

INVITED PAPER

**THE NEW OXFORD CLINICO-PATHOLOGICAL CLASSIFICATION
OF IgA NEPHROPATHY**

**Coppo R., Cattran D., Roberts Ian SD., Troyanov S., Camilla R.,
Cook T., Feehally J.**

*On behalf of the Working Group of the International IgA Nephropathy Network
& Renal Pathology Society*

Abstract: The new Oxford Classification of the Pathology of IgA nephropathy originated from an international collaborative effort of the Working Group of the International IgA Nephropathy Network & Renal Pathology Society. It provides a new common language to categorizing glomerular and tubulo-interstitial lesions in IgA nephropathy having a proved effect on progression. Although retrospective in design and requiring future prospective validation, the Oxford collaboration defined and scored four pathologic parameters having an influence on outcome (independently of clinical information at renal biopsy or during follow-up); including mesangial (M) and endocapillary (E) proliferation (hypercellularity), glomerulosclerosis (S) and tubular atrophy and interstitial fibrosis (T). The scheme will likely become known as the OXFORD-MEST scoring system.

Key words: IgA nephropathy, pathology, classification, risk factor, progression.

Introduction

IgA nephropathy (IgAN) is easily diagnosed by the presence of IgA-dominant or co-dominant mesangial deposits [1]. However, light microscopy shows a wide range of histological features, ranging from normal histology to highly proliferative or sclerosing changes, tubular atrophy and interstitial fibrosis. In parallel, the natural history of IgAN varies from non-progressive cases to slowly progressive (20% of the cases over 20 years), or even rapidly progressive ones. Individual histological lesions have been reported to be of prognostic value by several authors and a number of classifications have been proposed in which pathological features predict the final outcome [2–10].

The pathological systems used to classify renal lesions of IgAN, can be divided into two groups, lumped and split. The lumped systems assess the overall severity of the lesions based on the concomitant evaluation of the changes found in glomerular, tubular, interstitial and arteriolar compartments, as in the widely used classification of Lee [2] and Haas [7] of five classes. The split systems use semiquantitative severity grading of lesions in each of the four compartments of the kidney and permits the elaboration of a global or aggregate score for each compartment. An analysis of the literature performed by D'Amico some years ago [11] reported that the strongest independent predictors of progression using Cox multivariate analysis were the severity of glomerular sclerosis and interstitial fibrosis. The presence of crescents, in general not circumferential, was a risk factor in almost all studies at univariate analysis, but only in half of the reports did it retain significant predictive value at multivariate analysis, and only when crescents were analysed together with tuft adhesions, possibly resulting from previous segmental necrosis. The extent of mesangial proliferation and parietal expansion of deposits resulted significantly associated to unfavourable prognosis in a few studies only and never by multivariate analysis. Also the vascular lesions were only occasionally significant by multivariate analysis.

The apparently conflicting results of these studies reflect differences in patient cohort, treatment and clinical outcome measures. When the clinical endpoint is time to dialysis/renal failure, chronic lesions (tubular atrophy, interstitial fibrosis and glomerulosclerosis) are the only predictors of outcome. When the rate of loss of renal function is considered as outcome active glomerular lesions (mesangial, endocapillary or extracapillary proliferation, necrosis) are the most significant prognostic factors.

In general, the agreement among the various classifications is only reached when considering renal disease already progressed to sclerosis. However, from a clinical perspective, a pathological classification would have greater value if the renal biopsy could provide early signs predicting progression before the development of irreversible damage.

There is consensus about the prognostic value of relevant clinical features, mostly proteinuria, hypertension and excretory renal function [12]. Recent work also indicates the prognostic importance of reduction in proteinuria during follow up, the so called time average proteinuria [13]. However, there is continuing debate whether pathological features seen on renal biopsy contribute additional prognostic information beyond that provided by clinical features [14].

Aim of the International IgAN Group

In 2004, a proposal to develop a consensus clinicopathological classification came from the International IgA Nephropathy Network – an in-

formal network of nephrologists and scientists with representation from the majority of nephrology research groups around the world active in the field of IgAN – and members of the Renal Pathology Society interested in IgAN, who seek an agreement on an evidence-based clinicopathological consensus classification for IgAN (15–17).

The goals of the new classification were

- to identify pathological features predicting risk of progression of IgAN to improve individual patient prognostication.
- to provide a classification useful to identify specific features that may predict response to treatments, and
- to refine recruitment to clinical trials allowing a stratification of patients by their risk of progression.

The overall approach used by the working group was the following:

- agreement on a clinical dataset useful for outcome studies in IgAN.
- agreement on definitions and scoring of a wide range of pathological features.
- testing reproducibility between pathologists of scoring these features.
- analysis of informative pathological features in the context of clinical outcome to develop a classification.

Development of the Classification

Clinical data and renal biopsy material from 265 patients with IgAN were collected from 8 countries on 4 continents. 5 centres from Asia, 6 from Europe, 2 from USA, 1 from South America and 2 multicentre networks (Canada and USA) participated.

Histology slides from each case were circulated between five pathologists in batches of five, in a rolling fashion to ensure that no two batches were scored by the same five pathologists. A score sheet was completed by individual pathologists for each biopsy.

Agreement on definitions of each pathological feature was obtained after discussion.

Reproducibility was assessed statistically using intraclass correlation coefficients (ICC) and only lesions which had a good ICC were selected.

Where pathology variables were correlated so that using both of them would provide no additional value, only one was selected. For example, the "R" values for interstitial fibrosis and tubular atrophy (0.98) indicated that these pairs of variables were very closely linked and they were grouped in one only.

This process identified the following variables, all common in IgAN, to be further analysed in relation to the clinical data:

1. Mesangial cellularity score,
2. Percentage of glomeruli showing segmental adhesions or sclerosis,
3. Percentage of glomeruli showing endocapillary hypercellularity,
4. Percentage of glomeruli showing cellular or fibrocellular crescents,
5. Percentage of interstitial fibrosis/tubular atrophy,
6. Arterial score.

The independent predictive value of the continuous glomerular variables was assessed drawing ROC curves to determine the optimal cut-offs predicting a worse outcome (the rate of renal function declines faster than the median value).

The optimal cut-off for the mesangial hypercellularity score was approximated to 0.5, and proved to be efficiently substituted by considering if more than 50% of glomeruli showed mesangial proliferative changes (> 3 mesangial cells per mesangial area) to facilitate scoring. Segmental glomerulosclerosis, endocapillary hypercellularity and extracapillary proliferation were categorized as either present or absent as determined by ROC curve. Tubular atrophy/interstitial fibrosis was classified as absent (0%), mild (1–25%), moderate (26–50%) or severe (> 50%).

Results

Clinical features at time of biopsy included median age of 32 years (4–73); mean MAP of 98 ± 18 mmHg. The e-GFR values were evenly distributed within stages 1, 2 and 3 of the KDOQI classification of CKD, although most children had stage 1 CKD (77%). Median proteinuria was 1.7 g/24h (1.95 g/24h/1.73 m² in children). Median follow-up was 5 years (range: 1 to 22 years). The mean rate of renal function decline was -3.5 ± 8.4 ml/min/1.73m²/year (-3.7 ± 6.6 in adults and -2.7 ± 1.05 in children, $p > 0.1$). The end-point of 50% decline in e-GFR was reached in 22% of the cases and ESRD was reached in 13%.

Mesangial score, segmental glomerulosclerosis, endocapillary hypercellularity and extracapillary proliferation were strongly associated with proteinuria at the time of biopsy. Segmental glomerulosclerosis was associated with reduced eGFR and higher MAP at the time of biopsy. Tubular atrophy/interstitial fibrosis was associated with a reduced initial eGFR and higher initial MAP and proteinuria. Arterial disease was strongly associated with initial blood pressure and eGFR but had no relation to initial proteinuria.

By univariate analysis and by multivariate analysis the following lesions resulted independently predictive of clinical outcome (the rate of renal function decline as well as survival without ESRD or 50% reduction in initial eGFR)

- mesangial hypercellularity score > 0.5,
- endocapillary hypercellularity,
- segmental glomerulosclerosis,
- tubular atrophy/interstitial fibrosis.

Conclusion

The new Oxford Classification of the Pathology of IgAN originated from an international collaborative effort of a Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. It provides a new common language and a simple, user-friendly and reproducible systematic approach to categorizing glomerular and tubulo-interstitial lesions in IgAN having a proved effect on progression. Although retrospective in design and requiring future prospective validation, the Oxford collaboration defined and scored four pathologic parameters having an influence on outcome (independently of clinical information); including mesangial (M) and endocapillary (E) proliferation (hypercellularity), glomerulosclerosis (S) and tubular atrophy and interstitial fibrosis (T). The scheme will likely become known as the OXFORD-MEST scoring system. Necrotizing and crescentic lesions were not evaluated because of their rarity in the data set and immunofluorescence and electron microscopy were not included in the enumerated parameters, largely due to pragmatic considerations.

These results will need validation on an independent dataset collected prospectively and in a uniform manner. In the meantime these pathological features can reliably and consistently be evaluated, using the definitions provided, and both pathologists and nephrologists will benefit by integration of these features into their standard evaluations of the renal tissue in patients with IgAN.

Disclosure

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Резиме

НОВА ОКСФОРДСКА КЛИНИЧКО-ПАТОЛОШКА КЛАСИФИКАЦИЈА НА ИГА НЕФРОПАТИЈА

**Coppo R., Cattran D., Roberts Ian SD, Troyanov S.,
Camilla R., Cook T., Feehally J.**

*Од имейно на Работната група на интернационалната ИГА мрежа
и здружението за ренална патологија*

Новата оксфордска клиничко-патолошка класификација на ИГА нефропатијата потекнува од интернационален колаборативен труд на работната група на интернационалната ИГА мрежа и здружението за ренална патологија. Таа дава нов заеднички јазик за категоризацијата на гломеруларните и тубуло-интерстицијалните оштетувања кај ИГА нефропатијата што имаат докажан ефект врз прогресијата. Иако ретроспективна според дизајнот и која бара идна проспективна валидација, оксфордската соработка дефинираше и одреди четири патолошки параметри што имаат влијание на исходот (независно од клиничките информации

при бубрежна биопсија или за периодот потоа); вклучувајќи мезангијални (M) и ендокапиларни (E) пролиферации (хиперцелуларност), гломерулосклероза (S) и тубуларна атрофија и интерстицијална фиброза (T). Шемата веројатно ќе стане позната како OXFORD-MEST scoring system.

Клучни зборови: ИГА нефропатија, патологија, класификација, фактори на ризик, прогресија.

Corresponding Author:

Rosanna Coppo MD
Nephrology, Dialysis and Transplantation
Regina Margherita University Hospital
Piazza Polonia 94,
10126, Torino
Italy