IgA Nephropathy: Does Histologic Grading Really Matter?

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IgA nephropathy exhibits considerable histologic variability, ranging from normal histology to diffuse proliferative and crescentic glomerulonephritis (GN), although the majority of cases are characterized by focal or diffuse, predominantly mesangial proliferative GN. A number of different histologic classifications have been devised for IgA nephropathy, focusing on glomerular changes, tubulo-interstitial changes, or both, that demonstrate a significant correlation between histologic grade or score and clinical outcome, most often renal survival. However, the value of histologic grading in guiding the nephrologist’s therapeutic approach to patients with IgA nephropathy remains uncertain, and a recent study demonstrated that mean arterial pressure and severity of proteinuria over time were superior to histologic grading using either of the two most widely used classification systems in predicting the rate of deterioration of renal function in a large cohort of patients with IgA nephropathy. This review will focus on the strengths and weaknesses of currently used histologic grading systems for IgA nephropathy, and how our approach to histologic grading might be changed to make such grading more relevant to nephrologists treating patients with this disease. (Acta Nephrologica 2008; 22: 83-88)

Key words: IgA nephropathy, Berger’s disease, glomerulonephritis, renal biopsy

INTRODUCTION

In the original series of patients with IgA nephropathy published by Berger,1 the majority of renal biopsies showed focal glomerulonephritis (GN), although a significant number showed chronic GN and approximately 10% were histologically normal. Subsequent studies have confirmed that while focal or diffuse mesangial proliferative GN are the most common histologic lesions in IgA nephropathy, there is a wide degree of histologic variability in this disease, ranging from no detectable histologic lesion to diffuse proliferative and crescentic GN, much as is the case with lupus nephritis.2-8

Because of this histologic diversity of IgA nephropathy, a number of histologic classification systems have been devised and tested for their value in predicting clinical outcomes, most often actuarial renal survival. These systems are of two basic types: semiquantitative and single grade. Semiquantitative scoring systems, such as those employed by Alamartine et al,9 Kobayashi et al,10 and Radford et al,11 first assign a semiquantitative grade (e.g., 0, 1, 2, or 3 corresponding to absent, mild, moderate, and severe) to each of a number of histologic parameters in glomerular, tubular, interstitial, and vascular compartments. A sum score for each compartment is then determined, as well as an overall histologic score comprising the total of the compartmental sum scores. The number of individual histologic parameters scored in such systems generally ranges from 10 to 20. Semiquantitative scoring systems have the advantage of identifying specific morphologic changes, or combinations of these, which are best correlated with clinical outcome and/or with each other. However, despite generally good correlations between total histologic scores and rates of renal survival,9-11 semiquantitative scoring systems are felt by many pathologists to be too time-consuming to be used routinely in busy renal biopsy practices. Still, abbreviated versions of these, focusing on histologic changes in a single compartment (e.g., tubulo-interstitial changes) have been used at some centers and found to show good correlation with clinical outcomes.12,13

The majority of pathologists who regularly use a histologic classification system for IgA nephropathy use a single grade system. These systems combine vari-
ous glomerular and tubulo-interstitial features, in most instances with emphasis on the former, into a relatively small number (most often 5) of histologic grades. Of these, the two most widely used are those of Lee et al\textsuperscript{3} (Table 1) and of Haas\textsuperscript{4} (Table 2). Each of these classification systems has been independently verified to show significant correlation with renal survival rates,\textsuperscript{8,13-18} as shown for the latter classification system in Fig. 1. However, neither of these classifications was found to be as good as a model based on the mean arterial pressure and urinary protein excretion averaged over time during 2-3 years of observation in predicting the rate of decline of renal function in a study of 298 adults with IgA nephropathy.\textsuperscript{19}

The findings of the latter study indicate the limitations of current histologic classification systems for IgA nephropathy. Still, to improve on these systems, and develop a more clinically useful one, it may be instructive to first

Table 1. Histologic Classification of IgA Nephropathy of Lee et al\textsuperscript{3}

<table>
<thead>
<tr>
<th>Histologic Grade</th>
<th>Glomerular Changes</th>
<th>Tubular and Interstitial Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mostly normal</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Occasional slight mesangial thickening with or without hypercellularity</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Less than 50% of glomeruli show localized mesangial proliferation and sclerosis</td>
<td>Absent</td>
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<tr>
<td></td>
<td>Rarely, small crescents</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Diffuse mesangial proliferation with focal and segmental variation</td>
<td>Focal interstitial edema and infiltrate occasionally present</td>
</tr>
<tr>
<td></td>
<td>Occasional small crescents and adhesions</td>
<td>Tubular atrophy rare</td>
</tr>
<tr>
<td>IV</td>
<td>Marked diffuse mesangial proliferation and sclerosis</td>
<td>Tubular atrophy, interstitial inflammation and occasional interstitial foam cells</td>
</tr>
<tr>
<td></td>
<td>Crescents in up to 45% of glomeruli</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Similar to IV but more severe</td>
<td>Similar to IV but more severe</td>
</tr>
<tr>
<td></td>
<td>Crescents in more than 45% of glomeruli</td>
<td></td>
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</table>

Table 2. Histologic Classification of IgA Nephropathy of Haas\textsuperscript{4}

Class I – Minimal histologic lesion
Glomeruli are normocellular, without segmental sclerosis, necrosis, or crescents.

Class II – Focal-segmental glomerulosclerosis (FSGS)-like
Glomeruli show focal and segmental sclerosis without mesangial or endocapillary hypercellularity, crescents, or necrosis.

Class III – Focal proliferative glomerulonephritis
50% or fewer of the glomeruli (not including globally sclerotic glomeruli) are hypercellular. This hypercellularity may be limited to mesangial areas, or include endocapillary hypercellularity, crescents, or necrosis.

Class IV – Diffuse proliferative glomerulonephritis
More than 50% of the glomeruli (not including globally sclerotic glomeruli) are hypercellular. This hypercellularity may be limited to mesangial areas, or include endocapillary hypercellularity, crescents, or necrosis.

Class V – Advanced chronic glomerulonephritis
40% or more of the glomeruli are globally sclerotic, and/or there is > 40% estimated tubular atrophy or loss in the cortex.

If these criteria are met, the biopsy specimen is graded as class V regardless of other histologic features.
identify the strengths and weaknesses of the currently systems, particularly those that are most widely used.

**CURRENT HISTOLOGIC CLASSIFICATION SYSTEMS FOR IGA NEPHROPATHY: STRENGTHS AND WEAKNESSES**

Documentation of the clinical relevance of the histologic classifications of Lee et al$^3$ and of Haas$^4$, as well as other classifications$^7,12,13,16$ have been based on retrospective studies using development of end-stage renal disease (ESRD) as their primary endpoint$^4,7,8,13,16,20,21$. However, rates of progression to ESRD from the time of diagnosis (biopsy) are largely a function of factors not directly related to the immune complex-mediated glomerular injury that represents the primary event in IgA nephropathy and ultimately leads to disease progression and scarring. Rather, progression to ESRD is largely related to irreversible damage already present at the time of biopsy, as well as compensatory mechanisms (e.g., glomerular hyperfiltration) that result from this underlying nephron loss. This is borne out by the finding that the strongest and most consistent histologic predictors of development of ESRD in IgA nephropathy are tubular atrophy/interstitial fibrosis$^{12,13,21,23}$ and, to a somewhat lesser extent, glomerular sclerosis$^{12,22,23}$. By contrast, proteinuria, the strongest clinical correlate of the rate of decline of renal function in IgA nephropathy,$^{19,24}$ reflects in large part active glomerular injury. Still, proteinuria at the time of biopsy, as opposed to time-averaged proteinuria during follow-up, is of relatively limited predictive value with respect to rates of disease progression$^{19,24}$ perhaps, at least in part, because factors other than active glomerular injury contribute to proteinuria. As such, there remains a potentially important role for histologic assessment in guiding the clinician’s approach to the patient with IgA nephropathy, provided the right histologic parameters are evaluated.

A second feature of the Lee et al$^3$ and Haas$^4$ classifications, pointed out in the study of Bartosik et al$^{19}$ is that while these classifications each identify 5 histologic grades of IgA nephropathy, the great majority of cases, at least in adults, are clustered in two of these grades (grades II and III of Lee et al$^4$, and subclasses III and IV of Haas$^4$).$^{19,21,25}$ Furthermore, it is within these two histologic grades that the greatest degree of variability occurs with respect to clinical presentations and outcomes. Subclass I lesions in each classification are almost always quite benign, whereas the great majority of patients with subclass V lesions progress to ESRD within 3-4 years following the biopsy.$^{3,4,13,18,19,21,22}$ (Fig. 1). As such, there is little if any indication for using immunosuppressive therapy in these latter subclasses. More pressing therapeutic decisions are limited mainly to those lesions

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**Fig. 1.** Renal survival from the time of biopsy (Kaplan-Meier method) in 224 patients with proliferative IgA nephropathy (99 children and adolescents, 125 adults): comparison of different histologic subclasses according to the classification of Haas$^4$ (Table 2). Data represent findings in 42 patients (24 pediatric, 18 adult) with subclass I lesions, 19 (7 pediatric, 12 adult) with subclass II, 98 (45 pediatric, 53 adult) with subclass III, 41 (20 pediatric, 21 adult) with subclass IV, and 24 (3 pediatric, 21 adult) with subclass V. Because no patients with subclass I lesions and only one with a subclass II lesion developed end-stage renal disease, these subclasses are grouped together. Renal survival was significantly better in patients with subclass III lesions than in those with subclass IV lesions ($p < 0.01$ by both long-rank and Wilcoxon tests).
about which the most widely used current classifications provide relatively little differentiating information, although renal survival rates are clearly better with focal proliferative GN than with diffuse proliferative GN \cite{21,23} (Fig. 1).

In the latter regard, semiquantitative scoring systems may offer some advantage over single grade systems. An international committee comprised of pathologists and nephrologists from 4 continents is initially using such an approach in developing a new consensus histologic classification for IgA nephropathy. The pathologists are grading 15 different histologic parameters from biopsies of 300 closely monitored patients with active (i.e., with proteinuria, without advanced chronic renal insufficiency) IgA nephropathy. The histologic findings will then be correlated with rates of decline in renal function to determine those histologic parameters, or combinations of parameters, that are most predictive of disease progression. These latter parameters will then be formulated into an initial histologic classification, the clinical value of which will then be tested on a second group of patients and biopsies. Based on the latter results, the classification might then be further modified to arrive at a final consensus classification. This time-consuming effort has been ongoing since 2005, with the hope of developing the initial histologic classification during 2008.

**Insights from Repeat Biopsy Studies**

There have been a limited number of studies done, mainly in Asia, that have examined renal biopsy findings in the same IgA nephropathy patients at two separate points in time, most often before and after treatment with corticosteroids and/or other immunosuppressive agents. \cite{26-29} The main conclusion that can be drawn from these studies is that each morphologic lesion that is generally felt to represent a component of disease activity, including mesangial and endocapillary cell proliferation, glomerular necrosis, cellular crescents, and interstitial inflammation and edema, are all largely or completely reversible. Of these, endocapillary proliferation, crescents, and necrosis (the latter being an uncommon lesion in IgA nephropathy) \cite{30} were found to be fully reversible by Hotta et al. \cite{26}, consistent with findings in most studies that these lesions tend not to be independent prognostic indicators of renal survival by multivariate analysis. \cite{14,21,22} Mesangial proliferation is largely but not entirely reversible, even in patients responding to treatment with a marked decrease in proteinuria, \cite{26,27} and thus may represent a somewhat more ominous finding, particularly when diffuse and consisting of an increase in matrix as well as cellularity. \cite{27,28} This would appear consistent with our finding in 139 adults and children with Haas \cite{4} subclass III and IV lesions of IgA nephropathy that diffuse proliferative glomerular histology (subclass IV) was an independent predictor of progression to ESRD, even when also considering interstitial fibrosis, global and segmental glomerular sclerosis, and presence or absence of endocapillary hypercellularity \cite{21} (Fig. 1). Still, a repeat biopsy study in 61 Japanese children with IgA nephropathy \cite{28} found no individual histologic lesions on the initial biopsy that were significantly different among those patients whose proteinuria and hematuria resolved (with concomitant decreases in mesangial proliferation, tubulointerstitial changes, and intensity of glomerular IgA staining by immunofluorescence) and those who had persistent urinary abnormalities (with no decrease in mesangial proliferation or IgA deposition, and worsening of tubulointerstitial changes). Therefore, there does not appear to be a single histologic marker predictive of progressive disease in IgA nephropathy, and successful development of a more clinically valuable consensus morphologic classification for IgA nephropathy will almost certainly have to involve identification of specific combinations of histologic (or histologic and immunohistologic) findings that correlate with the rate of decline in renal function.

**IS THERE A MORPHOLOGIC “POINT OF NO RETURN”?**

Lai and coworkers \cite{21} examined correlations between the amounts of glomerular and tubulointerstitial scarring and development of renal insufficiency (serum creatinine > 1.4 mg/dl) in 144 adults with IgA nephropathy. Interestingly, they found that less than 5% of patients with very low levels of glomerular (estimated mean sclerosis per glomerulus < 10%) and tubulointerstitial (< 5% estimated tubular atrophy/interstitial fibrosis) scarring had renal insufficiency at a mean of 90 months post-biopsy, regardless of other histologic findings. By contrast, nearly 40% of patients with a mean estimated sclerosis per glomerulus of 10-25% and/or estimated tubular atrophy/interstitial fibrosis > 5% had renal insufficiency after 90 months of follow-up. These findings suggest that the prognosis of IgA nephropathy diagnosed and treated very early in its course is excellent, regardless of the level of active glomerular inflammation. By contrast, lesions that have developed even relatively mild levels of glomerular and/or tubulo-interstitial scarring may have already reached a “point of no return”, beyond which disease progression can be slowed, but no longer prevented. \cite{18}

**SUMMARY AND CONCLUSIONS**

A renal biopsy is absolutely needed to diagnose IgA
nephropathy, however the value of histologic grading of IgA nephropathy in predicting prognosis and especially in guiding potential therapy remains unclear. An exception to this may be early active lesions with very little or no scarring, as noted above. Histologic classification systems for IgA nephropathy now in use, such as those of Lee et al. and Haas, show significant correlations between certain histologic grades and renal survival, but are of limited usefulness with intermediate grade lesions that have the most variable clinical course. Furthermore, current histologic grading appears to be inferior to clinical parameters (proteinuria, hypertension) followed over time in predicting the rate of decline in renal function, although such a comparison is not really a fair one since the renal biopsy illustrates the nature of the disease at a single time point, and treatment decisions often cannot wait for a year or more of follow-up, even with a relatively slow-progressing disease like IgA nephropathy. The primary explanation for the limitations of histology as a predictor of the rate of decline of renal function in patients with IgA nephropathy may in fact be that renal biopsy is a single snapshot of a disease process that is not static. Histologic grading is relied on heavily to guide therapy in a number of other renal lesions, such as lupus nephritis and renal allograft rejection, however these lesions tend to be more rapidly progressive than IgA nephropathy and also have widely accepted treatment regimens that are still lacking for IgA nephropathy. Still, as more data becomes available from prospective, randomized clinical trials of immunosuppressive and other therapies in patients with IgA nephropathy, histology is likely to play a more important role in guiding such treatment, and the impending development of a new consensus histologic classification for IgA nephropathy should only enhance the value of the renal biopsy in this regard.

REFERENCES

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