary care center in Baltimore, Maryland. Potential patients were identified from a pathology database using the term “pauci-immune glomerulonephritis” and searching between the years 1995 and 2011. Only those individuals who had a urinalysis at least once every 4–6 weeks and follow-up for at least 1 year were included in the study. The study protocol was approved by the Johns Hopkins University Institutional Review Board.

Acquisition of clinical and laboratory data

Patient demographics and relevant clinical and laboratory data were abstracted from the electronic medical record. Proteinuria was defined as 1+ on dipstick testing and hematuria as >5 red blood cells per high-power field (rbc/hpf). Patients were classified as having GPA or MPA based on the Chapel Hill Consensus Conference criteria [6]. Clinical remission was defined as having a Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) = 0 or a BVAS/WG = 1 (if still with microscopic hematuria but otherwise in remission by all the other criteria) [7]. Estimated glomerular filtration rate (eGFR), as determined by the 4-variable modification of diet in renal disease (MDRD) formula, was recorded at the time of diagnosis and at 1 year after biopsy [8]. Other details regarding each

individual's clinical course, duration of cyclophosphamide therapy, prednisone dose at 6 months, and time to remission were also obtained.

Outcomes and predictors

The primary outcome of interest was eGFR 1 year from the date of renal biopsy. The primary exposure was hematuria duration, defined as <90 days or ≥90 days.

Statistical analyses

Baseline characteristics of patients with hematuria less than 90 days and patients with hematuria greater than or equal to 90 days were compared using Student's *t*-test or the Wilcoxon rank-sum test for continuous variables and Fisher's exact test was used for binary or categorical variables. Linear regression models were then constructed to determine independent predictors of eGFR at 1 year. The primary exposure was hematuria duration (<90 days vs. ≥90 days). Covariates included age at time of biopsy, gender, ANCA type, baseline eGFR, and baseline proteinuria. The above analyses were repeated treating hematuria as a continuous rather than a binary variable.

In sensitivity analyses, a second linear regression model was constructed to evaluate whether clinical remission with hematuria resolution (BVAS/WG = 0) was associated with higher eGFR values at 1 year compared to clinical remission with persistent hematuria (BVAS/WG = 1). Finally, predictors of prolonged hematuria were studied using simple and multiple logistic regression models, with the outcome being hematuria duration ≥90 days. Candidate predictors were the same as those used in our primary analyses.

Data were analyzed using the Stata statistical software (Version 12, 2011; College Station, TX). *p*-Values less than 0.05 were considered statistically significant.

Results

The baseline characteristics of the 55 patients included in this study are presented in Table 1. A total of 53 patients (96%) had a new diagnosis of ANCA-GN, while the remaining 2 patients had a relapse of their disease. Mean age was 57.5 [standard deviation (SD) = 14.9] years, and median eGFR was 26 [interquartile range (IQR) = 14–44] ml/min/1.73 m². A total of 46 individuals (84%) had positive ANCA serology (21 with c-ANCA and 25 with p-ANCA). Moreover, all patients with c-ANCA were positive for PR3-ANCA, whereas all patients with p-ANCA were positive for MPO-ANCA. The remaining 9 patients were negative for ANCA by immunofluorescence (c-ANCA or p-ANCA) and ELISA (PR3-ANCA or MPO-ANCA). Among the 55 patients, 34 (62%) had hematuria for <90 days and 21 (38%) had hematuria for ≥90 days. Mean time to hematuria resolution was 92 (SD = 77) days, and mean time to clinical remission was 77 (SD = 58) days. Among the 39 individuals who received cyclophosphamide for induction therapy, mean duration of exposure to cyclophosphamide was similar between the 2 groups: 207 (SD = 139) days among patients with hematuria <90 days and 215 (SD = 73) days among those with hematuria ≥90 days (*p* = 0.81). There was also no significant difference in mean prednisone dose at 6 months: 6.4 (SD = 4.5) mg for the hematuria <90 days group vs. 6.6 (SD = 3.7) mg for the hematuria

90 days group ($p = 0.90$). At 1 year, median eGFR was 41 ml/min/1.73 m² (IQR = 28–56 ml/min/1.73 m²).

Table 2 displays the results of both the unadjusted and the adjusted linear regression models. Older age and lower baseline eGFR were independently associated with a lower eGFR at 1 year (adjusted: $p = 0.03$ and $p < 0.001$, respectively). Hematuria duration was not predictive of eGFR at 1 year ($p = 0.93$). When hematuria duration was treated as a continuous rather than a binary variable, similar conclusions were obtained ($p = 0.32$). In sensitivity analyses, individuals with hematuria resolution at the time of clinical remission were not more likely to have a higher eGFR at 1 year compared to those with persistent hematuria at the time of clinical remission (adjusted β : 3.80; 95% CI -7.49 to 15.09, $p = 0.50$).

In logistic regression models, age, gender, and baseline proteinuria were not predictive of hematuria duration. Individuals with p-ANCA were more likely to have hematuria 90 days compared to individuals with c-ANCA (adjusted OR = 4.35; 95% CI: 1.01–18.75; $p = 0.047$) or those with no ANCA (adjusted OR = 10.23; 95% CI: 1.18–88.76; $p = 0.04$). Lower baseline eGFR was also associated with increased odds of having hematuria 90 days (adjusted OR = 1.42 per 10 ml/min/1.73 m² lower baseline eGFR; 95% CI: 1.00–2.00; $p = 0.047$).

Discussion

In this study of 55 patients, we demonstrated that hematuria persistence for more than 90 days following biopsy diagnosis of ANCA-GN was not associated with a lower eGFR at 1 year of follow-up. Moreover, individuals with hematuria resolution at the time of clinical remission (BVAS/WG = 0) had similar eGFR values at 1 year of follow-up compared to individuals with persistent hematuria (BVAS/WG = 1). We also confirmed that older age and lower baseline eGFR were predictive of lower eGFR at 1 year [9].

The significance of persistent hematuria in patients with AAV, who are otherwise considered to be in clinical remission, remains unclear. Magrey et al. previously reported their experiences in 10 patients who continued to have microscopic hematuria despite being in clinical remission for more than 6 months. Although hematuria duration ranged from 6 to 38 months following achievement of clinical remission, transition from induction to maintenance therapy was not delayed. Of note, renal biopsy was repeated in 2 patients and both had findings suggestive of chronic rather than active disease [3]. In another study, Geetha et al. reported a case series of 9 patients with AAV, 6 of who underwent a repeat renal biopsy for evaluation of persistent hematuria in the setting of otherwise apparent clinical remission. None had evidence of active ANCA-GN on biopsy. Among these 6 patients, 3 eventually relapsed, but this was not until 19–59 months following the second biopsy. Moreover, all 3 relapsing patients had other clinical and laboratory findings to suggest a recurrence of their ANCA-GN [4]. Given these findings, the authors of both studies proposed that persistent microscopic hematuria was more likely a marker of renal damage rather than active disease [3,4]. Our study further supports this hypothesis, demonstrating that prolonged hematuria beyond 90 days was not associated with a lower eGFR 1 year later.

In the absence of prompt initiation of immunosuppressive therapy, patients with ANCA-GN often progress to ESRD and/or death [5,10]. Treatment initiation should be swift, consisting of an induction phase (glucocorticoids plus either cyclophosphamide or rituximab) followed by a remission maintenance phase (azathioprine, methotrexate, or mycophenolate mofetil if intolerant to the 2 aforementioned drugs) [11–16]. Such forms of immunosuppressive therapy, however, are not without risk. Potential complications include infection, leukopenia, hemorrhagic cystitis, and malignancy, among others [5,11,14]. In clinical trials of AAV, the tapering of glucocorticoid therapy begins within the first month as most patients start to show signs of clinical improvement during this time [11,14,17]. Patients with renal involvement, however, tend to have hematuria and proteinuria that persist beyond the first month. While these patients should still undergo steady tapering of their glucocorticoid therapy, as long as serum creatinine is stable and no other features of active vasculitis are present, this does not always occur in clinical practice on account of persistent hematuria [3,4]. Such a delay in transition from induction to maintenance therapy is particularly concerning as infection is one of the leading causes of mortality among patients with AAV [5].

We also examined potential predictors of hematuria persistence. Age, gender, and baseline proteinuria were not predictive of hematuria duration, whereas lower baseline eGFR and p-ANCA status were each associated with an increased odds of persistent hematuria. Individuals with p-ANCA had 4-fold higher odds of having hematuria 90 days compared to individuals with c-ANCA. This is consistent with prior histopathologic studies demonstrating that patients with p-ANCA are more likely to have chronic renal injury, such as glomerulosclerosis and interstitial fibrosis, at the time of diagnosis compared to individuals with c-ANCA, who are more likely to have features consistent with active renal disease [18,19]. We propose that the prolonged hematuria observed in those with p-ANCA is likely a reflection of such chronic renal injury.

Our study is not without limitations. First, the study was retrospective and the sample size was small. Still, our cohort is larger than the aforementioned studies published by Magrey et al. [3] and Geetha et al. [4] on this topic. Second, follow-up was short at 1 year. Third, our interpretation on the influence of baseline proteinuria on eGFR at 1 year is limited due to the lack of urinary protein quantification beyond dipstick testing. Similarly, given the retrospective nature of this study, we only had data on the number of red blood cells on urine microscopy but not on their morphology. Fifth, only individuals with a urinalysis once every 4–6 weeks were included in the study. It is possible that patients with more rapid clearing of their hematuria might not have been tested as frequently, which could lead to a selection bias. Finally, we do not have to repeat renal biopsies to confirm our hypothesis that the persistence of hematuria was more a reflection of glomerular damage rather than of active disease. Despite these limitations, our study is still important, as it is the largest series to date to examine the impact of hematuria duration on renal outcomes among individuals with biopsy-proven ANCA-GN.

The notion that persistent hematuria is always a sign of active glomerulonephritis in patients with AAV, who by all other measures are considered to be in clinical remission, may be flawed. Given the lack of association between hematuria duration 90 days and eGFR at 1

year, we propose that among patients with microscopic hematuria but otherwise in clinical remission (BVAS/ WG = 1), transition from induction to maintenance immunosuppression should not be delayed. Additional studies are needed to investigate the long-term effects of persistent hematuria on renal outcomes.

Acknowledgments

We would like to thank the patients at The Johns Hopkins Vasculitis Center. We would also like to thank Pradeep Manoharan for his contributions in data collection.

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Table 1

Baseline characteristics of patients with ANCA-associated glomerulonephritis

	Hematuria < 90 days (n = 34)	Hematuria 90 days (n = 21)	p-Value
Mean age (years)	57.5 ± 15.4	57.6 ± 14.5	0.99
Female	18 (53%)	8 (38%)	0.41
Race			0.15
Caucasian	26 (76%)	18 (86%)	
African American	8 (24%)	2 (9%)	
Other	0 (0%)	1 (5%)	
Mean creatinine (mg/dL)	3.0 ± 2.5	3.3 ± 2.0	0.60
Median eGFR (ml/min/1.73 m ²)	26 (15–44)	21 (13–37)	0.33
Proteinuria ^a	32 (94%)	20 (95%)	1.00
ANCA status			0.35
PR3-ANCA	14 (41%)	7 (33%)	
MPO-ANCA	13 (38%)	12 (57%)	
Negative	7 (21%)	2 (10%)	
Vasculitis type			1.00
GPA	18 (53%)	11 (52%)	
MPA	16 (47%)	10 (48%)	
Histopathologic classification			0.69
Focal	9 (26%)	8 (38%)	
Crescentic	9 (26%)	6 (29%)	
Sclerotic	5 (15%)	3 (14%)	
Mixed	11 (32%)	4 (19%)	
Induction therapy			
Cyclophosphamide	23 (68%)	16 (76%)	0.91
Rituximab	8 (23%)	4 (19%)	
Other (MMF, methotrexate)	3 (9%)	1 (5%)	

Values presented as mean ± standard deviation, median (interquartile range), or n (%). Abbreviations: eGFR = estimated glomerular filtration rate, ANCA = anti-neutrophil cytoplasmic antibodies, PR3 = proteinase 3, MPO = myeloperoxidase, GPA = granulomatosis with polyangiitis, MPA = microscopic polyangiitis, MMF = mycophenolate mofetil.

^aProteinuria defined as 1+ on dipstick testing.

Table 2
Results of unadjusted and adjusted linear regression models relating clinical factors to eGFR at 1 year

	Unadjusted			Adjusted		
	Difference in eGFR at 1 year	95% CI	p-Value	Difference in eGFR at 1 year	95% CI	p-Value
Hematuria 90 days vs. < 90 days	-4.19	(-19.64 to 11.27)	0.59	0.51	(-11.26 to 12.28)	0.93
Age, per 10 years older	-6.31	(-11.10 to -1.53)	0.01	-4.31	(-8.15 to -0.47)	0.03
Female	2.96	(-12.10 to 18.02)	0.70	-9.92	(-21.73 to 1.89)	0.10
ANCA type						
Negative	REF	REF	REF	REF	REF	REF
MPO-ANCA	22.87	(2.16 to 43.59)	0.03	1.89	(-15.73 to 19.51)	0.83
PR3-ANCA	8.32	(-12.91 to 29.55)	0.44	-2.52	(-18.52 to 13.48)	0.75
Baseline eGFR, per 10 ml/min/1.73 m ² lower	-7.75	(-9.85 to -5.64)	< 0.001	-7.41	(-9.96 to -4.87)	< 0.001
Proteinuria 1 + vs. < 1 + on dipstick	-2.10	(-35.24 to 31.05)	0.90	10.19	(- 14.76 to 35.14)	0.42

Abbreviations: ANCA = anti-neutrophil cytoplasmic antibodies, PR3 = proteinase 3, MPO = myeloperoxidase, eGFR = estimated glomerular filtration rate, CI = confidence interval, REF = reference group.