Eosinophilia and Risk of Incident End Stage Kidney Disease

Anam Tariq (✉ tanam1@jhmi.edu)  
Johns Hopkins Medicine  https://orcid.org/0000-0002-0728-8436

Keisuke Okamato  
Medical University of South Carolina

Azka Tariq  
Johns Hopkins Medicine

Avi Z. Rosenberg  
Johns Hopkins Medicine

Karim Soliman  
Medical University of South Carolina

David W. Ploth  
Medical University of South Carolina

Mohamed G. Atta  
Johns Hopkins Medicine

Blaithin A. McMahon  
Medical University of South Carolina

Research article

**Keywords:** eosinophilia, kidney biopsy, interstitial nephritis, end-stage-kidney-disease, inflammation

**Posted Date:** August 19th, 2019

**DOI:** https://doi.org/10.21203/rs.2.13162/v1

**License:** ©  This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

**Version of Record:** A version of this preprint was published on January 13th, 2020. See the published version at https://doi.org/10.1186/s12882-020-1685-3.
Abstract

Background Eosinophils in kidney disease are poorly understood and are often incidental findings on kidney biopsy. Eosinophilia in blood and renal biopsy tissue is associated with a host of immune and non-immune kidney diseases. The significance of eosinophilia in renal diseases has not been well addressed. We evaluated the incidence of peripheral eosinophilia (>4% of blood leukocytes) with biopsy tissue eosinophilia and their association with end-stage-kidney-disease (ESKD). Methods A nested case-control of patients who underwent kidney biopsies at Johns Hopkins Hospital and Medical University of South Carolina from 2004-2018 were included in the study. From the 616 eligible patients, 178 patients were identified through the registry of kidney biopsies as 18 years or older without missing biopsy reports or hematology results. Controls had no ESKD at the time of case definition and assembled using incident density sampling, matched on age and sex. The association of peripheral eosinophilia (>4% of peripheral blood leukocytes) with the risk of progression to ESKD was evaluated using conditional logistic model after adjusting for clinical demographics. Results Among 178 patients, 65 (37%) had peripheral eosinophilia and 113 (63%) had no eosinophilia. Compared to patients without eosinophilia, patients with peripheral eosinophilia were notably male and had a higher serum creatinine at the time of their biopsy. Peripheral eosinophilia was significantly associated with higher risk of ESKD (OR 6.2 [1.6, 23.8]) adjusted for patient demographics including hypertension, proteinuria, race and eGFR at the time of kidney biopsy. Peripheral eosinophilia had a significant linear association with tissue eosinophilia, 22 (SD 20) per high power field (hpf) in 4-10% peripheral eosinophilia, 19 (SD 18) hpf in >10% eosinophilia and 3 (SD 7) hpf in no eosinophilia (P <0.001). Conclusions Peripheral eosinophilia is an independent predictor of tissue eosinophilia and subsequent progression to ESKD. Peripheral eosinophilia may be an early biomarker for underlying inflammation and disease, but further studies to investigate this clinical association are warranted.

Background

Production of eosinophils is closely related with inflammation and the immune response to parasitic illness, asthma, hypersensitivity reactions and allergic responses (1, 2). Eosinophil elevation has been hypothesized to cause tissue and organ damage by cytotoxic effects from reactive oxygen species, and other proteins (3). The role of hypereosinophilia in kidney failure has been reported in a small number of case-reports and observational studies (1, 2). The case-reports highlight the presence of peripheral eosinophilia in interstitial nephritis (IN) secondary to medications and rare autoimmune diseases, such as IgG4-related kidney disease and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which comprises of granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome) (1, 4–9). Other rare, but distinctive diseases include neuromyelitis optica, bullous pemphigoid, autoimmune myocarditis, HIV, and Hyperimmunoglobulin E Syndrome (7, 10, 11). We conducted this study to address the role of incident peripheral eosinophilia and progression to
ESKD. We hypothesized that peripheral eosinophilia correlates with higher tissue eosinophilia and both are independently associated with the increased risk of progression to ESKD.

**Methods**

Our case-control study was nested within a longitudinal study of patients who underwent native or transplant kidney biopsies at Johns Hopkins Hospital from 2004–2018 and at Medical University of South Carolina from 2017–2018. Eligible cases included those with confirmed diagnosis of incident ESKD after enrollment. Controls consisted of patients who underwent kidney biopsy from 2004–2018 who did not progress to ESKD after enrollment. This study was approved by the institutional review boards at Johns Hopkins University and the Medical University of South Carolina.

From the 616 eligible patients, 178 patients were identified through the registry of kidney biopsies excluding patients with kidney failure requiring dialysis (n = 19), chronic kidney disease (CKD) stage V patients with biopsy confirmed ESKD at the time of enrollment (n = 7), and those with missing biopsy or hematology data (n = 590) (Figure 1). Patients were 18 years and older who underwent kidney biopsy for confirmation of their kidney diagnosis. We included patients who met the Kidney Disease Improving Global Outcomes (KDIGO) criteria for acute kidney injury (AKI) (12) with and without abnormal clinical findings of hematuria, pyuria or proteinuria. For each case, two controls were selected and matched on sex, age and duration of follow-up time since biopsy. While we could not match on diagnoses given limited sample size, we did demonstrate the spectrum of etiologies in those with and without peripheral eosinophilia.

**Exposure measurement**

Incident peripheral eosinophilia was assessed at enrollment using hematology reports at the time of kidney biopsy and analyzed as a binary variable. Eosinophil percentage was used instead of absolute eosinophil count for clinical relevance and as previously described (6), no eosinophilia as <4% of peripheral blood leukocytes (WBC) and peripheral eosinophilia as >4% of WBC. We further categorized the severity of peripheral eosinophilia as 4%–10%, and ≥10%.

**Outcome measurement**

The primary outcome was defined as incident progression to ESKD, classified by estimated glomerular filtration rate (eGFR) <5 mL/min/1.73 m², an International Classification of Diseases Ninth/Tenth (ICD–9/10) revision code for a kidney disease-related hospitalization or death, per nephrologists diagnosis for patients requiring renal replacement therapy, and/or repeat kidney pathology suggesting extensive chronic, irreversible changes in the biopsy specimen.
Covariates

All socio-demographical and clinical information were obtained at enrollment using Epic electronic medical records (EMR). Past medical history (hx) of atopic illness, filarial disease, asthma, and kidney transplantation were defined as binary variables. Similarly, history of hypertension (HTN), diabetes and medication use of proton pump inhibitor (PPI) were defined as binary variables. eGFR was obtained as patients’ “normal” eGFR prior to study entry and assessed by combination of previous medical records and laboratory chemistries. Other baseline variables measured as continuous variables at the time of enrollment included serum creatinine (Cr), serum Immunoglobulin E (IgE) levels, complements (C3, C4), proteinuria, and urine eosinophils.

The indication for kidney biopsy was characterized by four categories as per the nephrologists’ standard orders in ICD–9/10: AKI, CKD, AKI on CKD (AOCKD), or nephrotic syndrome. We characterized urine proteinuria based on the urine-protein-creatinine ratio (UPCR) and on urinalyses, as trace, +1, + 2, + 3, or +4 as reported by standard laboratory processing. Urinalyses was also assessed for the presence of pyuria and hematuria.

Tissue from kidney biopsy specimens was processed in the pathology departments using standard methods for light, immunofluorescence, and electron microscopy. The exact locations of the eosinophils were captured on the tissue specimens, and other inflammatory markers (e.g. lymphocytes and plasma cells) were documented using individual biopsy reports. The number of eosinophils were documented as per hpf. Per pathologists, tissue eosinophilia was characterized as: “rare” if <5 hpf, “few” if 5–10 hpf, “many” if >10 hpf, and “numerous” if >25 hpf. Pathologists independently evaluated biopsy slides to establish primary and secondary diagnoses, including acute tubular injury, chronic changes, or other kidney biopsy abnormalities such as IN.

Statistical Methods

Analysis of variance (ANOVA) and X² t-test were used for statistical analysis on demographics and clinical characteristics. Results were reported as proportions for binary or categorical variables and mean for continuous variables. Pearson’s correlation was used to evaluate possible correlations amongst all the variables, but since no strong correlations existed, none of the variables were eliminated. Sex and age are known, strong confounders and therefore matched upon (13). Race was not matched in order to evaluate the independent effect of it on our outcome. Every case (n = 24) was matched to two controls, of the same sex, age and follow-up time (months) from biopsy.

Matched odds ratios (OR) for ESKD, calculated, as an estimate of the hazard ratio, and corresponding 95% confidence (CIs) were estimated using conditional logistic regression. Both univariate and multivariate models were used to show associations. A final multivariate model was created through stepwise elimination of variables of interest from univariate analysis while biologically relevant variables
were retained, with the intent of using one variable for every 10 outcomes to avoid overfitting of the model. Additional analyses were conducted for baseline clinical demographics and statistical significance was determined with the use of likelihood-ratio test. HTN, race, diabetes, and Cr. UPCR and eGFR were included in multivariate models because they are strong predictors for ESKD (14, 15). All analyses were performed using Stata version 15.1 (StataCorp, College Station, TX) (16).

Sensitivity analyses were performed using peripheral eosinophilia as a continuous variable. Univariate and multivariate analyses showed significant associations with higher degree of peripheral eosinophilia and ESKD. UPCR was also modeled as a binary variable and per KDIGO guidelines, normal UPCR defined as <0.5mg/dl in 24-hour urine (17). The area under the ROC (AUC) was calculated to assess the ability of peripheral eosinophilia to discriminate between ESKD progressors and non-progressors.

Results

In the overall study population, 65 (37%) of 178 patients had peripheral eosinophilia and 113 (63%) had no eosinophilia, 101 (57%) were male, 88 (49%) white and mean age of 52±17 years. Among those with peripheral eosinophilia, 38 (58%) had 4%–10% eosinophilia and 27 (42) >10% eosinophilia. Those with peripheral eosinophilia were significantly males with higher mean Cr at enrollment, but without significant hx of HIV, kidney transplantation or asthma (Table 1). The most common reasons for their consultations and kidney biopsies were AOCKD (51%), AKI (35%) and nephrotic syndrome (8%). Table 2A demonstrates the spectrum of etiologies which were comparatively balanced in this cohort when stratified by eosinophilia, however, there was a higher proportions of ANCA-associated vasculitis, FSGS, and lupus nephritis in the cohort of patients without eosinophilia compared to patients with peripheral eosinophilia, albeit non statistically significant.

Of those patients who progressed to ESKD and peripheral eosinophilia (n = 22), biopsy confirmed primary clinical diagnoses of interstitial nephritis, diabetic nephropathy, acute tubular injury, arteriosclerosis, ANCA-associated vasculitis and primary focal segmental glomerulosclerosis (FSGS) (Table 2B). Overall, mean follow-up time to incident ESKD was 64 ± 49 months. Seven patients with 4–10% eosinophilia and 14 patients with >10% eosinophilia had mean duration of 44±49 months and 35±24 months to ESKD, (P = 0.14), as shown in Table 3. Those with peripheral eosinophilia had significant relationship with ESKD compared to those without eosinophilia (P<0.001).

Figure 2 depicts the fastest decline of kidney function among those with >10% eosinophilia compared to those with 4–10% eosinophilia or no eosinophilia. Half of those with eosinophilia >10% progressed to ESKD by 65 months. Table 3 shows 4–10% eosinophilia had 22 (SD 20) per hpf kidney tissue eosinophil infiltrate on average compared to those patients without eosinophilia 3 (SD 7) per hpf. Patients with >10% eosinophilia had 19 (SD 18) per hpf. Tissue eosinophilia increased linearly for every 1% increase in peripheral eosinophilia (P<0.001).

Progressors to ESKD were more likely to have peripheral eosinophilia (92% cases versus 27% controls, P < 0.004) and higher UPCR at 4.7g/g (SD 5.4) in cases versus 2.4 g/g (SD 3.0) in controls (P < 0.039).
History of asthma, HIV, kidney transplantation or filarial disease were not associated with ESKD. The presence of urinary eosinophils had also had a positive, but non-significant association with ESKD in 72 patients (OR 6.4 [0.8, 53.9], \(P = 0.087\)) (data not shown).

Presence of peripheral eosinophilia was associated with higher risk of progression to cases of ESKD (crude OR 6.7 [2.1, 21.1], \(P < 0.001\)) compared to those who did not progress to ESKD (Table 3). Adjusting for baseline eGFR, UPCR and Cr, patients with peripheral eosinophilia had approximately 5-fold significantly higher association with ESKD (OR 4.9 [1.4, 17.2]) compared to those without eosinophilia. The association was also significantly increased after adjusting for HTN (OR 7.4 [2.4, 23.3]), race (OR 7.9 [2.4, 26.1]), or diabetes (OR 6.7 [2.1, 21.4]) in univariate models. African Americans had a significant 3-fold higher risk of ESKD compared to whites (OR 3.4 [1.1, 9.9], \(P < 0.001\)), when adjusted for eosinophilia. In the overall study population, the AUCs for peripheral eosinophilia in predicting progression to ESKD during follow-up was 0.87 compared to AUC of 0.85 in sensitivity analysis, where UPCR was used as binary variable, according to KDIGO normal and abnormal values of UPCR (Figure 3).

**Discussion**

These prospective findings demonstrate a positive association between peripheral eosinophilia and the subsequent progression to ESKD with significantly greater than 5-fold higher risk, even after fully adjusted models (OR 6.2 [1.6, 23.8], \(P = 0.007\)). This association was slightly stronger in African Americans and remained significant after adjustment for eGFR, proteinuria, and Cr. Overall, in the study population, mean follow-up was 64±49 months. These results suggest that the association between ESKD and peripheral eosinophilia is independent of HTN, diabetes, UPCR, eGFR, Cr, age, sex and race. Moreover, patients with peripheral eosinophilia who progressed to ESKD had a higher incidence of tissue eosinophil infiltration on biopsy specimens.

Generally, eosinophilia is associated with allergies, parasitical infections, fungal infections, asthmatic conditions, and drug reactions (e.g. nonsteroidal anti-inflammatory drug [NSAID], antibiotics, PPI) there are a number of case reports that have highlighted an association of eosinophilia in kidney diseases such as kidney carcinoma (4, 18–20), thrombotic thrombocytopenic purpura (21), transplant rejection (22–24), and kidney replacement modalities (25–28). However, eosinophilia has not been used as a marker for determining future risk of kidney disease. Patients with eosinophilia who developed ESKD in our cohort were less likely to have a history of asthma, filarial disease, atopic disease, allergic responses and were more likely to have diagnoses other than IN on renal biopsy, such as diabetic nephropathy, acute tubular injury, hypertensive renal disease and IgA nephropathy. This is consistent with a prior report highlighting the presence of urine eosinophils in other non-specific renal pathologies other than IN (29). In our study, the presence of urinary eosinophils had a positive, but non-significant association with ESKD in 72 patients.

Physiological studies have shown eosinophils are activated by receptors in response to inflammatory and immunological pathways in the presence of an allergen or pathogen, resulting in the release of cytokines,
chemokines and T cells (2, 30). Eosinophils can express MHC class II and may act as antigen presenting cells. After traveling to regional lymph nodes, where they encounter CD4 T cells, eosinophils promote proliferation and cytokine production of IL-4, IL-5, and IL-13. A potential key component may be via upregulation of dendritic cells, mast cells, basophils, neutrophils and T cells (2). One theory is that eosinophils are mediated by specific types of T-helper cells that result in higher cytokine production, including TNF-alpha and IL-9, and this contributes to interstitial atrophy, irreversible fibrosis, and eventually ESKD (31). This theory is evident in recent studies in the field of IgG4-related kidney disease, where peripheral and tissue eosinophilia can progress to irreversible fibrotic dysfunction or organ failure (32, 33). The upregulation of T helper cells and cytokines IL-4, IL-5, IL-13, and IL-21, are thought to trigger a cascade of IgE production, macrophage activation and differentiation of B cells to plasma cells, whereby producing IgG4. Upregulation of T cells may also result in activation of TGF-beta, increasing fibroblast activation and promoting additional fibrosis formation. Similarly, Macdonald et al. have shown that renal allograft dysfunction and acute vascular rejection are associated when there is extensive eosinophil infiltration in kidney biopsies (34). Taken together, these previous studies show support the paradigm of peripheral eosinophilia infiltration and accumulation of their cytokines to stimulate fibroblast proliferation and promote tissue destruction, specifically in the kidney. This theory is supported by our study, which demonstrates higher tissue eosinophil infiltration in biopsies among ESKD progressors. This strong association with ESKD outcomes was also seen when investigating the presence of tissue eosinophils, as either continuous or categorical. Peripheral eosinophilia on routine laboratory results of patients undergoing kidney biopsy may indicate increased risk from aberrant inflammatory states, including underlying comorbidity(ies) and specific medication use. Peripheral eosinophilia may be an indicator for kidney damage and the severity of this marker may predict future irreversible interstitial damage, similar to the utility of CRP as a good clinical marker for inflammation and atherosclerosis (35, 36).

There are several limitations to our study including a small study population, which made multivariate modeling challenging in order to avoid overfitting the model as well as presence of unmeasured covariates (i.e. use of polypharmacy medications). Second, peripheral eosinophilia was measured at single point in time, and there may be some element of residual confounding on repeat testing. Prognosis of renal outcomes may be dependent on the etiology of kidney disease but was not matched in this cohort due to the limited sample size and this could result in confounding and selection bias. However, both progressors and non-progressors had a similar spectrum of kidney disease diagnoses other than IN (Table 2A and 2B), with higher incidence of ANCA-associated vasculitis, primary FSGS, and lupus nephritis in the cohort of patients without eosinophilia who subsequently failed to progress to ESRD (P = 0.29).

Several factors should be considered in the interpretation of our findings. We believe our study highlights new information that has not been evaluated between eosinophilia and ESKD, specifically the higher incidence of peripheral eosinophilia and higher risk of progression to ESKD. We believe that matching one case to two controls by sex, age and follow-up time post kidney biopsy increased the power and precision over the course of a 14-year study. Conducting a nested case-control study in a prospective cohort rather
than a traditional case-control study reduces several forms of selection biases and allows for temporal relationship between the exposure and occurrence of outcome. Moreover, using a matched study design allowed direct estimation of risk from odds. Participants were hospitalized from two tertiary referral centers at Johns Hopkins Hospital and the Medical University of South Carolina, representing diverse cultural populations in the north and south US.

**Conclusions**

We conclude that eosinophilia can be seen in various kidney conditions and peripheral eosinophilia together with tissue eosinophil infiltration is significantly associated with progression to ESKD. Future prospective population-based studies should be conducted to determine the significance of biopsy tissue eosinophil infiltration and peripheral eosinophilia in the progression of ESKD, with a better emphasis on medication, comorbid illnesses, repeat biopsies and types of kidney disease diagnoses.

**List Of Abbreviations**

AKI - Acute Kidney Injury  
ANCA - antineutrophil cytoplasmic antibody  
ANOVA - Analysis of variance  
AOCKD - AKI on CKD  
CKD - chronic kidney disease  
C3, C4 - Complements  
CRP - C-reactive Protein  
Cr - creatinine  
EGPA - and eosinophilic granulomatosis with polyangiitis  
eGFR - estimated glomerular filtration rate  
EMR - electronic medical records  
ESKD - end-stage-kidney-disease  
GPA - granulomatosis with polyangiitis  
Hpf - high power field  
HTN - hypertension
Hx - history

ICD-9/19 - International Classification of Diseases Ninth/Tenth

IgE - Immunoglobulin E

IN - interstitial nephritis

KDIGO - Kidney Disease Improving Global Outcomes

MHC - Major histocompatibility complex

MPA - microscopic polyangiitis

NSAID - nonsteroidal anti-inflammatory drug

OR - odds ratios

PPI - proton pump inhibitor

UPCR - urine-protein-creatinine ratio

WBC - blood leukocytes

**Declarations**

**Acknowledgements**

We would like to thank Dr. Marco Delsante, Dr. Diener-West and Dr. Jim Tonascia for their help.

**Author Contributions**

Keisuke Okamato, David Ploth, Azka Tariq, and Karim Soliman helped with the data collection and reviewed the manuscript. Avi Z. Rosenberg extracted data from kidney biopsies, analyzed the kidney biopsy tissues and reviewed the manuscript. Anam Tariq, Mohamed G. Atta and Blaithin A. McMahon collected the data, analyzed it and prepared the manuscript.

**Statement of Ethics**

The research was conducted ethically in accordance with the World Medical Association of Helsinki. The study protocol was approved by the IRB at Johns Hopkins University and Medical University of South Carolina.

**Competing Interests**

The authors declare they have no competing interests.
Consent for Publication

Not applicable

Funding Statement

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Kargili A, Bavbek N, Kaya A, Kosar A, Karaaslan Y. Eosinophilia in rheumatologic diseases: a prospective study of 1000 cases. Rheumatol Int. 2004;24(6):321-4.
2. Akuthota P, Wang HB, Spencer LA, Weller PF. Immunoregulatory roles of eosinophils: a new look at a familiar cell. Clin Exp Allergy. 2008;38(8):1254-63.
3. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017;92(11):1243-59.
4. Kirkland GS, Savige J, Wilson D, Heale W, Sinclair RA, Hope RN. Classical polyarteritis nodosa and microscopic polyarteritis with medium vessel involvement–a comparison of the clinical and laboratory features. Clin Nephrol. 1997;47(3):176-80.
5. Ohashi N, Sugiura T, Isozaki T, Yamamoto T, Hishida A. Anti-glomerular basement membrane antibody-induced glomerulonephritis with periglomerular granulomatous reaction and massive renal eosinophilic infiltration. Am J Kidney Dis. 2003;42(3):E28-35.
6. Renston JP, Goldman ES, Hsu RM, Tomashfski JF, Jr. Peripheral blood eosinophilia in association with sarcoidosis. Mayo Clin Proc. 2000;75(6):586-90.
7. Ten RM, Torres VE, Milliner DS, Schwab TR, Holley KE, Gleich GJ. Acute interstitial nephritis: immunologic and clinical aspects. Mayo Clin Proc. 1988;63(9):921-30.
8. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore). 1999;78(1):26-37.
9. Hegarty J, Chiu DY, Middleton RJ, Haeney MM, Newstead CG, Bruce IN, et al. Systemic lupus erythematosus, eosinophilic vasculitis and acalculous cholecystitis. Nephrol Dial Transplant. 2006;21(3):792-5.
10. Kamali S, Kasapoglu E, Akturk F, Gul A, Inanc M, Ocal L, et al. Eosinophilia and hyperimmunoglobulinemia E as the presenting manifestations of Wegener's granulomatosis. Clin Rheumatol. 2003;22(4-5):333-5.
11. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. The prevalence and meaning of eosinophilia in renal diseases on a nephrology consultation service. Nephrol Dial Transplant. 2011;26(8):2549-58.
12. Chu R, Li C, Wang S, Zou W, Liu G, Yang L. Assessment of KDIGO definitions in patients with histopathologic evidence of acute renal disease. Clin J Am Soc Nephrol. 2014;9(7):1175-82.
13. Chang PY, Chien LN, Lin YF, Wu MS, Chiu WT, Chiu HY. Risk factors of gender for renal progression in patients with early chronic kidney disease. Medicine (Baltimore). 2016;95(30):e4203.
14. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63(4):1468-74.
15. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol. 2009;20(5):1069-77.
16. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. 2017.
17. Outcomes KDIG. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2013;3(3).
18. Hermida Lazcano I, Garcia Diez F, Nerin Sanchez C, Martinez Alvarez R, Jimenez Saenz J. [Eosinophilia: initial presentation form of hypernephroma]. An Med Interna. 1997;14(6):320-1.
19. Moroni M, Porta C, De Amici M, Quaglini S, Cattabiani MA, Buzio C. Eosinophils and C4 predict clinical failure of combination immunotherapy with very low dose subcutaneous interleukin-2 and interferon in renal cell carcinoma patients. Haematologica. 2000;85(3):298-303.
20. Hazouard E, Clement B, Ferrandiere M, Mayelo V, Linassier C, Legras A. [Major circulatory and medullary eosinophilia revealing renal cell carcinoma]. Presse Med. 1998;27(24):1218.
21. Liapis H, Ho AK, Brown D, Mindel G, Gleich G. Thrombotic microangiopathy associated with the hypereosinophilic syndrome. Kidney Int. 2005;67(5):1806-11.
22. Meleg-Smith S, Gauthier PM. Abundance of interstitial eosinophils in renal allografts is associated with vascular rejection. Transplantation. 2005;79(4):444-50.
23. Thomson PD, Meyers KE. Eosinophilia as an early predictor of acute cellular rejection in pediatric renal transplants. Transplant Proc. 1994;26(1):69-71.
24. Weir MR, Hall-Craggs M, Shen SY, Posner JN, Alongi SV, Dagher FJ, et al. The prognostic value of the eosinophil in acute renal allograft rejection. Transplantation. 1986;41(6):709-12.
25. Gwinner W, Menne J, Lonnemann G, Bahlmann F, Koch KM, Haller H. Life-threatening complications of extracorporeal treatment in patients with severe eosinophilia. Int J Artif Organs. 2005;28(12):1224-7.
26. Thakur SS, Unikowsky B, Prichard S. Eosinophilic peritonitis in CAPD: treatment with prednisone and diphenhydramine. Perit Dial Int. 1997;17(4):402-3.
27. Oh SY, Kim H, Kang JM, Lim SH, Park HD, Jung SS, et al. Eosinophilic peritonitis in a patient with continuous ambulatory peritoneal dialysis (CAPD). Korean J Intern Med. 2004;19(2):121-3.
28. Backenroth R, Spinowitz BS, Galler M, Golden RA, Rascoff JH, Charytan C. Comparison of eosinophilia in patients undergoing peritoneal dialysis and hemodialysis. Am J Kidney Dis.
Table 1. Baseline characteristics of patients who underwent kidney biopsy and their baseline eosinophilia on hematology
### Demographics

|                      | No Eosinophilia | Peripheral Eosinophilia |
|----------------------|-----------------|-------------------------|
|                      | ≤ 4% (N=113)    | > 4% (N=65)             |
| **Female**           | 56 (50%)        | 21 (31%)                |
| **Age, mean (SD), y**| 51 (17)         | 53 (18)                 |
| **Race**             |                 |                         |
| White                | 57 (50%)        | 31 (48%)                |
| Black                | 47 (42%)        | 30 (46%)                |
| Other                | 9 (8%)          | 4 (6%)                  |
| **Asthma**           | 17 (15%)        | 8 (12%)                 |
| **Filarial Disease** | 0 (0%)          | 1 (2%)                  |
| **HIV**              | 15 (14%)        | 4 (6%)                  |
| **Transplant**       | 18 (16%)        | 8 (13%)                 |
| **HTN**              | 80 (71%)        | 42 (70%)                |
| **eGFR stage**       |                 |                         |
| I - II               | 98 (87)         | 58 (91)                 |
| III                  | 10 (9)          | 3 (3)                   |
| IV-early V           | 5 (4)           | 4 (6)                   |
| **Diabetes**         | 19 (17)         | 15 (23)                 |
| **Mean UPCR (SD), g**| 3.4 (9.9)       | 3.2 (4.5)               |
| **Mean Cr at biopsy (SD), mg/dl** | 2.9 (2.9) | 3.9 (3.9) |
| **Indication for Kidney Biopsy** |           |                         |
| AKI                  | 43 (37)         | 24 (35)                 |
| CKD                  | 2 (1)           | 0 (0)                   |
| AKOCKD               | 39 (27)         | 35 (51)                 |
| Nephrotic Syndrome   | 31 (27)         | 6 (8)                   |

Results expressed as n (%), unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; HTN, hypertension; eGFR, estimated glomerular filtration rate; UPCR, urine-protein-creatinine-ratio; Cr, creatinine; AKI, acute kidney injury; CKD, chronic kidney disease; AKOCKD, acute on chronic kidney injury.

**Table 2A.** Etiology of kidney diseases stratified by presence or absence of eosinophilia.
| Primary Diagnosis                              | No Eosinophilia (N=113) | Peripheral Eosinophilia (N=65) |
|-----------------------------------------------|-------------------------|--------------------------------|
| Interstitial nephritis                        | 5 (4)                   | 18 (28)                        |
| Diabetic nephropathy                          | 14 (12)                 | 9 (14)                         |
| Hypertensive arteriosclerosis                 | 7 (6)                   | 4 (6)                          |
| Primary focal segmental glomerulosclerosis    | 19 (17)                 | 3 (5)                          |
| Membranous nephropathy                        | 3 (3)                   | 5 (8)                          |
| Membranoproliferative glomerulosclerosis      | 14 (12)                 | 5 (8)                          |
| Lupus nephritis                               | 10 (9)                  | 2 (3)                          |
| ANCA vasculitis                               | 11 (10)                 | 5 (8)                          |
| Acute tubular injury                          | 6 (5)                   | 8 (12)                         |
| T cell/Antibody-mediated rejection            | 7 (6)                   | 1 (2)                          |
| Amyloid                                       | 3 (3)                   | 0                              |
| Thrombotic microangiopathy                    | 4 (4)                   | 1 (2)                          |
| Scleroderma                                   | 2 (2)                   | 1 (2)                          |
| IgA nephropathy                               | 1 (1)                   | 1 (2)                          |
| Other*                                        | 7 (6)                   | 2 (3)                          |

Displayed as n (%).

ANCA defined as antineutrophil cytoplasmic antibody

* Other defined as minimal change disease, oxalate nephropathy, Alports disease, IgG Kappa nephropathy, calcineurin toxicity, thin basement membrane, post-infectious glomerulonephritis.

**Table 2B.** Etiology of kidney diseases stratified by presence or absence of eosinophilia – cases who progressed to ESRD.
| Primary Diagnosis                               | No Eosinophilia (n=2) | Peripheral Eosinophilia (n=22) |
|------------------------------------------------|------------------------|--------------------------------|
| Interstitial nephritis                         | -                      | 7 (31)                         |
| Diabetic nephropathy                           | -                      | 4 (18)                         |
| Hypertensive arteriosclerosis                  | -                      | 2 (9)                          |
| Primary focal segmental glomerulosclerosis     | 1 (50)                 | 1 (5)                          |
| Membranous nephropathy                         | -                      | -                              |
| Membranoproliferative glomerulosclerosis       | -                      | -                              |
| Lupus nephritis                                | -                      | -                              |
| ANCA vasculitis                                | -                      | 2 (9)                          |
| Acute tubular injury                           | -                      | 4 (18)                         |
| IgA nephropathy                                | -                      | 1 (5)                          |
| T cell/Antibody-mediated rejection             | 1 (50)                 | 1 (5)                          |
| Amyloid                                        | -                      | -                              |
| Thrombotic microangiopathy                     | -                      | -                              |
| Scleroderma                                    | -                      | -                              |
| *Other                                          | -                      | -                              |

Displayed as n (%).

ANCA defined as antineutrophil cytoplasmic antibody.

* Other defined as minimal change disease, oxalate nephropathy, Alport's disease, IgG Kappa nephropathy, calcineurin toxicity, thin basement membrane, post-infectious glomerulonephritis.

Table 3. Progressors and non-progressors to ESKD stratified by the presence and absence of eosinophilia in study population

|                                    | No Eosinophilia | Peripheral Eosinophilia | Peripheral Eosinophilia | P-value* |
|------------------------------------|-----------------|-------------------------|-------------------------|----------|
|                                    | ≤ 4% (N=113)    | 4-10% (N=38)            | ≥10% (N=27)             |          |
| ESKD, n (%)                        | 2 (2)           | 7 (18)                  | 15 (56)                 | < 0.001  |
| No ESKD, n (%)                     | 111 (98)        | 31 (82)                 | 12 (44)                 |          |
| Time to ESKD, mean (SD), months    | 74 (30)         | 44 (49)                 | 35 (24)                 | 0.14     |
| Renal tissue biopsy eosinophil      |                 |                         |                         |          |
| infiltrate                         | 96 (84)         | 27 (71)                 | 14 (52)                 | ---      |
| n (%)                              | 3 (7)           | 22 (20)                 | 19 (18)                 | < 0.001  |
| mean (SD), hpf                     |                 |                         |                         | 0.001**  |

*P-value calculated by analysis of variance (ANOVA) test of means for continuous variables and categorical variables. X² test calculated for binary variables. P<0.05 considered statistically significant.

Abbreviations: ESKD, end-stage-kidney-disease

Peripheral Eosinophilia is defined as eosinophils >4% of blood leukocytes; Time to ESKD defined as months from the time of kidney biopsy.

**linear association of peripheral eosinophilia on tissue eosinophils per high power field (hpf)
Figures

Figure 1

Nested Case-Control Study from a Prospective Kidney Biopsy Study

Figure 2
Survival Time from End-Stage-Kidney-Disease by Eosinophilia in the Cohort Study

Figure 3

AUC of peripheral eosinophilia to predict progression to ESKD in this study population and in sensitivity analysis