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Original contribution

Validation of a histopathologic classification scheme for antineutrophil cytoplasmic antibody–associated glomerulonephritis☆,☆☆

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Summary Antineutrophil cytoplasmic antibody–associated small-vessel vasculitides cause multiple organ system disease including rapidly progressive glomerulonephritis. Recently, Berden et al (*J Am Soc Nephrol*. 2010;21:1628-1636) proposed a new histopathologic classification scheme separating renal biopsies into 4 classes: focal, crescentic, mixed, and sclerotic. We validated the prognostic implications of this classification scheme in a retrospective cohort study of 67 individuals with antineutrophil cytoplasmic antibody glomerulonephritis who underwent kidney biopsy in Calgary, Alberta, between 2005 and 2010. Their biopsies were rescored according to the classification scheme of Berden et al. Additional tubulointerstitial parameters were also scored. Clinical information including demographics and creatinine values at presentation and 1-year follow-up was retrieved. The mean age was 60 years. Forty-one percent were female. Biopsies were classified as follows: 35% crescentic, 32% mixed, 21% focal, and 11% sclerotic. Ten patients (14%) died within 1 year. Among surviving patients, the overall mean (95% confidence interval) change in estimated glomerular filtration rate (eGFR) at 1 year was 11 (7-15) mL/min per 1.73 m^2, and this change significantly differed (P = .02) between the classes: 19 (11-27) mL/min per 1.73 m^2 with crescentic histology, 11 (1-21) mL/min per 1.73 m^2 with focal, 8 (3-13) mL/min per 1.73 m^2 with mixed, and −4 (−7 to −1) mL/min per 1.73 m^2 with sclerotic. Tubulointerstitial pathology parameters did not predict outcomes. Patients with crescentic class biopsies showed significantly more improvement in eGFR at 1 year compared with the mixed (P = .04) and sclerotic (P = .005) classes. The focal class was associated with the highest eGFR values at presentation and 1 year. These findings validate the prognostic utility of the Berden classification scheme and suggest that it may be generalizable.

☆ Author contributions: E. N. scored the biopsies, gathered the clinical data, performed statistical analysis, and drafted the manuscript. H. B. scored the biopsies as well and resolved discrepancies with E. N. at a double-headed microscope. L. G. aided in clinical data collection. M. J. supervised the statistical analysis. All authors contributed to the design of the study and helped draft the manuscript.

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1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitides (AAVs) can have multiple organ system manifestations, including renal involvement [1]. Renal disease in AAV commonly presents with positive serum antimyeloperoxidase (MPO) or antiproteinase 3 (PR3) titers and rapidly progressive glomerulonephritis (GN) [2,3]. AAV is responsible for 64.0% of rapidly progressive GN cases in Japan, where survival at 6 months varied from 85.7% to 53.8% and at 24 months varied from 85% to 36.9% depending on the disease severity [4]. AAV has an incidence of 1 to 2 cases per 100 000 in Europe and more commonly affects the elderly [5]. In a report from the United Kingdom, survival of patients with ANCA GN at 1 year was 82% and at 5 years was 76%, whereas end-stage renal disease (ESRD) occurred in 28% of patients and was associated with 47% mortality [6]. Because of the high risk of mortality and ESRD in ANCA GN, it is important to develop and refine clinical and histopathologic disease classification criteria, to provide prognostic information and inform treatment decisions.

Recently, Berden et al [7] proposed a histopathologic classification schema for ANCA GN designed to work in concert with baseline estimated glomerular filtration rate (eGFR) measurements to more accurately predict renal outcome. The scheme divides ANCA GN into 4 categories based on examination of at least 10 whole glomeruli from a patient: focal (≥50% normal glomeruli), crescentic (≥50% glomeruli with cellular crescents), mixed (<50% normal, <50% crescentic, <50% globally sclerotic glomeruli), and sclerotic (≥50% globally sclerotic glomeruli). Berden et al reported that the histologic category at baseline measurement strongly and independently correlated with renal function at 1-year and 5-year follow-up measurements in a cohort of 100 patients from 32 centers in 9 European countries. Because this classification scheme is new, validation of its prognostic utility in external cohorts is needed.

The purpose of this study was to determine whether the histopathologic classification scheme proposed by Berden et al could be used to predict changes in renal function and renal survival in an external cohort with AAV who underwent kidney biopsy in Calgary, Canada. We hypothesized that changes in eGFR at 1-year follow-up and renal survival would differ based on whether the histopathologic pattern was focal, crescentic, mixed, or sclerotic. We also sought to determine whether additional tubulointerstitial or glomerular pathology not included in the existing classification scheme was associated with these outcomes.

2. Methods

All patients who were diagnosed with ANCA GN (microscopic polyangiitis, granulomatous polyangiitis, or Churg-Strauss syndrome) and had a renal biopsy in the Calgary area between January 2005 and August 2010 were included in this retrospective study. The *presentation date* was defined as the date of biopsy. To be included in the study cohort, participants required at least 1 year of follow-up postpresentation (with the exception of those who died during this time) and adequate documentation of the laboratory parameters of interest. If a creatinine value within 1 week before or after the presentation date could not be found, the patient was excluded. Patients with less than 10 glomeruli sampled on the biopsy were excluded. Patients with any other known concurrent renal disease and those with positive antiglomerular basement membrane serology were excluded.

Cases of ANCA GN were identified by a search of the Department of Pathology Database (Foothills Medical Center, Department of Pathology Database). These patients' slides were pulled from the Department of Pathology Archives (Foothills Medical Center, Department of Pathology Archives). An experienced renal pathologist (H. Benediktsson) trained the student (E. Nohr) to apply the histologic criteria proposed by Berden et al in a systematic examination of all glomeruli present on the slides. The slides scored included hematoxylin and eosin, periodic acid–Schiff, methenamine silver, and trichrome (if available). The renal pathologist and student examined the cases individually and tabulated the results. Significant disagreements were resolved by examination at a double-headed microscope.

All glomeruli from each biopsy were scored. Normal glomeruli were allowed to have subtle signs of ischemia or few inflammatory cells (<4 neutrophils, lymphocytes, or monocytes). Cellular crescentic glomeruli contained crescents consisting of at least 3 stacked cells extending from Bowman capsule and consisting of a cellular component greater than 10%. Globally sclerotic glomeruli were required to show complete sclerosis of the glomerular tuft. If 50% or higher of the glomeruli present in the biopsy were normal, the classification was focal. If 50% or higher of the glomeruli were crescentic, the classification was crescentic. If 50% or higher of the glomeruli were globally sclerotic, the classification was sclerotic. If less than 50% of the glomeruli were normal, less than 50% of the glomeruli were crescentic, and less than 50% of the glomeruli were globally sclerotic, the classification was mixed. Other glomerular pathologic features that were scored included fibrous crescents (defined as crescents with a cellular component of <10%), segmental necrosis, and segmental sclerosis of the glomerular tuft. In addition, interstitial inflammation, interstitial fibrosis, tubulitis, tubular atrophy, arterial sclerosis, and arteriolar hyalinosis were scored on a scale from 0 to 3 according to the Banff criteria for classification of renal transplant pathology [8]. The presence or absence of any acute tubular injury was recorded.

For each patient, clinical data were retrieved including patient demographics, ANCA serology and immunofluorescence, creatinine/eGFR levels (the values closest to the presentation date and 1 year after presentation), date of death, the requirement for dialysis, transplantation status, use of immune suppression (prednisone, cyclophosphamide, and