A Novel Simpler Histological Classification for Renal Survival in IgA Nephropathy: A Retrospective Study

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Background: Patients with immunoglobulin A (IgA) nephropathy may progress to end-stage renal disease (ESRD) within 10 to 20 years after renal biopsy. We evaluated factors associated with long-term renal survival by using a novel simplified histological classification.

Study Design: Retrospective study.

Setting & Participants: 437 patients (296 men, 141 women) with IgA nephropathy seen at our single center from January 1971 to December 2006. Most patients received treatment with renin-angiotensin system inhibitors.

Predictors: Baseline age, sex, presence of hematuria, presence of hypertension, serum creatinine level, urine protein at baseline, and 2 histological classifications.

Outcomes & Measurements: Relationship of baseline factors to time to ESRD was evaluated by means of univariate and multivariate analysis with log-rank test and the Cox proportional hazard method.

Results: In a mean follow-up of 107.6 months, 72 ESRD events occurred. The 5-, 10-, 15-, and 20-year renal survival rates after renal biopsy were 94.1%, 82.1%, 73.1%, and 60.3%, respectively. Independent baseline predictors of increased ESRD risk were microhematuria with absence of recurrent macrohematuria (adjusted hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.30 to 3.65; $P = 0.003$), 1.0 mg/dL (88.4 μmol/L) higher serum creatinine level (HR, 1.50; 95% CI, 1.10 to 2.07; $P = 0.013$), proteinuria with 1.0 g/dL (10.0 g/L) greater protein (HR, 1.28; 95% CI, 1.07 to 1.52; $P = 0.006$), and grading of histological lesions. A 1-grade increase according to our 3-grade classification was associated with a nearly 6-fold ESRD risk increase (adjusted HR, 5.95; 95% CI, 3.54 to 10.01; $P < 0.0001$).

Limitations: Lack of adjustment for changes in treatment that may have occurred during the study period.

Conclusions: Renal damage progression in patients with IgA nephropathy was associated with microscopic hematuria at clinical onset, increased serum creatinine level, increased proteinuria, and grading of histological lesions. Our classification system appears simpler than other classifications and is associated with ESRD risk, which could help identify individual high-risk patients and stratify patients enrolled in randomized clinical trials into homogeneous groups.

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INDEX WORDS: Immunoglobulin A (IgA) nephropathy; histological classification; renal survival.

Primary immunoglobulin A (IgA) nephropathy occurs worldwide and is characterized by recurrent episodes of macroscopic hematuria (which usually arise during upper respiratory tract infections) or asymptomatic persistent microscopic hematuria with or without proteinuria. Few epidemiological studies examined the incidence of primary IgA nephropathy in various populations around the world.[1-4] National renal biopsy registries showed that IgA nephropathy is the most common form of primary glomerulonephritis worldwide (30% to 40% of all biopsy-proven primary glomerulonephritis),[5-11] with an incidence ranging from 8.4 to 11.1 cases per million population in Italy[5,10-11] compared with 5.4 to 12.4 per million population in central and

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eastern Kentucky (United States)[12] and 26 patients per million population in Cotes d'Armor (France).[13] Although initially believed to represent a benign condition,[14] IgA nephropathy is now recognized as a cause of end-stage renal disease (ESRD) in a substantial proportion of patients within 10 to 20 years from its apparent onset.[2] The clinical course is extremely variable and ranges from asymptomatic microscopic hematuria to rapidly progressive renal failure.

Certain renal lesions were associated in some studies with poorer renal prognosis, and several morphological classifications were adopted. The use of different types of classifications is responsible in part for existing controversies in the assessment of rates of progression to ESRD and other renal outcomes. In general, histological grading mainly was based on the presence of cellular proliferation, glomerulosclerosis, crescents, and tubulointerstitial damage. Despite assessment and validation in a cohort of only 20 patients, the most widely adopted classification was that developed by Lee et al,[15] which includes 5 histological grades of disease. This classification was revised subsequently by Haas,[16] who suggested that the classification of Lee et al[15] underscored tubulointerstitial damage. Even the revised classification of Haas[16] was validated in a single cohort of only 109 patients.

Single and multicenter biopsy data available from large cohorts of patients with IgA nephropathy allow for more sophisticated testing of the predictive value and validity of the classification of IgA nephropathy for renal outcomes. We updated and simplified the histological classification[17] of IgA nephropathy based on descriptive criteria of renal lesions made by Churg et al[18] and accepted by the World Health Organization and scored renal biopsy specimens of our patients. In this retrospective study, we assembled a large cohort of patients with IgA nephropathy and evaluated factors recorded at the time of renal biopsy and associated with long-term renal survival, then validated this novel simpler classification in predicting renal outcomes.

METHODS

Renal Biopsy

From January 1971 to December 2004, information for 2,710 renal biopsies of native kidneys performed and/or processed in our unit were collected. In 796 of these (29.4%), IgA nephropathy was diagnosed, and a cohort of 437 patients (296 men, 67.7%; 141 women, 32.3%) followed up for more than 1 year in our single center until December 2006 were included in the study population. In our clinical policy, main reasons for performing a renal biopsy were asymptomatic urinary abnormalities (persistent microscopic hematuria and mild to moderate proteinuria), recurrent episodes of macroscopic hematuria, nephrotic syndrome, acute renal failure, or chronic renal insufficiency of unknown origin without severe alterations shown by means of ultrasound imaging. Biopsies were performed at least 30 days after episodes of macroscopic hematuria. The diagnosis of IgA nephropathy was made by the detection of mesangial deposits staining predominantly for IgA with immunofluorescence studies. Patients with systemic lupus erythematosus, Henoch-Schönlein purpura, or chronic liver diseases were excluded. All biopsy specimens were reviewed by 2 separate pathologists masked to patient outcomes and clinical characteristics. Biopsy specimens were scored according to the morphological classification of Lee et al[15] and using our modified classification.[17]

To assess the severity of renal damage, we distinguish 3 grades (Gs): G1 (mild) includes patients with IgA nephropathy with minor or minimal lesions, G2 (moderate) includes patients with focal-segmental or diffuse proliferative glomerulonephritis, and G3 (severe) includes patients with sclerotic lesions in advanced chronic glomerulonephritis or ESRD. Mesangial hypercellularity was scored as follows: mild with more than 3 and 5 or fewer mesangial cells, and moderate-severe with more than 6 mesangial cells on average in at least 2 glomerular lobules. Sclerosis was defined as the obliteration of capillary loops caused by prevalent increase in matrix, capillary tuft adhesion to Bowman capsule, or both. Endocapillary proliferation was defined as obliteration of the capillary tuft by cells (endothelial, mesangial, or inflammatory cells). Biopsy specimens with normal glomeruli or glomeruli with only a mild increase in mesangial cellularity and no tubulointerstitial changes were assigned to grade G1. The presence of even only 1 glomerulus with segmentally sclerotic lesion excluded a case from being assigned to this grade. Biopsy specimens were assigned to grade G2 if 1 of the following signs was detected: moderate increase in mesangial cellularity (focal or diffuse), endocapillary proliferation, cellular crescents (up to 50% of glomeruli involved), segmental sclerosis, tubular atrophy, and interstitial fibrosis (up to one third of the cortical area). Biopsy specimens were assigned to grade G3 if cellular crescents were present in greater than 50% of glomeruli and/or fibrous crescents or global glomerulosclerosis were present in greater than one third of glomeruli and/or segmentally sclerotic lesions involved greater than 50% of glomeruli (ie, diffuse) and/or tubular atrophy and interstitial fibrosis involved greater than one third of cortical areas. Essential features of the 5- and 3-grade systems used for comparison are listed in Table 1. Patients followed up for at least 1 year, with an average follow-up for the entire cohort of 9 years, were included in the study.