Histologic Classification of IgA Nephropathy: Past, Present, and Future

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Summary: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. Since its description in 1968, a number of histologic descriptions and classification systems have emerged, the most recent of which is the Oxford Classification of IgAN. We present a historical panorama of histologic classifications of IgAN and discuss the most recent developments, updates, and future challenges of the Oxford Classification of IgAN.
Semin Nephrol 38:477–484 © 2018 Published by Elsevier Inc.
Keywords: IGA nephropathy, classification, diagnosis, pathology

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. Clinical presentation and outcome are highly variable and reflect the diverse light microscopic features. There have been a number of attempts to classify the histological changes to provide clinically relevant information, the most recent of them an international consensus classification—the Oxford Classification of IgAN—which is a truly evidence-based classification of glomerular disease.[1] This article provides an overview of the histologic classifications of IgAN, the current Oxford Classification of IgAN, and discusses future challenges and developments.

A HISTORY OF IgA NEPHROPATHY

The mid-1960s set the background for the increase of commercially available immunofluorescence antibodies and the incorporation of immunofluorescence microscopy to diagnostic medicine.[2] In 1967, Antoine et al[3] presented a panorama of immunofluorescence patterns in renal lesions, among which he identified a number of patients with chronic glomerulonephritis or with purpuric lesions whose biopsy specimens showed glomerular deposits of IgA. In 1968, Berger and Hinglais[4] described 25 patients with recurrent hematuria and mesangial IgA deposits that surmounted IgG deposits. This finding was groundbreaking at the time because IgG was thought to be the main immunoglobulin of pathogenic importance in glomerulonephritis, and was a consequence of the availability of purified anti-IgA antibody at Hopital Necker.[5] Thirty cases were added to this series in the following year, amounting to 55 cases of a glomerulonephritis with a myriad of focal segmental lesions, but a common denominator of strong and dominant IgA fluorescence.[6] Of note, 22 of the patients had a synpharingitic presentation, and 1 patient progressed to end-stage renal disease (ESRD). At the time, the newly described syndrome drew little attention from the Nephrology community and was thought for a while to be limited to France.

In the early 1970s, reports from North America, Europe, Asia, and Australia reignited the interest in patients with hematuria, focal nephritis, and mesangial IgA deposits. The eponym of Berger's disease was introduced in 1973, and by 1975 the defining features of IgA nephropathy were consolidated.[4] From these early descriptions of the condition, it was clear that IgAN showed hematuria and red blood cell casts, a slow but relentless evolution, with ESRD developing in some patients, an estimated 50% risk of recurrence in patients who had undergone a transplant, and a variable histopathologic picture, with proliferative glomerulonephritis, predominantly mesangial, but also focal and segmental, which overlapped with renal findings in Henoch-Schönlein purpura (HSP), as outlined by Meadow et al[7] in 1972.

HISTOLOGIC MARKERS OF OUTCOME IN IgAN: EARLY STUDIES

Increasing interest in the histopathology of IgAN followed in the 1980s. It was clear at that time that IgAN was primarily a glomerular disease, but many questions remained: Are glomerular lesions relevant to decreased renal function? Is there a marker of severity or irreversibility of immunologic damage? Do patterns of glomerular disease change during the clinical course? Is it possible to create an objective measurement of histologic damage and an algorithm to predict renal survival?[8]

In 1982, Lee et al[9] used morphologic markers to predict the progression of renal disease in IgAN. Their five-tier classification system was based on the Meadow et al[7] classification for Henoch-Schönlein nephritis and focused on the overall histologic activity in a given

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Financial disclosure and conflict of interest statements: none.
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0270-9295/ - see front matter

https://doi.org/10.1016/j.semnephrol.2018.05.017

biopsy. It combined the severity of mesangial hypercellularity, glomerular sclerosis, crescents, and tubulointerstitial changes in a single score. This schema was applied in 20 patients with IgAN, 13 of whom were followed up for a mean of 2.8 years. All patients with diffuse proliferative lesions (grade IV) or chronic advanced lesions (grade V) on the initial biopsy developed ESRD. Patients with normal histology or mild to moderate lesions (grades II and III) had a benign course without deterioration of renal function. This publication suggested the usefulness of pathologic markers of disease activity and chronicity to predict the clinical course in IgAN.

A number of reports by Droz et al[10] in 1984, Levy et al[11] in 1985, D'Amico et al[12] in 1986, Magil and Ballon[13] in 1987, and Lee et al[14] in 1987 confirmed Lee's observations[9] in more than 900 pediatric and adult patients. These studies showed a worse clinical outcome in patients with extensive glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Of note, the cohort of 292 patients followed up by D'Amico et al[12] showed that, in addition to the histopathologic features described earlier, proteinuria more than 1 g/d, crescents, and the degree of intracapillary hypercellularity were indicators of an adverse outcome. In 1990, Bogenschutz et al[15] analyzed 239 patients with nonproteinuric IgAN. In this series, glomerular findings were classified as minimal lesions, and as mild or moderate to severe mesangial proliferation. This report highlighted the fact that interstitial fibrosis and tubular atrophy might occur independently from glomerular lesions and are individual predictive markers of renal functional loss.

A later report of 18 IgAN patients by Haas[16] in 1996 focused on patients with focal segmental glomerulosclerosis (FSGS)-like lesions without crescents or interstitial chronic damage, a category that did not fit into any of Lee's classes[8,9]. Serum creatinine and proteinuria values among these patients did not differ from typical FSGS patients, and renal survival did not differ when compared with typical FSGS and other IgAN patients despite previous observations of nephrotic proteinuria being a marker of bad outcome.[13] The accumulated evidence encouraged further refinement of Lee's classification.

HAAS CLASSIFICATION OF IgAN

In 1997, Haas[17] published a new histologic grading system based on his observations of 244 patients with IgAN. The Haas[17] study aimed to establish relevant clinicopathologic correlations and to identify potential histopathologic markers of outcome. The schema borrowed features of both the Lee system[8,9] and the World Health Organization classification of lupus nephritis, and recognized FSGS-like lesions as part of the spectrum of IgAN. Five classes were described. A comparison between the Lee[8,9] and Haas[17] classes is presented in Table 1.

Nearly 25% of the cases showed no signs of an active proliferative glomerulonephritis (classes I and II); class III (focal proliferative glomerulonephritis) included the majority of cases in Haas's series[17]. A smaller percentage of patients (14%) showed diffuse proliferative glomerulonephritis (class IV) and chronic glomerulonephritis (class V); these patients had the highest serum creatinine levels and a higher prevalence of hypertension at the time of the biopsy. Outcome was measured by time to irreversible ESRD, defined by a requirement of renal replacement therapy. Notwithstanding the existence of five classes, only three different groups were recognized regarding clinical outcome: classes I and II with excellent prognosis, class III with intermediate prognosis, and classes IV and V with poor prognosis. The presence of crescents impacted negatively on renal survival in subclasses III and IV only when cases were not controlled by serum creatinine levels at the time of biopsy. Crescents were not classified according to their nature (cellular, fibrocellular, or fibrous) in this series. Serum creatinine level at the time of biopsy was predictive of renal survival in patients with classes IV and V, but was a less effective marker of renal survival in patients with class III. This finding might reflect the fact that higher serum creatinine level at presentation is usually a result of extensive baseline chronic damage and thus a herald of a less favorable prognosis. The impact of interstitial fibrosis and tubular atrophy on renal survival varied in different classes: although in class III the presence of interstitial fibrosis and tubular atrophy in 10% of the cortex was predictive of lower renal survival, in class IV this percentage was 20%.

Table 1. Lee and Haas Classification Systems

Grade	Lee	Haas
I	Mostly normal glomeruli	Minimal histologic lesion
II	<50% of glomeruli with mesangial hypercellularity and sclerosis Rare small crescents	Focal segmental glomerulosclerosis
III	Diffuse mesangial proliferation Occasional adhesions and small crescents	Proliferative glomerulonephritis in ≤50% of glomeruli Crescents might be present
IV	Diffuse marked mesangial proliferation ≤45% of glomeruli with crescents Frequent segmental and global sclerosis	Proliferative glomerulonephritis in >50% of glomeruli Crescents might be present
V	Severe mesangial proliferation >45% of glomeruli with crescents Frequent segmental and global sclerosis	≥40% glomerular sclerosis and/or tubular atrophy