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CLINICAL RESEARCH

Patient Outcomes in Renal-Limited Antineutrophil Cytoplasmic Antibody Vasculitis With Inactive Histology

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Introduction: Little is known about the anticipated disease course for individuals who present with renal-limited antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis but who lack inflammation on a kidney biopsy. The impact of immunosuppression on renal and overall survival is unknown.

Methods: Patients were recruited from 2005 to 2016 from 8 centers worldwide (N = 16) for this descriptive study. All had positive ANCA, elevated serum creatinine with active urine sediment, histologic evidence of pauci-immune glomerulonephritis without active lesions, and had no evidence of extrarenal vasculitis. We describe the characteristics of this cohort and the differences in the clinical, histologic, and therapeutic parameters of those who developed primary outcomes of end-stage renal disease (ESRD) and vasculitis relapse. The cohort was 63% Caucasian, and 75% were men, with a median age of 62 years. At entry, the mean ± SD estimated glomerular filtration rate (eGFR) was 24 ± 20 ml/min per 1.73 m^2, and 5 patients required dialysis. Twelve patients received immunosuppressive therapy, 25% experienced disease relapse, and 38% developed ESRD.

Results: Patients who developed ESRD had lower baseline eGFRs (8 ± 5 ml/min per 1.73 m^2 vs. 35 ± 18 ml/min per 1.73 m^2; $P = 0.001$) and more often required dialysis at presentation (83% vs. 0%; $P = 0.001$). Patients who relapsed were less likely to receive immunosuppression (25% for the relapsed group vs. 92% for the nonrelapsed group; relative risk: 0.27, risk difference: 67%; $P = 0.03$).

Conclusion: Among these patients, lower initial eGFR and dialysis dependence at presentation might increase the risk for ESRD. Immunosuppression did not affect renal outcomes in this sample of patients but was associated with a reduced risk for vasculitis relapse. More information is needed on factors that predict treatment response in this high-risk group.

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Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is characterized histologically by small vessel inflammation with few or no immune deposits.[1,2] Renal involvement is initially marked by crescentic glomerulonephritis with fibrinoid necrosis, and over time by glomerular sclerosis, fibrous crescents, and tubulointerstitial fibrosis.[2,3] Various histologic markers carry prognostic significance for renal survival. The percentage of normal glomeruli and active cellular crescents are associated with renal function recovery, but the percentage of global sclerosis, fibrous crescents, and tubulointerstitial disease predict poor outcomes.[2,4–8]

Rarely, the initial biopsy falls outside traditional histologic findings and is devoid of active glomerulonephritis, posing a prognostic and therapeutic dilemma for clinicians. It is believed that such patients experience prolonged subclinical disease, and by the time they present, they have severe renal dysfunction and no symptomatic or histologic evidence of active inflammation. In the setting of apparent irreversible damage and no acute activity, the benefit of an

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immunosuppression regimen that carries non-negligible toxicity is unclear. There is currently no data on outcomes or optimal therapy for these patients, and the impact of immunosuppression on renal and overall survival in this population is unknown.

We illustrate a series of patients with renal-limited AAV who presented without systemic evidence of inflammation and who had initial kidney biopsies that were devoid of active glomerulonephritis. The purpose of this study was to describe clinical, histologic, and therapeutic parameters in a group of patients with this rare clinical presentation. As an attempt to gain insight into the role of immunosuppression for these patients, our primary aim was to explore the relationship between receipt of immunosuppression and the development of end-stage renal disease (ESRD) and vasculitis relapse.

METHODS

Study Population

The study population was derived from a retrospective cohort from 8 centers worldwide (Johns Hopkins Hospital Vasculitis Clinic, Baltimore, MD, USA; Massachusetts General Hospital, Boston, MA, USA; Ohio State University, Cleveland, OH, USA; Peking University First Hospital, Beijing, China; Trinity Health Kidney Center, Dublin, Ireland; Mount Sinai Hospital, University Health Network, Toronto, Ontario, Canada; and University College London Centre for Nephrology, Royal Free Hospital, London, United Kingdom) between 2005 and 2016. Inclusion criteria for this study were the following: presence of clinical evidence of active glomerulonephritis manifested as an increase in serum creatinine, hematuria, and proteinuria; positive ANCA serology; no evidence of active vasculitis on renal biopsy; and absence of symptoms and signs of extrarenal vasculitis. Patients were excluded if they had antiglomerular basement membrane antibodies. The study protocol was approved by the institutional review board at each institution. Sixteen patients were eligible for analysis.

Clinical Data Acquisition

Age, sex, disease phenotype, ANCA serotype, new diagnosis versus established diagnosis, and clinical features at presentation were ascertained. Estimated glomerular filtration rate (eGFR) at presentation, 6 months, and at last follow-up, occurrence of disease relapse, need for renal replacement therapy at the time of presentation and at last follow-up, details of induction therapy, and maintenance immunosuppression were extracted from review of clinical source documents. All kidney biopsies were reviewed to ensure there was no evidence of active renal vasculitis. Adverse events, including new-onset diabetes, episodes of leukopenia (white blood count $<4000/mm^3$), and infections that required hospitalization were recorded.

Laboratory Data Acquisition

Serum creatinine at the time of diagnosis was recorded according to the local laboratory. ANCA testing was done by standard indirect immunofluorescence assay on ethanol fixed neutrophils for cytoplasmic ANCA and perinuclear ANCA. Proteinase-3 and myeloperoxidase (MPO) testing by direct enzyme-linked immunosorbent assay were performed according to the local laboratory.

Outcomes

We evaluated outcomes of ESRD and vasculitis relapse during follow-up.

Study Definitions

Disease phenotype was defined according to the Chapel Hill Consensus nomenclature.[1] Renal function was measured using the 4-variable Modification of Diet in Renal Disease formula for eGFR.[9] ESRD was defined by the ongoing need for renal replacement therapy for >3 months. Hematuria was defined as urinary red blood cell count of >5 per high-power field. Kidney involvement was defined by diagnostic renal biopsy. Lack of disease activity was defined by absence of cellular crescents, fibrocellular crescents, and necrotizing lesions on renal biopsy. Interstitial fibrosis was graded as mild, moderate, and severe depending on extent of involvement (<25%, 25%−50%, >50%). Remission was defined as stabilization or improvement in serum creatinine, resolution of hematuria, and absence of extrarenal signs of vasculitis for at least 1 month. Relapse was defined as occurrence of signs and symptoms of vasculitis in any organ that required a change in immunosuppressive therapy after achieving remission.

Statistical Analyses

All descriptive data are presented as median with range or mean ± SD. We described the differences between clinical and histologic parameters between the ESRD groups. Data were tabulated for the full sample and were also divided by ESRD and relapse group. The group differences were tested using Student's *t*-test and Fisher's exact tests. All tests of significance were 2-sided, and differences were considered significant if the *P* value was <0.05.

RESULTS

Patient Characteristics

Table 1 shows baseline patient characteristics. All patients presented with new-onset vasculitis. One patient

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